Activity of Melflufen in RR MM Patients With Extramedullary Disease in the Phase 2 HORIZON Study (OP-106): Promising Results in a High-Risk Population

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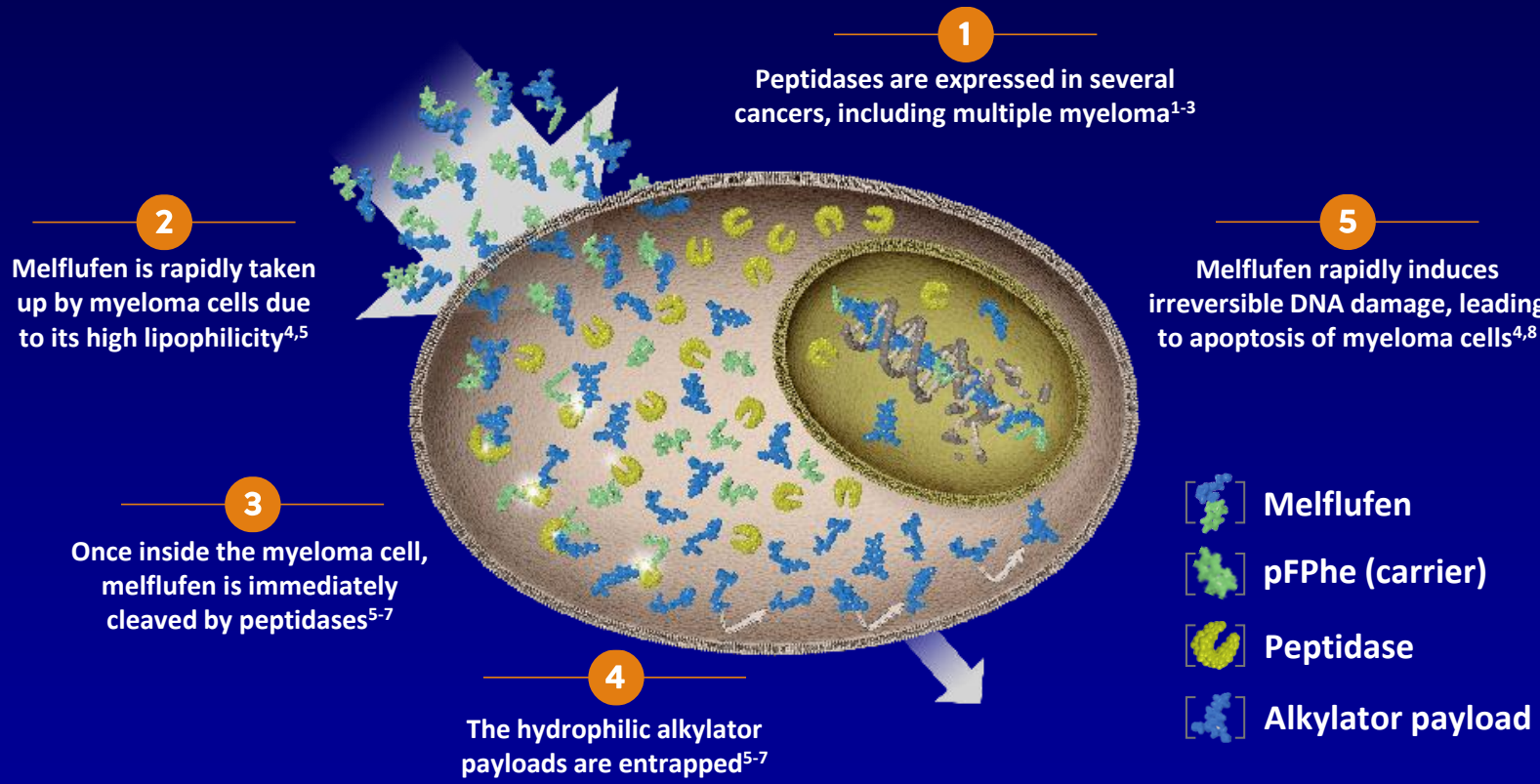
Background

- Outcomes for patients (pts) with relapsed refractory multiple myeloma (RR MM) and extramedullary disease (EMD) remain very poor despite advances in therapy
- Historically, EMD occurs at relapse in approximately 10%-15% of pts: incidence currently increasing with reported rates ≥40%[1-3]
- No significant responses reported to currently available treatments for RR MM pts with EMD[3-8]
  - Only daratumumab (dara) has shown single-agent activity: ORR 17% (3 of 18 dara-naïve EMD pts)[4]
- Melflufen is a lipophilic peptide-conjugated alkylator which rapidly delivers a highly cytotoxic payload into myeloma cells *in vitro*
  - Encouraging clinical activity and safety in RR MM pts (O-12-M1, N=45)
  - Phase 2 HORIZON study: activity in RR MM pts (n=121), including pts with EMD on preliminary analysis[9]

