Oncologic Drugs Advisory Committee Meeting

Introductory Comments

Rob Sokolic, MD
Chief, Malignant Hematology Branch
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research, FDA

March 15, 2024

Ciltacabtagene Autoleucel

- **Product Class:** BCMA-directed autologous T-cell immunotherapy
- **Current Approval:**
  - For the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
- **Proposed Indication:**
  - For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.
- **Proposed Approval Pathway:** Traditional Approval

Outline

- Meeting Purpose
- Overview of the CARTITUDE-4 trial
- Questions for Discussion

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Meeting Purpose

- Discuss and provide input on adequacy of data from the CARTITUDE-4 study to demonstrate the safety and effectiveness of ciltacabtagene autoleucel as treatment for RRMM
  - PFS benefit
  - Crossing hazards pattern
  - Decreased OS through 10 months

Outline

- Meeting Purpose
- Overview of the CARTITUDE-4 trial
- Questions for Discussion

CARTITUDE-4 Study

Design: Open-label randomized trial

Participants: 419 participants with RRMM after 1-3 Prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent refractory to lenalidomide

Treatment: Cilta-cel (single infusion) or standard of care until progression of disease or intolerable adverse effects.

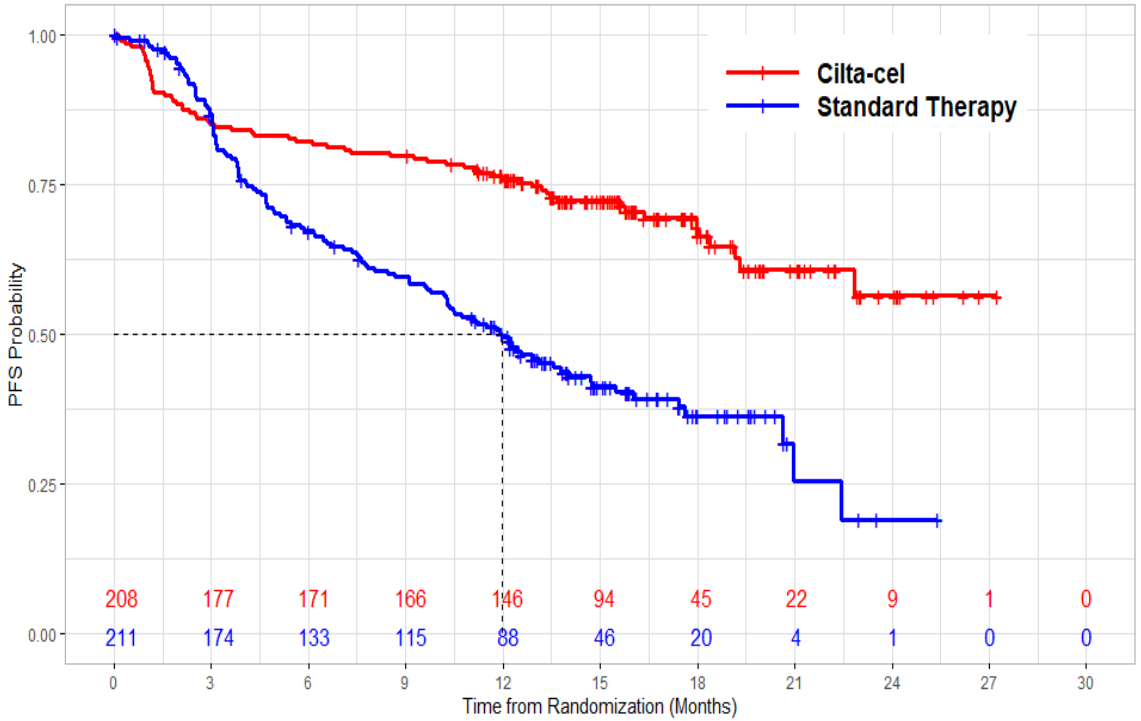
Treatment Response Assessment: 2016 IMWG response criteria

Results:

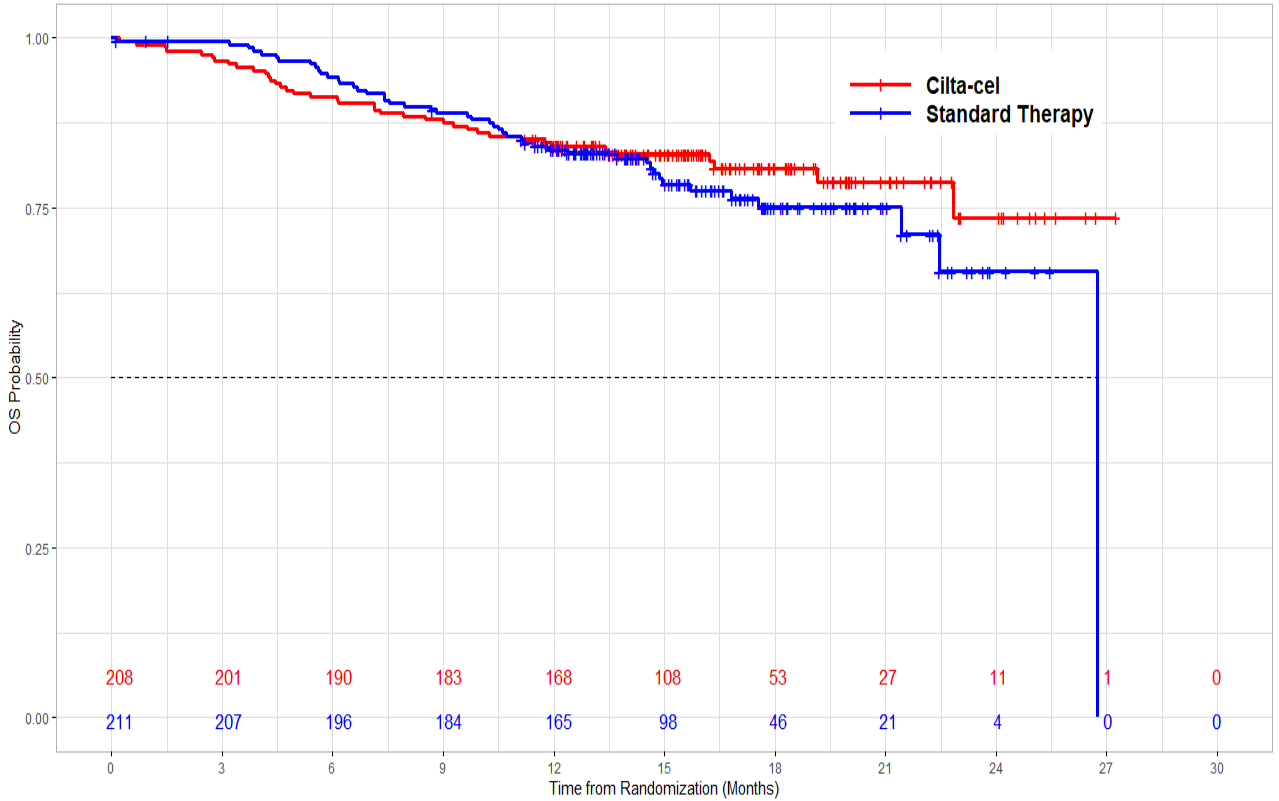
- Statistically significant improvement in PFS (12 months versus not reached)
- Hazard ratio 0.41
- $p < 0.0001$

