Idecabtagene vicleucel (ide-cel) in Patients With Triple-Class Exposed Relapsed/Refractory Multiple Myeloma

US Food & Drug Administration
Oncologic Drugs Advisory Committee
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Bristol Myers Squibb™

Introduction

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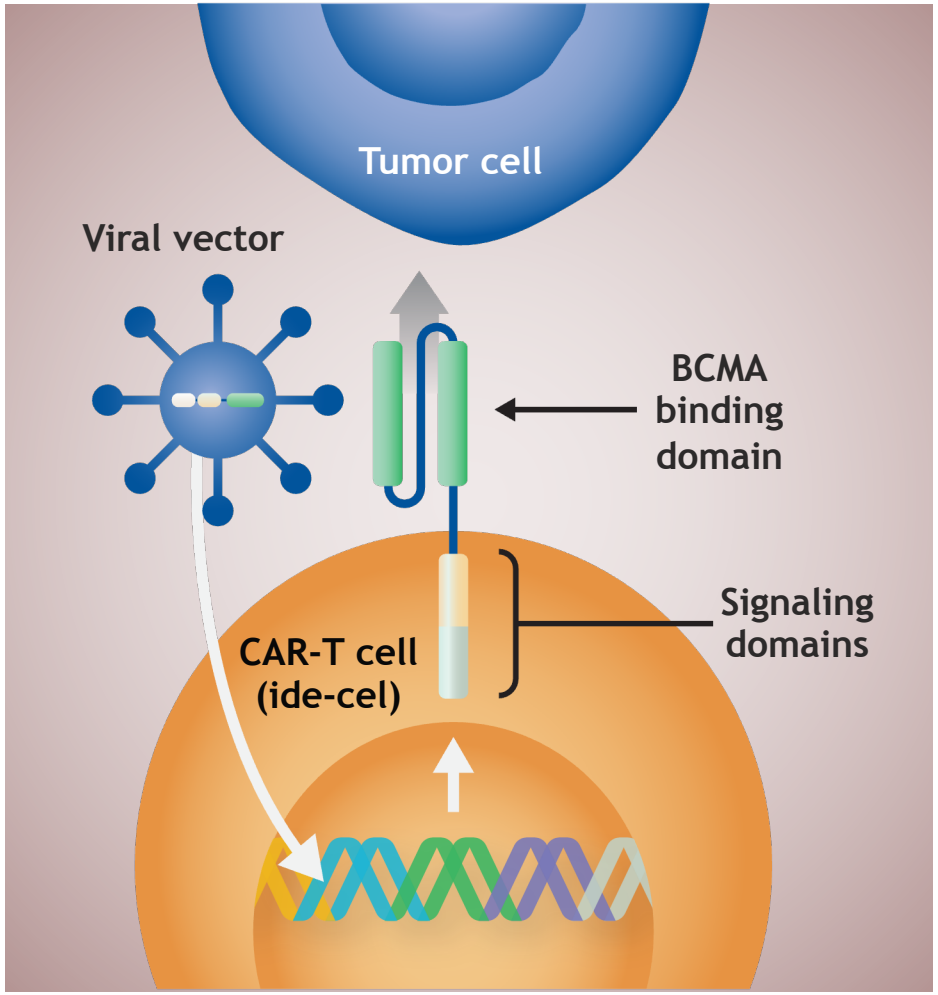
Agenda

Introduction	**Anne Kerber, MD** BMS
Disease Background	**Sagar Lonial, MD** Emory University School of Medicine
KarMMa-3 Design and PFS Results	**Eric Bleickardt, MD** BMS
KarMMa-3 Overall Survival Results	**Eric Bleickardt, MD** BMS
Clinical Safety	**Mark Cook, MBChB, PhD** BMS
Clinical Perspective	**Noopur Raje, MD** Massachusetts General Hospital
Moderator (Q&A)	**Anne Kerber, MD** BMS

Current and proposed indication

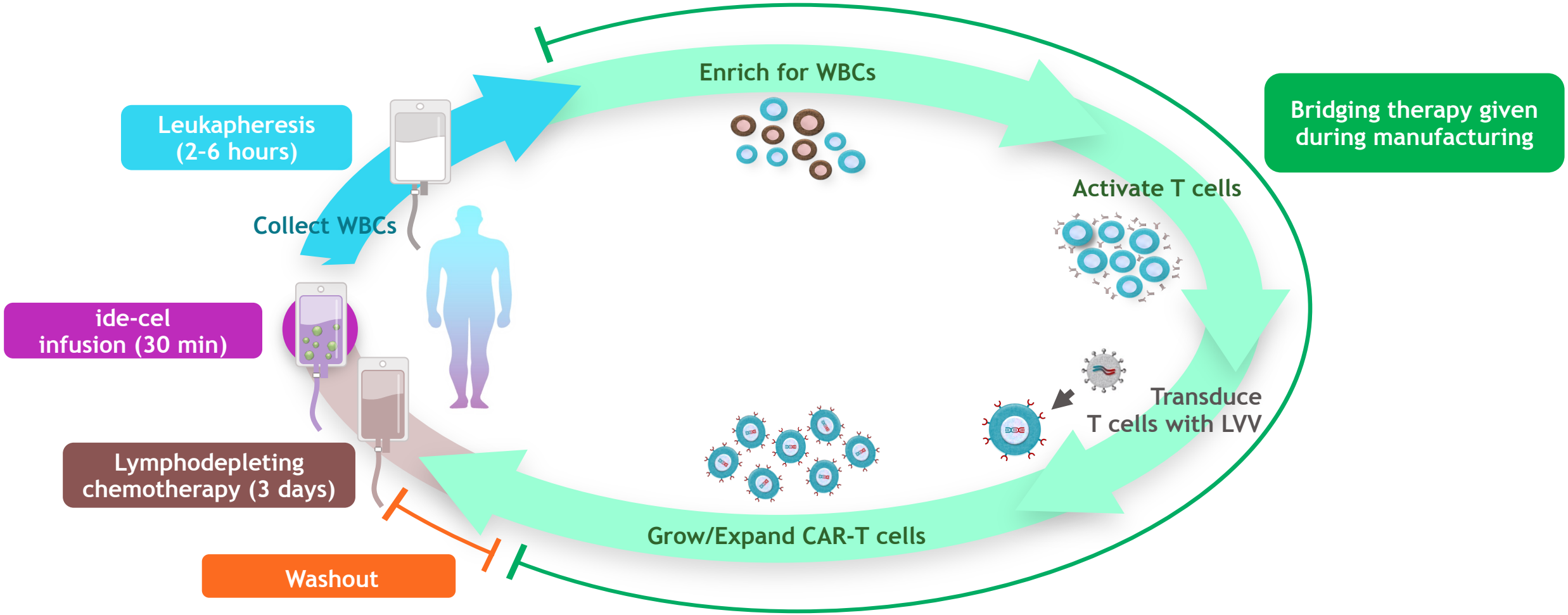
Current indication in the US for ABECMA	Treatment of adult patients with relapsed or refractory multiple myeloma **after four or more prior lines of therapy,** including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
Proposed indication	Treatment of adult patients with relapsed or refractory multiple myeloma who have received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

Ide-cel is a BCMA-directed CAR-T cell therapy



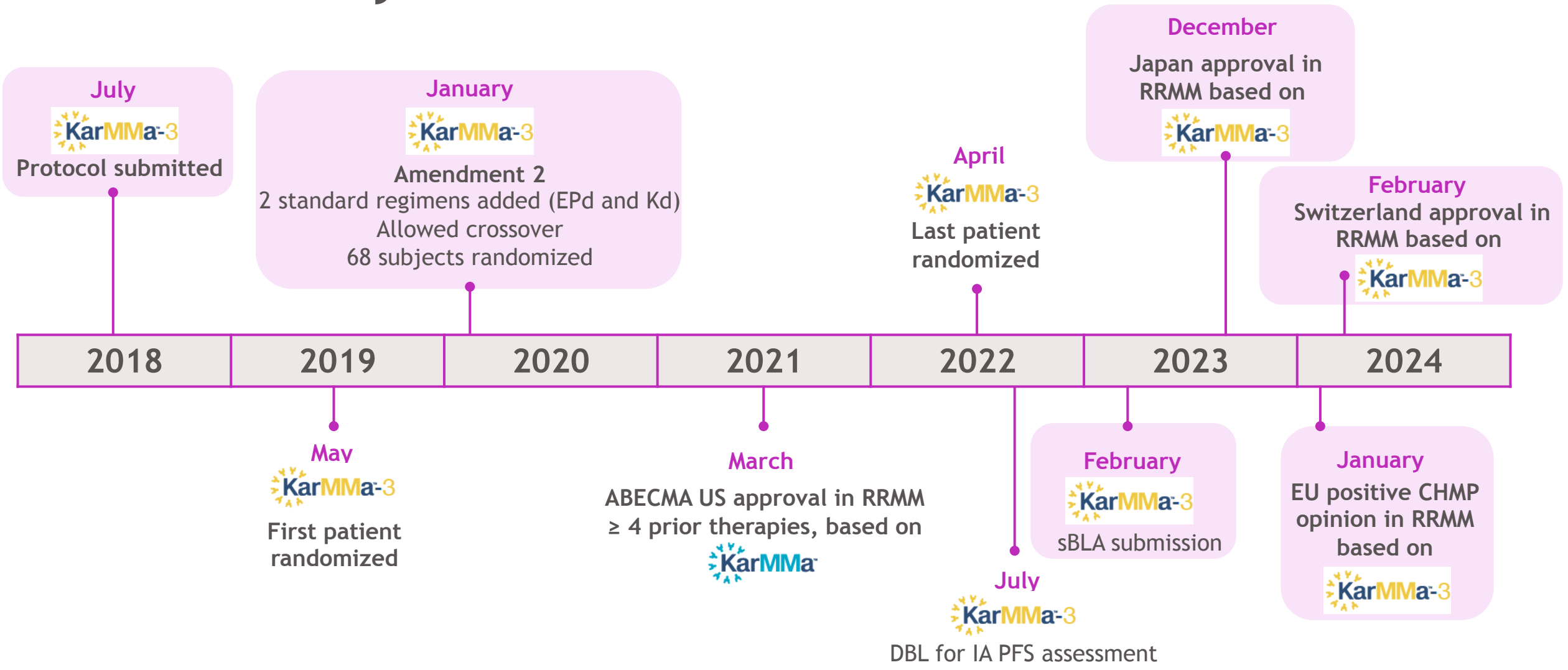
- Genetically modified cell therapy: **C**himeric **A**ntigen **R**eceptor **T** (CAR-T) cell therapy
- It targets B-cell maturation antigen (BCMA), which is highly expressed on myeloma cells
- Ide-cel is an autologous product that is manufactured individually for each patient

Ide-cel CAR-T cell therapy treatment journey



LVV = lentiviral vectors; WBC = white blood cells.

KarMMa-3: key milestones



CHMP = Committee for Medicinal Products for Human Use; DBL = database lock; EPd = elotuzumab + pomalidomide + low dose dexamethasone; EU = European Union; IA = investigator-assessed; Kd = carfilzomib + low-dose dexamethasone; MM = multiple myeloma; PFS = progression-free survival; RR = relapsed or refractory; sBLA = supplemental Biologics License Application; US = United States.

KarMMa-3 supports the use of ide-cel in patients with triple-class exposed RRMM

- KarMMa-3 is the **first randomized study of CAR-T** in patients with **triple-class exposed (TCE)**, **relapsed or refractory multiple myeloma (RRMM)**, which is a patient population with high unmet need
- KarMMa-3 **met both primary (PFS) and key secondary (ORR) endpoints**; results were highly statistically significant, clinically meaningful, and consistent across all prespecified subgroups
- Interpretability of **overall survival (OS) data is confounded** by the patient-centric design, which allowed crossover
- The numerically **higher proportion of early deaths** in the ide-cel arm was driven by **patients who never received ide-cel**; most early deaths were due to disease progression
- KarMMa-3 demonstrated a **favorable benefit-risk profile for ide-cel** in patients with TCE RRMM

ORR = overall response rate; OS = overall survival.

Ide-cel treatment earlier in the disease course is a key risk minimization approach

Bridging patients to ide-cel in clinical practice

- Start bridging therapy early (minimize time without anti-MM therapy)
- Individualize bridging therapy
- Continue bridging therapy as long as needed to control disease

BMS approach to risk minimization

- Include data in USPI for informed decision making
- Treatment only at qualified centers
- REMS training program established
- Registry with 15 years of follow-up
- US Manufacturing Reliability:
  - Commercial turnaround time = 25 days[a]
  - Commercial success rate > 92%

REMS = Risk Evaluation and Mitigation Strategies; USPI = United States prescribing information.
[a] From leukapheresis to product release.

Disease Background

Sagar Lonial, MD
Chief Medical Officer, Winship Cancer Institute of Emory University
Professor and Chair, Department of Hematology and Medical Oncology
Anne and Bernard Gray Family Chair in Cancer
Emory University School of Medicine

Multiple myeloma, a story of contrast

MM is an incurable hematologic cancer of plasma cells, which are found in bone marrow and produce antibodies[1-3]

Clinical complications of progressive MM include[4]

- Recurrent infections
- Cytopenias
- Renal failure
- Hypercalcemia
- Bone pain
- Pathologic fractures

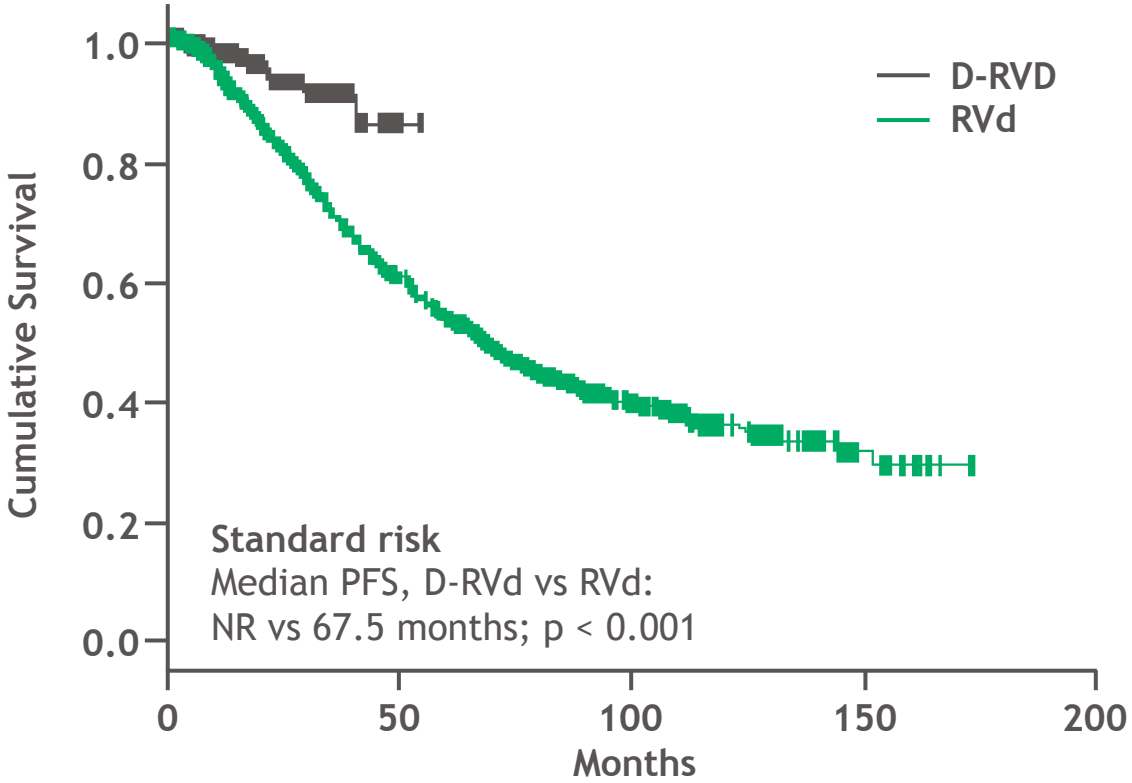
MM is a heterogeneous disease with a highly variable clinical course[5]

- Estimated deaths due to MM = 12,590 (2023)[6]
- MM incidence = 35,730 (2023)[6]
- MM prevalence = 170,405 (2020)[6]

