Module 12: EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC)

Current Management of Metastatic EGFR-Mutated NSCLC — Dr Goldman

Nonmetastatic EGFR-Mutated NSCLC, Exon 20 Insertion Mutations and Novel Agents — Dr Piotrowska

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Module 12: EGFR-Mutated Non-Small Cell Lung Cancer

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

Current Management of Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

Jonathan W. Goldman, MD

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Disclosures

Consulting Agreements	AbbVie Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, Janssen Biotech Inc, Lilly, Pfizer Inc, Summit Therapeutics
Contracted Research	AbbVie Inc, Agenus Inc, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, GSK, Janssen Biotech Inc, Lilly, Merck, Pfizer Inc, Puma Biotechnology Inc, RayzeBio, Summit Therapeutics, Tango Therapeutics

What's new for metastatic EGFR-mutated NSCLC therapy?

- First line options: FLAURA2 and MARIPOSA
- Subcutaneous amivantamab
- Data for continued TKI on progression
- Later-line options: MARIPOSA2 and Datopotamab deruxtecan

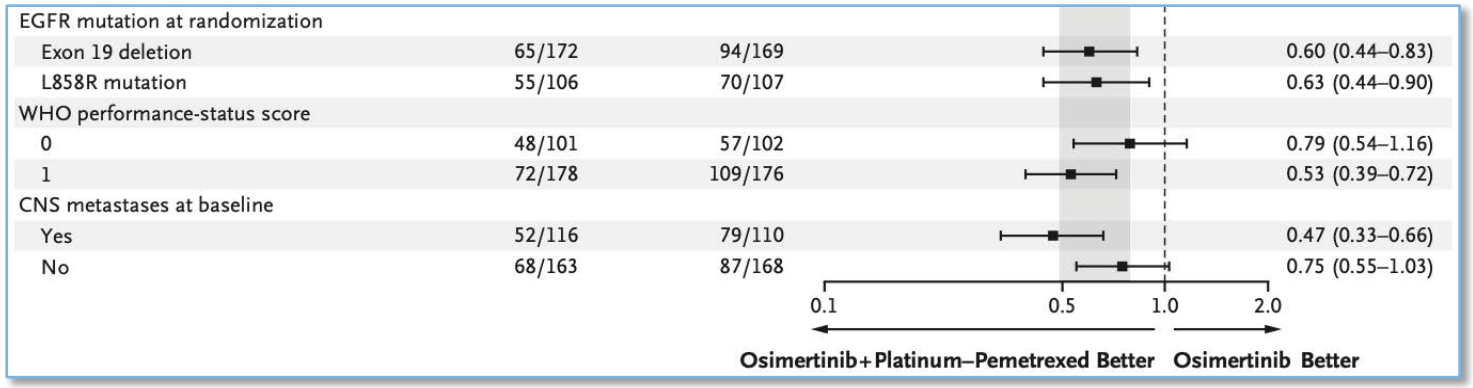
FLAURA2 Trial

- Osimertinib+Chemo vs Osimertinib
- Addition of platinum and pemetrexed improved:
  - ORR from 76 to 83%
  - Duration of response from 15.3 to 24.0m
  - mPFS from 16.7 to 25.5 months (HR 0.62)

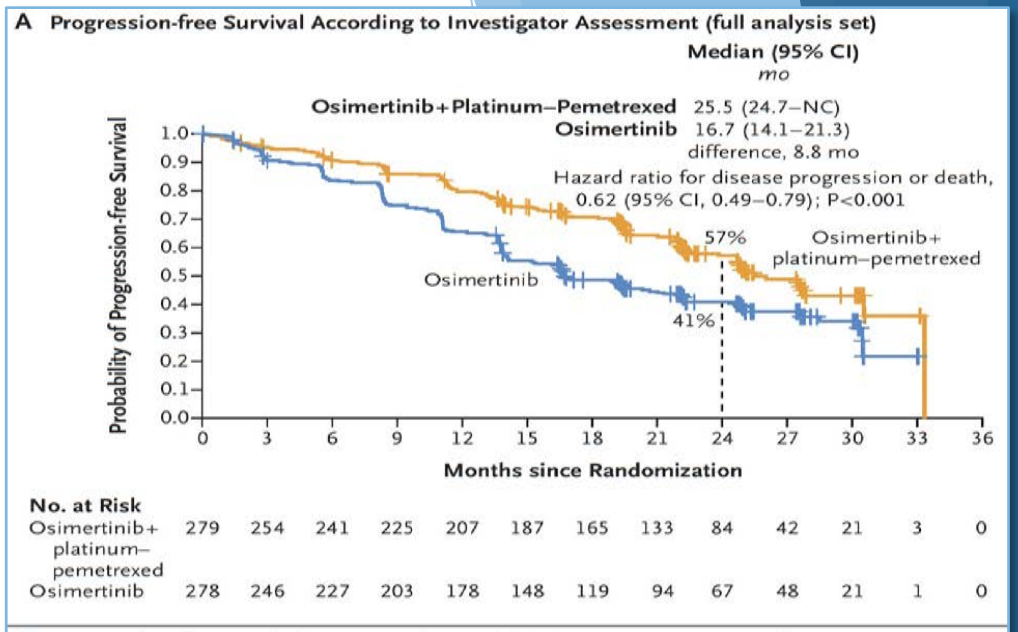
End Point	Analysis According to the Investigator	
	Osimertinib + Platinum–Pemetrexed (N = 279)	Osimertinib Monotherapy (N = 278)
Median progression-free survival (95% CI) — mo	25.5 (24.7–NC)	16.7 (14.1–21.3)
Hazard ratio for disease progression or death (95% CI)	0.62 (0.49–0.79)†	—
Progression-free survival (95% CI) — %		
At 12 mo	80 (74–84)	66 (60–71)
At 18 mo	71 (65–76)	49 (42–54)
At 24 mo	57 (50–63)	41 (35–47)
Objective response (95% CI) — %	83 (78–87)	76 (70–80)
Best objective response — no. (%)‡		
Complete response	1 (<1)	2 (1)
Partial response	231 (83)	208 (75)
Stable disease for ≥35 days§	34 (12)	51 (18)
Disease progression	1 (<1)	9 (3)
Death¶	6 (2)	3 (1)
Could not be evaluated	6 (2)	5 (2)
Disease control (95% CI) — %‖	95 (92–98)	94 (90–96)
Median duration of response (95% CI) — mo**	24.0 (20.9–27.8)	15.3 (12.7–19.4)
Continued response (95% CI) — %		
At 12 mo	80 (74–84)	64 (57–70)
At 18 mo	69 (62–75)	44 (37–51)
At 24 mo	49 (41–57)	35 (27–42)

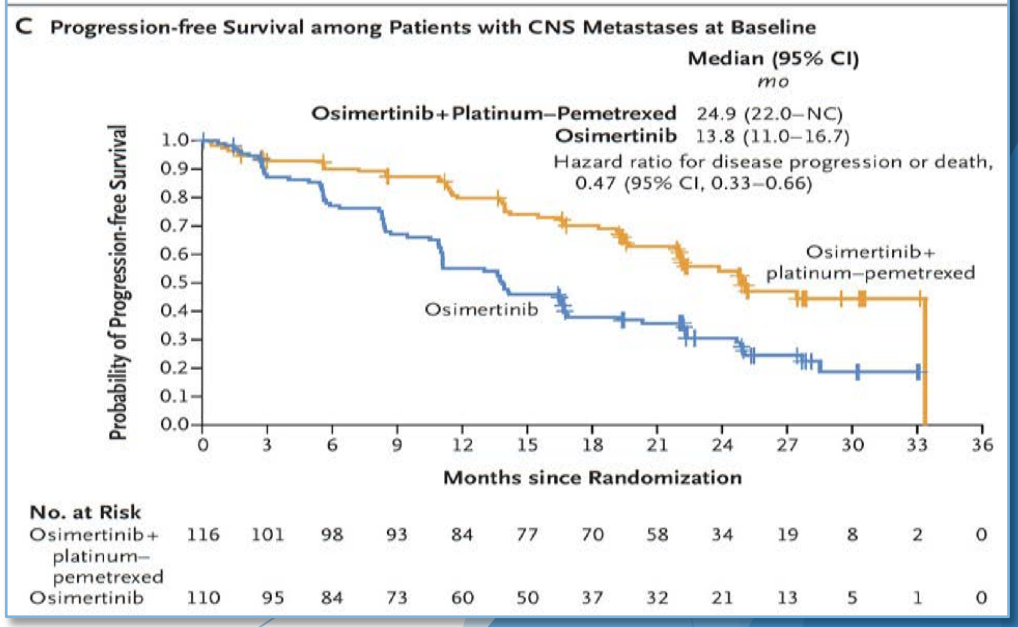
Planchard D, Janne P, Cheng Y, et al. NEJM 2023;389: 1935-1948

FLAURA2: Benefits



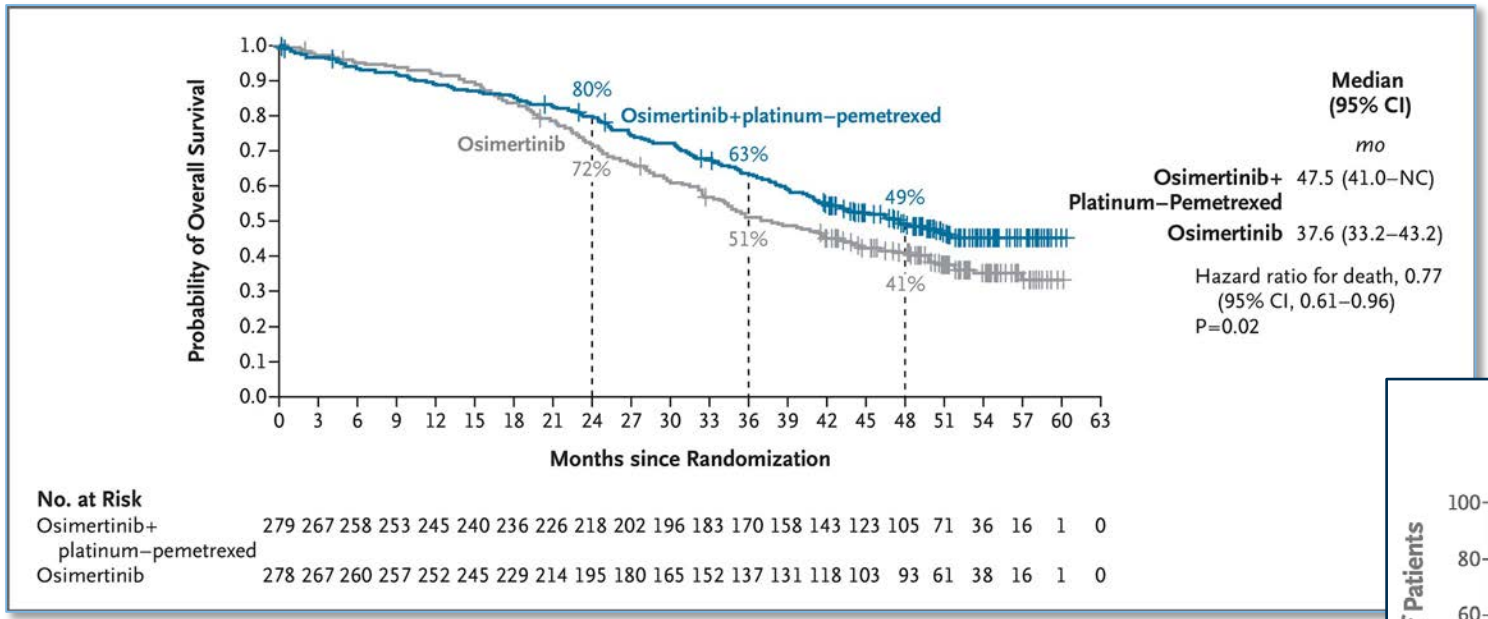
Efficacy Parameter	CNS Measurable Lesions	
	Osimertinib with pemetrexed and platinum-based chemotherapy (N=40)	Osimertinib (N=38)
CNS Tumor Response Assessment[*,†]		
CNS ORR, % (95% CI)	80 (64, 91)	76 (60, 89)
Complete response, %	48	16
Partial response, %	33	61
CNS Duration of Response[†,‡]		
Number of responders	32	29
Response Duration ≥6 months, %	75	50
Response Duration ≥12 months, %	65	34

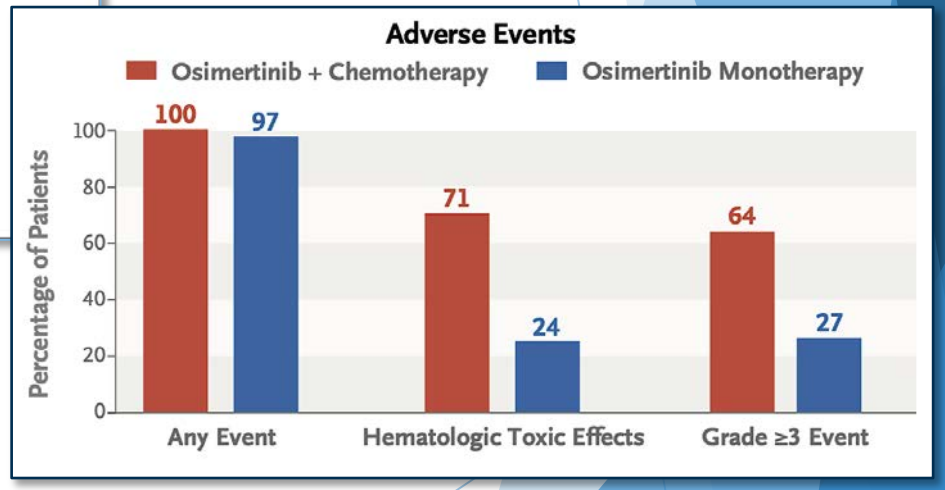




Planchard D, Janne P, Cheng Y, et al. NEJM 2023;389: 1935-1948
Osimertinib package insert, released 4/29/24, accessdata.fda.gov

FLAURA2: Overall Survival

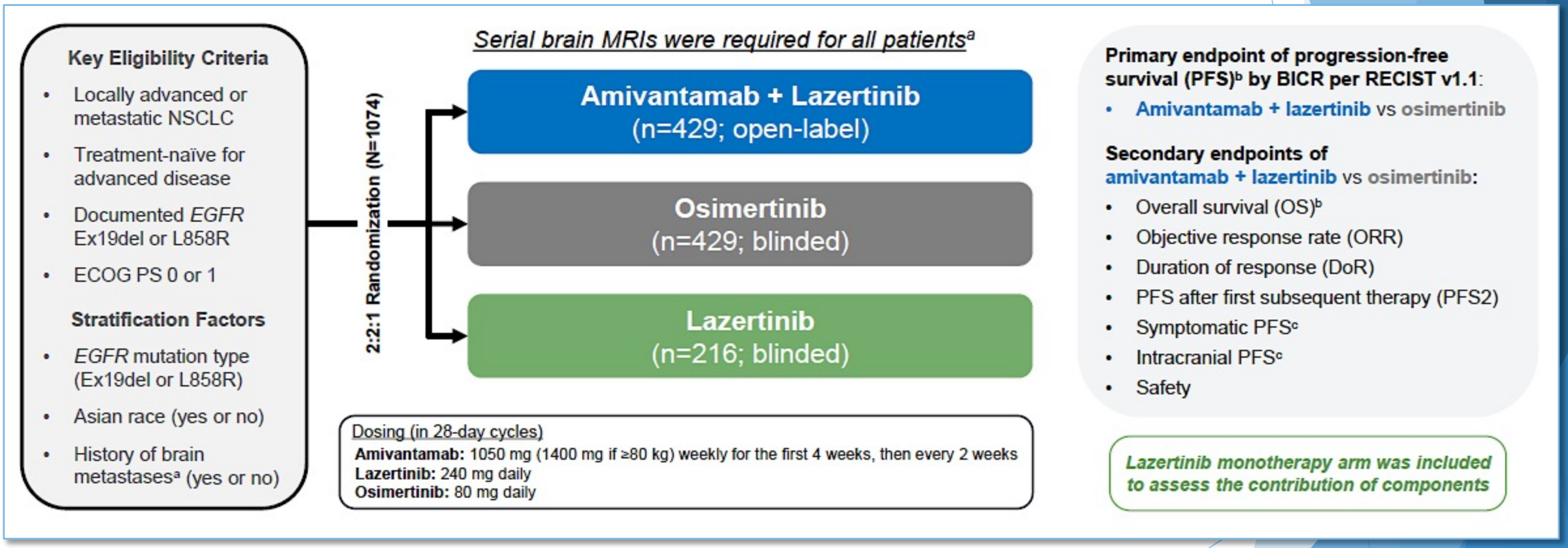




- Benefit similar across subgroups, including similar HR's for Exon 19 del'n & L858R, & those with/without brain mets.
- Most patients who discontinued 1L treatment due to disease progression received 2L treatment: 69% of pts on osimertinib-chemo and 77% of pts on osimertinib monotherapy.

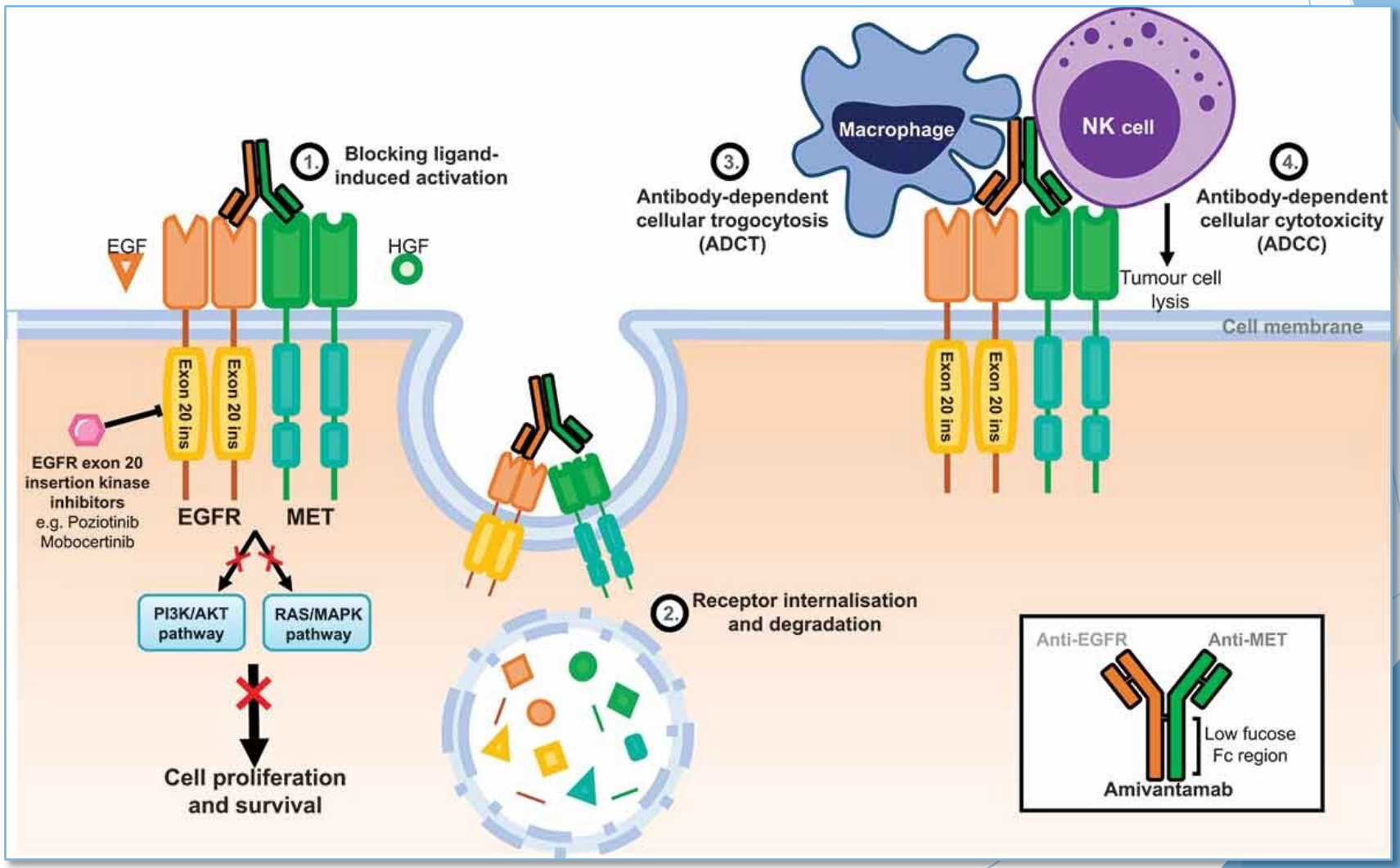
Jänne P, Planchard D, et al. NEJM 2026;39: 27-38.
Planchard, et al, NEJM Research Summary. DOI: 10.1056/NEJMoa2306434

MARIPOSA:



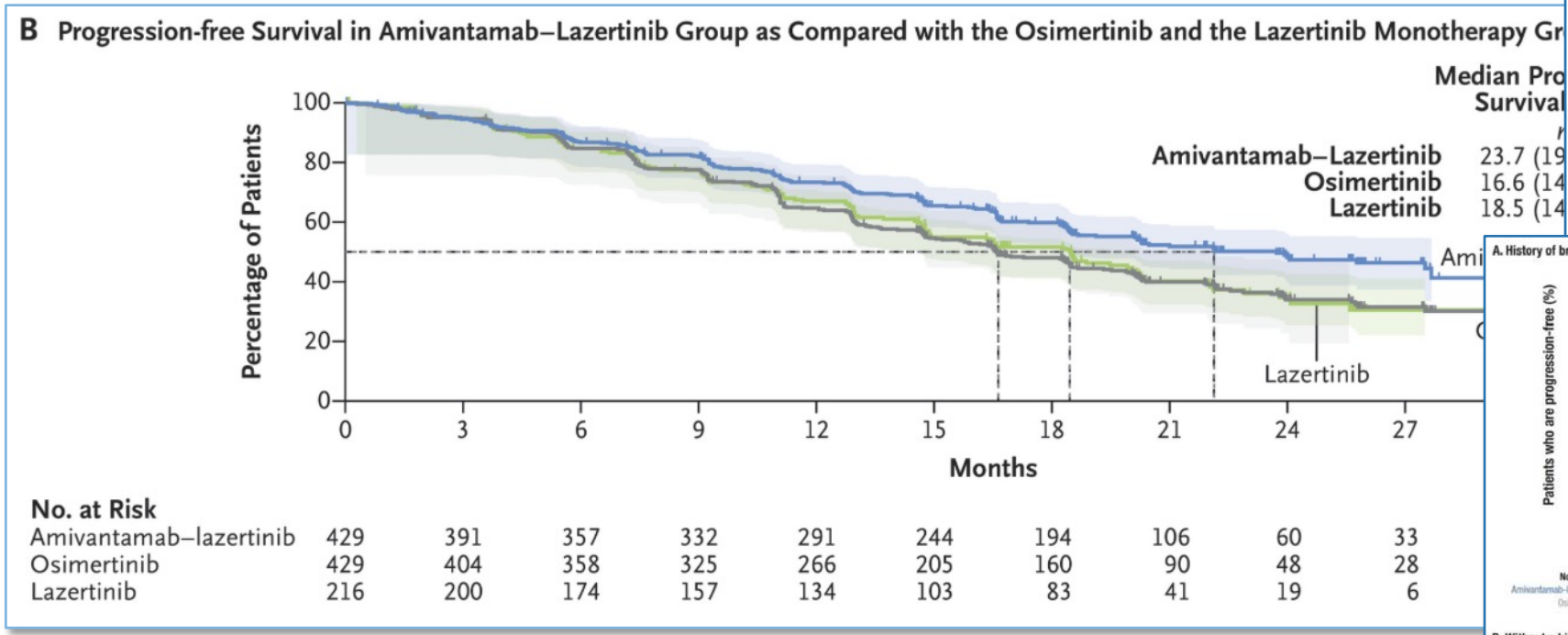
Cho BC, Felip E, Spira A. ESMO Congress, Madrid 2023.

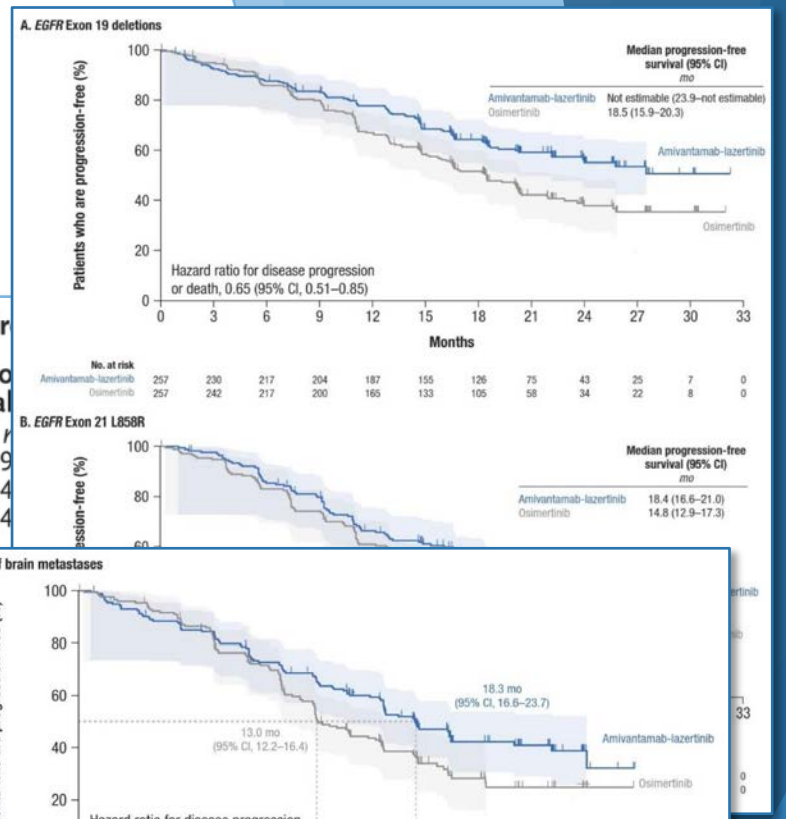
Amivantamab: Mechanism of Action

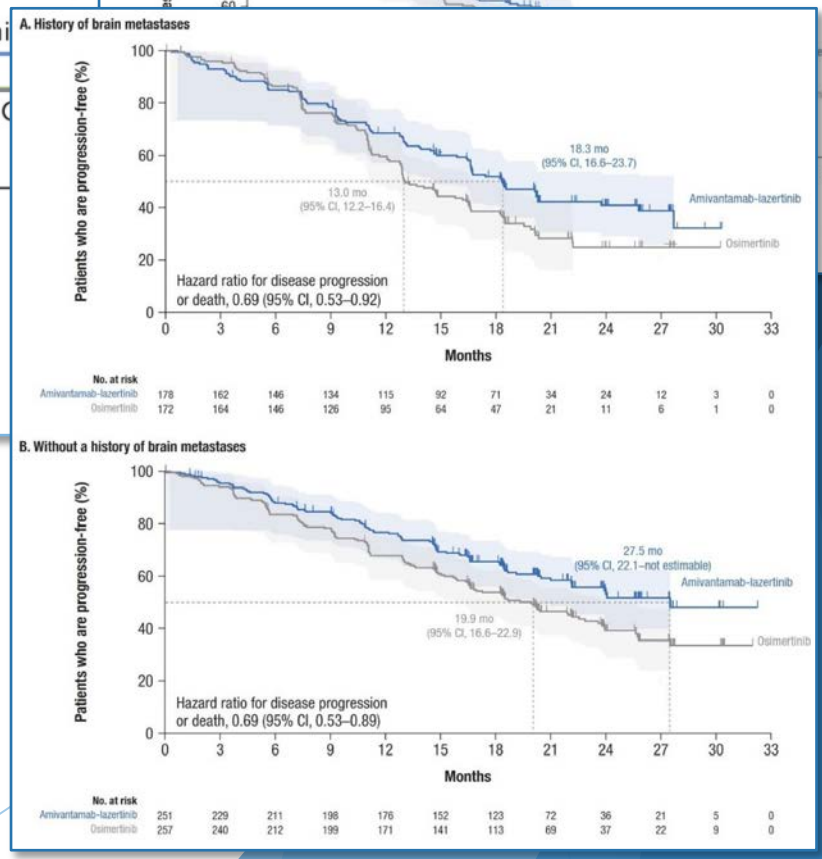


Vyse S, Huang PH. Expert Rev Anticancer Ther. 2022 Jan;22(1):3-16.

MARIPOSA: PFS Benefit

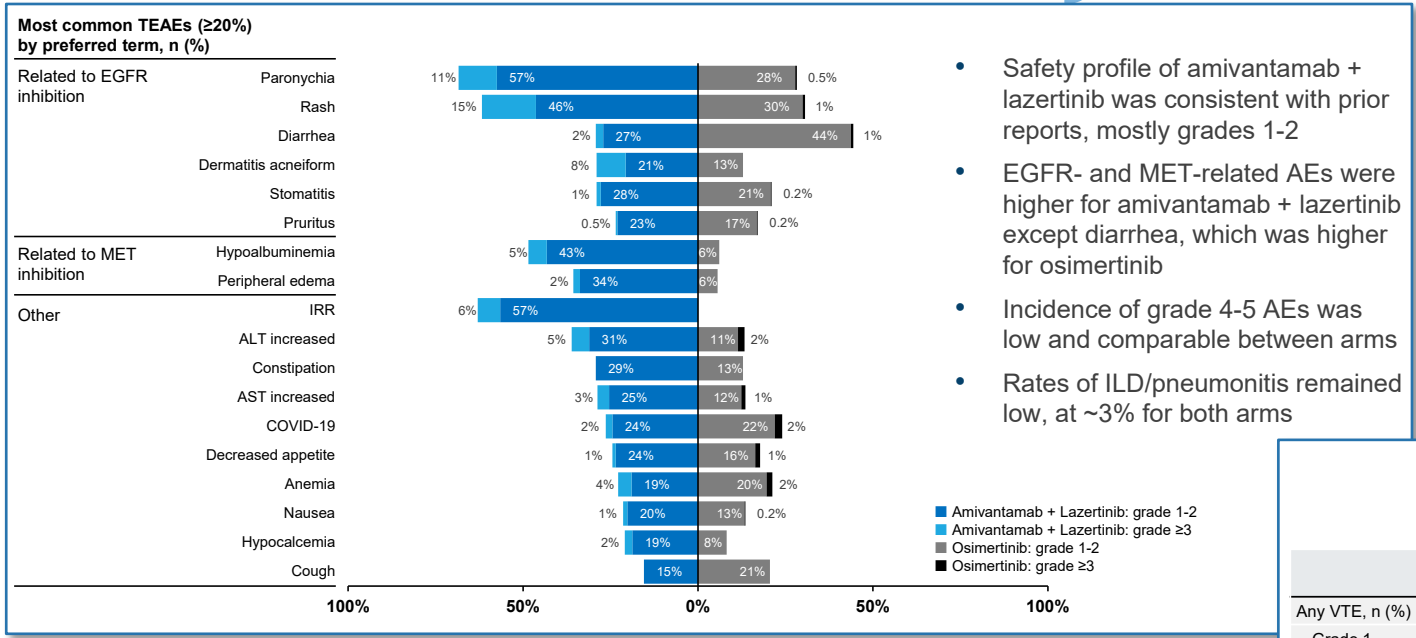






Cho BC, et al. NEJM, 2024

MARIPOSA: toxicity



- Safety profile of amivantamab + lazertinib was consistent with prior reports, mostly grades 1-2
- EGFR- and MET-related AEs were higher for amivantamab + lazertinib except diarrhea, which was higher for osimertinib
- Incidence of grade 4-5 AEs was low and comparable between arms
- Rates of ILD/pneumonitis remained low, at ~3% for both arms

Adverse Event of Special Interest: VTE[a]

	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any VTE, n (%)	157 (37)	39 (9)
Grade 1	5 (1)	0
Grade 2	105 (25)	24 (6)
Grade 3	43 (10)	12 (3)
Grade 4	2 (0.5)	1 (0.2)
Grade 5	2 (0.5)	2 (0.5)
Any VTE leading to death, n (%)	2 (0.5)	2 (0.5)
Any VTE leading to any discontinuation, n (%)	12 (3)	2 (0.5)
Anticoagulant use at time of first VTE, n (%)		
On anticoagulants	5 (1)	0
Not on anticoagulants	152 (36)	39 (9)
Median onset to first VTE	84 days	194 days
Within first 4 months, n (%)	97 of 157 (62)	13 of 39 (33)

- VTE rates were higher for amivantamab + lazertinib
  - Most common preferred terms were pulmonary embolism and deep vein thrombosis
  - Most VTEs were grade 1-2
  - Incidence of grade 4-5 VTEs was low (<1%) and comparable between arms
- Rates of discontinuations due to VTE were low and comparable between arms
- At time of first VTE:
  - Most patients were not on anticoagulants
  - Majority in the amivantamab + lazertinib arm occurred within the first 4 months
- Prophylactic dose anticoagulation is now recommended for the first 4 months of treatment in ongoing trials of amivantamab + lazertinib

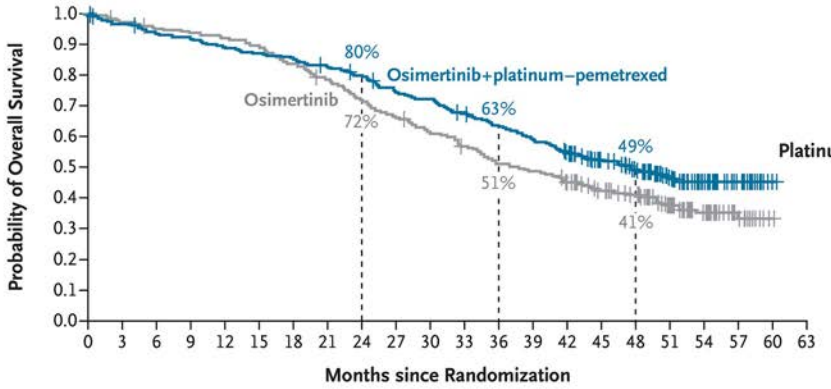
- Toxicities and QOL may determine if the benefit is “worth it.”
- SKIPPirr trial developed extended course dexamethasone to reduce infusion related reactions by 2/3
- COCOON trial optimized dermatologic management with oral doxy/minocycline, topical clindamycin and chlorhexidine, and ceramide moisturizer.

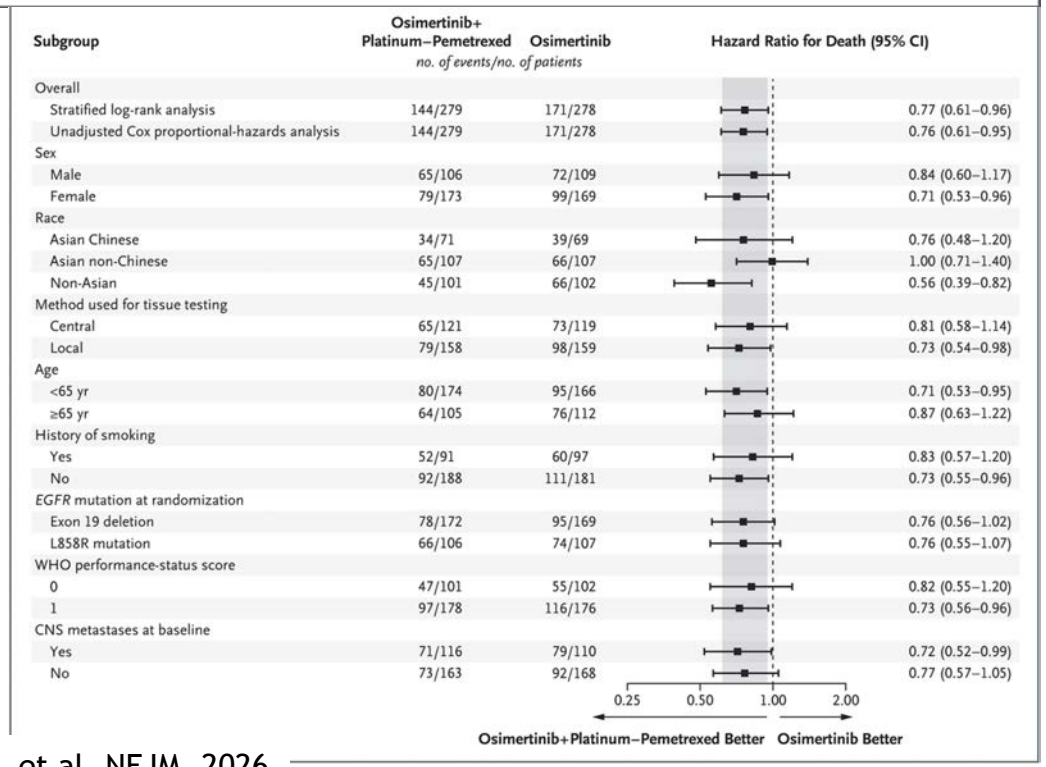
Cho BC, Felip E, Spira A. ESMO Congress, Madrid 2023.
Spira A, Paz-Ares L, Jan J-Y. JTO, 2025.
Cho BC, Li W, Spira A. JTO, 2025.