Abbreviation: RRMM, Relapsed and/or Refractory Multiple Myeloma
Source: San Miguel, et al. NEJM 2023

Progression-Free Survival at Interim Analysis by ITT



Overall Survival at Interim Analysis by ITT



Outline

- Meeting Purpose
- Overview of the CARTITUDE-4 trial
- Questions for Discussion

Summary of the Review Issues

- Ciltacabtagene autoleucel led to a significantly improved rate of progression-free survival, but with a decrement in overall survival in the first 10 months of the trial.
- The decrement in overall survival calls into question whether the risk-benefit assessment is favorable.

Discussion Questions

- Discuss whether the results of CARTITUDE-4 are sufficient to support a positive risk-benefit assessment of ciltacabtagene autoleucel for the proposed indication.
- Is the risk of early death associated with ciltacabtagene autoleucel treatment acceptable in the context of the PFS benefit?

Voting Question

- Is the risk-benefit assessment for ciltacabtagene autoleucel for the proposed indication, favorable?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CILTACABTAGENE AUTOLEUCEL (CARVYKTI)
sBLA 125746.74

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March 15, 2024

Helkha Peredo-Pinto, MD, MPH
Medical Officer/Clinical Reviewer
Malignant Hematology Branch,
Division of Clinical Evaluation Hematology
Office of Clinical Evaluation
Office of Therapeutic Products, CBER

Cong Wang, 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
Helkha Peredo-Pinto, MD, MPH

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
Cong Wang, PhD

Oncology Center of Excellence

Marc R. Theoret, MD
Bindu Kanapuru, MD

Main Topic for Discussion

Increased rate of early death in the ciltacabtagene autoleucel arm

Outline

- Treatment Landscape
- Regulatory History of ciltacabtagene autoleucel
- CARTITUDE-4: Efficacy and Safety Results
- Main Topic for Discussion
- Statistical Considerations
- Discussion and Voting Questions

Treatment Landscape: RRMM After Initial Therapy

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
Pomalidomide with Vd	≥2L including Len and PI
Elotuzumab with Pd	≥2L including Len and PI
Selinexor with Dex Selinexor with Vd	≥4L, including 2 PIs, 2 IMiDs and anti-CD38 ≥1L

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: d, dexamethasone; D, daratumumab; IMiD, immunomodulatory drug; K, kyprolis; P, pomalidomide; PI, proteasome inhibitor; V, velcade

Ciltacabtagene autoleucel (cilta-cel)

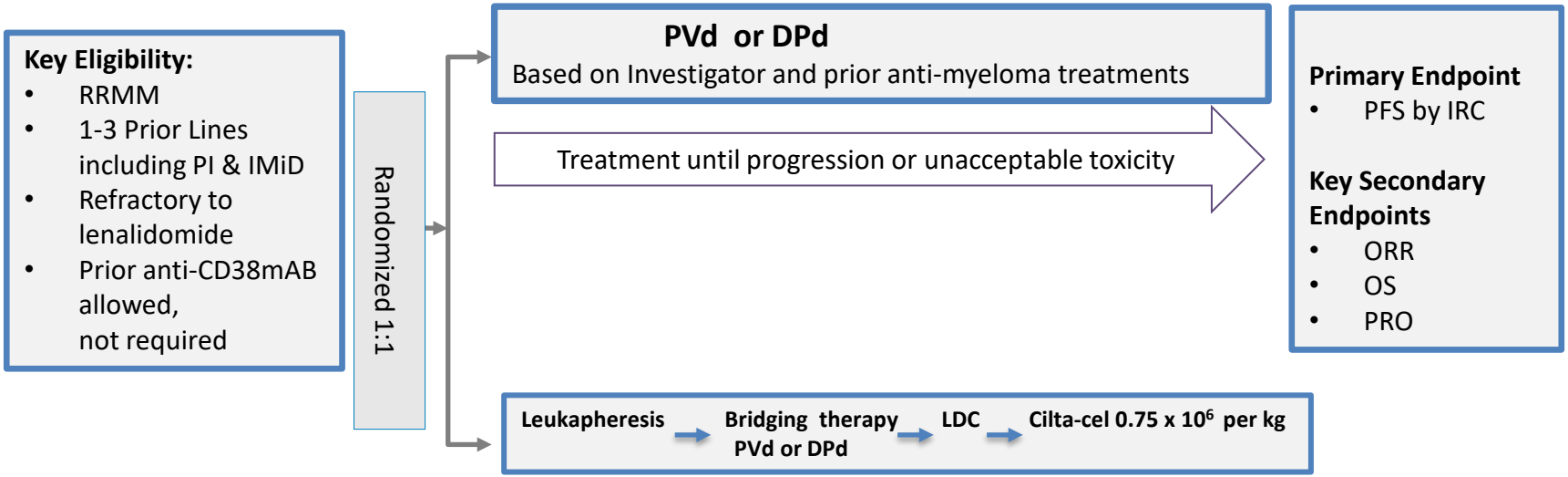
- Autologous T cell product transduced with a lentiviral vector (LVV) to express a chimeric antigen receptor (CAR) targeting BCMA
- Approved February 28, 2022, based on CARTITUDE-1 trial
  - **Indication**: Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of systemic therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD 38 monoclonal antibody
  - **CARTITUDE-1**: Single arm trial with 97 patients who received a median of 6 (range 3-18) prior lines of therapy
    - ORR: 97.9 % (95% CI: 92.7, 99.7)
    - Median DOR: not reached (95% CI: 21.8, NE)
  - **Dosage**: single dose infusion of 0.5-1.0 x 10^6 CAR positive viable T cells per kg of body weight (max 1.0 x 10^8 CAR-positive T cells)
  - Boxed warning in USPI: CRS, NT, HLH/MAS, Prolonged or Recurrent Cytopenias, Secondary Primary Malignancies

