Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

Agenda

Module 1 — HR-Positive Breast Cancer: *Drs O'Shaughnessy and Wander*

Module 2 — Prostate Cancer: *Drs M Smith and Srinivas*

Module 3 — Lung Cancer: *Drs Goldberg and Sabari*

Module 4 — Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia: *Drs Kahl and S Smith*

Module 5 — Multiple Myeloma: *Drs Lonial and Raje*

Lung Cancer Faculty

Sarah B Goldberg, MD, MPH
Associate Professor of Medicine (Medical Oncology)
Chief of Thoracic Oncology
Co-Director of the Center for Thoracic Cancers
Yale Cancer Center
New Haven, Connecticut

Joshua K Sabari, MD
Attending Physician
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New York, New York

Non-targeted Therapy for Lung Cancer

Research To Practice / FCS Retreat
October 26, 2024

Sarah Goldberg, MD, MPH

Associate Professor of Medicine (Medical Oncology)
Division Chief, Thoracic Oncology
Co-Director, Center for Thoracic Cancers
Yale School of Medicine and Yale Cancer Center

Agenda

- **Advanced NSCLC**
  - First-line treatment
    - Pembrolizumab, atezolizumab and cemiplimab as monotherapy or in combination with chemotherapy
    - Long-term data with dual immune checkpoint inhibition with or without chemotherapy
  - Previously-treated
    - Datopotamab deruxtecan
    - PD-L1 x 4-1BB bispecific antibody acasunlimab
- **SCLC**
  - Limited stage
    - Durvalumab as consolidation treatment (ADRIATIC)
  - Extensive stage
    - DLL3 x CD3 bispecific antibody tarlatamab
    - B7-H3-directed antibody-drug conjugate ifinatamab deruxtecan

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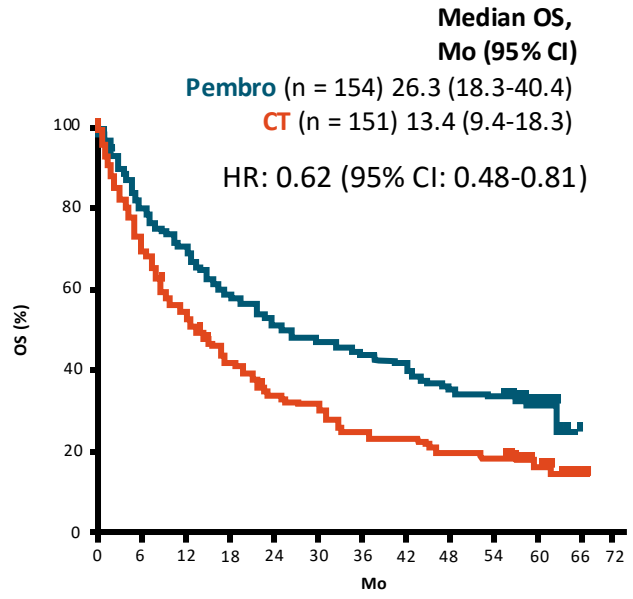
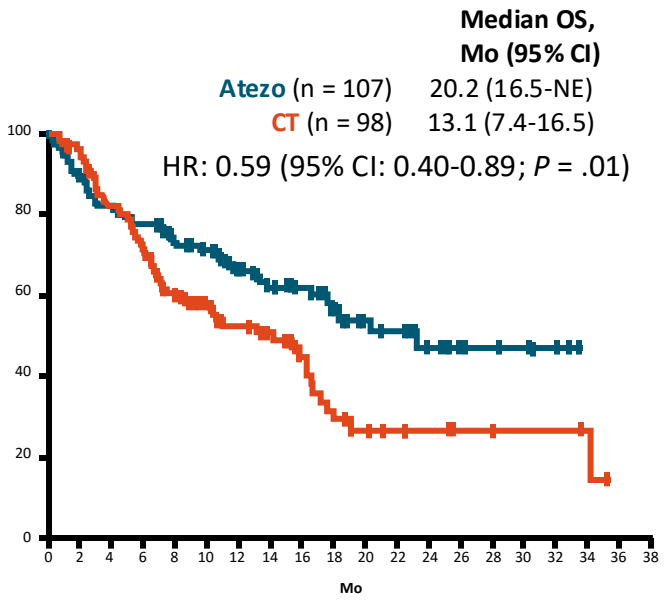
PD-(L)1 inhibitor monotherapy for upfront treatment of stage IV NSCLC with high PD-L1 expression

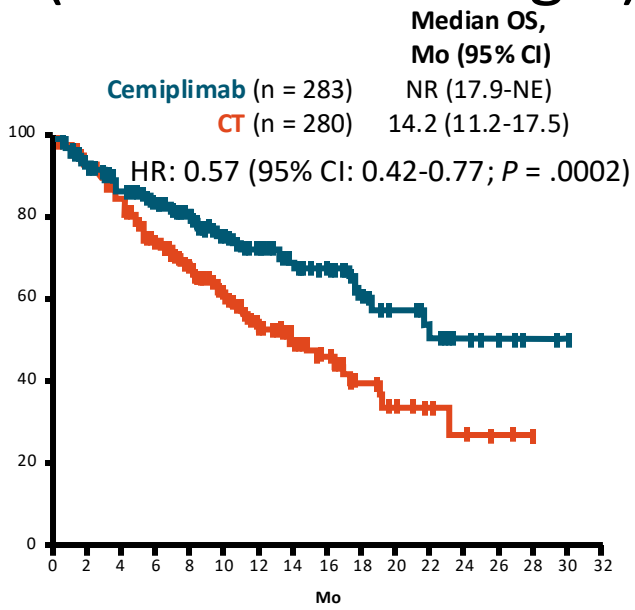
Pembrolizumab (KEYNOTE-024)



Atezolizumab (IMpower110)



Cemiplimab (EMPOWER-Lung 1)

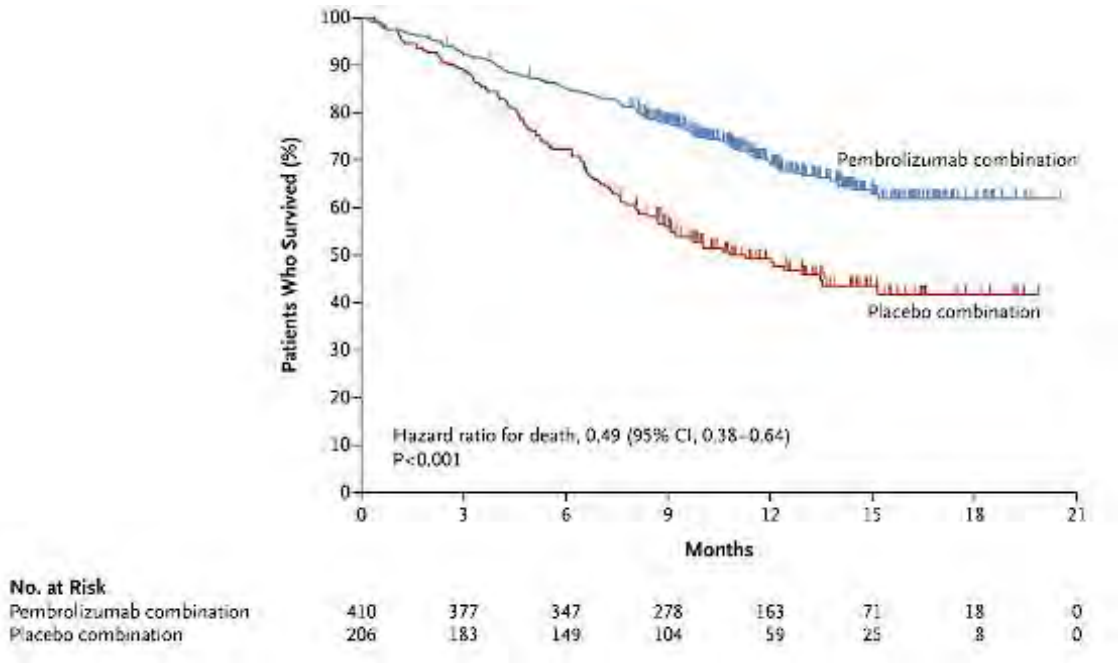


ORR is ~40%-50% → caution using single-agent IO in patients who have a high tumor burden or who are very symptomatic

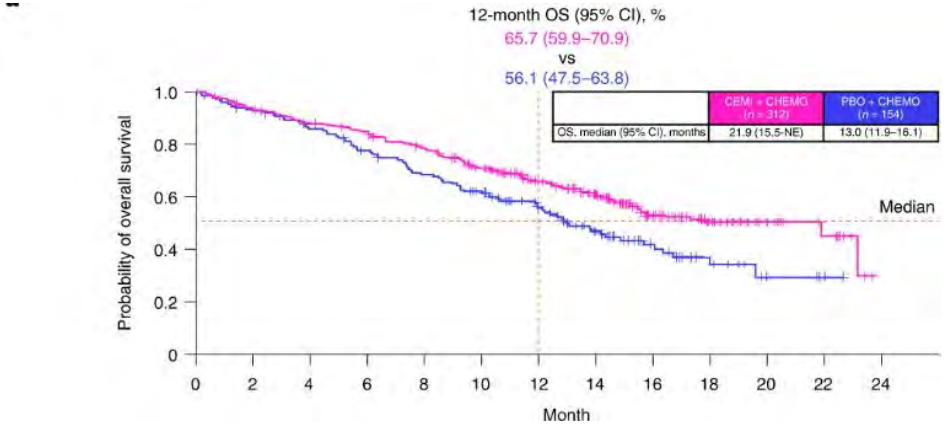
Reck M et al. *J Clin Oncol*. 2021
Herbst RS et al. *N Engl J Med*. 2020
Ozguroglu M et al. *Lancet Oncol*. 2023

Immunotherapy-based combinations for upfront treatment of stage IV NSCLC: IO plus chemotherapy

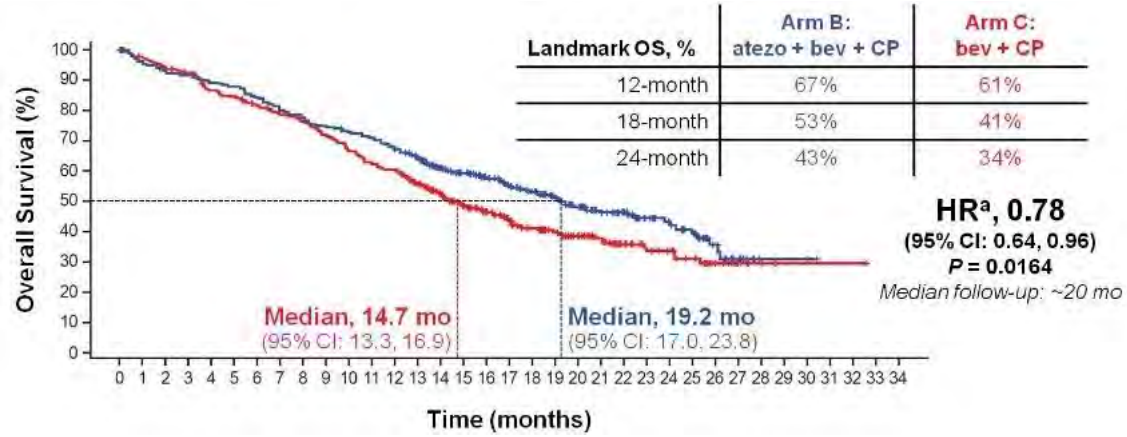
KEYNOTE-189: Pembrolizumab plus Chemotherapy



EMPOWER-Lung 3: Cemiplimab Plus Chemotherapy



IMpower150: Atezolizumab Plus Chemotherapy/Bevacizumab

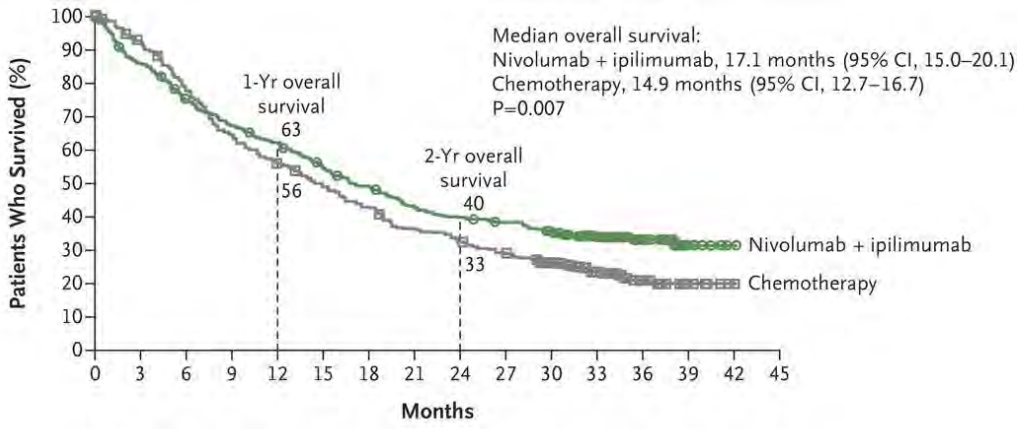


Ghandi L et al. NEJM 2018
Gogishvili M et al. *Nat Med*. 2022
Socinski MA et al. *N Engl J Med*. 2018

Immunotherapy-based combinations for upfront treatment of stage IV NSCLC: Combination IO

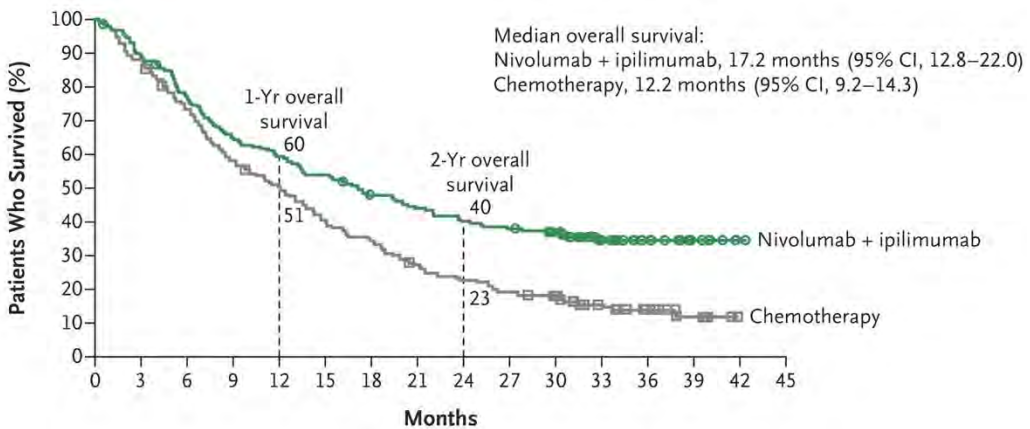
CheckMate 227: Nivo plus Ipi

PD-L1 ≥ 1%



No. at Risk																
Nivolumab + ipilimumab	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
Chemotherapy	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

PD-L1 < 1%

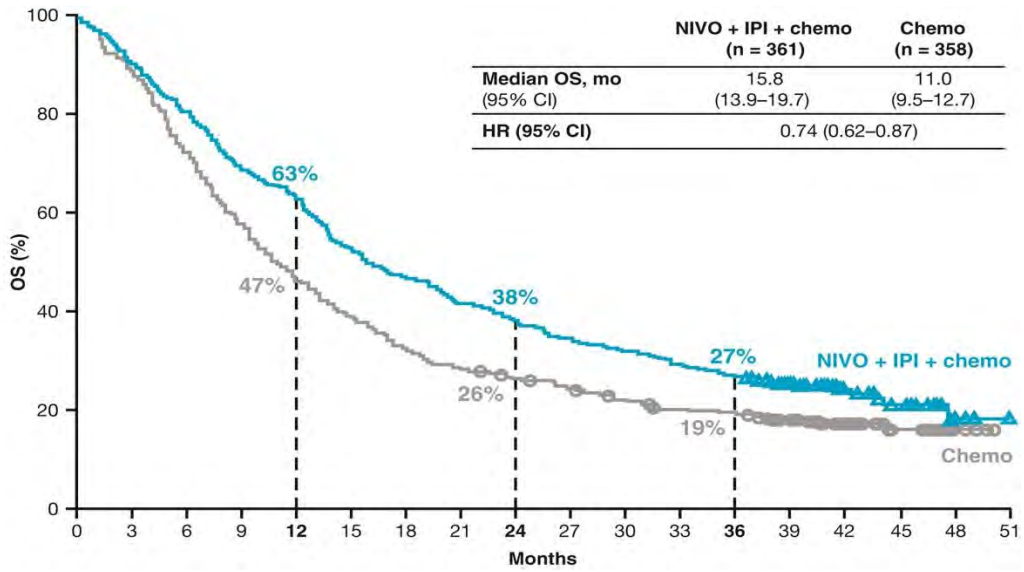


No. at Risk																
Nivolumab + ipilimumab	187	165	142	120	110	100	87	80	73	69	59	34	19	8	2	0
Chemotherapy	186	164	135	107	92	74	62	49	41	35	29	19	12	5	0	0

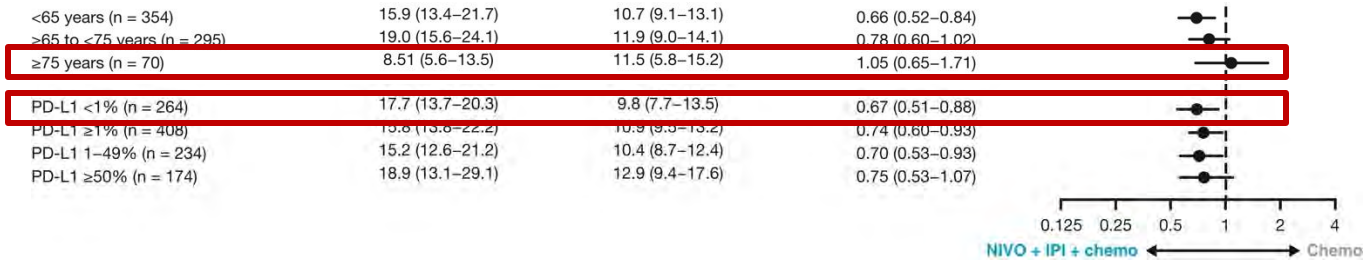
Hellman MD et al. NEJM 2019.

Immunotherapy-based combinations for upfront treatment of stage IV NSCLC: Combination IO plus chemo

Nivo/Ipi + 2 Cycles of Chemotherapy
CheckMate 9LA



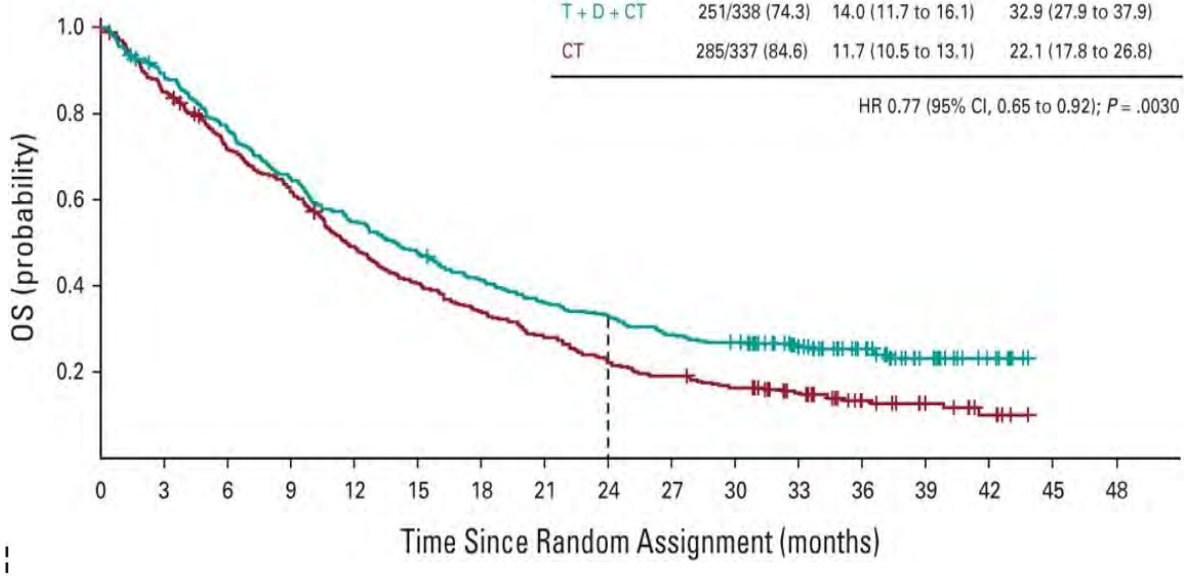
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.8 (13.9–19.7)	11.0 (9.5–12.7)
HR (95% CI)	0.74 (0.62–0.87)	



Durva/Treme + 4 Cycles of Chemotherapy
POSEIDON

	Events, n/N (%)	Median OS, Months (95% CI)	24-Month OS, % (95% CI)
T + D + CT	251/338 (74.3)	14.0 (11.7 to 16.1)	32.9 (27.9 to 37.9)
CT	285/337 (84.6)	11.7 (10.5 to 13.1)	22.1 (17.8 to 26.8)

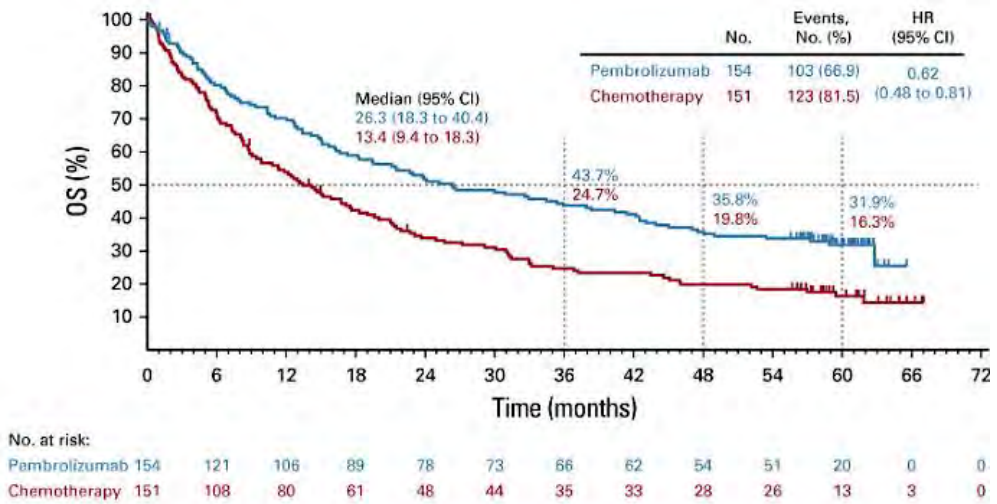
HR 0.77 (95% CI, 0.65 to 0.92); $P = .0030$

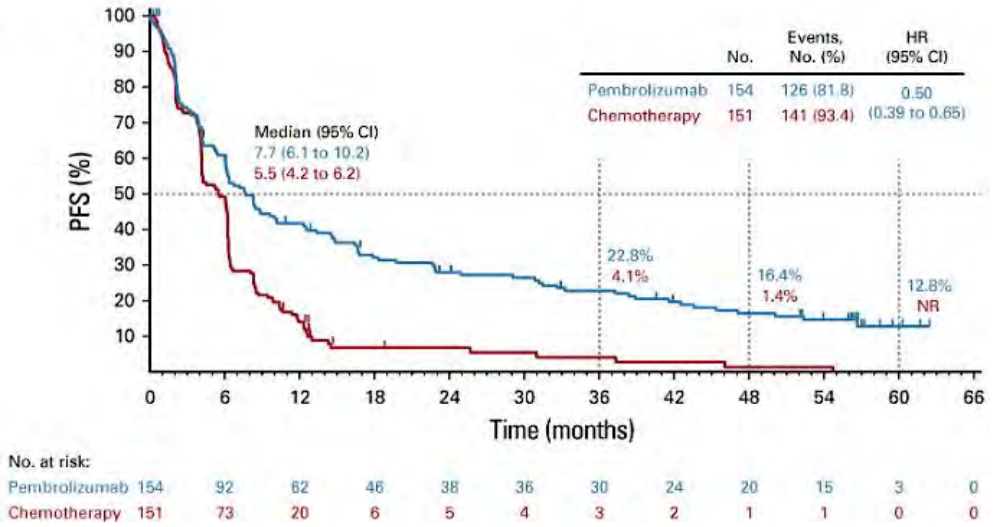


Paz-Ares L et al. *J Thoracic Oncol*. 2022
.Johnson ML et al. *J Clin Oncol*. 2023

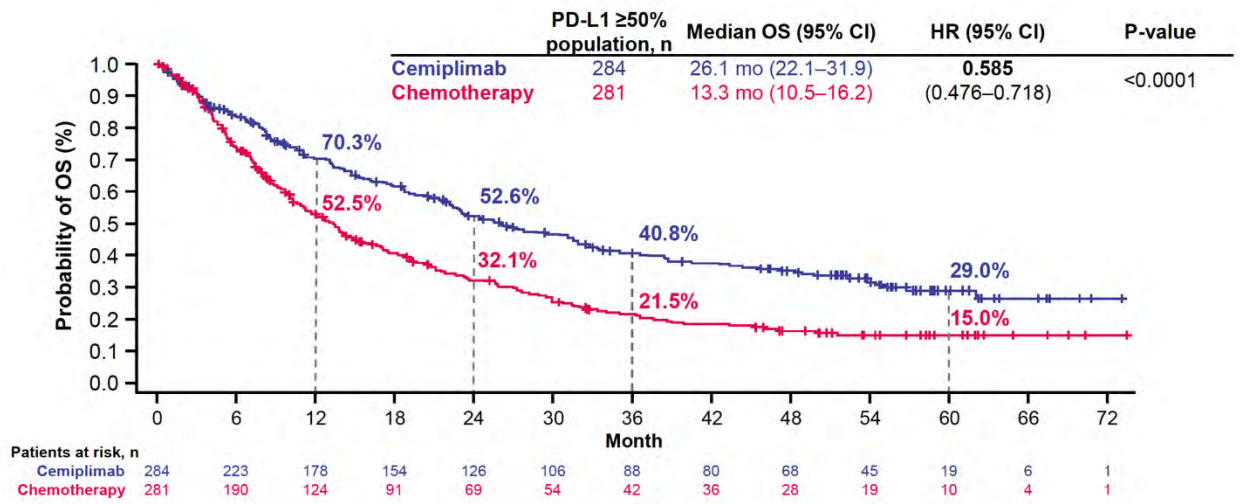
Long-term outcomes with single-agent immunotherapy

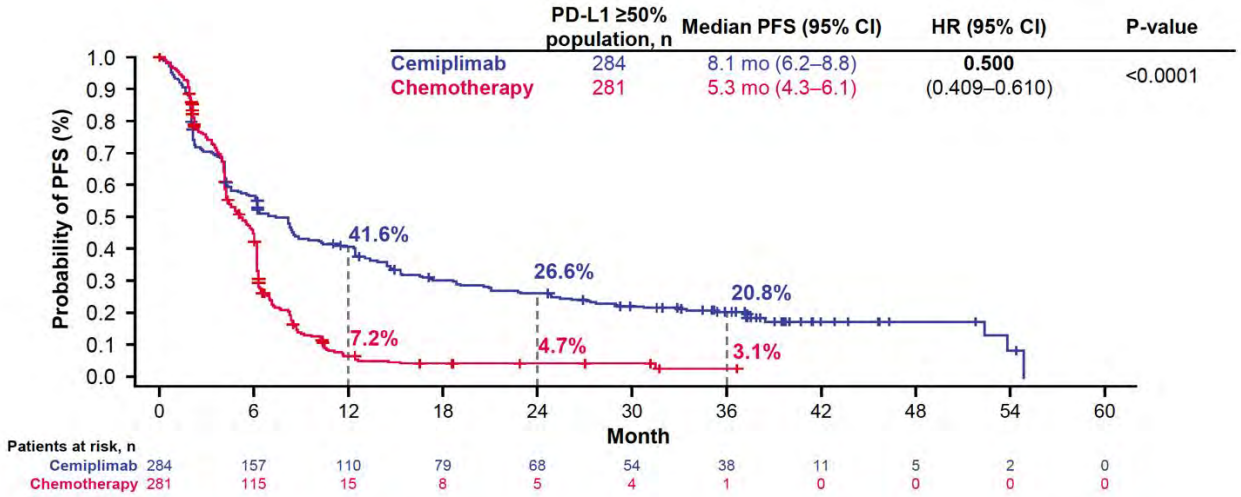
Pembrolizumab





Cemiplimab

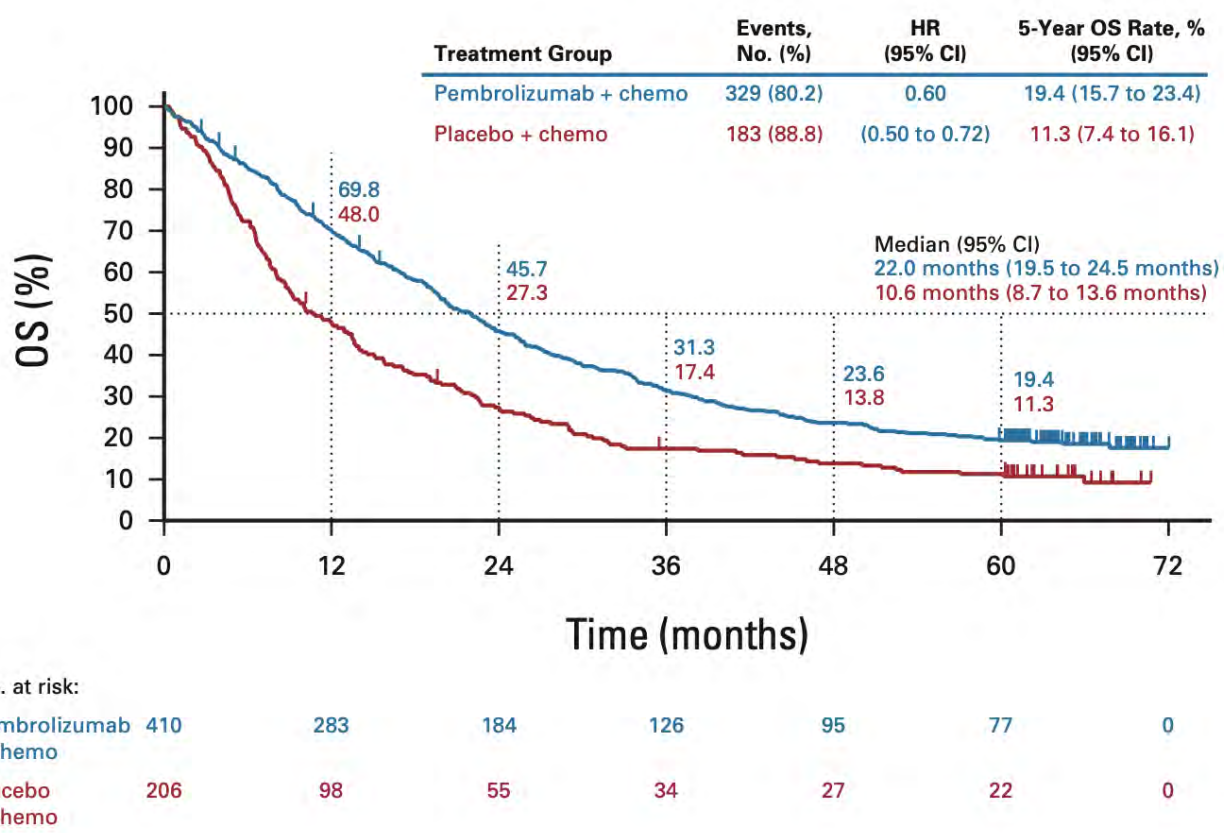


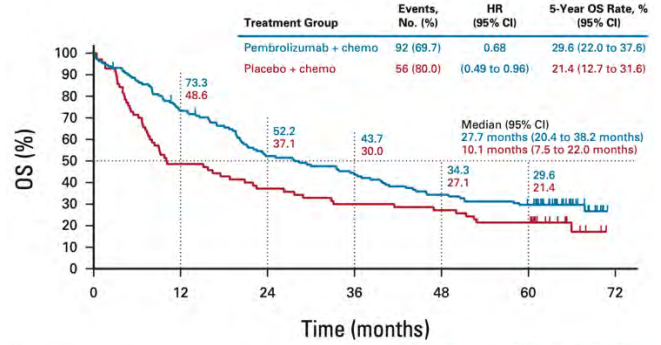


Reck M et al. JCO 2021
Baramidze et al. WCLC 2024 Abstract OA11.06.

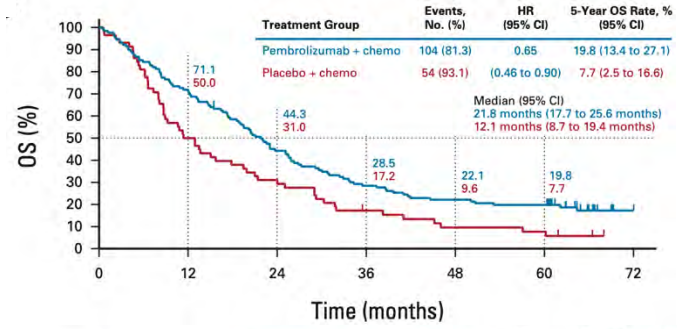
Long-term outcomes with chemo/immunotherapy

5-year OS updates from KEYNOTE-189

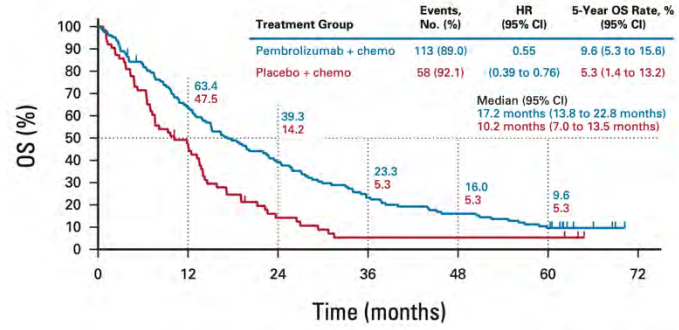




PD-L1 ≥ 50%



PD-L1 1-49%



PD-L1 < 1%

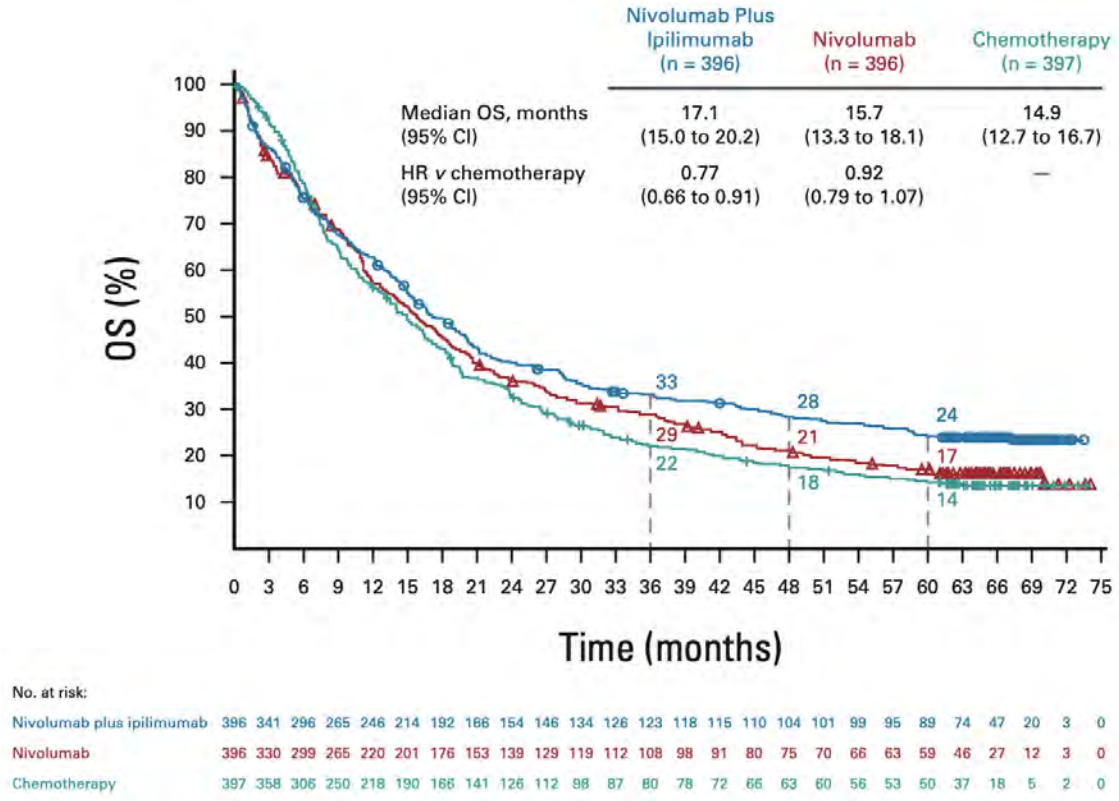
Persistent benefit also seen in the 5-year results from KEYNOTE-407

Garassino M, et al. JCO 2023

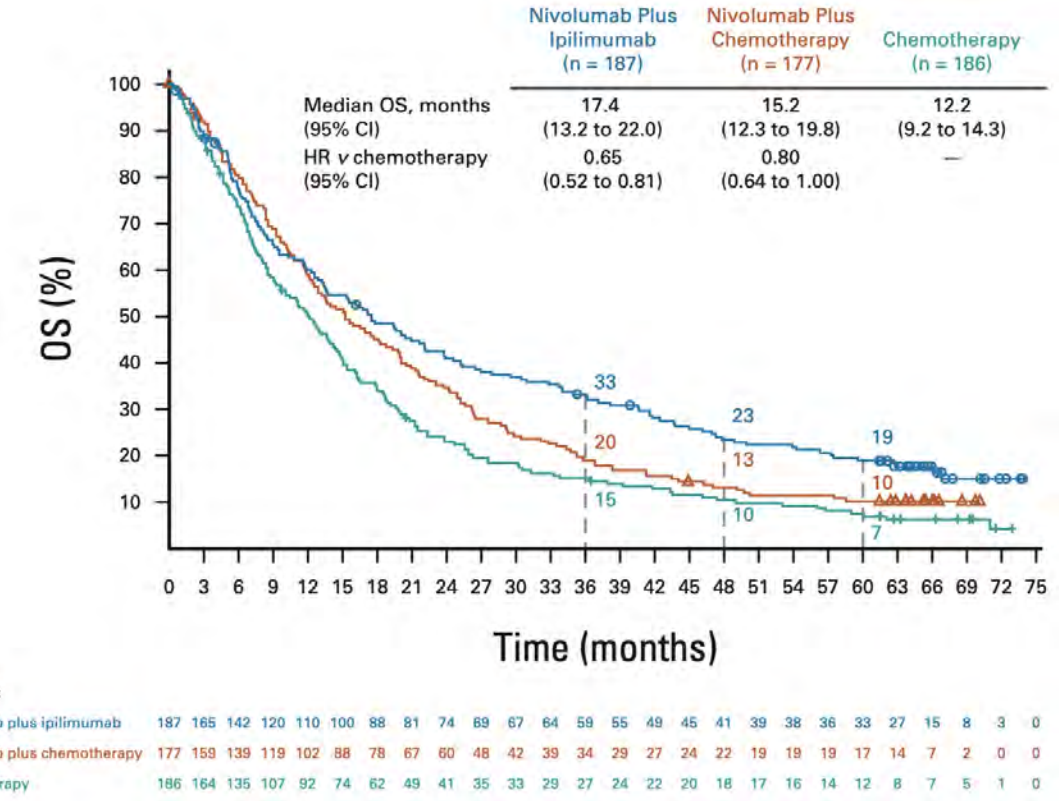
Long-term outcomes with combination immunotherapy

5-year OS updates from CheckMate 227

PD-L1 ≥ 1%



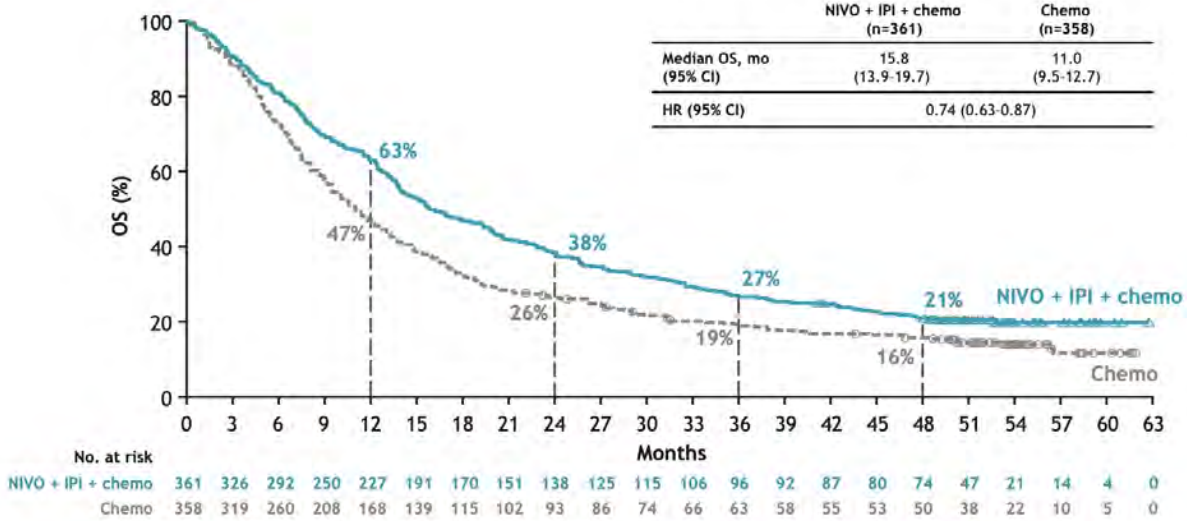
PD-L1 < 1%



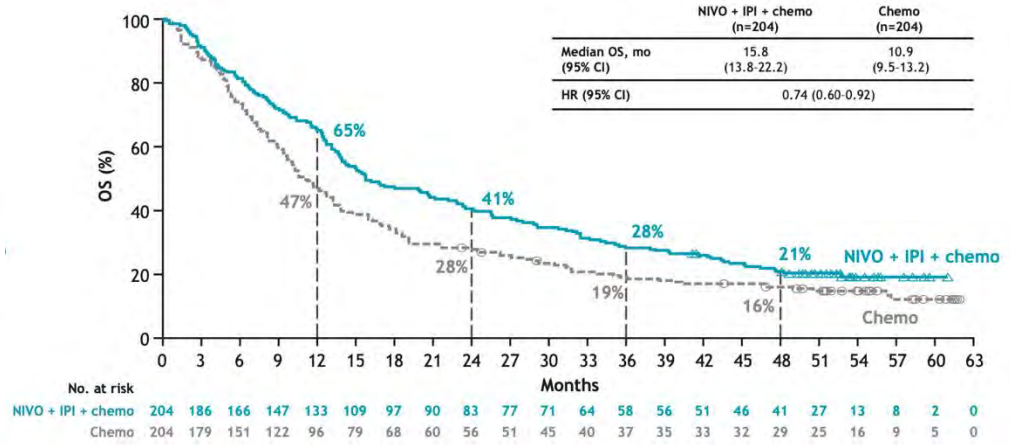
Brahmer JR, et al. JCO 2022

Long-term outcomes with combination immunotherapy plus chemotherapy

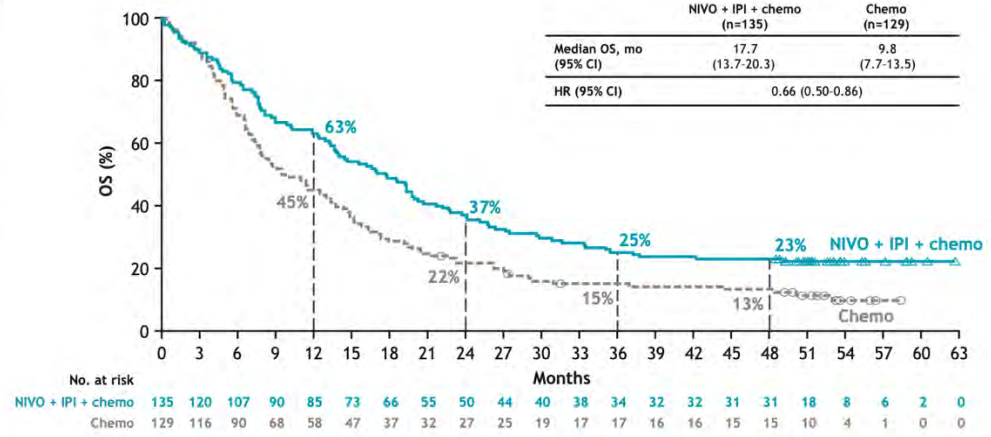
4-year OS updates from CheckMate 9LA



PD-L1 ≥ 1%



PD-L1 < 1%



Carbone DP, et al. JITC 2024

Agenda

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  - First-line treatment
    - Pembrolizumab, atezolizumab and cemiplimab as monotherapy or in combination with chemotherapy
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TROPION-Lung01: Dato-DXd vs docetaxel

Study Design (NCT04656652)[1]

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without AGA*
– 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With AGA
– Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
– 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

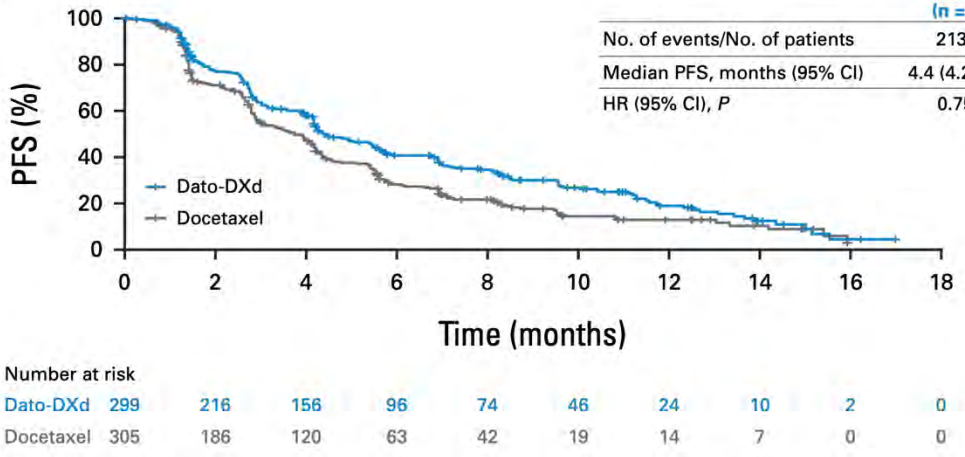
R 1:1

Dato-DXd
6 mg/kg q3w
N=299

Docetaxel
75 mg/m² q3w
N=305

Stratified by:
Histology†, AGA‡, anti–PD-(L)1 mAb included in most recent prior therapy, geography§

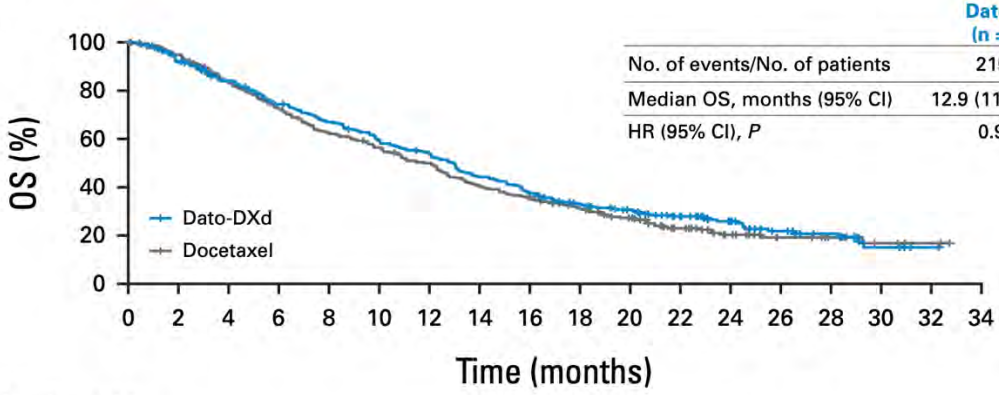
Dual Primary Endpoints: PFS by BICR; OS
Secondary Endpoints: ORR by BICR; DOR by BICR; Safety



	Dato-DXd (n = 299)	Docetaxel (n = 305)
No. of events/No. of patients	213/299	218/305
Median PFS, months (95% CI)	4.4 (4.2 to 5.6)	3.7 (2.9 to 4.2)
HR (95% CI), *P*	0.75 (0.62 to 0.91), *P* = .004	

Number at risk

Dato-DXd	299	216	156	96	74	46	24	10	2	0
Docetaxel	305	186	120	63	42	19	14	7	0	0



	Dato-DXd (n = 299)	Docetaxel (n = 305)
No. of events/No. of patients	215/299	218/305
Median OS, months (95% CI)	12.9 (11.0 to 13.9)	11.8 (10.0 to 12.8)
HR (95% CI), *P*	0.94 (0.78 to 1.14), *P* = .530	

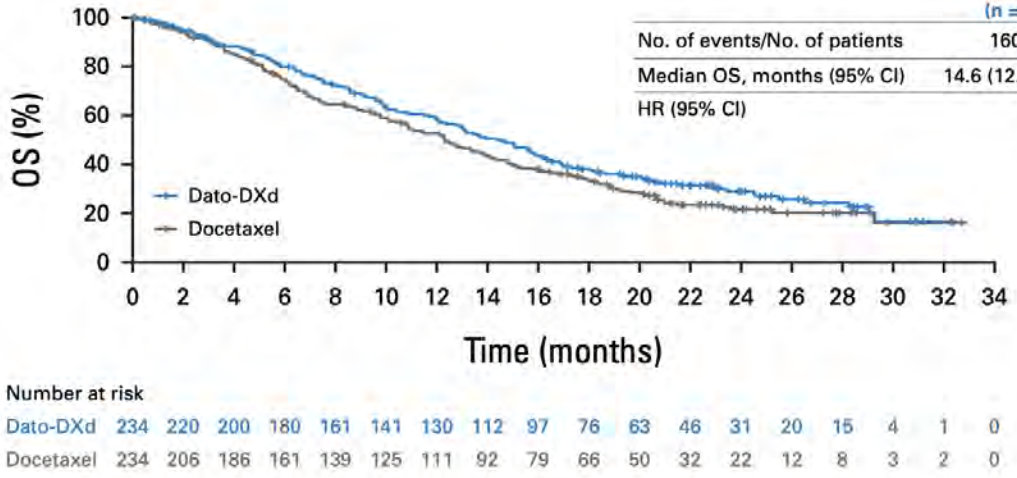
Number at risk

Dato-DXd	299	272	242	213	190	168	151	124	106	84	71	51	35	22	16	5	1	0
Docetaxel	305	273	239	205	175	157	138	112	98	81	63	41	26	15	11	4	2	0

Ahn, MJ, et al. JCO 2024

Biomarkers of benefit with Dato-DXd

Non-squamous

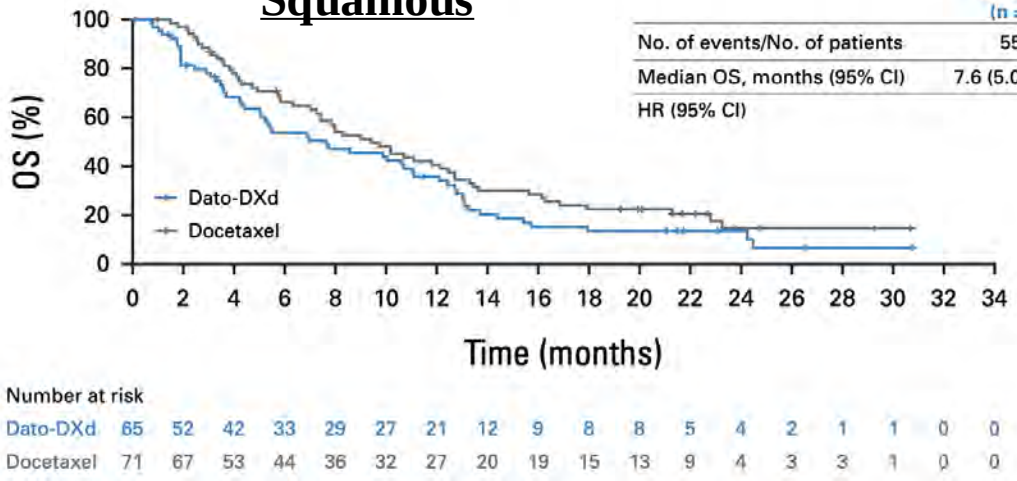


	Dato-DXd (n = 234)	Docetaxel (n = 234)
No. of events/No. of patients	160/234	163/234
Median OS, months (95% CI)	14.6 (12.4 to 16.0)	12.3 (10.7 to 14.0)
HR (95% CI)	0.84 (0.68 to 1.05)	

Number at risk

Dato-DXd	234	220	200	180	161	141	130	112	97	76	63	46	31	20	15	4	1	0
Docetaxel	234	206	186	161	139	125	111	92	79	66	50	32	22	12	8	3	2	0

Squamous



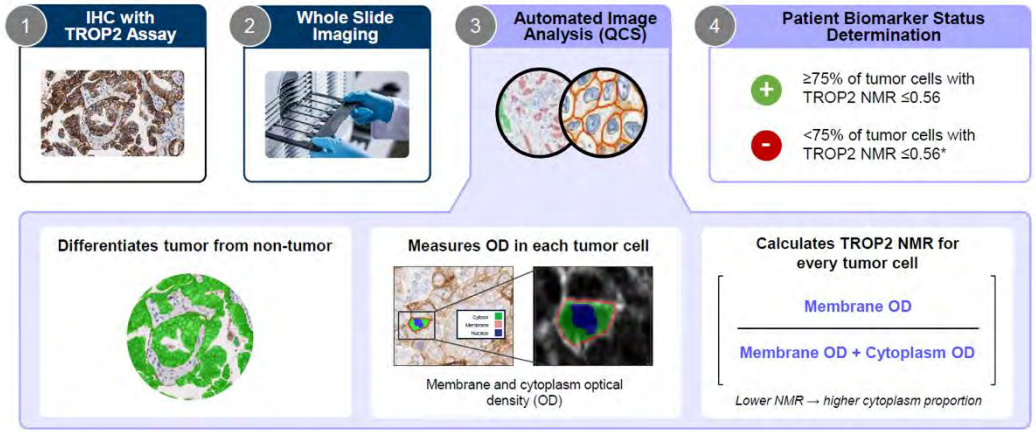
	Dato-DXd (n = 65)	Docetaxel (n = 71)
No. of events/No. of patients	55/65	55/71
Median OS, months (95% CI)	7.6 (5.0 to 11.0)	9.4 (7.2 to 12.5)
HR (95% CI)	1.32 (0.91 to 1.92)	

Number at risk

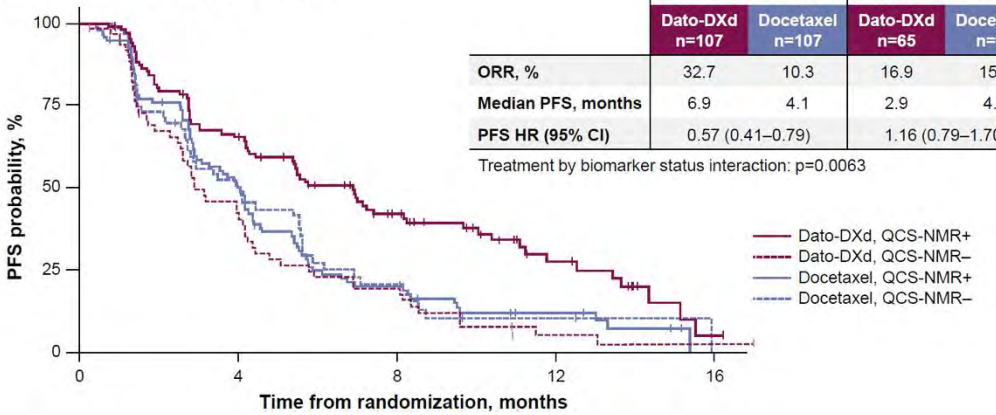
Dato-DXd	65	52	42	33	29	27	21	12	9	8	8	5	4	2	1	1	0	0
Docetaxel	71	67	53	44	36	32	27	20	19	15	13	9	4	3	3	1	0	0

TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2



Biomarker-evaluable population, n=352



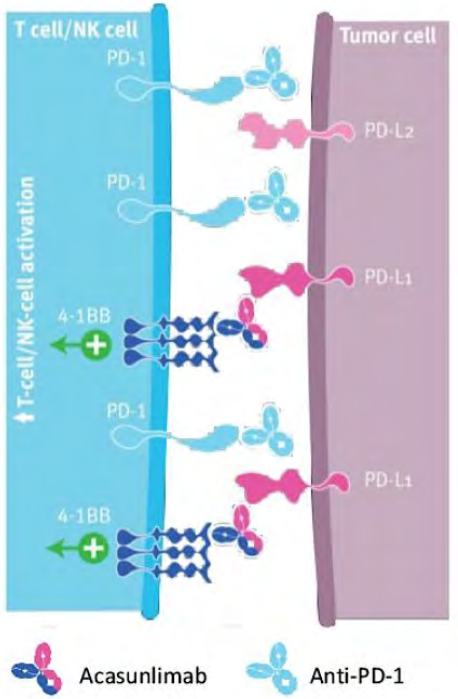
	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

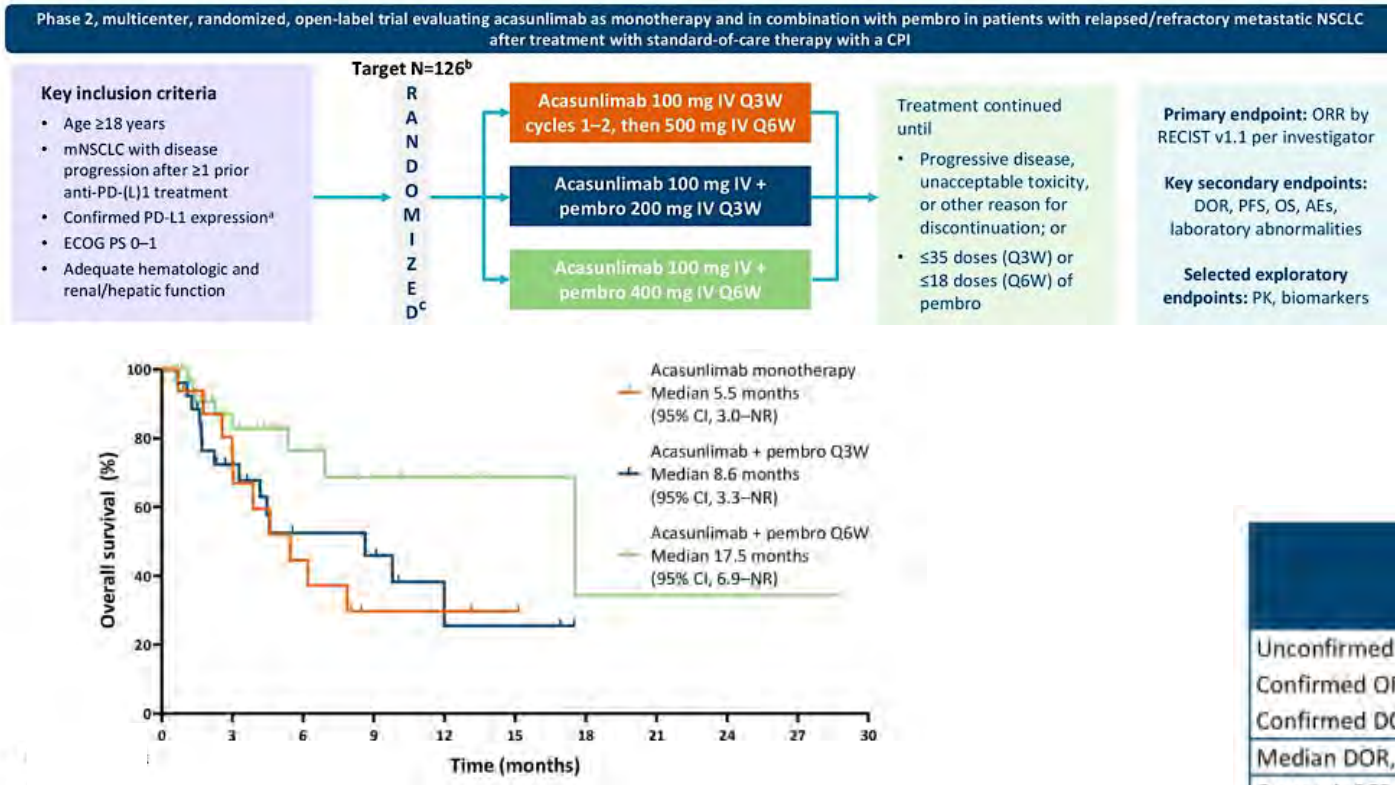
Treatment by biomarker status interaction: p=0.0063

Ahn, MJ, et al. JCO 2024
Garassino M, et al. WCLC 2024
Dacic S, WCLC 2024

Overcoming resistance to PD-(L)1 inhibitors

- Acasunlimab is a bispecific antibody against PD-L4 and 4-1BB
- Conditional activation of 4-1BB dependent on simultaneous binding of the PD-L1 arm





Activity in PD-L1+ subset

	Acasunlimab Monotherapy (n=16)	Acasunlimab + Pembro Q3W (n=22)[a]	Acasunlimab + Pembro Q6W (n=24)[b]
Unconfirmed ORR, % (95% CI)	31.3 (11.0–58.7)	20.8 (7.1–42.2)	29.6 (13.8–50.2)
Confirmed ORR, % (95% CI)	12.5 (1.6–38.3)	18.2 (5.2–40.3)	16.7 (4.7–37.4)
Confirmed DCR, % (95% CI)	50.0 (24.7–75.3)	59.1 (36.4–79.3)	75.0 (53.3–90.2)
Median DOR, mo (95% CI)	2.0 (1.6–NR)	5.2 (3.5–NR)	NR (NR–NR)
6-month PFS rate, % (95% CI)	0 (NA)	14 (3–31)	34 (13–56)
12-month OS rate, % (95% CI)	30 (9–54)	26 (6–52)	69 (43–85)

Data cutoff: March 22, 2024. Centrally confirmed PD-L1+ patients are shown.
[a]n=24 for unconfirmed ORR. [b]n=27 for unconfirmed ORR.

- 6-month PFS rate 34% with combination q6w dosing
- 12-month OS-rate 69%, median OS 17.5 months

Aerts J, et al. ASCO 2024

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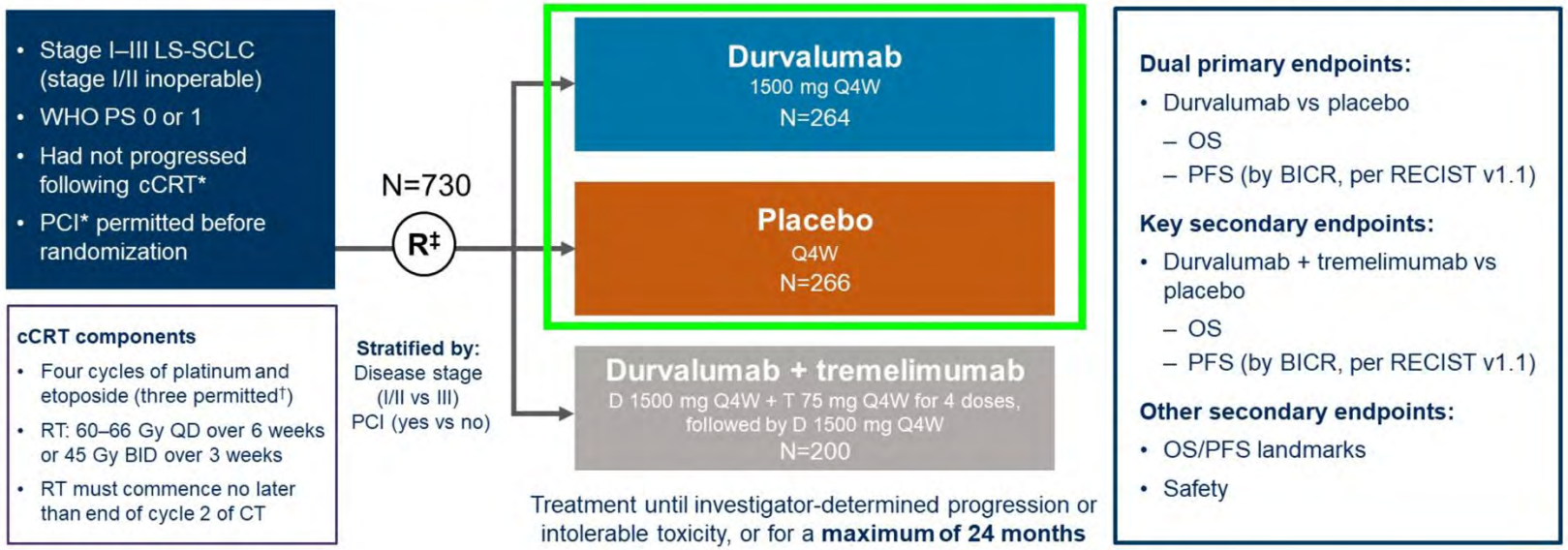
    - DLL3 x CD3 bispecific antibody tarlatamab
    - B7-H3-directed antibody-drug conjugate ifinatamab deruxtecan

ADRIATIC: Consolidation durvalumab for limited-stage SCLC

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)



Baseline characteristics

		Durvalumab (n=264)	Placebo (n=266)
Age, years	Median (range)	62.0 (28–84)	62.0 (28–79)
Sex, %	Male / Female	67.4 / 32.6	70.7 / 29.3
Race, %	White / Asian / Other	49.2 / 49.6 / 1.1	51.5 / 45.5 / 3.0
WHO performance status, %	0 / 1	50.0 / 50.0	47.4 / 52.6
Smoking status, %	Current / Former / Never	23.9 / 67.4 / 8.7	20.7 / 69.5 / 9.8
AJCC disease stage at diagnosis, %	I / II / III	3.0 / 9.5 / 87.5	4.1 / 8.6 / 87.2
Prior chemotherapy regimen, %*	Cisplatin-etoposide / Carboplatin-etoposide	65.5 / 34.5	66.9 / 33.1
Prior radiation schedule, %	Once daily / Twice daily	73.9 / 26.1	70.3 / 29.7
Best response to prior cCRT, %	CR / PR / SD	11.7 / 72.3 / 15.9	12.8 / 75.2 / 12.0
Prior PCI, %	Yes / No	53.8 / 46.2	53.8 / 46.2

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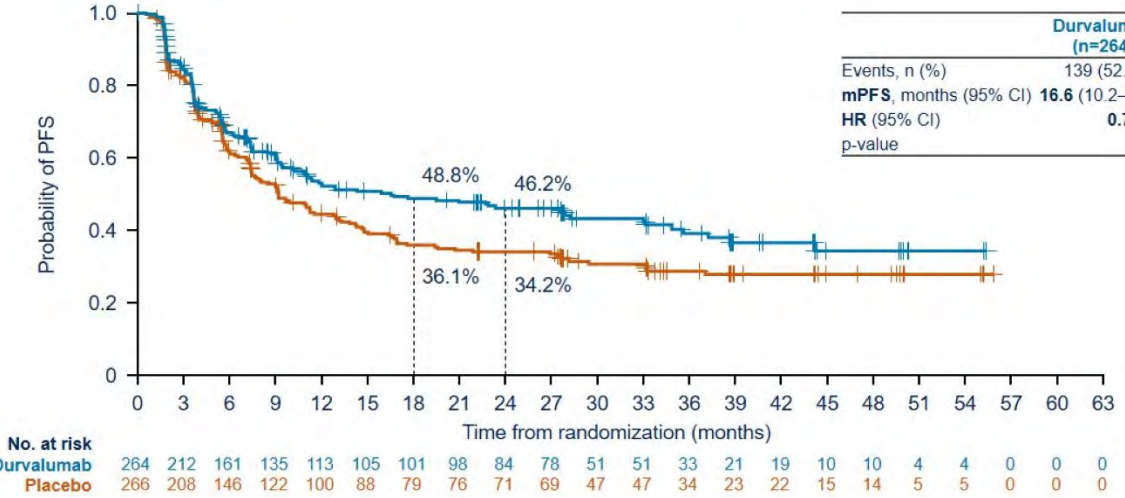
ADRIATIC: Consolidation durvalumab for limited-stage SCLC

Progression-free survival* (dual primary endpoint)

- Median duration of follow up in censored patients: 27.6 months (range 0.0–55.8)

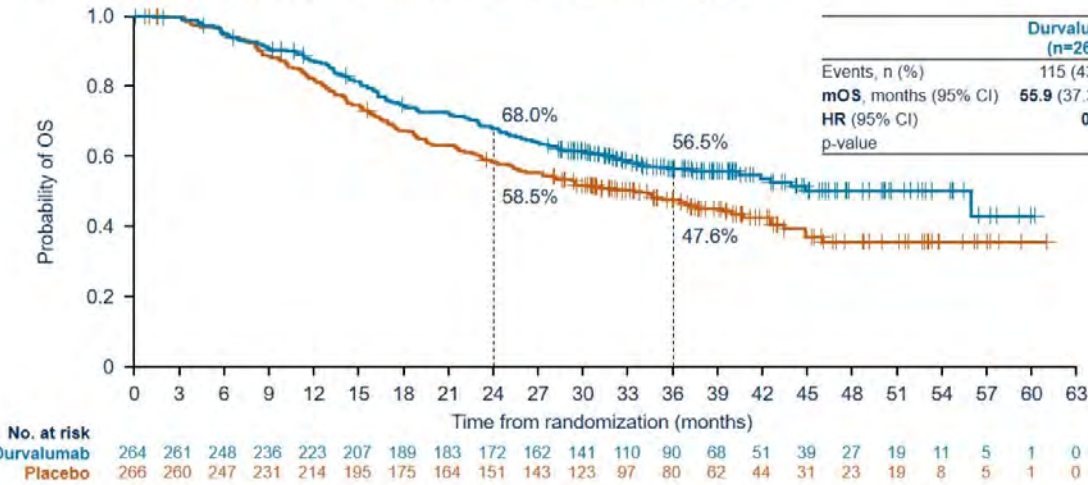


	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

No. at risk																						
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

Overall survival (dual primary endpoint)

- Median duration of follow up in censored patients: 37.2 months (range 0.1–60.9)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

No. at risk																						
Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

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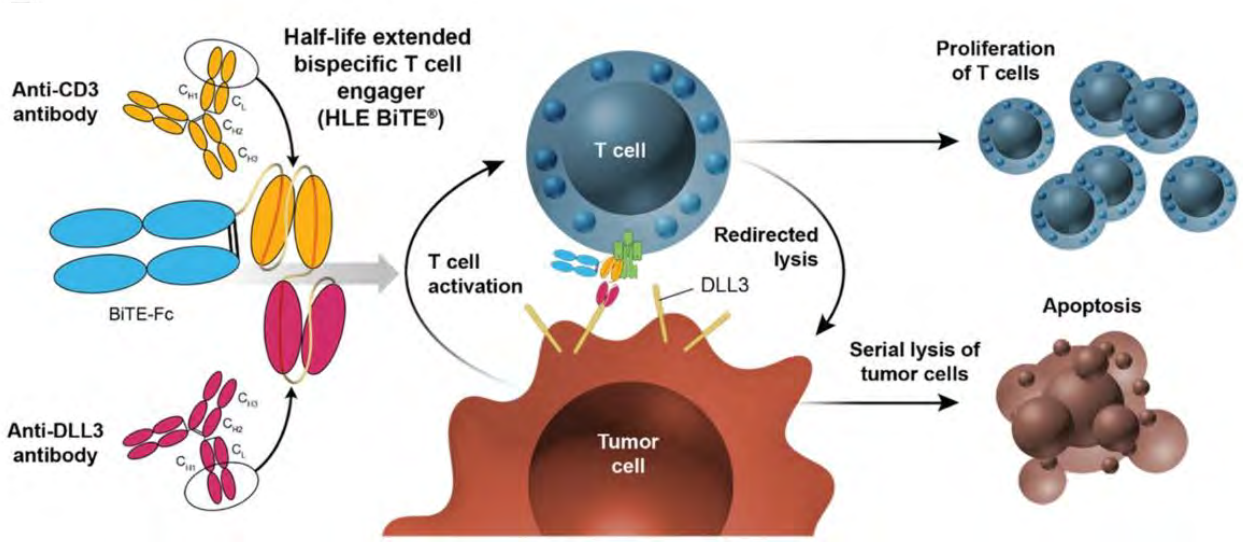
Agenda

- **Advanced NSCLC**
  - First-line treatment
    - Pembrolizumab, atezolizumab and cemiplimab as monotherapy or in combination with chemotherapy
    - Long-term data with dual immune checkpoint inhibition with or without chemotherapy
  - Previously-treated
    - Datopotamab deruxtecan
    - PD-L1 x 4-1BB bispecific antibody acasunlimab
- **SCLC**
  - Limited stage
    - Durvalumab as consolidation treatment (ADRIATIC)
  - Extensive stage
    - DLL3 x CD3 bispecific antibody tarlatamab
    - B7-H3-directed antibody-drug conjugate ifinatamab deruxtecan

Tarlatamab: a bispecific T cell engager

- Tarlatamab is a bispecific T cell engager (BiTE) combining the binding specificities for DLL3 and CD3 genetically fused to the IgG Fc region
- Designed to induce T cell proliferation and tumor cell lysis



Owen DH, et al. J Hematol Oncol 2019

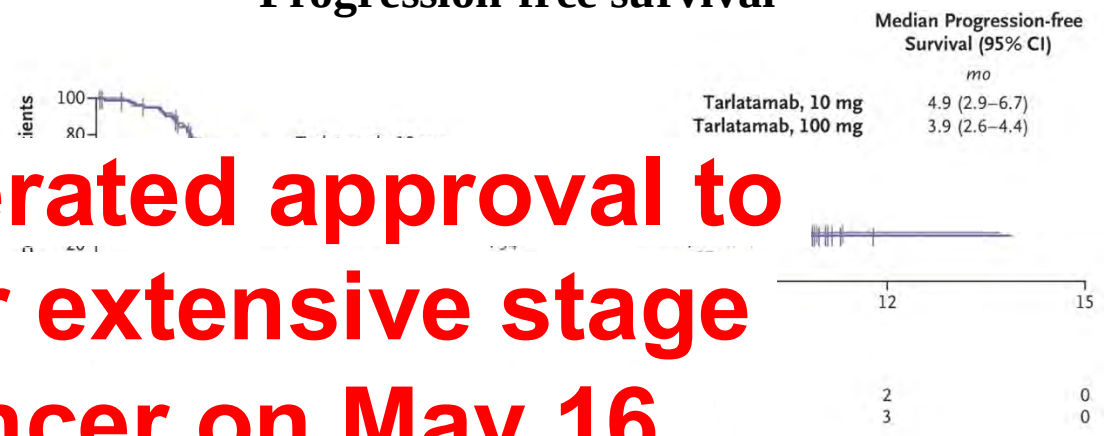
Phase II DeLLphi-301 study of Tarlatamab in patients with previously-treated extensive-stage SCLC

FDA grants accelerated approval to tarlatamab-dlle for extensive stage small cell lung cancer on May 16, 2024

Patient characteristics

Characteristic	Tarlatamab, 10 mg		Tarlatamab, 100 mg
	Parts 1 and 2 (N=100)	Part 3 (N=34)	Part 1 (N=88)
No. of previous lines of therapy — no. (%)			
1	2 (2)	0	2 (2)
2	65 (65)	22 (65)	48 (55)
3	19 (19)	6 (18)	22 (25)
>3	14 (14)	6 (18)	16 (18)
Median no. of previous lines of therapy (range)			
Median sum of target-lesion diameters (range) — mm			
Previous use of PD-L1 or PD-1 inhibitor — no. (%)			
Yes			
No			
Duration of sensitivity to platinum-based treatment — no. (%)§			
<90 days			
90 to <180 days			
≥180 days			
Unknown		1 (32)	34 (39)
DLL3 expression — no./total no. (%)¶		NA	71/74 (96)

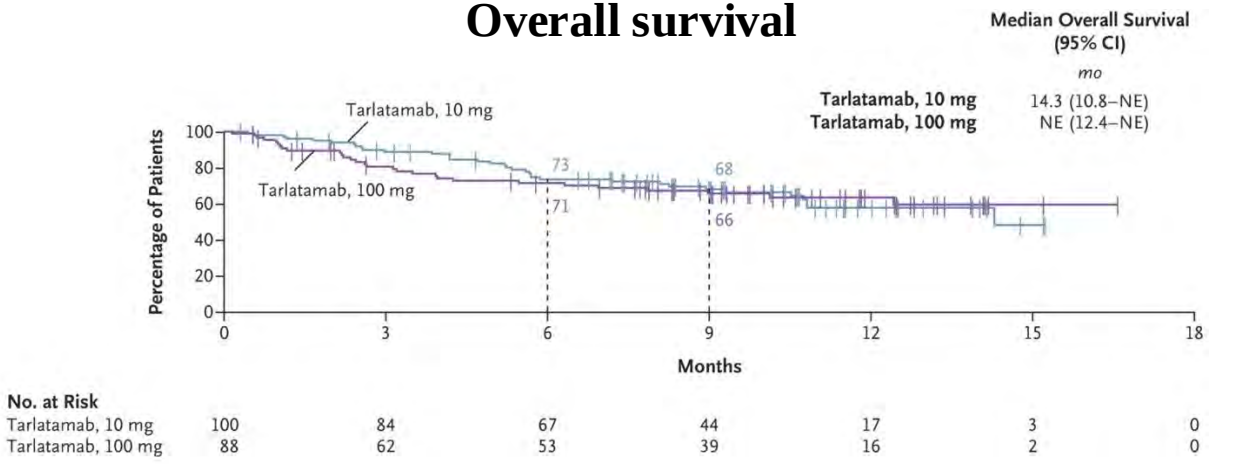
Progression-free survival



Treatment response

Variable	Tarlatamab, 10 mg (N=100)	Tarlatamab, 100 m (N=88)
Best overall response — no. (%)		
Objective response		
Confirmed complete response	1 (1)	7 (8)
Confirmed partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable†	2 (2)	4 (5)
Death before postbaseline scan†	6 (6)	13 (15)
No postbaseline scan†	2 (2)	3 (3)
Percentage of patients with objective response (97.5% CI)	40 (29–52)	32 (21–44)

Overall survival



Ahn M-J et al. N Engl J Med 2023

Toxicity with tarlatamab

Table 3. Adverse Events (Safety Analysis Population).*

Adverse Events	Tarlatamab, 10 mg		Tarlatamab, 100 mg
	Parts 1 and 2 (N=99)	Part 3, Reduced Monitoring (N=34)	Part 1 (N=87)
	number of patients (percent)		
Events during treatment period			
According to severity			
Any grade	96 (97)	34 (100)	87 (100)
Grade ≥2	86 (87)	33 (97)	83 (95)
Grade ≥3	57 (58)	22 (65)	56 (64)
Grade ≥4	16 (16)	7 (21)	13 (15)
Fatal	3 (3)	4 (12)	5 (6)
Serious adverse event	58 (59)	14 (41)	62 (71)
Event leading to dose interruption, dose reduction, or both	31 (31)	5 (15)	39 (45)
Event leading to tarlatamab discontinuation	7 (7)	3 (9)	6 (7)
Events of interest during treatment period			
Cytokine-release syndrome†			
Overall	49 (49)	19 (56)	53 (61)
Grade ≥3 severity	0	1 (3)	5 (6)
Serious	26 (26)	5 (15)	32 (37)
Leading to tarlatamab discontinuation	0	0	1 (1)
Fatal	0	0	0
ICANS and associated neurologic events‡			
Overall	7 (7)	4 (12)	24 (28)
Grade ≥3 severity	0	0	4 (5)
Serious	2 (2)	2 (6)	11 (13)
Leading to tarlatamab discontinuation	1 (1)	0	1 (1)
Fatal	0	0	0
Neutropenia			
Overall	18 (18)	5 (15)	14 (16)
Grade ≥3 severity	6 (6)	2 (6)	9 (10)
Serious	2 (2)	0	3 (3)
Leading to tarlatamab discontinuation	0	0	0
Fatal	0	0	0
Events related to treatment			
According to severity			
Any grade	89 (90)	29 (85)	81 (93)
Grade ≥2	69 (70)	23 (68)	66 (76)
Grade ≥3	29 (29)	5 (15)	29 (33)
Grade ≥4	5 (5)	2 (6)	3 (3)
Fatal	0	1 (3)	0
Serious	37 (37)	7 (21)	46 (53)
Event leading to dose interruption, dose reduction, or both	14 (14)	3 (9)	25 (29)
Event leading to tarlatamab discontinuation	4 (4)	0	3 (3)

