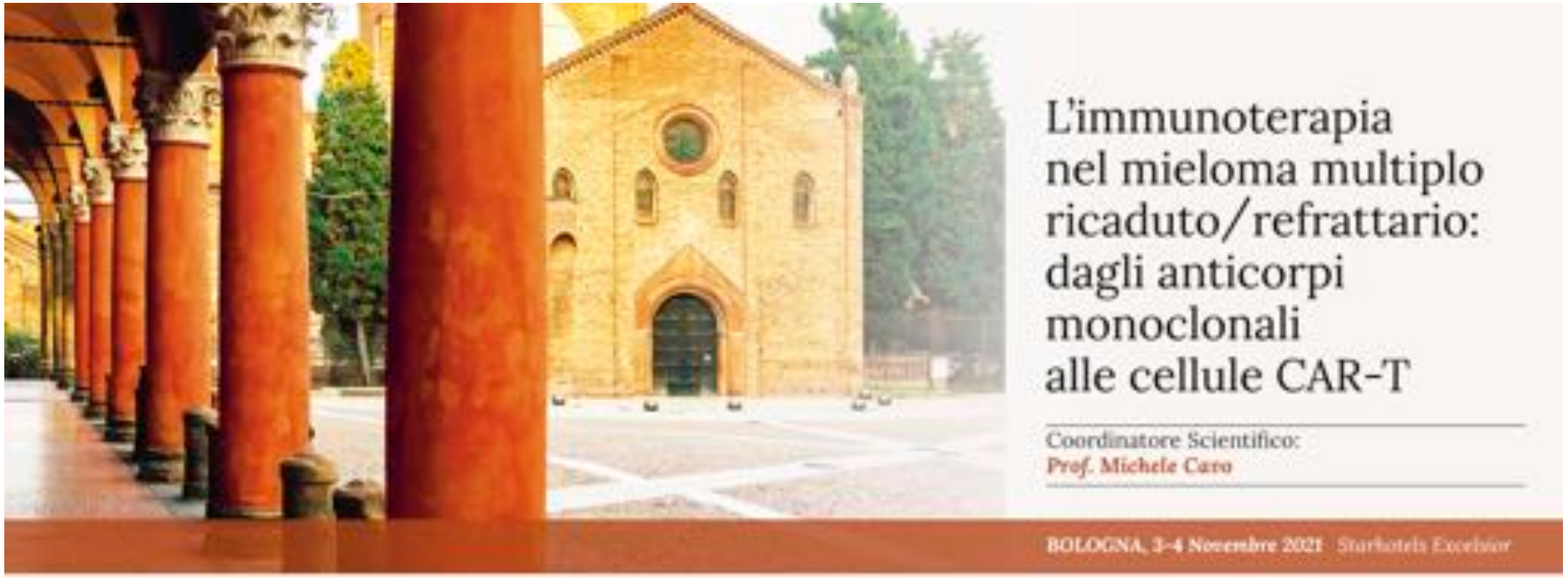

Terapia di seconda linea nel paziente refrattario agli IMiDs

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DISCLOSURES

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen					X		
BMS					X	X	
GSK						X	
Janssen					X	X	
Oncopeptides						X	
Sanofi			X			X	
Takeda			X			X	

CASE PRESENTATION

- D. D, 65 years old, male
- **COMORBIDITY**: appendectomy, benign prostatic hypertrophy
- **DIAGNOSIS 05/2018** : IgG kappa Multiple Myeloma with diffuse bone lytic lesions
- **STAGING** : ISS-1, R-ISS 1, FISH standard risk (including negative for 1q aberrations)
- **DATA AT DIAGNOSIS**: Hb 14.5 g/dl, Creatinine 0.77 mg/dl, Calcium 2.26 mmol/l, MC 3.8%, no Bence Jones detected, FLCr 50, LDH 310

ISS: International Staging System; R-ISS: revised International Staging System; FISH fluorescent in situ hybridization; MC monoclonal component

CASE PRESENTATION: FIRST LINE THERAPY

INDUCTION (05/2018) : VTDx6, complicated by G2 peripheral neuropathy →sCR

↓

MEL200 ASCT (12/2018), complicated by G2 airway infection and long hematologic recovery due to persistent thrombocytopenia→ sCR and MRD negative (MFC, 10^{-5})

