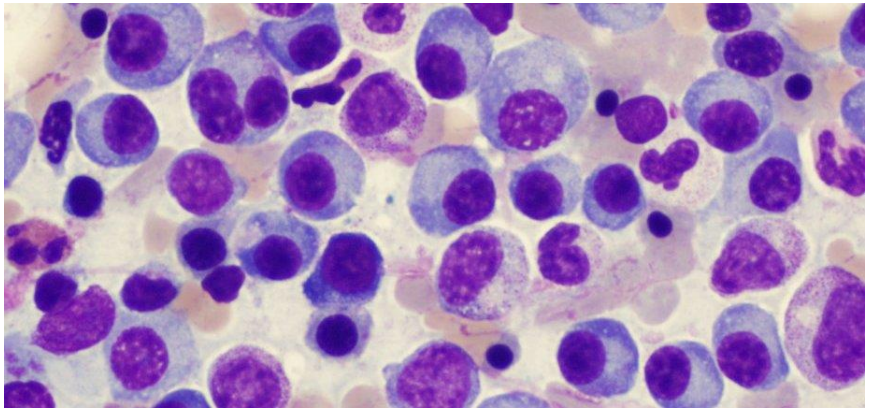


Esperienze di pratica clinica: dalle opzioni terapeutiche alla strategia terapeutica

Dott Claudio Cerchione

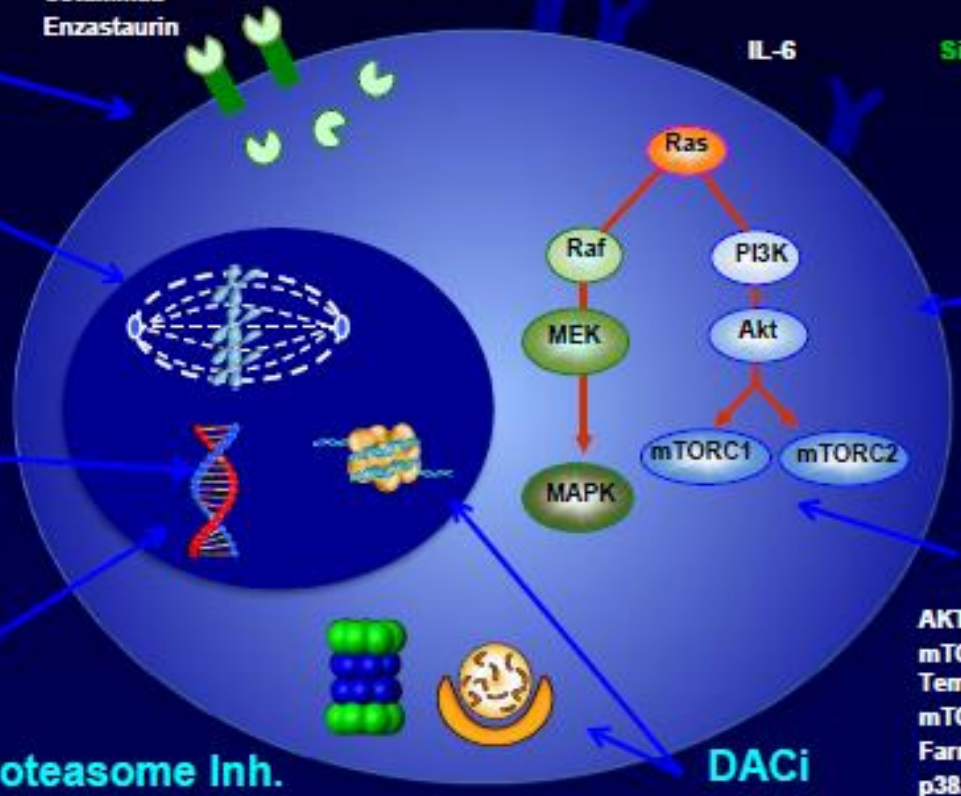
Ematologia – AOU Federico II – Napoli

IL MIELOMA
MULTIPLO

RESPONSABILI SCIENTIFICI
Felicetto Ferrara
Fabrizio Pane

NAPOLI
5 maggio 2017
HOTEL ROYAL CONTINENTAL

New drugs and mechanisms of action in MM



Kinase Inh.

CDK 1, 2, 5, 9	Dinaciclib
FGFR3 1877S	Dovitinib / AB1010 / MFGR
cKit /PDGFR	Imatinib / Dasatinib
VEGF-R	Bevacizumab
IGF-1R	AVE1642 / CP-751, 851
EGF-R	Cetuximab
PKC	Enzastaurin

MoAb

CS-1	Elotuzumab
CD38	Daratumumab / SAR650984
CD138	nBT062-DM4
CD56	Lorvotuzumab
CD40	Dacetuzumab / Lucatumumab
BAFF	Tabalumab
KiR	IPH2101
IL-6	Siltuximab

Lymph. NK cell

Cell cycle Inh.

KSP Inh	Arry-520
Aurora K Inh	MLN8237
CDK 4/6 Inh	Seleciclib

IMIDs

Thalidomide
Lenalidomide
Pomalidomide

Alkylators

Melphalan
Cyclophosphamide
Bendamustine
Melflufen

Signaling Pathways

AKT	Perifosine / GSK2110183
mTORC1	Everolimus / Temsirolimus
mTOR C1/C2	MLN0128 / INK128
Farn Transf	Tipifarnib
p38/MAPK inh	SCIO-469
p38/JNK act	Aplidin
MEK	Selumetinib

Other DNA damaging

DNA Damaging
Zalypsis
PARP Inhibitor
Veliparib
Hypoxia act. Alkylator
TH-302

Proteasome Inh.

Bortezomib
Carfilzomib
Ixazomib
Oprozomib
Marizomib

Hsp-90 Inh.

Tanespimycin
AUY922

DACi

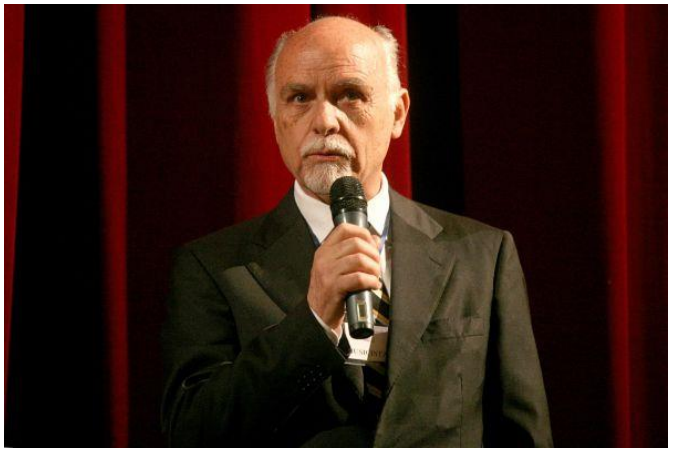
Panobinostat
Vorinostat
Romidepsin
Givinostat
Rocilinostat

Approved / Phase III development

Ocio et al, Leukemia 2014;28:525–42

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga, Altezza 158 cm, Peso 50 Kg (sempre stata magra)

Marzo 2003: ricovero c/o Osp Sessa Aurunca (per bronchite di ndd: terapia antibiotica)



OSSERVAZIONE… ambulatorio dott Lucio Catalano

2 Luglio 2003: per sospetto ***Mieloma Multiplo***… giunge **dal prof Bruno Rotoli,**

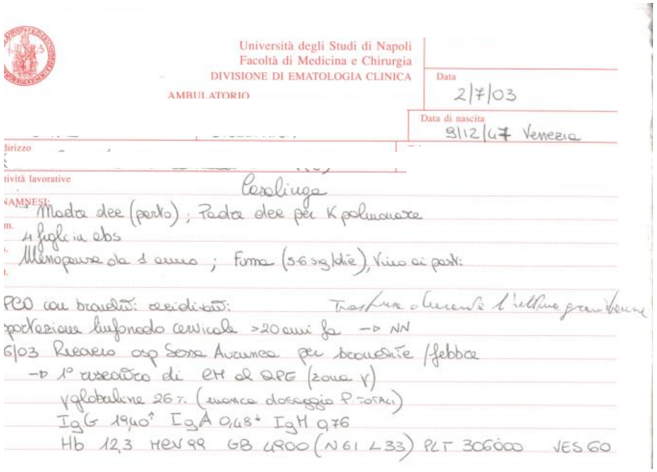
- QPE: C.M. in zona gamma,
- Hb 12.3, GB 4900 (N 61%). PLT 306.000
- Prot.Tot. 8.1, g/dl, Gamma: 25.2% (2.04 g/dL)
- Imaging: RX Scheletro negativa (No Osteolisi)

Si pone diagnosi: MGUS IgG k

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,
Altezza 158 cm, Peso 50 Kg

Marzo 2003: Giunge alla nostra osservazione

Anamnesi familiare: padre deceduto per k polmonare,
4 figli in abs,


Università degli Studi di Napoli
Facoltà di Medicina e Chirurgia
DIVISIONE DI EMATOLOGIA CLINICA
AMBULATORIO

Data 2/7/03
Data di nascita 9/12/47 Venezia

dirizzo

tività lavorative Casalinga

ANAMNESI: Madre dec (parto) ; Padre dec per K polmonare
4 figli in abs
Menopausa da 1 anno ; Fuma (5-6 sig/die), Vino ai pasti
PCO con bronchiti recidivanti ; Trasfusione durante l'ultima gravidanza
asportazione linfonodo cervicale >20 anni fa → NN
6/03 Ricovero osp Sessa Aurunca per bronchite /febbre
→ 1° riscontro di CM al QPE (zona γ)
γglobuline 26% (manca dosaggio P. totali)
IgG 1940↑ IgA 0,48↓ IgM 0,76
Hb 12,3 MCV 99 GB 4800 (N 61 L 33) PLT 306000 VES 60

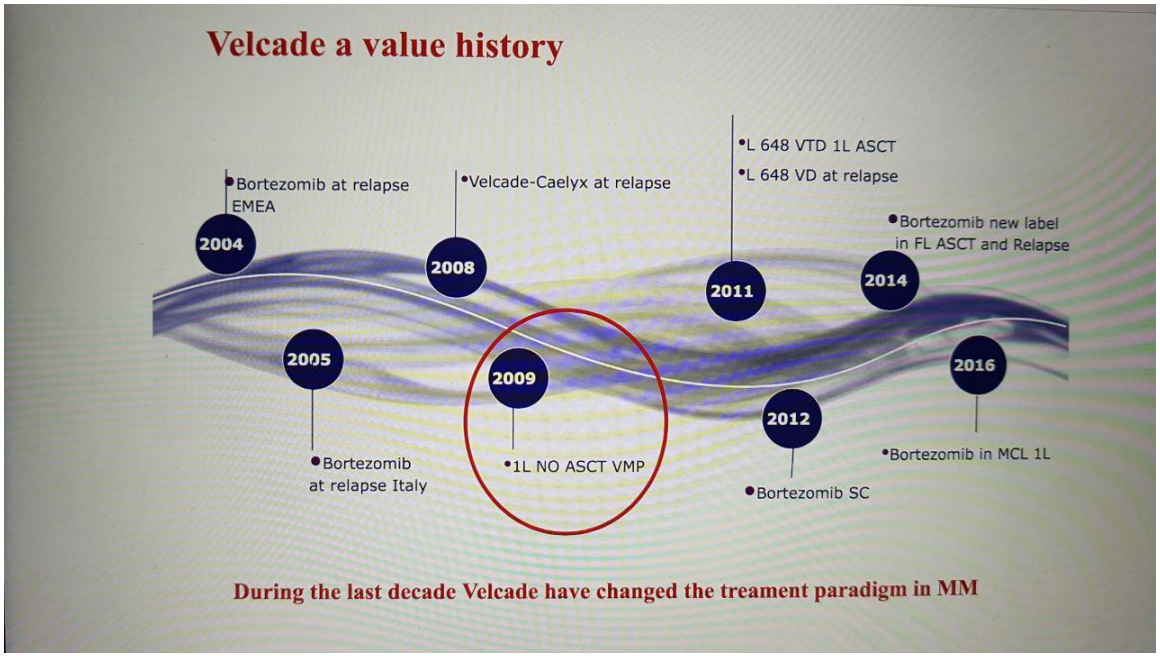
Anamnesi patologica remota:

- Menopausa da circa 1 anno, fuma (5-6 sig/die),
- BPCO con bronchiti recidivanti
- Trasfusione durante l'ultima gravidanza
- 20 anni fa asportazione linfonodo laterocervicale: neg

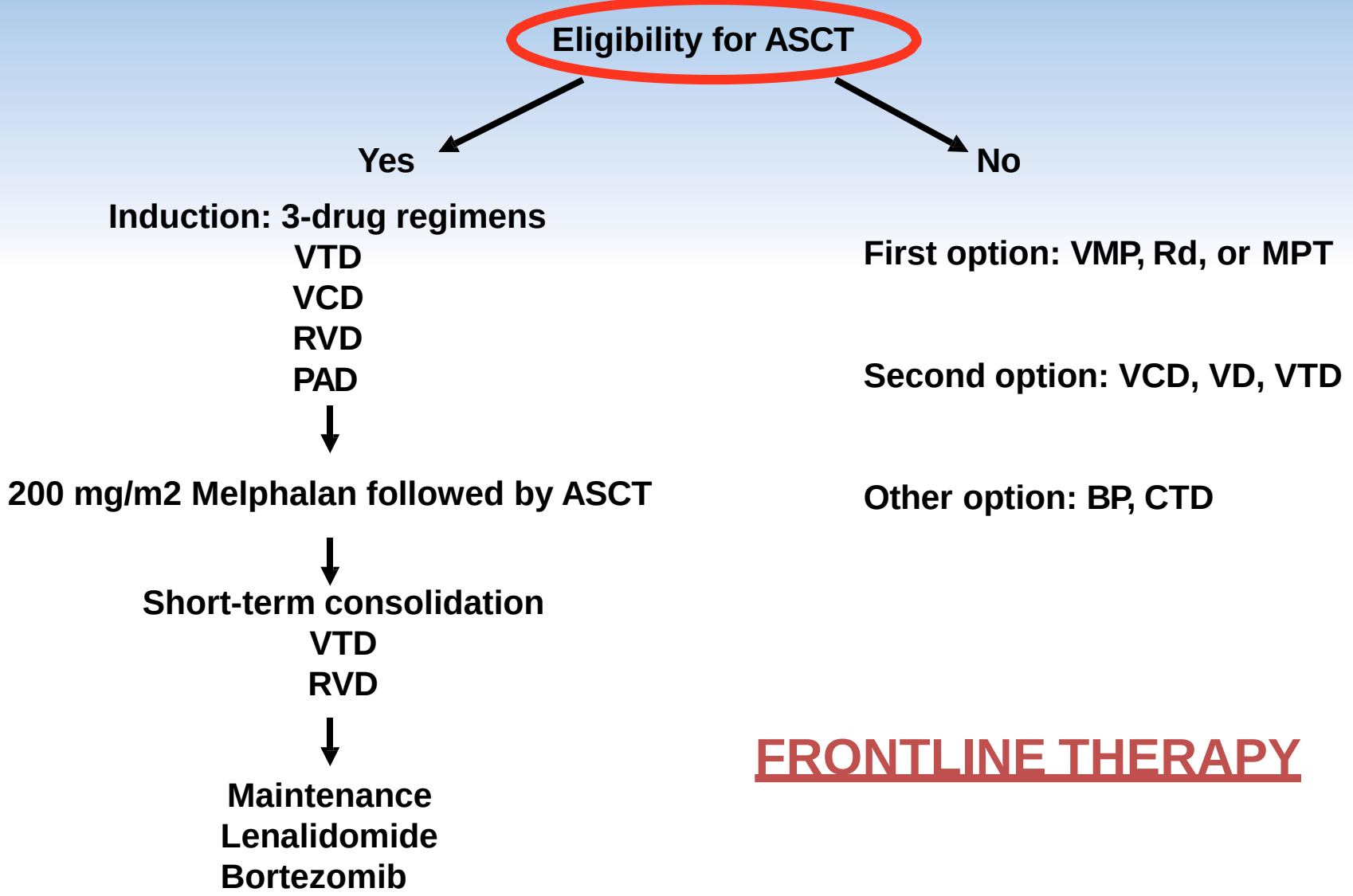
C.G. 59 y.o. (Venezia, 09/12/1947), F, casalinga,

MAGGIO 2006: Evoluzione: MM IgG k IIA + presenza osteolisi
Paziente nuova diagnosi, fit, candidabile a ASCT

Quale terapia scegliamo nel 2006?



