First in Human Study with GSK2857916, An Antibody Drug Conjugated to Microtubule-disrupting Agent Directed Against B-cell Maturation Antigen, in Patients with Relapsed/Refractory Multiple Myeloma: Results from Study BMA117159 Part 1 Dose Escalation

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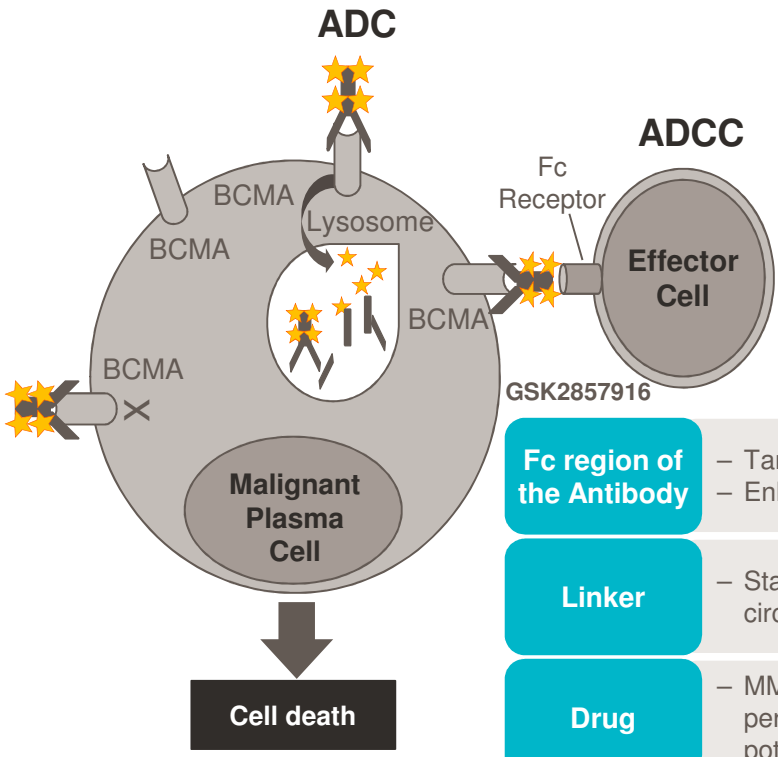
Background

- BCMA expression is restricted to B cells at later stages of differentiation and is requisite for the survival of long lived plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells
- GSK2857916 is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to a microtubule disrupting agent MMAF via a stable, protease resistant maleimidocaproyl linker
  - Preclinical studies demonstrate its selective and potent activity[1]



Fc region of the Antibody	– Target specific – Enhanced ADCC
Linker	– Stable in circulation
Drug	– MMAF (non cell permeable, highly potent auristatin

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

ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; Fc, Fragment crystallizable; IgG, immunoglobulin G; MMAF, monomethyl auristatin-F

[1]Tai YT, et al. Blood 2014;123(20):3128-38.

First-in-Human Study of GSK2857916: BMA117159 Study Design

Part 1: Dose escalation: N-CRM Bayesian model design

- **Schedule 1*:** escalating doses of GSK2857916 IV/60-min infusion once every 3 weeks (21-day cycle)
- Maximum number of cycles: 16

Premedication requirements: prophylaxis steroid eye drops each dose

Premedication for infusion reactions not permitted with first dose and not mandated at subsequent doses

