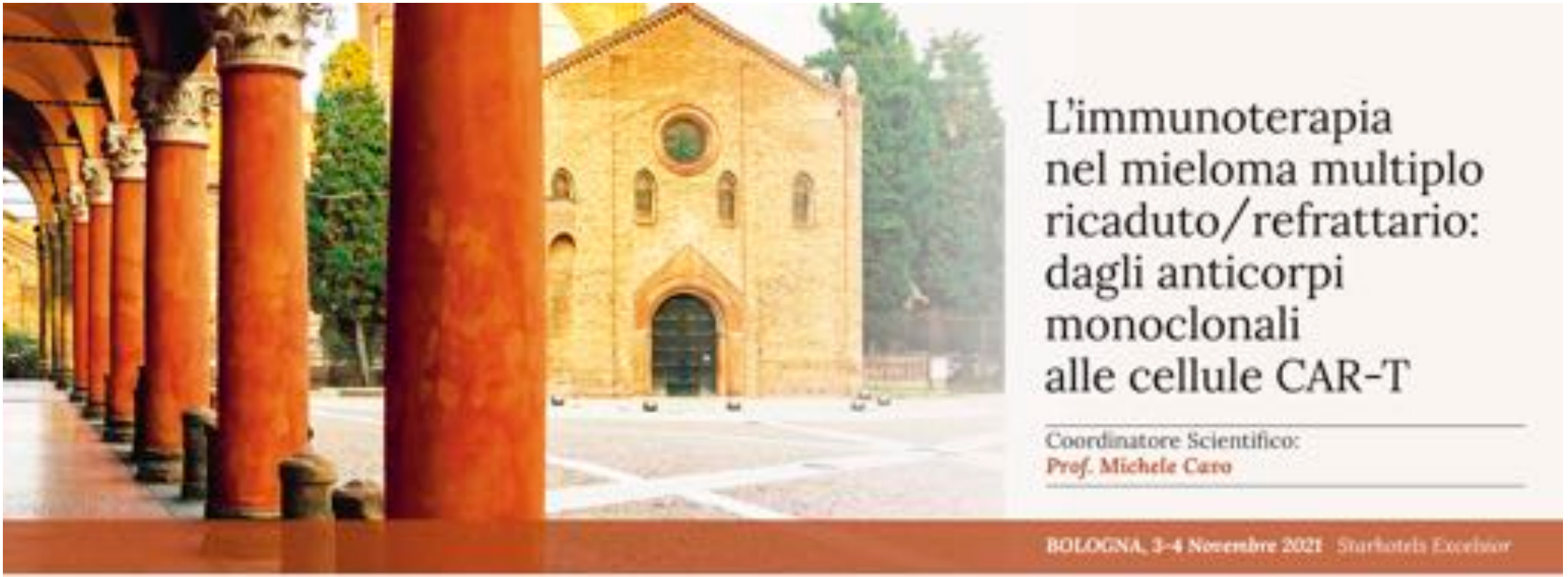
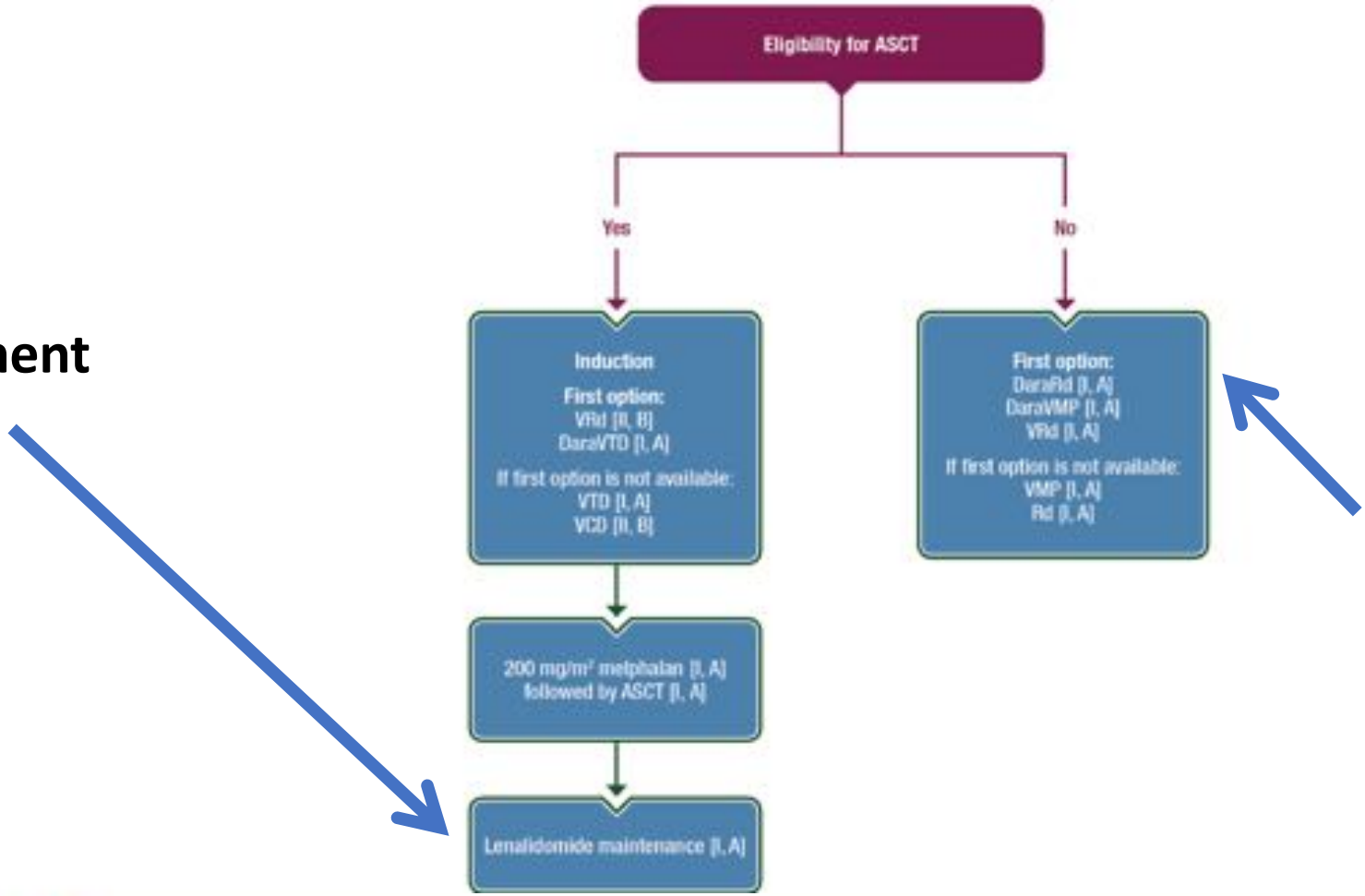


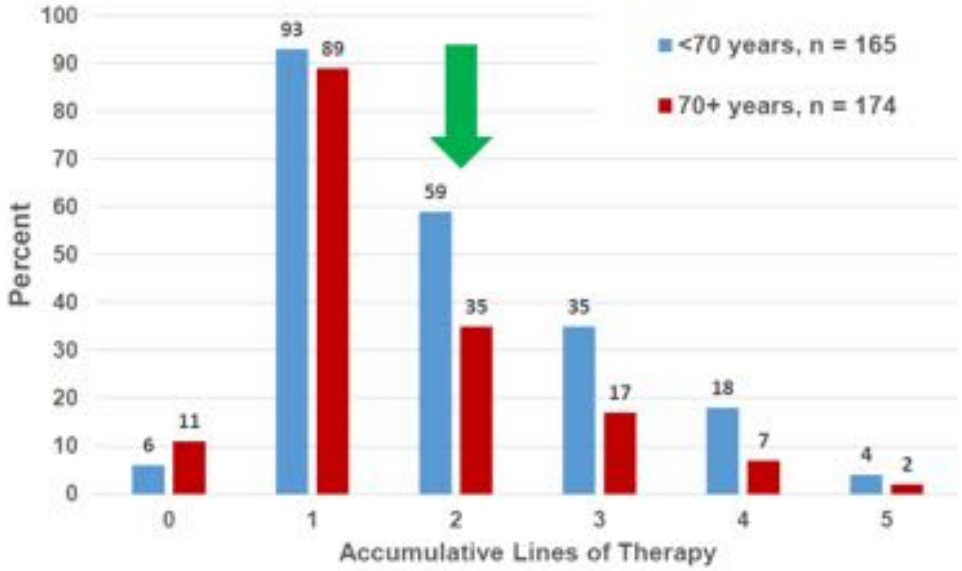
La refrattarietà agli IMIDS: criteri di definizione e fattori predittivi di risposta alla terapia

Patrizia Tosi
UO Ematologia Rimini

2021
first-line treatment



Accumulative Lines of Therapy Received by Age at Diagnosis : Best Therapy Should Be Used Upfront in Elderly Patients



Courtesy of A Spencer

Exposed:
Treatment interrupted while still responding

Refractory:
Relapse while on treatment or progression within 60 days of stopping treatment
Not achieving at least a PR

Phase 1/2 study of lenalidomide combined with low-dose cyclophosphamide and prednisone in lenalidomide-refractory multiple myeloma

