Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

MM refrattario a lenalidomide o doppio refrattario
opzioni con IMiDs + anticorpi monoclonali
o IMiDs + inibitore del proteasoma

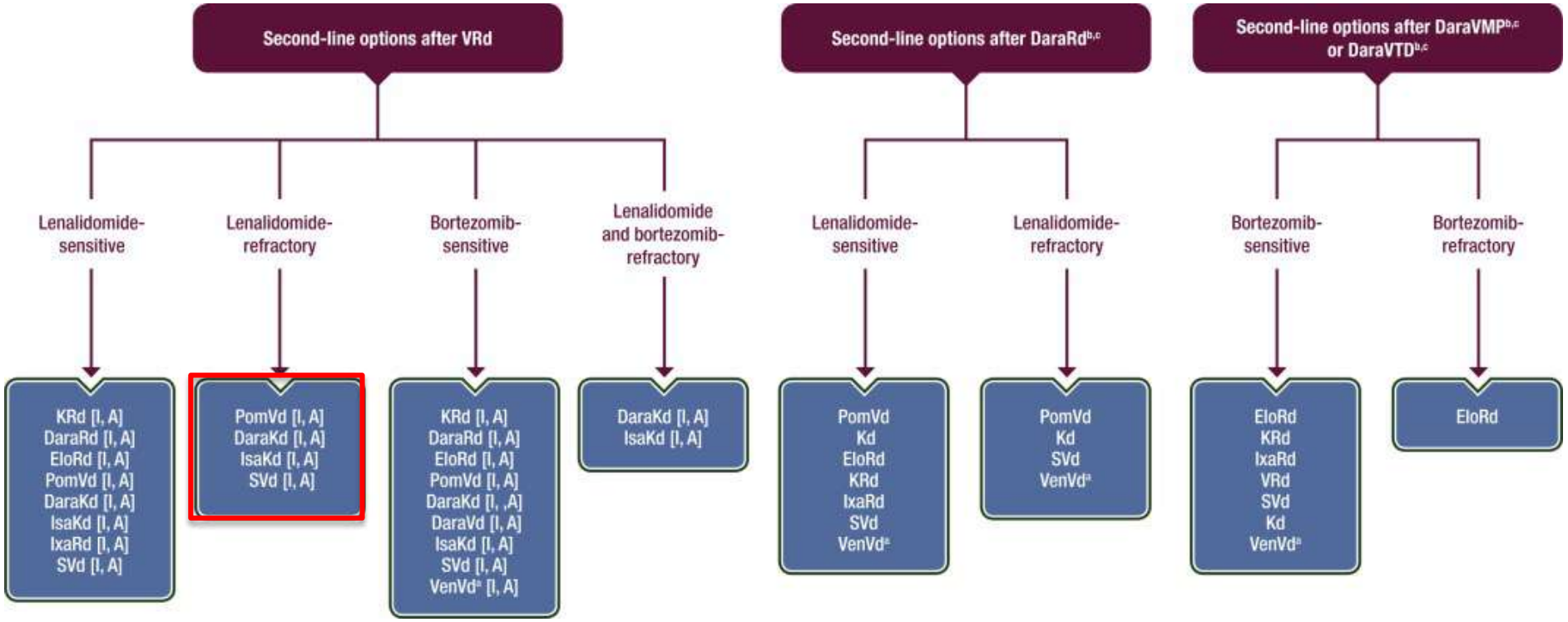
Gabriele Buda
Università di Pisa

Discloures

Honoraria

BMS
Celgene
Sanofi
Janssen
Amgen
Takeda

Recommendations for the first relapse of myeloma



Dimopoulos et al, Annals of Oncology 2021

Pomalidomide, bortezomib, and dexamethasone after 1 prior line of therapy in relapsed or refractory multiple myeloma: a safety subanalysis of the phase 3 OPTIMISMM trial

P-224

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Introduction

- Patients with newly diagnosed multiple myeloma (NDMM) are routinely treated with lenalidomide (LEN) until disease progression; thus, at first relapse, many patients have LEN-refractory disease[1]
- Patients with relapsed or refractory multiple myeloma (RRMM) need proven effective therapies that not only help achieve disease control[2] but also have a manageable safety profile
- Pomalidomide (POM) is an immunomodulatory drug with antitumor activity and immune-enhancing effects in patients with MM, including those with LEN-refractory disease[3-5]
- The European Commission approved the POM, bortezomib (BORT), dexamethasone (DEX) (PVd) treatment for patients with RRMM after first relapse, supported by data from the phase 3 OPTIMISMM trial (NCT01734928)[4,5]
  - Median progression-free survival (PFS) at first relapse: 20.7 vs 11.6 months; HR, 0.54 (95% CI, 0.36-0.82); P = 0.0027[4]
  - The individual safety profiles for POM, BORT, and DEX[6] were consistent with adverse events (AEs) reported with PVd in the overall population of the OPTIMISMM trial

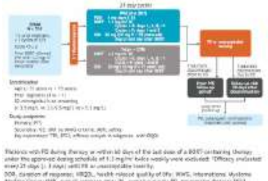
Objective

- To report a safety analysis of treatment-emergent adverse events (TEAEs) in the events of interest (EOI) category for PVd vs BORT and DEX (Vd) administered at first relapse in the OPTIMISMM trial

Methods

- Patients with RRMM were randomized 1:1 to receive PVd or Vd in the OPTIMISMM trial (Figure 1)

Figure 1. OPTIMISMM study design



- A subgroup of patients who received only 1 prior line of treatment were selected for this safety analysis
  - Patients were included who received ≥ 1 dose of study drug
- The NCI CTCAE (version 4.0 or higher) and MedDRA dictionary (version 20.0) were used to summarize AEs by system organ class and preferred term and assign AE grades
- Time to onset, duration, cycle timing, and supportive care for TEAE EOIs were explored
- Exposure-adjusted incidence rates were calculated as 100 × n/T
  - n = the number of patients with the selected AE
  - T = the total patient-years (PY)
- Grouped TEAE EOIs were used to enhance AE detection and present clinically relevant AE terms
- Patients with > 1 occurrence of the same TEAE EOI were counted once in that category by the highest grade experience

Results

- 226 of 559 patients (40%) in OPTIMISMM received 1 prior line of therapy and 221 (PVd, n = 111; Vd, n = 110) were included in the safety analysis population
- Baseline characteristics were generally well balanced between treatment arms (Table 1)

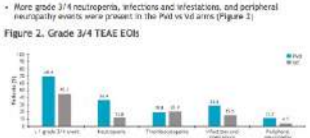
Table 1. Demographics and baseline characteristics

Characteristics	Patients with 1 prior line of treatment: PVd (n = 111)	Vd (n = 110)
Age, median (range), years	66 (29-87)	68 (27-89)
Male, n (%)	67 (60)	55 (50)
ECOG PS 0/1/2, %	60/37/3	53/42/6
ISS at study entry I/II/III, %	59/30/12	61/23/16
High-risk cytogenetics, n (%)	18 (16)	14 (13)
Time since MM diagnosis, median (range), years	3.0 (0.2-10.8)	3.2 (0.4-12.8)
Prior LEN, n (%) LEN refractory	111 (100) 64 (58)	110 (100) 62 (56)
Prior BORT, n (%) BORT refractory	67 (60) 11 (10)	64 (58) 5 (6)
Prior ASCT, n (%)	58 (51)	52 (47)

Safety

- At the data cutoff (26 October 2017), the median duration of treatment was longer in the PVd arm (47.4 weeks; range, 4.7-147.0) than the Vd arm (27.1 weeks; range, 0.4-162.0)
- Grade 3/4 TEAE EOIs occurred in 57.5% of patients (127/221)
- More grade 3/4 neutropenia, infections and infestations, and peripheral neuropathy events were present in the PVd vs Vd arms (Figure 2)

