Highlights from
IMS 20th meeting 2023

Nuovi agenti:
MELFALAN FLUFENAMIDE

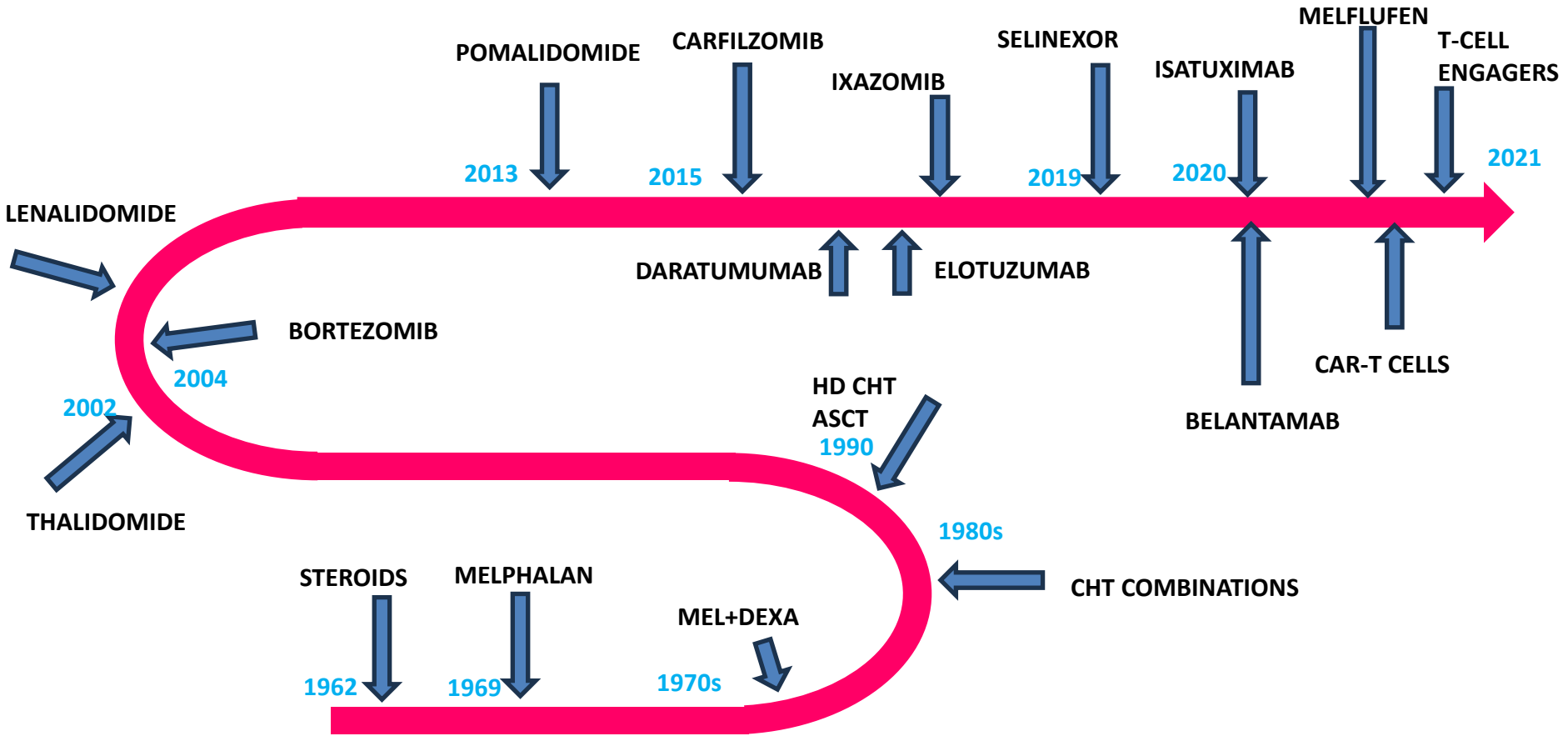
Elisabetta Antonioli
AOU Careggi, Firenze

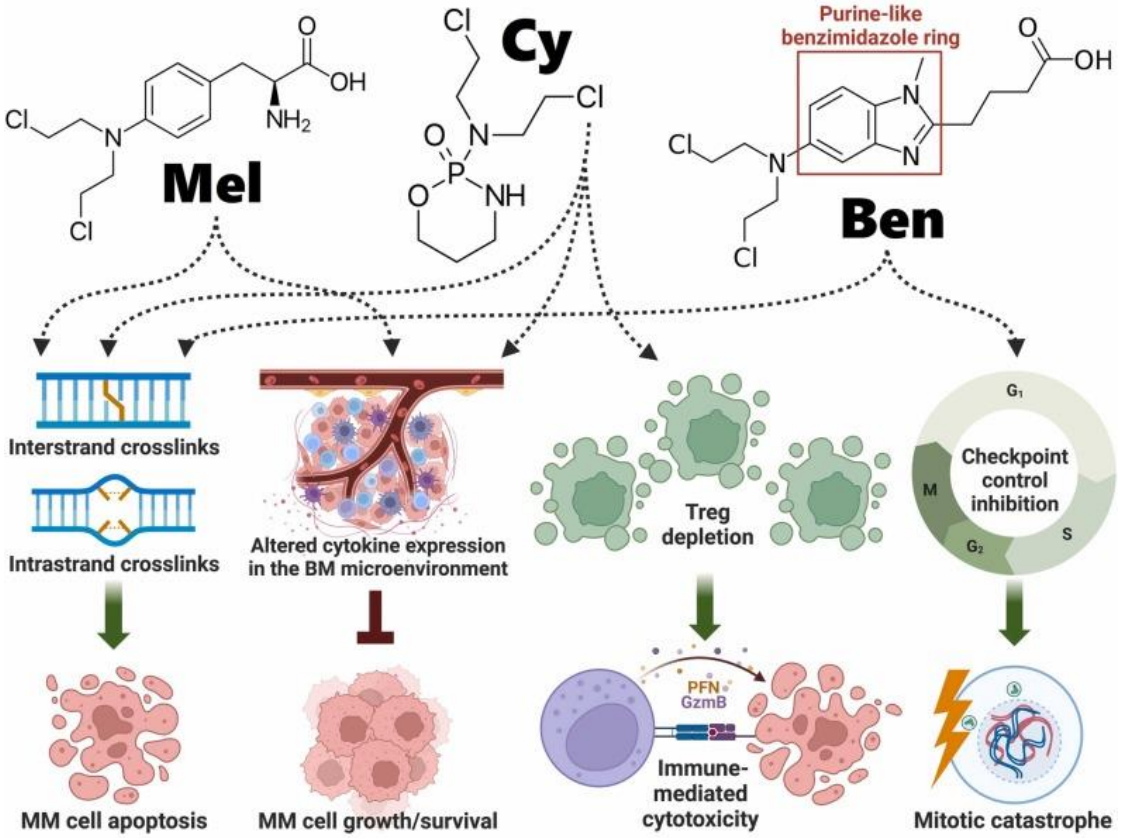
30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

DISCLOSURE:

Elisabetta Antonioli:

