What's new for relapsed MM in 2020?

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Topics

- Updates in CAR T for MM – Fred Hutch/SCCA data – BCMA CAR T + Gamma secretase inhibitor

- New approaches to treating relapsed MM:
  - Belantamab mafodotin – BCMA ADC – Now FDA Approved
  - Bispecific T cell engagers
  - CelMODs

Fully Human BCMA CAR T cells in Combination with a Gamma Secretase Inhibitor to Increase BCMA Expression in R/R Multiple Myeloma

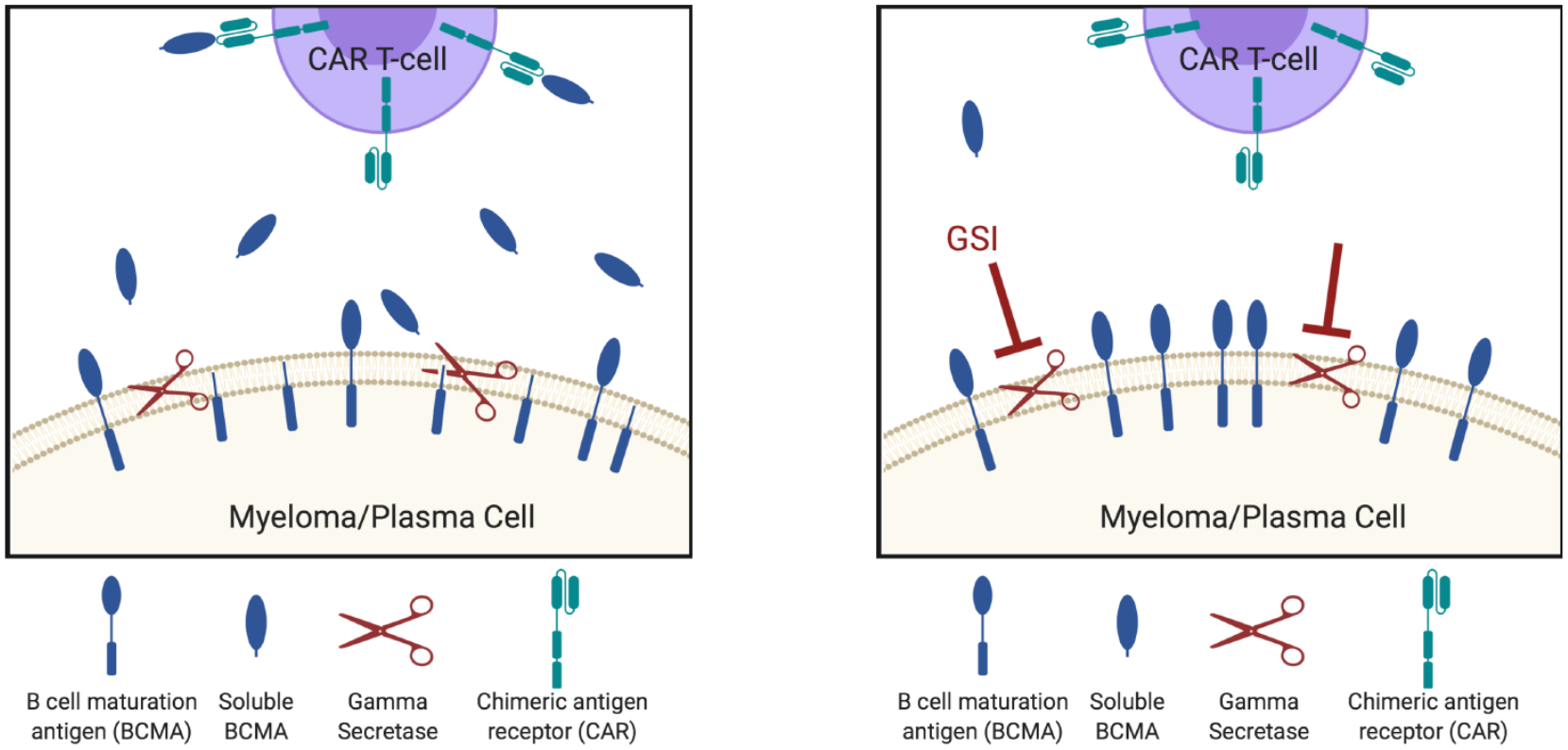
Andrew J. Cowan, Margot Pont, Blythe Duke Sather, Cameron J. Turtle, Brian G. Till, Anne M. Nagengast, Edward N. Libby III, Pamela S. Becker, David G. Coffey, Sherilyn A. Tuazon, Brent Wood, Michelle Blake, Melissa Works, Ted Gooley, Vicky Q. Wu, David G. Maloney, Stanley R. Riddell, and Damian J. Green