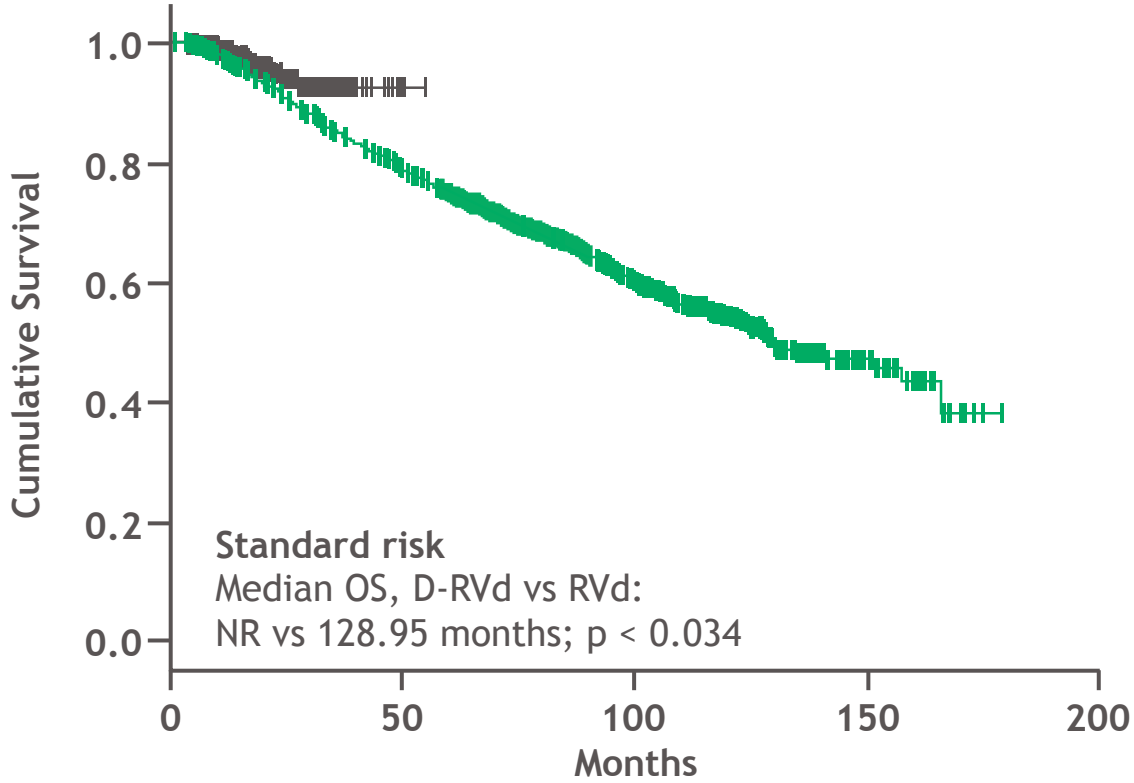
1. Kyle RA, Rajkumar SV. *Best Pract Res Clin Haematol*. 2007;20:637-664; 2. Cook G, Campbell JD. *Blood Rev*. 1999;13:151-162; 3. Encyclopaedia Britannica. https://www.britannica.com/science/plasma-cell. Accessed January 2021; 4. Munshi NC, Anderson KC. *Clin Cancer Res*. 2013;19(13):3337-3344; 5. Avet-Loiseau H, et al. *J Clin Oncol*. 2013;31:2806-2809; 6. SEER. https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed November 21, 2023.

Increasing use of more effective therapies in the frontline setting

Progression-free survival

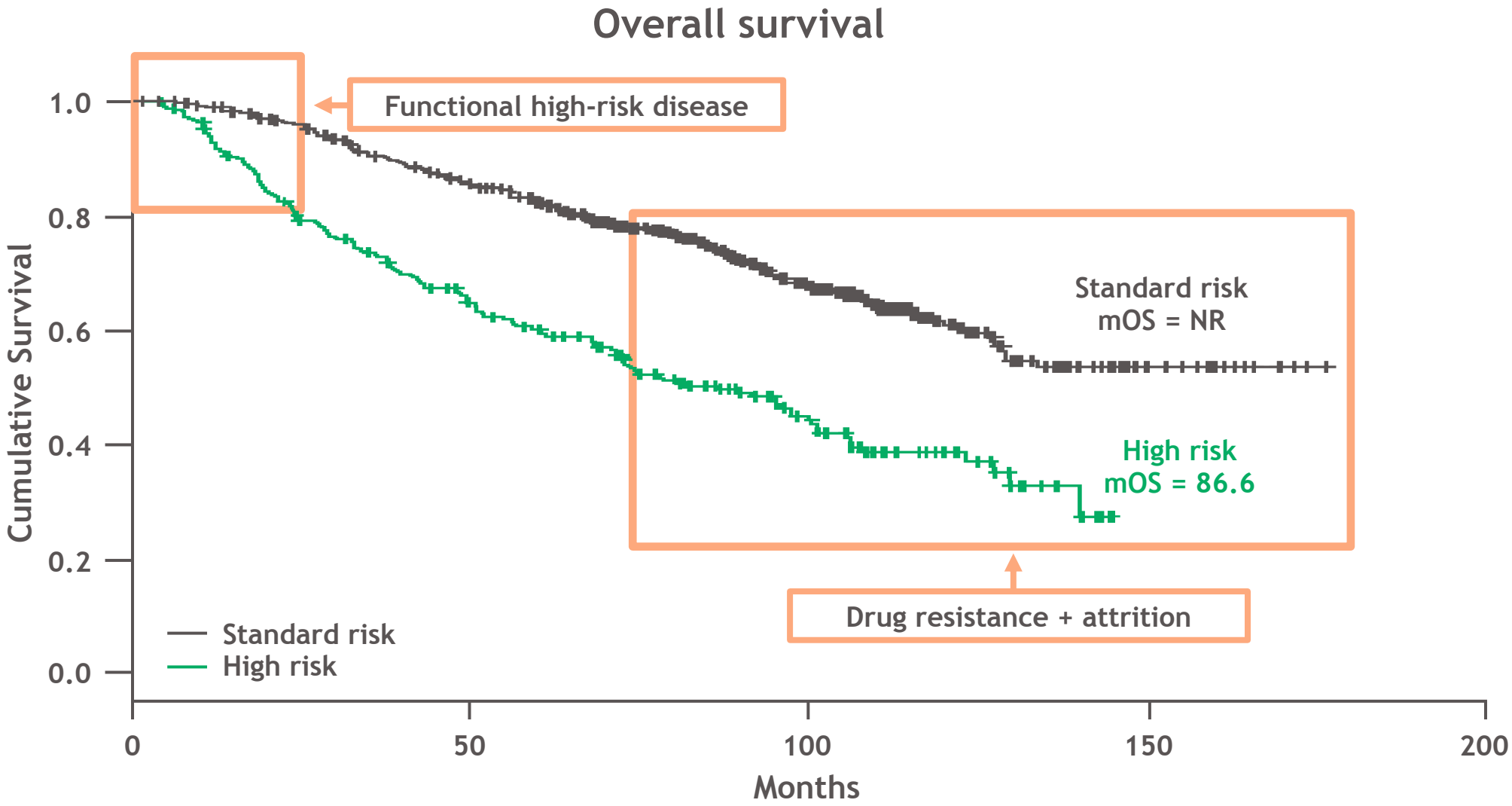


Overall survival



D-RVd = daratumumab, Revlimid, Velcade, dexamethasone; NR = not reached; RVd = Revlimid, Velcade, dexamethasone.

Patient outcomes remain challenging



M = median.

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High unmet need continues in myeloma

Resistance

- Early resistance/ high-risk disease
- 20% of patients die within the first 2 years, even with highly effective therapy

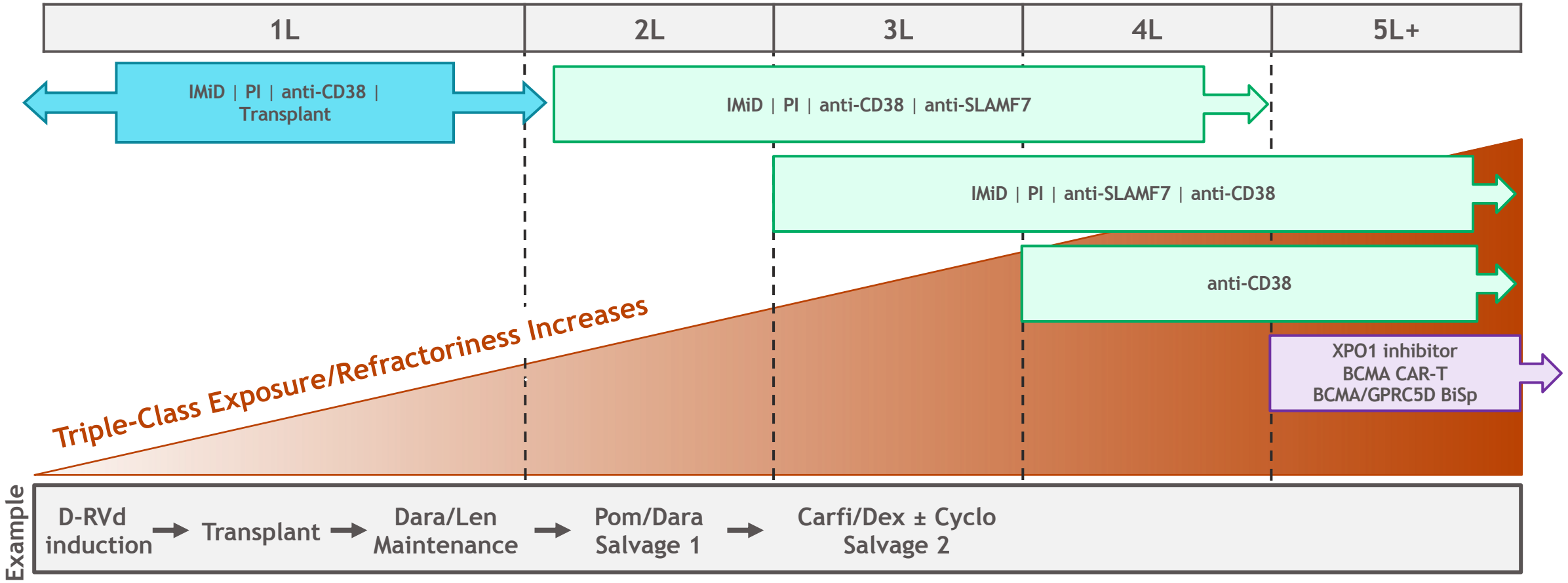
TCE early

- Patients are becoming TCE as early as after frontline therapy
- Patients continue to relapse with no plateau in the survival curve

Attrition

- 20%-30% patient attrition with each treatment line
- Most patients who relapse do not have the opportunity to benefit from ide-cel

The evolving treatment landscape leads to earlier exhaustion of the standard treatment options



anti-CD38 = anti-CD38 monoclonal antibody; anti-SLAMF7 = anti-signaling lymphocytic activation molecule family 7; BiSp = bi-specific T-cell engager; Carfi = carfilzomib; Cyclo = cyclophosphamide; Dara = daratumumab; Dex = dexamethasone; D-RVd = daratumumab, Revlimid, Velcade, dexamethasone; GPRC5D = G-protein coupled receptor family C group 5 member D; IMiD = immunomodulatory drug; Len = lenalidomide; PI = proteasome inhibitor; Pom = pomalidomide; XPO1 = nuclear export protein exportin-1.

High attrition rates and significant unmet need for triple-class exposed (TCE) patients in earlier treatment lines

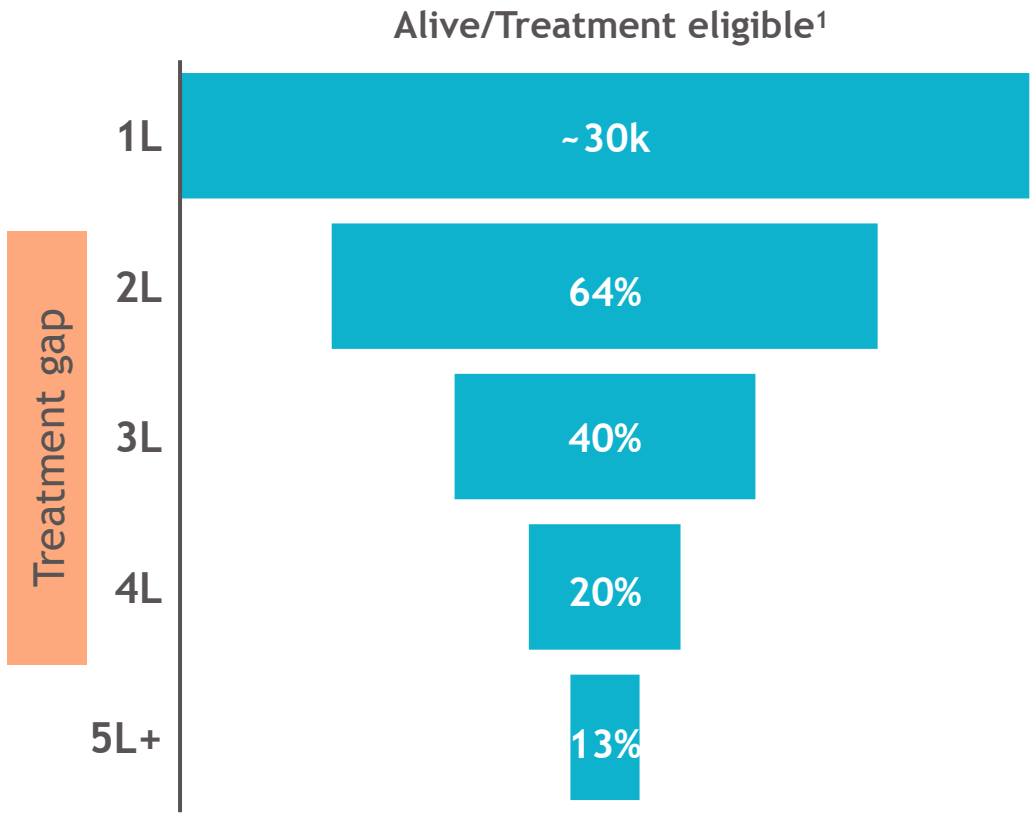
Increasing use of the 3 main classes of therapies in 1st and 2nd line

KarMMa

TCE RRMM,
≥ 4 prior therapies[a]

KarMMa-3

TCE RRMM,
2-4 prior therapies[a]



[a] Includes an IMiD, a PI, and daratumumab.
1. Quantitative MM Market Sizing Market Research.

Importance of moving CAR-T cell therapy earlier in the treatment course

Treatment gap

There are limited effective treatment options for patients with TCE RRMM, a growing patient segment in an earlier treatment line[1]

Attrition

With each treatment line, the risk of death increases and patients may not be able to benefit from novel therapies such as CAR-T cell therapy[2-3]

Bridging options

Risk for dropout from leukapheresis to ide-cel infusion increases with each additional prior line of treatment due to

- Declining performance status and disease-related complications
- Limited bridging options in the context of increasing refractoriness

1. NCCN Guidelines Version 2.2024 Multiple Myeloma. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf; 2. Goel U, et al. *Blood Cancer J*. 2023;13:11; 3. Fonseca R, et al. *BMC Cancer*. 2020;20:1087.

KarMMa-3 Design and PFS Results

Eric Bleickardt, MD
VP, Late Clinical Development, Cell Therapy
BMS

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KarMMa-3 study design

Key inclusion criteria

- 2–4 previous regimens (IMiD, PI, daratumumab)
- Refractory to the last regimen

Stratification factors

- Age
- Number of previous regimens
- High-risk cytogenetics

N = 386

R 2:1

Leukapheresis

Lymphodepleting chemotherapy

ide-cel (n = 254)

Optional bridging therapy ≤ 1 cycle (min 14 days of washout)

Single ide-cel infusion 150-450 x 10^6 CAR-T cells (n = 225)

Standard Regimens (DPd, DVd, IRd, Kd, EPd) (n = 132)

Treatment until PD, unacceptable toxicity, or withdrawal (n = 126)

Crossover to ide-cel after confirmed PD

DPd = daratumumab + pomalidomide + low-dose dexamethasone; DVd = daratumumab + bortezomib + low-dose dexamethasone; EPd = elotuzumab + pomalidomide; IRd = ixazomib + lenalidomide + low-dose dexamethasone; Kd = carfilzomib + low-dose dexamethasone; min = minimum; PD = progressive disease.

KarMMa-3 endpoints

Primary endpoint

- PFS by IRC

Key secondary endpoints

- ORR by IRC
- OS

Other secondary endpoints

- CRR by IRC, MRD, PROs
- Safety

CRR = complete response rate; IRC = Independent review committee; MRD = minimal residual disease; PRO = patient-reported outcome.