FLAURA-2

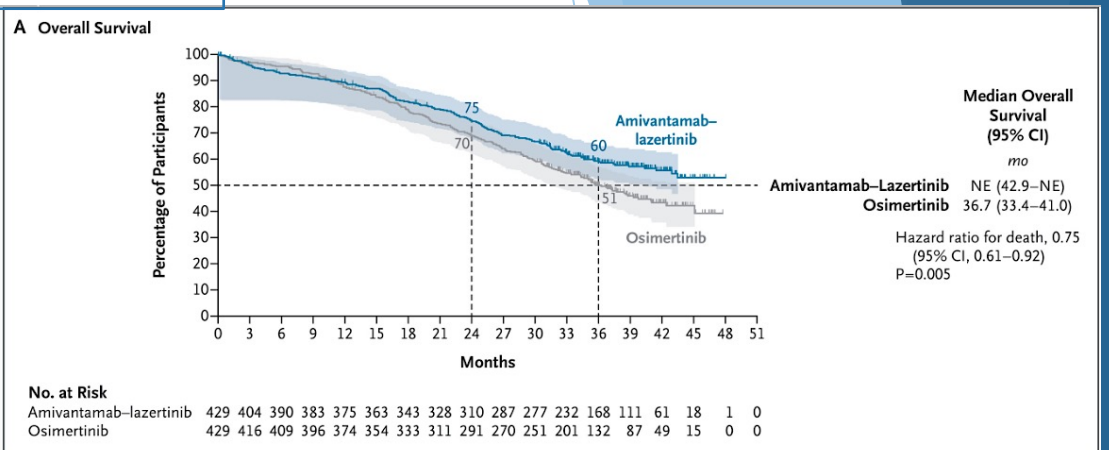
OS Comparison

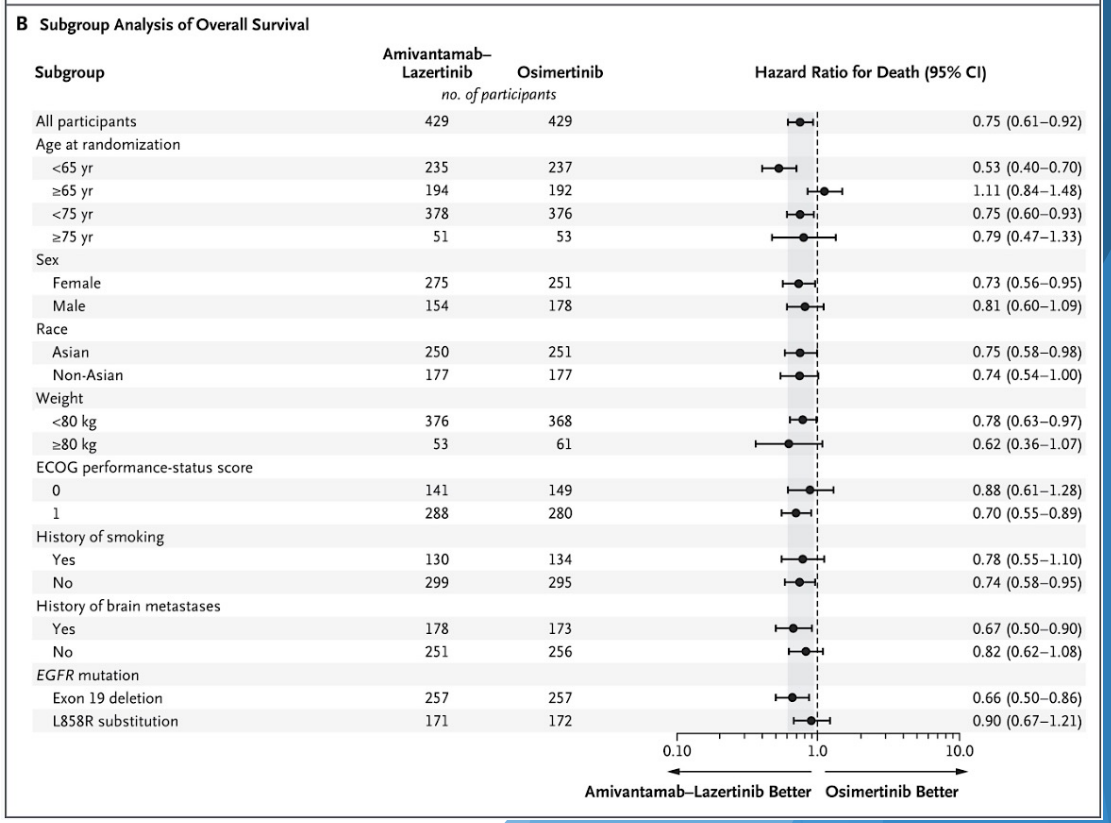
MARIPOSA





Janne PA, et al. NEJM, 2026

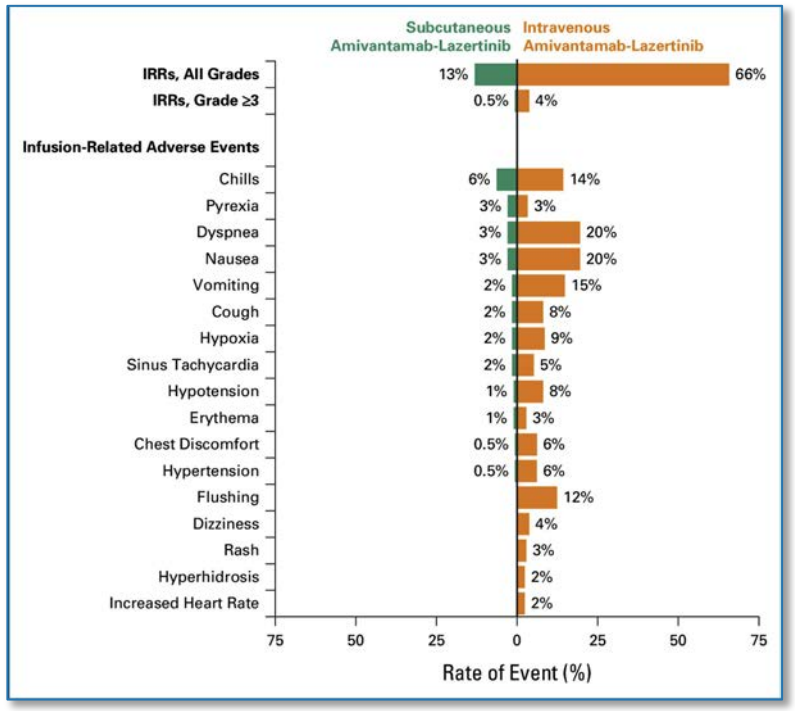


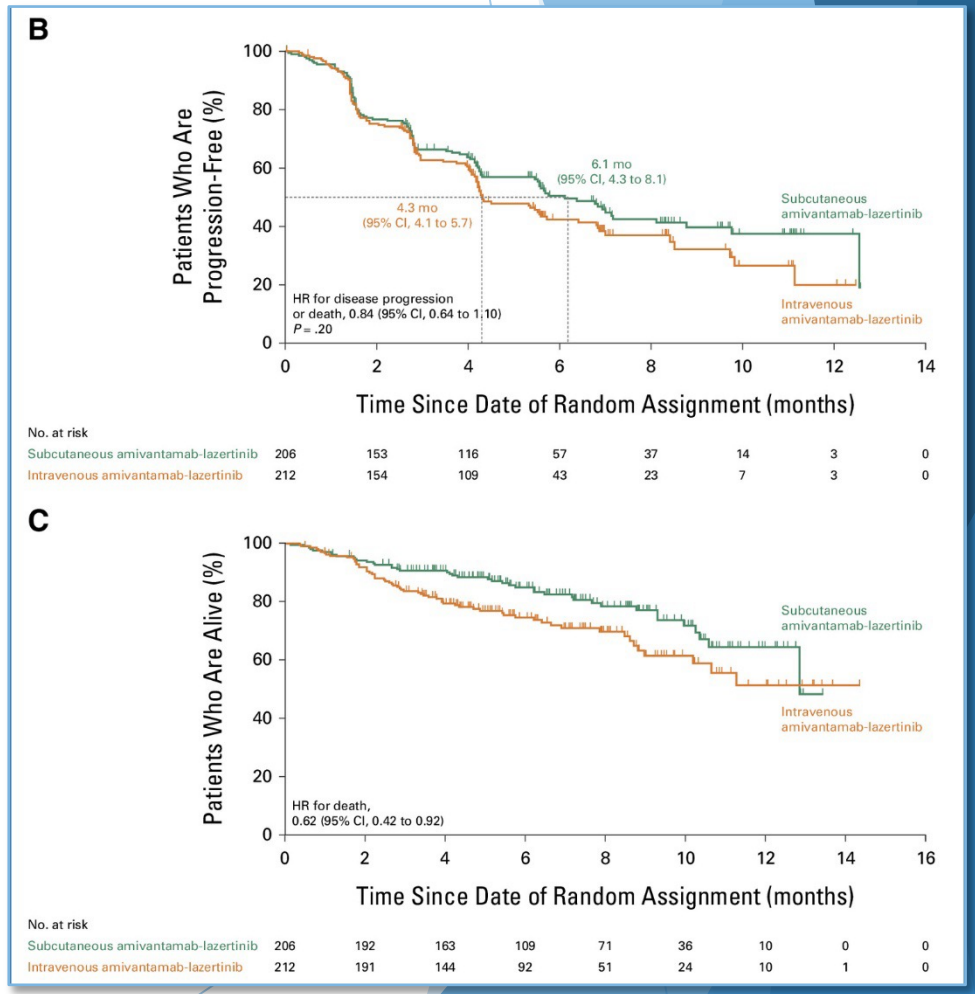


Yang JC, et al. NEJM, 2025

Subcutaneous Amivantamab

- Reduced infusion time and improved patient convenience
- Reduced infusion related reactions
- Similar dermatologic AE profile; no new safety signals
- Enhances therapeutic accessibility
- PALOMA-3 study unexpectedly with OS HR 0.62

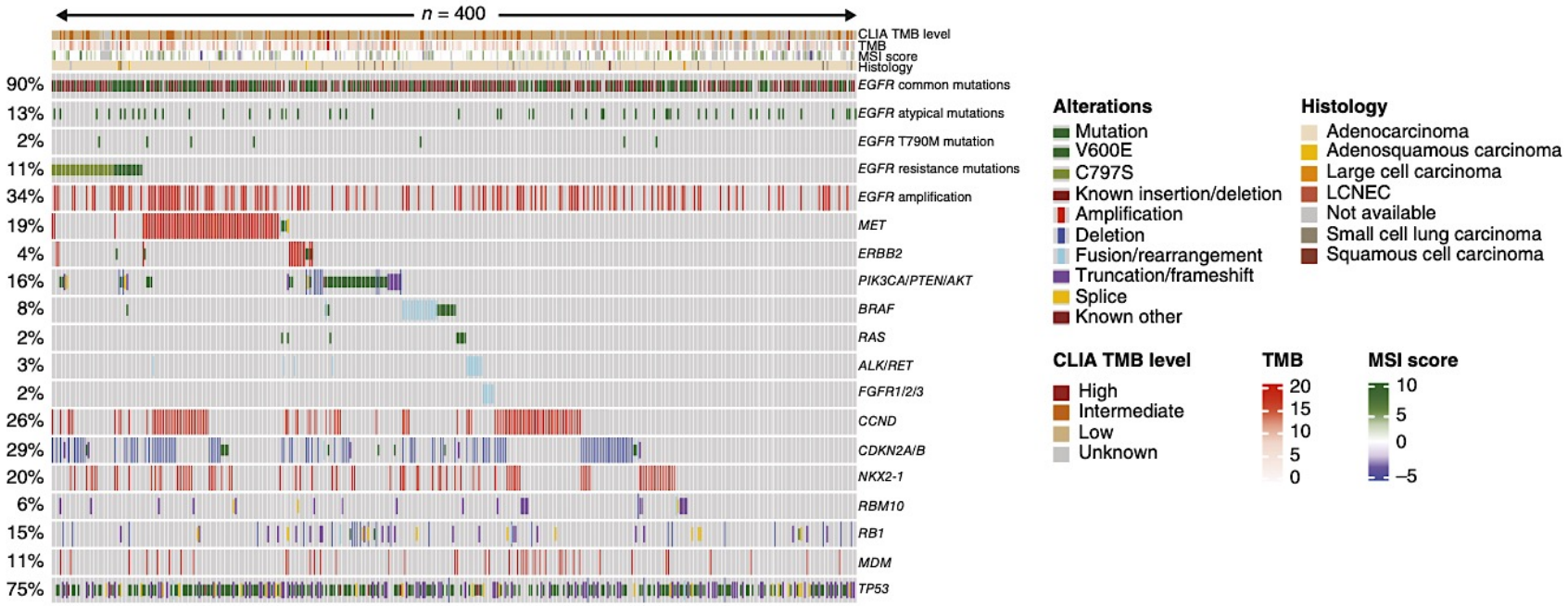




Leighl N, et al. JCO, 2025

Resistance mechanisms to first line osimertinib

UCLA Health | David Geffen School of Medicine

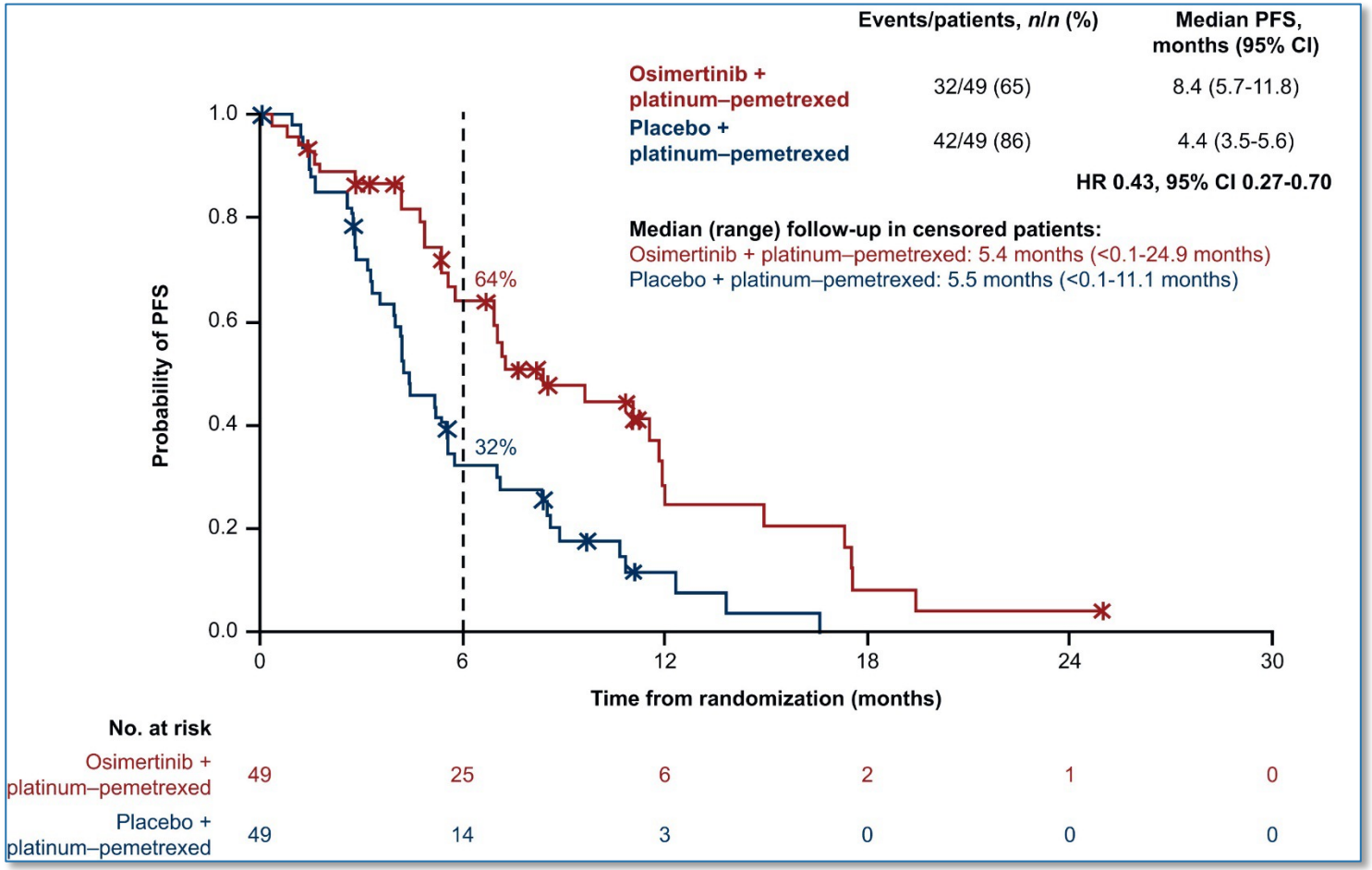


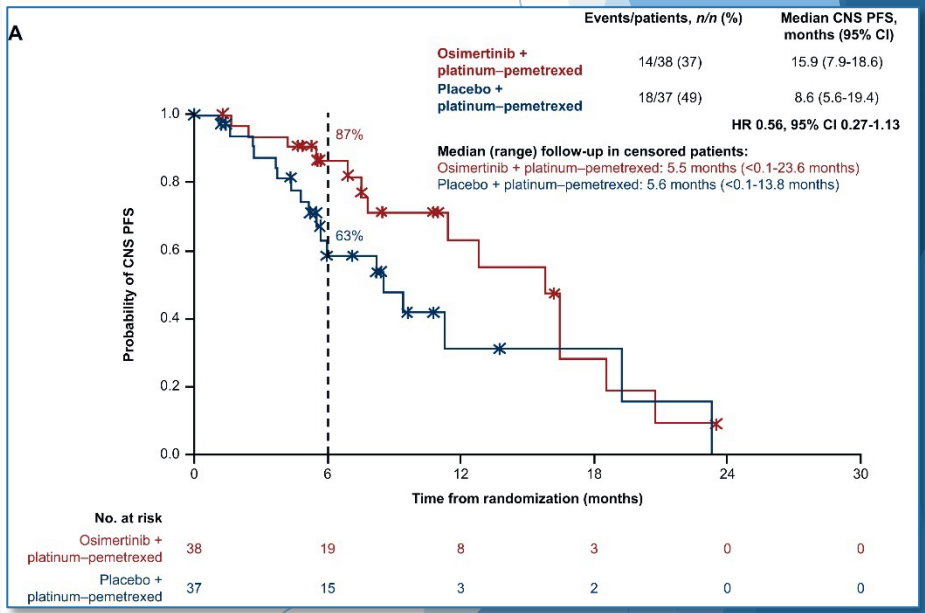
- **Orchard Trial:** biomarker-based platform trial with pts progressing on 1L osimertinib: 400 tissue and 191 plasma samples.
- 87% with resistance alterations, 46% with multiple ones
- **MET** amplification seen in 18%
- **Secondary EGFR** mut in 11% (21% in plasma)
- EGFR amplification in 35%
- **BRAF** fusion in 5%, mut 3%
- Alterations in **HER2**, **RAS** and **FGFR** in 4, 2 and 2%
- Histologic transformation in 5% (likely underrepresented)

Yu H…Goldman J…Piotrowska Z. Clin Cancer Res, 2026 Mar 6.

COMPEL Trial

- Phase III trial of platinum-based chemotherapy ± Osimertinib in patients with non-CNS progression after first-line Osimertinib





Peled N, et al. ESMO Open, 2025

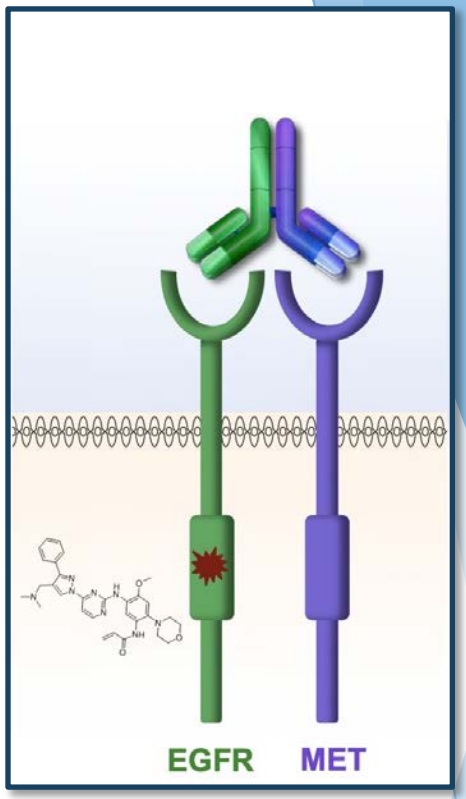
MARIPOSA-2

MADRID 2023 ESMO congress

Amivantamab Plus Chemotherapy (With or Without Lazertinib) vs Chemotherapy in *EGFR*-mutated, Advanced NSCLC After Progression on Osimertinib

MARIPOSA-2, a Phase 3, Global, Randomized, Controlled Trial

Antonio Passaro,[1] Byoung Chul Cho,[2] Yongsheng Wang,[3] Barbara Melosky,[4] Raffaele Califano,[5] Se-Hoon Lee,[6] Nicolas Girard,[7] Karen Reckamp,[8] Toshiaki Takahashi,[9] Enriqueta Felip,[10] Ryan D. Gentzler,[11] Sanjay Popat,[12] William Nassib William Jr,[13] Tao Sun,[14] Sujay Shah,[15] Brooke Diorio,[16] Roland E. Knoblauch,[15] Joshua M. Bauml,[15] Rosario Garcia Campelo,[17] Jie Wang[18]



Vyse, et al, Exp Rev of Anti-infective Therapy, 2021.

Serial brain MRIs were required for all patients[a]

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Documented *EGFR* Ex19del or L858R
- *Progressed on or after osimertinib monotherapy (as most recent line)*
- ECOG PS 0 or 1
- Stable brain metastases were allowed; radiation/definitive therapy was not required (untreated)

Stratification Factors

- Osimertinib line of therapy (1st vs 2nd)
- Asian race (yes or no)
- History of brain metastases (yes or no)

2:2:1 Randomization (N=657)

- **Amivantamab-Lazertinib-Chemotherapy (n=263)**
- **Chemotherapy (n=263)**
- **Amivantamab-Chemotherapy (n=131)**

Dosing (in 21-day cycles)

Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at Cycle 3 (week 7)

Lazertinib: 240 mg daily starting after completion of carboplatin[b]

Chemotherapy administered at the beginning of every cycle:

- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m² until disease progression

Dual primary endpoint of PFS[c] by BICR per RECIST v1.1:

- **Amivantamab-Lazertinib-Chemotherapy** vs **Chemotherapy**
- **Amivantamab-Chemotherapy** vs **Chemotherapy**

Secondary endpoints:

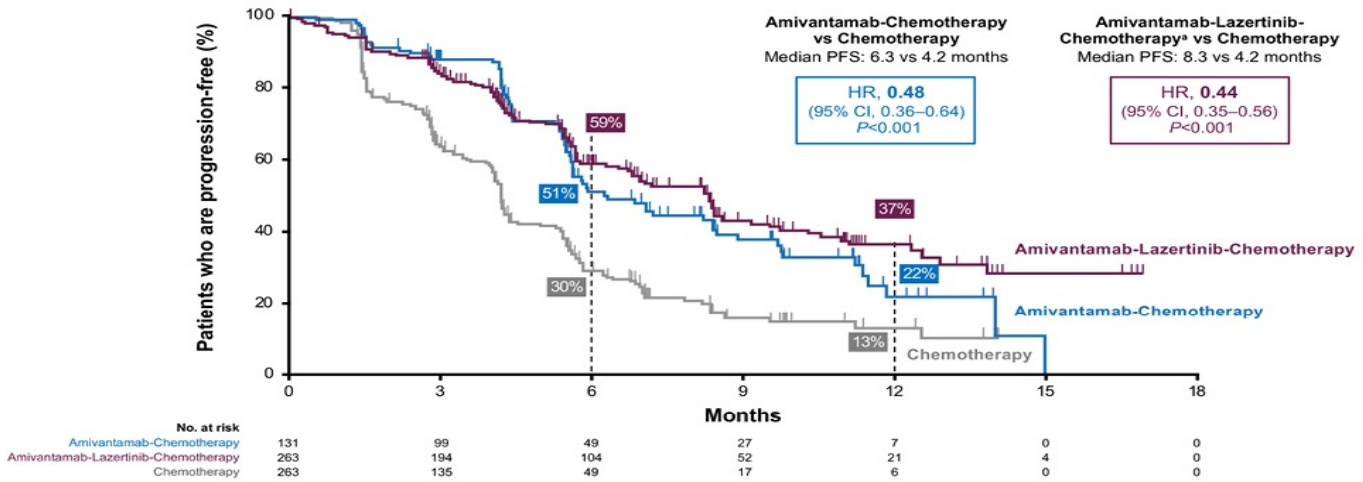
- Objective response rate (ORR)[c]
- Duration of response (DoR)
- Overall survival (OS)[c]
- Intracranial PFS
- Time to subsequent therapy[d]
- PFS after first subsequent therapy (PFS2)[d]
- Symptomatic PFS[d]
- Safety

Passaro A, Cho B.C., Wang Y, et al. ESMO Congress, Madrid 2023.

MARIPOSA-2: PFS Benefit

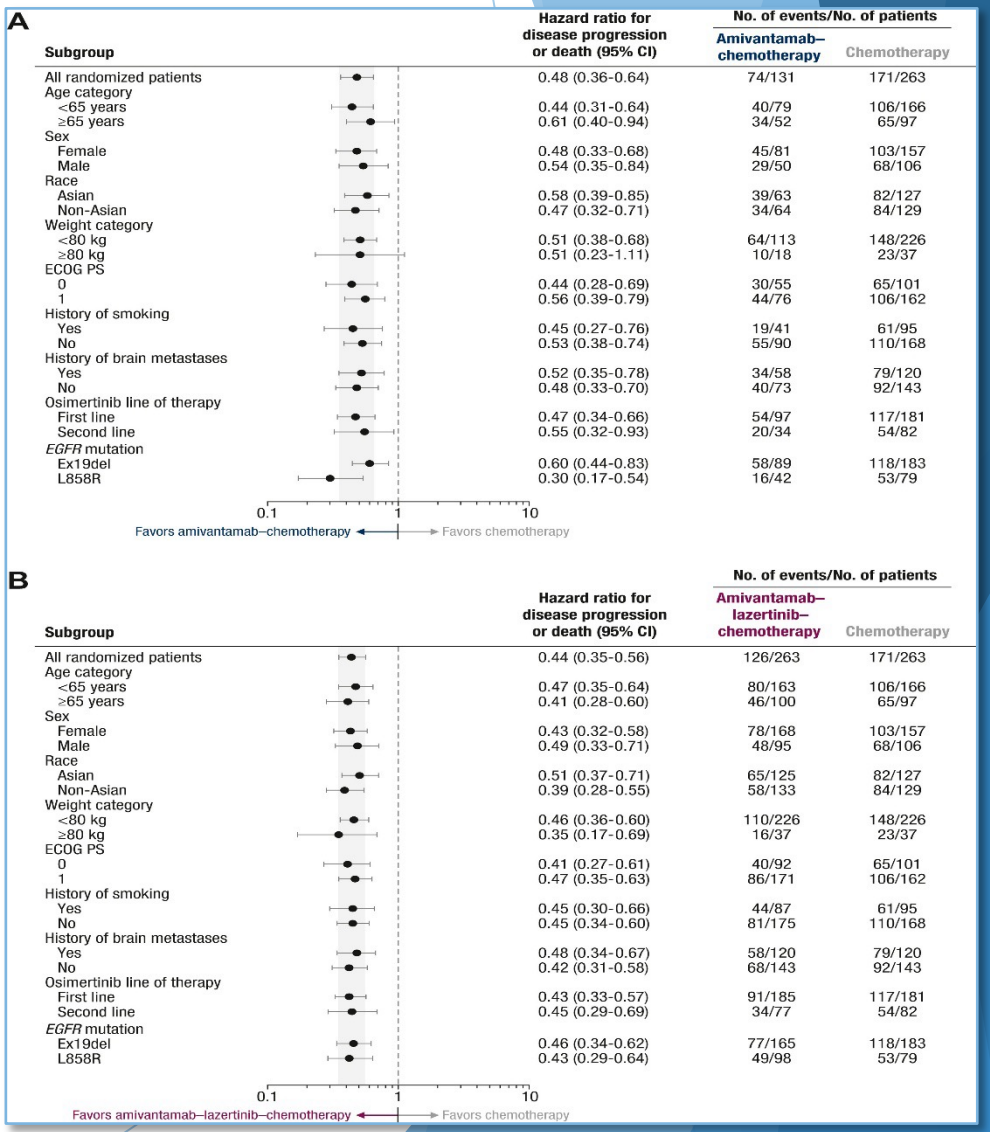
Primary Endpoint: Progression-free Survival by BICR

At a median follow-up of 8.7 months, amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of progression or death by 52% and 56%, respectively



Consistent PFS benefit by investigator: HR, 0.41 (8.2 vs 4.2 mo; P<0.001[b]) & HR, 0.38 (8.3 vs 4.2 mo; P<0.001[b])

Significantly longer mPFS with ami+chemo and ami+laz+chemo than with chemo alone

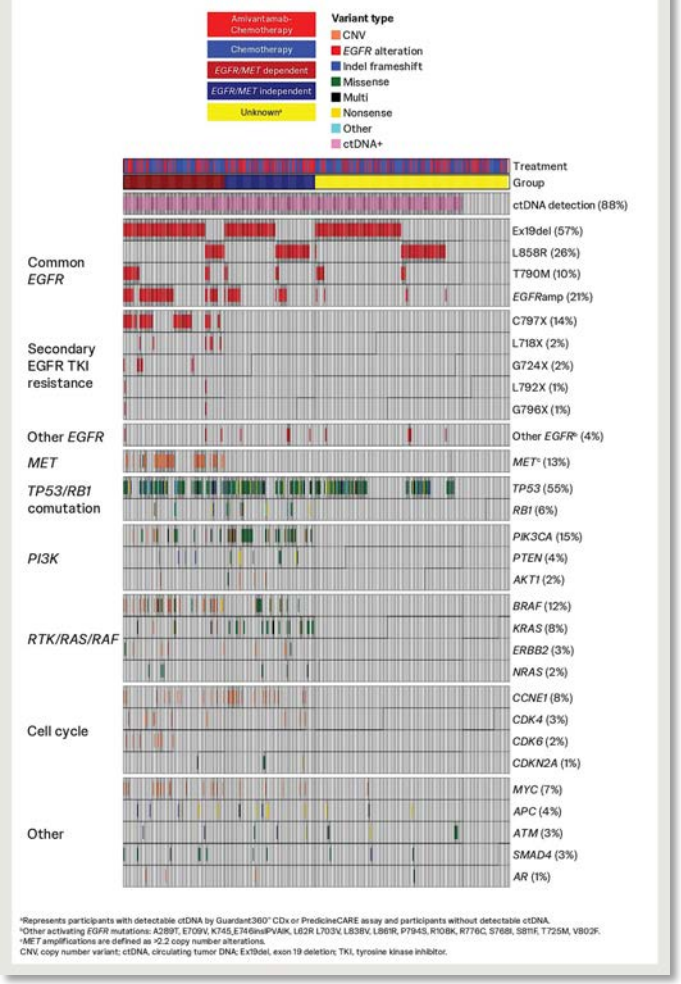


Passaro A, Cho B.C., Wang Y, et al. ESMO Congress, Madrid 2023.
Passaro A, Wang J, Wang Y, et al. Ann Oncol 2024 1:35;77-90.

MARIPOSA-2: PFS by subgroup

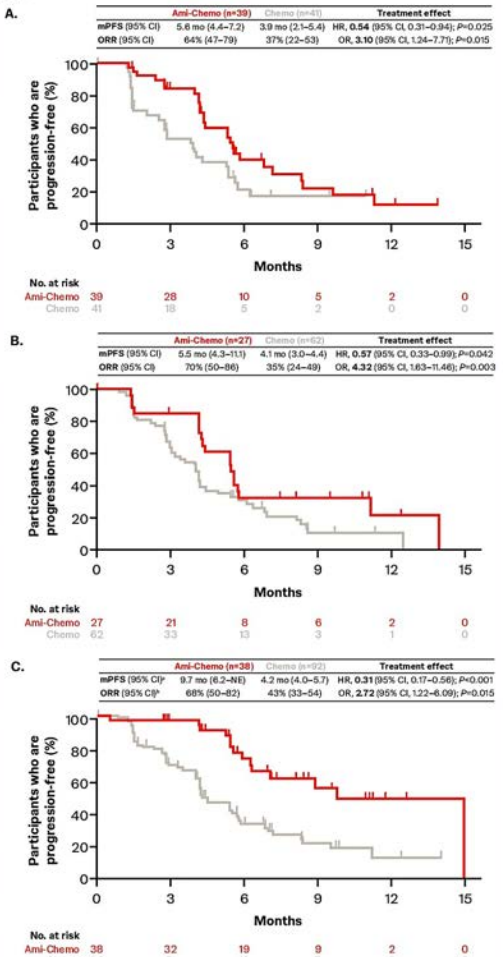
- *MET* amplification (10% vs 14%) and secondary *EGFR* resistance mutations (13% vs 18%) were the most common alterations at baseline for amivantamab-chemotherapy versus chemotherapy alone (**Figure 2**)
- Subsequent analyses included only participants with detectable ctDNA

FIGURE 2: Pathogenic alterations at baseline



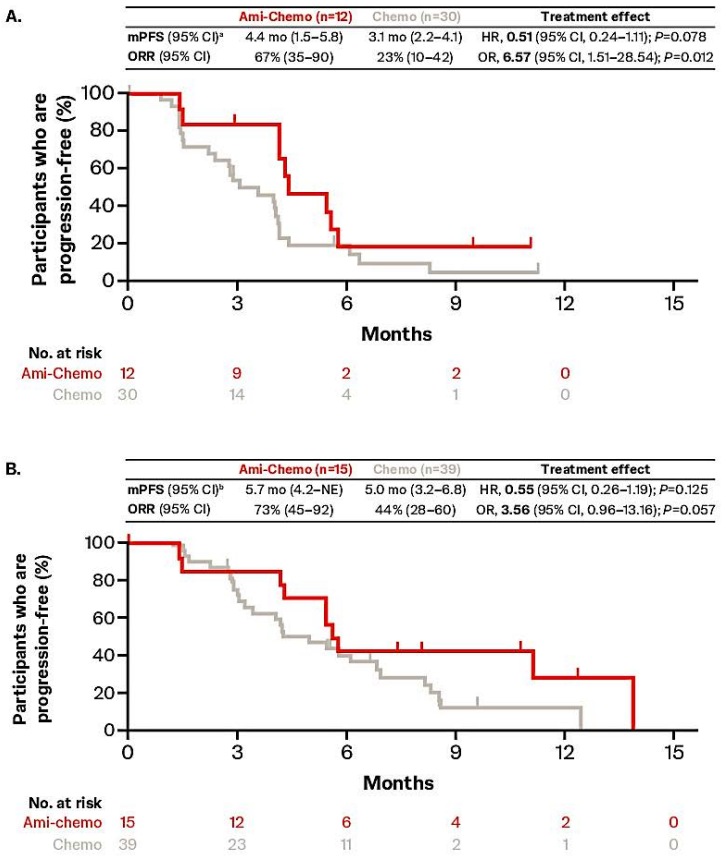
Califano, et al. Abstract 8639, ASCO 2025.

FIGURE 4: Efficacy among participants with (A) *EGFR/MET*-independent, (B) *EGFR/MET*-dependent, and (C) unknown resistance mechanisms



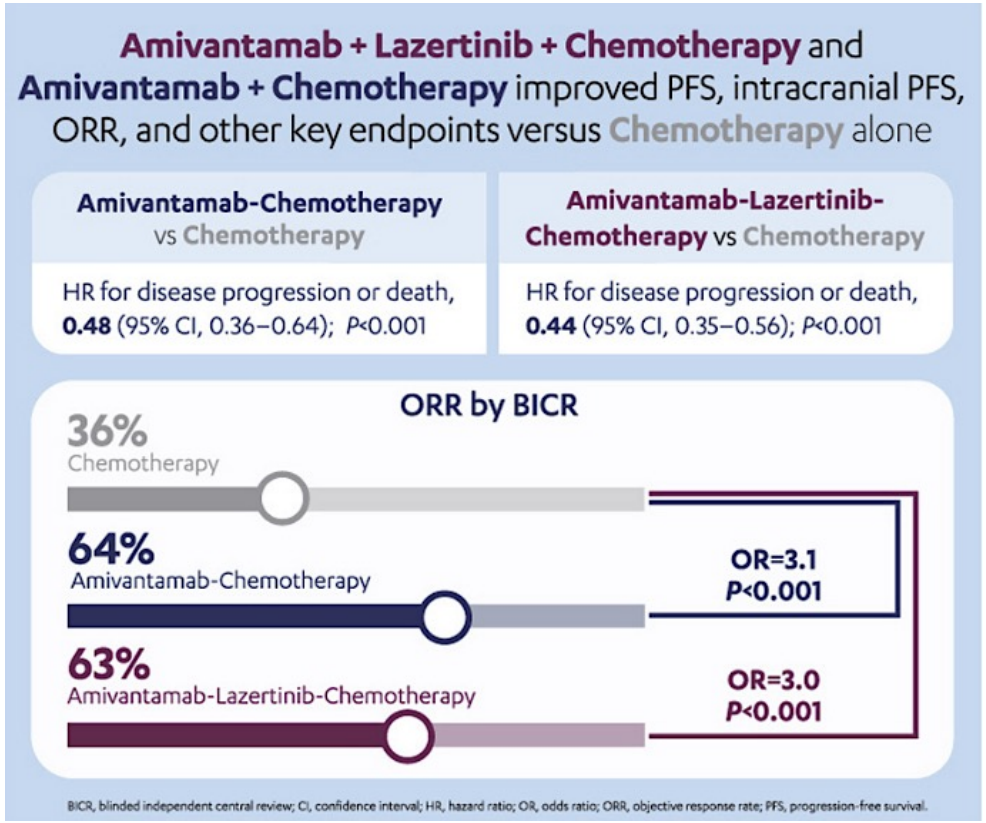
aMPFS for participants with independent/other resistance mechanisms was 7.0 months (95% CI, 5.6–9.6) for ami-chemo versus 4.2 months (95% CI, 4.0–5.4) for chemo (HR, 0.47; 95% CI, 0.32–0.68; P<0.0001).
bThe number of participants with unknown resistance mechanisms for the ORR analysis was 37 participants for ami-chemo and 90 participants for chemo.
Ami, amivantamab; chemo, chemotherapy; NE, not evaluable; OR, odds ratio.

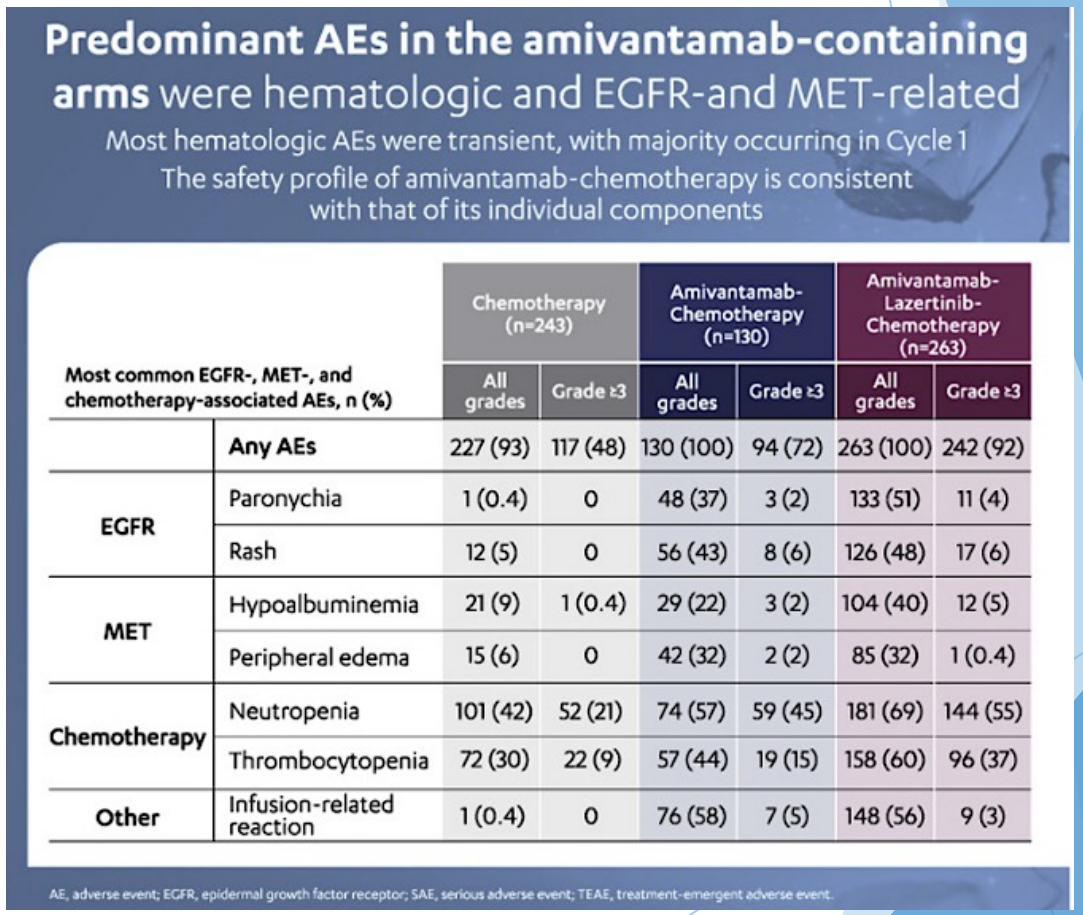
FIGURE 5: Efficacy among participants with (A) *MET*amp and (B) secondary *EGFR* mutations



Note: *MET*amp was defined as >2.2 copy number alterations.
aMPFS for participants without *MET*amp was 6.8 months (95% CI, 5.5–9.6) for ami-chemo versus 4.2 months (95% CI, 4.0–5.4) for chemo (HR, 0.50; 95% CI, 0.35–0.70; P<0.0001).
bMPFS for participants without secondary *EGFR* mutations was 6.2 months (95% CI, 5.5–8.4) for ami-chemo versus 4.2 months (95% CI, 3.8–4.4) for chemo (HR, 0.47; 95% CI, 0.34–0.67; P<0.0001).
Ami, amivantamab; chemo, chemotherapy; *MET*amp, *MET* amplification; NE, not evaluable; OR, odds ratio.

