Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

Piero Galieni

La malattia extramidollare

MECHANISMS OF EXTRAMEDULLARY SPREAD IN MM

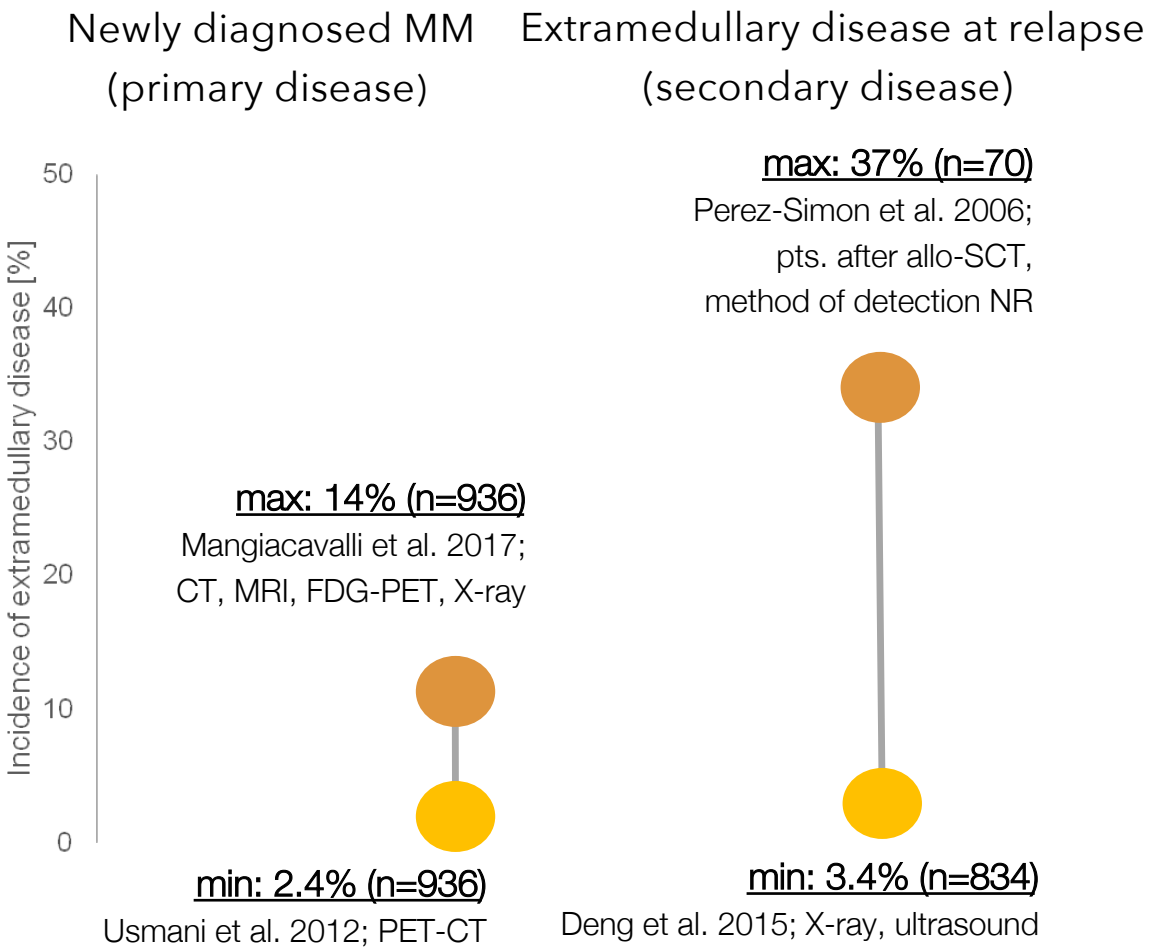
Poorly understood

Decreased exspression of adhesion molecules	**CD44 - VLA-4** **CD56 (loss)**
Downregolation of chemochines or chemochines receptors	**CXCR4 and its ligand SDF1-alpha** **CCR1 - CCR2**
Downregulation of Tetraspanines exspession	**TM4SF proteins**
Increased angiogenesis	

INCIDENCE OF EXTRAMEDULLARY DISEASE OF MM

Distinct in paraskeletal and other organs involvement

Extramedullary disease recognized at diagnosis of MM and at relapse



Sevcikova S et al. Blood Rev. 2019; 36:32-39.

AUTO-SCT FOR EXTRAMEDULLARY DISEASE OF MM

A STUDY FROM THE EBMT

METHODS

Data from database of 600 transplant centers located mainly in Europe.

Eligible patients:

- NDMM and extramedullary involvement received either single auto-SCT within 12 mo from diagnosis
- or subsequent auto-SCT (auto-auto)*
- or subsequent allo-SCT (auto-allo)*

Data registered between 2003 - 2015

* - subsequent transplant within 6 mo after the first

PATIENTS

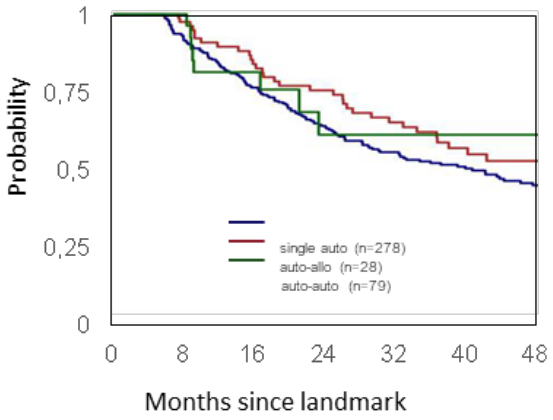
Characteristics	Patients [% of n=488]
Paraskeletal involvement	77%
Organ involvement	18%
Both	5%
ISS I	36
ISS II-III	64
KPS 90-100	74%
KPS <90	26%
Standard-risk	59%
High-risk	41%
1 site involved	92%
≥2 sites involved	8%
Single auto	77%
auto-auto	17%
auto-allo	6%

Gagelmann et al. Biol Blood Marrow Transplant. 2019;25(6):e204-e208.

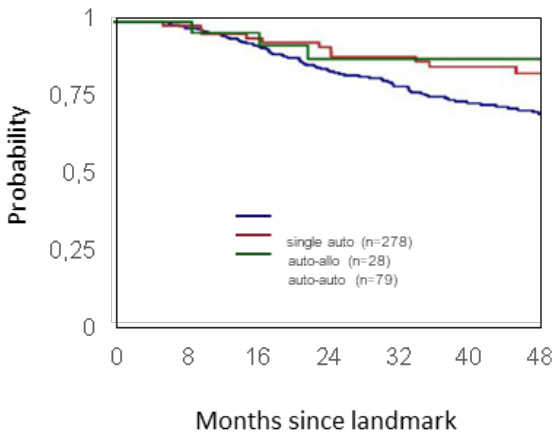
POSTTRANSPLANT OUTCOME by transplant type

- Overall survival appeared to be influenced by transplant in univariate analysis resulting in 4-years OS rates of 70% for single auto vs. 83% for auto-auto and 88% for auto-allo (p=0.06).
- The cumulative incidence of NRM was 2% for single auto, 1% for auto-auto, and 10% for auto-allo (p=0.09).

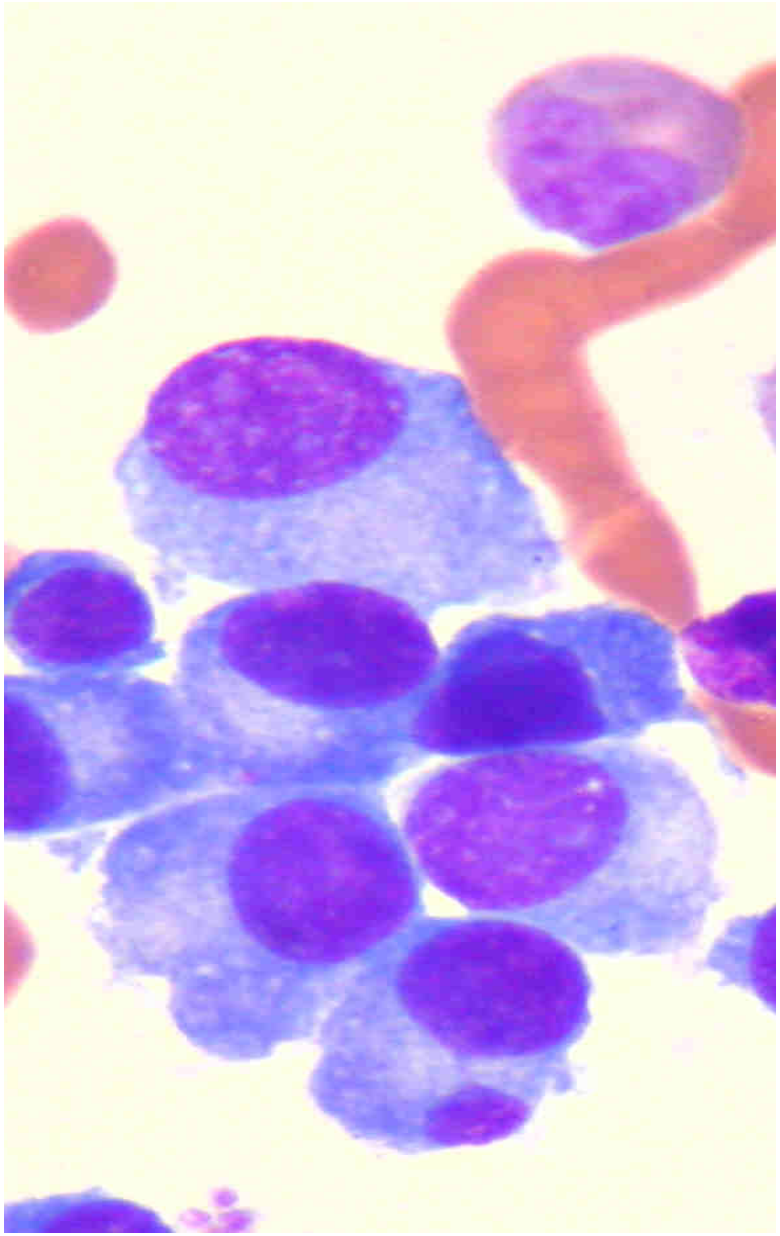
Progression-free survival did not significantly differ between three transplant types (p=0.30)



Overall survival appeared to affect by transplantation showing higher rates for auto-auto and auto-allo transplant (P=0.06)



Gagelmann et al. Biol Blood Marrow Transplant. 2019;25(6):e204-e208.

