IDECABTAGENE VICLEUCEL (ABECMA)
sBLA 125736.218

Oncologic Drugs Advisory Committee Meeting
March 15, 2024

Poornima Sharma, MD
Medical Officer/Clinical Reviewer
Malignant Hematology Branch
Division of Clinical Evaluation Hematology
Office of Clinical Evaluation
Office of Therapeutic Products, CBER

Xue (Mary) Lin, PhD
Mathematical Statistician
Therapeutics Evaluation Branch 1,
Division of Biostatistics
Office of Biostatistics and Pharmacovigilance
CBER

Review Team

Center for Biologics Evaluation and Research

Office of Therapeutic Products
Nicole Verdun, MD

Office of Clinical Evaluation
Lola Fashoyin-Aje, MD, MPH

Division of Clinical Evaluation- Hematology
Robert Sokolic, MD
Poornima Sharma, MD

Division of Pharmacovigilance
Meghna Alimchandani, MD
Mary Rubin, MD

Clinical Pharmacology
Xiaofei Wang, PhD

Center for Biologics Evaluation and Research (continued)

Division of Biostatistics
John Scott, PhD
Boguang Zhen, PhD
Zhenzhen Xu, PhD
Xue (Mary) Lin, PhD

Oncology Center of Excellence
Richard Pazdur, MD
Marc R. Theoret, MD
Bindu Kanapuru, MD
Vishal Bhatnagar, MD

Outline

- Treatment Landscape
- Overview of ide-cel Approval
- KarMMa-3: Efficacy and Safety Results
- Main Topics for Discussion
- Statistical Considerations
- Discussion and Voting Questions

Main Topics for Discussion

- Increased rate of early deaths in the idecabtagene vicleucel (ide-cel) arm

- Clinical benefit of treatment with ide-cel

Treatment Landscape: 2-4 Lines and Triple-Class Exposed MM

Regimen	Indication
Isatuximab with Pd Isatuximab with Kd	≥2L including Len and PI 1-3L
Daratumumb with Pd Daratumumb with Kd	≥2L including Len and PI 1-3L
Elotuzumab with Pd	≥2L including Len and PI
Selinexor with Dex Selinexor with Vd	≥4L, including 2 PIs, 2 IMiDs and anti-CD38 ≥1L
Abecma (ide-cel) Carvykti (cilta-cel)	**≥4, including PI, IMiD and anti-CD38** ≥4, including PI, IMiD and anti-CD38
Teclistamab Elranatamab Talquetemab	≥4, including PI, IMiD and anti-CD38 ≥4, including PI, IMiD and anti-CD38 ≥4, including PI, IMiD and anti-CD38

Other Options
Use drugs/classes not exposed or exposed to > 1 prior line
Autologous transplant
Bendamustine containing regimens
Combination chemotherapy: VTD-PACE, DCEP
Cytoxan in combination with carfilzomib

Sources: Moreau, P, et al. *Lancet Oncology*, 2021; NCCN Guidelines, 2024

Abbreviations: anti-CD38, anti-CD38 monoclonal antibody; d, dexamethasone; IMiD, immunomodulatory drug; K, kyprolis; PI, proteasome inhibitor; P, pomalidomide; V, velcade

Idecabtagene vicleucel (ide-cel)

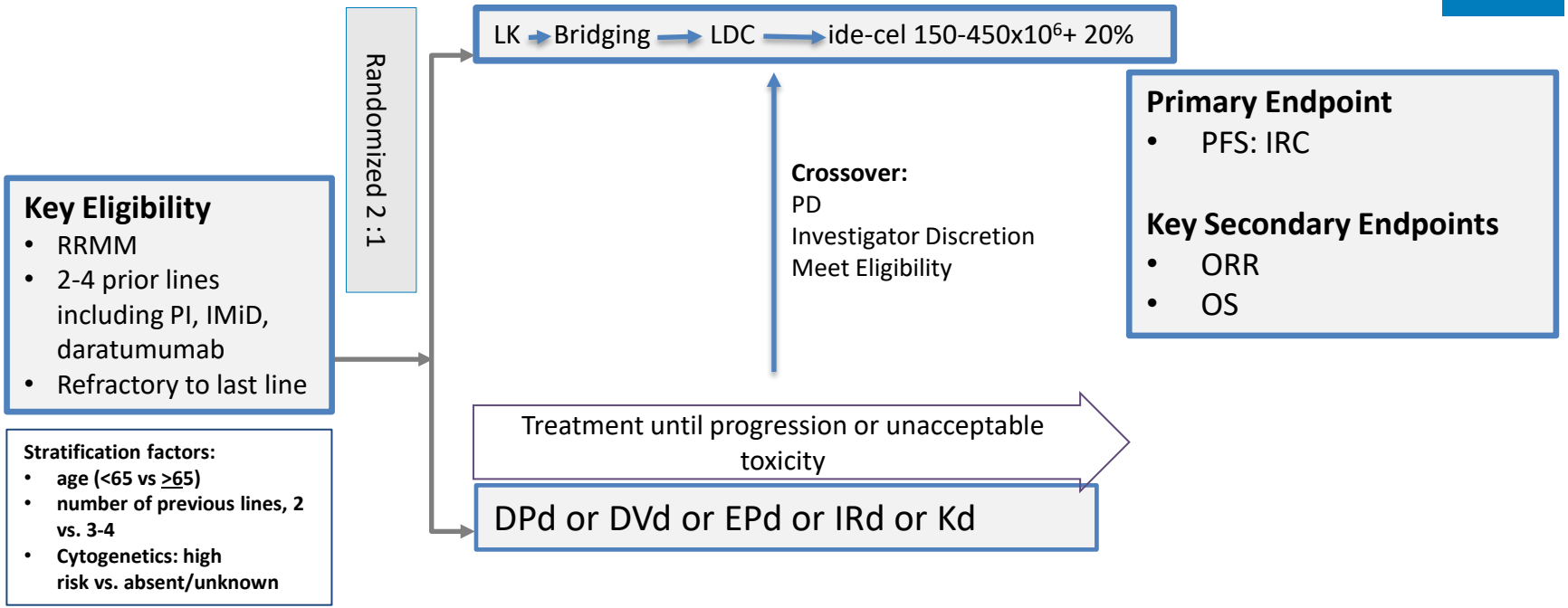
- Autologous T cell product transduced with a lentiviral vector (LVV) to express a chimeric antigen receptor (CAR) targeting BCMA
- Traditional Approval in 2021, based on KarMMa trial
  - **Indication**: Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of systemic therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD 38 monoclonal antibody
  - **KarMMa**: Single arm trial with 100 efficacy evaluable patients, median of 6 (range 3-16) prior lines of therapy
    - ORR: 72 % (95% CI: 62, 81)
    - Median DOR: 11 months (95% CI: 10.3, 11.4)
  - **Dosage**: 300-460 x 10^6 CAR positive T cells as single infusion
  - Boxed warning in USPI: cytokine release syndrome, neurologic toxicity, hemophagocytosis lymphohistiocytosis/macrophage activation syndrome, prolonged cytopenia