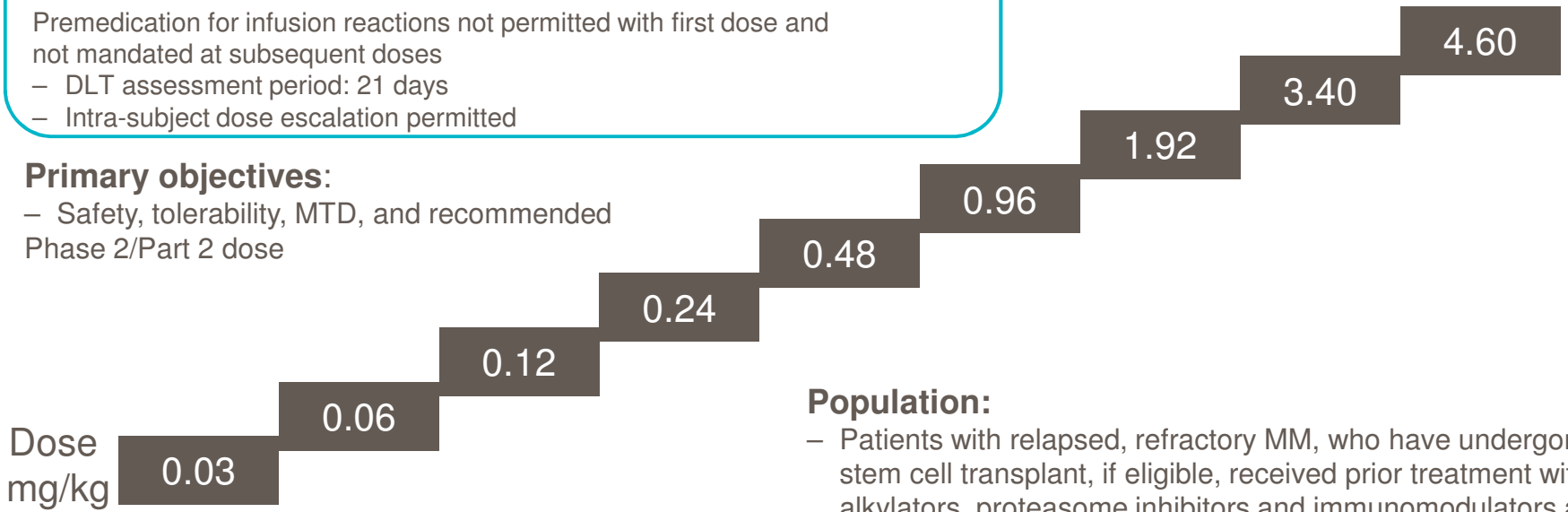
- DLT assessment period: 21 days
- Intra-subject dose escalation permitted

Part 2: Expansion (ongoing)

- Cohort 1: relapsed/refractory MM (n≈40)
- Cohort 2: BCMA-positive relapsed DLBCL or follicular lymphoma (n≈10)

Primary objectives:

- Safety, tolerability, MTD, and recommended Phase 2/Part 2 dose



Run in:

Cohort size=1 until first drug-related Grade 2 toxicity

Population:

- Patients with relapsed, refractory MM, who have undergone stem cell transplant, if eligible, received prior treatment with alkylators, proteasome inhibitors and immunomodulators and who have progression on, or within 60 days of completion of the last therapy

*Schedule 2: weekly dosing was not investigated.

DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; IV, intravenous; MM, multiple myeloma; MTD, maximum tolerated dose; N-CRM, continuous reassessment model

Part 1: Key Eligibility Criteria

- ECOG performance status 0 or 1
- Hematology:
  - ANC >1x10^9/L
  - Hemoglobin >8 g/dL
  - PLTs >50x10^9/L
- Coagulation:
  - INR <1.5
  - PTT <1.5xULN
- Total bili ≤1.25xULN
- AST/ALT <1.5xULN
- Serum creatinine <1.2xULN or calculated creatinine clearance >60 mL/min
- Albuminuria <500 mg/24h
- LVEF >50% and troponin <1xULN
- No current or history of corneal disease

Note: BCMA expression not required for eligibility, and will be analyzed retrospectively on BM plasma cells

ANC, absolute neutrophil count; ALT, alanine transaminase; AST, aspartate transaminase; bili, bilirubin; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio; LVEF, left ventricular ejection fraction; PLT, platelets; PTT, partial thromboplastin time; ULN, upper limit of normal