Figure 2. Grade 3/4 TEAE EOIs



- To adjust for the longer treatment duration in the PVd arm than the Vd arm, incidence rates per 100 PYs were calculated for each of these grade 3/4 TEAE EOIs (Table 2)
  - The incidences of grade 3/4 neutropenia and infections and infestations were greater with PVd vs Vd, whereas the incidence of grade 3/4 thrombocytopenia was greater with Vd
- Neutropenia was mostly grade 3/4 (Figure 3), began in the first cycle of treatment (Figure 4), and lasted a median of 6 days (Figure 5)
  - All febrile neutropenia cases (n = 4) were grade 3/4
- Infections and infestations and peripheral neuropathy were mostly grade 1/2 (Figure 3), began in the first 2 cycles of treatment (Figure 4), and had median durations of 12 and 19 days, respectively (Figure 5)

Table 2. Grade 3/4 TEAE EOI incidence rates per 100 PYs[a]

Patients with 1 prior line of treatment	Neutropenia	Thrombocytopenia	Infections and infestations	Peripheral neuropathy
PVd (n = 111)	46.15	21.10	32.91	11.31
Vd (n = 110)	18.14	32.96	23.71	6.39

Figure 3. Grade of TEAE EOIs in each cycle of PVd treatment

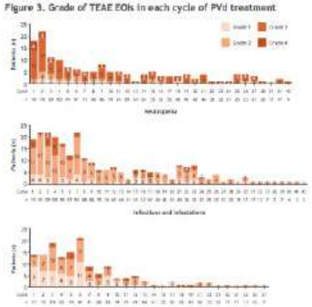
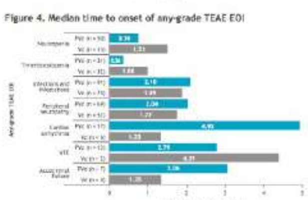
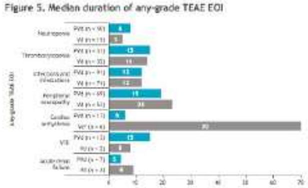


Figure 4. Median time to onset of any-grade TEAE EOI



VTE, venous thromboembolism.

Figure 5. Median duration of any-grade TEAE EOI



Dose modifications

- TEAE EOIs were mainly managed with dose reductions and interruptions of any drug in the PVd and Vd arms (Table 3)
- POM discontinuations due to ≥ 1 TEAE EOI of any grade were low (9.0%)
  - 55.5% of patients had POM interruptions and 45.9% of patients had POM dose reductions
  - The median relative POM dose intensity was 0.9 (range, 0.3-1.0)
- Infections and infestations were the primary cause of PVd dose interruptions (54.1%) (Table 3)
- Peripheral neuropathy was the most common TEAE EOI leading to dose reduction (32.4%) and discontinuation (16.2%) with PVd (Table 3)

Table 3. Dose modifications of any drug due to TEAE EOIs

	Any dose reduction due to TEAE EOI, n (%)		Any dose interruption due to TEAE EOI, n (%)		Any dose discontinuation due to TEAE EOI, n (%)	
	PVd (n = 111)	Vd (n = 110)	PVd (n = 111)	Vd (n = 110)	PVd (n = 111)	Vd (n = 110)
≥ 1 TEAE EOI leading to dose modifications of any drug	65 (58.6)	43 (39.1)	88 (79.3)	60 (54.5)	24 (21.6)	7 (15.5)
Neutropenia	13 (11.7)	1 (0.9)	22 (19.8)	2 (1.8)	0	0
Thrombocytopenia	12 (10.8)	6 (5.5)	11 (9.9)	13 (11.8)	1 (0.9)	1 (0.9)
Infections and infestations	8 (7.2)	4 (3.6)	60 (54.1)	40 (36.4)	4 (3.6)	1 (0.9)
Peripheral neuropathy	36 (32.4)	29 (26.4)	24 (21.6)	18 (16.4)	18 (16.2)	11 (10.0)
Somnolence (including dizziness and confusion)	8 (7.2)	1 (0.9)	8 (7.2)	3 (2.7)	1 (0.9)	1 (0.9)

Medical interventions of TEAE EOIs

- Antibiotics, antifungals, antiprotozoals, and antivirals were used to treat > 95% of patients in the PVd arm who experienced infections and infestations (Table 4)
- G-CSF treatments were used for patients with neutropenia (62.0%) and febrile neutropenia (66.7%) in the PVd arm (Table 4)
- Antiviral and G-CSF prophylaxes were recommended by study protocol and cannot be distinguished from supportive treatments after AE onset
- Among patients with thrombocytopenia, 29.0% (9/31) in the PVd arm and 28.1% (9/32) in the Vd arm received platelet transfusions
- Among patients with anemia, 57.7% of patients (15/26) in the PVd arm and 45.5% of patients (10/22) in the Vd arm received red blood cell transfusions

Table 4. Medications for TEAE management used in the PVd arm

Medications	PVd, n (%)
Antiviral use in patients with ≥ 1 infections and infestations event (n = 91)[a]	90 (98.9)
Antibiotics, antifungals, or antiprotozoals use in patients with ≥ 1 infections and infestations event (n = 91)	87 (95.6)
G-CSF use in patients with ≥ 1 neutropenia event (n = 50)[b]	31 (62.0)
G-CSF use in patients with ≥ 1 febrile neutropenia event (n = 3)[b]	2 (66.7)
Prophylaxis medication in patients with ≥ 1 DVT event (n = 4)[c] Acetylsalicylic acid Enoxaparin sodium Enoxaparin	 1 (25.0) 1 (25.0) 1 (25.0)

Conclusions

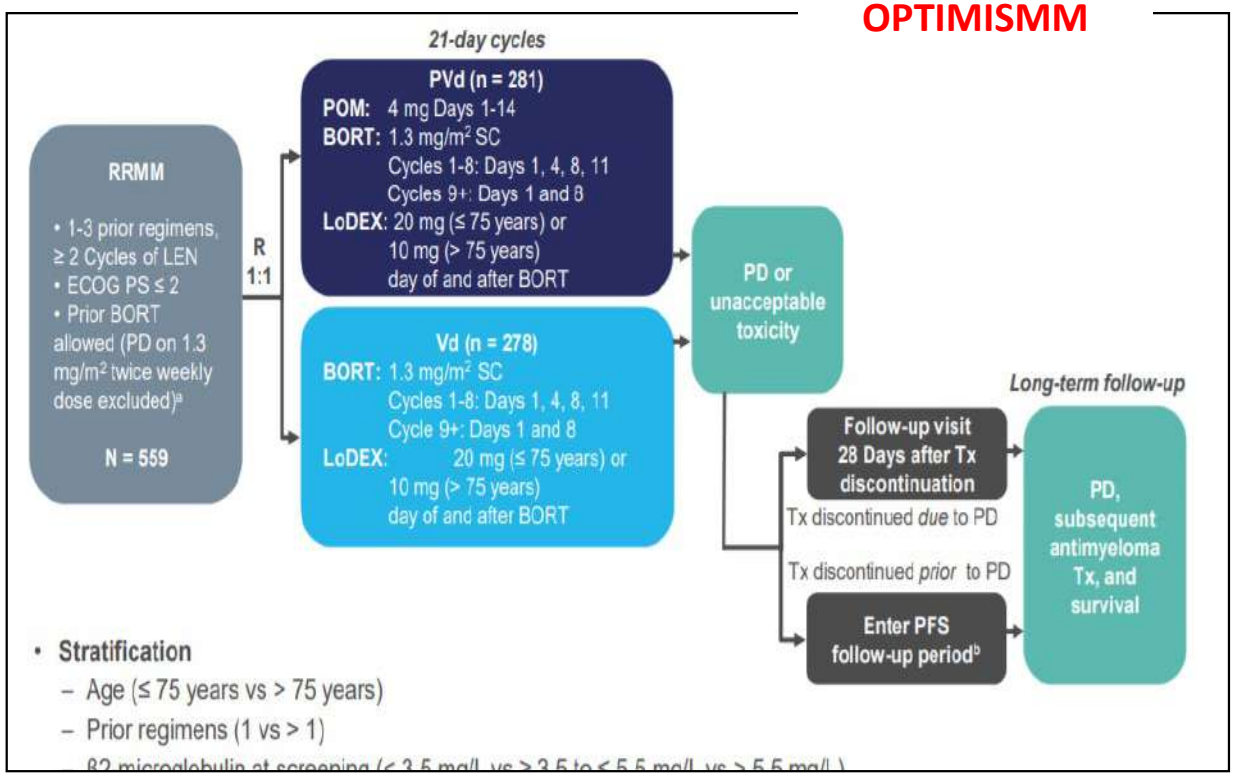
- The safety profile for PVd at first relapse in patients with RRMM is consistent with previous reports[6-8]
- Grade 3/4 TEAEs of neutropenia, peripheral neuropathy, and infections and infestations were more frequent with PVd vs Vd
  - Exposure-adjusted incidence rates were higher per 100 PYs in the PVd group than the Vd group
- Treatment durations were longer for patients who received PVd than Vd, and POM discontinuations were infrequent
- TEAE EOIs generally occurred in early cycles of treatment and were managed with dose modifications or appropriate supportive care
- The higher efficacy of PVd and consequent use of supportive strategies is recommended to minimize toxicity and maximize effect

