SESSIONE V
Terapia del MM ricaduto/refrattario dopo 1-2 precedenti terapie

Con CELMoDs o altri nuovi agenti

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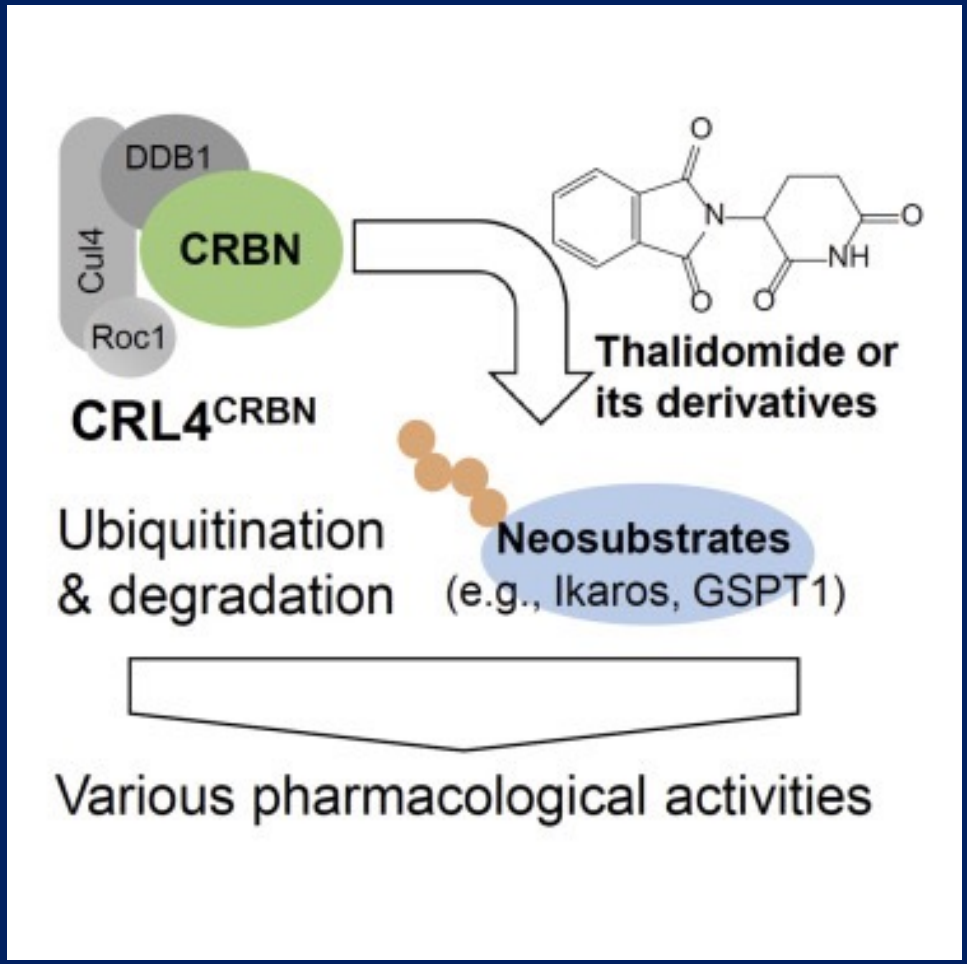
