



EUROPEAN
HEMATOLOGY
ASSOCIATION

haematologica

Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

**1st European Myeloma Network Meeting
Turin, Italy, April 19-21, 2018**

ABSTRACT BOOK

ISSN 0392-8660

Volume 103
APRIL
2018 | **s1**



EUROPEAN
HEMATOLOGY
ASSOCIATION



Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

Editor-in-Chief

Luca Malcovati (Pavia)

Managing Director

Antonio Majocchi (Pavia)

Associate Editors

Omar I. Abdel-Wahab (New York), Hélène Cavé (Paris), Simon Mendez-Ferrer (Cambridge), Pavan Reddy (Ann Arbor), Andreas Rosenwald (Wuerzburg), Monika Engelhardt (Freiburg), Davide Rossi (Bellinzona), Jacob Rowe (Haifa, Jerusalem), Wyndham Wilson (Bethesda), Paul Kyrle (Vienna), Swee Lay Thein (Bethesda), Pieter Sonneveld (Rotterdam)

Assistant Editors

Anne Freckleton (English Editor), Cristiana Pascutto (Statistical Consultant), Rachel Stenner (English Editor), Kate O'Donohoe (English Editor), Ziggy Kennell (English Editor)

Editorial Board

Jeremy Abramson (Boston); Paolo Arosio (Brescia); Raphael Bejar (San Diego); Erik Berntorp (Malmö); Dominique Bonnet (London); Jean-Pierre Bourquin (Zurich); Suzanne Cannegieter (Leiden); Francisco Cervantes (Barcelona); Nicholas Chiorazzi (Manhasset); Oliver Cornely (Köln); Michel Delforge (Leuven); Ruud Delwel (Rotterdam); Meletios A. Dimopoulos (Athens); Inderjeet Dokal (London); Hervé Dombret (Paris); Peter Dreger (Hamburg); Martin Dreyling (München); Kieron Dunleavy (Bethesda); Dimitar Efremov (Rome); Sabine Eichinger (Vienna); Jean Feuillard (Limoges); Carlo Gambacorti-Passerini (Monza); Guillermo Garcia Manero (Houston); Christian Geisler (Copenhagen); Piero Giordano (Leiden); Christian Gisselbrecht (Paris); Andreas Greinacher (Greifswald); Hildegard Greinix (Vienna); Paolo Gresele (Perugia); Thomas M. Habermann (Rochester); Claudia Haferlach (München); Oliver Hantschel (Lausanne); Christine Harrison (Southampton); Brian Huntly (Cambridge); Ulrich Jaeger (Vienna); Elaine Jaffe (Bethesda); Amon Kater (Amsterdam); Gregory Kato (Pittsburg); Christoph Klein (Munich); Steven Knapper (Cardiff); Seiji Kojima (Nagoya); John Koreth (Boston); Robert Kralovics (Vienna); Ralf Küppers (Essen); Ola Landgren (New York); Peter Lenting (Le Kremlin-Bicêtre); Per Ljungman (Stockholm); Francesco Lo Coco (Rome); Henk M. Lokhorst (Utrecht); John Mascarenhas (New York); Maria-Victoria Mateos (Salamanca); Giampaolo Merlini (Pavia); Anna Rita Migliaccio (New York); Mohamad Mohty (Nantes); Martina Muckenthaler (Heidelberg); Ann Mullally (Boston); Stephen Mulligan (Sydney); German Ott (Stuttgart); Jakob Passweg (Basel); Melanie Percy (Ireland); Rob Pieters (Utrecht); Stefano Pileri (Milan); Miguel Piris (Madrid); Andreas Reiter (Mannheim); Jose-Maria Ribera (Barcelona); Stefano Rivella (New York); Francesco Rodeghiero (Vicenza); Richard Rosenquist (Uppsala); Simon Rule (Plymouth); Claudia Scholl (Heidelberg); Martin Schrappe (Kiel); Radek C. Skoda (Basel); Gérard Socié (Paris); Kostas Stamatopoulos (Thessaloniki); David P. Steensma (Rochester); Martin H. Steinberg (Boston); Ali Taher (Beirut); Evangelos Terpos (Athens); Takanori Teshima (Sapporo); Pieter Van Vlierberghe (Gent); Alessandro M. Vannucchi (Firenze); George Vassiliou (Cambridge); Edo Vellenga (Groningen); Umberto Vitolo (Torino); Guenter Weiss (Innsbruck).

Editorial Office

Simona Giri (Production & Marketing Manager), Lorella Ripari (Peer Review Manager), Paola Cariati (Senior Graphic Designer), Igor Eboli Poletti (Senior Graphic Designer), Marta Fossati (Peer Review), Diana Serena Ravera (Peer Review)

Affiliated Scientific Societies

SIE (Italian Society of Hematology, www.siematologia.it)

SIES (Italian Society of Experimental Hematology, www.siesonline.it)



EUROPEAN
HEMATOLOGY
ASSOCIATION



Journal of the European Hematology Association
Owned & published by the Ferrata Storti Foundation

Copyright Information

©2018 by Ferrata-Storti Foundation/European Hematology Association. All rights reserved.

ISSN 0390-6078

All business correspondence and purchase and reprint requests should be addressed either to Haematologica Journal Office, via Giuseppe Belli 4, 27100 Pavia, Italy; phone: +39 0382 27129; fax: +39 0382 394705; e-mail: office@haematologica.org or to the European Hematology Association, Koninginnegracht 12b, 2514 AA The Hague, The Netherlands; phone: +31 (0)70 345 55 63; fax: + 31 (0)70 392 36 63; e-mail: info@ehaweb.org.

©2018 by the Ferrata-Storti Foundation/European Hematology Association. No part of this publication may be used (as hereinafter defined) in any form or by any means now or hereafter known, electronic or mechanical, without permission in writing from the Owner, Ferrata-Storti Foundation/European Hematology Association. For purpose of this notice, the term "use" includes but is not limited to reproduction, photocopying, storage in a retrieval system, translation, and educational purpose within the health field such as classroom instruction and clinical and residency training. This publication or any part thereof may be used for educational purposes at conferences, continuing education courses, and other educational activity, provided no fee or other compensation is charged therefore. All materials so used must acknowledge the Owner's copyright therein as "©2017 by Ferrata-Storti Foundation/European Hematology Association." When requesting the Owner's permission to use this publication or any part thereof, please contact either to Haematologica Journal Office, via Giuseppe Belli 4, 27100 Pavia, Italy; phone: +39 0382 27129; fax: +39 0382 394705; e-mail: office@haematologica.org or the EHA Executive Office, Koninginnegracht 12b, 2514 AA The Hague, The Netherlands; phone: +31 (0)70 345 55 63; fax: +31 (0)70 392 36 63; e-mail: info@ehaweb.org.

Rights and Permissions

For instructions on requesting permission to reprint or to order copies of manuscripts, figures or tables. Please follow the Right and Permission guidelines (<http://www.haematologica.org/misc/terms.dtl>). Questions regarding permission for should be directed to: info@haematologica.org or info@ehaweb.org.

Payment of royalties

To Ferrata Storti Foundation/European Hematology Association.

The Owner disclaims responsibility for opinions expressed by the authors.



Information for readers, authors and subscribers

Haematologica (print edition, pISSN 0390-6078, eISSN 1592-8721) publishes peer-reviewed papers on all areas of experimental and clinical hematology. The journal is owned by a non-profit organization, the Ferrata Storti Foundation, and serves the scientific community following the recommendations of the World Association of Medical Editors (www.wame.org) and the International Committee of Medical Journal Editors (www.icmje.org).

Haematologica publishes editorials, research articles, review articles, guideline articles and letters. Manuscripts should be prepared according to our guidelines (www.haematologica.org/information-for-authors), and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (www.icmje.org).

Manuscripts should be submitted online at <http://www.haematologica.org/>.

Conflict of interests. According to the International Committee of Medical Journal Editors (<http://www.icmje.org/#conflicts>), "Public trust in the peer review process and the credibility of published articles depend in part on how well conflict of interest is handled during writing, peer review, and editorial decision making". The ad hoc journal's policy is reported in detail online (www.haematologica.org/content/policies).

Transfer of Copyright and Permission to Reproduce Parts of Published Papers. Authors will grant copyright of their articles to the Ferrata Storti Foundation. No formal permission will be required to reproduce parts (tables or illustrations) of published papers, provided the source is quoted appropriately and reproduction has no commercial intent. Reproductions with commercial intent will require written permission and payment of royalties.

Detailed information about subscriptions is available online at www.haematologica.org. Haematologica is an open access journal. Access to the online journal is free. Use of the Haematologica App (available on the App Store and on Google Play) is free.

For subscriptions to the printed issue of the journal, please contact: Haematologica Office, via Giuseppe Belli 4, 27100 Pavia, Italy (phone +39.0382.27129, fax +39.0382.394705, E-mail: info@haematologica.org).

Rates of the International edition for the year 2017 are as following:

Print edition

<i>Institutional</i>	<i>Personal</i>
<i>Euro 500</i>	<i>Euro 150</i>

Advertisements. Contact the Advertising Manager, Haematologica Office, via Giuseppe Belli 4, 27100 Pavia, Italy (phone +39.0382.27129, fax +39.0382.394705, e-mail: marketing@haematologica.org).

Disclaimer. Whilst every effort is made by the publishers and the editorial board to see that no inaccurate or misleading data, opinion or statement appears in this journal, they wish to make it clear that the data and opinions appearing in the articles or advertisements herein are the responsibility of the contributor or advisor concerned. Accordingly, the publisher, the editorial board and their respective employees, officers and agents accept no liability whatsoever for the consequences of any inaccurate or misleading data, opinion or statement. Whilst all due care is taken to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this journal, should only be followed in conjunction with the drug manufacturer's own published literature.



EUROPEAN
HEMATOLOGY
ASSOCIATION



Journal of the European Hematology Association
Owned & published by the Ferrata Storti Foundation

1st European Myeloma Network Meeting

Turin, Italy
April 19-21, 2018

ABSTRACT BOOK



EUROPEAN
HEMATOLOGY
ASSOCIATION



Journal of the European Hematology Association
Owned & published by the Ferrata Storti Foundation

SCIENTIFIC BOARD

Mario Boccardo *(Italy)*
Hermann Einsele *(Germany)*
Maria-Victoria Mateos *(Spain)*
Philippe Moreau *(France)*
Pieter Sonneveld *(The Netherlands)*

SCIENTIFIC SECRETARIAT

Francesca Gay *(Italy)*
Niels van de Donk *(The Netherlands)*

ORGANIZING SECRETARIAT

Studio E.R. Congressi
Via Marconi 36 - 40122 Bologna - Italy
Ph +39 051 4210559 - Fax +39 051 4210174
E-mail: emn2018@ercongressi.it
www.ercongressi.it



EUROPEAN
HEMATOLOGY
ASSOCIATION



Journal of the European Hematology Association
Owned & published by the Ferrata Storti Foundation

TABLE OF CONTENTS

Main Program

.....1

Best Abstracts

.....9

Posters

session 1.	P01 - P16	Biology and preclinical.	15
session 2.	P17 - P35	Newly diagnosed multiple myeloma	21
session 3.	P36 - P59	Relapsed/refractory multiple myeloma.	30
session 4.	P60 - P75	Special conditions	40
session 5.	P76	Nurse	48

Index of Authors

.....a

1st European Myeloma Network Meeting

Turin, Italy, April 19-21, 2018

MAIN PROGRAM

M-PROTEIN RELATED DISEASES IN MONOCLONAL GAMMOPATHY OF “UNDETERMINED SIGNIFICANCE”

Bladé J.

Amiloidosis and Myeloma Unit, Department of Hematology, Hospital Clinic, IDIBAPS, Barcelona, Spain

Aside from the risk to evolve to MM or WM, or to be associated with AL amyloidosis or POEMS syndrome, the M-protein in persons with MGUS can cause “per se” renal, neurologic, skin, ocular or bleeding disorders. The term “monoclonal gammopathies of renal significance” (MGRS) was coined to highlight renal damage, different from cast nephropathy or amyloid deposition, linked to the M-protein which can result in: 1) monoclonal Ig deposition disease –IMDD- (Randall type), 2) proximal tubulopathy with Fanconi syndrome (kappa crystalline inclusions in proximal tubular cells with hypouricemia, aminoaciduria, osteomalacia and slowly progressive renal failure –RF-), 3) types I or II cryoglobulinemia, 4) proliferative glomerulonephritis (GN) with Ig deposits, immunotactoid GN or fibrillar GN, or 5) C3 glomerulopathy: C3 GN or C3 dense deposit disease. Most of the above conditions present with proteinuria and progressive RF, being the kidney biopsy crucial. In patients with MGUS and peripheral neuropathy (PN), and no evidence of AL amyloidosis or POEMS, a causal relationship must be considered. In the IgM type, a gammopathy-associated PN is likely (50% are MAG positive) while in the IgG and IgA types a CIDP with coincidental MGUS is the most likely diagnosis. The main skin conditions related to M-proteins are: 1) cryoglobulin (IgG/IgM) vasculitis with petechiae, purpura or ulcers, 2) Schnitzler syndrome (IgM, chronic urticaria, fever, arthralgia), 3) pyoderma gangrenosum (IgA, ulcers with central necrosis), 4) necrobiotic xanthogranuloma (IgG, yellow papules, nodules, plaques), 5) escleromixedema (IgG-lambda, mucine dermal deposition with occasional systemic involvement –cardiomyopathy, pulmonary fibrosis or reduced esophageal motility-) or 6) acquired generalized cutis laxa (lambda, elastolysis of the skin –premature ageing-, occasionally associated with kidney –fibrillar glomerulopathy-, heart or lung involvement). The most frequent ocular M-protein related condition is crystalline keratopathy (Ig deposition, corneal thickening, photophobia, visual loss). Bleeding can result from acquired von Willebrand deficiency or by impaired platelet aggregation induced by the M-protein. In summary, The M-protein in MGUS can cause relevant clinical conditions. If a causal relationship is proven or highly suspected, therapy against the plasma cell clone (rituximab-based in IgM-types and bortezomib-based, even including ASCT, in non-IgM) must be timely initiated.

WHAT KIND OF TRIALS DO WE NEED IN THE FUTURE TO ADDRESS OPEN ISSUES IN SMM?

Mateos M.V., González de la Calle V.

University Hospital of Salamanca/IBSAL, Salamanca, Spain

Smoldering Multiple Myeloma (SMM) is an asymptomatic disorder characterized by the presence of ≥ 3 g/dL serum M-protein and/or 10-60% bone marrow plasma cell infiltration with no myeloma-defining event. Kristinsson et al., through the Swedish Myeloma Registry, recently reported that 14% of patients diagnosed with myeloma had SMM and, taking the world population as a reference, that the age-standardized incidence of SMM was 0.44 cases per 100,000 people. The risk of progression to active MM is not uniform, and several markers are useful for identifying patients at high risk of progression, approximately 50% at 2 years. The definition of the disease has re-

cently been revisited and asymptomatic MMs at 80-90% of progression risk at 2 years are now considered to be MMs. For the rest of patients, the standard of care is observation, although a randomized trial in high-risk SMM patients comparing early treatment versus observation has shown early intervention to provide a significant benefit in terms of time to progression and overall survival. This trial has been the starting point to develop an activity in clinical research in patients with SMM at high risk of progression to MM that is increasing over the time. There are two types of approaches to plan an early treatment in high risk SMM patients: 1) Conservative approach: The objective is to delay the progression to MM and there are more than 40 clinical trials ongoing. Some examples include the combinations of lenalidomide-dexamethasone plus elotuzumab, lenalidomide-dexamethasone plus carfilzomib,... or daratumumab as single agent. 2) Curative approach: the objective is to cure some patients with high risk SMM through an optimised scheme of therapy that includes induction followed by autologous stem cell transplant, consolidation and maintenance using carfilzomib as second generation proteasome inhibitor plus lenalidomide and dexamethasone or this three drugs-based combination plus daratumumab. The main objective is to evaluate the proportion of patients with sustained minimal residual disease negative at 5 years as surrogate of cure.

MINIMAL RESIDUAL DISEASE IN MULTIPLE MYELOMA: IMAGING TECHNIQUES

Zamagni E.¹, Tacchetti P.¹, Pantani L.¹, Mancuso K.¹, Zannetti B.¹, Rocchi S.¹, Rizzello I.¹, Caratozzolo I.¹, Nanni C.², Fanti S.², Cavo M.¹

¹“Seràgnoli” Institute of Hematology, Bologna University School of Medicine, Bologna; ²Institute of Nuclear Medicine, Bologna University School of Medicine, Bologna, Italy

Multiple myeloma (MM) is a plasma cell (PC) malignancy, typically characterized by monoclonal protein (M-protein) specific biomarkers that are significant tools for monitoring and form the basis of response criteria.¹ Nonetheless, recent advances in understanding disease biology, along with the availability of high sensitive techniques and the development of several highly effective novel agents, leading to unprecedented high quality responses, have led to changes in the definition of response, and concepts such as depth of response and minimal residual disease (MRD) have been introduced.² Extensive data indicate a clear association between the depth of response and long term outcomes; thus MRD information can potentially be a biomarker of treatment effectiveness.

BMPCs infiltration can be often patchy, thus increasing the likelihood of a false negative assessment and in addition BM evaluations do not allow to identify EMD escape, a phenomenon that is increasingly detected, as a result of spatial heterogeneity of the disease.³ For this reason, the need to evaluate response to therapy and MRD, both with sensitive marrow assays and with functional imaging techniques, was introduced in 2016.²

FDG-PET/CT is an excellent imaging tool to assess tumor metabolic activity and to monitor response to treatment, in light of its ability to distinguish between active and inactive (e.g. fibrotic) disease. Several studies have demonstrated a prognostic role for PET positive lesions after the completion of therapy [4-6]. FDG-PET/CT negativity after ASCT predicted a lower risk of progression or death in patients with conventionally-defined CR, compared to patients with metabolically active sites of the disease⁷ and showed to be complementary to flow cytometry in the BM.⁶ On the basis of these results, ¹⁸F-DG PET/CT is actually considered the preferred imaging technique for evaluating and monitoring metabolic response to therapy.⁸ However, it is

important to emphasize that both false negative and false positive results may occur with use of FDG PET/CT. Moreover, it has been reported that, in a variable rate of patients, ranging from 10 to 15%, PCs may not be ¹⁸F-FDG-avid.⁹ In addition to ¹⁸F-FDG, new PET/CT tracers targeting different metabolic pathways or receptors expressed by MM cells, and acting as molecular imaging biomarkers, potentially more sensitive, have been preliminarily investigated in limited series of MM patients; however, their lower availability, the lack of direct comparisons with ¹⁸F-FDG and the inter-patient tumor heterogeneity regarding specific targets prevent any definite conclusion from being drawn.¹⁰ The standardization of PET/CT is currently on-going.¹¹

Changes in MRI patterns may be correlated with response to therapy and may be used to assess the effects of anti-myeloma treatment.¹² However, standard protocols for MRI are not allowing a clear definition of response and may often lead to false negative results. On the contrary, MRI functional approaches, such as dynamic contrast enhanced (DCE), quantifying perfusion and diffusion weighted imaging (DWI), enabling quantitative assessment of disease burden, influenced by tissue microarchitecture and related to marrow cellularity, seem promising tools to evaluate the disease after therapy.^{13,14} Initial experience with DWI MRI on several independent small series of patients showed a high sensitivity of the technique, in particular to detect diffuse marrow disease, a higher correlation with BM trephine samples in comparison with PET/CT and significant pattern changes in patients early on therapy and in remission after the end of treatment.¹³⁻¹⁵ However, published studies were mainly based on retrospective analyses of heterogeneous patients and no standardization in the interpretation of the results is currently available.

Homogeneous and prospective comparison of DWI-MRI with PET/CT, both prior and after treatment, are needed to optimize the use of imaging for prognosis and for evaluation of metabolic response to therapy. It will be important to establish the relationship between complete metabolic response and MRD negativity at the BM level, as well as to define the impact of MRD assessment on treatment strategies. Upcoming prospective trials, extensively applying novel techniques evaluating MRD both inside and outside the BM will help to address these issues and define the role of these promising tools in clinical practice.

References

1. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15:e538-548.
2. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; 17(8): e328-46.
3. Rasche L, Chavan SS, Stephens OW et al. Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing. *Nature communications* 2017; 8: 1-11
4. Zamagni E, Patriarca F, Nanni C, et al. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. *Blood*. 2011;118:5989-5995.
5. Bartel TB, Haessler J, Brown TL, et al. F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. *Blood*. 2009;114:2068-2076.
6. Moreau P, Attal M, Caillot D et al. Prospective Evaluation of Magnetic Resonance Imaging and [18F] Fluorodeoxyglucose Positron Emission Tomography Computed Tomography at Diagnosis and Before Maintenance Therapy in Symptomatic Patients With Multiple Myeloma Included in the IFM/DFCI 2009 Trial: Results of the IMAJEM Study. *J Clin Oncol* 2017; 35: 2911-2918
7. Zamagni E, Nanni C, Mancuso K, et al. PET/CT improves the definition of complete response and allows to detect otherwise unidentifiable skeletal progression in multiple myeloma. *Clin Cancer Res*. 2015;21:4384-4390.
8. Cavo M, Terpos E, Nanni C, et al. Role of 18F-FDG positron emission tomography/computed tomography in the diagnosis and management of multiple myeloma and other plasma cell dyscrasias: a consensus statement by the International Myeloma Working Group. *Lancet Oncol* 2017; 18(4): e206-217
9. Rasche L, Angtuaco E, McDonald JE et al. Low expression of Hexokinase-2 is associated with false-negative FDG-Positron Emission Tomography in Multiple Myeloma. *Blood* 2017
10. Caserta E, Chea J, Minnix M et al. Copper-64-labeled daratumumab as a PET/CT imaging tracer for multiple myeloma. *Blood* 2018, epub
11. Nanni C, Versari A, Chauvie S et al. Interpretation criteria for FDG PET/CT in multiple myeloma (IMPeTUs): final results. IMPeTUs (Italian myeloma criteria for PET Use). *European Journal of Nuclear Medicine and Molecular Imaging* 2017; epub
12. Dimopoulos MA, Hillengass J, Usmani S, et al. Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. *J Clin Oncol*. 2015;33:657-664.
13. Dutoit JC, Claus E, Offner F et al. Combined evaluation of conventional MRI, dynamic contrast-enhanced MRI and diffusion weighted imaging for response evaluation of patients with multiple myeloma. *Eur J Radiol*. 2016 Feb;85(2):373-82.
14. Lacognata C, Crimi F, Guolo A et al. Diffusion-weighted whole-body MRI for evaluation of early response in multiple myeloma. *Clinical Radiology* 2017; 850-857
15. Messiou C, Giles S, Collins DJ, et al. Assessing response of myeloma bone disease with diffusion-weighted MRI. *Br J Radiol*. 2012;85:e1198-1203.

EXTRAMEDULLARY DISEASE IN MULTIPLE MYELOMA

Rosiñol L.

Amiloidosis and Myeloma Unit, Department of Hematology, Hospital Clinic from Barcelona, IDIBAPS, Spain

Multiple myeloma (MM) is characterized by the proliferation of clonal bone marrow plasma cells (PC). However, sometimes the PC escapes the microenvironment of the bone marrow resulting in soft-tissue masses. According to the origin and location we can differentiate two types of plasmacytomas (Ps): 1) paraneoplastic Ps (PPs): soft tissue masses resulting from focal bone lesions and 2) extramedullary Ps (EMPs): soft tissue masses without contact with bone resulting from hematogenous spread. The incidence of PPs and EMPs at diagnosis ranges between 7-32% and 1.7-4.5%, respectively. The incidence at relapse remains unchanged for PPs while it is increased for EMPs (3.4-10%). The greatest risk factor for developing Ps at relapse is the presence of plasmacytomas at diagnosis. In fact, 43% of patients with Ps at diagnosis will develop plasmacytomas at relapse compared to only 14% of patients without plasmacytomas. The prognosis of patients with Ps is poor, particularly for patients with EMPs.

Concerning therapy, it seems that high-dose therapy can overcome the bad prognosis of paraneoplastic Ps. Bortezomib is effective in paraneoplastic involvement, with less evidence for hematogenous dissemination. The efficacy of other proteasome inhibitors is unknown. Thalidomide is not effective in this setting and there are no data on the efficacy of lenalidomide on plasmacytomas. The Mayo Clinic reported a response rate of 31% in a small series of 13 patients with EMPs treated with pomalidomide and dexamethasone, although it has not been confirmed in other series. There are no data with other new agents such as carfilzomib, ixazomib, daratumumab, elotuzumab or panobinostat.

The front-line therapy for patients non candidates to ASCT should be a combination of bortezomib with an alkylating agent or lenalidomide, such as MPV or VRD. For younger patients a triple induction regimen such as VTD, VRD, VCD, PAD followed by ASCT is the treatment of choice. Patients with pure EMPs should be considered as having ultra-high risk disease. In that case, an anti-lymphoma like therapy such as VTD/PACE followed by allogeneic stem cell transplantation in patients younger than 50 years or tandem auto/allo RIC in patients between 50-65 years should be considered.

In patients relapsing with Ps the most effective treatment consists of a lymphoma-like regimen such as PACE, dexamethasone-BEAM or HyperCAVD followed by high-dose therapy/stem cell transplantation whenever possible.

PLASMA CELL LEUKEMIA

Musto P.

Scientific Direction, IRCCS-CROB, Referral Cancer Center of Basilicata, Rionero in Vulture (Pz), Italy

Primary plasma cell leukemia (PPCL) is a rare and aggressive variant of multiple myeloma (MM), characterized by a higher prevalence of adverse clinical and laboratory features and operationally defined by the presence of 20% and/or an absolute number $>2 \times 10^9/L$ of clonal plasma cells in the peripheral blood, without a previous history of MM. PPCL should be distinguished from secondary PCL, which constitutes the leukemic evolution of a pre-existing, end-stage relapsed/refractory MM, and also from extra-medullary myeloma that, by definition, excludes peripheral blood dissemination. Conventional and high-throughput technologies have revealed an elevated genomic instability of PPCL, witnessed by a complex landscape of increased cytogenetic aberrations and other molecular lesions at diagnosis. The prognosis of PPCL, though partially improved after the introduction of novel agents in the clinical practice, remains unsatisfactory, with a median survival of 1-2 years in elderly patients, and about 3-years in patients undergoing transplant procedures. PPCL treatment should be immediate and oriented toward proteasome inhibitors (PI) and/or IMiDs-based combinations, with short treatment-free intervals. It should ideally include induction, single or, preferably, double autologous stem cell transplantation (AuSCT), consolidation, and maintenance. Though a myeloablative allogeneic stem cell transplantation (Allo-SCT) may be potentially curative, the results so far obtained upfront in PPCL do not show any survival advantage respect to AuSCT. Pros and cons of front-line Allo-SCT should be therefore carefully discussed with eligible patients, who electively are younger individuals with poor prognosis characteristics at baseline, but who have achieved a good response to first-line induction treatment. In this setting, a sequence of AuSCT followed by reduced-intensity or non-myeloablative Allo-SCT has provided promising preliminary data. In older and/or frailer individuals personalized approaches

should be applied, preferably giving continuous treatments with dose and time adjusted combinations. Salvage therapies for relapsed/refractory PPCL are generally poorly effective and novel combinations of drugs, including next generation PI/IMiDs and monoclonal antibodies, are under investigation. The bcl-2 inhibitor venetoclax could play a role in patients with t(11;14). Allo-SCT in relapsed and eligible patients with sensitive disease after salvage treatments is recommended.

TRANSPLANT STRATEGIES FOR ELDERLY MULTIPLE MYELOMA

Mohty M.

Sorbonne University, and Saint-Antoine Hospital, Paris, France

Two-thirds of multiple myeloma (MM) patients are over 65 years of age at the time of diagnosis. As the general population becomes older, this proportion is destined to increase. Autologous stem cell transplantation (ASCT) is a standard form of treatment for myeloma patients under the age of 65 years but is a controversial procedure for patients over this age, mostly because of a suspected increase in toxicity. However, there has been a considerable decrease in toxicity of ASCT due to better patient selection and improved supportive care. Nowadays, geriatric assessment is routinely performed in the clinic, which helps the treatment decision-making process. On the other hands, new and effective drugs have emerged, such as the immunomodulatory drugs and proteasome inhibitors. These, used most often in combination, have also shown very interesting results in the older MM population. This lecture aims to address the latest available research evidence and the latest advances for MM therapy in the elderly patients.

TRANSPLANTATION STRATEGIES

McCarthy P.L.

Roswell Park Comprehensive Cancer Center, State University of New York at Buffalo, USA

Multiple Myeloma (MM) is an incurable cancer. The majority of patients will have disease relapse/progression. New agents have improved the overall and depth of response to induction therapy improving progression free- and overall survival (PFS/OS). Recent studies have demonstrated median PFS of 50 to 60 months and OS beyond 10 years for transplant eligible MM patients. Two major approaches to prolonging disease response after autologous hematopoietic stem cell transplant (ASCT) are consolidation and maintenance therapy. Consolidation or intensification may be defined as treatment given after initial induction/ASCT that is designed to improve on the original response. Maintenance is considered a therapy that will improve PFS and optimally OS when compared to salvage therapy at relapse/progression. It should be well-tolerated with minimal toxicity. Several Phase II and Phase III studies have been completed or are underway to examine the role of consolidation and maintenance following induction/ASCT. These include second ASCT, combined and single agent therapy. The EMN 02 study found a PFS benefit for the second transplant and consolidation whereas the BMT CTN 0702 trial did not find benefit for either strategy. Both studies do not yet have final data analyses. Other consolidation strategies have included single agent or combinations of bortezomib (V), thalidomide (T), lenalidomide (R), and dexamethasone (D). More recent combinations have included R with or without V combined with elotuzumab (Elo) or daratumumab (Dara). Mature studies have reported a PFS benefit for V alone or in combination but no definitive OS benefit. Agents studied for maintenance have included T, R, ixazomib (Ixa), carfilzomib (K) and Dara. Mature studies have demonstrated a PFS and some an OS benefit for T but tolerability issues; PFS and OS benefit for R in a meta-analysis including the GIMEMA, IFM, Alliance and UK Myeloma studies and pending data with the newer proteasome inhibitors and monoclonal antibodies. ASCT remains a standard for eligible patients when compared to non-transplant therapy. The prolonged PFS and OS generated by more recent studies demonstrate the need for earlier time point surrogates such as Minimal Residual Disease testing and Immune Profiling. The introduction of new agents with novel mechanisms of action may continue to deepen responses, with improving outcomes as we look for the optimal strategies for long term disease control and eventual cure.

GERIATRIC ASSESSMENT IN THE ELDERLY

Larocca A.

Divisione Universitaria di Ematologia, Università di Torino, Italy

Multiple myeloma (MM) is a neoplastic disease of older adults, with a higher incidence in elderly patients. The prevalence of MM is likely to increase due to the extended survival and the growing life expectancy of the general population. Much progress has been made in the past few years thanks to the introduction of new drugs; an improvement of overall survival was primarily seen among patients over 65 years. Aging is associated with a high prevalence of frailty, that is, a state of increased vulnerability to stressors due to a critical decline in physiologic reserves. Elderly people may be categorized as fit or frail according to clinical, functional and cognitive criteria. The presence of frailty may complicate the management and outcome of MM patients. To date, the choice of treatment of MM patients has focused primarily on chronological age and performance status as markers of frailty. However, the elderly population is highly heterogeneous, and improved assessment strategies are needed to define the frailty profile of patients and provide them with the most adequate treatment, thus avoiding the overtreatment of frail patients and the undertreatment of fit patients. The geriatric assessment (GA) is a fundamental tool for the evaluation of cognitive and functional status. Because a full comprehensive GA is a time-consuming procedure that is difficult to use in every day clinical practice, a simplified GA that includes Activities of daily living (ADL) scale, Instrumental ADL (IADL) scale, and the Charlson Comorbidity Index (CCI), should be adopted for elderly patients. ADL is used to screen for disability in self-care tasks and IADL to explore tasks of household management. Recently in the myeloma setting the evaluation of frailty was introduced and different scores were proposed. On the basis of the results of a GA, patients can be stratified into a fit group, suitable for full-dose therapy or a frail group, requiring dose-adjusted therapies. Frail patients need effective tailored treatments to better control the disease while minimizing the risk of toxicity and treatment discontinuation. To date, there have been no prospective trials evaluating GA-driven treatments in elderly patients with newly diagnosed MM. Lenalidomide and bortezomib have an essential role in the treatment of frail patients. Additional studies are needed to define more precise GA-directed treatment selection.

RISK-ADAPTED THERAPY; ARE WE READY-YES

Dimopoulos M.A.

Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Several factors correlate with poor prognosis in multiple myeloma (MM) and thus they tailor treatment decisions. Age is a such a factor. Fit patients up to age of 70 are eligible for induction treatment followed by high-dose melphalan and autologous stem cell transplantation (ASCT). However, aging is associated with frailty and thus the IMWG geriatric score has to be calculated (mainly in the elderly patients) and frailty has to be documented. Suggestions for the treatment strategy and treatment schedule for frail myeloma population have been suggested by the IMWG.

For the management of renal impairment (RI) in MM patients. High fluid intake is indicated along with antimyeloma therapy based on bortezomib. High-dose dexamethasone should be administered at least for the first month of therapy. Thalidomide is effective in patients with myeloma with RI, and no dose modifications are needed, while lenalidomide is effective and safe, mainly in patients with mild to moderate RI and pomalidomide needs no dose modifications in this setting. High-dose therapy with ASCT (with melphalan 100 mg/m² to 140 mg/m²) is feasible. Carfilzomib can be safely administered to patients with eGFR >15 mL/min, whereas ixazomib in combination with lenalidomide and dexamethasone can be safely administered to patients eGFR >30 mL/min.

Regarding high-risk cytogenetics, the available data to-date suggest that PIs (bortezomib, carfilzomib or ixazomib) in combination with lenalidomide and dexamethasone (Rd) appear to improve CR, PFS and possibly OS in t(4;14) and del(17/17p), whereas daratumumab in combination with Rd also improves PFS in high-risk cytogenetics and elotuzumab/Rd is especially effective in t(4;14). Pomalidomide has also shown encouraging results in del17p patients. A meta-analysis showed that lenalidomide maintenance after ASCT offers approximately 2.5 OS advantage; however, patients with ISS-3 and high-risk cytogenetics had no benefit from lenalidomide maintenance. For patients with del17p, who are eligible for ASCT, bortezomib maintenance after bortezomib-based triplet induction and double tandem ASCT seems to be a reasonable option.

Finally, the Mayo clinic has adopted a risk stratification model for tailoring therapy in MM, which is depicted in the below figure. Although several researchers may not fully agree with this, Mayo model strongly suggests that we are ready for risk-adapted therapy in MM.

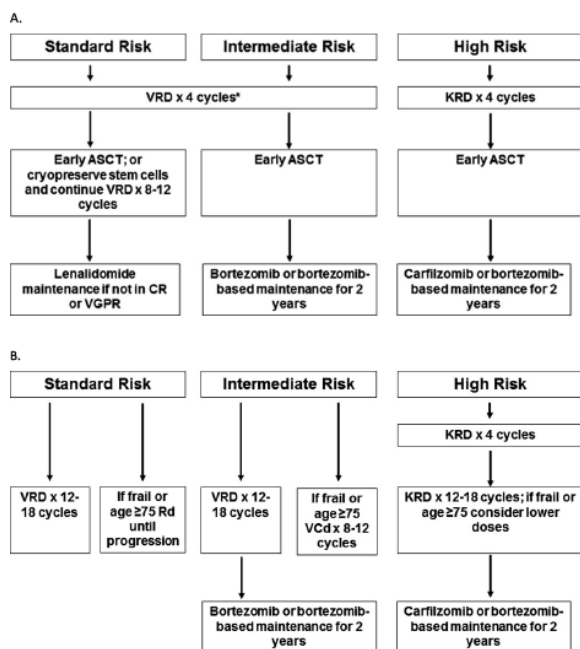


Figure. SMART recommendations for treatment in patients who are eligible for ASCT (A) and for those who are not eligible for ASCT (B).

COST AND EFFICACY CONSIDERATIONS IN MULTIPLE MYELOMA (MM) PATIENTS (PTS)

Engelhardt M.^{1,2}, Gengenbach L., Ihorst G.³, Reinhardt H.¹, Ajayi S.^{1,2}, Szymaniak-Vits M.^{1,2}, Naegele M.¹, Gramatzki M.⁴, Einsele H.⁵, Wäsch R.^{1,2}

¹Department of Hematology and Oncology, University Medical Center Freiburg, Germany; ²Comprehensive Cancer Center Freiburg (CCCF), University Medical Center Freiburg, Germany; ³Clinical Trials Center University of Freiburg, Germany; ⁴Division of Stem Cell Transplantation and Immunotherapy, University of Kiel, Kiel, Germany; ⁵Klinikum der Bayrischen Julius-Maximilians-Universität, Medizinische Klinik und Poliklinik II, Würzburg + DSMM (Deutsche Studiengruppe Multiples Myelom) study group center, Germany

Introduction: Over the last decade MM diagnosis and therapy have greatly improved; notably due to an increasing number of “novel agents” (NA). Anti-MM-therapy has gained complexity, therefore their continuous evaluation is relevant. Analyses of chemotherapy (CTx) management, including efficacy and costs, have grown due to the numerous anti-MM treatment choices. In order to determine MM therapy sequence -therein allowing efficacy and costs- we performed data assessment of clinical practice patterns. Substance use was analyzed in view of treatment lines, changes in 2 treatment periods (2005-2012 vs. 2013-2017), “MM-pathway conformity” and costs. **Methods:** Data on therapy composition were collected for the years 2005 to 2017, separating 2 treatment periods for 1st, 2nd and 3rd-line therapy (Figure 1); the time cut-off being chosen to discriminate between NA- and non-NA-based regimens, and first generation PI- (bortezomib [BOR]), IMiD- (thalidomide [THAL], lenalidomide [LEN]) and second generation NA-use. **Results:** Pt characteristics were representative for tertiary centers; the median age was 63 years (27-89), 54% were 60-79 and 14% ≥80 years old. The ISS was predominantly advanced (II/III:62%). Pts showed substantial comorbidities and were classified as fit vs. intermediate-fit or frail according to the R-MCI in 33% and 67%, respectively. Of interest, 33% of pts could be enrolled in clinical trials (CTs) and 88% received 1st-line treatment at our center. Expectedly, numbers of pts decreased with subsequent lines of treatment, albeit the median time to 2nd-line therapy due to progression amounted to 2 years: 100% (275 pts) received 1st-line, 54% 2nd-line and 35% 3rd-line treatment (Figure 1). As depicted in Figure 1, 1st-line conventional CTx (cCTx) alone was rare and substantially declined over time from 12% 2005-2012 to 1% in 2013-2017. 73% were treated with BOR in 1st-line, 63 of 106 reinduced pts received BOR in 2nd- or 3rd-line. IMiD 2nd- and 3rd-line treatment was also common within different regimens and the com-

bination of 2 NA increased over time. The use of second generation NA in 2nd- and 3rd-line treatment notably amplified in 2013 to 2017 in line with their approval. Our analysis also determined that 44% of second generation NA protocols were administered outside CTs, mainly due to tight CT inclusion criteria. Maintenance was performed in 57% of pts, predominantly with LEN and within DSMM CT protocols. **Conclusion:** NA combinations were used predominantly: while expectedly, BOR plays an important role in induction, LEN was subsequently used for maintenance and in outpt-regimens. A significant percentage of second generation NA was given outside CTs, displaying the fast implementation of MM-guideline care into clinical practice. Costs and efficacy results will be shown at the meeting, including via detailed review of the literature.

Conflicts of Interest (ME+RW): Educational Grants Amgen GmbH + Celgene GmbH.

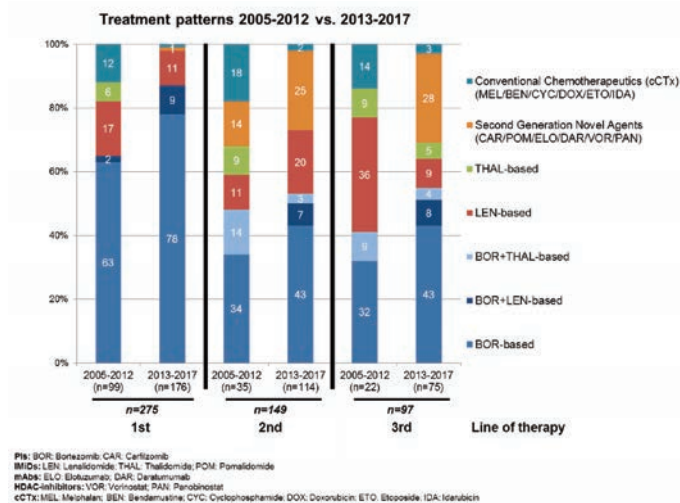


Figure 1. Clinical practice 2005-2012 vs. 2013-2017.

WHAT KIND OF TRIALS DO WE NEED IN THE FUTURE TO ADDRESS OPEN ISSUES IN NDMM? BETTER RESEARCH, BETTER IMPACT

Cook G.

Professor of Haematology & Myeloma Studies, Clinical Director NIHR MIC-DEL, University of Leeds, Leeds Cancer Centre, St James's University Hospital, Leeds, UK

Therapeutic options have greatly expanded & designing clinical trials that will impact on the delivery of a new standard of care has arrived at an interesting cross road. MM is a heterogeneous disease as are the patients it affects. It is time to consider a new clinical trial research strategy that answers these questions, as this is the fundamental principles of *Better Research, Better impact*. Designing clinical studies that utilise biomarkers is the key to stratified research studies in the future. These biomarkers include determinants of host response biology (HRB), tumour molecular landscaping & response biomarkers (minimal residual disease; MRD). HRB determinants can include end-organ damage parameters, clinical scoring systems of fitness, immune system quantitation and serial markers of age-related inflammation. Less fit patients represent a substantial proportion of newly diagnosed patients requiring treatment. Whilst age does not necessarily equate to fitness to tolerate therapy nonetheless age-related inflammation is perhaps the most important physiologic correlate of the age-related frailty syndrome. Recent clinical scoring systems which are able to delineate patients into fit, unfit & frail groupings, with respective differences in PFS and OS in clinical trials have been highlighted. The clinical relevance of genomic heterogeneity in MM (copy number variances, translocations & mutational aberrations) is reflected in the fact that a significant proportion of MM patients relapse early & show short survival with current therapies. Defining these high & ultra-high risk patients at diagnosis to stratify treatment & offer the prospect of improving outcomes remains a laudable goal. Two validated molecular approaches for risk prediction widely used include genetic risk profiling [e.g. del(17p), t(4;14)] & gene expression risk profiling, [e.g. EMC92]. However, what is the most relevant clinical intervention for such higher risk patients remains to be defined. In addition, in patients without such risk factors, could they be more appropriately treated using stop/start designations such as time limited maintenance? The presence of MRD is a reproducible and independent predictor of both progression-free (PFS) and overall (OS) survival outcomes

in MM. MRD is considered as a potential surrogate / intermediate end point for regulatory purposes. However, should MRD negativity not be utilized to direct treatment? Can MRD be used as a “stop/go” marker e.g. can maintenance strategies be safely withdrawn? If patients persist as MRD positive should we look to escalating on-gong therapy? Lastly, when real world databases are interrogated, it is clear that clinical studies, especially regulatory phase III studies, do not represent the patients we treat day-by-day in our clinic, equating to 40-50% of the true myeloma population. This represents a significant issue when translating the efficacy and tolerability of treatment regimens into practice as we see it. Therefore, in designing studies going forward, we need to be mindful of a number of disease and patient related determinants, realising the mantra that “one size doesn’t fit all” which will inevitably allow us to deliver *Better Research, Better Impact*.

HOW TO MAKE SENSE OF THE MANY TREATMENT OPTIONS AVAILABLE AT RELAPSE ? COST/EFFICACY CONSIDERATIONS

Harousseau J.L.

Institut De Cancerologie De L'ouest, Nantes, France

In the recent years, six new agents have been approved by FDA and EMA (Pomalidomide, Carfilzomib, Panobinostat, Elotuzumab, Ixazomib and Daratumumab). In relapsed Multiple Myeloma (MM), randomized studies comparing standard doublets (bortezomib-dexamethasone or lenalidomide-dexamethasone) versus triplets with the addition of one of these six agents, have all shown a significant improvement of PFS and sometimes of OS. Therefore these triplets are becoming new standards for the treatment of relapsed MM. However, all these agents are very expensive, and the cost of one month of treatment with triplets may reach 150 000 USD. In many countries, these costs are not affordable when they are not covered by public or private insurances. This situation raises the question of equal access to treatment for all patients. Even in rich countries, government policies for reducing health-care costs may induce limited prescriptions or reimbursement/pricing delays. This question of affordability/availability is a challenge for cancer treatment in general. In MM it is becoming critical because the number of patients treated and the duration of treatments are increasing dramatically thanks to the recent therapeutic advances. There are many stakeholders who may play a role in trying to control the costs of new combinations: pharma industries, regulatory and health-technology assessment agencies, payors, physicians and even patients. There is not a single solution for all countries since resources, healthcare policies and organizations, legislation vary greatly from one country to another. However the key question to be addressed is “what is the value of a new agent?”. In other words, does the observed benefit for the patient justify the financial effort of the payor? Then, the question is how to define the value? In some countries, the decision of coverage is entirely based on the clinical benefit, either the benefit/risk ratio as assessed for drug approval, like in the US or the clinical added value compared to existing drugs like in Germany. In other countries, the value is defined by a medico-economic assessment which aims at comparing the efficiency or cost/result ratio of the new agent versus the comparators. The cost/utility estimation is the most frequently used and evaluates the incremental cost/effectiveness ratio (ICER) (direct costs/quality-adjusted life-years). In some countries like UK, if the ICER in £/Qaly is superior to a pre-defined threshold, the drug is not covered. In other countries like France the is no decisional threshold and the ICER is used for pricing negotiations between the government pricing committee and the pharmaceutical company. Budget impact analysis is also used in some countries for helping reimbursement/pricing decision. These estimations are based on models and hypothesis and the level of uncertainty may be high in particular when the follow-up of clinical studies is short. Nevertheless, they are useful for decision-makers but also for physicians who should now be informed of financial constraints and, when choosing a treatment, should look not only at efficacy and safety but also at efficiency.

HOW I TREAT BONE DISEASE

Terpos E.

Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Osteolytic bone disease is the most common complication of multiple myeloma (MM). Bisphosphonate remain the cornerstone of the management of myeloma-related bone disease. All MM patients with normal renal function and osteolytic disease at diagnosis should be treated with zoledronic acid (preferably) or pamidronate, intravenously, in addition to specific anti-myeloma

therapy. Symptomatic patients, without bone disease, assessed by conventional radiography, should also receive zoledronic acid, but its advantage is not clear for patients with no bone involvement on MRI or PET/CT. In asymptomatic MM, bisphosphonates are not recommended. Zoledronic acid should be given for more than two years only in patients with active MM. For patients who have achieved CR or VGPR, 12-24 months of therapy with bisphosphonates should be adequate. At relapse, bisphosphonates have to be reinitiated. In cases of osteonecrosis of the jaw (ONJ), bisphosphonates should be discontinued and can be re-administered if ONJ has healed. In patients with CrCl <30 mL/min bisphosphonates are not recommended. Denosumab is a logical approach for these patients. However, until denosumab is fully approved for MM, patients with renal impairment have to be treated with a proteasome inhibitor-based regimen and when renal function is reversed and CrCl is >30 mL/min, bisphosphonates should be given. In the largest multicenter, placebo-controlled trial for myeloma patients to-date, denosumab was compared to zoledronic acid. Although, there was no difference regarding time to first skeletal-related event (SRE) between the two drugs, a landmark analysis at 15 months showed a superiority of denosumab in terms of time to first and subsequent on study SREs. Furthermore, denosumab showed a better renal safety profile with two-fold lower renal adverse events, especially in patients with CrCl between 30-60 mL/min. Another important finding of this study was a remarkable 10.7-month of median PFS advantage in favor of denosumab despite the well-balanced first line therapy between the two arms. Therefore, denosumab is another standard of care for myeloma-related bone disease. Low-dose radiation therapy (up to 30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture, or impending spinal cord compression. Balloon kyphoplasty should be considered for symptomatic vertebral compression fractures, while surgery is recommended for long-bone fractures, bony compression of the spinal cord, or vertebral column instability.

HOW I TREAT CARDIOVASCULAR TOXICITY

Brighen S.

Myeloma Unit, Division of Hematology, University of Torino, Azienda-Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Italy

Cardiovascular disease in myeloma (MM) patients may derive from factors related to the patient (age, diabetes, dyslipidemia, obesity, prior cardiovascular diseases), related to the disease (cardiac AL-amyloidosis, hyperviscosity, anemia, renal dysfunction) and to anti-MM treatment. Cardiac adverse events (AEs) are thought to be a class effect of proteasome inhibitors because they are reported with bortezomib, carfilzomib (CFZ) and ixazomib, but appear to be more frequent with CFZ. The most frequent cardiovascular AEs are hypertension (all grades: 14-33%; ≥ grade 3: 3-16%), heart failure (all grades: 5-11%; ≥ grade 3: 2-8%) and ischemic heart disease (all grades: 3-11%; ≥ grade 3: 2-6%). The incidence of heart failure increases up to 20-25% in patients ≥75 years of age. Etiology of cardiotoxicity is not entirely clear. One of the mechanisms could be the inhibition of sarcomeric protein turn-over, resulting in apoptosis and myocyte cell death. Other hypotheses are increased apoptosis of endothelial progenitor cells and endothelial nitric oxide synthase dysfunction. Although true CFZ-induced cardiac failure is infrequent and usually reversible, MM patients are typically elderly and may frequently show cardiovascular comorbidities. No prospective studies have as yet been conducted on the prevention, monitoring and treatment of cardiotoxicity in MM patients treated with CFZ. A detailed clinical assessment before starting CFZ is essential to identify patients at risk for cardiovascular AEs, an accurate monitoring of blood pressure and of the onset of signs and symptoms suggestive for cardiac dysfunction remains pivotal to prudently administer and perform sustained CFZ treatment. During treatment, regular clinical surveillance with blood pressure control is recommended and patients receiving hypertensive medication may need drug adjustments. Serial monitoring of cardiac function via echocardiogram or cardiac biomarkers are considered of limited value in mitigating the risk for cardiac AEs. In case of grade 3 or 4 cardiac AEs, CFZ should be withheld until recovery. CFZ may be resumed at the physician's discretion based on a benefit/risk assessment, however, preferably with a reduced-dose schedule. In general, the risk-benefit ratio for an agent must be perceived in the context of the disease nature and severity: CFZ has shown to prolong both PFS and OS and maximizing the benefit while reducing cardiovascular risks has become a priority.

DIAGNOSTIC AND PROGNOSTIC DISCRIMINATION OF WALDENSTROM'S MACROGLOBULINEMIA

Treon S.P.

Bing Center for Waldenstrom's Macroglobulinemia, Dana Farber Cancer Institute; and Department of Medicine, Harvard Medical School, USA

MYD88 mutations are present in 95% of Waldenstrom's Macroglobulinemia (WM) patients, and support diagnostic discrimination from other IgM-secreting B-cell malignancies.

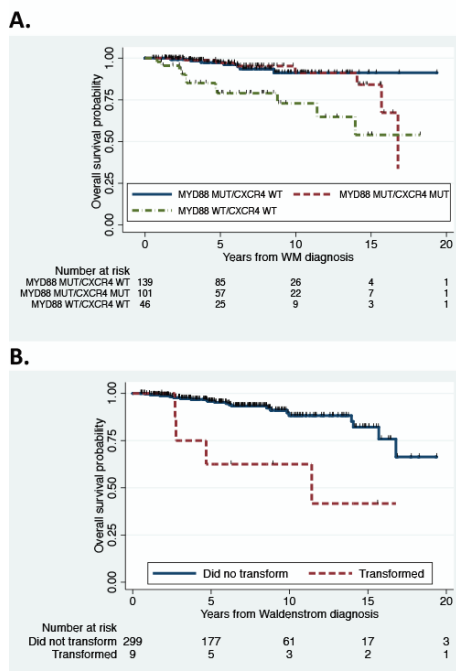


Figure 1.