Adv Board for: Amgen, BMS, Jansenn, Pfizer, Takeda


MELFLUFEN
T-CELL ENGAGERS
POMALIDOMIDE
CARFILZOMIB
SELINEXOR
ISATUXIMAB
IXAZOMIB
2013
2015
2019
2020
2021
LENALIDOMIDE
DARATUMUMAB
ELOTUZUMAB
BORTEZOMIB
2004
CAR-T CELLS
2002
HD CHT
ASCT
1990
BELANTAMAB
THALIDOMIDE
1980s
CHT COMBINATIONS
STEROIDS
MELPHALAN
MEL+DEXA
1962
1969
1970s

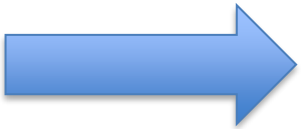


Costa B, Critical Reviews in Oncology / Hematology 2023

MELPHALAN FLUFENAMIDE (MELFLUFEN)

First-in-class peptide-drug conjugate (PDC) that targets aminopeptidases

Aminopeptidases are overexpressed in tumor cells. In multiple myeloma, increased aminopeptidase expression is associated with advanced disease.

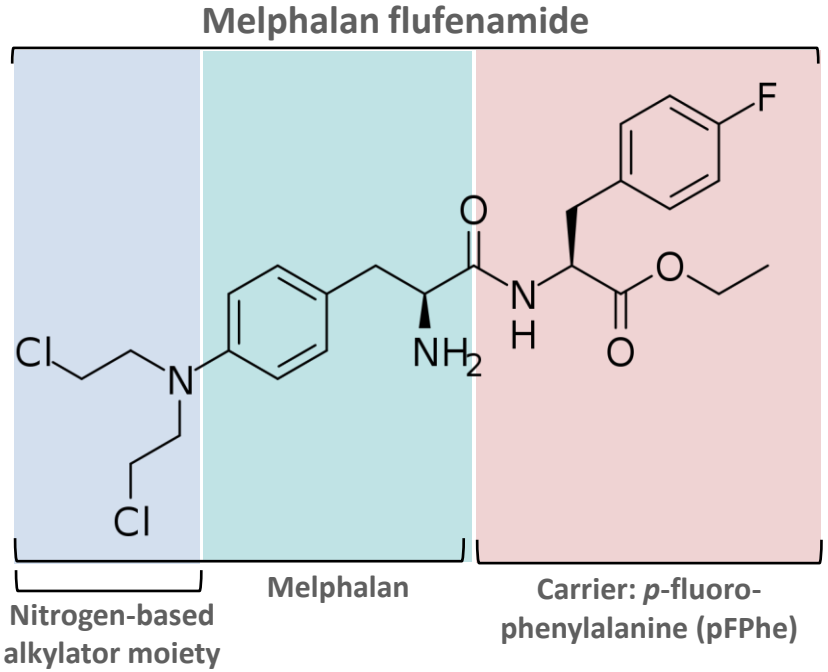


- ✓ Reduce drug resistance
- ✓ increase tumor specificity
- ✓ reduce toxicity

Pre-clinical studies demonstrated the ability to overcome resistance to melphalan and novel agents

Miettinen JJ, et al. Cancers (Basel). 2021;13(7):1527. Hitzerd SM, et al. Amino Acids. 2014;46(4):793-808. Sato T, et al. Sci Rep. 2019;9:18094. Wickström M, Oncotarget. 2017. Wickström M, Biochem Pharmacol. 2010. Ray A, Br J Haematol. 2016

MELPHALAN FLUFENAMIDE (MELFLUFEN)



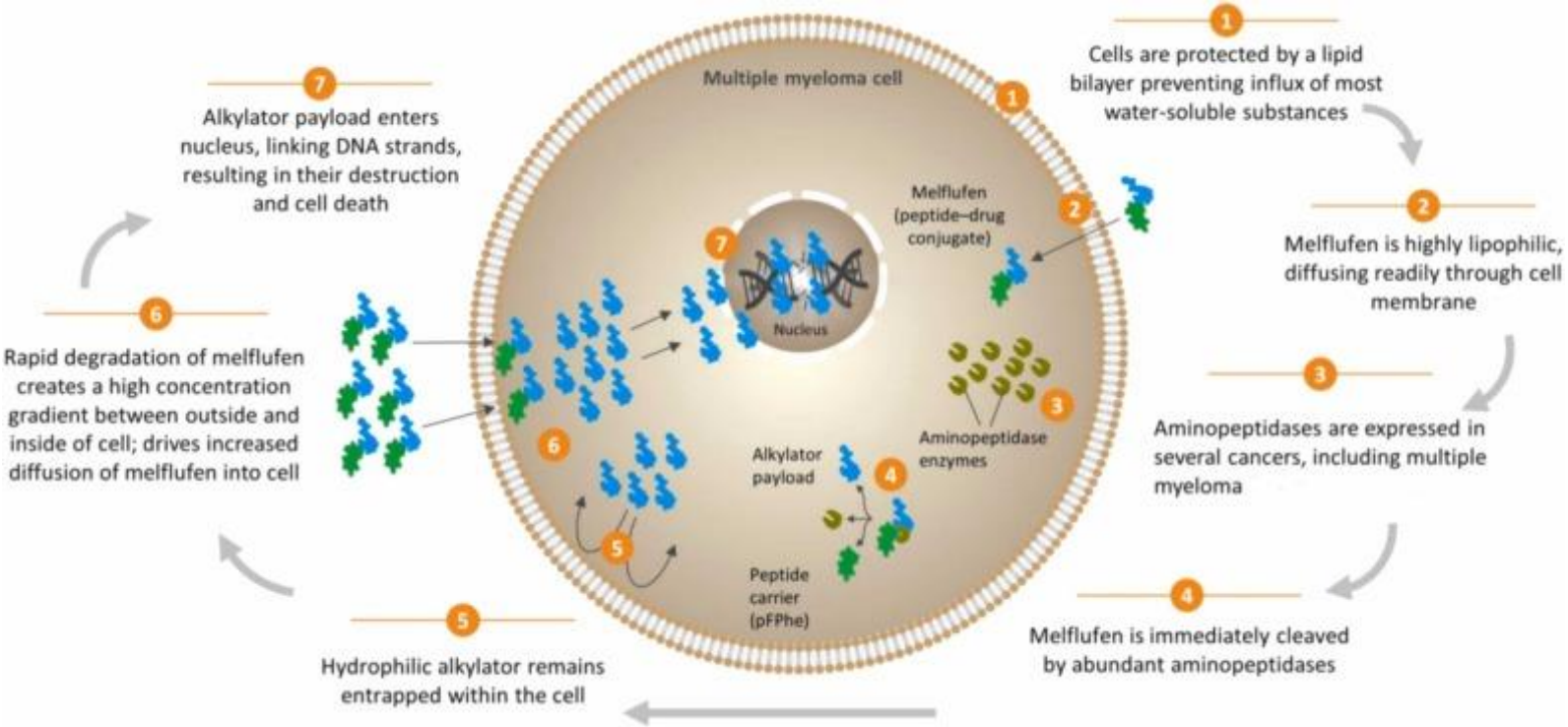
Peptide-conjugated structure of melphalan flufenamide

- Confers a high degree of lipophilicity
- Allows it to diffuse readily across the lipid bilayer membrane of the cell

Inside the cell

- Aminopeptidases and esterases mediate hydrolysis of the peptide bond and the ester bond, respectively
- Forms the hydrophilic alkylators melphalan and desethyl-melphalan flufenamide (Mel-pFPhe-OH)

Wickström M, et al. Oncotarget. 2017, National Center for Biotechnology Information. PubChem compound summary for CID 9935639, https://pubchem.ncbi.nlm.nih.gov/compound/Melphalan-flufenamide. Wickström M, et al. Biochem Pharmacol. 2010, Schepsky A, et al. AACR 2020. Poster 5205.



