Ciltacabtagene Autoleucel vs Standard of Care in Lenalidomide-Refractory Multiple Myeloma: Phase 3 CARTITUDE-4 Subgroup Analysis by Cytogenetic Risk

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Disclosure of Conflicts of Interest

HE has served in a consulting/advisory role for Amgen, BMS/Celgene, GSK, Janssen, and Sanofi; and has received honoraria and research funding from Amgen, BMS/Celgene, GSK, Janssen, and Sanofi. **RM** has received fees for consulting, advisory committees, and/or honoraria from Amgen, BMS, Celgene, Janssen, Pfizer, Sanofi, and Takeda. **BD** has served in a consulting/advisory role for, and received honoraria from, Arcellx, Genentech, GSK, Janssen, Karyopharm, Pfizer, and Sanofi; and has served on speakers' bureau for Arcellx, Genentech, GSK, Janssen, Karyopharm, Pfizer, and Sanofi. **JS-M** has served in a consulting/advisory role for, and received honoraria from, AbbVie, Amgen, BMS, Celgene, GSK, Haemalogix, Janssen, Karyopharm, MSD, Novartis, Pfizer, Regeneron, Roche, Sanofi, Secura Bio, and Takeda. **MK** has served in a consulting/advisory role for, and received honoraria from, Celgene, Gilead, Novartis, and Pfizer. **DP** has received honoraria from BMS/Celgene, Gilead, and Jazz Pharmaceuticals. **HM**, **MDutka**, and **SW** have no conflicts to disclose. **MDelforge** has served in a consulting/advisory role for Amgen, BMS, GSK, Janssen, Sanofi, StemlineTherapeutics, and Takeda. **RV** has received honoraria from BMS, Harpoon, Janssen, Karyopharm, Legend Biotech USA Inc., Pfizer, Sanofi, and Takeda; and has received research funding from BMS, Sanofi, and Takeda. **S-SY** has served in a consulting/advisory role for Amgen, Antengene, Astellas, Celgene, Janssen, Novartis, and Takeda; has received honoraria from Novartis; and has received research funding from Kyowa Hakko Kirin, Roche-Genentech, and Yuhan Pharma. **MCM** has served in a consulting/advisory role for CDR-Life, GSK, and Janssen-Cilag; has received research funding from BeiGene; and has served on speakers' bureau for Celgene/BMS, Janssen Medical Affairs, and Medscape. **NL**, **CL**, **MV**, **KL**, **DC**, **T-mY**, **NB**, and **TL** are employees of Janssen. **AS** is an employee of Cilag GmbH. **MZ** is an employee of IQVIA. **MK**, **NP**, **EF**, and **OCF** are employees of Legend Biotech USA Inc. **SM** has served in a consulting/advisory role for Adaptive Biotechnologies, Amgen, Celgene/BMS, Janssen, Pfizer, Regeneron, Roche/Genentech, and Sanofi,. **JM-L** has served in a consulting/advisory role for BMS, Janssen, and Novartis; has received research funding from Astellas and BMS; and speakers' bureau for BMS, Janssen-Cilag, and Roche.

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CARTITUDE-4 Study Overview

- The phase 3 CARTITUDE-4 study is evaluating cilta-cel vs SOC in patients with lenalidomide-refractory MM and 1–3 prior LOT[1,2]
- In the primary analysis:
  - Cilta-cel prolonged PFS (P<0.0001)[1]
  - ORRs were higher with cilta-cel vs SOC (85% vs 67%), as were rates of ≥CR (73% vs 22%)[1]
  - MRD-negativity rates were higher with cilta-cel vs SOC (61% vs 16%; 10^{-5} threshold)[1]
- Based on CARTITUDE-4 results, cilta-cel was recently approved in the US and the EU for patients with lenalidomide-refractory MM who have received ≥1 prior LOT[3,4]
- High-risk cytogenetic abnormalities in patients with lenalidomide-refractory MM negatively impact prognosis in real-world datasets (real-world PFS HR, 1.39 [95% CI, 1.20–1.61] vs standard risk)[5]
  - However, some treatments may partially overcome the adverse effects of high-risk cytogenetics[6]
- We report the efficacy of cilta-cel compared with SOC in CARTITUDE-4 patients with high-risk cytogenetic abnormalities, including t(4;14), del(17p), t(14;16), and gain/amp(1q)