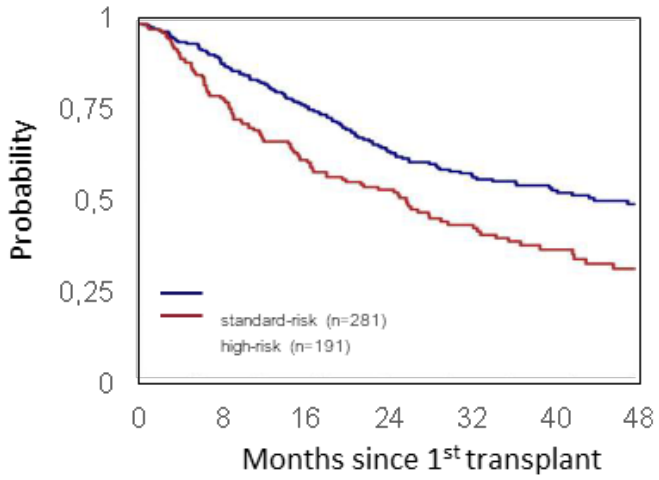


POSTTRANSPLANT OUTCOME
according to cytogenetic risk and disease site

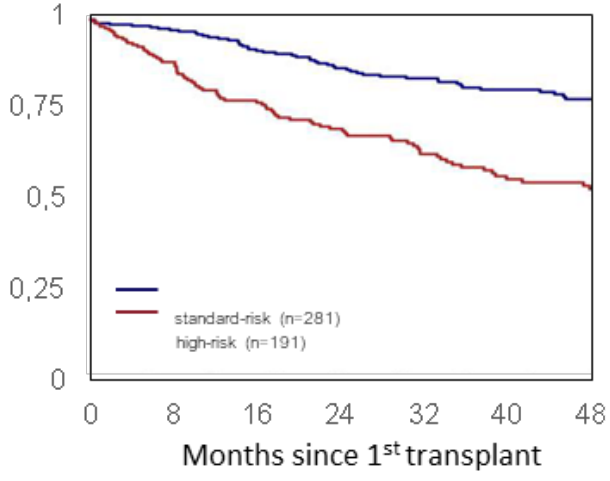
Patients with high-risk cytogenetics showed significantly worse OS and PFS of 54% (45-62%) and 29% (20-37%) vs. 78% (73-84%) and 49% (42-56%) of patients with standard-risk (p<0.001, respectively).

4-years OS according to type of involvement was 72% for paraskeletal vs. 60% for organ and 46% for both types of involvement (P=0.002). Univariate effect of different types of involvement disappeared in multivariate analysis when comparing paraskeletal with organ (P=0.87) or both types of involvement (P=0.65).

Progression-free survival was significantly worse in patients with high-risk cytogenetics vs. standard-risk (P<0.001).



Overall survival was significantly affected by cytogenetics being worse in high-risk patients (P<0.001).



Gagelmann et al. Biol Blood Marrow Transplant. 2019;25(6):e204-e208.

POSTTRANSPLANT OUTCOME
by cytogenetic risk and transplant type

- Auto-auto can overcome poor prognosis of high-risk cytogenetics
- Also outcome after first-line auto-allo transplant appeared to be improved compared with single transplant but more specific data are needed. N = 31 for auto-allo

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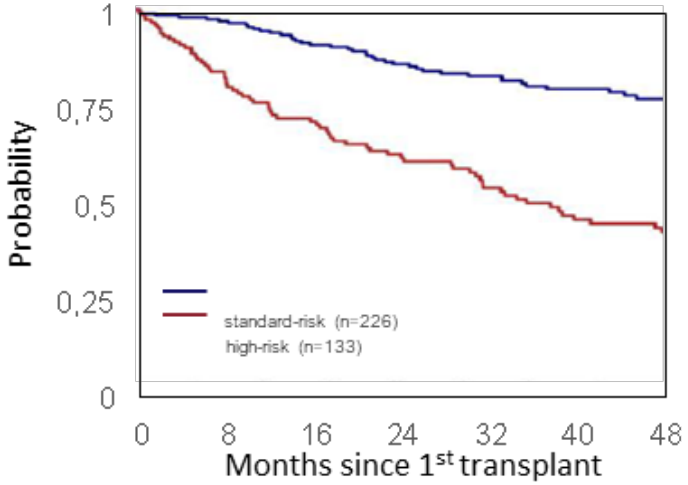
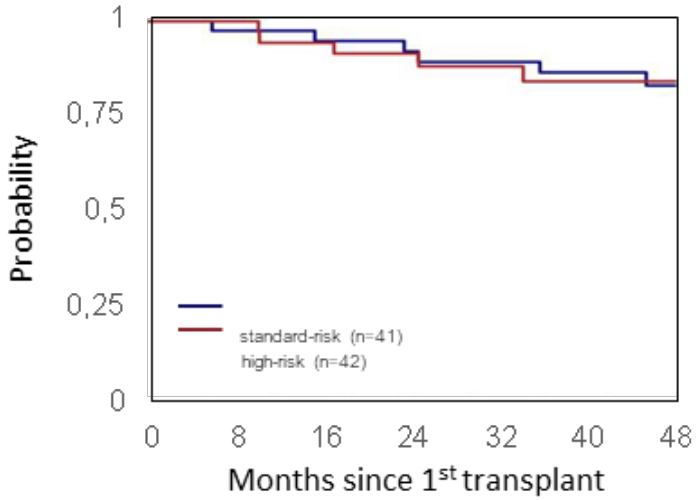
Afrer single auto overall survival was significantly affected by cytogenetics being worse in high-risk patients (P<0.001).



After tandem auto overall survival was the same for high-risk vs. standard-risk cytogenetics (P=0.99).



Gagelmann et al. Biol Blood Marrow Transplant. 2019;25(6):e204-e208.

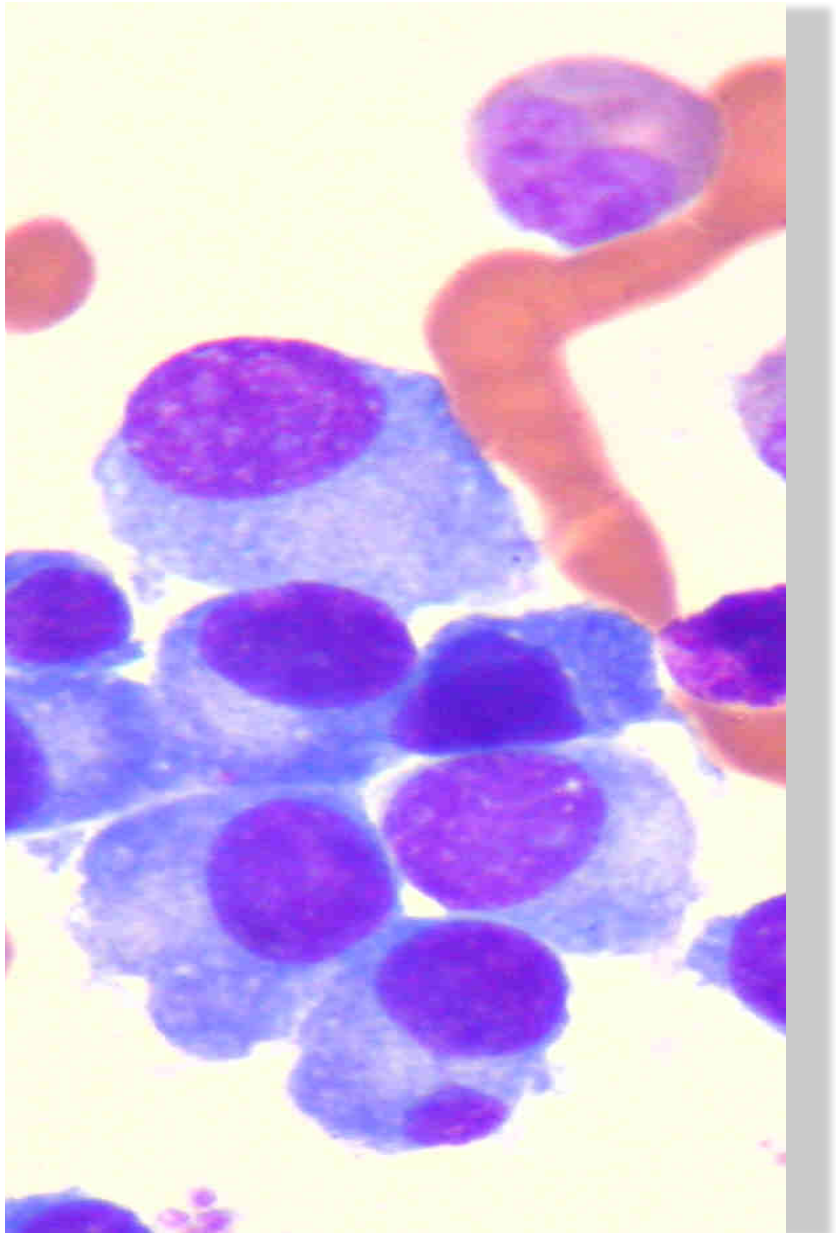
OUTCOMES AND PREDICTIVE FACTORS

Retrospective, multi-institutional study conducted in 19 centers from 11 countries in Europe. Included patients with MM who had a pathological and/or radiological diagnosis of extramedullary involvement at any time of follow up between 2010 and 2017.