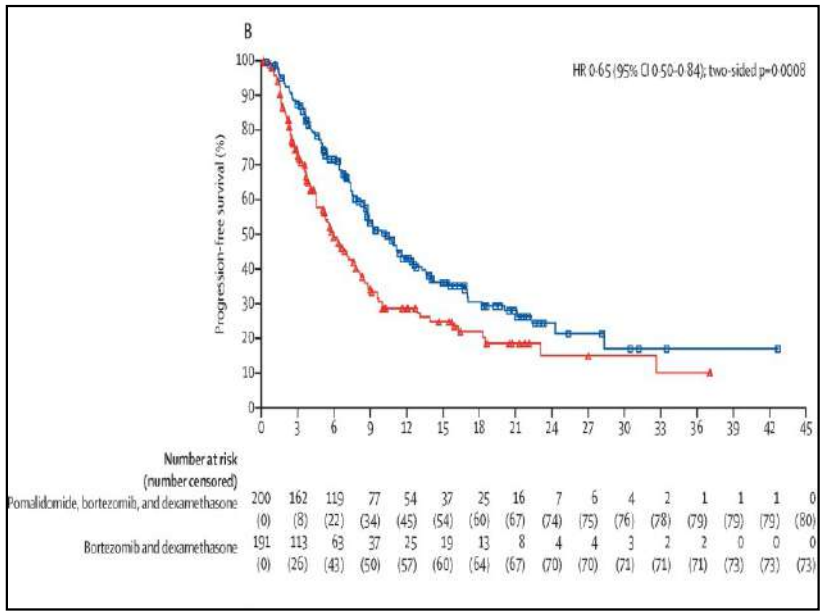
References

Acknowledgments

Disclosures

OPTIMISMM


21-day cycles
RRMM
• 1-3 prior regimens, ≥ 2 Cycles of LEN
• ECOG PS ≤ 2
• Prior BORT allowed (PD on 1.3 mg/m² twice weekly dose excluded)[a]
N = 559
R 1:1
PVd (n = 281)
POM: 4 mg Days 1-14
BORT: 1.3 mg/m² SC
Cycles 1-8: Days 1, 4, 8, 11
Cycles 9+: Days 1 and 8
LoDEX: 20 mg (≤ 75 years) or 10 mg (> 75 years) day of and after BORT
Vd (n = 278)
BORT: 1.3 mg/m² SC
Cycles 1-8: Days 1, 4, 8, 11
Cycle 9+: Days 1 and 8
LoDEX: 20 mg (≤ 75 years) or 10 mg (> 75 years) day of and after BORT
PD or unacceptable toxicity
Long-term follow-up
Follow-up visit 28 Days after Tx discontinuation
Tx discontinued due to PD
Tx discontinued prior to PD
Enter PFS follow-up period[b]
PD, subsequent antimyeloma Tx, and survival
• Stratification
– Age (≤ 75 years vs > 75 years)
– Prior regimens (1 vs > 1)
– β2 microglobulin at screening (< 3.5 mg/L vs ≥ 3.5 to ≤ 5.5 mg/L vs > 5.5 mg/L)


B
HR 0·65 (95% CI 0·50–0·84); two-sided p=0·0008
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45
Number at risk (number censored)
Pomalidomide, bortezomib, and dexamethasone 200 (0) 162 (8) 119 (22) 77 (34) 54 (45) 37 (54) 25 (60) 16 (67) 7 (74) 6 (75) 4 (76) 2 (78) 1 (79) 1 (79) 1 (79) 0 (80)
Bortezomib and dexamethasone 191 (0) 113 (26) 63 (43) 37 (50) 25 (57) 19 (60) 13 (64) 8 (67) 4 (70) 4 (70) 3 (71) 2 (71) 2 (71) 0 (73) 0 (73) 0 (73)

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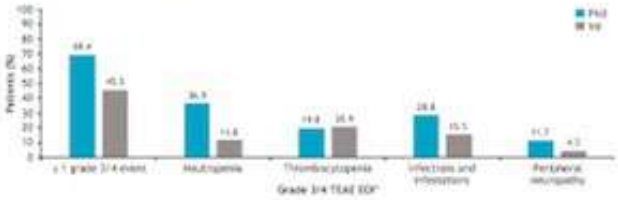

*Occurring in ≥ 10% of patients in either treatment arm.

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Peripheral neuropathy

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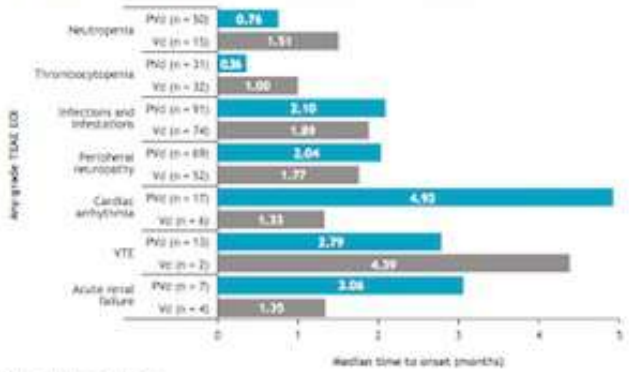

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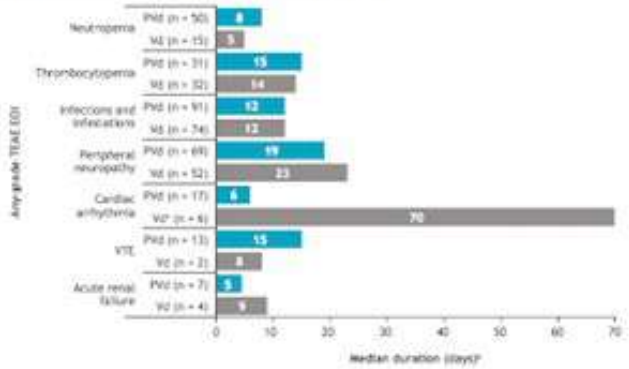
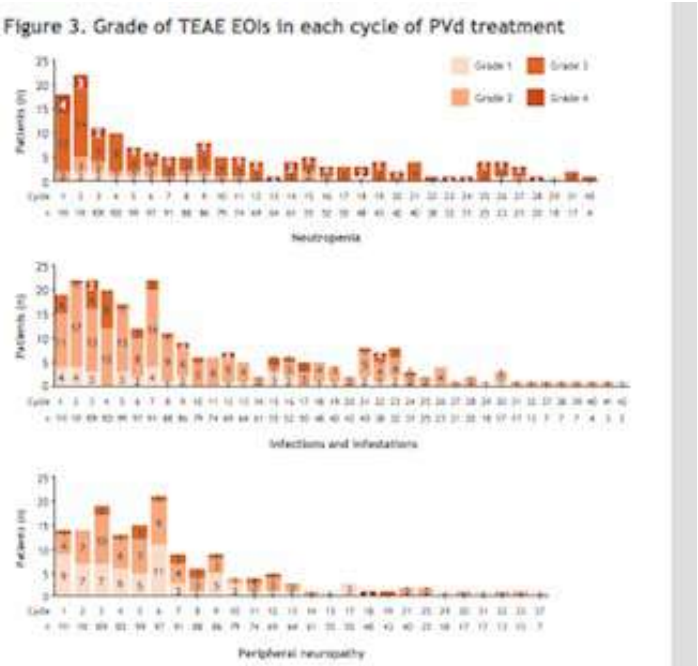


*Only 2 events, with values of 14 and 126 days; †Ongoing AEs were excluded from calculations.