Diagnostic discrimination can be difficult among suspected wild-type MYD88 (*MYD88^{WT}*) WM cases. We systematically reviewed clinical, pathological and laboratory studies for MYD88^{WT} and mutated MYD88 (*MYD88^{MUT}*) WM patients. WHO and WM consensus guidelines were used to establish clinicopathological diagnosis. Up to 30% of suspected MYD88^{WT} WM cases had an alternative clinicopathological diagnosis, including IgM multiple myeloma. The estimated 10-year survival was 73% (95% CI 52-86%) versus 90% (95% CI 82-95%) for MYD88^{WT} and MYD88^{MUT} WM patients (Log-rank $p < 0.001$). Overall survival was not impacted by CXCR4 mutations, which associate with MYD88^{MUT} disease (Figure 1A). Multivariate analysis only showed MYD88 mutation status ($p < 0.001$) as a significant determinant for overall survival. Diffuse large B-cell lymphoma was diagnosed in 15.2% and 0.76% of MYD88^{WT} and MYD88^{MUT} patients, respectively (Odds ratio 23.3; 95% CI 4.2-233.8; $p < 0.001$). Among MYD88^{WT} patients with an associated DLBCL event, overall survival was shorter (Figure 1B; Log-rank $p = 0.08$). The findings show that among suspected MYD88^{WT} WM cases, an alternative clinicopathological diagnosis is common and can impact clinical care. WM patients with MYD88^{WT} disease have a high incidence of associated DLBCL events and significantly shorter survival versus those with MYD88^{MUT} disease.

NOVEL TARGETED TREATMENT OPTIONS FOR WM: NEW CHALLENGES

Kastritis E.

Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Greece

Waldenström's Macroglobulinemia (WM) is rare lymphoma, which is characterized by bone marrow infiltration by CD20(+) cells that secrete IgM. Recently, a somatic mutation in MYD88 (L265P) was found in more than 90% of patients with WM; this mutation is associated with tonic signaling involving BTK and provides both a diagnostic tool but most importantly a target for therapy. For several years therapy of WM has been based on anti-

CD20 monoclonal antibodies combined with chemotherapy or with other agents, including proteasome inhibitors (PIs). The identification of MYD88 L265P led to the introduction of BTK inhibitors (BTKi), such as ibrutinib (and newer BTKi) for the treatment of WM. Ibrutinib has shown substantial activity in patients with relapsed or refractory WM, including patients with disease refractory to anti-CD20 therapy, is a very efficacious and rapidly acting, orally available therapy with a very favorable toxicity profile. However, ibrutinib has to be given continuously, until disease progression, cannot induce complete responses and its discontinuation may be associated with IgM rebound. Thus, new combinations which can lead to deep responses with fixed duration of therapy are needed. Such combinations are explored including combination with anti-CD20 monoclonal antibodies or with proteasome inhibitors (PIs). Efficacy of ibrutinib may be less impressive in patients with wild type MYD88 or in those harboring CXCR4 mutations. Another challenge is salvage treatment after ibrutinib (or other BTKi) failure. In this case other targeted drugs including PIs may be active. Anti-bcl2 therapy with venetoclax may be effective in WM and is under clinical investigation and may also provide a new option to patients failing BTKi but also may be part of a new combination with BTKi aiming to a fixed duration therapy that can induce very deep and durable responses; however, the safety of such an approach needs to be evaluated on clinical trials. The introduction of new treatment in WM has changed the approach to the disease but is also associated with new challenges regarding the optimal drug combination, aim of treatment and duration of therapy. Short and long term complications of the disease and of therapy, as well as the cost of the new approaches, are major challenges of current and future practice.

MANAGEMENT OF IGM-RELATED DISORDERS

Kersten M.J.

Department of Hematology, Academic Medical Center, Amsterdam

Approximately 15% of all cases of monoclonal gammopathy of unknown significance (MGUS) are of the IgM subtype. IgM MGUS can be the precursor lesion for Waldenström's macroglobulinemia (WM) or other B-cell lymphomas. The definition of the different entities which are part of the spectrum of IgM monoclonal gammopathies (IgM MGUS, smouldering/asymptomatic WM, IgM-related disorders and symptomatic WM) is not entirely consistent in the literature, but in general the classification as outlined in Table 1 is followed (adapted from J. Paludo et al., *F1000 Research* 2017, *g(F1000 Faculty Rev):2142*). IgM related disorders are defined as disorders considered to be related to the presence of an IgM M-protein in cases which otherwise do not qualify for a diagnosis of WM.

	IgM MGUS	Smoldering/ asymptomatic WM	Symptomatic WM	IgM related disorder
Serum IgM level	< 3 g/dl	≥ 3 g/dl	Any level	< 3 g/dl
BM LPL infiltration	<10%	≥10%	≥10%	<10%
End organ damage/ symptoms	No	No	Yes	Yes

Important examples of IgM-related disorders can be subclassified into disorders resulting from autoimmune properties of the IgM, such as peripheral neuropathy, cryoglobulinemia, acquired von Willebrand disease and Schnitzler syndrome and disorders resulting from deposition and/or abnormal folding of the M-protein, such as renal involvement and AL-amyloidosis. The most common IgM-related disorders are discussed in the presentation.

IgM-related peripheral neuropathies are relatively prevalent and have a variable clinical presentation. The relationship and causality are most clear for demyelinating neuropathy in patients in whom an anti-MAG (myelin associated glycoprotein) antibody is demonstrated. Other less prevalent antibody targets are the gangliosides GM1 and GD1b and sulphatide. The typical clinical picture in anti-MAG neuropathy is a slowly progressive sensorimotor PNP with a demyelination pattern on electromyography (EMG). Cases of neuropathy with a predominantly axonal pattern, non-symmetrical distribution and rapidly progressive or a relapsing and remitting clinical course are less likely to be causally related to the IgM M-protein. Treatment for anti-MAG demyelinating PN should only be initiated only in severe or progressive disease and can consist of rituximab, immunomodulatory treatment or, in case of signs/symptoms of WM of immunochemotherapy (reviewed by D'Sa et al., *Investigation and management of IgM and Waldenström-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel, BJH* 2017;176:728-742).

Type I cryoglobulinemia (composed of a monoclonal Ig) is associated with

an IgM M-protein in approximately 40% of the cases. The clinical picture is variable and can consist of often cold-induced Raynaud phenomenon, livedo reticularis, urticarial rash, vasculitis with skin ulceration, renal failure and neuropathy (sensorimotor or sensory PN, mononeuritis). The severity of symptoms is more dependent on the temperature at which precipitation occurs than on the M-protein level: patients with high cryoglobulin levels can be asymptomatic and vice versa. Management is based on severity of the symptoms and on the associated hematologic diagnosis and can range from avoidance of cold to treatment with rituximab or immunochemotherapy (reviewed by Harel, S. *Et al.*, *Clinico-biological characteristics and treatment of type I monoclonal cryoglobulinaemia: a study of 64 cases*. *BJH* 2014;168:671-678).

Primary cold agglutinin disease (pCAD) leads to complement-dependent agglutination and phagocytosis of erythrocytes, leading to anemia and acrocyanosis. Symptomatic patients should be treated with rituximab or rituximab in combination with fludarabine (reviewed in Berentsen, S. *Et al.*, *Cold agglutinin disease*. *Hematology Am Soc Hematol Educ Program* 2016;226-231). New treatment options include complement inhibition, e.g. with an anti-C1s monoclonal antibody.

AL amyloidosis is a relatively rare complication in patients with IgM MGUS or WM. Compared to non-IgM amyloidosis, clinically these patients present more frequently with neuropathy, lung involvement and lymphadenopathy and less frequently with cardiac involvement. As in non-IgM amyloidosis, treatment should be directed at suppressing the malignant clone and can include autologous stem cell transplantation in fit patients (reviewed in Milani P., *et al.* *Monoclonal IgM-related AL amyloidosis*. *Best Pract Res Clin Haematol* 2016;29:241-248).

Renal involvement in IgM MGUS or WM patients is not seen as frequently as in multiple myeloma with an estimated incidence of 5.1% at 15 years. It can be caused by light chain or heavy chain deposition disease, or by direct tumor cell infiltration or proliferative or cryoglobulinemic glomerulonephritis (reviewed by Vos, J.M., *et al.* *Renal disease related to Waldenström macroglobulinaemia: incidence, pathology and clinical outcomes*. *BJH* 2016;175:623-630).

In conclusion, several IgM-related disorders have been identified, most of which are treated by suppression of the underlying clonal disorder. The choice of treatment depends on the severity of symptoms and the presence of other signs and symptoms of WM.

AL AMYLOIDOSIS: DIAGNOSIS, RISK STRATIFICATION AND RESPONSE ASSESSMENT

Minnema M.C.

Department of Hematology, UMC Utrecht Cancer Center, Utrecht, the Netherlands

The diagnosis of systemic AL amyloidosis is based on 3 elements: 1. histological proof of amyloid in a biopsy specimen, 2. The systemic nature of the amyloidosis, 3. Characterisation as AL type. Therefore additional immunohistochemistry staining for AA, TTR and AL is advised and an underlying monoclonal plasma cell dyscrasia is a prerequisite. The use of serum Free Light Chain (FLC) measurements is indispensable but also immunofixation for light chains in 24 hours urine is advised. Caution should be made in elderly man with wild type TTR amyloidosis and a MGUS that can be easily mistaken for systemic AL amyloidosis. Bone scintigraphy with radioactive technetium can be very helpful in these cases.

After the diagnosis, it is essential to screen which organs are involved in the disease. Most affected organs are heart, kidney, nervous system (sensory, autonomic and motoric), liver, gastro intestinal tract and soft tissue such as blood vessels and tongue. Especially the degree of heart involvement is of major importance in the survival prognosis. In 2004 a cardiac staging system was developed and this was revised in 2012 by the Mayo Clinics. In this revised cardiac risk stratification model the NT-proBNP, Troponin T and the difference between de involved and uninvolved FLC (dFLC) is measured at diagnosis. Patients without any risk factor, which are defined as dFLC ≥ 180 mg/L, Troponin T ≥ 0.025 ng/mL, and NT-ProBNP $\geq 1,800$ pg/mL, have an excellent prognosis with a median survival of 94.1 months compared to 5.8 months for patients with all 3 risk factors. Recently, a renal staging system was developed and validated for the prediction of the risk of dialysis. Patients with renal involvement and an eGFR < 50 ml/min per 1.73 m² and a proteinuria > 5 g/day have a risk of 60-75% of dialysis dependency 2 years after diagnosis.

The goal of chemotherapy is to reach a complete hematological response (CHR). Patient with a CHR or VGPR have a significant better survival compared to patients with a PR or no response (see figure). The hematological response criteria differ from the Multiple Myeloma criteria. A bone marrow

biopsy is not mandatory for CR assessment. VGPR is defined as a dFLC < 40 mg/l and PR as a $\geq 50\%$ dFLC reduction. Organ responses are only defined for the heart, kidney and liver and can be seen in $\approx 30\%$, 30% and 10% of patients after treatment, respectively. Patients reaching a VGPR or CR have a higher chance for organ improvement.

AMYLOID LIGHT-CHAIN AMYLOIDOSIS: ESTABLISHED AND NOVEL THERAPIES

Palladini G., Basset M.

Amyloidosis Research and Treatment Center, Foundation IRCCS Policlinico San Matteo, and Department of Molecular Medicine, University of Pavia, Pavia, Italy

Light chain (AL) amyloidosis is the most common form of systemic amyloidosis and is caused by a usually small plasma cell clone producing light chain (LC) that are prone to misfold, aggregate and deposit in tissues as amyloid fibrils, leading to progressive organ failure and eventually death if treatment is late or not effective. Specific treatment is chemotherapy against the underlying plasma cell clone in order to reduce the amyloid LC supply. Patients with AL amyloidosis are particularly fragile and treatment should be adapted to severity of cardiac damage. Low-risk patients represent 15% of all subjects suffering from AL amyloidosis and can be considered for autologous stem cell transplantation (ASCT). Intermediate-risk patients account for 65% of patients with AL amyloidosis and are mostly treated with combinations of bortezomib, alkylating agents (cyclophosphamide or melphalan) and dexamethasone. High risk patients have an extremely poor outcome (3-7 months), hardly overcome by treatment that is generally administered with low-dose regimens. Elderly patients are a fragile subgroup, requiring dose-adapted regimens. Newer agents are emerging in relapsed/refractory setting. Ixazomib is an effective choice in bortezomib-naïve patients and trials of this agent in combination with cyclophosphamide and dexamethasone are ongoing in the upfront setting. Daratumumab is one of the most promising new agents and is being tested as upfront therapy in combination with bortezomib-based regimens. New agents targeting amyloid deposits or small molecules interfering with the amyloidogenic process are being evaluated in clinical trials. Doxycycline showed promising activity on cardiac AL amyloidosis in retrospective series. UK investigators developed an anti-SAP antibody, able to remove amyloid deposits after infusion of CHPC, a compound that removes SAP in the bloodstream. 11-1F4 and NEOD001 are two antibodies directly targeting the amyloid deposits. NEOD001 showed promising results in a phase I/II study, and the results of 2 phase III controlled trials will be available soon. If efficacy of these compounds is confirmed, anti-plasma cell and anti-amyloid drugs will be combined, potentially further improving survival and quality of life of patients with AL amyloidosis, moving towards a cure for this dreadful disease.

WHEN TO USE NOVEL PROTEASOME INHIBITORS AND IMMUNOMODULATORY DRUGS

Gay F.

Myeloma Unit, Ematologia I, AOU Città della Salute e della Scienza, Università di Torino, Italy

Treatment options for multiple myeloma (MM) patients have dramatically increased in recent years. Proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) were the first drugs to be introduced in the treatment regimens for MM patients, and they significantly improved progression-free survival (PFS) and overall survival (OS). For many years, bortezomib-dexamethasone (Vd) and lenalidomide-dexamethasone (Rd), followed by pomalidomide-dexamethasone (Pd), were the cornerstones of the treatment of relapsed/refractory MM. Recently, second generation PIs (carfilzomib and ixazomib) have been evaluated in combination with lenalidomide in the relapsed setting: Carfilzomib plus Rd (KRd) significantly improved PFS and OS vs Rd alone; ixazomib plus Rd (IRd) significantly improved PFS. Carfilzomib plus dexamethasone (Kd) significantly improved PFS and OS vs Vd. More recently, monoclonal antibodies anti-CD38 (Daratumumab) and anti-SLAMF7 (Elotuzumab) have been combined with standards of care in the relapse setting. Daratumumab plus Vd (DdVd) or plus Rd (DRd) increased PFS and PFS-2 vs Vd and Rd respectively. Elotuzumab plus Rd (ERd) significantly prolonged PFS and OS vs Rd. All these new combinations, Rd-based (KRd, IRd, DRd, ERd) and Vd-based (DdVd) or PI-based (Kd), are either already being used or will be available for relapsing patients in the near future. The major challenge for clinicians will be how to choose a regimen, when to administer it and in which patients, to maximize the efficacy, while minimizing toxicities and costs. A careful evaluation of the efficacy

data, also in specific subgroups of patients, and of the safety profile of each regimen can probably be the only way to pre-select the treatment options to be proposed to MM patients. Currently, Pd combination is available for patients previously treated and relapsed or relapsed/refractory to lenalidomide and bortezomib. If in the past the majority of patients used to receive lenalidomide and bortezomib in the relapse setting, in the near future it will be likely that a higher number of patients at first relapse might already have received both drugs. In this context, when choosing treatment, clinicians need to keep into account on the one hand the novel combinations available, and on the other hand also the effectiveness of this old Pd-combination in the earlier phases of the disease. Again, a careful evaluation of the efficacy data, including the efficacy in specific subgroups of patients, and of the safety profile of each regimen can help pre-select the appropriate treatment options to be proposed to MM patients. Furthermore, other Pd-based combinations, particularly in association with monoclonal antibodies, will potentially be available in the future, thus further changing the treatment landscape.

WHEN TO USE OTHER CLASSES OF DRUGS: HDACS, NUCLEAR PORE INHIBITORS, PROTEOMICS

Ocio E., Mateos M.V.

University Hospital of Salamanca (IBSAL), Cancer Research Center (IBMCC-CSIC), University of Salamanca, Spain

Since the introduction of PIs and IMiDs more than 10 years ago, the therapeutic landscape in MM has been continuously improving due to the appearance and approval of drugs with novel mechanisms of action, such as monoclonal antibodies and deacetylase inhibitors. However, novel drugs with novel mechanisms are still needed for refractory patients. In this regard, the advance in the understanding of MM pathogenesis and the influence of its microenvironment is necessary for the discovery of novel targets that could be active against MM plasma cells.

Among these novel agents, some represent novel generations of the already approved ones. Some examples are novel alkylators such as melflufen, novel IMiDs derivatives such as the so called “CelMods” or novel proteasome inhibitors such as oprozomib or marizomib. More important is the appearance of “brand new” novel druggable pathogenic targets such as the RAS pathway, that has been shown to be mutated in around 50% of patients. Based on this, some downstream molecules are targets for therapeutic intervention, with ERK inhibitors, AKT inhibitors or PIM kinase inhibitors showing 10-15% ORR in refractory patients; however, these responses are short lived. Other promising target is the Bcl2 inhibitor venetoclax, that has demonstrated activity in heavily pretreated patients, both alone and in combination with bortezomib. Finally, the XPO-1 (exportin) inhibitor, selinexor in combination with dexamethasone, was effective in 20% of penta-refractory patients. Another important field of development with good preliminary results, consist on the use of novel immunotherapeutic approaches such as MM targeted antibody Drug Conjugates, bispecific antibodies (BCMA-CD3) or CAR-T cells.

In all this scenario with novel agents targeting single mechanisms of the tumor cell, the search for biomarkers that could predict sensitivity or resistance to a given agent is of utmost importance. In line with this, the activity of venetoclax in monotherapy seems to be restricted to patients carrying the t(11;14), and this agent in combination with bortezomib benefits the most to patients with high Bcl-2 levels.

In summary, the future is optimistic in MM treatment, and it will probably rely in the use of the optimization of the currently available backbones, in combination with novel targeted agents, probably in selected population based on the use of biomarkers.

WHEN TO USE MONOCLONAL ANTIBODIES IN MULTIPLE MYELOMA

van de Donk N.

Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands

Recent years have shown marked progress in the treatment of multiple myeloma, which is by virtue of the introduction of novel agents in induction and maintenance regimens. For younger patients the application of autologous stem cell transplant has improved outcome as well. However, for the majority of patients myeloma is still an incurable disease, indicating that new novel agents with new mechanisms of action are needed.

CD38 antibodies (daratumumab, isatuximab, TAK-079, and MOR202) have pleiotropic modes of action including Fc-dependent immune effector mechanisms such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCP) and antibody-dependent cellular

phagocytosis (ADCP). Furthermore, CD38-targeting antibodies induce T cell expansion by elimination of immune suppressor cells such as regulatory T cells and myeloid-derived suppressor cells. The SLAMF7-directed antibody elotuzumab activates NK cells and also kills myeloma cells via ADCC.

CD38 antibodies have marked single agent activity in heavily pretreated patients, while elotuzumab lacks activity as monotherapy. However, there is synergy between both CD38 antibodies or elotuzumab and standards of care for relapsed/refractory myeloma such as lenalidomide-dexamethasone (Rd) and bortezomib-dexamethasone (Vd). Interestingly, the combination of daratumumab with Rd or Vd results in a high rate of minimal residual disease negativity, which translates into durable progression-free survival. Daratumumab also improves the activity of pomalidomide-dexamethasone, which led to its FDA approval. The toxicity profile of these antibodies consists primarily of infusion reaction. Infusion reactions are more common with CD38 antibodies, when compared to SLAMF7 antibodies.

Based on the activity and favorable toxicity profile of antibodies targeting cell surface antigens, these antibodies are also explored in newly diagnosed myeloma patients. Recently, it was demonstrated that adding daratumumab to VMP (bortezomib, melphalan and prednisone) results in improved response rates and improved progression-free survival in newly diagnosed, elderly myeloma patients. Clinical trials that incorporate these agents in induction, consolidation and maintenance regimens for transplant eligible patients are ongoing.

Finally, several other immunotherapies are currently evaluated in myeloma. This includes antibody-drug conjugates and bispecific antibodies, as well as CAR T cells.

WHEN DO WE CHOOSE CHECKPOINT INHIBITORS?

Rodríguez-Otero P.

Department of Hematology, Clínica Universidad de Navarra, University of Navarra, Spain

Immune checkpoint receptors play an important role in cancer immune evasion. The PD-1/PD-L1 pathway is frequently involved in tumor escape and several cancer cells upregulate PD-L1. In multiple myeloma (MM), PD-L1 is expressed in clonal plasma cells across all disease stages but this expression is significantly higher at relapse and in minimal residual disease positive patients. Similarly, expression of PD-1 on T cells is also increased in the bone marrow of patients at relapse and with MRD. These findings together with the positive results obtained with checkpoint inhibitors in other tumors encouraged the evaluation of these drugs in the field of MM.

The first results using Nivolumab in relapse and refractory MM (RRMM) patients failed to induce objective responses, and only stabilization of the disease was obtained in 67% of the patients. Experimental data showing a synergistic effect between the combination of PD-1 blockade and IMiDs was the rationale behind two phase I trials testing the combination of Pembrolizumab with Lenalidomide or Pomalidomide in patients with RRMM. The results of these 2 trials showed a promising overall response rate (ORR) of 44% for the Pembro-Len-Dex combination (35% in Len-refractory patients) and 66% for the Pom-dex combination (65% in Len-refractory).

These encouraging results triggered the launching of several phase III randomized trials evaluating the role of PD-1 inhibitors in combination with IMiDs both in the frontline and relapse settings. Nevertheless the results so far reported for these trials did not confirm the promising results of the previous phase I trials. In the MK-3475-185 trial (Pembrolizumab + Len + dex for newly diagnosed elderly patients), an increased risk of death was reported for the Pembro arm (HR 2.06; 95% CI: 0.93, 4.55) and the same occurred in the Pembro-Pom-Dex trial (MK-3475-183) with a HR 1.61 (95% CI: 0.91, 2.85). These results forced the premature closure of these two trials and have interrupted the recruitment in all the trials evaluating the combination of checkpoint inhibitors and IMiDs.

Despite initial encouraging results with checkpoint inhibitors in MM, recent results showing an increased risk of death among patients receiving PD-1 inhibitors have paused the development of these drugs in the field of MM, and now its use in this disease remains controversial. Nevertheless, further results with other drugs or combinations, may help to redeploy the use of these drugs in the treatment of MM.

WHICH WILL BE THE BEST PLACE FOR BISPECIFIC ANTIBODIES IN NOVEL THERAPIES.

Einsele H.

University Hospital Wuerzburg, Germany

Currently three strategies to redirect T-cells to generate myeloma specific immune effector cells are: bispecific/trispecific antibodies, CAR T-cells and TCR transduced T-cells.

There are only limited data available on the use of the three strategies in patients with multiple myeloma. There are several formats of bispecific antibodies targeting the BCMA target molecule on the tumor cell. In preclinical testing these bispecific antibodies have shown to be very effective and early clinical trials are ongoing now already showing complete remissions in heavily pretreated patients. Up to now, only limited toxicity has been observed in these early clinical trials. TCR- transduced-cells have been administered in the setting of autologous stem cell transplantation to consolidate the efficacy of autologous stem cell transplantation.

In the relapse setting this strategy has been applied in patients with multiple myeloma and prolonged PFS has been reported. Due to the fact that in these trials two strategies have been combined (high dose chemotherapy and autologous stem cell transplantation plus administration of TCR- transduced T-cells) the efficacy of each of the two components is difficult to assess.

CAR T-cells are currently tested directing the BCMA antigen, SLAMF7 antigen, CD44V6 antigen, chains, CD38 and CD138 molecules on the myeloma cell. Only a limited number of patients have been included in these trials with most of the patients receiving a BCMA CAR T-cell product. The results have been encouraging in most of these trials with high efficacy even in patients that had received a median of seven lines of prior therapy or even including patients with extramedullary disease. Due to the effect that also with these novel immunotherapies an increasing resistance has to be expected in these heavily pretreated patients and the functionality of the autologous T-cells or NK-cells that are going to be redirected will be diminished in patients with far advanced multiple myeloma. Thus, administration of these novel immunotherapies should be moved to earlier lines of treatment.

1st European Myeloma Network Meeting

Turin, Italy, April 19-21, 2018

BEST ABSTRACTS

BA1

SLAMF7 CAR-T CELLS WITH ENHANCED ANTI-MYELOMA EFFICACY

Prommersberger S., Danhof S., Einsele H., Hudecek M.

Universitätsklinikum Würzburg, Germany

Immunotherapy with chimeric antigen receptor-modified T cells (CAR-T) is investigated as a curative treatment for multiple myeloma (MM). We have recently shown that T cells engineered by lentiviral gene-transfer to express a SLAMF7-specific CAR are effective against MM in pre-clinical models [Gogishvili Blood 2017]. The prototypic CAR comprised a binding domain derived from the huLuc63 mAb (Elotuzumab), and a CD28 costimulatory moiety. Recent clinical experience with CD19 CAR-T suggests that providing 4-1BB instead of CD28 co-stimulation may endow T cells with improved longevity and potency. Therefore, we generated a novel SLAMF7 CAR where we replaced CD28 with 4-1BB and interrogated the function of T cells expressing either of these CARs. *In vitro*, we did not detect a major difference in antimyeloma reactivity. However, *in vivo* the performance of T cells expressing the 4-1BB costimulated CAR was markedly improved. We employed the MM1.S/NSG xenograft model, and administered a single dose of SLAMF7 CAR-T with either CD28 or 4-1BB on day 14 after myeloma inoculation. In both cohorts, we observed rapid MM regression. Two weeks after CAR-T transfer, we analyzed their frequency in bone marrow (BM) and found a higher percentage with the 4-1BB compared to the CD28 construct (0.15% vs. 0.01%, $p < 0.04$). In this model, MM1.S cells may re-occur in anatomical niches even if BM is cleared from MM, which limits overall survival (OS). The OS of mice that received the SLAMF7 4-1BB CAR was longer compared to the SLAMF7 CD28 CAR (mean 59.5 vs. 49 days). Upon necropsy, we confirmed that SLAMF7 4-1BB CAR-T had persisted longer and at higher frequency compared to SLAMF7 CD28 CAR-T in BM (0.02% vs. 0.00% at day 56). Collectively, these data demonstrate that replacing CD28 with 4-1BB co-stimulation enhanced the antimyeloma potency of SLAMF7 CAR-T. SLAMF7 is expressed on a fraction of NK, B and T cells. We have shown that SLAMF7 CAR-T confer selective fratricide of these lymphocytes if they express high levels of SLAMF7 *in vitro*. We sought to assess this phenomenon *in vivo* to anticipate potential toxicities in a clinical setting. We injected human PBMC into NSG mice which led to rapid engraftment of T and B cells. We treated mice with autologous SLAMF7 4-1BB CAR-T or control T cells and analyzed size and composition of the 'endogenous' lymphocyte compartment. Treatment with SLAMF7 CAR-T reduced the percentage of CD45+ lymphocytes in BM compared to untransduced T cells (4.7% vs. 3.5% of live cells). In comparison, CD19 CAR-T reduced the amount of CD45+ lymphocytes to 3.1%. The proportion of CD8+ (and CD4+) T cells was similar for untransduced and SLAMF7 CAR-T (75.3% vs. 70.6% of CD45+). The 'endogenous' CD8+ T cells in the SLAMF7 CAR-T cohort had a SLAMF7-neg/low phenotype, suggesting that fratricide of SLAMF7-pos/high T cells had occurred. These data suggest that treatment with SLAMF7 CAR-T will lead to depletion of SLAMF7-pos/high lymphocytes but preserve a close-to-normal lymphocyte compartment. We have integrated our optimized SLAMF7 CAR into a virus-free Sleeping Beauty gene engineering platform, and produced SLAMF7 CAR-T under GMP-compatible conditions. In each test run, we obtained therapeutic doses of CAR-T from as low as 1×10^6 input T cells. These data provide the basis for a soon to begin

clinical trial with SLAMF7 CAR-T in MM that will be conducted as a phase I/IIa multinational trial in GER, ITA, ESP and FRA with support from the EU H2020 program.

BA2

NOVEL KINASE INHIBITORS AFURESERTIB AND PIM447 ARE ACTIVE ALONE AND IN COMBINATION WITH STANDARD THERAPIES, RESPECTIVELY, IN A PREDICTIVE MM IN VIVO MODEL, AND A CRISPR GENOME-WIDE SCREENING APPROACH IDENTIFIES CLINICALLY-RELEVANT BIOMARKERS DETERMINING SUSCEPTIBILITY TO THESE THERAPEUTIC STRATEGIES

Keane N., Natoni A., Sharik M., Chesi M., Bergsagel P.L., O'Dwyer M.

National University of Ireland Galway, National University of Ireland Galway, Mayo Clinic Arizona, Mayo Clinic Arizona, Mayo Clinic Arizona, National University of Ireland Galway, USA

Introduction: Novel therapies for advanced Multiple Myeloma (MM) constitute an unmet clinical need and increasing knowledge of the genetic and molecular abnormalities driving MM places an onus on clinicians to tailor treatment to the individual. The overlapping Pim and AKT pathways play a role in MM pathogenesis. Our group reported potent synergy with Pim inhibitor pim447 and Akt inhibitor afuresertib in combination in MM. Investigation of this combination in the VK*MYC murine MM model failed to identify a therapeutic window due to significant toxicity. We hypothesise that these inhibitors will complement current standard therapies proteasome inhibitors (PIs) and immunomodulatory drugs (ImiDs) without significant toxicity given their non-overlapping mechanisms of action, and use of a CRISPR screen will identify molecular signature of patients likely to benefit from these novel combination strategies. **Methods:** The CoMMpass dataset was analysed for patterns of expression of Akt and Pim kinases in MM. Cell viability was determined using MTS assay. pAKT was measured by immunoblotting and Pim-2 levels by RNA sequencing. *In vivo* studies were performed in the VK*MYC de novo or transplantable models. Cas9-expressing MM cells were transfected with TKO CRISPR knockout library. Cells were treated with novel combinations and sequencing performed on Illumina HiSeq2500. Differential gene expression was determined between combinations and controls, and pathways identified using Ingenuity pathway analysis. **Results:** Pim-2 expression is highest in Non-Hyperdiploid (NHRD) MM, while Akt expression increases with advancing disease across all subtypes. Afuresertib and pim447 activity increases with greater pAkt and Pim-2 expression, respectively. Combination of each inhibitor with PIs/ImiDs is synergistic in MM cell lines. *In vivo* investigation of combinations with bortezomib in VK*MYC12598 model reveals synergy with bortezomib/pim447, with significant reduction in M-Spike and improvement in overall survival in the combination arm. CRISPR screening identifies Ras pathway activation as the key determinant of sensitivity to this combination. By contrast we observed no synergy *in vivo* with the bortezomib/afuresertib combination, although we did observe improved survival in the afuresertib-only arm in this highly resistant model unexpectedly. Furthermore, afuresertib is inactive in the de novo VK*MYC model, indicating that afuresertib will likely find a niche in treatment of advanced, highly proliferative MM as opposed to relatively indolent disease. Though ImiD combinations cannot be tested in this model we establish that synergy in combining ImiDs with afuresertib/pim447 results from additive degradation of Ikaros and Aiolos followed by downstream synergistic depletion of MYC and IRF4. CRISPR

screening of these promising combinations suggest that the Ras signaling pathway is also important in determining sensitivity to combined Imid/AKT inhibition and that upregulation of NF κ B signaling may predict resistance to combined Imid/Pim inhibition. **Conclusions:** We identify novel therapeutic strategies to exploit kinase signaling in MM. Combination of bortezomib with pim447 is synergistic in an *in vivo* model with PPV 67% for drugs entering the clinic and may find a niche in NHRD MM. Afuresertib is identified as a therapeutic option for advanced MM. MM subtypes with Ras pathway activation and suppression of NF κ B pathway are most likely to benefit from combinations incorporating Pim- or Akt-inhibition with standard therapies.

BA3

ARGININE DEPRIVATION SUSTAINS PLASMA CELL FITNESS AND BIOENERGETICS IN MULTIPLE MYELOMA

Romano A.^{1,2}, Oliva L.¹, Parrinello N.L.², Manteiga J.³, Todoerti K.⁴, Canziani L.¹, Trudu M.¹, Orfanelli U.¹, La Cava P.², Tibullo D.², Giallongo C.², Conticello C.², Marcatti M.⁵, Ciceri F.⁵, Tonon G.³, Neri A.⁶, Cenci S.¹, Di Raimondo F.²

¹Division of Genetics and Cell Biology, Age related disease unit, San Raffaele Scientific Institute, Milano; ²Department of Surgery and Medical Specialties, University of Catania; ³Center for Translational Genomics and Bioinformatics, San Raffaele Scientific Institute, Milano, Italy; ⁴Laboratory of Pre-Clinical and Translational Research, Reference Cancer Center of Basilicata, IRCCS CROB, Rionero in Vulture; ⁵Department of Oncohematology; Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milan; ⁶Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

Multiple myeloma (MM) originates from a clone of transformed plasma cells (PCs) residing in the bone marrow (BM), which establish vicious interactions with the multicellular microenvironment. Disease progression depends on the ability of malignant plasma cells (PC) to subvert the local microenvironment and reshape host immunity to support tumor growth. Little being known on metabolic changes during MM progression, we deployed a comprehensive metabolic analysis at different stages of disease. Experimental design: First, we adopted ultra-high performance liquid and gas chromatography followed by mass spectrometry (UHPLC/GC-MS) on an independent series of 167 samples of bone marrow (BM) and peripheral plasma collected ad hoc from 125 individuals, comprising newly diagnosed MM (n=16), patients with relapsing or progressive disease (n=20), in clinical remission (n=13), with MGUS (n=30), smoldering MM (SMM) (n=17), and age-matched healthy volunteers (n=29). Second, we explored the expression levels of key metabolic genes in a large series of highly purified BM PC samples from healthy donors (4N), 129 MM, 24 primary plasma cell leukemia (pPCL), 12 secondary PCL (sPCL) cases from a proprietary dataset (GSE66293). Found aminoacid shortage associated to clinical MM progression, we evaluated the adaptive response of human MM cell lines and primary BM samples of MGUS and MM to arginine shortage. Metabolomics revealed the presence of robust metabolic differences in the progression from MGUS to MM, sustained by reduced amount of lysolipids and amino acids. These findings were validated by HPLC and ELISA in an independent cohort showing that arginine deprivation was associated to progression from MGUS through MM. Upon MM progression, enolase-1 (ENO-1), phosphoglycerate kinase 1 (PGK-1), and dihydrolipoamide dehydrogenase (DLD) were increased, suggesting that branched chain amino acids, alpha-ketoglutarate, and glycine cleavage products are used in MM to sustain NADH availability and energy production. Using arginine deprivation and pharmacological inhibitors of glucose metabolism (2-deoxyglucose) and GCN2 we collected evidence that MM cells generally deploy TCA and oxidative phosphorylation, with glucose catabolism as a major source of ATP. Next, we sought to determine whether the adaptation to amino acid starvation through autophagy altered cellular glucose dependence in three MM cell lines chosen for their cytogenetic alterations: U266 (t 11;14); H929 (t 4; 14) and MM.1s (t 14; 16). Progressive arginine deprivation (range 1000-10 nM) did not affect proliferation *in vitro*, even in low-glucose media. However, long-term arginine deprivation, or short-term treatment with human recombinant arginase-1 (which reduced extra-cellular arginine availability within 12 hours of exposure), altered the cellular dependence on mitochondrial ATP generation via oxidative phosphorylation and increased glutamine anaplerosis, and induced increased expression of p62 and IRF4 in a time dependent manner. In primary MGUS and MM samples we found that the major source of Arg-1 was CD11b+CD33+CD15+CD14-HLA-DR- myeloid cells, while Arg-1 was not expressed by T-cells, CD11b+CD33+CD15-CD14-HLA-DR- or plasma

cells. **Conclusions:** Overall, our study reveals arginine shortage implied in MM progression, due to increased Arg-1 in myeloid cells. Arginine shortage can promote an adaptive response of MM offering new putative targets for synthetic lethality.

BA4

ENHANCED CYTOTOXICITY OF MULTIPLE MYELOMA CELLS USING DARATUMUMAB IN COMBINATION WITH NK CELLS ENGINEERED TO EXPRESS HIGH-AFFINITY CD16 (F158V)

Chauhan S.^{1,2}, Duggan T.¹, Daly J.¹, Sarkar S.^{1,2}, O'Dwyer M.^{1,2}

¹Apoptosis Research Centre, Biomedical Sciences, National University of Ireland, Galway; ²Onkimmune Ltd., Ireland

Background: Multiple Myeloma (MM) is a clonal plasma B-cell malignancy, typically associated with strong expression of the CD38 antigen. Recent clinical trials with the anti-CD38 monoclonal Antibody (moAb) Daratumumab (Dara) have shown promising results. NK cells are an important immune effector of moAb therapy, mediating ADCC via Fc RIII (CD16).

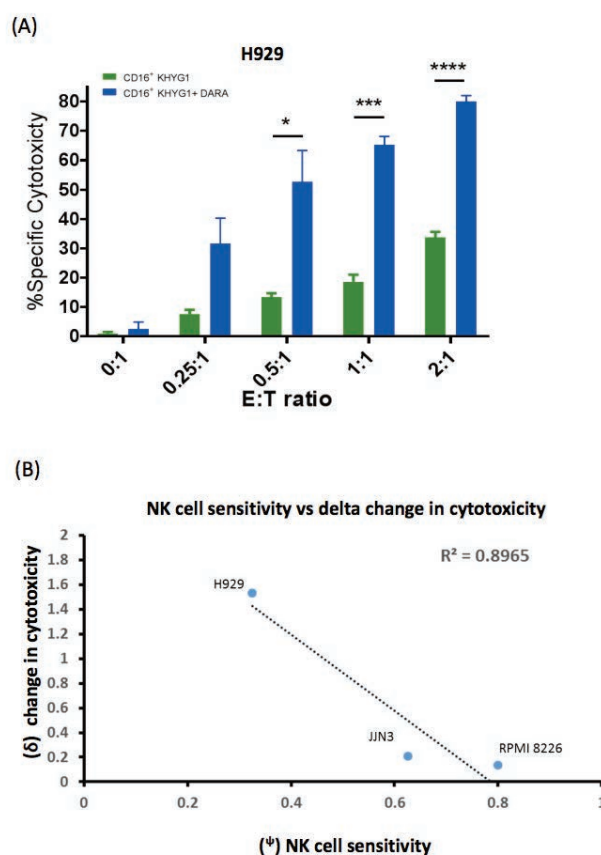


Figure 1. (A) 14-hours ADCC assay with CD16 mRNA nucleofected KHYG1 against H929 cells with or without Daratumumab. Data represents mean of n=4 independent experiments. **(B)** Correlation plots of NK cell sensitivity of MM cells vs delta change in cytotoxicity. Data represents mean of n=4 independent experiments. Datasets were analysed by paired t-test on Graphpad prism.

However, clinical data indicate rapid depletion of CD38 expressing NK cells in patients receiving Dara, questioning the role of NK cells in Dara mediated disease control. 15% of the population express a higher affinity form of CD16, due to a single point polymorphism (F158V) and this has been linked to higher responsiveness to therapeutic moAbs in the clinic. Therefore, we hypothesize that the combination of Dara with "off-the-shelf" NK cells, engineered to express high affinity (HA) CD16, could offer a new therapeutic strategy for treating MM patients, both to enhance initial response as well as to recapture response in patients progressing on Dara alone. In the current study, we investigated an mRNA-based approach to develop a high affinity CD16 expressing KHYG1 NK cells for application as an off the shelf therapeutic. **Methods:** CD38 expression was determined on a panel of cell lines RPMI-8226, H929, MM.1S, U266 and JIN3. m-RNA transcripts coding for high affinity CD16 protein was synthesized using *in vitro* transcription (IVT),

and KHYG1 cells were subsequently nucleofected using AMAXA Nucleofactor II. 24 hours post-nucleofection cells were analyzed for surface expression of CD16, and further co-cultured with MM cell lines either alone or in combination with Dara. NK cell induced cytotoxicity was measured by FACS-based methods. Experimental assays were performed with MM cell lines at E:T ratios of 0.25:1, 0.5:1, 1:1 and 2:1. **Results:** Immunophenotyping revealed that MM cell lines have a broad-spectrum cell surface expression of CD38, and therefore we classified them as CD38hi (RPMI 8226, H929), CD38mod (MM1S), and CD38lo (U266, JJN3). Thereafter ADCC assay with against a panel of MM cell lines (JJN3, H929, and RPMI8226) with HA-CD16 nucleofected KHYG1 either alone or in combination with Dara. HA-CD16 nucleofected KHYG1 in combination with Dara was significantly more cytotoxic towards NK resistant MM cell lines JJN3 and H929 (Figure 1A) at E:T 0.5:1, 1:1, and 2:1, as compared to HA-CD16 KHYG1 alone. Furthermore, the combination was also significantly cytotoxic against NK sensitive cell line RPMI 8226, albeit at a lower NK: MM E:T ratio E:T 0.25:1, 1:1. Correlation plot analyzing sensitivity towards NK cells and change in cytotoxicity revealed that MM cells which are intrinsically resistant towards NK cells may benefit significantly more from this combination therapy ($r^2=0.89$) (Figure 1B). Importantly, Dara had no significant effect on viability of HA-CD16 KHYG1, which has moderate CD38 expression. **Conclusions:** This study provides the proof-of-concept for combination therapy of Dara and an “off-the-shelf” HA CD16 expressing NK cells for treating MM patients. Notably, this approach was effective against MM cell lines even with low CD38 expression (JJN3). Finally, we propose that this combination therapy may also be of significant benefit to patients, whose MM cells are intrinsically resistant towards NK cytotoxicity. **Conflict of Interest:** Michael O'Dwyer: Founder, Board of Directors, Equity in Onkimmune. Subhashis Sarkar is supported by a fellowship from Onkimmune.

BA5

MAGNETIC RESONANCE IMAGING BEFORE AND AFTER UPFRONT AUTOLOGOUS TRANSPLANTATION IDENTIFIES PATIENTS WITH ADVERSE OUTCOME BUT RESPONSE TO TREATMENT WITHIN THE PROSPECTIVE GMMG MM5 PHASE III TRIAL

Merz M., Hielscher T., Seckinger A., Jauch A., Mai E.K., Bertsch U., Raab M.S., Neben K., Salwender H., Blau I.W., Lindemann H.W., Dürig J., Scheid C., Haenel M., Weisel K., Delorme S., Kauczor H.U., Hose D., Goldschmidt H., Hillengass J.

¹Medizinische Klinik V, University Hospital Heidelberg, Heidelberg; ²Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg; ³Institute of Human Genetics, University Heidelberg, Heidelberg, Germany; ⁴Max-Eder Research Group Experimental therapies for hematologic malignancies, DKFZ, Heidelberg, Germany; ⁵Asklepios Klinik Altona, Hamburg; ⁶Department of Internal Medicine III, Charité Campus Benjamin Franklin, Berlin; ⁷Hämatologie/Onkologie, Kath. Krankenhaus Hagen gem. GmbH, Hagen; ⁸Department of Hematology and Oncology, University Hospital of Essen, Essen; ⁹Department of Internal Medicine I, University of Cologne, Cologne; ¹⁰Klinikum Chemnitz gGmbH, Chemnitz; ¹¹University Hospital of Tuebingen, Tuebingen; ¹²Department of Radiology, German Cancer Research Center DKFZ, Heidelberg; ¹³Department of Radiology, University Hospital Heidelberg, Heidelberg; ¹⁴National Center for Tumor Diseases (NCT), Heidelberg, Germany

Purpose: We investigated the prognostic significance of magnetic resonance imaging (MRI) before and after autologous transplantation for newly diagnosed patients enrolled in the prospective, multicenter MM5 phase III trial from the German Speaking Myeloma Multicenter Group (GMMG). **Methods:** Patients in the GMMG MM5 phase III trial were treated with a bortezomib-based induction therapy (either PAd or VCD), high dose melphalan followed by autologous stem cell transplantation (ASCT) as well as consolidation and maintenance treatment with lenalidomide (for 2 years or until complete response (CR)). Primary endpoints of the study were reported at ASH 2017 (Goldschmidt *et al*, Blood, 2017). 502 patients were enrolled from July 2010 to October 2012. In the cohort recruited at the University Hospital of Heidelberg, 83 of 167 patients received an MRI before and 77 patients after ASCT. We investigated prognostic significance of initial and residual bone marrow involvement as detected by MRI as well as changes in signal intensity after ASCT. **Results:** All patients showed either diffuse and/or focal bone marrow lesions in the initial MRI. Extramedullary disease (EMD) was detected in 25.3% of patients and was associated with shorter overall survival (5 year OS 59%, 95% confidence interval (CI) [40%;87%] vs 83% [73%;93%], p log-rank: 0.03). The second MRI was performed after ASCT and before lenalidomide consolidation/ maintenance therapy (median: 98 days, interquartile range: 20 days). Most of the patients (95%) showed a response in the second MRI depicted by decreasing size of focal lesions or focal/diffuse signal attenuation in T2-weighted sequences or normalization of signal intensity in T1-weighted sequences compared to the initial MRI. However, 81% ($n=62$) and 61% ($n=47$) of patients showed residual focal lesions or diffuse marrow infiltration, respectively. For the entire cohort, there were no significant differences in progression-free survival (PFS) and OS between patients with or without residual focal or diffuse marrow infiltration. Patients without CR after ASCT ($n=55$) showed shorter PFS, when diffuse marrow signal alterations were present at the second MRI (Median PFS: 26 months 95%CI [24;34] vs. 54 months [32, not reached], p log-rank: 0.03). Additionally, 36% of patients ($n=28$) had residual focal lesions that underwent T2-hyperintense signal transformation after ASCT (Figure 1). Although patients with T2-hyperintense transformed lesions more frequently achieved a (near) complete response (75% vs. 41%, $p=0.005$), the occurrence of T2-hyperintense focal lesions after ASCT was associated with shortened PFS (Median PFS: 17 months 95%CI [14;34] vs. 45 months [29, not reached], p log-rank: 0.014; Figure 1). Since these lesions showed water-equivalent signal intensity on T2 weighted images, we assumed that this effect was caused by cystic transformation upon tumor cell necrosis in proliferative disease. Analysis of initial baseline characteristics revealed that patients with cystic transformation of focal lesions after therapy harbored more frequently deletion 13q (62% vs. 33%, $p=0.03$) as well as EMD (48% vs. 7%, $p<0.001$) and more often showed a medium/high proliferation index as assessed by gene expression profiling (92% vs. 67%, $p=0.03$). **Conclusions:** We demonstrate that MRI identifies a subgroup of patients with deep responses but adverse outcome after a novel agent-based induction therapy followed by ASCT.

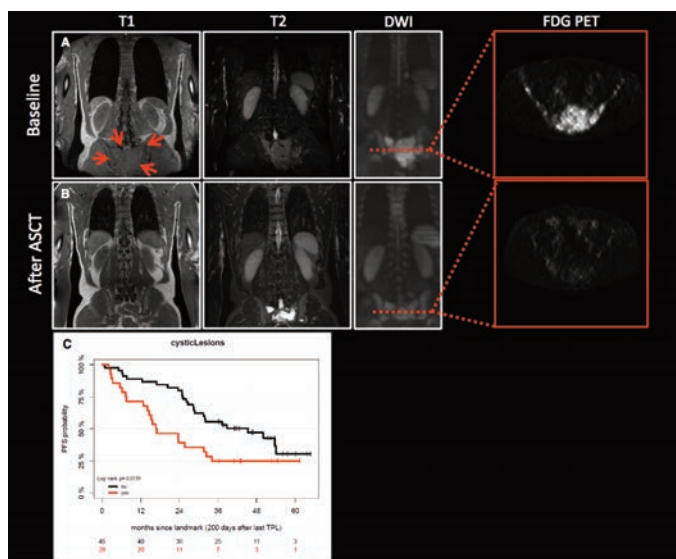


Figure 1. A: Baseline findings of a focal sacral lesion on T1- and T2-weighted MRI as well as diffusion weighted imaging (DWI) and FDG PET. **B:** follow-up images after autologous transplantation show a decrease in size but hyperintense transformation in T2-weighted images with PET negativity. **C:** Kaplan Meier plot for patients with (red) and without (black) cystic MRI lesions after.

BA6

MINIMAL RESIDUAL DISEASE (MRD) FOLLOW UP OF MM PATIENTS OBTAINING STRINGENT COMPLETE REMISSION (sCR) IN THE NMSG/EMN02 CLINICAL TRIAL - DEFINING sCR NUMBERS AND PREDICTION OF DISEASE PROGRESSION BY MULTIPARAMETRIC FLOW CYTOMETRY (MFC)

Johnsen H.E.^{1,2,4}, Schmitz A.^{1,4}, Støve-Bødker J.^{1,2}, Sonneveld P.³, Hofste op Bruinink D.³, van der Holt B.³, van der Velden V.H.J.³, Abildgaard N.⁴, Ahlberg L.⁴, Andersen N.⁴, Andreasson B.⁴, Brandefors L.⁴, Christiansen H.B.⁴, Faxoe S.⁴, Fransson C.⁴, Friestad M.⁴, Gregersen H.⁴, Hammerlund Y.⁴, Hansson M.⁴, Haukaas E.⁴, Hector M.⁴, Helleberg C.⁴, Holst M.⁴, Jönsson A.K.⁴, Karlsson V.⁴, Klostergaard A.⁴, Kjær S.⁴, Lauri B.⁴, Lenhoff S.⁴, Lonn I.⁴, Myhr E.⁴, Pedersen B.H.⁴, Renna R.⁴, Sjøgren T.V.⁴, Svirskaitė A.⁴, Szatkowski D.L.⁴, Vangsted S.⁴, Waage A.⁴, Schjesvold F.H.⁴, Mellqvist U.H.⁴, Høholt H.¹, Madsen L.H.¹, Christensen H.S.¹, Froberg Brøndum R.^{1,2}, Bøgsted M.^{1,2}, Dybkær K.^{1,2,4}

¹Department of Haematology, Clinical Cancer Research Center, Aalborg University Hospital, Denmark; ²The Department of Clinical Medicine, Aalborg University, Denmark; ³Department of Hematology, Erasmus University, Medical Center Rotterdam, The Netherlands; ⁴The Nordic Myeloma Study Group (NMSG)

Introduction: Novel and more effective treatment strategies against MM have resulted in a need for methods to estimate the level of MRD, beyond the response assessment criteria like CR and sCR (stringent complete remission) during follow up, such as MRD assessment by MFC. Here we present results from a prospective bone marrow sample follow up in MM patients, who have obtained sCR (1) in a NMSG (Nordic Myeloma Study Group) study as a part of the EMN-02/HOVON-95 MM trial. The hypothesis is that patients in sCR may have myeloma plasma cells (mPC) undetectable by MFC that will expand months before clinical detectable relapse and therefore can be enumerated and predict imminent disease progression, before abnormal free light chain (FLC) ratio occur associated with clinical objective manifestations. The goals of our study was 1) to generate prospective evidence for the MFC based definition of sCR and 2) to document the predictive potential of MRD assessment in sCR, during maintenance therapy. **Patients, Materials and Methods:** 136 patients from 22 different Nordic centers have been enrolled in the study, of which 30 patients obtained sCR after treatment and inclusion in the EMN-02 trial. At the time of sCR and each 3rd month a bone marrow and blood sample was planned to be sent to the NMSG central Biobank at Aalborg University Hospital. The MRD follow up study was initiated following EMN training and validation studies during 2011-2016 involving laboratories from Aalborg (DK), Torino (I), Brno (CR) and Rotterdam (NL) to define a EMN MRD standard strategy for enumeration of mPC in MM bone marrow aspirates (2). So far, we received between 1 to 16 sequential follow up sample(s) from 44 patients every 3rd-12th months until clinical observed progression/relapse. By MFC, we analysed 1-2 ml of fresh bone marrow sample within 48h after aspiration and used the first generation standardized 2 tube diagnostic Euro flow PCD-Panel to identify and enumerate mPC among 10^6 to 10^7 nucleated cells acquired for analysis. Corresponding clinical data were received from the involved clinic and the EMN02/Hovon95 trial database. **Results:** First, at inclusion, 30 patients were documented in sCR by normal FLC ratios (range 1,65-0,25). The 1st bone marrow sample received at the central laboratory for MRD analysis, identified 25 samples with zero detectable mPC and 5 samples with 17-463 mPC enumerated (Figure 1). Six samples received from patients with slightly increased FLC ratios (range 2.13-3.79 or 0.20-0.02) and therefore not in sCR had 2759-42665 mPC enumerated by the standard method (Figure 1). These results allowed us to define sCR by mPC numbers below 500 of 10^6 analyzed nucleated cells. Second, during follow up and analysis of >200 bone marrow aspirates, we observed seven patients with disease progression/clinical relapses. Three patients at the first/second follow up and four patients, who was predicted by increased numbers of mPC 6-12 months before abnormal FLC ratios. Twenty three patients are still in sCR and 18 followed (>390 days) as planned with <500 mPC enumerated during 1-16 follow up samples. These results document the predictive potential of MRD assessment in sCR follow up. **Conclusions:** We have documented 1) that sCR defined by MFC is a number of mPC below 500 events out of 10^6 nucleated cells and 2) MRD assessment in sCR cases identify increasing mPC cell frequencies during follow up that predict disease progression, 6-12 months before abnormal plasma level of FLC ratios.