Wickström M, Oncotarget. 2017. Wickström M, Biochem Pharmacol. 2010. Ray A, Br J Haematol. 2016. Oriol A Exp Opin on Inv Drugs 2020

O-12-M1

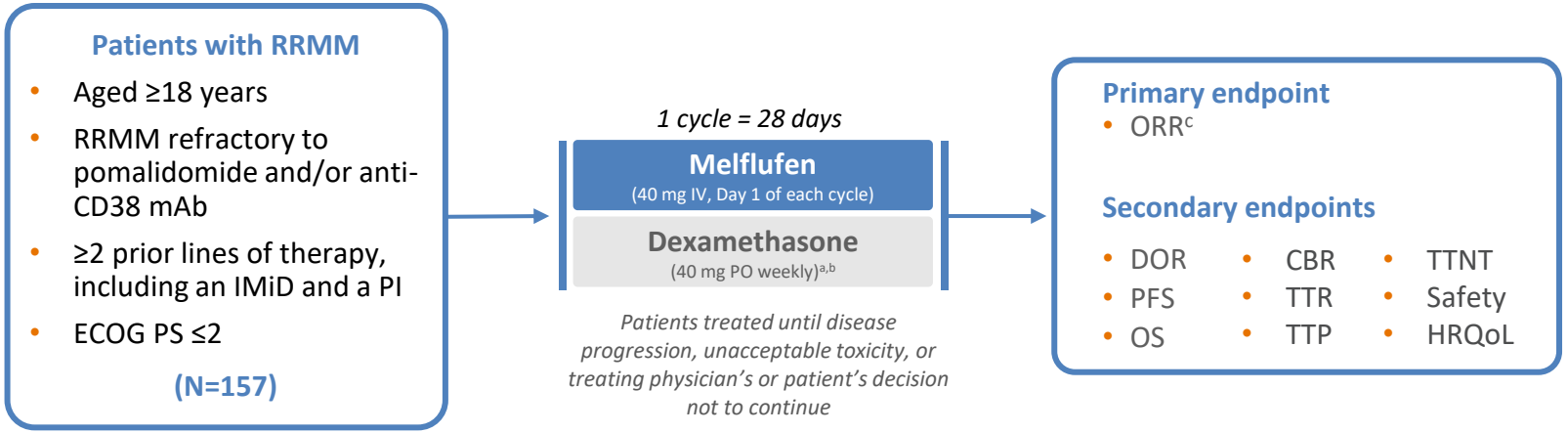
Open-label, multicentre, international, phase 1–2 study done in patients with relapsed and refractory multiple myeloma

- In phase 1 (23 pts) the established maximum tolerated dose was 40 mg of melflufen in combination with dexamethasone.
- In phase II (58 pts) dose-expansion portion of the study, the cycle length was increased from 21 to 28 days, providing additional time for recovery of the platelet and neutrophil counts

Richardson Lancet Oncol 2020

HORIZON (OP-106)

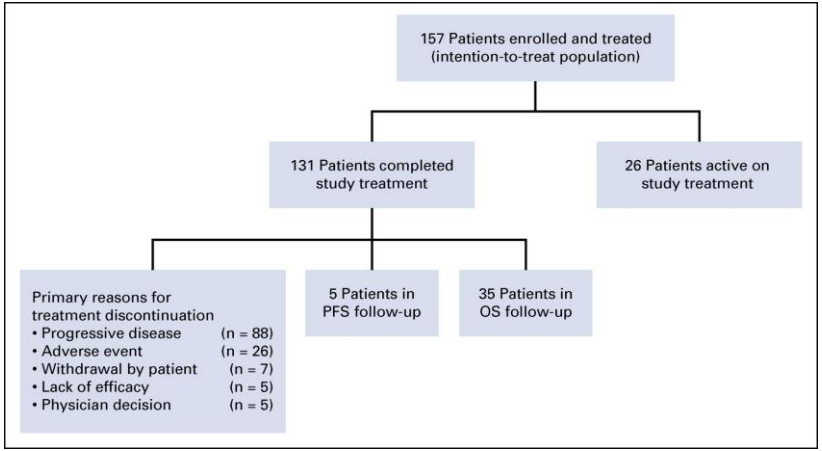
- single-arm, multicenter, phase II study
- melflufen plus dexamethasone in patients with RRMM refractory to pomalidomide and/or an anti-CD38 monoclonal antibody



Richardson JCO 2021

HORIZON (OP-106)

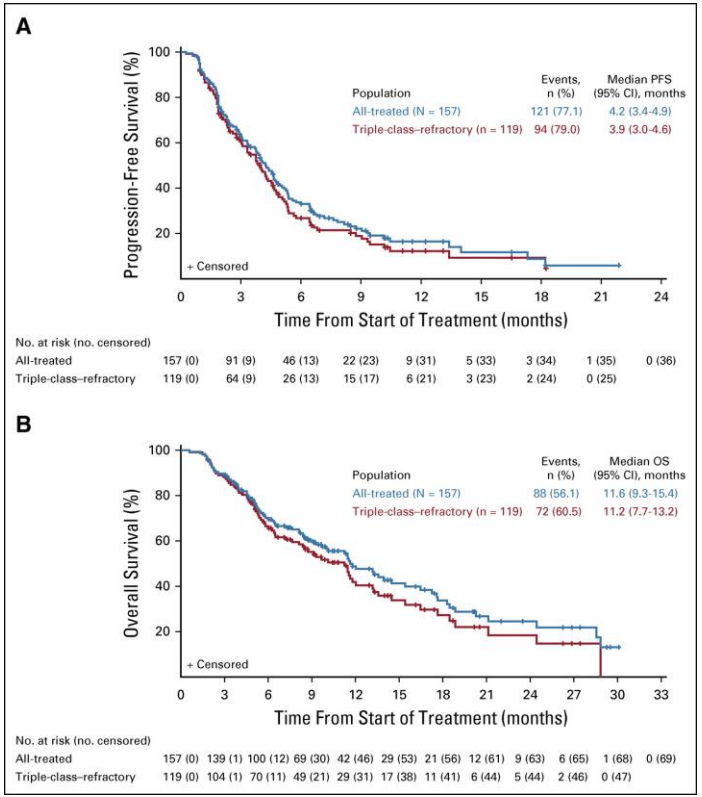
Characteristic	PTS
Median age	65 yrs (35-86)
Median previous LOT	5 (2-12)
Extramedullary disease	55 (35%)
HR Cytogenetics	59 (38%)
refractory to the last line	154 (98%)
triple-class–refractory disease	119 (76%)
refractory to prior alkylator therapy	92 (59%)



