Highlights from IMW 2019

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Bologna
Royal Hotel Carlton

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Anticorpi Coniugati con Farmaci

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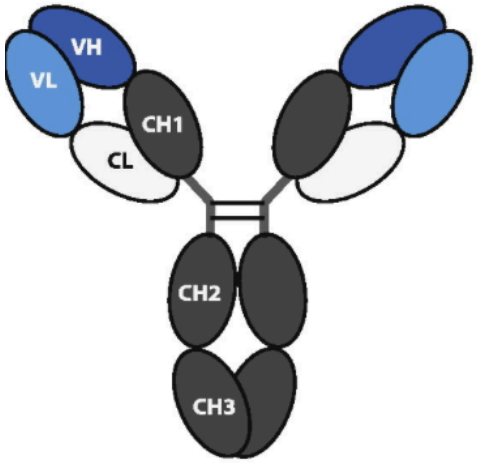
DISCLOSURES:
ADVISORY BOARD CELGENE JANNSEN

Next generation antibody therapeutics

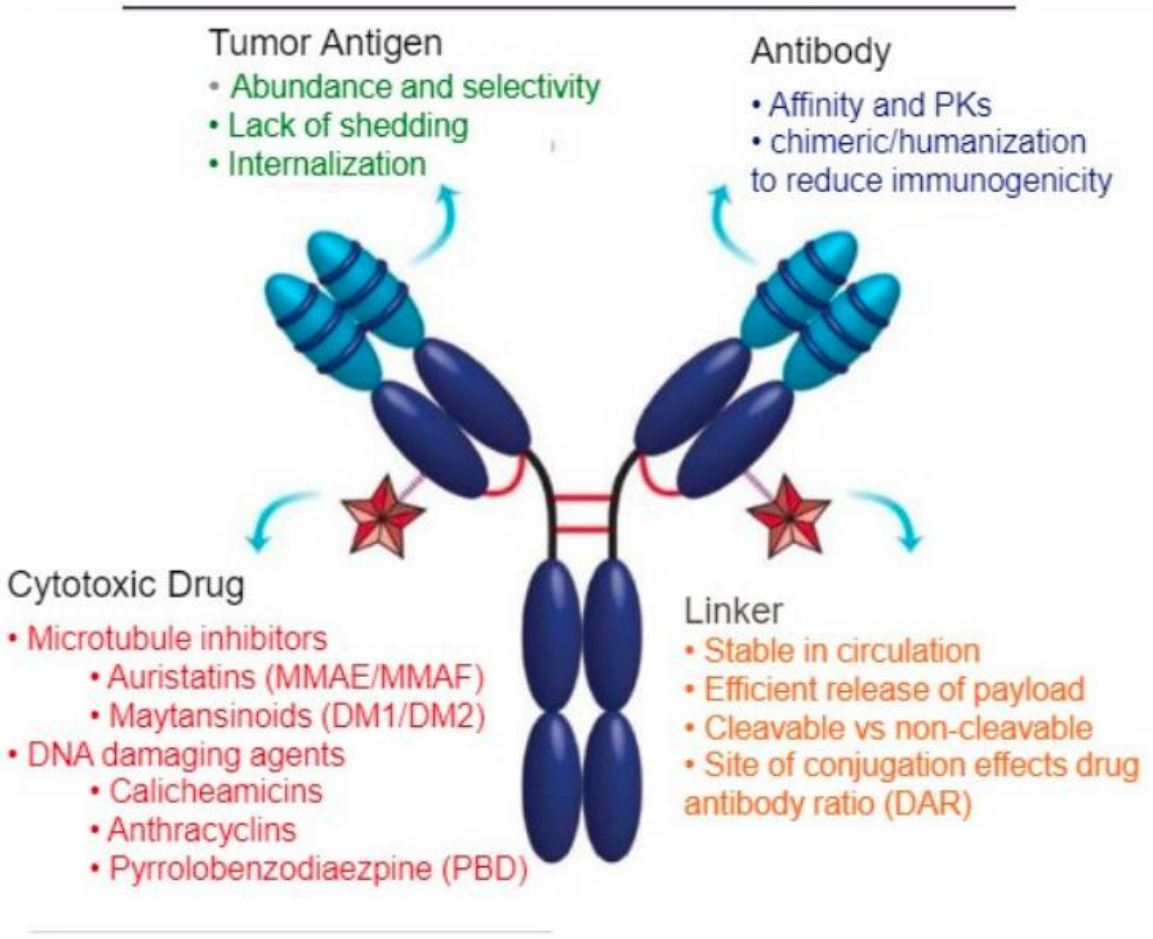
Monoclonal Antibody



IgG

Elgundi Z et al Advanced Drug Delivery Reviews 2017

Structure and Mechanism of Action of Antibody Drug Conjugated



ADC developed for Myeloma therapy

Agent	Target	Payload	Phase 1 activity	Current status
Indatuximab Ravtansine [1]	CD138	DM4	ORR 11%, SD 41%	Phase i/II completed
Lorvotuzumab Mertansine [2]	CD56	DM1	OR 18% SD28%	Discontinued in myeloma
Milatuzumab-DOX[3]	CD74	Doxorubicin	SD26%	Phase I completed
DFRF4539A[4]	FcRH5	MMA-E	OR 5% SD49%	Development discontinued