↓

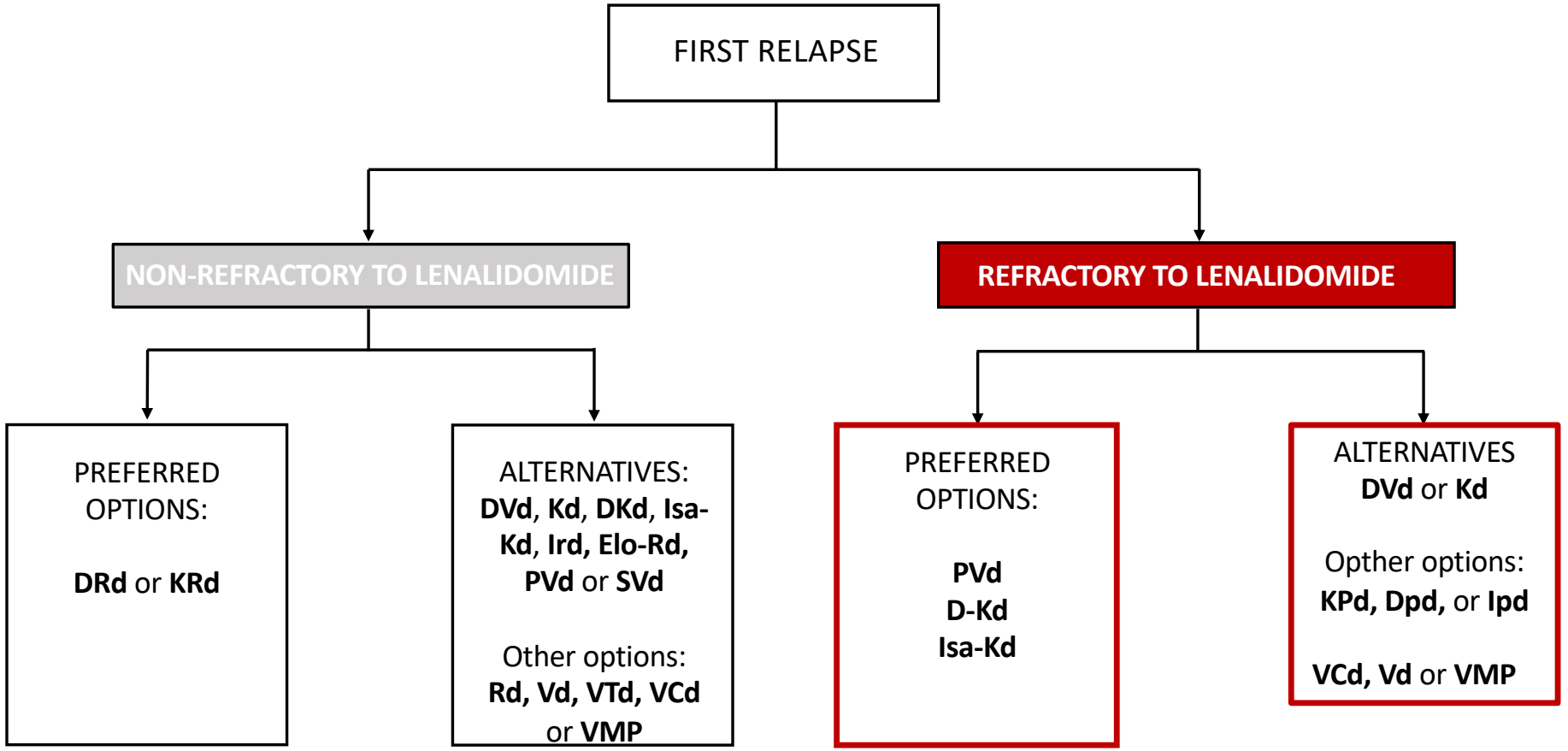
MAINTENANCE (10/2019) : Lenalidomide 10 mg 21/28

↓

DISEASE PROGRESSION (08/2020) with osteolytic lesions and FLCr increase

VTD: Velcade, Thalidomide, Dexamethasone; MEL200 : melphalan 200 mg/m^2; ASCT: autologous stem cell transplantation, sCR: stringent complete response; MRD: minimal residual disease; MFC ,multiparametric flow cytometry; PD: progression disease, FLCr: free light chain ratio.

TREATMENT AT FIRST RELAPSE: IMWG RECCOMENDATIONS 2021



D: daratumumab, R: revlimid, d: dexamethasone, V: velcade, K carfilzomib, Isa: isatuximab, Elo: elotuzumab,P:pomalidomide,M: melphalan

Moreau, Lancet Oncol 2021

FIRST RELAPSE IN LENALIDOMIDE REFRACTORY PATIENTS IN 2021: ITALIAN PERSPECTIVE

STANDARD REGIMENS:
- Carfilzomib-dexamethasone (Kd)
- Daratumumab-Vd
- Pomalidomide-Vd

CONSIDER CLINICAL TRIALS WHENEVER POSSIBLE (CAR-T cell, ADC, BiTEs…)