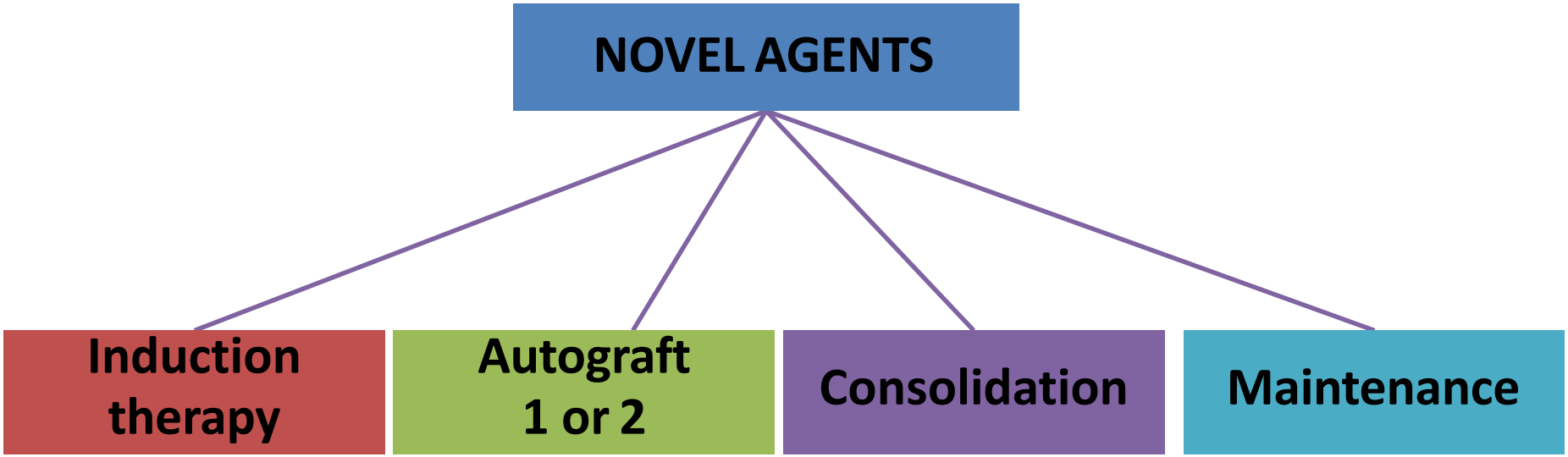
Quale terapia sceglieremmo nel 2017?



FRONTLINE THERAPY

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

Actual treatment paradigm for patients who are eligible for ASCT



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

Cavo M et al. Blood 2011;117(23):6063-73; Cavo et al. Blood 2012;120(1):9-19.

Meta-analysis: Bortezomib-based versus non-bortezomib-based induction prior to ASCT

- Integrated analysis (n=1572) of 3 randomized trials: Bortezomib-based versus non-bortezomib-based induction regimens

Response rate	Bortezomib-based induction (n=775)	Non-bortezomib-based induction (n=772)	OR	95% CI	P
Post-transplant (%)					
CR+nCR	38	24	2.05	1.64–2.56	< 0.001

- Median follow-up ~37 months

	Bortezomib-based induction	Non-bortezomib-based induction	HR	95% CI	P
Median PFS, mos	35.9	28.6	0.75	0.65–0.85	< 0.001
3-yr PFS, %	50.0	41.1			

Primary end point: Post transplant CR+nCR and PFS

Sonneveld et al. J Clin Oncol 2013;31(26):3279-87

VTD vs VCD induction: Response

IFM 2013-04 trial (prospective, intent-to-treat analysis)[1]

	VTD (4-cycles)* N = 169	VCD (4-cycles)† N = 169	p-value
≥ CR	13.0%	8.9%	0.22
≥ VGPR	66.3%	56.2%	0.05

*Bortezomib 1.3 mg/m^2/day SC D1,4,8,11 + Thalidomide 100 mg/day PO D1–21 + Dexamethasone 40 mg/day PO D1–4, D9–12
†Bortezomib 1.3 mg/m^2 /day SC D1,4,8,11 + Cyclophosphamide 500 g/m^2 /day PO D1,8,15 + Dexamethasone 40 mg/day PO D1–4, D9–12

GIMEMA MMY-3006 and EMN-02 studies (retrospective, case-matched analysis)[2]

	VTD (3-cycles)‡ N = 236	VCD (3-cycles)§ N = 236	p-value
≥ CR	19%	6%	< 0.001
≥ VGPR	64%	37%	< 0.001

‡ Bortezomib 1.3mg/m^2 twice weekly + Thalidomide 100➔200mg/day + Dexamethasone 320mg/cycle (3 X 21-day cycles)
§ Bortezomib 1.3mg/m^2 SC D1,4,8,11 + Cyclophosphamide 500 g/m^2/day IV D1,8 + Dexamethasone 40 mg/day PO D 1, 2, 4, 5,8, 9,11, 12 (3 X 21-day cycles)

1. Moreau, P et al. Blood 2016;127:2569-74;
2. Cavo et al. Leukemia 2015;29(12):2429-31.

VTD vs VCD induction: Toxicity

IFM 2013-04 trial (prospective, intent-to-treat analysis)[1]

%	VTD, N = 169	VCD, N = 169	p-value
Any grade 3 or 4 AEs	63.9	68.2	0.40
Hematologic toxicities, grade 3 or 4			
Anemia	4.1	9.5	0.05
Neutropenia	18.9	33.1	0.003
Thrombocytopenia	4.7	10.6	0.04
Non-hematologic toxicities, grade 3 or 4			
Peripheral neuropathy	7.7	2.9	0.05

GIMEMA MMY-3006 and EMN-02 studies (retrospective, case-matched analysis)[2]

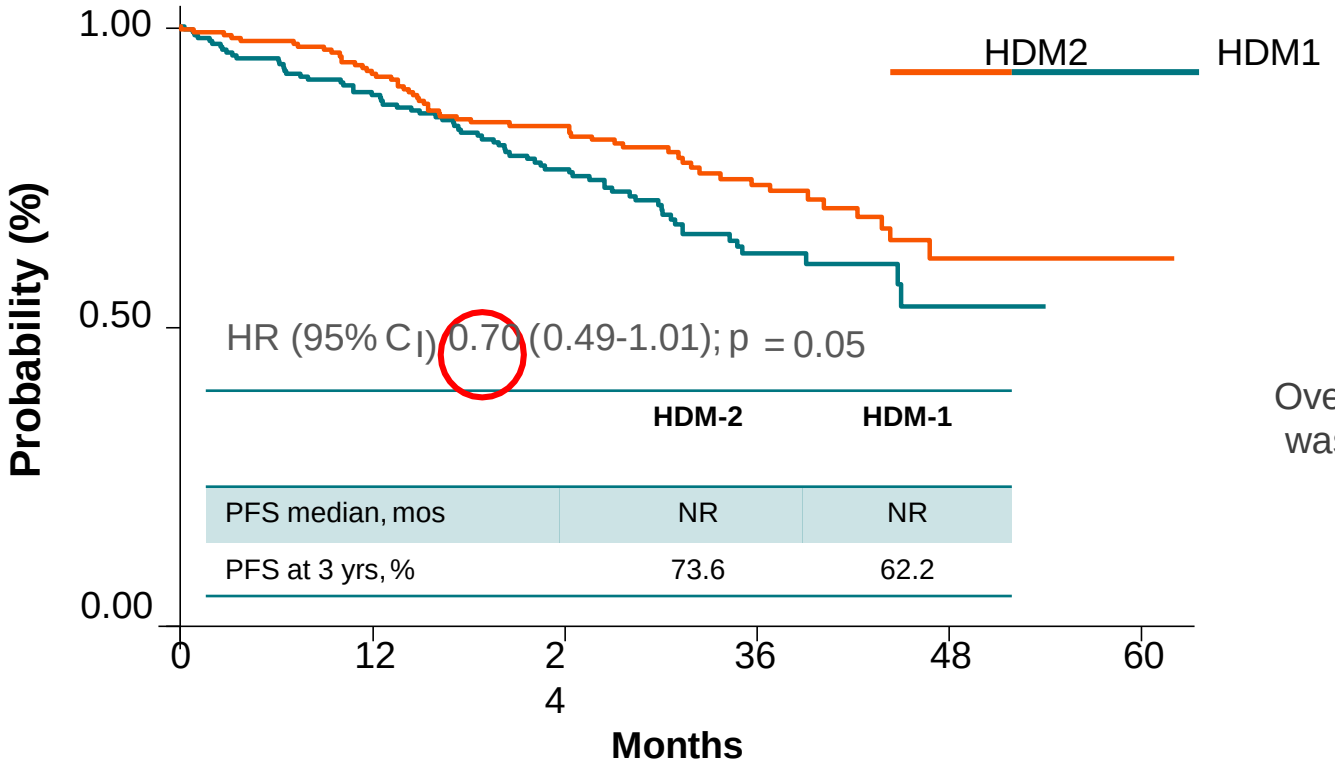
	VTD, N = 236	VCD, N = 236	p-value
Any grade 3 or 4 AE	27%	26%	0.754
Hematologic toxicities, grade 3 or 4			
Anemia	0	7%	<0.001
Neutropenia	2%	8%	0.003
Thrombocytopenia	<1%	4%	0.006
Non-hematologic toxicities, grade 3 or 4			
Peripheral neuropathy	7%	2%	0.009

Toxicities assessed according to NCI CTCAE, version 4.0.

1. Moreau, P et al. Blood 2016;127:2569-74;
2. Cavo et al. Leukemia 2015;29(12):2429-31.

Upfront single vs double ASCT:
EMN02/HO95 MM phase 3 trial

PFS by randomization 1 (HDM-1 *vs* HDM-2)



Overall survival data was not yet mature

Number at risk

HDM2	207	185	145	69	19	1
HDM1	208	171	132	50	9	0

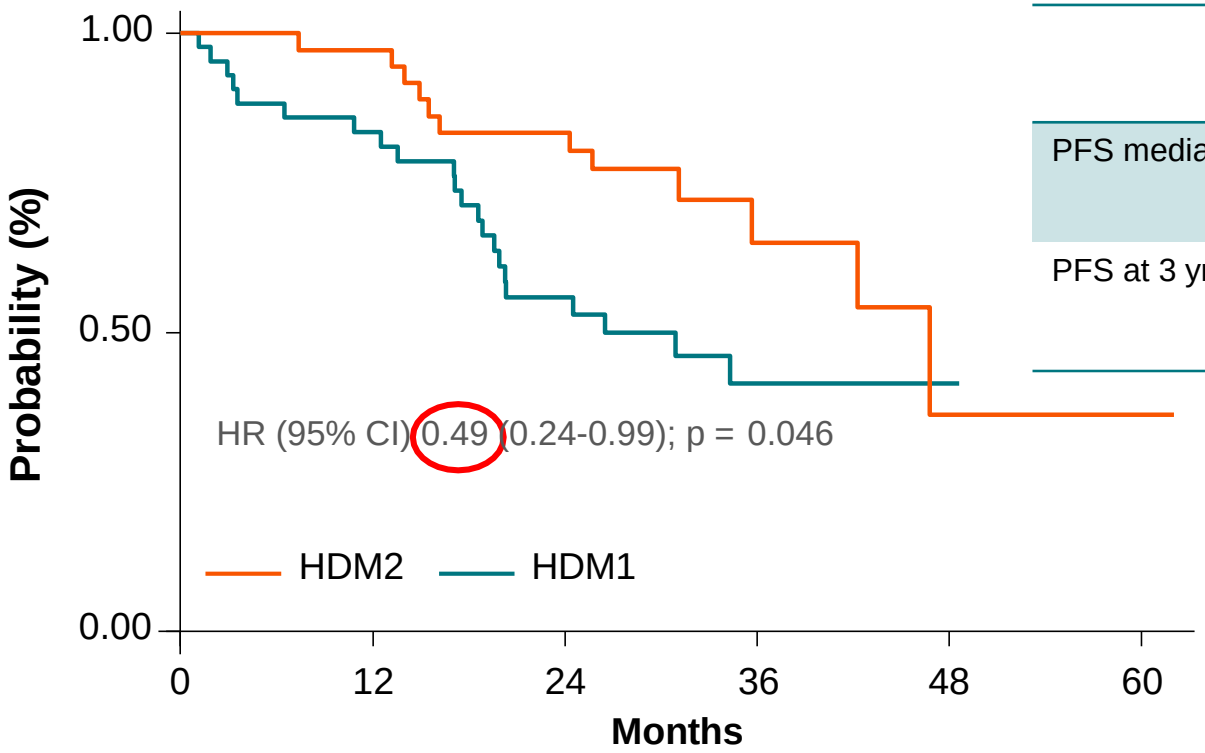
Median follow-up: 32 months (IQR 26-41)

Cavo M, et al. Blood. 2016;128:991; as presented at ASH 2016.

Upfront single vs double ASCT in patients with high-risk cytogenetics

EMN02/HO95 MM trial

PFS by randomization 1 (HDM-1 *vs* HDM-2)



	HDM-2	HDM-1
PFS median, mos	46.8	26.5
PFS at 3 yrs, %	64.9	41.4

Number at risk

HDM2	38	35	28	9	2	1
HDM1	43	34	20	7	1	0

Cavo M, et al. Blood. 2016;128:991; as presented at ASH 2016.