Belantamab Mafodotin [5]	BCMA	MMA-F	OR 60% (54% $\geq$ VGPR)	Phase II completed
ABBV-838	SLAMF7	MMA-E	NR	Phase I terminated
SGN-CD48A	CD48	MMA-E	NR	Phase I
STRO-001	CD74	MMA-F	NR	Phase I recruiting
CC-99712	BCMA	pAMF		IND approved
MEDI2228	BCMA	PBD	NR	Phase I
FOR46	CD46	PBD	NR	Phase I recruiting

HDP-101 anti-BCMA α-amantadin conjugated ADC, Sing et al FP 167; MEDI2228 Tai et al FP-171; anti-CD46 DCA Sherbenou FP166

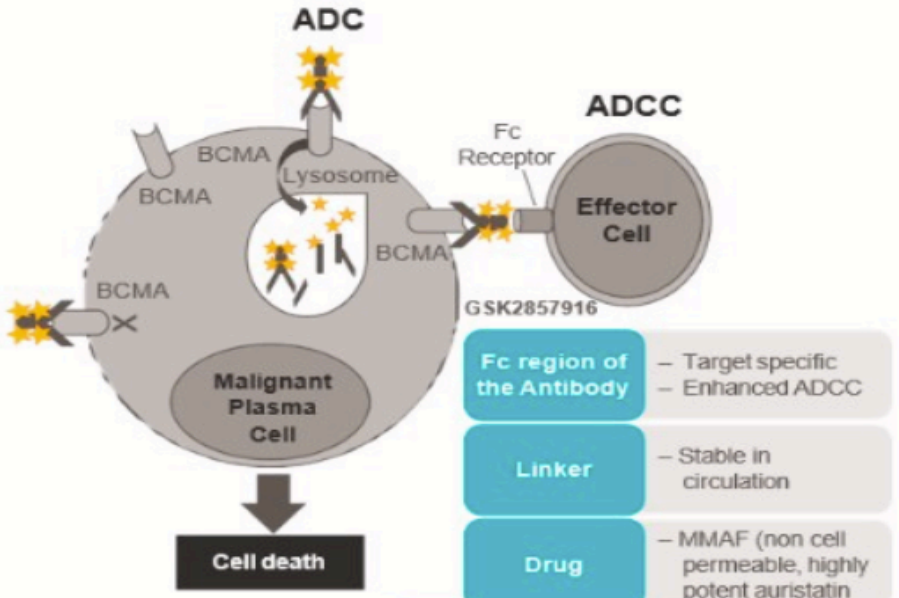
Monomethyl Auristatina E (MMAE) and F (MMAF); PBD Pyrrolobenzodiazepine; maytamsinoid (DM1) and ravtansine (DM4)

[1]Jagganath S et al Clin Lymphoma Myeloma Leuk 2019, 19:372; [2]Alawadi et al Clin Lymphoma Myeloma Leuk 2019; [3]Kaufman et al Br J Haematol 2013; [4]Stewart AK BCJ 2019; [5]Trudel et al BCJ 2019

Belantamab mafodotin: First-in-class anti-BCMA ADC agent for treatment of multiple myeloma