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; DOR, duration of response; ORR, overall response rate

Current Supplemental BLA

- Submitted on February 15, 2023
- KarMMa-3 (data cutoff date of April 18, 2022)
- **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
- **Proposed Dose:** 300-510 x 10^6 CAR-positive T cells as single infusion

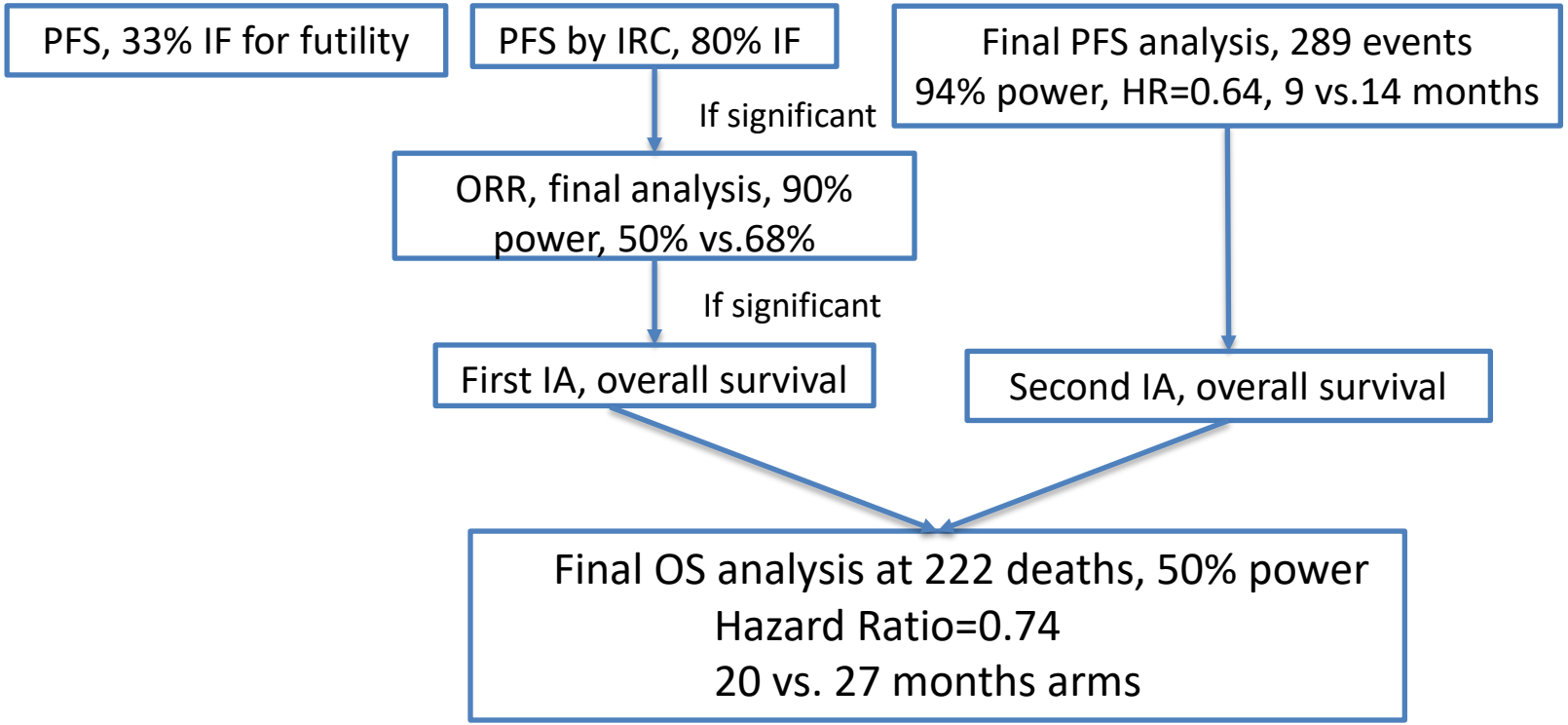
KarMMa-3



Source: FDA

Abbreviations: DPd, daratumumab, pomalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; EPd, elotuzumab, pomalidomide and dexamethasone; IMiD, immunomodulatory drug; IRC, independent review committee; IRD, ixazomib, lenalidomide, dexamethasone; Kd, carfilzomib and dexamethasone; LDC, lymphodepleting chemotherapy; LK, leukapheresis; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma

Efficacy Analysis Plan – KarMMa-3



Source: FDA

Abbreviations: HR, hazard ratio; IA, interim analysis; IF, information fraction; OS, overall survival; PFS, progression-free survival

Demographic Characteristics

	ide-cel (N=254)	SOC (N=132)
Age		
Median, years (range)	63 (30-81)	63 (42-82)
< 65, %	59	59
65-74, %	36	34
≥75, %	4.7	6.8
Race and ethnic group		
Asian, %	3	4
Black or African American, %	7	14
White, %	68	59
Hispanic, %	4	6
Geographical region		
United States, %	53	55
Rest of world, %	47	45

Source: FDA
Abbreviations: SOC, standard of care

Disease and Treatment Characteristics

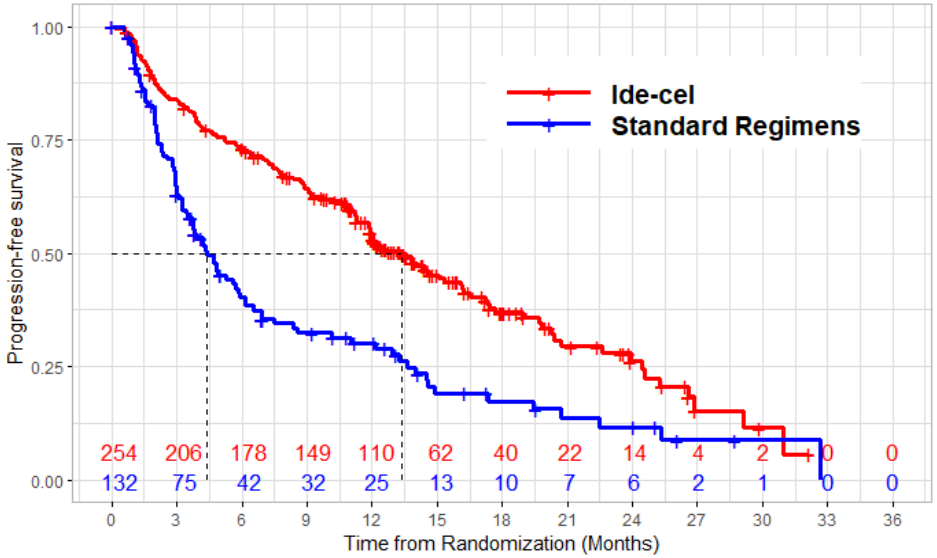
	ide-cel (N=254)	SOC (N=132)
Cytogenetics		
High risk*, %	41	44
R-ISS		
I/II/III, %	20/59/12	20/62/11
Extramedullary plasmacytoma		
Present, %	24	24
Number of prior therapies		
Median (range)	3 (2-4)	3 (2-4)
Prior lines of therapy		
2/3/4, %	31/37/32	30/37/33
Refractory status		
IMiD/PI/anti-CD38 antibodies, %	88/74/95	94/72/94
Triple class refractory, %		
Yes, %	65	67