MARIPOSA-2: Adverse Events





Most common EGFR-, MET-, and chemotherapy-associated AEs, n (%)		Chemotherapy (n=243)		Amivantamab-Chemotherapy (n=130)		Amivantamab-Lazertinib-Chemotherapy (n=263)	
		All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
	Any AEs	227 (93)	117 (48)	130 (100)	94 (72)	263 (100)	242 (92)
EGFR	Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
	Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
MET	Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)	104 (40)	12 (5)
	Peripheral edema	15 (6)	0	42 (32)	2 (2)	85 (32)	1 (0.4)
Chemotherapy	Neutropenia	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
	Thrombocytopenia	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Other	Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)

Passaro A, Wang J, Wang Y, et al. Ann Oncol 2024 1:35;77-90.

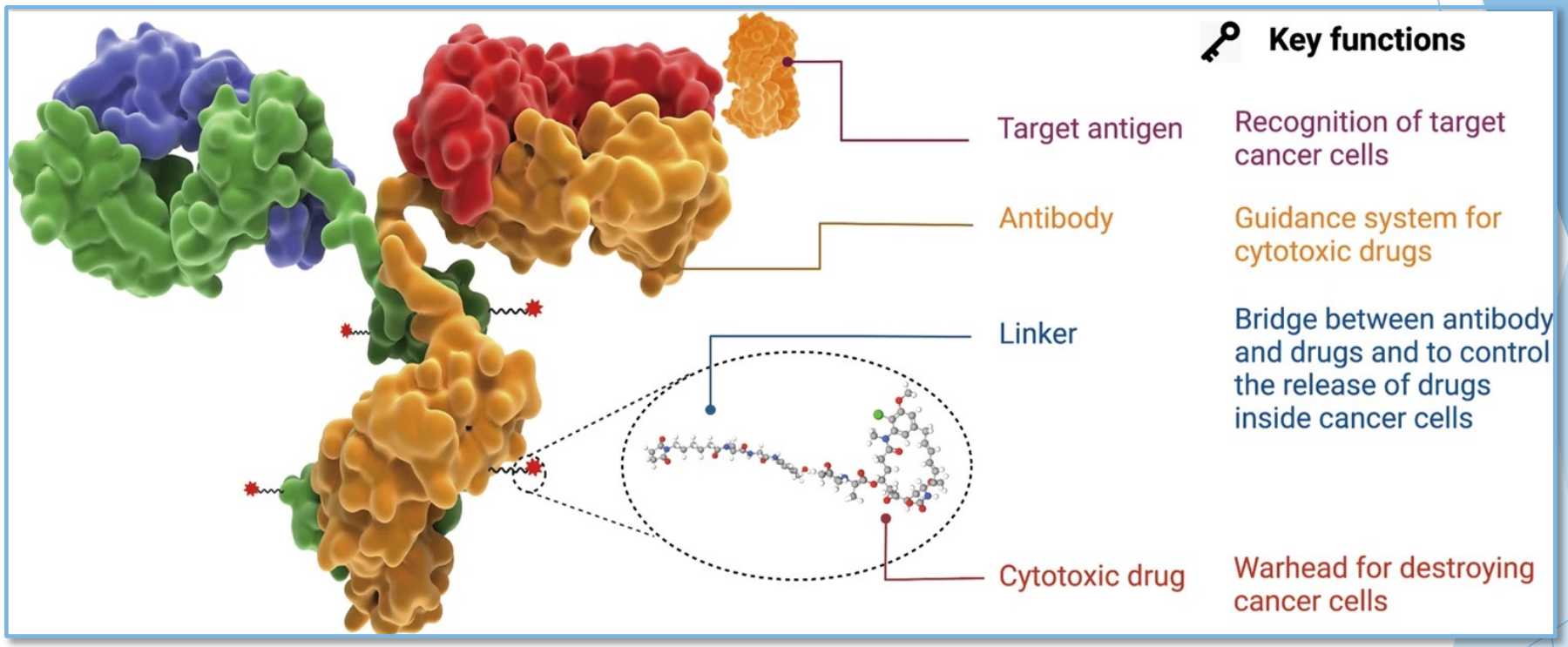
MARIPOSA-2: 2nd Interim OS update

Table: LBA54 Efficacy outcomes

Endpoint	Ami-chemo (n = 131)	Chemo (n = 263)
Median follow-up, mo	18.6	17.8
OS events, n (%)	65 (50)	143 (54)
Median OS, mo (95% CI)	17.7 (16.0–22.4)	15.3 (13.7–16.8)
HR for OS (95% CI)	0.73 (0.54–0.99); *P*=0.039	
18-mo OS rate, % (95% CI)	50 (40–59)	40 (33–46)
Median TTD, mo (95% CI)	10.4 (7.9–11.6)	4.5 (4.2–5.0)
HR for TTD (95% CI)	0.42 (0.33–0.53); *P*<0.0001	
Median TTST, mo (95% CI)	12.2 (10.7–14.3)	6.6 (6.1–7.4)
HR for TTST (95% CI)	0.51 (0.39–0.65); *P*<0.0001	
Median PFS2, mo (95% CI)	16.0 (13.9–17.6)	11.6 (10.1–13.0)
HR for PFS2 (95% CI)	0.64 (0.48–0.85); *P*=0.002	

Popat S, et al. Abstract LBA54, ESMO 2024.

Antibody Drug Conjugates



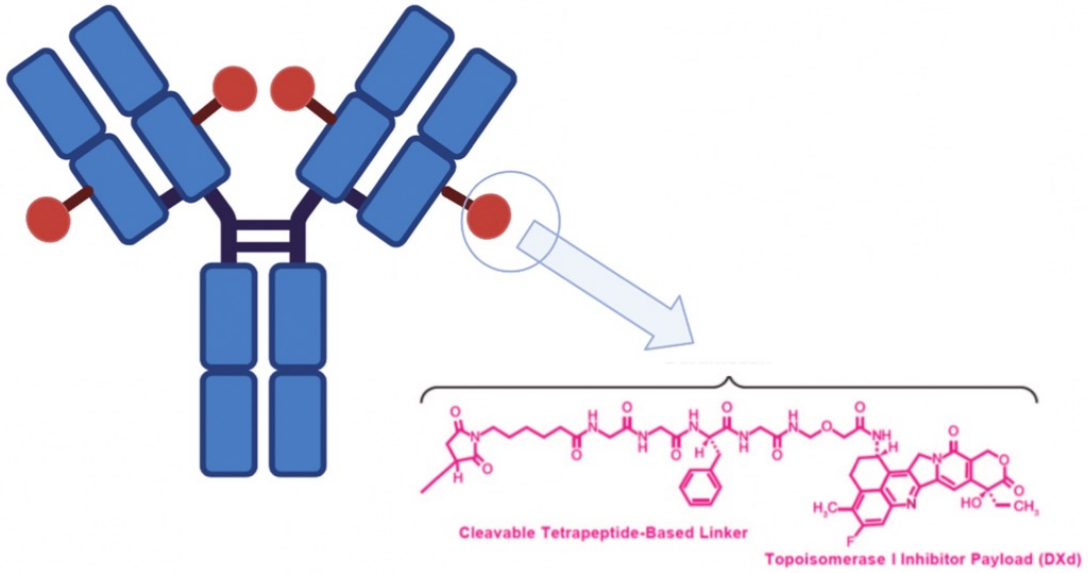
ADC COMPONENTS

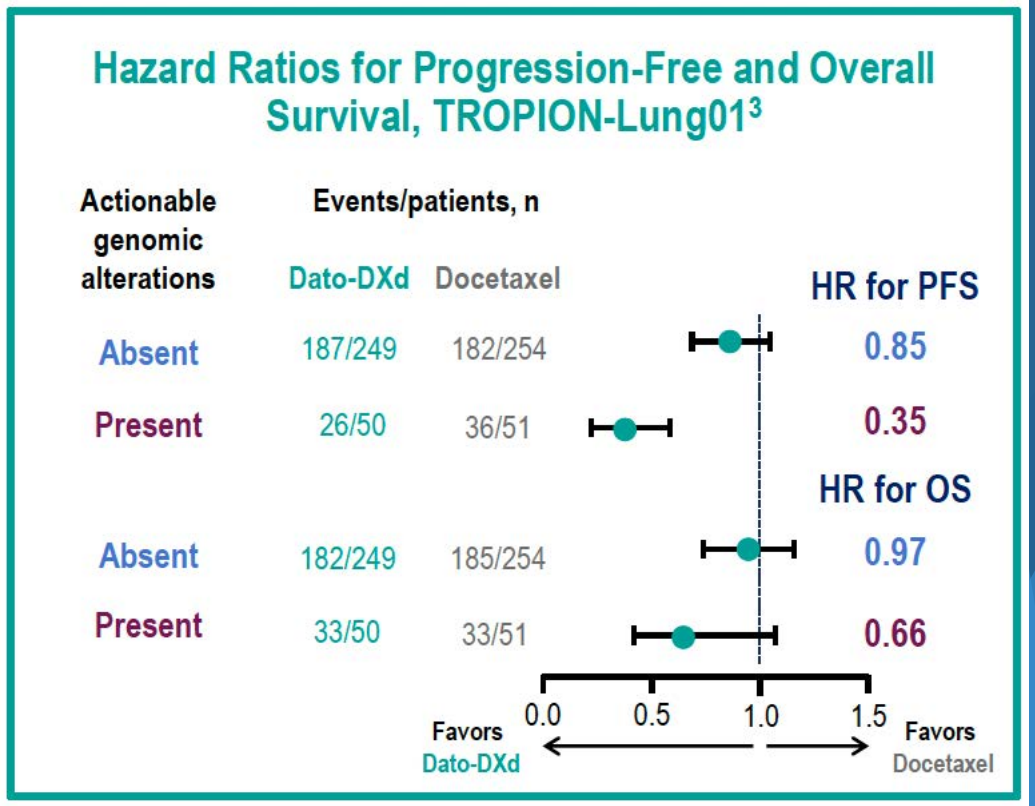
Target antigen selection, antibody subtype, internalization optimization, linkers, cytotoxic payloads, conjugation methods, Drug-Antibody Ratio.

Fu, Z., et al. Antibody drug conjugate. Sig Transduct Target Ther 7, 93 (2022).

Datopotamab deruxtecan (Dato-DXd)

- Trop2-directed ADC
- Topoisomerase I inhibitor payload



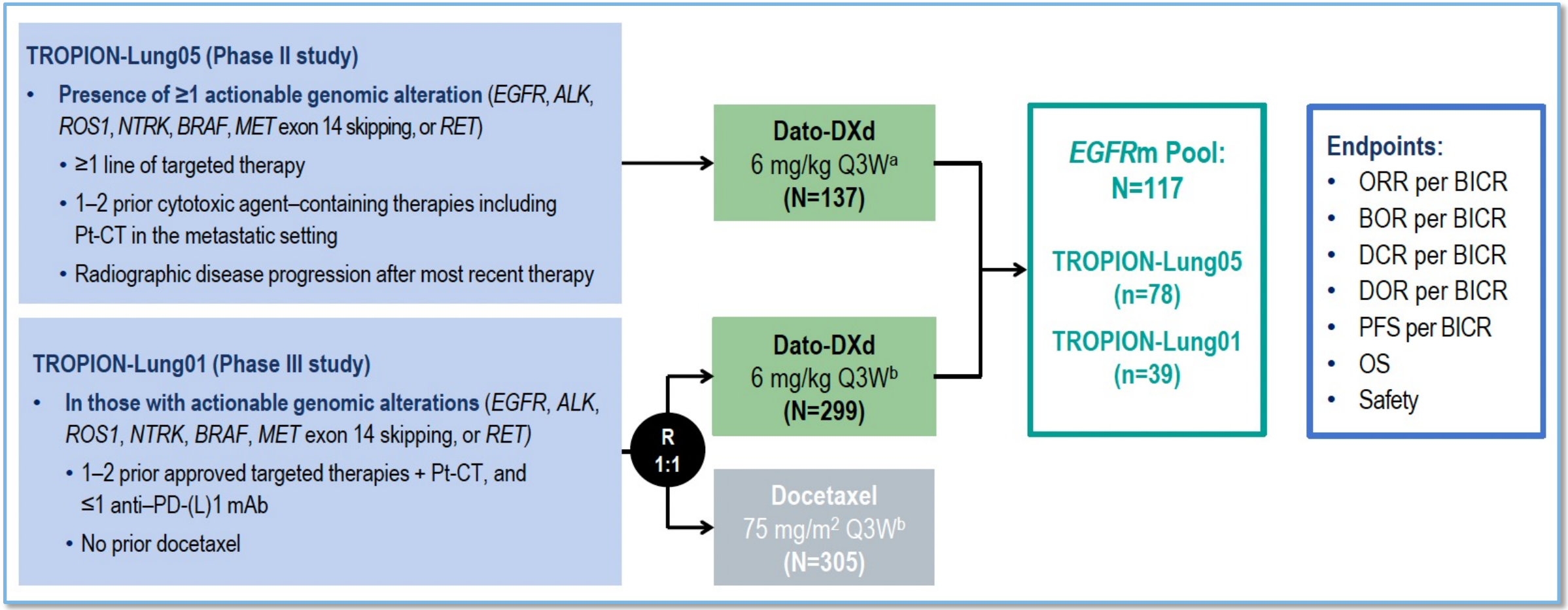


Ahn, M-J, ESMO Asia, 2024.

Dato-DXd in EGFRm NSCLC

UCLA Health | David Geffen School of Medicine

Pooled Analysis from TROPION-Lung05 and 01



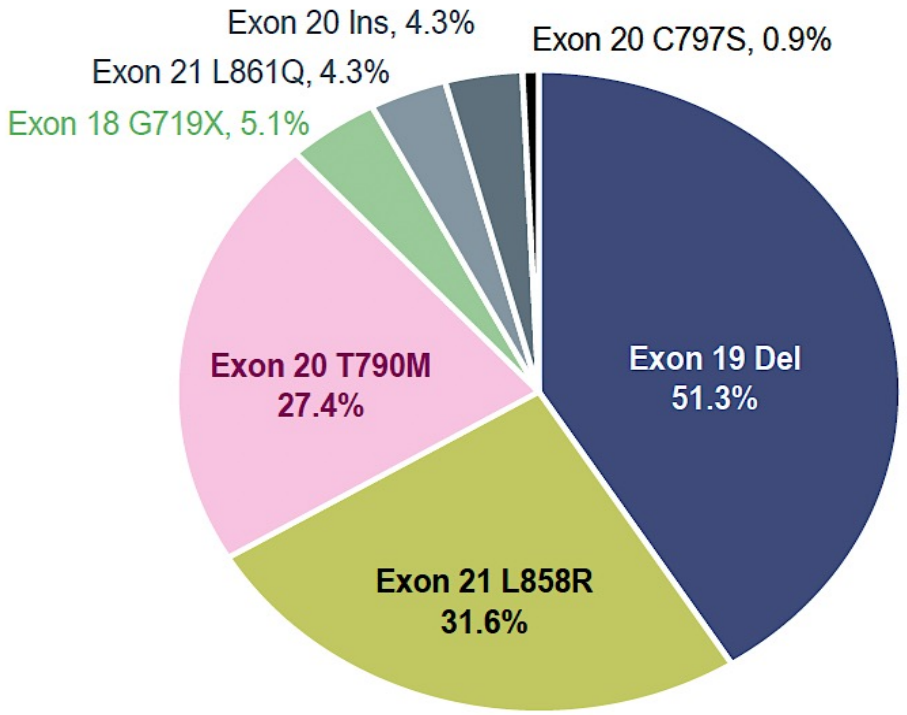
Ahn, M-J, ESMO Asia, 2024.

TROPION-Lung01 & 05 EGFRm cohort

Demographics and Baseline Characteristics

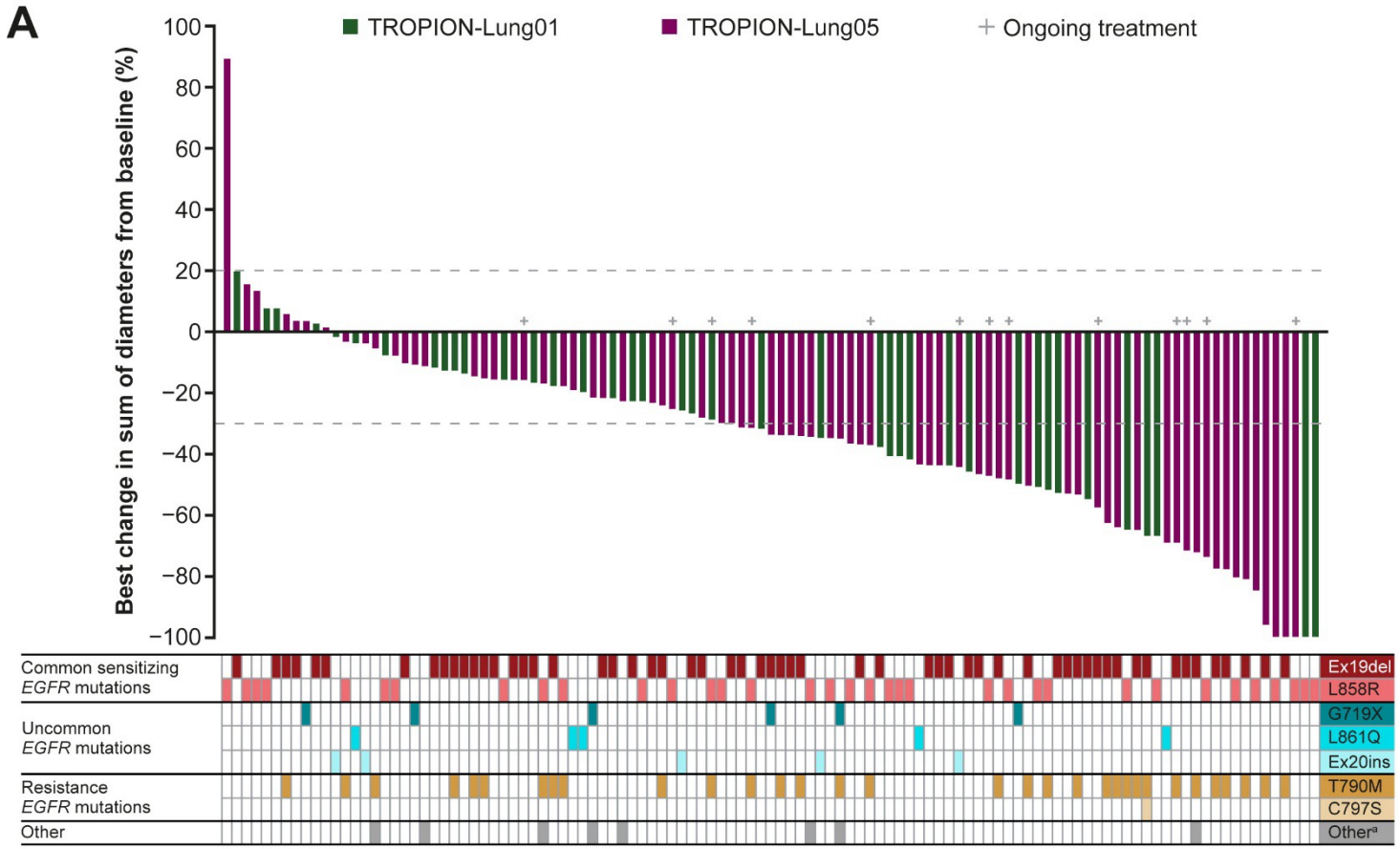
Characteristic	*EGFR*m Pool (N=117)	TROPION-Lung05 (N=78)	TROPION-Lung01 (N=39)
Median age (range), years	63 (36–81)	63 (36–77)	62 (39–81)
Sex, female, n (%)	73 (62.4)	52 (66.7)	21 (53.8)
Race, n (%)			
Asian	81 (69.2)	55 (70.5)	26 (66.7)
White	27 (23.1)	20 (25.6)	7 (17.9)
Black or African American	1 (0.9)	0	1 (2.6)
Other/missing	8 (6.8)	3 (3.8)	5 (12.8)
ECOG PS, n (%)			
0	39 (33.3)	24 (30.8)	15 (38.5)
1	78 (66.7)	54 (69.2)	24 (61.5)
Smoker[a], n (%)	55 (47.0)	34 (43.6)	21 (53.8)
Nonsquamous histology[b], n (%)	115 (98.3)	77 (98.7)	38 (97.4)
Brain metastasis at study entry, n (%)	36 (30.8)	21 (26.9)	15 (38.5)
Median lines systemic therapy (range)[c]	3 (1–5)	3 (1–5)	2 (1–5)
Prior osimertinib[d], n (%)	96 (82.1)	61 (78.2)	35 (89.7)
First line	47 (40.2)	27 (34.6)	20 (51.3)
Second line	34 (29.1)	20 (25.6)	14 (35.9)

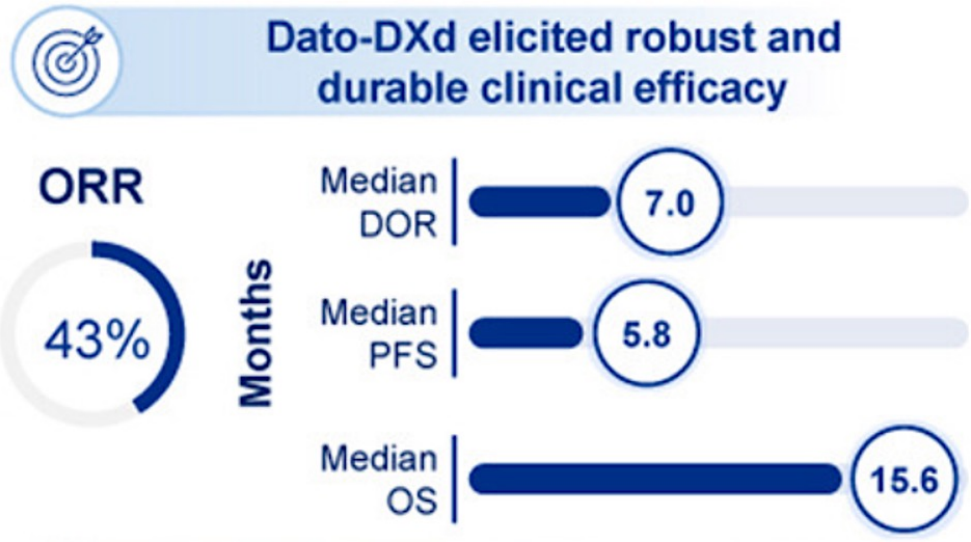
EGFR Mutational Profile (N=117)[e]



Ahn, M-J, ESMO Asia, 2024.

Dato-DXd Efficacy in EGFRm cohort





- Confirmed ORR 43%
- For 45 docetaxel-treated pts ORR 9%

Ahn, M-J, Lisberg A, Goto Y, et al. J Thor Oncol, 2025 Nov.

Dato-DXd Efficacy in EGFRm cohort

UCLA Health | David Geffen School of Medicine

Safety profile consistent with the individual studies

	Any grade	Grade 3
Oral mucositis/stomatitis	69%	9%
Ocular surface events	32%	3%
Adjudicated drug-related ILD/pneumonitis	4%	1%

- No new safety signals
- No grade 4 or 5 AESIs

Ahn, M-J, Lisberg A, Goto Y, et al. J Thor Oncol, 2025 Nov.

For metastatic EGFR-mutated NSCLC, we reviewed:

- First line options: FLAURA2 and MARIPOSA
- Subcutaneous amivantamab
- Data for continued TKI on progression
- Later-line options: MARIPOSA2 and Datopotamab deruxtecan

QUESTIONS?

Module 12: EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC)

Current Management of Metastatic EGFR-Mutated NSCLC — Dr Goldman

Nonmetastatic EGFR-Mutated NSCLC, Exon 20 Insertion Mutations and Novel Agents — Dr Piotrowska

Massachusetts General Hospital
Founding Member, Mass General Brigham

Other Relevant Topics in EGFR Mutation-Positive NSCLC (eg, Nonmetastatic Disease, Exon 20 Insertion Mutations, Novel Agents)

Zosia Piotrowska, MD, MHS
Associate Professor of Medicine, Harvard Medical School
Clinical Co-Director, MGB Thoracic Medical Oncology Program
Massachusetts General Hospital
Boston, MA

Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Black Diamond Therapeutics Inc, BlossomHill Therapeutics, Boehringer Ingelheim Pharmaceuticals Inc, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Janssen Biotech Inc, Lilly, Natera Inc, Regeneron Pharmaceuticals Inc, Revolution Medicines Inc, Summit Therapeutics, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tubulis
Contracted Research	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BlossomHill Therapeutics, Blueprint Medicines, Cullinan Therapeutics, Daiichi Sankyo Inc, Janssen Biotech Inc, Novartis, Nuvalent, Spectrum Pharmaceuticals Inc, SystImmune Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company
Data and Safety Monitoring Boards/Committees	Genentech, a member of the Roche Group

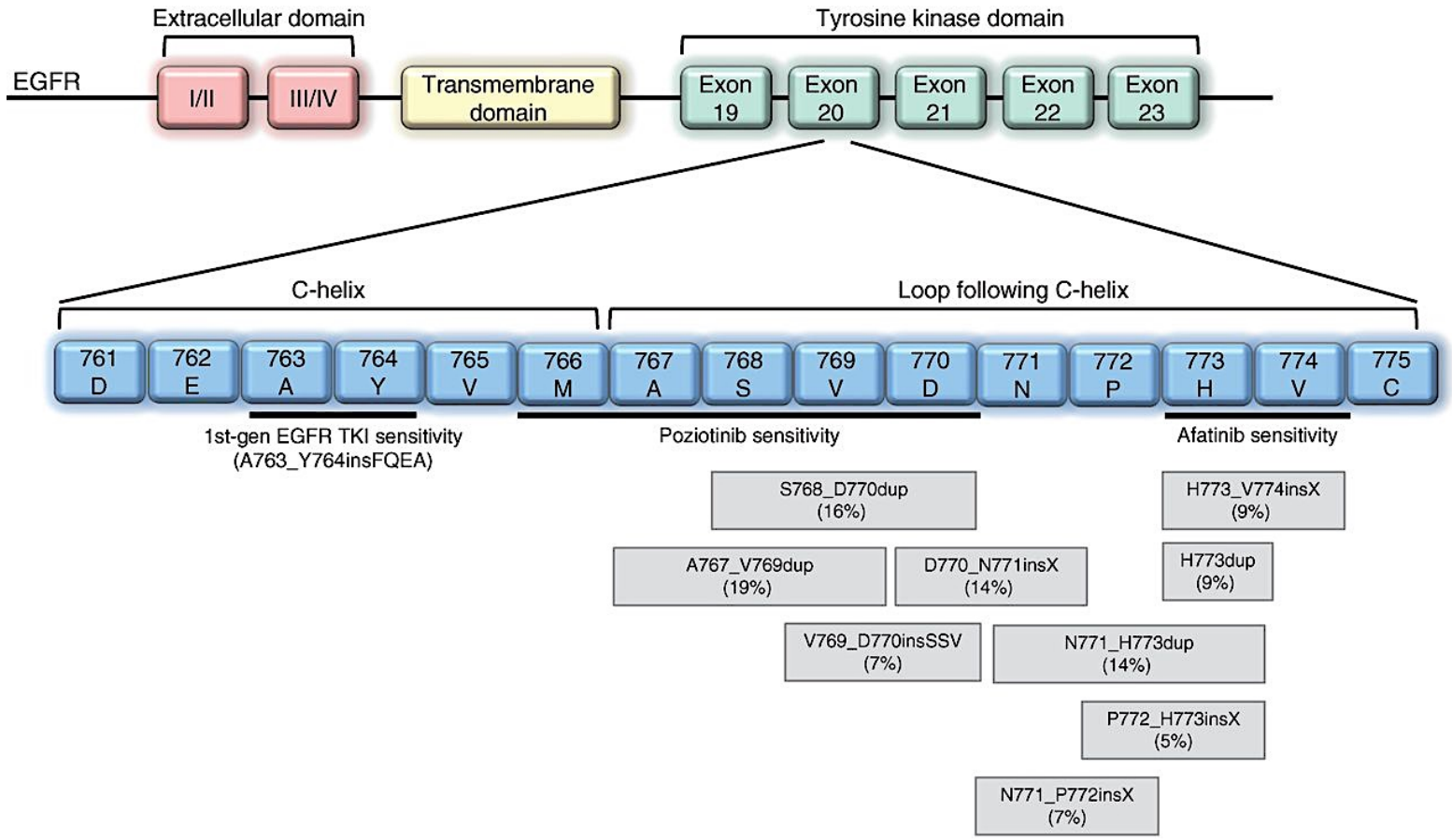
Other Relevant Topics in EGFR-mutation Positive NSCLC

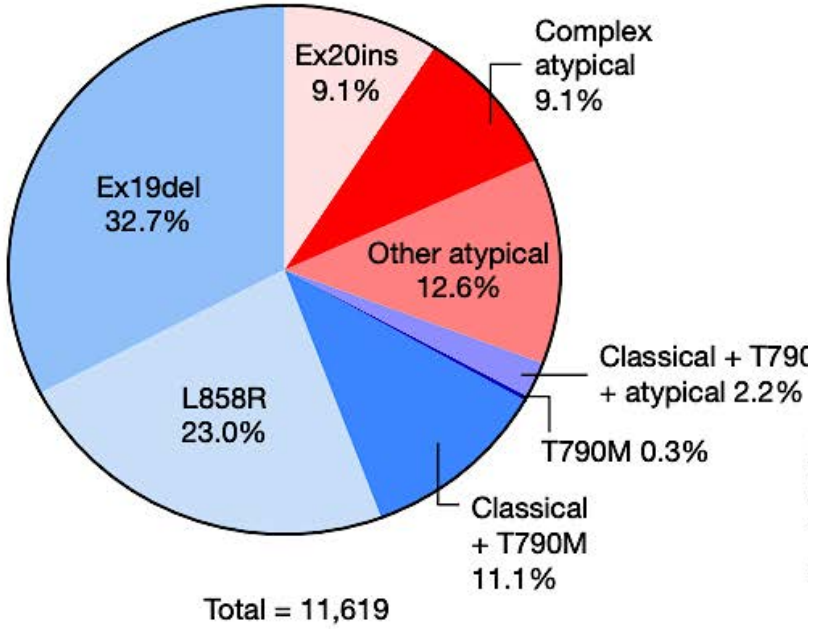
- EGFR Exon 20 Insertions
- Novel agents in EGFR-mutant NSCLC
- Non-metastatic EGFR-positive disease

Other Relevant Topics in EGFR-mutation Positive NSCLC

- EGFR Exon 20 Insertions
- Novel agents in EGFR-mutant NSCLC
- Non-metastatic EGFR-positive disease

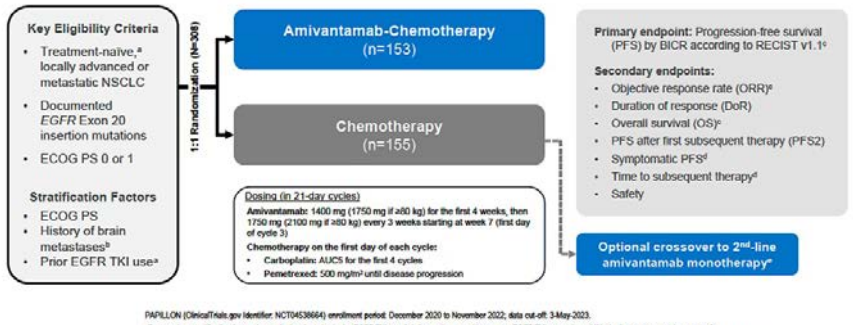
Molecular Landscape of EGFR Exon 20 Insertions



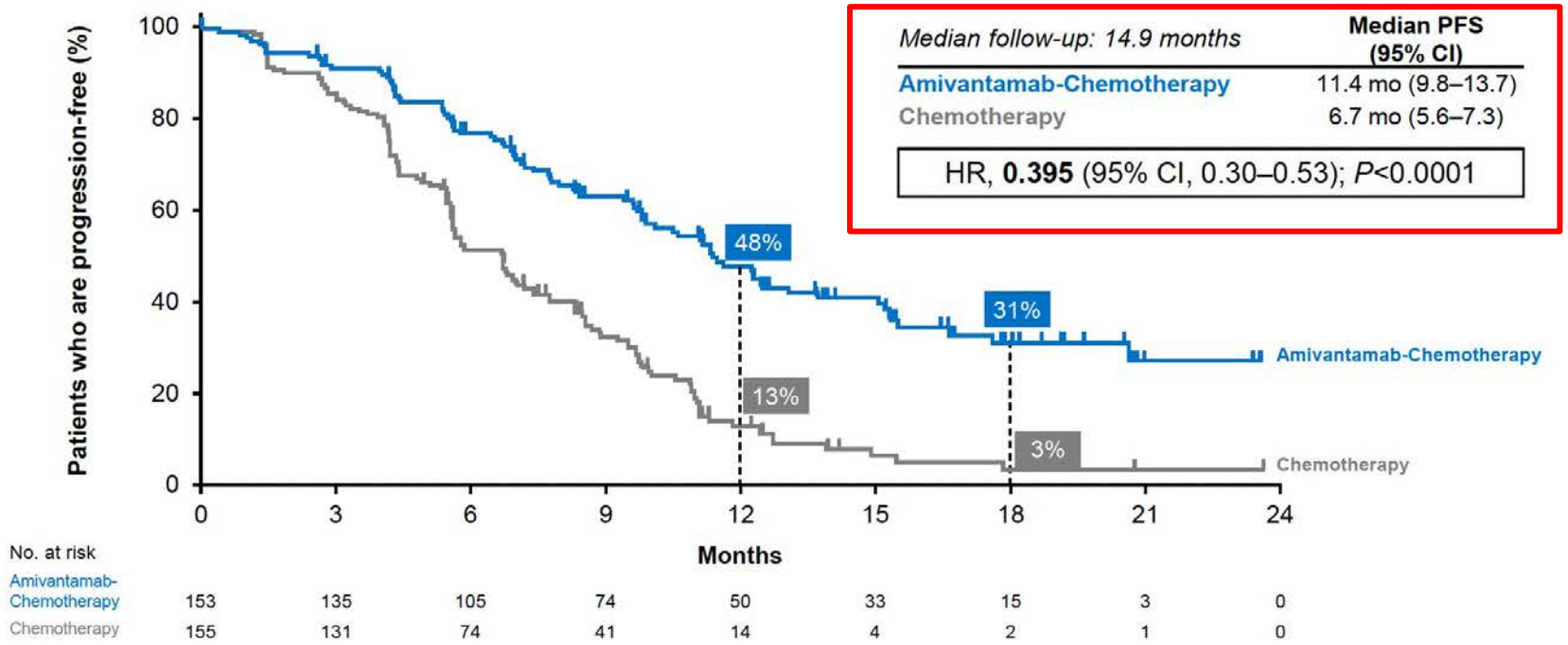


Robichaux JP et al. *Nature*. 2021;597:732-737. Meador CB et al. *Cancer Disc.* 2021;11(9):2145-2157.

PAPILLON: Front-Line Amivantamab + Chemo



Progression-Free Survival by BICR



	Amivantamab-Chemo	Chemo	
ORR	73% (95% CI, 65-80)	47% (95% CI, 39-56)	
mPFS	11.4 mo (9.8-13.7)	6.7 (95% CI, 5.6-7.3)	HR 0.395 (95% CI, 0.30-0.53)
[OS (interim)*	*NE*	*24.4 mo (95% CI, 22.1-NE)*	*HR 0.675 (95% CI, 0.42-1.09)]*

Girard N et al. ESMO 2023. Abstract LBA5.
Zhou C et al. *N Engl J Med*. 2023;389(22):2039-2051.

OS data are immature (~33% maturity), 66% of patients who progressed crossed over to amivantamab.

Positive Top-Line Phase III Results from the WU-KONG28 Study: Oral, Once-Daily Sunvozertinib versus Platinum-Containing Chemo Doublet for First-Line NSCLC with EGFR Exon 20 Insertion Mutation
Press Release: March 31, 2026

"[The manufacturer] today announced that its multinational Phase 3 WU-KONG28 study evaluating sunvozertinib monotherapy as first-line treatment in non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations (exon20ins) met its primary endpoint with positive topline results.

The findings suggest that sunvozertinib monotherapy has the potential to become the first and only chemo free, oral agent to treat newly diagnosed NSCLC patients with EGFR exon20ins.

In the first-line setting, sunvozertinib has been granted Breakthrough Therapy Designations by both the U.S. Food and Drug Administration (FDA) and China Center for Drug Evaluation (CDE). Based on WU-KONG28 study results, [the Manufacturer] plans to engage with regulatory authorities regarding potential new drug applications (NDAs)."

https://www.dizalpharma.com/news/detail?id=109

RTP RESEARCH TO PRACTICE

Sunvozertinib (DZD9008)

WU-KONG 1B Global Phase 2 Study:
NSCLC with EGFR exon 20 insertions, post-chemotherapy

	200 mg (N = 85)	300 mg (N = 89)
Confirmed ORR	45.9 (33.6, 58.5)	47.2 (35.1, 59.5)
mDOR	11.1 (8.2, NE)	13.8 (8.3, NE)
mPFS	8.4 (6.8, 13.9)	7.7 (6.0, 9.8)
Prior Ami (n = 12/cohort)	25%	41.7%
Baseline CNS mets (n = 21/cohort)	28.6%	52.4%

Janne P et al. WCLC 2025. Abstract PL02.06. Yang JCH et al. *J Clin Oncol*. 2025;43:3198-3208.

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mPFS	8.4 (6.8, 13.9)	7.7 (6.0, 9.8)
Prior Ami (n = 12/cohort)	25%	41.7%
Baseline CNS mets (n = 21/cohort)	28.6%	52.4%

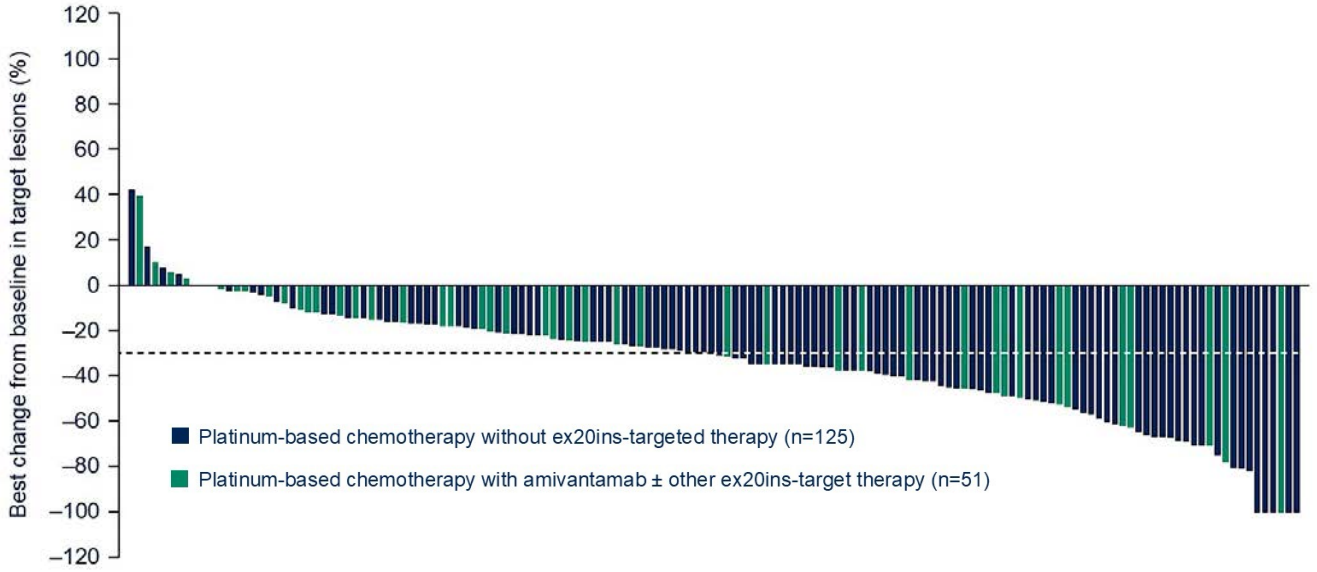
TABLE A4. The Common (≥20%) TRAE by Maximum CTCAE Grade

	200 mg-Rand (n = 91), No. (%)				
Preferred Term	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Patients with any TRAE	86 (94.5)	12 (13.2)	37 (40.7)	34 (37.4)	3 (3.3)
Diarrhea	62 (68.1)	44 (48.4)	16 (17.6)	2 (2.2)	0 (0.0)
Blood creatine phosphokinase increased	32 (35.2)	14 (15.4)	12 (13.2)	6 (6.6)	0 (0.0)
Rash	37 (40.7)	26 (28.6)	7 (7.7)	4 (4.4)	0 (0.0)
Nausea	25 (27.5)	15 (16.5)	8 (8.8)	2 (2.2)	0 (0.0)
Anemia	28 (30.8)	15 (16.5)	9 (9.9)	4 (4.4)	0 (0.0)
Paronychia	24 (26.4)	13 (14.3)	11 (12.1)	0 (0.0)	0 (0.0)
Vomiting	26 (28.6)	16 (17.6)	10 (11.0)	0 (0.0)	0 (0.0)
Decreased appetite	39 (42.9)	26 (28.6)	13 (14.3)	0 (0.0)	0 (0.0)
Dry skin	18 (19.8)	12 (13.2)	6 (6.6)	0 (0.0)	0 (0.0)
Blood creatinine increased	25 (27.5)	19 (20.9)	5 (5.5)	1 (1.1)	0 (0.0)
Pruritus	23 (25.3)	20 (22.0)	2 (2.2)	1 (1.1)	0 (0.0)
Stomatitis	20 (22.0)	14 (15.4)	5 (5.5)	1 (1.1)	0 (0.0)
Lipase increased	21 (23.1)	11 (12.1)	8 (8.8)	1 (1.1)	1 (1.1)

Janne P et al. WCLC 2025. Abstract PL02.06. Yang JCH et al. *J Clin Oncol*. 2025;43:3198-3208.