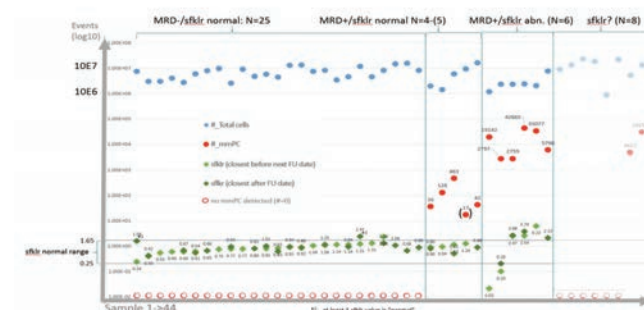


Figure 1. The 1st bone marrow sample received at the central laboratory for MRD assessment by MFC in CR patients (N=30), with normal FLC ratios (green), at inclusion. On the left 25 samples are illustrated with zero detectable multiple myeloma PC (open red dots) and 5 samples with <500 mPC enumerated (red dots). Further six samples had slightly increased FLC ratios and not in sCR had >2500 mPC enumerated. This defines CR by mPC numbers below 500 of 10^6 analyzed nucleated cells by MFC.

BA7

PRELIMINARY DATA OF THE ONGOING OPEN-LABEL, SINGLE-ARM PHASE II STUDY OF MP0250 IN COMBINATION WITH BORTEZOMIB + DEXAMETHASONE IN PATIENTS WITH RELAPSED REFRACTORY MULTIPLE MYELOMA

Goldschmidt H.¹, Raab M.S.¹, Duerig J.², Szarejko M.³, Jurczyszyn A.⁴, Grzasko N.⁵, Vacca A.⁶, Bringhen S.⁷, D'Agostino M.⁷, Gamberi B.⁸, Haunschild J.⁹, Hermann F.⁹, Fiedler U.⁹, Dawson K.⁹, Harstrick A.⁹, Acosta J.⁹, Schreder M.¹⁰, Knop S.¹⁰

¹Department of Hematology, Oncology, and Rheumatology, Heidelberg University Hospital, Germany; ²Department of Hematology, University Hospital Essen, Germany; ³University Clinical Centre, Department of Haematology and Transplantology Gdansk, Poland; ⁴University Hospital, Clinical Department of Haematology, Krakow, Poland; ⁵Department of Hematology, Centre of Oncology of the Lublin Region, Poland; ⁶Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine, University of Bari Medical School, Bari, Italy; ⁷Department of Oncology and Hematology, Clinical trials in onco-hematology and multiple myeloma, City of Health and Science of Turin, Italy; ⁸Hematology Complex Operative Unit, Senior Hospital Santa Maria Nuova, Reggio Emilia, Italy; ⁹Molecular Partners AG, Zürich, Switzerland; ¹⁰Department of Medicine II, University Hospital Würzburg, Germany

Background: Patients with relapsed refractory multiple myeloma (RRMM) have an increasing number of available therapeutic options. However, even with these advances, patients still relapse and novel treatments are needed. Upregulation of both the vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) pathways has been implicated in loss of response to therapy and linked to poor prognosis in RRMM. MP0250 is a first-in-class, tri-specific multi-DARPin® drug candidate neutralizing VEGF-A and HGF as well as binding to human serum albumin to increase plasma half-life. MP0250 shows activity in multiple preclinical tumor models, including enhancing the effects of bortezomib on tumor growth, inhibition of M protein production and of bone lysis in an MM xenograft. **Aims:** To study the safety and efficacy of MP0250 in combination with bortezomib and dexamethasone (Dex) in patients with RRMM. **Trial Design:** This trial (NCT03136653) is recruiting adults ≥18 years of age with RRMM who have progressed after at least two prior treatment regimens of myeloma therapy (including bortezomib and an immunomodulatory drug [IMiD]). A dose-escalation phase (part 1) consisting of two cohorts will define a safe dose of the combination followed by a dose expansion phase. Up to 40 patients will be enrolled. The primary endpoint is efficacy in terms of overall response rate (ORR). Secondary endpoints include safety, immunogenicity, PFS and DOR. **Methods:** MP0250 is being evaluated in combination with bortezomib and Dex in a Phase 2 study in RRMM. Cohort 1 in part 1 has evaluated a dose of 8 mg/kg q3w iv of MP0250 on day 1 with bortezomib on days 1, 4, 8 and 11 and Dex on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21 day cycles in RRMM patients. Response is investigator assessed at each cycle by IMWG criteria. Patients receive treatment until there is documented disease progression or unacceptable toxicity. Patients who have received at least 1 dose of combination of MP0250 plus bortezomib + Dex are included in the safety analysis. **Results:** In cohort 1, 8 patients have been treated with 8 mg/kg MP0250 and were included in the safety analysis set, with the last patient enrolled on 02 January 2018. Median time from initial diagnosis to first dose of MP0250 was 4.75 years (1-10). Median number of prior therapies was 3.3 (2-5). All 8 patients had been exposed to IMiDs and proteasome inhibitors. There were no infusion-related reactions. The most frequent drug-related grade ≥ 3 AEs included: thrombocytopenia, proteinuria, hypertension and transitory liver enzyme elevation observed in 4 patients. One dose-limiting toxicity (DLT) has been reported to date. Of 8 response-evaluable patients receiving MP0250 in combination with bortezomib and Dex, 4 (50%) achieved a partial response (PR). **Summary:** Early data with MP0250 plus bortezomib + Dex shows an acceptable safety profile and promising activity in RRMM patients. **Keywords:** MP0250, HGF, VEGF, relapsed and refractory multiple myeloma

BA8

OUTCOME OF ELDERLY PATIENTS WITH LIGHT CHAIN AL AMYLOIDOSIS

Milani P., Basset M., Nuvolone M., Mussinelli R., Perlini S., Foli A., Palladini G., Merlini G.

Amyloidosis Research and Treatment Center, Foundation IRCCS Policlinico San Matteo and Department of Molecular Medicine, University of Pavia, Italy

Introduction: Introduction of new therapies has led to significant improvements in managing systemic AL amyloidosis. However, the treatment of the elderly is still challenging, even if deep clonal responses can improve survival. We explored the clinical characteristics and outcome of patients older than 75 years and compared with the younger ones. **Methods:** The study population is composed of 1065 consecutive, newly diagnosed patients with AL amyloidosis evaluated between 2004 and 2015 at the Pavia Amyloidosis Center and prospectively followed. We compared 168 subjects (16%) older than 75 years of age (Senior group) with 897 patients (Junior group). Response was evaluated by intention to treat. **Results:** No differences in sex and involved light-chain types between the two groups were seen. Heart involvement was more common in the Senior group (85% vs 75%, P=0.002), but no differences were seen in the rate of advanced Mayo stages (stage IIIa 21% vs 18% P=0.217 and stage IIIb 21% vs 17%, P=0.114). Renal involvement was less frequent (59% vs 67%, P=0.019) and more advanced in the Senior-group [stage I 37% vs 47% (P=0.009), stage II 40% vs 38% (P=0.373) and stage III 19% vs 11% (P=0.003)]. After a median follow-up of living patients of 42.5 months, 114 (68%) and 492 (55%) patients died in the Senior and Junior groups, respectively. Overall survival was better in the Junior group (median 46 vs 11 months, P<0.001). Within Mayo stage II, Senior group had a shorter survival (median 58 vs 22.5 months, 68% vs 51% surviving at 24 months, P<0.001). No difference in survival was observed in stage III patients according to the age cutoff (median 7.8 vs 6 months, P=0.239). The median n. of cycles delivered was lower in the Senior group (3 vs. 4, P=0.034) with a higher proportion of patients treated with oral melphalan and dexamethasone (MDex) (49% vs 39%, P=0.008) and bortezomib-MDex (11% vs. 19%, P=0.003), while cyclophosphamide, bortezomib and dexamethasone (CyBORd) was a more frequent regimen in the Junior group (30% vs. 14%, P<0.001). Treatment with CyBORd was characterized by higher rates of overall hematologic response in the Junior group (25% vs. 55%, P=0.002) and higher quality of response (CR/VGPR 21% vs. 44%, P=0.013). No difference in overall hematologic response and in rates of CR/VGPR, between the two groups amongst patients treated with MDex (48% and 50% in Senior and Junior group respectively, P=0.43) or BMDex (65% and 58% in Senior and Junior group respectively, P=0.22). Overall survival was longer in the Junior group in all treatment groups (not shown). In the Senior group, obtaining any type of hematologic response was associated with a better overall survival (median 41 vs. 13 months, 70% vs 40% surviving at 24 months, P=0.01). Cardiac response was more frequent in the Junior-group (27% vs. 17%, P=0.030), while there was no difference in renal response rate (32% vs. 26%, P=0.196). Amongst patients who obtained cardiac response, the Junior group patients had a better outcome (median survival 85 vs. 45 months, 83% vs. 69% surviving at 24 months, P=0.011). **Conclusions:** Older age reduces median and 2 year survival in patients with AL amyloidosis across cardiac stages. However, hematologic response to therapy improves survival in these patients. Melphalan-based combinations appear to provide higher response rates in elderly patients and melphalan should be included in the treatment of these subjects.

POSTER

Biology and preclinical

P02

MAJOR CHANGES IN LEVELS OF REGULATORY CYTOKINES AND FUNCTIONAL ANTIBODIES CONTRIBUTE TO SEVERE IMMUNODEFICIENCY OF MYELOMA PATIENTS AND PERSIST AT ONE YEAR POST DIAGNOSIS

Chicca I.J., Heaney J.L.J., Iqbal G., Bowcock S., Planche T., Wood J., Raynes K., Hawkey P., Pratt G., Yong K., Dunn J.A., Drayson M.T.

Clinical Immunology Service University of Birmingham, Warwick Clinical Trial Unit University of Warwick, King's College Hospital NHS Trust, Department of Medical Microbiology St George's University of London, Department of Medical Microbiology, West Midlands Public Health Laboratory Heart of England NHS Trust, University Hospital Birmingham NHS Trust, Department of Haematology UCL Cancer Institute, UK

Introduction. Multiple myeloma is associated with severe immunodeficiency and increased susceptibility to infections. Bacterial infections are recurrent and a major cause of morbidity in myeloma patients. Cytokines interleukin-10 (IL-10) and -13 (IL-13) are regarded as anti-inflammatory which down regulate innate immune functions against infections. Interleukin-7 (IL-7) has been shown to promote myeloma growth through the inhibition of osteoblast differentiation. Acting together immunoparesis (a reduction in normal polyclonal immunoglobulin levels below the lower limit of normal) and the dysregulation of cytokine network may contribute to increased susceptibility to bacterial infections, perpetuation of inflammation and disease development. This study investigated functional antibodies levels and IL-7, IL-10 and IL-13 at disease presentation, in response to induction treatment and in remission in the UK Tackling Early Morbidity and Mortality in Myeloma trial (TEAMM). Method Serum samples at disease presentation, after 12 weeks of therapy and after 1 year were collected from 890 multiple myeloma patients (aged 35–90 years old) enrolled in TEAMM. Multiplex Luminex assay was used for the analysis of IgG antibody levels against 19 bacterial antigens (12 pneumococcal (Pn), 4 meningococcal (Men), haemophilus influenza b (HiB) polysaccharide, and diphtheria and tetanus toxoids) and of serum cytokines IL-7, IL-10 and IL-13. Anti-bacterial antibodies and cytokines levels from patients with myeloma were compared to healthy blood donors. Results A significantly lower proportion of myeloma patients demonstrated protective levels against all bacterial antigens compared to the healthy donors ($p < 0.05$) (see Table attached). At disease presentation, less than 6% of multiple myeloma patients had serum IgG antibodies above the WHO 0.35 µg/mL protective threshold for at least 8 of the 12 investigated Pn serotypes. A higher proportion of patients aged < 65 years old were protected against Men serotypes, HiB and tetanus while more patients in the ≥ 65 age group were protected against Pn serotypes which may result from UK vaccination of 65 year olds with pneumovax. Following induction therapy, serum IgGs levels against all investigated bacteria were significantly lower than presentation levels ($p < 0.01$). Regulatory cytokines IL-7, IL-10 and IL-13 were significantly higher in TEAMM patients compared to healthy volunteer ($p < 0.05$) at disease presentation, after induction therapy and during remission. Patients who had suffered episodes of infection during TEAMM trial presented higher concentrations of IL-7 compared to patients without infection episodes ($p < 0.05$). Discussion This study shows anti-bacterial immunological responses are severely compromised in a large population of multiple myeloma patients. The overwhelming majority of patients failed to meet protective levels of functional antibodies and after treatment these levels are significantly reduced even further. Regulatory cytokines were elevated in myeloma patients compared to healthy controls suggesting their involvement in the down-regulation of immune responses to bacterial infection and in multiple myeloma disease progression. This project is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health.

P03

A COMPENDIUM OF LONG NON-CODING RNAs TRANSCRIPTIONAL FINGERPRINT IN MULTIPLE MYELOMA

Taiana E., Ronchetti D., Agnelli L., Todoerti K., Manzoni M., Vinci C., Favasuli V., Pelizzoni F., Neri A.

Department of Oncology and Hemato-oncology, University of Milan, Italy, Hematology Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

Multiple myeloma (MM) is a malignant proliferation of bone marrow plasma cells characterized by highly heterogeneous genetic background and clinical course, and whose pathogenesis remains largely unknown. Long non-coding RNAs (lncRNAs) are a large class of non-protein-coding RNA, involved in many physiological cellular and genomic processes as well as in carcinogenesis, cancer metastasis and invasion. Although still in its infancy, the knowledge of the role of lncRNAs in MM is progressively expanding. Besides studies on selected candidates, lncRNAs expression at genome-wide transcriptome level is confined to microarray technologies, thus investigating a limited collection of transcripts. Herein, we assessed the lncRNAs expression profiling in 30 MM patients by RNA-sequencing, with the aim of providing a first exhaustive catalogue of lncRNAs specifically associated with the main MM molecular subgroups and genetic alterations. We applied a custom annotation pipeline based on the GENCODE encyclopedia that considered only those genes with unambiguously mapped transcripts, namely including 14,202 annotated lncRNAs; among them, we investigated the 9,540 lncRNAs detectable upon removal of those unexpressed across the whole dataset. We identified 391 deregulated lncRNAs, 67% of which were also detectable and validated by whole-transcript microarrays. Among them, we identified the well-known lncRNA MIAT specifically downregulated in MM carrying t(11;14) chromosomal translocation. In addition, we defined a repertoire of 35 lncRNAs, with potential relevance in MM, as they meet the requirements of being both co-expressed and in close proximity (combinations selected under criteria of Pearson coefficient > 0.4 or < -0.4 and p -value < 0.01) to genes that have been described as relevant to this neoplasia, thus suggestive of a cis-regulatory relationship. Overall, such a compendium may provide the scientific community with valuable references for future research into the involvement of lncRNAs in MM.

P04

SINGLE PLATFORM FLOW CYTOMETRIC ABSOLUTE COUNT OF CIRCULATING PLASMA CELLS IN MULTIPLE MYELOMA IS A FEASIBLE METHOD WELL ASSOCIATED TO WORST BASELINE CHARACTERISTICS AT DIAGNOSIS

Muccio V.¹, Gilestro M.², Saraci E.¹, Spada S.¹, Ruggeri M.¹, Caltagirone S.¹, Oddolo D.¹, Musto P.³, Cavo M.³, Pavone V.³, Ronconi S.³, Vincelli D.³, Cafro A.M.³, Cellini C.³, Musolino C.³, Molica S.³, Bernardini A.¹, Gay F.¹, Boccadoro M.¹, Omedè P.²

¹Myeloma Unit, Division of Hematology, University of Torino; ²Myeloma Unit, Division of hematology, AOU Città della Salute e della Scienza di Torino; ³Italian Multiple Myeloma Network, GIMEMA, Italy

Multiple myeloma (MM) patients with poor outcome can be characterized at diagnosis by different clinical and laboratory parameters. Previous data demonstrated that the presence of circulating plasma cells (CPC) in peripheral blood (PB) is a marker of worse prognosis. Nevertheless, detection methods included density gradient stratification – which can affect plasma cells recovery – or flow cytometry – requiring a definite number of total events, which is not always reachable. For the first time, we performed a single platform flow cytometric absolute count of CPC and compared them with patients' baseline characteristics. Whole PB samples from 413 newly diagnosed young MM patients enrolled in the UNITO-MM-01/FORTE trial were collected. For the single platform tube, the antibody combination CD38PC7/CD138PC5.5/ CD45KO/CD56PE/CD19PB was mixed with 100 µL of EDTA peripheral blood dispensed with reverse pipetting, added with 500 µL of lysing solution and, after 15 min, 100 µL of flow count fluorospheres were dispensed with reverse pipetting and cells acquired with Navios flow cytometer. Intracytoplasmic tube was performed to confirm the clonality of CPC. CPC were detected in 390 out of 413 samples (94.4%), with median values of 0.03% (range: 0%-51%) and 2.37/mm³ (range: 0/mm³-6272/mm³). White blood cells were 5710/mm³ (range: 1752/mm³-26102/mm³); total events acquired 1.285.000 (range: 40.000-2.000.000); median CPC events 58 (range: 0-441.000); cellular events acquired were

190.000 (range: 4.428-1.300.000). The percentage and absolute values of CPC were highly correlated (Pearson $r=0.90$ $p<0.001$) and these values, for their statistical normal distribution, were compared with the patients' baseline characteristics. According to different baseline characteristics, median values of absolute CPC were compared using Kruskal–Wallis test: hemoglobin <10 ($18.84/\text{mm}^3$) vs ≥ 10 ($1.89/\text{mm}^3$) $p<0.001$; International Staging System (ISS) I ($1.35/\text{mm}^3$) vs ISS II ($4.95/\text{mm}^3$) vs ISS III ($7.55/\text{mm}^3$) $p<0.001$; Revised ISS (R-ISS) I ($1.34/\text{mm}^3$) vs II ($4.64/\text{mm}^3$) vs III ($7.55/\text{mm}^3$) $p<0.001$; Albumin $<3.5\text{g/dL}$ ($5.03/\text{mm}^3$) vs $\geq 3.5\text{g/dL}$ ($2.04/\text{mm}^3$) $p<0.001$; β_2 -microglobulin $<3.5\text{mg/dL}$ ($1.62/\text{mm}^3$) vs 3.5 – 5.5mg/dL ($5.08/\text{mm}^3$) vs $>5.5\text{mg/dL}$ ($21.47/\text{mm}^3$) $p<0.001$; lactate dehydrogenase \leq upper limit ($2.14/\text{mm}^3$) vs $>$ upper limit ($8.10/\text{mm}^3$) $p<0.001$; Plasma Cells in biopsy $<60\%$ ($1.70/\text{mm}^3$) vs $\geq 60\%$ ($4.38/\text{mm}^3$) $p<0.001$; with del13 (mm^3 $4.84/\text{mm}^3$) vs without del13 ($2.05/\text{mm}^3$) $p<0.001$; with t(11;14) ($7.42/\text{mm}^3$) vs without t(11;14) ($2.76/\text{mm}^3$) $p=0.004$; with amp1 ($4.85/\text{mm}^3$) vs without amp1 ($2.2/\text{mm}^3$) $p=0.01$; Fonseca Standard-risk ($2.31/\text{mm}^3$) vs High-risk ($4.90/\text{mm}^3$) $p=0.004$; ECOG 0 ($1.96/\text{mm}^3$) vs 1 ($3.24/\text{mm}^3$) vs 2 ($4.94/\text{mm}^3$) vs 3 ($26.00/\text{mm}^3$) $p<0.001$. In this study, single platform absolute count method identified CPC in 94.4% of PB samples, comparable with previous studies. The absolute number of CPC was higher in patients with the worst prognostic factors at diagnosis. This method is fast, allows an easy quantification of CPC and can be used, along with the other prognostic factors, to better stratify MM patients at diagnosis.

P06

SILENCING THE INHIBITORY CHECKPOINT CD96 ENHANCES THE CYTOTOXIC POTENTIAL OF NATURAL KILLER CELLS AGAINST MULTIPLE MYELOMA

Duggan T.¹, Chauhan S.^{1,2}, Daly J.¹, Sarkar S.^{1,2}, O'Dwyer M.^{1,2}

¹Apoptosis Research Centre, Biomedical Sciences, National University of Ireland Galway; ²Onkimmune Ltd., Ireland

Background: Cellular immunotherapeutic approaches, including Natural Killer (NK) cell therapy, have recently shown very promising results in the treatment of blood cancers, including Multiple Myeloma (MM). CD96 (TAC-TILE) is a newly identified inhibitory checkpoint receptor expressed on the surface of NK cells. Ligand binding studies have shown that CD96 competes with CD226 (DNAM-1), a co-activating receptor on the surface of NK cells. This competitive interaction between CD96 and CD226 for binding to tumor bound CD155 could influence the cytotoxic activity of NK cells. Although the precise role of CD96 in regulating NK cells is not clearly understood, recent studies have shown that blocking CD96 with a monoclonal antibody can reduce tumor cell metastasis in murine models of solid tumors. In contrast, blocking CD96 receptors on human NK cells *in vitro* has shown conflicting results, with CD96 acting as an activating or inhibitory receptor depending on the tumor subtype. However, despite the importance of DNAM-1 in NK mediated cytotoxicity in MM, the immunomodulatory role of CD96 in MM remains poorly investigated. In this study we investigated for the first time the immunomodulatory role of CD96 in mediating NK cell cytotoxicity against MM. **Methods:** CD155 expression was determined on a panel of cell lines MM1S, RPMI-8226, JN3, H929, and U266. CD96 surface expression of KHYG1 NK cell line was knocked-down by nucleofection with either scrambled control (SC) siRNA or CD96 siRNA (GE, cat: L-020045-02) using AMAXA Nucleofector II. 72 hours post-nucleofection cells were analyzed for surface expression of CD96, and subsequently co-cultured with MM cell lines. NK cell induced cytotoxicity was measured by FACS-based methods, and experimental assays were performed with MM cell lines at E:T ratios of 0.125:1, 0.25:1, 0.5:1, 1:1, 2:1 and 4:1. **Results:** Immunophenotyping revealed that MM cell lines have a broad spectrum cell surface expression of CD155, the ligand for CD96, and therefore we classified them as CD155-high (JN3), CD155-mod (U266, MM1S, RPMI 8226), and CD155-low (H929). Thereafter cytotoxicity assays were performed against a panel of MM cell lines (JN3, U266, and H929) with control SC siRNA KHYG1 or CD96 siRNA KHYG1. CD96 siRNA KHYG1 was significantly more cytotoxic towards moderately expressing CD155 cell line U266 at E:T 1:1, 2:1, and 4:1, as compared to SC siRNA KHYG1 (Figure 1A). Furthermore, this increase in cytotoxicity was also observed against the CD155-high cell line JN3 at E:T 0.5:1 and 4:1 (Figure 1B). Interestingly, no significant increase in cytotoxicity was observed for the CD155-low cell line H929, suggesting the presence of the CD155 ligand on the tumor cell surface is necessary for CD96 mediated impairment of NK cell cytotoxic function. **Conclusions:** This study demonstrates the immunosuppressive function of the CD96 receptor during NK cell mediated cytotoxicity against MM. The enhanced cytotoxicity observed upon knockdown of CD96 could be of further therapeutic benefit

during treatment with Bortezomib, as this is known to upregulate DNAM-1 ligands (CD155). Finally, we propose that siRNA based targeting of CD96 during NK cell therapy using clinical grade electroporation systems (Maxcyte GT) could be of significant benefit in the clinical outcome of NK cell based therapy. **Conflict Of Interest:** Michael O'Dwyer: Founder, Board of Directors, Equity in Onkimmune. Subhashis Sarkar is supported by a fellowship from Onkimmune.

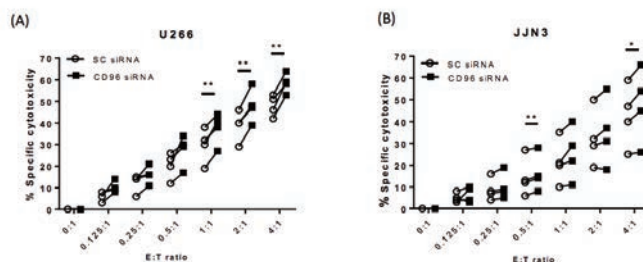


Figure 1. 14-hours cytotoxicity assay with scrambled control (SC) siRNA or CD96 siRNA nucleofected KHYG1 against (A) U266 cells and (B) JN3. Each data-point represents mean of an independent experiment performed in triplicate. For each cell line n=4 independent experiments were performed. Datasets were analysed by paired t-test on GraphPad prism.

P07

LOW DOSE CYCLOPHOSPHAMIDE POTENTIATES THE ANTI-MYELOMA ACTIVITY OF DARATUMUMAB THROUGH AUGMENTATION OF MACROPHAGE-INDUCED ADCP

Naicker S., Rigalou A., McEllistram C., Henderson R., Natoni A., Chiu C., Sasser K., Ryan A., O'Dwyer M.

Regenerative Medicine Institute (REMEDI), College of Medicine Nursing and Health Sciences, Discipline of Pharmacology and Therapeutics National University of Ireland Galway, Haematology Services Galway University Hospital, Saolta University Health Group, Janssen Research & Development, LLC Spring House PA USA

Introduction: Here we focused on potential mechanisms of enhancing macrophage (Mφ)-mediated ADCP and have highlighted that exposure of MM cells to low doses of Cyclophosphamide (Cy) led to a secretory response, which greatly augments Mφ-induced ADCP of Dara-coated MM cells¹. We confirm this phenomenon in MM and establish the in-vivo relevance of these findings as seen in newly diagnosed MM patients enrolled in CyBorD-DARA phase 1b clinical trial (NCT02951819). **Methods:** Bone Marrow (BM) and peripheral blood (PB) samples were collected from newly diagnosed MM patients recruited to the CyBorD-DARA clinical trial prior to- and 24hrs after Cy (150-300mg/m²) treatment. Major circulating immune cells were quantified by flow cytometry. Mononuclear cells were analysed to quantify monocyte, lymphocyte and plasma subsets and determine changes in surface expression profiles following treatment. Serum cytokines levels were also quantified by multi-plex assay prior to- and 24hrs after Cy treatment. MM cells were conditioned with low-dose Cy for 24hrs. Media containing chemotherapy agents were replaced with fresh media for 24hrs (TCM)¹. Mφ were conditioned with TCM for 48hrs and characterised or incubated at 2:1 effector target ratio with CFSE labelled MM1S cells ± Cytochalasin D in the presence or absence of Dara/Isotype control. The % of Dara-specific tumour cell clearance was calculated to determine if the mechanism of tumour cell clearance was Mφ-mediated ADCP and confirmed using imaging flow cytometry. **Results:** In patients receiving Cy for 24hrs, BM and PB neutrophils were increased ($P<0.01$, $n=11$), lymphocytes were decreased ($P<0.01$, $n=11$) while monocyte numbers remain unchanged ($P>0.05$, $n=11$). An increase in B cells ($P<0.05$, $n=6$) and a decrease in natural killer cells (NK) ($P<0.05$, $n=6$) were observed. Interestingly, the number of Mφ precursor monocytes did not change following Cy treatment in BM and PB of these patients. As innate immune cells are essential in immune surveillance, coupled with our finding that NK cells are reduced, this highlights a potential role for Mφ in Cy induced anti-tumour activity. Our data previously highlighted that exposure of Mφ to TCM from Cy treated MM cells significantly enhanced % of Dara-specific clearance of MM cells ($p<0.01$) and confirmed ADCP as a likely mechanisms of tumour clearance *in vitro*. We also observed a marked reduction in the "don't eat me" antigen, CD47, on Cy-treated MM cells *in vitro*, which

we have now confirmed in MM cells isolated from PB and BM of patients (n=3) following Cy treatment, which may enhance phagocytosis. Furthermore, our *in vitro* observation of induced CD64 Fc gamma receptor expression on conditioned Mφ following single-agent Cy is seen in Mφ isolated from both BM (P<0.05, n=11) and PB (P<0.01, n=11) of newly diagnosed MM patients following Cy treatment. Serum levels of TNFα (P<0.01, N=11), IFNγ (P<0.05, N=11) and VEGF (P<0.058, N=11) were higher after Cy treatment. These findings emphasize the physiological relevance of our *in vitro* data, implicating Cy in the potentiation of Mφ mediated ADCP in Dara specific anti-tumour immunity. **Conclusions:** Mφ precursors isolated from patients' BM and PB following 24hrs Cy treatment confirm our *in vitro* findings which suggest Cy potentiation of Mφ mediated ADCP in anti-tumour efficacy of Dara. This provides a rationale for the efficacy observed when combining Cy with Dara in the on-going clinical trial.

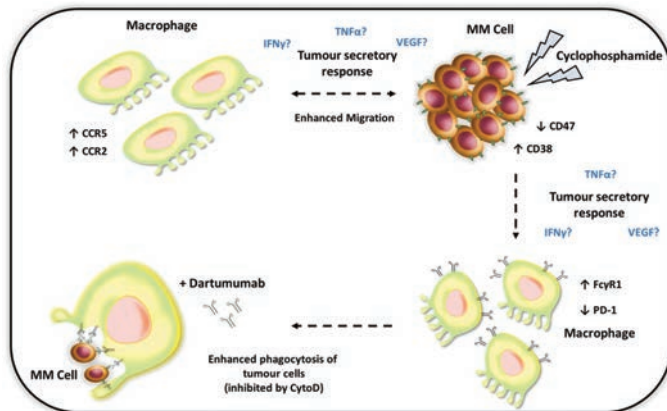


Figure 1: Schematic overview of mechanisms associated with low dose cyclophosphamide potentiation of Daratumumab anti-tumour cytotoxicity via augmentation of macrophage-mediated ADCP

Reference

1. Naicker et al, Blood 2017 Volume 130:121-121

P08

TARGETING SIGLEC-7: A NOVEL IMMUNOTHERAPEUTIC APPROACH TO POTENTIATE THE CYTOTOXIC FUNCTIONS OF NATURAL KILLER CELLS AGAINST MULTIPLE MYELOMA

Daly J.¹, Sarkar S.^{1,2}, Natoni A.¹, Hu J.¹, Chauhan S.^{1,2}, Henderson R.¹, Duggan T.¹, McCarthy P.L.¹, McEllistirm C.¹, O'Dwyer M.^{1,2}

¹National University of Ireland, Galway; ²Onkimmune Ltd. Ireland

Background: Multiple Myeloma (MM) is a malignant plasma cell disorder, accounting for approximately 10% of all haematological malignancies. The intrinsic ability of the malignant cells to evade the host immune system is associated with poor overall survival of MM patients. The immune-suppressive functions of sialylated glycans, abundantly expressed on the surface of myeloma cells, has not previously been addressed. We hypothesize that hypersialylation of MM enables evasion of cytotoxic Natural Killer (NK) cells within the MM bone-marrow (BM) niche. Disrupting the immune-suppressive interactions between sialylated glycans on MM cells and their cognate sialic acid-binding lectin (Siglec) receptors on NK cells could pave the way for the development of novel immunotherapeutic strategies for treating MM patients. **Methods and Results:** Using a recombinant Siglec-7 Fc chimera we observed that Siglec-7 ligands (Siglec-7L) are highly expressed across a panel of commonly used MM cell lines. Furthermore, Siglec-7L expression was also observed on CD38+/CD138+ primary MM cells isolated from BM aspirates of newly diagnosed and relapsed MM patients. Immunophenotyping analysis revealed that NK cells circulating within the BM of MM patients have significant cell surface expression of the cognate Siglec-7 receptor (Siglec-7R) (82±25%, n=5). To investigate the immune-suppressive effects of Siglec-7L and Siglec-7R interactions in dampening the cytotoxic functions of NK cells, we treated MM cell lines RPMI-8226, H929 and MM1S with a sialyltransferase inhibitor (SIA) (3Fax-Peracetyl Neu5Ac, 200uM) for 5 days. As expected, this treatment resulted in a complete eradication of Siglec-7L from the surface of MM cells. Subsequently, SIA treated MM cells

were co-cultured with the human NK cell line KHYG1 at E:T ratios of 1:1, 2.5:1 and 5:1 for 12 hours. Flow cytometry based analysis of cell viability revealed that abolishing sialylated glycans from the cell surface of MM cells results in a 1.3-1.6 fold increase (p<0.05) in NK cell induced cell death in MM cell lines RPMI8226 and H929, but not MM1S. (n=3) (Figure 1). Furthermore, to validate our observations we pre-treated RPMI8226 cells with 10 µg/ml of recombinant Siglec-7 Fc chimera in order to block Siglec-7L on the cell surface. We carried out 4 hour cytotoxicity assays with the pre-treated RPMI cells and KHYG1 NK cells at 1:1, 2.5:1 and 5:1 E:T ratios. Cell death was measured by flow cytometry using 1 µg/ml PI to stain dead cells. We observed enhanced cytotoxicity against the Siglec-7 Fc chimera treated RPMI 8226 versus an isotype Fc control and, using paired t-test analysis, determined that the increases were statistically significant at all E:T ratios (P = 0.003 1:1, P = 0.001 2.5:1, P = 0.03 5:1). **Conclusion:** We observed that Siglec-7L are abundantly expressed on the surface of MM cells. Additionally, the cognate receptors of the ligands are significantly expressed on primary NK cells circulating within the BM of MM patients. Functional assays revealed that Siglec-7L and Siglec-7R receptor interactions have significant immune suppressive effects on the cytotoxicity of NK cells towards MM cell lines. Thus, we can leverage the findings of this study to develop NK cell based cellular therapies to target Siglec-7 ligand- receptor interactions in MM. **Conflict of Interest:** Michael O'Dwyer: Founder, Board of Directors, Equity in Onkimmune. Dr. Sarkar is supported by a fellowship from Onkimmune.

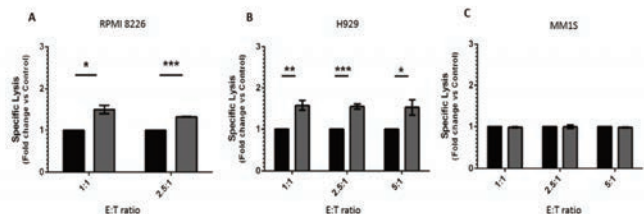


Figure 1: Enhanced NK cell mediated killing of MM by the KHYG1 NK cell line post-treatment with a specific sialyltransferase inhibitor. (A) RPMI (B) H929 (C) MM1S cell lines were pre-treated with 200µM 3Fax-Peracetyl Neu5Ac sialyltransferase inhibitor for 5 days prior to 12 hour cytotoxicity with KHYG1 at 1:1, 2.5:1, 5:1 E:T ratios. Cell death was measured by flow cytometry using Annexin V and Sytox Green death stains. An anti-CD2 antibody to distinguish between KHYG1 and MM cells. Graphs depict fold increase of KHYG1 specific lysis vs. control (DMSO) treated cells. Data is presented as Mean ± SD. Statistical analysis was carried out using student's unpaired t-test. *p<0.05, **p<0.01, ***p<0.0001. N=3 for each group.

P09

LONG TERM CR MULTIPLE MYELOMA PATIENTS STUDIED WITH NGF SHOW CURED OR MGUS-LIKE MINIMAL RESIDUAL DISEASE

Gozzetti A., Raspadori D., Pacelli P., Tocci D., Staderini M., Antonioli E., Sicuranza A., Bosi A., Bocchia M.

¹Hematology, Azienda Ospedaliera Universitaria Senese, Siena; ²Hematology, University of Florence, Florence, Italy

CR is a prerequisite for long term responses, PFS, OS and cure. In the era of novel agents, many MM patients can achieve stringent CR (sCR). Most of these patients will relapse and minimal residual disease (MRD) detection will play a crucial role. Recently, two 8 colours tubes panel developed by the EuroFlow Consortium can detect MRD with an increased sensitivity (≥ 1 in 105 cells) and can be applied as standardized method to study MM patients.

While many studies have looked at MRD status sequentially and soon after autologous or allogeneic stem cell transplantation with multiparameter flow cytometry or molecular techniques, little is known about long term remission patients (> 2-10 years) and in particular if more sensitive techniques such as next-generation flow cytometry (NGF) or next-generation sequencing (NGS) can still detect minimal disease in those patients. Aim of the study was to analyze patients with MM in response > very good partial remission (VGPR) with NGF at > 2 and > 5 years of lasting remission after several treatments included or not stem cell transplantation.

Clinical assessment definition of CR status included serum and urine immunofixation, FLC, CT-PET, bone marrow aspirate, bone core biopsy. 74 patients were studied of which 70/74 were evaluable, bone marrow aspirates of 4/74 patients were too hemodiluted and have not been analyzed. 70 samples of MM patients (M/F= 41/29) were studied with NGF between February 2016 and January 2018. Median age was 61 years (range 37-77 ys).

29/70 (%) patients were in sCR at the moment of the study, [4/29 patients were under therapy, the others 25 sCR were evaluated at a median of 47 months after therapy (range 3-140)]. 30/70 (52.5%) patients were in VGPR at study analysis according to new IMWG response criteria, 21/30 patients

were off therapy from a median of 9 months (range 2-186 months). 11/70 patients were under treatment at the time of the study with a long period of stable disease. A total of 16 patients had a remission disease >5 years. A total of 20 patients had a remission duration of >2 years but < 5 years. OneFlow™ PCST and PCD, BD Biosciences were utilized to detect MRD level with a lyse-wash-and-stain sample preparation protocol by flow cytometry (FAC-Scanto II, BD, Biosciences). MRD+ status was detected in 27/70 (45%), 3/16 (18%) were MRD positive at >5 years remission (2 sCR, 1 VGPR) (median 84 months, range 72-186 months); 8/20 (36%) were MRD + after >2 years of remission (3 sCR, 5 VGPR) (median 48 months, range 28-186 months). On the other hand, MRD+ was present in 16/34 (48%) responding patients with <2 years of follow up. As expected being in sCR was correlated with a low percentage of MRD+ status 7/29 (24%) (2 patients after >5 years, 5 patients after <5 years). Interestingly looking at long lasting remission, i.e. >5 years, the 3/12 patients that resulted MRD+ displayed an MGUS like - plasmacell immunophenotype (prevalence of normal plasmacells vs aberrant monoclonal) with a PCn/PCtot ratio of 48%, 85%, 30%. CT/PET was positive in 7/59 patients. All patients in sCR were CT/PET negative. NGF showed that MM patients with long remission status can be considered disease free/cured with a high sensitivity method. MM patients that display an MGUS-like phenotype after achieving a CR can have long lasting remissions meaning disease control. Patients in sustained CR after 2 years can have high percentage of MRD negativity.

P10

KIR 3DL1-EDU, HLA GENOTYPES AND KIR HAPLOTYPE INFLUENCE CLINICAL OUTCOME OF HIGH-RISK YOUNG MULTIPLE MYELOMA PATIENTS TREATED UP-FRONT WITH NOVEL AGENTS

Leotta S., Puglisi F., Parisi M., Calafiore V., Martino E., Romano A., Conticello C., Toscano S., Sortino G., Azzaro M.P., Di Raimondo F.

UOC Hematology and Bone Marrow Transplantation Units - AOU Policlinico Vittorio Emanuele, Catania, Italy; UOC Hematology and Bone Marrow Transplantation Units - AOU Policlinico Vittorio Emanuele, Catania, Italy; UOC Hematology and Bone Marrow Transplantation Units - AOU Policlinico Vittorio Emanuele, Catania, Italy; UOC Hematology and Bone Marrow Transplantation Units - AOU Policlinico Vittorio Emanuele, Catania, Italy; UOC Hematology and Bone Marrow Transplantation Units - AOU Policlinico Vittorio Emanuele, Catania, Italy; UOC Hematology and Bone Marrow Transplantation Units - AOU Policlinico Vittorio Emanuele, Catania, Italy; UOC Hematology and Bone Marrow Transplantation Units - AOU Policlinico Vittorio Emanuele, Catania, Italy; Tissue Typing Laboratory - Hematology and Bone Marrow Transplantation Units - Policlinico Vittorio Emanuele Catania Italy; Tissue Typing Laboratory - Hematology and Bone Marrow Transplantation Units - Policlinico Vittorio Emanuele Catania Italy; Tissue Typing Laboratory - Hematology and Bone Marrow Transplantation Units - Policlinico Vittorio Emanuele Catania Italy; UOC Hematology and Bone Marrow Transplantation Units - AOU Policlinico Vittorio Emanuele, Catania, Italy

In Multiple Myeloma (MM) microenvironment, different cells contribute to immune-escape, among them there are Natural Killer cells (NKs). NKs are functional through the education via killer cell immunoglobulin-like receptor (KIRs) that interacts with HLA class I molecules (or ligands C1, C2, Bw4). KIR and HLA genotypes influence clinical outcome in relapsed patients treated with lenalidomide-based regimens, but poor is known about their impact on high-risk young (HRY) MM patients. The aim of this study is to evaluate whether KIR and HLA genotypes is able to influence clinical outcome of HRY-MM patients. KIR genes and their HLA ligands were analyzed in 30 healthy subjects (controls) and 69 MM patients using the Genotyping SSP and SSO kit. In 50 HRY-MM patients (median age 54.1 years, 30 males), treated up-front with novel agents-based induction treatment, followed by consolidation with one autologous stem cell transplantation and randomly assigned to lenalidomide maintenance until progression, we evaluated the role of KIR expression and KIR haplotype AA/Bx on progression free survival (PFS). In HRY-MM patients, predictors of outcome were achievement of complete remission after induction treatment, LDH and consolidation treatment ($p < 0.01$), but not maintenance and monoclonal component at diagnosis. Lacking KIR 3DL1-edu was more frequent in MM than in healthy subjects (76.7% vs 43.5%, $p < 0.0023$; CI=95%). After median follow-up of 45 months, HRY-MM-patients carrying on 3DL1-edu had longer PFS than those without 3DL1-edu (53.8 versus 41.5 months, $p = 0.08$), although no significant differences and overall survival (OS). There wasn't

any significant differences in KIR haplotype AA/Bx frequencies in MM versus healthy patients. However, in HRY-MM-patients, Bx haplotype was associated with longer PFS (56.4 versus 27.8 months, $p = 0.06$), without any effects on OS. KIR 3DL1-edu or Bx haplotype are associated to clinical outcome in HRY-MM-patients, implying a role of NK cytotoxicity against MM residual cells. Our data need to be confirmed in larger prospective series.

P11

A NEW, NON INVASIVE TEST TO INVESTIGATE EXTRACELLULAR VESICLES AS BIOMARKER IN MULTIPLE MYELOMA

Caivano A.^{1*}, Laurenzana I.^{1*}, Trino S.¹, De Luca L.¹, Lamorte D.¹, D'Auria F.², La Rocca F.³, Villani O.³, Pietrantonio G.³, Del Vecchio L.^{4,5}

Musto P.⁶ *these authors contributed equally to work

¹Laboratory of Preclinical and Translational Research, IRCCS-Referral Cancer Center of Basilicata (CROB), Rionero in Vulture (PZ); ²Laboratory of Clinical Research and Advanced Diagnostics, IRCCS-CROB, Rionero in Vulture (PZ); ³Department of Onco-Hematology, IRCCS-CROB; ⁴CEINGE-Biotecnologie Avanzate scrl, Naples; ⁵Department of Molecular Medicine and Medical Biotechnologies, Federico II University, Naples; ⁶Scientific Direction, IRCCS-CROB, Rionero in Vulture, Italy; Biotechnologies, Federico II University, Naples, Italy

Extracellular vesicles (EVs) are lipid membrane particles of different size and biogenesis, released from normal and neoplastic cells. They have an important role in cell-to-cell cross-talk within a large number of physiological and pathological processes. In particular, EVs from bone marrow (BM) stromal cells may induce proliferation of neoplastic cells and drug resistance in Multiple Myeloma (MM). In turn, EVs from MM plasma cells influence the BM niche, promoting angiogenesis and suppression of immunity. Our group has recently reported that circulating microvesicles (cMV), an EV sub-micron type purified from MM patient sera, express specific tumor related-antigens, such as CD38 and CD138, and that their number correlate with ISS. In addition, we have also shown that microRNA-155, whose decrease has been associated with MM drug resistance, is reduced in MM serum EVs as compared to healthy controls and other hematological malignancies. Therefore, cMVs could represent a new, non-invasive and promising biomarker, able to avoid more difficult sampling, i.e. from BM. Thus, in a context of liquid biopsy (or, preferably, of "cell biopsy"), we describe here a novel approach to analyze EVs, as a new serum test for monitoring MM. Blood samples have been so far collected from MM patients and healthy subjects. Patients included *de novo*, treatment responders (according to the IMWG guidelines), and relapsed MM subjects. In order to carry out a precise and standardized analysis, we first proceeded to set up flow cytometry assay to analyze exactly the most visible EVs in terms of size. The first question we tried to answer was: is it possible to stain the EVs directly in serum or do we need to convert it in a phosphate buffer in order to better visualize them by flow cytometry? To answer, EVs were stained with lipid membrane or, alternatively, protein binding dyes. Phenotyping and quantitating of EVs were performed by FACSCanto flow cytometric analysis. Overall, the best results were obtained after conversion of serum in phosphate buffer, using both dyes. This approach allowed us: i) to analyze lipid membrane particles and not artefacts, and ii) to recognize EVs with size inferior to 200 nm, not otherwise visible by using the physic parameter setting of flow cytometer. Second question was: how is it possible to identify and analyze MM "specific" EVs into the "tide" of EVs released from other cell types and displayed by flow cytometry? To answer, we are currently testing immuno-labelling of EVs for CD38 and CD138. In this setting, preliminary data indicate the feasibility of such an approach, with high quality results in terms of specificity and possibility to investigate EV genetic content. The final aim of this study will be the application of EVs as a new biomarker useful for prognostic assessment and monitoring of MM. Updated data will be presented at the meeting.

P12**SINGLE CELL EXOMES IN AN INDEX CASE OF AMP1Q21 MULTIPLE MYELOMA REVEAL MORE DIVERSE MUTANOMES THAN THE WHOLE TUMOUR POPULATION**

Sahota S.S., Tapper W., Weston-Bell N.J., Bolomsky A., Collins A.R., Zojer N., Bryant D.

Tumour Immunogenetics Group, Cancer Sciences Academic Unit, Faculty of Medicine, University of Southampton, United Kingdom (SSS, NJWB, DB); Human Health and Development Academic Unit, Faculty of Medicine, University of Southampton, United Kingdom (WT, ARC); Department of Medicine I, Wilhelminenspital, Wilhelminen Cancer Research Institute, Austria (AB, NZ).

Clonal evolution in a tumor occurs by competition between single cells (SCs) for dominance in growth and survival. In this, a major driver mechanism is acquired genome-wide somatic mutations and their functional outcomes in SCs. To determine a true and unbiased map of genomic mutations in SCs, a necessary approach is to carry out whole exome sequencing (WES) of individual cell genomes. We initiate this in an index case of amp1q21 multiple myeloma (MM), and report on WES in bulk tumor population and in 20 separate tumor SCs, identifying acquisition of genomic somatic variants against autologous germline DNA. Using a robust bioinformatics pipeline, we identified a total of 69 unique mutations, of which 23 somatic variants strikingly were only called in 2 or more SC exomes, but not in the bulk tumor population genome. Validation of selected variants confirmed 100% concordance with bioinformatics calls. Our data thus reveal a more diverse mutanome at the SC level than hitherto identified in the whole tumor population in MM, with important implications for understanding clonal evolution and tumor behaviour. Understanding SC functional variation and its outcomes will be essential to inform and develop new personalised therapeutic strategies, including immunotherapy.

P13**A PRELIMINARY ANALYSIS OF SOMATIC EXOME MUTATIONS OF MINIMAL RESIDUAL DISEASE IN MULTIPLE MYELOMA**

Zatopkova M.^{1,2}, Stracquandano G.³, Sevcikova T.^{1,2,4}, Vojta P.⁵, Simicek M.^{1,2,4}, Growkova K.^{1,2,4}, Chyra Kufova Z.^{1,4,6}, Filipova J.^{1,2,4}, Jelinek T.^{1,2}, Rihova L.⁷, Bezdekova R.⁷, Smejkalova J.¹, Hajdich M.⁵, Minarik J.⁸, Jungova A.⁹, Maisnar V.¹⁰, Pour L.¹¹, Kryukov F.¹², Hajek R.^{1,4}

¹Department of Haematology, University Hospital Ostrava, Czech Republic; ²Department of Biology and Ecology, Faculty of Science, University of Ostrava, Czech Republic; ³School of Computer Science and Electronic Engineering, University of Essex, United Kingdom; ⁴Department of Clinical Studies, Faculty of Medicine, University of Ostrava, Czech Republic; ⁵Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic; ⁶Department of Experimental Biology, Faculty of Science, Masaryk University, Brno, Czech Republic; ⁷Department of Clinical Hematology, University Hospital Brno, Czech Republic; ⁸Department of Haemato-Oncology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic; ⁹Department of Haemato-Oncology, University Hospital in Plzen, Czech Republic; ¹⁰4th Department of Medicine – Haematology, University Hospital Hradec Kralove, Czech Republic; ¹¹Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Czech Republic; ¹²Medical Department, JCS BIOCAD, Saint Petersburg, Russian Federation

Introduction. Multiple myeloma (MM) is a malignancy of plasma cells. Despite new effective drugs emerged in the last decade, a small amount of aberrant plasma cells (A-PCs) can persist after treatment and cause a disease relapse. Design of targeted therapy for patients with minimal residual disease (MRD) is becoming a priority to improve the overall outcome. To do that, it is instrumental to unveil the underlying genomic mutational landscape underpinning this disease to identify suitable druggable targets. Our aim is to analyze somatic mutations in exome of A-PCs from patients with MM MRD and to identify novel targets for personalized therapy. Material and methods Samples of bone marrow and peripheral blood were collected from 7 MRD patients. Most of them received standard MM therapy, using a Velcade-based treatment. Successively, the A-PCs were identified by 8-color multiparametric flow cytometry and isolated from a bone marrow samples by fluorescent activated cell sorting according to surface markers CD38, CD45, CD56 and CD19. Genomic DNA was isolated and amplified by the Single cell amplification kit (QIAGEN). SureSelect Human All Exon V6 Kit

was used to prepare libraries. 100bp long reads were sequenced on Illumina HiSeq 4000 platform with expected coverage 100x. Reads were aligned to the reference sequence Hg38 using the BWA. VarScan2 was used for variant calling and a custom post-processing pipeline was used for annotation and filtering of variants. All resulting genes were compared with the M3P (MM mutation panel) panel created for ultra deep sequencing of MM patients. Interaction of affected gene products was evaluated using the Drug Gene Interaction database. Results Sequencing data of the patient's cohort revealed at least one single nucleotide variant (SNV) in 1324 affected genes. Median number of affected genes was 288 per patient (min 213, max 313). Variants in 8 genes (JPH4, MAPRE3, LARP1, SRRT, LOXL3, ELAVL3, ZBTB4, HPS1) were shared by all 7 patients. Variants in 340 genes were shared by at least 2 patients and variants in 984 genes were patient-specific. Further, we compared the list of all genes possessing SNV (1324) with M3P which was created as a list of 88 most commonly mutated genes in MM. We found mutations in genes also presented in M3P (BRAF, DIS3, EGR1, FGFR3, IDH2, IKZF3, KRAS, MYC, NFKBIA, NRAS, PIM3, SHC1, TRAF3). From those, 3 genes (out of 13) were shared by at least 2 patients and 10 genes were patient specific. Search in the Drug Gene Interaction database showed that products of 24 out of all 1324 genes interact with drugs used for MM treatment (e.g. Bortezomib, Carfilzomib, Lenalidomide). Conclusion We were able to detect genomic variants in 7 patients with MM MRD. These variants need to be further validated by other sequencing methods and expression of the affected genes in MM has to be validated. Obtained data will be further compared with data from monoclonal gammopathies cohorts from other sequencing projects, as well as augmenting our dataset by enrolling more patients for sequencing. The functional impact of chosen genetic variants will be analysed in more details through *in vitro* functional studies. This work represents a primer towards the identification of new therapeutic targets in MM MRD. Supported by Ministry of Health of the Czech republic (17-30089A, CZ-DRO-FNOs/2016), Ministry of Education of the Czech republic (SGS18/P F/2017-2018) and company Takeda Pharmaceuticals Czech republic s.r.o.