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Cilta-cel, ciltacabtagene autoleucel; CR, complete response; EU, European Union; HR, hazard ratio; LOT, lines of therapy; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival; SOC, standard of care; US, United States. 1. San-Miguel J, et al. *N Engl J Med* 2023;389:335-47. 2. ClinicalTrials.gov, NCT04181827. 3. CARVYKTI® (ciltacabtagene autoleucel). Prescribing information. Horsham, PA, and Somerset, NJ: Janssen Biotech, Inc., and Legend Biotech; 2022. 4. CARVYKTI® (ciltacabtagene autoleucel). Summary of product characteristics. Horsham, PA, and Somerset, NJ: Janssen Biotech, Inc., and Legend Biotech; 2023. 5. Dhakal B, et al. Manuscript submitted for publication. 2024. 6. Sonneveld P, et al. *Blood* 2016;127:2955-62.

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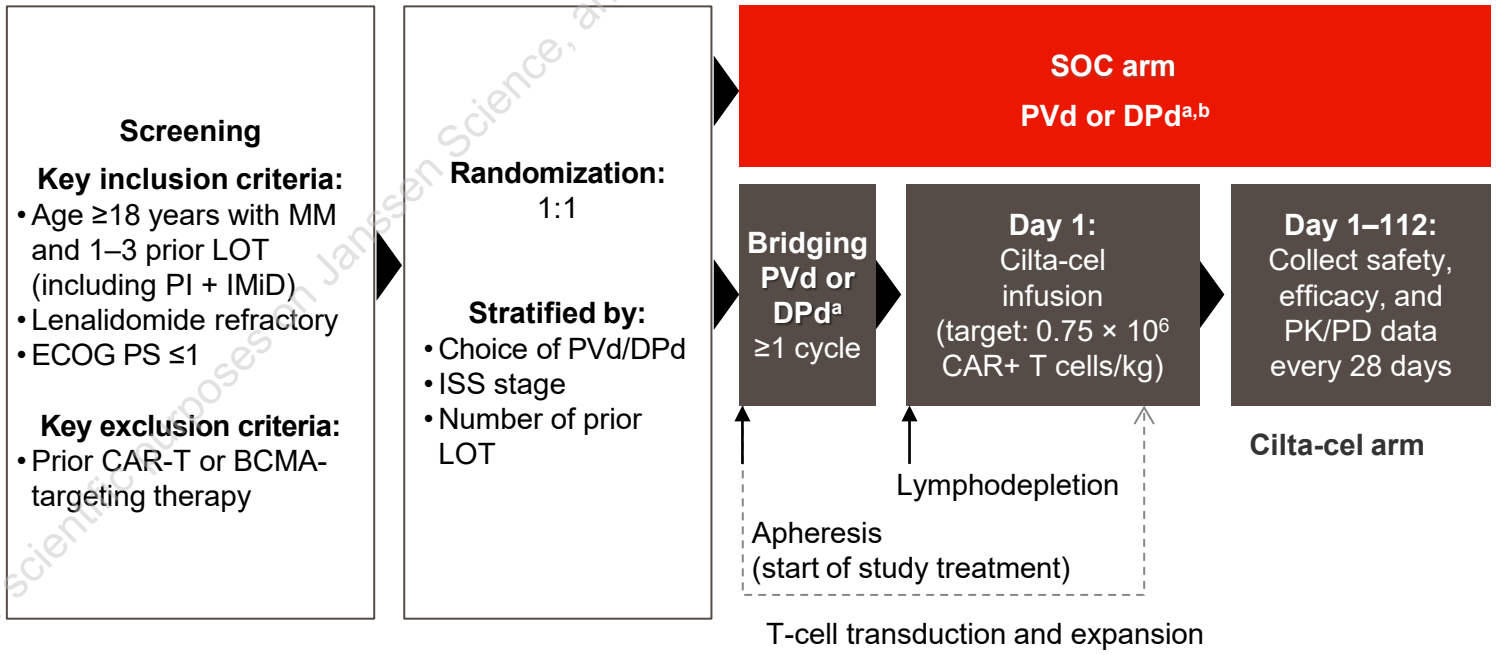
CARTITUDE-4: Methods

- CARTITUDE-4 is a randomized, open-label trial
- Patients with high-risk cytogenetics had ≥1 of the following cytogenetic abnormalities at baseline determined by fluorescence in situ hybridization: t(4;14), del(17p), t(14;16), or gain/amp(1q)
- Due to low patient numbers, data for patients with t(14;16) are not shown as a separate subgroup but are included in the high-risk group

CARTITUDE-4 study design



[a]Physicians' choice. [b]Administered until disease progression.
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; DPd, daratumumab, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; ISS, International Staging System; LOT, line of therapy; MM, multiple myeloma; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics; PVd, daratumumab, bortezomib, and dexamethasone; SOC, standard of care.

