

# 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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## **Disclosures:**

**Paul G. Richardson: Advisory role for Oncopeptides and research funding from Oncopeptides.**

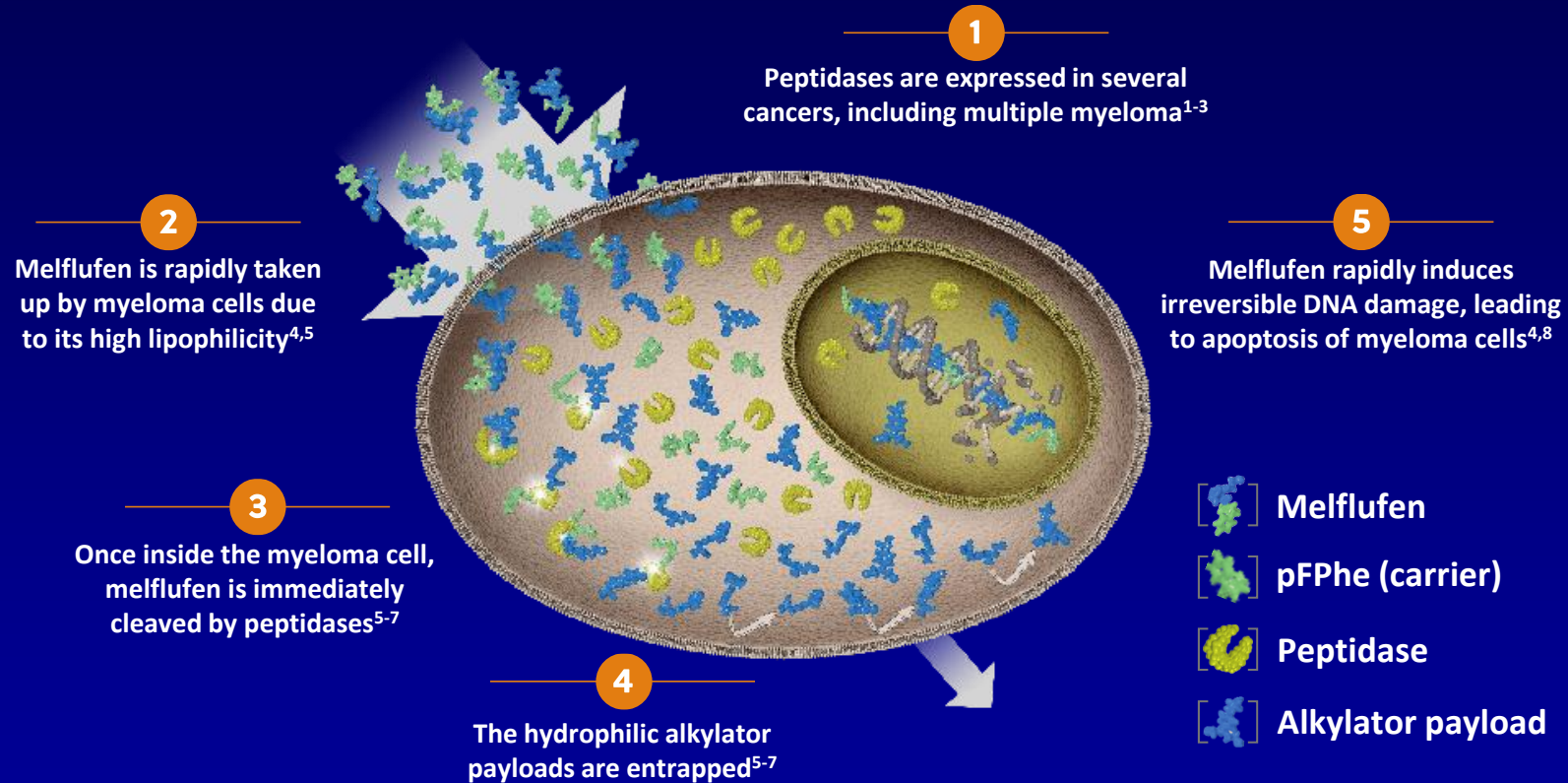
# Background

- **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  $\geq 40\%$ <sup>1-3</sup>**
- **No significant responses reported to currently available treatments for RR MM pts with EMD<sup>3-8</sup>**
  - Only daratumumab (dara) has shown single-agent activity: ORR 17% (3 of 18 dara-naïve EMD pts)<sup>4</sup>
- **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<sup>9</sup>