FRED HUTCH

UNIVERSITY of WASHINGTON

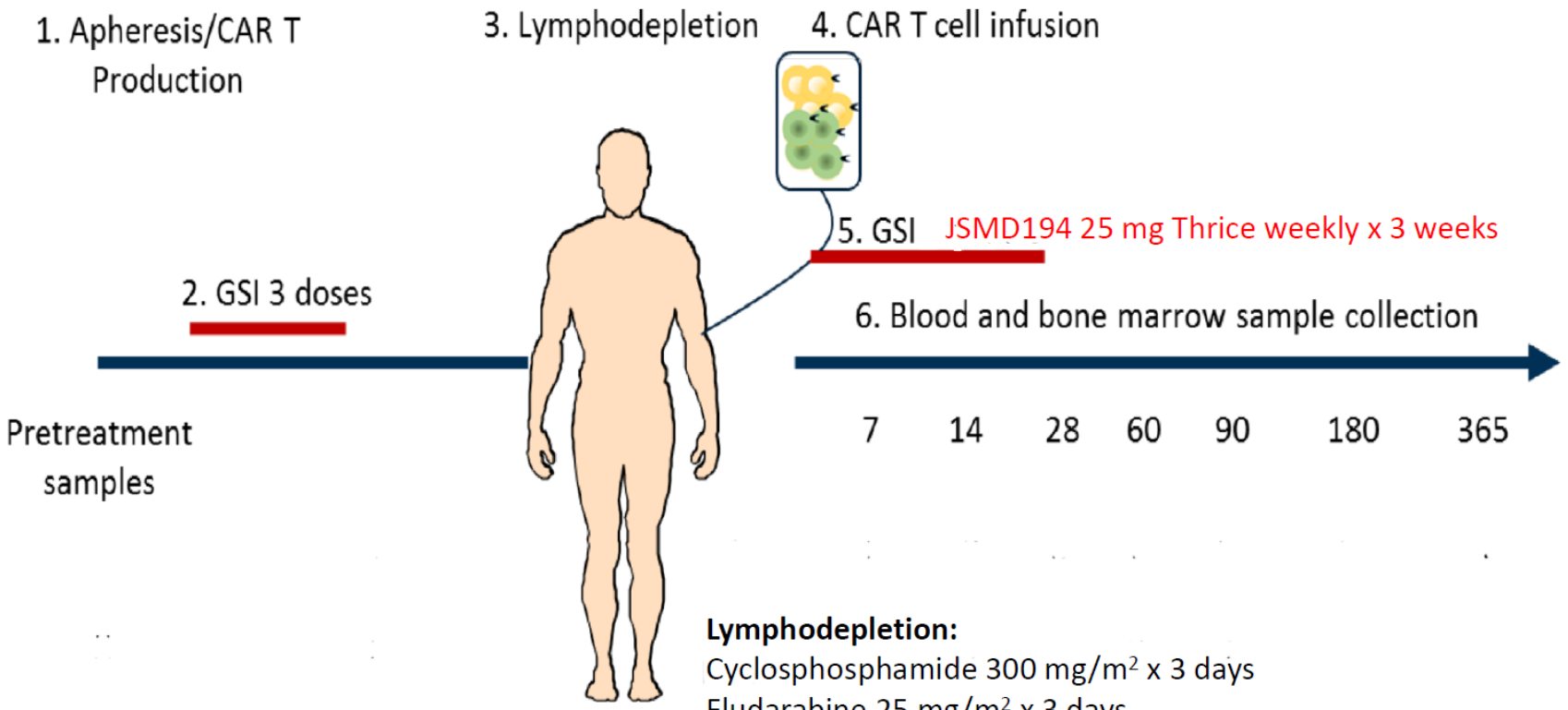
Seattle Cancer Care Alliance

Gamma Secretase Cleaves BCMA from Plasma Cells



Pont MJ et al. Blood. 2019 Nov 7; 134(19):1585-1597

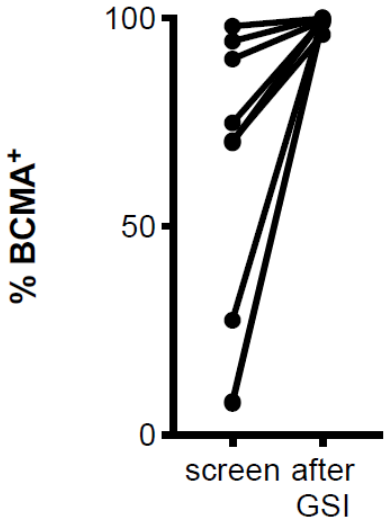
Study Design



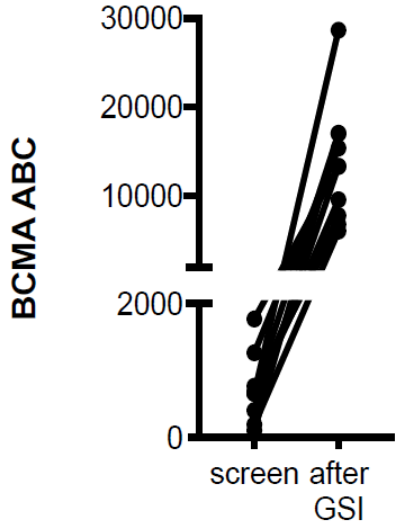
Lymphodepletion:
Cyclosphosphamide 300 mg/m^2 x 3 days
Fludarabine 25 mg/m^2 x 3 days

Gamma Secretase Inhibition Increases BCMA Expression and Surface Density

See ASH Abstract #1856



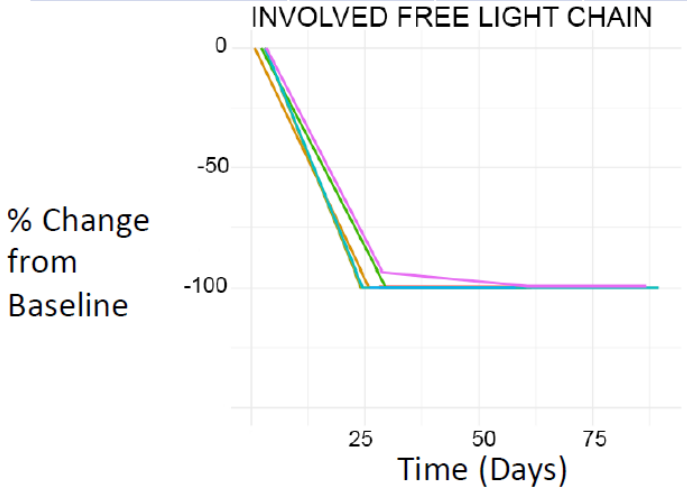
Median BCMA Expression Post GSI 99% (96 – 100%)

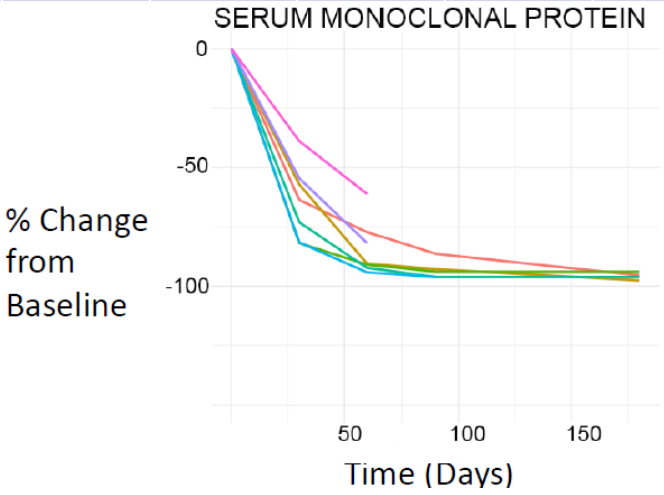


Median 20-Fold Increase in BCMA Surface Density (8 – 157 fold)