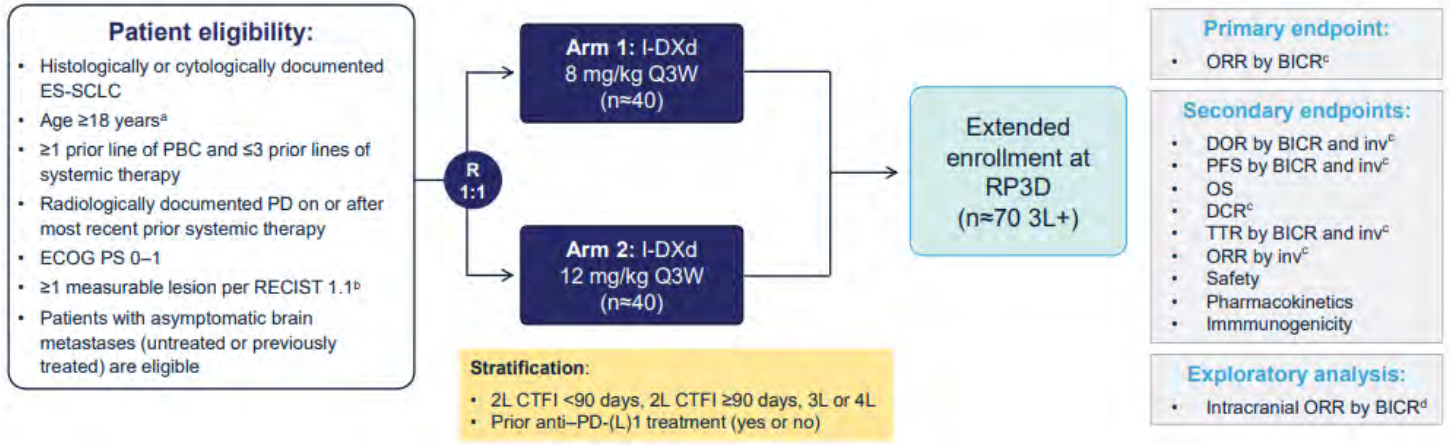
Cytokine-Release Syndrome and Immune effector cell-associated neurotoxicity syndrome (ICANS)

Ahn M-J et al. N Engl J Med 2023

ADCs for SCLC: Ifinatamab deruxtecan

- Ifinatamab Deruxtecan (I-DXd) is an ADC against B7-H3 with a topoisomerase I inhibitor payload (an exatecan derivative)

Phase 2 IDeate-Lung01 study (NCT05280470)

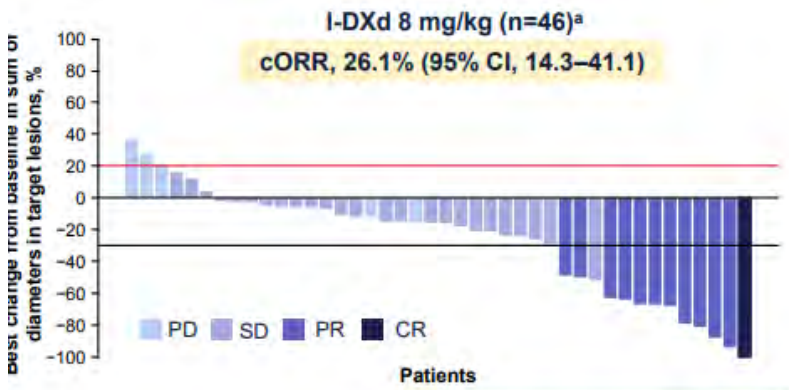


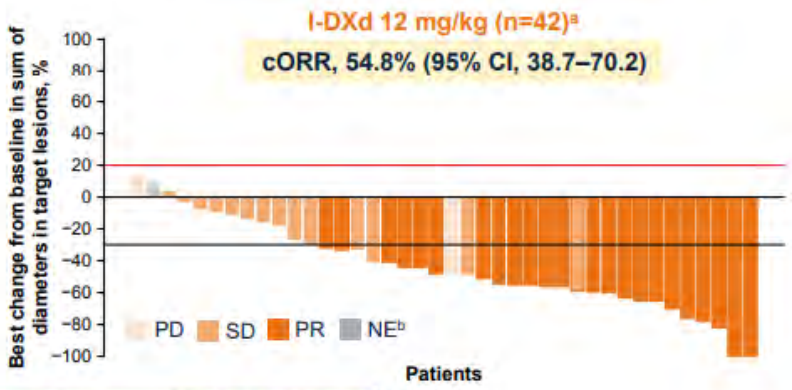
Patient demographics and baseline characteristics

	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42	Total N=88
Age, median (range)	64 (42–85)	64 (34–79)	64 (34–85)
Male, n (%)	30 (65.2)	33 (78.6)	63 (71.6)
ECOG PS, n (%)			
0	13 (28.3)	6 (14.3)	19 (21.6)
1	33 (71.7)	36 (85.7)	69 (78.4)
ES-SCLC at diagnosis, n (%)	32 (69.6)[a]	35 (83.3)	67 (76.1)
Patients with brain metastasis at baseline, n (%)	19 (41.3)	18 (42.9)	37 (42.0)
Number of prior lines of systemic therapy, n (%)			
1	13 (28.3)	12 (28.6)	25 (28.4)
2	22 (47.8)	22 (52.4)	44 (50.0)
3	11 (23.9)	8 (19.0)	19 (21.6)
Chemotherapy-free interval[b]			
<90 days	22 (47.8)	23 (54.8)	45 (51.1)
≥90 days	22 (47.8)	19 (45.2)	41 (46.6)
Select prior anticancer therapy received, n (%)			
Lurbinectedin	11 (23.9)	3 (7.1)	14 (15.9)
Irinotecan or topotecan	14 (30.4)	17 (40.5)	31 (35.2)
Tarlatamab	4 (8.7)	2 (4.8)	6 (6.8)
Amrubicin	3 (6.5)	3 (7.1)	6 (6.8)
Prior anti–PD-(L)1 therapy received,[c] n (%)	35 (76.1)	32 (76.2)	67 (76.1)

Rudin C, et al. WCLC 2024

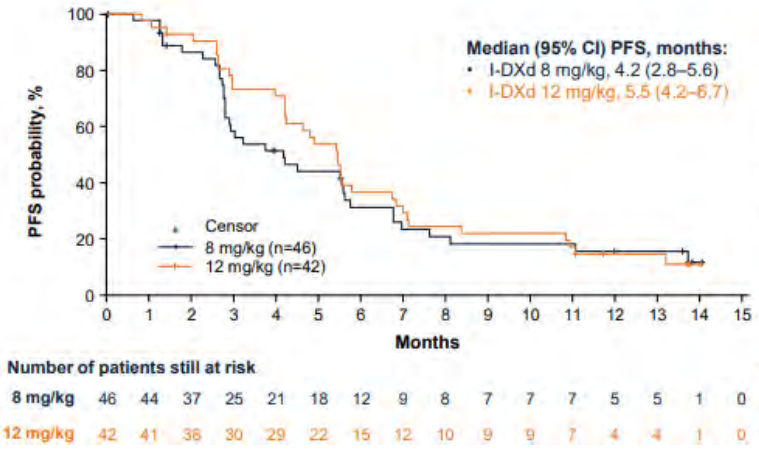
Activity of I-DXd



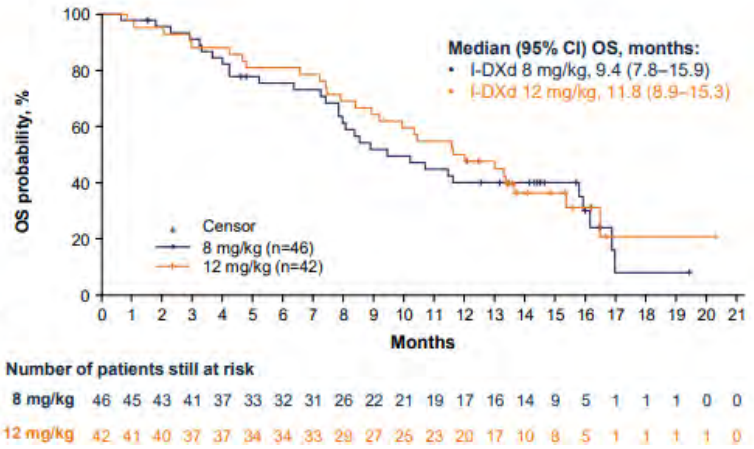


Confirmed response by BICR[c]	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
ORR, % (95% CI)	26.1 (14.3–41.1)	54.8 (38.7–70.2)
CR, n (%)	1 (2.2)	0
PR, n (%)	11 (23.9)	23 (54.8)
DCR, % (95% CI)	80.4 (66.1–90.6)	90.5 (77.4–97.3)
Median (range) TTR,[a] months	1.4 (1.2–1.5)	1.4 (1.0–8.1)
Median (95% CI) DOR,[a,b] months	7.9 (4.1–NE)	4.2 (3.5–7.0)

Progression-free Survival



Overall Survival



Rudin C, et al. WCLC 2024

Conclusions on non-targeted therapy for lung cancer

- Immunotherapy alone or in combination is standard first-line therapy for metastatic NSCLC
  - Long-term disease control and survival is seen in a subset of patients
- Durvalumab improves both PFS and OS as consolidation therapy after chemoradiation in patients with limited-stage SCLC
- Novel immunotherapies are emerging
  - Tarlatamab is now approved for previously-treated SCLC
  - Bispecific antibodies are showing promise in NSCLC, such as the PD-L1/4-1BB inhibitor acasunlimab
- ADCs have activity in patients with previously-treated NSCLC and SCLC
  - For example, Dato-DXd in non-squamous NSCLC and I-DXd in SCLC

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

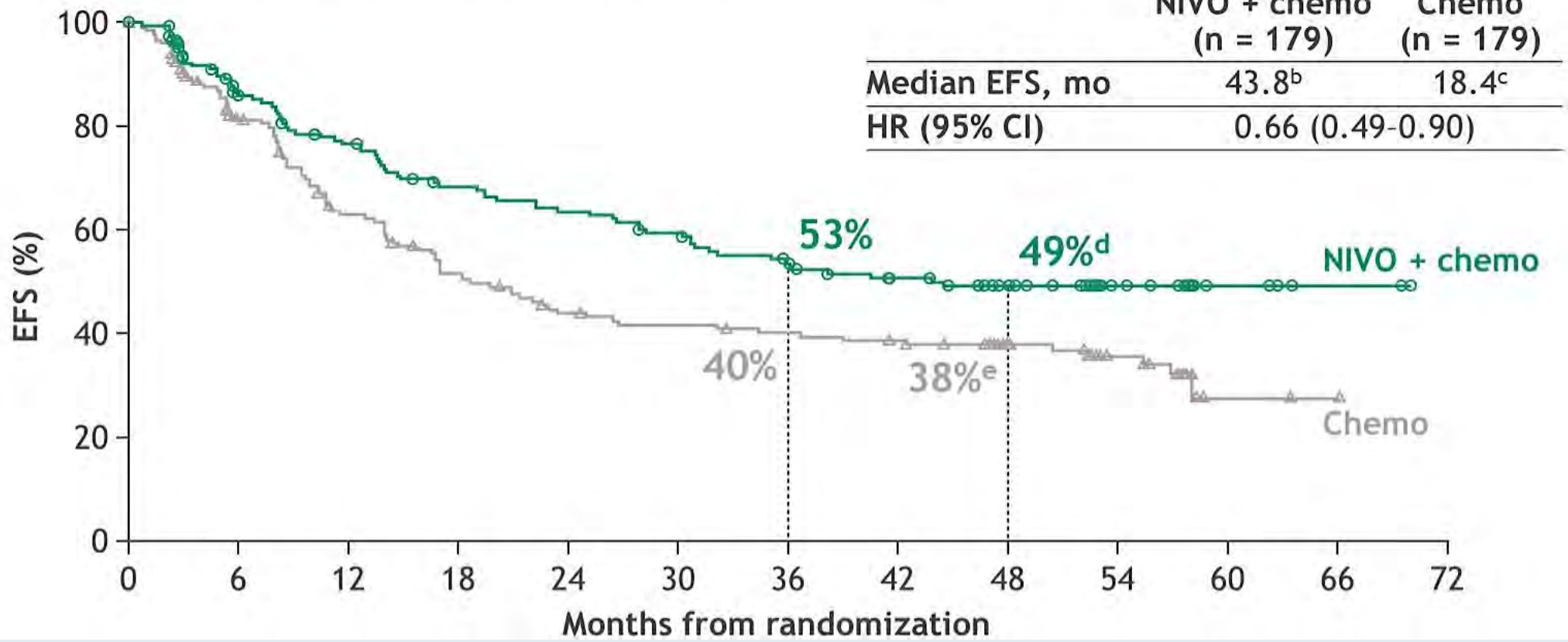
Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

Phase III CheckMate 816 Study: 4-Year EFS Update with Neoadjuvant Nivolumab

- In CheckMate 816, neoadjuvant NIVO + chemo significantly improved the primary endpoints of EFS and pCR vs chemo and demonstrated a favorable OS trend in patients with resectable NSCLC[1,2]

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo	43.8[b]	18.4[c]
HR (95% CI)	0.66 (0.49-0.90)	



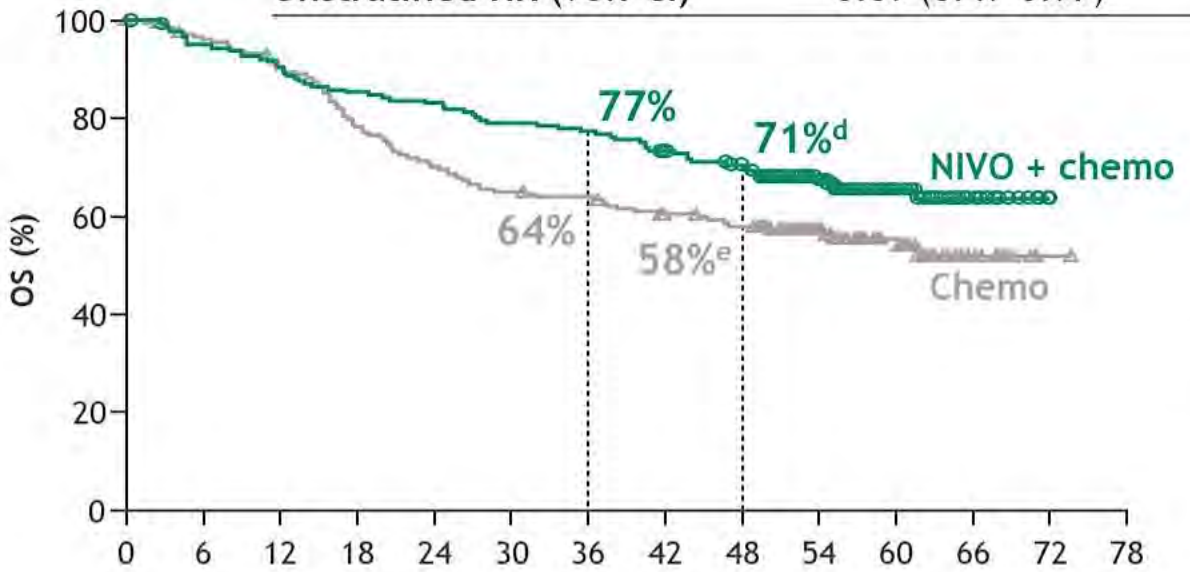
EFS = event-free survival; pCR = pathologic complete response; OS = overall survival

Spicer JD et al. ASCO 2024;Abstract LBA8010.

Phase III CheckMate 816 Study: 4-Year OS Update with Neoadjuvant Nivolumab

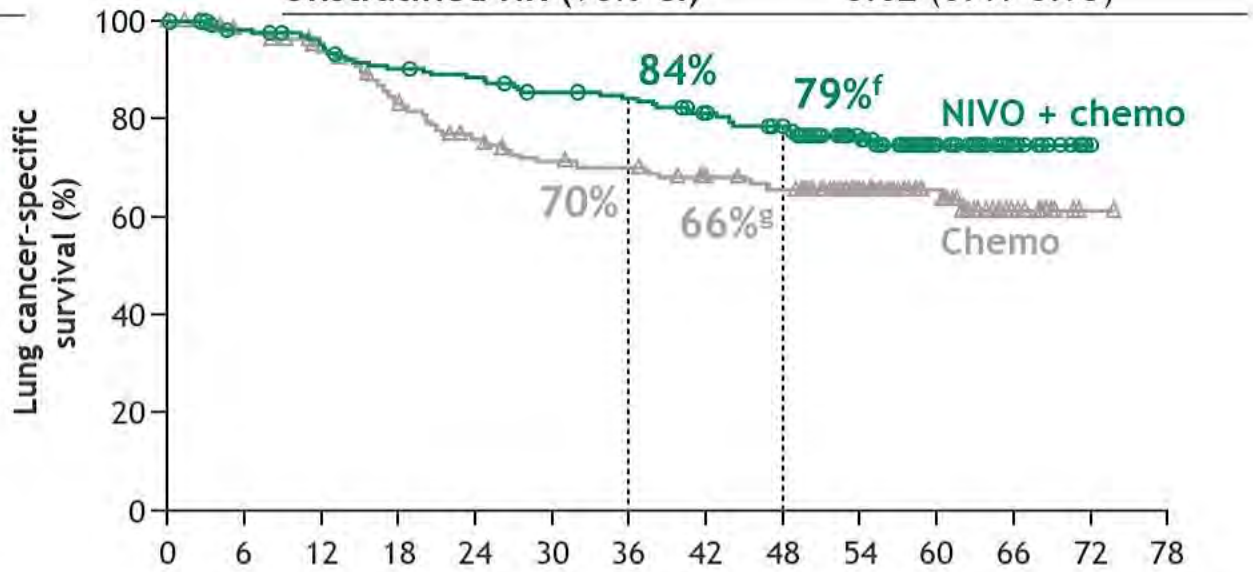
OS

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR[c]
HR (98.36% CI); *P* value	0.71 (0.47-1.07); 0.0451[b]	
Unstratified HR (95% CI)	0.69 (0.49-0.97)	



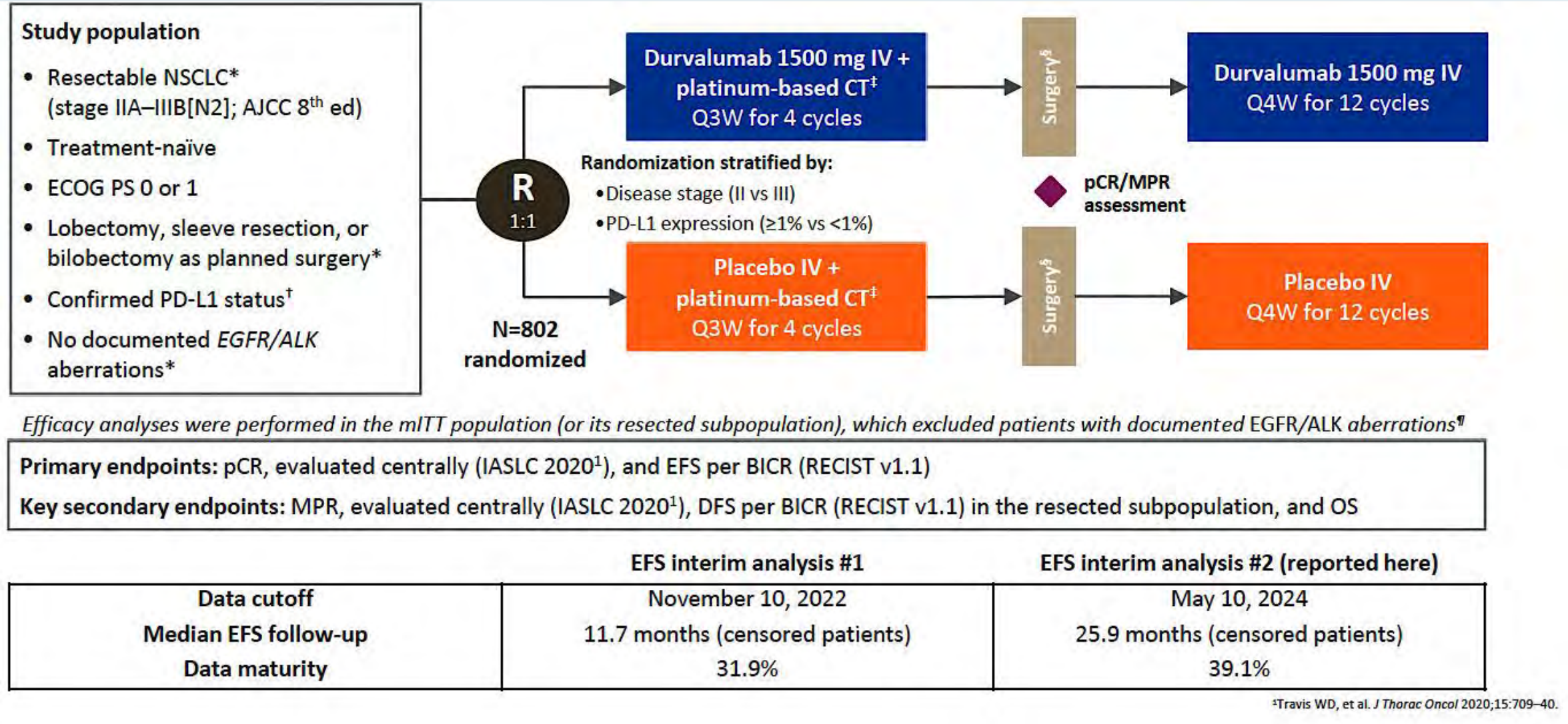
Lung cancer-specific survival[h]

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median lung cancer-specific survival, mo	NR	NR
Unstratified HR (95% CI)	0.62 (0.41-0.93)	



Spicer JD et al. ASCO 2024;Abstract LBA8010.

AEGEAN Trial: Perioperative Durvalumab for Resectable NSCLC



Efficacy analyses were performed in the mITT population (or its resected subpopulation), which excluded patients with documented EGFR/ALK *aberrations*¶

Primary endpoints: pCR, evaluated centrally (IASLC 2020[1]), and EFS per BICR (RECIST v1.1)

Key secondary endpoints: MPR, evaluated centrally (IASLC 2020[1]), DFS per BICR (RECIST v1.1) in the resected subpopulation, and OS

	EFS interim analysis #1	EFS interim analysis #2 (reported here)
Data cutoff	November 10, 2022	May 10, 2024
Median EFS follow-up	11.7 months (censored patients)	25.9 months (censored patients)
Data maturity	31.9%	39.1%

‡Travis WD, et al. *J Thorac Oncol* 2020;15:709–40.

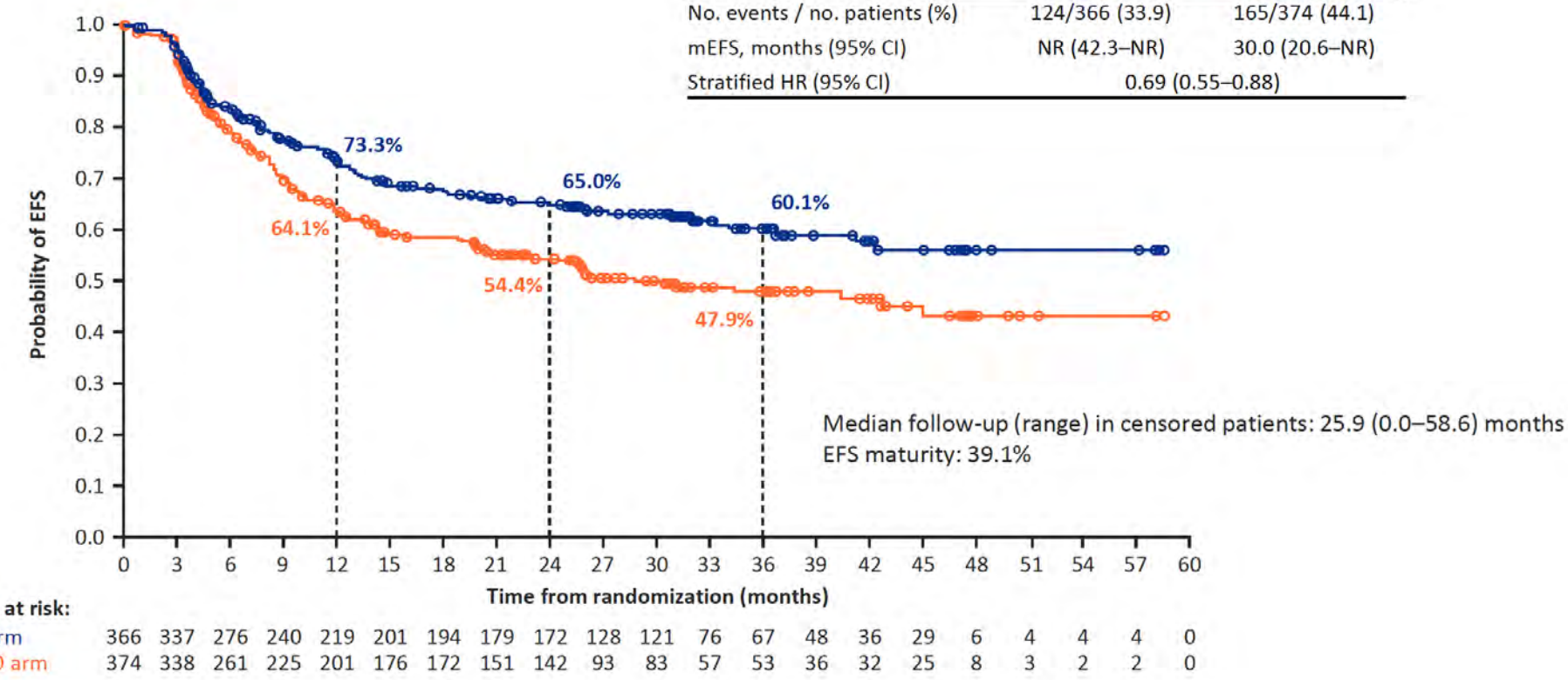
CT = chemotherapy; pCR = pathological complete response; MPR = major pathological response; EFS = event-free survival; DFS = disease-free survival; OS = overall survival

Morris MJ et al. *Lancet* 2024;404(10459):1227-39.

AEGEAN: Perioperative Durvalumab – EFS

- EFS benefit favoring the durvalumab arm was maintained and consistent with that reported previously[1]

	D arm	PBO arm
No. events / no. patients (%)	124/366 (33.9)	165/374 (44.1)
mEFS, months (95% CI)	NR (42.3–NR)	30.0 (20.6–NR)
Stratified HR (95% CI)	0.69 (0.55–0.88)	



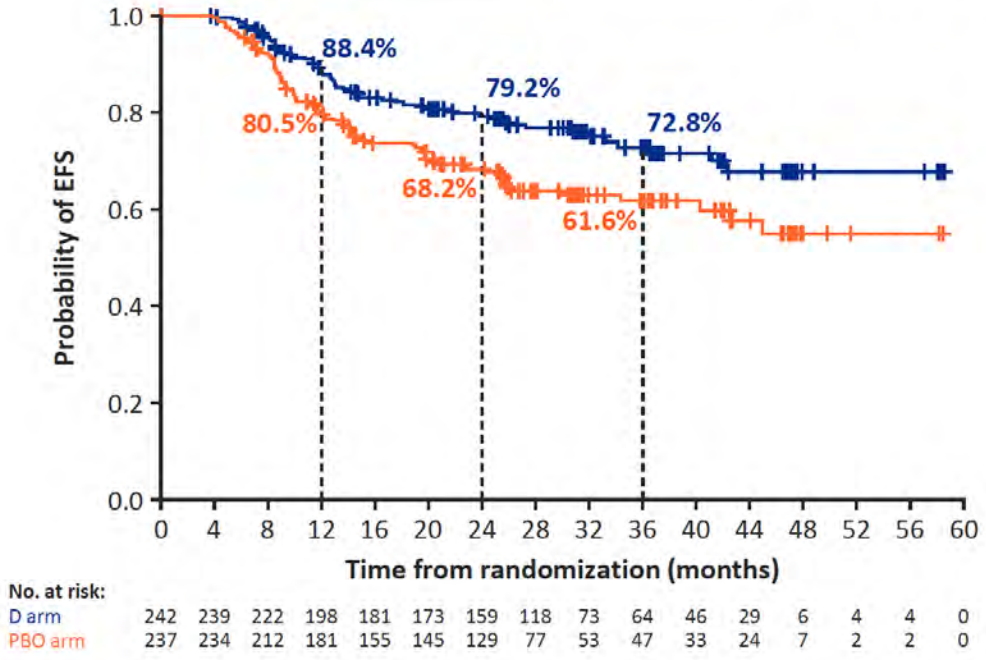
Heymach JV et al. WCLC 2024;Abstract OA13.03

AEGEAN: Perioperative Durvalumab – EFS by Adjuvant Treatment Status

- EFS benefit in the durvalumab arm was more pronounced in patients who received adjuvant treatment

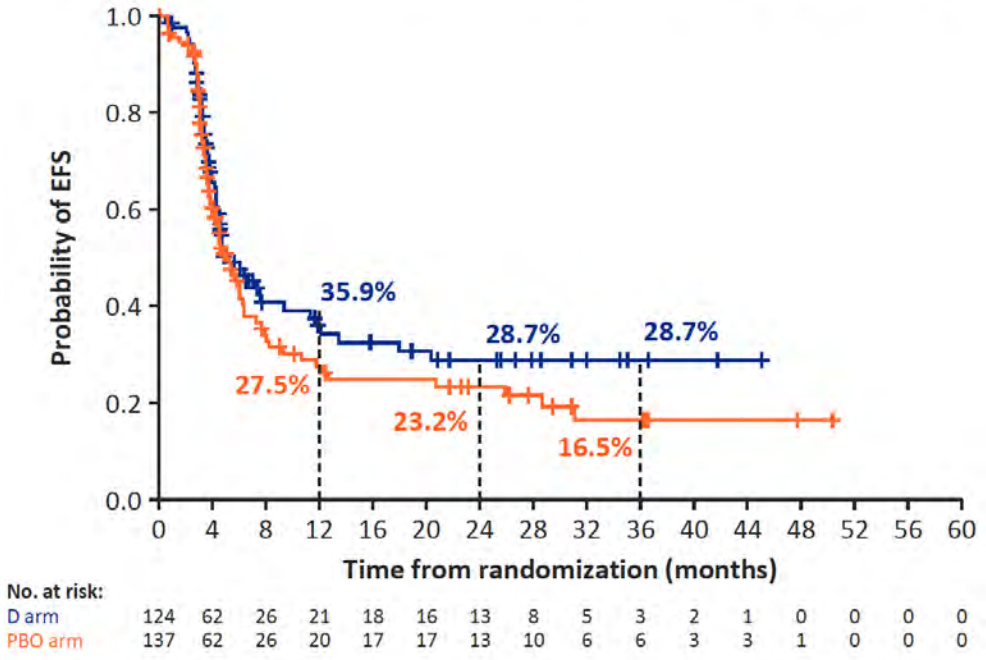
Received adjuvant treatment

	D arm	PBO arm
No. events / no. patients (%)	58/242 (24.0)	83/237 (35.0)
mEFS, months (95% CI)	NR (NR–NR)	NR (42.6–NR)
Unstratified HR (95% CI)	0.62 (0.44–0.86)	



Did not receive adjuvant treatment

	D arm	PBO arm
No. events / no. patients (%)	66/124 (53.2)	82/137 (59.9)
mEFS, months (95% CI)	5.1 (4.5–9.3)	5.2 (4.1–6.3)
Unstratified HR (95% CI)	0.83 (0.60–1.14)	



Heymach JV et al. WCLC 2024;Abstract OA13.03

Perioperative nivolumab vs placebo in patients with resectable NSCLC: clinical update from the phase 3 CheckMate 77T study

ESMO 2024; Abstract LBA50

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Neoadjuvant nivolumab plus chemotherapy vs chemotherapy in patients with resectable NSCLC: 4-year update from CheckMate 816

ASCO 2024; Abstract LBA8010

Jonathan D. Spicer,[1] Nicolas Girard,[2] Mariano Provencio Pulla,[3] Changli Wang,[4] Tetsuya Mitsudomi,[5] Mark M. Awad,[6] Everett E. Vokes,[7] Janis M. Taube,[8] Lorena Lupinacci,[9] Gene B. Saylors,[10] Fumihiro Tanaka,[11] Moishe Liberman,[12] Sung Yong Lee,[13] Aurelia Alexandru,[14] Manolo D'Arcangelo,[15] Phuong Tran,[16] Javed Mahmood,[16] Vishwanath Gharpure,[16] Apurva Bhingare,[16] Patrick M. Forde[8]

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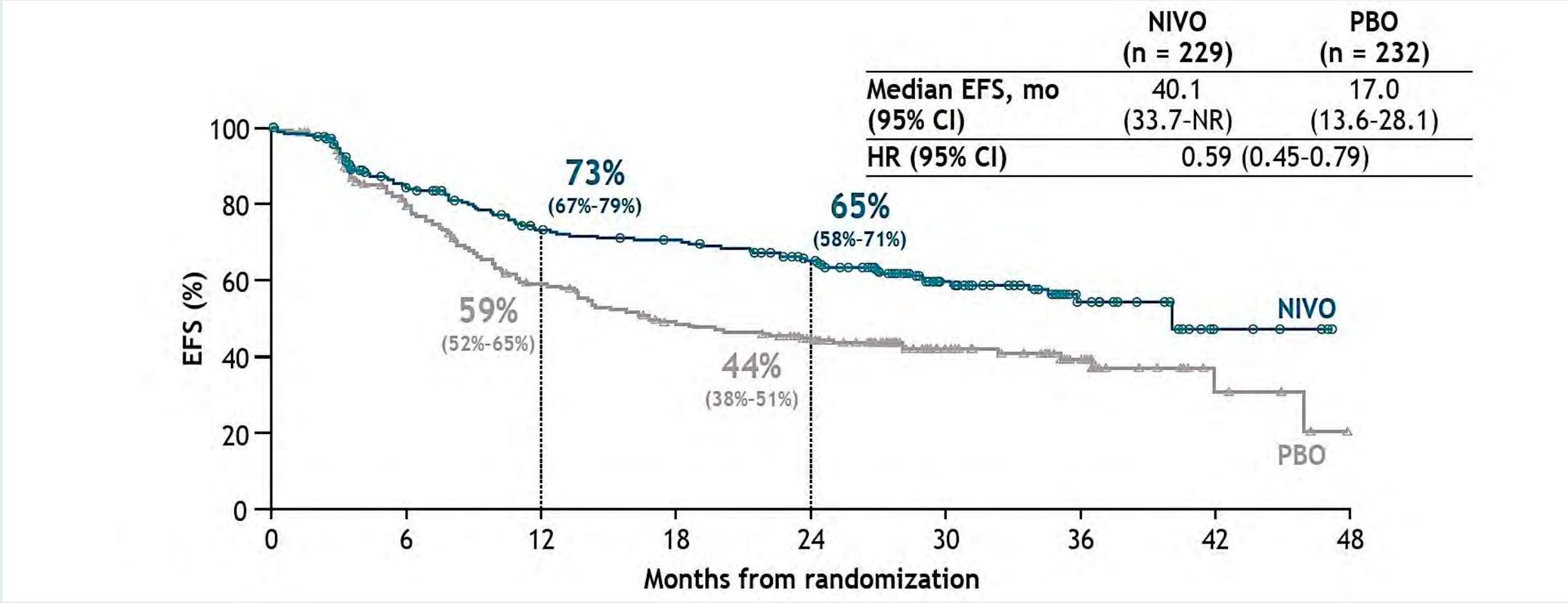
RTP RESEARCH TO PRACTICE

Phase III CheckMate 77T Study: Primary Endpoint (EFS per BICR) with Perioperative Nivolumab



EFS = event-free survival; BICR = blinded independent central review

Pulla MP et al. ESMO 2024;Abstract LBA50.

Lancet 2024;404(10459):1240-52.

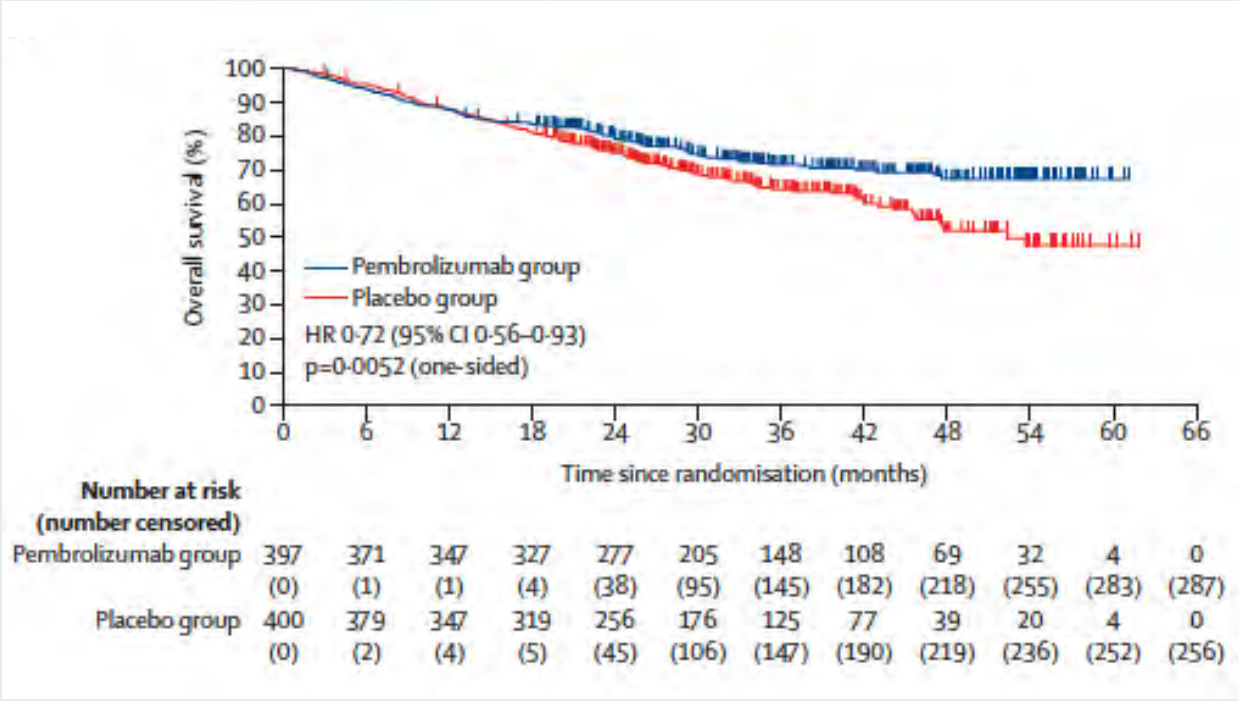
Articles

Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial

Jonathan D Spicer, Marina C Garassino*, Heather Wakelee, Moishe Liberman, Terufumi Kato, Masahiro Tsuboi, Se-Hoon Lee, Ke-Neng Chen, Christophe Dooms, Margarita Majem, Ekkehard Eigendorff, Gastón L Martinengo, Olivier Bylicki, Delvys Rodríguez-Abreu, Jamie E Chaft, Silvia Novello, Jing Yang, Ashwini Arunachalam, Steven M Keller, Ayman Samkari, Shugeng Gao, on behalf of the KEYNOTE-671 Investigators†*

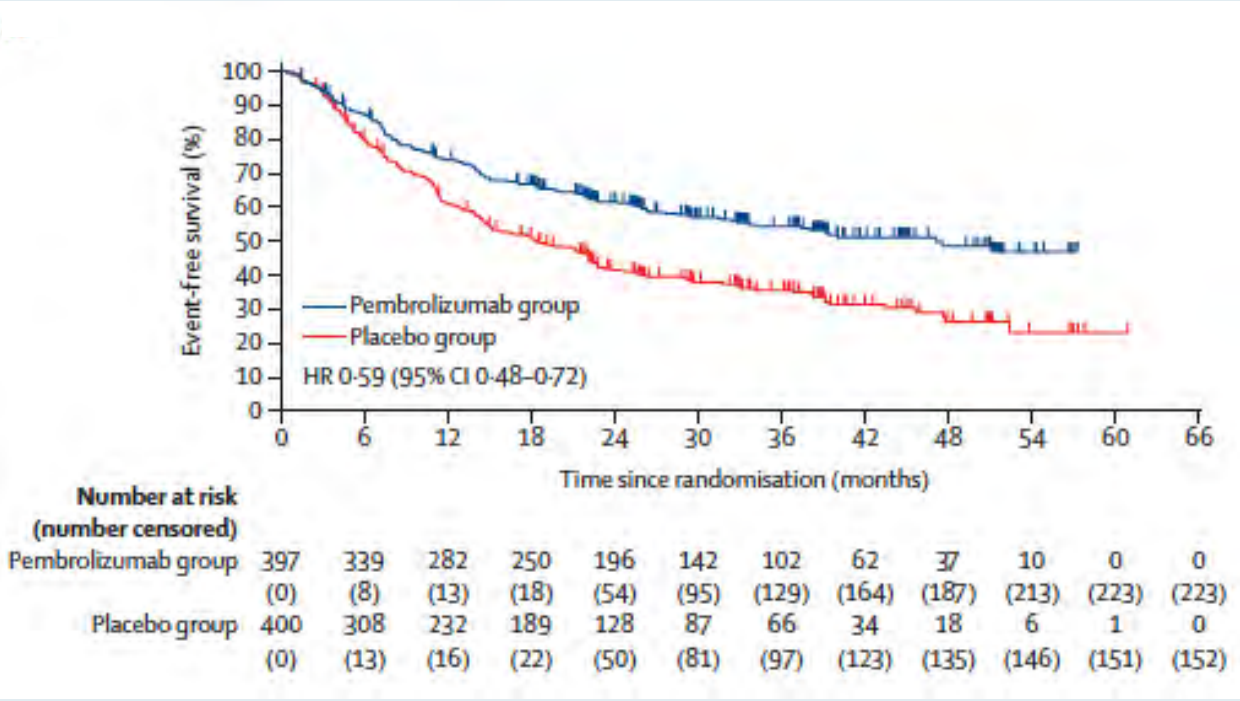
KEYNOTE-671: Dual Primary Endpoints OS and EFS with Perioperative Pembrolizumab

Overall survival



Number at risk (number censored)												
Pembrolizumab group	397	371	347	327	277	205	148	108	69	32	4	0
	(0)	(1)	(1)	(4)	(38)	(95)	(145)	(182)	(218)	(255)	(283)	(287)
Placebo group	400	379	347	319	256	176	125	77	39	20	4	0
	(0)	(2)	(4)	(5)	(45)	(106)	(147)	(190)	(219)	(236)	(252)	(256)

Event-free survival



Number at risk (number censored)												
Pembrolizumab group	397	339	282	250	196	142	102	62	37	10	0	0
	(0)	(8)	(13)	(18)	(54)	(95)	(129)	(164)	(187)	(213)	(223)	(223)
Placebo group	400	308	232	189	128	87	66	34	18	6	1	0
	(0)	(13)	(16)	(22)	(50)	(81)	(97)	(123)	(135)	(146)	(151)	(152)

Spicer JD et al. *Lancet* 2024;404(10459):1240-52.

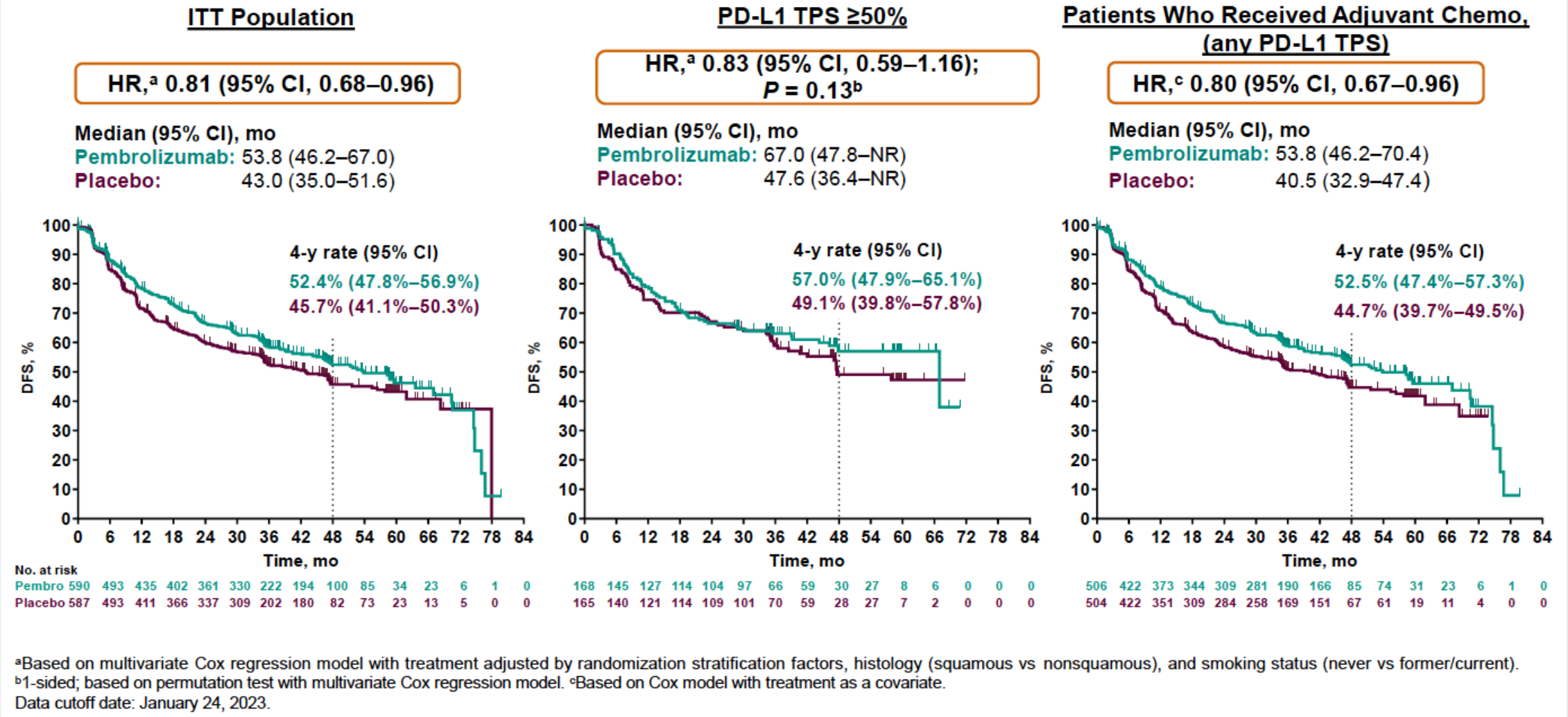
ESMO Immuno-Oncology 2023;Abstract 120MO

Adjuvant Pembrolizumab versus Placebo for Early-Stage NSCLC After Resection and Optional Chemotherapy: Updated Results From PEARLS/KEYNOTE-091

Benjamin Besse[1]; Libor Havel[2]; Solange Peters[3]; Sandrine Marreaud[4]; Nitish Jha[4]; Kersti Oselin[5]; Emilio Esteban[6]; Dolores Isla[7]; Alex Martinez-Marti[8]; Martin Faehling[9]; Jong-Seok Lee[10]; Yiwen Luo[11]; Steven M. Keller[11]; Urania Dafni[12]; Murielle Mauer[4]; Rolf Stahel[13]; Mary O'Brien[14]; Masahiro Tsuboi[15]; Luis Paz-Ares[16]

[1]Paris Saclay University, Institut Gustave Roussy, Villejuif, France; [2]First Faculty of Medicine, Charles University, Thomayer Hospital, Prague, Czech Republic; [3]Lausanne University Hospital, Lausanne, Switzerland; [4]European Organisation for Research and Treatment of Cancer, Brussels, Belgium; [5]North Estonia Medical Centre, Tallinn, Estonia; [6]Hospital Universitario Central de Asturias, Oviedo, Spain; [7]University Hospital Lozano Blesa, IIS Aragon, Zaragoza, Spain; [8]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; [9]Klinik für Kardiologie und Pneumologie, Klinikum Esslingen, Esslingen, Germany; [10]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; [11]Merck & Co., Inc., Rahway, NJ, USA; [12]ETOP Statistical Center, Frontier Science Foundation Hellas and National and Kapodistrian University of Athens, Athens, Greece; [13]ETOP IBCSG Partners Foundation, Berne, Switzerland; [14]Royal Marsden Hospital, London, UK; [15]National Cancer Center Hospital East, Kashiwa, Japan; [16]Hospital Universitario 12 de Octubre, CNIO, Ciberonc & Universidad Complutense, Madrid, Spain

PEARLS/KEYNOTE-091: Adjuvant Pembrolizumab — Final Disease-Free Survival Analysis at Third Interim Analysis



[a]Based on multivariate Cox regression model with treatment adjusted by randomization stratification factors, histology (squamous vs nonsquamous), and smoking status (never vs former/current).
[b]1-sided; based on permutation test with multivariate Cox regression model. [c]Based on Cox model with treatment as a covariate.
Data cutoff date: January 24, 2023.

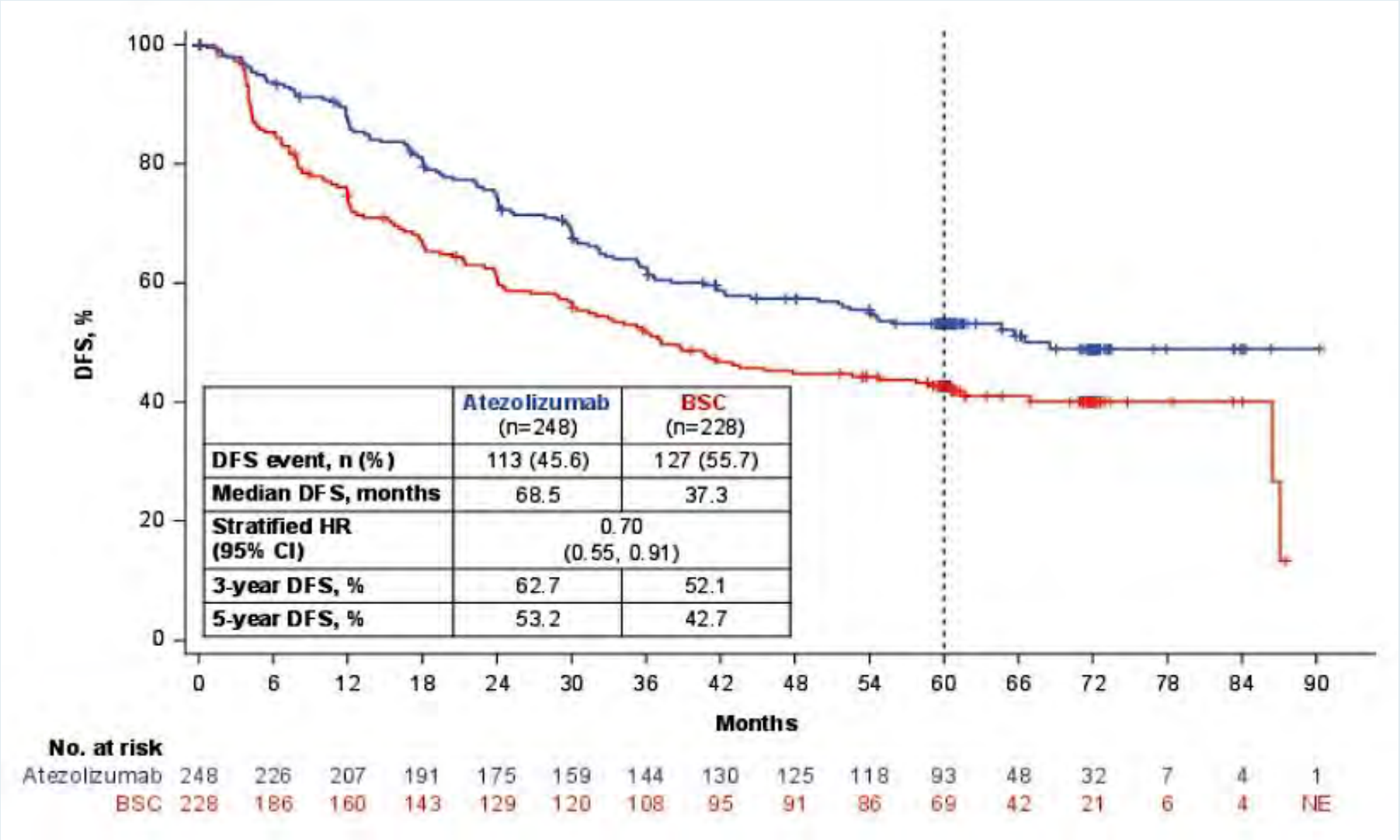
Besse B et al. ESMO Immuno-Oncology 2023;Abstract 120MO.

IMpower010: Final disease-free survival (DFS) and second overall survival (OS) interim results after ≥5 years of follow up of a phase III study of adjuvant atezolizumab vs best supportive care in resected stage IB-IIIA non-small cell lung cancer (NSCLC).

Heather A. Wakelee, Nasser K. Altorki, Caicun Zhou, Tibor Csőszi, Ihor O. Vynnychenko, Oleksandr Goloborodko, Achim Rittmeyer, Martin Reck, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, Chenqi Fu, Marcus Ballinger, Yu Deng, Minu K Srivastava, Elizabeth Bennett, Barbara Jenifer Gitlitz, Enriqueta Felip; Stanford University Medical Center, Stanford, CA; NewYork-Presbyterian Hospital, Weill Cornell Medicine, New York, NY; Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai, China; Jasz-Nagykun-Szolnok Megyei Hetenyi Geza Korhaz-Rend.Int., Szolnok, Hungary; Regional Municipal Institution Sumy Regional Clinical Oncology Dispensary, Sumy, Ukraine; MI Zaporizhzhia Regional Clinical Oncological Dispensary Zaporizhzhia SMU Ch of Oncology, Zaporizhzhya, Ukraine; LKI Lungenfachklinik Immenhausen, Immenhausen, Germany; LungenClinic Grosshansdorf, German Center for Lung Research, Grosshansdorf, Germany; Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; Shizuoka Cancer Center, Shizuoka, Japan; Taipei Veterans General Hospital, Taipei, Taiwan; Pneumology Unit, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; Sendai Kousei Hospital, Miyagi, Japan; Genentech, Inc., South San Francisco, CA; Medical Oncology Service, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

ASCO 2024;Abstract LBA8035.

IMpower010 Phase III Study of Adjuvant Atezolizumab for Resected Stage IB to IIIA NSCLC: Disease-Free Survival (DFS) at ≥5 Years of Follow-Up



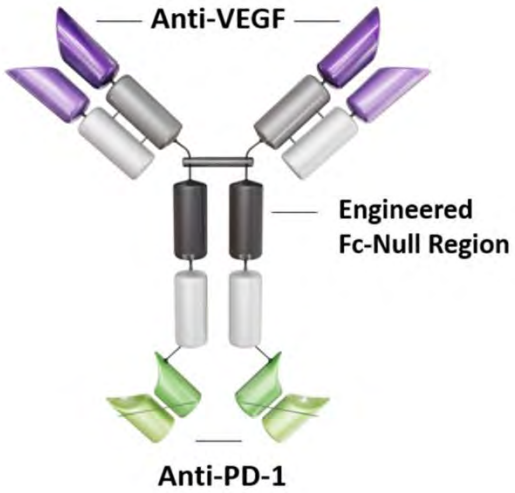
	Atezolizumab (n=248)	BSC (n=228)
DFS event, n (%)	113 (45.6)	127 (55.7)
Median DFS, months	68.5	37.3
Stratified HR (95% CI)	0.70 (0.55, 0.91)	
3-year DFS, %	62.7	52.1
5-year DFS, %	53.2	42.7

Wakelee HA et al. ASCO 2024;Abstract LBA8035.

HARMONi-2: Phase 3 Study of Ivonescimab vs. Pembrolizumab as 1L Treatment for PD-L1-positive Advanced NSCLC – Study Design

Ivonescimab (AK112/SMT112) is an anti-PD-1/VEGF bispecific antibody displaying cooperative binding characteristics.

A randomized, double-blind, phase 3 study[a]



Patient Population

- Stage IIIB-IV aNSCLC
- No prior systemic therapy
- No *EGFR* mutations or *ALK* rearrangements
- ECOG PS 0 or 1
- PD-L1 TPS ≥1%

R 1:1

N=398

Ivonescimab
20 mg/kg Q3W (N=198)

Pembrolizumab
200 mg Q3W (N=200)

Treatment until no clinical benefit, unacceptable toxicity or up to 24 months

Stratification

- Clinical stage (IIIB/C vs. IV)
- Histology (SQ vs. non-SQ)
- PD-L1 TPS (≥50% vs. 1-49%)

Endpoints

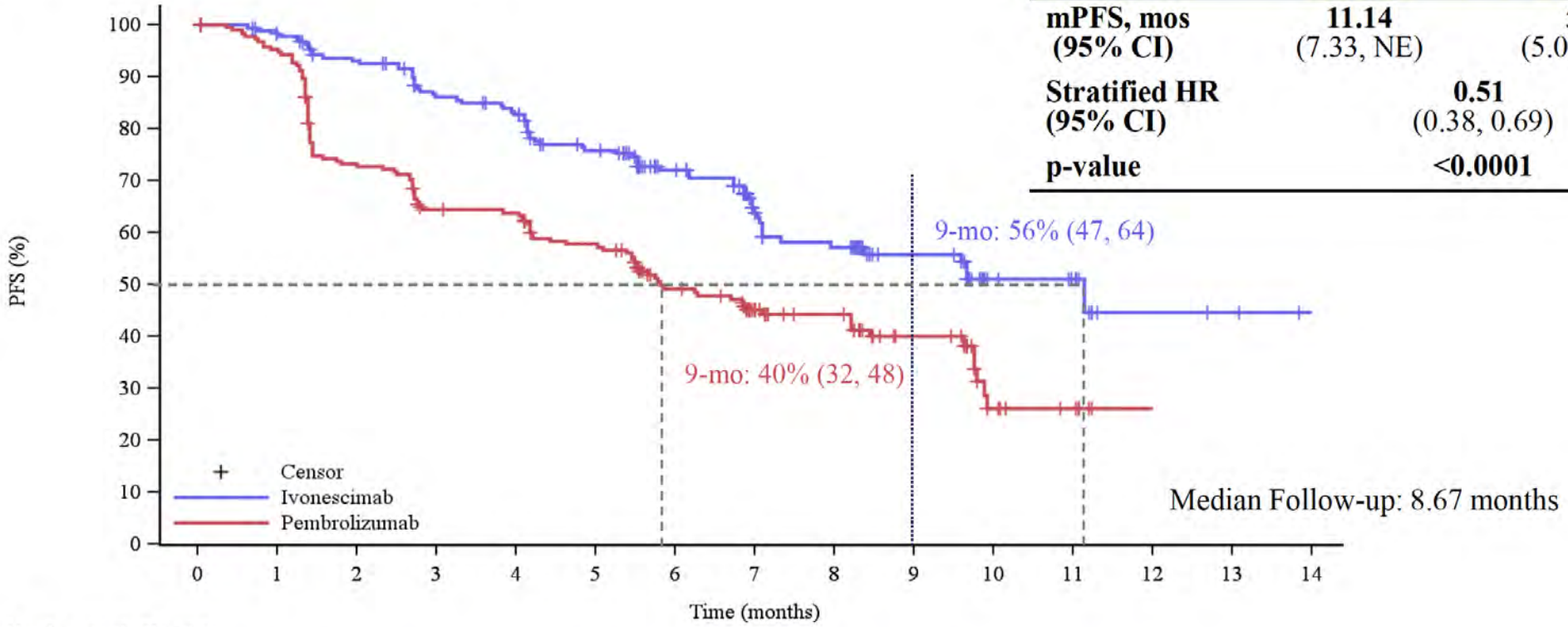
Primary: PFS by blind IRRC per RECIST v1.1
Secondary: OS, PFS assessed by INVs, ORR, DoR, TTR and safety
Exploratory: QoL

Zhang L et al. ASCO 2024;Abstract 8508.
Zhou C et al. WCLC 2024;Abstract PL02.04.

HARMONi-2: Phase 3 Study of Ivonescimab vs. Pembrolizumab as 1L Treatment for PD-L1-positive Advanced NSCLC – PFS

Primary endpoint: PFS per IRRC

	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	**11.14** (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	**0.51** (0.38, 0.69)	
p-value	**<0.0001**	



Number at risk (Events)

Ivonescimab	198(0)	189(3)	175(13)	156(26)	148(32)	128(44)	99(50)	68(60)	59(67)	38(68)	14(71)	11(71)	3(72)	2(72)	0(72)
Pembrolizumab	200(0)	187(9)	141(52)	121(69)	119(70)	103(81)	74(95)	53(101)	45(102)	25(106)	9(112)	5(112)	0(112)		

Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 months improvement in mPFS.

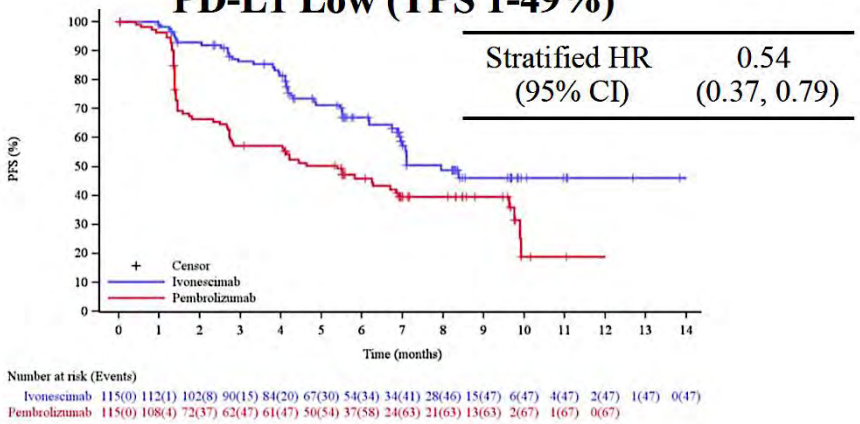
Zhou C et al. WCLC 2024;Abstract PL02.04.

HARMONi-2: Phase 3 Study of Ivonescimab vs. Pembrolizumab as 1L Treatment for PD-L1-positive Advanced NSCLC – Subgroups

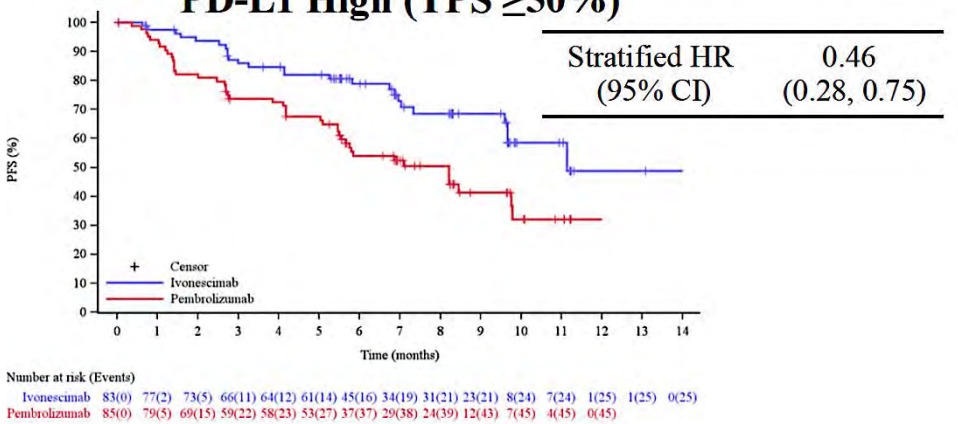
Key PFS Subgroup Analyses

PD-L1 expression

PD-L1 Low (TPS 1-49%)

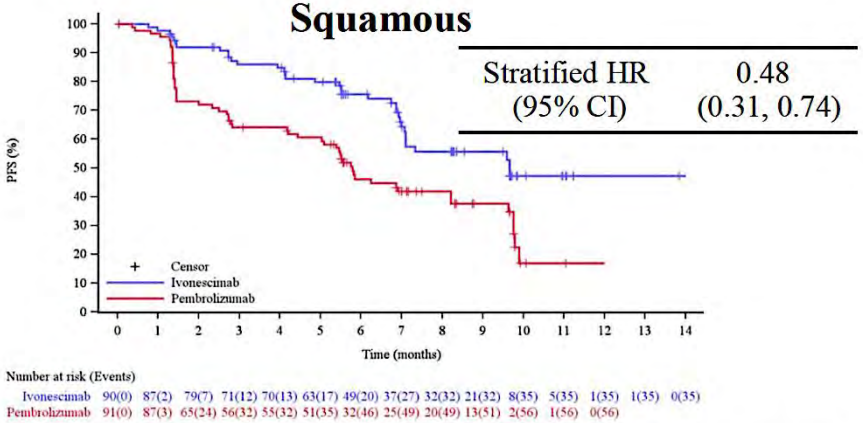


PD-L1 High (TPS ≥50%)

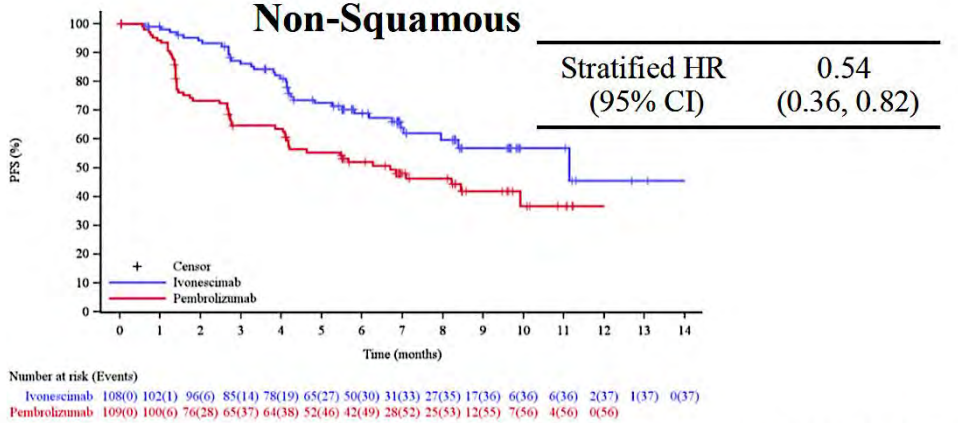


NSCLC Histology

Squamous



Non-Squamous



Ivonescimab showed meaningful improvement in PFS vs. pembrolizumab in patients with both low and high PD-L1, with squamous or non-squamous advanced NSCLC.

Zhou C et al. WCLC 2024;Abstract PL02.04.

HARMONi-2: Phase 3 Study of Ivonescimab vs. Pembrolizumab as 1L Treatment for PD-L1-positive Advanced NSCLC – Safety

TRAEs

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
TRAEs (all grades)	177 (89.8)	163 (81.9)
Grade≥3	58 (29.4)	31 (15.6)
Serious TRAEs	41 (20.8)	32 (16.1)
Leading to discontinuation	3 (1.5)	6 (3.0)
Leading to death	1 (0.5)	2 (1.0)

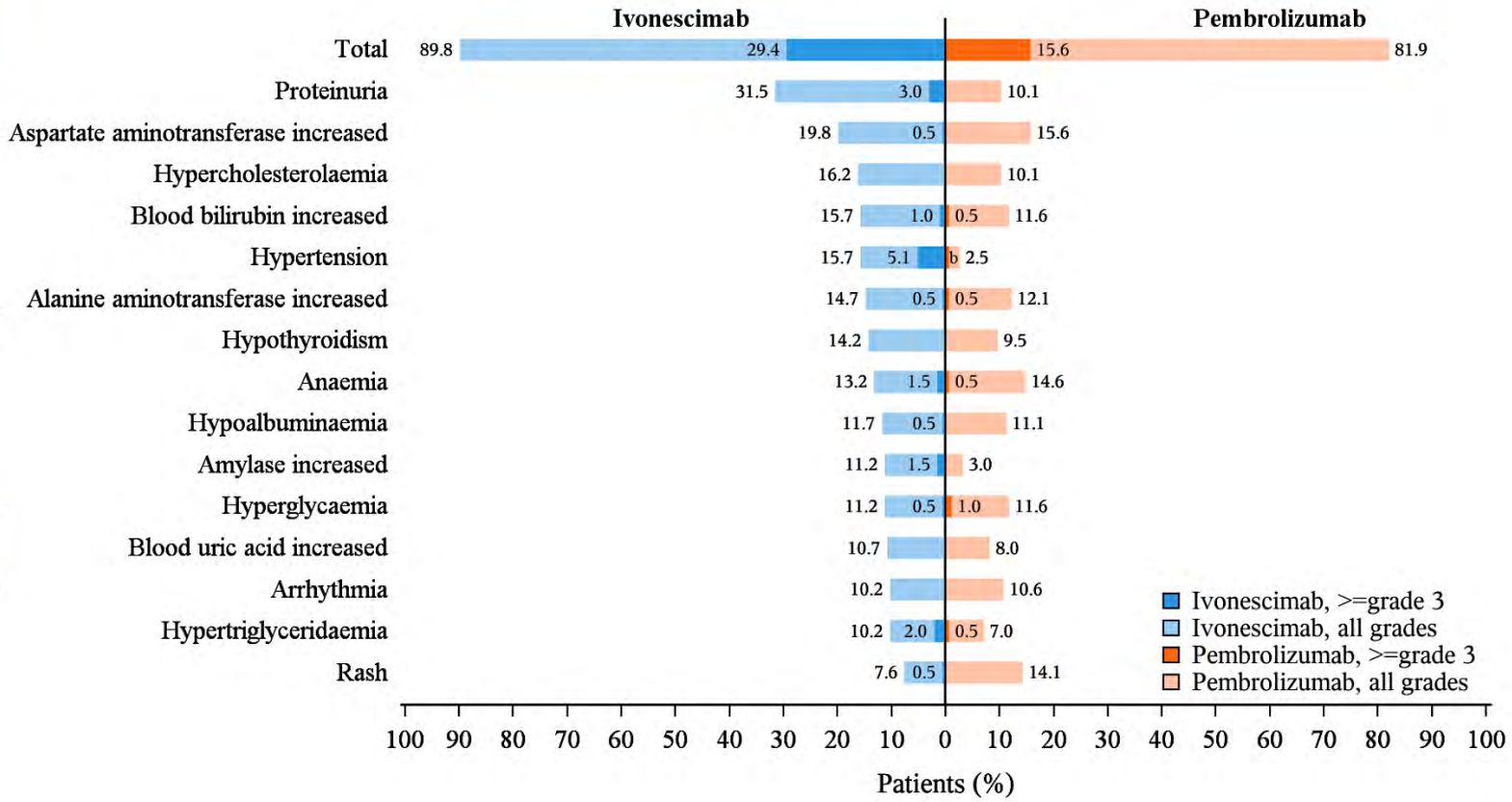
Ivonescimab showed a manageable safety profile, which was consistent with previous studies.

TRAEs in SQ Subgroup

Safety Summary, n (%)	Ivonescimab (n = 90[a])	Pembrolizumab (n = 91[a])
TRAEs (all grades)	77 (85.6)	73 (80.2)
Grade≥3	20 (22.2)	17 (18.7)
Serious TRAEs	17 (18.9)	17 (18.7)
Leading to discontinuation	2 (2.2)	3 (3.3)
Leading to death	0	1 (1.1)

Ivonescimab also demonstrated a tolerable safety profile in SQ patients.

The Most Common TRAEs (incidence ≥10%)



The differences in AEs were predominantly proteinuria, hypertension, and laboratory abnormalities.

Zhou C et al. WCLC 2024;Abstract PL02.04.

2024 ASCO ANNUAL MEETING

Ivonescimab combined with chemotherapy in patients with EGFR-mutant non-squamous non-small cell lung cancer who progressed on EGFR-TKIs treatment: a randomized, double-blind, multi-center, phase 3 trial (HARMONi-A study)

Li Zhang[1], Wenfeng Fang[1], Yuanyuan Zhao[1], Yongzhong Luo[2], Runxiang Yang[3], Yan Huang[1], Zhiyong He[4], Hui Zhao[5], Mingjun Li[6], Kai Li[7], Qibing Song[8], Xiaobo Du[9], Yulan Sun[10], Wei Li[11], Fei Xu[12], Zhiyu Wang[13], Kunning Yang[14], Yun Fan[15], Wenting Li[16], Michelle Xia[16]

[1]Sun Yat-sen University Cancer Center, Guangzhou, China; [2]Hunan Cancer Hospital, Changsha, China; [3]Yunnan Cancer Hospital, Kunming, China; [4]Fujian Provincial Tumor Hospital, Fuzhou, China; [5]The Second Hospital of Anhui Medical University, Hefei, China; [6]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [7]Tianjin Medical University Cancer Institute&Hospital, Tianjin, China; [8]Renmin Hospital of Wuhan University, Wuhan, China; [9]Mianyang Central Hospital, Mianyang, China; [10]Shandong Cancer Prevention and Treatment Institute, Jinan, China; [11]The First Affiliated Hospital of Bengbu Medical University, Bengbu, China; [12]The First Affiliated Hospital of Nanchang University, Nanchang, China; [13]The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; [14]Weifang No.2 People's Hospital, Weifang, China; [15]Zhejiang Cancer Hospital, Hangzhou, China; [16]Akeso Biopharma, Inc., Zhongshan, China

Abstract 8508

FDA Approves Tumor Treating Fields (TTFields) for the Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC)

Press Release: October 15, 2024

The FDA has approved TTFields for concurrent use with PD-1/PD-L1 inhibitors or docetaxel in the treatment of metastatic NSCLC for adult patients who have experienced disease progression on or after a platinum-based regimen.

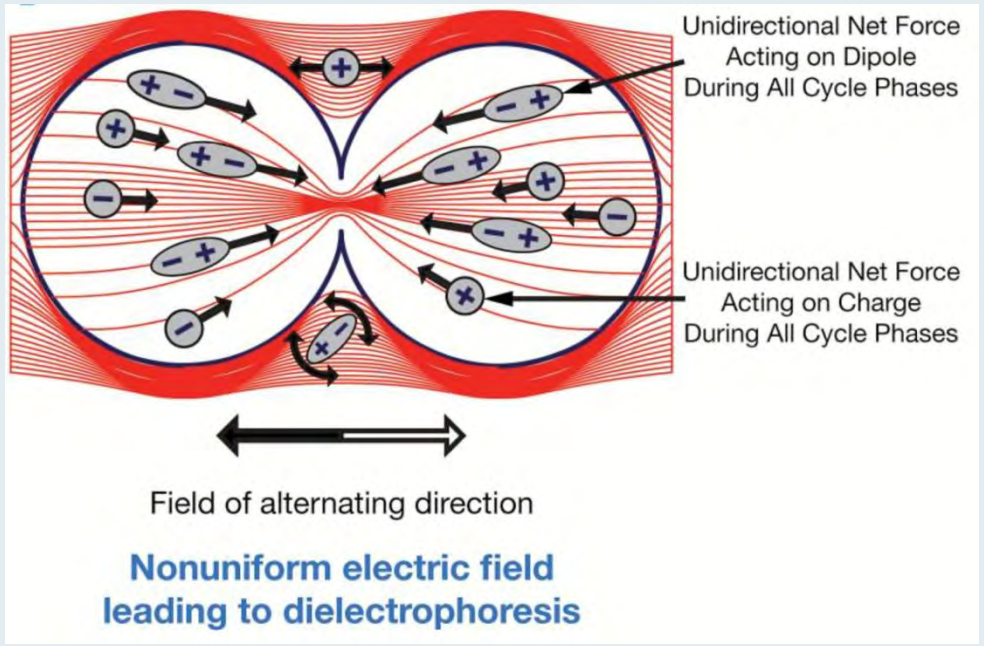
Approval was based on results of the Phase III LUNAR trial that compared TTFields concurrent with PD-1/PD-L1 inhibitors or docetaxel (experimental arm) to PD-1/PD-L1 inhibitors or docetaxel alone (control arm) for patients with metastatic NSCLC whose disease progressed during or after platinum-based therapy.

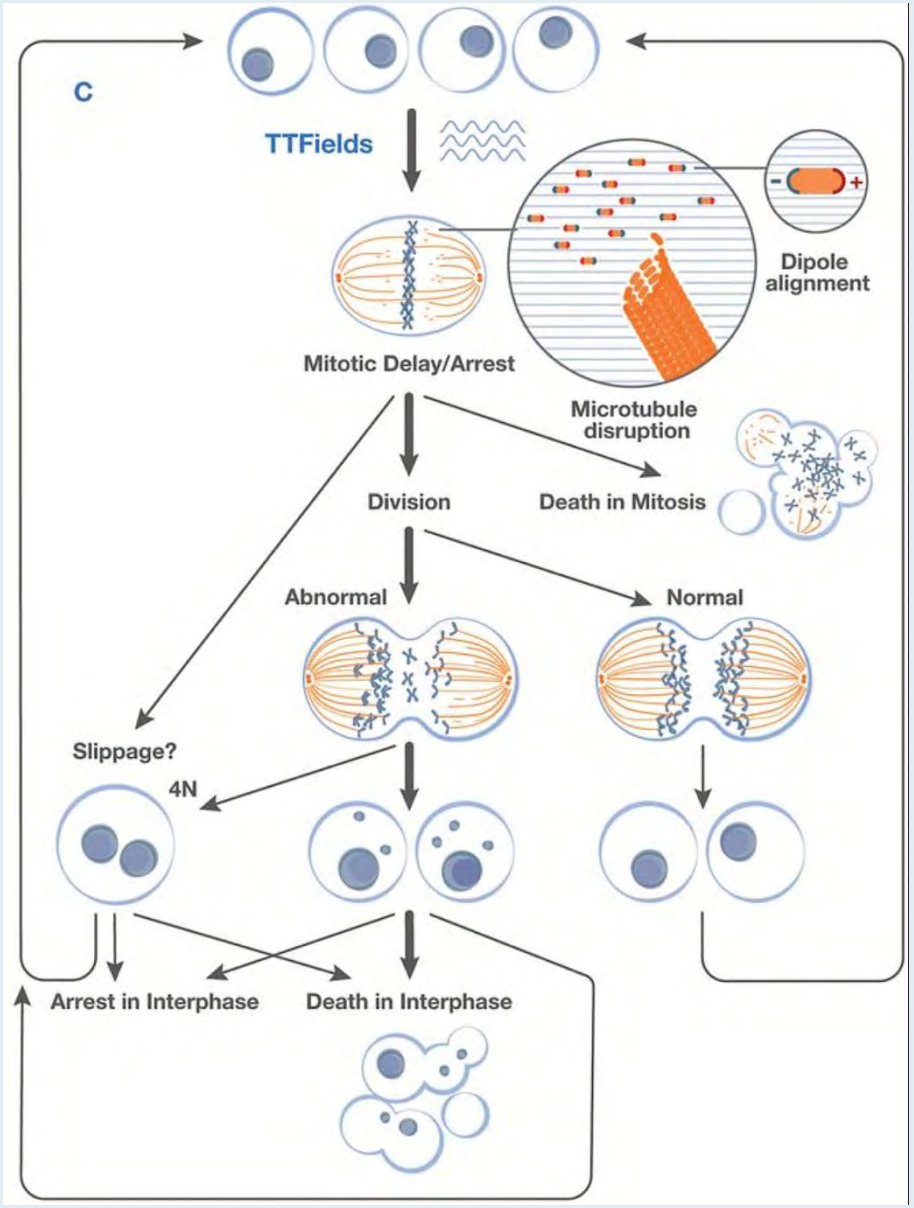
The primary endpoint of the study was achieved demonstrating a statistically significant and clinically meaningful 3.3-month (p = 0.04) extension in median overall survival (OS) for patients who received TTFields concurrently with a PD-1/PD-L1 inhibitor or docetaxel (n = 145). The group treated with TTFields concurrently with a PD-1/PD-L1 inhibitor or docetaxel had a median OS of 13.2 months (95% CI, 10.3 to 15.5 months) compared to a median OS of 9.9 months (95% CI, 8.2 to 12.2 months) in the group who received a PD-1/PD-L1 inhibitor or docetaxel (n = 146).

