Adjusted comparison of outcomes between patients from CARTITUDE-1 *versus* multiple myeloma patients with prior exposure to proteasome inhibitors, immunomodulatory drugs and anti-CD38 antibody from the prospective, multinational LocoMMotion study of real-world clinical practice

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APPENDICES

Appendix 1: Complete Details of Study Methods

Section 2 of the main text provided a synopsis of the study methods for this research. **Section 2.1** through **Section 2.5** below present the details of the research approach for this work.

2.1 Data Sources

2.1.1 *Patients Treated with Ciltacabtagene Autoleucel in CARTITUDE-1*

CARTITUDE-1 (NCT03548207) is an open-label, single arm phase 1b/2 clinical trial studying the safety and efficacy of cilta-cel in adult patients with triple-class exposed RRMM.[1] In short, a total of 113 patients were enrolled from multiple centers in the United States between July 2018 and October 2019. Enrolled patients underwent apheresis, and the collected T-cells were subsequently used to produce cilta-cel. A total of 97 patients received cilta-cel infusion, 16 discontinued: due to death (n=9), withdrawal (n=5) or progressive disease (n=2). The results presented here use data from CARTITUDE-1 as of July 2021, with a median duration of patient follow-up of 21.7 months.[2]

2.1.2 *Patients Receiving Treatments from Real World Clinical Practice in LocoMMotion*

LocoMMotion (NCT04035226) is the first prospective, multinational, non-interventional study of therapies used in RWCP in triple-class exposed patients with RRMM and was described elsewhere in detail.[3, 4] A total of 76 centers from nine European countries and the United States enrolled a total of 248 patients (Italy (24%), Germany (15%), France (14%), UK (11%), Spain (10%), United States (9%), Belgium (5%), Poland (5%), Netherlands (4%) and Russia (3%)) between August 2, 2019 and October 26, 2020. Response and progression events were assessed by a response review committee (RRC). Safety data in the form of incidence and severity of treatment emergent adverse events (TEAE) and patient reported outcomes (PROs) were also captured. The data used for analyses in this study included data from LocoMMotion as of May 2021, with a median duration of patient follow-up of 11 months.

2.2 *Analysis Populations and Design*

In CARTITUDE-1, 113 patients were enrolled and underwent apheresis. Sixteen patients discontinued the study between apheresis and infusion with cilta-cel. For analyses in the current study, data from the set of 97 patients infused with cilta-cel in CARTITUDE-1 were compared with the set of 170 patients from LocoMMotion who were progression free and alive 52 days after treatment initiation (see **Appendix 2** for additional rationale regarding this duration), the average number of days from apheresis to infusion in CARTITUDE-1; these groups (referred to as the *infused/aligned populations*) were analyzed to inform comparisons to assess the effectiveness of cilta-cel compared to RWCP. Second, analyses were also performed that involved the 113 patients enrolled in CARTITUDE-1, along with all 248 patients who were enrolled in LocoMMotion (from here forward referred to as the *enrolled populations*).

In CARTITUDE-1, index date was the date of apheresis for the enrolled population and the date of infusion for the infused population. The index date for the enrolled population from LocoMMotion was the date of treatment initiation, while the date of treatment initiation plus 52 days was used as the index date for the aligned population.

Baseline characteristics for population alignment

Analyses comparing the outcomes of non-randomized populations can be prone to bias due to confounding, driven by imbalances in prognostic baseline characteristics and hence require

adjustment. In the current study, potentially prognostic baseline patient covariates were identified by literature reviews and consulting with clinical experts. The following factors, available in both CARTITUDE-1 and LocoMMotion, were adjusted for in the analyses: refractory status, International Staging System (ISS), time to progression on last prior line, presence of extramedullary disease, number of prior lines of treatment (LOT), years since MM diagnosis, average duration of prior LOTs, age, sex, hemoglobin, lactate dehydrogenase (LDH), creatinine clearance, ECOG PS, and MM type. Values were measured at index date if available.

Complete data were available for CARTITUDE-1, whereas for LocoMMotion, variables with a proportion of missing values less than 25% (ISS 12.5%, hemoglobin 10.1%, LDH 23.8%, creatinine clearance 5.2%, ECOG 1.2% and MM type 16.5%) were imputed using multiple imputation with chained equations. Univariate and multivariable regression analyses were performed to evaluate the prognostic strength of the above listed factors, and imbalances between groups were evaluated using standardized mean differences (SMD), where values >0.2 were considered indicative of potentially important differences.[5] Three additional covariates of interest, i.e., race, history of stem cell transplant (SCT) and cytogenetic risk were included in sensitivity analyses in models for propensity scores and regression, but not considered in the base case scenario, as cytogenetic risk had high missingness in LocoMMotion (37.9%) whilst inclusion of race and history of SCT led to worse balance between populations (see **Appendix 4**).

Outcome Measures

Outcome measures were aligned between CARTITUDE-1 and LocoMMotion by protocol. An independent review committee was responsible for evaluation of response outcomes in CARTITUDE-1, and an RRC in LocoMMotion. Three response measures, i.e., overall response rate (ORR), very good partial response or better (≥VGPR) and complete response or better (≥CR), and two survival endpoints, i.e., progression-free survival (PFS), overall survival (OS), were compared between cilta-cel and RWCP. Response measures were defined according to the IMWG criteria.[6] PFS was defined as the time from the index date to the date of the first documented disease progression, as defined by IMWG criteria and assessed by review committee, or death due to any cause, whichever occurred first. Patients who were still progression free and alive at the time of the data cut were censored at the last disease evaluation before the start of any subsequent antimyeloma therapy. OS was defined as the time from the index date to the date of the subject's death. If the patient was alive or the vital status was unknown, then the subject's data were censored at the date the subject was last known to be alive.

Two patient PROs, the EuroQoL Group's EQ visual analog scale (EQ VAS) and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) global health status (GHS) are reported in this study. These were collected at screening, days 7, 28, 56, 78 and 100 after infusion, and every 28 days thereafter for CARTITUDE-1 and at screening, day 1 cycle 1, day 8 cycle 1 and at day 1 of every subsequent cycle for LocoMMotion. Index date for CARTITUDE-1 was infusion. As baseline PROs were assessed at screening only, screening values were used to impute values at infusion. For LocoMMotion, index date was day 1.

Adverse events (AE) in CARTITUDE-1 were collected from informed consent until 100 days after infusion. Specific AEs were also collected after 100 days.[1] In LocoMMotion, AEs were collected

from day of first use until 30 days after the last use of the first antimyeloma therapy or until the start of subsequent antimyeloma therapy if earlier.[3, 4]

2.3 *Statistical Methods*

Individual patient data (IPD) available for CARTITUDE-1 and LocoMMotion were used to conduct the comparative analyses. Adjusted comparisons for all outcomes were performed for both the enrolled and infused/aligned populations, and findings from unadjusted and adjusted analyses are presented.

Differences in baseline covariates between patient cohorts were addressed through inverse probability weighting (IPW) analyses. As a first step, the propensity score for each subject was estimated using a multivariable logistic regression model. In a second step, different sets of weights were derived and used in the weighted analyses. In the main analysis patients were re-weighted to derive the average treatment effect in the treated population (IPW-ATT). It maintains the CARTITUDE-1 cohort as observed (i.e., assigned a weight of 1), while patients from LocoMMotion cohort were re-weighted to make the group similar to CARTITUDE-1. These patients were assigned weights of p/(1-p), where p is the propensity score which reflects the probability for patients to belong to the CARTITUDE-1 cohort conditional on the baseline characteristics, estimated based on a multivariable logistic regression including all baseline characteristics. The IPW-ATT approach assigned patients in the RWCP LocoMMotion cohort a larger weight if they were similar to patients from CARTITUDE-1 and assigned a lower weight if they were different. As a sensitivity analysis, we performed an alternative form of re-weighting to estimate the average treatment effect in the overlap population (IPW-ATO).[7, 8]

Comparative effectiveness between cilta-cel and RWCP was assessed through weighted logistic regression models for binary outcomes to derive Odds Ratios (OR) and 95% Confidence Intervals (CI), transformed into Response-rate Ratios (RR), whereas weighted Cox proportional hazards (PH) models were used for time-to-event outcomes to estimate Hazard Ratios (HR). Multivariable logistic regression and multivariable Cox PH regression models were fitted to investigate the prognostic value of each covariate included in the model, and to derive unbiased estimates of relative treatment effect comparing cilta-cel and RWCP.

For time-to-event endpoints, the proportional hazards assumption was evaluated through visual inspection of the log-cumulative hazard plot, visual inspection of the Schoenfeld residuals plot, and performance of the Grambsch-Therneau test[9] (with a p-value less than 0.05 considered to indicate a violation of the assumption). Visual assessments were also performed to evaluate the shape of the curves over time.

