Fourth Annual
National General Medical Oncology Summit

Sunday, March 2, 2025

Moderator

Neil Love, MD

Faculty

Thomas A Abrams, MD
Prithviraj Bose, MD
Natalie S Callander, MD
Ramaswamy Govindan, MD
Shilpa Gupta, MD
Yelena Y Janjigian, MD
Ahmed Omar Kaseb, MD, CMQ
Samuel J Klempner, MD
Andrew T Kuykendall, MD
Christopher Lieu, MD
Stephen V Liu, MD
Thomas Martin, MD
Paul E Oberstein, MD, MS
Philip A Philip, MD, PhD
Kanwal Raghav, MD
Jonathan E Rosenberg, MD

Module 12: Multiple Myeloma

Current and Emerging Therapeutic Approaches for MM — Dr Callander

CAR T-Cell Therapy, Bispecific Antibodies and Antibody-Drug Conjugates — Dr Martin

Module 12: Multiple Myeloma

Current and Emerging Therapeutic Approaches for MM — Dr Callander

CAR T-Cell Therapy, Bispecific Antibodies and Antibody-Drug Conjugates — Dr Martin

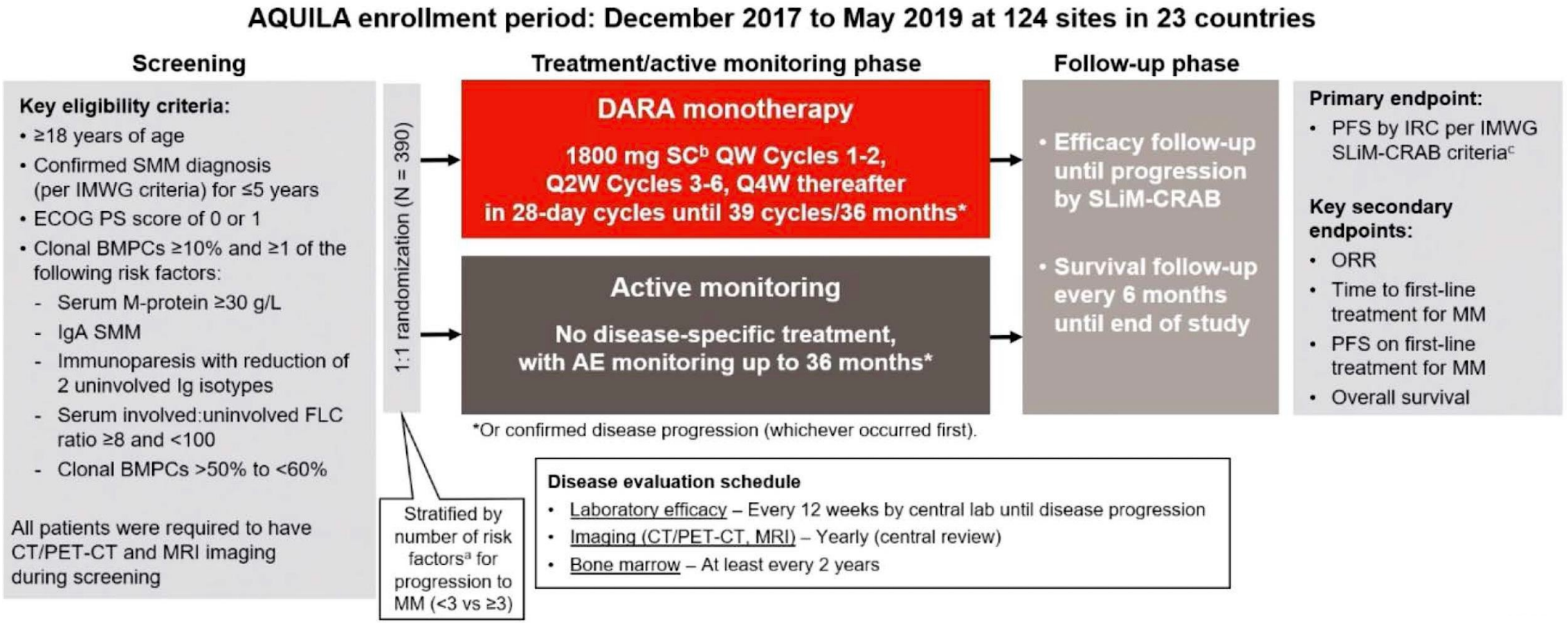
Current and Emerging Therapeutic Approaches for Multiple Myeloma

Natalie S Callander, MD
Director, Myeloma Clinical Program
University of Wisconsin Carbone Cancer Center
Madison, Wisconsin

Disclosures

No relevant conflicts of interest to disclose.

AQUILA: Study Design



IMWG, International Myeloma Working Group; ECOG PS, Eastern Cooperative Oncology Group performance status; BMPC, bone marrow plasma cell; FLC, free light chain; CT, computed tomography; MRI, magnetic resonance imaging; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; AE, adverse event; IRC, independent review committee; ORR, overall response rate. [a]Risk factors included involved:uninvolved FLC ratio ≥8 (yes vs no), serum M-protein ≥30 g/L (yes vs no), IgA SMM (yes vs no), immunoparesis (reduction of 2 uninvolved immunoglobulins vs other), or clonal BMPCs (>50% to <60% vs ≤50%). [b]DARA SC (1800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc.]). [c]PFS was defined as duration from randomization to initial documented progression to active MM or death due to any cause, whichever occurred first.

Dimopoulos. ASH 2024. Abstr 773. Dimopoulos. NEJM. 2024;[Epub].

AQUILA: Baseline Disease Characteristics and Patient Disposition

Characteristic	DARA (n = 194)	Active monitoring (n = 196)
Age		
Median (range), years	63.0 (31-86)	64.5 (36-83)
18 to <65 years, n (%)	106 (54.6)	98 (50.0)
65 to <75 years, n (%)	67 (34.5)	74 (37.8)
≥75 years, n (%)	21 (10.8)	24 (12.2)
Sex, n (%)		
Female	99 (51.0)	103 (52.6)
Male	95 (49.0)	93 (47.4)
ECOG PS score, n (%)		
0	165 (85.1)	160 (81.6)
1	29 (14.9)	36 (18.4)
Median time from diagnosis of SMM to randomization (range), years	0.80 (0-4.7)	0.67 (0-5.0)
Median BMPCs (range), %	20.0 (8.0-59.5)	20.0 (10.0-55.0)

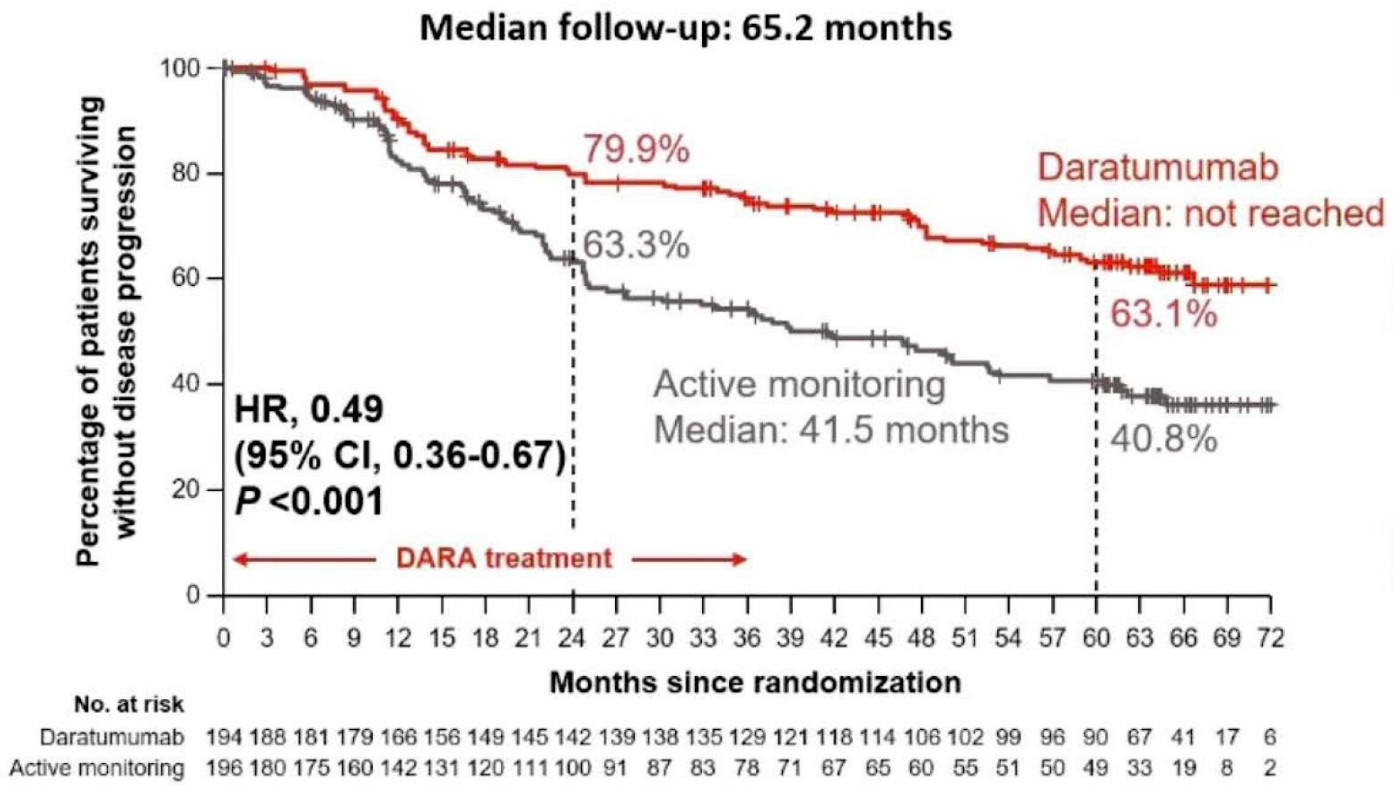
Characteristic	DARA (n = 194)	Active monitoring (n = 196)
Type of SMM, n (%)		
IgG	127 (65.5)	138 (70.4)
IgA	55 (28.4)	42 (21.4)
Other	12 (6.2)	16 (8.2)
AQUILA risk factors for progression to MM, n (%)[a]		
<3	154 (79.4)	156 (79.6)
≥3	40 (20.6)	40 (20.4)
Cytogenetic risk profile[b]	n = 167	n = 170
≥1 of del(17p), t(4;14), and/or t(14;16), n (%)	29 (17.4)	22 (12.9)
Mayo 2018 risk criteria, n (%)[c]		
Low	45 (23.2)	34 (17.3)
Intermediate	77 (39.7)	76 (38.8)
High	72 (37.1)	86 (43.9)

Baseline characteristics were generally balanced between groups

[a]Risk factors: serum M-protein ≥30 g/L, IgA SMM, immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes, serum involved:uninvolved FLC ratio ≥8 and <100, or clonal BMPCs >50% to <60% with measurable disease. [b]Cytogenetic risk was assessed by fluorescence in situ hybridization. [c]Mayo 2018 risk criteria: serum M-protein >2 g/L, involved:uninvolved FLC ratio >20, and clonal BMPCs >20%. Patients with 0 factors = low risk, 1 factor = intermediate risk, ≥2 factors = high risk (Lakshman A, et al. *Blood Cancer J.* 2018;8(6):59).

Dimopoulos. ASH 2024. Abstr 773. Dimopoulos. NEJM. 2024;[Epub].

AQUILA: PFS and PD or Deaths by IRC



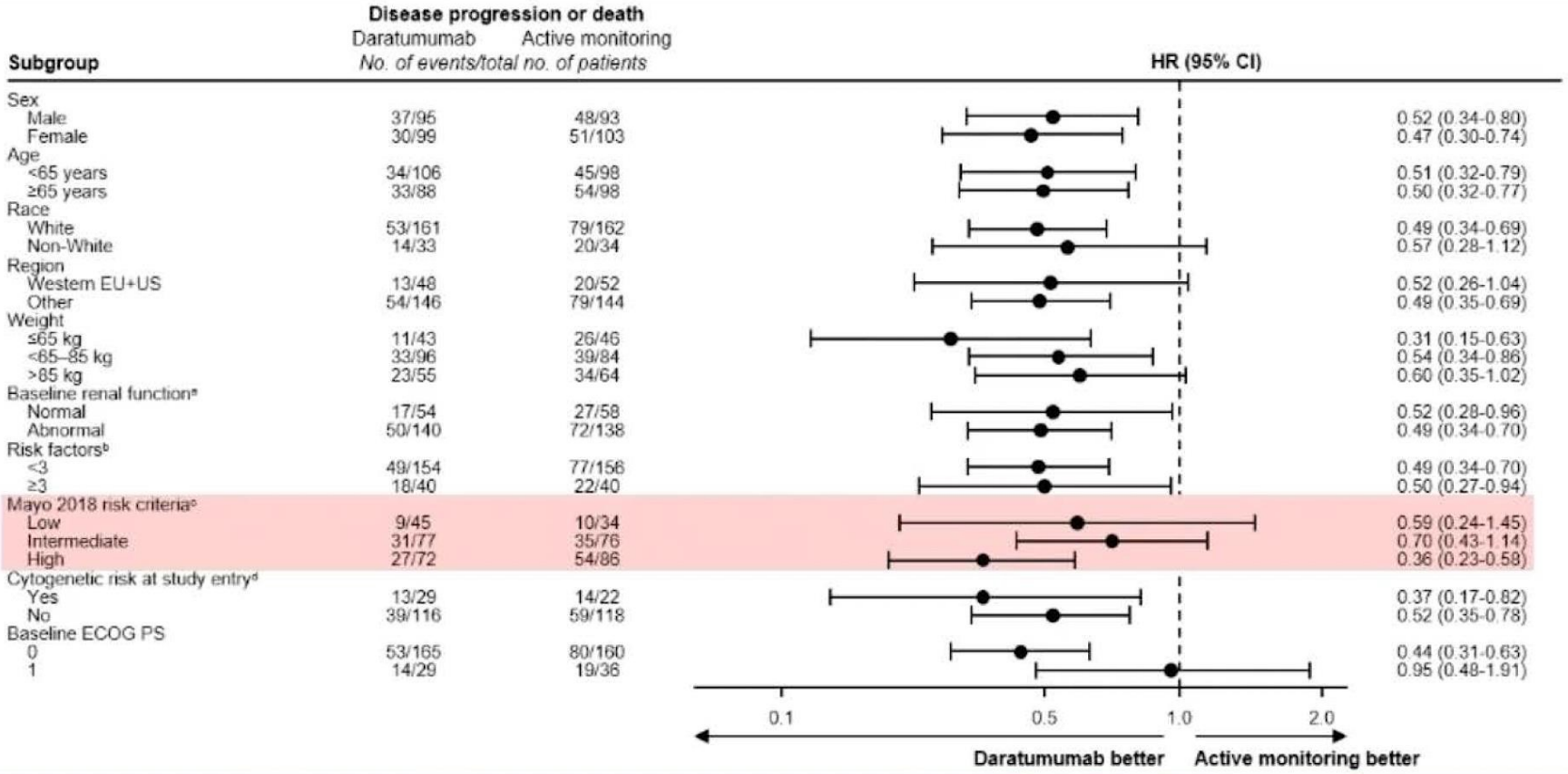
	DARA (n = 194)	Active monitoring (n = 196)
PFS event, n (%)	67 (34.5)	99 (50.5)
Death without disease progression	5 (2.6)	5 (2.6)
Disease progression[a]	62 (32.0)	94 (48.0)
CRAB criteria	12 (6.2)	34 (17.3)
Calcium elevation	0	2 (1.0)
Renal insufficiency[b]	0	0
Anemia	2 (1.0)	14 (7.1)
Bone disease	10 (5.2)	18 (9.2)
SLiM criteria	50 (25.8)	65 (33.2)
Clonal BMPCs	5 (2.6)	16 (8.2)
Serum FLC	33 (17.0)	33 (16.8)
Focal lesion by MRI	12 (6.2)	16 (8.2)

DARA significantly reduced the risk of progression to MM or death by 51% versus active monitoring; the benefit continued beyond 36 months

HR, hazard ratio; CI, confidence interval. [a]A patient may show disease progression based on ≥1 criterion. [b]Some patients met the CRAB criteria for renal insufficiency, but the investigator attributed this to a cause other than disease progression to MM. Adapted with permission © The *New England Journal of Medicine* (2024).

Dimopoulos. ASH 2024. Abstr 773. Dimopoulos. NEJM. 2024;[Epub].

AQUILA: Disease Progression by Subgroups

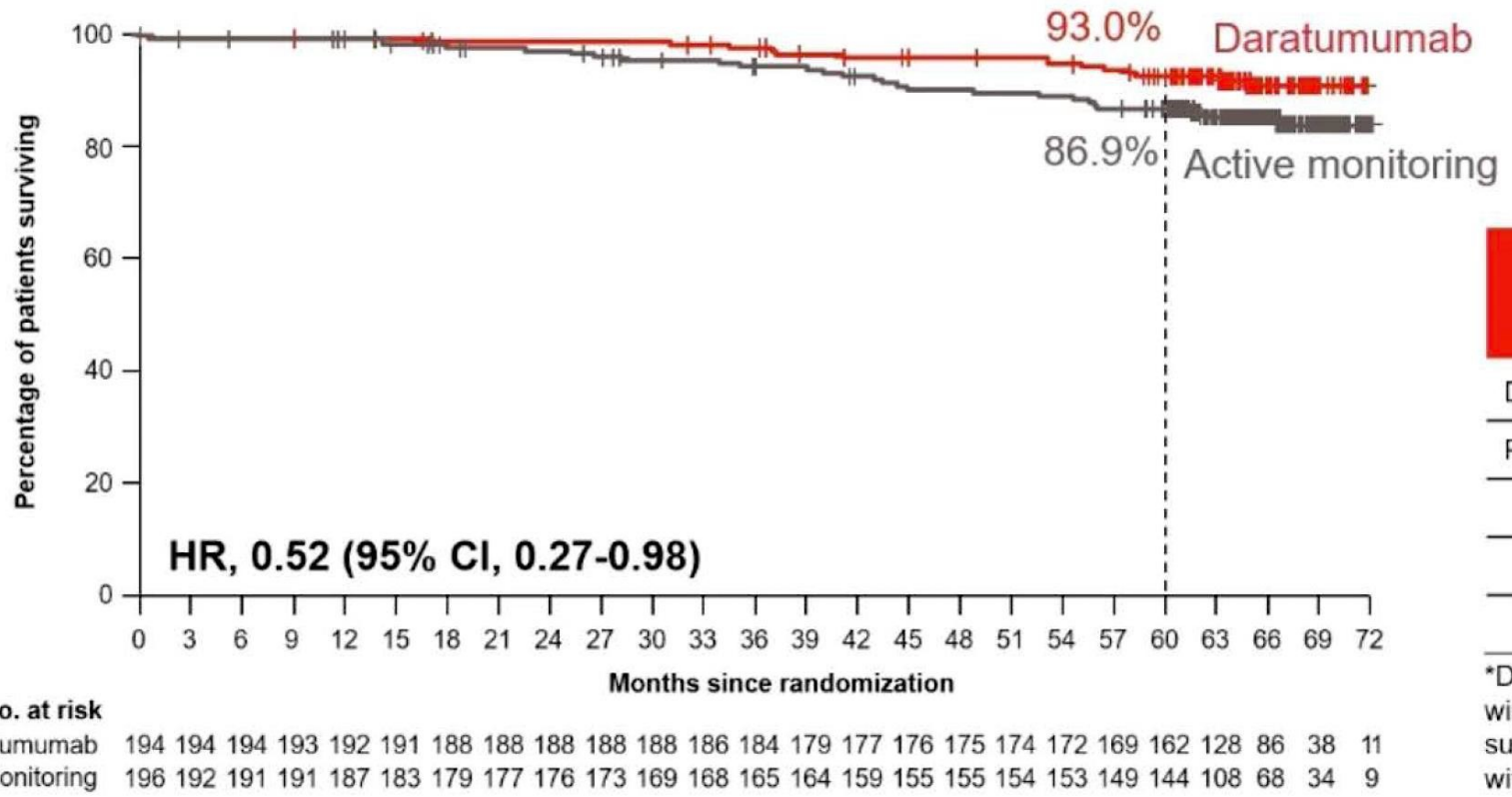


PFS benefit with DARA was seen across all prespecified subgroups, including all Mayo 2018 risk criteria groups

[a]Normal renal function is a glomerular filtration rate ≥90 mL/min/1.73 m^2. [b]Risk factors were serum M-protein ≥30 g/L, IgA SMM, immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes, serum involved:uninvolved FLC ratio ≥8 and <100, or clonal BMPCs >50% to <60% with measurable disease. [c]Mayo 2018 risk was retrospectively assessed; criteria included serum M-protein >2 g/L, involved:uninvolved FLC ratio >20, and clonal BMPCs >20%. Patients with 0 factors = low risk, 1 factor = intermediate risk, ≥2 factors = high risk (Lakshman A, et al. *Blood Cancer J.* 2018;8(6):59). [d]Cytogenetic risk was assessed by fluorescence in situ hybridization; "yes" = presence of del(17p), t(4;14), or t(14;16) and "no" = testing for these probes but no abnormality. Reproduced with permission © The *New England Journal of Medicine* (2024).

Dimopoulos. ASH 2024. Abstr 773. Dimopoulos. NEJM. 2024.

AQUILA: OS



	DARA (n = 194)	Active monitoring (n = 196)
Deaths, n (%)	15 (7.7)	26 (13.3)
Primary cause, n		
Disease progression	3	9
AE	2	4
Other*	10	13

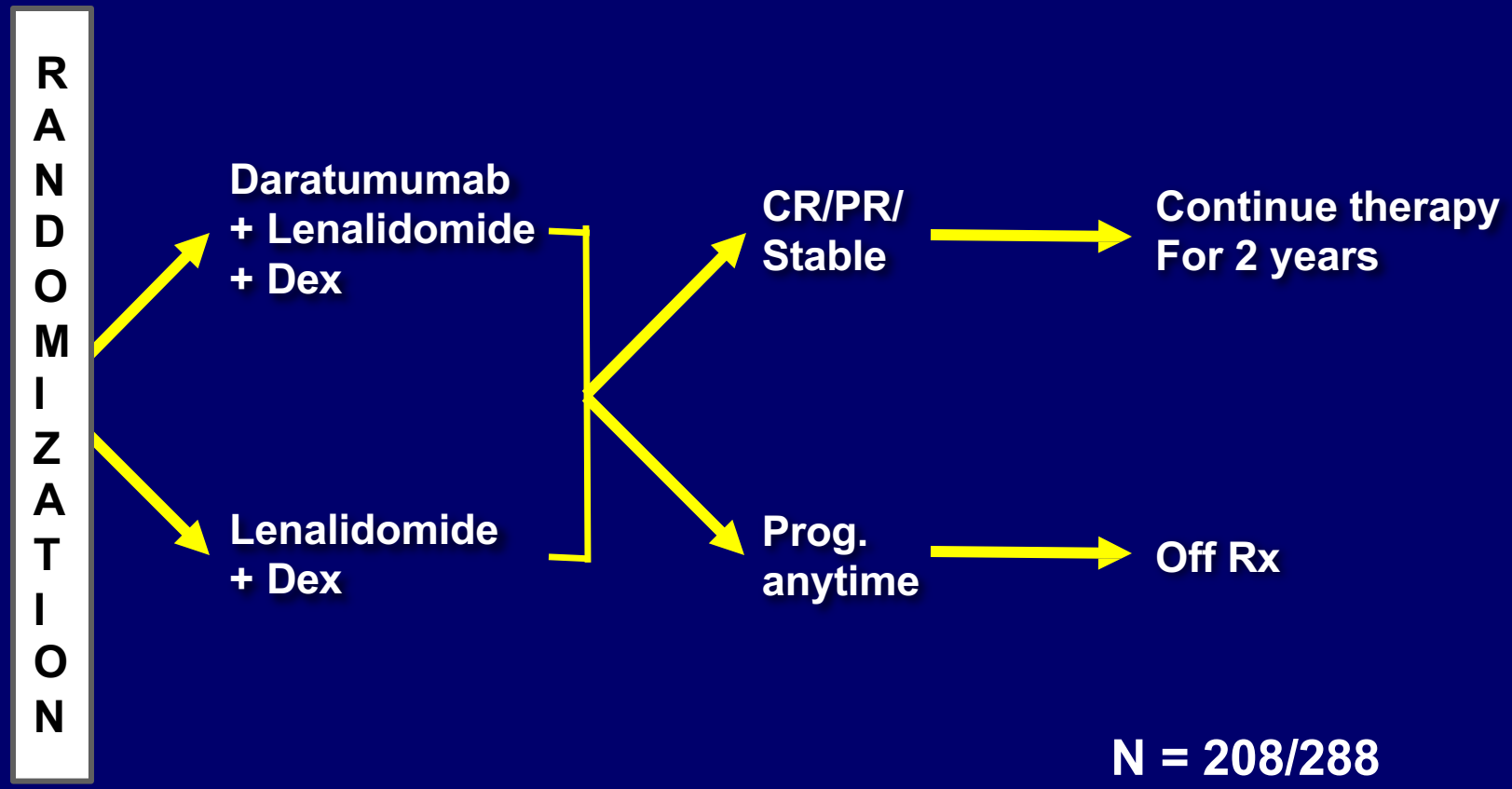
*Deaths due to an event occurring after the AE reporting window (ie, events that happened after patient started subsequent therapy or >30 days after last dose) or deaths with unknown reason.

Early intervention with fixed duration DARA extended overall survival versus active monitoring

Dimopoulos. ASH 2024. Abstr 773. Dimopoulos. NEJM. 2024;[Epub].

Smoldering MM

EAA173: Phase III –Daratumumab to Enhance Therapeutic Effectiveness of Lenalidomide in Smoldering Myeloma (DETER-SMM)(PI: NC)

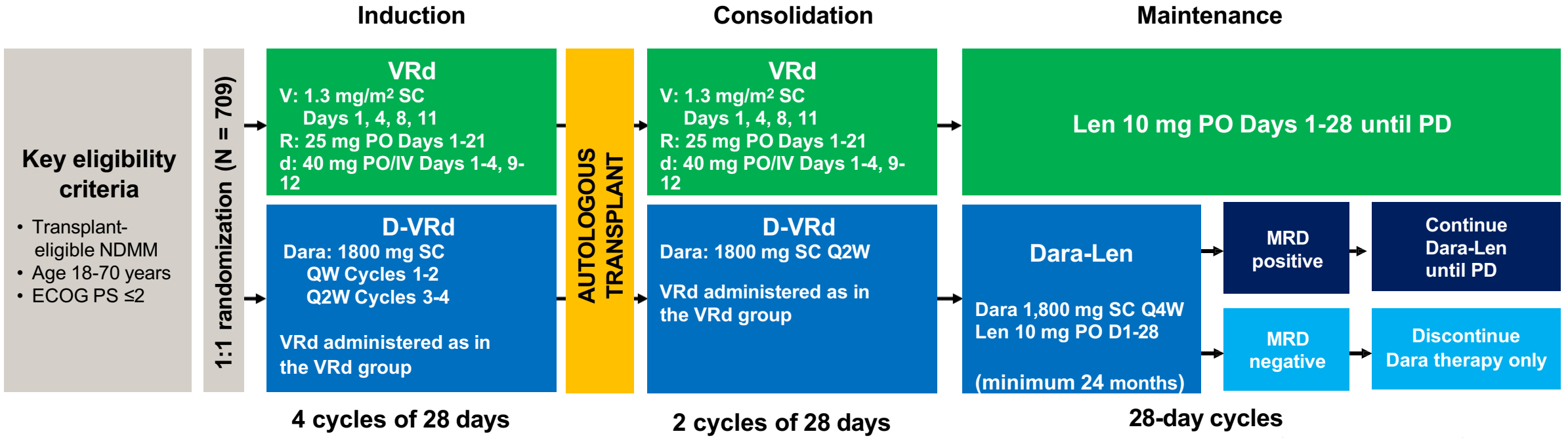


N = 208/288

PI: Natalie Callander

(Activated 4/30/20 19)

Phase III PERSEUS: Study Design: era of quadruplet induction, ASCT, maintenance



Primary endpoint: PFS

Key secondary endpoints: Overall ≥CR rate, overall MRD-negativity rate, OS

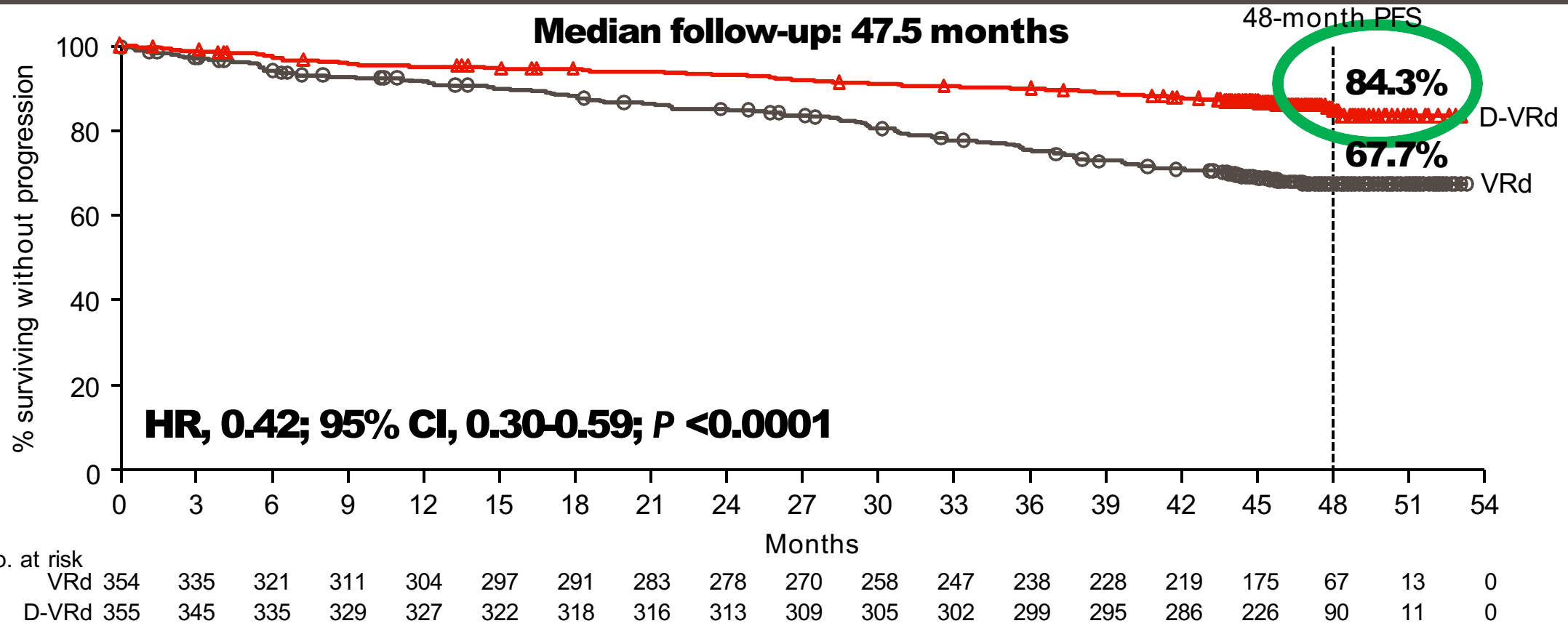
Discontinue Dara therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of (sustained) MRD negativity

Restart Dara therapy upon confirmed loss of CR without PD or recurrence of MRD

MRD was assessed using the clonoSEQ assay in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

P Sonneveld NEJM 2024

PERSEUS: Progression-free Survival

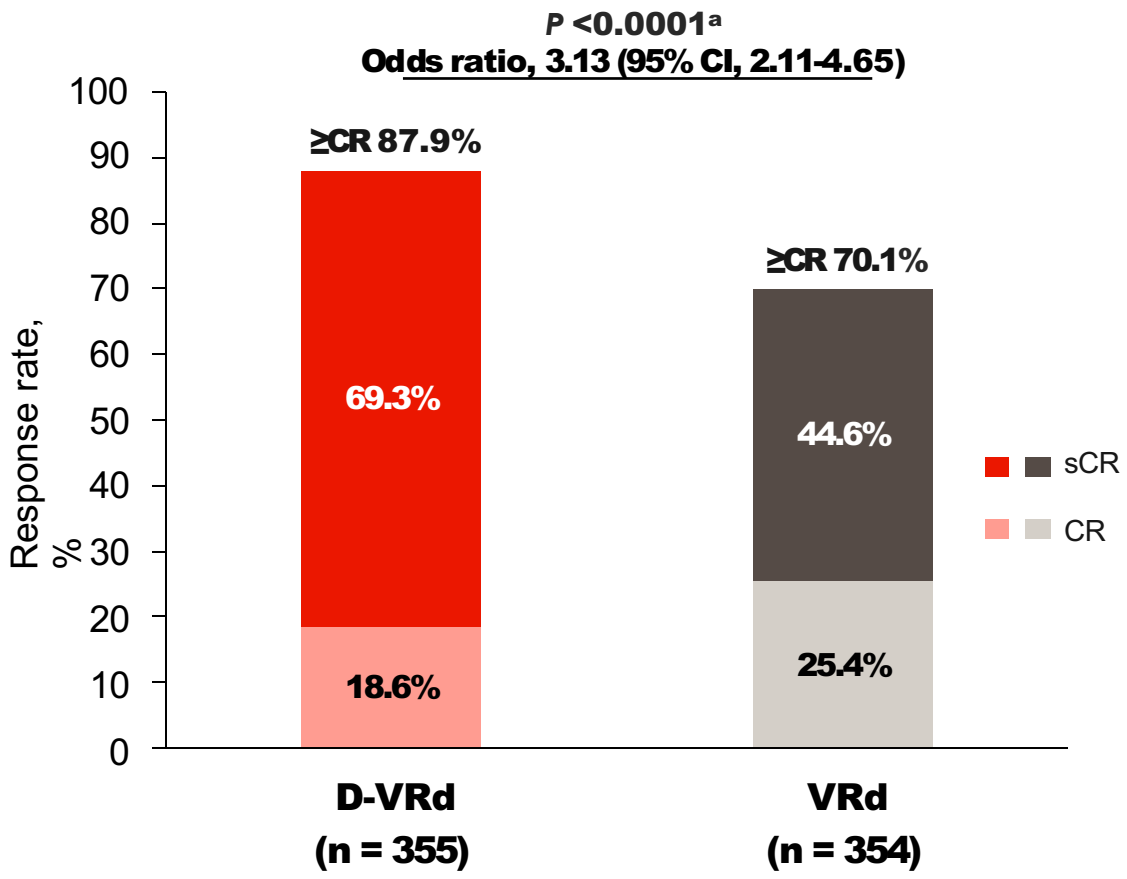


- **58% reduction in the risk of progression or death in patients receiving D-VRd**
- **66% of patients were able to STOP daratumumab after 2 years**

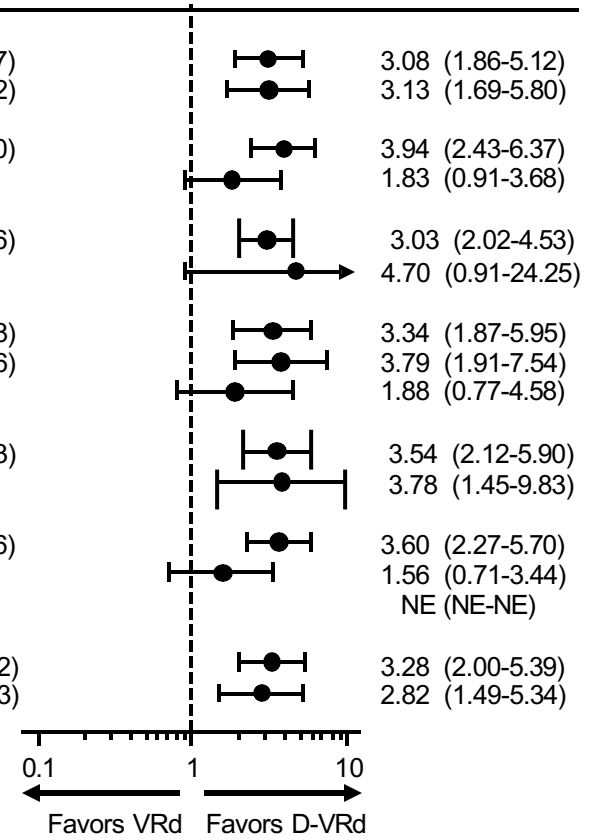
HR, hazard ratio; CI, confidence interval.

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

PERSEUS: Overall ≥CR Rates



Subgroup	VRd no. of patients with ≥CR/total no. (%)	D-VRd no. of patients with ≥CR/total no. (%)	Odds ratio (95% CI)
Sex			
Male	143/205 (69.8)	185/211 (87.7)	3.08 (1.86-5.12)
Female	105/149 (70.5)	127/144 (88.2)	3.13 (1.69-5.80)
Age			
<65 y	186/267 (69.7)	235/261 (90.0)	3.94 (2.43-6.37)
≥65 y	62/87 (71.3)	77/94 (81.9)	1.83 (0.91-3.68)
Race			
White	226/323 (70.0)	289/330 (87.6)	3.03 (2.02-4.53)
Other	22/31 (71.0)	23/25 (92.0)	4.70 (0.91-24.25)
ISS stage			
I	129/178 (72.5)	167/186 (89.8)	3.34 (1.87-5.95)
II	84/125 (67.2)	101/114 (88.6)	3.79 (1.91-7.54)
III	34/50 (68.0)	44/55 (80.0)	1.88 (0.77-4.58)
Type of MM			
IgG	122/185 (65.9)	178/204 (87.3)	3.54 (2.12-5.90)
Non-IgG	73/96 (76.0)	72/78 (92.3)	3.78 (1.45-9.83)
Cytogenetic risk			
Standard risk	182/266 (68.4)	234/264 (88.6)	3.60 (2.27-5.70)
High risk	59/78 (75.6)	63/76 (82.9)	1.56 (0.71-3.44)
Indeterminate	7/10 (70.0)	15/15 (100)	NE (NE-NE)
ECOG PS			
0	160/230 (69.6)	195/221 (88.2)	3.28 (2.00-5.39)
≥1	88/124 (71.0)	117/134 (87.3)	2.82 (1.49-5.34)

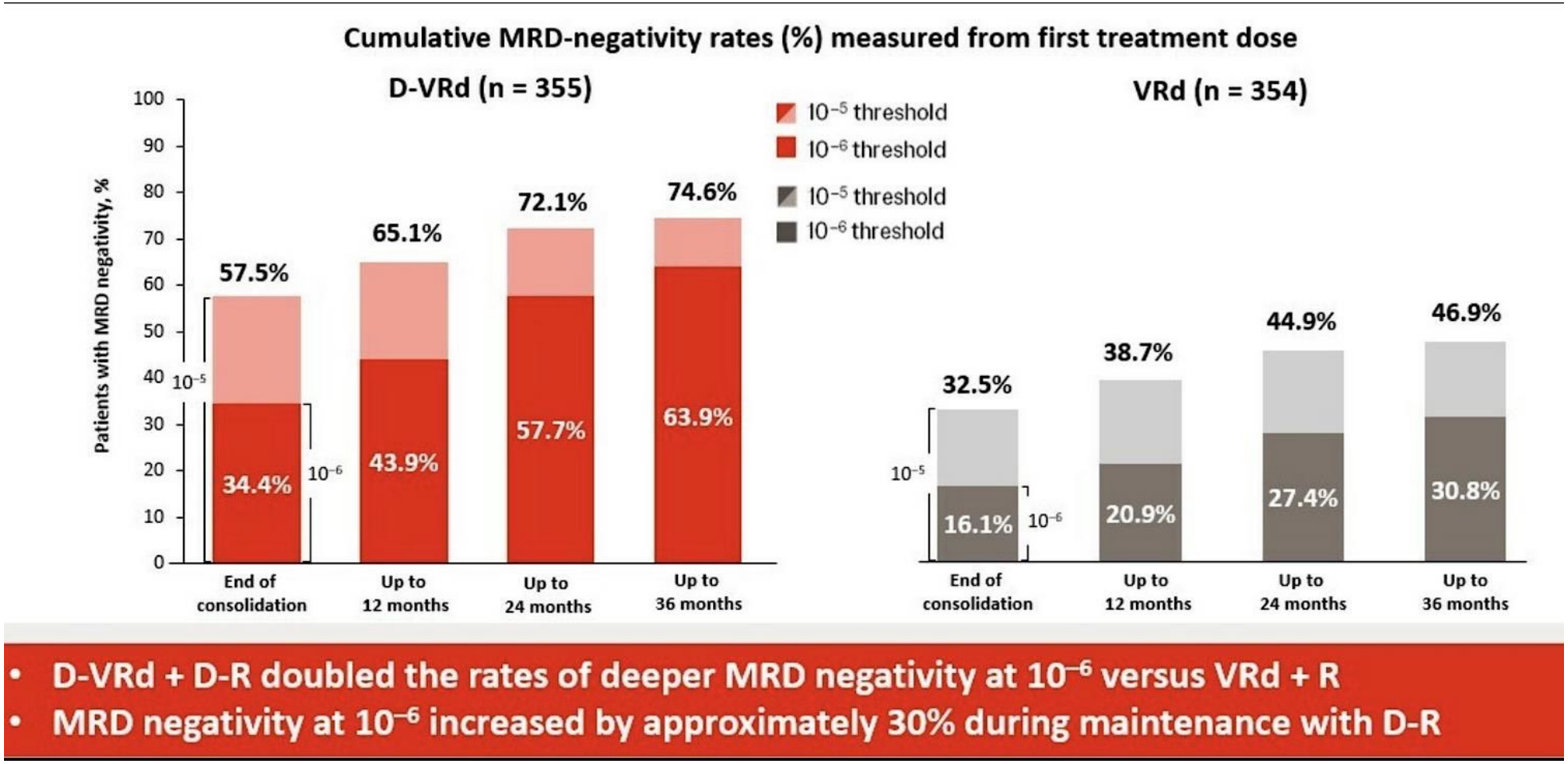


- **Overall ≥CR rate was significantly higher with D-VRd versus VRd**
- **≥CR rate was improved with D-VRd versus VRd across subgroups**

sCR, stringent complete response; NE, not estimable. [a]*P* value (2-sided) was calculated with the use of the stratified Cochran–Mantel–Haenszel chi-squared test.

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

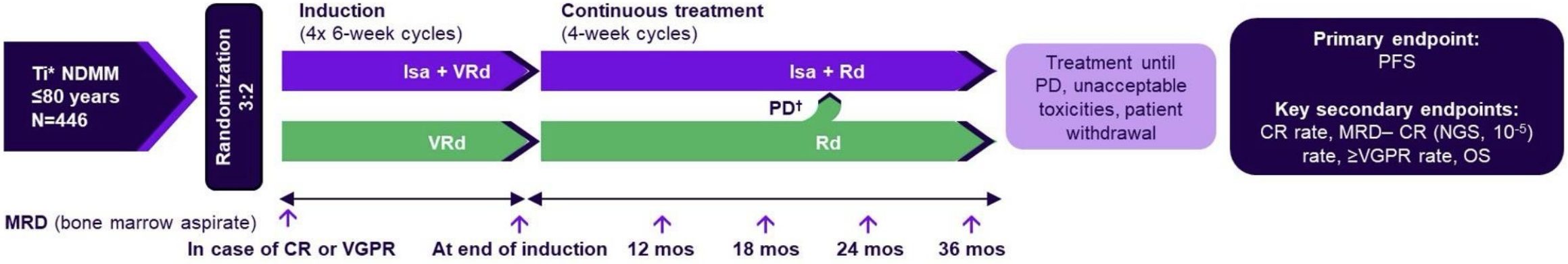
PERSEUS: Improved rates of MRD negativity with the addition of transplant

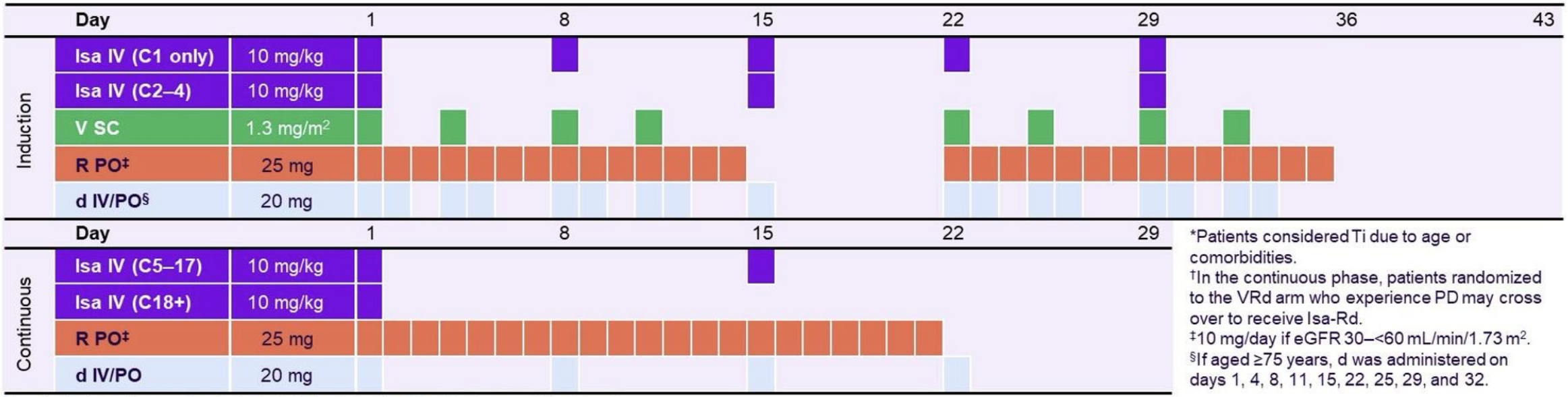


- D-VRd + D-R doubled the rates of deeper MRD negativity at 10^{-6} versus VRd + R
- MRD negativity at 10^{-6} increased by approximately 30% during maintenance with D-R

Rodriguez-Otero ASCO 2024 Abstract 7502

2025: Great options without transplant!
IMROZ: Isatuximab + VRd in Transplant Ineligible NDMM



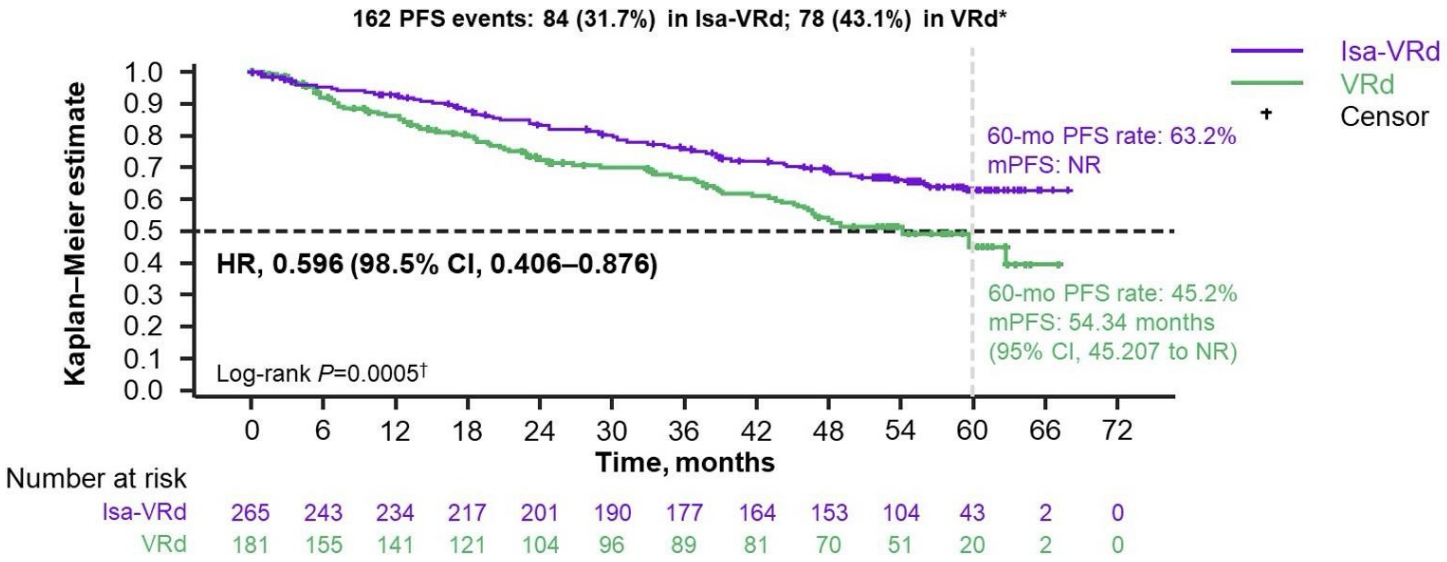


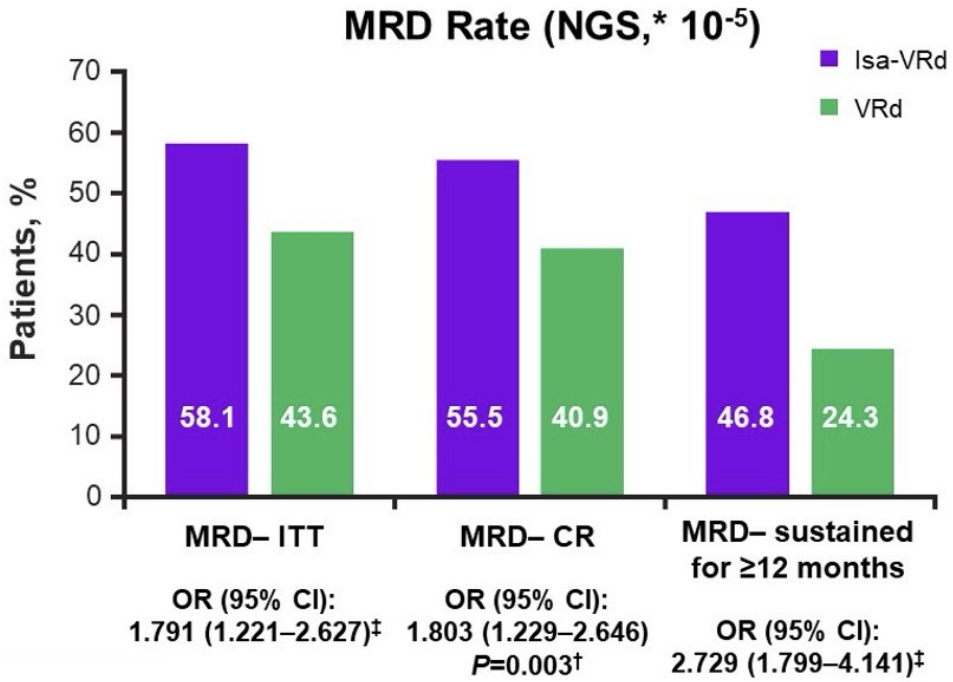
*Patients considered Ti due to age or comorbidities.
†In the continuous phase, patients randomized to the VRd arm who experience PD may cross over to receive Isa-Rd.
‡10 mg/day if eGFR 30–<60 mL/min/1.73 m^2.
§If aged ≥75 years, d was administered on days 1, 4, 8, 11, 15, 22, 25, 29, and 32.

C, cycle; d, dexamethasone; Isa, isatuximab; R, lenalidomide; SC, subcutaneous; V, bortezomib.
Orlowski RZ, et al. ASCO 2018.

Facon. ASCO 2024. Abstr 7500. Facon. NEJM. 2024;[Epub].

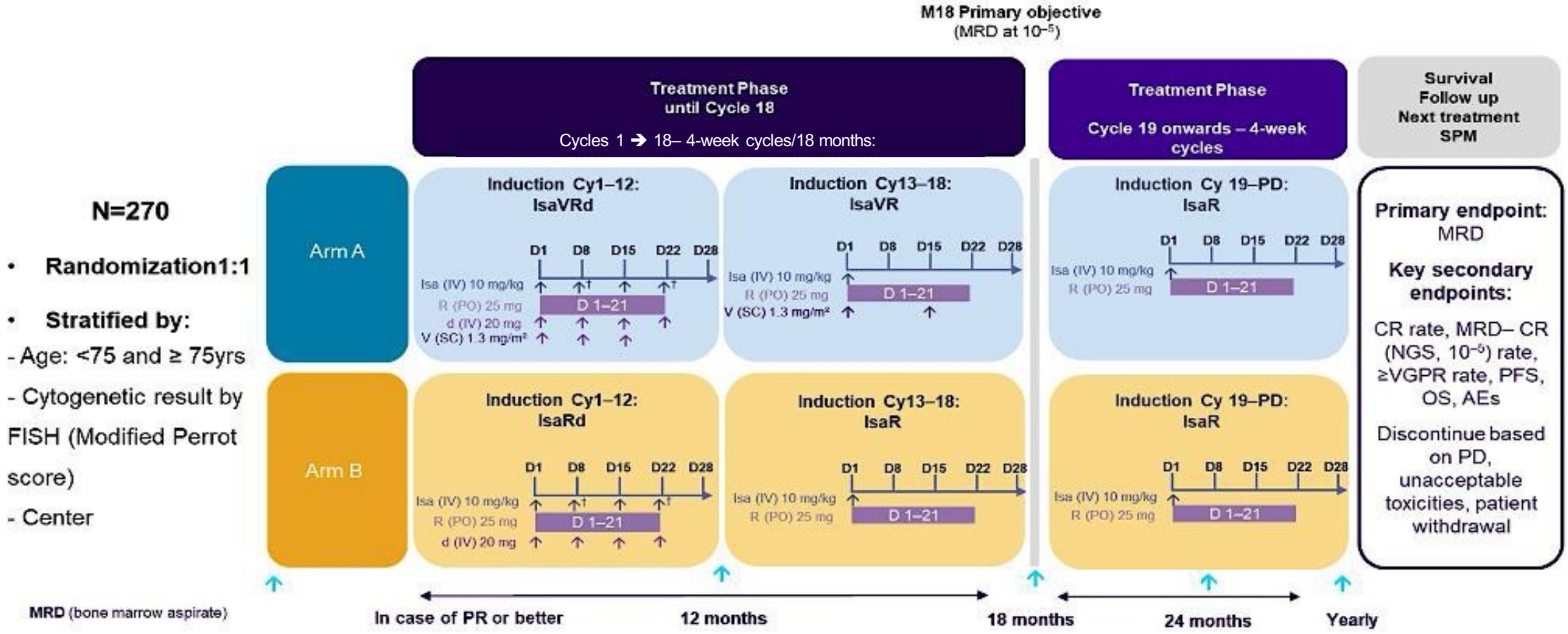
IMROZ: PFS and MRD Negativity Rate that rivals transplant





Facon. ASCO 2024. Abstr 7500. Facon. NEJM. 2024;391:1597.

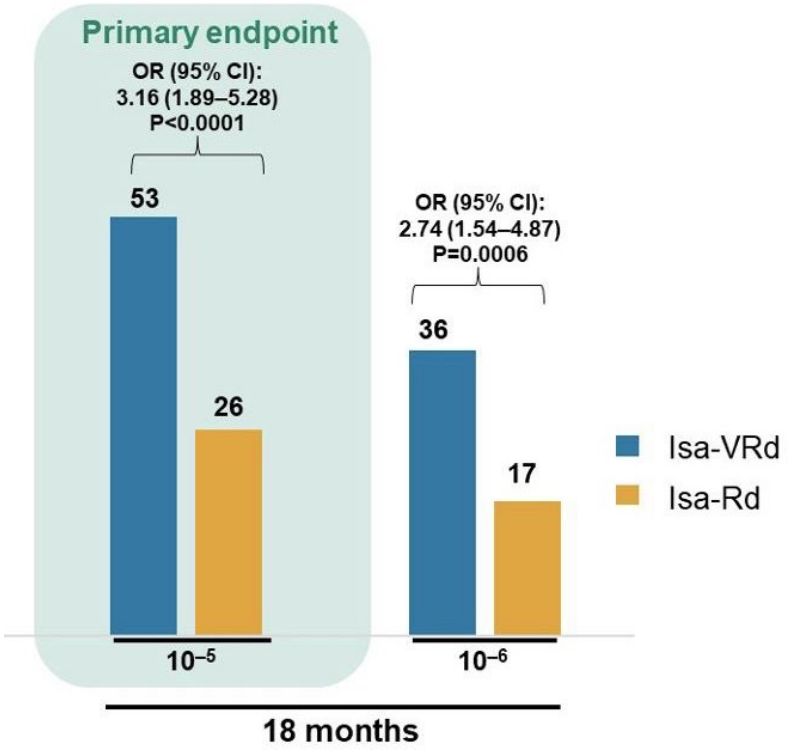
BENEFIT Study Design: Isa-VRd vs Isa-Rd in TI NDMM



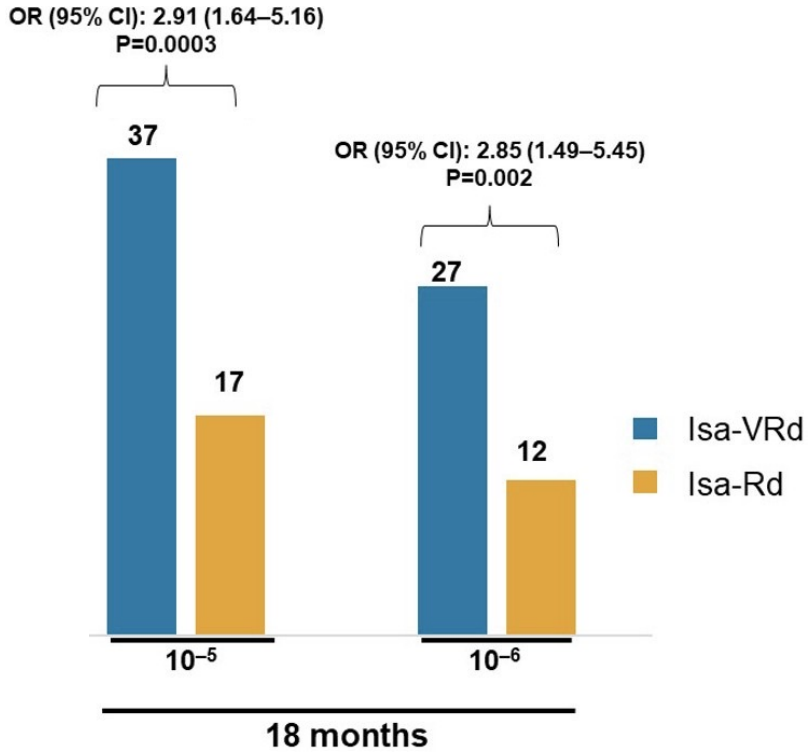
Leleu X et al. ASCO 2024, Abstr 7501.

BENEFIT Trial: Isa-VRd vs. Isa-RD in TI NDMM

Results: **Primary Endpoint MRD(-)**



Secondary Endpoint MRD(-) CR rates



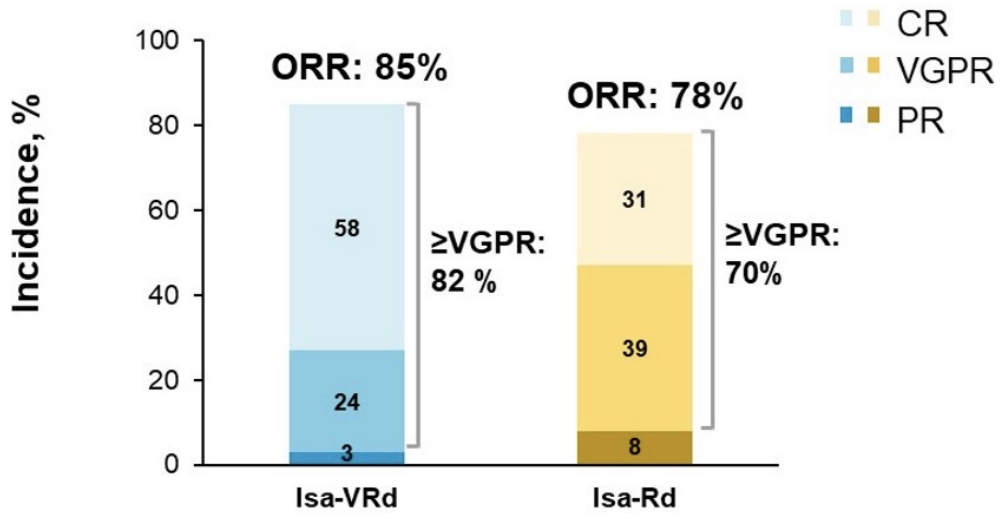
Isa-VRd resulted in significant improvements in MRD- and MRD- CR rates at 18 months and at the 10^{-5} and 10^{-6} levels

*MRD was assessed on the basis of IMWG recommendations.[1]
CI, confidence interval; CR, complete response; Isa, isatuximab; ITT, intent-to-treat; MRD–, minimal residual disease negativity; NGS, next generation sequencing; OR, odds ratio; R, lenalidomide; V, bortezomib.
1. Kumar S, et al. *Lancet Oncol* 2016;17:e328–e346.

Leleu X et al. ASCO 2024, Abstr 7501.

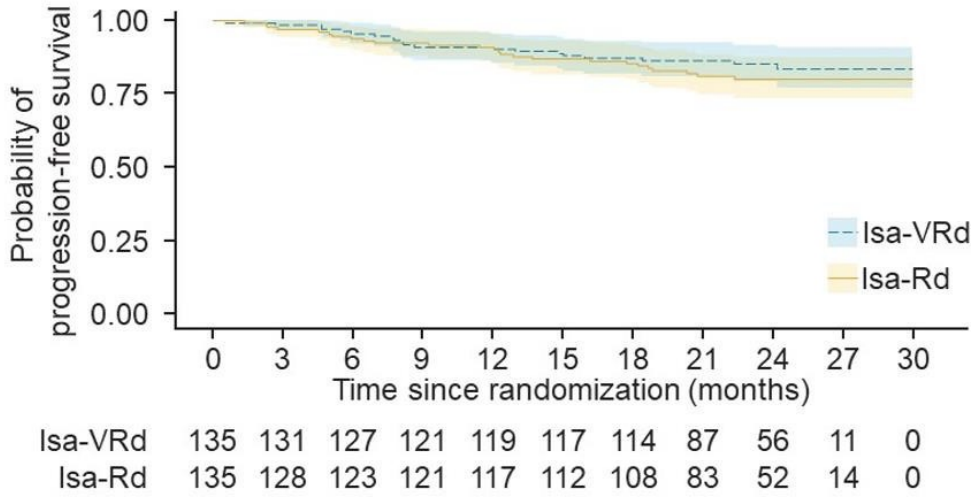
BENEFIT Trial: Isa-VRd vs. Isa-RD in TI NDMM

Results: Depth of Response (at 18 mos)



≥CR rate 58% vs. 31%, OR (95% CI): 2.97 (2–5), p<0.0001

Preliminary PFS (Median F/U 23.5 mos)



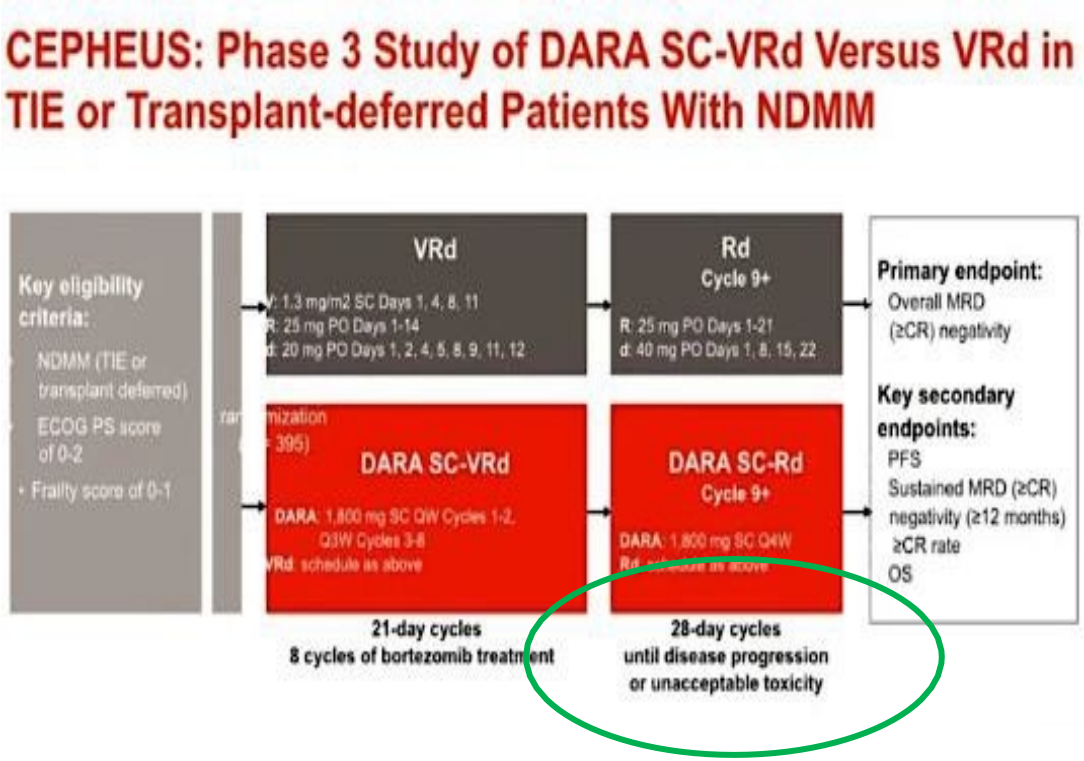
Estimated 24 months PFS
85.2% (95%CI 79.2–91.7) for Isa-VRd
80.0% (95% CI 73.3–87.4) for Isa-Rd

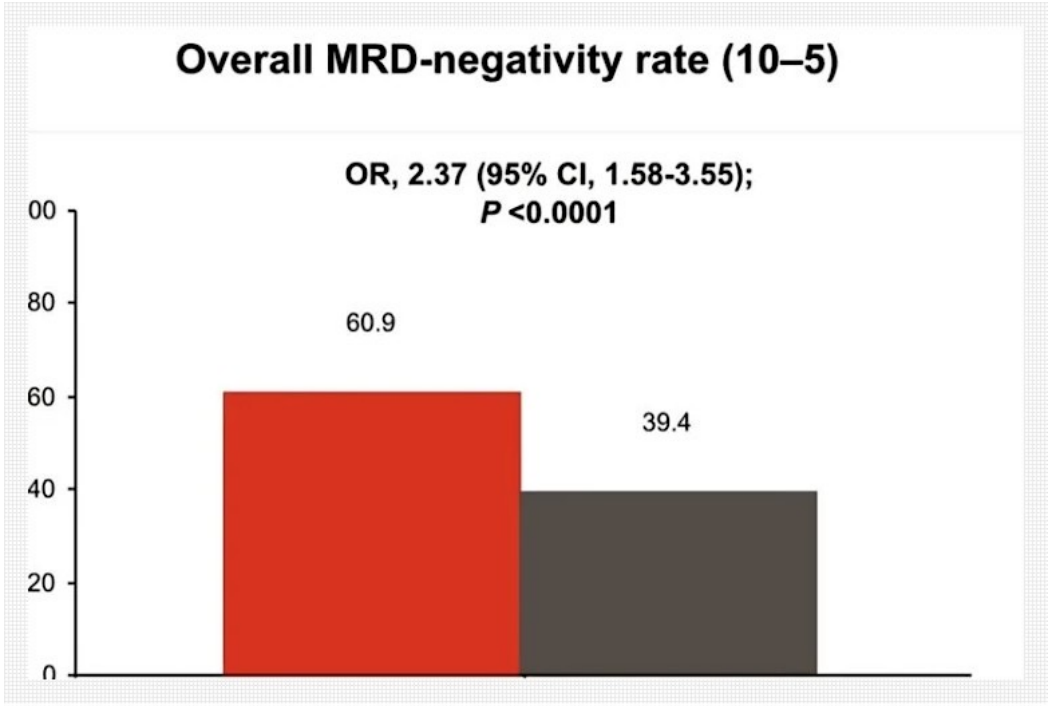
Isa-VRd resulted in deep response rates, particularly CR at 18 months and PFS is still immature

*MRD was assessed on the basis of IMWG recommendations.[1]
CI, confidence interval; CR, complete response; Isa, isatuximab; ITT, intent-to-treat; MRD–, minimal residual disease negativity; NGS, next generation sequencing; OR, odds ratio; R, lenalidomide; V, bortezomib.
1. Kumar S, et al. *Lancet Oncol* 2016;17:e328–e346.