RTP RESEARCH TO PRACTICE

https://www.novocure.com/fda-approves-novocures-optune-lua-for-the-treatment-of-metastatic-non-small-cell-lung-cancer/

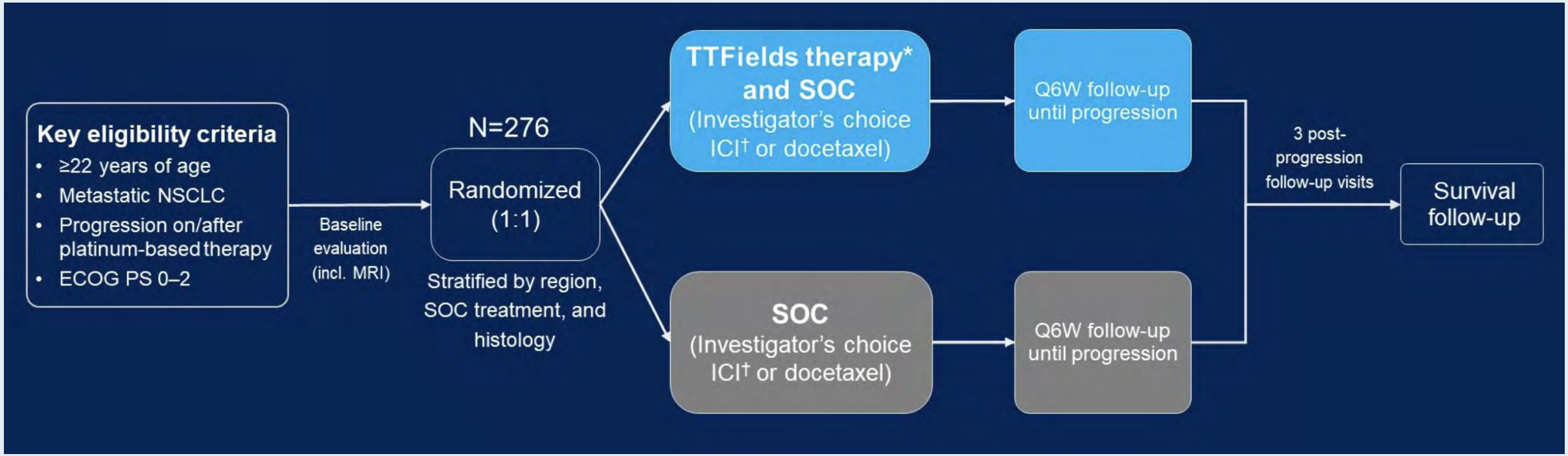
TTFields Mechanism of Action





Hottinger AF et al. *Neuro Oncol* 2016;18(10):1338-49.

LUNAR: A Phase III Study of TTFields for Metastatic NSCLC Progressing on Platinum-Based Therapy

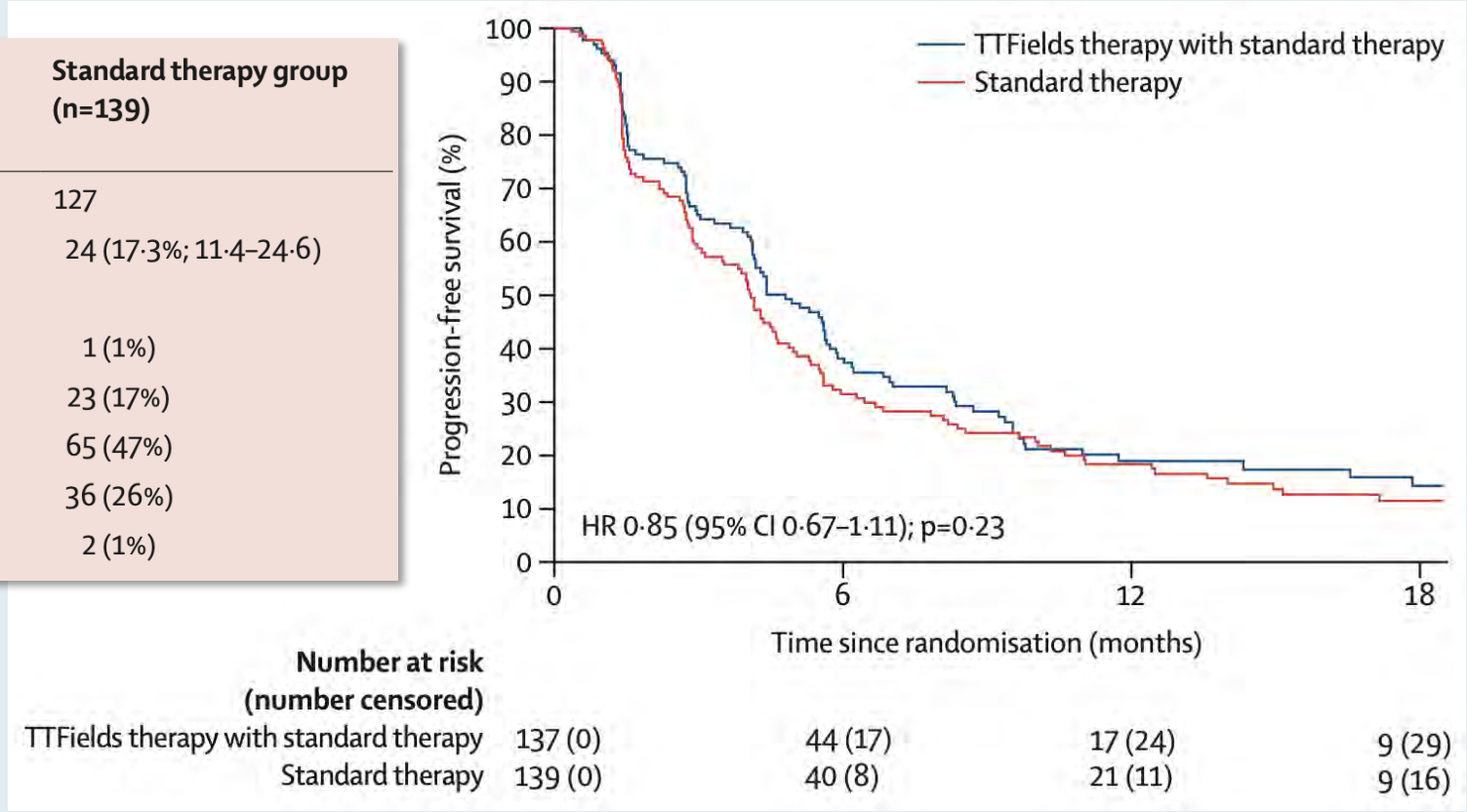


SOC = standard of care; ICI = immune checkpoint inhibitor

Leal T et al. ASCO 2023;Abstract LBA9005. Leal T et al. *Lancet Oncol* 2023;24(9):1002-17.

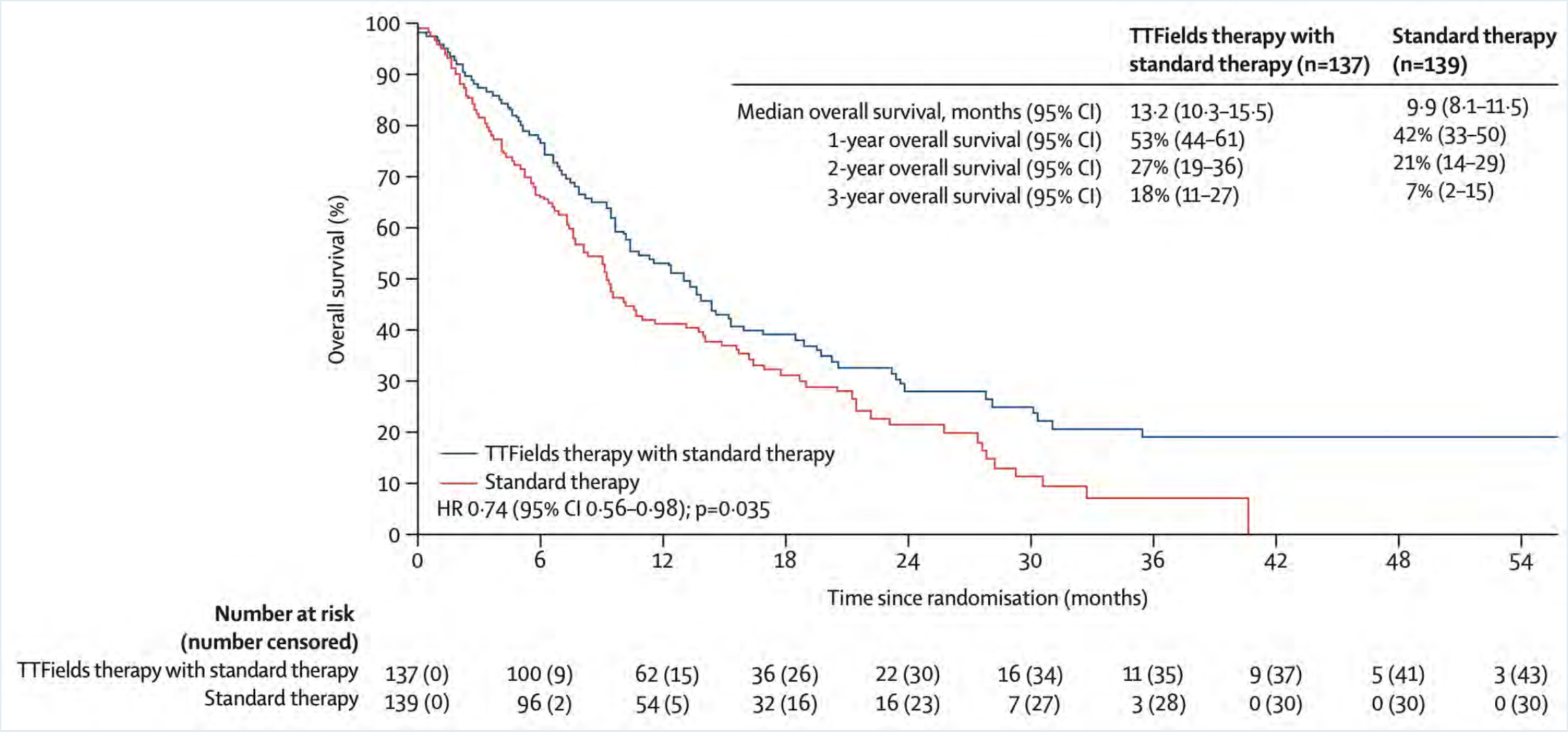
LUNAR: Response and Progression-Free Survival Outcomes

	TTFields therapy with standard therapy group (n=137)	Standard therapy group (n=139)
Patients with at least one post-baseline scan, n	122	127
Overall response, n (%; 95% CI)	28 (20·4%; 14·0–28·2)	24 (17·3%; 11·4–24·6)
Best overall response, n (%)		
Complete response	4 (3%)	1 (1%)
Partial response	24 (18%)	23 (17%)
Stable disease	67 (49%)	65 (47%)
Progressive disease	24 (18%)	36 (26%)
Not evaluable	3 (2%)	2 (1%)



Leal T et al. ASCO 2023;Abstract LBA9005. Leal T et al. *Lancet Oncol* 2023;24(9):1002-17.

LUNAR: Overall Survival Outcomes in the Intention-to-Treat Population

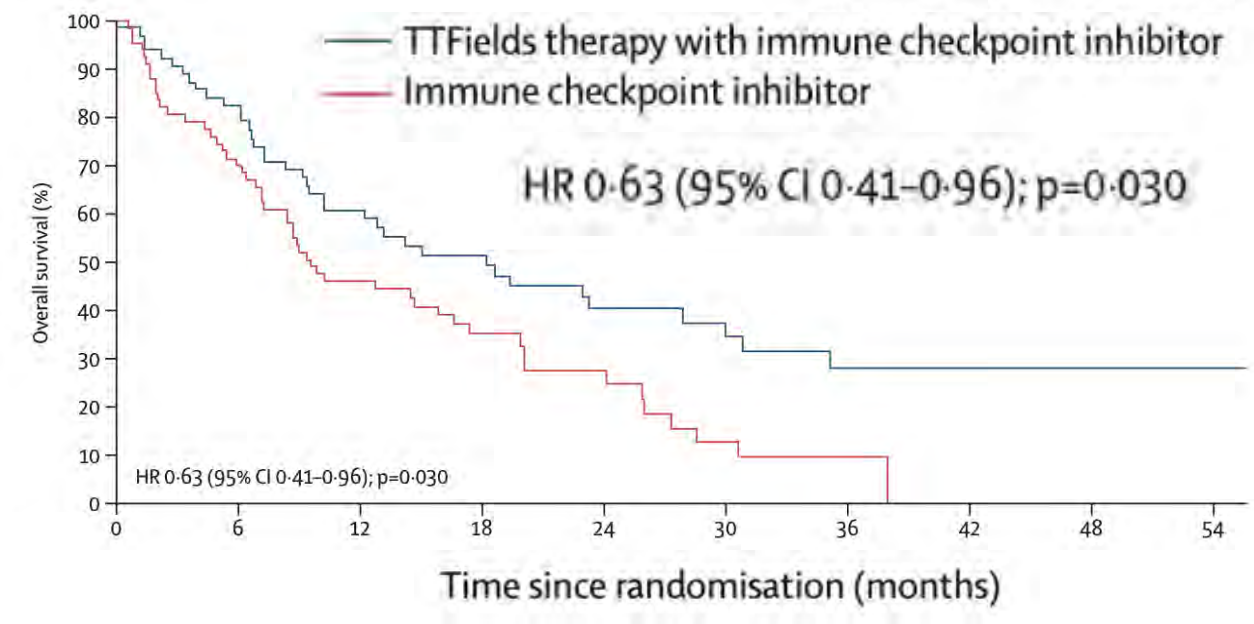


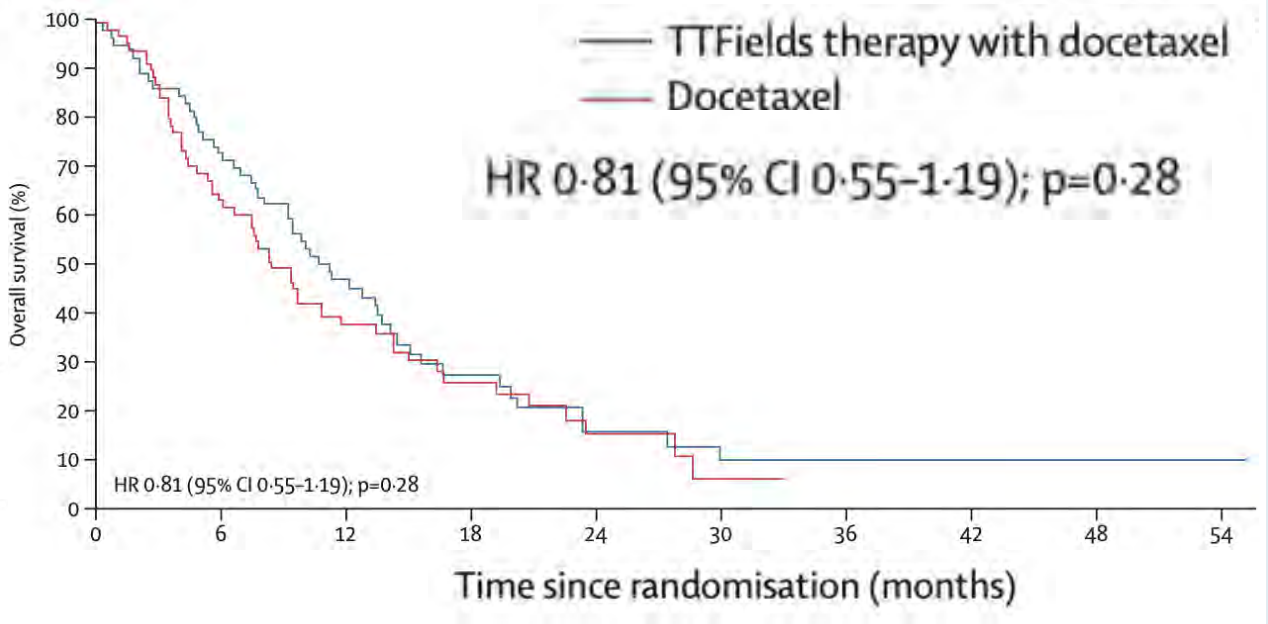
	TTFields therapy with standard therapy (n=137)	Standard therapy (n=139)
Median overall survival, months (95% CI)	13·2 (10·3–15·5)	9·9 (8·1–11·5)
1-year overall survival (95% CI)	53% (44–61)	42% (33–50)
2-year overall survival (95% CI)	27% (19–36)	21% (14–29)
3-year overall survival (95% CI)	18% (11–27)	7% (2–15)

Number at risk (number censored)										
TTFields therapy with standard therapy	137 (0)	100 (9)	62 (15)	36 (26)	22 (30)	16 (34)	11 (35)	9 (37)	5 (41)	3 (43)
Standard therapy	139 (0)	96 (2)	54 (5)	32 (16)	16 (23)	7 (27)	3 (28)	0 (30)	0 (30)	0 (30)

Leal T et al. ASCO 2023;Abstract LBA9005. Leal T et al. *Lancet Oncol* 2023;24(9):1002-17.

LUNAR: TTFields with ICI vs TTFields with Docetaxel – OS Outcomes





Leal T et al. ASCO 2023;Abstract LBA9005. Leal T et al. *Lancet Oncol* 2023;24(9):1002-17.

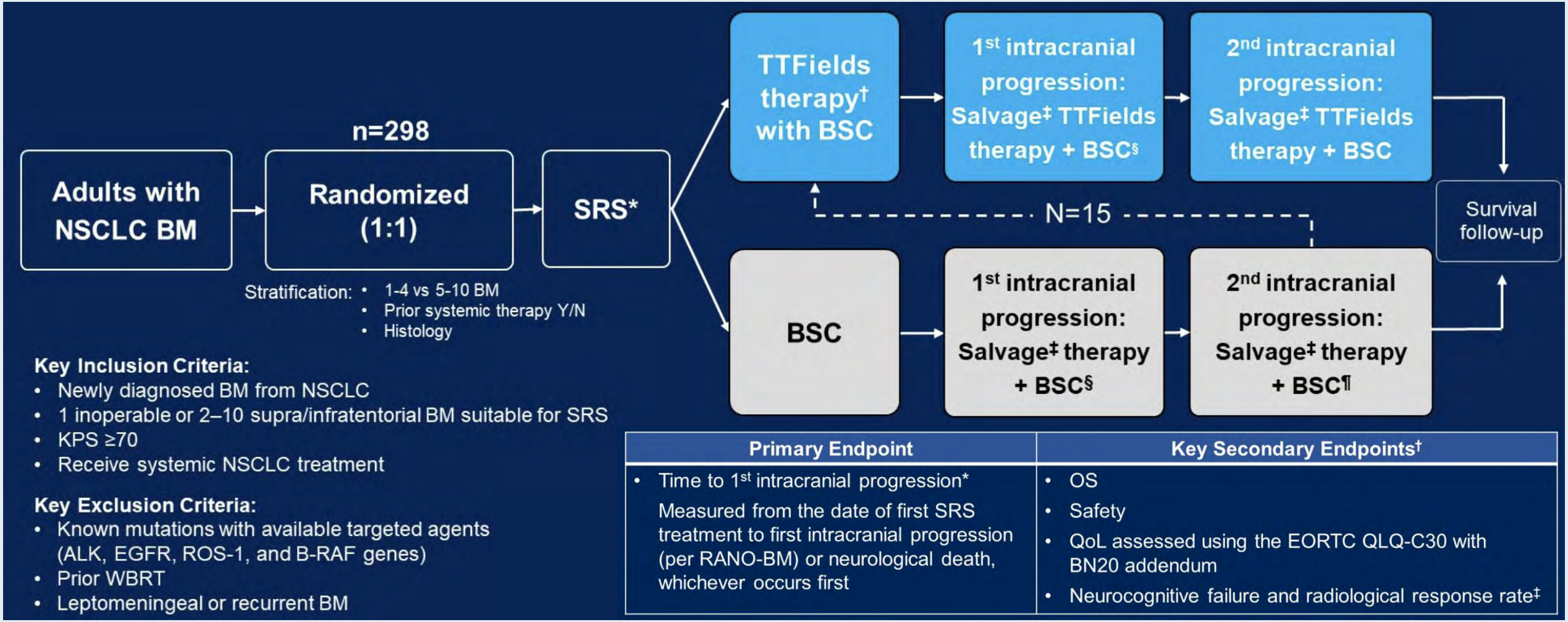
LUNAR: Safety Outcomes

	TTFields + SOC (n=133)		SOC (n=134)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any AE*	97%	59%	91%	56%
Most frequent AEs				
Dermatitis	**43%**	**2%**	**2%**	**0%**
Fatigue	28%	4%	37%	8%
Musculoskeletal pain	36%	3%	27%	4%
Dyspnea	20%	7%	25%	3%
Anemia	23%	8%	22%	8%
Diarrhea	19%	2%	19%	0%
Cough	18%	0%	19%	1%
Nausea	19%	0%	16%	1%
Leukopenia	17%	14%	18%	14%
Pneumonia	15%	11%	17%	11%
Alopecia	10%	0%	17%	1%
Respiratory tract infection	15%	3%	16%	0%
Localized edema	15%	1%	16%	2%
Any serious AE	53%		38%	
Any AE leading to discontinuation	36%		20%	
Any AE leading to death	10%		8%	

AE = adverse event

Leal T et al. ASCO 2023;Abstract LBA9005. Leal T et al. *Lancet Oncol* 2023;24(9):1002-17.

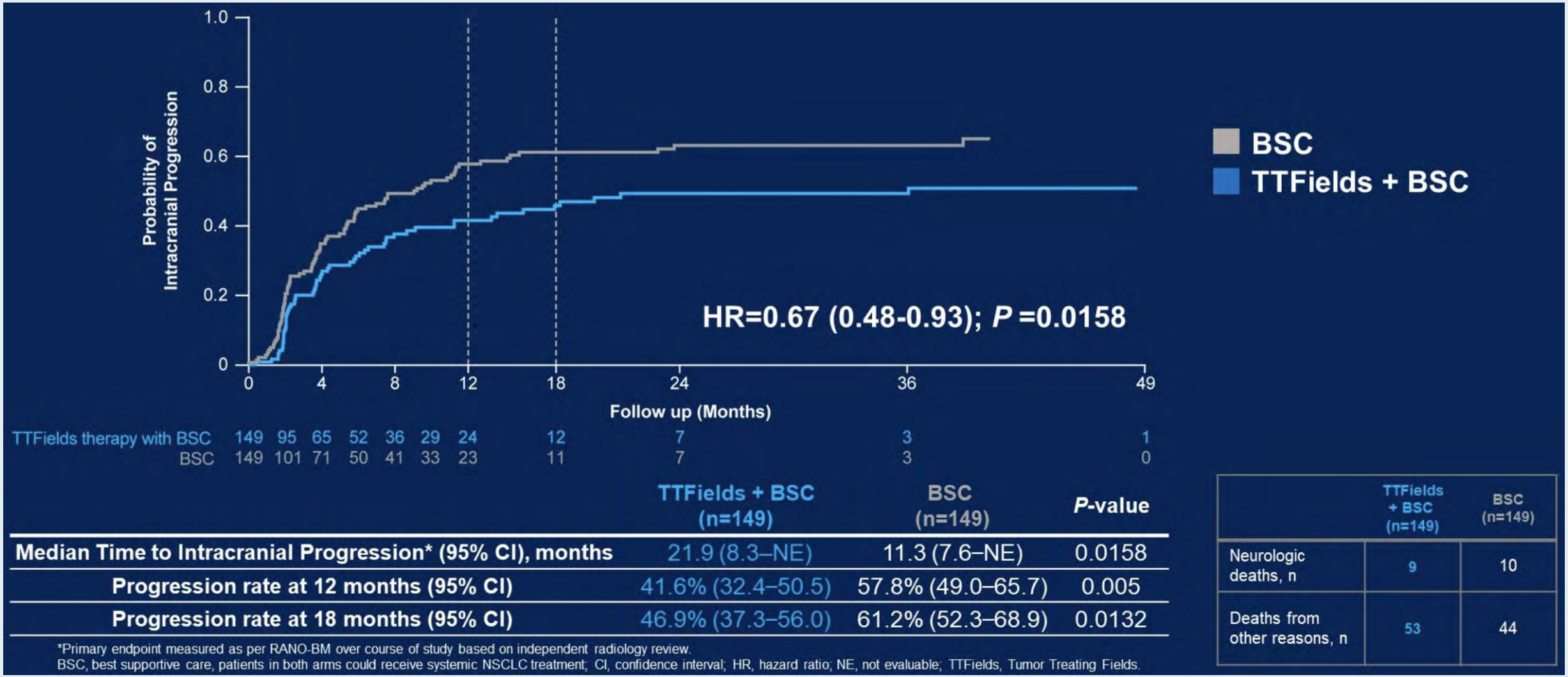
METIS: An International, Multicenter Phase III Randomized Study of TTFields for NSCLC with Brain Metastases



SRS = stereotactic radiosurgery; BSC = best supportive care; BM = brain metastases; WBRT = whole brain radiotherapy; QoL = quality of life

Mehta MP et al. ASCO 2024;Abstract 2008.

METIS: Primary Endpoint of Time to First Intracranial Progression or Neurologic Death



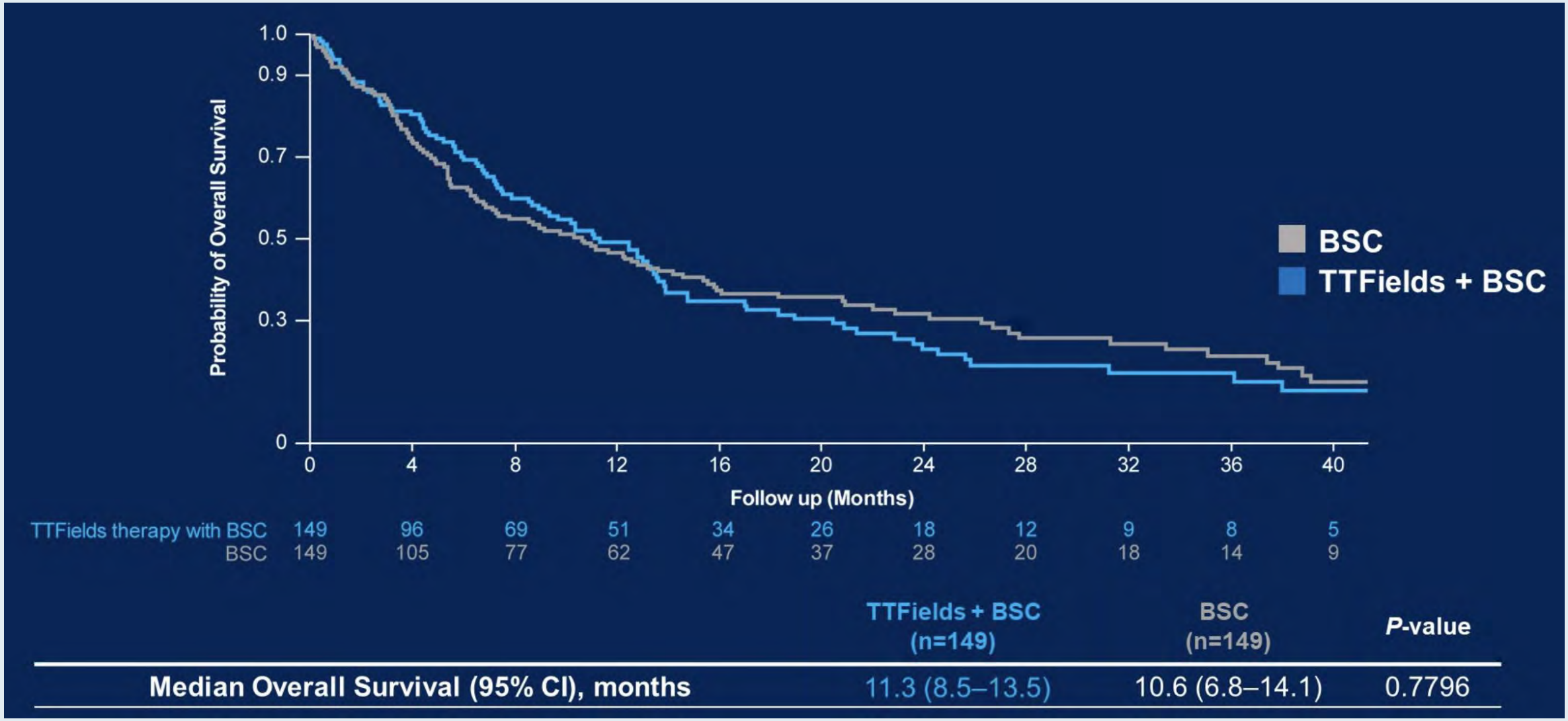
	TTFields + BSC (n=149)	BSC (n=149)	*P*-value
Median Time to Intracranial Progression* (95% CI), months	21.9 (8.3–NE)	11.3 (7.6–NE)	0.0158
Progression rate at 12 months (95% CI)	41.6% (32.4–50.5)	57.8% (49.0–65.7)	0.005
Progression rate at 18 months (95% CI)	46.9% (37.3–56.0)	61.2% (52.3–68.9)	0.0132

*Primary endpoint measured as per RANO-BM over course of study based on independent radiology review.
BSC, best supportive care, patients in both arms could receive systemic NSCLC treatment; CI, confidence interval; HR, hazard ratio; NE, not evaluable; TTFields, Tumor Treating Fields.

	TTFields + BSC (n=149)	BSC (n=149)
Neurologic deaths, n	9	10
Deaths from other reasons, n	53	44

Mehta MP et al. ASCO 2024;Abstract 2008.

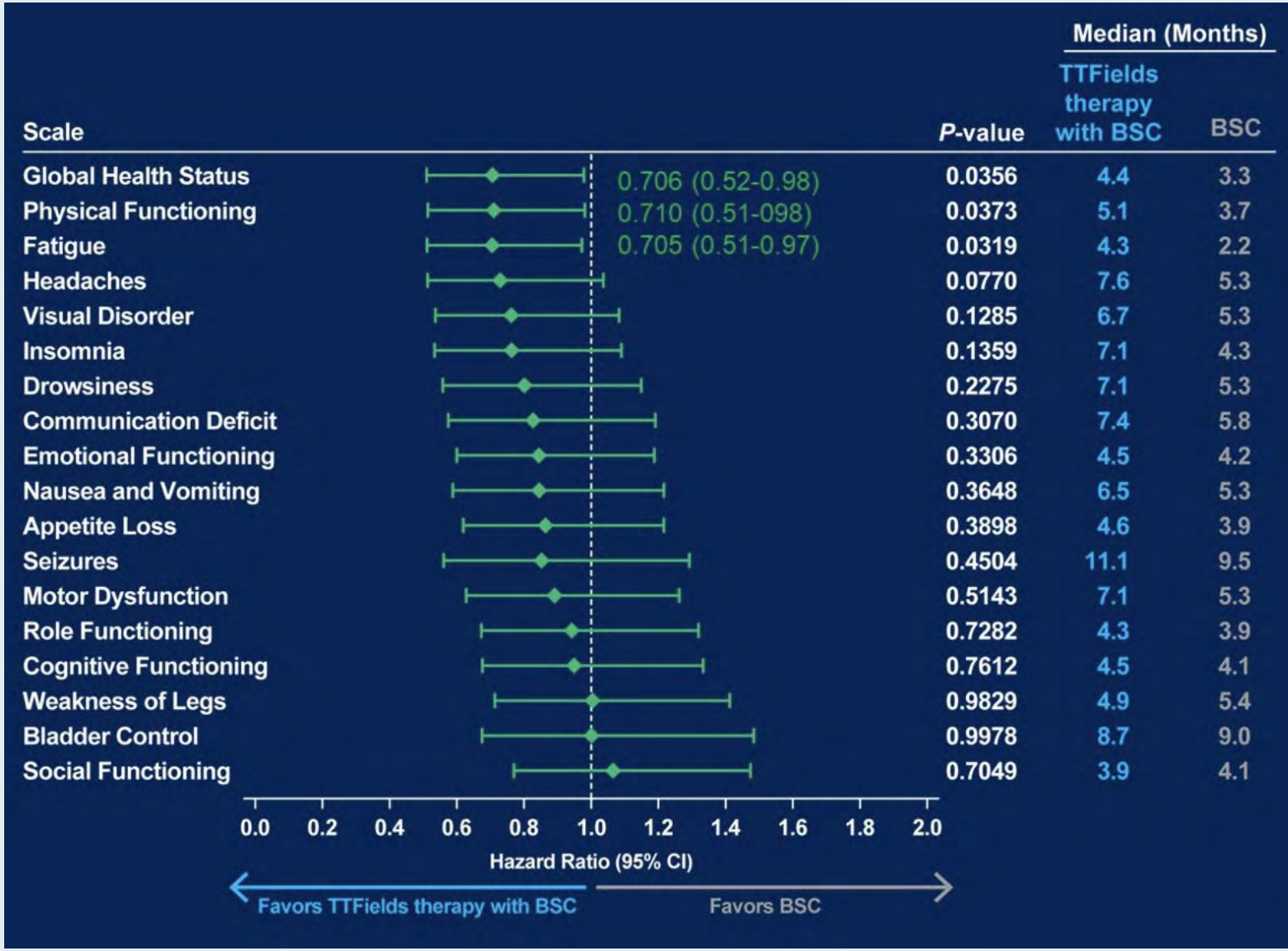
METIS: Overall Survival Outcomes



	TTFields + BSC (n=149)	BSC (n=149)	*P*-value
Median Overall Survival (95% CI), months	11.3 (8.5–13.5)	10.6 (6.8–14.1)	0.7796

Mehta MP et al. ASCO 2024;Abstract 2008.

METIS: Quality of Life



- Overall positive trend in most of the 18 scales and items assessed by EORTC QLQ-C30 and -BN20*
- Improvement of global health status, physical functioning, and fatigue
- Similar time to neurocognitive failure in both arms (low number of subjects at risk in both arms beyond 3 months), subset analysis pending

*Evaluable patients as per deterioration-free survival analysis

BN, brain neoplasm; BSC, best supportive care, patients in both arms could receive systemic NSCLC treatment; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; TTFields, Tumor Treating Fields.

Mehta MP et al. ASCO 2024;Abstract 2008.

METIS: Safety Profile

	TTFields + BSC (n=127)		BSC (n=160)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any AE (BSC +- TTFields)*	95%	60%	88%	64%
Most frequent AEs (≥10%)	89%	60%	81%	64%
Anaemia	26%	7%	24%	10%
Headache	24%	1%	19%	3%
Fatigue	22%	3%	20%	4%
Oedema peripheral	22%	1%	14%	1%
Nausea	20%	2%	18%	3%
Constipation	17%	1%	16%	1%
Decreased appetite	16%	0%	13%	2%
Pneumonia	14%	9%	13%	10%
Skin irritation	**13%**	**0%**	**1%**	**0%**
Pruritus	**13%**	**1%**	**4%**	**0%**
Muscular weakness	13%	2%	9%	1%
Cough	13%	0%	11%	1%
Metastases to central nervous system	13%	10%	10%	9%
Dyspnoea	13%	2%	13%	3%
Dermatitis	**12%**	**0%**	**2%**	**0%**
Pyrexia	12%	0%	8%	0%
Dizziness	12%	0%	9%	1%
Hypokalaemia	11%	2%	8%	1%
Diarrhoea	10%	0%	8%	3%
White blood cell count decreased	10%	2%	6%	2%
Alanine aminotransferase increased	10%	1%	4%	0%
Insomnia	9%	0%	11%	1%
Any serious AE	51%		59%	
Any AE leading to discontinuation	17%		4%	
Any AE leading to death	15%		24%	

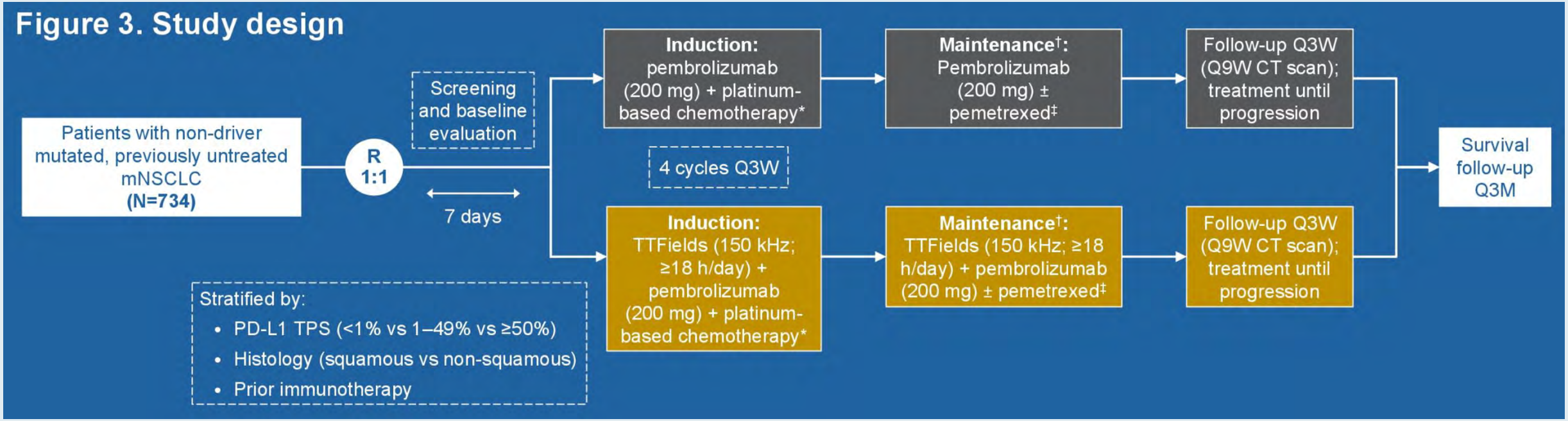
- 66 (52%) TTFields patients developed device-related AE (any grade, mostly G1/2 skin), of which only 3 (2.4%) were Grade ≥3 (1 was G5, ascribed to seizures/tumor progression and scored as device-related by the investigator)
- Of the 15 cross over patients, one device related grade 3 (headache) was reported
- Comparable incidence of grade ≥3 SAEs between arms (TTFields + BSC [n=63], 49.6%; BSC [n=87], 54.4%)

AE, adverse event; BSC, best supportive care, patients in both arms could receive systemic NSCLC treatment; G, grade; SAE, serious adverse event; TTFields, Tumor Treating Fields.

Mehta MP et al. ASCO 2024;Abstract 2008.

LUNAR-2 Trial: Front-Line TTFields with an Immune Checkpoint Inhibitor and Chemotherapy for mNSCLC

Figure 3. Study design



Inclusion criteria

- Histologically/cytologically confirmed stage IV NSCLC
- No prior systemic treatment for mNSCLC
- Evaluable (measurable or non-measurable) disease in the thorax per RECIST v1.1
- ≥18 years old (≥22 years in the US)
- ECOG PS 0–1

Endpoints

Primary*	• OS and PFS per RECIST v1.1 as assessed by a BICR
Secondary	• OS and PFS (by histology and PD-L1 TPS) per RECIST v1.1 as assessed by BICR • ORR, DoR, and DCR (all per RECIST v1.1 as assessed by BICR and by investigator) • PFS rates at 6, 12, 24 and 36 months per RECIST v1.1 as assessed by BICR • 1-, 2-, and 3-year survival rates • Safety profile
Exploratory	• PFS and OS according to in-field or out-of-field location of the disease

TPS = tumor proportion score; OS = overall survival; PFS = progression-free survival; BICR = blinded independent central review; ORR = objective response rate; DoR = duration of response; DCR = disease control rate

Eaton M et al. ASCO 2024;Abstract TPS8665.

FDA Approves Osimertinib for Locally Advanced, Unresectable (Stage III) NCSLC After Chemoradiation Therapy

Press Release: September 25, 2024

The FDA has approved osimertinib for adult patients with locally advanced, unresectable (Stage III) NSCLC whose disease has not progressed during or after concurrent or sequential platinum-based chemoradiation therapy and whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

Efficacy was evaluated in LAURA (NCT03521154), a double-blind, randomized, placebo-controlled trial of 216 adult patients with locally advanced, unresectable Stage III NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations who had not experienced disease progression during or after definitive platinum-based chemoradiation within 42 days prior to study randomization. Patients were randomized (2:1) to receive either osimertinib 80 mg orally once daily or placebo until disease progression or unacceptable toxicity.

The major efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR). Additional efficacy outcome measures included overall survival (OS). Osimertinib demonstrated a statistically significant improvement in PFS compared to placebo with a hazard ratio of 0.16 (95% CI: 0.10, 0.24; *p*-value <0.001). The median PFS was 39.1 months (95% CI: 31.5, NE) in the osimertinib arm and 5.6 months (95% CI: 3.7, 7.4) in the placebo arm.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-osimertinib-locally-advanced-unresectable-stage-iii-non-small-cell-lung-cancer

FDA Approves Lazertinib with Amivantamab-vmjw for NSCLC

Press Release: August 19, 2024

The FDA has approved lazertinib in combination with amivantamab-vmjw for the first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test.

Efficacy was evaluated in MARIPOSA (NCT04487080), a randomized, active-controlled, multicenter trial of 1,074 patients with locally advanced or metastatic NSCLC with an exon 19 deletion or exon 21 L858R substitution mutation and no prior systemic therapy for advanced disease. Patients were randomized (2:2:1) to receive lazertinib in combination with amivantamab, osimertinib monotherapy or lazertinib monotherapy (an unapproved regimen for NSCLC) until disease progression or unacceptable toxicity.

The major efficacy outcome measure was PFS as assessed by BICR between lazertinib with amivantamab and osimertinib. OS was a key secondary outcome measure. Lazertinib with amivantamab demonstrated a statistically significant improvement in PFS compared to osimertinib with a hazard ratio of 0.70 (95% CI): 0.58, 0.85; *p*-value = 0.0002). The median PFS was 23.7 months (95% CI: 19.1, 27.7) in the lazertinib with amivantamab arm and 16.6 months (95% CI: 14.8, 18.5) in the osimertinib arm.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lazertinib-amivantamab-vmjw-non-small-lung-cancer

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

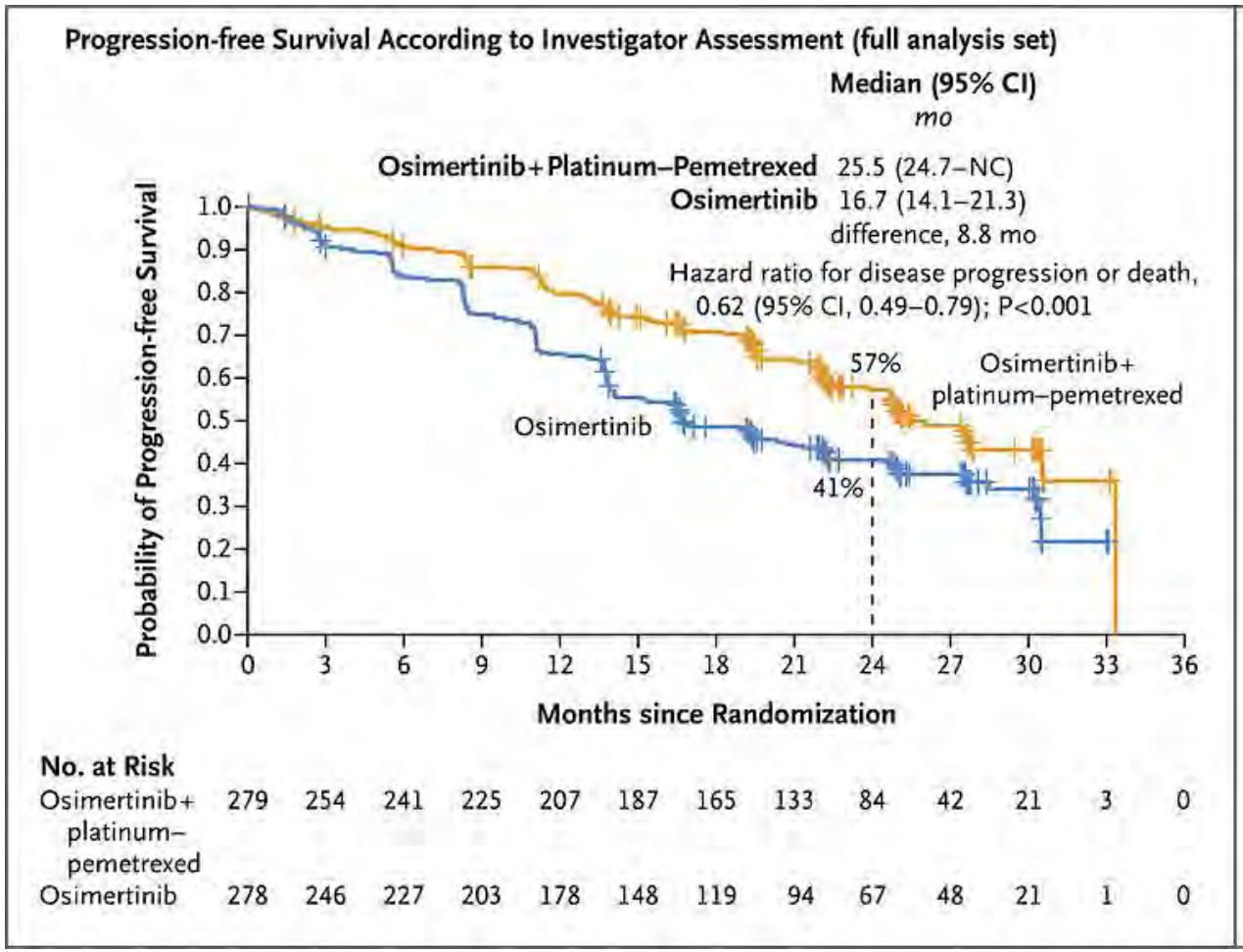
Targeted Therapy for Non-Small Cell Lung Cancer

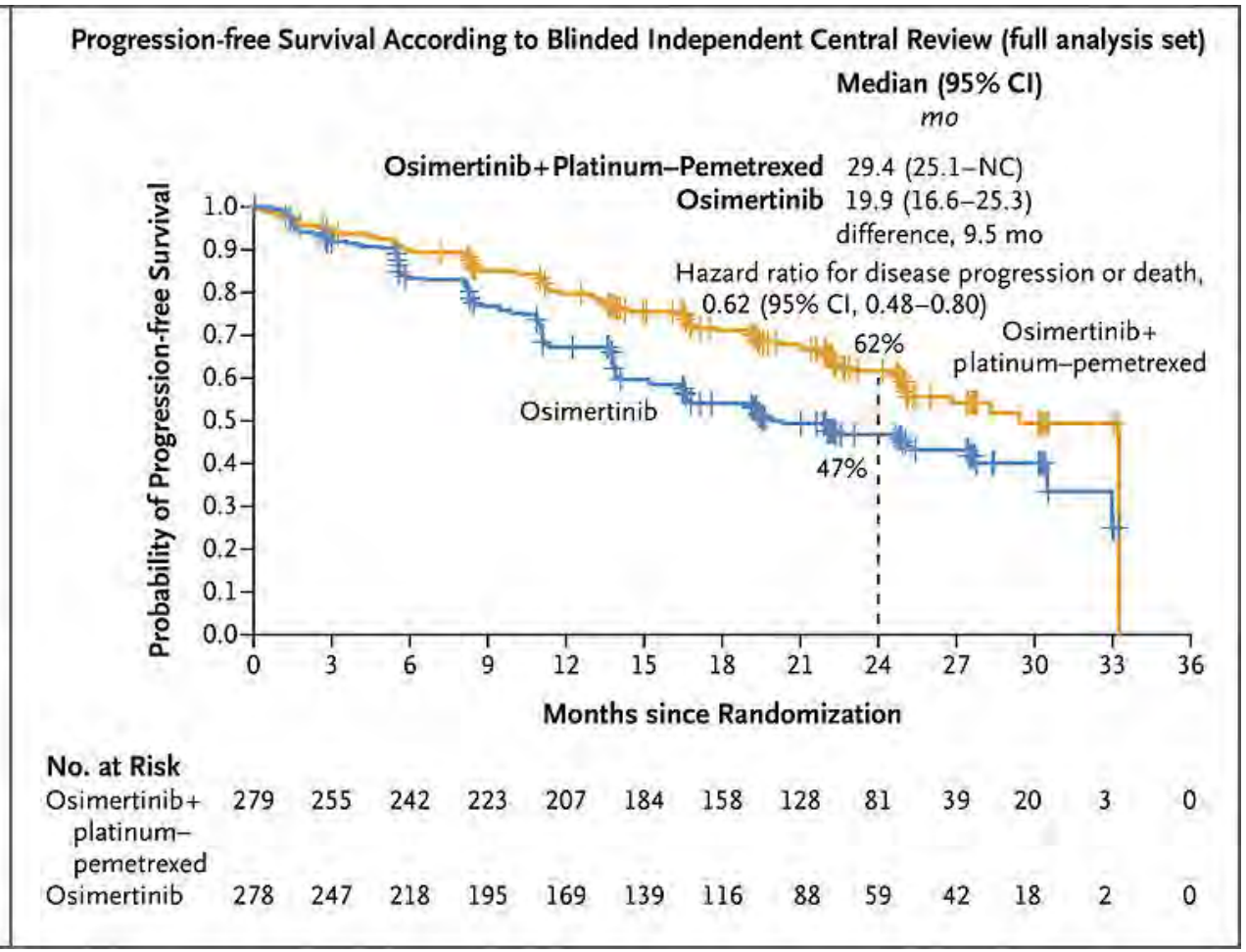
Joshua K Sabari, MD
Attending Physician
Thoracic Medical Oncology
Assistant Professor of Medicine
NYU Langone Health
Perlmutter Cancer Center
New York, New York

Outline

- EGFR
  - FLAURA
  - FLAURA2
  - MARIPOSA
  - Strategies to overcome resistance
- HER2
- MET
- ALK

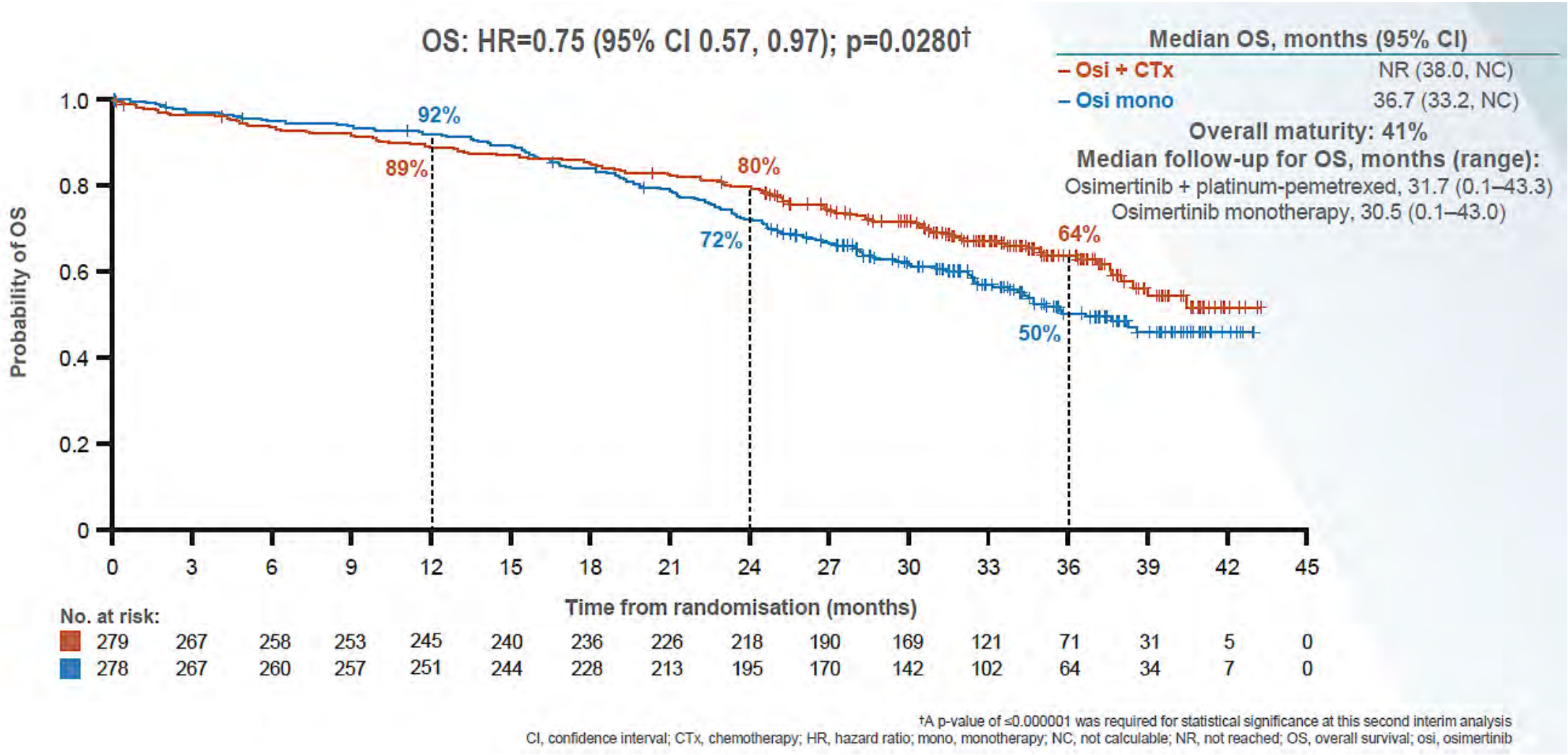
FLAURA2 Trial: Progression-Free Survival with Osimertinib and Chemotherapy for Advanced NSCLC with EGFR Mutations





Planchard D et al. *N Engl J Med* 2023;389(21):1935-48.

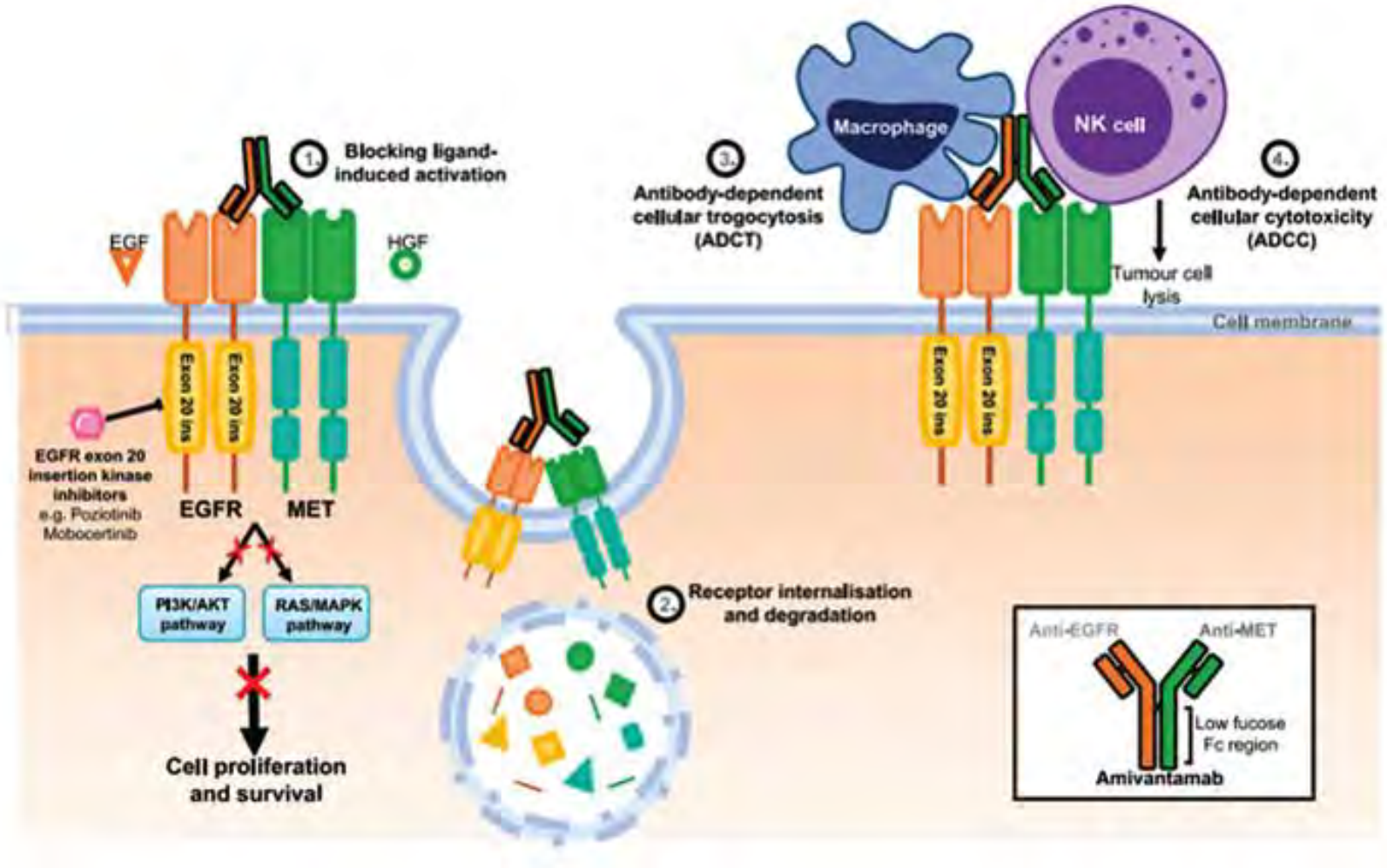
FLAURA2: Second Interim Overall Survival (OS) Analysis with Osimertinib and Chemotherapy for Advanced NSCLC with EGFR Mutations



†A p-value of ≤0.000001 was required for statistical significance at this second interim analysis
CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; mono, monotherapy; NC, not calculable; NR, not reached; OS, overall survival; osi, osimertinib

Valdiviezo N et al. ELCC 2024;Abstract 4O.

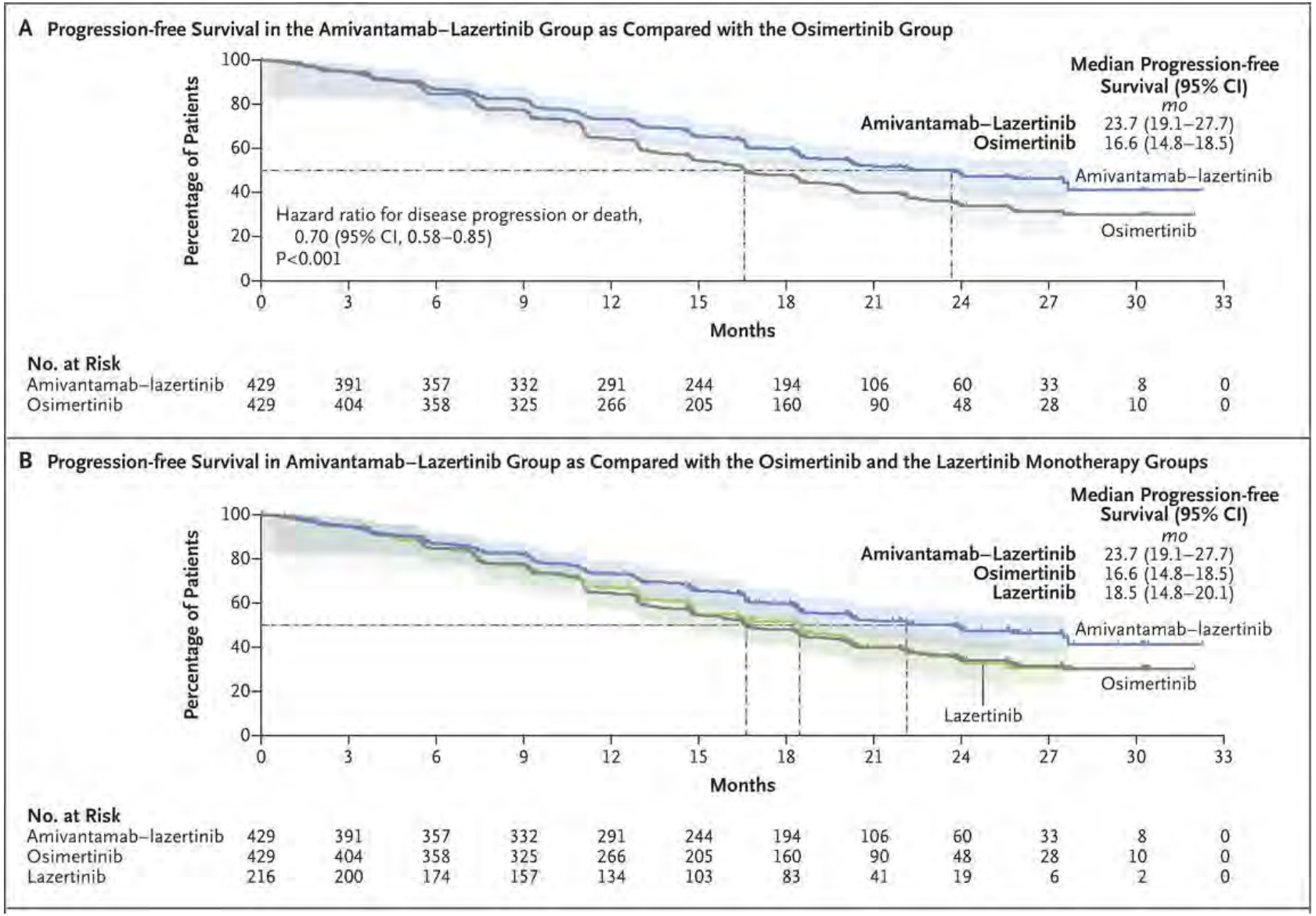
Amivantamab Mechanism of Action



- Secondary resistance is a major cause of TKI resistance (secondary EGFR mutations and met mutations/amp)

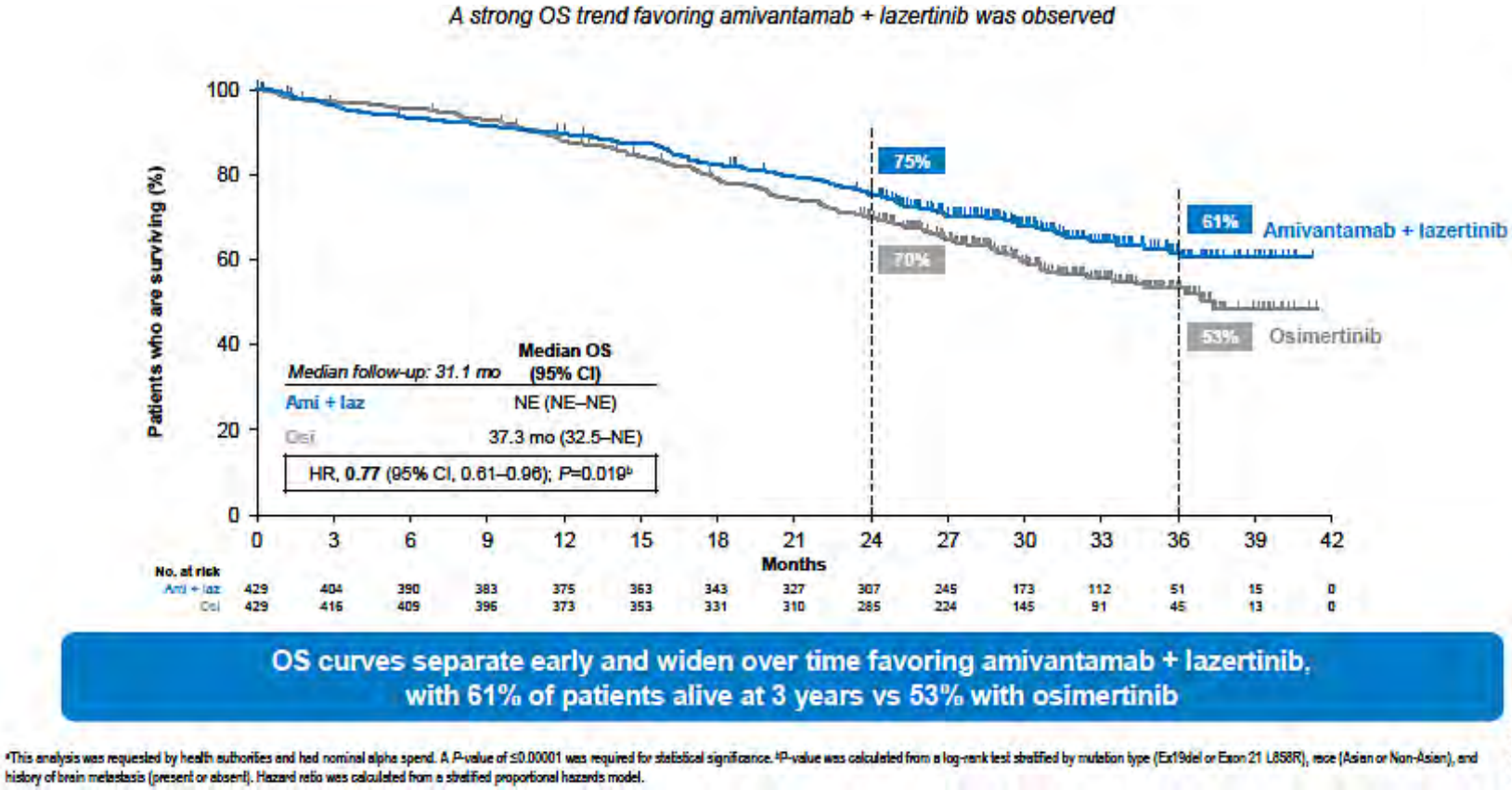
Courtesy of Alexander I Spira, MD, PhD

MARIPOSA Trial: Progression-Free Survival with Amivantamab and Lazertinib for Previously Untreated Advanced NSCLC with EGFR Mutations



Cho BC et al. *N Engl J Med* 2024 June 26;[Online ahead of print].

MARIPOSA: Longer Follow-Up with First-Line Amivantamab and Lazertinib for Advanced NSCLC with EGFR Mutations

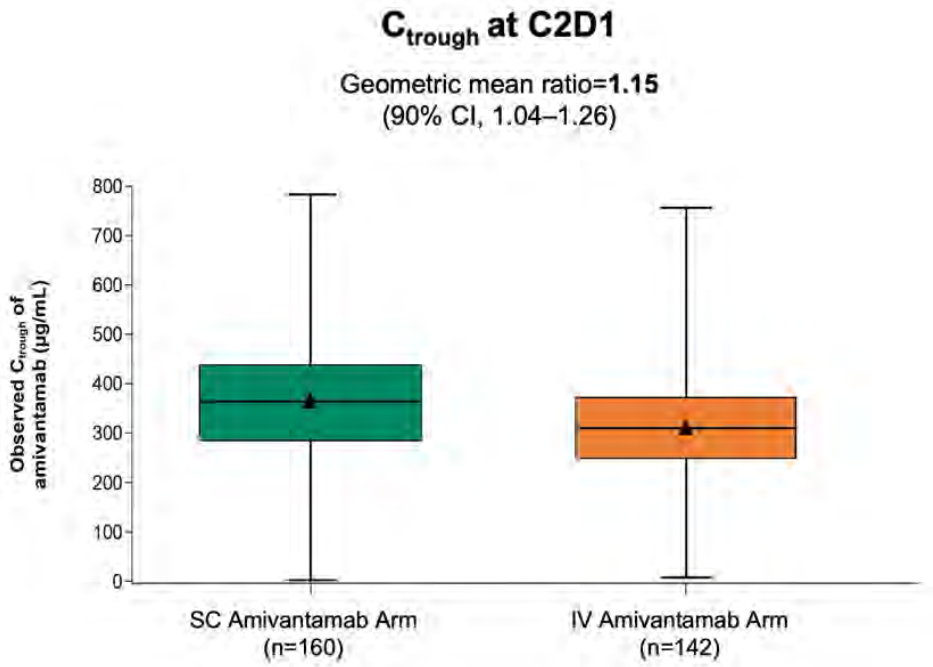


- Three-year intracranial PFS was double for amivantamab with lazertinib versus osimertinib (38% vs 18%)
- Amivantamab with lazertinib showed a favorable trend for intracranial duration of response (NE vs 24.4 months)
- Postprogression outcomes (time to deterioration, time to symptomatic progression, progression-free survival after first subsequent therapy) were significantly improved with first-line amivantamab and lazertinib versus osimertinib

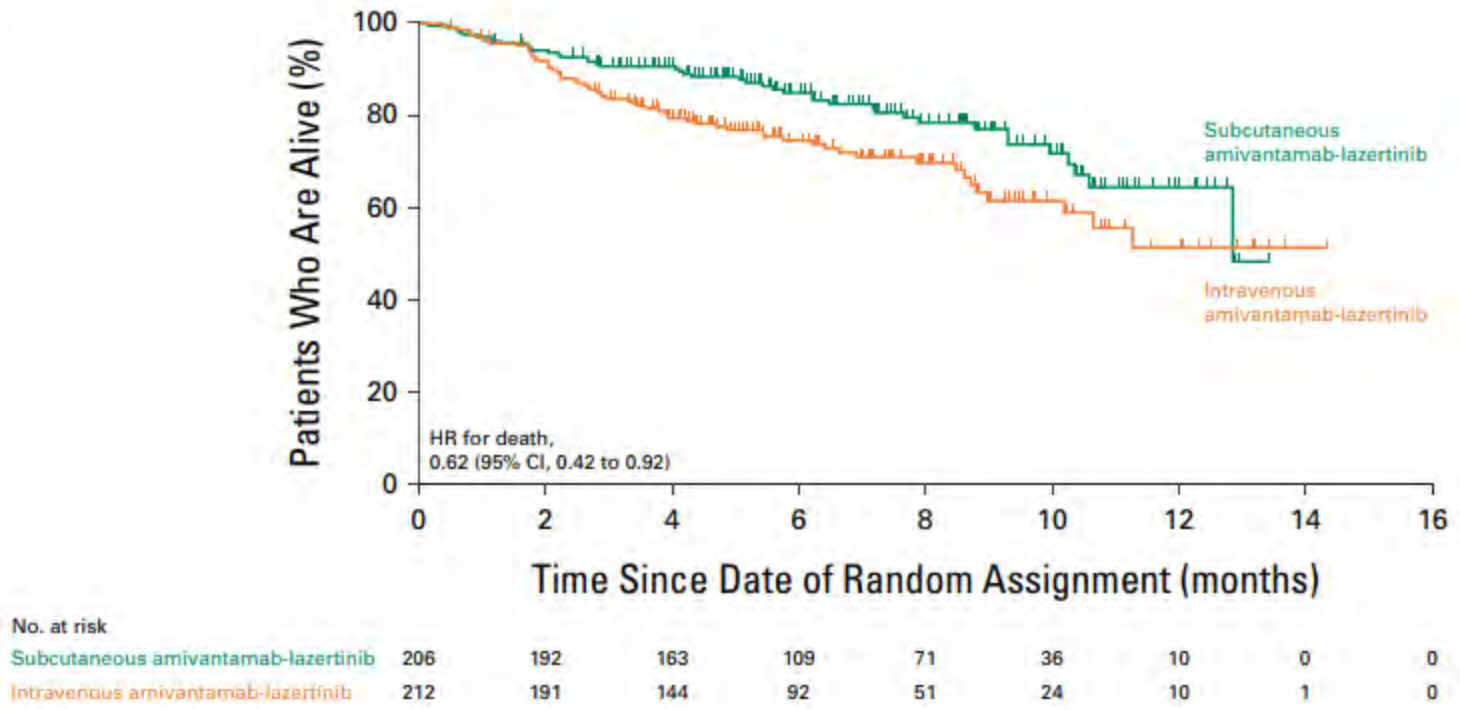
Gadgeel S et al. WCLC 2024;Abstract OA02.03.

PALOMA-3: Subcutaneous vs IV Amivantamab + Lazertinib in Advanced EGFRm NSCLC

Pharmacokinetics: Primary Endpoint: C_{trough} at C2D1



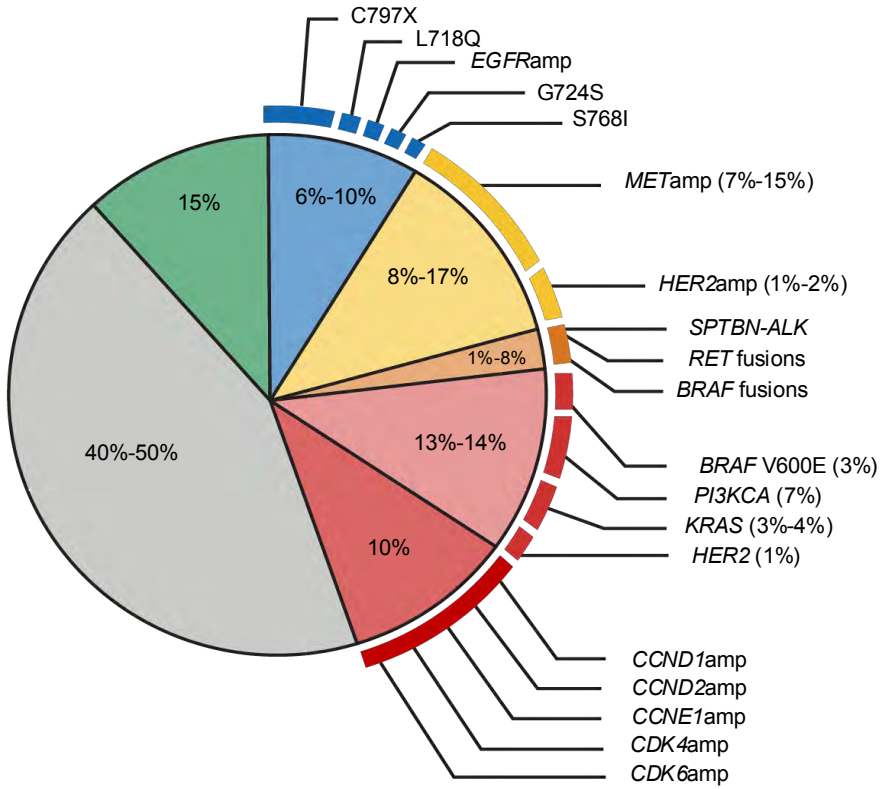
Overall Survival: Amivantamab SC + Lazertinib vs Amivantamab IV + Lazertinib



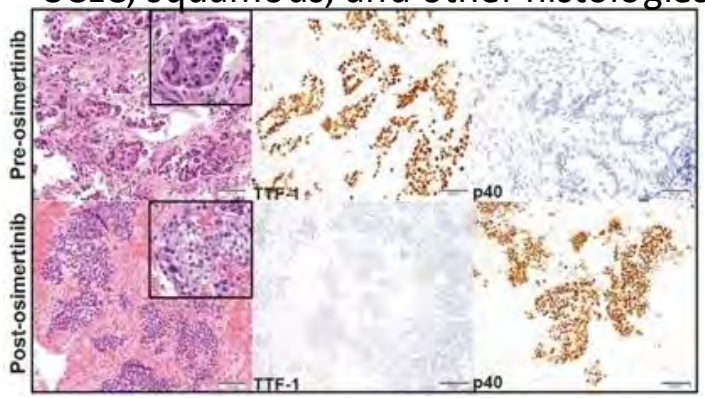
Leighl NB et al JCO 2024 42; 3593-3605

Acquired Resistance to EGFR Tyrosine Kinase Inhibitors

Resistance to First Line Osimertinib



- **Histologic transformation:** up to 15%
  - SCLC, squamous, and other histologies



  - Tissue biopsy is critical in the evaluation of osimertinib resistance
- **On-target resistance** (*EGFR* C797S, G724S, etc): 5%-10%
- **Bypass pathway activation** (most notably *MET*amp): up to 15% pts
- **50%-60% patients don't have a targetable resistance mechanism**

1. Leonetti A et al. *Br J Cancer*. 2019;121:725-737
2. Sequist LV et al. *Lancet Oncol*. 2020;21:373-386

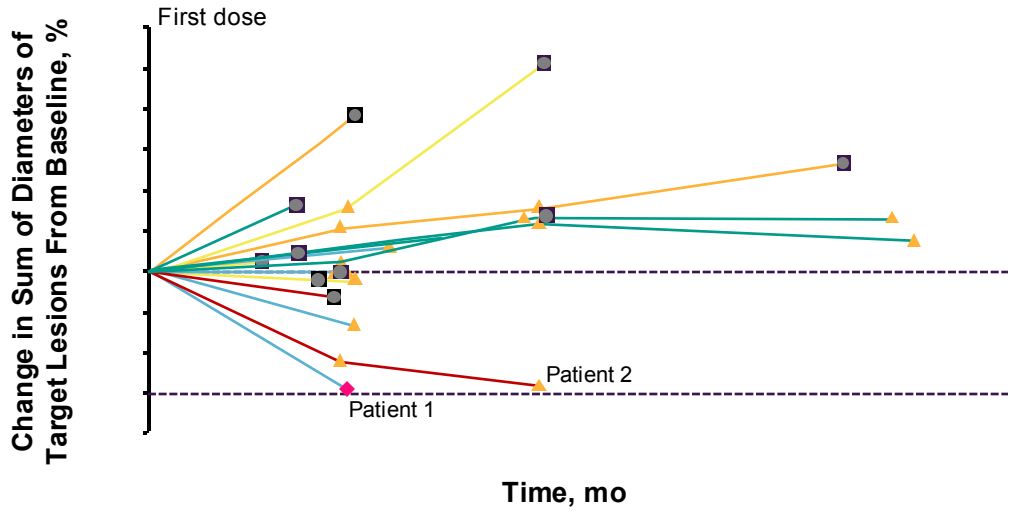
Targeting *EGFR* C797S

- Limited data for 1st-gen EGFR TKIs
- "4th-gen" EGFR TKIs with activity against C797S are now entering the clinic
- Other novel agents, including amivantamab and patritumab deruxtecan, may have activity

	1G	3G	4G		Potential Combinations	
***EGFR* Mutational Coverage[a]**	**Gefitinib**	**Osimertinib**	**BLU-701**	**BLU-945**	**BLU-701 + Osimertinib**	**BLU-701 + BLU-945**
L858R (LR)						
ex19del						
LR or ex19del/T790M						
LR or ex19del/C797S						
LR or ex19del/T790M/C797S						

IC_{50} ≤10 nM
10 nM < IC_{50} ≤50 nM
IC_{50} >50 nM

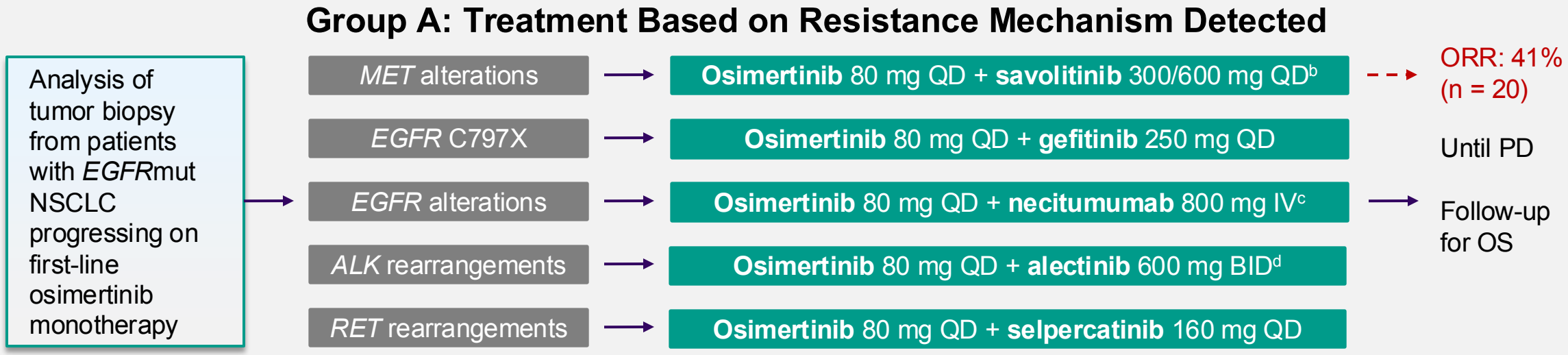
Dose-Dependent Tumor Shrinkage With BLU-945



1. Conti C et al. American Association for Cancer Research Annual Meeting 2021 (AACR 2021). Abstract 1262. 2. Shum E et al. AACR 2021. Abstract CT184

ORCHARD: Biomarker-Directed Study in Patients with Advanced EGFRm NSCLC Progressing on 1L Osimertinib

- Open-label, multicenter, multidrug, biomarker-directed phase 2 platform trial

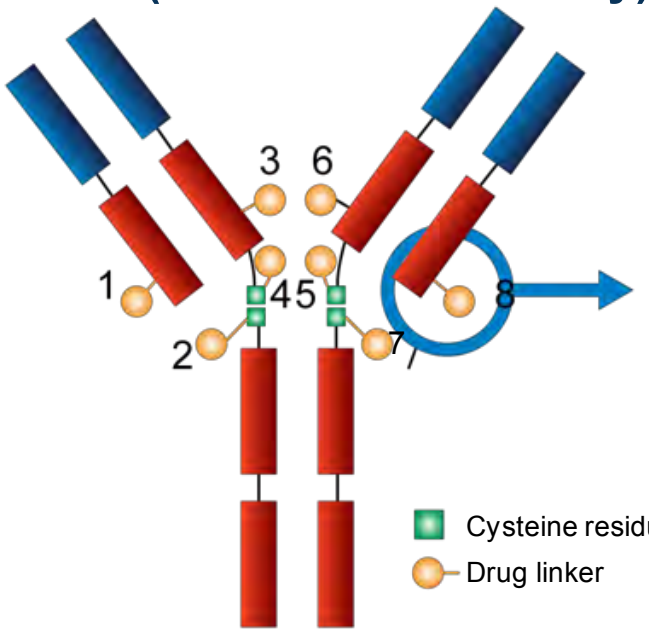


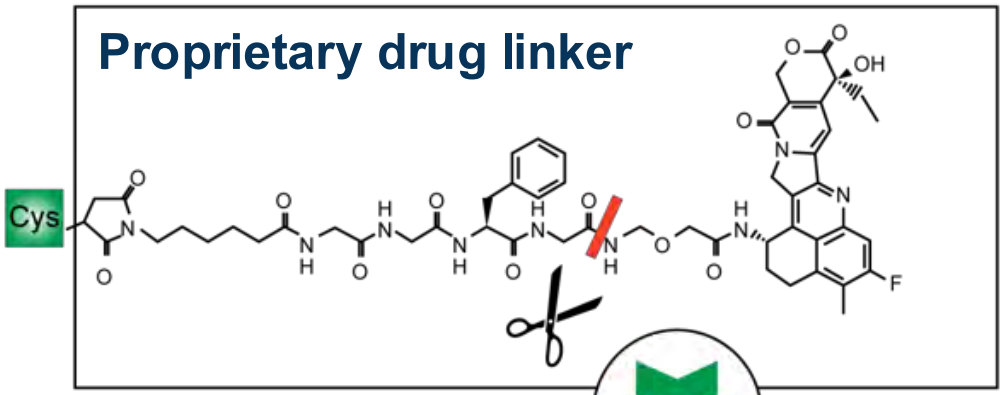
- **Group B**: Nonmatched arm for patients without a detectable resistance mechanism will sequentially be assigned to durvalumab + chemotherapy > osimertinib + necitumumab > others
- **Group C**: Observational arm for patients whose optimal treatment falls outside of group A or B (eg, transformation to SCLC)
- Patients with failed baseline NGS results go directly to follow-up

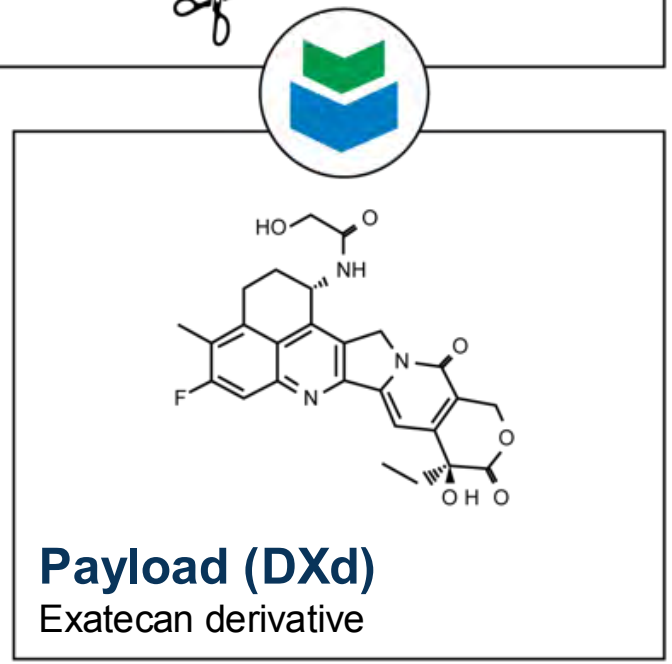
1. Cho BC et al. *J Thorac Oncol*. 2021;16:S598. 2. Yu H et al. *Clin Lung Cancer*. 2021;22:601. 3. Yu H et al. ESMO 2021. Abstract 1239P.