The target	▪ BCMA plays a key role in plasma cell survival ▪ It is found on the surfaces of plasma cells and is expressed on malignant plasma cells ▪ Not expressed in healthy tissues
The agent	▪ Belantamab mafodotin* is a humanized IgG1 antibody targeting BCMA (B-cell maturation antigen) ▪ Linked to the anti-mitotic agent MMAF ▪ Afucosylated to enhance ADCC
Key attributes	Easy and convenient to administer: 1h infusion q3w • Pre-medication for infusion reactions not permitted with 1st dose; pre-medication was recommended for subsequent infusions if the patient had an IRR • Prophylactic steroid eye drops before each dose

ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; MMAF, monomethyl auristatin-F



Mechanisms of Action:
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death
4. BCMA receptor signalling inhibition

DREAMM-1 Study: Overview

- **Primary objectives: safety and tolerability, MTD, recommended Phase 2/Part 2 dose**
- Secondary objectives: ORR, PK, ADA (anti-drug antibodies)

Population:
- Relapsed, refractory MM
- Undergone stem cell transplant (if eligible)
- Prior treatment with ≥3 classes of alkylators, proteasome inhibitors and immunomodulatory drug (if eligible)
- Progression on, or within 60 days of completion of the last therapy
- measurable disease

- Overall, 38 patients were evaluated in **Part 1 (doses 0.3-4.6 mg/kg) – no DLTs were observed**
- **Part 2: Expansion**
  - Relapsed/refractory MM (N=35; enrollment complete)
- **Expansion dose:** 3.4 mg/kg
- **Schedule:** 1h IV, once every 3 weeks
- **Treatment duration:** up to 16 cycles (up to 1 year)

Premedication:
- Premedication for infusion reactions not permitted with first dose and not mandated at subsequent doses
- Prophylactic steroid eye drops before each dose

Trudel et. al. BCJ 2019

DREAMM-1 Part 2: Demographics and Baseline Characteristics

Characteristic	Part 2 (N=35)
Age (years), median (min, max)	60 (46–75)
ISS at diagnosis I/II/III/unknown n (%)	19 (54)/6(17)/4(11)/6(17)
ECOG PS 0/1, n (%)	10 (29)/25 (71)
≥5 prior lines, n (%)	20 (57)
ASCT	31 (89)
IMiDs, n (%) Lenalidomide Pomalidomide **Refractory to IMiD**	**35 (100)** 33 (94) 22 (63) **33 (94)**
PI, n (%) Bortezomib/Carfilzomib **Refractory to PI, n (%)**	**35 (100)** 34 (97)/29 (83) **34 (97)**
Daratumumab, n (%) **Refractory to daratumumab, n (%)**	**14 (40)** **14 (40)**
Refractory to IMiD/PI, n (%)	**32 (91)**
Refractory to IMiD/PI and prior daratumumab, n (%)	**13 (37)**
Cytogenetics risk, n (%)* High risk Other (non-high risk, not done, or missing)	 10 (29) 25 (71)

*Patients with any of the following genetic abnormalities were considered high risk: t(4:14), del17, t(14:16), t(14:20), nonhiperdiploidy, or gain 1q

