Comparative efficacy of ciltacabtagene autoleucel in CARTITUDE-1 versus physician's choice of therapy in the long-term follow-up of POLLUX, CASTOR, and EQUULEUS clinical trials for the treatment of patients with relapsed or refractory multiple myeloma

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Online Resource 1 (Supplemental Material)

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Table S1: Ranking of prognostic factors and availability in CARTITUDE-1 and physician's choice cohort

Prognostic Factor	Rank	Available in CARTITUDE-1?	Available in Physician's Choice Cohort?	Categories
Refractory status[a]	Required*	Yes	Yes	Penta refractory (at least 2 IMiDs, 2 PIs, and an anti-CD38 MoAB); triple or quad refractory (2 IMiDs and 1 PI; or 2 PIs and 1 IMiD; or 2 IMiDs and 2 PIs); Others
Cytogenetic profile	Required*	Yes	Yes	High risk (at least one of del17p, t[4;14], or t[14;16]); standard risk; unknown
ISS stage	Required*	Yes	Yes	I; II; III
Extramedullary plasmacytoma[b]	Required*	Yes	Yes	No; yes
Time to progression on last regimen	Required*	Yes	Yes	≤ 4 months; > 4 months
Number of prior LOTs	Required*	Yes	Yes	≤ 4; > 4
Years since MM diagnosis	Required*	Yes	Yes	< 6; ≥ 6
Age (years)	Required*	Yes	Yes	< 65; ≥ 65
Hemoglobin	9	Yes	Yes	< 12 g/dL; ≥ 12 g/dL
LDH levels	10	Yes	**No**	**NA**
Prior stem cell transplant	11	Yes	Yes	No; yes
ECOG status	12	Yes	Yes	0; 1
Race	13	Yes	Yes	White; black/ African American; not reported / other
Sex	14	Yes	Yes	Female; male
Type of MM	15	Yes	Yes	IgG; light chain; other

* Variables labelled "required" were considered equally important by clinical experts and were included in the base case analysis.

[a] Refractoriness was defined as from the case report form as progressive disease/relapsed per investigator assessment (physician's choice cohort) and by International Myeloma Working Group consensus criteria (CARTITUDE-1).[1]

[b] Refers to soft-tissue mass that is not in contact with bone; does not include bone-based plasmacytomas.[2]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ISS, International Staging System; LDH, lactate dehydrogenase; LOTs, lines of therapy; MM, multiple myeloma; MoAB, monoclonal antibody; NA, not applicable; PI, proteasome inhibitor

Table S2: Detailed overview of additional analyses

	Main Analysis	Exploratory Analysis	Sensitivity Analyses				Subgroup Analysis
		First Eligible LOT Only for Patients in the Physician's Choice Cohort	**1. Enrolled Population of CARTITUDE-1**	**2. Multivariable Regression**	**3. Adjustment for All Variables**	**4. Modified PFS Definition (Physician's Choice Cohort Only)**	**Penta-refractory (to at least two IMiDs, two PIs, and an anti-CD38 MoAB)**
CARTITUDE-1 Population	All treated patients	All treated patients	All enrolled patients	All treated patients	All treated patients	All treated patients	All treated patients who were penta-refractory
Inclusion Criteria for Physician's Choice Cohort	Key criteria from CARTITUDE-1[a] + no PD or death ≤ 47 days of index date[b]	Key criteria from CARTITUDE-1[a] + no PD or death ≤ 47 days of index date[b]	Key criteria from CARTITUDE-1[a]	Key criteria from CARTITUDE-1[a] + no PD or death ≤ 47 days of index date[b]	Key criteria from CARTITUDE-1[a] + no PD or death ≤ 47 days of index date[b]	Key criteria from CARTITUDE-1[a] + no PD or death ≤ 47 days of index date[b]	Key criteria from CARTITUDE-1[a] + no PD or death ≤ 47 days of index date[b] + penta-refractory
Statistical Method	IPTW with ATT weights (doubly robust)	IPTW with ATT weights (doubly robust)	IPTW with ATT weights (doubly robust)	Multivariable regression	IPTW with ATT weights (doubly robust)	IPTW with ATT weights (doubly robust)	IPTW with ATT weights (doubly robust)
Included LOTs for Patients in the Physician's Choice Cohort	All eligible LOTs	Patients' first eligible LOT only	All eligible LOTs	All eligible LOTs	All eligible LOTs	All eligible LOTs	All eligible LOTs
Covariates	Base case[c]	Base case[c]	Base case[c]	Base case[c]	Base case[c] + Hgb, prior SCT, ECOG status, race, sex, and type of MM	Base case[c]	Base case[c] excluding refractory status
Outcomes	ORR, ≥CR rate, PFS, OS, TTNT	ORR, ≥CR rate, PFS, OS, TTNT	ORR, ≥CR rate, PFS, OS, TTNT	ORR, ≥CR rate, PFS, OS, TTNT	ORR, ≥CR rate, PFS, OS, TTNT	Modified PFS definition (physician's choice cohort only)[d]	ORR, ≥CR rate, PFS, OS, TTNT