Leleu X et al. ASCO 2024, Abstr 7501.

Impressive results in recent CEPHEUS trial without transplant

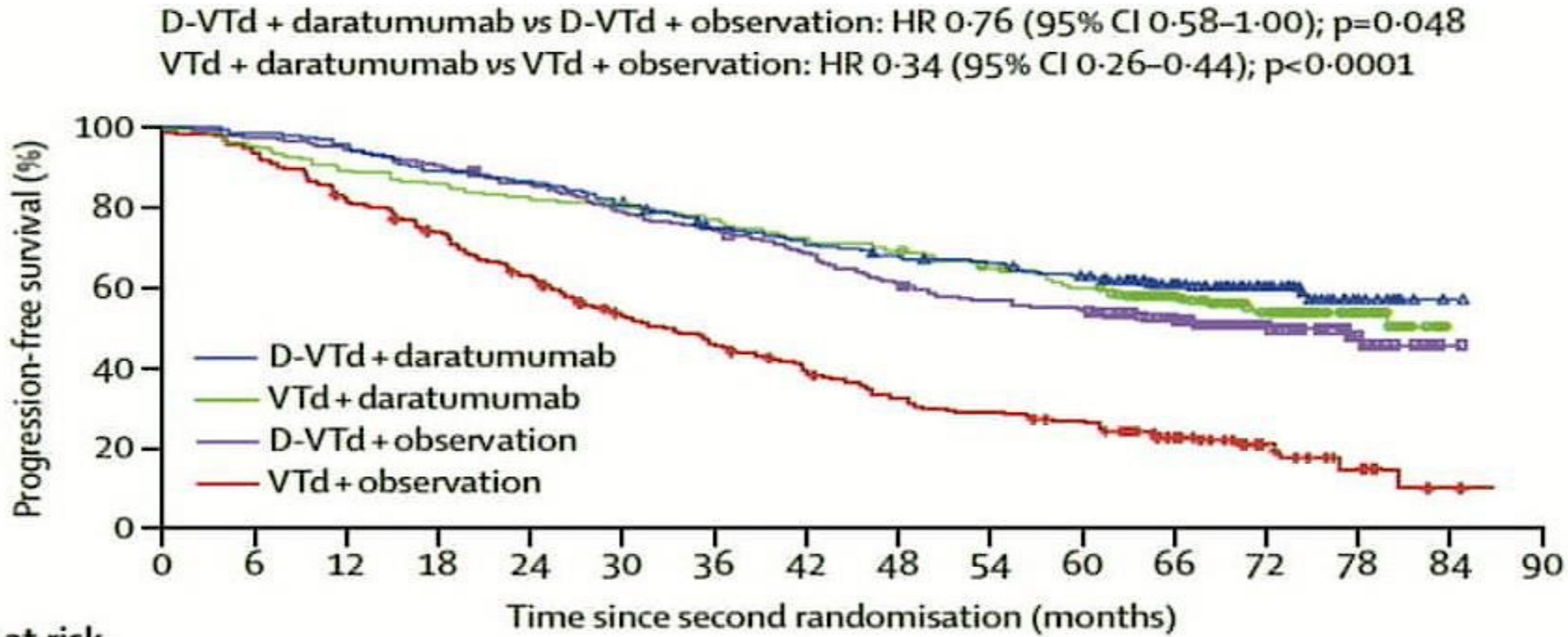




This trial was done in the middle of COVID. There were more COVID related deaths in quad arm. But OS attend favors Dara VRd.

Usmani S IMS 2024, Usmani Nat Med 2025

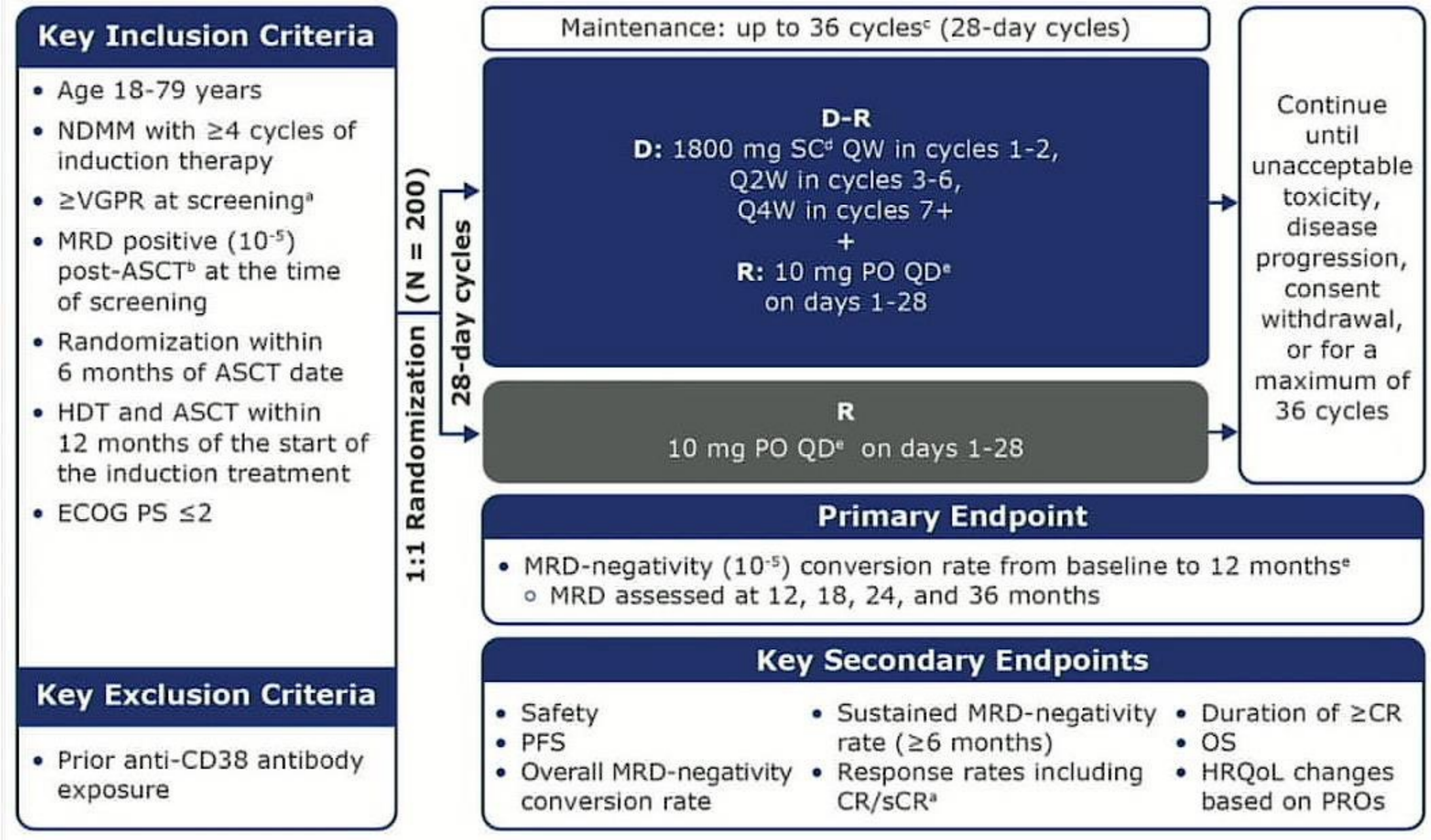
Is anti CD 38 needed in both induction and maintenance?



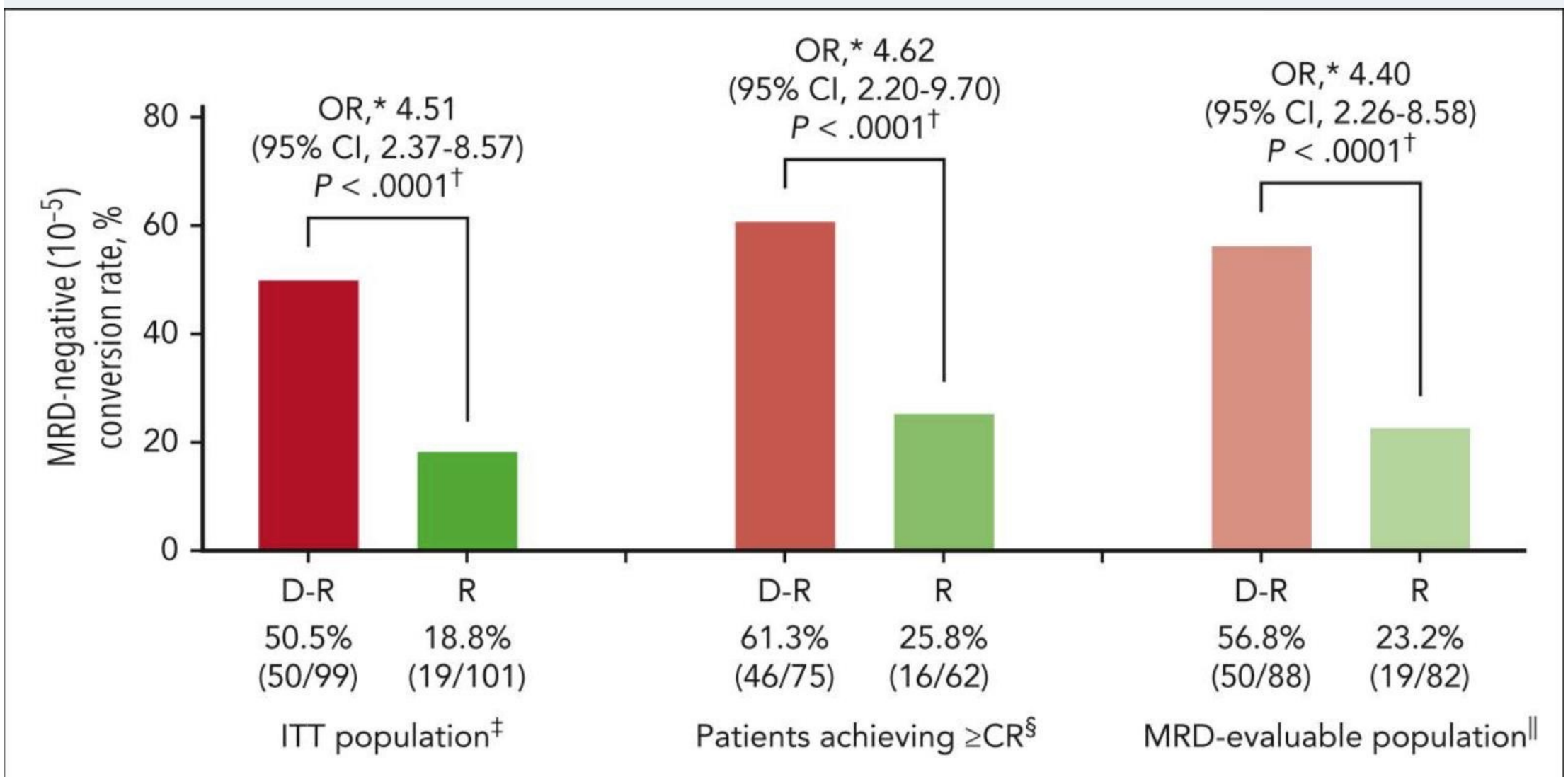
Number at risk (number censored)																
VTd + observation	215	201	176	156	132	107	92	77	63	56	50	32	13	5	1	0
	(0)	(0)	(1)	(3)	(4)	(8)	(8)	(10)	(11)	(11)	(13)	(24)	(41)	(46)	(49)	(50)
VTd + daratumumab	213	203	190	183	175	172	164	153	147	135	123	92	48	23	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(5)	(32)	(71)	(96)	(118)	(118)
D-VTd + observation	229	223	216	207	195	179	169	155	138	127	122	90	55	22	1	0
	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(2)	(2)	(3)	(3)	(31)	(63)	(94)	(114)	(115)
D-VTd + daratumumab	229	226	217	204	198	187	168	158	151	146	137	106	51	19	1	0
	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(4)	(5)	(6)	(8)	(35)	(89)	(119)	(137)	(138)

Moreau P Lanc Oncol 2024 25:1003

AURIGA Trial

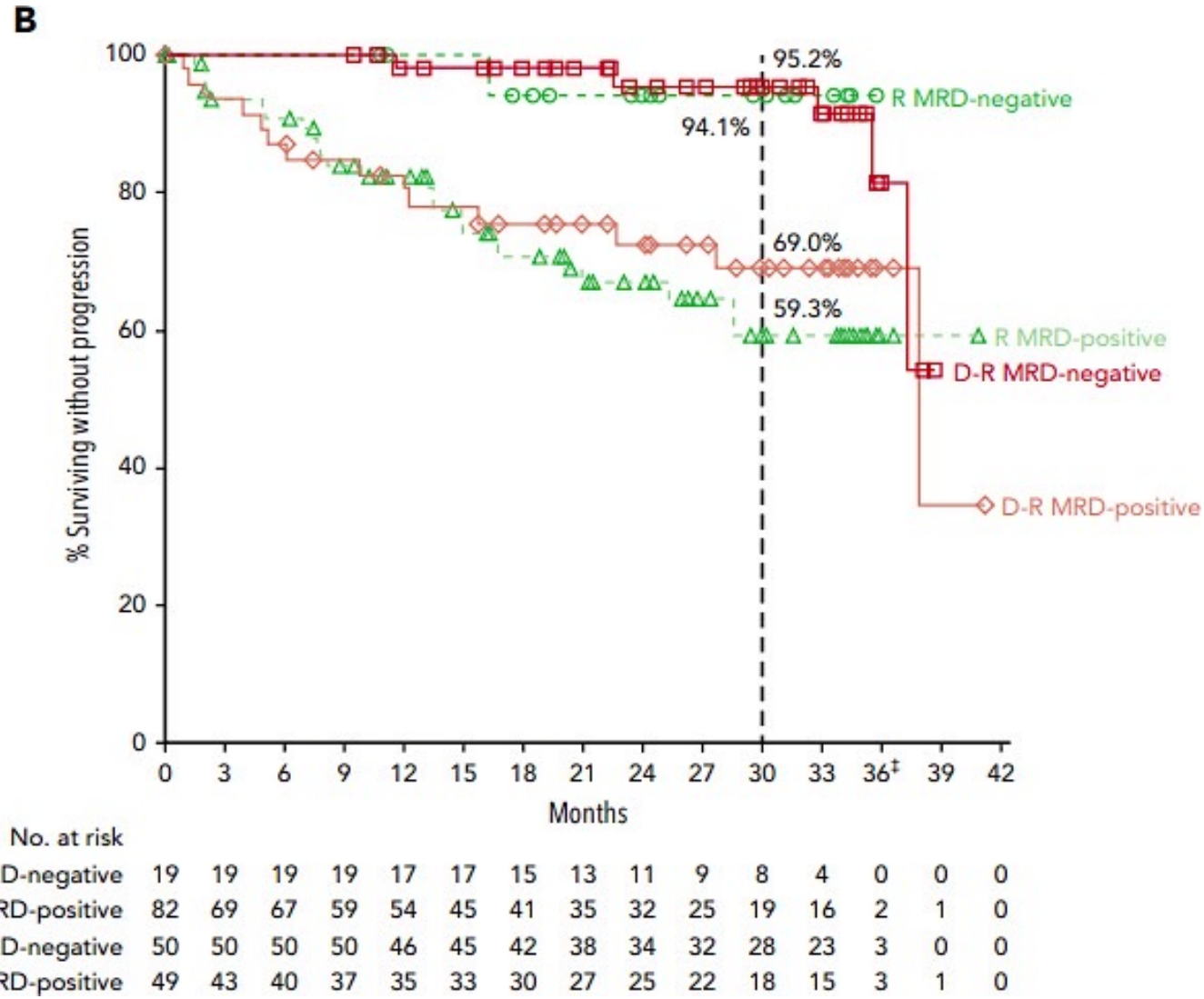


Badros A Blood 2024 145:300



Badros A Blood 2024 145:300

- Narrow eligibility requirements (no previous anti CD 38, MRD positive)
- Addition of daratumumab increases incidence of infections, mostly URIs
- Increases incidence of hypogammaglobulinemia

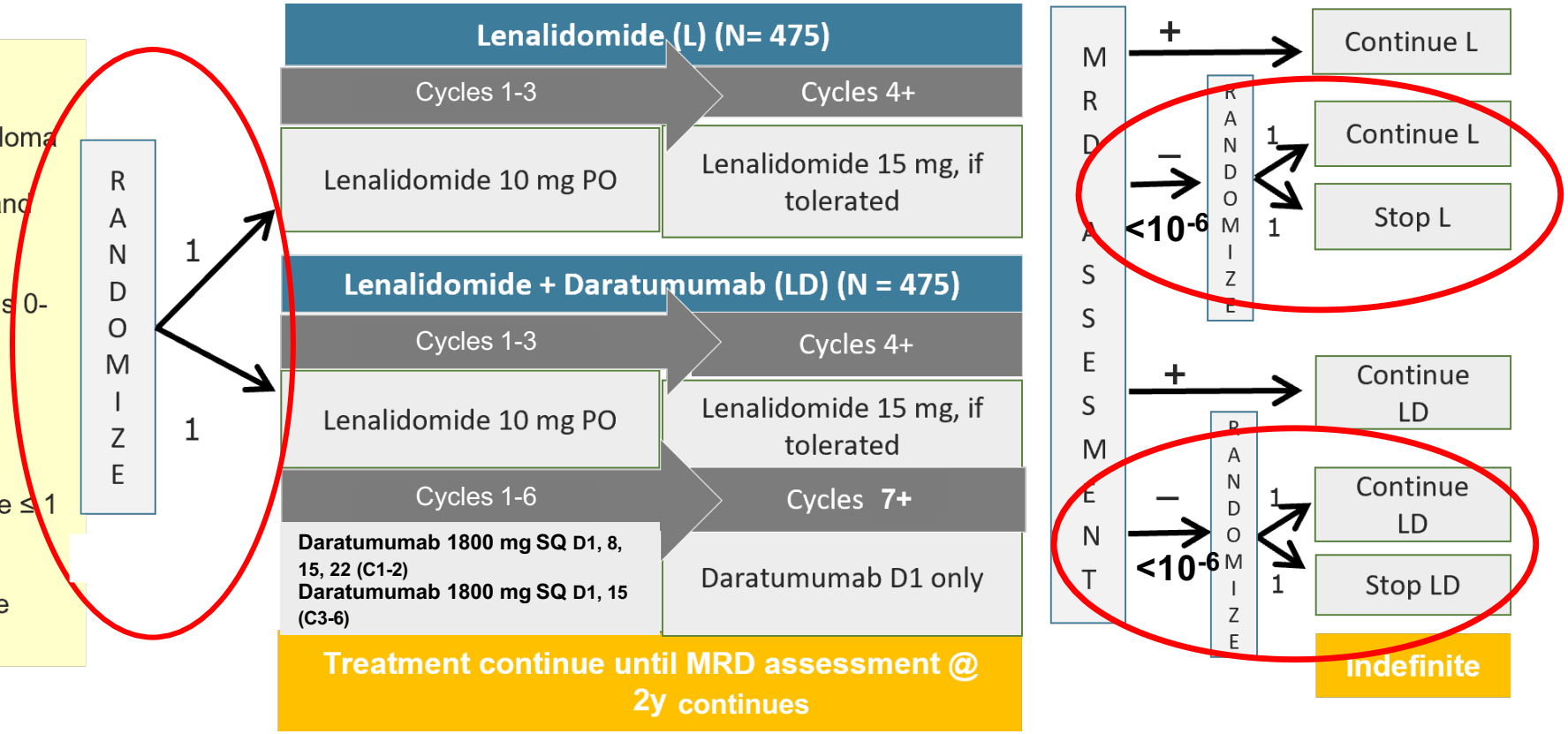


Badros A Blood 2024 145:300

DRAMMATIC Trial Schema (SWOG 1803)

Key eligibility

- First Registration: Study-Entry
  - Symptomatic multiple myeloma requiring systemic therapy prior to induction therapy and ASCT
  - Age 18-75
  - Zubrod Performance Status 0-2
- Second Registration: Eligibility
  - Lenalidomide REMS requirements
  - Lab normalization
  - ASCT related toxicity grade ≤ 1
- Third Registration: Second Randomization
  - Received 2 yr maintenance
  - MRD results



- Registration Step 1: *baseline specimen for ID (B-cell clonality) mandatory
- Registration Step 2: within 180 days after ASCT (***1st randomization***)
- Registration Step 3: completed 24 months of maintenance and MRD-neg + ≥VGPR (*<10^{-6}) (***2nd randomization***)

DRAMMATIC: Objectives

- **Primary objective**: Overall survival (OS) from 1st randomization:
  lenalidomide + daratumumab/rHuPH20 vs. lenalidomide

- **Secondary objectives** include traditional efficacy outcomes, including MRD-neg rate between the treatment arms.
  - OS of MRD-neg (+≥VGPR) pts who continue maintenance on each arm vs. those who discontinue (**objective of 2nd randomization**)
  - **24-month MRD analysis**
  - Patient-reported health-related quality of life (PROs: HR-QoL) **(n=250)**

Long term follow up for IKEMA (IKd): mPFS 35.7mo; responses in +1q

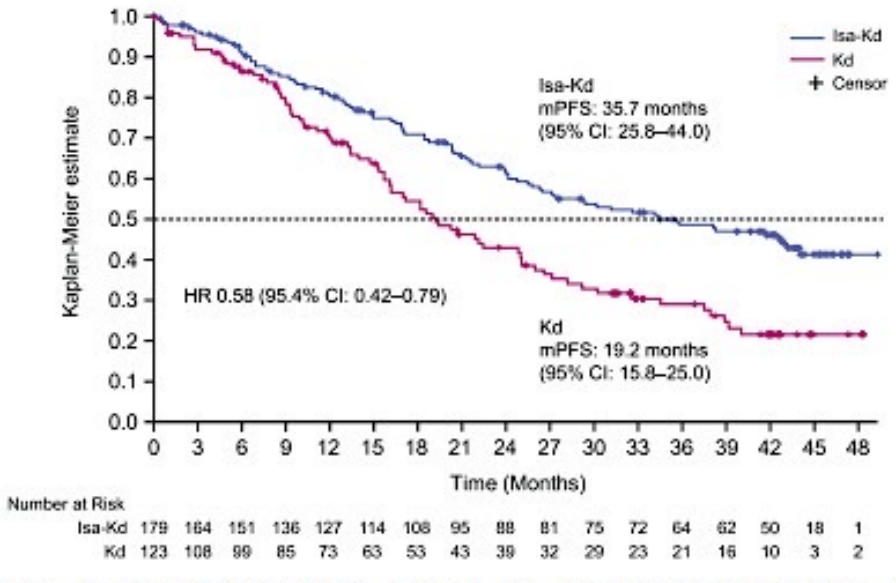
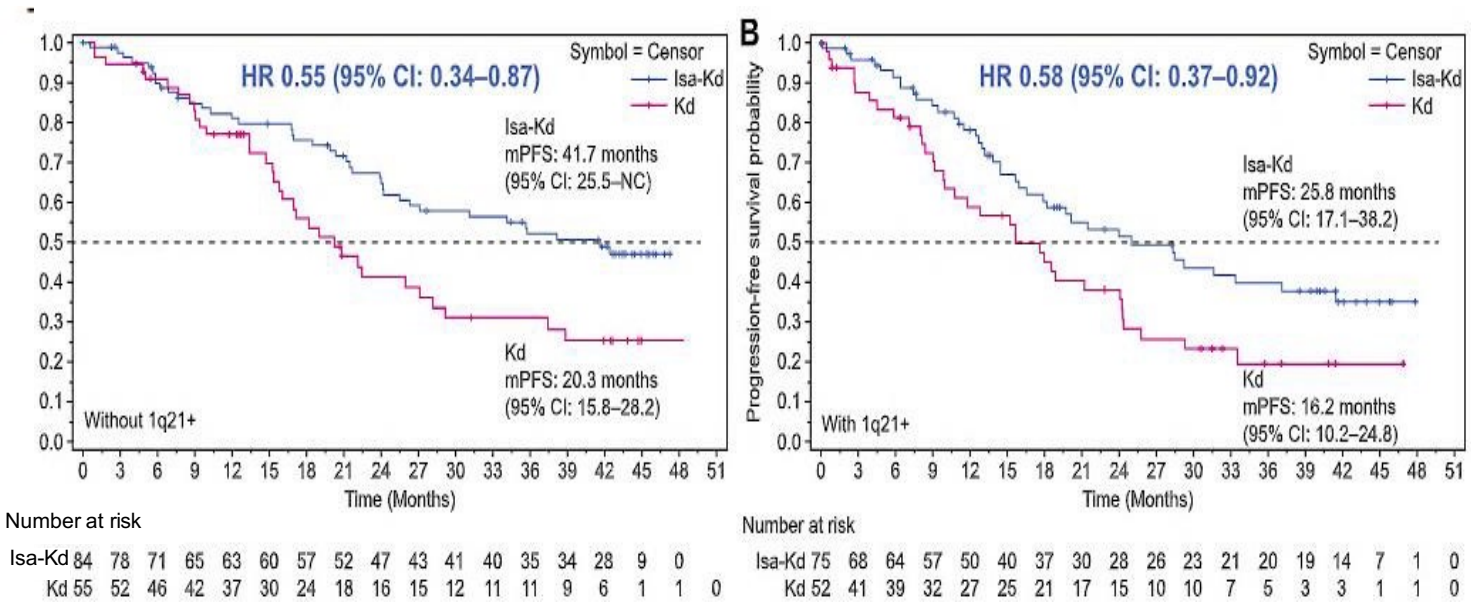
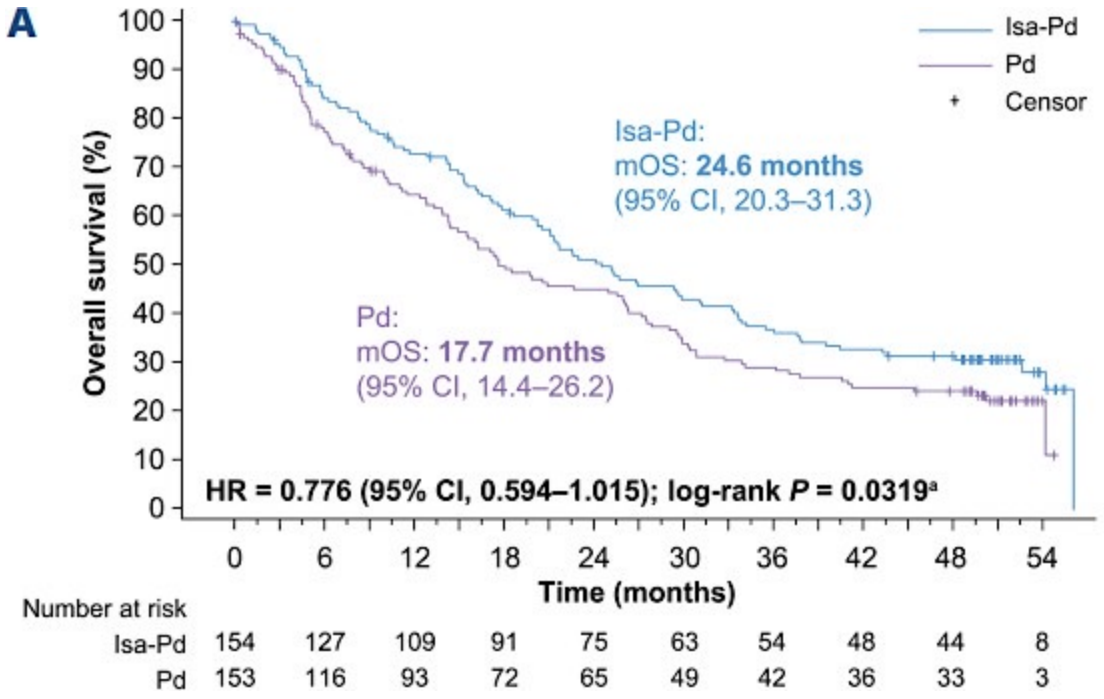


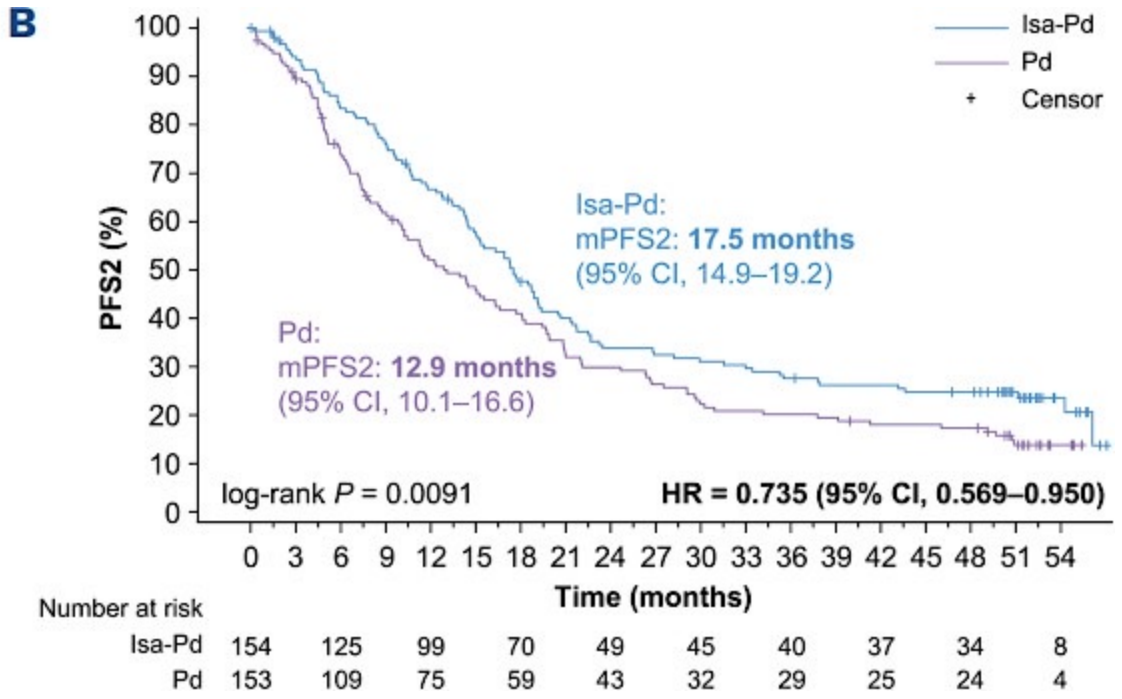
Fig. 2 Updated PFS with Isa-Kd vs Kd (ITT population). CI confidence interval, d dexamethasone, HR hazard ratio, Isa isatuximab, ITT intent to treat, K carfilzomib, mPFS median progression-free survival.



Martin T Blood Cancer Journal (2023) 13:72; Facon T Hematol Oncol 2024 42:e4258

Long term follow up of ICARIA (isa/pom/dex): superior overall survival and PFS2





Richardson P 2024 Haematologica 109:2239

Isatuximab Subcutaneous Formulation Met Co-Primary Endpoints in the IRAKLIA Phase III Study in MM

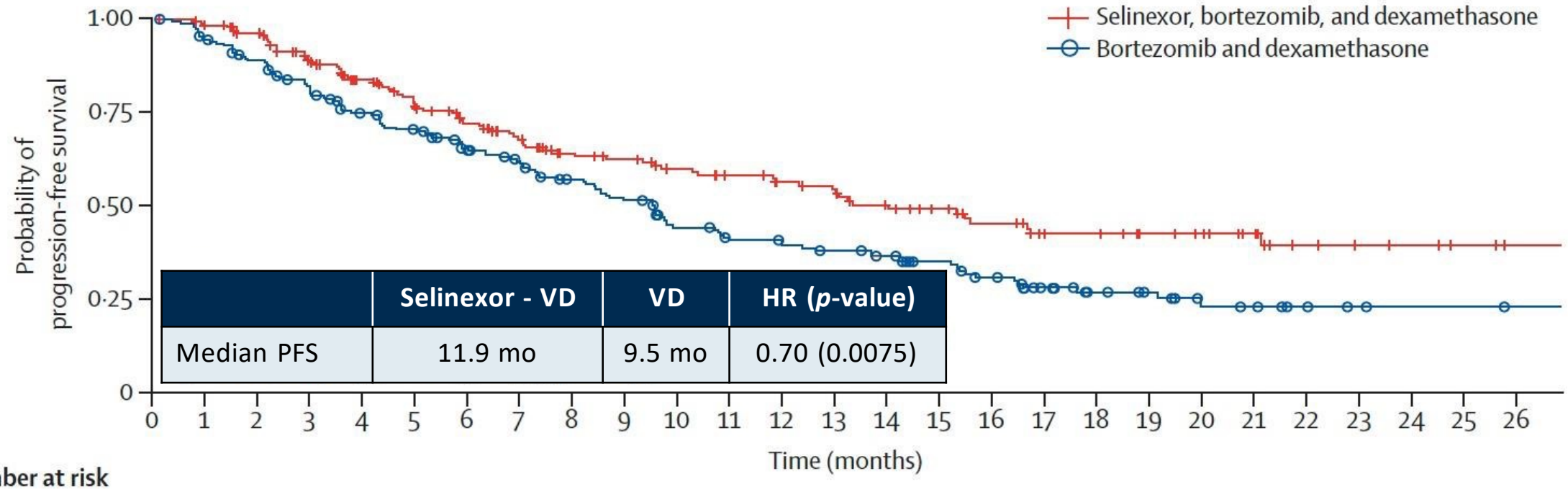
Press Release: January 9, 2025

"Results from the investigational, randomized, open-label IRAKLIA phase 3 study demonstrated that isatuximab administered at a fixed dose subcutaneously (SC) via an on-body delivery system in combination with pomalidomide and dexamethasone (Pd) met its co-primary endpoints of non-inferior objective response rate (ORR) and observed concentration before dosing (C trough) at steady state compared to intravenous (IV) isatuximab administered at a weight-based dose in combination with Pd in patients with relapsed or refractory multiple myeloma.

Key secondary endpoints, including very good partial response, incidence rate of infusion reactions and C trough at cycle 2 were also achieved. The study is ongoing, and the full results will be presented at a forthcoming medical meeting."

https://www.sanofi.com/en/media-room/press-releases/2025/2025-01-09-06-00-00-3006798.

BOSTON Trial: Progression-Free Survival (ITT) with Selinexor, Bortezomib and Dexamethasone for Relapsed/Refractory MM



	Selinexor - VD	VD	HR (*p*-value)
Median PFS	11.9 mo	9.5 mo	0.70 (0.0075)

Number at risk (number censored)

Selinexor, bortezomib, and dexamethasone	195 (0)	187 (5)	175 (12)	152 (21)	135 (31)	117 (37)	106 (42)	89 (50)	79 (57)	76 (59)	69 (63)	64 (66)	57 (71)	51 (73)	45 (76)	41 (80)	35 (83)	27 (89)	26 (90)	22 (94)	19 (97)	14 (102)	9 (106)	7 (108)	6 (109)	4 (111)	2 (113)
Bortezomib and dexamethasone	207 (0)	187 (8)	175 (10)	152 (15)	138 (20)	127 (22)	111 (29)	100 (32)	90 (37)	81 (37)	66 (41)	59 (43)	56 (44)	53 (45)	49 (47)	42 (52)	35 (55)	26 (60)	20 (65)	16 (69)	10 (73)	8 (75)	5 (78)	4 (79)	3 (80)	3 (80)	2 (81)

Grosicki S et al. *Lancet* 2020;396(10262):1563-73.

BOSTON: Select Adverse Events

Adverse event	Selinexor + Bort/dex (n = 195)		Bort/dex (n = 204)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	60%	39%	27%	17%
Fatigue	42%	13%	18%	1%
Anemia	36%	16%	23%	10%
Peripheral neuropathy	32%	5%	47%	9%
Neutropenia	15%	9%	6%	3%

Grosicki S et al. *Lancet* 2020;396(10262):1563-73.

BOSTON: Efficacy Outcomes with and without Selinexor Dose Reduction

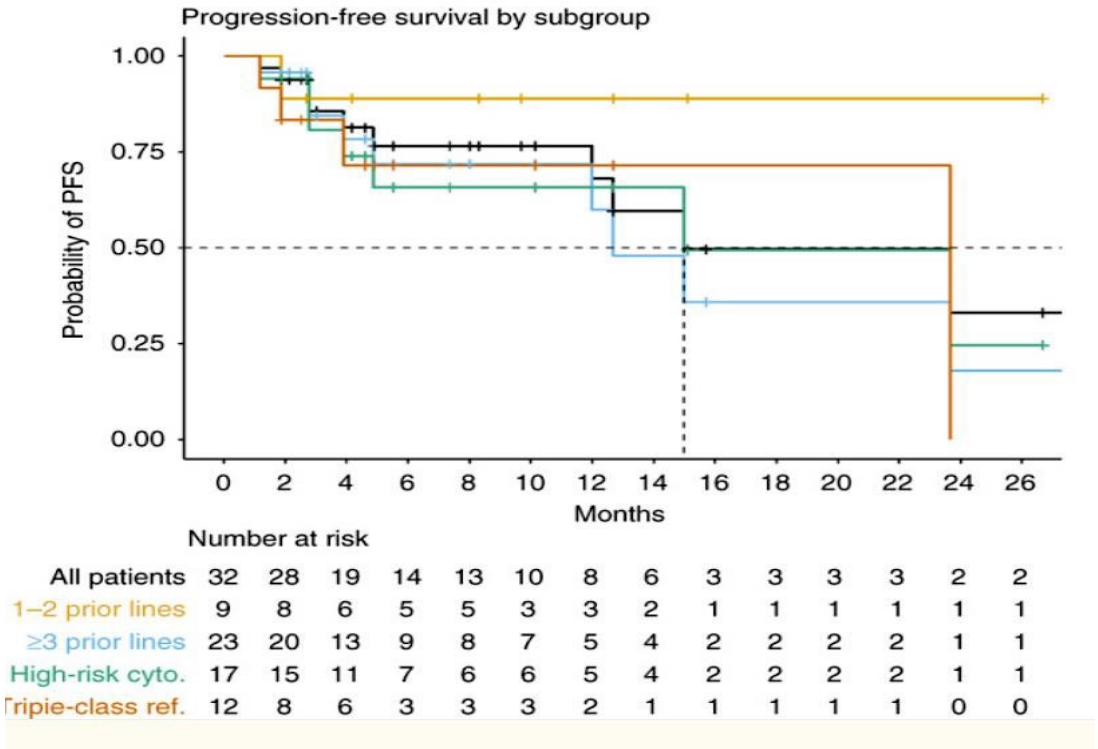
Outcome	With Selinexor Dose Reduction N = 126	Without Selinexor Dose Reduction N = 69
Progression-free survival, months, median (95% CI)	16.6 (12.9, NE)	9.2 (6.8, 15.5)
Overall response rate, n (%), [95% CI]	103 (81.7) [73.9, 88.1]	46 (66.7) [54.3, 77.6]
Stringent complete response, n (%)	16 (12.7)	3 (4.3)
Complete response, n (%)	11 (8.7)	3 (4.3)
≥Very good partial response, n (%), [95% CI]	65 (51.6) [42.5, 60.6]	22 (31.9) [21.2, 44.2]
Very good partial response, n (%)	38 (30.2)	16 (23.2)
Partial response, n (%)	38 (30.2)	24 (34.8)
Minimal response, n (%)	10 (7.9)	6 (8.7)
Stable disease, n (%)	12 (9.5)	13 (18.8)
Progressive disease, n (%)	0	1 (1.4)
Not evaluable, n (%)	1 (0.8)	3 (4.3)
Duration of response, months, median (95% CI)	NR (13.8, NE)	12.0 (8.3, NE)
Time to next treatment, months, median (95% CI)	22.6 (14.6, NE)	10.5 (6.3, 18.2)

Jagannath S et al. *Clin Lymphoma Myeloma Leuk* 2023;23(12):917-23.e3.

RTP RESEARCH TO PRACTICE

Selinexor in combination with IMID or PI showing good activity in RRMM: key is lower doses

Once weekly selinexor, carfilzomib and dexamethasone in carfilzomib non-refractory multiple myeloma patients



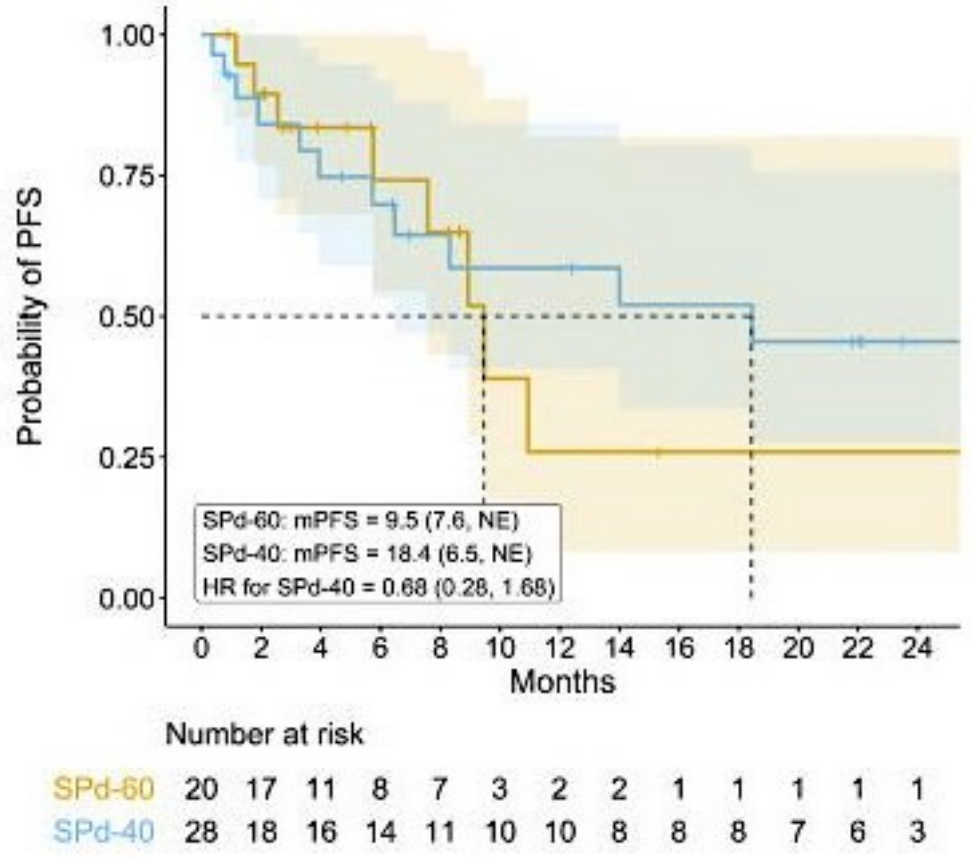
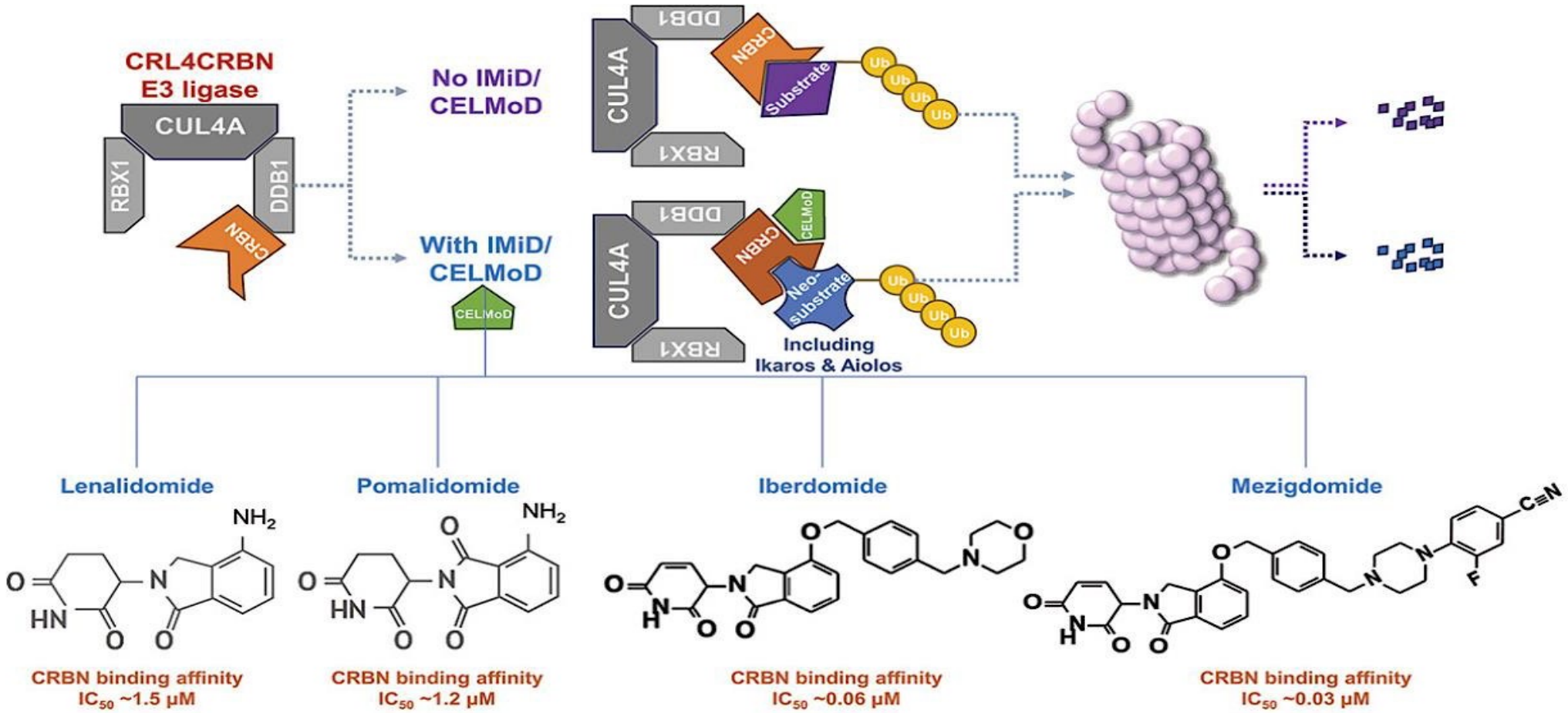


FIGURE 1
Kaplan-Meier curve comparing progression-free survival in patients who received SPd-40 versus those who received SPd-60.

Gasparetto Br J Cancer 2022;126:718; White D Front. Oncol. 14:1352281. 2024

CELMoDs: bind with higher affinity to cereblon



Liu Y Exp Rev Hematol 2024 https://doi.org/10.1080/17474086.2024.2382897

1025 Mezigdomide (MEZI) Plus Dexamethasone (DEX) and Bortezomib (BORT) or Carfilzomib (CFZ) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Updated Results from the CC-92480-MM-002 Trial

- RRMM, median lines 3(2-4)
- Median age 65.5
- Refractory to IMID 85.7-88.9%
- Refractory to PIs 50.0% to 51.7%

Gr ¾ AEs: thrombocytopenia 26.5%, neutropenia 63.3%, infections 32.7%

- Cohort A: 0.3, 0.6 or 1 mg mezi with Bort/Dex n=28
- Cohort C: Mezi/Carf/Dex n=27
- Cohort D: Mezi/VD dose expansion n=49 with either 0.6 or 1 mg Mezi

ORR A: 75%, VGPR 39.3%

ORR C: 85.2%, VGPR 44.4%

Addition of Mezi seems to re sensitize refractory pts

Sandhu I et al. ASH 2024

Discussion Questions

- Regulatory and reimbursement issues aside, what is your preferred initial regimen for an older (78-year-old), otherwise healthy patient with standard-risk MM who is not eligible for transplant?

- In general, when incorporating an anti-CD38 antibody into first-line treatment for patients with newly diagnosed MM, which agent do you prefer? How, if at all, does age and transplant-eligibility impact your choice? Do you generally partner with a doublet or triplet regimen? What is your preferred regimen to partner an anti-CD38 antibody with?

Discussion Questions

- In general, to which patients, if any, with relapsed/refractory MM do you currently administer selinexor? What are your preferred agents to partner it with? What is your usual starting dose of selinexor? Does that dose vary depending on the agents it is being combined with?

Module 12: Multiple Myeloma

Current and Emerging Therapeutic Approaches for MM — Dr Callander

CAR T-Cell Therapy, Bispecific Antibodies and Antibody-Drug Conjugates — Dr Martin

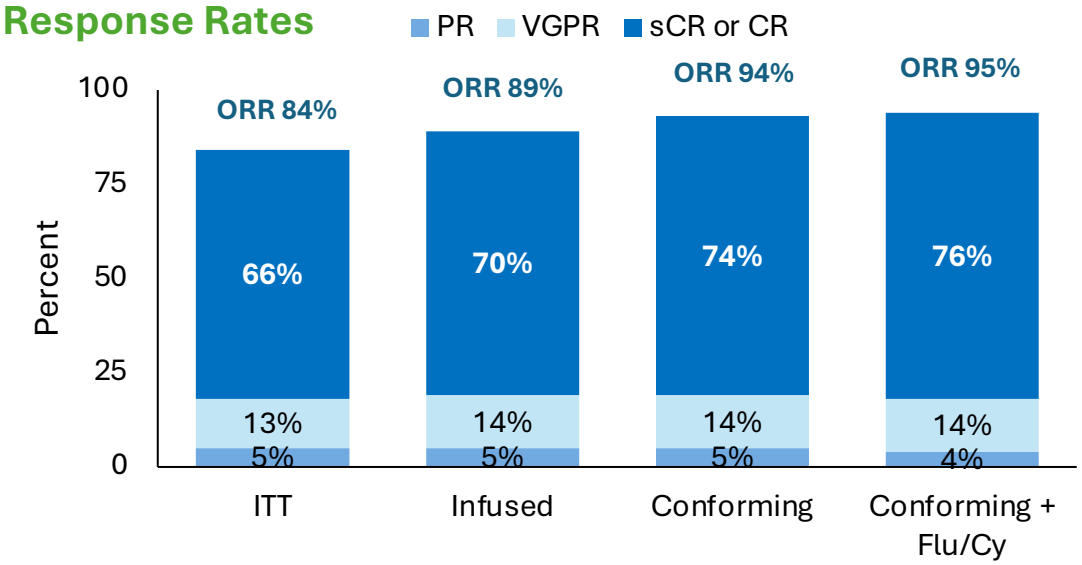
Immunotherapy for Multiple Myeloma:
Everything works better in MM

Thomas Martin, MD
Helen Diller Family Comprehensive Cancer Center
UCSF Medical Center
San Francisco, California

Disclosures

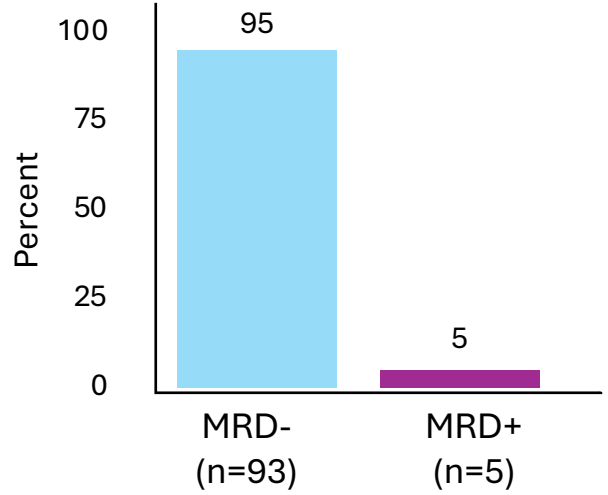
Consulting Agreements	GSK, Lilly, Pfizer Inc
Contracted Research	Amgen Inc, Bristol Myers Squibb, Johnson & Johnson Pharmaceuticals, Sanofi
Data and Safety Monitoring Boards/Committees	Lilly

Real-World Experience With Cilta-Cel in Patients With RRMM: Response



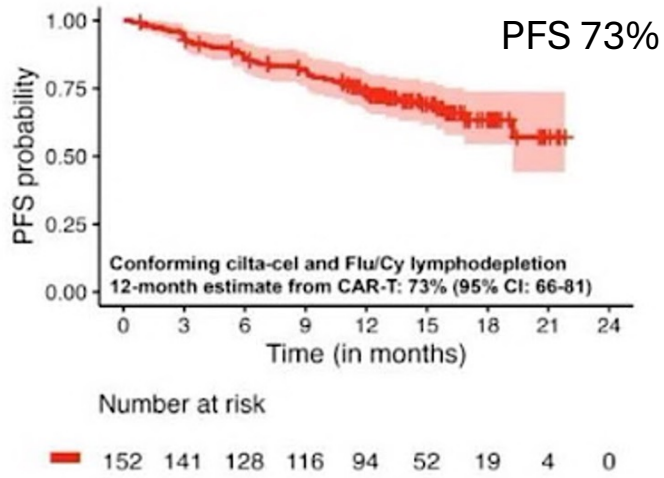
Response, %	RWE Cilta-Cel (N=236)	Conforming (n=192)	Conforming + Flu/Cy (n=152)	CARTITUDE-1 (N=97)
ORR	89	94	95	98
CR rate	70	74	76	83

MRD Data for Patients in CR (N=98)



Conforming Cilta-Cel + Flu/Cy

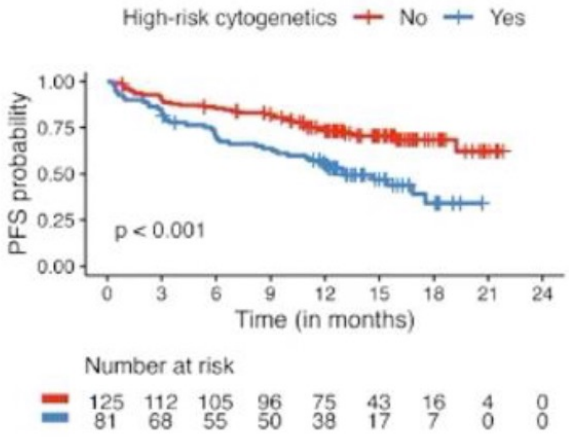
PFS 73% @12m



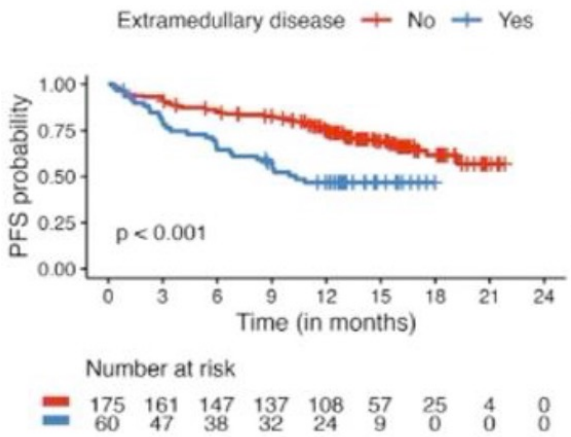
Sidana S, et al. IMS 2024. Abstract OA-11.
CARTITUDE-1: Berdeja JG, et al. *Lancet*. 2021;398(10297):314-324. Martin TM, et al. *J Clin Oncol*. 2023;41(6):1265-1274.

Real-World Experience With Cilta-Cel in Patients With RRMM: *PFS by Subgroup*

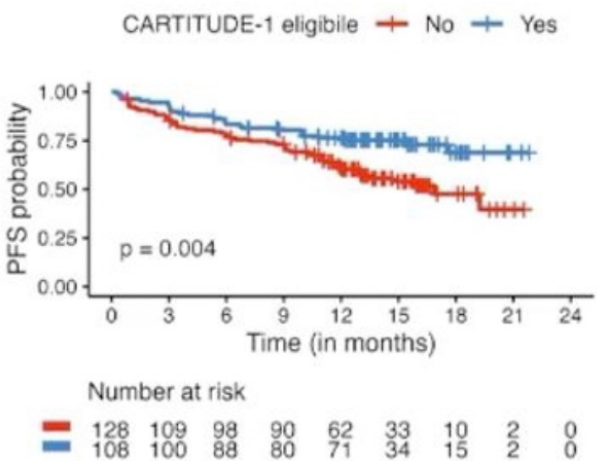
High-Risk Cytogenetics



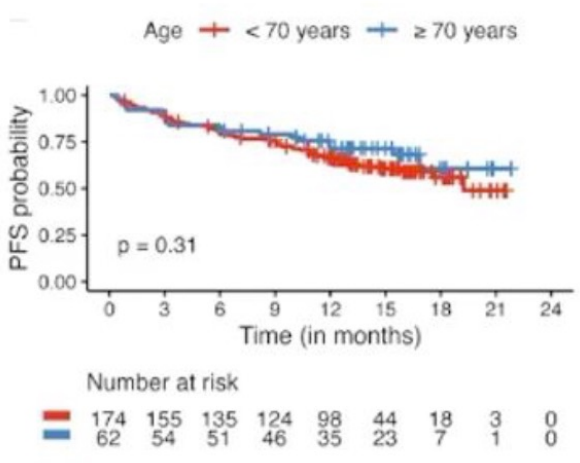
EMD



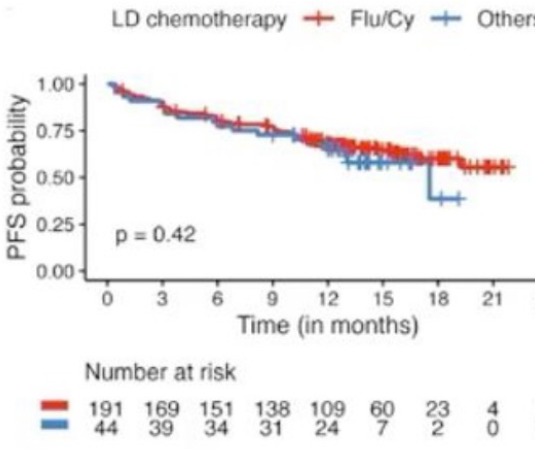
CARTITUDE-1 Eligible



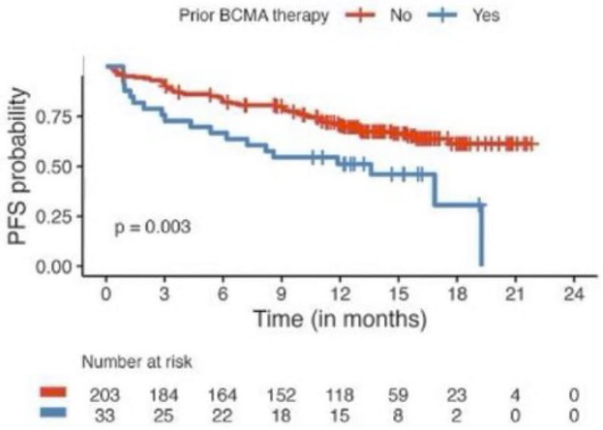
Age

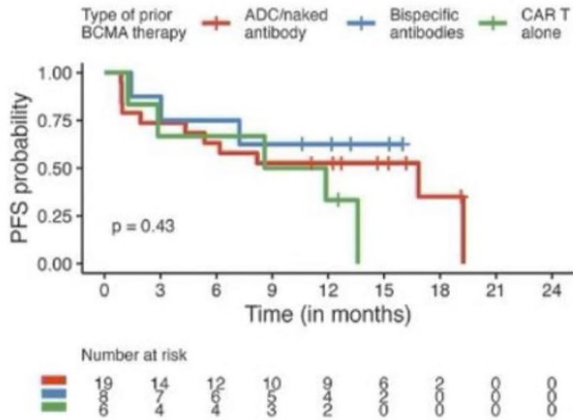


LD Chemo

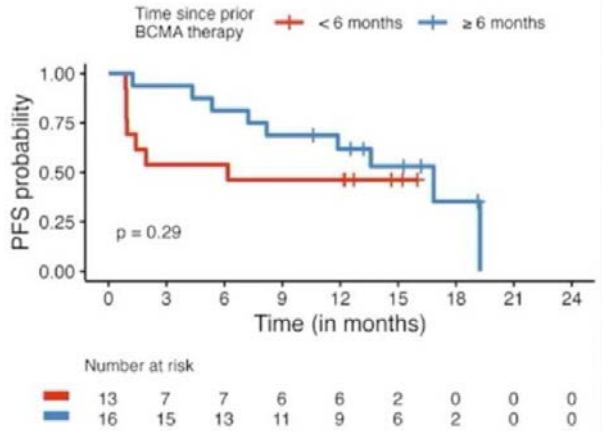


PFS by Prior BCMA Status (L) and Type of BCMA Therapy (R)





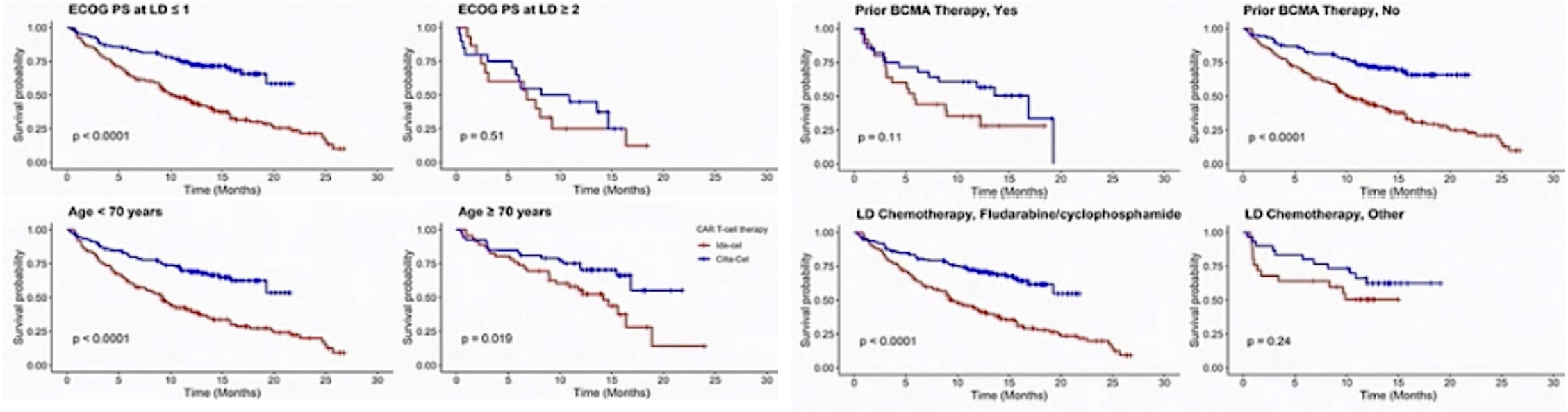
PFS by Time Since Prior BCMA-Directed Therapy



Sidana S, et al. IMS 2024. Abstract OA-11.