AVAILABLE FRONTLINE THERAPY IN NEWLY DIAGNOSED MM PATIENTS NOT ELIGIBLE FOR ASCT

- **First option: VMP (EMA approved 2008), Ld (EMA approved 2015), or MPT (EMA approved 2008)**
- **Second option: VCD, VD, VTD**
- **Other options: BP, CTD**

Fayers et al. *Blood* 2011
San Miguel JF, et al. *N Engl J Med* 2008;359:906-17
Mateos MV, *J Clin Oncol* 2010, April 5

Rajkumar SV, et al. *Lancet Oncol* 2010;11:29-37
Benboubker et al. N Engl J Med. 2014 Sep 4;371(10):906-17
Mateos MV et al. *Haematologica* 2015

Summary- First Line Studies in No-ASCT pts

	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

VMP modifications:

- **Bi weekly, VISTA** (San Miguel, N Engl J Med 2008)

- **Once a week** (Mateos, Lancet Oncol 2010)

- **Maintenance** (Mateos, Blood 2012 & Blood 2014)

- **Bortezomib sc** (Moreau, Lancet Oncol 2011)

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

Maggio 2006: Evoluzione: MM IgG k IIA : 1 LINEA: Thalidomide-Dexamethasone x 6 : PR

Gennaio 2007: Ciclofosfamide 4g/mq:
Raccolta CD34+: 6.4 x 10^6/Kg

Giugno 2007: 1° ASCT (Condizionamento MEL200): PR

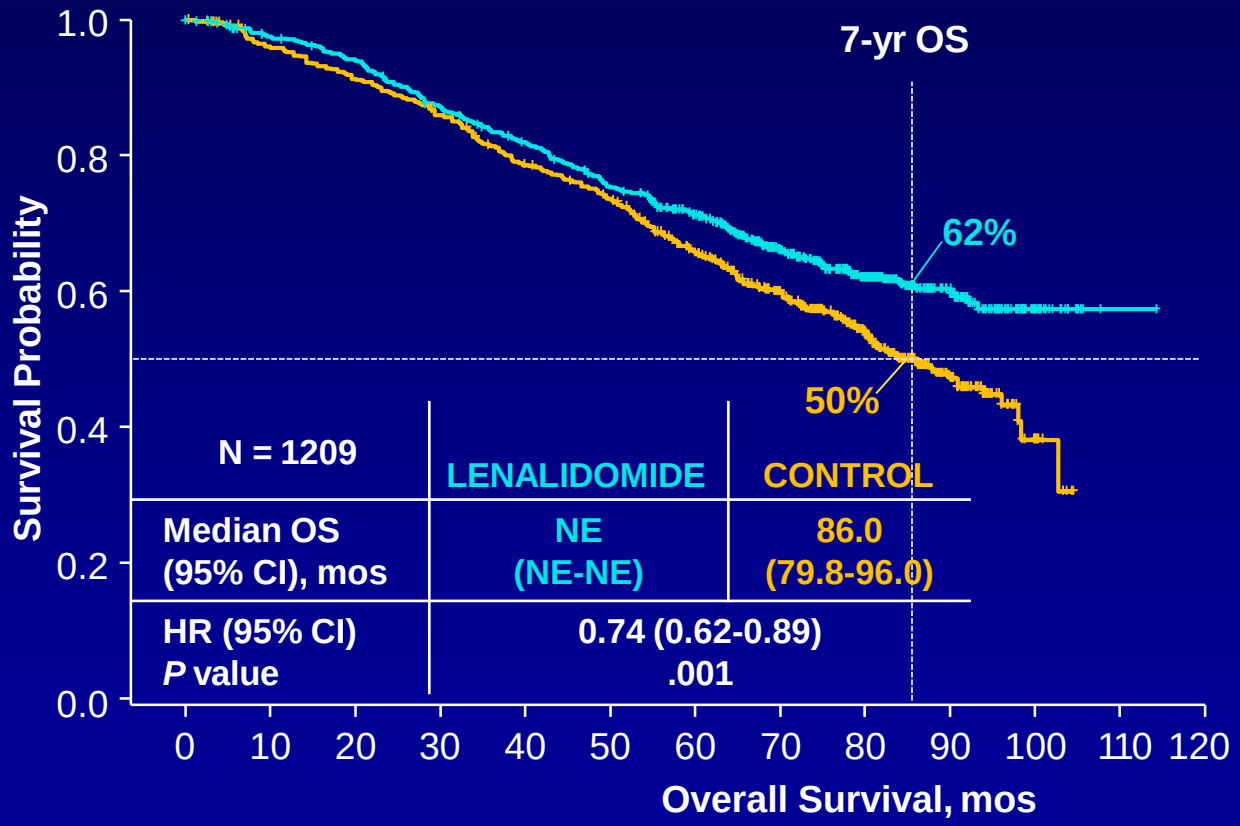
…e adesso?

Settembre 2007: Tentativo di mantenimento con IFN:
Sospeso (<1 mese) per tossicità cutanea

METANALYSIS OF LENALIDOMIDE MAINTENANCE RADOMIZED STUDIES

OS: Median Follow-Up of 80 Months

There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival



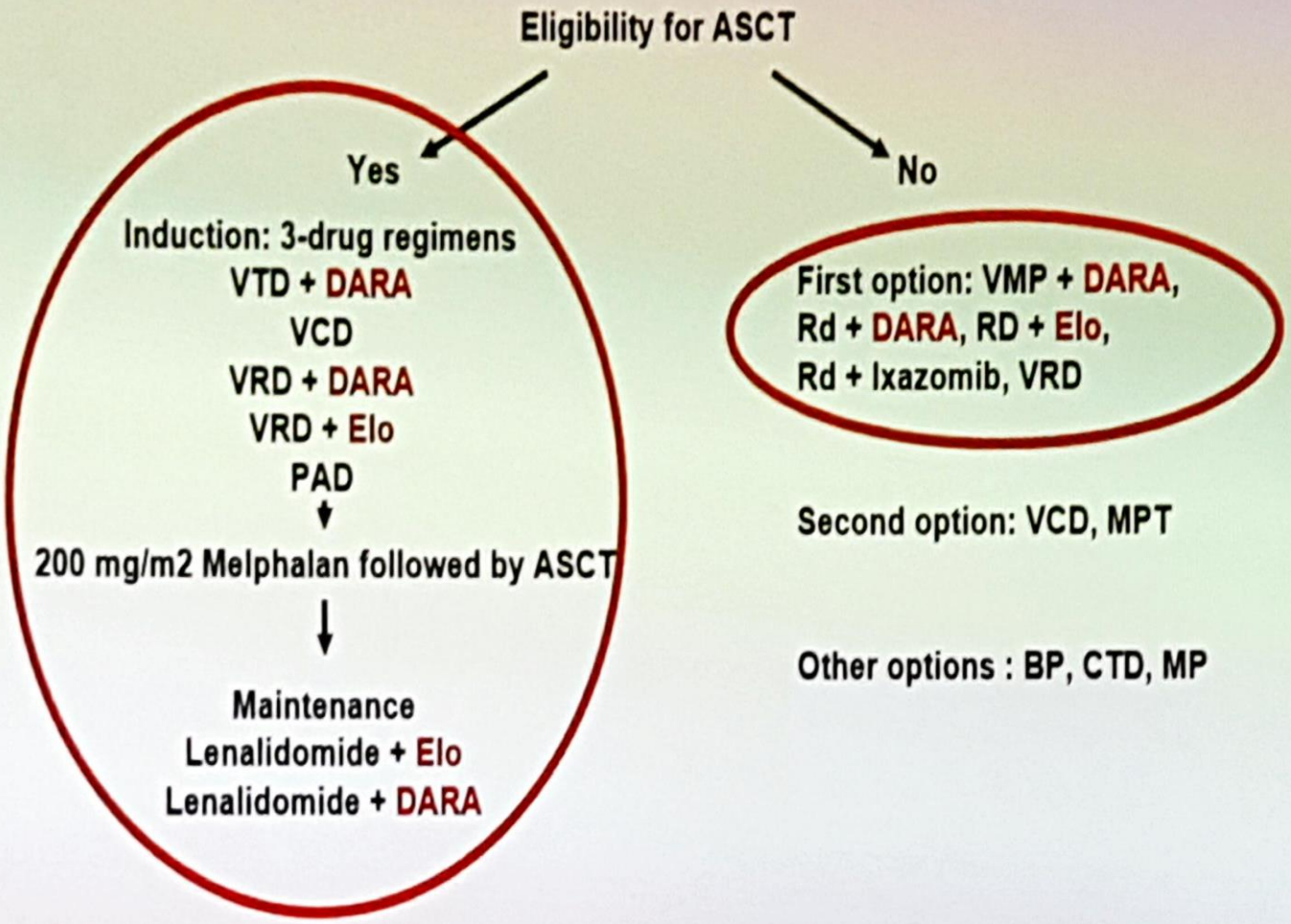
Problemi aperti nella terapia frontline:

- Ruolo del doppio trapianto autologo (dati contrastanti studio EMN02 e STaMINA (BMT-CTN)
- Ruolo del consolidamento (dati contrastanti studio EMN02 e STaMINA)
- Disponibilità e durata ottimale della terapia di mantenimento
- Terapia modellata sul rischio

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

MAGGIO 2006: Evoluzione: MM IgG k IIA

…e quale terapia frontline nel 2019/2020???



FRONTLINE THERAPY
ESMO guidelines 2019-2020

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

Maggio 2006: Evoluzione: MM IgG k IIA : 1° linea: Thalidomide-Dexamethasone x 6 : PR

Gennaio 2007: Ciclofosfamide 4g/mq: 6.4 x 10^6/Kg CD34+

Giugno 2007: 1° ASCT (Mel200): PR

Settembre 2007: Tentativo di mantenimento con IFN, interrotto per tossicità cutanea

Ottobre 2007: Mantenimento con Thalidomide x 3 mesi

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

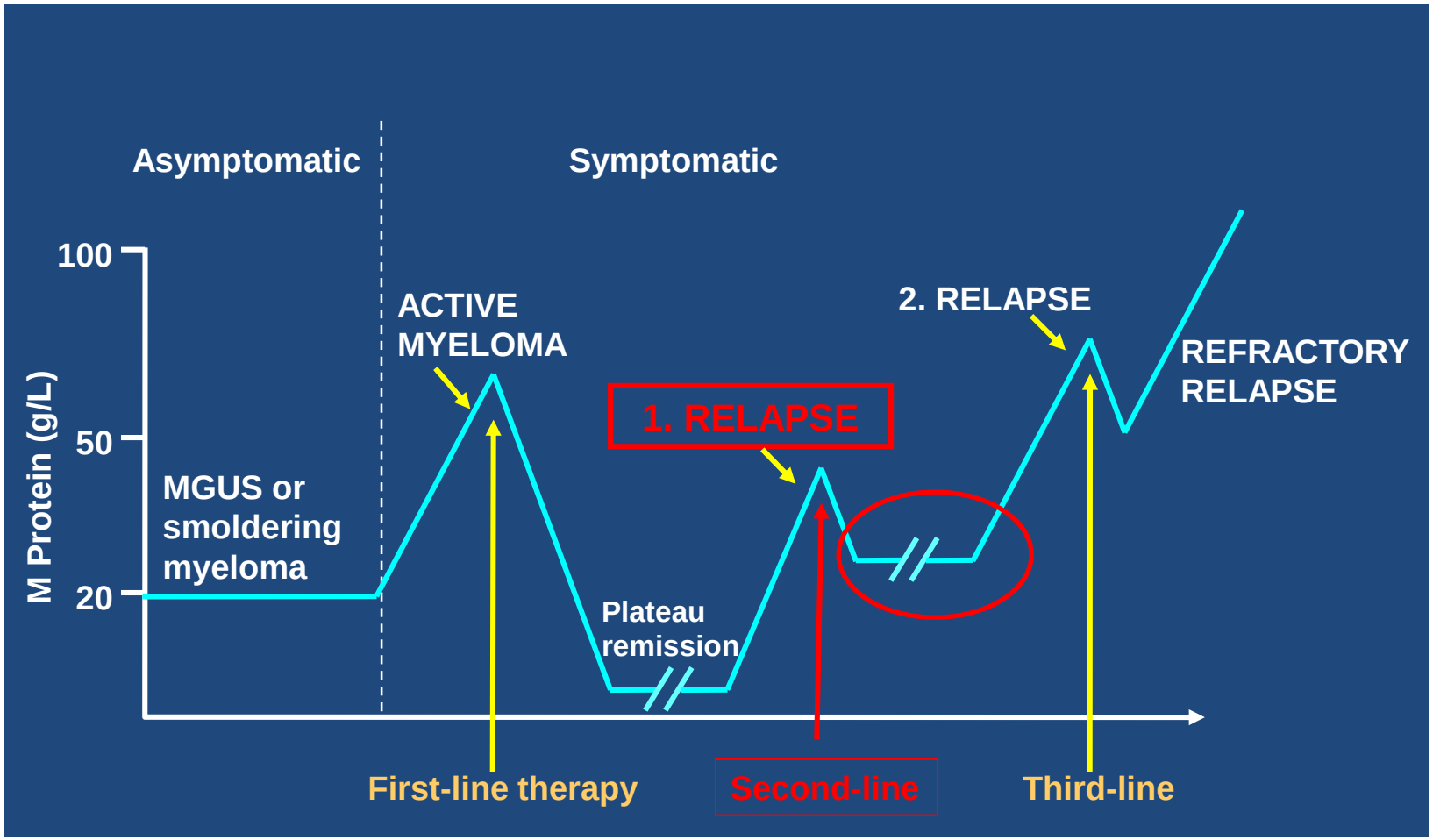
Febbraio 2008: 1° Recidiva di malattia (biochimica e ossea)

…quale terapia di seconda linea nel 2008?

…quale terapia di seconda linea nel 2017?

…quale terapia di seconda linea nel 2018?

Natural History of MM



TREATMENT AT RELAPSE:

DISEASE AND PATIENT RELATED FACTORS

The challenge when treating patients with relapsed or refractory disease is to select the optimal treatment by **BALANCING EFFICACY, TOXICITY and SEVERITY OF RELAPSE.**

It is necessary to consider:

❖**DISEASE RELATED FACTORS**: quality and duration of response to initial therapy, class of agent used, indolent or aggressive relapse, high risk features such as cytogenetic abnormalities (del17p, t(4;14), ampl1q21), extramedullary disease (EMD), plasma cell leukemia;

❖**PATIENT RELATED FACTORS**: age, performance status (PS), comorbidities, quality of life, renal function, hematopoietic reserve, prior drug exposure, ongoing toxicities from prior therapies, peripheral neuropathy (PN), venous thromboembolism (VTE).

Mohty B et al, Leukemia 2012; Ludwig H et al, Leukemia Research 2012; Castelli R et al, Oncology 2013

Main randomized trials in R/R MM 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

RETREATMENT WITH BORTEZOMIB

META-ANALYSIS of the efficacy and safety of Bortezomib retreatment in patients with multiple myeloma

	ORR, %	TTP, months	OS, months	PN G 3-4, %
All patients (n = 1051)	39	7,5	16,6	3
Prior therapies: ≤ 4 > 4	 43 29	 8,2 7,1	 13,3 20,0	
Therapy: - Bortezomib ± Dex (5 studies) - Combination (18 studies)	 51 36	 7,9 7,1	 19,2 16,1	
Only relapsed not refractory to Bortezomib	57	8,5	19,7	

Knopf K et al, ASH 2012

Treatment options for R/R MM

Transplant Eligible Patients

Bortezomib-based Induction

↓

ASCT

Transplant Inelegible Patients

VMP/MPT

FIRST RELAPSE

Second Transplant

- **Lenalidomide-dexamethasone**
- **Bortezomib-dexamethasone/Doxil**

SECOND RELAPSE

- **Lenalidomide-dexamethasone**
- **Bortezomib-dexamethasone/Doxil**
- **Pomalidomide-Dexamethasone***

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

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

Febbraio 2008: Recidiva di malattia (biochimica e ossea)

2° LINEA: Vel-Dexa x 4: CR,
ma…

STOP per neuropatia periferica invalidante

…Settembre 2008: 2° Recidiva di malattia (biochimica e ossea)

…e ora???

Settembre 2008: 3° linea: RD x 21: PR

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

Dicembre 2011: Recidiva di malattia (biochimica e ossea)

4° Linea: CED… CED cosa???

doi:10.1111/ejh.12705

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.

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

Dicembre 2011: Recidiva di malattia (biochimica e ossea)

4° Linea: CED x 2: Progressione di malattia

…e ora???