Source: FDA

R-ISS, revised international staging system; *High risk cytogenetics by FISH include t(4;14), t(14;16), deletion 17p

Triple-class refractory: refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody

Progression-Free Survival, KarMMa-3

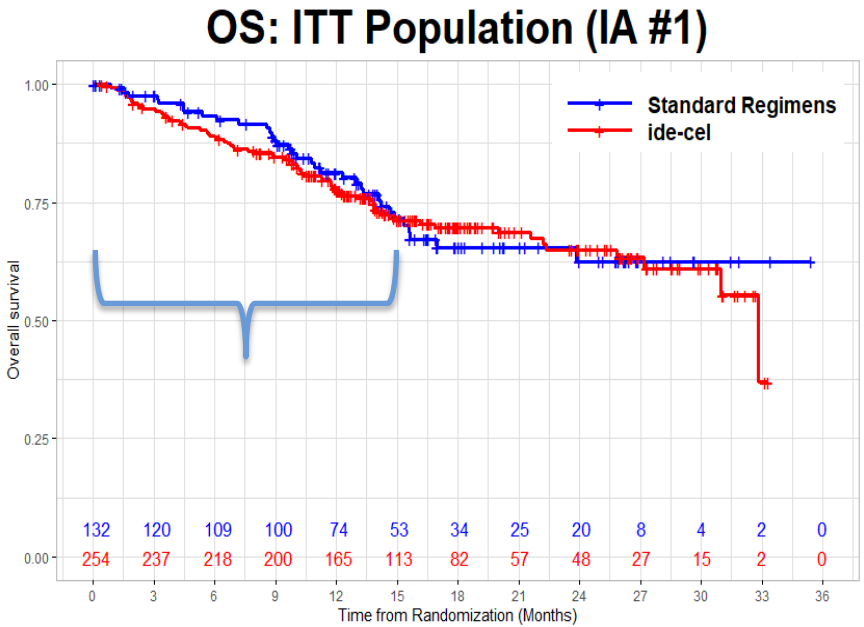


	ide-cel (N=254)	SOC (N=132)
Events, n (%)	149 (59)	93 (70)
Progression, n, (%)	129 (51)	89 (67)
Death, n (%)	20 (8)	4 (3)
Median, months (95% CI)	13.3 (11.8, 16.1)	4.4 (3.4, 5.9)
Hazard ratio (95% CI)	0.495 (0.379, 0.647)	
p-value[1]	<0.0001	

PFS per IMWG 2016 consensus criteria for response
Median is based on Kaplan-Meier estimate
[1] One-sided stratified log-rank test

Source: FDA
Data cutoff April 18, 2022
Median f/u of 15.9 months

Overall Survival, First Interim Analysis



	ide-cel (N=254)	SOC (N=132)
Death events	29.5%	25.8%
Median OS	32.8	NE
(95% CI)	(30.9, NE)	(NE)
Hazard ratio (95% CI)	1.093 (0.727, 1.645)	
Information fraction	49%	
Crossover to ide-cel arm	45%	

Abbreviations: NE, not evaluable

Source: FDA
Data cutoff April 18, 2022
Median f/u of 16.9 months

Summary: Efficacy Results

- Statistically significant improvement in median PFS with ide-cel
  - Median PFS: 13.3 months (95% CI: 11.8, 16.1) in ide-cel arm versus 4.4 months (95% CI: 3.4, 5.9) in the SOC arm, p value <0.0001
  - Higher proportion of deaths as PFS events in ide-cel arm compared to SOC arm
    - 20 deaths in ide-cel arm (8%) versus 4 deaths in the SOC arm (3%)

- OS detriment observed for up to 15 months in the ide-cel arm with pattern of crossing of the curves

Overview: Safety

	ide-cel (N=222) %	SOC* (N=126) %	SOC Prior to Crossover (N=126) %
Any TEAE	100	98	98
SAEs	43	56	36
Grade ≥ 3	95	90	75
Grade 3	18	28	43
Grade 4	64	51	25
Fatal AE	9	8	4

Source: FDA

Data cutoff April 18, 2022

Safety population in ide-cel arm includes patients who received conformal ide-cel

*SOC arm includes AEs after crossover

Abbreviations: AE, adverse event; TEAE, treatment emergent adverse event; SAE, serious adverse event

Adverse Events of Special Interest

	ide-cel (N =222) %		SOC (N =126) %	
	All Grades	Grade ≥3	All Grades	Grade ≥3
CRS	91	5	40	0.8
Neurotoxicity	46	5	21	0.8
HLH/MAS	2	2	1	0
Infection	56	20	64	25
Second primary malignancy	6	2.7	4	2.4
Hematologic neoplasm	1.4	0.9	0	0
Neutropenia	100	96	88	72
Thrombocytopenia	92	59	90	46