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

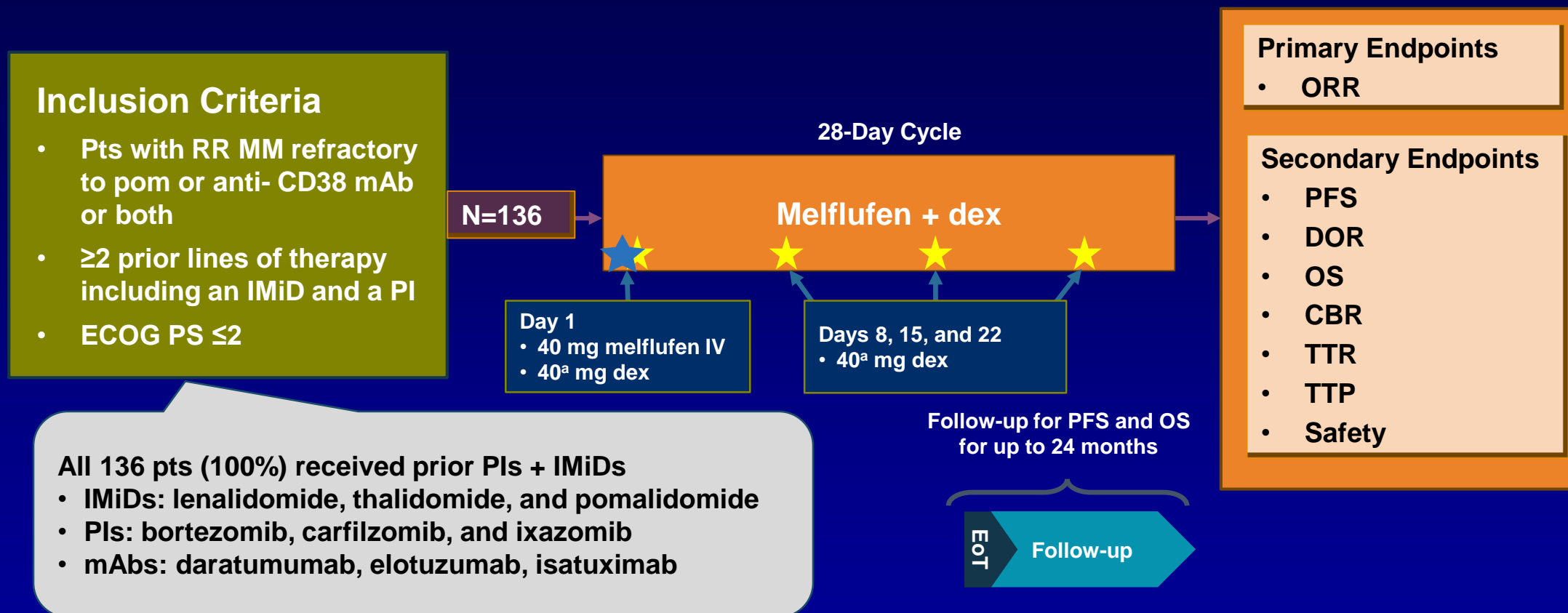


Melflufen is 50-fold more potent than melphalan in myeloma cells *in vitro* due to increased intracellular alkylator activity<sup>4,5</sup>

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.