Bone Marrow and IMWG Responses

Patient	50 x 10^6 Dose					150 x 10^6 Dose			300 x 10^6 Dose	
	1	2	3	4	5	6	7	8	9	10
Pre	15%	30%	40%	50%	25%	10%	80%	70%	10%	90%
D28	--	--	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**1%**	**0%**
Best Response	VGPR	VGPR	CR	VGPR	PR	sCR	VGPR	VGPR	PR	sCR
Days on Study	444	71	413	280	184	136	150	111	79	51





Data Cut Off 11/7/2019

Conclusions

- BCMA CAR T cells in combination with a gamma secretase inhibitor appears to be well tolerated
- At the lowest dose level, 50 x 10^6, we report a 100% overall response rate
- No patients have relapsed or progressed to date, even amongst the lowest dose cohort
- 9/10 patients are alive and disease free at time data cut off
- Elucidation of impact on durability and CAR T cell persistence is ongoing in follow up

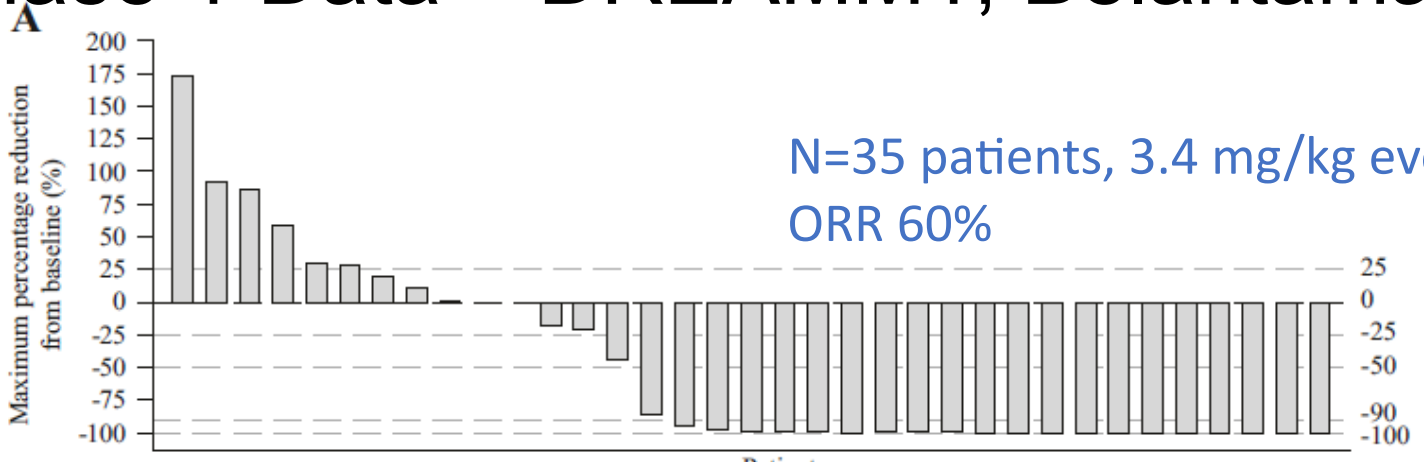
Belantamab mafodotin (Blenrep)

- BCMA Antibody drug conjugate – mafodotin is the toxin (microtubule inhibitor)

- FDA granted accelerated approval based on response rate as of 8/2020:

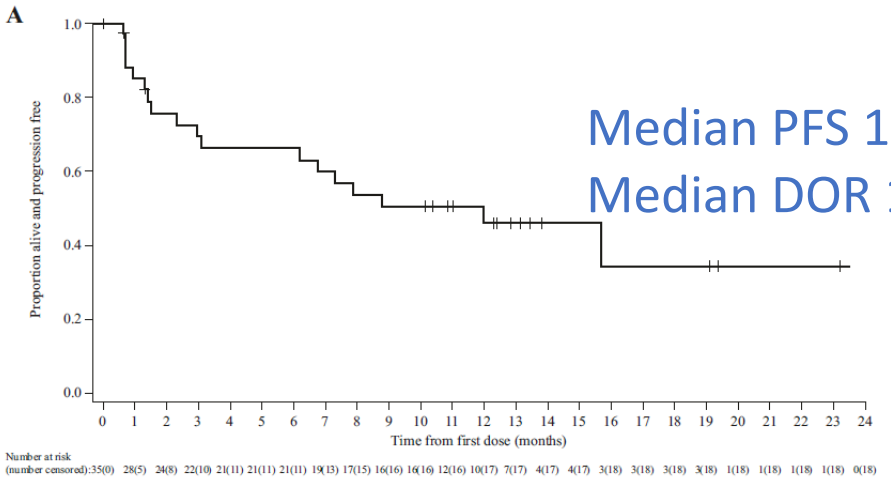
- Relapsed or refractory MM who have received at least 4 prior therapies, including:
  - CD38 monoclonal antibody
  - PI
  - IMiD

