UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

Napoli, 1 Dicembre 2017
Palazzo Esedra

Presentazione del progetto

Dr Claudio Cerchione, MD, PhD

Dipartmento di Medicina Clinica e Chirurgia –

Divisione di Ematologia - AOU Federico II - Napoli

Prima occasione di confronto sul management delle maggiori patologie ematologiche tra giovani campani che operano in ematologia, afferenti ai vari centri di riferimento

Non esisteranno lezioni plenarie classiche, non esistono docenti e discenti, le presentazioni saranno totalmente interattive, e soprattutto non esistono risposte giuste o sbagliate, e ogni quesito è sempre ben accetto

Ognuno di noi può proporre dei progetti da portare avanti nel tempo favorendo l'interazione, il confronto e lo scambio di idee tra i vari centri

Oggi si parte da MM ed LLC, ma ci proponiamo di allargare il lavoro anche alle altre principali patologie ematologiche (Leucemie acute, SMD, SMP, Linfomi)

Obiettivo è la nascita di un gruppo di confronto, finalizzato successivamente anche alla creazione di un team multidisciplinare

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L'approccio terapeutico nel Mieloma Multiplo (MM)

Dr Claudio Cerchione, MD, PhD

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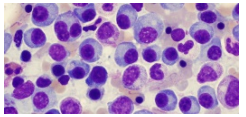
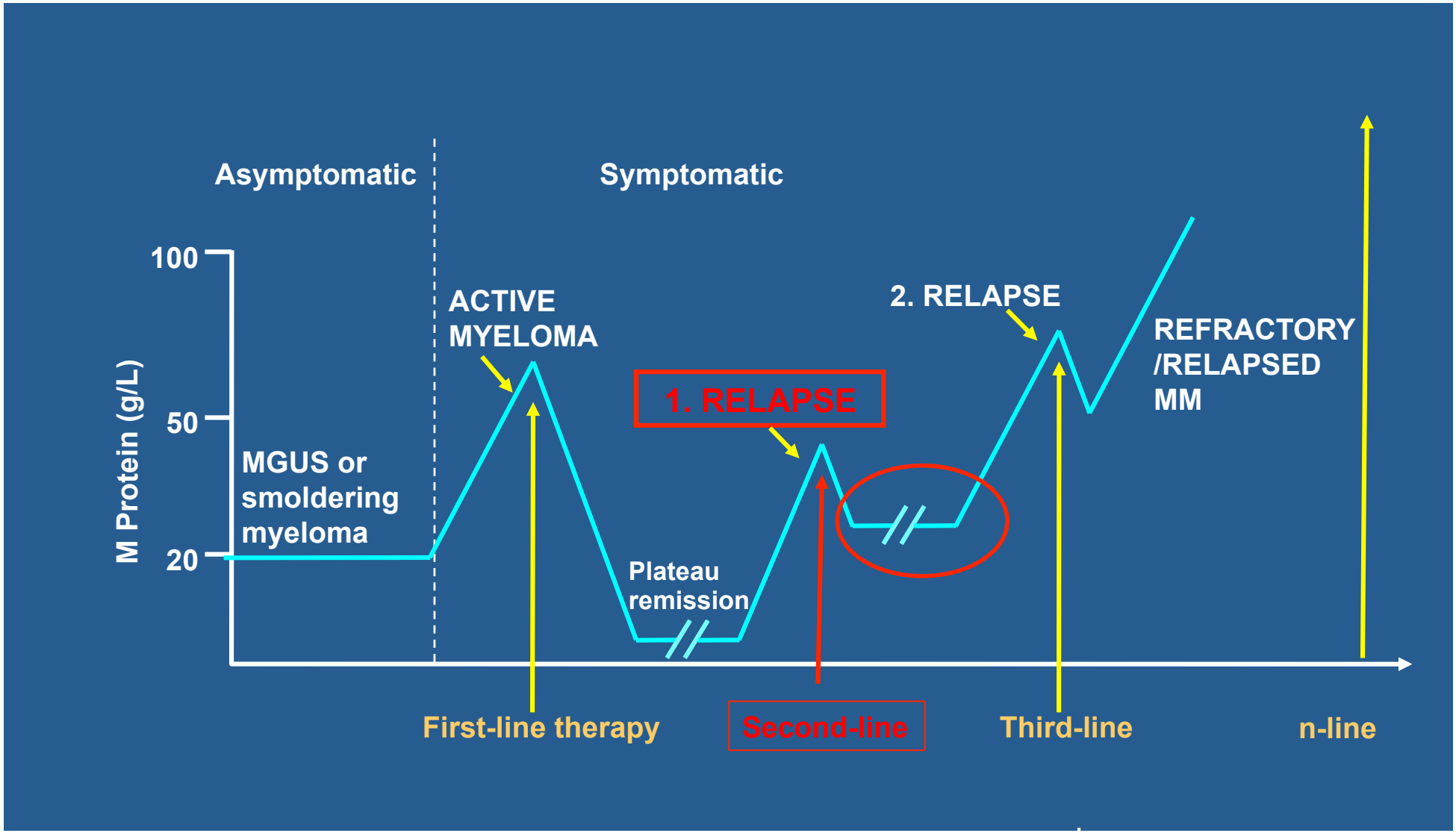
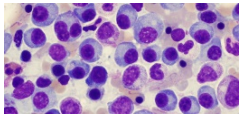
Divisione di Ematologia - AOU Federico II - Napoli