Multicenter Retrospective Analysis of Ide-Cel and Cilta-Cel for Patients With RRMM: *PFS Across Subgroups (cont'd) and Summary*

PFS by Patient and Treatment Characteristics



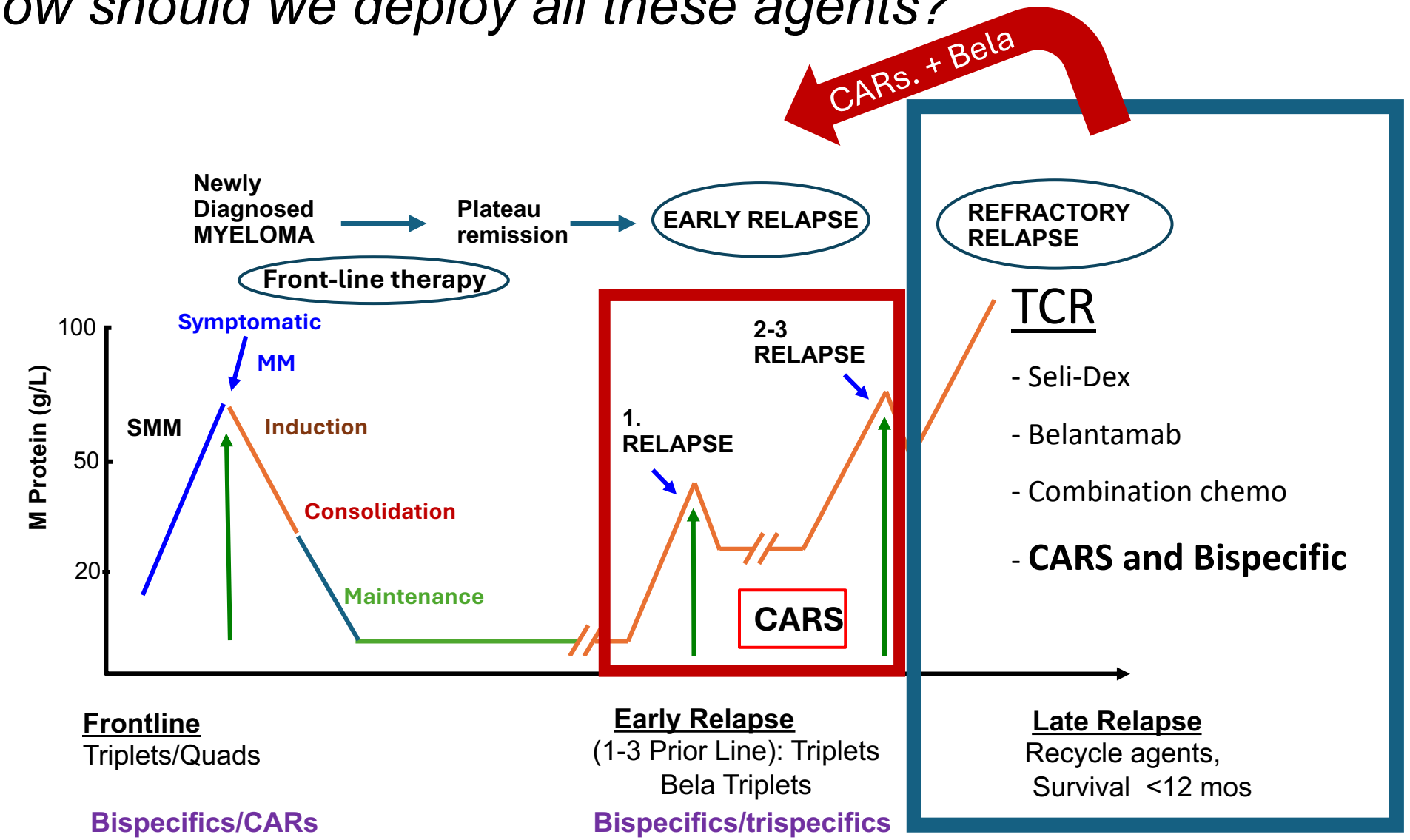
Authors' Conclusions

- This analysis of Cilta-cel vs Ide-cel demonstrated higher efficacy, including responses and survival (overall and by patient subgroups); higher rates of some toxicities (severe CRS, delayed NR, infection); no difference in the rates of other toxicities and NRM
- Results remained consistent in sensitivity analyses, and these results may aid in clinical decision-making, patient counseling, and may help guide CAR T-cell therapy selection; however, the study was limited by being retrospective and due to potential biases in real-world data

Hansen DK, et al. IMS 2024. Abstract OA-07.

Sequencing Therapy in MM:

How should we deploy all these agents?

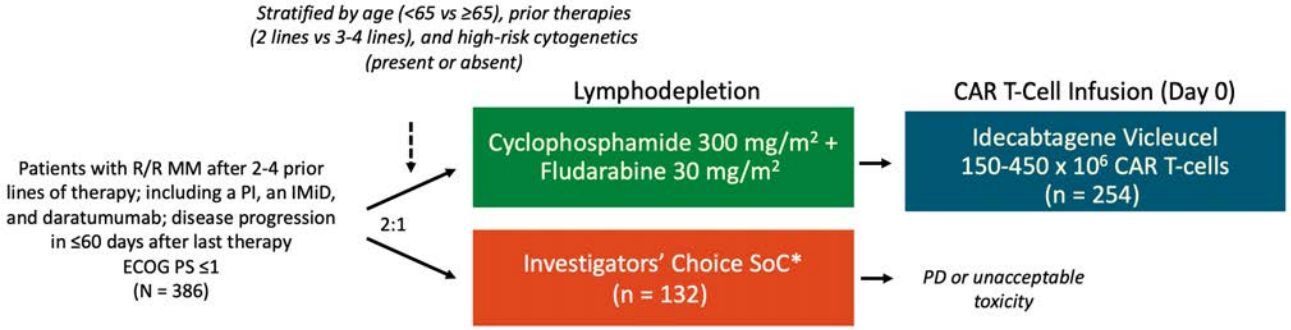


Trials:

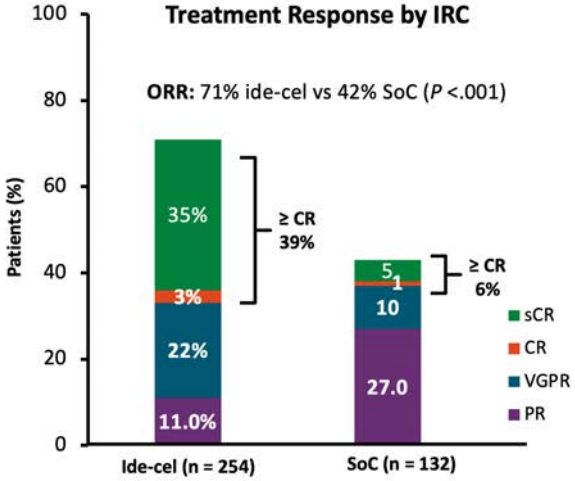
CART in Earlier Lines

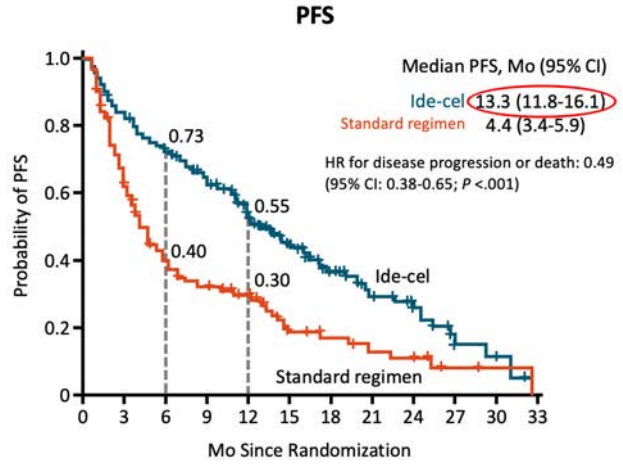
KarMMa-3: Phase III Trial of Ide-Cel vs SoC in R/R MM

- International, open-label, randomized phase III trial

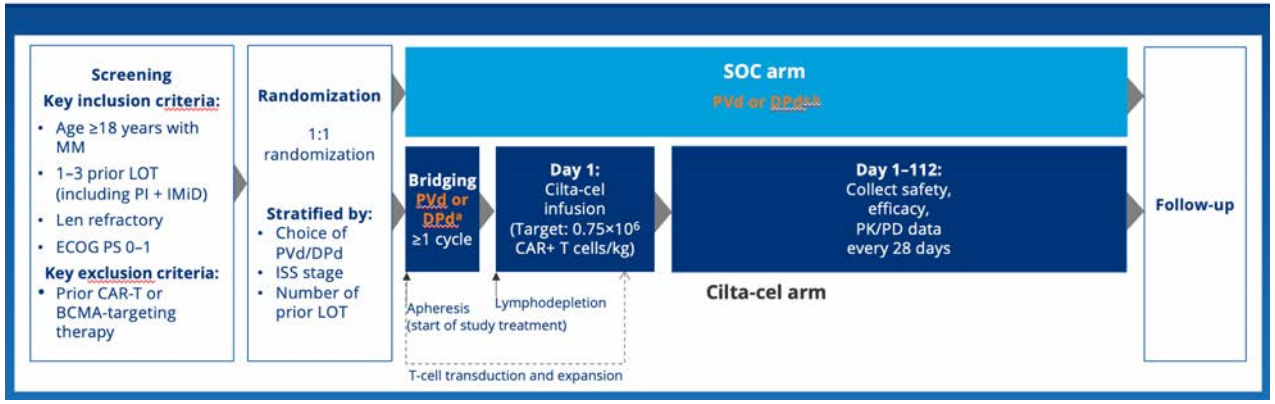


Median 3 PLT (TCR 65%): ORR 71%, PFS 13.3m

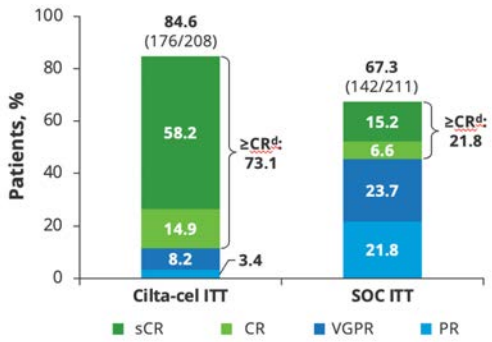


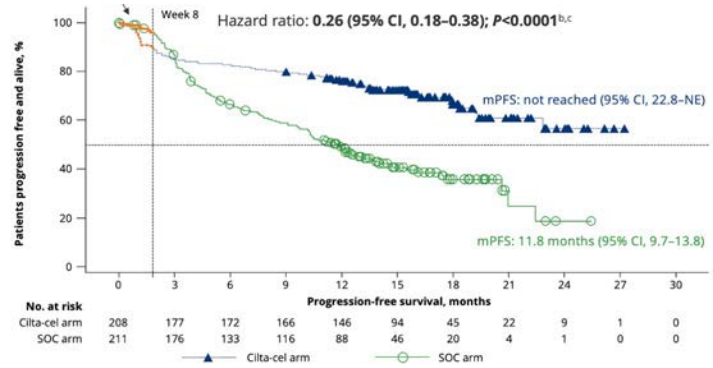


CARTITUDE-4: Study Design and Endpoints

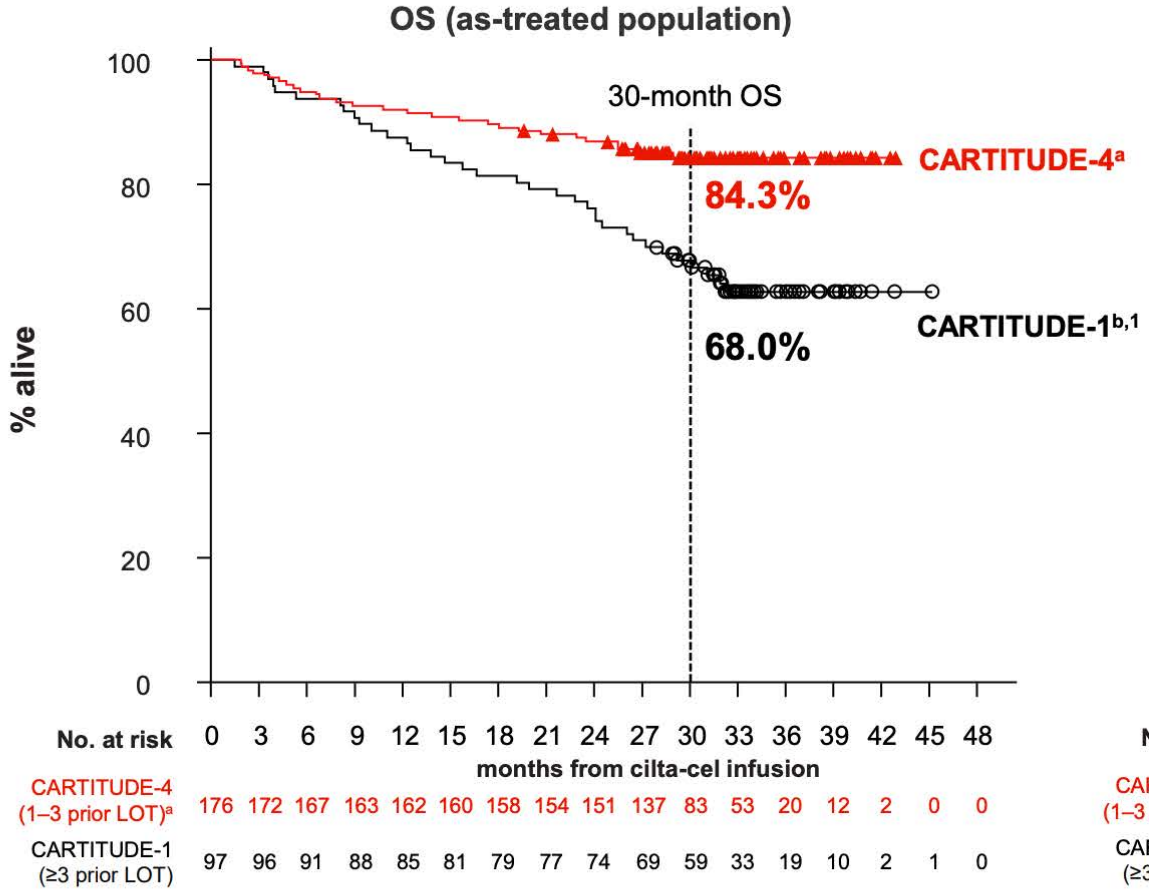


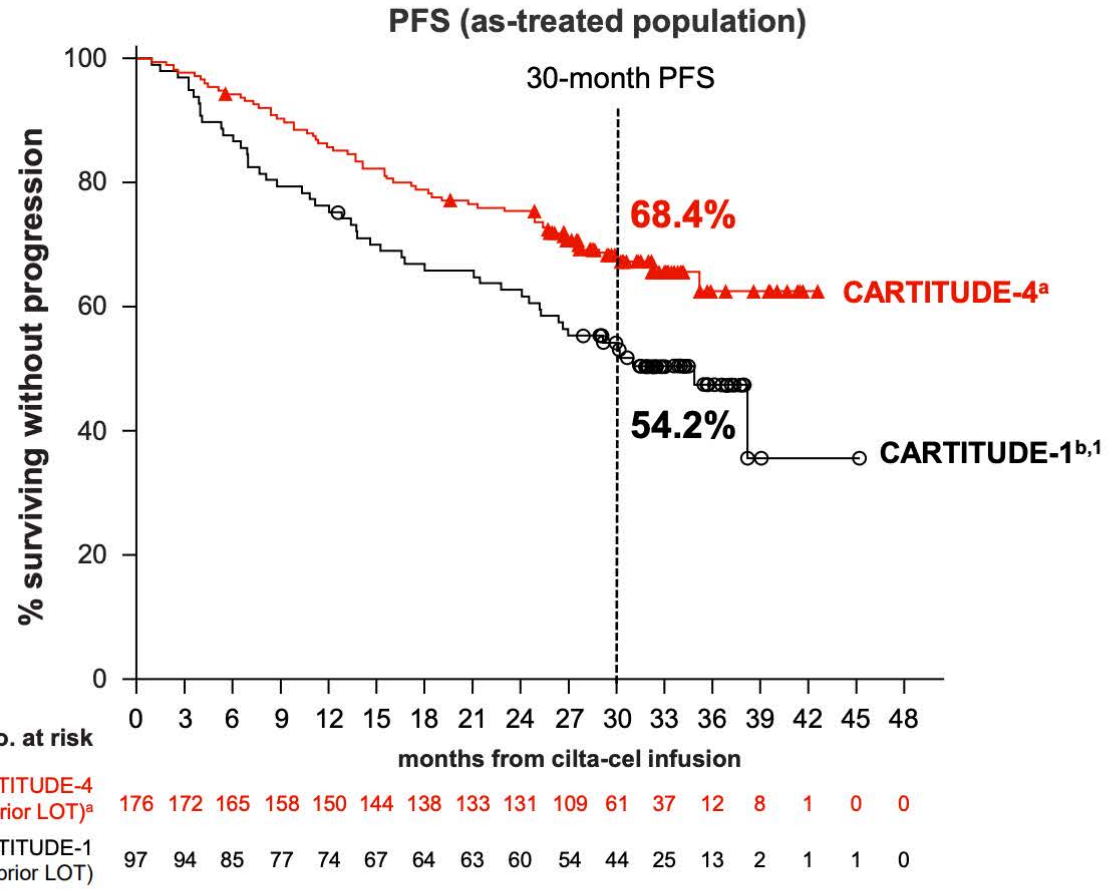
Median 2 PLT (TCR 15%): ORR 99%, PFS NR





Long-Term CARTITUDE-4 Update (34 Months): Numerically Higher Overall and Progression-Free Survival Rates Versus CARTITUDE-1





Cilta-cel use in earlier lines demonstrated numerically higher rates of overall and progression-free survival

[a]Re-baselined to begin at time of cilta-cel infusion for patients who received cilta-cel as study treatment, with median follow-up of 30.5 months. [b]33.4-month median follow-up.
Cilta-cel, ciltacabtagene autoleucel; LOT, line of therapy; OS, overall survival; PFS, progression-free survival; SOC, standard of care.
1. Lin et al. Abstract 8009, presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual.

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

CARTITUDE-4: CRS and CAR T Neurotoxicity

- CRS occurred in 76.1% of patients and were mostly grade 1/2; all cases resolved[1,2]
- CAR-T cell neurotoxicity occurred in 20.5% of patients; none were fatal, and most were grade 1/2[1,2]
  - All cases of ICANS resolved[1,2]
  - By the CCO, all but 2 of the cranial nerve palsy and 2 of the peripheral neuropathy cases had resolved; the MNT case (grade 1) had not yet resolved by the CCO[1,2]

*Secondary malignancies similar in both arms

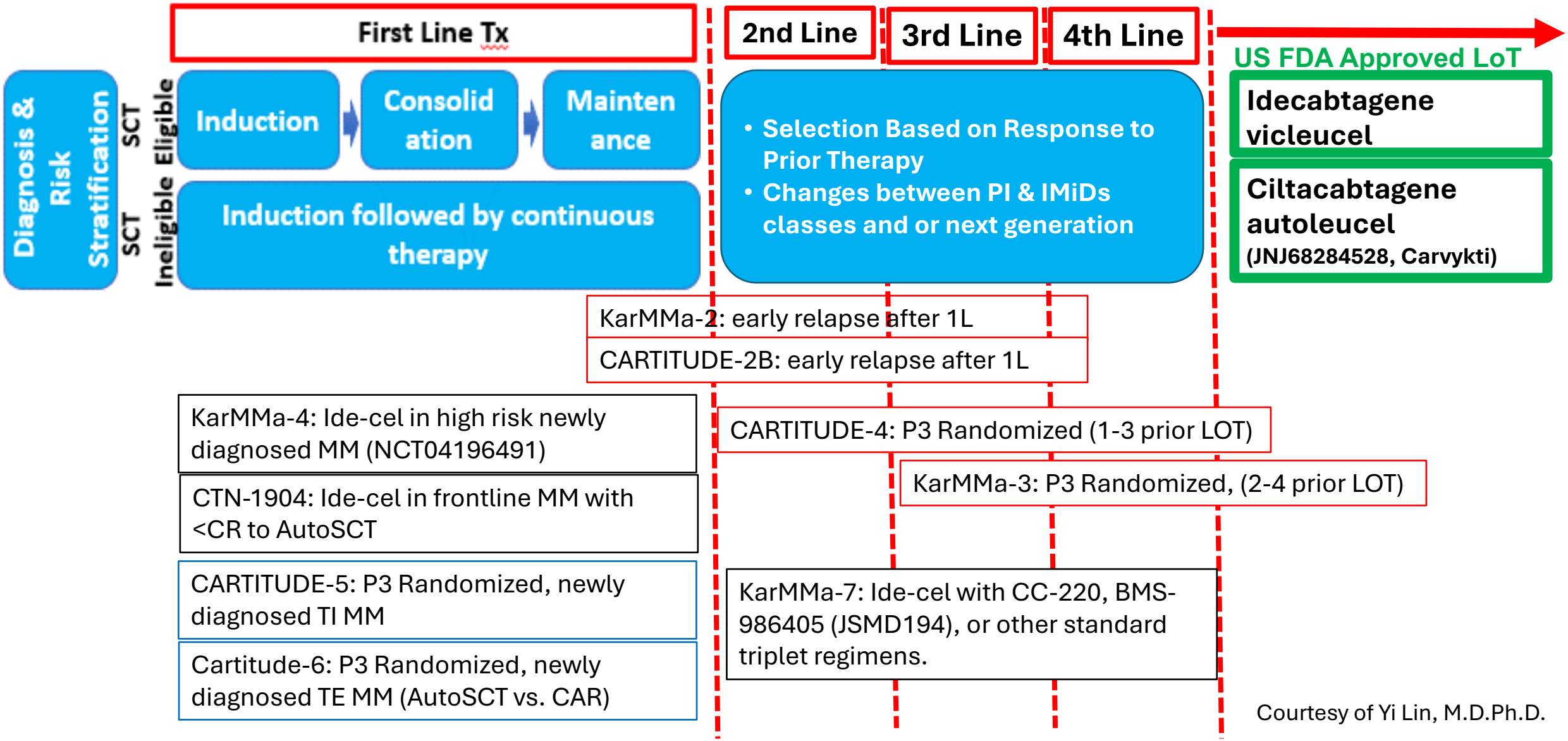
AE, n (%)	As-treated population (n=176)			
	Any Grade	Grade 3/4	Median time to onset,[a] days	Median duration,[b] days
CRS	134 (76.1)	2 (1.1)	8	3
Neurotoxicity	36[c] (20.5)	5 (2.8)	–	–
ICANS	8 (4.5)	0[d]	10	2
Other[e]	30 (17.0)	4 (2.3)	–	–
Cranial nerve palsy	16 (9.1)[f]	2 (1.1)	21	77
Peripheral neuropathy	5 (2.8)	1 (0.6)	63	201
MNT	1 (0.6)	0	85	253[g]

[a]Time to onset from cilta-cel infusion. [b]Calculated regardless of resolution of event. [c]Several patients had both ICANS and "other" neurotoxicity. [d]Grade 3 syncope reported as a symptom of grade 2 ICANS. [e]Other neurotoxicities include AEs reported as CAR-T cell neurotoxicity that are not ICANS or associated symptoms. These included (but were not limited to) MNTs, cranial nerve palsy, and peripheral neuropathy. [f]All cases involved cranial nerve VII; 2 cases involved a second cranial nerve (cranial nerves III and V; each n=1). [g]Ongoing at CCO; last known date alive is October 17, 2022 (day 337 post infusion) in this patient.

AE, adverse event; CAR, chimeric antigen receptor; CCO, clinical cut-off; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity; MNT, movement/neurocognitive treatment-emergent adverse event. 1. San-Miguel J, et al. *N Engl J Med* 2023;389:335-47. 2. Dhakal B, et al. Presented at American Society of Clinical Oncology (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA.

Sidiqi MH, et al. ASH 2023. Abstract 4866.

CAR-T investigations in earlier lines of therapy



Courtesy of Yi Lin, M.D.Ph.D.

BCMAxCD3 Bispecifics

Accelerated approval

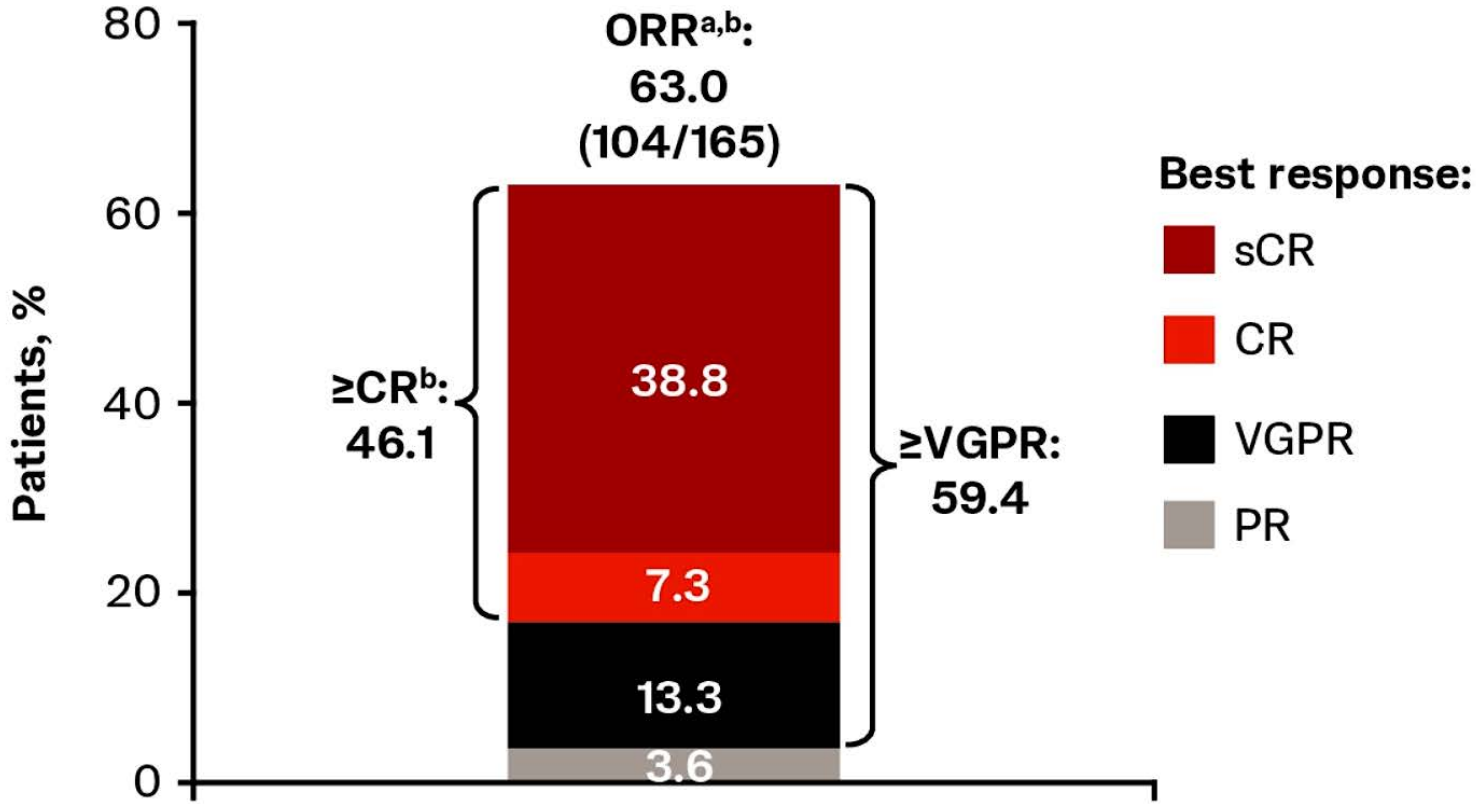
In Development

Bispecific Antibody	Teclistamab (JNJ-64007957)	Elranatamab (PF-06863135)	Linvoseltamab (REGN5458)	ABBV-383	Alnuctamab BMS-93269	HPN217
Structure/Function	Humanized antibody	Humanized antibody	*Veloci-Bi*® platform fully human antibody	**Low CD3 affinity fully human antibody**	**Humanized antibody 2 BCMA + 1 CD3**	Trispecific 50kDa (albumin)
Treatment	Weekly SC	Weekly SC	Weekly IV	IV q3w	Qwk -> Q4wk SQ	Q2wk IV
Patients	n= 165	n= 123	n= 252	n= 220	n= 68	n= 97
Median prior lines	5	5	5	5	4	6
Triple-class refr	78%	100%	74%	80%	63%	78%
ORR at RP2D (n)	63% 1.5 mg/kg SC **(n=165)**	61% 76 mg SQ **(n=123)**	71% 200 mg IV (n=117)	60-64%% 40 to 60 mg IV (n=55 n=61)	65% 30 mg SQ (n=26)	63%% 12 mg (n=19)
PFS	12.5 mos (8.8-17.2)	17.2 mos (9.8-NE)	66% @ 12 mos	13.7 or 11.2 mos	NR	NR
OS	21.9 mo (16.0–NE)					
DOR	24 mos (16.2 - NE)	69% @ 18 mos	NR @ 8 mos	70% and 66% @ 12 mos	NE	NR
Median f/u	22 mos	17.6 mos	11 mos		4.6 mos	
AEs, (All/(Gr 3+);				43-70% (0-2%)		
CRS	72% (0.6%)	58% (0%)	46% (1%)	(22%)	53% (0%)	30 (2%)
Infections	80% (55%)	70% (41%)	73% (34%)	56-71% (25-34%)	34% (9%)	59% (25%)
Neutropenia	72% (66%)	50% (50%)	*32% (31%)*	41-43% (13-31%)	37%(32%)	40% (34%)
Anemia Thrombocyt	54% (38%)	49% (37%)		38-55% (13-33%)	38%(25%)	44% (34%)
openia	42% (22%)	32% (24%)		3-5% (0-2%)	24%(9%)	28% (18%)
Neuro	Neurotoxicity 15% (0.1)	NR/ PN?	8% (3%)	NR	ICANS 3 (0%)	21% (0%)
# Deaths	68/(41 due to PD)	25 (/11 due to PD)	14	NR	1	5(2 due to PD
Hypogamma/IVIg	75%//39%	75%/40%	/22%			

Moreau et al. *N Engl J Med.* Jun 5 2022. Lesohkin et al Nature med 2023 Jagannath et al ASH 2023 Vij et al ASH 2023 Wong et al ASH 2022;; Madan et al ASH 2023. Van de Donk IMS 2023. Tomasson et al, ASH 2023

MajesTEC-1: ORR

Figure 2: ORR



[a]Response assessed by independent review committee. [b]At 30-month mFU of the phase 2 efficacy population (patients enrolled in cohort A on or before March 18, 2021; n=110 patients supporting the USPI[1]): ORR, 61.8%; ≥CR, 46.4% (n=51).
sCR, stringent complete response; USPI, United States prescribing information.

Garfall A et al. ASCO 2024; Abstract 7540.

MajesTEC-1: DOR and PFS

Figure 3: DOR

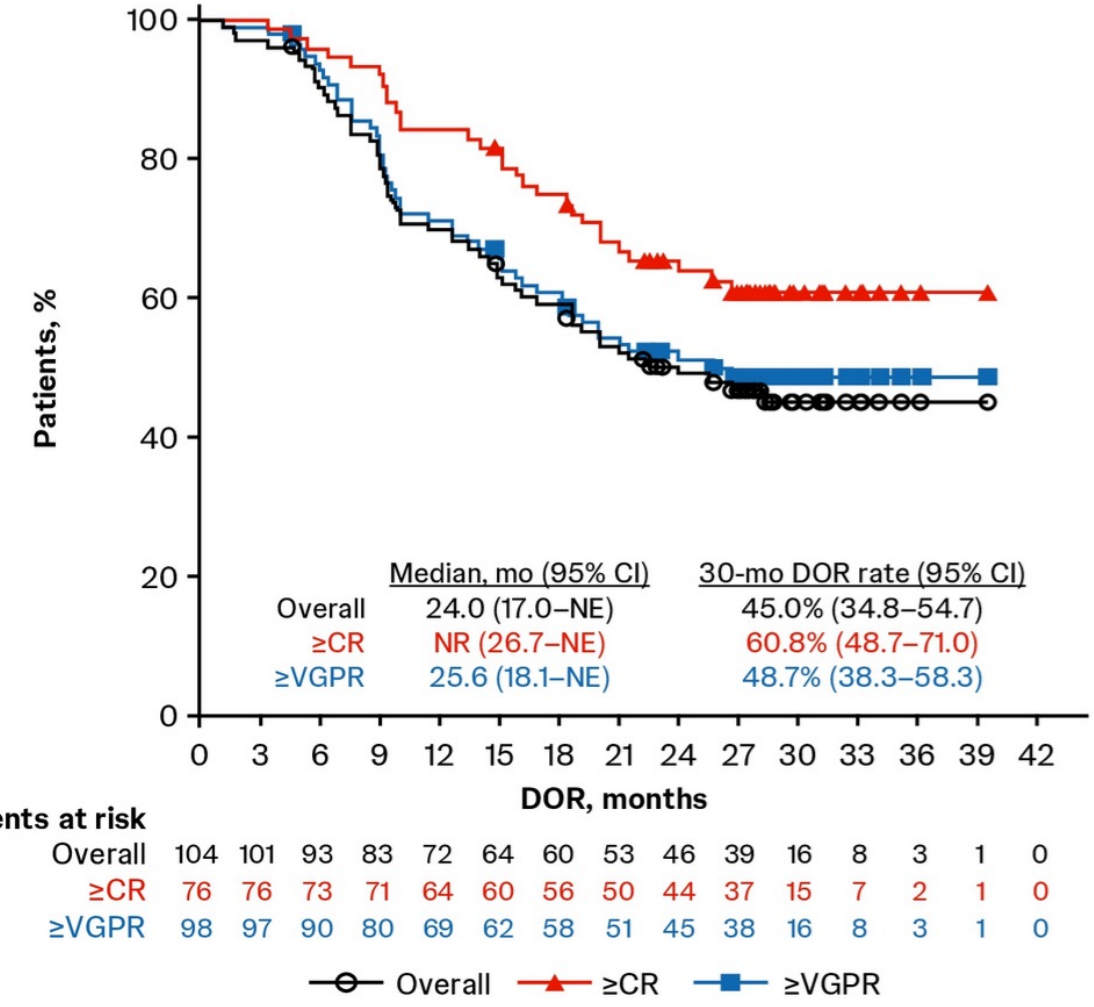
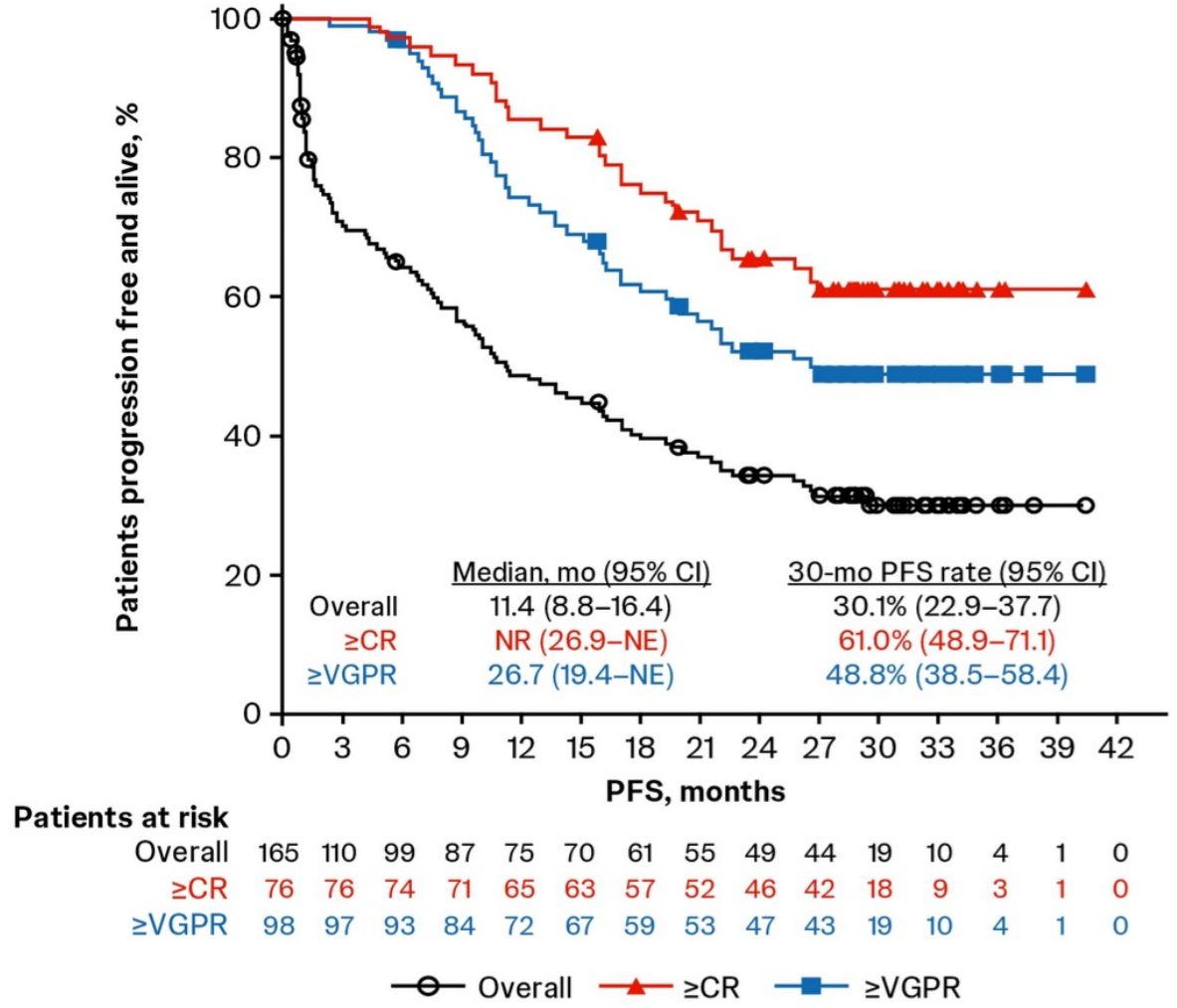


Figure 4: PFS



Garfall A et al. ASCO 2024; Abstract 7540.

MajesTEC-1: Safety

TEAEs, n (%)	N=165	
	Any Grade	Grade 3/4
Any TEAE	**165 (100)**	**156 (94.5)**
Hematologic		
Neutropenia	118 (71.5)	108 (65.5)
Anemia	91 (55.2)	62 (37.6)
Thrombocytopenia	69 (41.8)	38 (23.0)
Lymphopenia	60 (36.4)	57 (34.5)
Leukopenia	33 (20.0)	15 (9.1)

TEAEs, n (%)	N=165	
	Any Grade	Grade 3/4
Nonhematologic		
Infections	130 (78.8)	91 (55.2)
COVID-19	48 (29.1)	35 (21.2)
CRS	119 (72.1)	1 (0.6)
Diarrhea	57 (34.5)	6 (3.6)
Pyrexia	51 (30.9)	1 (0.6)
Fatigue	50 (30.3)	4 (2.4)
Cough	46 (27.9)	0
Nausea	45 (27.3)	1 (0.6)
Injection site erythema	44 (26.7)	0
Arthralgia	42 (25.5)	2 (1.2)
Headache	40 (24.2)	1 (0.6)
Constipation	37 (22.4)	0
Hypogammaglobulinemia	36 (21.8)	3 (1.8)
Back pain	33 (20.0)	4 (2.4)

Garfall A et al. ASCO 2024; Abstract 7540.

MagnetisMM-3: Long-Term Update – Survival

PFS and OS

- Median PFS was 17.2 (95% CI 9.8–NE) months (**Figure 1**)
- Median OS was 24.6 (95% CI 13.4–NE) months (**Figure 2**)

Figure 1. PFS

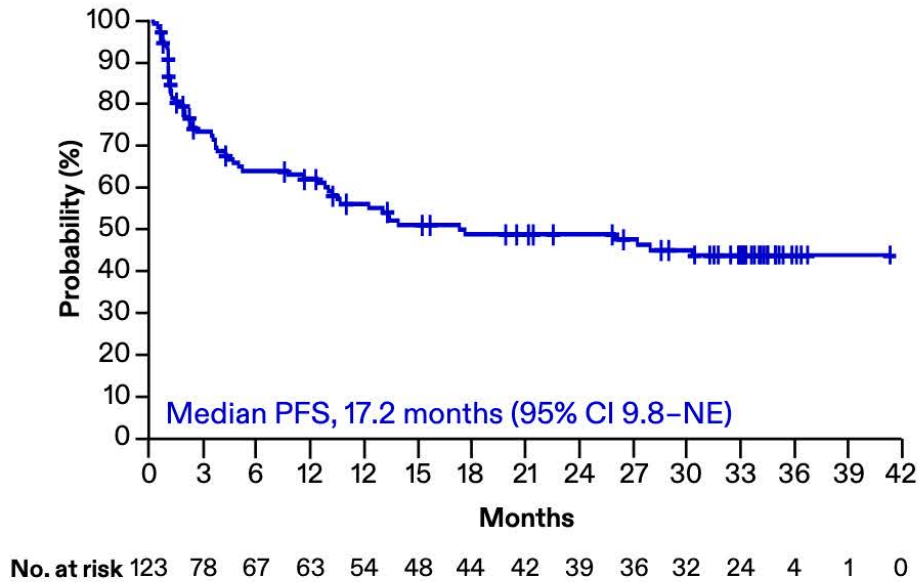
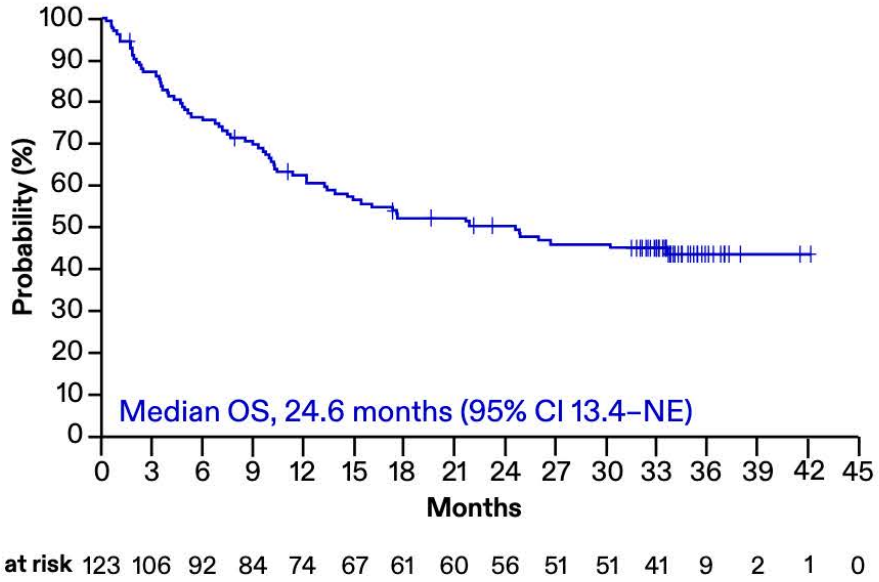


Figure 2. OS



CI = confidence interval; NE = not evaluable; OS = overall survival; PFS = progression-free survival.

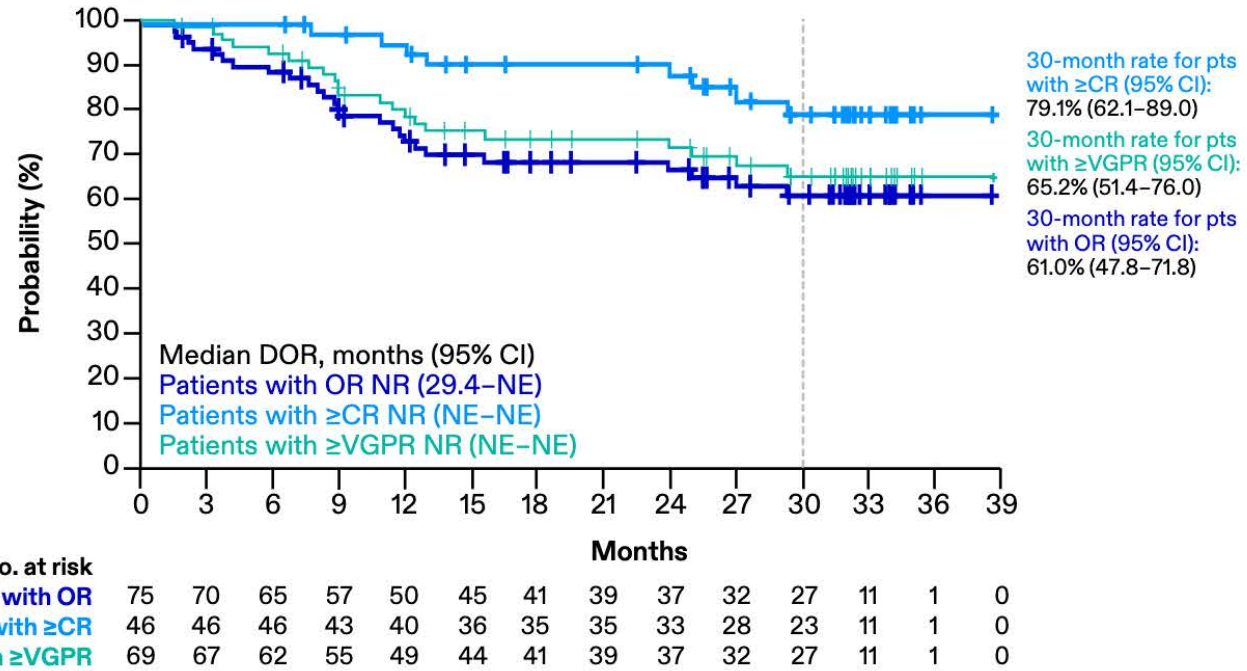
Prince HM et al. Poster presentation at ASH 2024 (Abstract 4738).

MagnetisMM-3: Long-Term Update and Efficacy and Safety of Less Frequent Dosing of Elranatamab in Patients with R/R MM

Efficacy: ORR, MRD Negativity, and DOR

- With extended follow-up, ORR per BICR was 61.0% (≥CR rate 37.4%)
  - sCR, 16.3%; CR, 21.1%; VGPR, 18.7%; PR 4.9%
  - MRD negativity (10^{-5}) rate was 90.3% in patients with ≥CR who were evaluable for MRD (n=31)
- Median DOR was NR (95% CI 29.4–NE) (**Figure**)
- Among responders per BICR who switched to Q4W dosing ≥6 months before the data cutoff (n=27), 25 (92.6%) maintained their response ≥6 months after the switch, including 22 (88.0%) who maintained ≥CR
- 1 (3.7%) patient had PD* and 1 (3.7%) patient permanently discontinued elranatamab 6 months after the switch to Q4W

Figure. DOR



No. at risk														
Pts with OR	75	70	65	57	50	45	41	39	37	32	27	11	1	0
Pts with ≥CR	46	46	46	43	40	36	35	35	33	28	23	11	1	0
Pts with ≥VGPR	69	67	62	55	49	44	41	39	37	32	27	11	1	0

*Per IMWG criteria in ≥1 assessment.
BICR = blinded-independent central review; CI = confidence interval; CR = complete response; DOR = duration of response; IMWG = International Myeloma Working Group; MRD = minimal residual disease; NE = not evaluable; NR = not reached; OR = objective response; ORR = objective response rate; PD = progressive disease; PR = partial response; Q4W = once every 4 weeks; sCR = stringent complete response; VGPR = very good partial response.

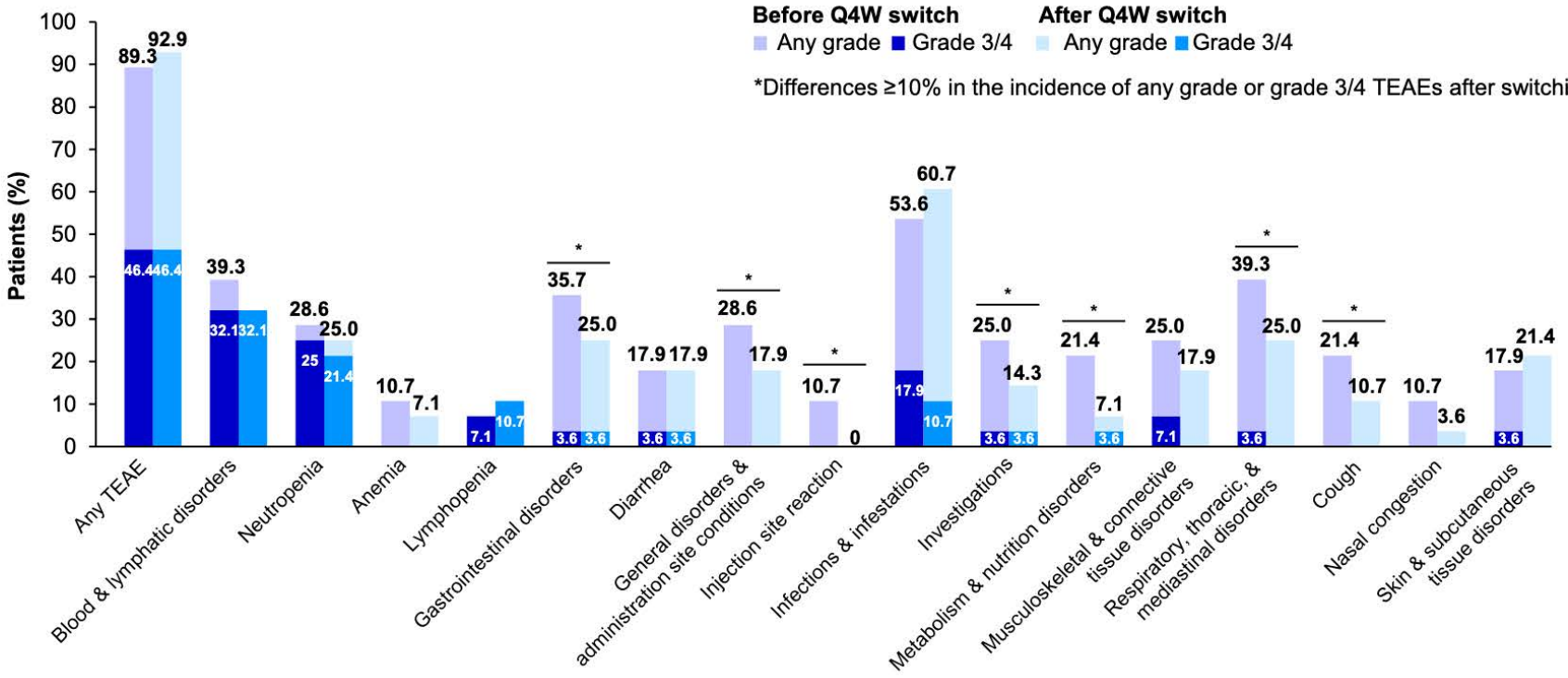
Prince HM et al. Poster presentation at ASH 2024 (Abstract 4738).

MagnetisMM-3: Most Common TEAEs Before and After Switch to Q4W Dosing

Safety

- No new safety signals were observed with extended follow-up
  - Infections: any grade, 70.7%; grade 3/4, 41.5%; grade 5, 7.3%
  - CRS: 57.7%
  - ICANS: 4.9%
- There were 3 new deaths with an additional ~6 months of follow-up since the last report,[1] with 1 each due to PD, treatment toxicity, and unknown reason
- The incidence and severity TEAEs up to 6 months before and after switching to Q4W dosing are presented in the **Figure**

Figure. Most Common TEAEs Before and After Switch to Q4W Dosing†



†TEAEs occurring in ≥20% of patients at the level of SOC and in ≥10% of patients at the level of PT up to 6 months before or after switching to Q2W.
CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; PD = progressive disease; PT = preferred term; Q4W = once every 4 weeks; SOC = system organ class; TEAE = treatment-emergent adverse event.

1. Mohty M et al. Presentation at EHA 2024 (Poster P932).
Prince HM et al. Poster presentation at ASH 2024 (Abstract 4738).

Bispecific Antibodies With Other Targets

Parameter	Talquetamab*			Cevostamab†
Target	GPCR5D			FcHR5
Patients (n)	MonumenTAL-1 Study			161
	0.4 mg/kg SC QW TCR naive (143)	0.8 mg/kg SC Q2W TCR naive (145)	Prior TCR (51)	
ORR, %	74.1	71.7	64.7	57 (higher doses)
Median PFS, mos	7.5	14.2	5.1	--
12 mo OS, %	76	77	63	--
CRS, any (grade ≥3), %	79 (2)	75 (1)	77 (2)	81
ICANS, %	11	11	3	14
Infection, any (grade ≥3), %	59 (20)	66 (15)	73 (28)	43 (19)

Unique Toxicities with GPRC5D:

- Skin and nail: rash, dryness, brittle, nail loss
- Dysgeusia, dry mouth, stomatitis
- Appetite loss and weight loss
- Emerging: neurologic toxicity; dysarthria, dizziness, balance abnl

*Approved by the FDA in August 2023 for adults with R/R MM after ≥4 prior lines of therapy, including a PI, an immunomodulatory agent, and an anti-CD38 mAb †Investigational

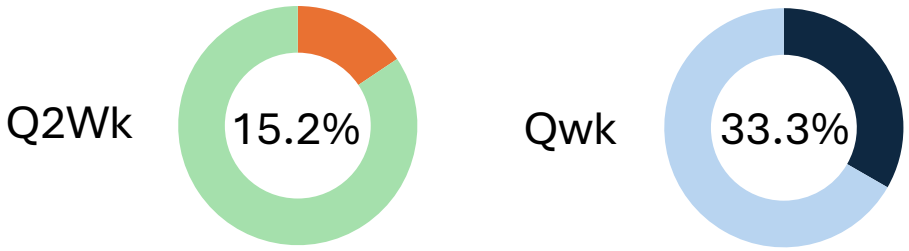
Schinke. ASCO 2023. Abstr 8036. Trudel. ASH 2021. Abstr 157.

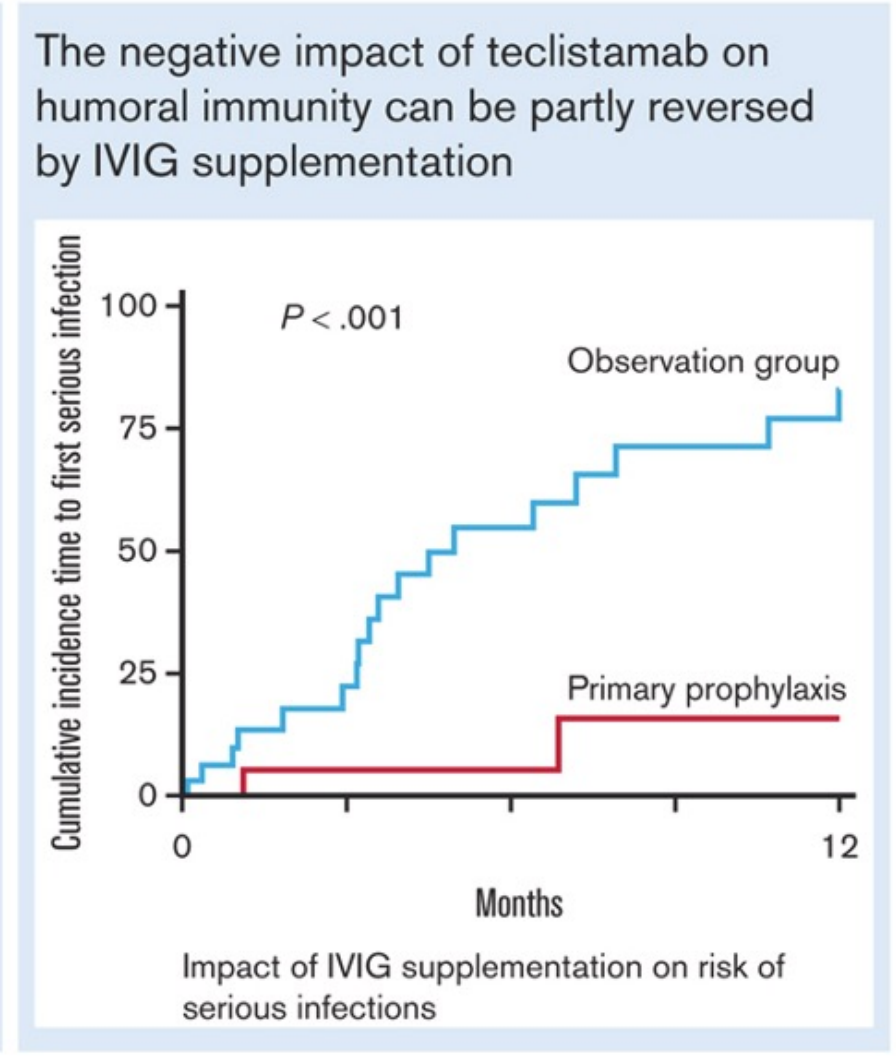
Treatment of Infections

- Infection ➔Bispecific (BCMA >GPRC5D)
  - ACV - throughout treatment *(+3m)*
  - PJP – throughout treatment (+*3m*)
  - Anti-Bact/anti-fungal prn
  - IVIG – while on therapy/until >400

  - Lower infection rates over time have been noted with less frequent dosing

New-onset grade ≥3 infections at 1–1.5 years[1]



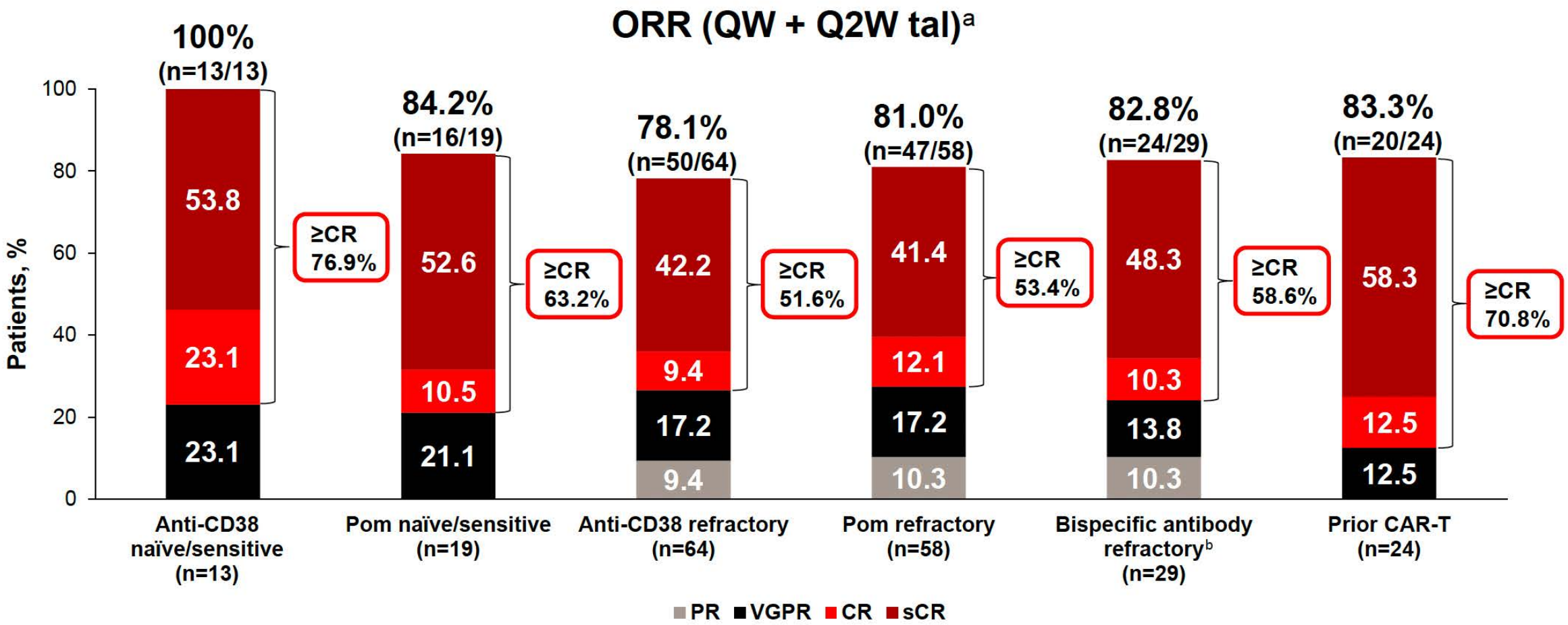


General trend has been for PRIMARY prophylaxis with IVIG (don't wait for infection) especially with BiAbs

- Even in IgG MM with IgG levels >1000mg/dL

Frerich KA et al. Blood Adv 2023, Rodriquez-Otero P et al Lancet Oncology 2024;

TRIMM-2 Tal + Dara + Pom Cohort: High ORRs in Prior Exposure Subgroups

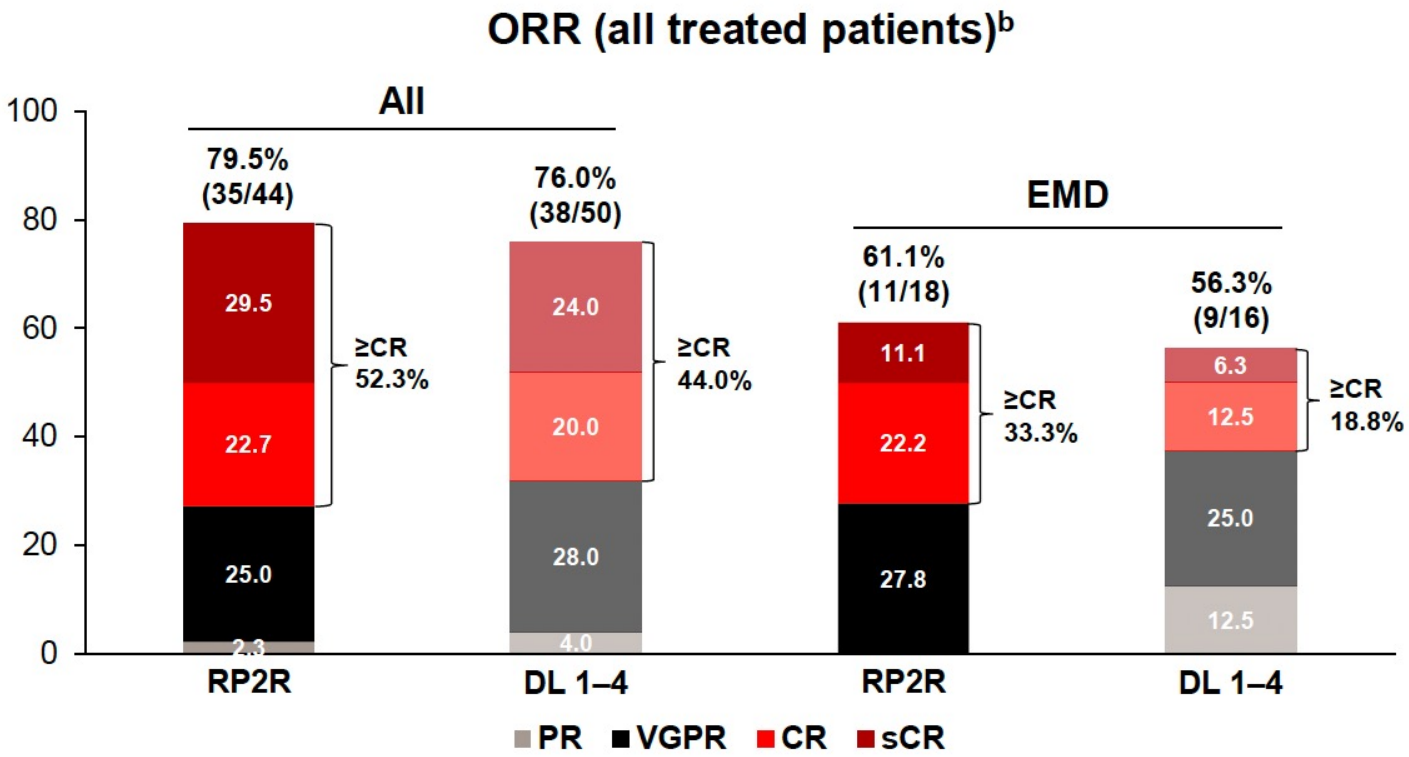


Data cut-off: July 29, 2024.

Anti-CD38 naïve = never received anti-CD38 therapy; anti-CD38 sensitive = minimal response or better during treatment; anti-CD38 refractory = best response of SD or PD during treatment or within 60 days of completing anti-CD38 therapy. [a]Response was assessed by investigators, based on IMWG criteria. Percentages are calculated with the number of patients in each group as denominator. [b]All 29 patients who received prior bispecific antibody therapy were refractory. CAR, chimeric antigen receptor; CR, complete response; dara, daratumumab; IMWG, International Myeloma Working Group; ORR, overall response rate; pom, pomalidomide; PD, progressive disease; PR, partial response; Q2W, every other week; QW, weekly; sCR, stringent complete response; SD, stable disease; tal, talquetamab; VGPR, very good partial response.

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

RedirecTT-1 Tal + Tec: High ORR and Deep Responses, Including in EMD[a]



All patients	RP2R (n=44)	DL 1–4 (n=50)
Median (range) follow-up, months	18.2 (0.7–27.0)	29.0 (0.5[c]–37.1)
Median (range) time to first response, months	1.4 (0.3–5.1)	2.1 (1.1–7.7)
Median (range) time to best response, months	4.9 (1.4–19.8)	4.9 (1.1–30.6)

Patients with EMD	RP2R (n=18)	DL 1–4 (n=16)
Median (range) follow-up, months	13.6 (0.7–25.9)	18.7 (0.5[c]–33.8)
Median (range) time to first response, months	3.0 (1.4–5.1)	2.6 (2.1–3.8)
Median (range) time to best response, months	6.3 (3.0–10.7)	3.9 (2.1–10.7)

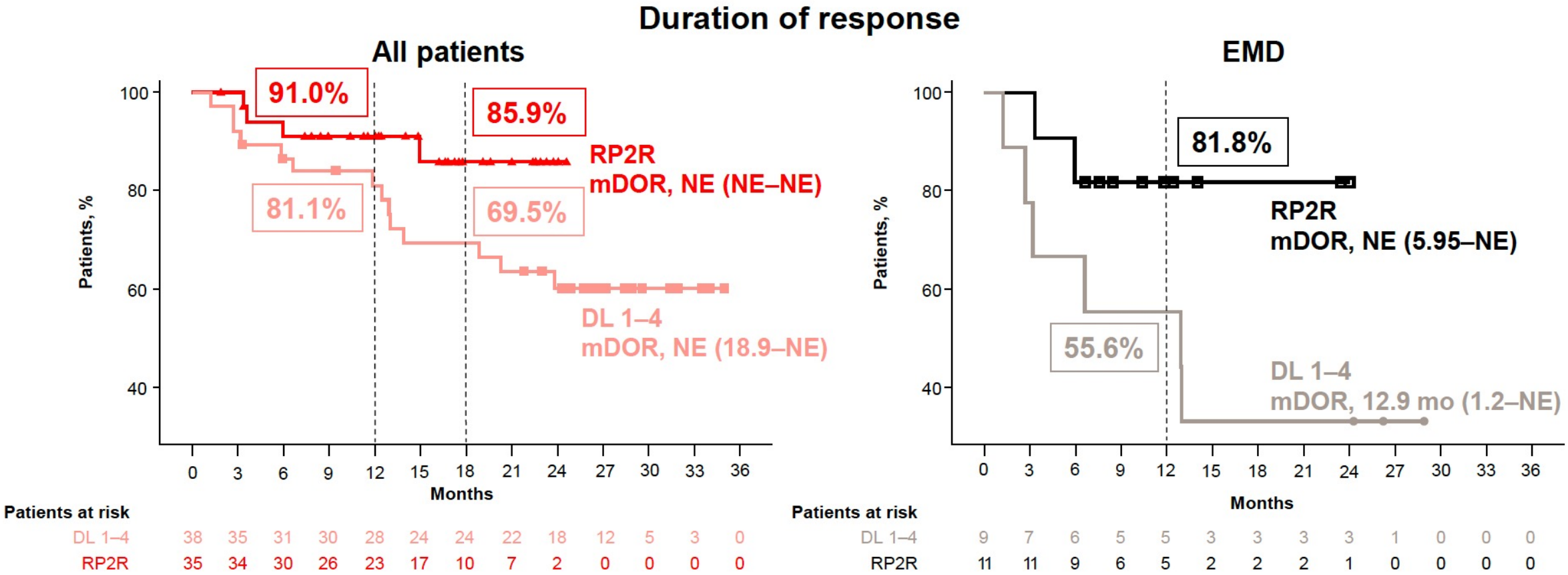
ORR 79.5% (61.1% in EMD) at RP2R with rapid and deep responses

Data cut-off date: March 15, 2024.