Part 1: Patient Status

Enrollment by dose level N=30									
Dose cohort	1	2	3*	4	5	6	7	8	9
GSK2857916 dose, mg/kg	0.03	0.06	0.12	0.24	0.48	0.96	1.92	3.4	4.6
Patients enrolled, n	1	1	4	4	4	3	4	3	6

*Cohort size >1 due to ≥Grade 2 toxicity

Treatment status	
Status, n (%)	**N=30**
Ongoing	10 (33)
Discontinued	20 (67)
Reason for discontinuation, n (%)	**N=20**
Disease progression	17 (85)
Completed treatment (16 cycles)	1 (5)
Adverse event	2 (10)

Part 1: Baseline Patient and Disease Characteristics

Characteristic	Total population N=30
Age (years), median (min, max)	59.5 (39, 72)
Females/males, %	43/57
≥5 prior lines*, n (%)	21 (70)
IMiDs Lenalidomide Pomalidomide Thalidomide **Refractory to IMiD**	**30 (100)** 29 (97) 23 (77) 15 (50) **30 (100)**
Proteasome inhibitor Bortezomib Carfilzomib **Refractory to PI**	**30 (100)** 29 (97) 18 (60) **27 (90)**
Double refractory (IMiD/PI)	**27 (90)**
Chemotherapy ASCT Daratumumab Refractory to Daratumumab	28 (93) 20 (67) 5 (17) 4 (13)
High-risk genetics, n (%) del17p13 t(4:14)	7 (23) 6 (20) 2 (7)

*One patient had missing data

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

Part 1: AEs Regardless of Relationship
No DLTs Were Reported at Any Dose Level

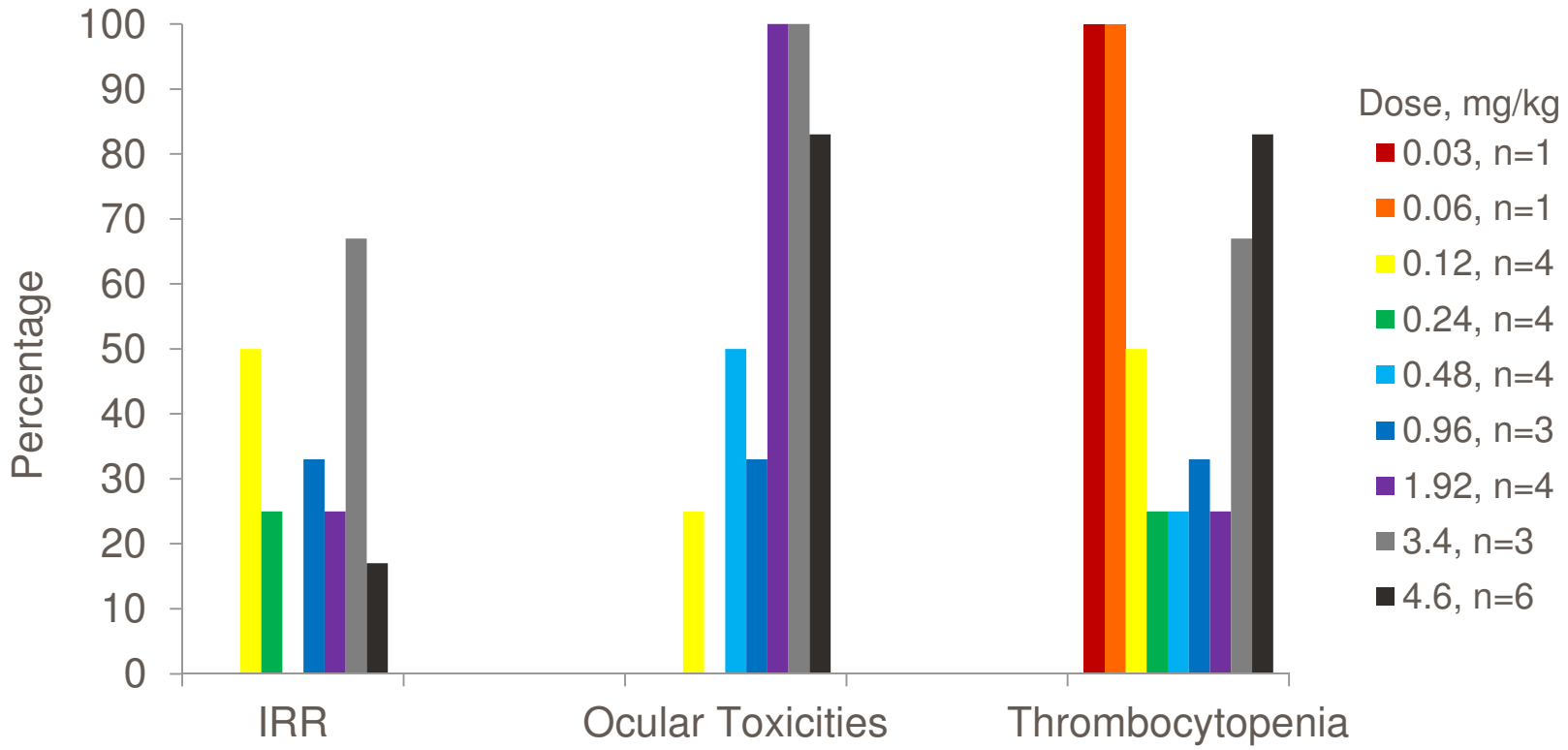
AEs reported in ≥20% patients, n (%)	N=30	
	Any grade	≥Grade 3*
Any event	29 (97)	22 (73)
Ocular Toxicity	16 (53)	2 (7)
Nausea	15 (50)	0
Thrombocytopenia	15 (50)	13 (43)
Fatigue	14 (47)	1 (3)
Anemia	10 (33)	6 (20)
Pyrexia	10 (33)	0
Chills	8 (27)	0
AST increased	6 (20)	0
Hypercalcemia	6 (20)	3 (10)
Neutropenia	6 (20)	4 (13)