Statistical consideration

The primary endpoint and key secondary endpoints are evaluated using a **group sequential** design and a **hierarchical testing strategy** to maintain an overall type I error of 0.025 (1-sided)

Planned comparisons:

- PFS and ORR ~90% power
- **OS ~50% power**

Planned and conducted key analyses

Analysis timing	PFS events (IF)[a]	ORR	OS events (IF)[b]	Median follow-up
Interim PFS April 2022	242 (84%)	Final analysis	109 (49%)	18.6 mo
Final PFS April 2023	289 (100%)	NA	164 (74%)	30.9 mo

IF = information fraction; NA = not available.
[a] Total Planned PFS events = 289; [b] Total Planned OS events = 222 and the final OS analysis timing is not reached yet.

KarMMa-3 enrolled high-risk patients who were triple-class exposed (TCE)

Characteristic	ide-cel (N = 254)	Standard Regimens (N = 132)
Median (range) age, years	63 (30-81)	63 (42-83)
Region		
North America	144 (56.7)	82 (62.1)
Europe	106 (41.7)	45 (34.1)
Japan	4 (1.6)	5 (3.8)
Median (range) time from diagnosis to screening, years	4.1 (0.6-21.8)	4.0 (0.7-17.7)
R-ISS disease stage III, n (%)	31 (12)	14 (11)
Extramedullary plasmacytoma, n (%)	61 (24)	32 (24)
High tumor burden, n (%)	71 (28)	34 (26)
High-risk cytogenetics, n (%)	107 (42)	61 (46)
Median (range) prior lines of therapy	3 (2-4)	3 (2-4)
Triple-class refractory, n (%)	164 (65)	89 (67)
Refractory to daratumumab	242 (95)	123 (93)

R-ISS = Revised International Staging System.

KarMMa-3 study: protocol-specified treatment flow

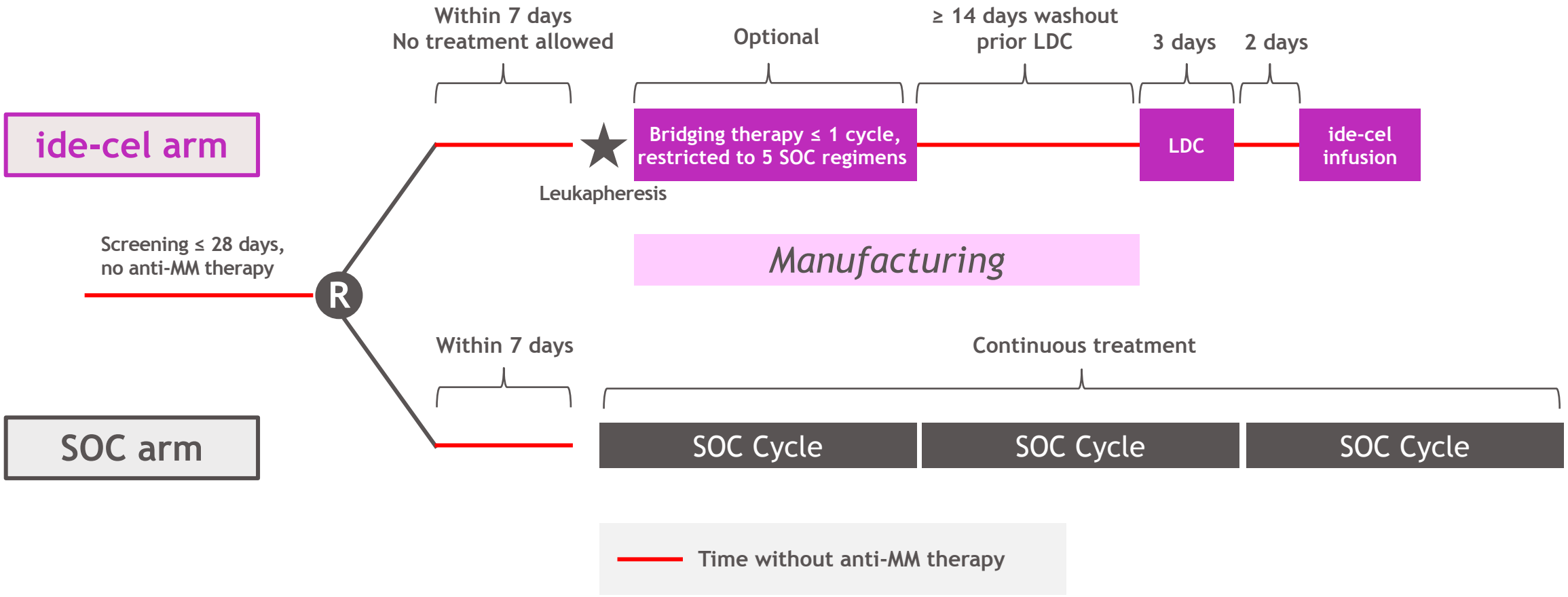
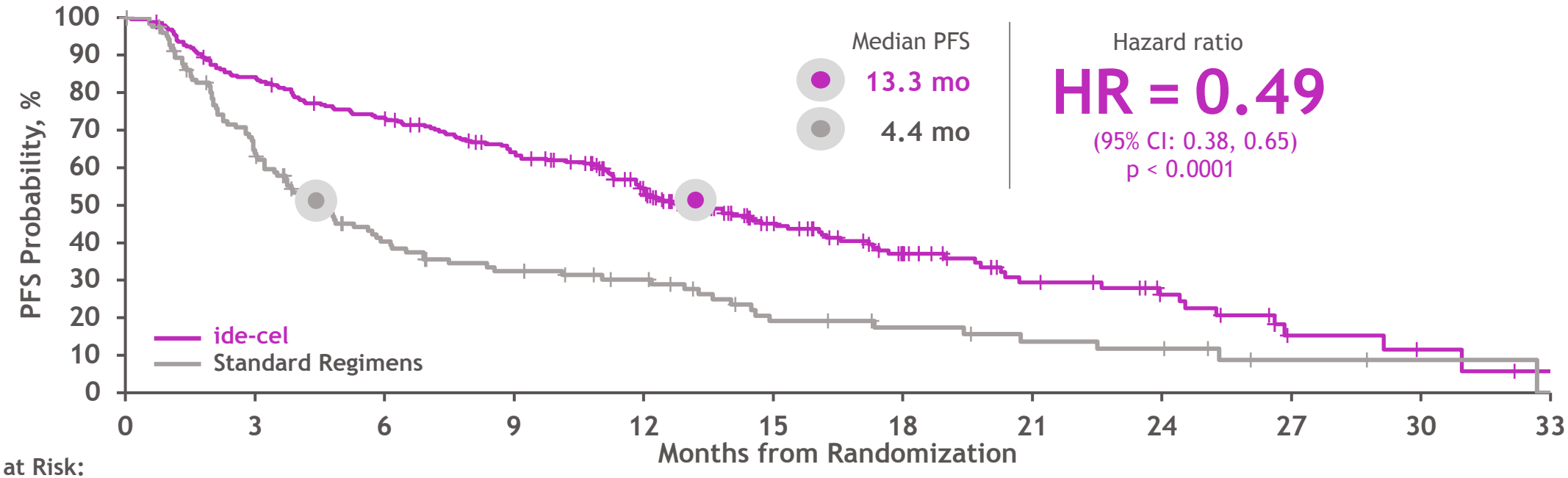


Figure is illustrative only
LDC = lymphodepleting chemotherapy; SOC = standard of care.

Significant benefit in PFS with ide-cel (ITT population)



Patients at Risk:												
ide-cel	254	206	178	149	110	62	40	22	14	4	2	0
Standard Regimens	132	75	42	32	25	13	10	7	6	2	1	0

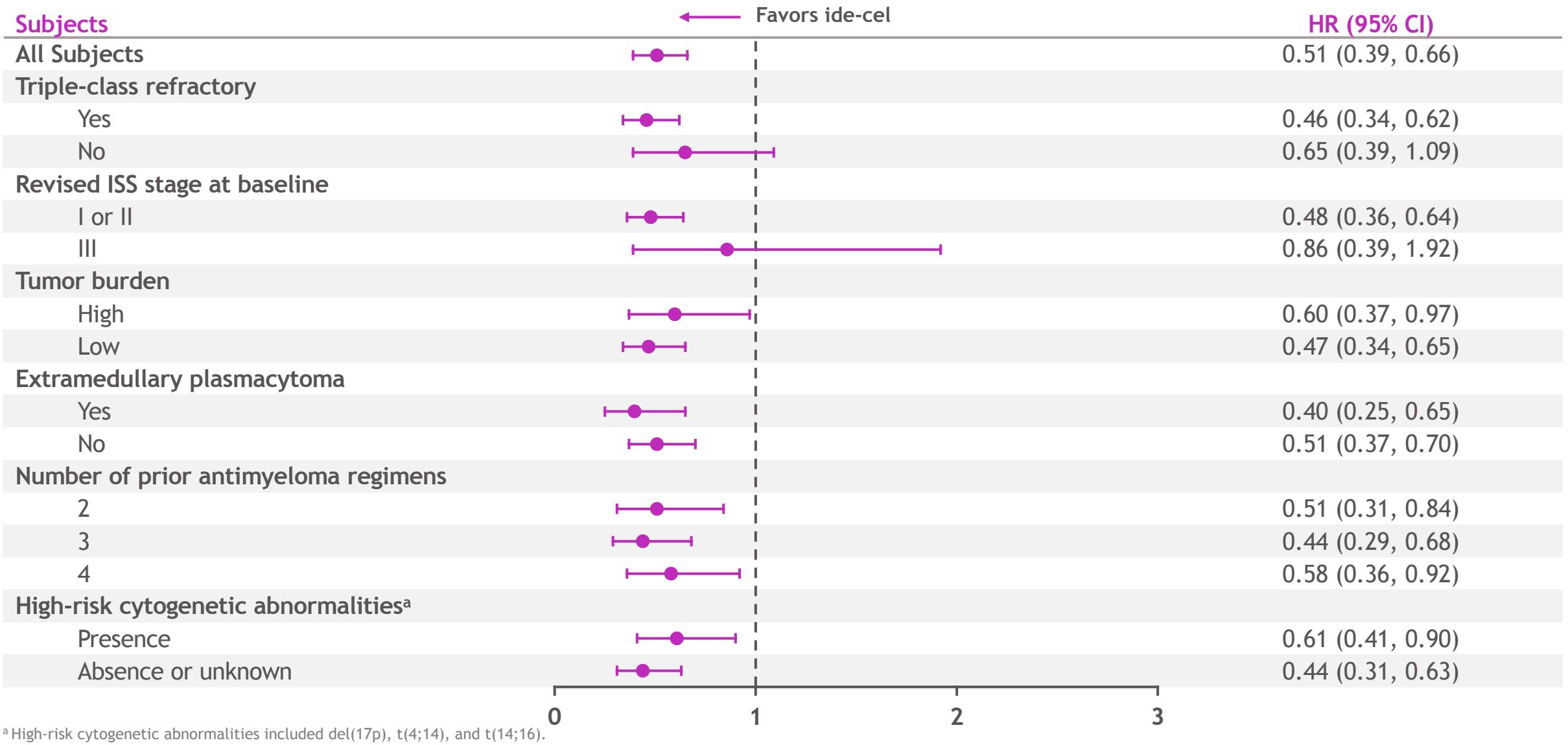
External Control for PFS (TCE RRMM)	PREAMBLE[1] (N = 194)	CONNECT-MM[2] (N = 232)	FlatIron[3] (N = 897)	COTA Vantage[3] (N = 795)	LocoMMotion[4] (N = 248)	MAMMOTH[5] (N = 275)	CARTITUDE-4[6] (N = 55)
Median PFS (mo) (95% CI)	4.9 (3.5, 5.8)	4.4 (3.0, 5.6)	4.8 (4.4, 5.3)	4.9 (4.4, 5.5)	4.6 (3.9, 5.6)	3.4 (2.8, 4.0)	4.7 (3.6, 7.5)

CI = confidence interval; HR = hazard ratio; ITT = intent to treat.

1. Ramasamy K, et al. *Hemasphere*. 2023;7(suppl):e642555a; 2. Lee JH, et al. *Clin Lymphoma Myeloma and Leuk*. 2023;23(suppl 2):S192-S193; 3. Lee H, et al. *Blood*. 2023;143(suppl 1):3775; 4. Moreau P, et al. *Hemasphere*. 2023;7(suppl):e05307aa; 5. Gandhi UH, et al. *Leukemia*. 2019;33:2266-2275; 6. Manier S, et al. 20th International Myeloma Society (IMS) Annual Meeting; September 27-30, 2023; Athens, Greece [oral].

Cutoff Date: 18APR2022

Consistent PFS benefit across subgroups (ITT)



[a] High-risk cytogenetic abnormalities included del(17p), t(4;14), and t(14;16).

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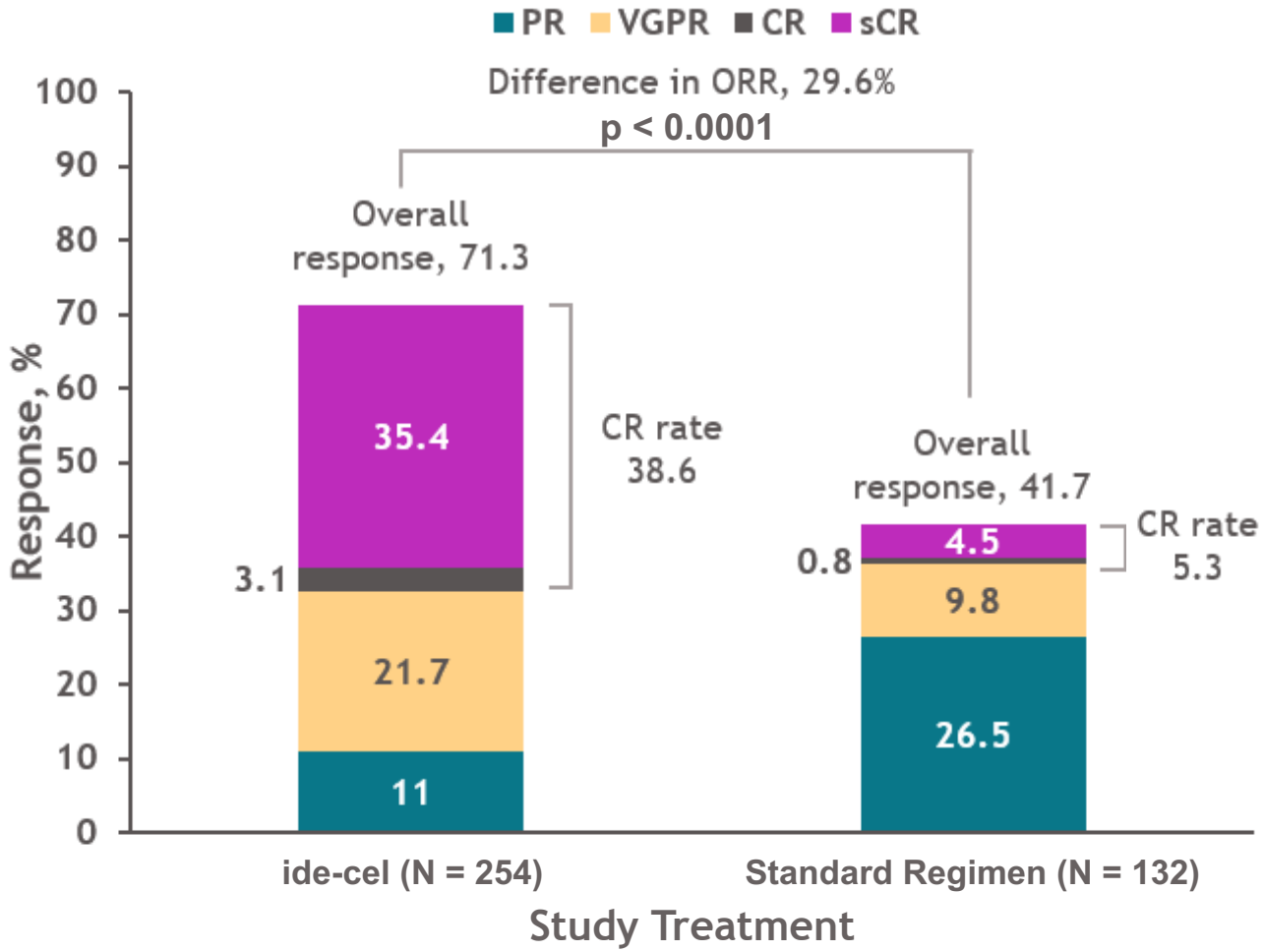
Ide-cel demonstrates significant improvement in response rates (ITT)