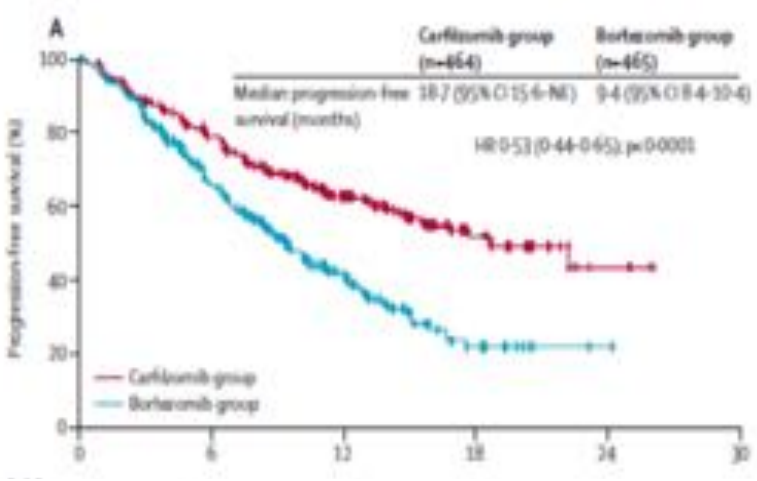
OPEN QUESTIONS:
- Lenalidomide re-challenge
- ASCT consolidation
- Future combinations
- Continuous vs fixed-MRD driven treatment

Kd: carfilzomib, dexamethasone, Vd: bortezomib,dexamethasone; CAR-T: chimeric antigen receptor T, ADC: antibody drug conjugates, BiTEs: bispecific T cell engager, ASCT: autologous stem cell transplantation, MRD: minimal residual disease

FIRST RELAPSE IN LENALIDOMIDE REFRACTORY PATIENTS: AVAILABLE OPTIONS IN 2020

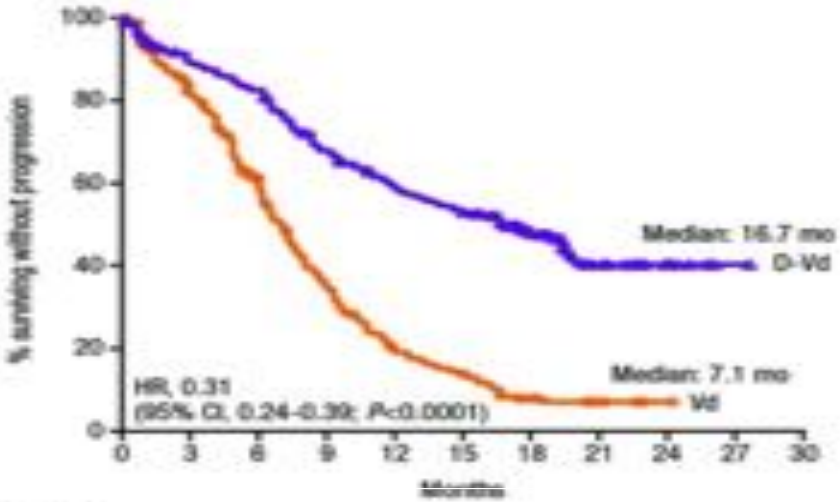
ENDEAVOR[1-2]

Kd vs Vd



CASTOR[3]

DVd vs Vd



	ENDEAVOR[1-2] Kd vs Vd	CASTOR[3] DVd vs Vd
≥ VGPR	54% vs 29%	63% vs 29%
Median PFS (months)	18.7 vs 9.4, HR 0.53	16.7 vs 7.1, HR 0.31
Median OS (months)	47.8 vs 38.8, HR 0.76	NR

K: carfilzomib, d: dexamethasone, V: bortezomib, D: daratumumab. PFS: progression free survival, VGPR very good partial response

[1]Dimopoulos MA et al. Lancet Oncology 2016; [2]Orlowski et al Clin Lymphoma Myeloma Leuk. 2019; [3]Spencer et al; Haematologica 201

FIRST RELAPSE IN LENALIDOMIDE REFRACTORY PATIENTS: AVAILABLE OPTIONS IN 2020

	ENDEAVOR[1] Kd vs Vd	CASTOR[2] DaraVd vs Vd
Patients at first relapse	50% vs 50%	49% vs 46%
Median PFS, months	22.2 vs 10.1, HR 0.45	27 vs 7.9, HR 0.22
Prior Lena exposure	38% vs 38%	36% vs 49%
Median PFS, (months)	12.9 vs 7.3, HR 0.69	13.1 vs 6.6, HR 0.35
Prior Lena refractory	24% vs 26%	24% vs 33%
Median PFS, (months)	8.6 vs 6.6, HR NR	7.8 vs 4.9, HR 0.44

Kd carfilzomib-dexamethasone; Vd bortezomib-dexamethasone; Dara: daratumumab; PFS progression free survival; Lena lenalidomide

- Both Kd and daraVd yelds better PFS when used at first relapse
- However the advantage over Vd in lenalidomide refractory patients is less pronounced