PRO endpoints were analyzed using mixed model repeated measures (MMRM) with change from baseline as the outcome and treatment, baseline value, visit, and interaction between treatment and visit as fixed effects. Subject identifier was used to model the correlation between the repeated measurements from the same subject. Available case analyses were used in the modeling, i.e., subjects who were infused with cilta-cel (CARTITUDE-1) or started RWCP (LocoMMotion) and for which both a baseline and a post baseline measurement was available. To estimate the treatment effect over time, two naïve comparisons were carried out. For the first approach, only observed PRO values captured prior to start of the subsequent therapy were used, without any imputation of

missing data. However, this approach is prone to survivorship bias, as only surviving patients contribute to the results and this may bias results in favor of the treatment with worse survival outcomes. To adjust for this bias, we implemented a second approach, i.e., the adjusted-for-informative-dropout analysis. In this analysis, observed PRO values captured before subsequent therapy were used and missing observations after confirmed death were imputed with a value of 0 corresponding to the worst possible health status.[10]

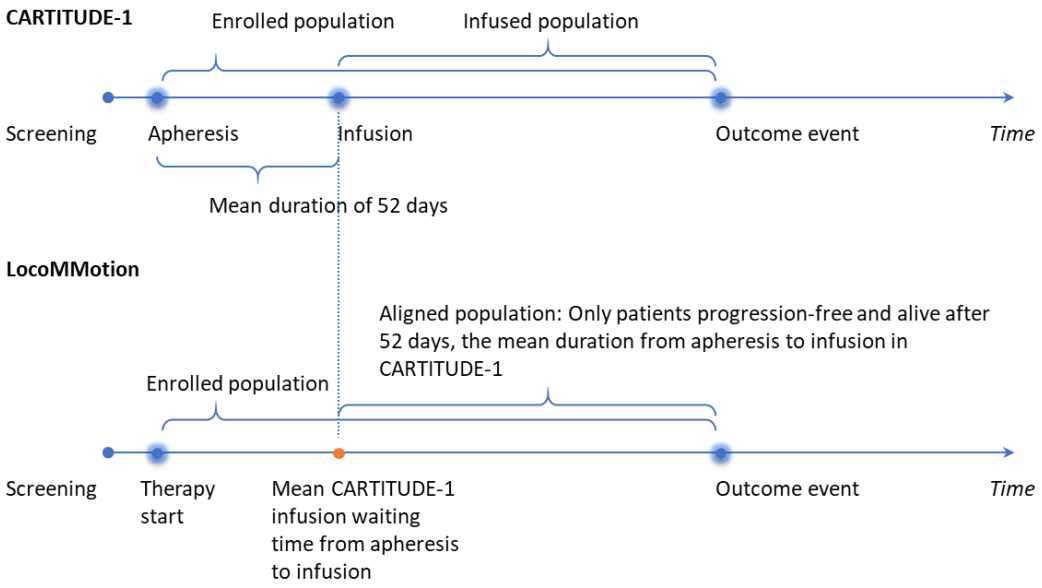
Analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Appendix 2: Approach to Alignment of the CARTITUDE-1 and LocoMMotion Populations

To limit the effect of immortal time bias, data analyses in the current study included adjusted comparisons which sought to align the LocoMMotion population with the set of CARTITUDE-1 patients that were infused with cilta-cel. Within the CARTITUDE-1 clinical trial, the average time per patient from apheresis to the time of infusion with cilta-cel was 52 days. During this time period, CARTITUDE-1 patients were required to not progress and to be alive in order to be infused with cilta-cel; any CARTITUDE-1 patient that experienced disease progression or died during this time period could not receive cilta-cel, and therefore was not part of the infused population.

Within the LocoMMotion study, enrolled patients could have experienced disease progression or died during the first 52 days after start of therapy. To align with the CARTITUDE-1 population infused with cilta-cel, in the current study the LocoMMotion population was adjusted to include only those patients that were progression-free and alive after 52 days.

A graphical representation of the approach and rationale for the selection of the 52-day period for alignment of the LocoMMotion population is provided below.



Appendix 3: Treatment Regimens, LocoMMotion Cohort

Treatment Regimen	Frequency (%)	RWCP subgroup 1[a]	RWCP subgroup 2[b]
Carfilzomib-Dexamethasone	32 (12.9%)	No	Yes
Pomalidomide-Cyclophosphamide-Dexamethasone	27 (10.9%)	Yes	Yes
Pomalidomide-Dexamethasone	24 (9.7%)	No	Yes
Ixazomib-Lenalidomide-Dexamethasone	13 (5.2%)	Yes	Yes
Panobinostat-Bortezomib-Dexamethasone	11 (4.4%)	Yes	Yes
Carfilzomib-Cyclophosphamide-Dexamethasone	7 (2.8%)	Yes	Yes
Bortezomib-Bendamustine-Dexamethasone	6 (2.4%)	Yes	Yes
Elotuzumab-Pomalidomide-Dexamethasone	6 (2.4%)	Yes	Yes
Bortezomib-Doxorubicin-Dexamethasone	5 (2.0%)	Yes	Yes
Carfilzomib-Pomalidomide-Dexamethasone	5 (2.0%)	Yes	Yes
Lenalidomide-Dexamethasone	5 (2.0%)	No	Yes
Belantamab Mafodotin	4 (1.6%)	No	Yes
Bendamustine-Prednisone	4 (1.6%)	No	No
Cyclophosphamide-Dexamethasone	4 (1.6%)	No	No
Daratumumab-Bortezomib-Dexamethasone	3 (1.2%)	Yes	Yes
Bortezomib-Lenalidomide-Dexamethasone	3 (1.2%)	Yes	Yes
Bortezomib-Dexamethasone-Venetoclax	3 (1.2%)	Yes	Yes
Daratumumab-Carfilzomib-Cisplatin-Cyclophosphamide-Etoposide	3 (1.2%)	Yes	Yes
Daratumumab-Carfilzomib-Dexamethasone	3 (1.2%)	Yes	Yes
Carfilzomib-Lenalidomide-Dexamethasone	3 (1.2%)	Yes	Yes
Cisplatin-Cyclophosphamide-Doxorubicin-Etoposide-Dexamethasone	3 (1.2%)	Yes	No
Daratumumab-Pomalidomide-Dexamethasone	3 (1.2%)	Yes	Yes
Elotuzumab-Lenalidomide-Dexamethasone	3 (1.2%)	Yes	Yes
Melphalan-Dexamethasone	3 (1.2%)	No	No
Bendamustine	2 (0.8%)	No	No
Bortezomib-Cisplatin-Cyclophosphamide-Doxorubicin-Etoposide	2 (0.8%)	Yes	Yes
Daratumumab-Bortezomib-Cyclophosphamide	2 (0.8%)	Yes	Yes
Bortezomib-Cyclophosphamide-Dexamethasone	2 (0.8%)	Yes	Yes
Cisplatin-Cyclophosphamide-Doxorubicin-Etoposide	2 (0.8%)	Yes	No
Cyclophosphamide	2 (0.8%)	No	No
Daratumumab-Lenalidomide-Dexamethasone	2 (0.8%)	Yes	Yes
Ixazomib-Dexamethasone	2 (0.8%)	No	Yes
Ixazomib-Pomalidomide-Dexamethasone	2 (0.8%)	Yes	Yes
Melphalan	2 (0.8%)	No	No
Melphalan-Prednisone	2 (0.8%)	No	No
Bortezomib-Belantamab Mafodotin-Dexamethasone	1 (0.4%)	Yes	Yes
Belantamab Mafodotin-Dexamethasone	1 (0.4%)	No	Yes
Bortezomib-Bendamustine	1 (0.4%)	No	Yes
Ixazomib-Bendamustine-Dexamethasone	1 (0.4%)	Yes	Yes

Treatment Regimen	Frequency (%)	RWCP subgroup 1[a]	RWCP subgroup 2[b]
Bendamustine-Dexamethasone-Prednisone	1 (0.4%)	Yes	No
Bendamustine-Rituximab	1 (0.4%)	No	Yes
Bortezomib-Cisplatin-Cyclophosphamide-Etoposide-Dexamethasone	1 (0.4%)	Yes	Yes
Bortezomib-Thalidomide-Cisplatin-Doxorubicin	1 (0.4%)	Yes	Yes
Bortezomib-Cyclophosphamide	1 (0.4%)	No	Yes
Bortezomib-Cyclophosphamide-Doxorubicin-Etoposide-Dexamethasone	1 (0.4%)	Yes	Yes
Bortezomib-Thalidomide-Cyclophosphamide-Etoposide-Dexamethasone	1 (0.4%)	Yes	Yes
Daratumumab-Bortezomib-Pomalidomide-Doxorubicin-Dexamethasone	1 (0.4%)	Yes	Yes
Bortezomib-Pomalidomide-Dexamethasone	1 (0.4%)	Yes	Yes
Bortezomib-Melphalan-Prednisone	1 (0.4%)	Yes	Yes
Melphelan-Busulfan-Dexamethasone	1 (0.4%)	Yes	No
Carfilzomib	1 (0.4%)	No	Yes
Carfilzomib-Thalidomide-Cisplatin-Cyclophosphamide-Etoposide	1 (0.4%)	Yes	Yes
Carfilzomib-Cyclophosphamide	1 (0.4%)	No	Yes
Daratumumab-Carfilzomib-Cyclophosphamide-Dexamethasone	1 (0.4%)	Yes	Yes
Carfilzomib-Thalidomide-Cyclophosphamide-Dexamethasone	1 (0.4%)	Yes	Yes
Daratumumab-Carfilzomib-Pomalidomide-Dexamethasone	1 (0.4%)	Yes	Yes
Daratumumab-Carfilzomib-Selinexor-Dexamethasone	1 (0.4%)	Yes	Yes
Daratumumab-Carfilzomib-Doxorubicin	1 (0.4%)	Yes	Yes
Panobinostat-Carfilzomib-Dexamethasone	1 (0.4%)	Yes	Yes
Carfilzomib-Venetoclax-Dexamethasone	1 (0.4%)	Yes	Yes
Carmustine-Cyclophosphamide-Melphalan-Vincristine-Prednisone	1 (0.4%)	Yes	No
Thalidomide-Cisplatin-Cyclophosphamide-Etoposide-Dexamethasone	1 (0.4%)	Yes	Yes
Daratumumab-Lenalidomide-Doxorubicin-Cyclophasphamide-Dexamethasone	1 (0.4%)	Yes	Yes
Daratumumab-Lenalidomide-Cyclophasphamide	1 (0.4%)	Yes	Yes
Cyclophosphamide-Doxorubicin-Vincristine-Dexamethasone	1 (0.4%)	Yes	No
Ixazomib-Cyclophosphamide-Dexamethasone	1 (0.4%)	Yes	Yes
Ixazomib-Pomalidomide-Cyclophosphamide-Dexamethasone	1 (0.4%)	Yes	Yes
Thalidomide-Cyclophosphamide-Dexamethasone	1 (0.4%)	Yes	Yes
Isatuximab-Cyclophosphamide	1 (0.4%)	No	Yes
Pomalidomide-Cyclophosphamide	1 (0.4%)	No	Yes
Pomalidomide-Cyclophosphamide-Prednisone	1 (0.4%)	Yes	Yes
Cyclophosphamide-Prednisone	1 (0.4%)	No	No
Lenalidomide-Melphalan-Dexamethasone	1 (0.4%)	Yes	Yes
Lenalidomide-Melphalan-Dexamethasone-Prednisone	1 (0.4%)	Yes	Yes
Venetoclax-Dexamethasone	1 (0.4%)	No	Yes
Pomalidomide	1 (0.4%)	No	Yes
Selinexor-Prednisone	1 (0.4%)	No	Yes