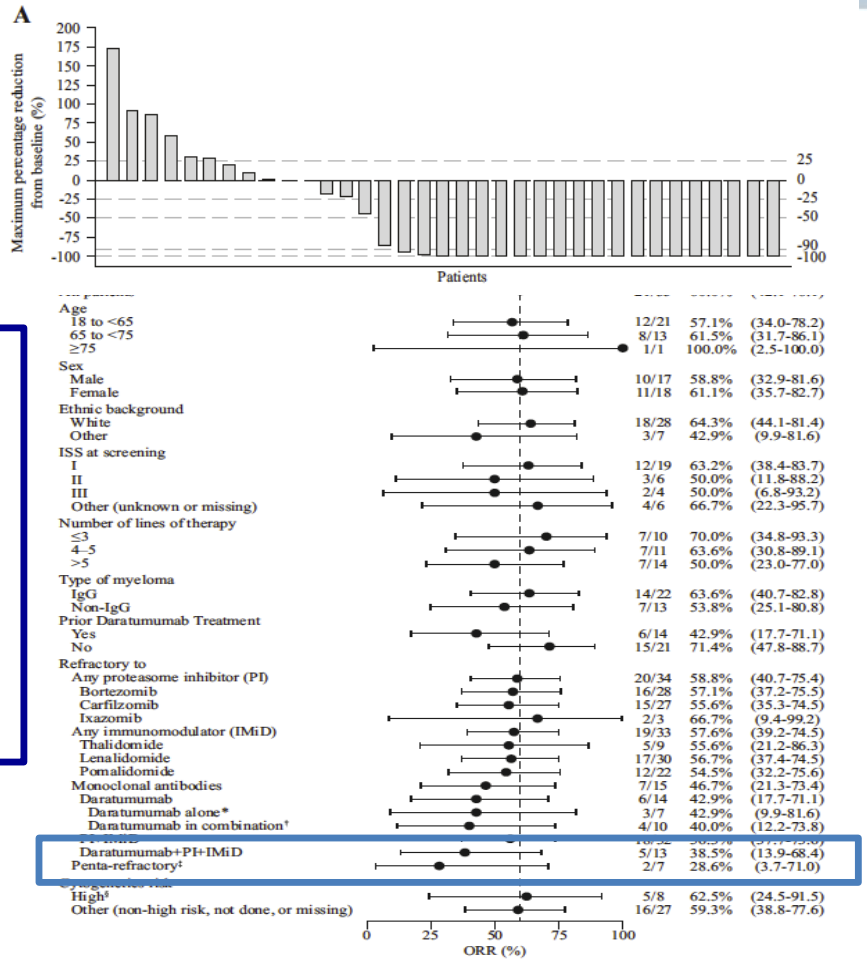
ASCT, autologous stem cell transplant; IMiD, immunomodulator; PI, proteasome inhibitor

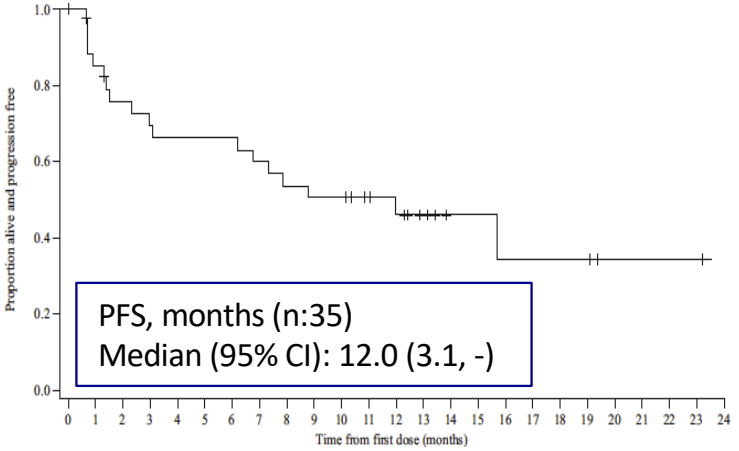
DREAMM 1: Efficacy

21/35 (60%) ORR

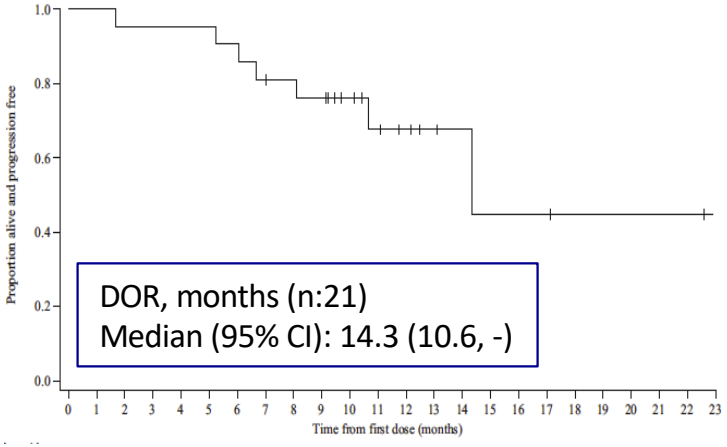
2(6%)	sCR
3 (9%)	CR
14 (40%)	VGPR
2 (6%)	PR

