PEPAXTO® (melphalan flufenamide)

September 22, 2022

Oncopeptides AB (publ)

Oncologic Drugs Advisory Committee

Introduction

Jakob Lindberg

Chief Executive Officer

Chief Scientific Officer

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Primary Endpoint of PFS Met – Complex Heterogeneous OS Result

- OCEAN met primary endpoint of superior PFS based on prespecified IRC evaluation using IMWG guidelines
- OS HR (95% CI) in ITT = 1.14 (0.91 – 1.43)
  - PEPAXTO heterogeneity by ASCT, merits limitations of use
  - Unexpected pomalidomide heterogeneity driven by patient age confounds OS result interpretation
- OCEAN fulfills accelerated approval obligation for patients with RRMM

ASCT = autologous stem cell transplant

OS update February 2022

Heterogeneity Confounds OS and Identifies a Group at Risk

PEPAXTO Heterogeneity
Prior ASCT

PEPAXTO + dex
n = 246

ASCT	Post-ASCT Progression ≤ 36 Months (n=101)	No ASCT or Post-ASCT Progression > 36 Months (n=145)
Median PFS (95% CI), months	**4.3** (3.7-5.1)	**9.3** (7.2-1.8)
Median OS* (95% CI), months	**15.7** (11.9-20.5)	**23.6** (18.9-28.0)

Pomalidomide Heterogeneity
Age (Details provided in BD)

Pomalidomide + dex
n = 249

Age	< 65 Years (n=85)	≥ 65 to < 75 Years (n=125)	≥ 75 Years (n=39)
Median PFS (95% CI), months	**4.9** (3.8-5.7)	**4.9** (3.8-6.9)	**4.9** (3.0-6.6)
Median OS* (95% CI), months	**31.7** (21.3-NE)	**20.9** (17.0-26.5)	**17.5** (7.2-32.1)

*OS update February 2022

Identification of Risk Using Prespecified Subgroups[1,2,3]

- Study needs to meet prespecified primary endpoint
- Prespecified subgroups should be analyzed since ITT may not adequately characterize treatment effects
  - To identify subgroup that may represent risk
  - Should be supported by biologic rationale, precedent and other supportive endpoints
- Prior ASCT (Yes / No) prespecified subgroup in OCEAN

1. ICH E9 guidance; 2. Amatya et al, Clin Cancer Res, 2021; 3. EMA/CHMP/539146, 2013

Biologic Rationale for Risk in Patients with Prior ASCT Treated with PEPAXTO

- Pre-ASCT conditioning therapy typically with high dose melphalan
- Tumors relapsing early after ASCT more resistant to further alkylator treatment
  - IMWG and ESMO guidelines define less successful ASCT as time-to-progression < 36 months after ASCT[1-2]
- Identified risk isolated, post-hoc, in patients with less successful ASCT, a patient population defined in ASCT guidelines

1. Dimopoulos et al, Ann Oncol, 2021; 2. Moreau et al, Lancet Oncol 2021.

Recommendation that PEPAXTO Label Include Limitations of Use

PEPAXTO is not recommended in patients who have progressed less than 3 years after an autologous stem cell transplant

OCEAN Data Support Positive PEPAXTO Benefit-Risk

FDA Issues	Key Considerations
PFS benefit	• **PEPAXTO met primary endpoint, with statistically significant superior PFS** • **IRC used IMWG guidelines for disease progression**

Overall survival	• **Prespecified subgroup analysis identified risk in patients with prior ASCT**
	  • **Biologically plausible risk**
	• **Removal of subgroup with risk* improves efficacy and safety**
	  • **PFS, OS, ORR, DOR, AEs**

Appropriate dose	• **PEPAXTO is an alkylating cytotoxic dosed to MTD** • **Improved tolerability and less dose modifications by removal of subgroup with risk***

*** Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)**

Agenda

Treatment Patterns and Unmet Need with TCR Multiple Myeloma	**Paul Richardson, MD** R.J. Corman Professor of Medicine Harvard Medical School Dana-Farber Cancer Institute
OCEAN Study Clinical Results	**Klaas Bakker, MD, PhD** Executive VP and Chief Medical Officer Oncopeptides AB
Clinical Perspective	**Yvonne Efebera, MD, MPH** Professor, Medical Director of Blood and Marrow Transplant and Cellular Therapy Ohio Health

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Treatment Patterns and Unmet Need in Patients with Triple-Class Refractory Multiple Myeloma

Paul G. Richardson, MD

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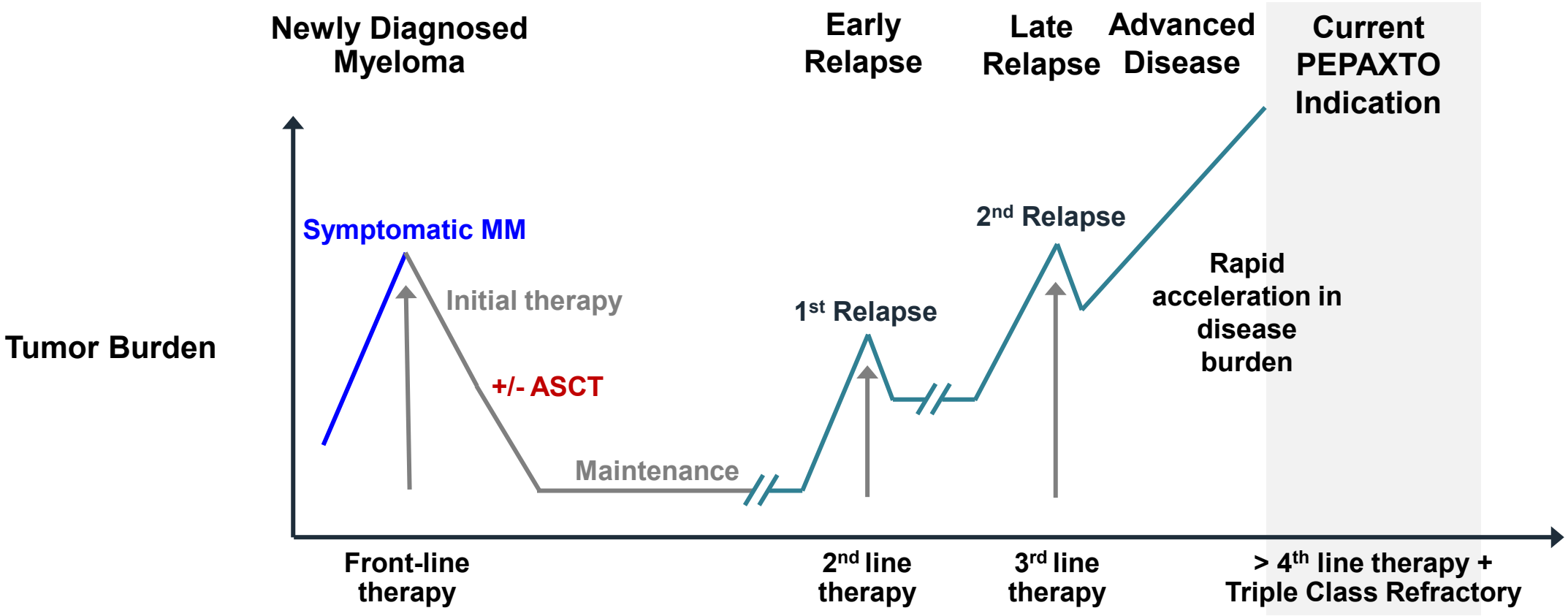
Treatment of MM is a Marathon Not a Sprint – Strategic and Practical Considerations Key



Treatment options rapidly diminish with each progression
Goal in advanced RRMM: stop further progression, maintain disease control, preserve QoL

Adapted from Borrello, Leuk Res, 2012; Richardson et al., Blood Cancer J, 2018

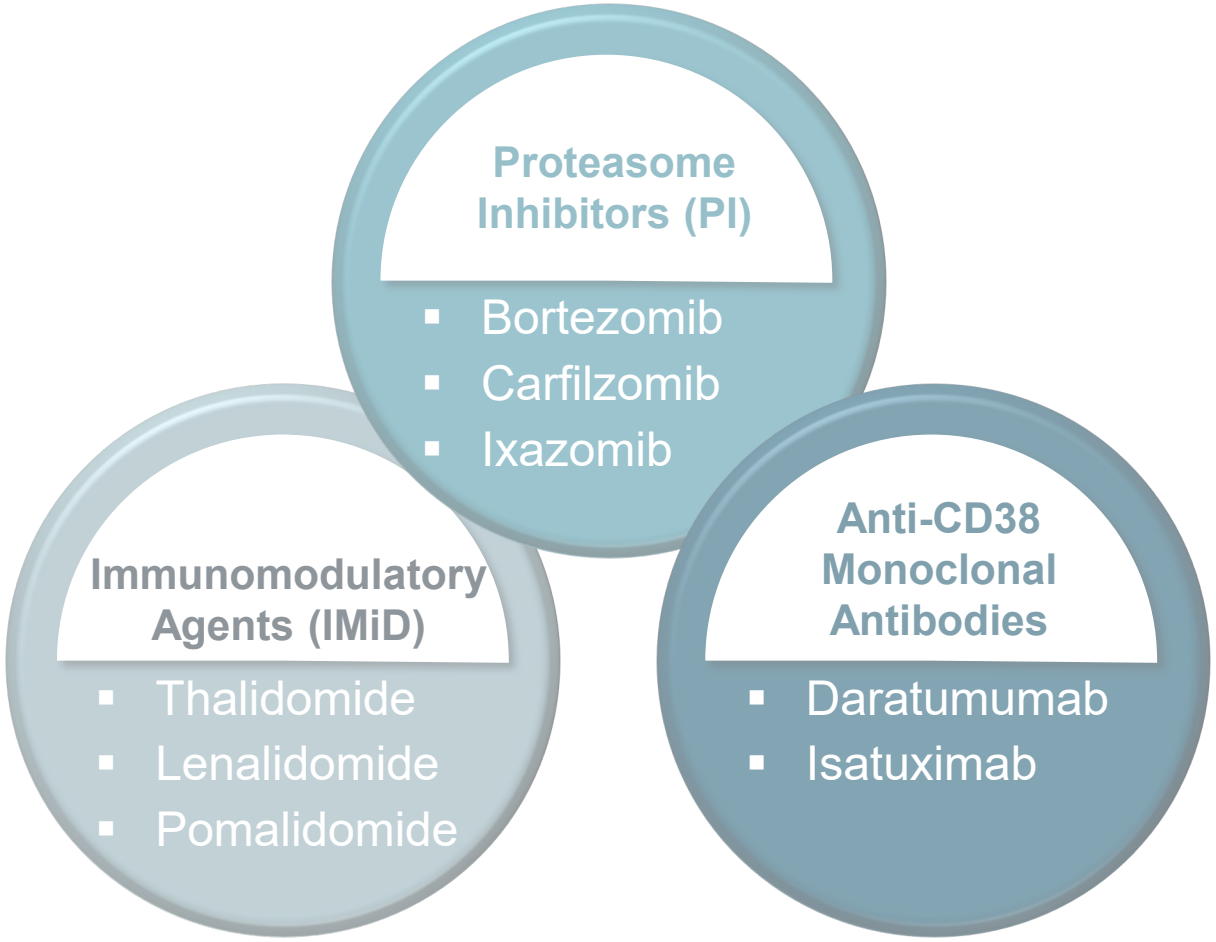
ASCT as a First Line Treatment in Younger, Fit and Eligible Patients[1]