Patritumab Deruxtecan (HER3-DXd; U3-1402): A Novel Anti-HER3 ADC[1]

Patritumab (Anti-HER3 Antibody)







Conjugation chemistry

The linker is connected to cysteine residue of the antibody

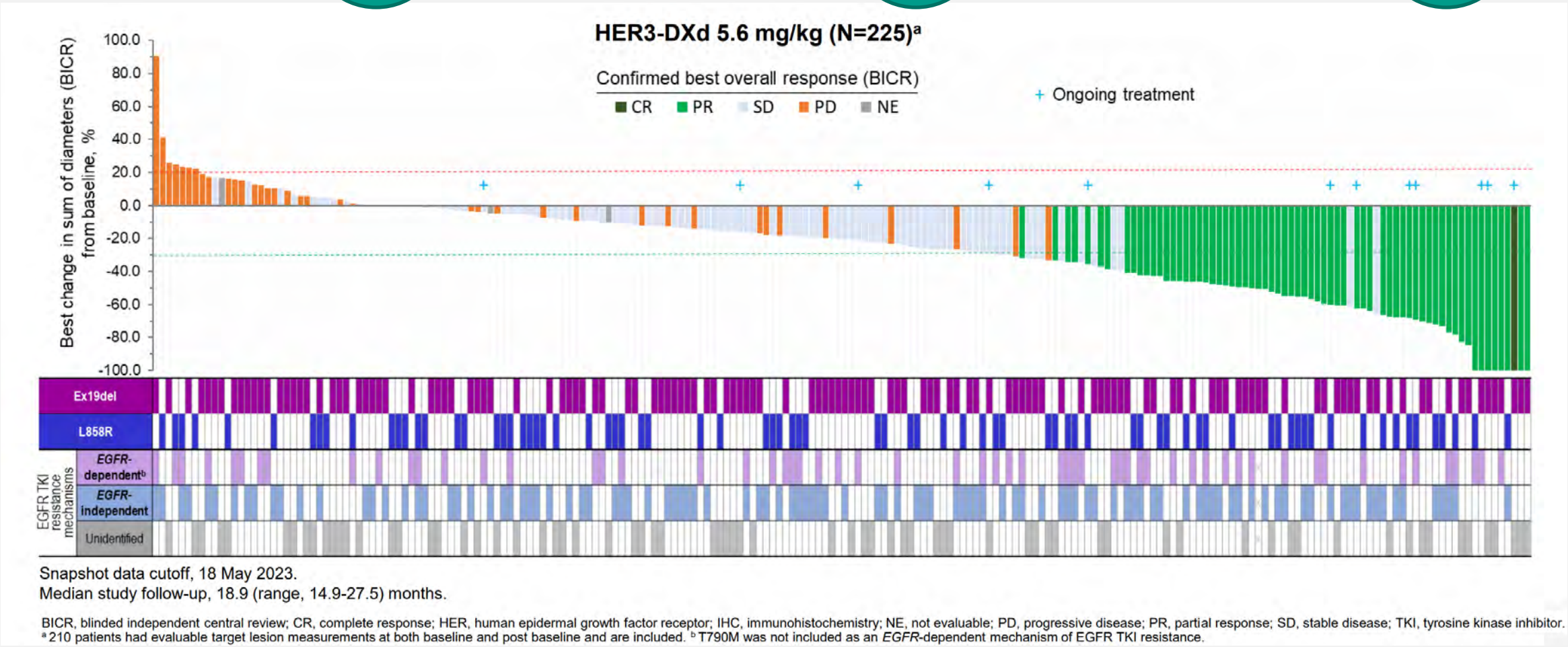
Yonemori K et al. *Ann Oncol*. 2019;30(suppl 3)

HERTHENA-Lung01: Patritumab Deruxtecan (HER3-DXd) in Patients with Diverse Mechanisms of EGFR TKI Resistance

Confirmed ORR **30%**

Median DOR **6.4 mo**

Median PFS **5.5 mo**



Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

BICR, blinded independent central review; CR, complete response; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] 210 patients had evaluable target lesion measurements at both baseline and post baseline and are included. [b] T790M was not included as an *EGFR*-dependent mechanism of EGFR TKI resistance.

Yu et al., WCLC 2023. Yu et al., *J Clin Oncol* 2023;41(35):5363-5375.

HERTHENA-Lung02: 2L Patritumab Deruxtecan (HER3-DXd) vs Chemotherapy in EGFRm NSCLC

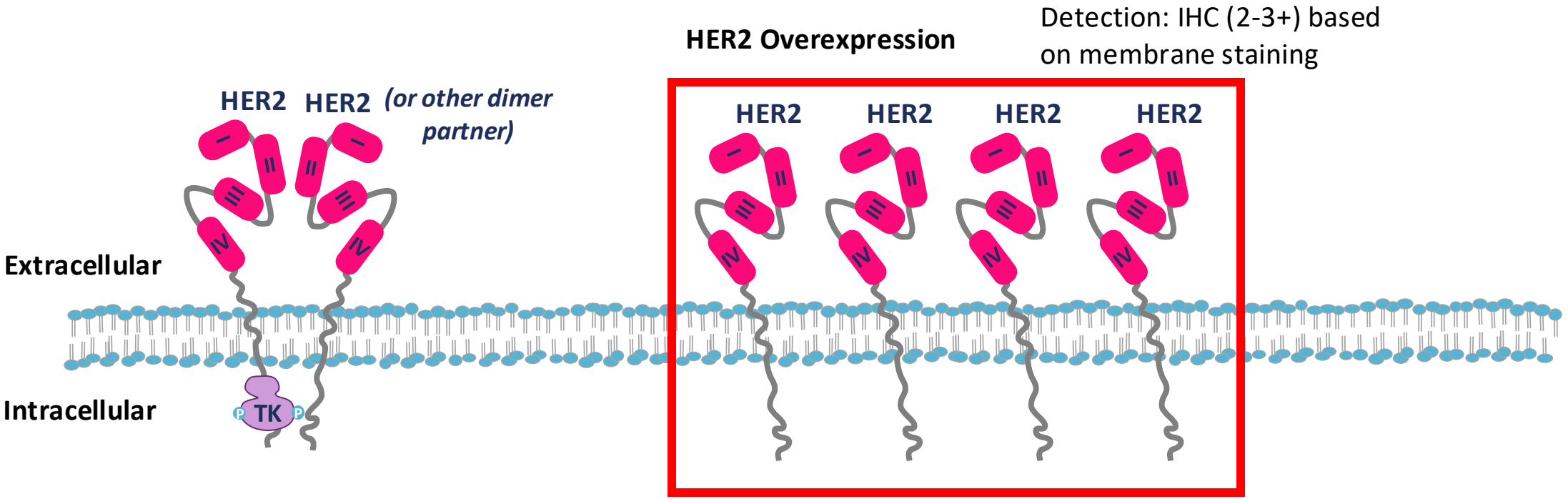
Patritumab Deruxtecan Demonstrated Statistically Significant Improvement in Progression-Free Survival Versus Doublet Chemotherapy in Patients with Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer in HERTHENA-Lung02 Phase 3 Trial

September 17, 2024 6:00 am ET

… **patritumab deruxtecan demonstrates a statistically significant progression-free survival improvement in this EGFR-mutated non-small cell lung cancer population with high unmet need following prior EGFR TKI treatment**

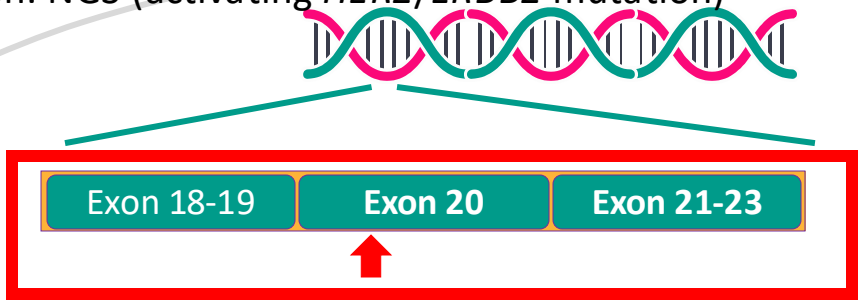
https://www.merck.com/news/patritumab-deruxtecan-demonstrated-statistically-significant-improvement-in-progression-free-survival-versus-doublet-chemotherapy-in-patients-with-locally-advanced-or-metastatic-egfr-mutated-non-small/

HER2 Alterations in NSCLC



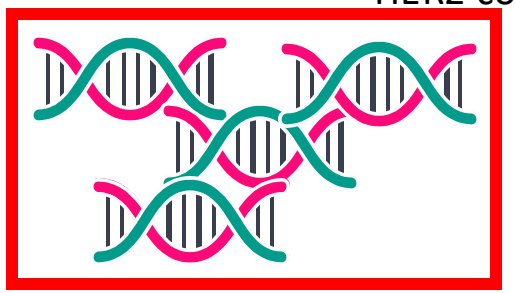
***HER2* Gene Mutation**

Detection: NGS (activating *HER2*/*ERBB2* mutation)

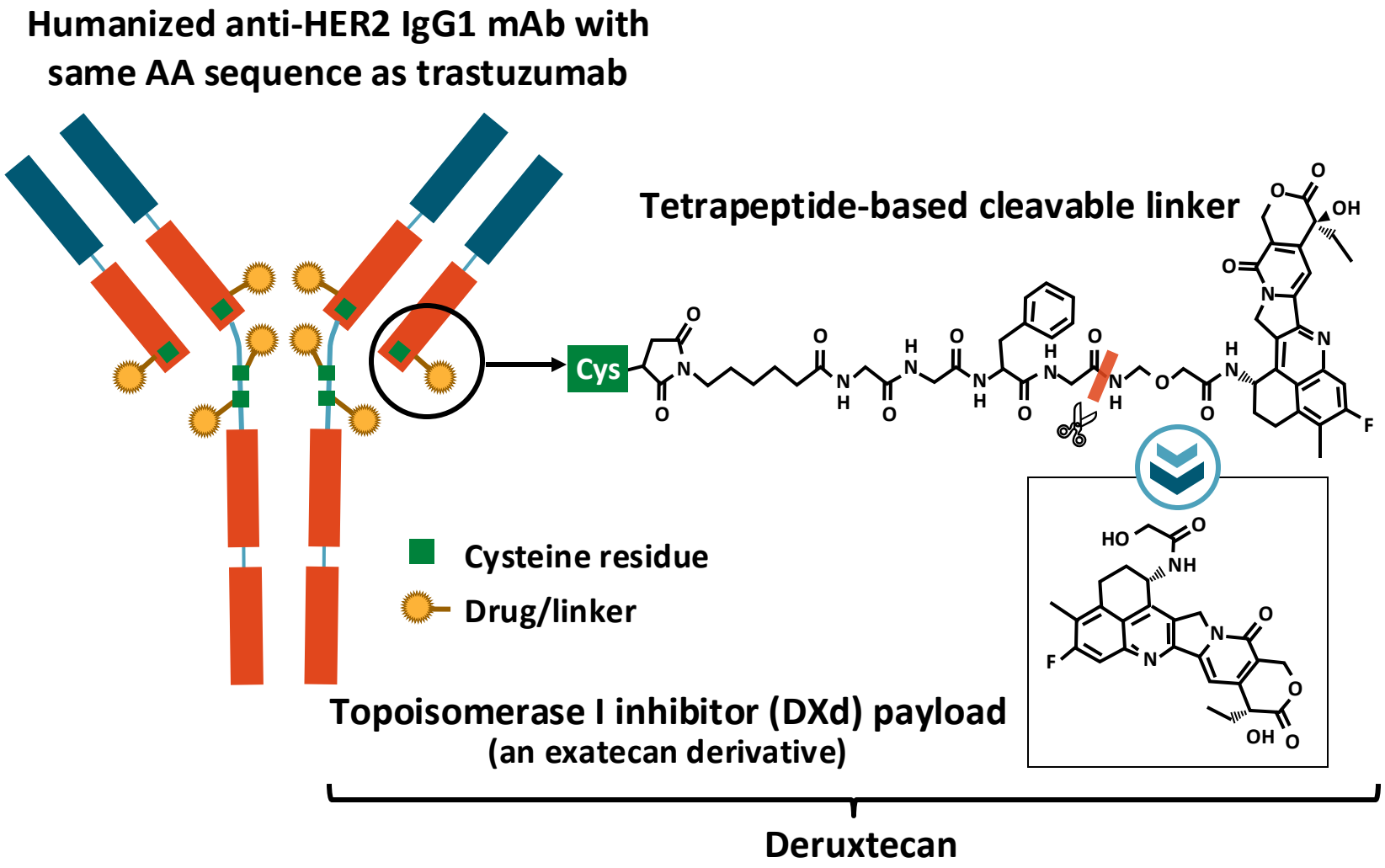


***HER2* Amplification**

Detection: FISH (*HER2*/*CEP17* ratio >2 and/or HER2 copy number > 6) or NGS



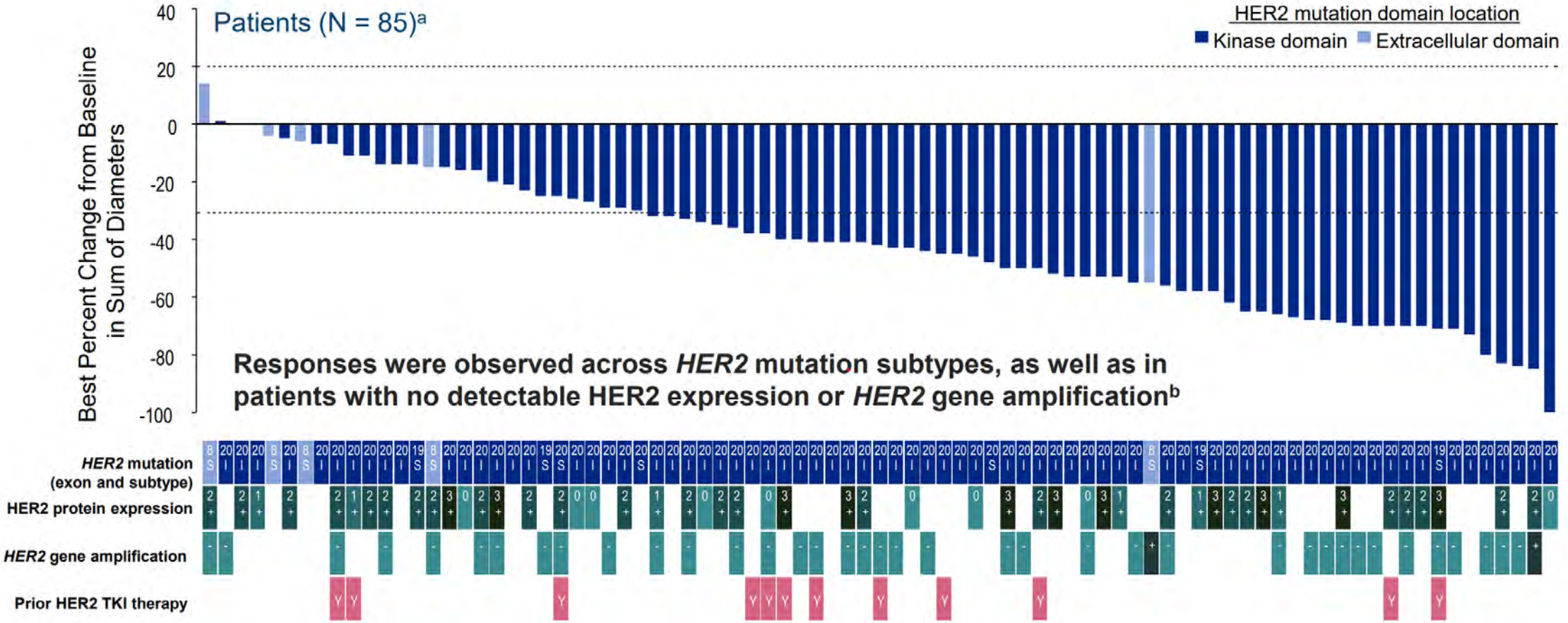
HER2-Targeted ADC: Trastuzumab Deruxtecan (T-DXd)



- High drug to antibody ratio: ~8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

Efficacy: DESTINY-Lung01: T-DXd

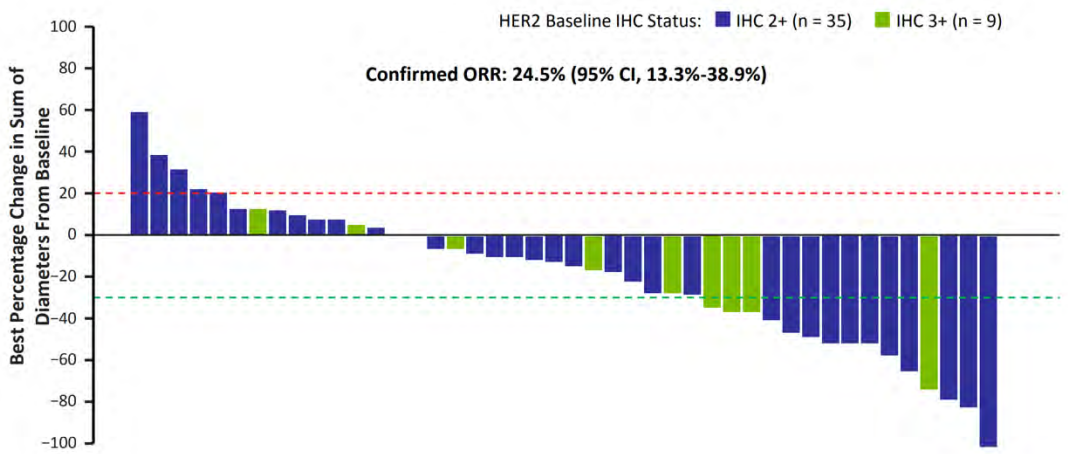


Li et al., NEJM 2022.

DESTINY-Lung01: Lessons in Biomarker Selection

- In wild-type, HER2 overexpressed NSCLC, response rates to T-DXd were much lower.
  - Little correlation was observed between response and IHC score.
- Mutant HER2 receptors have a much more efficient internalization capacity.
- Biomarker selection is not straightforward.

Recent FDA approval: Pan-tumor IHC 3+

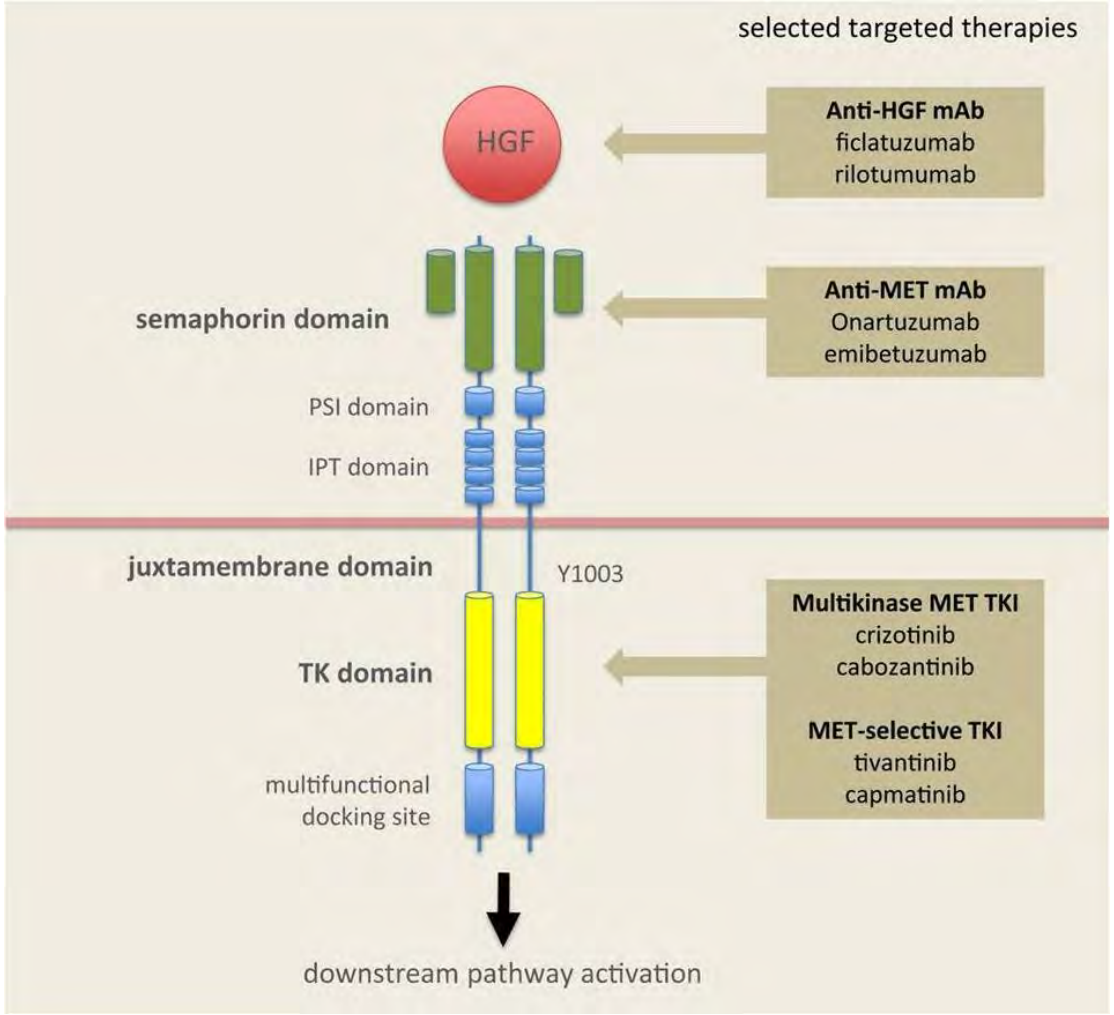


Response Assessment by ICR	IHC 3+ (n = 10)	IHC 2+ (n = 39)	Overall (N = 49)
Confirmed ORR, n (95% CI)	**20.0%** 2 (2.5-55.6)	**25.6%%** 10 (13.0-42.1)	**24.5%** 12 (13.3-38.9)
CR, n (%)	0	1 (2.6%)	1 (2.0%)
PR, n (%)	2 (20.0%)	9 (23.1%)	11 (22.4%)
SD, n (%)	6 (60.0%)	16 (41.0%)	22 (44.9%)
PD, n (%)	1 (10.0%)	10 (25.6%)	11 (22.4%)
Not evaluable, n (%)	1 (10.0%)	3 (7.7%)	4 (8.2%)
DCR, n (95% CI)	**80.0%** 8 (44.4-97.5)	**66.7%** 26 (49.8-80.9)	**69.4%** 34 (54.6-81.8)
Median DOR, months (95% CI)	**6.0 (NE-NE)**	**5.8 (3.2-NE)**	**6.0 (3.2-NE)**

Smit EF et al. *Lancet Oncol* 2024;25(4):439-454.
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2

MET Alterations in NSCLC

- MET activation occurs via
  - *METex14* skipping and *MET* amplification
- Type of *MET* aberrations
  - Single nucleotide variants
  - Amplification
  - Exon 14 skipping alterations
  - Fusions

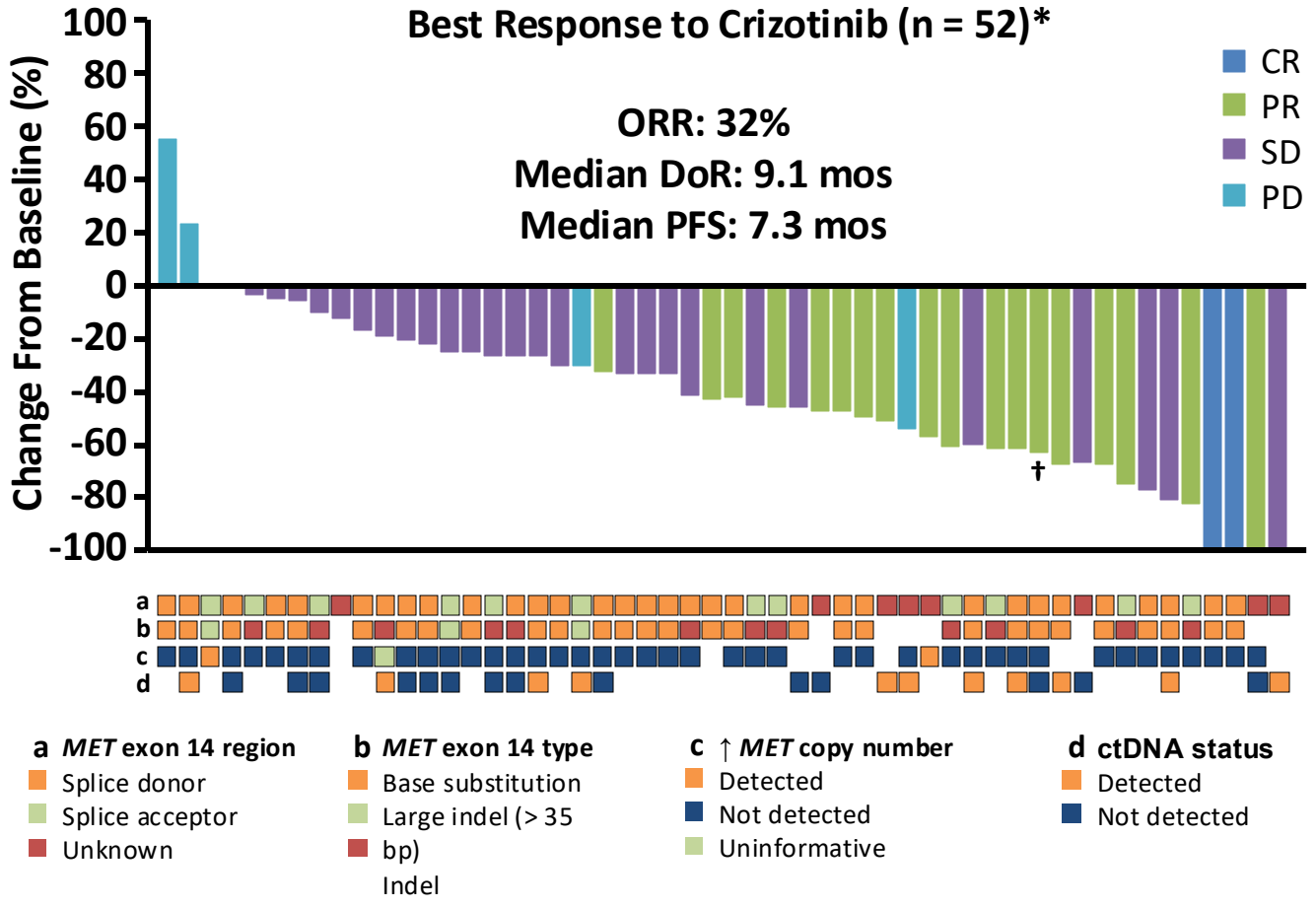


Van der Steen et al J Thorac Oncol 2016; Drilon et al J Thorac Oncol 2017; Comoglio et al Nat Rev Cancer 2018

PROFILE 1001: Crizotinib in MET exon 14 Skip NSCLC

- Open-label, multicohort phase I study evaluating efficacy, safety of crizotinib in NSCLC
  - *MET*ex14 cohort (N = 69)

- ORR 32%
- mPFS 7.3m
- mOS 20.5m

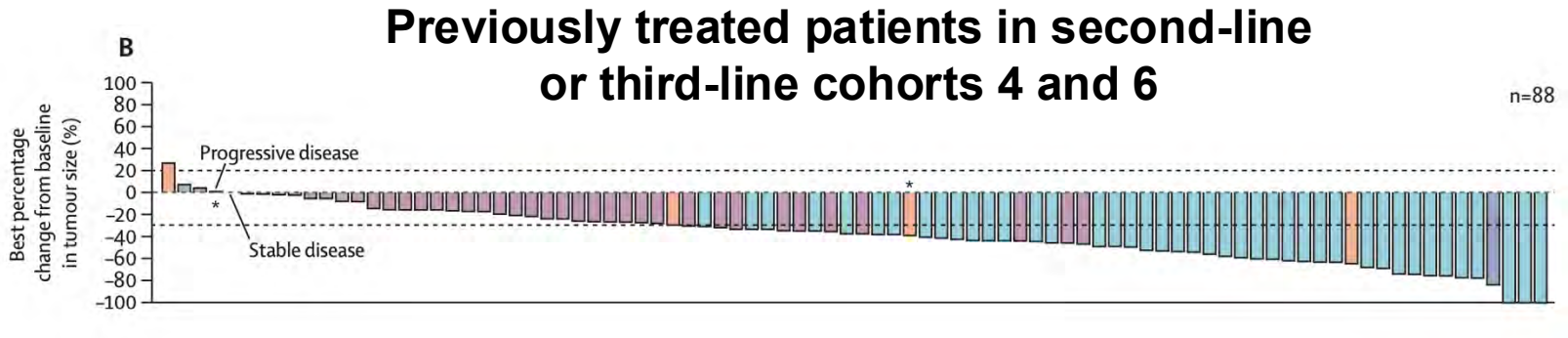


*n = 13 not evaluable for response. †Positive for *MET*ex14 by local testing but WT for *MET*ex14 and positive for *ROS1* rearrangement by central testing.

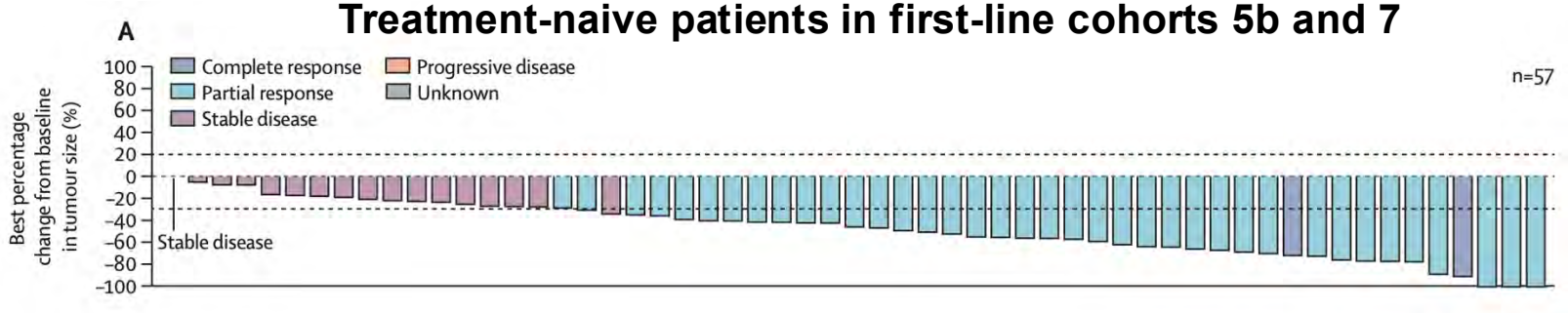
Drilon. Nat Med. 2020;26:47

GEOMETRY mono-1: Capmatinib

- Previously treated:
  - ORR 44%
  - mDOR 9.7m
  - mPFS 5.5m
  - mOS 16.8m



- Treatment naïve
  - ORR 68%
  - mDOR 16.6 months
  - mPFS 12.5m
  - mOS 21.4m



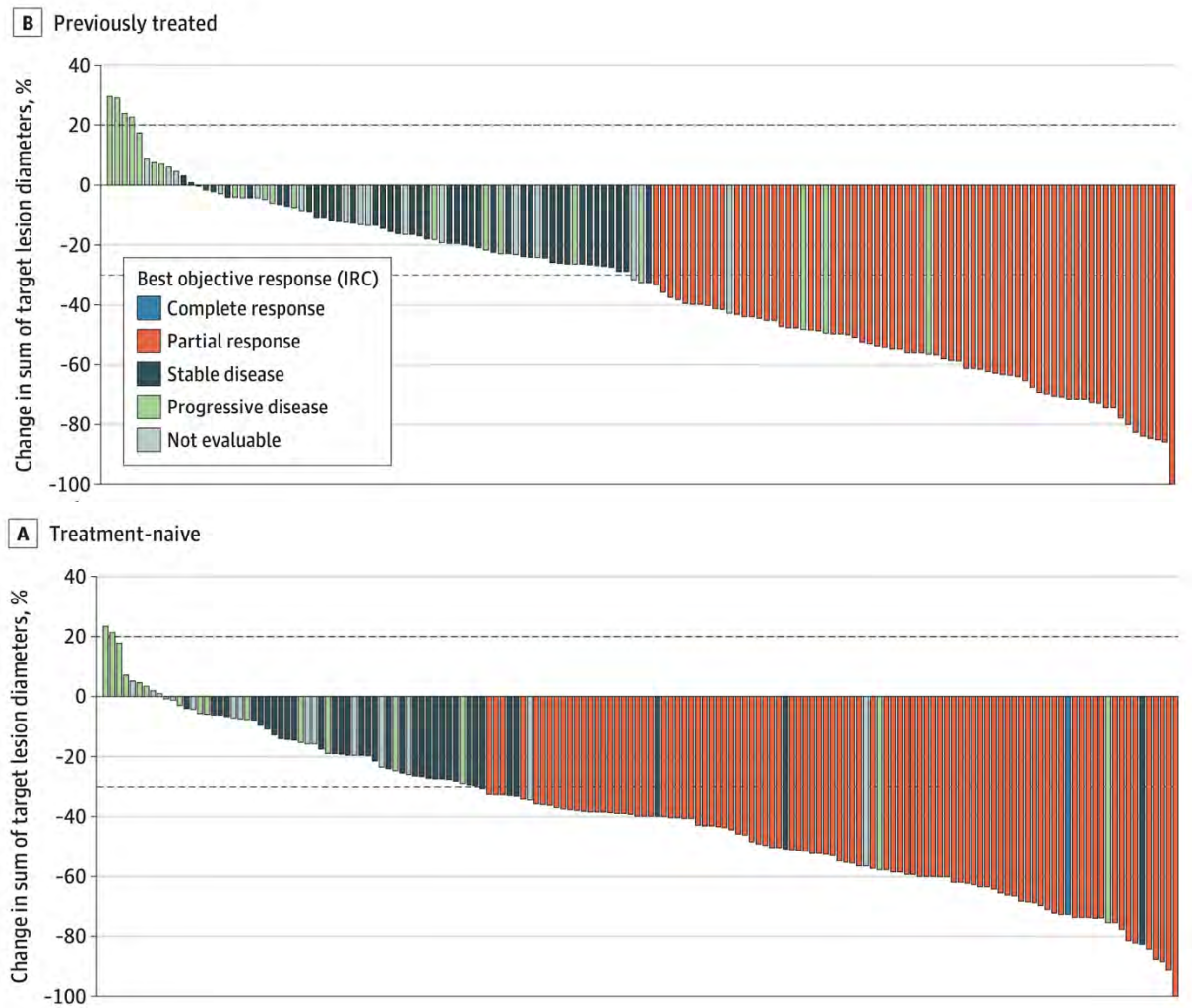
Intracranial response rate: 57%

Wolf J et al. *Lancet Oncol* 2024;25(10):1357-1370.

VISION: Tepotinib

- Previously treated:
  - ORR 45%
  - mDOR 12.6m
  - mPFS 11.0m
  - mOS 19.3m

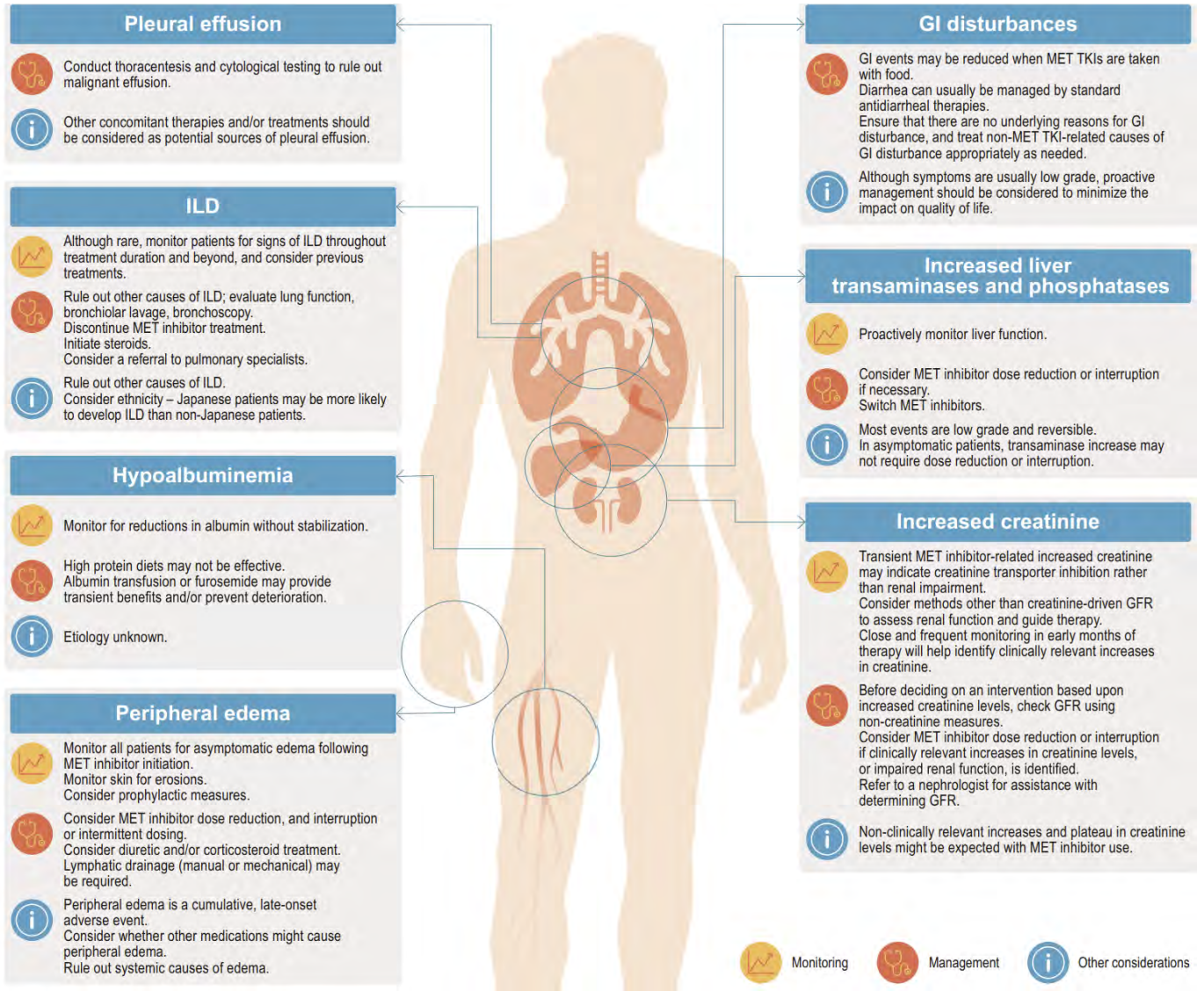
- Treatment naïve:
  - ORR 57%
  - mDOR 46.4m
  - mPFS 12.6m
  - mOS 21.3m



Intracranial response rate 56%

Mazieres J et al. *JAMA Oncol* 2023;9(9):1260-1266.

MET TKI Toxicities

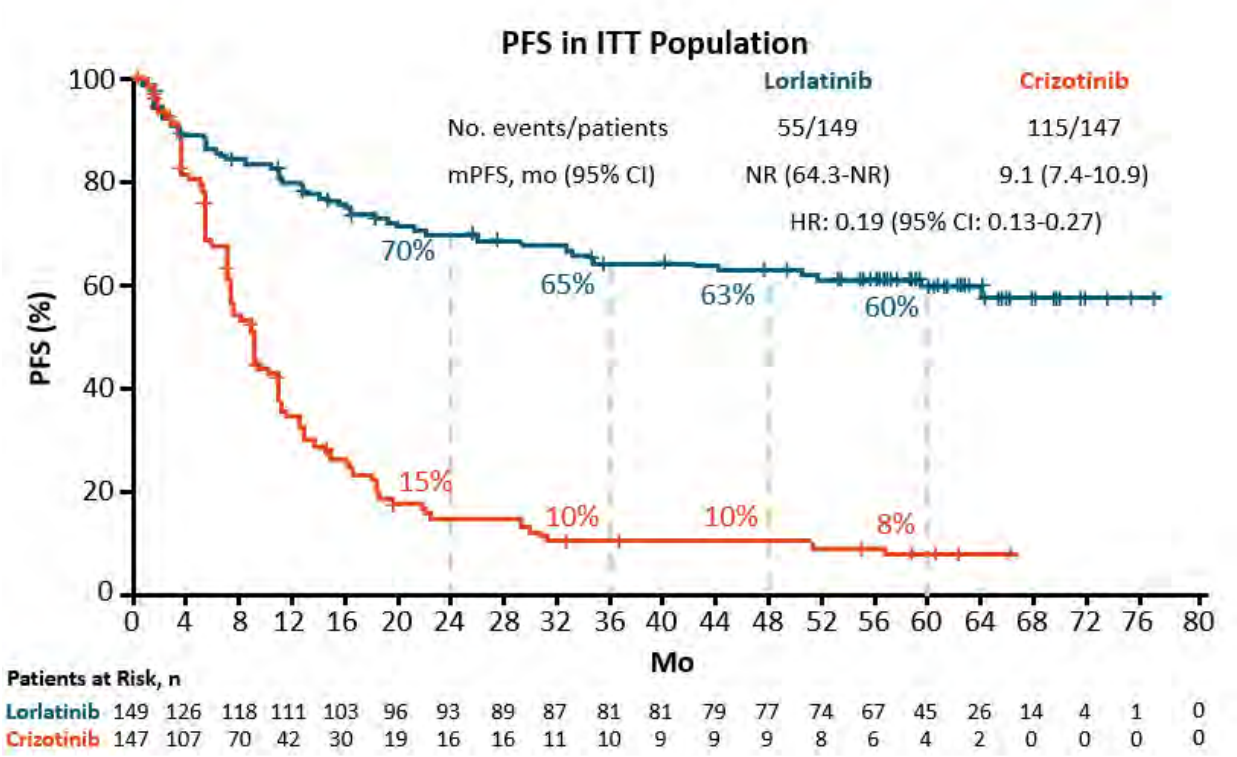


Cortot et al. Clinical Lung Cancer. 2022

ALK Rearranged NSCLC

- Alectinib, Lorlatinib and Brigatinib FDA approved
  - Studied vs Crizotinib
- CROWN Trial
  - Lorlatinib vs Crizotinib
- PFS favored lorlatinib vs crizotinib
- HR for PFS (95% CI): 0.19 (0.13 – 0.27)
  - With BL brain mets: 0.08 (0.04-0.19)
  - Without BL brain mets: 0.24 (0.16-0.36)
- OS immature

Crown Trial: 5-year Update PFS



Solomon. ASCO 2024. Abstr LBA8503. Solomon. JCO. 2024

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

Agenda

Module 1 — HR-Positive Breast Cancer: *Drs O'Shaughnessy and Wander*

Module 2 — Prostate Cancer: *Drs M Smith and Srinivas*

Module 3 — Lung Cancer: *Drs Goldberg and Sabari*

Module 4 — Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia: *Drs Kahl and S Smith*

Module 5 — Multiple Myeloma: *Drs Lonial and Raje*

Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia Faculty

Brad S Kahl, MD
Professor of Medicine
Washington University School of Medicine
Director, Lymphoma Program
Siteman Cancer Center
St Louis, Missouri

Sonali M Smith, MD
Elwood V Jensen Professor of Medicine
Chief, Section of Hematology/Oncology
Co-Leader, Cancer Service Line
Co-Director, Lymphoma Program
The University of Chicago
Chicago, Illinois

Updates in Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma

Brad Kahl, MD

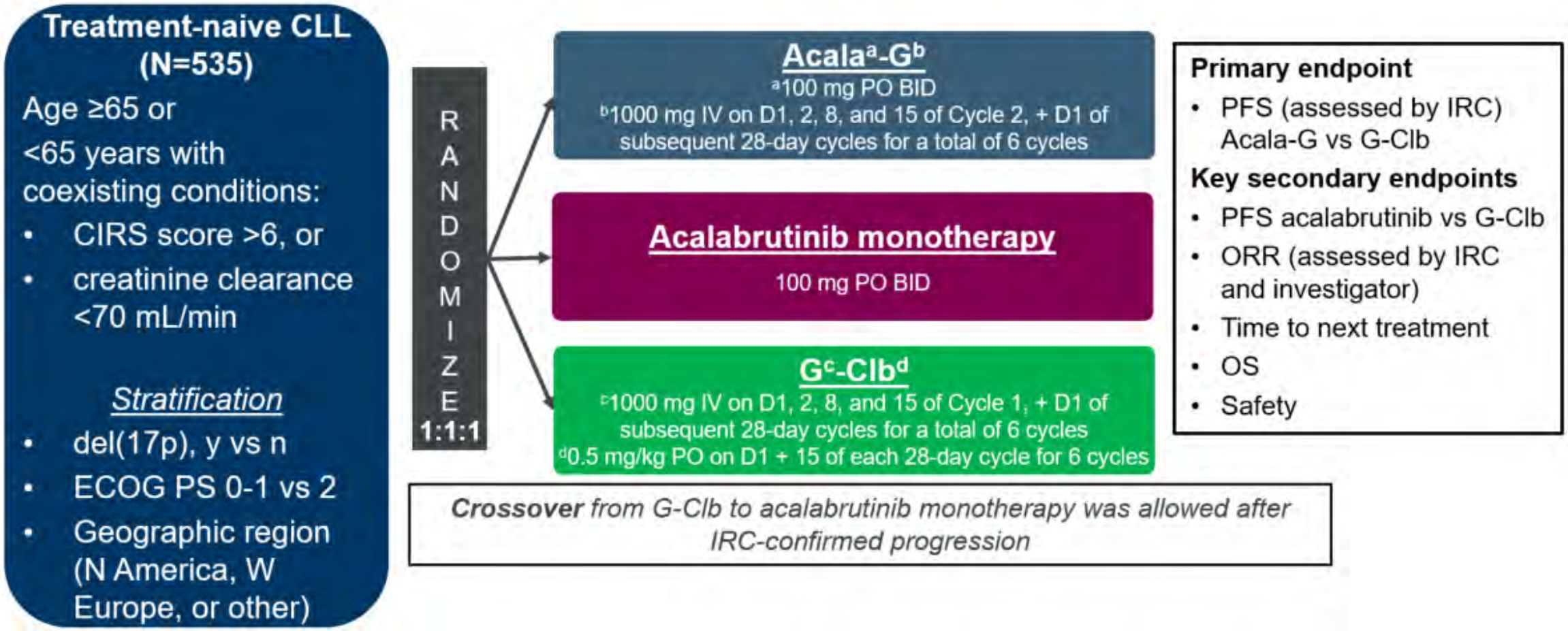
SITEMAN CANCER CENTER
A NATIONAL CANCER INSTITUTE COMPREHENSIVE CANCER CENTER
BARNES-JEWISH Hospital BJC HealthCare
Washington University in St. Louis SCHOOL OF MEDICINE
SITEMAN Kids AT ST. LOUIS Children's HOSPITAL Washington University Physicians
NCI Designated Comprehensive Cancer Center
NCCN National Comprehensive Cancer Network®

Novel agents are superior to CIT in first line

Patients	Study	Investigational arm	Control arm	Primary endpoint	Winner
	E1912	Ibrutinib + R	FCR	PFS	Ibrutinib + R
	A041202	Ibrutinib ± R	BR	PFS	Ibrutinib ± R
	SEQUOIA	Zanubrutinib	BR	PFS	Zanubrutinib
 	iLLUMINATE	Ibrutinib + G	CHL+G	PFS	Ibrutinib + G
 	ELEVATE-TN	Acalabrutinib ± G	CHL+G	PFS	Acalabrutinib ± G
 	CLL14	Venetoclax + G	CHL+G	PFS	Venetoclax + G
 	GLOW	Venetoclax + Ibrutinib	CHL+G	PFS	Venetoclax + Ibrutinib

CIT=chemoimmunotherapy ; G = Obinutuzumab; R = rituximab

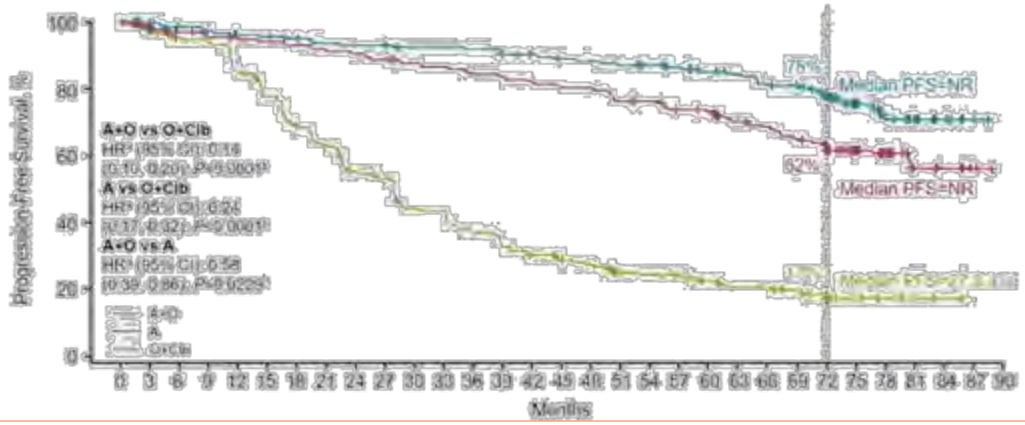
Acalabrutinib ± G vs. Clb+G:(ELEVATE-TN)



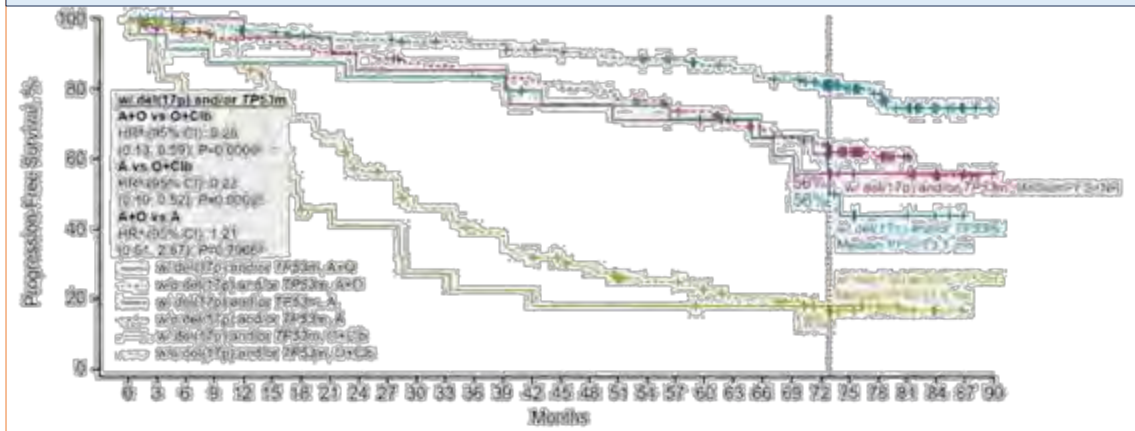
Sharman et al. Lancet. 2020 Apr 18;395(10232):1278-1291.

Acalabrutinib ± G vs Clb + G: ELEVATE-TN – 6-Year Update

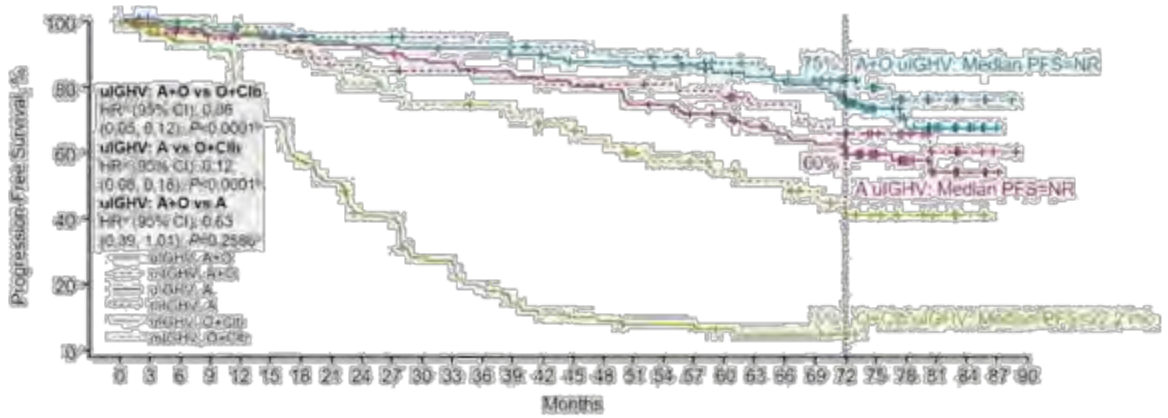
INV-Assessed PFS (median follow-up: 74.5 months)



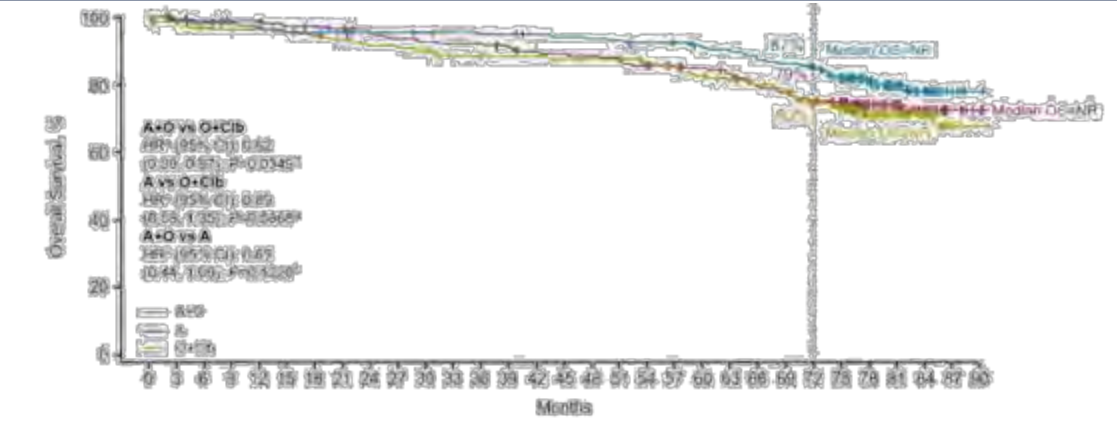
INV-Assessed PFS in Del(17p) and/or *TP53* Mutated



INV-Assessed PFS in Unmutated *IGHV*



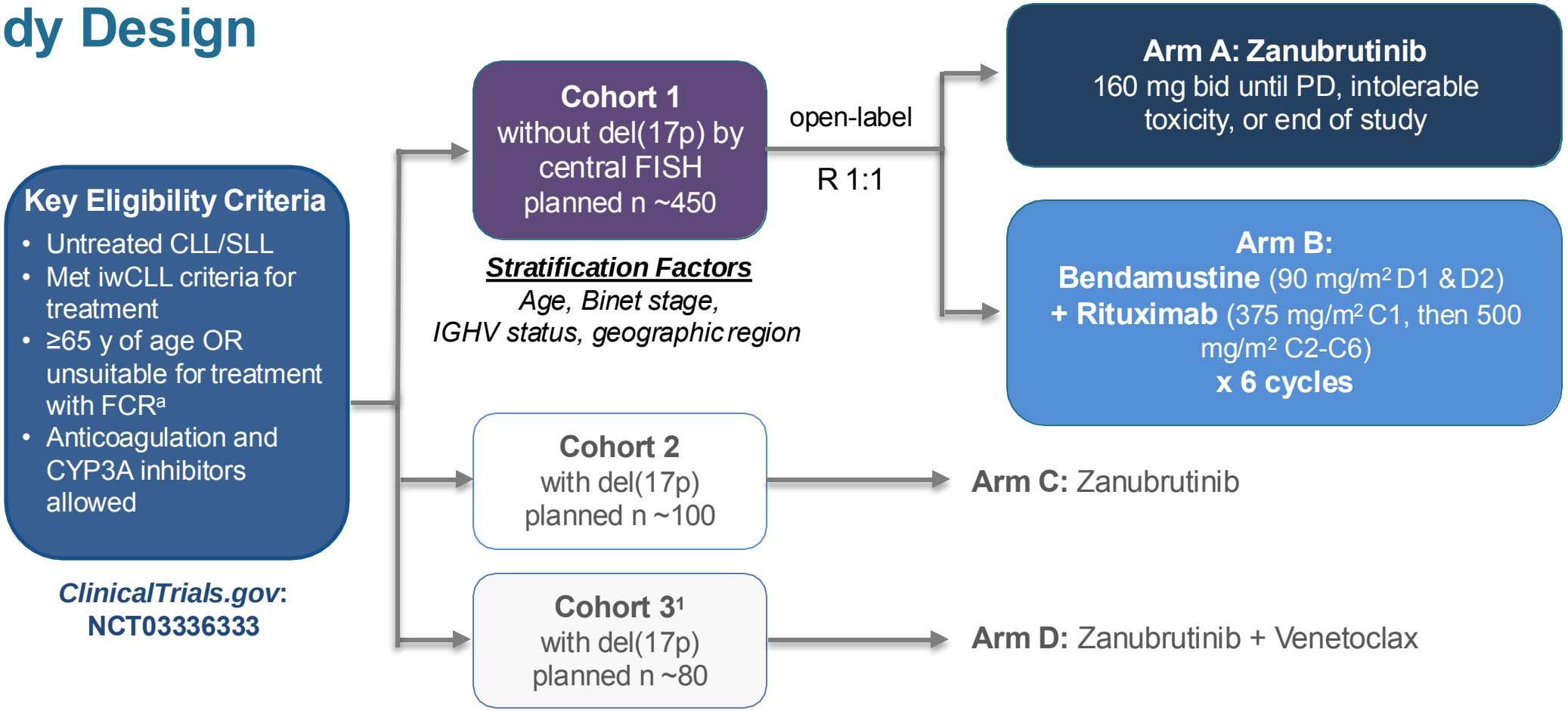
Overall Survival



Sharman et al. ASH 2023; Abstract 636

SEQUOIA (BGB-3111-304)

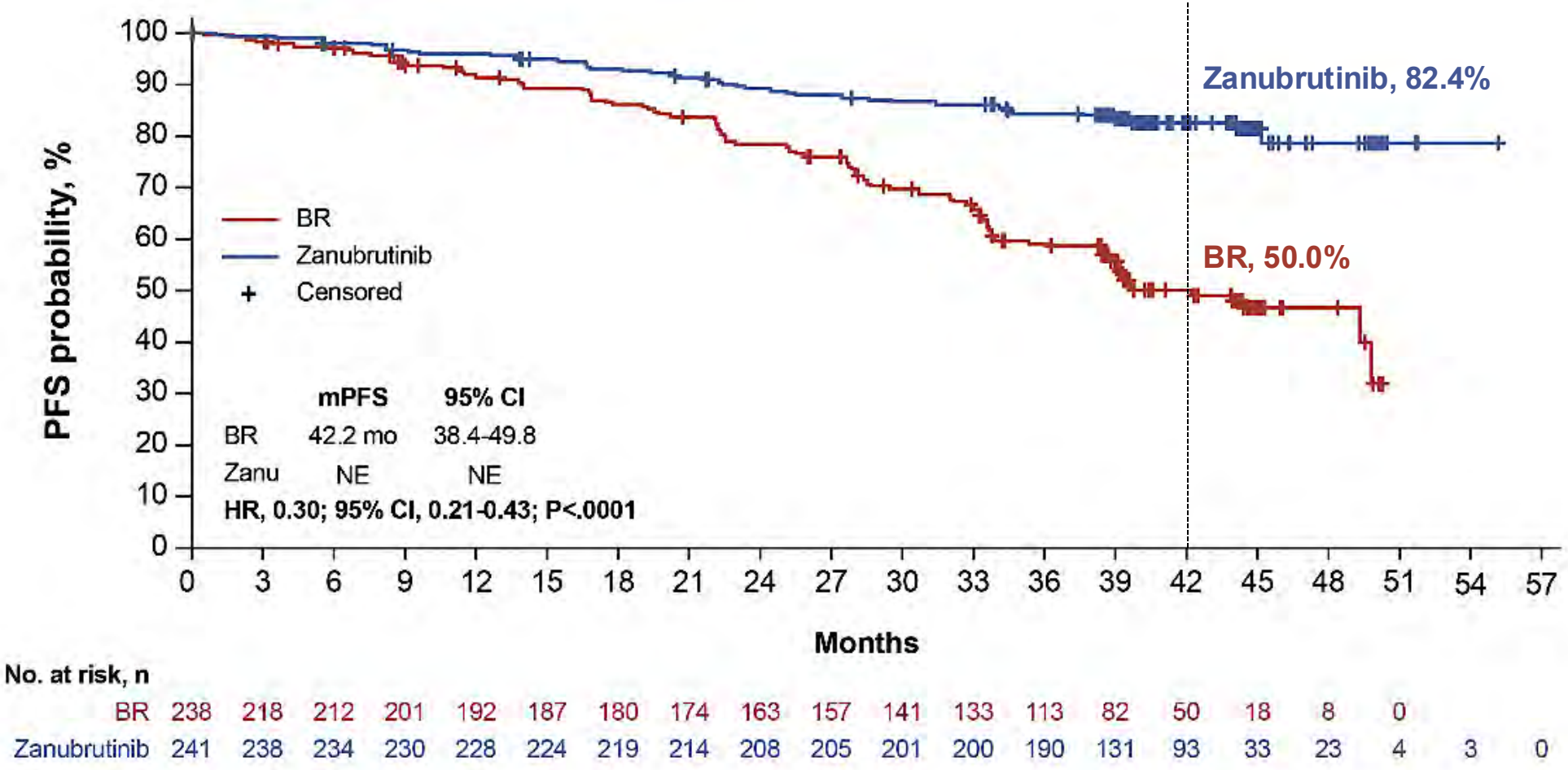
Study Design



Tam et al. Lancet Oncol. 2022 Aug;23(8):1031-1043.

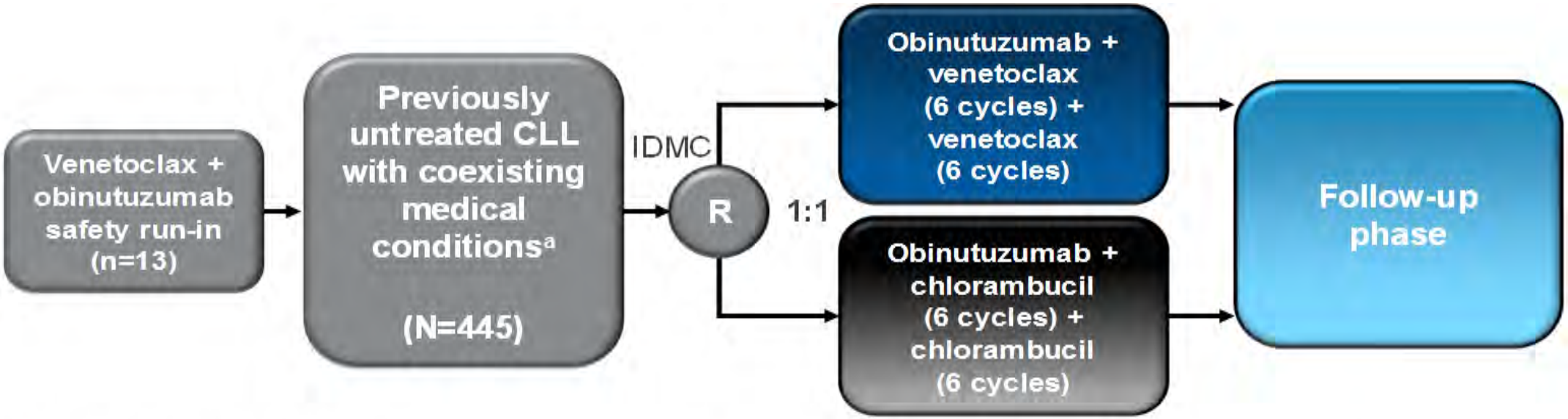
Cohort 1: PFS in Patients Without del(17p)

Median follow-up: 43.7 months



Munir et al. EHA 2023; Abstract P639

Venetoclax + G vs Clb + G: (CLL-14)



Primary endpoint:

- PFS as assessed by investigator[3]

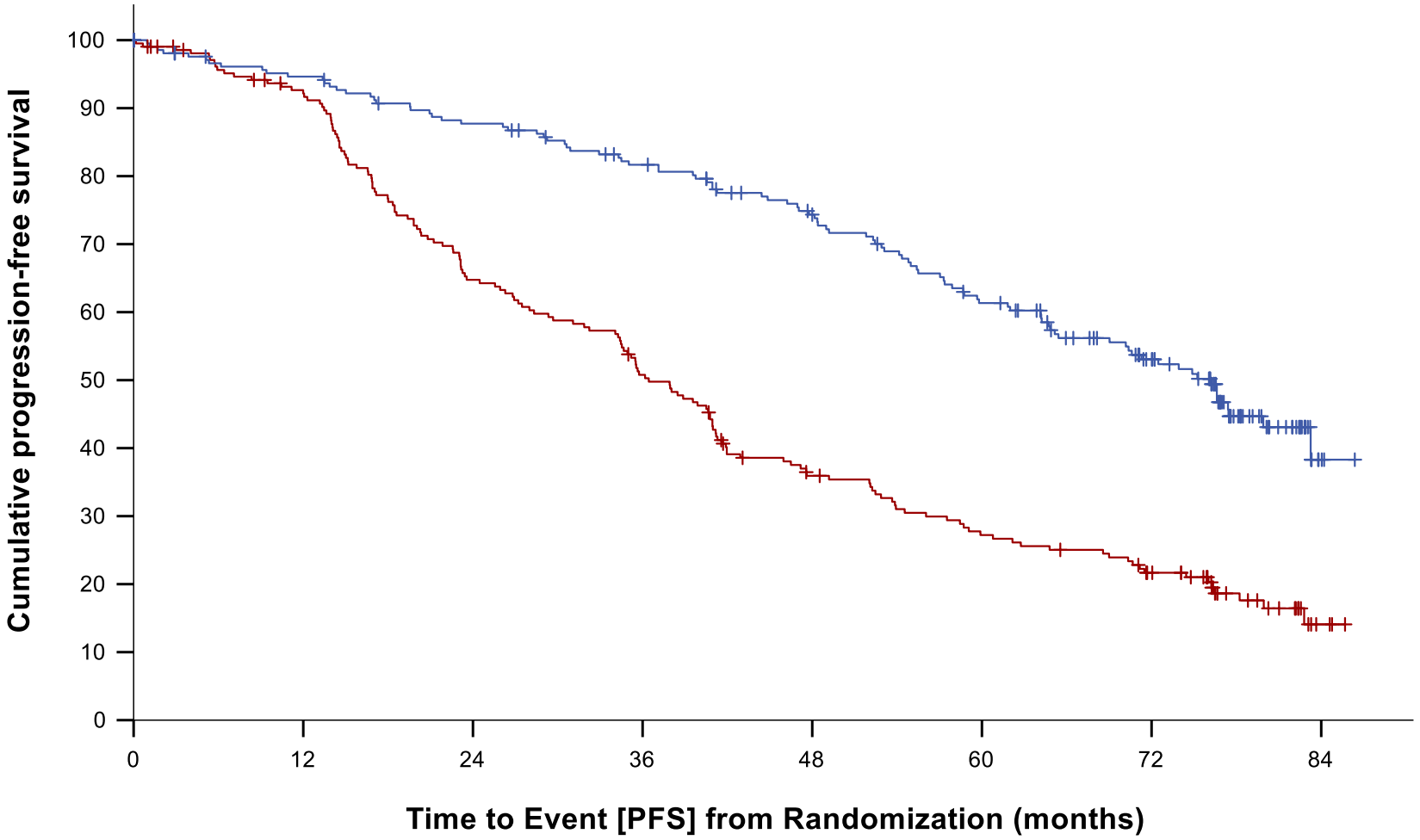
Secondary endpoints[3]:

- PFS as assessed by IRC
- MRD
- ORR
- CR rate
- DOR
- EFS
- OS
- TTNT
- Safety

[a]CIRS >6 and/or CrCl <70 mL/min

Fischer et al. N Engl J Med 2019;380:2225-2236

Venetoclax + G vs Clb + G: CLL-14 – 6-Year Follow-Up



Median PFS
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

6-year PFS rate
Ven-Obi: 53.1%
Clb-Obi: 21.7%

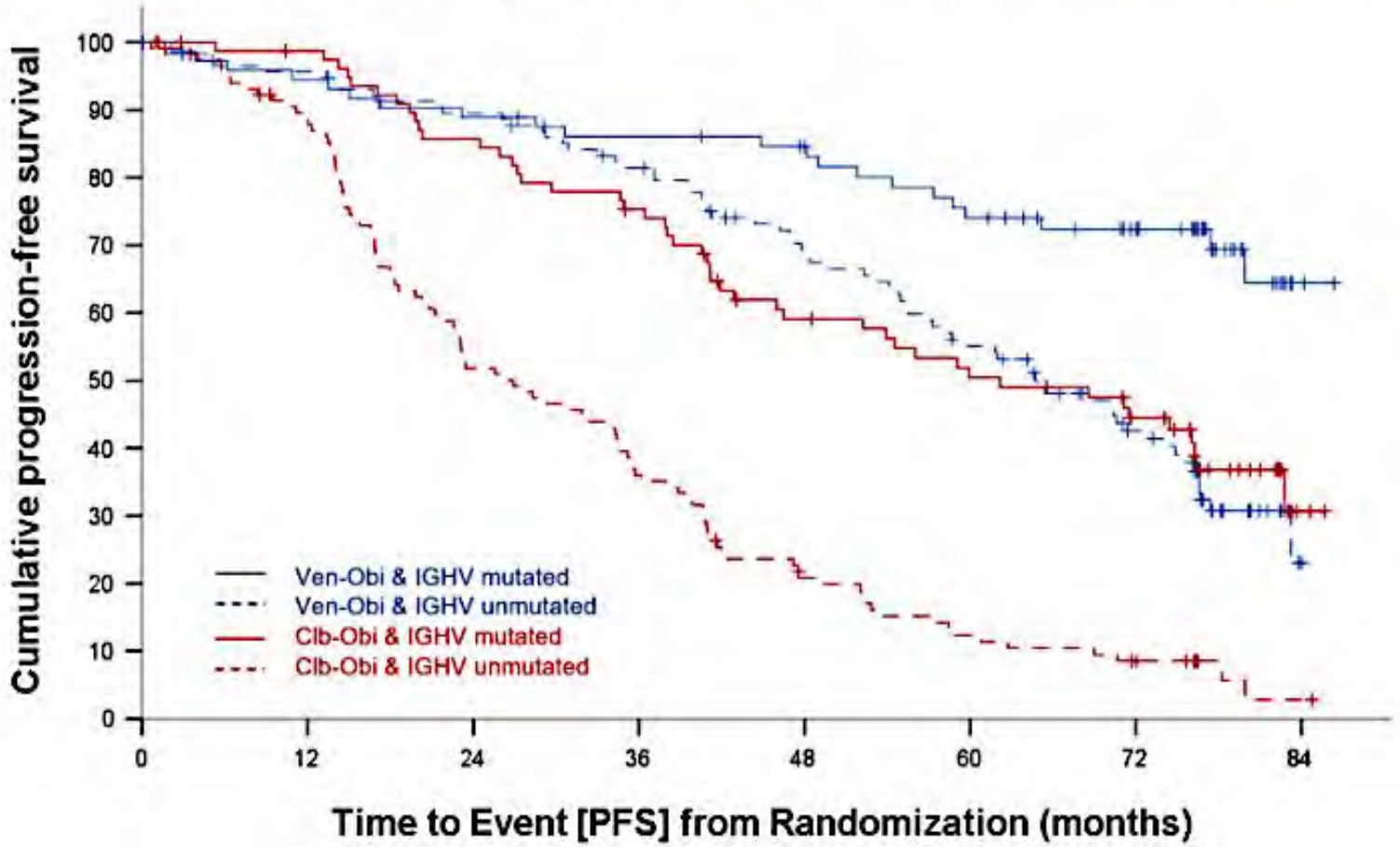
HR 0.40, 95% CI (0.31–0.52)
P <.0001

Al-Sawaf et al. EHA 2023; Abstract S145

Venetoclax + G vs Clb + G: CLL-14 – 6-Year Follow-Up

PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months



Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.8 m

HR 0.38, 95%CI [0.23-0.61], p<0.001

Clb-Obi & IGHVmut: 62.2 m

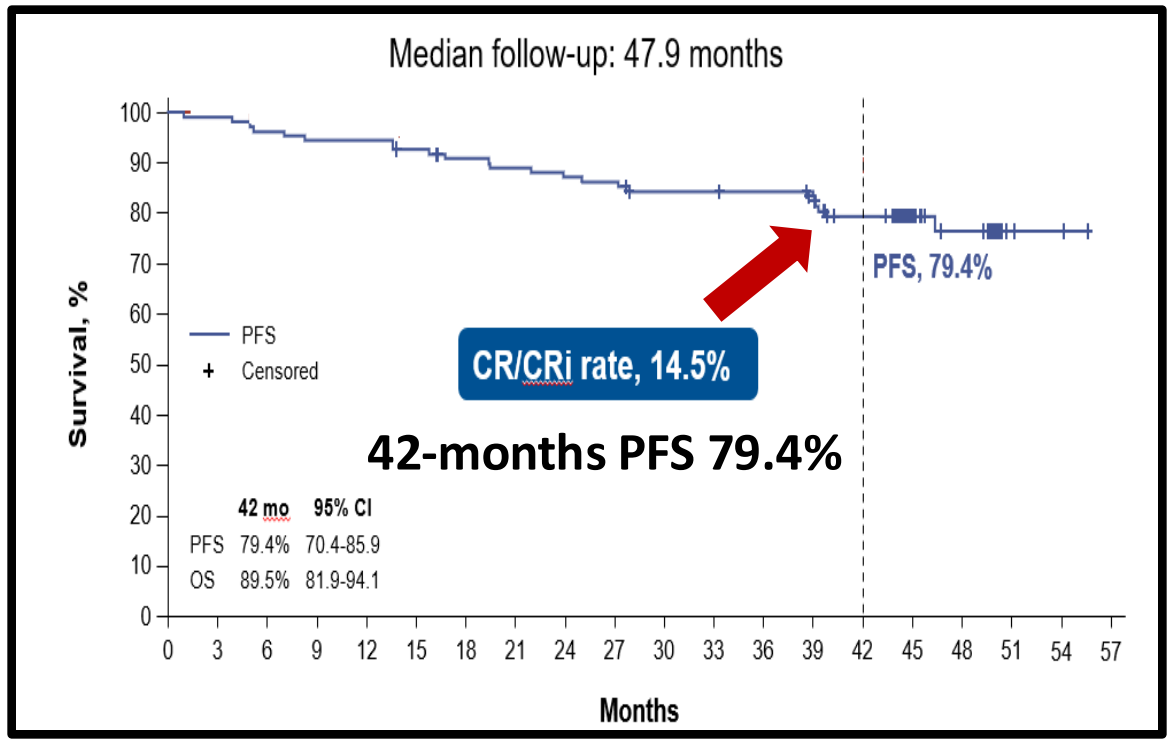
Clb-Obi & IGHVunmut: 26.9 m

HR 0.33, 95% CI [0.23-0.47], p<0.001

Al-Sawaf et al. EHA 2023; Abstract S145.