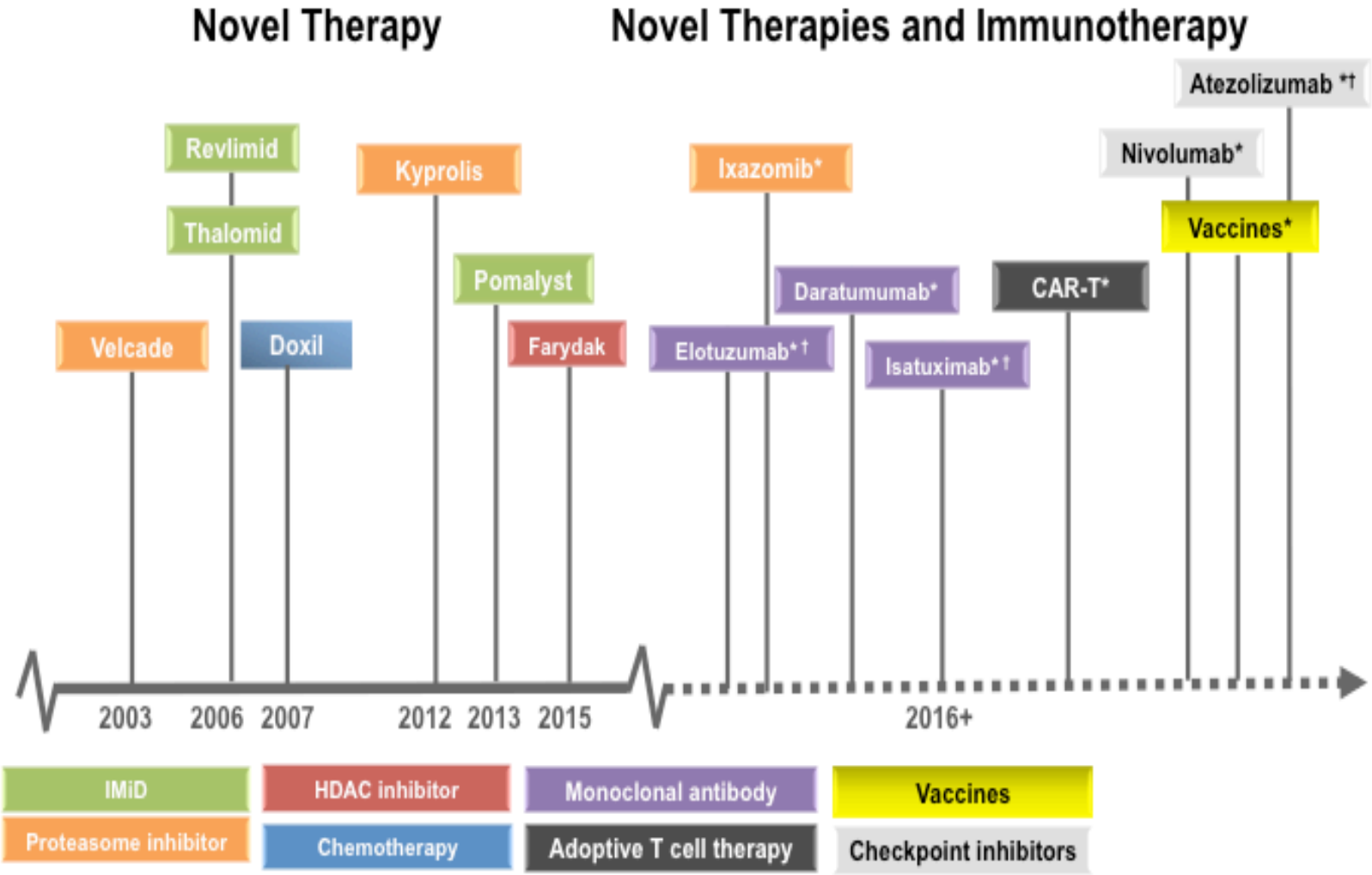
Natural History of MM





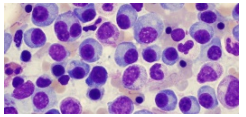
New drugs and mechanisms of action in MM