Median time to 1st response 1,2 months



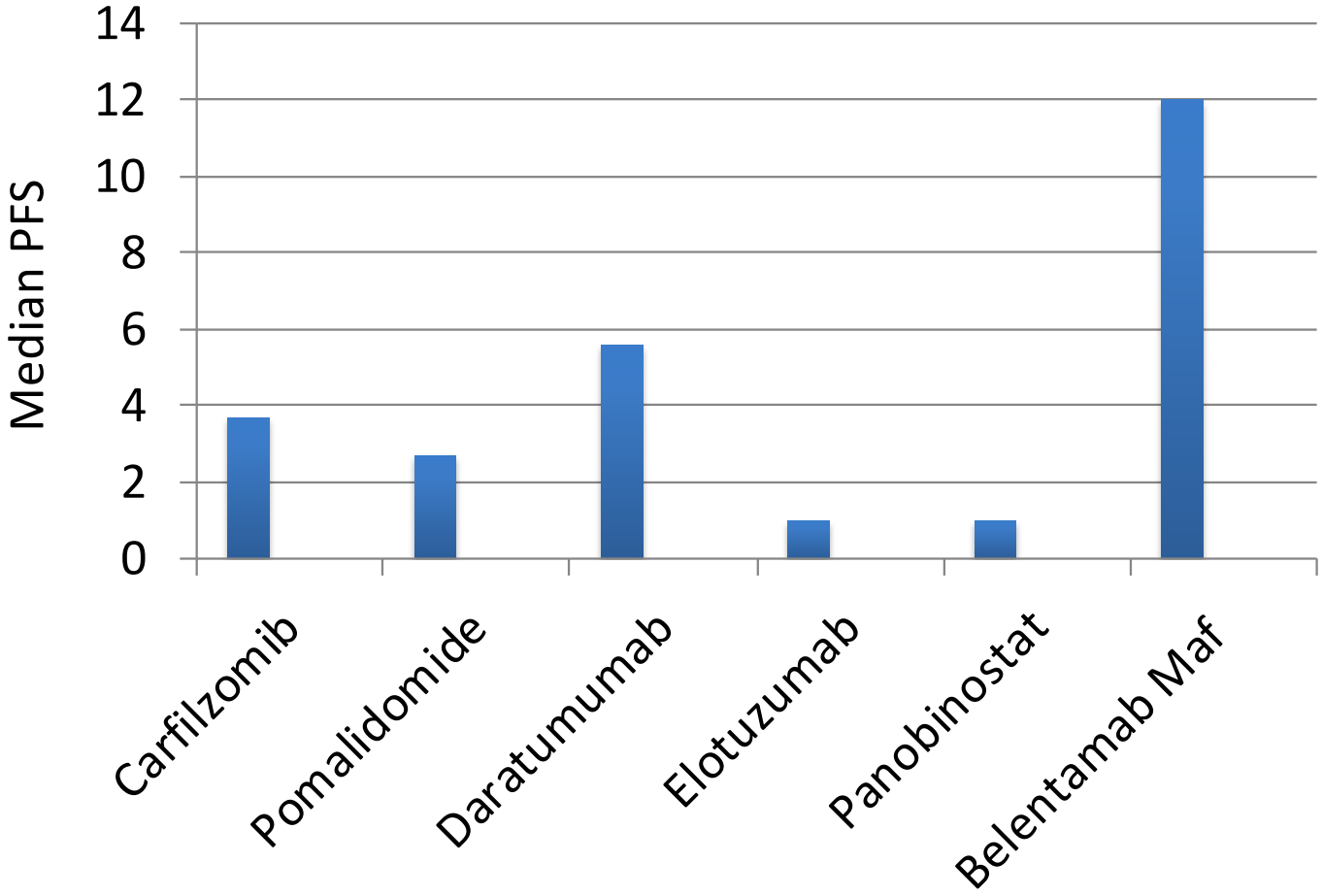


PFS, months (n:35)
Median (95% CI): 12.0 (3.1, -)



DOR, months (n:21)
Median (95% CI): 14.3 (10.6, -)

ORR new drugs as single agent



DREAMM-1 Study: Adverse Events Regardless of Relationship (Part 2)