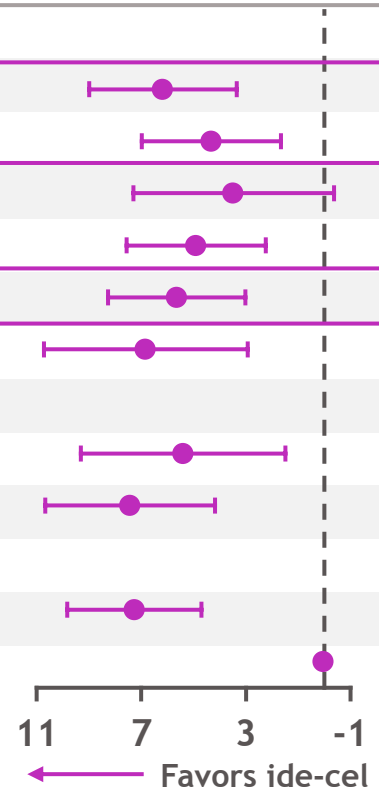
	n (%)	
	ide-cel (N = 254)	Standard Regimens (N = 132)
Median DoR (IRC) [95% CI]	14.8 mo [12.0, 18.6]	9.7 mo [5.4, 16.3]
MRD-negative CR [95% CI]	51 (20.1) [15.2, 25.0]	1 (0.8) [0.0, 2.2]

CR = complete response; DoR = duration of response; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

Ide-cel showed meaningful improvements in QoL compared to Standard Regimens

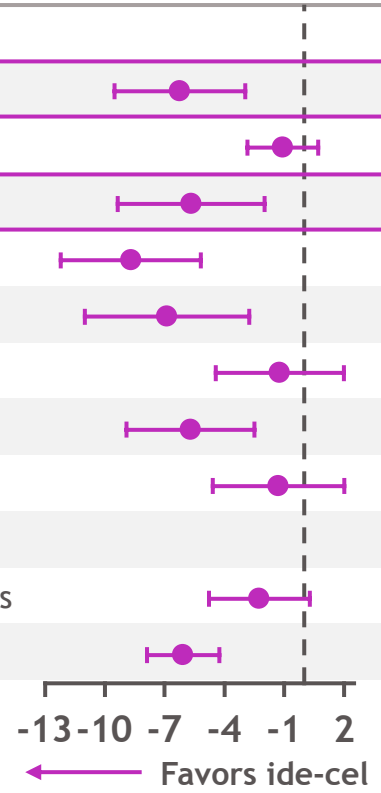
Quality-of-life and functioning domains

Domain	Difference in overall LSM change (95% CI)
EORTC QLQ-C30	
GHS/QoL	**6.17** (3.35, 8.99)
Physical functioning	**4.32** (1.66, 6.98)
Role functioning	**3.47** (-0.37, 7.30)
Emotional functioning	**4.90** (2.24, 7.56)
Cognitive functioning	**5.64** (3.02, 8.27)
Social functioning	**6.83** (2.93, 10.72)
EORTC QLQ-MY20	
Body image	**5.40** (1.49, 9.31)
Future perspective	**7.43** (4.18, 10.67)
EQ-5D-5L	
EQ-VAS	**7.26** (4.70, 9.83)
Health utility index	**0.02** (-0.01, 0.05)



MM symptoms and side-effects domains

Domain	Difference in overall LSM change (95% CI)
EORTC QLQ-C30	
Fatigue	**-6.24** (-9.52, -2.96)
Nausea/vomiting	**-1.08** (-2.85, 0.70)
Pain	**-5.68** (-9.36, -1.99)
Dyspnea	**-8.70** (-12.22, -5.19)
Insomnia	**-6.88** (-11.01, -2.76)
Appetite loss	**-1.22** (-4.44, 1.99)
Constipation	**-5.71** (-8.92, -2.50)
Diarrhea	**-1.29** (-4.59, 2.01)
EORTC QLQ-MY20	
Disease symptoms	**-2.25** (-4.78, 0.28)
Side effects	**-6.08** (-7.89, -4.26)



Delforge M, et al. Presented at American Society of Hematology annual meeting; December 9, 2023; San Diego, CA. Abstract 96 [oral].

EORTC = European Organisation for Research and Treatment of Cancer; EQ = EuroQol; GHS = global health status; QLQ-C30 = Quality-of-Life Questionnaire-Core 30; QLQ-MY20 = Quality of Life Questionnaire Multiple Myeloma Module; QoL = quality of life; VAS = visual analog scale.

KarMMa-3 demonstrates significant benefit of ide-cel in patients with TCE RRMM

- KarMMa-3 is **the first randomized phase 3 clinical study** comparing a CAR-T cell therapy with standard regimens in TCE RRMM
- Ide-cel treatment demonstrated **significant and clinically meaningful benefit in PFS**
  - Risk of disease progression or death (PFS) was **decreased by 51% with ide-cel** ($p < 0.0001$)
- Ide-cel **significantly increased the ORR** versus standard regimens ($p < 0.0001$)
- PFS and ORR benefit were consistent across preplanned subgroups
- Ide-cel led to **clinically meaningful improvement in QoL and prolonged treatment-free intervals**

KarMMa-3
Overall Survival Results

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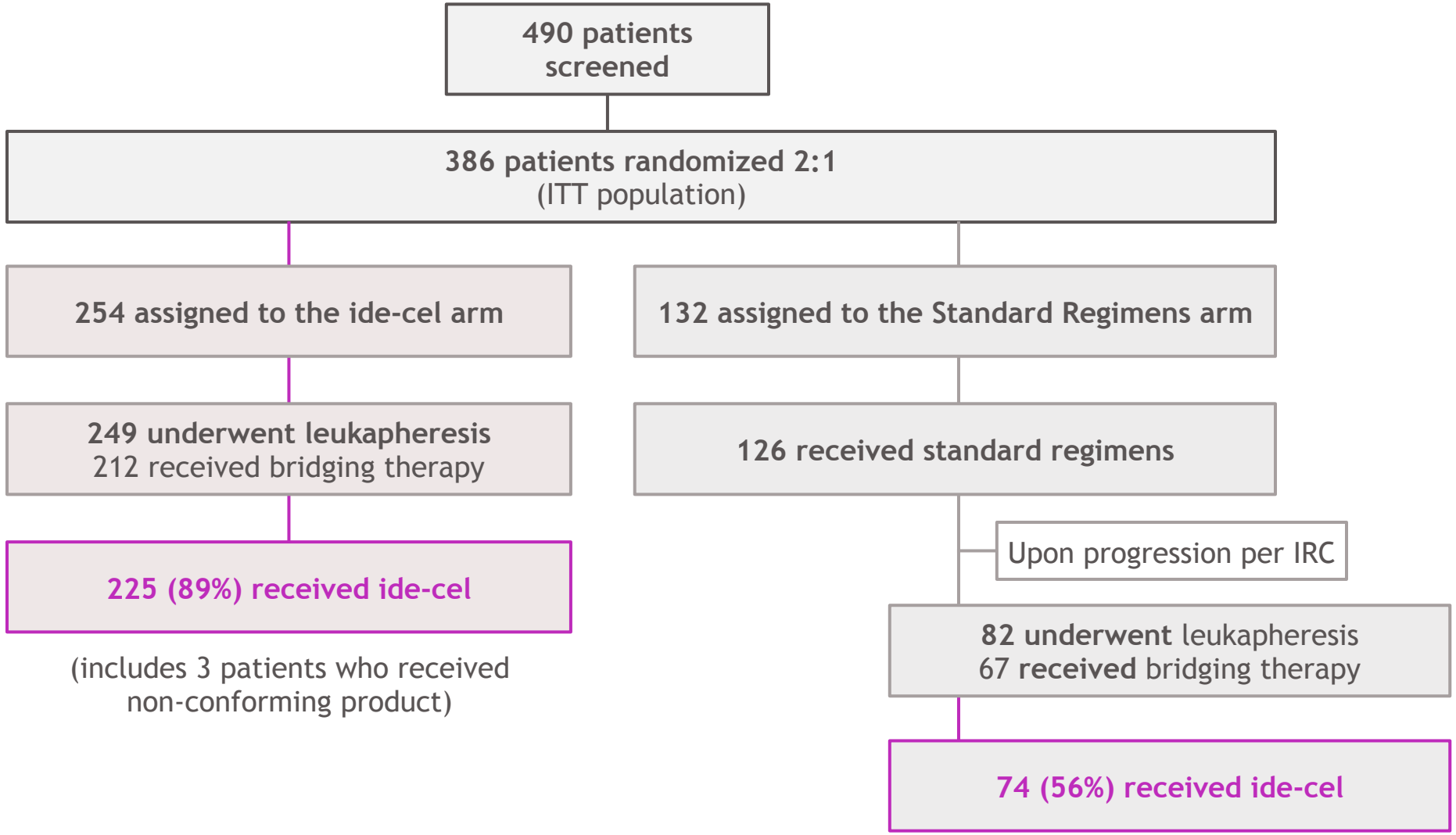
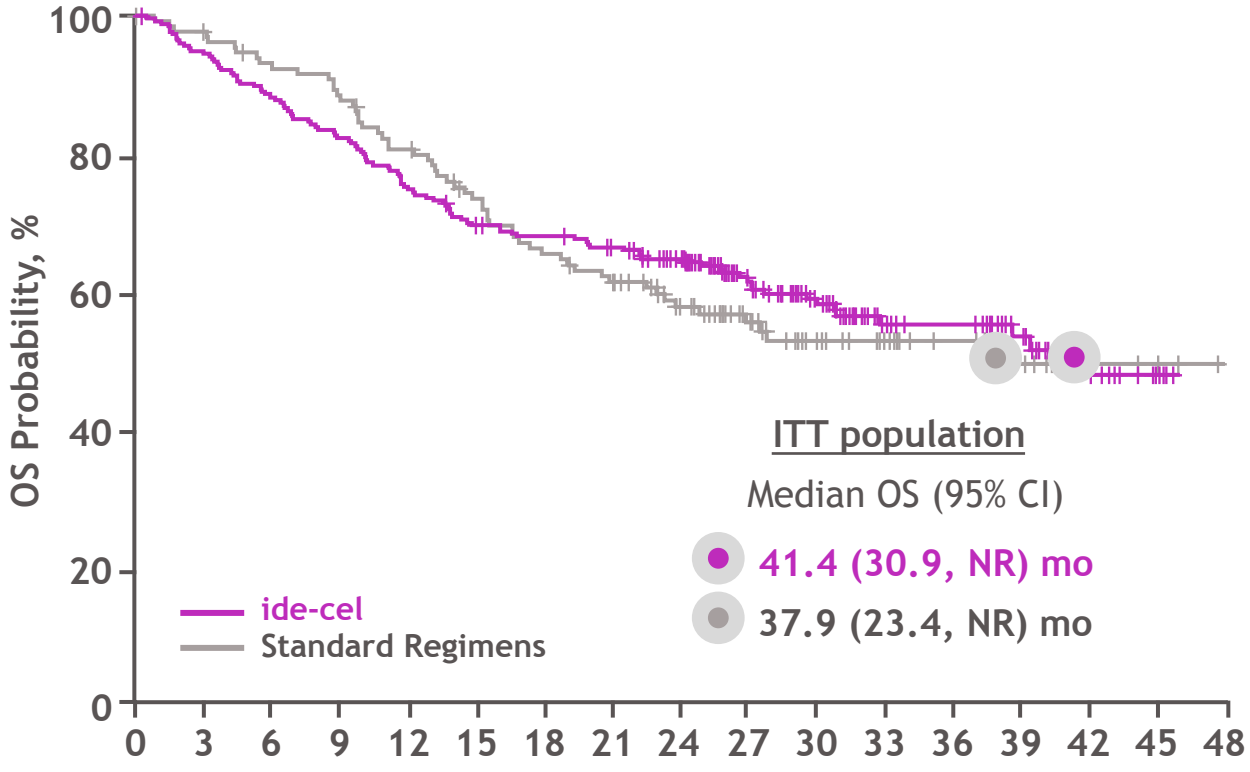
KarMMa-3: CONSORT diagram (abbreviated)



CONSORT = Consolidated Standards of Reporting Trials.

Overall survival analysis is confounded by crossover and shows no difference in the ITT population



Patients at risk:

ide-cel	254	240	223	208	190	175	169	161	143	103	75	48	44	30	13	4	0
Standard Regimens	132	128	120	114	103	91	81	75	59	45	32	24	18	11	4	3	0

HR (95% CI) = 1.01 (0.73, 1.40)

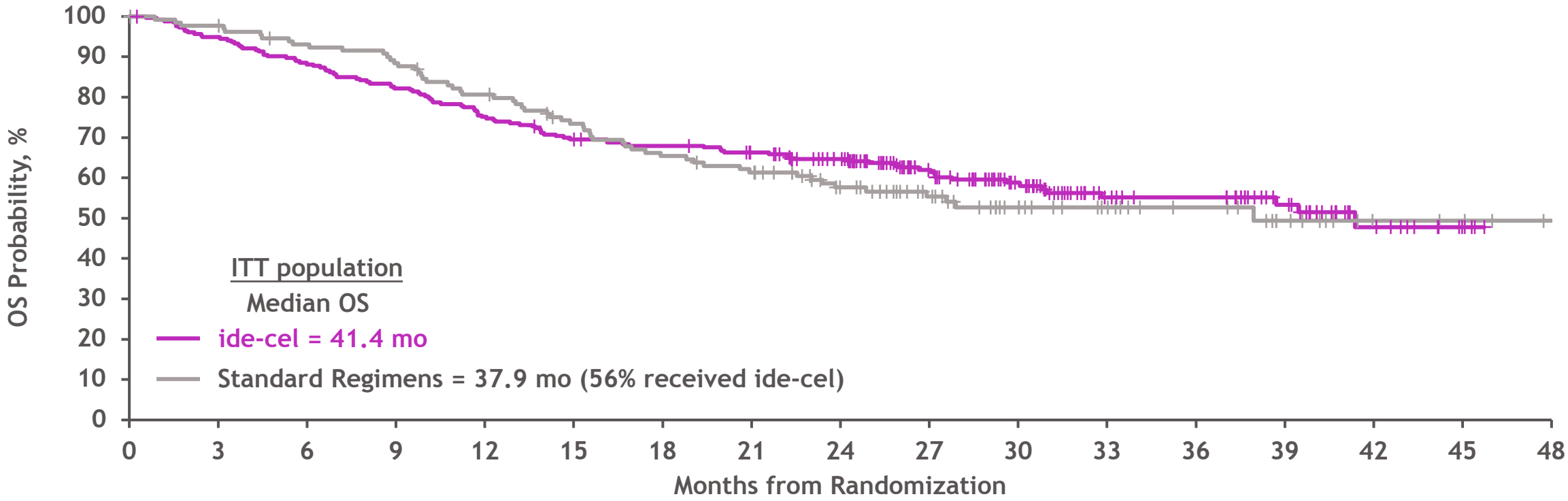
56% of patients in the Standard Regimens arm received ide-cel as part of the crossover design

Crossover affected OS early; the majority of patients crossed over within 3-16 months of randomization