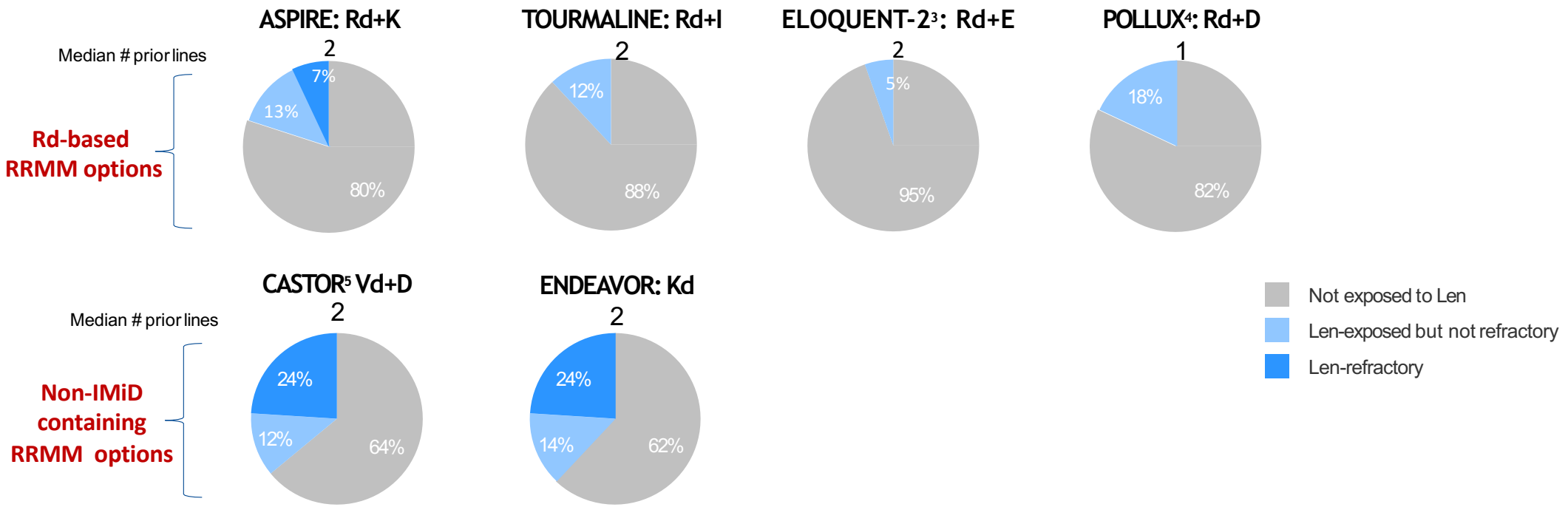
Inger S. Nijhof,[1,2] Laurens E. Franssen,[1,2] Mark-David Levin,[3] Gerard M. J. Bos,[4] Annemiek Broijl,[5] Saskia K. Klein,[6] Harry R. Koene,[7] Andries C. Bloem,[8] Aart Beeker,[9] Laura M. Faber,[10] Ellen van der Spek,[11] Paula F. Ypma,[12] Reinier Raymakers,[2] Dick-Johan van Spronsen,[13] Peter E. Westerweel,[3] Rimke Oostvogels,[2] Jeroen van Velzen,[8] Berris van Kessel,[1] Tuna Mutis,[1] Pieter Sonneveld,[5] Sonja Zweegman,[1] Henk M. Lokhorst,[1] and Niels W. C. J. van de Donk[1]

	All patients (all len-refractory), n = 66, %	Len- and bor-refractory patients, n = 42, %	Patients with high-risk cytogenetic abnormalities,* n = 24, %	Patients treated with REP, directly following development of len-refractory disease (25 mg len or equivalent in case of renal insufficiency), n = 46, %
sCR	1.5	0	0	0
CR	3.0	2.4	0	0
VGPR	18.2	21.4	20.8	15.2
PR	44.0	36.1	45.9	50.0
MR	16.6	21.1	16.6	17.4
SD	7.6	9.5	4.2	10.9
PD	9.1	9.5	12.5	6.5
≥VGPR	22.7	23.8	20.8	15.2
≥PR	66.7	59.9	66.7	65.2
≥MR	83.3	81.0	83.3	82.6

Blood 2016

Len exposed/refractory patients in clinical trials

% Len-exposed, Len-refractory and non-Len exposed patients in early-RRMM* combination trials

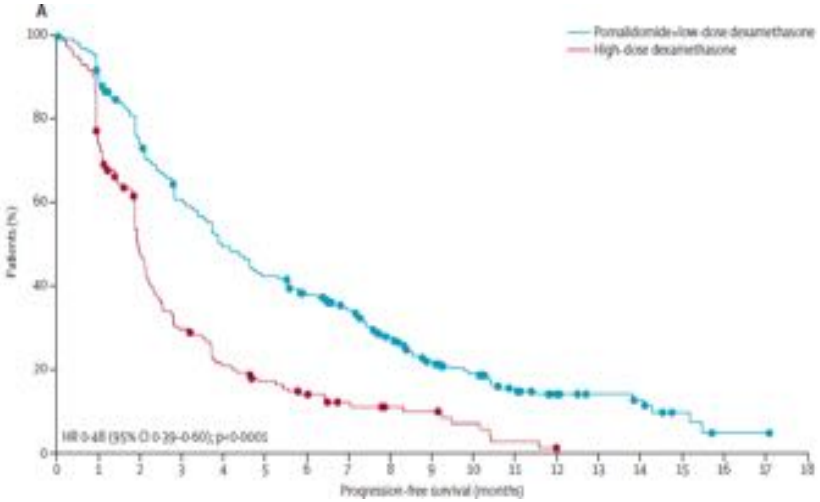


Len exposed/refractory patients in clinical trials

Trial	Control	Intervention	Total Patients		Median Age (range)		Median Prior Regimens (range)		Len Refractory		PI Refractory		Previous Stem Cell Transplant		High Risk Cytogenetics[a]	
			Cont.	Int.	Cont.	Int.	Cont.	Int.	Cont.	Int.	Cont.	Int.	Cont.	Int.	Cont.	Int.
MM-003	Dex (HD)	Pom/Dex	153	302	65 (35-87)	64 (35-84)	5 (2-17)	5 (2-14)	286 (95%)	141 (92%)	121 (79%)	238 (79%)	105 (69%)	214 (71%)	–	–
ICARIA	Pom/Dex	Isa/Pom/Dex	153	154	[b]66 (39-77)	[b]68 (60-74)	[b]3 (2-4)	[b]3 (2-4)	144 (94%)	140 (92%)	115 (75%)	116 (77%)	90 (59%)	83 (54%)	36 (24%)	24 (16%)
OPTIMISMM	Bor/Dex	Pom/Bor/Dex	278	281	[b]68 (59-73)	[b]67 (60-73)	[b]2 (1-3)	[b]2 (1-3)	191 (69%)	200 (71%)	37 (13%)	37 (13%)	163 (59%)	161 (57%)	49 (18%)	61 (22%)
ENDEAVOR	Bor/Dex	Car/Dex	465	464	65 (30-88)	65 (35-89)	2 (1-3)	2 (1-3)	122 (26%)	113 (24%)	[b]252 (54%)	[b]250 (54%)	[b]272 (58%)	[b]268 (57%)	113 (24%)	97 (21%)
CASTOR	Bor/Dex	Dara/Bor/Dex	247	251	64 (33-85)	64 (30-88)	2 (1-10)	2 (1-8)	60 (24%)	45 (18%)	[b]172 (70%)	[b]169 (67%)	149 (60%)	157 (63%)	51 (21%)	44 (18%)
ELOQUENT-1	Pom/Dex	Elo/Pom/Dex	57	60	66 (36-81)	69 (43-81)	3 (2-8)	3 (2-8)	48 (84%)	54 (90%)	47 (82%)	47 (78%)	[b]33 (58%)	[b]31 (52%)	14 (25%)	13 (22%)
CANDOR	Car/Dex	Dara/Car/Dex	154	312	[b]65 (59-71)	[b]64 (57-70)	[b]2 (1-3)	[b]2 (1-3)	55 (36%)	99 (32%)	55 (36%)	100 (32%)	75 (49%)	135 (62%)	26 (17%)	46 (15%)

Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial

Jesus San Miguel, Katja Weisel, Philippe Moreau, Martha Lacy, Kevin Song, Michel Delforge, Lionel Karlin, Hartmut Goldschmidt, Anne Banos, Albert Oriol, Adrian Alegre, Christine Chen, Michele Cavo, Laurent Garderet, Valentina Ivanova, Joaquin Martinez-Lopez, Andrew Belch, Antonio Palumbo, Stephen Schey, Pieter Sonneveld, Xin Yu, Lars Sternas, Christian Jacques, Mohamed Zaki, Meletios Dimopoulos



Patients with an overall response

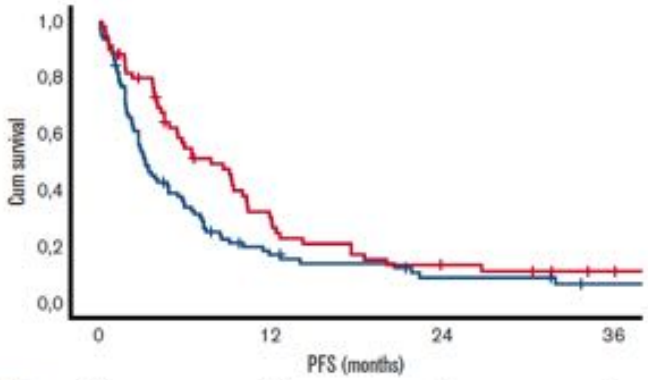
	Pomalidomide plus low-dose dexamethasone	High-dose dexamethasone
Refractory to lenalidomide	85/286 (30%)	13/141 (9%)
Intolerant to bortezomib	14/45 (31%)	3/23 (13%)
Refractory to both bortezomib and lenalidomide	64/225 (28%)	13/113 (12%)
Lenalidomide as last previous treatment	28/85 (33%)	3/49 (6%)
Bortezomib as last previous treatment	45/132 (34%)	8/66 (12%)

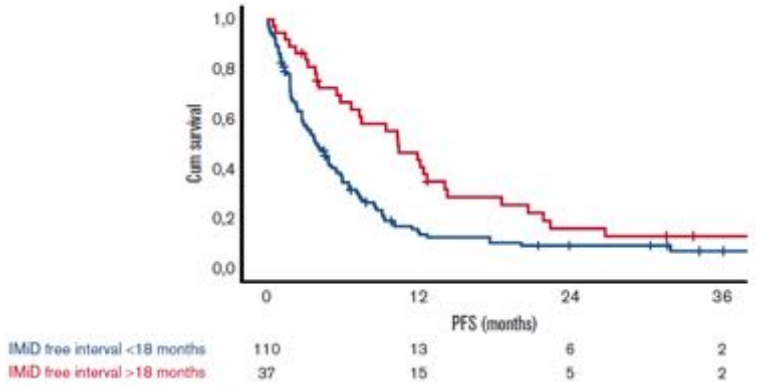
Data are n/N (%).

