Highlights in seconda linea nel mieloma multiplo

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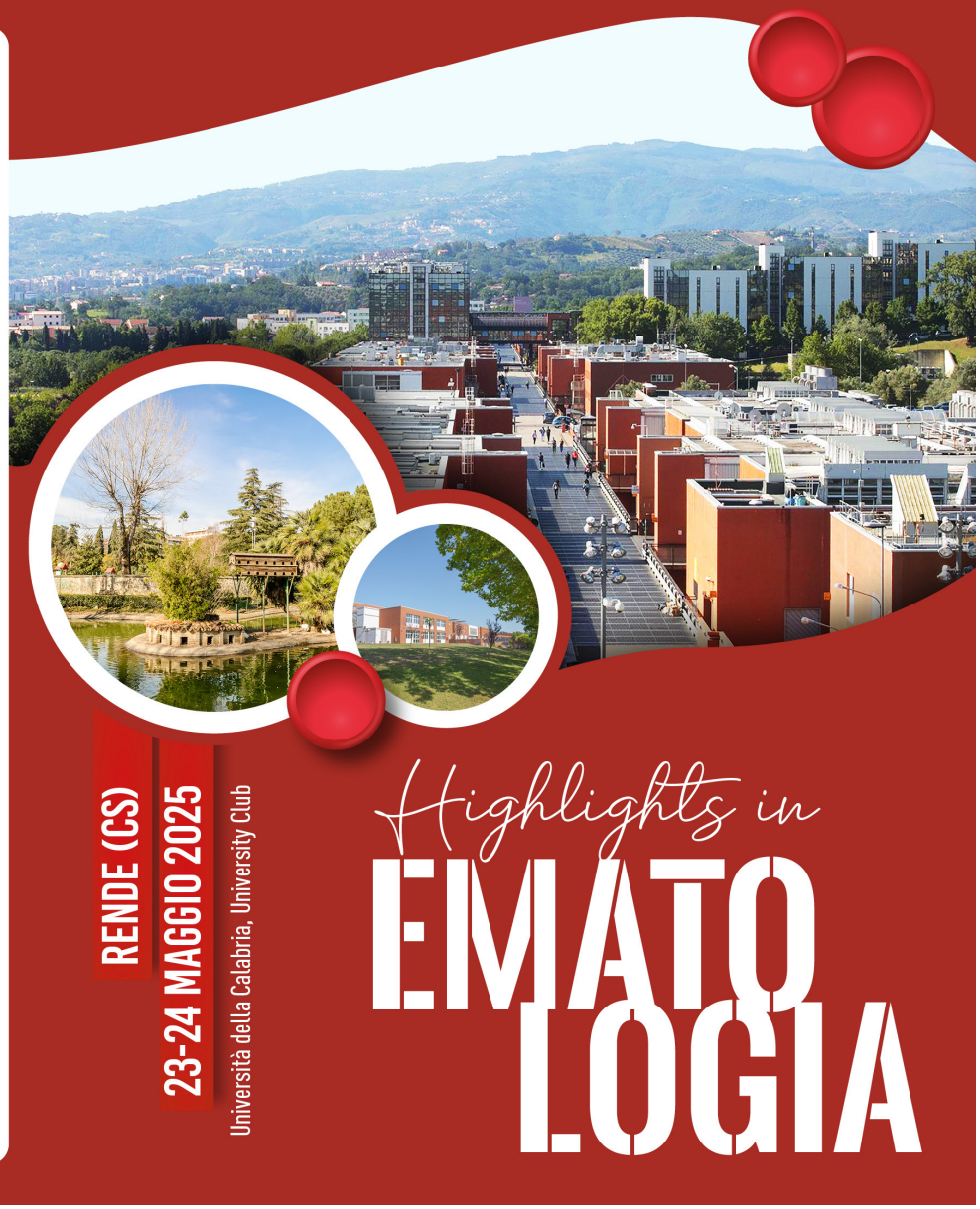

Key issues

- Treatment paths are rapidly evolving as of occurrence of new therapies and shifting of the most efficaceous combos in I line

- As a consequence, emergence of lenalidomide refractoriness is a challenging issue in early lines of MM treatment

- Clinical data from trials and RW have shown the impact of lena refractoriness on overall outcomes

Len Ref outcomes in Clinical Trials

PI-Based Regimens														
Overall									Len Refractory					
Studio [Ref]	Regimens	Prior LOTs (m)	mFU (mos)	mPFS (mos)	mOS (mos)	ORR (%)	≥CR (%)	MRD- (%)	Len-ref (%)	mPFS (mos)	mOS (mos)	ORR (%)	≥CR (%)	MRD- (%)
CASTOR [30–32]	D-Vd vs. Vd	2 (1–9)	72.6	16.7 vs. 7.1 **(27.0 vs. 7.9 as 2nd LOT)**	49.6 vs. 38.5	84 vs. 63	29 vs. 10	14 vs. 2	24	7.8 vs. 4.9	/	/	/	/
ENDEAVOR [33–35]	Kd56 vs. Vd	2 (1–3)	44.3	18.7 vs. 9.4	47.8 vs. 38.8 **(51.3 vs. 43.7 as 2nd LOT)**	77 vs. 63	13 vs. 6	/	25	8.6 vs. 6.6	29.2 vs. 21.4	/	15.5 (Kd56)	/
CANDOR [36–38]	D-Kd vs. Kd	2 (1–5)	50.6	28.4 vs. 15.2	50.8 vs. 43.6	84 vs. 73	22 vs. 8	28 vs. 9	32 vs. 36	28.1 vs. 11.1	NR vs. 38.2	79.8 (D-Kd)	/	/
IKEMA [39–44]	isa-Kd vs. Kd	2 (1–4)	56.6	35.7 vs. 19.2	NR vs. 50.6	87 vs. 84	44 vs. 29	34 vs. 15	32 vs. 34	HR 0.6 in favor of isa-Kd	/	/	39 vs. 12	25 vs. 10
BOSTON [45]	SVd vs. Vd	2 (1–3)	28	13.2 vs. 9.5 **(21.0 vs. 10.7 as 2nd LOT)**	36.7 vs. 32.8 **(NR vs. 32.8 as 2nd LOT)**	76 vs. 62	17 vs. 11	/	37 vs. 39	10.2 vs. 7.1	26.7 vs. 18.6	67.9 vs. 47.2	/	/

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Len Ref outcomes in Clinical Trials

IMiD-based regimens														
		Overall							Len Refractory					
Studio	Regimens	Prior LOTs (m)	mFU (mos)	mPFS (mos)	mOS (mos)	ORR (%)	≥CR (%)	MRD- (%)	Len-ref (%)	mPFS (mos)	mOS (mos)	ORR (%)	≥CR (%)	MRD- (%)
OPTIMISMM [46–48]	PVd vs. Vd	2 (1–3)	64.5	11.7 vs. 6.9 (**20.73 vs. 11.63 as 2nd LOT**)	35.6 vs. 31.6	82 vs. 50	13 vs. 3	/	71 vs. 69	17.8 vs. 9.5 (**2nd LOT**)	29.8 vs. 24.2	85.9 vs. 50.8	/	/
APOLLO [49–51]	D-Pd vs. Pd	2 (1–5)	39.6	12.4 vs. 6.9	34.4 vs. 23.7	69 vs. 46	25 vs. 4	9 vs. 2	63 vs. 73	9.9 vs. 6.5	/	/	/	/
MM-014 [63.64]	D-Pd	2 (1–2)	41.9	23.7	56.7	78.6	26.8	/	76	23.0	53.6	77.6	22.4	/
ICARIA [52–54]	isa-Pd vs. Pd	3 (2–4)	52.4	11.5 vs. 6.5	24.6 vs. 17.7	60 vs. 35	9 vs. 2	/	94 vs. 92	/	22.7 vs. 17.5	/	/	/
ELOQUENT-3 [55,56]	elo-Pd vs. Pd	3 (2–8)	45	10.3 vs. 4.7	29.8 vs. 17.4	53 vs. 26	20 vs. 9	/	90 vs. 84	/	/	/	/	/
CAR-T-based regimens														
cilta-cel vs. SOC [57,58]	CARTITUDE-4	2 (1–3)	33.6	NR vs. 11.8 (30-mos PFS: 59.4% vs. 25.7%)	NR (30-mos OS: 76.4% vs. 63.8%)	85 vs. 67	77 vs. 24	62 vs. 19 (ITT) 89 vs. 38 (MRD evaluable pts)	All	/	/	/	/	/

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Dara based Clinical Trials

Daratumumab clinical trials overview.