[a]EMD defined as ≥1 nonradiated, bone-independent lesion ≥2 cm. [b]Responses were investigator-assessed per IMWG 2016 criteria. Data shown are confirmed responses and calculated in all treated patients. [c]Denotes patients who died. CR, complete response; DL, dose level; EMD, extramedullary disease; IMWG, International Myeloma Working Group; ORR, overall response rate; PR, partial response; RP2R, recommended phase 2 regimen; sCR, stringent complete response; tal, talquetamab; tec, teclistamab; VGPR, very good partial response.

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

RedirecTT-1 Tal + Tec: Highly Durable Responses, Including in EMD[a]



18-mo DOR of 85.9% at RP2R (81.8% 12-mo rate in EMD)

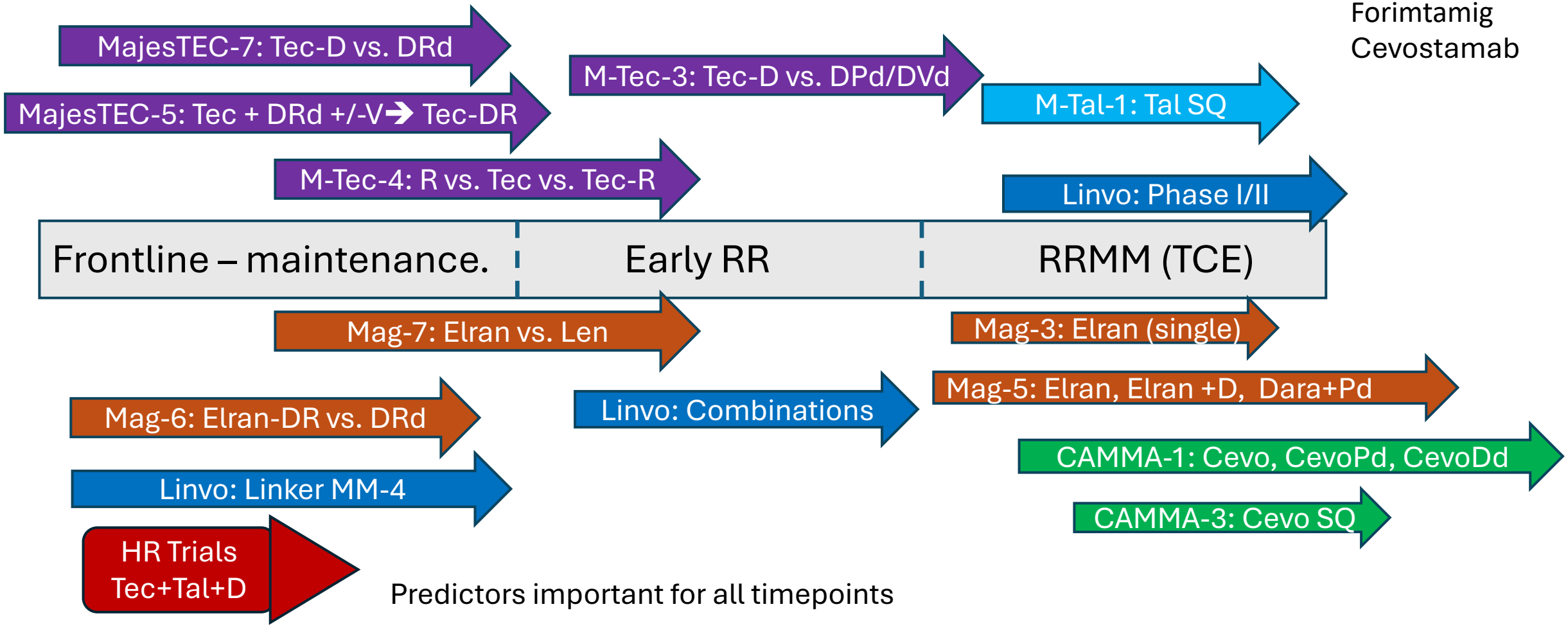
Data cut-off date: March 15, 2024. Median follow-up: 18.2 months (RP2R) and 29.0 months (dose levels 1–4). **Eighteen-month DOR rate at the RP2R was 81.8% in EMD patients.** [a]EMD defined as ≥1 nonradiated, bone-independent lesion ≥2 cm. DL, dose level; EMD, extramedullary disease; mDOR, median duration of response; NE, not evaluable; RP2R, recommended phase 2 regimen; tal, talquetamab; tec, teclistamab.

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

Immunotherapy Bispecific Trials

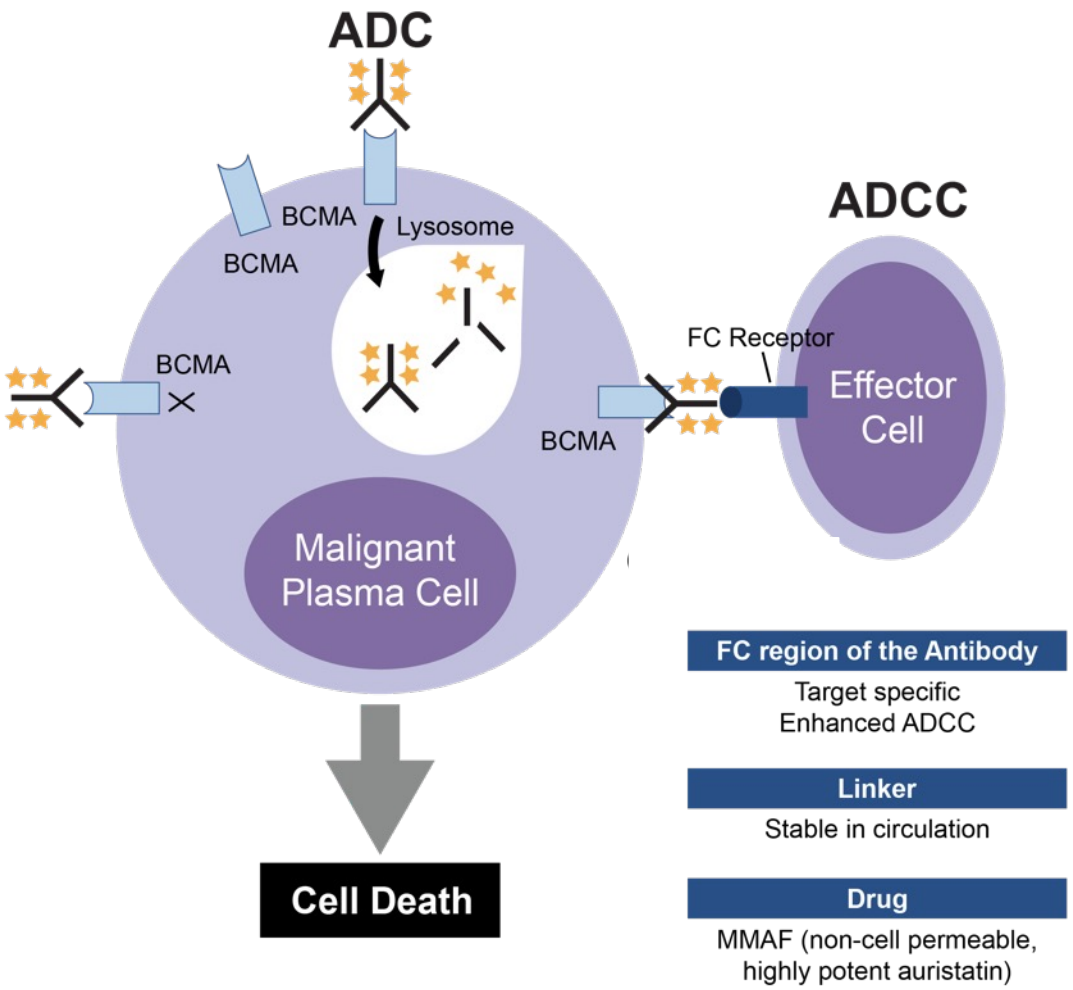
Current and planned (not inclusive of all trials)

- Myeloma Treatment Paradigm



BCMA
Teclistamab
Elranatamab
Linvoseltamab
ABBV-383
Non-BCMA
Talquetamab
Forimtamig
Cevostamab

BCMA: Antibody-drug conjugate (ADC) - Belantamab



- Belantamab mafodotin is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to monomethyl auristatin (MMAF)
- FDA approved for patients previously treated with 4 ***prior therapies*** then withdrawn due to failed P3 trial B vs. Pd.

- DREAMM-7 – Phase 3: 494 patients
  - Randomized: BVd vs. DVd – RRMM 1-3 PLT
- DREAMM-8 – Phase 3:
  - Randomized P3: BPd vs. PVd

Single agent activity in RRMM => ORR 32%

- **Comeback-Kid of the year!!**

DREAMM-7: **BVd**

- Improved
  - ORR
  - CR
  - ≥ VGPR

DREAMM-7: deeper responses with BVd vs DVd[a]

≥ CR MRD negativity[b]:

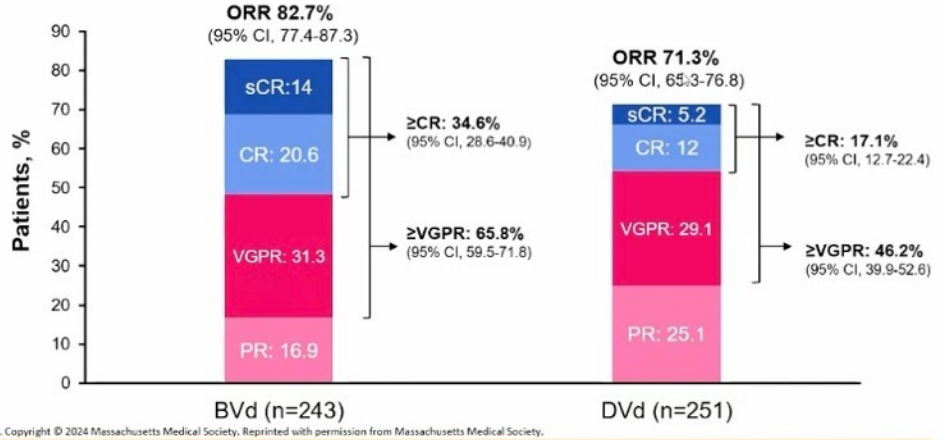
24.7% vs 9.6%

(95% CI, 19.4-30.6) (95% CI, 6.2-13.9)

≥ VGPR MRD negativity[b]:

38.7% vs 17.1%

(95% CI, 32.5-45.1) (95% CI, 12.7-22.4)



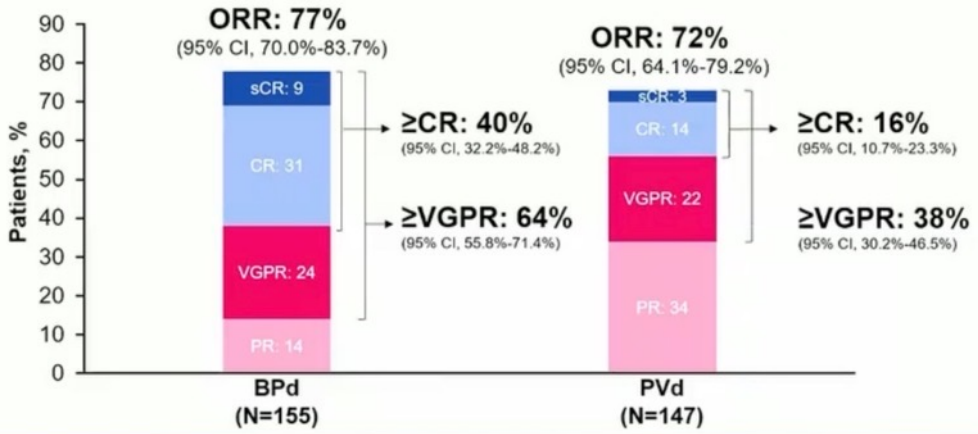
BVd was associated with a greater depth of response with double the ≥CR rate and more than double the MRD negativity rates (sensitivity of 10^{-5}) of DVd (*P* value <.00001)[c]

, complete response; DVd, daratumumab, bortezomib, and dexamethasone; ITT, intent to treat; MRD, minimal residual disease; NGS, next-
national Staging System; sCR, stringent complete response; VGPR, very good partial response.
ulation were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b]MRD negativity
e by NGS based on a sensitivity of 10^{-5}. [c]Nominal *P* value. Cochran–Mantel–Haenszel test was used and adjusted for stratification factors,
ortezomib, and R-ISS stage at screening (I vs II or III).

9

DREAMM-8 | Belantamab Mafodotin + Pd

Deeper Responses With BPd vs PVd



The CR or better rate in the BPd arm was more than twice that in the PVd arm

CIs were based on the exact method. All percents are based on the ITT population.
BPd, belamaf, pomalidomide, and dexamethasone; CR, complete response; ITT, intent to treat; ORR, objective response rate; PR, partial response; PVd, pomalidomide, bortezomib, and dexamethasone; sCR, stringent complete response; VGPR, very good partial response.

13

DREAMM-7: **BPd**

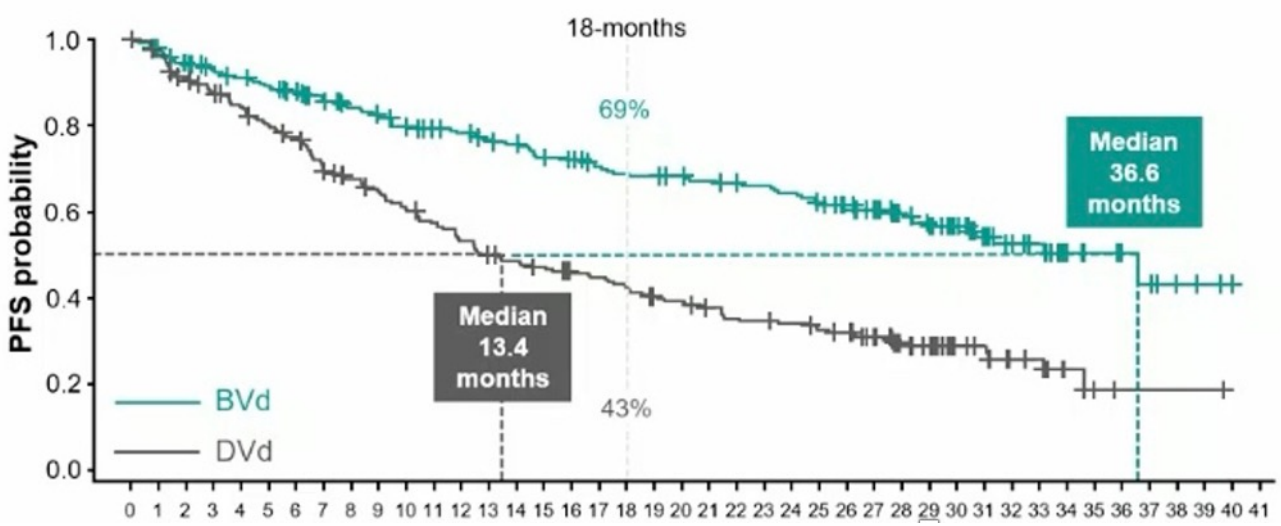
- Improved
  - ORR
  - CR
  - ≥ VGPR

Both DREAMM-7 and -8 Show Significant PFS Benefit – No Blurriness Here

DREAMM

7

Mateous et al.
EHA2024

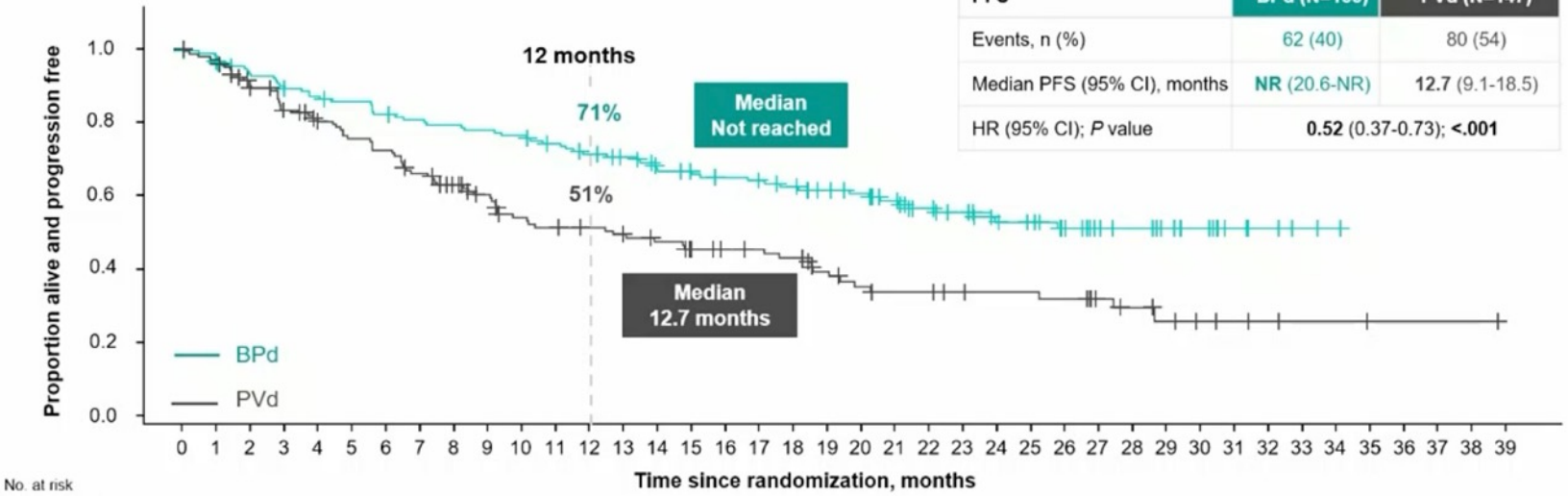


PFS[a]	BVd (N=243)	DVd (N=251)
Events, n (%)	91 (37)	158 (63)
PFS, median (95% CI),[b] months	36.6 (28.4-NR)	13.4 (11.1-17.5)
HR[c] (95% CI)	0.41 (0.31-0.53)	
P value[d]	<.00001	

Dimopoulos et al.
EHA2024

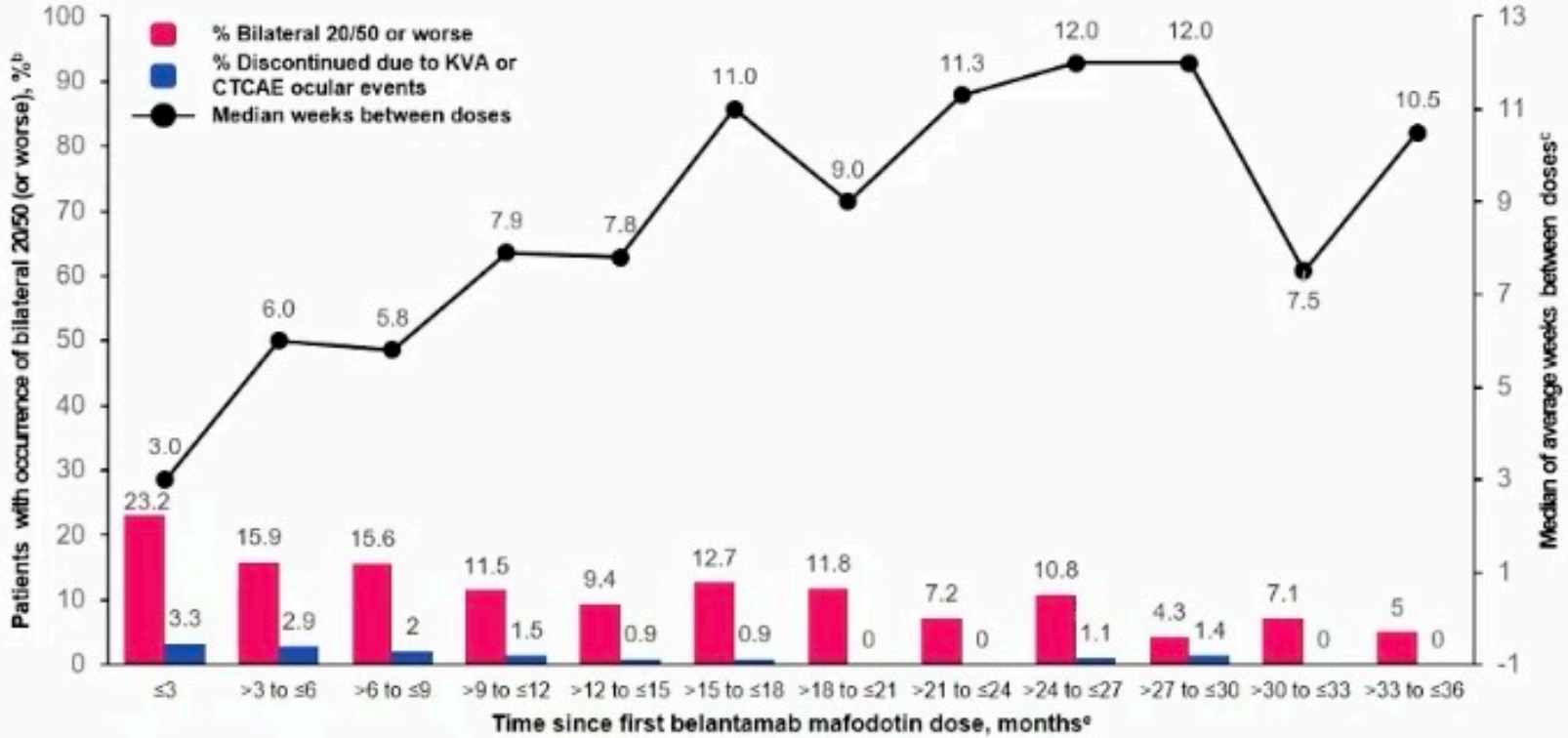
8

Significant PFS Benefit with BPd vs PVd



PFS	BPd (N=155)	PVd (N=147)
Events, n (%)	62 (40)	80 (54)
Median PFS (95% CI), months	NR (20.6-NR)	12.7 (9.1-18.5)
HR (95% CI); *P* value	0.52 (0.37-0.73); <.001	

DREAMM-7: impact of dose modifications on PFS and ocular management[a]



	≤3	>3 to ≤6	>6 to ≤9	>9 to ≤12	>12 to ≤15	>15 to ≤18	>18 to ≤21	>21 to ≤24	>24 to ≤27	>27 to ≤30	>30 to ≤33	>33 to ≤36
No. of patients on treatment[e]	211	170	147	131	117	110	102	97	93	69	42	20
No. of patients with bilateral 20/50 or worse	49	27	23	15	11	14	12	7	10	3	3	1
Median days between doses	21	42	41	55	54	77	63	79	84	84	53	74
No. of patients who discontinued due to KVA or ocular CTCAE event	7	5	3	2	1	1	0	0	1	1	0	0

- Median time between doses increased with treatment duration
- **Dose delays did not have a negative impact on PFS[d]**
  - BVd patients with ≥1 dose delay of ≥12 weeks (N= 126), **mPFS 36.6 months**
- 23% of patients experienced 20/50 or worse events in first 3 months; prevalence decreased thereafter
- Rate of treatment discontinuation due to ocular events were low

CTCAE, Common Terminology Criteria for Adverse Events; KVA, Keratopathy and Visual Acuity scale; mPFS, median progression-free survival; PFS, progression-free survival; PD, progressive disease.
[a] Only belantamab mafodotin treatment period considered in these post hoc analyses. [b] Only patients with 20/25 or better in either or both eyes at baseline are considered. [c] Mean of days between doses, for each patient, per interval is used. [d] Only patients receiving ≥6 months of treatment included in analysis to exclude early discontinuations (eg, rapid PDs). [e] Graph is truncated at 36 months because the data beyond 36 months represented a low number of patients on treatment (>36 to ≤39 months, n=8 and >39 to ≤42 months, n=3).

Summary

- CAR-T therapy and bispecifics: Unprecedented response rates/PFS in triple class refractory MM.
- CRS and ICANS are manageable.
- Cytopenias and infections are common, can be long term in a subset of patients.
- Delayed neurotoxicity can occur with both CARS and Bispecifics (BCMA and GPRC5D)
- BCMA ADC – in combination data very promising
- Selecting which therapy, when and Sequencing are key questions
- New unmet need: Relapse after BCMA therapies. Non-BCMA targets have shown promising activity.

Discussion Questions

- Regulatory and reimbursement issues aside, what do you currently believe is the optimal point at which CAR T-cell therapy should be administered for patients with high-risk MM? What about for patients with lower-risk disease?

- Based on your personal clinical experience and knowledge of available data, how would you compare the global efficacy and tolerability and complications of idecabtagene vicleucel to that of ciltacabtagene autoleucel for R/R MM?

Discussion Questions

- In general, when administering a bispecific antibody to a patient with relapsed/refractory MM, what is your preferred agent? How does prior therapy impact your choice?

- How would you indirectly compare the efficacy and tolerability of the available bispecific antibodies? Which adverse events are commonly observed in patients receiving talquetamab but NOT in those receiving BCMA-targeted bispecific antibodies, such as teclistamab or elranatamab?

Discussion Questions

- Based on recent data, if belantamab mafodotin becomes available, to which patients with MM would you like to administer it? What agent(s) would you partner it with?

- Based on available data and your personal clinical experience, do you believe that belantamab mafodotin is as efficacious in patients with relapsed/refractory MM who have received a BCMA-targeted bispecific antibody or CAR T-cell therapy as those who have not?

Module 13: Hepatocellular Carcinoma

Current Treatment for Advanced Hepatocellular Carcinoma (HCC) — Dr Abrams

Promising Novel Approaches to HCC Management — Dr Kaseb

Module 13: Hepatocellular Carcinoma

Current Treatment for Advanced Hepatocellular Carcinoma (HCC) — Dr Abrams

Promising Novel Approaches to HCC Management — Dr Kaseb

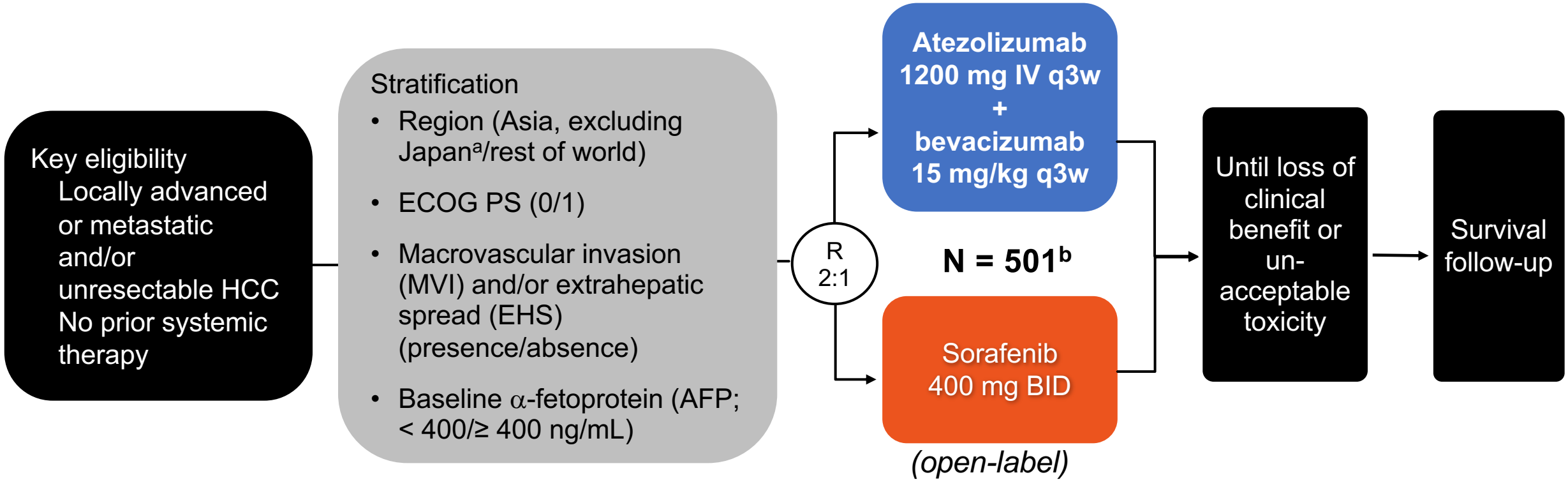
Current Treatment for Advanced Hepatocellular Carcinoma (HCC)

Thomas Abrams, MD
Institute Physician, Dana-Farber Cancer Institute
Asst. Professor, Harvard Medical School

Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Eisai Inc, HistoSonics
Consulting Agreements	Elevar Therapeutics
Contracted Research	AstraZeneca Pharmaceuticals LP

IMbrave150 study design

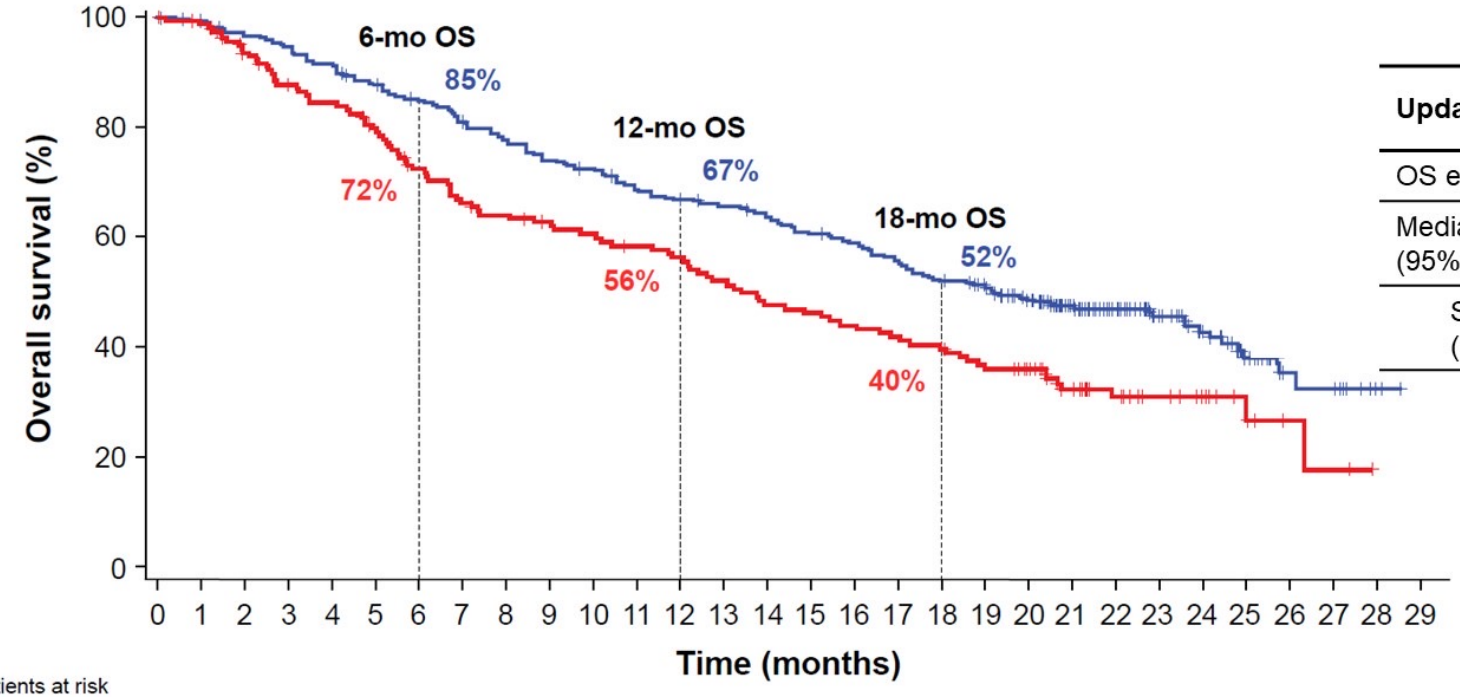


Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

Updated OS



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

No. of patients at risk

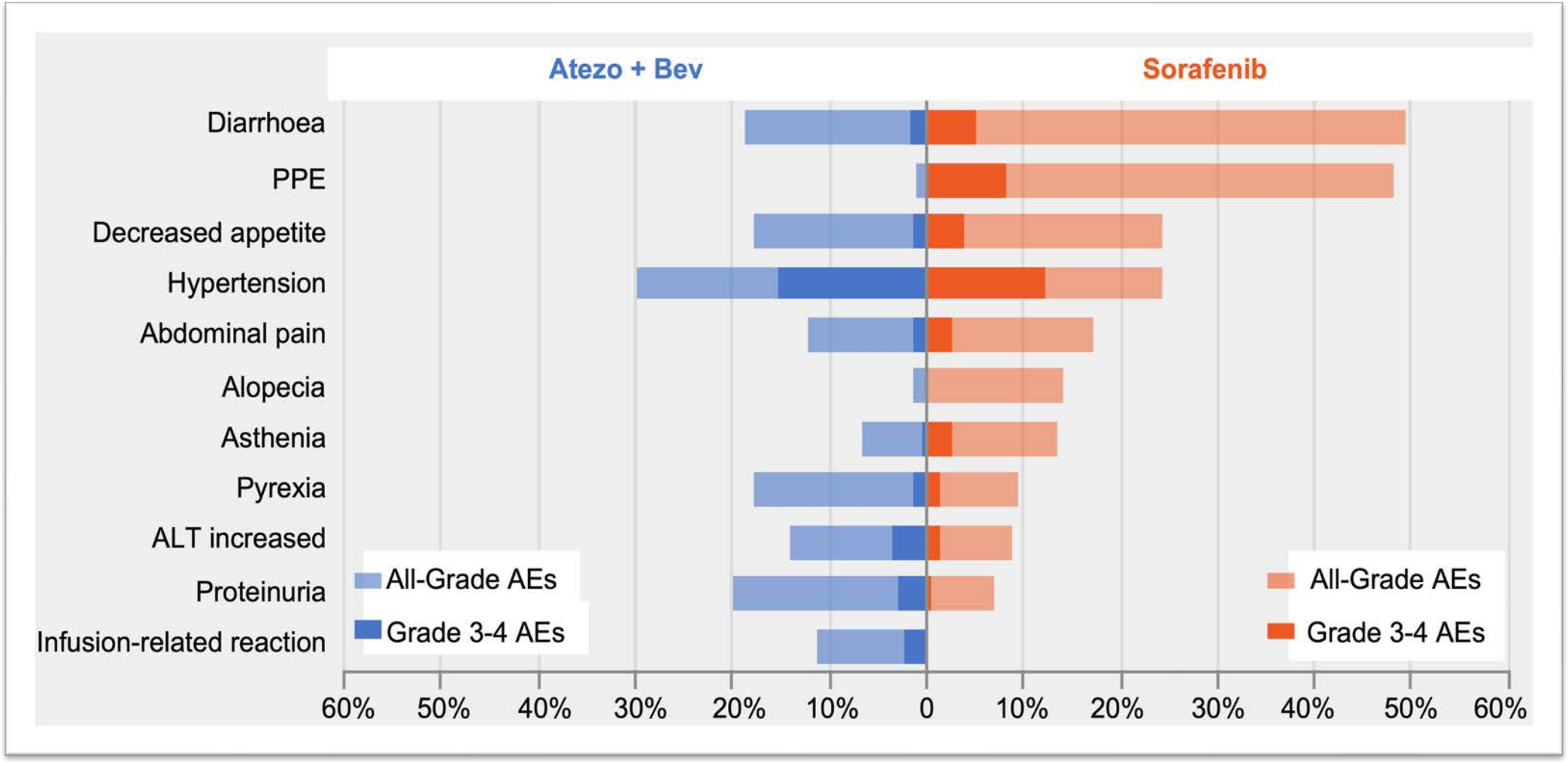
Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

Safety

≥ 10% frequency of AEs in either arm and > 5% difference between arms



Finn R et al. N Engl J Med 2020; 382:1894-1905

HIMALAYA study design

HIMALAYA was an open-label, multicenter, global, Phase 3 trial

Study population
- Patients with confirmed uHCC
- BCLC B (not eligible for locoregional therapy) and C
- No prior systemic therapy
- ECOG PS 0–1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

Stratification factors
- Macrovascular invasion: Y / N
- Etiology of liver disease: HBV / HCV / others
- Performance status: ECOG 0 / 1

R
N=1324

T300+D (n=393):
Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W*

Durvalumab (n=389):
Durvalumab monotherapy 1500 mg Q4W*

Sorafenib (n=389):
Sorafenib 400 mg BID*

T75+D (n=153): *arm closed* †
Tremelimumab 75 mg Q4W × 4 doses + durvalumab Q4W*

Primary objective
- OS for T300+D vs sorafenib

Key secondary objective
- OS for durvalumab vs sorafenib

Additional secondary objectives
- PFS, ORR, and DoR as assessed by investigator per RECIST v1.1
- Safety

Multiple testing procedure

OS *superiority* for T300+D vs sorafenib

↓

OS *noninferiority* for durvalumab vs sorafenib
Noninferiority margin: 1.08

↓

OS *superiority* for durvalumab vs sorafenib

*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks.

Tumor response

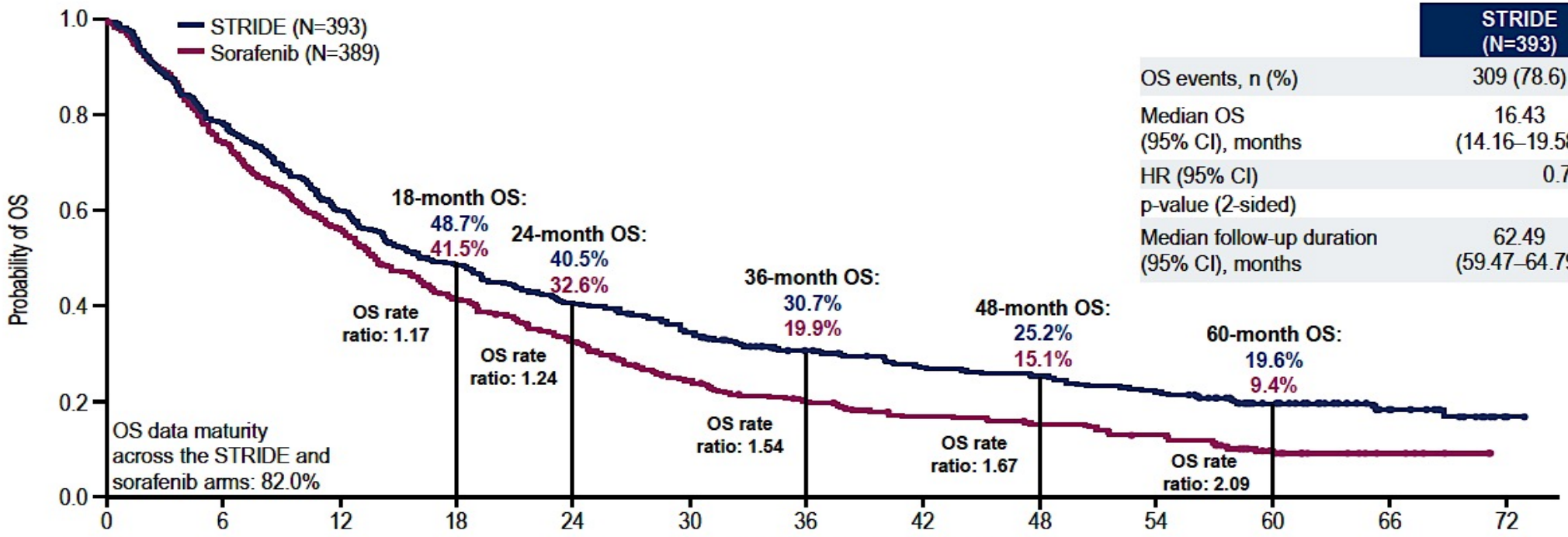
	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* n (%)	**79 (20.1)**	**66 (17.0)**	**20 (5.1)**
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months 25th percentile 75th percentile	22.34 8.54 NR	16.82 7.43 NR	18.43 6.51 25.99
Median TTR (95% CI), months	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response,‡ % 6 months 12 months	 82.3 65.8	 81.8 57.8	 78.9 63.2

*By investigator assessment according to RECIST v1.1. Responses are confirmed. †Defined as neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD. ‡Calculated using Kaplan-Meier technique.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTR, time to response.

Five-year updated OS for STRIDE versus sorafenib

STRIDE demonstrated a sustained OS benefit versus sorafenib, with OS rates of 19.6% versus 9.4% at 5 years and the OS rate ratios for STRIDE versus sorafenib increasing over time



	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	309 (78.6)	332 (85.3)
Median OS (95% CI), months	16.43 (14.16–19.58)	13.77 (12.25–16.13)
HR (95% CI)	0.76 (0.65–0.89)	
p-value (2-sided)	0.0008	
Median follow-up duration (95% CI), months	62.49 (59.47–64.79)	59.86 (58.32–61.54)

No. of participants at risk

STRIDE:	393	308	235	190	158	131	104	89	83	72	46	20	2
Sorafenib:	389	283	211	155	121	84	66	51	45	37	18	6	0

BARCELONA 2024 ESMO congress

OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. Updated analysis data cut-off: 01 March 2024.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MVI, macrovascular invasion; OS, overall survival; PS, performance status; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

Rimassa L et al. ESMO 2024;Abstract 947MO.

Five-year OS by disease control for STRIDE versus sorafenib

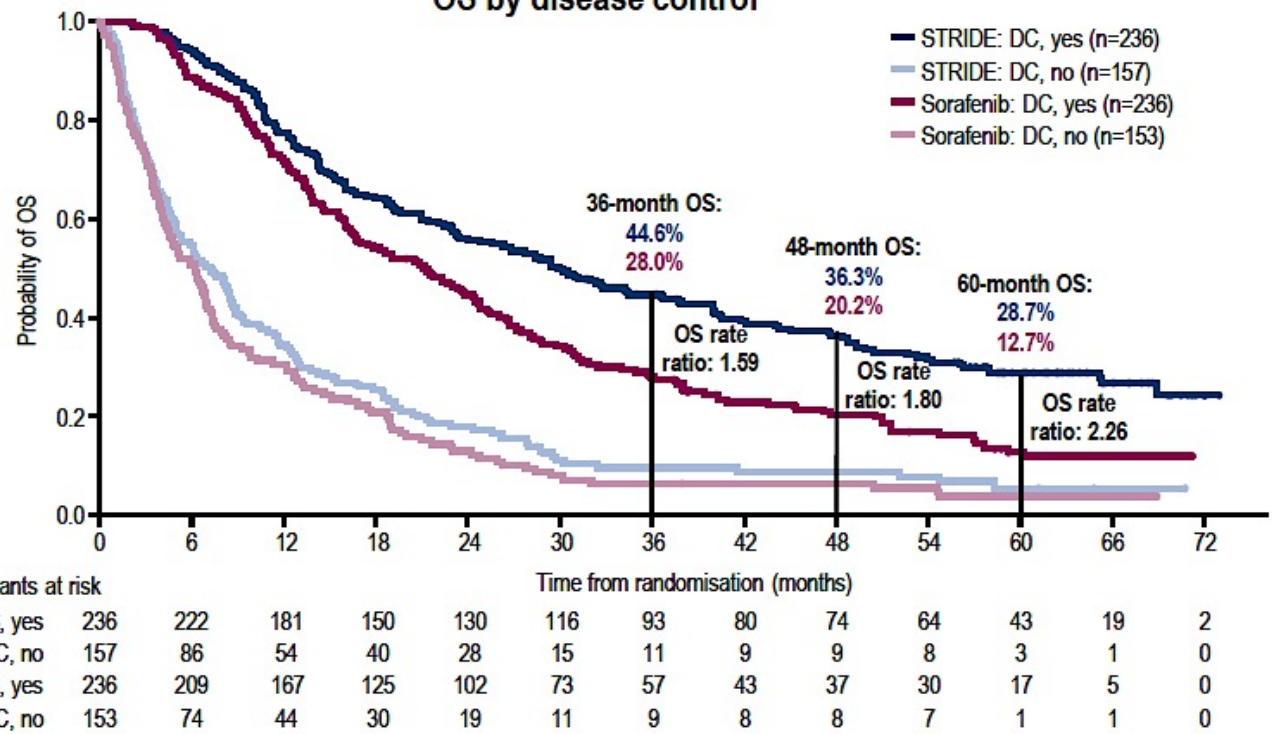
OS benefit with STRIDE was enhanced in participants experiencing disease control per RECIST v1.1, with OS rates of 28.7% for STRIDE and 12.7% for sorafenib at 5-years and the OS rate ratios for STRIDE versus sorafenib increasing over time

Best objective response (RECIST v1.1)

	Full analysis set[1]		eLTS† (≥48 months)	
	STRIDE (n=393)	Sorafenib (n=389)	STRIDE (n=83)	Sorafenib (n=45)
BOR, n (%)				
CR	12 (3.1)	0	10 (12.0)	0
PR	67 (17.0)	20 (5.1)	41 (49.4)	7 (15.6)
SD	157 (39.9)	216 (55.5)	23 (27.7)	30 (66.7)
PD	141 (35.9)	118 (30.3)	8 (9.6)	6 (13.3)
NE	16 (4.1)	35 (9.0)	1 (1.2)	2 (4.4)
Median TTR (IQR), months	2.17 (1.84–3.98)	3.78 (1.89–8.44)	2.10 (1.84–3.94)	5.49 (1.64–11.01)
Median DoR (IQR), months	22.34 (8.54–NR)	18.43 (6.51–25.99)	NR (20.50–NR)	NR (8.31–NR)
DCR*, n (%)	**236 (60.1)**	**236 (60.7)**	**74 (89.2)**	**37 (82.2)**

eLTS included participants regardless of response

OS by disease control*



No. of participants at risk

STRIDE: DC, yes	236	222	181	150	130	116	93	80	74	64	43	19	2
STRIDE: DC, no	157	86	54	40	28	15	11	9	9	8	3	1	0
Sorafenib: DC, yes	236	209	167	125	102	73	57	43	37	30	17	5	0
Sorafenib: DC, no	153	74	44	30	19	11	9	8	8	7	1	1	0

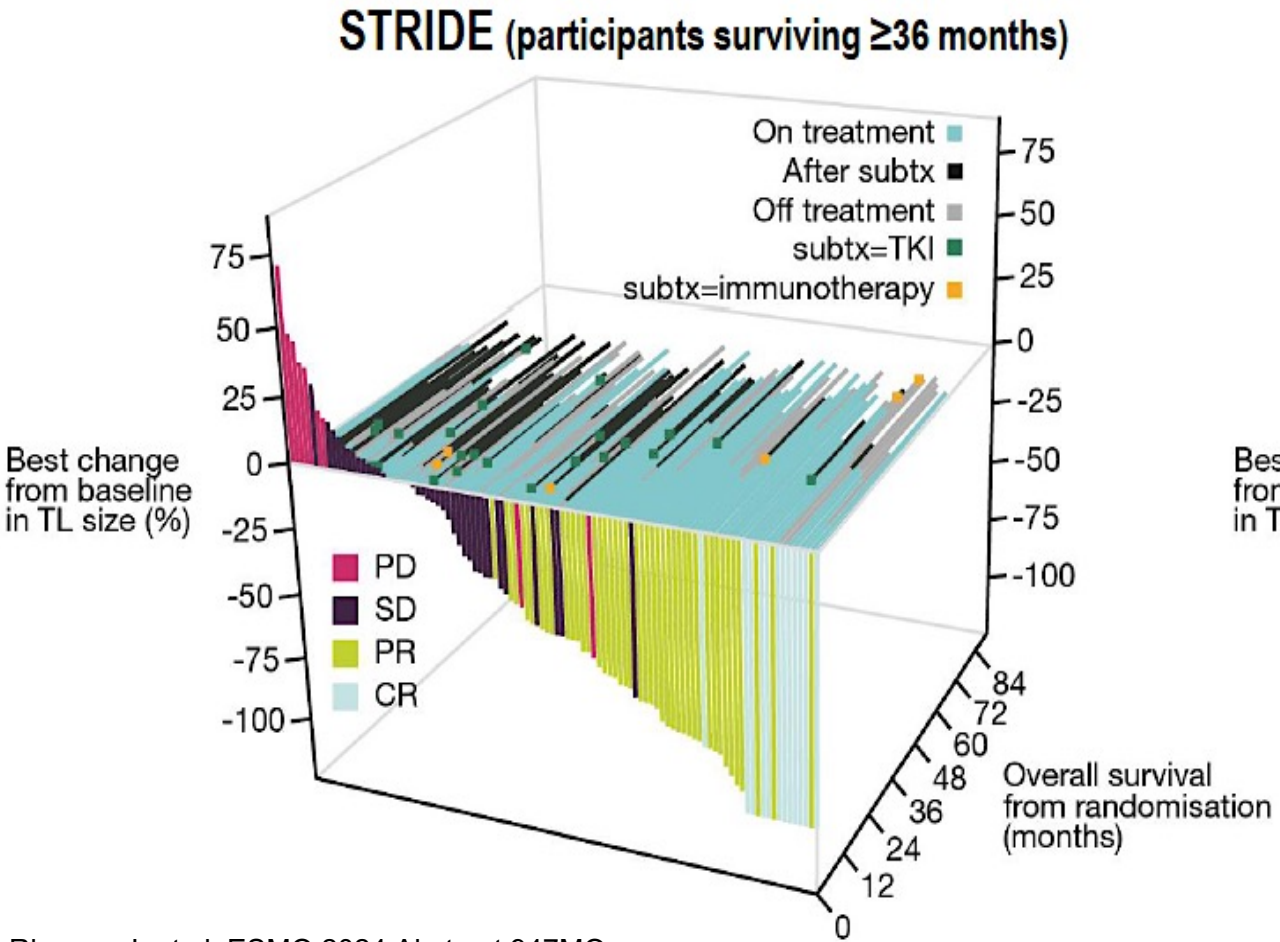
Responses were based on investigator assessment according to RECIST v1.1. Responses were confirmed. Response data for both the full analysis set and eLTS were from the primary analysis (data cut-off: 27 August 2021). Updated analysis data cut-off: 01 March 2024.
*Disease control was defined as CR, PR or SD. †eLTS were defined as participants surviving ≥48 months beyond randomisation.
BOR, best objective response; CR, complete response; DC, disease control; DCR, disease control rate; DoR, duration of response; eLTS, extended long-term survivors; IQR, interquartile range; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TTR, time to response.
1. Abou-Alfa GK, et al. *NEJM Evid* 2022;1(8):EVIDoa2100070.

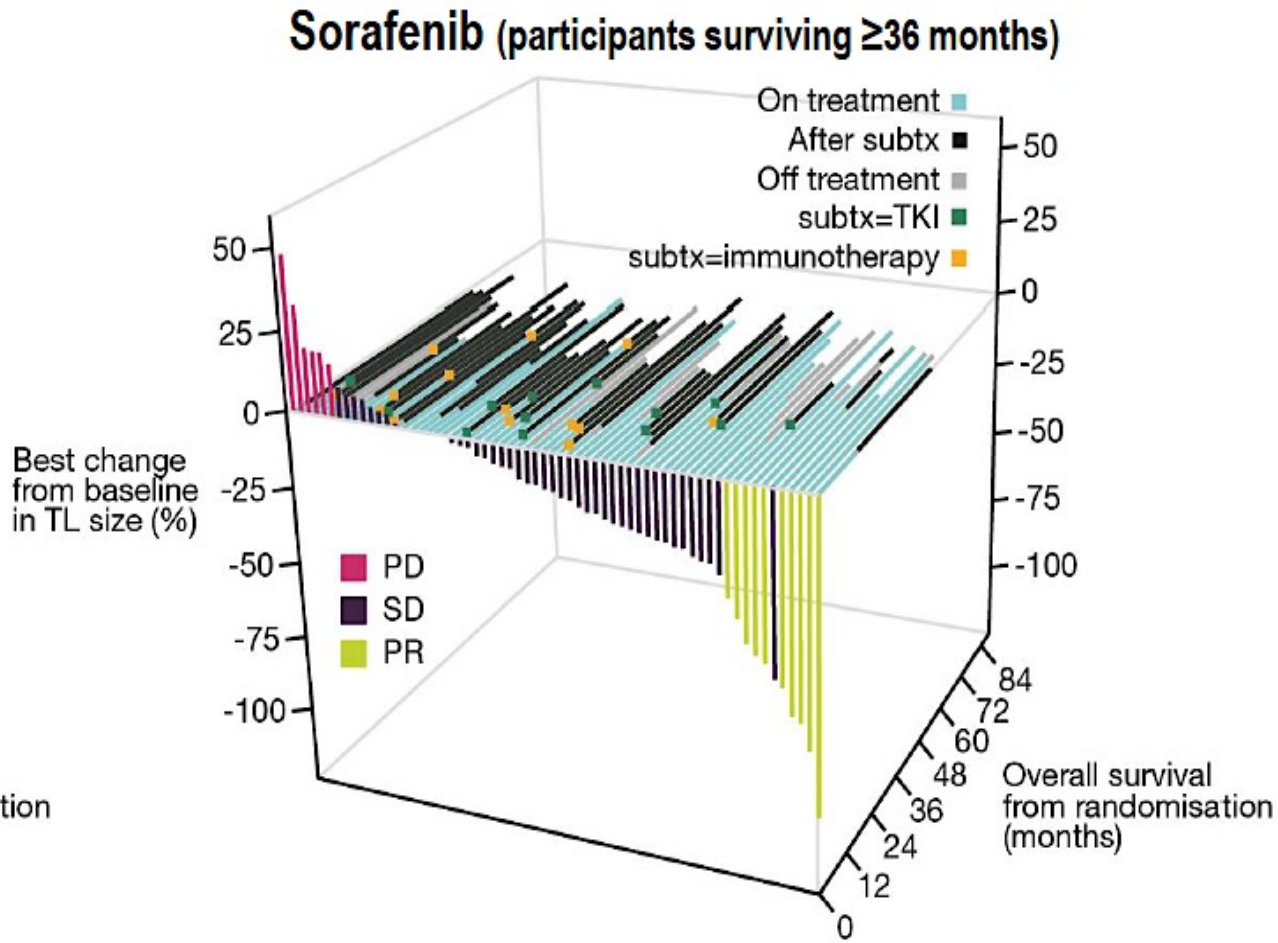
BARCELONA 2024 ESMO congress

Rimassa L et al. ESMO 2024;Abstract 947MO.

Change in target lesion size, subsequent therapy, and OS

More participants treated with STRIDE versus sorafenib were still alive, still on study treatment and fewer received subsequent therapy at 5 years; subsequent therapy was initiated later in participants treated with STRIDE versus sorafenib





Rimassa L et al. ESMO 2024;Abstract 947MO.

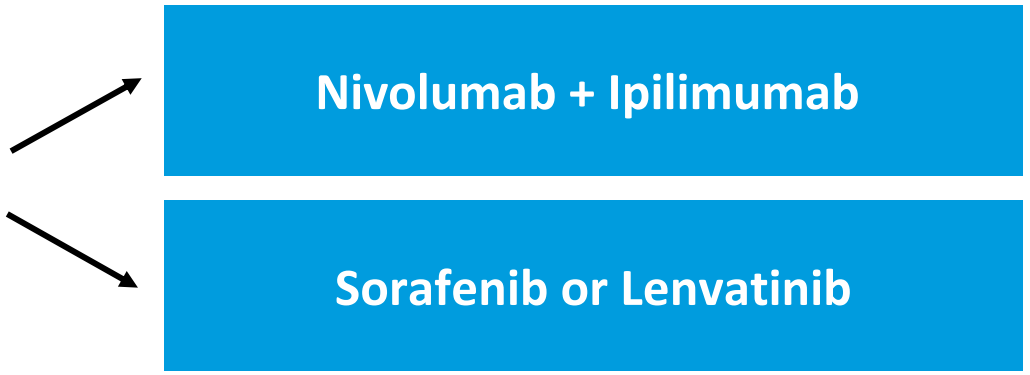
HIMALAYA: immune mediated events

Event, n (%)	STRIDE (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypophysitis	4 (1.0)	0	1 (0.3)	0	1 (0.3)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Thyroiditis	6 (1.5)	0	1 (0.3)	0	2 (0.5)	0	0	0
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0

CheckMate 9DW: Nivolumab + Ipilimumab vs Sorafenib or Lenvatinib as First-Line Treatment for Advanced HCC

- Multicenter, randomized, open-label, phase III trial

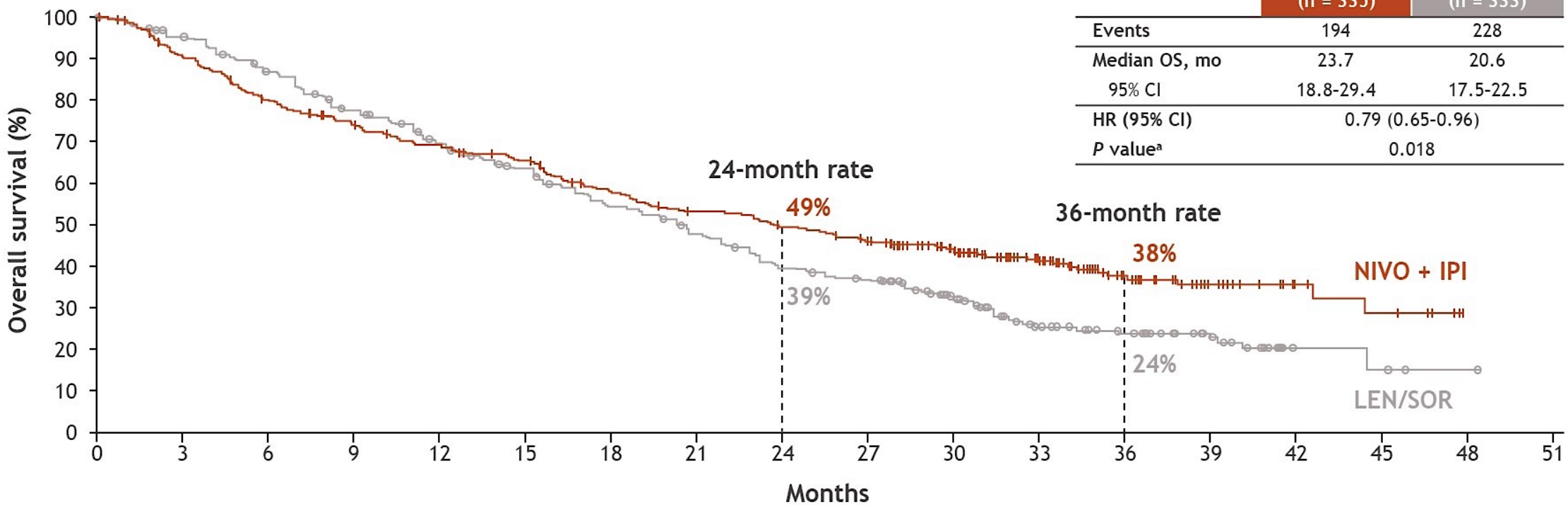
Patients with advanced HCC; no previous systemic therapy,
Child-Pugh 5 or 6;
ECOG PS ≤ 1
(Planned N = 1084)



- Primary endpoint: OS
- Secondary endpoints: ORR, DOR, TTSD

NCT04039607.

Overall survival



	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	194	228
Median OS, mo	23.7	20.6
95% CI	18.8-29.4	17.5-22.5
HR (95% CI)	0.79 (0.65-0.96)	
P value[a]	0.018	

No. at risk																		
NIVO + IPI	335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
LEN/SOR	333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR
  - Longer median OS and long-term survival benefit with higher OS rates at 24 and 36 months

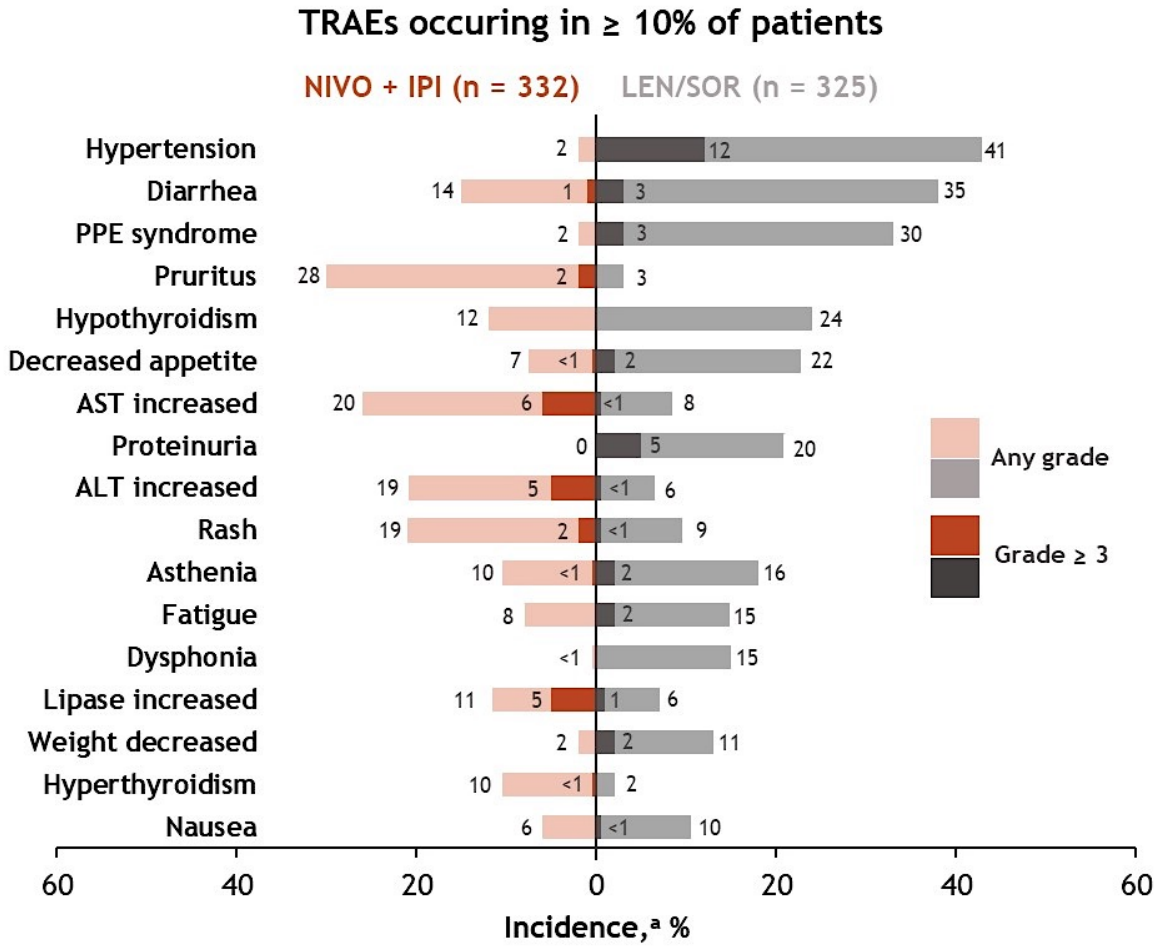
Median (range) follow-up, 35.2 (26.8-48.9) months. Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a]Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0257.

Galle PR et al. ASCO 2024;Abstract LBA4008.

Treatment-related adverse events

All treated patients, n (%)	NIVO + IPI (n = 332)	LEN/SOR (n = 325)
Median (range) duration of treatment, mo	4.7 (< 1 to 24.4)	6.9 (< 1 to 45.8)

All treated patients, n (%)	NIVO + IPI (n = 332)		LEN/SOR (n = 325)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs[a]				
Any TRAEs	278 (84)	137 (41)	297 (91)	138 (42)
Serious TRAEs	94 (28)	83 (25)	47 (14)	42 (13)
TRAEs leading to discontinuation	59 (18)	44 (13)	34 (10)	21 (6)
Treatment-related deaths[b]	12 (4)[c]		3 (< 1)[d]	



[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Treatment-related deaths were reported regardless of time frame. [c]TRAEs leading to death in the NIVO + IPI arm included immune-mediated hepatitis (n = 4), hepatic failure (n = 3), hepatic insufficiency (n = 1), decompensated cirrhosis (n = 1), diarrhea-colitis (n = 1), autoimmune hemolytic anemia (n = 1), and dysautonomia (n = 1). [d]TRAEs leading to death in the LEN/SOR arm included hepatorenal syndrome (n = 1), ischemic stroke (n = 1), and acute kidney injury (n = 1).

Galle PR et al. ASCO 2024;Abstract LBA4008.