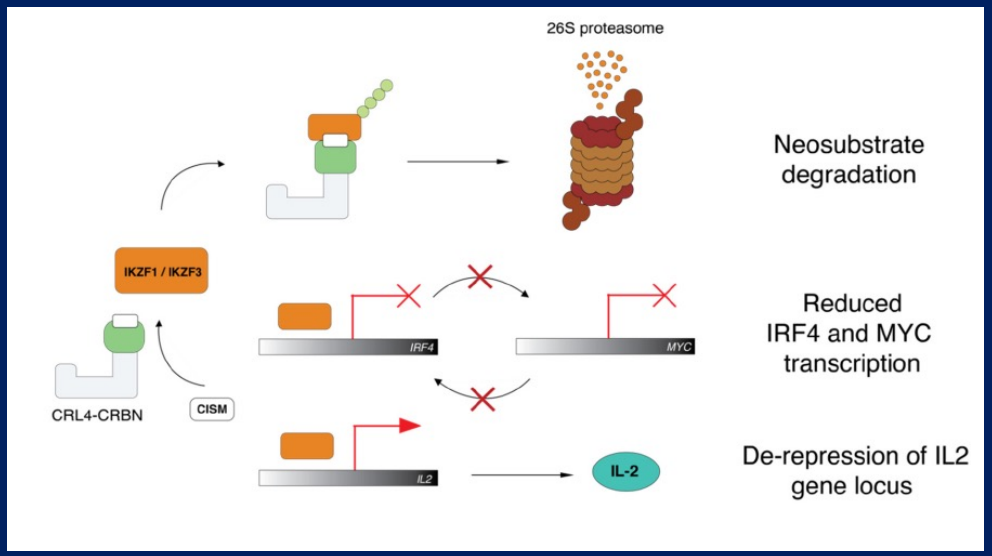
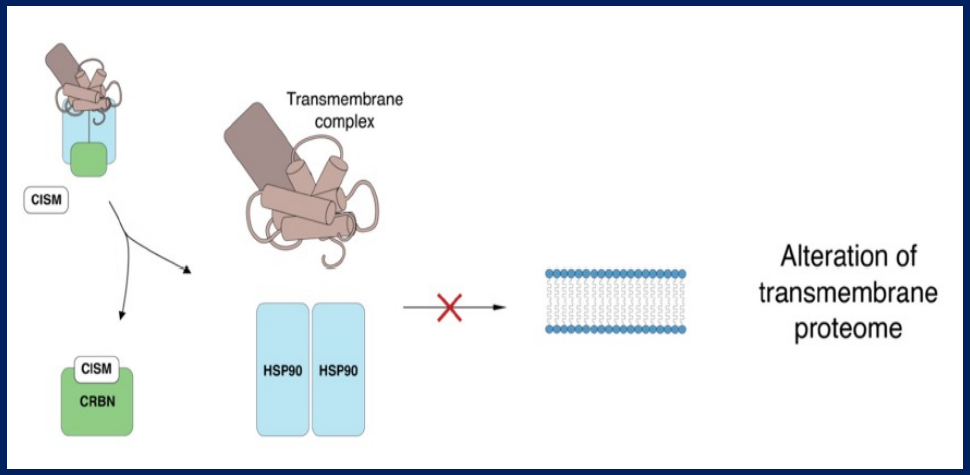
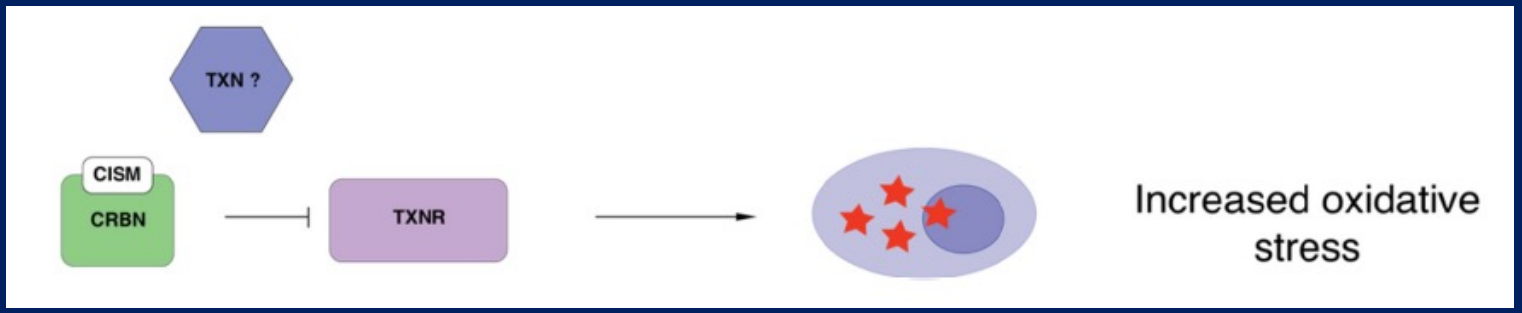
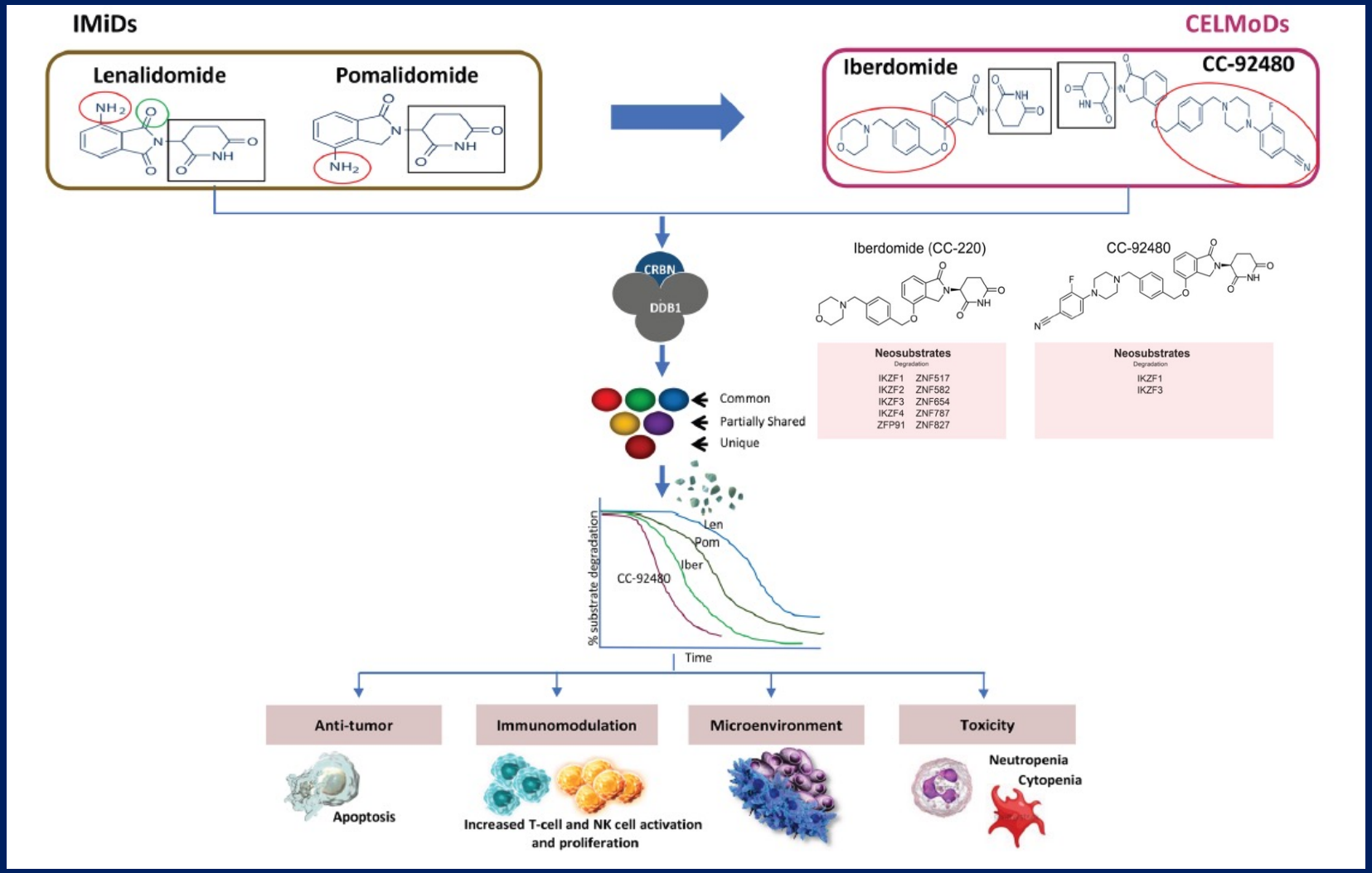