1. Pour L, et al. *Haematologica.* 2014;99:360-364. 2. Bishnoi R, et al. *Blood*. 2018;132:Abstract 5668. 3. Sevcikova S, et al. *Blood Rev*. 2019;36:32-39. 4. Usmani SZ, et al. *Blood*. 2016;128:37-44. 5. Celotto K, et al. *Am J Hematol Oncol*. 2017;13:21-23. 6. Jiménez-Segura R, et al. *Blood*. 2016;128:Abstract 5709. 7. Jiménez-Segura R, et al. *Eur J Haematol*. 2019;102:389-394. 8. Ichinohe T, et al. *Exp Hematol Oncol*. 2016;5:11. 9. Richardson PG, et al. EHA 2019. Oral Presentation #S1605.

Melflufen: a Lipophilic Peptide-Conjugated Alkylator Rapidly Delivers a Cytotoxic Payload Into Myeloma Cells

Peptidase-enhanced activity in multiple myeloma cells

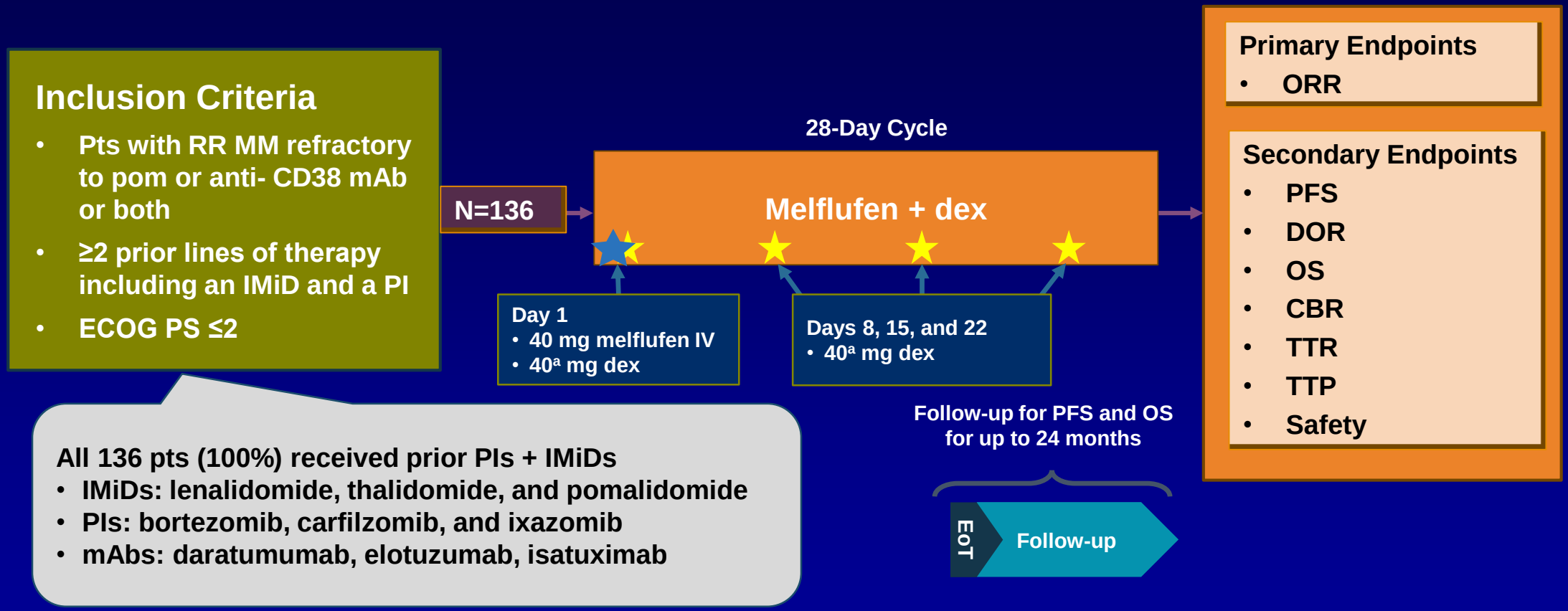


Melflufen is 50-fold more potent than melphalan in myeloma cells *in vitro* due to increased intracellular alkylator activity[4,5]

1. Hitzerd SM, et al. *Amino Acids.* 2014;46:793-808. 2. Moore HE, et al. *Mol Cancer Ther.* 2009;8:762-770. 3. Wickström M, et al. *Cancer Sci.* 2011;102:501-508. 4. Chauhan D, et al. *Clin Cancer Res.* 2013;19:3019-3031. 5. Wickström M, et al. *Oncotarget.* 2017;8:66641-66655. 6. Wickström M, et al. *Biochem Pharmacol.* 2010;79:1281-1290. 7. Gullbo J, et al. *J Drug Target.* 2003;11:355-363. 8. Ray A, et al. *Br J Haematol.* 2016;174:397-409.