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CARTITUDE-4: Patients with High-Risk Cytogenetics

- At data cut-off on November 1, 2022, the median follow-up was 15.9 (range, 0.1–27.3) months
- Of 419 randomized patients, 394 were evaluable, 255 had high-risk cytogenetics, and 139 had standard-risk cytogenetics
- Baseline characteristics were similar in patients with high-risk cytogenetics in the cilta-cel vs SOC arms

Characteristic	High risk	
	Cilta-cel (n=123)	SOC (n=132)
Age, median (range), years	62 (40–78)	62 (35–80)
Male	65 (52.8)	71 (53.8)
Cytogenetic high-risk abnormality		
gain/amp(1q)	**89 (72.4)**	**107 (81.1)**
del(17p)	**49 (39.8)**	**43 (32.6)**
t(4;14)	**30 (24.4)**	**30 (22.7)**
t(14;16)	**3 (2.4)**	**7 (5.3)**
≥2 high-risk abnormalities	**43 (35.0)**	**49 (37.1)**
del(17p), t(14;16), or t(4;14)	**73 (59.3)**	**69 (52.3)**
ISS stage		
I	77 (62.6)	79 (59.8)
II	38 (30.9)	46 (34.8)
III	8 (6.5)	7 (5.3)
Soft tissue plasmacytomas	27 (22.0)	20 (15.2)
Years since diagnosis, median (range)	3.2 (0.5–12.1)	3.4 (0.5–13.2)
Prior LOT, median (range)		
1	39 (31.7)	45 (34.1)
2–3	84 (68.3)	87 (65.9)
Previous ASCT	104 (84.6)	120 (90.9)
Triple-class exposed[a]	33 (26.8)	34 (25.8)
Refractory status		
Daratumumab	29 (23.6)	27 (20.5)
Triple-class[a]	17 (13.8)	20 (15.2)
To last LOT	121 (98.4)	130 (98.5)
Bridging therapy		
DPd	106 (86.2)	116 (87.9)
PVd	17 (13.8)	16 (12.1)

All data are n (%) unless otherwise specified.
[a]Includes ≥1 PI, ≥1 IMiD, and 1 anti-CD38 monoclonal antibody.
ASCT, autologous stem cell transplant; cilta-cel, ciltacabtagene autoleucel; DPd, daratumumab, pomalidomide, and dexamethasone; IMiD, immunomodulatory drug; ISS, International Staging System; LOT, line of therapy; PI, proteasome inhibitor; PVd, daratumumab, bortezomib, and dexamethasone; SOC, standard of care.

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Efficacy Outcomes by Cytogenetic Risk

- Overall, high-risk cytogenetics were not associated with poorer outcomes with cilta-cel; by contrast, efficacy in the SOC arm was lower in patients with high-risk cytogenetics than in those with standard-risk cytogenetics

Endpoint	Cilta-cel		SOC	
	Standard risk (n=69)	High risk (n=123)	Standard risk (n=70)	High risk (n=132)
ORR, n (%)	59 (85.5)	105 (85.4)	50 (71.4)	87 (65.9)
≥CR, n (%)	51 (73.9)	90 (73.2)	18 (25.7)	26 (19.7)
MRD negativity (10^{-5}), n (%)	34 (49.3)	86 (69.9)	13 (18.6)	19 (14.4)
PFS, median (95% CI), mo	NE (NE–NE)	NE (18.4–NE)	20.6 (11.2–NE)	10.3 (7.6–12.5)

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cilta-cel, ciltacabtagene autoleucel; CR, complete response; mo, month(s); MRD, minimal residual disease; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival; SOC, standard of care.