P14**FISH IN MULTIPLE MYELOMA: BENEFITS AND OBSTACLES**

Denčić Fekete M.¹, Bila J.^{1,2}, Jeličić J.¹, Sretenović A.¹, Jovanović J.¹, Peruničić-Jovanović M.¹, Jaković Lj.^{1,2}, Bogdanović A.^{1,2}, Mihaljević B.^{1,2}

¹Clinic of Hematology, Clinical Center of Serbia; ²Medical Faculty, University of Belgrade, Belgrad

Introduction: For the past two decades, the most widely used technique for the assessment of molecular genetics in multiple myeloma (MM) was interphase fluorescent in-situ hybridization (iFISH) analysis. However, today we are faced with disadvantages of this technique, mainly due to the time consuming technical procedure, and incompleteness of acquired impression of individual patient's genetic profile due to the limitations of the applied panel of recommended iFISH probes. The aim of study was to analyse the applicability, precision and accuracy of routine iFISH analysis in MM patients. Patients and methods: In this single-center study, during five-year period, December 2012. -December 2017, the iFISH analysis was performed in 234 newly diagnosed MM on the isolated plasma cells from the bone marrow aspirates. The panel of the following iFISH probes was applied: 17p13.1 (TP53), 13q14 (D13S25), 1p32/1q21 (CDKN2C/CKS1B), 14q32 (IGH breakapart), t(4;14) (IGH/FGFR3) and t(14;16) (IGH/MAF) (Abbott/Vysis) in accordance to the standard protocol procedure. **Results:** The successful iFISH results were obtained in 222 patients (95%), while it was failed in 12 patients due to insufficient number of plasma cells. The aberrant iFISH signals were recorded in 135 of patients (61%). Rearrangements of the analysed regions were further present in a descending order: 13q14 (60%), 1q21 (32%), 17p13 (16%), t(4;14) (11%), del1p (10%), IGH break apart (excluding t(4;14) and t(14;16)) (9%), and t(14;16) (2%). When analysing the type of rearrangement for each of the FISH probes, we got the expected aberrant pattern in majority of the patients, eg.: del(13q14), del(17p13), t(4;14) etc. However, less prevalent types of aberrations, such as accompanied trizomies of the D13S25, TP53, FGFR3, IGH and MAF genes, were recorded as well (7%) indicating hyperdiploidy. On the other hand, the monosomy of MAF gene was present in 4% of the patients, while the rearrangement of the IGH gene (without t(4;14) and t(14;16)) was seen in 9% of them, implicating possibility of hypodiploid karyotype. Furthermore, two groups of patients with 1q rearrangements were recorded: those with a simple gain of 1q (trizomic signals), and those with a real 1q amplification (more than 5 signals) indicating hyperdiploid pattern. **Conclusion:** Because of the complexity of cytogenetic ab-

normalities in MM, iFISH provide initial, rather robust, impression of individual prognostic profile of MM patients. However, the other more advanced methods as next generation sequencing, RNA sequencing, or whole-genome sequencing may offer additional answers for genetic doubts unsolved by iFISH method.

P15

ACCELERATED INFUSION OF DARATUMUMAB IS SAFE IN MULTIPLE MYELOMA PATIENTS

Jak M., Oostvogels R., Minnema M.C.

UMC Utrecht, the Netherlands

Daratumumab, a human anti-CD38 monoclonal antibody (mAb), has demonstrated superior efficacy in the treatment of relapsed multiple myeloma patients. The approved initial infusion lasts at least 6.5 hours, a second infusion 4 hours and all subsequent infusions around 3.5 hours. This results in long treatment days for patients and high pressure on the treatment capacity of outpatient clinic. In this single center observational study patients who received 8 prior doses of daratumumab were treated with accelerated infusion time of 90 minutes. No adverse events of any grade were observed. We conclude that fast infusion of daratumumab is safe in multiple myeloma patients. The accelerated dosing schedule of daratumumab addresses several concerns; reducing time on the outpatient clinic and thereby increasing quality-of life of patients, reducing costs and increasing the capacity for daratumumab treatment. This latter is of great importance since increasing numbers of patients will be treated with daratumumab as standard of care for multiple myeloma in the near future.

P16

MONITORING OF INTERLEUKIN-6, INTERLEUKIN-10 AND TUMOUR NECROSIS FACTOR-ALPHA, AS PROLIFERATIVE FACTORS IN MULTIPLE MYELOMA

Kovacs-Benke E.

Cancer Immunology Research, Birsfelden, Switzerland

MULTIPLE MYELOMA (MM) is a haematological disorder of clonal malignant plasma cells, accounts for 1–2% of all human cancers. Plasma cells are non-dividing cells of the B-cells, myeloma cell is a malignant plasma cell. Multiple myeloma is characterised (a) by slow proliferation of the tumor cells in the bone marrow, (b) by production of large amounts of immunoglobulins, (c) osteolytic lesions. Cytokines are subtypes of Growth Factors. In the patholo-

gical condition cytokines influence stepwise the development of cancer cells. The pathological effects include apoptosis, cell proliferation, angiogenesis, cell-metabolisms. Interleukin-6 (IL-6) is a major proliferative factor for malignant plasma cells. It produces by myeloma cells (endogenous production) and by bone marrow stromal cells (exogenous production). Biological effects of IL-6: by specific membrane receptors. The receptor complex consists: (1) IL-6R alpha subunit and (2) signal-transducing component gp130. The interleukin-6 receptor alpha-chain is expressed by neoplastic but not normal plasma cells. The signal-transducing component gp130 is expressed ubiquitously on all viable cells in the body. The two membrane receptors are released from the cells as soluble receptor proteins (sIL-6R and sgp130). As agonist, sIL-6R enhances the biological activity of IL-6. Sgp130 is an antagonist against the complex IL-6+sIL-6R. Interleukin-10 (IL-10) is a proliferative factor for malignant plasma cells. It is produced by the malignant plasma cells (endogenous production) and by Interleukin-6 (exogenous production). Biologic effects: by its specific cell surface receptor. Tumour necrosis factor-alpha (TNF-alpha) is a proliferative factor for myeloma cells. It produces by IL-6 (exogenous production) but not by myeloma cells. Biologic effects: by TNF receptor 1 and TNF receptor 2. The three cytokines as proliferative factors present a significant increased serum values in myeloma patients showing a correlation with disease activity. Clinical studies have given evidence, that about in half of myeloma patients these cytokines are promoters in the development of multiple myeloma. Bone disease is the major feature of multiple myeloma. It is due to increased activity of osteoclast and decreased activity of osteoblast. The cytokines Interleukin-6 and Tumour necrosis factor-alpha are chief factors for producing bone disease in myeloma patients. Different morphological and biochemical features identify the different steps during the tumour cell development. Staging is important for prognosis of the disease, treatment options, and the evaluation of treatment. For this reason, the serum values of IL-6, IL-10 and TNF-alpha will be measured in the different stages (I. II. III.) of multiple myeloma. Additionally the following serum parameters also will be measured: soluble IL-6R as agonist for IL-6 and soluble gp130 as antagonist against the complex IL-6+sIL-6R. AIM - In which stage of myeloma are these cytokines effective? - Correlation with Laboratory-Parameters. - Correlation with Clinical Parameters/Condition. The simultaneous determinations of the Serum Parameters with the Laboratory-Parameters simplify the monitoring disease status in multiple myeloma and can justify a specific-targeted therapy - a so called "made to order" therapy - in myeloma patients. Such therapy is important and efficient. *Conclusions:* Today multiple myeloma is diagnosed in earlier stages than a few years ago. For this reason specific-targeted therapy modalities have priority.

Newly diagnosed multiple myeloma

P17

LENALIDOMIDE, ADRIAMYCIN AND DEXAMETHASONE (RAD) REGIMEN INCREASES BONE FORMATION AND REDUCES BONE RESORPTION AND ANGIOGENESIS AS INDUCTION REGIMEN FOR NEWLY DIAGNOSED MYELOMA PATIENTS ELIGIBLE FOR AUTOLOGOUS TRANSPLANTATION: FINAL RESULTS OF A PHASE 2 STUDY OF THE GREEK MYELOMA STUDY GROUP

Terpos E., Zagouri F., Katodritou E., Symeonidis A., Geroftotis A., Christopoulou G., Gavriatopoulou M., Christoulas D., Kourakli A., Konstantinidou P., Kastiris E., Dimopoulos M.A.

Greek Myeloma Study Group, Athens, Greece

This was a phase II open label, non-comparative, non-randomized study for the assessment of the efficacy and safety of lenalidomide, adriamycin and low dose dexamethasone combination (RAD) in newly diagnosed, symptomatic MM patients who are eligible for high dose therapy and ASCT. The effect of RAD on bone metabolism and angiogenesis was also tested. RAD regimen was given as induction before ASCT for 4 cycles. Lenalidomide was administered po at a dose of 25 mg daily, on days 1 to 21 of a 28-day cycle, while adriamycin was administered as intravenous bolus infusion at a dose of 9 mg/m², on days 1-4 of a 28-day cycle and dexamethasone was administered po at a dose of 40 mg, on days 1, 8, 15, and 22. Bone remodeling was studied by the measurement of the following serum indices on day 1 of cycle 1 and on day 28 of cycle 4 of RAD induction: i) osteoclast regulators [sRANKL and osteoprotegerin (OPG)], ii) osteoblast inhibitor Dkk-1, iii) bone resorption markers [CTX and TRACP-5b] and iv) bone formation markers [bALP, PINP and osteocalcin (OC)]. The following angiogenic cytokines were also evaluated: angiogenin, angiopoietin-1 (ang1), angiopoietin-2 (ang2), VEGF, VEGF-A and bFGF. Thirty healthy individuals who served as controls were also tested. Forty-five patients were enrolled. All but one patient completed 4 cycles of RAD. Best response included one (2.2%) CR, 8 (17.8%) VGPRs, 21 (46.7%) PRs, for an ORR of 66.7%, while 14 (31%) patients had stable disease and one progressed during the 4th cycle of treatment. Adverse events of grade 3 or 4 included: anemia (4 patients, 9%), neutropenia (3 patients, 6.6%), febrile neutropenia (one patient), hypocalcemia (one patient), acute renal failure (one patient), pulmonary embolism (one patient), fatigue (one patient) and pathological fracture (one patient). Forty (89%) patients had adequate stem cell collection post-RAD induction (mean±SD: 8.94±6.50x10⁶/kg CD34+ cells). Three patients failed to collect adequate number of stem cells and two patients refused to proceed to stem cell collection. These patients continued on RD till disease progression. Patients at baseline had elevated levels of CTX, TRACP-5b, sRANKL/OPG, Dkk-1, Ang, VEGF, VEGF-A, bFGF and reduced levels of Angp-1/Angp-2, bALP and PINP compared to controls (p<0.01 for all comparisons). RAD therapy resulted in a reduction of circulating CTX (p=0.03), TRACP-5b (p<0.01), Ang (p=0.02), VEGF (p=0.01) and bFGF (p<0.01). On the contrary, RAD increased serum levels of bALP (p=0.036), PINP (from 45±15 mg/l to 110±57 mg/l; p=0.028) and Ang-1/Ang-2 ratio (13.3±10.9 to 18.8±12.6; p=0.022). These alterations occurred irrespective of response, although patients who achieved at least VGPR tended to have more profound differences in the above parameters. All patients who received an ASCT (n=40) received lenalidomide maintenance (10 mg daily). With a median follow-up of 26 months the median PFS has not been achieved yet. The probability of 2-year PFS and TTP was 60% respectively. We conclude that RAD resulted in successful induction for NDMM patients and produced an ORR of approximately 67%. RAD reduced bone resorption and increased bone formation; the latter has not been previously described with lenalidomide-based regimens. Furthermore, RAD reduced angiogenic cytokines and this supports the action of the regimen also through the disruption of the interactions between myeloma and stromal cells.

P18

WEEKLY CYBORD-DARA IS A SAFE AND EFFECTIVE UPFRONT TREATMENT FOR NEWLY DIAGNOSED MULTIPLE MYELOMA. PRELIMINARY RESULTS OF THE EARLY-PHASE 16-BCNI-001/CTRIAL-IE (ICORG) 16-02 STUDY

McEllistrim C.¹, Cahill M.R.², Murphy P.³, Mykytiv V.⁴, Quinn J.⁵, Bray A.⁶, Walsh J.¹, Lenihan E.⁴, Kenny T.³, Hirakata G.⁷, Parker I.⁷, Hernando A.⁷, O'Dwyer M.^{8,9}

¹University Hospital Galway, Galway, Ireland; ²Cork Cancer Research Centre (UCC), Cork, Ireland; ³Beaumont Hospital, Dublin, Ireland; ⁴Cork University Hospital, Cork, Ireland; ⁵Department of Haematology, Beaumont Hospital, Dublin 9, Ireland; ⁶Blood Cancer Network Ireland, Galway, Ireland; ⁷Cancer Trials Ireland, Dublin, Ireland; ⁸Department of Haematology, National University of Ireland Galway, Galway, Ireland; ⁹Department of Haematology, University

Hospital Galway, Galway, Ireland

Introduction: Daratumumab (Dara) is a human IgG1k monoclonal antibody licensed for second line use as monotherapy or in combination with either lenalidomide or bortezomib (Bor) plus dexamethasone (D) for patients who have received at least one prior therapy. There are no published data on front line use of Dara in combination regimens. CyBorD is a safe and effective induction regimen for patients with newly diagnosed MM eligible for transplantation. Up to 60% of patients achieve very good partial response (VGPR) or better following 4 cycles of induction (Reeder CB *et al.*, Blood 2010). Since our pre-clinical data showed enhanced antibody dependent cellular phagocytosis (ADCP) following Cyclophosphamide (Cy) exposure (Rigalou *et al.*, ASH 2016, Naicker *et al.* ASH 2017), we set out to explore the feasibility of combining Dara with weekly CyBorD in newly diagnosed transplant eligible MM patients. **Primary Objectives:** 1. To determine the Maximum Tolerated Dose (MTD) for cyclophosphamide and bortezomib that can be safely administered with DARA. 2. To evaluate the efficacy of CyBorD in combination with DARA in terms of the rate of complete response post autologous stem cell transplantation (ASCT). **Primary endpoints:** 1. Incidence of dose limiting toxicity (DLT) within the first cycle of combination at each dose level 2. Complete Response (CR) rate post ASCT. **Secondary endpoints:** safety, CR rates at the end of induction, consolidation and maintenance, best overall response, minimal residual disease (MRD) negative rate, progression-free survival, clinical benefit rate and overall survival. **Study Design:** this is an ongoing phase Ib, open-label, single arm, dose escalation study. his trial is registered at www.clinicaltrials.gov as NCT02955810. **Results:** Between December 2016 and June 2017 12 patients were enrolled using a 3+3 algorithm across 3 sites in Ireland. Here we report outcomes from the dose escalation cohort, a dose expansion cohort is still recruiting. Baseline demographic factors are outlined in Table 1. Twelve patients were accrued (3 female, 9 male) with a median age of 57.5 (Range 35-66). Gastrointestinal side effects secondary to CyBorD were the most common non-haematological adverse events (AE) [constipation (40%), diarrhoea (66%) and nausea(66%)]. The majority of these were ≤ grade 2. Adverse events of grade 3 severity or higher were lymphopenia, postoperative wound infection, urinary tract infection, hyponatraemia, back pain and bone pain (Table 2). Five serious adverse events (SAE) were reported but none related to the study treatment. No DLT occurred in any group. Early Response data is encouraging. Overall response rate (ORR) was 100%. Pre-transplant, 75% (n=9) achieved a VGPR or better, including 16.6% who achieved a CR. Of the three patients classed as having a partial response one had a very small monoclonal proteins in the Beta region which was difficult to quantify. Clinically it was felt that patient 7 was likely to have achieved a VGPR and had <5% plasma cells on C4D28 marrow. At subsequent assessments post transplant, all of these patients had achieved at least a VGPR. **Conclusion:** Weekly CyBorD Dara is a safe and well tolerated induction regimen. MTD/ RP2D is Cy 300 mg/m² and Bor 1.5 mg/m² in combination with Dara. Early analysis demonstrates promising efficacy comparable to other front line Dara containing regimens. CyBorD Dara could prove to be a safe, potent and cost effective treatment for newly diagnosed MM patients

Characteristic	n=12 %
Age	
Median (range)	57 (35-66)
Sex	
Male	3 (25)
Female	9 (75)
ISS	
I	12 (80)
II	3 (20)
III	0
Cytogenetic Profile	
t(4,14)	0
del17p	2
t(14,16)	0
Hyperdiploidy	7
1q gain	2
Completed 4 induction Cycles	15 (100%)

Table 1.

P19

DARATUMUMAB PLUS BORTEZOMIB, MELPHALAN, AND PREDNISONE (D-VMP) VERSUS BORTEZOMIB, MELPHALAN, AND PREDNISONE (VMP) IN NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM) PATIENTS (PTS) INELIGIBLE FOR TRANSPLANT: A PHASE 3 RANDOMIZED STUDY (ALCYONE)

Mateos M.V.¹, Dimopoulos M.A.², Cavo M.³, Suzuki K.⁴, Jakubowiak A.⁵, Knop S.⁶, Doyen C.⁷, Lucio P.⁸, Nagy Z.⁹, Kaplan P.¹⁰, Pour L.¹¹, Cook M.¹², Grosicki S.¹³, Crepaldi A.¹⁴, Liberati A.M.¹⁵, Campbell P.¹⁶, Shelekova T.¹⁷, Yoon S.S.¹⁸, Iosava G.¹⁹, Fujisaki T.²⁰, Garg M.²¹, Chiu C.²², Wang J.²³, Carson R.²², Crist W.²², Deraedt W.²⁴, Nguyen H.²³, Qi M.²², San-Miguel J.²⁵

¹University Hospital of Salamanca/IBSAL; ²National and Kapodistrian University of Athens; ³Institute of Hematology Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna; ⁴Japanese Red Cross Medical Center, Department of Hematology; ⁵University of Chicago Medical Center; ⁶Würzburg University Medical Center; ⁷Université catholique de Louvain, CHU UCL Namur; ⁸Champalimaud Centre for the Unknown; ⁹Semmelweis Egyetem; ¹⁰Dnepropetrovsk City Clinical Hospital #4; ¹¹University Hospital Brno; ¹²University Hospitals Birmingham NHS Trust; ¹³Department of Cancer Prevention, School of Public Health, Silesian Medical University in Katowice; ¹⁴Clinica de Tratamento E; ¹⁵Azienda Ospedaliera "Santa Maria, "; ¹⁶Andrew Love Cancer Centre; ¹⁷Clinic of Professional Pathology; ¹⁸Department of Internal Medicine, Seoul National University College of Medicine; ¹⁹LTD "Medinvent" Institute of Health; ²⁰Matsuyama Red Cross Hospital; ²¹Leicester Royal Infirmary – Haematology; ²²Janssen Research & Development; ²³Janssen Research & Development; ²⁴Janssen Research & Development; ²⁵Clinica Universidad de Navarra-CIMA, IDISNA, CIBERONC

Introduction: VMP is a standard of care (SOC) for transplant ineligible NDMM. Daratumumab (D), a human IgG anti-CD38 monoclonal antibody, significantly improves PFS and depth of response combined with SOC in relapsed/refractory MM. Treatment-naïve pts may benefit from adding D to SOC regimens. We report the results from the ALCYONE study of D + VMP in transplant ineligible NDMM. **Methods:** Pts ≥65 yrs or ineligible for high-dose chemotherapy with autologous stem-cell transplant were randomized 1:1 to VMP ± D. All pts received up to nine 6-week VMP cycles. V: 1.3 mg/m² SC Days 1, 4, 8, 11, 22, 25, 29, 32 (Cycle 1) and Days 1, 8, 22, 29 (Cycles 2-9); M: 9 mg/m² PO; P: 60 mg/m² PO Days 1-4 (Cycles 1-9). D 16 mg/kg IV was given QW for Cycle 1, Q3W for Cycles 2-9, and Q4W for Cycles 10+ (post VMP-treatment phase) until progression. The primary endpoint was PFS. Secondary endpoints included ORR, ≥VGPR rate, ≥CR rate, minimal residual disease (MRD)–negativity rate (10⁻⁵ threshold), OS, and safety. **Results:** Of 706 pts randomized (350 D-VMP; 356 VMP), median (range) age was 71 (40-93) y; 29.9% were ≥75 y. Of 616 pts evaluable for cytogenetic analysis, 84.1% and 15.9% were standard and high risk (del17p, t[14;16], and/or t[4;14]), respectively. At prespecified PFS analysis (231 events) on 12 June 2017, pts had received a median (range) of 12 (1-24) vs 9 (1-9) cycles of D-VMP vs VMP. At a median follow-up of 16.5 months, HR for PFS was 0.50 (95% CI, 0.38-0.65, P<0.0001), representing a 50% reduction in risk of progression or death with D-VMP. Median PFS was not reached vs 18.1 months for D-VMP vs VMP; 18-month PFS rate was 72% vs 50%, respectively. PFS treatment benefit of D-VMP vs VMP was consistent across all pre-specified subgroups, including age ≥75 y, ISS stage III, and high-risk cytogenetics. ORR (90.9% vs 73.9%), ≥VGPR (71.1% vs 49.7%), ≥CR (42.6% vs 24.4%) and MRD-negativity rate (22.3% vs 6.2%) were significantly higher for D-VMP vs VMP (all P<0.0001). OS data were immature after 93 deaths (45 vs 48 deaths for D-VMP vs VMP). Common (≥20%) treatment emergent adverse events (TEAE; D-VMP/VMP) were neutropenia (49.7%/52.5%), thrombocytopenia (48.8%/53.7%), anemia (28.0%/37.6%), peripheral sensory neuropathy (28.3%/34.2%), upper respiratory tract infection (26.3%/13.8%), diarrhea (23.7%/24.6%), pyrexia (23.1%/20.9%), and nausea (20.8%/21.5%). Common (≥10%) grade 3/4 TEAEs (D-VMP/VMP) were neutropenia (39.9%/38.7%), thrombocytopenia (34.4%/37.6%), anemia (15.9%/19.8%), and pneumonia (11.3%/4.0%). Only 1 pt in each arm discontinued due to pneumonia. Rates of grade 3/4 infections were 23.1% vs 14.7% and discontinuations due to infections were 0.9% vs 1.4% for D-VMP vs VMP. D-associated infusion-related reactions (27.7%) mostly were grade 1/2 (grade 3/4, 4.3%/0.6%) and most (92.7%) occurred during the first infusion. Tumor lysis syndrome occurred in <1% of pts in each arm. Second primary malignancy occurred in 2.3% vs 2.5% of pts in D-VMP vs VMP. **Conclusions:** The combination of D and VMP in transplant ineligible NDMM pts doubled PFS (HR 0.50) vs VMP, which was driven by more pts achieving deep responses, including significantly higher ≥CR and MRD-negativity rates. No new safety signals were observed. Three phase 3

studies have now demonstrated a consistent doubling of PFS and more than threefold increase in MRD-negativity rate with the combination of D and SOC regimens. These results support the use of D-VMP in transplant ineligible NDMM.

P20

ANALYSIS OF THE PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL IN ELDERLY PATIENTS (65 YEARS OLD) WITH MULTIPLE MYELOMA PATIENTS ELIGIBLE FOR AUTOLOGOUS STEM CELL TRANSPLANTATION.

Cejalvo M.J.¹, Rubio L.¹, Romero S.², Legarda M.¹, Jiménez M.¹, Perla A.², Jarque I.², Ribas P.¹, Arnao M.², Andreu R.², Domínguez E.², De la Rubia J.¹

¹Hospital Universitario Dr. Peset.; ²Hospital Universitario y Politécnico La Fe, Valencia, Spain

Background: In the novel agent era, front-line autologous hematopoietic stem cell transplantation (ASCT), has shown to prolong survival in patients with multiple myeloma (MM) in randomized clinical trials. However, most of these trials only included patients aged <65 years. Given that the median age at diagnosis is >65 years, it is important to know the potential role of ASCT in elderly patients with newly diagnosed MM (NDMM). Patients and **Methods:** We have analyzed the role of front-line ASCT as consolidation therapy in a series of 175 consecutive patients with NDMM from two Spanish institutions diagnosed between 2012 and 2016. For this study, patients were divided into three different cohorts: patients ≤65 years undergoing ASCT (cohort 1; N=117), patients >65 years undergoing ASCT (cohort 2; N=21), and patients >65 years not undergoing ASCT (cohort 3; N=37). The primary end-points were to assess progression-free survival (PFS) and overall survival (OS) in the 3 groups of patients. **Results:** Median (range) age at diagnosis was 58 (36-65), 67 (65-71), and 68 (65-71) in cohorts 1, 2, and 3, respectively. Other baseline characteristics at time of MM diagnosis were similar in the 3 cohorts, except for an increased incidence of chronic kidney disease in patients in cohort 3 (Table 1).

Characteristic	Cohort 1 (N=117)	Cohort 2 (N=21)	Cohort 3 (N=37)
Age, median, (range), years	58 (36-65)	67 (65-71)	68 (65-71)
Male, n (%)	68 (58)	13 (62)	26 (70)
ECOG performance status, n (%)			
0-1	71 (63)	6 (29)	10 (27)
2	14 (12)	9 (43)	9 (24)
ISS, n (%)			
1	32 (27)	3 (14)	3 (8)
2	30 (26)	7 (33)	6 (16)
3	37 (32)	6 (27)	13 (35)
Type of myeloma, n (%)			
IgG	53 (45)	9 (43)	14 (38)
IgA	32 (27)	4 (19)	5 (14)
IgM	4 (3)	0 (0)	0 (0)
Light chain	24 (21)	1 (5)	10 (24)
Other	2 (2)	3 (14)	2 (3.7)
Previous renal chronic disease, n (%)*	6 (5)	0 (0)	5 (14)
Presentation, n (%)			
-Renal impairment	26 (22)	5 (24)	14 (38)
-Hypercalcemia	13 (11)	5 (24)	3 (8)
-Anemia	59 (50)	8 (38)	13 (35)
-Bone pain	86 (74)	15 (71)	11 (30)
-Plasmacytomas	35 (30)	5 (24)	2 (5)

COHORT: 1: <65 years old eligible for ASCT; 2: 65-70 years old eligible for ASCT; 3: 65-70 years old not eligible for ASCT. *P<0.05; ISS: international staging system.

Table 1. Baseline characteristics.

Most patients in cohorts 1 and 2 received front-line MM therapy with different triplet regimens (71% and 52%, respectively), while patients in cohort 3 received induction therapy with two drug regimens based on IP or IMiDs (27% and 8%) or different triplet regimens (32%). Finally, there were no significant differences in terms of MM response at transplantation between patients in cohorts 1 and 2. Melphalan 200 was the most commonly administered conditioning regimen (57% and 67% of patients in cohort 1 and 2, re-

spectively) followed by the combination of busulfan and melphalan 36% and 33%, respectively). Transplant-related mortality was 3% and 0% in cohorts 1 and 2, respectively (Table 2).

	Cohort 1 (N=117)	Cohort 2 (N=21)	Cohort 3 (N=37)
Type of induction, n (%)			
Based on Bortezomib			
Doublets	30 (26)	7 (33)	10 (27)
Triplets	83 (71)	11 (52)	8 (22)
Based on IMiDs	-	1 (5)	2 (2)
Other	4 (3.5)	1 (5)	1 (3)
NA	-	1 (5)	15 (41)
Conditioning regimen			
MEL200	66 (57)	14 (67)	-
BUMEL	42 (36)	7 (33)	-
MEL140	6 (5)	0 (0)	-
Status at time of ASCT, n (%)			
ORR (\geq VGPR)	82 (70)	18 (85.7)	11 (29.7)
CR	55 (47)	10 (47.6)	6 (16.2)
VGPR	27 (23.1)	8 (38.1)	5 (13.5)
PR	30 (25.6)	1 (4.8)	3 (8.1)
SD	1 (1)	1 (4.8)	2 (5.4)
PD	1 (1)	0 (0)	10 (27)
NA	3 (2.6)	1 (4.8)	11 (29.7)
Response after ASCT, n (%)			
ORR (\geq VGPR)	90 (76.9)	18 (85.7)	-
CR	64 (54.7)	13 (61.9)	-
VGPR	26 (22.2)	5 (23.7)	-
PR	13 (11.1)	1 (4.8)	-
SD	2 (1.7)	0 (0)	-
PD	3 (2.6)	1 (4.8)	-
Transplant-related mortality	4 (3.4)	0 (0)	-
NA	5 (4.3)	1 (4.8)	-
Relapse after 1 st line, n (%)	31 (29)	8 (40)	15 (40)

COHORT: 1: <65 years old eligible for ASCT; 2: 65-70 years old eligible for ASCT; 3: 65-70 years old not eligible for ASCT.
ASCT: Autologous stem cell transplantation; ISS: international staging system; MEL200: Melphalan 200 mg/m²; BUMEL: Busulfan and melphalan; MEL140: Melphalan 140 mg/m²; ORR: overall response rate; CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease; NA: not available; IMiDs: immunomodulatory drugs.

Table 2. Results.

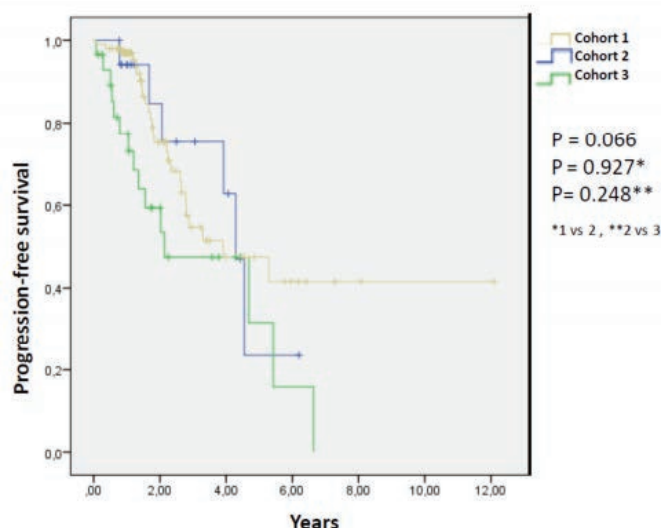


Figure 1. Progression-free survival as a function of treatment.

The median (range) follow-up period for the young group was 22 months (6-145) compared with 29 months (9-91) and 33 (2-96) months in cohorts 2 and 3, respectively. The median PFS at 7 years was 3.9 years (95% confidence interval [CI], 1.4-6.4) for patients in cohort 1, 4.2 (95% CI, 3.7-4.9), and 2.1 (95% CI, 0-4.6) for the other two groups of patients ($P = 0.06$) (Figure 1). The median OS at 8 years was 6.8 years (95% CI, 6.2-9.5) for the young group, not reached, and 4.8 (95% CI, 3.3-6.4) for patients in cohorts 2 and 3 ($P = 0.35$) (Figure 2). **Conclusion:** Our data suggest that front-line intensification with ASCT is a feasible, safe, and effective approach in NDMM patients up to 70 years of age.

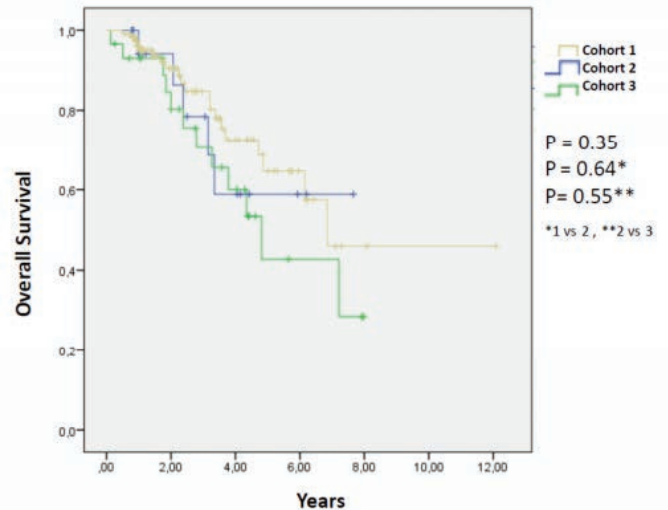


Figure 2. Overall survival as a function of treatment.

P21

ANALYSIS OF B LYMPHOCYTE SUBSETS IN MULTIPLE MYELOMA PATIENTS ACCORDING TO EUROCLASS TRIAL

Barilà G., Cinetto F., Liço A., Checuz L., Leoncin M., Trimarco V., Carraro S., Faccio M., Semenzato G., Zambello R.

Department of Medicine, Hematology and Clinical Immunology section, Padua University School of Medicine, Padua, Italy

Multiple Myeloma (MM) is a hematological malignancy characterized by the accumulation of pathological plasmacells (PC) in the bone marrow as a result of aberrations in B lymphocyte development. Secondary immunodeficiency due to impairment of the immune system is a typical feature of the disease. In particular, immunoparesis and hypogammaglobulinemia related to secondary immunodeficiency, represent well known risk factors for progression to symptomatic MM and infections, respectively. The aim of this study is to identify by EUROclass analysis different B lymphocyte subsets characterizing secondary immunodeficiency of MM patients and to compare this pattern to healthy donors and to patients with primary immunodeficiency as those affected by Common Variable Immunodeficiency (CVID). Flow cytometry for CD19, CD27, CD38, CD21, IgM and IgD antigens was performed in peripheral blood of patients with newly diagnosed MM, patients with CVID and healthy donors. According to EuroClass trial, B naïve (IgM+/IgD+/CD27-), B marginal (IgM+/IgD+/CD27+), B switched memory (IgM-/IgD+/CD27-), B activated (CD21low/CD38low), B transitional (IgM-high/CD38high) and B plasmoblast (CD38high/IgM-) subsets were recognized. A cohort of 31 patients affected by newly diagnosed symptomatic MM was included in this study. ISS Stage III and high risk cytogenetic were present in 6/31 (19%) and 9/31 (29%) patients respectively. In these patients, EUROclass analysis was performed with 23 (74%) resulting B+ (CD19+ lymphocytes within total leucocytes >1%) while 8 (26%) B- (CD19+ lymphocytes within total leucocytes <1%). B+ MM patients were compared to a cohort of 18 healthy donors. Although no significant differences in B lymphocyte percentages were found between the two cohorts ($3.69 \pm 0.74\%$ vs $3.67 \pm 0.28\%$, $p = 0.977$), significant differences among B lymphocyte subsets were detected. MM patients were characterized by significantly higher percentages of B marginal (14.85 ± 1.8 vs 5.72 ± 1.087 , $p = 0.0002$), B memory (21.51 ± 2.29 vs 2.029 ± 0.55 , $p < 0.0001$) and B activated (7.22 ± 0.78 vs

1.74±0.36, $p<0.0001$) and by a significantly lower percentage of B naïve (54.7±3.63 vs 67.11±2.98, $p=0.152$) and B transitional (0.23±0.034 vs 1.38±0.16, $p<0.0001$); no significant differences were found in B plasmoblast percentages (1.24±0.38 vs 0.79±0.41, $p=0.436$). The same MM patients were compared to a cohort of 19 patients affected by CVID. Of notice, MM patients presented significantly higher B marginal (14.85±1.8 vs 8.17±2.5, $p=0.0267$), B memory (21.51±2.29 vs 2.029±0.55, $p<0.0001$) and B activated (7.22±0.78 vs 4.59±1.61, $p=0.1278$) and significantly lower B naïve (54.7±3.63 vs 86.28±2.9, $p<0.0001$), B transitional (0.23±0.034 vs 1.32±0.35, $p<0.0001$) and B plasmoblast 1.24±0.38 vs 4.85±1.17, $p=0.0029$). By flow analysis, different subsets of peripheral blood B lymphocyte can be recognized in symptomatic MM patients. The distribution of these subsets is significantly different from healthy people, resulting in a higher prevalence of B marginal, B memory and B activated in MM patients. More interesting, the B lymphocyte distribution found in MM is different from CVID patients, meaning that in these two diseases, the mechanisms underlying hypogammaglobulinemia are different. Further studies are needed investigating whether this B lymphocyte pattern is predictive of response to induction therapy and whether treatment can modify the MM B lymphocyte distribution consensually to immunoglobulin improvement.

P22

COMPARISON OF TWO MOBILIZATION REGIMENS FOR NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS

Marigliò E., Lombardi L., Vozella F., Fazio F., Piciocchi A., Foà R., Petrucci M.T.

Hematology, Department of Cellular Biotechnologies and Hematology, "Sapienza" University, Italy

Introduction: Induction therapy with novel agents followed by autologous stem cell transplantation (ASCT) is the worldwide gold standard for frontline treatment of younger patients with multiple myeloma (MM). Notwithstanding, a variable proportion of these patients fail to mobilize CD34+ peripheral blood stem cells (PBSC) at all or to collect an adequate number for a safe ASCT or sufficient for tandem or salvage procedures ("poor mobilizer"). The use of lenalidomide and hematological toxicity developed during induction were taken into account as possible factors associated with poor mobilization. The use of Plerixafor with G-CSF for PBSC mobilization significantly improves the chances of a successful mobilization. **Patients and Methods:** We report the unicentric experience of the Department of Cellular Biotechnologies and Hematology, "Sapienza" University, Rome in 48 patients (pts) with newly diagnosed MM treated as induction therapy with Bortezomib, Thalidomide, dexamethasone (VTd; 33 pts 68.7%) or Carfilzomib, Lenalidomide-dexamethasone (KRd; 15 pts 31.3%). The median age was 55.4 years (range 48 - 61), 28 men (58.3%) and 20 women (41.7%). In all cases the mobilizing regimen was cyclophosphamide (3 g/m²) associated to G-CSF (10 mcg/Kg). International Staging System (ISS) was I-II in 25 (52.1%), 19 (39.6%) and 4 (8.3%) patients respectively. After induction, 7 pts (14.6%) achieved complete response (CR), 27 pts (56.3%) achieved a very good partial response (VGPR), and 14 (29.2%) partial response (PR). Filgrastim was used as G-CSF in 38 pts (79.2%) and Lenograstim in 10 pts (20.8%). The use of Plerixafor was necessary in 7 cases (46.7%) for patients treated with KRd induction regimen, in 3 cases (9 %) for VTd. **Results:** The use of Plerixafor (yes or not) has been compared with the following variables: sex, age, ISS, type of G-CSF, Induction Regimen, type of monoclonal component, time between mobilization date and therapy end. In univariate analysis type of induction regimen was the only statistically significant factor (KRd 7 cases used Plerixafor vs 3 VTd); $p=0.003$. CD34+ cell median final collection ($\times 10^6$ /Kg) was 8.60±10⁶/Kg (range 4.40-17) for KRd and 10.38±10⁶/Kg (range 1.49-18.8) for VTd respectively; the difference is statistically significant, $p=0.047$. **Conclusions:** Our data though revealing a possible negative effect of lenalidomide-based regimens on PBSC mobilization used also with carfilzomib association. Lenalidomide is myelosuppressive and alters the stromal milieu thereby suppressing stem cell mobilization. Plerixafor with G-CSF has been shown to improve successful stem cell mobilization rates in patients receiving Lenalidomide based induction therapy.

P23

EFFECT OF NOVEL AGENTS ON THE CLINICAL OUTCOMES AND THE RISK OF EARLY DEATH OF NEWLY DIAGNOSED SYMPTOMATIC MULTIPLE MYELOMA: A SINGLE CENTRE RETROSPECTIVE ANALYSIS

Galli M.¹, Paris L.¹, Pavoni C.¹, Delaini F.¹, Rambaldi A.^{1,2}

¹Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII,

²Department of Oncology and Hematology, Università Statale di Milano, Italy

Introduction and aim: Several clinical trials have shown that the incorporation of novel agents (i.e., proteasome inhibitor, Bortezomib and immunomodulatory drugs, Thalidomide and Lenalidomide) in the treatment of newly diagnosed symptomatic multiple myeloma (MM) patients improves their time to first response and survival outcomes. Nevertheless, some patients still die within 90 days (early death, ED) from starting treatment. Thus, we investigated the effect of novel agents-containing first line treatments on the risk of ED, overall survival (OS) and progression-free survival (PFS) of MM patients. **Study design:** Retrospective analysis of a cohort of 991 newly diagnosed symptomatic MM patients consecutively treated at a single Institution from 1997 until 2015 at the Hematology Division of the Ospedale Papa Giovanni XXIII (formerly, Ospedali Riuniti) of Bergamo, Italy.

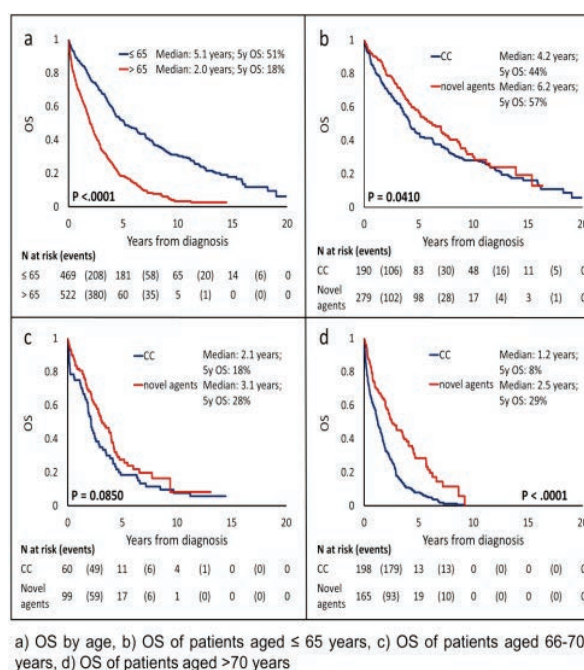


Figure 1. Overall survival by age and type of first-line treatment.

Results: During the entire period of analysis (18 years), 708 of the 991 treated MM patients (71.4%) died. They were 374 men and 334 women, aged 25-94 years (median 68 years). Durie and Salmon clinical stages were: I (n=75), II (n=111), III (n=479), unknown (n=43). A/B stages were: A (n=518), B (n=147), unknown (n=43). Treatments were as follows: conventional chemotherapy (CC) (n=255), CC + autotransplantation (ASCT) (n=150), novel agents (n=181), novel agents + ASCT (n=122). Ninety-two patients (13%) experienced an early death (ED cohort) and the other 616 patients died > 90 days (late death, LD, cohort) (87%) from starting first-line treatment for MM. Patients in the ED cohort were significantly older ($p=0.0001$, Odds Ratio, OR, 1.04, 95% Confidence Interval, CI, 1.01-1.06 and $p=0.0088$; OR 1.03; 95% CI 1.01-1.06, by univariate and multivariate analysis, respectively), had more commonly plasma cell leukemia ($p=0.0024$, OR 7.02, 95% CI 1.99-24.8 and $p=0.0252$, OR 7.02; 95% CI 1.27-38.7, by univariate and multivariate analysis, respectively) and stage B MM ($p<0.0001$, OR 3.21, 95% CI 1.97-5.21 and $p<0.0001$, OR 3.21; 95% CI 1.96-5.28, by univariate and multivariate analysis, respectively) compared to patients in the LD cohort. In contrast, incorporation of at least a novel agent in the first line treatment resulted in a significant reduction of ED. This beneficial effect was only seen in patients not enrolled in ASCT programs, in whom the incorporation of novel drugs reduced the prevalence of ED from 22% to 9% ($p<0.001$, OR 0.37, 95% CI 0.20-0.69 and $p=0.009$, OR 0.42;

95% CI 0.22-0.81, by univariate and multivariate analysis, respectively). The prevalence of ED of patients enrolled in ASCT programs was 7% irrespective of inclusion of novel agents in induction. Progression of MM was the cause of all ED events. The median OS and PFS of the 991 patients were 3.1 and 1.8 years, respectively. Patients aged < 65 years had a median OS of 5.1 years and a median PFS of 2.7 years, which were statistically significantly longer than those of patients aged > 65 years (median OS 2 years, $p<0.0001$; median PFS 1.2 years, $p<0.0001$). When data were analyzed according to the type of first-line treatment, incorporation of a novel agent improved the OS irrespective of age and the PFS of patients aged > 70 years (Figure 1). Conclusions: Administration of first line regimens containing at least a novel agent significantly improved the outcomes and reduced the ED rate of patients with MM. Particularly, this improved survival was beneficial in patients not enrolled in ASCT programs.

P24

CYTOGENETIC HETEROGENEITY OF HYPERDIPLOID MULTIPLE MYELOMA IMPACTS PATIENT'S OVERALL SURVIVAL

Barilà G.¹, Bonaldi L.², Liço A.¹, Martines A.², Macri N.², Nalio S.², Leoncin M.¹, Checuz L.¹, Carrino M.¹, Canovas Nunes S.¹, Manni S.¹, Piazza F.¹, Semenzato G.¹, Zambello R.¹

¹Dept of Medicine, Hematology and Clinical Immunology section, Padua University School of Medicine, Padua; Immunology and Molecular Oncology Unit, Veneto Institute of Oncology, IOV-IRCCS- Padua, Italy

Multiple myeloma (MM) represents the second most common hematological malignancy characterized by the clonal proliferation of plasma cells in the bone marrow. In MM, primary events include chromosome translocations involving the immunoglobulin heavy chain (IgH) locus or hyperdiploidy. Hyperdiploid (HRD) MM represents at least half of MM cases and is generally associated to favourable outcome. This subset of MM is characterized by trisomies involving odd chromosomes, but IgH translocation, 17p deletion (17p-) or 1q gain (+1q) can be found with lower frequencies. The aim of this study was to analyse the cytogenetic aberrations of our MM patient's cohort using both conventional karyotyping (CK) and Fluorescent *In situ* Hybridization (FISH) and to investigate the impact of some aberrations on overall survival (OS) in specific subgroups. Bone marrow of 67 patients affected by newly diagnosed MM was studied by CK and by FISH for high risk cytogenetic aberrations including t(4;14), t(14;16), 17p13 deletion and 1q21 gain. Patient's characteristics including ISS stage, symptoms at diagnosis, type of treatment and OS were collected. Based on the cytogenetic clone, 50 patients of our cohort (75%) were classified as hyperdiploid (HRD-MM) (47-57 chromosomes) while 17 patients (25%) were hypodiploid (35-45 chromosomes). All patients received treatment with novel agents, including bortezomib (98%), lenalidomide (72%) or both (68%). Although hypodiploid patients were characterized by more aggressive disease with higher frequency of ISS III (59% vs 36%) and significant higher frequency of renal injury and hypercalcemia at diagnosis (41% vs 14%, $p=0.03$ and 30% vs 6%, $p=0.02$, respectively), no significant difference in OS was found between the two subsets (42 vs 53 months, $p=0.81$).

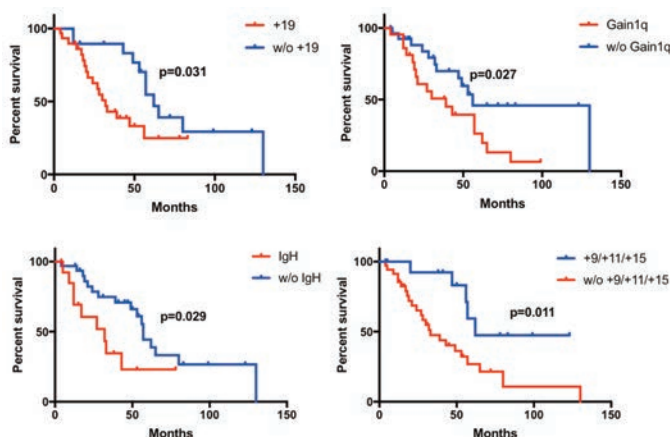


Figure 1. Overall survival by age and type of first-line treatment.

Among HRD-MM patients, trisomies of chromosomes 3 (60%), 5 (56%), 9 (72%), 11 (68%), 15 (54%) and 19 (62%) were the most represented. High risk chromosomal changes were detected in 27/50 (54%) cases, including 22 (44%) with +1q, one with t(4;14) and 8 (16%) with 17p-. Moreover, 14 (28%) patients displayed an IgH rearrangement. In HDR-MM cohort, major features associated to decreased OS were trisomy 19 (32 vs 62 months, $p=0.031$), +1q (39 vs 56 months, $p=0.027$) and IgH rearrangement (32 vs 57 months, $p=0.029$), while concomitant trisomy of 9, 11 and 15 chromosomes was associated to a better outcome (62 vs 33 months, $p=0.011$). Interestingly, karyotypes showing the coexistence of trisomy 9, 11 and 15 present an inferior number of structural rearrangements (≤ 2) than cases where the three numerical changes are absent ($p=0.0289$). Patients with 17p- displayed reduced OS although not statistically significant (40 vs 56 months, $p=0.34$). In our cohort of patients, cytogenetically defined HRD MM represents a heterogeneous group of MM where numerical changes coexist with structural aberrations. Within this subset, patients with IgH translocations and high risk cytogenetic features like 17p- and +1q are also present and these abnormalities are associated to a reduced OS, even in the era of novel agents. Interestingly, also the type of trisomy has clinical relevance, with isolated 19 trisomy associated to a worse prognosis whereas concomitant 9, 11 and 15 trisomy correlated to a better outcome, identifying probably the true hyperdiploid clone. Classical cytogenetics in combination with FISH may give a broader picture of complexity of HRD MM and a better definition of genetic subtypes.

P25

SMOLDERING MYELOMA APPROACH BASED ON RISK ADAPTED THERAPEUTIC STRATEGY. REPORT OF A RETROSPECTIVE REAL-LIFE STUDY PRE AND POST IMWG UPDATE

Torti L., Morelli A., Bacci F., Di Bartolomeo P.