Source: FDA Data cutoff April 18, 2022

Safety population includes conformal ide-cel

SOC arm includes 58 patients who crossed over and received conformal ide-cel

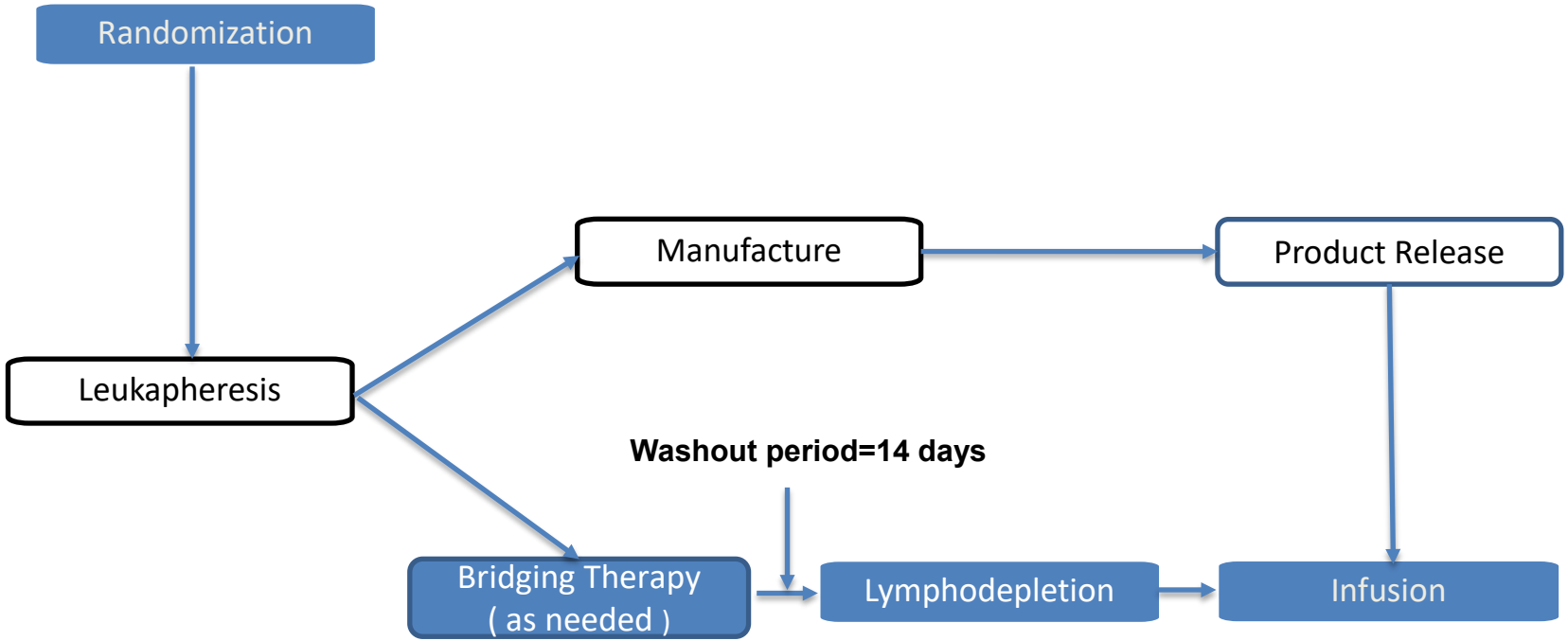
CRS is graded by Lee's criteria 2014. All other AEs are graded per NCI-CTCAE v4.03

Abbreviations: HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome

Main Topics for Discussion

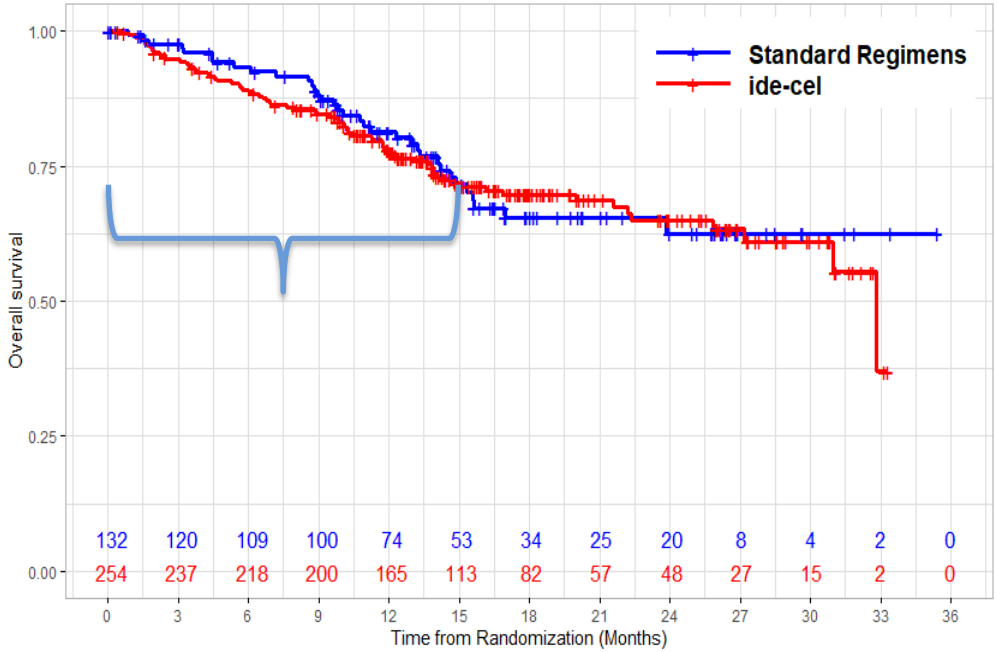
- Increased rate of early deaths in the ide-cel arm
- Clinical benefit of treatment with ide-cel

CAR T Therapy



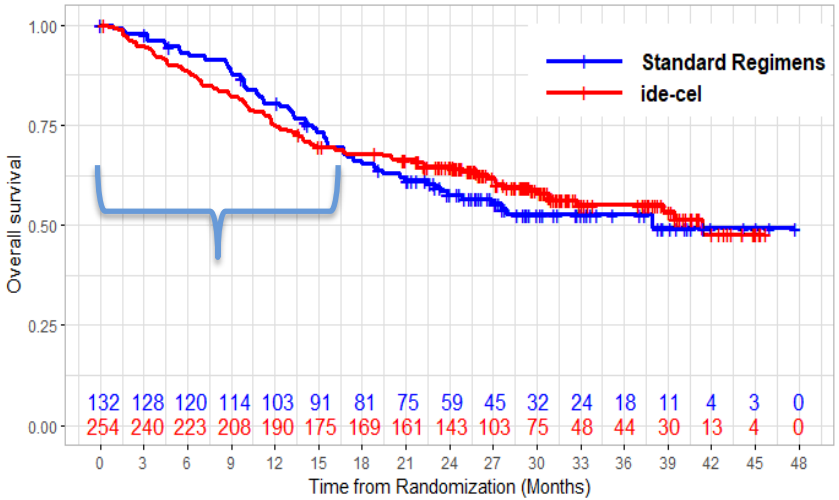
Source: FDA

Overall Survival, First Interim Analysis, ITT Population



Source: FDA
Data cutoff April 18, 2022
Median f/u of 16.9 months

Overall Survival, Second Interim Analysis, ITT Population



Source: FDA
Data cutoff April 28, 2023
Median f/u 29.7 months

	ide-cel (N=254)	SOC (N=132)
Death events	41.7%	43.9%
Median OS (95% CI)	41.4 (30.9, NE)	37.9 (23.4, NE)
Hazard ratio (95% CI)	1.012 (0.731, 1.400)	
Information fraction	74%	
Crossover	56%	

Abbreviations: NE, not evaluable

Overview of Deaths, ITT Population

	ide-cel (N=254) %	SOC (N=132) %
Total deaths	42	44
Disease progression	24	27
Adverse event	11	11
Unknown cause	7	6
Deaths in the first 9 months	18	11
Disease progression	10	7
Adverse event	6	4.5*
Unknown cause	2.4	0
Deaths beyond 9 months	24	33