[a] Key criteria from CARTITUDE-1 were applied as follows: triple-class exposed (to at least one IMiD, at least one PI, and at least one anti-CD38 MoAB), at least three prior LOTs[i], ECOG score < 2, creatinine ≤ 2 mg/dL[ii], and progressed within 12 months of most recent LOT. Patients must also have received at least one subsequent treatment after triple-class exposure.

[b] 47 days was the median time between apheresis and infusion in CARTITUDE-1. This criterion was applied to avoid survivorship bias in favor of cilta-cel when the treated population of CARTITUDE-1 was included in the comparative analyses.

[c] Refractory status, cytogenetic profile, International Staging System stage, time to progression on last regimen, extramedullary plasmacytoma, number of prior LOTs, years since MM diagnosis, and age.

[d] Defined as the time from index date to disease progression, switch to subsequent treatment, or death due to any cause, whichever occurred first.

Abbreviations: ATT, average treatment effect in the treated; ≥CR, complete response or better; ECOG, Eastern Cooperative Oncology Group; Hgb, hemoglobin; IMiD, immunomodulatory drug; IPTW, inverse probability of treatment weighting; LOT, line of therapy; MM, multiple myeloma; MoAB,

[i] CARTITUDE-1 inclusion criteria required at least three prior LOTs *or* double refractoriness to an IMiD and a PI; however, all enrolled patients received at least three prior LOTs.

[ii] CARTITUDE-1 inclusion criterion was creatinine clearance of ≥40 mL/min/1.73 m^2; however, all enrolled patients had creatine levels ≤ 2 mg/dL.

monoclonal antibody; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; SCT, stem cell transplant; TTNT, time to next treatment

Table S3. Response outcomes in the penta-refractory subgroups of CARTITUDE-1 and the physician's choice cohort

	Observed Response		Unadjusted Comparison for Cilta-cel vs Physician's Choice	Adjusted[a] Comparison for Cilta-cel vs Physician's Choice
	CARTITUDE-1 (N = 41)	**Physician's Choice (N = 69)**	**Odds Ratio (95%CI), p-value**	**Odds Ratio (95%CI), p-value**
ORR	95.1%	29.0%	47.77 (12.98, 311.37), $p < 0.0001$	68.34 (13.76, 638.72), $p < 0.0001$
≥CR Rate	80.5%	1.4%	280.50 (50.32, 5338.17), $p < 0.0001$	2784.04 (98.08, 4062427.42), $p = 0.0009$

Odds ratios >1 indicate a favorable treatment effect for cilta-cel.

[a] Adjusted for International Staging System stage, cytogenetic profile, time to progression on last regimen, extramedullary plasmacytoma, number of prior lines of therapy, years since multiple myeloma diagnosis, and age.

Abbreviations: ≥CR, complete response or better; ORR, overall response rate

Table S4. Survival outcomes in the penta-refractory subgroups of CARTITUDE-1 and the physician's choice cohort