HORIZON: Study Design

Phase 2, Single-Arm, Open-Label, Multicenter Study



ClinicalTrials.gov Identified: NCT02963493.

CBR, clinical benefit rate; dara, daratumumab; dex, dexamethasone; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; IMiD, immunomodulatory agent; IV, intravenous; mAbs, monoclonal antibodies; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; pom, pomalidomide; pts, patients; RR MM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.

[a]Pts aged >75 years received dex 20 mg.

Baseline Characteristics and Prior Therapy

Patient Characteristics (n=130)	Non-EMD (n=86)	EMD (n=44)
Age, median (range), years	64 (35-86)	64 (43-82)
Time since diagnosis, median, years	6.6 (1.6-24.2)	5.5 (0.6-12.7)
No. of prior lines of therapy, median (range)	5 (2-10)	5 (3-12)
	%	%
Gender (male / female)	53 / 47	59 / 41
ISS stage I / II / III / unknown	42 / 29 / 23 / 6	43 / 23 / 27 / 7
ECOG PS 0 / 1 / 2 / unknown	27 / 58 / 13 / 2	18 / 64 / 16 / 2
High-risk cytogenetics[a] ≥2 high-risk abnormalities Del(17p)	57 25 19	52 10 13
Double-class (IMiD+PI) exposed / refractory	100 / 90	100 / 93
Triple-class (IMiD+PI+anti-CD38) exposed / refractory	71 / 63	93 / 91[b]
Anti-CD38 mAb exposed / refractory	72 / 72	93 / 93
Alkylator exposed / refractory	91 / 58	82 / 59
≥1 Prior ASCT ≥2 Prior ASCTs Relapsed/progressed within 1 year of ASCT	69 13 17	73 14 23
Refractory in last line of therapy	95	100

[a]High-risk cytogenetics [t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperdiploidy, gain(1q) or karyotype del(13)] at study entry; data pending for 33 pts in the non-EMD group and 13 pts in the EMD group.
[b]Includes 2 PI-intolerant pts.

Data cutoff 30 July 2019.

EMD and Prior Therapy

- 91% of EMD pts triple-class refractory and 73% penta-refractory
- No other significant differences seen between EMD and non-EMD pts, except anti-CD38 exposure
- EMD incidence higher with prior anti-CD38 exposure (*P*=0.01)
  - 41 of 103 (40%) anti-CD38 mAb exposed pts had EMD
  - 3 of 27 (11%) not anti-CD38 mAb exposed pts had EMD