Daratumumab trial	Clinicaltrials.gov trial number	Study start year	Clinical study phase	Study population, N*	Summary
APOLLO	NCT03180736	2017	3	299	D-Pd *vs* Pd in RRMM
CASTOR	NCT02136134	2014	3	480	D-Vd *vs* Vd in RRMM
CANDOR	NCT03158688	2017	3	461	D-Kd *vs* Kd in RRMM
EQUULEUS	NCT01998971	2014	1b	240	Safety and tolerability of D-Pd or D-Kd in RRMM
ALCYONE	NCT02195479	2014	3	700	D-VMP *vs* VMP in transplant-ineligible NDMM
MAIA	NCT02252172	2015	3	729	D-Rd *vs* Rd in frontline therapy in transplant-ineligible patients with NDMM
GRIFFIN	NCT02874742	2016	2	217	D-RVd *vs* RVd in transplant-eligible patients with NDMM
POLLUX	NCT02076009	2014	3	564	D-Rd *vs* Rd in RRMM
CASSIOPEIA	NCT02541383	2015	3	1074	D-VTd *vs* VTd as induction and D monotherapy *vs* observation as maintenance in transplant-eligible NDMM

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Individual patient level analysis in Len ref MM pts

Baseline characteristic	Total (N = 915)	1 prior LOT (n = 114)	2 prior LOT (n = 462)	3 prior LOT (n = 339)
ISS stage, n (%)				
I	339 (37·0)	46 (40·4)	174 (37·7)	119 (35·1)
II	285 (31·1)	20 (17·5)	162 (35·1)	103 (30·4)
III	159 (17·4)	10 (8·8)	76 (16·5)	73 (21·5)
Unknown	132 (14·4)	38 (33·3)	50 (10·8)	44 (13·0)
Prior stem cell transplant, n (%)	539 (58·9)	68 (59·6)	247 (53·5)	224 (66·1)
ECOG PS, n (%)				
0	452 (49·4)	69 (60·5)	223 (48·3)	160 (47·2)
1	463 (50·6)	45 (39·5)	239 (51·7)	179 (52·8)
Time to PD on last regimen, median months (IQR)[§]	11·9 (5·4–24·7)	22·4 (11·7–36·2)	10·8 (4·6–22·1)	11·0 (5·0–21·2)
Prior treatments, n (%)				
Bortezomib	880 (96·2)	105 (92·1)	445 (96·3)	330 (97·3)
Thalidomide	295 (32·2)	8 (7·0)	136 (29·4)	151 (44·5)
Daratumumab	166 (18·1)	10 (8·8)	91 (19·7)	65 (19·2)
Carfilzomib	109 (11·9)	7 (6·1)	49 (10·6)	53 (15·6)
Ixazomib	72 (7·9)	7 (6·1)	38 (8·2)	27 (8·0)
Pomalidomide	33 (3·6)	2 (1·8)	7 (1·5)	24 (7·1)
Elotuzumab	23 (2·5)	0 (0)	10 (2·2)	13 (3·8)
Isatuximab	0 (0)	0 (0)	0 (0)	0 (0)
Refractory status, n (%)				
Last LOT	835 (91·3)	111 (97·4)	411 (89·0)	313 (92·3)
PI	585 (63·9)	110 (96·5)	240 (51·9)	235 (69·3)
Anti-CD38 mAb	140 (15·3)	10 (8·8)	67 (14·5)	63 (18·6)
Triple refractory[¶]	87 (9·5)	10 (8·8)	32 (6·9)	45 (13·3)
Penta refractory[‖]	9 (1·0)	0 (0)	6 (1·3)	3 (0·9)

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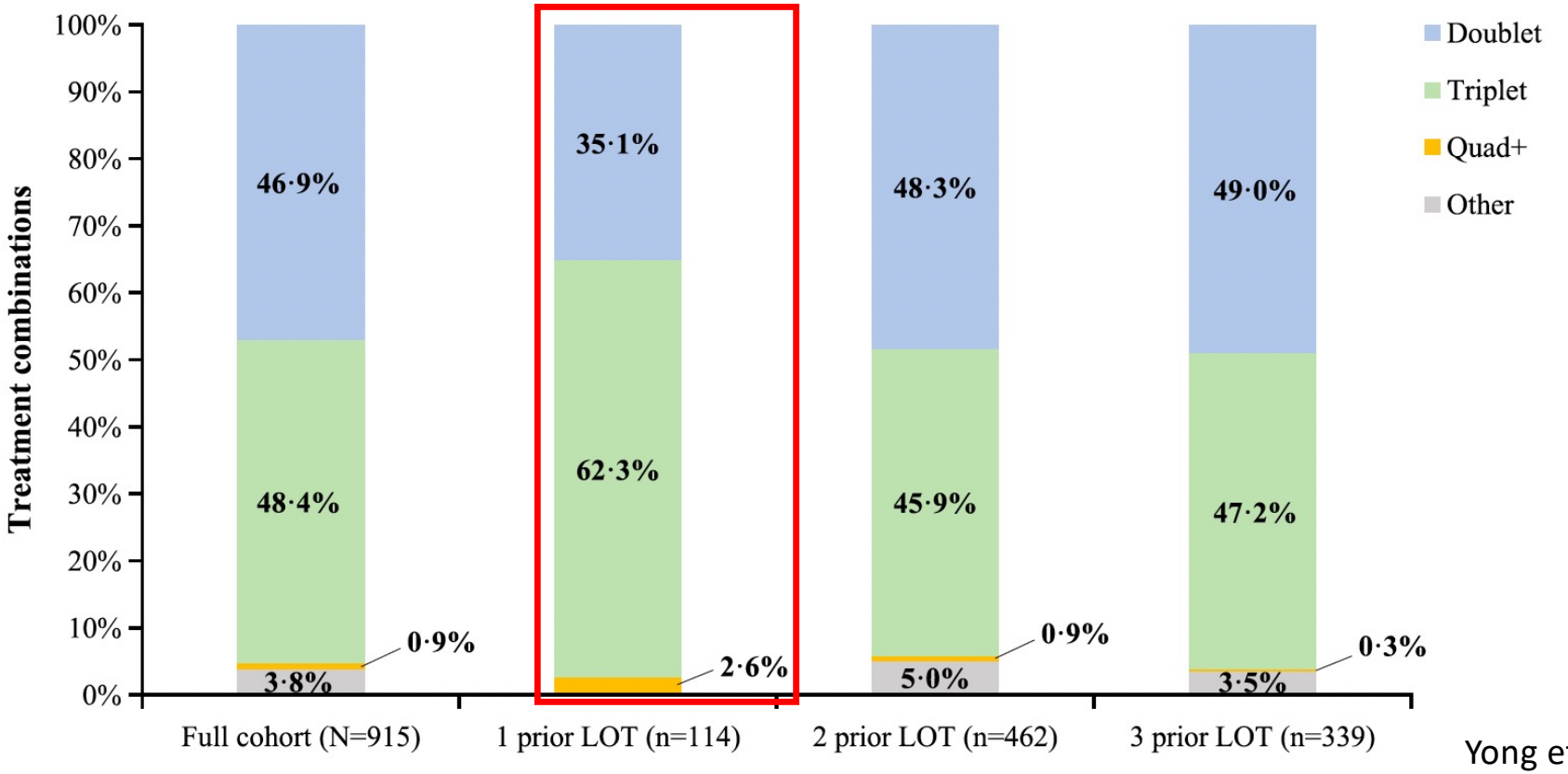
Most Common Treatment combos in Len ref MM pts



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RR by prior LOT in Len ref MM pts