*No Grade 5 events reported

- Majority of AEs were Grade 1/2 and predicted
- 8/30 (27%) patients experienced IRR, chills was the most common symptom
- Grade 3 ocular events: dry eye in 1 patient improved; in another, limbal stem cell deficiency and blurred vision resolved

AE, adverse event; IRR, infusion-related reactions

Part 1: Frequency of AEs of Interest by Dose Level



- IRR reported across dose levels, occurred at first dose administration, all were Grade1/2
- Majority of ocular toxicities presented after first cycle, blurred vision and dry eyes were most common symptoms; majority were manageable with steroid and lubrication eye drops, and dose modifications
- Thrombocytopenia was transient

Part 1: AEs Leading to Dose Reductions, Delays or Treatment Discontinuation

Dose level, mg/kg	Number of enrolled patients	AEs leading to dose delay n (%)	AEs leading to dose reductions n (%)	AEs leading to dose delay or dose reduction n (%)
0.48	4	1 (25)	0	1 (25)
0.96	3	1 (33)	1 (33)	1 (33)
1.92	4	3 (75)	2(50)	3 (75)
3.4	3	3 (100)	2(67)	3 (100)
4.6	6	3 (50)	4 (67)	5 (83)

– The primary cause of GSK2857916 dose modifications was ocular toxicities (7/13, 54%) followed by thrombocytopenia (3/13, 23%)

AEs leading to study treatment discontinuation:

– One patient at the 1.92 mg/kg dose level discontinued due to Grade 3 corneal toxicity (limbal stem cell deficiency)

– One patient at the 4.6 mg/kg dose level discontinued due to Grade 3 hypercalcemia that was related to disease progression