<sup>a</sup>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)             |
|   | <b>%</b>         | <b>%</b>             |
| 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 <sup>a</sup>                   | 57               | 52                   |
| ≥2 high-risk abnormalities                            | 25               | 10                   |
| Del(17p)  | 19               | 13                   |
| Double-class (IMiD+PI) exposed / refractory           | 100 / 90         | 100 / 93             |
| Triple-class (IMiD+PI+anti-CD38) exposed / refractory | 71 / 63          | 93 / 91 <sup>b</sup> |
| Anti-CD38 mAb exposed / refractory                    | 72 / 72          | 93 / 93              |
| Alkylator exposed / refractory                        | 91 / 58          | 82 / 59              |
| ≥1 Prior ASCT   | 69               | 73                   |
| ≥2 Prior ASCTs  | 13               | 14                   |
| Relapsed/progressed within 1 year of ASCT             | 17               | 23                   |
| Refractory in last line of therapy                    | 95               | 100                  |

<sup>a</sup>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.

<sup>b</sup>Includes 2 PI-intolerant pts.

# 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 <sup>a</sup>              | 44 (100) | 5 (11)          |
| Soft tissue <sup>b</sup>               | 26 (59)  | 2 (5)           |
| Bone-related <sup>c</sup>              | 18 (41)  | 3 (7)           |

CNS, central nervous system; EMD, extramedullary disease; Pt, patient.

<sup>a</sup>Majority of pts had multiple lesions at baseline.

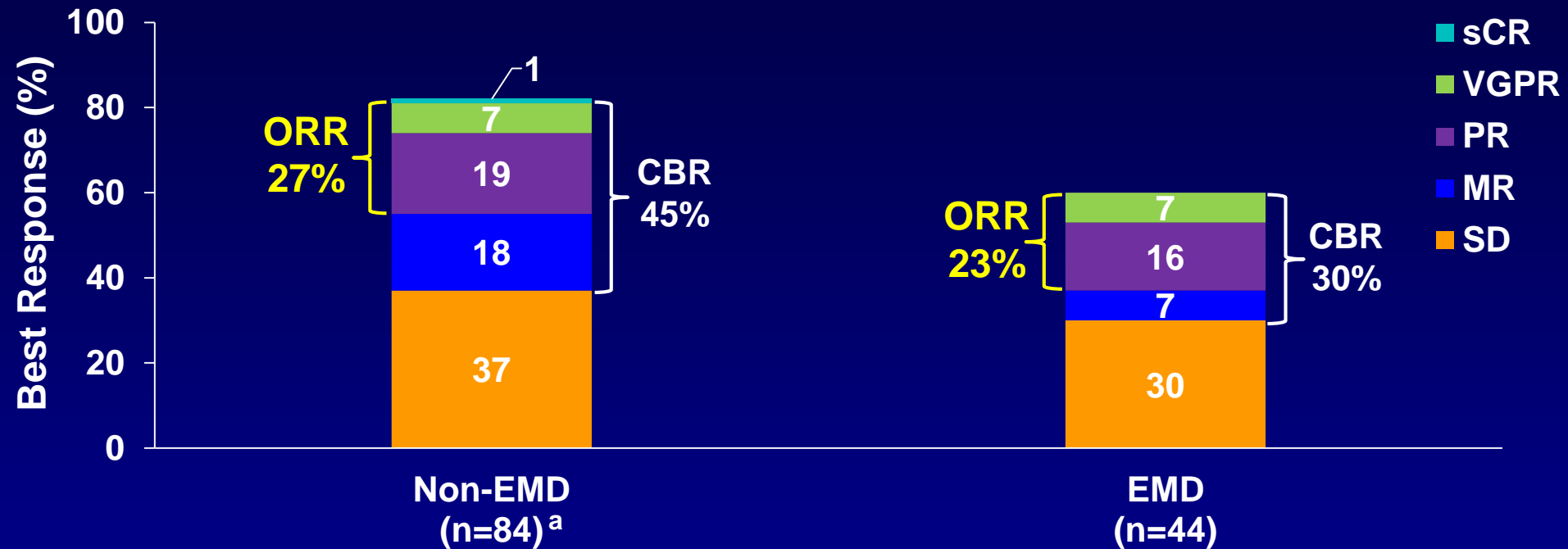
<sup>b</sup>Includes pts with both bone-related and soft tissue EMD.