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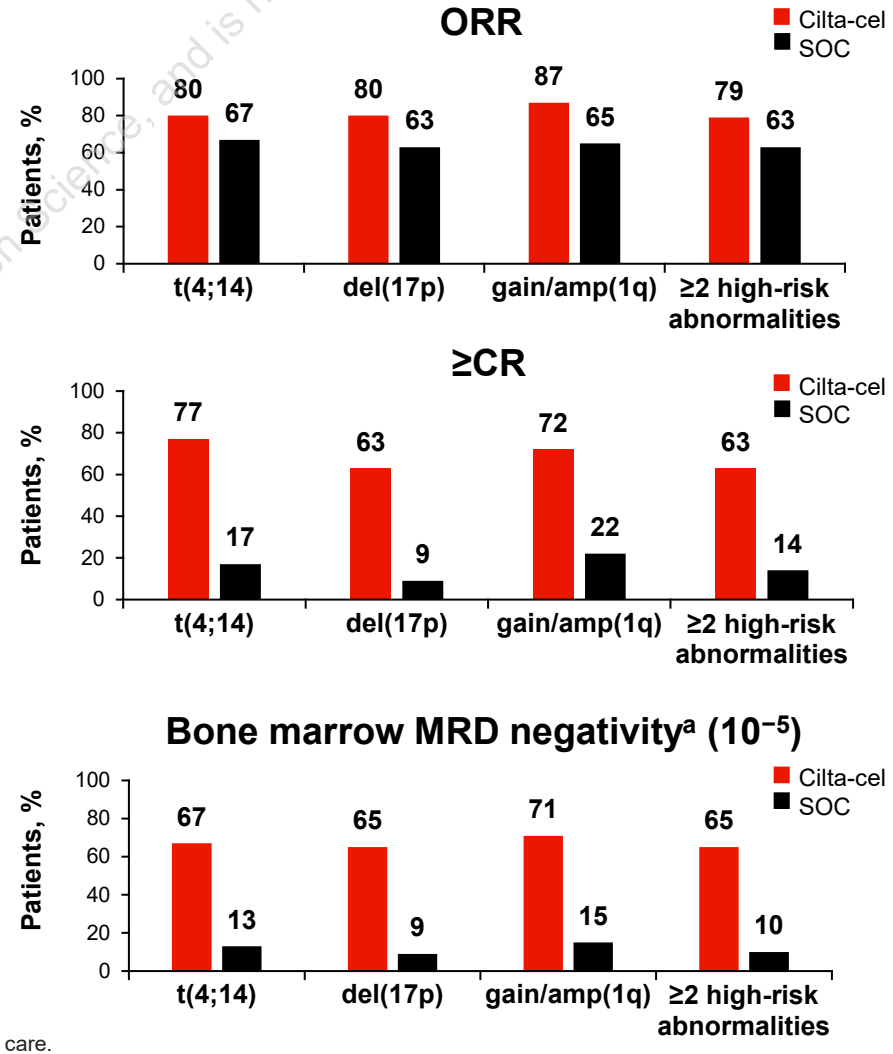
Treatment Response by Cytogenetic Risk Abnormality

- The ORR was higher, and the rates of ≥CR and bone marrow MRD negativity were substantially higher, with cilta-cel than with SOC for each abnormality



[a]MRD was assessed centrally by next-generation sequencing.
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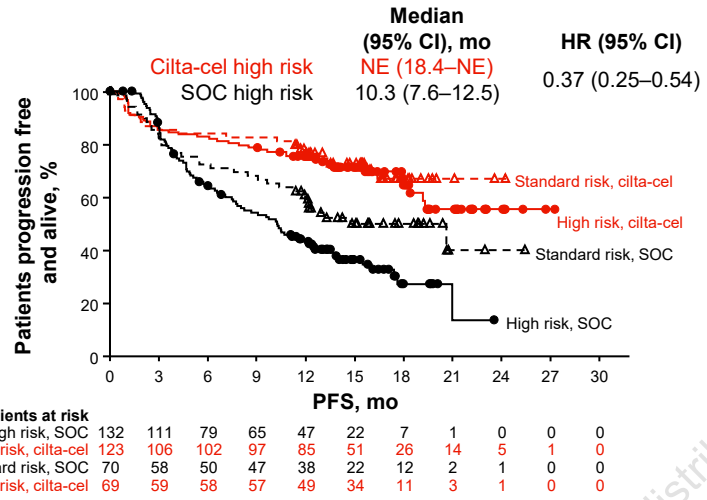
PFS by Cytogenetic Risk Abnormality