Figure 3. Grade of TEAE EOIs in each cycle of PVd treatment



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Prophylaxis medication in patients with ≥ 1 DVT event (n = 4)[c] Acetylsalicylic acid Enoxaparin sodium Enoxaparin	3 (75.0) 1 (25.0) 1 (25.0)

[a]Acyclovir prophylaxis was not mandatory, but was recommended per protocol; [b]G-CSF prophylaxis was not mandatory, but recommended per protocol; [c]In the PVd arm (n = 111), 4 patients had a 1 DVT event (3.6%): 2 had prior DVT events

Conclusions

- The safety profile for PVd at first relapse in patients with RRMM is consistent with previous reports[1-8]
- Grade 3/4 TEAEs of neutropenia, peripheral neuropathy, and infections and infestations were more frequent with PVd vs Vd
  - Exposure-adjusted incidence rates were higher per 100 PYs in the PVd group than the Vd group
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References

1. Moreau P, et al. *Br J Haematol* 2017;179:198-218.
2. Dimopoulos M, et al. *Leukemia* 2020. doi: 10.1038/s41375-020-01021-3.
3. Quach H, et al. *Leukemia* 2010;24:22-32.
4. Richardson PG, et al. *Lancet Oncol* 2019;20:781-794.
5. European Medicines Agency. Innovid. https://www.ema.europa.eu/en/medicines/human/EPAR/innovidalauthorisation-details-section.
6. Moreau P, et al. *Lancet Oncol* 2011;12:431-440.
7. Miguel JS, et al. *Lancet Oncol* 2013;14:1055-1066.
8. Richardson PG,et al. *Leukemia* 2017;31:2695-2701.

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- All authors contributed to and approved the presentation
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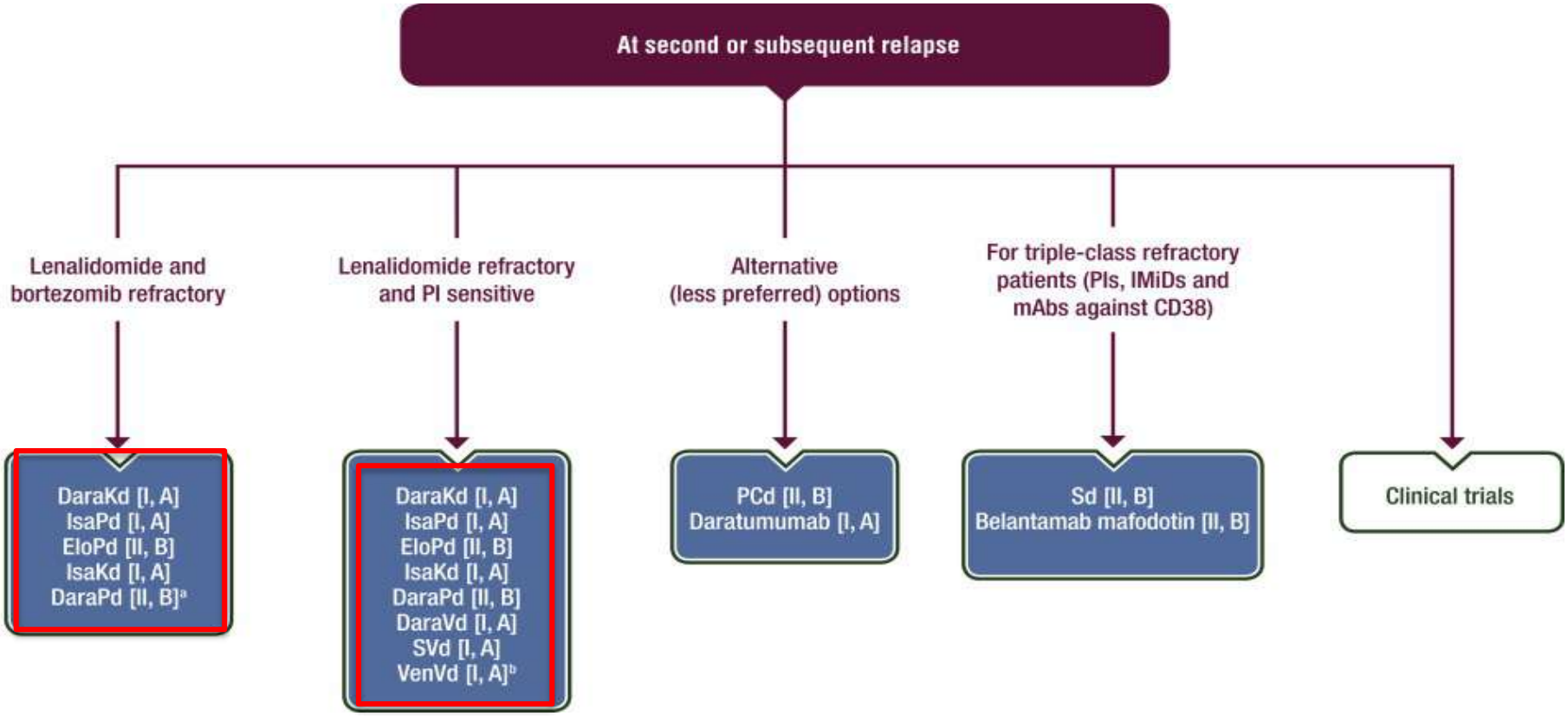
Disclosures

KW: honoraria from Amgen, Bristol-Myers Squibb, Janssen, and Takeda and consultancy for or serving on a board of directors or advisory committee for Amgen, Bristol-Myers Squibb, Janssen, Juno, Sanofi, and Takeda; MD: honoraria from Janssen, Takeda, Amgen, and Bristol-Myers Squibb; AO: advisory board fees from Bristol-Myers Squibb, Janssen, and Amgen; MB: advisory board fees from Janssen-Cilag, Amgen, Takeda, and Sanofi, and speaker bureau fees from Janssen-Cilag, Bristol-Myers Squibb, Takeda, and Amgen; FS: paid lecturer or advisory board fees from Amgen, Bristol-Myers Squibb, Takeda, AbbVie, Janssen, Bayer, and Adaptive Biotechnologies; AML: nothing to report; JL: commercial sponsorship and personal fees from Bristol-Myers Squibb and non-financial support from Bristol-Myers Squibb, Takeda, and Amgen; DW: honoraria from serving on a board of directors or advisory committee for Amgen, Bristol-Myers Squibb, Janssen, and Takeda; JSM: honoraria from Janssen, Bristol-Myers Squibb, Amgen, Novartis, Sanofi, and Roche; PM: honoraria from serving on a board of directors or advisory committee for Amgen, Bristol-Myers Squibb, Janssen, Takeda, and AbbVie; LDA,F: serving on a speakers bureau for Bristol-Myers Squibb, Amgen, and Takeda; AL: honoraria and personal fees from Amgen, honoraria, advisory board, and personal fees from Bristol-Myers Squibb, Janssen, and serving on advisory boards for Takeda; PR: research funding from Bristol-Myers Squibb; PV, RJ, and TP: employment with and equity ownership in Bristol-Myers Squibb; LG: employment with Bristol-Myers Squibb; PR: serving on a board of directors or advisory committee for Karyopharm, Oncopeptides, Bristol-Myers Squibb, Takeda, Amgen, and Jazz Pharmaceuticals.