Treatment Regimen	Frequency (%)	RWCP subgroup 1[a]	RWCP subgroup 2[b]
Venetoclax	1 (0.4%)	No	Yes

Note: Treatments and values thereof are based on the treatment patient received at first study visit. Frequencies are based on N=248 patients.

[a] RWCP subgroup 1 - RWCP patients who received three or more substances in combination

[b] RWCP subgroup 2 - RWCP patients who received as part of their treatment a “novel therapy”. (Novel therapies were defined as IMIDs, PIs, monoclonal antibodies or any further compounds which have received regulatory approval in the past ten years.

Appendix 4: Pre-/Post-IPW Balance, IPW-ATT and IPW-ATO Analyses

Using Base Model (refractory status, ISS stage, time to progression on prior line, extramedullary disease, # prior lines, years since diagnosis, average duration of prior lines, age, hemoglobin, LDH, creatinine clearance, ECOG performance status, gender, MM type)

Group Demographic Balance Before and After IPW-ATO Weighting (infused/aligned Population)

Covariate	Categories	Cilta-cel (CARTITUDE-1), % (N=97)	Pre-IPW ATO		Post-IPW ATO		
			RWCP Cohort, % (N=170)	SMD	Cilta-cel Cohort, % (N=41)	RWCP Cohort, % (N=41)	SMD
Refractory status	≤ Double	12.4%	28.2%	0.85	17.6%	17.6%	0
	Triple	8.2%	27.6%		14.1%	14.1%	
	Quadruple	37.1%	27.1%		35.4%	35.4%	
	Penta	42.3%	17.1%		32.9%	32.9%	
ISS stage at study entry	I	62.9%	35.9%	0.62	49.2%	49.2%	0
	II	22.7%	28.2%		29,5%	29,5%	
	III	14.4%	35.9%		21.3%	21.3%	
Time to progression in prior line	<3 months	37.1%	22.4%	-0.33	29.7%	29.7%	0
	≥3 months	62.9%	77.6%		70.3%	70.3%	
Extramedullary disease	Yes	13.4%	12.4%	-0.03	14.1%	14.1%	0
	No	86.6%	87.6%		85.9%	85.9%	
# prior LOTs	≤4	34.0%	51.2%	0.35	40.1%	40.1%	0
	5+	66.0%	48.8%		59.9%	59.9%	
Years since diagnosis	<6	46.4%	41.8%	-0.09	41.8%	41.8%	0
	6+	53.6%	58.2%		58.2%	58.2%	
Average duration of prior lines	<8.14 months	20.6%	9.4%	0.40	13.2%	13.2%	0
	8.14 to <11.76 months	22.7%	17.6%		20.1%	20.1%	
	11.76+ months	56.7%	72.9%		66.6%	66.6%	
Age	<65 years	63.9%	35.9%	-0.58	52.9%	52.9%	0
	65+ years	36.1%	64.1%		47.1%	47.1%	
Hemoglobin (g/dL)	<12	92.8%	71.2%	-0.59	91.2%	91.2%	0
	12+	7.2%	28.8%		8.8%	8.8%	
LDH (units/L)	<280	87.6%	74.7%	-0.34	82.1%	82.1%	0
	280+	12.4%	25.3%		17.9%	17.9%	
Creatinine clearance (mL/min)	<60	17.5%	40.6%	0.60	23.5%	23.5%	0
	60 - <90	30.9%	31.8%		34.3%	34.3%	
	90+	51.5%	27.6%		42.2%	42.2%	
ECOG PS	0	40.2%	27.1%	-0.50	29.4%	29.4%	0
	1	59.8%	72.9%		70.6%	70.6%	
Gender	Male	58.8%	52.9%	-0.12	56.1%	56.1%	0
	Female	41.2%	47.1%		43.9%	43.9%	
MM Type	IgG	58.8%	42.4%	-0.33	52.8%	52.8%	0
	Non-IgG	41.2%	57.6%		47.2%	47.2%	
Summary Diagnostics							
# SMDs with absolute value >0.2		11 / 14 = 78.6%			0 / 14 = 0%		
Mean absolute SMD		0.41			0		

The pre-weighting and post-weighting distributions of demographics by intervention group are shown. SMDs >0.2 were considered to indicate differences between groups.

Abbreviations: ATO, average treatment effect in the overlap population; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ISS, International Staging System; LDH, lactate dehydrogenase; LOTs, lines of therapy; MM, multiple myeloma; RWCP, real-world clinical practice; SMD, standardized mean difference.

Using Extended Model (refractory status, ISS stage, time to prior on prior line, , extramedullary disease, # prior lines, years since diagnosis, average duration of prior lines, age, hemoglobin, LDH, creatinine clearance, ECOG performance status, gender, MM type, race, history of stem cell transplant, cytogenetic risk)

Group Demographic Balance Before and After IPW-ATT Weighting (infused/aligned Population)

Covariate	Categories	Cilta-cel (CARTITUDE-1), % (N=97)	Pre-IPW ATT		Post-IPW ATT	
			RWCP Cohort, % (N=170)	SMD	RWCP Cohort, % (N=93)	SMD
Refractory status	≤ Double	12.4%	28.2%	0.85	12.6%	0.32
	Triple	8.2%	27.6%		9.2%	
	Quadruple	37.1%	27.1%		22.6%	
	Penta	42.3%	17.1%		55.7%	
ISS stage at study entry	I	62.9%	35.9%	0.62	65.3%	0.04
	II	22.7%	28.2%		21.8%	
	III	14.4%	35.9%		12.9%	
Time to progression in prior line	<3 months	37.1%	22.4%	-0.33	25.0%	-0.26
	≥3 months	62.9%	77.6%		75.0%	
Extramedullary disease	Yes	13.4%	12.4%	-0.03	10.5%	-0.09
	No	86.6%	87.6%		89.5%	
# prior LOTs	≤4	34.0%	51.2%	0.35	29.9%	-0.09
	5+	66.0%	48.8%		70.1%	
Years since diagnosis	<6	46.4%	41.8%	-0.09	48.4%	0.04
	6+	53.6%	58.2%		51.6%	
Average duration of prior lines	<8.14 months	20.6%	9.4%	0.40	9.4%	0.36
	8.14 to <11.76 months	22.7%	17.6%		31.7%	
	11.76+ months	56.7%	72.9%		58.9%	
Age	<65 years	63.9%	35.9%	-0.58	66.5%	0.05
	65+ years	36.1%	64.1%		33.5%	
Hemoglobin (g/dL)	<12	92.8%	71.2%	-0.59	95.7%	0.12
	12+	7.2%	28.8%		4.3%	
LDH (units/L)	<280	87.6%	74.7%	-0.34	89.9%	0.07
	280+	12.4%	25.3%		10.1%	
Creatinine clearance (mL/min)	<60	17.5%	40.6%	0.60	13.8%	0.38
	60 - <90	30.9%	31.8%		48.8%	
	90+	51.5%	27.6%		37.4%	
ECOG PS	0	40.2%	27.1%	-0.50	40.8%	0.01
	1	59.8%	72.9%		59.2%	
Gender	Male	58.8%	52.9%	-0.12	41.5%	-0.35
	Female	41.2%	47.1%		58.5%	
MM Type	IgG	58.8%	42.4%	-0.33	50.2%	-0.17
	Non-IgG	41.2%	57.6%		49.8%	
Prior stem cell transplant	Yes	89.7%	61.8%	-0.69	88.4%	-0.04
	No	10.3%	38.2%		11.6%	
Race	Caucasian	71.1%	71.8%	0.01	75.2%	0.09
	Other/not reported	28.9%	28.2%		24.8%	
Cytogenetic risk	Standard risk	70.1%	34.1%	0.98	69.7%	0.09
	High risk	23.7%	25.3%		22.3%	
	Missing	6.2%	40.6%		8.0%	
Summary Diagnostics						
# SMDs with absolute value >0.2		13 / 17 = 76.5%			5 / 17 = 29.4%	
Mean absolute SMD		0.44			0.15	

The pre-weighting and post-weighting distributions of demographics by intervention group are shown. SMDs >0.2 were considered to indicate differences between groups.