Zipalertinib: Activity after Amivantamab

	ORR
Prior Chemo only (n = 125)	40% (31-49)
Prior Ami, no other Exon 20 TKIs (n = 30)	30% (15-49)
Prior Ami + prior Exon 20 TKIs (n = 21)	14% (3-36)



Yu HA et al. ASCO 2025;Abstract 8503. Piotrowska Z. *J Clin Oncol*. 2025;43(13):1523-1526. Yu HA et al. ESMO 2025;Abstract 1847MO.

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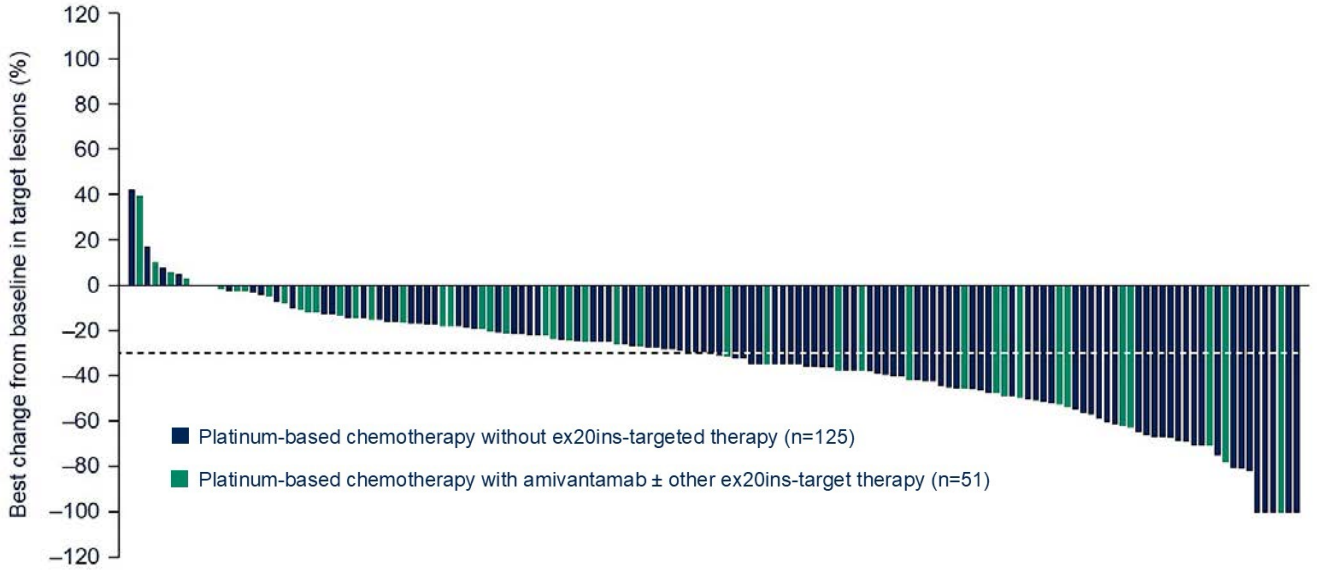

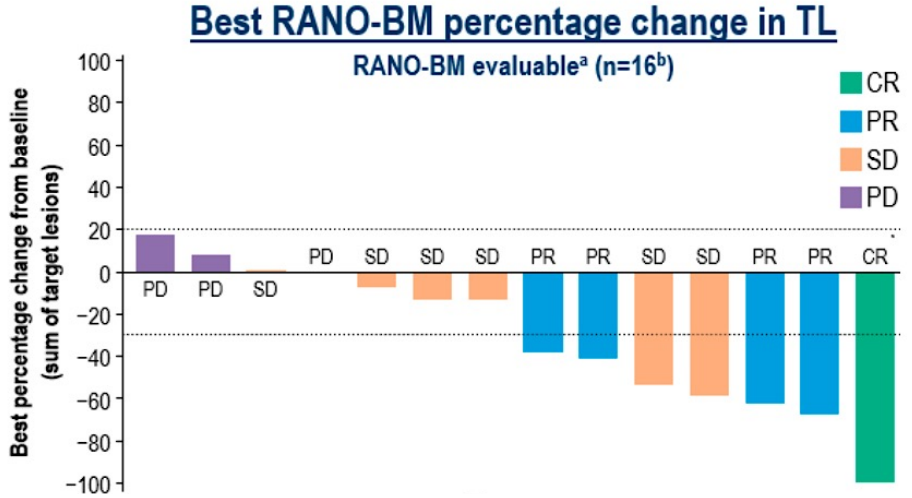

Yu HA et al. ASCO 2025;Abstract 8503. Piotrowska Z. *J Clin Oncol*. 2025;43(13):1523-1526. Yu HA et al. ESMO 2025;Abstract 1847MO.

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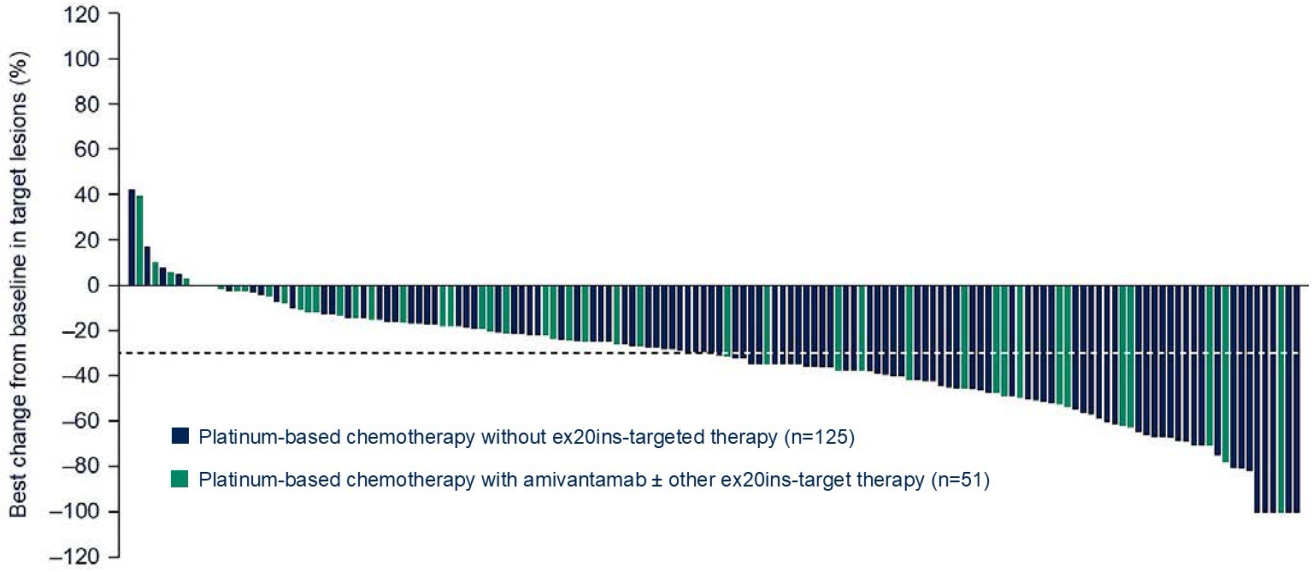
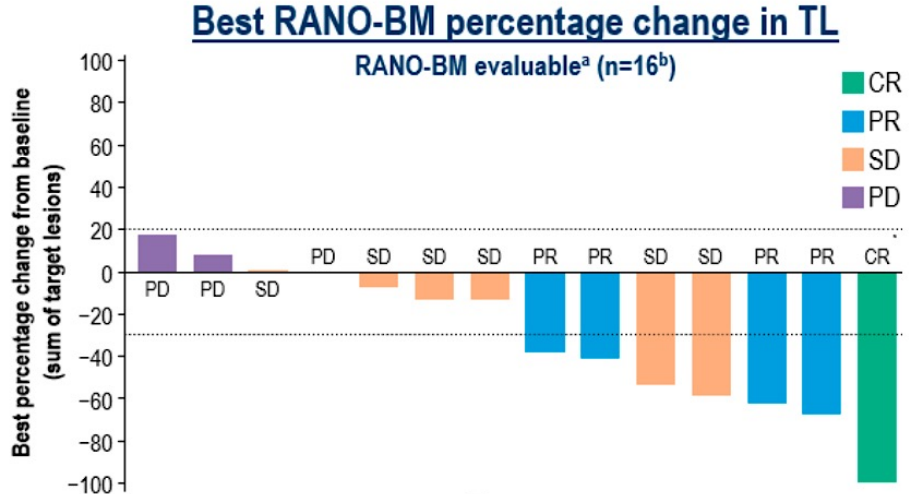
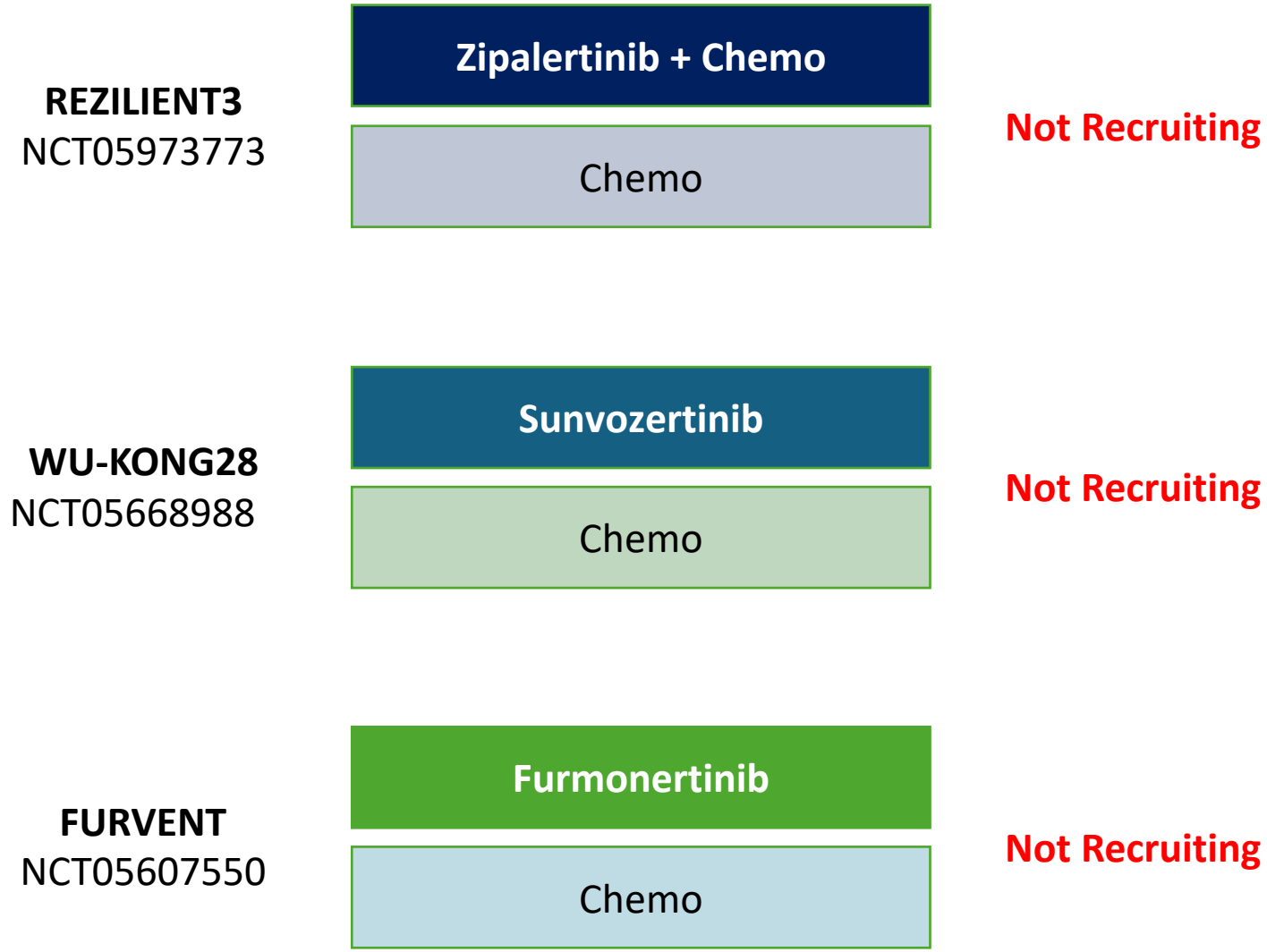




Any-grade TRAEs reported in ≥10% of patients, No. (%)	Any grade	Grade 3
Paronychia	94 (38.5)	0
Rash	74 (30.3)	6 (2.5)
Dermatitis acneiform	60 (24.6)	1 (0.4)
Dry skin	60 (24.6)	0
Diarrhea	53 (21.7)	5 (2.0)
Stomatitis	49 (20.1)	4 (1.6)
Anemia	48 (19.7)	17 (7.0)
Pruritus	44 (18.0)	1 (0.4)
Nausea	35 (14.3)	2 (0.8)
Rash maculopapular	34 (13.9)	3 (1.2)
Fatigue	29 (11.9)	0

Yu HA et al. ASCO 2025;Abstract 8503. Piotrowska Z. *J Clin Oncol*. 2025;43(13):1523-1526. Yu HA et al. ESMO 2025;Abstract 1847MO.

Ongoing First-Line EGFR Exon 20 TKI Trials

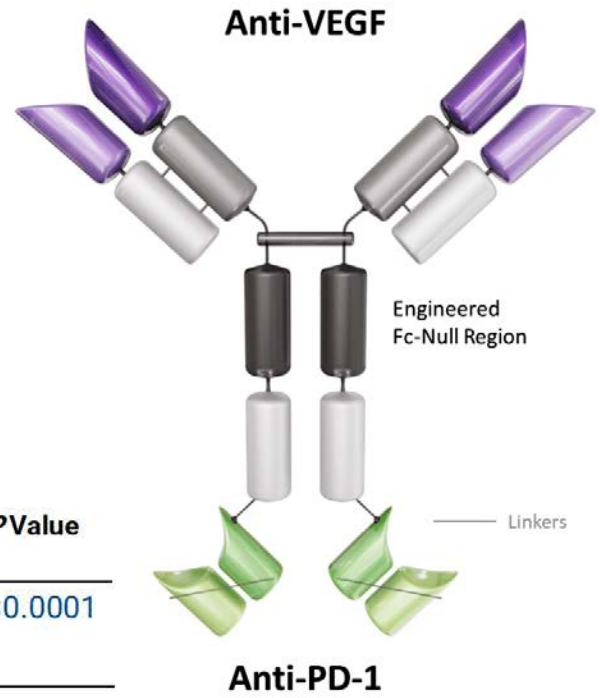


Other Relevant Topics in EGFR-mutation Positive NSCLC

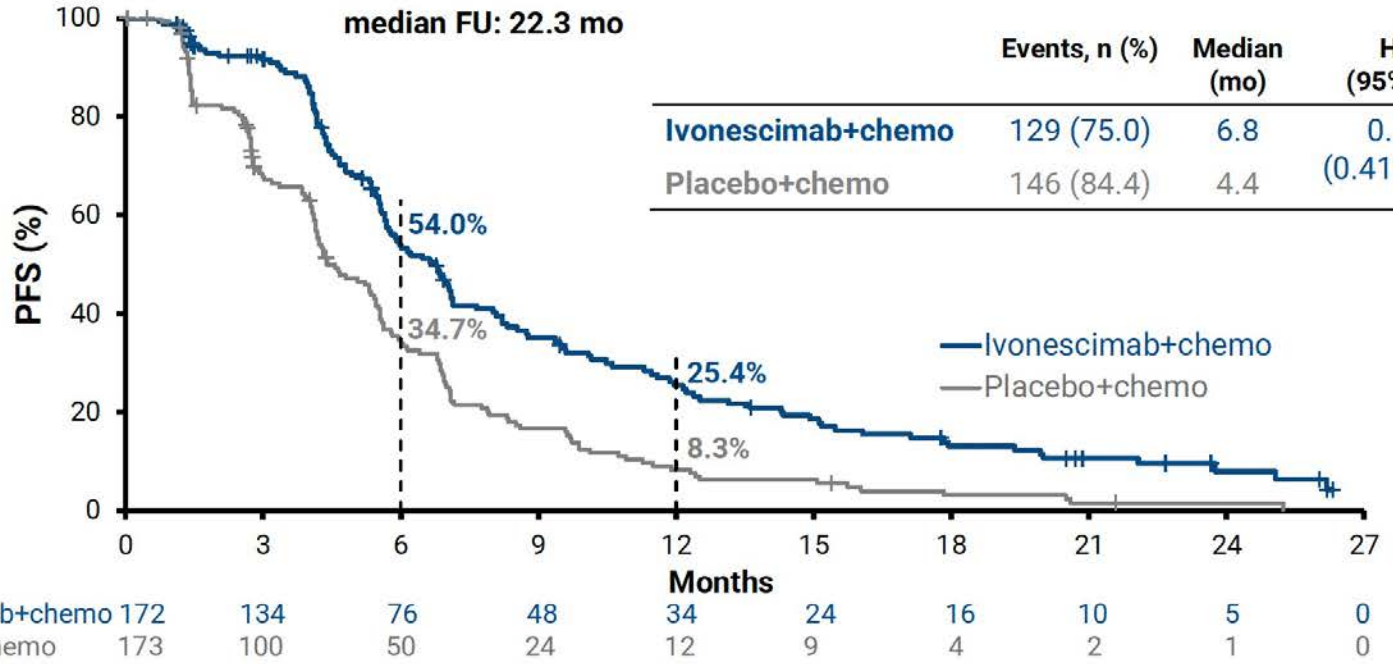
- EGFR Exon 20 Insertions
- Novel agents in EGFR-mutant NSCLC
- Non-metastatic EGFR-positive disease

Ivonescimab

Ivonescimab vs Placebo Plus Chemo, Phase 3 in Patients with EGFR+ NSCLC Progressed with 3rd gen EGFR-TKI Treatment: HARMONi



Primary Endpoint: PFS (BICR)



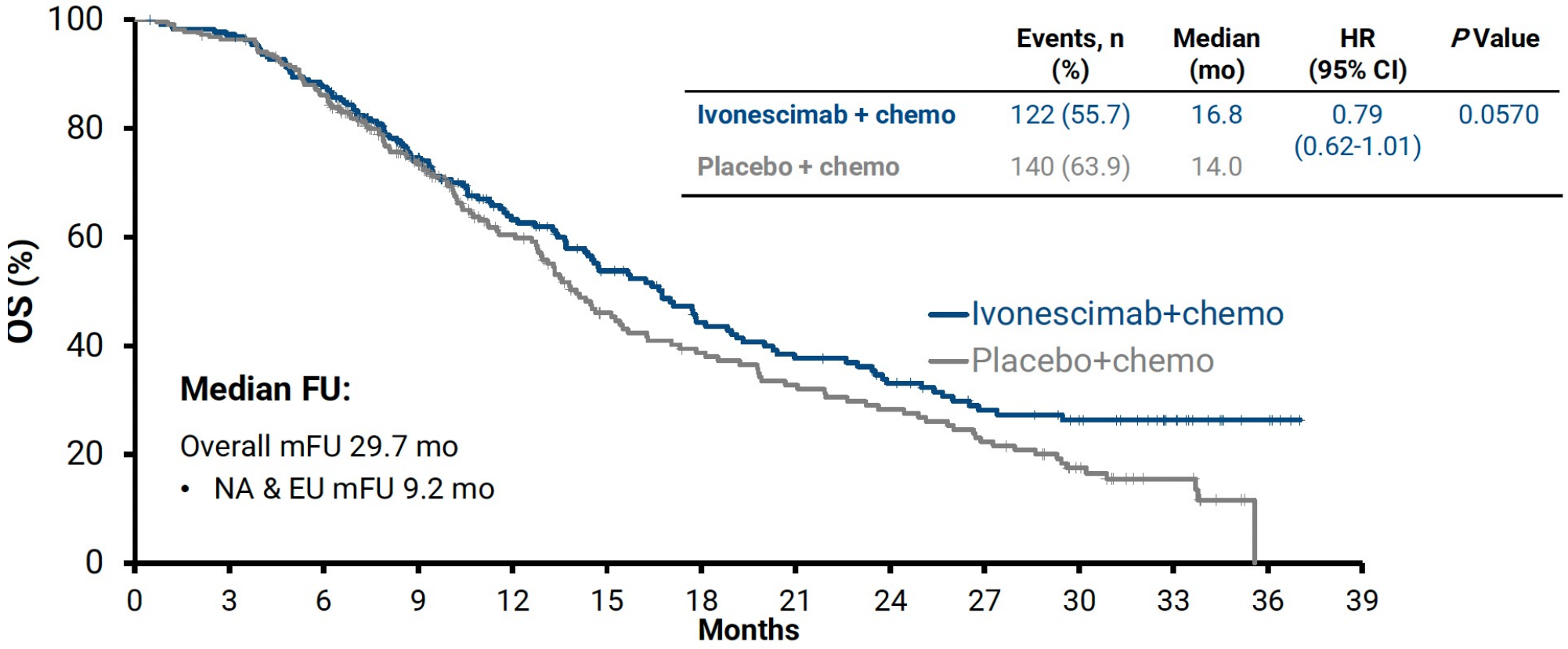
	Events, n (%)	Median (mo)	HR (95% CI)	*P* Value
Ivonescimab+chemo	129 (75.0)	6.8	0.52 (0.41-0.66)	<0.0001
Placebo+chemo	146 (84.4)	4.4		

Goldman J, et al, WCLC 2025

Ivonescimab

Ivonescimab vs Placebo Plus Chemo, Phase 3 in Patients with
EGFR+ NSCLC Progressed with 3rd gen EGFR-TKI Treatment: HARMONi

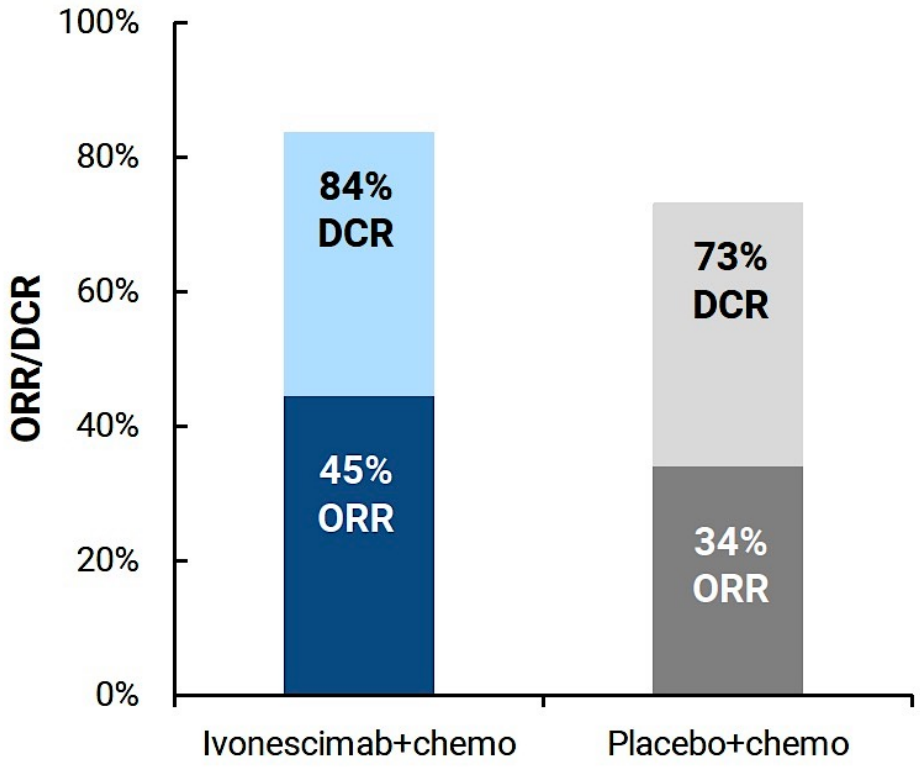
Primary Endpoint: OS



	Events, n (%)	Median (mo)	HR (95% CI)	*P* Value
Ivonescimab + chemo	122 (55.7)	16.8	0.79 (0.62-1.01)	0.0570
Placebo + chemo	140 (63.9)	14.0		

Goldman J, et al, WCLC 2025

Phase III HARMONi: Responses (by IRRC)



DoR (mo)	Ivonescimab + chemo	Placebo + chemo
n	98	75
Median (95% CI)	**7.6** (5.5-10.6)	**4.2** (2.9-4.7)

CI=confidence interval; DCR=disease control rate; DoR=duration of response; ORR=overall response rate; IRRC= independent radiographic review committee.

Goldman JW et al. WCLC 2025;Abstract PL02.12

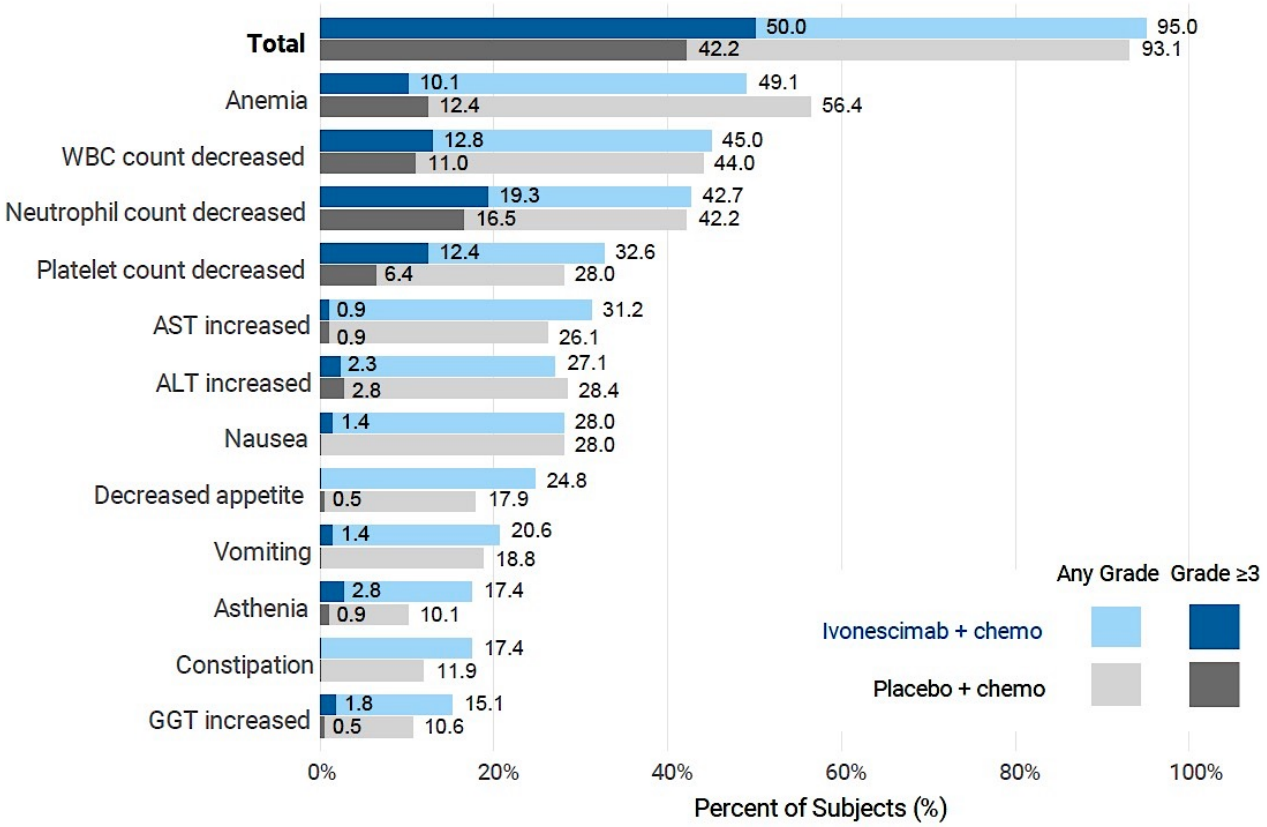
RTP RESEARCH TO PRACTICE

Phase III HARMONi: Safety

Most common were lab abnormalities, nausea, decreased appetite

TRAE, n(%)	Ivonescimab + chemo (N=218)	Placebo + chemo (N=218)
Any Grade	207 (95.0)	203 (93.1)
Grade ≥3	109 (50.0)	92 (42.2)
Serious	61 (28.0)	33 (15.1)
Led to d/c of ivonescimab/placebo	16 (7.3)	11 (5.0)
Led to death	4 (1.8)	5 (2.3)
Grade ≥3 irAE	21 (9.6)	13 (6.0)
Grade ≥3 VEGF-related	16 (7.3)	7 (3.2)

One patient in each treatment arm did not receive study drug



d/c=discontinuation; irAE=immune-related adverse events; VEGF= vascular endothelial growth factor.

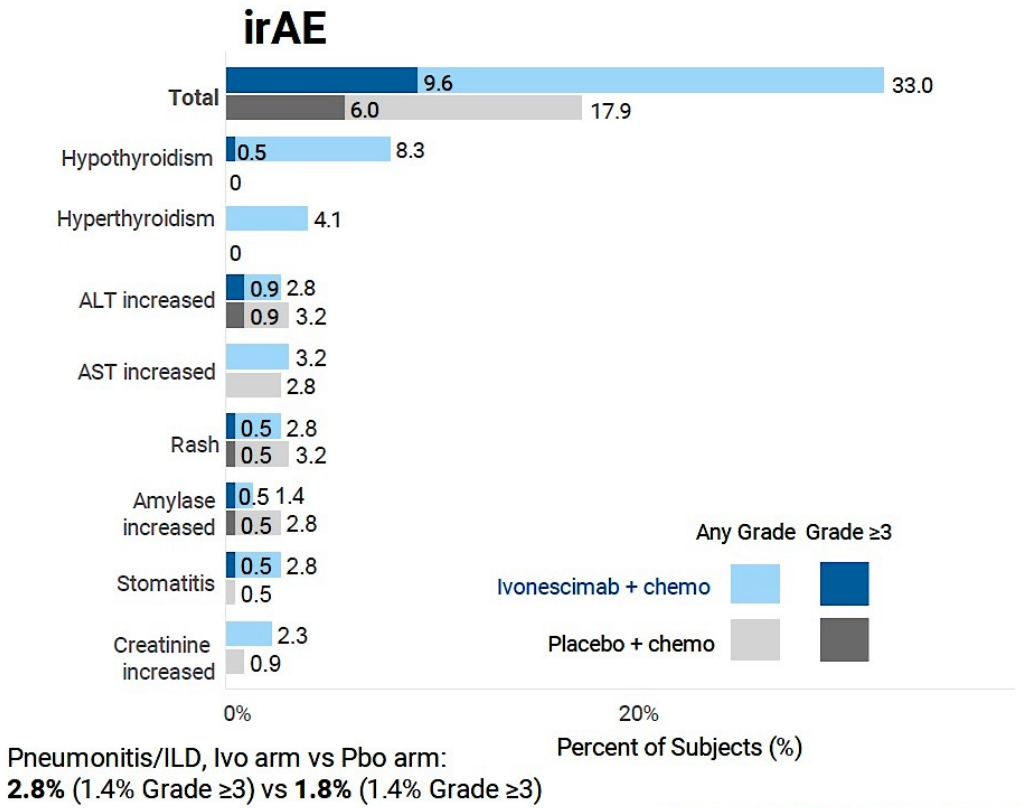
TRAE = treatment-related adverse event

Goldman JW et al. WCLC 2025;Abstract PL02.12

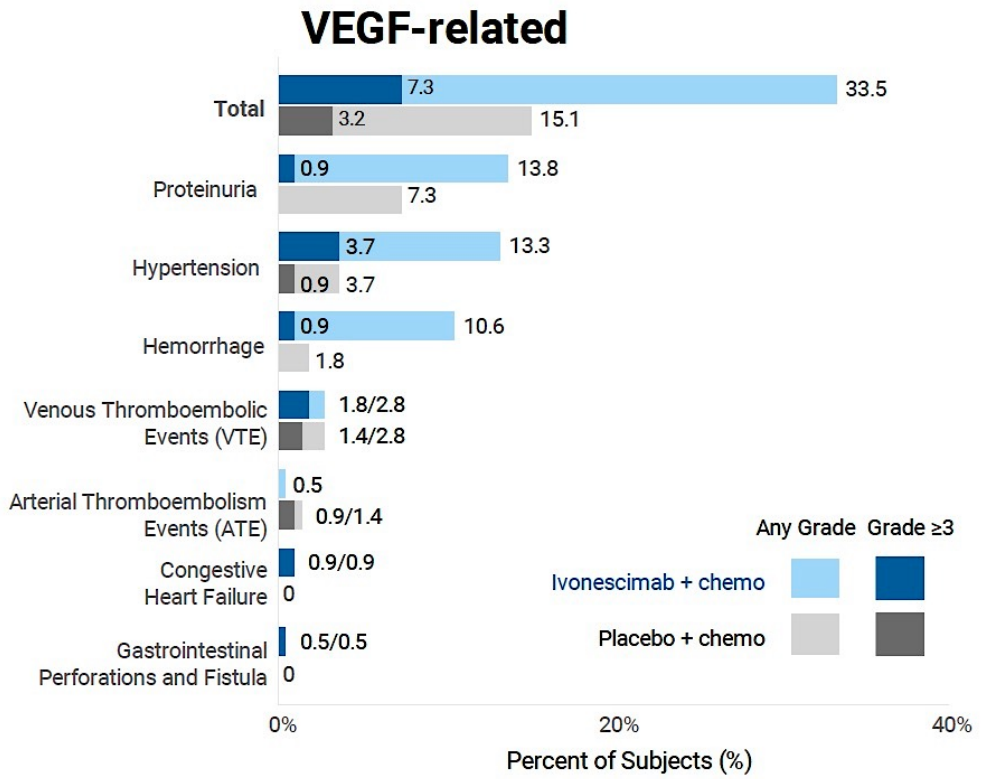
RTP RESEARCH TO PRACTICE

Phase III HARMONi: irAEs and VEGF-Related TRAEs

Most common irAEs: hypo/hyperthryroidism, transaminase elevation, rash; mostly low grade
Most common VEGF-related TRAEs: proteinuria, hypertension, hemorrhage; mostly low grade



Pneumonitis/ILD, Ivo arm vs Pbo arm:
2.8% (1.4% Grade ≥3) vs **1.8%** (1.4% Grade ≥3)



d/c=discontinuation; ILD=interstitial lung disease; irAE=immune-related adverse events; ivo=ivonescimab; pbo=pembrolizumab; TRAE=treatment-related adverse events; VEGF= vascular endothelial growth factor.

Goldman JW et al. WCLC 2025;Abstract PL02.12

RTP RESEARCH TO PRACTICE

Emerging Agents in TKI-resistant, EGFR-mutant NSCLC

		MoA	n	ORR	mPFS HR vs. chemo (95% CI)	mOS (HR vs chemo)	Key Toxicities	Grade ≥ 3 AEs
Randomized vs. PBC	**Amivantamab + Chemo** MARIPOSA-2[1,2]	EGFR/MET Ab	130	64%	**6.3 mo** HR 0.48 (0.36-0.64)	**17.7 mo** *IA2 HR 0.73 (0.54–0.99) P=0.039	Paronychia, rash, neutropenia, edema, hypoalbuminemia	72% (TEAEs)
	Ivonescimab + Chemo Harmoni-A[4]	PD1/VEGF Ab	219	45%	**6.8 mo** HR 0.52 (0.41-0.66)	**16.8 mo** HR 0.79 (0.62-1.01) P=0.0570	Anemia, leukopenia, neutropenia, thrombocytopenia, VEGF-related tox	50% (TRAEs)
	Sac-TMT Opti-Trop4[5]	Trop2 ADC (Topo I)	188	61%	**8.3 mo** HR 0.49 (0.39–0.62)	**Median NE**** HR 0.60 (0.44–0.82) P=0.001	Anemia, leukopenia, alopecia, stomatitis, nausea	58% (TRAEs)
Non-randomized	**Dato-Dxd**[6]	Trop2 ADC (Topo I)	117 Post-TKI, post-PBC	43%	**5.8 months**	**15.6 mos** (13.1–19.0)	Stomatitis, alopecia, nausea, ocular surface events	23% (TRAEs)
	Iza-Bren[7]	EGFR/HER3 ADC (Topo I)	50 Post-TKI, chemo naive	56%	**12.5 months**	Not Reached (12-mo OS rate 80%)	High-grade (grade 3-4) hematologic toxicities	NR

* Interim Analysis 2; **Median OS for chemotherapy 17.4 months

1. Passaro A, et al. Annals of Oncology, Volume 35, Issue 1, 77 – 90; 2. Popat S, et al, Annals of Oncology, Volume 35, S1244 - S1245; 3. Peled N, et al. ESMO Open, Volume 10, Issue 10, 105807; 4. Goldman J, et al. WCLC 2025; 5. Fang W, et al. NEJM 2024; 6. Ahn MJ, et al. ESMO Asia 2024; 7. Fang W, et al. WCLC 2025.