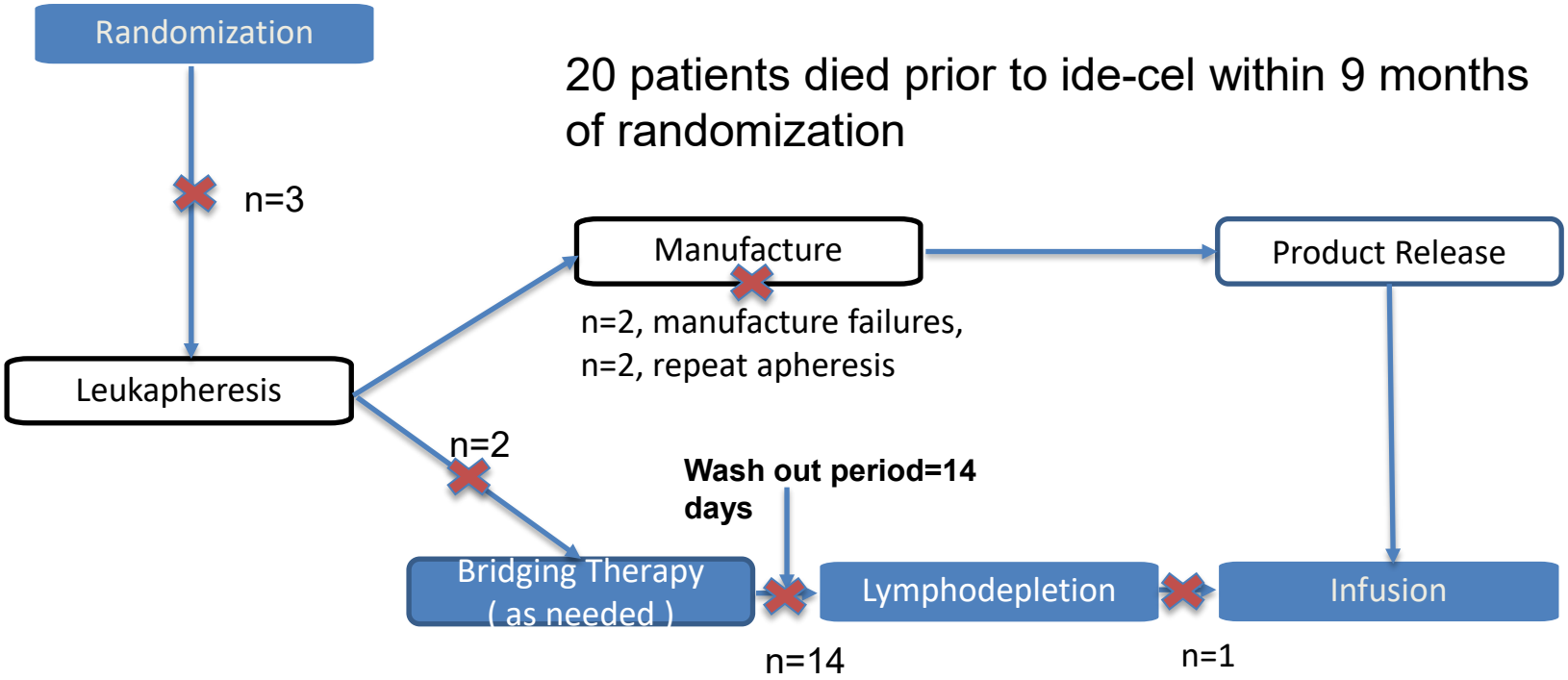
Source: FDA
Data cutoff April 28, 2023
* 3 out of 6 deaths occurred after crossover to ide-cel arm

Ide-cel Arm: Higher Rate of Death in First 9 Months

	ide-cel (N=254) %	SOC (N=132) %
Total	**18**	**11**
Prior to ide-cel/SOC	**8**	**0**
Disease progression	6	0
Adverse event	1.2	0
Unknown cause	0.8	0
After ide-cel/SOC	**10**	**11**
Disease progression	4	7
Adverse event	4.3	*4.5
Unknown cause	1.6	0

Source: FDA
Data cutoff April 28, 2023
* 3 out of 6 deaths after crossover to ide-cel arm

CAR T Process



20 patients died prior to ide-cel within 9 months of randomization

Source: FDA

Bridging Therapy

	ide-cel (N=254)	
	ide-cel (N=225)	**No ide-cel* (N=20)**
Received BT (%)	85	75
Time from randomization to BT start Median in days (range)	8 (1-51)	7 (2-33)
Type of BT (%)		
Protocol specified	76	75
Non-protocol specified	10	0
Duration of BT (days) Median (range)	22 (1-88)	24 (1-100)
Number of cycles (%)		
1	70	40
2	11	15
> 2	0	10
Missing/unknown	5	10
Time from leukapheresis to product release (days) Median (range)	35 (24-102)	30 (26-85)

Source: FDA and Applicant

* Death within 9 months

Abbreviations: BT, bridging therapy

Bridging Therapy vs. SOC Regimen

Regimens	ide-cel (N=254) %	SOC (N=132) %
EPd	24	23
DPd	20	31
Kd	11	21
IRd	10	15
DVd	8	5
Nonprotocol specified bridging	10	N/A
Received SOC/bridging	84	95
No SOC/bridging	16	4.5

Source: FDA and Applicant

Abbreviations: DPd, daratumumab, pomalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; EPd, elotuzumab, pomalidomide and dexamethasone, IRD, ixazomib, lenalidomide, dexamethasone; Kd, carfilzomib and dexamethasone

Exploratory Analyses for Early Mortality, Prognostic Factors

Prognostic Factor	ide-cel (N=254) %	SOC (N=132) %
Extramedullary plasmacytoma		
Present	7	3.8
Absent	10	8
Revised ISS Stage		
Stage III	4.7	1.5
Stage I/II	13	9
Cytogenetics		
High-risk	11	5
Absent high-risk	6	3.8
Age (years)		
>/=65	7	3.8
<65	11	8
ECOG performance status		
>/=1	12	8
0	6	3
Lines of therapy		
2	3.9	4.5
3-4	14	7
Triple-class refractory		
Yes	15	9.8
No	2.4	1.5

Source: FDA

In first 9 months:
45 deaths in ide-cel arm
15 deaths in SOC arm

Exploratory Analyses

- No prognostic subgroup was associated with observed early mortality with ide-cel

*

Deaths in Safety Population

	ide-cel (N=222) %	SOC (N=126) %
Total deaths	36	43
Progressive disease	19	29
Adverse event	11	10
Unknown	6	4.8
Deaths within 90 days after treatment start	4.1	3.2
Adverse event	2.7	1.6
Progressive disease	1.4	1.6
Deaths beyond 90 days after last dose	32	40
Progressive disease	18	27
Adverse event	8	8*
Unknown	6	4.8

Source: FDA
Data cutoff April 28, 2023
*SOC arm: Six out of 10 deaths occurred after cross-over to ide-cel arm

Death From TEAE, Safety Population: KarMMa-3

	ide-cel (N=222) %	SOC (N=126) %	ide-cel in SOC (N=72) %
Total deaths	36	43	29
Adverse events	11	10	6
CRS and/or HLH/MAS	0.9	0	0
Neurotoxicity	0.5	0.8	1.4
Infection	6	6	2.8
Second primary malignancy	1.4	0.8	1.4
Other AEs*	2.3	1.6	0

Source: FDA
Data cutoff April 28, 2023
Includes hemorrhage, respiratory failure, coronary artery dissection, sudden death, stroke from atrial fibrillation in ide-cel arm.
Includes respiratory failure in SOC arm.