DDB1
CRBN
Cul4
Roc1
CRL4CRBN
Thalidomide or
its derivatives
Ubiquitination
& degradation
Neosubstrates
(e.g., Ikaros, GSPT1)
Various pharmacological activities

Pathways modulated by cereblon





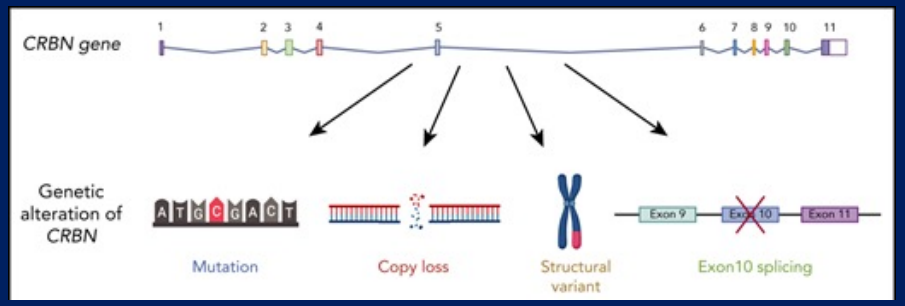


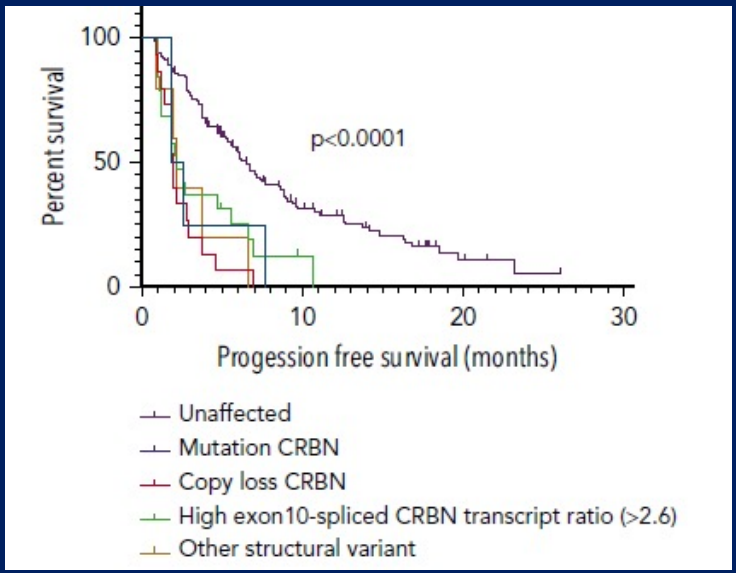

IMiDs
CELMoDs
Lenalidomide
Pomalidomide
Iberdomide
CC-92480
CRBN
DDB1
Iberdomide (CC-220)
CC-92480
Neosubstrates
Degradation
IKZF1 ZNF517
IKZF2 ZNF582
IKZF3 ZNF654
IKZF4 ZNF787
ZFP91 ZNF827
Neosubstrates
Degradation
IKZF1
IKZF3
Common
Partially Shared
Unique
% substrate degradation
Len
Pom
Iber
CC-92480
Time
Anti-tumor
Immunomodulation
Microenvironment
Toxicity
Apoptosis
Increased T-cell and NK cell activation and proliferation
Neutropenia
Cytopenia