[1]Moreau et al, Leukemia 2017; [2] Mateos MV, Clin Lymphoma Myeloma Leuk. 2020

SAFETY OF AVAILABLE PI-BASED REGIMENS IN THE RELAPSE SETTING

	ENDEAVOR[1] Kd vs Vd	CASTOR[2] DVd vs Vd
G≥3 hematological AEs (%)		
Neutropenia	3 vs 2	14 vs 5
Thrombocytopenia	13 vs 15	46 vs 33
G≥3 non hematological AEs (%)		
Diarrhea	4 vs 9	4 vs 1
Infection	31 vs 21	29 vs 19
Hypertension	15 vs 3	7 vs 1
Cardiac	9 vs 4	NR
AKI	6 vs 4	NR
PNP	2 vs 10	5 vs 7
IRRs	NR	9 vs 0
Discontinuation due to Aes (%)	30 vs 27	10 vs 9
Toxic deaths (%)	7 vs 5	5 vs 6

Kd carfilzomib-dexamethasone; Vd bortezomib-dexamethasone; Dara: daratumumab; AEs: adverse events, AKI: acute kidney injure, PNP: peripheral neuropathy; IRR infusion related reaction

[1] Orlowski RZ et al, Clin Lymphoma Myeloma Leuk. 2019 [2]Spencer et al, Haematologica 2018

ASCT CONSOLIDATION IN SECOND LINE: IF, WHEN, FOR WHOM?

UK MYELOMA X [1]

PAD ± ASCT
in patients relapsing at ≥ 12 months from first ASCT

	ASCT vs no ASCT
TTP, months	19 vs 11, HR 0.45
OS, months	67 vs 52 , HR 0.56

GMGG phase II study [2]

RD ± ASCT
in patients at first to third relapse

	ASCT vs no ASCT
PFS, months	18.8 vs 20.7, HR 0.87
OS, months	NR vs 62.7, HR 0.81

IMWG RECOMENDATIONS 2021[3]

Salvage ASCT should **not** be recommended for patients with a **response duration of less than 3 years** after the first ASCT, but this cutoff is arbitrary and could be reduced to 2 years if the patient has not received maintenance therapy

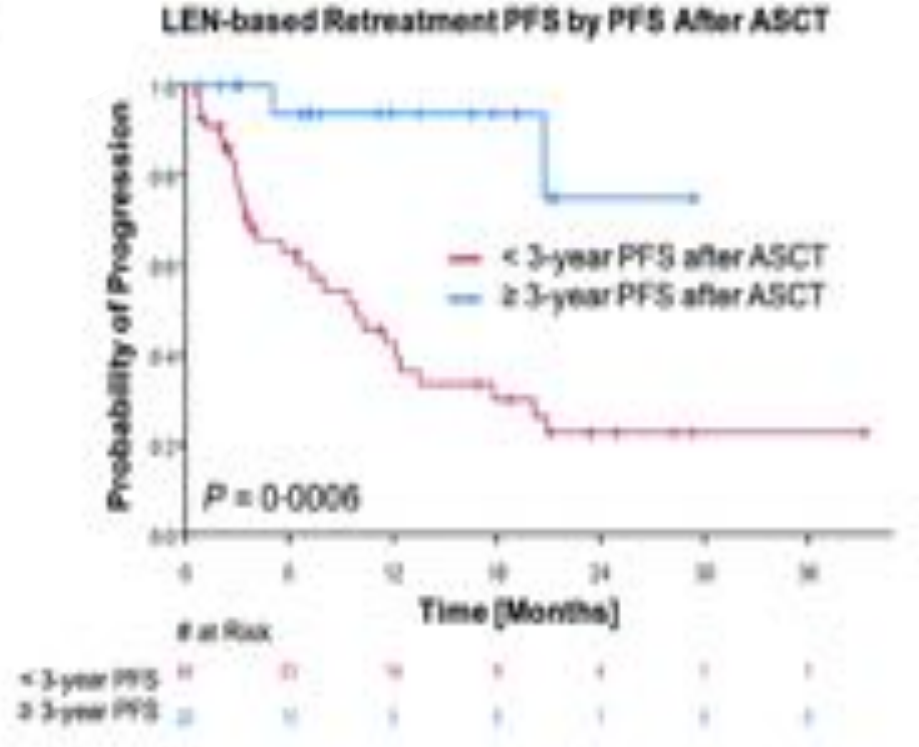
ASCT: autologous stem cell transplantation, PAD: bortezomib, doxorubicin, dexamethasone, R: revlimid, TTP: time to progression, OS: overall survival, PFS: progression free survival

1. Cook G, Lacet Oncol 2014; Goldschmidt, Leukemia 2020; Moreau, Lancet Oncol 2021

LENALIDOMIDE RE-CHALLENGE

Full-dose lenalidomide (25mg) based triplets at disease progression from lenalidomide maintenance (10 mg)

	Overall (n 64)
Triplet delivered	
EloRd	34%
IxaRd	17%
VRd	10%
KRd	30%
Dara-Rd	10%
ORR	58%
≥ VGPR	34%
Median PFS	14 months
Median OS	40 months



Rd: lenalidomide-dexamethasone; Elo: elotuzumab; Ixa: ixazomib; V bortezomib; K carfilzomib, dara: daratumumab; OR overall response rate; VGPR very good partial response; PFS progression free survival; OS overall survival; ASCT autologous tranplantation

Kunacheewa et al. Br J Haematol. 2021

QUESTION

- Which second-line therapy would you have opted for?
  - Kd
  - Dara-Vd
  - PVd
  - ASCT
  - Lenalidomide triplet regimen

CASE PRESENTATION: II LINE THERAPY

Daratumumab,bortezomib,dexamethasone (DaraVd) from 09/2020

- Patient was fit to receive both regimens (no cardio-vascular comorbidities, no COPD/asthma..). The choice was driven by personal preference due to less hospital accesses in the long-term.