Abbreviations: BCMA, B-cell maturation antigen; CAR, Chimeric Antigen Receptor; CRS, Cytokine release syndrome; DOR, Duration of Response; HLH/MAS, Hemophagocytic lymphohystiocitosis/Macrophage activation syndrome; NT, Neurotoxicity ORR, overall response rate

Current Supplemental BLA

- Submitted on June 6, 2023
- CARTITUDE-4 (data cutoff date of November 1, 2022)
- **Proposed Indication**: for the treatment of adult patients with relapsed or refractory multiple myeloma, **who have received at least 1** prior line of therapy, including a proteasome inhibitor**, and** an immunomodulatory agent, **and are refractory to lenalidomide.**

CARTITUDE-4 Study

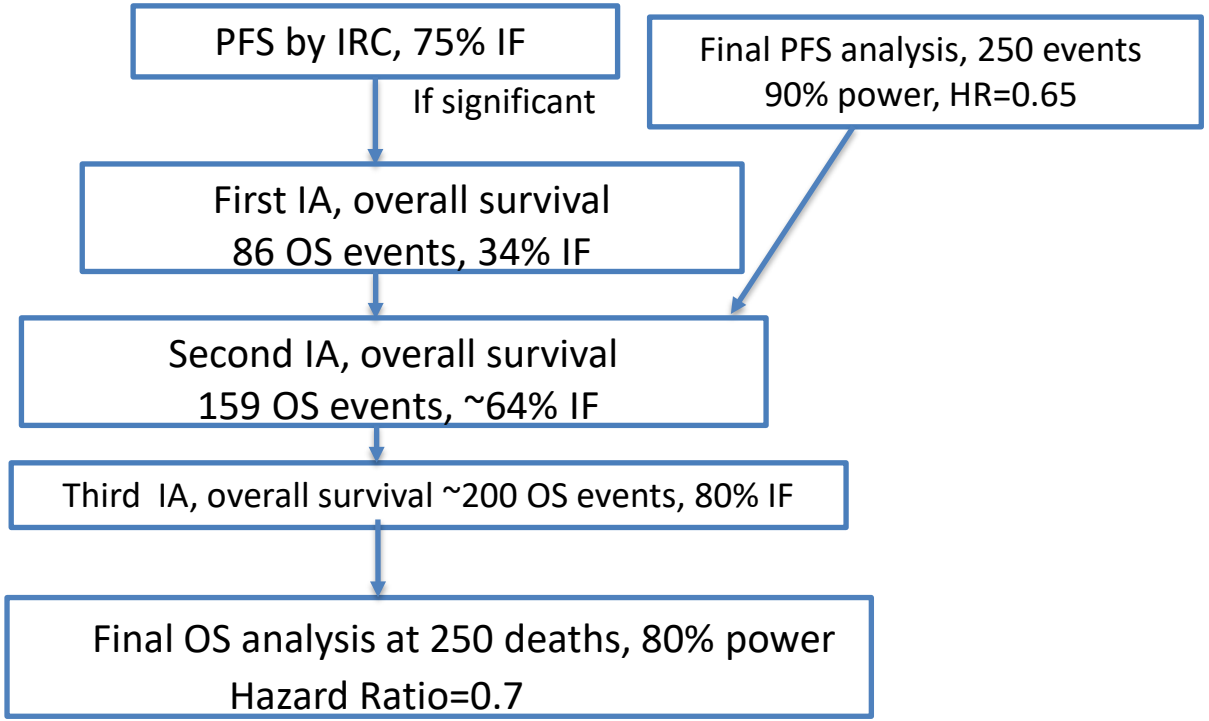


[i] **Randomization** stratified by (1) PVD vs. DPd (2) ISS Score (I vs. II vs. III) and (3) Number of previous lines (1 vs. 2 or 3)

Source: FDA

Abbreviations: d, dexamethasone; D, Daratumumab; IRC, Independent Review Committee; ISS, International Staging System; IV, intravenous; LDC, lymphodepleting chemotherapy; ORR, overall response rate; OS, overall survival; P, pomalidomide; PFS, progression-free survival; PI, proteasome inhibitor; PRO, patient-reported outcomes; RRMM, relapsed refractory multiple myeloma; V, Velcade (bortezomib)

Efficacy Analysis Plan - CARTITUDE-4



Source: FDA

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

Demographic Characteristics

	Cilta-cel (N=208)	Standard Therapy (N=211)
Age	-	-
Median, years (range)	61.5 (27-78)	61(35-80)
<65, %	61	62
65-75, %	37.5	36
>75, %	1.9	1.9
Race or ethnic group	-	-
Asian, %	8	10
Black or African American, %	3	3
Hispanic, %	9	5
White, %	76	74
Not reported, %	14	12
Geographic region	-	-
Europe	61.5	61
North America	15	15