Response rate, n (%)	Total (N = 915)	1 prior LOT (n = 114)	2 prior LOT (n = 462)	3 prior LOT (n = 339)
ORR	507 (55·4)	84 (73·7)	249 (53·9)	174 (51·3)
VGPR or better	305 (33·3)	57 (50·0)	152 (32·9)	96 (28·3)
CR or better	131 (14·3)	22 (19·3)	70 (15·2)	39 (11·5)

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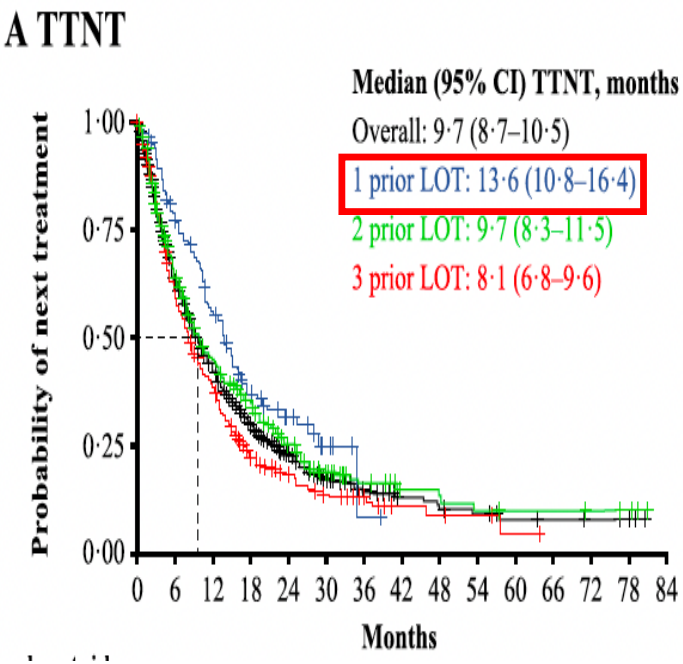
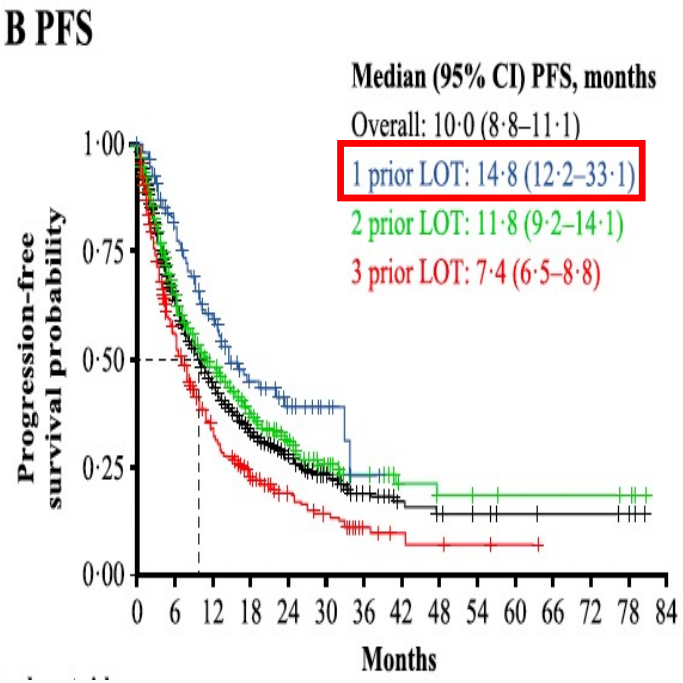
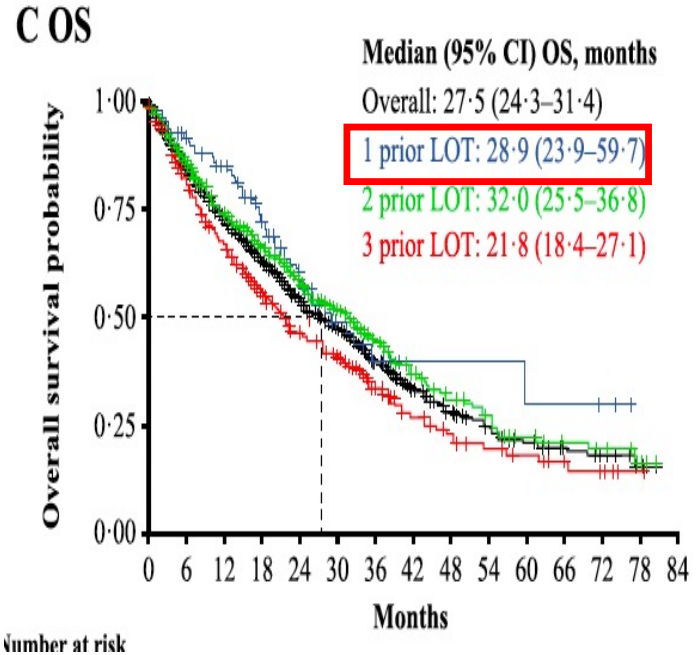
Overall Outcomes by prior LOT in Len ref MM pts







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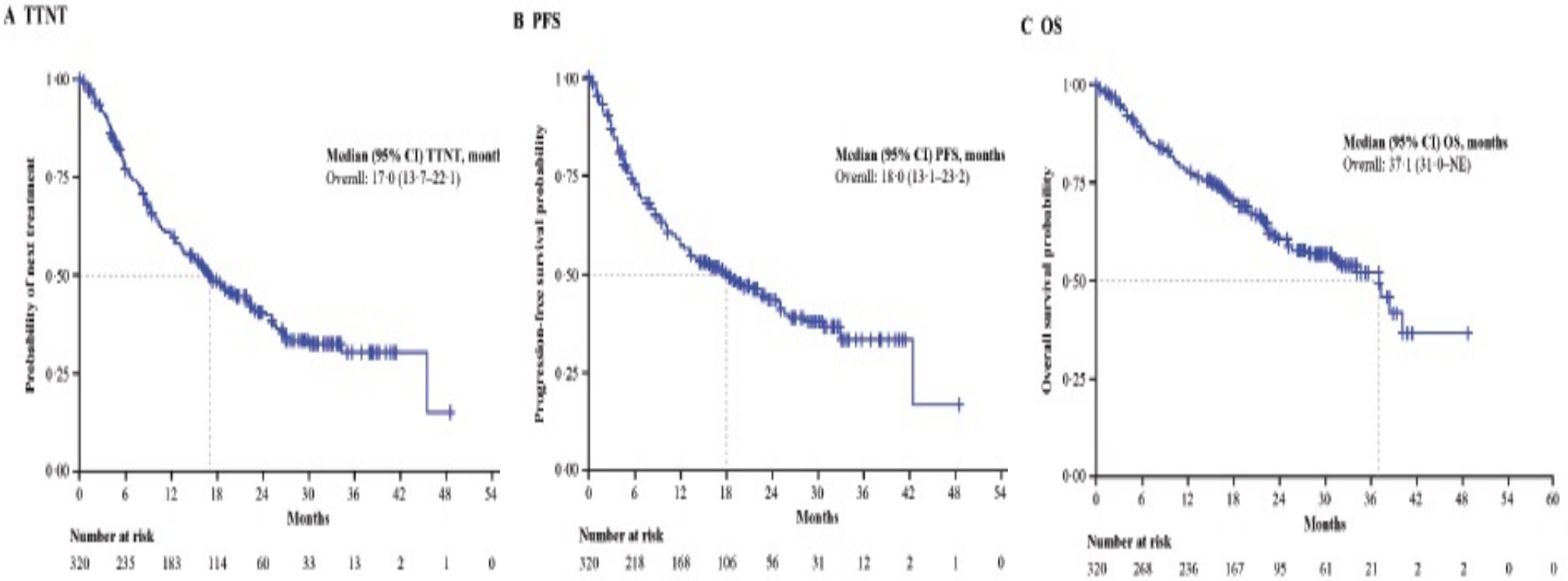
Overall Outcomes by prior LOT in Len ref MM pts treated according to ESMO guidelines