Phase 1 Data – DREAMM1, Belantamab



N=35 patients, 3.4 mg/kg every 3 weeks

ORR 60%



Median PFS 12 months

Median DOR 14.3 months

Trudel et al Blood Cancer J 2019

Phase 2 Data, DREAMM2

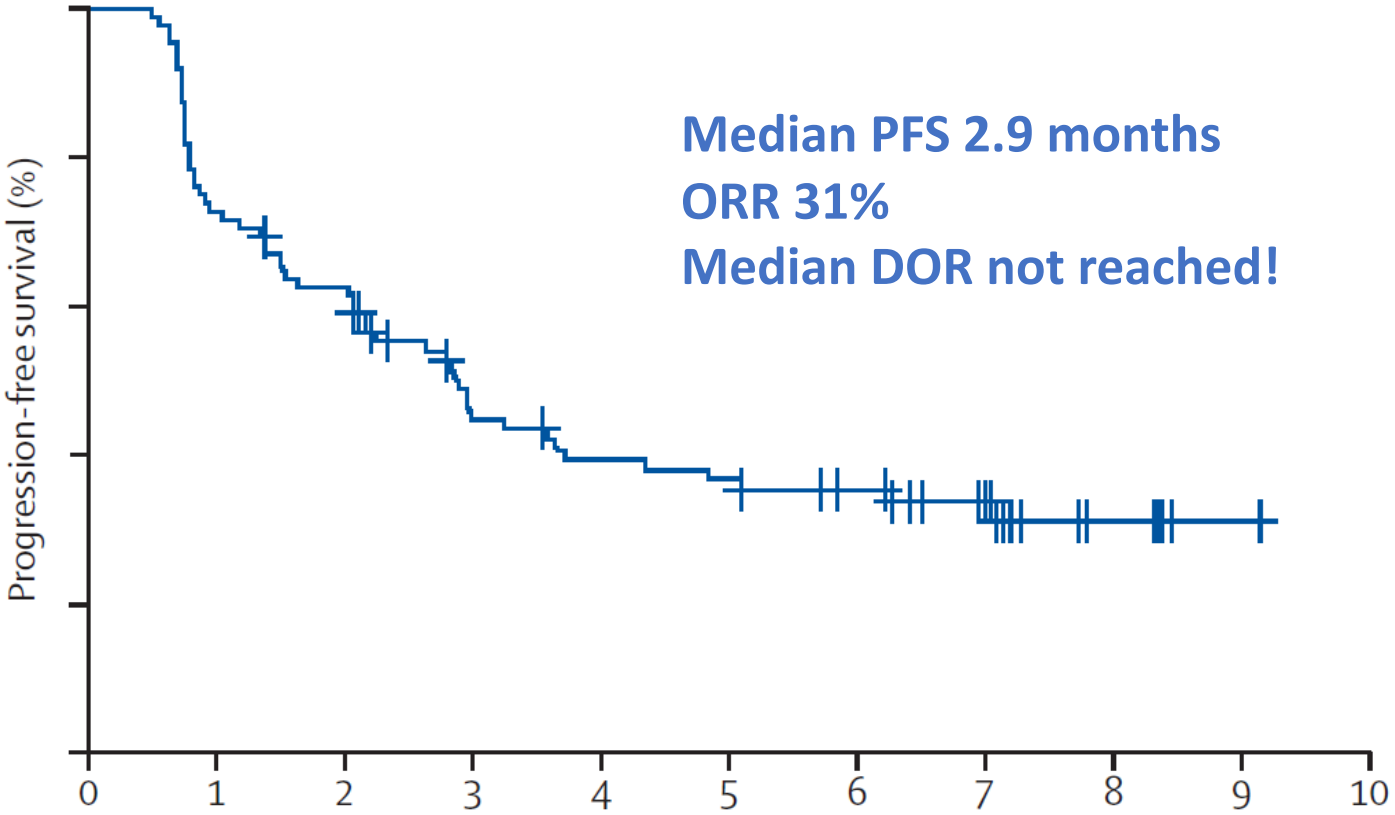
- Open label Phase 2 Global Study

- Eligibility:
  - >= 3 prior lines of therapy
  - Refractory to IMIDs, Pis, and refractory or intolerant of CD38 Mab.

- Randomization:
  - 1:1, 3.4 mg/kg vs 2.5 mg/kg

Lonial S et al Lancet Onc 2020

Outcomes of DREAMM2



Median PFS 2.9 months
ORR 31%
Median DOR not reached!

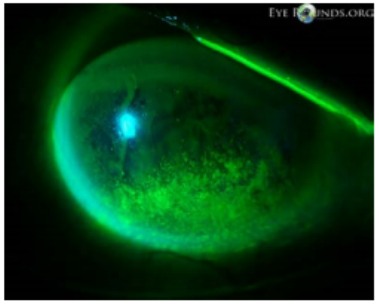
Lonial S et al Lancet Onc 2020

Ocular toxicity from BLENREP: Keratopathy

Mechanism of Ocular Toxicity

- Mechanism not completely understood; class effect for MMAF-containing ADCs
- Keratopathy: damage to the corneal epithelium; risk of corneal ulcers
- Ophthalmic exams at baseline and prior to each dose in DREAMM-2
- Dose modifications are the primary mitigating strategy
- Topical corticosteroids showed no impact in DREAMM-2 ocular sub-study

ADC=antibody-drug conjugate, MMAF=monomethyl auristatin F (mafodotin)



Source: https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/Punctate-epithelial-erosions/Exposure-PEE-LRG.jpg

- 44% had severe keratopathy
- Decreased visual acuity and severe vision loss in some patients
- Interference in ADLs, driving, reading
- Can occur with or without anti-Myeloma response

Source: FDA ODAC BLA 761158 July 14 2020

Ocular Symptoms in Patients with Keratopathy

Adverse Event	2.5 mg/kg (N=95) n (%)	3.4 mg/kg (N=99) n (%)
Patients with keratopathy	67 (71)	76 (77)
Symptoms in patients with keratopathy		
Any ocular symptoms*	29 (43)	42 (55)
Blurred vision	21 (31)	29 (38)
Dry eye	12 (18)	18 (24)
Photophobia	3 (4)	5 (7)
Eye pain	1 (1)	3 (4)

*Includes preferred terms diplopia, dry eye, eye irritation, eye pain, eye pruritus, foreign body sensation in eyes, lacrimation increased, ocular discomfort, ocular hyperemia, photophobia, vision blurred, visual acuity reduced, and visual impairment

Source: FDA Analysis

Source: FDA ODAC BLA 761158 July 14 2020

Outcomes of Keratopathy

	Primary Analysis 2.5 mg/kg (N=95) n (%)	90-Day Update 2.5 mg/kg (N=95) n (%)
Any grade keratopathy*	67 (71)	68 (72)†
Grade ≥2 keratopathy	59 (62)	60 (63)
Recovery rate (Grade ≥2 events)	24 (41)	29 (48)
Not resolved, treatment ongoing	17 (29)	13 (22)
Not resolved, follow-up ongoing	4 (7)	3 (5)
Not resolved, follow-up ended$^{\Delta}$	14 (24)	15 (25)
Median time to resolution (Grade ≤1), days (range)	62 (11-193)	78 (11-232)

*Based on grading of keratopathy identified on ophthalmic exam (corneal exam component of KVA scale)

†Includes a Grade 4 keratopathy event of bilateral corneal ulcers in 1 patient

$^{\Delta}$Includes patients who either died or were lost to follow-up with persistent keratopathy at the final assessment