Other Relevant Topics in EGFR-mutation Positive NSCLC

- EGFR Exon 20 Insertions
- Novel agents in EGFR-mutant NSCLC
- Non-metastatic EGFR-positive disease

ADAURA demonstrated improvement in DFS and OS with adjuvant osimertinib in EGFR+ NSCLC

ADAURA Study Design

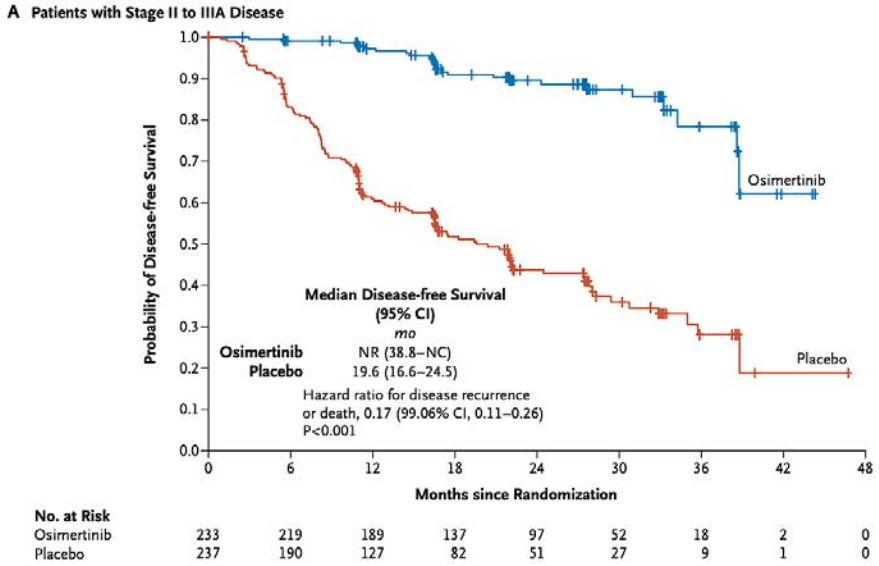
Stage IB-IIIA (7th ed) NSCLC
Fully resected
Classical EGFR mutations

N=682

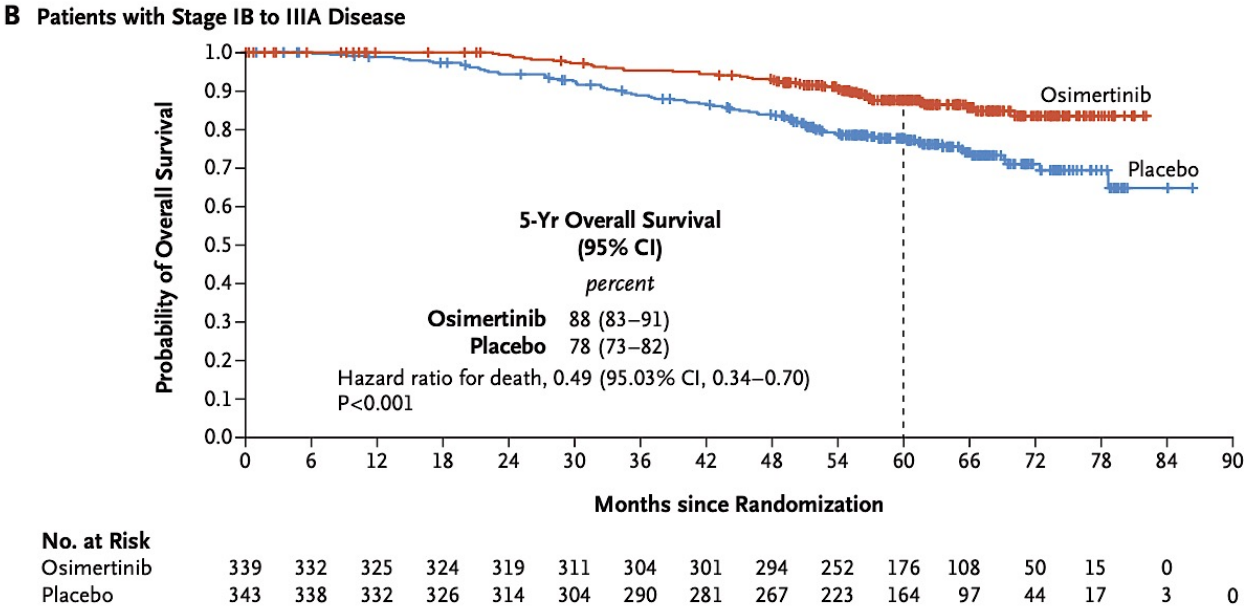
→ Adjuvant Chemo (if clinically indicated) → R

- Adjuvant osimertinib x **3 years**
- Placebo

Primary Endpoint: PFS in Stage II-IIIA Disease



Overall Survival, Stage IB-IIIA Disease



Wu YL, NEJM 2020 and Tsuboi M, et al, NEJM 2023

NeoADAURA demonstrated improvement in MPR with neoadjuvant Osi and Osi/Chemo

NeoADAURA Study Design

Resectable
stage II-IIIB
NSCLC
Classical EGFR
mutations

N=358

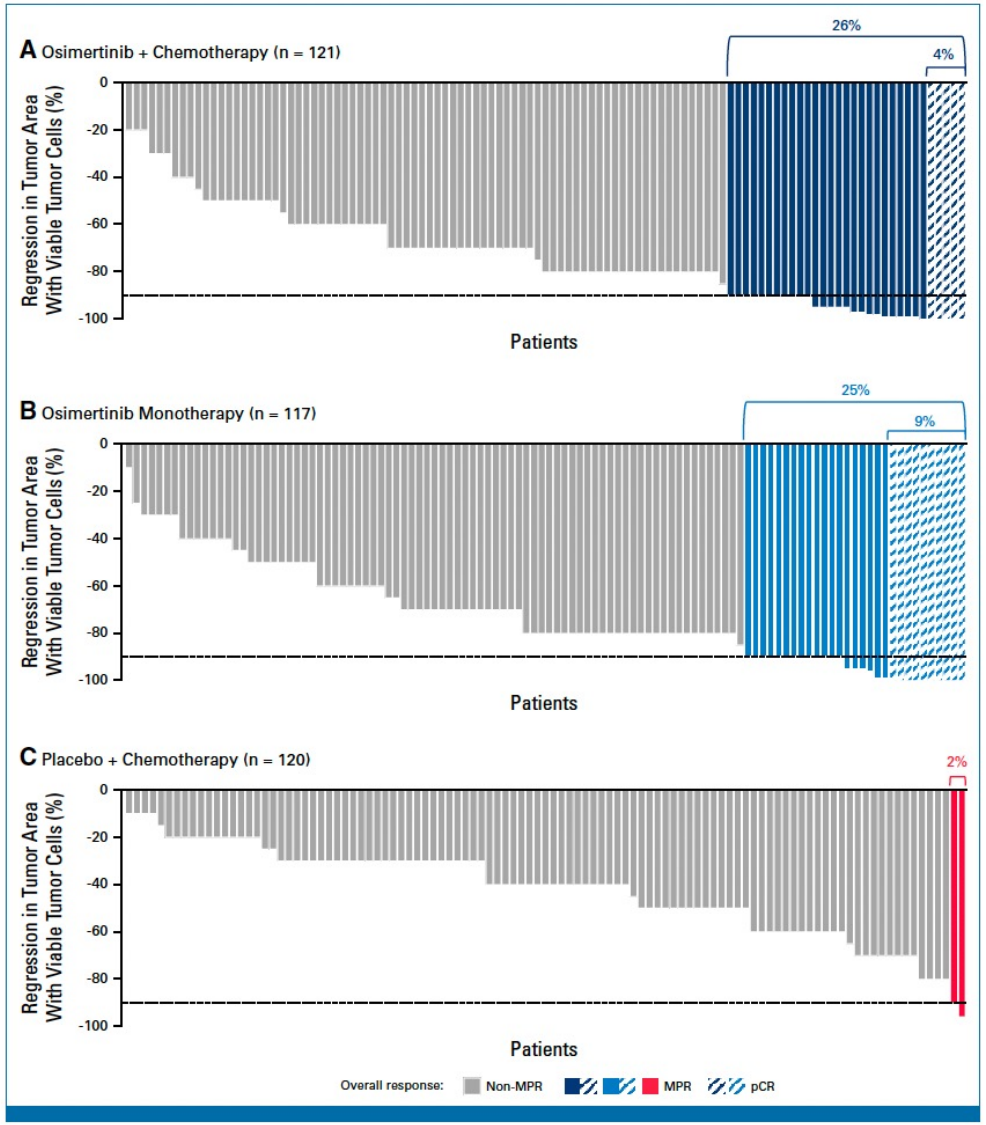
R

- Chemo + Osi (3 cycles)
- Osimertinib (9 wks)
- Chemo + PBO (3 cycles)

MPR 26%
pCR 4%
EFS* HR 0.5

MPR 25%
pCR 9%
EFS* HR 0.73

MPR 2%
pCR 0%

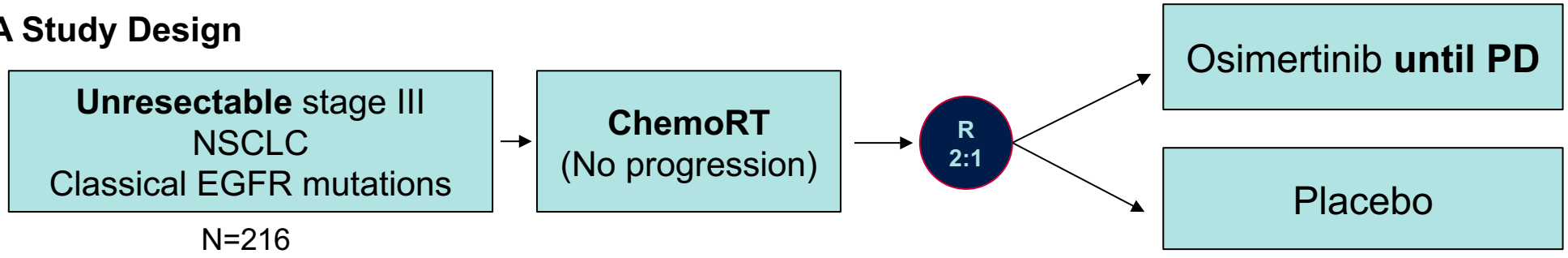


He J et al, *J Clin Oncol* 43, 2875-2887(2025)

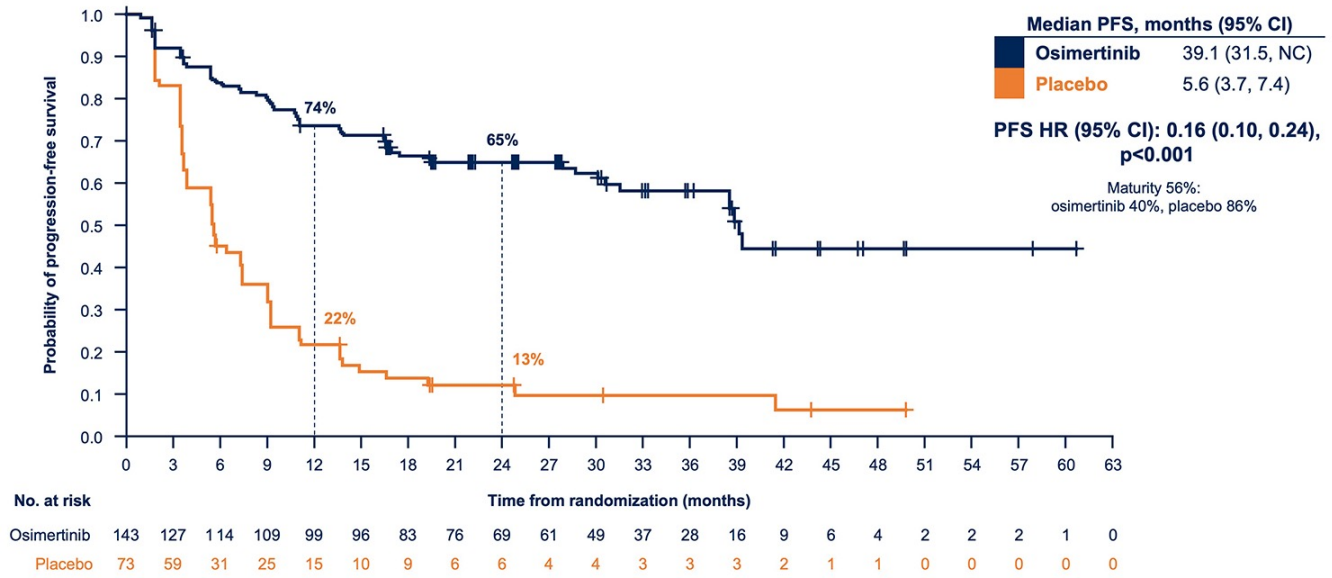
*EFS vs chemo; immature.

LAURA demonstrated improvement in PFS with consolidation after chemoRT

LAURA Study Design

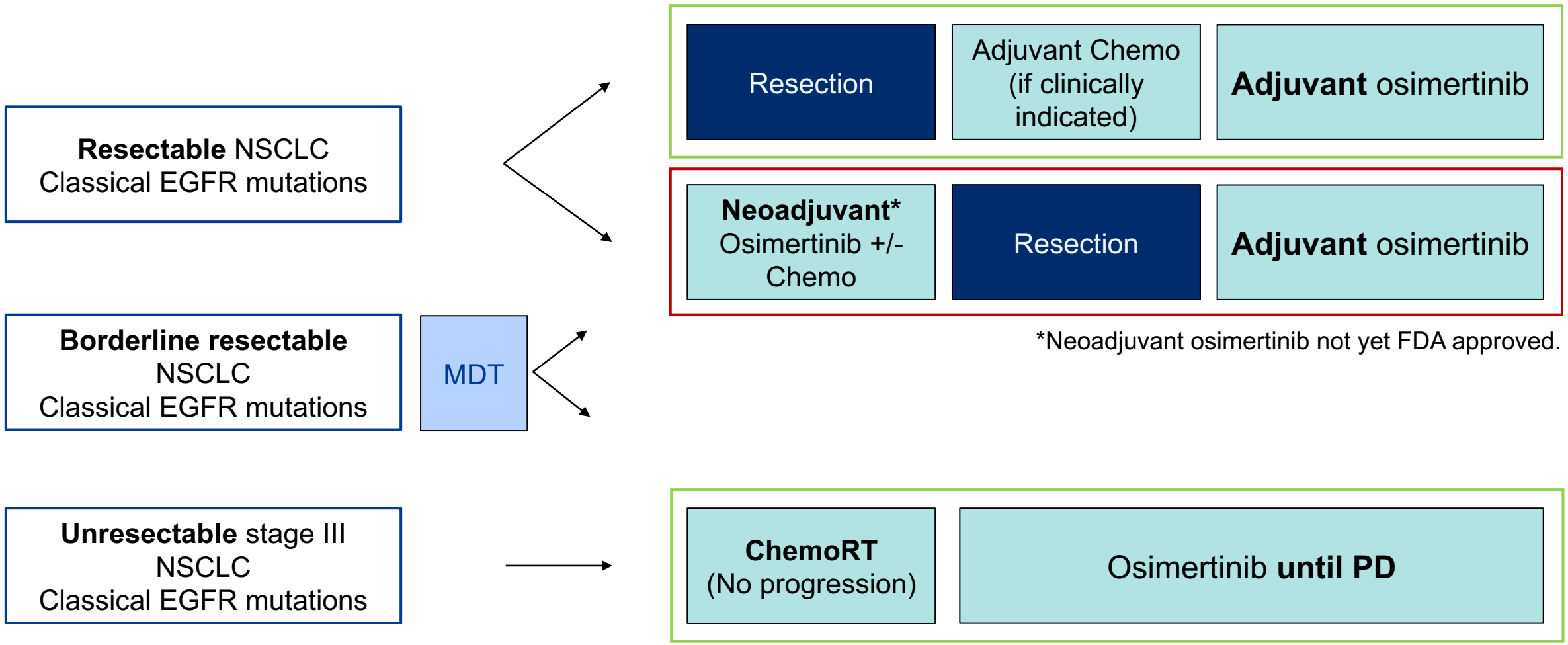


Progression-free survival by BICR



Lu S, et al, N Engl J Med 2024;391:585-597 and Ramalingam S, ASCO 2024

Treatment Approaches for nonmetastatic EGFR-mutant NSCLC



*Neoadjuvant osimertinib not yet FDA approved.

Summary and Conclusions

- **EGFR exon 20 insertions represent a unique NSCLC subtype and are treated differently than classical EGFR mutations.**
  - Carboplatin/Pemetrexed/Amivantamab remains the preferred first-line therapy
  - Sunvozertinib has accelerated approval post-chemotherapy but is not currently available in the US market

- **New agents in development for EGFR-mutant NSCLC include ivonescimab, sac-TMT and other novel ADCs.**

- **Osimertinib now has a growing role in early-stage disease (adjuvant, post-chemoRT and likely neoadjuvant)**

QUESTIONS?

Module 13: Prostate Cancer

Optimizing the Role of Hormonal Therapy in the Care of Patients with Prostate Cancer — Dr Bryce

Other Available and Emerging Therapeutic Approaches — Dr Agarwal

Faculty

Neeraj Agarwal, MD, FASCO
University of Utah Huntsman Cancer Institute
Salt Lake City, Utah

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

Alan H Bryce, MD
Translational Genomics Research Institute (TGen)
City of Hope
Phoenix, Arizona

Co-Moderator
Uday Dandamudi, MD
Florida Cancer Specialists & Research Institute
New Port Richey, Florida

Second Opinion: Clinical Investigators Provide Perspectives on the Future Role of AKT Inhibition in the Management of Prostate Cancer

A CME Symposium Held Adjunct to the
2026 ASCO® Genitourinary Cancers Symposium

Friday, February 27, 2026
6:00 PM – 7:30 PM PT (9:00 PM – 10:30 PM ET)

Faculty

Professor Karim Fizazi, MD, PhD
Daniel George, MD

Moderator

Elisabeth I Heath, MD

RTP
RESEARCH
TO PRACTICE

Faculty

Professor Karim Fizazi, MD, PhD
Head of Service and Full Professor
Institut Gustave Roussy
University of Paris Saclay
Villejuif, France

Moderator

Elisabeth I Heath, MD
Chair, Department of Oncology
Mayo Clinic
Rochester, Minnesota

Daniel George, MD
Eleanor Easley Distinguished Chair
Professor of Medicine, Surgery and Urology
Duke University School of Medicine
ACS Research Professor
Co-Lead, DCI Center for Prostate and Urologic Cancers
Duke Cancer Institute
Durham, North Carolina

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RESEARCH
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Second Opinion

Neeraj Agarwal, MD, FASCO
Professor of Medicine
Senior Director for Clinical Research
Huntsman Cancer Institute Presidential Endowed Chair of Cancer Research
Director, Center of Investigational Therapeutics
Director, Genitourinary Oncology Program
Huntsman Cancer Institute, University of Utah (NCI-CCC)
Salt Lake City, Utah

Neil Love, MD
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Miami, Florida

Rana R McKay, MD, FASCO
Professor of Medicine, Urology, and Radiation
Medicine and Applied Sciences
Associate Director, Clinical Research
Co-Lead, Genitourinary Program
Moores Cancer Center
University of California San Diego
San Diego, California

RTP
RESEARCH
TO PRACTICE

Module 13: Prostate Cancer

Optimizing the Role of Hormonal Therapy in the Care of Patients with Prostate Cancer — Dr Bryce

Other Available and Emerging Therapeutic Approaches — Dr Agarwal

Module 13: Prostate Cancer

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

Optimizing the Role of Hormonal Therapy in the Care of Patients with Prostate Cancer (PC)

Fifth Annual National General Medical Oncology (GMO) Summit

Alan H. Bryce, M.D.

Chief Clinical Officer, City of Hope Cancer Center, Phoenix
Clinical Professor, Department of Medical Oncology
Professor of Molecular Medicine, TGen Research Institute

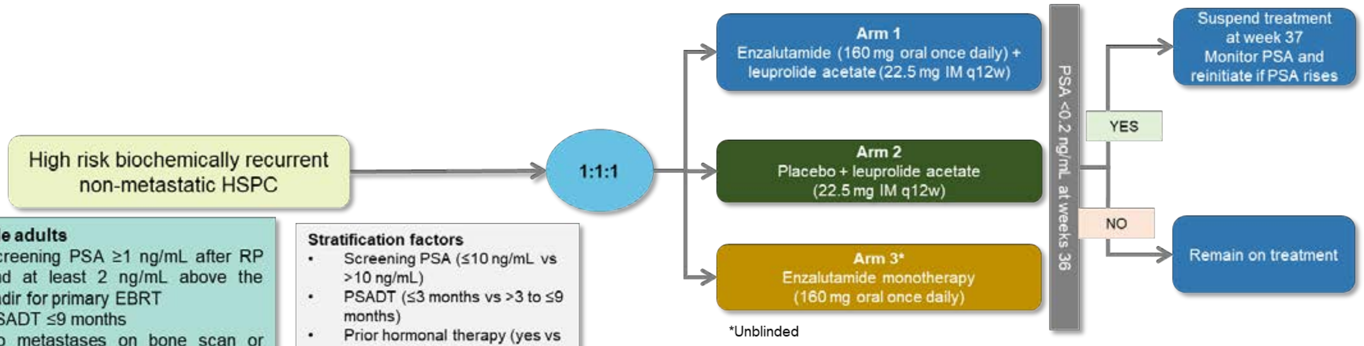
@AlanBryce9

Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Johnson & Johnson, Lantheus, MOMA Therapeutics, Novartis, Pfizer Inc
Consulting Agreements	Astellas, Johnson & Johnson
Contracted Research	Johnson & Johnson
Data and Safety Monitoring Boards/Committees	Lantheus

Phase III EMBARK Trial

Study Design & Results



Eligible adults

- Screening PSA ≥1 ng/mL after RP and at least 2 ng/mL above the nadir for primary EBRT
- PSADT ≤9 months
- No metastases on bone scan or CT/MRI per central read
- Testosterone ≥150 ng/dL
- Prior hormonal therapy ≤9 months prior to randomization (neoadjuvant/adjuvant for ≤36 months OR ≤6 months for rising PSA)

Stratification factors

- Screening PSA (≤10 ng/mL vs >10 ng/mL)
- PSADT (≤3 months vs >3 to ≤9 months)
- Prior hormonal therapy (yes vs no)

PRIMARY ENDPOINTS

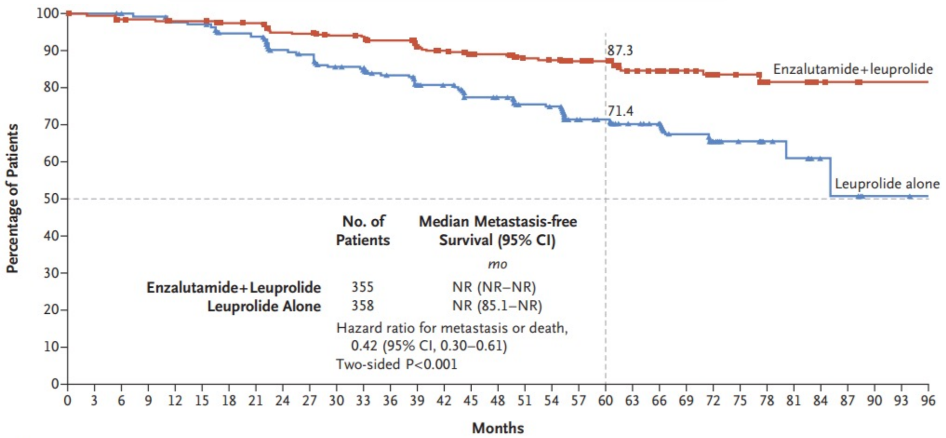
MFS by BICR: enzalutamide + leuprolide acetate vs leuprolide acetate alone

SECONDARY ENDPOINTS

- MFS by BICR: enzalutamide monotherapy vs leuprolide acetate alone
- Time to PSA progression
- Time to first use of new antineoplastic therapy
- Overall survival (OS)
- Safety

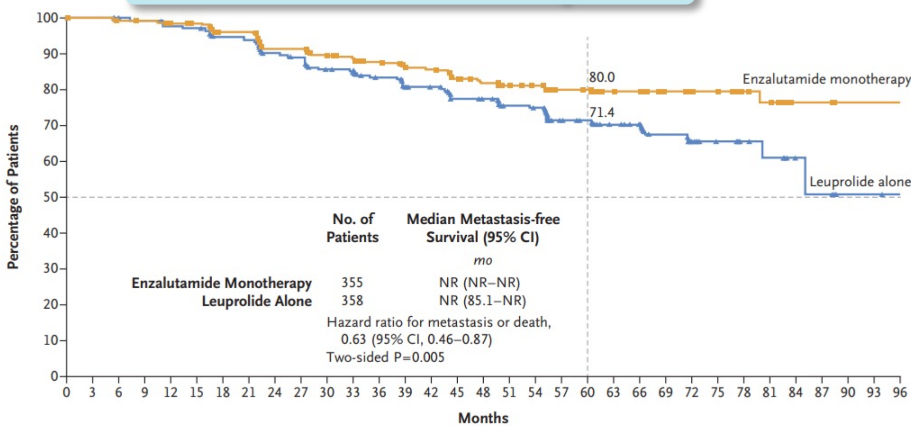
Metastasis-free survival

Enzalutamide + Leuprolide



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90	93	96
Enzalutamide+ leuprolide	355	339	331	330	324	324	318	317	304	303	292	290	281	270	265	252	251	236	234	183	180	119	116	83	60	51	24	22	6	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

Enzalutamide only



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90	93	96
Enzalutamide monotherapy	355	350	342	341	328	326	309	309	287	287	273	269	260	248	247	235	228	211	209	172	171	109	108	76	52	49	26	24	5	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

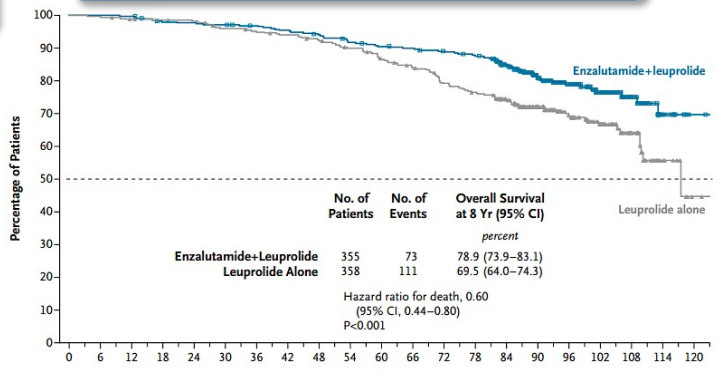
Freedland SJ et al, NEJM 2023

Phase III EMBARK Trial

Additional Secondary Endpoints

Enzalutamide + Leuprolide

Overall survival



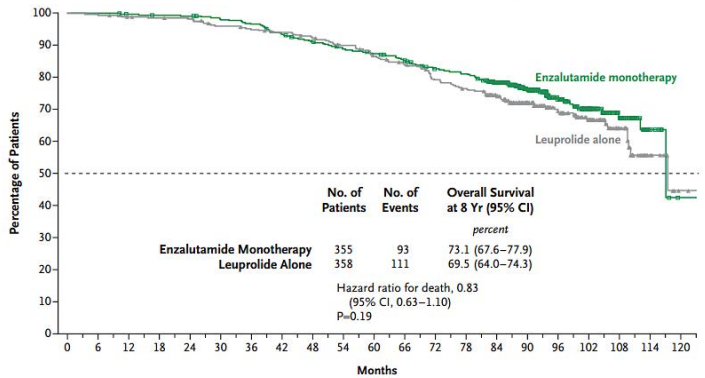
No. at Risk

Enzalutamide+leuprolide	355	355	354	345	344	342	338	333	327	318	313	310	305	299	262	190	126	81	60	41	25	12	5	1	0
Leuprolide alone	358	357	352	350	348	338	333	329	322	312	298	288	270	259	228	171	117	81	56	39	18	10	6	1	0

No. of Events/Cumulative No. of Events

Enzalutamide+leuprolide	0/0	0/0	1/1	3/7	0/8	0/10	0/11	2/16	2/21	5/29	3/33	1/35	1/38	2/43	6/52	5/63	1/67	2/70	1/71	1/73	0/73
Leuprolide alone	0/0	1/1	2/4	1/5	1/6	4/14	4/18	2/21	3/27	5/35	8/47	3/55	13/71	5/81	5/89	0/95	3/100	3/104	2/106	0/110	1/111

Enzalutamide only



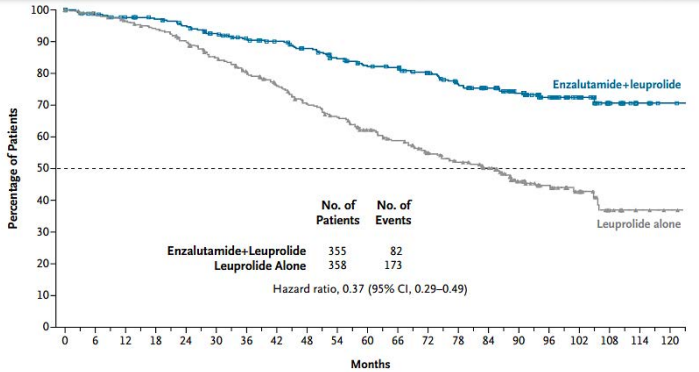
No. at Risk

Enzalutamide monotherapy	355	355	352	350	349	343	338	326	316	306	300	291	276	271	237	170	114	77	51	39	22	8	3	0	0
Leuprolide alone	358	357	352	350	348	338	333	329	322	312	298	288	270	259	228	171	117	81	56	39	18	10	6	1	0

No. of Events/Cumulative No. of Events

Enzalutamide monotherapy	0/0	0/0	1/1	0/2	1/3	3/7	4/12	6/23	4/31	5/39	3/44	5/51	4/60	2/65	3/74	4/80	4/85	1/89	1/91	1/92	1/93
Leuprolide alone	0/0	1/1	2/4	1/5	1/6	4/14	4/18	2/21	3/27	5/35	8/47	3/55	13/71	5/81	5/89	0/95	3/100	3/104	2/106	0/110	1/111

First use of new antineoplastic therapy

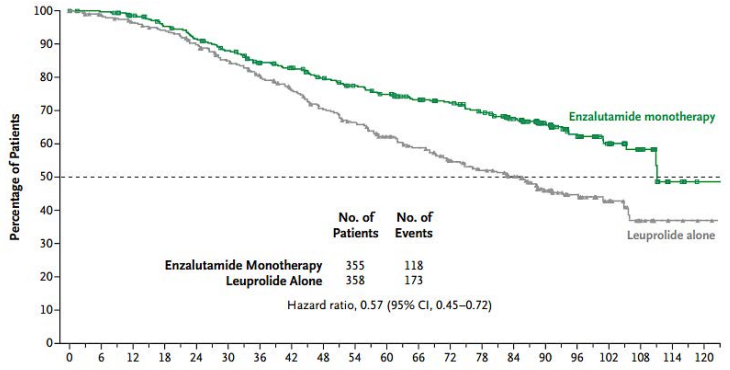


No. at Risk

Enzalutamide+leuprolide	355	341	334	327	317	301	290	282	270	254	242	239	224	208	175	126	90	77	62	38	24	15	6	2	1	0
Leuprolide alone	358	342	332	322	304	281	262	240	219	205	186	172	153	142	124	86	58	50	34	22	13	5	3	2	1	0

No. of Events/Cumulative No. of Events

Enzalutamide+leuprolide	0/0	1/5	0/8	2/10	5/17	4/25	2/30	1/33	3/40	6/50	5/57	1/58	1/63	4/73	0/76	1/79	1/81	0/81	0/82	0/82	0/82
Leuprolide alone	0/0	2/5	4/12	3/20	9/35	9/51	8/65	7/80	8/98	7/110	5/123	4/133	7/144	3/152	3/157	5/166	1/168	1/170	2/173	0/173	0/173



No. at Risk

Enzalutamide monotherapy	355	352	341	326	312	297	278	268	253	241	231	218	207	194	167	124	83	71	56	39	24	11	4	1	0	0
Leuprolide alone	358	342	332	322	304	281	262	240	219	205	186	172	153	142	124	86	58	50	34	22	13	5	3	2	1	0

No. of Events/Cumulative No. of Events

Enzalutamide monotherapy	0/0	1/1	3/5	8/16	10/29	7/41	8/53	3/58	6/68	3/75	4/83	3/88	2/91	3/99	2/104	1/107	3/112	2/115	1/116	1/118	0/118
Leuprolide alone	0/0	2/5	4/12	3/20	9/35	9/51	8/65	7/80	8/98	7/110	5/123	4/133	7/144	3/152	3/157	5/166	1/168	1/170	2/173	0/173	0/173

Freedland SJ et al., NEJM, 2023; Shore ND et al., NEJM, 2026

Phase III EMBARK Trial

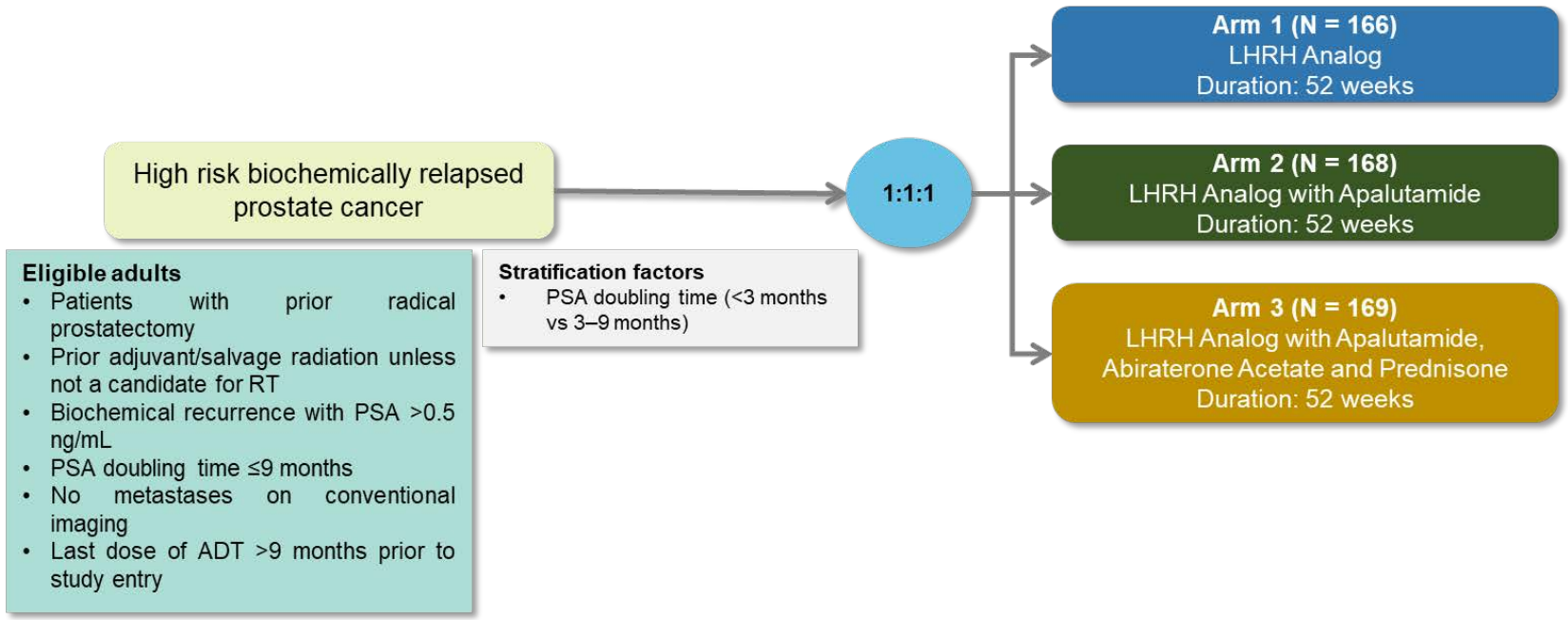
Safety

Adverse Events – N (%)	Enzalutamide + Leuprolide (N=353)	Leuprolide Alone (N=354)	Enzalutamide Monotherapy (N=354)
Adverse event that emerged during treatment	346 (98.0)	347 (98.0)	348 (98.3)
AE primary reason for discontinuation of treatment	97 (27.5)	45 (12.7)	73 (20.6)
AE during treatment leading to death	10 (2.8)	5 (1.4)	12 (3.4)
Any grade ≥3 AE during treatment	185 (52.4)	175 (49.4)	203 (57.3)
AE during treatment related to trial drug	307 (87.0)	286 (80.8)	316 (89.3)
Grade ≥3 AE during treatment related to trial drug	68 (19.3)	34 (9.6)	72 (20.3)
Serious AE during treatment	143 (40.5)	133 (37.6)	154 (43.5)
Serious AE during treatment related to trial drug	30 (8.5)	9 (2.5)	27 (7.6)
Hot flash	246 (69.7)	206 (58.2)	80 (22.6)
Fatigue	154 (43.6)	119 (33.6)	170 (48.0)
Arthralgia	104 (29.5)	75 (21.2)	89 (25.1)
Fall	104 (29.5)	60 (16.9)	71 (20.1)
Hypertension	92 (26.1)	75 (21.2)	76 (21.5)
Back pain	62 (17.6)	56 (15.8)	67 (18.9)
Diarrhea	55 (15.6)	31 (8.8)	47 (13.3)
Constipation	53 (15.0)	35 (9.9)	38 (10.7)
Hematuria	50 (14.2)	57 (16.1)	53 (15.0)
Dizziness	46 (13.0)	44 (12.4)	47 (13.3)
Headache	46 (13.0)	36 (10.2)	47 (13.3)
Insomnia	45 (12.7)	40 (11.3)	26 (7.3)
Nausea	43 (12.2)	31 (8.8)	57 (16.1)
Asthenia	42 (11.9)	21 (5.9)	41 (11.6)
Pain in arm or leg	42 (11.9)	37 (10.5)	44 (12.4)
Coronavirus disease 2019	38 (10.8)	51 (14.4)	50 (14.1)
Urinary incontinence	38 (10.8)	35 (9.9)	40 (11.3)
Urinary tract infection	33 (9.3)	28 (7.9)	46 (13.0)
Peripheral edema	32 (9.1)	40 (11.3)	37 (10.5)

Shore ND et al., NEJM, 2026

Phase III PRESTO Trial

Study Design



PRIMARY ENDPOINTS

- **PSA progression-free survival:** PSA progression defined as nadir + 2 ng/mL during treatment or > 0.2 ng/mL following treatment confirmed on repeat measurement (> 2 weeks)

SECONDARY ENDPOINTS

- **PSA progression-free survival in testosterone-evaluable population** (T > 50 ng/dL)
- **Time to recovery of serum testosterone** (T > 50 ng/dL)
- **Safety profile**
- **36-month PSA progression-free survival rate**
- **Metastasis-free survival**
- **Time to castration resistance**
- **Short- and long-term patient reported quality of life**

Aggarwal R et al., ESMO, 2025

Phase III PRESTO Trial

Baseline Characteristics

	ADT (N=166)	Apalutamide + ADT (N=168)	Apalutamide + Abiraterone Acetate + ADT (N=169)
Median age in years (IQR)	67.0 (60.3, 71.1)	66.0 (60.7, 70.3)	67.3 (62.4, 71.3)
Race — N (%)			
White	142 (85.5)	144 (85.7)	135 (79.9)
Black or African-American	7 (4.2)	13 (7.7)	12 (7.1)
Asian	3 (1.8)	0 (0.0)	2 (1.2)
Native Hawaiian/Pacific Islander	1 (0.6)	0 (0.0)	1 (0.6)
American Indian/Alaska Native	1 (0.6)	0 (0.0)	2 (1.2)
Other/Unknown/Not Reported/Missing	12 (7.1)	11 (6.6)	9 (5.3)
Ethnicity — N (%)			
Non-Hispanic	151 (91.0)	152 (90.5)	155 (91.7)
Hispanic	10 (6.0)	10 (6.0)	7 (4.1)
Unknown/Not Reported/Missing	5 (3.0)	6 (3.6)	7 (4.1)
Prior androgen-deprivation therapy — N (%)	71 (42.8)	75 (44.6)	67 (39.6)
Prior radiotherapy — N (%)	147 (88.6)	142 (84.5)	137 (81.1)