Previously presented at the European Hematology Association (EHA) Virtual Meeting;



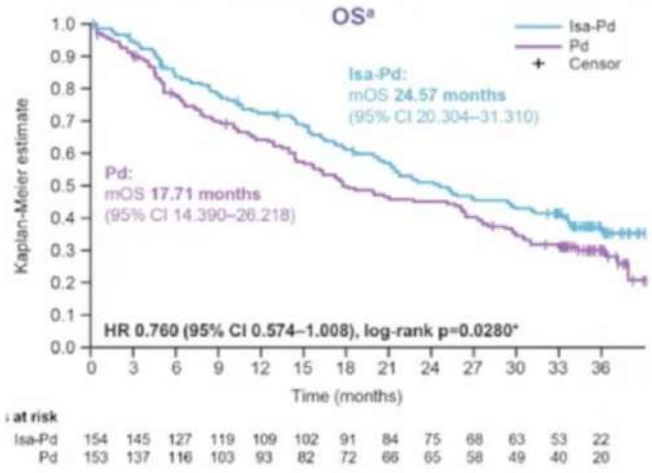
Moreau, Lancet Oncol 2021

Pomalidomide-based combinations approved for 3L + RRMM
Evidence and limitations

ICARIA: IsaPd vs Pd

ORR IsaPD vs Pd: 63% vs 33%. ≥ VGPR: 38.3% vs 10.5

With prolonged follow-up, Isa-Pd continues to improve PFS[a]:
mPFS 11.1 months vs 5.8 months with Pd alone (HR 0.599, p<0.0001)



Perrot A et al. EHA 2021. Oral presentation. Abstract #S186

ELOQUENT-2: EloPd vs Pd

ORR EloPd vs Pd: 53% vs 26%. ≥ VGPR: 20% vs 9%

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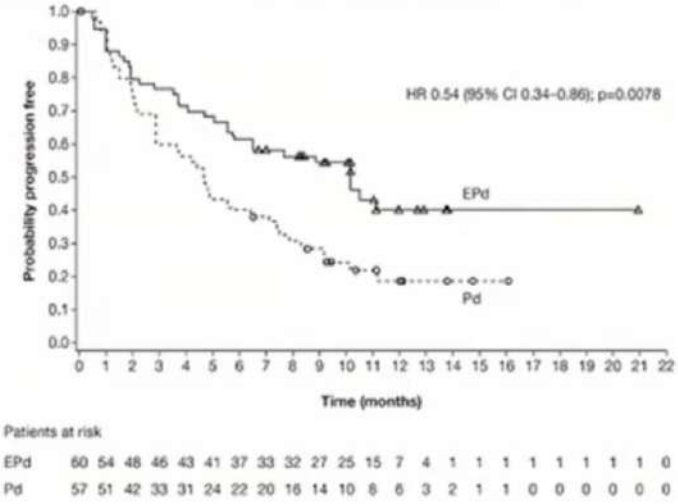
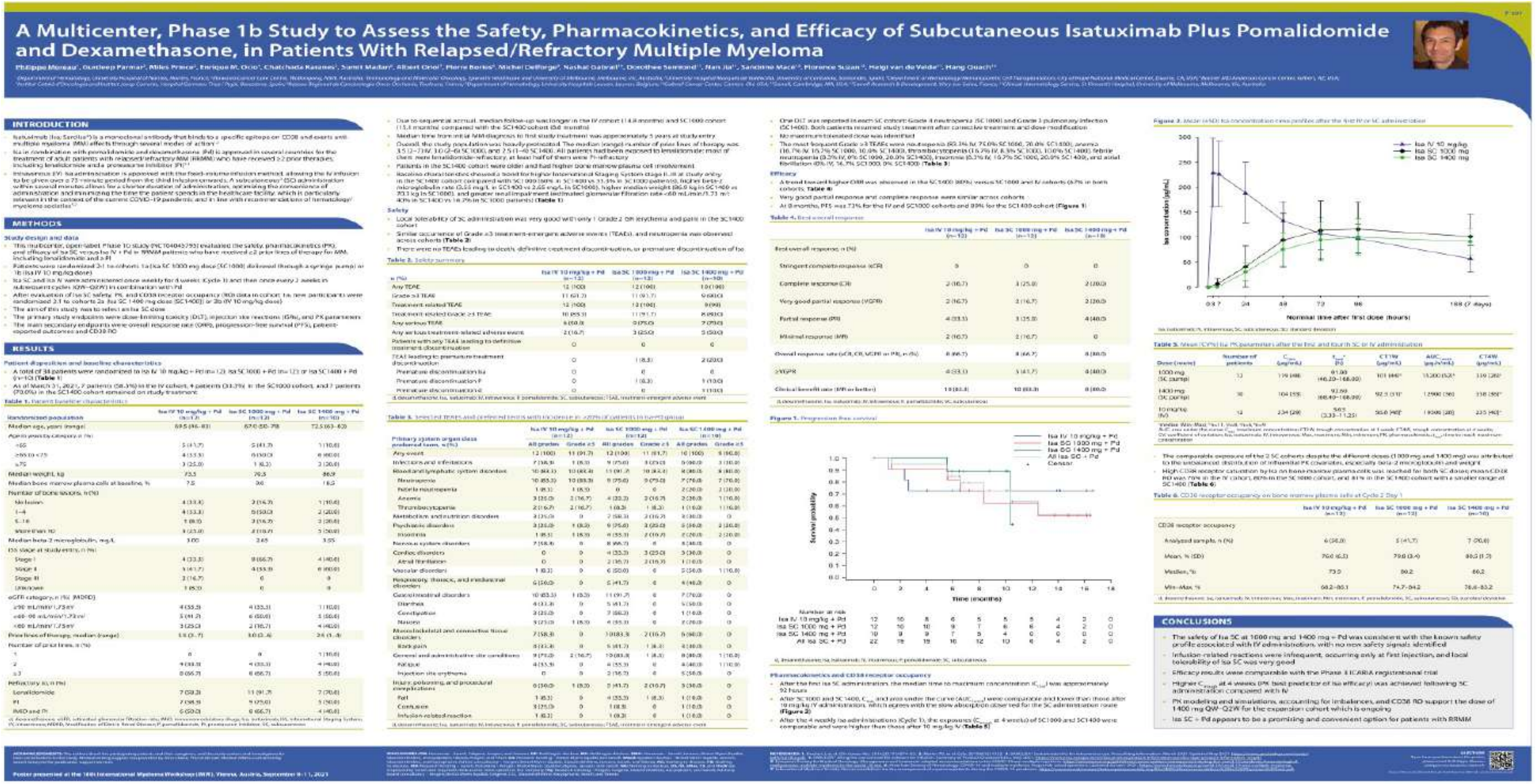


Dimopoulos MA et al. NEJM 2018


A Multicenter, Phase 1b Study to Assess the Safety, Pharmacokinetics, and Efficacy of Subcutaneous Isatuximab Plus Pomalidomide and Dexamethasone, in Patients With Relapsed/Refractory Multiple Myeloma
INTRODUCTION
METHODS
RESULTS
CONCLUSIONS

A Multicenter, Phase 1b Study to Assess the Safety, Pharmacokinetics, and Efficacy of Subcutaneous Isatuximab Plus Pomalidomide and Dexamethasone, in Patients With Relapsed/Refractory Multiple Myeloma

- Philippe Moreau[1], Gurdeep Parmar[2], Miles Prince[3], Enrique M. Ocio[4], Chatchada Karanes[5], Sumit Madan[6], Albert Oriol[7], Pierre Bories[8], Michel Delforge[9], Nashat Gabrail[10], Dorothee Semiond[11], Nan Jia[11], Sandrine Macé[12], Florence Suzan[12], Helgi van de Velde[11], Hang Quach[13]