Source: FDA ODAC BLA 761158 July 14 2020

Blenrep REMS

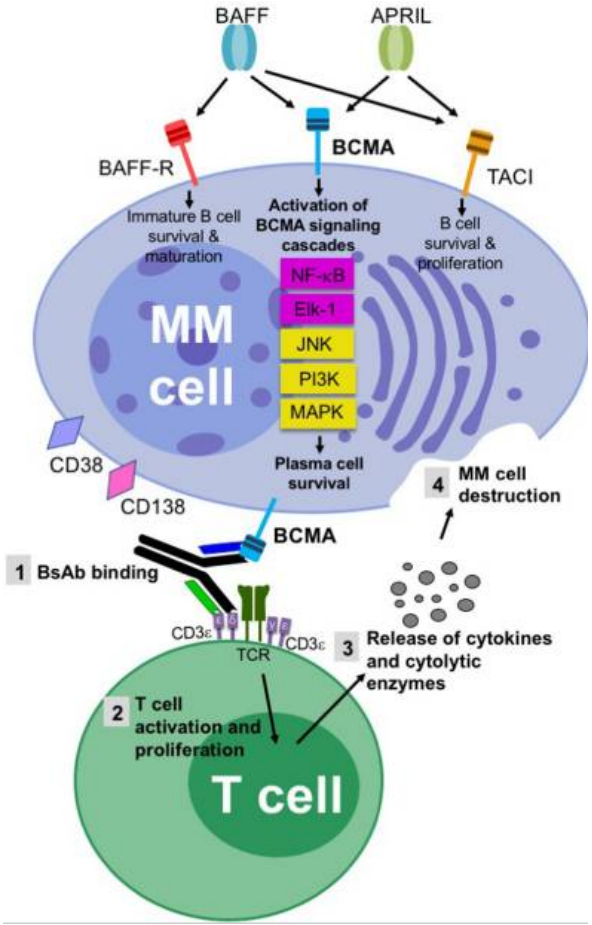
- REMS (like we have for Revlimid – Risk Evaluation and Mitigation Strategy
- Required by FDA given the risk of ocular toxicity
- Baseline ophthalmic examinations are required at baseline, prior to each dose, and promptly for worsening symptoms
- Patients need to use preservative-free lubricant eyedrops and avoid contact lenses

Summary: Blenrep Approval 2020

- Belantamab – first new approval for a BCMA targeted therapy
- Although PFS was modest, the duration of response was very promising (currently median DOR not reached)!
- Ocular toxicities a major concern – can happen even if there is no clinical benefit from the drug
- REMS program in place – will likely pose challenges towards widespread use outside academic centers
- UW/FH/SCCA will plan on being able to offer Belantamab to patients, soon

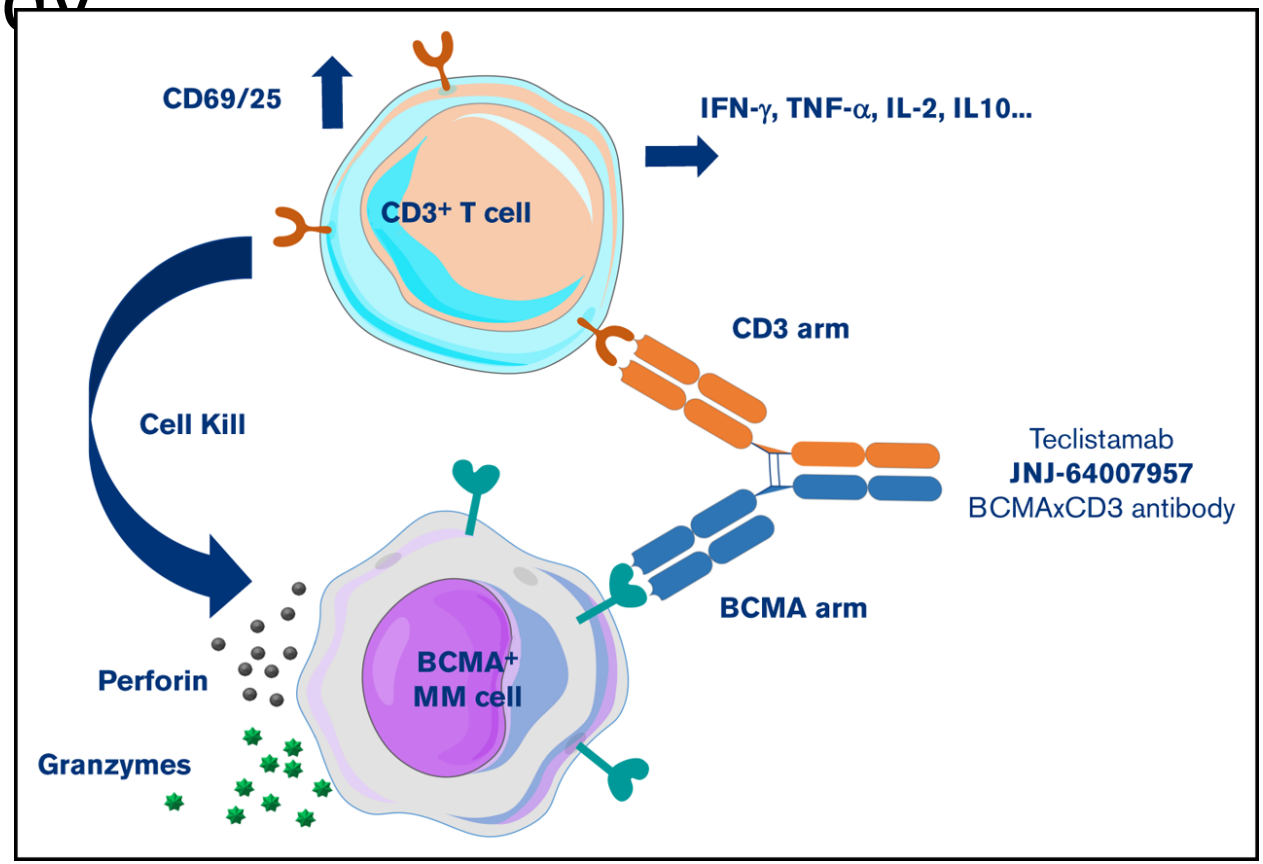
T Cell Engagers – BCMA

- Teclistimab – Janssen, BCMA/CD3 TCE
- CC93269 – BCMA x CD3 TCE
- AMG 420, AMG 701 – BCMA BITE, Amgen
- HPN217 – BCMA TriTAC
- TNB-383B – BCMA x CD3 BITE