Abbreviations: ATT, average treatment effect in the treated population; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ISS, International Staging System; LDH, lactate dehydrogenase; LOTs, lines of therapy; MM, multiple myeloma; RWCP, real-world clinical practice; SMD, standardized mean difference.

Group Demographic Balance Before and After IPW-ATO Weighting (infused/aligned Population)

Covariate	Categories	Cilta-cel (CARTITUDE-1), % (N=97)	Pre-IPW ATO		Post-IPW ATO		
			RWCP Cohort, % (N=170)	SMD	Cilta-cel Cohort, % (N=32)	RWCP Cohort, % (N=32)	SMD
Refractory status	≤ Double	12.4%	28.2%	0.85	19.5%	19.5%	0
	Triple	8.2%	27.6%		15.2%	15.2%	
	Quadruple	37.1%	27.1%		30.2%	30.2%	
	Penta	42.3%	17.1%		35.1%	35.1%	
ISS stage at study entry	I	62.9%	35.9%	0.62	50.0%	50.0%	0
	II	22.7%	28.2%		29.1%	29.1%	
	III	14.4%	35.9%		21.0%	21.0%	
Time to progression in prior line	<3 months	37.1%	22.4%	-0.33	31.9%	31.9%	0
	≥3 months	62.9%	77.6%		68.1%	68.1%	
Extramedullary disease	Yes	13.4%	12.4%	-0.03	13.7%	13.7%	0
	No	86.6%	87.6%		86.3%	86.3%	
# prior LOTs	≤4	34.0%	51.2%	0.35	41.6%	41.6%	0
	5+	66.0%	48.8%		58.4%	58.4%	
Years since diagnosis	<6	46.4%	41.8%	-0.09	41.3%	41.3%	0
	6+	53.6%	58.2%		58.7%	58.7%	
Average duration of prior lines	<8.14 months	20.6%	9.4%	0.40	11.1%	11.1%	0
	8.14 to <11.76 months	22.7%	17.6%		19.4%	19.4%	
	11.76+ months	56.7%	72.9%		69.5%	69.5%	
Age	<65 years	63.9%	35.9%	-0.58	51.3%	51.3%	0
	65+ years	36.1%	64.1%		48.7%	48.7%	
Hemoglobin (g/dL)	<12	92.8%	71.2%	-0.59	89.8%	89.8%	0
	12+	7.2%	28.8%		10.2%	10.2%	
LDH (units/L)	<280	87.6%	74.7%	-0.34	82.8%	82.8%	0
	280+	12.4%	25.3%		17.2%	17.2%	
Creatinine clearance (mL/min)	<60	17.5%	40.6%	0.60	22.8%	22.8%	0
	60 - <90	30.9%	31.8%		34.6%	34.6%	
	90+	51.5%	27.6%		42.5%	42.5%	
ECOG PS	0	40.2%	27.1%	-0.50	29.6%	29.6%	0
	1	59.8%	72.9%		70.4%	70.4%	
Gender	Male	58.8%	52.9%	-0.12	54.2%	54.2%	0
	Female	41.2%	47.1%		45.8%	45.8%	
MM Type	IgG	58.8%	42.4%	-0.33	50.5%	50.5%	0
	Non-IgG	41.2%	57.6%		49.5%	49.5%	
Prior stem cell transplant	Yes	89.7%	61.8%	-0.69	82.7%	82.7%	0
	No	10.3%	38.2%		17.3%	17.3%	
Race	Caucasian	71.1%	71.8%	0.01	75.4%	75.4%	0
	Other/not reported	28.9%	28.2%		24.6%	24.6%	
Cytogenetic risk	Standard risk	70.1%	34.1%	0.98	54.2%	54.2%	0
	High risk	23.7%	25.3%		31.0%	31.0%	
	Missing	6.2%	40.6%		14.8%	14.8%	
Summary Diagnostics							
# SMDs with absolute value >0.2		13 / 17 = 76.5%			0 / 17 = 0%		
Mean absolute SMD		0.44			0		

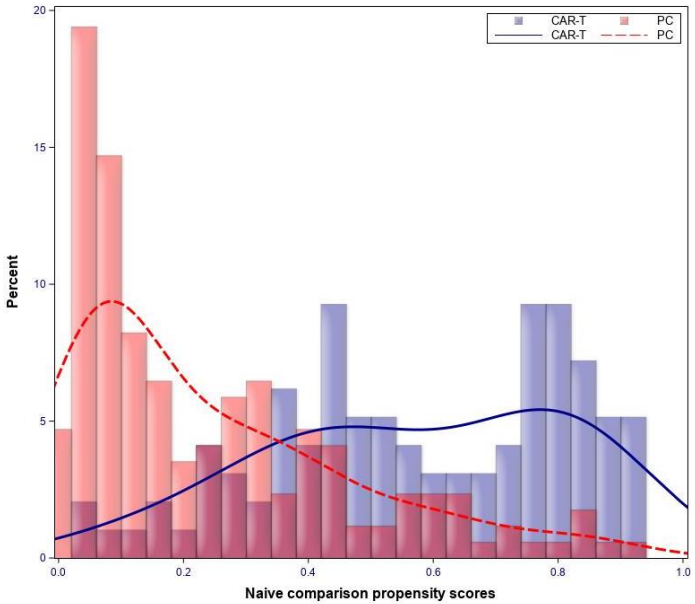
The pre-weighting and post-weighting distributions of demographics by intervention group are shown. SMDs >0.2 were considered to indicate differences between groups.

Abbreviations: ATO, average treatment effect in the overlap population; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ISS, International Staging System; LDH, lactate dehydrogenase; LOTs, lines of therapy; MM, multiple myeloma; RWCP, real-world clinical practice; SMD, standardized mean difference.

Appendix 5: Propensity Score Distributions and Standardized Mean Difference plots

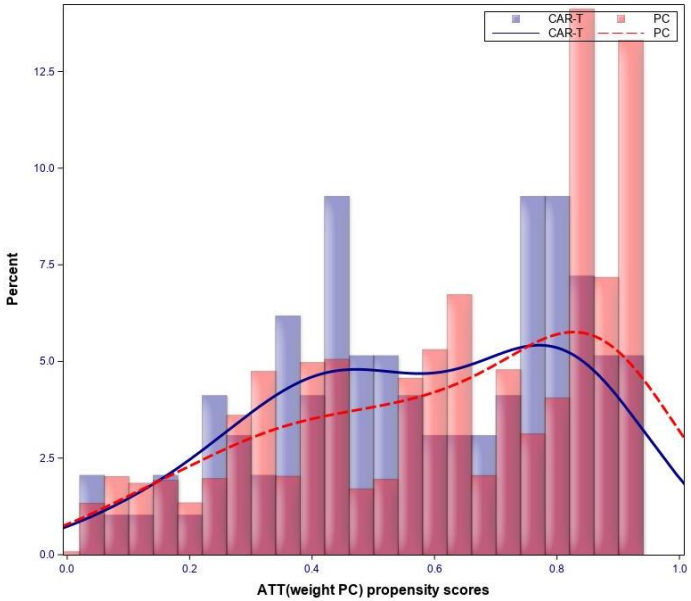
Propensity score distributions for (a) observed, and (b) ATT weighted infused/aligned populations

Prior to IPW Weighting
(Naïve Comparison)



(a)

IPW-ATT Weighting

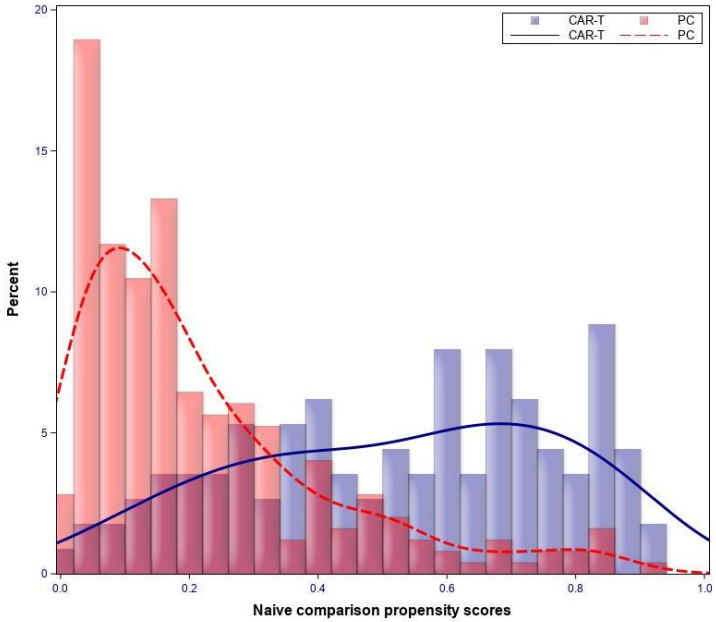


(b)