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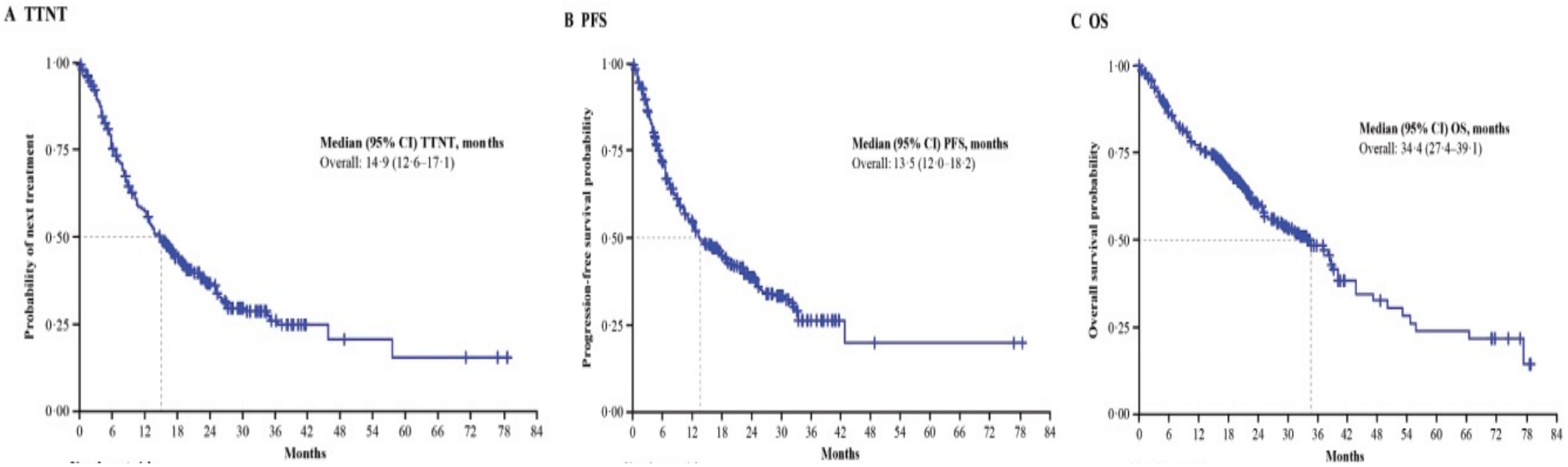
Overall Outcomes by prior LOT in Len ref MM pts treated according to NCCN guidelines



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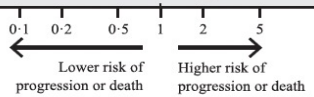
HR for PFS adn OS in Len ref MM pts

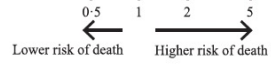
A PFS

Variable		N	Hazard ratio	p
Age, years	<65	431	Reference	
	65–70	202	0·86 (0·70–1·06)	0·160
	≥70	282	0·97 (0·81–1·18)	0·788
Sex	Female	398	Reference	
	Male	517	1·11 (0·94–1·31)	0·224
Race	White	693	Reference	
	Black	31	0·64 (0·39–1·06)	0·084
	Other	152	1·05 (0·82–1·35)	0·697
Years since MM diagnosis	<4	522	Reference	
	≥4	393	0·93 (0·79–1·10)	0·409
Prior LOT	1	114	Reference	
	2	462	1·37 (1·03–1·83)	0·031
	3	339	2·01 (1·50–2·69)	<0·001
ECOG PS	0	452	Reference	
	1	463	1·09 (0·92–1·28)	0·321
ISS	I	339	Reference	
	II	285	1·37 (1·13–1·67)	0·002
	III	159	1·71 (1·36–2·15)	<0·001
MM subtype	IgG	524	Reference	
	Light chain	168	0·92 (0·74–1·15)	0·456
	Other	223	1·01 (0·83–1·23)	0·946
Presence of plasmacytoma	No	862	Reference	
	Yes	53	1·64 (1·17–2·29)	0·004
Prior stem cell transplant	No	376	Reference	
	Yes	539	1·13 (0·95–1·34)	0·164
Time to PD on last LOT, months	≤12	456	Reference	
	>12	447	0·83 (0·70–0·97)	0·023
Cytogenetic risk status	Standard risk	338	Reference	
	High risk	122	1·41 (1·08–1·84)	0·012
Hemoglobin, g/dL	<12	585	Reference	
	≥12	313	0·69 (0·58–0·82)	<0·001
Refractory status				
PI	No	330	Reference	
	Yes	585	1·04 (0·88–1·23)	0·655
Anti-CD38 mAb	No	775	Reference	
	Yes	140	1·53 (1·22–1·92)	<0·001
Triple-refractory	No	828	Reference	
	Yes	87	1·43 (1·07–1·92)	0·016
Penta-refractory	No	906	Reference	
	Yes	9	2·18 (0·81–5·83)	0·122



B OS

Variable		N	Hazard ratio	p
Age, years	<65	431	Reference	
	65–70	202	1·07 (0·85–1·35)	0·576
	≥70	282	1·18 (0·96–1·46)	0·115
Sex	Female	398	Reference	
	Male	517	1·26 (1·04–1·51)	0·016
Race	White	693	Reference	
	Black	31	0·54 (0·30–0·96)	0·037
	Other	152	1·38 (1·07–1·79)	0·013
Years since MM diagnosis	<4	522	Reference	
	≥4	393	0·66 (0·55–0·79)	<0·001
Prior LOT	1	114	Reference	
	2	462	1·14 (0·83–1·56)	0·413
	3	339	1·53 (1·11–2·10)	0·009
ECOG PS	0	452	Reference	
	1	463	1·24 (1·04–1·49)	0·018
ISS	I	339	Reference	
	II	285	1·66 (1·33–2·06)	<0·001
	III	159	2·36 (1·83–3·03)	<0·001
MM subtype	IgG	524	Reference	
	Light chain	168	0·84 (0·66–1·08)	0·182
	Other	223	1·01 (0·82–1·26)	0·912
Presence of plasmacytoma	No	862	Reference	
	Yes	53	1·98 (1·42–2·78)	<0·001
Prior stem cell transplant	No	376	Reference	
	Yes	539	0·97 (0·81–1·17)	0·786
Time to PD on last LOT, months	≤12	456	Reference	
	>12	447	0·72 (0·60–0·87)	<0·001
Cytogenetic risk status	Standard risk	338	Reference	
	High risk	122	1·67 (1·29–2·16)	<0·001
Hemoglobin, g/dL	<12	585	Reference	
	≥12	313	0·67 (0·55–0·82)	<0·001
Refractory status				
PI	No	330	Reference	
	Yes	585	1·20 (1·00–1·45)	0·055
Anti-CD38 mAb	No	775	Reference	
	Yes	140	1·72 (1·36–2·17)	<0·001
Triple-refractory	No	828	Reference	
	Yes	87	1·65 (1·23–2·21)	<0·001
Penta-refractory	No	906	Reference	
	Yes	9	4·01 (1·66–9·72)	0·002