Summary of Early Deaths in KarMMa-3

- Higher rate of death in the first 9 months in ide-cel arm versus SOC arm; 18% versus 11%
- Higher rate of death from adverse events within 90 days of treatment in ide-cel versus SOC arm; 2.7% vs. 1.6%
- A higher proportion of deaths before disease progression in ide-cel arm compared to SOC arm; 8% vs. 3%

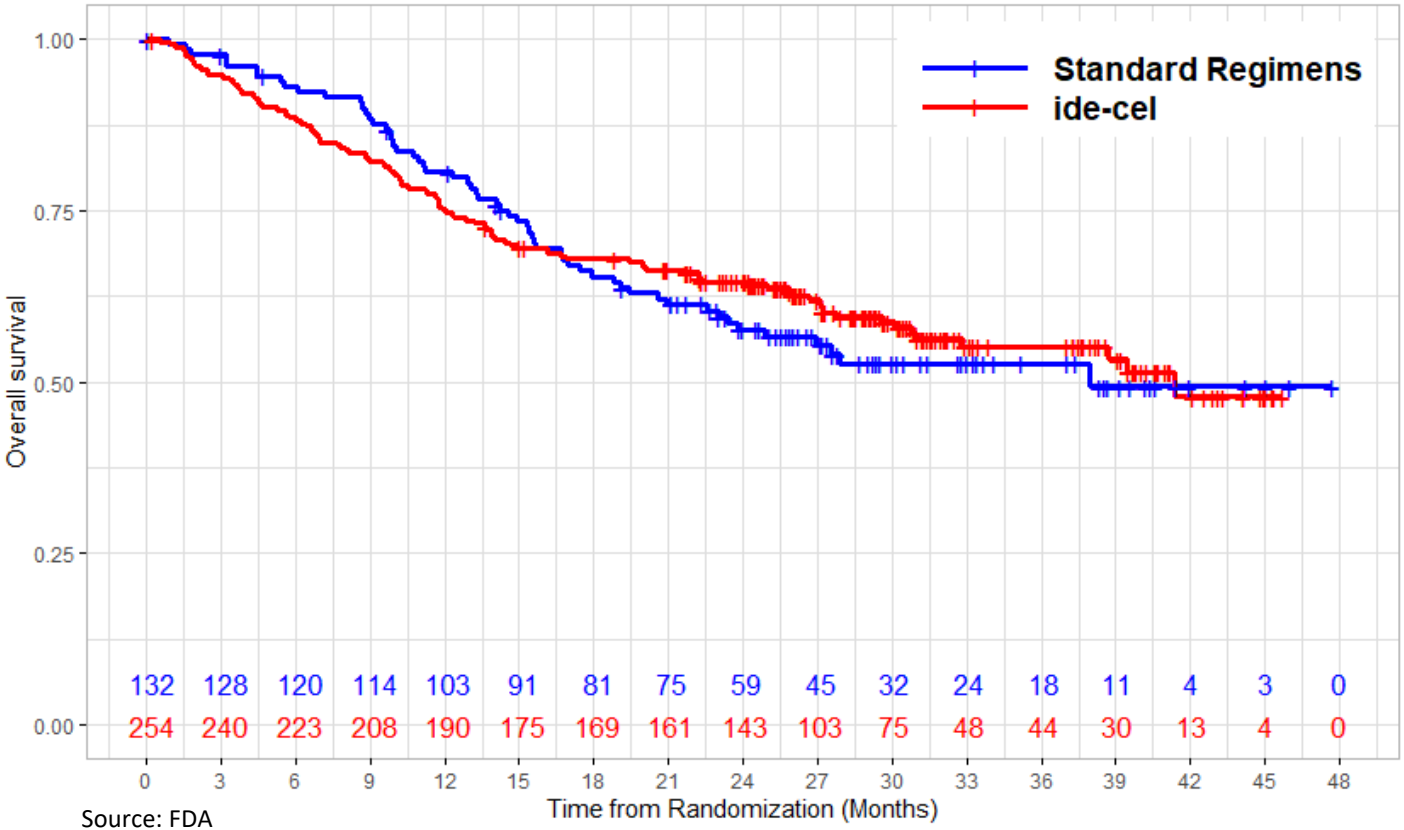
Overall Survival

- OS is the ultimate clinical benefit endpoint in Oncology
- OS is a measure of safety and efficacy
- Discordance between PFS and OS
- PFS as primary endpoint to expedite drug development
- OS as key secondary endpoint for benefit-risk assessment

Clinical Benefit With ide-cel

- Benefit on PFS and ORR
- Increased rate of early deaths in ide-cel arm for 9 months
- OS detriment for 15 months
- Uncertainty in clinical benefit

Overall Survival, ITT Population



Source: FDA
Data cut off April 28, 2023

Key Points

- Impact of Crossover:
  - KarMMr-3 study allowed crossover upon disease progression
  - Sensitivity analyses can not provide convincing evidence that ide-cel reduced the risk of death after adjusting for treatment crossover
- Duration of Early OS Detriment:
  - Early OS data demonstrate detrimental effect of ide-cel lasted for up to 9 months

IMPACT OF CROSSOVER

Limitation of Crossover Analyses

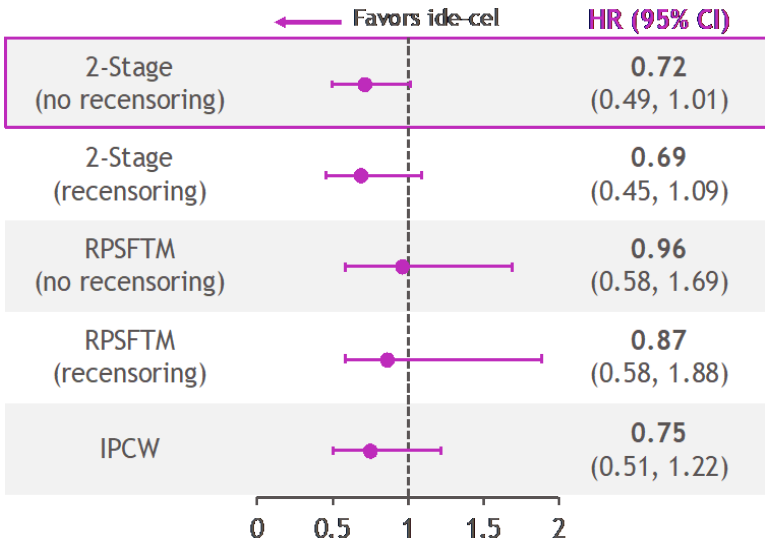
- Per Statistical Analysis Plan (SAP), the primary analysis of OS was the ITT analysis
- Two prespecified crossover analyses as sensitivity analyses:
  - Rank preserving structural failure time (RPSFT) method: rank preserving structural failure time method
  - Accelerated failure time (AFT) model: 2-stage accelerated failure time model
- Additional post hoc crossover analysis:
  - Inverse Probability of Censoring Weighting (IPCW) method: Inverse Probability of Censoring Weighting

Limitations: All three sensitivity analyses rely on unverifiable model assumptions, limiting their ability to explain OS detriment.