<sup>c</sup>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



# Overall Response (n=128)

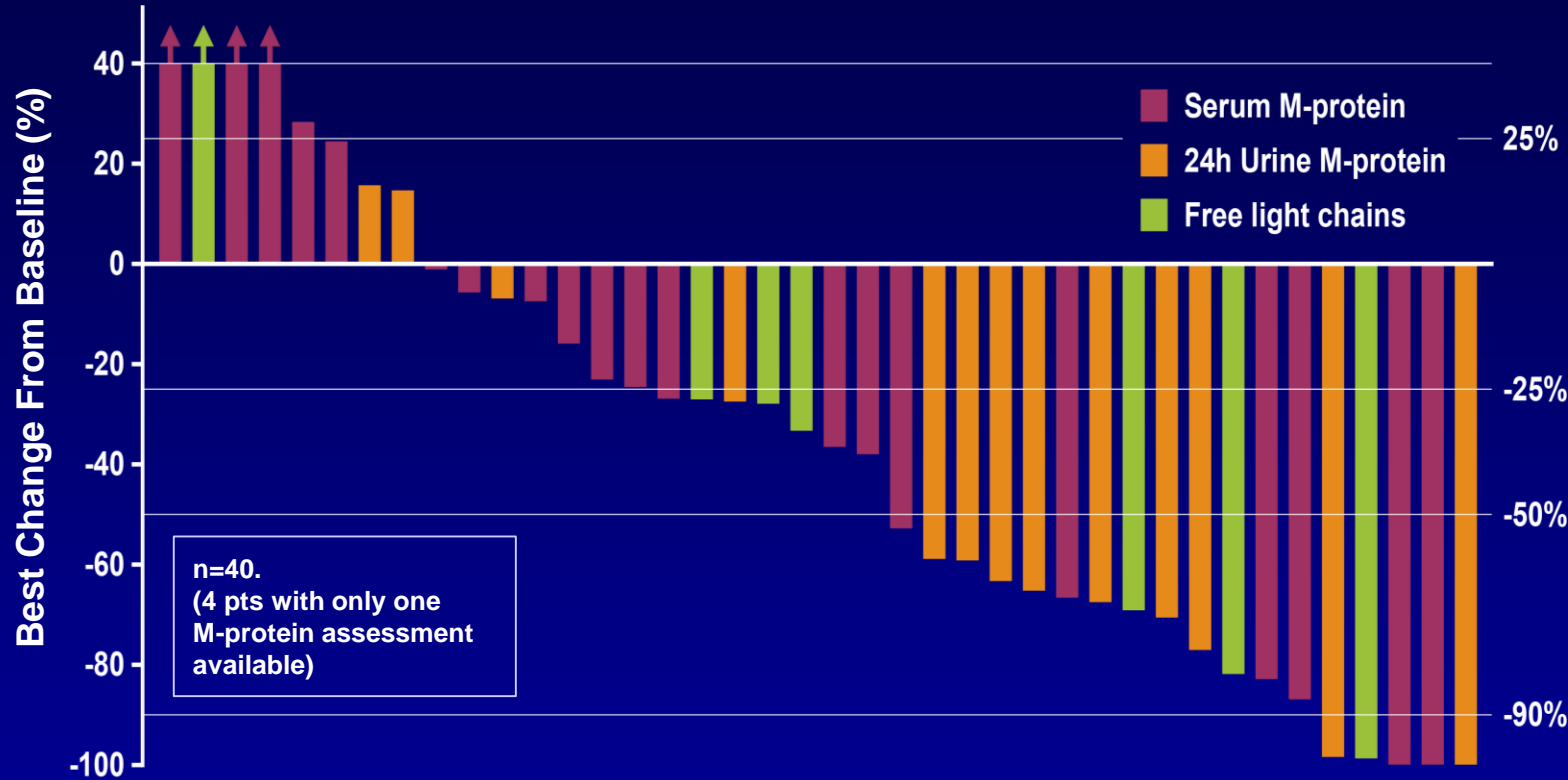


- Similar ORR in non-EMD and EMD pts, with an ORR of 27% and 23% respectively
  - Investigator-assessed response<sup>1</sup>
  - IRC review ongoing
- Median DOR for non-EMD pts 4.4 mos (95% CI, 3.5-11.2)
- Median DOR for EMD pts 3.4 mos (95% CI, 1.8-15.4)