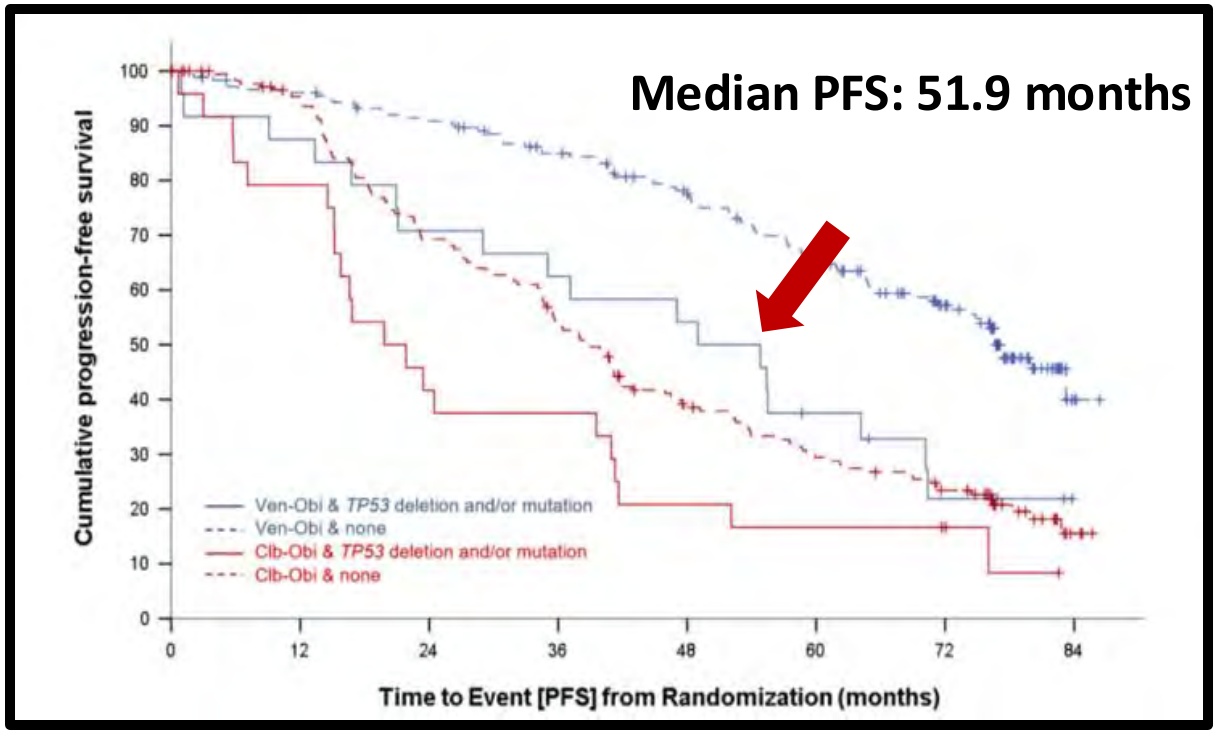
BTKi vs. Ven-Obin for first-line treatment in CLL patients with abnormal TP53

Zanubrutinib



Shadman, 17-ICML,2023

Venetoclax + Obinutuzumab



Al-Sawaf, EHA, 2023

Factors guiding therapy

- Does your patient prefer time limited therapy?
  - If yes, then Venetoclax-Obinutuzumab is done in 12 months
- Does your patient wish to avoid infusions and frequent monitoring?
  - BTKi is simpler than VO
- Does your patient have an underlying bleeding risk or need for anticoagulation?
  - Perhaps wish to avoid BTKi
- Does your patient have significant underlying renal impairment?
  - Increases risk for TLS, may wish to avoid VO and opt for BTKi
- Does your patient have a 17p del or p53 mutation?
  - BTKi appears to control disease better than time limited options

Ongoing questions

1. What about novel-novel combinations?
   - Acalabrutinib plus Venetoclax x 1 year (AMPLIFY trial)
2. Could MRD assessments guide therapy duration in a rational way?
   - CAPTIVATE and MAJIC may inform on this question
3. Are there newer "better" targeted agents on the horizon?
   - 3rd generation BTK inhibitors looking promising

What science can do · R&D · Our therapy areas · Our company · Careers · Investors · Media · Sustainability · Partnering

Fixed-duration acalabrutinib plus venetoclax, with or without obinutuzumab, significantly improved progression-free survival in 1st-line chronic lymphocytic leukaemia in AMPLIFY Phase III trial

PUBLISHED
29 July 2024

Pirtobrutinib for R/R CLL

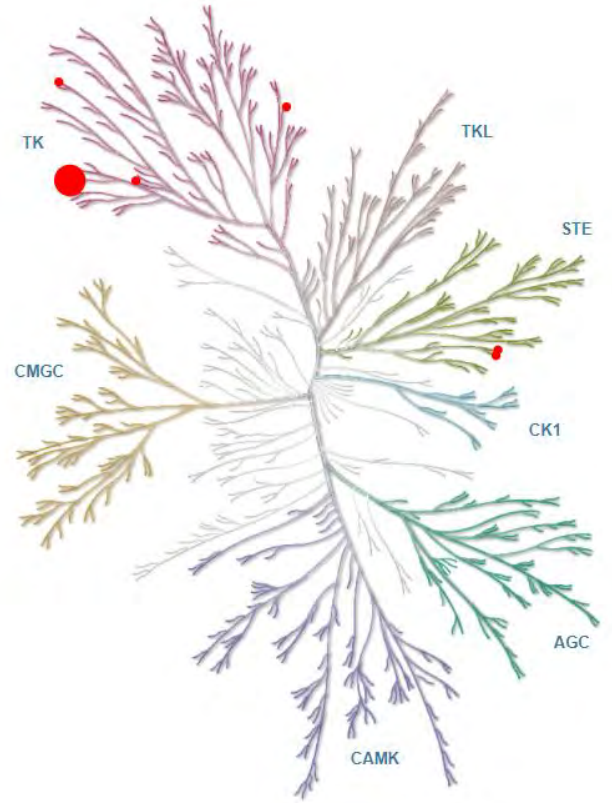
A third generation BTKi
Reversible (non-covalent) BTKi
High selectivity for BTK
Potency against WT & C481-mutant BTK in cell and enzyme assays

Phase 1/2 study included high-risk patients (n=261):

Prior BTKi 100% ; BTKi PD 77%
Prior Venetoclax 41%
Prior CAR-T 6%
BTK C481 mutant 38%
PLCG2 mutant 8%
Abnormal TP53 46% ; both del and mut 28%
Unmutated IGHV 84%

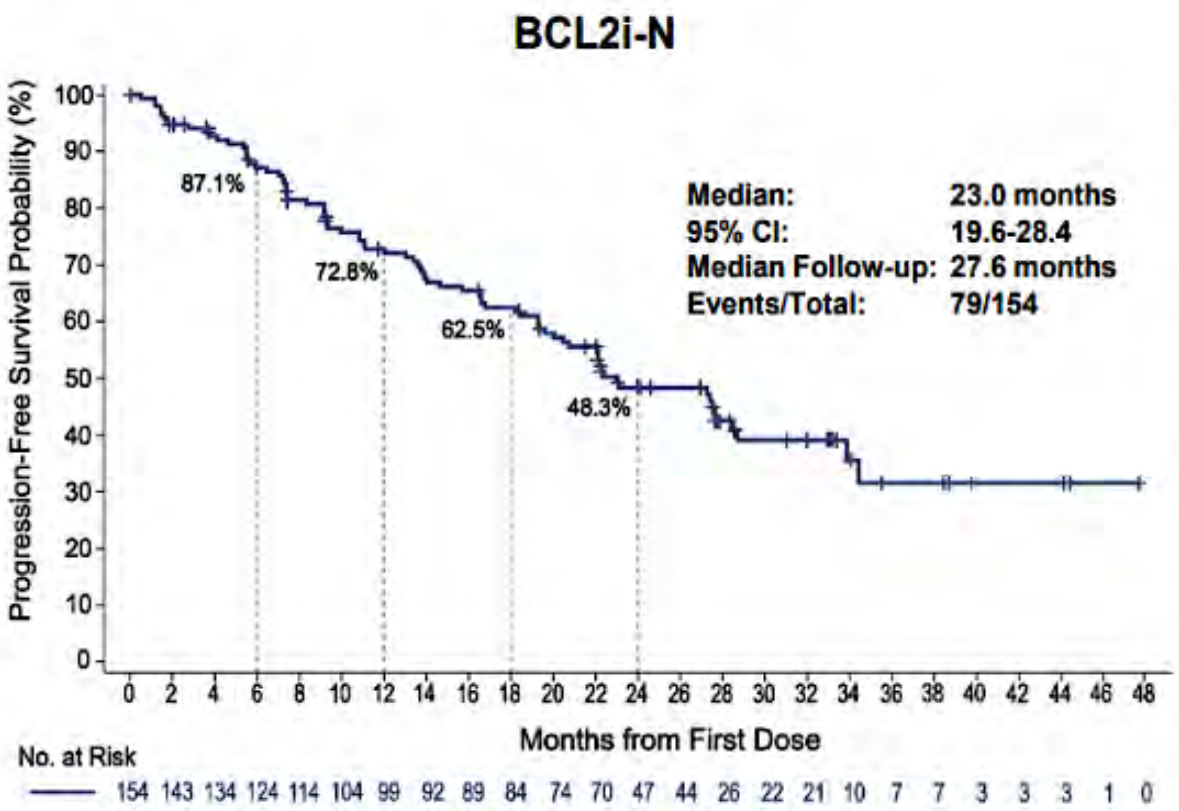
Mato et al. N Engl J Med 2023;389:33-44

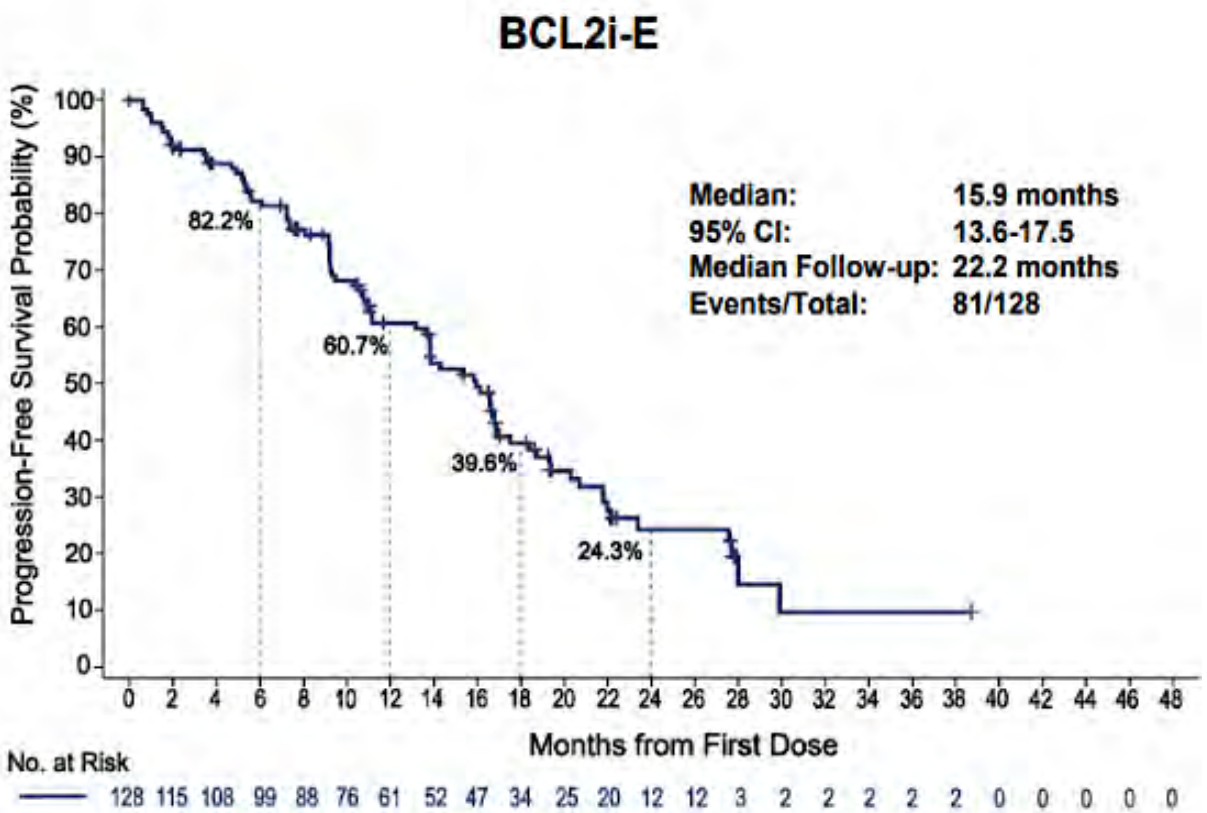
Kinome selectivity
Highly selective for BTK



Pirtobrutinib for R/R CLL

ORR: 82% in BTKi exposed





Mato et al. N Engl J Med 2023;389:33-44; Woyach et al. ASH 2023;Abstract 325

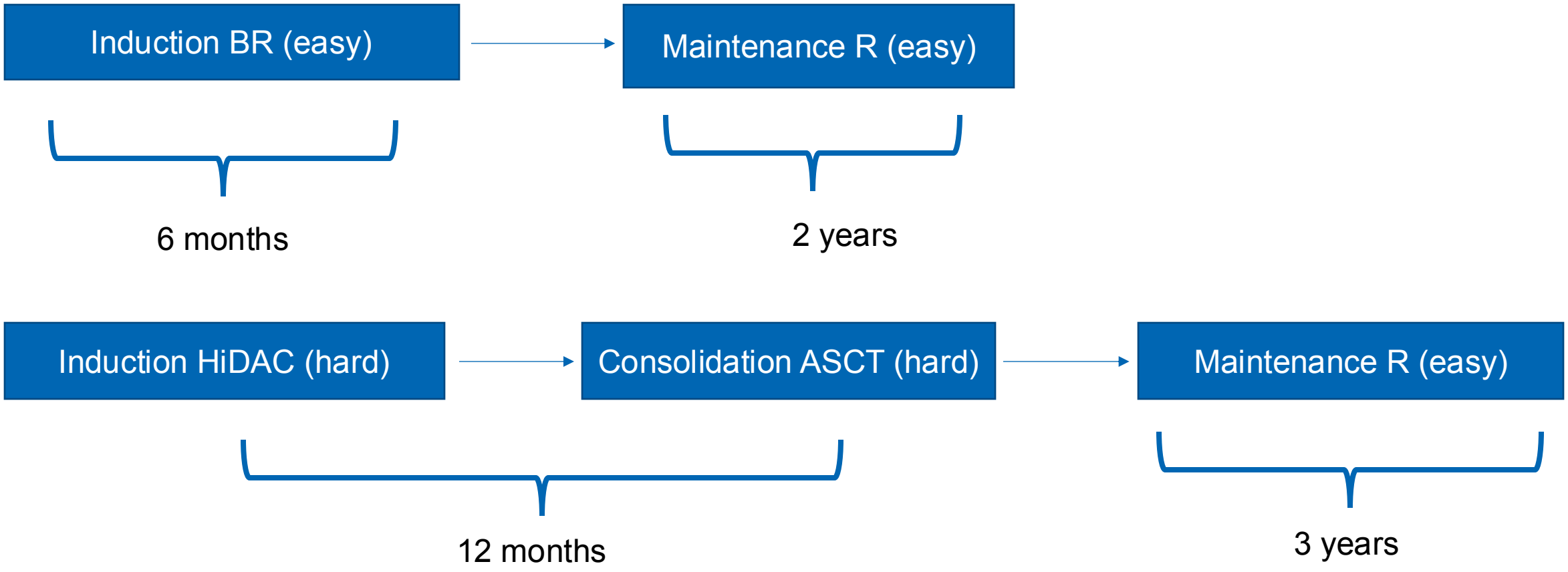
MCL: Reasonable Standards of Care in 2024

FRONTLINE MANAGEMENT

- Younger/Fit
  - High dose cytarabine containing induction
  - ASCT in 1st remission
  - Maintenance Rituximab for 3 years
  - **Did the TRIANGLE Study Just Change Everything?**

- Older/Less Fit
  - Bendamustine-Rituximab (BR) Induction + Maintenance Rituximab
  - **Will the ECHO Study Change SOC?**

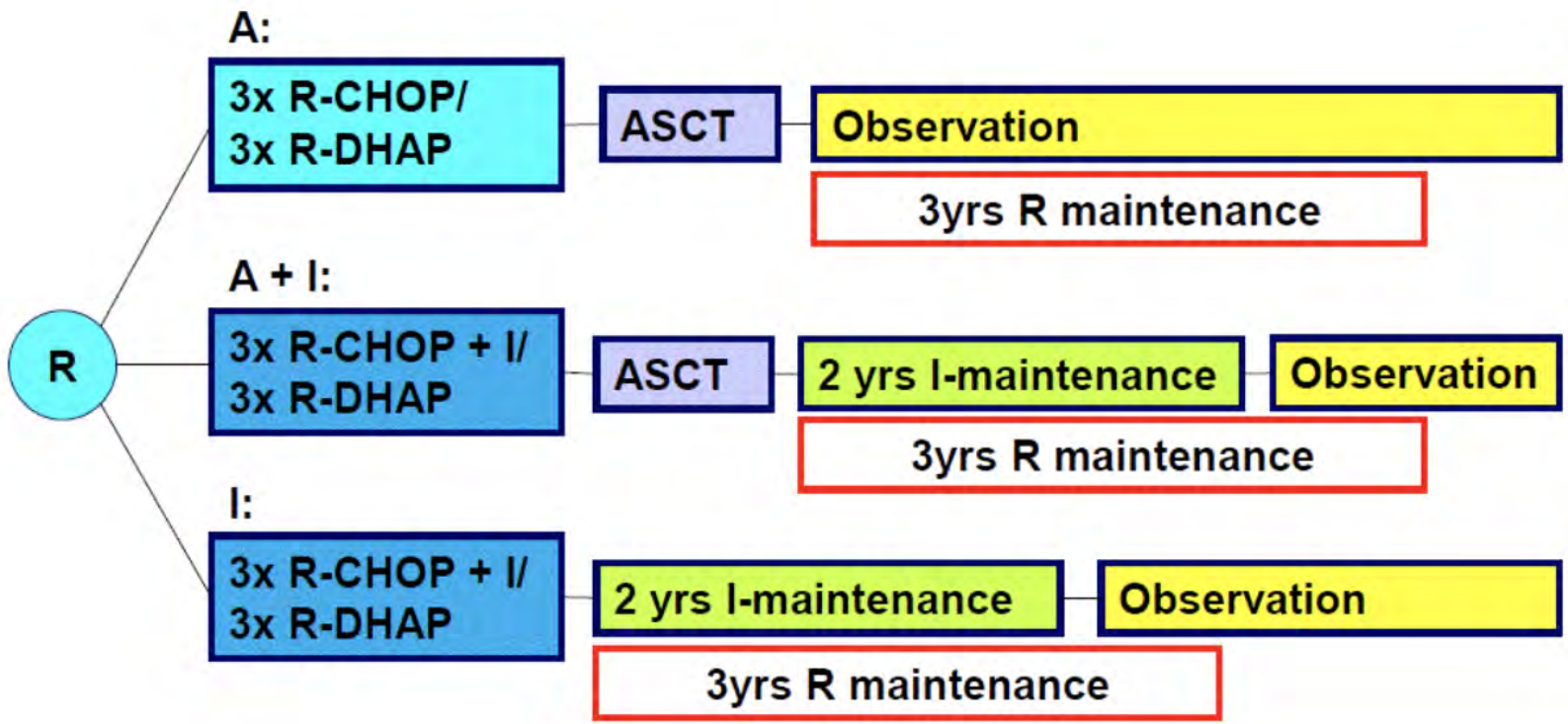
The difference between intensive and non intensive



Can be quite a decision for a 65 year old with typical MCL

TRIANGLE Trial (European MCL Network)

- Target 870 pts (290 per arm)
- Activated Oct 2017
- Completed accrual Dec 2020
- 1st results ASH 2022
- Published 2024



TRIANGLE Trial

- Ibrutinib containing arms improved FFS
- Not enough events to compare FFS of A+I to I
- Visually- curves very similar at 3 yrs
- Suggests that 2 years of BTKi obviates the need for ASCT for FFS benefit
- More toxicity/infections in A+I arm
- What should one do with this information?

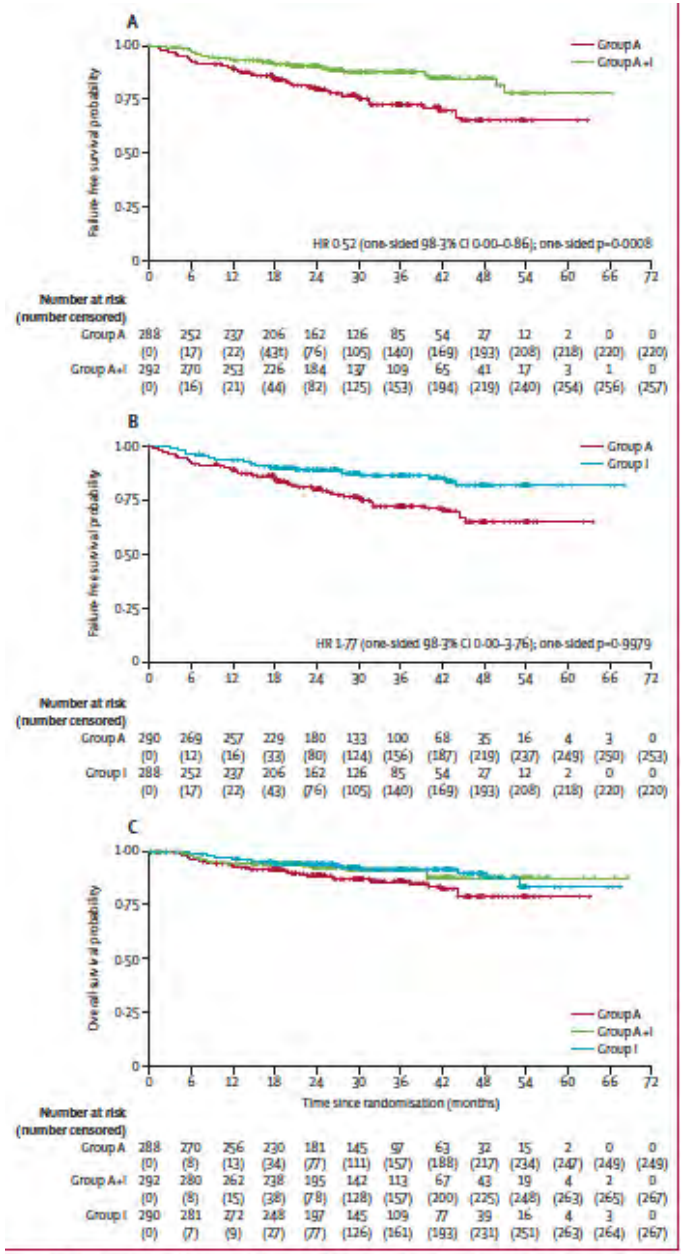


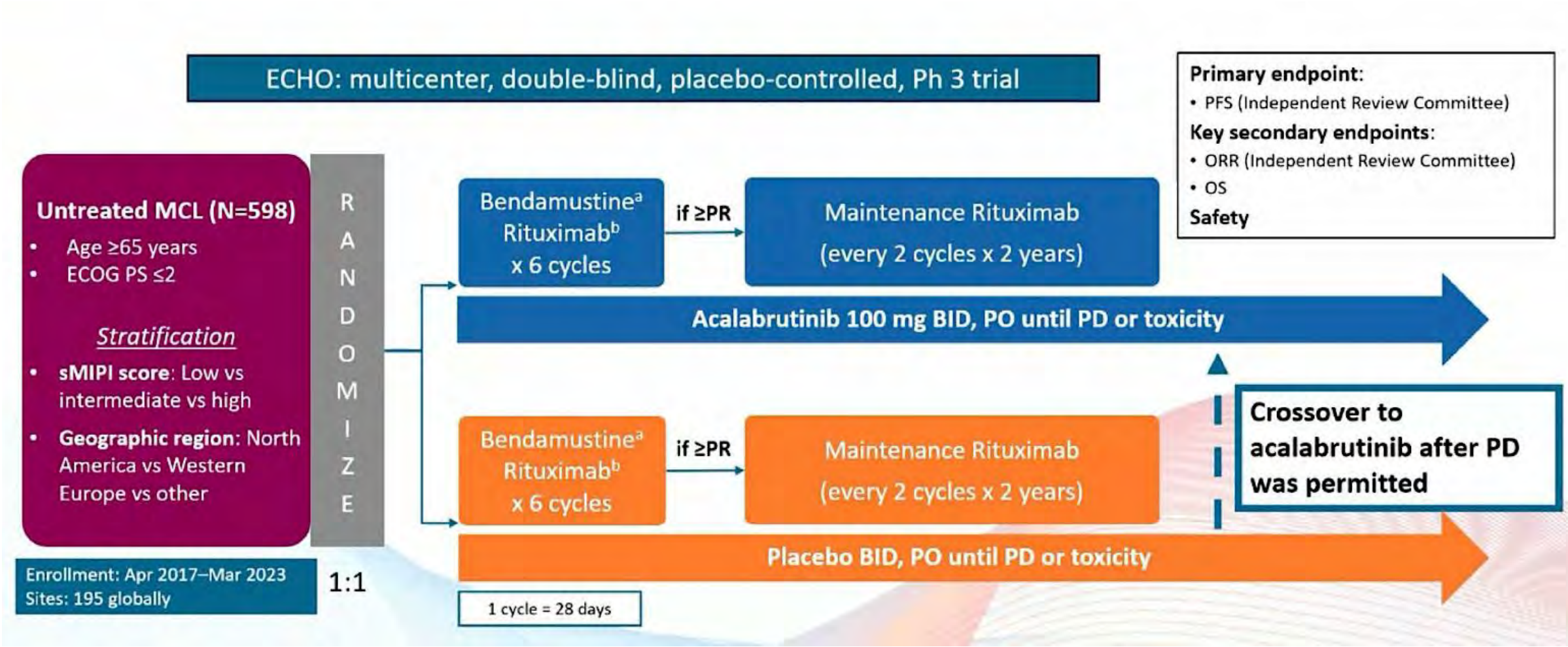
Figure 2: Failure-free survival for group A+I vs group A (A), group A vs group I (B), and overall survival for all treatment groups (C)

Dreyling et al. Lancet 2024; 403: 2293-306

TRIANGLE Trial Impact

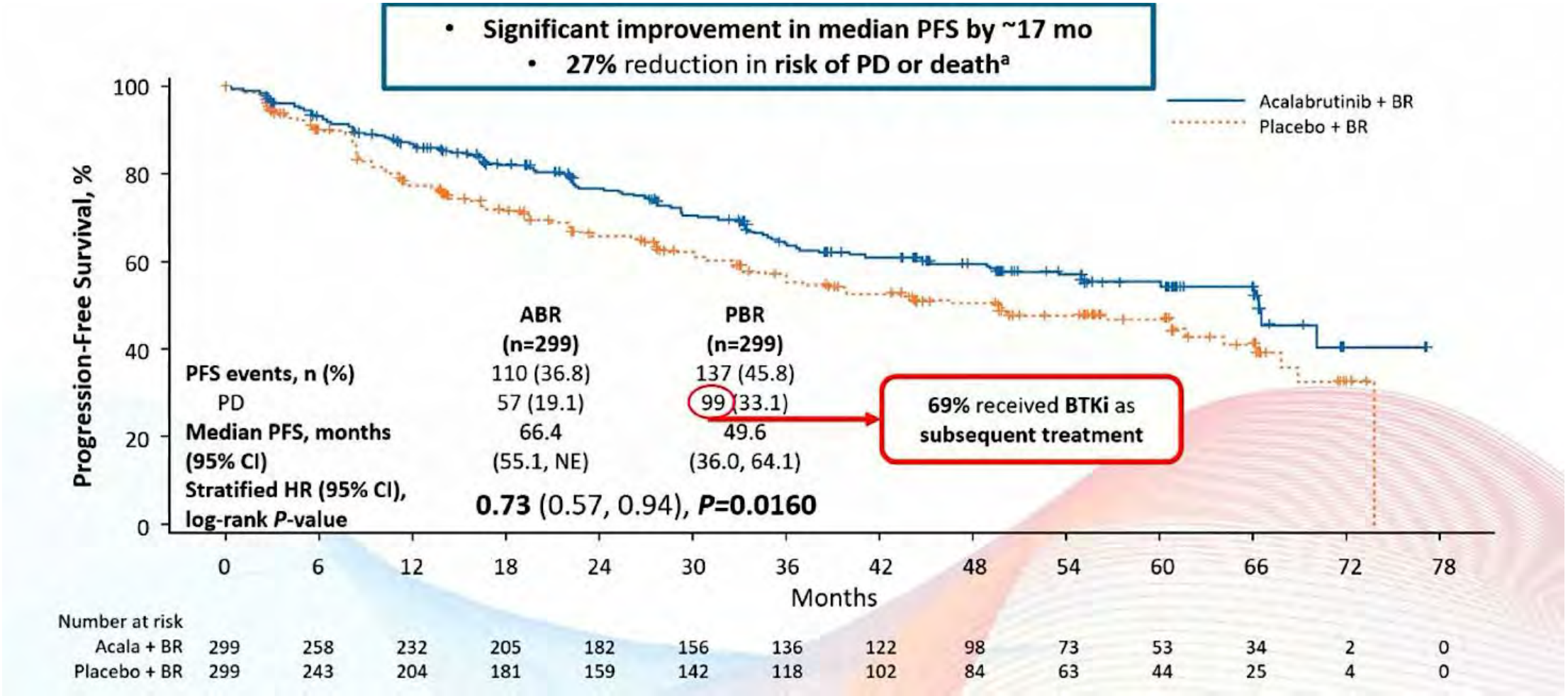
- Some US centers converted to BTKi minus ASCT immediately after ASH 2022
- Some US centers added BTKi and continued ASCT (A+I)
- My strategy was to wait for publication (May 2024)
  - I have converted to BTKi and no ASCT
  - Admittedly do not have true LTFU at this point
  - I anticipate more centers adopting this strategy (personal communication)
- Caveats
  - Ibrutinib pulled from US market in spring 2023
  - Must substitute acalabrutinib or zanubrutinib (NCCN guidelines just say BTKi)
  - I am comfortable with this extrapolation
- A major appeal here is the BTKi exposure is **TIME LIMITED**

ACALABRUTINIB PLUS BR IN MANTLE CELL LYMPHOMA: RESULTS FROM THE PHASE 3 ECHO TRIAL.



Wang et al. EHA 2024; Abstract LB3439

ECHO… ECHO…



Wang et al. EHA 2024; Abstract LB3439

ECHO Results in MCL

- No difference in OS
  - Fewer MCL deaths on Acala arm
  - More COVID deaths on Acala arm

- If Acalabrutinib gets approval in older MCL first-line, should you use it?
  - Tough call. PFS benefit without OS benefit
  - BTKi given until PD, meaning not available for 2nd line
  - Although now have Pirtobrutinib

- I do not see myself adopting this strategy
  - More appealing if time limited…

MCL Frontline Summary

MCL Younger

- Transplant may not be needed if adding 2 years of BTKi (TRIANGLE Trial)

MCL Older

- BR with R maintenance remains a good SOC
- Unclear if ECHO will change SOC

Why is BTKi OK in younger but not older MCL?

- Allowed subtraction of ASCT
- Was time limited in TRIANGLE

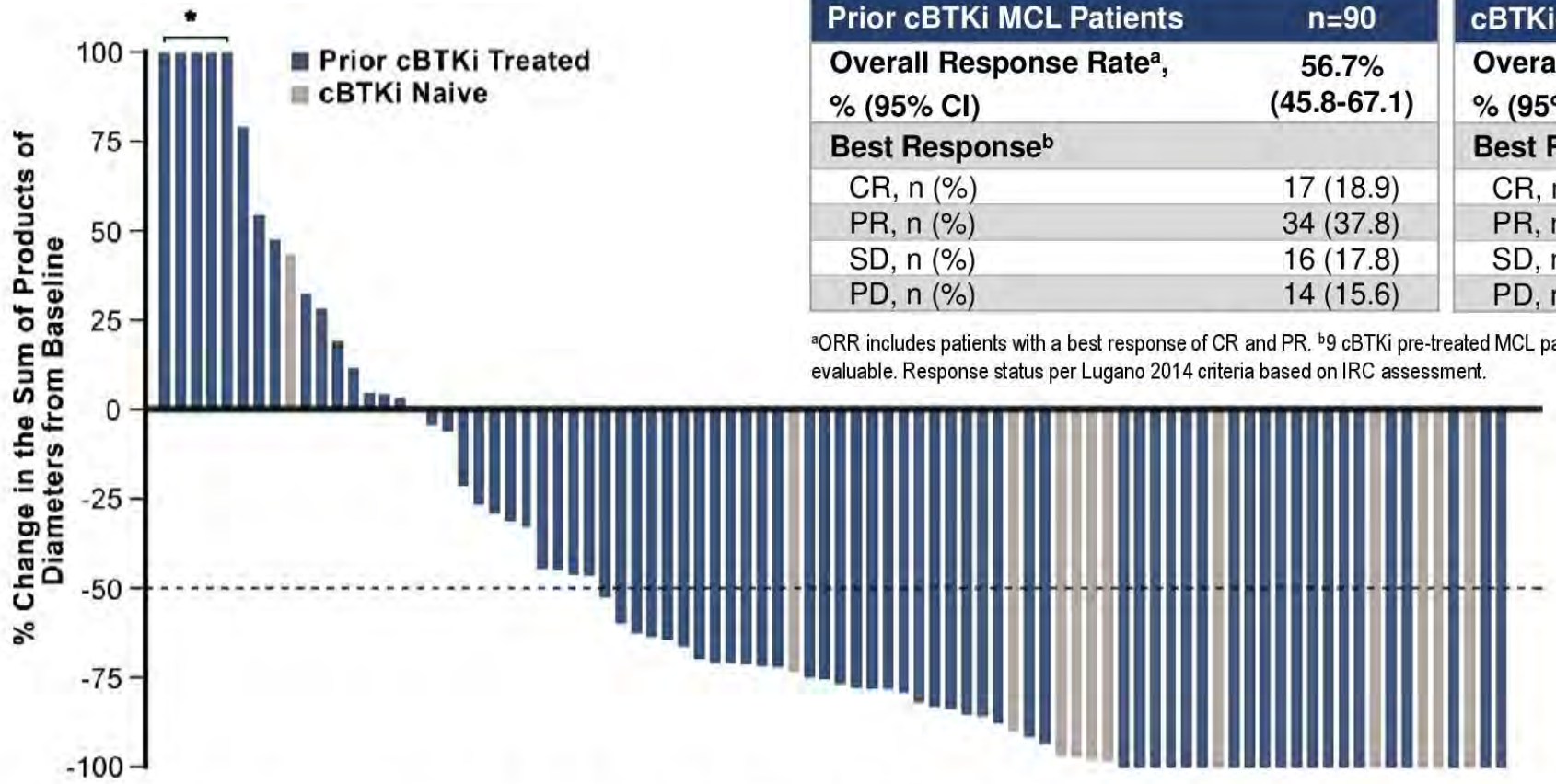
Novel Approaches for R/R MCL

Agent	N	Response Rate	mDOR
Bortezomib	155	33%	9.2 months
Lenalidomide	134	28%	16.6 months
Lenalidomide-rituximab	52	57%	18.9 months
Ibrutinib*	111	68%	18 months
Acalabrutinib	124	81%	24 months
Zanubrutinib	86	84%	36 months
Pirtobrutinib**	124	49%	18 months
Venetoclax*	28	75%	12 months
Ibrutinib-Venetoclax*	134	82%	42 months

*Not FDA approved in MCL

**Approved after covalent BTK failure

Pirtobrutinib: Responses in R/R MCL



Pirtobrutinib Efficacy in Patients with MCL Based on IRC Assessment

Prior cBTKi MCL Patients	n=90
Overall Response Rate[a], % (95% CI)	56.7% (45.8-67.1)
Best Response[b]	
CR, n (%)	17 (18.9)
PR, n (%)	34 (37.8)
SD, n (%)	16 (17.8)
PD, n (%)	14 (15.6)

cBTKi-Naïve MCL Patients	n=14
Overall Response Rate[a], % (95% CI)	85.7% (57.2-98.2)
Best Response[c]	
CR, n (%)	6 (42.9)
PR, n (%)	6 (42.9)
SD, n (%)	0 (0.0)
PD, n (%)	1 (7.1)

[a]ORR includes patients with a best response of CR and PR. [b]9 cBTKi pre-treated MCL patients were not evaluable. [c]1 cBTKi naïve patient was not evaluable. Response status per Lugano 2014 criteria based on IRC assessment.

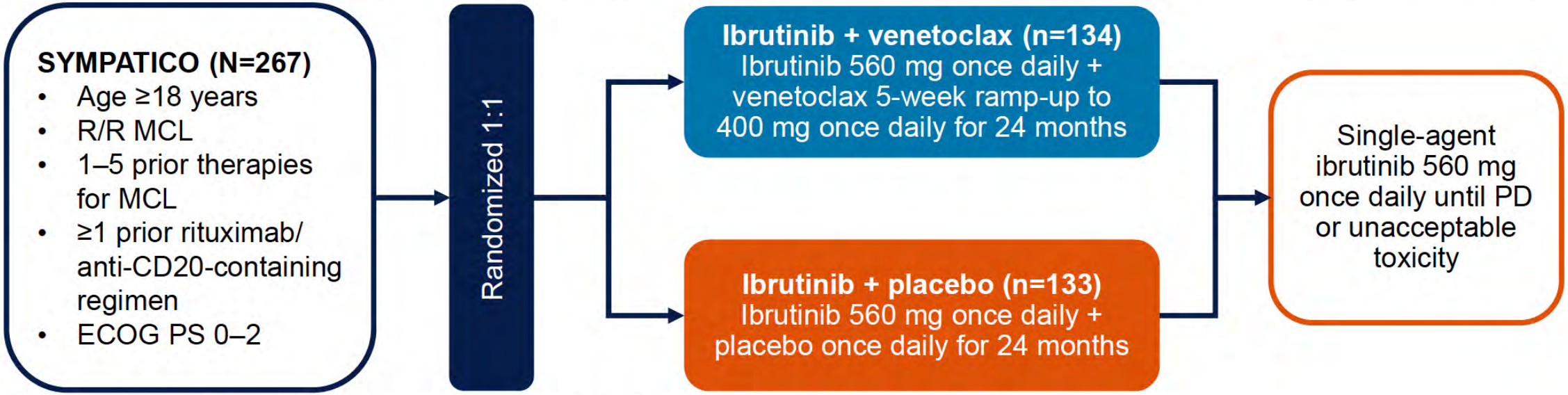
- ORR w/prior SCT (n = 19): 57.9% (95% CI: 33.5-79.7)
- ORR w/prior CAR T-cell (n = 4): 50% (95% CI: 6.8-93.2)

Data cutoff date of 29 Jul 2022. Data for 18 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD

Wang et al. *J Clin Oncol* 2023 January 20;41(3):555-67; Wang et al. ASH 2022;Abstract 4218; Shah et al. ASCO 2023;Abstract 7514.

SYMPATICO Study Design

- SYMPATICO (NCT03112174) is multinational, randomized, double-blind, placebo-controlled, phase 3 study

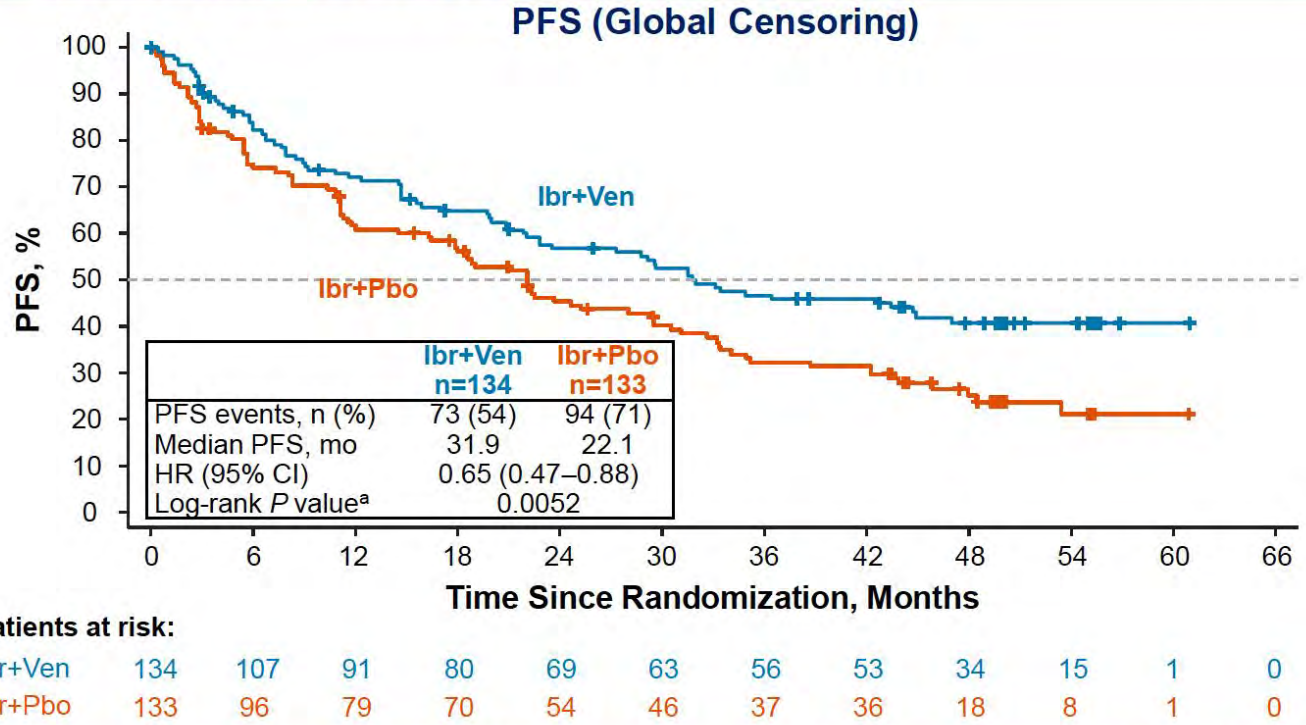


Stratification: ECOG PS, prior lines of therapy, TLS risk[a]

- **Primary endpoint:**
  - PFS by investigator assessment using Lugano criteria
- **Secondary endpoints (tested hierarchically in the following order):**
  - CR rate by investigator assessment
  - TTNT[b]
  - OS (interim analysis)
  - ORR by investigator assessment

Wang et al. ASH 2023; Abstract LBA-2

Primary Endpoint: Investigator-Assessed PFS Was Significantly Improved With Ibrutinib + Venetoclax Versus Ibrutinib + Placebo



Median PFS, mo	Global Censoring[b]				US FDA Censoring[c]			
	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]
Investigator assessment	31.9	22.1	0.65 (0.47–0.88)	0.0052	42.6	22.1	0.60 (0.44–0.83)	0.0021
IRC assessment	31.8	20.9	0.67 (0.49–0.91)	0.0108	43.5	22.1	0.63 (0.45–0.87)	0.0057

Wang et al. ASH 2023; Abstract LBA-2

Management of R/R MCL

- I typically start patients on BTKi (Zanu or Acala)
  - If achieve CR by 6 months, keep going
  - If only PR, start looking at CAR-T options
- Options not great when relapse after CAR-T
  - Pirtobrutinib
  - Trials
  - Glofitamab showing some activity
    - ORR 85%. CR 78%.
    - mPFS 16.8 months
- We definitely need more options for R/R MCL

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

AT THE FOREFRONT
UChicago Medicine

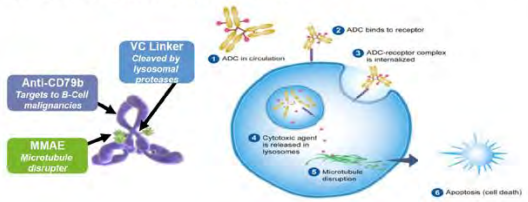
Updates in Diffuse Large B-Cell Lymphoma and Follicular Lymphoma

Sonali Smith, MD FASCO
Elwood V. Jensen Professor of Medicine
Chief, Section of Hematology/Oncology
Co-Leader, Cancer Service Line

Frontline DLBCL:
RCHOP has been the standard of care since 2002

POLARIX: randomized, double-blind, placebo-controlled phase 3 international trial of Pola-RCHP vs. R-CHOP in high-risk TN DLBCL

- Microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



Patients

- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

Stratification factors

- IPI score (2 vs 3–5)
- Bulky disease (<7.5 vs ≥7.5cm)
- Geographic region (Western Europe, US, Canada, & Australia vs Asia vs rest of world)

R 1:1

Pola-R-CHP

Polatuzumab vedotin (1.8mg/kg)*
R-CHP + vincristine placebo

Cycles 1–6
(1 cycle=21 days)

R-CHOP

R-CHOP† +
polatuzumab vedotin placebo

Rituximab
375mg/m²

Cycles 7 & 8

COO was *not* a stratification factor

PRIMARY ENDPT: PFS
Med f/u 28.2m

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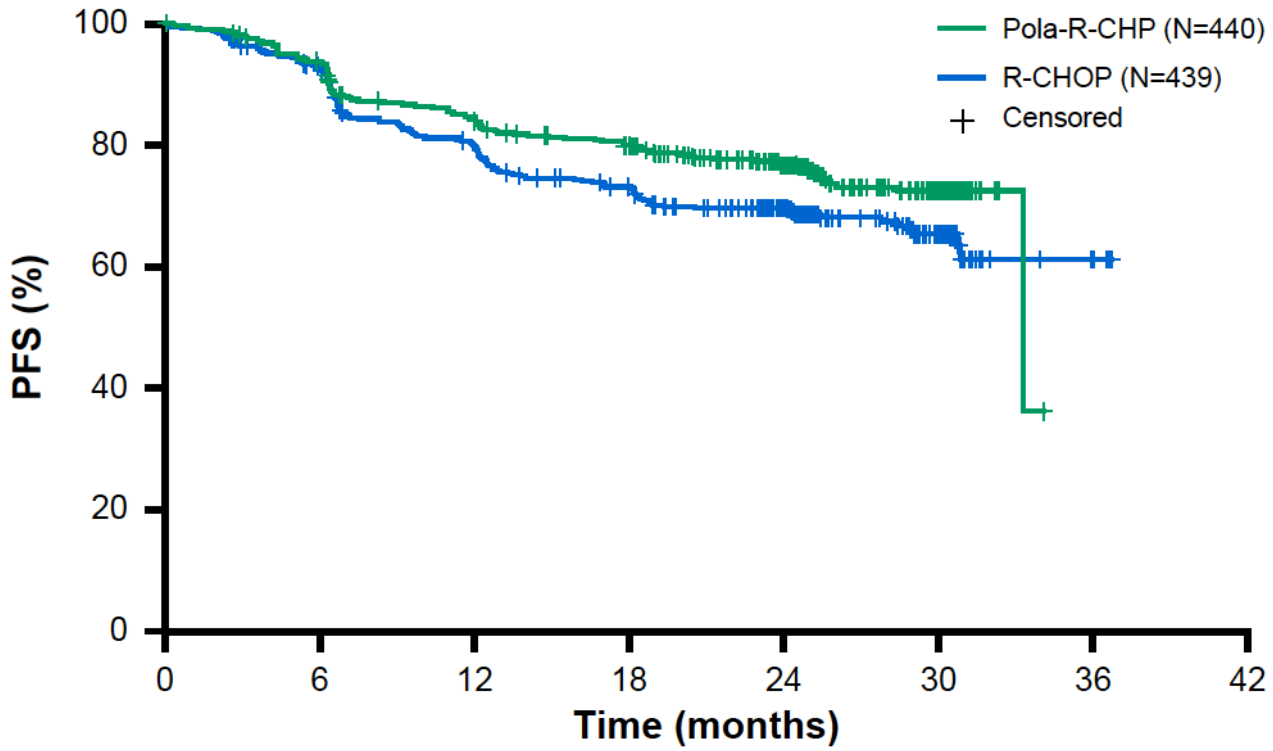
UChicago Medicine

Tilly N Engl J Med. 2022 Jan 27;386(4):351-363

POLARIX: primary endpoint of inv-assessed PFS was met (***1st positive trial in TN DLBCL since 2002***)



No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

HR 0.73 (P<0.02)
95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (Δ=**6.5%**)

Med f/u 28m
No difference in OS

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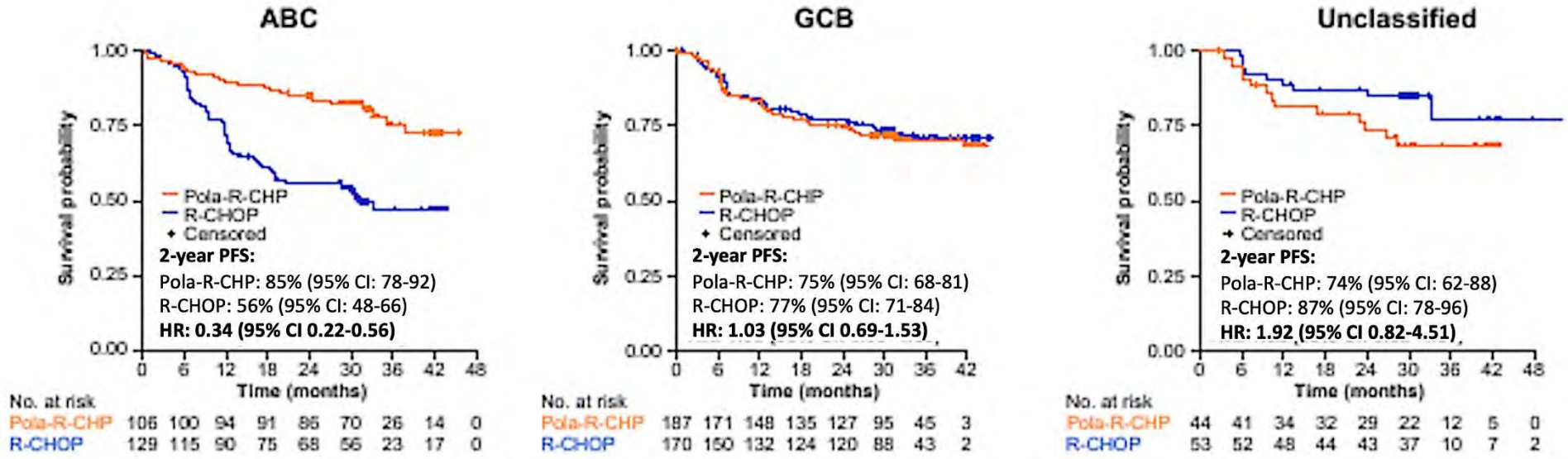
Tilly N Engl J Med. 2022 Jan 27;386(4):351-363

Pola-RCHP vs R-CHOP by cell of origin



CAVEATS:

- 25% of enrolled patients did not have COO assessment
- Not clear that COO designation for the primary publication was centrally determined
- Only ~one-third of patients had ABC subtype

Is cell-of-origin guided treatment selection ready for prime time?

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Russler-Germain Blood 2023 Dec 21;142(25):2216-2219;
Morchauser ASH 2023, abstract 3000

Peripheral Neuropathy: on-target effect of both polatuzumab vedotin AND vinca alkaloids

	Pola-RCHP	R-CHOP
PN any grade	52.9%	53.9%
PN > grade 1	13.8%	16.7%
Time to onset of PN	2.3m	1.9m
Time to resolution of PN	4m	4.6m
Discontinuation d/t PN	0.2%	0.9%
Dose reduction d/t PN	4.4%	8.0%

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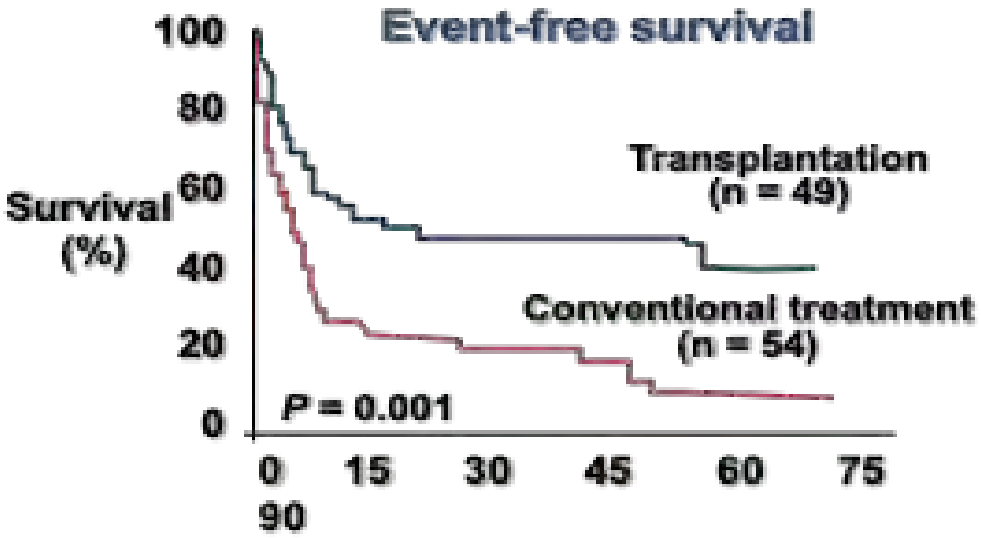
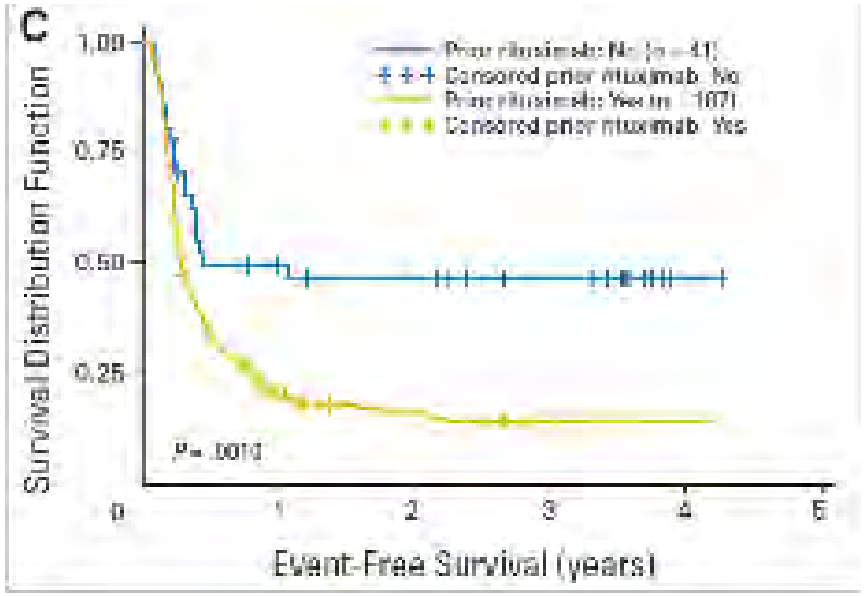
Tilly N Engl J Med. 2022 Jan 27;386(4):351-363

Rel/Ref large B-cell lymphoma

Second line DLBCL: More is better…until it's not





PARMA Trial:

High dose chemotherapy/autoHCT is better than standard chemotherapy

CORAL Trial:

prior rituximab and early relapse make HDT/autoHCT less effective

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RP3 Trials comparing CAR-T vs autoHCT in 2L DLBCL

ZUMA-7
Axicabtagene ciloleucel

TRANSFORM
Lisocabtagene maraleucel

BE NDA
Tisa en leucel

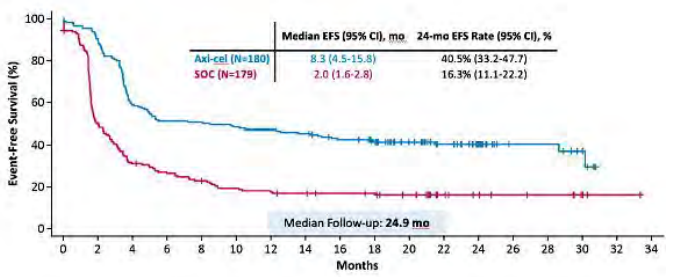
High-risk DLBCL/
B-cell lymphomas:
§ Refractory to first-line tx
§ Relapsed after first-line tx

CAR T-cell therapy

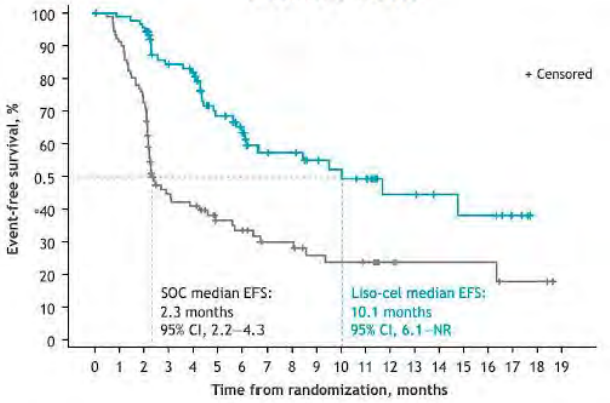
Salvage therapy/ auto-transplant

NCT03391466. NCT03570892. NCT03575351.

ZUMA-7



TRANSFORM



ZUMA-7

med EFS 2m vs 8.3m

OS 32% vs 65%

TRANSFORM

med EFS 2.3m vs 10.1m

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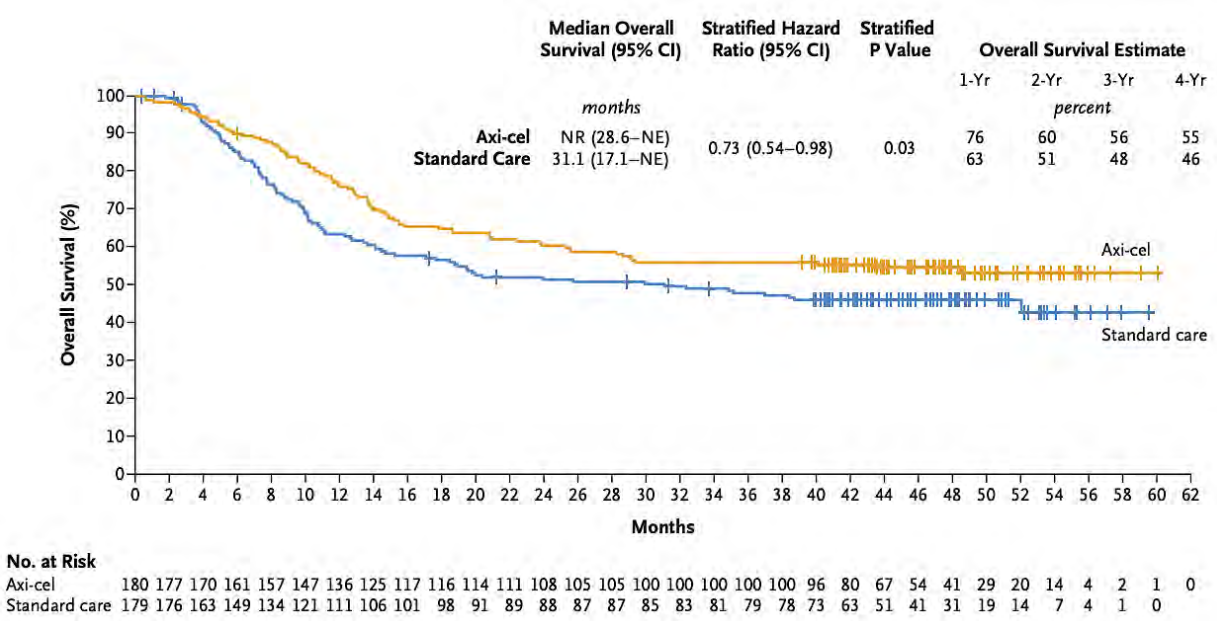
Locke FL, et al. *N Engl J Med*. 2021; Dec 11.
Kamdar M, et al. *Blood*. 2021;138(suppl 1):91.
Bishop MR, et al. *N Engl J Med*. 2021;Dec 14.

Does CAR-T retain superiority in 2L DLBCL with long-term follow up?



Efficacy outcomes (intent-to-treat set).

	Liso-cel Arm (n = 92)	SOC Arm (n = 92)
EFS[b]	29.5 (9.5–NR)	2.4 (2.2–4.9)
36-mo rate[c]	45.8 (35.2–56.5)	19.1 (11.0–27.3)
ORR[d]	80 (87) (78.3–93.1)	45 (49)(38.3–59.6)
CR rate[d]	68 (74) (63.7–82.5)	40 (43) (33.2–54.2)
PFS[b]	NR (12.6–NR)	6.2 (4.3–8.6)
36-mo rate[c]	50.9 (39.9–62.0)	26.5 (15.9–37.1)
OS[b]	NR (42.8–NR)	NR (18.2–NR)
36-mo rate[c]	62.8 (52.7–72.9)	51.8 (41.2–62.4)
DOR[b]	NR (16.9–NR)	9.1 (5.1–NR)

ZUMA-7: With med f/u 47.2m, superior OS for axi-cel over autoHCT

TRANSFORM: 3y EFS 29.5m vs 2.4m
3y PFS NR vs 6.2m
OS NR for both arms

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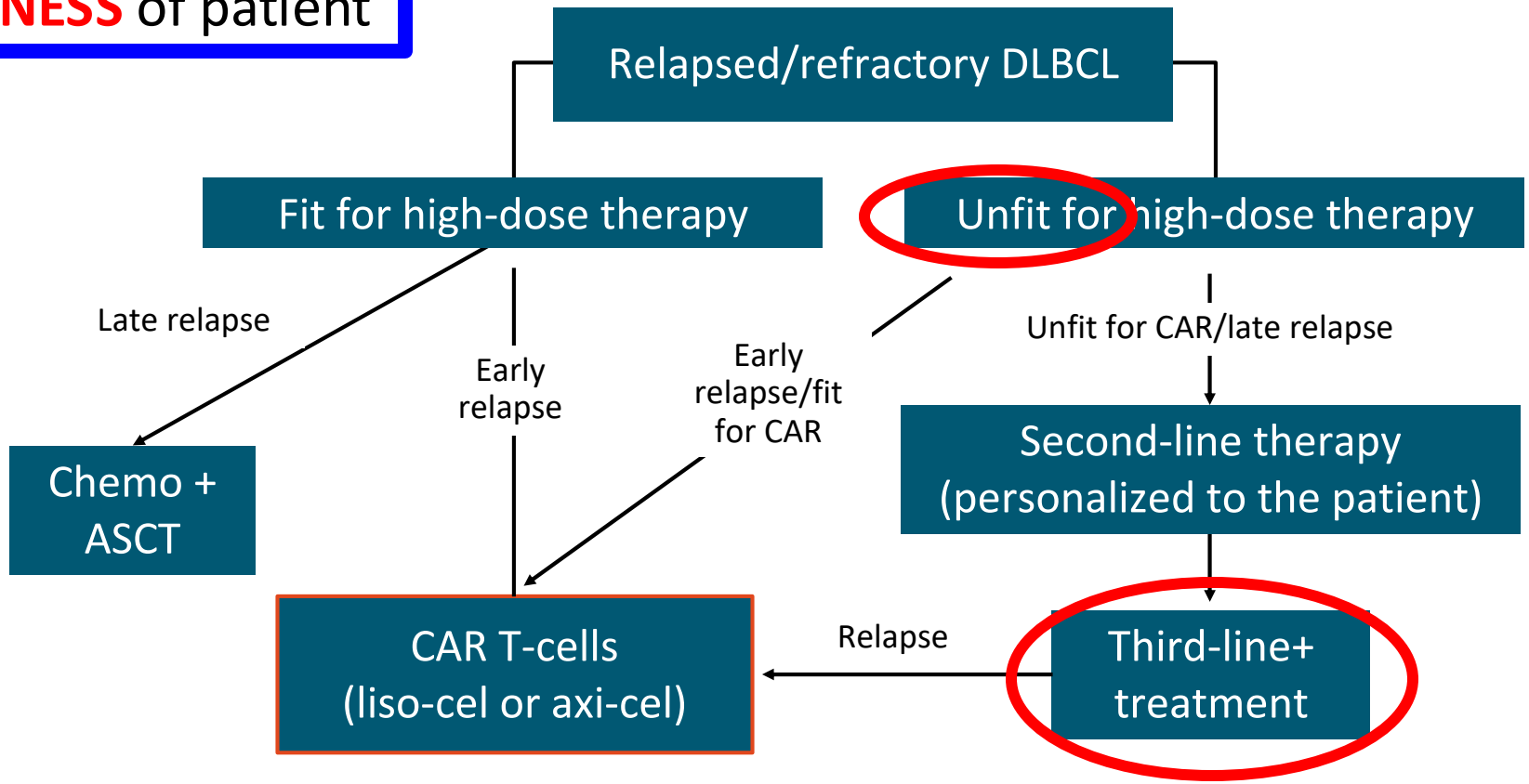
Kamdar ASCO 2024, Abstract 7013; Westin N Engl J Med 2023;389:148-157

A new algorithm for rel/ref DLBCL

TIMING of relapse
FITNESS of patient



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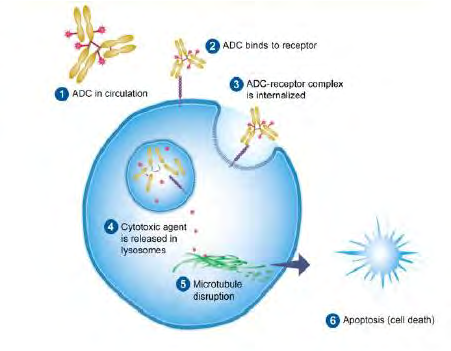
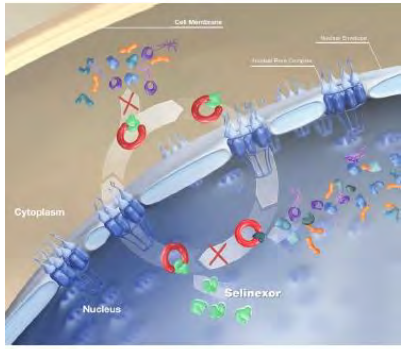
Slide courtesy of Michael Bishop

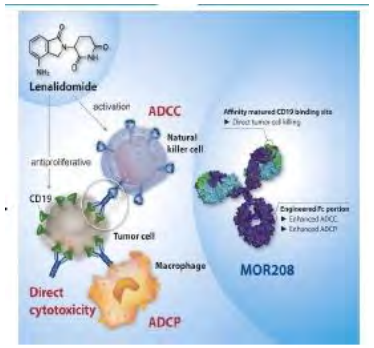
Options for rel/ref DLBCL if CAR-T is not an option



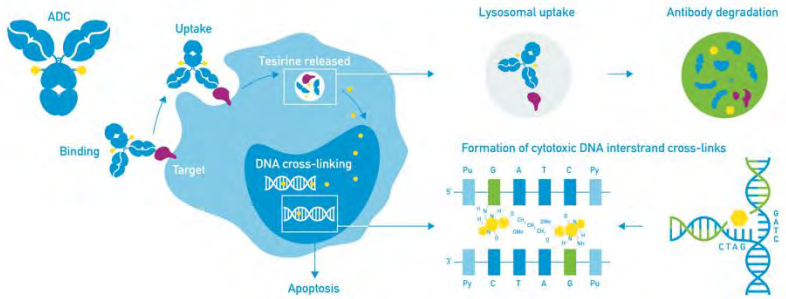
Polatuzumab vedotin (antiCD79 ADC) plus BR



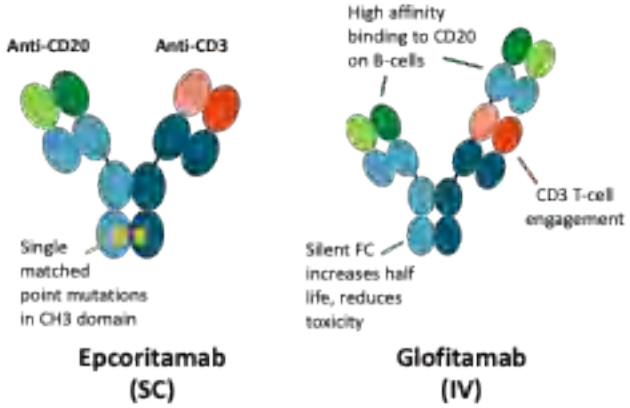
Selinexor (XPO1 inhibitor)



Tafasitamab (enhanced anti-CD19 moAb) plus lenalidomide



Loncastuximab tesirine (Anti-CD19 with PBD dimer payload)



CD20xCD3 bispecific antibodies

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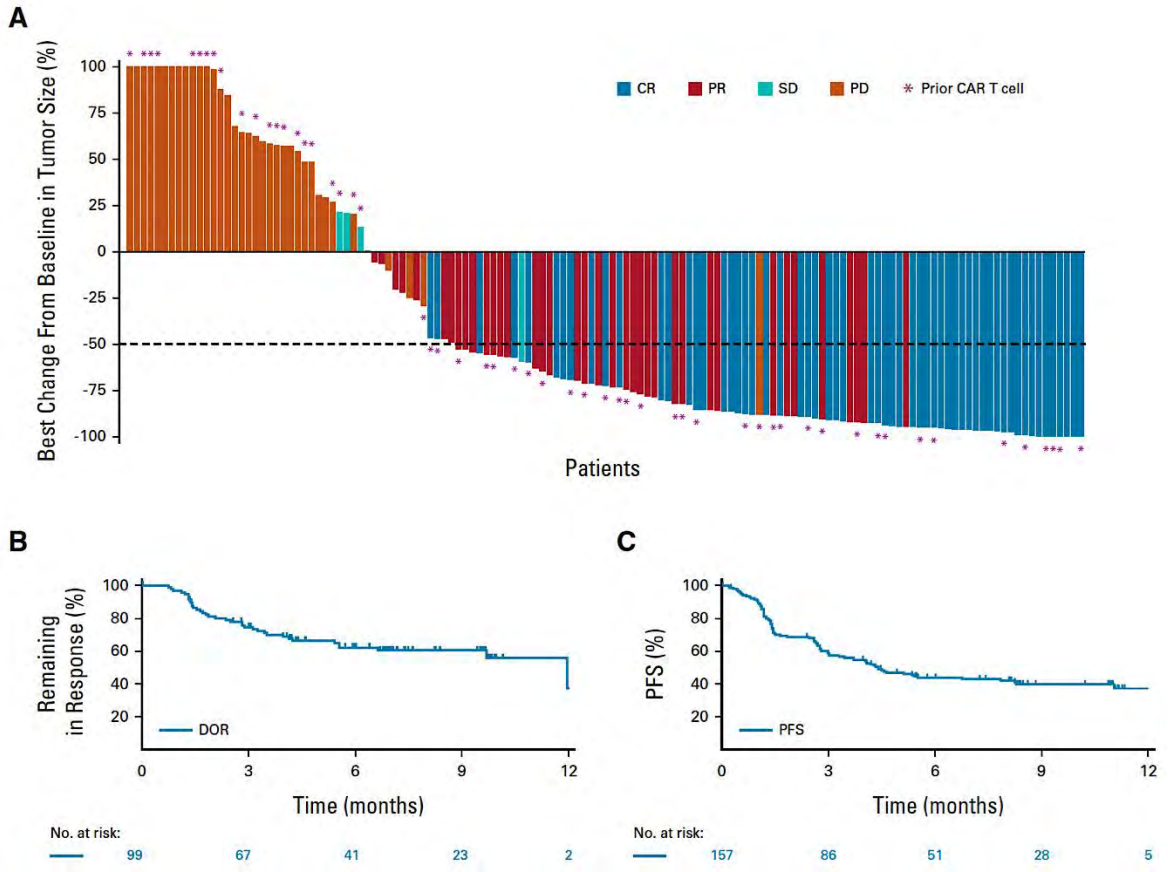
Subcutaneous epcoritamab in rel/ref DLBCL (phase I/II trial)



DOR **PFS**

- ~76% refractory to at least 2 lines of treatment
- ~40% with prior CAR-T
- 75% of prior CAR-T recipients progressed within 6 months

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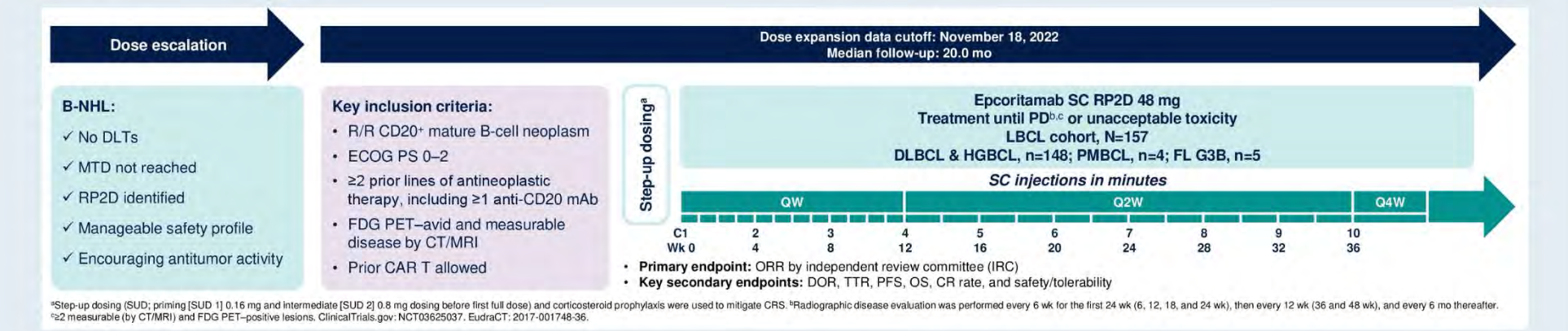
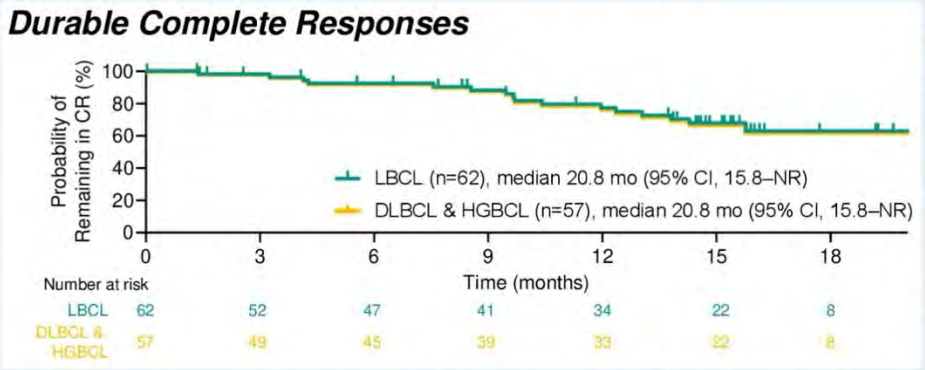
Thieblemont Journal of Clinical Oncology 41, no. 12 (April 20, 2023) 2238-2247.

Epcoritamab SC in aggressive B-cell lymphoma (med f/u 20m)





Best Overall Response, n (%)	DLBCL & HGBCL, n=148[a]	LBCL, N=157[a]
Overall response	90 (61) [95% CI, 53–69]	99 (63) [95% CI, 55–71]
Complete response	57 (39) [95% CI, 31–47]	62 (39) [95% CI, 32–48]
Partial response	33 (22)	37 (24)
Stable disease	5 (3)	5 (3)
Progressive disease	37 (25)	37 (24)

Based on IRC per Lugano criteria. [a]16 patients were not evaluable.

- The most common AE was CRS in 51% of patients (mostly grade 1-2), followed by neutropenia in 25% of patients.

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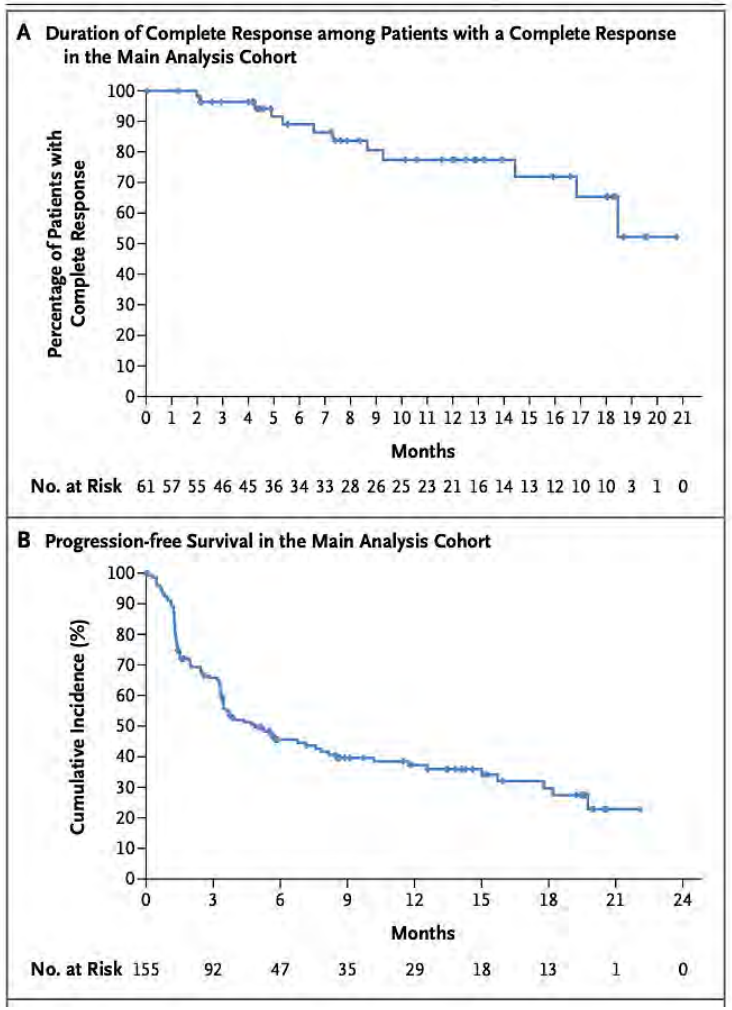
Karimi ASCO 2023, Abstract 7525

Glofitamab in 3L+ DLBCL: phase II

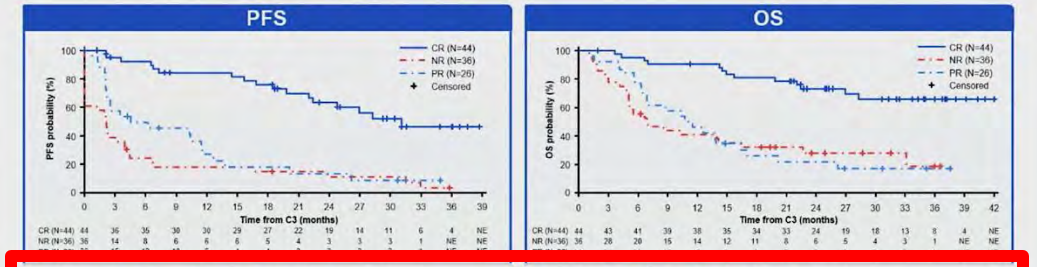


CRS Mitigation:
C1D1 Obinu 1000mg IV pre-treatment
C1D8 glofit 2.5mg
C1D15 glofit 10mg

C2D1+ glofit 30mg

Intravenous infusion
Fixed duration (12 cycles)
Obinutuzumab pre-treatment

Landmark analysis by response at Cycle 3

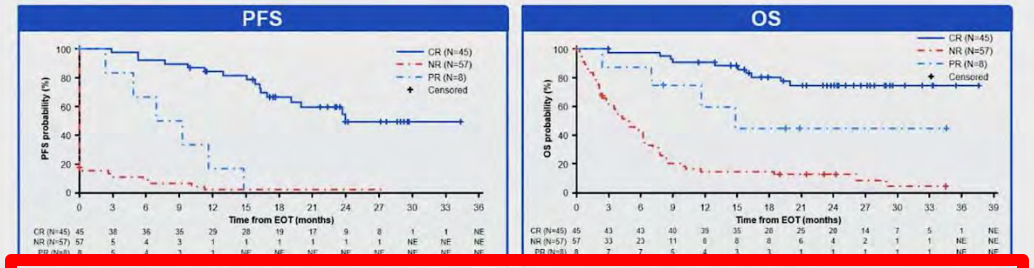


Landmark PFS from C3 in patients with CR at C3*	N=44	Landmark OS from C3 in patients with CR at C3*	N=44
Median PFS, months (95% CI)	31.1 (22.4–NE)	Median OS, months (95% CI)	NE (NE)
24-month PFS rate, % (95% CI)	63.5 (47.5–79.6)	24-month OS rate, % (95% CI)	73.4 (59.9–87.0)

A high proportion of patients with a CR at C3 remained progression-free and alive after 24 months

*KM estimates. NR, no response.

Landmark analysis by response at EOT



Landmark PFS from EOT in patients with CR at EOT*	N=45	Landmark OS from EOT in patients with CR at EOT*	N=45
Median PFS, months (95% CI)	24.0 (19.1–NE)	Median OS, months (95% CI)	NE (NE)
18-month PFS rate, % (95% CI)	66.6 (51.0–82.2)	18-month OS rate, % (95% CI)	80.7 (68.6–92.8)

Majority of patients with a CR at EOT remained progression-free and alive at 18 months after EOT

*KM estimates.
EOT, end-of-treatment; NR, no response.