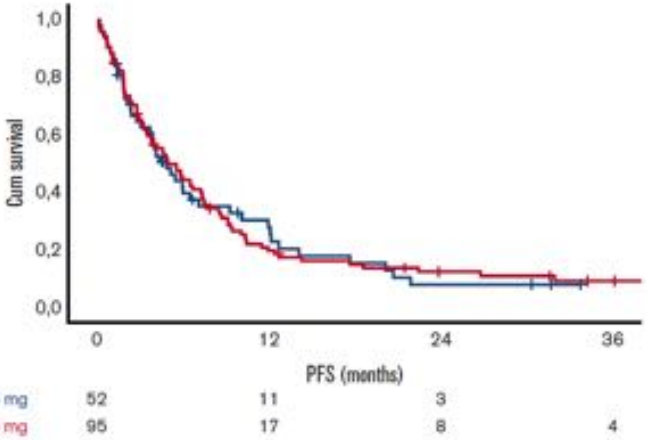
Lancet Oncol. 2013

Impact of last lenalidomide dose, duration, and IMiD-free interval in patients with myeloma treated with pomalidomide/dexamethasone

Efstathios Kastritis,[1] Maria Roussou,[1] Maria Gavriatopoulou,[1] Nikolaos Kanellias,[1] Magdalini Migkou,[1] Evangelos Eleutherakis-Papaiakovou,[1] Dimitrios C. Ziogas,[1] Despina Fotiou,[1] Ioannis Ntanasis-Stathopoulos,[1] Ioanna Dialoupi,[1] Stavroula Giannouli,[2] Panagiotis Tsirigotis,[3] Sossana Delimpasi,[4] Despina Mparmparousi,[5] Mairylin Spyropoulou-Vlachou,[6] Aikaterini Xirokosta,[5] Evangelos Terpos,[1] and Meletios A. Dimopoulos[1]







Blood Adv 2019

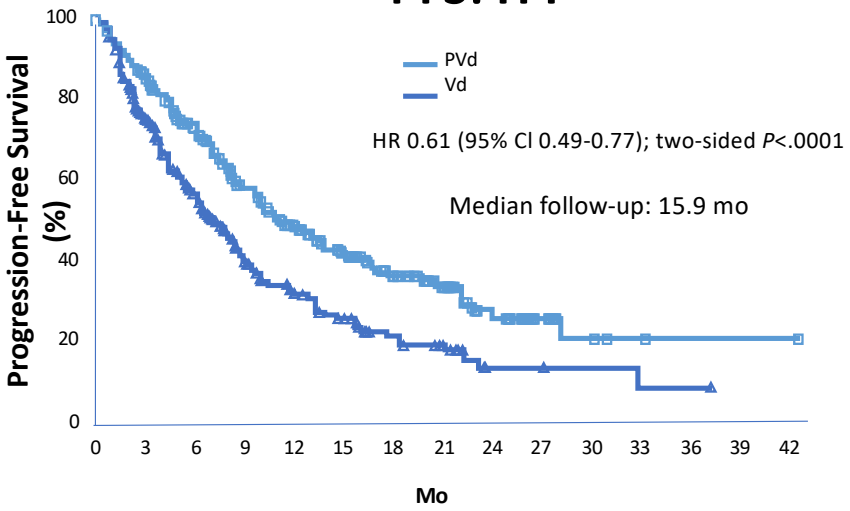
Phase III OPTIMISMM: Pom + Vd vs Vd in R/R MM

R/R MM patients previously treated with 1-3 lines of Tx, including ≥2 cycles Len (N = 559)

- **Pomalidomide + Bortezomib + Dexamethasone (PVd)** (n = 281)
- **Bortezomib + Dexamethasone (Vd)** (n = 278)

Dosing (21-day cycles): Pom: 4 mg/day PO for 14 days; V: 1.3 mg/m^2 Days 1, 4, 8, 11 of C1-8, then days 1 and 8; d: 20 mg PO (10 mg if ≥75 yr of age) on days of and after V.

PFS: ITT



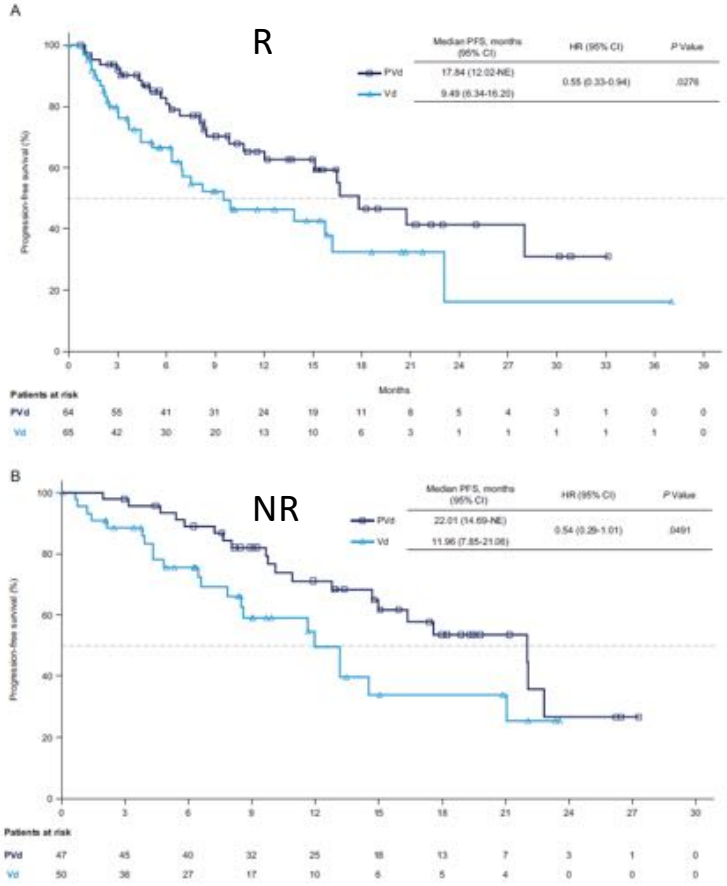
- ORR: 82.2% with PVd vs 50.0% with Vd
- ≥VGPR: 52.7% with PVd vs 18.3% with Vd

Richardson. Lancet Oncol. 2019

Pomalidomide, bortezomib, and dexamethasone for multiple myeloma previously treated with lenalidomide (OPTIMISMM): outcomes by prior treatment at first relapse

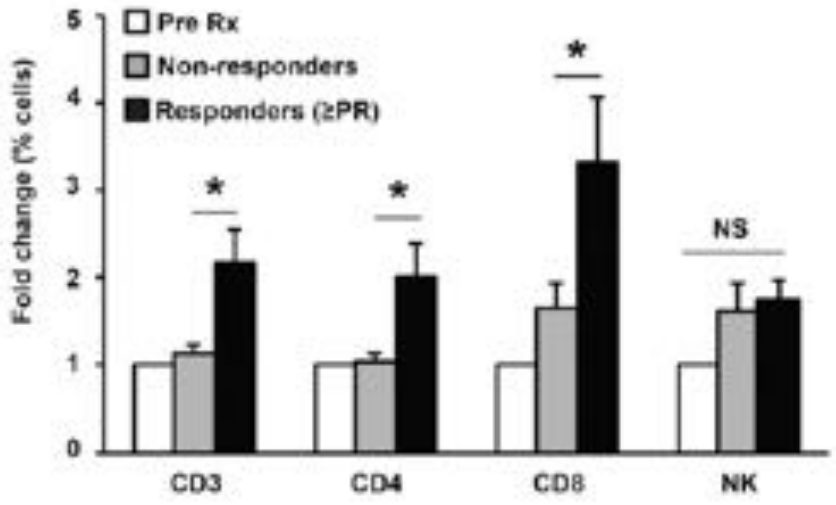
Meletios Dimopoulos[1] · Katja Weisel[2] · Philippe Moreau[3] · Larry D. Anderson Jr[4] · Darrell White[5] · Jesus San-Miguel[6] · Pieter Sonneveld[7] · Monika Engelhardt[8] · Matthew Jenner[9] · Alessandro Corso[10] · Jan Dürig[11] · Michel Pavic[12] · Morten Salomo[13] · Eva Casal[14] · Shankar Srinivasan[14] · Xin Yu[14] · Tuong Vi Nguyen[14] · Tsvetan Biyukov[15] · Teresa Peluso[15] · Paul Richardson[16]