Part 1: SAEs by Dose Level

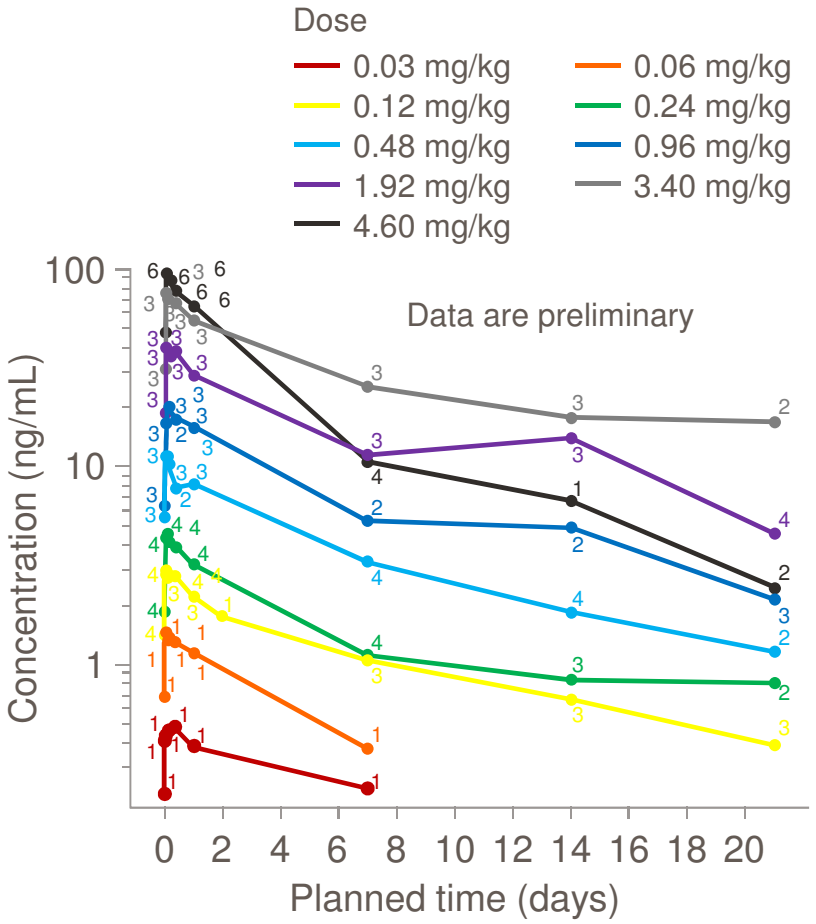
Dose (mg/kg)	Part 1 population, N=30		
	SAE	Grade	Relationship to GSK2857916
0.12	Hyperviscosity	3	No
0.24	Hypotension	2	No
	Pyrexia	1	No
0.48	Nausea	2	No
	Vomiting	2	No
1.92	Blurred vision; limbal stem cell deficiency	3	**Yes**
	Spinal cord compression	3	No
3.4	Pharyngeal hemorrhage	1	No
4.6	Pyrexia	1	**Yes**
	Pyrexia	1	**Yes**
	Hypercalcemia	3	No

9/30 (30%) patients experienced at least one SAE

SAE, serious adverse event

Part 1: Pharmacokinetics and Immunogenicity

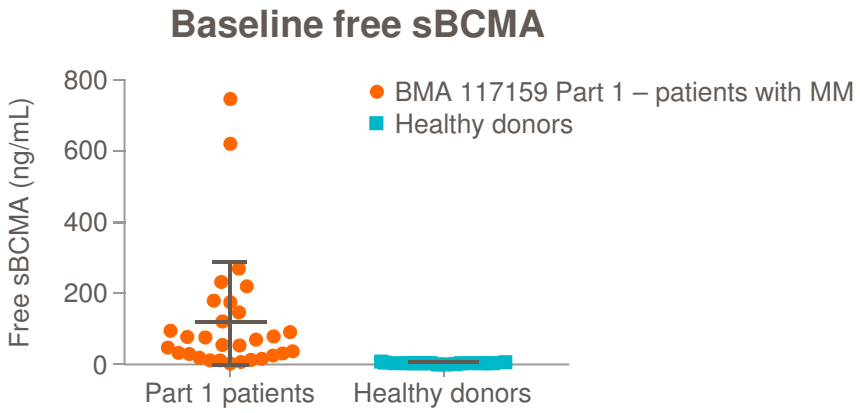
- Dose proportional exposure with 9-day half-life
- No accumulation on the once every 3 weeks dosing regimen
- Unbound MMAF is 0.1% of intact ADC concentrations
- BCMA receptor binding levels estimation:
  - Engagement from 0.12 mg/kg
  - Saturation from 1.92 mg/kg
  - Free receptor recovery by Day 7 at higher dose levels
- No anti-drug antibodies detected at any dose level