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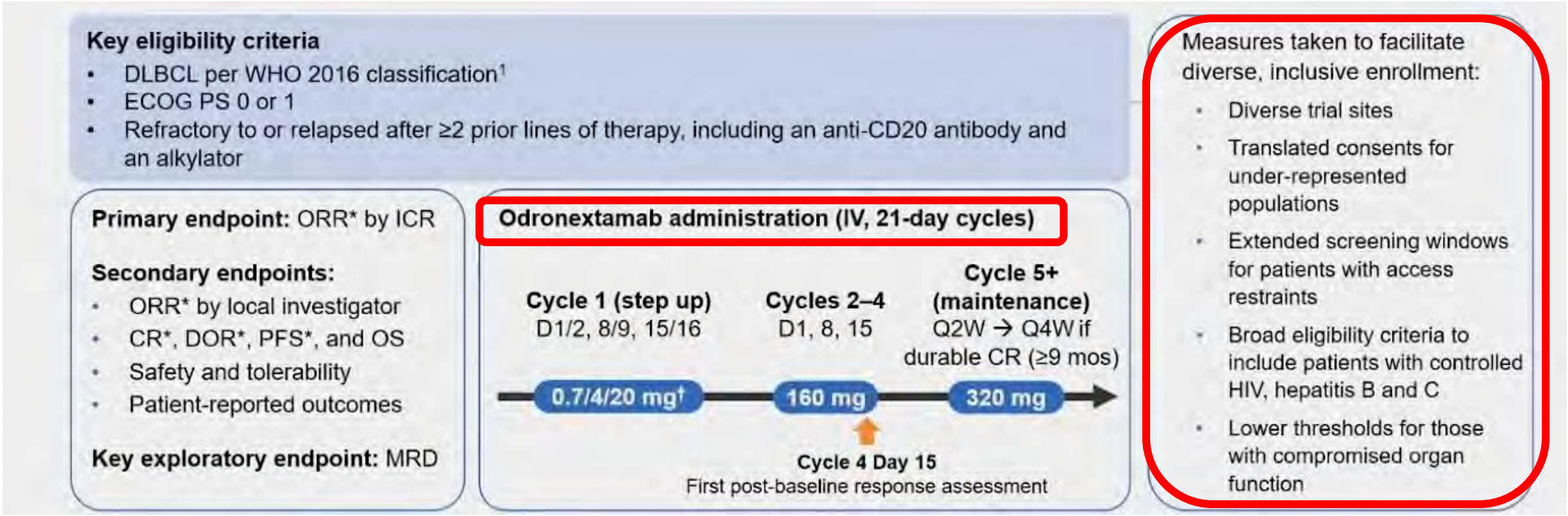
Hutchings ASH 2023, Abstract 433; Dickinson December 15, 2022 N Engl J Med 2022; 387:2220-2231

Odronextamab: phase II trial in rel/ref DLBCL (ELM-2)



- Med age 67y (range, 24-88)
- 24% ≥ 75y
- Prior tx 2 (range, 2-8)
- 86% refractory to last line of treatment

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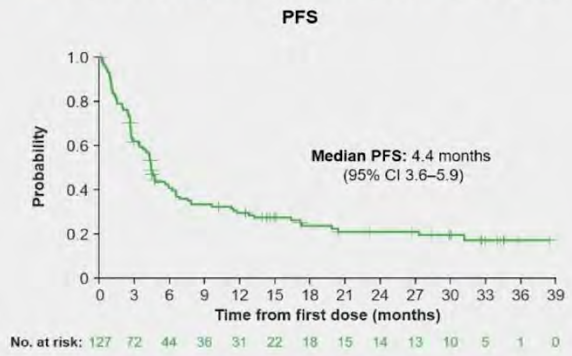
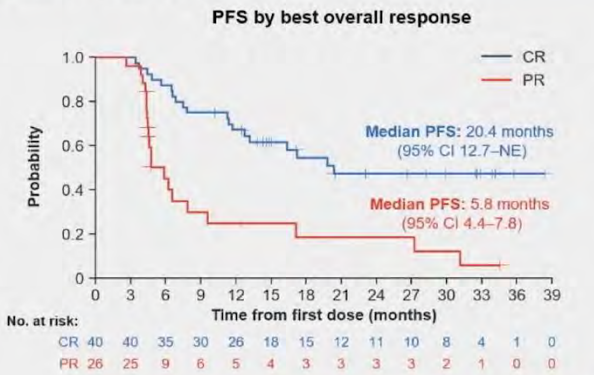
Ayyapan ASH 2023; Abstract 436

Odronextamab in 3L+ DLBCL: PFS and OS (med f/u 26.2m)

ELM-2: Progression-free survival

- Median PFS was 20.4 months in complete responders versus 5.8 months in partial responders



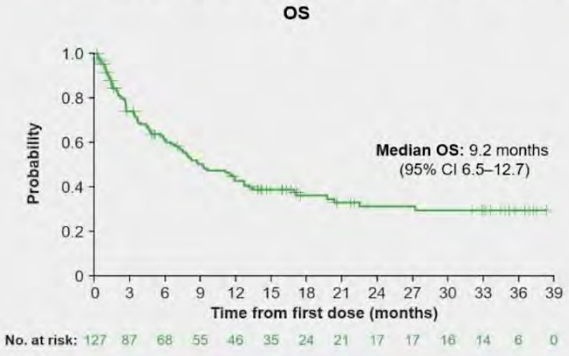


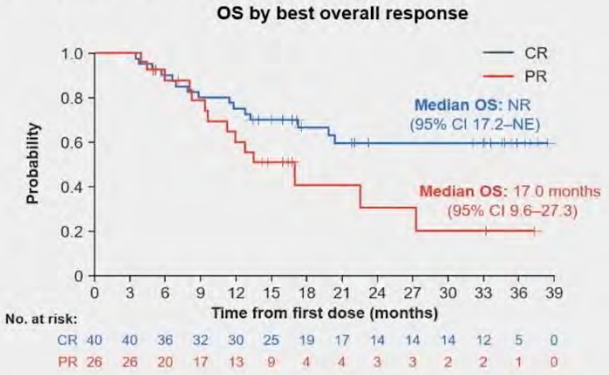
	N=127
12-month PFS rate, % (95% CI)	29.6 (21.5–38.2)
24-month PFS rate, % (95% CI)	21.1 (13.7–29.7)

	CR (n=40)	PR (n=26)
12-month PFS rate, % (95% CI)	67.2 (50.3–79.5)	25.2 (9.5–44.7)
24-month PFS rate, % (95% CI)	47.5 (29.9–63.1)	18.9 (5.4–38.6)

ELM-2: Overall survival

- Median OS was not reached in complete responders versus 17.0 months in partial responders





	N=127
12-month OS rate, % (95% CI)	42.9 (33.7–51.8)
24-month OS rate, % (95% CI)	31.6 (22.4–41.1)

	CR (n=40)	PR (n=26)
12-month OS rate, % (95% CI)	75.0 (58.5–85.7)	60.2 (37.2–77.0)
24-month OS rate, % (95% CI)	59.6 (41.7–73.7)	30.5 (9.3–55.3)

- IV treatment with 21d cycles, mandatory steroid use
- Step-up doses of 0.7/4/20 mg during C1, followed by 160 mg on Days 1, 8, and 15 of C2-4
- C4+: 320 mg every 2 weeks until PD or intolerance
- (If there is CR that is durable for ≥9 months, can dose q4 weeks

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Ayyapan ASH 2023; Abstract 436

STARGLO: RP3 Trial of GEMOX vs. glofit-GEMOX in rel/ref LBCL

Rel/Ref LBCL
(autoHCT inelig)
1 vs ≥2 Rx
Rel vs ref dz

1. GEMOX x 8 cycles (n=91)
2. Glofit plus GEMOX x 8 cycles → glofit x 4 (n=183)

Primary endpoint: OS

Med f/u 20.7m
Med OS 25.5m vs 12.9m
(HR 0.62)

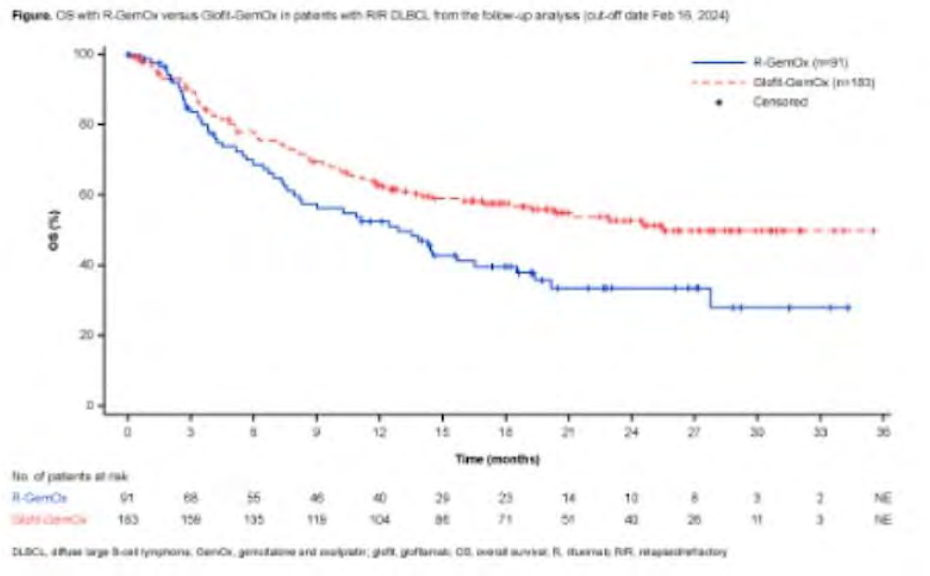

Figure. OS with R-GemOx versus Glofit-GemOx in patients with R/R DLBCL from the follow-up analysis (cut-off date Feb 16, 2024)

DLBCL, diffuse large B-cell lymphoma; GemOx, gemcitabine and oxaliplatin; glofit, glofitamab; OS, overall survival; R, rituximab; R/R, relapsed/refractory

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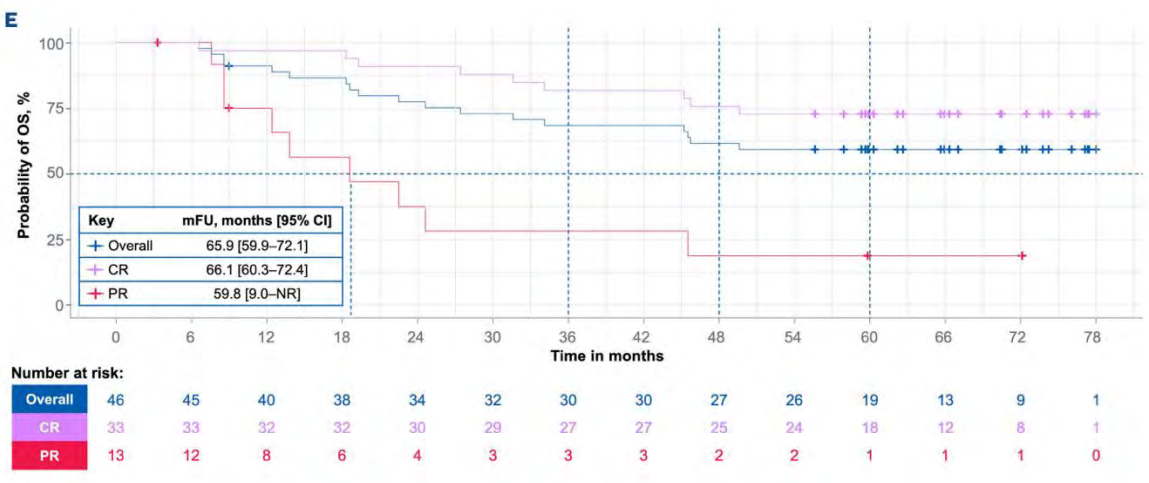
UChicago Medicine

Abramson EHA 2024; Abstract LB3438

Final 5-year analysis: tafasitamab-lenalidomide in rel/ref LBCL (med f/u 44m)

DR by line of therapy



OS by CR vs PR

- **Depth of response matters more than line of therapy**
- **Some durable responses**
- **Toxicity: cytopenias**

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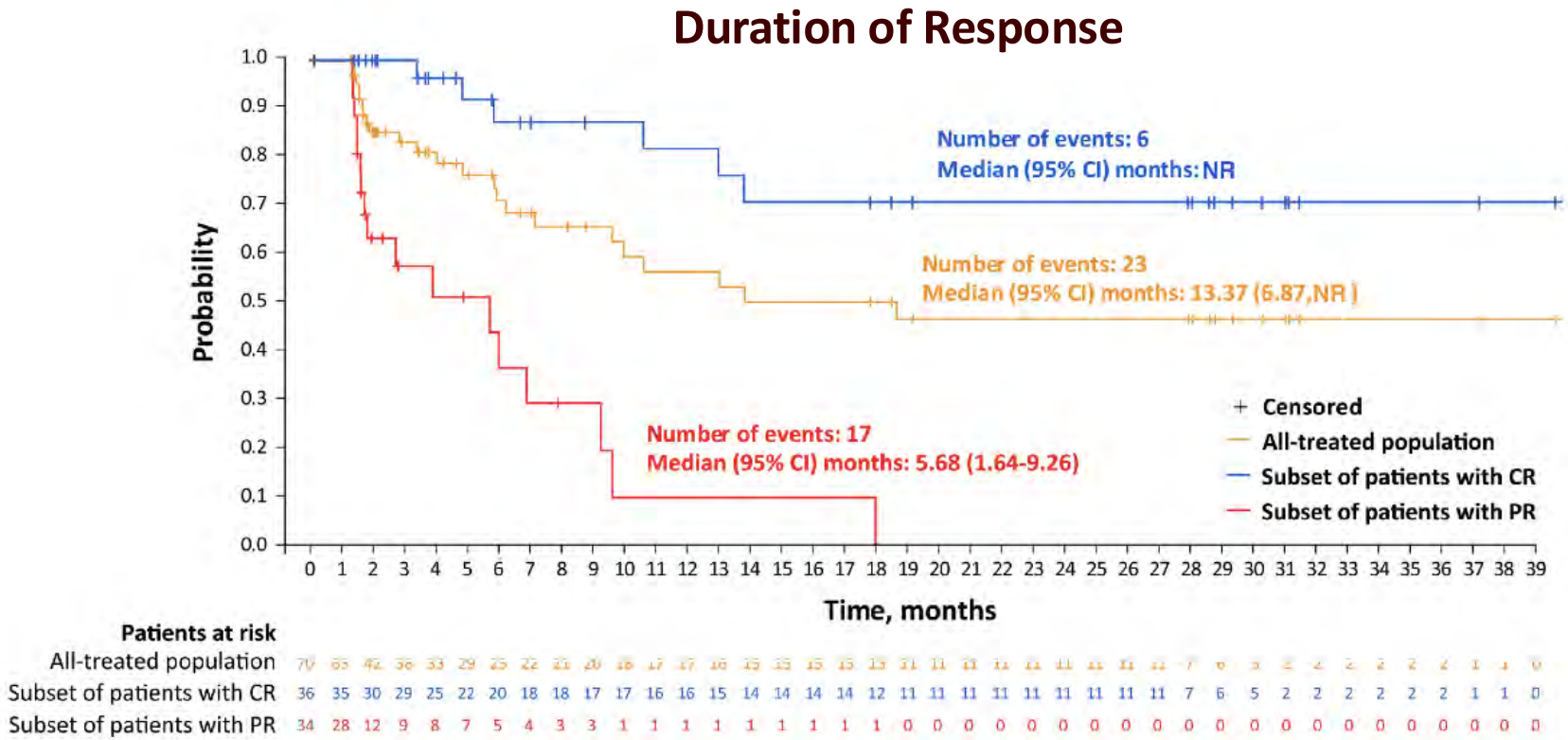
Duell Haematologica 2024 Feb 1;109(2):553-566

Loncastuximab tesirine: Long-term efficacy and safety data from the phase II LOTIS-2 trial in rel/ref LBCL (n=145)



- Lonca 0.15mg/kg q21d x 2 cycles, then 0.075mg/kg q21d up to 1 year
- Median f/u 7.8m all pts, >35m for responders
- **Toxicity**: increased GGT, cytopenias

AT THE FOREFRONT
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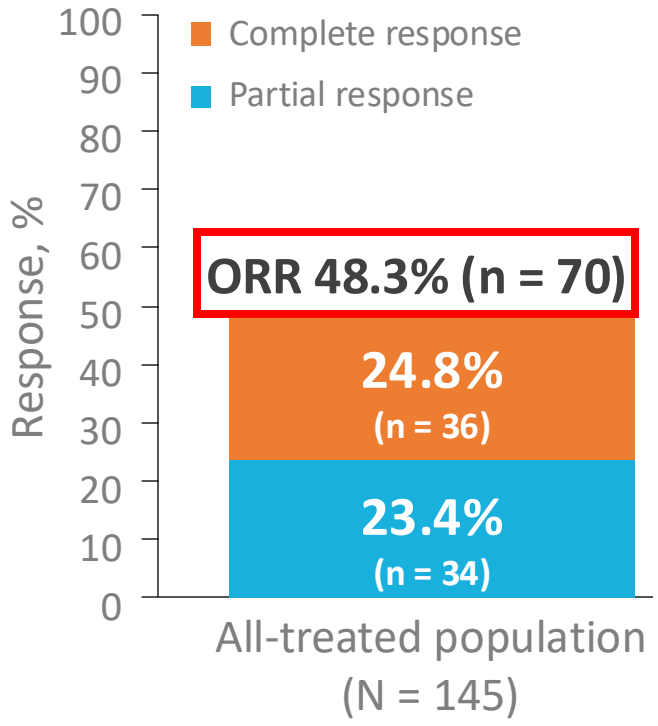
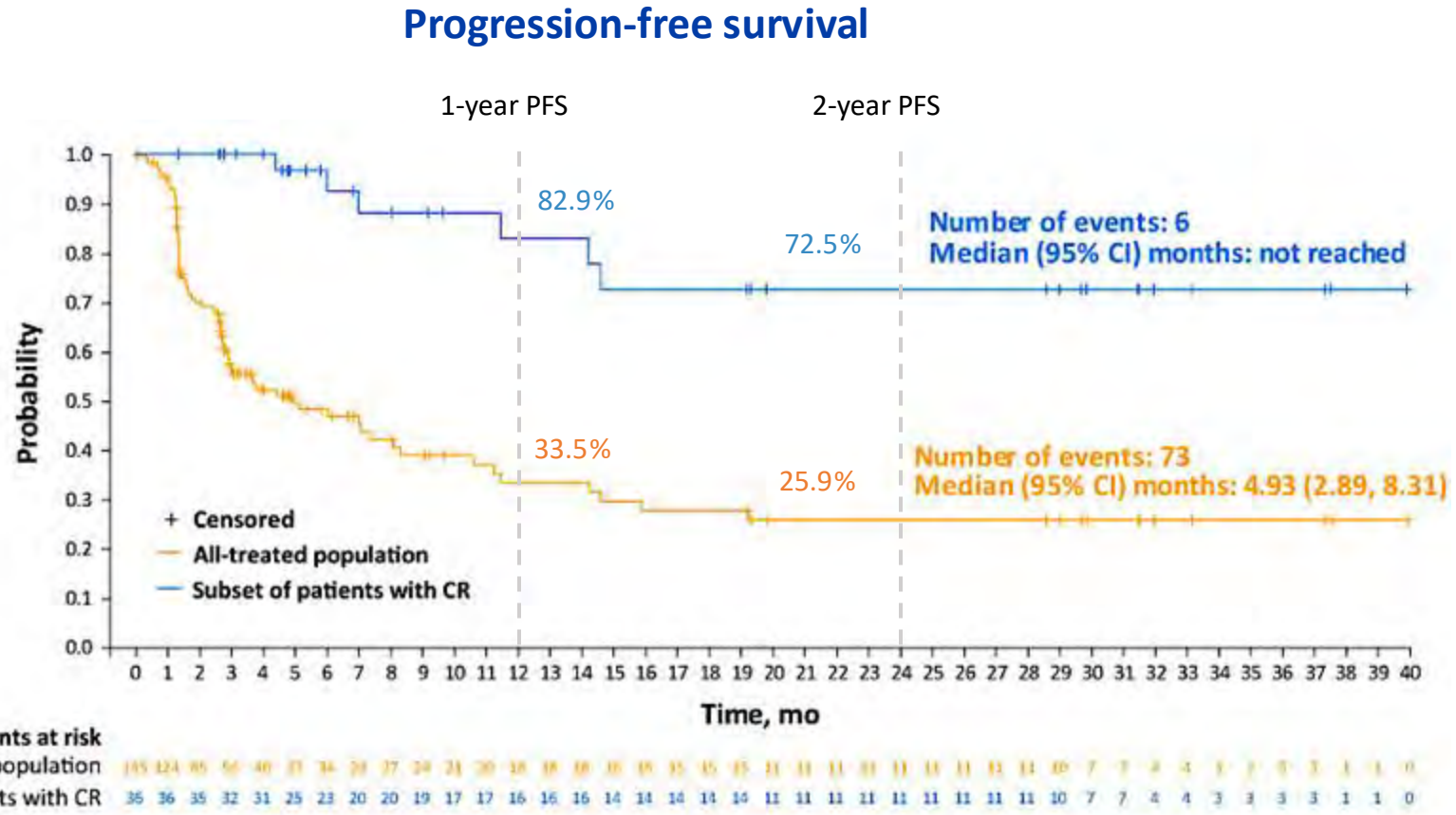
Caimi Haematologica. 2024 Apr 1;109(4):1184-1193.

LOTIS-2: Overall response rate and long-term PFS with loncastuximab tesirine in rel/ref DLBCL





Caimi et al ICML 2023; Caimi Haematologica. 2024 Apr 1;109(4):1184-1193.

Follicular Lymphoma

Treatment options for rel/ref FL

2L Options

Chemo + rituximab or obinutuzumab

Len + ritux or obin

Anti-CD20 monotherapy +/- maintenance

(tazemetostat)

(autoHCT)

3L+ Options

Bispecific antibody

- Mosunetuzumab
- Epcoritamab
- ***Odronextamab (not approved)*

CAR-T

- Axi-cel
- Tisa-cel
- Liso-cel

Tazemetostat

Zanubrutinib + obin

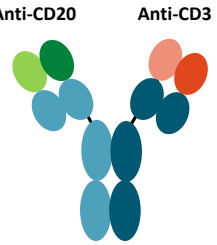
(alloHCT)

inMIND trial: RP3 double-blind len-rituximab +/- tafasitamab in rel/ref FL

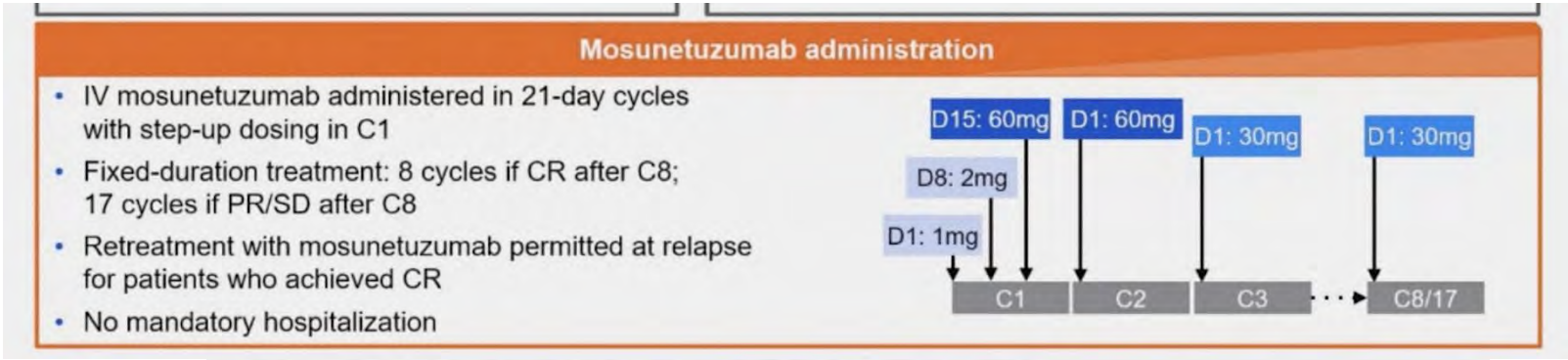
- **Primary endpoint of inv-assessed PFS was met**
- A total of 654 patients aged 18 years and older with relapsed or refractory FL deemed grade 1 to 3a or relapsed or refractory nodal, splenic, or extranodal marginal zone lymphoma (MZL) were enrolled
- QUESTIONS:
  - value of dual anti-CD19/CD20?
  - Patient characteristics (relapsed versus refractory)?

https://www.targetedonc.com/view/phase-3-trial-of-tafasitamab-in-follicular-lymphoma-meets-primary-end-point

Mosun in FL



Mosunetuzumab (IV/SC)



Baseline patient characteristics

n, unless stated	N=90
Median age, years (range)	60 (29–90)
Male	55 (61%)
ECOG PS 0 1	 53 (59%) 37 (41%)
Ann Arbor stage I/II III/IV	 21 (23%) 69 (77%)
Median lines of prior therapy, (range)	3 (2–10)
Prior autologous stem cell transplant	28 (31%)*
Refractory to last prior therapy	62 (69%)
Refractory to any prior anti-CD20 therapy	71 (79%)
POD24	47 (52%)
Double refractory to prior anti-CD20 and alkylator therapy	48 (53%)

Schuster ASH 2023; Abstract 603.

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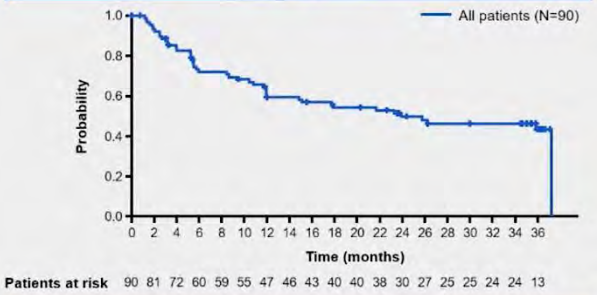
Mosun in r/r FL: 3-year follow up

PFS and OS; median follow-up >36 months

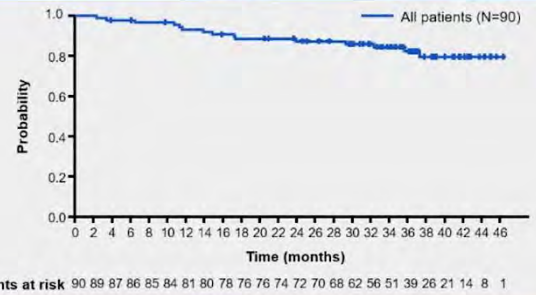
PFS



Patients at risk 90 81 72 60 59 55 47 46 43 40 40 38 30 27 25 25 24 24 13

	N=90
Median PFS, months (95% CI)	**24.0** (12.0–NE)
36-month PFS, months (95% CI)	**43.2%** (31.3–55.2)

OS



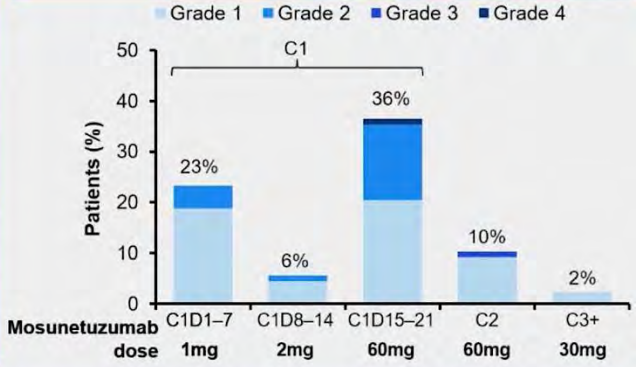
Patients at risk 90 89 87 86 85 84 81 80 78 76 76 74 72 70 68 62 56 51 39 26 21 14 8 1

	N=90
Median OS, months (95% CI)	**NR** (NE–NE)
36-month OS, months (95% CI)	**82.4%** (73.8–91.0)

CRS summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade), n	40 (44%)
Grade 1	23 (26%)
Grade 2	15 (17%)
Grade 3	1 (1%)
Grade 4	1 (1%)
Median time to CRS onset, hours (range)	
C1D1	5 (1–24)
C1D15	27 (0–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management, n	10 (11%)*
Tocilizumab for CRS management, n	7 (8%)*
Events resolved	100%

CRS by cycle and grade



CRS was predominantly low-grade and occurred during C1
All CRS events resolved; no new events have been reported in this extended follow-up

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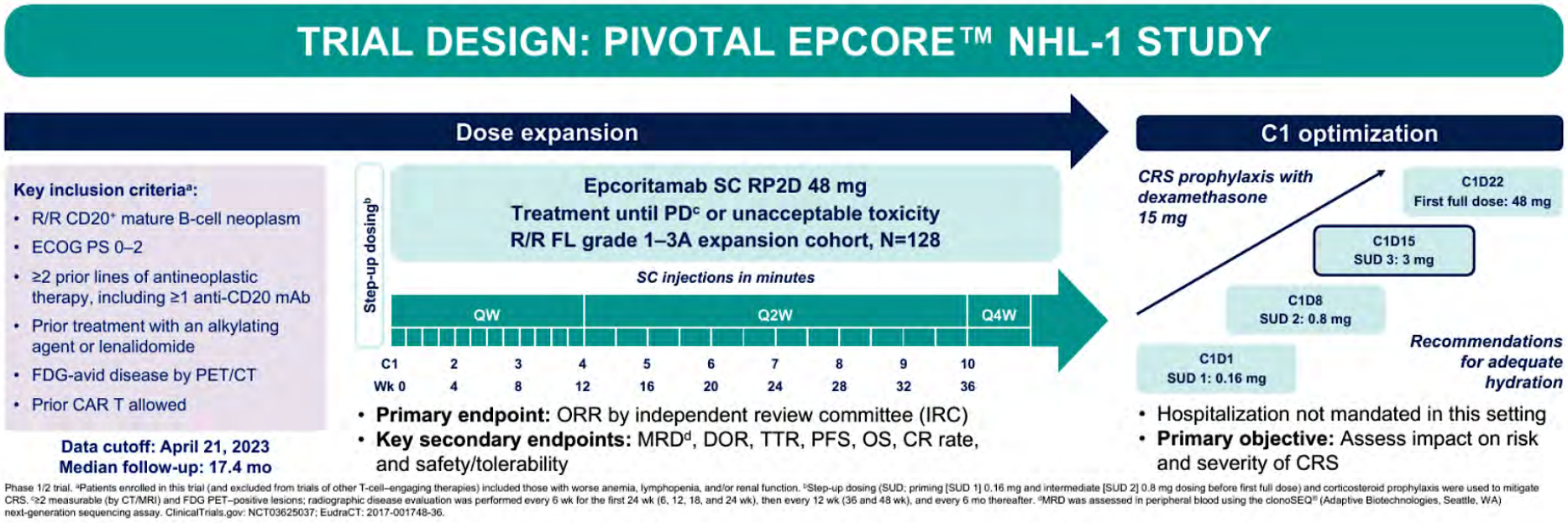
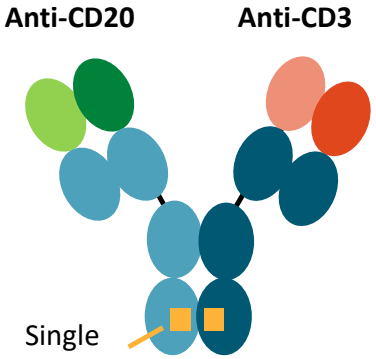
Schuster ASH 2023; Abstract 603.

EPCORE NHL-1: epco in r/r FL



Phase 1/2 trial. [a]Patients enrolled in this trial (and excluded from trials of other T-cell–engaging therapies) included those with worse anemia, lymphopenia, and/or renal function. [b]Step-up dosing (SUD; priming [SUD 1] 0.16 mg and intermediate [SUD 2] 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [c]≥2 measurable (by CT/MRI) and FDG PET–positive lesions; radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [d]MRD was assessed in peripheral blood using the clonoSEQ® (Adaptive Biotechnologies, Seattle, WA) next-generation sequencing assay. ClinicalTrials.gov: NCT03625037; EudraCT: 2017-001748-36.



Epcoritamab (SC)

Key clinical features:

- Med age 65y
- FLIPI 3-5 61%
- Med prior Rx = 3
- POD24 42%
- Double refractory 70%
- Primary refractory 54%
- Refractory to last Rx 69%

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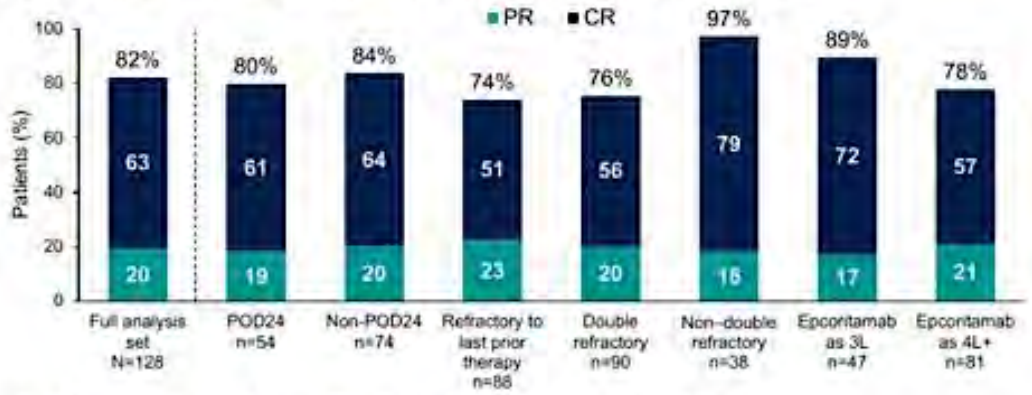
Linton ASH 2023; Abstract 1655.

EPCORE NHL-1: epco in r/r FL results

Efficacy Results

ORRs and CR Rates Were High Regardless of Subgroup



C1 Optimization Reduced Risk and Severity of CRS

	Pivotal Cohort N=128	C1 Optimization Cohort[a] N=50
CRS, n (%)[b]	85 (66)	24 (48)
Grade 1	51 (40)	20 (40)
Grade 2	32 (25)	4 (8)
Grade 3	2 (2)	0
Treated with tocilizumab, n/n (%)	31/85 (36)	6/24 (25)
Leading to epcoritamab discontinuation, n (%)	**0**	**0**
CRS resolution, n/n (%)	**85/85 (100)**	**24/24 (100)**
Median time to resolution, d (range)	2 (1–54)	3 (1–14)

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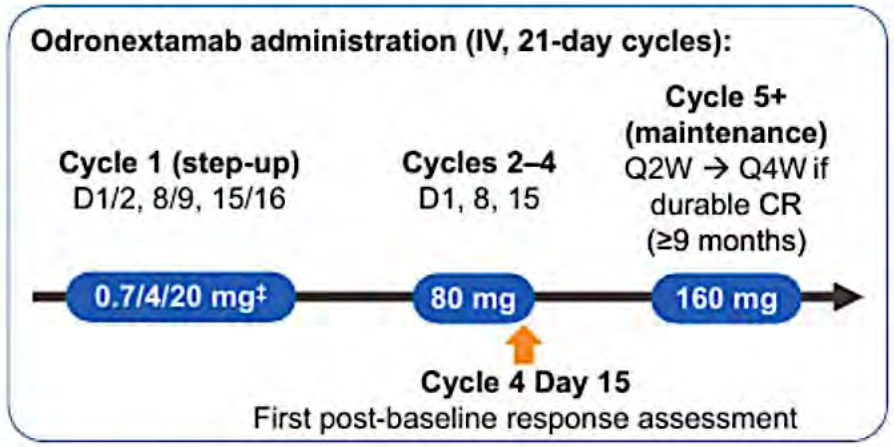
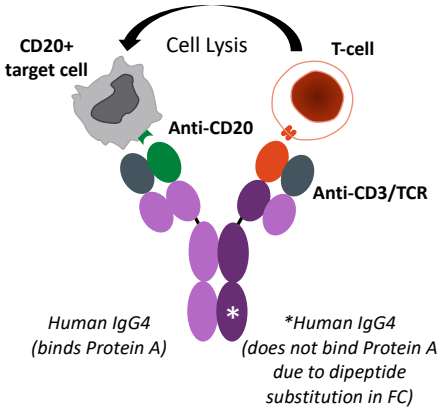
Linton ASH 2023; Abstract 1655.

Odronextamab (ELM-2 trial)





Primary endpt: ORR

Patient and disease characteristics		N=128
Median age, years (range)		61.0 (22–84)
Age ≥75 years, %		9.4
Male, %		53.1
Race, %	White / Asian / other / unknown / not reported	61.7 / 26.6 / 0.8 / 1.6 / 9.4
ECOG PS, %	0 / 1 / 2	50.8 / 48.4 / 0.8
Ann Arbor stage III–IV, %		85.2
FLIPI risk score, %	0–1 / 2 / 3–5	16.4 / 25.8 / 57.8
Bulky disease, investigator assessment, %		14.1
Median prior lines, n (range)		3 (2–13)
Prior PI3K inhibitor, %		14.1
Prior R², %		13.3
Prior ASCT, %		30.5
Refractory to last line of therapy, %		71.9
Refractory to anti-CD20 antibody, %		74.2
Double refractory to alkylator/anti-CD20 antibody, %		41.4
POD24, %		49.2

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Villasboas ASH 2023; Abstract 3041.

Odronextamab in r/r FL: outcomes

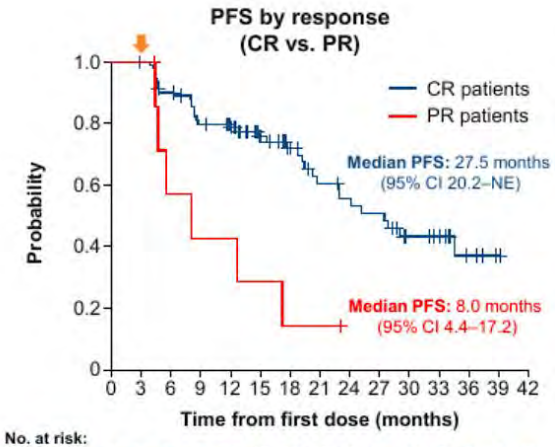
Table 5. CRS

		0.7/4/20 mg N=60
Any grade, n (%)		34 (56.7)
Grade 1 / 2		27 (45.0) / 6 (10.0)
Grade 3 / 4		1 (1.7) / 0
Median time to CRS onset, hours (range)		19.7 (0.7–159.0)
Median CRS duration, days (range)		2.00 (1.0–10.0)
CRS management, n (%)	Systemic steroids / tocilizumab	20 (33.3) / 10 (16.7)

CRS per Lee 2019 criteria[5]. CRS, cytokine release syndrome.

Conclusions

- **Heavily pretreated patients with R/R FL achieved deep and durable responses with continued odronextamab treatment**
  - ORR, 81%; CR, 73%; 2-year CR rate, 49%
  - Median PFS, 20.7 months; median OS, NR
  - PROs were maintained from baseline to Week 50
- **The safety profile of odronextamab was generally manageable**
  - CRS was mostly Grade 1/2 and one low-grade ICANS event was reported with 0.7/4/20 mg Cycle 1 step-up
  - Any-grade infection TEAEs were reported in 80% of patients, and over a third of patients had COVID-19 infection, reflective of a study conducted during the pandemic in a patient population with increased underlying risk for infections
- **Phase 3 randomized trials are ongoing in FL patients in earlier lines of therapy**
  - OLYMPIA-1 (NCT06091254), OLYMPIA-2 (NCT06097364), OLYMPIA-5 (NCT06149286)



	CR (n=94)	PR (n=9)
12-month PFS, % (95% CI)	78.8 (68.7–85.9)	42.9 (9.8–73.4)
24-month PFS, % (95% CI)	55.8 (41.7–67.8)	NE (NE–NE)

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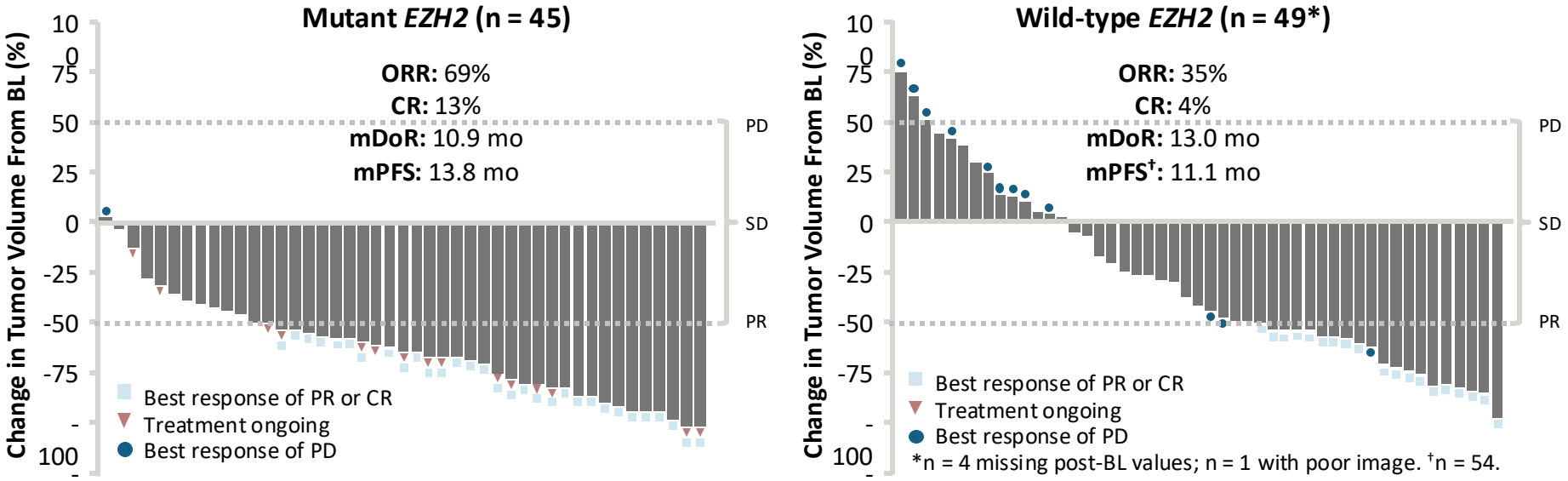
Villasboas ASH 2023; Abstract 3041.

OTHER TARGETED AGENTS

Tazemetostat Phase II Study: Response



Response by Subgroup	Mutant *EZH2*			Wild-type *EZH2*		
	POD24 (n = 19)	Rituximab Refractory (n = 22)	Prior Tx Refractory (n = 33)	POD24 (n = 32)	Rituximab Refractory (n = 32)	Prior Tx Refractory (n = 42)
ORR, n (%) [95% CI]	12 (63) [38.4-83.7]	13 (59) [36.4-79.3]	21 (64) [45.1-79.6]	8 (25) [11.5-43.4]	10 (31) [16.1-50.0]	12 (29) [15.7-44.6]
▪ CR, n (%)	2 (11)	2 (9)	5 (15)	1 (3)	1 (3)	1 (2)

By IRC.

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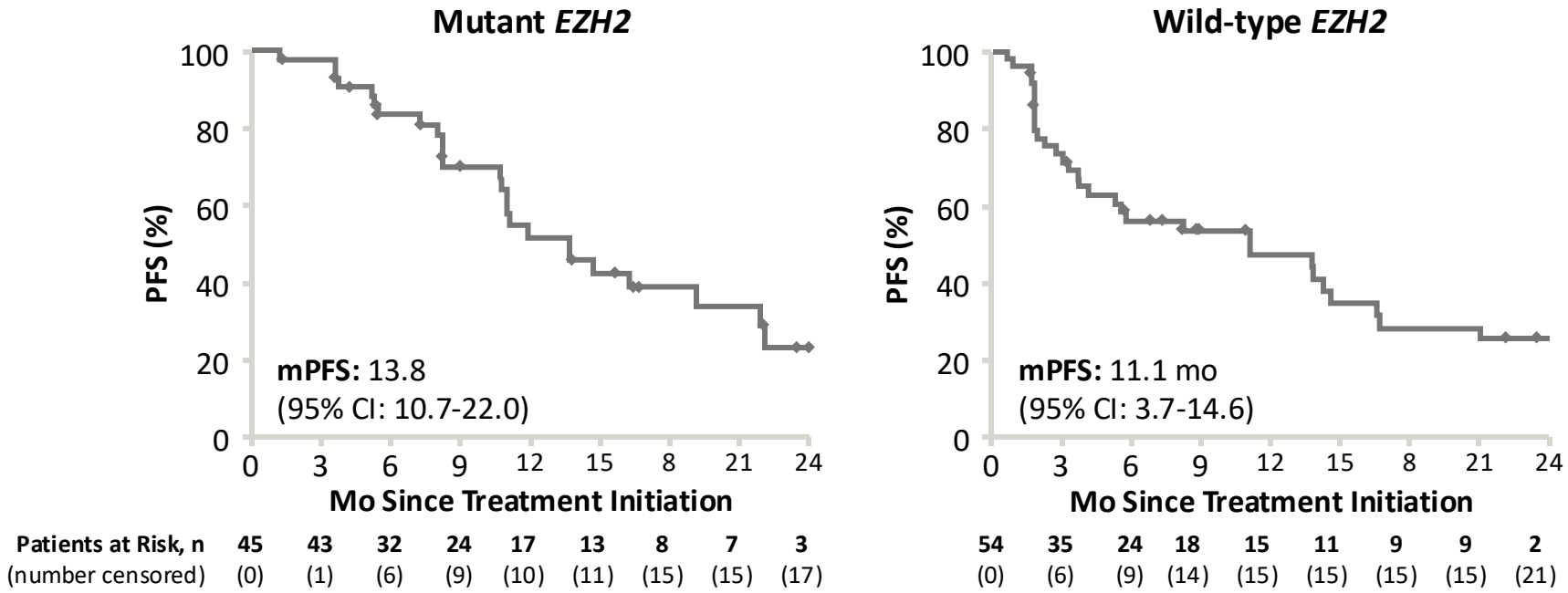
Morschhauser Lancet Oncol. 2020;21:1433. Morschhauser ASH 2019; Abstract 123

Tazemetostat Phase II Study: PFS (by IRC)



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Well-tolerated; no sig AE's

Morschhauser Lancet Oncol. 2020;21:1433.

ROSEWOOD: RP2 (2:1) trial of zanu-obin vs. obin in R/R FL

Pt features	ZO (n=145)	O (n=72)	P value
Med age	63y	65.5y	
Prior Tx	3 (2-11)	3 (2-9)	
High FLIPI	53%	51%	
POD24	34%	42%	
Ref to last Tx	32%	40%	
Results			
ORR	69%	46%	0.001
CR	39%	19%	0.004
Med DOR	NE	14m	
Med PFS	28m	10.4m	<0.001
Med OS	NE	34.6m	0.085

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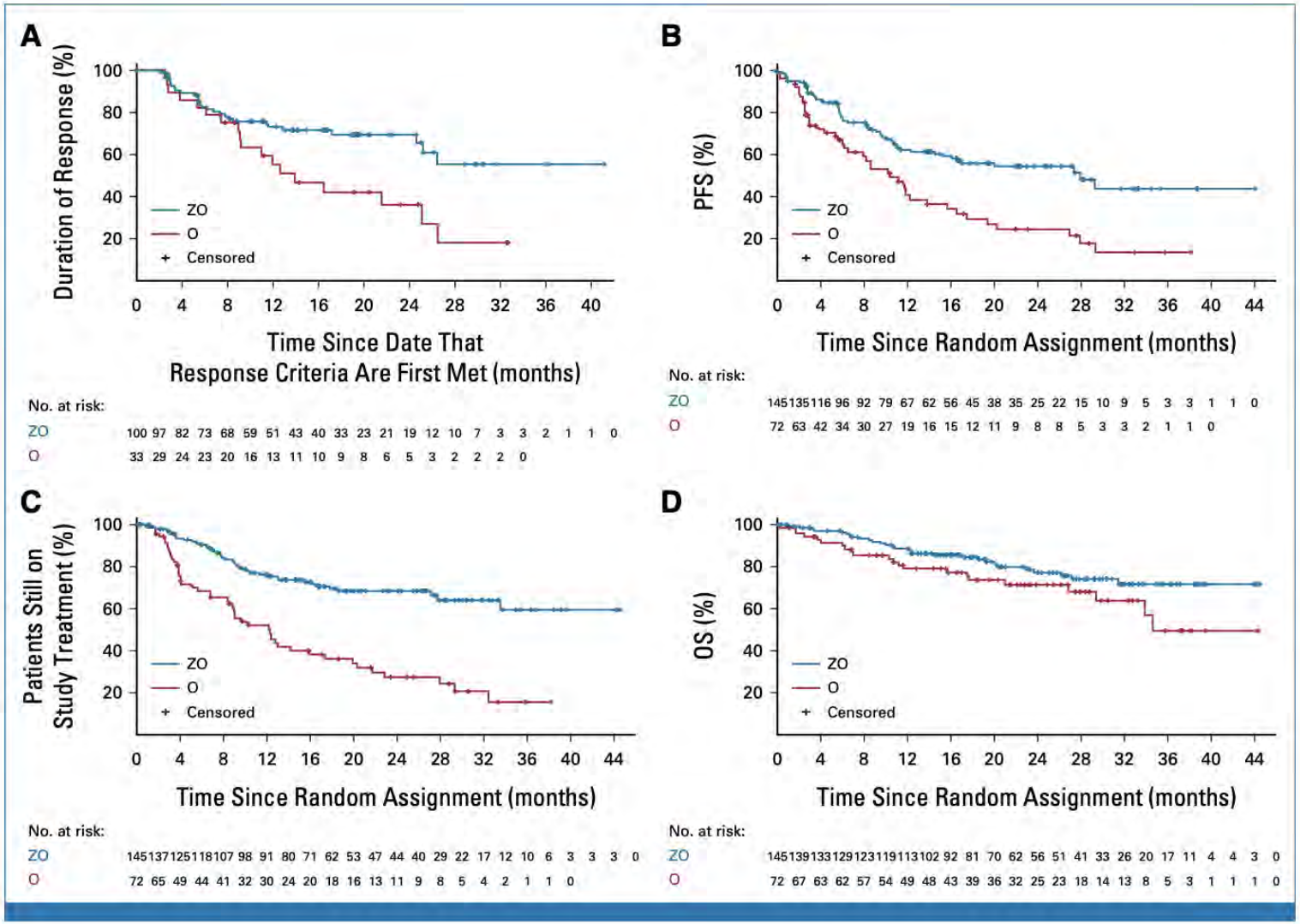
Zinzani *JCO* **41**, 5107-5117(2023).

ROSEWOOD: RP2 (2:1) zanu-obin versus obin



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Zinzani *JCO* **41**, 5107-5117(2023).

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

Agenda

Module 1 — HR-Positive Breast Cancer: *Drs O'Shaughnessy and Wander*

Module 2 — Prostate Cancer: *Drs M Smith and Srinivas*

Module 3 — Lung Cancer: *Drs Goldberg and Sabari*

Module 4 — Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia: *Drs Kahl and S Smith*

Module 5 — Multiple Myeloma: *Drs Lonial and Raje*

Multiple Myeloma Faculty

Sagar Lonial, MD
Chair and Professor
Department of Hematology and Medical Oncology
Anne and Bernard Gray Family Chair in Cancer
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Noopur Raje, MD
Director, Center for Multiple Myeloma
Massachusetts General Hospital Cancer Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Current Therapeutic Approaches for Multiple Myeloma

Sagar Lonial, MD
Chair and Professor
Department of Hematology and Medical Oncology
Anne and Bernard Gray Family Chair in Cancer
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Newly Diagnosed MM-ASCT eligible

Courtesy of Shaji K Kumar, MD

FDA Approves Daratumumab and Hyaluronidase-fihj with Bortezomib, Lenalidomide and Dexamethasone for Multiple Myeloma

Press Release: July 30, 2024

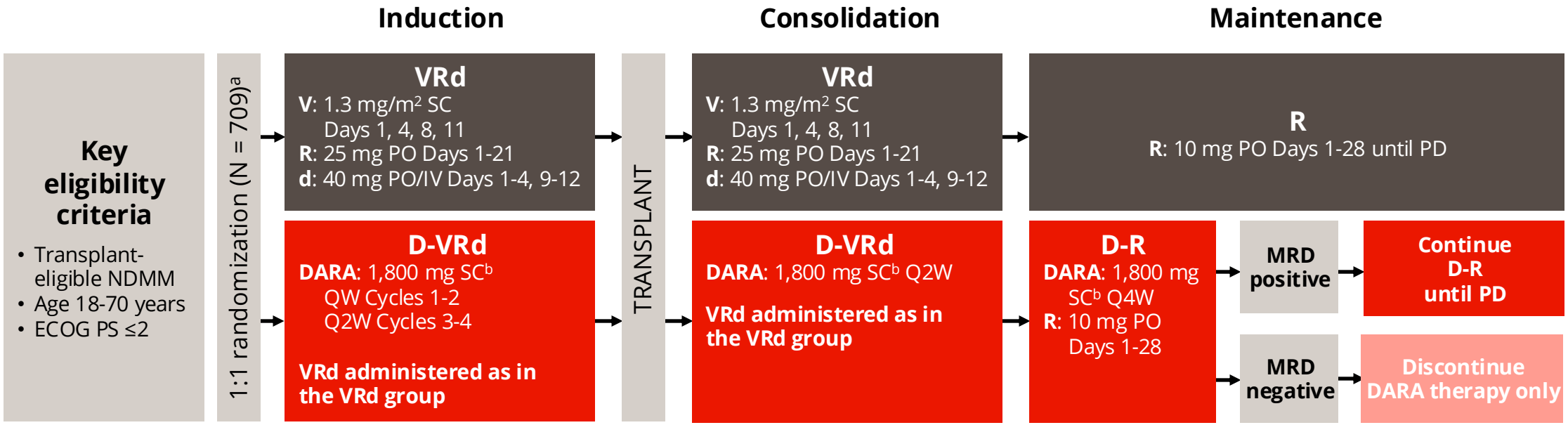
The FDA approved daratumumab and hyaluronidase-fihj in combination with bortezomib, lenalidomide and dexamethasone for induction and consolidation for newly diagnosed multiple myeloma in patients who are eligible for autologous stem cell transplant (ASCT).

Efficacy was evaluated in PERSEUS (NCT03710603), an open-label, randomized, active-controlled trial in patients with newly diagnosed multiple myeloma eligible for ASCT. Enrollment was limited to patients 70 years of age and younger. A total of 709 patients were randomized: 355 to the daratumumab with bortezomib, lenalidomide and dexamethasone arm and 354 to the bortezomib, lenalidomide and dexamethasone (VRd) arm.

PERSEUS demonstrated an improvement in progression-free survival (PFS) in the daratumumab arm as compared to the VRd arm; the median PFS had not been reached in either arm. Treatment with daratumumab-VRd resulted in a reduction in the risk of disease progression or death by 60% compared to VRd alone (HR [95% CI]: 0.40 [0.29, 0.57]; *p*-value < 0.0001).

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-daratumumab-and-hyaluronidase-fihj-bortezomib-lenalidomide-and-dexamethasone-multiple

PERSEUS: Study Design



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

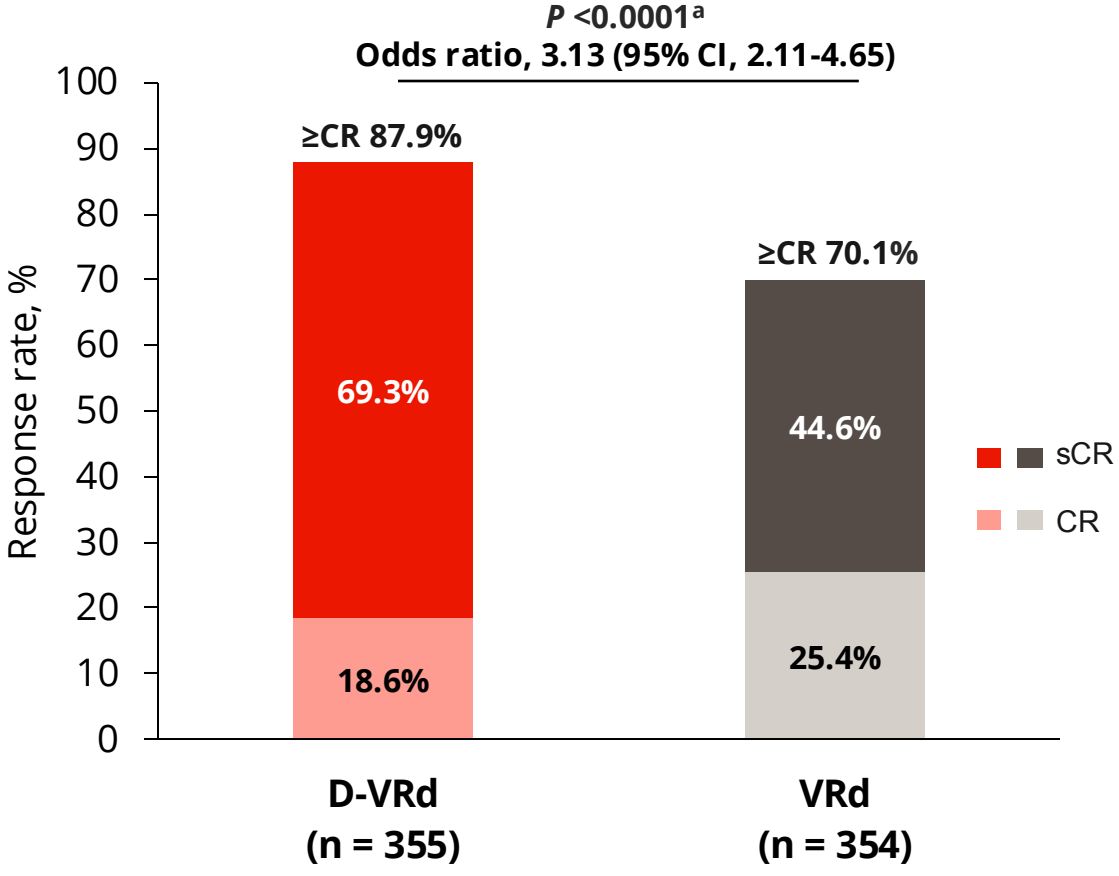
Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

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

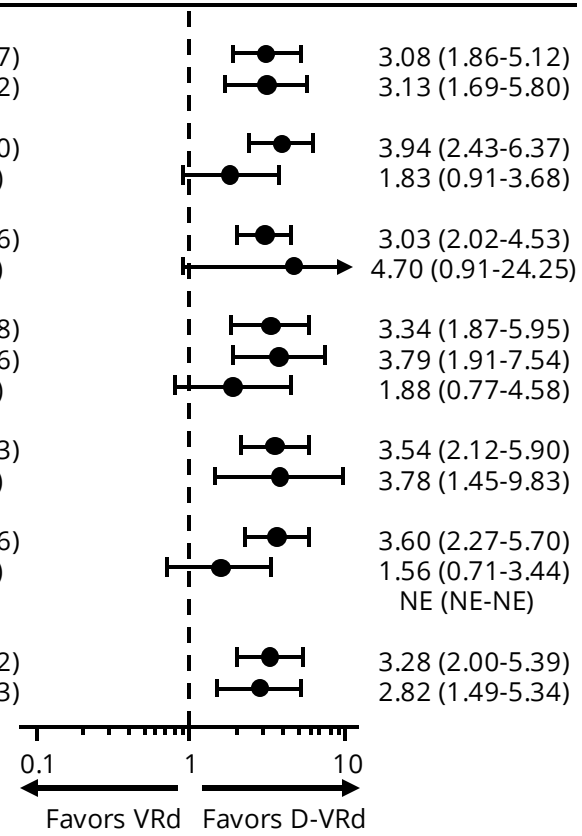
Courtesy of Shaji K Kumar, MD

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)



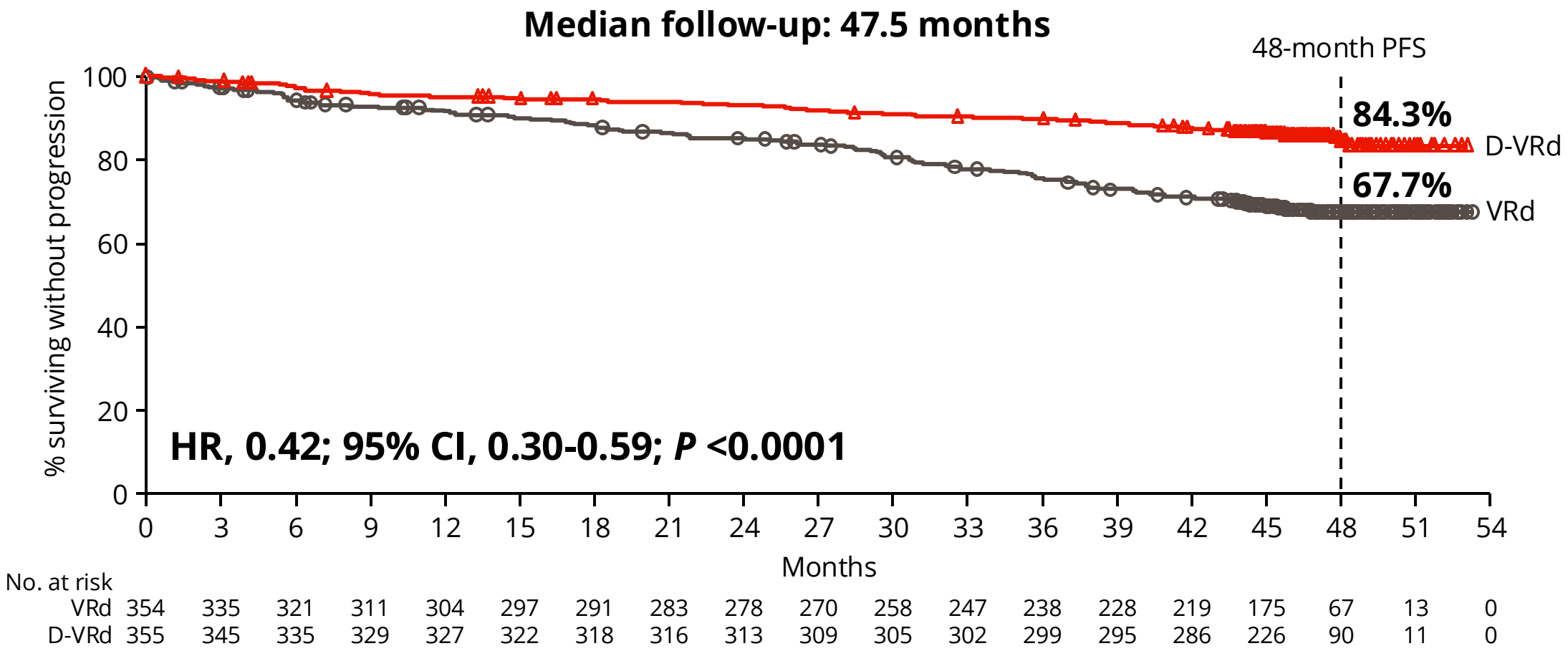
- **Overall ≥CR rate was significantly higher with D-VRd versus VRd**
- **≥CR rate was improved with D-VRd versus VRd across subgroups**

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.

Courtesy of Shaji K Kumar, MD

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

PERSEUS: Progression-free Survival



- **58% reduction in the risk of progression or death in patients receiving D-VRd**

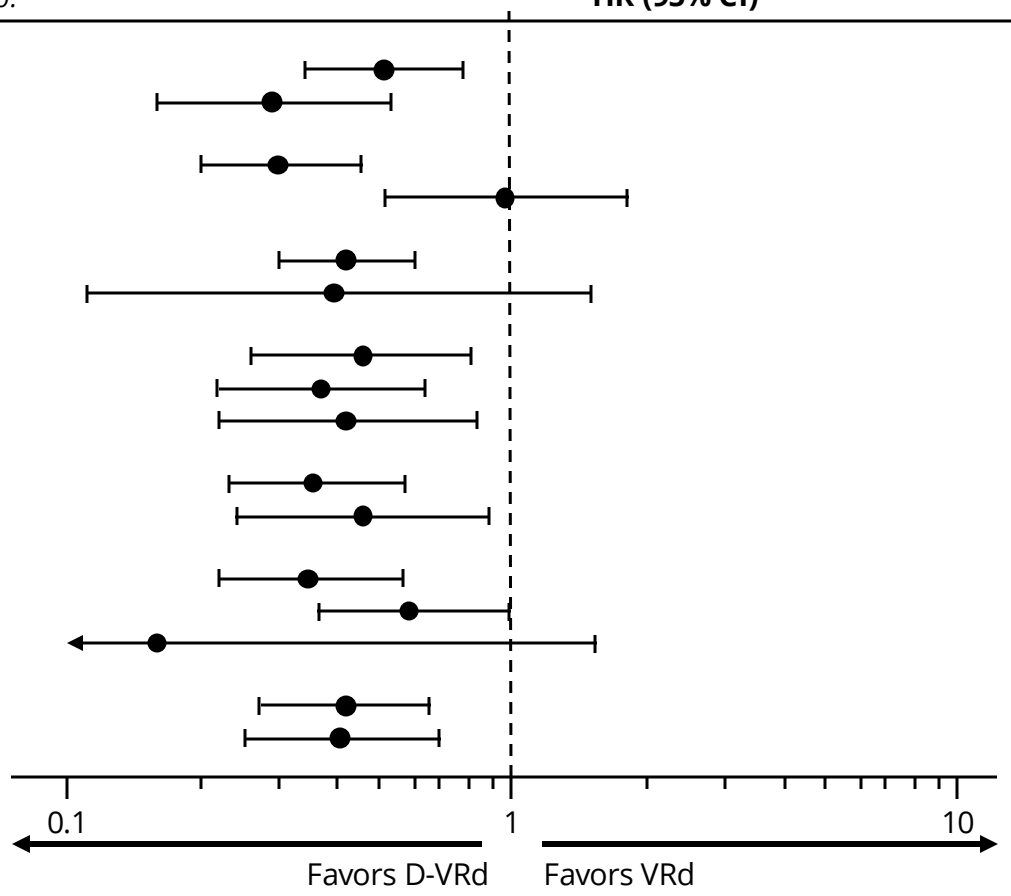
HR, hazard ratio; CI, confidence interval.

Courtesy of Shaji K Kumar, MD

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

PERSEUS: PFS in Prespecified Subgroups

Subgroup	D-VRd *no. of progression events or deaths/total no.*	VRd	HR (95% CI)
Sex			
Male	36/211	61/205	0.51 (0.34-0.77)
Female	14/144	42/149	0.29 (0.16-0.53)
Age			
<65 y	30/261	84/267	0.30 (0.20-0.46)
≥65 y	20/94	19/87	0.97 (0.52-1.81)
Race			
White	47/330	95/323	0.42 (0.30-0.60)
Other	3/25	8/31	0.40 (0.11-1.50)
ISS stage			
I	18/186	35/178	0.46 (0.26-0.81)
II	19/114	43/125	0.37 (0.22-0.64)
III	13/55	25/50	0.42 (0.22-0.83)
Type of MM			
IgG	28/204	58/185	0.36 (0.23-0.57)
Non-IgG	13/78	31/96	0.46 (0.24-0.88)
Cytogenetic risk			
Standard risk	25/264	62/266	0.35 (0.22-0.56)
High risk	24/76	38/78	0.59 (0.36-0.99)
Indeterminate	1/15	3/10	0.16 (0.02-1.56)
ECOG PS			
0	28/221	60/230	0.42 (0.27-0.66)
≥1	22/134	43/124	0.41 (0.25-0.69)



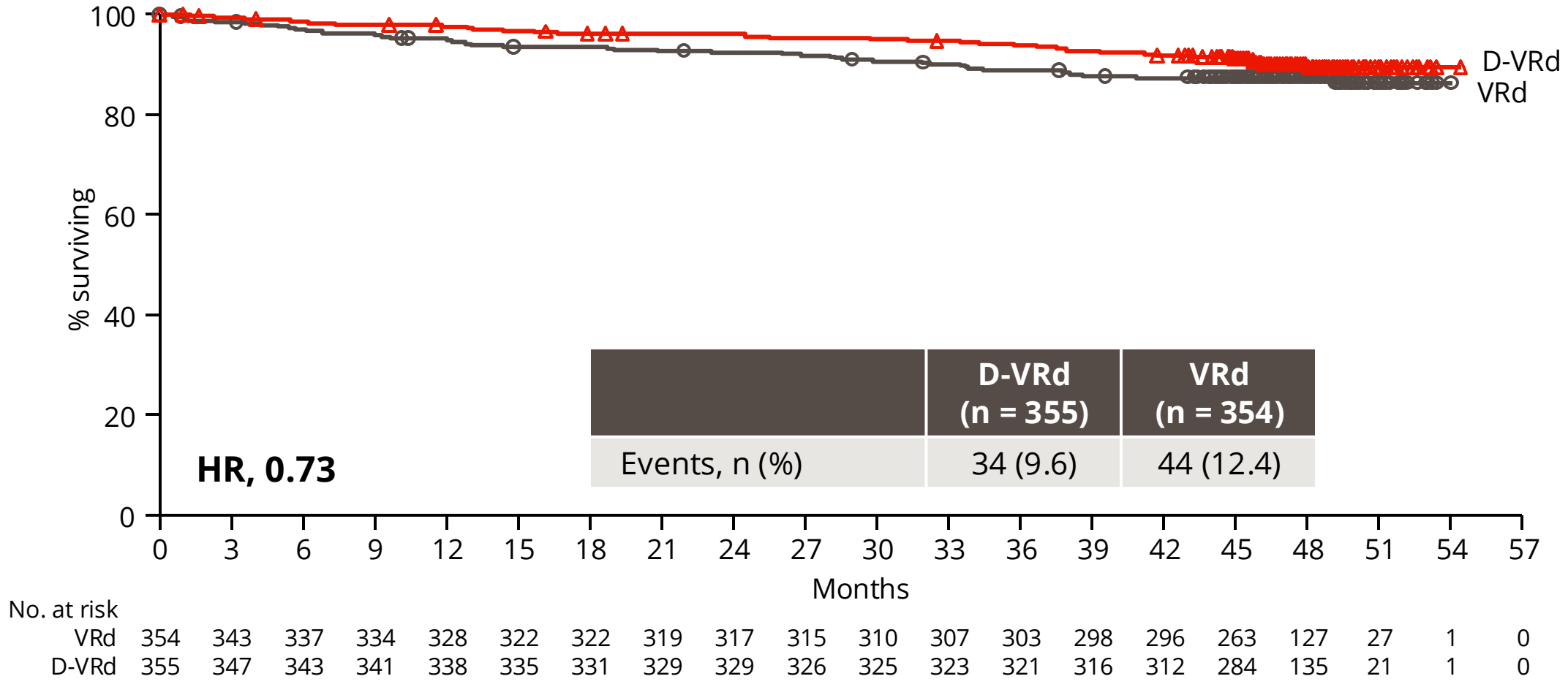
- **PFS was improved with D-VRd versus VRd across clinically relevant subgroups**

The subgroup analysis for type of MM was performed on data from patients who had measurable disease in serum. Cytogenetic risk was assessed by fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).

Courtesy of Shaji K Kumar, MD

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

PERSEUS: Overall Survival



	D-VRd (n = 355)	VRd (n = 354)
Events, n (%)	34 (9.6)	44 (12.4)

No. at risk

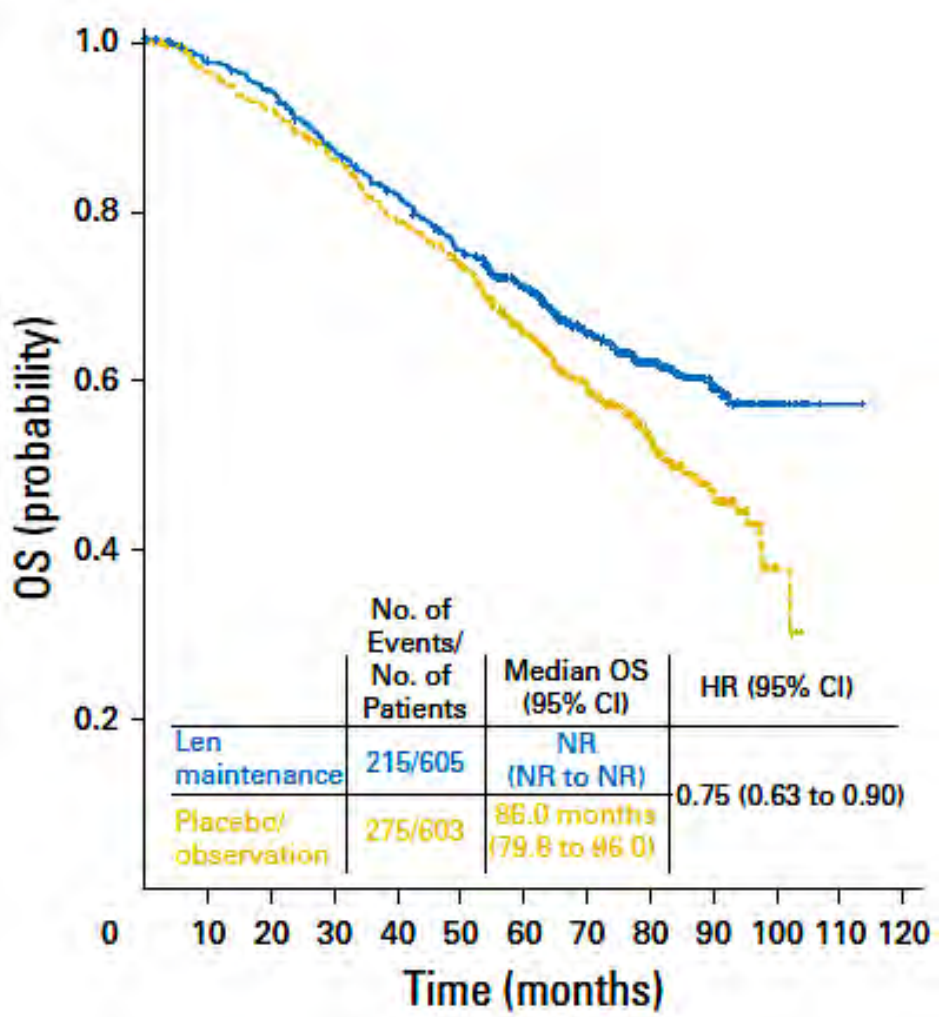
VRd	354	343	337	334	328	322	322	319	317	315	310	307	303	298	296	263	127	27	1	0
D-VRd	355	347	343	341	338	335	331	329	329	326	325	323	321	316	312	284	135	21	1	0

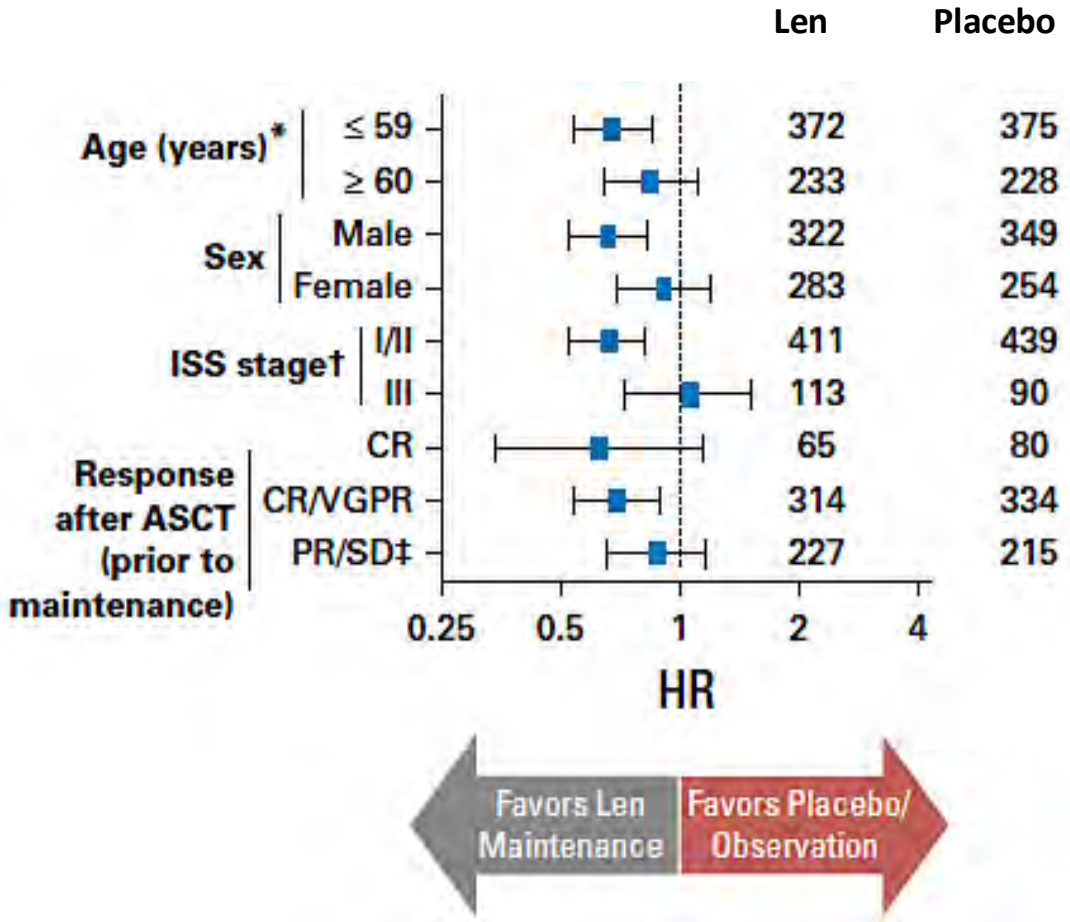
- **OS data trend favorably for D-VRd**

Courtesy of Shaji K Kumar, MD

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

Lenalidomide maintenance

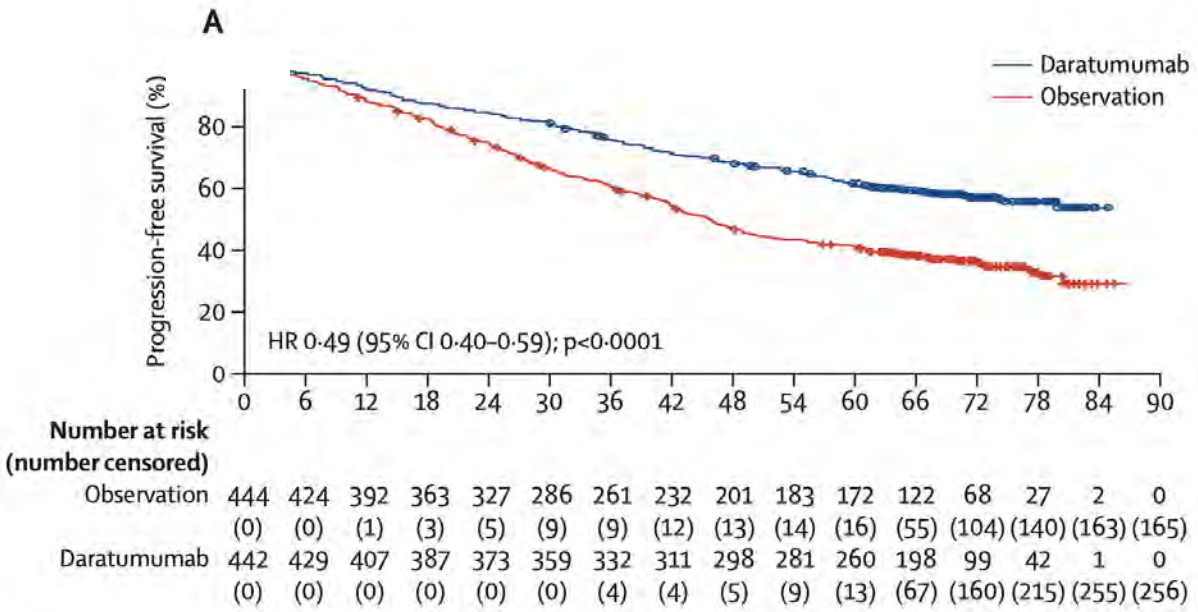


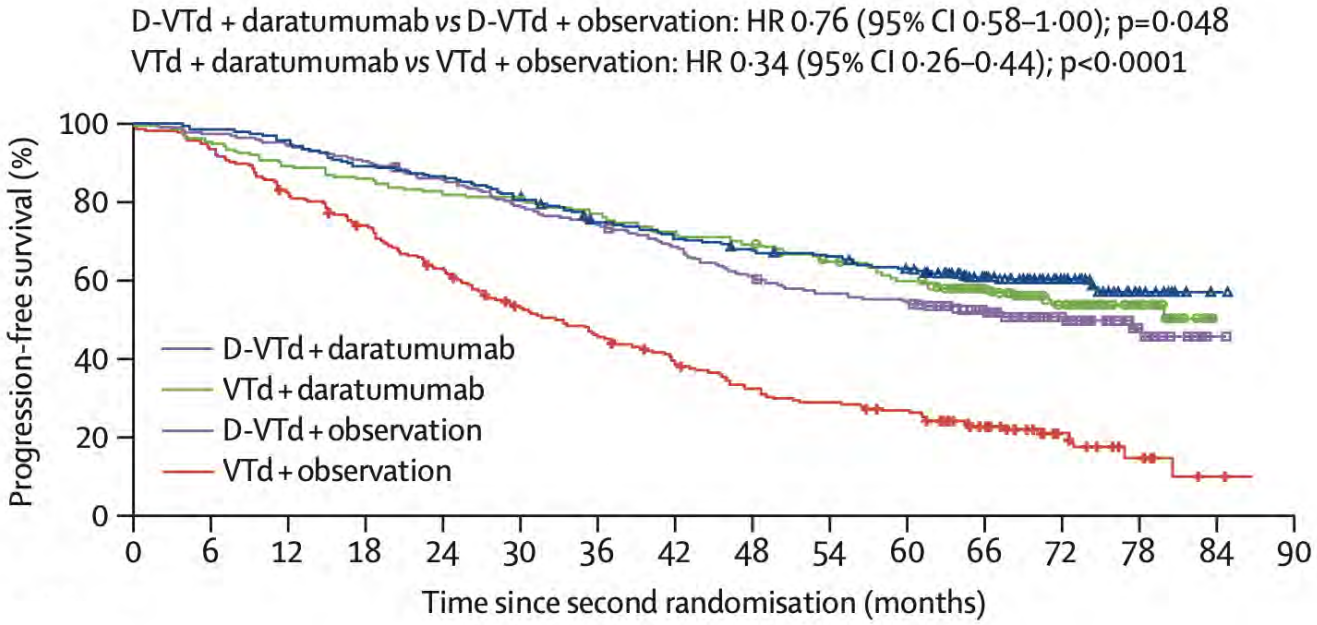


McCarthy et al, JCO 2017

Courtesy of Shaji K Kumar, MD

Daratumumab maintenance: CASSIOPEIA





Moreau P et al. *Lancet Oncol* 2024;25(8):1003-1014.