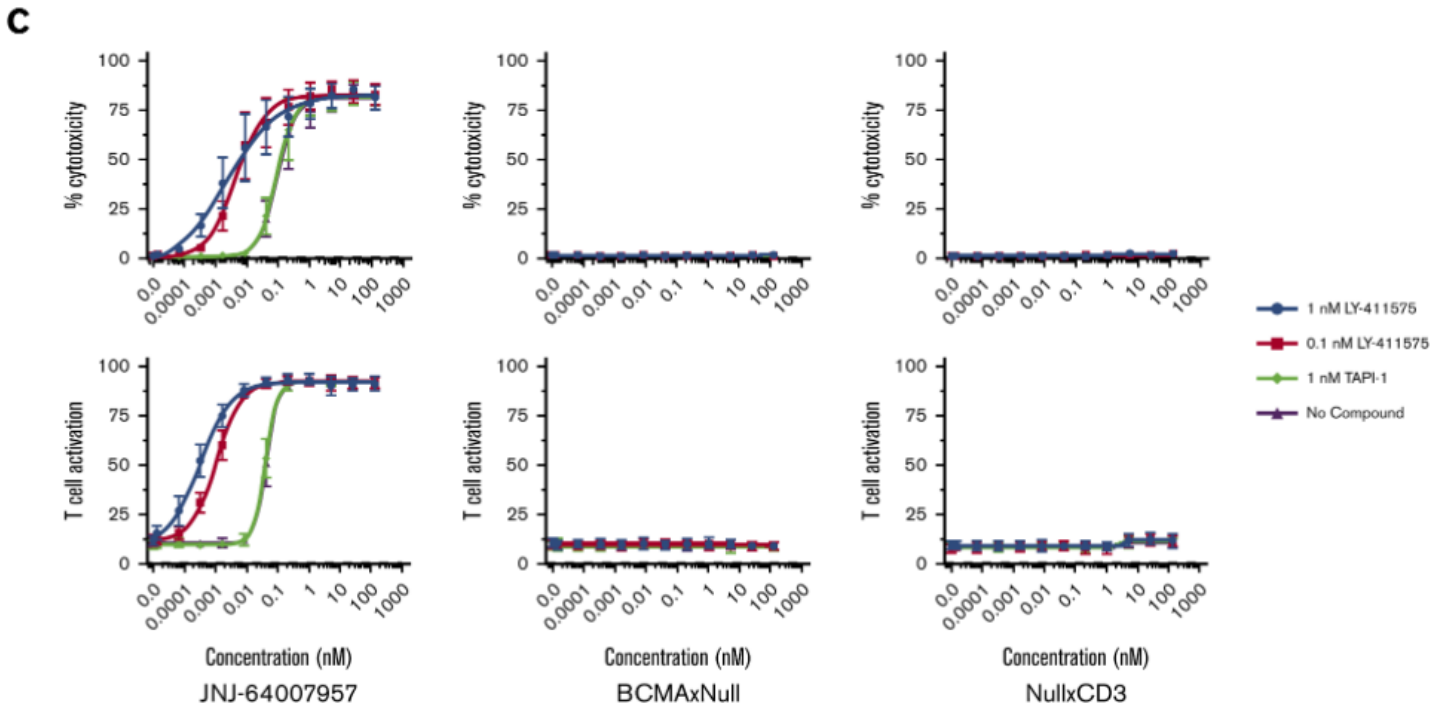
Caraccio et al Frontiers in Immunology 2020

Teclistimab – BCMA T cell redirecting antibody



Kodandaram Pillarisetti, Teclistamab is an active T cell–redirecting bispecific antibody against B-cell maturation antigen for multiple myeloma, Blood Adv, 2020

Teclistimab in combination with a GSI



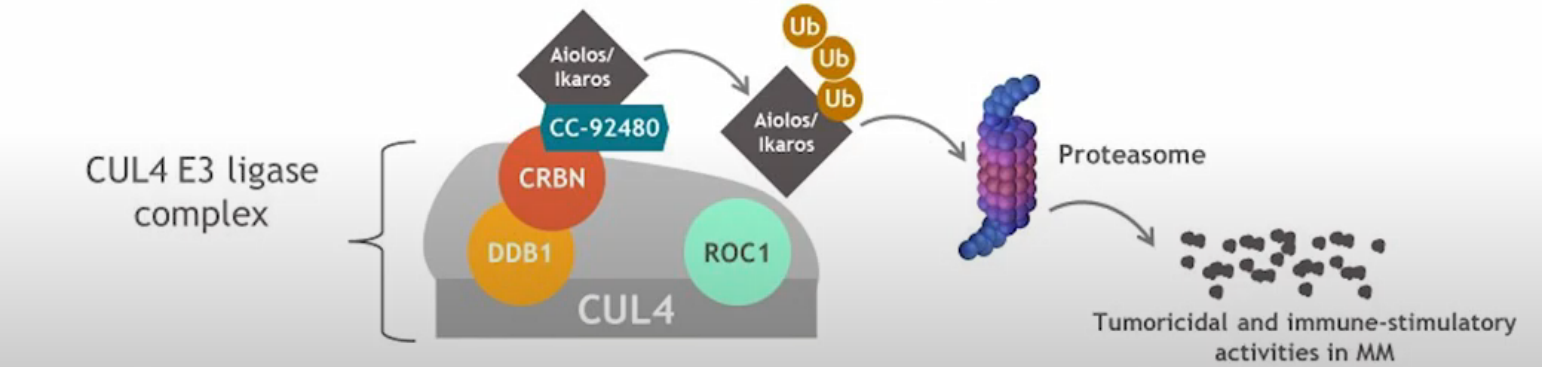
Kodandaram Pillarisetti, Teclistamab is an active T cell–redirecting bispecific antibody against B-cell maturation antigen for multiple myeloma, Blood Adv, 2020