Note Y-axis scales differ between graphs

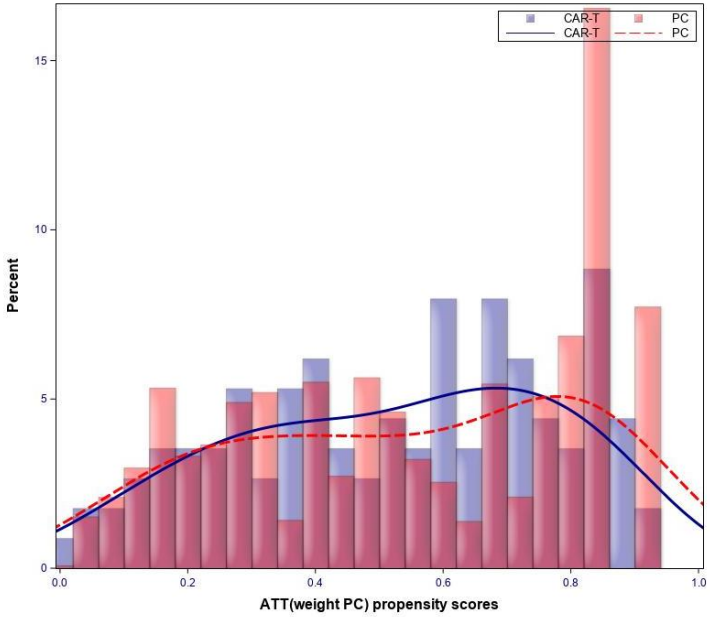
Propensity score distributions for (a) observed, and (b) ATT weighted enrolled populations

Prior to IPW Weighting
(Naïve Comparison)



(a)

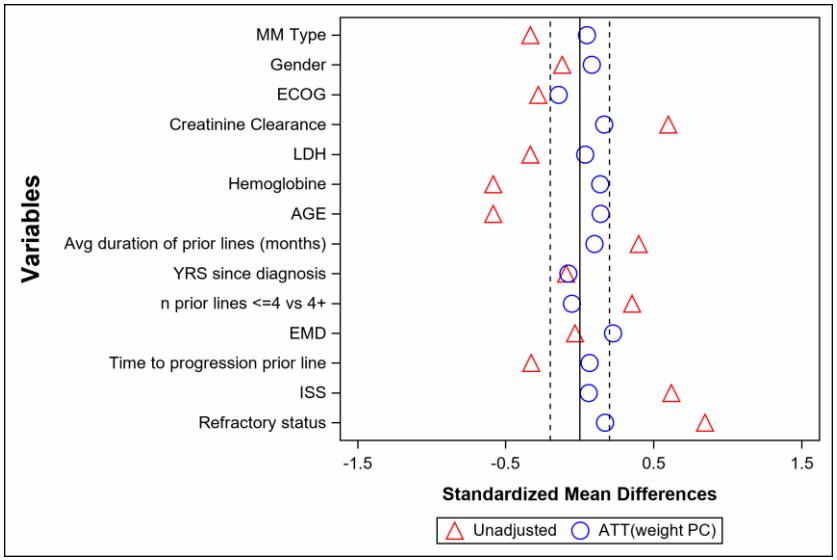
IPW-ATT Weighting

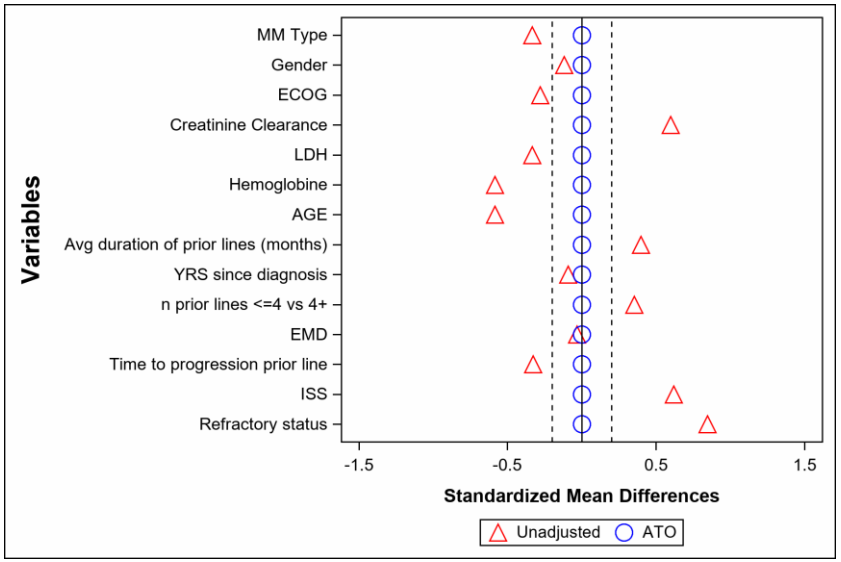


(b)

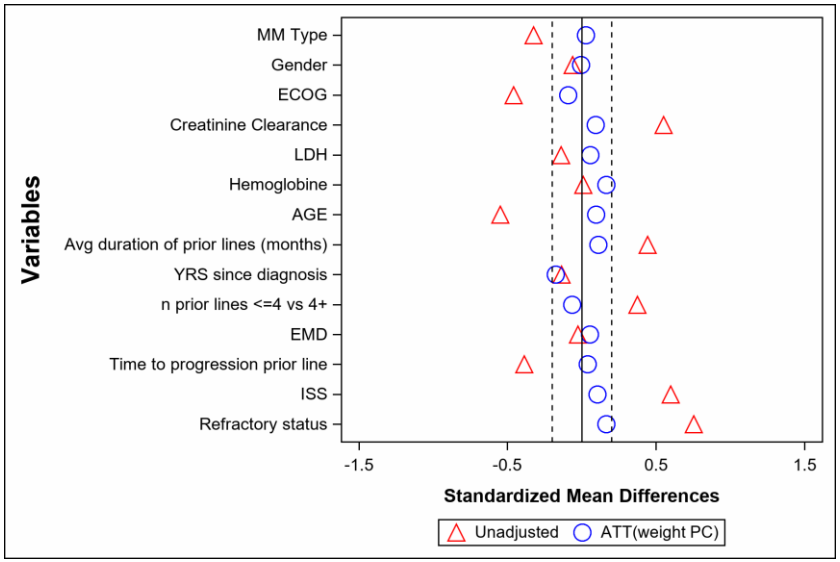
Note Y-axis scales differ between graphs

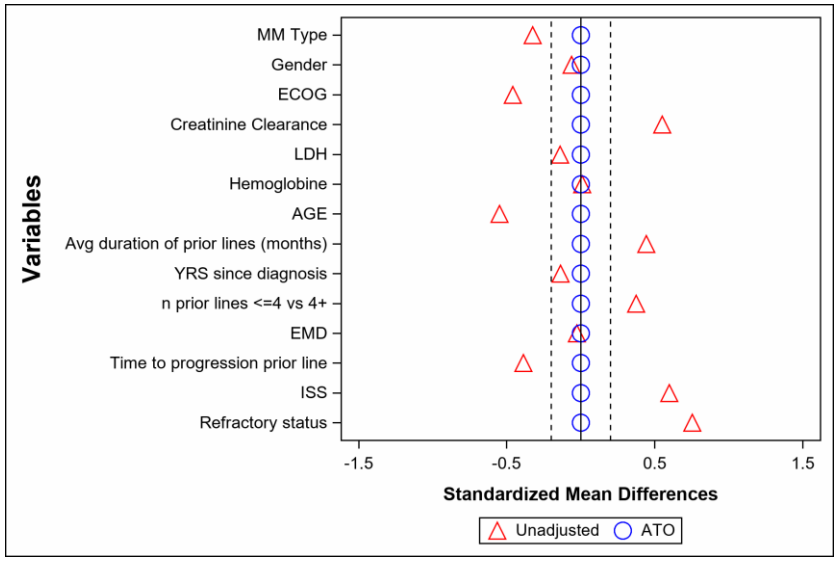
Standardized Mean Difference plots before and after reweighting using (a) IPW-ATT, and (b) all IPW-ATO: Infused/Aligned Populations