Camrelizumab plus rivoceranib vs sorafenib as first-line therapy for unresectable HCC

Key eligibility criteria

- Unresectable or metastatic HCC
- BCLC Stage B (unsuitable for radical surgery and/or locoregional therapy) or C
- No prior systemic therapy
- ECOG PS 0 or 1
- Child-Pugh A
- At least one measurable lesion per RECIST v1.1

N=543 → R

- N=272: **Camrelizumab** 200 mg iv Q2W + **rivoceranib** 250 mg po QD
- N=271: **Sorafenib** 400 mg po BID

Treatment until loss of clinical benefits or intolerable toxicity

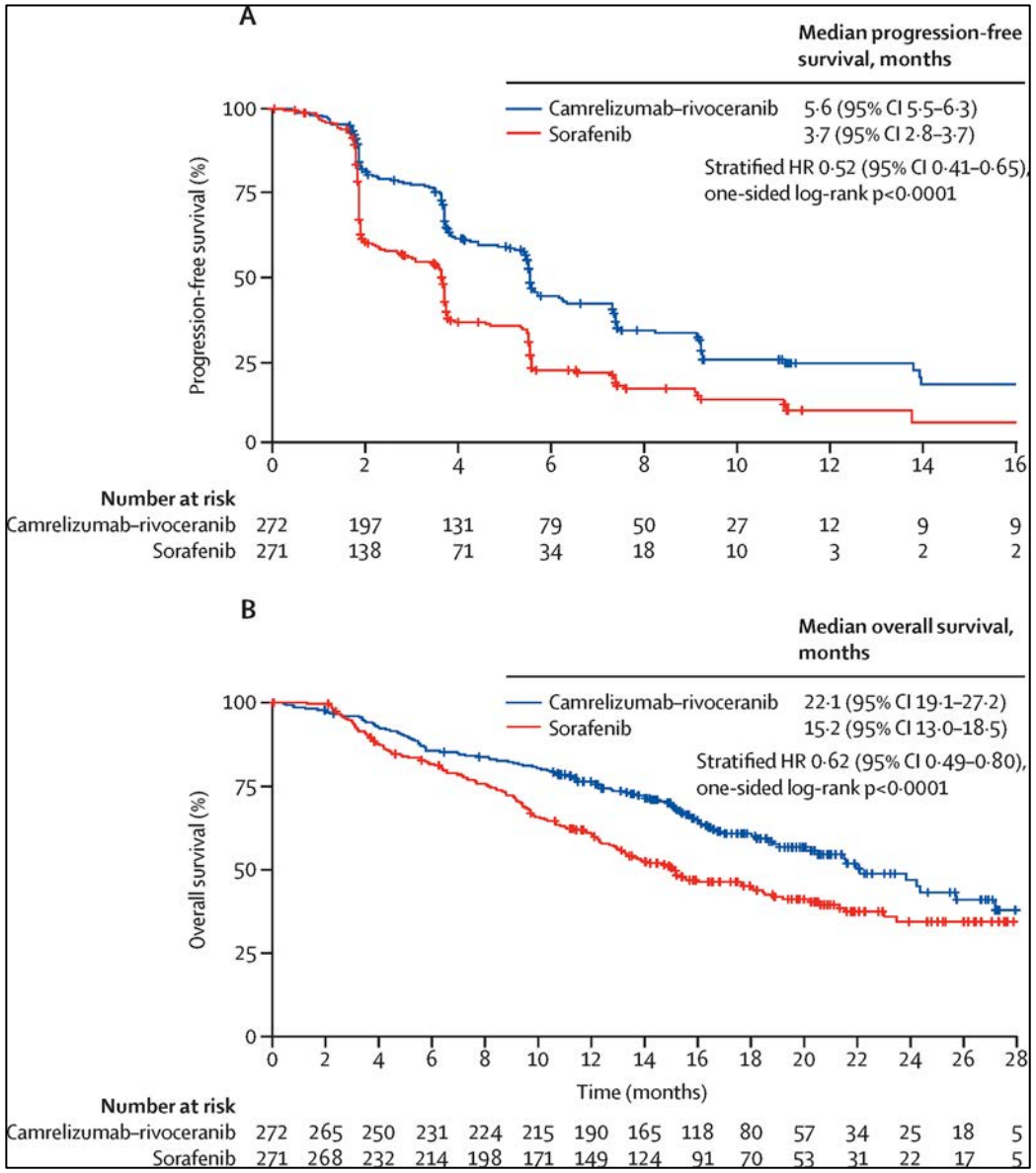
Primary endpoints
- PFS‡
- OS

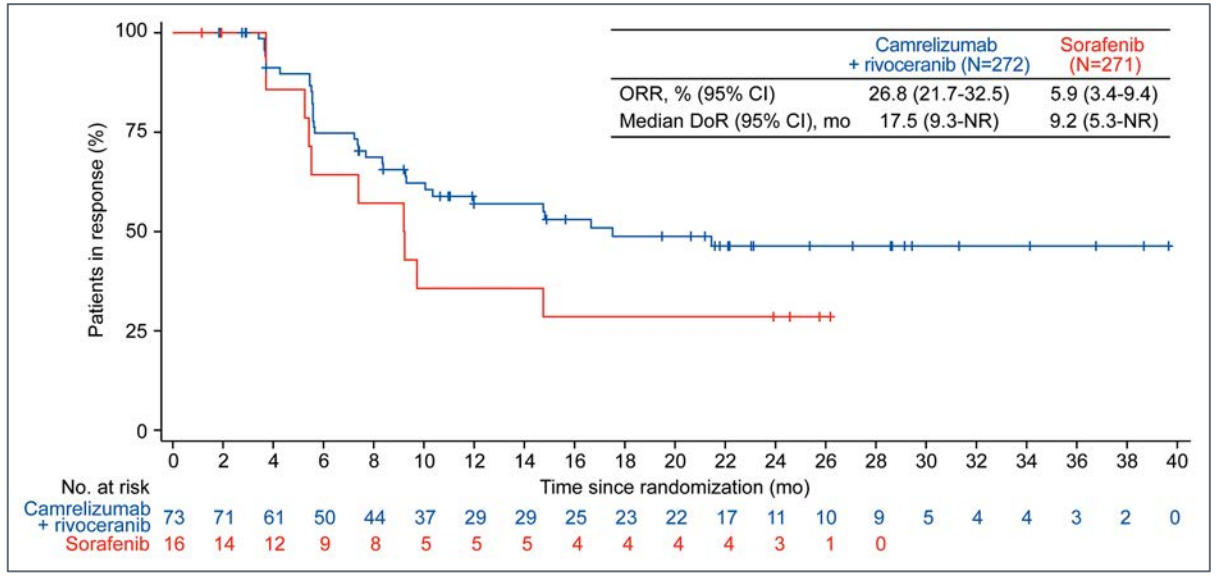
Key secondary endpoint
- ORR‡

	Camrelizumab + rivoceranib (N=272)	Sorafenib (N=271)
Age, years	58 (48-66)	56 (47-64)
Male	227 (83.5)	230 (84.9)
Geographical region		
Asia*	225 (82.7)	224 (82.7)
Non-Asia†	47 (17.3)	47 (17.3)
BCLC stage		
B	38 (14.0)	40 (14.8)
C	234 (86.0)	231 (85.2)
Child-Pugh score		
A (5)	38 (14.0)	40 (14.8)
A (6)	234 (86.0)	231 (85.2)
ECOG PS 1	152 (55.9)	155 (57.2)
AFP ≥400 ng/mL	96 (35.3)	100 (36.9)
MVI and/or EHS	200 (73.5)	200 (73.8)
MVI	40 (14.7)	52 (19.2)
EHS	175 (64.3)	180 (66.4)
Etiology‡		
HBV	208 (76.5)	197 (72.7)
HCV	22 (8.1)	29 (10.7)
Non-viral¶	42 (15.4)	42 (15.4)
Previous local therapy	161 (59.2)	149 (55.0)

Courtesy of Dr. Ahmed O Kaseb

Camrelizumab plus rivoceranib vs. sorafenib as frontline tx for uHCC: a randomized ph 3 (CARES-310) Survival Endpoints



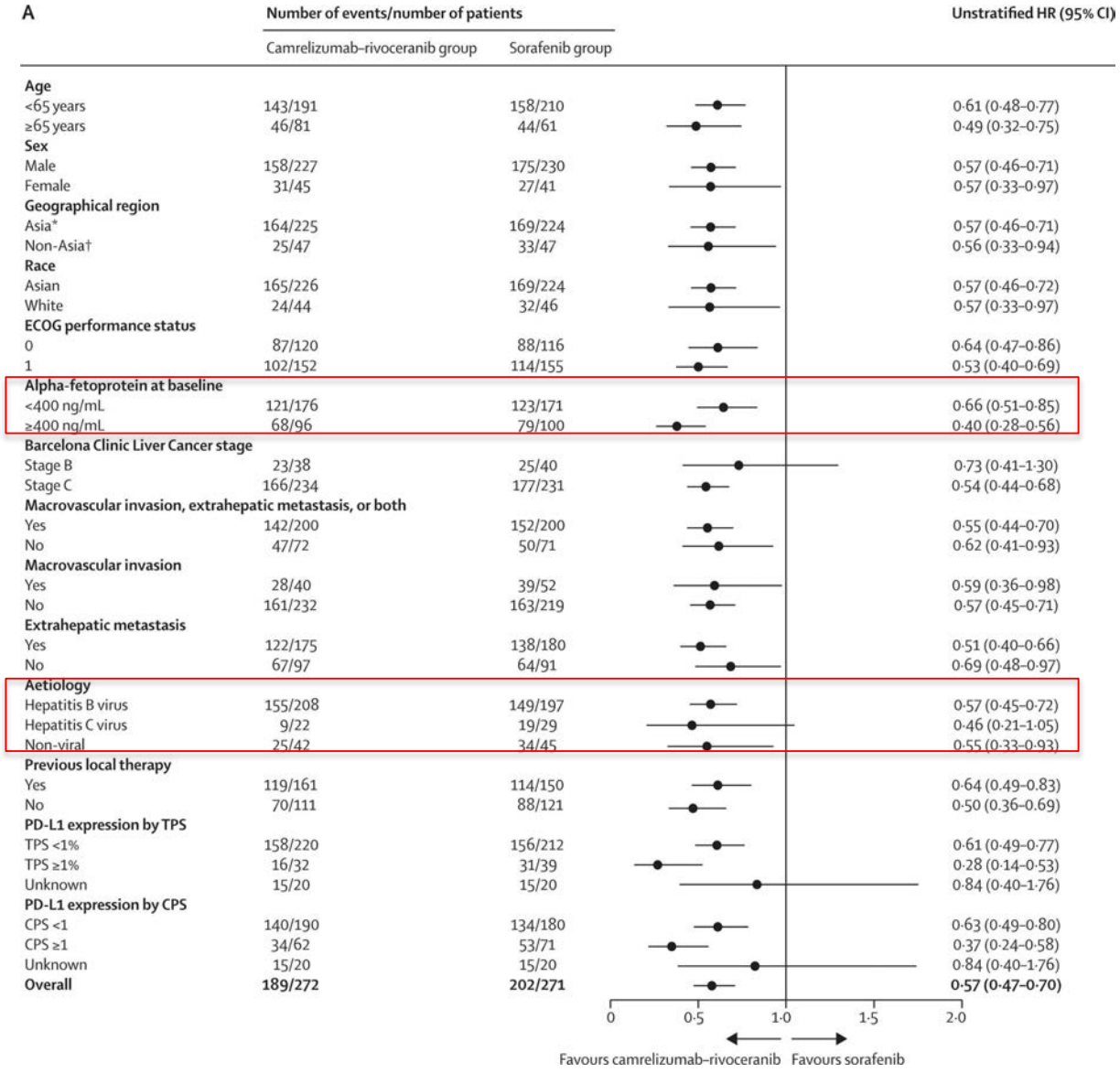


Kaplan-Meier curve of DoR (BIRC per RECIST v1.1).

Qin S, and Kaseb AO, and Vogel A, et al. Lancet, July 2023

Courtesy of Dr. Ahmed O Kaseb

Camrelizumab plus rivoceranib vs. sorafenib as frontline tx for uHCC: a randomized ph 3 (CARES-310) – Subset Analysis



A	Number of events/number of patients		Unstratified HR (95% CI)
	Camrelizumab–rivoceranib group	Sorafenib group	
Age			
<65 years	143/191	158/210	0·61 (0·48–0·77)
≥65 years	46/81	44/61	0·49 (0·32–0·75)
Sex			
Male	158/227	175/230	0·57 (0·46–0·71)
Female	31/45	27/41	0·57 (0·33–0·97)
Geographical region			
Asia*	164/225	169/224	0·57 (0·46–0·71)
Non-Asia†	25/47	33/47	0·56 (0·33–0·94)
Race			
Asian	165/226	169/224	0·57 (0·46–0·72)
White	24/44	32/46	0·57 (0·33–0·97)
ECOG performance status			
0	87/120	88/116	0·64 (0·47–0·86)
1	102/152	114/155	0·53 (0·40–0·69)
Alpha-fetoprotein at baseline			
<400 ng/mL	121/176	123/171	0·66 (0·51–0·85)
≥400 ng/mL	68/96	79/100	0·40 (0·28–0·56)
Barcelona Clinic Liver Cancer stage			
Stage B	23/38	25/40	0·73 (0·41–1·30)
Stage C	166/234	177/231	0·54 (0·44–0·68)
Macrovascular invasion, extrahepatic metastasis, or both			
Yes	142/200	152/200	0·55 (0·44–0·70)
No	47/72	50/71	0·62 (0·41–0·93)
Macrovascular invasion			
Yes	28/40	39/52	0·59 (0·36–0·98)
No	161/232	163/219	0·57 (0·45–0·71)
Extrahepatic metastasis			
Yes	122/175	138/180	0·51 (0·40–0·66)
No	67/97	64/91	0·69 (0·48–0·97)
Aetiology			
Hepatitis B virus	155/208	149/197	0·57 (0·45–0·72)
Hepatitis C virus	9/22	19/29	0·46 (0·21–1·05)
Non-viral	25/42	34/45	0·55 (0·33–0·93)
Previous local therapy			
Yes	119/161	114/150	0·64 (0·49–0·83)
No	70/111	88/121	0·50 (0·36–0·69)
PD-L1 expression by TPS			
TPS <1%	158/220	156/212	0·61 (0·49–0·77)
TPS ≥1%	16/32	31/39	0·28 (0·14–0·53)
Unknown	15/20	15/20	0·84 (0·40–1·76)
PD-L1 expression by CPS			
CPS <1	140/190	134/180	0·63 (0·49–0·80)
CPS ≥1	34/62	53/71	0·37 (0·24–0·58)
Unknown	15/20	15/20	0·84 (0·40–1·76)
Overall	**189/272**	**202/271**	**0·57 (0·47–0·70)**

Qin S, and Kaseb AO, and Vogel A, et al. Lancet, July 2023

Courtesy of Dr. Ahmed O Kaseb

Camrelizumab plus rivoceranib vs. sorafenib as frontline tx for uHCC: a randomized ph 3 (CARES-310)

	Camrelizumab–rivoceranib (n=272)				Sorafenib (n=269)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any treatment-related adverse event	45 (17%)	193 (71%)	26 (10%)	1 (<1%)	128 (48%)	128 (48%)	12 (4%)	1 (<1%)
Hypertension	87 (32%)	100 (37%)	2 (1%)	0	76 (28%)	40 (15%)	0	0
Aspartate aminotransferase increased	102 (38%)	42 (15%)	3 (1%)	0	85 (32%)	14 (5%)	0	0
Proteinuria	118 (43%)	16 (6%)	0	0	67 (25%)	5 (2%)	0	0
Alanine aminotransferase increased	92 (34%)	34 (13%)	1 (<1%)	0	72 (27%)	8 (3%)	0	0
Platelet count decreased	94 (35%)	28 (10%)	4 (1%)	0	85 (32%)	4 (1%)	0	0
Blood bilirubin increased	92 (34%)	24 (9%)	0	0	71 (26%)	4 (1%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	69 (25%)	33 (12%)	0	0	122 (45%)	41 (15%)	0	0
Diarrhoea	77 (28%)	6 (2%)	0	0	91 (34%)	14 (5%)	0	0
Reactive cutaneous capillary endothelial proliferation	72 (26%)	7 (3%)	0	0	0	0	0	0
Neutrophil count decreased	57 (21%)	14 (5%)	2 (1%)	0	24 (9%)	1 (<1%)	2 (1%)	0
White blood cell count decreased	66 (24%)	7 (3%)	0	0	35 (13%)	3 (1%)	0	0
Gamma-glutamyltransferase increased	39 (14%)	25 (9%)	2 (1%)	0	29 (11%)	15 (6%)	5 (2%)	0
Hypothyroidism	58 (21%)	0	0	0	16 (6%)	0	0	0
Fatigue	46 (17%)	7 (3%)	0	0	20 (7%)	1 (<1%)	0	0
Blood alkaline phosphatase increased	44 (16%)	3 (1%)	0	0	30 (11%)	3 (1%)	0	0
Conjugated blood bilirubin increased	34 (13%)	10 (4%)	2 (1%)	0	28 (10%)	6 (2%)	2 (1%)	0
Rash	40 (15%)	5 (2%)	0	0	47 (17%)	3 (1%)	0	0
Anaemia	41 (15%)	4 (1%)	0	0	19 (7%)	2 (1%)	0	0
Decreased appetite	39 (14%)	3 (1%)	0	0	31 (12%)	3 (1%)	0	0
Unconjugated blood bilirubin increased	33 (12%)	2 (1%)	0	0	20 (7%)	1 (<1%)	0	0
Hypoalbuminaemia	34 (13%)	0	0	0	21 (8%)	0	0	0
Weight decreased	28 (10%)	4 (1%)	0	0	33 (12%)	6 (2%)	0	0
Asthenia	29 (11%)	3 (1%)	0	0	15 (6%)	0	0	0
Haematuria	31 (11%)	0	0	0	12 (4%)	0	0	0
Nausea	31 (11%)	0	0	0	14 (5%)	0	0	0
Headache	28 (10%)	2 (1%)	0	0	4 (1%)	1 (<1%)	0	0
Blood lactate dehydrogenase increased	26 (10%)	1 (<1%)	0	0	29 (11%)	0	0	0
Lymphocyte count decreased	18 (7%)	8 (3%)	0	0	14 (5%)	3 (1%)	0	0
Amylase increased	15 (6%)	9 (3%)	1 (<1%)	0	6 (2%)	0	1 (<1%)	0
Hyponatraemia	13 (5%)	8 (3%)	0	0	8 (3%)	1 (<1%)	0	0
Lipase increased	7 (3%)	7 (3%)	6 (2%)	0	6 (2%)	4 (1%)	1 (<1%)	0
Hypophosphataemia	17 (6%)	2 (1%)	0	0	27 (10%)	12 (4%)	0	0
Upper gastrointestinal haemorrhage	2 (1%)	6 (2%)	0	0	0	0	0	0
Alopecia	4 (1%)	0	0	0	52 (19%)	0	0	0

Data are n (%). Treatment-related adverse events of grade 1–2 occurring in at least 10% of patients or of grade 3–5 occurring in at least 2% of patients in either group are reported.

Table 2: **Treatment-related adverse events in the safety analysis set at the interim analysis for overall survival**

Qin S, and Kaseb AO, and Vogel A, et al. Lancet, July 2023

Courtesy of Dr. Ahmed O Kaseb

1L TKIs in Advanced HCC

- Sorafenib
- Lenvatinib
- Who should receive a TKI in 1L?
  - History of autoimmune disease (Crohn's, AI hepatitis, MS, RA, etc.)
  - Post-organ transplantation incl. liver

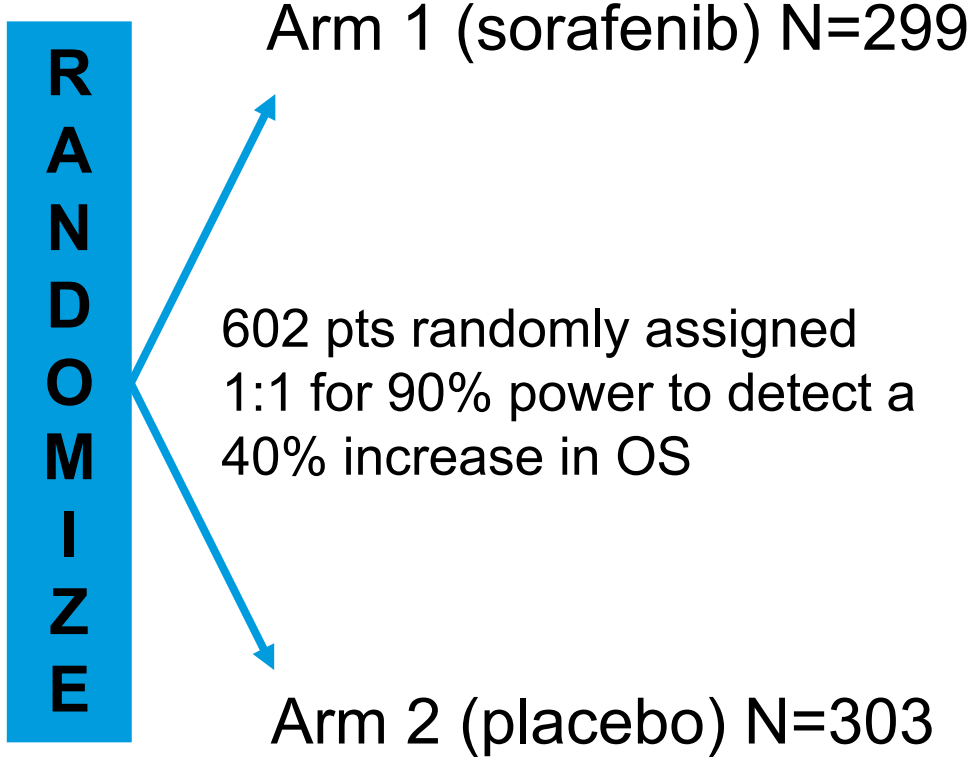
SHARP: Phase III Trial of Sorafenib in Advanced HCC

Eligibility

Advanced stage HCC
ECOG PS ≤2
Child-Pugh A
No prior treatment
Age ≥18 years

Study Design

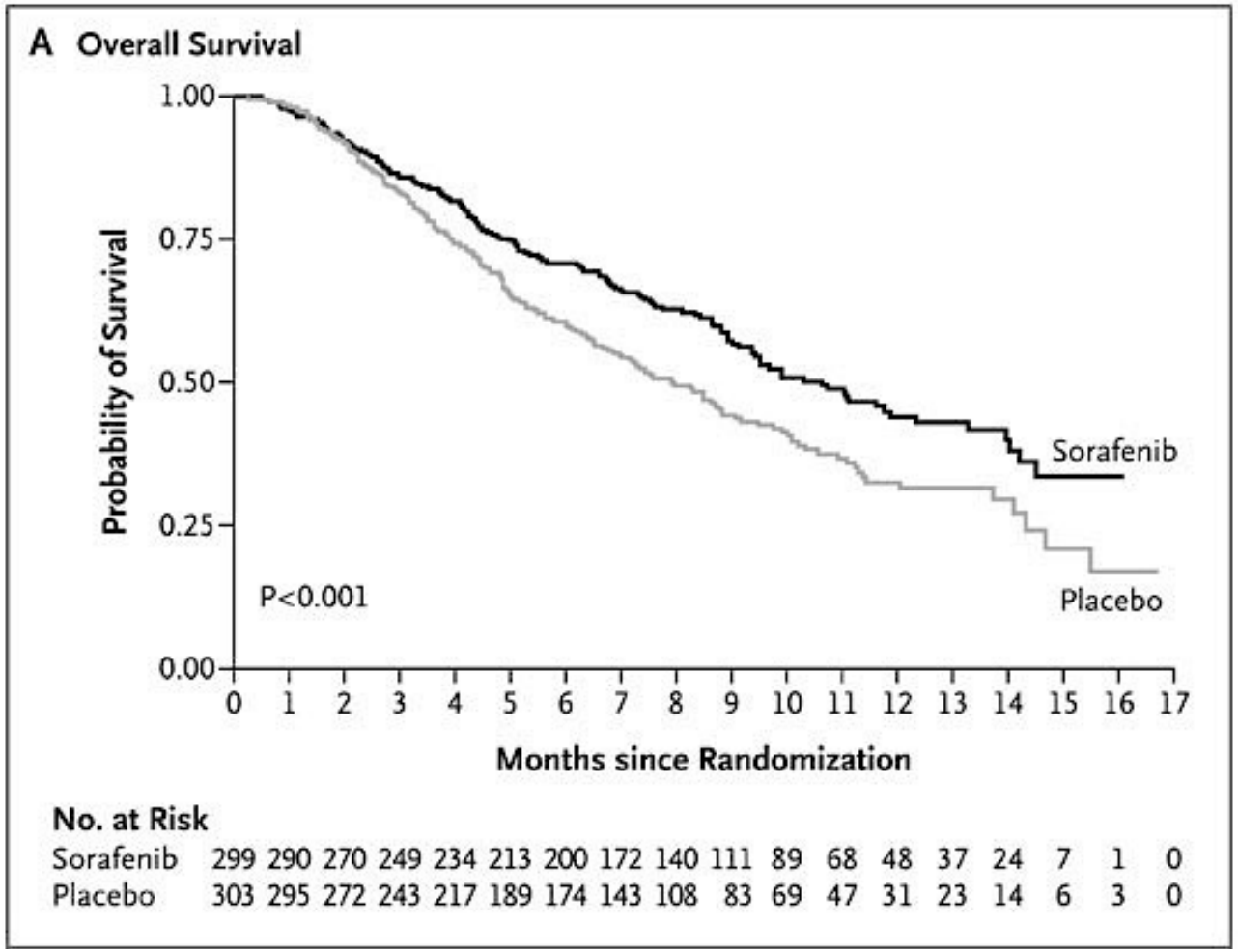
Double blind, placebo-controlled
121 sites primarily in North America and Europe
Primary end point: OS



OS = overall survival

Llovet et al, N Engl J Med 2008

SHARP: Overall Survival



Llovet et al, N Engl J Med 2008

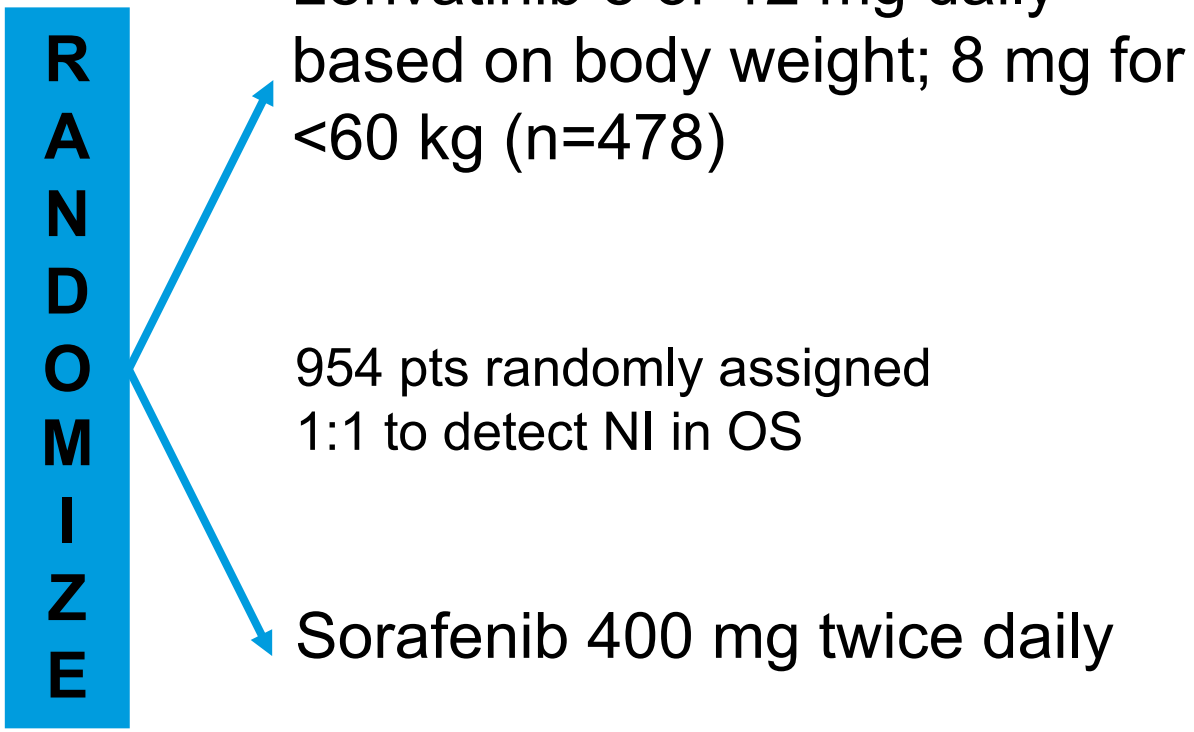
REFLECT: Lenvatinib vs Sorafenib in 1L for Advanced HCC

Eligibility

- Unresectable HCC with no prior treatment
- ECOG PS 0 or 1
- BCLC stage B or C
- Child-Pugh A
- Age ≥18 years

Study Design

- Phase III, open-label, randomized NI study
- Primary end point: OS
- Secondary end points: PFS, TTP



NI = noninferiority; PFS = progression-free survival

Cheng et al, 2017

REFLECT: Outcomes

Outcomes	Lenvatinib	Sorafenib	HR
Median OS, mo (95% CI)	13.6 (12.1-14.9)	12.3 (10.4-13.9)	0.92 (0.79-1.06)
Median PFS, mo (95% CI)	7.4 (6.9-8.8)	3.7 (3.6-4.6)	0.66 (0.57-0.77)
Median TTP, mo (95% CI)	8.9 (7.4-9.2)	3.7 (3.6-5.4)	0.63 (0.53-0.73)
ORR, n (%)	115 (24%)	44 (9%)	

Cheng et al, 2017

Discussion Questions

- Regulatory and reimbursement issues aside, which first-line systemic treatment would you most likely recommend for a 65-year-old patient with HCC and a Child-Pugh A score? What would you recommend if the patient had Grade 1 esophageal varices being managed with a beta blocker? What if the patient had a history of recurrent deep vein thrombosis?

Discussion Questions

- Regulatory and reimbursement issues aside, which first-line systemic treatment would you most likely recommend for a 78-year-old patient with HCC, a Child-Pugh B7 score and a PS of 1?

- What would be your most likely second-line systemic therapy for a 65-year-old patient with HCC, a Child-Pugh B7 score and a PS of 1 who received first-line atezolizumab/bevacizumab with minimal toxicity, had stable disease for 14 months and then experienced disease progression (AFP = 2,500 ng/mL)?

Discussion Questions

- What would be your most likely third-line systemic therapy recommendation for an otherwise healthy 65-year-old patient with HCC who experienced disease progression on first-line atezolizumab/bevacizumab and second-line lenvatinib (AFP = 2,500 ng/mL)?

Module 13: Hepatocellular Carcinoma

Current Treatment for Advanced Hepatocellular Carcinoma (HCC) — Dr Abrams

Promising Novel Approaches to HCC Management — Dr Kaseb

Promising Novel Approaches to HCC Management

Fourth Annual National General Medical Oncology (GMO) Summit

February 28 – March 2, 2025 - Miami Beach, Florida

Ahmed O Kaseb, MD

John E. and Dorothy J. Harris Professorship in Gastrointestinal Cancer Research

Professor and Director, HCC Program

Member, US National Hepatobiliary Task Force, NCI

Clinical PI and Director, MD Anderson HCC SPORE Grant

Dept of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Editor-in-Chief: Journal of Hepatocellular Carcinoma

Disclosures

Advisory Committees, Consulting Agreements and Contracted Research	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Merck, Roche Laboratories Inc

Educational Objectives

- **Updated data of adjuvant treatment for early-stage HCC at high risk of recurrence following surgery or ablation**

- The changing landscape in combining TACE and systemic therapies in patients with unresectable HCC eligible for embolization

- Conclusion

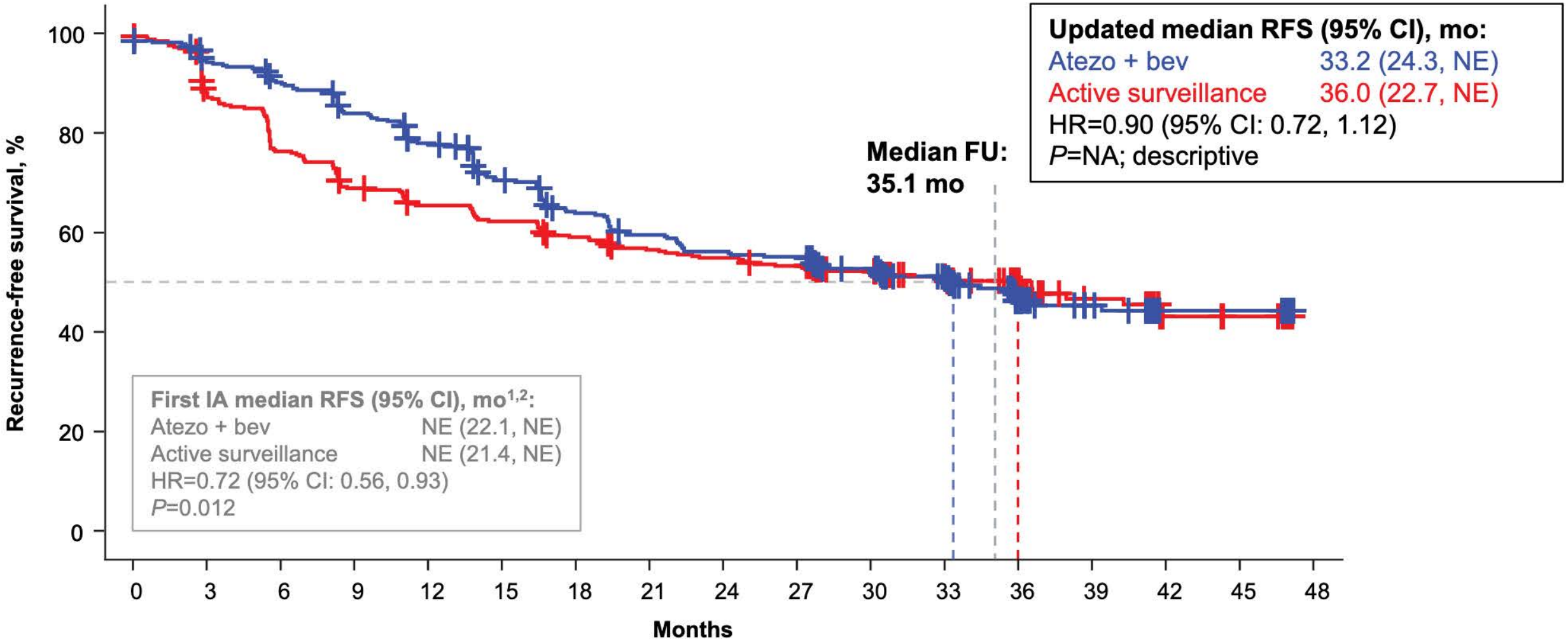
“Select” Phase 3 Trials of Adjuvant Immunotherapy

- High risk for HCC recurrence after resection or ablation
- Child-Pugh A

EMERALD-2[1]	CheckMate 9DX[2]	IMbrave050[3]	KEYNOTE-937[4]
• Durvalumab ± bevacizumab + vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Nivolumab vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Atezolizumab + bevacizumab vs active surveillance • ECOG PS 0-1 • Primary endpoint: RFS	• Pembrolizumab vs placebo • ECOG PS 0 • AFP <400 ng/mL • Primary endpoints: RFS and OS

1. https://clinicaltrials.gov/ct2/show/NCT03847428. 2. https://clinicaltrials.gov/ct2/show/NCT03383458. 3. https://clinicaltrials.gov/ct2/show/NCT04102098.
4. https://clinicaltrials.gov/ct2/show/NCT03867084.

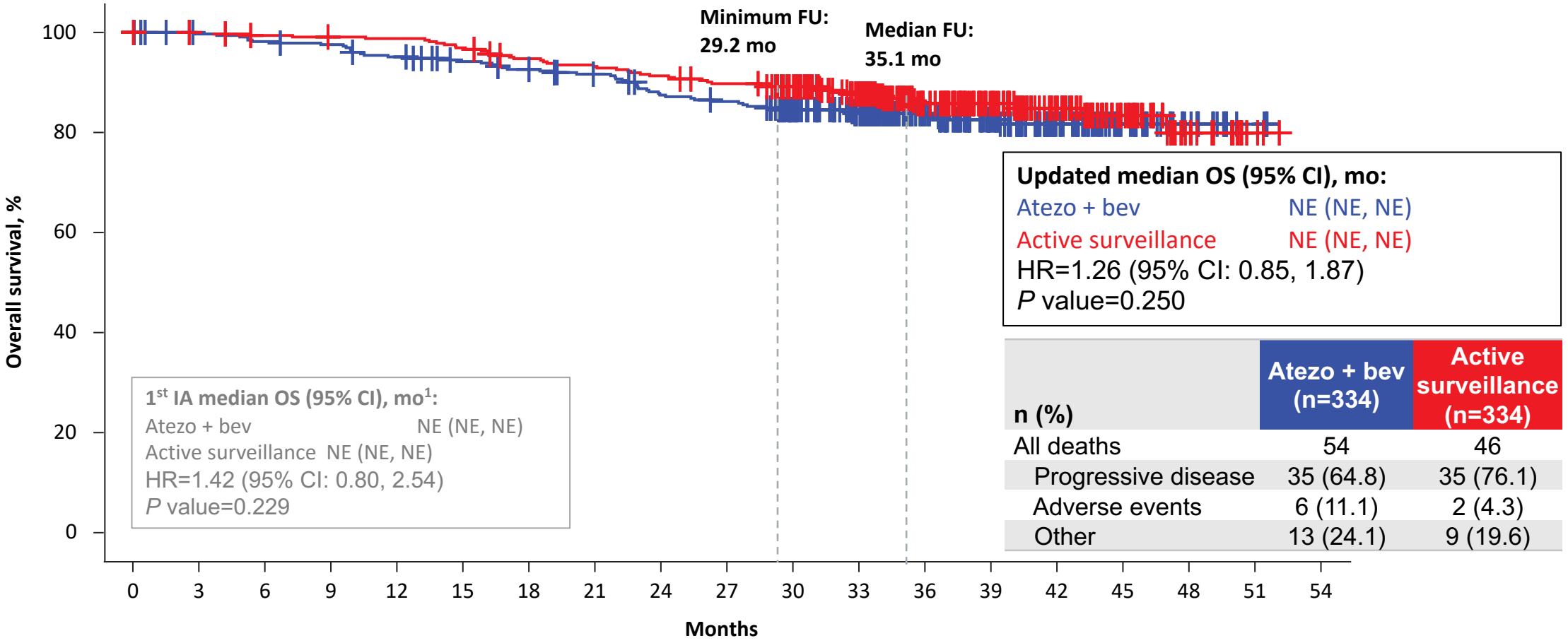
Updated Efficacy Data from IMbrave050



Early RFS benefit was not maintained with longer follow-up

Yopp A et al. ESMO 2024.

Updated OS – IMbrave050



n (%)	Atezo + bev (n=334)	Active surveillance (n=334)
All deaths	54	46
Progressive disease	35 (64.8)	35 (76.1)
Adverse events	6 (11.1)	2 (4.3)
Other	13 (24.1)	9 (19.6)

No. at risk

Atezo + bev	334	327	322	319	310	301	294	286	271	266	243	206	142	101	60	34	16	3	NE
Active surveillance	334	327	323	321	320	314	304	299	293	286	266	226	157	108	71	38	15	3	NE

- Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. HRs are stratified. *P* values are log rank.
- 1. Qin et al. Lancet 2023.

Yopp et al.
IMbrave050 update
https://bit.ly/XXXXXXX

August 2024

IMPORTANT DRUG WARNING

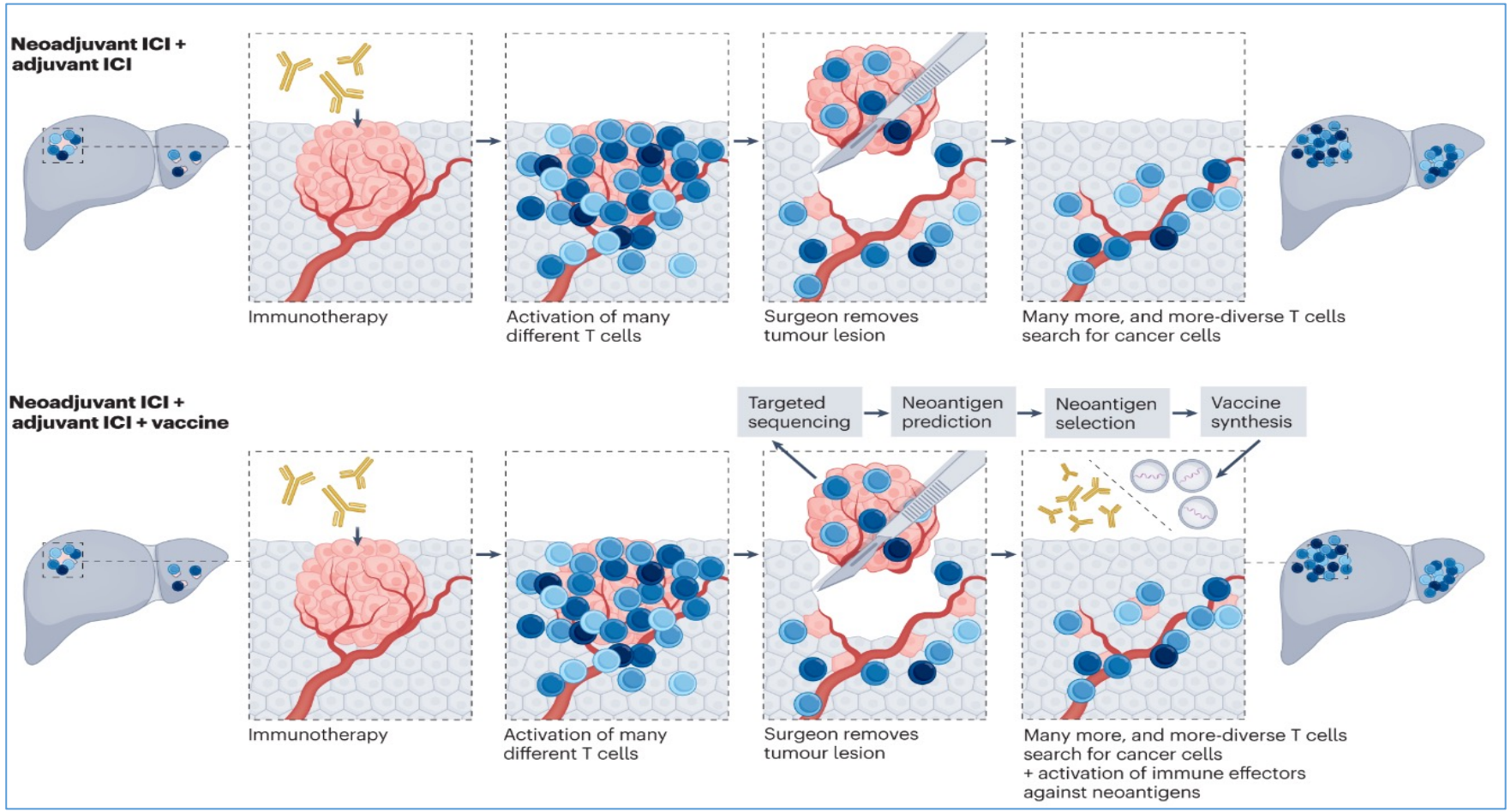
Subject:
Atezolizumab in combination with bevacizumab is NOT approved as adjuvant therapy in patients with hepatocellular carcinoma at high risk of recurrence after surgical resection or ablation and should not be used in this setting.

Prescriber Action

Do not prescribe off-label use of atezolizumab in combination with bevacizumab for the adjuvant treatment of HCC.

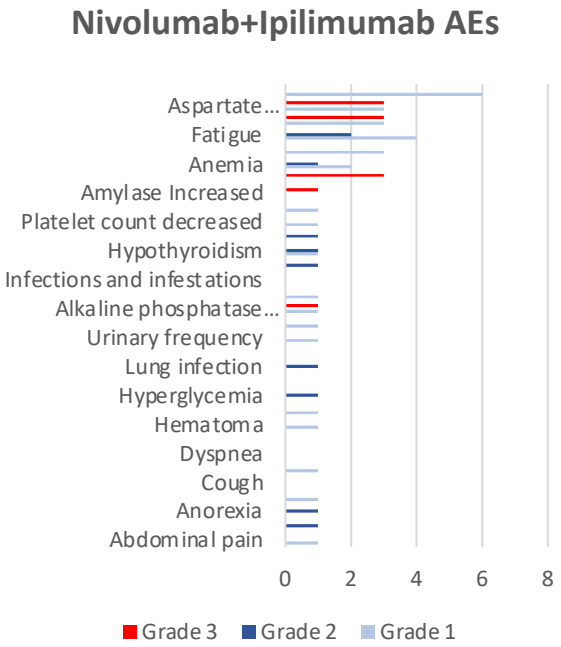
How about neoadjuvant and perioperative setting?

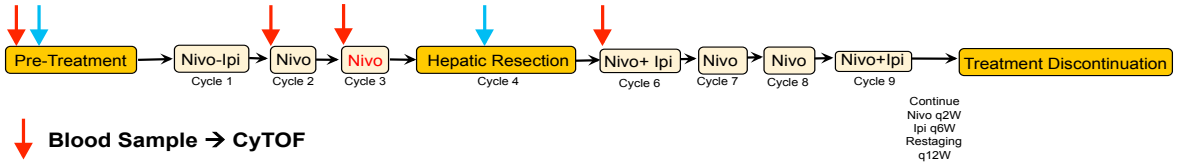
Mechanism of action of immunotherapies and vaccines in the neoadjuvant and adjuvant setting in

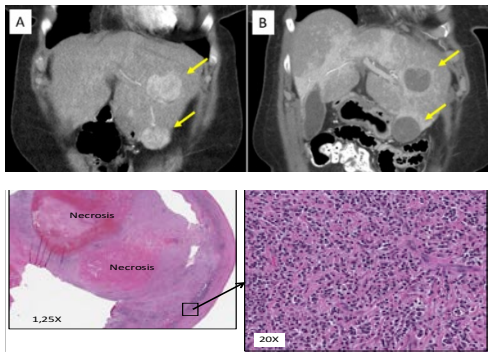


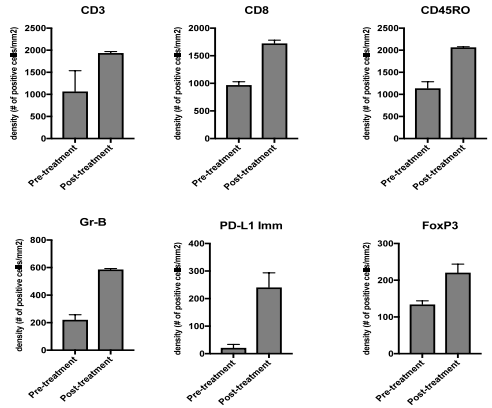
Llovte JM, *Nature Reviews Clinical Oncology* **volume 21**, pages294–311 (2024)

Perioperative Phase II Study Evaluating Nivolumab Alone versus Nivolumab plus Ipilimumab in Resectable HCC









No AEs led to cancellation of surgery

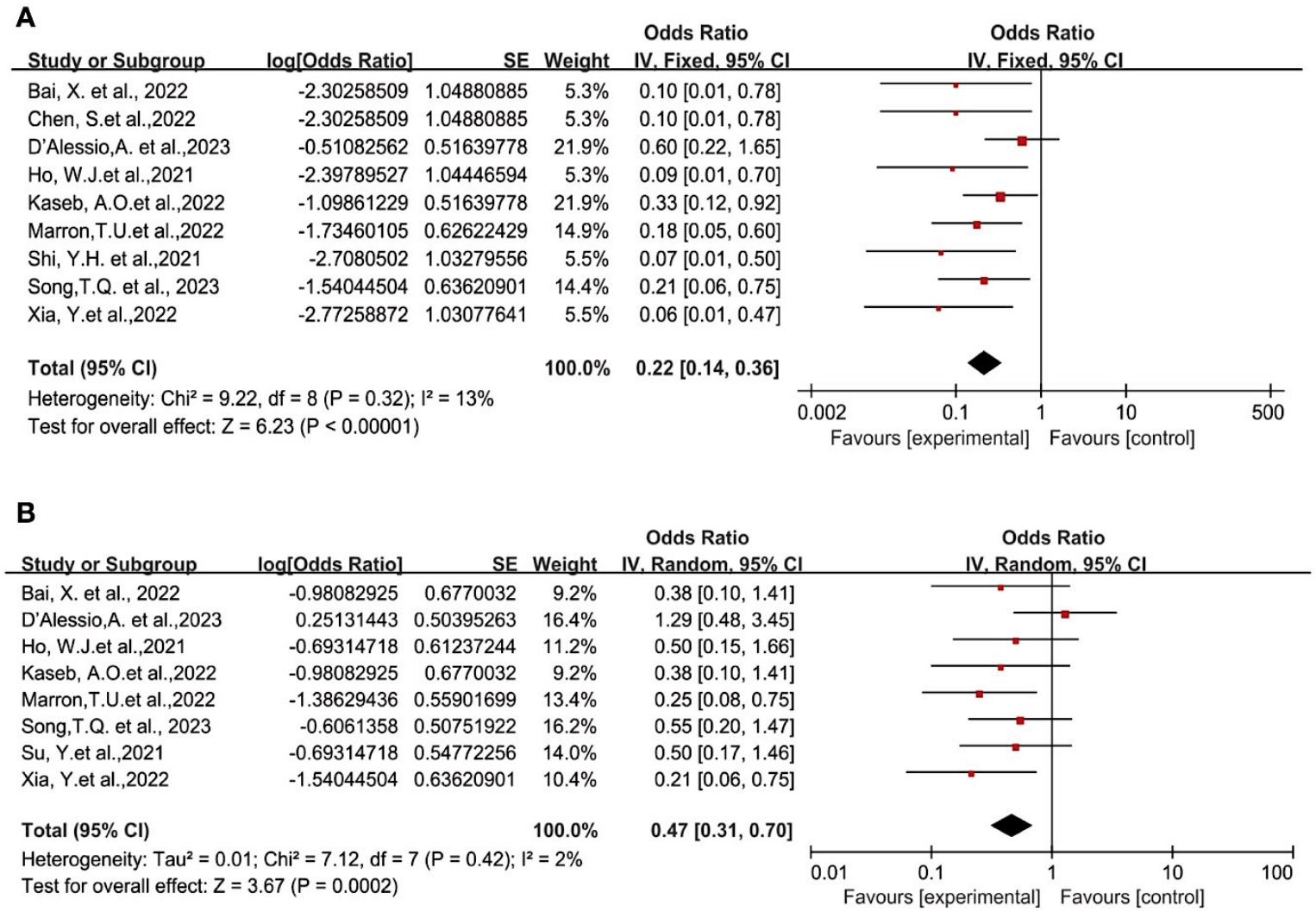
Most grade 3-4 treatment related toxicity occurred during adjuvant therapy after surg.

6/20 (30%) achieved pathologic response (5 had path CR and 1 >50% necrosis)

- CR correlated with a strong increase in CD8+ T cell infiltration
- 11-fold increase in CD3+CD8+CD45RO+Eomes+ clusters
- 6-fold increase in CD3+CD8+CD45RO+Eomes+CD57+CD38low clusters
- CD8+cytotoxic T cells : Tregs ratio→ increased significantly after therapy

Kaseb AO, et al. Lancet Gastroenterol Hepatol. 2022

Forest plot of the efficacy of neoadjuvant immune checkpoint inhibitors in resectable HCC. (A) pCR, (B) MPR



Tian C, et al. Front. Immunol., 18 February 2024

Neoadjuvant Atezolizumab Plus Bevacizumab Is Also Being Assessed (MDACC)

Atezolizumab + Bevacizumab Before Surgery for the Treatment of Resectable Liver Cancer[1]

- Resectable HCC
- Child–Pugh A
- ECOG PS ≥1

N = 30

R

Atezolizumab + bevacizumab

- **Primary endpoints:** safety, tolerability, and pCR
- **Secondary endpoints:** correlation between pCR, ORR at time of surgery, DOR as defined by time to recurrence/recurrence-free survival, and OS

2024: 13 cases resected

Only 1 case 100% necrosis (Path CR)
1 Case >70% necrosis (MPR)
6 cases PR on imaging

1. https://clinicaltrials.gov/ct2/show/NCT04721132.

Neoadjuvant radiotherapy provided survival benefit compared to adjuvant radiotherapy for HCC

Table 2 Univariate analysis of factors associated with OSS and CSS for hepatocellular carcinoma patients before and after propensity score matching

	OSS						CSS					
	Before propensity score weighting			After propensity score weighting			Before propensity score weighting			After propensity score weighting		
	3-year OSS (%)	χ^2	*P*-value	3-year OSS (%)	χ^2	*P*-value	3-year CSS (%)	χ^2	*P*-value	3-year CSS (%)	χ^2	*P*-value
Radiation type		6.15	0.105		11.68	0.008		6.59	0.086		11.16	0.011
Beam radiation	35.7			49.3			39.0			52.4		
Radioactive implants	59.6			30.1			63.8			31.5		
Radioisotopes	39.9			15.6			44.1			16.8		
Unknown	—			—			—			—		
Radiation sequence		23.95	<0.001		14.29	<0.001		22.14	<0.001		13.57	<0.001
Radiation after surgery	29.1			24.3			32.8			26.9		
Radiation before surgery	73.0			62.6			75.2			66.1		

CSS, cancer-specific survival; OSS, overall survival.

Lin H, et al. ANZ J Surg 2018

Educational Objectives

- Updated data of adjuvant treatment for early-stage HCC at high risk of recurrence following surgery or ablation

- **The changing landscape in combining TACE and systemic therapies in patients with unresectable HCC eligible for embolization**

- Conclusion

Q: Is there a role for combining systemic and local therapies even in Intermediate/advanced HCC to improve OS?

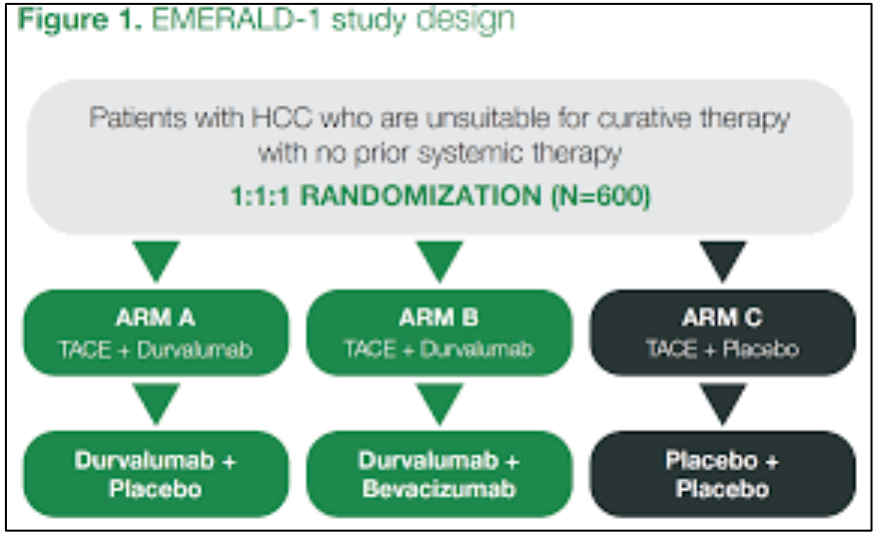
Select ongoing trials of local plus systemic therapies in HCC

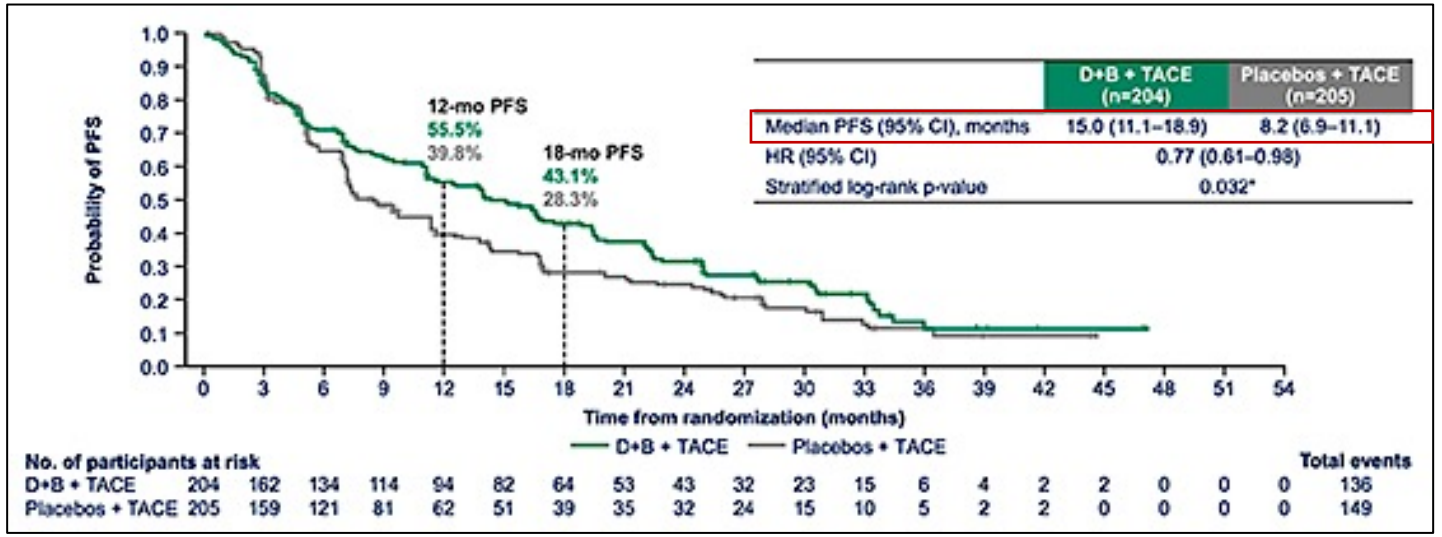
Trial	Identifier	Phase	BCLC Stage	Treatment Arms	Primary Endpoint(s)	Setting
LEAP-012	NCT04246177	Phase 3	B	• Lenvatinib + pembrolizumab + TACE • TACE	• PFS per RECIST 1.1 • OS	First-line
EMERALD-1	NCT03778957	Phase 3	B	• Durvalumab + TACE • Durvalumab + bevacizumab + TACE • TACE	• PFS per RECIST 1.1	First-line
CheckMate 74W	NCT04340193	Phase 3	B	• Nivolumab + ipilimumab + TACE • Nivolumab + TACE • TACE	• Time to TACE progression • OS	First-line
ABC-HCC	NCT04803994	Phase 3	B	• Atezolizumab + bevacizumab • TACE	• Time to failure of treatment strategy	First-line
RENOTACE	NCT04777851	Phase 3	B	• Regorafenib + nivolumab • TACE	• PFS per mRECIST	First-line

BCLC, Barcelona Clinic Liver Cancer; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; TACE, transarterial chemoembolization.

https://www.researchgate.net/figure/Current-clinical-trials-combining-or-comparing-systemic-treatments-with-TACE_tbl2_350981309

EMERALD-1 Trial Shows PFS Benefit With Addition of Durvalumab/Bevacizumab to TACE in Unresectable, Embolization-Eligible HCC





Patients continue to be followed for OS

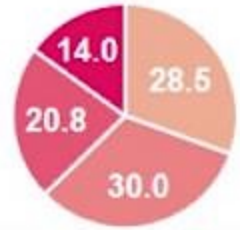
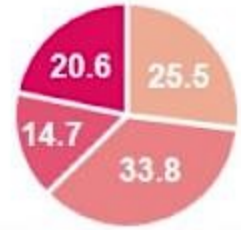
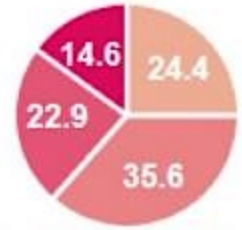
LRNCIONI R, ET AL. 2024 ASCO GASTROINTESTINAL CANCERS SYMPOSIUM

Sangro B, Kudo M, Erinjeri JP, et al. *Lancet*. 2025;405(10474):216-232.

Participant disposition

The majority of participants had 1 or 2 TACE procedures with or without durvalumab

616 participants randomised

	D + TACE	D + B + TACE	Placebos + TACE
Randomised	**207**	**204**	**205**
No. of TACE procedures,* %				
Dosed with durvalumab,† n / N (%)	193 / 207 (93.2%)	193 / 204 (94.6%)	200 / 205 (97.6%)
Dosed with combination n / N (%)	162 / 207 (78.3%)	154 / 204 (75.5%)	155 / 205 (75.6%)
Ongoing study, n / N (%)	**88 / 207 (42.5%)‡**	**89 / 204 (43.6%)§**	**82 / 205 (40.0%)‖**
On durvalumab treatment†	25 / 193 (13.0%)	27 / 193 (14.0%)	27 / 200 (13.5%)
Discontinued study treatment, n / N (%)¶	**168 / 193 (87.0%)****	**166 / 193 (86.0%)††**	**173 / 200 (86.5%)‡‡**
Condition under investigation worsened§§	122 / 193 (63.2%)	85 / 193 (44.0%)	119 / 200 (59.5%)

*Number of TACE procedures given prior to disease progression. Some participants had additional TACE procedures beyond progression, while remaining on study treatment. †Participants in arm C (placebos + TACE) received placebo for durvalumab. ‡57.5% no longer ongoing study: 51.2% due to death; 5.8% due to withdrawal by participant; 0.5% due to other. §56.4% no longer ongoing study: 51.5% due to death; 4.4% due to withdrawal by participant; 0.5% due to other. ‖60.0% no longer ongoing study: 52.7% due to death; 7.3% due to withdrawal by participant. ¶Other reasons for 'discontinued study treatment' include AEs, participant decision, severe non-compliance to protocol, development of study-specific discontinuation criteria, lost to follow-up, due to COVID-19 pandemic or other. **10.9% due to AEs; 7.3% due to participant decision; 5.2% due to other. ††22.8% due to AEs; 12.4% due to participant decision; 4.7% due to other. ‡‡8.0% due to AEs;12.5% due to participant decision; 6.0% due to other. §§Clinical or objective progression, or investigator determined participants no longer benefitting from treatment.

AE, adverse event; B, bevacizumab; D, durvalumab; TACE, transarterial chemoembolisation.

Safety: summary

AEs were consistent with the known safety profiles of durvalumab, bevacizumab and TACE

	D + TACE (n=232)* n (%)	D + B + TACE (n=154)* n (%)	Placebos + TACE (n=200)* n (%)
Any AE, n (%)	**215 (92.7)**	**151 (98.1)**	**186 (93.0)**
Possibly related to study treatment	117 (50.4)	124 (80.5)	90 (45.0)
Possibly provoked by TACE	101 (43.5)	78 (50.6)	95 (47.5)
SAEs (including AEs with outcome of death), n (%)	**84 (36.2)**	**74 (48.1)**	**62 (31.0)**
Possibly related to any treatment	13 (5.6)	30 (19.5)	10 (5.0)
Any AE of max CTCAE Grade 3 or 4, n (%)	**64 (27.6)**	**70 (45.5)**	**46 (23.0)**
Any AE of max CTCAE Grade 3 or 4 possibly related to study treatment, n (%)	**15 (6.5)**	**41 (26.6)**	**12 (6.0)**
Any AE possibly provoked by TACE of max CTCAE Grade 3 or 4, n (%)	**21 (9.1)**	**13 (8.4)**	**17 (8.5)**
Any AE with outcome of death, n (%)	**21 (9.1)**	**16 (10.4)**	**11 (5.5)**
Possibly related to study treatment	3 (1.3)	0	3 (1.5)
Possibly related to durvalumab / placebo	2 (0.9)	0	1 (0.5)
Possibly related to bevacizumab / placebo	1 (0.4)	0	2 (1.0)
AE leading to discontinuation, n (%)	**30 (12.9)**	**43 (27.9)**	**15 (7.5)**
Possibly related to study treatment	8 (3.4)	19 (12.3)	6 (3.0)
Possibly related to durvalumab / placebo	6 (2.6)	11 (7.1)	3 (1.5)
Possibly related to bevacizumab / placebo	3 (1.3)	13 (8.4)	4 (2.0)

*Safety analysis set: all randomised patients who received any amount of study treatment (i.e. durvalumab, bevacizumab or placebo) regardless of arm randomised to.
AE, adverse event; B, bevacizumab; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab; SAE, serious adverse event; TACE, transarterial chemoembolisation

Sangro B, Kudo M, Erinjeri JP, et al. *Lancet*. 2025;405(10474):216-232.