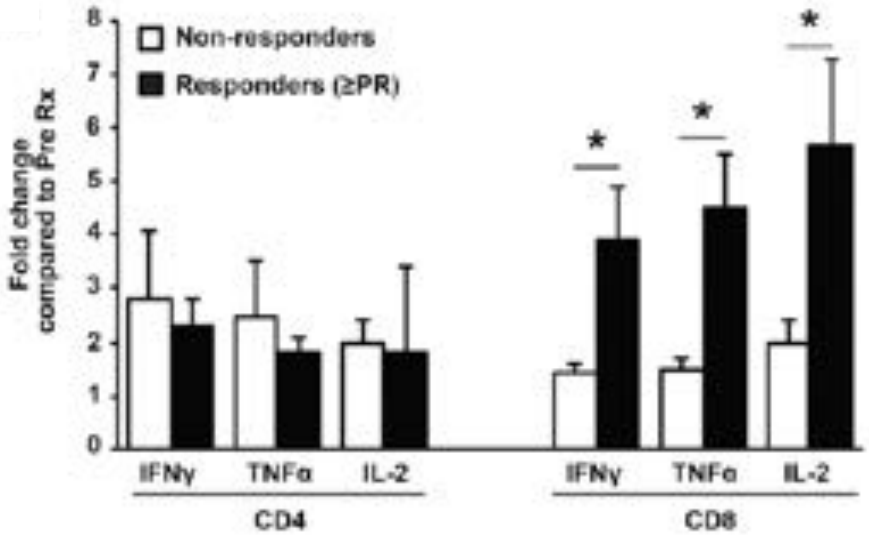
	Patients at first relapse[a]			
	LEN refractory		LEN nonrefractory	
Response rate, *n* (%)	PVd (*n* = 64)	Vd (*n* = 65)	PVd (*n* = 47)	Vd (*n* = 50)
Overall response rate	55 (85.9)	33 (50.8)	45 (95.7)	30 (60.0)
≥VGPR	36 (56.3)	≥15 (23.1)	32 (68.1)	11 (22.0)
sCR	2 (3.1)	2 (3.1)	4 (8.5)	0
CR	6 (9.4)	3 (4.6)	8 (17.0)	2 (4.0)
VGPR	28 (43.8)	10 (15.4)	20 (42.6)	9 (18.0)
PR	19 (29.7)	18 (27.7)	13 (27.7)	19 (38.0)
SD	8 (12.5)	28 (43.1)	2 (4.3)	12 (24.0)
PD	1 (1.6)	1 (1.5)	0	3 (6.0)
NE	0	3 (4.6)	0	5 (10.0)



Clinical and pharmacodynamic analysis of pomalidomide dosing strategies in myeloma: impact of immune activation and cereblon targets

Kartik Sehgal,[1] Rituparna Das,[1] Lin Zhang,[1] Rakesh Verma,[1] Yanhong Deng,[2] Mehmet Kocoglu,[1] Juan Vasquez,[3] Srinivas Koduru,[1] Yan Ren,[4] Maria Wang,[4] Suzana Couto,[4] Mike Breider,[4] Donna Hansel,[4] Stuart Seropian,[1,5] Dennis Cooper,[1,5] Anjan Thakurta,[4] Xiaopan Yao,[2,5] Kavita M. Dhodapkar,[3,5] and Madhav V. Dhodapkar[1,5,6]





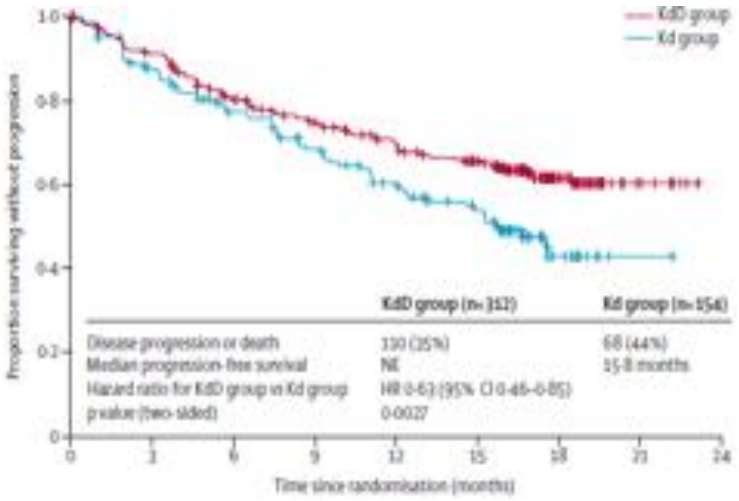
Blood 2015

Phase III CANDOR: PFS With Dara-Kd vs Kd in R/R MM

R/R MM pts treated with 1-3 prior Tx with ≥PR to ≥1 prior tx (N = 466)

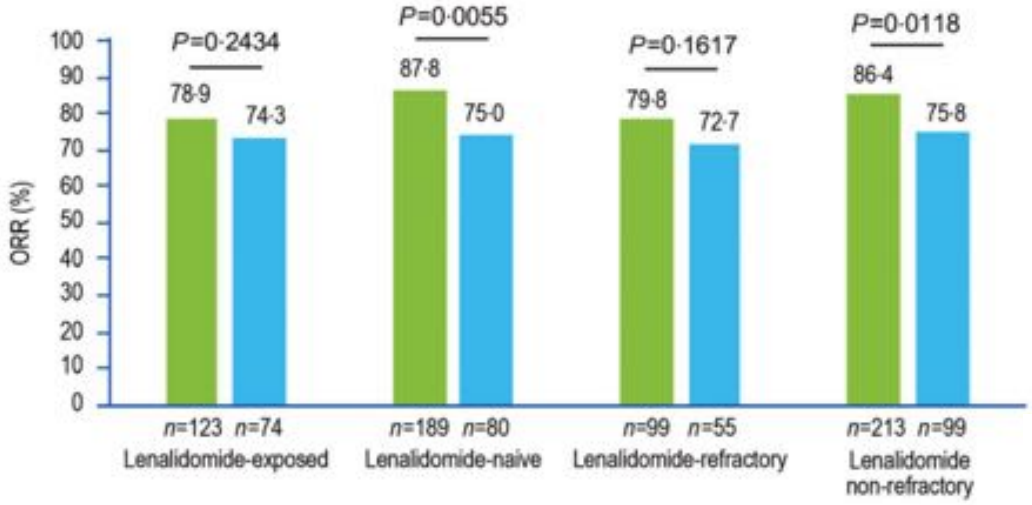
- **Daratumumab + Carfilzomib + Dexamethasone (Dara-Kd) (n = 312)**
- Carfilzomib + Dexamethasone (Kd) (n = 154)

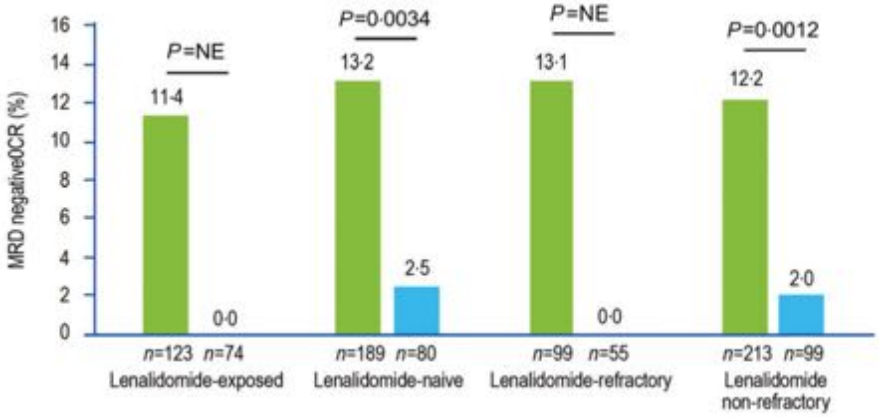
Response, %	DKd (n = 312)	Kd (n = 154)
ORR	84.3[a]	74.7
≥VGPR	69.2	48.7
≥CR	28.5	10.4
MRD negative at 12 mo (10^{-5} threshold)	17.6	3.9
MRD negative CR at 12 mo (10^{-5} threshold)	12.5[b]	1.3
Best MRD negative CR (10^{-5} threshold)	13.8	3.2



Dimopoulos.Lancet. 2020

Carfilzomib, dexamethasone and daratumumab in relapsed or refractory multiple myeloma: results of the phase III study CANDOR by prior lines of therapy





Quach Br J Haematol 2021

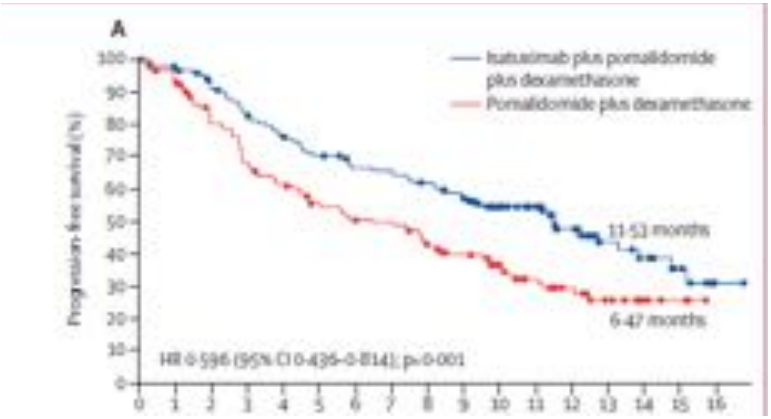
Phase III ICARIA-MM: PFS With Isa-Pd vs Pd in R/R MM

R/R MM patients previously treated
≥2 lines; PD on last line; no response to Len or PIs; pomalidomide naive, CD38 antibody naive/sensitive
(N = 307)

Isatuximab + Pomalidomide + Dexamethasone (Isa-Pd)
(n = 151)

Pomalidomide + Dexamethasone (Pd)
(n = 153)

Response	Pd	Isa-Pd
ORR, %	35	60
▪ sCR	<1	0
▪ CR	1	5
▪ VGPR	7	27
▪ PR	27	29
Median DoR, mo	11.1	13.3



Attal. Lancet. 2019.