CASE PRESENTATION: II LINE THERAPY

Daratumumab,bortezomib,dexamethasone (DaraVd) from 09/2020

- Patient was fit to receive both regimens (no cardio-vascular comorbidities, no COPD/asthma..). The choice was driven by personal preference due to less hospital accesses in the long-term.

- No IRR occurred; from cycle 2 Dara was delivered with accelerated 90-minute infusion as adopted by our center

Daratumumab: optimizing administration

Dara as single agent in 90 minutes

90 min infusion time (total volume 550 mL) is feasible

- 20% over 30 minutes (200 mL/hr)
- 80% over 60 minutes (450 mL/hr)

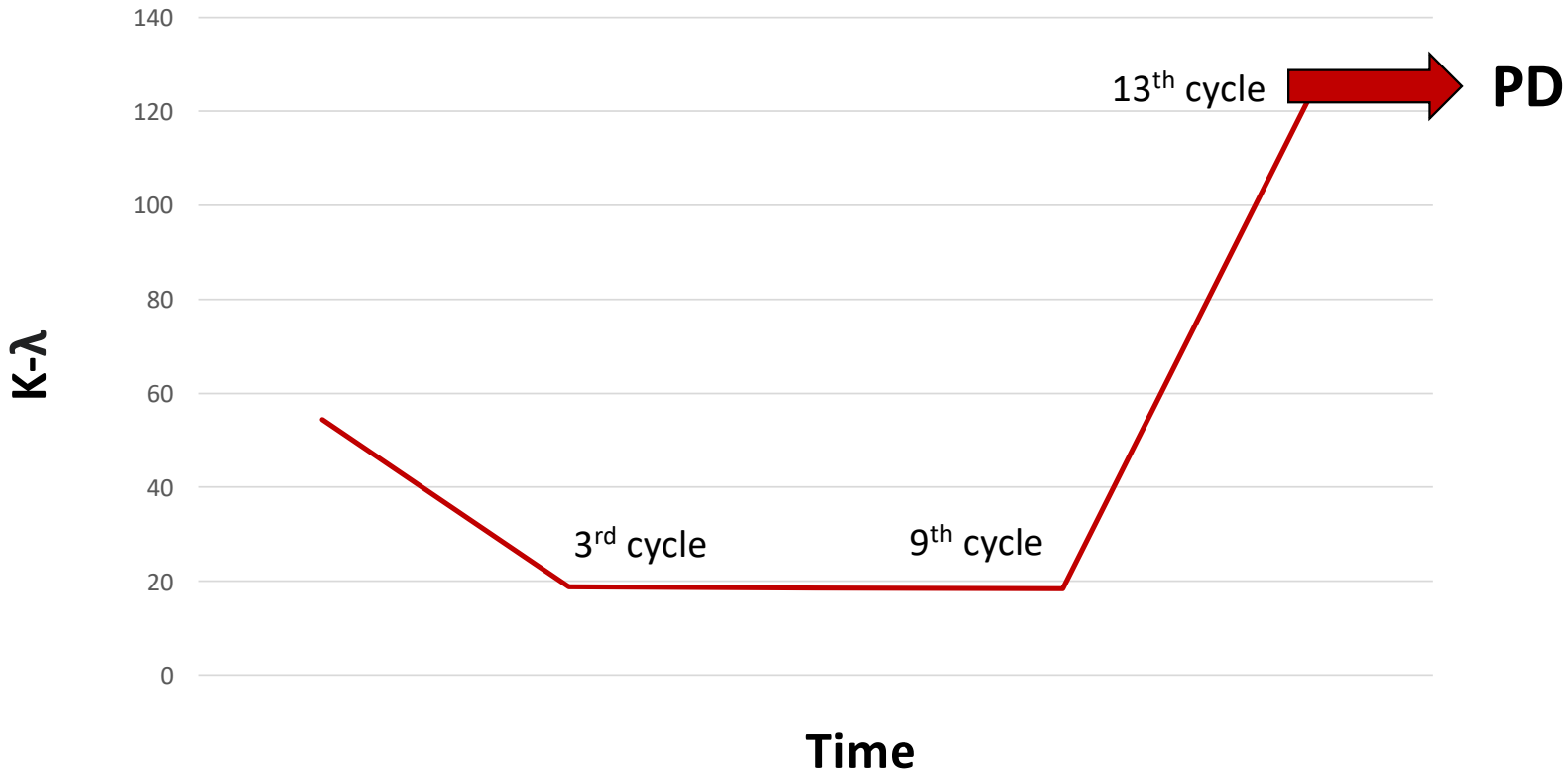
Only 1 adverse reaction occurred (G2 hypertension reversible)

No G3 IRRs were observed.