- ASCT is an important standard of care but most MM patients do not undergo transplant
- Eligibility often based on age and frailty, cardiac and pulmonary status
  - Only about half of patients with MM are eligible for ASCT[2]
  - Only about 1/3 of those eligible actually undergo ASCT[2]
- PFS benefit with ASCT, but no OS benefit[3]
- Novel therapies are critical to improving long-term outcome[3-4]

1. Kumar et. al, Blood, 2019; 2. Kanas et. al, ASH 2020; 3. Richardson et. al, NEJM, 2022; 4. Moreau et. al, Lancet Oncol, 2021

Current Treatment Landscape in RRMM

3 Primary Classes of Drugs:
Triplet and Quadruplet Combinations Evolving as Standards of Care



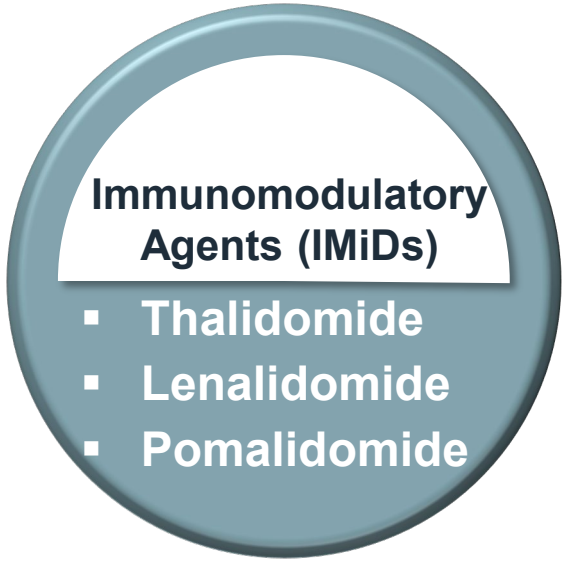
- Additional agents include
  - Corticosteroids
  - Cyclophosphamide
  - Bendamustine
  - Liposomal doxorubicin

1. Moreau et. al, Lancet 2021; 2. Richardson et. al, COMy World Congress 2022

Challenges with the Efficacy of Current Therapies in RRMM

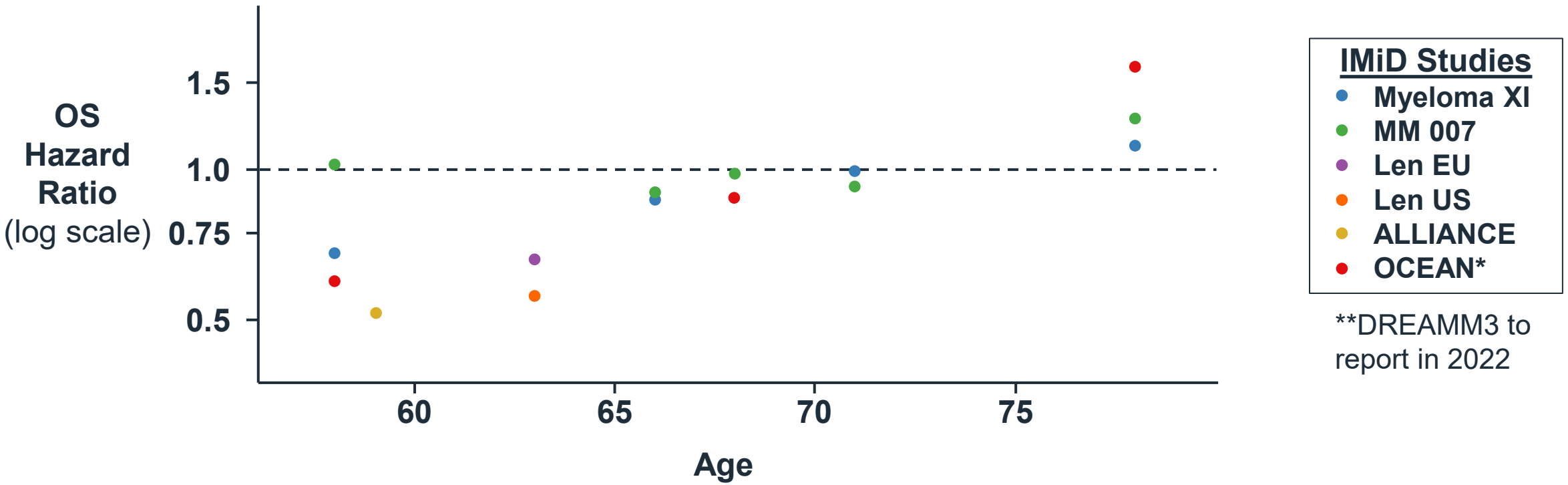
- OCEAN OS results call into question IMiD use and correlation between PFS and OS in elderly patients with RRMM

- IMiDs extensively used for patients with RRMM and are considered a back-bone of therapy
  - ~ 80% > 65 years with RRMM receive an IMiD[1]



1. Swedish Drug Register, 2021

Recent Analysis and a Forthcoming Publication Identifies Important Age Interaction for IMiDs[1]



Each included IMiD study reported OS by ITT and prespecified age subgroups, represented by common color for each study shown in legend

*OS update February 2022

1. Pawlyn et al. manuscript in preparation

**DREAMM 3 ~ Pom/dex vs. Bela/dex in RRMM

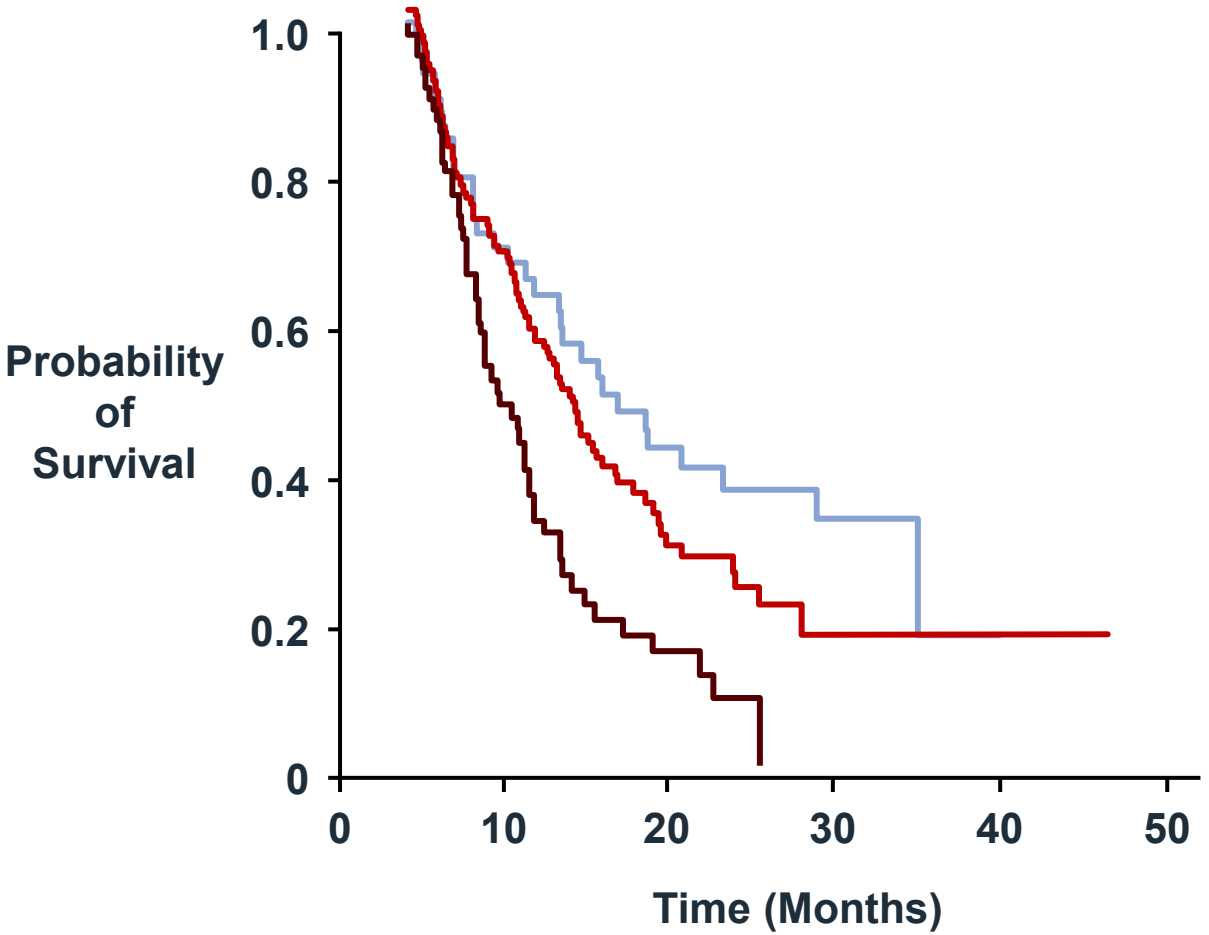
Other Recently Approved RRMM Therapies also have Limitations