<sup>a</sup> Two non-EMD pts with pending response information available at data cut off 30<sup>th</sup> July 2019.

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

# Response in EMD Pts (n=44)



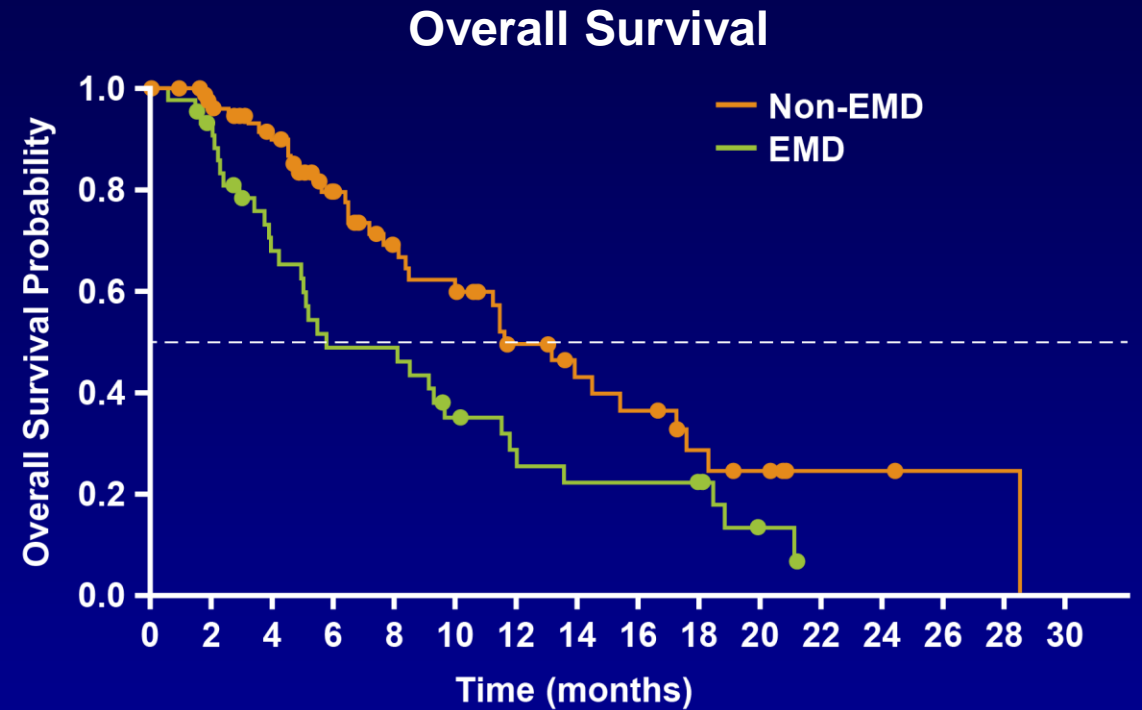
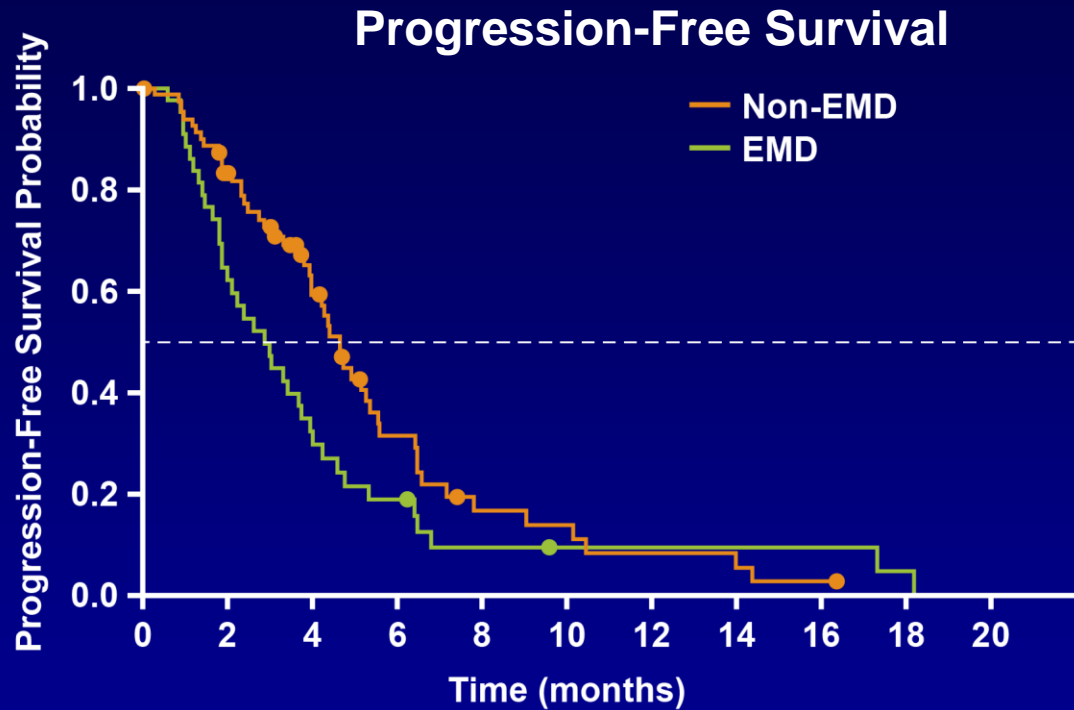
| n=44                 | ORR |
|----------------------|-----|
| Soft tissue<br>n=26  | 19% |
| Bone-related<br>n=18 | 28% |
| CNS<br>n=5           | 0%  |