Courtesy of Shaji K Kumar, MD

Subcutaneous Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Therapy in Newly Diagnosed Multiple Myeloma After Transplant: Primary Results From the Phase 3 AURIGA Study

Ashraf Badros[1], Laahn Foster[2], Larry D Anderson Jr[3], Chakra P Chaulagain[4], Erin Pettijohn[5], Andrew J Cowan[6], Caitlin Costello[7], Sarah Larson[8], Douglas W Sborov[9], Kenneth H Shain[10], Rebecca Silbermann[11], Nina Shah[12,*], Alfred Chung[12], Maria Krevvata[13], Huiling Pei[14], Sharmila Patel[15], Vipin Khare[15], Annelore Cortoos[15], Robin Carson[13], Thomas S Lin[15], Peter Voorhees[16]

[1]Greenebaum Cancer Center, University of Maryland, Baltimore, MD, USA; [2]Division of Hematology Oncology, University of Virginia, Charlottesville, VA, USA; [3]Myeloma, Waldenstrom's and Amyloidosis Program, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [4]Department of Hematology and Oncology, Myeloma and Amyloidosis Program, Cleveland Clinic Florida, Weston, FL, USA; [5]Cancer and Hematology Centers of Western Michigan, Grand Rapids, MI, USA; [6]Division of Medical Oncology, University of Washington, Seattle, WA, USA; [7]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA; [8]Division of Hematology and Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [9]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [10]Department of Malignant Hematology, H Lee Moffitt Cancer Center, Tampa, FL, USA; [11]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; [12]Department of Medicine, University of California San Francisco, San Francisco, CA, USA; [13]Janssen Research & Development, LLC, Spring House, PA, USA; [14]Janssen Research & Development, LLC, Titusville, NJ, USA; [15]Janssen Scientific Affairs, LLC, a Johnson & Johnson company, Horsham, PA, USA; [16]Levine Cancer Institute, Atrium Health Wake Forest University School of Medicine, Charlotte, NC, USA

*Affiliation at the time of the study.

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

AURIGA: Study Design

- Objective: To determine the impact of adding DARA to R maintenance on MRD-negative conversion

Key eligibility criteria

- 18-79 years of age
- NDMM with ≥4 cycles of induction therapy and underwent ASCT within 12 months of the start of induction
- ≥VGPR at screening[a]
- MRD[b] positive (10^{-5}) post-ASCT
- No prior anti-CD38
- Randomization within 6 months of ASCT date

Stratification factor

- Cytogenetic risk[c] (standard risk/unknown vs high risk)

1:1 RANDOMIZATION (N = 200)

Maintenance: up to 36 cycles[d] (28-day cycles)

D-R

D: 1,800 mg SC[e] QW Cycles 1-2, Q2W Cycles 3-6, Q4W Cycles 7+

R: 10 mg PO daily Days 1-28 (after Cycle 3, 15 mg PO daily if tolerated)

R

R: 10 mg PO daily Days 1-28 (after Cycle 3, 15 mg PO daily if tolerated)

Primary endpoint

- MRD-negative (10^{-5}) conversion rate from baseline to 12 months after maintenance treatment
  - N = 214 planned to achieve ≥85% power to detect 20% improvement

Secondary endpoints

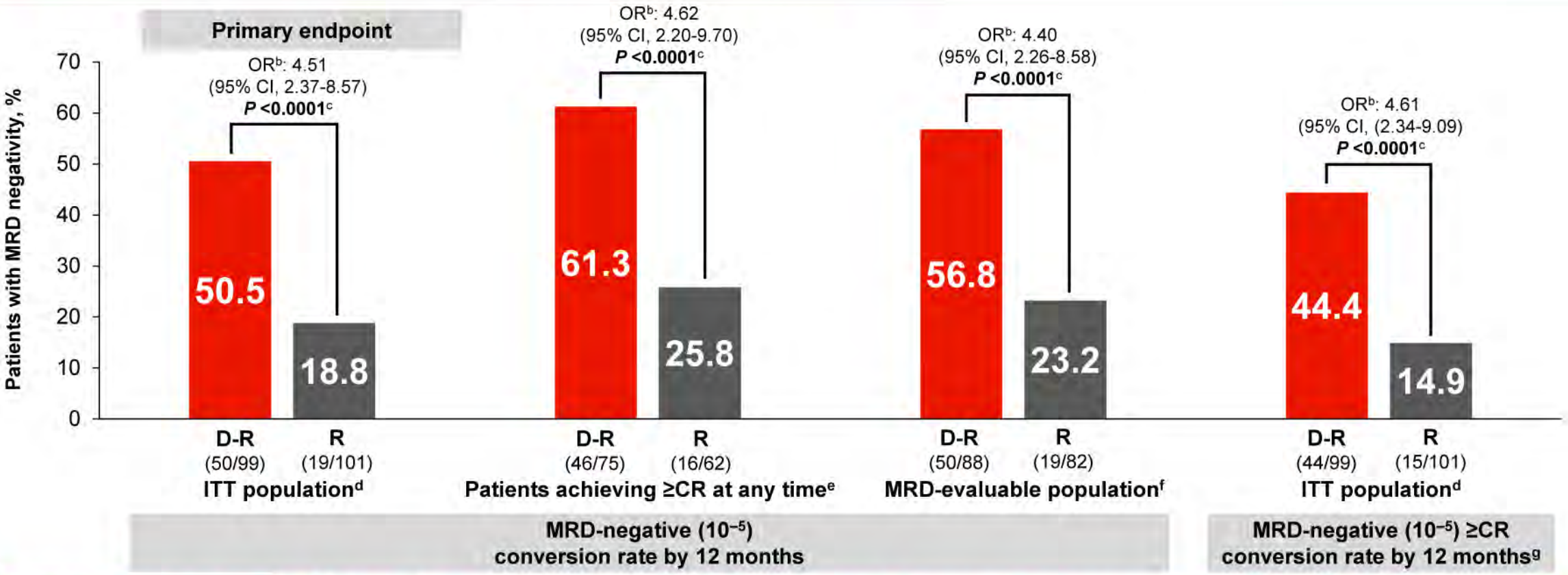
- PFS, overall MRD-negative conversion rate, sustained MRD-negative rate, response rates, duration of ≥CR, OS, safety

MRD[b] obtained after 12, 18, 24, and 36 cycles

VGPR, very good partial response; D, daratumumab; SC, subcutaneous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; PO, orally; CR, complete response. [a]As assessed by International Myeloma Working Group 2016 criteria. [b]MRD based upon NGS (clonoSEQ®; Adaptive Biotechnologies). [c]For stratification, cytogenetic risk was evaluated per investigator assessment, in which high risk was defined as the presence of ≥1 of the following cytogenetic abnormalities: del[17p], t[4;14], or t[14;16]. [d]Study treatment continued for a planned maximum duration of 36 cycles or until progressive disease, unacceptable toxicity, or withdrawal of consent. After the end of the study treatment period of 36 months and after the end of the study, patients benefiting from treatment with DARA and/or R could continue receiving treatment per the investigator's discretion. [e]DARA SC (DARA 1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA]).

Presented by A Badros at the 21st International Society of Myeloma (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil

AURIGA: MRD-negative (10^{-5}) Conversion Rate From Baseline to 12 Months of Maintenance Treatment[a]



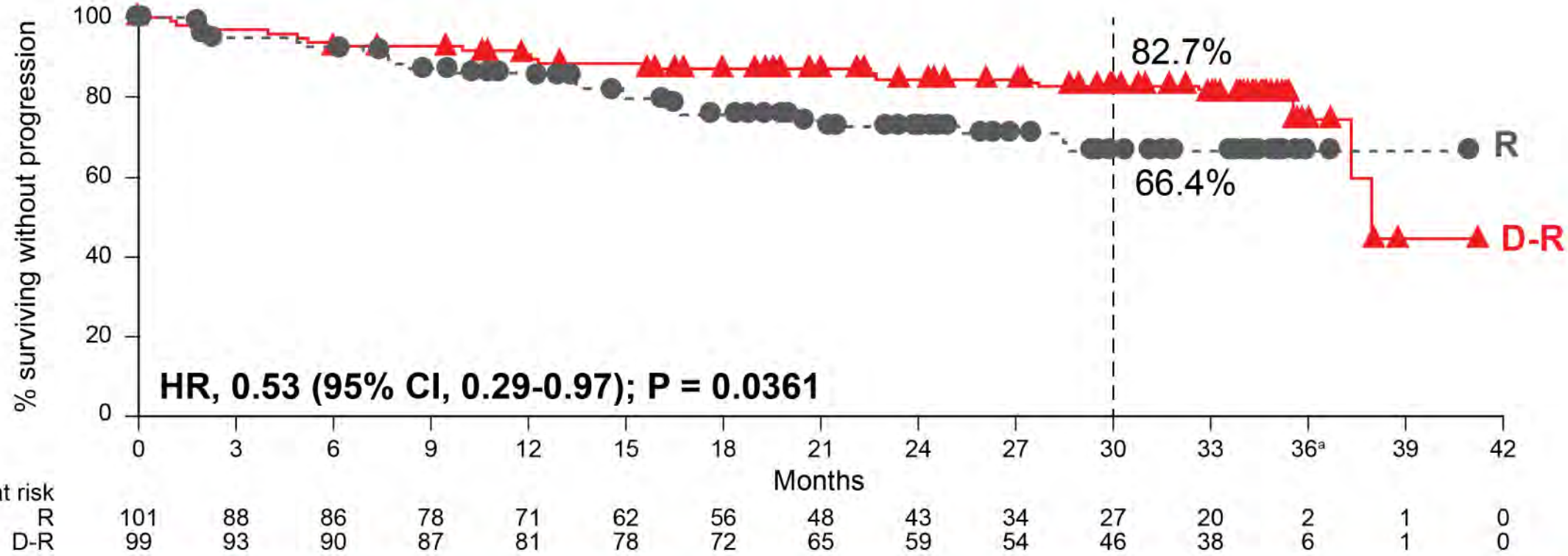
- **The addition of DARA to R more than doubled the MRD-negative conversion rate by 12 months**
- **Similar benefits were seen in supplemental MRD analyses**

OR, odds ratio; CI, confidence interval. [a]Defined as the proportion of patients who achieved MRD-negative status (at 10^{-5}) by NGS by 12 months after maintenance treatment and prior to progressive disease or subsequent antimyeloma therapy. [b]Mantel–Haenszel estimate of the common OR for stratified tables was used. The stratification factor was baseline cytogenetic risk per investigator assessment (high vs standard/unknown), as used for randomization. An OR >1 indicates an advantage for D-R. [c]*P* <0.0001 from Fisher's exact test. [d]ITT analysis set is defined as all patients who were randomized to treatment. [e]Patients who achieved ≥CR at any time during the study per International Myeloma Working Group computerized algorithm. [f]MRD-evaluable analysis set included all randomized patients who had an MRD assessment at baseline and had ≥1 post-baseline MRD evaluation. [g]Defined as the proportion of patients who achieved ≥CR response and had MRD negative status (at 10^{-5}) by NGS by 12 months after maintenance and prior to progressive disease and subsequent anti-myeloma therapy.

Presented by A Badros at the 21st International Society of Myeloma (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil

AURIGA: PFS in the ITT Population

- Median follow-up: **32.3** months

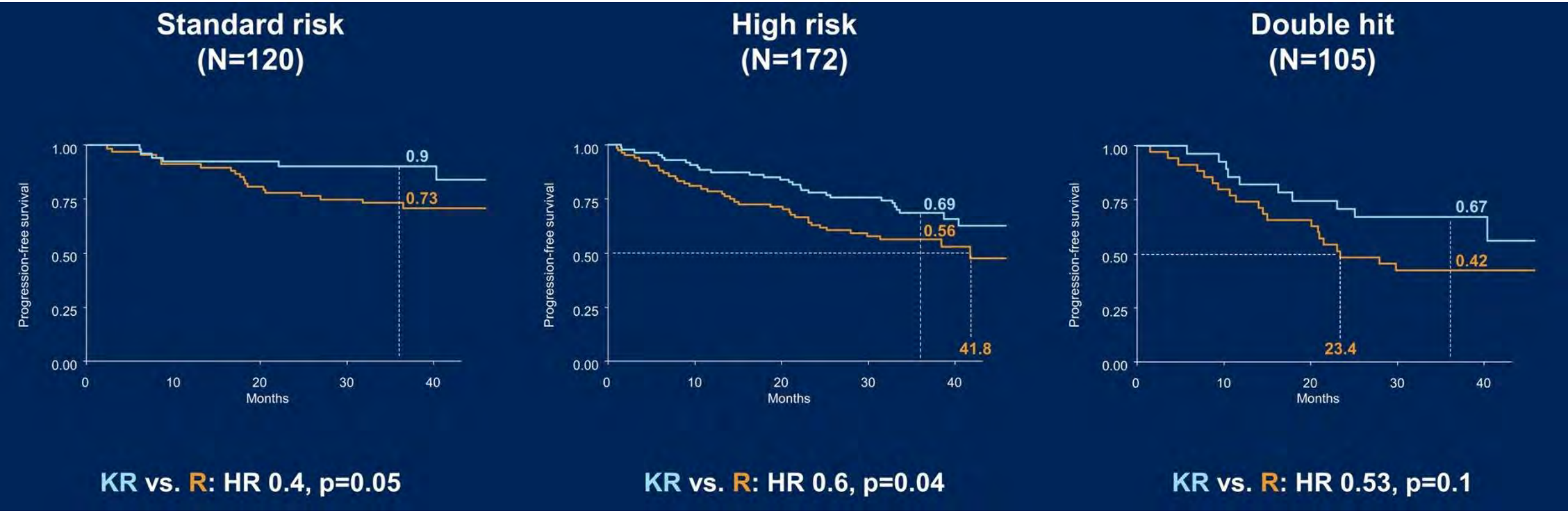


PFS favored D-R versus R, with a 47% reduction in the risk of disease progression or death

HR, hazard ratio. [a]Per study protocol, disease assessments stopped at the end of study treatment (Cycle 36), after which patients were only followed for survival. At the time of this analysis, the number of patients who reached end of study treatment was low, thus resulting in a low number of patients at risk.

Presented by A Badros at the 21st International Society of Myeloma (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil

FORTE trial: KR vs. R maintenance



Gay F et al. Lancet Oncol. 2021;22(12):1705-1720. Mina R et al. Lancet Oncol. 2023;24(1):64-76.

Courtesy of Shaji K Kumar, MD

Newly Diagnosed MM-ASCT ineligible

Courtesy of Shaji K Kumar, MD

FDA Approves Isatuximab-irfc with Bortezomib, Lenalidomide and Dexamethasone for Newly Diagnosed Multiple Myeloma

Press Release: September 20, 2024

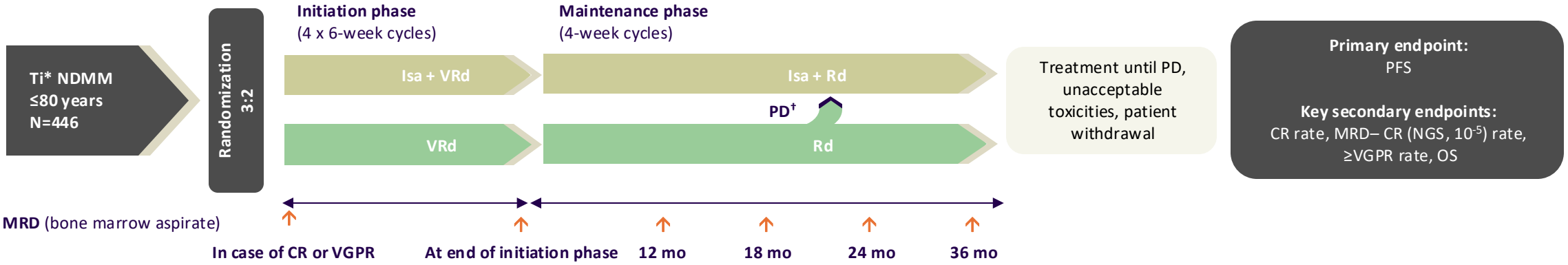
The FDA approved isatuximab-irfc with bortezomib, lenalidomide and dexamethasone for newly diagnosed multiple myeloma in adults who are not eligible for autologous stem cell transplant (ASCT).

Efficacy was evaluated in IMROZ (NCT03319667), an open-label, randomized, active-controlled Phase III trial in patients with newly diagnosed multiple myeloma who were not eligible for ASCT. Enrollment was limited to patients 80 years of age and younger. A total of 446 patients were randomized (3:2) to receive either isatuximab-irfc with bortezomib, lenalidomide and dexamethasone (Isa-VRd) or bortezomib, lenalidomide and dexamethasone (VRd).

The main efficacy outcome measure was progression-free survival (PFS) as assessed by an independent review committee based on International Myeloma Working Group criteria. IMROZ demonstrated an improvement in PFS in the Isa-VRd arm with a 40% reduction in risk of disease progression or death (hazard ratio 0.60 [95% CI: 0.44, 0.81]; *p*-value 0.0009); the median PFS was not reached (NR) (95% CI: NR, NR) in the Isa-VRd arm and was 54.3 months (95% CI: 45.2, NR) in the VRd arm.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-isatuximab-irfc-bortezomib-lenalidomide-and-dexamethasone-newly-diagnosed-multiple

IMROZ – Isa-VRd - Study design



	Day		1	8	15	22	29	36	43
Initiation	Isa IV (C1 only)	10 mg/kg							
	Isa IV (C2–4)	10 mg/kg							
	V SC	1.3 mg/m²							
	R PO‡	25 mg							
	d IV/PO §	20 mg							

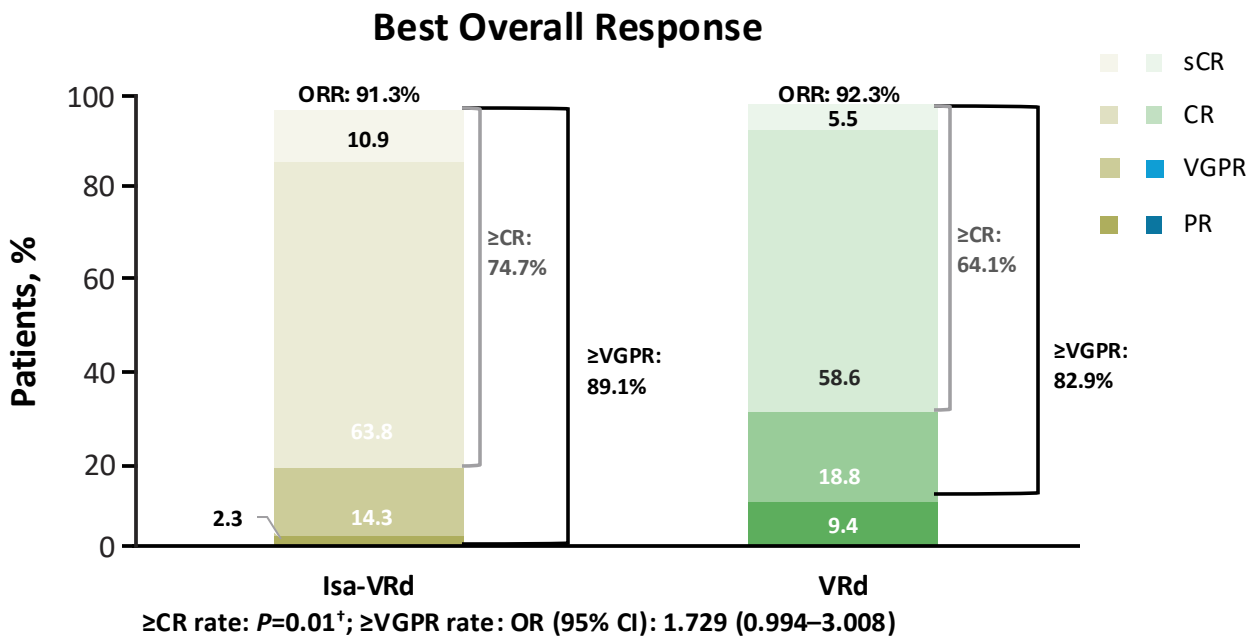
	Day		1	8	15	22	29
Maintenance	Isa IV (C5–17)	10 mg/kg					
	Isa IV (C18+)	10 mg/kg					
	R PO‡	25 mg					
	d IV/PO	20 mg					

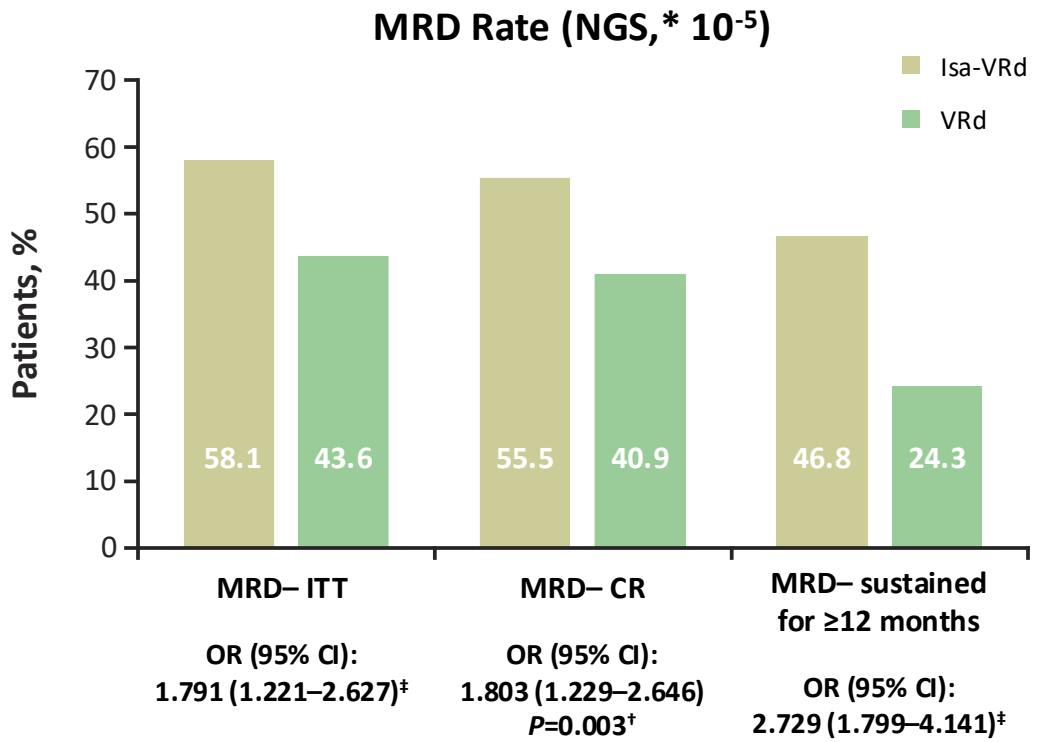
*Patients considered Ti due to age or comorbidities.
†In the maintenance phase, patients randomized to the VRd arm who experience PD may cross over to receive Isa-Rd.
‡10 mg/day if eGFR 30 to <60 mL/min/1.73 m².
§ If aged ≥75 years, d was administered on days 1, 4, 8, 11, 15, 22, 25, 29, and 32.

Facon et al, ASCO 2024

Courtesy of Shaji K Kumar, MD

IMROZ – Treatment Response

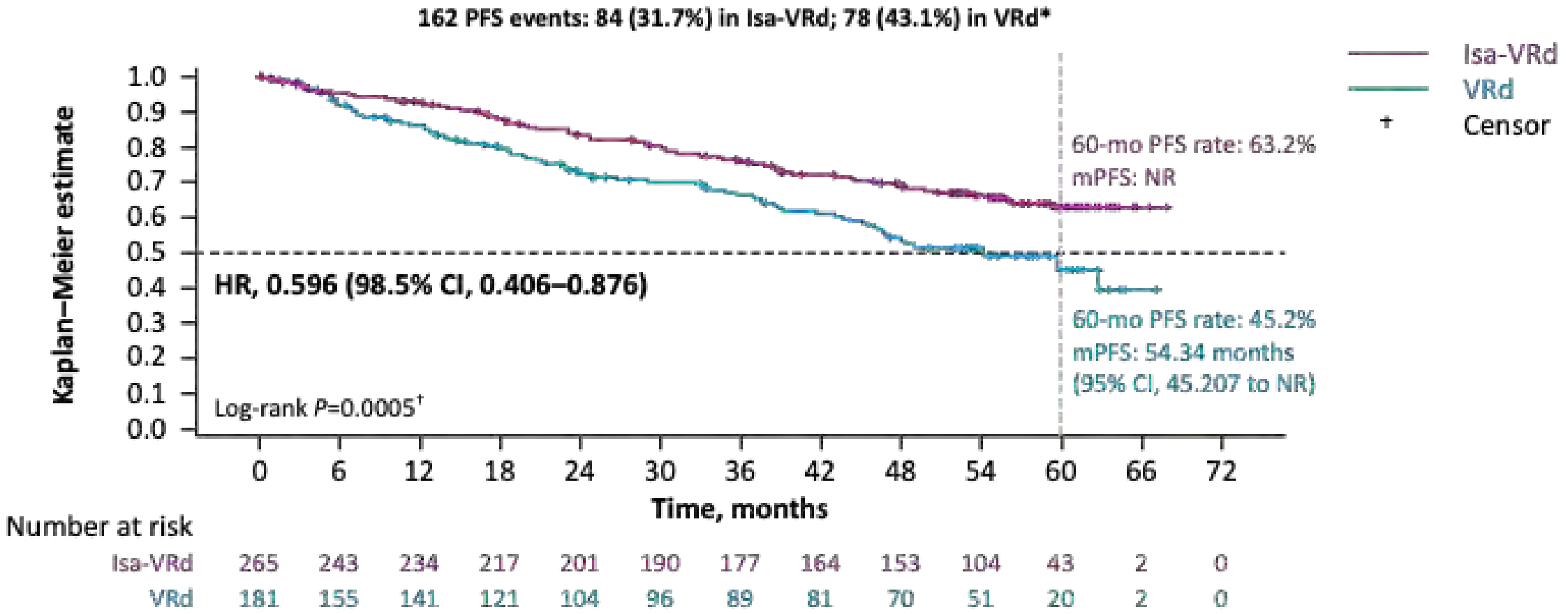




Facon et al, ASCO 2024

Courtesy of Shaji K Kumar, MD

IMROZ – Progression Free Survival



Facon et al, ASCO 2024

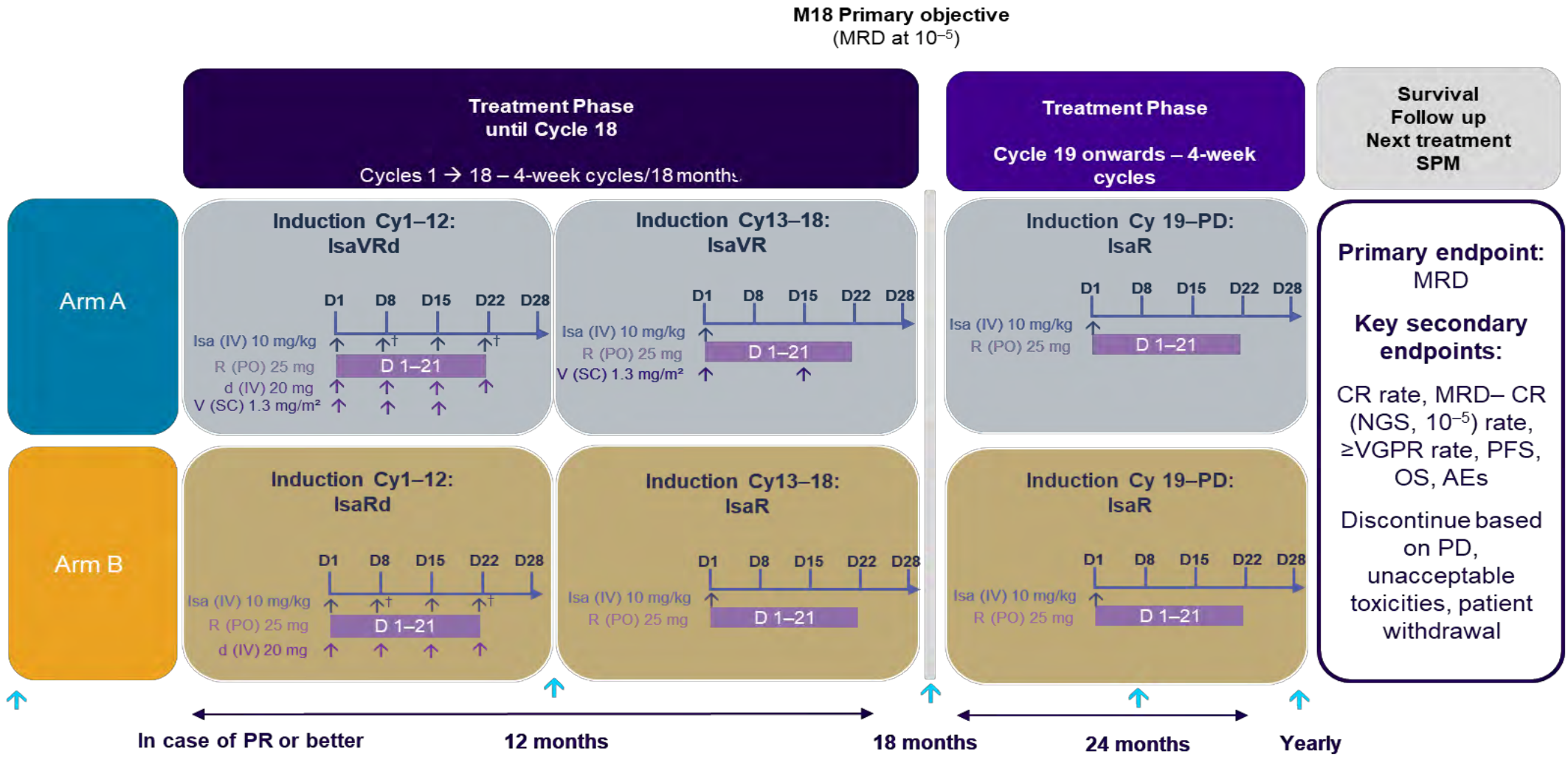
Courtesy of Shaji K Kumar, MD

BENEFIT - Study design: Isa-VRd vs Isa-Rd

N=270

- **Randomization1:1**
- **Stratified by:**

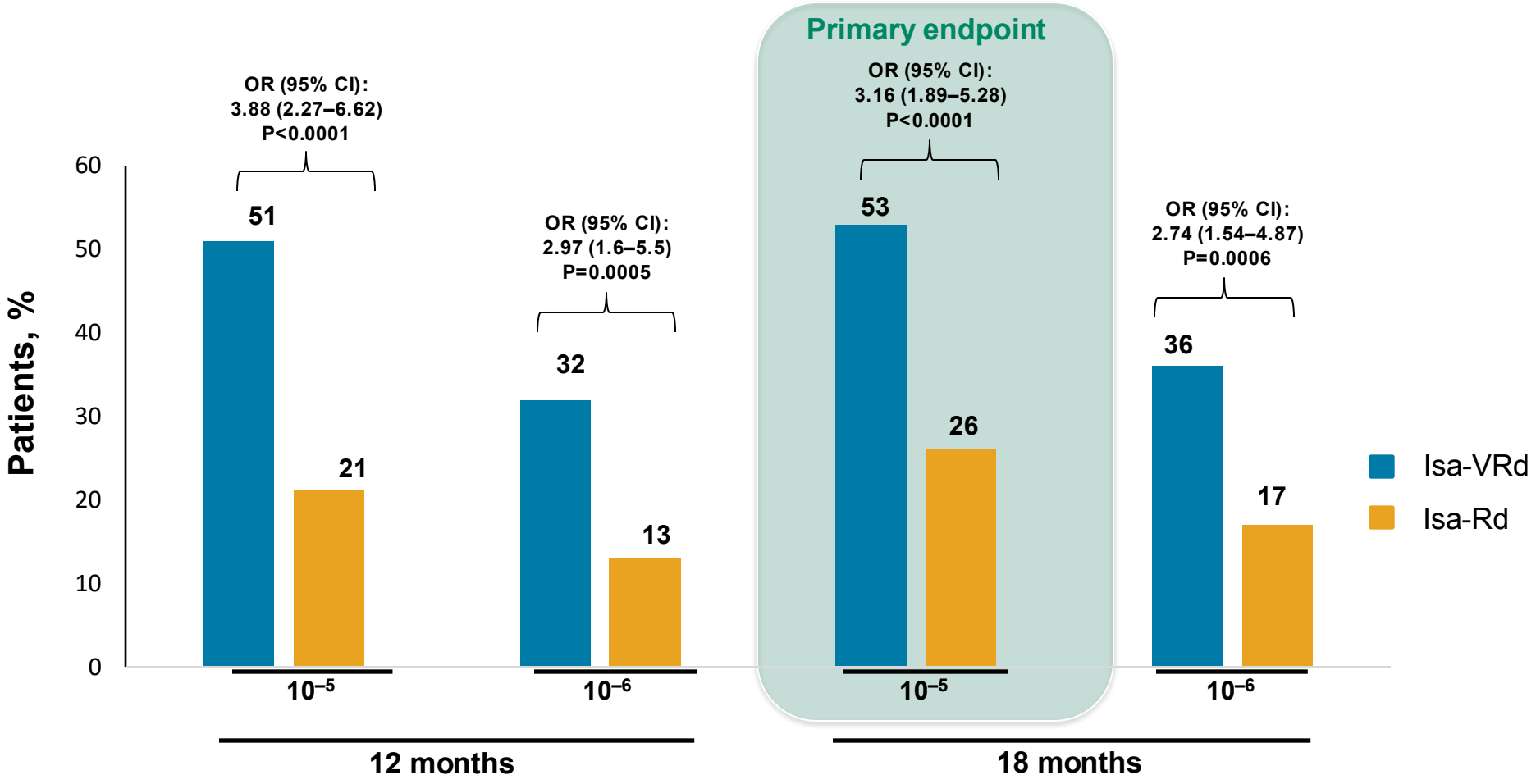
- Age: <75 and ≥ 75yrs
- Cytogenetic result by FISH (Modified Perrot score)
- Center



Leleu et al, ASCO 2024

Courtesy of Shaji K Kumar, MD

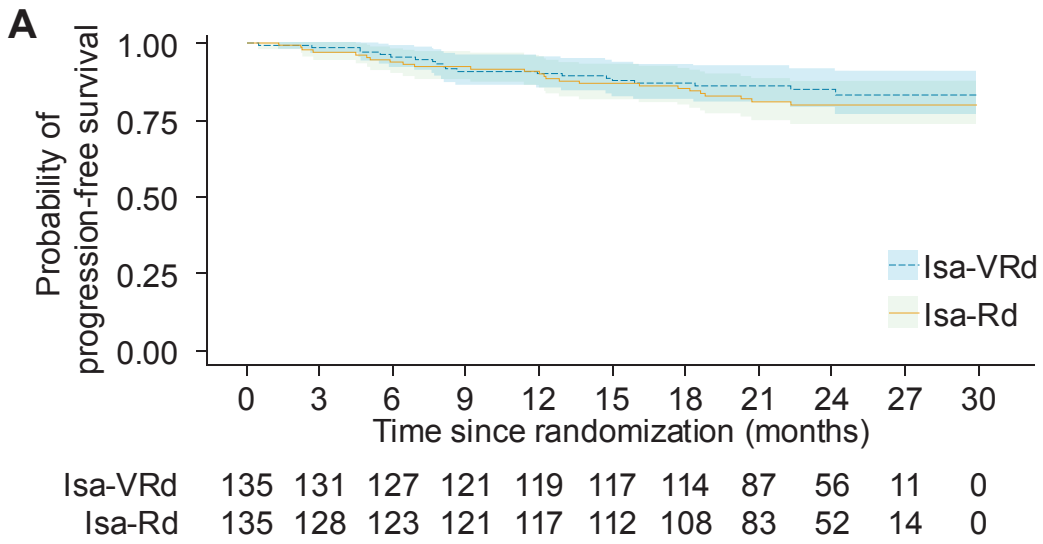
BENEFIT: MRD– rate at 18 months



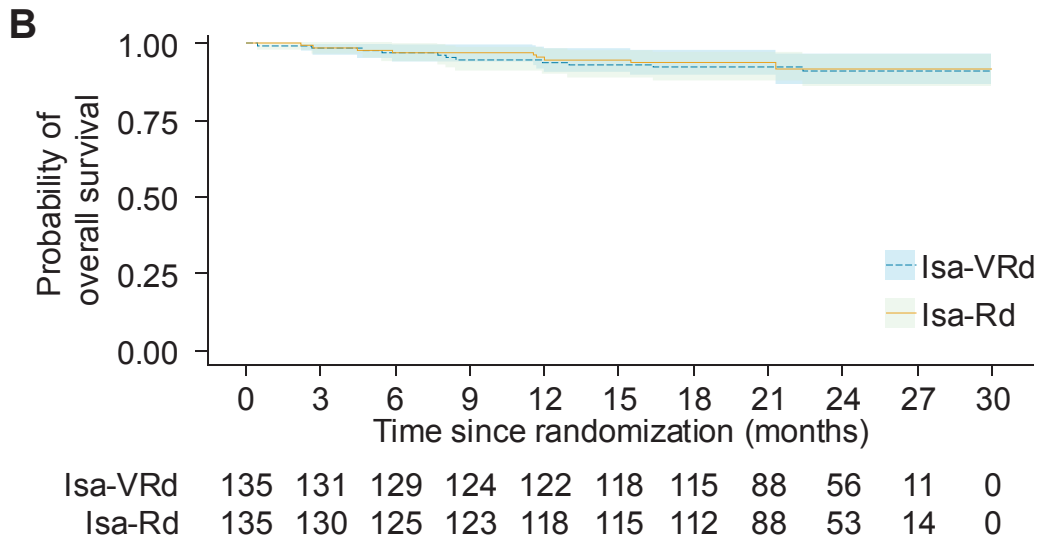
Leleu et al, ASCO 2024

Courtesy of Shaji K Kumar, MD

BENEFIT - Survival



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

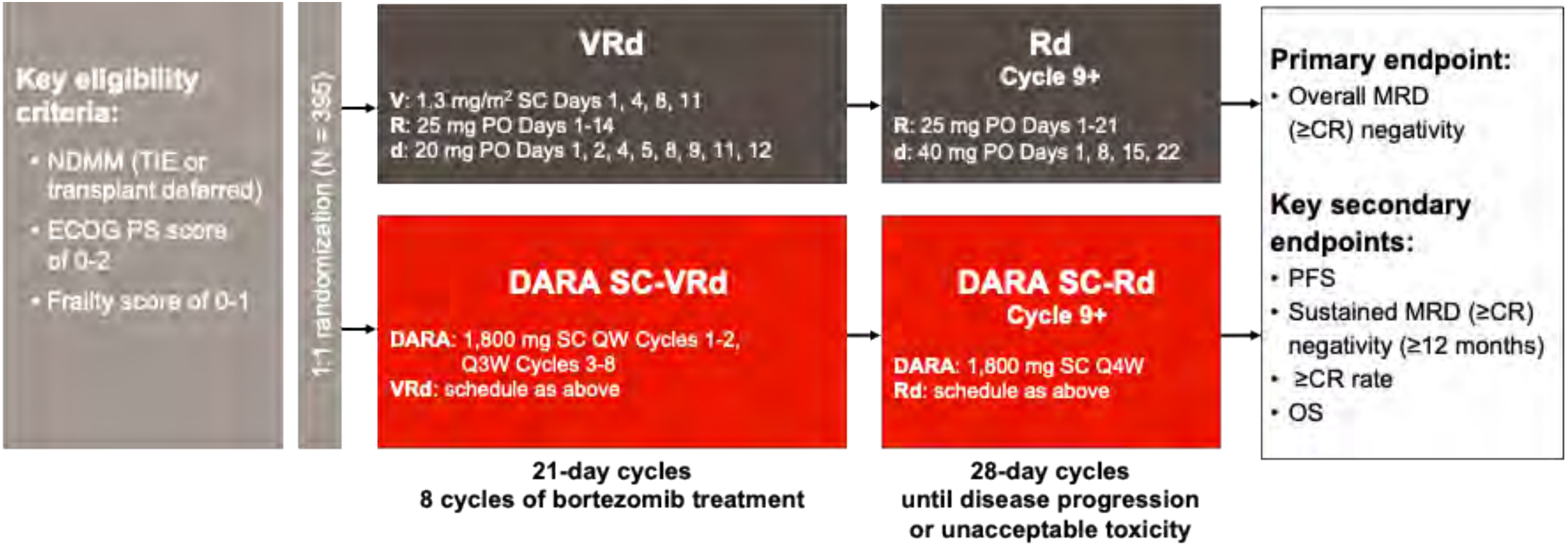


Estimated 24 months OS
91.1% (95%CI 86.1–96.4) for Isa-VRd
91.5% (95%CI 86.5–96.8) for Isa-Rd

Leleu et al, ASCO 2024

Courtesy of Shaji K Kumar, MD

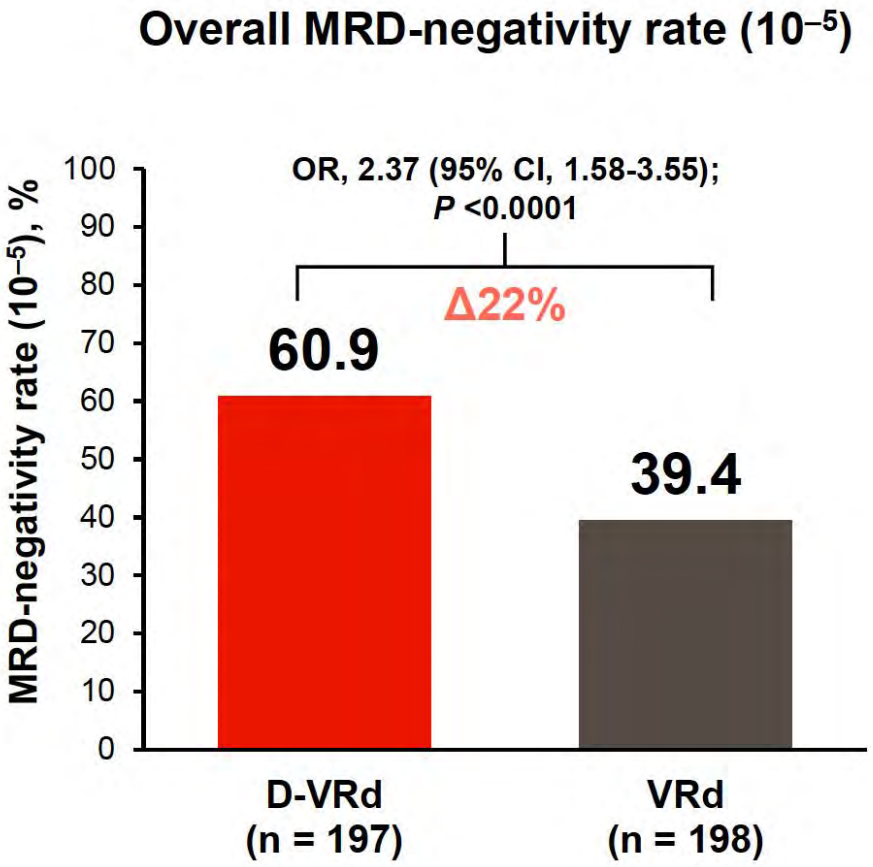
CEPHEUS

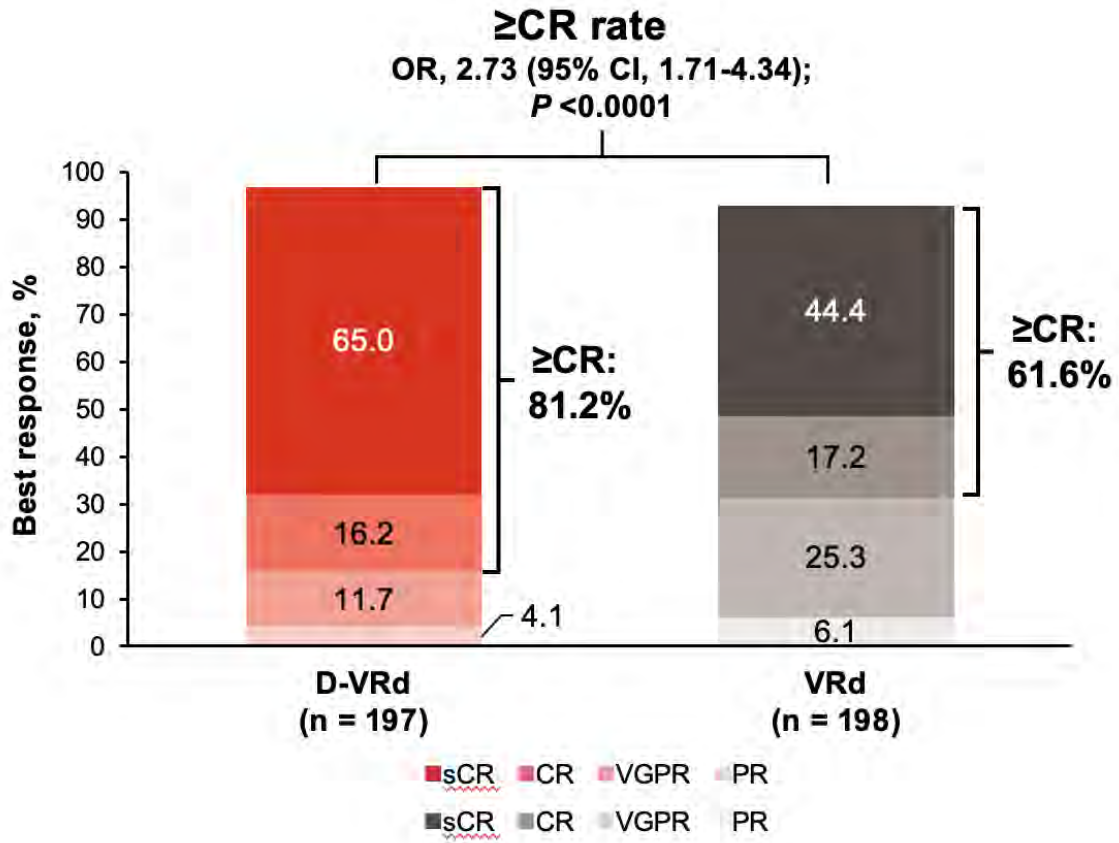


Usmani et al, IMS Annual Meeting, 2024

Courtesy of Shaji K Kumar, MD

CEPHEUS - Response

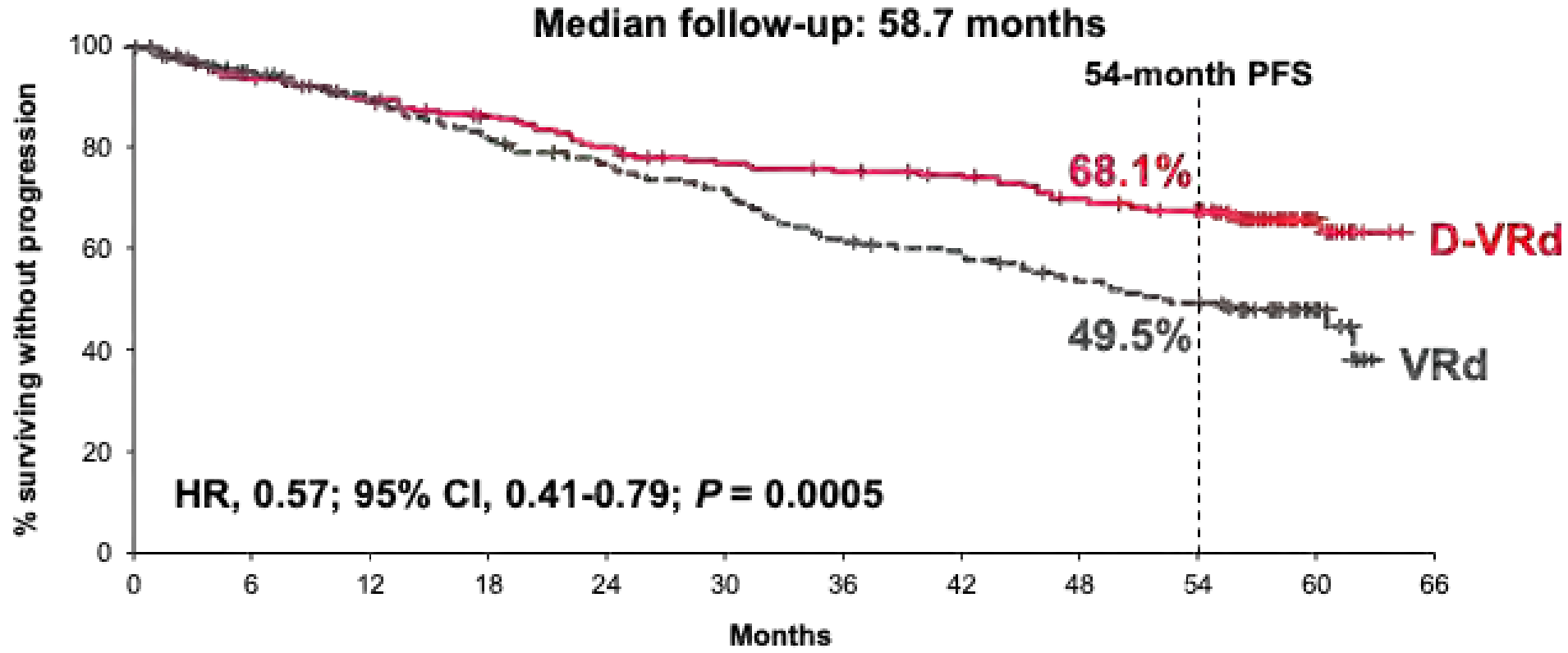




Usmani et al, IMS Annual Meeting, 2024

Courtesy of Shaji K Kumar, MD

CEPHEUS - PFS

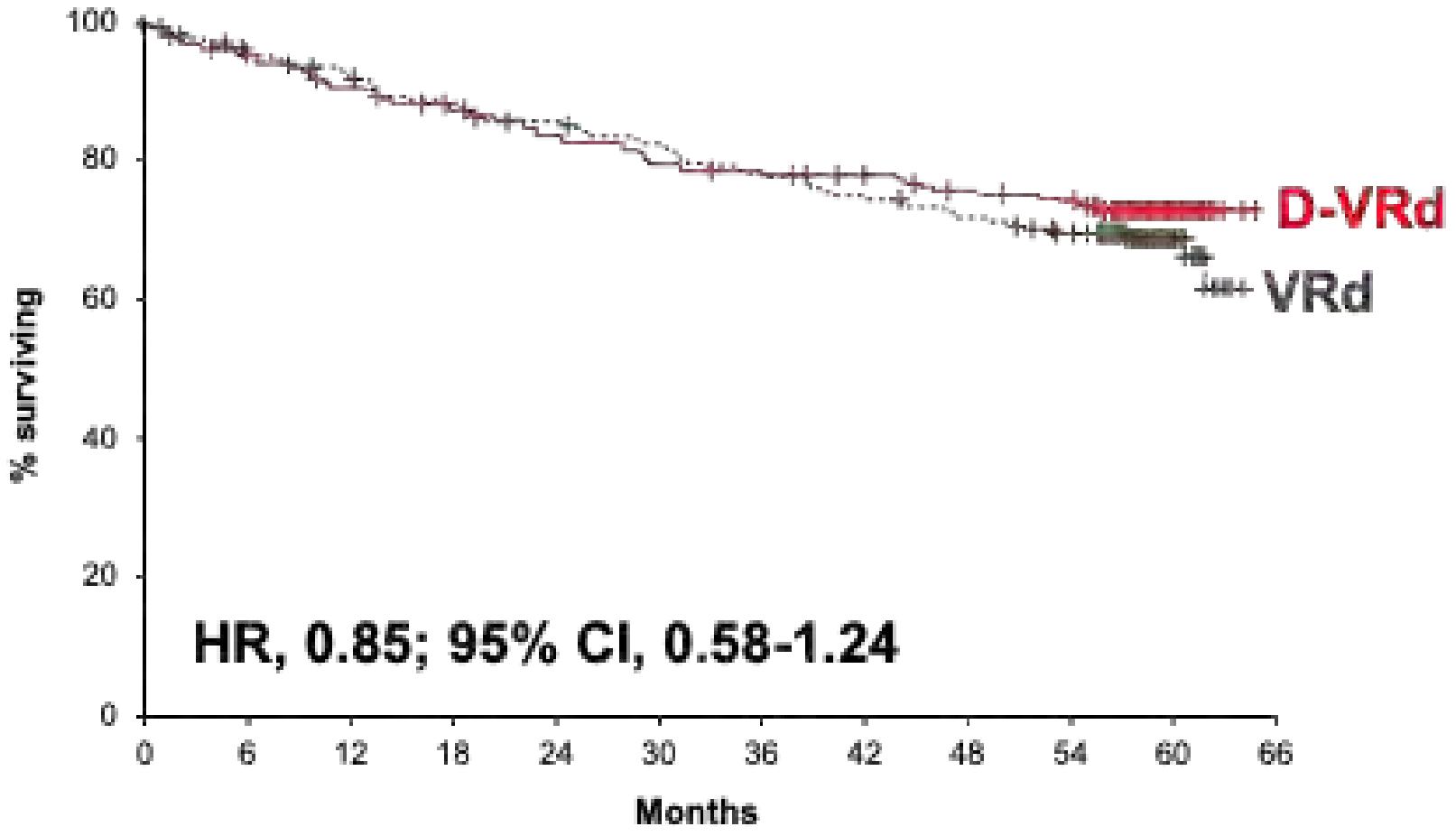


No. at risk												
D-VRd	197	180	170	160	149	140	136	132	122	115	33	0
VRd	198	174	157	143	131	123	105	98	88	81	21	0

Usmani et al, IMS Annual Meeting, 2024

Courtesy of Shaji K Kumar, MD

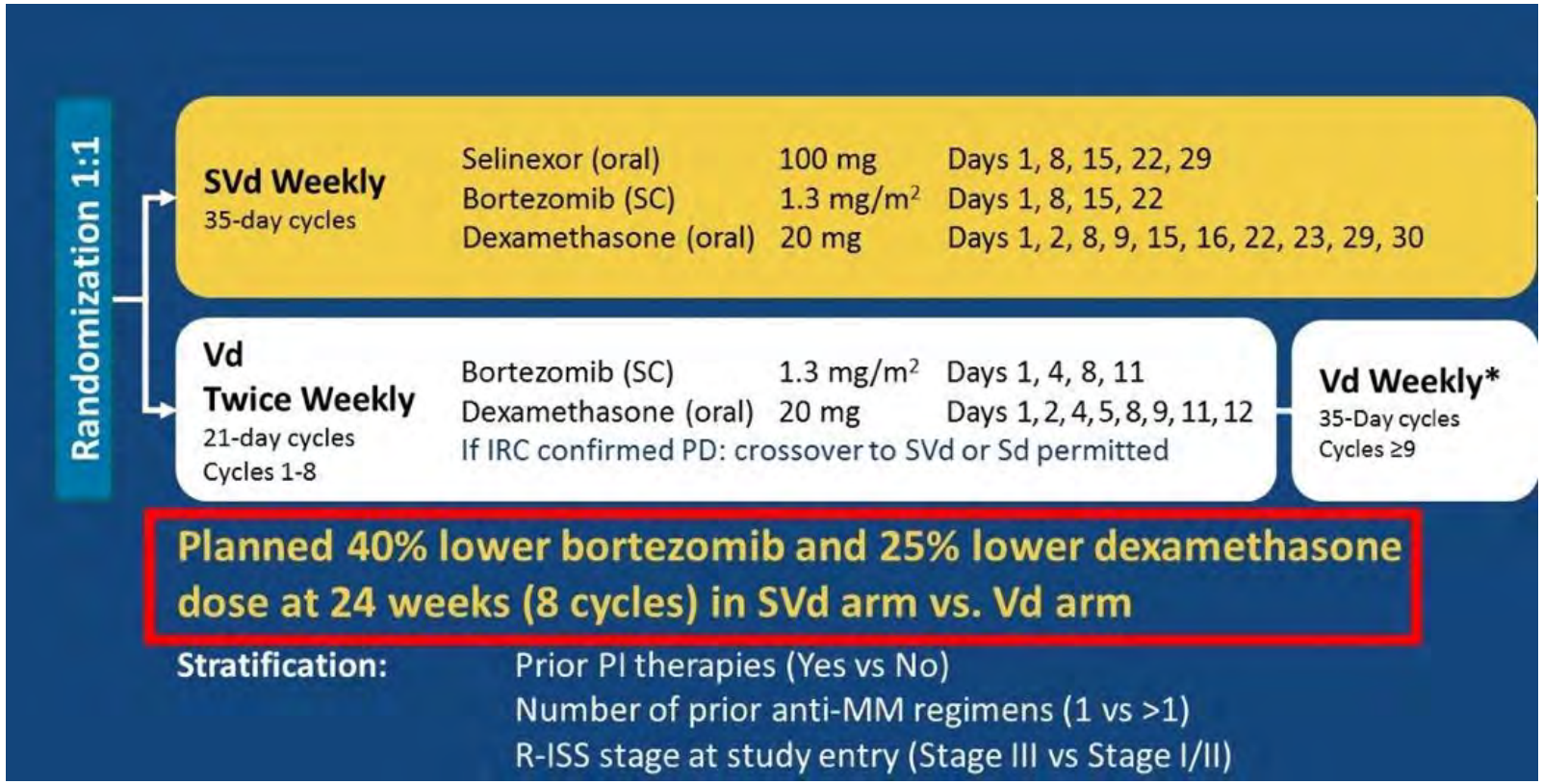
CEPHEUS - Overall Survival



Usmani et al, IMS Annual Meeting, 2024

Courtesy of Shaji K Kumar, MD

BOSTON Trial

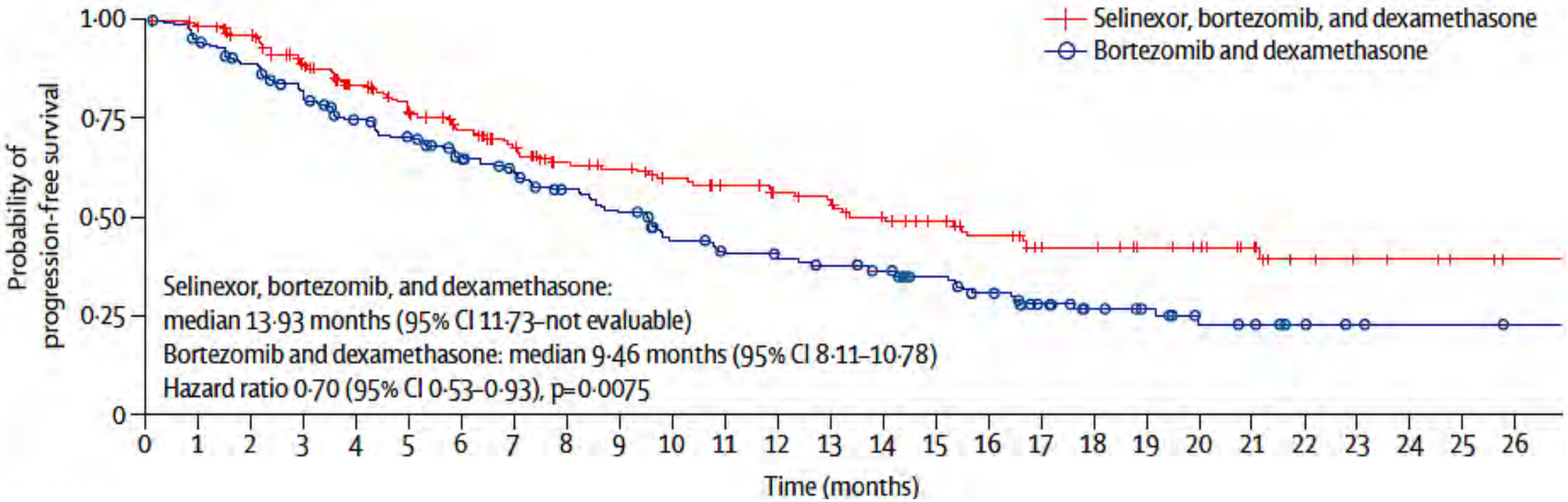


	Selinexor, bortezomib, and dexamethasone group (n=195)	Bortezomib and dexamethasone group (n=207)
Overall response rate*	149 (76·4% [69·8–82·2])	129 (62·3% [55·3–68·9])
Best overall response†		
Stringent complete response	19 (10%)	13 (6%)
Complete response	14 (7%)	9 (4%)
Very good partial response	54 (28%)	45 (22%)
Partial response	62 (32%)	62 (30%)
Minimal response	16 (8%)	20 (10%)
Stable disease	25 (13%)	40 (19%)
Progressive disease	1 (1%)	10 (5%)
Non-evaluable	4 (2%)	8 (4%)
Negative status for minimal residual disease‡	9 (5%)	8 (4%)

Groscki et al, Lancet, 2020

Courtesy of Shaji K Kumar, MD

BOSTON Trial: PFS



Groscki et al, Lancet, 2020

Courtesy of Shaji K Kumar, MD

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

A CME/MOC-, ACPE- and NCPD-Accredited Event

Saturday, October 26, 2024
7:15 AM – 12:30 PM ET

RTP
RESEARCH TO PRACTICE

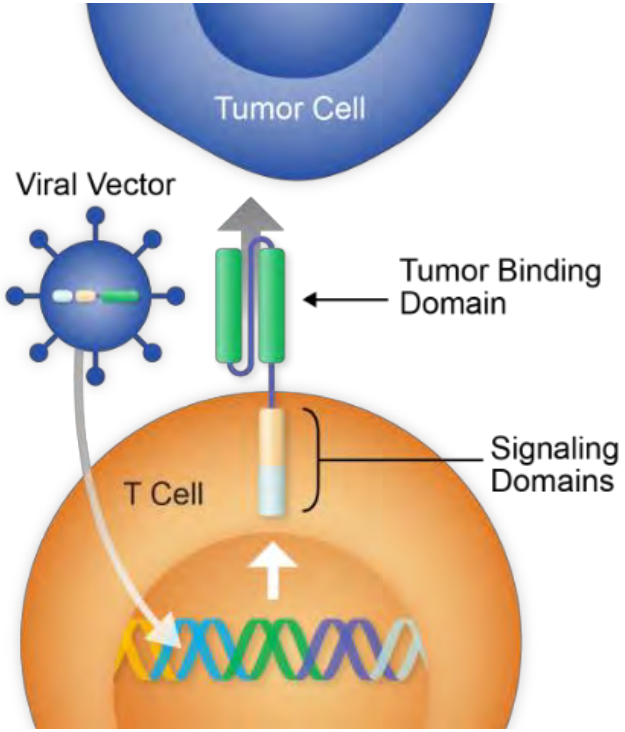
Chimeric Antigen Receptor (CAR) T-Cell Therapy, Bispecific Antibodies and Antibody-Drug Conjugates

Noopur Raje, MD
Center for Multiple Myeloma
MGH Cancer Center

Professor of Medicine
Harvard Medical School

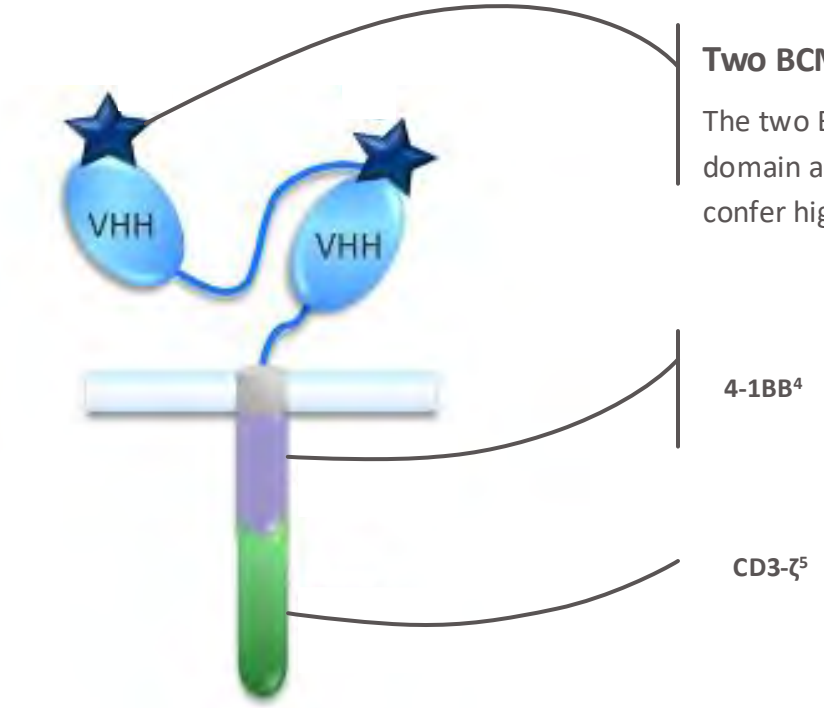
Ide-cel and Cilta-cel Constructs

Idecabtagene Vicleucel (ide-cel) CAR T



Second-generation CAR construct[1]

Ciltacabtagene Autoleucel (cilta-cel) CAR T

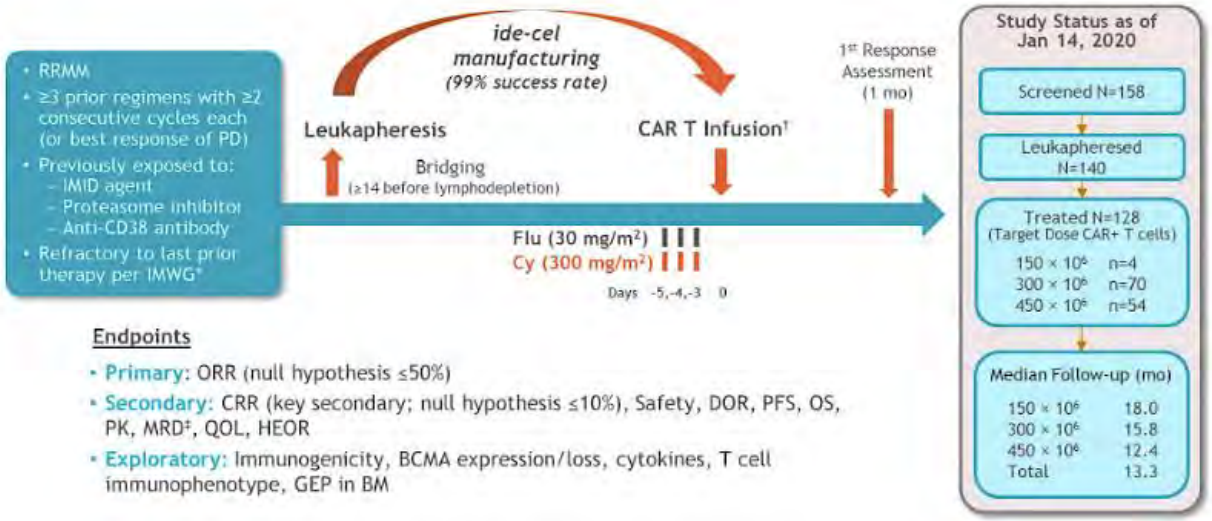


Dual epitope-binding CAR construct[1,2]

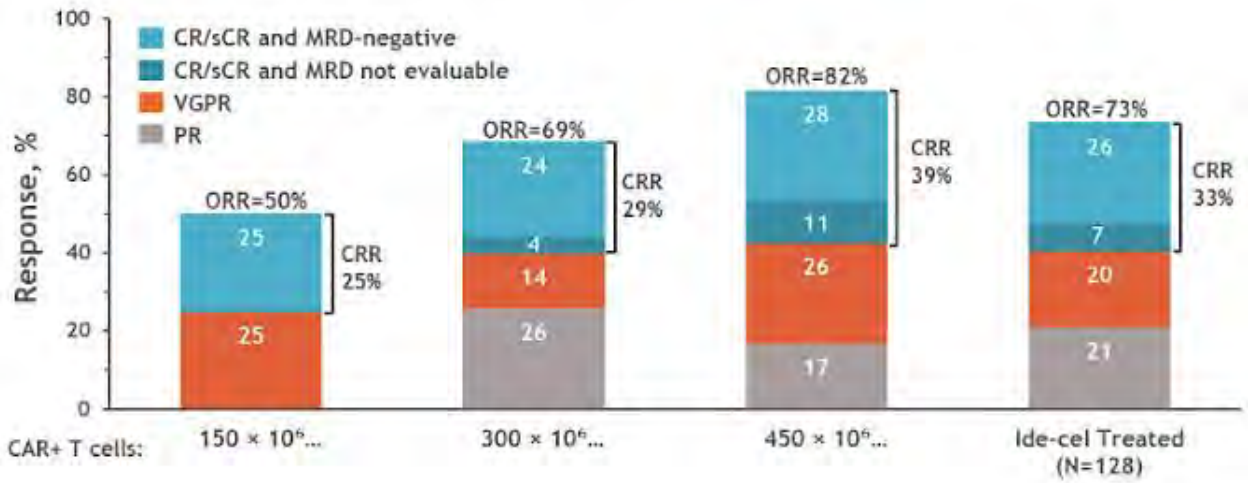
- BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD, cluster of differentiation; ide-cel, idecabtagene vicleucel; MM, multiple myeloma; MND, murine leukemia-derived promoter; scFv, single-chain variable fragment.
- 1. Raje N et al. *N Engl J Med*. 2019;380(18):1726-1737. 2. Friedman KM et al. *Hum Gene Ther*. 2018;29(5):585-601. 3. Song DG et al. *Cancer Res*. 2011;71(13):4617-4627. 4. Zhao WH et al. *J Hematol Oncol*. 2018;11(1):141. 5. Berdeja JG et al. ASCO 2020. Abstract 8505.

KarMMa: Ide-cel Registration Study

Trial design



Response

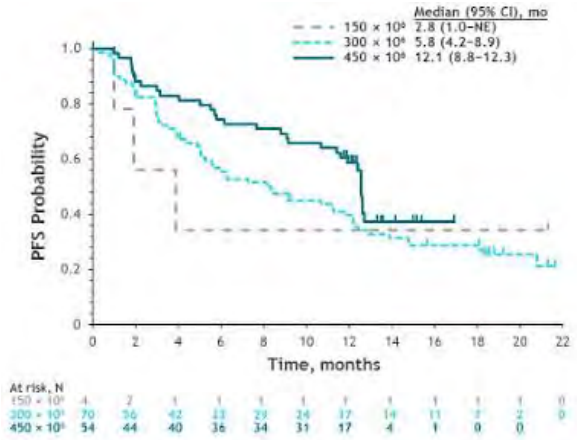


- Primary (ORR > 50%) and key secondary (CRR >10%) endpoints met in the Ide-cel treated population
  - *ORR of 73% (95% CI, 65.8-81.1; P<0.0001)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7-40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5-8.8); median time to CR of 2.8 mo (range, 1.0-11.8)
- Median follow-up of 13.3 mo across target dose levels

Munshi et al. N Engl J Med 2021;384:705-16.

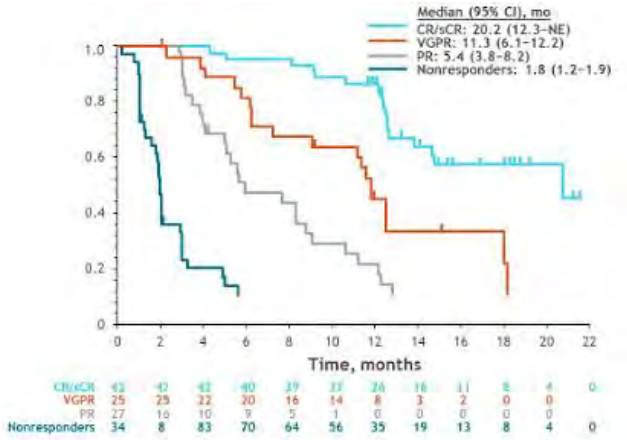
KarMMa: PFS and MRD-negativity

PFS by Target Dose



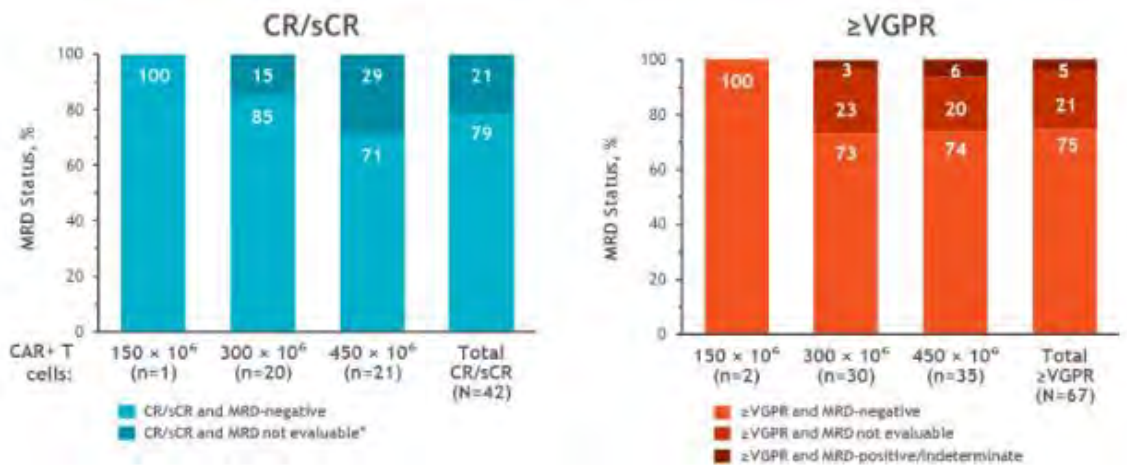
- PFS increased with higher target dose
- Median PFS was 12 mo at 450 x 10^6 CAR+ T cells

PFS by Best Response



- PFS increased by depth of response
- Median PFS was 20 mo in patients with CR/sCR

MRD-negativity by target dose



- mOS 24.8 months (95% CI: 19.9-31.2) among all treated patients

Target Dose, CAR+ T cells	150 x 10^6	300 x 10^6	450 x 10^6	Total
All ide-cel treated	N=4	N=70	N=54	N=128
MRD-negative and >CR, n(%) [95% CI]	1 (25) [0.6-80.6]	17 (24) [14.8-36.0]	15 (28) [16.5-41.6]	33 (26) [18.5-34.3]
MRD-negative and >VGPR, n(%) [95% CI]	2 (50) [6.8-93.2]	22 (31) [20.9-43.6]	26 (48) [34.4-62.2]	50 (39) [30.6-48.1]

Munshi et al. N Engl J Med 2021;384:705-16.

CARTITUDE-1: Cilta-cel Registration Study

Trial design

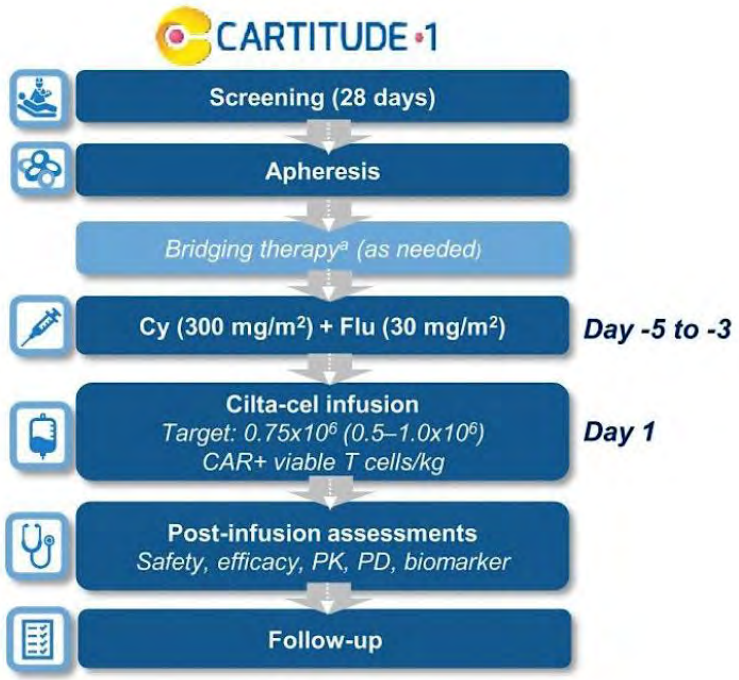
Primary objectives

- Phase 1b: Characterize the safety of cilta-cel and confirm the recommended phase 2 dose
- Phase 2: Evaluate the efficacy of cilta-cel by ORR

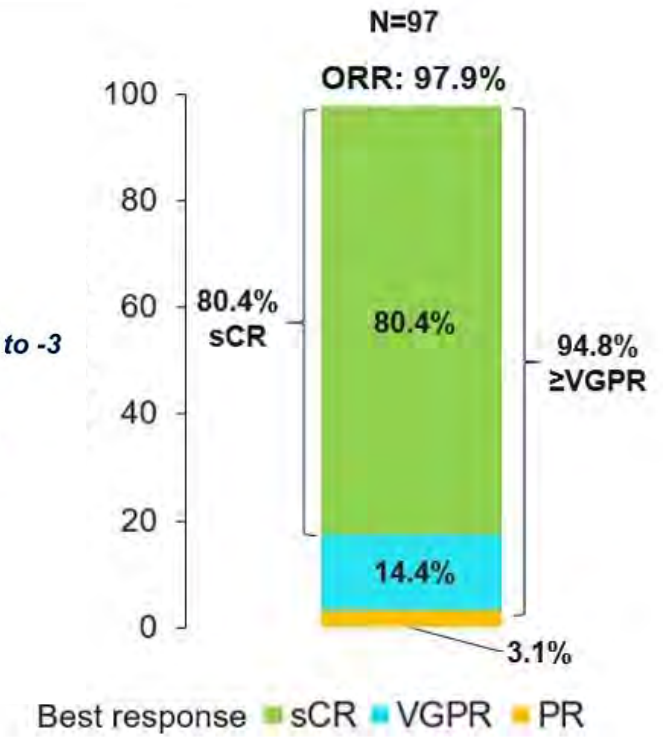
Key eligibility criteria

- Progressive MM per IMWG criteria
- ECOG PS ≤1
- Measurable disease
- ≥3 prior therapies or double refractory
- Prior PI, IMiD, anti-CD38 therapy

- Median administered dose: 0.71×10^6 ($0.51–0.95 \times 10^6$) CAR+ viable T cells/kg



Response



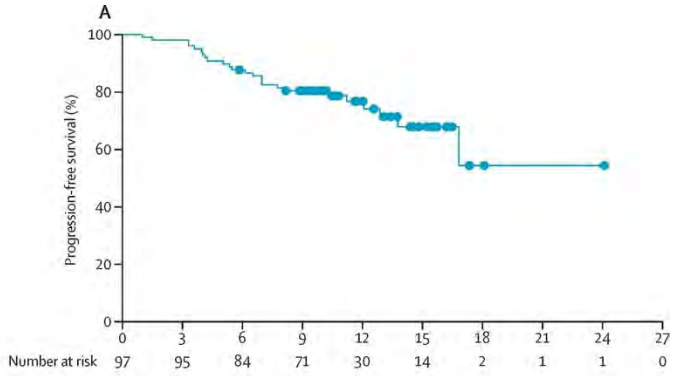
Berdeja et al. Lancet 2021; 398: 314–24

CARTITUDE-1 Follow Up

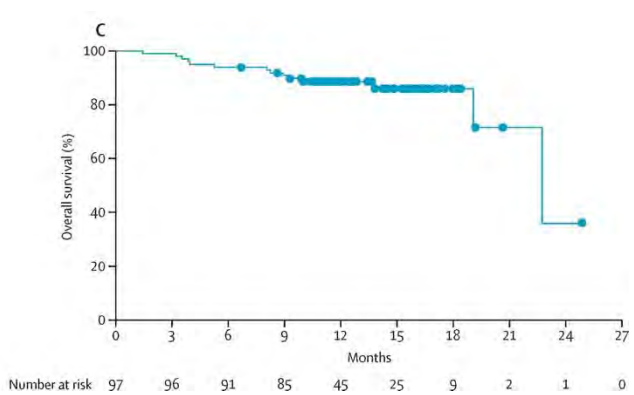
~27 months

~3 years

PFS

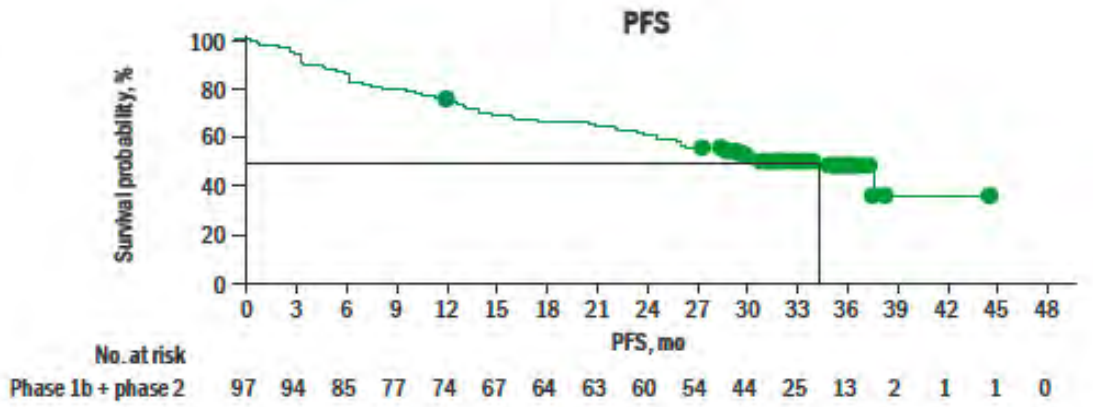


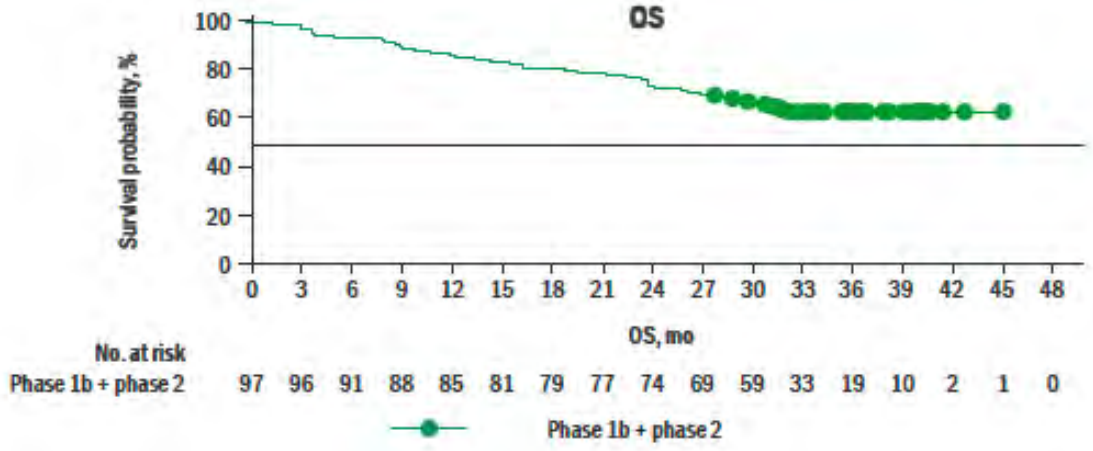
OS



PFS by CR and sustained MRD negativity

Subgroups	mPFS (95% CI), mo	30-mo PFS rate	36-mo PFS rate
All patients	34.9 (25.2–NE)	54.2%	47.5%
≥CR[a]	38.2 (34.9–NE)	66.8%	59.8%
12-mo sustained MRD negativity[b]	NR (NE–NE)	74.9%	NE
12-mo sustained MRD-negative ≥CR[b]	NR (NE–NE)	78.5%	NE





Berdeja et al. Lancet 2021; 398: 314–24
Lin et al. ASCO 2023;Abstract 8009.