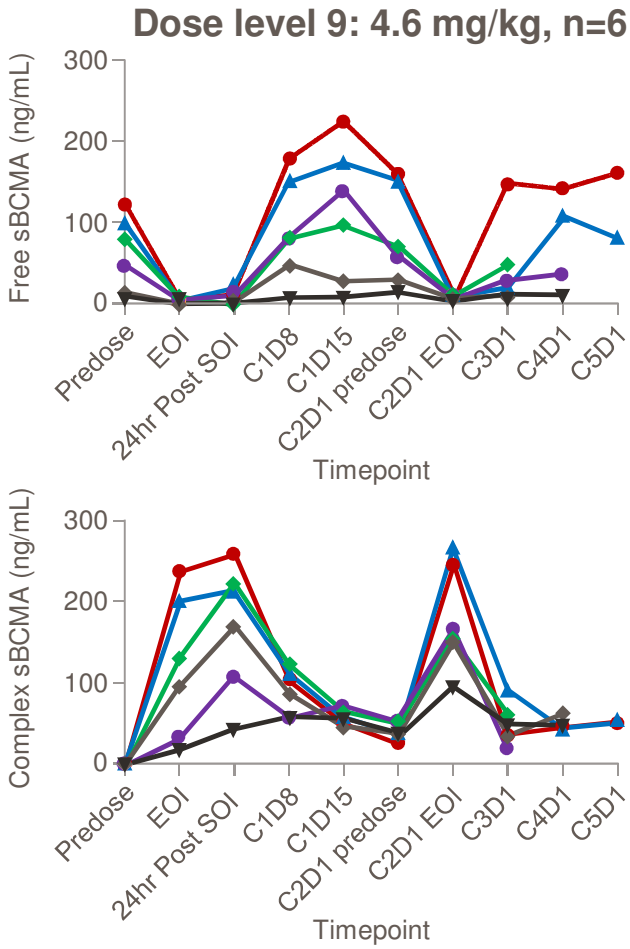
Patient numbers shown per data point

Part 1: Serum sBCMA Analyses

Free sBCMA and Complex ('drug-bound') sBCMA



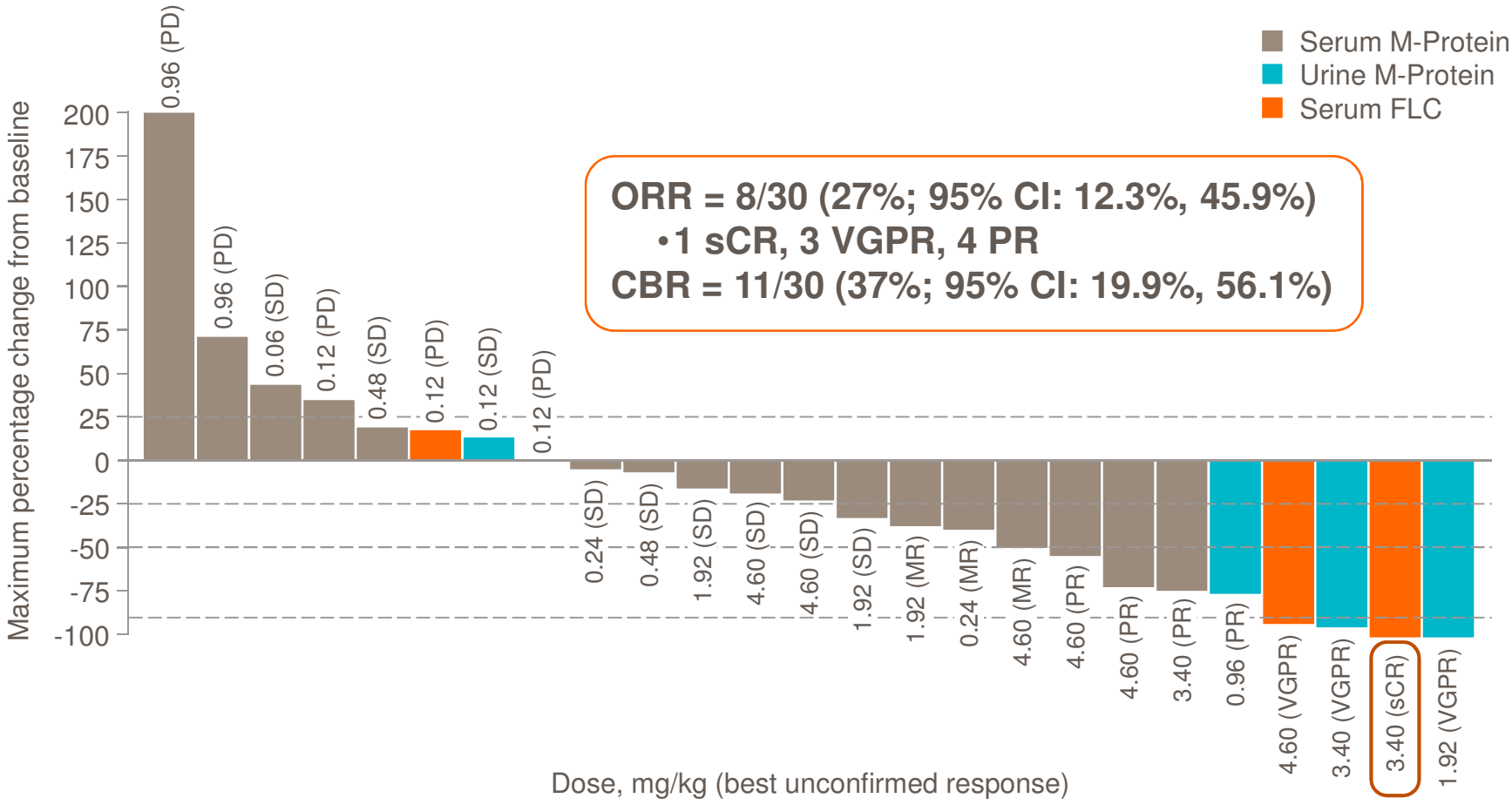
All patients had detectable levels of free sBCMA at baseline



– From dose level 3 (0.12 mg/kg) to dose level 8 (3.4 mg/kg), free and complex sBCMA results show trends similar to dose level 9