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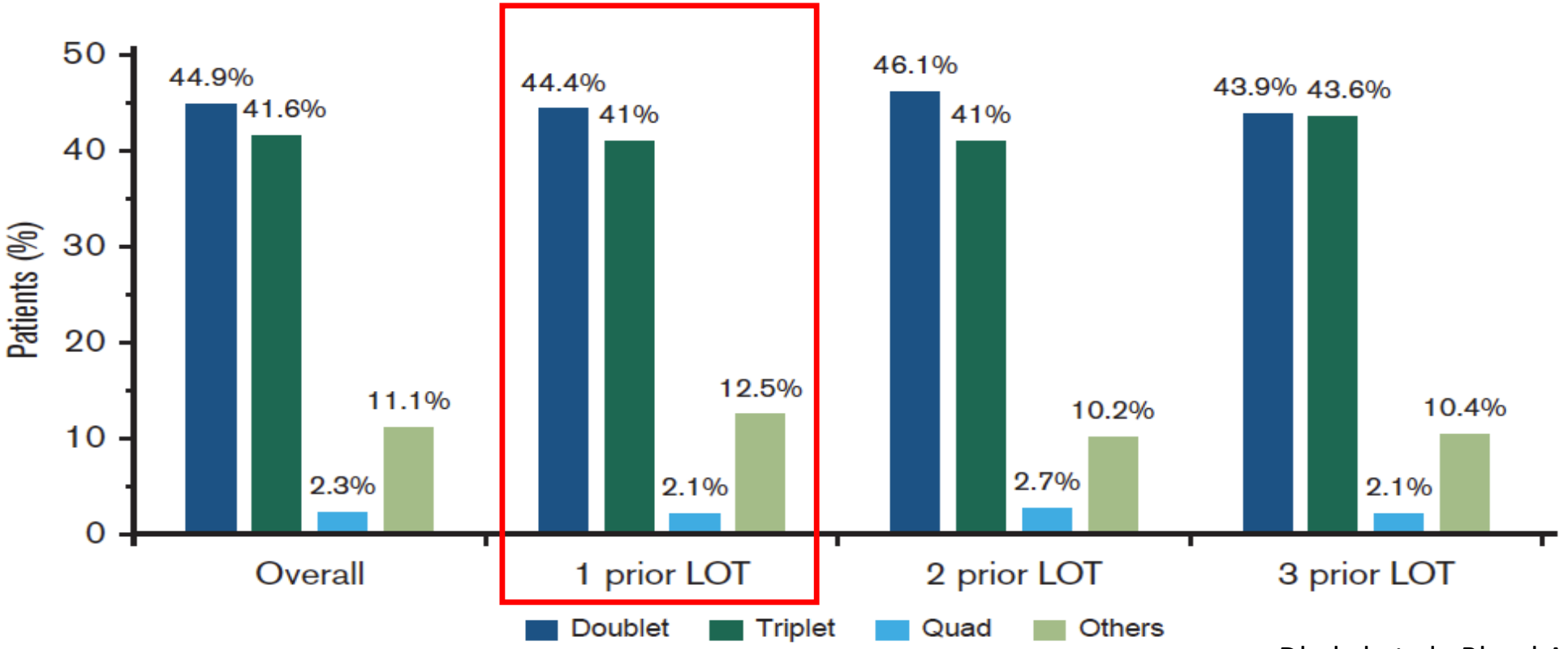
Most Common Treatment combos in Len ref MM pts RW data



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Main Treatment Regimens delivered in Len ref MM pts RW data

Treatment regimen, n (%)	Overall (N = 1455)	1 prior LOT (LOT 2) (n = 561)	2 prior LOT (LOT 3) (n = 566)	3 prior LOT (LOT 4) (n = 328)
NCCN-preferred regimens for lenalidomide-refractory 1-3 PL RRMM*				
DPd	192 (13.2)	58 (10.3)	80 (14.1)	54 (16.5)
KPd	104 (7.1)	53 (9.4)	34 (6.0)	17 (5.2)
DVd	95 (6.5)	48 (8.6)	32 (5.7)	15 (4.6)
DKd	56 (3.8)	24 (4.3)	25 (4.4)	7 (2.1)
PVd	39 (2.7)	23 (4.1)	11 (1.9)	5 (1.5)
IxaPd	14 (1.0)	4 (0.7)	6 (1.1)	4 (1.2)
IsaKd	3 (0.2)	1 (0.2)	2 (0.4)	0
IsaPd	3 (0.2)	0	2 (0.4)	1 (0.3)
Total	506 (34.8)	211 (37.6)	192 (33.9)	103 (31.4)

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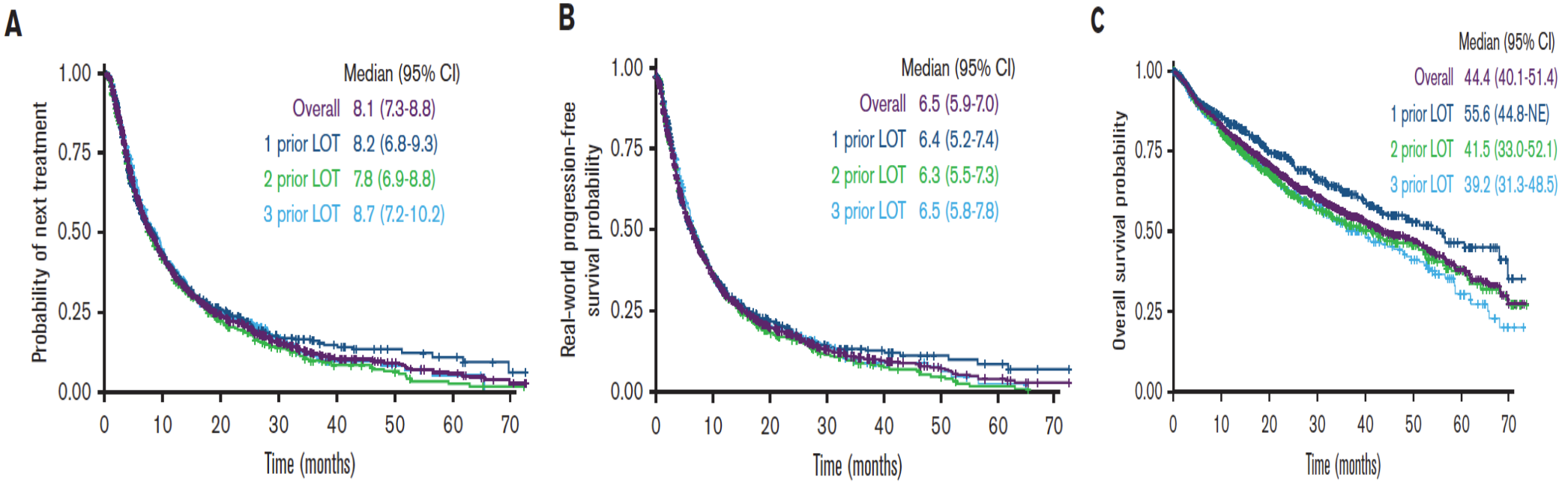
Overall Outcomes in Len ref MM pts by prior LOT RW data



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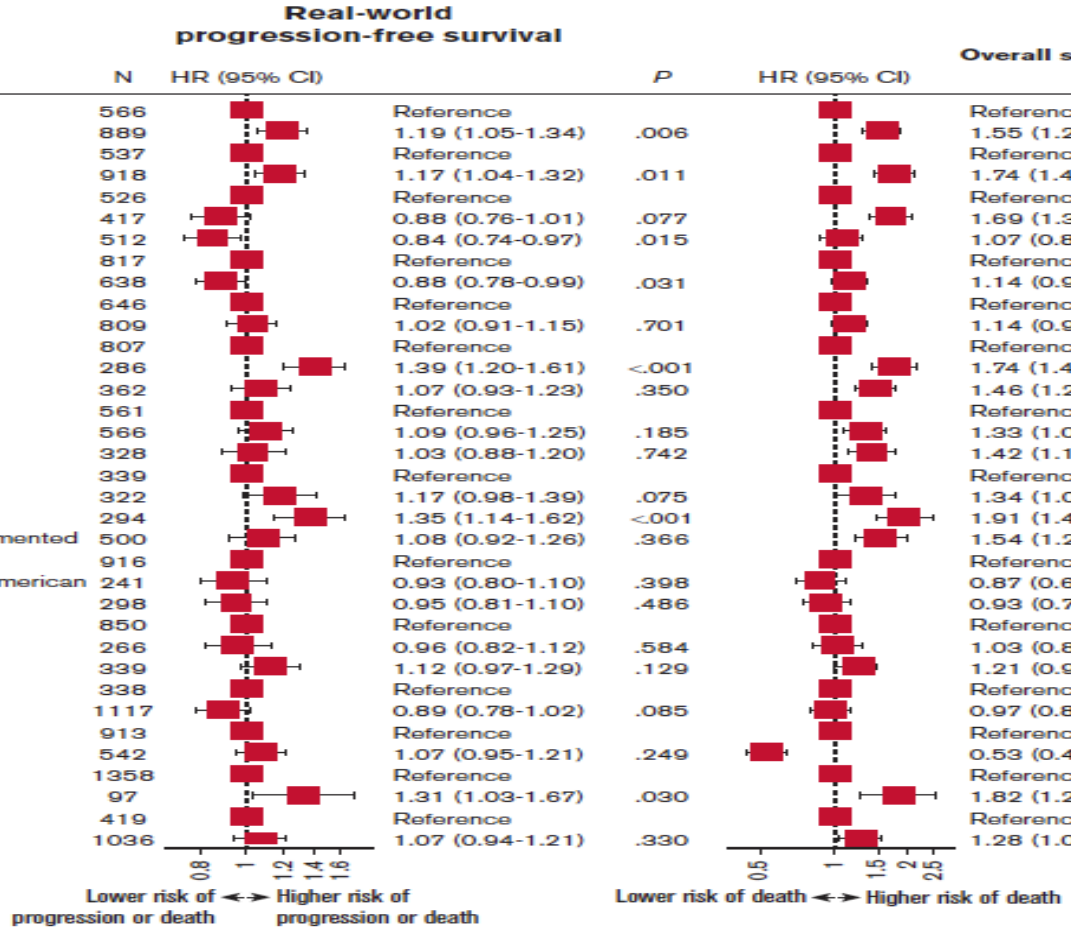
HR for PFS adn OS in Len ref MM pts