EMD Characteristics

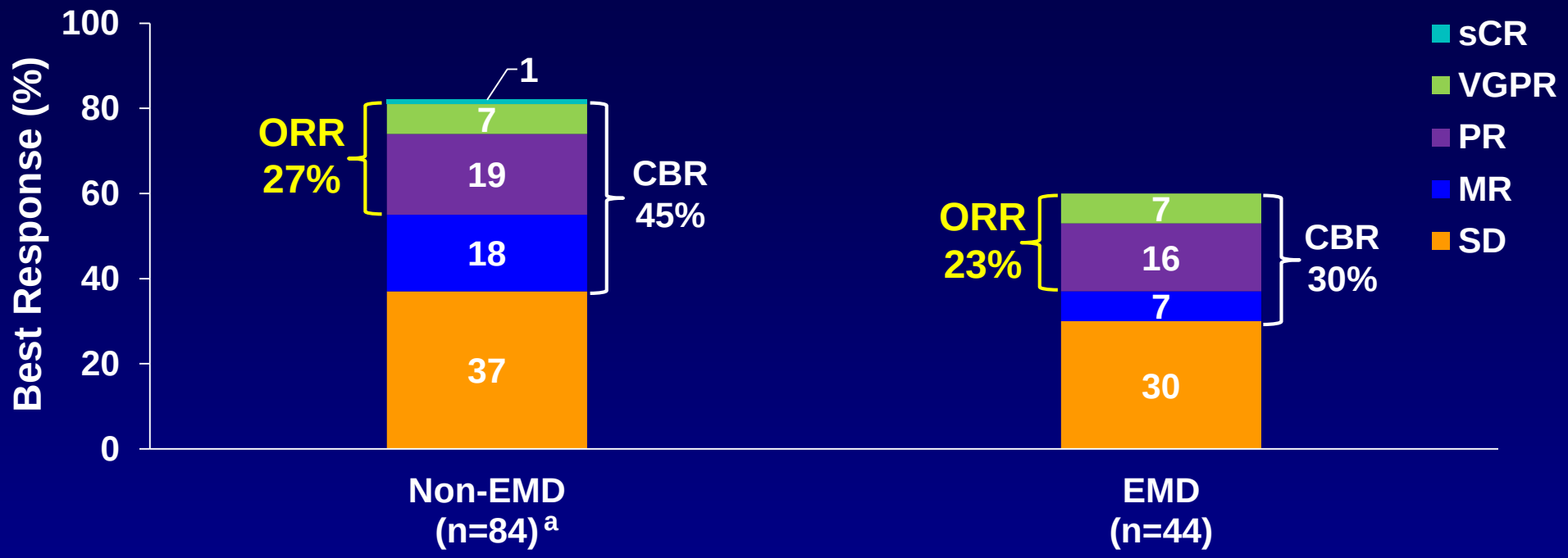
Bone-related or Soft Tissue EMD, n (%)	EMD Pts	CNS Involvement
Pts with EMD[a]	44 (100)	5 (11)
Soft tissue[b]	26 (59)	2 (5)
Bone-related[c]	18 (41)	3 (7)

CNS, central nervous system; EMD, extramedullary disease; Pt, patient.
[a]Majority of pts had multiple lesions at baseline.
[b]Includes pts with both bone-related and soft tissue EMD.
[c]Three pts had bone-related EMD with extension into CNS.

- Method of baseline assessment for known or suspected EMD was by investigator choice including PET/CT, MRI and physical examination
- 59% of pts had soft-tissue EMD (with or without additional bone-related EMD) and 41% had bone-related EMD alone
- 5 pts (11%) had CNS involvement, of which 3 pts had bone-related EMD with extension into CNS
- Majority of pts (29 of 44) had multiple sites of EMD

Data cutoff 30 July 2019.

Overall Response (n=128)