Source: FDA, Data cutoff November 1, 2022

Disease and Treatment Characteristics

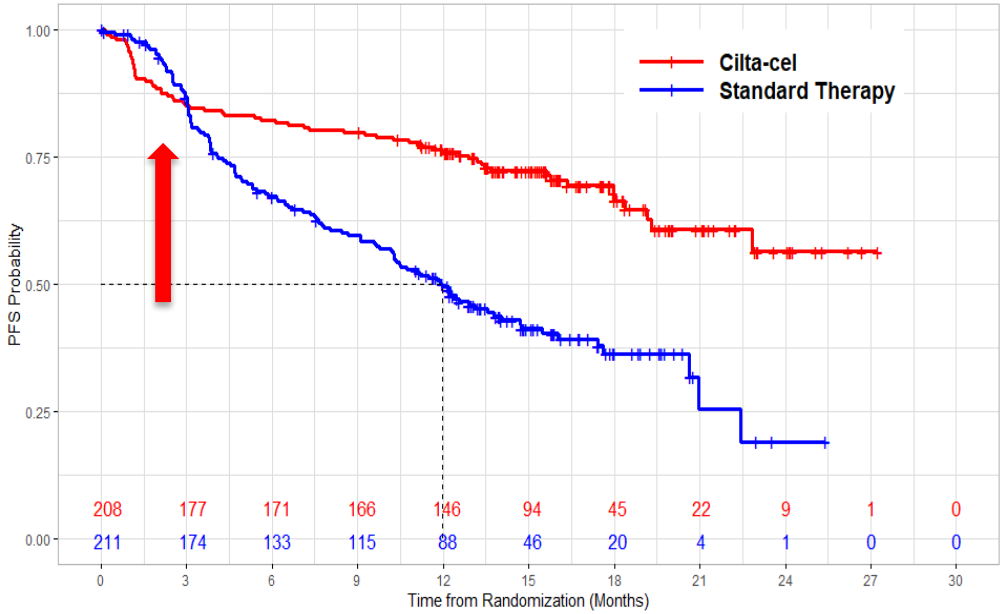
	Cilta-cel (N=208)	Standard Therapy (N=211)
ECOG performance status score	-	-
0/1/2, %	55/44/1	57/42/1
International Staging System stage, %	-	-
I/II/III, %	65/30/6	63/30/7
Cytogenetics	-	-
High Risk, %*	39	38
Extramedullary plasmacytoma	-	-
Present	21	17
Prior lines of therapy	-	-
1/2/3	33/40/27	32/41/27
Previous anti-CD38 antibody	26	26
Refractory status	-	-
IMiD/PI/anti-CD38 antibodies (%)	100/50/24	100/46/22
Triple-class^	14	16

Source: FDA, Data cutoff November 1, 2022

* 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, Intention-to-Treat (ITT)

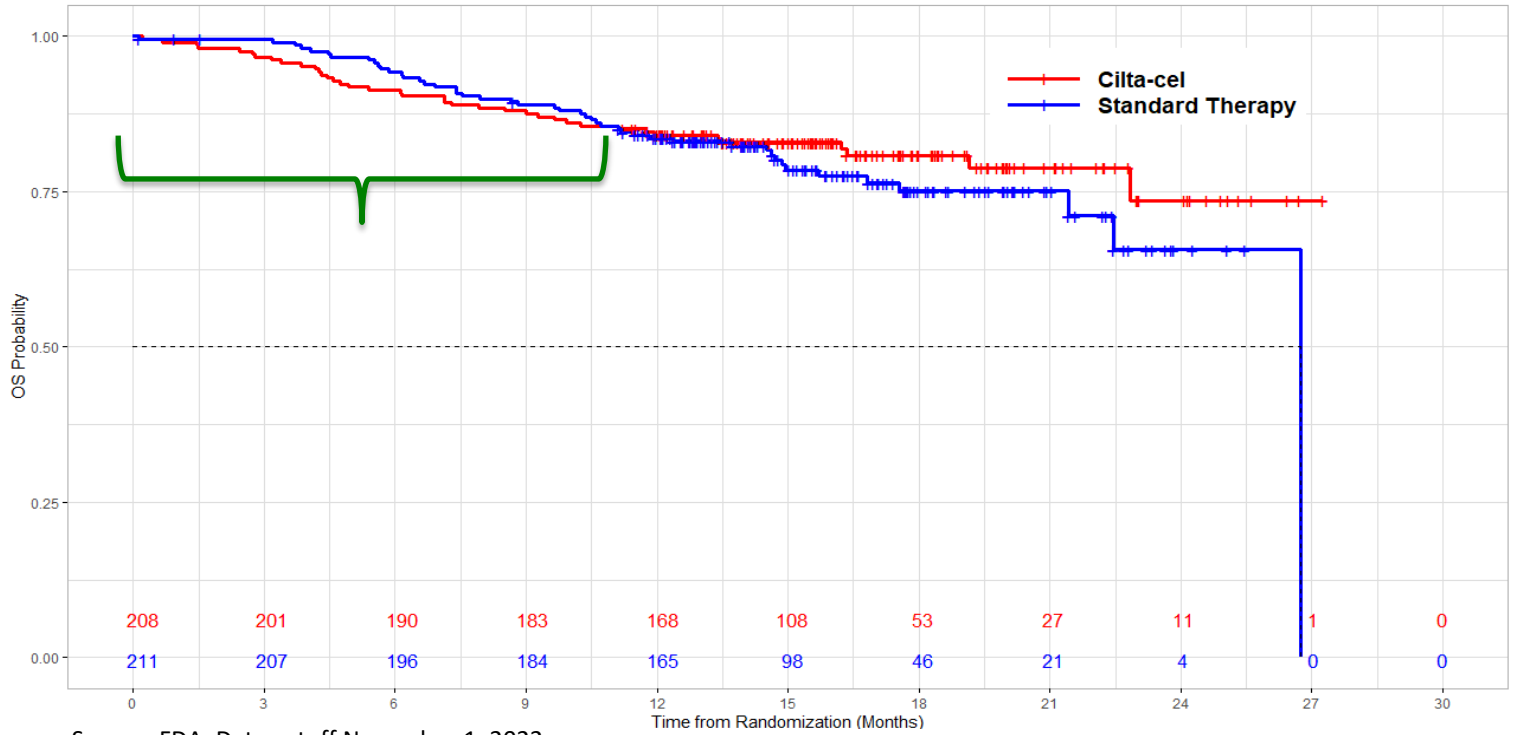


	Cilta-cel (N=208)	Standard Therapy (N=211)
Events, n (%)	65 (31)	122 (58)
PD, n (%)	48 (23)	118 (56)
Death, n (%)	**17 (8)**	**4 (2)**
Median, months (95% CI)	NE (22.8, NE)	11.8 (9.7,13.8)
Hazard ratio (95% CI)	0.41 (0.30, 0.56)	
p-value	<0.0001	

PFS per IMWG 2016 consensus criteria for response
Median is based on Kaplan-Meier estimate

Source: FDA
Data cutoff November 1, 2022
Abbreviations: CI, confidence interval; IMWG, International Myeloma Working Group; NE, not evaluable; PD, progressive disease; PFS, progression-free survival

Overall Survival, Interim Analysis-1 (ITT)