		CR [%]	Median PFS [mo]	Median OS [mo]
Paraskeletal involvement	primary	34%	51.7	NR
	secondary	54%	20.9	39.8
Organ involvement	primary	19%	38.9	46.5
	secondary	9%	13.6	11.4

- Almost half of patients had unfavorable cytogenetics
- Patients with paraskeletal involvement had better survival than with organ involvement (median OS not reached vs 19.2 months)
- Diagnosis of extramedullary disease at relapse had poor survival prognosis (8.4 mo vs 59.2 mo for primary disease)
- Survival benefit with extramedullary disease from auto-PBSCT (median OS 79.5 mo vs 34.7 mo for no auto-SCT)

Beksac et al. Haematologica. 2019; pii: haematol.2019.219139.

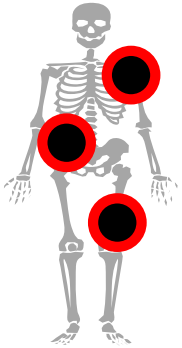


OTHER RISK FACTORS

Extramedullary disease is associated with the presence of:

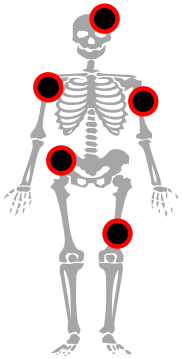
- anemia,
- thrombocytopenia,
- elevated serum LDH

NEW RISK FACTOR – SIZE OF FOCAL LESIONS



Multiple LARGE focal lesions

Poor prognosis



Multiple SMALL focal lesions

Indifferent prognosis

Patients with ≥3 large FLs with a product of the perpendicular diameters >5 cm^2 were associated with poor PFS (2.3 years) and OS (3.6 years)

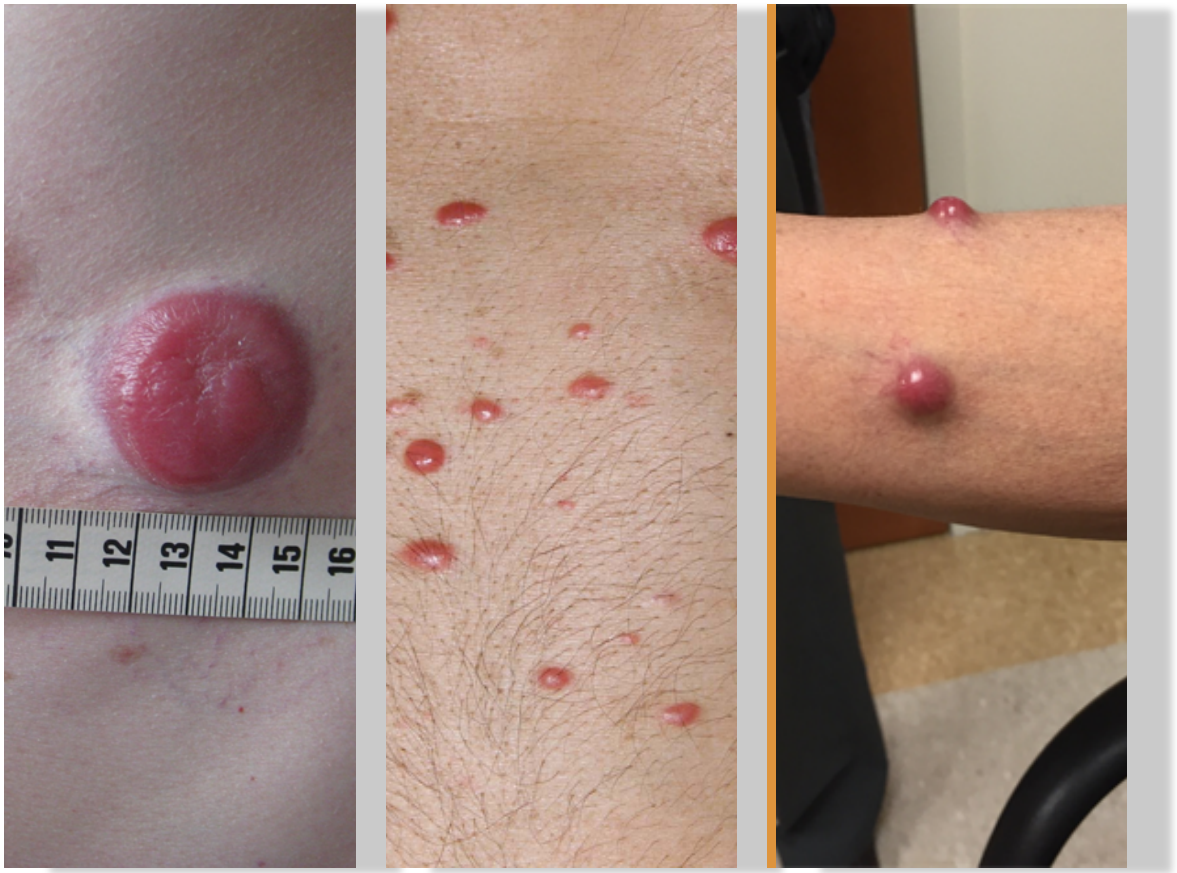
Usmani SZ et al. Haematologica. 2012;97:1761-1767.
Rache L et al. Blood. 2018;132:59–66.

ORGAN-SPECIFIC DISEASE CLINICAL PICTURE OF SKIN DISEASE

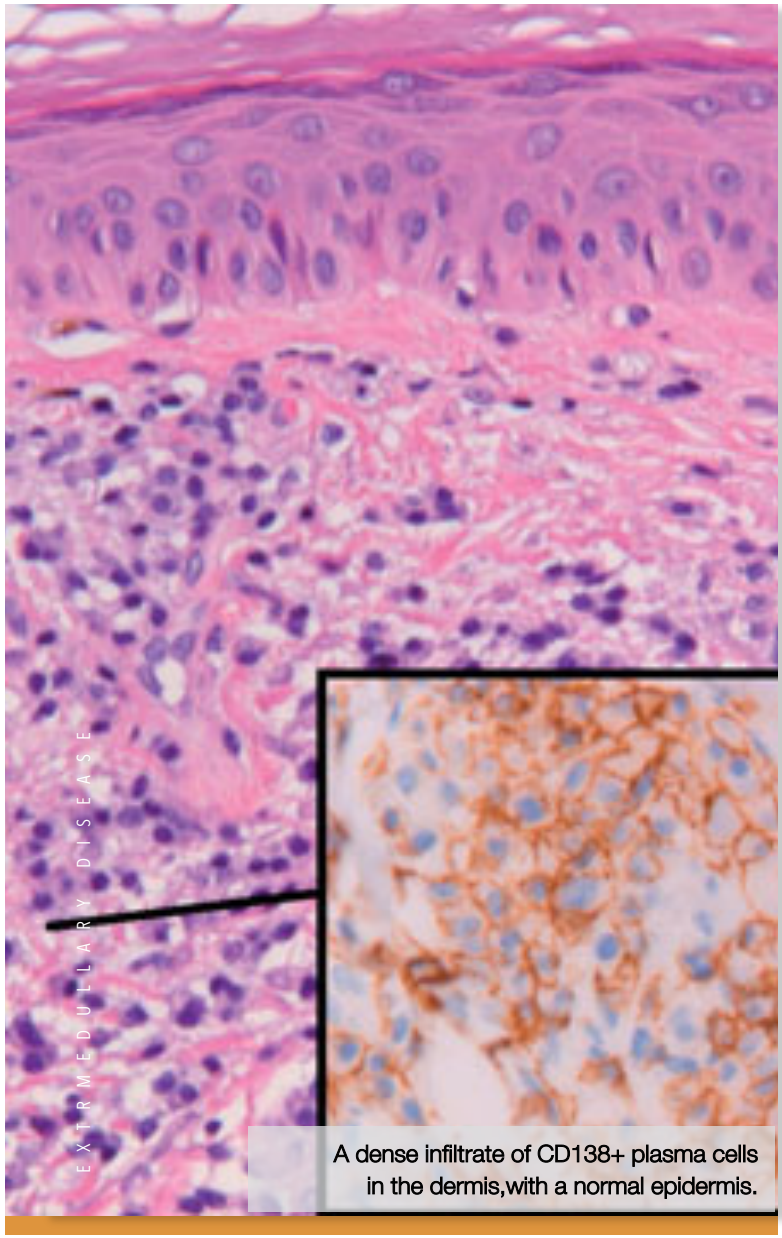
- Skin infiltration in MM is a rare clinical problem, which usually manifests during end-stage disease.

- Plasmacytic infiltrates typically present as red–violet spots, nodules or lumps, which can ulcerate, or as dome-shaped plates having a smooth surface and diameter from 0.5” to 2”.

- The most common locations for skin MM lesions were the chest, lower extremities, back and buttocks; some lesions were located on the upper extremities and less often on the face.



Jurczyszyn et al. Leuk Lymphoma. 2016; 57: 2071-2076.
Image courtesy of Rasche Leo, Germany



A dense infiltrate of CD138+ plasma cells in the dermis,with a normal epidermis.

METHODS

- Multi-institutional, retrospective study conducted in 24 centers from 13 countries in Europe and Americas.
- All pts. with a pathological diagnosis of MM involving the skin were included in this analysis.
- This is the largest group of patients with this rare clinical manifestation of multiple myeloma described in the literature.