Variable		N	Real-world progression-free survival HR (95% CI)	P	Overall survival HR (95% CI)	P
ECOG PS	0	566	Reference		Reference	
	1	889	1.19 (1.05-1.34)	.006	1.55 (1.29-1.85)	<.001
Hemoglobin (g/dL)	≥12	537	Reference		Reference	
	<12	918	1.17 (1.04-1.32)	.011	1.74 (1.45-2.09)	<.001
Age (years)	<65	526	Reference		Reference	
	≥75	417	0.88 (0.76-1.01)	.077	1.69 (1.38-2.07)	<.001
	65-74	512	0.84 (0.74-0.97)	.015	1.07 (0.87-1.31)	.540
Time since diagnosis (years)	<2	817	Reference		Reference	
	≥2	638	0.88 (0.78-0.99)	.031	1.14 (0.97-1.35)	.118
Sex	F	646	Reference		Reference	
	M	809	1.02 (0.91-1.15)	.701	1.14 (0.97-1.35)	.121
Cytogenetic risk	Standard risk	807	Reference		Reference	
	High risk	286	1.39 (1.20-1.61)	<.001	1.74 (1.41-2.15)	<.001
	Unknown	362	1.07 (0.93-1.23)	.350	1.46 (1.20-1.78)	<.001
Prior lines of therapy	1	561	Reference		Reference	
	2	566	1.09 (0.96-1.25)	.185	1.33 (1.09-1.62)	.005
	3	328	1.03 (0.88-1.20)	.742	1.42 (1.14-1.76)	.002
ISS stage	I	339	Reference		Reference	
	II	322	1.17 (0.98-1.39)	.075	1.34 (1.03-1.75)	.032
	III	294	1.35 (1.14-1.62)	<.001	1.91 (1.47-2.47)	<.001
	Unknown/undocumented	500	1.08 (0.92-1.26)	.366	1.54 (1.20-1.96)	<.001
Race	White	916	Reference		Reference	
	Black or African American	241	0.93 (0.80-1.10)	.398	0.87 (0.69-1.10)	.256
	Other/unknown	298	0.95 (0.81-1.10)	.486	0.93 (0.74-1.16)	.503
MM type	IgG	850	Reference		Reference	
	Light chain	266	0.96 (0.82-1.12)	.584	1.03 (0.82-1.28)	.823
	Others	339	1.12 (0.97-1.29)	.129	1.21 (0.99-1.49)	.061
Time to progression on last line (months)	≤4	338	Reference		Reference	
	>4	1117	0.89 (0.78-1.02)	.085	0.97 (0.80-1.17)	.728
Prior stem cell transplant	N	913	Reference		Reference	
	Y	542	1.07 (0.95-1.21)	.249	0.53 (0.45-0.64)	<.001
CD38 mAb-refractory	N	1358	Reference		Reference	
	Y	97	1.31 (1.03-1.67)	.030	1.82 (1.29-2.57)	<.001
PI-refractory	N	419	Reference		Reference	
	Y	1036	1.07 (0.94-1.21)	.330	1.28 (1.06-1.55)	.012



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Potential strategies in len ref MM upon approval

			Overall						Len Refractory					
Regimen	**Studi**	**Prior LOTs (m)**	**mFU (mos)**	**mPFS (mos)**	**mOS (mos)**	**ORR (%)**	**≥CR (%)**	**MRD- (%)**	**Len-ref (%)**	**mPFS (mos)**	**mOS (mos)**	**ORR (%)**	**≥CR (%)**	**MRD- (%)**
ide-cel vs. SOC [74,75]	KarMMa-3	6 (3–16)	30.9	13.8 vs. 4.4	41.4 vs. 37.9	71 vs. 42	44 vs. 6	35 vs. 2	73 vs. 79	/	/	/	/	/
bela-Vd vs. D-Vd [76–78]	DREAMM-7	≥1	39.4	36.6 vs. 13.4	NR in either group (36-mos OS: 74% vs. 60%)	83 vs. 71	34.6 vs. 17.1	39 vs. 17	33 vs. 35 (**28 vs. 31 ref 1 prior LOT**)	25.0 vs. 8.6	/	84 vs. 61	35 vs. 11	42 vs. 13
			Overall						**Len Refractory**					
bela-Pd vs. PVd [79,80]	DREAMM-8	≥1	21.8	NR vs. 12.7 (**NR vs. 18.5 as 2nd LOT**)	NR in either group (12-mos OS: 83% vs. 76%)	77 vs. 72	40 vs. 16	24 vs. 5 (CR) 32 vs. 5 (VGPR)	81 vs. 76	24.0 vs. 9.2 (**NR vs. 13.1 as 2nd LOT**)	NR in either group (12-mos OS: 82% vs. 72%)	75 vs. 68	38 vs. 14	23 vs. 5 (CR) 31 vs. 5 (VGPR)