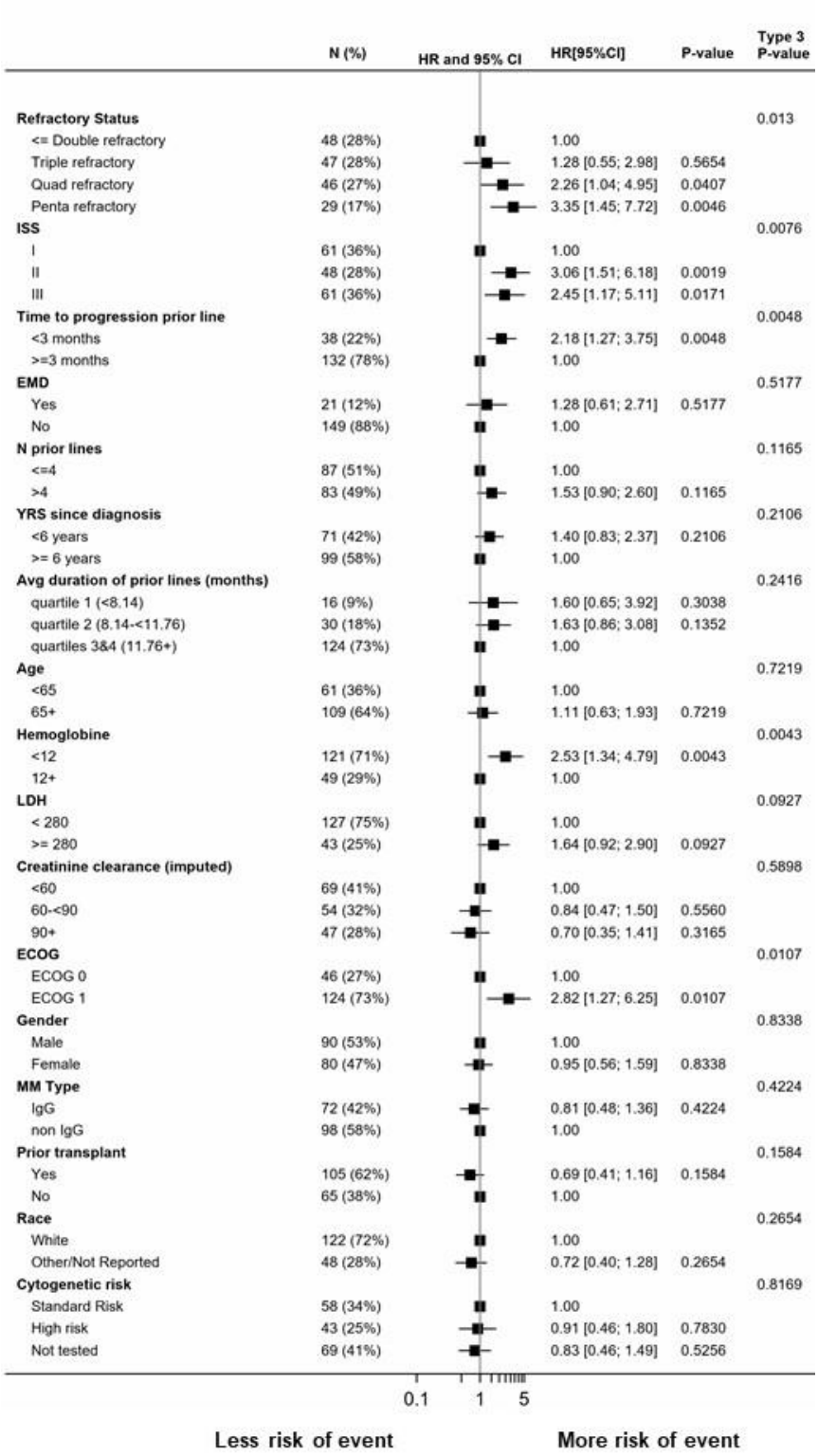
Standardized Mean Difference plots before and after reweighting using (a) IPW-ATT, and (b) all IPW-ATO: Enrolled Populations





Appendix 6: Covariate Effects from Multivariable Cox and Logistic Regression Analyses

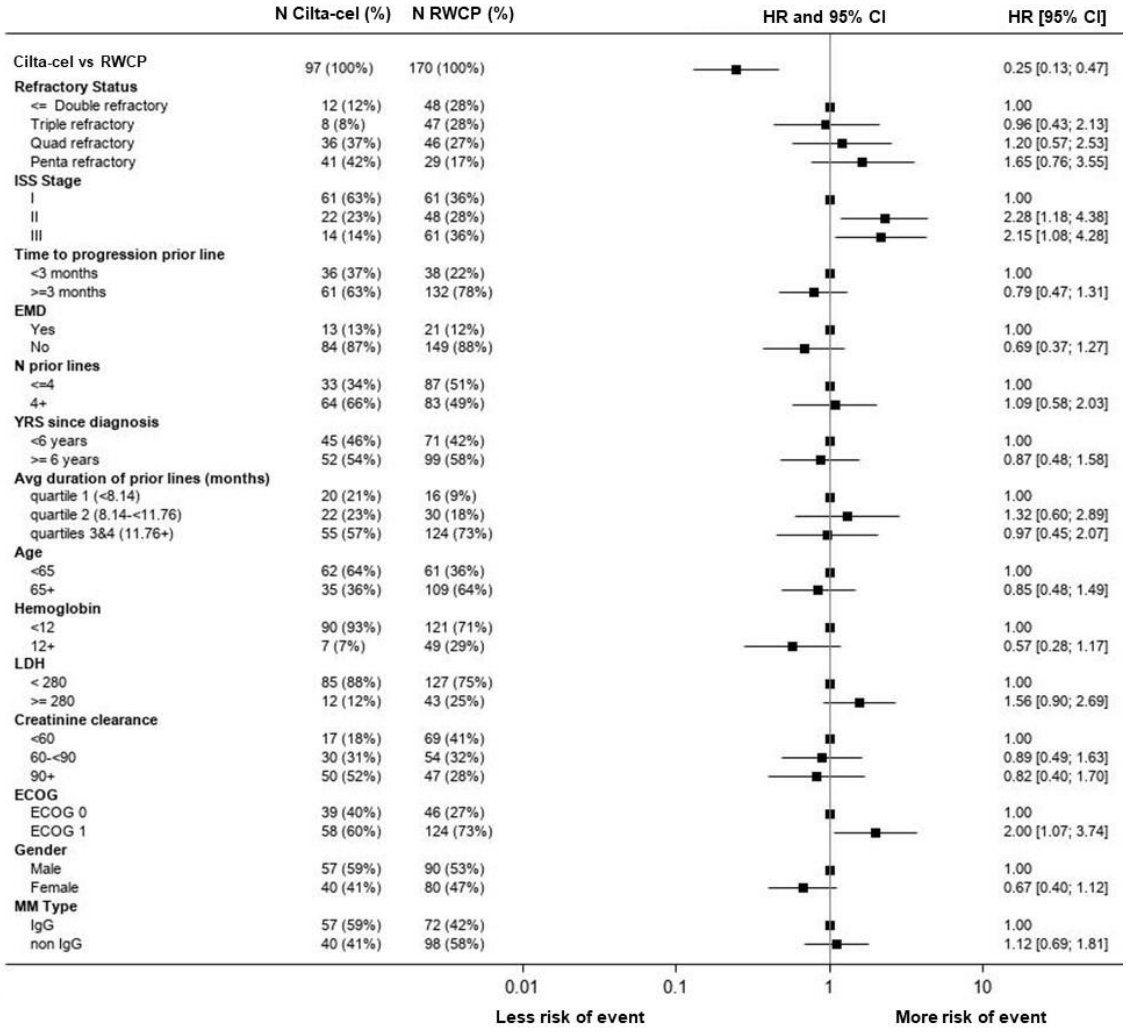
OS Findings from Univariate Regression for OS, aligned LocoMMotion Population



Hazard ratios and corresponding 95% CIs from a univariate Cox proportional hazards regression analyses for each variable are shown. The analysis was conducted on the aligned LocoMMotion RWCP population.

Abbreviations: ECOG PS, Eastern Co-Operative Oncology Group Performance Status; EMD, extramedullary disease; HR, hazard ratio; ISS, International Staging System; LDH, lactate dehydrogenate; LOT, line of therapy; MM, multiple myeloma; OS, overall survival; RWCP, real-world clinical practice; YRS, years.

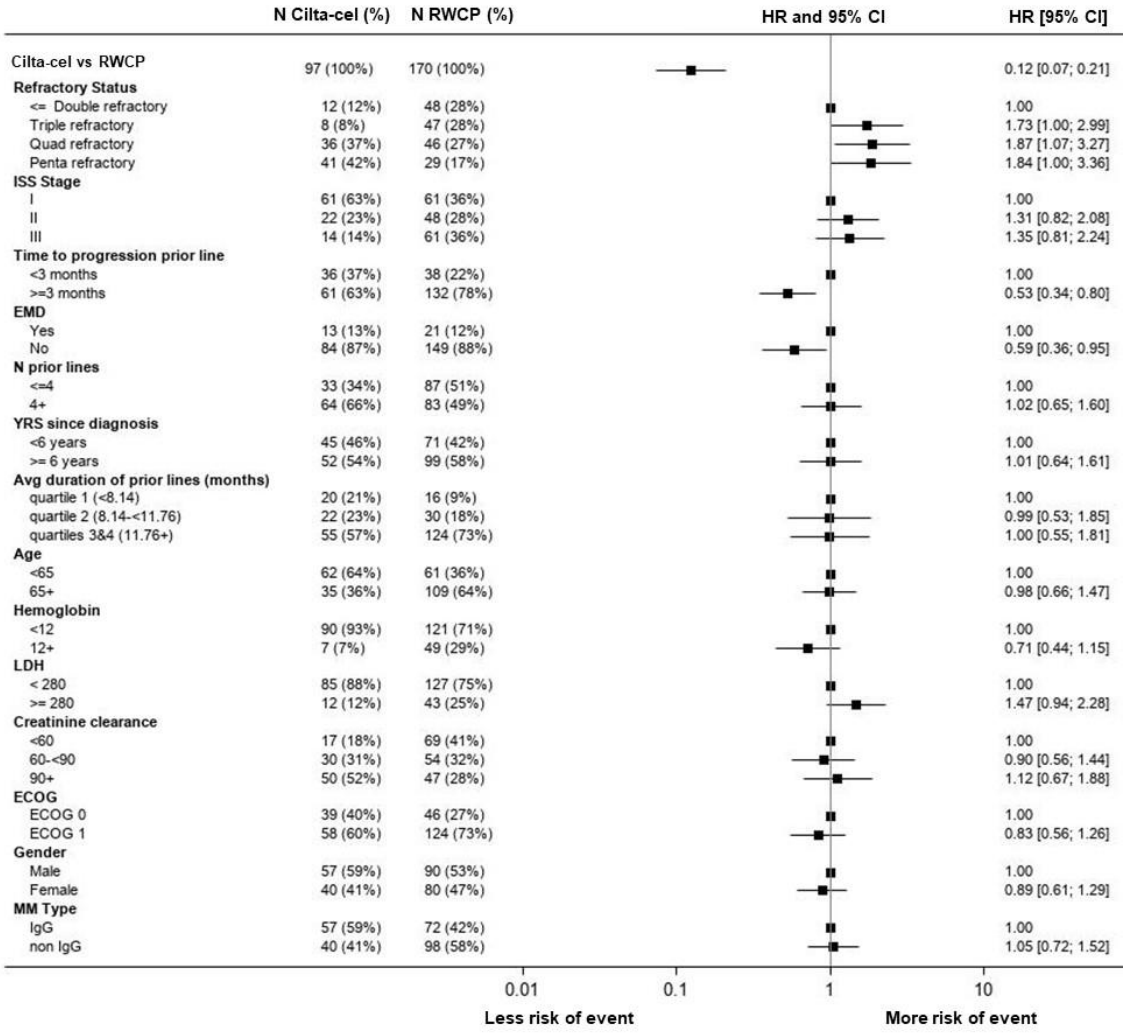
OS Findings from Multivariable Regression, infused/aligned Populations