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Study design and data

- This multicenter, open-label, Phase 1b study (NCT04045795) evaluated the safety, pharmacokinetics (PK), and efficacy of Isa SC versus Isa IV + Pd in RRMM patients who have received ≥2 prior lines of therapy for MM, including lenalidomide and a PI
- Patients were randomized 2:1 to cohorts 1a (Isa SC 1000 mg dose [SC1000] delivered through a syringe pump) or 1b (Isa IV 10 mg/kg dose)
- Isa SC and Isa IV were administered once weekly for 4 weeks (Cycle 1) and then once every 2 weeks in subsequent cycles (QW–Q2W) in combination with Pd
- After evaluation of Isa SC safety, PK, and CD38 receptor occupancy (RO) data in cohort 1a, new participants were randomized 2:1 to cohorts 2a (Isa SC 1400 mg dose [SC1400]) or 2b (IV 10 mg/kg dose)
- The aim of this study was to select an Isa SC dose
- The primary study endpoints were dose-limiting toxicity (DLT), injection site reactions (ISRs), and PK parameters
- The main secondary endpoints were overall response rate (ORR), progression-free survival (PFS), patient reported outcomes and CD38 RO

Patient disposition and baseline characteristics

- A total of 34 patients were randomized to Isa IV 10 mg/kg + Pd (n=12); Isa SC1000 + Pd (n=12); or Isa SC1400 + Pd (n=10) (**Table 1**)
- As of March 31, 2021, 7 patients (58.3%) in the IV cohort, 4 patients (33.3%) in the SC1000 cohort, and 7 patients (70.0%) in the SC1400 cohort remained on study treatment

Table 1. Patient baseline characteristics

Randomized population	Isa IV 10 mg/kg + Pd (n=12)	Isa SC 1000 mg + Pd (n=12)	Isa SC 1400 mg + Pd (n=10)
Median age, years (range)	69.5 (46–83)	67.0 (50–78)	72.5 (63–83)
Age in years by category, n (%)			
<65	5 (41.7)	5 (41.7)	1 (10.0)
≥65 to <75	4 (33.3)	6 (50.0)	6 (60.0)
≥75	3 (25.0)	1 (8.3)	3 (30.0)
Median weight, kg	73.5	70.3	86.9
Median bone marrow plasma cells at baseline, %	7.5	9.0	18.5
Number of bone lesions, n (%)			
No lesion	4 (33.3)	2 (16.7)	1 (10.0)
1–4	4 (33.3)	6 (50.0)	2 (20.0)
5–10	1 (8.3)	2 (16.7)	2 (20.0)
More than 10	3 (25.0)	2 (16.7)	5 (50.0)
Median beta-2 microglobulin, mg/L	3.00	2.65	3.55
ISS stage at study entry, n (%)			
Stage I	4 (33.3)	8 (66.7)	4 (40.0)
Stage II	5 (41.7)	4 (33.3)	6 (60.0)
Stage III	2 (16.7)	0	0
eGFR category, n (%) [MDRD]			
≥90 mL/min/1.73 m²	4 (33.3)	4 (33.3)	1 (10.0)
≤60–90 mL/min/1.73 m²	5 (41.7)	6 (50.0)	5 (50.0)
<60 mL/min/1.73 m²	3 (25.0)	2 (16.7)	4 (40.0)
Prior lines of therapy, median (range)	3.5 (2–7)	3.0 (2–6)	2.5 (1–4)
Number of prior lines, n (%)			
1	0	0	1 (10.0)
2	4 (33.3)	4 (33.3)	4 (40.0)
≥3	8 (66.7)	8 (66.7)	5 (50.0)
Refractory to, n (%)			
Lenalidomide	7 (58.3)	11 (91.7)	7 (70.0)
PI	7 (58.3)	9 (75.0)	5 (50.0)
IMID and PI	6 (50.0)	8 (66.7)	4 (40.0)

d, dexamethasone; eGFR, estimated glomerular filtration rate; IMiD, immunomodulatory drugs; Isa, isatuximab; ISS, International Staging System; IV, intravenous; MDRD, Modification of Diet in Renal Disease; P, pomalidomide; PI, proteasome inhibitor; SC, subcutaneous

Efficacy

- A trend toward higher ORR was observed in the SC1400 (80%) versus SC1000 and IV cohorts (67% in both cohorts; **Table 4**)
- Very good partial response and complete response were similar across cohorts

Table 4. Best overall response

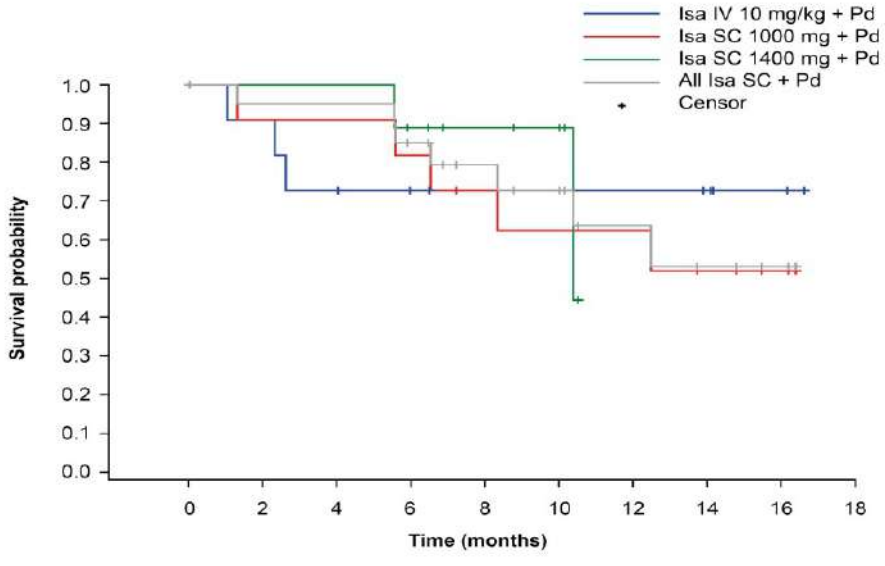
	Isa IV 10 mg/kg + Pd (n=12)	Isa SC 1000 mg + Pd (n=12)	Isa SC 1400 mg + Pd (n=10)
Best overall response, n (%)			
Stringent complete response (sCR)	0	0	0
Complete response (CR)	2 (16.7)	3 (25.0)	2 (20.0)
Very good partial response (VGPR)	2 (16.7)	2 (16.7)	2 (20.0)
Partial response (PR)	4 (33.3)	3 (25.0)	4 (40.0)
Minimal response (MR)	2 (16.7)	2 (16.7)	0
Overall response rate (sCR, CR, VGPR or PR), n (%)	8 (66.7)	8 (66.7)	8 (80.0)
≥VGPR	4 (33.3)	5 (41.7)	4 (40.0)
Clinical benefit rate (MR or better)	10 (83.3)	10 (83.3)	8 (80.0)

d, dexamethasone; Isa, isatuximab; IV, intravenous; P, pomalidomide; SC, subcutaneous

Efficacy (contd.)