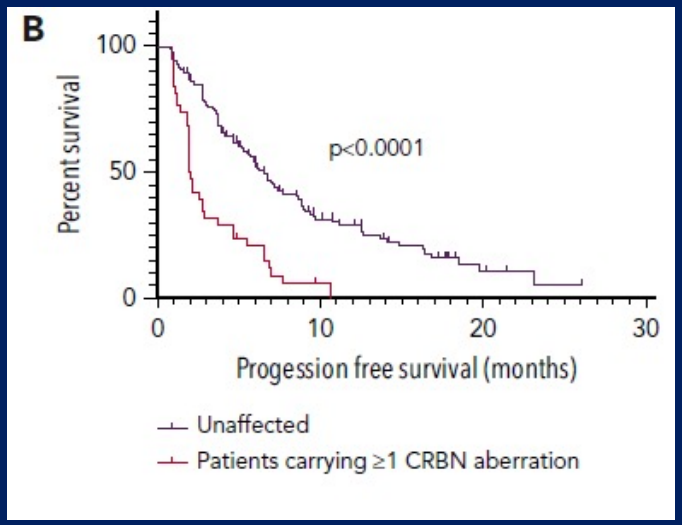
LYMPHOID NEOPLASIA

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,*] María 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]



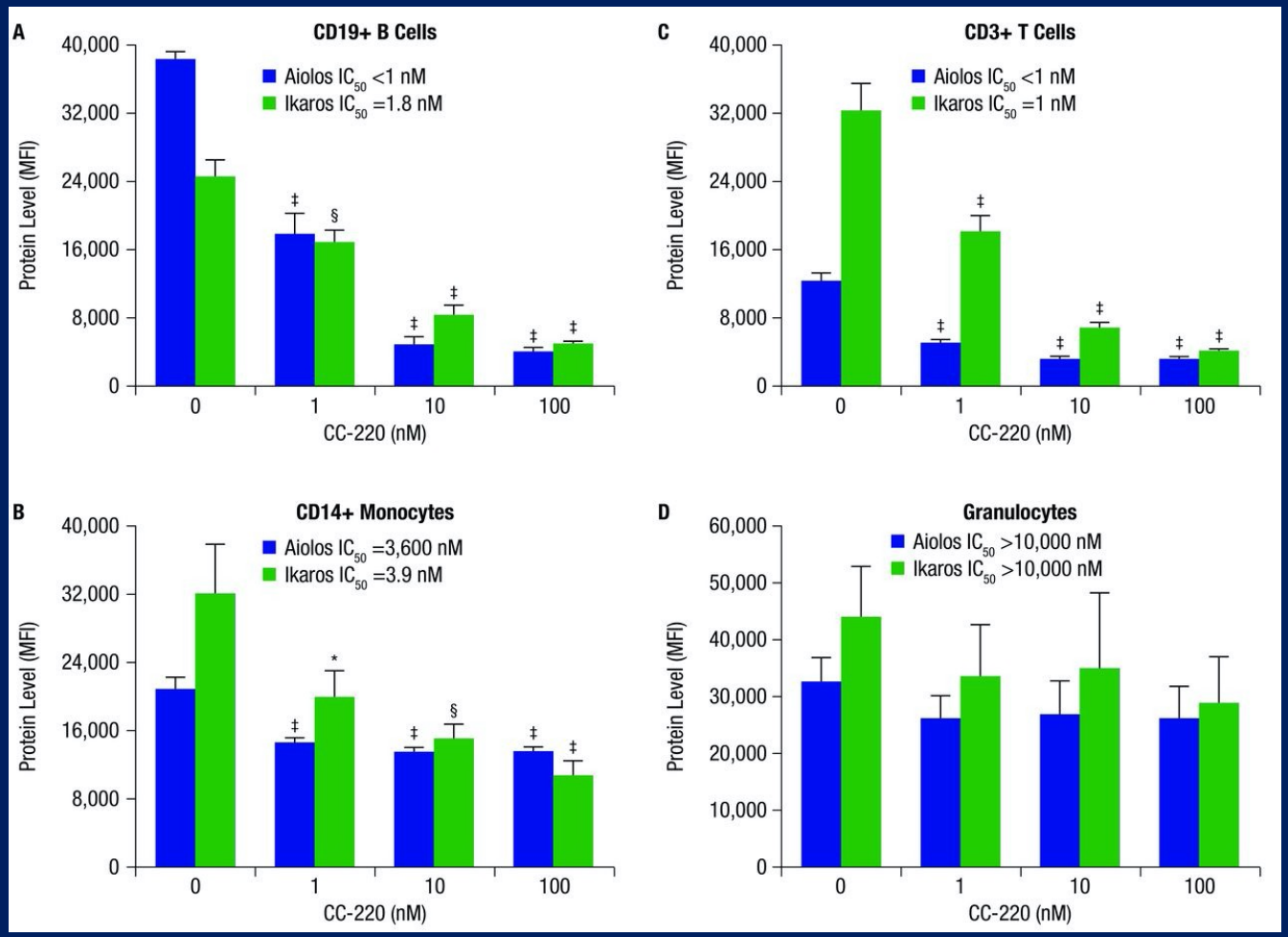




Found in
~5% at new diagnosis
~20% at Lenalidomide resistance
~30% at Pomalidomide resisitance