Clinical Hematology, Department of Hematology, Transfusion Medicine and Biotechnology, "Spirito Santo" Civic Hospital, Pescara; Section of Hematopathology, Department of Hematology and Oncological Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Italy

Smoldering myeloma is a heterogeneous clinical-entity where a watch-and-wait-approach has been the standard of care up to now. Recently, it has been demonstrated that a subset of high-risk cases can benefit from early-treatment. IMWG revised diagnostic-criteria adding three markers as MDE, allowing earlier intervention. We aimed to study diagnostic-workup and prognostic-factors predicting progression. We also focus on role of early -treatment in this setting. We retrospectively reviewed 134 smoldering -myeloma - patients diagnosed from 1998 to 2016 in order to assess risk-profile and evolution in symptomatic-myeloma. Our aim was to define risk-factors and to organize an effective-followup-strategy. We also tried to understand when is right-time to start therapy comparing old-CRAB with new-MDE-events. We evaluated 134 SMM-patients consecutively diagnosed at our centre in the median -time of 18 years (median followup 13 years, range 2-19). We have found 58 low-risk SMM, 45 high-risk-SMM and 31-ultrahigh-risk-SMM in a retrospective single-center analysis. 58 patients have evolved in myeloma requiring treatment and respectively: 25/31 of the ultra-high-risk-group progressed in a medium-time-span of 11 months (range 6-39) Figure 1, 23/45 of the high-risk-group ended in symptomatic myeloma with a median time of 32 months (range 24-72) from diagnosis and only 10/58 of the low-risk-series after 94 median-months (range 39-140). If the low-risk evolved-patients an important risk-factor for evolution was the amount of monoclonal-protein over time: most of patients evolved (8/10) have shown an evolving type SMM. In the high-risk-patients the most powerful predictive-factors of progression were an unfavorable cytogenetic-picture (17 patients with a prevalence of amplification of 1q in 11 patients) Figure 2, focal lesions in MRI or PETCT (17 and 15 patients) (Figure 2) and LDH-values (high in 13 patients). Among MDEs the most meaningful biomarker was FLCratio >100 (21/31 patients) followed by MRI-lesions (7/31 patients) and lastly by bone-marrow-plasma cell involvement greater than 60% (3/31 patients). Between ultrahigh risk SMM 21 were diagnosed before 2014 IMWG-update through a retrospective analysis and 10 after. Of the first group 18 patients have evolved in MM requiring therapy, median time of 11 months (Fig. 3). Conversely in the second-group not all patients started therapy. In fact 3 young patients were not treated until now and continued a close-observation with a monthly-followup. They presented stable-monoclonal-protein and laboratory-profile, excellent clinical-condition. They presented only one slim-CRAB for at least 9 months (respectively plasma-cell-involvement >60% and in 2 patients FLCratio >100). Here earlier-treatment could not be beneficial but might instead results in greater toxicity. The other 7 presented deteriora-

tion of clinical-conditions with at least two-slimCRAB(respectively FLC ratio >100 and lesions on MRI)not preexisting. They showed an evolving-type-SMM. Biological-behavior in this subgroup was very aggressive and they started conventional treatment. They are under therapy with a good -disease-control. Clinical-judgement must help physicians in making decisions. Risk of progression of SMM is not uniform and several-markers as described here (cytogenetic evaluation, evolving type, lesions on advanced imaging, kind of paraprotein Figure 4, LDH-levels Figure 5) are usefull in clinical-practice to predict evolution. In the future novel biomarkers will be available to plan followup as well as to identify group benefiting of early-treatment.

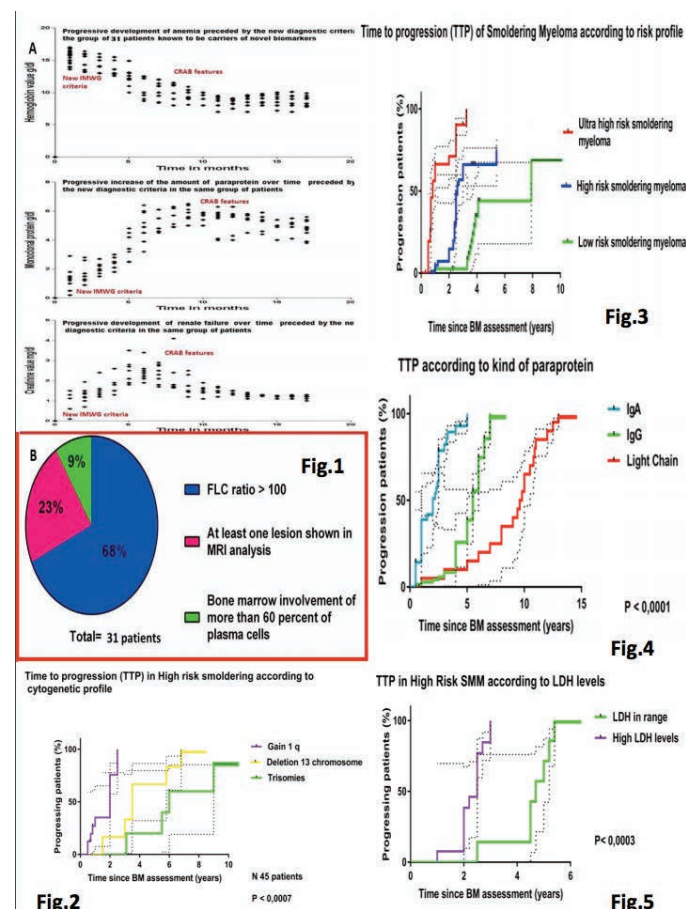


Figure 1.

P26

COMPARISON OF RADIODIAGNOSTIC METHODS (CONVENTIONAL RADIOGRAPHY, LOW-DOSE COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING) WITH SELECTED MARKERS OF BONE METABOLISM AND BONE MARROW MICROENVIRONMENT

Krhovska P.¹, Hermanova Z.², Hrbek J.³, Herman M.³, Petrova P.⁴, Zapletalova J.⁵, Pika T.¹, Bacovsky J.¹, Minarik J.¹

¹Departement of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc; ²Departement of Immunology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc; ³Departement of Radiology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc; ⁴Departement of Clinical Biochemistry, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc; ⁵Departement of Medical Biophysics, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic

Objective: Comparison of radiodiagnostic methods, conventional radiography (X-ray), low-dose computed tomography (LD-CT) and magnetic resonance imaging (MRI) with selected markers of bone metabolism and bone marrow microenvironment in patients with multiple myeloma (MM). Mate-

rial and **Methods:** We prospectively examined 81 patients with newly diagnosed MM. All patients were examined by X-ray, MRI and LD-CT. Following parameters of bone marrow microenvironment derived from bone marrow were assessed: osteoprotegerin (OPG), macrophage inflammatory protein 1 (MIP-1), receptor-activated nuclear factor- κ B (RANK) and its ligand (RANKL), Annexin A2, Activin A, tartrate-resistant acid phosphatase (TRAP), Dickkopf-1 protein (DKK-1), Runt-related transcription factor 2 (Runx2) and Matrix Metalloproteinase-9 (MMP-9). For statistics we used Spearman's correlation analysis and a Kruskal-Wallis test with a post-hoc test by Dunn, at $p < 0,05$. **Results:** We found a positive correlation between the extent of osteolytic involvement on LD-CT and MIP-1 ($k = 0,306$, $p = 0,035$). For other parameters the correlation was not statistically significant. **Conclusion.** Indicators of bone marrow microenvironment have a potential to improve the understanding of biological processes in MBD. MIP-1 is a promising parameter in the assessment of the MBD's extent, still, most of the parameters appear to be independent of the extent of osteolytic involvement and rather display the actual activity of osteoresorption. Supported by the IGA-LF-2018-001

P27

RESULTS OF TRANSPLANT-INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA AFTER INCORPORATING BORTEZOMIB SUBCUTANEOUS IN CLINICAL PRACTICE. EXPERIENCE OF ONE CENTER

Garcia-Guiñón A., Seres Y., Marco V., Luaña A., Iserte L., Rivero E., Garcia-Cerecedo T.

Department of Hematology, Hospital Universitari Arnau de Vilanova, Lleida, Spain

Introduction: Bortezomib combined with melphalan-prednisone (VMP) is a standard treatment for transplant-ineligible (TNE) patients (pts) with newly diagnosed multiple myeloma (NDMM). Phase III VISTA trial allowed the approval of the scheme given the benefit in terms of progression free and overall survival. Unfortunately, a large group of patients require adjustment of the scheme due to toxicity and it is well known that the results of this scheme are associated with the cumulative dose of bortezomib received. Subsequently, the subcutaneous (SC) administration of bortezomib with less toxicity has allowed to improve its tolerance. We report the results of TNE patients with NDMM treated in our center after incorporation of SC bortezomib in clinical practice. **Patients and Methods:** We analyzed the results in terms of response and survival (progression free survival (PFS) and overall survival (OS)) of TNE patients with NDMM diagnosed in our centre between 2013 and 2016. Secondly, we have analyzed the impact of accumulated dose in relation to having received 9 cycles of VMP regimen. The standard treatment in our center was the VMP scheme (VISTA scheme); some patients received bortezomib-dexamethasone (VD) for presenting acute renal insufficiency related to myeloma and poor ECOG; and finally, other patients received palliative treatment (PT) including melphalan-prednisone or cyclophosphamide-prednisone by physician's decision. **Results:** Fifty-seven patients (pts) were included. Median age was 77 years (70-88), 28 (49%) were male. Myeloma subtypes were: 51% IgG, 32% IgA, 17% Bence-Jones. Nine per cent were ISS1, 39% ISS2 and 52% ISS3. Regimens of treatment were: 26 pts (46%) received VMP, 17 pts (30%) VD and 14 pts (24%) PT. Patients with PT not included in analysis. Overall response (\geq PR) rates (ORR) were: 62% VMP and 35% VD. Complete response (CR) rate were 27% and 18% in VMP and VD, respectively. After a median follow-up of 20 months, progression free survival (PFS) were 15,8 months and 8,7 months and overall survival (OS) were 46,8 months and 15,2 months in VMP and VD treatment, respectively. Eleven pts (4 pts (15%) in VMP group, 7 pts (41%) in VD group) died within 2 months after the start of treatment due to clinical deterioration (6 pts), myeloma related complications (infection: 2 pts, hemorrhage: 2 pts) or treatment toxicity (paralytic ileus: 1 pt). Thirty-two pts (74%) with a follow-up longer than 2 months received VMP (22 pts) and VD (10 pts). In these patients, ORR was 77% (CR: 32%) and 70% (CR: 30%) in VMP and VD treatments, respectively. PFS were 16,1 months and 15,3 months and OS were not reached and 35 months in VMP and VD treatment, respectively. Eleven of 22 pts (50%) treated with VMP regimen received less than 9 cycles due to toxicity (peripheral neuropathy (n=3, 13,5%), hematological (n=3; 13,5%), asthenia (n=2, 9%), cutaneous (n=2, 9%), pulmonary hypertension (n=1, 4,5%)). ORR, PFS and OS were 81% (CR 55%), 27,8 months and not reached in patients received 9 cycles of MPV and 64% (CR 9%), 12,6 months and 47,7 months in patients received less than 9 cycles of MPV, respectively. **Conclusion:** The SC bortezomib has allowed to improve

the tolerance of the drug allowing a greater number of patients to receive an optimal treatment, especially in older patients. Anyway there is a significant number of patients that show toxicity limiting the applicability of the schemas and associate worse results.

P28

A RARE CASE OF IGM-MULTIPLE MYELOMA

Rizzi R.¹, Mestice A.¹, Ingravalle G.², Ranieri P.³, Vitucci A.¹, Mallano S.¹, Urbano M.¹, Albano F.¹, Curci P.¹, Specchia G.¹

¹Department of Emergency and Organ Transplantation-Hematology Section, ²Department of Emergency and Organ Transplantation-Pathology Section, ³Department of Clinical Pathology, University of Bari Medical School, Italy

IgM-Multiple Myeloma (MM) is rare, accounting for 0.5-1% of all MM subtypes. Although it may share clinical manifestations with Waldenström's macroglobulinemia (WM), pathological features, prognosis, and treatment of the two diseases are divergent. Extended bone marrow (BM) cell immunophenotyping by flow cytometry and/or immunohistochemistry, and search for molecular characteristics result helpful to diagnose IgM-MM, and discriminate between IgM-MM and WM. Consistently, distinction between IgM-plasma cell MGUS and IgM-lymphoid/lymphoplasmacytic MGUS can be made usually by morphology, according to the most recent WHO classification. Here, we report on a 47 year-old female patient who was referred recently with anemia, new onset of headache, and easy bruising. She had been followed elsewhere because of an IgM λ -MGUS diagnosed in 2006, when bone marrow (BM) biopsy was described with <10% interstitial infiltration composed of predominantly λ + plasma cells, and few CD20+ lymphocytes. Eleven years later, re-assessment workup revealed among others: haemoglobin 8.4 g/dl, serum IgM paraprotein spike 5.68 g/dl, increase of total IgM from the initial level of 1.1 to 66.2 g/dl (0.40-2.30), free light chain (FLC)- λ 105.34 mg/L (5.71-26.30), FLC κ/λ ratio 0.05 (0.26-1.65), total proteins 10.9 g/dl (6.4-8.2), immunoparesis, λ -Bence-Jones proteinuria, β 2-microglobulin 3.36 mg/L (1.09-2.53). In addition prolonged aPTT ratio 1.42 (<1.20), in presence of low levels of vonWillebrand (vW) Ag 31% (60-150), vW activity 35% (60-150) and factor VIII 30% (60-120), was found consistently with the diagnosis of acquired low-level vW disease (AVWD). Low-dose whole-body CT and 18F-FDG PET-CT demonstrated neither lytic skeletal lesions nor splenomegaly and/or adenopathy. At this time, BM biopsy showed diffuse infiltration (80%) with λ -restricted plasma cells alone. Peripheral blood (PB) film showed rouleaux, whereas no retinal vessel engorgement was seen with funduscopy. Flow cytometry studies were performed on BM aspirate and PB. B-cells, identified on the basis of side-scatter characteristics and CD19 expression, were present in low numbers (0.8% in BM and 1.5% in PB); they were polyclonal with respect to surface light-chain expression and lacked any abnormal expression of all the evaluated lymphocyte-associated markers; plasma cells, identified on the basis of CD38 and CD138 expression, were present in BM (20%) as well as in PB (0.02%); the absence of CD45, CD5, CD10, CD19, CD20, CD56, CD117 was detected whereas CD43, CD200, cytoplasmic λ -chains and, partially, CD81 were positive. Besides, MM diagnosis was further supported by immunohistochemistry demonstrating cyclin-D1 expression, and by FISH analysis of immunoselected BM plasma cells, identifying deletion of 13q14 (94%), t(11;14) (q13;q32) (90%), and amplification of 1q21 (70%). AS-PCR was performed on unselected BM aspirate to explore the presence of MYD88 L265 mutation with negative results. In conclusion, in our patient on long-term follow-up for her IgM λ -MGUS, progression to symptomatic IgM λ -MM, presenting with anemia and AVWD, occurred. The diagnosis of IgM-plasma cell neoplasm relies in particular on clear BM findings, consisting of massive clonal infiltration with pure plasma cell morphology, and t(11;14) demonstrated by FISH. Of note, the morphological changes found at baseline BM biopsy favour a retrospective diagnosis of "IgM λ -plasma cell MGUS" progressed to MM over 11 years..

P29

THALIDOMIDE S DOSING WITHIN VTD INDUCTION SCHEME DOES NOT INFLUENCE IN THE PRETRASPLANT EFFICACY IN PATIENTS WITH NEW DIAGNOSIS OF MULTIPLE MYELOMA

Cabrera Ruiz F.J., González Fernández A., Moreno Carrasco G., Revelles Peñas M., García Fortes M., Ruiz Arredondo J.J., García Sánchez R.

Hospital Universitario Virgen de la Victoria, Málaga, Spain

Introduction. The induction treatment with VTD scheme (bortezomib, thalidomide and dexamethasone) represents the standard of treatment for patients with new diagnosis of multiple myeloma (MM) that be candidates for autologous hematopoietic stem cell transplantation (TASPE). Peripheral neuropathy is a side effect secondary to bortezomib and thalidomide, which is sometimes limiting when it comes to reaching full doses of one or the other drug or both. **Objectives.** To analyze if the administered dose of thalidomide in VTD induction scheme influences about the efficacy of the treatment before the TASPE. **Materials and Methods.** We included 35 patients with new diagnosis of MM candidates for TASPE who received VTD induction scheme from July 2011 to February 2017. The induction treatment consisted in the administration of 6 VTD cycles (bortezomib SC, 1.3 mg / m² days 1, 4, 8, 11, thalidomide VO, 50 mg / day during the first 15 days with dose escalation up to 200 mg / day if the patient tolerated it, associated with dexamethasone 40 mg / day days 1-4 and 9-12) every 28 days. The response rate was evaluated according to the IMWG criteria and the adverse effects according to the NCI-CTCAE-4.0 scale. **Results.** Of the 35 patients included, 77% of them completed at least the 6 planned cycles with a median number of cycles received of 6 (1-7). The median cumulative dose of bortezomib was 50.4 mg and the median dose of thalidomide administered was 100 mg / day. As for thalidomide, the maximum tolerated dose was 50 mg / day in 9 patients (26%), 100 mg / day in 16 patients (46%), 150 mg / day in 5 patients and 200 mg / day in another five. In 31% of cases, the dose of dexamethasone was reduced to 20 mg / day. After the induction treatment, 89% obtained a response equal to or higher than partial response. Of the 22 patients who have consolidated with TAPH, 86% reached a response equal to or greater than very good partial response. Regarding the adverse effects, 24 patients (69%) presented non-haematological toxicity, with peripheral neuropathy being the most frequent cause, which was observed in 18 patients (51%), with 9% grade 3-4. We analyzed the response rate according to the dose of thalidomide received without finding statistically significant differences, as with the progression-free survival and overall survival, no differences were found either. **Conclusions.** The dose level of thalidomide received does not seem to influence in the efficacy of the induction treatment with VTD scheme. The maximum tolerated dose of thalidomide should be administered in order to minimize the neurological toxicity that sometimes leads to serious consequences for the patient.

P30

PATIENTS WITH MULTIPLE MYELOMA NOT CANDIDATES FOR TRANSPLANTATION: REAL WORLD DATA

Sánchez-Raga J.M., Pérez-Montaña A., Beltrán N., Ros T., Toledo N., Sampol A.

Hematology and Hemotherapy Department, Hospital Universitari Son Espases, Fundació Institut d'Investigació Sanitària Illes Balears, Spain

Objectives. The aim of the study is to perform a retrospective descriptive analysis of the general demographic characteristics of patients diagnosed with multiple myeloma who are not candidates for transplantation and to know the response results, progression-free survival and follow-up losses before relapse or progression, according to the therapeutic scheme used. **Methods.** For the collection of data we have reviewed the computerized clinical history of the patients, the laboratory data (Gestlab®), as well as the chemotherapy treatments (Farmis®). We use SPSS statistics V18 to analyze our data. We included all patients diagnosed of Myeloma not candidates for autologous transplantation between 2012 and 2017. **Results.** 37 patients (54% women) were diagnosed with multiple myeloma and were not considered candidates for transplantation. The median age was 77 years (range of 68-88 years). In their majority 92% presented a 0-2 performance status (ECOG) and 89% presented some degree of renal failure at the time of diagnosis. 54.5% of patients were IgG type, 21.6% IgA, 16% Bence-Jones and 2.7% IgM type. The risk stratification according to the International Staging System showed that 77% were in the high risk group (ISS III). The treatments

received were: 12 Bortezomib-Melphalan-Prednisone (VMP) scheme, 11 Lenalidomide-Dexamethasone (RD), 10 Bortezomib-Dexamethasone (VD), 2 sequential VMP-RD scheme, 1 Bortezomib in monotherapy and 1 Melphalan-Prednisone. The demographic characteristics of the groups were not homogeneous, with younger patients included in the VMP-RD clinical trial and older patients in the Lenalidomide-dexamethasone group. In addition, the patients in the Bortezomib-Dexamethasone group had a greater degree of renal failure. The number of cycles received was significantly lower in the VMP and Bortezomib-Dexamethasone group. The Overall Response Rate obtained was: 58.3% with Bortezomib-Melphalan-Prednisone, 88.8% with Lenalidomide-Dexamethasone, 100% with VMP-RD and 60% with VMP. The best PFS achieved was in the group VMP-RD, although the Lenalidomide-Dexamethasone group has not yet been reached. In all groups (except for Lenalidomide-dexamethasone) there was a loss of follow-up before starting the second line of 50% of the patients, including 8 deaths. **Conclusions.** Our results are similar to those reported in the literature. It is a very heterogeneous patient population who can be offered different therapeutic options. More studies are needed to better categorize these patients and be able to offer them the best tailored treatment.

P31

BORTEZOMIB-CYCLOPHOSPHAMIDE-DEXAMETHASONE AS INDUCTION THERAPY FOR TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA PATIENTS IN A SPANISH CENTRE

Solé M., Zapata R., Palma A., Ruiz M.A., Gil E., Rodríguez J.N., Domínguez J.F., Gómez K., Ramírez S.

Department of Hematology and Hemotherapy, Hospital Juan Ramón Jiménez, Huelva, Spain

Background: Multiple myeloma (MM) is the second most common hematologic cancer accounting 10% of hematologic malignances. Despite of the incorporation of novel agents to the MM therapy, MM is still consider a fatal disease and induction chemotherapy regimens or triplet regimens of novel drugs followed by consolidation with autologous stem cell transplantation (AHCT) continues being the standard of care in previously untreated fit transplant-eligible patients. Different regimens can be used as induction therapy prior to trasplant in this setting but currently Bortezomib-Lenalidomide-Dexamethasone appears to be the more effective one. Unfortunately the economical cost prevents some centers from using this scheme. In our centre we have been treating MM transplant-eligible patients with the scheme Bortezomib-Cyclophosphamide-Dexamethasone (CyBorDex) so we aim to evaluate the effectivity of this regimen as induction therapy for transplant-eligible patients with newly diagnosed MM in our context.

Table 1. Baseline characteristics of the patients

Number of patients	23
Age, years median (range)	56 (43-66)
Gender:	
Male (frequency, percent)	4/7 (57.1 %)
Combined Score:	
→ Low risk (frequency, percent)	7/23 (30.4%)
→ Intermediate risk (frequency, percent)	12/23 (52.2%)
→ High risk (frequency, percent)	7/23 (3%)
→ Unknown (frequency, percent)	1/23 (4.3%)
Multiple Myeloma Ig subtype:	
→ IgG Kappa (frequency, percent)	8/23 (34.8%)
→ IgG Lambda (frequency, percent)	5/23 (21.7%)
→ IgA Kappa (frequency, percent)	3/23 (13%)
→ CLL Kappa (frequency, percent)	2/23 (8.7%)
→ CLL Lambda (frequency, percent)	5/23 (21.7%)

Methods: We retrospectively evaluated the responses achieved with CyBorDex as induction therapy prior to AHCT of transplant-eligible patients with newly diagnosed MM from June 2015 to January 2018. **Results:** Twenty-three transplant-eligible patients were diagnosed with MM in this period. The baseline characteristics of the patients are summarized in Table 1. Patients received a median of 5 courses of CyBorDex (range 3-7). No pa-

tient discontinued treatment due to severe toxicity. The overall response rate was 69,5% with a 39,1% of complete responses but six patients (26%) are currently receiving a second line treatment based in lenalidomide before to proceed to AHCT. **Conclusions.** Overall responses with CyBorDex in our cohort are similar to previously published studies. Taking into consideration the frequent use of lenalidomide based regimens as a second line therapy before AHCT in our centre, we need to perform further analysis to determine if CyBorDex is a cost-effective regimen in this setting and wether its use as first line therapy before AHCT is really justified in economic terms in our country.

P32

VTD EXPERIENCE AS AN INDUCTION TREATMENT TO TRANSPLANT IN PATIENTS WITH NEW DIAGNOSIS OF MULTIPLE MYELOMA

González Fernández A., Cabrera Ruiz F.J., Revelles Peñas M., García Fortes M., Ruiz Arredondo J.J., Heiniger Mazo A.I., García Sánchez R.

Hospital Universitario Virgen de la Victoria, Málaga, Spain

Introduction. Induction therapy, based on the combination of 3 drugs that include bortezomib and dexamethasone associated with an immunomodulatory agent, such as thalidomide, is currently the standard of treatment prior to TAPH young patients with new diagnosis of multiple myeloma (MM). **OBJECTIVES** To evaluate the efficacy and toxicity of the induction scheme with VTD (Bortezomib, thalidomide and dexamethasone) followed by TAPH and consolidation in our center. **RESULTS** From July 2011 to February 2017, 35 patients were included (median age 56 years: men 17, women 18). 77% of the patients completed 6 cycles of induction (median of cycles received 6, range 1-7) with a median cumulative dose of bortezomib of 50.4 mg. As for thalidomide, the median dose received was 100 mg / day. Regarding the adverse effects of the treatment, 18 patients (51%) presented peripheral neuropathy (20% grade 1, 23% grade 2 and 9% grade 3), gastrointestinal toxicity in 4 patients (26%) with grade 3 being 3 %. Likewise, 8 patients presented haematological toxicity, 6 patients suffered anemia (2 grade 1 and 4 grade 2), 4 patients presented neutropenia (1 grade ≥3) and there was no case of thrombocytopenia grade 3-4. As a consequence of this toxicity, 34% of the patients required dose adjustment of bortezomib and 54% of thalidomide. Five patients discontinued the treatment, 2 of them due to progression, 2 due to toxicity and one voluntarily. After a median follow-up of 26 months (range 1-56), 14 patients progressed, 4 of them (11%) before the TAPH and 10 post-transplant patients, with a median progression-free survival of 23 months and median global survival of 26 months. **CONCLUSIONS** Our study shows that the induction with VTD results in a high rate of complete remission that improves after the TAPH which results in a prolonged progression free survival and global survival, being also a safe scheme. All this supports the use of VTD as gold standard of induction treatment in patients with MM candidates for TAPH.

P33

AUTOLOGOUS STEM CELL TRANSPLANT IN MULTIPLE MYELOMA IN THE ERA OF CONVENTIONAL CHEMOTHERAPY AND NOVEL DRUGS - A SINGLE CENTRE EXPERIENCE

Minarik J.¹, Faber E.¹, Raida L.¹, Szotkowski T.¹, Skoumalová I.¹, Pika T.¹, Krhovská P.¹, Bacovsky J.¹, Zapletalova J.², Scudla V.¹, Papajik T.¹

¹Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc; ²Department of Biophysics and Statistics, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic

Aims: The aim is to present the outcomes of first autologous stem cell transplants (ASCT) in multiple myeloma (MM) within a 20-year transplant program at our site, including the effectiveness of using of conventional chemotherapy and novel drugs. **Patients and Methods:** We assessed 274 patients with MM undergoing first ASCT at our department. The patients had standard baseline characteristics including age, gender, immunoglobulin and light chain type, Durie-Salmon (DS) and International Staging System (ISS). The induction regimens included VAD (vincristine, adriamycin, dexamethasone) in 34%, thalidomide (THAL) based regimens in 15%, bortezomib (BTZ) based regimens in 34%, the rest (17%) were polychemotherapeutic and lenalidomide (LEN) based regimens. 163 patients (59%) had maintenance after ASCT, mostly interferon based (32%), conventional chemothe-

P34**TRANSPLANT-INELIGIBLE PATIENTS TREATED FIRST LINE WITH LENALIDOMIDE AND DEXAMETHASONE. EXPERIENCE IN ONE CENTER**

Pérez-Montaña A., Sánchez-Raga J.M., Beltrán N., Ros T., Sampol A.

Hospital Universitari Son Espases, Palma, Islas Baleares, Spagna

Objectives: Patients with multiple myeloma who are ineligible for autologous stem-cell transplantation have limited therapeutic options, both because of their age and their functional status. Treatment with continuous lenalidomide and dexamethasone (RD) until disease progression has recently been approved as a first-line regimen for this group of patients. The objective of our work was to analyze the casuistry and outcomes of the patients of our center treated with RD. **Methods:** This is a retrospective descriptive analysis of 9 patients treated with RD between January 2016 and November 2017. Their clinical-biological characteristics as well as the results obtained during the treatment were analyzed, including response rates and progression free survival (PFS). The patients received the lenalidomide dose adjusted to their renal function (21 out of 28 day cycles), and the dose of dexamethasone was 40 milligrams weekly for patients under 75 years old, and 20 milligrams for those over that age. **Results:** We analyzed 9 patients, including 5 males (55%) and 4 women (45%). The median age at diagnosis was 77 years old (range 72-86). The performance status (ECOG) was between 0-2 in 88% of patients. 6 patients (66%) had an IgG multiple myeloma, 2 IgA and 1 IgM. 4 patients (45%) had renal failure grade 3 or more at diagnosis. The median number of cycles received was 7 (range 1-25). Most of the patients (89%) presented adverse events during treatment, basically grade 1 or 2. The responses achieved were: 1 complete remission, 4 very good partial response, 3 partial response, 4 very good partial response, 1 complete remission. 2 patients died during the study period for causes not related with the disease or drug toxicity. The median follow-up was 10,3 months and the PFS was not reached. **Conclusions:** Lenalidomide and dexamethasone is an effective and easy to administer regimen for patients, being useful in those with difficulties to go to the hospital. The results obtained are similar with those published in the literature.

rapy (11%) or THAL based (9%), 41% of patients had no maintenance. We assessed the response rates including complete remission (CR), very good partial remission (VGPR), partial remission (PR), minimal response (MR), stable disease (SD), progressive disease (PG) and overall response rate (ORR – defined as \geq PR). Survival measures were assessed by progression free survival (PFS). We assessed the efficacy of ASCT with respect to treatment line, pre-transplant and post transplant response achieved (day +100), and with respect to DS and ISS as well as to treatment modality used for induction and maintenance. **Results:** Median PFS was 35 months. Patients with deeper responses after ASCT had better median PFS outcomes (CR 48 months, VGPR 36 months, PR 33 months, MR and SD 13 months, PG 9 months $p < 0,0001$). There were no differences in PFS with respect to ISS but advanced DS stage correlated with worse prognosis (stage I – 58 months, II – 42 months, III – 31 months, $p = 0,012$). Novel drugs (THAL, BTZ and LEN) resulted in better pre-transplant as well as post-transplant responses: CR plus VGPR was only 37.1% after VAD, 65-78.2% after BTZ based induction, 85% after THAL based induction, 87.5% after LEN based induction and 70% after BTZ+THAL regimen. There was, however, no statistically significant difference in PFS regardless of induction regimen. None of the maintenance (chemotherapy, interferon, THAL-based) lead to a better PFS, however, there were only few patients treated with BTZ, LEN or ixazomib maintenance precluding valid statistical analysis. No differences were found in responses or PFS with regard to treatment line (first transplant in the 1st line versus 2nd and higher line) but there were only 19 patients not having ASCT as their first regimen. **Conclusion:** ASCT is still the gold standard for MM patients. Regardless of treatment line, it brings significant treatment outcomes and survival measures, which are the function of the depth of response. The induction treatment with novel drugs induces deeper pre-transplant responses, still, the major advantage against conventional chemotherapy is in the speed of response and absence of severe adverse events, thus enabling more patients to reach ASCT. As reported, maintenance therapy accounts for better survival, however, this is true only for novel drugs (such as bortezomib, lenalidomide) whereas older modalities including interferon, post-transplant chemotherapy, steroids or thalidomide do not improve progression free survival. Supported by the grant IGA-LF-2017-007.

Relapsed/refractory multiple myeloma

P36

TARGETING B-CELL MATURATION ANTIGEN (BCMA) WITH GSK2857916 ANTIBODY-DRUG CONJUGATE PROVIDES DURABLE RESPONSES IN PATIENTS (PTS) WITH HEAVILY-PRETREATED RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): PRELIMINARY RESULTS FROM STUDY BMA117159

Popat R.¹, Trudel S.², Lendvai N.³, Voorhees P.⁴, Reeves B.⁵, Libby E.⁶, Richardson P.⁷, Anderson L. Jr.⁸, Sutherland H.⁹, Yong K.¹, Hoos A.¹⁰, Gorczyca M.¹⁰, Lahiri S.¹⁰, He Z.¹⁰, Jewell R.¹⁰, Opalinska J.¹⁰, Cohen A.¹¹

¹University College London Hospitals NHS Foundation Trust, London UK; ²Princess Margaret Cancer Centre, Toronto, Canada; ³Memorial Sloan-Kettering Cancer Center, New York USA; ⁴Levine Cancer Institute, Carolinas HealthCare System, Charlotte, USA; ⁵Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, USA; ⁶Seattle Cancer Care Alliance, Washington, USA; ⁷Dana-Farber Cancer Institute, Boston, USA; ⁸University of Texas Southwestern, Dallas, USA; ⁹Vancouver General Hospital, Vancouver, Canada; ¹⁰GlaxoSmithKline, Brentford, UK; ¹¹Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA

Background: BCMA, a cell-surface receptor required for late-stage B-cell development and survival, is broadly expressed on MM cells. The humanized IgG1 antibody-drug conjugate GSK2857916 selectively binds BCMA and releases active cytotoxic monomethyl auristatin-F (MMAF) during cellular uptake. GSK2857916 is afucosylated to enhance antibody-dependent cell-mediated cytotoxicity. We report results from the Part 2 expansion of a study evaluating the safety, tolerability and clinical activity of GSK2857916 monotherapy. **Methods:** This was a single-arm, open-label, 2-part Phase I trial (BMA117159; NCT02064387). Eligible pts with RRMM had undergone stem cell transplantation (if eligible) and treatment with alkylators, proteasome inhibitors (PI) and immunomodulators (IMiD), and had a progression \leq 60 days after last therapy. Primary study objectives were safety and determining the recommended Phase 2 dose (RP2D; established as 3.4 mg/kg in Part 1; Blood 2016;128:1148). In Part 2 GSK2857916 was dosed at RP2D via 1-h intravenous infusion q3w, until unacceptable toxicity, consent withdrawal or completion of 16 treatment cycles. Primary prophylaxis for infusion-related reactions (IRR) was not permitted. Pts received steroid eye drops to mitigate MMAF-associated corneal events. **Results:** In Part 2 35 pts with MM were treated (median age 60 years [range 46–75]; 49% male). Most pts (57%) had received \geq 5 prior lines of therapy (range 1–10); 97% and 91% were refractory to PIs and IMiDs, respectively (all pts had received), 89% were double-refractory to PI/IMiDs, 37% were refractory to daratumumab (40% had received). Median number of GSK2857916 infusions: 5 (range 1–13); 54% pts received \geq 5 infusions. Overall response rate (ORR) was 60% (21/35; 95%CI 42.1–76.1), including 1 stringent complete response (sCR), 2 CR, 15 very good partial response (VGPR) and 3 PR. In pts previously treated with daratumumab, ORR was 43% (6/14, 95%CI 17.7–71.1). Median duration of response was not reached; median progression-free survival (PFS) was 7.9 months (95%CI 3.1–not estimable). All pts had \geq 1 adverse event (AE); the most frequent any-cause AEs (\geq 25%) were corneal events (63%), thrombocytopenia/platelet count decreased (57%), anemia (29%), aspartate aminotransferase increased (29%) and cough (26%). Corneal events (most frequent [\geq 20%]: vision blurred, dry eye, photophobia) were mostly Grade (Gr) 1/2 and reversible. Gr 3/4 AEs reported in \geq 10% of pts: thrombocytopenia/platelet count decreased (34%) and anemia (14%). Serious AEs were reported in 40% (14/35) of pts. Eight pts had IRRs (2 Gr1, 3 Gr2, 3 Gr3) with the first infusion, which resolved and did not recur with subsequent infusions. Treatment was discontinued by 18 pts owing to: disease progression (n=15), AE (n=2; thrombocytopenia, creatinine phosphokinase elevation), patient decision (n=1). Treatment for 17 pts is ongoing. **Conclusions:** Single-agent GSK2857916 demonstrated a manageable safety profile and strong clinical activity with deep (51% \geq VGPR) and durable (median PFS 7.9 months) responses in pts with heavily pre-treated RRMM. The mechanism of action of GSK2857916 is distinct from currently approved MM drugs; further monotherapy and combination studies are planned. Study funded by GSK; drug linker technology licensed from Seattle Genetics; monoclonal antibody produced using POTELLIGENT® Technology licensed from BioWa. Editorial support from Fishawack Indicia, funded by GSK. This abstract was originally presented at ASH 2017.

P37

UPDATED EFFICACY AND SAFETY ANALYSIS OF DARATUMUMAB, BORTEZOMIB, AND DEXAMETHASONE (DVD) VERSUS BORTEZOMIB AND DEXAMETHASONE (VD) FOR RE-LAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM; CASTOR)

Mateos M.M.,¹ Spencer A.,² Hungria V.,³ Nooka A.K.,⁴ Estell J.,⁵ Barreto W.,⁶ Corradini P.,⁷ Min C.K.,⁸ Medvedova E.,⁹ Thiagarajah P.,¹⁰ Deraedt W.,¹¹ Chiu C.,¹² Schecter J.M.,¹³ Weisel K.¹⁴

¹University Hospital of Salamanca/IBSAL, Spain; ²Malignant Haematology and Stem Cell Transplantation Service, Alfred Health-Monash University, Melbourne VIC, Australia; ³Irmandade Da Santa Casa De Misericordia De São Paulo, Brazil; ⁴Winship Cancer Institute, Emory University, Atlanta, USA; ⁵Haematology Department, Concord Cancer Centre, Concord Hospital; ⁶Hospital Santa Marcelina, Concord Nuovo Galles del Sud, Australia; ⁷Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; ⁸Seoul St. Mary's Hospital, Seoul, South Korea; ⁹Oregon Health & Science University, Oregon, USA; ¹⁰Janssen Research & Development, LLC, Raritan, USA; ¹¹Janssen Research & Development, LLC, Raritan, USA; ¹²Janssen Research & Development, LLC, Raritan, USA; ¹³Janssen Research & Development, LLC, Raritan, USA; ¹⁴Universitätsklinikum Tuebingen der Eberhard-Karls-Universität, Abteilung fuer Innere Medizin II, Tuebingen, Germany

Introduction: Daratumumab (D) is an anti-CD38 human monoclonal antibody approved as monotherapy and combined with standard of care regimens for patients (pts) with RRMM. We report an update of CASTOR (NCT02136134), a phase 3 study of DVD vs Vd in RRMM. **Methods:** Pts with \geq 1 prior line of therapy were randomized to 8 cycles of Vd (V 1.3 mg/m² SC Days 1, 4, 8, and 11; d 20 mg PO or IV Days 1–2, 4–5, 8–9, and 11–12) +/- D (16 mg/kg IV once weekly Cycles 1–3, every 3 weeks Cycles 4–8, and every 4 weeks thereafter until progression). Pts who progressed on Vd could cross over to D monotherapy. Progression-free survival (PFS) was the primary endpoint. Minimal residual disease (MRD) via next generation sequencing (NGS) was assessed at 3 sensitivity thresholds (10⁻⁴, 10⁻⁵, and 10⁻⁶) using the clonoSEQ® assay (V.1.3). Cytogenetic risk was determined by NGS: high-risk pts had t(4;14), t(14;16), and/or del17p abnormalities. PFS on subsequent line of therapy (PFS2) was also examined. **Results:** 251 pts received DVD and 247 pts received Vd. Median (range) age was 64.0 (30–88) years. Pts received a median of 2 (1–10) prior therapies; 61% prior autologous stem cell transplant, 66% bortezomib, 42% lenalidomide, 48% proteasome inhibitor plus immunomodulatory drug, and 28% were refractory to lenalidomide. Median duration of single-agent D in DVD arm after 8 cycles of Vd was 11.9 months. At median follow-up of 19.4 months, median PFS was significantly prolonged with DVD vs Vd (16.7 vs 7.1 months; HR, 0.31; 95% CI, 0.24–0.39; P<0.0001) regardless of number of prior lines of therapy, but was most pronounced in pts with 1 prior line of therapy (not reached [NR] vs 7.9 months; HR, 0.19; 95% CI, 0.12–0.29; P<0.0001). ORR (84% vs 63%) and rates of \geq VGPR (62% vs 29%) and \geq CR (29% vs 10%) were significantly higher with DVD vs Vd (all P<0.0001). MRD-negative rates were $>$ 3 times higher with DVD vs Vd in the intent-to-treat (ITT) population and in pts with 1 prior line of therapy at all sensitivity thresholds. At 10⁻⁵ threshold, MRD-negativity was associated with prolonged PFS. PFS2 was significantly improved with DVD vs Vd in the ITT population (HR, 0.56; 95% CI, 0.40–0.78; P=0.0005), in pts with 1 prior line of therapy (HR, 0.38; 95% CI, 0.21–0.69; P=0.0009), and in pts with \geq VGPR (HR, 0.34; 95% CI, 0.17–0.70; P=0.002). No PFS2 events occurred in MRD-negative pts (at 10⁻⁵) treated with DVD. Among high cytogenetic risk pts, median PFS2 was NR in DVD vs 15.9 months in Vd (HR, 0.51; 95% CI, 0.24–1.05; P=0.0647). Median time to next therapy (TTNT) was significantly longer with DVD vs Vd in the ITT population (NR vs 9.7 months; HR, 0.30; 95% CI, 0.23–0.39; P<0.0001), in pts with 1 prior line of therapy (NR vs 11.1 months; HR, 0.23; 95% CI, 0.15–0.36; P<0.0001), and in high cytogenetic risk pts (21.2 vs 9.8 months; HR, 0.38; 95% CI, 0.21–0.71; P=0.0015). Common ($>$ 10%) grade 3/4 TEAEs were thrombocytopenia (46% vs 33%), anemia (15% vs 16%), and neutropenia (14% vs 5%). 10% of DVD and 9% of Vd pts discontinued treatment due to TEAEs. No new safety signals were reported. Updated data will be presented. **Conclusions:** DVD continues to significantly prolong PFS and induce deep and durable responses, and safety remains consistent. DVD improved efficacy regardless of prior lines of therapy, with greatest benefit in pts with only 1 prior line of therapy. Durable responses with single-agent D in the DVD arm translated to longer PFS2 and TTNT.

P38

UPDATED EFFICACY AND SAFETY ANALYSIS OF DARATUMUMAB, LENALIDOMIDE, AND DEXAMETHASONE (DRd) VERSUS LENALIDOMIDE AND DEXAMETHASONE (Rd) FOR RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM; POLLUX)

Moreau P.¹, White D.², Benboubker L.³, Cook G.⁴, Leiba M.⁵, Morton J.⁶, Ho P.J.⁷, Kim K.⁸, Takezako N.⁹, Trivedi S.¹⁰, Wu K.¹⁰, Casneuf T.¹, Chiu C.¹⁰, Schecter J.M.¹², Dimopoulos M.A.¹³

¹Hematology, University Hospital Hôtel-Dieu, Nantes, France; ²Dalhousie University and QEII Health Sciences Centre, Halifax, Canada; ³Service d'Hématologie et Thérapie Cellulaire, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire (CHRU), Paris, France; ⁴St James's Institute of Oncology, Leeds Teaching Hospitals NHS Trust and University of Leeds, UK; ⁵Sheba Medical Center, Ramat Gan, Israel; ⁶Icon Cancer Care, South Brisbane, Australia; ⁷Institute of Haematology, Royal Prince Alfred Hospital, Sydney, Australia; ⁸Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, South Korea; ⁹Department of Hematology, National Hospital Organization Disaster Medical Center of Japan; ¹⁰Janssen Research & Development, Raritan, USA; ¹¹Janssen Research & Development, Raritan, USA; ¹²Janssen Research & Development, LLC, Raritan, USA; ¹³National and Kapodistrian University of Athens, Greece

Introduction: Daratumumab (DARA), a human IgG monoclonal antibody targeting CD38, induces rapid, deep, and durable responses in combination with bortezomib or an immunomodulatory drug (lenalidomide or pomalidomide) in RRMM. At pre-specified interim analysis of the phase 3 POLLUX study (median follow-up, 13.5 months), DRd reduced the risk of disease progression or death by 63% and significantly improved overall response rate (ORR) vs Rd alone. We report updated efficacy and safety data for POLLUX based on longer follow-up. **Methods:** Patients (pts) with ≥ 1 prior line of therapy were randomized (1:1) to Rd (lenalidomide 25 mg Days 1-21 of each 28-day cycle; dexamethasone 40 mg/week) with or without DARA (16 mg/kg IV weekly for Cycles 1-2, q2w for Cycles 3-6, then q4w until progression). The primary endpoint was progression-free survival (PFS). Minimal residual disease (MRD) was assessed at suspected complete response (CR) and 3 and 6 months after suspected CR at sensitivity thresholds of 10^{-4} , 10^{-5} , and 10^{-6} via the clonoSEQ® next-generation sequencing assay (V.1.3; Adaptive Biotechnologies, Seattle, WA). PFS on subsequent line of therapy (PFS2; time from randomization to progression after next line of subsequent therapy or death) was an exploratory endpoint. **Results:** Pts in both groups (DRd, n=286; Rd, n=283) received a median of 1 prior line of therapy and 18% received prior lenalidomide. After a median follow-up of 25.4 months, PFS was significantly prolonged with DRd vs Rd (median not reached [NR] vs 17.5 months; 24-month PFS rate: 68% vs 41%; HR, 0.41; 95% CI, 0.31-0.53; $P<0.0001$). ORR was greater with DRd vs Rd (93% vs 76%; $P<0.0001$), including significantly higher rates of \geq very good partial response (79% vs 48%; $P<0.0001$) and \geq CR (51% vs 21%; $P<0.0001$). DRd prolonged duration of response vs Rd (median NR vs 26.0 months). MRD-negative rates with DRd vs Rd were >3 -fold higher at all sensitivity thresholds evaluated. At 10^{-5} threshold, MRD-negative rates were 26% with DRd vs 6% for Rd ($P<0.0001$); pts with MRD-negative status accumulated more rapidly with DRd vs Rd. Regardless of treatment group, PFS was prolonged in pts who achieved MRD-negative vs MRD-positive status. PFS2 was significantly improved with DRd vs Rd in the intent to treat (ITT) population (HR, 0.55; 95% CI, 0.40-0.76; $P=0.0002$). For MRD-negative (10^{-5}) pts who received DRd (n=75) or Rd (n=18), no significant differences in PFS2 were observed between groups. Time to next therapy was also significantly prolonged with DRd vs Rd in the ITT population (median NR vs 22.7 months; HR, 0.34; 95% CI, 0.25-0.46; $P<0.0001$). Common ($\geq 10\%$) grade 3/4 TEAEs with DRd vs Rd were neutropenia (54% vs 40%), anemia (16% vs 21%), thrombocytopenia (14% vs 16%), and pneumonia (12% vs 9%). Incidence of TEAE-related discontinuations (12% in each group) and incidence of secondary primary malignancies (6% in each group) were similar between groups. Updated data will be presented. **Conclusion:** DRd continues to demonstrate a significant PFS benefit vs Rd alone. Pt responses continued to deepen with DRd and the favorable safety profile was maintained with longer follow-up. Pts who received DRd demonstrated longer time to next therapy and responded more favorably to subsequent therapy as evidenced by prolonged PFS2, suggesting that pts continue to gain clinical benefit from prior DARA treatment. These data support the addition of DARA to standard of care regimens in RRMM.

P39

FIRST REPORT ON OS AND IMPROVED PFS IN A COMPLETED PHASE 2 STUDY (0-12-M1) OF MELFLUFEN IN ADVANCED RRMM

Brighen S.¹, Paba-Prada C.², Voorhees P.³, Plesner T.⁴, Sonneveld P.⁵, Melqvist U.H.⁶, Zonder J.⁷, Reeves B.⁸, Palumbo A.⁹, Byrne C.¹⁰, Harmenberg J.¹⁰, Nordström E.¹⁰, Zubair H.¹⁰, Lindberg J.¹⁰, Richardson P.G.²

¹Divisione di Ematologia dell'Università di Torino, A.O.U. Città della Salute e della Scienza, Italy; ²Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; ³Levine Cancer Institute, Carolinas HealthCare System, Charlotte, USA; ⁴Dept. of Hematology, Vejle Hospital, Danimarca; ⁵Hematology, Erasmus Medical Center, Rotterdam, Netherlands; ⁶Dept. of Hematology, Borås Hospital, Sweden; ⁷Karmanos Cancer Institute, Wayne State University, Detroit, USA; ⁸Lineberger Comprehensive Cancer Center, University of North Carolina, USA; ⁹Takeda AG, Freienbach, Switzerland; ¹⁰Oncopeptides AB, Stockholm, Sweden

Background: Melflufen is a next generation alkylator, belonging to the novel class Peptidase Enhanced Cytotoxics (PENCs), designed for efficient targeting of tumor cells with a unique mechanism of action. Melflufen provides a peptidase enhanced therapy with an alkylating payload and triggers fast, robust and irreversible DNA damage. The lipophilicity of melflufen leads to rapid and extensive distribution into cells where it is readily metabolized by intracellular peptidases (often over-expressed in malignant cells) into hydrophilic alkylating metabolites leading to 50-fold enrichment of these metabolites in MM cells. Melflufen also has potent anti-angiogenic properties. **Methods:** 40 mg melflufen was given iv on D1 of each 28d cycle, with 40 mg dexamethasone weekly for up to 8 cycles, or more at the discretion of PI and sponsor. Patients had RRMM with measurable disease and ≥ 2 prior lines including lenalidomide and bortezomib (NCT01897714). Response was investigator assessed at each cycle by IMWG criteria. After progression (PD) or start of subsequent therapy, patients were followed for survival every 3m for up to 24m. **Results:** Enrollment was closed in Dec 2016. 45 patients were included in data cut 9 Nov 2017. Median age 66 years (47-78), 60% ISS stage 2-3, 38% high-risk cytogenetics. Median time since initial diagnosis 5.1 years (1-21). Median number of prior lines 4 (2-14). 64% double refractory and 53% alkylator refractory. At data cut-off, 1 patient was ongoing, 18 discontinued due to AEs, 13 due to PD, 2 died, and 9 completed treatment as planned. 2 patients discontinued for other reasons. Median 5 (1-14) cycles of melflufen given. ORR was 41% among 34 efficacy evaluable patients (≥ 2 doses of melflufen with baseline and follow-up assessments) including VGPR in 5 patients (15%) and PR in 9 (26%). 8 (24%) additional patients achieved MR for a CBR of 65%. ORR in all treated patients was 31%. Median PFS in all treated patients was 5.7m (95% CI: 3.7-9.3) based on 41 events in 45 patients. In patients with \geq PR the PFS was 11.7m (95% CI: 9.8- ∞ , event rate 93%). Median DOR was 8.4m (95% CI: 5.8- ∞). Median OS in all treated patients was 20.7m (95% CI: 11.8 - ∞) based on 23 events in 45 patients. Of note, among the 12 patients that achieved SD, median OS was 30.2m (95% CI: 14.8- ∞ , event rate 42%). 14 (31%) patients were alive 24m after end of treatment, including 4 patients with high-risk cytogenetics. Most frequent AEs, irrespective of grade and relationship, were thrombocytopenia (73%), neutropenia (69%) and anemia (64%). Treatment related hematologic grade 3/4 events were reported in 37 patients (82%), with those occurring in $\geq 5\%$ being thrombocytopenia (58%), neutropenia (51%) and anemia (42%). **Conclusions:** Treatment with melflufen, a peptidase enhanced alkylator, shows long-term benefit in late-stage RRMM patients where conventional therapies have failed. The median PFS of 5.7m is encouraging in this heavily pre-treated population. The median OS of 20.7m, along with the extended median OS of 30.2m in SD patients, warrants further investigation as it suggests benefit regardless of depth of response, and that treatment with melflufen enables subsequent treatments. The treatment was well tolerated with reversible and clinically manageable hematologic toxicity as the most common AE. Non-hematologic AEs were infrequent. Melflufen is further evaluated in the ongoing studies OCEAN (ph3, NCT03151811) and HORIZON (ph2, NCT02963493).