PATIENTS

Characteristics	Patients, N=53
Males, [%]	60%
Median age	63 (38-86)
Median time from diagnosis	2.2 (0-11)
ISS I, [%]	27.5%
ISS II-III, [%]	72.5%
1-5 lesions	67%
≥6 lesions	33%
Chest	44%
Legs	24%
Back/buttocks	22%
Face/neck	20%

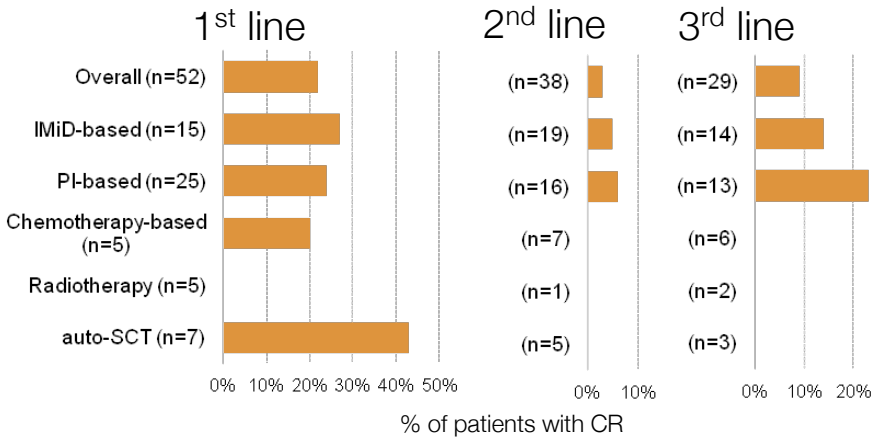
Jurczyszyn et al. Leuk Lymphoma. 2016; 57: 2071-2076.

PATHOLOGICAL CHARACTERISTICS

Characteristic	n positive/ N tested (%)
Immunochemistry	
CD38/CD138	29/29 (100%)
IRF4/MUM1	4/4 (100%)
CD56	9/11 (82%)
CD79A	4/5 (80%)
CD45	1/3 (33%)
CD20	1/10 (10%)
EBER	0/2 (0%)
Fluorescent in situ hybridization	
Complex (3 + abnormalities)	10/23 (43%)
Deletion 13q	9/24 (38%)
Translocation (4;14)	6/24 (25%)
Deletion 17p	2/24 (8%)
Translocation (14;16)	2/24 (8%)
Translocation (11;14)	1/23 (4%)

TREATMENT

Nearly all patients received initial therapy for skin MM (98%), 73% received 2nd-line therapy, and 56% received 3rd-line of therapy.

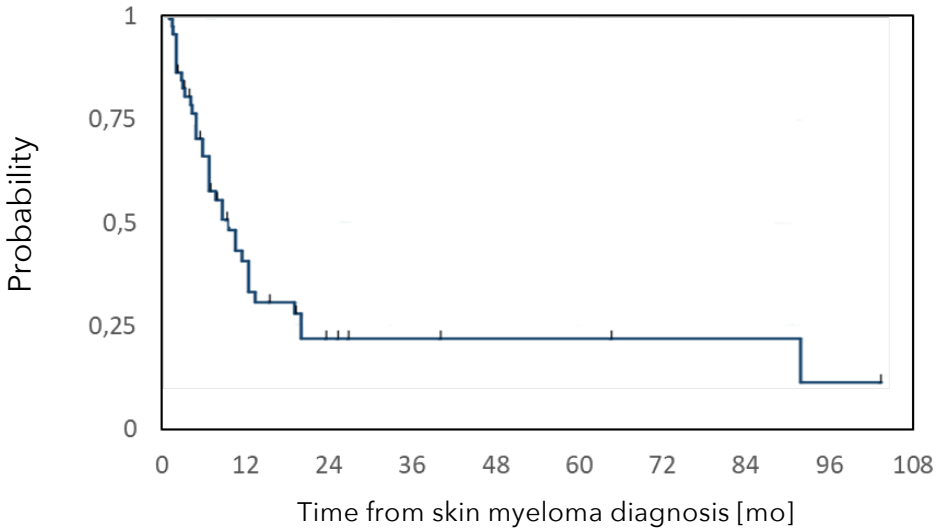


There were some responders observed in the later lines of therapy, especially to novel drugs such as carfilzomib and pomalidomide. No drug superiority was observed in terms of response.

Jurczyszyn et al. Leuk Lymphoma. 2016; 57: 2071-2076.

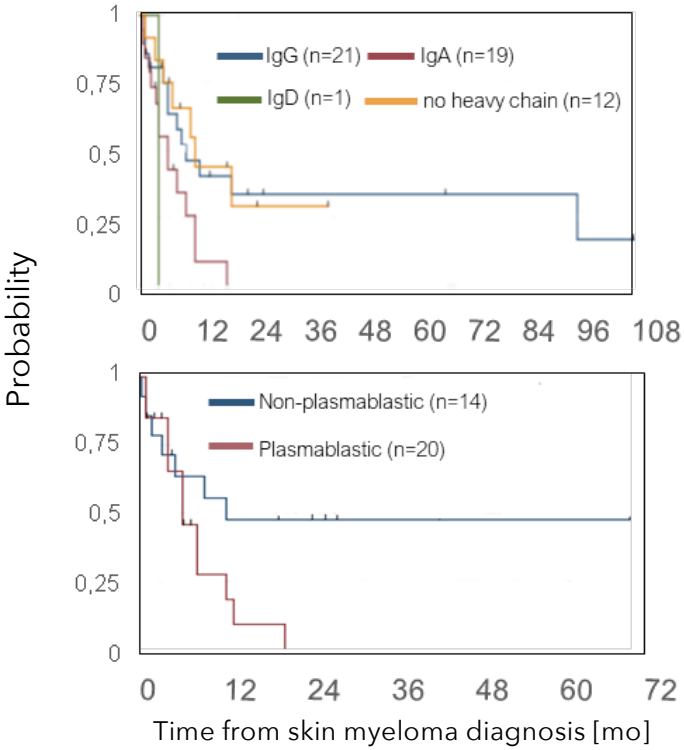
OVERALL SURVIVAL

With a median follow-up of 24 months, the median OS from time of skin MM diagnosis was 8.5 months.



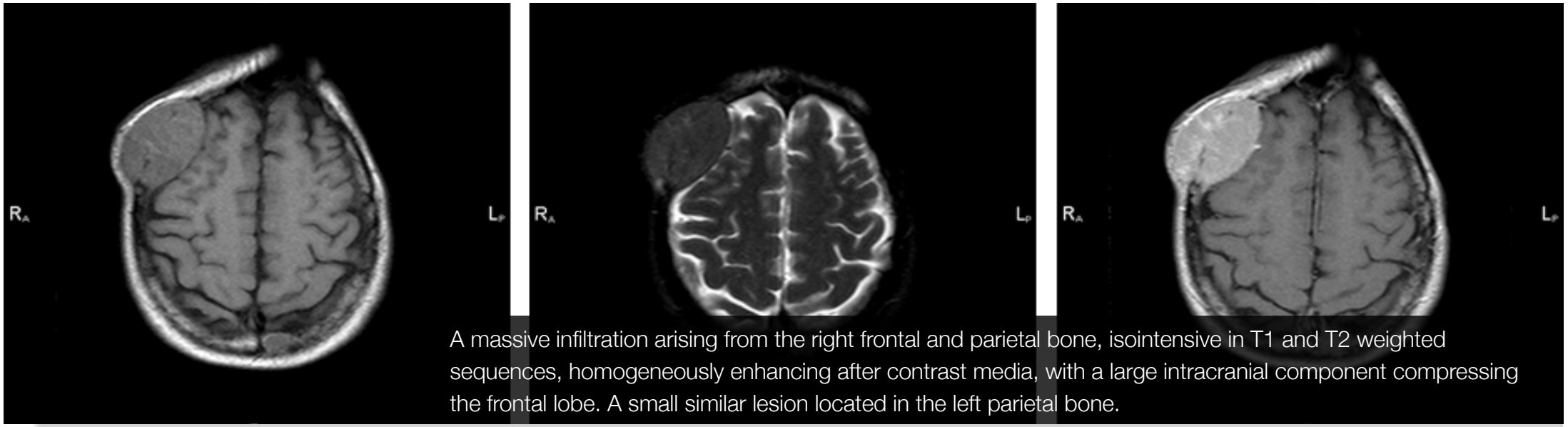
Causes of death were MM progression in 83%, infection in 14%, and pancreatic obstruction in 3% of the patients.

PROGNOSTIC FACTORS



In the univariate analysis, patients with IgA heavy chain disease and plasmablastic morphology were associated with worse OS (P=0.044 and P=0.047, rrespectively).

Jurczyszyn et al. Leuk Lymphoma. 2016; 57: 2071-2076.



A massive infiltration arising from the right frontal and parietal bone, isointensive in T1 and T2 weighted sequences, homogeneously enhancing after contrast media, with a large intracranial component compressing the frontal lobe. A small similar lesion located in the left parietal bone.

ORGAN-SPECIFIC DISEASE | CNS

- The central nervous system is a very rare location of extramedullary involvement and is diagnosed in less than 1% of MM patients.
- Patients usually present with focal neurological deficits, changes of vision, radiculopathy, headache, altered mental status, or cognitive impairment.
- CNS MM may present with solitary or multiple intraparenchymal lesions and/or leptomeningeal disease with the presence of monoclonal plasmacytes in the CSF.

Varettoni et al. Ann Oncol. 2010; 21:325–330.
Fassas et al. Br J Haematol. 2002; 117:103–108.