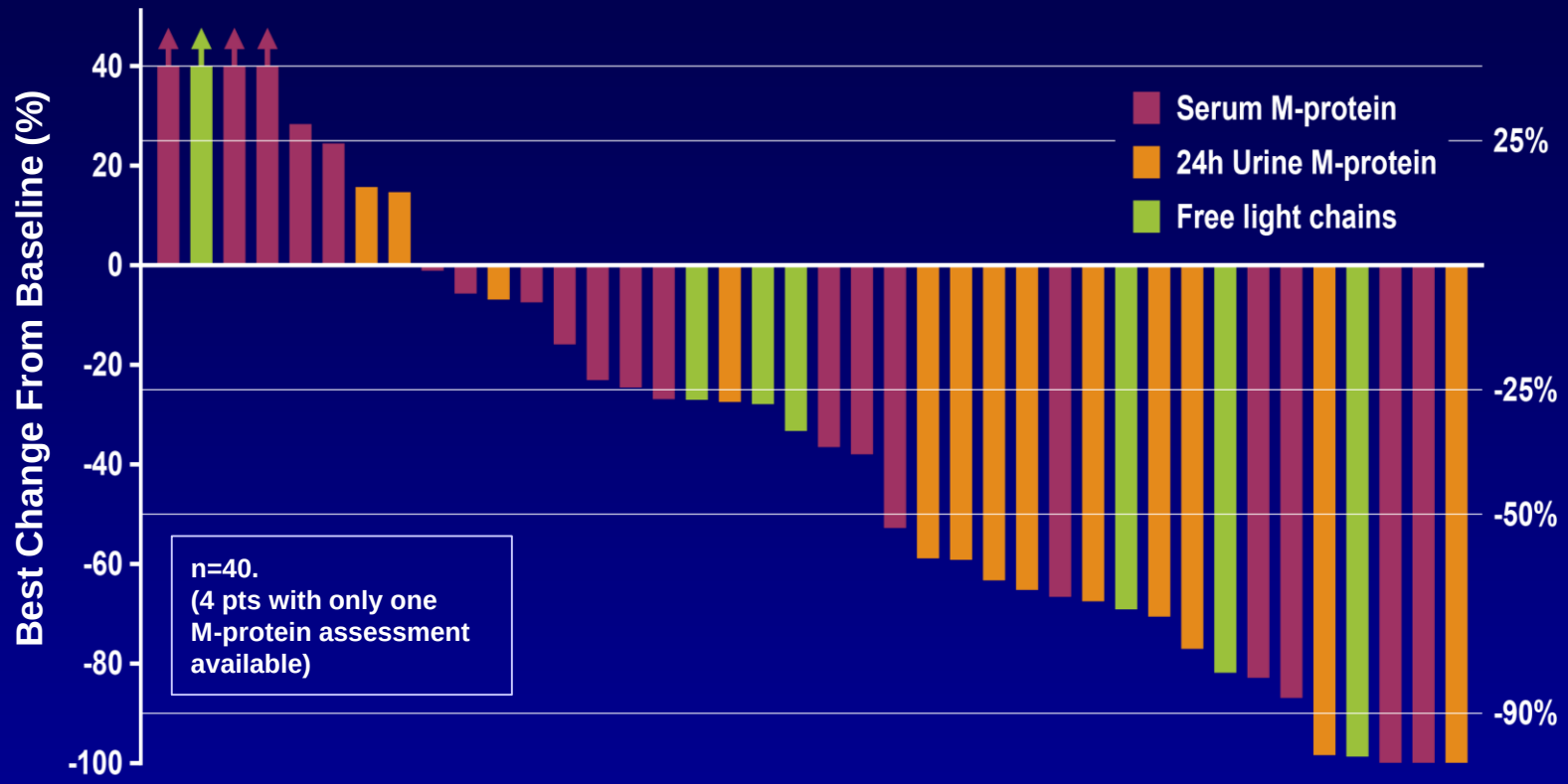


- Similar ORR in non-EMD and EMD pts, with an ORR of 27% and 23% respectively
  - Investigator-assessed response[1]
  - IRC review ongoing
- Median DOR for non-EMD pts 4.4 mos (95% CI, 3.5-11.2)
- Median DOR for EMD pts 3.4 mos (95% CI, 1.8-15.4)

[a] Two non-EMD pts with pending response information available at data cut off 30th July 2019.

1. Rajkumar SV, et al. *Blood*. 2011;117:4691-4695.

Response in EMD Pts (n=44)



n=44	ORR
Soft tissue n=26	19%
Bone-related n=18	28%
CNS n=5	0%

- PET/CT (including TIMC), MRI, physical exam for EMD assessment
- "Flaring" observed in EMD PET/CT imaging (reported by 2 lead sites)

Data cutoff 30 July 2019.

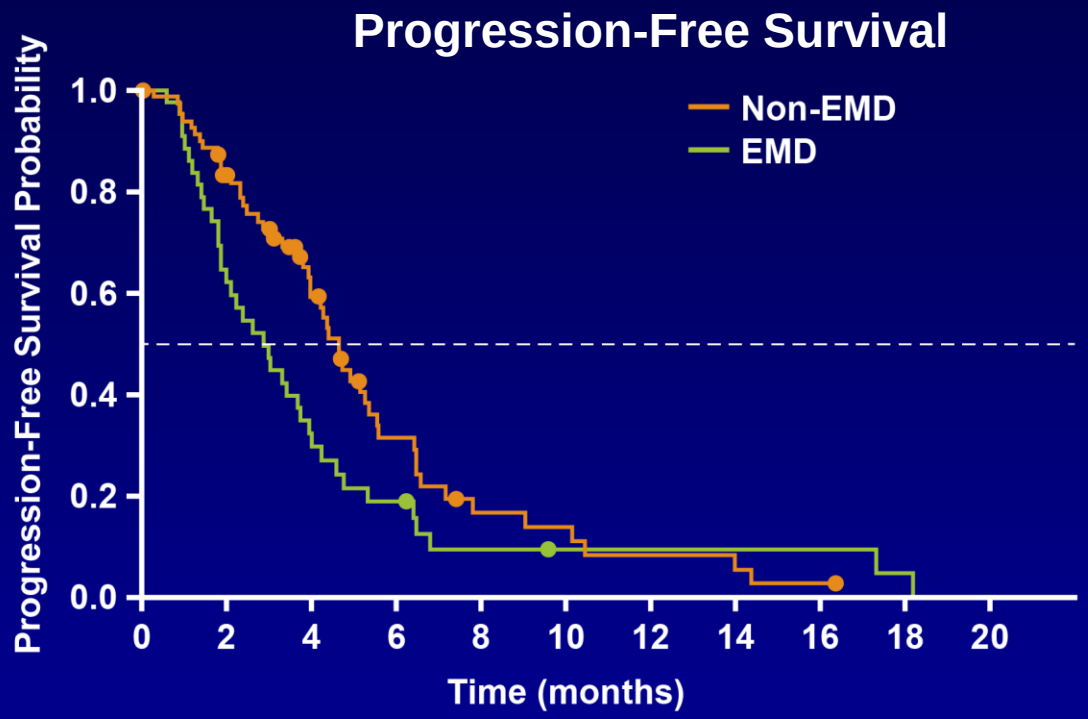
Disease Characteristics in Responding EMD Pts