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

# Disease Characteristics in Responding EMD Pts

| 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       |

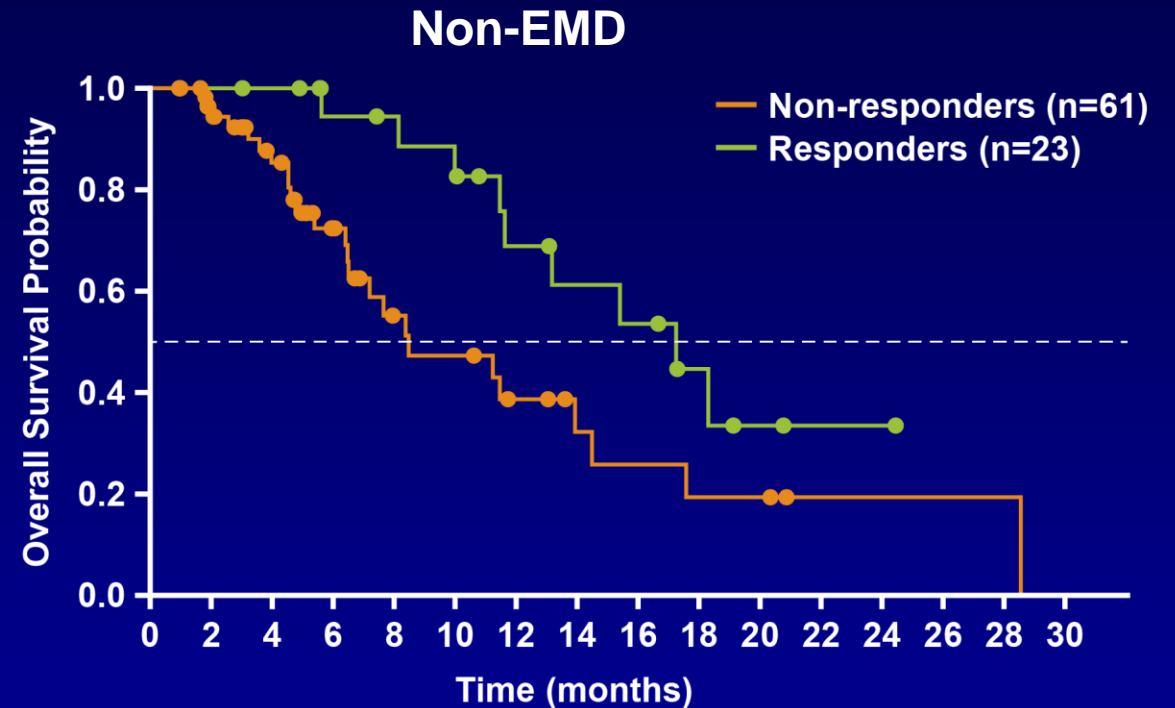
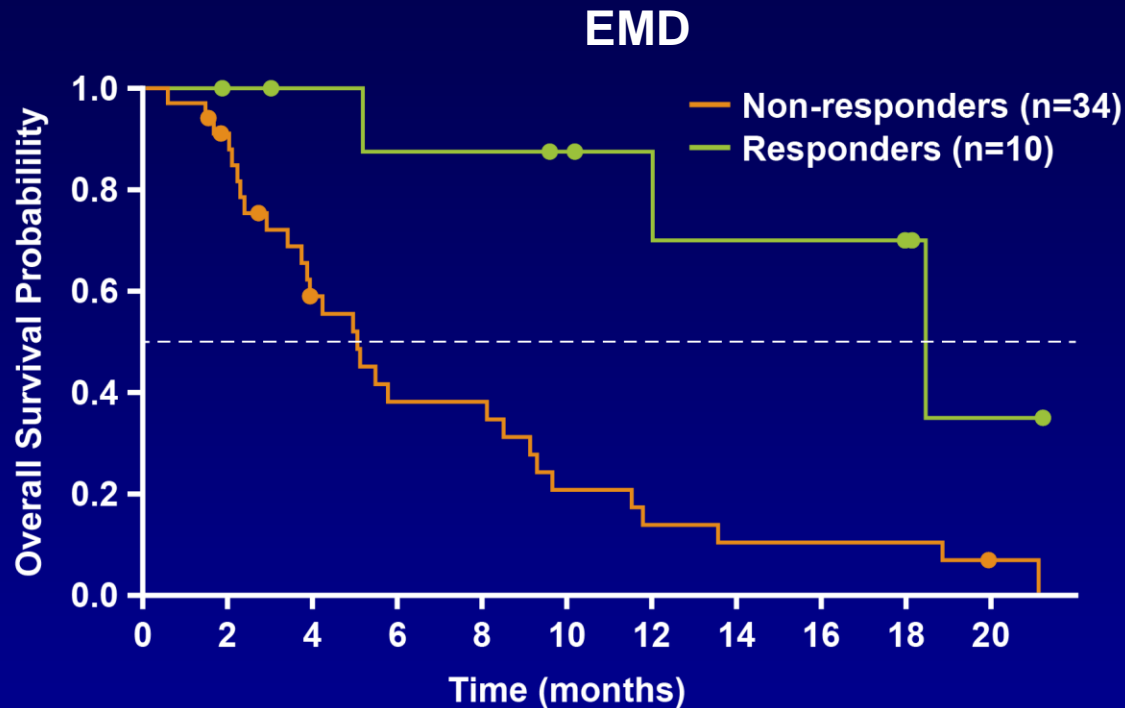
# Progression-Free and Overall Survival EMD vs Non-EMD Pts



- **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**

# OS in EMD and Non-EMD Pts Stratified by Response



- 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<sup>1</sup>

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

| TEAEs, <sup>a</sup> n (%)        | ITT (n=136) |         |
|----------------------------------|-------------|---------|
|                                  | Grade 3     | Grade 4 |
| Any AE                           | 38 (28)     | 77 (57) |
| <b>Hematologic AEs</b>           |             |         |
| 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)   |
| <b>Non-hematologic AEs</b>       |             |         |
| Pneumonia                        | 9 (7)       | 2 (1)   |

AE, adverse event; ITT, intention-to-treat; TEAE, treatment-emergent adverse event.