Source: FDA, Data cutoff November 1, 2022
Abbreviations: ITT, intent-to-treat

Summary: Efficacy Results

- Statistically significant improvement in median PFS with cilta-cel compared to standard therapy
  - Median PFS was not reached for cilta-cel compared to 12 months for the standard therapy
  - Higher proportion of PFS events in the cilta-cel arm are due to deaths compared to standard therapy.
    - 17 deaths in cilta-cel arm (8%) versus only 4 deaths in the standard therapy arm (2%)
- OS immature (IF: 34%)
  - Observed early OS detriment in the cilta-cel arm with pattern of crossing of the curves

Overview: Safety CARTITUDE-4

Adverse Event	Cilta-cel* (N=188) %	Standard Therapy (N=208) %
Any TEAE	100	100
Any Grade 3-4	84	91
Grade 3	21	35
Grade 4	**63**	**56**
Serious AEs	37.8	38.9
AEs leading to death*	**11**	**8**

Source: FDA
Data cutoff November 1, 2022
* Safety population includes subjects receiving conforming cilta-cel: treated under study and treated after progression
Abbreviations: AE, adverse event; TEAE, treatment adverse event

Adverse Events of Special Interest

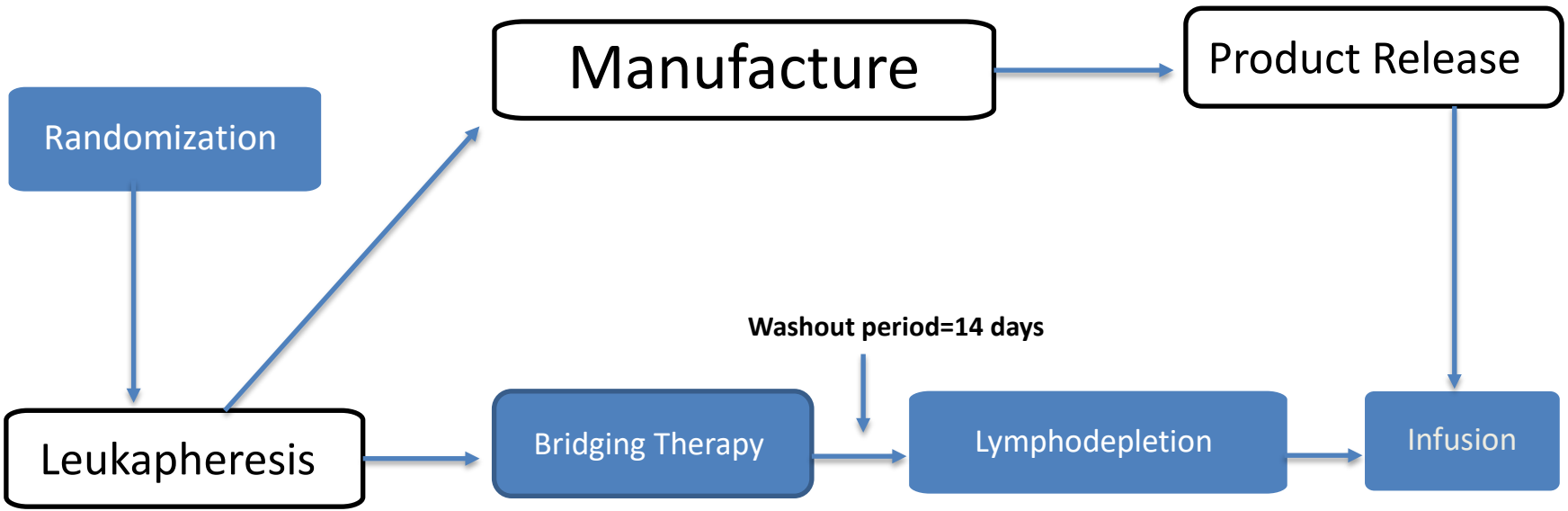
	Cilta-cel (N=188) %		Standard Therapy (N=208) %	
AESI	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
CRS	77	3	1	0
Neurotoxicity	23	4	0	0
HLH/MAS	1	0.5	0	0
Infections	57	24.5	71	22.6
Secondary primary malignancy	4.3	N/A	6.7	N/A
Hematologic neoplasm	**1.6**	**1.6**	0	-
Cytopenia *	-	-	-	-
Neutropenia	99	95	98	87
Thrombocytopenia	94	44	87	20

Source: FDA
Data cutoff November 1, 2022
* Based on laboratory results
Safety population includes conformal cilta-cel including patients who received cilta-cel on progression as subsequent therapy.
Abbreviations: AESI, adverse events of special interest; CRS, cytokine release syndrome; HLH/MAS, hemophagocytic lymphohistiocytosis

Major Issue

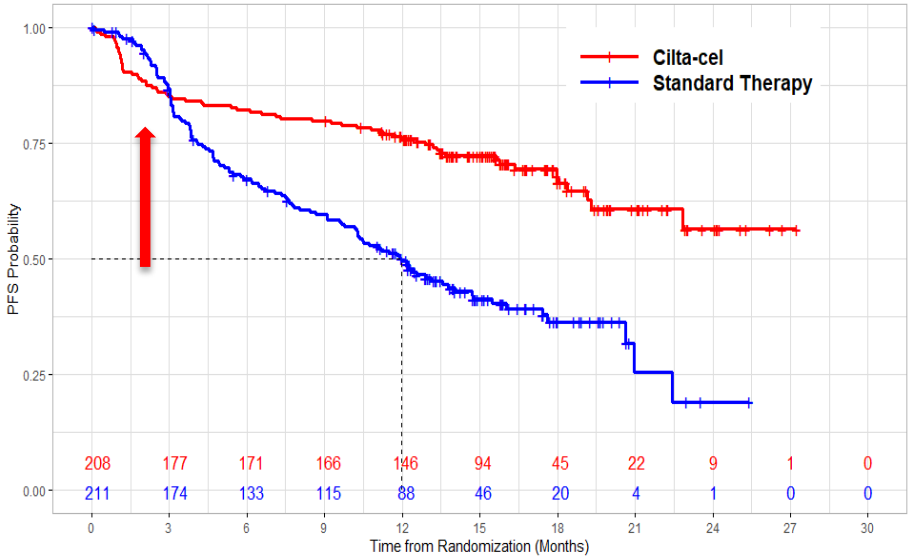
Increased rate of early deaths in the cilta-cel arm

CAR-T Therapy



Source: FDA

Progression Free Survival, Intention-to-Treat (ITT)



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PFS per IMWG 2016 consensus criteria for response
Median is based on Kaplan-Meier estimate

Source: FDA
Data cutoff November 1, 2022
Abbreviations: CI, confidence interval; IMWG, International Myeloma Working Group; NE, not evaluable; PD, progressive disease; PFS, progression free survival

Overview of Deaths, ITT Population

Deaths	Cilta-cel (N=208) %	Standard Therapy (N=211) %
Total deaths, ITT	18.8	22.3
Progressive disease	6.7	14.7
Adverse event	**11**	**7.1**
Death 0 to ≤10 months	**14**	**12**
Progressive disease	6.2	7.1
Adverse event	**7.7**	**4.7**
Death >10 months	4.8	10
Progressive disease	1.9	7
Adverse event	2.8	3.3

Data cutoff, November 1, 2022

Table includes deaths in all randomized subjects including three subjects who received nonconformal cilta-cel.