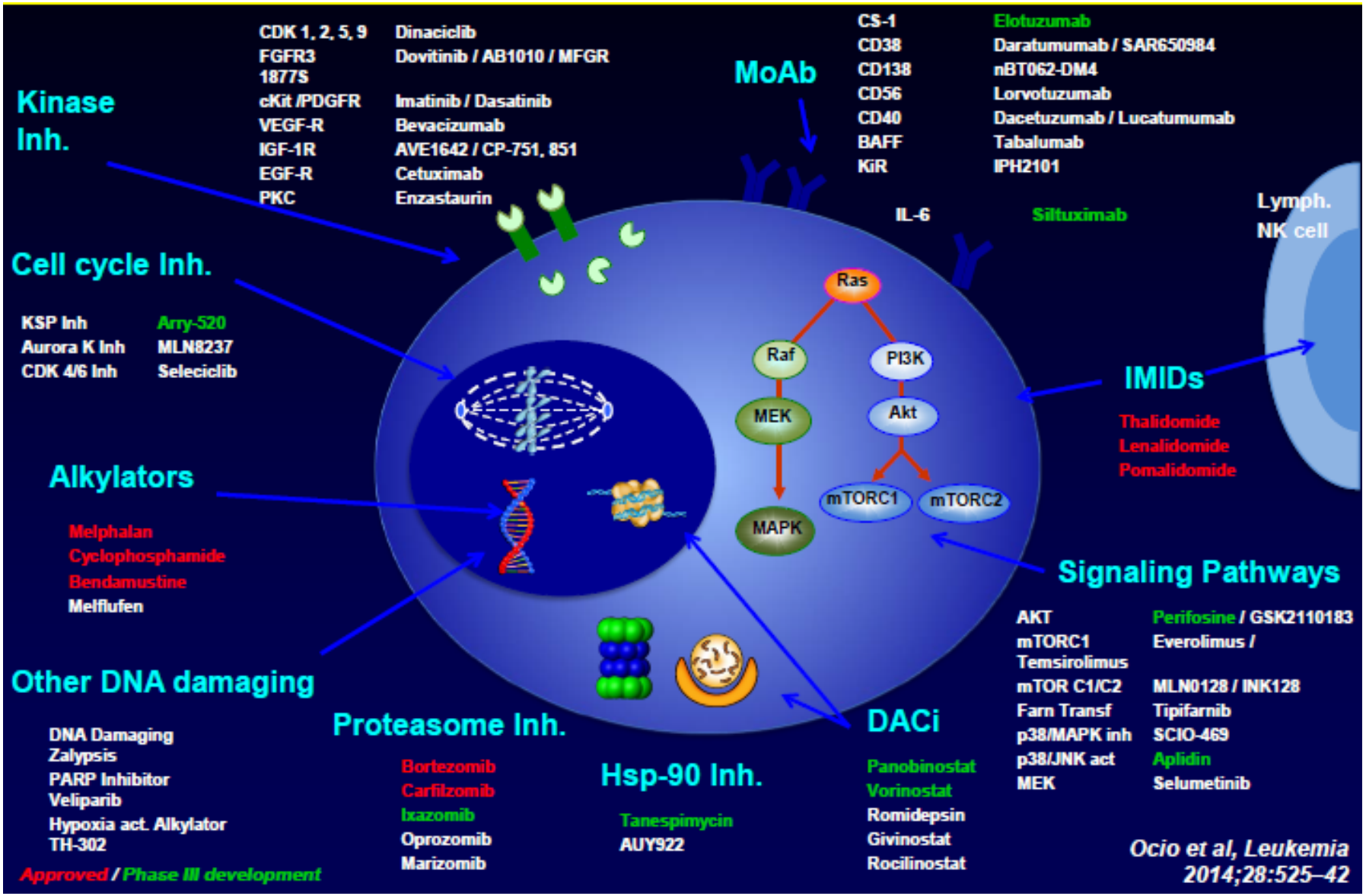




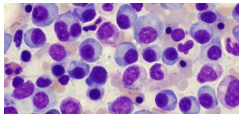
IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
*Not yet FDA-approved for MM; only available in clinical trials
†Treatments studied in MMRC trials

New drugs and mechanisms of action in MM





Frontline Therapy in MM



Eligibility for ASCT

Yes

Induction: 3-drug regimens
- VTD
- VCD
- RVD
- PAD

↓

200 mg/m2 Melphalan followed by ASCT

↓

Short-term consolidation
- VTD
- RVD

↓

Maintenance
- Lenalidomide
- Bortezomib

No

First option: VMP, Rd, or MPT

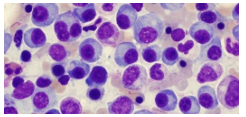
Second option: VCD, VD, VTD

Other option: BP, CTD

Aims:
- Maximize the depth of response
- Minimize the burden of residual tumor cells

Frontline therapy of multiple myeloma.
Moreau P, Attal M, Facon T.
Blood. 2015 May 14;125(20):3076-3084. Epub 2015 Apr 2. Review

Frontline Therapy in MM



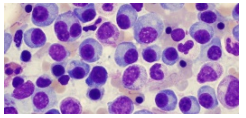
	VISTA (VMP arm)	VMP (OW) GIMEMA	VMPT-VT (OW) GIMEMA	VMP-VT (OW) PETHEMA	MM-015 (MPR-R)	FIRST (Continuous Rd)	MPT (FIRST)
CR	30%	24%	38%	42%	9.9%	15.1%	9.3%
PFS	21.7m	24.8m	35.3m	37m	31m	25.5m	21.2
OS	Median **56.4m** 5-year OS: 46.0%	Median **60.6m** 5-year OS: 51%	5-year OS: 61%	5-year OS: 69%	3-year OS: 70%	Median **58.9m** 4-yearOS: 60%	Median **48.5m** 4-year OS: 51%

Continous treatment

San Miguel et al. N Engl J Med 2008; 359: 906-917
San Miguel et al. J Clin Oncol 2012;31(4):448-55
Palumbo et al. ASH 2012 (Abstract 200), oral presentation
Mateos et al. Blood 2012; 120: 2581-2588