Isatuximab for relapsed/refractory multiple myeloma: review of key subgroup analyses from the Phase III ICARIA-MM study

Paul G Richardson*[1], Simon J Harrison[2], Sara Bringhen[3], Fredrik Schjesvold[4,5], Kwee Yong[6], Frank Campana[1,7,10], Solenn Le-Guennec[8], Sandrine Macé[8] & Meletios A Dimopoulos[9]

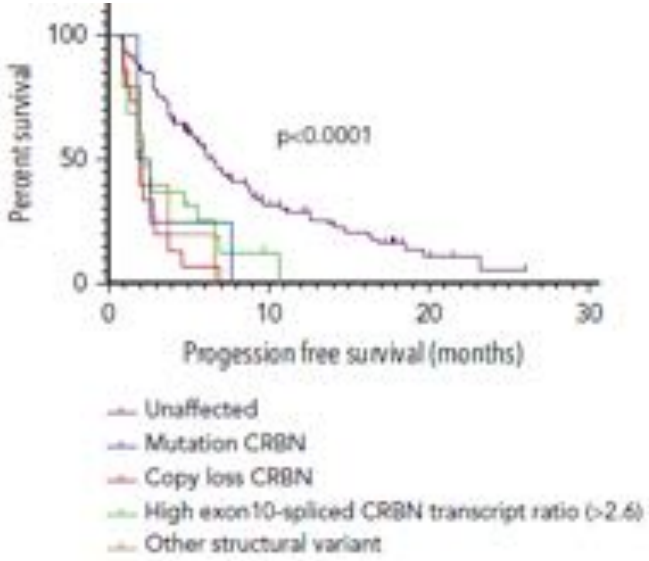
	PFS (months)		ORR (%)		Any TEAE, n (%)[†]		Grade ≥3 TEAE, n (%)[†]		Serious TEAE, n (%)[†]		TEAE leading to definitive treatment discontinuation, n (%)[†]	
	Isa-Pd	Pd	Isa-Pd	Pd	Isa-Pd	Pd	Isa-Pd	Pd	Isa-Pd	Pd	Isa-Pd	Pd
Overall ICARIA-MM population	11.5	6.5	60.4	35.3	151 (99.3)	146 (98.0)	132 (86.8)	105 (70.5)	94 (61.8)	80 (53.7)	11 (7.2)	19 (12.8)
High-risk cytogenetics												
– High risk	7.5	3.7	50.0	16.7	23 (100)	32 (94.1)	22 (95.7)	23 (67.6)	17 (73.9)	17 (50.0)	2 (8.7)	8 (23.5)
– Standard risk	11.6	7.4	65.0	42.3	102 (99.0)	75 (98.7)	88 (85.4)	58 (76.3)	60 (58.3)	47 (61.8)	7 (6.8)	6 (7.9)
Renal impairment												
– <45 ml/min/1.73 m^2	7.5	2.8	35.0	23.5	–	–	–	–	–	–	–	–
– <60 ml/min/1.73 m^2	9.5	3.7	56.4	24.5	54 (100)	47 (100)	49 (90.7)	37 (78.7)	42 (77.8)	28 (59.6)	6 (11.1)	7 (14.9)
– ≥60 ml/min/1.73 m^2	12.7	7.9	67.8	42.7	85 (98.8)	91 (96.8)	74 (86.0)	63 (67.0)	44 (51.2)	48 (51.1)	5 (5.8)	11 (11.7)
Elderly												
– ≥75 years	11.4	4.5	53.1	31.0	32 (100)	28 (100)	30 (93.8)	21 (75.0)	22 (68.8)	16 (57.1)	5 (15.6)	4 (14.3)
– 65–74 years	11.6	8.6	64.7	38.9	66 (100)	52 (98.1)	56 (84.8)	40 (75.5)	41 (62.1)	32 (60.4)	2 (3.0)	8 (15.1)
– <65 years	11.5	5.0	59.3	34.3	53 (98.1)	66 (97.1)	46 (85.2)	44 (64.7)	31 (57.4)	32 (47.1)	4 (7.4)	7 (10.3)
Prior lines and refractory status												
– 2 prior lines	12.3	7.8	57.8	35.6	–	–	–	–	–	–	–	–
– 2–3 prior lines	12.3	7.8	56.9	38.6	45 (100)	43 (97.7)	39 (86.7)	28 (63.6)	27 (60.0)	21 (47.7)	1 (2.2)	3 (6.8)
– ≥3 prior lines	11.4	5.6	61.5	35.2	106 (99.1)	103 (98.1)	93 (86.9)	77 (73.3)	75 (62.6)	59 (56.2)	10 (9.3)	16 (15.2)
– ≥4 prior lines	9.4	4.3	67.3	26.9	–	–	–	–	–	–	–	–
– 4 prior lines	8.5	3.3	56.3	28.6	–	–	–	–	–	–	–	–
– Len refractory	11.4	5.6	59.0	31.4	–	–	–	–	–	–	–	–
– PI refractory	11.4	5.6	60.2	32.2	–	–	–	–	–	–	–	–
– Len + PI refractory	11.2	4.8	58.6	29.9	–	–	–	–	–	–	–	–
– Refractory to Len at last line	11.6	5.7	55.9	29.5	–	–	–	–	–	–	–	–

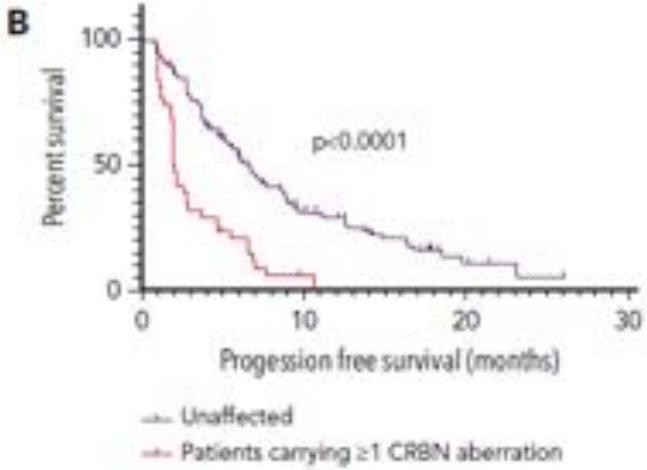
Richardson Front Oncol 2021

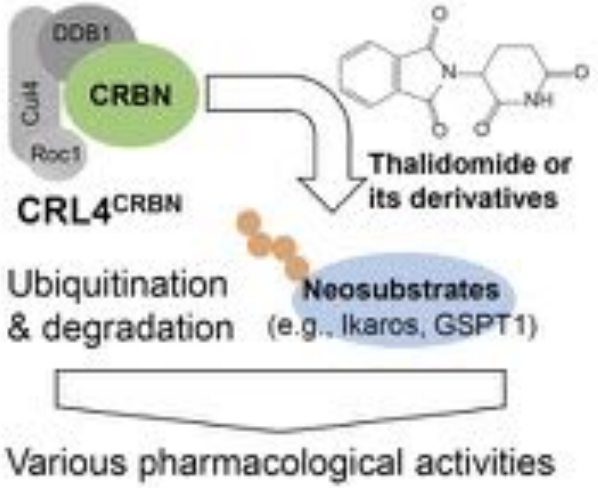
LYMPHOID NEOPLASIA

Multiple cereblon genetic changes are associated with acquired resistance to lenalidomide or pomalidomide in multiple myeloma

Sarah Gooding,[1-4] Naser Ansari-Pour,[3,5,*] Fadi Towfic,[6,*] Maria Ortiz Estévez,[7] Philip P. Chamberlain,[6] Kao-Tai Tsai,[8] Erin Flynt,[9] Marissa Hirst,[10] Dan Rozelle,[10] Paula Dhiman,[3,11] Paola Neri,[12] Karthik Ramasamy,[1-4] Nizar Bahlis,[12] Paresh Vyas,[1-3] and Anjan Thakurta[9]







Blood 2021

CC-220-MM-001 Cohorts E-G: Iberdomide + Dexamethasone Plus Daratumumab, Bortezomib, or Carfilzomib in R/R MM

- Open-label, multicenter, multicohort, phase Ib/IIa trial

Patients with R/R MM; ≥2 prior regimens (≥1 in cohort F) including lenalidomide/pomalidomide, and PI; who progressed within 60 days of last therapy

Dosing schedules

Cohort E (28-day cycles)
- *Iberdomide D1-21*
- *Dexamethasone D1,8,15,22*
- *Daratumumab C1-2: D1,8,15,22; C3-6: D1,15; C7+: D1*

Cohort F (21-day cycles)
- *Iberdomide D1-14*
- *Dexamethasone D1,8,15*
- *Bortezomib C1-8: D1,4,8,11; C9+: D1,8*

Cohort G (28-day cycles)
- *Iberdomide D1-21*
- *Dexamethasone D1,8,15,22*
- *Carfilzomib D1,8,15,22*