P40

MELFLUFEN THERAPY FOR HEAVILY PRETREATED RELAPSED REFRACTORY MULTIPLE MYELOMA (RRMM) PATIENTS REFRACTORY TO DARATUMUMAB AND/OR POMALIDOMIDE: EARLY EFFICACY DATA (HORIZON)

Mateos M.V.¹, Oriol Rocafiguera A.² Rodríguez-Otero P.³, Bladé J.⁴, Larocca A.⁵, Moreb S.J.⁶, Cavo M.⁷, Mazumder A.⁸, Alegre A.⁹, Hassoun H.¹⁰, Maisel C.¹¹, Paner A.¹², Gabrail N.¹³, Halka K.¹⁴, Zonder J.¹⁵, Ocio E.¹, Byrne C.¹⁶, Harmenberg J.¹⁶, Lindberg J.¹⁶, Nordström E.¹⁶, Thuresson S.¹⁶, Richardson G.P.¹⁷

¹Hospital Clínico Universitario de Salamanca, Spain; ²ICO Badalona - Hospital Germans Trias i Pujol, Barcelona, Spain; ³Clinica Universidad de Navarra, Spain; ⁴Hospital Clínica de Barcelona, Servicio de Onco-Hematología, Barcelona, Spain; ⁵A.O.U. Città della Salute e della Scienza di Torino - S.C. Ematologia U., Torino, Italy; ⁶UF Health Shands Cancer Hospital, Gainesville, USA; ⁷Policlinico S. Orsola Malphigi, Bologna, Italy; ⁸Hudson Valley Hematology Oncology Associates RLLP, Poughkeepsie, USA; ⁹Hospital Universitario La Princesa, Madrid, Spain; ¹⁰Memorial Sloan Kettering Cancer Center, New York, USA; ¹¹Baylor Scott & White Charles A Sammons Cancer Center, Dallas, USA; ¹²Rush University Medical Center, Chicago, USA; ¹³Gabrail Cancer Center Research, Canton, USA; ¹⁴Scott & White Memorial Hospital and Clinic, Texas, USA; ¹⁵Karmanos Cancer Institute, Detroit, USA; ¹⁶Oncopptides AB, Stockholm, Sweden; ¹⁷Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA

Background: Melflufen is a next generation alkylator, belonging to the novel class of Peptidase Enhanced Cytotoxics (PENCs), designed for efficient targeting of tumor cells with a unique mechanism of action. Melflufen provides a peptidase enhanced therapy with an alkylating payload and triggers fast, robust and irreversible DNA damage. The lipophilicity of melflufen leads to rapid and extensive distribution into cells where it is readily metabolized by intracellular peptidases (often over-expressed in malignant cells) into hydrophilic alkylating metabolites leading to 50-fold enrichment of these metabolites in MM cells. Melflufen also has potent anti-angiogenic properties. **Methods:** 40 mg melflufen is given i.v. on Day 1 of each 28-day cycle, with 40 mg weekly dexamethasone, in relapsed-refractory multiple myeloma (RRMM) patients refractory to pomalidomide and/or daratumumab with measurable disease and at least 2 prior lines of therapy including an IMiD and a PI (NCT02963493). Response is investigator assessed at each cycle by IMWG criteria. The primary objective is overall response rate (ORR). Patients receive treatment until there is documented disease progression or unacceptable toxicity. **Results:** As of 13 November 2017, 38 patients had received at least one dose of melflufen. Median time from initial diagnosis was 6.3 years (0.6-16). Median number of prior lines was 6 (3-11). 21 patients (57%) were alkylators refractory, 32 patients (86%) were double refractory, 23 patients (62%) were refractory to pomalidomide and daratumumab, and 18 (47%) were quadruple refractory (refractory to at least 1 PI + 1 IMiD, exposed to 2 PIs + 2 IMiDs and PD on or within 60 days of last treatment). A total of 92 doses of melflufen were given with a median of 2 cycles (1-8). 3 patients (8%) discontinued treatment due to AEs, 17 (45%) due to PD and 1 patient (2%) due to physician's decision. Treatment was still ongoing in 17 patients (45%). AEs, regardless of grade, were reported in 35 patients (92%). Treatment-related grade 3/4 AEs were reported in 22 patients (58%), with those that occurred in >5% of the patients being thrombocytopenia in 17 (45%), neutropenia in 15 (39%) and anemia in 8 (21%). ORR was 27% among 30 patients who received at least 1 dose of melflufen and had an assessment of response. This includes 2 patients with VGPR and 6 patients with PR. 2 patients achieved MR for a CBR of 33%. **Conclusion:** Following treatment with IMiDs and PIs, patients refractory to pomalidomide and daratumumab have little to no treatment options. Melflufen, a peptidase enhanced therapy with an alkylating payload, demonstrates activity in a heavily refractory population with a median of 6 prior lines of therapy. The efficacy results in this interim analysis are encouraging with an ORR of 27% (including 2 VGPRs) and a CBR of 33%. Melflufen showed a good safety and tolerability profile. Thrombocytopenia and neutropenia were, as expected, the most common AEs, and non-hematologic AEs were infrequent. Melflufen is further evaluated in this ongoing study and the phase 3 study OCEAN (NCT03151811).

P41

SUBCUTANEOUS DARATUMUMAB IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM): AN OPEN-LABEL, MULTICENTER, DOSE ESCALATION PHASE 1B STUDY (PAVO)

Mateos M.V.¹, Chari A.², Nah H.³, Lokhorst H.⁴, Kaufman J.L.⁵, Moreau P.⁶, Oriol A.⁷, Plesner T.⁸, Benboubker L.⁹, Hellems P.¹⁰, Master-son T.¹¹, Clemens P.L.¹¹, Liu K.¹², San-Miguel J.¹³, Usmani S.Z.¹⁴

¹University Hospital of Salamanca/IBSAL, Spain; ²Tisch Cancer Institute, Mount Sinai School of Medicine, New York, USA; ³Karolinska Institute, Department of Medicine, Division of Hematology, Karolinska University Hospital at Huddinge, Stockholm, Sweden; ⁴Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands; ⁵Winship Cancer Institute, Emory University, Atlanta, USA; ⁶University Hospital of Nantes, France; ⁷Institut Català d'Oncologia, HGTiP, Girona, Spain; ⁸Vejle Hospital and University of Southern Denmark; ⁹Service d'Hématologie et Thérapie Cellulaire, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire (CHRU), Paris, France; ¹⁰Janssen Research & Development, LLC, Raritan, USA; ¹¹Janssen Research & Development, LLC, Raritan, USA; ¹²Janssen Research & Development, LLC, Raritan, USA; ¹³Clinica Universidad de Navarra-CIMA, IDISNA, CIBERONC, Spain; ¹⁴Levine Cancer Institute/Carolinas HealthCare System, Charlotte, USA

Introduction: Daratumumab (DARA), a CD38-targeted human monoclonal antibody is administered intravenously (IV) and is associated with infusion related reactions (IRRs) in 46% of pts. Previous data from PAVO (NCT02519452), an open-label phase 1b study in RRMM, showed subcutaneous (SC) DARA with recombinant human hyaluronidase enzyme (rHuPH20) by SC infusion of a mix and deliver formulation (DARA-MD) was well tolerated with low IRR rates (Usmani SZ, *et al.* ASH 2016; abstract 1149). DARA + rHuPH20 also showed similar efficacy with IV DARA. Updated data are presented, including initial findings from a cohort receiving DARA co-formulated with rHuPH20 (DARA SC) delivered by manual SC injection. **Methods:** RRMM pts had ≥2 prior lines of therapy including a proteasome inhibitor and immunomodulatory drug. In Part 1 DARA-MD was administered via SC infusion through a syringe pump from 20-30 min to identify the dose for Part 2. Pts received DARA 1200 mg + rHuPH20 30000 U (in 60 mL) or DARA 1800 mg + rHuPH20 45000 U (in 90 mL) in 28-day cycles: weekly Cycles 1-2, every 2 weeks Cycles 3-6, and every 4 weeks thereafter. The 1800 mg dose was chosen for Part 2. In Part 2, a concentrated co-formulation of DARA SC (1800 mg in 15 mL) and rHuPH20 (30000 U) in a single, pre-mixed vial was administered in 3-5 min by manual SC injection. In both parts, primary endpoints were DARA Cough and safety. **Results:** As of June 30, 2017, 53 pts were enrolled in Part 1 (DARA-MD 1200 mg, n=8; DARA-MD 1800 mg, n=45) and 25 pts were enrolled in Part 2 (DARA SC 1800 mg), and 0%, 27%, and 100%, respectively, remain on treatment. Median treatment duration was 2.6 (0.7-12.0), 5.4 (0.7-16.6+), and 1.4 (0.5-2.3+) months. In Part 1, pts discontinued in the DARA-MD 1200 mg/DARA-MD 1800 mg cohorts, respectively, due to progressive disease (75%/58%), physician decision (0%/9%), death (13%/2%), pt withdrawal (13%/2%), and other (0%/2%); in Part 2 with shorter follow up, no pt discontinued.

Table. Grade 3 or 4 treatment-emergent adverse events in ≥1 pt

N (%)	DARA-MD 1200 mg (n = 8)	DARA-MD 1800 mg (n=45)	DARA SC 1800 mg (n = 25)
Fatigue	2 (25)	1 (2)	1 (4)
Hypertension	2 (25)	2 (4)	2 (8)
Anemia	1 (13)	7 (16)	1 (4)
Thrombocytopenia	1 (13)	3 (7)	2 (8)
Neutropenia	1 (13)	3 (7)	1 (4)
Influenza	1 (13)	2 (4)	0
Pneumonia	1 (13)	2 (4)	0
Dyspnea	1 (13)	2 (4)	0
Lymphopenia	0	5 (11)	2 (8)
Device related infection	0	2 (4)	0
Hyponatremia	0	2 (4)	1 (4)

One pt (DARA-MD 1200 mg) died due to adverse event (aspiration pneumonia) and 2 pts (DARA-MD 1800 mg) died due to disease progression; no deaths occurred with DARA SC 1800 mg. IRRs occurred in 13%, 24% and 4% of pts with DARA-MD 1200 mg, DARA-MD 1800 mg, and DARA SC

1800 mg, respectively. One grade 3 IRR (dyspnea) was reported (DARA-MD 1200 mg); no grade 3/4 IRRs occurred with DARA-MD 1800 mg or DARA SC 1800 mg. SC administration was well tolerated in the DARA-MD 1200 mg, DARA-MD 1800 mg, and DARA SC 1800 mg cohorts, with 63%, 29%, and 20% reporting reversible erythema and 50%, 22%, and 0% reporting reversible induration at the infusion/injection site, respectively. Treatment-emergent adverse events (TEAEs) occurred in 100%, 98% and 84% of pts with DARA-MD 1200 mg, DARA-MD 1800 mg, and DARA SC 1800 mg, respectively; 63%, 49% and 32% were grade 3 or 4 (Table). Serious TEAEs occurred in 50%, 31%, and 4% of pts. No pt discontinued due to TEAEs. As of August 1, 2017, ORR was 42%, and rates of \geq VGPR and \geq CR were 20% and 7%, respectively, with DARA-MD 1800 mg. In the DARA SC 1800 mg cohort, preliminary ORR was 42%, but requires confirmation. Updated data will be presented. Conclusions: SC administration of DARA + rHuPH20 was well tolerated, with lower rates of IRRs than expected, particularly in pts treated with DARA SC 1800 mg over only 3-5 minutes. Planned phase 3 studies will use DARA SC at the Part 2 dose.

P42

CAROTID-FEMORAL PULSE WAVE VELOCITY AND CARDIOVASCULAR EVENTS IN MULTIPLE MYELOMA PATIENTS TREATED WITH CARFILZOMIB

Bruno G., Maffei I., Iannaccone A., Crea T., Salvini A., Gay F., Brighen S., Veglio F., Milan A.

Hypertension Unit, Department of Medical Sciences, Città della Salute e della Scienza, University of Turin, Italy; Department of Haematology, Città della Salute e della Scienza, University of Turin, Italy

Background: Carfilzomib is a second-generation proteasome inhibitor that has been approved for the treatment of relapsed/refractory multiple myeloma (MM). Previous studies have demonstrated it improves the overall rate response and progression free survival in MM patients compared to other chemotherapeutic strategies. However, carfilzomib seems to determine a wide range of cardiovascular (CV) side effects, first of all arterial hypertension. The pathogenesis of these adverse events is still unknown and, so far, the CV risk profile of patients undergoing treatment with carfilzomib has not been studied yet. **Aim:** The aim of our study was to determine the CV risk profile of MM patients who had to be treated with carfilzomib and to recognize predictors of future CV events. **Methods:** 71 patients affected by MM, seen at the Department of Haematology of this hospital, were prospectively enrolled from March 2014 to December 2017. A comprehensive CV evaluation was performed in our EchoLab: each patient underwent transthoracic echocardiogram (TTE), assessment of carotid-femoral pulse wave velocity (cfPWV), evaluation of office blood pressure and ambulatory blood pressure monitoring (ABPM) prior to carfilzomib infusion. All patients were followed up to determine the incidence of CV adverse events.

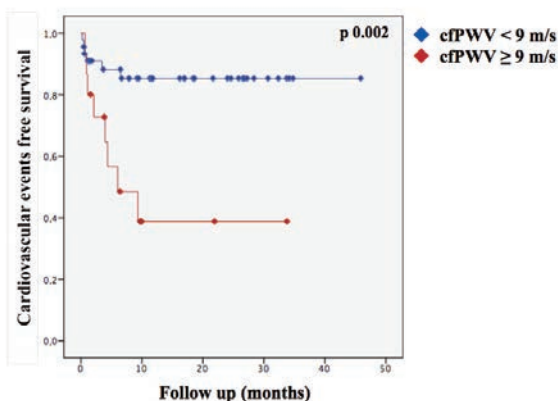


Figure 1. Cardiovascular events free survival in MM patients based on baseline cf PWV.

Results. Mean age was 62.8±9.1, 52% were male. Most common CV risk factors were arterial hypertension (46%), dyslipidemia (14%), diabetes (11%). Mean MM duration was 3.9±3.6 years and most patients had received previous chemotherapy (31% anthracyclines, 63% and 86% immunomodulator and alkylating agents, 74% bortezomib). Mean blood pressure values at ABPM were normal (121±12/71±7 mmHg); TTE showed a mean left ven-

tricular (LV) mass within normal limits (92 g/m²), but 26% patients had LV hypertrophy; mean cfPWV was 7.8±3.0 m/s. These patients were followed up for 14.4±11.8 months and 23% experienced a first CV event within 3.2±2.8 months, mainly (96%) uncontrolled hypertension requiring a stronger antihypertensive treatment and occasionally a temporary interruption of carfilzomib infusions. We compared patients with and without CV events: no significant differences in general characteristics, CV risk factors and oncological history were noticed between groups; office and ABPM blood pressure values as well as TTE parameters were similar in both groups; however, cfPWV was significantly higher in patients who had CV events (8.9±1.9 vs 7.5±1.5 m/s, p=0.006). The logistic regression showed a significant association of cfPWV and CV events (O=0.009, r²=0.23). Furthermore, we proved that 60% patients with a cfPWV≥9 m/s had CV events within 10 months after the beginning of carfilzomib treatment while less than 15% patients with cfPWV<9 m/s experienced CV adverse events (p=0.002). **Conclusions.** CfPWV could be a predictor of CV events in patients affected by MM treated with carfilzomib. It should be considered as a fundamental parameter during the baseline evaluation of these patients in order to recognize subjects at higher risk of CV adverse effects and to prevent them.

P43

EFFICACY OF RETREATMENT WITH IMMUNOMODULATORY DRUGS AND PROTEASOME INHIBITORS FOLLOWING DARATUMUMAB TREATMENT IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA PATIENTS

Oostvogels R., Jak M., Minnema M.C.

University Medical Center Utrecht, The Netherlands

In a single-center retrospective observational study, we analysed the efficacy of retreatment with immunomodulatory agents (IMiDs) and/or proteasome inhibitors (PIs) after treatment with daratumumab monotherapy in patients with relapsed and/or refractory multiple myeloma. In total, 55 patients were treated with daratumumab monotherapy between 2010 and 2017. From this group 29 IMiD-refractory patients were retreated with an IMiD after progression on daratumumab treatment and 6 PI-refractory patients were retreated with a PI-based regimen and had available follow-up data. From the IMiD-refractory patients 20/29 (69%) had an improved response (defined as stable disease or better) compared to their previous IMiD-therapy before daratumumab treatment. In the PI-refractory patients 5/6 (83%) had an improvement in response compared to the prior pre-daratumumab PI-treatment. In most patients however variable regimens and/or doses were used, making an exact comparison difficult. Possibly the immunomodulatory effects of daratumumab treatment leading to an altered balance between immunosuppressive cell subsets and effector T cells play a role in these high response rates in previously refractory patients. Furthermore, the tolerability of daratumumab may enable patients to recover from prior lines of treatment and receive full dosing of subsequent therapies. In conclusion, a striking high proportion of IMiD and PI refractory patients benefitted from retreatment with IMiDs and PIs after daratumumab treatment and therefore this option should be explored in patients progressing on daratumumab treatment.

P44

FIRST SYMPTOMATIC RELAPSE/PROGRESSION OF MULTIPLE MYELOMA: A SINGLE CENTRE RETROSPECTIVE ANALYSIS OF THE DETERMINANTS OF CHOICE OF SECOND-LINE TREATMENTS

Galli M.¹, Paris L.¹, Pavoni C.¹, Delaini F.¹, Rambaldi A.^{1,2}

¹Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII,

²Department of Oncology and Hematology, Università Statale di Milano, Italy

Introduction: The incorporation of novel agents (i.e., proteasome inhibitors, bortezomib and carfilzomib, and immunomodulatory drugs, thalidomide and lenalidomide) in the treatment of newly diagnosed symptomatic multiple myeloma (MM) patients improves their clinical outcomes. Nevertheless, most patients eventually relapse or progress and require a 2° line treatment. During the last decade, the Italian Regulatory Drug Agency approved as > 2° line treatments the following: bortezomib-dexamethasone (Bd), lenalidomide-dexamethasone (Rd) alone or in combination with carfilzomib (KRd) or elotuzumab (ERd). Since April 2017 all of these treatments became available in Italy. Although algorithms have been proposed to help choosing among them, such a choice may still be difficult in the single patient. Indeed, both patient-related and disease-related factors must be considered to provide the treatment option with the best benefit and the lowest toxicity. Aim &

study design: To evaluate the determinants of choice of the most appropriate 2° line treatment, we performed a retrospective study to analyze the characteristics of the MM patients at first symptomatic progression/relapse, who started their treatment at our Institution from April to December 2017. *Results:* 31 patients - 16 males and 15 females, aged 48-85 years (median 70 years) - were analyzed. At first diagnosis, the characteristics of MM were as follows: isotype (A, n=6; D, n=2; G, n=17; light chain, n=6; kappa, n=19; lambda, n=12), Durie & Salmon stage (I, n=1; II, n=5; III, n=25; A, n=24; B, n=7), ISS (1, n=13; 2, n=6; 3, n=10; not available, n=2). As 1° line treatments, 13 patients entered programs with high dose therapy and autotransplant (inductions included: bortezomib, thalidomide and dexamethasone, n=10; lenalidomide and dexamethasone, carfilzomib, cyclophosphamide and dexamethasone, adriamycin, vincristine and dexamethasone, n=1 each). The other 18 patients received: melphalan and prednisone with bortezomib (n=14) or thalidomide (n=2); lenalidomide and dexamethasone (n=1); carfilzomib, lenalidomide and dexamethasone (n=1). The patients' median PFS1 was 18.4 months (range 1.7-150.2 months), and their median time to next treatment (TTNT1) was 22.6 months (range 2.0-271.8 months). As 2° line treatments they received: Rd (n=12), ERd (n=11), KRd (n=4), Bd (n=2), prednisone only (n=1). This last patient is not included in the following analysis. Clinical and biological characteristics of the remaining 30 patients are shown in the Table: data are grouped according to the type of 2° line treatment. On average, patients receiving a 2-drug combination were 10 years older and had a higher frailty score (median 2 vs 1) than patients receiving a 3-drug combination. Among patients treated with a 3-drug combination, those in the ERd group had enjoyed longer times to first relapse and next treatment compared to those treated with KRd. Patients in this latter group had also lower values of hemoglobin and platelets and higher LDH value. The only patient with a plasma cell leukemia relapse received KRd. At last follow-up, 21 patients (70%) are still on treatment. *Conclusions:* A 2-drug combination (Rd or Bd) was chosen for elderly and frail patients, whereas a 3-drug combination (ERd or KRd) was reserved to younger and fitter patients. The choice between the 3-drug combinations was mostly determined by the biology of MM relapse, as KRd was chosen in the more aggressive conditions.

Table. Clinical and biological characteristics at 1° relapse.

	Rd	ERd	KRd	Bd
	N = 12	N = 11	N = 4	N = 3
Gender, M / F	7 / 5	4 / 7	3 / 1	1 / 2
Age, years	77 (48-85)	68 (57-78)	64 (53-80)	77 (67-78)
PFS1, months	12.3 (1.7-37.3)	24.9 (14.4-150.2)	18.5 (11.6-91.8)	44.0 (15.7-64.7)
TTNT1, months	15.0 (2.0-38.2)	37.0 (15.3-271.8)	19.8 (11.8-99.1)	44.0 (16.5-79.6)
ECOG	1 (0-2)	0 (0-2)	0 (0-2)	2 (1-2)
CIRS	3 (0-5)	2 (0-4)	1 (0-7)	2 (2-2)
Frailty score	2 (0-4)	1 (0-3)	1 (0-2)	2 (1-3)
Hemoglobin, g/dl	11.8 (8.1-14.7)	12.1 (8.0-15.0)	10.9 (7.8-14.8)	10.2 (9.5-10.9)
WBC, x10 ³ /ml	6.4 (2.6-15)	7.6 (4.3-17.3)	6.7 (4.0-38.5)	7 (5.6-8.4)
Neutrophil count, x10 ³ /ml	4.4 (1.1-11.2)	5.8 (2.1-15.5)	3.3 (2.4-3.4)	4.5 (4.0-4.9)
Platelet count, x10 ³ /ml	167 (71-307)	215 (8-291)	63 (6-254)	226 (91-253)
LDH value, U/l	451 (308-775)	393 (285-1062)	659 (344-4161)	381 (288-1229)
Serum creatinine, mg/dl	0.85 (0.62-4.05)	0.76 (0.54-2.32)	0.86 (0.84-1.74)	0.89 (0.65-0.99)
% bone marrow plasma cells	35 (2-80)	70 (5-90)	10 (5-60)	60 (40-80)

Data are expressed as median (range)

P45

ORAL CYCLOPHOSPHAMIDE'S ADDITION IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS WITH BIOCHEMICAL PROGRESSION DURING LENALIDOMIDE-DEXAMETHASONE TREATMENT

Cesini L.¹, Siniscalchi A.², Grammatico S.¹, Andriani A.³, Fiorini A.⁴, De Rosa L.⁵, Za T.⁶, Rago A.⁷, Caravita T.², Petrucci M.T.¹

¹Department of Cellular Biotechnologies and Haematology, Sapienza University of Rome, Rome; ²Institute of Haematology, S. Eugenio Hospital, Rome; ³Department of Haematology, Nuovo Regina Margherita Hospital, Rome; ⁴Department of Hematology, Belcolle Hospital, Viterbo; ⁵Department of Haematology, S. Camillo Hospital, Rome; ⁶Institute of Haematology, Catholic University, Rome, Italy

Introduction: Multiple Myeloma (MM) remains an incurable disease despite recent advances in therapy and supportive care. Lenalidomide combined with dexamethasone (Rd) is one of the current standards for treatment of relapsed-refractory multiple myeloma (RRMM). However, since the majority of patients (pts) become resistant to Rd, we evaluated the addition of oral cyclophosphamide (CRd) in patients who experienced biochemical relapse, without organ damage MM-related, during the treatment. **Patients and Methods:** We performed a multicenter retrospective analysis of 31 patients with RRMM treated with Rd, who received cyclophosphamide at biochemical relapse. Data were collected in 7 Italian Centers of the Multiple Myeloma GIMEMA-Latium Region Working Group. The median age of patients was 70 years (range: 50-86); 15 males and 16 females. The median line of previous treatments was 1 (range: 1-4), including novel agents used in 18 patients. The CRd regimen, consisted of lenalidomide (25 mg/day on days 1-21 every 28 days) and dexamethasone orally provided at the dose of 40 mg (20 mg for elderly pts) once a week, combined with cyclophosphamide (50 mg/day on days 1-21 every 28 days). Median time from diagnosis to the first CRd cycle was 32.4 months (range: 8.5-187). The CRd regimen was continued in responding patients or in stable disease (SD) until disease progression (PD). **Results:** According to the protocol all patients developed a biochemical relapse during Rd treatment, after a median time of 18.5 months (range: 1-49) and received cyclophosphamide without lenalidomide dose modification. All patients received Rd with a median of 15 cycles (range: 1-52). Side effects (grade 3/4) were neutropenia (19%), anemia (9.7%), muscle cramps (9.7%), polyneuropathy (9.7%), diarrhea (6.5%), infections (6.5%), esophagitis (3.2%) and rash (3.2%). One patient experienced pulmonary embolism (3.2%). The median number of CRd cycles administered was 8 (range: 1-35) and the median time to response after CRd was 2.5 months. A response was observed in 9 (29%) patients, particularly 3 very good partial response (VGPR) and 6 partial response (PR). Ten patients obtained a SD and 12 a PD. Among the responding patients, 3 are still in therapy. No correlation between Rd and CRd responses was observed. After a median observation time of 40 months, the median overall survival (OS) from the diagnosis of MM and from the beginning of CRd were 78.8 and 17.7 months, respectively. No significant difference in OS was observed between patients who added cyclophosphamide after 1 or > 1 prior antimyeloma regimen (OS 22.9 months vs. 13.5 months, p=0.65). The age at diagnosis (> or < 70 years) was not predictive of outcome, with a median OS of 17.7 and 13.8 months for pts > or < 70 years, respectively (p=0.94). In addition, median time to progression (TTP) was 7.6 months (range: 1-33) and the median progression free survival (PFS) from the beginning of CRd was 13.1 months. No additional adverse events were observed by adding cyclophosphamide to Rd. After a median follow up of 11 months (range: 1.3-50.9), there were no treatment-related deaths, but 17 pts (55%) died for progressive myeloma, with a median time of 9.1 months (range: 1-38). **Conclusions:** We confirm that Rd is an effective and well tolerated regimen for patients with RRMM and the addition of oral cyclophosphamide delays the progression in patients, who present a biochemical relapse during Rd treatment.

P46**THE OUTCOME OF SECOND AUTOLOGOUS STEM CELL TRANSPLANTATIONS IN MULTIPLE MYELOMA – A SINGLE CENTRE EXPERIENCE**

Minarik J.¹, Faber E.¹, Raida L.¹, Sztokowski T.¹, Skoumalová I.¹, Pika T.¹, Krhovská P.¹, Bacovsky J.¹, Zapletalová J.², Scudla V.¹, Papajik T.¹

¹Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc; ²Department of Biophysics and Statistics, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic

Aims: The aim is to present the outcomes of the second autologous stem cell transplant (ASCT) in patients with relapsed multiple myeloma (MM). **Patients and Methods:** Altogether 74 patients underwent ASCT for relapse at our department. 62 patients had second autologous transplants, the rest were tandem transplants or third autologous transplants. The conditioning used included BEM (BCNU, etoposid and melphalan) in 24% (15/62), BuMel (busulfan, melphalan) in 42% (26/62), high-dose melphalan in 18% (11/62) and other regimens in 16% (such as melphalan combined with other chemotherapeutics or steroids). The re-induction regimens included conventional chemotherapy – regimen CAD (cyclophosphamide, adriamycin, dexamethasone) in 27% (17/62), bortezomib (BTZ) based regimen in 31% (19/62) and thalidomide (THAL) based regimen in 18% (11/62), other patients (24%) had lenalidomide (LEN) based regimens, polychemotherapy or no re-induction. We assessed response rates, i.e. the rate of complete remissions (CR), very good partial remission (VGPR), partial remission (PR), minimal response (MR), stable disease (SD), progressive disease (PG) and overall response rate (ORR – defined as \geq PR) based on International Myeloma Working Group (IMWG) criteria, both pre-transplant and at day +100 after ASCT. The survival measures were evaluated by means of progression free survival (PFS). We assessed the efficacy of ASCT with respect to pre-transplant and post transplant response achieved, and with respect to Durie-Salmon (DS) and International Staging System (ISS) as well as to treatment modality used for induction. **Results:** The response rates after re-induction before second ASCT were as follows: CR 6.9%, VGPR 3.4%, PR 37.9%, MR+SD in 19% and PG in 32.8%. The response rates after transplant were: CR 26.7%, VGPR 13.3%, PR 38.3%, MR+SD 8.3% and PG 13.3%. Median PFS after the second ASCT was 20 months. Despite low patient counts, we found significant differences in PFS with regard to depth of response (CR 34.8 months, VGPR 22.5 months, PR 33.1 months, MR and SD 18.8 months, PG 6.6 months $p < 0.0001$). There were no differences in PFS with respect to either ISS or DS stage, and with respect to re-induction treatment used (i.e. conventional chemotherapy, BTZ or THAL based induction). Patients transplanted in their first relapse tended to have better PFS than in later relapses, the low patient counts in these sub-cohorts, however, precluded valid statistical analysis. **Conclusion:** The use of second ASCT represents a fair alternative to current treatment modalities in relapsed MM. Despite poorer pre-transplant responses, the final post-transplant outcomes as well as PFS are comparable to most of recent therapeutic approaches including combination regimens with novel drugs, moreover with unexpectedly high rate of complete responses. As expected, ISS and DS staging were not predictive of therapeutic outcome at relapse, interestingly, neither were re-induction treatment approaches. Supported by the grant IGA-LF-2017-007.

P47**COMFORTABLE MANAGEMENT OF INFUSION-RELATED DURING DARATUMUMAB FIRST INFUSION**

Parisi M., Del Fabro V., Martino E., Calafiore V., Sapienza G., Conticello C., Romano A., Di Raimondo F.

Division of Hematology, A.O. "Policlinico-Vittorio Emanuele", University of Catania, Catania, Italy

Background: In patients with relapsed/refractory multiple myeloma (RRMM) treatment with Daratumumab (Darzalex®), a novel MoAb whose target is MM cells specific antigen CD38, improves ORR, at least VGPR, and PFS compared to non-MoAb-based regimens. Its efficacy and safety is evident both in monotherapy and in triplet regimens (daratumumab, lenalidomide, and dexamethasone), suggesting the relevant role of CD38 as an effective target for treatment of RRMM. However, clinical trials with daratumumab (DARA) showed a high occurrence of any grade Infusion-Related Reactions – IRRs – (about 50% of cases), while at least grade 3 IRRs are

present in about 5% of patients. **Aim:** Since 1) the occurrence of IRRs can be influenced by the infusion rate, 2) highest risk of reaction is during the first or second exposure to MoAb, 3) IRRs can induce infusion delayed or interruption and need of patient hospitalization, 4) the first patient treated with DARA in our Division requested hospitalization and infusion lasted more than 12 hours; despite the use of pre-medication, we try to manage differently first infusion of DARA. **Methods:** In order to prevent or reduce IRRs and manage in a more comfortable way DARA treatment, we decided to split DARA administration over 2 days for the first infusion of cycle 1, and, to this aim, first infusion solution was prepared as 250 ml dilution of DARA, for the first day, and 750 ml for the second day. Infusion was anticipated by standard pre-medication. This management was performed in seven RRMM patients. Among these patients 2 had a high risk of IRRs because they had a history of known obstructive pulmonary disease and recurrent episodes of pneumonia. All patients were heavily pre-treated RRMM patients. **Results:** Of 7 RRMM patients in which DARA first infusion was split in 2 days of infusion, all seven patients completed treatment. 4 patients are almost at third cycle, the others are completing the second. During first day infusion all patients but one presented a IRR. Six patients presented grade 1-2 IRR, treated with suspension of infusion for about 20-30 minutes and, in case of persistence of IRRs, infusion of antipyretics or antihistamine. IRRs were cough in 4 patients, congestion and runny nose in 3 patients, throat tightness and dyspnea in 2 patients and chills in 1 patient. IRRs started in every case during infusion at rate of 100 ml/h. Restarted infusion after IRRs at 50 ml/h did not presented any problem for patients. Rarely, a second manifestation of IRRs occurred again when infusion rate was incremented at 100 or 150 ml/h. Symptoms were treated in the same way and resolved promptly. During the first day the time of infusion of 250 ml of diluted drug lasted variably but not more than 5-6 hours (pre-medication included). In the second day of first infusion, after premedication with 60 mg of methyl-prednisolone, antipyretic and antihistamine, patients did not experienced any IRRs, ending DARA administration in about 6 hours. In this way, patients and clinicians worries for DARA-IRR were completely resolved. **Conclusion:** Despite premedication first infusion of DARA has an high incidence of any grade IRRs. Splitting infusion in two days seems to be more accepted by patients. IRRs in our experience presented only at first day. During the second part of infusion in the second day, no reaction was observed.

P48**EFFICACY, SAFETY AND TOLERABILITY OF CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE (KRd) REGIMEN IN RR/MM**

Calafiore V.*, Martino E.*, Parisi M., Sapienza G., Del Fabro V., Leotta S., Romano A., Conticello C., Di Raimondo F. *these authors are co-authors

Division of Hematology, A.O. "Policlinico-Vittorio Emanuele", University of Catania, Catania, Italy

Carfilzomib, Lenalidomide and Dexamethasone (KRd) is currently utilized in relapsed/refractory multiple myeloma (RRMM) patients that have experienced almost one line of treatment. Improved progression free survival and overall survival was detected in this setting of patients treated with this combination in clinical trials. Although the onset of new cardiovascular events (CV) or worsening of pre-existing CV events have been described in less than 10% of patients, the regimen has an acceptable safety and tolerability. Since its approval in Italy on November 2016, data on real life use of this regimen are still lacking. We therefore conducted an analysis of RRMM patients treated with KRd out of clinical trials to provide further insights on efficacy, tolerability and safety of this second line therapy. From November 2016 up to now 30 RR patients (previous lines 1-6) were exposed to KRd regimen; 47% was classified as high risk patients (r-ISS). We report results of the first five 9-months safety interim analysis on KRd treatment of RRMM. Data cut-off was August 15, 2017. 30 pts with a median age of 64.5 years (range 49-77) were evaluated. At least 5 KRd treatment cycles were given to 16 (53%) patients. Response to treatment starts from first/second cycle. At the end of the second cycle 21 (70%) patients obtained a response. Overall response rate was nearly 90% among the 16 patients that have completed 5 cycles. Partial response were observed in 6 patients (20%). Rate of \geq Very good PR was 27% (8 patients); 4 patient (13%) achieved complete response (CR), 7 patient minimal response (MR), 3 patients obtained respectively CR, PR and PD and then progressed; progression occurred in all of the 3 patients after 3 cycles. To identify patients that could obtain the most advantage by KRd treatment, we distinguished patients that have completed almost three cycles in two groups, based on previous exposure or not to le-

lenalidomide (Table 1). The 13 patients previously treated with lenalidomide (group A), compared to 15 patients not exposed to lenalidomide (group B), showed a worst profile: in the group A there was a higher percentage of refractory patients (25% vs 11%, $p=0.0007$) who received more prior treatments, despite the duration of the last treatment was similar in both groups. The regimen was well tolerated, with grade 3-4 hematological and non-hematological adverse events on 6 (20%) and 15 (50%) patients respectively. Grade 3-4 non-haematological AEs occurred in 30% of patients, the most common being pneumonia/fever (10/7%), hypertension (23%) hyperglycemia (3%), and cardiac failure (7%). CV AEs were 30%. Patients with ≥ 1 CV risk factor at enrolment had an increased risk of developing a CV AE during treatment as compared to patients with no CV risk factors. One patient died of infection (not treatment-related). In patients who developed serious AE, KRd dose reduction (7%) and discontinuation (10%) were applied. Onset of CV events significantly increased the rate of dose reductions and treatment discontinuation. Rate of VGPR obtained with KRd combination was high with an overall response of about 90%. Safety profile was acceptable with a 30% percentage of CV events. Additional analyses are needed to evaluate the impact of these patterns on efficacy. It is likely that to obtain maximum benefit from carfilzomib, particularly those patients with pre-existing CV events, should be carefully assessed for most appropriate dosage of treatment.

Table 1. Evaluation of KRd efficacy based on previous lenalidomide exposure.

	Previous exposure to lenalidomide (n = 13) Group A	No previous exposure to lenalidomide (n = 15) Group B	p-value
Median age, years (range)	65 (49-77)	66 (51-78)	0.2
Males, n (%)	10 (77%)	8 (55%)	0.2
Paraproteins (isotype), n (%)			
Immunoglobulin G	10	7	0.13
Immunoglobulin A	1	3	0.6
Light chain only	2	5	0.39
Cytogenetics			
del13q	2	2	>0.99
t4,14 or t11,14	3	4	>0.99
del17p	1	1	>0.99
normal	7	8	>0.99
Stage ISS			
I	7	6	0.7
II	2	4	0.65
III	4	5	>0.99
Prior treatments			
Single autologous SCT	4 (14%)	1 (3.5%)	0.15
Double autologous SCT	4 (14%)	7 (25%)	0.46
Median of prior treatments	5	2	0.46
Status disease			
Relapse	6 (21%)	12 (43%)	0.0007
Refractory	7 (25%)	3 (11%)	
PFS from the last treatment			
< 6 months	5 (18%)	5 (18%)	0.12
6-12 months	4 (14%)	6 (21%)	0.11
> 12 months	4 (14%)	4 (14%)	0.12
Response after two cycles			
At least PR	5 (18%)	11 (39%)	0.0005
Less than PR	8 (29%)	4 (14%)	
Best response			
At least PR	6 (22%)	12 (43%)	0.0004
Less than PR	7 (25%)	3 (10%)	

P50

KRD (CARFILZOMIB PLUS LENALIDOMIDE PLUS DEXAMETHASONE) IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA: A REAL LIFE SURVEY IN CAMPANIA REGION IN SOUTHERN ITALY

Palmieri S., Rocco S., Migliaccio I., Cerchione C., Catalano L., Ferrara K., Peluso I., Monaco G., Farina G., Gagliardi A., Barone M., Esposito D., Amico V., Arcamone M., Fontana R., Sementa A., Sica A., Svanera G., Pane F., Ferrara F.

Hematology and SCT Unit "Cardarelli" Hospital, Naples; Hematology AUOP "Federico II", Naples; Onco-Hematology "S. Anna e S. Sebastiano" Hospital, Naples; Hematology "Ascalesi" Hospital, Naples; Onco-Hematology "Tortora" Hospital, Salerno; Hematology "San Giuseppe Moscati" Hospital, Taranto; Hematology "Rummo" Hospital, Benevento; Hematology/Oncology and SCT Unit Fondazione "Pascale", Naples; Hematology AOU "Ruggi d'Aragona", Salerno; Hematology and SCT Unit "San Giuseppe Moscati" Hospital, Avellino; Onco-Hematology AOU "Vanvitelli", Naples; Hematology "San Giuliano" Hospital, Naples, Italy

From April 2016, Carfilzomib, a second generation proteasome inhibitor, became available for use in routine practice in Italy. Approved indication is in combination with Lenalidomide and Dexamethasone (KRd) for patients with relapsed or refractory Multiple Myeloma (MM). Schedule includes initial 12 courses to be repeated every 28 days of: K 27 mg/sqm dd 1, 2, 8, 9, 15, 16 (20 mg/sqm in the first two doses of first cycle); R 25 mg dd 1 to 21; D 40 mg dd 1, 8, 15, 22; then further 6 cycles with only 4 doses of K; and finally maintenance with R only. We performed a survey in the whole Campania region to evaluate number and characteristics of patients treated accordingly so far. In all the 12 Hematologic Divisions of the region at least one patient has been treated with KRd. Most relevant clinical and disease data of the total 66 patients are summarized in the Table.

Table. Patients characteristics.

Number of patients	66
Sex: M/F	41/25
Median age at diagnosis, years (range)	58 (38-76)
Median age at KRd, years (range)	62 (42-81)
Number of previous lines:	
One	17 (26%)
Two	26 (39%)
Three	16 (24%)
≥ Four	7 (11%)
Previous ASCT: Y/N	48 (73%) / 18 (27%)
Previous Bortezomib: Y/N	62 (94%) / 4 (6%)
Previous Lenalidomide: Y/N	30 (45%) / 36 (55%)
Best response to previous treatments:	
Complete remission	24 (36%)
Very good partial remission	31 (47%)
Partial remission	9 (14%)
No response	2 (3%)
Median duration of PFS1, months (range)	29 (3-110)
Reason for treatment with KRd:	
Biochemical relapse	11 (17%)
Symptomatic relapse	27 (41%)
Refractory to last treatment	28 (42%)
Laboratory at KRd:	
Median WBC (x10E3/ul) (range)	4.87 (1.45-10.4)
Median Hb (g/dl)(range)	11.2 (7-16.4)
Median Plt (x10E3/ul) (range)	161 (16-383)
Median Creatinine Clearance (ml/min)(range)	98 (15-122)
Median LDH (IU/L)(range)	277 (107-551)

Median number of courses administered so far is 5 (range 1-16). At last data collection, 56 cases were evaluable for response, Overall Response Rate being 86%. More in detail, we observed: Complete Remission=14 (median time to CR: 5 cycles), Very Good Partial Remission=22, Partial Remission=12. In eight cases there was no response to treatment (Stable disease=3, Progression=5). Seven responding patients have relapsed after a median of

8 months of Progression Free Survival (PFS), and have stopped treatment. A total of nine patients have died (8 patients from progressive disease; 1 patient in PR from sepsis). Hematologic toxicity was negligible and present especially during the first courses. Transfusion support was necessary in only 6 patients. Infections were recorded in 22 patients (1 fatal; 21 grade two or three, mainly bronchitis). In 21 patients at least one episode of arterial hypertension requiring treatment was observed. One patient with previous cardiopathy and diabetes suffered from acute myocardial infarction, resolved without functional sequelae after cardiologic treatment, one patient experienced atrial fibrillation, and in both cases treatment with K was discontinued. Finally, 7 cases of thrombosis and one case of tumor lysis syndrome were recorded. On the other side, in 30/66 patients (45%) no toxicity at all was observed. Delay of treatment was necessary in 29 patients. Dose of K was reduced in 3 cases during treatment, while in 7 less fit patients a lower dose (20 mg/sqm) was used from the beginning. Above all, therapy has been stopped in 17 patients (Toxicity=4; No response=3; Progression=7; Medical decision=3). Medium number of admissions to Day Hospital Unit per single cycle was 6.6, which compares unfavorably to other regimens, namely RD. Hospitalization for treatment was needed in only one patient, due to MM related poor performance status. Finally, after splitting our cases in two groups based on their chronological time of treatment (first 33 vs second 33), we observed that KRD was used as second or third line in 17 (51%) vs 27 (81%) cases, and as fourth line or more in 16 (49%) vs 6 (19%) cases, respectively. In conclusion, our data confirm that KRD is highly effective in relapsed refractory MM but needs careful evaluation of toxic effects, especially cardiologic. KRD has rapidly become a standard treatment for RRMM, but longer follow up is needed to further confirm its superiority to other regimens. As expected, our survey shows that as time goes and more experience is acquired, there is an evident trend to anticipate KRD in the therapeutic algorithm.

P51

LONG TERM DISEASE CONTROL WITH POMALIDOMIDE AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS: A REAL LIFE EXPERIENCE

Parisi M., Conticello C., Leotta S., Martino E., Calafiore V., Del Fabro V., Piroso M.C., Romano A., Di Raimondo F.

Division of Hematology, A.O. "Policlinico-Vittorio Emanuele", University of Catania, Italy

Pomalidomide is currently utilized in relapsed/refractory multiple myeloma (RR MM) patients that have experienced bortezomib and lenalidomide treatment. In this setting the drug has shown in clinical trials improved survival and good tolerability. Approval in Italy has been on 2015 and data on real life are still poor. We conducted an analysis of RR MM patients treated with pomalidomide and dexamethasone (PomaD) in real life, previously enrolled in an interventional (STRATUS, MM-010) or currently enrolled in an observational study (MM-015) to provide further insights on this salvage therapy. Between January 2016 and July 2017, 41 RR MM patients were treated with pomalidomide 4 mg daily po on days 1–21 of each 28-day cycle and dexamethasone 40 mg weekly (≤ 75 years) and 20 mg weekly (> 75 years). Among patients 14 were enrolled in MM-015 study (an observational study) whereas additional 15 come from MM-010 study (a single-arm phase 3b study). We describe a total of 56 patients (median age 68 years, range 42–78). Median number of prior therapies was 4 (range 2–7). 29 (51%) patients had pre-existing severe anemia, 5 (9%) thrombocytopenia, 14 (25%) had renal impairment, 10 (18%) extramedullary myeloma; 14 (25%) was high risk patients (r-ISS), 7 (12%) previously allo-transplanted. A median number of 8 (range 1–21) PomaD treatment cycles were given. Overall treatment duration mean was 7.7 months. About a half of the patients (27, 48%) responded after at least one cycle. After a median follow-up of 12 months, median PFS and OS for patients were 6,7 and 9,9 months, respectively. At enrollment, 29 (51%) of patients were anemic, 15 (27%) neutropenic. The regimen was well tolerated with grade 3–4 haematological and non-haematological adverse events in 10 (18%) and 27 (48%) patients respectively. Grade 3–4 non-haematological AEs occurred in 48% of patients [most common: fatigue (7, 12,5%), pneumonia (6, 11%), diarrhea (3, 5%), glucose metabolism alteration (3, 5%), thromboembolism (2, 3,5%), diffuse erythema (2, 3,5%), hyponatremia (2, 3,5%), atrial flutter (1, 2%), acute renal failure (1, 2%)]. In pts who developed serious AE, pomalidomide dose reduction (7, 12,5%) and discontinuation (11, 20%) were applied. All patients responded to treatment at the first/second cycle. Mostly PR and SD were observed. After a median time of 8 months (range 2–21) all patients relapsed. Data on 6-Months control of disease are favorable and related to Durie and Salmon stage. Almost 50% of

patients obtained a control of disease with clinical benefit lasting 6 months. Moreover, patients with Stage I-IIA at PomaD-beginning had better probabilities of obtaining control of disease lasting almost 6 months. An unexpected data was the comparison between PFS obtained with the treatment before pomalidomide (previous treatment PFS, pPFS) and the PFS obtained with PomaD treatment (poPFS). 17 patients (30%) obtained a PFS longer than the precedent one. Among these patients, 6 were enrolled in STRATUS protocol and treatment was stopped at biochemical progression (25% increase in protein M) according to the indication of the protocol. Difference between poPFS and pPFS was not statistically significant (log-rank p value 0.5). Results indicate that in real life PomaD is well tolerated in RR MM patients prolonging PFS and OS with acceptable toxicity. Notably PFS could be superior to that obtained with precedent treatment and treatment may induce almost 6 months disease control in most patients intensively pre-treated.

P52

RELEVANT REDUCTION OF POMALIDOMIDE-RELATED NEUTROPENIA BY INTENSIVE USE OF MYELOID GROWTH FACTOR

Parisi M., Calafiore V., Martino E., Del Fabro V., Romano A., Sapienza G., Conticello C., Di Raimondo F.

Division of Hematology, A.O. "Policlinico-Vittorio Emanuele", University of Catania, Italy

Neutropenia and complications of neutropenia such as febrile neutropenia (FN) or pneumonia, are one of major hematological toxicity associated with cancer chemotherapy. It often results in drug dose reduction or delay or interruption, thus leading to morbidity, mortality, and high costs of patient management. Granulocyte colony-stimulating factor (G-CSF) is a myeloid growth factor able to reduce the risk of neutropenia and its complications, enabling safe and effective chemotherapy dose intensity. Hematological and not hematological toxicity of immunomodulatory drug pomalidomide has been studied in association with dexamethasone (PomaD) particularly in three main clinical trials (MM02, MM03 and MM10) in relapsed refractory multiple myeloma (RRMM) patients. The most frequent hematological adverse event of grade 3/4 is neutropenia (48%-50%), followed by anemia (22%-32%) and thrombocytopenia (19-31%).

Table 1.

	pre-treatment	I cycle	II cycle	III cycle	IV cycle	V cycle	VI cycle	Total
Median of leukocyte count $\cdot 10^9/L$	3,76	3,94	4,04	4,1	4	4,28	4,12	4,04
Median of ANC $\cdot 10^9/L$	2,04	1,95	1,62	1,86	1,91	1,79	1,71	1,86
Mean of leukocyte count $\cdot 10^9/L$	4,11	4,26	4,07	4,17	4,26	4,23	4,02	4,16
Mean of ANC $\cdot 10^9/L$	2,42	2,46	1,79	2,04	2,06	2,03	1,86	2,09

Among non-hematological grade 3/4 adverse events pulmonary infections have an incidence between 10% and 20%. In the same clinical trials the frequency of dose reduction was about 30 % and treatment was temporary interrupted in about 60%, of patients, while it was definitively interrupted in about 5% of patients. Here we describe the analysis of a total of 51 RRMM patients treated with PomaD. G-CSF was used (mean dose 60 MU) one week after starting pomalidomide therapy when leukocyte counts were $\leq 2.5 \times 10^9/L$ and neutrophils $\leq 1.5 \times 10^9/L$. Median age was 68 years (range 42–78), median number of prior therapies was 4 (range 2–7) and the majority of patient (33/51) were treated for almost 6 cycles (overall treatment duration mean 7.7 months). We decided to maintain a $> 2.0 \times 10^9/L$ leukocyte count with ANC $> 1.5 \times 10^9/L$ in attempt to reduce the incidence of neutropenia and its complications. In our cohort of patients, hematological adverse events occurred at a reduced rate. In particular, neutropenia was present only in 9% of cases, anemia in 5,5% and thrombocytopenia in 3,5%. Reduced frequency of neutropenia among our patients should be attributable to the use of prophylaxis with G-CSF one week after starting of PomaD in that patients with leukocyte counts $\leq 2.5 \times 10^9/L$ and ANC $\leq 1.0 \times 10^9/L$. In this way, we maintained for almost 6 cycles a median of $> 3.5 \times 10^9$ leukocyte count (mean $4 \times 10^9/L$) with a median of neutrophils $> 1.5 \times 10^9/L$ (mean $2 \times 10^9/L$). Table 1 describes mean

and median of leukocyte count and ANC for every cycle till the sixth in 33/51 RRMM patients that were treated for almost six cycles with PomaD. We also obtain a significant reduction of the incidence of FN, present only in 11% of patients. In addition, in this setting of prophylaxed patients, the dose of pomalidomide was reduced only in 12.5% and temporary interrupted in less than 20%. Our data suggest that intensification of G-CSF prophylaxis can reduce frequency of serious adverse events and enable full dosage of pomalidomide with limited reduction or interruption of this drug.

P53

CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: A SINGLE CENTRE REAL-LIFE EXPERIENCE

Guidotti F., Ferla V., Gregorini A.I., Rossi F.G., Pompa A.

Hematology Unit, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico and University of Milan, Italy

Background: Carfilzomib is a second-generation proteasome inhibitor approved in combination with dexamethasone or with lenalidomide plus dexamethasone (KRd) for the treatment of relapsed/refractory multiple myeloma (MM) after 1-3 prior lines. KRd has shown efficacy in phase III trials with improved PFS and OS when compared to Rd together with a good toxicity profile. Here we describe our real-life experience with KRd in patients with relapsed/refractory MM outside clinical trials, reporting efficacy and toxicity data available until now. **Methods and Results:** At our institution, 20 patients were treated with KRd (administered at standard schedule) between November 2016 and January 2018. ISS and R-ISS groups at diagnosis were respectively: stage 1 11/7, stage 2 5/13, stage 3 4/0. Four patients had high risk cytogenetic. Median number of previous lines of therapy was 2 (range 1-6). Patients exposed/refractory to Bortezomib and Lenalidomide were respectively 95%/16% and 60%/25%. Eighty percent of patients received at least one ASCT (9 of them double ASCT). One patient received alloSCT. Median age at KRd treatment was 62 (range 47-79) with a male ratio of 55%. Median time from diagnosis to KRd treatment was 6.1 years (range 0.3-13.2). Laboratory parameters at treatment initiation were: median Hb 10.8 g/dl (range 8.6-13.5), median CM value 2.4 g/dl (0-4.1); 25% of patients had a creatinine clearance below 60 ml/min. Patients received a median of 8 KRd cycles (range 1-14). Median follow up was 6.75 months. Overall response rate was 80% (CR 15%, VGPR 20% and PR 45%) with a median time to best response of 2.1 months (0.9-21.0). Median duration of response was of 6.7 months. Most common adverse events were hematological with 50% and 40% of patients experiencing respectively grade 1-2 and 3-4 toxicity. Other major toxicity was cardiovascular with 5 (25%) and 2 (10%) cases of respectively grade 2 and 3 hypertension; 2 (10%) patients had grade 3 left ventricular (LV) systolic dysfunction and 1 of them developed also pulmonary hypertension. Five patients (25%) had grade 2 hypertriglyceridemia and 1 (5%) grade 3, while 4 (20%) patients had grade 1-2 hypercholesterolemia. Grade 1-2 infections occurred in 5 patients (20%), and grade 3-4 in 3 (15%). Finally one patient had grade 3 tumor lysis syndrome with transient acute renal failure. Five patients interrupted KRd because of disease progression. Only one patient stopped Carfilzomib because of cardiac toxicity: it occurred after ten KRd cycles and was detected thanks to pro-BNP monitoring; subsequent echocardiography confirmed a global moderate reduction of LV ejection fraction (40%). The remaining fourteen patients are still on treatment with good compliance. **Conclusions:** KRd appears to be an effective and safe regimen also in the real-life population. ORR was 80% (35% > VGPR) and toxicities mainly hematologic. A major concern remains the risk of cardiovascular complications which may also lead to treatment discontinuation. Therefore, even if cardiologic follow up is not standardized for these patients, a careful evaluation of cardiovascular risk factors at baseline and periodic monitoring of LV function, indirectly through pro-BNP and directly with echocardiography, is mandatory to prevent serious damages. In particular, long-term periodic BNP monitoring can be useful given the possibility of later cardiotoxicity.