Hazard ratios and corresponding 95% CIs from a multivariable Cox proportional hazards regression analysis are shown. The analysis was conducted on the infused/aligned population for both treatment groups.

Abbreviations: ECOG PS, Eastern Co-Operative Oncology Group Performance Status; EMD, extramedullary disease; HR, hazard ratio; ISS, International Staging System; LDH, lactate dehydrogenate; LOT, line of therapy; MM, multiple myeloma; OS, overall survival; RWCP, real-world clinical practice; YRS, years.

PFS Findings from Multivariable Regression, infused/aligned Population

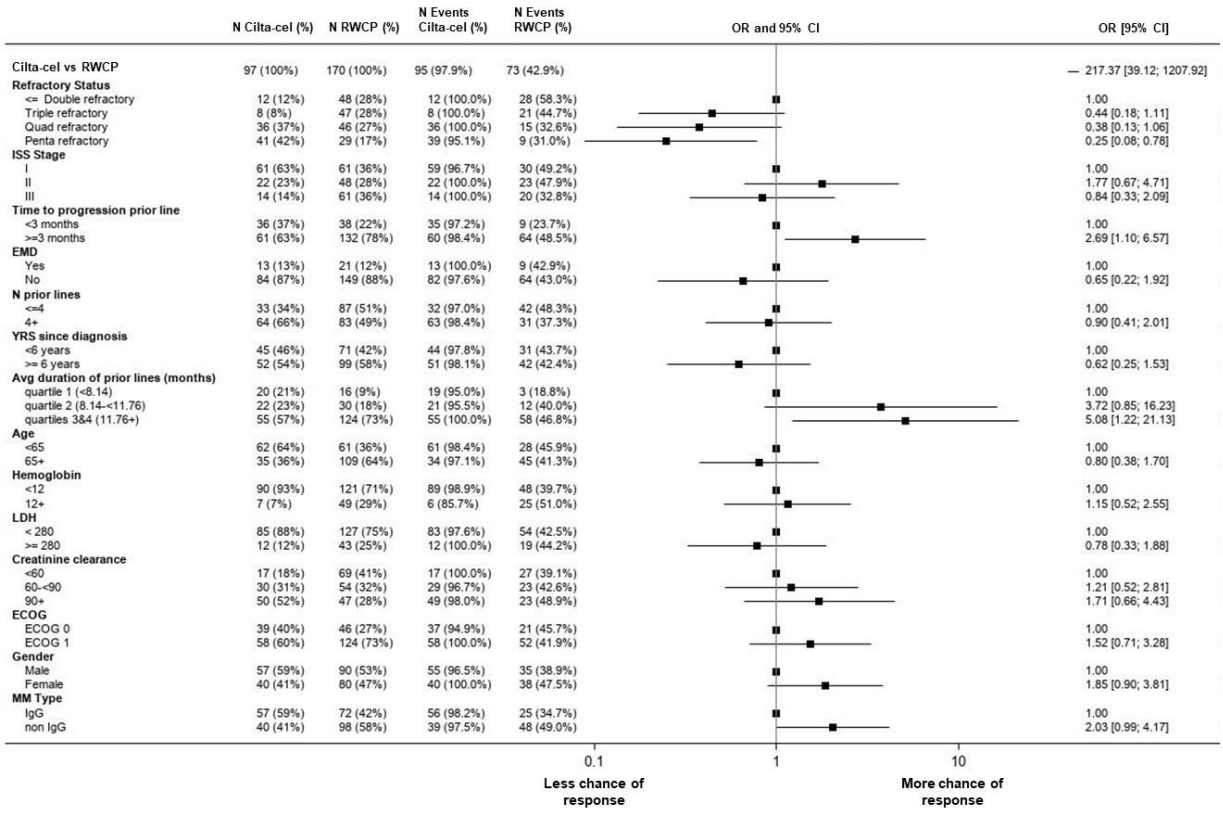


Hazard ratios and corresponding 95% CIs from a multivariable Cox proportional hazards regression analysis are shown. The analysis was conducted on the infused/aligned population for both treatment groups.

Abbreviations: ECOG PS, Eastern Co-Operative Oncology Group Performance Status; EMD, extramedullary disease; HR, hazard ratio; ISS, International Staging System; LDH, lactate dehydrogenate; MM, multiple myeloma; PFS, progression-free survival; RWCP, real-world clinical practice; YRS, years.

Overall Response Rate (ORR)

ORR Findings from Multivariable Regression, infused/aligned Population

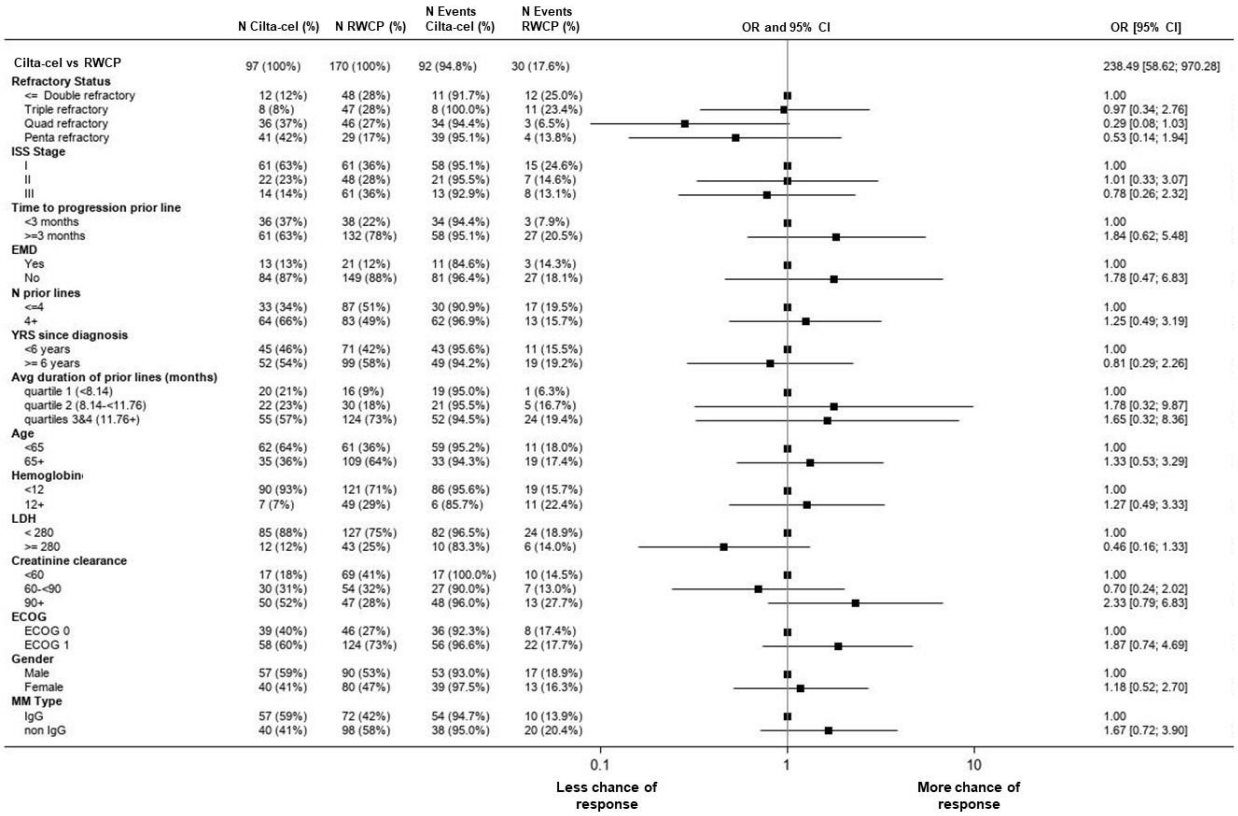


Odds ratios and corresponding 95% CIs from a multivariable logistic regression analysis are shown. The analysis was conducted on the infused/aligned population for both treatment groups.