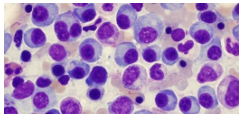
Facon et al. JCO 2015:33 Abs8524
Palumbo et al. N Engl J Med 2012;366(19):1759-69

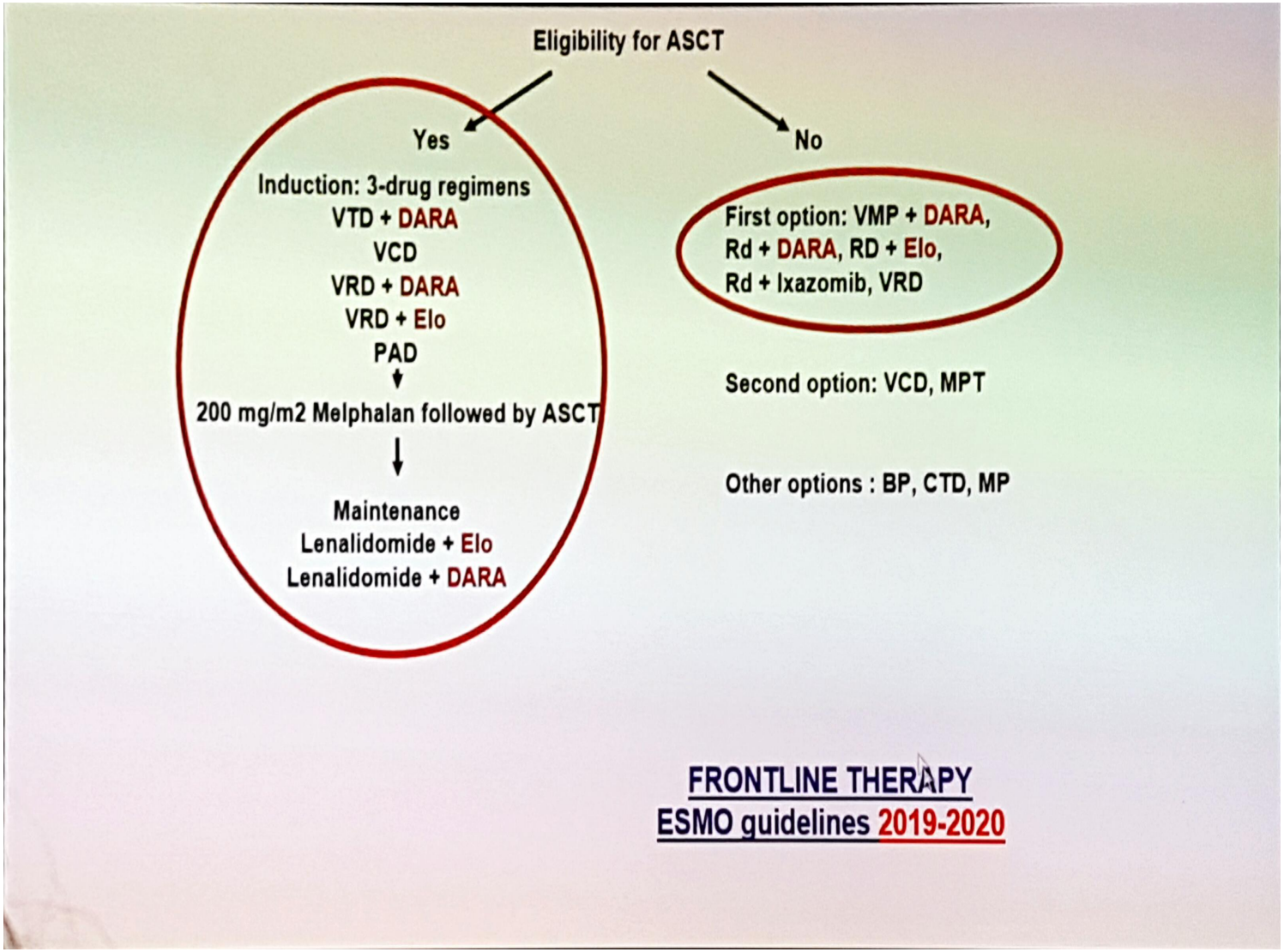
Open questions in frontline treatment in MM



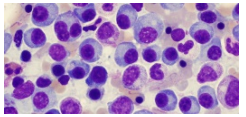
- Double vs single Autologous SCT (EMN02 vs STaMINA (BMT-CTN)
- Role of Consolidation treatment (EMN02 vs STaMINA)
- Role of maintenance treatment
- Risk-based treatment

Frontline Therapy in MM in 2020





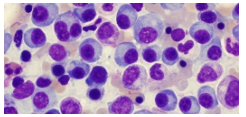
Main randomized trials in rrMM until 2015