HPN-217 – BCMA TCE – will open soon at FH/SCCA

- HPN-217: TriTAC – Trispecific T cell Activating Construct – designed to address shortcomings of existing TCE:
  - Current drawbacks: short t1/2, limited tissue penetration, suboptimal activity
  - TriTAC – potentially allows for extended half life, and size (50 kDa) is smaller than an MaB, potentially allowing for greater tissue diffusion.
- Phase 1/2 dose finding and expansion study will open soon at SCCA/ FH; already open at Swedish

Cereblon E3 Ligase Modulators (CELMoDs)

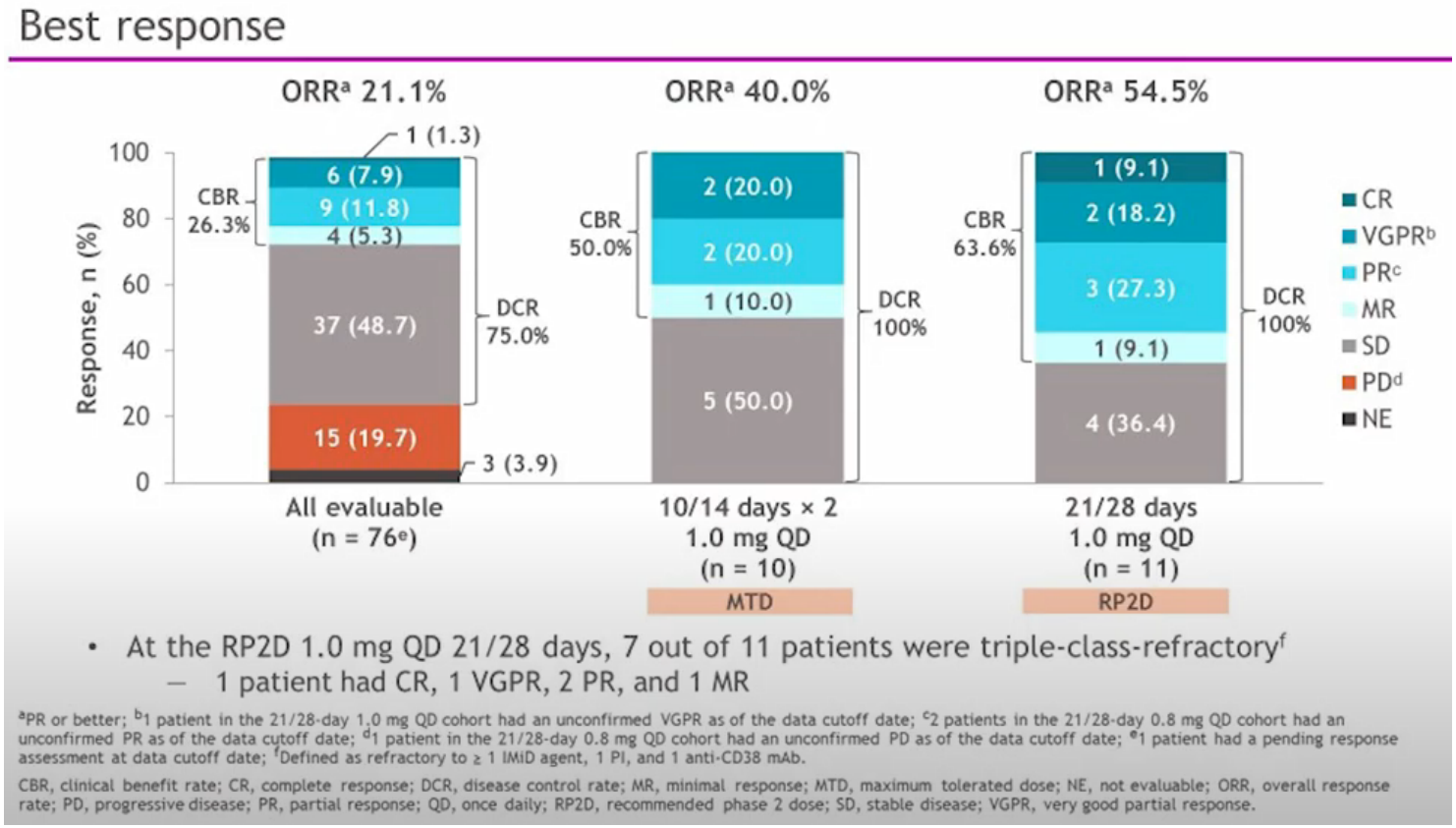
- CELMoDs: agents designed for degradation of target proteins – Ikaros and Aiolos
  - Increased anti-myeloma activity in vitro
  - Efficacy in LEN and POM resistant cell lines



CRBN, cereblon; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; DEX, dexamethasone; LEN, lenalidomide; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; POM, pomalidomide; ROC1, ring-box 1, E3 ubiquitin protein ligase; SoC, standard of care; Ub, ubiquitin.

1. Hansen J et al. *J. Med. Chem.* 2020. 2. Lopez-Girona A, et al. *Blood*. 2019:134:abstract 1812. 3. Wong L, et al. *Blood*. 2019;134:abstract 1815.

CC92480 – a new, potent CELMoD



Richardson P et al, ASCO Annual Meeting, 2020

CC92480 – Common side effects

TEAEs all cycles

Common (> 20 % all grade) TEAEs and events of interest, n (%)	All doses (N = 76)		
	All grade	Grade 3	Grade 4
Neutropenia	56 (73.7)	23 (30.3)	26 (34.2)
Febrile neutropenia	6 (7.9)	4 (5.3)	1 (1.3)
Anemia	42 (55.3)	24 (31.6)	-
Thrombocytopenia	33 (43.4)	5 (6.6)	7 (9.2)
Infections	54 (71.1)	25 (32.9)	2 (2.6)
Pneumonia[a]	13 (17.1)	11 (14.5)	-
Fatigue	29 (38.2)	7 (9.2)	-
Pyrexia	17 (22.4)	3 (3.9)	-
Peripheral sensory neuropathy	4 (5.3)	-	-
Diarrhea	18 (23.7)	1 (1.3)	-
Nausea	17 (22.4)	1 (1.3)	-
Deep vein thrombosis	1 (1.3)	-	-

- Prophylactic G-CSF was not permitted during Cycle 1
- Neutropenia was managed with dose interruption/reduction and G-CSF
- Dose reductions of CC-92480 occurred in 17 (22.4%) patients
- No patients discontinued due to treatment-related AEs

[a]Includes Medical Dictionary for Regulatory Activities Terminology version 22.0 preferred terms pneumonia, pneumocystis jirovecii pneumonia, respiratory syncytial viral pneumonia, and staphylococcal pneumonia.