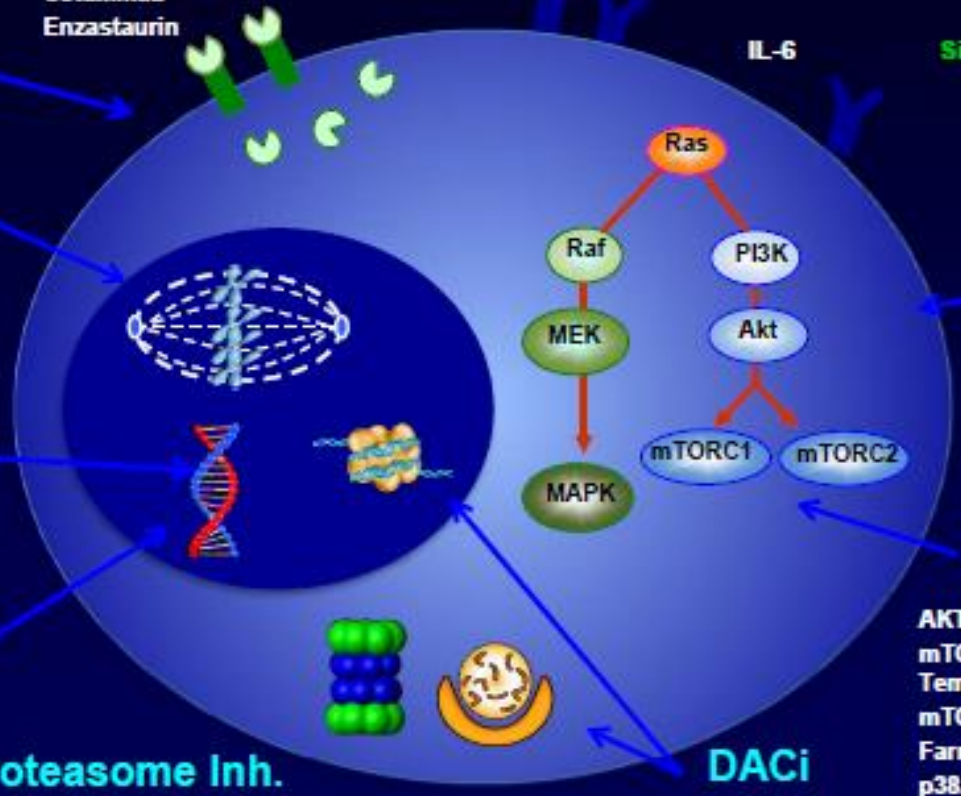
Febbraio 2012: 5° linea: MelDexa x 2: PR

Aprile 2012: 6° linea: 2° ASCT di Salvataggio (Mel140): VGPR

Oggi cosa avremmo fatto in prima/seconda recidiva?

Durante/dopo Len-dexa in seconda linea?

New drugs and mechanisms of action in MM



Kinase Inh.

CDK 1, 2, 5, 9	Dinaciclib
FGFR3 1877S	Dovitinib / AB1010 / MFGR
cKit /PDGFR	Imatinib / Dasatinib
VEGF-R	Bevacizumab
IGF-1R	AVE1642 / CP-751, 851
EGF-R	Cetuximab
PKC	Enzastaurin

MoAb

CS-1	Elotuzumab
CD38	Daratumumab / SAR650984
CD138	nBT062-DM4
CD56	Lorvotuzumab
CD40	Dacetuzumab / Lucatumumab
BAFF	Tabalumab
KiR	IPH2101
IL-6	Siltuximab

Lymph. NK cell

Cell cycle Inh.

KSP Inh	Arry-520
Aurora K Inh	MLN8237
CDK 4/6 Inh	Seleciclib

IMIDs

Thalidomide
Lenalidomide
Pomalidomide

Alkylators

Melphalan
Cyclophosphamide
Bendamustine
Melflufen

Signaling Pathways

AKT	Perifosine / GSK2110183
mTORC1	Everolimus / Temsirolimus
mTOR C1/C2	MLN0128 / INK128
Farn Transf	Tipifarnib
p38/MAPK inh	SCIO-469
p38/JNK act	Aplidin
MEK	Selumetinib

Other DNA damaging

DNA Damaging
Zalypsis
PARP Inhibitor
Veliparib
Hypoxia act. Alkylator
TH-302

Proteasome Inh.

Bortezomib
Carfilzomib
Ixazomib
Oprozomib
Marizomib

Hsp-90 Inh.

Tanespimycin
AUY922

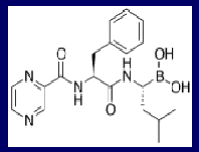
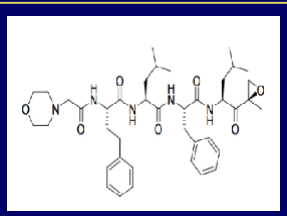
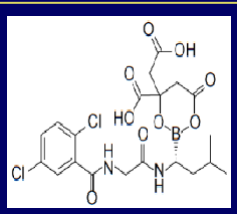
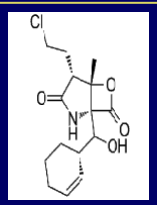
DACi

Panobinostat
Vorinostat
Romidepsin
Givinostat
Rocilinostat

Approved / Phase III development

Ocio et al, Leukemia 2014;28:525–42

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)		+	

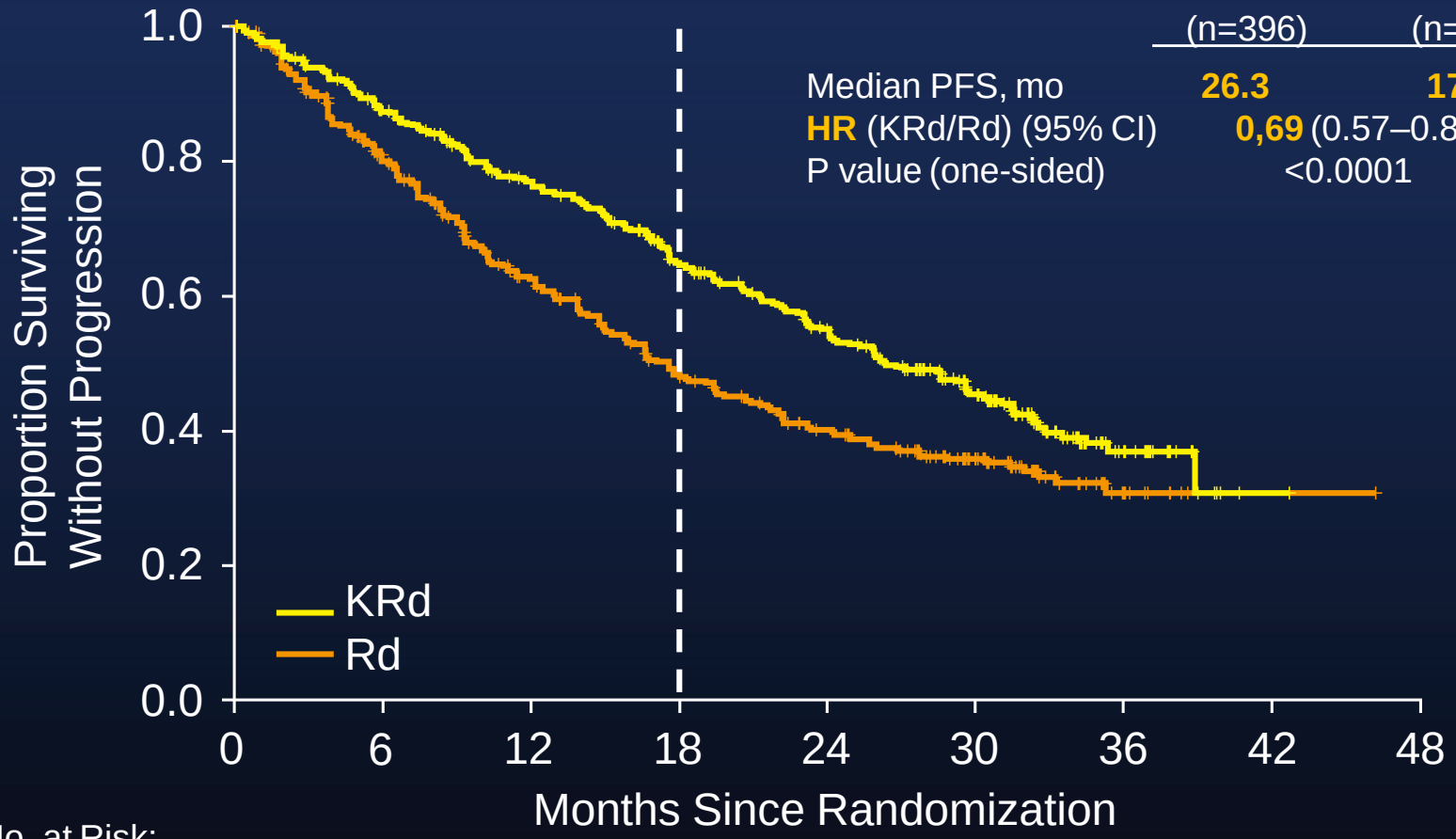
MM: multiple myeloma; ADCC: antibody depandent cell-mediated cytotoxicity; ADCP: antibody depedent cell-mediated phagocytosis; CDC; complement dependent cytotoxicity; VD: bortezomib-dexamethasone; Rd: lenalidomide;dexamethasone; Pd: pomalidomide-dexamethasone; VCD: bortezomib-cyclophosphamide-dexamethasone;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

Relapse following VMP or VTD/VCD based ASCT

- Lenalidomide-dex

- Lenalidomide-dex + third agent
  - Carfilzomib (ASPIRE)
  - Elotuzumab (ELOQUENT)
  - Ixazomib (TOURMALINE)
  - Daratumumab (POLLUX)

ASPIRE: Carfilzomib, Lenalidomide, and Dexamethasone (KRd) vs Lenalidomide and Dexamethasone (Rd) PFS



No. at Risk:

KRd	396	332	279	222	179	112	24	1
Rd	396	287	206	151	117	72	18	1

Stewart K et al, NEJM 2015

Safety: KRd vs Rd

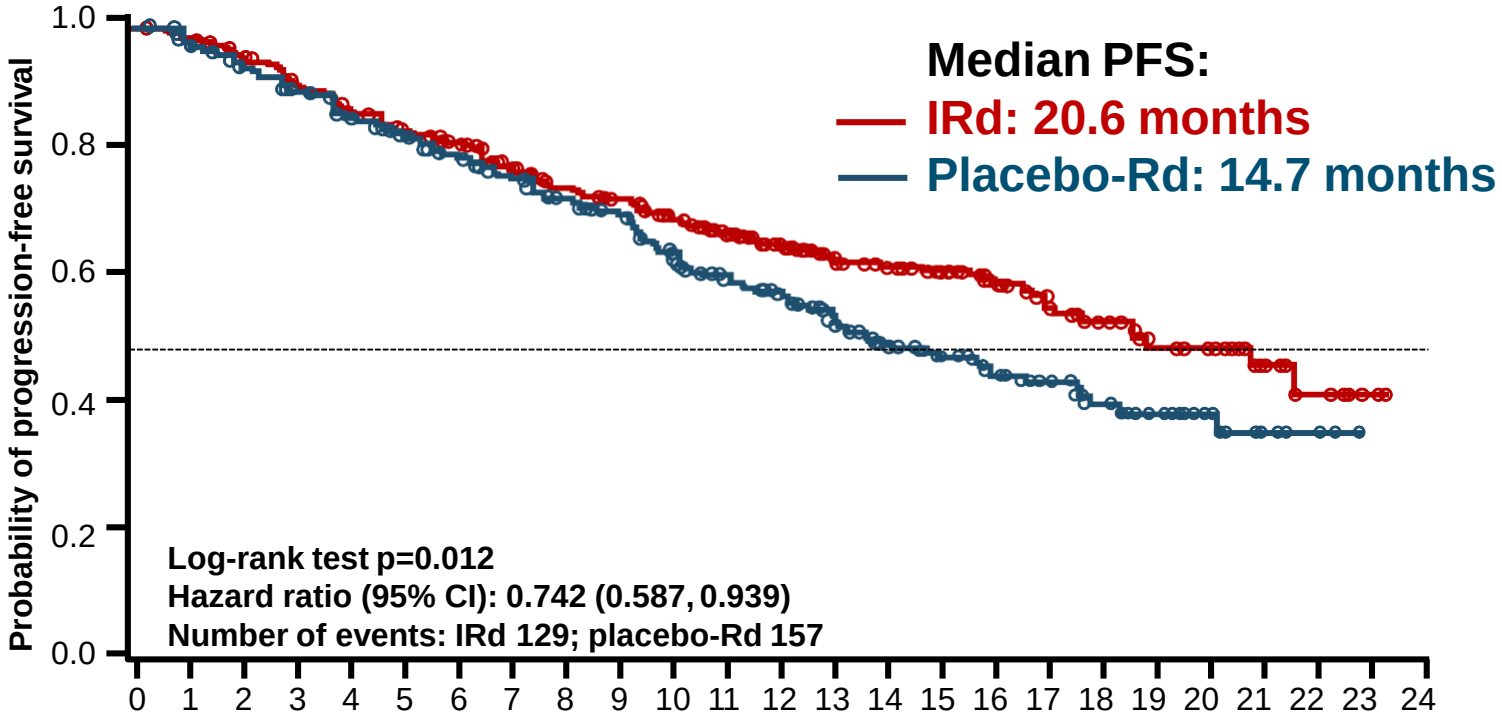
Category	KRd (n=392)	Rd (n=389)
Median treatment duration, weeks	88.0	57.0
Any AE, % Grade ≥3 treatment-emergent AE	96.9 83.7	97.2 80.7
Treatment discontinuations, % PD AE	69.9 39.8 15.3	77.9 50.1 17.7
Serious AE, %	59.7	53.7
Deaths within 30 days of last dose, % PD Aes	7.7 0.5 6.9	8.5 1.3 6.9

Adverse event of interest, %	KRd (n=392)		Rd (n=389)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Dyspnoea	19.4	2.8	14.9	1.8
Peripheral neuropathy†	17.1	2.6	17.0	3.1
Hypertension	14.3	4.3	6.9	1.8
Acute renal failure†	8.4	3.3	7.2	3.1
Cardiac failure†	6.4	3.8	4.1	1.8
Deep vein thrombosis	6.6	1.8	3.9	1.0
Ischaemic heart disease†	5.9	3.3	4.6	2.1
Pulmonary embolism	3.6	3.1	2.3	2.3
Second primary	2.8	2.3	3.3	2.8

AE, adverse event; KRd, carfilzomib with lenalidomide and weekly dexamethasone; Rd, lenalidomide and weekly dexamethasone.

Stewart AK, et al. N Engl J Med 2015;372:142–52.