- GI toxicity and asthenia with XPO1 inhibition (Selinexor)[1]
  - Upwards of 40% discontinuation rates
- Ocular toxicity with ADC's (Belantamab Mafadotin)[2]
  - Not well tolerated and logistically challenging to follow, particularly in elderly
- Lack of timely accessibility with cellular therapies (Ide-cel, Cilta-cel)[3]
  - ~ 6 month wait time, not practical for patients in need of immediate treatments
  - CRS, CNS toxicity and need for hospitalization in the COVID era an ongoing challenge[4,5]

XPO1 = exportin 1; ADCs = antibody drug conjugates; CRS = cytokine release syndrome

1. Selinexor USPI; 2. Belantamab Mafadotin USPI; 3. Kourelist et al., ASCO, 2022; 4. Madduri et al., ASH 2020 (177); 5. Munshi et al., ASCO 2020 (8503)

OS in Triple-Class Refractory Patients with RRMM; Multiple New Drugs Needed



	MAMMOTH Median OS Months (95% CI)[1]
Double refractory (N=57)	11.2 (5.4-17.1)
Triple- and quad-refractory (N=148)	9.2 (7.1-11.2)
Penta-refractory (N=70)	5.6 (3.5-7.8)

Majority Refractory Status	PEPAXTO Study	Median OS Months (95 % CI)
Double	O-12-M1[2] N = 45	20.7 (11.8-NR)
Double	OCEAN[3] N = 246	20.2* (15.8-24.3)
Penta	HORIZON[4,5] N = 97	9.1 (6.4-11.5)

1. Gandhi et al., Leukemia, 2019; 2. Richardson et al., Lancet Haematology, 2020; 3. Schjesvold et al., Lancet Haematology, 2022;
4. PEPAXTO USPI, 2021; 5. Inhouse ONCOPEPTIDES data, previously submitted to the FDA

*OS update February 2022

Special Considerations for Patients With RRMM

- Elderly and frail[1]
- New mode of action / class switch[1]
- Extra Medullary Disease (EMD), especially after CD38 mAb treatment failure[1]
- Frequency of visits and outpatient-based treatment (especially in COVID era)[2]
- Reduction of infectious risk[2]
- Convenience and off the shelf, with ready application in real world practice[3]

1. Moreau et. al, Lancet Oncology 2021; 2. Chari et. al, Blood 2020; 3. Richardson et. al, Blood Cancer 2018

Conclusion: Urgent Unmet Medical Need in Triple-Class Refractory RRMM

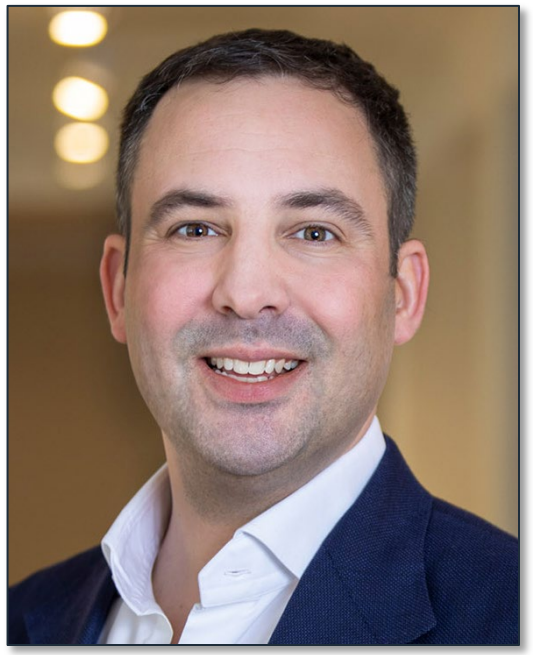
- Multiple myeloma remains an incurable disease
- More salvage therapy options urgently needed for triple-class refractory RRMM, and now after BCMA failure
- Importance of real-world, off the shelf agents with efficacy in out-patient setting, especially in COVID era
- Need clinically meaningful efficacy and a manageable safety profile, with minimal non-hematological side effects
- Importance of novel MoA and independence from immune exhaustion, as well as activity in EMD

OCEAN Study Clinical Results

Klaas Bakker, MD, PhD

Executive VP and Chief Medical Officer

Oncopeptides AB (publ)

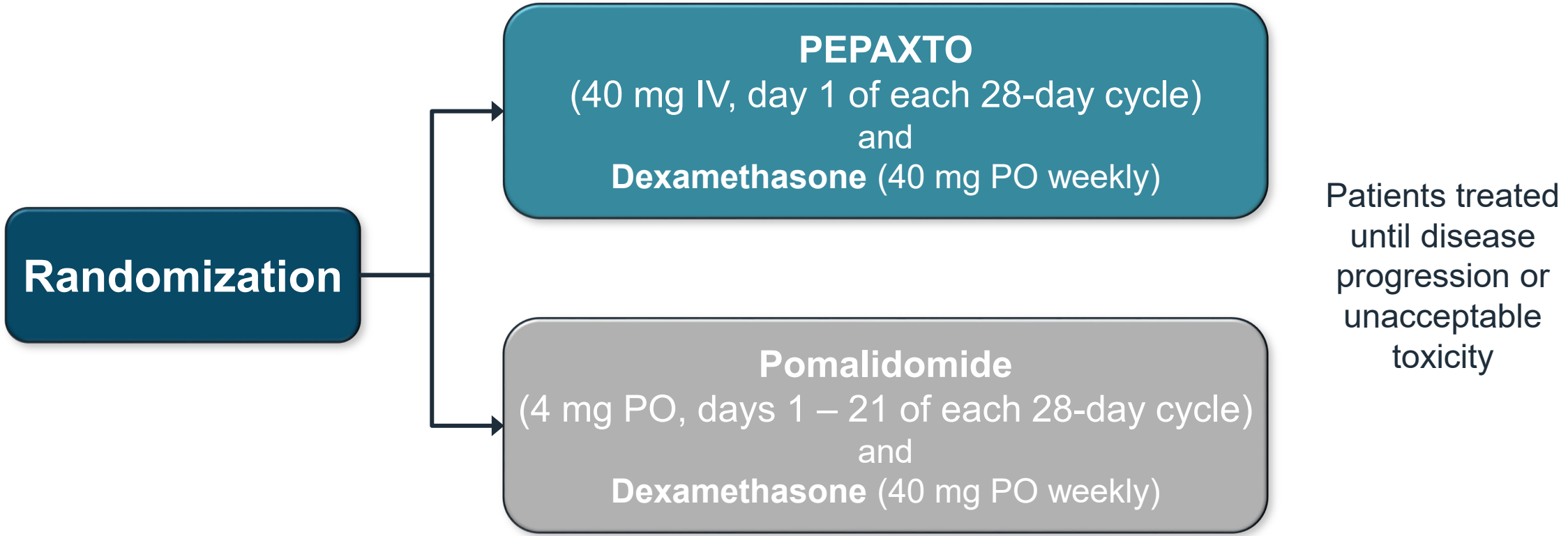


OCEAN Results Confirm PEPAXTO Benefit-Risk

- Active-control, head-to-head study design
- Efficacy results in ITT
- Results in prespecified subgroups
  - ASCT interaction identified for PEPAXTO
  - Advise against use in patients with post-ASCT progression within 36 months
  - Age interaction with IMiDs impacts OS interpretation*
- Safety from safety population and recommended population

* IMiD interaction addressed in BD

OCEAN: Randomized Active-Control Phase 3 Study Comparing PEPAXTO to Pomalidomide



OCEAN: Inclusion Criteria

- ≥ 18 years old
- 2 – 4 prior lines of therapy
- Refractory to lenalidomide and last line of therapy
- ECOG PS ≤ 2

- HORIZON enrolled patients
  - Average of 5 lines prior treatment
  - Mostly triple-class refractory

OCEAN: Efficacy Endpoints

- Primary endpoint (IRC assessed)
  - Progression free survival (PFS)
- Key secondary endpoints
  - Overall response rate (ORR)
  - Overall survival (OS)