EMERALD-3 Study Design: Durva + Treme + TACE ± Lenvatinib in uHCC

EMERALD-3
AZ IO TRIALS

POPULATION

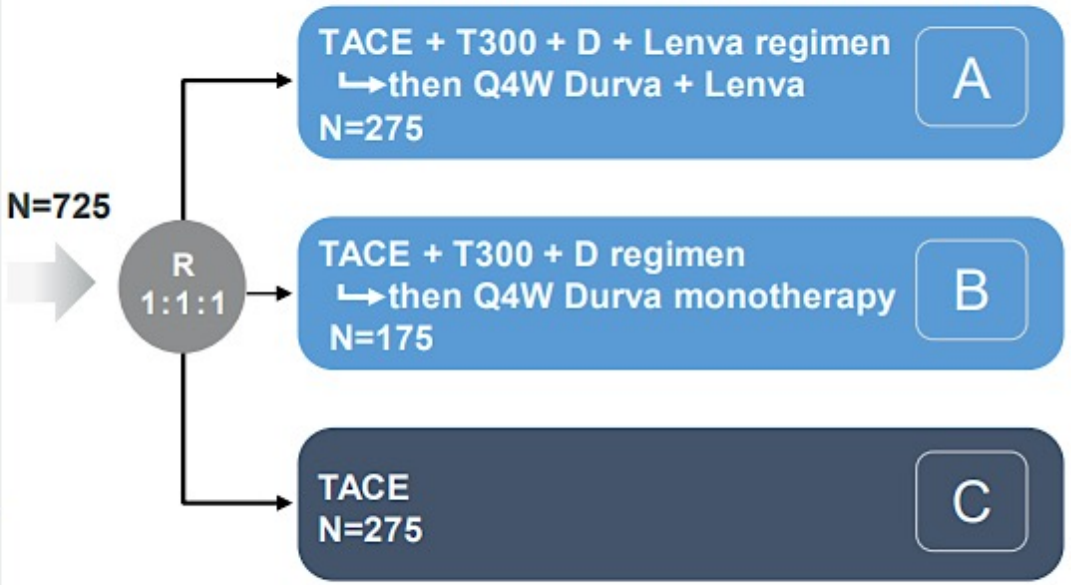
- Pathologically or radiologically confirmed HCC
- Unsuitable for curative treatment e.g. surgical resection, transplantation, ablation
- No prior systemic therapy
- No extrahepatic disease
- Child-Pugh class A
- ECOG: 0 or 1
- Exclude Vp3 and Vp4

Stratification factors

- Region (Japan vs. Asia non-Japan vs. others)
- Prior Palliative LR therapy (1>6m vs. 1≤6m vs. none))
- Baseline tumor burden (> up to 7 vs ≤ up to 7)

TREATMENT

Open label, Phase-3, multi-center study



ENDPOINTS

Primary Endpoint:
PFS (RECIST 1.1 by BICR)

Secondary Endpoint:
OS, ORR, Landmark OS, PROs, Safety

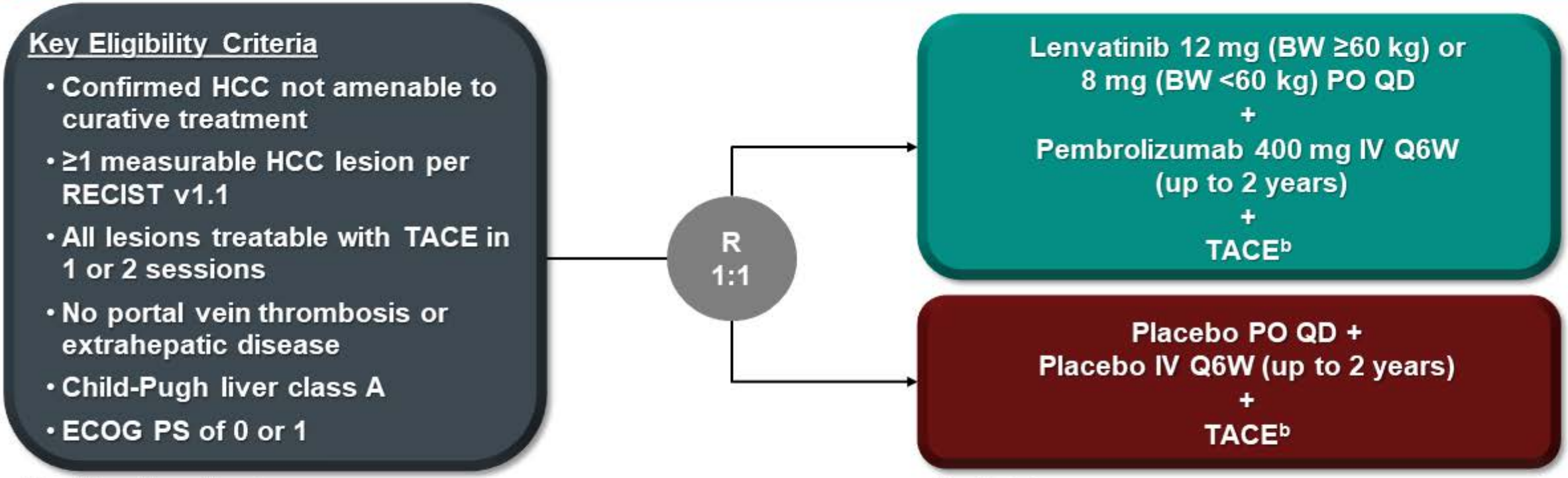
Dosing:

- Treme 300mg + Durva 1500mg IV on Cycle 1 Day 1(C1D1) for one dose
- Followed by Durva Q4W until progression
- Lenvatinib will start Day 1 (D1=first day of systemic therapy) and continue daily

TACE modalities :

- cTACE, DEB-TACE

LEAP-012 Study Design (NCT04246177)



Stratification Factors

- Study site
- Alpha fetoprotein (≤400 ng/mL vs >400 ng/mL)
- ECOG PS (0 vs 1)
- ALBI grade (1 vs 2 or 3)
- Tumor burden score[1,a] (≤6 vs >6 but ≤12 vs >12)

End Points

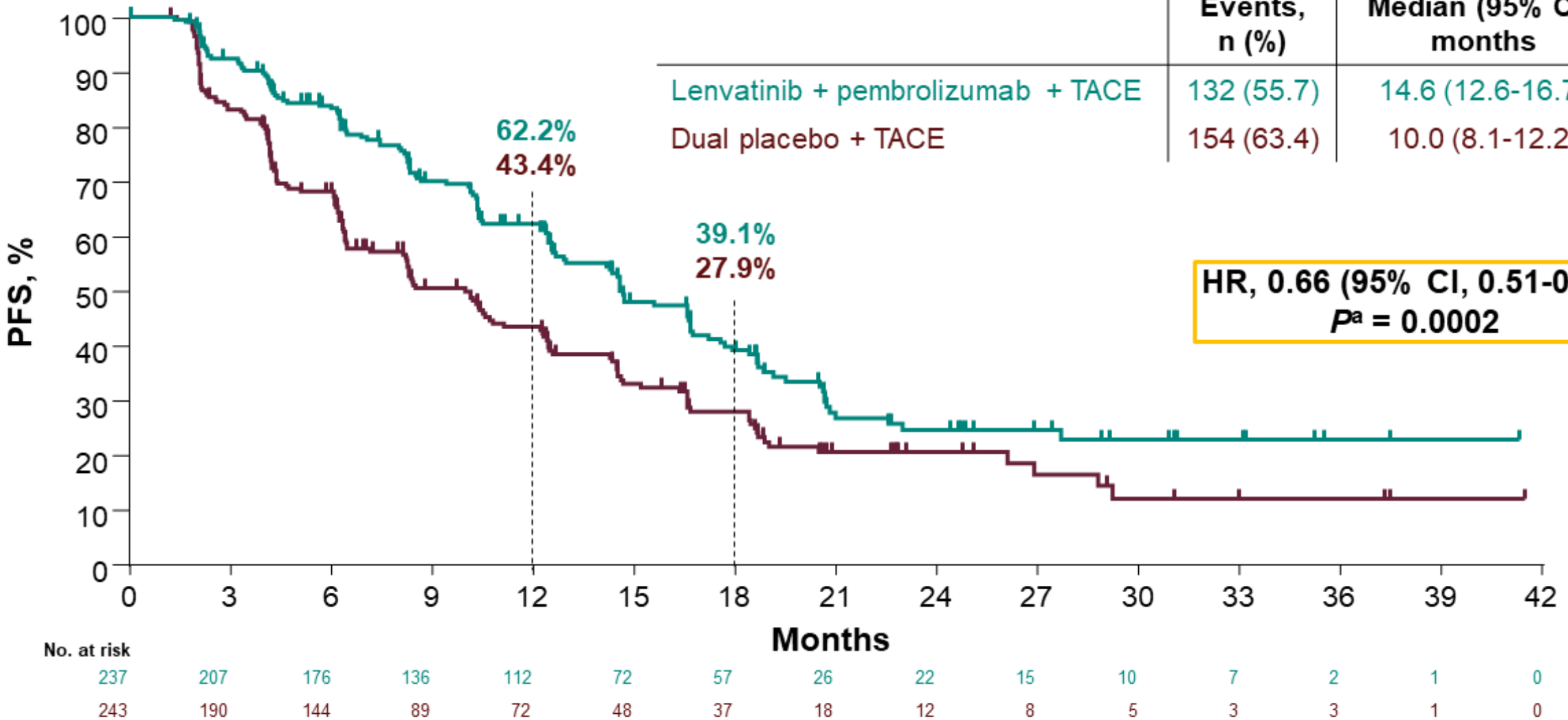
- Primary: PFS[c] and OS
  - IA1 is the **final analysis** for PFS
  - Initial alpha of 0.025 (1-sided) allocated to PFS; passed to OS if PFS is statistically significant
- Secondary: ORR,[c,d] DOR,[c,d] DCR,[c,d] TTP,[c,d] PFS,[d] and safety

1. Wang Q et al. *J Hepatol*. 2019;70:893-903.

[a]Largest tumor in centimeters + number of tumors. [b]2-4 weeks after the start of systemic therapy with a maximum of 2 treatments per tumor (4 total) and no more than 1 treatment per month. [c]Per RECIST v1.1 by BICR. [d]Per mRECIST by BICR.

Progression-Free Survival per RECIST v1.1 by BICR

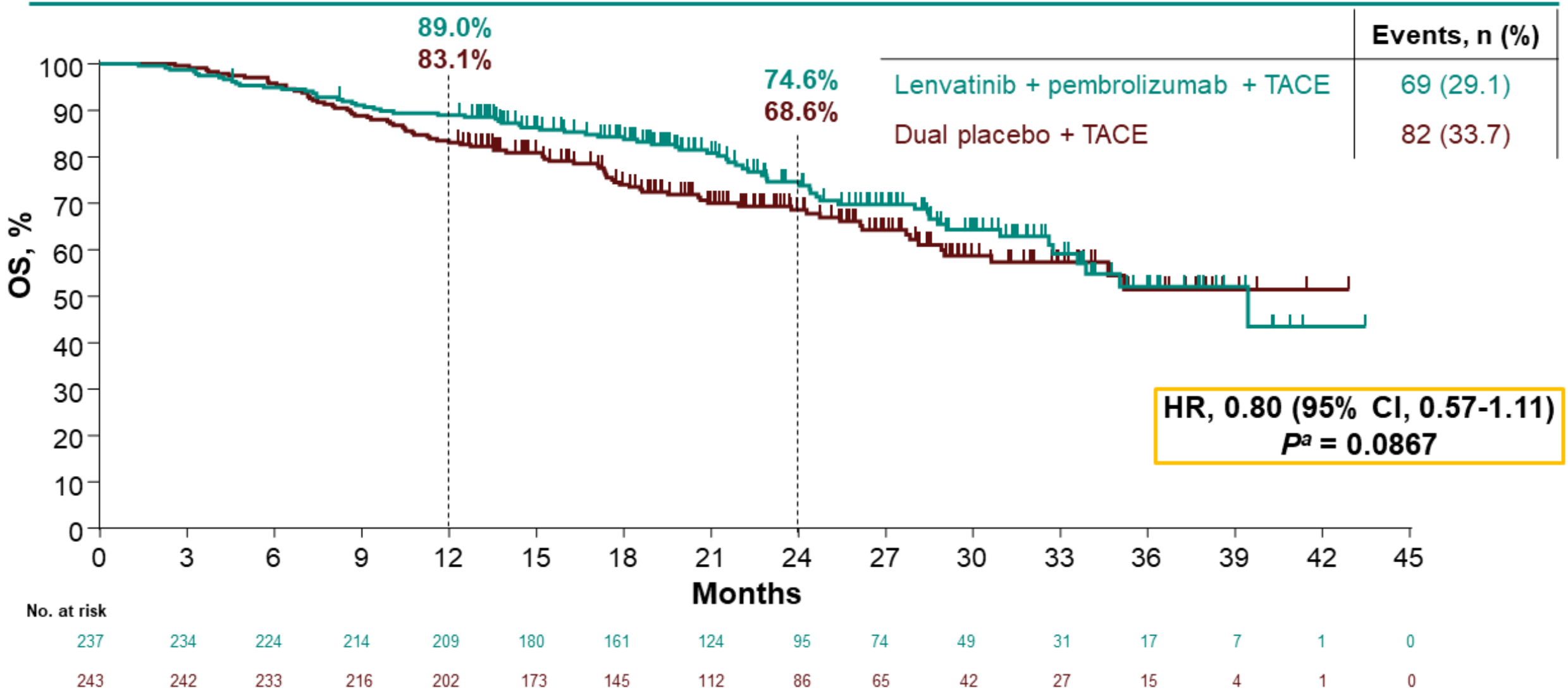
	Events, n (%)	Median (95% CI), months
Lenvatinib + pembrolizumab + TACE	132 (55.7)	14.6 (12.6-16.7)
Dual placebo + TACE	154 (63.4)	10.0 (8.1-12.2)



[a]One-sided *P* from re-randomization test; threshold *P* = 0.025. Data cutoff date for IA1: January 30, 2024.

Kudo M, Ren Z, Guo Y, et al. *Lancet*. 2025;405(10474):203-215.

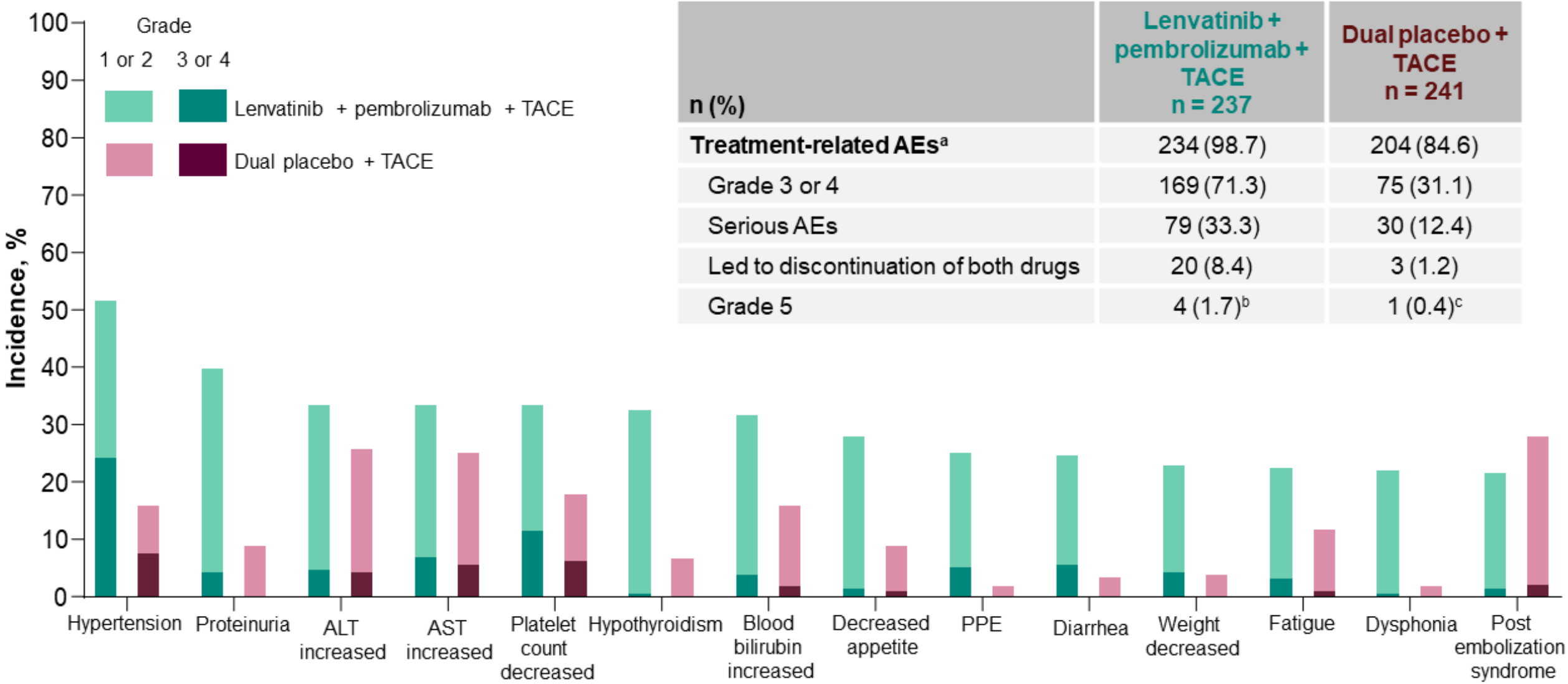
Overall Survival



[a]One-sided *P* from re-randomization test; threshold *P* = 0.0012. Data cutoff date for IA1: January 30, 2024.

Kudo M, Ren Z, Guo Y, et al. *Lancet*. 2025;405(10474):203-215.

Most Common Treatment-Related Adverse Events[a] (≥25%)



n (%)	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 241
Treatment-related AEs[a]	234 (98.7)	204 (84.6)
Grade 3 or 4	169 (71.3)	75 (31.1)
Serious AEs	79 (33.3)	30 (12.4)
Led to discontinuation of both drugs	20 (8.4)	3 (1.2)
Grade 5	4 (1.7)[b]	1 (0.4)[c]

[a]Related to pembrolizumab, lenvatinib, and/or TACE. [b]1 patient each died from hepatic failure, gastrointestinal hemorrhage, myositis, and immune-mediated hepatitis. [c]1 patient died from brain stem hemorrhage. Data cutoff date for IA1: January 30, 2024. Kudo M, Ren Z, Guo Y, et al. *Lancet*. 2025;405(10474):203-215.

Answer:

Combining Local and Systemic Immunotherapies carry the promise of controlling hepatic tumors, delaying liver failure and potentially improving OS

However, OS benefit is still lacking/under investigation
And
Large randomized clinical trials are needed ..

Educational Objectives

- Updated data of adjuvant treatment for early-stage HCC at high risk of recurrence following surgery or ablation
- The changing landscape in combining TACE and systemic therapies in patients with unresectable HCC eligible for embolization
- **Conclusion**

Conclusions

- Recent advances in IO therapy in HCC in intermediate/advanced HCC are being translated into higher response rates and improved progression-free survival → However, IO tx remains palliative and predictive biomarkers are needed to identify candidates for curative tx

- New therapeutic targets to lower IO resistance are emerging and expected to improve curative rates. Dual CPI and cancer vaccines seem to lower resistance to IO.

- Integrating Immunotherapy into early-stage (operable) HCC requires an understanding of Benefit-Risk ratio, TME, and specific regimens MOA to address resistance to IO.

- Notably, designing future trials should be customized based on disease etiology, underlying liver disease, and tumor characteristics and requires global participation to address disparity in healthcare/trials access

Discussion Question

- A 75-year-old man with a history of hepatitis C is diagnosed with HCC with a Child-Pugh A score and a total of 5 lesions in both lobes of the liver. The lesions are amenable to TACE. Regulatory and reimbursement issues aside, which therapy would you most likely recommend?

Module 14: Systemic Mastocytosis and Myelofibrosis

Systemic Mastocytosis — Dr Bose

Myelofibrosis — Dr Kuykendall

Module 14: Systemic Mastocytosis and Myelofibrosis

Systemic Mastocytosis — Dr Bose

Myelofibrosis — Dr Kuykendall

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Systemic Mastocytosis

Prithviraj Bose, M.D.
Professor, Department of Leukemia
Co-Leader, Section of Myeloproliferative Neoplasms

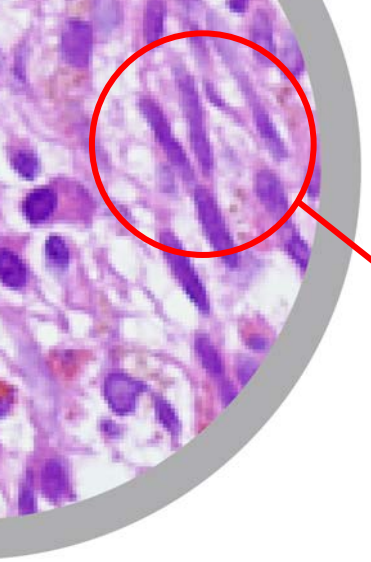
Fourth Annual General Medical Oncology Summit
Miami, FL, March 2, 2025

Disclosures

Advisory Committees	Blueprint Medicines, Geron Corporation, GSK, Karyopharm Therapeutics, Keros Therapeutics, PharmaEssentia, Sumitomo Dainippon Pharma Oncology Inc
Consulting Agreements	AbbVie Inc, Blueprint Medicines, Bristol Myers Squibb, Cogent Biosciences, CTI BioPharma, a Sobi Company, Disc Medicine, Geron Corporation, GSK, Incyte Corporation, Ionis Pharmaceuticals Inc, Jubilant Pharma Limited, Karyopharm Therapeutics, Keros Therapeutics, Morphic Therapeutic, MorphoSys, Novartis, Ono Pharmaceutical Co Ltd, PharmaEssentia, RayThera, Sumitomo Dainippon Pharma Oncology Inc
Contracted Research	Ajax Therapeutics, Blueprint Medicines, Bristol Myers Squibb, Cogent Biosciences, CTI BioPharma, a Sobi Company, Disc Medicine, GSK, Incyte Corporation, Ionis Pharmaceuticals Inc, Janssen Biotech Inc, Kartos Therapeutics, Karyopharm Therapeutics, MorphoSys, Sumitomo Dainippon Pharma Oncology Inc, Telios Pharma Inc

Slide courtesy of Jason Gotlib

WHO Diagnostic Criteria for Systemic Mastocytosis

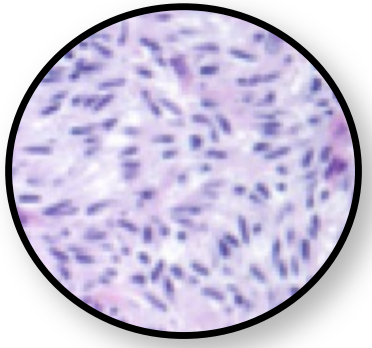


Major
- Mast cell aggregates (≥ 15) in the marrow or other extracutaneous tissue

Minor
- Spindle-shaped mast cells
- *KIT* D816V or other activating *KIT* mutation
- CD2 +/- CD25 expression on mast cells
- Serum tryptase > 20 ng/mL

Diagnosis requires:
1 major + 1 minor or ≥ 3 minor criteria)[1]

~65%



Indolent SM (ISM)

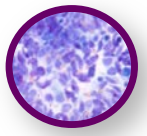
0 or 1 B-findings

Smoldering SM (SSM)

2 or more B-findings

Advanced SM

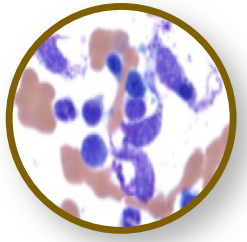
~10%



Aggressive SM (ASM)

≥1 or more C-findings

~25%



SM with an Associated Hematologic Neoplasm (SM-AHN)

1%

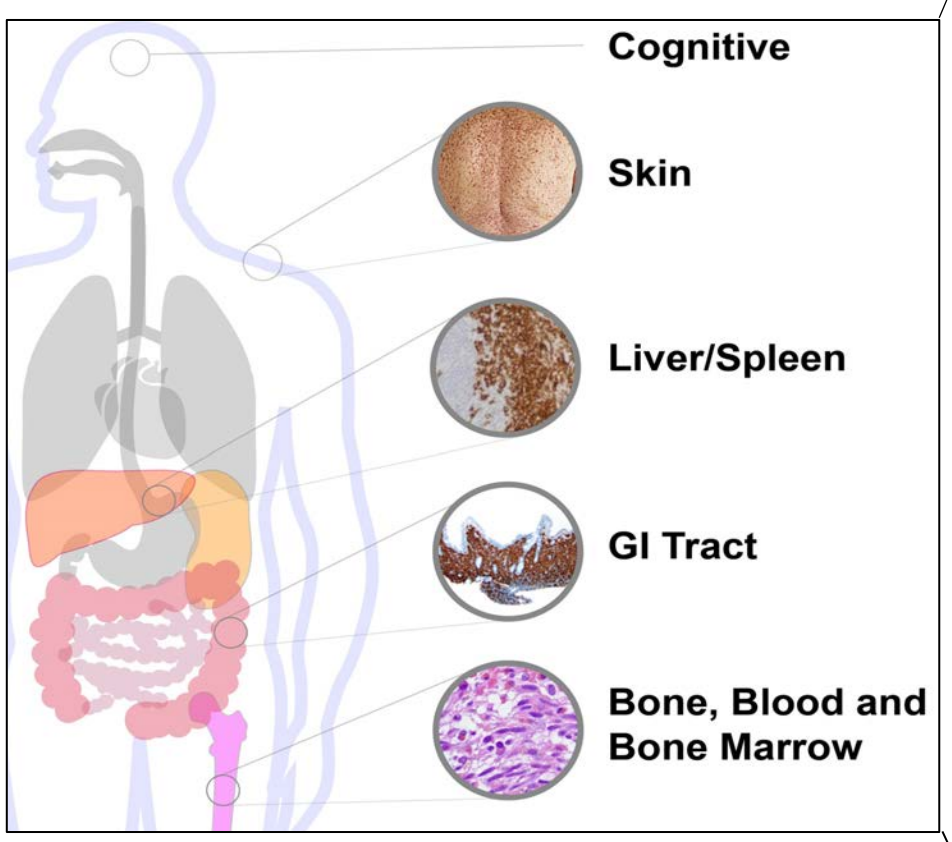
Mast Cell Leukemia (MCL)

≥20% mast cells on BM aspirate

[1]Horny H-P, *et al*, WHO Classification, 2017

Slide courtesy of Jason Gotlib

Heterogeneous extent and severity of SM-related organ involvement: B- and C-Findings



Neoplastic mast cells are not equal opportunity organ offenders

e.g. low marrow burden but severe liver disease in the same patient

'B Findings' (Higher Burden Disease)

1. BM: ≥30% mast cells and/or tryptase level ≥200 ng/ml and/or *KIT* D816V VAF ≥10% in BM or PB leukocytes
2. Hepatomegaly or splenomegaly without liver dysfunction or hypersplenism; or lymphadenopathy (> 2cm on CT or US)
3. Signs of dysplasia or myeloproliferation, without a frank AHN; normal or mildly abnormal blood counts

'C Findings' (Organ Damage) (Need for Cytoreduction)

1. Cytopenias (ANC <1/Hgb <10/plts <100) due to BM infiltration
2. Ascites and elevated liver enzymes ± hepatomegaly or cirrhotic liver ± portal hypertension
3. Large-sized osteolysis (≥2 cm) with pathologic fracture ± bone pain
4. Palpable splenomegaly with hypersplenism ± weight loss ± hypoalbuminemia
5. Malabsorption with hypoalbuminemia ± weight loss

ISM

0 or 1 B-finding

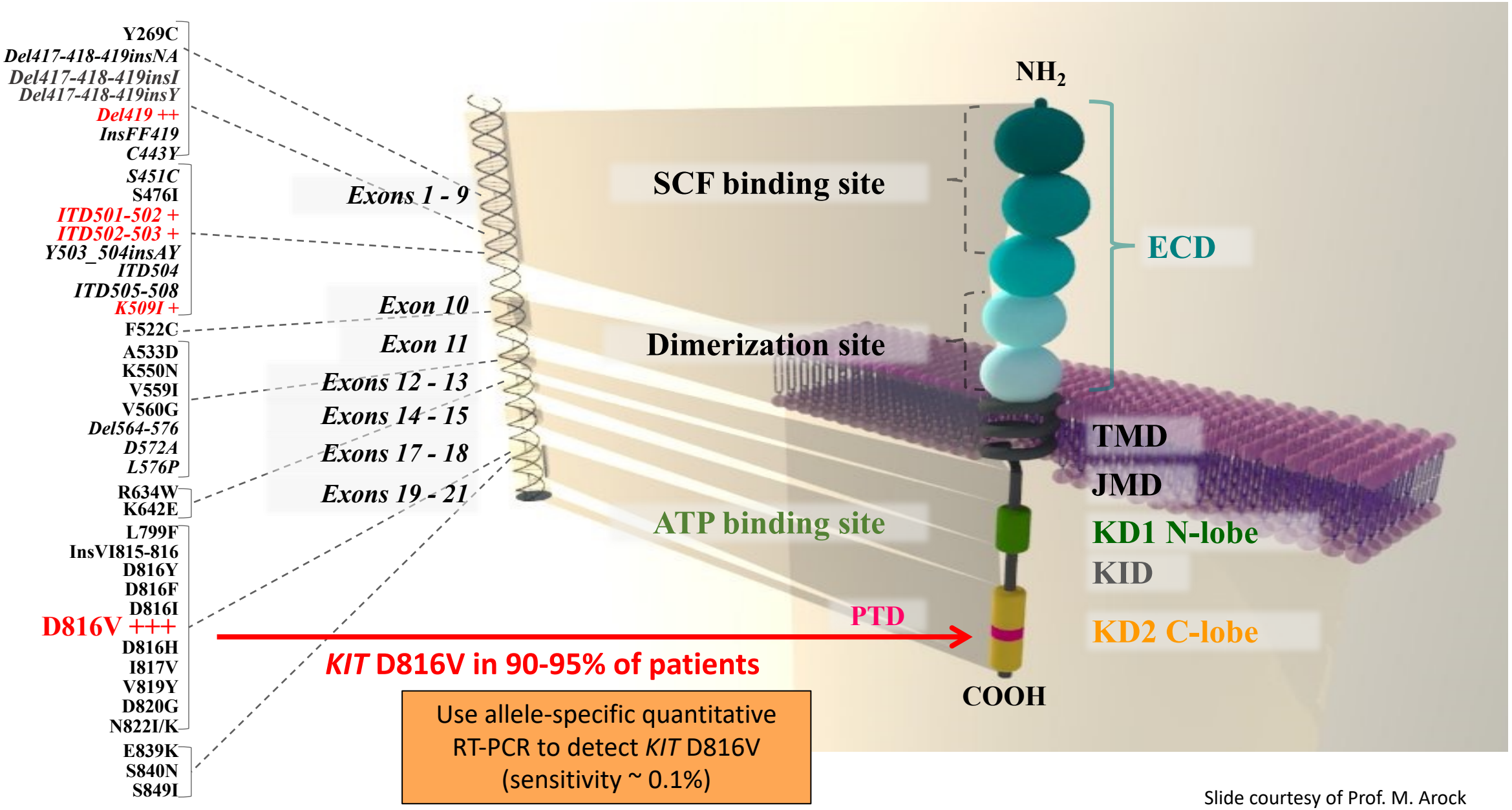
SSM

≥ 2 B-findings

ASM

≥1 C-findings

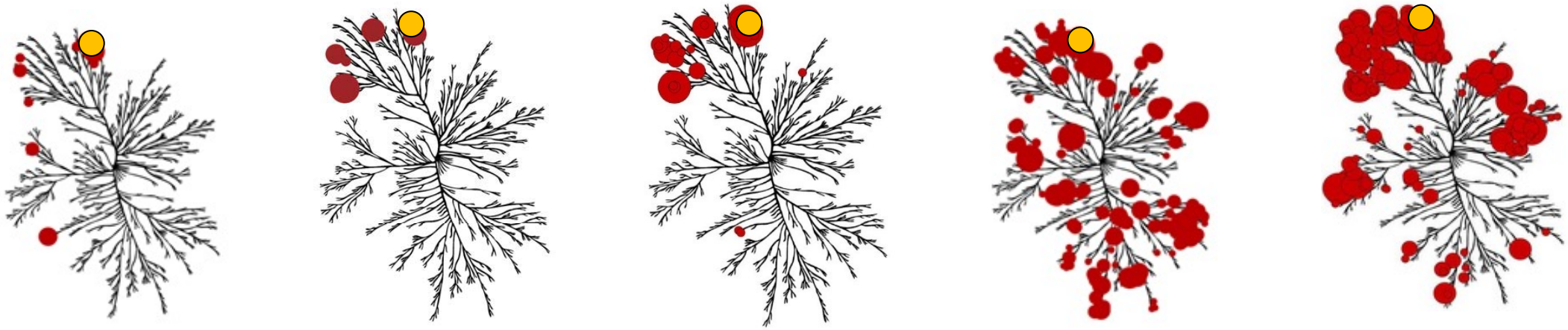
KIT Mutations are Found in the Vast Majority of SM Patients



Use allele-specific quantitative RT-PCR to detect *KIT* D816V (sensitivity ~ 0.1%)

Slide courtesy of Prof. M. Arock

Avapritinib potently and selectively targets *KIT* D816V



avapritinib imatinib masitinib midostaurin ripretinib

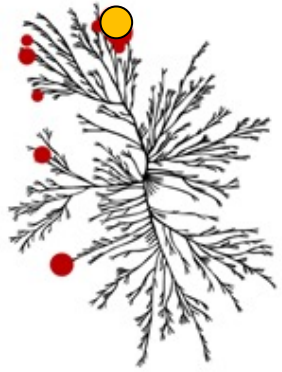
Binding to KIT Binding to other kinases (size is proportional to binding)

KIT D816V biochemical IC_{50}				
avapritinib*	imatinib*	masitinib#	midostaurin*	ripretinib#
0.27 nM	8150 nM	>1000 nM	2.9 nM	2.6 nM

Biochemical binding by DiscoverRX at 3uM

**Evans EK et al. Sci Transl Med. 2017;9(414)*
#Blueprint Medicines internal data on file

Avapritinib: phase I EXPLORER & phase 2 PATHFINDER studies



Avapritinib

- Binding to KIT
- Binding to other kinases

Avapritinib KIT D816V biochemical IC_{50}

0.27 nM

ORR: 75%*

N=69 evaluable patients

EXPLORER	**Phase 1 Open label single-arm**	**Enrollment complete (N=86)**
Dose Expansion (n=54) 300 mg QD 200 mg QD	***Primary Endpoint*** Maximum Tolerated Dose Recommended Phase 2 Dose	***Secondary Endpoint*** Overall Response Rate (ORR, in evaluable patients) **Changes in BM MC burden, *KIT* D816V VAF in PB and BM**
PATHFINDER	**Phase 2 Open label single-arm**	**Enrollment complete (N=107)**
200mg QD Central review Cohort 1 evaluable by mIWG Interim analysis after 32 patients evaluated for response Cohort 2 non-evaluable	***Primary Endpoint*** Overall Response Rate (ORR) (in evaluable cohort 1)	***Secondary Endpoint*** Mean Change in Total Symptom Score (both cohorts) **Changes in BM MC burden, *KIT* D816V VAF in PB and BM**

N=32 evaluable patients

Interim Analysis ORR: 75%*

BM, bone marrow; MC, mast cell;
mIWG, modified mIWG-MRT-ECNM response criteria,
PB; peripheral blood; VAF, variant allele frequency; QD, once a day

* per modified mIWG-MRT-ECNM response criteria

DeAngelo *et al*, *Nat Med*, 2021
Gotlib *et al*, *Nat Med*, 2021

EXPLORER: Overall response rate by modified IWG-MRT-ECNM criteria

30% molecular remission of *KIT* D816V using ddPCR with LOD of 0.17%

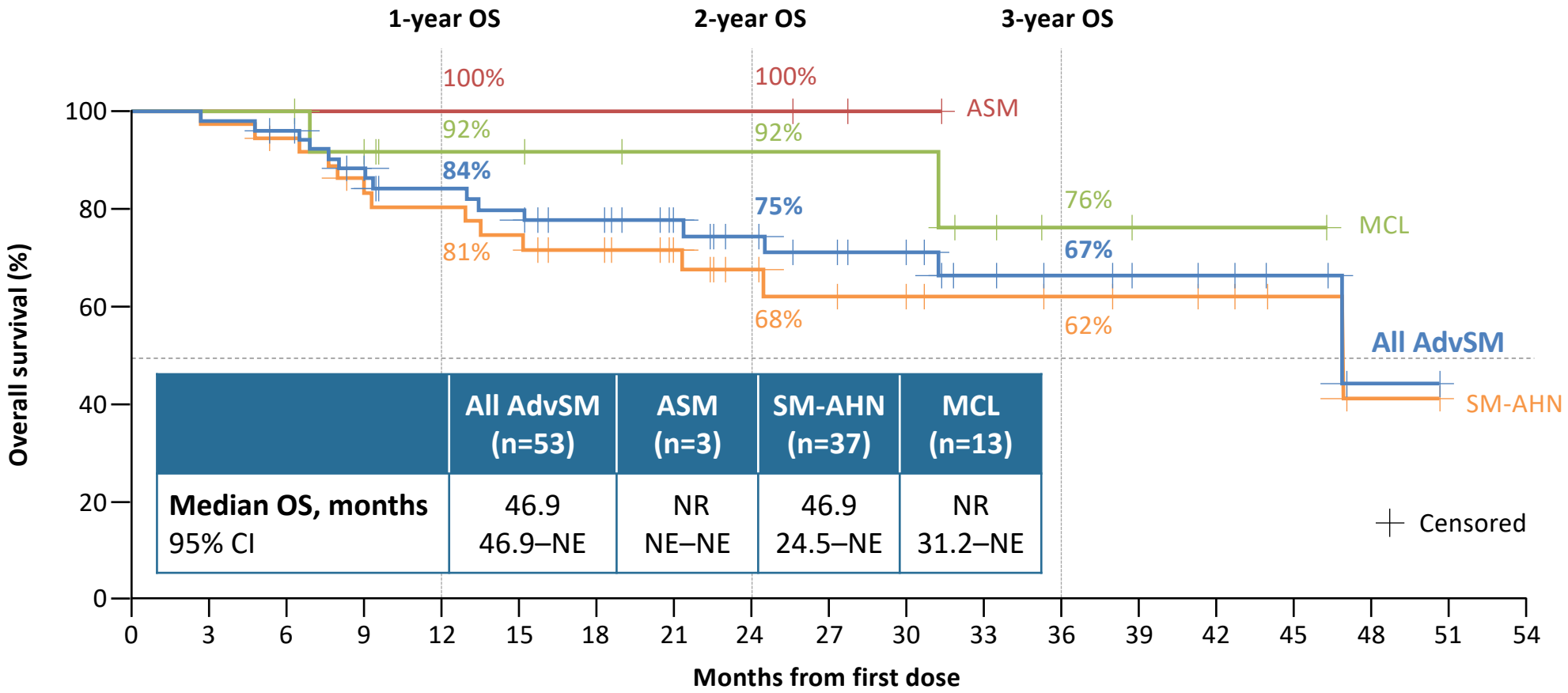
Best confirmed central response, n (%)	All evaluable (n=53)	ASM (n=3)	SM-AHN (n=37)	MCL (n=13)	Midostaurin naïve (n=36)	Post midostaurin (n=17)
ORR (CR + CRh + PR + CI)	40 (75)	3 (100)	28 (76)	9 (69)	30 (83)	10 (59)
CR or CRh[a]	19 (36)	2 (67)	14 (38)	3 (23)	16 (44)	3 (18)
Complete remission (CR)	8 (15)	0	5 (14)	3 (23)	6 (17)	2 (12)
CRh	11 (21)	2 (67)	9 (24)	0	10 (28)	1 (6)
Partial remission (PR)	18 (34)	1 (33)	13 (35)	4 (31)	12 (33)	6 (35)
Clinical improvement (CI)	3 (6)	0	1 (3)	2 (15)	2 (6)	1 (6)
Stable disease (SD)	12 (23)	0	8 (22)	4 (31)	6 (17)	6 (35)
Progressive disease (PD)	0	0	0	0	0	0
Not evaluable (NE)	1 (2)[b]	0	1 (3)[b]	0	0	1 (6)[b]

All data in this presentation is as of a data cut-off of May 27, 2020
LOD=limit of detection

DeAngelo *et al*, *Nature Med*, 2021

[a]Partial hematologic recovery: ANC >0.5×10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) *and* platelet count >50×10^9/L *and* Hgb level >8.0 g/dL.
[b]Not evaluable due to ending study with insufficient follow-up for response assessment (<13 weeks).
ASM, aggressive systemic mastocytosis; MCL, mast cell leukemia; SM-AHM, systemic mastocytosis with associated hematologic neoplasm.

Overall survival on avapritinib (efficacy population of EXPLORER)



	All AdvSM (n=53)	ASM (n=3)	SM-AHN (n=37)	MCL (n=13)
Median OS, months	46.9	NR	46.9	NR
95% CI	46.9–NE	NE–NE	24.5–NE	31.2–NE

Patients at risk:

All AdvSM	53	52	50	43	39	37	33	26	22	19	16	12	9	7	6	4	1	0
ASM	3	3	3	3	3	3	3	3	3	2	1	0						
SM-AHN	37	36	34	30	28	26	23	17	13	11	9	8	7	6	5	3	1	0
MCL	13	13	13	10	8	8	7	6	6	6	6	4	2	1	1	1	0	

NR, not reached; NE, not estimable; OS, overall survival.

DeAngelo *et al*, *Nature Med*, 2021

PATHFINDER: Avapritinib demonstrated a high response rate across subtypes and regardless of prior treatment

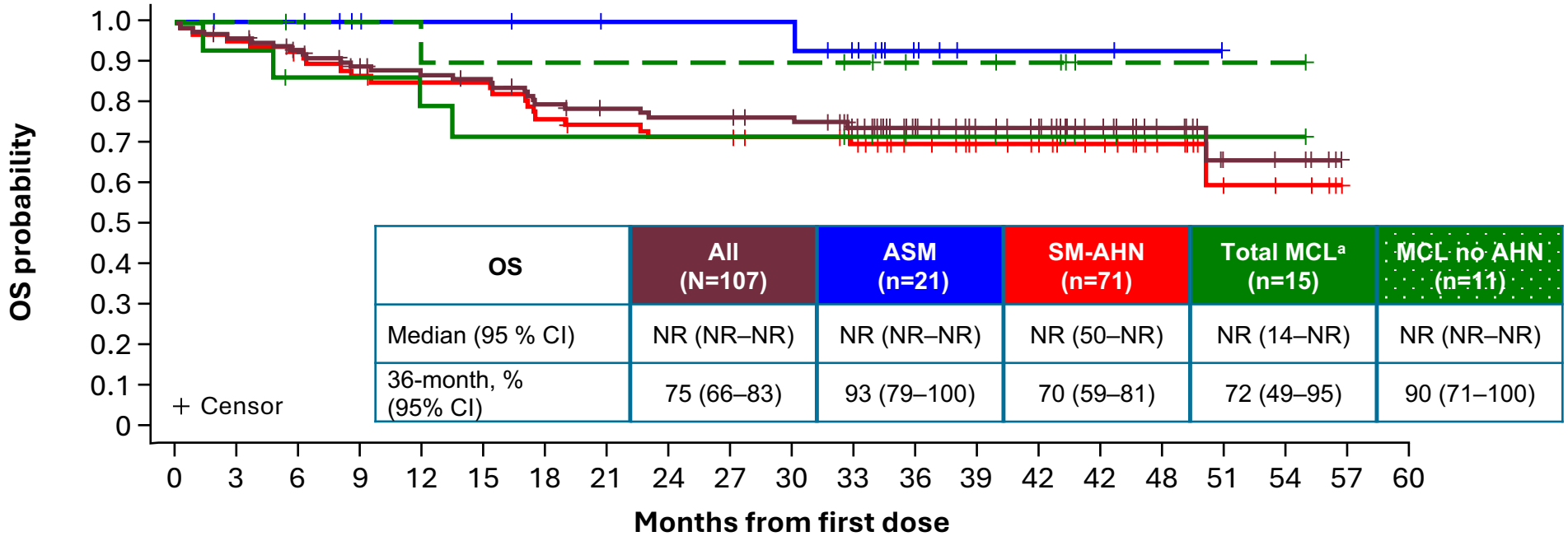
	All[a] (n=83)	AdvSM subtype			Treatment-naïve (n=30)	Patients with ≥1 prior systemic therapy (n=53)
		ASM (n=13)	SM-AHN (n=55)	MCL (n=15)		
ORR,[b] n (%) **95% CI**	**61 (73)** **63–83**	10 (77) 46–95	41 (75) 61–85	10 (67) 38–88	26 (87) 69–96	35 (66) 52–79
Best response						
CR or CRh[c]	**24 (29)**	3 (23)	18 (33)	3 (20)	13 (43)	11 (21)
CR	**13 (16)**	1 (8)	9 (16)	3 (20)	7 (23)	6 (11)
CRh	**11 (13)**	2 (15)	9 (16)	0	6 (20)	5 (9)
PR[d]	**33 (40)**	7 (54)	19 (35)	7 (47)	13 (43)	20 (38)
CI	**4 (5)**	0	4 (7)	0	0	4 (8)
SD	**13 (16)**	3 (23)	7 (13)	3 (20)	3 (10)	10 (19)
PD	**2 (2)**	0	1 (2)	1 (7)	0	2 (4)
NE	**7 (8)**	0	6 (11)	1 (7)	1 (3)	6 (11)
Patients with best *KIT* D816V VAF response <1%, n (%)[e]	55 (67)	8 (62)	38 (70)	9 (60)	27 (90)	28 (54)

Data cut-off date: September 15, 2023. Median follow-up of 38 months. [a]ORR evaluable per mIWG-MRT-ECNM criteria at baseline. [b]Best confirmed response per mIWG-MRT-ECNM criteria. CR+CRh+PR+CI. [c]CRh requires full resolution of all evaluable C-findings, elimination of BM mast cell aggregates, serum tryptase <20 ng/mL, resolution of palpable hepatosplenomegaly, and partial hematologic recovery (defined as absolute neutrophil count >0.5×10^9/L with normal differential, platelet count >50×10^9/L, and hemoglobin level >8.0 g/dL). [d]PR requires full resolution of ≥1 evaluable C-findings and ≥50% reduction in both bone marrow mast cells and serum tryptase. [e]82 of 83 patients had baseline and post baseline VAF measurements; 1 patient (SM-AHN with prior systemic treatment) had no post baseline VAF measurement.

95% CI, 95% confidence interval; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; mCR, morphologic complete remission; mCRh, morphologic complete remission with partial recovery of peripheral blood counts; mPR, morphologic partial remission; NR, not reached; PR, partial response; PD, progressive disease; SD, stable disease.

Reiter A et al. EHA 2024;Abstract S224

PATHFINDER: Median overall survival was not reached regardless of AdvSM subtype



OS	All (N=107)	ASM (n=21)	SM-AHN (n=71)	Total MCL[a] (n=15)	MCL no AHN (n=11)
Median (95 % CI)	NR (NR–NR)	NR (NR–NR)	NR (50–NR)	NR (14–NR)	NR (NR–NR)
36-month, % (95% CI)	75 (66–83)	93 (79–100)	70 (59–81)	72 (49–95)	90 (71–100)

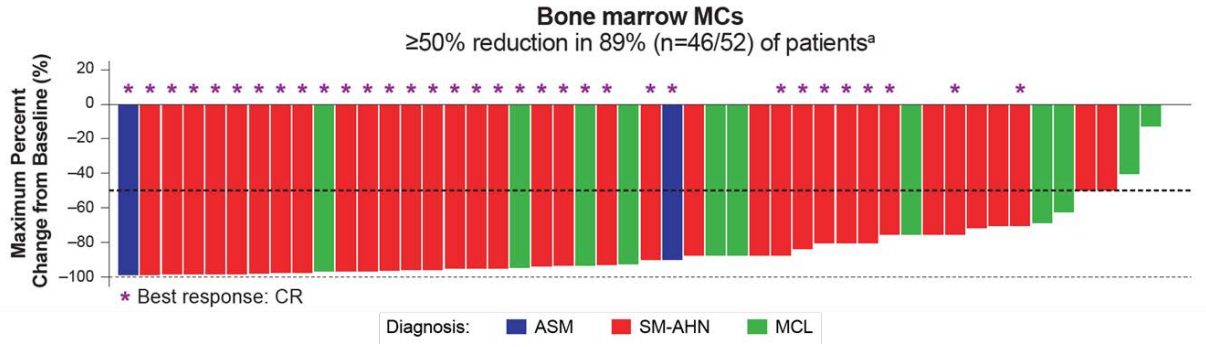
At risk																				
All AdvSM	107	102	96	89	85	83	76	73	71	71	69	61	46	35	32	22	13	6	5	0
ASM	21	20	20	17	16	16	15	14	14	14	14	11	6	3	3	2	1	0		
SM-AHN	71	68	64	60	58	57	51	49	47	47	45	41	33	25	23	18	11	5	4	0
Total MCL[a]	15	14	12	12	11	10	10	10	10	10	10	9	7	7	6	2	1	1	1	0
MCL no AHN	11	11	10	10	9	9	9	9	9	9	9	8	6	6	5	1	1	1	1	0

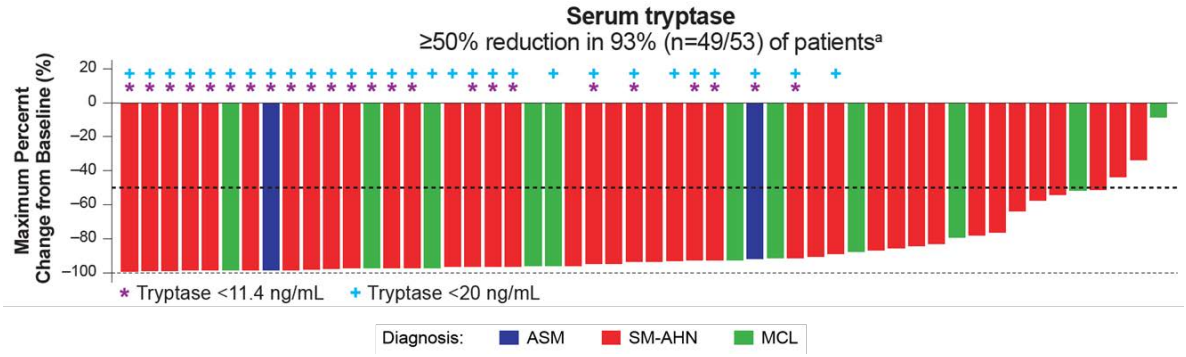
Data cut-off date: September 15, 2023. Median (range) follow-up was 38 months (95% CI; 35.5–42.0). [a]Includes subset with no AHN (n=11) and subset with AHN (n=4). Per WHO classification, the diagnostic criteria for subtyping MCL includes BM aspirate smears ≥20% (regardless of the presence of AHN).

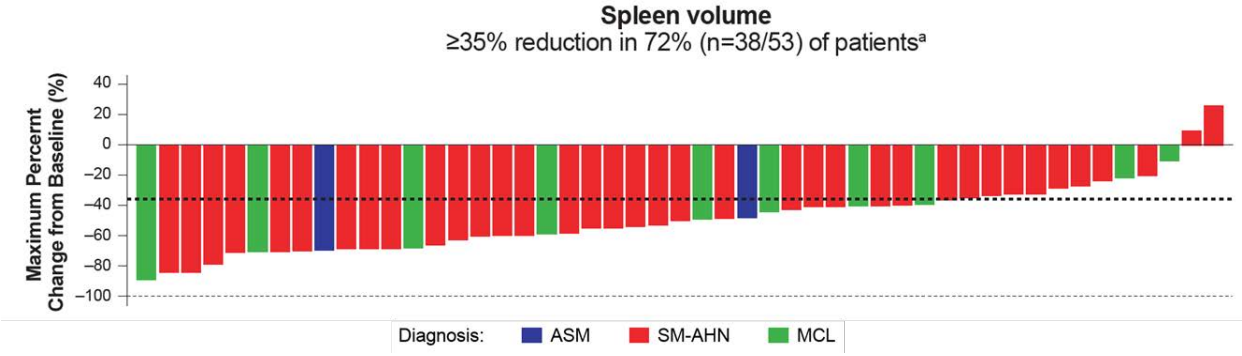
Reiter A et al. EHA 2024;Abstract S224

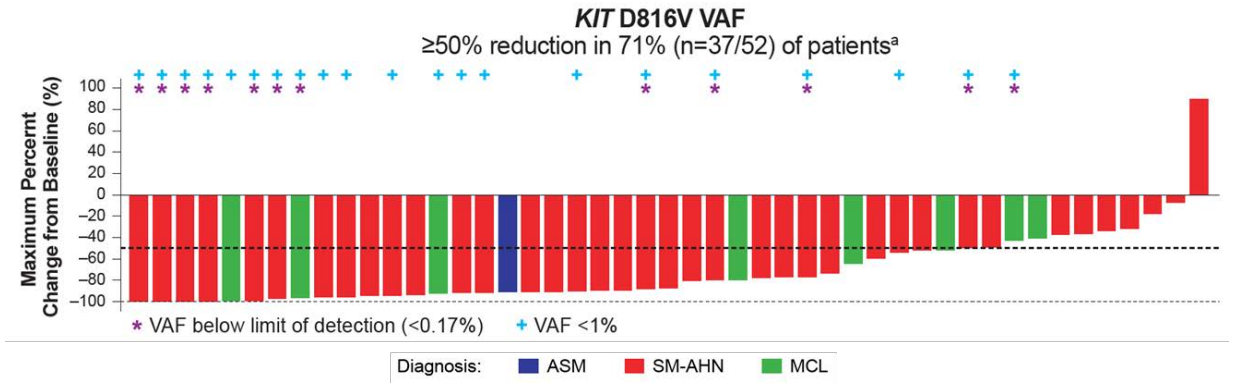
Reduction in measures of mast cell burden: pooled data from EXPLORER / PATHFINDER

(Response-evaluable population)









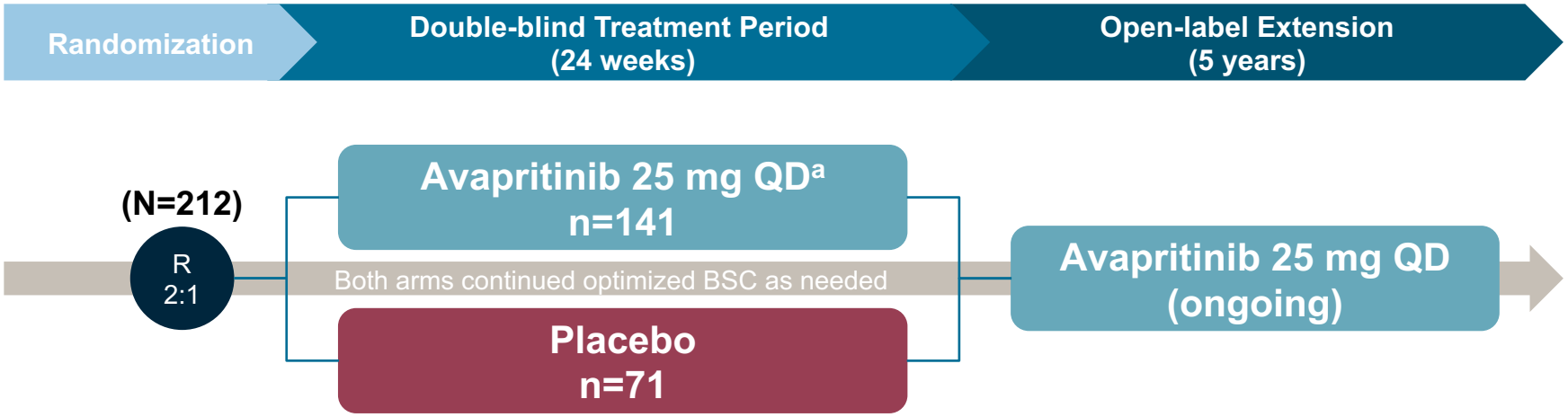
Data cut-off date of May 27, 2020, for EXPLORER and June 23, 2020, for PATHFINDER. [a]Calculation includes patients without post-baseline assessments who were excluded from the waterfall plot. VAF, variant allele fraction.

Reiter A et al. Blood Adv. 2022 Jun 2;6(21):5750–5762.

Registrational PIONEER study: randomized, double-blind, placebo-controlled study in patients with ISM

Screening Period

- Best supportive care medications (BSC) optimized for 2–3 months
  - Antihistamines, cromolyn, anti-IgE antibody, leukotriene inhibitors, corticosteroids, etc.
- Eligibility
  - Age ≥18 years
  - ISM confirmed by central pathology review
  - Uncontrolled moderate-to-severe (TSS ≥28) symptoms after at least 2 BSC medications



Symptoms

- Mean change in ISM-SAF Total Symptom Score (TSS) from baseline to Week 24 (primary endpoint)
- Mean change in individual symptom scores of ISM-SAF
- Mean change in most severe symptom score

Biomarkers of Mast Cell Burden

- ≥50% reduction in serum tryptase levels
- ≥50% reduction in KIT D816V VAF in peripheral blood (or below level of detection [<0.02%] for patients with a detectable mutation at baseline)
- ≥50% reduction in in bone marrow mast cell aggregates

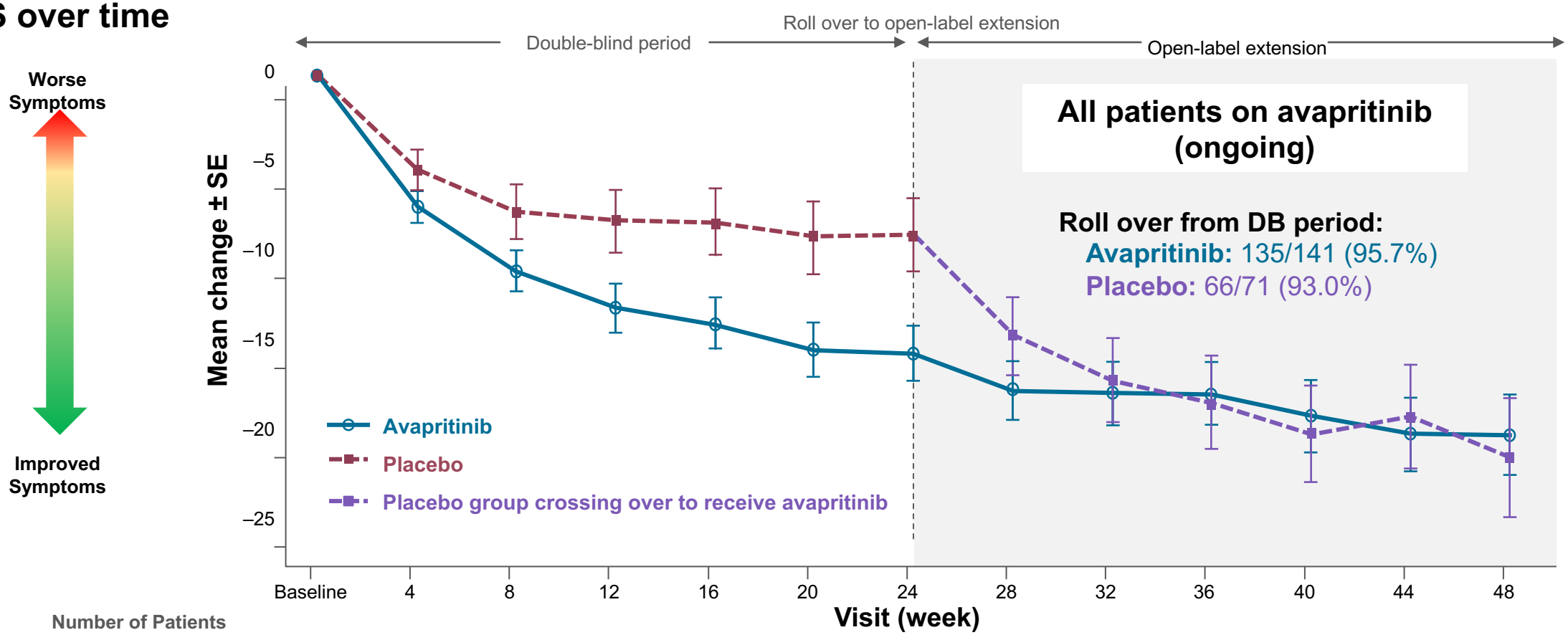
Quality of Life

- Mean % change in QoL score, as measured by MC-QoL

[a]The recommended dose of avapritinib for Part 2 and Part 3 was identified based on efficacy and safety results from Part 1 that included 4 cohorts: 25 mg avapritinib (n=10), 50 mg avapritinib (n=10), 100 mg avapritinib (n=10) and placebo (n=9). Patients treated with high dose steroids within 7 days of primary endpoint (n=4) were excluded from the week 24 analysis, but included at other timepoints of the study.
Percentages were calculated based on available data at the timepoint. One-sided *P*-values are reported for primary and key secondary endpoints.
ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; QD, once-daily. QoL, quality of life; R, randomized; VAF, variant allele fraction.

Avapritinib demonstrated significant and durable improvement in symptoms versus placebo

TSS over time



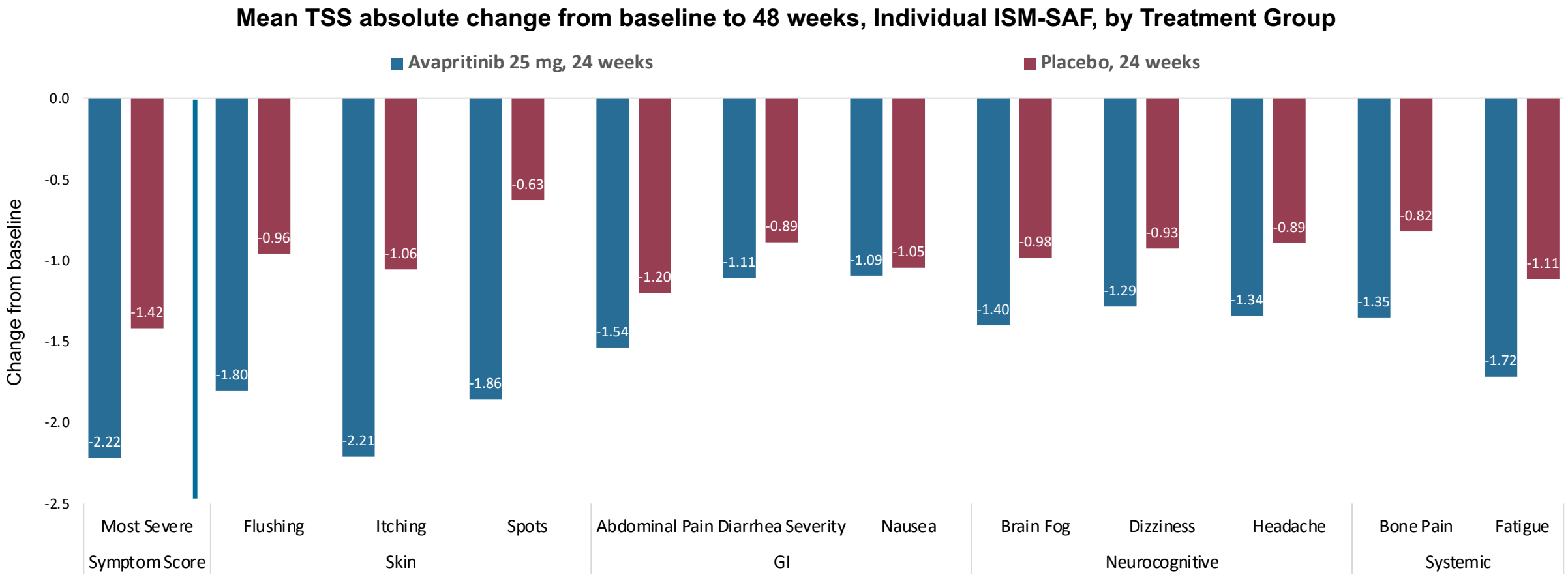
Number of Patients	Baseline	4	8	12	16	20	24	28	32	36	40	44	48
Avapritinib	139	137	135	135	137	136	133	123	106	91	76	70	60
Placebo	71	71	71	68	67	66	66	60	51	41	39	33	26

At Week 24	Avapritinib 25 mg (N=141)	Placebo (N=71)	P-value
Mean change in TSS (95% CI)	-15.58 (-18.61, -12.55)	-9.15 (-13.12, -5.18)	0.003

A one-sided P-value of <0.025 was needed to declare avapritinib as superior in reducing TSS versus placebo.
DB, double-blind.