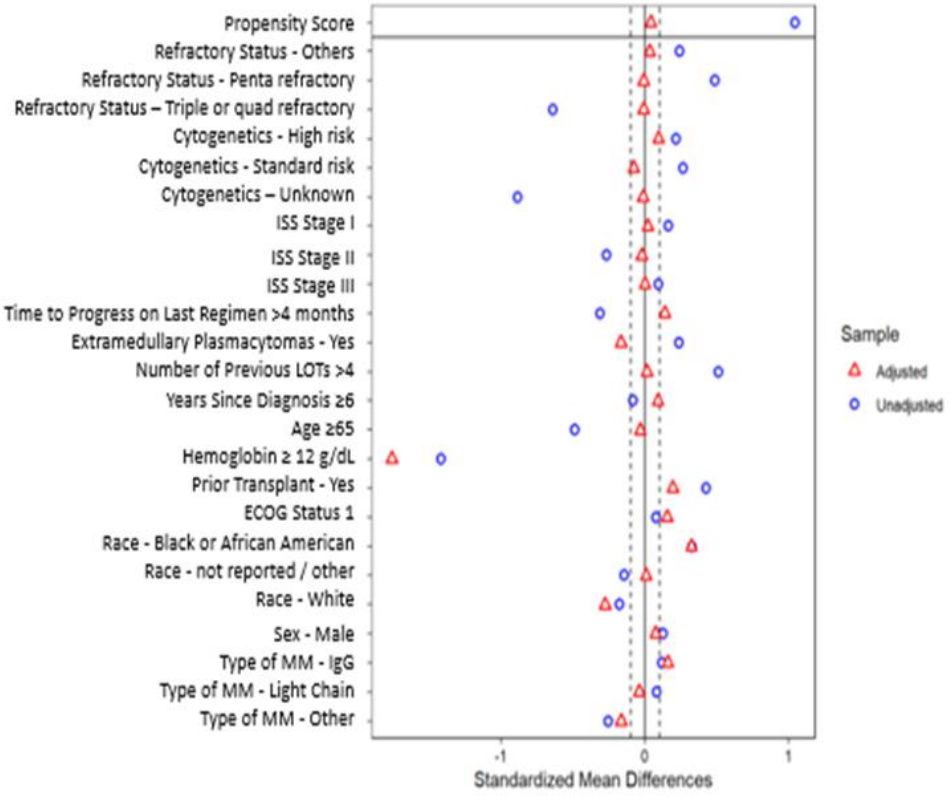
	Median (months) (95% CI)		Unadjusted Comparison for Cilta-cel vs Physician's Choice	Adjusted[a] Comparison for Cilta-cel vs Physician's Choice
	CARTITUDE-1 (N = 41)	Physician's Choice (N = 69)	Hazard Ratio (95%CI), p-value	Hazard Ratio (95%CI), p-value
PFS	NR (15.3, NR)	5.3 (3.2, 8.0)	0.21 (0.11, 0.41), p < 0.0001	0.21 (0.08, 0.55), p = 0.0013
TTNT	NR (NR, NR)	4.3 (3.1, 6.0)	0.15 (0.08, 0.29), p < 0.0001	0.12 (0.05, 0.30), p < 0.0001
OS	23.6 (NR, NR)	11.6 (8.0, 17.2)	0.26 (0.12, 0.53), p = 0.0003	0.23 (0.08, 0.66), p = 0.0059

Hazard ratios <1 indicate a favorable treatment effect for cilta-cel.

[a] Adjusted for International Staging System stage, cytogenetic profile, time to progression on last regimen, extramedullary plasmacytoma, number of prior lines of therapy, years since multiple myeloma diagnosis, and age.