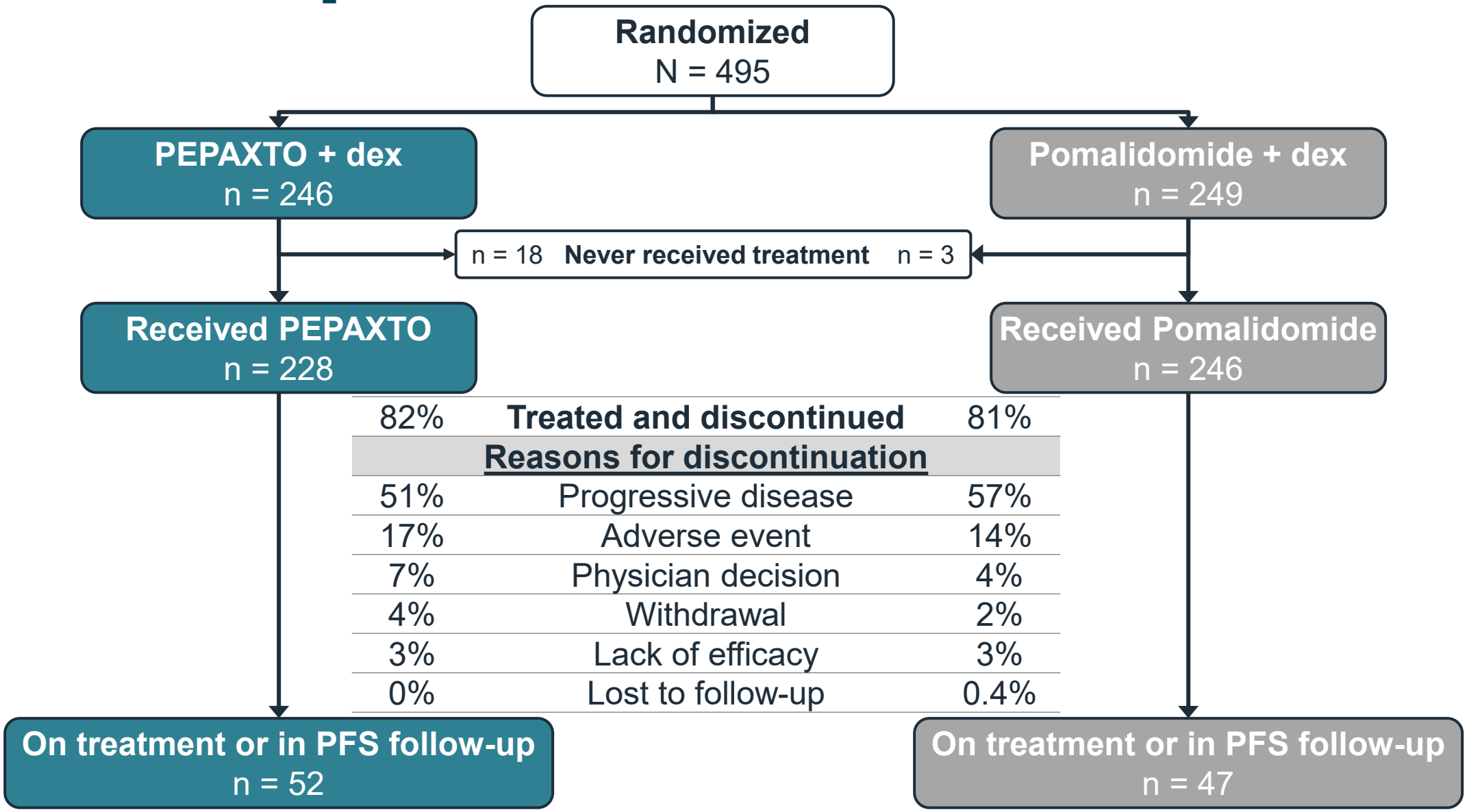
OCEAN: Statistical Analysis Plan

- Prespecified difference for superiority median PFS: 1.54 mos
  - Assumption: pomalidomide 3.6 and PEPAXTO 5.14 mos
- Prespecified censoring rules
  - Confirmed PD defined as two consecutive PD assessments unless
    - When progression of EMD confirmed PD
    - PD was the last assessment

OCEAN: Balanced Baseline Demographics and Characteristics

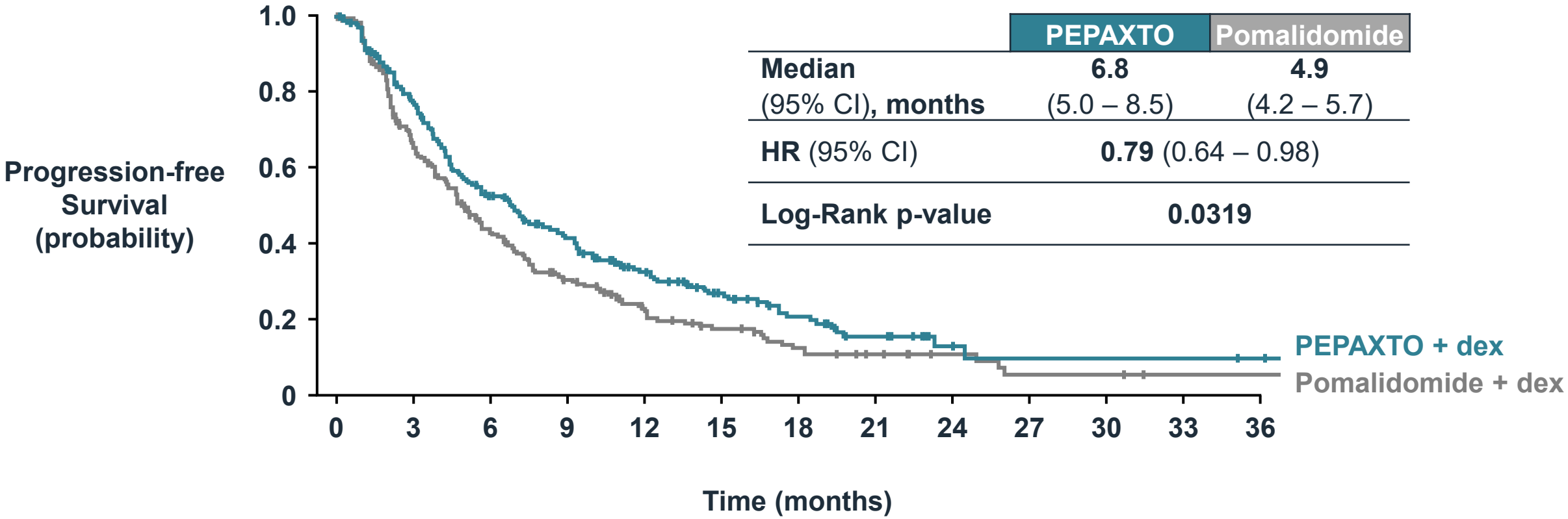
	PEPAXTO + dex (N = 246)	Pomalidomide + dex (N = 249)
Age, median (range), years	68 (41 – 91)	68 (39 – 87)
< 65	39%	34%
65 to < 75	46%	50%
≥ 75	15%	16%
Male	57%	56%
ISS stage at study entry		
I	48%	50%
II	38%	38%
III	13%	12%
Number of prior regimens		
2	46%	45%
3 – 4	54%	55%
Creatinine clearance		
< 45	2%	4%
45 – < 60	18%	23%
60 – < 90	48%	45%
≥ 90	31%	28%
EMD at study entry	13%	12%
≥ 1 ASCT	51%	48%

OCEAN: Disposition



OCEAN ITT Efficacy Results

OCEAN Study Met Primary Endpoint of PFS by IRC Per Statistical Analysis Plan



	PEPAXTO	Pomalidomide
Median (95% CI), **months**	**6.8** (5.0 – 8.5)	**4.9** (4.2 – 5.7)
HR (95% CI)	**0.79** (0.64 – 0.98)	
Log-Rank p-value	**0.0319**	

Number at Risk

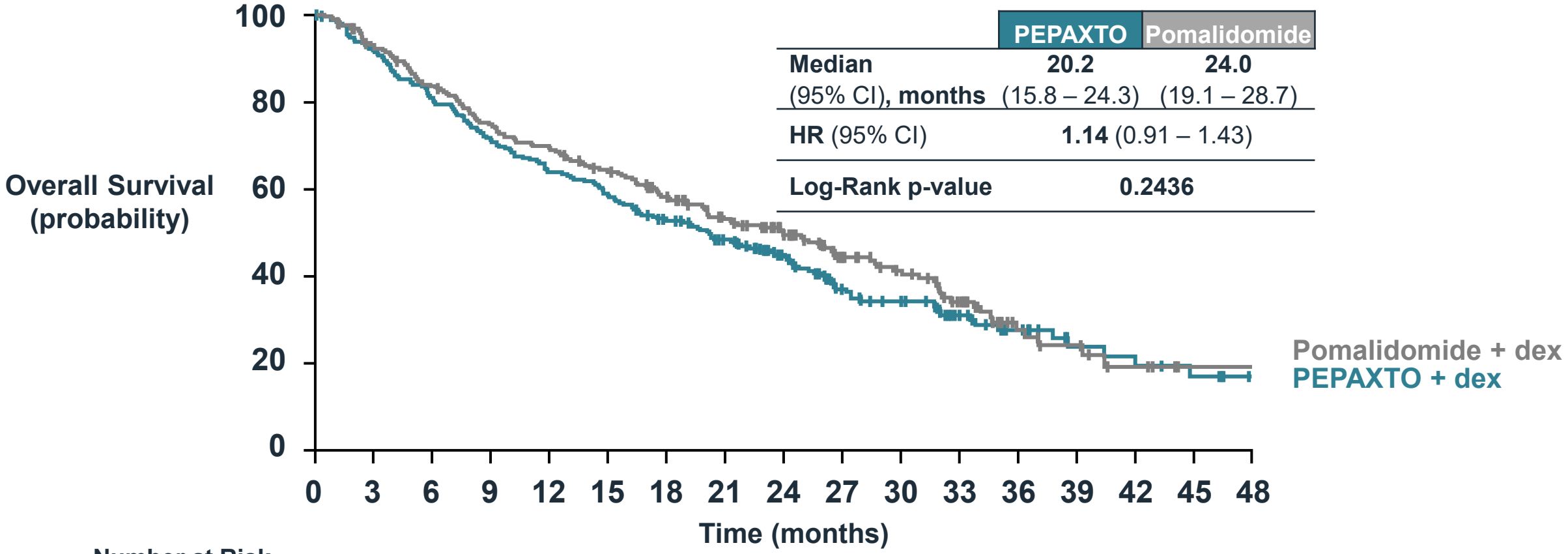
PEPAXTO	246	168	109	80	50	34	22	13	5	3	3	3	2
Pomalidomide	249	150	90	58	37	23	15	10	6	3	3	1	1