METHODS

- This was a multi-institutional, retrospective study conducted
- in 38 centers from 20 countries in Europe, Asia, Australia, and Americas.
- Adult patients with a pathological and/or radiological diagnosis of CNS MM in a location non-contiguous with a bone, between January 1995 and December 2014 were included.
- This is the largest group of patients with this rare clinical manifestation of multiple myeloma described in the literature.

*- cytogenetics information was available for 122 pts.

PATIENTS

Characteristics	Patients, N=171
Males, [%]	55%
Median age	56 (33-82)
Median time from MM	2.1 (0-18)
Primary disease	22%
ISS I, [%] ISS II-III, [%]	32% 68%
Normal LDH Elevated LDH	53% 47%
No FISH abnormalities* 1 FISH abnormality* ≥2 FISH abnoralities*	47% 30% 34%

TREATMENT OF CNS MM

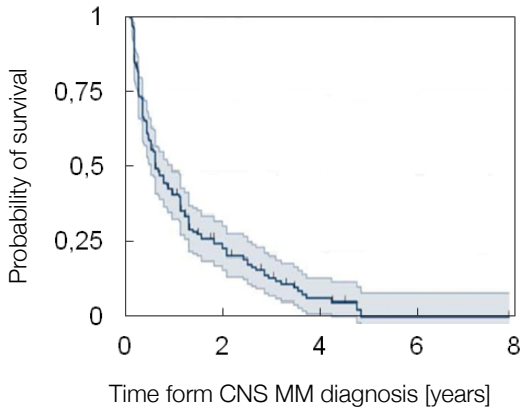
Of the 172 patients, 166 (97%) received initial therapy for CNS MM. Auto-SCT or allo-SCT was performed in 21% of patients.

- 73 (44%) received second line therapy,
- 28 (17%) received third line therapy,
- 1 (1%) patient received fourth line therapy.

Initial therapy	N (%)
Systemic only	69 (40%)
Systemic + radiotherpay	22 (13%)
Systemic + intrathecal	16 (9%)
Systemic + intrathecal + radiotherapy	10 (6%)
Intrathecal only	21 (12%)
Radiotherapy only	20 (12%)
Intrathecal + radiotherapy	2 (1%)
Steroids only	5 (3%)
Resection + radiotherapy	1 (1%)

Jurczyszyn et al. Am J Hematol. 2016; 91: 575–580.

OVERALL SURVIVAL



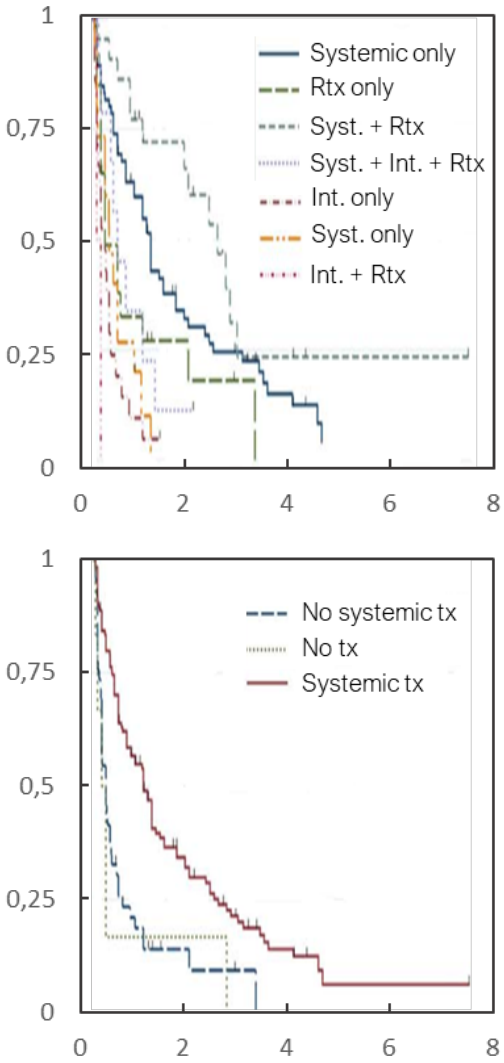
After a median follow-up of 3.5 years, the median OS for the entire group was 6.7 months.

The patients who received

- No treatment for CNS MM had a median OS of 2 months,
- Treated patients had a median OS of 7 month,139 patients (81%) died.

ROLE OF SYSTEMIC TREATMENT

- Patients who received systemic therapy only and systemic therapy plus radiotherapy appeared to have better OS.
- The OS in patients in all the other treatment groups were not significantly different than the OS of patients who were not treated.
- The median OS for patients who received systemic therapy vs those who received no systemic therapy was 12 mo vs. 3 mo (HR 0.44, 95% CI 0.29–0.65; p<0.001).



Jurczyszyn et al. Am J Hematol. 2016; 91: 575–580.

TREATMENT OF RELAPSED EXTRAMEDULLARY DISEASE

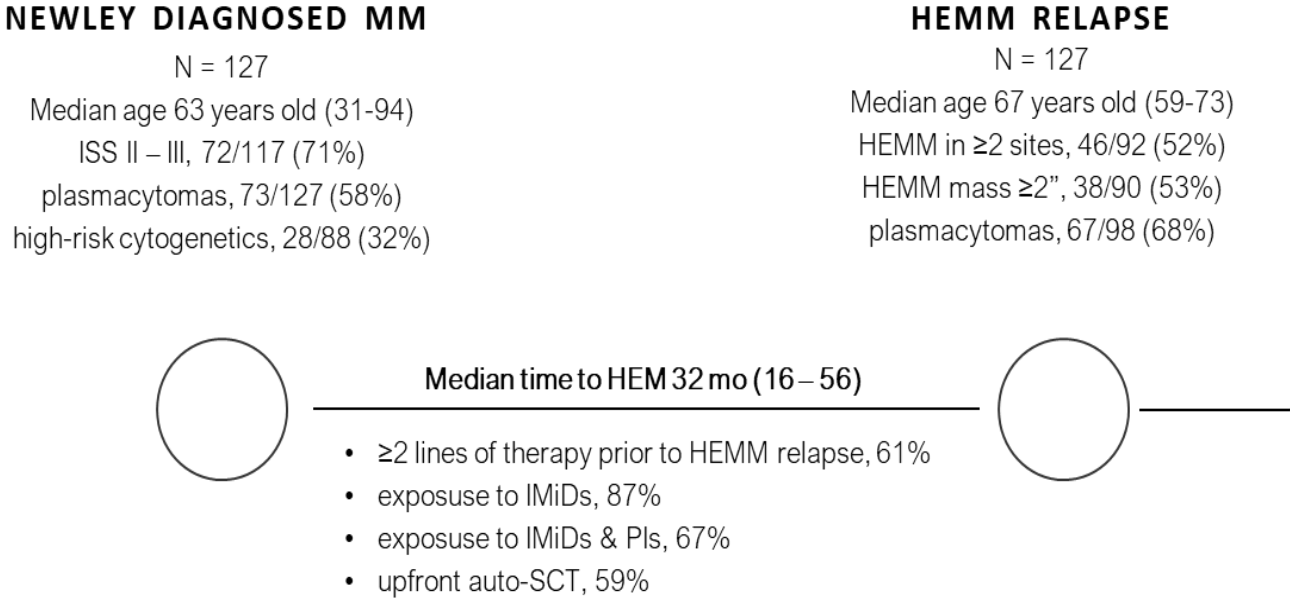
METHODS

This was a multi-institutional, retrospective study conducted in 15 centers.
Inclusion criteria:

- pts. with imaging scan that demonstrated HEMM or a histological confirmation of HEMM

Exclusion criteria:

- pts. with HEMM relapse involving the CNS as their single HEMM site



Avivi et al. Am J Hematol. 2019; doi: 10.1002/ajh.25579.

CHARACTERISTICS OF PATIENTS

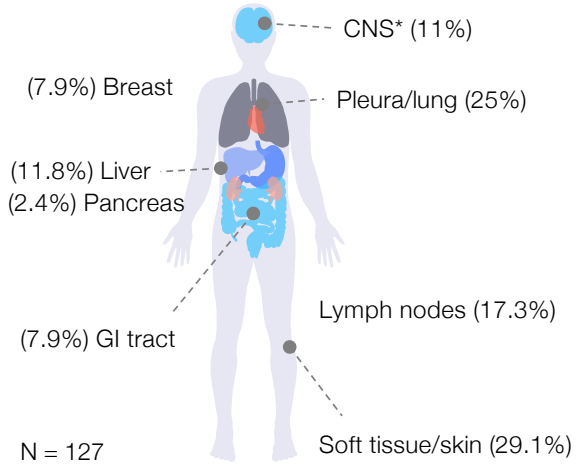
AT DIAGNOSIS

Characteristic	Medin (range) or n/N tested (%)
Age	63 (50 - 70)
Males	76/127 (60%)
IgG	59/120 (50%)
IgA	31/127 (26%)
Other	2/127 (1.6%)
Light chain	29/127 (23%)
ISS I	35/117 (30%)
ISS II - II	71/117 (71%)
t(4;14)	17/88 (19%)
t(14;16)	2/88 (2%)
t(14;20)	0/88 (0%)
Del17p	10/88 (11%)
Del13q	28/88 (32%)
t(11;14)	6/88 (7%)
CD56(+)	
CD20(+)	
Plasmacytoma at diagnosis	73/127 (57.5%)
Bone plasmacytoma	69/127 (54.3%)
HEMM	20/127 (15.7%)