KarMMa and CARTITUDE-1 CRS and NT

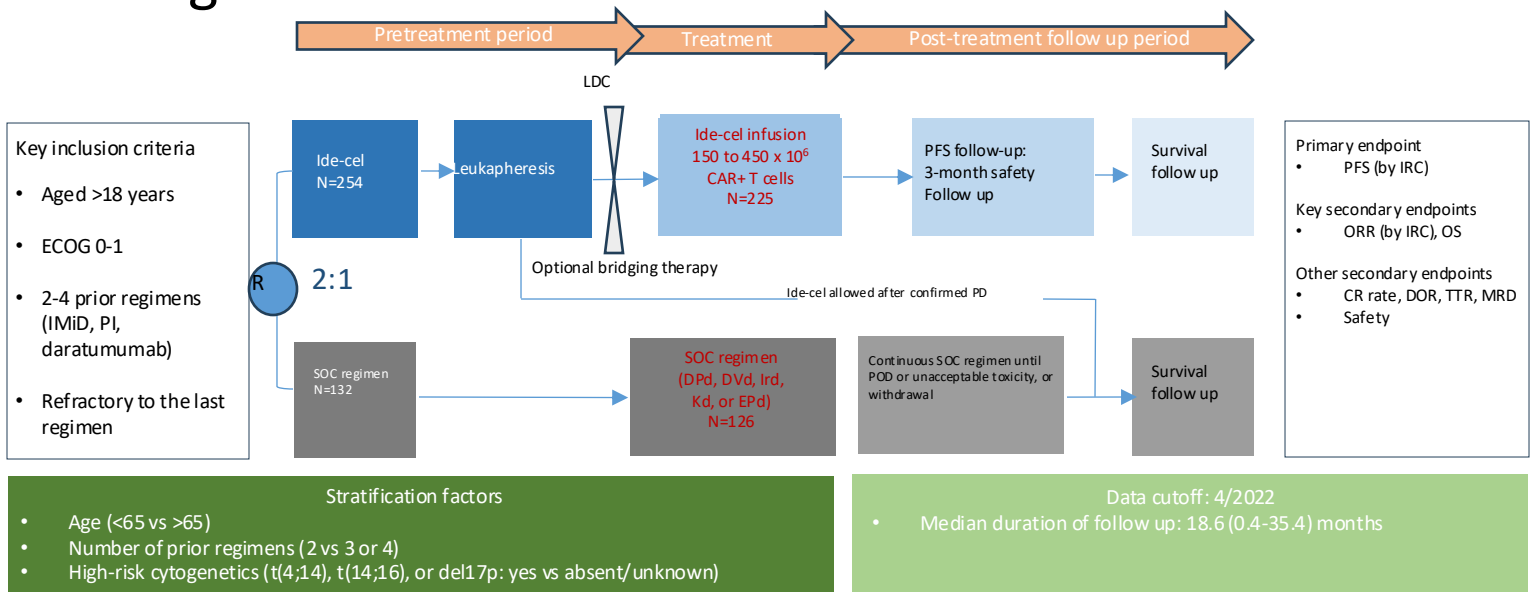
	Ide-cel	Cilta-cel
FDA approval Trial, Reference Publication	KarMMa (n=124) Munshi NEJM 2021	CARTITUDE-1 (n=97) Berdeja Lancet 2021
Safety		
CRS (all; grades 3–4)	84% (5%)	95% (5%)
Median onset of CRS	1 day	7 days
ICANS (all; grades 3–4)	18% (3%)	17% (2%)
Delayed neurotoxicity (all; grades 3-4)	None	12% (9%)
Infections (all; grades 3–4)	69% (22%)	58% (20%)
Grades 3–4 neutropenia > 1 month Grades 3–4 thrombocytopenia > 1 month	41% 48%	10% 25%

Berdeja et al. Lancet 2021; 398: 314–24
Munshi et al. N Engl J Med 2021;384:705-16.

CAR T-cell therapy in earlier lines

KarMMa-3: Ide-cel vs SOC After 2-4 Lines

Trial design



Baseline characteristics

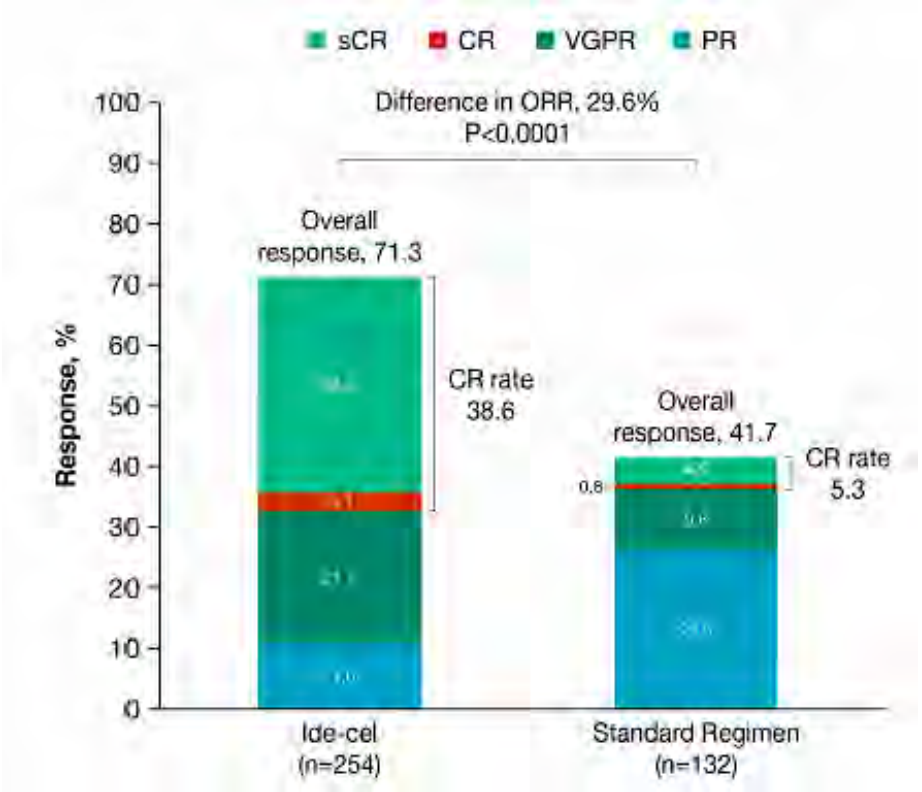
Median age	63 yrs
Median time since diagnosis	4.1 yrs
Median prior therapies	N=3
Triple-class refractoriness	66%
Daratumumab refractoriness	95%
High-risk cytogenetics	44%

Phase 3 KarMMa-3 study compared ide-cel vs SOC in R/R patients MM after 2-4 prior lines

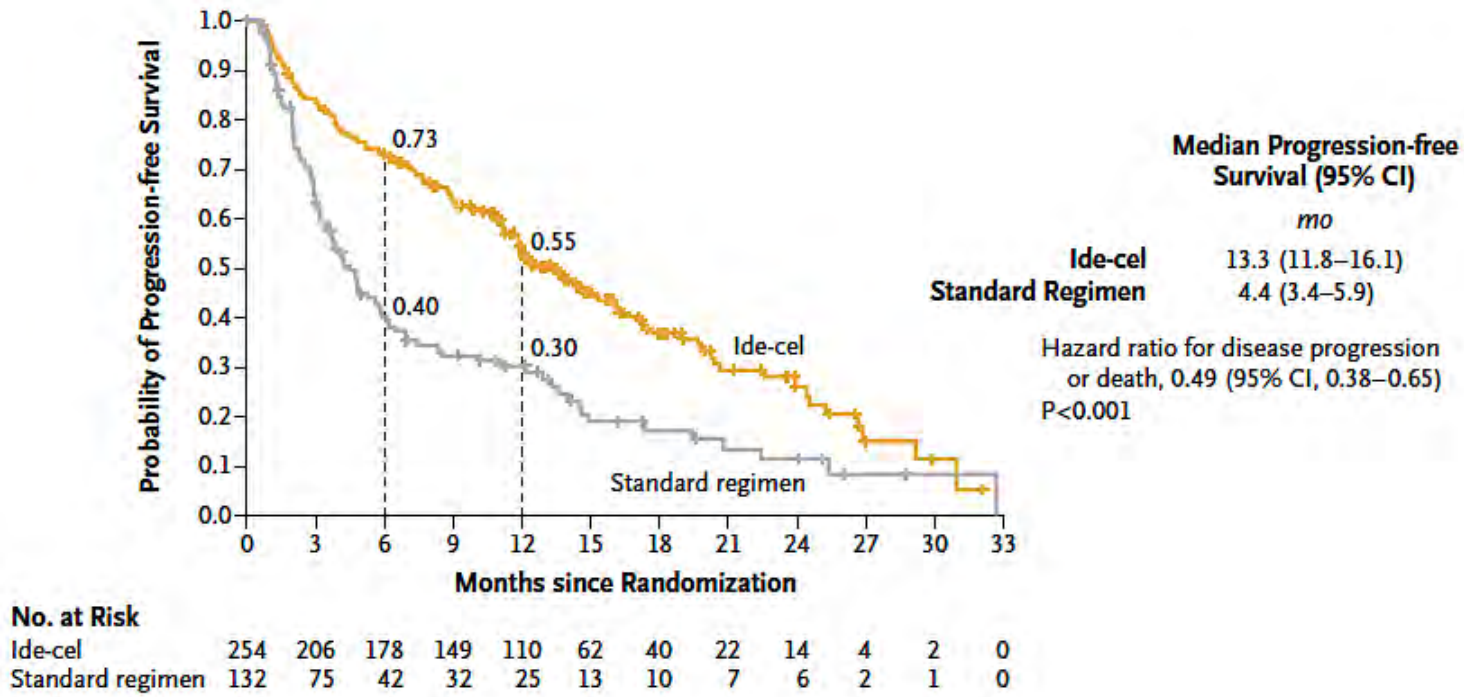
Paula Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014

KarMMa-3: Response and PFS

Response



PFS

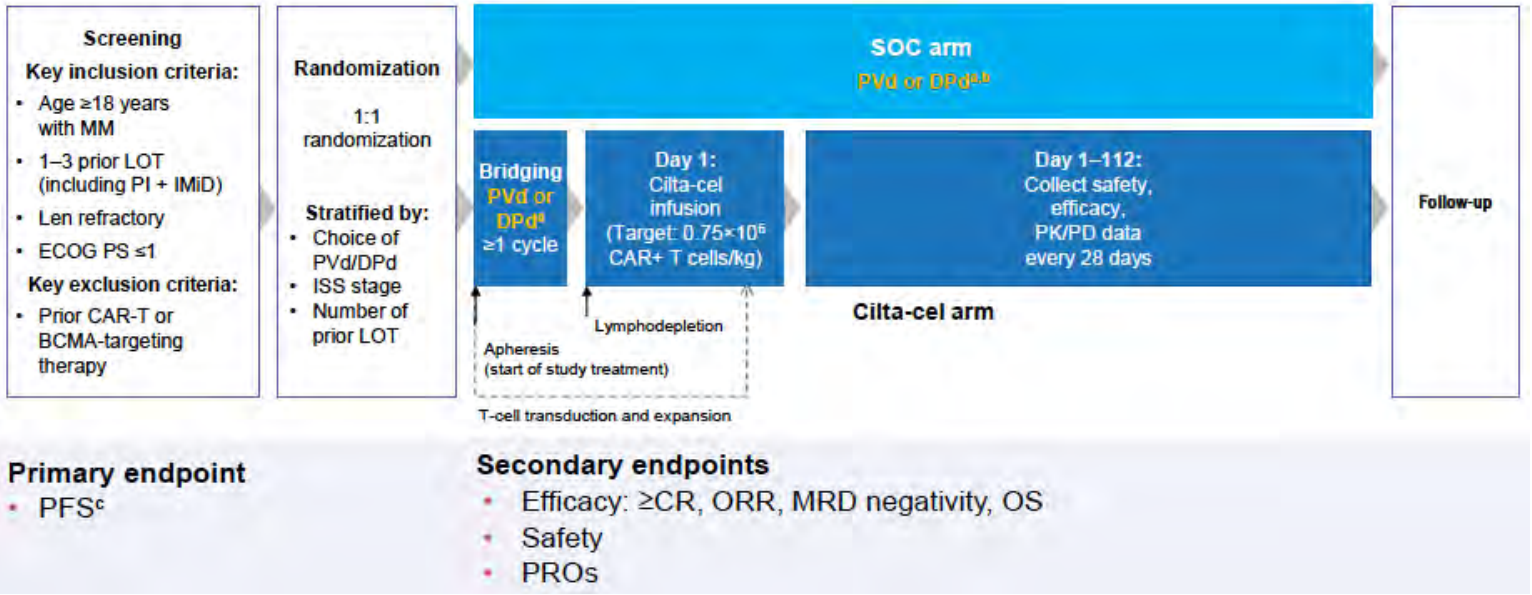


Phase 3 KarMMa-3 study compared ide-cel vs SOC in R/R patients MM after 2-4 prior lines

Paula Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014

CARTITUDE-4: Cilta-cel vs DPd/PVd After 1-3 Lines

Trial design



Baseline characteristics

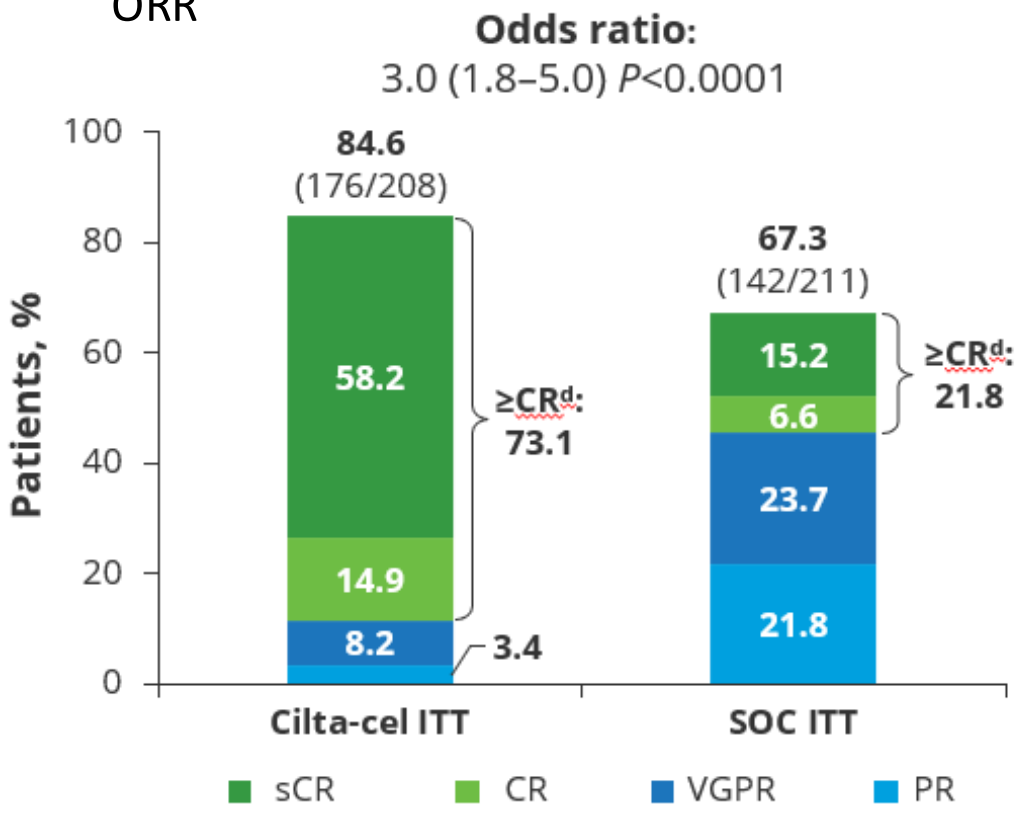
Median age	61.5 yrs
Median time since diagnosis	3 yrs
Median prior therapies	N=2
Triple-class refractoriness	14.4%
Daratumumab refractoriness	23.1%
High-risk cytogenetics	59.4%

Phase 3 CARTITUDE-4 compared cilta-cel vs SOC in R/R patients MM after 1-3 prior lines

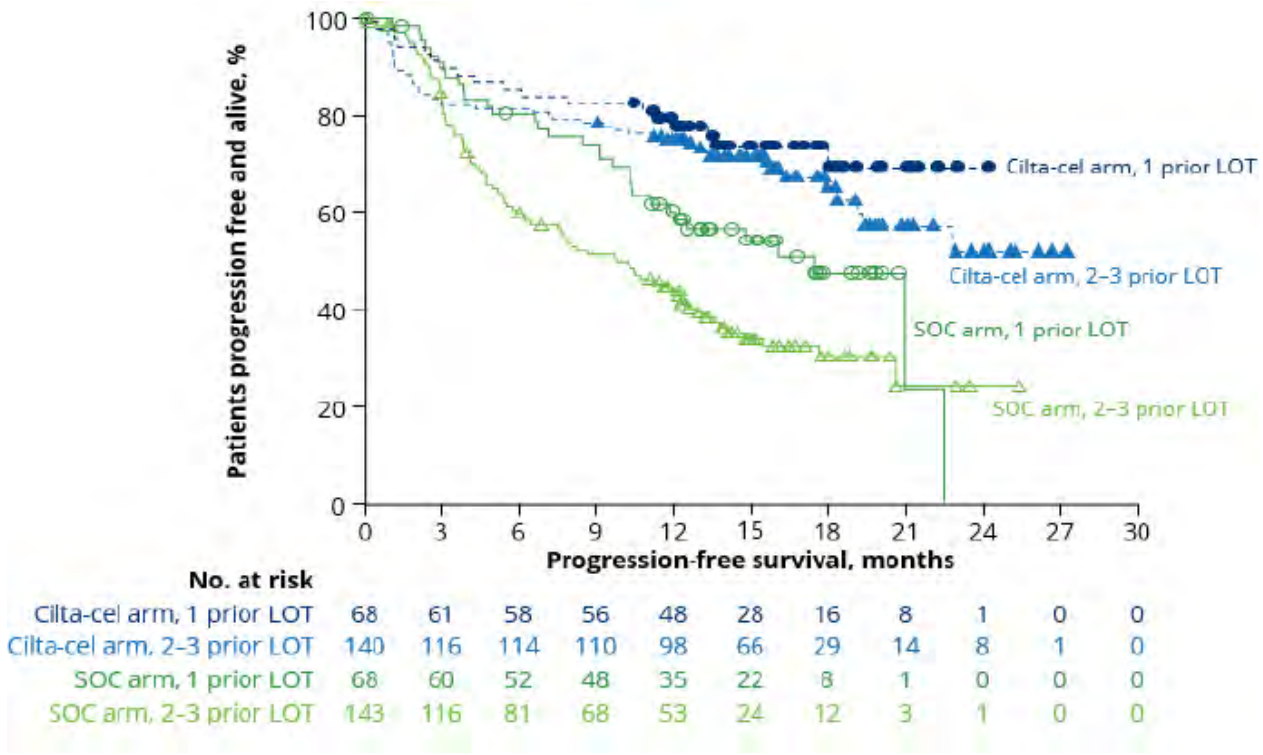
Jesús San-Miguel et al. N Engl J Med 2023; 389:335-347

CARTITUDE-4: Response and PFS

ORR



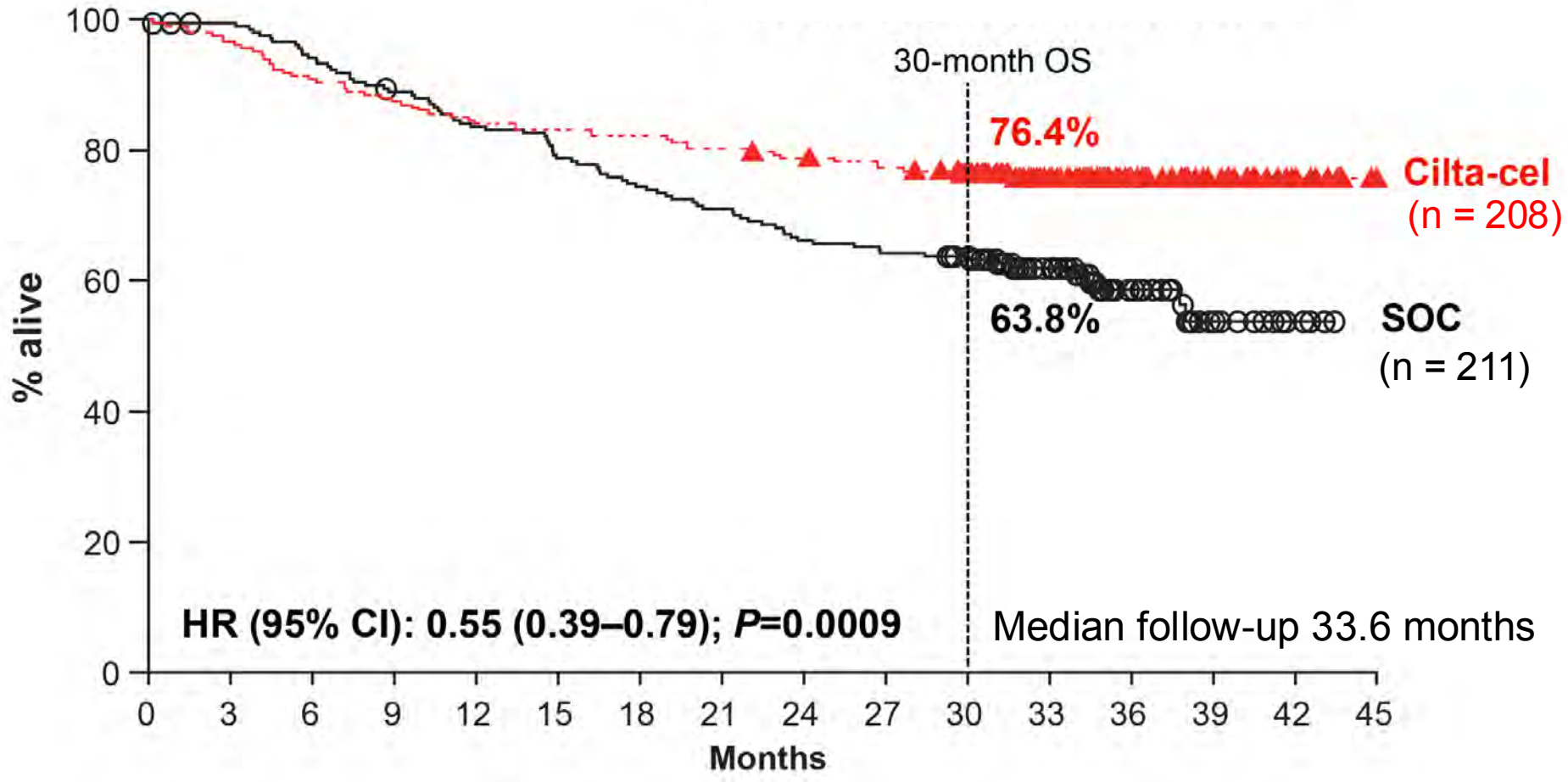
PFS by treatment and number of prior lines



Phase 3 CARTITUDE-4 compared cilta-cel vs SOC in R/R patients MM after 1-3 prior lines

Jesús San-Miguel et al. N Engl J Med 2023; 389:335-347

CARTITUDE-4 Study Update: Overall Survival with Ciltacabtagene Autoleucel in Lenalidomide-Refractory MM



Mateos M-V et al. Oral presentation at IMS 2024, September 25-28 2024, Rio de Janeiro, Brazil.

FDA warns of secondary cancer risk tied to CAR-T therapies that treat cancer

By Jacqueline Howard, CNN

5 minute read · Updated 4:36 PM EST, Wed January 24, 2024

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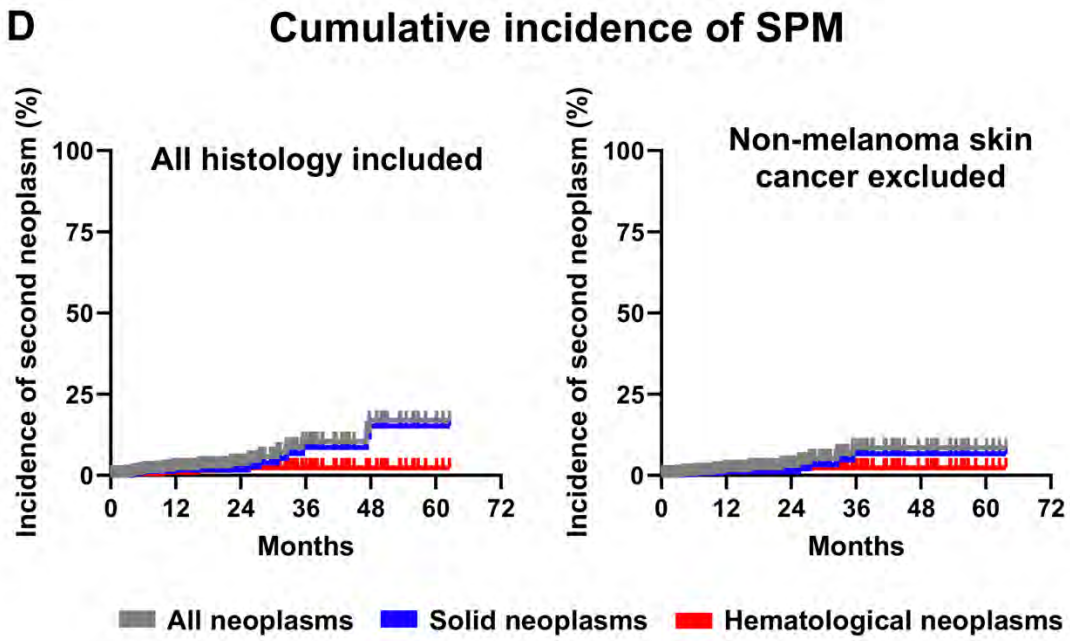
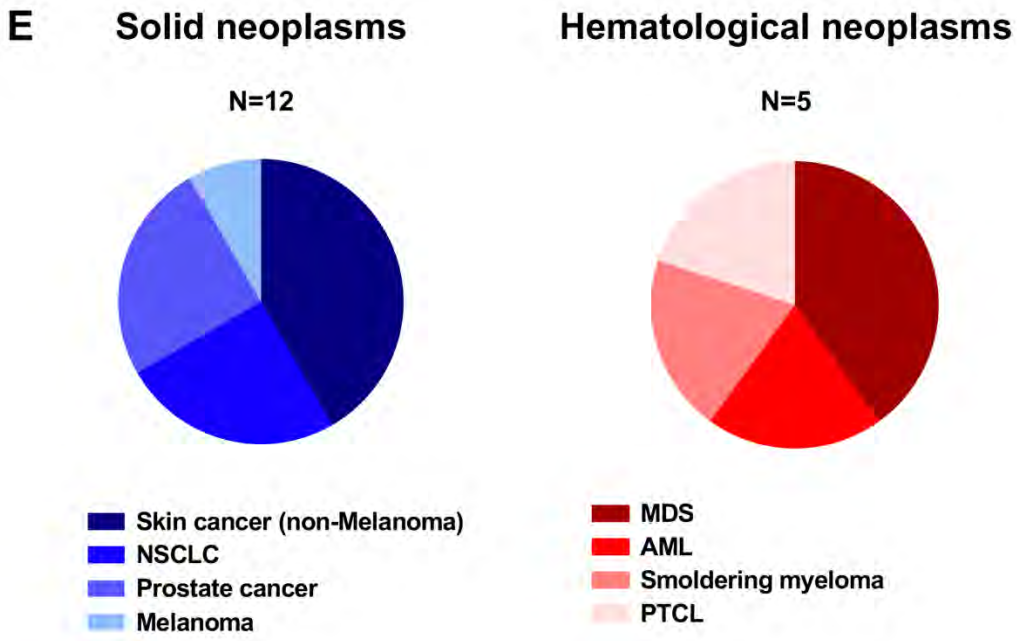
Global cancer cases will jump 77% by 2050, WHO report ...

FDA looking into reports of hair loss, suicidal thoughts in ...

FDA urges consumers not to buy tianeptine

Second Primary Cancers after CAR T Cells





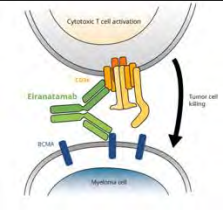
Ghilardi et al Nat Medicine 2024

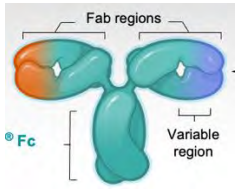
BCMA-Targeting Bispecific Antibodies

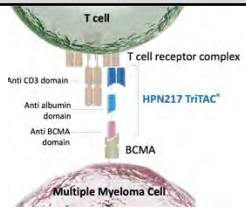
IV infusion

Approved BsAb | 2:1 binding | Trispecifics

	Teclistamab MajesTEC-1[1] (n = 165)	Elranatamab MagnetisMM-3[2] (n = 123)	Alnuctamab[5] CC-93269 (n = 68)	ABBV-383[3] (n = 118)	Linvoseltamab LINKER-MM1[4] (n = 117)	HPN217[6] (n = 62)
Phase	1/2	1/2	1/2	1	2	1
Target	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3-Albumin
scFv	Humanized	Humanized	Humanized	Human	Human	Humanized
Ig	IgG4	IgG2a	IgG1-based	IgG4	IgG4	Small globular protein
Administration	SC	SC	SC	IV	IV	IV
# prior lines	5 (2-14)	5 (2-22)	4 (3-11)	5 (1-15)	5 (2-14)	6 (2-19)
Age	64 (33-84)	68 (36-89)	64 (36-79)	68 (35-88)	70 (37-91)	69 (38 – 85)







1. Nooka AK et al. ASCO 2022. Abstract 8007. 2. Lesokhin AM et al., Nat Med 2023. 3. Voorhees PM et al. *Blood*. 2022;140(Supplement 1):4401-4404. 4. Hans CL et al. ASCO 2023. Abstract 8006. 5. Wong S et al. ASH 2019. Abstract 162. 6. Suvannasankha A et al. AACR 2023. Abstract CT013. 7. Abdallah AO et al. *Blood*. 2022;140(Supplement 1):7284-7285

Teclistamab: MajesTEC-1 in relapsed/refractory myeloma

Eligibility

≥3 prior lines
Prior PI, IMiD, and anti-CD38 therapy
No prior BCMA therapy

Patient demographics

Treatment history	N = 165
Prior lines of therapy, median (range)	5 (2-14)
Triple-class exposed | refractory	100% | 77.6%
Penta-drug exposed | refractory	70.3% | 30.3%
Refractory to last line of therapy	89.7%

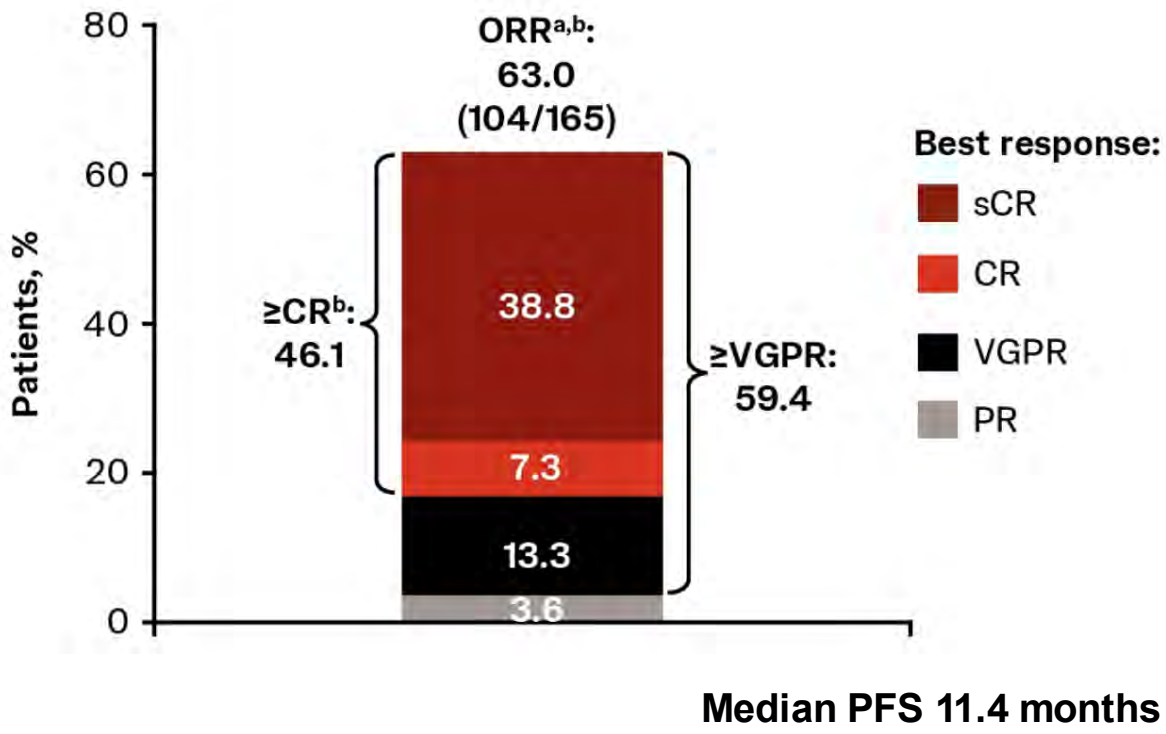
Treatment

Step-up doses, subcutaneous: 0.06 and 0.3 mg/kg in week 1
1.5 mg/kg sc weekly
48 hour hospitalization after step up doses and first full dose to monitor for CRS

Step up dosing to mitigate risk of severe CRS
CRS generally observed during step up and first full doses of teclistamab
Subcutaneous injection: greater convenience and may delay CRS due to more gradual absorption (trial initially used iv route before moving to sc route)

Nooka A et al., ASCO 2022; Moreau P et al., *N Engl J Med* 2022

Teclistamab continued



Median PFS 11.4 months

Parameter	N = 165
Cytokine release syndrome	
Any CRS	72.1%
Grade 1	50.3%
Grade 2	21.2%
Grade 3	0.6%
≥2 CRS events	32.7%
Time to onset, median (range)	2 (1-6)
Tocilizumab	36.4%
Supplemental oxygen	12.7%
Corticosteroids	8.5%
Single vasopressor	0.6%
Neurotoxicity	
Headache	8.5%
ICANS	3%

CRS in cycle 2+ 3.6%

Among patients with CRS and times recorded (N = 59), median time to CRS was 29 hours (range 4-72) after step up dose 1 and 31 hours (range 9-72) after step up dose 2

Belantamab mafodotin, ORR 31%, median PFS 2.9 months
Lonial S et al., *Lancet Oncol* 2019

Promising ORR 63% and median PFS 11.4 months in triple-class treated patients in an off-the-shelf treatment, requiring monitoring for CRS (72.1% of patients)

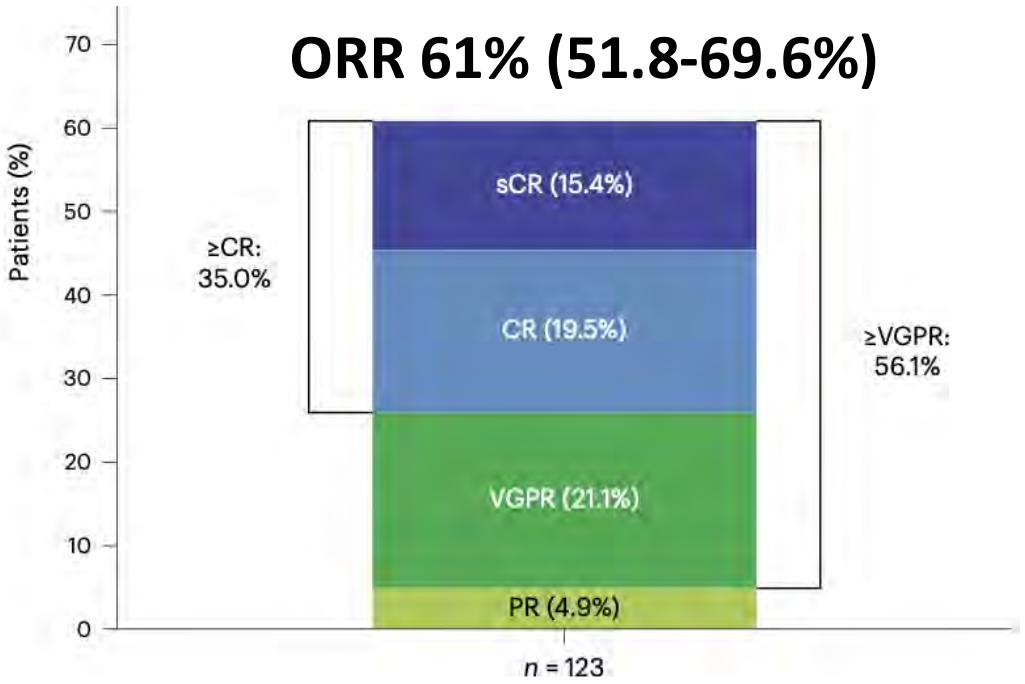
Moreau P et al., ASCO 2022; Moreau P et al., *N Engl J Med* 2022; Garfall A et al, ASCO 2024

Adverse events related to infection
Grade 3-4 infections, 44.8%
123 patients, 74.5% had hypogammaglobulinemia
65 of these patients received IVIG at physician discretion
PCP pneumonia: 6 patients
Serious COVID19 infections: 24 patients (includes 12 deaths)
Trial enrolled patients between March 2020 and August 2021

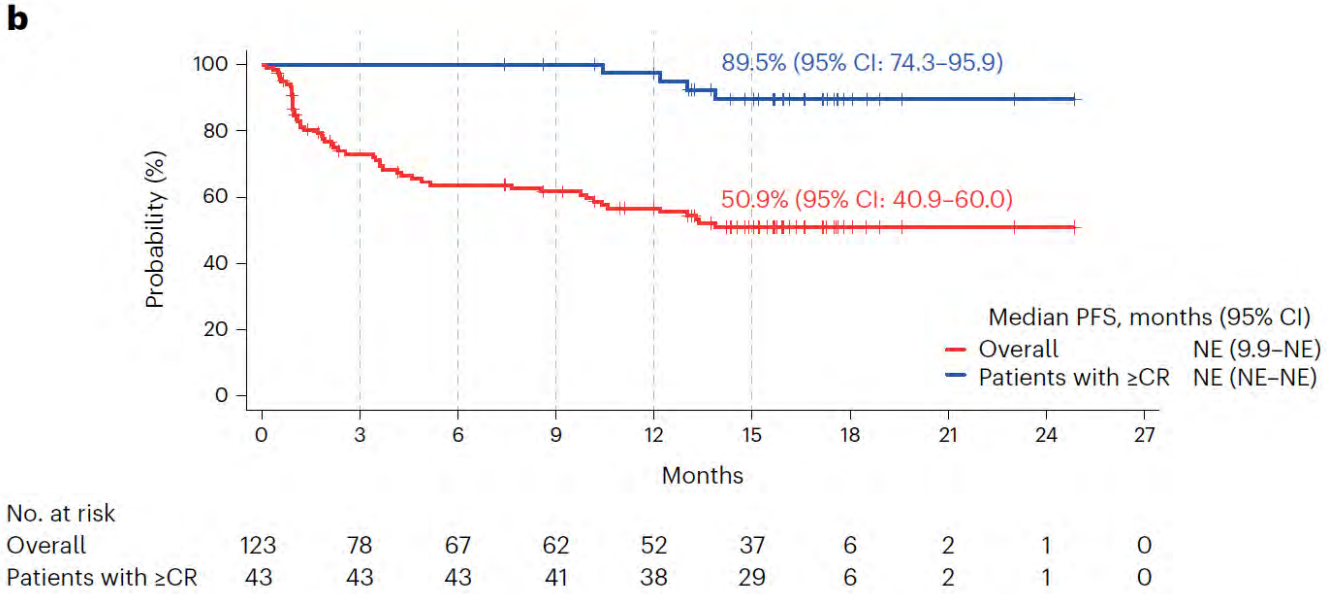
Elranatamab, 2nd anti-BCMA bispecific antibody approved (Aug 2023)

MagnetisMM-3
Phase 2 study in triple class refractory patients
Cohort A (N = 123), BCMA naive

ORR 61% (51.8-69.6%)

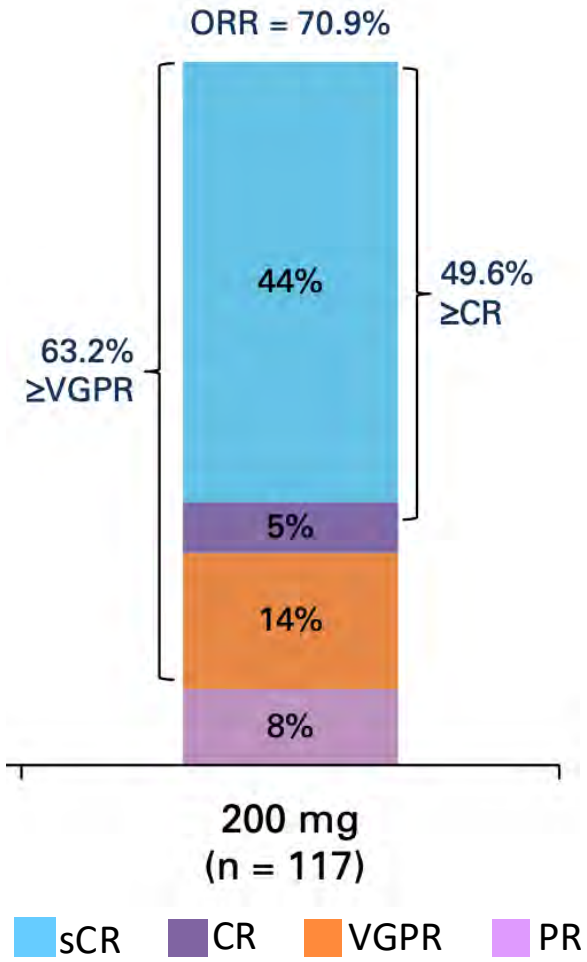


PFS at 15 months, 50.9%



Lesokhin AM et al., *Nat Med* 2023

Linvoseltamab induced high response rate and deep responses

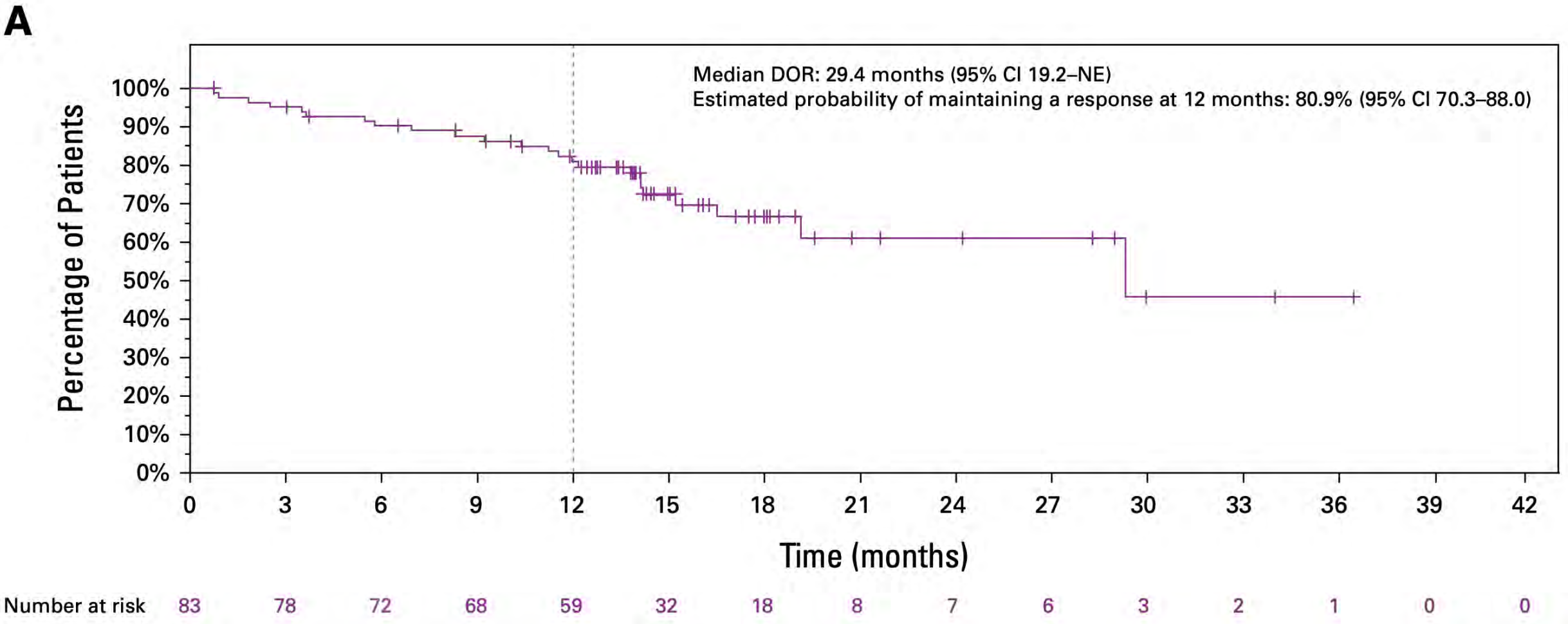


- Median duration of follow-up for the 117 patients enrolled into the 200 mg dosing cohorts* was 14.3 months.
- ORR was 71%, with 49.6% of patients achieving CR or better.
- 56 phase II patients switched to Q4W dosing after ≥24 weeks treatment.**
- Among patients with ≥CR and MRD evaluable (threshold 10^{-5}) by either EuroFlow† or clonoSEQ†, 92.6% (25/27) were MRD negative.

*phase 1: 12 patients; phase 2: 105 patients.
**In the Phase 2 portion of the trial (n=105), 62 patients who had ≥24 weeks of therapy; 56/62 achieved ≥VGPR and switched to Q4W therapy.
†EuroFlow, N=6, clonoSEQ, N=21.
CR, complete response; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent CR; VGPR, very good partial response.

Bumma N et al. *J Clin Oncol* 2024;42(22):2702-2712.

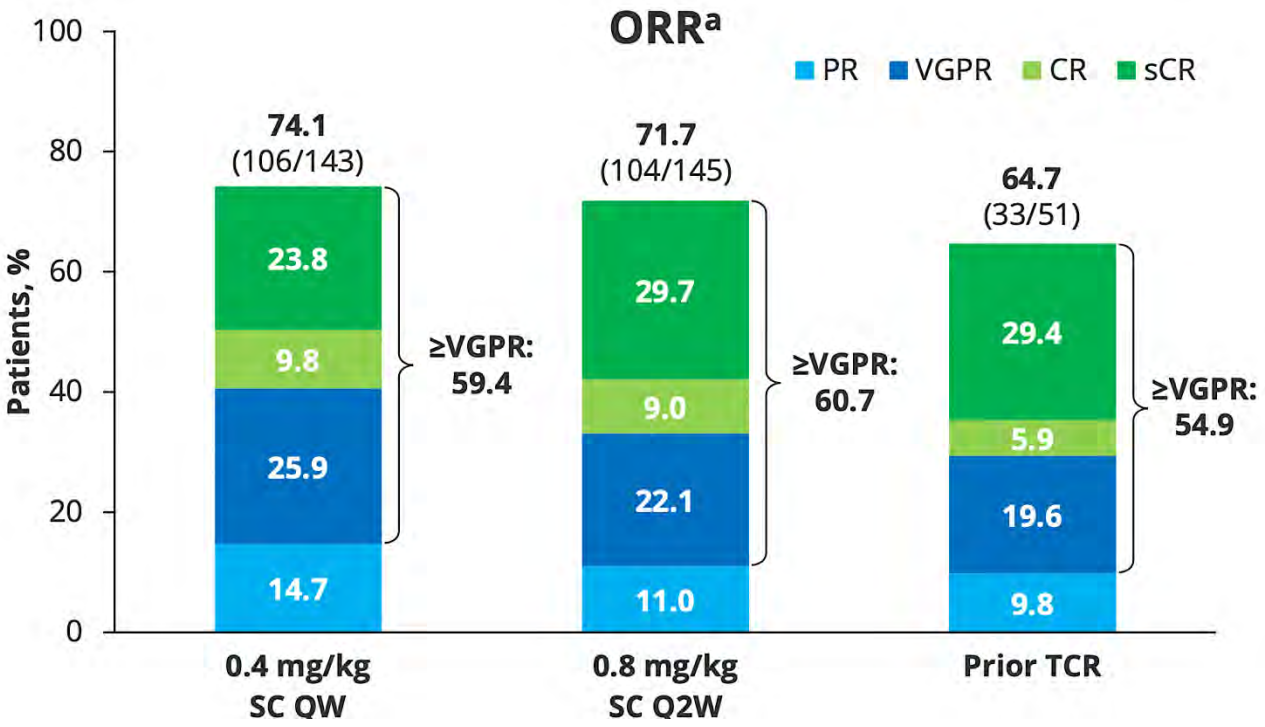
Responses to linvoseltamab were durable



CI, confidence interval; DOR, duration of response; NE, not evaluable.

Bumma N et al. *J Clin Oncol* 2024;42(22):2702-2712.

Talquetamab: MonumenTAL-1



	0.4 mg/kg SC qW N = 143	0.8 mg/kg SC q2W N = 145	Prior TCR N = 151
Triple class exp | refractory	100% | 74%	100% | 69%	100 | 84%
BCMA	0%	0%	100%
ORR	74%	72%	65%
12 m PFS	34.9%	54.4%	38.1%
12 m OS	76.4%	77.4%	62.9%

Prior TCR = CAR T-cells (N = 36) and prior bispecific antibody (N = 18); patients were on either dosing schedule

Schinke C et al., ASCO 2023

Dysgeusia, skin, and nail changes are notable adverse events with anti-GPRC5D therapy

MonumenTAL-1

Less infections than with e.g. teclistamab

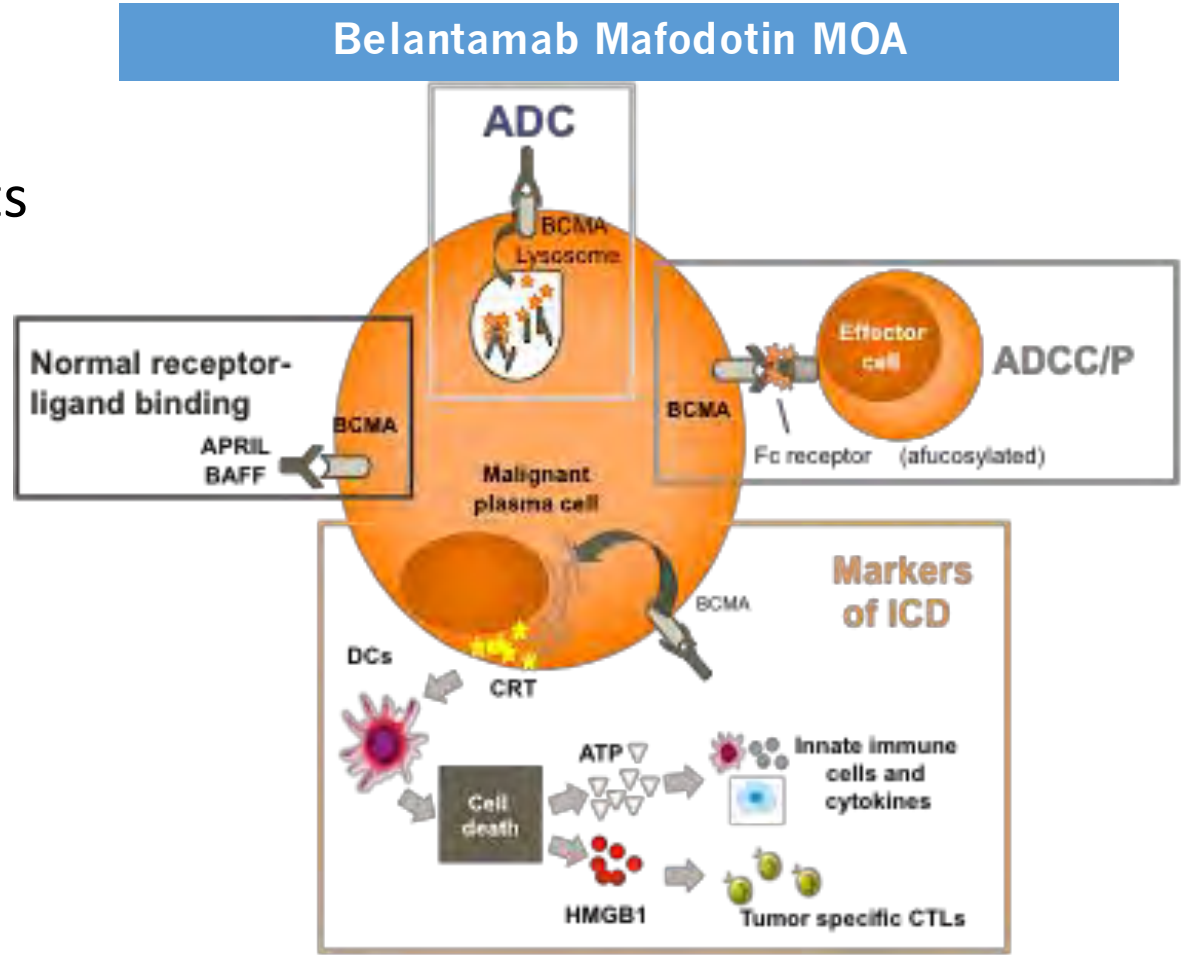
AEs (≥30% in any cohort), n (%)	0.4 mg/kg SC QW (n=143)		0.8 mg/kg SC Q2W (n=145)		Prior TCR (n=51)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Nonhematologic AEs						
CRS[b]	113 (79.0)	3 (2.1)	108 (74.5)	1 (0.7)	39 (76.5)	1 (2.0)
Dysgeusia[c]	103 (72.0)	NA	103 (71.0)	NA	39 (76.5)	NA
Infections[d]	84 (58.7)	28 (19.6)	96 (66.2)	21 (14.5)	37 (72.5)	14 (27.5)
Skin related[e]	80 (55.9)	0	106 (73.1)	1 (0.7)	35 (68.6)	0
Nail related[f]	78 (54.5)	0	78 (53.8)	0	32 (62.7)	0
Weight decreased	59 (41.3)	3 (2.1)	60 (41.4)	8 (5.5)	15 (29.4)	0
Rash related[g]	57 (39.9)	2 (1.4)	43 (29.7)	8 (5.5)	18 (35.3)	2 (3.9)
Pyrexia	56 (39.2)	4 (2.8)	40 (27.6)	2 (1.4)	16 (31.4)	0
Dry mouth	38 (26.6)	0	58 (40.0)	0	26 (51.0)	0
Fatigue	35 (24.5)	5 (3.5)	40 (27.6)	1 (0.7)	23 (45.1)	1 (2.0)

Schinke C et al., ASCO 2023

Belantamab Mafodotin: Come back kid?

- B-cell maturation antigen (BCMA)
  - Selectively expressed on plasmablasts and plasma cells
  - Requisite for long-lived plasma cell survival

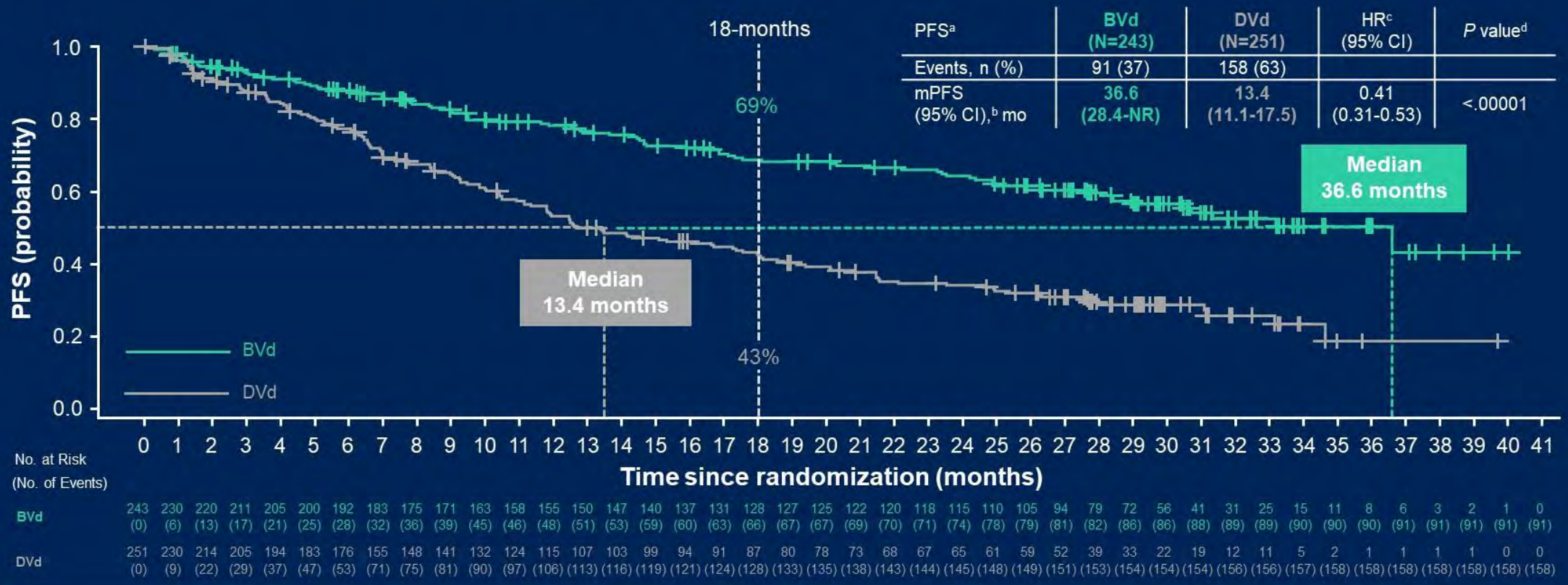
- Belantamab mafodotin
  - Humanized afucosylated IgG1 ADC targeting BCMA
  - Multimodal mechanisms of action (MOA)
  - Convenient IV 0.5-1–hour outpatient infusion



IV = intravenous.

Cho et al, 2018; Sheikh et al, 2020.

DREAMM-7: BVd led to a significant increase in PFS vs DVd



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

No. at Risk (No. of Events)

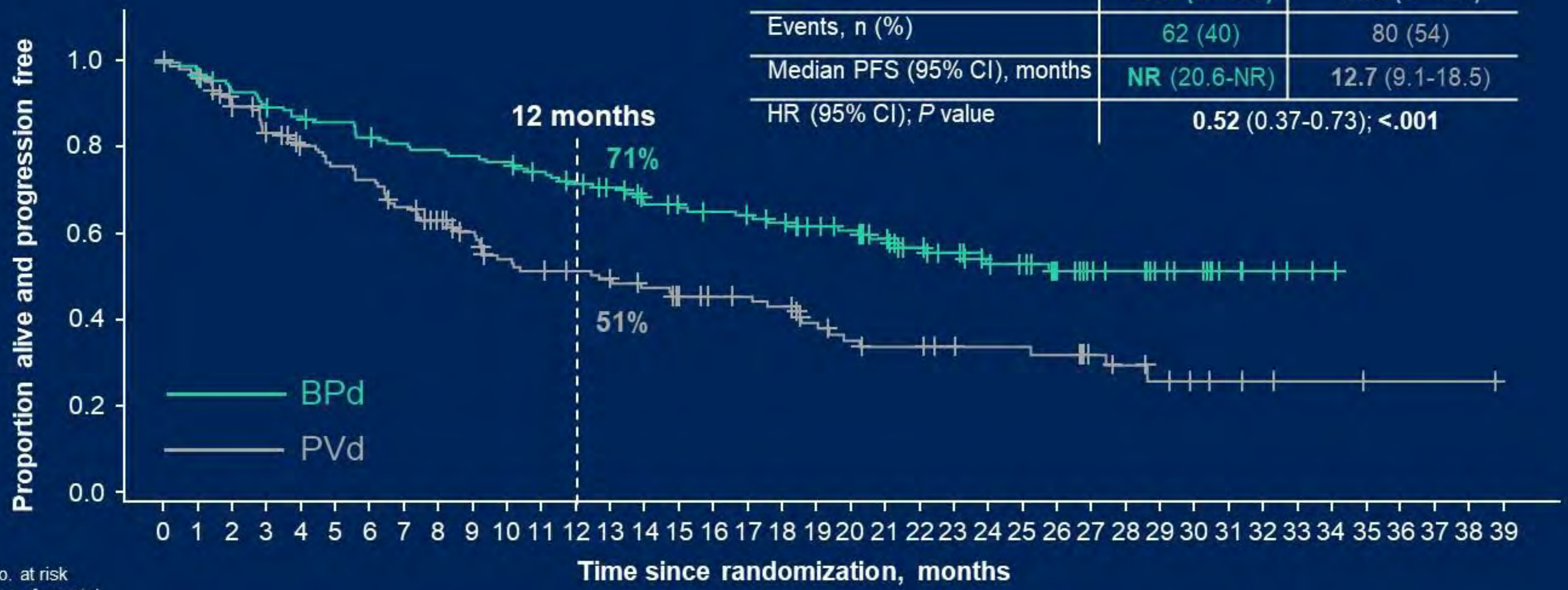
BVd	243 (0)	230 (6)	220 (13)	211 (17)	205 (21)	200 (25)	192 (28)	183 (32)	175 (36)	171 (39)	163 (45)	158 (46)	155 (48)	150 (51)	147 (53)	140 (59)	137 (60)	131 (63)	128 (66)	127 (67)	125 (67)	122 (69)	120 (70)	118 (71)	115 (74)	110 (78)	105 (79)	94 (81)	79 (82)	72 (86)	56 (86)	41 (88)	31 (89)	25 (89)	15 (90)	11 (90)	8 (90)	6 (91)	3 (91)	2 (91)	1 (91)	0 (91)
DVd	251 (0)	230 (9)	214 (22)	205 (29)	194 (37)	183 (47)	176 (53)	155 (71)	148 (75)	141 (81)	132 (90)	124 (97)	115 (106)	107 (113)	103 (116)	99 (119)	94 (121)	91 (124)	87 (128)	80 (133)	78 (135)	73 (138)	68 (143)	67 (144)	65 (145)	61 (148)	59 (149)	52 (151)	39 (153)	33 (154)	22 (154)	19 (154)	12 (156)	11 (156)	5 (157)	2 (158)	1 (158)	1 (158)	1 (158)	1 (158)	0 (158)	0 (158)

BVd demonstrated a statistically significant and clinically meaningful IRC-assessed PFS benefit with a median PFS that was 23 months longer than DVd (36.6 vs 13.4 months)

HR, hazard ratio; IRC, independent review committee; mPFS, median PFS; NR, not reached.
[a] Two patients in the ITT population were randomized, not treated, re-screened, and re-randomized. They are counted as 4 unique patients in this output. [b] CIs were estimated using the Brookmeyer Crowley method. [c] HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS at screening (I vs II/III), with a covariate of treatment. [d] *P* value from 1-sided stratified log-rank test.

BPd Led to a Significant PFS Benefit 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**	



No. at risk (no. of events)

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
BPd	155 (0)	143 (5)	135 (10)	130 (15)	125 (19)	122 (21)	117 (26)	113 (28)	111 (30)	109 (32)	107 (34)	102 (37)	97 (41)	93 (42)	82 (47)	80 (47)	77 (49)	75 (50)	72 (52)	67 (53)
PVd	147 (0)	138 (4)	123 (14)	111 (23)	102 (27)	96 (33)	92 (37)	83 (45)	75 (49)	68 (52)	59 (59)	56 (62)	54 (62)	51 (64)	47 (66)	43 (68)	40 (68)	39 (68)	37 (70)	30 (73)

	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
BPd	64 (54)	59 (56)	50 (58)	45 (59)	38 (61)	36 (61)	28 (62)	23 (62)	21 (62)	16 (62)	13 (62)	8 (62)	4 (62)	2 (62)	1 (62)	0 (62)	0 (62)	0 (62)	0 (62)	0 (62)
PVd	25 (76)	22 (77)	22 (77)	19 (77)	18 (77)	18 (77)	17 (78)	13 (78)	11 (79)	7 (80)	5 (80)	4 (80)	3 (80)	2 (80)	2 (80)	1 (80)	1 (80)	1 (80)	1 (80)	0 (80)

BPd led to a statistically significant and clinically meaningful reduction in risk of disease progression or death vs PVd (HR, 0.52; 95% CI, 0.37-0.73; *P*<.001)

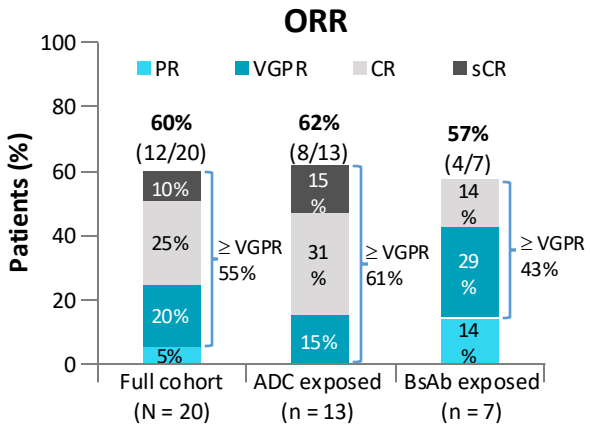
Median follow-up, 21.8 months (range, 0.03-39.23 months)
The treatment effect (HR and corresponding 95% CIs) was estimated using the stratified Cox proportional hazards model, and the *P* value was produced based on the 1-sided stratified log-rank test. Stratified analyses were adjusted for number of prior lines of therapy and prior bortezomib use.
BPd, belamaf, pomalidomide, and dexamethasone; HR, hazard ratio; NR, not reported; PFS, progression-free survival; PVd, pomalidomide, bortezomib, and dexamethasone.

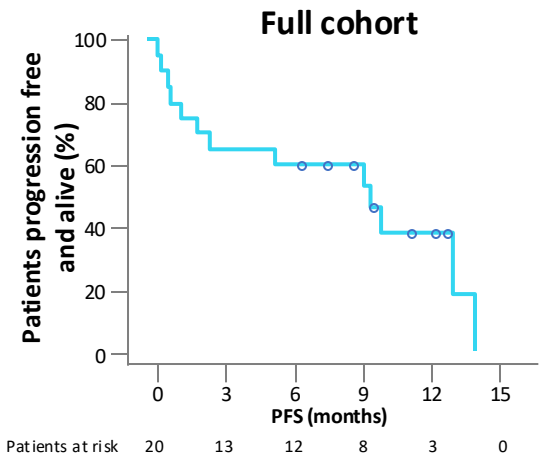
Questions and Challenges

- Moving therapies early
- Sequencing
- Duration
- Combinations

Sequencing: CAR-T Cell Therapy After BCMA-Targeted Therapy

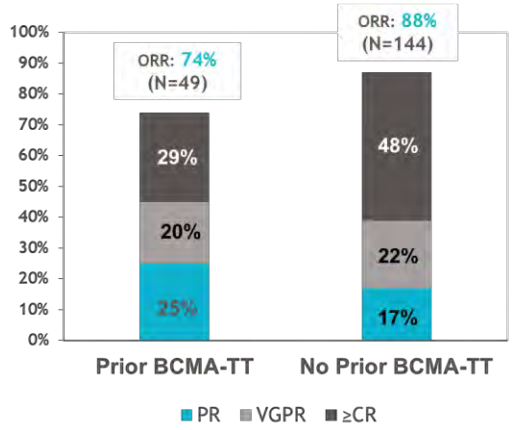
CARTITUDE-2, Cohort C: Cilta-cel
Patients with RRMM with previous exposure to PI, IMiD agent, anti-CD38 mAb, and a non-cellular BCMA-targeting therapy[1]

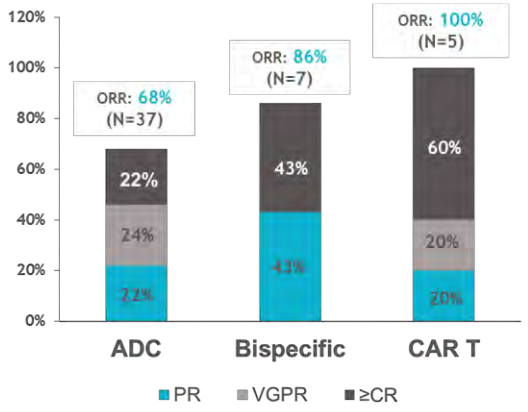


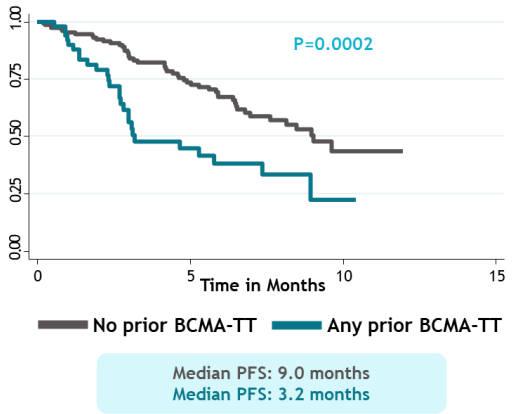


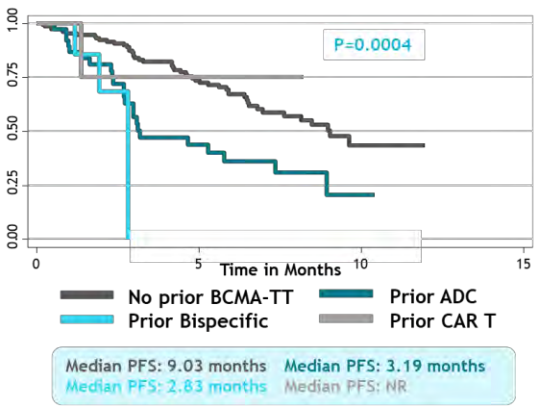
Median PFS			
	Full cohort (N = 20)	ADC exposed (n = 13)	BsAb exposed (n = 7)
PFS, mo (95% CI)	9.1 (1.5-13.2)	9.5 (1.0-15.2)	5.3 (0.6-NE)

Real-world experience of patients with multiple myeloma receiving ide-cel after a prior BCMA-targeted therapy[2]



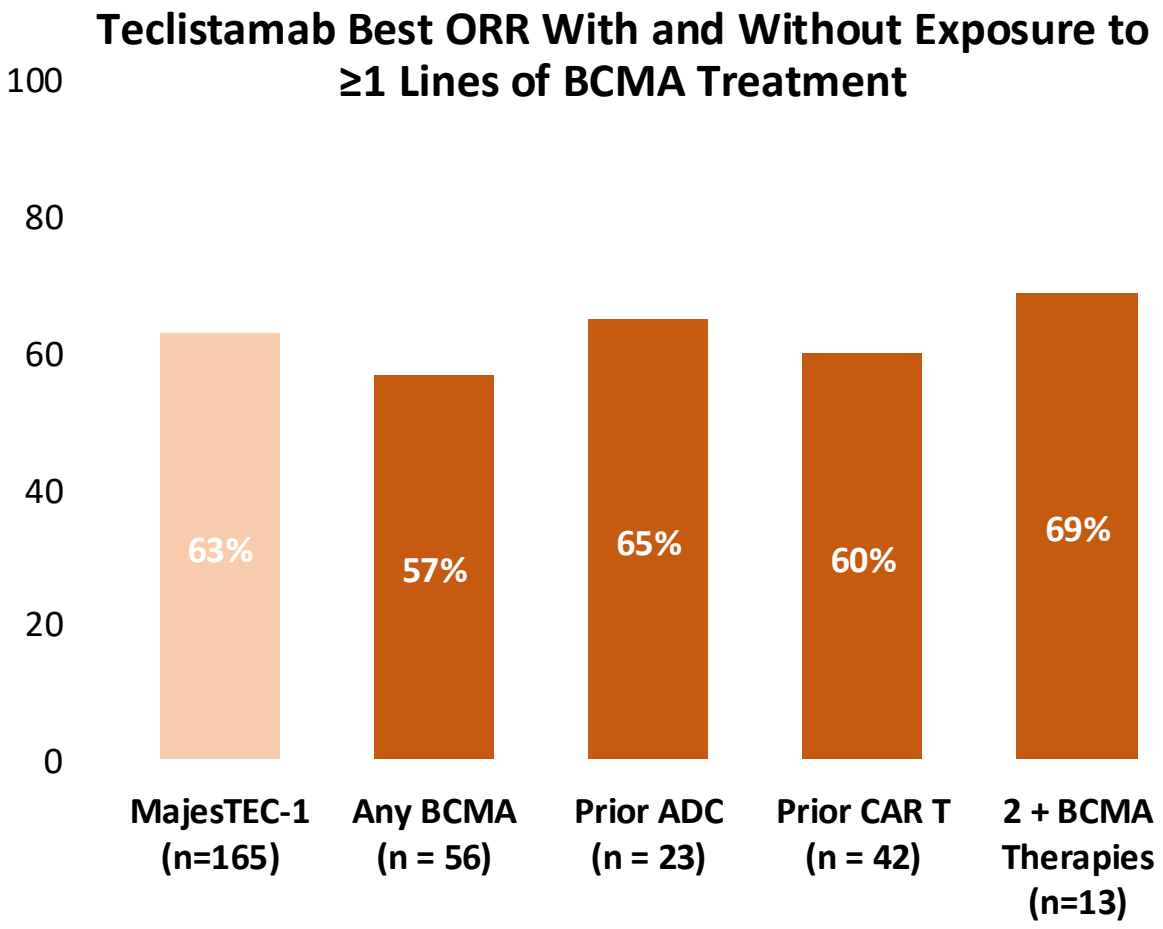


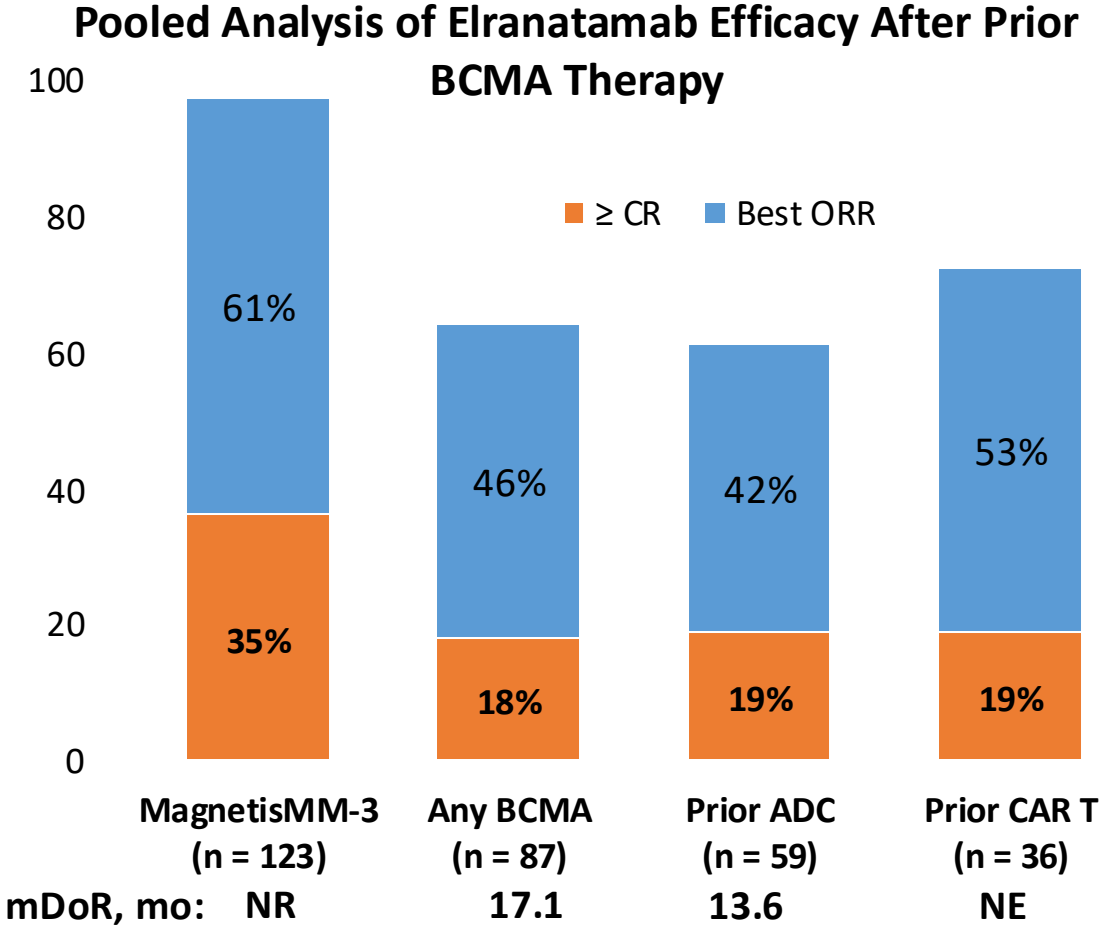




1. Cohen et al. *Blood*. 2023;141(3):219-230. 2. Ferreri CJ et al. *Blood Cancer J*. 2023;13:117; abstract 766.

Outcomes With Bispecific Antibodies After Prior BCMA-Directed Therapy





Moreau. NEJM. 2022;387:495. Dima. ASH 2023. Abstr 91.
Lesokhin. Nat Med. 2023;29;2259-2267. Nooka. ASCO 2023. Abstr 8008

Challenges

- Moving therapies early can impact later therapies
- Sequencing and maintenance?
- With early—no more one and done?
- Combinations

Questions over the next 5 years

- Can we use fixed duration treatment based on MRD?
- Can we use immunotherapy early and replace transplant with immunotherapies?
- Can we use risk adapted approaches?
- Can we combine TCRs?
- Where will belamaf fit?
- Will we compare CARs versus Bispecifics?

Oncology Today – Managing Peripheral T-Cell Lymphoma

Steven Horwitz, MD

DR LOVE: Any thoughts about the T-cell lymphomas reported after patients receive CAR T-cell therapy?

DR HORWITZ: Some of those cases are probably people who had underlying angioimmunoblastic T-cell lymphoma that wasn't appreciated, because sometimes the large B-cell lymphoma is the dominant process at diagnosis and you'll treat those people with R-CHOP and then at recurrence you see the T-cell lymphoma. And when we see those people, often we've been able to go back and find evidence of a T-cell lymphoma in the genetics from the baseline sample. So we think those are probably people who had both a follicular helper T-cell lymphoma and an EBV-driven large B-cell lymphoma. So some of those cases the T-cell lymphoma we think was preexisting and not just CAR if that makes sense. The follicular helper biology is interesting.

Thank you for joining us!

CME/MOC, ACPE and NCPD credit information will be emailed to each participant within 5 business days.