OCEAN: ORR, CBR, and DOR

	PEPAXTO + dex (N = 246)	Pomalidomide + dex (N = 249)
Overall response rate (95% CI)	**33%** (27 – 39)	**27%** (22 – 33)
Clinical benefit rate (95% CI)	**50%** (43 – 56)	**41%** (35 – 47)
Median DOR (95% CI), months	**11.2** (8.5 – 17.5)	**11.1** (7.6 – 15.4)

CBR: sCR+CR+VGPR+PR+MR

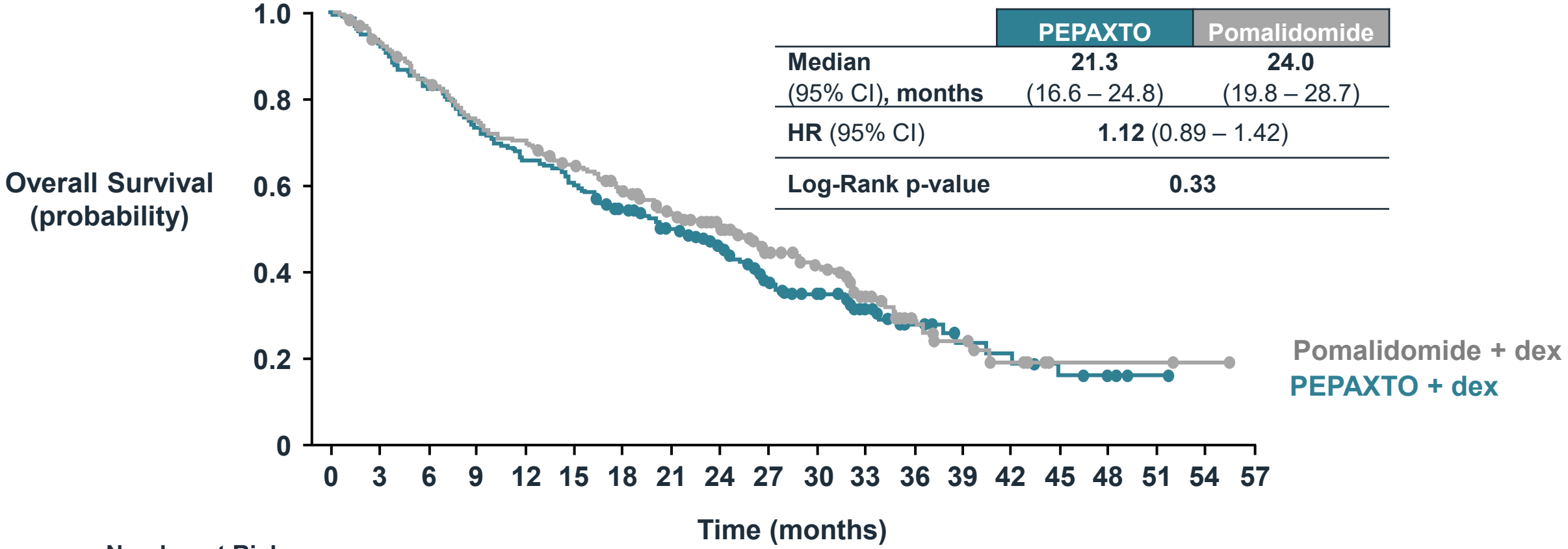
OCEAN: OS (ITT Population Through Feb 3, 2022)



Number at Risk

PEPAXTO	246	223	197	174	155	143	124	107	85	57	46	32	19	11	10	7	3
Pomalidomide	249	225	201	179	167	151	131	109	89	63	50	34	17	12	6	2	2

OCEAN: OS in Treated Population (Safety Population[1] Through Feb 3, 2022)



	PEPAXTO	Pomalidomide
Median (95% CI), **months**	**21.3** (16.6 – 24.8)	**24.0** (19.8 – 28.7)
HR (95% CI)	**1.12** (0.89 – 1.42)	
Log-Rank p-value	**0.33**	

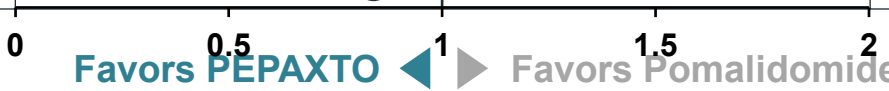
Number at Risk

PEPAXTO	228	213	189	169	150	139	120	105	83	55	44	30	17	10	9	6	3	1	0	0
Pomalidomide	246	223	200	178	167	151	131	109	89	63	50	34	17	12	6	2	2	2	1	0

1. Omits patients randomized but never treated (18 for PEPAXTO and 3 for pomalidomide)

OCEAN Prespecified Subgroups: OS

	PEPAXTO	Pomalidomide	Hazard Ratio* (95% CI)
OVERALL	162 / 246	147 / 249	**1.14** (0.91 – 1.42)
Age			
< 65	63 / 96	40 / 85	**1.68** (1.13 – 2.49)
65 – 74	79 / 113	82 / 125	**1.03** (0.76 – 1.41)
≥ 75	20 / 37	25 / 39	**0.62** (0.35 – 1.13)
Sex			
Male	91 / 139	86 / 140	**1.00** (0.74 – 1.34)
Female	71 / 107	61 / 109	**1.34** (0.95 – 1.89)
Region			
USA	4 / 11	5 / 15	**1.13** (0.30 – 4.22)
Europe	130 / 180	110 / 176	**1.20** (0.93 – 1.55)
ROW	28 / 55	32 / 58	**0.88** (0.53 – 1.46)
Prior Lines			
2	77 / 114	70 / 111	**1.00** (0.73 – 1.39)
3 – 4	85 / 132	77 / 138	**1.26** (0.93 – 1.72)
Creatinine clearance			
< 60	33 / 50	46 / 68	**0.92** (0.59 – 1.43)
60 – 90	76 / 119	66 / 112	**1.04** (0.75 – 1.45)
≥ 90	52 / 76	35 / 69	**1.65** (1.07 – 2.53)
Autologous stem cell transplant			
Yes	87 / 125	66 / 120	**1.53** (1.11 – 2.11)
No	75 / 121	81 / 129	**0.84** (0.61 – 1.15)



*Unstratified

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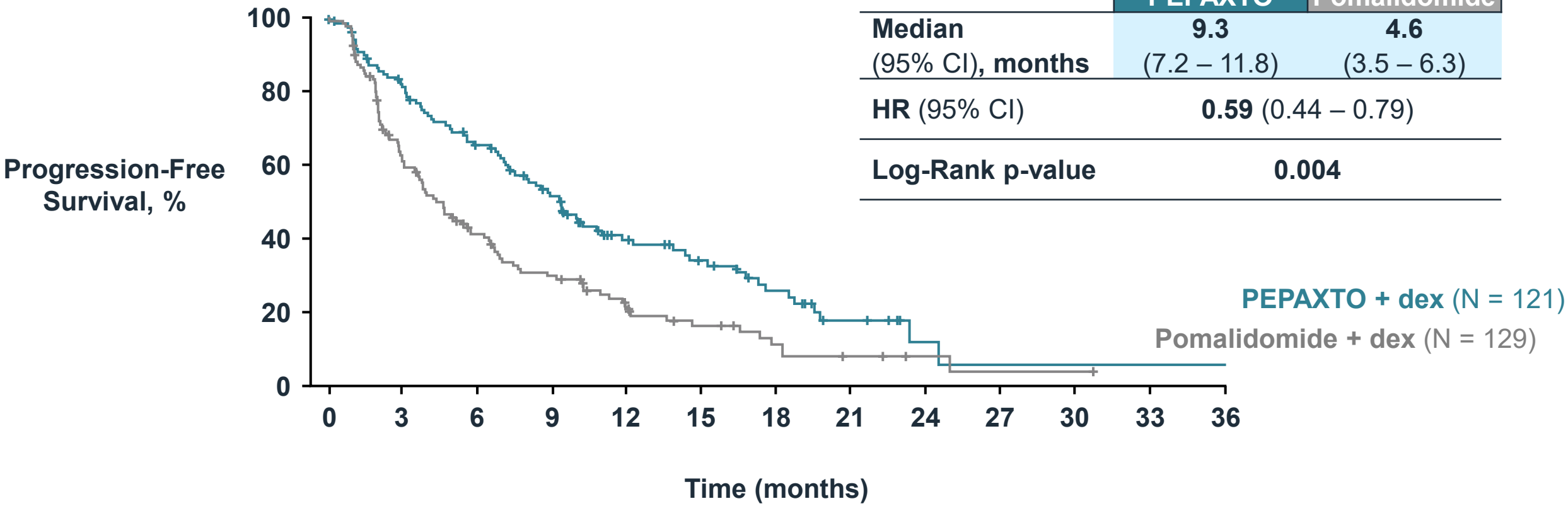
OCEAN Efficacy Results in Prespecified Subgroup of Prior ASCT

OCEAN: PFS in Patients with No ASCT

	PEPAXTO	Pomalidomide
Median (95% CI), **months**	**9.3** (7.2 – 11.8)	**4.6** (3.5 – 6.3)
HR (95% CI)	**0.59** (0.44 – 0.79)	
Log-Rank p-value	**0.004**	



Number at Risk													
PEPAXTO	121	94	73	54	31	23	15	7	2	1	1	1	1
Pomalidomide	129	73	45	32	19	12	7	4	2	1	1	0	0

OCEAN: ORR, CBR, and DOR in Patients with No ASCT

	PEPAXTO + dex (N = 121)	Pomalidomide + dex (N = 129)
Overall response rate (95% CI)	**42%** (33 – 51)	**27%** (20 – 36)
Clinical benefit rate (95% CI)	**60%** (51 – 69)	**41%** (33 – 50)
Median DOR (95% CI), months	**13.4** (8.5 – 17.5)	**11.1** (7.4 – 16.3)