Number of prior daratumumab doses	**2**	**28.6%**
	3–5	25%
	6–9	0
	10 or more	46.4%
	Median (range)	5 (2–26)
History of daratumumab reactions,	First dose	39.3%
	Second dose	0
Premedication use	APAP + H1A + H2A + DEX,	53.6%
	APAP + H1A + H2A + LRA + DEX, n (%)	25%
	APAP + H1A + H2A, n (%)	14.3%
	APAP + H1A + H2A + LRA, n (%)	3.6%
	H1A + H2A + DEX, n (%)	3.6%
Delayed dexamethasone use	Yes, n (%)	35.7%

APAP acetaminophen, H1A histamine1 antagonist (diphenhydramine or hydroxyzine), H2A histamine2 antagonist (famotidine), LRA leukotriene receptor antagonist (montelukast), DEX dexamethasone

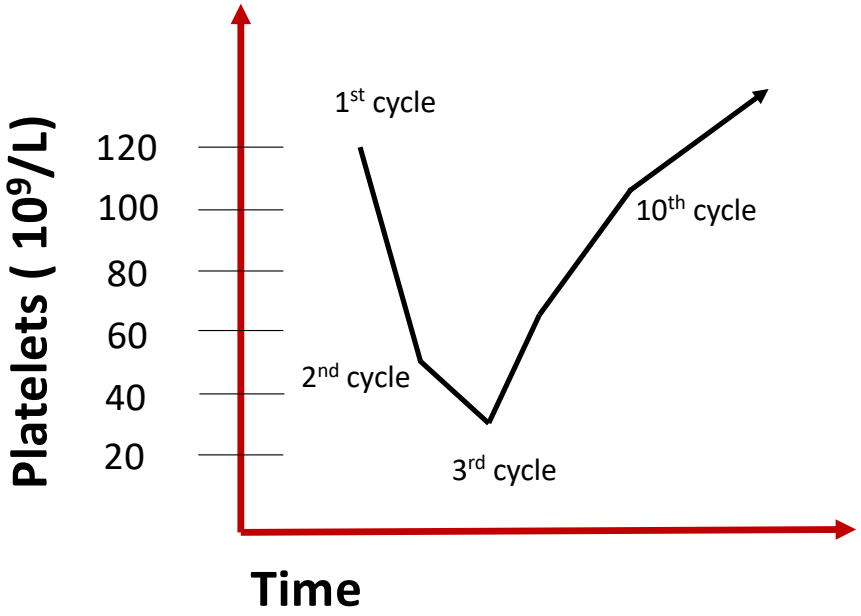
CASE PRESENTATION: II LINE THERAPY and FLC TREND



PD: progression disease

CASE PRESENTATION: II LINE THERAPY and TOXICITIES

THROMBOCYTOPENIA



MOST COMMON AEs OF BORTEZOMIB AND DARATUMUMAB

BORTEZOMIB[1]	DARATUMUMAB[2] as SINGLE AGENT (MOST COMMON in ≥25% PATIENTS)
FATIGUE 65%	FATIGUE
NAUSEA 64%	NAUSEA
DIARRHEA 51%	ANEMIA
THROMBOCYTOPENIA 43%	THROMBOCYTOPENIA
PERIPHERAL NEUROPATHY 37%	ALLERGIC RHINITIS

1: Mateos M.V.et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol 2010;28:2259-2266.
AEs: adverse events, PIs: proteasome inhibitors
2: Nooka et al. Daratumumab in multiple myeloma. Cancer 2019;125:2364-2382

QUESTION

- In relation to side effects, how would you adjust the dose of Velcade?
  - Twice -> once weekly
  - Dose reduction 1.3 -> 1 mg/m^2

CASE PRESENTATION: II LINE THERAPY

Daratumumab,bortezomib,dexamethasone (DaraVd) from 09/2020

- Patient was fit to receive both regimens (no cardio-vascular comorbidities, no COPD/asthma..). The choice was driven by personal preference due to less hospital accesses in the long-term.
- No IRR occurred; from cycle 2 Dara was delivered with accelerated 90-minute infusion as adopted by our center
- Best response: Partial Response after 2 cycles
- Bortezomib was reduced at 1 mg/m^2 from cycle 2 for G3 thrombocytopenia