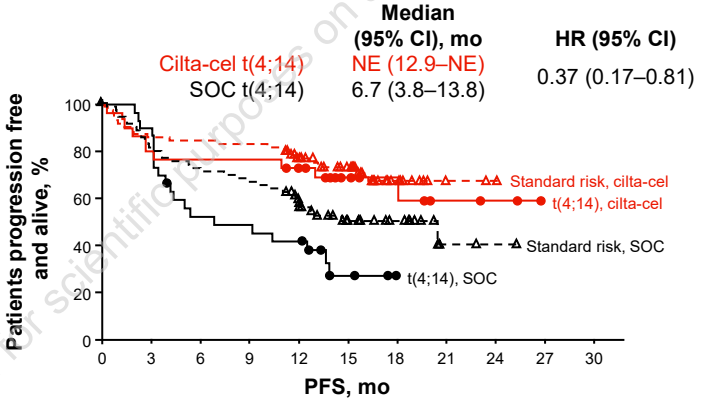
- Cilta-cel lessens the impact of high-risk cytogenetics on PFS and also improved PFS vs SOC
  - In patients with gain/amp(1q), the median PFS was NE with cilta-cel (95% CI, 18.4–NE) vs 10.3 (95% CI, 7.5–14.0) months with SOC (HR, 0.37 [95% CI, 0.24–0.59])

High risk



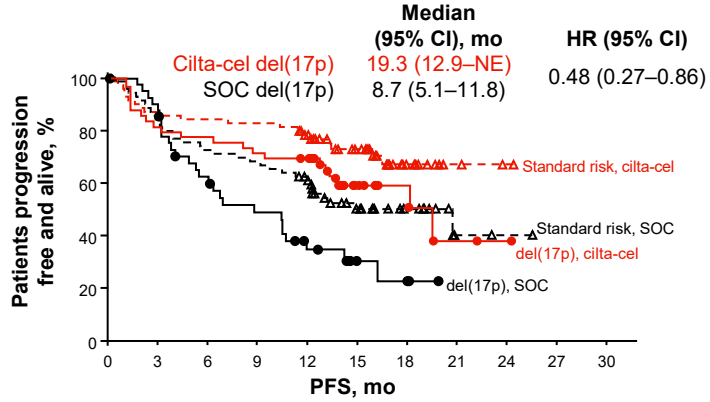
Patients at risk											
High risk, SOC	132	111	79	65	47	22	7	1	0	0	0
High risk, cilta-cel	123	106	102	97	85	51	26	14	5	1	0
Standard risk, SOC	70	58	50	47	38	22	12	2	1	0	0
Standard risk, cilta-cel	69	59	58	57	49	34	11	3	1	0	0

t(4;14)



Patients at risk											
t(4;14), SOC	30	26	15	14	12	4	0	0	0	0	0
t(4;14), cilta-cel	30	24	23	23	20	11	7	4	2	0	0
Standard risk, SOC	70	58	50	47	38	22	12	2	1	0	0
Standard risk, cilta-cel	69	59	58	57	49	34	11	3	1	0	0

del(17p)



Patients at risk											
del(17p), SOC	43	34	23	18	10	4	2	0	0	0	0
del(17p), cilta-cel	49	40	38	35	31	13	5	2	1	0	0
Standard risk, SOC	70	58	50	47	38	22	12	2	1	0	0
Standard risk, cilta-cel	69	59	58	57	49	34	11	3	1	0	0

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cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; mo, month(s); NE, not evaluable; PFS, progression-free survival; SOC, standard of care.

Conclusions

- Cilta-cel demonstrated favorable efficacy outcomes—including higher ORRs, higher rates of ≥CR and MRD negativity, and improved PFS—vs SOC in patients with high-risk cytogenetic abnormalities and standard-risk cytogenetics
- The efficacy of cilta-cel vs SOC in CARTITUDE-4 supports cilta-cel as a potential new SOC in lenalidomide-refractory MM as early as first relapse, including in patients with high-risk cytogenetics

Cilta-cel demonstrated consistent and robust efficacy regardless of cytogenetic risk status

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