	Phase I: Dose-escalation	Phase II: Dose Expansion
A	Iberdomide	Cohort D: at RP2D
B	Iberdomide + Dex	(post-BCMA): at RP2D
E	Iberdomide 1.0-1.6 mg/day + Daratumumab 16 mg/kg + Dex 40 mg	Cohort J1: (ND MM, ASCT-ineligible)
F	Iberdomide 1.0-1.6 mg/day + Bortezomib 1.3 mg/m^2 + Dex 40 mg	Cohort J2: (ND MM, ASCT-eligible)
G	**Iberdomide** 1.0-1.3 mg/day + Carfilzomib 56 mg/m^2 + **Dex** 40 mg	

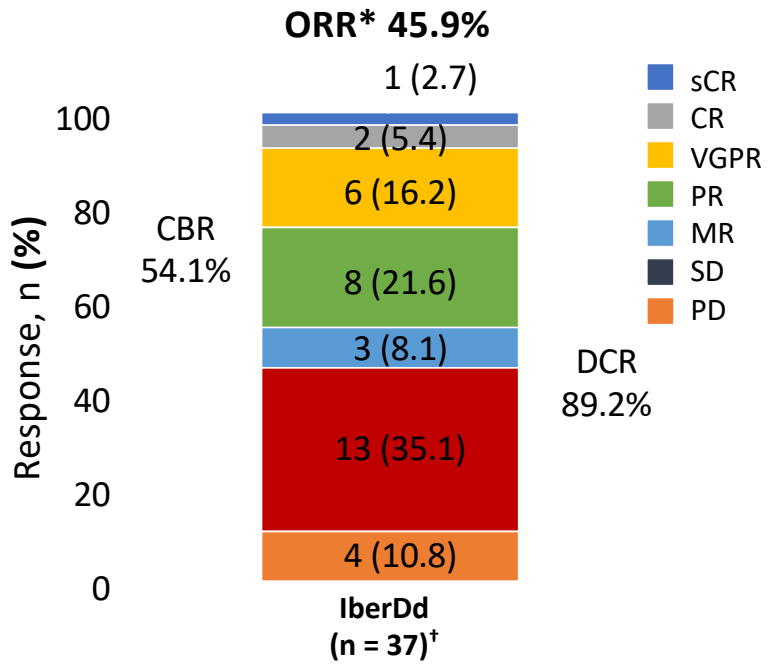
- Primary endpoints: MTD and RP2D
- Secondary endpoints: safety and preliminary efficacy

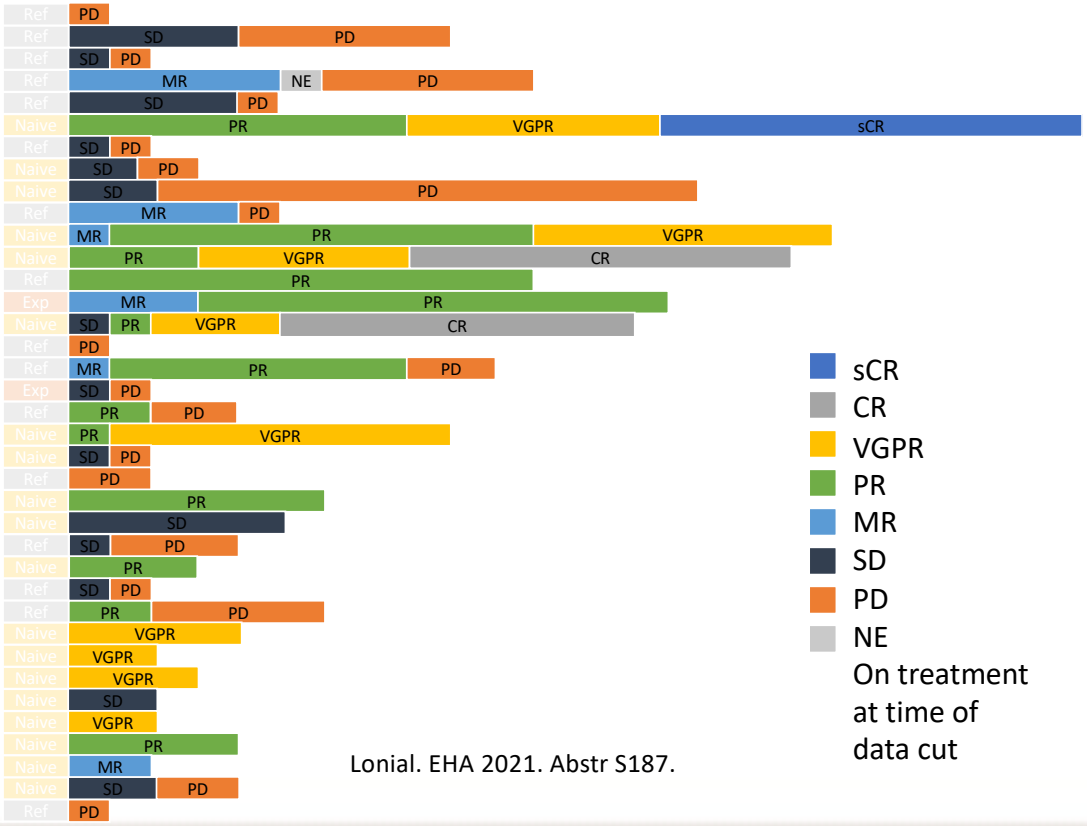
Lonial. EHA 2021. Abstr S187.

CC-220-MM-001 Cohorts E-G: Previous Therapies and Refractory Status

Characteristic	IberDd (n = 43)	IberVd (n = 25)	IberKd (n = 9)
Median prior therapies, n (range)	4 (2-13)	5 (1-14)	6 (2-8)
ASCT, n (%)	34 (79.1)	22 (88.0)*	9 (100)†
IMiD agent, n (%)	43 (100)	25 (100)	9 (100)
▪ Pomalidomide	28 (65.1)	19 (76.0)	8 (88.9)
PI, n (%)	43 (100)	25 (100)	9 (100)
▪ Bortezomib	41 (95.3)	24 (96.0)	9 (100)
Anti-CD38 mAb, n (%)	21 (48.8)	23 (92.0)	9 (100)
IMiD refractory, n (%)	41 (95.3)	20 (80.0)	8 (88.9)
▪ Pomalidomide	28 (65.1)	14 (56.0)	5 (55.6)
PI-refractory,‡ n (%)	37 (86.0)	17 (68.0)	6 (66.7)
▪ Bortezomib	17 (39.5)	11 (44.0)	4 (44.4)
▪ Carfilzomib	25 (58.1)	9 (36.0)	5 (55.6)
▪ Ixazomib	13 (30.2)	4 (16.0)	0
Anti-CD38 mAb-refractory, n (%)	16 (37.2)	20 (80.0)	7 (77.8)
Triple-class refractory§, n (%)	14 (32.6)	12 (48.0)	5 (55.6)

CC-220-MM-001 Cohorts E (IberDd): Best Response





- Median DoR not reached; responses ongoing in 14/17 responders
- Median time to response was 4.1 wk