CASE PRESENTATION: II LINE THERAPY

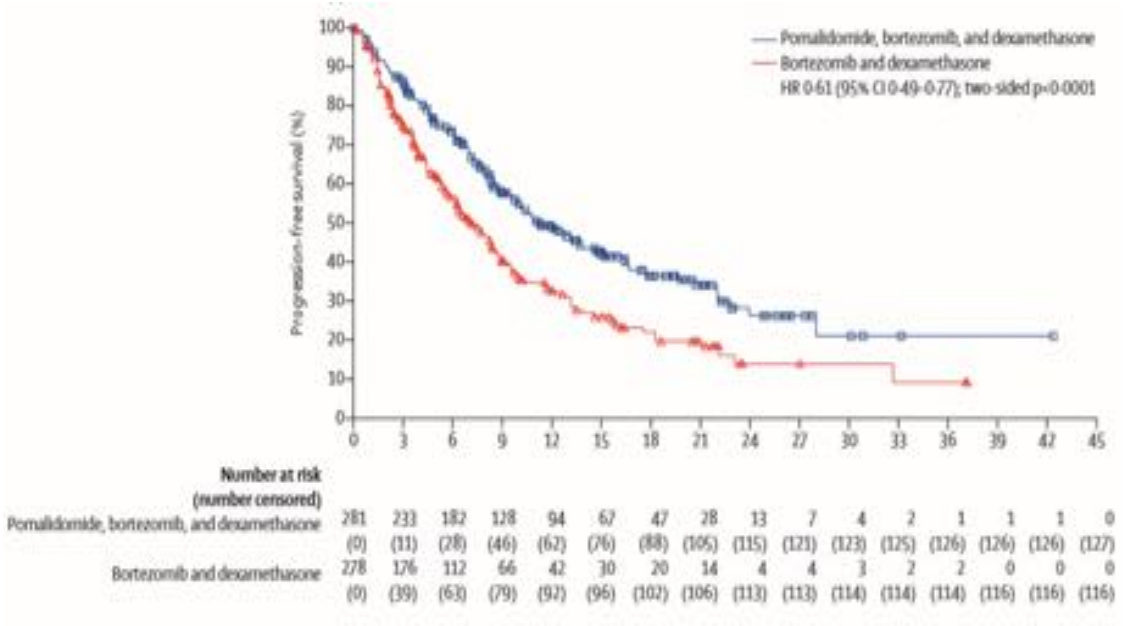
Daratumumab,bortezomib,dexamethasone (DaraVd) from 09/2020

- Patient was fit to receive both regimens (no cardio-vascular comorbidities, no COPD/asthma..). The choice was driven by personal preference due to less hospital accesses in the long-term.
- No IRR occurred; from cycle 2 Dara was delivered with accelerated 90-minute infusion as adopted by our center
- Best response: Partial Response after 2 cycles
- Bortezomib was reduced from cycle 2 for G3 thrombocytopenia
- Treatment was complicated by non-severe Sars-CoV2 infection in 03/2021
- Total of 13 cycles delivered

BROADENING TREATMENT OPTIONS LENALIDOMIDE REFRACTORY PATIENTS IN 2021

OPTIMISMM[1-2]

PVd vs Vd



	OPTIMISMM[1]	
	PVd	Vd
Median PFS, (months)	11.2 vs 7.1, HR 0.61	
≥ VGPR	53% vs 18%	
Lena refractory	71% vs 69%	
Median PFS (months)	9.5 vs 5.6, HR 0.65	
Lena refractory + 1° relapse	23% vs 23%	
Median PFS (months)	17.8 vs 9.5, HR 0.55	

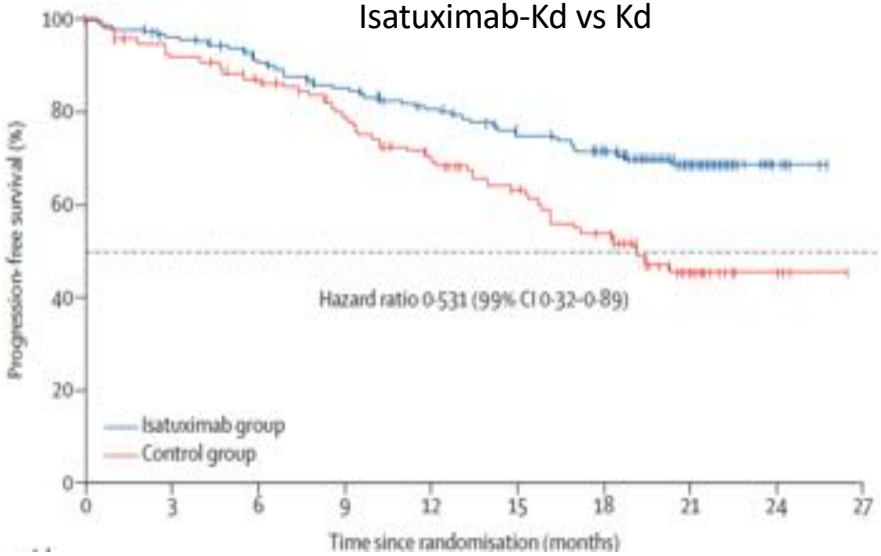
PVd: pomalidomide, bortezomib, dexamethasone. PFS: progression free survival; VGP very good partial response

