

Bispecific Therapy in Early Relapse for Myeloma

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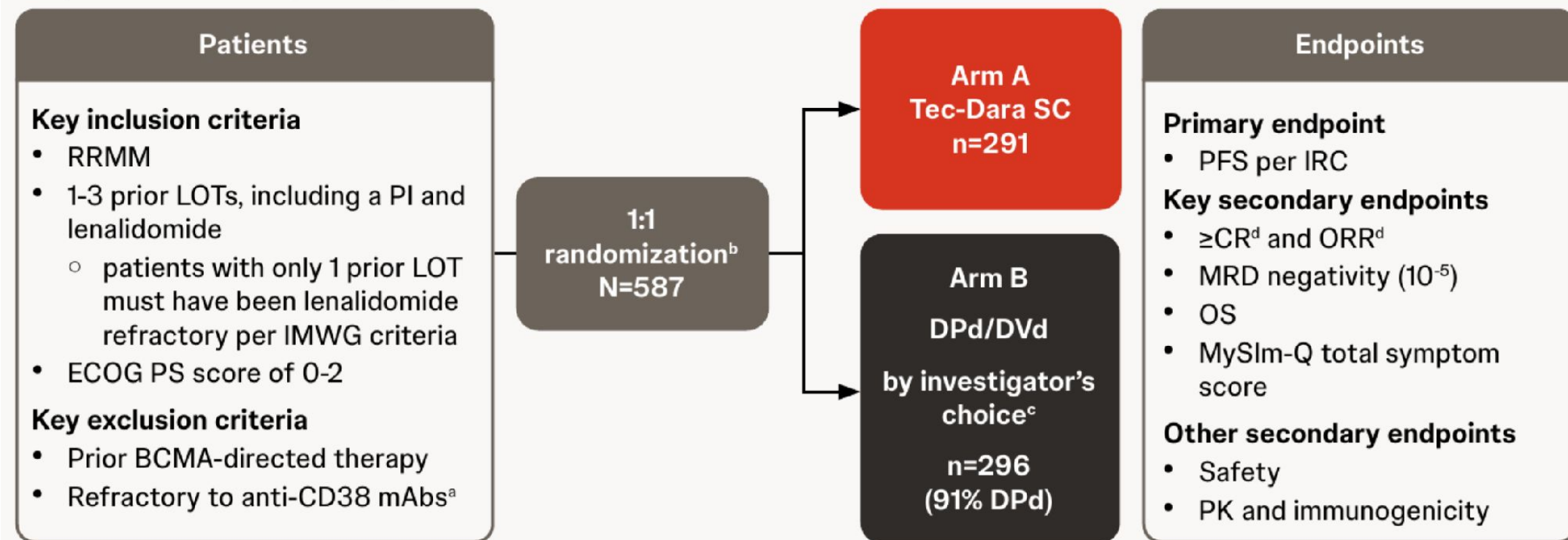
Moffitt at Memorial Healthcare System

Disclosures

- Celgene, Janssen, Pfizer: consultancy, honoraria

MajesTEC-3: Teclistamab with Daratumumab for Relapsed Myeloma

MajesTEC-3 study design¹⁻³



^aPrior exposure to anti-CD38 mAbs was permitted.

^bRandomization was stratified by choice of DPd or DVd, ISS disease stage, previous anti-CD38 exposure, and the number of prior LOTs.

^cDPd/DVd were administered per the approved schedules.