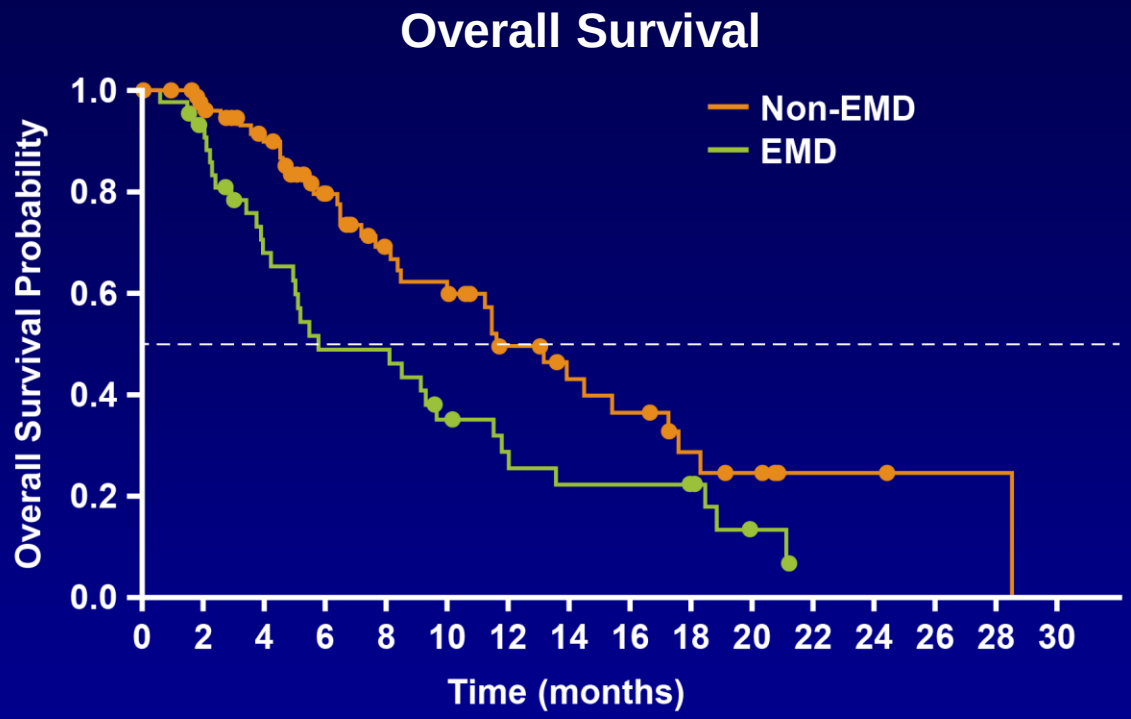
HORIZON

No. Prior Lines of Therapy	Refractory Status	EMD	Response
5	Penta	Lymph nodes and paramediastinal masses	VGPR
6	Penta	Skull based mass with soft tissue extension	VGPR
6	Triple	Pulmonary masses	VGPR
8	Quad	Mandibular mass with soft tissue extension	PR
5	Quad	Multiple soft tissue plasmacytoma arising from iliac bone	PR
3	Quad	Pleural masses, hepatobiliary tract, right orbital plasmacytoma, L5 mass with spinal canal extension	PR
7	Penta	Multiple masses arising from the skull and ribs with soft tissue extension	PR
5	Penta	Multiple subcutaneous plasmacytoma affecting the trunk and extremities	PR
4	Penta	Multiple pleural and spinal masses with soft tissue extension	PR
4	Penta	Masses in mandible and sternum with soft tissue extension	PR