ADT: LHRH Analog as Androgen Deprivation Therapy

Aggarwal R et al., ESMO, 2025

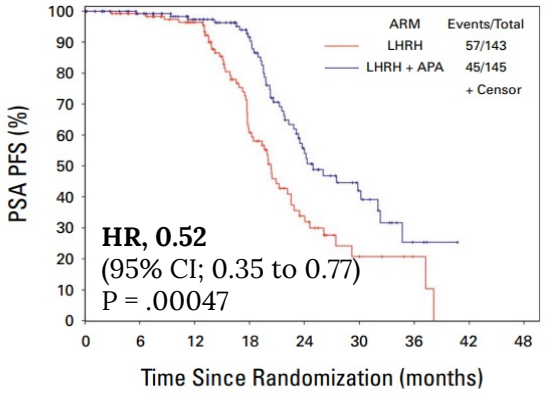
Phase III PRESTO Trial

Results

Apalutamide

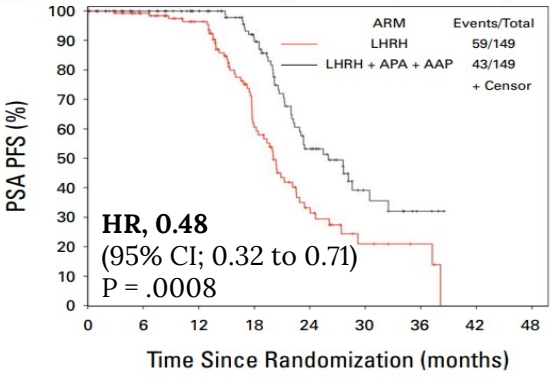
Apalutamide + Abiraterone

PSA Progression-free Survival



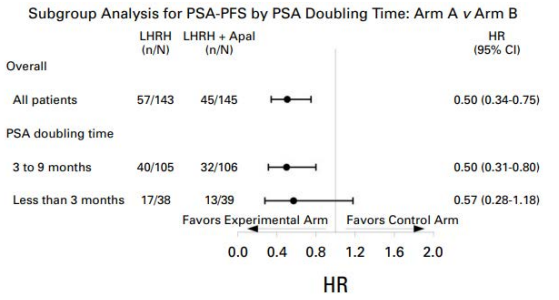
No. at risk:

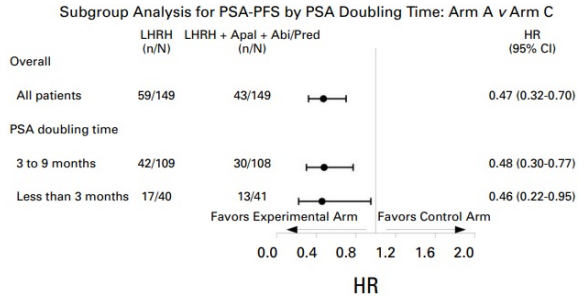
LHRH	143	94	18	2	0
LHRH + APA	145	101	32	3	0



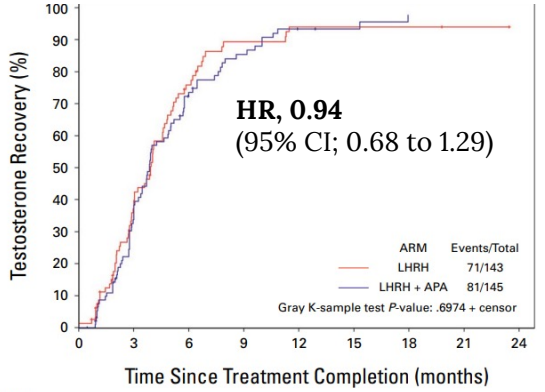
No. at risk:

LHRH	149	97	18	3	0
LHRH + APA + AAP	149	103	35	3	0



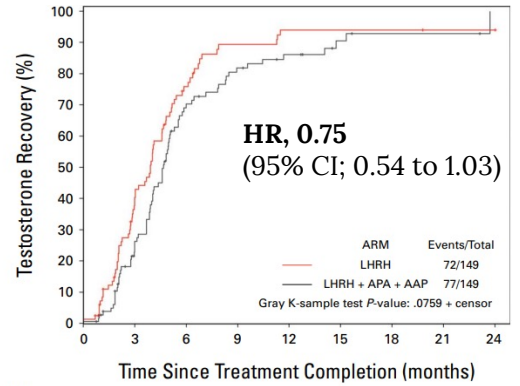


Time to Testosterone Recovery



No. at risk:

LHRH	143	46	16	6	3	3	2	1	0
LHRH + APA	145	53	21	11	4	2	0		



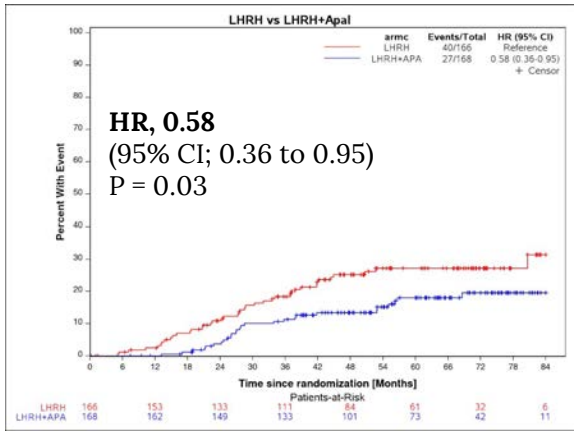
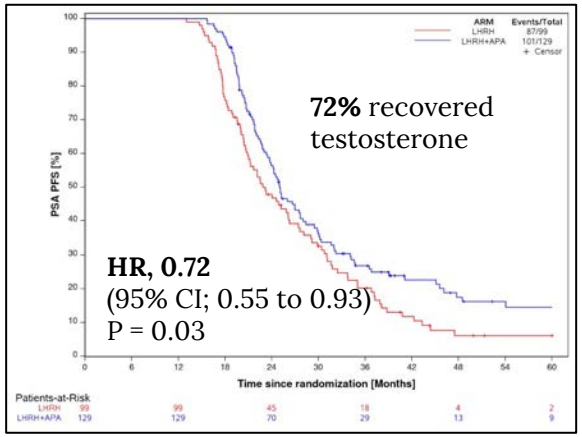
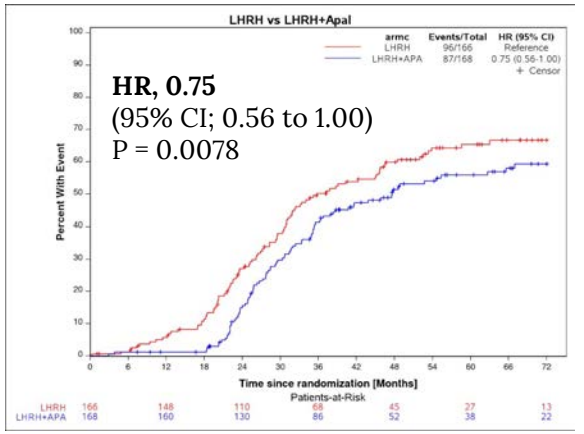
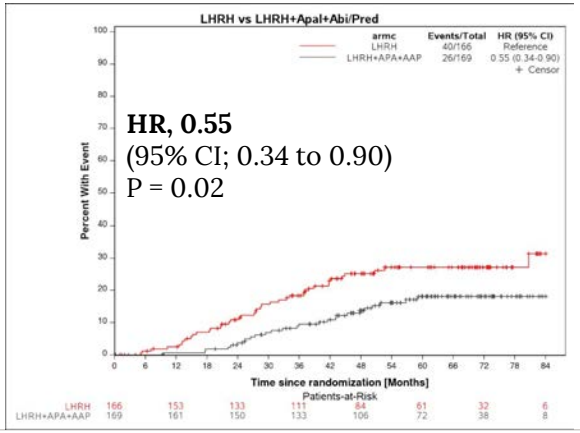
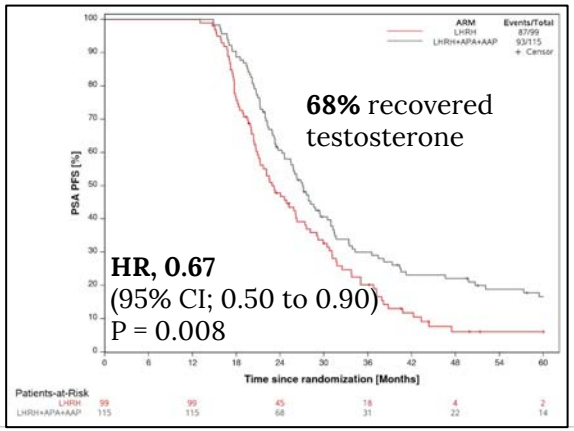
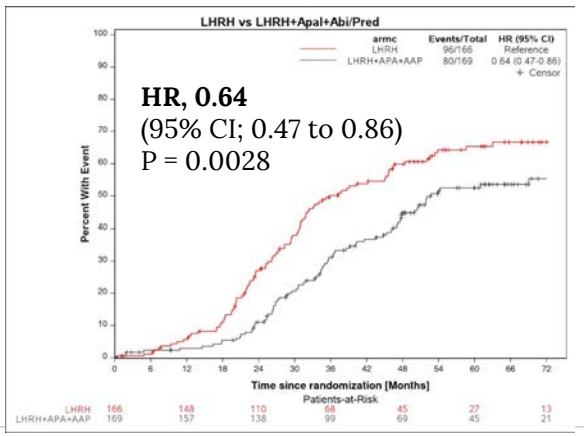
No. at risk:

LHRH	149	46	16	6	3	3	2	1	1
LHRH + APA + AAP	149	63	24	14	9	4	2	2	0

Aggarwal R et al., JCO, 2024

Phase III PRESTO Trial

Results: Secondary Endpoint(s)

	Time to mCRPC	PSA-PFS in testosterone recovered subset	Time to subsequent therapy (both focal and systemic)
Apalutamide	 **HR, 0.58** (95% CI; 0.36 to 0.95) P = 0.03	 **72%** recovered testosterone **HR, 0.72** (95% CI; 0.55 to 0.93) P = 0.03	 **HR, 0.75** (95% CI; 0.56 to 1.00) P = 0.0078
Apalutamide + Abiraterone	 **HR, 0.55** (95% CI; 0.34 to 0.90) P = 0.02	 **68%** recovered testosterone **HR, 0.67** (95% CI; 0.50 to 0.90) P = 0.008	 **HR, 0.64** (95% CI; 0.47 to 0.86) P = 0.0028

Aggarwal R et al., ESMO, 2025

Phase III PRESTO Trial

Results: Adverse Events

Arm 1
LHRH Analog

Arm 2
LHRH Analog with Apalutamide

Arm 3
LHRH Analog with Apalutamide, Abiraterone Acetate and Prednisone

Adverse Events (AE) - N (%)	Arm A (n=160)	Arm B (n=167)	Arm C (n=164)
Any AE	153 (96)	167 (100)	163 (99)
Grade 3 or 4 AE	35 (22)	43 (26)	67 (41)
AE leading to treatment discontinuation	1 (0.6)	2 (1)	4 (2)

Adverse Events (AE) - N (%)	Arm A		Arm B		Arm C	
	Grade 2	Grade ≥3	Grade 2	Grade ≥3	Grade 2	Grade ≥3
Hypertension	19 (12)	12 (8)	30 (18)	13 (8)	20 (12)	34 (21)
Hot flashes	22 (14)	1 (1)	12 (7)	1 (1)	24 (15)	1 (1)
Fatigue	16 (10)	0	9 (5)	3 (2)	19 (12)	2 (1)
Injection site reaction	11 (7)	0	11 (7)	0	11 (7)	0
Insomnia	11 (7)	0	6 (4)	0	8 (5)	0
Hyperglycemia	1 (1)	3 (2)	7 (4)	2 (1)	6 (4)	6 (4)
Rash	2 (1)	1 (1)	8 (5)	3 (2)	3 (2)	5 (3)
Erectile dysfunction	9 (6)	1 (1)	6 (4)	1 (1)	3 (2)	0
Arthralgia	4 (3)	1 (1)	4 (2)	0	2 (1)	0
Fall	0	3 (2)	7 (4)	0	4 (2)	0

Aggarwal R et al., ESMO, 2025

Abiraterone acetate
STAMPEDE trial

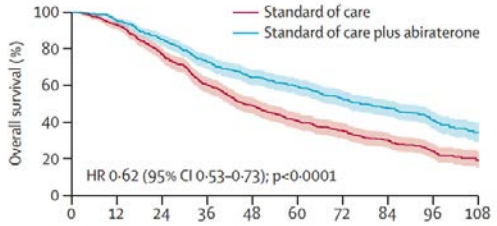
Abiraterone acetate plus prednisolone with or without enzalutamide for patients with metastatic prostate cancer starting androgen deprivation therapy: final results from two randomised phase 3 trials of the STAMPEDE platform protocol

Gerhardt Attard, Laura Murphy, Noel W Clarke, Ashwin Sachdeva, Craig Jones, Alex Hoyle, William Cross, Robert J Jones, Christopher C Parker, Silke Gillessen, Adrian Cook, Chris Brawley, Clare Gilson, Hannah Rush, Hoda Abdel-Aty, Claire L Amos, Claire Murphy, Simon Chowdhury, Zafar Malik, J Martin Russell, Nazia Parkar, Cheryl Pugh, Carlos Diaz-Montana, Carmel Pezaro, Warren Grant, Helen Saxby, Ian Pedley, Joe M O'Sullivan, Alison Birtle, Joanna Gale, Narayanan Srihari, Carys Thomas, Jacob Tanguay, John Wagstaff, Prantik Das, Emma Gray, Mymoona Alzouebi, Omi Parikh, Angus Robinson, Amir H Montazeri, James Wylie, Anjali Zarkar, Richard Cathomas, Michael D Brown, Yatin Jain, David P Dearnaley*, Malcolm D Mason*, Duncan Gilbert, Ruth E Langley, Robin Millman, David Matheson, Matthew R Sydes†, Louise C Brown†, Mahesh K B Parmar†, Nicholas D James†, for the STAMPEDE investigators‡

Overall survival

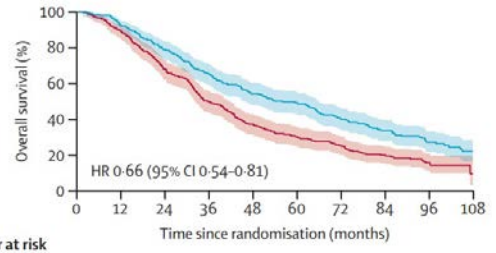
Abiraterone w/ pred + ADT

Overall population



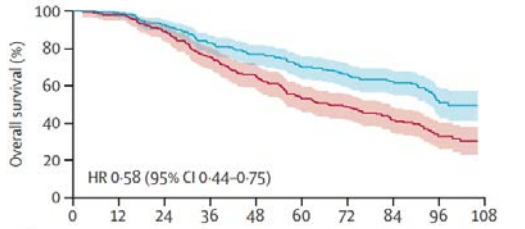
Number at risk (number censored); events										
Standard of care	502 (0); 0	463 (5); 34	380 (8); 114	297 (9); 196	241 (10); 251	199 (11); 292	167 (16); 319	125 (34); 343	53 (86); 363	14 (118); 370
Standard of care plus abiraterone	501 (0); 0	474 (4); 23	421 (6); 74	357 (10); 134	314 (12); 175	290 (12); 199	250 (18); 233	199 (46); 256	96 (126); 279	23 (188); 290

High volume



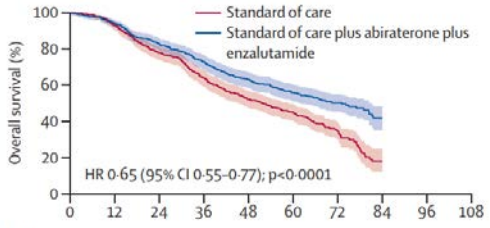
Number at risk (number censored); events										
Standard of care	271 (0); 0	241 (2); 28	181 (4); 86	133 (4); 134	98 (5); 168	79 (6); 186	63 (9); 199	40 (19); 212	13 (39); 219	1 (49); 221
Standard of care plus abiraterone	253 (0); 0	233 (1); 19	198 (2); 53	161 (5); 87	132 (7); 114	120 (7); 126	98 (7); 148	77 (12); 164	38 (38); 177	9 (62); 182

Low volume

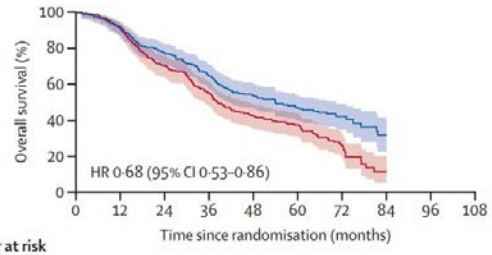


Number at risk (number censored); events										
Standard of care	204 (0); 0	197 (3); 4	178 (4); 22	150 (5); 49	131 (5); 68	108 (5); 91	95 (7); 102	79 (13); 112	37 (42); 125	12 (63); 129
Standard of care plus abiraterone	222 (0); 0	218 (2); 2	203 (3); 16	180 (4); 38	167 (4); 51	155 (4); 63	138 (10); 74	110 (31); 81	15 (76); 91	12 (114); 96

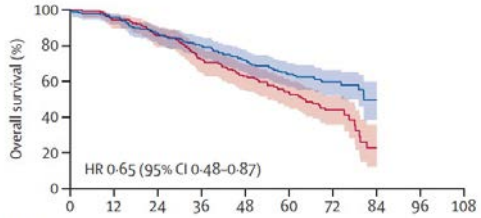
Abiraterone w/ pred + Enzalutamide + ADT



Number at risk (number censored); events										
Standard of care	454 (0); 0	416 (6); 32	347 (8); 99	282 (11); 161	228 (14); 212	163 (49); 242	65 (116); 273	4 (159); 291	..	..
Standard of care plus abiraterone plus enzalutamide	462 (0); 0	428 (6); 28	376 (7); 79	330 (8); 124	282 (12); 168	217 (45); 200	108 (136); 218	19 (216); 227	..	..



Number at risk (number censored); events										
Standard of care	209 (0); 0	191 (1); 17	146 (2); 61	114 (2); 93	88 (2); 119	63 (17); 129	24 (41); 144	1 (55); 153	..	..
Standard of care plus abiraterone plus enzalutamide	196 (0); 0	177 (0); 19	152 (0); 44	126 (1); 69	103 (3); 90	82 (11); 103	38 (48); 110	8 (73); 115	..	..



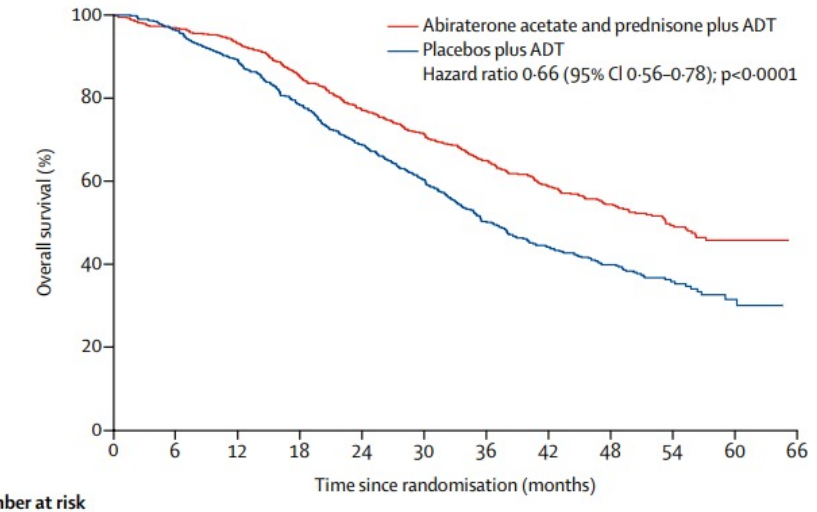
Number at risk (number censored); events										
Standard of care	162 (0); 0	151 (2); 9	136 (3); 23	114 (4); 44	98 (5); 59	71 (19); 72	30 (48); 84	2 (69); 91	..	..
Standard of care plus abiraterone plus enzalutamide	195 (0); 0	187 (0); 8	169 (0); 26	156 (0); 39	139 (1); 55	103 (22); 70	56 (63); 76	8 (107); 80	..	..

Attard G et al., Lancet Oncol, 2023

Abiraterone acetate
LATITUDE trial

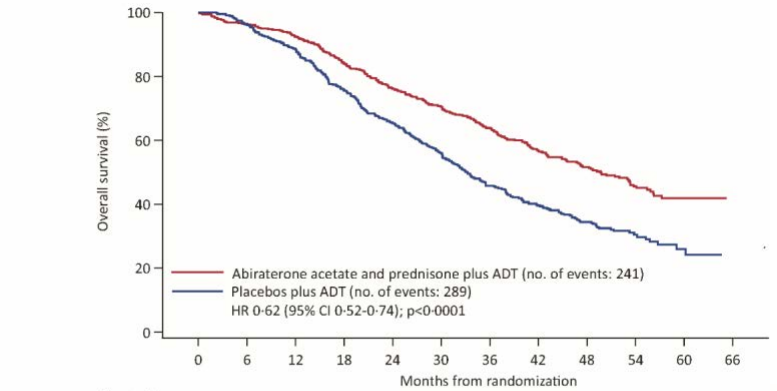
Overall survival

Overall population



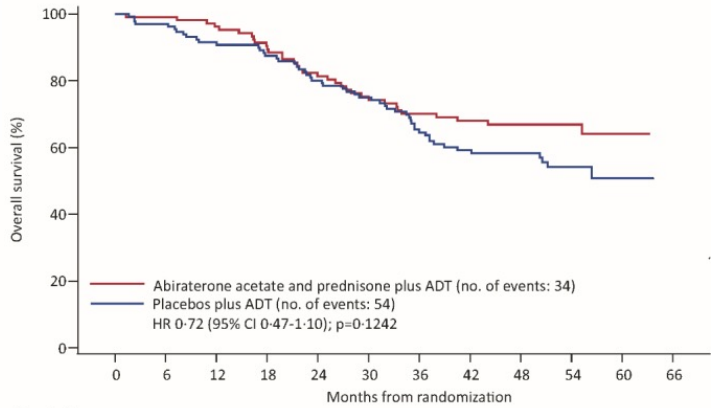
Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597	565 (14)	529 (28)	479 (34)	425 (42)	389 (46)	351 (50)	311 (57)	240 (106)	124 (205)	40 (282)	0 (322)
Placebos plus ADT	602	564 (17)	505 (34)	432 (47)	368 (58)	315 (37)	256 (74)	220 (79)	165 (114)	69 (197)	23 (237)	0 (259)

High volume



No. at risk (No. censored)												
Abiraterone acetate and prednisone plus ADT	487	460 (10)	429 (22)	386 (27)	345 (31)	317 (34)	283 (38)	246 (44)	188 (81)	97 (115)	31 (215)	0 (246)
Placebos plus ADT	468	438 (13)	389 (27)	323 (38)	270 (47)	266 (53)	181 (57)	154 (60)	113 (82)	46 (139)	14 (166)	0 (179)

Low volume



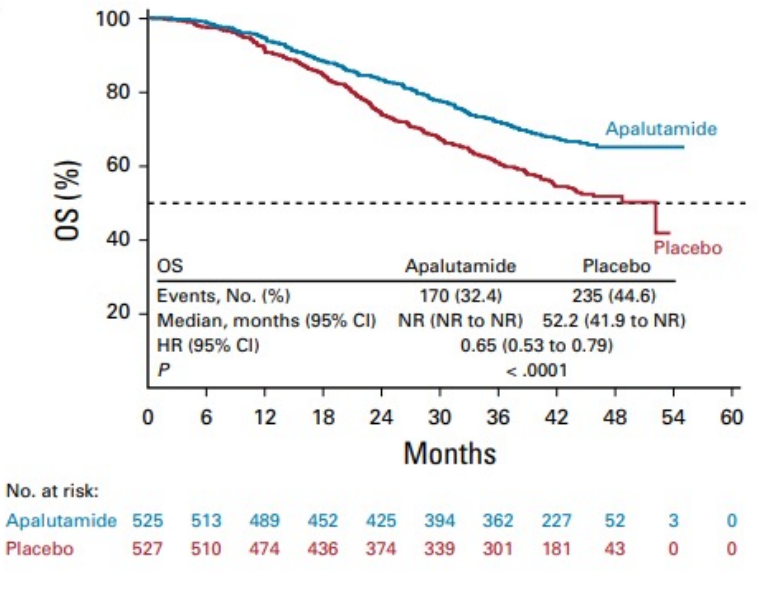
No. at risk (No. censored)												
Abiraterone acetate and prednisone plus ADT	110	105 (4)	100 (6)	93 (7)	80 (11)	72 (12)	68 (12)	65 (13)	52 (25)	27 (50)	9 (67)	0 (76)
Placebos plus ADT	133	125	115	108	97	88	74	66	52	23	9	0

Fizazi K et al., Lancet Oncol, 2019

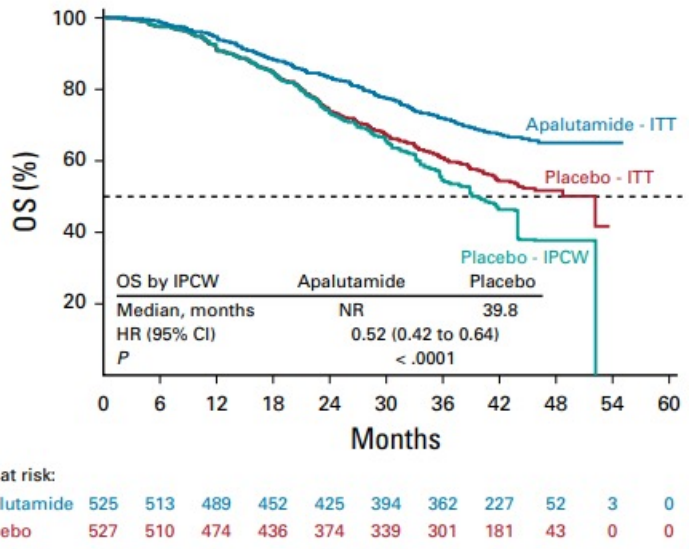
Apalutamide
TITAN Trial

original reports
Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study
Kim N. Chi, MD[1]; Simon Chowdhury, MD, PhD[2]; Anders Bjartell, MD, PhD[3]; Byung Ha Chung, MD, PhD[4]; Andrea J. Pereira de Santana Gomes, MD[5]; Robert Given, MD[6]; Alvaro Juárez Soto, MD[7]; Axel S. Merseburger, MD, PhD[8]; Mustafa Özgüroğlu, MD[9]; Hirotsugu Uemura, MD, PhD[10]; Dingwei Ye, MD, PhD[11]; Sabine Brookman-May, MD[12,13]; Suneel D. Mundle, PhD[14]; Sharon A. McCarthy, BPharm[15]; Julie S. Larsen, PharmD[15]; Weili Sun, MD, PhD[16]; Katherine B. Bevans, PhD[15]; Ke Zhang, PhD[16]; Nibedita Bandyopadhyay, PhD[15]; and Neeraj Agarwal, MD[17]

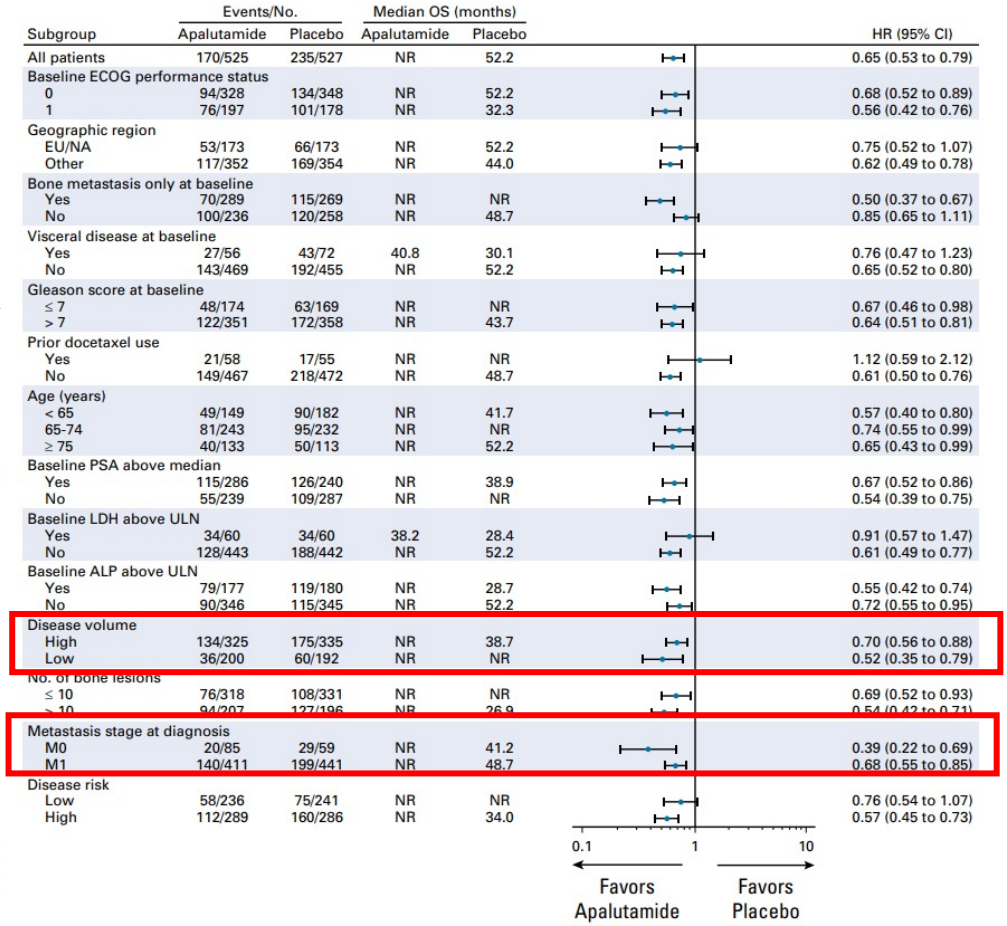
Overall survival



Cross-over adjusted analysis



Subgroup analysis



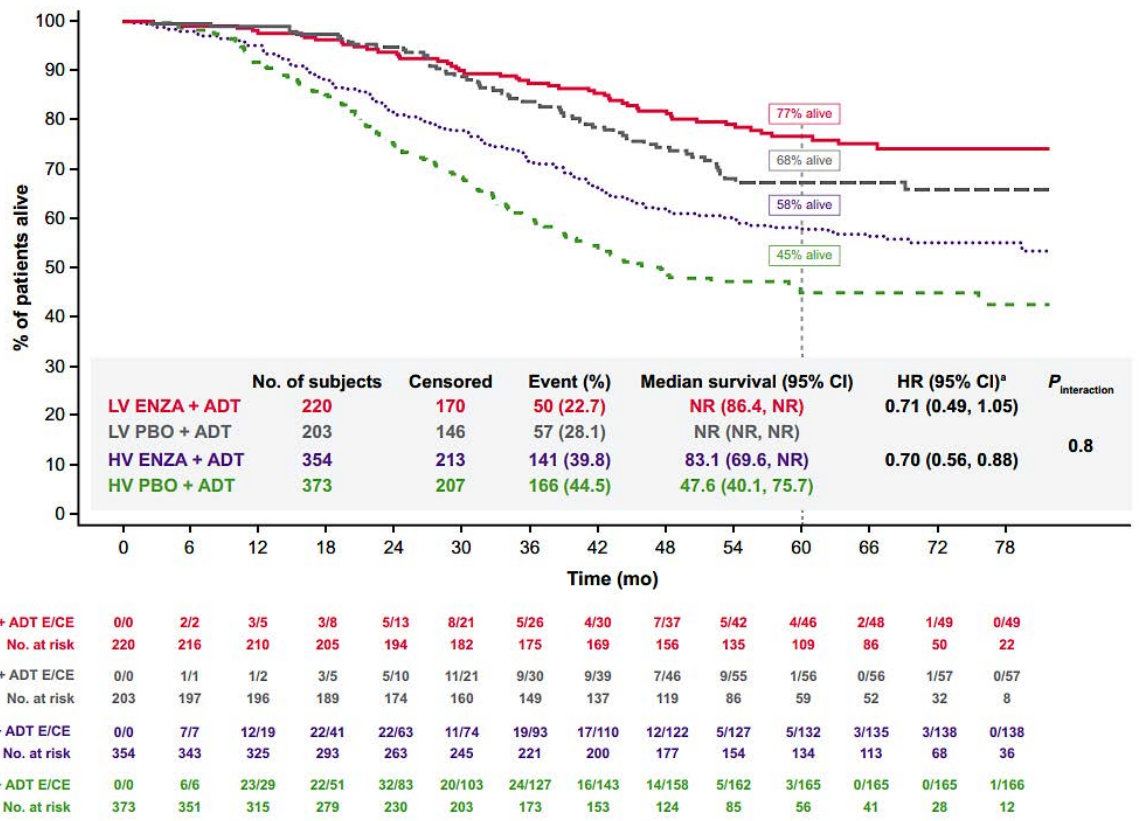
Chi K et al., JCO, 2021

Enzalutamide
ARCHES Trial

Brief Report

ARCHES 5-year Survival with Enzalutamide Plus Androgen-deprivation Therapy in Metastatic Hormone-sensitive Prostate Cancer Patients

Andrew J. Armstrong[a,], Daniel P. Petrylak[b], Neal D. Shore[c], Russell Z. Szmulewitz[d], Jeffrey Holzbeierlein[e], Arnauld Villers[f], Antonio Alcaraz[g], Boris Alekseev[h], Taro Iguchi[i], Francisco Gomez-Veiga[j], Ruslan Croitoru[k], Ruishan Wu[k], Matko Kalac[l], Yiyun Tang[l], Arnulf Stenzl[m], Arun A. Azad[n]*

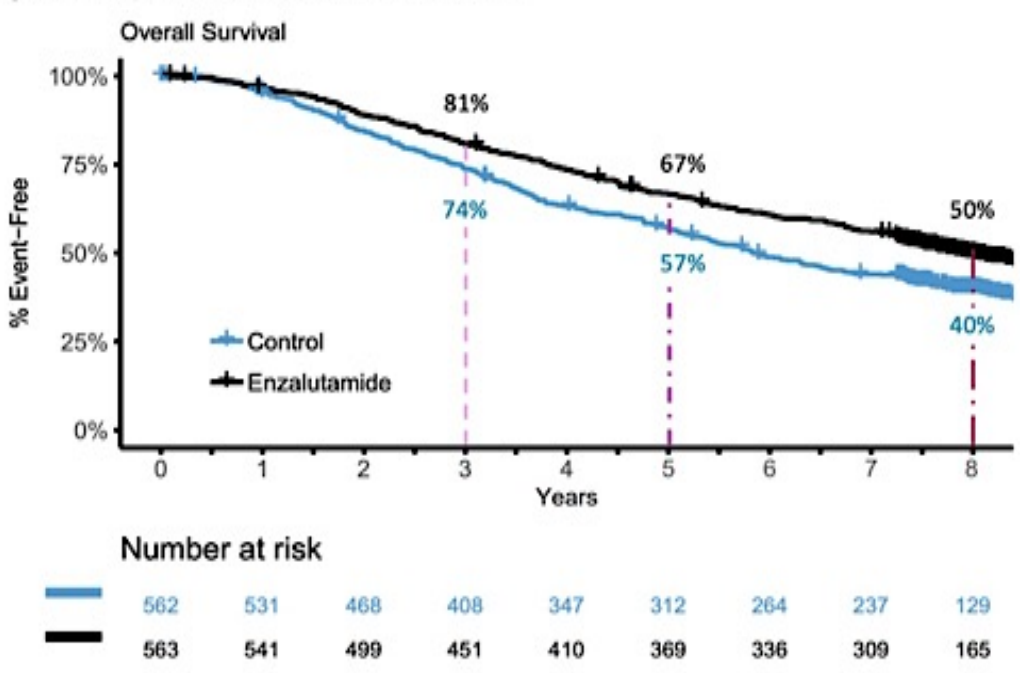


LV: Low volume; HV: High volume

Enzalutamide
ENZAMET Trial

8-year outcomes of enzalutamide (ENZA) versus a non-steroidal anti-androgen (NSAA) for metastatic, hormone-sensitive prostate cancer (ENZAMET; ANZUP 1304)

Alison Y. Zhang[1,2,13], Ian D. Davis[1,3], Hayley Thomas[2], Ronan Andrew McLaughlin[4], Thean Hsiang Tan[1,5], David William Pook[1,6], Gavin M. Marx[1,7], Robert Richard Zielinski[1,8], Shahneen Sandhu[1,9], Alastair Thomson[10], M. Neil Reaume[11], Scott A. North[11], John McCaffrey, Raymond S. McDermott[4], Nicola Jane Lawrence[1,12], Lisa Horvath[1,13], Simon Chowdhury[14], Kim N. Chi[15], Martin R. Stockler[1,2], Christopher Sweeney[1,16]



Median OS: **8.0** vs 5.8 years
8-year OS: 50% vs 40%
HR **0.73** (95% CI, 0.63–0.86; p=0.0001)

Outcome	ENZA (N=563)	NSAA (N=562)
All participants		
Deaths due to prostate cancer, n	207	261
sdHR (95% CI)	0.72 (0.60–0.87)	
Deaths due to other causes, n	78	76
sdHR (95% CI)	1.24 (1.06–1.45)	
Participants with PSA ≤0.2 at 7 months		
8-year survival	56%	54%
8-year PC mortality rate	26%	31%
8-year non-PC mortality rate	13%	10%
Participants with PSA >0.2 at 7 months		
8-year survival	25%	22%
8-year PC mortality rate	57%	61%
8-year non-PC mortality rate	11%	14%

Zhang AY et al., ASCO, 2025

Phase III ARANOTE Trial

Darolutamide + ADT

Study Design

Metastatic hormone sensitive prostate cancer

2:1

Experimental Arm (N = 446)
Darolutamide 600 mg BID + ADT

Control Arm (N = 223)
Placebo + ADT

Eligible adults
- ECOG PS 0–2
- Patients who received prior ARPi or chemotherapy were excluded
- Patients with regional LN metastases only were excluded

Stratification factors
- Visceral disease: Y/N
- Prior local therapy: Y/N

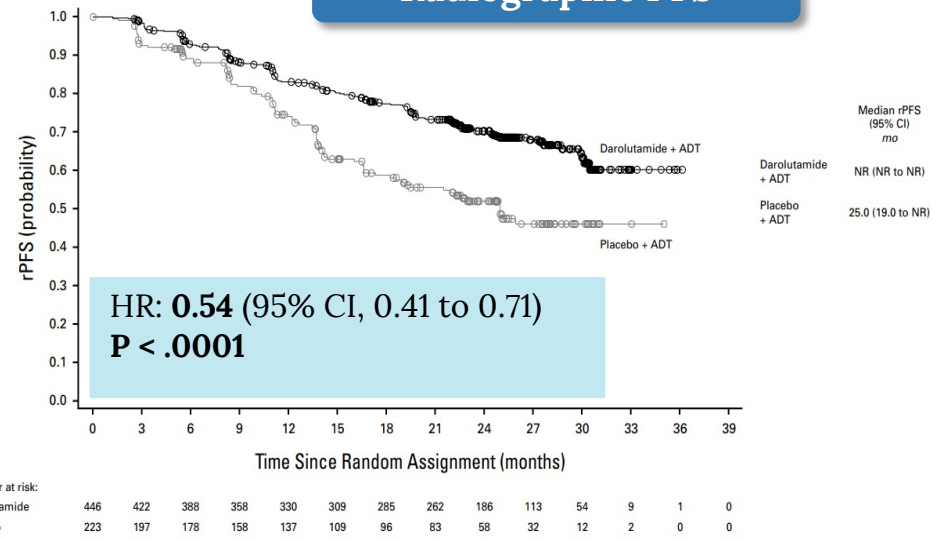
PRIMARY ENDPOINTS

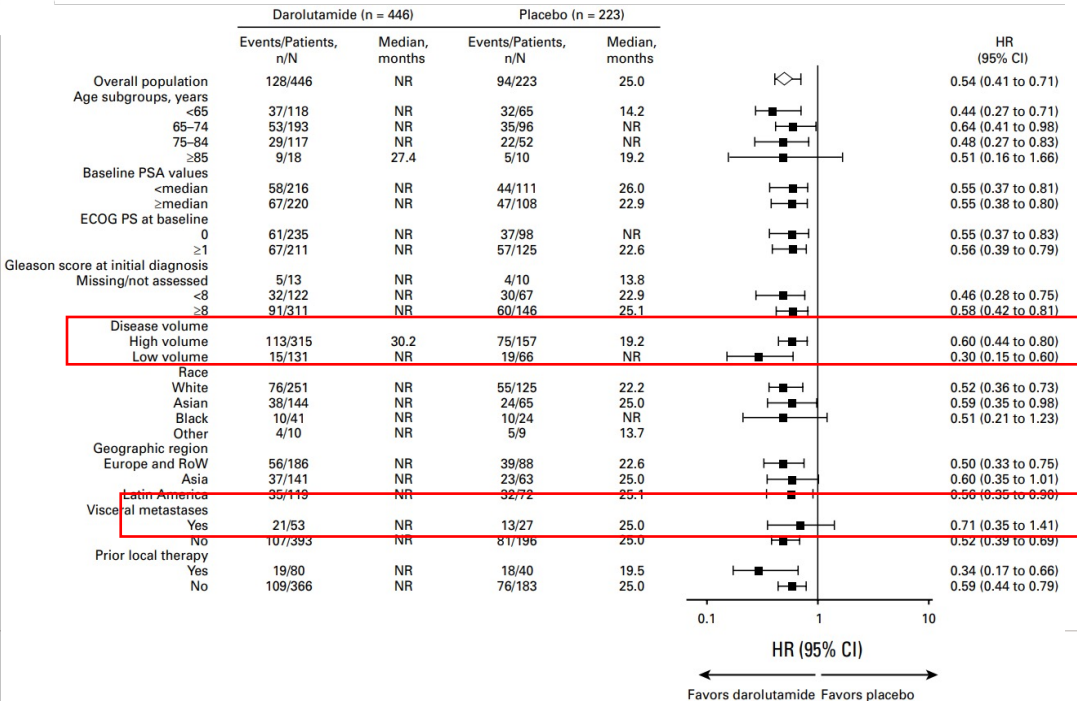
Radiographic progression-free survival (rPFS) by central blinded review