1. Richardson et al. Lancet Oncol 2019; 2.Dimopoulous, Leukemia 2021

NEW COMBINATIONS: ANTI-CD38 + CARFILZOMIB

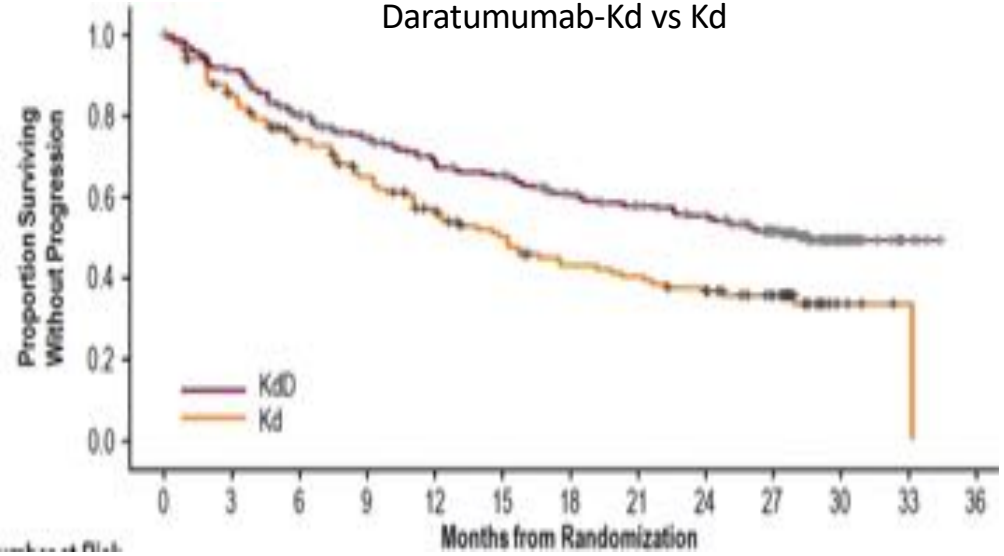
IKEMA[1]

Isatuximab-Kd vs Kd



CANDOR[2]

Daratumumab-Kd vs Kd



	Isatuximab-Kd vs Kd	Daratumumab-Kd vs Kd
Median PFS (months)	NR* vs 19, HR 0.53	28.6 vs 15.2, HR 0.59
Lena refractory	32% vs 34%	32% vs 36%
Median PFS (months)	→ NR* vs 15, HR 0.60	→ 28.1 vs 11.1, HR 0.46

* Median follow-up 20 months; Kd carfilzomib-dexamethasone; PFS progression free survival

[1] Moreau et al. Lancet 2021; [2] Dimopoulous, Lancet 2020

FIRST RELAPSE IN LENALIDOMIDE REFRACTORY PATIENTS IN 2021: AVAILABLE CLINICAL TRIALS AT OUR CENTER

DREAMM-7

Phase III randomized study

Efficacy and Safety of Belantamab Mafodotin (Belamaf) with Bortezomib, and Dexamethasone (B-Vd) compared to Daratumumab- Bortezomib-Dexamethasone

CARTITUDE-4

Phase III randomized study

Chimeric Antigen Receptor T cell (CAR-T) therapy directed against BCMA compared to Pomalidomide-Bortezomib-Dexamehtasone (PVd) or Daratumumab-Pomalidomide-Dexamethasone (DPd)

CONCLUSIONS AND FUTURE DIRECTIONS

- Lenalidomide refractory patients represent a **high-risk subgroups** of patients with poorer outcome and are often under-represented in clinical trials

- Combination of **monoclonal antibodies** + second generation proteasome inhibitor **carfilzomib** represent the most effective strategy for these patients (though not yet available in Italy)

- In the near future most patients will receive both monoclonal antibodies and lenalidomide frontline(dara-VTD, daraRd..) --> Patients at first relapse refractory to both monoclonal antibodies and lenalidomide will become the **new target population for second line treatment**

- New **immuno-therapeutic strategies** (CAR-T, BiTEs, ADCs) appear promising and data from ongoing clinical trials are eagerly awaited

CASE PRESENTATION: CURRENT STATUS

09/21: RELAPSE after 13 cycles of dara-Vd with increased FLC and diffuse bone lesions

Enrolled in CARTITUDE-4 trial

Chimeric Antigen Receptor T cell (CAR-T) therapy directed against BCMA compared to Pomalidomide-Bortezomib-Dexamehtasone (PVd) or Daratumumab-Pomalidomide-Dexamethasone (DPd)

Randomized in CAR-T arm

Ongoing PVd bridging


Thank You !


L'immunc
nel mielo
ricaduto/
dagli anti
monoclor
alle cellul
Coordinatore Scier
Prof. Michele Cavo
BOLOGNA, 3-4 Novet