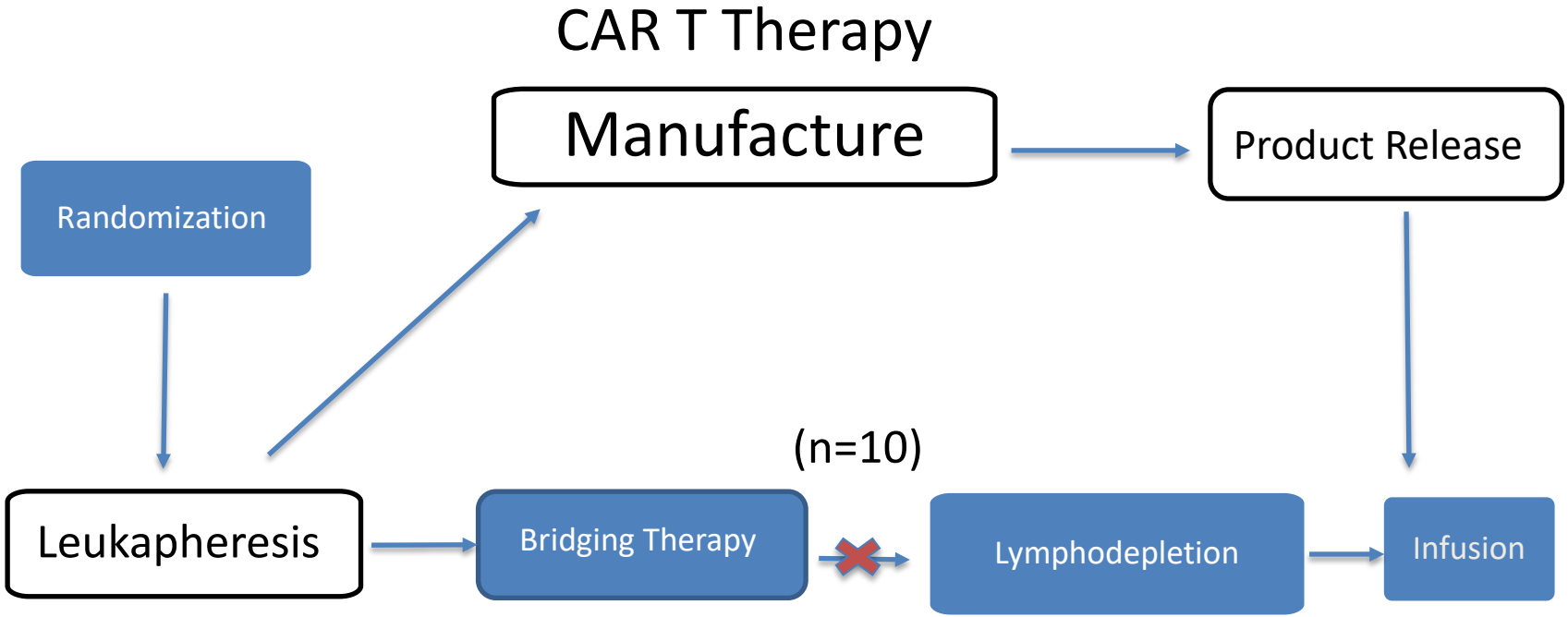
Table includes all deaths after treatment from AEs including infection related AEs following disease progression and subsequent AMT.

Abbreviation: ITT, intent-to-treat

Higher Rate of Death in First 10 Months After Randomization

	Cilta-cel (N=208) %	Standard Therapy (N=211) %
Total	**14**	**12**
Prior to treatment	**4. 8**	**0.5**
PD	4.8	0.5
AE	-	-
After treatment	9.1*	11.3
PD	1.4	7.1
AE	**7.7**	**4.2**

Source: FDA
Data cutoff November 1, 2022
* 8/19 deaths occurred after receiving cilta-cel as subsequent anti-myeloma therapy following progression
Abbreviations: AE, adverse event; PD, progressive disease; ST, standard therapy



Source: FDA, Data cutoff November 1, 2022

Early Progressive Disease or Death

32 subjects in the cilta-cel arm had progressive disease or died prior to receiving cilta-cel

- 12 subjects never received cilta-cel
  - 10 subjects died within 10 months after randomization
- 20 received cilta-cel as subsequent therapy
  - 8 died within 10 months after randomization

Bridging Therapy in Patients Receiving Cilta-cel as Per Study Treatment and Patients Who Progressed or Died Early

	Cilta-cel (N=208)	
	Cilta-cel (N=176)	Rapid PD or Death (N=32)
Received BT (%)	100	100
Type of BT (%)		
DPd	90	75
PVd	10	25
Duration of BT (months)		
Median (range)	1.6 (0.41, 6.1)	1.4 (0.03, 4.3)
Number of cycles (%)		
1	33	25
2	59	59
3	18	9
>4	3	6
Time from leukapheresis to product release (days) Median (Range)	79 (45, 246)	55 (29, 66)

Source: FDA; Abbreviation: BT, bridging therapy

Exploratory Analysis for Early Mortality, Prognostic Factors

Prognostic Factor	Cilta-cel (N=208) %	Standard Therapy (N=211) %
EMP	-	-
Present	4.8	3.8
Absent	9	8
R-ISS	-	-
Stage III	1	2
Stage I/II	8/5	5/5
Cytogenetics	-	-
High-risk	6.2	4.7
Absent high-risk	10	7.1
Age (years)		
65-75	5	5
<65	9	7
ECOG PS		
1	9	7
0	4	5
Lines of therapy	-	-
1	5	2
2 or 3	9	9
Triple-class refractory	-	-
Yes/No	2.8/11	2.8/9