P54

BENDAMUSTINE-BORTEZOMIB-DEXAMETHASONE (BVD) IN THE MANAGEMENT OF RELAPSED AND REFRACTORY MULTIPLE MYELOMA: A REAL-LIFE EXPERIENCE

Cerchione C.¹, Catalano L.¹, Pareto A.E.¹, Nappi D.¹, Basile S.¹, Marano L.¹, Peluso I.¹, Simeone L.¹, Vitagliano O.¹, Romano A.³, Palmieri S.², Rocco S.², Pane F.¹, Ferrara F.²

¹Hematology, AOU Federico II, Naples; ²Hematology, AORN A. Cardarelli, Naples; ³Age Related Diseases Unit - Division of Genetics and Cell Biology - San Raffaele Scientific Institute, & Università Vita-Salute San Raffaele, Milano, Italy

Bendamustine is a bifunctional alkylating agent, with low toxicity, proved to be effective in relapsed, refractory and in new diagnosed Multiple Myeloma (MM). It has been evaluated efficacy and tolerance of Bendamustine, in combination with bortezomib-dexamethasone (BVD) in patients with relapsed and refractory MM (rrMM), whose prognosis is particularly severe. A regional retrospective real-life analysis of patients with rrMM who had been treated with BVD as salvage therapy has been performed. 56 patients (31 M/25 F), with rrMM, median age at diagnosis 57.3 years (r. 36-82), median age at start of treatment 61.8 years (r.37-83) treated with several lines of treatments (median 6, r. 2-11), every refractory to all the drugs previously received (also Bortezomib), received BVD (Bendamustine 90 mg/sqm days 1,2; Bortezomib 1.3 mg/sqm days 1,4,8,11, Dexamethasone 20 mg days 1,2,4,5,8,9,11,12, Pegfilgrastim day +4) every 28 days, until progression. ISS was equally distributed, and cytogenetic was evaluable in 12 patients, and in particular one del13q and one t(11;14). All the patients had previously been treated with schedule containing bortezomib and IMiDs, and 30% had also received radiotherapy. 67% of them had undergone at least to a single auSCT. All patients were relapsed and refractory to last therapies received before BVD. Bendamustine was well tolerated, with grade 3 transfusion-dependent anemia in 41% of patients, and 37% grade 3 neutropenia (no hospitalization was required, no septic shocks were observed). No severe extrahematologic toxicity was observed, only grade 1 gastrointestinal side effect (nausea), treated by common antiemetic drugs. According to IMWG, after a median follow-up of 14 months (r.2-36), ORR was 64% (36/56 : 4 CR, 7 VGPR, 16 PR, 9 MR) with 8 PD and 12 patients in SD, which can be considered as an impressive result in this subset of rrMM patients. In particular, for 11 patients, BVD was, after having achieved at least a PR, a bridge to second auSCT, and for two patients a bridge to alloSCT. Three patients have shown a notable PR after failure of novel agents (i.e. Carfilzomib and Pomalidomide). Median time to response was 1.2 months (r.1-3), median OS from diagnosis was 62.7 months (range 6-151), median OS from start of Bendamustine was 9.8 months (range 2-36). The triplet Bendamustine-Bortezomib-Dexamethasone has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, and, in particular cases, it could be considered as a bridge to a second autologous or allogenic SCT.

P55

IMPACT OF NOVEL AGENTS ON AGGRESSIVE RELAPSE OF MULTIPLE MYELOMA: A SINGLE CENTER EXPERIENCE

Martino E., Parisi M., Calafiore V., Sapienza G., Del Fabro V., Romano A., Conticello C., Di Raimondo F.

Division of Hematology, A.O. "Policlinico-Vittorio Emanuele", Catania, Italy

Background: Therapeutic advances, notably the development of regimens that incorporate immune-modulatory drugs (lenalidomide and pomalidomide) and proteasome inhibitors (e.g. bortezomib and carfilzomib), have improved survival outcome in multiple myeloma (MM). However, MM remains largely incurable and patients invariably develop relapsed or refractory (R/R) disease, a new unmet clinical need to face for hematologists. Relapse can be characterized according to disease aggressiveness and the presence of clinical symptoms. Aggressive disease relapse can occur at biochemical level, due to rapid and relevant increase of monoclonal component or LDH, or at clinical level it can be defined by the presence of extramedullary disease, acute renal injury or progression to secondary plasma cell leukemia. In this retrospective study we evaluated 76 patients who relapsed after a front-line regimen containing lenalidomide or bortezomib to identify the rate of biochemical and clinical aggressive relapses and clinical outcome upon treatment with second generation novel agents (pomalidomide and carfilzomib). **Methods:** From July 2014 we evaluated 76 R/R patients (41 males and 35

females, median age 62 years, range 45-78). Median number of previous line was 3 (1-6), half of them (43/76) underwent ASCT. Pd consisted of pomalidomide 4 mg daily given orally on Days 1-21 of each 28-day cycle and dexamethasone 40 mg weekly. KRd consisted of Carfilzomib 20 mg/m² IV on days 1 and 2 of the first cycle, then 27 mg/m² on days 8, 9, 15, 16 of the first cycle and days 1, 2, 8, 9, 15 and 16 of the subsequent cycles, Dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16 and lenalidomide 25 mg daily given orally on days 1-21 of each 28-day cycle. **Results:** 51 patients were both bortezomib and/or lenalidomide refractory and received Pd according to Italian Health System. 7 of them further progressed and received KRd, the remain 25 received KRd as second and third line therapy. 53 patients had a non aggressive relapse, while the remain 23 experienced an aggressive relapse of disease. 43 patients experiencing relapse after ASCT, 44% had asymptomatic serological relapse or progression, 66% experienced symptomatic relapse (with 38% high risk cytogenetic detected by FISH) and one-third experienced relapse featuring extramedullary disease, plasma cell leukemia or severe renal failure. In the remaining 33 patients not eligible to ASCT, 78% had not aggressive relapse. As expected median PFS obtained in Pd patients was higher for NA group (6 vs 4 months). Even if the majority of KRd patients are still under treatment, the OR was 90% with greater PFS in NA than in A group (8 vs 6 months). **Conclusions:** In our community setting data, heavily pretreated patients achieved improvement of outcome obtaining a median PFS >4 months, using KRd and Pd as salvage therapies. We found that an aggressive relapse was more frequent in young patients and that earlier treatment at biochemical asymptomatic relapse is associated to better outcome.

P56

CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE IN THE MANAGEMENT OF LENALIDOMIDE-REFRACTORY MULTIPLE MYELOMA: A REAL-LIFE EXPERIENCE

Cerchione C., Ferrara K., Peluso I., Di Perna M., Zacheo I., Nappi D., Pareto A.E., Pane F., Catalano L.

Hematology - AOU Federico II, Naples, Italy

Carfilzomib is an epoxyketone proteasome inhibitor of second generation, proved to be effective in relapsed and refractory Multiple Myeloma (rrMM). In this retrospective observational trial, it has been evaluated efficacy and tolerance of Carfilzomib, in combination with lenalidomide-dexamethasone (KRd) as salvage regimen in patients with rrMM, refractory to lenalidomide, whose prognosis is particularly severe. 21 patients (12 M/9 F), with rrMM, median age at diagnosis 62 years (r. 47-75), median age at start of treatment 65 years (r. 53-81) treated with several lines of treatments (median 3, r. 2-10), underwent to KRd regimen (ASPIRE trial schedule) for a median treatment cycles of 2 (r. 1-8). ISS was equally distributed, and cytogenetic was evaluable in 8 patients, and in particular one del13q14 1qgain, one del 13q14 and one t(11;14). 86% of patients had previously been treated with bortezomib and IMiDs. 57% of them had undergone at least to a single autologous SCT. Carfilzomib was well tolerated, with grade 2 anemia in 28% of patients, successfully managed by ESAs, without necessity of blood transfusions; 9.5% grade 3-4 neutropenia (pegfilgrastim in primary prophylaxis was given, no ospedialization was required, no septic shocks were observed); 33% grade 2, 19% grade 3 and 5% grade 4 thrombocytopenia, without hemorrhagic events and necessity of transfusions. Concerning severe extra-hematologic toxicity, it was observed pneumonia in 42% of patients, treated by common antibiotic drugs; grade 2 hypertension in 24% of patients; arrhythmias in 5% of patients; dyspnea in 5% of patients; fatigue in 33% of patients. All patients were carefully monitored by expert cardiologists. According to IMWG criteria, after a median follow-up of 3 months (r.1-13), ORR was 66,7%(14/21: 8 VGPR, 6 PR) with 3 progressive diseases and 2 patients in stable disease, which can be considered as an impressive result in this subset of rrMM patients, refractory to lenalidomide. In particular, for 1 patient, KRd was, after having achieved at least a PR, a bridge to second autologous SCT. Median time to response was 2 months (r.1-4), median OS from diagnosis was 47 months (r. 9-170), median OS from start of Carfilzomib was 3 months (r. 1-13). KRd has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, also lenalidomide, and, in particular cases, it could be considered as a bridge to a second autologous or allogeneic SCT.

P57

POMALIDOMIDE-DEXAMETHASONE IN THE MANAGEMENT OF HEAVILY PRETREATED MULTIPLE MYELOMA

Cerchione C., Nappi D., Pareto A.E., Migliaccio I., Zacheo I., Di Perna M., Peluso I., Ferrara K., Pane F., Catalano L.

Hematology - AOU Federico II, Naples, Italy

In this retrospective observational trial, It has been evaluated efficacy and tolerance of pomalidomide plus dexamethasone (PD) as salvage regimen in heavily pretreated patients with relapsed and refractory MM (rrMM), whose prognosis is particularly severe. 22 patients (13 M/9 F), with rrMM, median age at diagnosis 68 years (r. 54-80), and median age at start of treatment 71.5 years (r.61-36) treated with several lines of treatments (median 5, r. 2-8), every refractory to all the drugs previously received (also Bortezomib, Thalidomide and Lenalidomide), received PD (Pomalidomide 4 mg for 21 days, Dexamethasone 40 mg days 1,8,15,22, Pegfilgrastim day +8) every 28 days, until progression with ISS was equally distributed, and cytogenetic was evaluable in 12 patients, and in particular three del13q and one t(11;14) were present. All the patients had previously been treated with schedule containing bortezomib and IMiDs. 50% of them had undergone at least to a single ASCT. All patients were relapsed and refractory to last therapies received before PD. Pomalidomide was well tolerated, with grade 3 transfusion-dependent anemia in 45% of patients, 4% grade 3 neutropenia (pegfilgrastim in primary prophylaxis was given, no ospedialization was required, no septic shocks were observed), 18% grade 3 thrombocytopenia without hemorrhagic events and transfusion-dependence. No severe extrahematologic toxicity was observed. According to IMWG, after a median follow-up of 7.5 months (r.1-14), ORR1 (≥PR) was 39.1% (1 CR, 2 VGPR, 6 PR), but, considering that we are evaluating a cohort of heavily pretreated patients without any other alternative treatment, with really poor prognosis, another parameter should be considered, ORR2 (≥SD), considering stable disease as a successful result in progressive MM. ORR2 was 77% (1 CR, 2 VGPR, 6 PR, 8 SD). These can be considered as impressive result in this subset of rrMM patients Oral treatment gives a really good compliance, in frail and unfit patients, and response, when present, is always really fast (median time to response: 2 months (r.1-11)), median OS from diagnosis was 84 months (range 27-228), median OS from start of pomalidomide was 8 months (range 1-14). Pomalidomide-dexamethasone has shown significant efficacy and a very good compliance, thanks to oral administration, in a particularly severe setting of heavily pretreated patients, relapsed and refractory to all available therapeutic resources.

P58

BORTEZOMIB, LENALIDOMIDE AND DEXAMETHASONE IN THE MANAGEMENT OF RELAPSED AND REFRACTORY MULTIPLE MYELOMA: A REAL-LIFE EXPERIENCE

C. Cerchione, Zacheo I., Di Perna M., Nappi D., Pareto A.E., Peluso I., Ferrara K., Pane F., Catalano L.

Hematology - AOU Federico II, Naples, Italy

Bortezomib, Lenalidomide and Dexamethasone is one of the best option for frontline treatment, approved in USA but not available in Italy. However, it can show interesting results also in relapsed and refractory patients, thanks to the synergistic effect of these agents. In this retrospective observational study, it has been evaluated the tolerability and efficacy of the combination of bortezomib plus lenalidomide plus dexamethasone (VRD) in patients with relapsed and refractory Multiple Myeloma (rrMM). 22 patients (16 M, 6 F), with rrMM, median age 66 years (M, range 38-74) and 59.5 years (F, range 54-69), 36.3% of patients had ISS-1, 50% ISS-2 and 13.6% ISS-3; 3 patients had high cytogenetics risk with deletion of chromosome 13 (del13q). Patients were treated with the VRD regimen (Bortezomib 1.3 mg/sqm days 1,4,8,11; Dexamethasone 20 mg days 1,2,4,5,8,9,11,12 and oral Lenalidomide 25 mg daily on days 1-21), with a median of 4 cycles (range 1-17). Patients had received 2.5 median (range 1-5) lines of therapy. 16 of them had been treated with schedules containing Bortezomib and Thalidomide in first line therapy, 1 had been treated with alkylating agents and Bortezomib, 2 treated with Melphalan and Prednisone. 11 of them had undergone to autologous SCT. 15 patients received VRD in second line, 6 patients in third line and 1 in fifth line. According to IMWG, ORR (>SD) was 77.2% (17/22: 4.5% CR, 45.4% PR, 27.3% SD, 22.73% PD). Median time to response was 3 months (range 1-23), median OS from diagnosis was 48 months (range 12-214). Considering safety, VRD was well tolerated, with grade 1 anemia in 3 patients and grade 2 anemia in 1 patient successfully managed with ESAs, and thanks to

the way of administration, also compliance is good. Bortezomib-lenalidomide-dexamethasone triplet, thanks to a notable proved synergistic mechanism of action between bortezomib and lenalidomide, had shown significant efficacy in severe setting of heavily pretreated patients, relapsed and refractory to bortezomib and lenalidomide.

P59

IXAZOMIB, LENALIDOMIDE, AND DEXAMETHASONE FOR RELAPSED MULTIPLE MYELOMA: AN EARLY SINGLE CENTER EXPERIENCE IN RUSSIA

Luchinin A.¹, Semochkin S.², Minaeva N.¹, Samarina S.¹

¹Kirov Scientific Research Institute of Hematology and Blood Transfusion of the Medical-Biological Agency, Kirov; ²Pirogov Russian National Research Medical University, Moscow, Russian Federation

Introduction: Ixazomib is an oral proteasome inhibitor for the treatment of multiple myeloma (MM). We introduce small experience of the treatment relapse patients with MM by triplet combination including ixazomib, lenalidomide and dexamethasone. **Methods:** In this study we included 10 patients who had relapsed MM to receive ixazomib plus lenalidomide-dexamethasone (IRD treatment option). The study is ongoing. The median of age of patients is 64 years (range: 50-68). All patients have previous history MM treatment, 90% of them – only one line. The scheme IRD includes Ixazomib 4 mg on 1, 8, 15 days; dexamethasone 40 mg weekly and lenalidomide 15-25 mg daily on days 1 to 21 of a 28-day cycle. The primary end-point is treatment response. The median of the amount of cycles therapy is 3. **Results:** The overall response is 67% on the current time, including 30% of complete response plus very good partial response. The response of 1 patient is still unknown because he received only 1 cycle of therapy. The 1 patient (11%) had progression after 2 cycles and finished the treatment. Early he had 4 previous lines of treatment. Two patients (22%) was not achieved positive response after 3 and 4 cycles but they had no progression. The median follow-up is approximately 4 months (range: 1-17 months). The rate of serious adverse events is 40% including severe lung infection with hospitalization (2 patients), severe thrombocytopenia of grade 3 (1 patient) and significant urinary tract infection with temporary treatment discontinuation (1 patient). The rash of grade 2 occurred in 1 (10%) patient. There was no cases of peripheral neuropathy and all other side effects were not clinical significant and did not influence on quality of life. **Conclusion:** The addition of ixazomib to a regimen of lenalidomide and dexamethasone associates with quite high rate of positive response on relapsed MM treatment for short time. The rate of serious adverse events is also high, but these are good managed. The second end-point of this study should be progressive free survival assessment.

Special conditions

P60

A RANDOMIZED, OPEN-LABEL, MULTICENTER PHASE 2 STUDY OF DARATUMUMAB MONOTHERAPY FOR PATIENTS (PTS) WITH INTERMEDIATE OR HIGH-RISK SMOLDERING MULTIPLE MYELOMA (SMM): CENTAURUS

Cavo M.¹, Hofmeister C.C.², Chari A.³, Cohen Y.C.⁴, Spencer A.⁵, Voorhees P.⁶, Estell J.⁷, Venner C.⁸, Sandhu I.⁸, Jenner M.⁹, Williams C.¹⁰, van de Donk N.¹¹, Beksac M.¹², Kuppens S.¹³, Bandekar R.¹⁴, Neff T.¹⁴, Heuck C.¹⁴, Qi M.¹⁴, Goldschmidt H.¹⁵, Ola Landgren C.¹⁶

¹"Seragnoli" Institute of Hematology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Italy; ²Division of Hematology, Department of Internal Medicine, College of Medicine, The Ohio State University, Columbus, USA; ³Tisch Cancer Institute, Mount Sinai School of Medicine, New York, USA; ⁴Department of Hematology, Tel-Aviv Sourasky (Ichilov) Medical Center, and Sackler School of Medicine, Tel Aviv University, Israel; ⁵Malignant Haematology and Stem Cell Transplantation Service, Alfred Health-Monash University, Melbourne VIC, Australia; ⁶Levine Cancer Institute, Carolinas HealthCare System, Charlotte, USA; ⁷Haematology Department, Concord Cancer Centre, Concord Hospital, Concord, USA; ⁸Cross Cancer Institute, University of Alberta, Edmonton, Canada; ⁹Southampton General Hospital, Southampton, UK; ¹⁰School of Veterinary Medicine and Science, University of Nottingham, UK; ¹¹Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands; ¹²Department of Hematology, Ankara University, Yenimahalle/Ankara, Turkey; ¹³Janssen Research & Development; ¹⁴Janssen Research & Development, Raritan, USA; ¹⁵University Hospital Heidelberg and German Cancer Research Center, Heidelberg, Germany; ¹⁶Myeloma Service, Memorial Sloan Kettering Cancer Center, New York, USA

Introduction: While current guidelines recommend monitoring pts every 3-6 months for active MM before initiating treatment, early intervention to delay or prevent evolution of SMM to active disease could benefit pts. Daratumumab (DARA) is a humanized anti-CD38 monoclonal antibody approved as monotherapy and combined with standard of care regimens for relapsed or refractory MM (RRMM). We hypothesized that DARA may delay SMM progression to symptomatic MM. We report preliminary data from a phase 2 study (CENTAURUS: NCT02316106) of DARA in pts with intermediate or high-risk SMM. **Methods:** Pts had SMM for <5 years, no prior anti-SMM or antimyeloma therapy, and no evidence of MM or primary amyloid light chain amyloidosis. Intermediate or high-risk SMM was defined as ≥10% to <60% plasma cells in bone marrow and ≥1 of the following: serum M-protein ≥3 g/dL; urine M-protein >500 mg/24 h; abnormal involved:uninvolved free light chain (FLC) ratio (<0.126 or >8) with serum M-protein <3 g/dL but ≥1 g/dL; and/or involved serum FLC ≥100 mg/L with abnormal FLC ratio (<0.126 or >8), but not ≥100. Pts were randomized to 1 of 3 treatment arms of DARA 16 mg/kg IV in 8-week cycles: long intense (Long; weekly [QW] in Cycle 1, every other week in Cycle 2-3, every 4 weeks in Cycle 4-7, and every 8 weeks [Q8W] up to Cycle 20), intermediate (Int; QW in Cycle 1, Q8W to Cycle 20), and short intense (Short; QW for 1 cycle). Co-primary endpoints were complete response (CR) rate and progressive disease (PD; as defined by 2014 IMWG criteria for SMM)/death rate (proportion of pts who progressed to MM or died per pt-year). Other endpoints were overall response rate (ORR) and progression-free survival (PFS). We report a prespecified interim analysis of CR, which occurred 6 months after randomization of last pt; prespecified interim analysis of PD/death rate is planned at 12 months after randomization of last pt. **Results:** 123 pts were enrolled (41 in each arm). Median (range) time since initial SMM diagnosis was 6.83 (0.4-56) months. Number of pts with ≥2 risk factors at screening was balanced between arms (81% for Long and Int; 83% for Short), but more pts with high bone marrow aspirate plasma cell percentage (≥30-60%) were enrolled in Long (26%) vs Int (14%) and Short (16%). In Arm Long, Int, and Short, 10%, 10%, and 5% of pts discontinued treatment, respectively, for adverse events (AEs; 5%, 2%, and 5%), PD (2%, 5%, and 0%), pt refused further treatment (2% in Int) and withdrawal of consent (2% in Long). Common (>25%) treatment-emergent AEs (TEAEs) were fatigue, cough, headache, and insomnia; common (>1 pt) grade 3/4 TEAEs were hypertension and hyperglycemia. No hematologic TEAE was >10% across arms. Rates of grade 3/4 infection (pneumonia or sepsis) were ≤5%. Infusion-related reactions occurred in 56%, 37%, and 55% of pts; 2% in Long,

0% in Int, and 3% in Short were grade 3/4. At clinical cut-off, no deaths were observed. With median follow-up of 9.6 (range, 0-17.9) months, ORR was higher in Long than Int and Short (Table 1). Median PFS was not reached in any arm; 12-month PFS rates were 98%, 93%, and 89% in Long, Int, and Short, respectively. Updated data including prespecified analysis of PD/death rate will be presented. Conclusions: DARA was well tolerated in SMM, with a safety profile similar to that in RRMM. Efficacy follow-up is ongoing. A phase 3 study (Smm³001) of long intense dosing with subcutaneous DARA in high-risk SMM pts is planned.

Table 1.

n (%)	Long (n = 41)	Int (n = 41)	Short (n = 40)
ORR	23 (56; 95% CI, 42-69)	21 (51; 95% CI, 37-65)	15 (38; 95% CI, 25-52)
≥CR	1 (2)	0 (0)	0 (0)
sCR	1 (2)	0 (0)	0 (0)
CR	0 (0)	0 (0)	0 (0)
≥VGPR	9 (22)	7 (17)	6 (15)
VGPR	8 (20)	7 (17)	6 (15)
PR	14 (34)	14 (34)	9 (23)

Note: 1 patient in the Short intense dosing schedule was randomized but did not receive treatment.

P61

SEMAPHORIN 4D CORRELATES WITH INCREASED BONE RESORPTION, HYPERCALCEMIA AND DISEASE STAGE IN NEWLY DIAGNOSED PATIENTS WITH MULTIPLE MYELOMA

Terpos E., Ntanasis-Stathopoulos I., Christoulas D., Bagratuni T., Bakogeorgos M., Gavriatopoulou M., Eleutherakis-Papaiaikovou E., Kanellias N., Kastritis E., Dimopoulos M.A.

Department of Clinical Therapeutics, Alexandra General Hospital, National and Kapodistrian University of Athens, School of Medicine, Greece

Multiple myeloma (MM) is characterized by bone destruction due to increased bone resorption and decreased bone formation. Semaphorin-4D (CD100, Sema4D) is expressed by osteoclasts, binds to its receptor plexin-B1 and acts as a mediator of osteoclast-osteoblast interaction that ultimately inhibits osteoblastic bone formation. Preclinical data suggest that Sema4D/Plexin-B1 pathway is implicated in MM-induced bone disease. However, there is no information on the role of Sema4D in MM patients. Thus, we evaluated Sema4D and Plexin-B1 in six myeloma cells lines *in vitro*; in the bone marrow plasma (BMP) and serum of 72 newly-diagnosed symptomatic MM (NDMM) patients and in 25 healthy controls. Only one myeloma cell line produced high Sema4D (MR20: 104.45 ng/ml) compared to all others (mean±SD: 1.6±1.4 ng/ml), while there were undetectable Sema4D levels in the supernatants of all ovarian cancer cell lines. Regarding plexin-B1, two myeloma cells lines (H929: 25.3 ng/ml and JIN3: 30.8 ng/ml) and two ovarian cancer cell lines (OVCA3: 5125 ng/ml and SKOV3: 3516 ng/ml) produced high levels compared to the other myeloma (4±2.5 ng/ml) and ovarian cancer cell lines (27.6±3.8 ng/ml). The levels of Sema4D and plexin-B1 in the RPMI+FBS medium were not detectable. The plexin-B1 levels in the supernatants of the myeloma cell lines (76±140 ng/ml) were decreased compared to the respective levels of the ovarian cancer cell lines (963±1440 ng/ml, $p=0.008$). The mean Sema4D levels of the bone marrow plasma of the MM patients were dramatically elevated compared to controls (149 ng/ml±112 vs 23±12 ng/ml, $p<0.01$). Similarly, the circulating Sema4D was increased in MM patients compared to controls (71±110 vs 18±10.9 ng/ml; $p<0.001$). A strong correlation between Sema4D serum levels and bone marrow plasma levels was demonstrated ($r=0.628$, $p<0.001$). Sema4D levels in MM patients correlated with serum calcium ($r=0.628$, $p<0.001$), ISS stage (ANOVA $p<0.001$) and CTX serum levels ($r=0.524$, $p<0.01$). Sema4D showed no significant correlation with bALP ($r=-0.112$). Furthermore, there was a trend for higher Sema4D bone marrow plasma levels in patients with osteolysis in plain radiographs compared to patients without detectable bone disease ($p=0.07$). Patients with diffuse MRI pattern of marrow infiltration had higher levels of bone marrow plasma Sema4D compared to all other patients (161±98 vs 93±72 ng/ml, $p=0.02$). Regarding plexin-B1, bone marrow plasma and serum levels were increased in myeloma patients compared to controls (44±29 ng/ml vs. 3.4±0.8 ng/ml, $p<0.01$ and 11±20 ng/ml vs. 2.6±2.7 ng/ml, $p=0.01$, for bone marrow plasma and serum, respectively). There were no strong correlations between plexin-B1 and other studied parameters. The median follow-up of the patients was 61 months and the median OS was 46 months. Serum or plasma levels of Sema4D or plexin-B1 had no impact on patients' survival. In multivariate analysis, only ISS stage was predictive for

survival (HzR 3.58, $p<0.01$). In conclusion, we demonstrated that the levels of semaphorin-4D and its receptor plexin-B1 in both bone marrow plasma and serum are elevated in patients with symptomatic NDMM. These high semaphorin-4D levels correlate with increased bone resorption, hypercalcemia and higher ISS stage and seem to contribute to myeloma induced bone disease. Inhibition of semaphorin-4D/plexin-B1 signaling pathway may be of therapeutic value in MM patients.

P62

TWO DOSE SERIES OF HIGH-DOSE INFLUENZA VACCINE IS ASSOCIATED WITH LONGER DURATION OF SEROLOGIC IMMUNITY IN PATIENTS WITH PLASMA CELL DISORDERS

Branagan A., Duffy E., Foster C., Zhang L., Verma R., Gan G., Li F., Dhodapkar M.

Massachusetts General Hospital Cancer Center, Yale Cancer Center, Yale School of Public Health, USA

Background: Infections, such as influenza, are a major source of morbidity and mortality in patients with plasma cell disorders (PCDs). Seasonal flu vaccination is routinely administered to patients with PCDs, yet influenza infections remain common. Few studies have focused on serologic responses to influenza vaccination in PCD patients and there are none to the authors' knowledge which have measured longitudinal serologic responses over a single flu season. **Methods:** We conducted a double-blind, randomized clinical trial over the 2015-16 flu season, comparing two doses of Fluzone High-Dose influenza vaccination (separated by 30 days) to standard of care influenza vaccination. Patients were allocated to the experimental arm 2:1. US standard of care influenza vaccination was considered single age-based vaccine (standard dose <65 years, high-dose 65 years) and patients in this arm received a saline placebo injection at 30 days to assist in blinding. HAI titers were analyzed by standardized procedure at four time points, baseline, 30 days following the initial vaccine, 30 days following the second vaccine, and at the end of the flu season (April 30). **Results:** 122 total plasma cell disorder patients were enrolled. Forty-eight patients received a single standard of care influenza vaccination and 74 patients received two doses of High-Dose vaccine. Median age was 67 years. Following the second vaccine / placebo, rates of total seroprotection (against all 3 flu vaccine strains) were 86.3% following two high dose vaccines and 63.9% following standard vaccination. At the end of the flu season, rates of total seroprotection were 58.5% for patients who received two high dose vaccines and 33.3% for standard vaccination patients. Chi-square testing revealed that patients receiving the two dose vaccine strategy experienced significantly higher rates of total seroprotection following second vaccine ($p<0.05$). At the end of the flu season rates of seroprotection trended toward significance at the end of the flu season against all 3 vaccine strains ($p=0.07$), against the H3N2 strain ($p=0.05$) and were significantly higher against the H1N1 strain ($p<0.05$). **Conclusions:** We previously reported a two dose strategy of high-dose influenza vaccine is safely tolerated in patients with plasma cell disorders and associated with fewer laboratory-confirmed influenza infections (Branagan, et al, ASH 2016). Unexpectedly, the current analysis revealed that protective HAI antibody titers rapidly fall in PCD patients. Typically, HAI titers slowly decrease following a peak protective response, but are stable for over 6 months. However, PCD patients in this study began to lose HAI seroprotection even as little as 30 days. Interestingly, patients who received the two dose series of high-dose influenza vaccine maintained higher rates of seroprotection at the end of the influenza season. Importantly, these results suggest that a two dose series of high-dose vaccine provides may mitigate loss of vaccine-induced HAI titers and allow more durable serologic protection throughout the flu season. More studies are warranted to help determine the optimal dose and timing of influenza vaccination in PCD patients, particularly in Europe where high-dose influenza vaccine is not commercially available. Understanding the unique kinetics of serologic responses in PCD patients may have practice changing implications for other vaccines and therapies in this population.

P63

OUTCOME OF CYTOGENETICS IN PATIENTS WITH NEWLY DIAGNOSED EXTRAMEDULLARY MYELOMA UNDERGOING STEM-CELL TRANSPLANTATION

Gagelmann N., Eikema D.J., Koster L., Caillot D., Pioltelli P., Lleonart J.B., Reményi P., Blaise D., Schaap N., Trneny M., Passweg J., Porras R.P., Cahn J.Y., Musso M., Poiré X., Kobbe G., Itälä-Remes M., Pavone V., Fouillard L., Maertens J., Bron D., Pouli A., Schroyens W., Garderet L., Kröger N.

University Hospital Eppendorf, Hamburg, Germany, EBMT Statistical Unit Data Office Leiden, Leiden, The Netherlands, EBMT Data Office Leiden, Leiden, The Netherlands, CHU de Dijon, Dijon, France, Ospedale San Gerardo, Monza, Italy, Hospital son LLatzer, Palma de Mallorca, Spain, St. István & St. Laszlo Hospital, Budapest, Hungary, Institut Paoli Calmettes, Marseille, France, Radboud University Medical Centre, Nijmegen, The Netherlands, Charles University Hospital, Prague, Czech Republic, University Hospital, Basel, Switzerland, ICO – Hospital Duran i Reynals, Barcelona, Spain, Hospital A. Michallon, Grenoble, France, Ospedale La Maddalena, Palermo, Italy, Cliniques Universitaires St. Luc, Brussels, Belgium, Heinrich Heine Universität, Duesseldorf, Germany, Turku University Hospital, Turku, Finland, Hospital C. Panico, Tricase, Italy, Grand Hôpital de l'Est Francilien, Meaux, France, University Hospital Gasthuisberg, Leuven, Belgium, Institut Jules Bordet, Brussels, Belgium, St. Savvas Oncology Hospital, Athens, Greece, Antwerp University Hospital, Antwerp, Belgium, Hospital Saint Antoine, Paris, France

Extramedullary manifestation of multiple myeloma is associated with poor outcome. Here, we aimed to analyse the impact of cytogenetics on outcome after single-, tandem-autologous (tandem-auto) and autologous/reduced-intensity allogeneic (auto-allo) stem-cell transplantation in newly diagnosed multiple myeloma (NDMM) patients with extramedullary disease (EMD). Within the EBMT registry, we identified 488 patients (59% male, 41% female) with available data on extramedullary involvement and cytogenetics at diagnosis who received upfront single-auto (n = 373), tandem-auto (n = 84) or auto-allo (n = 31) between 2003 and 2015. Extramedullary involvement was defined as manifestations resulting from bone lesions (paraskelatal, n = 376) or hematogenous spread into different organs (n = 85), or both (n = 27). High-risk cytogenetics were defined as presence of at least one of the following abnormalities: del(17p), t(4;14), t(14;16), t(14;20), and gain(1q). At least one high-risk abnormality was detected in 190 (39%) patients. Isolated high-risk cytogenetic was found in 92 patients (48%), two in 56 (29%), three 28 (15), four in 11 (6%), and five in three patients (2%). The remaining patients had documented normal cytogenetics (n = 250) or other (n = 48), including other translocations or deletions, hyper- or hypodiploidy. Patients receiving auto-allo were younger (median, 49 years) and tended to have more high-risk cytogenetics (52%) vs. single-auto (60 years and 37%) and tandem-auto (60 years and 44%; p < 0.001 and p = 0.15). Single- and tandem-auto groups showed balanced characteristics. Median follow-up was 49.3 months. In univariate analysis, high-risk cytogenetics showed significant lower progression-free survival (PFS) and overall survival (OS) of 28.4% (95% confidence interval, 19.6-37.2) and 48.2% (40.0-56.4) vs. 48.5% (41.4-54.8) and 78.0% (72.5-83.5; p < 0.001, respectively). The number of high-risk abnormalities showed no impact on PFS (p = 0.53) and OS (p = 0.19). Disease site (paraskelatal vs. organ vs. both) was associated with worse OS (p = 0.02). PFS appeared to be better after tandem-auto and auto-allo with 51.5% (39.3-63.7; p = 0.06) and 60.7% (32.7-88.7; p = 0.14) vs. 38.3% (32.0-44.6) for single-auto while OS was significantly better for tandem-auto with 77.8% (68.4-87.2) vs. single-auto showing 62.1% (56.2-68.0; p = 0.04), and not significant for auto-allo (81.1%, 66.0-96.2) vs. single-auto (p = 0.17). Cumulative incidence of relapse and non-relapse mortality at four years was 47.1% and 1.4% for tandem-auto, 37.1% and 8.6% for auto-allo, and 58.8% and 3.0% for single-auto (p = 0.21 and p = 0.14). In patients with EMD and high-risk cytogenetics tandem-auto resulted in a significantly improved PFS and OS (p = 0.02 and p = 0.001) in comparison to single-auto while auto-allo showed significantly improved OS versus single-auto (p = 0.05). Tandem-auto overcame poor prognosis of high-risk vs. normal or other cytogenetics in the univariate (PFS: 50.4% vs. 53.6%, p = 0.49; OS: 80.8% vs. 80.4% p = 0.92) as well as in the multivariate analysis in terms of PFS (hazard ratio, 1.17; p = 0.70) and OS (hazard ratio, 0.92; p = 0.90). High-risk cytogenetic is seen in nearly 40% of NDMM with extramedullary disease and significantly influences PFS and OS. In comparison to single autografting, tandem-autologous transplantation improves survival and overcomes poor prognosis of high-risk cytogenetics.

P64

A REAL WORLD MULTICENTER RETROSPECTIVE ANALYSIS OF EXTRAMEDULLARY DISEASE FROM BALKAN MYELOMA STUDY GROUP AND BARCELONA UNIVERSITY: COMPARISON OF PARAOSSEOUS AND SOFT TISSUE PLASMACYTOMAS

Beksac M., Kanellias N., Rosiñol L., Seval G.C., Ozet G., Goranova-Marinova V., Coriu D., Bila J., Ozsan H., Balic L.I., Ivanaj A., Kastritis E., Bladé J., Dimopoulos M.

Ankara University, National and Kapodistrian University of Athens, University of Barcelona, Numune Hospital, University of Plovdiv, University of Bucuresti, University of Belgrade, Dokuz Eylul University, University of Sarajevo, University of Tirana

Introduction: Extramedullary disease (EMD), defined as a clonal plasmacytic infiltration at anatomic sites distant from the bone marrow or adjacent soft tissue, appear to account for 6-7.5% of the total myeloma population at diagnosis and tend to increase at relapse with an unfavorable prognosis (Blade, Usmani). Here, following an international collaborative effort, we are reporting the outcome of myeloma patients with EMD and paraosseous involvement. **Methods:** This multicenter retrospective study conducted in 16 centers from 11 countries included 206 adult patients diagnosed with EMD between January 2010 and November 2017. The diagnosis of EMD was rendered in accordance with the International Myeloma Working Group Guidelines. Eligibility criteria included EMD at any time following the initial diagnosis of Multiple Myeloma (MM) excluding plasma cell leukemia or solitary plasmacytoma. Those patients with pathological or radiological evidence of neoplastic plasma cells in the soft tissues adjacent to axial skeleton were deemed to have paraosseous(PO) involvement of locally-advanced myeloma, but not EMD. Outcome was determined as response to treatment, progression free survival (PFS) and overall survival (OS) in months by Kaplan-Meier analysis using SPSS (IBM SPSS Statistics 21; IBM Corp., Chicago, IL) statistical tool kit. We also compared the PFS and OS between the paraosseous and EMD cohorts. **Results:** A total of 195 patients met the pre-determined criteria for inclusion. Baseline characteristics of the patients are summarized in Table 1.

Table 1. Baseline characteristics of the patients.

Characteristic (n=195)	Results
Age, years, Median (range)	62 (34-87)
ISS stage (at myeloma diagnosis)	
Stage I, n (%)	66 (33.8%)
Stage II, n (%)	58 (29.7%)
Stage III, n (%)	65 (33.3%)
Number of FISH abnormalities	
No abnormalities, n (%)	50 (49.2%)
1 abnormality, n (%)	28 (27.4%)
2 abnormalities, n (%)	12 (11.7%)
≥3 abnormalities, n (%)	12 (11.7%)
Del17p, n (%)	10 (9.8%)
Del13q, n (%)	20 (19.8%)
t(4;14), n (%)	8 (7.8%)
t(14;16), n (%)	2 (2%)
t(11;14), n (%)	4 (4%)
Anatomical locations of EMD	
Soft tissue (muscle/skin), n (%)	51 (26.2%)
Lymph nodes, n (%)	20 (10.3%)
Chest, n (%)	19 (9.3%)
Liver, n (%)	17 (8.7%)
Central nervous system, n (%)	14 (7.2%)
Oropharynx, n (%)	8 (4.1%)
Lung, n (%)	6 (3.1%)
Abdominal, n (%)	6 (3.1%)
Testis, n (%)	4 (2.1%)
Others, n (%)	5 (2.6%)
Initial therapy for EMD	
Systemic chemo with radiotherapy, n (%)	55 (28.2%)
PI, n (%)	104 (55%)
IMiDs, n (%)	53 (27.3%)
Only radiotherapy, n (%)	9 (4.8%)
Monoclonal antibodies (CD38,CS1), n (%)	8 (4.2%)
Lines of therapy (Myeloma+EMD)	
1-2 lines, n (%)	75 (56.4%)
>2 lines, n (%)	58 (43.7%)
Autologous stem cell transplantation, n (%)	76 (39%)
CR diagnosis	
EMD, % (n)	18.3% (15/82)
PO, % (n)	28.1% (9/32)
CR relapse	
EMD, % (n)	2.9% (2/69)
PO, % (n)	41.7% (5/12)
PFS diagnosis	
EMD, Mean±SD	52.2±5.3
PO, Mean±SD	75.9±11.4
PFS relapse	
EMD, Mean±SD	21.3±5.0
PO, Mean±SD	20.8±4.2
OS diagnosis	
EMD, Mean±SD	55.7±6.2
PO, Mean±SD	108.7±13.0
OS relapse	
EMD, Mean±SD	37.9±7.9
PO, Mean±SD	30.1±4.7

The median age at diagnosis of EMD was 62 years (range 34-87 years). Out of 114 patients at diagnosis EMD/PO were 82/32 and of the 81 patients at relapse 69/12 respectively. The median time from MM diagnosis to the

development of EMD in the relapse/progression group was 28.4 months (range 1-157 months). Imaging approach for EMD was CT (n:109), PET-CT (n:48) or MRI (n:30). The most common locations for EMD at the time of diagnosis of MM were the soft tissues ie muscle and/or skin (26.2%) and lymph nodes (10.3%). FISH analyses prior to the diagnosis of EMD were available for 102 patients (52.3%). The entire group received a median number of two lines of treatment following the diagnosis of EMD/MM. Although response was higher for PO vs EMD at relapse, PFS was similar (Table 1). At the time of this report, 101 patients (52.3%) have died. The estimated median OS from time of diagnosis was 2.2 years (EMD) and 6.3 (PO) years ($p=0.001$). For both PO and EMD, outcomes DFS and OS were better when detected at diagnosis vs relapse ($p=0.000$). In addition, PO disease had a better outcome(OS) compared to EMD at diagnosis ($p=0.02$) and relapse ($p=0.032$) (Figure 1). **Discussion and Conclusion:** EMD is an uncommon, but by no means rare, manifestation of MM. This cohort of 195 patients represents a large group of patients with EMD demonstrating CR as a reachable but not sustainable target for both PO and EMD. EMD at relapse, but not at diagnosis, is the worst group with the poorest response and survival. The study results highlight an unmet and urgent need to improve response and survival for patients presenting with PO and EMD either at diagnosis or relapse. **Acknowledgement:** Authors are grateful to additional members of Balkan Myeloma Study Group who also participated but could not qualify for authorship: Guenova M, Markovic O, Djurdjevic P, Kinda SB, Karanfilyk O, Unal A, Dapcevic M, Zver S.

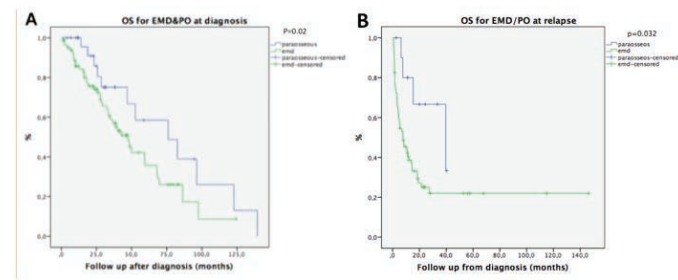


Figure 1. OS estimate in patients with EMD and PO lesions at diagnosis (A) and relapse (B).

P65

TREATMENT WITH POMALIDOMIDE AND DEXAMETHASONE IN PATIENTS WITH LIGHT CHAIN AL AMYLOIDOSIS AND MULTIPLE MYELOMA

Basset M., Milani P., Foli A., Merlini G., Palladini G.

Amyloidosis Research and Treatment Center, Foundation IRCCS Policlinico San Matteo and Department of Molecular Medicine, University of Pavia, Italy

Introduction: Pomalidomide is an immunomodulatory agent active in patients with relapsed/refractory multiple myeloma, including those previously exposed to lenalidomide and bortezomib. Phase II clinical trials showed that pomalidomide is also effective in primary AL amyloidosis. After this drug was marketed for multiple myeloma (in Italy since September 2015), pomalidomide and dexamethasone became a feasible treatment for patients with myeloma-associated AL amyloidosis, a particularly fragile population. This study reports the efficacy of this regimen in patients with multiple myeloma-associated AL amyloidosis in a real life setting. **Materials and Methods:** The prospectively maintained database of the Pavia Amyloid Research and Treatment Center was searched for patients with a diagnosis of multiple myeloma and AL amyloidosis treated with pomalidomide and dexamethasone (PDex). The patients received 28-day cycles of pomalidomide (4 mg from day 1 to 21) and dexamethasone (20 or 40 mg weekly, according to cardiac dysfunction). All patients gave written informed consent for their clinical data to be used for research purposes, in accordance with the Declaration of Helsinki. Forty-eight consecutive patients who started PDex between September 2015 and September 2017 were included in the study. **Results:** Median age was 66 years [interquartile range (IQR): 59-74 years] and 30 (62%) patients were men. Heart involvement was present in 27 patients (56%) and kidney involvement in 28 (58%). At the time of PDex initiation, ten (21%) patients were Mayo Stage I, 21 (44%) stage II, 14 (29%) stage IIIa and 3 (6%) stage IIIb. Nineteen (40%) subject were renal stage I, 17 (35%) and 4 (8%) were renal stage II and III respectively and 8 (17%) patients were on dialysis. Median bone marrow plasma cell infiltrate was 22% (IQR: 10-30%). Only one patient had lytic bone lesions. Median time from diagnosis to tre-

atment initiation was 59 months (IQR: 26-91 months). Thirty-nine (81%) patients were refractory to all previous lines of therapy. The median number of prior treatments was 3 (range: 2-5 lines). All patients were previously treated with bortezomib and lenalidomide. Fourteen subjects (29%) underwent autologous stem cell transplant and 12 (25%) received previous thalidomide-based regimens. Adverse events were observed in 5 (10%) subjects: skin rash in two cases and mild increase in serum creatinine in 3 (6%) that resolved after decreasing the dose of pomalidomide. The median number of PDex cycles performed was 4 (range: 1-20 cycles). Fifteen patients (55%) achieved at least partial response, with 2 complete responses (CR), 2 very good partial responses (VGPR) and 1 low-dFLC partial response. Cardiac responses were observed in 2 of 10 patients with measurable NT-proBNP (20%), but this can be underestimated due to the pomalidomide-related increase of NT-proBNP, and renal response in 3 of the 15 evaluable patients (20%). Median follow-up of living patients was 10 months (IQR: 5-19 months) and 15 (31%) died due to progressive disease. Median survival from pomalidomide initiation was 23 months. **Discussion and Conclusions.** The combination of pomalidomide and dexamethasone is well tolerated and effective in heavily pretreated patients with multiple myeloma-associated AL amyloidosis and can be a valuable rescue option in this high-risk population.

P66

THE ROLE OF 18F-FDG PET/ CT IN NEWLY DIAGNOSED PATIENTS WITH MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFIKANCE (MGUS): ONE CENTER EXPERIENCE FROM CZECH REPUBLIC

Sandacká V.¹, Ševčíková S.^{2,3}, Zdeňek A.¹, Krejčí M.¹, Štork M.¹, Zdeňek K.¹, Pour L.¹

¹Department of Internal Medicine, Hematology and Oncology, University Hospital, Brno, Czech Republic; ²Babak Myeloma Group, Department of Pathological Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic; ³Department of Experimental Biology, Faculty of Science, Masaryk University, Brno, Czech Republic

Introduction: 18-F-FDG-PET/CT examination allows for assessing early skeletal involvement and can change the diagnosis of MGUS into symptomatic multiple myeloma (MM). This technique has been recently incorporated into the updated International Myeloma Working Group criteria for MGUS diagnosis. **Patients and Methods:** We prospectively studied 390 patients meeting the diagnostic criteria of MGUS who were diagnosed and monitored at the Department of Internal Hematology and Oncology in Brno, Czech Republic, from January to December 2010 (IMWG 2016). All patients were screened by PET/CT within 6 months of MGUS diagnosis. We aimed to evaluate the benefit of this technique for patients where the PET/CT finding did not lead to a reassessment of the diagnosis of MGUS into MM. At the time of the PET/CT imaging, no specific symptoms were present that determined the newly diagnosed serious illnesses. **Results:** Presence of pathological accumulation of 18-fluorodeoxyglucose was recorded in 8.4% (33/390) of MGUS patients. The most common pathology was lymphadenopathy, occurring in 2.8% (12/390) of all examined patients. After histological verification of the lymph node, eight people were diagnosed with a lymphoproliferative disease (1 lymphoplasmacytic lymphoma, 1 peripheral T-lymphoma, 1 marginal zone nodal lymphoma, 1 CD20 + low-grade MZL-type lymphoma, 2 indolent mature B neoplasias and 2 lymphoblastic lymphomas). In four patients, we found one case of plasma cells lymph node infiltration, one case of Sjögren's syndrome, one of sarcoidosis, and one case of reactive lymphadenopathy without detection of malignant cells. None of the patients had symptoms typical for lymphoproliferative disease. Thyreopathy was the second most common pathology and was observed in 2.1% (8/390) of cases. In seven patients, we found nontoxic struma; there was also one case of thyroid carcinoma. All patients' thyroid hormones tested within the normal range. Rheumatologic disease was the third most common pathology according to PET/CT, occurring in 1.8% (7/390) of all scanned patients. Specifically, there were four patients of rheumatoid arthritis, two of polymyalgia rheumatica and one case of giant-cell temporal arteritis. As other diseases are concerned, colon cancer was detected in 2 cases, thymoma in 1 case, schwannoma of the femoral nerve and prostate cancer in one case. For all these patients, all diseases were early-onset without typical symptoms. **Summary:** PET/CT imaging shows that more than 8% of MGUS patients were randomly but timely diagnosed with a serious illness before first symptoms. PET/CT imaging can be recommended not only to evaluate whether patients transformed into symptomatic MM, but also for identification of other pathologies early.

P67

LOW INCIDENCE OF SKELETAL-RELATED EVENTS AT THE TIME OF FIRST RELAPSE IN PATIENTS WITH MULTIPLE MYELOMA WHO RECEIVED BORTEZOMIB-BASED REGIMENS AS FIRST LINE TREATMENT

Terpos E., Kanellias N., Mouloupoulos L.A., Christoulas D., Gavriatopoulou M., Migkou M., Fotiou D., Koureas A., Bagratuni T., Koutoulidis V., Kastritis E., Dimopoulos M.A.