Progression-Free and Overall Survival EMD vs Non-EMD Pts

HORIZON



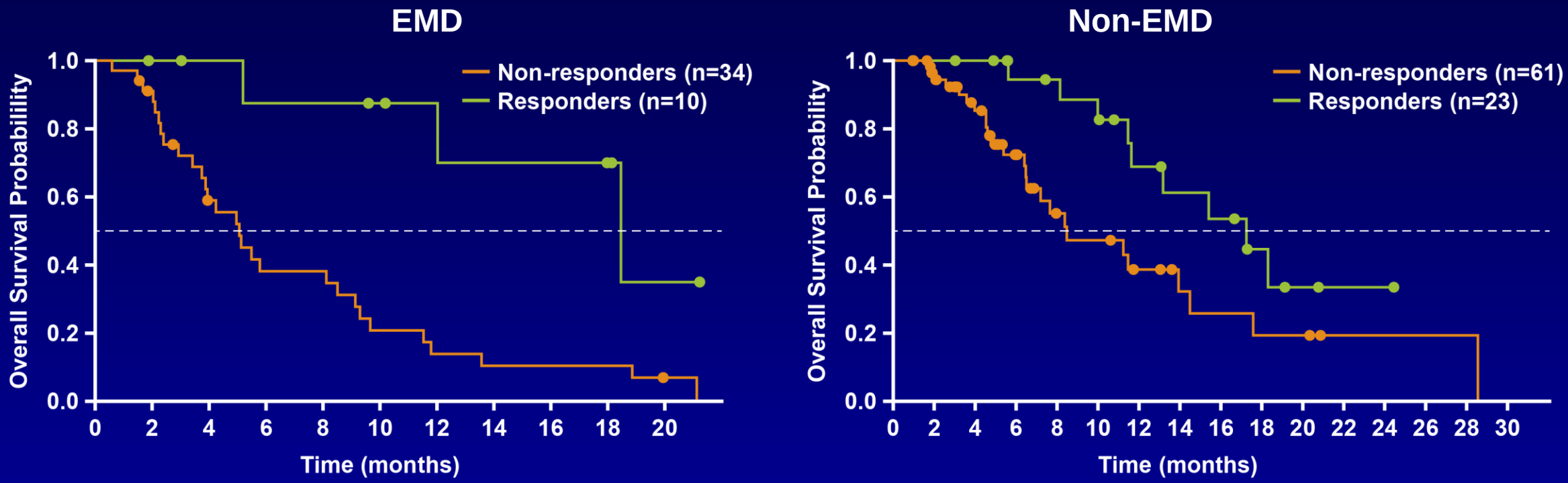


- Median PFS 2.9 mos (95% CI, 2.0-4.0) for pts with EMD vs. 4.6 mos (95% CI, 4.0-5.6) without EMD
- Median OS 5.8 mos (95% CI, 5.0-11.8) for pts with EMD vs. 11.6 mos (95% CI, 10.0-17.6) without EMD

Data cutoff 30 July 2019.

OS in EMD and Non-EMD Pts Stratified by Response

HORIZON



- Median OS in EMD responders vs. non-responders: 18.5 vs. 5.1 mos
- Median OS in Non-EMD responders vs. non-responders: 17.2 vs. 8.5 mos
  - Similar trend for PFS in responders vs. non-responders: 4.8 vs. 2.2 mos in EMD pts; 6.4 vs. 3.8 mos in non-EMD pts
- 54% of ITT pts received subsequent therapy with no significant difference in outcome between EMD vs. non-EMD pts[1]

Data cutoff 30 July 2019.

1. Gandhi UH, et al. *Blood*. 2018;132(suppl 1):Abstract 3233.

Grade 3 and 4 TEAEs (≥5%) in ITT Population

TEAEs,[a] n (%)	ITT (n=136)	
	Grade 3	Grade 4
Any AE	38 (28)	77 (57)
Hematologic AEs		
Thrombocytopenia	30 (22)	63 (46)
Neutropenia	44 (32)	48 (35)
Anemia	48 (35)	1 (1)
White blood cell count decreased	14 (10)	10 (7)
Leukopenia	4 (3)	5 (4)
Febrile neutropenia	6 (4)	2 (1)
Lymphopenia	5 (4)	2 (1)
Non-hematologic AEs		
Pneumonia	9 (7)	2 (1)

AE, adverse event; ITT, intention-to-treat; TEAE, treatment-emergent adverse event.
[a]Grade 3 and 4 AEs occurring in ≥5% of pts.

- Safety profiles for EMD and non-EMD pts similar
- Generally well tolerated, with manageable toxicity: no alopecia, 1 grade 2 mucositis only, no peripheral neuropathy
- Low overall incidence of other non-hematologic AEs including infections; no treatment-related deaths

Data cutoff 30 July 2019.