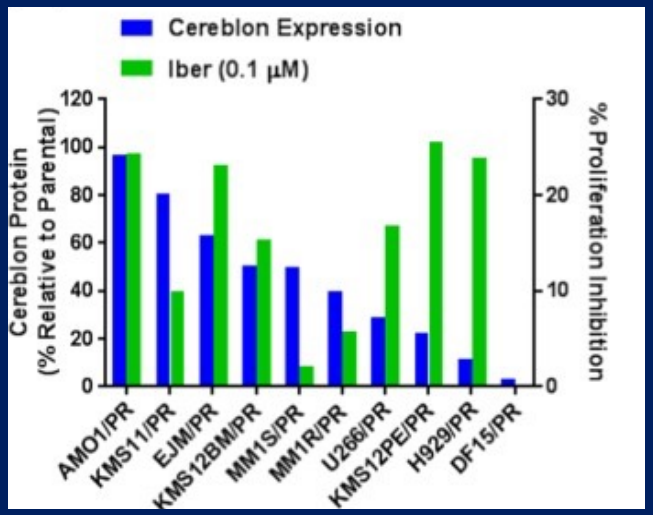
Blood 2021

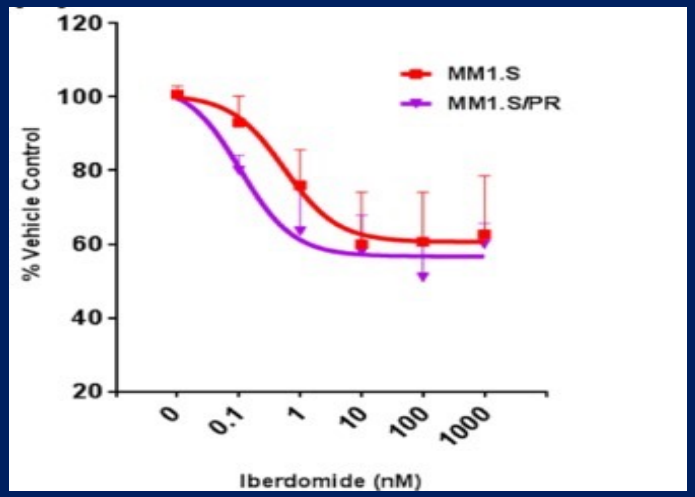
Iberdomide (CC-220) reduces Ikaros and Aiolos protein levels in whole blood leucocyte subsets: (A) CD19+ B cells, (B) CD14+ monocytes, (C) CD3+ T cells and (D) granulocytes.

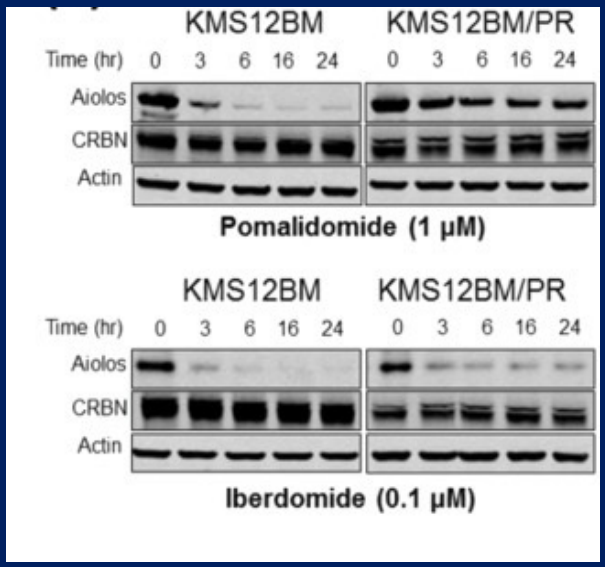


Schafer et al, Ann Reumatol Disease 2018

Iberdomide activity in pomalidomide-resistant cell lines







Bjorklund et al Leukemia 2020

CC-220-MM-001

OBJECTIVE

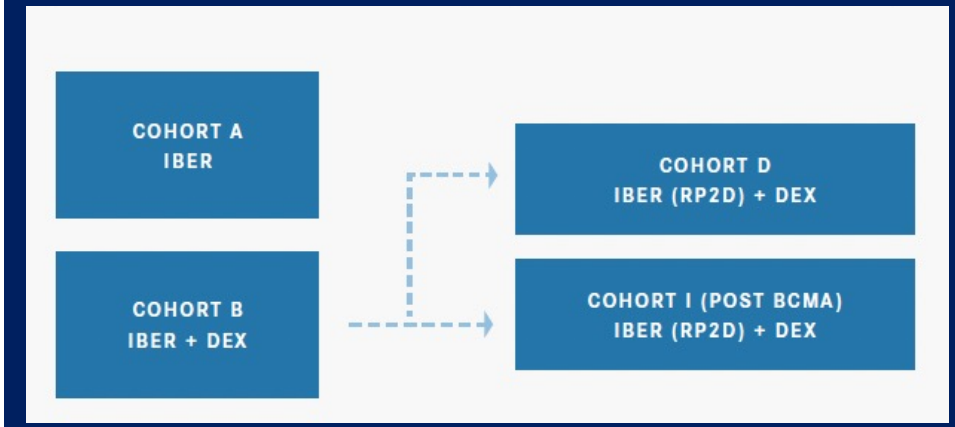
present safety and efficacy data of IBER + DARA + DEX (IberDd; cohort E), IBER + BORT + DEX (IberVd; cohort F), and IBER + CFZ + DEX (IberKd; cohort G)