Regimen	ORR, %	CR, %	TTP/PFS, mo	OS
Bortezomib vs Dexamethasone[1]	38 vs 18	6 vs 1	6.2 vs 3.5	80% vs 66% @ 1 year
Bortezomib+Doxil vs Bortezomib[2]	44 vs 41	4 vs 2	9.3 vs 6.5	76% vs 65% @ 15 mo
Lenalidomide-dexamethasone vs Dexamethasone[3,4]	61/60.2 vs 19./24	14.1/15.9 vs 0.6/3.4	11.1/11.3 vs 4.7/4.7	29.6/NR vs 20.2/20.6 mo
Pomalidomide – dexamethasone vs Dexamethasone[5]	31 vs 10	1 vs 0	4 vs 1.9	12.7 vs 8.1 mo

1.Richardson PG, et al. N Engl J Med. 2005; 352:2487-2498 2.Orlowski RZ, et al J Clin Oncol. 2007: 3892-3901.
3.Weber DM, et al N Engl J Med. 2007; 357: 2133-2142 4. Dimopoulous M, et al. N Engl J med,. 2007; 357: 2123-2132, 5. San Miguel et al, Lancet Oncol 2013; 14(11): 1055-66

Treatment options in rrMM in 2015



Transplant Eligible Patients

Bortezomib-based Induction

↓

ASCT

Transplant Inelegible Patients

VMP/MPT

FIRST RELAPSE

Second Transplant

Lenalidomide-dexamethasone

Bortezomib-dexamethasone/Doxil

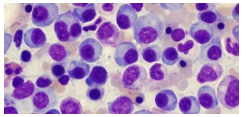
*at second or subsequent relapse in pts previously treated with both lenalidomide and bortezomib

SECOND RELAPSE

Lenalidomide-dexamethasone

Pomalidomide-Dexamethasone*

Bortezomib-dexamethasone/Doxil



doi:10.1111/ejh.12705

European Journal of Haematology

LETTER TO THE EDITOR

Salvage therapy with pegylated liposomial doxorubicin-based regimen in relapsed/refractory multiple myeloma: comments to the article by Romano *et al.*

Claudio Cerchione, Mariano Lucignano, Fabrizio Pane, Lucio Catalano

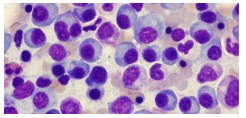
Hematology, AOU Federico II, Napoli, Italy

Correspondence Dr Claudio Cerchione, Hematology, AOU Federico II, Via Pansini 5, 80131 Napoli, Italy. Tel: +390817462037; Fax: +390817462165; e-mail: claudiocerc@hotmail.com

Since 2009, in our Institution, some patients affected by multiple myeloma, relapsed and refractory to most of the available therapeutic options (2–7), have been treated with courses of pegylated liposomial doxorubicin (35 mg/sqm, day 1), cyclophosphamide (800 mg/sqm, day 1), and dexamethasone (20 mg days 1–4), with pegfilgrastim at day +4, every 28 d (Caelyx, Endoxan, Dexamethasone (CED) regimen), until progression of disease.

both of them not requiring hospitalization. According to International Myeloma Working Group (IMWG) response criteria, after a median follow-up of 6 months of treatment (range: 2–17+), overall response ratio (ORR) was 51% (2 Complete Response (CR), 2 VGPR, 8 Partial Response (PR), 4 Minimal Response (MR)) with 10 disease progressions and five patients in stable disease. Median OS from start of CED was 5.9 months (range: 2–17). These effects appear impressive in patients so far lacking available therapeutic options. Together to Romano's results, our observations underline the efficacy of pegylated liposomial doxorubicin, which seems to give a contribution in a particular severe setting of patients, without significant side effects.

Treatment options for rrMM in 2017



Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT
Rd

FIRST RELAPSE

Second Autologous SCT

Rd, KRd, ERd,IRd, Dara-Rd, BVD

Vd, EVd, Kd, Dara-Vd, BVD

SECOND RELAPSE

Rd,KRd,ERd,Ird, Dara-Rd, Kd, BVD

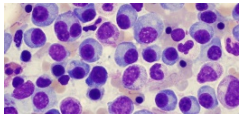
Vd,EVd,Kd, Dara-Vd, BVD

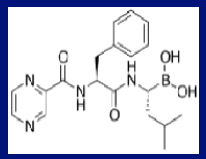
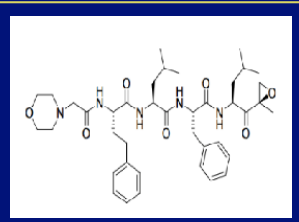
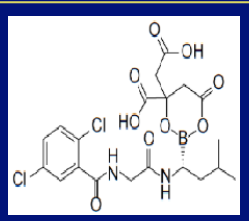
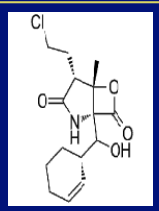
Pomalidomide-Dexamethasone

Daratumumab Single Agent

Clinical Trials

Proteasome inhibitors

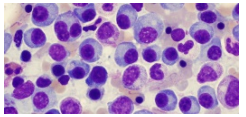


	Bortezomib	Carfilzomib	Ixazomib	Marizomib
Structure & chemical class	 Boronate[3]	 Epoxyketone	 Boronate[3]	 Lactam/β-lactone[3]
Type of Inhibition	Reversible[4]	**Irreversible**[4]	Reversible[4]	**Irreversible**[4]
Mechanism of Action	•Inhibits preferentially **β5**, but also **β1** and **β2**[2] •Formation of tetrahedral intermediate with side-chain hydroxyl groups (with proteasome and other classes of proteases)[6]	•Inhibits preferentially **β5**, but also **β1** and **β2**[2] •Formation of covalent adduct with N-terminal threonine active site (exclusively within the proteasome)[6]	•Inhibits preferentially **β5**, but also **β1** and **β2**[2]	•Inhibits **all three** proteolytic activities, with **IC50 values** in the **nM range**[5]
Route of Administration	Intravenous, subcutaneous[4]	Intravenous[3]	Oral[4]	Intravenous[4]