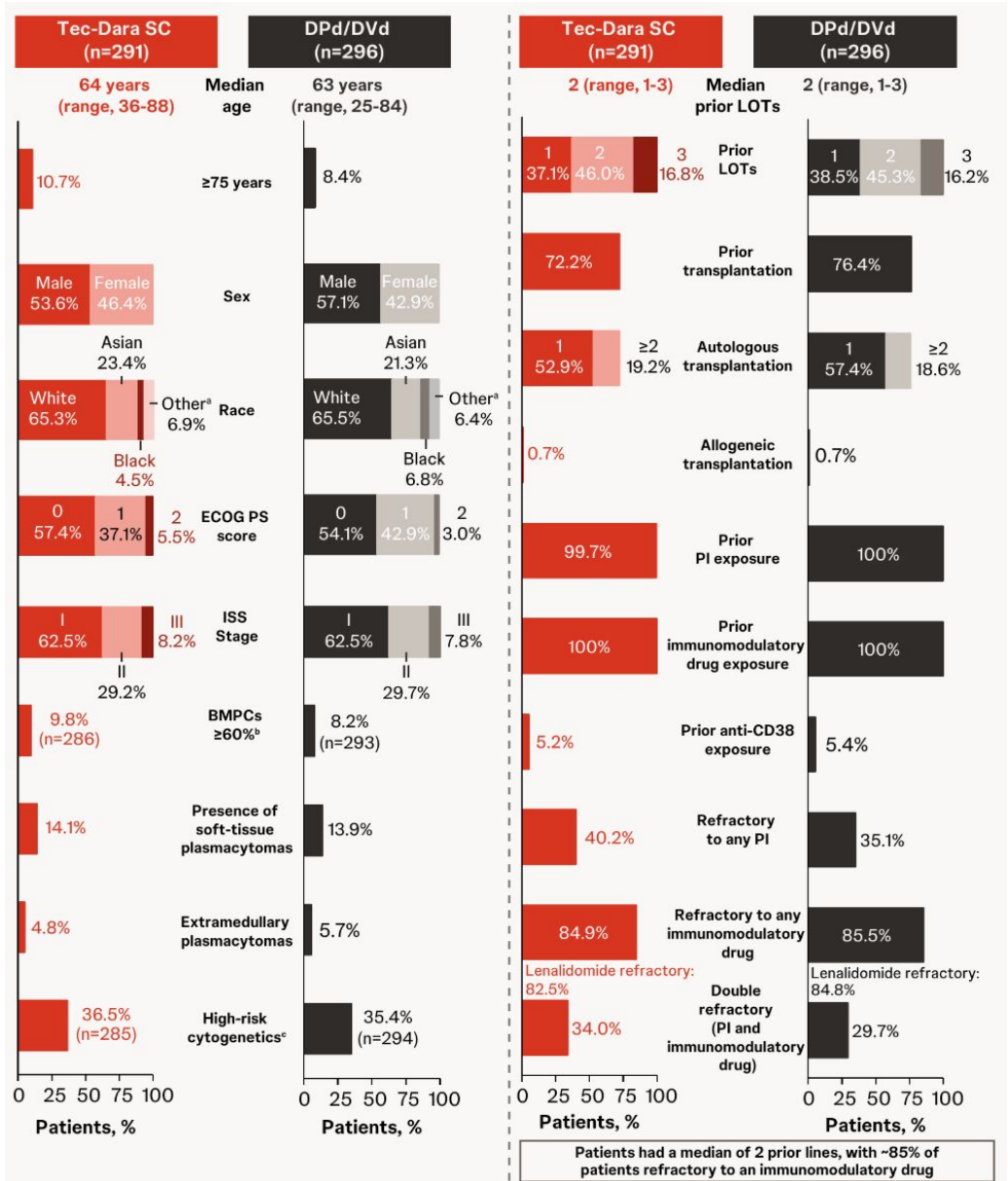
^dResponse and disease progression were assessed by a blinded IRC per IMWG criteria.

MajesTEC 3: Treatment Schedule

Cycle	1						2				3-6		7+
Day	1	2	4	8	15	22	1	8	15	22	1	15	1
Teclistamab step-up dose	-	0.06 mg/kg	0.3 mg/kg	-	-	-	-	-	-	-	-	-	-
Teclistamab treatment dose	-	-	-	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	3 mg/kg	3 mg/kg	3 mg/kg
Daratumumab SC 1800 mg	✓	-	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dexamethasone^a (pre-med)	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-
Diphenhydramine (pre-med)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Acetaminophen (pre-med)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

^aDexamethasone premedication was required for the first 2 weeks; subsequent dexamethasone was not required thereafter.