<sup>a</sup>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

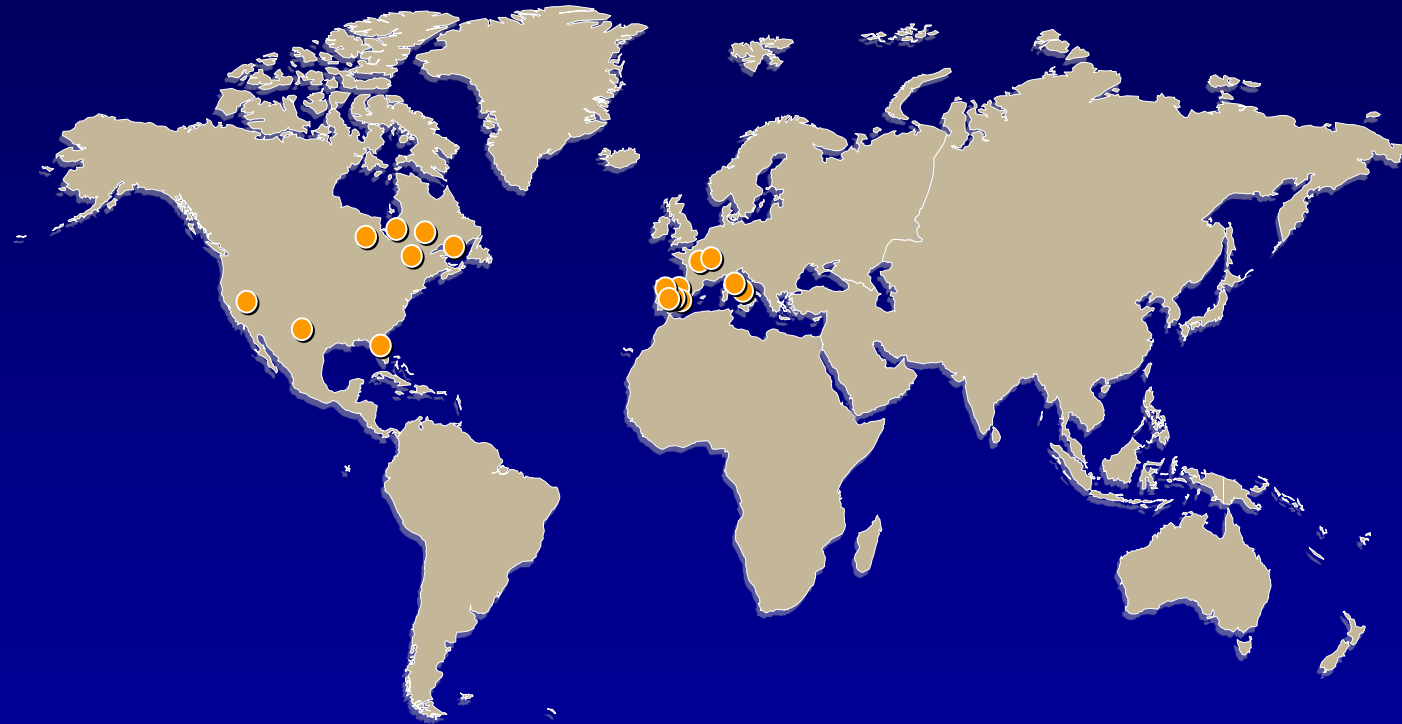
# Conclusions and Future Directions

- **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<sup>1-5</sup>**
- **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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