- At 8 months, PFS was 73% for the IV and SC1000 cohorts and 89% for the SC1400 cohort (**Figure 1**)

Figure 1. Progression-free survival



Number at risk										
Isa IV 10 mg/kg + Pd	12	10	8	6	5	5	5	4	2	0
Isa SC 1000 mg + Pd	12	10	10	9	7	6	6	4	2	0
Isa SC 1400 mg + Pd	10	9	9	7	5	4	0	0	0	0
All Isa SC + Pd	22	19	19	16	12	10	6	4	2	0

d, dexamethasone; Isa, isatuximab; IV, intravenous; P, pomalidomide; SC, subcutaneous

CONCLUSIONS

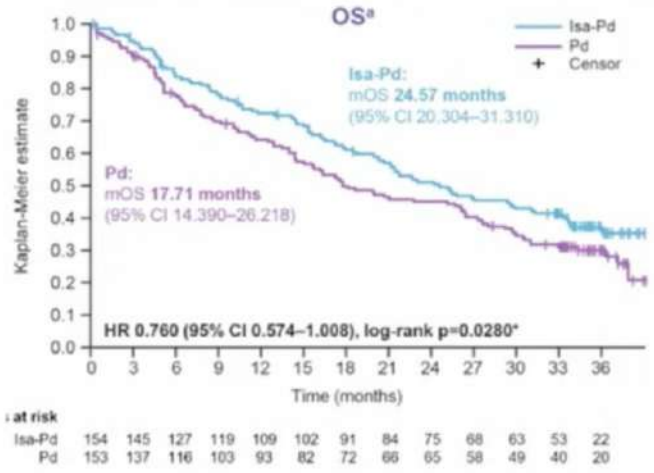
- The safety of Isa SC at 1000 mg and 1400 mg + Pd was consistent with the known safety profile associated with IV administration, with no new safety signals identified
- Infusion-related reactions were infrequent, occurring only at first injection, and local tolerability of Isa SC was very good
- Efficacy results were comparable with the Phase 3 ICARIA registrational trial
- Higher C_{trough} at 4 weeks (PK best predictor of Isa efficacy) was achieved following SC administration compared with IV
- PK modeling and simulations, accounting for imbalances, and CD38 RO support the dose of 1400 mg QW–Q2W for the expansion cohort which is ongoing
- Isa SC + Pd appears to be a promising and convenient option for patients with RRMM

Pomalidomide-based combinations approved for 3L + RRMM
Evidence and limitations

ICARIA: IsaPd vs Pd

ORR IsaPD vs Pd: 63% vs 33%. ≥ VGPR: 38.3% vs 10.5

With prolonged follow-up, Isa-Pd continues to improve PFS[a]:
mPFS 11.1 months vs 5.8 months with Pd alone (HR 0.599, p<0.0001)



Perrot A et al. EHA 2021. Oral presentation. Abstract #S186

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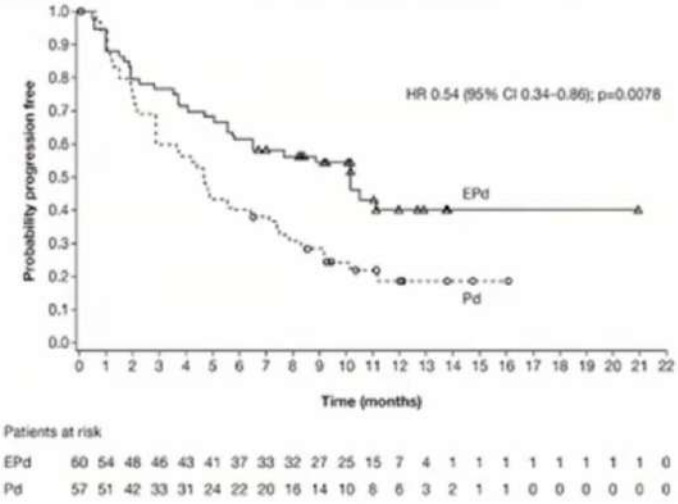

Dimopoulos MA et al. NEJM 2018

Elotuzumab plus pomalidomide/dexamethasone for relapsed/refractory multiple myeloma: final overall survival from the phase 2 ELOQUENT-3 trial

Meletios A Dimopoulos,[1] Dominik Dytfeld,[2] Sebastian Grosicki,[3] Philippe Moreau,[4] Naoki Takezako,[5] Mitsuo Hori,[6] Xavier Leleu,[7] Richard LeBlanc,[8] Kenshi Suzuki,[9] Marc S Raab,[10] Paul G Richardson,[11] Mihaela Popa McKiver,[12] Ying-Ming Jou,[12] David Yao,[12] Prianka Das,[12] Jesús San-Miguel[13]

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Presentation P-193

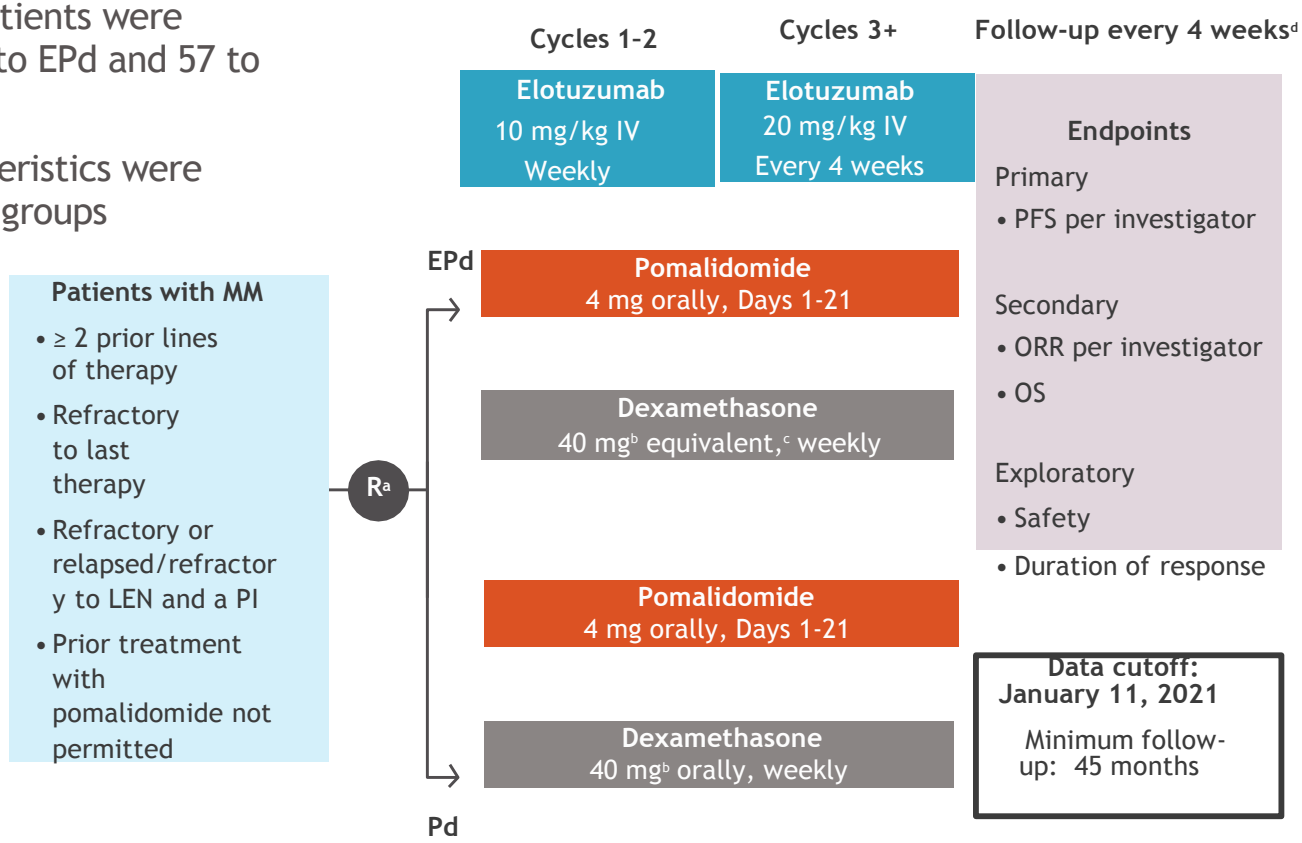
Introduction

- Therapies that extend overall survival (OS) are needed for patients with relapsed/refractory multiple myeloma (RRMM) and prior exposure to lenalidomide (LEN) and a proteasome inhibitor (PI)
- Elotuzumab, an immunostimulatory monoclonal antibody that targets SLAMF7, exerts multiple mechanisms of action to enable selective killing of myeloma cells[1-3]
- Pomalidomide, like LEN, is an immunomodulatory agent that has tumoricidal and immune- enhancing effects[4] and activity in LEN-refractory disease[5,6]
- In the randomized phase 2 ELOQUENT-3 trial, elotuzumab plus pomalidomide/dexamethasone (EPd) significantly improved progression-free survival (PFS) versus Pd in patients with RRMM and ≥ 2 prior therapies including LEN and a PI (median 10.3 months vs 4.7 months; HR 0.54 [95% CI, 0.34–0.86]; *P* = 0.008)[7]
  - Regulatory approval was granted in regions including the USA, EU, and Japan[8,9]
- Preliminary analysis of OS from ELOQUENT-3 (minimum follow-up of 9.1 months) showed a trend favoring EPd over Pd[7] which was maintained in a subsequent unplanned interim analysis (minimum follow-up of 18.3 months)[10]