Patient Characteristics



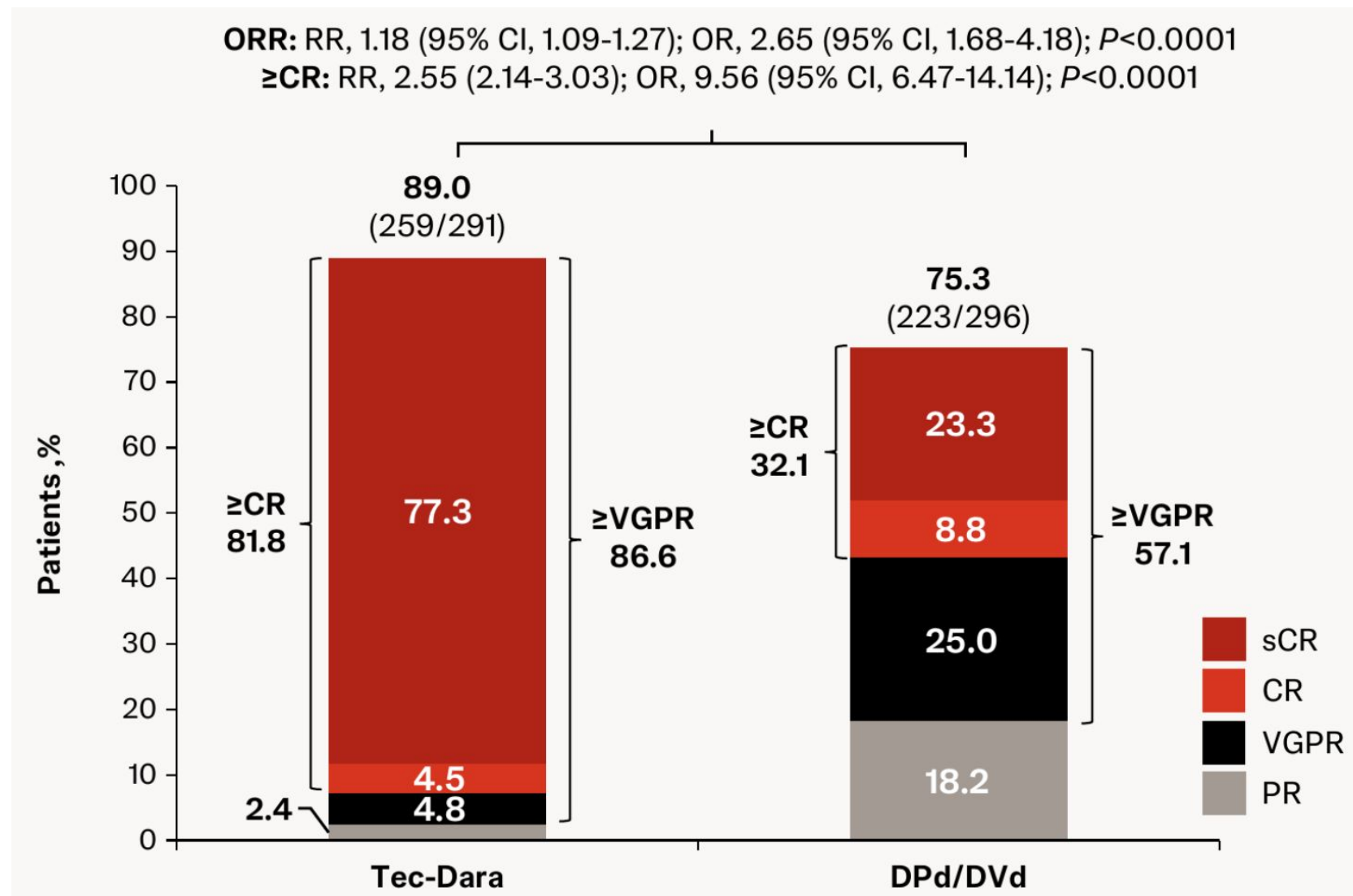
- Patients with an average of 2 prior lines of therapy
- 83% of patients lenalidomide refractory

Characteristic	Tec-Dara SC (n=291)	DPd/DVd (n=296)
Baseline cytogenetic risk ^{a,b} per prespecified definition, n (%)		
Standard risk	126 (43.3)	145 (49.0)
High risk	104 (35.7)	104 (35.1)
Baseline cytogenetic risk ^{a,c} per revised definition, n (%)		
Expanded standard risk (0 HRCAs)	52 (17.9)	55 (18.6)
Expanded high risk (≥1 HRCA)	169 (58.1)	180 (60.8)
1 HRCA	105 (36.1)	111 (37.5)
≥2 HRCAs	64 (22.0)	69 (23.3)
Functional high-risk status		
Number of patients with 1 prior LOT only, n	108	114
Yes, n (%)	26 (24.1)	20 (17.5)
No, n (%)	82 (75.9)	94 (82.5)

^aCytogenetic risk was assessed centrally with FISH or on local FISH or karyotype testing if central FISH was not available.
^bPrespecified standard risk: none of del(17p), t(4;14), or t(14;16). Prespecified high risk: ≥1 of del(17p), t(4;14), or t(14;16).
^cExpanded standard risk: none of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21). Expanded high risk: ≥1 of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21).