Treatment-emergent AEs		
n (%)	N=35	
	Any grade*	≥Grade 3
Any event	35 (100)	29 (83)
Thrombocytopenia†	22 (63)	12 (34)
Vision blurred	18 (51)	1 (3)
Cough	14 (40)	0 (0)
AST increased	13 (37)	2 (6)
Dry eye	13 (37)	1 (3)
Nausea	11 (31)	0 (0)
Anemia	10 (29)	6 (17)
Diarrhea	12 (34)	4 (11)
Photophobia	10 (29)	0 (0)
Pyrexia	10 (29)	0 (0)
Chills	9 (26)	0 (0)
Fatigue	8 (23)	0 (0)
URT infection	8 (23)	0 (0)

No Grade 5 events were reported

Most frequent ≥Grade 3 treatment-emergent AEs:

- Thrombocytopenia (n=12; 34%)
- Anemia (n=7; 17%)

SAEs were reported in 17 patients (49%), most frequently:

- Pneumonia (n=3; 9%)
- Lung infection (n=2; 6%)
- IRR (n=2; 6%)

AESIs included corneal events (n=24; 69%), **thrombocytopenia** (n=22; 63%) and **IRR** (n=10; 29%)

AEs leading to study treatment discontinuation (n=4; 11%) included:

- Thrombocytopenia, keratopathy, fatigue, cough, and increased ALT, AST,

Trudel et al, Lancet Oncol. 2108; 19: 1641; Trudel et al, BJC 2019;9:37

DREAMM-1 Part 2: Corneal Adverse Events by Grade

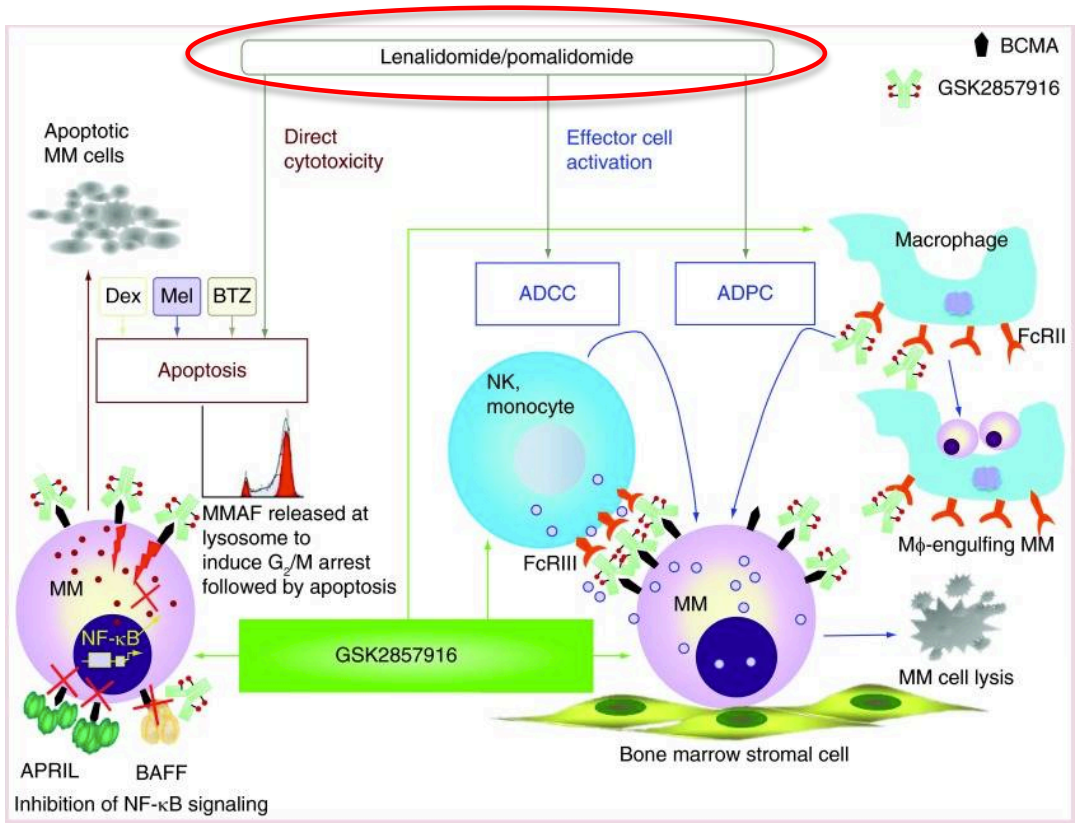
	Maximum Grade, n (%)		
Preferred term	**1-2**	**3**	**Total**
Vision blurred	17 (49)	1 (3)	18 (51)
Dry eye	12 (34)	1 (3)	13 (37)
Photophobia	10 (29)	0	10 (29)
Lacrimation increased	4 (11)	0	4 (11)
Keratitis	1 (3)	2 (6)	3 (9)
Eye pain	3 (9)	1 (3)	2 (6)
Keratopathy	3 (9)	0 (0)	3 (9)
Eye pruritus	1 (3)	0	1 (3)
Night blindness	0	1 (3)	1 (1)
Any event	**19 (54)**	**5 (14)**	**24 (69)**