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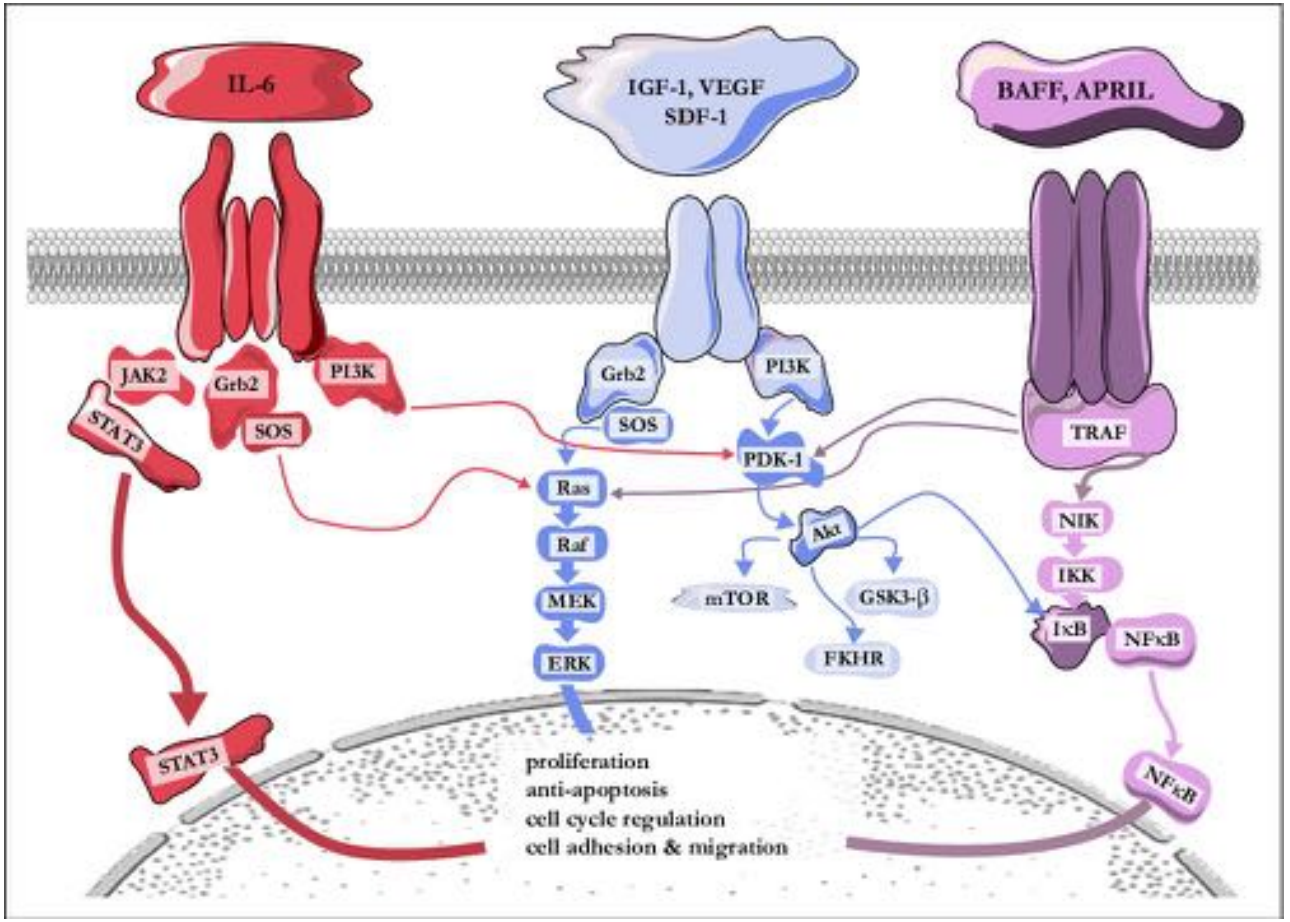
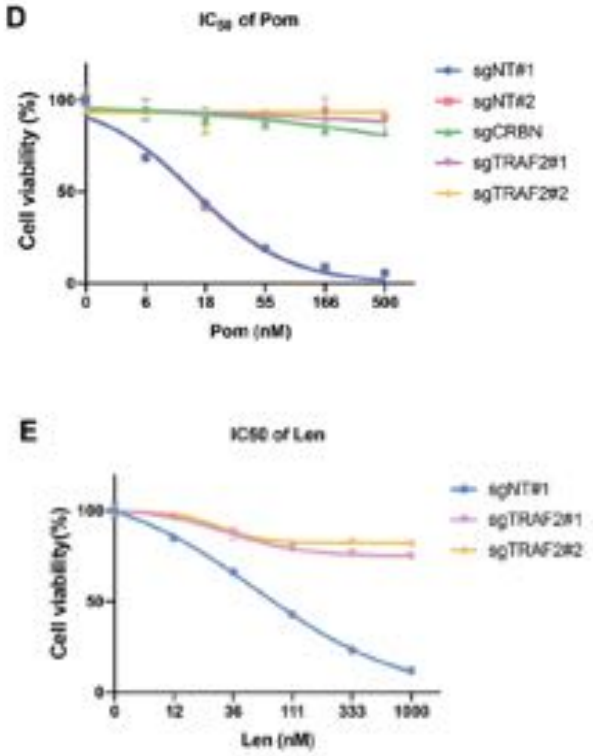
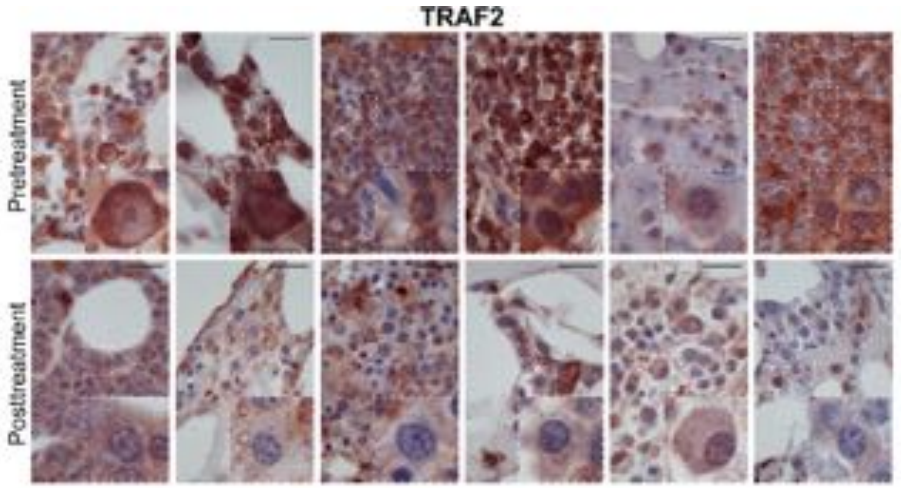

IL-6
IGF-1, VEGF
SDF-1
BAFF, APRIL
JAK2
Grb2
PI3K
STAT3
SOS
Grb2
PI3K
SOS
TRAF
PDK-1
Ras
Raf
MEK
ERK
Akt
mTOR
GSK3-β
FKHR
NIK
IKK
IκB
NFκB
STAT3
NFκB
proliferation
anti-apoptosis
cell cycle regulation
cell adhesion & migration

ERK signaling mediates resistance to immunomodulatory drugs in the bone marrow microenvironment

Jiye Liu[1†], Teru Hideshima[1†], Lijie Xing[1,2], Su Wang[3‡], Wenrong Zhou[4], Mehmet K. Samur[1,5], Tomasz Sewastianik[6,7], Daisuke Ogiya[1§], Gang An[8], Shaobing Gao[9], Li Yang[10], Tong Ji[11], Giada Bianchi[12], Kenneth Wen[1], Yu-Tzu Tai[1], Nikhil Munshi[1], Paul Richardson[1], Ruben Carrasco[6,13], Yong Cang[14], Kenneth C. Anderson[1*]





Immunomodulatory drugs (IMiDs) have markedly improved patient outcome in multiple myeloma (MM); however, resistance to IMiDs commonly underlies relapse of disease. Here, we identify that tumor necrosis factor (TNF) receptor-associated factor 2 (*TRAF2*) knockdown (KD)/knockout (KO) in MM cells mediates IMiD resistance via activation of noncanonical nuclear factor κB (NF-κB) and extracellular signal–regulated kinase (ERK) signaling. Within MM bone marrow (BM) stromal cell supernatants, TNF-α induces proteasomal degradation of TRAF2, noncanonical NF-κB, and downstream ERK signaling in MM cells, whereas interleukin-6 directly triggers ERK activation. RNA sequencing of MM patient samples shows nearly universal ERK pathway activation at relapse on lenalidomide maintenance therapy, confirming its clinical relevance. Combination MEK inhibitor treatment restores IMiD sensitivity of *TRAF2* KO cells both in vitro and in vivo. Our studies provide the framework for clinical trials of MEK inhibitors to overcome IMiD resistance in the BM microenvironment and improve patient outcome in MM.

Sci Adv 2021

The Effect of Duration of Lenalidomide Maintenance and Outcomes of Different Salvage Regimens in Patients with Multiple Myeloma (MM)

Matthew Ho[1,3], Saurabh Zanwar[1,2,3], Prashant Kapoor[2], Morie Gertz[2], Martha Lacy[2], Angela Dispenzieri[2], Suzanne Hayman[2], David Dingli[2], Francis Baudi[2], Eli Muchtar[2], Nelson Leung[2], Taxiarchis Kourelis[2], Rahma Warsame[2], Amie Fonder[2], Lisa Hwa[2], Miriam Hobbs[2], Robert Kyle[2], S. Vincent Rajkumar[2] and Shaji Kumar[2]✉

Factors impacting outcome		Years from diagnosis				Years from start of maintenance		
		Median OS (95% CI)	p	Median PFS (95% CI)	p	Median OS(95% CI)	p	Median PFS (95% CI)
Cytogenetics	High-risk	8 (4.9–11) (5 y OS: 65%)	0.007	3.3 (2.5–4.1) (5 y PFS: 22%)	0.004	7.3 (3.9–10.7) (5 y OS: 58%)	0.009	2.4 (1.7–3) (5 y PFS: 10%)
	Standard-risk	Not reached (5 y OS: 82%)		4.4 (3.5–5.4) (5 y PFS: 44%)		Not reached (5 y OS: 76%)		3.4 (2.7–4.1) (5 y PFS: 35%
ISS	Stage 3	Not reached (5 y OS: 62%)	0.017	3 (1.6–4.4) (5 y PFS: 28%)	0.097	Not reached (5 y OS: 58%)	0.022	2.1 (0.8–3.4) (5 y PFS: 23%
	Stage 1 and 2	Not reached (5 y OS: 84%)		4.4 (3.7–5.1) (5 y PFS: 42%)		Not reached (5 y OS: 77%)		3.4 (2.8–4) (5 y PFS: 31%)
Lenalidomide at induction	Yes	Not reached (5 y OS: 77%)	0.884	3.7 (2.7–4.7) (5 y PFS: 42%)	0.409	8.1 (NR, NR) (5 y OS: 73%)	0.346	3.2 (2.5–3.9) (5 y PFS: 32%
	No	Not reached (5 y OS: 76%)		4 (3.2–4.7) (5 y PFS: 28%)		Not reached (5 y OS: 66%)		2.9 (1.9–4) (5 y PFS: 21%)
Deep response within 2 years of starting maintenance	≥VGPR	Not reached (5 y OS: 82%)	0.003	4.4 (3.9–4.9) (5 y PFS: 41%)	0.003	Not reached (5 y OS: 76%)	0.003	3.6 (3.1–4.1) (5 y PFS: 32%
	<PR	8 (5.5–10.4) (5 y OS: 67%)		3.3 (2.2–4.3) (5 y PFS: 30%)		8.3 (4.7–9.9) (5 y OS: 59%)		2.6 (1.6–3.6) (5 y PFS: 20%
Year of maintenance initiation	≥2014	Not reached (5 y OS: 89%)	<0.0001	4.3 (3.9–4.8) (5 y PFS: 40%)	0.59	Not reached (5 y OS: 76%)	<0.0001	3.4 (2.8–4) (5 y PFS: 23%)
	<2014	8.2 (not estimable) (5 y OS: 64%)		3.5 (2.8–4.2) (5 y PFS: 35%)		7.5 (not estimable) (5 y OS: 61%)		2.6 (1.9–3.3) (5 y PFS: 28%
Timing of first achievement of ≥ VGPR	Prior to mx	Not reached (5 y OS: 77%)	0.405	4.3 (3.5–5.2) (5 y PFS: 33%)	0.166	Not reached (5 y OS: 71%)	0.401	3.1 (2.2–4) (5 y PFS: 26%)
	Within 2 years of mx	Not reached (5 y OS: 80%)		5 (3.6–6.5) (5 y PFS: 54%)		Not reached (5 y OS: 75%)		4.4 (2.7–6) (5 y PFS: 40%)