Response	PTS
ORR	46 (29%)
sCR-CR	1 (1%)
VGPR	17 (11%)
PR	28 (18%)
Median DOR (95% CI), months	**7.6** (3.0-12.3)

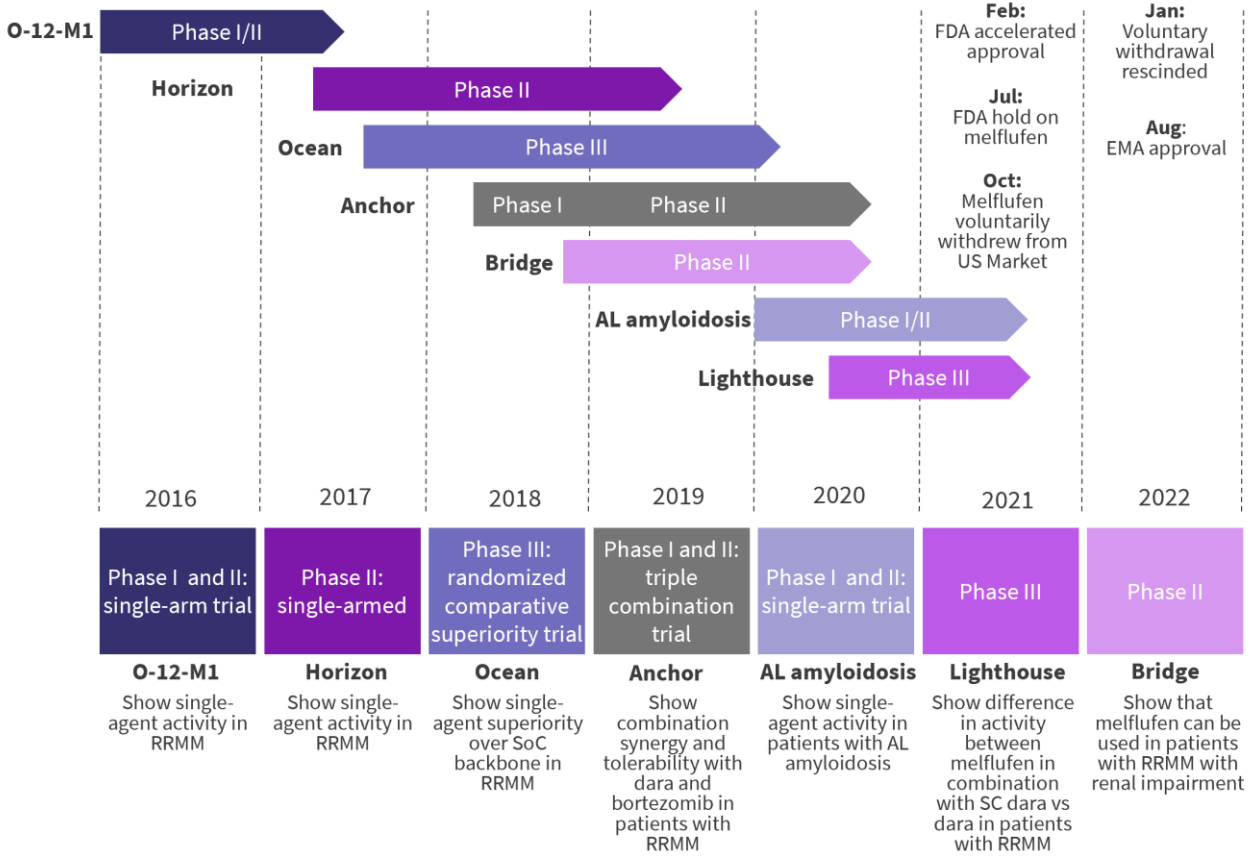
Richardson JCO 2021

HORIZON (OP-106)



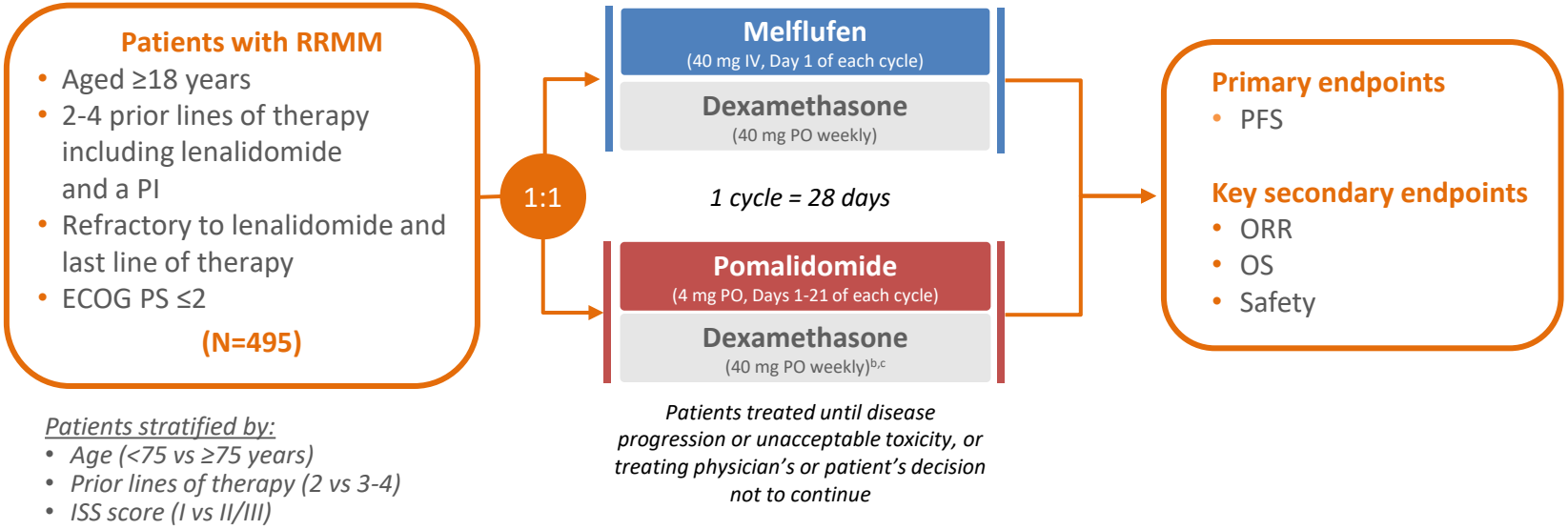
	Patients (N = 157)				
TEAE[a]	Any-Grade[b]	Grade 1	Grade 2	Grade 3	Grade 4
Any[c,d]	157 (100)	0	7 (4)	40 (25)	100 (64)
Hematologic					
Neutropenia[e]	129 (82)	1 (< 1)	4 (3)	50 (32)	74 (47)
Thrombocytopenia[e]	128 (82)	5 (3)	3 (2)	40 (25)	80 (51)
Anemia[e]	111 (71)	3 (2)	41 (26)	66 (42)	1 (< 1)
Nonhematologic					
Nausea	50 (32)	31 (20)	18 (11)	1 (< 1)	0
Fatigue	46 (29)	17 (11)	25 (16)	4 (3)	0
Asthenia	42 (27)	13 (8)	23 (15)	5 (3)	1 (< 1)
Diarrhea	42 (27)	24 (15)	18 (11)	0	0
Pyrexia	38 (24)	24 (15)	11 (7)	3 (2)	0
Cough	26 (17)	16 (10)	10 (6)	0	0
Upper respiratory tract infection	25 (16)	3 (2)	19 (12)	3 (2)	0
Constipation	23 (15)	18 (11)	4 (3)	1 (< 1)	0
Decreased appetite	22 (14)	10 (6)	11 (7)	1 (< 1)	0
Hypokalemia	22 (14)	14 (9)	6 (4)	2 (1)	0
Peripheral edema	22 (14)	15 (10)	5 (3)	2 (1)	0
Headache	21 (13)	13 (8)	8 (5)	0	0
Vomiting	21 (13)	12 (8)	9 (6)	0	0
Bone pain	20 (13)	9 (6)	8 (5)	3 (2)	0
Pain in extremity	20 (13)	7 (4)	10 (6)	3 (2)	0
Pneumonia	20 (13)[f]	0	3 (2)	14 (9)	2 (1)
Back pain	19 (12)	9 (6)	9 (6)	1 (< 1)	0
Insomnia	18 (11)	14 (9)	3 (2)	1 (< 1)	0
Dizziness	17 (11)	14 (9)	3 (2)	0	0
Dyspnea	17 (11)	9 (6)	6 (4)	2 (1)	0
Arthralgia	16 (10)	11 (7)	5 (3)	0	0
Exertional dyspnea	16 (10)	13 (8)	3 (2)	0	0
Hypocalcemia	16 (10)	9 (6)	6 (4)	1 (< 1)	0