Crossover Model Assumptions

- RPSFT: Common treatment effect
  - Assumes the treatment effect of ide-cel on OS is the same when administered after disease progression on the standard regimens arm as when administered after initial randomization
- AFT & IPCW: No unmeasured confounders at the time of treatment crossover
  - Assumes that any systematic differences between subjects who cross over and those who do not can be explained by model covariates
- These assumptions are unverifiable

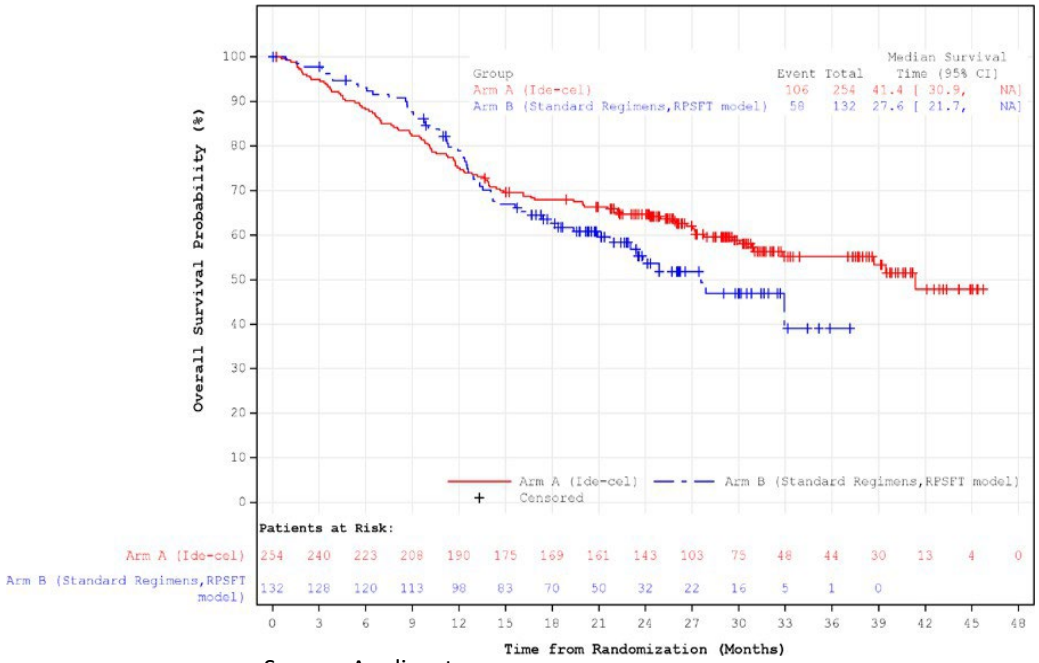
Estimated HR From Sensitivity Analysis Adjusting for Crossover



Source: Applicant

Abbreviations: IPCW, inverse probability of censoring weighting; RPSFTM, rank preserving structural failure time

Kaplan-Meier Curve of Overall Survival by RPSFT Model With Re-Censoring, ITT Population



Source: Applicant

Data cut off April 28, 2023

HR=0.870
(95% CI: 0.581, 1.878)

Limitations:

1. Early OS detriment persisted
2. Average HR is no longer interpretable
3. Wide confidence interval

Summary of Crossover Impact Assessment

Limitations of sensitivity analyses to assess the impact of crossover

- Relying on untestable assumptions
- Cannot be used to ascertain that ide-cel treatment has OS benefit when the ITT analysis clearly indicates OS disadvantage

In conclusion, the sensitivity analyses adjusting for treatment crossover can not provide convincing evidence that ide-cel reduces the risk of death

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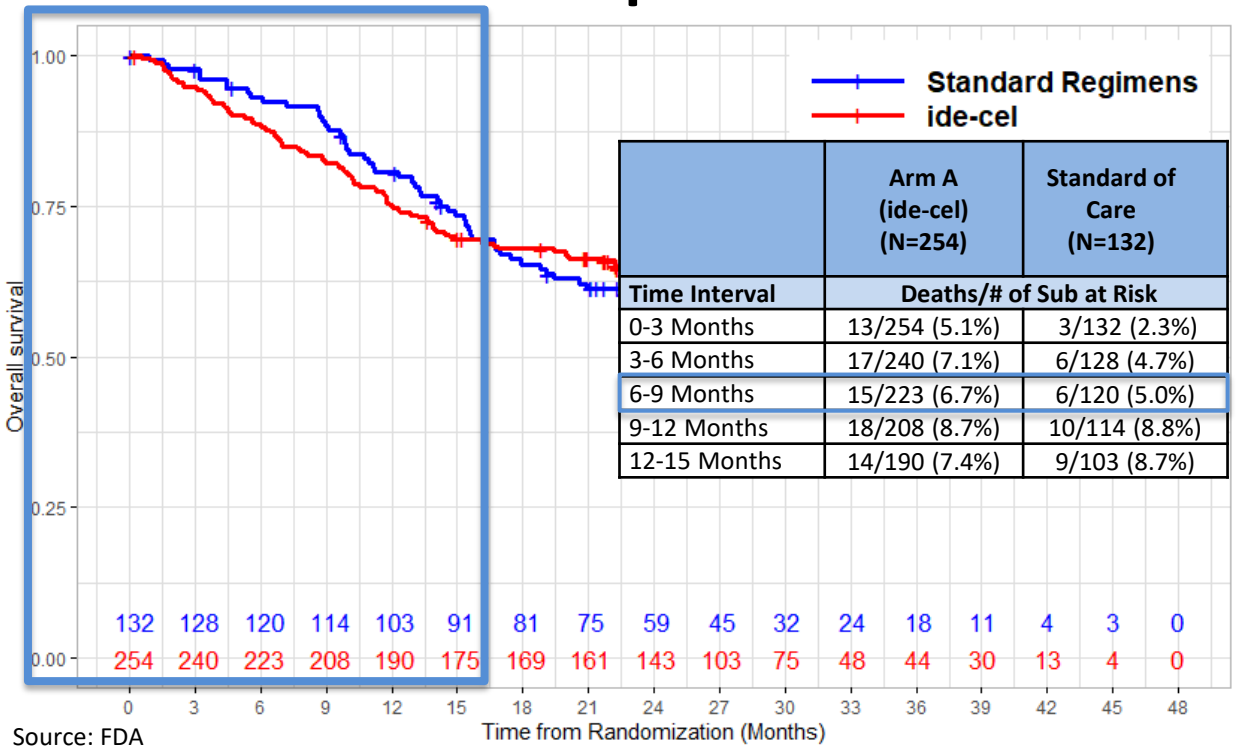
Detrimental Effect of Ide-cel Lasted Up to 9 Months