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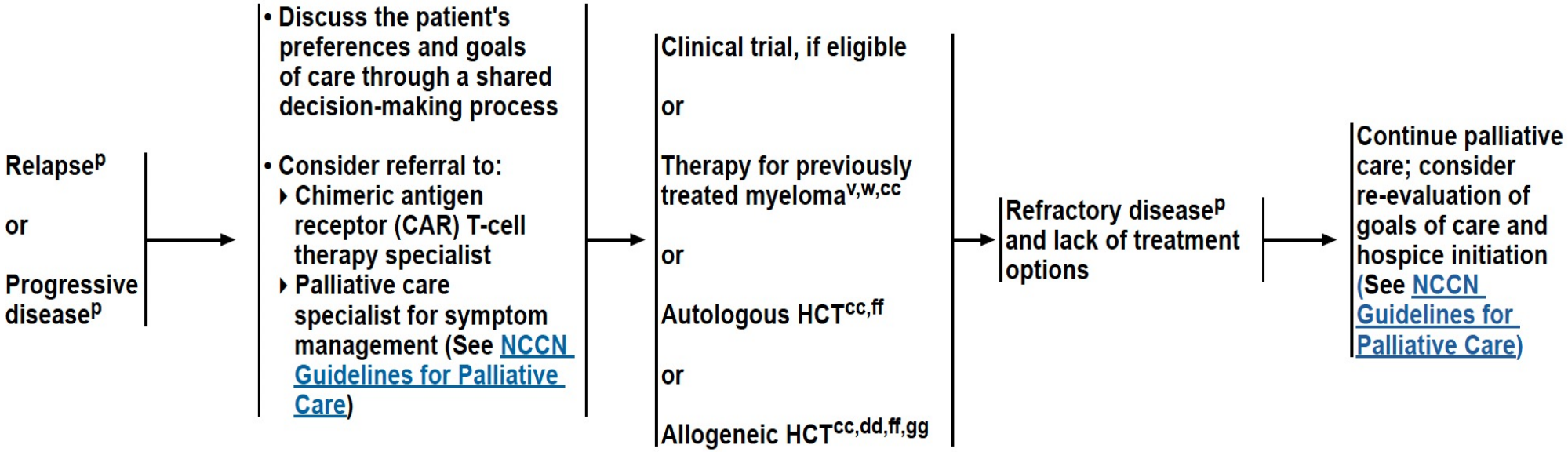
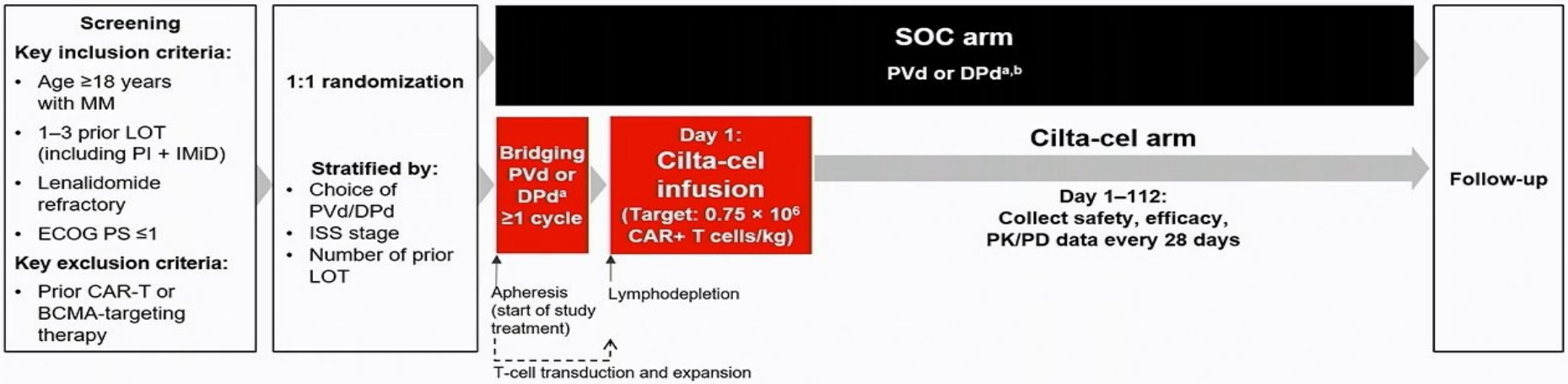
CAR-T as second line option



NCCN Guidelines ; Version 2.2025

CARTITUDE-4:
Study Design and Endpoints[1]



Primary endpoint
- PFS[c,d]

Secondary endpoints
- Efficacy: ≥CR, ORR, MRD negativity, OS[d]
- PROs
- Incidence and severity of AEs[e]

[a]Physicians' choice. [b]Administered until disease progression. [c]Time from randomization to disease progression/death. [d]Prespecified first and second interim analyses performed after approximately 75% or 100% of planned 250 PFS events were accumulated, respectively. [e]Assessed per CTCAE version 5.0. CRS and ICANS were graded per ASTCT criteria. AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DPd, daratumumab, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ICANS, immune effector cell–associated neurotoxicity syndrome; IMiD, immunomodulatory drug; ISS, International Staging System; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PRO, patient-reported outcome; PVd, pomalidomide, bortezomib, and dexamethasone; SOC, standard of care. 1. San-Miguel J, et al. *N Engl J Med* 2023;389:335-47.

Presented by M-V Mateos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

CAR-T as second line option

Clinical history		
ECOG performance-status score — no. (%)‡		
0	114 (54.8)	121 (57.3)
1	93 (44.7)	89 (42.2)
2	1 (0.5)	1 (0.5)
International Staging System stage — no. (%)		
I	136 (65.4)	132 (62.6)
II	60 (28.8)	65 (30.8)
III	12 (5.8)	14 (6.6)
Median time since diagnosis (range) — yr	3.0 (0.3–18.1)	3.4 (0.4–22.1)
Presence of soft-tissue plasmacytomas — no. (%)§	44 (21.2)	35 (16.6)
Bone marrow plasma cells ≥60% — no./total no. (%)¶	42/206 (20.4)	43/208 (20.7)
Cytogenetic risk — no./total no. (%)		
Standard	69/207 (33.3)	70/210 (33.3)
High	123/207 (59.4)	132/210 (62.9)
Gain/amp(1q)	89/207 (43.0)	107/210 (51.0)
del(17p)	49/207 (23.7)	43/210 (20.5)
t(4;14)	30/207 (14.5)	30/210 (14.3)
t(14;16)	3/207 (1.4)	7/210 (3.3)
With ≥2 high-risk abnormalities	43/207 (20.8)	49/210 (23.3)
With del(17p), t(4;14), or t(14;16)	73/207 (35.3)	69/210 (32.9)
Missing data	15/207 (7.2)	8/210 (3.8)
Tumor BCMA expression ≥50% — no. (%)	141 (67.8)	138 (65.4)

Table 1. (Continued.)

Characteristic	Cilta-cel (N=208)	Standard Care (N=211)
Previous lines of therapy — no. (%)		
1	68 (32.7)	68 (32.2)
2	83 (39.9)	87 (41.2)
3	57 (27.4)	56 (26.5)
Previous immunomodulatory drug — no. (%)	208 (100.0)	211 (100.0)
Lenalidomide	208 (100.0)	211 (100.0)
Pomalidomide	8 (3.8)	10 (4.7)
Previous anti-CD38 antibody	53 (25.5)	55 (26.1)
Daratumumab	51 (24.5)	54 (25.6)
Isatuximab	2 (1.0)	2 (0.9)
Previous proteasome inhibitor — no. (%)	208 (100.0)	211 (100.0)
Bortezomib	203 (97.6)	205 (97.2)
Carfilzomib	77 (37.0)	66 (31.3)
Ixazomib	21 (10.1)	21 (10.0)
Triple-class exposure — no. (%)‖	53 (25.5)	55 (26.1)
Penta-drug exposure — no. (%)**	14 (6.7)	10 (4.7)
Refractory status — no. (%)		
Lenalidomide	208 (100.0)	211 (100.0)
Bortezomib	55 (26.4)	48 (22.7)
Carfilzomib	51 (24.5)	45 (21.3)
Any anti-CD38 antibody	50 (24.0)	46 (21.8)
Daratumumab	48 (23.1)	45 (21.3)
Ixazomib	15 (7.2)	17 (8.1)
Pomalidomide	8 (3.8)	9 (4.3)
Triple-class‖	30 (14.4)	33 (15.6)
Penta-drug**	2 (1.0)	1 (0.5)

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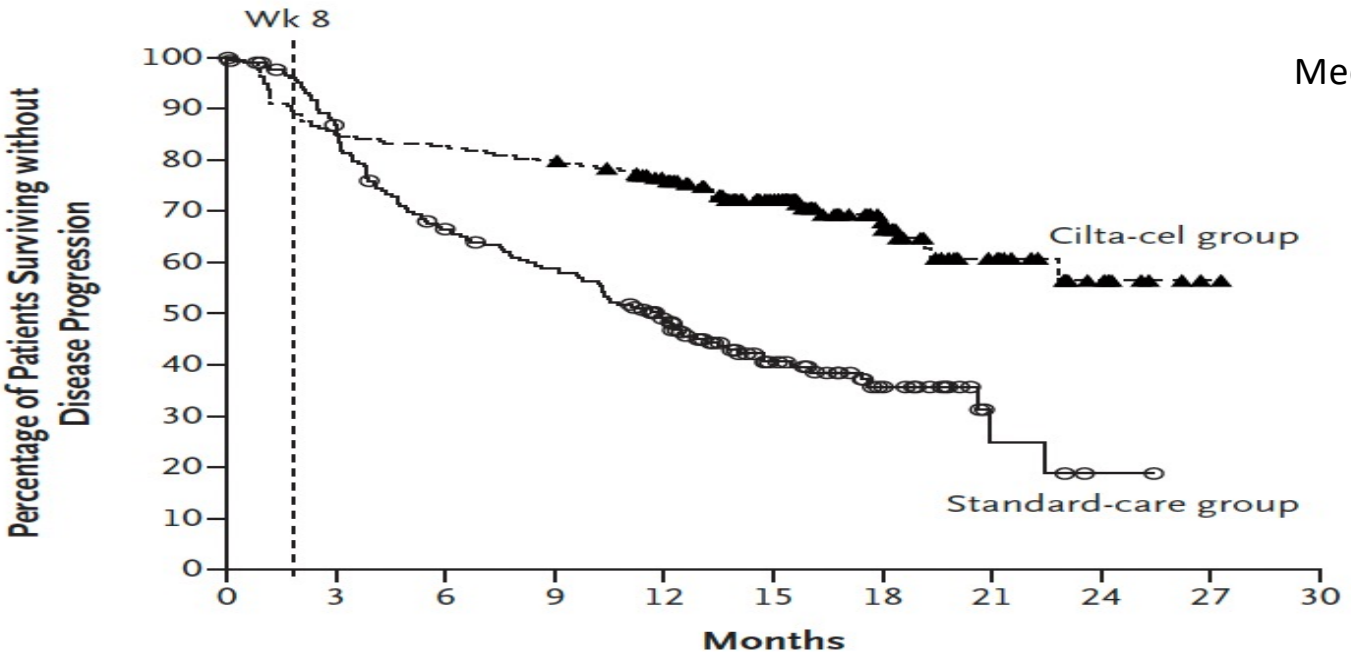