Proteasome inhibitors vary by chemical class, mechanism of action, type of inhibition[1-6]

[1] Mujtaba and Dou. Discov Med 2011;12(67):471-80; [2] Muz et al., Drug Des Devel Ther 2016;10:217-26; [3] Wang. Oncology (Williston Park) 2011; 25 Suppl 2:19-24; [4] Kurtin and Bilotti. J Adv Pract Oncol 2013;4(5):307-21; [5] Potts et al., Curr Cancer Drug Targets 2011;11(3):254-84; [6] Arastu-Kapur et al. Clin Cancer Res 2011;17:2734-43.

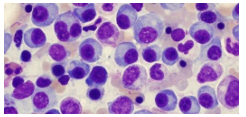
Monoclonal antibodies



Target	Antibody	Mechanism of action	Activity as single agent	Activity/under evaluation in combo
CS1 (SLAM F7)	**Elotuzumab (Humanized IgG1k)**	ADCC Enhance NK activity Interference with cell interaction	-	+ VD + Rd
CD38	**Daratumumab (Fully human IgG1k)**	ADCC CDC ADCP	+	+ V-based + Rd + Pd
	Isatuximab (SAR650984; chimeric IgG1k)	Direct induction of apopotosis Modulation CD38 function	+	+ VCD + Rd
	MOR202 (fully human IgG1λ)		+	

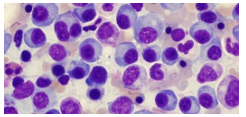
MM: multiple myeloma; ADCC: antibody depandent cell-mediated cytotoxicity; ADCP: antibody depedent cell-mediated phagocytosis; CDC; complement dependent cytotoxicity; VD: bortezomib-dexamethasone; Rd: lenalidomide;dexamethasone; Pd: pomalidomide-dexamethasone; VCD: bortezomib-cyclophosphamide-dexamethasone; V: bortezomib

Main regimens for rrMM

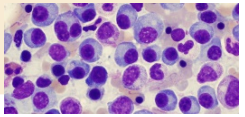


	V +/- D RETRIEVE 8 cycles (EV)	VD up to 8 cycle (EV)	V+PLD up to 8 cycle (EV)	BVD (EV)	RD MM009-MM010	EloRd Eloquent-2	Ixa Rd Tourmaline	KRd Aspire	Kd Endeavor	DRd POLLUX	DVd CASTOR	PomD MM-003 (NIMBUS)	PomD MM-010 (STRATUS)
Previous lines	2 (2=62% - 3=18%)	1	≥2 (66%)	1-2 (1=53%, 2=29%)	≥2 (82%)	Median 2	1-3	Median 2	Median 2	median 1 >1 48%	median 2	Median 5	Median 5
ORR%	40	75	44	77	60	79	78.3	87	77	93	84	32	35
CR%	1	10	4	20	16	4	11.7	32	13	46	26	0	0
Median PFS	8.4 mTTP	13.6 mTTP	9.3 mTTP	14 m	11.1 m	19.4 m	20.6 m	26.3 m	18.7 m	NR HR 0.37 (0.28-0.50)	NR HR 0.33 (0.26-0.43)	4.0 m	4.2 m
Median OS	NR	70% @2yrs	76% @15mo	24 m	38.0 m	43.7 m	NR	At 24 mo 73.3%	NR	NR	NR	12.7 m	11.9 m
	Petrucci et al. BJH 2013	Dimopoulos et al, Hematol 2014	Orlowsky et al. J Clin Oncol 2007	Offidani et al. Blood Cancer Journal 2013	Stadmauder et al. E.J of Haematol 2009	Lonial S, et al. N Engl J Med. 2015	Moreau, et al. N Engl J Med. 2016	Stewart, et al. N Engl J Med. 2015	Dimopoulos et al., Lancet Oncol 2015	Usmani, et al. N Engl J Med. 2016	Mateos, et al. N Engl J Med. 2016	San Miguel et al Lancet Oncol 2013	Dimopolous et.al, Blood 2016

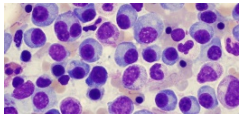
rrMM Trials: Adverse Events



	COMBINATION	GRADE 3 / 4 (%)
ASPIRE	Rd + Carfilzomib	HYPERTENSION (4) CARDIAC FAILURE (4) ACUTE RENAL FAILURE (3)
ELOQUENT	Rd + Elotuzumab	INFUSION REACTION (1)
TOURMALINE	Rd + Ixazomib	RASH (5)
POLLUX	Rd + Daratumumab	INFUSION REACTION (5)
PANORAMA	Vd + Panobinostat	DIARRHEA (25) FATIGUE (24) VOMITING (7)
ENDEAVOR	Kd	HYPERTENSION (9) DYSPNEA (5) CARDIAC FAILURE (5)
POLLUX	Rd + Daratumumab	INFUSION REACTION (9) HYPERTENSION (7)