Hazard Ratio < 1 from crossover adjusted analyses

Cutoff Date: 28APR2023

Ide-cel results in improved OS in both arms

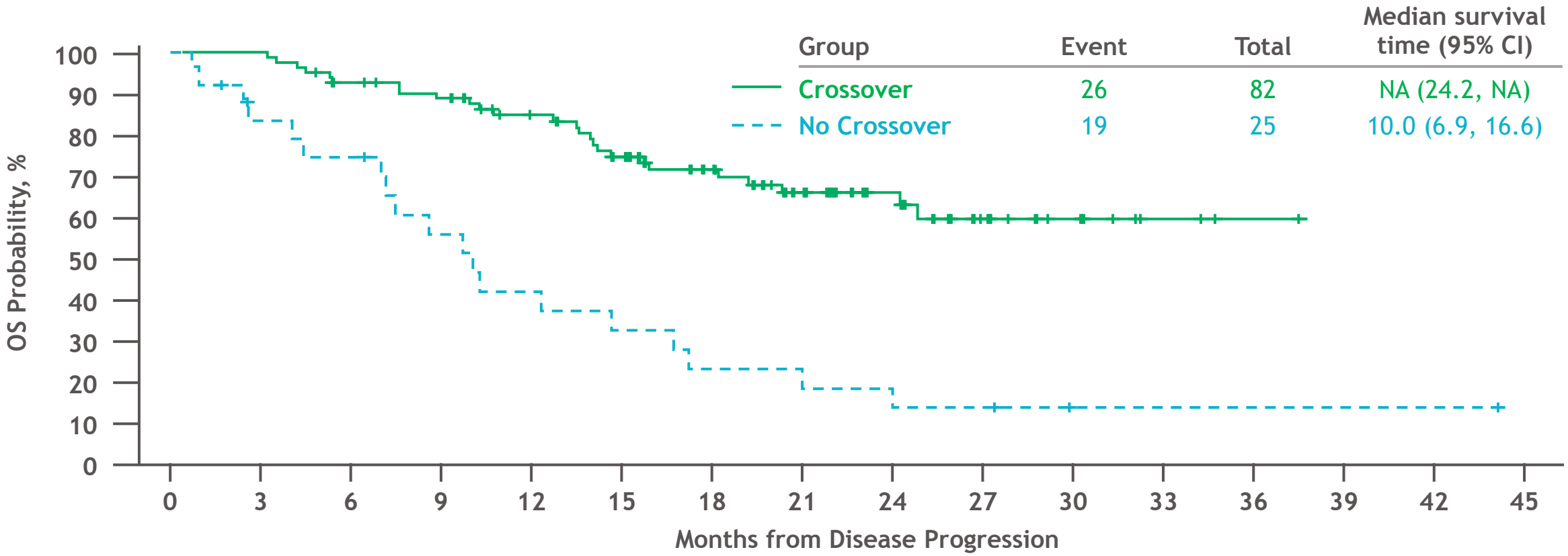


External Control for OS (TCE RRMM)	PREAMBLE[1] (N = 194)	CONNECT-MM[2] (N = 232)	FlatIron[3] (N = 897)	COTA Vantage[3] (N = 795)	LocoMMotion[4] (N = 248)	MAMMOTH[5] (N = 275)
Median OS (mo) (95% CI)	18.3 (14.0, 25.9)	12.5 (10.2, 15.3)	22.3 (19.0, 25.8)	20.4 (17.8, 23.6)	13.8 (10.8, 17.0)	9.3 (8.1, 10.6)

1. Ramasamy K, et al. *Hemasphere*. 2023;7(suppl):e642555a; 2. Lee JH, et al. *Clin Lymphoma Myeloma and Leuk*. 2023;23(suppl 2):S192-S193; 3. Lee H, et al. *Blood*. 2023;143(suppl 1):3775;
4. Moreau P, et al. *Hemasphere*. 2023;7(suppl):e05307aa; 5. Gandhi UH, et al. *Leukemia*. 2019;33:2266-2275.

Cutoff Date: 28APR2023

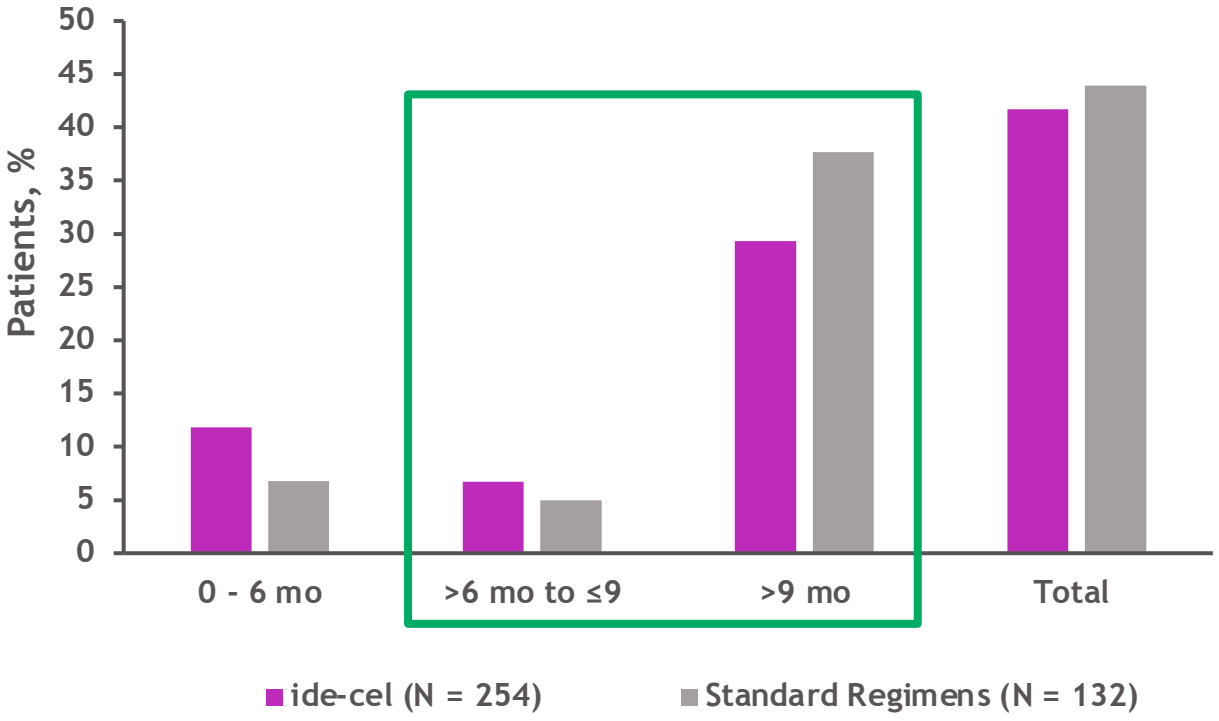
Standard Regimens arm: post-progression OS is better in patients who crossed over



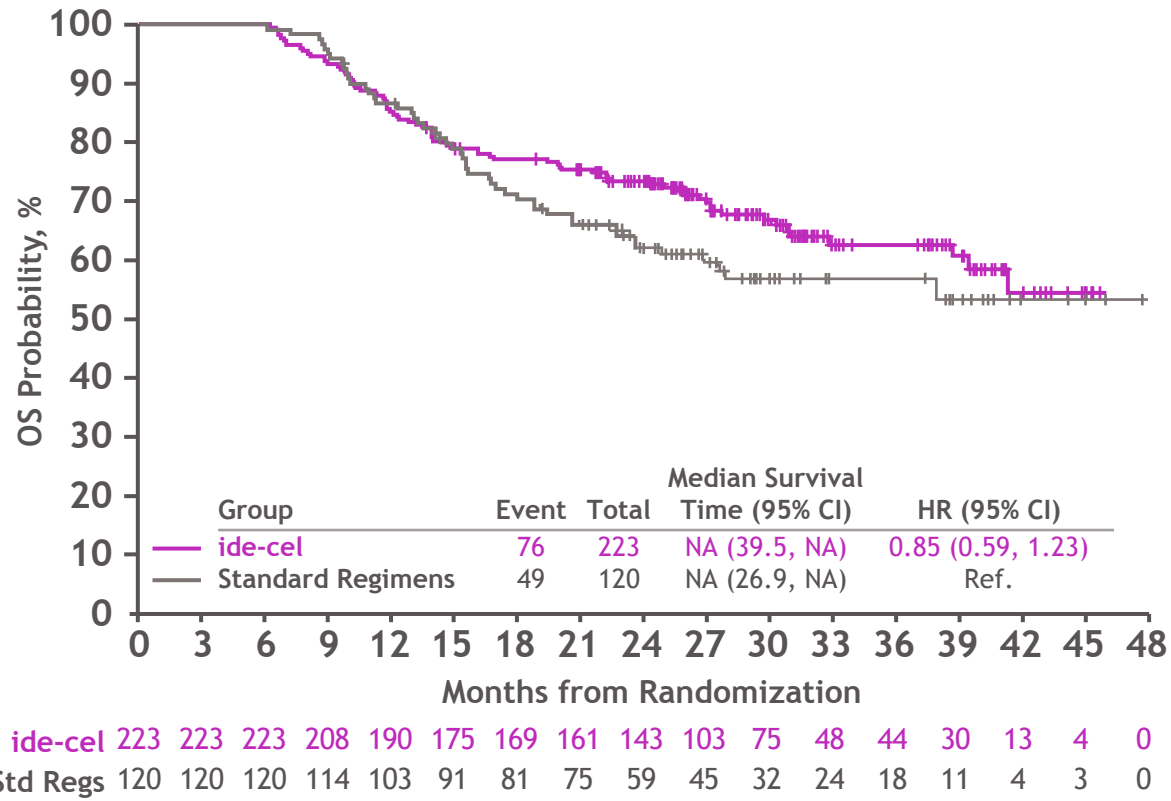
Crossover includes patients who underwent leukapheresis with or without ide-cel infusion.

OS landmark analysis at 6 months

Summary of deaths by time (ITT)



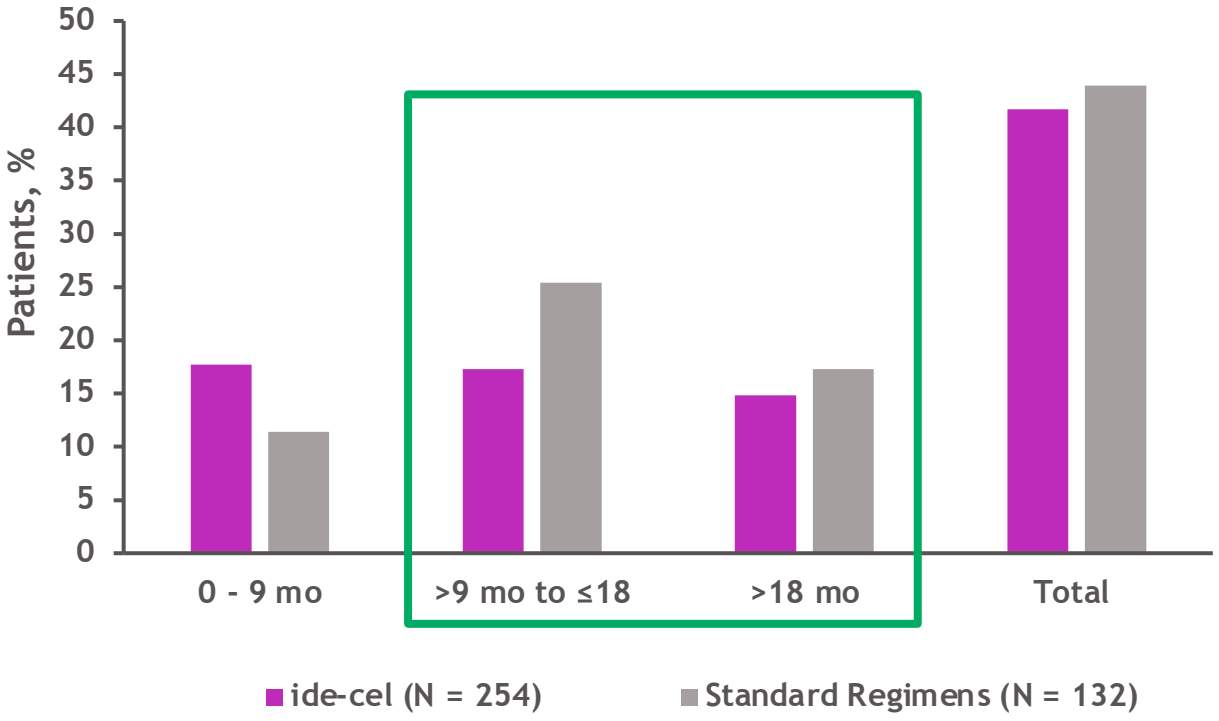
Landmark OS analysis at 6 months



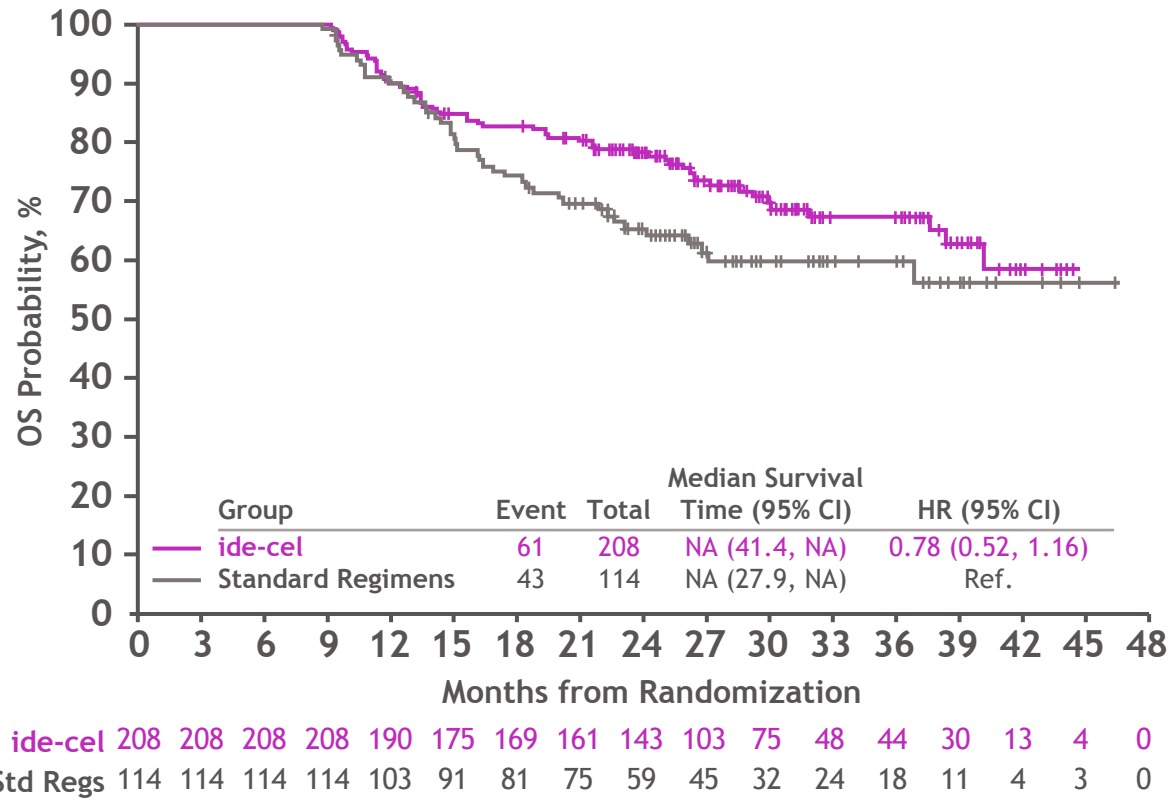
Ref = reference.

OS landmark analysis at 9 months

Summary of deaths by time (ITT)



Landmark OS analysis at 9 months



Cutoff Date: 28APR2023

What drives the OS results in the first 6 or 9 months?