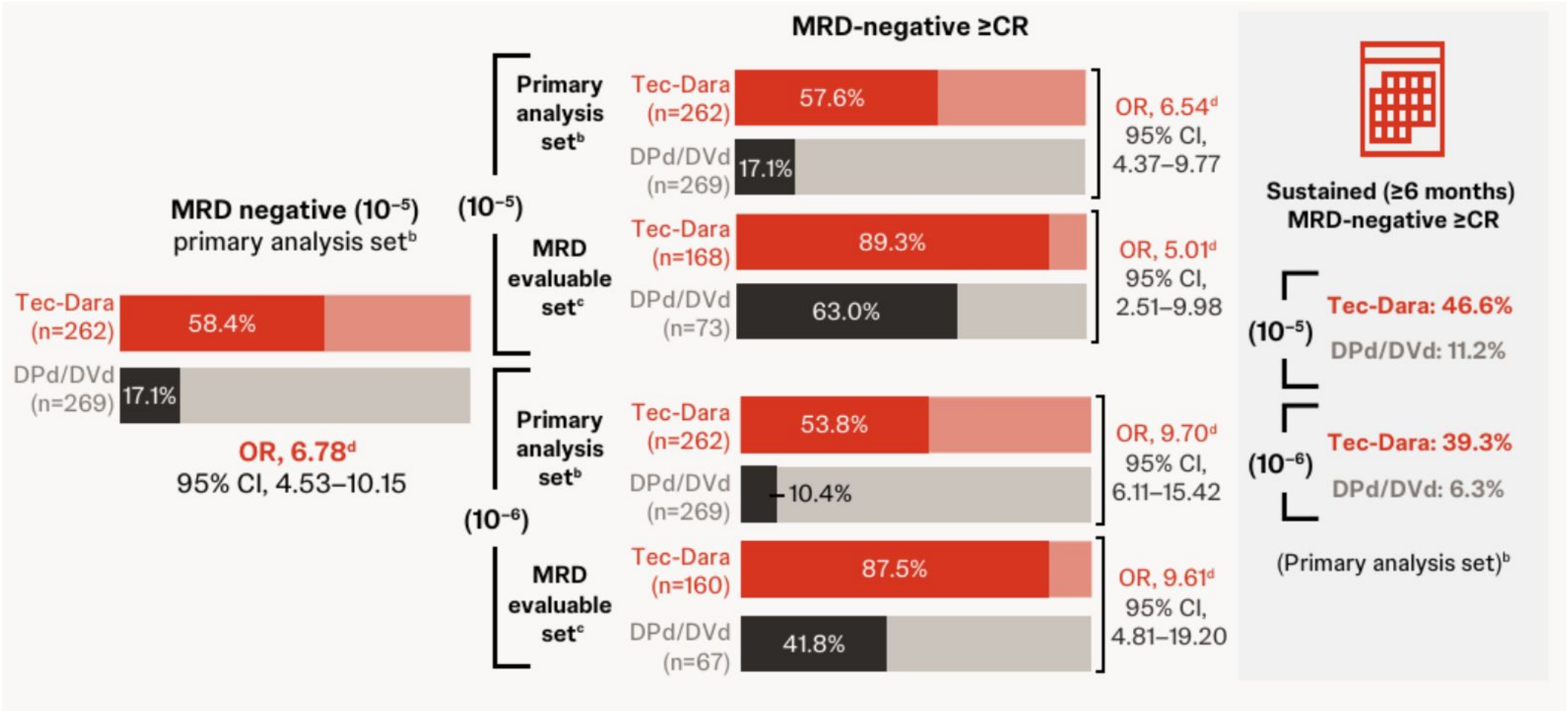
MajesTEC 3: Response

Higher rates of
CR with
teclistamab
and
daratumumab!



MajesTEC 3: MRD Negativity

Higher rates of MRD negativity, and sustained MRD negativity with teclistamab and daratumumab



MajesTEC 3: Benefit Across High-Risk Subgroups

Subgroups	Tec-Dara SC			DPd/DVd			HR (95% CI)
	Events n/N	Median PFS (months)	Estimated 36-month PFS rate (%)	Events n/N	Median PFS (months)	Estimated 36-month PFS rate (%)	
Prespecified cytogenetic risk ^a							
Standard risk	15/126	NE	87.4	84/145	24.7	37.1	0.16 (0.09-0.27)
High risk	20/104	NE	77.7	78/104	14.4	11.5	0.15 (0.09-0.25)
Expanded cytogenetic risk ^b							
Expanded standard risk	5/52	NE	90.1	34/55	24.2	31.9	0.12 (0.04-0.30)
Expanded high risk	30/169	NE	79.9	122/180	15.8	23.6	0.18 (0.12-0.26)
Number of expanded HRCA ^c							
0 ^d		-	90.1		-	31.9	0.12 (0.04-0.30)
1	17/105	NE	82.0	69/111	17.9	30.7	0.19 (0.11-0.32)
≥2	13/64	NE	76.4	53/69	14.4	13.7	0.16 (0.08-0.29)
Functional high-risk after 1 prior LOT ^e							
FHR	5/26	NE	77.3	14/20	23.3	0	0.22 (0.08-0.62)
Non-FHR	8/82	NE	89.9	8/82	20.8	35.9	0.11 (0.05-0.23)

^aPrespecified standard risk: none of del(17p), t(4;14), or t(14;16). Prespecified high risk: ≥1 of del(17p), t(4;14), or t(14;16).
^bExpanded standard risk: none of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21). Expanded high risk: ≥1 of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21).
^cHRCA number is defined as the number of abnormalities present from: del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21).
^dIn the subgroup with no HRCA, n=52 for Tec-Dara and n=55 for DPd/DVd.
^eFunctional high-risk status defined as patients with 1 prior LOT and progressive disease within 18-months of ASCT or start of initial therapy.