New world of rrMM in 2017



Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT
Rd

FIRST RELAPSE

Second Transplant

Rd, KRd, ERd,IRd, Dara-Rd

Vd, EVd, Kd, Dara-Vd

SECOND RELAPSE

Rd,KRd,ERd,Ird, Dara-Rd

Kd

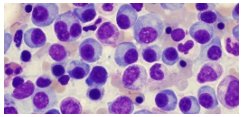
Vd,EVd,Kd, Dara-Vd

Pomalidomide-Dexamethasone

Daratumumab Single Agent

Clinical trials
(MoAbs, check-point inhibitors, venetoclax, selinexor, anti BCMA…)

New era of rrMM (2017)



ESMO Guidelines 2017; Moreau et al; Ann Oncol

RELAPSE / REFRACTORY MULTIPLE MYELOMA

First relapse after IMiD-based induction

- Doublets: Kd / Vd
- Triplets based on Bortezomib: DaraVD or PanoVD or EloVD or VCD

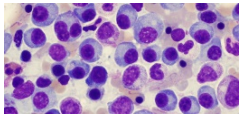
First relapse after Bortezomib-based induction

- Rd
- Triplets (with Rd as backbone): DaraRd or KRd or IxaRd or EloRd

At second or subsequent relapse

- Pomalidomide-Dex (as a backbone) + Cyclo or Ixa or Bort or Dara or Elo
- Daratumumab (single agent or combination)
- Clinical trial

Future of rrMM (2022 ??)



ESMO Guidelines 2022 ??
RELAPSE / REFRACTORY MULTIPLE MYELOMA

First relapse after IMiD-based induction

- Doublets: Kd + Isa / Vd
- Triplets based on Bortezomib: DaraVD or PanoVD or EloVD or VCD

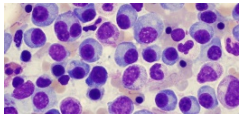
First relapse after Bortezomib-based induction

- Rd
- Triplets (with Rd as backbone): DaraRd or KRd or IxaRd or EloRd or Pom-dex dara

At second or subsequent relapse

- Pomalidomide-Dex (as a backbone) + Cyclo or Ixa or Bort or Dara or Elo or Isa
- Daratumumab (single agent or combination)
- Clinical trial

Conclusions



- High response rates, extended TTP, PFS and TTNT
- Favorable safety profile of new regimens
- Warning for cardiac toxicity of Carfilzomib
- Infusion reactions for MoAbs
- Similarity but also differences in between studies (previous drugs exposure/refractoriness, drugs duration, cytogenetic high-risk cut off)
- **Need to identify sub-groups of patients mostly benefiting from each combo**
- **Need to identify from the very beginning a long-term treatment strategy**

UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

Acknowledgements

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Napoli, 1 Dicembre 2017
Palazzo Esedra

Lavori di gruppo

16.30-17.00
Discussione sulle "Nuove Idee di Sviluppo" sul Mieloma Multiplo

17.00-18.00
Discutiamone insieme

GRUPPI DI LAVORO SU: Linee Guida – Analisi dei nuovi criteri diagnostici – Analisi delle nuove opportunità terapeutiche – – Possibili cambiamenti negli approcci diagnostici e terapeutici in funzione dell'arrivo delle nuove terapie

GRUPPO A	GRUPPO B	GRUPPO C
Leucemia Linfatica Cronica (LLC)	Mieloma Multiplo (MM)	Linfoma Mantellare (MCL)

18.00-18.30
Presentazione outcomes dei 3 gruppi:
Real World nella pratica clinica
C. Cerchione (Napoli), G. Svanera (Giugliano - NA), M.R. Villa (Napoli)

Dr Claudio Cerchione, MD, PhD
Dipartmento di Medicina Clinica e Chirurgia –
Divisione di Ematologia - AOU Federico II - Napoli

1) Linee guida: quali e quando?

1.1) Candidabile al trapianto: solo età come criterio?

1.2) Quale terapia in prima linea? (Candidabile vs non candidabile ad ASCT)

1.3) Autotrapianto nel candidabile: single/double?

1.4) Consolidamento si vs no...e con quale farmaco?

1.5) Mantenimento si vs no...e con quale farmaco?

1.6) Terapie in prima recidiva

1.6) Terapie nelle recidive successive

Real World MM – AOU Federico II

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

	Numero pazienti	Età diagnosi	Età inizio th	Terapie precedenti	ORR: (≥PR)	ORR: (≥SD)	OS da diagnosi	OS da inizio th	TTR
Pom-Dexa	22 (13 M/9 F)	68 (r. 54-80)	71.5 (r. 55-83)	5 (r. 2-8)	40.9%	77.2%	84 (r. 27-228)	8 (r. 1-14)	2 (r.1-4)
KRD	21 (12 M/9 F)	62 (r. 47-75)	65 (r. 53-81)	3 (r. 2-10)	76.1%	85.7%	47 (r. 9-170)	5 (r. 1-13)	2 (r.1-3)
VRD	22 (16 M/6 F)	56 (r. 38-74)	59.5 (r. 54-69)	2.5 (r. 1-5)	50%	77.2%	48 (r. 12-214)	26 (r. 15-39)	3 (r.1-3)
BVD	56 (31 M/25 F)	57.3 (r. 36-82)	61.8 (r. 37-83)	6 (r. 2-11)	64%	85.7%	62.7 (r. 6-151)	9.8 (r. 2-36)	1.2 (r.1-3)

...e gli anticorpi monoclonali?