Factors that did NOT contribute

- Not direct ide-cel–related mortality
- Not manufacturing delays

Factors that could have contributed

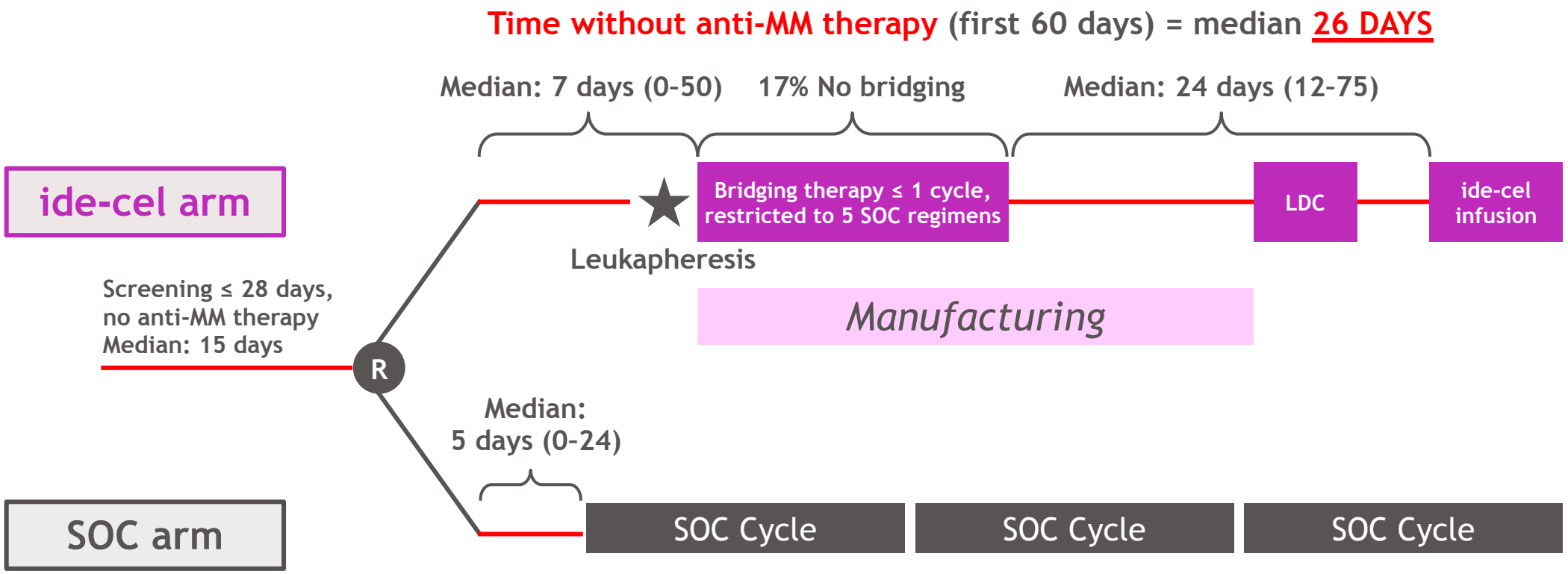
- Bridging therapy
- Random variation

Differences in early death rate (at 6 and 9 months) driven by patients who did not receive ide-cel

Deaths	≤ 6 months		≤ 9 months	
	ide-cel (N = 254) n (%)	Standard Regimens (N = 132) n (%)	ide-cel (N = 254) n (%)	Standard Regimens (N = 132) n (%)
Total number of patients who died	30 (11.8)	9 (6.8)	45 (17.7)	15 (11.4)
Number of patients who received study treatment	13 (5.1)	9 (6.8)	25 (9.8)	15 (11.4)
Primary reason for death				
AE	5 (2.0)	3 (2.3)	7 (2.8)	5 (3.8)
Progressive disease	5 (2.0)	6 (4.5)	12 (4.7)	9 (6.8)
Other cause	3 (1.2)	0	6 (2.4)	1 (0.8)
Number of patients who did not receive study treatment	17 (6.7)	0	20 (7.9)	0
Primary reason for death				
AE	3 (1.2)	0	3 (1.2)	0
Progressive disease	13 (5.1)	0	15 (5.9)	0
Other cause	1 (0.4)	0	2 (0.8)	0

AE = adverse event.

Protocol specifications led to more time without antimyeloma therapy in the ide-cel arm in the first 60 days

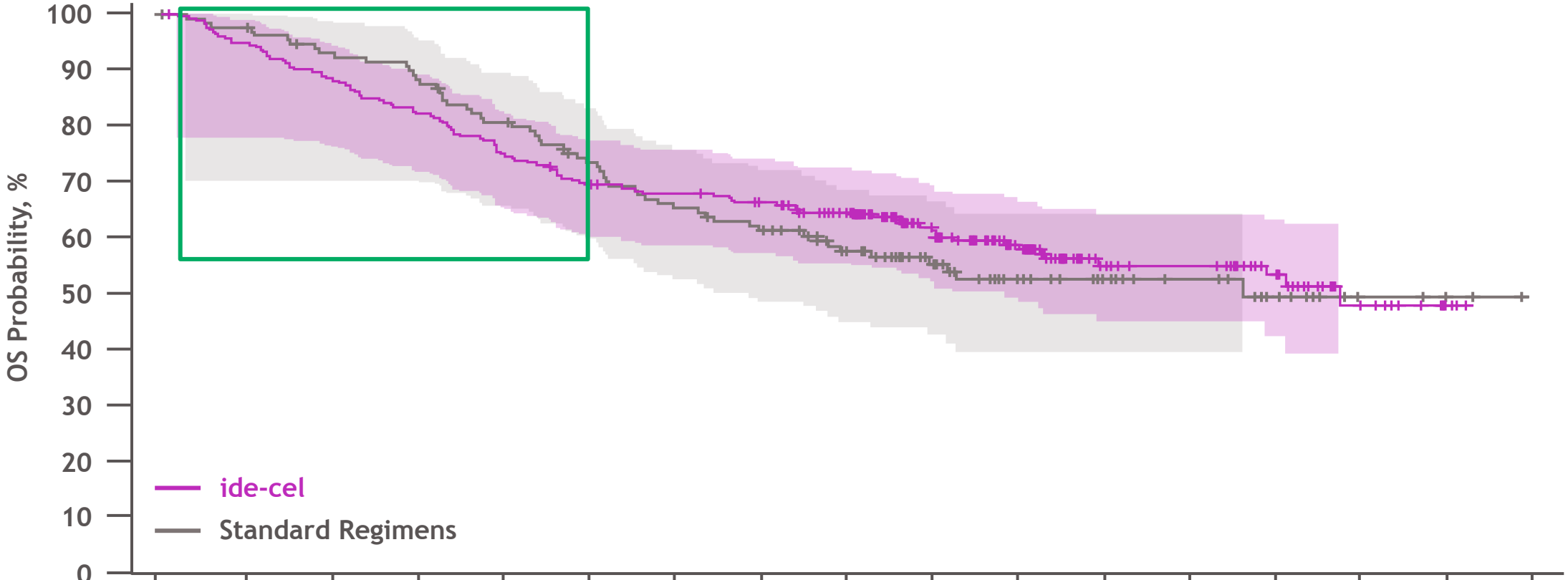


Patients with early death were enriched for high-risk factors, a group where effective bridging therapy is critical

	ide-cel		Standard Regimens	
Baseline characteristics, n (%)	Deaths ≤ 6 months from randomization (N = 30)	ITT population (N = 254)	Deaths ≤ 6 months from randomization (N = 9)	ITT population (N = 132)
R-ISS stage III	9 (30%)	31 (12%)	2 (22%)	14 (11%)
High-risk cytogenetics[a]	21 (70%)	107 (42%)	6 (67%)	61 (46%)
Extramedullary plasmacytoma	12 (40%)	61 (24%)	3 (33%)	32 (24%)
High tumor burden[b]	14 (47%)	71 (28%)	2 (22%)	34 (26%)

[a] Included del17p13 (reflective of del[17p]), t(14;16), or t(4;14); [b] Low tumor burden: < 50%, high tumor burden: ≥ 50%.

Overall survival: overlapping confidence intervals



ide-cel	254	240	223	208	190	175	169	161	143	103	75	48	44	30	13	4	0
Standard Regimens	132	128	120	114	103	91	81	75	59	45	32	24	18	11	4	3	0

Cutoff Date: 28APR2023

Summary of overall survival

KarMMa-3 design allowed crossover, confounding OS interpretation

- Numerically higher number of **early deaths** driven by **patients who did not receive ide-cel**
- **No increased ide-cel–associated mortality** compared to standard regimens

Ide-cel resulted in improved OS in both arms

- OS with standard regimens substantially longer than expected for this patient population
- **Individualized bridging** is required to allow patients to receive ide-cel
- CAR-T therapy is prescribed by dedicated experts at qualified centers who have **deep knowledge of how to treat and bridge patients**

Clinical Safety

Mark Cook, MBChB, PhD
Senior Clinical Trial Physician
BMS

Bristol Myers Squibb™

Selected adverse events of special interest for ide-cel

- ≥ Grade 3 AE of CRS
- ≥ Grade 3 AE of neurologic toxicity
- ≥ Grade 3 AE of infection
- New malignancies including SPMs

AE = adverse event; CRS = cytokine release syndrome; SPM = second primary malignancy.

Low incidence of ≥ grade 3 cytokine release syndrome (CRS) in patients treated with ide-cel

	ide-cel (N = 225)
Cytokine release syndrome (CRS),[a] n (%)	
Any grade	197 (88)
Grade 3/4	9 (4)
Grade 5	2 (1)
Median (range) time to first onset, days[b]	1.0 (1.0–14.0)
Median (range) duration, days[c]	3.5 (1.0–51.0)

Two grade 5 CRS events:

- 1 from multi-organ failure, day 6 after ide-cel infusion
- 1 from concomitant grade 5 *Candida* sepsis, day 21 after ide-cel infusion

Overall incidence, severity, onset, and resolution consistent with previously reported safety profile

[a] CRS was graded according to Lee's criteria[1]; [b] Time to first onset of CRS: first start date of CRS – infusion date + 1; [c] Ongoing CRS was excluded from calculation of duration of CRS.

1. Lee DW, et al. *Blood*. 2014;124:188-195.

Low incidence of ≥ grade 3 investigator-identified neurotoxicity (iiNT) in patients treated with ide-cel

	ide-cel (N = 225)
Investigator-identified neurotoxicity (iiNT),[a] n (%)	
Any grade	34 (15)
Grade 3/4	7 (3)
Grade 5	0
Median (range) time to first onset, days[b]	3.0 (1.0–317.0)
Median (range) duration, days[c]	2.0 (1.0–37.0)

Severity, incidence, onset, and time to recovery was consistent with previously reported safety profile

No parkinsonism or Guillain-Barré Syndrome reported

[a] Includes immune effector cell-associated neurotoxicity syndrome reported by investigator as a neurological toxicity AE; [b] Time to first onset of iiNT: first start date of iiNT – infusion date + 1; [c] Ongoing iiNT was excluded from calculation of duration of iiNT.

Higher rates of cytopenias in the ide-cel arm

	ide-cel (N = 225)			Standard Regimens (N = 126)		
	Any Grade (%)	Grade 3/4 (%)	Grade 5 (%)	Any Grade (%)	Grade 3/4 (%)	Grade 5 (%)
Cytopenia	**91.6**	**89.8**	**0**	**72.2**	**60.3**	**0**
Neutropenia	85.8	84.0	0	45.2	40.5	0
Anemia	67.1	50.7	0	35.7	18.3	0
Thrombocytopenia	56.0	44.0	0	29.4	17.5	0
Lymphopenia	32.0	31.1	0	19.8	18.3	0
Febrile neutropenia	8.9	8.9	0	2.4	1.6	0
Infections	**61.3**	**24.4**	**4.4**	**54.0**	**18.3**	**2.4**
Pathogen unspecified	40.9	13.3	2.2	33.3	9.5	0
Viral	22.2	8.0	0.9	21.4	6.3	0.8
Bacterial	18.7	6.2	0.4	15.9	8.7	0.8
Fungal	6.7	2.2	0.9	5.6	0.8	0

Overall safety profile of ide-cel remains consistent

Treated population, n (%)	ide-cel (N = 225)	Standard Regimens (N = 126)
Any-grade AE	225 (100)	124 (98)
Serious AE	105 (47)	52 (41)

ITT population, n (%)	ide-cel (N = 254)	Standard Regimens (N = 132)
Overall deaths	106 (42)	58 (44)
Cause of death		
Disease progression	64 (25)	37 (28)
AEs	17 (7)	8 (6)
Other causes	23 (9)	12 (9)
SPMs[a]	2 (1)	1 (1)

Similar rates of deaths due to AEs in the ide-cel and Standard Regimens arms

No new safety signals

[a] Deaths due to SPMs in the ide-cel arm were leukemia (n = 1) and pancreatic adenocarcinoma (n = 1); death due to SPMs in the Standard Regimens arm was malignant neoplasm of unknown primary site (n = 1).

Summary of second primary malignancies (SPMs)

	ide-cel (N = 225) n (%)	Standard Regimens (N = 126) n (%)
Subjects ≥ 1 SPM	15 (6.7)	5 (4.0)
Invasive SPMs[a]	**11 (4.9)**	**3 (2.4)**
Myelodysplastic syndrome	4 (1.8)	0
Acute myeloid leukemia	1 (0.4)	0

Invasive SPMs Incidence/100 person-years (95% CI)

ide-cel	Standard Regimens
2.93 (1.62, 5.28)	**2.61** (0.84, 8.09)

No SPMs of T-cell origin were reported in the ide-cel arm

Incidence of invasive SPMs, including MDS and AML, as expected in this RRMM population

AML = acute myeloid leukemia; MDS = myelodysplastic syndrome.

[a] Invasive SPMs exclude: basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the breast, incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system) or prostate cancer that can be treated with curative intent.

Summary of safety

No new safety concerns identified in KarMMa-3

Deaths due to AEs were similar across arms

No cases of Guillain-Barré Syndrome, parkinsonism, or T-cell malignancies

No increase in incidence of invasive SPM

CRS and CAR-T associated neurotoxicity was generally low-grade and manageable

Clinical Perspective on Benefits and Risks of Ide-cel Treatment for Triple-class Exposed Multiple Myeloma Patients

Noopur Raje, MD
Director, Center for Multiple Myeloma
Massachusetts General Hospital
Professor of Medicine
Harvard Medical School

KarMMa-3 trial

KarMMa-3 addresses a growing treatment gap

Patient-centric design allowing crossover confounds OS assessment (~60% crossed over)

Bridging therapy specifications in the trial:

- Optional bridging therapy (limited to 1 cycle)
- Minimum washout period
- Limited to treatment options used in Standard Regimens arm

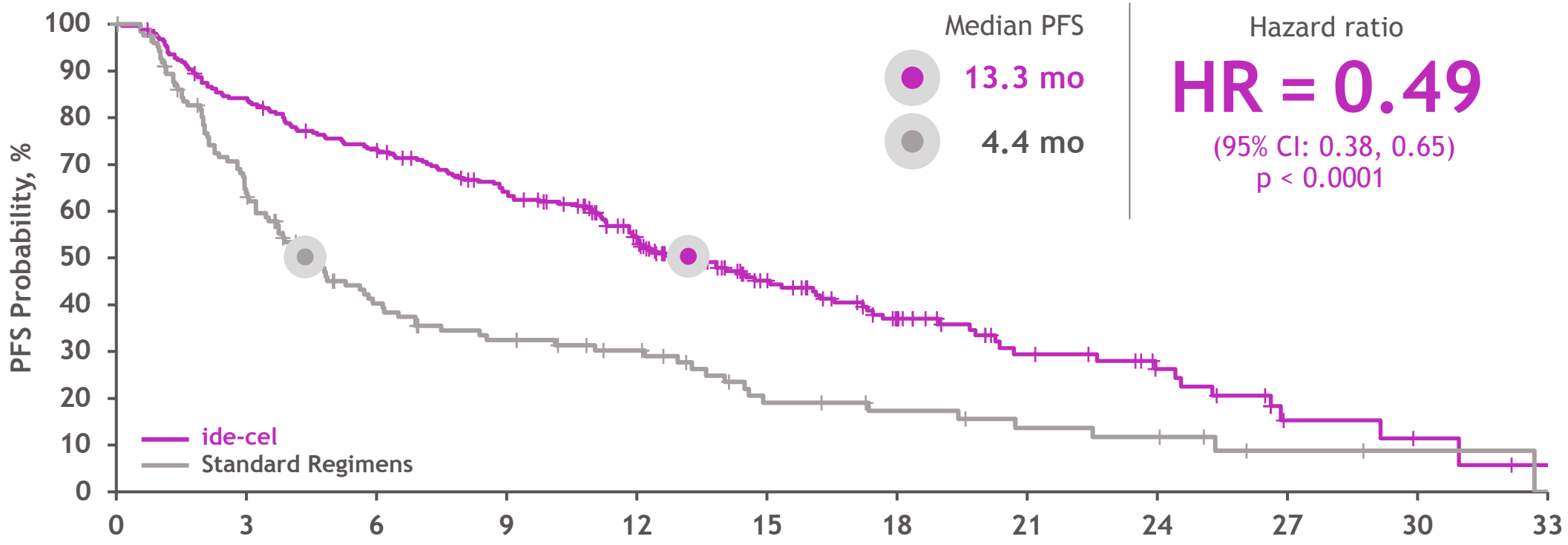
KarMMa-3 enrolled patients with high-risk, difficult-to-treat disease

Characteristic	ide-cel (N = 254)	Standard Regimens (N = 132)
Median (range) age, years	63 (30-81)	63 (42-83)
Median (range) time from diagnosis to screening, years	4.1 (0.6-21.8)	4.0 (0.7-17.7)
R-ISS disease stage, n (%)		
I/II	50 (20)/150 (59)	26 (20)/82 (62)
III	31 (12)	14 (11)
Extramedullary plasmacytoma, n (%)	61 (24)	32 (24)
High tumor burden, n (%)	71 (28)	34 (26)
High-risk cytogenetics, n (%)	107 (42)	61 (46)
Median (range) time to progression on last prior antimyeloma therapy, months	7.1 (0.7-67.7)	6.9 (0.4-66.0)
Median (range) prior lines of therapy	3 (2-4)	3 (2-4)
Median (range) prior anti-myeloma regimens per year since diagnosis	0.7 (0.1-8.1)	0.7 (0.2-3.2)
Triple-class refractory, n (%)	164 (65)	89 (67)
Refractory to daratumumab	242 (95)	123 (93)

R-ISS = Revised International Staging System.