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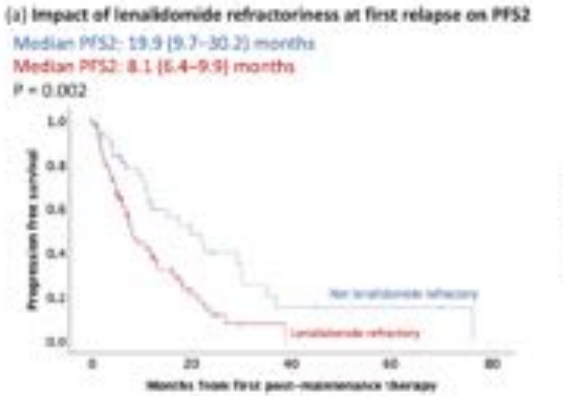

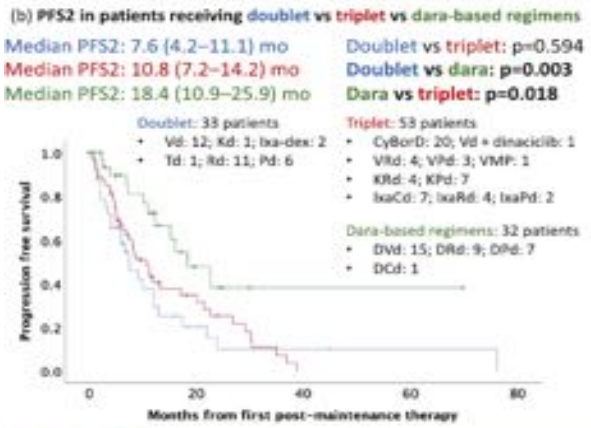

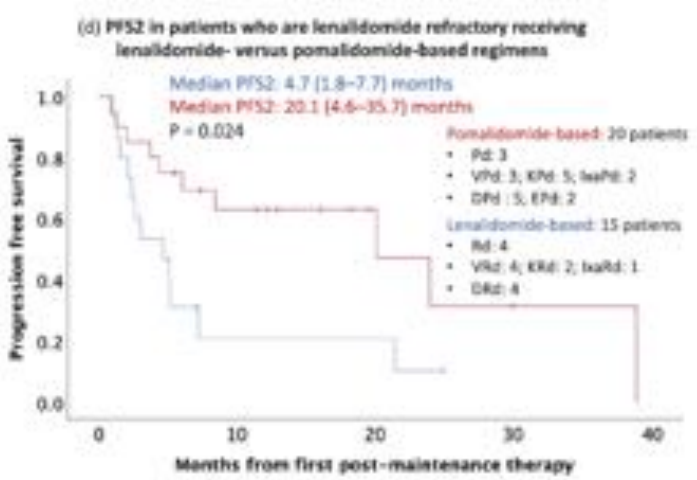

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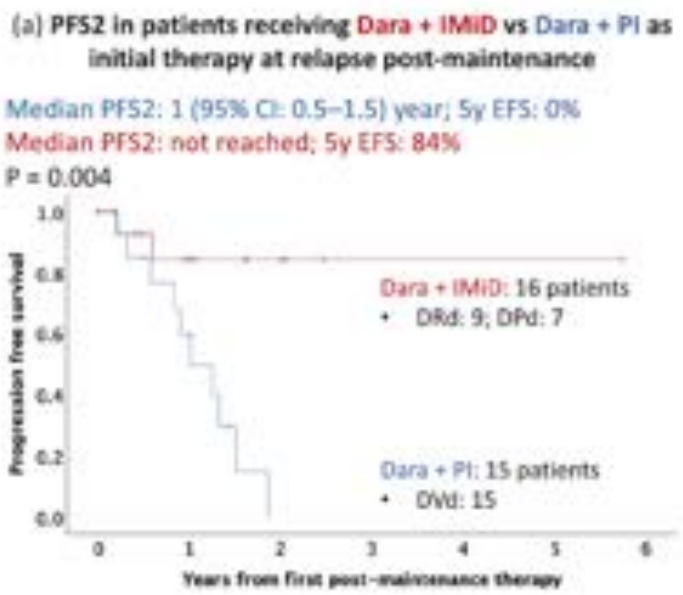
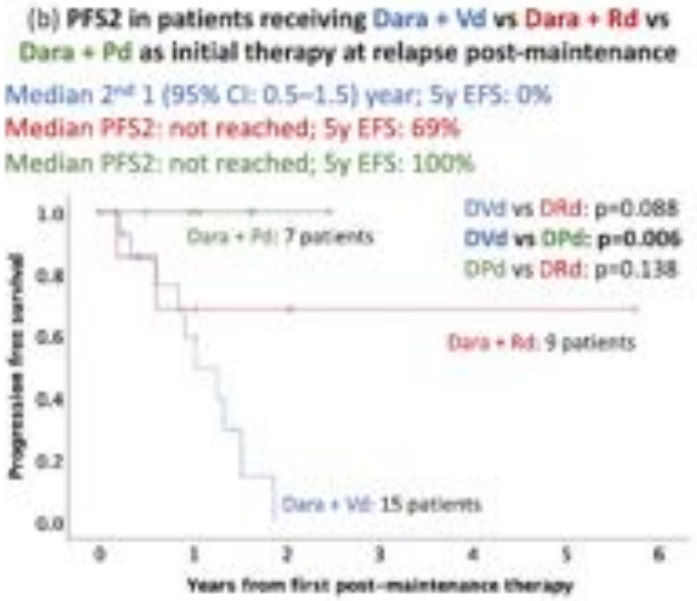
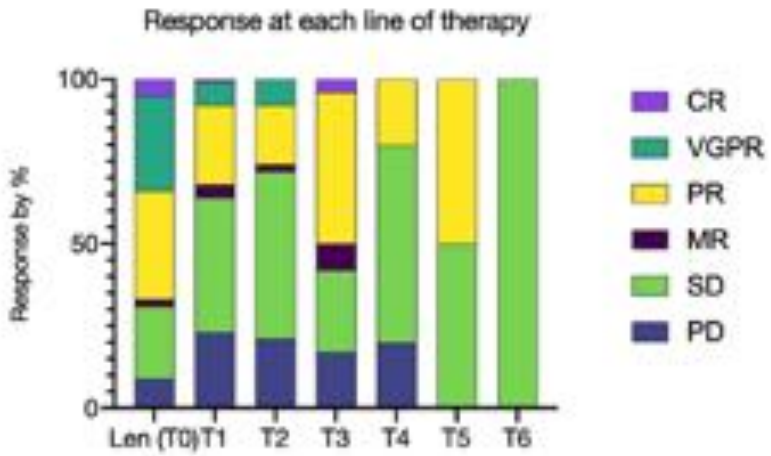




Defining Unmet Need Following Lenalidomide Refractoriness: Real-World Evidence of Outcomes in Patients With Multiple Myeloma

Catherine S. Y. Lecat[1,2†], Jessica B. Taube[1†], William Wilson[3], Jonathan Carmichael[4,5], Christopher Parrish[4], Gabriel Wallis[1], Charalampia Kyriakou[1], Lydia Lee[2], Shameem Mahmood[1], Xenofon Papanikolaou[1], Neil K. Rabin[1], Jonathan Sive[1], Ashutosh D. Wechalekar[1], Kwee Yong[2], Gordon Cook[4,5] and Rakesh Popat[1]



Univariate analysis	N	HR	95% CI	P-value
Trial enrolment at any point post-Lenalidomide *(trial vs no trial)*	37 vs 76	0.369	0.22 - 0.63	**0.000**
ECOG pre-T1 *(ECOG 0-1 vs ECOG 2-4)*	45 vs 22	0.398	0.2 – 0.79	**0.008**
Age pre-T1	113	0.99	0.98 - 1.02	0.86
Cytogenetics at diagnosis *(standard vs high-risk)*	89 vs 24	1.15	0.66 - 1.99	0.63
Albumin pre-T1	87	0.91	0.86 - 0.96	**0.004**
Calcium pre-T1	93	1.31	0.33 - 5.16	0.69
eGFR pre-T1	93	0.99	0.99 - 1.01	0.18
CRP pre-T1	81	1.01	0.99 - 1.01	0.25
Haemoglobin pre-T1	94	0.97	0.96 - 0.99	**0.001**
Neutrophils pre-T1	94	0.89	0.76 - 1.06	0.2
Platelets pre-T1	113	0.99	0.99 - 1.01	0.28
Multivariate analysis	34 died vs 26 censored (53 incomplete data)			
Trial enrolment at any point post - Len *(trial vs no trial)*	23 vs 37	0.23	0.09 - 0.62	**0.004**
ECOG pre-T1 *(ECOG 0-1 vs ECOG 2-4)*	41 vs 19	0.26	0.12 - 0.6	**0.001**
Haemoglobin pre-T1	60	0.97	0.95 - 0.99	**0.006**
Albumin pre-T1	60	0.92	0.85 - 0.99	**0.03**

Front Oncol 2021

- Better knowledge of mechanisms causing drug resistance
- Improve patients evaluation

- Identify the best strategy

Strategies:

Switch IMID
Add PI
Change PI
Add MoAb
Triplet
Newer strategies
……