CBR: sCR+CR+VGPR+PR+MR

OCEAN: OS by ASCT Status

	N for PEPAXTO + dex / Pomalidomide + dex	Median OS, months		HR (95% CI)
		PEPAXTO + dex	Pomalidomide + dex	
No ASCT	**121 / 129**	**22.2**	**17.5**	**0.84** (0.61 – 1.15)
ASCT	**125 / 120**	**16.7**	**28.7**	**1.53** (1.11 – 2.11)

OCEAN Efficacy Results Based on Time to Progression Post ASCT

No ASCT or Post-ASCT Progression > 36 Months* [Supported by Biology and Guidelines]

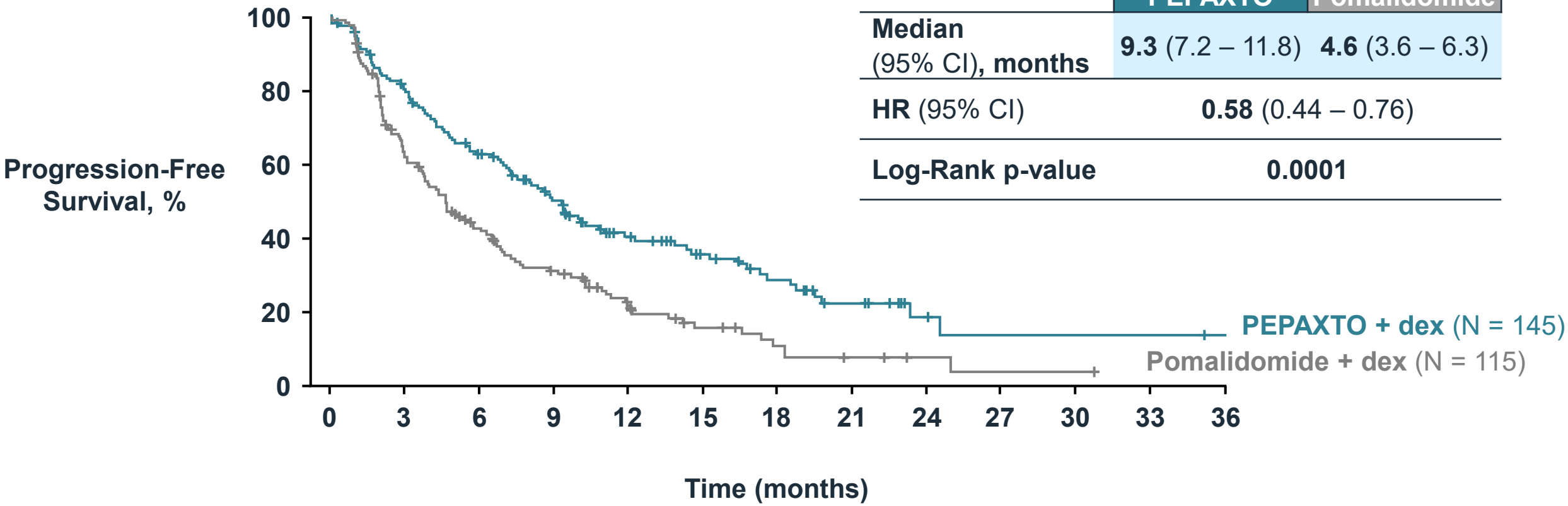
*Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)

OCEAN: OS Associated with Time to Progression Post ASCT

	N for PEPAXTO + dex / Pomalidomide + dex	Median OS, months		HR (95% CI)
		PEPAXTO + dex	Pomalidomide + dex	
ITT	246 / 249	**20.2** (15.8 – 24.3)	**24.0** (19.1 – 28.7)	**1.14** (0.91 – 1.43)
Progression following ASCT				
< 12 months	31 / 32	**13.1** (5.8 – 19.3)	**20.5** (13.6 – 37.1)	**1.74** (0.95 – 3.21)
12 – 24 months	47 / 51	**14.8** (7.6 – 20.5)	**30.1** (20.1 – NA)	**2.50** (1.49 – 4.19)
24 – 36 months	23 / 18	**26.2** (15.1 – 40.4)	**30.9** (20.1 – 34.7)	**1.11** (0.52 – 2.38)
> 36 months	24 / 19	**35.0** (10.0 – NA)	**32.6** (11.2 – NA)	**0.79** (0.33 – 1.89)

OCEAN: PFS in Patients with No ASCT or Post-ASCT Progression > 36 Months*

	PEPAXTO	Pomalidomide
Median (95% CI), **months**	**9.3** (7.2 – 11.8)	**4.6** (3.6 – 6.3)
HR (95% CI)	**0.58** (0.44 – 0.76)	
Log-Rank p-value	**0.0001**	



Number at Risk

PEPAXTO	145	110	84	62	39	28	20	12	5	3	3	3	2
Pomalidomide	148	86	54	37	21	12	7	4	2	1	1	0	0

Data cut: Feb 3, 2022

*** Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)**

OCEAN: Identified Risk in Patients with Post-ASCT Progression ≤ 36 Months*

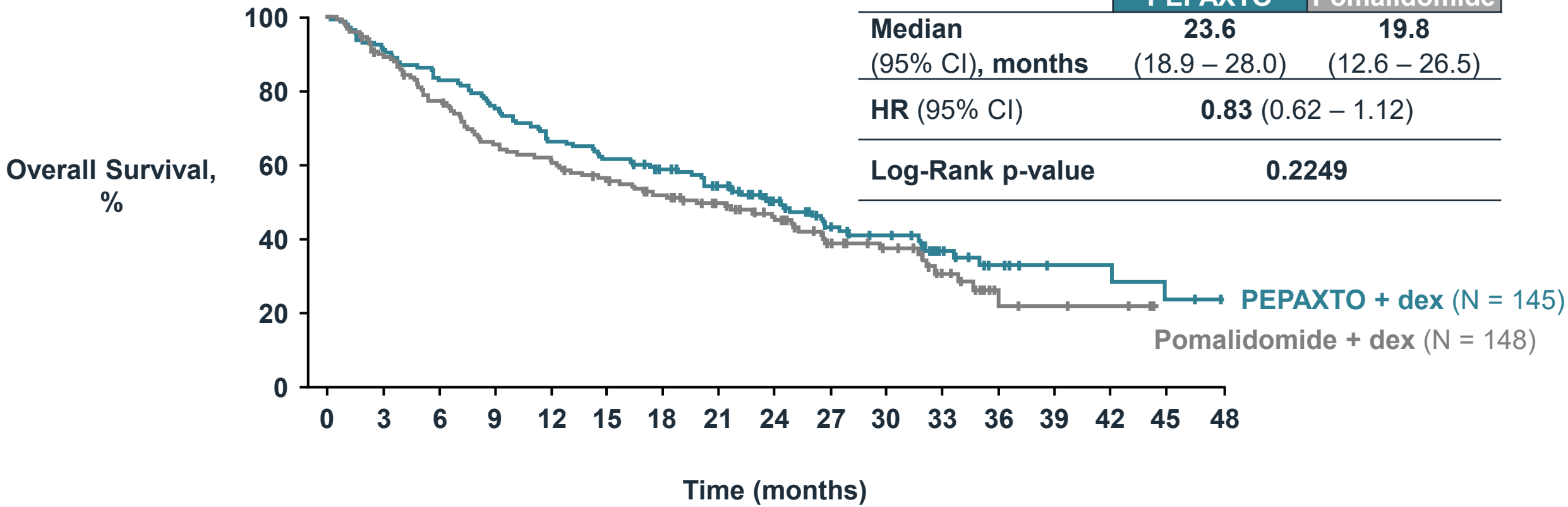
	N PEPAXTO + dex / Pomalidomide + dex	Median OS, months PEPAXTO + dex	 Pomalidomide + dex	HR (95% CI)
ITT	246 / 249	**20.2** (15.8 – 24.3)	**24.0** (19.1 – 28.7)	**1.14** (0.91 – 1.42)
No ASCT or Post-ASCT progression > 36 mos*	145 / 148	**23.6** (18.9 – 28.0)	**19.8** (12.6 – 26.5)	**0.83** (0.62 – 1.12)
Post-ASCT progression ≤ 36 mos	101 / 101	**15.7** (11.9 – 20.5)	**28.7** (20.2 – 34.1)	**1.80** (1.27 – 2.55)

OS update February 2022

*** Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)**

OCEAN: OS in Patients with No ASCT or Post-ASCT Progression > 36 Months*

	PEPAXTO	Pomalidomide
Median (95% CI), **months**	**23.6** (18.9 – 28.0)	**19.8** (12.6 – 26.5)
HR (95% CI)	**0.83** (0.62 – 1.12)	
Log-Rank p-value	**0.2249**	