Does ide-cel offer a clinically meaningful benefit for patients with TCE RRMM?

Ide-cel shows a clinically meaningful PFS benefit in patients with difficult-to-treat disease

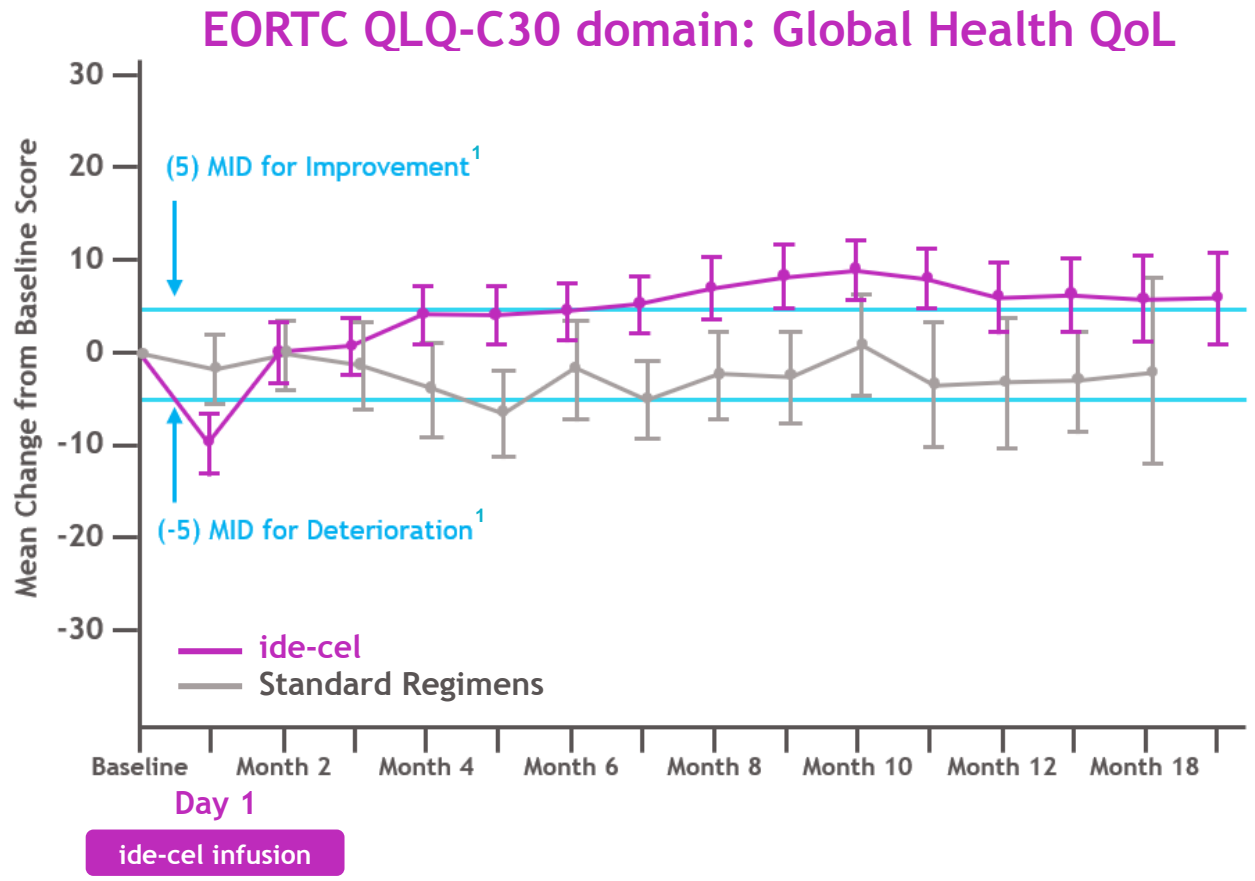


Patients at Risk:												
ide-cel	254	206	178	149	110	62	40	22	14	4	2	0
Standard Regimens	132	75	42	32	25	13	10	7	6	2	1	0

Cutoff Date: 18APR2022

The benefits of ide-cel in TCE RRMM are clinically meaningful

- **PFS is an established clinical endpoint**
  - Basis for treatment selection
- **Treatment goal is prolonging time to progression**
  - Progression associated with significant complications
- **Ide-cel achieves a long treatment-free period with a one-time therapy**
  - Myeloma dominated by chronic, continuous therapy
- **QoL improvement in favor of ide-cel**



QoL = quality of life; MID = minimal important difference.

1. MID per Cocks K, et al. *Eur J Cancer*. 2012;48:1713-1721.

Can we manage the safety profile of ide-cel?

Ide-cel has a well-characterized and manageable safety profile

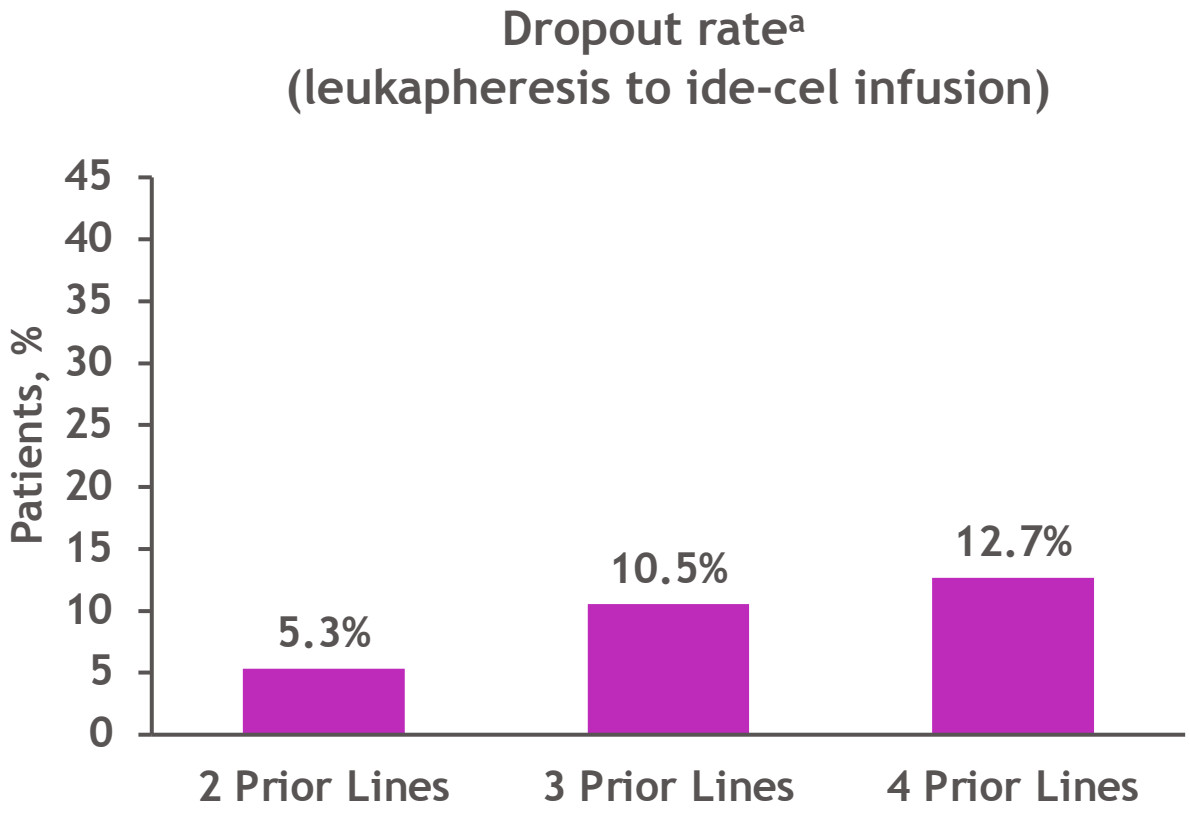
- Safety profile is **predictable** and **manageable**, including cytopenias, CRS, and neurotoxicity
  - CAR-T therapy is **administered by CAR-T cell experts at qualified centers** who are used to managing the specific side effects
- Real-world data have reproduced clinical trial results in **> 800 patients**[1]

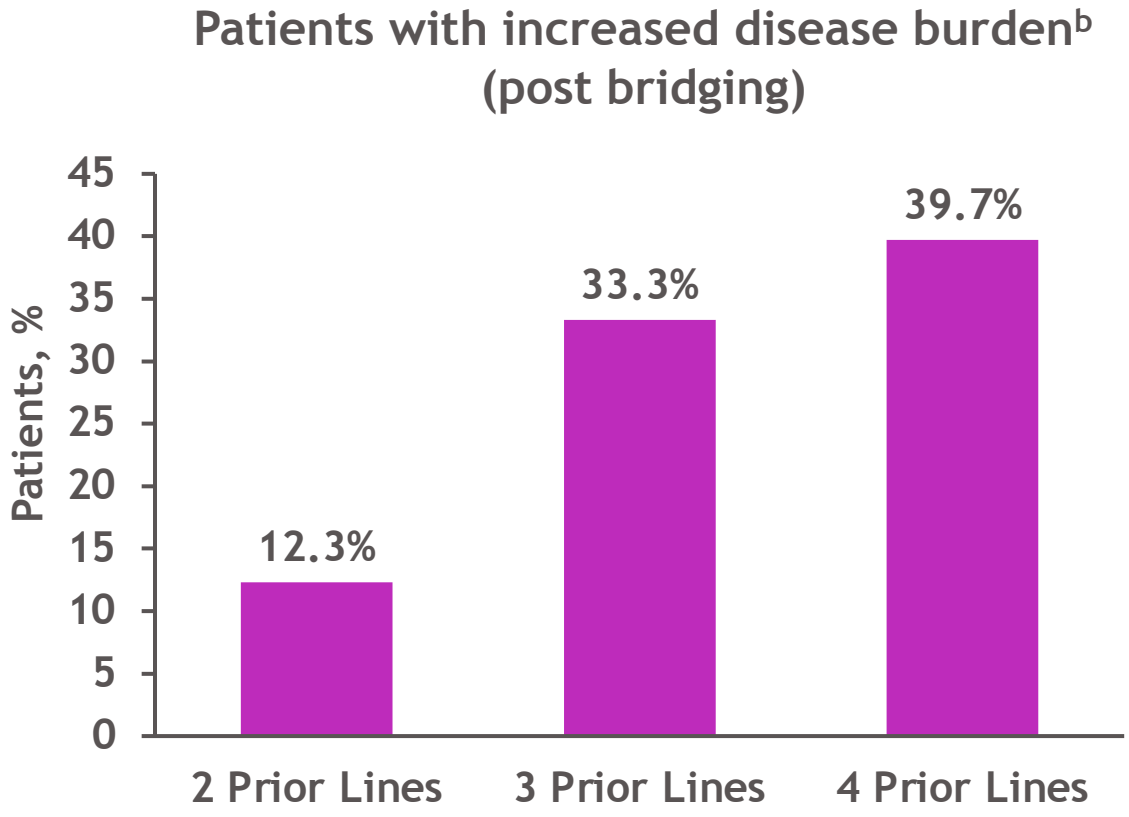
- **No new safety signal** in KarMMa-3 versus KarMMa as well as in the real-world setting
- Observed imbalance in early deaths is **not due to ide-cel–related toxicity**

1. Sidana S, et al. *Blood*. 2023;142(suppl 1): Abstract 1027.

Why should we use ide-cel earlier in the course of disease?

KarMMa-3: earlier-line treatment improves ability to receive ide-cel and benefit from bridging therapy

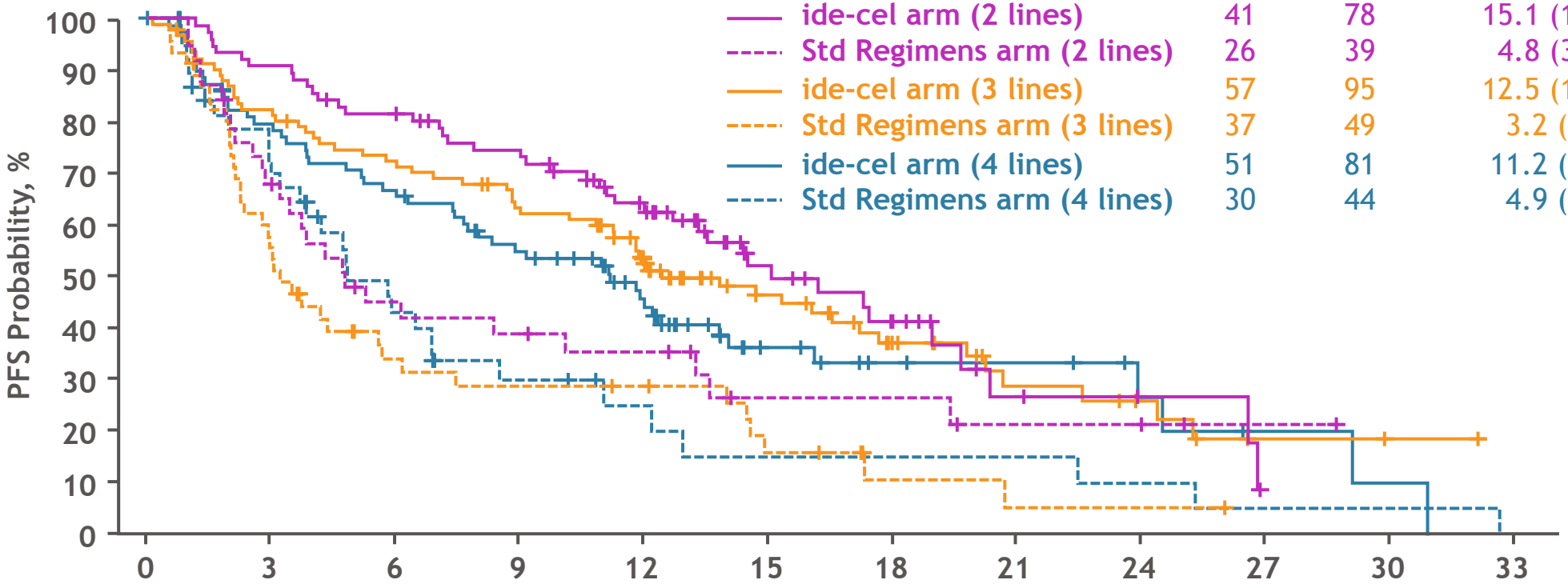




[a] Dropout rate = % of patients who discontinued between leukapheresis and ide-cel infusion; [b] Increase in disease burden = a rise of 25% or more in measurable disease parameter in those with measurable disease from leukapheresis to last assessment before ide-cel administration.