Abbreviations: ECOG PS, Eastern Co-Operative Oncology Group Performance Status; EMD, extramedullary disease; ISS, International Staging System; LDH, lactate dehydrogenate; MM, multiple myeloma; OR, odds ratio; ORR, overall response rate; RWCP, real-world clinical practice; YRS, years.

Very Good Partial Response or better (≥VGPR)

≥VGPR Findings from Multivariable Regression, infused/aligned Population



Odds ratios and corresponding 95% CIs from a multivariable logistic regression analysis are shown. The analysis was conducted on the infused/aligned population for both treatment groups.

Abbreviations: ECOG PS, Eastern Co-Operative Oncology Group Performance Status; EMD, extramedullary disease; ISS, International Staging System; LDH, lactate dehydrogenate; MM, multiple myeloma; OR, odds ratio; RWCP, real-world clinical practice; VGPR, very good partial response; YRS, years.

Appendix 7: Findings from Sensitivity Analyses

Findings from sensitivity analyses that were performed using an extended set of clinical covariates (adding race, history of stem cell transplant and cytogenetic risk) are presented below for measures of clinical response and survival. As reported for main analyses, there were limitations in the ability to estimate odds ratios and response ratios for the ≥CR outcome, and in place we summarize relevant information.

Table: Summary of Adjusted Comparisons of Clinical Response, Extended Variable Set

Outcome	IPW-ATT		IPW-ATO	Multivariable logistic regression
	OR	RR	OR	OR
Infused/aligned Population				
ORR	108.47 (24.98, 470.90)	3.22 (2.22, 4.21)	152.38 (3.69, 6298.91)	234.76 (38.49, 1431.92)
≥VGPR	160.25 (52.25, 491.47)	9.21 (3.63, 14.79)	71.09 (13.58, 372.20)	220.12 (49.28, 983.19)
Enrolled Population				
ORR	22.59 (11.27, 45.26)	4.44 (2.67, 6.21)	11.74 (4.45, 30.92)	29.84 (12.30, 72.43)
≥VGPR	47.85 (20.95, 109.32)	9.71 (3.59, 15.83)	25.59 (8.18, 80.06)	63.56 (23.59, 171.25)

Abbreviations: ATT, average treatment effect in the treated population; ATO, average treatment effect in the overlap population; IPW, inverse propensity weighting; OR, odds ratio; ORR, overall response rate; RR, response ratio; VGPR, very good partial response rate.

Table: Summary of Adjusted Comparisons of PFS and OS (HR and 95% CI), Extended Variable Set

Outcome	IPW-ATT	IPW-ATO	Multivariable logistic regression
Infused/aligned Population			
PFS	0.12 (0.07, 0.19)	0.15 (0.09, 0.27)	0.11 (0.06, 0.20)
OS	0.15 (0.08, 0.30)	0.28 (0.14, 0.57)	0.23 (0.12, 0.48)
Enrolled Population			
PFS	0.17 (0.11, 0.27)	0.23 (0.14, 0.36)	0.18 (0.11, 0.28)
OS	0.24 (0.14, 0.43)	0.39 (0.22, 0.68)	0.39 (0.23, 0.67)

Abbreviations: ATT, average treatment effect in the treated population; ATO, average treatment effect in the overlap population; HR, hazard ratio; IPW, inverse propensity weighting; OS, overall survival; PFS, progression-free survival.

In the LocoMMotion cohort, a wide range of treatment regimens were observed, reflecting current clinical practice, and illustrating that there is no standard of care in the treatment of this advanced patient population. Given the heterogeneity of therapies included in the LocoMMotion study,

sensitivity analyses examining the impact of excluding patients who received specific therapies/therapy classes were performed. The first of these analyses only included RWCP patients who received three or more substances in combination – **RWCP subgroup 1**. The second of these analyses only included RWCP patients who received as part of their treatment a novel therapy – **RWCP subgroup 2**. Novel therapies were defined as IMIDs, PIs, monoclonal antibodies and any further compounds which have received regulatory approval in the past ten years.

The results of these analyses can be found below. As can be seen, results from both sensitivity analyses were consistent with the overall results, only differing by wider confidence intervals, illustrating that the overall comparative efficacy estimates for cilta-cel vs RWCP are consistent across treatment combinations, and not being driven by the heterogeneity of treatments includes or by patients receiving a particular therapy/combination.

Table: Relative efficacy for Cilta-cel versus RWCP for OS and PFS (HR [95% CI]) for all RWCP, and subgroups of RWCP, based on IPW-ATT.

Outcome	Cilta-cel versus full RWCP cohort (Base case)	Cilta-cel versus ≥triplet RWCP (subgroup 1[a])	Cilta-cel versus "novel RWCP" (subgroup 2[b])
Infused/aligned Population			
PFS	0.15 (0.08; 0.29)	0.17 (0.08; 0.36)	0.16 (0.08, 0.32)
OS	0.20 (0.09, 0.41)	0.22 (0.10; 0.50)	0.35 (0.16, 0.75)
Enrolled Population			
PFS	0.19 (0.11, 0.32)	0.22 (0.11; 0.42)	0.20 (0.11, 0.36)
OS	0.32 (0.17, 0.58)	0.35 (0.18; 0.68)	0.41 (0.21, 0.79)

[a] Only RWCP patients who received three or more substances in combination were included in the analysis – Infused/Aligned N=104, Enrolled N=149

[b] Only RWCP patients who received a novel therapy as part of their treatment were included in the analysis – Infused/Aligned N=152, Enrolled N=219

Abbreviations: ATT, average treatment effect in the treated population; HR, hazard ratio; IPW, inverse propensity weighting; OS, overall survival; PFS, progression-free survival.

Figure: Kaplan Meier Plot of Progression Free Survival in the Infused/Aligned Population for Subgroups of Patients receiving "Novel RWPC" and "≥triplet RWCP"

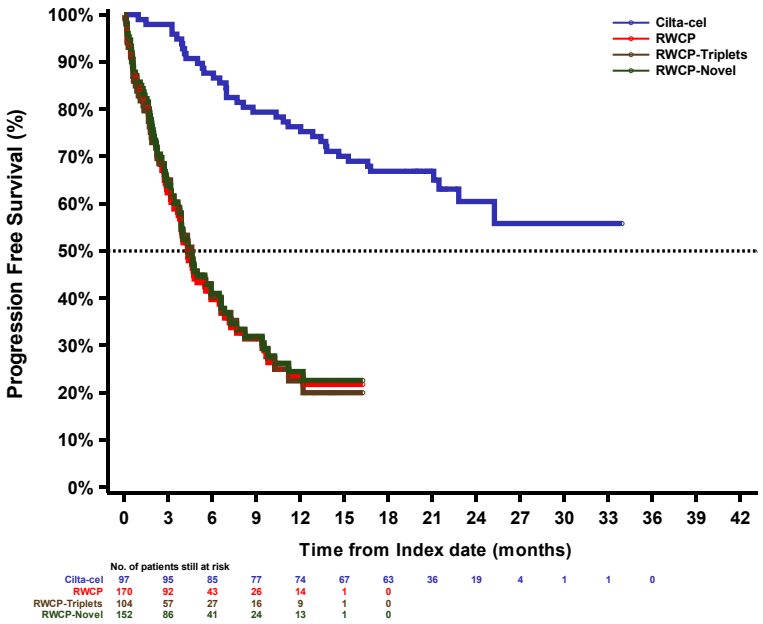
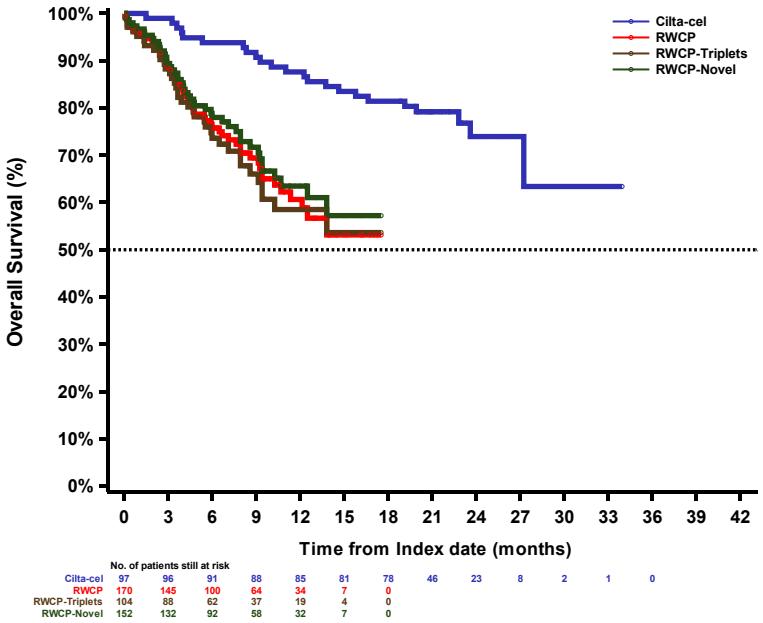


Figure: Kaplan Meier Plot of Overall Survival in the Infused/Aligned Population for Subgroups of Patients receiving "Novel RWPC" and "≥triplet RWCP"



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