SECONDARY ENDPOINTS

- Overall survival (OS)
- Time to initiation of subsequent anticancer therapy
- Time to mCRPC
- Time to PSA progression
- Rates of undetectable PSA (<0.2 ng/mL)
- Time to pain progression (BPI-SF)Safety

Radiographic PFS



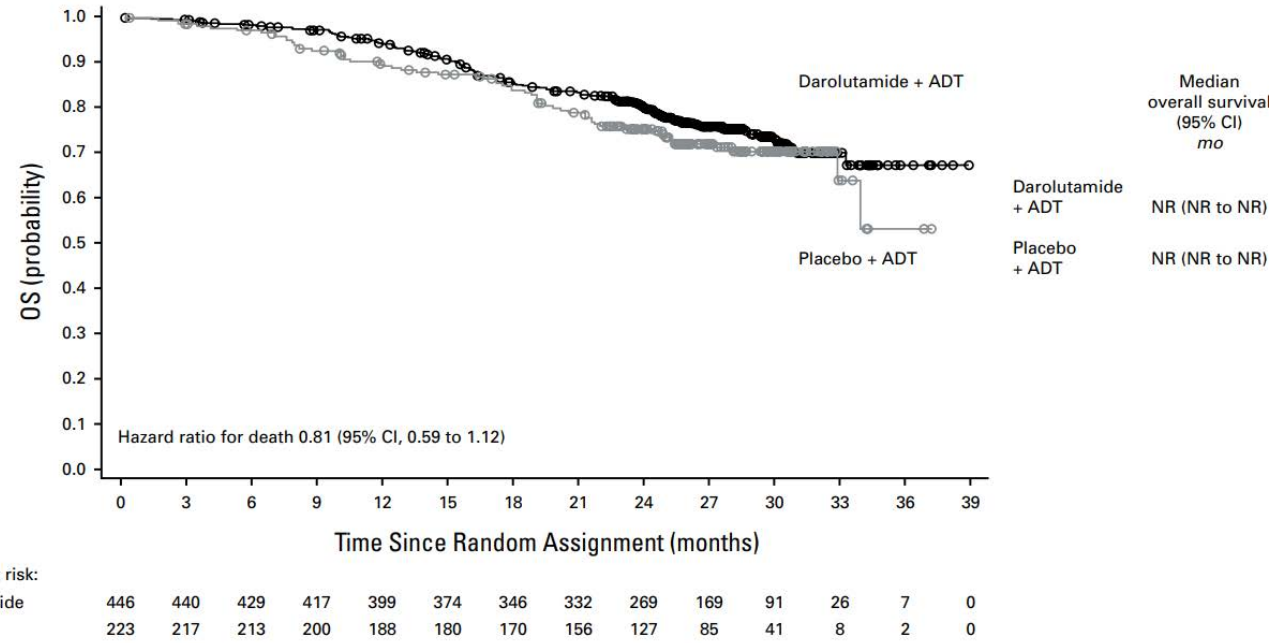


Saad F et al., JCO, 2024

Phase III ARANOTE Trial

Darolutamide + ADT

Overall survival

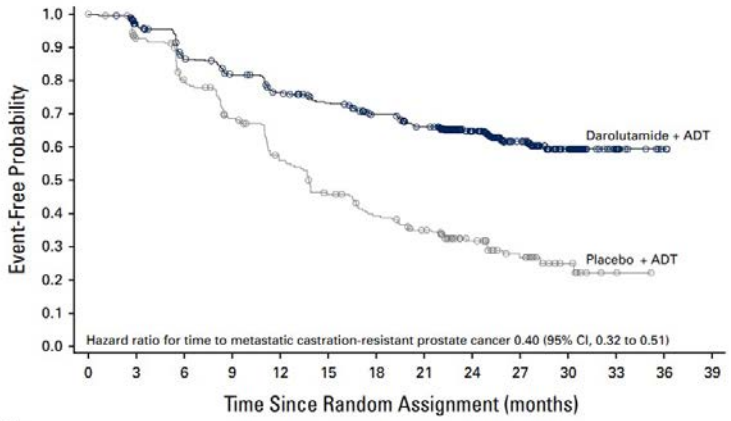


	Median overall survival (95% CI) *mo*
Darolutamide + ADT	NR (NR to NR)
Placebo + ADT	NR (NR to NR)

Number at risk:

Darolutamide	446	440	429	417	399	374	346	332	269	169	91	26	7	0
Placebo	223	217	213	200	188	180	170	156	127	85	41	8	2	0

Time to mCRPC

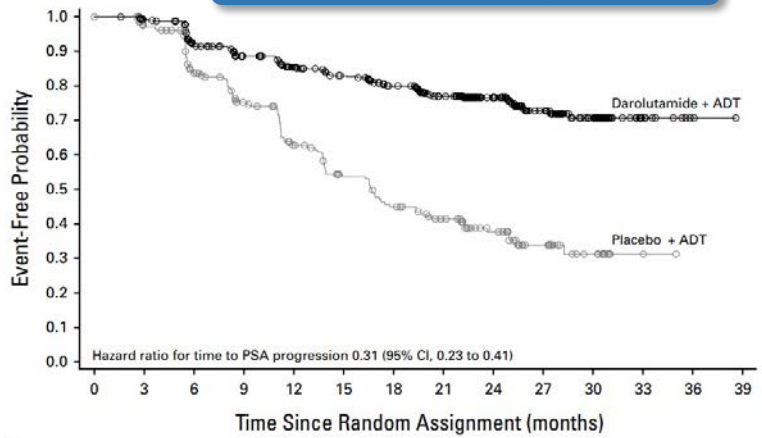


	Median time to metastatic castration resistant prostate cancer (95% CI) *mo*
Darolutamide + ADT	NR (NR to NR)
Placebo + ADT	13.8 (12.0 to 16.8)

Number at risk:

Darolutamide	446	417	364	339	312	293	268	245	177	110	51	14	2	0
Placebo	223	197	167	139	110	88	73	61	42	25	10	2	0	0

Time to PSA Progression



	Median time to PSA progression (95% CI) *mo*
Darolutamide + ADT	NR (NR to NR)
Placebo + ADT	16.8 (13.9 to 20.1)

Number at risk:

Darolutamide	446	408	357	330	301	280	256	220	158	95	48	12	2	0
Placebo	223	195	158	130	102	81	67	54	36	20	9	2	0	0

Saad F et al., JCO, 2024

Phase III ARANOTE Trial

Darolutamide + ADT

Adverse Event - N (%)	Darolutamide + ADT (n=445)	Placebo + ADT (n=221)
Any adverse event	405 (91.0)	199 (90.0)
Serious adverse event	105 (23.6)	52 (23.5)
Grade 3 or 4 adverse event	137 (30.8)	67 (30.3)
Grade 5 adverse event	21 (4.7)	12 (5.4)
Adverse event leading to permanent discontinuation of study drug	27 (6.1)	20 (9.0)

Adverse Event - N (%)	Darolutamide		Placebo	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Anemia	91 (20.4)	14 (3.1)	39 (17.6)	8 (3.6)
Arthralgia	55 (12.4)	5 (1.1)	25 (11.3)	0
Urinary tract infection	52 (11.7)	8 (1.8)	17 (7.7)	1 (0.5)
Back pain	43 (9.7)	5 (1.1)	23 (10.4)	2 (0.9)
Increased aspartate aminotransferase	43 (9.7)	10 (2.2)	17 (7.7)	1 (0.5)
Constipation	42 (9.4)	0	16 (7.2)	0
Hot flush	41 (9.2)	0	16 (7.2)	0
Increased alanine aminotransferase	40 (9.0)	9 (2.0)	18 (8.1)	1 (0.5)
Pain in extremity	38 (8.5)	1 (0.2)	20 (9.0)	4 (1.8)
Hypertension	38 (8.5)	19 (4.3)	19 (8.6)	8 (3.6)
Bone pain	33 (7.4)	9 (2.0)	27 (12.2)	3 (1.4)
Increased weight	33 (7.4)	4 (0.9)	17 (7.7)	1 (0.5)
COVID-19	32 (7.2)	1 (0.2)	15 (6.8)	2 (0.9)
Increased alkaline phosphatase	30 (6.7)	0	13 (5.9)	3 (1.4)
Insomnia	28 (6.3)	0	6 (2.7)	1 (0.5)
Hyperglycemia	27 (6.1)	1 (0.2)	8 (3.6)	0
Fatigue	25 (5.6)	0	18 (8.1)	1 (0.5)
Increased creatinine	21 (4.7)	2 (0.4)	15 (6.8)	0
Headache	18 (4.0)	0	14 (6.3)	2 (0.9)

Saad F et al., JCO, 2024

Phase III ARASENS Trial

Darolutamide + Docetaxel + ADT

Study Design

Metastatic hormone sensitive prostate cancer

1:1

Experimental Arm
Darolutamide 600 mg twice daily + ADT + Docetaxel × 6

Control Arm
Placebo twice daily + ADT + Docetaxel × 6

Eligible adults
- Metastatic hormone sensitive prostate cancer
- ECOG PS 0 or 1
- Patients who were candidates for ADT + docetaxel were included

Stratification factors
- Extent of Disease: M1a/b/c
- ALP < vs ≥ ULN

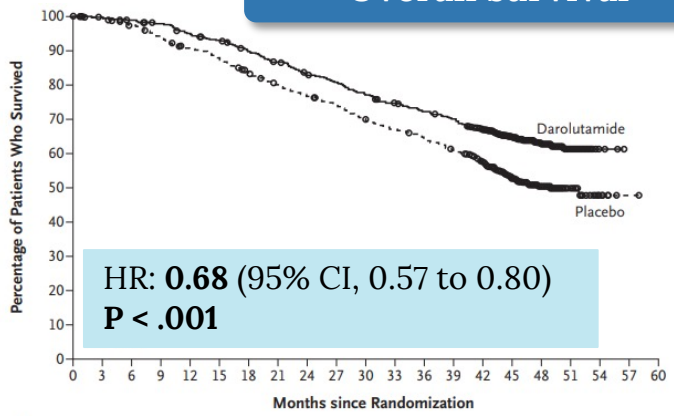
PRIMARY ENDPOINTS

Overall survival (OS)

SECONDARY ENDPOINTS

- Time to CRPC
- Time to pain progression
- SSE-free survival
- Time to first SSE
- Time to initiation of subsequent systemic antineoplastic therapy
- Time to worsening of disease-related physical symptoms
- Time to initiation of opioid use for ≥7 consecutive days
- Safety

Overall survival



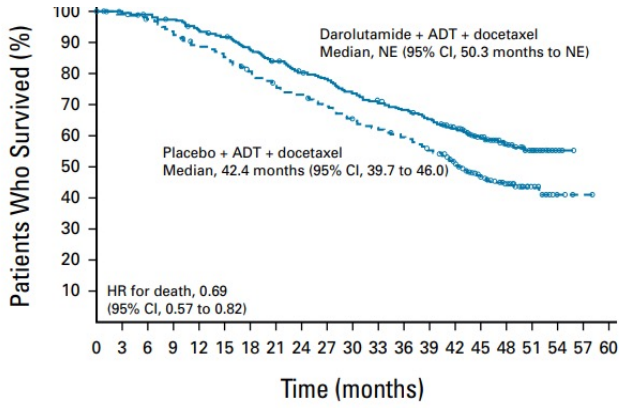
HR: **0.68** (95% CI, 0.57 to 0.80)
P < .001

	Median Survival (95% CI) *mo*
Darolutamide	NE
Placebo	48.9 (44.4–NE)

No. at Risk

Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

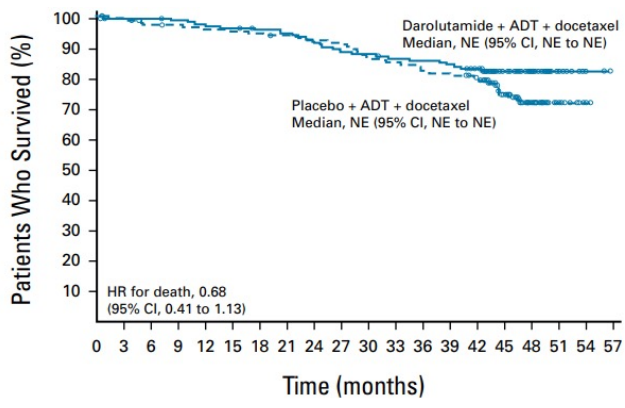
High volume



No. of high-volume patients at risk:

Darolutamide	497	494	486	479	462	449	429	408	389	378	356	341	326	312	285	193	103	43	6	0	0
Placebo	508	502	491	469	444	430	401	378	358	341	319	304	286	269	233	153	72	23	4	1	0

Low volume



No. of low-volume patients at risk:

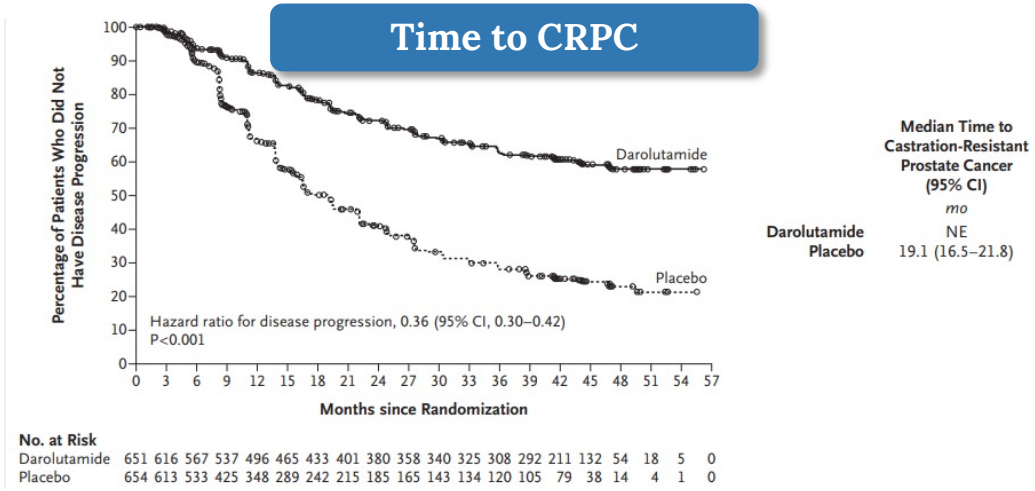
Darolutamide	154	151	151	148	146	144	141	140	136	131	130	127	126	124	117	74	36	13	3	0	
Placebo	146	144	139	138	136	135	134	132	130	129	122	120	116	114	107	65	35	14	2	0	

Smith M et al., NEJM, 2022; Hussain M et al., JCO, 2023

Phase III ARASENS Trial

Darolutamide + Docetaxel + ADT

Time to CRPC



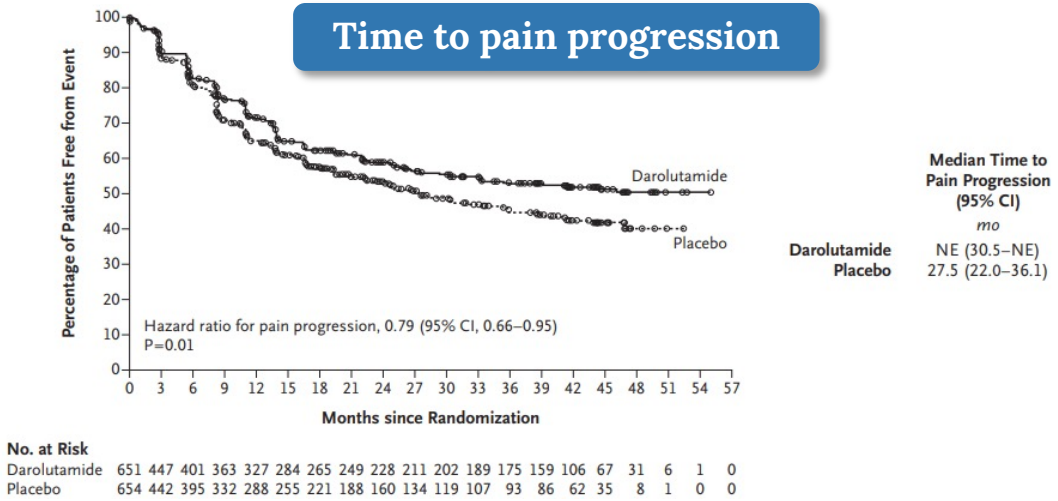
Median Time to Castration-Resistant Prostate Cancer (95% CI)

mo

Darolutamide: NE

Placebo: 19.1 (16.5–21.8)

Time to pain progression



Median Time to Pain Progression (95% CI)

mo

Darolutamide: NE (30.5–NE)

Placebo: 27.5 (22.0–36.1)

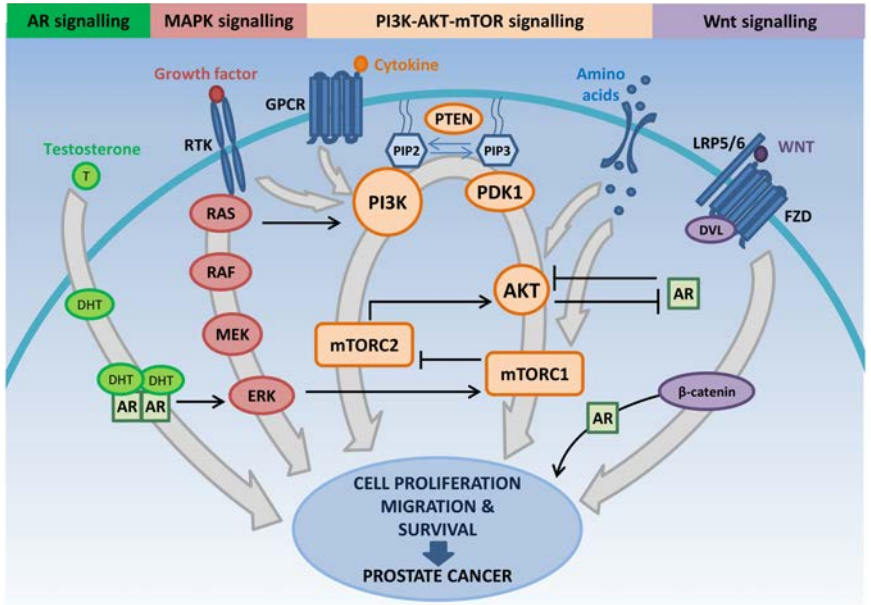
Adverse Event – N (%)	Darolutamide–ADT–Docetaxel (N=652)	Placebo–ADT–Docetaxel (N=650)
Any adverse event	649 (99.5)	643 (98.9)
Worst grade		
Grade 1	28 (4.3)	35 (5.4)
Grade 2	162 (24.8)	169 (26.0)
Grade 3	248 (38.0)	232 (35.7)
Grade 4	183 (28.1)	181 (27.8)
Grade 5	27 (4.1)	26 (4.0)
Serious adverse event	292 (44.8)	275 (42.3)
Adverse event leading to permanent discontinuation of trial agent		
Darolutamide/placebo	88 (13.5)	69 (10.6)
Docetaxel	52 (8.0)	67 (10.3)
Selected grade 3 or 4 adverse event		
Neutropenia	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased ALT	18 (2.8)	11 (1.7)
Increased AST	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)

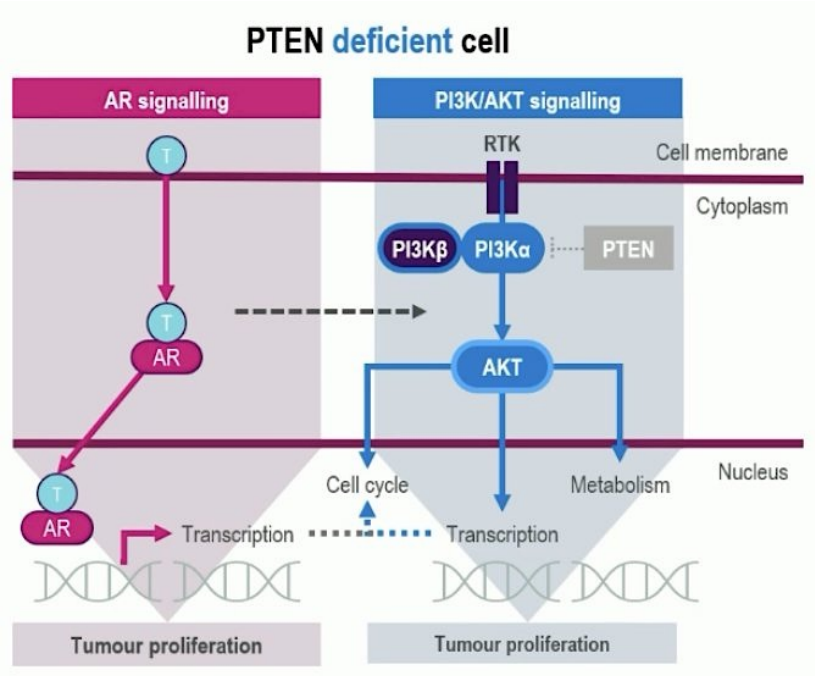
Smith M et al., NEJM, 2022

Biologic justification for targeting the PI3K/AKT/mTOR pathway

Capivasertib in PTEN-deficient PC

- PTEN loss removes pathway inhibition, causing oncogenic PI3K/Akt/mTOR hyperactivation.
- PTEN loss occurs in ~40–50% of advanced PC and is associated with worse prognosis and reduced benefit from AR-targeted therapy.
- PTEN loss with subsequent AKT activation may also promote radiation and chemotherapy resistance.





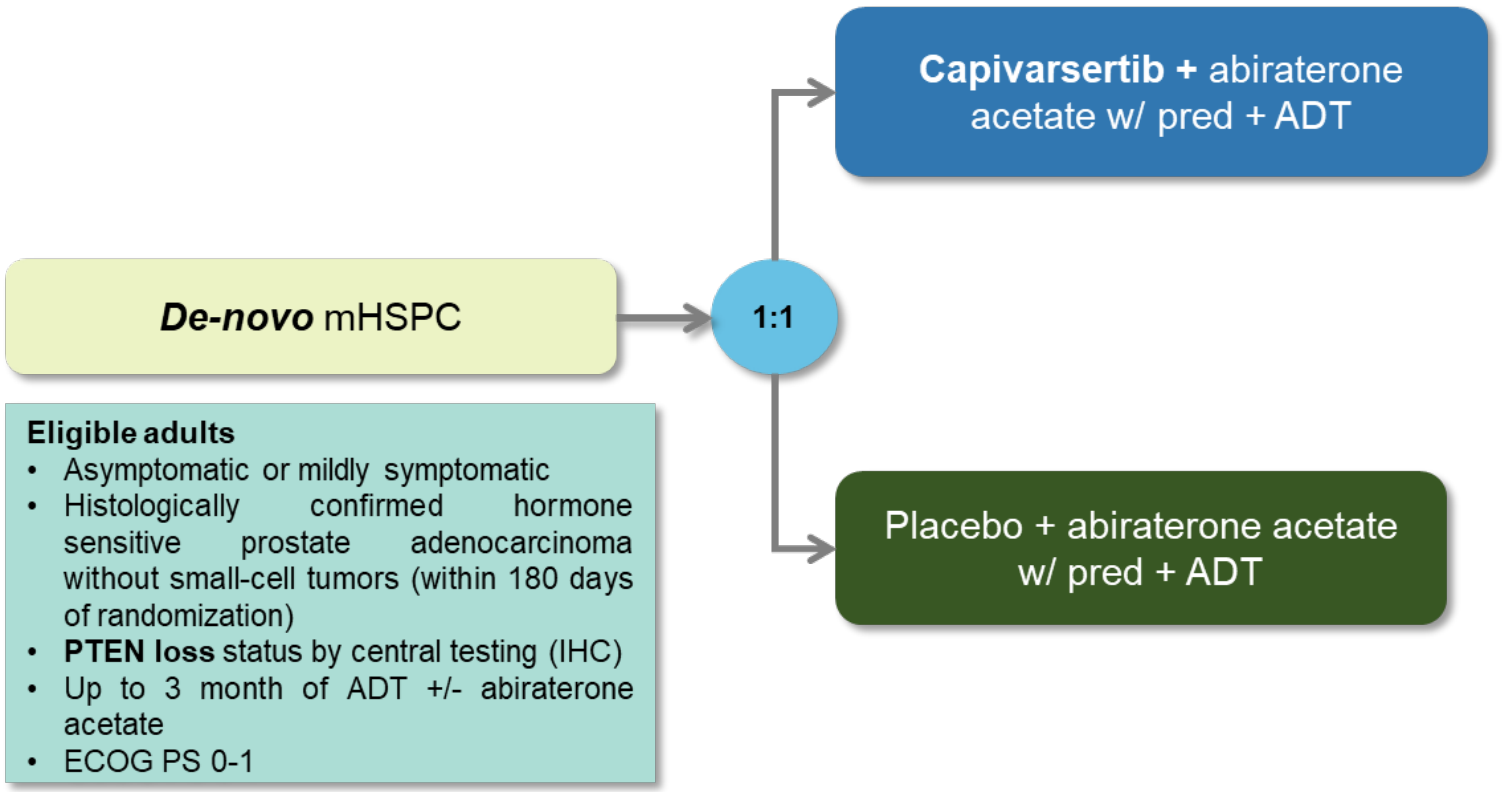
- Capivasertib, a pyrrolopyrimidine-derived compound, is a potent and selective inhibitor of all three AKT isoforms (AKT1-3).
- By binding to AKT and inhibiting phosphorylation of downstream substrates, **capivasertib reduces the activation of AKT signaling processes that contribute to tumor growth**

Shorning BY et al., Int J. Mol. Sci, 2020; Taylor BS et al., Cancer cell, 2010; Robinson D et al., Cell, 2015; Jamaspishvili T et al., Nat Rev Urol 2018; Grunwald V et al., Cancer research, 2002; Qian DZ et al., The Prostate, 2010; Fizazi K et al., ESMO, 2025

Capivasertib in PTEN-deficient PC

Phase III CAPItello-281 Trial

Study Design



Eligible adults

- Asymptomatic or mildly symptomatic
- Histologically confirmed hormone sensitive prostate adenocarcinoma without small-cell tumors (within 180 days of randomization)
- **PTEN loss** status by central testing (IHC)
- Up to 3 month of ADT +/- abiraterone acetate
- ECOG PS 0-1

Endpoints

Primary endpoint

- Radiographic progression-free survival

Secondary endpoints

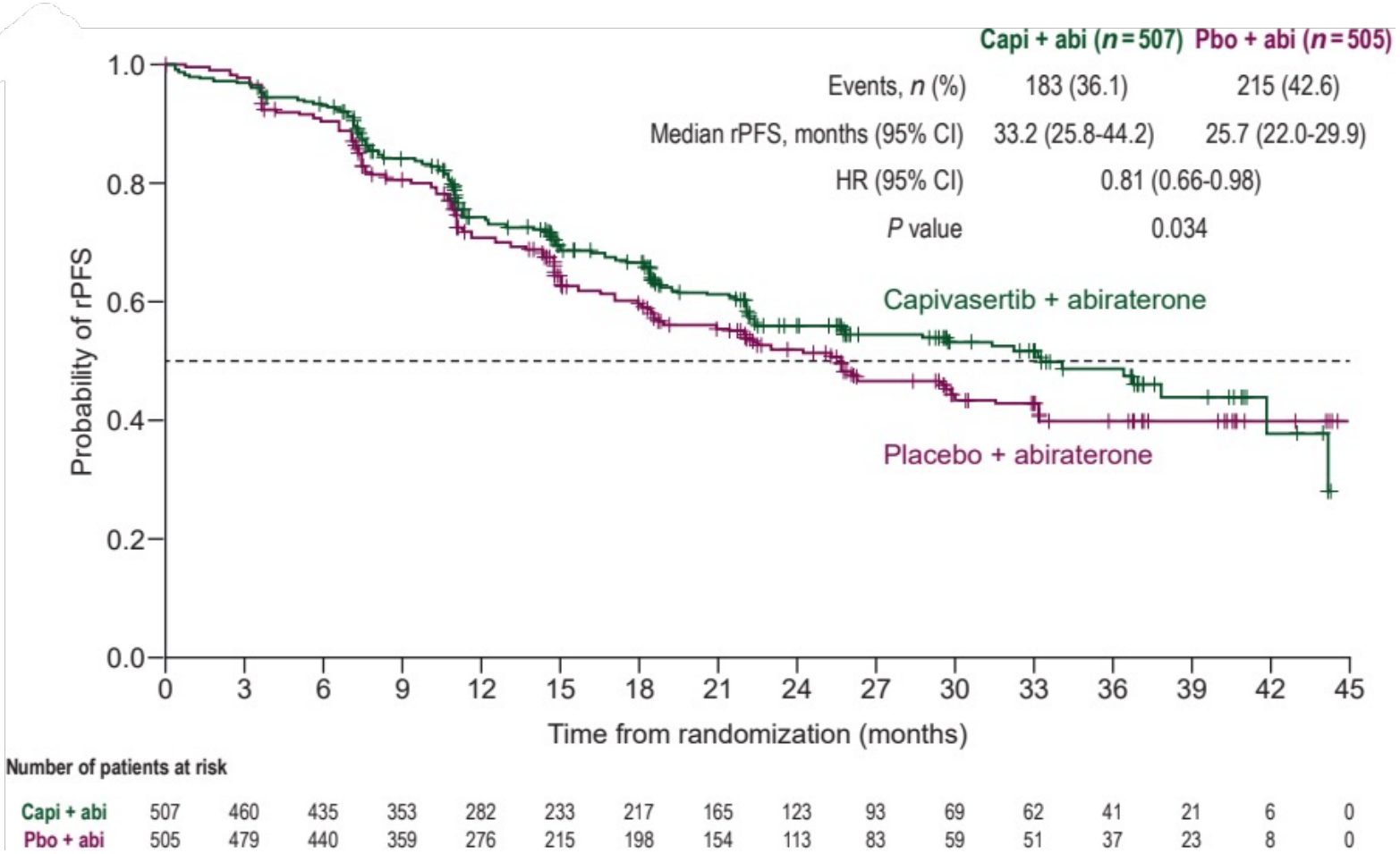
- Overall survival
- Time to start of first subsequent therapy or death
- Symptomatic skeletal event-free survival
- Time to pain progression
- Time to prostate-specific antigen progression
- Time to castration resistance
- Fatigue intensity, severity, and interference
- Pain severity and pain interference
- Disease-related symptoms and quality of life
- Progression-free survival after next-line treatment
- Plasma concentration of capivasertib (pre-dose and post-dose)

Fizazi K et al., ESMO, 2025; Fizazi K et al., Ann Oncol, 2026

Capivasertib in PTEN-deficient PC

Phase III CAPItello-281 Trial

Radiographic progression free survival

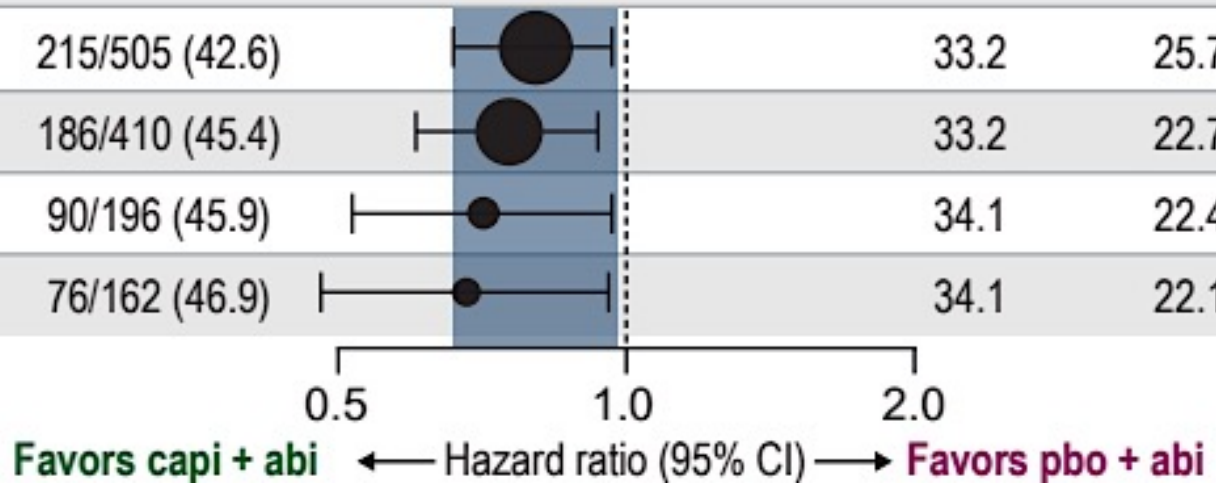


Fizazi K et al., ESMO, 2025; Fizazi K et al., Ann Oncol, 2026

Capivasertib in PTEN-deficient PC

Phase III CAPItello-281 Trial

	Number of events/number of patients (%)		Median, months		
	Capi + abi	Pbo + abi	Capi + abi	Pbo + abi	HR (95% CI)
***Post hoc* analysis**					
All randomized patients	183/507 (36.1)	215/505 (42.6)	33.2	25.7	0.81 (0.66-0.98)
PTEN score ≥95%	146/404 (36.1)	186/410 (45.4)	33.2	22.7	0.75 (0.60-0.94)
PTEN score ≥99%	69/205 (33.7)	90/196 (45.9)	34.1	22.4	0.71 (0.52-0.97)
PTEN score 100%	57/169 (33.7)	76/162 (46.9)	34.1	22.1	0.68 (0.48-0.96)



Fizazi K et al., ESMO, 2025; Fizazi K et al., Ann Oncol, 2026

Capivasertib in PTEN-deficient PC

Phase III CAPItello-281 Trial

Adverse Event - N (%)	Capivasertib + Abiraterone (n=503)		Placebo + Abiraterone (n=503)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	497 (98.8)	337 (67.0)	463 (92.0)	203 (40.4)
Diarrhea	261 (51.9)	31 (6.2)	40 (8.0)	2 (0.4)
Hyperglycemia	191 (38.0)	52 (10.3)	65 (12.9)	3 (0.6)
Rash	178 (35.4)	62 (12.3)	35 (7.0)	1 (0.2)
Anemia	120 (23.9)	26 (5.2)	64 (12.7)	5 (1.0)
Hypokalemia	111 (22.1)	44 (8.7)	64 (12.7)	24 (4.8)
Hypertension	100 (19.9)	29 (5.8)	120 (23.9)	39 (7.8)
Fatigue	80 (15.9)	2 (0.4)	63 (12.5)	4 (0.8)
ALT increased	71 (14.1)	22 (4.4)	67 (13.3)	17 (3.4)
Urinary tract infection	69 (13.7)	21 (4.2)	51 (10.1)	6 (1.2)
AST increased	65 (12.9)	13 (2.6)	59 (11.7)	10 (2.0)
Nausea	61 (12.1)	3 (0.6)	22 (4.4)	0
COVID-19	59 (11.7)	4 (0.8)	44 (8.7)	3 (0.6)
Asthenia	57 (11.3)	4 (0.8)	25 (5.0)	2 (0.4)
Pyrexia	55 (10.9)	6 (1.2)	14 (2.8)	0
Hot flush	53 (10.5)	1 (0.2)	68 (13.5)	0
Pruritus	53 (10.5)	1 (0.2)	13 (2.6)	0
Back pain	50 (9.9)	3 (0.6)	55 (10.9)	0
Constipation	42 (8.3)	1 (0.2)	60 (11.9)	0
Arthralgia	38 (7.6)	2 (0.4)	51 (10.1)	2 (0.4)

Fizazi K et al., Ann Oncol, 2026

QUESTIONS?

Module 13: Prostate Cancer

Optimizing the Role of Hormonal Therapy in the Care of Patients with Prostate Cancer — Dr Bryce

Other Available and Emerging Therapeutic Approaches — Dr Agarwal

Other Available and Emerging Therapeutic Approaches in Metastatic Prostate Cancer

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Senior Director for Clinical Research, Huntsman Cancer Institute (HCI)
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Director, Center of Investigational Therapeutics
Director, Genitourinary Oncology Program
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Disclosures

No relevant financial relationships to disclose.