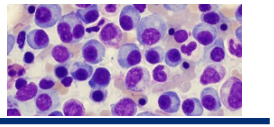
2) Stadiazione: quali esami?

2.1) Monitoraggio: quali esami? Differiscono dal trattamento?

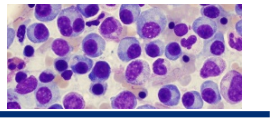
2.2) Recidiva: quali esami?

3) I nuovi trattamenti: Real World vs Clinical Trials

4) Malattia minima residua nel MM: la valutiamo? Con quale metodica e in quali pazienti?



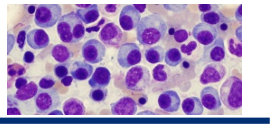
Why is this important?



Possible impact on treatment choice

- Selection of the best treatment for multiple myeloma will be based on:
  - Depth of response – MRD negativity
  - Duration & sustainability of MRD
  - Number of patients that can be put into MRD status

Kumar S, et al. Lancet Oncology 2016; 17(8): e328-46.



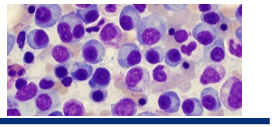
Important potential applications in treating MM

- In clinical trials, MRD assessment after initial treatment could be a **useful surrogate endpoint** for **PFS and/or OS**. Importantly, as the frequency of CR has increased, MRD negativity is emerging as a key end point for clinical studies and is now included in the IMWG response criteria.

- In clinical practice MRD testing:
  - ✓ may aid in **prognostication**
  - ✓ **help make decisions** regarding subsequent treatment, especially consolidation treatment
  - ✓ in the near future, **guide** the **type** and **duration** of **maintenance** therapy.

- MRD assessment in multiple myeloma has the potential to become a **surrogate clinical endpoint** that could be used to **support regulatory** purposes for drug review.

Munshi et al. JAMA Oncol. 2017;3(1):28-35; Kumar S, et al. Lancet Oncology 2016;17 (8):e328-46; Gormley N et al. Cytometry B Clin Cytom. 2016;90(1):73-80.

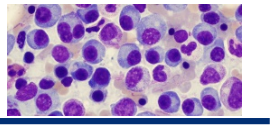


Unanswered questions (1)

- How to treat sustained MRD negative patients:
  - Treat or not?
  - If yes, for how long?
  - Treatment goal?

- How to treat sustained MRD positive patients:
  - Same treatment or switch treatments?
  - Duration of treatment?
  - Treatment goal?

- How to define relapse in MRD era?
  - MRD neg to positive
  - MRD positive to biochemical relapse
  - MRD positive to clinical relapse

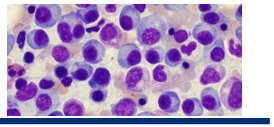


Unanswered questions (2)

- Should MRD only be **assessed** in those who are in **CR** or those that attain a very good partial response (**VGPR**)?
- Given the impact of **cytogenetics** on MRD, should MRD negativity in patients with high-risk cytogenetics be considered the same as MRD negativity in those with standard-risk cytogenetics? What trial design or analysis features should be implemented to address this issue? Is stratification based on cytogenetic risk sufficient?
- What is the **appropriate timing** of MRD assessment?
- How will novel agents, such as **monoclonal antibodies**, **affect** the MRD assessment?
- Can blood assessment replace bone marrow MRD testing (as it is less invasive)?

Gormley N et al. JAMA Oncol. 2017;3(1):18-20.

Key takeaways on MRD in MM



- Depth of response is linked with improved long-term outcomes
- Conventional CR or better doesn't reflect the real status of depth of response and more sensitive assays evaluating minimal residual disease have been developed
- Definition of MRD based on the recent IMWG consensus criteria:
  - MRD in the bone marrow assessed by NGS or NGF
  - MRD outside the bone marrow assessed by imaging (PET-CT)
  - Sustained MRD defined as MRD negativity in the marrow (NGF or NGS, or both) and by imaging confirmed minimum of 1 year apart
- Retrospective data from 2 meta-analyses support MRD in the bone marrow as a surrogate marker for PFS and OS
- The magnitude of daratumumab-induced MRD negativity in the relapsed/refractory MM setting is unprecedented
- The potential benefit of MRD-negative status induced by daratumumab in newly diagnosed MM is being explored in ongoing studies
- Future trials in the frontline setting will evaluate MRD based on the updated IMWG consensus criteria including sustained MRD
- Less invasive approaches in testing MRD (CTCs) are under investigation and evaluation
- Future research and data from clinical trials are needed to evaluate MRD as a decision point for selection of treatment and treatment duration