Richardson JCO 2021


O-12-M1
Phase I/II
Horizon
Phase II
Ocean
Phase III
Anchor
Phase I
Phase II
Bridge
Phase II
AL amyloidosis
Phase I/II
Lighthouse
Phase III
Feb: FDA accelerated approval
Jul: FDA hold on melflufen
Oct: Melflufen voluntarily withdrew from US Market
Jan: Voluntary withdrawal rescinded
Aug: EMA approval
2016
2017
2018
2019
2020
2021
2022
Phase I and II: single-arm trial
Phase II: single-armed
Phase III: randomized comparative superiority trial
Phase I and II: triple combination trial
Phase I and II: single-arm trial
Phase III
Phase II
O-12-M1
Show single-agent activity in RRMM
Horizon
Show single-agent activity in RRMM
Ocean
Show single-agent superiority over SoC backbone in RRMM
Anchor
Show combination synergy and tolerability with dara and bortezomib in patients with RRMM
AL amyloidosis
Show single-agent activity in patients with AL amyloidosis
Lighthouse
Show difference in activity between melflufen in combination with SC dara vs dara in patients with RRMM
Bridge
Show that melflufen can be used in patients with RRMM with renal impairment

OCEAN (OP-103): STUDY DESIGN

A phase 3, randomized, open-label, global study



Patients stratified by:
- *Age (<75 vs ≥75 years)*
- *Prior lines of therapy (2 vs 3-4)*
- *ISS score (I vs II/III)*

Patients treated until disease progression or unacceptable toxicity, or treating physician's or patient's decision not to continue

Schjesvold FH, Lancet Hematol 2022

OCEAN (OP-103): PTS characteristics

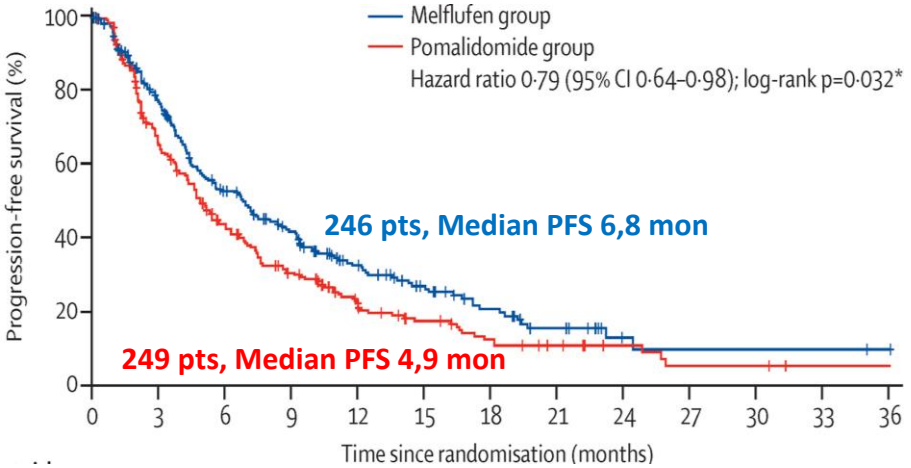
Characteristics	Melflufen + dexamethasone n=246	Pomalidomide + dexamethasone n=249
Age, median (IQR), years	68 (60-72)	68 (61-72)
<65 years, n (%)	96 (39)	85 (34)
65 to <75 years, n (%)	113 (46)	125 (50)
≥75 years, n (%)	37 (15)	39 (16)
Male sex, n (%)	139 (57)	140 (56)
ECOG PS (0 / 1 / 2), %	37 / 53 / 11	37 / 55 / 8
ISS score (I / II / III) at study entry, %	48 / 38 / 13	50 / 38 / 12
High-risk cytogenetics at study entry, n (%)[a]	83 (34)	86 (35)
EMD at study entry n (%)	31 (13)	31 (12)
Previous lines of therapy, median (IQR)	3 (2-3)	3 (2-3)
2 vs 3 or 4, %	46 / 54	45 / 55
Previous ASCT, n (%)	125 (51)	120 (48)
Refractory to an alkylator, n (%)	78 (32)	75 (30)
Refractory to a PI, n (%)	163 (66)	163 (65)
Refractory to an anti-CD38 mAb, n (%)	48 (20)	39 (16)
Double refractory disease, n (%)[b]	162 (66)	163 (65)
Triple-class refractory disease, n (%)[c]	39 (16%)	30 (12%)

Schjesvold FH, Lancet Hematol 2022

OCEAN (OP-103) STUDY

Median follow-up: 15.5 months (melflufen + dex) vs 16.3 months (pom + dex).