AT HEMM RELAPSE

Characteristic	Medin (range) or n/N tested (%)
Age	67 (59 - 73)
Bone marrow involvement	67/98 (68%)
Non-secretory	21/105 (20%)
Light chain	29/127 (23%)
HEMM >2"	38/90 (53%)
HEMM ≥2 sites	46/92 (52%)
Elevated LDH	64/127 (59%)
CD56(+)	33/127 (55%)
CD20(+)	8/127 (14%)
0 prior lines of tx	13/127 (10%)
1 prior line of tx	37/127 (29%)
≥2 lines of tx	77/127 (61%)
Prior expousure to IMiD	110/127 (87%)
Prior expousure to IMiD & PI	85/127 (67%)

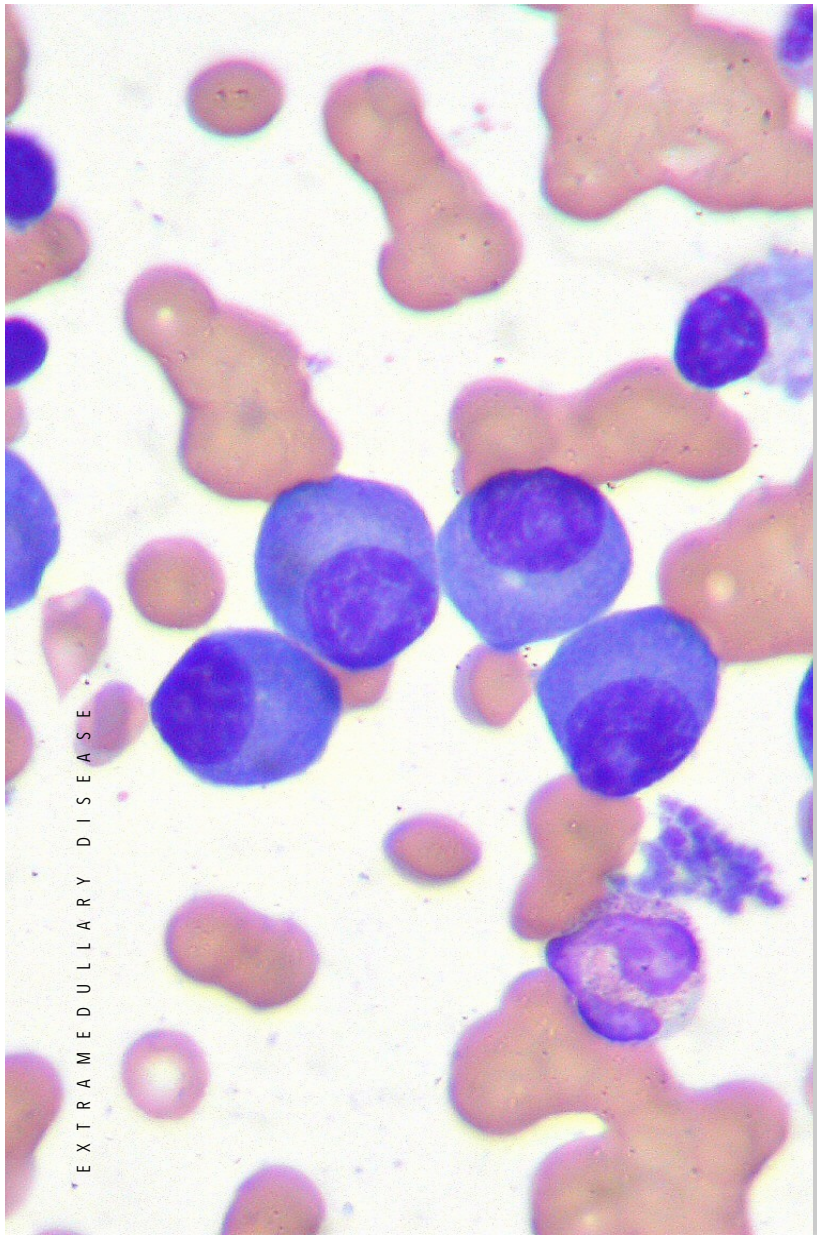
SITES OF HEMM



Other sites: genitourinary organs, gums, spleen – 1 pt. each

* - always in addition to another HEMM site;

Avivi et al. Am J Hematol. 2019; doi: 10.1002/ajh.25579.



FACTORS ASSOCIATED WITH DURATION TO THE DEVELOPMENT OF HEMM

UNIVARIATE

Factors associated with shorter time to relapse:

- **increased beta-2-microglobulin level** (r=-0.296, P=0.002)
- **advanced ISS stage** (median time: I-46m, II-34m, III-23m, P=0.01)
- **presence of del17p** (median time: 8m vs. 27m, P=0.006)
- **Extramedullary plasmacytomas at MM diagnosis** (median time: 27 mo vs. 38 mo, P=0.0006)

Factors associated with longer time to relapse:

- **Upfront auto-SCT** (median time 42 mo vs. 22 mo, P=0.001)
- **Use of IMiDs prior relapse** (median time: 38 mo vs. 25 mo, P=0.04)

MULTIVARIATE

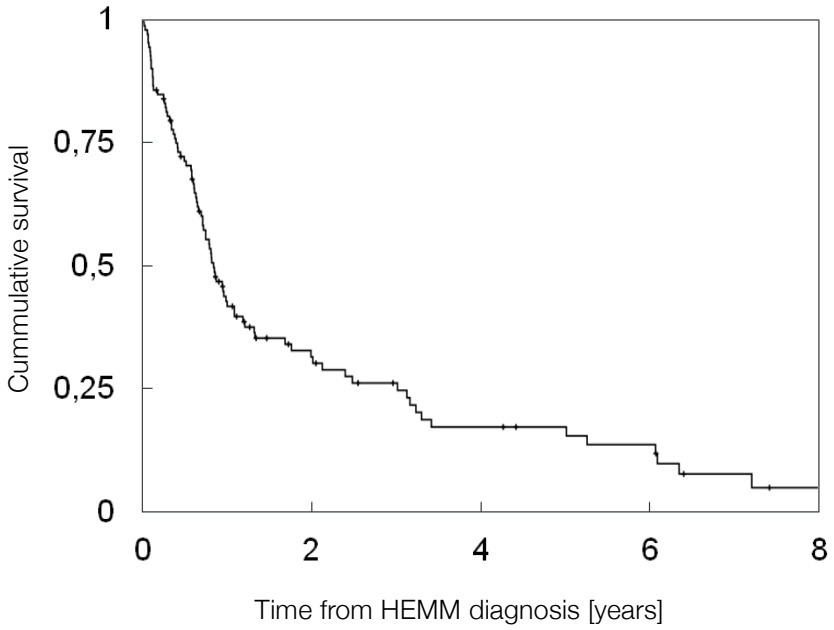
Patients who presented with ISS3 (compared with ISS1) had reduction of 43.7% in time to HEMM development (95% CI=16.5%-62.0%, p=0.005).

Patients with bone plasmacytoma at diagnosis had a 35.8% shorter time to HEMM relapse (95% CI=11.1%-53.6%, p=0.008).

Upfront auto-HSCT was significantly associated with a delayed time (85%) to HEMM occurrence (95% CI=27%-170%, p=0.002)

Avivi et al. Am J Hematol. 2019; doi: 10.1002/ajh.25579.

TREATMENT, RESPONSE AND SURVIVAL



First treatment for HEMM included PIs in 50%, IMiDs in 39%, mAbs in 10% and chemotherapy in 53% of patients

Overall response rate (ORR) was 57%, including:

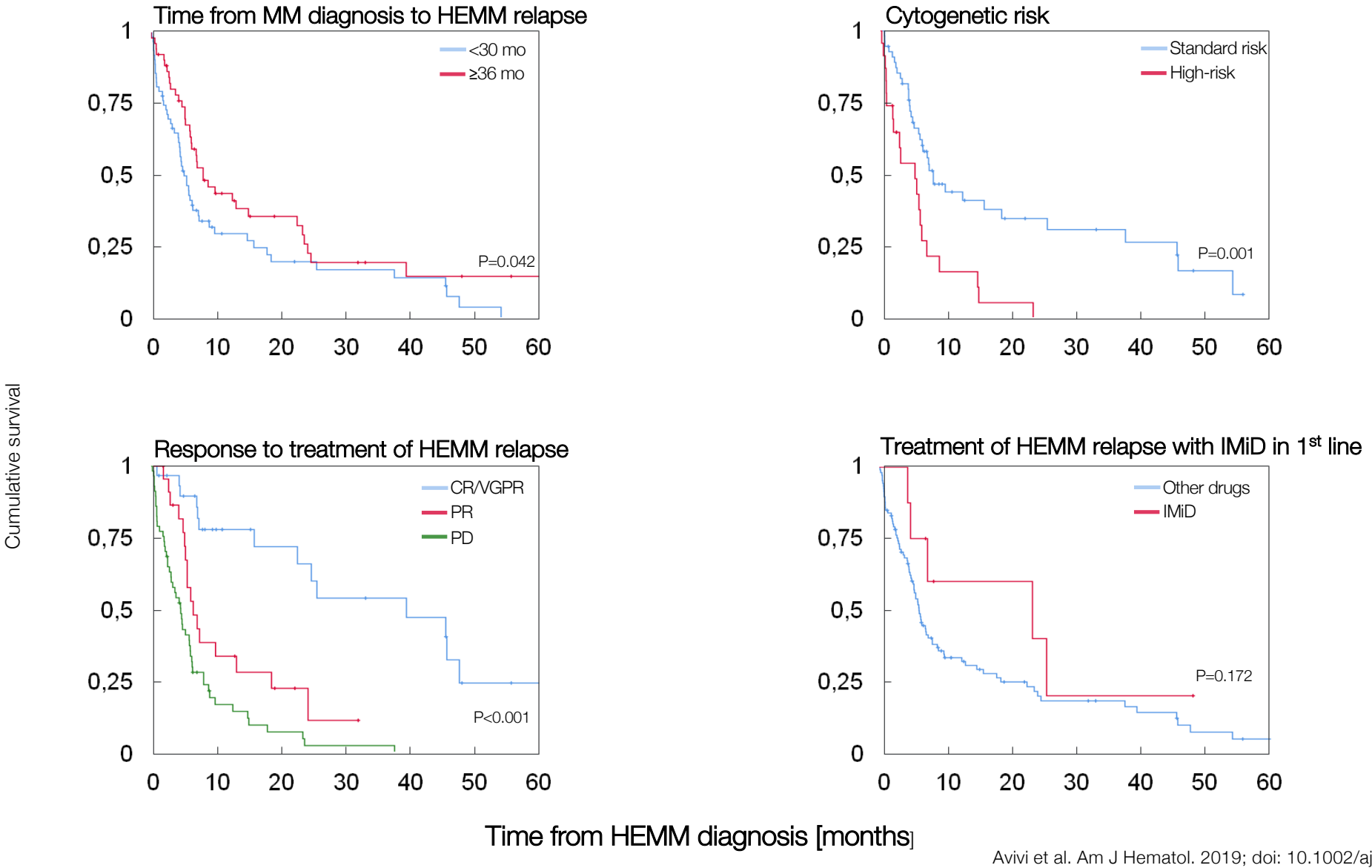
- 17 (15%) CR,
- 15 (13%) VGPR,
- 25 (22%) PR.