Number at Risk

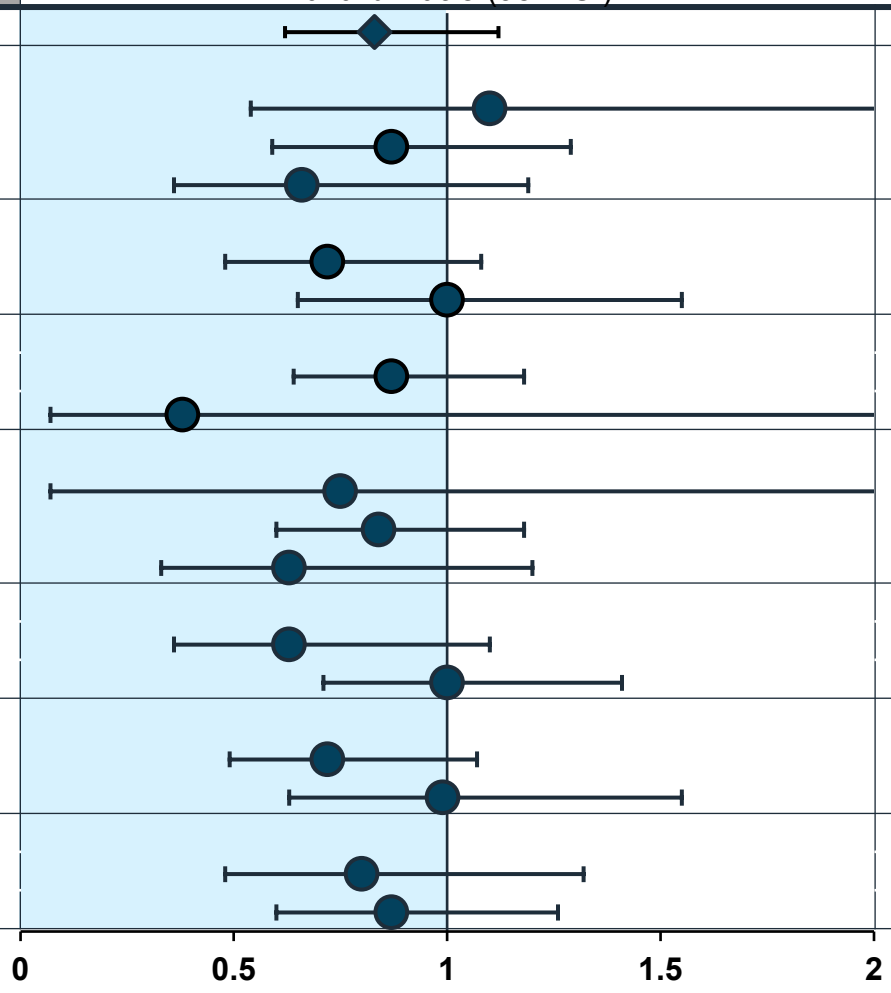
PEPAXTO	145	133	121	110	96	89	80	70	54	39	32	21	11	7	7	5	3
Pomalidomide	148	130	111	93	88	78	68	58	47	33	25	15	5	4	3	0	0

OS update February 2022

*** Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)**

OCEAN: OS in Patients with No ASCT or Post-ASCT Progression > 36 Months*

	PEPAXTO	Pomalidomide	Hazard Ratio (95% CI)
OVERALL	87 / 145	91 / 148	**0.83** (0.62 – 1.12)
Age			
< 65	21 / 41	13 / 30	**1.10** (0.54 – 2.21)
≥ 65 to < 75	46 / 69	53 / 80	**0.87** (0.59 – 1.29)
≥ 75	20 / 35	25 / 38	**0.66** (0.36 – 1.19)
Sex			
Male	44 / 75	53 / 83	**0.72** (0.48 – 1.08)
Female	43 / 70	38 / 65	**1.00** (0.65 – 1.55)
Race			
White	81 / 131	85 / 139	**0.87** (0.64 – 1.18)
All other races	2 / 7	4 / 7	**0.38** (0.07 – 2.06)
Region			
USA	1 / 6	2 / 10	**0.75** (0.07 – 8.24)
Europe	71 / 106	65 / 99	**0.84** (0.60 – 1.18)
ROW	15 / 33	24 / 39	**0.63** (0.33 – 1.20)
ECOG			
0	26 / 54	24 / 45	**0.63** (0.36 – 1.10)
1 – 2	61 / 91	67 / 103	**1.00** (0.71 – 1.41)
Prior Lines			
2	49 / 76	53 / 77	**0.72** (0.49 – 1.07)
3 – 4	38 / 69	38 / 71	**0.99** (0.63 – 1.55)
Cytogenetics			
High risk	28 / 42	35 / 48	**0.80** (0.48 – 1.32)
Not high risk	59 / 103	56 / 100	**0.87** (0.60 – 1.26)



OS update February 2022

* Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)

OCEAN: Identified ASCT Interaction and OS

	PEPAXTO	Pomalidomide	Hazard Ratio* (95% CI)
OVERALL	**162 / 246**	**147 / 249**	**1.14** (0.91 – 1.43)
ASCT (Prespecified)			
ASCT	**61 / 125**	**41 / 120**	**1.61** (1.09 – 2.40)
No ASCT	**56 / 121**	**67 / 129**	**0.78** (0.56 – 1.12)
ASCT (Time to progression post ASCT)			
Post-ASCT progression ≤ 36 mo	**75 / 101**	**56 / 101**	**1.80** (1.27 – 2.55)
No ASCT / Post-ASCT progression > 36 mo*	**87 / 145**	**91 / 148**	**0.83** (0.62 – 1.12)

OS update February 2022

* Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)

OCEAN Safety Population

Ocean: Overview of Adverse Events

Patients with	PEPAXTO + dex (N = 228)	Pomalidomide + dex (N = 246)
Adverse event	99%	98%
Grade 3 or 4 AE	90%	74%
Serious adverse events	42%	46%
AEs leading to dose modification	78%	59%
AEs leading to discontinuation	26%	22%
Total deaths	46%	43%

Safety Population

OCEAN: Important Grade 3/4 AEs

Patients with	PEPAXTO + dex (N = 228)	Pomalidomide + dex (N = 246)
≥ 1 Grade 3 or 4 AEs	90%	74%
Thrombocytopenia	76%	13%
Bleeding	2.2%	0.4%
Grade 3/4 Thrombocytopenia with Grade 3/4 Bleeding	0.9%	0
Neutropenia	64%	49%
Infection	13%	22%
Grade 3/4 Neutropenia with Grade 3/4 Infection	3%	7%

* Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)

OCEAN Safety in Recommended Population

No ASCT or Post-ASCT Progression > 36 Months*

* Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)

OCEAN: AEs per Patient Year Decreases with Post ASCT Time to Progression

Safety Population PEPAXTO + dex	Events/Patient Year				
	Time to Progression Post ASCT				No ASCT
	< 12 Months (n = 29)	12 – 24 Months (n = 42)	24 – 36 Months (n = 20)	> 36 Months (n = 21)	(n = 116)
Grade 3/4 AEs	17	16	17	8	12
SAEs	2	2	1	1	1
AEs leading to dose modification	6	6	7	4	4
AEs leading to discontinuation	0.8	0.6	0.9	0.5	0.3
Fatal AEs	0.4	0.3	0.1	0.1	0.1

* Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)

OCEAN: Safety by ASCT, With Longer PEPAXTO Exposure in Target Population

	Post-ASCT progression ≤ 36 months		No ASCT or Post-ASCT progression > 36 months*	
Safety Population	PEPAXTO + dex (N = 91)	Pomalidomide + dex (N = 99)	PEPAXTO + dex (N = 137)	Pomalidomide + dex (N = 147)
Exposure to study drug, Median	3.7 months	5.5 months	8.1 months	5.1 months
Patients with				
Grade 3/4 AEs	92%	79%	88%	71%
SAEs	38%	47%	44%	45%
AEs leading to dose modification	84%	57%	74%	60%
AEs leading to discon.	31%	17%	23%	27%
Fatal AEs	13%	7%	11%	17%

* Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)

OCEAN: Less AEs per Patient Year in Patients With No ASCT or Post-ASCT Progression > 36 Months

Safety Population	Post-ASCT progression ≤ 36 months		No ASCT or Post-ASCT progression > 36 months*	
	PEPAXTO + dex (N = 91)	Pomalidomide + dex (N = 99)	PEPAXTO + dex (N = 137)	Pomalidomide + dex (N = 147)
	Events/ Patient Year	Events/ Patient Year	Events/ Patient Year	Events/ Patient Year
Grade 3 or 4 AEs	16.6	4.8	11.2	5.7
SAEs	1.6	1.3	1.1	1.8
AEs leading to dose modification	6.8	2.3	4.5	3.3
AEs leading to discon.	0.85	0.36	0.40	0.69
Fatal AEs	0.32	0.13	0.17	0.30

* Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)

Fewer Deaths in Recommended Population*

Pepaxto + dex (Safety Population)	Post-ASCT progression ≤ 36 months (N = 91)	No ASCT or Post-ASCT progression > 36 months* (N = 137)
Total number of deaths n (%)	47 (51.6%)	59 (43.1%)
Number of deaths ≤ 30 days after last dose n (%)	8 (8.8%)	15 (10.9%)
Progressive disease n (%)	1 (1%)	6 (4%)
Adverse event n (%)	7 (8%)	9 (7%)
Number of deaths > 30 days after last dose n (%)	39 (42.9%)	44 (32.1%)
Progressive disease n (%)	26 (29%)	27 (20.0%)
Adverse event n (%)	4 (4%)	2 (1%)
Other n (%)	5 (5%)	6 (4%)
Unknown n (%)	4 (4%)	9 (7%)

* Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)

PEPAXTO Dosing in Recommended Population*

* No ASCT or Post-ASCT Progression > 36 Months

PEPAXTO Recommended Dosing in Patients with RRMM and No ASCT or Post-ASCT Progression > 36 Months*

- MTD appropriate strategy for cytotoxic therapies
  - Dose modifications to manage hematological AEs
- 40 mg dose for most patients
- Proposed dose changes
  - 30 mg for patients with body weight ≤ 60 kg
    - Based on PK data and cytopenias
  - Modification guidance with earlier dose reductions

MTD: Maximum tolerated dose

***Recommended population for PEPAXTO treatment**

OCEAN Confirms Positive Benefit-Risk for PEPAXTO with Proposed Limitations of Use

- PEPAXTO has positive benefit-risk when used in patients with no ASCT or post ASCT progression > 36 months
  - Improved efficacy
  - Better safety
  - Fewer dose modifications
- Future use and development only in recommended population

Clinical Perspective

Yvonne Efebera, MD, MPH

Professor, Medical Director, Blood and Marrow Transplant and Cellular Therapy

OhioHealth

RRMM Remains Incurable: Patients Continue to Need Options

- Once a disease becomes multi-refractory, survival quickly diminishes as there are few options for our patients
- PEPAXTO MoA acts in a different pathway
- PEPAXTO benefit consistently observed across clinical studies in patients with high unmet need