Final PFS analysis(median fup: 23 mos): A significant, 35% improvement in PFS with IRd vs placebo-Rd



Number of patients at risk:																									
IRd	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0
Placebo-Rd	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0

Median follow-up: ~15 months

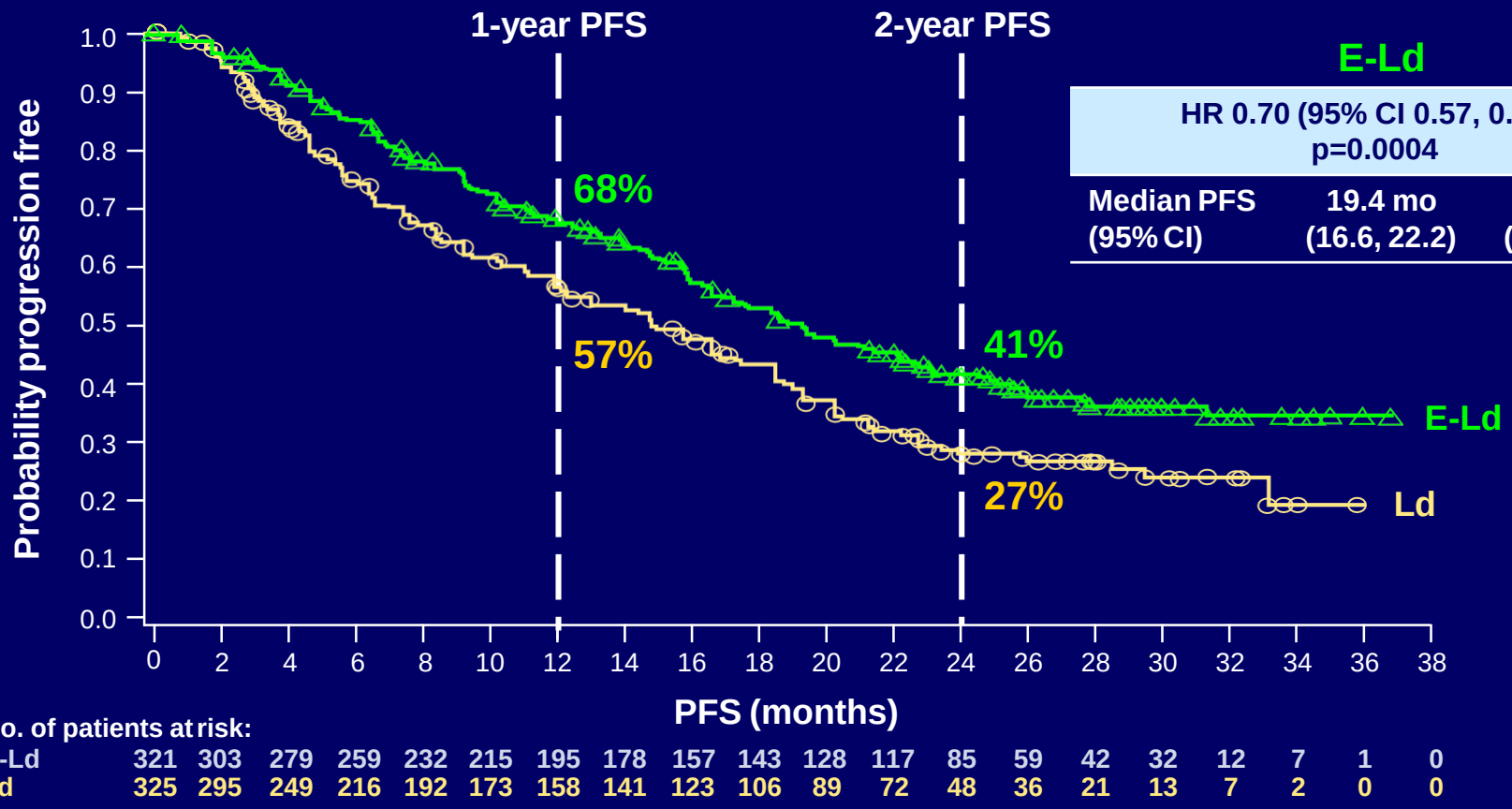
Moreau P et al, NEJM 2016

AEs after median follow-up of 23 months: increased rates with IRd driven by low-grade events

	IRd (N=361), %			Placebo-Rd (N=359), %		
Preferred terms	All-grade	Grade 3	Grade 4	All-grade	Grade 3	Grade 4
AEs overlapping with lenalidomide						
Diarrhea	45	6	0	39	3	0
Constipation	35	<1	0	26	<1	0
Nausea	29	2	0	22	0	0
Vomiting	23	1	0	12	<1	0
Rash	36	5	0	23	2	0
Back pain	24	<1	0	17	3	0
Upper respiratory tract infection	23	<1	0	19	0	0
Thrombocytopenia	31	12	7	16	5	4
AEs with proteasome inhibitors						
Peripheral neuropathy	27	2	0	22	2	0
Peripheral edema	28	1	0	20	1	0
AEs with lenalidomide						
Thromboembolism	8	2	<1	11	3	<1
Neutropenia	33	18	5	31	18	6

Moreau P et al, NEJM 2016

ELOQUENT-2: Elo Rd vs Rd Progression-Free Survival



	E-Ld	Ld
HR 0.70 (95% CI 0.57, 0.85); p=0.0004		
Median PFS (95% CI)	19.4 mo (16.6, 22.2)	14.9 mo (12.1, 17.2)

No. of patients at risk:

E-Ld	321	303	279	259	232	215	195	178	157	143	128	117	85	59	42	32	12	7	1	0
Ld	325	295	249	216	192	173	158	141	123	106	89	72	48	36	21	13	7	2	0	0

E-Ld–treated patients had a 30% reduction in the risk of disease progression or death; treatment difference at 1 and 2 years was 11% and 14%, respectively

PFS analysis used the primary definition of PFS

Infusion Reactions

Events, n (%)	E-Ld (n=318)		
	Grade 1/2	Grade 3	Grade 4/5
Infusion reaction	**29 (9)**	**4 (1)**	**0**
Pyrexia	10 (3)	0	0
Chills	4 (1)	0	0
Hypertension	3 (1)	1 (<1)	0

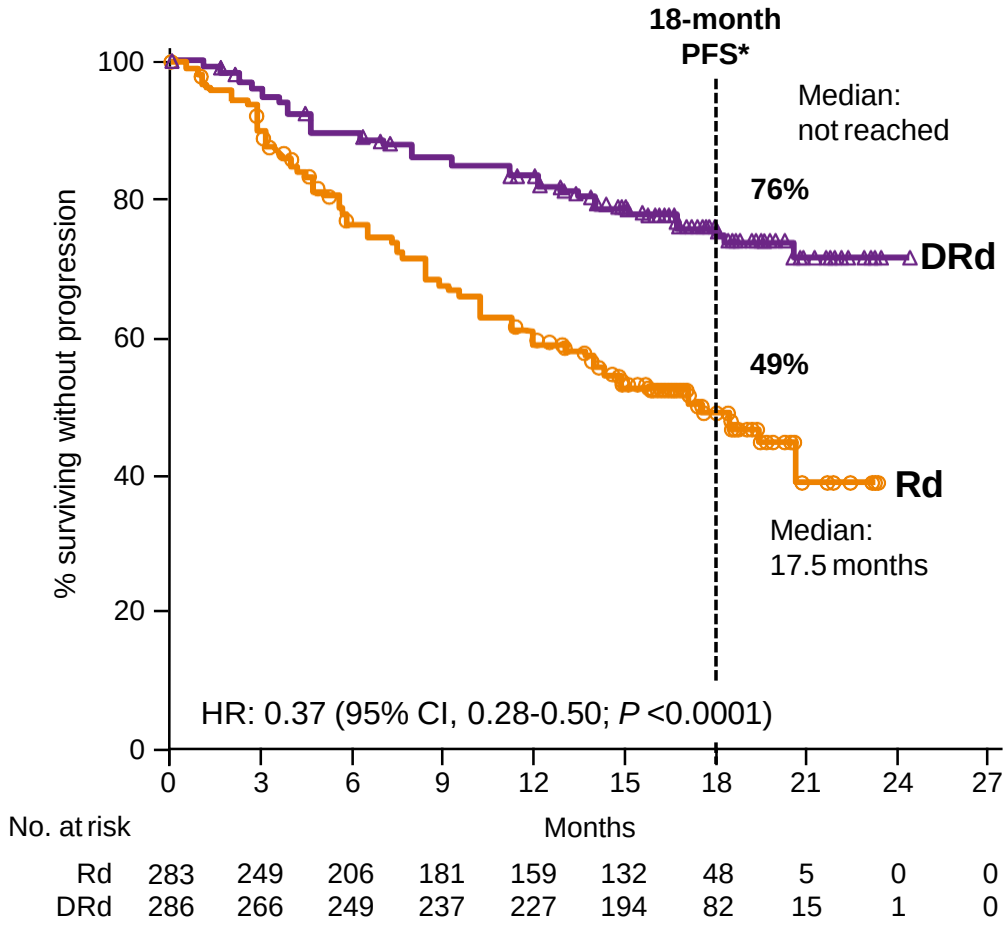
- **Infusion reactions occurred in 10% of patients**
- **70% of infusion reactions occurred with the first dose**
- **No Grade 4 or 5 infusion reactions**
- **Elotuzumab infusion was interrupted in 15 (5%) patients due to an infusion reaction (median interruption duration 25 minutes)**
- **2 (1%) patients discontinued the study due to an infusion reaction**

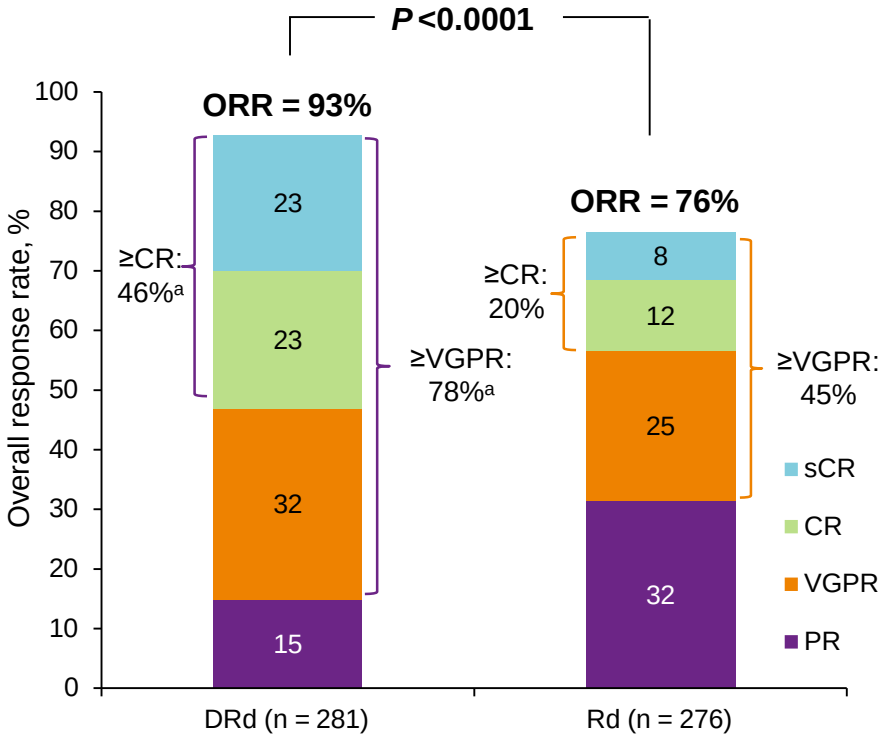
POLLUX: Dara Rd vs Rd

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*





- **Median follow-up: 17.3 (range, 0-24.5) months**
- Responses continue to deepen in the DRd group with longer follow-up

Note: PFS: ITT population; ORR: response-evaluable population.
*Kaplan-Meier estimate;
[a]*P* <0.0001 for DRd vs Rd.

Burden on Healthcare System and Patients

	Ixazomib-Rd	Carfilzomib-Rd	Elotuzumab-Rd	Dara-Rd
Route of administration	**PO**	IV	IV	IV
Dosing schedule	Days 1, 8, and 15 of 28-day cycle	Days 1, 2, 8, 9, 15, and 16 of 28-day cycle	Days 1, 8, 15, 22 of 28-day of cycles 1-2 then Days 1 and 15, cycle 3+	Days 1, 8, 15, 22 of cycles 1-2 Days 1, 15 of cycles 3-6 Day 1 of cycle 7+
Hospital/clinic visit	Every 4 ks	Twice a k	Weekly x 8 then twice montly	Weekly x 8 then twice monthly
Minimum clinic visits based on 18 cycles	**18**	96	44	28
Administration time in clinic/ hospital per visit	**0 hours**	Over 2 hrs	About 2- 5 hrs	3-6 hrs
Premedication	N	N	Y	Y
Prehydration	N	Additional IV hydration needed especially before each dose in cycle 1, may be in other cycles	N	N

Which regimen to choose with Ld?

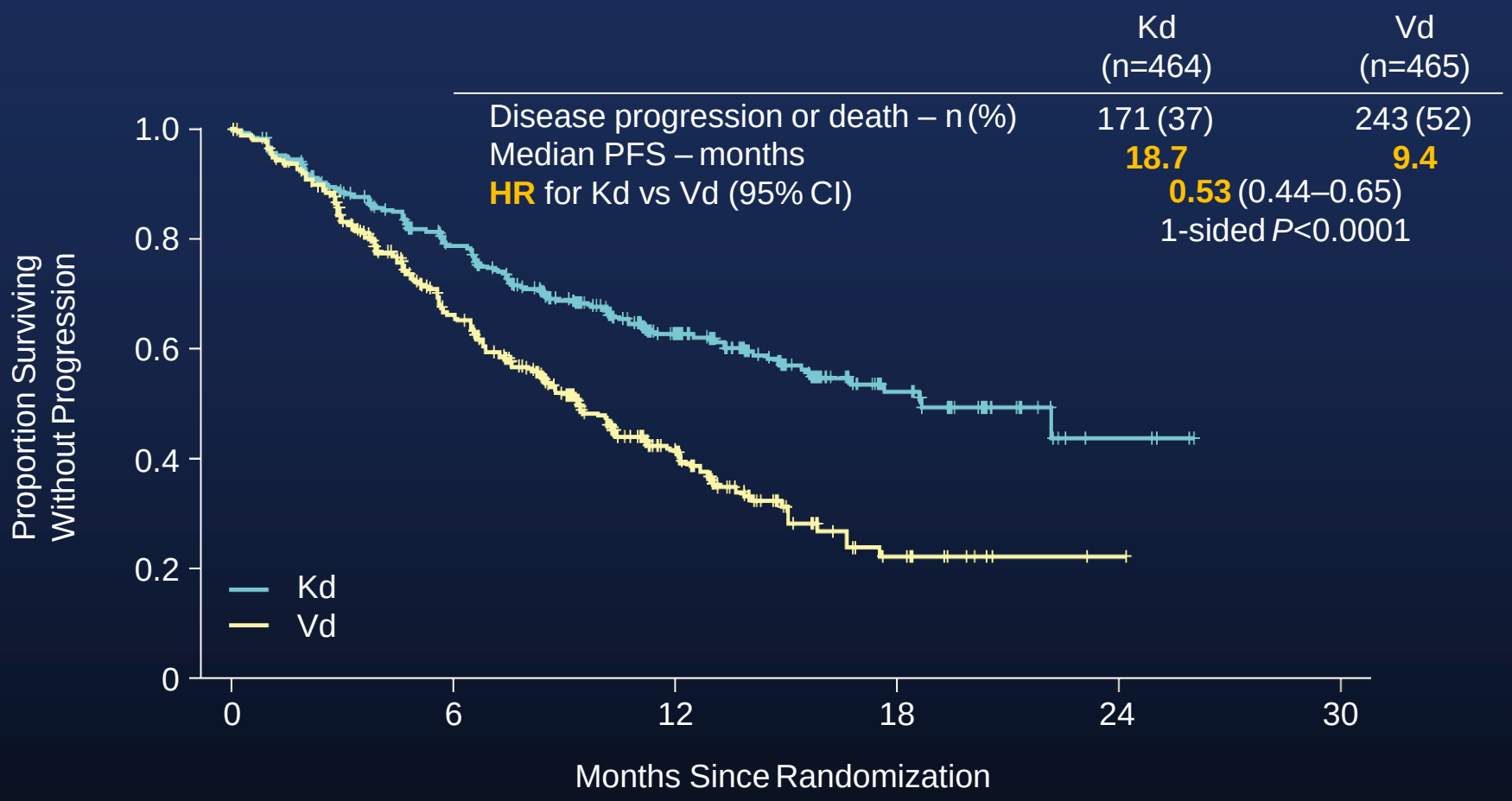
Young patient, no cardiac co-morbidities, aggressive relapse, need to achieve MRD negativity (HR cyto) → **KRd**, **Dara-Rd**

Elderly patient, indolent disease, biochemical relapse, RI?, del 17p? → **Elo-Rd**

Elderly patient, difficulties of access to the hospital → **Ixa-Rd**

Relapse following Ld or lena maintenance

ENDEAVOR: Carfilzomib and Dexamethasone (Kd) vs Bortezomib and Dexamethasone (Vd): PFS