- Across oncology indications > 300 patients have been dosed with MMAF-Containing ADCs across different cancer types
  → All Associated with Corneal Toxicity, **MMAF-induced corneal toxicity seems to be reversible**

Trudel et al. Lancet Oncol. 2108; 19: 1641; Trudel et al. BJC 2019;9:37

Belantamab Mafodotin future directions

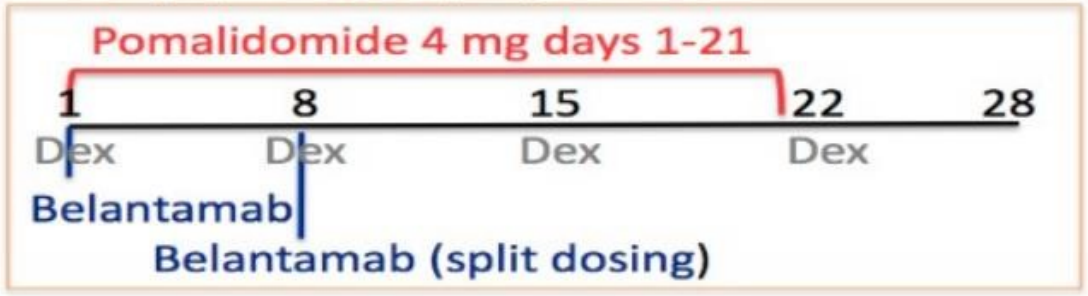
The mechanism of actions favours combination activity, particularly with ImiDs



Yai et al Immunotherapy 2015, 7:1187

The ALGONQUIN Study: A Phase 1/2 Study to Determine the RP2D, Safety and Efficacy of belantamab mafodotin (GSK2857916) in Combination with Pomalidomide and Low Dose Dexamethasone in Subjects with RRMM

28 day cycles until progression



- Pomalidomide eligible patients
  - -≥ 2 prior lines of treatment and lenalidomide refractory and proteosome inhibitor exposed
- 7 patients enrolled at 2.5 mg/kg single dose (Cohort 1a)
  - one unevaluable for DLT assessment
  - 7 evaluable for response after at least one cycle

Determination of MTD and Recommended Phase 2 Dose (RP2D)

		POM mg Days 1-21	DEX mg Days 1.8.15.22	GSK2857916 mg/kg
Phase I	Cohort -1	4	40 mg QD ≤ 75 years of age	1.92 (single)
	Cohort 1a	4	20 mg QD > 75 years of age	2.5 (single)
	Cohort 1b			2.5 split*
	Cohort 2	4		3.4 split**

35 patients at the RP2D to determine ORR

ORR, overall response rate;
*1.25 mg/kg days 1 and 8; **1.7 mg/kg days 1 and 8

Clinicaltrials.gov identifier: NCT03715478

Algonquin Study 2.5 mg/kg single cohort: Safety, Maximum Response and Duration of Study Treatment