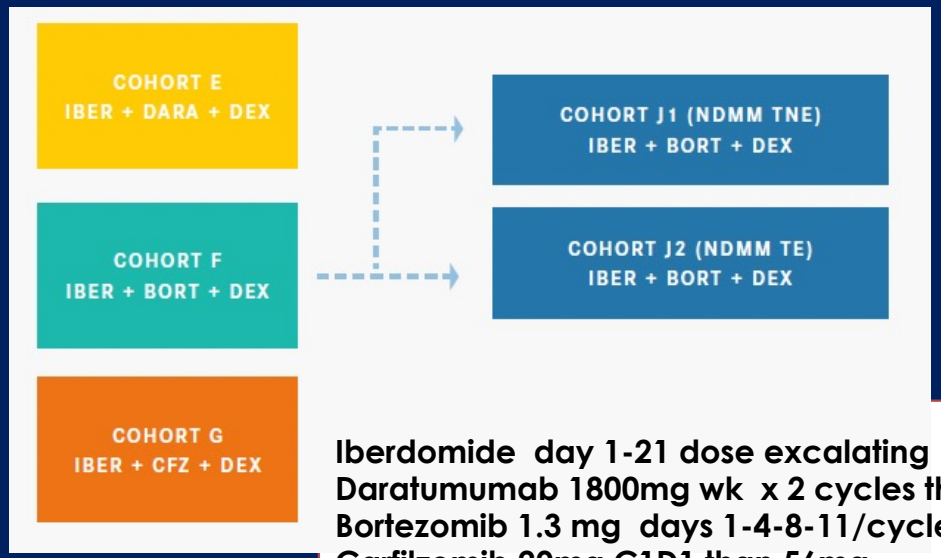
END POINTS

PRIMARY
Determine MTD/RP2D

SECONDARY
assess safety and preliminary efficacy

≥ 2 lines of therapy
(≥1 in cohort F)





Iberdomide day 1-21 dose excalating 1.1→1.6mg
Daratumumab 1800mg wk x 2 cycles than days 1-15
Bortezomib 1.3 mg days 1-4-8-11/cycle
Carfilzomib 20mg C1D1 than 56mg

Lonial et al IMW 2021

Baseline characteristics

Characteristic	IberDd (N=43)	IberVd (N=25)	IberKd (N= 9)
Median age (yrs)	67	64	61
Male N (%)	21 (48.8)	18 (72)	6 (66.7)
Time since dg (yrs)	7.35	7.1	6.7
Ecog PS (%)			
0	44.2	36	33.3
1	53.5	60	66.7
2	2.3	4	0
ISS at study entry			
I	58.1	56	77.8
II	25.6	36	11.1
III	11.6	8	11.1
Extramedullary plasmacytoma (%)	16.3	16	22
Cr clearance < 60ml/min (%)	25.6	16	33.3

Lonial et al IMW 2021

Grade 3-4 adverse events

	IberDd (N=43)	IberVd (N=25)	IberKd (N= 9)
Neutropenia (%)	66	28	33
Febrile neutropenia (%)	5	0	0
Thrombocytopenia (%)	12	24	11
Anemia (%)	20	12	0
Fatigue (%)	2	0	11
Diarrhea (%)	2	4	0
Constipation (%)	0	0	0
IRR (%)	0	0	0
PNP (%)	0	0	0
Rash (%)	0	4	0
Thrombosis (%)	0	0	0
Infection (%)	15	20	33

Lonial et al IMW 2021

Response

	IberDd (N =37)	IberVd (N=25)	IberKd (N= 9)
ORR (%)	45.9	56	50
sCR (%)	1 (2.7)	1 (4)	1 (12.5)
CR (%)	2 (5.4)	6 (24)	0
VGPR (%)	6 (16.2)	7 (28)	2 (25)
PR(%)	8 (21.6)	2 (8)	1 (12.5)
MR (%)	3 (8.1)	0	0
SD (%)	13 (35.1)	6 (24)	3 (37.5)
PD (%)	4 (10.8)	2 (8)	1 (12.5)