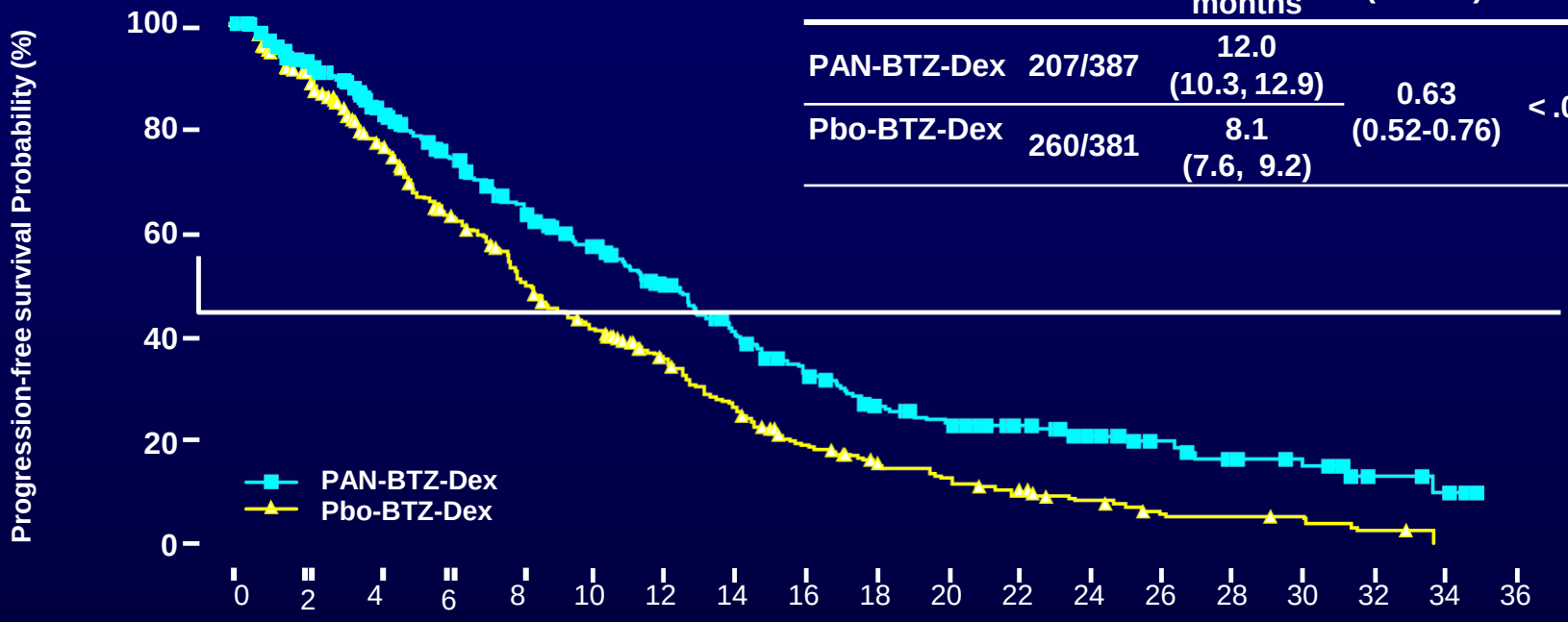


- **Median follow-up: 11.2 months**
- **OS advantage with extended FUP (IMW New Delhi 2017)**

Dimopoulos D et al, Lancet Oncology 2016

Panorama 1 : VD vs VD-panobinostat, PFS

	Events	Median PFS (95% CI) months	HR (95% CI)	*P* value
PAN-BTZ-Dex	207/387	12.0 (10.3, 12.9)	0.63 (0.52-0.76)	< .0001
Pbo-BTZ-Dex	260/381	8.1 (7.6, 9.2)		



Number of patients at risk

PAN-BTZ-Dex	387	288	241	202	171	143	113	89	69	52	44	35	26	18	13	10	5	3	0
Pbo-BTZ-Dex	381	296	235	185	143	114	89	64	42	32	24	18	12	5	5	3	2	0	0

San Miguel et al. Lancet Oncology 2014

Non-Hematologic AEs

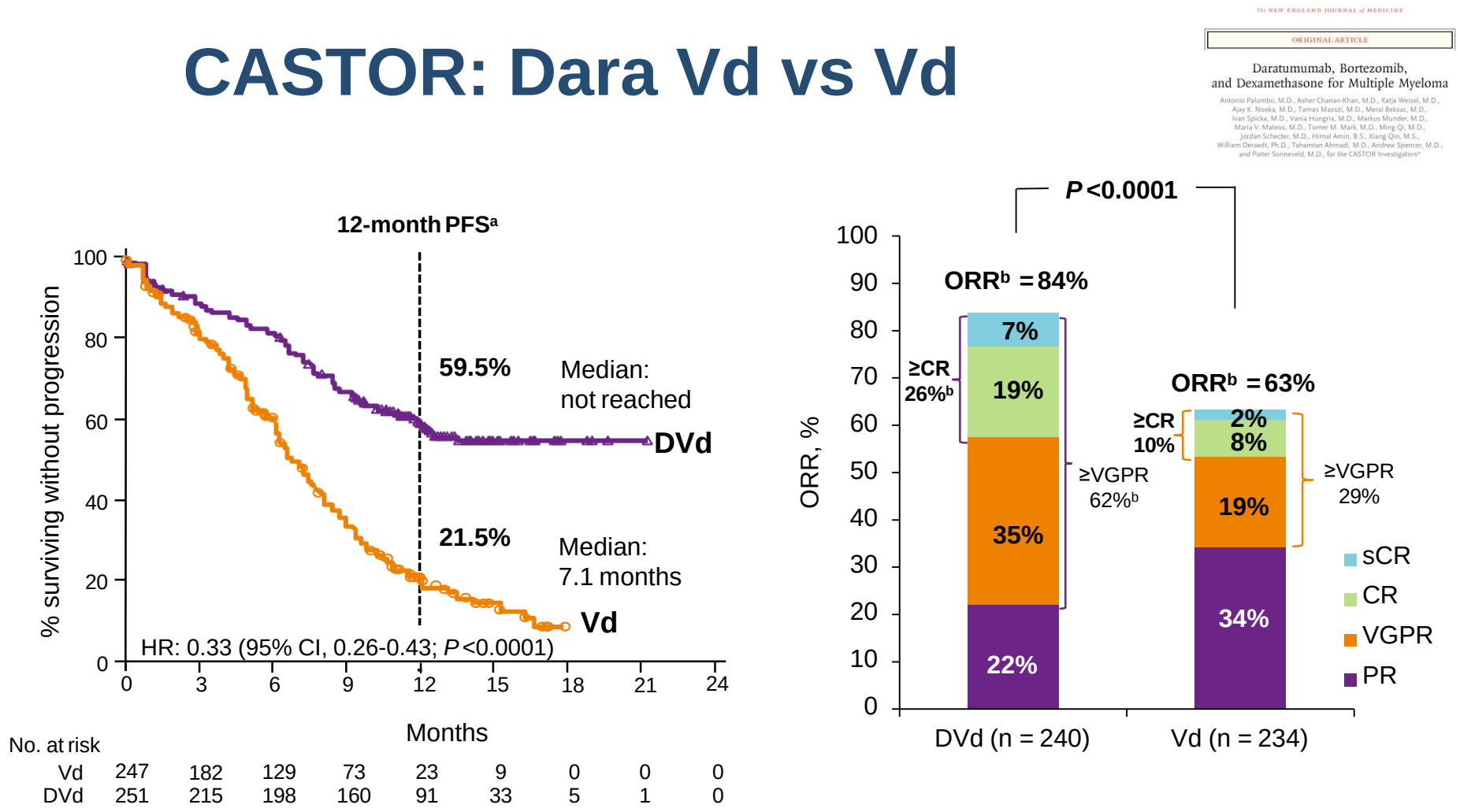
Grade 3/4 Diarrhea and Asthenia/Fatigue Observed

	PAN-BTZ-Dex (n = 381)		Pbo-BTZ-Dex (n = 377)	
Preferred term – %	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhea	68.2	25.5	41.6	8.0
Peripheral neuropathy[a]	60.6	17.6	67.1	14.6
Asthenia/fatigue	57.0	23.9	40.6	11.9
Nausea	36.2	5.5	20.7	0.5
Peripheral edema	28.6	2.1	19.1	0.3
Decreased appetite	28.1	3.1	12.5	1.1
Constipation	26.8	1.0	32.6	1.1
Pyrexia	26.0	1.3	14.9	1.9
Vomiting	25.7	7.3	13.0	1.3
Cough	21.3	1.0	18.6	0

- Discontinuation due to diarrhea (4.5%) and fatigue (2.9%) on PAN arm

[a]Combined incidence of hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy.

CASTOR: Dara Vd vs Vd



The New England Journal of Medicine
ORIGINAL ARTICLE

Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., Ajay K. Nooka, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., Jordan Schecter, M.D., Himal Amin, B.S., Xiang Qin, M.S., William Deraedt, Ph.D., Tahamtan Ahmadi, M.D., Andrew Spencer, M.D., and Pieter Sonneveld, M.D., for the CASTOR Investigators*

- Median (range) follow-up: 13.0 (0-21.3) months
- Responses continue to deepen in the DVd group with longer follow-up
  - An additional 7% achieved ≥CR with longer follow-up

ITT, intent to treat.
Note: PFS: ITT population; ORR: response-evaluable population.
[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DVd versus Vd.

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)

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	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, 160, 649–659	Dimopoulos et al.doi:10.3324/haematol.2014.112037	Orlowsky et al. J Clin Oncol 2007	Offidani et al. Blood 2013	Stadmauder et al. E.J of Haematology 2009	Lonial S, et al. N Engl J Med. 2015;373(7):621-631	Moreau P, et al. N Engl J Med. 2016;374(17):1621-1634.	Stewart AK, et al. N Engl J Med. 2015;372(2):142-152	Dimopoulos MA, et al. ASCO 2015. Abstract 8509	Saad Z. Usmani, et al. Abstract 489 ASH 2016	Maria-Victoria Mateos,et al. Abstract 1150 ASH 2016	San Miguel et al Lancet Oncol 2013; 14: 1055–66	Dimpolous et.al, Blood 2016

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

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

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

Settembre 2014: Recidiva di malattia (biochimica e ossea)

Cosa resta, nel 2014, in settima linea?

7° Linea: BVD x 7: PR (No effetti collaterali invalidanti)

14. Myeloma and other monoclonal gammopathies - Clinical

EHA-3685

BENDAMUSTINE-BORTEZOMIB-DESAMETASONE (BVD) IN THE MANAGEMENT OF RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Claudio Cerchione* [1], Lucio Catalano[1], Anna Emanuele Pareto[1], Santina Basile[1], Luana Marano[1], Ilaria Peluso[1], Luigia Simeone[1], Orsola Vitagliano[1], Salvatore Palmieri[2], Stefano Rocco[2], Felicetto Ferrara[2], Fabrizio Pane[1]

[1]Hematology, Ematologia e trapianto/au federico ii, [2]Hematology, AORN Cardarelli, Napoli, Italy

BVD Protocol schedule

Bendamustine 90 mg/sqm i.v. days 1, 2

Bortezomib 1/1.3 mg/sqm s.c. days 1, 4, 8, 11

Dexamethasone 20 mg, p.o., days 1, 2, 4, 5, 8, 9, 11, 12

Cycles were repeated every 28 days, until progression

14. Myeloma and other monoclonal gammopathies - Clinical

EHA-3685

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[1]Hematology, Ematologia e trapianto/au federico ii, [2]Hematology, AORN Cardarelli, Napoli, Italy

BVD Protocol schedule

Supportive care

- Pegfilgrastim 6 mg s.c. day + 4
- Levofloxacin 500 mg/d, p.o., days 9-21
- ESAs s.c. if required

Support Care Cancer
DOI 10.1007/s00520-016-3430-9

LETTER TO THE EDITOR

Managing neutropenia by pegfilgrastim in patients affected by relapsed/refractory multiple myeloma treated with bendamustine-bortezomib-dexamethasone

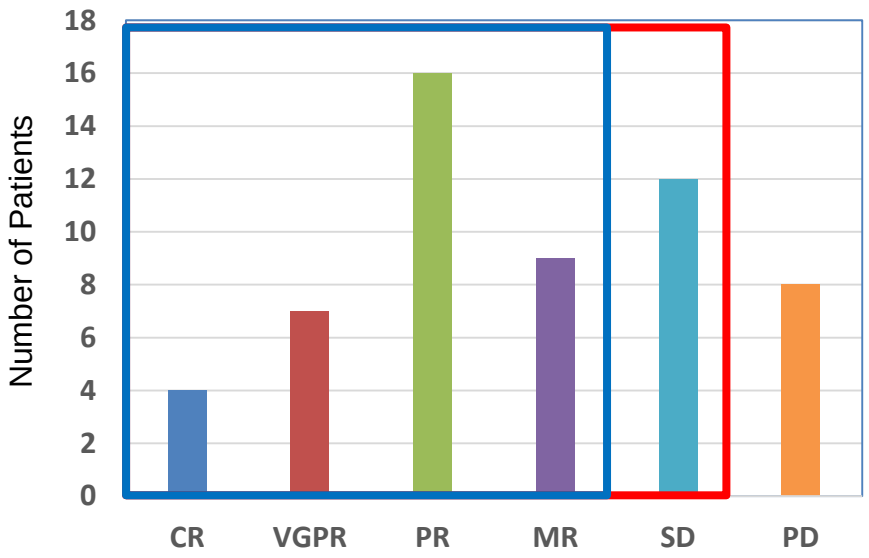
Claudio Cerchione[1] · Lucio Catalano[1] · Ilaria Peluso[1] · Davide Nappi[1] · Maria Di Perna[1] · Dalila Salvatore[1] · Ilaria Migliaccio[1] · Marco Picardi[1] · Fabrizio Pane[1]

Received: 12 April 2016 / Accepted: 26 September 2016

Baseline characteristics of patients

Total patients	56
Male	31
Female	25
Median age, years	
at diagnosis, (range)	57.3 (36-82)
at start of BVD, (range)	61.8 (37-83)
Previous regimens	
median no. (range)	6 (2-11)
FISH analysis	12/56
negative	10
del13q	1
t(11;14)	1
Previous therapies : no. of patients/(%)	
Bortezomib	56 (100%)
IMIDs	56 (100%)
Autologous SCT	38 (67%)

Results – Primary Endpoint



Standard IMWG response criteria[‡]	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions)§§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in SPD§§ of soft tissue plasmacytomas is also
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease ¶¶,‖‖	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0.5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Overall Response Rate 2 (≥SD)	**48/56 (85.7%)**
Stringent complete response (sCR) – no. (%)	**1/56 (1.8%)**
Complete response (CR) – no. (%)	**3/56 (5.3%)**
Very good partial response (VGPR) – no. (%)	**7/56 (12.5%)**
Partial response (PR) – no. (%)	**16/56 (28.5%)**
Minimal response (MR) – no. (%)	**9/56 (16%)**
Stable disease (SD) – no. (%)	**12/56 (21.4%)**
Progressive disease (PD) – no. (%)	**8/56 (14.3%)**

Results – Secondary Endpoint (1)

14. Myeloma and other monoclonal gammopathies - Clinical

EHA-3685

BENDAMUSTINE-BORTEZOMIB-DESAMETASONE (BVD) IN THE MANAGEMENT OF RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Claudio Cerchione* [1], Lucio Catalano[1], Anna Emanuele Pareto[1], Santina Basile[1], Luana Marano[1], Ilaria Peluso[1], Luigia Simeone[1], Orsola Vitagliano[1], Salvatore Palmieri[2], Stefano Rocco[2], Felicetto Ferrara[2], Fabrizio Pane[1]

[1]Hematology, Ematologia e trapianto/au federico ii, [2]Hematology, AORN Cardarelli, Napoli, Italy

Overall survival (OS) from diagnosis – median, mo. (range)	**62.7 (6-151)**
Overall survival (OS) from BVD start – median, mo. (range)	**9.8 (2-36)**
Progression free survival (PFS) – median, mo. (range)	**8.5 (7-25)**
Time to response (TTR) – median, mo. (range)	**1.2 (1-3)**

Follow-up – median, mo. (range)	**14 (2-36)**

Safety

HEMATOLOGICAL TOXICITIES	
ANEMIA, grade	%, no.
4 (Transfusion-dependent)	0
3 (Transfusion-dependent)	41% (23/56)
2 (ESAs)	52% (29/56)
1/NO	7% (4/56)
NEUTROPENIA, grade	%, no.
4	0
2-3	37% (21/56)
Infections (No hospitalization)	11/56 (19%)
THROMBOCYTOPENIA, grade	%, no.
4	0
2/3	34% (19/56)
1/NO	66% (37/56)
Withdrawal (for hematological toxicity)	1.7% (1/56) (Gastric cancer)