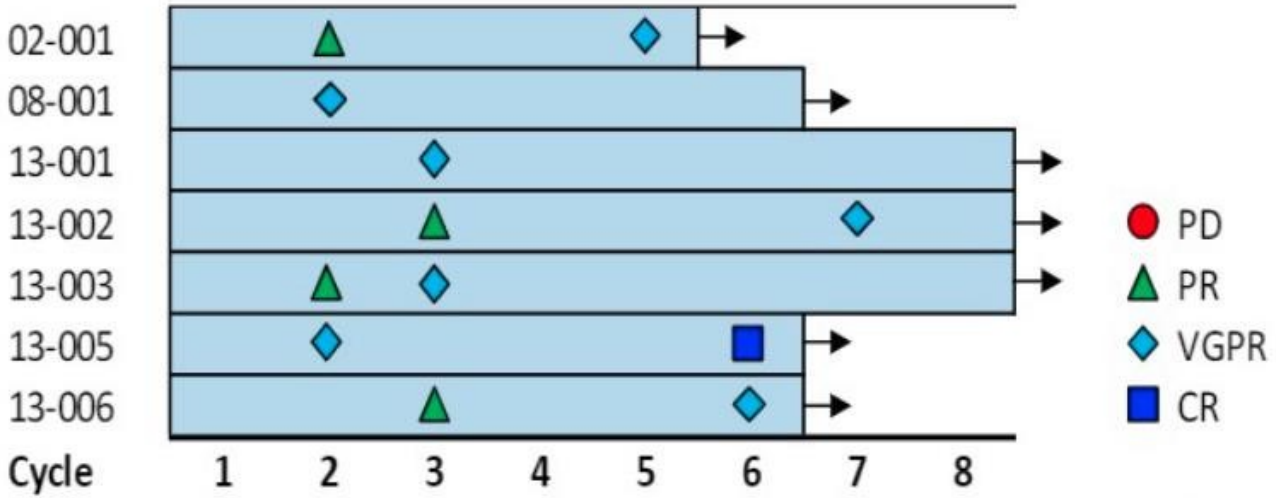
Patient Characteristics

- Median prior lines of therapy, min-max: 3 (2-5);
- 100% LEN refractory; 100% PI exposed, 86% PI refractory; 86% refractory to LEN/PI; 14% dara exposed/refractory
- 4/7 (54%) high risk (t(4;14); del17, t(14:16), t(14:20) or gain 1q)

ORR = 7/7 (100%)
•1 sCR, 6 VGPR

Safety

- One DLT: grade 3 corneal toxicity
- With the exception of grade 2 pneumonitis, no unexpected safety signal
- Most frequent ≥Grade 3 AEs were eye disorder (100%)* and thrombocytopenia (34%)
- No AEs leading to study treatment discontinuation
- No Grade 4/5 AEs were reported
- No SAEs



data cut August 26, 2019

CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response; LEN, lenalidomide, PI, proteosome inhibitor, dara, daratumamab; DLT, dose limiting toxicity, AEs, adverse events, SAEs, serious AEs,

Pros/Cons of Anti BCMA Antibody Therapies

	AMG420	belantamab mafodotin
Pros	• Off the shelf • Deep responses seen • Limited severe CRS - ? elderly • Can be given in community settings ?	• Off the shelf • Encouraging response rates • No CRS • Can be given in community settings • 1 hour infusion every 3 weeks
Cons	• No data in triple class/penta refractory • Toxicities require further study – neuropathy • Treatment until progression • ? admissions with initial doses until CRS risk low • Dosing/schedule to be determined -? half life extender	• Limited data in triple class/penta refractory • Ocular toxicity – will require close collaboration with opthamology and ? impact on quality of life • Thrombocytopenia • Treatment until progression

Conclusions

- **Single agent belantamab mafodotin induces deep and durable responses in heavely pretreated/ refractory MM population**

  DREAMM2 phase 2 expected to result in regulatory approval for MM patients refracyory to PI, IMiDs and anti CD38 MoAbs

- **Activity in combination with POM Dex is promising**
- **Balantamab Mafodotin monotherapy shows a manageble safety profile (corneal events need specific management)**

- **Open questions**
  optimal dosing schedule and management of corneal toxicities
  optimal combination for Balantamab Mafodotin
  how do the different antiBCMA modalities (ADC, bispecific T cell engagers, CAR-T) compare and how will these optimally positioned
  what will be the efficacy and toxicity profile of novel ADCs with alternative targets and/or payload

GRAZIE PER L'ATTENZIONE