Conclusions and Future Directions

- HORIZON has one of the largest cohorts of RR MM pts with EMD in a prospective clinical trial: enrollment near complete (N=156), final analysis pending
- Melflufen/dex has encouraging activity in advanced RR MM with EMD (ORR 23%, CBR 30%) or without EMD (ORR 27%, CBR 45%)
- Response to melflufen/dex in EMD higher than reported for other agents[1-5]
- Current median OS in responding EMD pts 18.5 mos vs. 5.1 mos in non-responders
- Incidence of EMD is higher than expected, and appears increased after prior anti-CD38 mAb therapy
- Results support continued evaluation of melflufen-based combination therapies for this population with unmet medical need
- Melflufen is being studied in 4 ongoing phase 2 and 3 trials with further trials planned

1. Usmani SZ, et al. *Blood*. 2016;128:37-44. 2. Celotto K, et al. *Am J Hematol Oncol*. 2017;13:21-23. 3. Jiménez-Segura R, et al. *Blood*. 2016;128:Abstract 5709. 4. Jiménez-Segura R, et al. *Eur J Haematol*. 2019;102:389-394. 5. Ichinohe T, et al. *Exp Hematol Oncol*. 2016;5:11.

Acknowledgments

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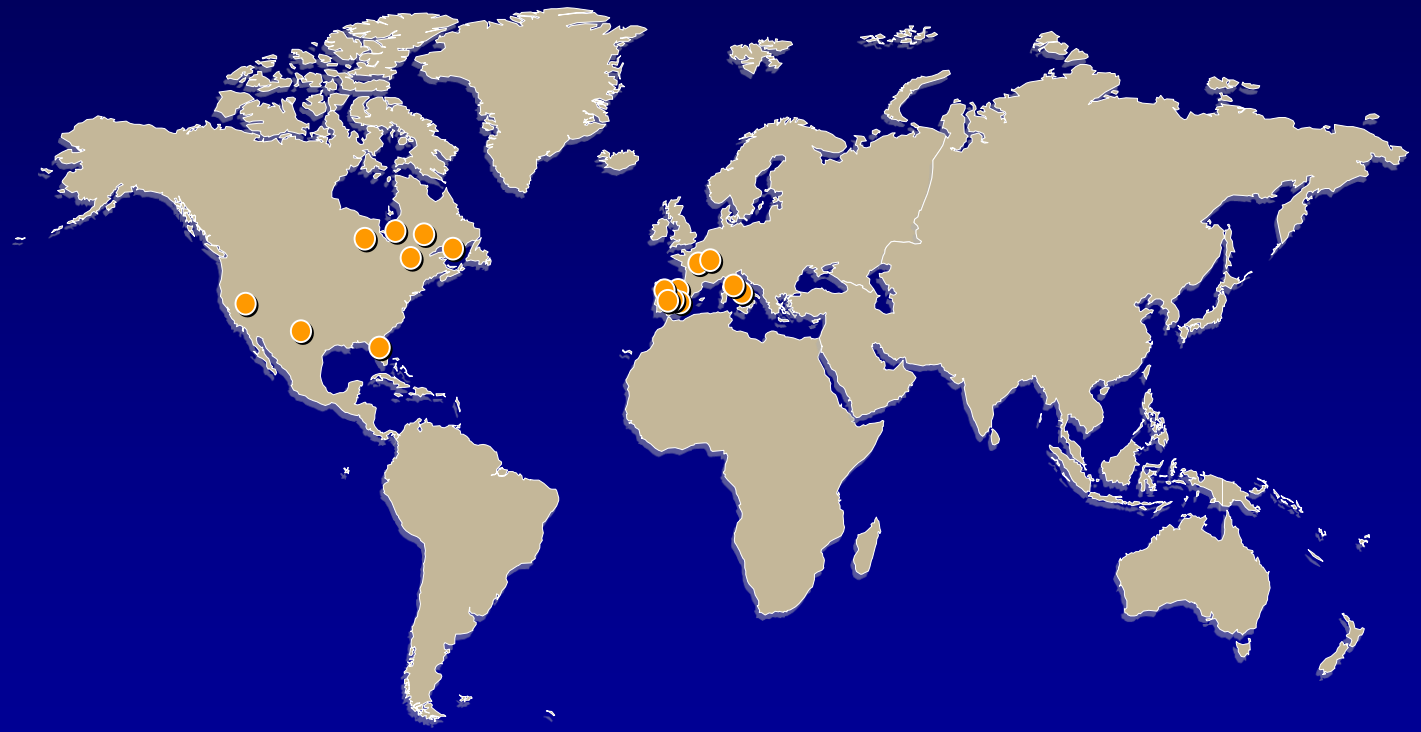

Global Study With 16 Sites in 4 Countries

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