CRITERI CTCAE	
ANEMIA	HB (g/dl)
GRADE 1	12-10 g/dL
GRADE 2	10-8 g/dL
GRADE 3	6.5-8 g/dL
GRADE 4	Life threatening
NEUTROPENIA	Neutrophils
GRADE 1	< 2000-1500/mm3
GRADE 2	< 1500-1000/mm3
GRADE 3	< 1000-500/mm3
GRADE 4	< 500/mm3
PLT-PENIA	Platelets
GRADE 1	< N.V. - 75.000/mm3
GRADE 2	75.000-50.000/mm3
GRADE 3	50.000-25.000/mm3
GRADE 4	< 25.000/mm3

EXTRA-HEMATOLOGICAL TOXICITY (GASTROINTESTINAL TOXICITIES) Grade 1 (antiemetic drugs)	31/56 (55%)

Particular cases

Benda as bridge to transplant	No. Patients (%)
To autologous SCT	11/56 (19%)
To allogenic SCT	2/56 (3.5%)

Efficacy after failure of novel agents	No. Patients (%)
BVD post Pomalidomide-Dexa	2/56 (3.5%)
BVD post Carfilzomib-Dexa	1/56 (1.8%)

Efficacy after failure of Bortezomib-retreatment	No. Patients (%)
BVD post bortezomib-based-retreatment	21/56 (37.4%)

Efficacy of BVD-retreatment post autoSCT	1/56 (1.8%)

Hindawi Publishing Corporation
Case Reports in Hematology
Volume 2016, Article ID 6745286, 3 pages
http://dx.doi.org/10.1155/2016/6745286

Hindawi

Case Report

Retreatment with Bendamustine-Bortezomib-Dexamethasone in a Patient with Relapsed/Refractory Multiple Myeloma

Claudio Cerchione, Davide Nappi, Maria Di Perna, Irene Zacheo, Anna Emanuele Pareto, Marco Picardi, Lucio Catalano, and Fabrizio Pane

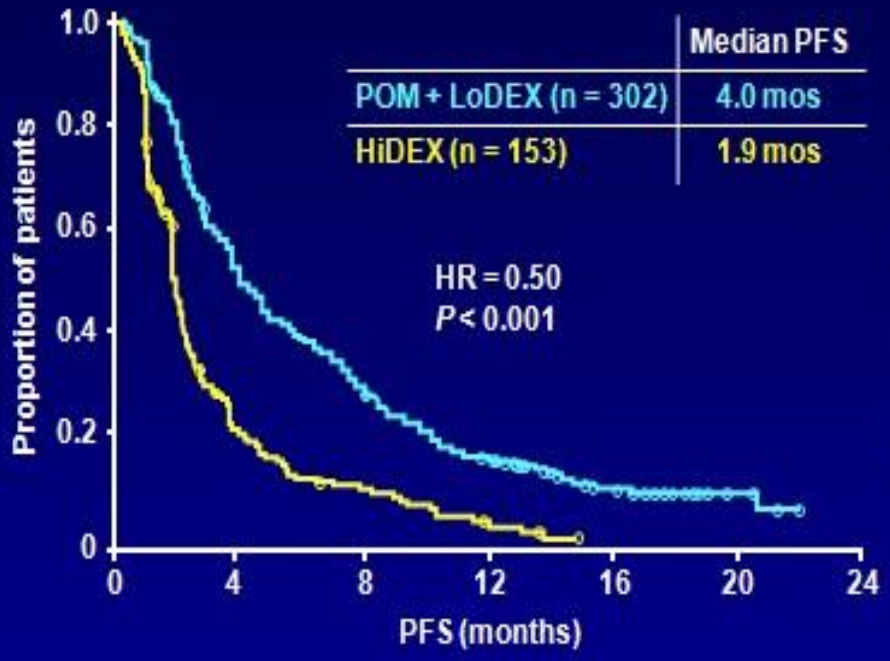
Hematology, University Federico II, Via Pansini 5, 80131 Napoli, Italy

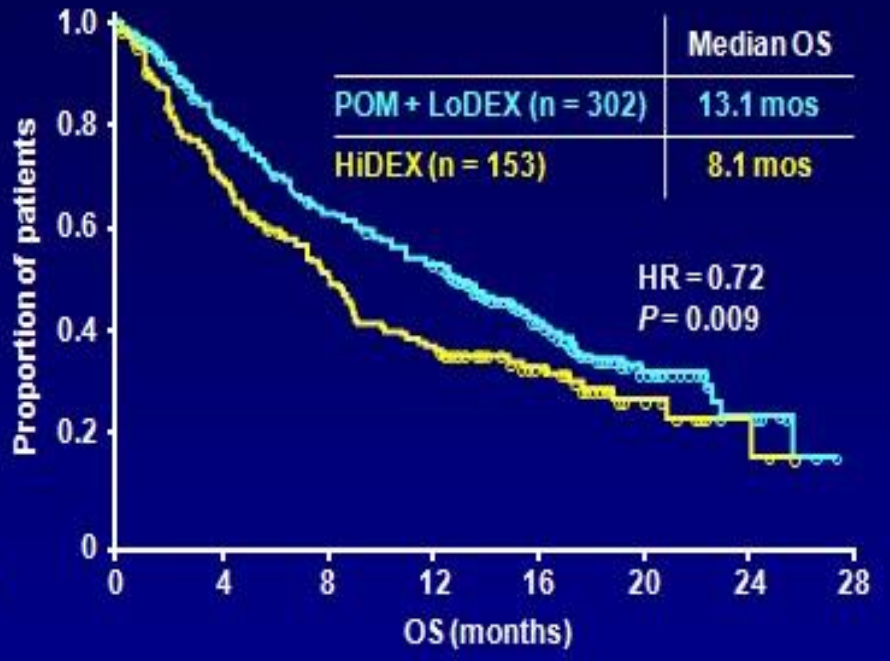
C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

Novembre 2015: Recidiva di malattia (biochimica e ossea)

Che terapia di 8° linea nel 2015?

MM-003 trial: Pom-dex vs Dex





- Compared with HiDEX, POM + LoDEX significantly improved PFS (4.0 vs 1.9 months; P < 0.001) and OS (13.1 vs 8.1 months; *P* = 0.009)
- 85 patients (56%) in the HiDEX arm received subsequent POM

San Miguel et al, Lancet Oncol 2013;14:1055-66
Dimopoulos et al, Blood 2013 (suppl,abstr 408)

Abstract Submission

14. Myeloma and other monoclonal gammopathies - Clinical

EHA-4091

POMALIDOMIDE-DEXAMETHASONE IN THE MANAGEMENT OF HEAVILY PRETREATED MULTIPLE MYELOMA

Claudio Cerchione[*1,1], Davide Nappi[1], Anna Emanuele Pareto[1], Ilaria Migliaccio[1], Irene Zacheo[1], Maria Di Perna[1], Ilaria Peluso[1], Katia Ferrara[1], Fabrizio Pane[1], Lucio Catalano[1]

[1]Hematology, Ematologia e trapianto/au federico ii, Napoli, Italy

Pomalidomide 4 mg/die days 1 ➔ 21

Dexamethasone 40 mg (unfit 20 mg), p.o., days 1, 8, 15, 22

Supportive care

- Levofloxacin 500 mg/d, p.o., days 9-21
- Fluconazole 100 mg/d, p.o., days 9-21
- ESAs and G-CSF (pegfilgrastim, filgrastim) s.c. if required

Cycles were repeated every 28 days, until progression

Baseline characteristics of patients

Total patients	22
Male	13
Female	9
Median age, years	
at diagnosis, (range)	68 (54-80)
at start of Pom-Dexa, (range)	71.5 (61-86)
Previous regimens	
median no. (range)	5 (2-8)
FISH analysis	12/22
negative	10
del13q	3
t(11;14)	1
Previous therapies : no. of patients/(%)	
Bortezomib	56 (100%)
IMIDs	56 (100%)
Autologous SCT	11 (50%)

Results

Overall survival (OS) from diagnosis – median, mo. (range)	84 (27-228)
Overall survival (OS) from Pom-Dexa start – median, mo. (range)	8 (1-14)

Time to response (TTR) – median, mo. (range)	2 (1-4)

Standard IMWG response criteria[‖]	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)[††]
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions)[§§] of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in SPD[§§] of soft tissue plasmacytomas is also
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease [¶¶,‖‖]	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0.5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD[§§] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Overall Response Rate 2 (≥SD)	17/22 (77%)
Complete response (CR) – no. (%)	1/22 (5.3%)
Very good partial response (VGPR) – no. (%)	2/22 (12.5%)
Partial response (PR) – no. (%)	6/22 (28.5%)
Stable disease (SD) – no. (%)	8/22 (21.4%)
Progressive disease (PD) – no. (%)	5/22 (14.3%)

Safety

HEMATOLOGICAL TOXICITIES	
ANEMIA, grade	%, no.
4 (Transfusion-dependent)	9% (2/22)
3 (Transfusion-dependent)	45% (10/22)
2 (ESAs)	18% (4/22)
1/NO	27% (6/22)
NEUTROPENIA, grade	%, no.
4	18% (4/22)
3	22% (5/22)
THROMBOCYTOPENIA, grade	%, no.
4	9% (2/22)
2/3	18% (4/22)
1/NO	72% (16/22)

CRITERI CTCAE	
ANEMIA	HB (g/dl)
GRADE 1	12-10 g/dL
GRADE 2	10-8 g/dL
GRADE 3	6.5-8 g/dL
GRADE 4	Life threatening
NEUTROPENIA	Neutrophils
GRADE 1	< 2000-1500/mm3
GRADE 2	< 1500-1000/mm3
GRADE 3	< 1000-500/mm3
GRADE 4	< 500/mm3
PLT-PENIA	Platelets
GRADE 1	< N.V. - 75.000/mm3
GRADE 2	75.000-50.000/mm3
GRADE 3	50.000-25.000/mm3
GRADE 4	< 25.000/mm3

Previous regimens	
Median no. (range)	5 (2-8)

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

Novembre 2015: Recidiva di malattia (biochimica e ossea)

Che terapia di 8°linea nel 2015?

8° Linea: Pom-Dexa x 9: frequenti episodi infettivi: SD

…e ora???

Daratumumab single agents Trials

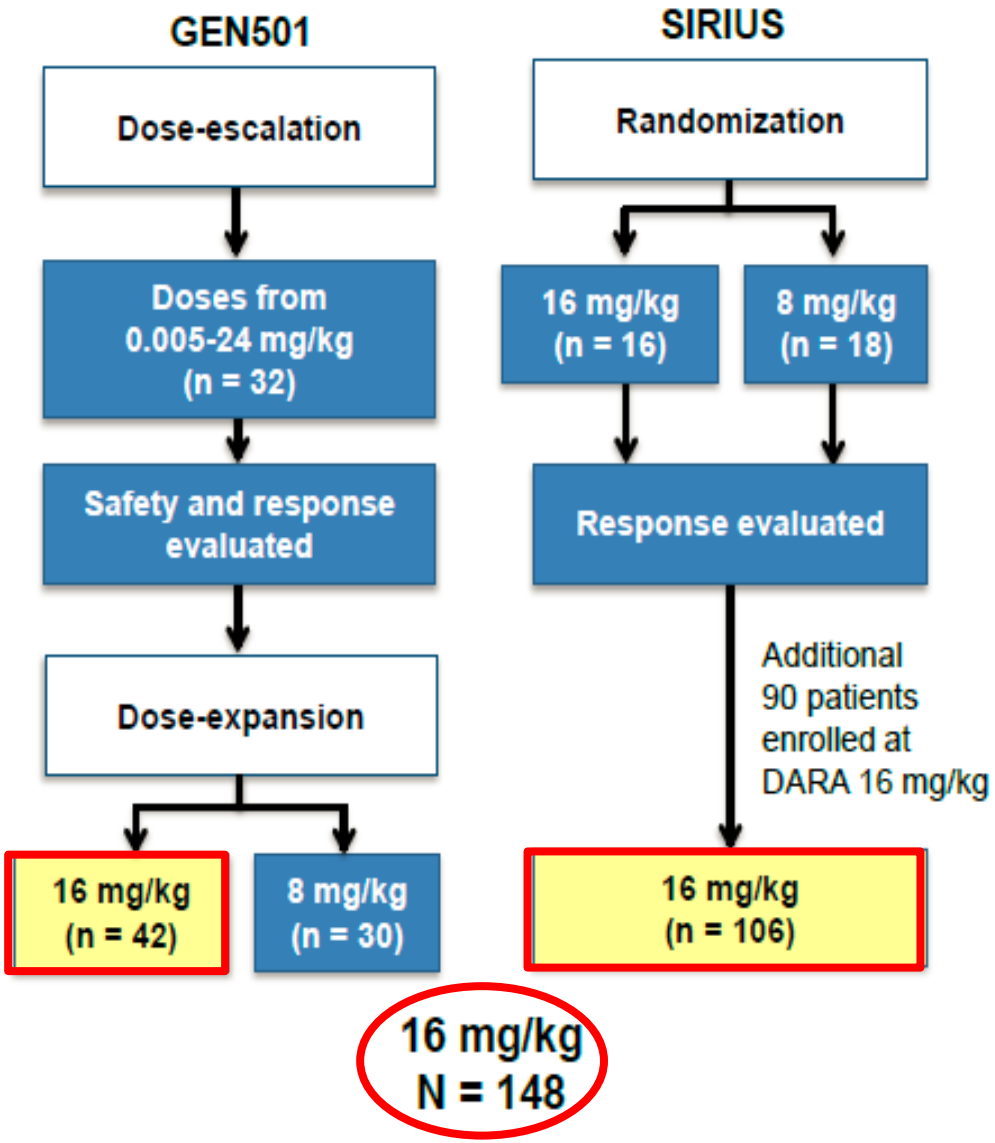
≥18 years of age, ECOG status ≤2[1,2]

GEN501[1]

- Open-label, multicenter, phase 1/2, dose-escalation and dose-expansion study
- Relapsed from or refractory to ≥2 prior lines of therapy including PIs and IMiDs

SIRIUS[2]

- Open-label, multicenter, phase 2 study
- Patients had received ≥3 prior lines of therapy, including a PI and an IMiD, or were double refractory to a PI and an IMID



Usmani S, et al. Oral presentation: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 29. FUp 14.8 months

Follow-up of 20.7 months

1. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219.
2. Lonial S, et al. *Lancet*. 2015. I

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

Daratumumab single-agent *Baseline Characteristics*

The 2 study populations were well balanced with heavily pretreated patients having a median duration of follow-up of 20.7 months

	16 mg/kg		
	GEN501, Part 2 n = 42	SIRIUS n = 106	Combined N = 148
Median (range) age, y ≥65 years of age, n (%)	64.0 (44-76) 20 (48)	63.5 (31-84) 48 (45)	64 (31-84) 68 (46)
Female/male sex, %	36/64	51/49	53/47
ECOG score, n (%) 0 1 2	 12 (29) 28 (67) 2 (5)	 29 (27) 69 (65) 8 (8)	 41 (28) 97 (66) 10 (7)
Median (range) time since diagnosis, y	5.8 (0.8-23.7)	4.8 (1.1-23.8)	5.1 (0.8-23.8)
Median (range) number of prior lines of therapy >3 prior lines of therapy, n (%)	4 (2-12) 26 (62)	5 (2-14) 87 (82)	5 (2-14) 113 (76)
Prior ASCT, n (%)	31 (74)	85 (80)	116 (78)
Prior PI, n (%) Bortezomib Carfilzomib	42 (100) 42 (100) 8 (19)	106 (100) 105 (99) 53 (50)	148 (100) 147 (99) 61 (41)
Prior IMiD, n (%) Lenalidomide Pomalidomide Thalidomide	40 (95) 40 (95) 15 (36) 19 (45)	106 (100) 105 (99) 67 (63) 47 (44)	146 (99) 145 (98) 82 (55) 66 (45)

Usmani S, et al. Oral presentation: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 29.