No. at Risk											
Cilta-cel group	208	177	172	166	146	94	45	22	9	1	0
Standard-care group	211	176	133	116	88	46	20	4	1	0	0

Median FU: 15.9 months

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CAR-T as second line option

Variable	Cilta-cel (N=208)	Standard Care (N=211)	Odds Ratio (95% CI)*
Overall response — no. (%)†	176 (84.6)	142 (67.3)	3.0 (1.8–5.0)
Type of response — no. (%)			
Stringent complete response	121 (58.2)	32 (15.2)	
Complete response	31 (14.9)	14 (6.6)	
Very good partial response	17 (8.2)	50 (23.7)	
Partial response	7 (3.4)	46 (21.8)	
Minimal response	1 (0.5)	11 (5.2)	
Stable disease	13 (6.2)	47 (22.3)	
Progressive disease	17 (8.2)	6 (2.8)	
Not evaluable	1 (0.5)	5 (2.4)	
Complete response or better	152 (73.1)	46 (21.8)	10.3 (6.5–16.4)
Very good partial response or better	169 (81.2)	96 (45.5)	5.9 (3.7–9.4)
12-month duration of response — % (95% CI)	84.7 (78.1–89.4)	63.0 (54.2–70.6)	
Median time to first response (range) — mo	2.1 (0.9–11.1)	1.2 (0.6–10.7)	
Median time to best response (range) — mo	6.4 (1.1–18.6)	3.1 (0.8–20.6)	
No minimal residual disease — no. (%)‡	126 (60.6)	33 (15.6)	8.7 (5.4–13.9)
12-month progression-free survival — % (95% CI)	75.9 (69.4–81.1)	48.6 (41.5–55.3)	

San Miguel et al., NEJM 2023

655.MULTIPLE MYELOMA: CELLULAR THERAPIES

Ciltacabtagene Autoleucel (Cilta-cel) Vs Standard of Care (SoC) in Patients with Lenalidomide (Len)-Refractory Multiple Myeloma (MM) after 1-3 Lines of Therapy: Minimal Residual Disease (MRD) Negativity in the Phase 3 Cartitude-4 Trial

Rakesh Popat[1], Albert Oriol[2], Michele Cavo, MD[3], Lionel Karlin[4], Irit Avivi Mazza[5], Wilfried Roeloffzen[6], Seok Jin Kim, MDPhD[7], Brea Lipe[8], Noffar Bar, MD[9], Noemi Horvath[10], Andrew Spencer, MBBS[11], Chang-Ki Min[12], Diana Chen[13], Quanlin Li[14], Katherine Li[15], Ana Slaughter[16], Carolina Lonardi[17], Nina Benachour[18], Arnab Ghosh[19], Martin Vogel[20], Nikoletta Lendvai[19], Tamar Lengil[21], Nitin Patel[22], Octavio Costa Filho[22], Erika Florendo[22], Yi Lin, MD PhD[23]

- At median FU of 33.6 months: MRD rates at 10^{-5} : 89% vs 38%
- MRD at d56: 48%; at 6 months: 60%
- MRD neg CR: 44%vs 8%; at 33.6 months: 57% vs 12%
- Median PFS in MRD neg: NR

ASH 2024

Comparative Efficacy of Ciltacabtagene Autoleucel Versus Isatuximab, Carfilzomib and Dexamethasone in the Treatment of Patients with Lenalidomide-Refractory Multiple Myeloma with 1-3 Prior Lines of Therapy Using a Matching-Adjusted Indirect Comparison

Roberto Mina[1,2,3], Paolo Corradini, MD[4], Michele Cavo, MD[5], Jesús F. San-Miguel, MD PhD[6], Leyla O. Shune, MD[7], Abdullah Mohammad Khan, MD MBBS[8], Surbhi Sidana, MD[9], Xavier Leleu[10], Salomon Manier[11], Brea Lipe[12], Katja C. Weisel, MD[13], Suzy van Sanden[14], Joris Diels[14], João Mendes[15], Seina Lee[15], Sandra Van Hoorenbeeck[16], Adrián Pons[17], Ana Slaughter[18], Nina Benachour[19], Carolina Lonardi[20], Arnab Ghosh[21], Nitin Patel[22], Erika Florendo[22], Joaquín Martínez-Lopez[23]

Methods:
The unanchored MAIC was carried out by initially applying the primary exclusion criteria from the IKEMA study to the patient-level data (IPD) of cilta-cel. Subsequently, the IPD for cilta-cel cohort were reweighted to align the average baseline characteristics with those reported for IsaKd. To generate the necessary patient-level data for IsaKd for the MAIC analysis of PFS, we employed a two-step process. First, an exponential model was fitted between each of the provided data points to approximate the complete KM curve. Next, the Guyot algorithm was utilized, leveraging the KM curve and reported event data, to simulate the patient-level data for PFS. A weighted Cox proportional hazards model was then applied to all the IPD from both treatments to obtain hazard ratios (HRs) with 95% confidence intervals (CIs). For binary endpoints, relative effects were quantified using relative response ratios (RRs) with 95% CIs derived from a weighted logistic regression analysis.

Results:
After applying the exclusion criteria from IKEMA to the IPD from CARTITUDE-4 (excluding patients refractory to an anti-CD38 monoclonal antibody), 158 cilta-cel patients were retained. When further adjusting for differences in cytogenetic risk and ISS stage, patients in the cilta-cel group (effective sample size [ESS]=79) had a 49% reduction in risk of disease progression or death (PFS) versus IsaKd (adjusted median not reached vs 19.4 months; HR: 0.51 [0.29,0.90], p=0.0213). Cilta-cel also demonstrated superior efficacy in response rates vs IsaKd (ORR RR: 1.07 [0.93,1.23], p=0.3497; ≥VGPR RR: 1.26 [1.02,1.55], p=0.0191; ≥CR RR: 2.09 [1.48,2.95], p<0.0001).
A sensitivity analysis additionally excluding patients with prior carfilzomib exposure confirmed previous reported results with a PFS HR of 0.45 [0.22,0.94], p=0.0338, in favor of cilta-cel vs IsaKd. Additional sensitivity analyses, matching patients based on prior lines and age, yielded consistent findings, showing the robustness of the results.

Conclusions:
This analysis demonstrated favorable efficacy outcomes of cilta-cel compared to IsaKd, despite the limited data available on lenalidomide-refractory patients in the IKEMA trial. Notably, cilta-cel demonstrated significant clinical improvement in terms of progression-free survival and depth of response, underscoring its potential as an effective therapeutic option for patients with PI exposed and len-refractory MM as early as first relapse. The findings of this analysis will be particularly relevant for countries where len-refractory patients may be treated with IsaKd.

Take Home Messages

- Lena refractoriness is the most relevant challenge for II line strategies
- II line should be defined as part of a planned path according to disease and pt characteristics
- Although CAR-T has unveiled unprecedented results, innovative combos can be a valid alternative option in this poor prognosis subgroup