KarMMa-3: greatest PFS benefit of ide-cel in earlier treatment line

Group	Event	Total	Median PFS (95% CI)
ide-cel arm (2 lines)	41	78	15.1 (12.7, 19.7)
Std Regimens arm (2 lines)	26	39	4.8 (3.2, 13.3)
ide-cel arm (3 lines)	57	95	12.5 (10.8, 17.7)
Std Regimens arm (3 lines)	37	49	3.2 (2.3, 5.7)
ide-cel arm (4 lines)	51	81	11.2 (7.4, 14.1)
Std Regimens arm (4 lines)	30	44	4.9 (3.2, 6.9)



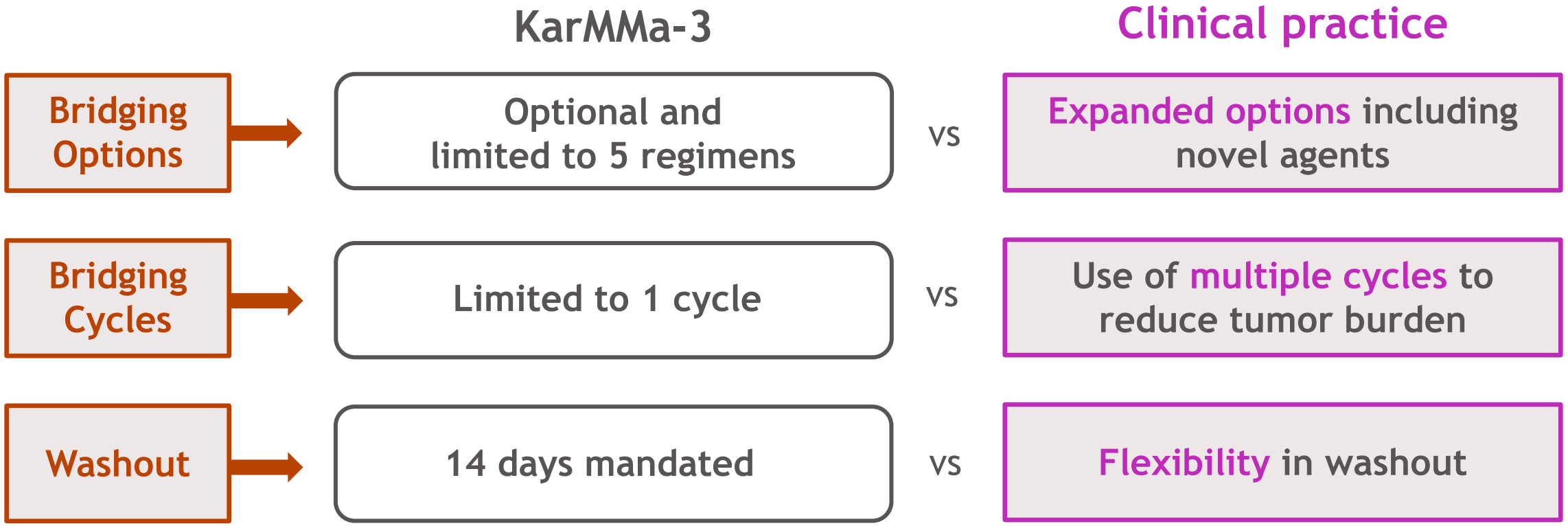
Patients at Risk

ide-cel arm (2 lines)	78	69	61	53	40	22	14	5	3	0	
Std Regimens arm (2 lines)	39	25	15	13	10	5	5	3	3	1	0
ide-cel arm (3 lines)	95	75	65	55	42	27	18	10	7	2	1
Std Regimens arm (3 lines)	49	25	13	11	10	5	2	1	1	0	
ide-cel arm (4 lines)	81	62	52	41	28	13	8	7	4	2	1
Std Regimens arm (4 lines)	44	25	14	8	5	3	3	3	2	1	1

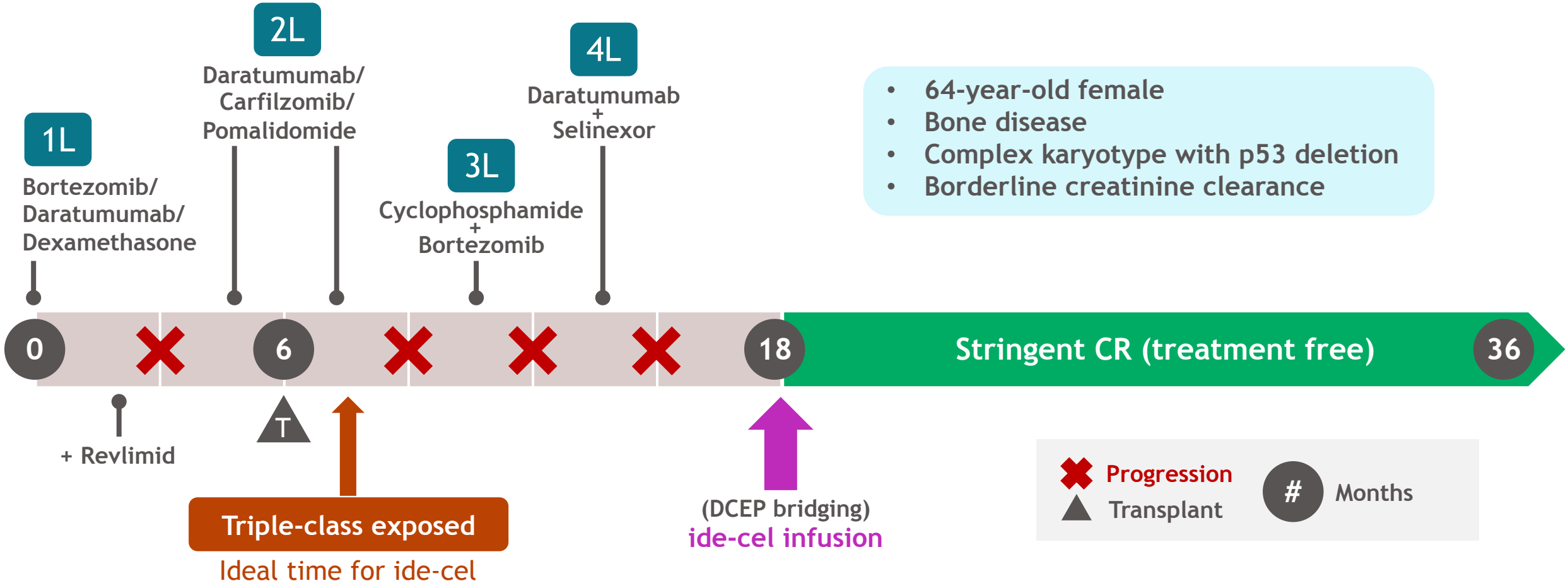
Cutoff Date: 18APR2022

How can we bridge patients to ide-cel effectively?

Bridging to ide-cel: differences between KarMMa-3 and clinical practice



Today's patient journey with myeloma



- 64-year-old female
- Bone disease
- Complex karyotype with p53 deletion
- Borderline creatinine clearance

DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin.

Clinical perspective on the favorable benefit/risk profile of ide-cel in patients with TCE RRMM

- **High unmet medical need** in TCE RRMM, a growing segment of patients who become triple-class exposed early in the disease course
- **Clinically meaningful benefit in PFS** with long treatment-free interval, a clinically relevant endpoint for clinicians and patients
- **Clinically meaningful improvement in quality of life** after a single infusion

- **No new safety signal observed**, no increase in ide-cel–related deaths
- **Earlier use is critical** to enable optimal PFS benefit and effective bridging
- **Early death in KarMMa-3 was disease related and can be mitigated** in the real-world setting

Ide-cel has an overall favorable benefit-risk in patients with triple-class exposed multiple myeloma

Thank you

Back up Slides Shown

OS restricted mean survival time (RMST)

RMST up to	Ide-cel (months)	Standard Regimens (months)	Difference (95% CI) (months)
31 months (median follow-up time)	23.08	23.02	0.06 (-2.1, 2.2)

With 31 months of OS follow-up, the average survival time is similar between ide-cel and standard regimen arm.

Summary of Deaths per FDA within 9m of randomization

ITT population

Primary Reason for Death	ide-cel N=254		Standard Regimens N=132	
	Subjects (n=254)	Subjects Who Received Subsequent AMT (n=146)	Subjects (n=132)	Subjects who received ide-cel as crossover (n=74)
Total Deaths n (%)	**106 (41.7)**	**61 (41.8)**	**58 (43.9)**	**21 (28.4)**
PD n (%)	60 (23.6)	44 (30.1)	36 (27.3)	15 (20.3)
From AE n (%)	29 (11.4)	8 (5.5)	14 (10.6)	4 (5.4)
Unknown n (%)	17 (6.7)	9 (6.2)	8 (6.1)	2 (2.7)
Deaths ≤ 9m after randomization	**45[1] (17.7)**	**14 (9.6)**	**15 (11.4)**	**3 (4.1)**
PD n (%)	25 (9.8)	11 (7.5)	9 (6.8)	2 (2.7)
From AE n (%)	14 (5.5)	2 (1.4)	6 (4.5)	1 (1.4)
Unknown n (%)	6[2] (2.4)	1 (0.7)	0	0

Data cutoff 28Apr23

Table includes all deaths after randomization from AEs including infection related AEs following disease progression and subsequent AMT.

1. Out of the 45 early deaths in ide-cel arm, 20 did not receive ide-cel
2. Out of the 6 unknown cause of death ≤ 9m, 4 subjects died after PD by Investigator, 1 subject died after PD and SAMT, 3 subjects withdrew consent, 2 subjects did not receive ide-cel

Ide-cel arm: Reasons for not receiving ide-cel

	Not received Ide-cel infusion		
	Died <=6 months (N=17)	Alive at 6 months (N=12)	Total (N=29)
Subject who discontinued after randomization without receiving ide-cel	17 (100.0)	12 (100.0)	29 (100.0)
Reason for pre-treatment discontinuation n (%)			
Failure to meet treatment criteria	6 (35.3)	2 (16.7)	8 (27.6)
Physician decision*	4 (23.5)	2 (16.7)	6 (20.7)
Adverse event	2 (11.8)	3 (25.0)	5 (17.2)
Death	4 (23.5)	0	4 (13.8)
Study drug manufacturing failure	1 (5.9)	2 (16.7)	3 (10.3)
Withdrawal by subject	0	3 (25.0)	3 (10.3)

* Patients with rapid progressive disease who died soon after discontinuation. In most of cases, they received an alternative treatment while ide-cel was being manufactured

DCO 28Apr2023

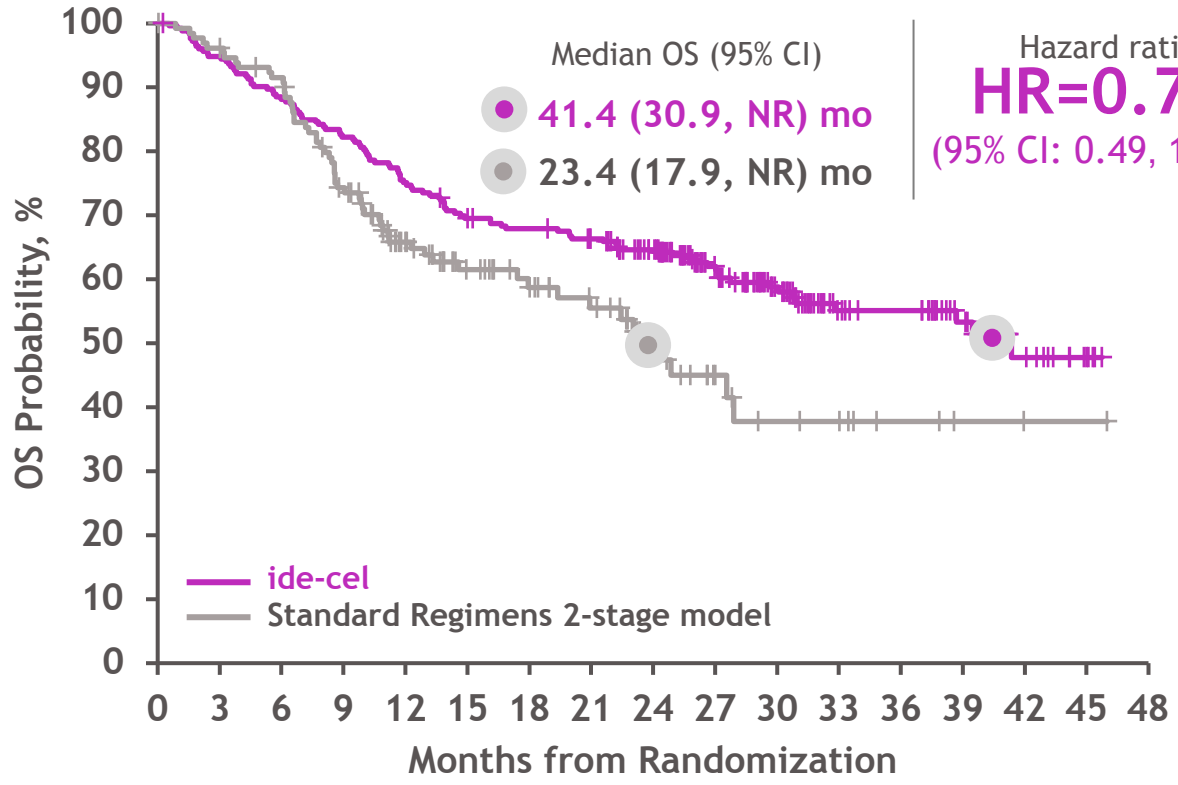
Bridging Therapy in the ide-cel arm: early deaths vs ITT population

	Not received ide-cel infusion	Received ide-cel infusion		
	Died ≤6 months (N=17)	Died ≤6 months (N=13)	All Early Deaths (n=30)	ITT population (N=254)
No bridging therapy	4 (23.5)	1 (7.7)	5 (16.7)	42 (16.5)
Patients who received bridging therapies - n (%)	13 (76.5)	12 (92.3)	25 (83.3)	212 (83.5)
DVd	0	2 (15.4)	2 (6.7)	21 (8.3)
DPd	4 (23.5)	3 (23.1)	7 (23.3)	50 (19.7)
EPd	4 (23.5)	2 (15.4)	6 (20.0)	61 (24.0)
IRd	2 (11.8)	1 (7.7)	3 (10.0)	27 (10.6)
Kd	1 (5.9)	1 (7.7)	2 (6.7)	29 (11.4)
Other	2 (11.8)	3 (23.1)	5 (16.7)	24 (9.4)
Median treatment-free days	22	21	21.5	26
Duration of bridging therapy (days)				
Median	24.0	22.0	22.0	22.0
Increase in disease burden after BT	5 (29)	7 (54)	12 (40)	

DCO Apr2023

Hazard Ratios from prespecified crossover adjusted OS analyses favor ide-cel

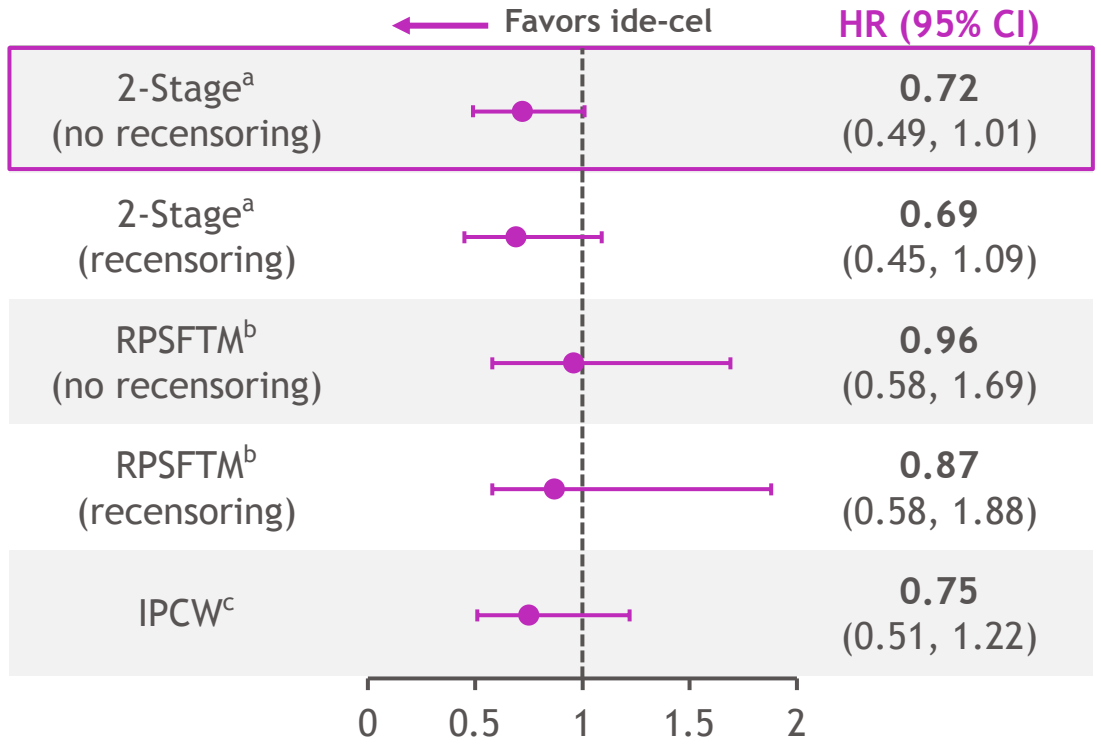
OS Sensitivity Analysis Adjusted for Crossover (2-Stage Model)



Patients at Risk:

ide-cel	254	240	223	208	190	175	169	161	143	103	75	48	44	30	13	4	0
Standard Regimens 2-stage model	132	126	118	93	67	50	42	34	21	14	9	8	4	2	1	1	0

OS Sensitivity Analyses



[a] 2-Stage (Latimer et al., 2014); [b] RPSFTM , rank-preserving structural failure time (Robins and Tsiatis, 1991); [c] IPCW, inverse probability of censoring weighting (Robins, 2000) Cutoff Date: 28APR2023