Detrimental Effect of Ide-cel on Overall Survival, ITT Population



	Arm A (ide-cel) (N=254)	Standard of Care (N=132)
Time Interval	**Deaths/# of Sub at Risk**	
0-3 Months	13/254 (5.1%)	3/132 (2.3%)
3-6 Months	17/240 (7.1%)	6/128 (4.7%)
6-9 Months	15/223 (6.7%)	6/120 (5.0%)
9-12 Months	18/208 (8.7%)	10/114 (8.8%)
12-15 Months	14/190 (7.4%)	9/103 (8.7%)

Source: FDA
Data cut off April 28, 2023

Piecewise Hazards Ratio Estimate, ITT Population

Time Interval	0-9 Months	9-18 Months			
HR (95% CI)	1.65 (0.92, 2.97)	0.71 (0.43, 1.15)			
Time Interval	**0-3 Months**	**3-6 Months**	**6-9 Months**	**9-12 Months**	**12-15 Months**
HR (95% CI)	2.41 (0.68, 8.46)	1.58 (0.62, 4.01)	1.35 (0.52, 3.49)	1.05 (0.48, 2.28)	0.88 (0.38, 2.04)

Source: FDA

Summary of Detrimental Effect of Ide-cel

FDA interpretation of the overall survival data:

- There was clear and persistent increased mortality for the ide-cel arm compared with standard regimen arm with increased rates of death up to 9 months
- The overall survival disadvantage persisted to 15 months after randomization when the survival curves finally cross

Conclusions

- Ide-cel in triple class exposed RRMM after 2-4 prior lines
  - PFS benefit, improvement in ORR
- Increased rate of early death
  - Unlikely to be overcome with additional follow up
  - Study was not designed to identify predictive factors for early mortality
  - Inherent risk of ide-cel
- Uncertain benefit-risk of ide-cel in the proposed population

Discussion Questions

- Discuss whether the results of KarMMa-3 are sufficient to support a positive risk-benefit assessment of idecabtagene vicleucel for the proposed indication.
- Is the risk of early death associated with idecabtagene vicleucel treatment acceptable in the context of the PFS benefit?

Voting Question

Is the risk-benefit assessment for idecabtagene vicleucel for the proposed indication, favorable?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Back-up Slides Shown

KarMMa-3 vs. KarMMa (ITT)

	KarMMa 3 (N=254)	KarMMa (N=140)
Deaths, n(%)	106 (42)	52 (37)
Median follow up (months)	29.7	16.3
Deaths in first 9 months*	18%	18%
Untreated	8%	6%
Treated	10%	12%

*From randomization for KarMMa 3 and from leukapheresis in KarMMa

Both arms represent conformal ide-cel

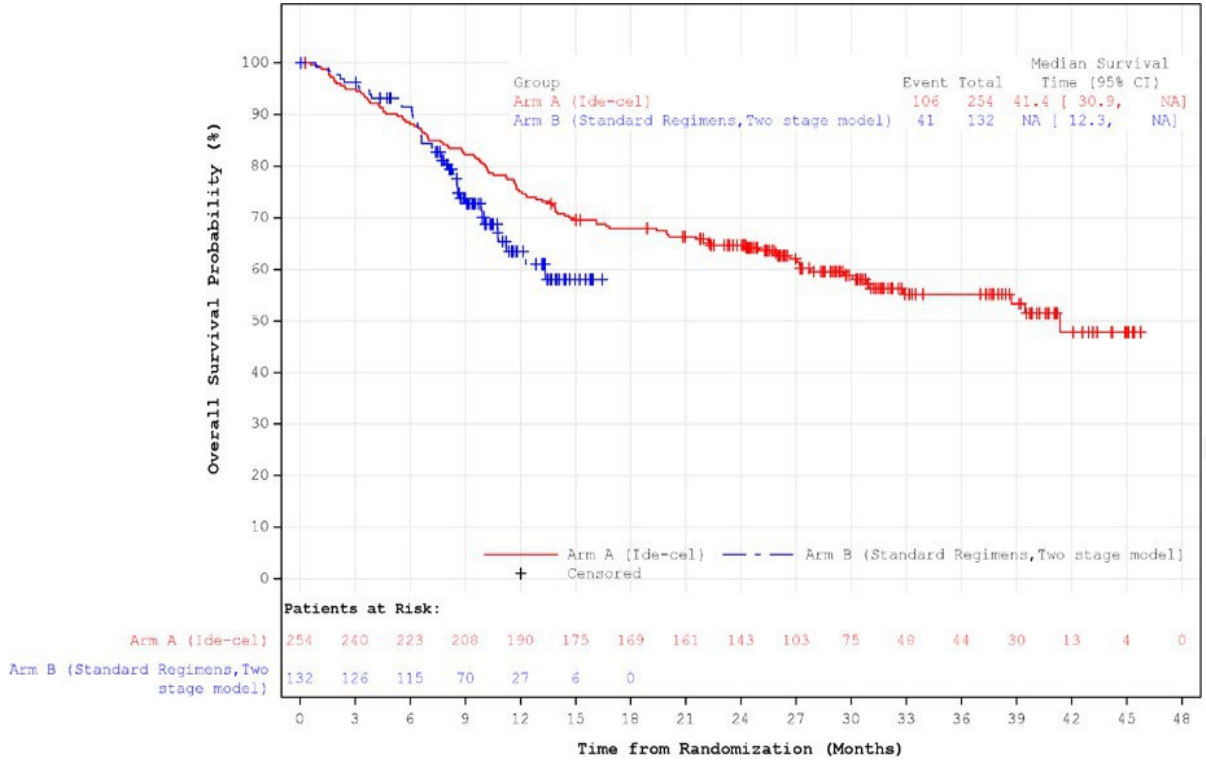
Median follow up for OS is estimated using the reverse Kaplan-Meier method

Two-Stage AFT Model

- Key model assumption: no unmeasured confounders at the time of treatment crossover
  - The Applicant included in the model
    - 6 baseline covariates: age, number of prior antimyeloma regimens, cytogenetic risk, triple refractory status, tumor burden, and extramedullary disease status
    - 2 covariates before crossover: last nonmissing value of ECOG, LDH before the time of disease progression
- Critical concerns:
  - Treatment crossover was not random but at the discretion of the investigator
  - There may exist systematic difference and unmeasured confounding effect between subjects who crossed over versus those who did not, which may still exist after adjusting for the covariates in the model

Limitation: As a result, attributing overall survival differences solely to treatment crossover becomes unreliable and highly questionable. This limitation underscores the need for caution when interpretating the model's findings

Kaplan-Meier Curve of Overall Survival by 2-Stage AFT Model With Re-Censoring, ITT Population



Limitations:

1. No data beyond Month 17
2. Heavy censoring

→ Analysis results uninterpretable