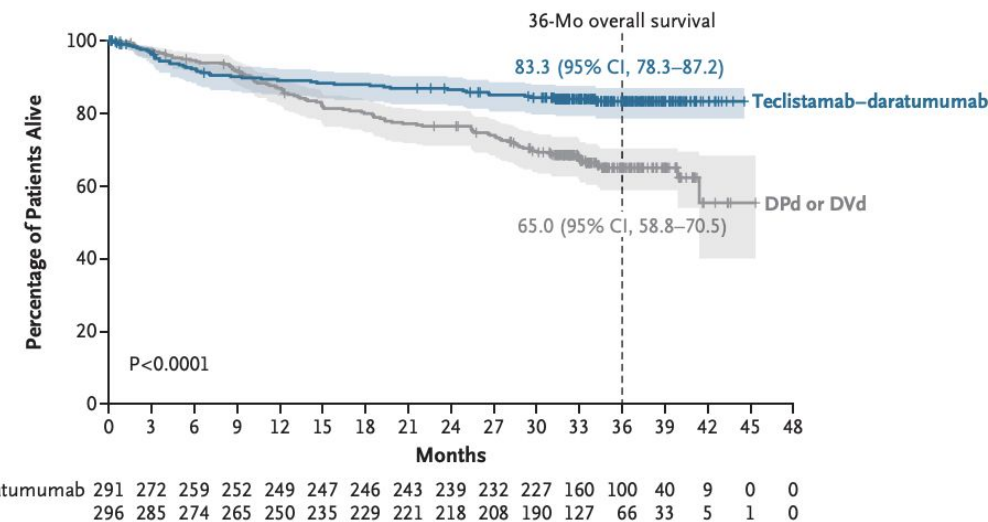
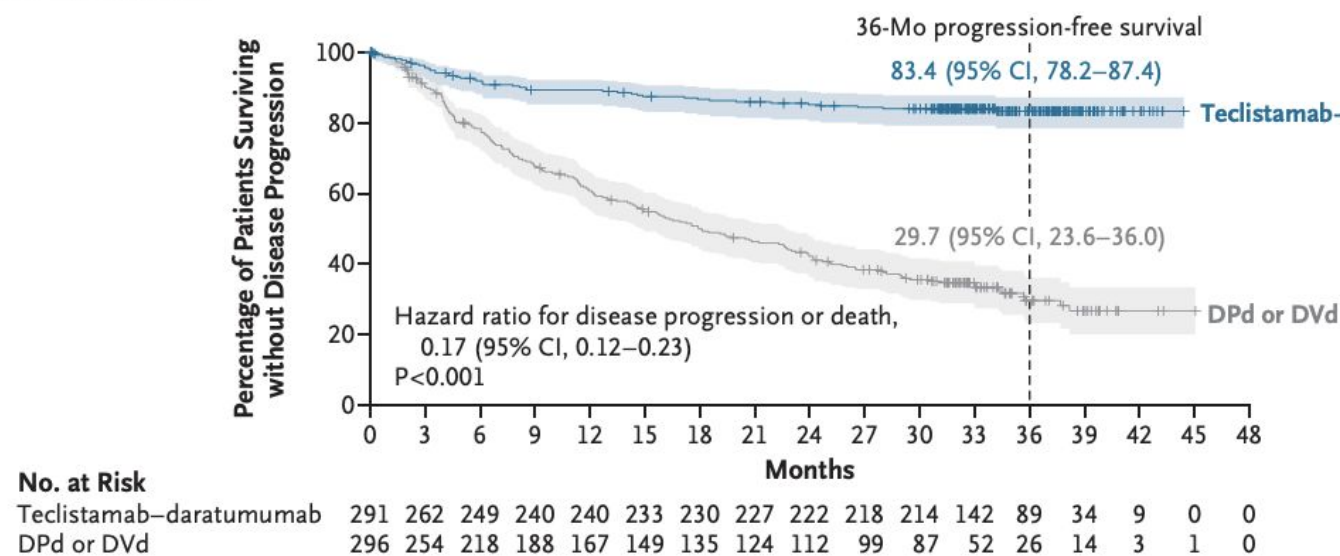
Significant benefit among HR subgroups with teclistamab-daratumumab vs SOC