The median number of therapies administered following the development of HEMM relapse was 2 (range: 1-3).

IMiDs compared with PIs and chemotherapy, were associated with higher response rates (OR 2.2, 95% CI 1.02-4.7, p=0.04).

Median survival from HEMM development was 6.5 months (95%CI: 95% 5.1-7.8).

Avivi et al. Am J Hematol. 2019; doi: 10.1002/ajh.25579.



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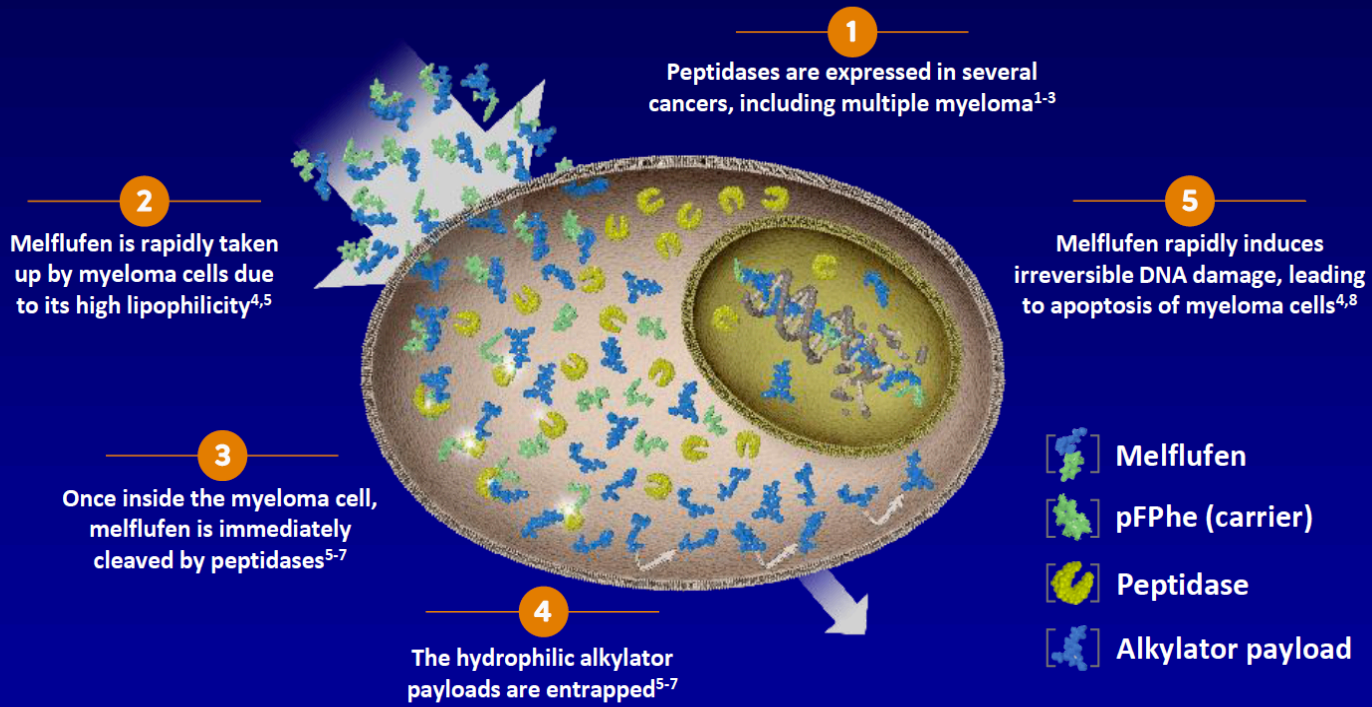
Melflufen: a Lipophilic Peptide-Conjugated Alkylator Rapidly Delivers a Cytotoxic Payload Into Myeloma Cells

HORIZON

Peptidase-enhanced activity in multiple myeloma cells

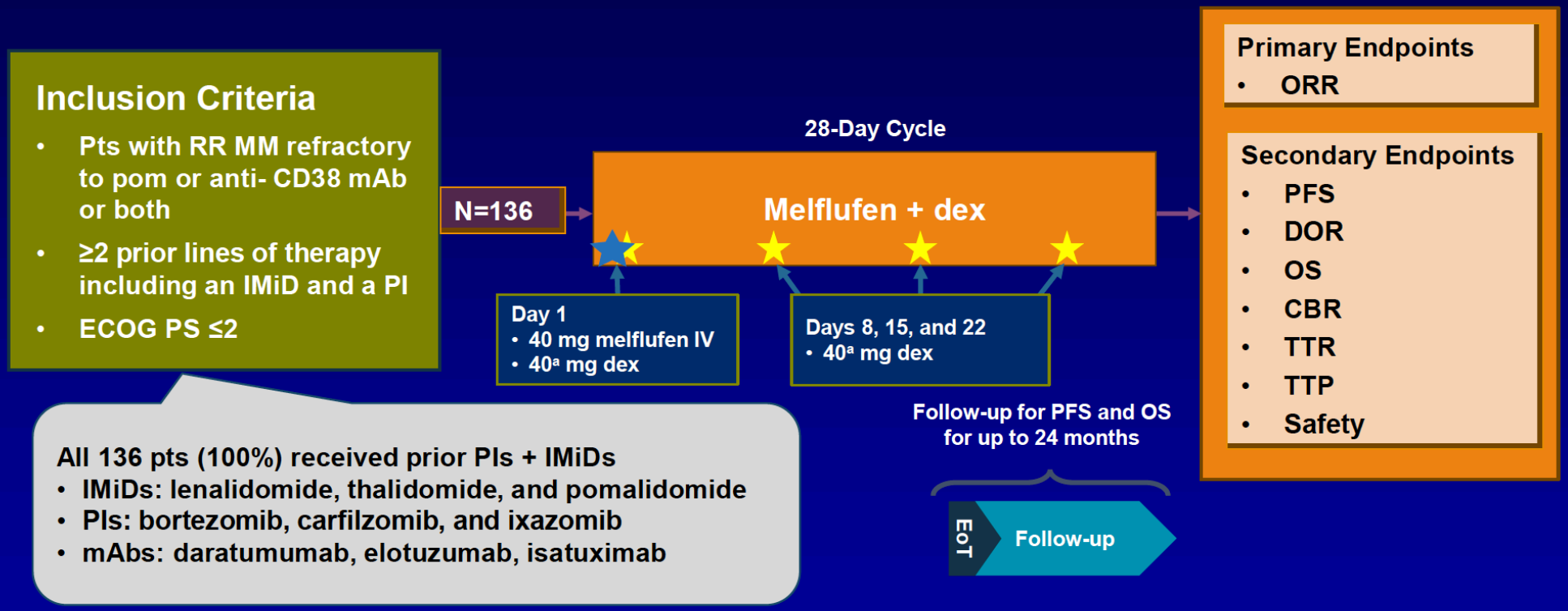


Melflufen is 50-fold more potent than melphalan in myeloma cells *in vitro* due to increased intracellular alkylator activity[4,5]

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

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- 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