Baseline Refractory Status

	16 mg/kg		
Refractory to, n (%)	**GEN501, Part 2 n = 42**	**SIRIUS n = 106**	**Combined N = 148**
Last line of therapy	32 (76)	103 (97)	135 (91)
Both PI and IMiD	27 (64)	101 (95)	128 (86)
PI only	3 (7)	3 (3)	6 (4)
IMiD only	4 (10)	1 (1)	5 (3)
PI + IMiD + alkylating agent	21 (50)	79 (75)	100 (68)
Bortezomib	30 (71)	95 (90)	125 (84)
Carfilzomib	7 (17)	51 (48)	58 (39)
Lenalidomide	31 (74)	93 (88)	124 (84)
Pomalidomide	15 (36)	67 (63)	82 (55)
Thalidomide	12 (29)	29 (27)	41 (28)
Alkylating agent only	25 (60)	82 (77)	107 (72)

Usmani S, et al. Oral presentation: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 29.

Responses

Responses deepened with continued daratumumab treatment in 14 patients across the 2 studies

Follow-Up 20.7 Months	16 mg/kg (N = 148)	
Response	n (%)	95% CI
ORR	46 (31.1)	23.7-39.2
Clinical benefit (ORR + MR)	55 (37.2)	29.4-45.5
VGPR or better (sCR+CR+VGPR)	20 (13.5)	8.5-20.1
CR or better (sCR+CR)	7 (4.7)	1.9-9.5
sCR	3 (2.0)	0.4-5.8
CR	4 (2.7)	0.7-6.8
VGPR	13 (8.8)	4.8-14.6
PR	26 (17.6)	11.8-24.7
MR	9 (6.1)	2.8-11.2
SD	68 (45.9)	37.7-54.3
PD	18 (12.2)	7.4-18.5
NE	7 (4.7)	1.9-9.5

Precedent FUp 14.7
Actual FUp 20.7

Median (range) time to response = 0.95 (0.5-5.6) months

Of 10 patients with an initial PR, 7 went to on to achieve VGPR with further treatment and 3 patients with an initial PR achieved deeper responses of CR (1 patient) and sCR (2 patients)

Responses in 4 patients with an initial VGPR continued to deepen to CR (3 patients) and sCR (1 patient)

In many patients, responses deepened with continued DARA treatment

CI, confidence interval; ORR, overall response rate; MR, minimal response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

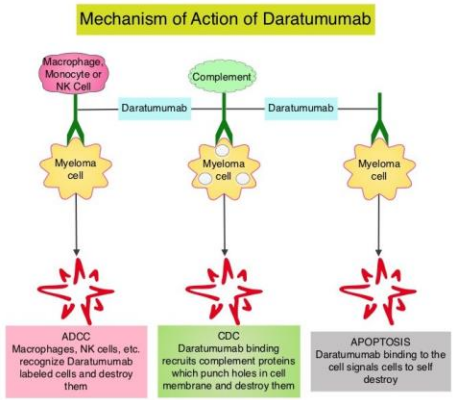
C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

Novembre 2015: Recidiva di malattia (biochimica e ossea)

Che terapia nel 2015?

8° LINEA: Pom-Dexa x 9: frequenti episodi infettivi: SD

Agosto 2016: Richiesta di Daratumumab *single agent* in uso compassionevole (NPP per pazienti senza alternative terapeutiche)



C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

Dicembre 2016: Terapia con Daratumumab single agent

DH o Ricovero Ordinario?

15/12/2016: Ricovero Ordinario Federico II + PICC (Prof M. Picardi)

16/12/2016: 1° Infusione Daratumumab 1000 mg
27/12/2016: 2° Infusione Daratumumab 1000 mg
04/01/2017: 3° Infusione Daratumumab 1000 mg
Ottima compliance, nessuna reazione infusionale, terapia molto ben tollerata
…ma…
Polmonite di ndd (no isolati): Antibiotici e.v. + O2 terapia

08/02/2017: Pratica esami di rivalutazione:
progressione di malattia + condizioni scadute

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

22/02/2017: Richiesta di trasferimento Hospice Casavatore

23/02/2017: Trasferimento

asl napoli2nord

Hospice di Casavatore
Polo del Sollievo per la Vita
Direttore Sanitario: Dr. Giacomo Russo

Proposta di Ricovero in Hospice

Promossa da: ☐ paziente stesso ☐ familiare caregiver
☐ medico di medicina generale ☒ medico ospedaliero

Cognom ___M ☐ F ☒

nato/a a VENEZIA (VE) il 09 12 1947

reside

tel.: _

paziente affetto da malattia in fase avanzata con assenza o inopportunità di indicazione a trattamenti di cura specifici.

Il paziente è attualmente assistito:

☐ nel proprio domicilio senza assistenza domiciliare
☐ nel proprio domicilio in ADI.....N° accessi IP/settimana_____
☐ nel proprio domicilio in ADO..... N° accessi IP/settimana_____
☒ ricoverato in Ospedale AOU FEDERICO II .reparto EMATOLOGIA
☐ ospite nella struttura residenziale_____

Caregiver: ☐ nessuno
☒ familiare
☐ badante

Criticità logistico-strutturali del domicilio: SI ☐ NO ☒

Data 22 / 02 / 2017 Firma e recapito telefonico del proponente

Dott.ssa Simona Avilla
Specialista Ambulatoriale
UOC di Ematologia e di Trapianti di Midollo
AOU Federico II - Napoli
COD. NA31621
tel. 081/7462164
081/7462167

Hospice di Casavatore (Na) Via Nicola Amore, Tel. 081 0402167 ; Fax: 081 0402168 ; e-mail: hospice@aslnapoli2nord.it

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

In Hospice: Controllo settimanale emocromo + biochimica (senza QPE)

1 Marzo 2017: Alla nostra visita in Hospice condizioni generali ed emocromo in netto miglioramento

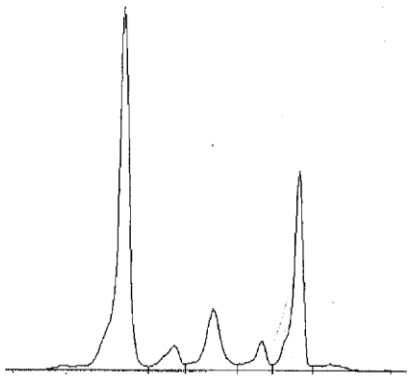
Avreste ripetuto il QPE?

REGIONE CAMPANIA
AZIENDA SANITARIA LOCALE NAPOLI 2 NORD
DIPARTIMENTO DI MEDICINA DI LABORATORIO
Ospedale "S. Giuliano" - Giugliano (NA)
LABORATORIO DI PATOLOGIA CLINICA
Direttore: Dott. R. Iovine

Pagina 1 di 2

Identificativo:	7030203200	Prenotato il	01/03/2017	alle	17.26
		Accettazione n°	32 del 02/03/2017	alle	10.01
		Sesso F		Data di Nascita	09/12/1947
Provenienza	HOSPICE	Note del Paziente:			

Analisi Richieste	Risultati		Unita'	Valori di Riferimento
Quadro Proteico (Elettroforesi capillare)				
Albumina	52,0	L	%	55,8 - 66,1
Alfa-1	5,0	H	%	2,9 - 4,9
Alfa-2	12,3	H	%	7,1 - 11,8
Beta1	4,6	L	%	4,7 - 7,2
Beta2	24,2	H	%	3,2 - 6,5
Gamma	1,9	L	%	11,1 - 18,8
Rapporto Albumina/Globuline	1,06			



Commento: Presenza di componente monoclonale in zona beta 2

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,

14 Marzo 2017: Alla nostra visita in Hospice le condizioni generali continuano a migliorare

Alla ripetizione, il QPE si conferma!!!

Si programma ri-trasferimento per riprendere Daratumumab presso Reparto di Ematologia…

…ma…

REGIONE CAMPANIA
AZIENDA SANITARIA LOCALE NAPOLI 2 NORD
DIPARTIMENTO DI MEDICINA DI LABORATORIO
Ospedale "S. Giuliano" - Giugliano (NA)
LABORATORIO DI PATOLOGIA CLINICA
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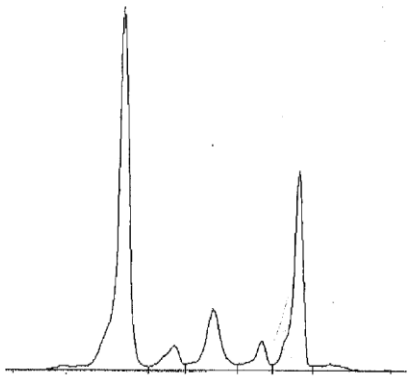
Pagina 1 di 2

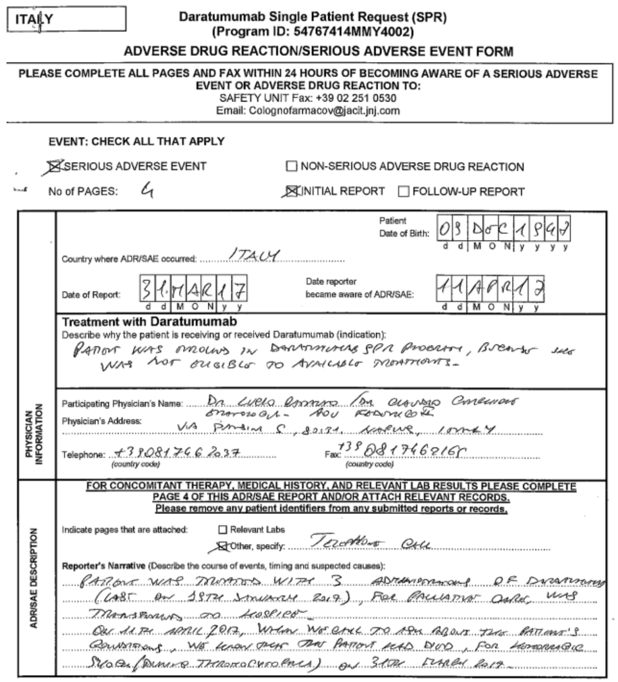
identificativo: 7030203200 — Prenotato il 01/03/2017 alle 17.26
Accettazione n° 32 del 02/03/2017 alle 10.01
Sesso F — Data di Nascita 09/12/1947
Provenienza HOSPICE — Note del Paziente:

Analisi Richieste	Risultati		Unita'	Valori di Riferimento
Quadro Proteico (Elettroforesi capillare)				
Albumina	52,0	L	%	55,8 - 66,1
Alfa-1	5,0	H	%	2,9 - 4,9
Alfa-2	12,3	H	%	7,1 - 11,8
Beta1	4,6	L	%	4,7 - 7,2
Beta2	24,2	H	%	3,2 - 6,5
Gamma	1,9	L	%	11,1 - 18,8
Rapporto Albumina/Globuline	1,06			



Commento: Presenza di componente monoclonale in zona beta 2

C.G. 58 y.o. (Venezia, 09/12/1947), F, casalinga,



ITALY

Daratumumab Single Patient Request (SPR)
(Program ID: 54767414MMY4002)

ADVERSE DRUG REACTION/SERIOUS ADVERSE EVENT FORM

PLEASE COMPLETE ALL PAGES AND FAX WITHIN 24 HOURS OF BECOMING AWARE OF A SERIOUS ADVERSE EVENT OR ADVERSE DRUG REACTION TO:
SAFETY UNIT Fax: +39 02 251 0530
Email: Colognofarmacov@jacit.jnj.com

EVENT: CHECK ALL THAT APPLY

☒ SERIOUS ADVERSE EVENT ☐ NON-SERIOUS ADVERSE DRUG REACTION

No of PAGES: 4 ☒ INITIAL REPORT ☐ FOLLOW-UP REPORT

Patient Date of Birth: 09 DEC 1947 (dd MON yyyy)

Country where ADR/SAE occurred: ITALY

Date of Report: 31 MAR 17 (dd MON yy)

Date reporter became aware of ADR/SAE: 11 APR 17 (dd MON yy)

Treatment with Daratumumab
Describe why the patient is receiving or received Daratumumab (indication):
PATIENT WAS ENROLLED IN DARATUMUMAB SPR PROGRAM, BECAUSE SHE WAS NOT ELIGIBLE TO AVAILABLE TREATMENTS.

PHYSICIAN INFORMATION

Participating Physician's Name: DR. [illegible] / DR. [illegible]
[illegible] - AOU [illegible]
Physician's Address: VIA PANSINI 5, 80131, NAPOLI, ITALY
Telephone: +39 081 746 2037 (country code) Fax: +39 081 746 2165 (country code)

ADR/SAE DESCRIPTION

FOR CONCOMITANT THERAPY, MEDICAL HISTORY, AND RELEVANT LAB RESULTS PLEASE COMPLETE PAGE 4 OF THIS ADR/SAE REPORT AND/OR ATTACH RELEVANT RECORDS.
Please remove any patient identifiers from any submitted reports or records.

Indicate pages that are attached: ☐ Relevant Labs ☒ Other, specify: TELEPHONE CALL

Reporter's Narrative (Describe the course of events, timing and suspected causes):
PATIENT WAS TREATED WITH 3 ADMINISTRATIONS OF DARATUMUMAB (LAST ON 19TH JANUARY 2017), FOR PALLIATIVE CARE, WAS TRANSFERRED TO HOSPICE.
ON 11TH APRIL 2017, WHEN WE CALL TO ASK ABOUT THE PATIENT'S CONDITIONS, WE KNOW THAT THE PATIENT HAD DIED, FOR HEMORRAGIC SHOCK (DURING THROMBOCYTOPENIA) ON 31TH MARCH 2017.

31/03/2017: Alla nostra chiamata in Hospice per concordare il trasferimento, ci viene comunicato il decesso della paziente per 'shock emorragico' (???)

Treatment options for R/R MM

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…)

Conclusioni

- Disponibilità di **nuove combinazioni e nuove classi di agenti** nel Mieloma Recidivato/Refrattario
- **Alti tassi di risposta,** aumento di TTP, PFS e TTNT
- Ottimo profilo di **safety** delle nuove triplette
- Warning per la **cardiotossicità** dei regimi Carfilzomib-based
- **Reazioni infusionali** dei MoAbs
- **Difficoltà** nel **confrontare studi simili ma diversi** (precedente esposizione/refrattarietà ad altri farmaci, durate di risposta nelle linee precedenti, alto rischio citogenetico)
- Necessità di identificare **sottogruppi di pazienti** che possano beneficiare da ogni combinazione
- Necessità di impostare una **strategia terapeutica**

AOU Federico II – Napoli

Prof. Fabrizio Pane
Dott. Lucio Catalano
Prof. Marco Picardi
Prof. Vincenzo Martinelli

A.O.R.N. Cardarelli – Napoli

Prof. Felicetto Ferrara
Dott. Salvatore Palmieri
Dott. Stefano Rocco

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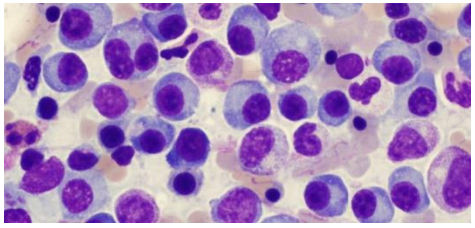
Dott.ssa Katia Ferrara
Dott. Davide Nappi
Dott.ssa Anna Emanuele Pareto
Dott.ssa Ilaria Peluso
Dott.ssa Irene Zacheo



Grazie a tutti per l'attenzione…