AE, adverse event; G-CSF, granulocyte colony-stimulating factor; MTD, maximum tolerated dose; TEAE, treatment-emergent adverse event.

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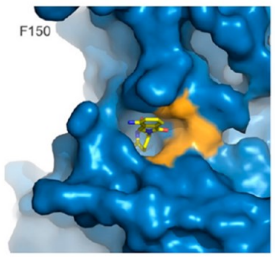
Richardson P et al, ASCO Annual Meeting, 2020

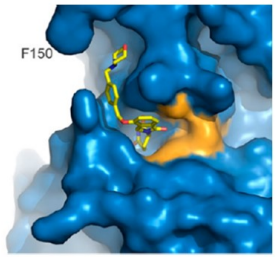
IBERDOMIDE MECHANISM OF ACTION

- IBER enhances in vitro immune stimulatory activity versus LEN and POM[1]

LEN[2]

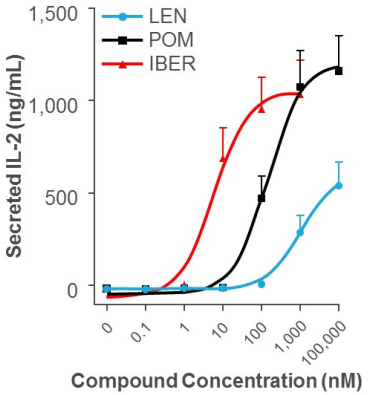


IBER[2]

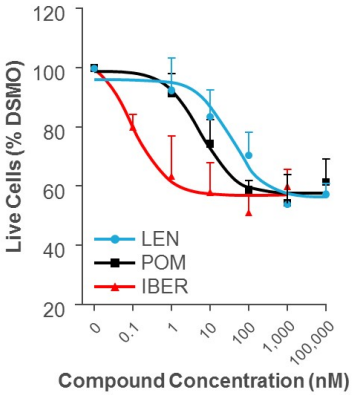


EC_{50}, nM[2]	Ikaros	Aiolos
LEN	67	87
POM	24	22
IBER	1	0.5

IL-2 Secretion by Treated PBMCs[1]



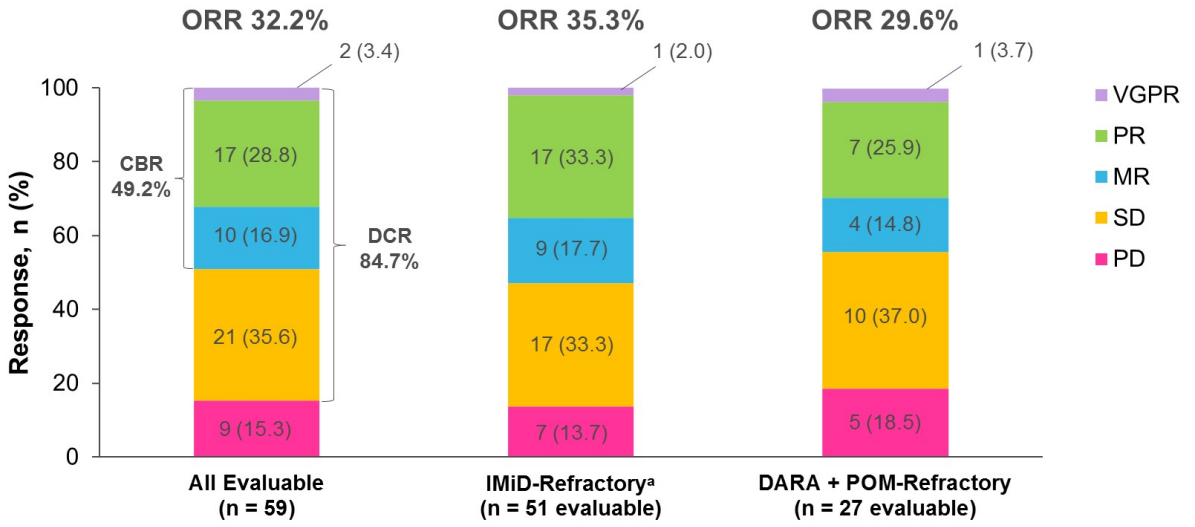
MM Cell Survival in Co-Culture With Treated PBMCs[1]



BORT, bortezomib; DARA, daratumumab; DSMO, dimethylsulfoxide; EC_{50}, half maximal effective concentration; IL, interleukin; NK, natural killer; PBMC, peripheral blood mononuclear cell.

1. Bjorklund CC, et al. Unpublished data. 2. Adapted with permission from Matyskiela ME, et al. J Med Chem. 2018;61:535-542 © 2018 American Chemical Society.

RESPONSE



Evaluable patients include patients who have received ≥ 1 dose of IBER, had measurable disease at baseline, and ≥ 1 post-baseline response assessment.

[a] Includes LEN and POM.

CBR, clinical benefit rate; DCR, disease control rate; MR, minimal response; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response.

Presented By Sagar Lonial at 2019 ASCO Annual Meeting

CONCLUSIONS

- IBER is a novel CELMoD compound with enhanced tumoricidal and immune stimulatory effects in preclinical studies[1]
  - Overcomes LEN and POM resistance[2]
- IBER + DEX showed a favorable safety and activity profile in patients with heavily pretreated RRMM
  - MTD / RP2D has not yet been reached
- ORR in patients refractory to LEN, POM, and / or CD38 antibody therapy was similar to that observed for whole cohort
- Enrollment continues in cohorts evaluating the combination of IBER + DEX with BORT, DARA, and CFZ as part of a broad development program for iberdomide

1. Bjorklund CC, et al. Blood. 2016;128:abstract 1591. 2. Bjorklund CC, et al. Unpublished data.

Summary

- Many new active agents are coming soon for relapsed/refractory MM

- BCMA Targeting:
  - Now FDA approved – belantamab mafodotin – ocular toxicity/REMS
  - T Cell engagers
  - CAR T cells

- CELMoDs: iberdomide and CC-92480

Questions?

- Andrew Cowan, acowan@uw.edu