Lonial et al IMW 2021

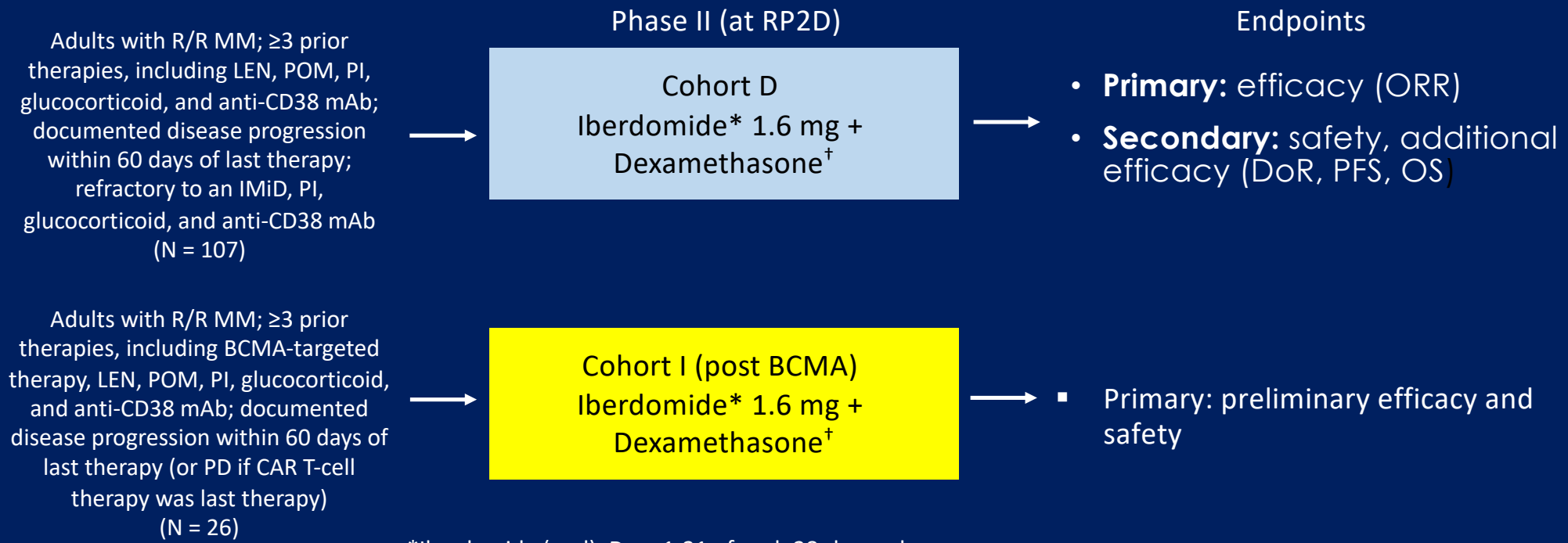
Response

	IberDd (N =17)	IberVd (N=14)	IberKd (N= 4)
Time to response	4.1 wks	3.6 wks	4.1 wks
Response duration	NR	35.7 wks	NR

Lonial et al IMW 2021

CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: Study Design

- Open-label phase Ib/IIa trial



*Iberdomide (oral): Days 1-21 of each 28-day cycle.
†Dexamethasone (oral): 40 mg (20 mg if >75 yr) on Days 1, 8, 15, and 22 of each 28-day cycle.

Lonial. ASH 2021. Abstr 162. NCT02773030.

CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: Baseline Characteristics and Prior Therapy

Characteristic	Cohort D (N = 107)	Cohort I (Post BCMA) (N = 26)
Median age, yr (range)	64 (44-83)	65 (50-78)
Male, n (%)	60 (56.1)	15 (57.7)
Median time since diagnosis, yr (range)	6.90 (1.6-24.5)	7.75 (0.6-24.8)
ECOG PS, n (%) 0 1 2	 42 (39.3) 55 (51.4) 10 (9.3)	 6 (23.1) 20 (76.9) 0
ISS at entry, n (%) ▪ Stage I ▪ Stage II ▪ Stage III	 46 (43.0) 45 (42.1) 16 (15.0)	 15 (57.7) 6 (23.1) 5 (19.2)
Extramedullary plasmacytoma, n (%)	27 (25.2)	8 (30.8)
High-risk cytogenetics, n (%)	(n = 57) 32 (29.9)	(n = 18) 6 (23.1)

Prior Therapy	Cohort D (N = 107)	Cohort I (Post BCMA) (N = 26)
Median prior lines of therapy, n (range)	6 (3-23)	7 (4-15)
ASCT, n (%)	84 (78.5)	23 (88.5)
IMiD refractory, n (%) ▪ Pomalidomide ▪ Lenalidomide	107 (100) 102 (95.3) 91 (85.0)	26 (100) 23 (88.5) 22 (84.6)
PI refractory, n (%) Bortezomib Carfilzomib	104 (97.2) 62 (57.9) 66 (61.7)	25 (96.2) 14 (53.8) 21 (80.8)
Anti-CD38 mAb refractory, n (%)	107 (100)	22 (84.6)
Triple-class refractory, n (%)	104 (97.2)	21 (80.8)
BCMA exposed, n (%) ▪ CAR T-cell therapy ▪ ADC ▪ T-cell engager	1 (0.9) 0 1 (0.9) 0	26 (100) 6 (23.1) 13 (50.0) 8 (30.8)

Data cutoff: June 2, 2021

Lonial. ASH 2021. Abstr 162.

CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: Patient Disposition and Treatment Exposure

Disposition, n (%)	Cohort D (N = 107)	Cohort I (Post BCMA) (N = 26)
Treatment ongoing	13 (12.1)	13 (50.0)
Discontinued	94 (87.9)	13 (50.0)
PD	74 (69.2)	11 (42.3)
Physician decision*	7 (6.5)	1 (3.8)
AE	5 (4.7)	0
Death	4 (3.7)†	1 (3.8)‡
Withdrawal	3 (2.8)	0
Other	1 (0.9)	0

Treatment Exposure	Cohort D (N = 107)	Cohort I (Post BCMA) (N = 26)
Median cycles received, n (range)	4 (1-17)	3 (1-8)
Iberdomide dose reduction, n (%)	20 (18.7)	4 (15.4)
Iberdomide relative dose intensity, % (range)	92.31 (37.72-133.33)	88.89 (49.96-100.00)

*Unconfirmed or non-IMWG PD. †2 deaths due to COVID-19, 1 due to unknown cause, 1 due to general physical health deterioration.
‡Death due to COVID-19.

Lonial. ASH 2021. Abstr 162.

CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: ORR

Response, n (%)	Cohort D (N = 107)	Cohort I (Post BCMA) (N = 24)
ORR	28 (26.2)	6 (25.0)
▪ sCR	1 (0.9)	0
▪ CR	0	1 (4.2)
▪ VGPR	8 (7.5)	1 (4.2)
▪ PR	19 (17.8)	4 (16.7)
MR	11 (10.3)	4 (16.7)
SD	46 (43.0)	8 (33.3)
PD	15 (14.0)	4 (16.7)
NE	7 (6.5)	2 (8.3)
CBR (sCR + CR + VGPR + PR + MR)	39 (36.4)	10 (41.7)
DCR (sCR + CR + VGPR + PR + MR + SD)	85 (79.4)	18 (75.0)

Lonial. ASH 2021. Abstr 162.

CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: Additional Efficacy Outcomes for Cohort D

Efficacy Outcome, Wk (Range)	Cohort D (N = 107)
Median TTR	4.21 (3.9-19.9)
Median DoR	30.3 (19.57-49.14)
Median PFS	13.1 (12.00-16.00)
Median OS	46.6 (38.14-NR)
Responders	NR (48.86-NR)
Nonresponders	34.9 (28.57-46.57)

- All HRQoL measures remained stable over time, including measures of global health status/QoL, pain, and fatigue
- Iberdomide remained active and able to stimulate immune responses in patients with late-line, triple-refractory R/R MM
  - Decreased Aiolos levels observed during treatment, as well as increased proliferating NK cells and T-cells

Lonial. ASH 2021. Abstr 162.

CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: TEAEs

TEAEs of Interest, n (%)	Cohort D (N = 107)			Cohort I (Post BCMA) (N = 26)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Hematologic						
▪ Neutropenia	64 (59.8)	27 (25.2)	21 (19.6)	11 (42.3)	8 (30.8)	3 (11.5)
▪ Febrile neutropenia	5 (4.7)	4 (3.7)	1 (0.9)	1 (3.8)	1 (3.8)	0
▪ Anemia	44 (41.1)	30 (28.0)	0	9 (34.6)	4 (15.4)	0
▪ Thrombocytopenia	38 (35.5)	7 (6.5)	16 (15.0)	8 (30.8)	3 (11.5)	3 (11.5)
▪ Leukopenia	30 (28.0)	11 (10.3)	11 (10.3)	4 (15.4)	2 (7.7)	1 (3.8)
Nonhematologic						
Fatigue	25 (23.4)	2 (1.9)	1 (0.9)	6 (23.1)	1 (3.8)	0
Diarrhea	25 (23.4)	1 (0.9)	0	4 (15.4)	0	0
Constipation	23 (21.5)	0	0	3 (11.5)	0	0
Rash	21 (19.6)	3 (2.8)	0	2 (7.7)	1 (3.8)	0
Infections	62 (57.9)	26 (24.3)	3 (2.8)	13 (50.0)	6 (23.1)	0
▪ Pneumonia	13 (12.1)	9 (8.4)	0	5 (19.2)	4 (15.4)	0
▪ COVID-19	10 (9.3)	5 (4.7)	2 (1.9)	1 (3.8)	1 (3.8)	0

Lonial. ASH 2021. Abstr 162.

CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: Investigators' Conclusions

- Iberdomide + dexamethaxone conferred clinically meaningful and durable responses in patients with heavily pretreated R/R MM, 97% of whom were triple-class refractory
  - Similar results observed in patients previously treated with BCMA-directed therapy
- Iberdomide + dexamethaxone generally well tolerated; TEAEs manageable with dose reductions/interruptions
  - Grade 3/4 TEAEs primarily hematologic; few patients discontinued due to TEAEs
- HRQoL maintained during iberdomide + dexamethaxone treatment
- Results support future development of iberdomide-based regimens in MM, including phase III combination studies with PIs and anti-CD38 mAbs

Lonial. ASH 2021. Abstr 162.

CC- 92480 –MM-001 phase I trial

RRMM resistant or intolerant to or not otherwise candidate for current available therapy

Continuous schedules

Intensive schedules

Baseline characteristics

Characteristic (76 pts)	
Median age (yrs)	66
Male N (%)	57.9
Ecog PS (%)	
0	27.6
1	63.2
2	9.2
ISS at study entry	
I	32.9
II	44.7
III	22.4
Extramedullary plasmacytoma (%)	36.8

Prior therapy	%
ASCT	76.3
PI	100
LEN	97.4
POM	92.1
Anti CD38	75
LEN refractory	73.7
POM refractory	78.9
IMID refractory	89.5
PI refractory	73.7
Anti CD38 refractory	69.7
Triple refractory	50

Richardson et al, ASH 2020

Adverse events

	All grades	Grade 3-4
Neutropenia (%)	73.7	64.2
Febrile neutropenia (%)	7.9	6.6
Thrombocytopenia (%)	43.4	15.8
Anemia (%)	55.3	31.6
Fatigue (%)	38.2	9.2
Diarrhea (%)	23.7	1.3
PNP (%)	5.3	0
Thrombosis (%)	1.3	0
Infection (%)	71.1	35.5

Richardson et al, ASH 2020

Response

	All evaluable (76)	Intensive (10)	Continuous (11)
ORR (%)	21.1	40	54
CR (%)	1 (1.3)	0	1 (9.1)
VGPR (%)	6 (7.9)	2 (20)	2 (18.2)
PR(%)	9 (11.8)	2 (20)	3 (27.3)
MR (%)	4 (5.3)	1(10)	1 (9.1)
SD (%)	37 (48.7)	5 (50)	4 (36.4)
PD (%)	15 (19.7)		

Richardson et al ASH 202

CELMoDs

- Able to overcome IMIDs resistance
  - Effective in patients IMIDs pretreated that now represent an unmet clinical need
- Optimal toxicity profile
  - Attractive combinations for earlier stages or for intolerant patients