29 deaths in cilta-cel arm
25 deaths in standard therapy arm

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

Source: FDA

Deaths in Safety Population Within 90 Days of Treatment Start

Deaths	Cilta-cel (N=188) %	Standard Therapy (N=208) %
Total deaths	13	22
Adverse event	**11**	**8**
Progressive disease	3	14
Deaths ≤90 days after treatment start	**5**	**0**
Adverse event	**4**	**0**
Progressive disease	0.5	0
Deaths >90 days after treatment start	8.5	22
Adverse event	6.4	8
Progressive disease	2	14

Source: FDA
Data cutoff November 1, 2022

Death From TEAEs Safety Population

Category	Cilta-cel (N=188) %	Standard Therapy (N=208) %
Total deaths	**13**	**22**
Adverse events	**11**	**8**
COVID-19 pneumoniae	3.7	0.5
Pneumoniae^	1	1.9
Sepsis	1.6	0.9
Hemorrhage*	4	0.9
CMV colitis	2	0
Others AE	1.6	3.4

Data cutoff November 1, 2022

^ Pneumoniae includes influenza pneumoniae, respiratory infection, pneumoniae, and pneumocystis jiroveci pneumonia

* Hemorrhage includes intraparenchymal bleeding, intracranial hemorrhage, retroperitoneal bleed, and subdural hematoma

Abbreviations: AE, adverse events; CMV, cytomegalovirus; COVID-19, Coronavirus Disease 2019; JC, John Cunningham; TEAE, treatment adverse event

Summary of Deaths

- Higher rate of death in the first 10 months in the ITT population: 14% in the cilta-cel arm versus 12% in the standard therapy arm
- Higher rate of deaths due to AEs in the safety population
- Higher rate of death from TEAEs within 90 days of treatment start: 4% in cilta-cel versus 0% in standard therapy arm in safety population

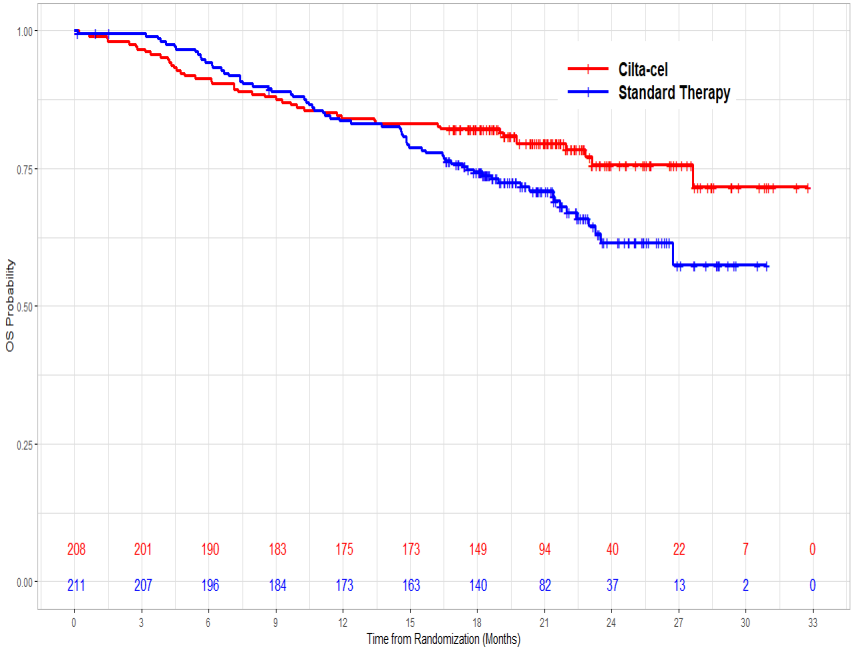
Abbreviations: AE, adverse event; ITT, intent-to-treat; TEAE, treatment adverse event

Overall Survival

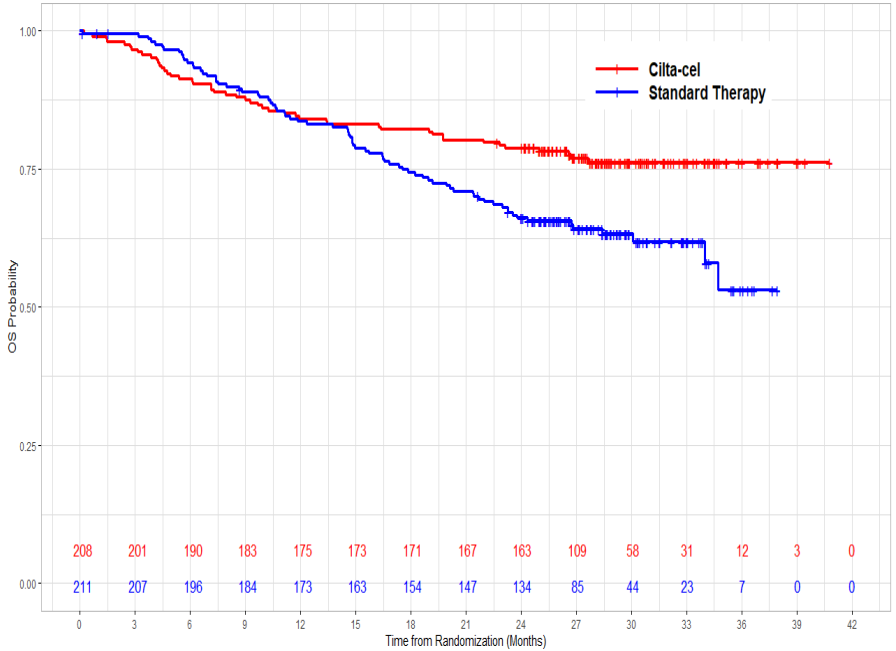
- OS is gold standard endpoint in Oncology
- OS is clinically meaningful measure of safety and efficacy
- OS plays an important role in the benefit-risk determination in the context of totality of data

OS Results With Longer Follow-Up Data

Data Cutoff April 17, 2023



Data Cutoff December 13, 2023



Due to heavy censoring, longer term follow up is needed to confirm the OS benefit.