Figure 1. ELOQUENT-3 study design (NCT02654132)

Patients and treatment disposition

- A total of 117 patients were randomized, 60 to EPd and 57 to Pd
- Baseline characteristics were similar between groups

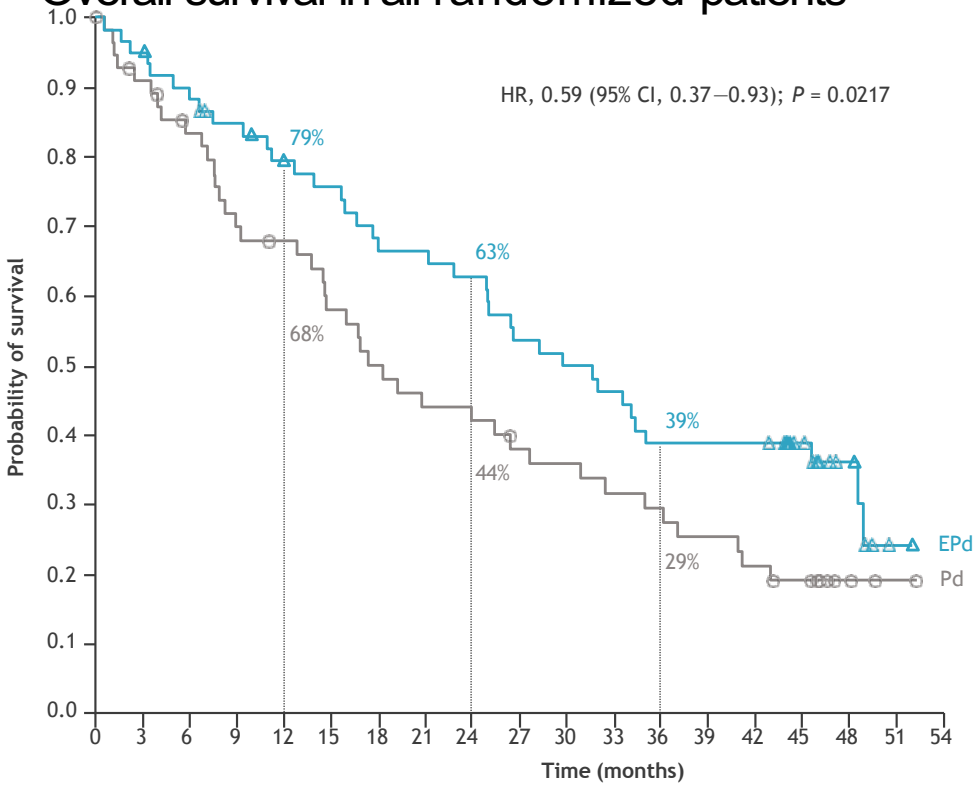


[a]Randomization was stratified by prior lines of therapy (2–3 vs ≥ 4) and ISS stage at time of enrollment (I-II vs III); [b]20 mg in patients aged > 75 years; [c]Dexamethasone was split between oral (28 or 8 mg in patients aged ≤ 75 or > 75 years) and IV (8 mg) doses on days with elotuzumab; [d]Follow-up continued until disease progression; follow-up for survival occurred at least every 12 weeks.
ISS, International Staging System; ORR, overall response rate.

Efficacy

- At final analysis, there were 37 (61.7%) deaths in the EPd group and 41 (74.5%) in the Pd group
  - The most common cause of death in both groups was disease progression (EPd 41.7%, Pd 49.1%)
- OS was significantly improved with EPd versus Pd: median OS was 29.8 months (95% CI, 22.9– 45.7) versus 17.4 months (95% CI, 13.8–27.7), respectively, with a HR of 0.59 (95% CI, 0.37–0.93; 2-sided stratified log-rank *P* = 0.0217)
- OS rates were consistently higher with EPd than Pd at 1 year (79% vs 68%), 2 years (63% vs 44%), and 3 years (39% vs 29%)
- The OS benefit observed with EPd was maintained across most subgroups, although sample sizes were small
  - These included patients aged ≥ 75 years, patients with ≥ 4 prior lines of therapy, patients with disease refractory to LEN and a PI, and patients who had received LEN as their most recent prior therapy

Overall survival in all randomized patients



No. at risk

EPd	60	57	53	48	43	41	37	36	34	29	27	25	21	21	21	15	7	1	0
Pd	57	49	43	36	34	29	25	22	22	18	17	15	14	12	10	8	3	1	0

conclusions

- In this final analysis of OS from ELOQUENT-3, EPd demonstrated a statistically significant and clinically meaningful improvement in OS versus Pd in patients with RRMM and ≥ 2 prior therapies including LEN and a PI
  - 41% reduction in the risk of death
  - 1-year increase in median OS
- Subsequent therapies were balanced between treatment groups, suggesting that the effect on OS was primarily due to EPd
- OS benefit was consistent in key patient subgroups, including patients who had received LEN as their most recent prior therapy
- The safety profile of EPd was consistent with previous reports and no new safety signals were detected[7,10]
- ELOQUENT-3 is the first randomized controlled study of a triplet regimen incorporating a monoclonal antibody and Pd in RRMM to show both significant PFS and OS benefits

SELECT Trial in Progress

Study Design

- The SELECT study is an open-label phase 2 study ongoing at ~ 40 sites in the EU and US, with expansion to more countries planned
- This study will evaluate the novel primary endpoint of MRD-negative CR to assess the efficacy of KPd in patients with one or two relapses of MM

N ~ 85[a]

Key inclusion criteria:

- RRMM
- One or two prior lines of therapy
- Refractory to lenalidomide
- ≥ PR to lenalidomide
- Prior exposure to a PI or anti-CD38 antibody is allowed

Treatment Until Disease Progression

KPd
Carfilzomib[b] (20/56 mg/m^2) + pomalidomide[c] + dexamethasone[d]

Primary endpoint: MRD-negative CR in the bone marrow at 12 months by NGS (sensitivity of 10^{-5})
Secondary endpoints: ORR, best MRD-negative response at any time, sustained MRD-negative CR, DoR, TTR, PFS, OS, and safety

[a]Twenty-six patients are currently enrolled; the target for enrollment completion is January 2022. [b]IV on days 1, 8, and 15 of each 28-day cycle for cycles 1–12 and on days 1 and 15 from cycle 13 until progression or end of study (20 mg/m^2 on day 1 of cycle 1 and 56 mg/m^2 thereafter). [c]PO 4 mg on days 1–21 of all cycles. [d]PO or IV 40 mg prior to carfilzomib on days 1, 8, 15, and 22 of cycles 1–12 (20 mg for patients ≥ 75 years old) and 20 mg on days 1 and 15 of cycle 13 onwards (10 mg for patients ≥ 75 years old).
CD38, cluster of differentiation 38; CR, complete response; DoR, duration of response; EU, European Union; IV, intravenous; KPd, carfilzomib, pomalidomide, and dexamethasone; MM, multiple myeloma; MRD, minimum residual disease; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PO, per oral; PR, partial response; RRMM, relapsed/refractory multiple myeloma; TTR, time to response; US, United States.
Moreau P, et al. Presented at: 18th IMW; September 8-11, 2021; Vienna, Austria. Abstract P-206.