Gotlib J et al. NEJM Evid 2023

Avapritinib demonstrated improvement in all individual ISM symptoms versus placebo including the most severe symptom at baseline



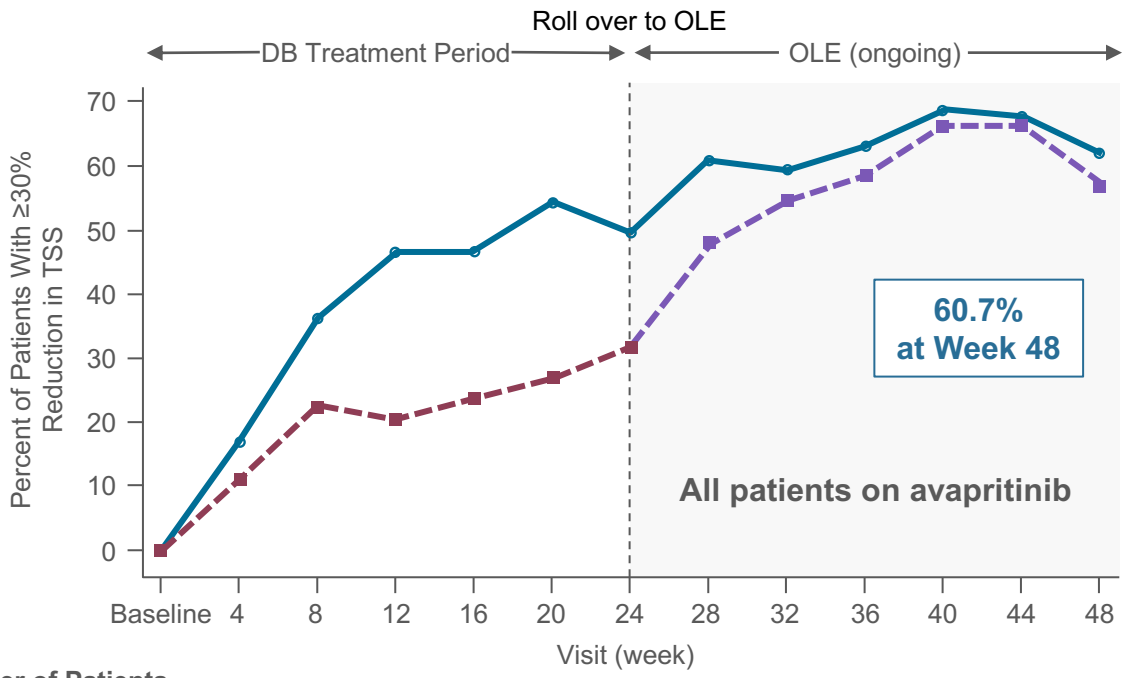
Mean Change in Most Severe Symptom Score (SD)	Avapritinib 25 mg (n=128)	Placebo (n=65)	P-Value
	-2.22 (2.302)	-1.42 (1.875)	0.015

Regardless of which symptom was rated most severe at baseline, avapritinib patients had a significant reduction in this symptom versus placebo

Gotlib J et al. NEJM Evid 2023

Avapritinib-treated patients were significantly more likely than placebo to reach the TSS ≥30% and TSS ≥50% thresholds over time

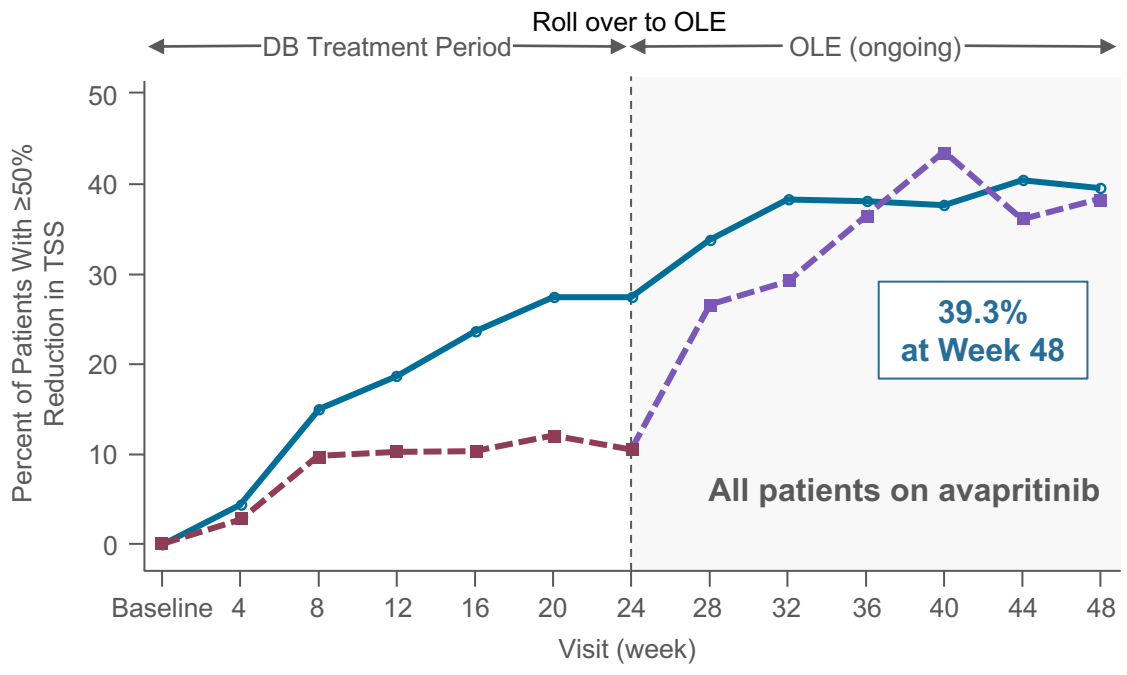
≥30% reduction in ISM-SAF TSS score over time



Number of Patients

Avapritinib + BSC	139	135	133	133	135	134	131	121	104	89	74	69	58
Placebo + BSC	71	71	71	68	67	66	66	60	51	41	39	33	26

≥50% reduction in ISM-SAF TSS score over time



	139	135	133	133	135	134	131	121	104	89	74	69	58
	71	71	71	68	67	66	66	60	51	41	39	33	26

Treatment group: Avapritinib 25 mg QD + BSC; Placebo + BSC; Placebo + BSC group crossing over to receive avapritinib 25 mg QD

At Week 24	Avapritinib 25 mg (N=141)	Placebo (N=71)	P-value
Proportion of patients with **≥30% reduction in TSS** (95% CI)	45.4% (37.0, 54.0)	29.6% (19.3, 41.6)	0.009

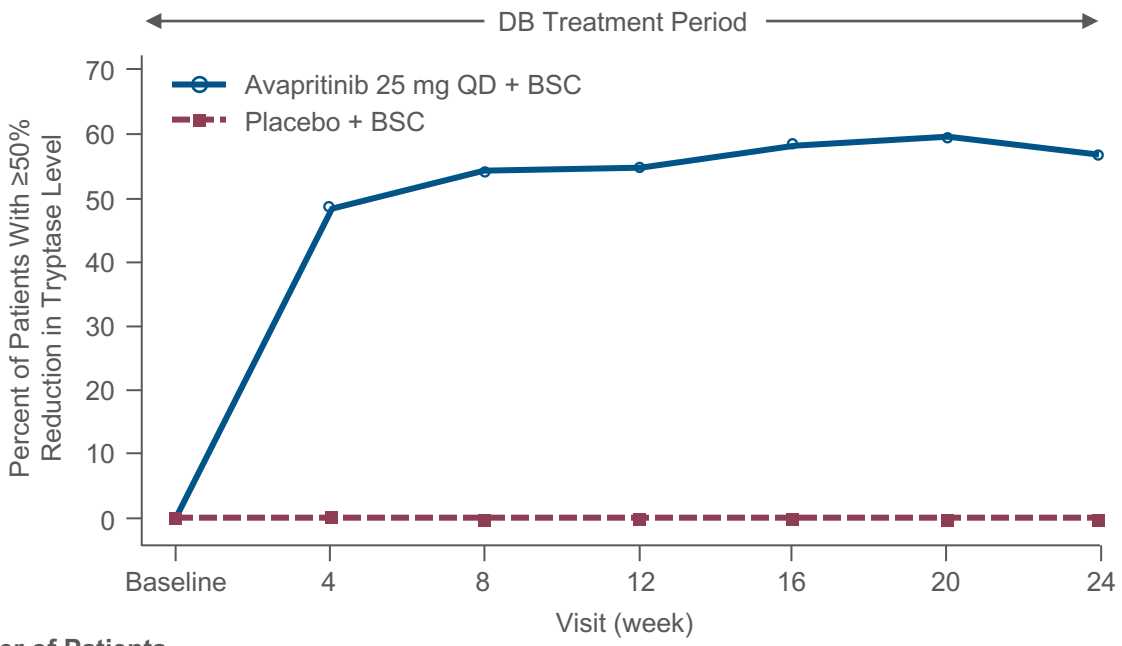
At Week 24	Avapritinib 25 mg (N=141)	Placebo (N=71)	P-value
Proportion of patients with **≥50% reduction in TSS** (95% CI)	24.8% (17.9, 32.8)	9.9% (4.1, 19.3)	0.005

BSC, best supportive care; CI, confidence interval; DB; double blind; ISM-SAF, ISM symptom assessment form; OLE, open-label extension; QD, once-daily; TSS, total symptom score.

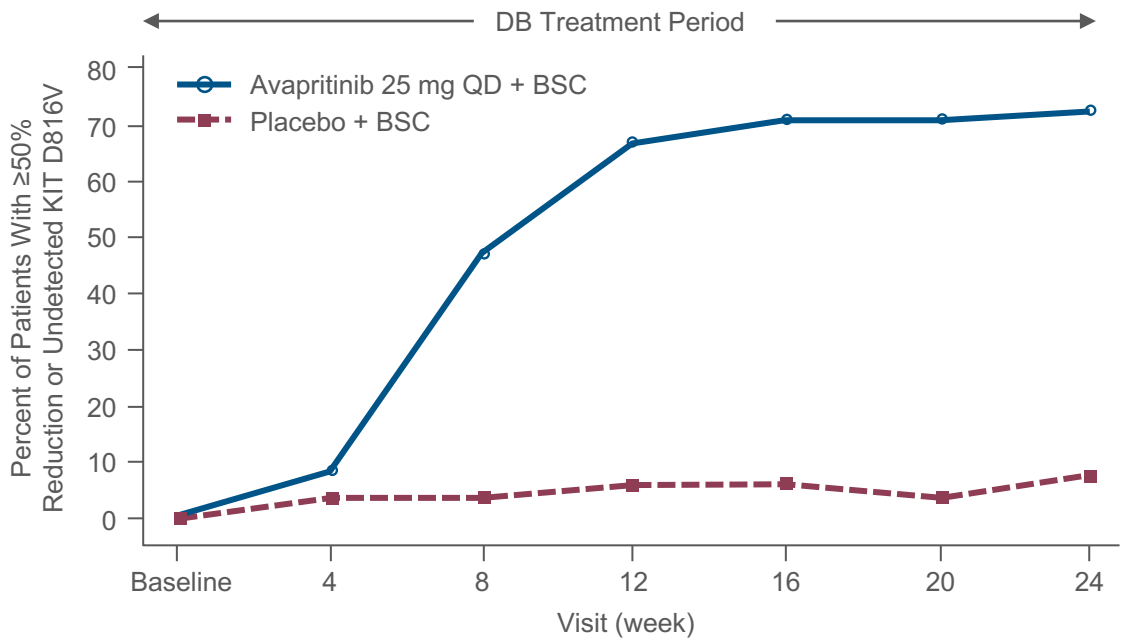
Gotlib J et al. NEJM Evid 2023

Rapid and sustained reductions in biomarkers of mast cell burden in avapritinib-treated patients vs. placebo

Patients with ≥50% reduction in tryptase[a]



Patients with ≥50% reduction in *KIT* D816V VAF[a]



Number of Patients

Avapritinib + BSC	141	133	136	132	133	128	134
Placebo + BSC	71	66	62	61	60	62	64

Avapritinib + BSC	118	110	113	109	107	104	109
Placebo + BSC	63	57	54	52	51	53	54

At Week 24	Avapritinib 25 mg (N=141)	Placebo (N=71)	P-value
Proportion of patients with **≥50% reduction in serum tryptase** (95% CI)	53.9% (45.3, 62.3)	0.0% (0.0, 5.1)	<0.0001

At Week 24	Avapritinib 25 mg (N=141)	Placebo (N=71)	P-value
Proportion of patients with **≥50% reduction in *KIT* D816V VAF** (95% CI)	67.8% (58.6, 76.1)	6.3% (1.8, 15.5)	<0.0001

At Week 24	Avapritinib 25 mg (N=141)	Placebo (N=71)	P-value
Proportion of patients with **≥50% reduction in BM MC aggregates** (95% CI)	52.8% (42.9, 62.6)	22.8% (12.7, 35.8)	<0.0001

BM, bone marrow; BSC, best supportive care; CI, confidence interval; MC, mast cell; QD, once-daily; VAF, variant allele fraction.

Gotlib J et al. NEJM Evid 2023

Bezuclastinib potently and selectively inhibits KIT-D816V[1]

- Oral, selective, and type I tyrosine kinase inhibitor (TKI) with potent activity against *KIT* D816V, an activation loop mutation[1]
- In non-clinical models, spares closely related kinases, has minimal brain penetration, and favorable PK properties[1]
- Inhibition of closely related kinases have been linked to off-target toxicities, such as bleeding, edema, and pleural effusions[1]

Kinase inhibition profile of clinical stage and approved *KIT*–D816V agents; Cell IC_{50} (nm)

Compound	KIT V560G/D816V (HMC 1.2)	WT KIT	PDGFRα	PDGFRβ	CSF1R	FLT3	KDR
Bezuclastinib	**14**	**121**	**>10,000**	**>10,000**	**>10,000**	**>1000**	**>1000**
Avapritinib	13	114	53	10	249	305	>1000
Elenestinib	6	355	21	6	161	345	>1000

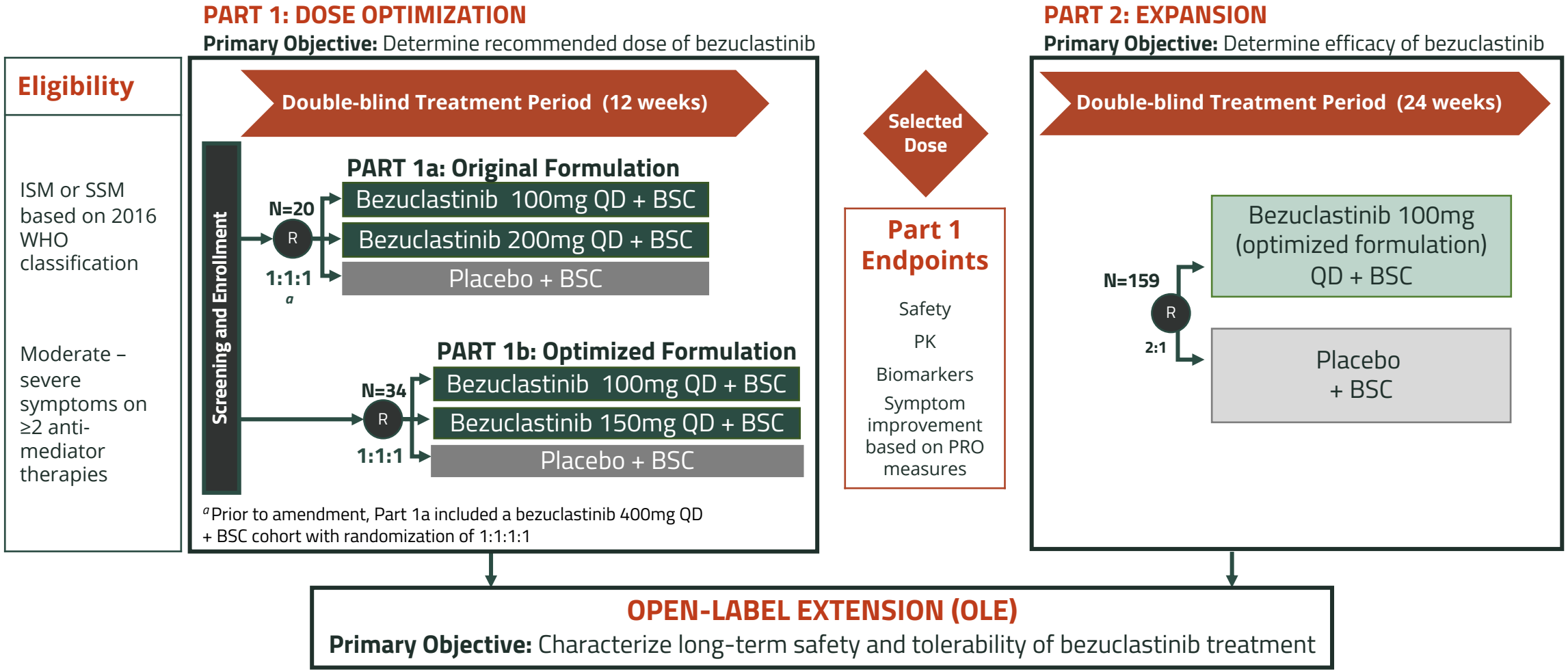
Higher IC50 numbers indicate lower levels of activity against other off-target kinases, limiting associated toxicities, e.g. edema, hypertension, and pleural effusion

Adapted from: Guarieri et al. AACR 2022;Abstract 147. Castells M et al. EHA 2022;Abstract P1017.

1. Dave N et al. Presented at AACR 2021;Abstract CT122.

Summit (NCT05186753): Phase 2 Double-Blind, Placebo-Controlled Randomized Clinical Study Evaluating Bezuclastinib in NonAdvSM

Figure 2. Summit Phase 2 Study Design

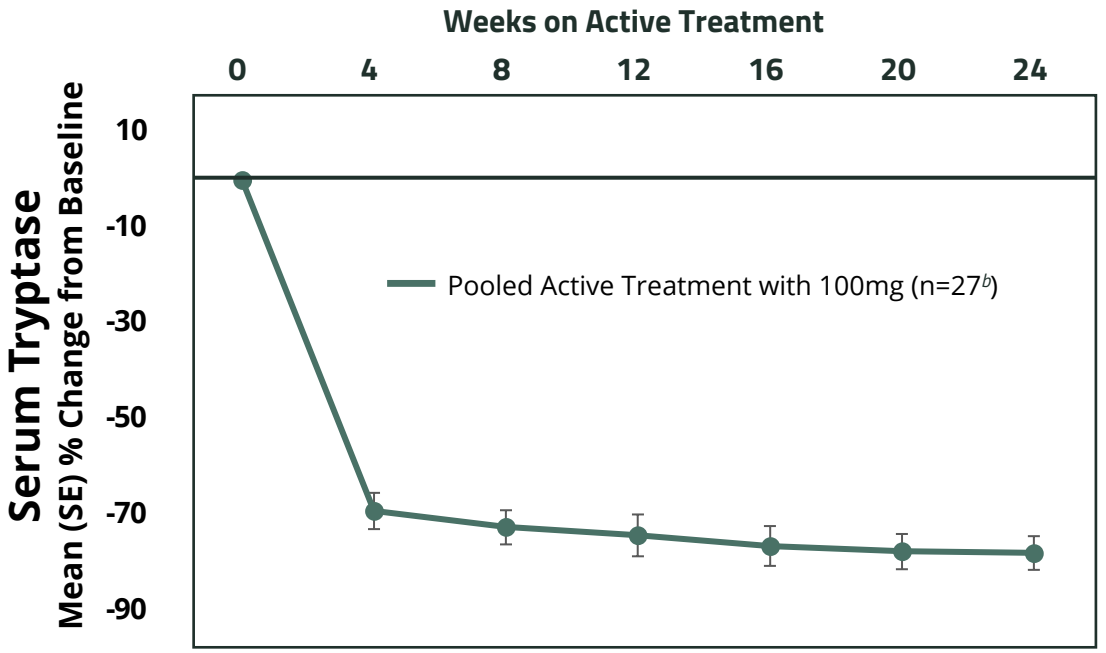


All data herein are as of data cut-off date of 29-Aug-2024.
BSC: Best supportive care

Bezuclastinib 100mg Led to Rapid, Deep, and Sustained Reductions in Serum Tryptase Over the Course of 24 Weeks of Treatment

- 89% of patients had a ≥50% decrease in serum tryptase levels by 4 weeks of treatment with bezuclastinib 100mg QD
- Of patients with baseline serum tryptase ≥20ng/mL, 95% (20/21) of patients treated with 100mg bezuclastinib achieved <20ng/mL
- Of patients with baseline serum tryptase ≥11.4ng/mL, 84% (21/25) of patients treated with 100mg bezuclastinib achieved <11.4ng/mL

Figure 5. Mean Percent Change from Baseline in Serum Tryptase in Pooled[a] Patients Receiving 100mg Bezuclastinib



[a]Includes all patients who received bezuclastinib 100mg QD during Part 1 or OLE. Change from baseline is taken during 24 weeks of active therapy.
[b]n=24, 25, or 26 at some timepoints

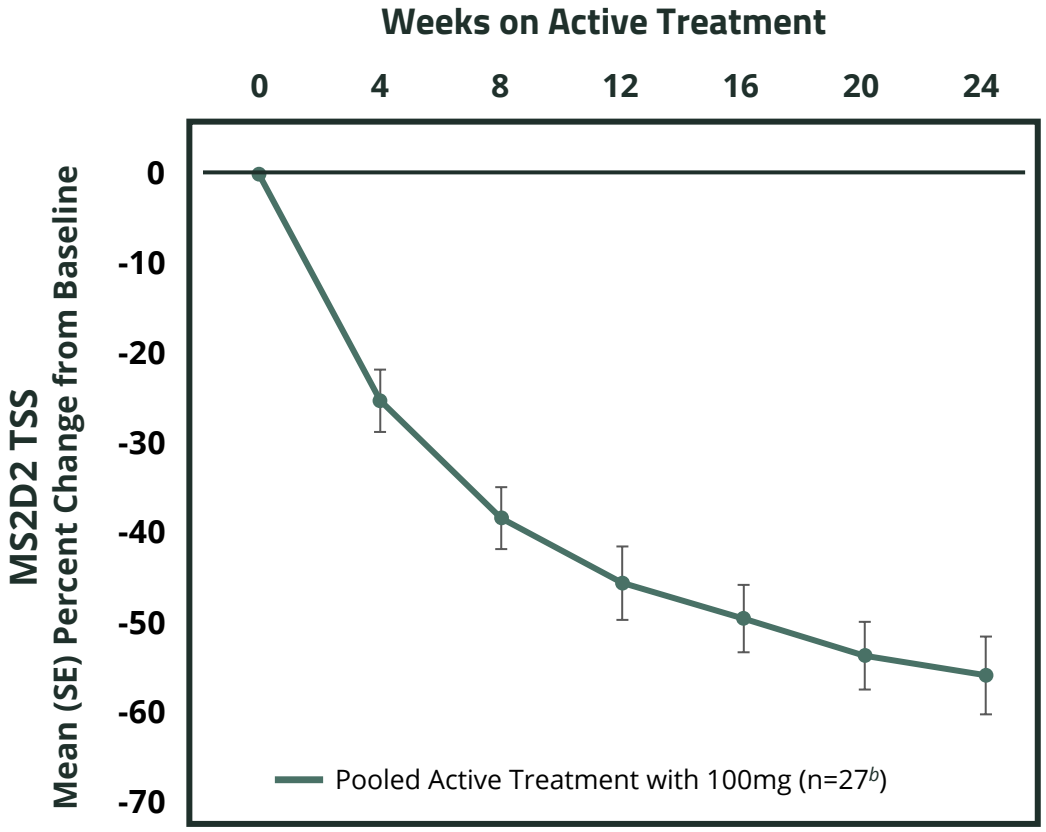
Summit NONADVANCED SM

Rein LAM et al. ASH 2024;Abstract 4556

Data cut 29-Aug-2024

Patients Receiving Bezuclastinib 100mg in Part 1 + OLE Reported Sustained Improvements in Symptom Severity

Figure 6. Mean Percent Change from Baseline in MS2D2 Total Symptom Score Over Time in Pooled[a] Patients Receiving 100mg Bezuclastinib



Among patients receiving 100mg active treatment with bezuclastinib for 24 weeks:

- MS2D2 Total Symptom Score reduced by a mean of 27.6 points
- MS2D2 Total Symptom Score reduced from baseline by a mean of 55.8%

By 24 weeks of active treatment, 31% of patients had reductions or discontinuations in BSC medications[c]

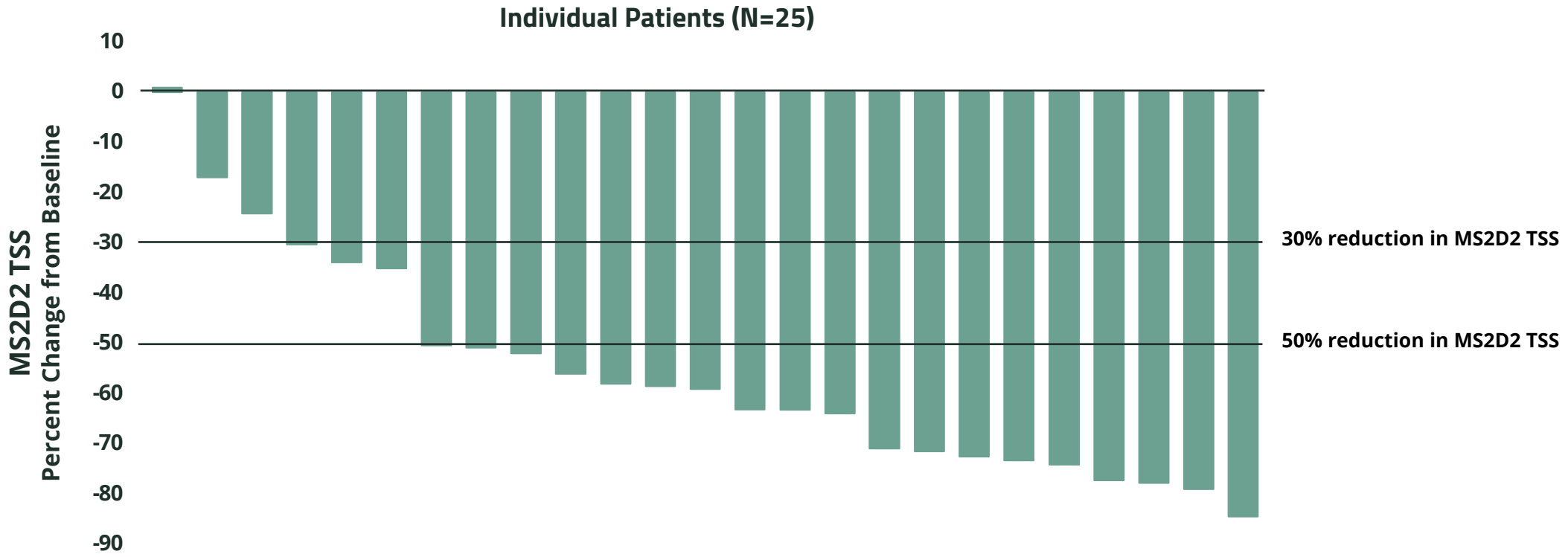
[a]Includes all patients who received bezuclastinib 100mg QD through 24 weeks of active treatment.
[b]n=25 or 26 at some timepoints
[c]Per protocol, best supportive care (BSC) modification was only allowed in the OLE.

Rein LAM et al. ASH 2024;Abstract 4556

Data cut 29-Aug-2024

Bezuclastinib 100mg in Part 1 + OLE Showed Significant Clinical Improvements in Symptoms of Non-Advanced SM

Figure 7. Percent Change from Baseline in MS2D2 Total Symptom Score after 24 Weeks Active Treatment in Individual Patients Receiving 100mg Bezuclastinib



Among patients receiving 100mg active treatment with bezuclastinib for 24 weeks:

- 88% of patients reached at least 30% reduction in MS2D2 TSS
- 76% of patients reached at least 50% reduction in MS2D2 TSS

Summit NONADVANCED SM

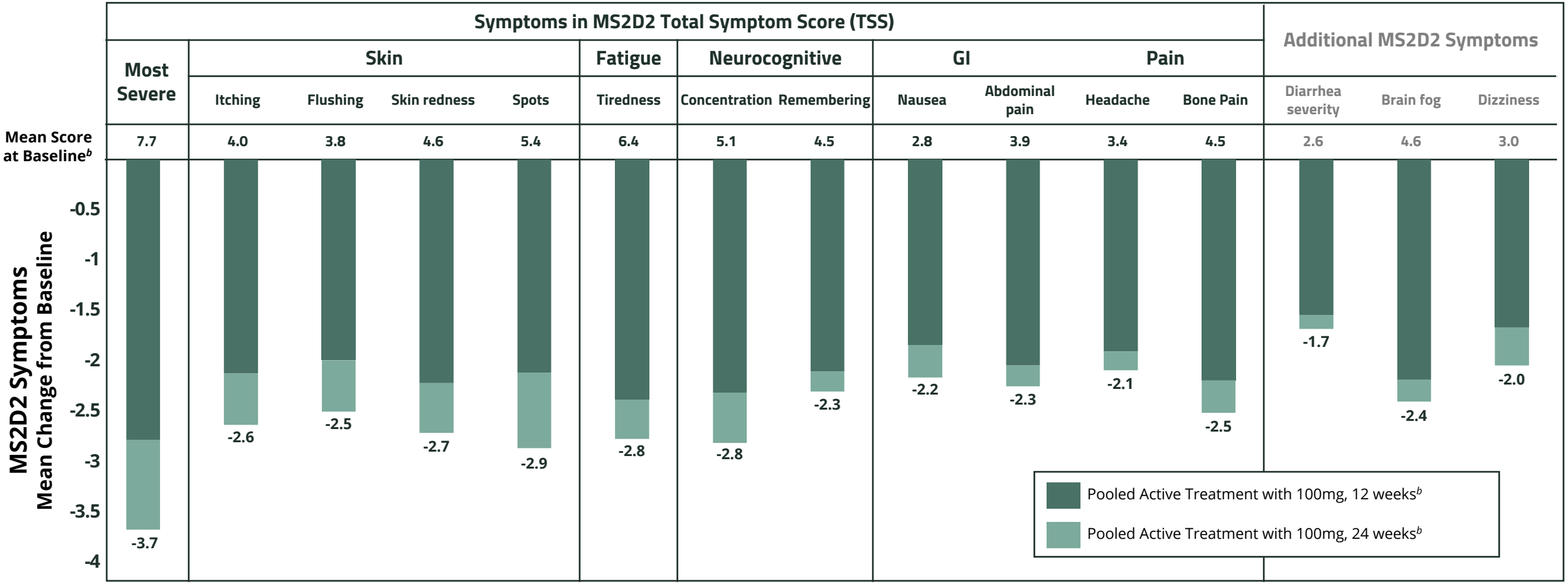
[a]Includes all patients who received bezuclastinib 100mg QD during Part 1 or OLE. The reported change is at 24 weeks of active therapy.

Rein LAM et al. ASH 2024;Abstract 4556

Data cut 29-Aug-2024

Patients Receiving Bezuclastinib 100mg Demonstrated Clinically Meaningful Changes in Symptoms that Deepened with 24 Weeks of Treatment

Figure 8. Mean Change from Baseline in MS2D2 Symptom Score in Pooled[a] Patients Receiving 100mg Bezuclastinib



[a]Includes all patients who received bezuclastinib 100mg QD during Part 1 or OLE. Change from baseline is taken after 12 and 24 weeks of active therapy.
[b]N=27 at baseline, N=26 at 12 weeks, and N=25 at 24 weeks.

Rein LAM et al. ASH 2024;Abstract 4556

Data cut 29-Aug-2024

Apex (NCT04996875): A Phase 2 Open-Label, Multicenter Clinical Study of Bezuclastinib in Patients with Advanced Systemic Mastocytosis

FOCUS OF PRESENTATION

PART 1: DOSE OPTIMIZATION
ORIGINAL FORMULATION

- 50 mg BID
- 100 mg BID
- 200 mg BID
- 400 mg QD

PART 2
OPTIMIZED FORMULATION[a]

STAGE 1
DOSE CONFIRMATION

- 150mg QD
- 300 mg QD

Selected Exposure/Dose: 150mg QD

STAGE 2
EXPANSION

~55 patients with measurable C-findings per mIWG-MRT-ECNM

PART 2: ADDITIONAL COHORTS

- ~15 patients without measurable C-findings per mIWG-MRT-ECNM
- ~20 high-risk AHN patients w/concurrent azacitidine or hydroxyurea

Mean (CV%) Steady-State (Cycle 2 Day 1) Exposures

Study Part (Formulation)	Part 1 (Original Formulation)	Part 2 Stage 1 (Optimized Formulation[a])
Bezuclastinib Dose	100 mg BID (N=7)	150 mg QD (N=10)
$C_{max, ss}$ (ng/mL)	861 (26.8)	850 (29.9)
$AUC_{0-24hr,ss}$ (ng*hr/mL)	18,900 (30.8)	17,600 (31.3)

150 mg QD of the optimized formulation delivers similar exposures to 100 mg BID of original formulation

[a]The original formulation was modified to improve bioavailability.

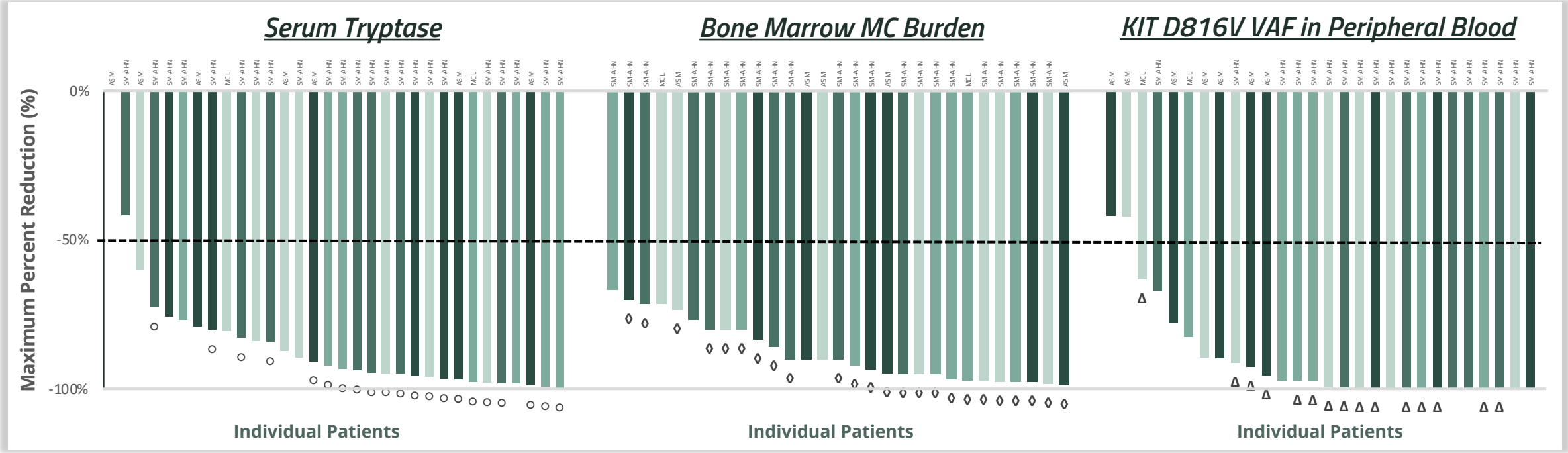
DeAngelo DJ, et al. American Society of Hematology (ASH) 2024; San Diego, CA, 8 Dec 2024: Publication Number: 659

Apex Part 1: Responses by mIWG-MRT-ECNM Criteria Were Observed In Both TKI Exposed and Naïve Patients

	Confirmed mIWG-MRT-ECNM Responses per CRRC		
Best Response, n (%) [a]	**All**	**TKI‡ Therapy Naïve**	**Prior TKI[b] Exposure**
	N=27	**N=18**	**N=9**
Overall response rate			
CR + CRh + PR + CI[c]	**14 (52)**	**11 (61)**	**3 (33)**
CR + CRh + PR	**13 (48)**	**10 (56)**	**3 (33)**
Complete Response (CR + CRh)	**7 (26)**	**7 (39)**	**0**
Partial Response (PR)	**6 (22)**	**3 (17)**	**3 (33)**
Clinical Improvement (CI)	**1 (4)**	**1 (6)**	**0**
Stable Disease (SD)	**10 (37)**	**6 (33)**	**4 (44)**
Not evaluable	**3 (11)**	**1 (6)**	**2 (22)**

[a] 5 patients without measurable C-finding at baseline were excluded for being non-evaluable per mIWG-MRT-ECNM criteria; one additional patient was excluded due to discontinuation prior to first dose (not dosed [ND]).
[b] SM-directed therapy with midostaurin only (n=4) or midostaurin and avapritinib (n=5)
[c] Primary endpoint of Apex study
Data as of: 11Oct2024
DeAngelo DJ, et al. American Society of Hematology (ASH) 2024; San Diego, CA, 8 Dec 2024: Publication Number: 659

Bezuclastinib Demonstrates Deep Reductions in Markers of Mast Cell Burden



- 94% (30/32) achieved ≥50% reduction
- 100% (29/29) with at least 2 cycles of treatment achieved ≥50% reduction
- 66% (21/32) achieved <20 ng/mL

- 100% (29/29) with baseline and ≥1 post-baseline assessment achieved ≥50% reduction
- 83% (24/29) achieved complete clearance of mast cell aggregates by central review

- 93% (26/28) achieved a ≥50% reduction
- 71% (15/21) achieved VAF <1%

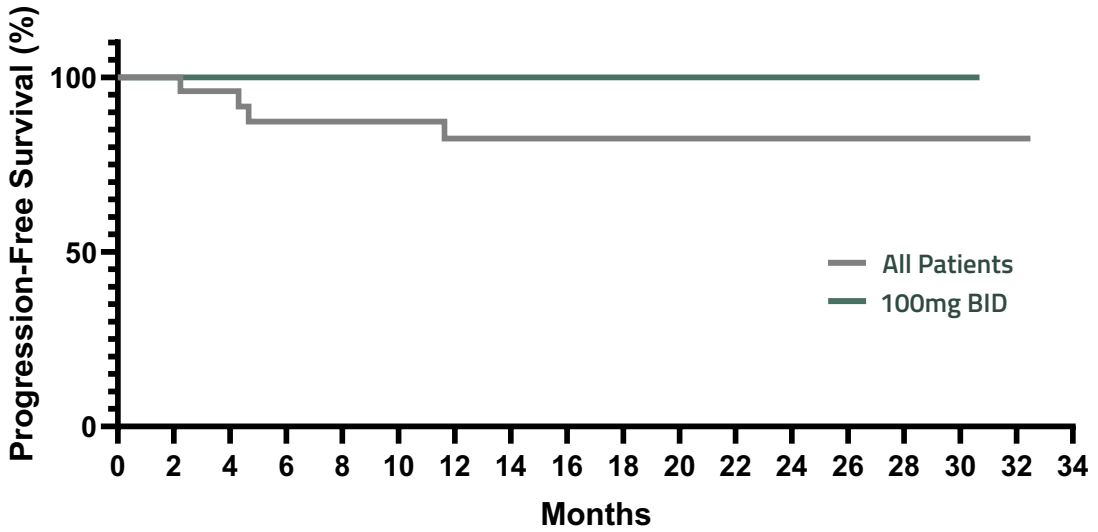
50 mg BID
100 mg BID
200 mg BID
400 mg QD

Milestone Achieved
○ <20 ng/mL serum tryptase
◊ Complete clearance of mast cell aggregates
Δ < 1% *KIT* D816V VAF

Data as of: 11Oct2024
DeAngelo DJ, et al. American Society of Hematology (ASH) 2024; San Diego, CA, 8 Dec 2024: Publication Number: 659

Median PFS and Duration of Response Were Not Reached

Progression-free survival (PFS[a]) in mIWG-MRT-ECNM-evaluable population (n=27)



Pts at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
All Pts	27	25	22	19	19	19	17	15	12	9	9	7	6	6	2	2	1	0
100 BID	7	7	7	7	7	7	7	7	6	5	4	4	3	3	3	2	0	0

- Median PFS not yet reached at median study follow-up of 20 months
- PFS rate was 82% at 24 months

Duration of response (DOR) (N=27)

- Median duration of response not yet reached
- Median (range) time to achieve mIWG-MRT-ECNM confirmed response of PR or better (CR, CRh, PR) was 2.2 (1.9-7.5) months

Disease Progression in Overall Population (N=32)

- No patients had SM progression
- 7 patients developed progression of AHN
  - AML transformation (3), progression of MDS (2), worsening of CMML (2)
  - 3 patients remained on bezuclastinib and began treatment with azacitidine in the rollover cohort

[a]PFS progression includes death or CRRC assessment of progressive disease
Data as of: 11Oct2024
DeAngelo DJ, et al. American Society of Hematology (ASH) 2024; San Diego, CA, 8 Dec 2024: Publication Number: 659

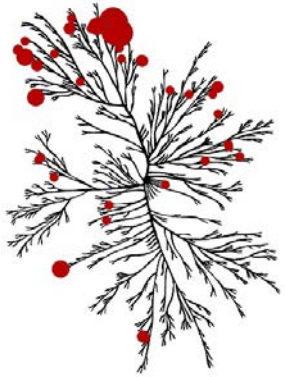
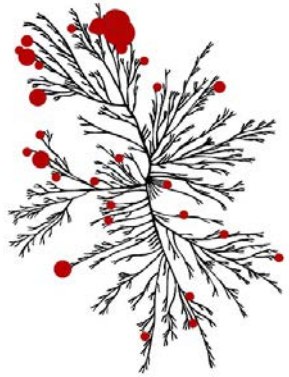
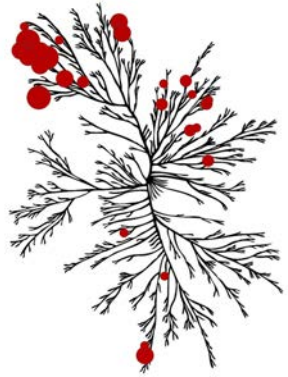
Elenestinib (BLU-263): A next-generation, potent, selective KIT D816V inhibitor

- **Elenestinib** is a novel, investigational, oral, next-generation tyrosine kinase inhibitor that is non-brain penetrant[1,2]
- **Potently** and **selectively** inhibits KIT D816V while **preferentially sparing** wild-type KIT

	KIT D816V phosphorylation IC_{50}	WT KIT proliferation IC_{50}	WT KIT phosphorylation IC_{50}
Elenestinib	**3.1 nM**	**95.9 nM**	**82.6 nM**
Avapritinib	**3.1 nM**	**85.8 nM**	**89.5 nM**
Bezuclastinib	**3.4 nM**	**26.4 nM**	**32.5 nM**

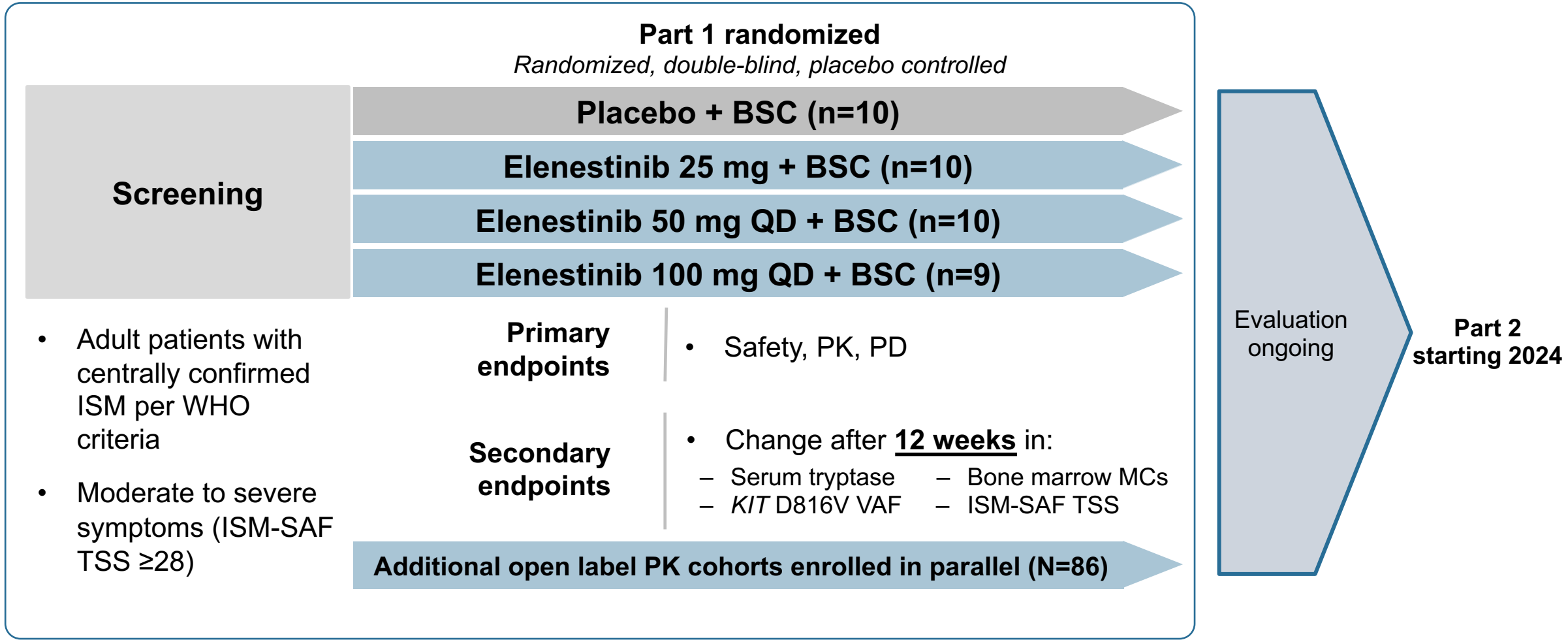
- **Well-characterized** product formulation allowing for **once-daily** (QD) dosing[1,2]

Selectivity profiles of KIT D816V inhibitors in clinical development or approved for systemic mastocytosis

Drug:	Elenestinib	Avapritinib	Bezuclastinib
Kinome tree[a]:			
Selectivity S-score: (fraction of kinome bound by drug, more selective = lower s-score)	0.035	0.035	0.057
	First in human 2020, investigational	First in human Oct 2015, **approved**	First in human Mar 2015, investigational

[a]Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines is not responsible for its content.
IC_{50}, half-maximal inhibitory concentration; QD, once daily; WT, wild-type.
1. Dave N et al. Presented at AACR 2021. Poster #CT122; 2. Castells M et al. Presented at EHA 2022. Poster #1017

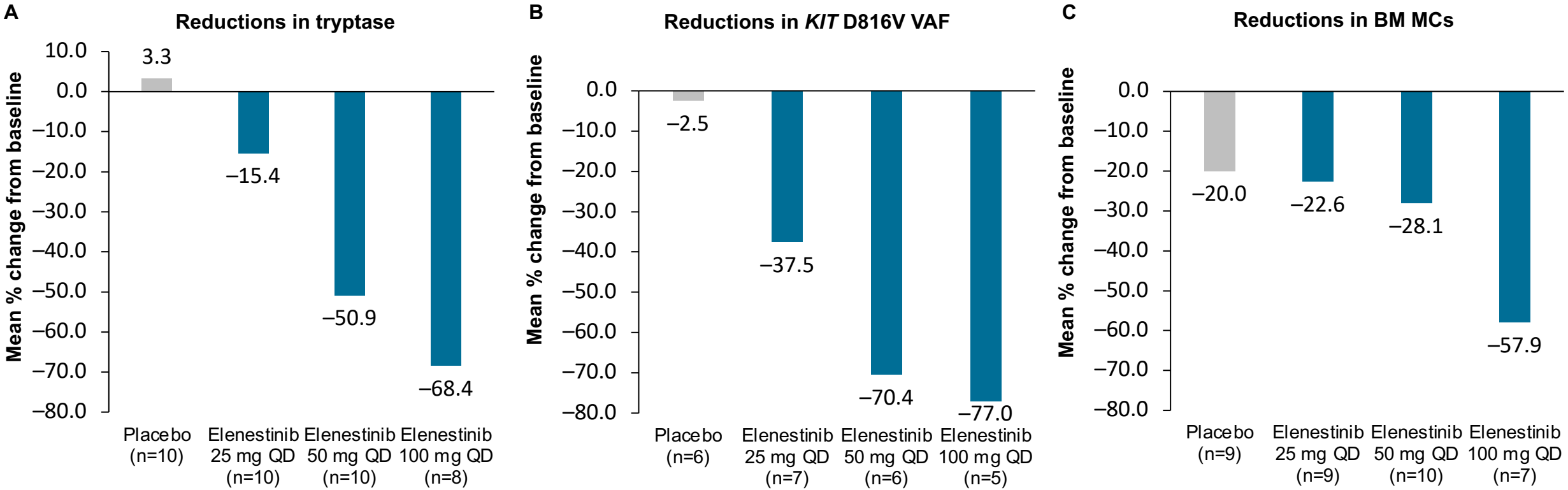
HARBOR Part 1[a]: Randomized, double-blind, placebo-controlled dose-finding part of elenestinib



[a]NCT04910685.
BSC, best supportive care; PD, pharmacodynamics; PK, pharmacokinetic; VAF, variant allele fraction; WHO, World Health Organization.

After 12 weeks of elenestinib, all biomarkers of disease burden improved

- Patients receiving elenestinib at doses of 25 mg, 50 mg, and 100 mg QD demonstrated dose-dependent mean percent reductions from baseline in **serum tryptase levels (A), *KIT* D816V VAF (B)**, and **bone marrow MCs (C)** *versus* placebo

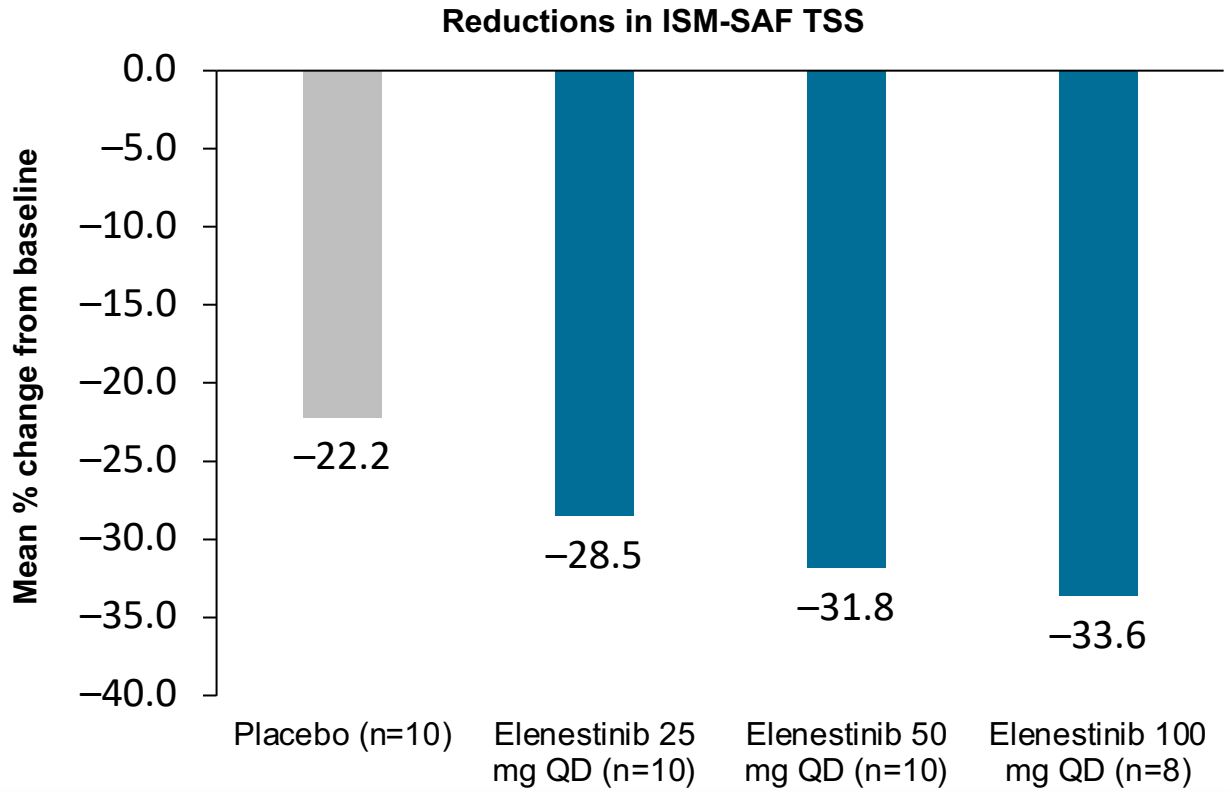


BM, bone marrow.

Tashi T et al. ASH 2023;Abstract 76.

After 12 weeks of elenestinib, symptom improvement was observed for all dose cohorts

- All elenestinib dose cohorts demonstrated clinically meaningful changes in symptoms without clear dose dependence
- Percentage change of symptom reduction in TSS was greater for patients on elenestinib *versus* placebo in the blinded portion of Part 1



Tashi T et al. ASH 2023;Abstract 76.

Discussion Questions

- A patient with indolent systemic mastocytosis is initially treated with H1 and H2 blockers, montelukast and cromolyn sodium but after 6 months continues to report daily pruritus, frequent urticarial reactions to various stimuli, brain fog and fatigue (platelet count ≥50,000/μL). What would you most likely recommend?

Discussion Questions

- Regulatory and reimbursement issues aside, what initial therapy would you most likely recommend for a patient with aggressive systemic mastocytosis and mild to moderate cognitive impairment (platelet count ≥50,000/μL)?

- How, if at all, does the presence of thrombocytopenia affect your choice of treatment of systemic mastocytosis?

Module 14: Systemic Mastocytosis and Myelofibrosis

Systemic Mastocytosis — Dr Bose

Myelofibrosis — Dr Kuykendall

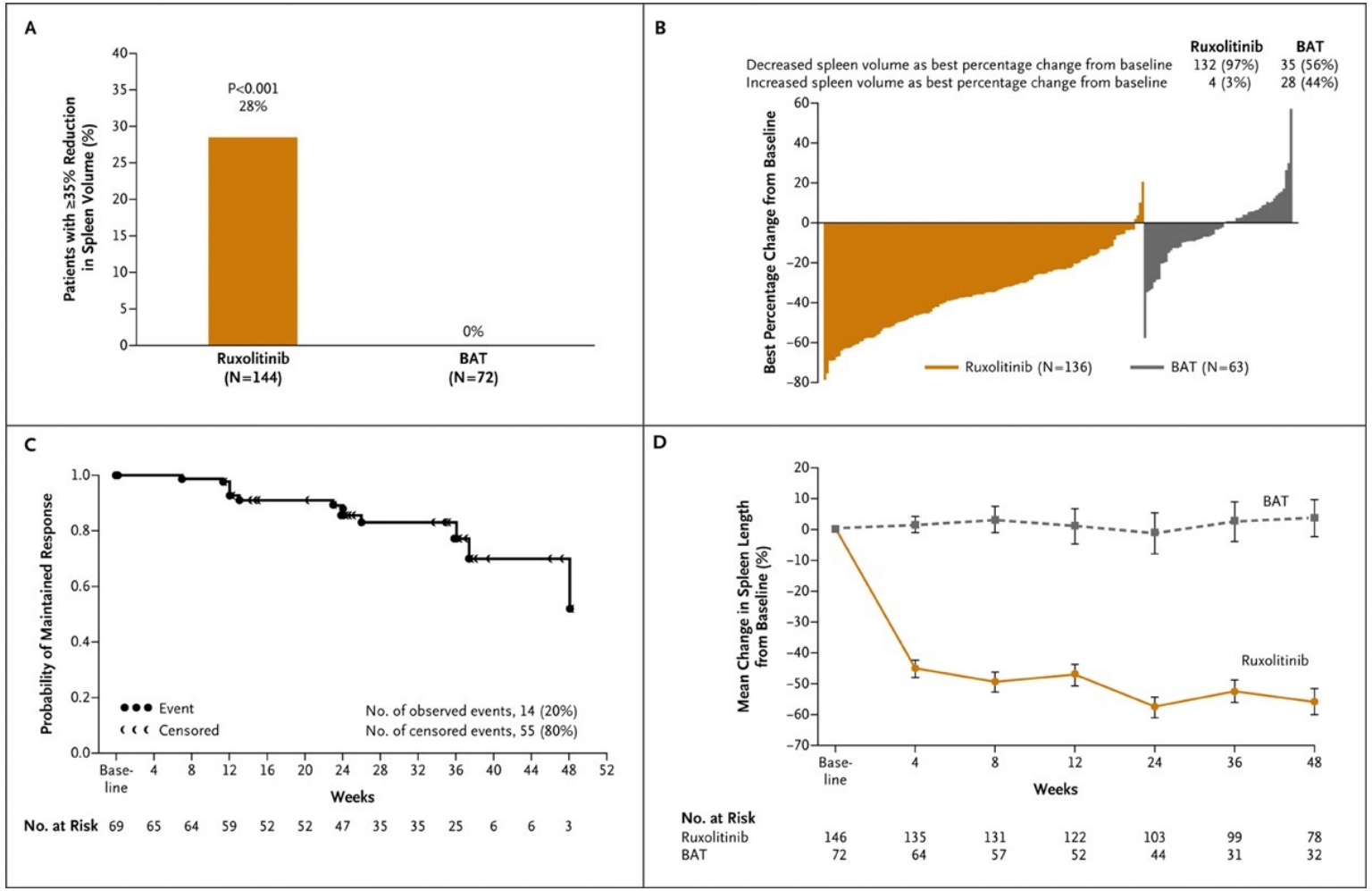
State of the Art Treatment of Myelofibrosis

Andrew Kuykendall, MD
Associate Member, Department of Malignant Hematology
Moffitt Cancer Center
Tampa, Florida

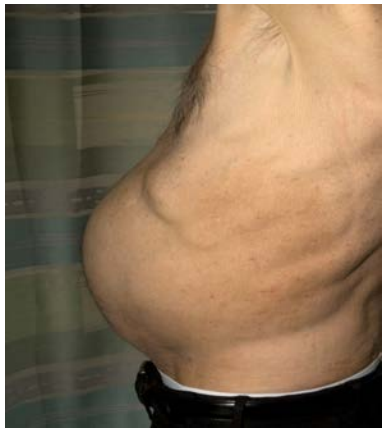
Disclosures

Advisory Committees	AbbVie Inc, Blueprint Medicines, Bristol Myers Squibb, Cogent Biosciences, CTI BioPharma, a Sobi Company, Incyte Corporation, Karyopharm Therapeutics, PharmaEssentia
Consulting Agreements	AbbVie Inc, Karyopharm Therapeutics, MorphoSys
Contracted Research	Blueprint Medicines, Bristol Myers Squibb, Geron Corporation, Janssen Biotech Inc, Protagonist Therapeutics, MorphoSys
Data and Safety Monitoring Boards/Committees	Geron Corporation

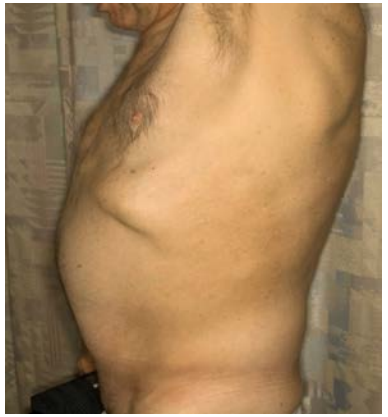
Ruxolitinib reduces spleen volume, improves symptoms and is associated with a survival benefit



Pre Ruxolitinib

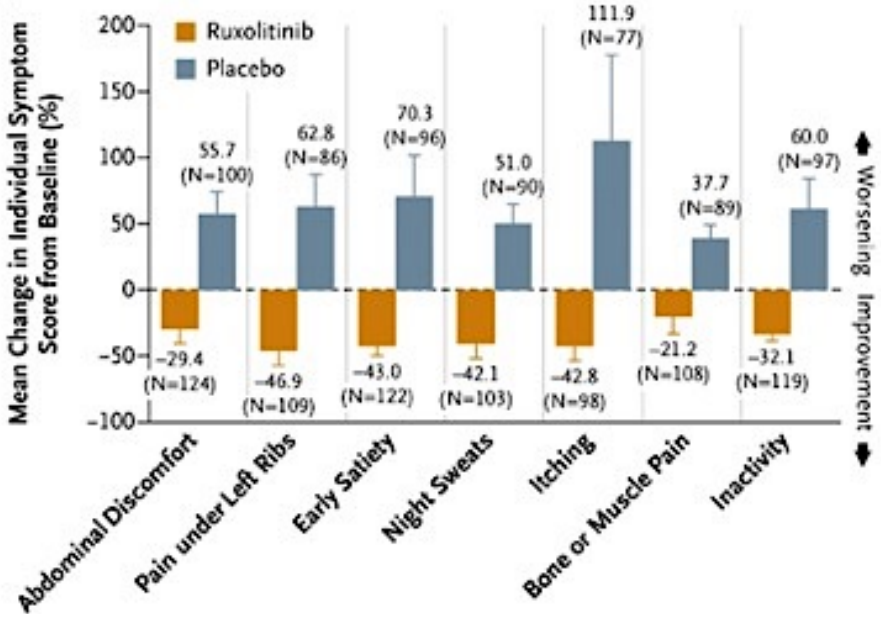


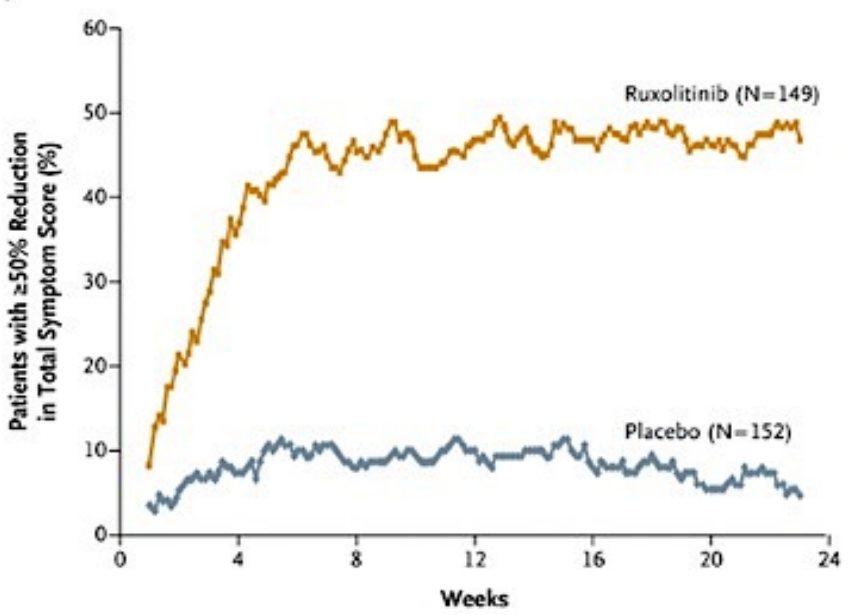
After 2 Mo Therapy

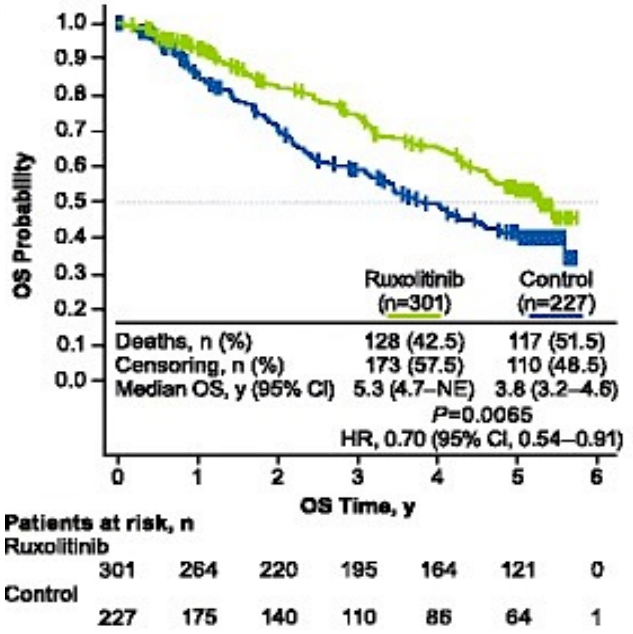


Harrison et al., NEJM, 2012; Images courtesy of Srdan Verstovsek, MD, PhD.