MajesTEC 3: Survival

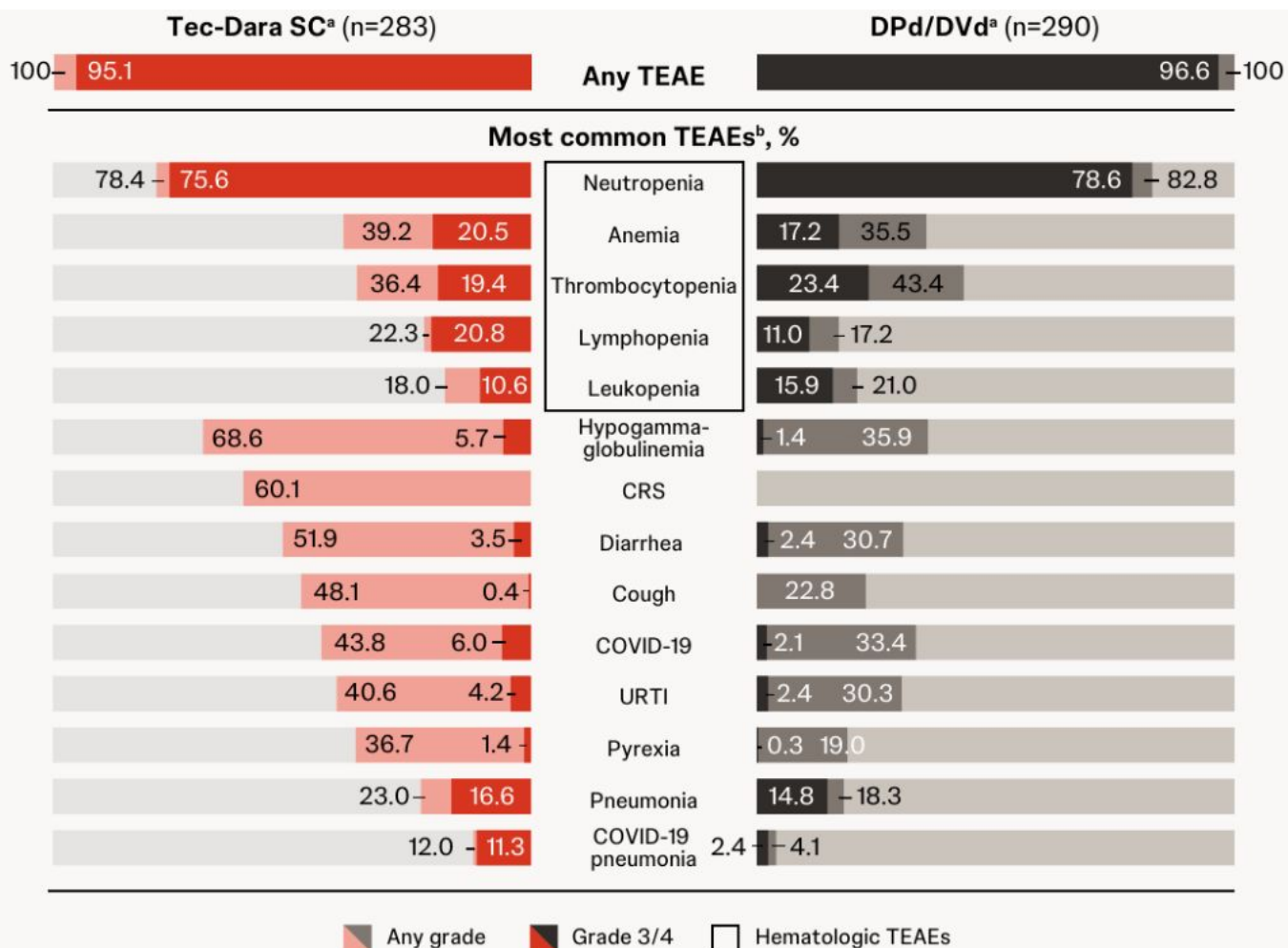
36-month PFS 83.4% for
teclistamab-daratumumab vs SOC

HR for risk of progression or death HR = 0.17
(95% confidence interval, 0.12 to 0.23; P<0.001)

A Progression-free Survival

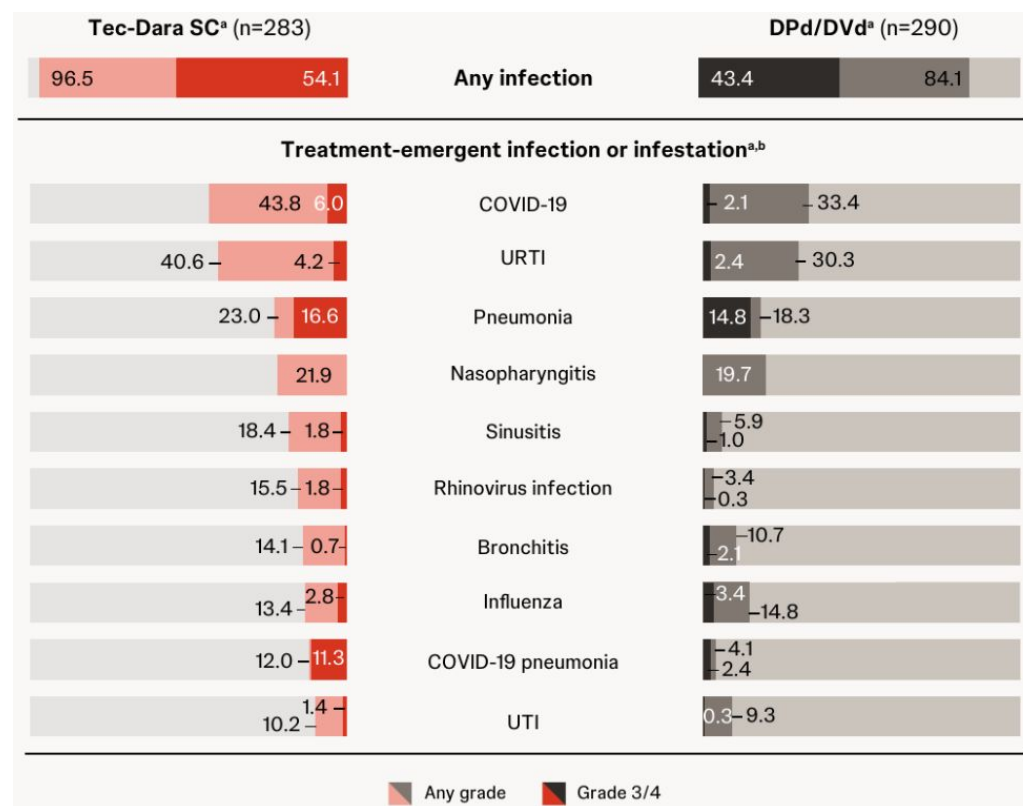


Adverse Events, Infections



Treatment AE manageable:

- Mostly low-grade CRS, all grade 1-2
- ICANS 1%, no delayed neurotoxicity
- Hematologic AE consistent with known data
- Risk for infections still need vigilant monitoring and prophylaxis, especially within first 6m



Challenges with CAR-T Cell Therapy

Average turnaround time?

Ciltacabtagene autoleucel:

-About 4 weeks (29-32) days

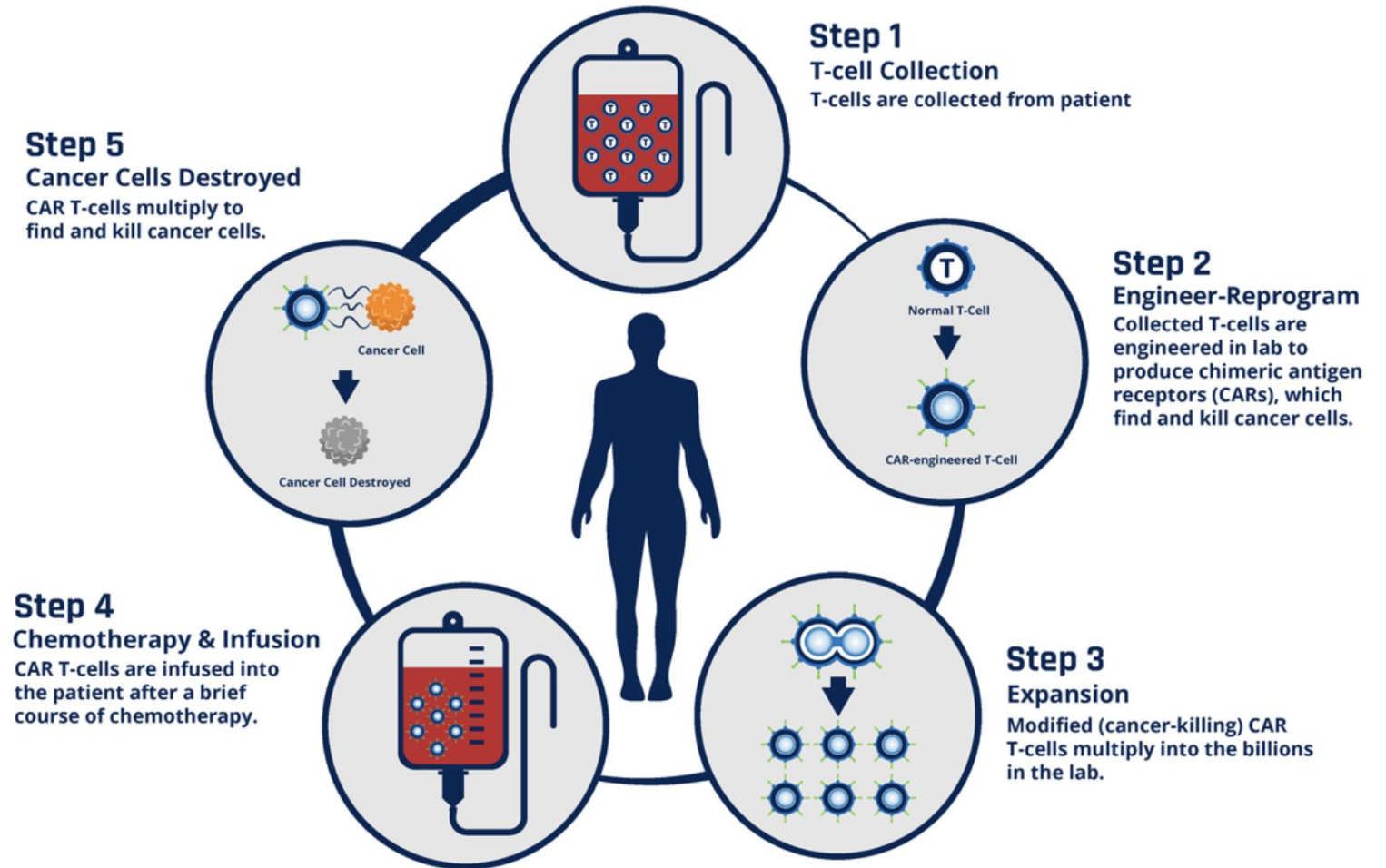
Idecabtagene autoleucel:

-About 24 days

*Consider additional time for consult, vital organ testing, manufacturing issues (out of specification) and product delays

-OOS rates cilta-cel peaked ~30%, now about 8.3%, OOS products even in patients with 1 prior line of therapy!