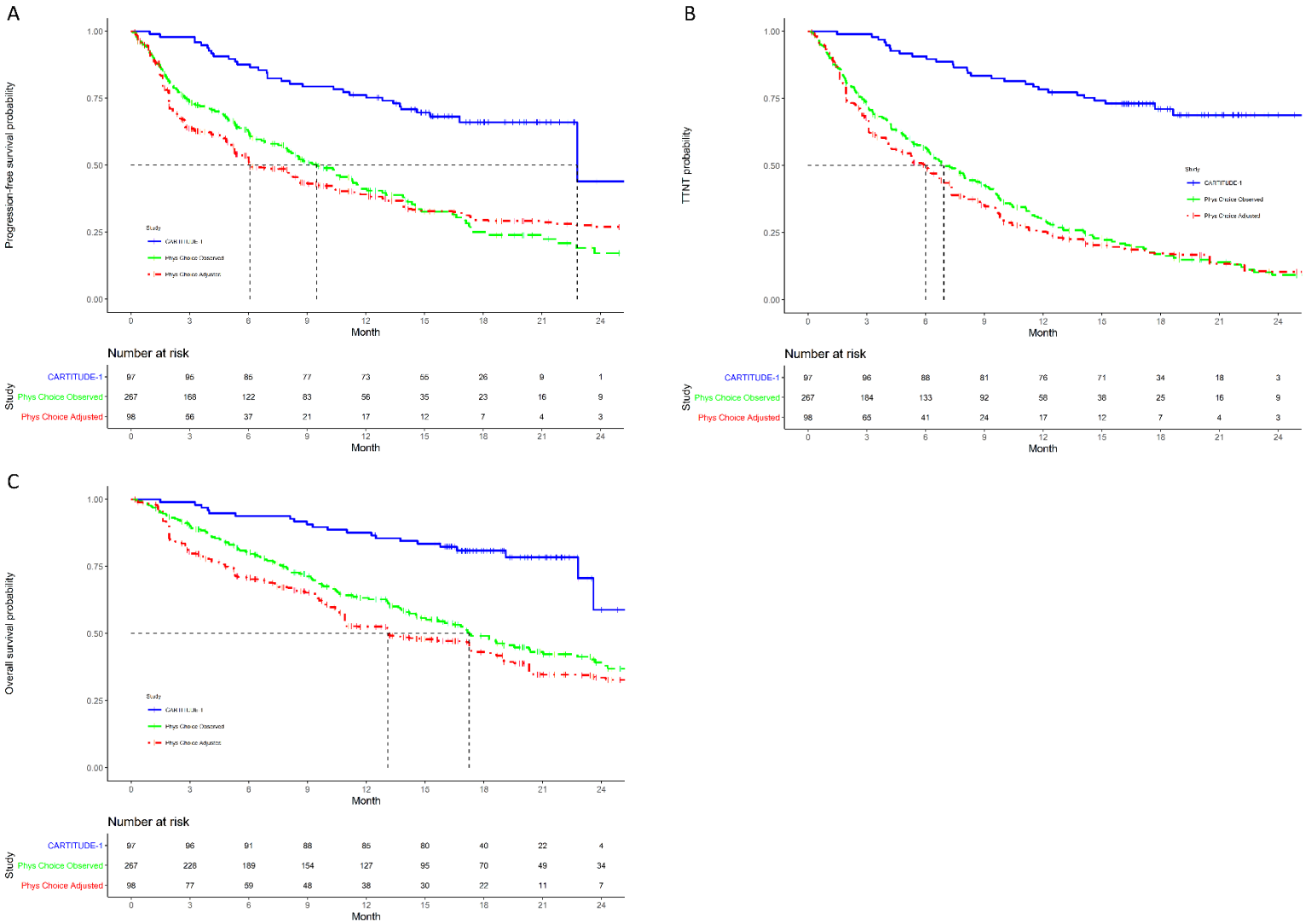
Abbreviations: NR, not reached; OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment

Fig. S1 Balance of covariates before and after ATT weighting for the base case



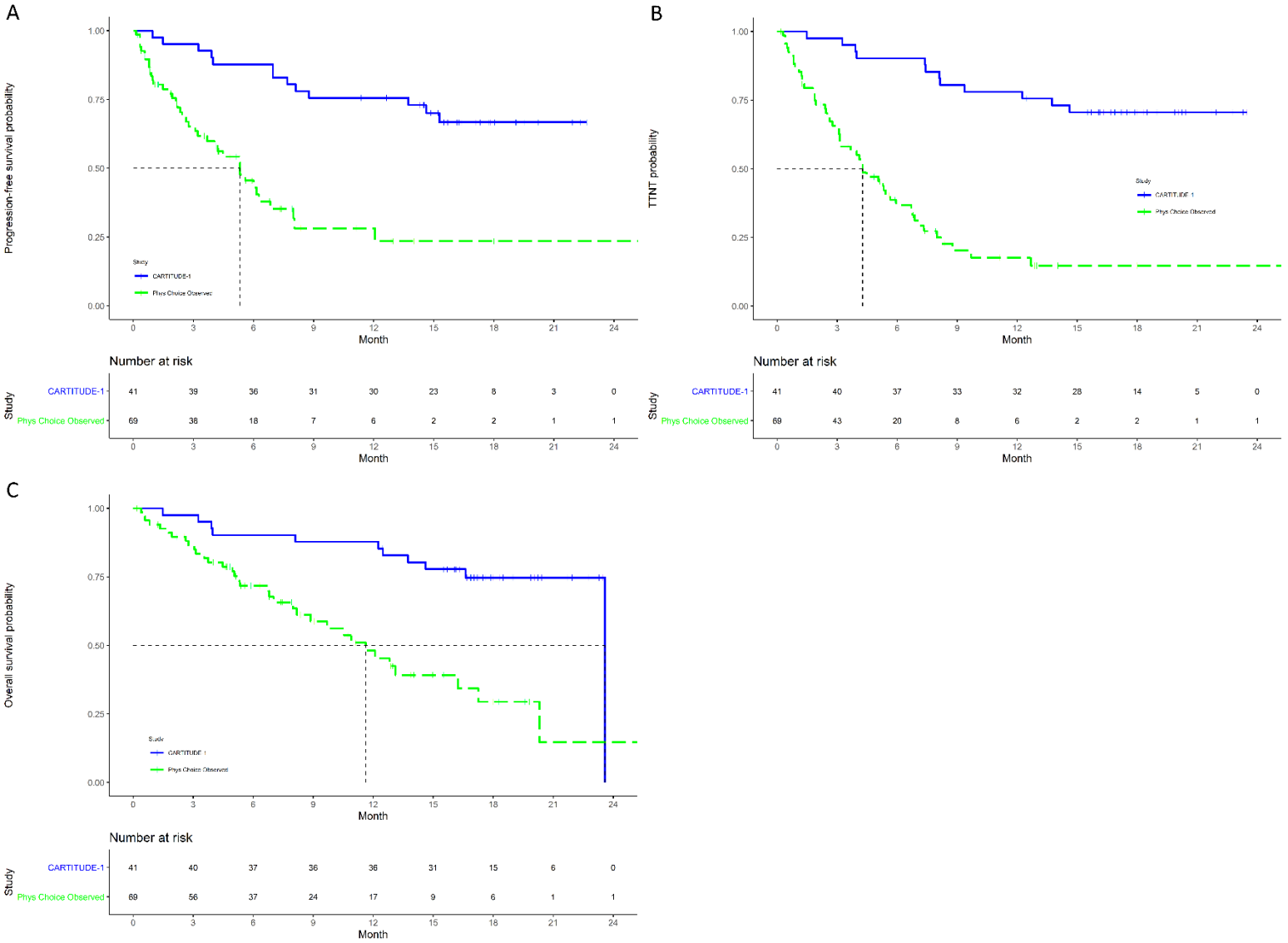
Note: the vertical dashed lines correspond to SMD=-0.1 and SMD=0.1
Penta refractory was defined as refractory to at least two IMiDs, two PIs, and an anti-CD38 MoAB; triple or quad refractory was defined as refractory to two IMiDs and one PI; or two PIs and one IMiD; or two IMiDs and two PIs. High risk cytogenetics included at least one of del17p, t(14;16), and t(4;14).
Abbreviations: ATT, average treatment effect in the treated; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ISS, International Staging System; LOTs, lines of therapy; MM, multiple myeloma; MoAB, monoclonal antibody; PI, proteasome inhibitor; SMD, standardized mean difference

Fig. S2 Kaplan–Meier estimated (A) progression-free survival, (B) time to next treatment, and (C) overall survival for CARTITUDE-1 (observed) and the physician's choice cohort (observed and adjusted); exploratory analysis including only patients' first eligible line of therapy in the physician's choice cohort



Note: Number at risk for the adjusted physician's choice cohort represents the sum of the propensity score weights, not the effective sample size. Adjusted results correspond to the base case scenario which adjusted for refractory status, cytogenetic profile, International Staging System stage, extramedullary plasmacytoma, time to progression on last regimen, number of prior lines of therapy, years since multiple myeloma diagnosis, and age. The adjusted curves reflect inverse probability of treatment weighting with average treatment effect in the treated weights (not doubly robust).

Fig. S3 Kaplan–Meier estimated (A) progression-free survival, (B) time to next treatment, and (C) overall survival for the penta-refractory subgroups of CARTITUDE-1 (observed) and the physician's choice cohort (observed)



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