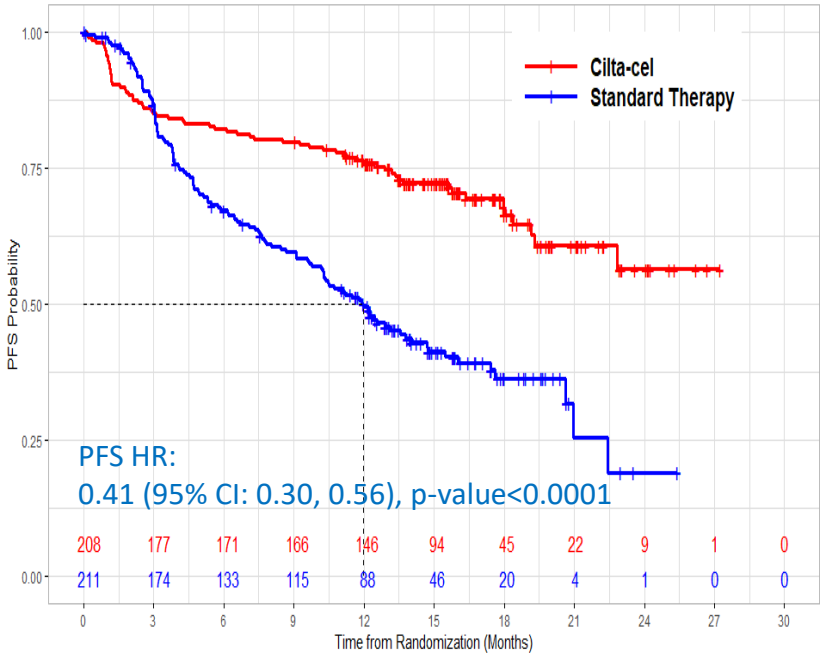
Uncertain Clinical Benefit

- Improvement in PFS and Response rates
- Increased rate of early deaths in the cilta-cel arm, persisting for first 10 months
- Uncertainty in clinical benefit

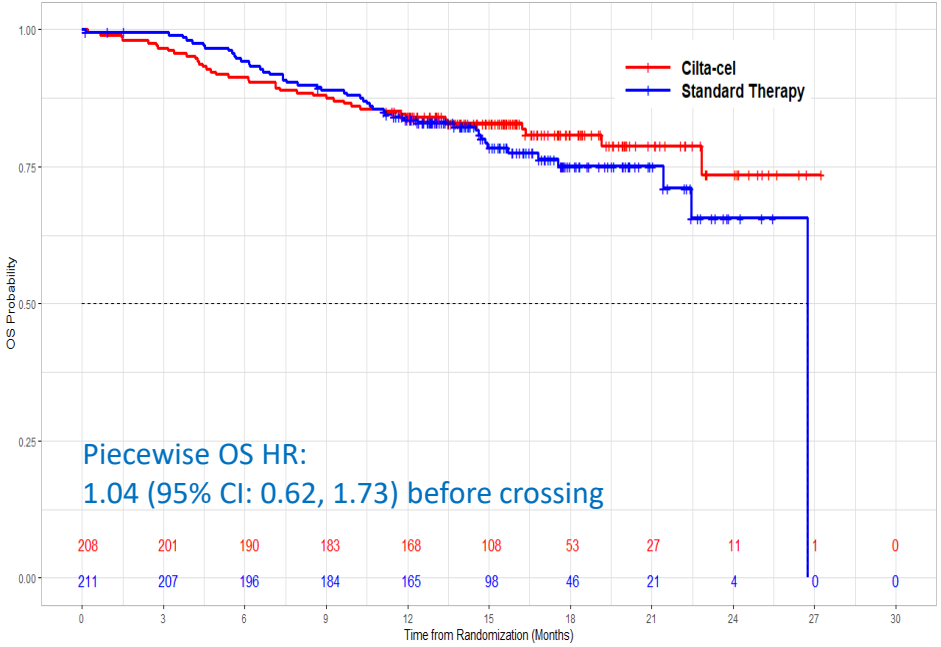
Abbreviations: OS, overall survival; PFS, progression-free survival

FDA's Efficacy Results

PFS per IRC (ITT), Data Cutoff November 1, 2022



OS (ITT), Data Cutoff November 1, 2022



FDA's Primary Concern

- Early OS detriment, in the context of PFS benefit
- Possible causes:
  - Delayed administration
  - Cilta-cel toxicity

Duration of Increased Risk of Early Death

- FDA sought to quantify the duration of increased risk of early death in the cilta-cel arm compared to the standard therapy arm
- Piecewise hazard ratio assessment based on different landmark timepoints to estimate the treatment effect

Piecewise HR Assessment

Time Interval	Piecewise HR	95% CI
Time interval of 3 months		
0-≤3	6.24	(0.75, 51.85)
3-≤6	1.07	(0.46, 2.47)
6-≤9	0.65	(0.25, 1.68)
9-≤12	0.72	(0.29, 1.78)
Time interval of 5 months		
0-≤5	2.40	(0.99, 5.85)
5-≤10	0.69	(0.33, 1.42)
10-≤15	0.35	(0.14, 0.90)
Time interval of 10 months		
0-≤10	1.16	(0.68, 1.99)

Data cutoff November 1, 2022

* >15 months not reported due to heavy censoring

- Detrimental effect on OS extends beyond 3 months after randomization

Patient-Reported Outcomes (PRO)

- PRO endpoint Time to Worsening of Symptoms in the MySIm-Q Total Symptom Score was not formally tested since it follows OS in statistical hierarchy
- Infrequent assessment of PROs early in trial during acute CAR T toxicity
- Longitudinal PRO data does not include experience of patients with early mortality

Conclusions

- **Cilta-cel in RRMM after 1-3 prior lines and lenalidomide refractory**
  - PFS benefit
  - Improvement in ORR
- **Increased rate of early death**
  - Study was not designed to identify predictive factors for early mortality
  - Inherent risk of autologous CAR T therapy
- **Uncertain benefit-risk of cilta-cel in the proposed population**

Discussion Questions

- Discuss whether the results of CARTITUDE-4 are sufficient to support a positive risk-benefit assessment of ciltacabtagene autoleucel for the proposed indication.
- Is the risk of early death associated with ciltacabtagene autoleucel treatment acceptable in the context of the PFS benefit?

Voting Question

Is the risk-benefit assessment for ciltacabtagene autoleucel for the proposed indication, favorable?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