National and Kapodistrian University of Athens, School of Medicine, Greece

Skeletal-related events (SREs) which include pathological fractures, spinal cord compression (SCC) and need for radiotherapy or surgery to bone are frequent complications of multiple myeloma (MM). The aim of the study was to evaluate SRE rate in MM patients who received frontline therapy with bortezomib or IMiD-based therapies and explore possible correlations with disease or genetic features. We studied MM patients who received frontline therapy with novel agents in a single center, since 2007. All patients had a whole body skeletal survey using conventional radiography (WBXR) at diagnosis and then at the time of relapse or whenever clinically indicated; MRI of the spine and pelvis at diagnosis was recorded if available. SNPs in genes that are involved in bone destruction were also evaluated: LRP5 (rs4988321), GC vitamin D (rs4588), TNFRSF11A (rs3018362), DKK1 (rs1569198), RANKL (rs9594759), OPG (rs6469804) and ERS1 (rs1038304). Since 2007, 463 consecutive patients with symptomatic MM (237M/226F, median age: 68 years) were studied. At diagnosis, the skeletal survey detected osteolytic disease in 328 (71%) patients. MRI was available in 243 patients: 36% of patients had focal, 40% diffuse, 20% normal, and 4% variegated pattern of marrow involvement. SREs were observed in 194 (42%) patients at diagnosis: 120 (26%) patients presented with pathological fractures (89 with vertebral fractures, 21 with rib fractures and 17 with fractures of the long bones; 28 patients had both vertebral and long bone or rib fractures), while 22 (4.7%) patients needed surgery to bone, 21 (4.5%) radiotherapy and 20 (4.3%) patients presented with SCC. The incidence of SREs was higher in patients with osteolytic lesions (52% vs. 19%, $p < 0.001$) or abnormal MRI pattern (51% vs. 22%, $p = 0.001$). However, we noted that approximately 1/4 patients without lytic lesions in WBXR or with normal MRI pattern presented with a SRE at diagnosis. No correlation was found between the presence of SREs and a specific polymorphism of those studied. Frontline therapy with IMiD-based regimens was given in 38% of patients; 36% patients received bortezomib-based regimens and 26% both IMiD and bortezomib (VTD or VRD). BPs were given in all but 86 patients (18.5%) at diagnosis, mainly due to renal insufficiency; however, almost 60% of them ($n = 51$) received BPs later in the course of their therapy. The vast majority (91%) of patients received zoledronic acid. During first line treatment, 8 (1.7%) patients developed a SRE: 2 on bortezomib- and 6 on IMiD-based regimens. The rate of SREs was higher in patients who did not receive upfront BPs (5% vs. 1%; $p = 0.021$). The median follow-up was 63 months. At the time of first relapse (data available for 218 patients), 12 patients presented with fractures and 35 patients required local radiotherapy to bone (SRE rate: 21.5%). Patients who had received only bortezomib-based regimens had lower SRE rate (8% vs. 24%, $p = 0.06$). In total, during the course of their disease, 52.8% of the patients presented with at least one SRE. Our data, from the first systematic report on the incidence and characteristics of SREs in the era of novel agents, indicate that SREs remain a significant complication in MM at diagnosis. Importantly, despite high response rates after first line therapy more than 20% of patients develop an SRE, which was lower in patients who received first line therapy with bortezomib-based regimens.

P68

ALLOGRAFT IN MULTIPLE MYELOMA: EXPERIENCE OF MULTIPLE MYELOMA GIMEMA LAZIO GROUP

Vozella F., Iori A.P., Cerretti R., Severino A., Chiusolo P., Piciocchi A., Cesini L., Mariggio E., Fazio F., Cudillo L., Franceschini L., Za T., Sica S., Petrucci M.T., De Stefano V., De Rosa L., Arcese W., Foà R.

Hematology, Department of Cellular Biotechnologies and Hematology, "Sapienza" University, Hematology, Department of Biomedicine and Prevention, Università di Roma "Tor Vergata", Hematology Division, San Camillo Hospital, Hematology, Department of Hematology, Università Cattolica del Sacro Cuore, GIMEMA Data Center, GIMEMA Foundation, Italy

Introduction: In the era of new drugs prognosis of patients (pts) with multiple myeloma (MM) has significantly improved. New or old drugs, followed

by single or tandem autologous stem cell transplant, is the standard of care for pts with newly diagnosed MM. In the last three years MM received the most drug approvals for any one malignancy, both in the United States as well as in Europe. Nevertheless, MM is still considered to be an incurable disease and current therapies can only slow disease progression, prolong survival, and minimize symptoms. In fact, the majority of pts with MM will relapse or become refractory and the remission duration in relapsed MM decreases with each regimen. If the role of autologous stem cell transplantation has been confirmed by many trials, allogeneic hematopoietic cell transplantation (HCT) is less commonly used due to high treatment related mortality (TRM) and worsening of the quality of life. As a result of this issues, it is still unclear how to best utilize this potent and effective treatment modality. **Patients and Methods:** We report the experience of Multiple Myeloma GIMEMA Lazio Group in 70 pts with newly diagnosed (38) or relapsed/refractory (32) MM who underwent HCT between February 1985 and February 2017. The median age was 45.7 years (range, 32.1 - 67.1), 43 men and 27 women. Median age at HCT was 48.6 years (range, 32.6 - 65.8), median time from diagnosis to HCT was 16.8 months (range, 3 - 130.6). As induction treatment 43/70 pts received old drugs, i.e. vincristine, doxorubicin and dexamethasone (VAD; $n = 33$) or melphalan and prednisone (MP; $n = 10$), while 27/70 pts were treated with novel agents, i.e. velcade-based ($n = 13$) or IMiD-based regimens ($n = 14$). Among newly diagnosed MM, HCT was performed as frontline therapy in 24/38 pts and in a tandem autologous/allogeneic in 14/38 pts. No differences in terms of OS and PFS were found between HCT "frontline vs relapse", $p = 0.72$ and $p = 0.34$ respectively, neither between induction treatment with "old vs new drugs", $p = 0.72$ and $p = 0.15$ respectively. After induction, 9 pts (13%) achieved complete response (CR), 8 pts (11.3%) achieved a very good partial response (VGPR), 41 pts (58.6%) achieved partial response (PR), 1 patient (1.4%) maintained a stable disease (SD) and 11 pts (15.7%) performed HCT in progression disease (PD). **Results:** Overall, 65 pts (93%) achieved a response (CR; $n = 32$, VGPR; $n = 2$, PR; $n = 31$), 2 pts (2.8%) showed PD during or immediately after HCT, 3 pts (4.2%) died for TRM. More in detail a CR was observed in 7/9 pts who underwent HCT in CR, 4/8 in VGPR, 17/41 in PR and 4/11 in PD. Among 65 pts who obtained a response, 35 pts (54%) presented, a disease recurrence in 48% and 54% at 5 and 10 years, respectively. TRM was 14% and 18% at 5 and 10 years, respectively. Acute and chronic GVHD occurred in 37 and 36 pts respectively. Overall survival (OS) and progression-free survival (PFS) at 10 years was 43.1% (range, 32.3 - 57.4) and 25.1% (range, 16.5 - 38.2) respectively. **Conclusions:** Autologous stem cell transplant remains the standard of care for young MM pts but it's not curative. Our retrospective analysis presents some methodological limitations but it shows that the role of HCT is not clear. Physicians should evaluate its combination in prospective trials for young high-risk or relapsed/refractory pts (not beyond the first relapse), in a tandem autologous/allogeneic transplant, with an induction and a possible maintenance based on new drugs.

P69

PECULIARITIES AND HETEROGENEITIES OF EXTRAMEDULLARY DISEASE OF MULTIPLE MYELOMA IN THE "NOVEL AGENTS ERA". COMPARISON OF SOFT-TISSUE AND BONE-RELATED SHAPES IN A RETROSPECTIVE REAL-LIFE ANALYSIS

Torti L., Morelli A., Bacci F., Di Bartolomeo P.

Clinical Hematology, Department of Hematology, Trasfusion Medicine and Biotechnology, "Spirito Santo" Civic Hospital, Pescara Italy. Section of Hematopathology, Department of Hematology and Oncological Sciences, S.Orsola Malpighi Hospital, University of Bologna, Italy

Extramedullary-disease(EMD)is an uncommon manifestation in myeloma and seems to have a different pathogenesis from its medullary-counterpart. EMD is an aggressive disease entity, representing a poor-prognostic-marker. There are nowadays concerns about increase of EM-relapses with the expanding use of novel-agents. We aimed to compare features of skeletal and soft-tissue-plasmacytomas in the context of novel agents and to analyze clinical-outcomes (Figure 1). We retrospectively reviewed 124 myeloma patients with detectable extramedullary plasmacytoma, consecutively diagnosed at Our Department between 1999 to 2016. In our study were included 62 patients presenting bone-related-extramedullary-disease (b-EM) and 62-patients with soft-tissue related (s-EM) comparing clinical and biological characteristics and outcome. 51 among sEM were dead and 11 were alive, 14 of bEM patients were dead and 48 were still alive. Of the first group 10 presented EMD at diagnosis and 52 at relapse as well as 7 and 55 respectively of the second-series. Among sEM group we have described involvement of skin

(30 patients), parenchyma (lung, breast and liver in 15 patients), lymph-nodes (12 patients) and lastly central nervous system (CNS) in 5 patients. We have shown that soft tissues plasmacytoma occurred more frequently in males (45/62) and had higher levels of B2microglobulin and LDH (47/62) and high frequency of advanced-disease according to International-Staging-System (III stadium in 49, II in 10, I in 3 patients). These results were compared to the skeletal-plasmacytoma-group: they were 45 females, 17 males, only 11 had high LDH or B2 microglobulin-high-levels and majority of them has a low or intermediate-ISS-score (46 I, 11 II and 5 III). Compared to patients with bEM (Figure 2 a-f), patients with sEM had worse global median overall survival (30 months versus 48months $P<0,0001$ HR1,6 95% CI 1,03-2,47). The same kind of results was obtained about median-overall-survival from EMD-diagnosis (respectively 10 months versus 30 months $P<0,0001$ HR 3 95% CI 1,93-4,64). Specifically in our series of patients with s-EM the worst prognosis belongs to CNS-involvement (median OS from EM diagnosis 4 months), followed by parenchyma-EM (OS median of 7 months) and by lymph-nodes EM (median OS of 20 months) and lastly by skin-EM (median OS always from EM diagnosis of 26 months) $P<0,0001$. Kaplan-Meier estimates were used for survival-analysis and differences between survival times were tested using the log rank test. EM was diagnosed using imaging-techniques such as PET-CT (45%) or MRI (68%). Biopsies were carried out only if the lesion was accessible (65%) (Figure 2 g-l). Interestingly extramedullary spread can be triggered by an invasive-procedures (surgery). We have a case of breast-plasmacytoma diagnosed accidentally after breast-surgery, where PCR of immunoglobulin gene-rearrangement confirmed monoclonal CD138/lambda plasma-cells. Furthermore often it has been described association between EMD, IgD-subtype and FLC-escape. In fact we have reviewed 6 cases of IgD and 6 FLC-escape, all of them were observed in relapse-setting and in sEM-group. Finally the mechanism of extramedullary spread are poorly established: maybe a decrease expression of integrins is involved. Absence of CD56-protein was shown in 66% of sEM group and in 19% of bEM case-series. Even in the era of novel-drugs sEM has a poor prognosis especially in relapse-setting. This work shows a significant difference in prognosis for different type of EMD even between sEM, suggesting a different biological-behavior.

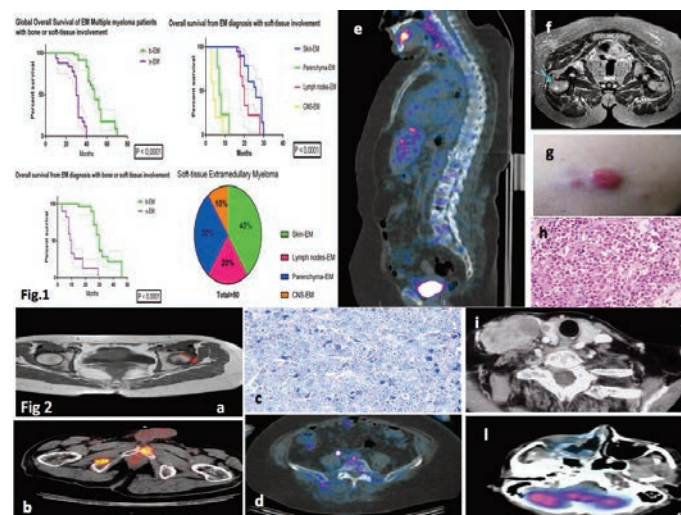


Figure 1.

P70

SAFETY AND COMFORT OF DOMESTIC BORTEZOMIB INJECTION IN REAL LIFE EXPERIENCE

Cerchione C., Nappi D., Pareto A.E., Romano A., Di Perna M., Zacheo I., Pane F., Catalano L.

Hematology - AOU Federico II, Napoli Italy

Subcutaneous bortezomib administration has huge advantages to treat patients with poor venous accesses and, generally, it is convenient for both patients and physicians because it overcomes problems related to a prolonged intravenous infusion or the insertion of a long-term central venous access device. Moreover, overall incidence of peripheral neuropathy is lower with

the subcutaneous administration in comparison with the intravenous route, reducing the possibility of a therapy discontinuation related to this adverse event. In recent years, for some non-histotoxic anti-cancer drugs, such as rituximab, trastuzumab or cladribine, the subcutaneous route, as alternative to the intravenous one, has been successfully compared and the possibility of a self-administration modality for adequately informed patients or adult caregivers was also demonstrated. Previous randomized trials proved that subcutaneous bortezomib administration is pharmacologically and clinically equivalent to the intravenous one, with an equal safety profile. We focused our retrospective study on a population of elderly patients not eligible for high-dose therapy with autologous hematopoietic stem-cell transplantation (HDT-HSCT) as frontline therapy, but treated with VMP regimen, that was demonstrated to be highly effective in this setting. Since 2009, in our Hematology Unit, 63 patients requiring bortezomib for the treatment of MM, in association with orally administered prednisone and melphalan (VMP), performed subcutaneous injection of bortezomib at home for personal or logistic reasons. Initially, the drug was administered by qualified personnel; subsequently, the patient or an adult care-giver learned to inject it in the deltoid muscle. Patient were supplied with bortezomib in ready-to-use plastic syringes, where the drug was appropriately constituted in saline solution, under hood in sterile conditions by qualified personnel. Patients received 4-weeks cycles of melphalan (9 mg/m²) and prednisone (60 mg/m²) on days 1 to 4, bortezomib (1.0 mg/m²) on days 1, 8, 15 and 22 (mean number of cycles 9, r. 3-12), according to a schedule adapted for frail patients [4,9,10]. The first cycle was usually administered at hospital to assess and confirm the safety of this route. We evaluated the overall response rate (ORR): 45 patients (72%) achieved a response; in particular, 20 patients (32%) achieved a complete response (CR), 25 patients (40%) achieved a partial response (PR) and 6 patients (9%) achieved a minimal response (MR) after four cycles of therapy and the adverse events rate. Data about efficacy and safety were similar to those observed in major clinical trials. In particular, results showed the equal incidence of adverse events (AEs) for domestic administration. There were no severe AEs requiring hospitalization or access to Emergency Unit. These results confirm the effectiveness and safety of subcutaneous bortezomib, in a real-life-experience, and define a new possibility of safe auto-administration in a comfortable domestic setting. We believe that domestic treatment can significantly improve the quality of life of the patients, avoiding unnecessary transfer to the hospital without reducing treatment efficacy.

P71

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION IN ELDERLY PATIENTES WITH MULTIPLE MYELOMA

Solé M., Zapata R., Palma A., Ramírez S., Domínguez J.F., Rodríguez J.N., Gómez K., Gil E.

Department of Hematology and Hemotherapy. Hospital Juan Ramón Jiménez, Huelva, Spain

Background: Multiple myeloma (MM) accounts for 10% of haematological malignancies and has a median age at onset of 69 years. Autologous hematopoietic cell transplantation (AHCT) is a standard of care as consolidation in upfront therapy in MM patients aged <65 years. With advances in supportive care, AHCT is increasingly being performed for patients older than 65 years. However, its potential toxicity in this group of patients is still a matter of concern and its role in this setting is controversial especially in the new drugs era. The aim of this study was to compare complications and outcome of AHCT in younger (< age 65) versus elderly (> age 65) MM patients. **Methods:** We retrospectively evaluated the complications and outcome of first AHCT performed as consolidation in upfront therapy in MM patients older than 60 years who underwent AHCT in one single centre from October 2013 to January 2018. We compared two groups of patients: elderly MM patients (>65 years) with a similar cohort of younger patients (<65 years but older than >60 years). **Results:** We performed 12 AHCT in this period: seven in patients younger than 65 years and 5 in patients equal or older than 65 years. The baseline characteristics of patients are summarized in Table 1. The conditioning regimen was Mel200 in 71.4% of the patients in the younger group and in 60% in the elderly one. The rest of patients received Mel140 due to renal impairment or to medical choice considering comorbidities and status performance. Unexpectedly, the median of CD34+ cells infused was slightly superior in the elderly group (without reaching statistical significance): 3.91x10⁶/kg CD34+ cells (range 2.99-5.08) in the younger group and 5.43x10⁶/kg CD34+ cells (range 3.76-6.60) in the elderly one. There were no statistically significance differences between the groups in terms of com-

plications being the most common one in both groups febrile neutropenia (71.2% in younger patients vs 80% in elderly patients (p-value=0.63)). There were also no statistical differences between the groups in terms of hematopoietic recovery: neutrophil engraftment ($>0.5 \times 10^9/l$) occurred on average on day 12 (range 10-13) in both groups and platelet engraftment ($>20 \times 10^9/l$) occurred on average on day 13 (range 10-13) in younger patients and on day 12 (range 11-14) in the elderly ones. Hospitalization average was 20 days in both groups (range 17-26). There were no deaths related to the procedure due to any causes before the 100 days after AHCT. Patients were evaluated in day +100 after AHCT. No patients in any group progressed in this period: in the younger group 42.8% patients (3/7) improved previous response after AHCT while in the elderly group was 40% (2/5). The median follow-up was 36.3 months in the young group and 10.8 months in the elderly one. Only one patient died in this period due to disease progression in the younger group. **Conclusions:** In our experience AHCT in elderly MM patients appears to be as safe and effective as in younger patients.

Table 1. Baseline characteristics of patients.

Multiple Myeloma Elderly	Between >60<65 years	> 65 years
N	7	5
Age, years median (range)	62 (60-64)	67 (65-71)
Gender, Male (frequency, percent)	4/7 (57.1 %)	4/5 (80%)
Combined Score:		
→ Low risk (frequency, percent)	1/7 (14.3%)	2/5 (40%)
→ Intermediate risk (frequency, percent)	4/7 (57.1%)	1/5 (20%)
→ High risk (frequency, percent)		1/5 (20%)
→ Unknown (frequency, percent)	1/7 (14.3%)	1/5 (20%)
Multiple Myeloma Ig subtype:		
→ IgG Kappa (frequency, percent)	2/7 (28.6 %)	2/5 (40 %)
→ IgG Lambda (frequency, percent)	2/7 (28.6 %)	1/5 (20 %)
→ IgD Lambda (frequency, percent)		1/5 (20 %)
→ IgA Kappa (frequency, percent)	1/7 (14.3 %)	
→ IgA Lambda (frequency, percent)	1/7 (14.3 %)	
→ Bence Jones (frequency, percent)	1/7 (14.3 %)	1/5 (20 %)
Status performance:		
→ Karnofsky > 90% (frequency, percent)	5/7 (71.5 %)	4/5 (80 %)
Comorbidity index (HCT-CI):		
→ Without comorbidities (frequency, percent)	4/7 (57.1 %)	2/5 (40 %)
Initial therapy:		
→ Bortezomib/Dexamethasone (frequency, percent)	5/7 (71.5%)	1/5 (20%)
→ Cyclophosphamide/Bortezomib/Dexamethasone (frequency, percent)	2/7 (28.6%)	4/5 (80%)
Response to treatment:		
→ Progressive disease (PD) (frequency, percent)	1/7 (14.3 %)	1/5 (20%)
→ Stable disease (SD) (frequency, percent)	1/7 (14.3%)	1/5 (20%)
→ Partial response (PR) (frequency, percent)	2/7 (28.6 %)	2/5 (40%)
→ Very good partial response (VGPR) (frequency, percent)		
→ Complete response (CR) (frequency, percent)	3/7 (42.9%)	1/5 (20%)

P72

EXTRAMEDULLARY PLASMACYTOMA-LIKE POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD): A RARE COINCIDENCE OR SOMETHING MORE?

Ferla V., Guidotti F., Gregorini A.I., Rossi F.G., Pompa A.

Hematology Unit, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico and University of Milan, Italy

Introduction. PTLD with plasma cell differentiation has been reported as an extremely rare disorder. Here we describe a patient who developed a pararenal lambda extramedullary plasmacytoma eight years after the explant of a lambda plasma cells infiltrated graft liver. **Case Report:** In January 2009, a 62-year-old man was referred to our hepatology department for hepatocellular carcinoma in cirrhosis for B and C hepatitis virus, treated with radio-frequency ablation and transcatheter arterial chemoembolization. In August 2009, he underwent liver transplantation. Histological examination of the graft revealed the presence of sinusoidal infiltration of CD138 positive plasma cells with monoclonal lambda light chain restriction, suggestive for hepatic localization of plasma cell dyscrasia. For this reason, after ten days graft was explanted and a new liver transplanted without complications. He started immunosuppressive therapy with cyclosporine and mycophenolate. In September 2016, a total body CT scan was performed during hepatological follow up revealing three doubtful small solid formations at right para-renal level. A radiologic follow-up was performed by MRI in January 2017, showing conglomerate nodules at the right kidney superior pole with altered vascularization, increasing in size (diameter 34 x 29 mm). Subsequent PET

scan was performed with no evident area at increased glucidic metabolism. In March 2017, the patient underwent exploratory laparotomy and removal of the right para-renal neoformation. Histological examination showed a lambda light chain restricted CD138 positive plasma cell proliferation. An association with latent EBV infection was excluded with immunohistochemical staining. Biochemical investigations for hemogram, serum creatinine, calcium, total protein, serum and urine electrophoresis and serum free light chain ratio were within normal limits. BM aspirate and biopsy showed 1-2% of polyclonal plasma cells. Whole body low-dose CT scan revealed no osteolytic lesions. According to WHO classification, a diagnosis of post-transplant lymphoproliferative disease (PTLD), monomorphic, plasmacytoma-like, was performed. The patient received a reduction of immunosuppression as initial therapeutic intervention. Local radiotherapy was excluded because of the site of plasmacytoma. The patient was treated with subcutaneous biweekly bortezomib at standard dose combined with dexamethasone. After three cycles, MRI of the abdomen showed a good reduction of the para-renal nodules (diameter 5 mm). The patient is currently at fifth cycle of treatment and we are evaluating the feasibility of cyberknife radiotherapy as consolidation. **Conclusions:** We report a rare case of para-renal lambda-restricted plasmacytoma-like PTLD, successfully treated with Bortezomib-based therapy. Unfortunately, we couldn't perform molecular biology to compare the lambda chains of the plasma cells identified in the transplanted liver with those of the pararenal plasmacytoma because of insufficiency of material. However, it is difficult to believe that the clone at the base of these two pathologies is not the same.

P73

BVD IS EFFECTIVE IN RELAPSED LYMPHOPLASMACYTIC LYMPHOMA PATIENTS REFRACTORY OR INTOLLERANT TO RITUXIMAB: 2 CLINICAL CASE REPORTS

Liço A., Barilà G., Checuz L., Leoncin M., Semenzato G., Zambello R.

Hematology and Clinical Immunology, Department of Medicine, Padua University School of Medicine, Italy

Lymphoplasmacytic lymphoma (LPL) is a rare subtype of non-Hodgkin lymphoma, characterized by lymphoplasmacytoid cells infiltration of bone marrow and monoclonal paraproteinemia, typically IgM type. Although in most patient's survival can be measured in decades with current treatment options, LPL remains an incurable disease. When chemotherapy is required, several regimens can be used as rituximab (R) alone or in combination with alkylators, purine analogs, bendamustine, proteasome inhibitors and more recently ibrutinib. Here we report two cases of relapsed LPL, refractory or intolerant to Rituximab, who received Bendamustine in association with Bortezomib and Dexamethasone (BVD) as salvage regimen. Bendamustine was administered intravenously at 70 mg/m² on days 1 and 8, Bortezomib subcutaneously at 1,3 mg/m² and dexamethasone 20 mg orally at days 1, 8, 15 and 22 repeated every four weeks for 6 cycles. Patient 1 was a 39 years old male with an IgA/k LPL symptomatic for anemia, lymphadenopathies, and B symptoms. He initially underwent treatment with 6 cycles of R-CHOP followed by Rituximab maintenances. During maintenances, he developed progressive disease with lymph nodes involvement and increase of M-protein. Bone marrow biopsy revealed a 25% lymphoid infiltration positive for MYD88 mutation. Patient started salvage chemotherapy with BVD therapy for 4 cycles obtaining a Very Good Partial Response (VGPR) followed by Autologous Stem Cell Transplantation consolidation. Progression Free Survival (PFS) was 22 months. BVD was well tolerated and no relevant complications were observed. Patient 2 was a 63 years old female with a long story of IgM/k LPL characterized at the diagnosis by lymphoid infiltration of bone marrow of 50% and autoimmune haemolytic anemia and immune thrombocytopenia (ITP). She initially received 6 cycles of R-CHOP with early R withdrawal due to severe infusion related reaction, obtaining a complete hematological recovery and biochemical partial response. Due to disease relapse with increase of M-protein and onset of ITP, patient was initially treated with Bendamustine single agent and then underwent splenectomy with normalization of platelet count. However, patient developed an early ITP relapse associated to not haemolytic anemia and M-protein increase; bone marrow biopsy revealed a 20% lymphocyte infiltration with MYD88 mutation positivity. She received 6 cycles of BVD regimen with concomitant romiplostin administration, obtaining a complete hematological recovery with interruption of TPO mimetics therapy and VGPR biochemical response. PFS was 14 months. No relevant therapy related complication occurred. In this issue, we report the efficacy and safety of BVD treatment in patients with relapsed LPL. Not less important, BVD has a favourable cost effective-

veness ratio compared to Ibrutinib and similar PFS. Both Bendamustine and Bortezomib are well known drugs separately used in this disease but, to our knowledge, this is the first report of the combined application of this drugs in LPL. Besides, this regimen, that is extensively used in Multiple Myeloma, is associated to high quality and durable responses, with acceptable safety profile. This treatment appears a valid option in relapsed LPL, especially in those in which rituximab therapy is not applicable due to intolerance or high M-protein amount, also representing a well-tolerated bridge to transplant approach.

P74

SAFE AND EFFECTIVE TREATMENT OF MULTIPLE MYELOMA IN A PATIENT AFFECTED BY BRUGADA SYNDROME

Sapienza G., Calafiore V., Di Martino E., Parisi M., Del Fabro V., Conticello C., Romano A., Di Raimondo F.

UOC Hematology and Bone Marrow Transplantation Units - AOU Policlinico Vittorio Emanuele, Catania, Italy

The Brugada syndrome is an inherited cardiac channelopathy associated with an increased risk of ventricular arrhythmias and sudden death. These symptoms often occur during sleep or resting conditions. The syndrome is associated with right ventricular conduction delay and ST elevation in the right precordial leads. Several genes have been implicated in Brugada syndrome. (E. S. Kaufman, *Hearst Rhythm* 2009) There are some drugs that can unmask the Brugada syndrome ECG and that have therefore to be avoided: vagotonic agents, alpha adrenergic agonists, beta adrenergic antagonists, tricyclic antidepressants, first generation antihistamines, cocaine. (Antzelevitch *et al.* *Circ Res.* 2002). Multiple myeloma is a cytogenetically heterogeneous clonal plasmacells proliferative disorder (Palumbo A, Anderson K. *NEJM* 2011) that accounts for 1% of all cancers and 10% of all hematological malignancies. (Palumbo A *et al.* *Blood* 2011). Diagnosis of multiple myeloma is based on the detection and evaluation on monoclonal M component in serum and/or urine, evaluation of bone marrow plasma cell infiltration and evidence of end organ damage (the so called CRAB criteria), the latter is an indication for disease treatment. (P. Moreau *et al.* *Annals of oncology* 2017). Nowadays, there aren't any suggestion on anti myeloma agents and Brugada syndrome. It is widely accepted that there is an high risk for cardiovascular events when Carfilzomid is used but also velcade has a low cardiotoxicity. Lenalidomide, a derivative of thalidomide is less toxic and more potent than the parent drug; it was firstly approved in Italy from second line treatment of relapsed/refractory multiple myeloma patients, while currently it has also been approved for first line treatment of newly diagnosed multiple myeloma patients ineligible for high dose chemotherapy. Herein we report a case of multiple myeloma patient with coexisting Brugada Syndrome that was successfully treated without any significant adverse events with low dose lenalidomide (10 mg from day 1 to day 21) and dexamethasone (40 mg per week) as second line therapy. On September 2011, when MM diagnosis occurred, only one bone lesion was present, the ISS stage at baseline was I, and patient was treated as first line with high dose of dexamethasone and radiation therapy. On June 2016, when first relapse occurred, the patient developed anemia, monoclonal protein elevation, and skeletal lesions on MRI. After careful evaluation of anti-myeloma drugs cardiotoxicity, considering young age of the patient, we decided to treat him with RD schema. He is currently doing seventeenth cycle without any adverse events until now. In addition to safety and tolerability since the beginning treatment was effective and patient obtained a stable PR already after the fourth cycle. To the best of our knowledge this is the first case of anti-MM use of lenalidomide in a patient affected by Brugada syndrome.

P75

A RARE CASE OF POLYCYTHEMIA VERA AND PLASMA CELL MYELOMA IN THE SAME PATIENT

Ozatli D., Meletli Ö.

Department of Hematology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey

Purpose. Multiple myeloma (MM) and polycythemia Vera (PSV) are originated from different cell lines. JAK-STAT pathway plays important role in the pathogenesis of those disease, but in a different ways. An acquired somatic mutation in exon 12 of JAK2 gene has been described in higher frequency in PSV and has also been identified in lower frequency in other myeloproliferative neoplastic disorders, acute myeloid leukemia, myelodysplastic syndrome and in atypical chronic myeloid leukemia (BCR-ABL negative) but not in MM. The coexisting MM and PSV are very rare and the manipulation of the treatment may be difficult. Here we present a 68-year-old male patient having beta-thalassemia with the diagnosis of simultaneous MM and Jak2 positive PSV. CASE A 68-year-old male patient having beta-thalassemia was referred to our hematology department due to leukocytosis and thrombocytosis 10 months ago. Upon initial presentation, the patient's labs were as follows: white blood cell count 25 000 / μ L, hemoglobin 12.2 gr/dL, MCV 55 and thrombocyte 794 000/ μ L, BUN: 26 mg/dl, creatinine: 1,16 mg/dl, sodium: 130 mEq/L, potassium: 3.2mEq/L, chloride: 98 mmol/L, calcium: 9.7 mg/dl, ALT: 19 IU/L, AST: 36 IU/L, LDH: 425 IU/L, alkaline phosphatase: 135 IU/L, total protein: 9.4 g/dl, albumin: 4.9 g/dl, and Beta-2 microglobulin: 3883 ng/ml. Peripheral smear showed neutrophilia, anisocytosis, hypochromia and microcytosis. Bone marrow aspiration examination showed 20% plasma cell. Bone marrow biopsy was reported as plasma cell myeloma. No lytic lesions were identified in craniography and long bones. Immuno-electrophoretic examination of the serum and urine consistent with IgG heavy, kappa light chain disease (Serum IgG 3330 mg/dL, serum IgA 221 mg/dL, serum IgM 146 mg/dL, serum kappa light chain 77 mg/dl, serum lambda light chain 7 mg/dl. JAK-2 mutation was positive. The patient's abdominal CT scan showed minimal splenomegaly (138 mm). Hydroxyurea and acetyl salicylic acid were started. After 9 months, his WBC was 10 000 / μ L, hemoglobin 10.5 gr/dL, and thrombocyte 378 000 / μ L, serum IgG 3200 mg/dL, Ig A 210 mg/dL and Ig M 140 mg/dL. In conclusion, the treatment choose of such kind of this patients must be modified according to the situations of those diseases. Because MM was smoldering type in our patient the treatment was directed to PSV disease. But when MM becomes an overt type the treatment will be focused more on treating the myeloma and monitoring PSV. Because of the rarity coexisting of those diseases the prognosis of those patients are not known well.

Nurse

P76

PROGRESSION FREE SURVIVAL AND OVERALL SURVIVAL FIVE YEARS AFTER ORAL CRYOTHERAPY IMPLEMENTED IN HIGH-DOSED MELPHALAN CONDITIONING FOR THE PREVENTION OF ORAL MUCOSITIS

Naegele M., Leppla L., Ihorst G., Hasemann M., Rebafka A., Mößner U., Koller A., Engelhardt M.

Department of Hematology/Oncology, University of Freiburg Medical Center, Germany Clinical Trials Unit, University of Freiburg, Germany Institute of Nursing Science, University of Vienna, Austria

Background: Oral mucositis (OM) is a common side effect of high-dose (HD) melphalan (MEL) with 87% of patients developing OM and 44% developing severe OM. OM does not only result in severe pain, discomfort, and difficulties in eating and drinking, but also in prolonged hospitalization, increased costs, substantial risk for systemic infections and higher mortality. Oral cryotherapy represents an effective prophylaxis of OM in HD MEL and autologous and allogeneic stem cell transplantation (ASCT/allo-SCT) and is suggested for this indication by the guideline of the Multinational Association of Supportive Care in Cancer. We successfully implemented oral cryotherapy in all protocols containing MEL ≥ 140 mg/m² in our large tertiary hospital in 2011. Severe OM could be significantly reduced by 11% (31% vs. 20%) in patients receiving BEAM, while severe OM was entirely avoided in multiple myeloma (MM) patients receiving MEL200 or MEL140 mg/m² (20%/33% vs. 0%). Although research has clearly demonstrated the effectiveness of oral cryotherapy in preventing severe OM, there is still ongoing concern that cryotherapy may reduce the effectiveness of chemotherapy leading to increased relapse and decreased survival rates; which therefore needs to be thoroughly assessed likewise. **Methods:** The aim of this study was therefore to explore possible differences in progression free survival (PFS) and overall survival (OS) in patients who received oral cryotherapy (intervention group [IG]) vs. a control group (CG), without oral cryotherapy being performed. We conducted a retrospective, detailed chart analysis of all patients we had included in the implementation study in 2011 (L. Leppla, *Onkologische Pflege* 2016, 6(1), 40-46). At that time, we surveyed 100 patients in the IG with oral cryotherapy and compared them with a historic control group of 76 patients without oral cryotherapy (CG). Variables of interest were PFS and OS in months after ASCT over a period of 5 years. Kaplan-Meier estimation plots were used to display results and the log-rang test for significance testing. We included all patients in whom we could clearly assess relapse and survival. **Results:** Of the 176 patients in our implementation study group, 151 patients could be included in this analysis: 62% in the IG were male (64% in the CG), mean age at HD MEL and ASCT was 56.7 (54.7), 49% of patients had a MM and received MEL200/140 mg/m² (47%), 38% had a lymphoma and underwent BEAM (36%) conditioning, and 13% had other HD Mel-containing conditioning regimens (17%). Most underwent ASCT vs. allo-SCT in the IG vs. CG with 94% vs. 83% and 6% vs. 17%, respectively. Five years after HD MEL, PFS was 48% in the IG vs. 47% in the CG, and OS was 71% in the IG vs. 72% in the CG. Thus, patients' characteristics as well as outcome including PFS and OS of IG vs. CG were very similar and insignificantly different. More multivariate analysis will be presented at the meeting. **Conclusions:** For the prevention of OM in HD Mel, oral cryotherapy is highly effective and safe regarding relapse and survival rates. Thus, concerns against oral cryotherapy lack justification; making the latter a standard prevention method to effectively avoid OM at our center.

INDEX OF AUTHORS

A

Abildgaard N. 12
Acosta J. 13
Agnelli L. 15
Ahlberg L. 12
Ajayi S. 4
Albano F. 27
Alegre A. 32
Amico V. 36
Andersen N. 12
Anderson L. Jr 30
Andreasson B. 12
Andreu R. 22
Andriani A. 34
Antonoli E. 17
Arcamone M. 36
Arcese W. 44
Arnao M. 22
Azzaro M.P. 18

B

Bacci F. 25, 44
Bacovsky J. 26, 28, 35
Bagratuni T. 41, 44
Bakogeorgos M. 41
Balic L.I. 42
Bandeckar R. 40
Barilà G. 23, 25, 46
Barone M. 36
Barreto W. 30
Basile S. 38
Basset M. 7, 13, 43
Beksac M. 40, 42
Beltrán N. 27, 29
Benboubker L. 31, 32
Bergsagel P.L. 9
Bernardini A. 15
Bertsch U. 11
Bezdekova R. 19
Bila J. 19, 42
Bladé J. 1, 32, 42
Blaise D. 42
Blau I.W. 11
Boccadoro M. 15
Bocchia M. 17
Bogdanović A. 19
Bøgsted M. 12
Bolomsky A. 19
Bonaldi L. 25
Bosi A. 17
Bowcock S. 15
Branagan A. 41
Brandefors L. 12
Bray A. 21
Bringham S. 5, 13, 31, 33
Bron D. 42
Bruno G. 33

Bryant D. 19

Byrne C. 31, 32

C

Cabrera Ruiz F.J. 27, 28
Cafro A.M. 15
Cahill M.R. 21
Cahn J.Y. 42
Caillot D. 42
Caivano A. 18
Calafiore V. 18, 35, 37, 38, 47
Caltagirone S. 15
Campbell P. 22
Canovas Nunes S. 25
Canziani L. 10
Caratozzolo I. 1
Caravita T. 34
Carraro S. 23
Carrino M. 25
Carson R. 22
Casneuf T. 31
Catalano L. 36, 38, 39, 45
Cavo M. 1, 15, 22, 32, 40
Cejalvo M.J. 22
Cellini C. 15
Cenci S. 10
Cerchione C. 36, 38, 39, 45
Cerretti R. 44
Cesini L. 34, 44
Chari A. 32, 40
Chauhan S. 10, 16, 17
Checuz L. 23, 25, 46
Chesi M. 9
Chicca I.J., 15
Chiu C. 16, 22, 30, 31
Chiusolo P. 44
Christensen H.S. 12
Christiansen H.B. 12
Christopoulou G. 21
Christoulas D. 21, 41, 44
Chyra Kufova Z. 19
Ciceri F. 10
Cinetto F. 23
Clemens P.L. 32
Cohen A. 30
Cohen Y.C. 40
Collins A.R. 19
Conticello C. 10, 18, 35, 37, 38, 47
Cook G. 4, 31
Cook M. 22
Coriu D. 42
Corradini P. 30
Crea T. 33
Crepaldi A. 22
Crist W. 22
Cudillo L. 44
Curci P. 27

D

D'Agostino M. 13
D'Auria F. 18
Daly J. 10, 16, 17
Danhof S. 9
Dawson K. 13
De la Rubia J. 22
De Luca L. 18
De Rosa L. 34, 44
De Stefano V. 44
Del Fabro V. 35, 37, 38, 47
Del Vecchio L. 18
Delaini F. 24, 33
Delorme S. 11
Denčić Fekete M. 19
Deraedt W. 22, 30
Dhodapkar M. 41
Di Bartolomeo P. 25, 44
Di Martino E. 47
Di Perna M. 39, 45
Di Raimondo F. 10, 18, 35, 37, 38, 47
Dimopoulos M.A. 3, 21, 22, 31, 41, 42, 44
Domínguez E. 22
Domínguez J.F. 28, 45
Doyen C. 22
Drayson M.T. 15
Duerig J. 13
Duggan T. 10, 16, 17
Dunn J.A. 15
Dürig J. 11
Dybæk K. 12

E

Eikema D.J., 42
Einsele H. 4, 8, 9
Eleutherakis-Papaikovou E. 41
Engelhardt M. 4, 48
Esposito D. 36
Estell J. 30, 40

F

Faber E. 28, 35
Facco M. 23
Fanti S. 1
Farina G. 36
Favasuli V. 15
Faxoe S. 12
Fazio F. 24, 44
Ferla V. 38, 46
Ferrara F. 36, 38
Ferrara K. 36, 39
Fiedler U. 13
Filipova J. 19
Fiorini A. 34
Foà R. 24, 44
Foli A. 13, 43

Fontana R. 36
Foster C. 41
Fotiou D. 44
Fouillard L. 42
Franceschini L. 44
Fransson C. 12
Friestad M. 12
Froberg Brøndum R. 12
Fujisaki T. 22

G

Gabraïl N. 32
Gagliardi A. 36
Galli M. 24, 33
Gamberi B. 13
Gan G. 41
García Fortes M. 27, 28
García Sánchez R. 27, 28
Garcia-Cerecedo T. 26
Garcia-Guiñon A. 26
Garderet L. 42
Garg M. 22
Gavriatopoulou M. 21, 41, 44
Gay F. 7, 15, 33
Gengenbach L. 4
Gerofotis A. 21
Giallongo C. 10
Gil E. 28, 45
Gilestro M. 15
Goldschmidt H. 11, 13, 40
Gómez K. 28, 45
González de la Calle V. 1
González Fernández A. 27, 28
Goranova-Marinova V. 42
Gorczyca M. 30
Gozzetti A. 17
Gramatzki M. 4
Grammatico S. 34
Gregersen H. 12
Gregorini A.I. 38, 46
Grosicki S. 22
Growkova K. 19
Grzasko N. 13
Guidotti F. 38, 46

H

Haenel M. 11
Hajduch M. 19
Hajek R. 19
Halka K. 32
Hammerlund Y. 12
Hansson M. 12
Harmenberg J. 31, 32
Harousseau J.L. 4
Harstrick A. 13
Hasemann M. 48
Hassoun H. 32
Haukaas E. 12

- Haunschild J. 13
Hawkey P. 15
He Z. 30
Heaney J.L.J. 15
Hector M. 12
Heiniger Mazo A.I. 28
Helleberg C. 12
Hellemans P. 32
Henderson R. 16, 17
Herman M. 26
Hermann F. 13
Hermanova Z. 26
Hernando A. 21
Heuck C. 40
Hielscher T. 11
Hillengass J. 11
Hirakata G. 21
Ho P.J. 31
Hofmeister C.C. 40
Hofste op Bruinink D. 12
Høholt H. 12
Holst M. 12
Hoos A. 30
Hose D. 11
Hrbek J. 26
Hu J. 17
Hudecek M. 9
Hungria V. 30
- I**
Iannaccone A. 33
Ihorst G. 4, 48
Ingravallo G. 27
Iori A.P. 44
Iosava G. 22
Iqbal G. 15
Iserte L. 26
Itälä-Remes M. 42
Ivanaj A. 42
- J**
Jak M. 20, 33
Jaković Lj. 19
Jakubowiak A. 22
Jarque I. 22
Jauch A. 11
Jeličić J. 19
Jelinek T. 19
Jenner M. 40
Jewell R. 30
Jiménez M. 22
Johnsen H.E. 12
Jönsson A.K. 12
Jovanović J. 19
Jungova A. 19
Jurczyszyn A. 13
- K**
Kanellias N. 41, 42, 44
Kaplan P. 22
- Karlsson V. 12
Kastritis E. 6, 21, 41, 42, 44
Katodritou E. 21
Kauczor H.U. 11
Kaufman J.L. 32
Kenny T. 21
Kersten M.J. 6
Kim K. 31
Kjær S. 12
Klostergaard A. 12
Knop S. 13, 22
Kobbe G. 42
Koller A., 48
Konstantinidou P. 21
Koster L. 42
Kourakli A. 21
Koureas A. 44
Koutoulidis V. 44
Kovacs-Benke E. 20
Krejčí M. 43
Krhovska P. 26, 35
Krhovská P. 28
Kröger N. 42
Kryukov F. 19
Kuppens S. 40
- L**
La Cava P. 10
La Rocca F. 18
Lahiri S. 30
Lamorte D. 18
Larocca A. 3, 32
Laurenzana I. 18
Lauri B. 12
Legarda M. 22
Leiba M. 31
Lendvai N. 30
Lenhoff S. 12
Lenihan E. 21
Leoncin M. 23, 25, 46
Leotta S. 18, 35, 37
Leppla L. 48
Li F. 41
Libby E. 30
Liberati A.M. 22
Liço A. 23, 25, 46
Lindberg J. 31, 32
Lindemann H.W. 11
Liu K. 32
Lokhorst H. 32
Lombardi L. 24
Lonn I. 12
Luaña A. 26
Luchinin A. 40
Lucio P. 8, 22
- M**
Macrì N. 25
Madsen L.H. 12
Maertens J. 42
- Maffei I. 33
Mai E.K. 11
Maisel C. 32
Maisnar V. 19
Mallano S. 27
Mancuso K. 1
Manni S. 25
Manteiga J. 3, 10
Manzoni M. 15
Marano L. 38
Marcatti M. 10
Marco V. 26
Mariggiò E. 24, 44
Martines A. 25
Martino E. 18, 35, 37, 38
Masterson T. 32
Mateos M.M. 30
Mateos M.V. 1, 7, 22, 32
Mazumder A. 32
McCarthy P.L. 2, 17
McEllistim C. 16, 17, 21
Medvedova E. 30
Meletli Ö. 47
Mellqvist U.H. 12, 31
Merlini G. 13, 43
Merz M. 11
Mestice A. 27
Migkou M. 44
Migliaccio I. 36, 39
Mihaljević B. 19
Milan A. 33
Milani P. 13, 43
Min C.K. 30
Minaeva N. 40
Minarik J. 19, 26, 28, 35
Minnema M.C. 7, 20, 33
Mohty M. 2
Molica S. 15
Monaco G. 36
Moreau P. 31, 32
Moreb S.J. 32
Morelli A. 25, 44
Moreno Carrasco G. 27
Morton J. 31
Mößner U. 48
Mouloupoulos L.A. 44
Muccio V. 15
Murphy P. 21
Musolino C. 15
Musso M. 42
Musto P. 15, 18
Myhr E. 12
Mykytiv V. 21
- N**
Naegle M. 4, 48
Nagy Z. 22
Nah H. 32
Naicker S. 16
Nalio S. 25
- Nanni C. 1
Nappi D. 38, 39, 45
Natoni A. 9, 16, 17
Neben K. 11
Neff T. 40
Neri A. 10, 15
Nguyen H. 22
Nooka A.K. 30
Nordström E. 31, 32
Ntanasis-Stathopoulos I. 41
Nuvolone M. 13
- O**
O'Dwyer M. 9, 10, 16, 17, 21
Ocio E. 7, 32
Oddolo D. 15
Ola Landgren C. 40
Oliva L. 10
Omedè P. 15
Oostvogels R. 20, 33
Opalinska J. 30
Orfanelli U. 10
Oriol A. 32
Oriol Rocafiguera A. 32
Ozatli D., 47
Ozet G. 42
Ozsán H., 42
- P**
Paba-Prada C. 31
Pacelli P. 17
Palladini G. 7, 13, 43
Palma A. 28, 45
Palmieri S. 36, 38
Palumbo A. 31
Pane F. 36, 38, 39, 45
Paner A. 32
Pantani L. 1
Papajik T. 28, 35
Pareto A.E. 38, 39
Pareto A.E., 39, 45
Paris L. 24, 33
Parisi M. 18, 35, 37, 38, 47
Parker I. 21
Parrinello N.L. 10
Passweg J. 42
Pavone V. 15, 42
Pavoni C. 24, 33
Pedersen B.H. 12
Pelizzoni F. 15
Peluso I. 36, 38, 39
Pérez-Montaña A. 27, 29
Perla A. 22
Perlini S. 13
Peruničić-Jovanović M. 19
Petrova P. 26
Petrucci M.T. 24, 34, 44
Piazza F. 25
Piciocchi A. 24, 44
Pietrantuono G. 18

- Pika T. 26, 28, 35
 Pioltelli P. 42
 Piroso M.C. 37
 Planche T. 15
 Plesner T. 31, 32
 Poiré X. 42
 Pompa A. 38, 46
 Popat R. 30
 Porras R.P. 42
 Pouli A. 42
 Pour L. 19, 22, 43
 Pratt G. 15
 Prommersberger S. 9
 Puglisi F. 18
- Q**
 Qi M. 22, 40
 Quinn J. 21
- R**
 Raab M.S. 11, 13
 Rago A. 34
 Raida L. 28, 35
 Rambaldi A. 24, 33
 Ramírez S. 28, 45
 Ranieri P. 27
 Raspadori D. 17
 Raynes K. 15
 Rebafka A. 48
 Reeves B. 30, 31
 Reinhardt H. 4
 Reményi P. 42
 Renna R. 12
 Revelles Peñas M. 27, 28
 Ribas P. 22
 Richardson G.P. 32
 Richardson P. 30, 31
 Rigalou A. 16
 Rihova L. 19
 Rivero E. 26
 Rizzello I. 1
 Rizzi R. 27
 Rocchi S. 1
 Rocco S. 36, 38
 Rodríguez J.N. 28, 45
 Rodríguez-Otero P. 8, 32
 Romano A. 10, 18, 35, 37, 38, 45, 47
 Romero S. 22
 Ronchetti D. 15
 Ronconi S. 15
- Ros T. 27, 29
 Rosiñol L. 2, 42
 Rossi F.G. 38
 Rubio L. 22
 Ruggeri M. 15
 Ruiz Arredondo J.J. 27, 28
 Ruiz M.A. 28
 Ryan A. 16
- S**
 Sahota S.S. 19
 Salvini A. 33
 Salwender H. 11
 Samarina S. 40
 Sampol A. 27, 29
 San-Miguel J. 22
 Sánchez-Raga J.M. 27, 29
 Sandecká V. 43
 Sandhu I. 40
 Sapienza G. 35, 37, 38, 47
 Saraci E. 15
 Sarkar S. 10, 16, 17
 Sasser K. 16
 Schaap N. 42
 Schecter J.M. 30, 31
 Scheid C. 11
 Schjesvold F.H. 12
 Schmitz A. 12
 Schreder M. 13
 Schroyens W. 42
 Scudla V. 28, 35
 Seckinger A. 11
 Sementa A. 36
 Semenzato G. 23, 25, 46
 Semochkin S. 40
 Seres Y. 26
 Ševčíková S. 43
 Ševčíková T. 19
 Severino A. 44
 Sharik M. 9
 Shelekhova T. 22
 Sica A. 36
 Sica S. 44
 Sicuranza A. 17
 Simeone L. 38
 Simicek M. 19
 Siniscalchi A. 2 34
 Sjøgren T.V. 12
 Skoumalová I. 28, 35
 Smejkalova J. 19
- Solé M. 28, 45
 Sonneveld P. 12, 31
 Sortino G. 18
 Spada S. 15
 Specchia G. 27
 Spencer A. 30, 40
 Sretenović A. 19
 Staderini M. 17
 Štork M. 43
 Støve-Bødker J. 12
 Stracquadanio G. 19
 Sutherland H. 30
 Suzuki K. 22
 Svanera G. 36
 Svirskaite A. 12
 Symeonidis A. 21
 Szarejko M. 13
 Szatkowski D.L. 12
 Szotkowski T. 28, 35
 Szymaniak-Vits M. 4
- T**
 Tacchetti P. 1
 Taiana E. 15
 Takezako N. 31
 Tapper W. 19
 Terpos E. 5, 21, 41, 44
 Thiagarajah P., 30
 Thuresson S. 32
 Tibullo D. 10
 Tocci D. 17
 Todoerti K. 10, 15
 Toledo N. 27
 Tonon G. 10
 Torti L. 25, 44
 Toscano S. 18
 Treon S.P. 5
 Trimarco V. 23
 Trino S. 18
 Trivedi S. 31
 Trneny M. 42
 Trudel S. 30
 Trudu M. 10
- U**
 Urbano M. 27
 Usmani S.Z. 32
- V**
 Vacca A. 13
 van de Donk N. 8, 40
- van der Holt B. 12
 van der Velden V.H.J. 12
 Vangsted S. 12
 Veglio F. 33
 Venner C. 40
 Verma R. 41
 Villani O. 18
 Vincelli D. 15
 Vinci C. 15
 Vitagliano O. 38
 Vitucci A. 27
 Vojta P. 19
 Voorhees P. 30, 31, 40
 Vozella F. 24, 44
- W**
 Waage A. 12
 Walsh J. 21
 Wang J. 22
 Wäsch R. 4
 Weisel K. 11, 30
 Weston-Bell N.J. 19
 White D. 2 31
 Williams C. 40
 Wood J. 15
 Wu K. 31
- Y**
 Yong K. 15, 30
 Yoon S.S. 22
- Z**
 Za T. 34, 44
 Zacheo I. 39, 45
 Zagouri F. 21
 Zamagni E. 1
 Zambello R. 23, 25, 46
 Zannetti B. 1, 9, 13
 Zapata R. 28, 45
 Zapletalova J. 26, 28, 35
 Zatopkova M. 19
 Zdeňek A. 43
 Zdeněk K. 43
 Zhang L. 41
 Zojer N. 19
 Zonder J. 31, 32
 Zubair H. 31
 Zucca E. 41, 42