*Attrition exists even after CAR-T referrals, mostly due to progressive disease



Challenges with CAR-T Cell Therapy

- Access to care
 - Can only be given at centers with certified cellular therapy teams
- Social issues
 - Requires caregiver
- Toxicity
 - Requirement of lymphodepletion chemotherapy
 - Delayed neurologic and movement disorders (NMTs)
 - Enterocolitis (IEC-EC)
 - Hematotoxicity (ICAHT)



Why Bispecific Antibodies?

Access, Timing, Flexibility

1

No manufacturing wait

Tec-Dara starts immediately. CAR-T requires apheresis and 3–6+ weeks of vein-to-vein time, during which aggressive disease can progress.

2

No lymphodepleting chemo

Cilta-cel requires cyclophosphamide/fludarabine conditioning; Tec-Dara does not add cytotoxic chemotherapy to the regimen.

3

Community-deliverable

Subcutaneous dosing allows administration outside specialized cellular-therapy centers, widening access for rural and underserved patients.

4

No bridging-therapy gap

Patients avoid the disease-control gap between apheresis and infusion that can compromise CAR-T candidacy.

5

Dose-adjustable

Continuous dosing allows the regimen to be modified or paused for toxicity — a one-time CAR-T infusion cannot be titrated after the fact.

6

Preserves CAR-T as a later option

Reserving cell therapy for subsequent relapse keeps a powerful one-time option in reserve rather than spending it early.

Sequencing?

May Be Less of a Problem in the Future With Fixed Duration Use of Bispecifics and Different Tar

Trial	Name	Description
NCT05552222	MajesTEC-7	Teclistamab in Combination With Daratumumab and Lenalidomide (Tec-DR) and Talquetamab in Combination With Daratumumab and Lenalidomide (Tal-DR) in Participants With Newly Diagnosed Multiple Myeloma
NCT05695508	MajesTEC-5	Phase 2 Study to Evaluate Safety and Efficacy of Teclistamab- and Talquetamab-based Combination Regimens in Participants with Newly Diagnosed Transplant Eligible Multiple Myeloma
NCT06505369	TALTEC	Bispecific T-cell Redirectors as Part of First Line Treatment in Transplant Eligible Multiple Myeloma
NCT05849610	GEM-TECTAL	Teclistamab-Daratumumab and Talquestamab-Daratumumab in Newly Diagnosed High-risk Multiple Myeloma
NCT05572229	IFM2021-01	Study of Teclistamab in Combination in Elderly Patients With Multiple Myeloma
NCT05623020	MagnetisMM-6	Combination of Elranatamab,Daratumumab, Lenalidomide or Elranatamab and Lenalidomide Compared With Daratumumab, Lenalidomide, and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma Who Are Not Candidates for Transplant
NCT06207799		Pre-transplant Purging and Post-transplant MRD-guided Maintenance Therapy With Elranatamab in Patients With High-risk Multiple Myeloma

Great Potential for Outpatient Step Up Dosing, Relationship Building

- Outpatient step up dosing programs are being implemented, expanding access and implementation of use in community settings
 - Various models published
 - With or without tocilizumab prophylaxis
 - Greatly decreases incidence of CRS
 - Use of dexamethasone and acetaminophen for grade 1 CRS
 - Should require reliable caregiver, however
- For centers who cannot do step up dosing but can continue maintenance dosing, physician to physician relationships should be made to facilitate step up then transition back to local physician

Summary

TECLISTAMAB + DARATUMUMAB

- CRS typically low-grade, front-loaded to first 1–2 doses, resolves within days
- No reported cases of delayed or immune-effector-cell neurotoxicity (ICANS) at CAR-T's severity
- Manageable with step-up dosing and outpatient monitoring after the initial cycle
- No conditioning-chemotherapy cytopenias layered on top of the regimen
- Grade 3–4 infection rates comparable to standard triplet regimens with routine IVIG support
- Likely better for frail, less-fit patient cohort
- Off the shelf availability
- Earlier line use may lead to fixed duration therapy of bispecific agent, allowing CAR-T cell for later or next lines

CAR-T (CILTA-CEL)

- CRS and ICANS require inpatient monitoring for 7–10+ days post-infusion
- Documented risk of delayed neurotoxicity, including movement and neurocognitive changes
- Prolonged cytopenias from lymphodepleting chemotherapy increase infection risk
- Requires certified treatment centers with REMS-trained staff and ICU backup
- Requires caregiver support
- Requires manufacturing time resulting in need for bridging therapy to reduce burden and decrease potential for Aes
- Rare but serious reports of secondary T-cell malignancies prompted an FDA boxed warning

THANK YOU!