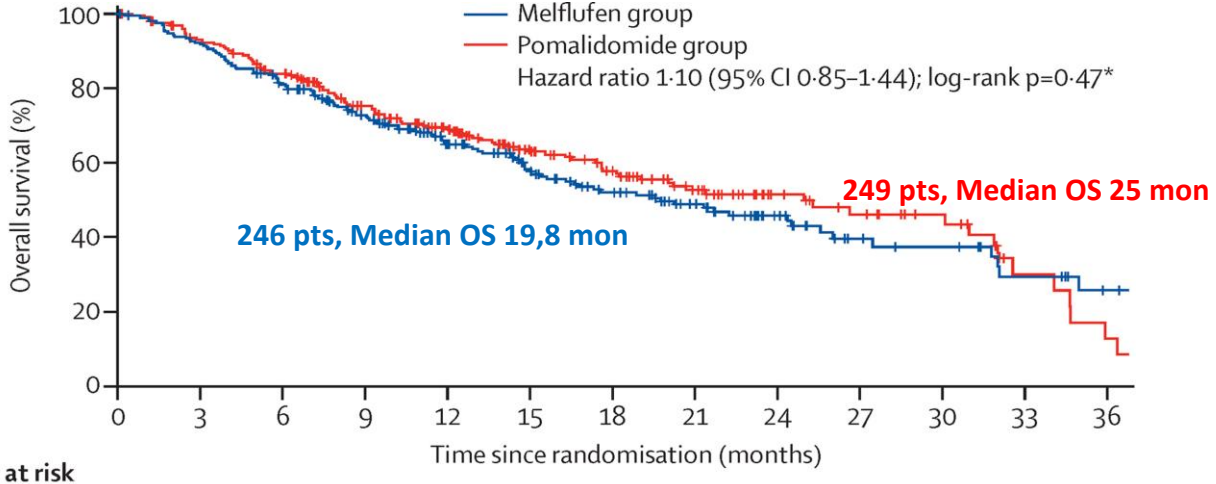
	Melflufen + Dex (N=246)	Pomalidomide + Dex (N=249)
ORR, % (95% CI)[a]	**33 (27-39)**	**27 (22-33)**
CBR, % (95% CI)[b]	50 (43-56)	41 (35-47)
Best confirmed response[c], n (%)		
Stringent complete response	0 (0)	0 (0)
Complete response	7 (3)	3 (1)
Very good partial response	23 (9)	18 (7)
Partial response	50 (20)	46 (18)
Minimal response	42 (17)	35 (14)
Stable disease	68 (28)	72 (29)
Progressive disease	36 (15)	60 (24)
Not evaluable	20 (8)	15 (6)
Time to best response, median (IQR), months	2.1 (1.1-3.7)	2.0 (1.1-2.9)



Schjesvold FH, Lancet Hematol 2022

OCEAN (OP-103) STUDY

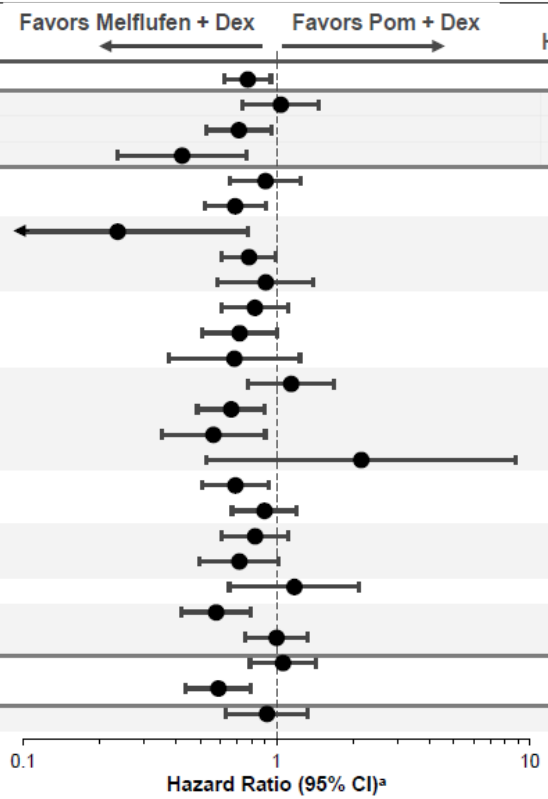
Median follow-up: 19,8 months (melflufen + dex) vs 18,6 months (pom + dex).



Number at risk (number censored)													
Melflufen group	246 (0)	223 (3)	192 (8)	160 (21)	119 (46)	91 (63)	70 (75)	53 (88)	34 (104)	20 (114)	17 (116)	11 (119)	6 (123)
Pomalidomide group	249 (0)	225 (7)	196 (14)	157 (33)	129 (50)	95 (74)	75 (86)	53 (102)	31 (123)	24 (127)	18 (133)	7 (139)	3 (139)