The Right Patient Continues to Need PEPAXTO: Patient Example

- Myeloma, a disease of the elderly, > 80% of patients ≥ 65 years
- Patient narrative
  - 74 year-old Caucasian woman, diagnosed with MM in 2005
  - 4 prior lines of treatment between 2005 – 2019
- Past medical history
  - Insulin dependent diabetes, hyperlipidemia, hypertension, CHF, COPD and class III obesity
  - Not considered an ASCT candidate due to co-morbidities
- 2019 – 2021: PEPAXTO given: VGPR followed by PD
  - Well tolerated, no hospitalizations and heme toxicity only
  - Two dose reductions (40 to 30 mg after 6 months, 20 mg after 12 months – 2 years)

EMD in RRMM: Clinical Considerations

- Associated with poor patient outcome and is not well studied[1]
  - Patients typically excluded from clinical trials – though in high unmet need
- HORIZON represents largest cohort of patients with EMD evaluated to date in a prospective clinical trial (N = 55)[2]
- PEPAXTO showed activity in patients with advanced RRMM[2]
  - ORR: 24%
  - Median PFS: 2.9 months
  - Median OS: 6.5 months
- Safety profile consistent to overall population

1. Bhutani M, et al. Leukemia. 2020; 2. Richardson et al., J Clin Oncol, 2021

OCEAN (OP-103): Important Trial to Inform the Benefit/Risk Profile of PEPAXTO

- Subgroup data key from OCEAN
  - Data in patients with no prior ASCT or TTP > 36 months post ASCT
    - Median PFS: 9.3 months vs 4.6 months for pomalidomide
    - Median OS: 23.6 months vs 19.8 months for pomalidomide
- Clear biological rationale supporting these subgroup data

Expected and Manageable Safety Profile

- Tolerable drug profile
- Limited non-hematologic AEs (e.g absence of alopecia, no cardiac toxicity, no neuropathy, minimal mucositis)
  - Majority grade 1 – 2
- Myelosuppression is expected with active cytotoxic agents
- Hematologic AEs managed with dose modifications and supportive care
  - Dose modifications as standard approach proved effective
  - Comparable discontinuation rates between PEPAXTO and pomalidomide
- Convenient monthly infusion schedule

Patients with RRMM Should Have PEPAXTO as an Option

- Triple-class refractory RRMM is an urgent unmet medical need
- Multiple studies demonstrate PEPAXTO's benefit in this setting
- Consistent and manageable safety profile
- Clinically meaningful data in patients who progressed > 36 months after an ASCT and in patients without prior ASCT

OCEAN Data Support Positive PEPAXTO Benefit-Risk

FDA Issues	Key Considerations
PFS benefit	• **PEPAXTO met primary endpoint, with statistically significant superior PFS** • **IRC used IMWG guidelines for disease progression**

Overall survival	• **Prespecified subgroup analysis identified risk in patients with prior ASCT**
	  • **Biologically plausible risk**
	• **Removal of subgroup with risk* improves efficacy and safety**
	  • **PFS, OS, ORR, DOR, AEs**

Appropriate dose	• **PEPAXTO is an alkylating cytotoxic dosed to MTD** • **Improved tolerability and less dose modifications by removal of subgroup with risk***

*** Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)**

PEPAXTO® (melphalan flufenamide)

September 22, 2022

Oncopeptides AB (publ)

Oncologic Drugs Advisory Committee

Q&A Backup Slides Shown

MAYO CLINIC

Shaji Kumar, M.D.
Hematology & Internal Medicine
200 First Street SW
Rochester, MN 55905
507-284-2511

September 12, 2022

Re: ODAC on Pepaxto (melphalan flufenamide), FDA-2022-N-0634

Dear Members of the Oncologic Drugs Advisory Committee,

In my capacity as Chair of the Independent Review Committee (IRC) of the OCEAN Study (OP-103) I would like to clarify potential confusion on the response assessment procedures in the OCEAN trial.

- **Re-assessment of 29 patients after unblinding of the data**

The IRC has always been completely blinded during the response assessments of patients enrolled in OCEAN. The re-assessment, also done in a blinded fashion, should not be seen as a post-hoc analysis but considered as the final blinded review of patients where initially not all response data was available.

- **Assessment of response and definition of PD event**

The response assessment has always been performed using IMWG criteria, as stipulated in the Statistical Analysis Plan (SAP) as well as the IRC charter. Response assessment has been performed using the same method during the full duration of the study. As such, there can be no confusion which method was used. Specifically, we want to be clear that we did require confirmation for progression as we assessed the response *and* progression.

Along with the other members of the IRC, I am happy to provide further clarifications.

Sincerely,

Shaji Kumar, MD
Chair, Hematology Research
Professor of Medicine
Mark and Judy Mullins Professor of Hematological Malignancies
Consultant, Division of Hematology and Blood and Marrow Transplantation
Chair, Myeloma, Amyloidosis, Dysproteinemia Group
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IMiD Age Interaction: Awaiting DREAMM3 Data

OCEAN PEPAXTO vs Pomalidomide[1] (N = 495) [2021]	Ixazomib vs Pomalidomide[2] (N = 122) [2022]	DREAMM3 Belantamab vs Pomalidomide (N = 380) [Reporting in 2022]
ITT PFS HR 0.79	**ITT PFS HR 0.85**	ITT PFS HR TBD
ITT OS HR 1.14	**ITT OS HR 1.43**	ITT OS HR TBD
< 75 years* OS HR 1.26	**< 75 years* OS HR 1.60**	< 75 years* OS HR TBD
≥ 75 years* OS HR 0.62	**≥ 75 years* OS HR 0.87**	≥ 75 years* OS HR TBD

- **Age-related interaction observed in CC-5013-MM-015 and CALGB100104**
  - **Other 3 studies cited by FDA compared to high dose dex or crossover**

* Presented as 75 years to align with ixazomib publication (did not report for 65 years)

1.Schjesvold et.al, Lancet Haematol, 2022; 2. Dimopoulos et. al, Blood Cancer J, 2022

Data cut for OCEAN OS data: Feb 2,

OCEAN: Subsequent Therapy

	PEPAXTO + dex (N = 246)	Pomalidomide + dex (N = 249)
Any subsequent therapy	57%	54%
Alkylator	8%	12%
Cyclophosphamide	7%	6%
Melphalan	0%	4%
Melphalan flufenamide	0%	0.4%
Anti-CD38 monoclonal antibody,	16%	27%
Daratumumab	16%	26%
Isatuximab	0%	1%
IMiD	26%	10%
Pomalidomide	20%	2%
Lenalidomide	5%	6%
Thalidomide	1%	1%
PI	23%	26%
Bortezomib	12%	15%
Carfilzomib	9%	10%
Ixazomib	2%	1%

OCEAN: Deaths ≤ 60 Days After First Dose

Deaths	PEPAXTO + dex (N = 246)	Pomalidomide + dex (N = 249)
Number of Deaths	46%	43%
Number of Deaths ≤ 60 days after first dose	5%	3%
Primary cause of Deaths ≤ 60 days after first dose		
Adverse Event	3%	0.8%
Progressive Disease	3%	2%
Other	0	0.4%

OCEAN and HORIZON: Fatal AEs by SOC Balanced Between Treatment Groups

	HORIZON Study	OCEAN Study	
System Organ Class, n (%)	Pepaxto+Dex (N=157)	Pepaxto+Dex (N=228)	Pomalidomide+Dex (N=246)
Number of Patients with at least 1 Fatal AE	10 (6%)	27 (12%)	32 (13%)
Infections and infestations	1 (0.6%)	12 (5%)	13 (5%)
General disorders and administration site conditions	3 (2%)	3 (1%)	9 (4%)
Respiratory, thoracic and mediastinal disorders	4 (3%)	3 (1%)	4 (2%)
Cardiac disorders	1 (0.6%)	2 (0.9%)	2 (0.8%)
Renal and urinary disorders	1 (0.6%)	2 (0.9%)	2 (0.8%)
Injury, poisoning and procedural complications	0	2 (0.9%)	1 (0.4%)
Nervous system disorders	0	2 (0.9%)	1 (0.4%)
Blood and lymphatic system disorders	0	2 (0.9%)	0
Gastrointestinal disorders	0	2 (0.9%)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1%)	1 (0.4%)	1 (0.4%)
Metabolism and nutrition disorders	1 (0.6%)	0	0

OCEAN: Time to Resolution of First Grade 3 or 4 Neutropenia and Thrombocytopenia

	PEPAXTO + dex (N = 228)	Pomalidomide + dex (N = 246)
Median Time to Resolution of Grade 3 or 4 Neutropenia, days (min, max)	**8** (2 – 42)	**8** (3 – 78)
Median Time to Resolution of Grade 3 or 4 Thrombocytopenia, days (min, max)	**15** (2 – 55)	**9** (7 – 22)
Patients with ≥ 1 MDS (Myelodysplastic Syndromes)	1 **(0.4%)**	1 **(0.4%)**

HORIZON: Efficacy in US Patients

	Post-ASCT progression ≤ 36 months N = 25	No ASCT or Post-ASCT progression > 36 months* N = 44
OS (95% CI), **months**	**9.5** (6.5 – 17.8)	**16.5** (11.3 – 22.9)
PFS (95% CI), **months**	**3.0** (1.6 – 4.5)	**5.4** (3.9 – 9.4)
DOR (95% CI), **months**	**3.9** (1.8 – NA)	**9.9** (5.3 – 15.4)
ORR (95% CI)	**20** (6.8 – 40.7)	**48** (32.5 – 63.3)

* Limitation of Use to exclude patients with post-ASCT progression ≤ 36 months (i.e., use in patients with no prior ASCT or post-ASCT progression > 36 months)