Ruxolitinib effectively reduces spleen volume, improves disease related symptoms, and is associated with a survival benefit

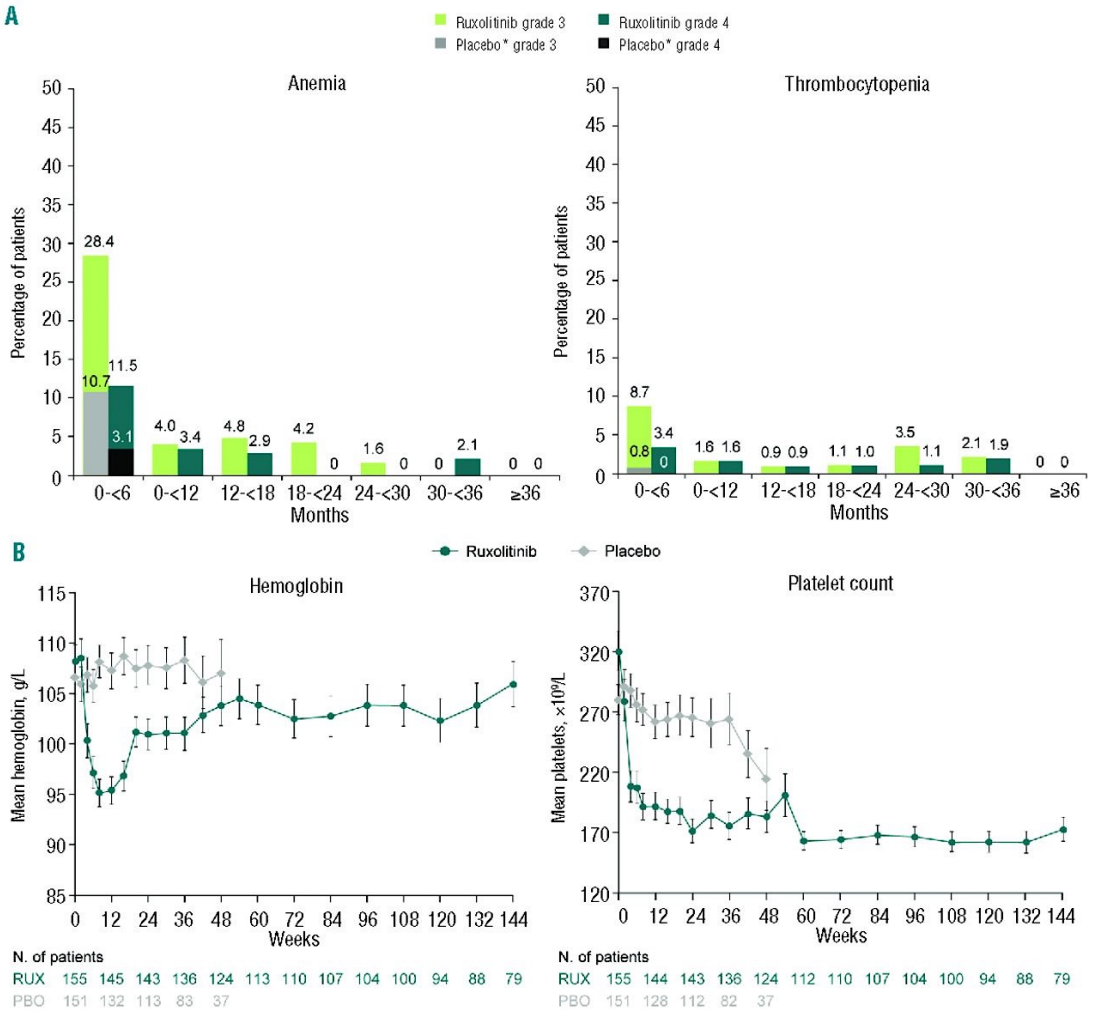


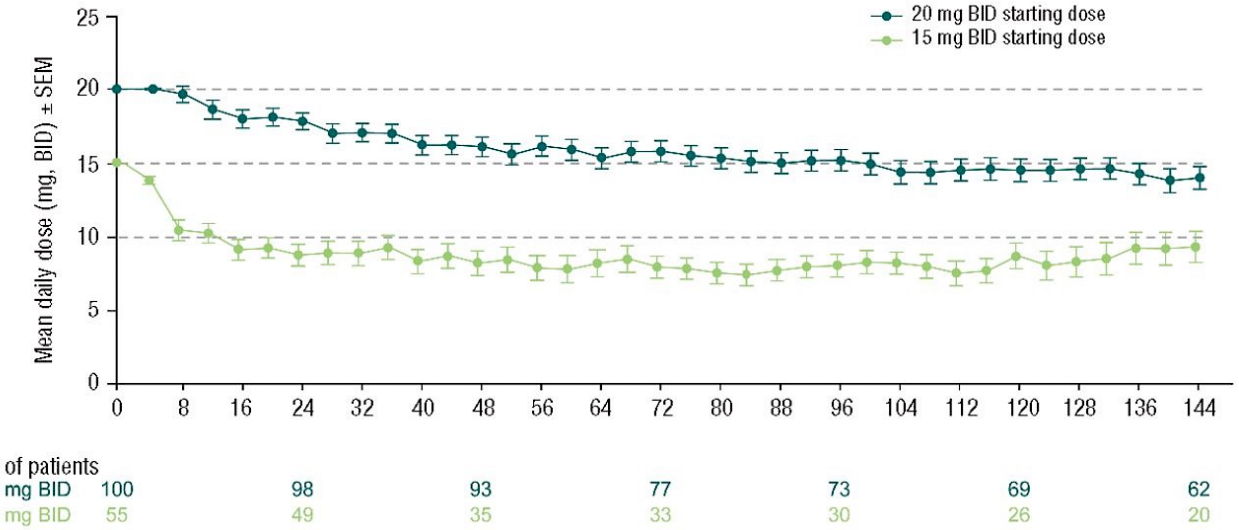




Verstovsek et al., NEJM, 2012; Verstovsek et al., J Hematol Oncol, 2017

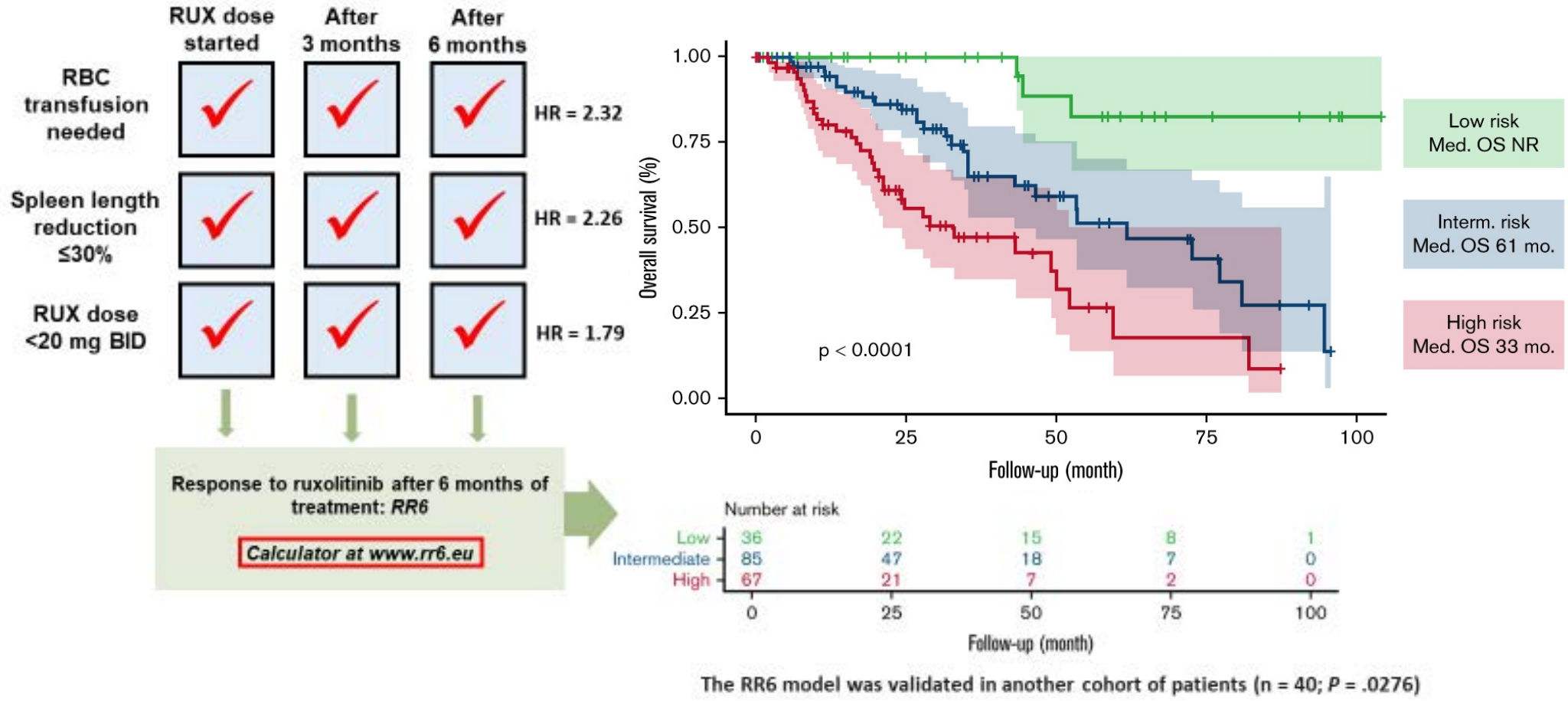
Ruxolitinib associated with anemia and thrombocytopenia that frequently lead to dose reductions





Verstovsek et al. Haematologica. 2015.

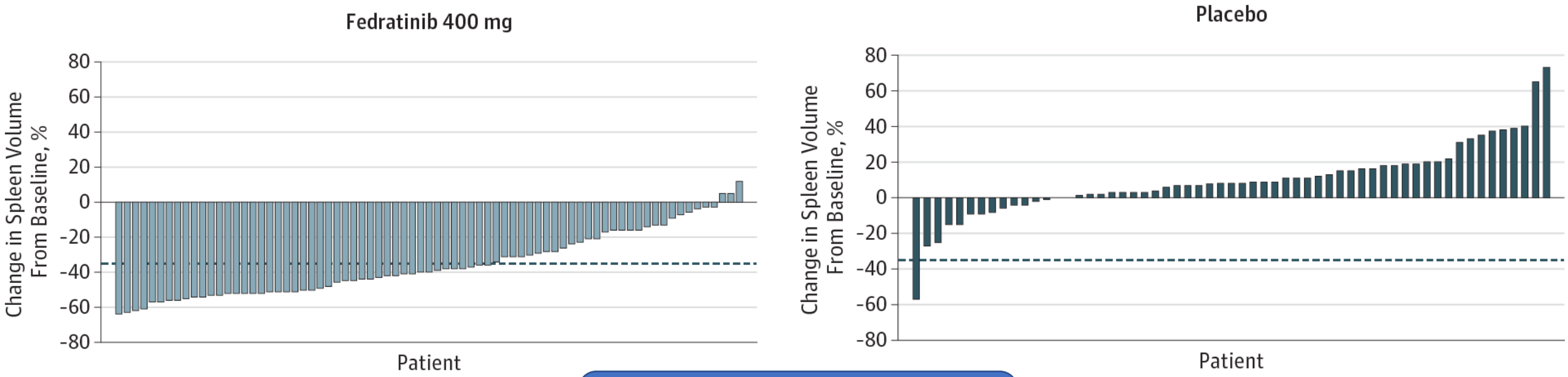
The RR6 model identifies transfusion requirements, lack of spleen response, and suboptimal dosing as risk factors for worse outcomes in patients treated with ruxolitinib



The RR6 model was validated in another cohort of patients (n = 40; *P* = .0276)

Maffioli et al., Blood Adv. 2022;6:1855-1864

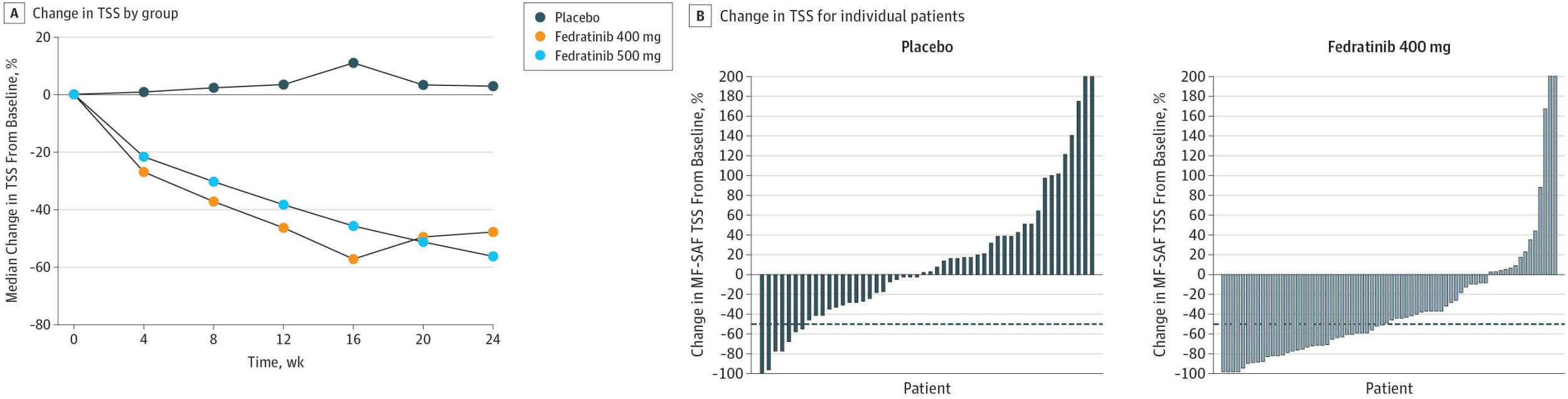
Fedratinib improves splenomegaly and symptoms comparably to ruxolitinib



Approved for int-2 and high-risk MF in August, 2019

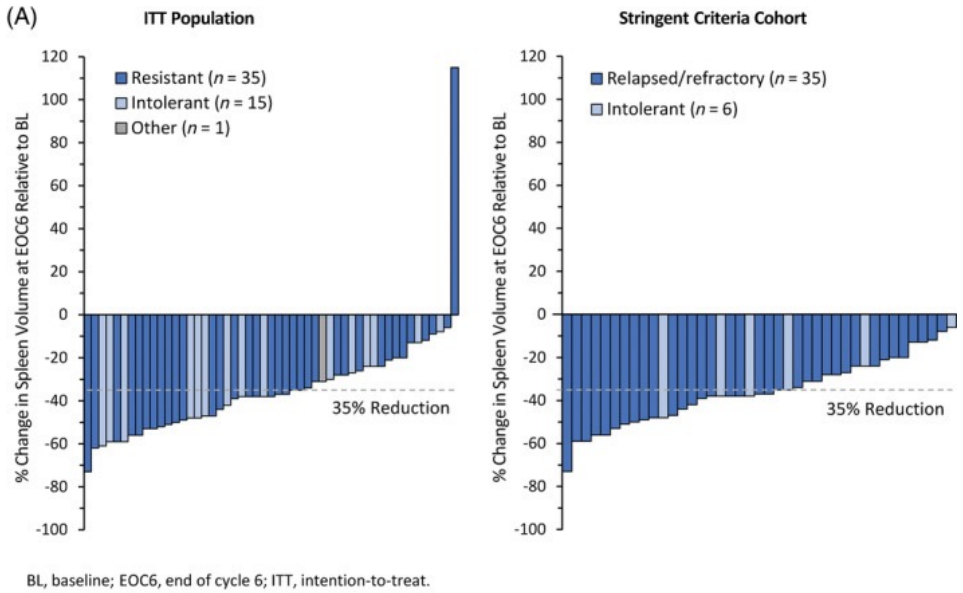
Pardanani et al., JAMA Oncology, 2015

Fedratinib improves splenomegaly and symptoms comparably to ruxolitinib

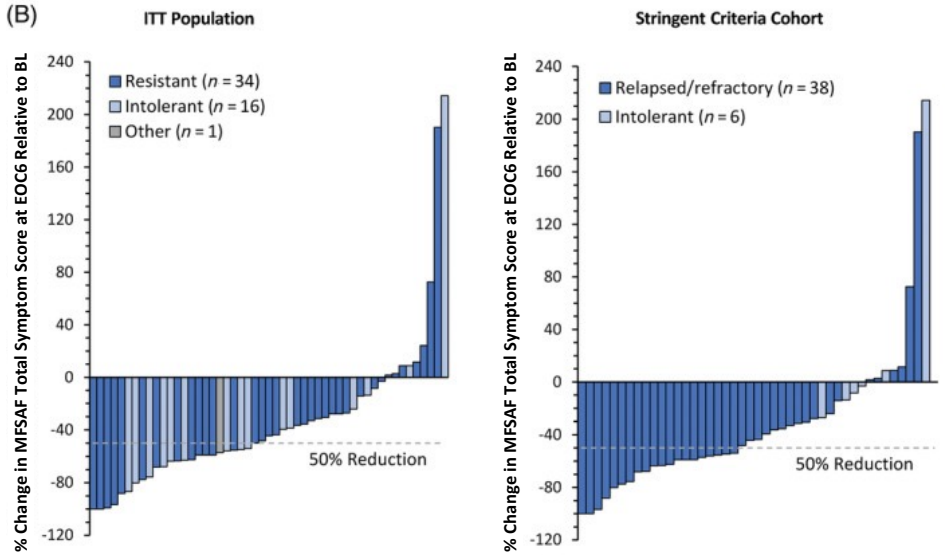


Pardanani et al., JAMA Oncology, 2015

Fedratinib improved splenomegaly and symptoms in the second-line setting in JAKARTA-2



BL, baseline; EOC6, end of cycle 6; ITT, intention-to-treat.

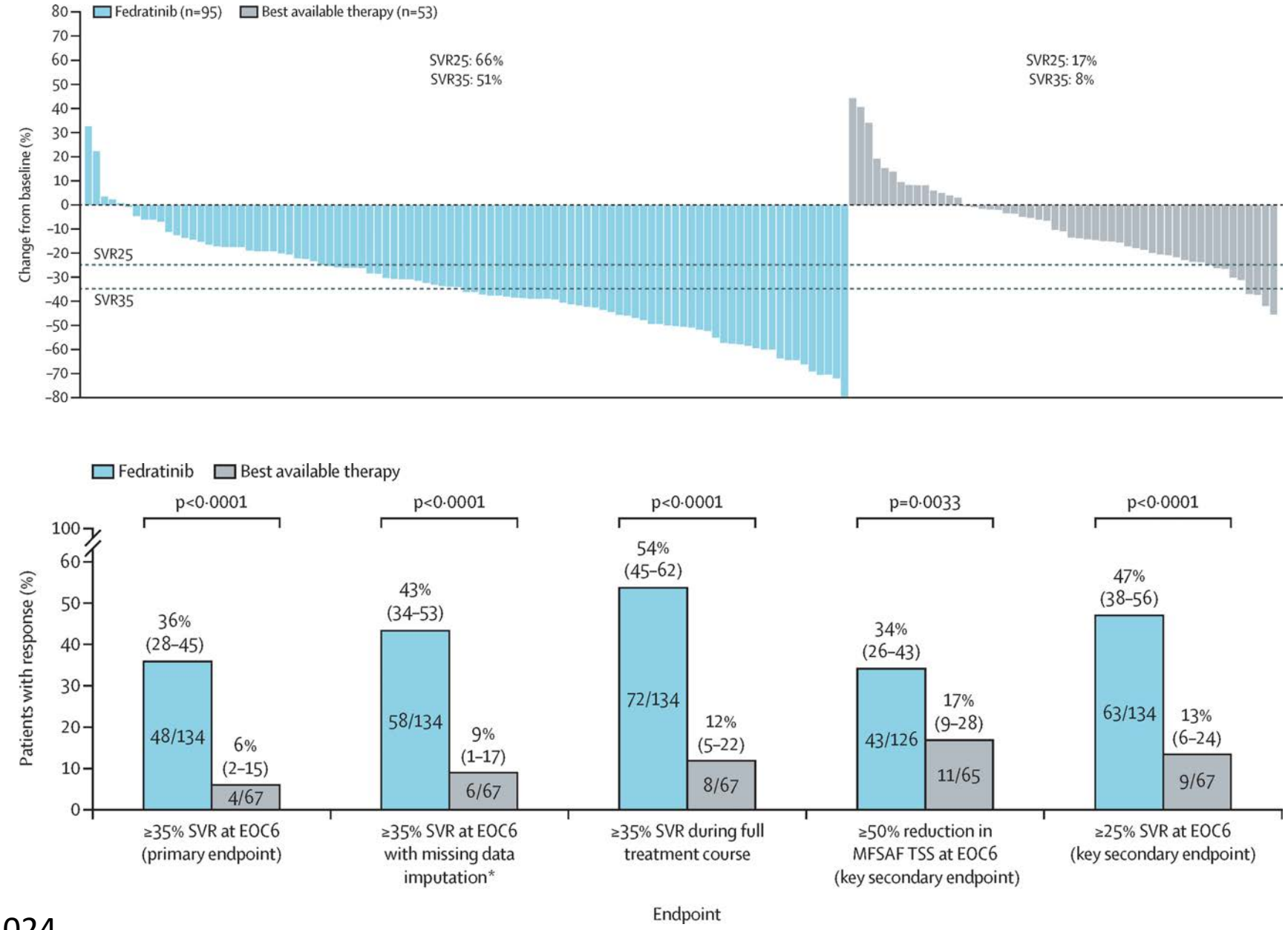


BL, baseline; EOC6, end of cycle 6; ITT, intention-to-treat; MFSAF, Myelofibrosis Symptom Assessment Form; TSS, total symptom score.

Harrison et al., Am J Hematology, 2020

FREEDOM-2 study largely recapitulated data seen in JAKARTA-2

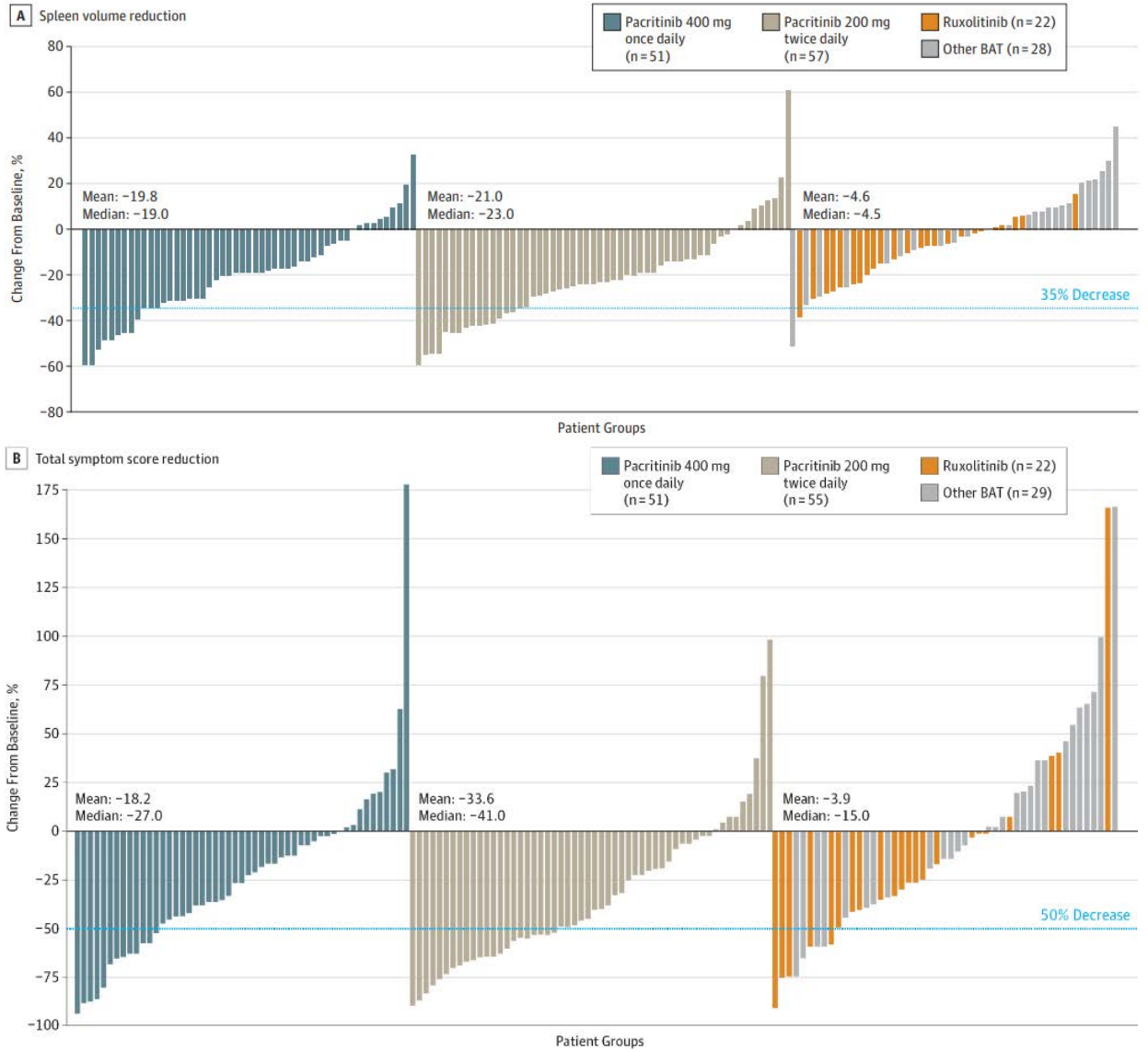
Dose reduction due to TEAE in 31% of fedratinib-treated patients



Harrison et al., Lancet Haematology. 2024

Pacritinib is a JAK2 inhibitor with accelerated approval for MF with marked thrombocytopenia

PERSIST-2 Study enrolled patients with MF with platelet count < 100 x 10^9/L

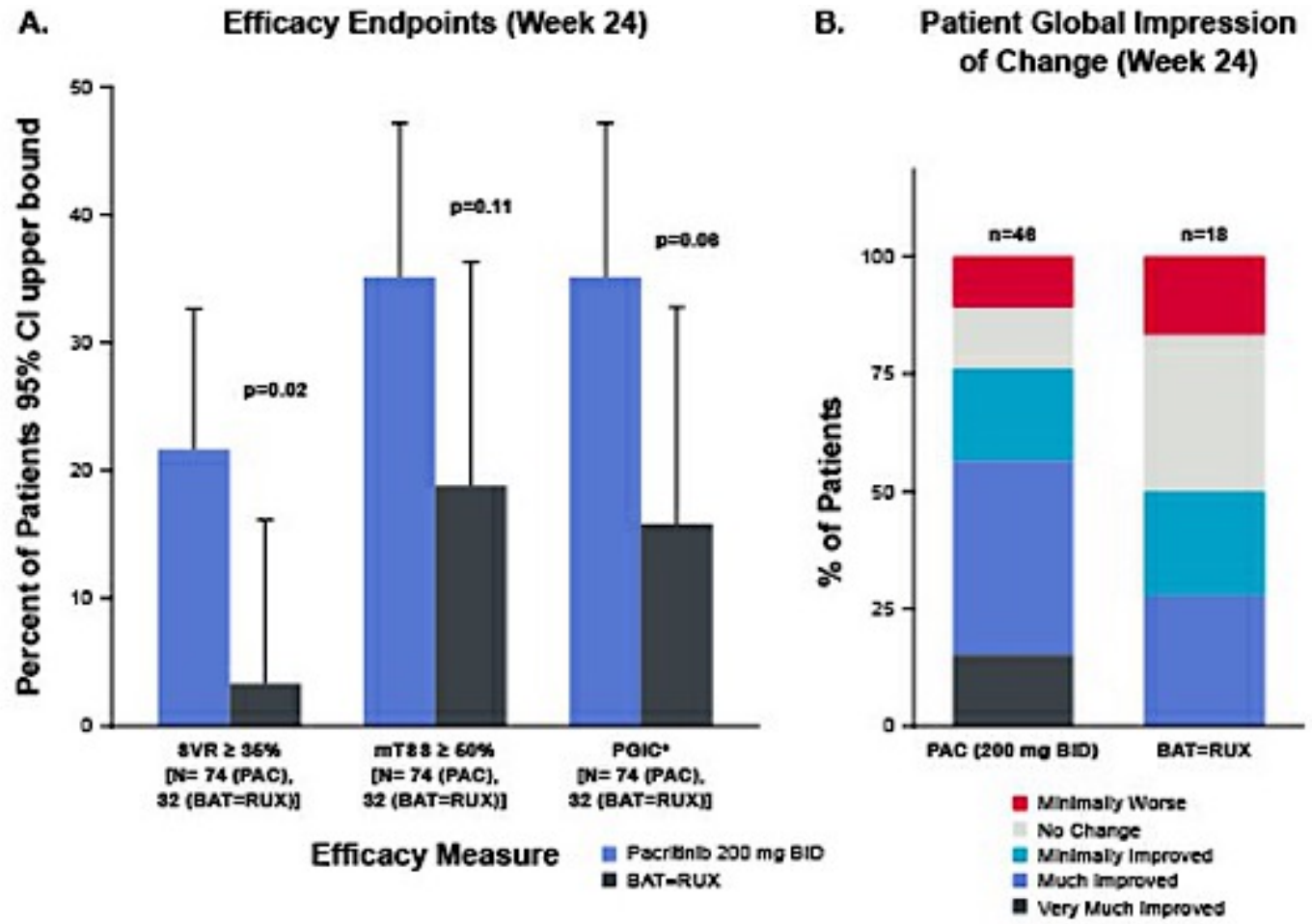


Received accelerated approval for MF with marked thrombocytopenia in February, 2022

Pacritinib inhibits JAK2, FLT3, IRAK1, and ACVR1

Mascarenhas et al., JAMA Oncol, 2018

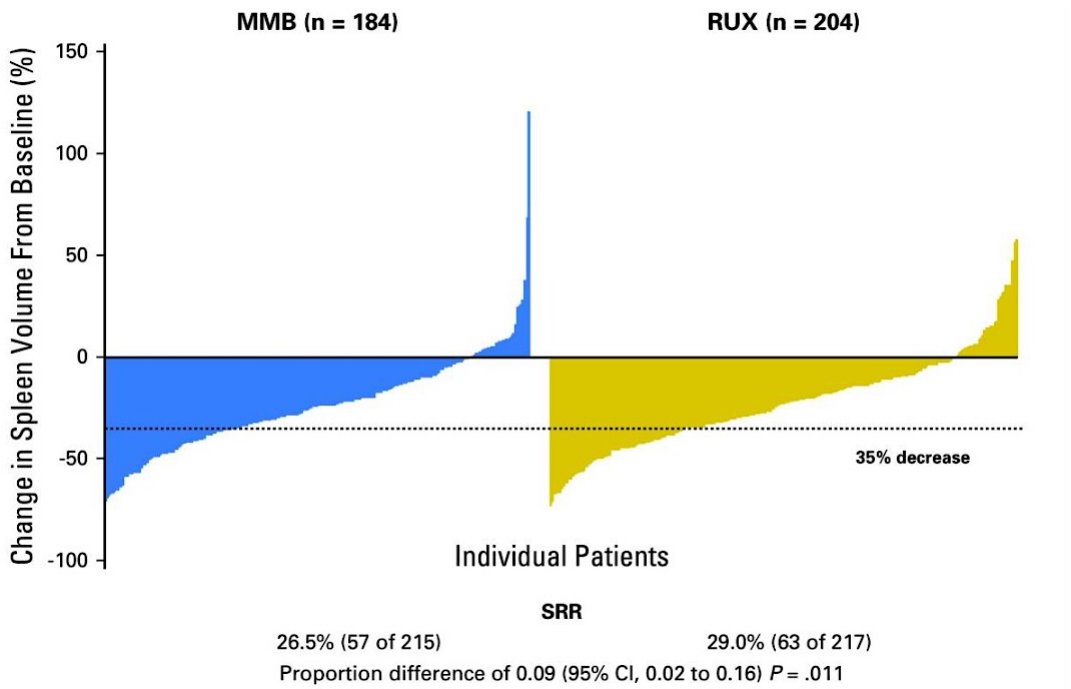
Pacritinib shows favorable efficacy profile in markedly thrombocytopenic patients compared to ruxolitinib

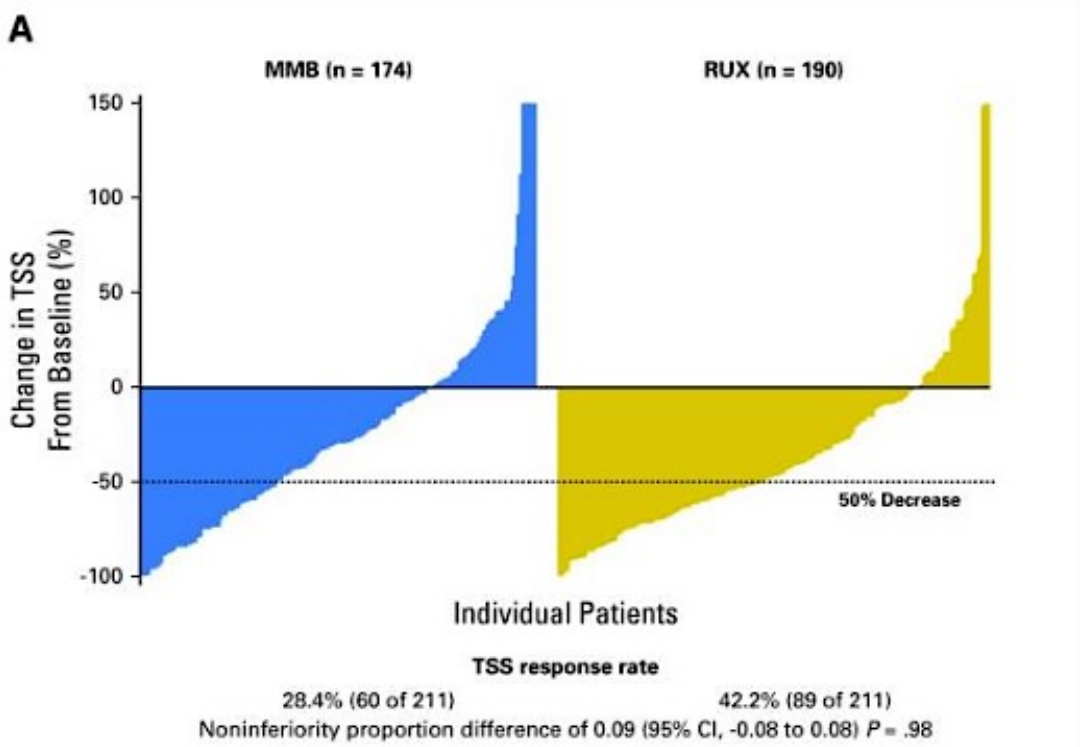


Harrison et al. Presented at EHA 2022.

Momelotinib was studied head-to-head vs. ruxolitinib in the SIMPLIFY-1 study.

Head-to-head vs. ruxolitinib: Momelotinib non-inferior for spleen reduction but NOT non-inferior for symptom improvement



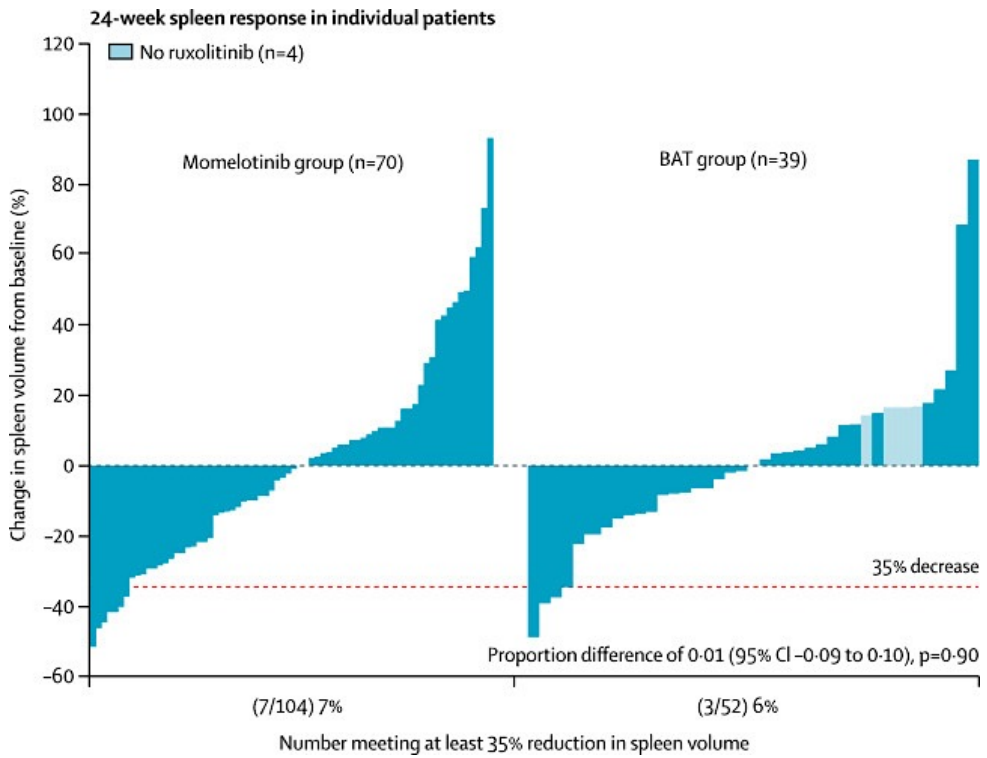


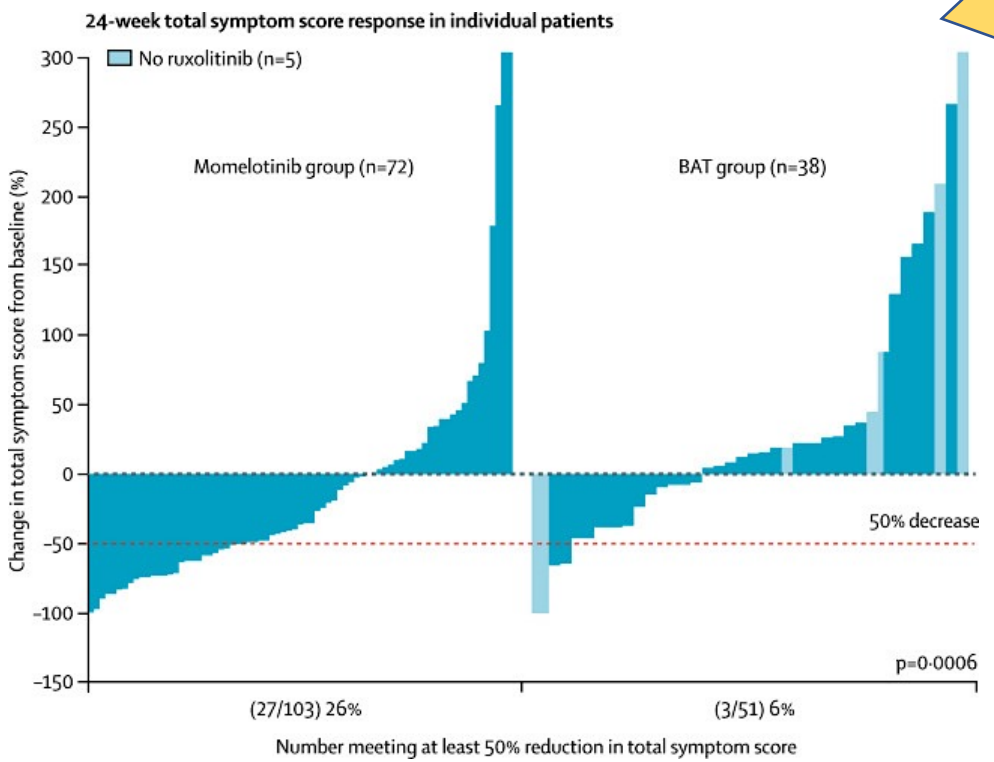
Mesa et al., JCO, 2017

Momelotinib was studied vs. BAT in rux-exposed patients in the SIMPLIFY-2 study

In comparison to BAT (89% rux) in rux-exposed patients, momelotinib was superior in terms of symptom response but not superior in terms of spleen response

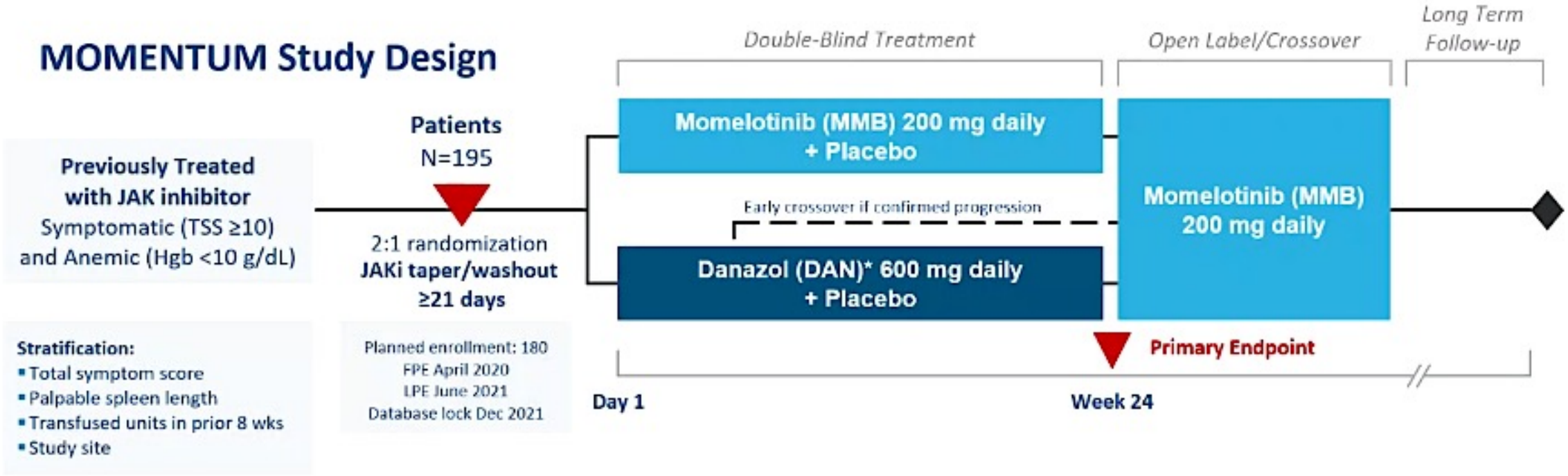
No washout





Harrison et al., Lancet Haematology, 2018

The experience in SIMPLIFY-1 and SIMPLIFY-2 trials led to the unique MOMENTUM study design



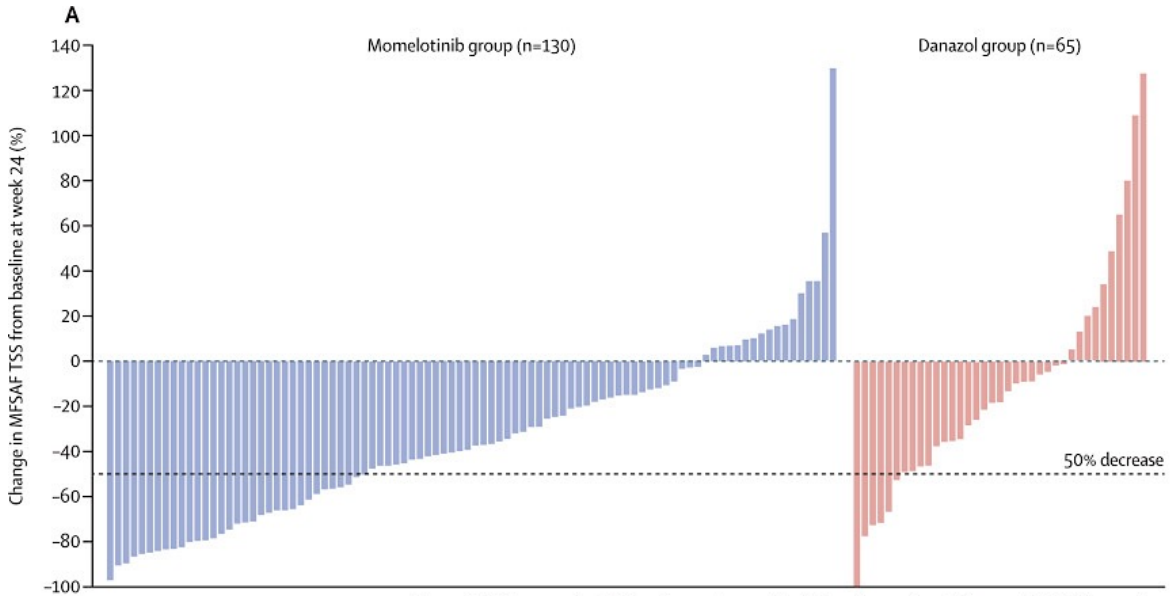
Primary Endpoint

- Total symptom score (TSS) response rate at Week 24

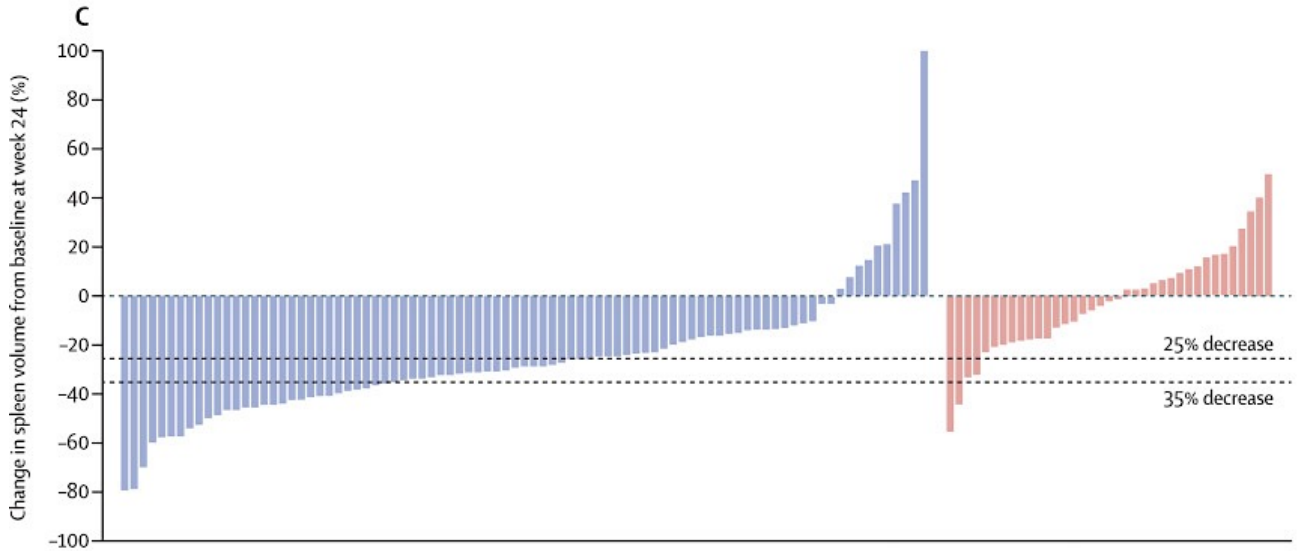
Key Secondary Endpoints

- Transfusion independence (TI) rate at Week 24
- Splenic response rate (SRR) at Week 24

Momelotinib was superior to danazol in the MOMENTUM study



	Momelotinib group (n=130)	Danazol group (n=65)	Proportion difference (95% CI)	p value
Number meeting at least 50% reduction in MSAF TSS at week 24	32 (25% [95% CI 17–33])	6 (9% [95% CI 4–19])	16% (6–26)	0·0095

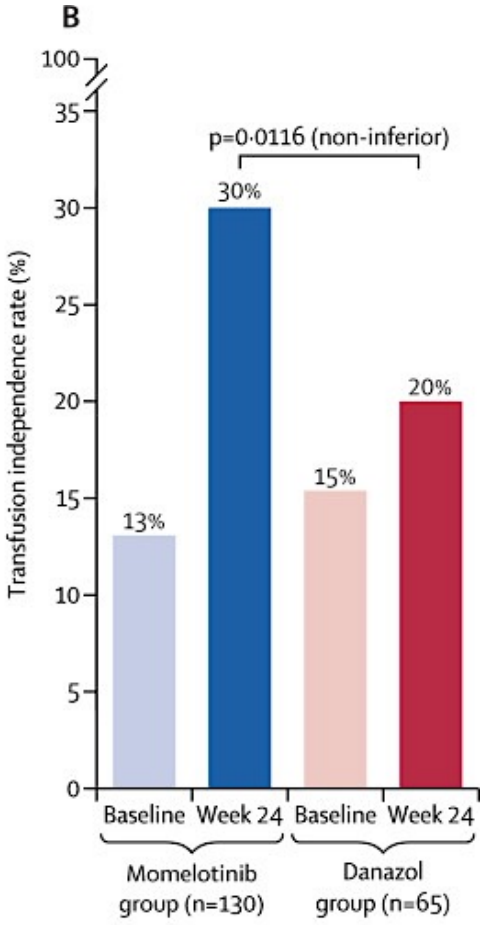


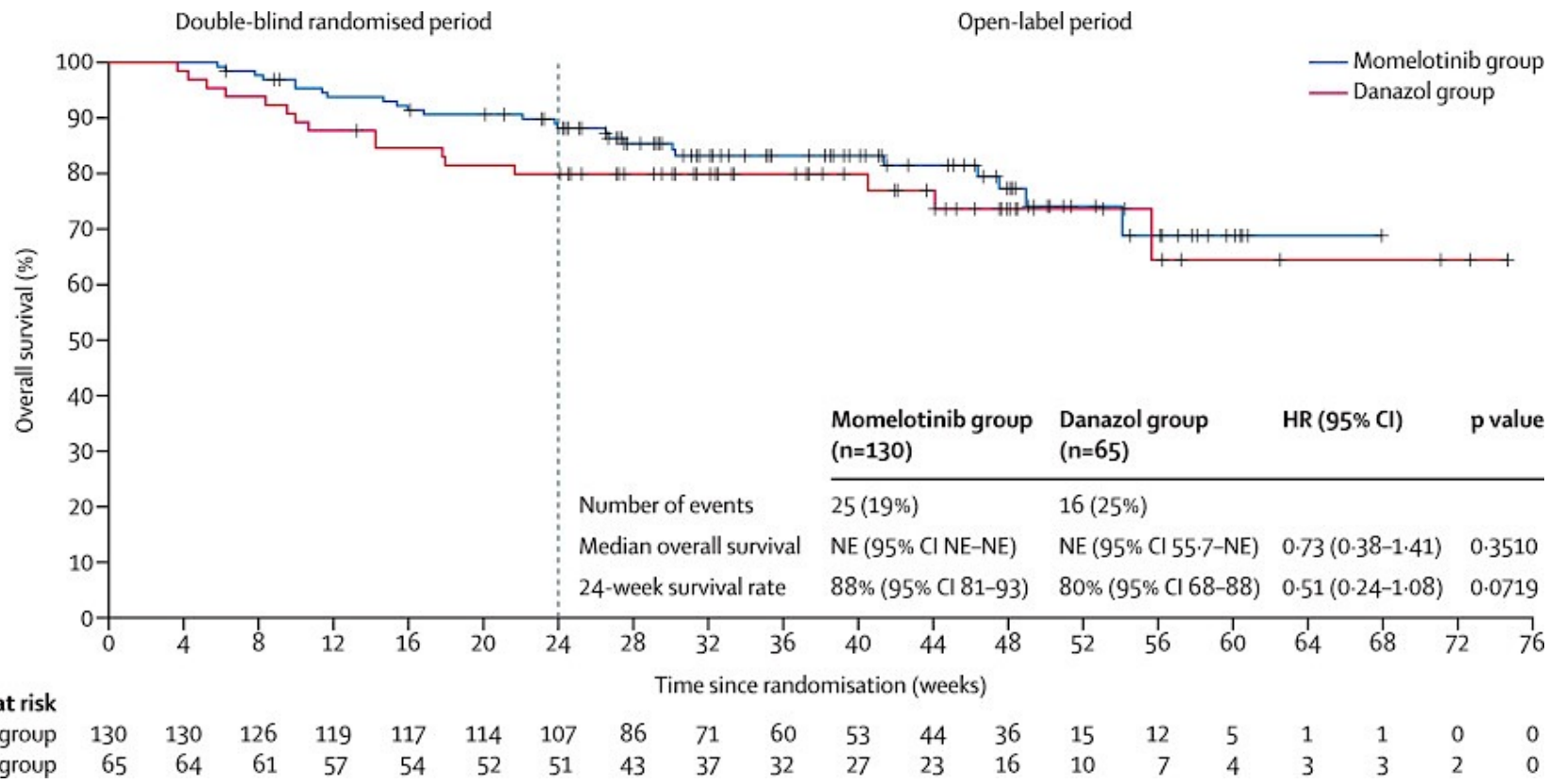
	Momelotinib group (n=130)	Danazol group (n=65)	Proportion difference (95% CI)	p value
Number meeting at least 25% reduction in spleen volume	51 (39% [95% CI 31–48])	4 (6% [95% CI 2–15])	33% (23–44)	<0·0001
Number meeting at least 35% reduction in spleen volume	29 (22% [95% CI 15–30])	2 (3% [95% CI 0–11])	18 (10–27)	0·0011

Momelotinib inhibits JAK1, JAK2, and ACVR1

Verstovsek et al., Lancet, 2023

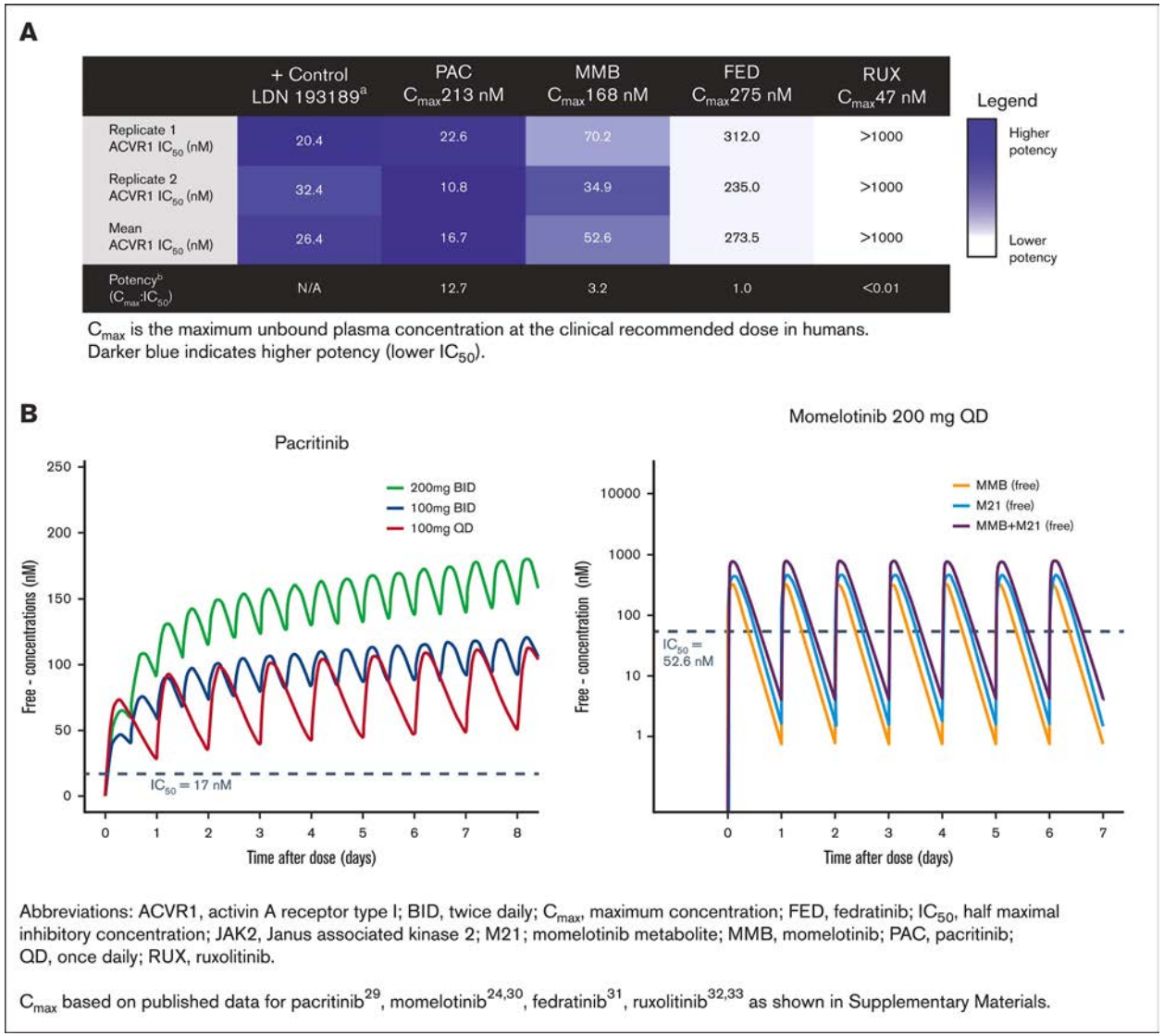
Beyond spleen/symptoms, momelotinib performed better than danazol in terms of anemia





Verstovsek et al., Lancet, 2023

Pacritinib is also a potent ACVR1 inhibitor



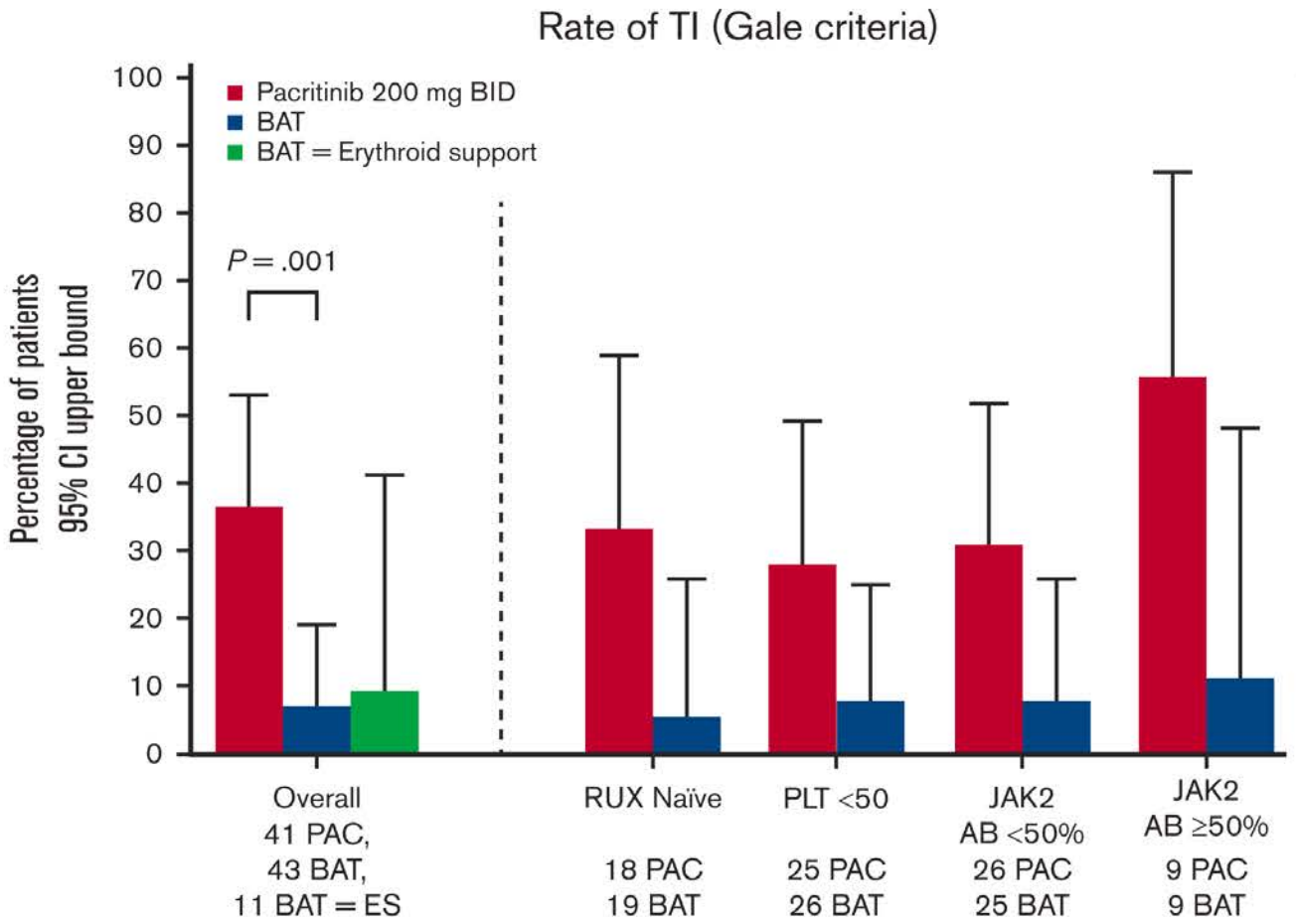
Oh S, et al. *Blood Advances*. 2023;7(19):5835-5842

In a reanalysis of the PERSIST-2 study, pacritinib was associated with favorable anemia outcomes

TI Conversion Rate

Pacritinib N = 41	BAT N = 43	*P* Value
37%	7%	.001

- TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT
- Erythroid support agents were prohibited on the pacritinib arm



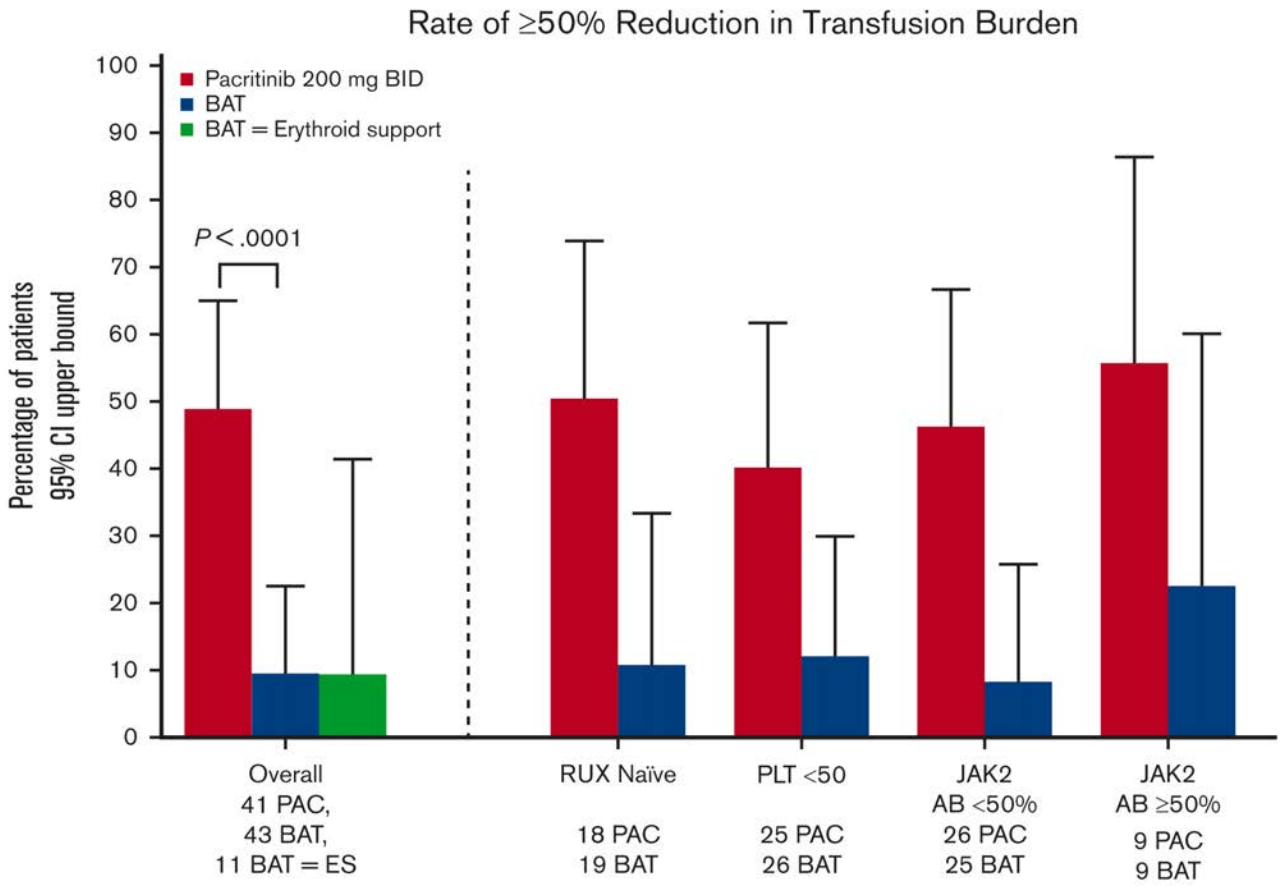
Oh S, et al. *Blood Advances*. 2023;7(19):5835-5842

In a reanalysis of the PERSIST-2 study, pacritinib was associated with favorable anemia outcomes

Transfusion Reduction

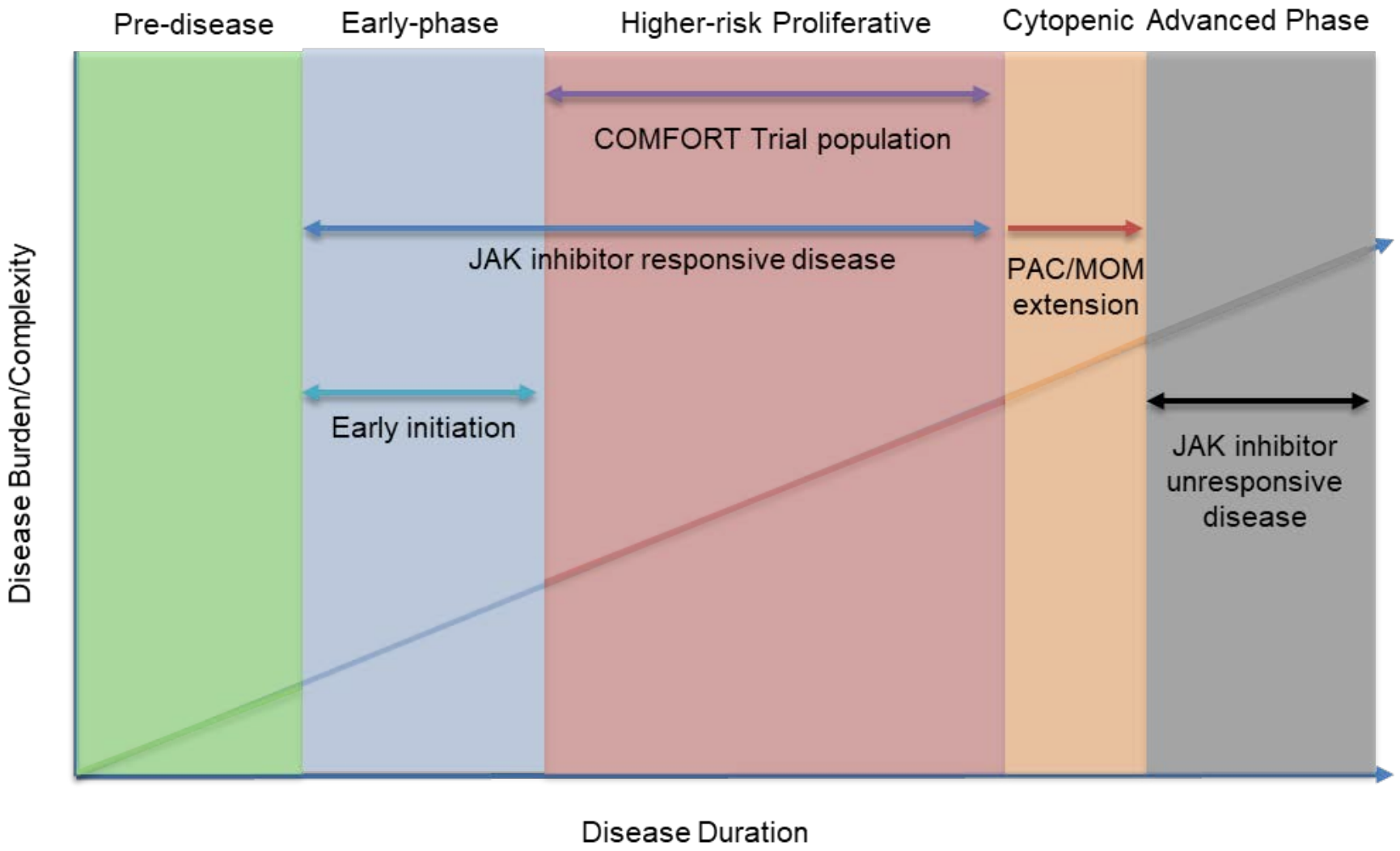
Pacritinib N = 41	BAT N = 43	*P* Value
49%	9%	.0001

- Clinically significant reduction in transfusion burden more common on pacritinib



Oh S, et al. *Blood Advances*. 2023;7(19):5835-5842

Recently approved JAK inhibitors have extended the lifespan of JAK-inhibition



Unmet Needs in Myelofibrosis

- Restore effective haematopoiesis
  - Reduce hepcidin levels
- Alter natural history of disease
  - Combination therapy
  - Direct targeting of core driver mutations
  - More comprehensive suppression of JAK-STAT pathway

Unmet Needs in Myelofibrosis

- Restore effective haematopoiesis
  - Luspatercept, ~~zilurgisertib~~, elritercept, DISC-0974
- Alter natural history of disease
  - Combination therapy
    - Pelabresib, Selinexor, Navtemadlin, Imetelstat
  - Direct targeting of core driver mutations
    - INCA033989, JNJ88549968, INCB0160058, AJ1-11095
  - More comprehensive suppression of JAK-STAT pathway

Discussion Questions

- Which JAK inhibitors, if any, have been associated with a survival benefit for patients with JAK inhibitor-naïve MF?

- A patient with intermediate-risk MF receives ruxolitinib 15 mg BID, and after 10 months he develops increasing asymptomatic splenomegaly. Platelet count = 150,000/µL, Hgb = 13.8 g/dL. Regulatory and reimbursement issues aside and assuming the patient is not a transplant candidate, which treatment would you most likely recommend?

We are taking a short break!

The program will resume at 1:00 PM ET

Up Next…

Drs Ramaswamy Govindan and Stephen V Liu discuss the management of immunotherapy and other nontargeted approaches for NSCLC

RTP
RESEARCH
TO PRACTICE