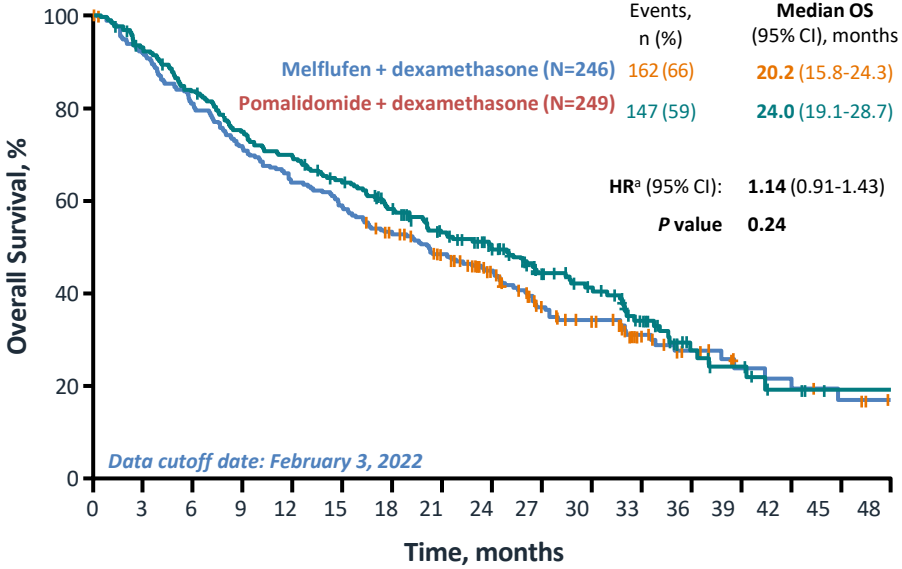
OCEAN (OP-103) STUDY

Subgroup		Melflufen+ Dex, n	Pom + Dex, n	Hazard Ratio (95% CI)[a]	*P* Value[b]
Overall		**246**	**249**	**0.77 (0.63-0.95)**	**0.014**
Age category, years	<65	96	85	1.04 (0.74-1.47)	0.83
	65-74	113	125	0.71 (0.53-0.96)	0.03
	≥75	37	39	0.43 (0.24-0.76)	<0.01
Sex	Female	107	109	0.90 (0.65-1.25)	0.55
	Male	139	140	0.69 (0.52-0.91)	<0.01
Region	USA	11	15	0.24 (0.07-0.77)	0.01
	Europe	180	176	0.78 (0.61-0.99)	0.04
	ROW	55	58	0.91 (0.59-1.40)	0.66
ISS score	I	112	119	0.82 (0.61-1.12)	0.21
	II	88	95	0.72 (0.51-1.01)	0.05
	III	28	29	0.68 (0.38-1.24)	0.21
Creatinine clearance (mL/min)	≥90	76	69	1.14 (0.77-1.69)	0.51
	≥60 to <90	119	112	0.66 (0.49-0.90)	<0.01
	≥45 to <60	44	58	0.56 (0.35-0.90)	0.02
	<45	6	10	2.16 (0.53-8.80)	0.27
Median body surface area	≤1.855 m²	116	128	0.69 (0.51-0.93)	0.02
	>1.855 m²	126	117	0.90 (0.67-1.20)	0.46
Cytogenetic risk group	Standard	128	130	0.82 (0.61-1.11)	0.21
	High[c]	83	86	0.71 (0.50-1.02)	0.06
EMD at baseline		30	26	1.18 (0.65-2.12)	0.59
Number of prior regimens	2	114	111	0.58 (0.42-0.79)	<0.001
	3-4	132	138	1.00 (0.76-1.32)	1.00
Previous ASCT	Yes	125	120	1.06 (0.79-1.43)	0.69
	No	121	129	0.59 (0.44-0.79)	<0.001
Refractory to prior alkylator		78	75	0.92 (0.63-1.33)	0.65



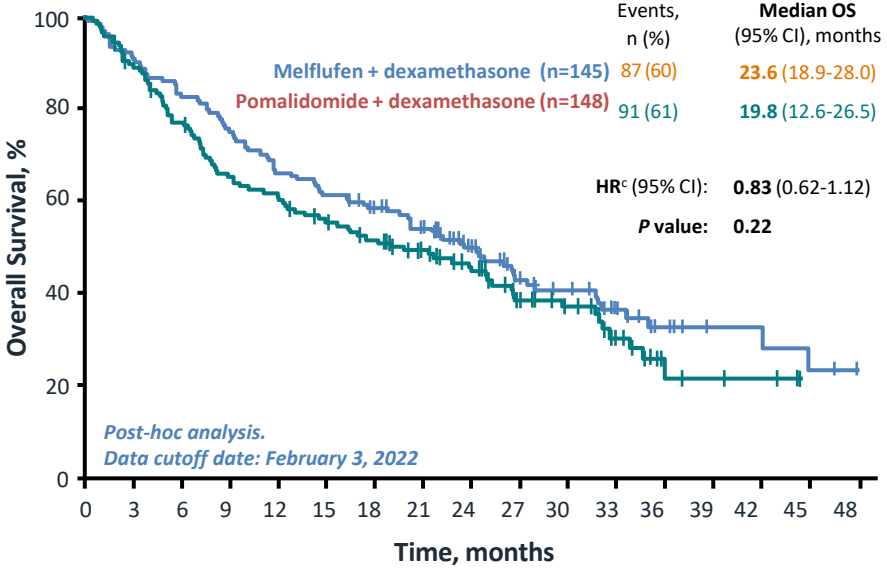
Schjesvold FH, IMS 2021

OS in the Intention-to-treat population



OS in the Target* population

*Patients with no ASCT or time to progression ≥36 months after an ASCT



ORR, % (95% CI)	Melflufen + dexamethasone	Pomalidomide + dexamethasone	P-value
Intention-to-treat population (N=246 vs. N=249)[2]	**33** (27-39)	**27** (22-33)	**0.16**
Target population (n=145 vs. n=148)[1,3]	**42** (34-51)	**26** (20-34)	**0.0046**[3]

Sonneveld P et al. Clin Lymphoma Myeloma Leuk. 2023

OCEAN (OP-103) STUDY

Treatment-Emergent Adverse Events of Special Interest, n (%)[a]	Melflufen + Dex (n=228)	Pom + Dex (n=240)
Thrombocytopenia	198 (87)	58 (24)
Grade 3/4	174 (76)	31 (13)
Haemorrhage	36 (16)	16 (7)
Grade 3/4 haemorrhage and concomitant grade 3/4 thrombocytopenia	2 (1)	0
Neutropenia	161 (71)	135 (55)
Grade 3/4	147 (64)	121 (49)
Infection	114 (50)	137 (56)
Grade 3/4	30 (13)	53 (22)
Grade 3/4 infection and concomitant grade 3/4 neutropenia	7 (3)	16 (7)
Infective pneumonia	38 (17)	60 (24)
Grade 3/4	12 (5)	30 (12)
Grade 3/4 infective pneumonia and concomitant grade 3/4 neutropenia	2 (1)	8 (3)
Febrile neutropenia	6 (3)	4 (2)
Anaemia	153 (67)	93 (38)
Second primary malignancy	3 (1)	6 (2)
Myelodysplastic syndromes or acute myeloid leukaemia	1 (<1)	1 (<1)

Schjesvold FH, IMS 2021

Safety overview – HORIZON and OCEAN

Nature of AE	Adverse event	HORIZON	OCEAN	
		Melflufen + Dexamethasone (N=157)	Melflufen + Dexamethasone (n=228)	Pomalidomide + Dexamethasone (n=246)
Patients with ≥ 1 Grade 3 or 4 AE		96%	90%[5]	74%[5]
Grade 3/4 Hematologic AEs	Thrombocytopenia[a]	80%[b]	76%[b]	13%[b]
	Grade 3/4 thrombocytopenia with grade 3/4 bleeding	3%	1%[c]	0%
	Neutropenia[a]	79%[d]	64%[e]	49%[e]
	Grade 3/4 neutropenia with grade 3/4 infection	12%	3%	7%
	Anaemia	47%[f]	43%[g]	18%[g]
Grade 3/4 non-hematologic AEs	Pneumonia (MedDRA PT)	11%[h]	4%[i]	9%[j]
	Infection	27%	13%	22%
Serious AEs	Any serious AE	56%	42%	46%
Fatal AEs	Any fatal AE	9%	12%	13%

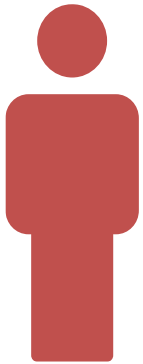
Data cutoff date: February 2, 2022

Data cutoff date: February 03, 2022

Richardson PG, et al. J Clin Oncol. 2021; Schjesvold FH et al. Lancet Haematol. 2022; Sonneveld P et al. Clin Lymphoma Myeloma Leuk 2023

Melflufen Received Full EMA Approval in August 2022

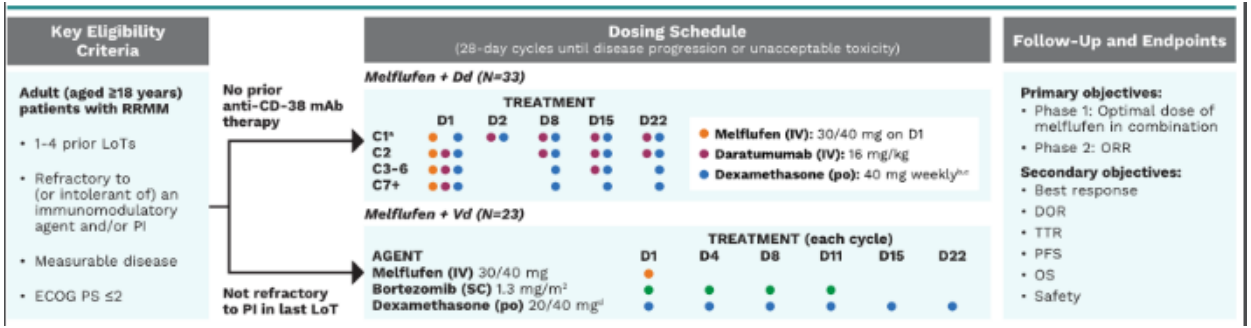
Melflufen in combination with dexamethasone is indicated for the treatment of:



Adult patients with multiple myeloma who have:

- Received ≥3 prior lines of therapies and whose disease is refractory to ≥1 each:
  - Proteasome inhibitor
  - Immunomodulatory agent
  - Anti-CD38 monoclonal antibody
- Demonstrated disease progression on or after the last therapy
- For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation

ANCHOR (OP-104): STUDY DESIGN



Safety and efficacy analyses determined melflufen 30 mg to be the recommended dose in triplet regimens.

Figure 2. Melflufen + Dd: Overall Response Rate and Progression-Free Survival

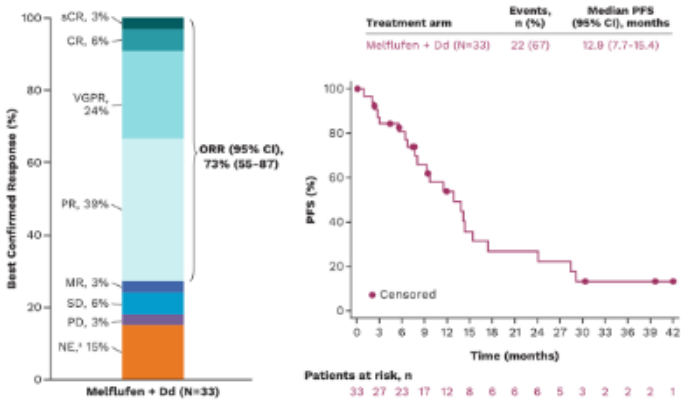
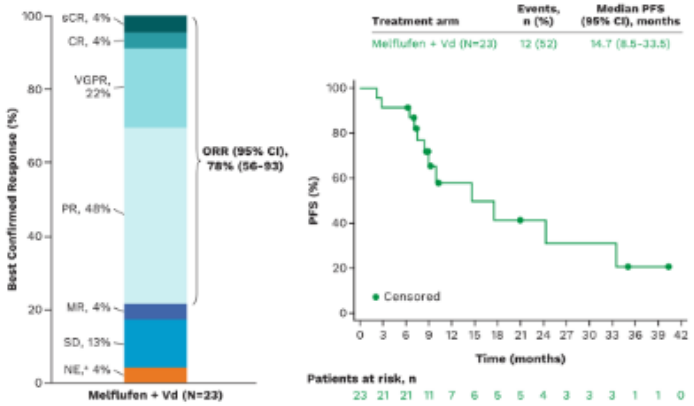
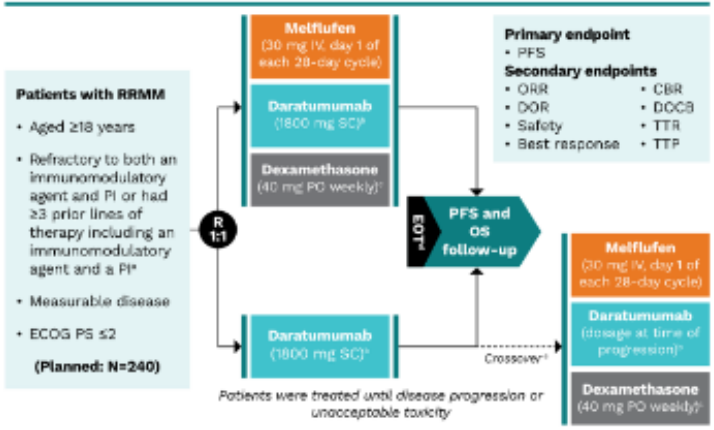


Figure 3. Melflufen + Vd: Overall Response Rate and Progression-Free Survival



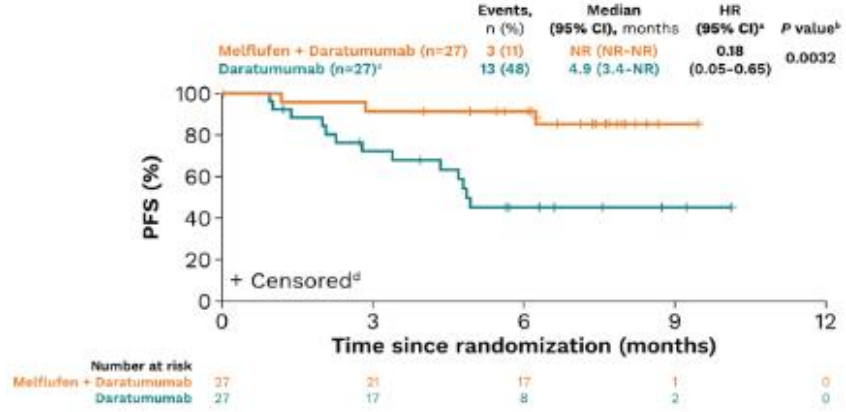
Ocio E, IMS 2023 P-302

LIGHTHOUSE (OP-108): STUDY DESIGN



Response Category	Melflufen + Daratumumab (n=27)	Daratumumab (n=27)
Best confirmed response, n (%)		
Complete response	1 (4)	0 (0)
Very good partial response	4 (15)	3 (11)
Partial response	11 (41)	5 (19)
Minimal response	3 (11)	5 (19)
Stable disease	3 (11)	5 (19)
Progressive disease	1 (4)	5 (19)
Not evaluable	4 (15)	4 (15)
ORR (95% CI), %	59 (39-78)	30 (14-50)
Unstratified *P* value	0.0300	

Melflufen + Dd showed superior PFS and ORR vs Dara, including in pts with no prior ASCT or with a TTP >36 mo after a prior ASCT, which resembles the population with confirmed benefit from OCEAN. The safety profile of melflufen + Dd was consistent with previous reports of melflufen



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MELFLUFEN KEY TAKE-AWAYS

Melflufen, in combination with dexamethasone, is indicated for the treatment of patients with TCR MM who have received ≥3 prior lines of therapy and who have disease that progressed on or after last therapy. For patients with prior ASCT, the TTP should be at least 3 years.

Melflufen enters the cell due to its lipophilicity. Melflufen is efficiently hydrolyzed by peptidases, and cytotoxic payload irreversibly damages tumor DNA and induces apoptosis.

Efficacy was demonstrated in **HORIZON,** and **confirmed** in **OCEAN**

PFS superiority over pomalidomide was shown in **OCEAN,** with a **trend towards a favorable OS** in the target population

Consistent safety profile in **HORIZON** and **OCEAN,** characterized primarily by hematologic adverse events that are clinically manageable and monitorable