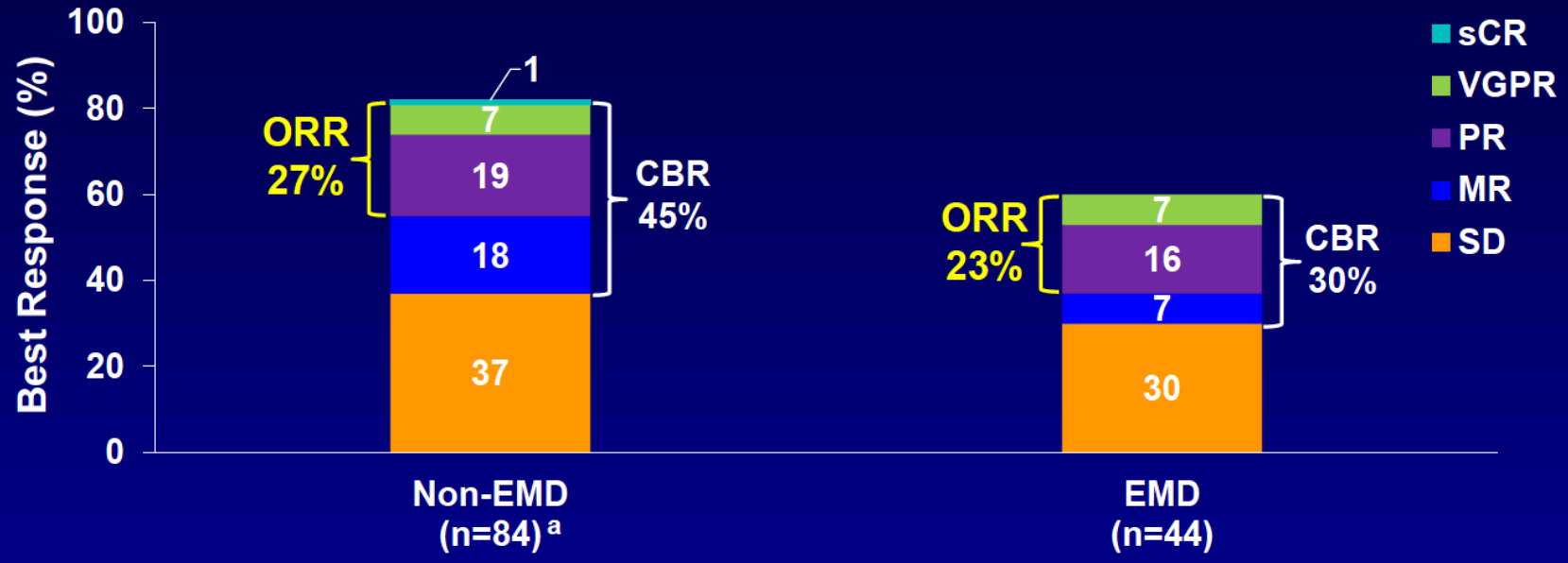
Bone-related or Soft Tissue EMD, n (%)	EMD Pts	CNS Involvement
Pts with EMD[a]	44 (100)	5 (11)
Soft tissue[b]	26 (59)	2 (5)
Bone-related[c]	18 (41)	3 (7)

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.

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

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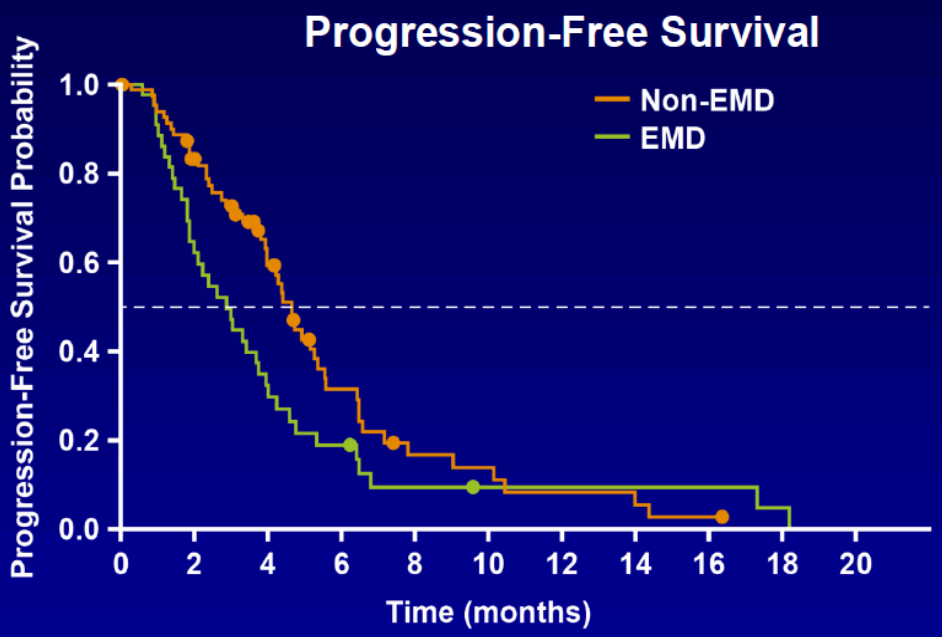
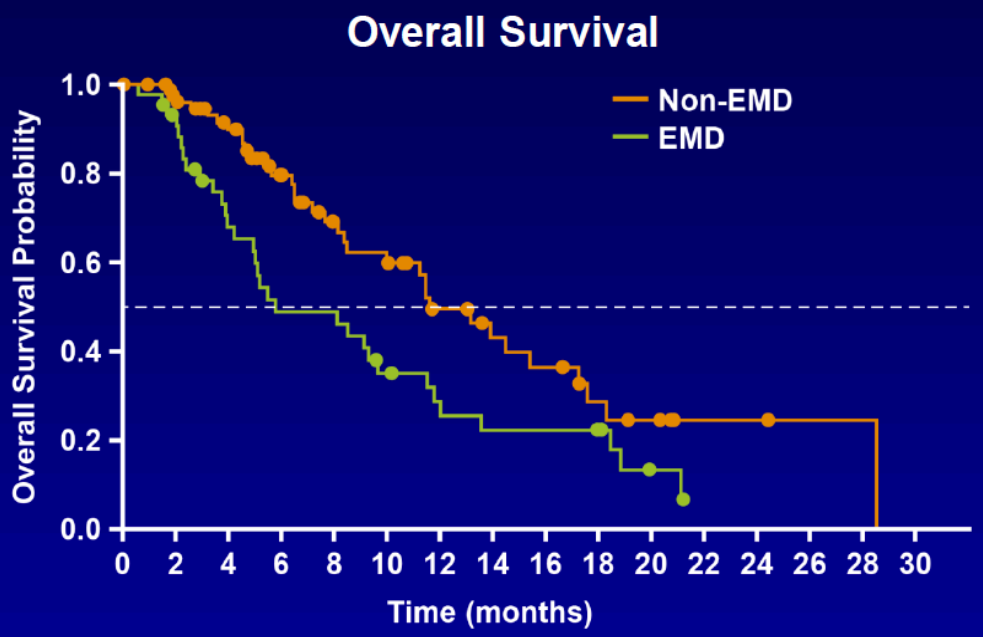


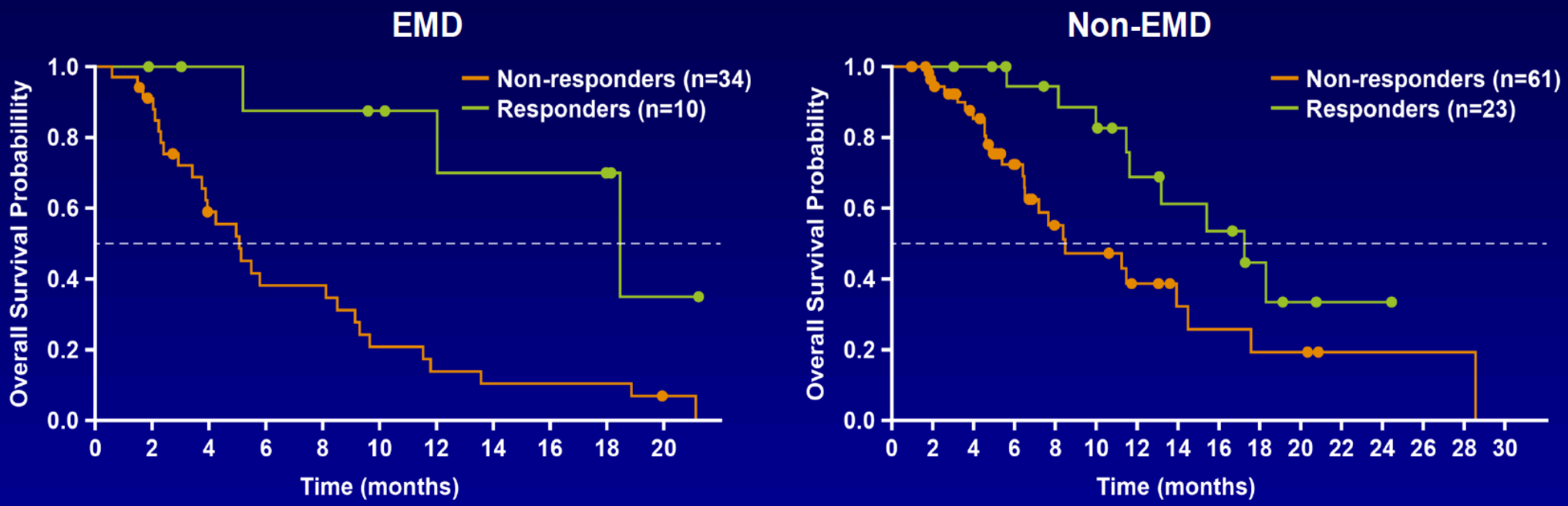


- Median PFS 2.9 mos (95% CI, 2.0-4.0) for pts with EMD vs. 4.6 mos (95% CI, 4.0-5.6) without EMD
- Median OS 5.8 mos (95% CI, 5.0-11.8) for pts with EMD vs. 11.6 mos (95% CI, 10.0-17.6) without EMD

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

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- 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.

TAKE HOME MESSAGES

- No prospective study of specific extramedullary disease treatment has been published
- Organ involvement has worst prognosis compared to paraskeletal involvement. Extramedullary relapse is terminal pathway in MM
- Since the disease is associated with high-risk features it should be treated as high-risk myeloma:
  - For patients eligible for high-dose therapy consider triplet induction followed with auto-SCT and the best tandem auto-SCT. Use triplet consolidation and maintenance
  - For transplant ineligible patients VMP and RVD followed by maintenance tx are currently the most effective standards of care for up-front therapy. However, the impact of these strategies in extramedullary myeloma is currently unknown.
  - At relapse there is no rationale to favor a specific therapeutic class: new drugs, CAR-T cells?
  - Always consider radiotherapy
  - For CNS extramedullary myeloma, consider the combination of systemic, intrathecal and radiotherapy

Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

Piero Galieni

Grazie per l'attenzione

Coordinatore Scientifico
Michele **CAVO**

Comitato Scientifico
Mario **BOCCADORO**
Michele **CAVO**
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