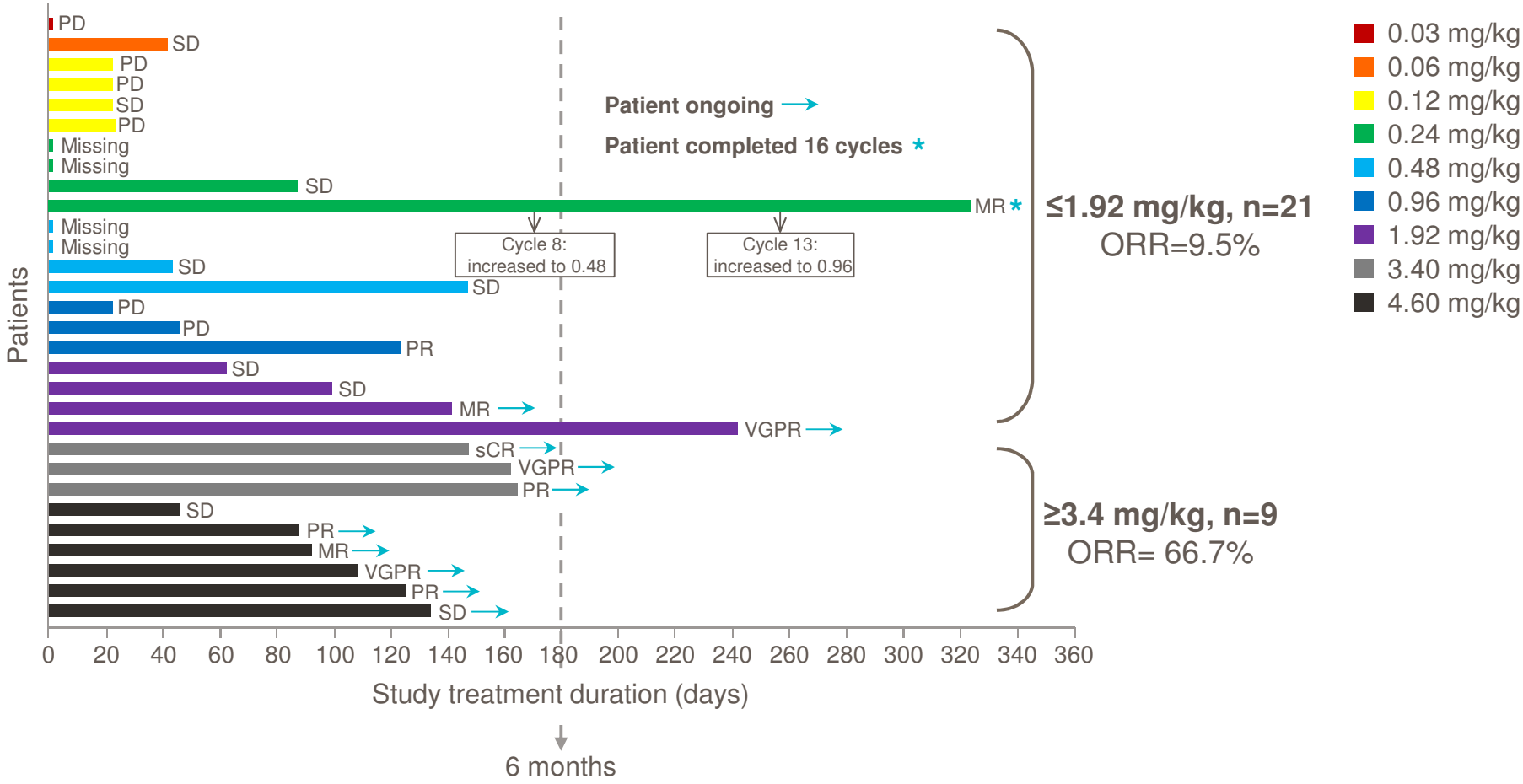
EOI, end of infusion; sBCMA, soluble B-cell maturation antigen; SOI, start of infusion

Maximum % Change in M-Protein or Free Light Chain



CBR, clinical benefit rate; CI, confidence interval; FLC, free light chain; M-protein, myeloma protein; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

Part 1: Summary of Clinical Activity and Duration on Study



Conclusions

- GSK2857916 was well tolerated with no DLTs up to 4.6 mg/kg q3w; MTD was not reached
- AEs were manageable with ocular toxicity emerging as the most frequent reason for dose modifications
- Hematologic toxicities such as thrombocytopenia and anemia are expected in the disease under study
  - Thrombocytopenia emerged more frequently as treatment-related at higher doses; although events were transient and manageable
- 66.7% ORR including a stringent CR observed at higher doses of GSK2857916 in this refractory population
- 3.4 mg/kg was selected as the dose to investigate in the expansion phase of the study based on the totality of the data from Part 1
- Pharmacodynamic and correlative analyses are ongoing

Acknowledgments

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– We especially thank the patients and their families who participated in this study

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