Emerging Therapeutics in Metastatic Prostate Cancer

- PARP inhibitors
- Radioligand therapies
- Antibody-drug conjugates
- T-cell engagers
- CYP11A1 inhibitor

The Rationale for Combining PARPi with ARPI

ARPIs induce a phenotype resembling HRR deficiency

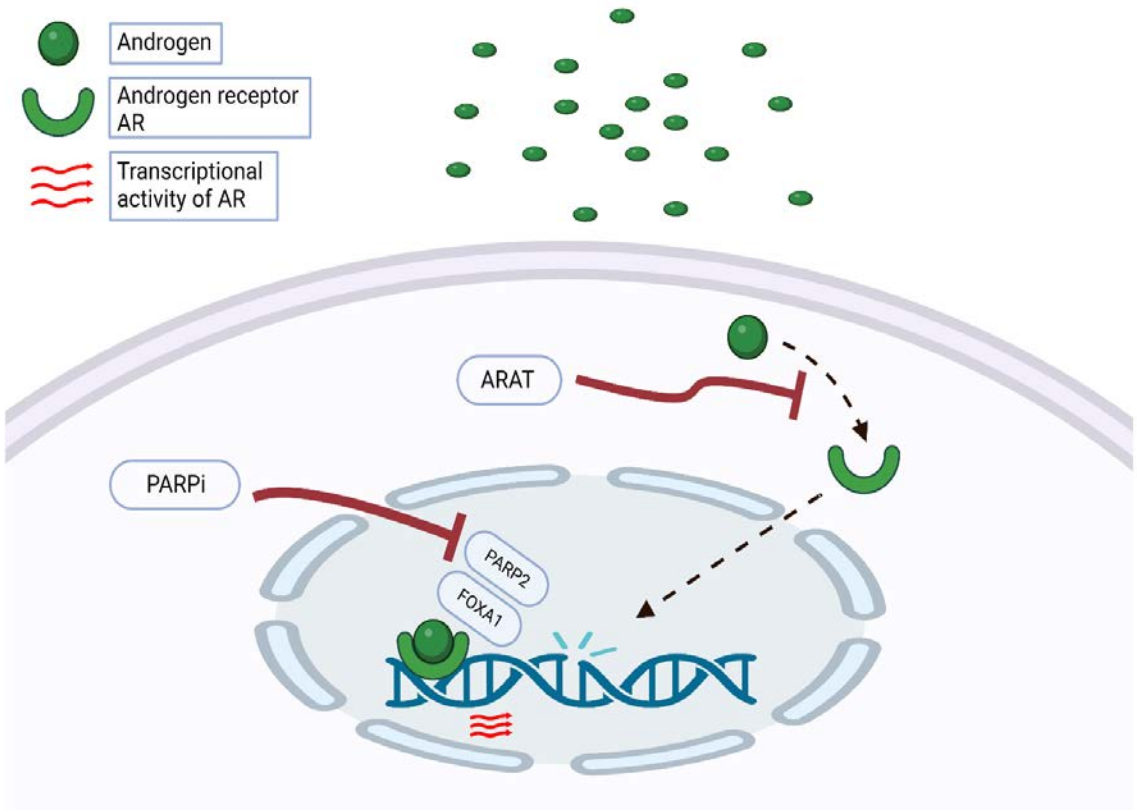
Suppressed AR function causes an upregulation of PARP

ARPIs prime tumor cells for PARP inhibition

PARP augments AR activity

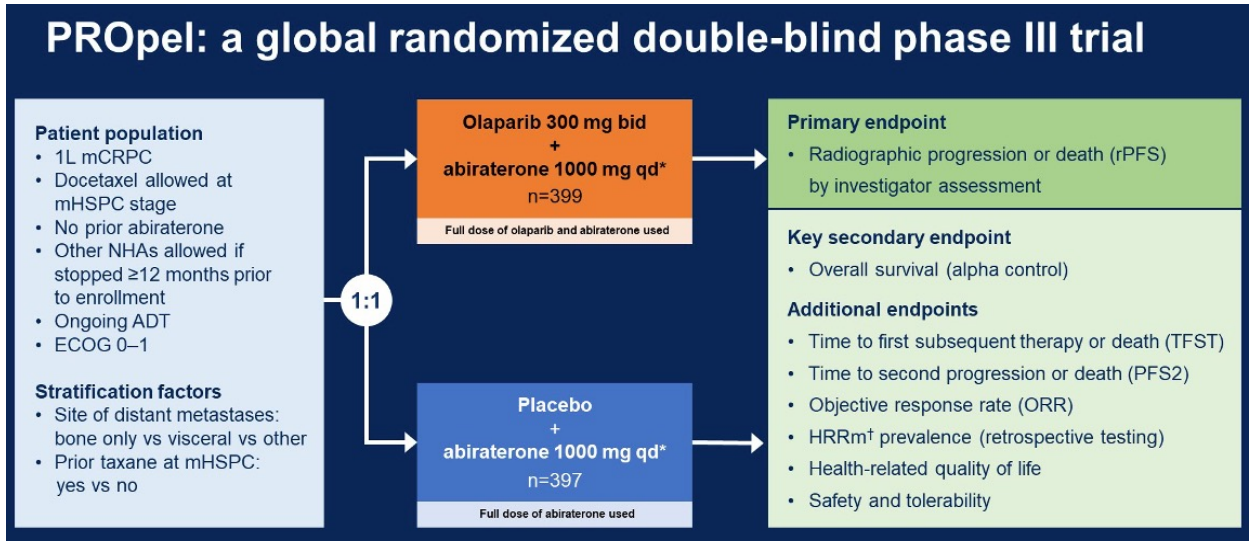
PARP inhibitors may attenuate resistance to ARPIs

PARP inhibitors extend the benefits of ARPIs

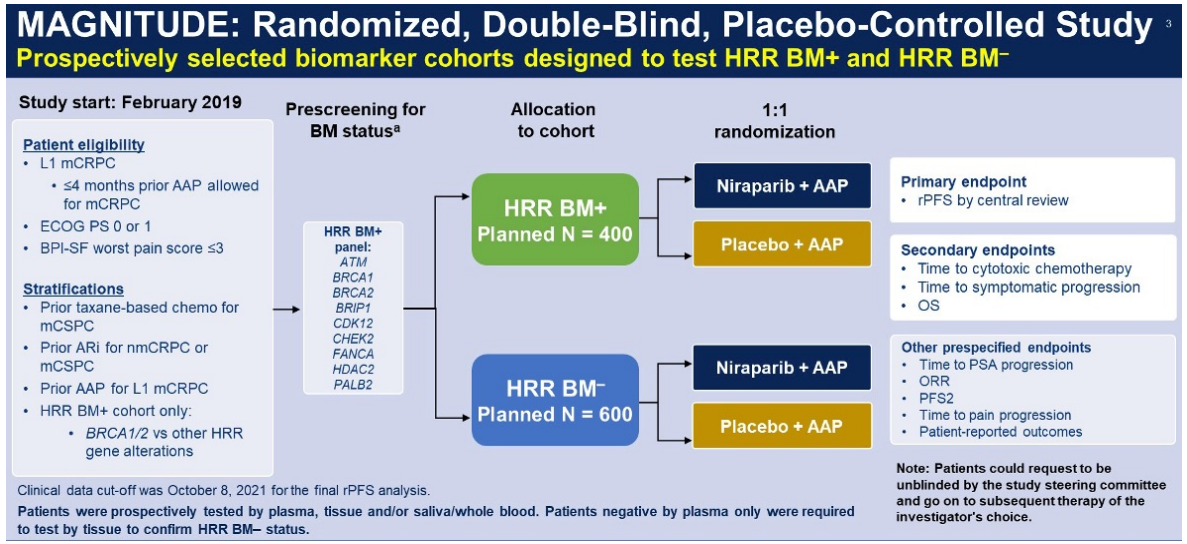


1. Adapted from Bin Gui et al., *PNAS* 2019 June, DOI https://doi.org/10.1073/pnas.1908547116
2. Agarwal N, European Journal of Cancer, 2023.

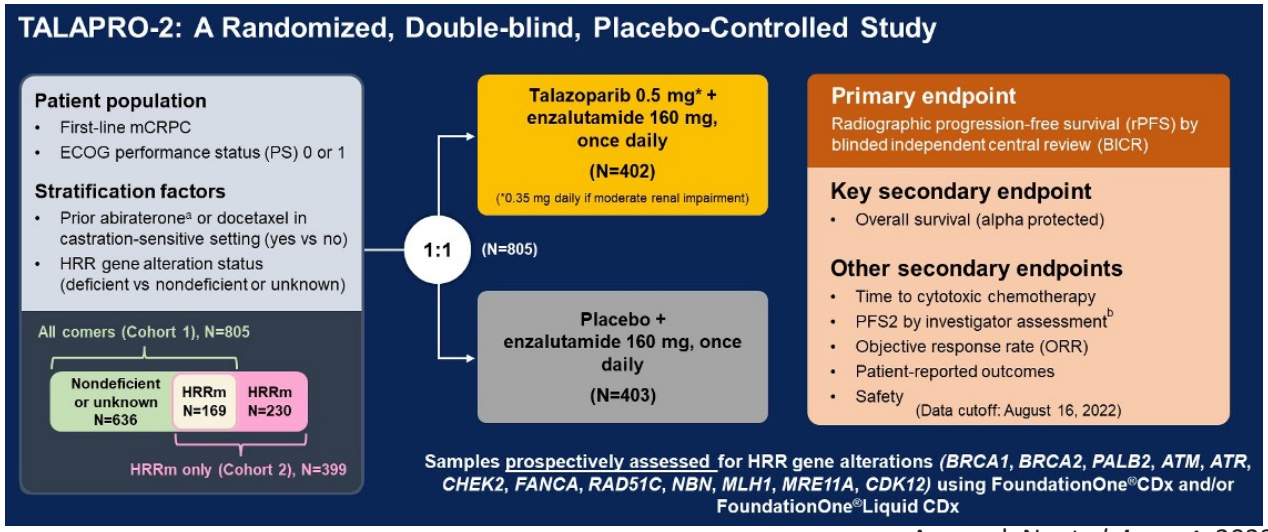
Phase 3 PARPi + ARPI Trials Design



Clarke, NW. *et al.* ***NEJM Evidence,*** 2022



Chi, KN. *et al*. ***JCO,*** 2022

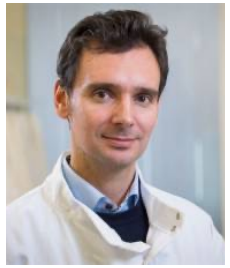


Agarwal, N. *et al.* ***Lancet,*** 2023

Phase 3 Combination trials of PARP inhibitors with an ARPI

	PROpel (N = 796)	MAGNITUDE (N = 423)	TALAPRO-2 (Cohort 1: N = 805)	TALAPRO-2 (Cohort 2: N = 399)
Trial population mCRPC 1st line	Docetaxel / ARSI in mCSPC setting allowed (ARSI without progression and > 12 months ago)	Docetaxel / ARSI in mCSPC setting allowed ; Abiraterone in mCRPC allowed if given < 4 months	Docetaxel / Abiraterone in mCSPC setting allowed	
Design and randomization	1 : 1 randomisation Abiraterone + olaparib (n = 399) vs abiraterone + placebo (n = 397)	Cohort 1: HRR cohort 1 : 1 randomisation abiraterone + niraparib (n = 212) vs abiraterone + placebo (n = 211) Cohort 2: non-HRR cohort (closed prematurely because of futility)	All-comer population 1 : 1 randomisation Enzalutamide + talazoparib (n = 402) vs enzalutamide + placebo (n = 403)	HRR cohort 1 : 1 randomisation Enzalutamide + talazoparib (n = 200) vs enzalutamide + placebo (n = 199)
HRR analysis	Tissue or ctDNA / retrospective	100% tissue / prospective	100% tissue / prospective	99.5% tissue / prospective 0.5% ctDNA or unspecified tissue source / prospective
Primary endpoint	rPFS (investigator review)	rPFS (central review)	rPFS (central review)	rPFS (central review)
rPFS, HR (95% CI)				
All comers	HR 0.66 (0.54-0.81)	NR	HR 0.63 (0.51-0.78)	Not included
HRR -ve	HR 0.76 (0.6-0.97)	HR 1.09 (0.75-1.57)	HR 0.70 (0.54-0.89)	Not included
HRR +ve	HR 0.50 (0.34-0.73)	HR 0.73 (0.56-0.96)	HR 0.46 (0.30-0.70)	HR 0.45 (0.33-0.61)
BRCA+	HR 0.23 (0.12-0.43)	HR 0.53 (0.36-0.79)	HR 0.23 (0.10-0.53)	HR 0.20 (0.11-0.36)
ORR (all comers)	58% vs 48%	60% vs 28% (only HRR+ pts)	61.7% vs 43.9%	67% vs 40%
OS (all comers)	HR 0.81 (0.67-1)	HR 0.66 (0.46-0.95) (only for BRCA 1/2)	**45.8 vs 37 months** **HR 0.80 (0.66–0.96)**	**45.1 vs 31.1 months** **HR 0.62 (0.48–0.81)**
FDA approval; EMA approval	**mCRPC with BRCA1/2 mutations; mCRPC when chemotherapy is not indicated**	**mCRPC with BRCA1/2 mutations**	**mCRPC with any HRR mutations; mCRPC when chemotherapy is not clinically indicated**	
Publication	Clarke N.…Saad F. ***NEJM Evidence***, 2022	Chi K.…Sandhu S. ***JCO***, 2023	**Agarwal N**.…Fizazi K. ***The Lancet***, 2025	Fizazi K.…**Agarwal N.** ***The Lancet***, 2025

AMPLITUDE Phase 3 Trial: PARPi in mHSPC



Key Eligibility

- Pathological diagnosis of prostate adenocarcinoma
- Positive for deleterious homologous recombination repair (HRR) gene mutations
- Radiation with curative intent or prior treatment with PARPi is not allowed
- Patients with long-term use of systemically administered corticosteroids or a history of MDS or AML were excluded

RANDOMIZED

n=788

Niraparib 200 mg qd
+
Abiraterone Acetate 1000 mg qd.
+
Prednisone 5 mg qd

Placebo
+
Abiraterone Acetate 1000 mg qd.
+
Prednisone 5 mg qd

Efficacy end points

Primary:

- rPFS

Secondary:

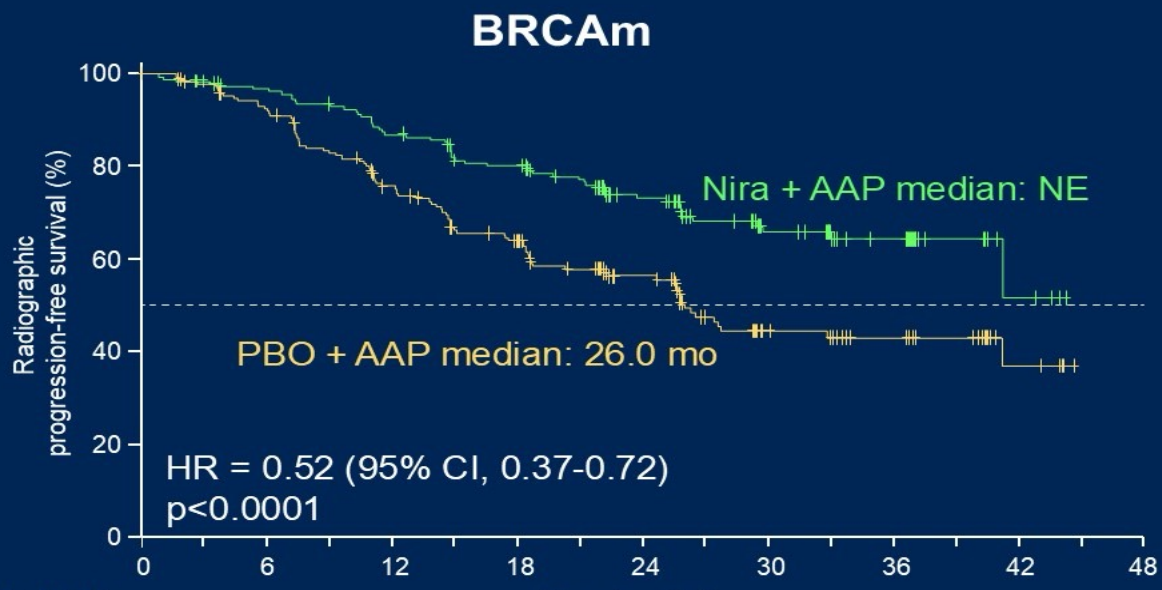
- OS
- Symptomatic PFS
- Time to subsequent therapy
- Duration of response (DOR)
- Safety and tolerability

www.clinicaltrials.gov: (NCT04497844)

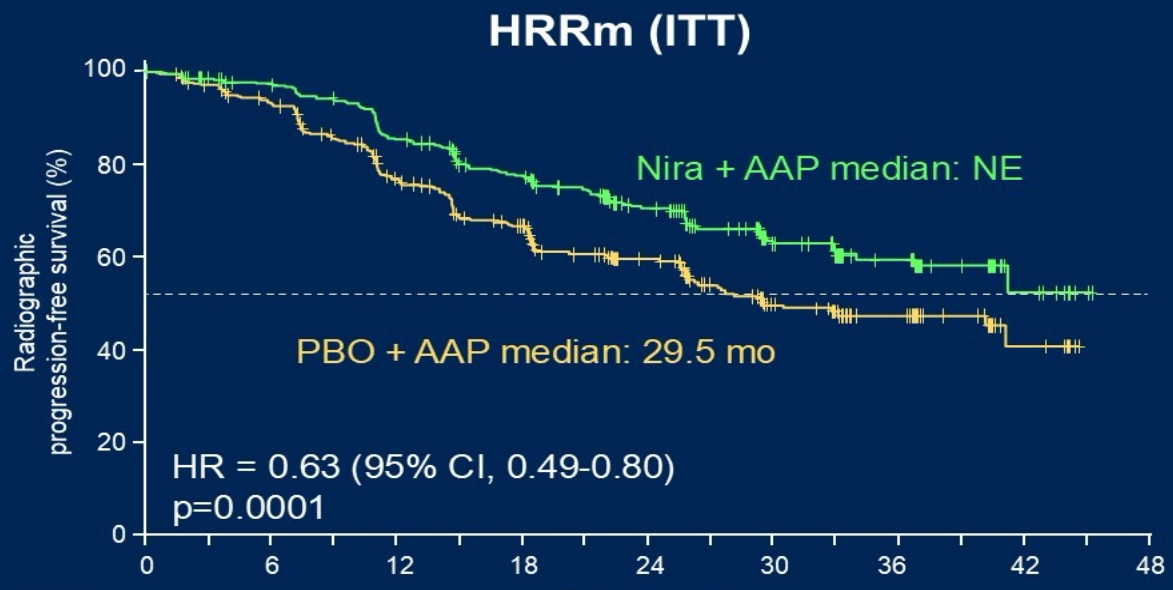
Eligible HRR genes were:
BRCA1, *BRCA2*, *BRIP1*, *PALB2*, *RAD51B*, *RAD54L*, *CDK12*, *CHEK2* and *FANCA*.

Attard, **Agarwal**…Rathkopf. *Nature Medicine*, 2025

Primary End Point: Radiographic Progression-Free Survival



No. at risk									
Nira + AAP	191	177	158	142	95	55	30	4	0
PBO + AAP	196	174	137	109	73	33	22	6	0

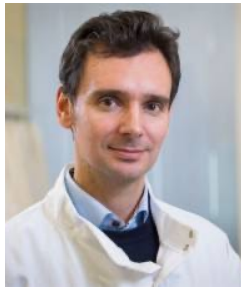


No. at risk									
Nira + AAP	348	321	280	246	164	91	54	9	0
PBO + AAP	348	312	245	201	135	70	43	9	0

AMPLITUDE met the primary end point: Nira + AAP significantly reduced the risk of radiographic progression[a] or death by 48% in BRCAm group and by 37% in HRRm population

[a]rPFS by investigator review; rPFS improvement by blinded independent central review was as large: HR = 0.51 (95% CI, 0.37-0.72) for BRCAm group and 0.61 (95% CI, 0.47-0.79) for HRRm group.
NE, not estimable.

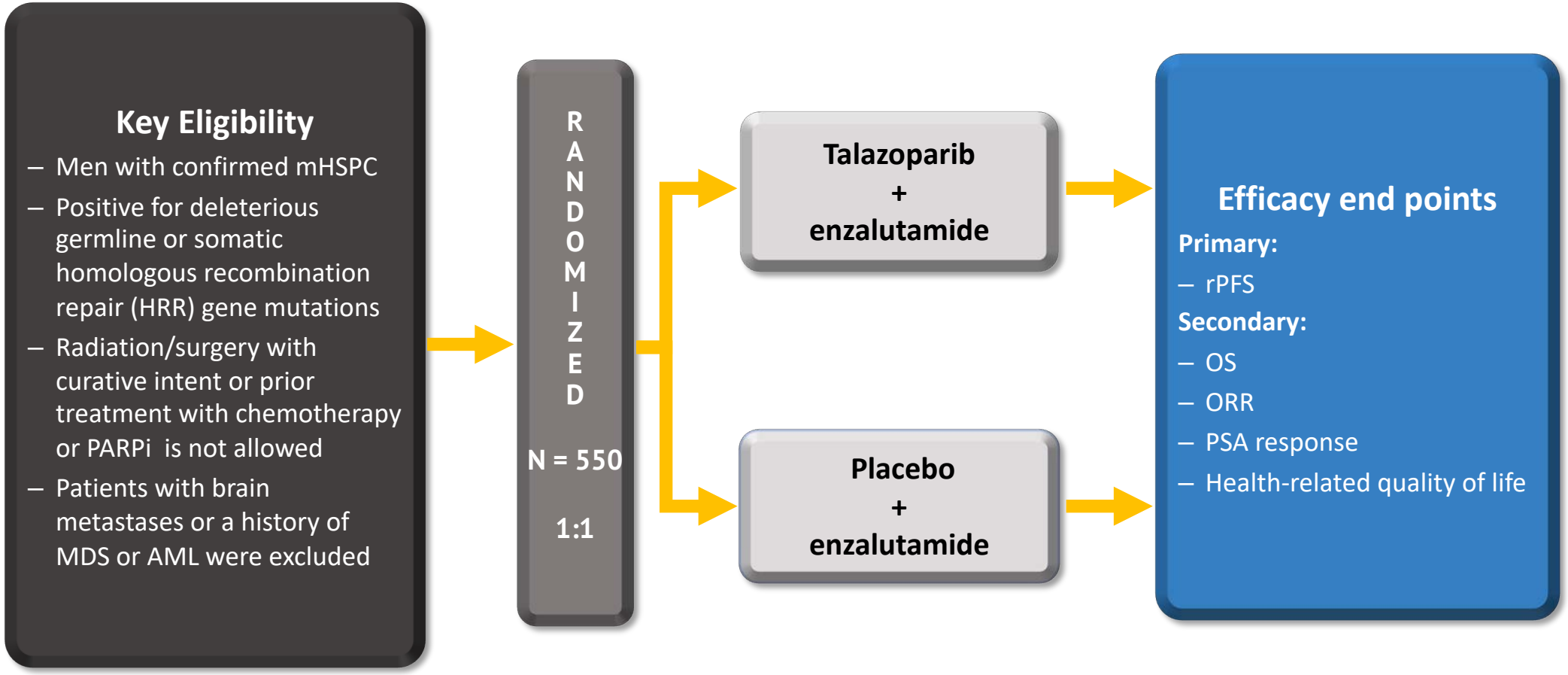
AMPLITUDE Trial: PARPi in mHSPC



Endpoint		Niraparib + Abiraterone	Placebo + Abiraterone	Hazard Ratio (HR) (95% CI)	P-value
rPFS (median, mo)	All	Not reached	29.5	**0.63** (0.49–0.80)	0.0001
	BRCA1/2	Not reached	26	**0.52** (0.37-0.72)	<0.0001
Time to pain progression (median, mo)	All	Not reached	Not reached	**0.50** (0.36–0.69)	<0.0001
	BRCA1/2	Not reached	Not reached	**0.44** (0.29-0.68)	0.0001
OS (median, mo)	All	Not reached	Not reached	0.79 (0.59–1.04)	0.10
	BRCA1/2	Not reached	Not reached	0.75 (0.51-1.11)	0.15

Attard G, Agarwal N…. Rathkopf. Nature Medicine 2025

Phase 3 TALAPRO-3 Trial



www.clinicaltrials.gov: (NCT04821622)

Agarwal… Fizazi. *Future Oncology*, 2024

Phase 3 TALAPRO-3 Trial Press Release

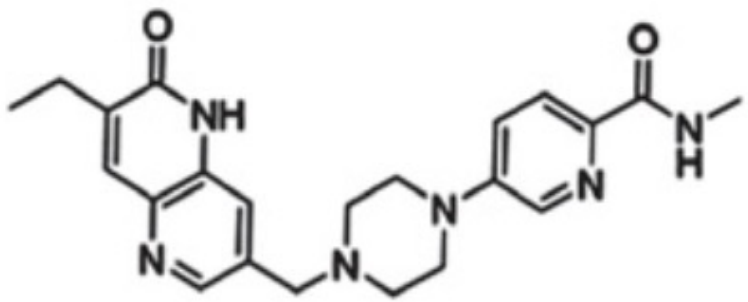
TALAZOPARIB Plus ENZALUTAMIDE Significantly Improves Radiographic Progression-Free Survival in Metastatic Prostate Cancer

Thursday, March 19, 2026

- P*rimary endpoint met in Phase 3 TALAPRO-3 study demonstrating* a statistically significant and clinically meaningful reduction in risk of disease progression or death *in HRR gene-mutated metastatic hormone sensitive prostate cancer*
- *Consistent rPFS efficacy benefit was observed in patients whose tumors harbored BRCA and non-BRCA HRR gene alterations*
- *Interim analysis showed a strong trend toward improvement in overall survival*
- *These results will be discussed with global health authorities to potentially expand TALAZOPARIB indication in this earlier stage disease*

Saruparib (AZD5305) – Selective PARP1 Inhibitor

AZD5305



AZD5305	Biochemical assay*	Cellular assay
PARP1 IC_{50} (nmol/L)	3	**1.5**
PARP2 IC_{50} (nmol/L)	1,400	**653**
PARP1/2 fold selectivity	460	**435**

**Johannes et al., 2021*

Illuzzi G et al. *Clin Cancer Res* 2022;28(21):4724-36.

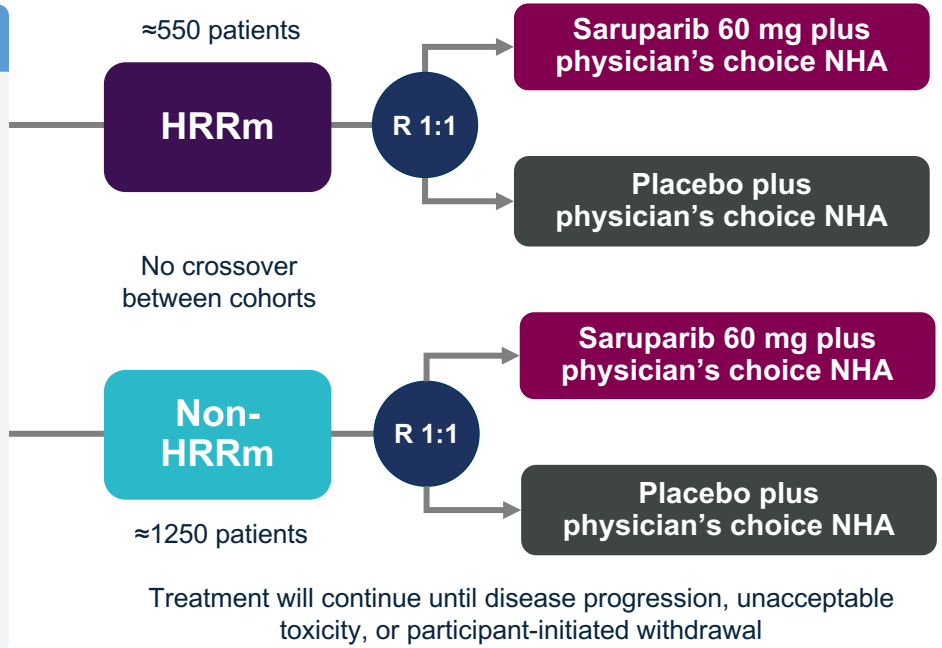
RTP RESEARCH TO PRACTICE

EvoPAR-Prostate01 : Phase 3 Trial Design (mHSPC)

A Phase III, 2-cohort, 2-arm, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of saruparib plus physician's choice of NHA (abiraterone, darolutamide, or enzalutamide) versus placebo plus physician's choice of NHA in participants with mCSPC

Eligibility criteria

- Aged ≥18 years
- Histologically confirmed mCSPC (*de novo* or recurrent low- or high-volume disease)
- ECOG PS 0–1
- Prospectively defined HRRm status*
- Must be receiving ADT throughout the study or have undergone bilateral orchiectomy, and must be suitable for treatment with NHAs
- No prior treatment with PARP inhibitors, CT, or NHAs in the metastatic setting†
- No suspected or prior history of myelodysplastic syndrome/acute myeloid leukemia



Treatment will continue until disease progression, unacceptable toxicity, or participant-initiated withdrawal

Select endpoints

HRRm cohort
- rPFS
- OS

Non-HRRm cohort
- rPFS
- OS

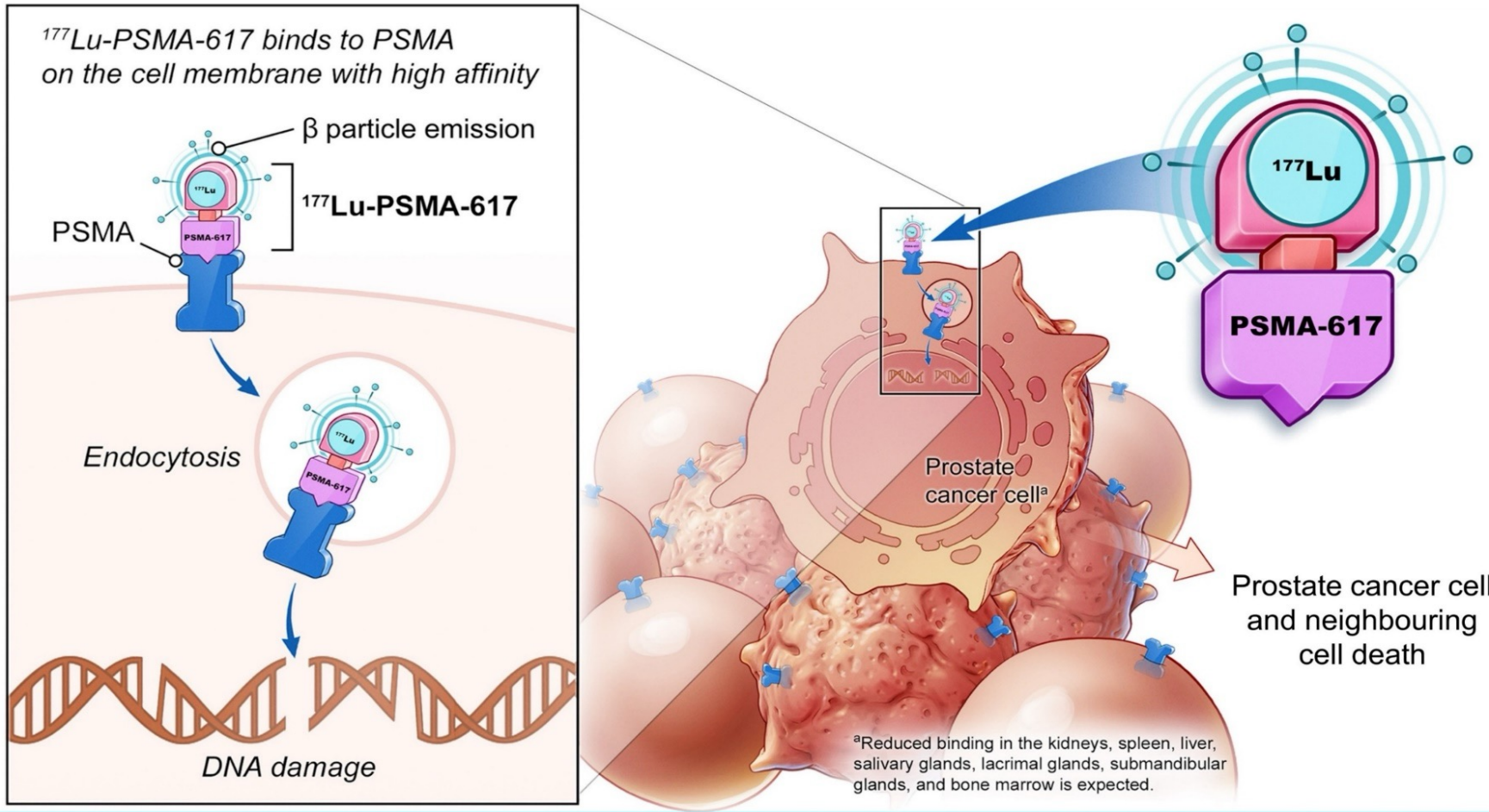
Statistical analyses

rPFS and OS will be tested for each cohort separately using a stratified log-rank test

www.clinicaltrials.gov: (NCT06120491)

Agarwal N. *et al*, **AUA** 2024;
Azad A et al, ASCO 2025

^{177}Lu-PSMA-617 Targeted Radioligand Therapy

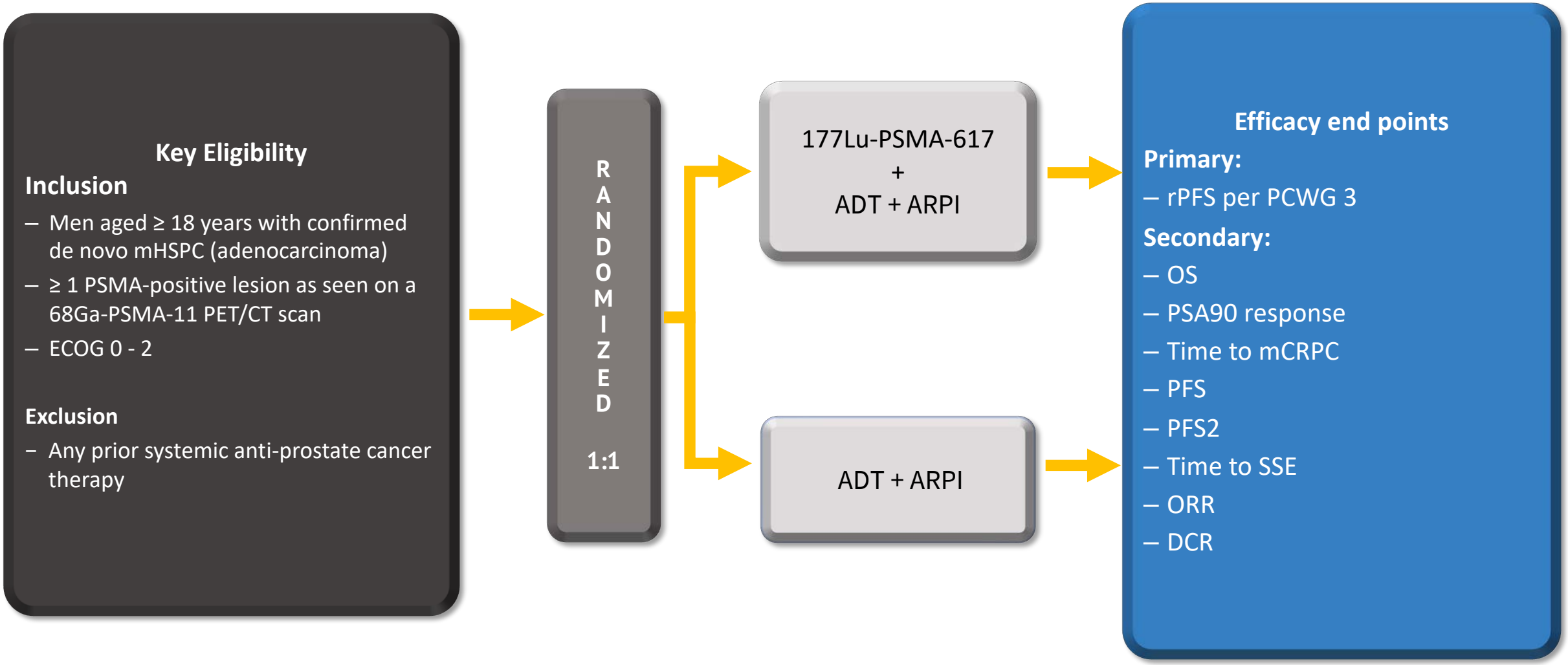


Phase 3 trials with Lu-177-PSMA-617

	VISION	PSMAfore
Patient Population	mCRPC with prior progression on ≥ 1 ARPI and 1 or 2 taxane regimens and PSMA positive disease	Taxane-naïve mCRPC with progression once on prior ARPI and PSMA positive disease
Design of the trial	2 : 1	1 : 1
Control Arm	Protocol-permitted SOC (not including chemotherapy, radium-223, immunotherapy, or investigational drugs)	ARPI change
Primary endpoints	rPFS (central review); OS	rPFS (central review)
Key secondary endpoints	Objective response and disease control (per RECIST v1.1); time to first symptomatic skeletal event	OS (prespecified crossover-adjusted analysis)
rPFS	**8.7 vs. 3.4 mo (HR 0.4, 99.2% CI 0.29 – 0.57, *p* < 0.001)**	**Primary analysis: 9.3 vs. 5.6 mo (HR 0.41, 95% CI 0.29 – 0.56) Updated 3rd analysis: 11·6 vs. 5·59 mo (HR 0·49 [95% CI 0·39-0·61]).**
OS	**15.3 vs. 11.3 mo (HR 0.62, 95% CI 0.52 – 0.74, *p* < 0.001)**	**24.5 vs. 23.1 mo (HR 0.91, 95% CI 0.72 – 1.14) (77.5% crossover)**

Sartor et al., ***NEJM***, 2021; Morris **Lancet,** 2024

Phase 3 PSMAddition Trial Design



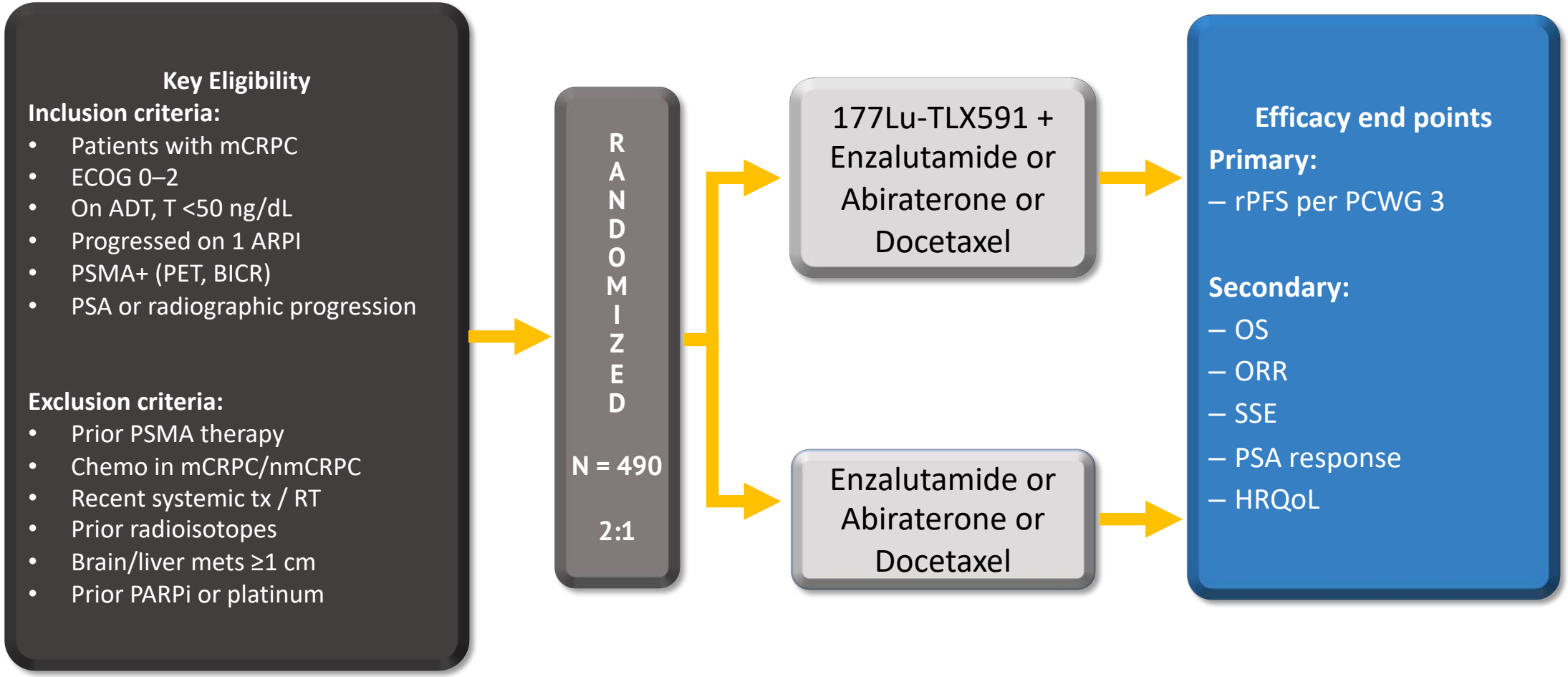
www.clinicaltrials.gov: NCT04720157

Phase 3 PSMAddition trial

	PSMAddition
NCT#	NCT04720157
Radioligand	177Lu-PSMA-617
Patient Population	Patients with PSMA-positive mHSPC, and who are either treatment-naïve or minimally treated with short-term hormone therapy or AR-targeted therapy
Number of patients	1144
Randomization	1:1
Treatment arm	177Lu-PSMA-617 + ADT + ARPI
Primary endpoints	rPFS
Key secondary endpoints	OS, PSA90, time to mCRPC, composite PFS, safety and tolerability, health-related quality of life
rPFS	**NR vs. NR HR 0.72 (0.58- 0.90), p = 0.002**
OS	**HR 0.84 (95% CI, 0.63–1.13) p = 0.125**

Tagawa S, ESMO 2025

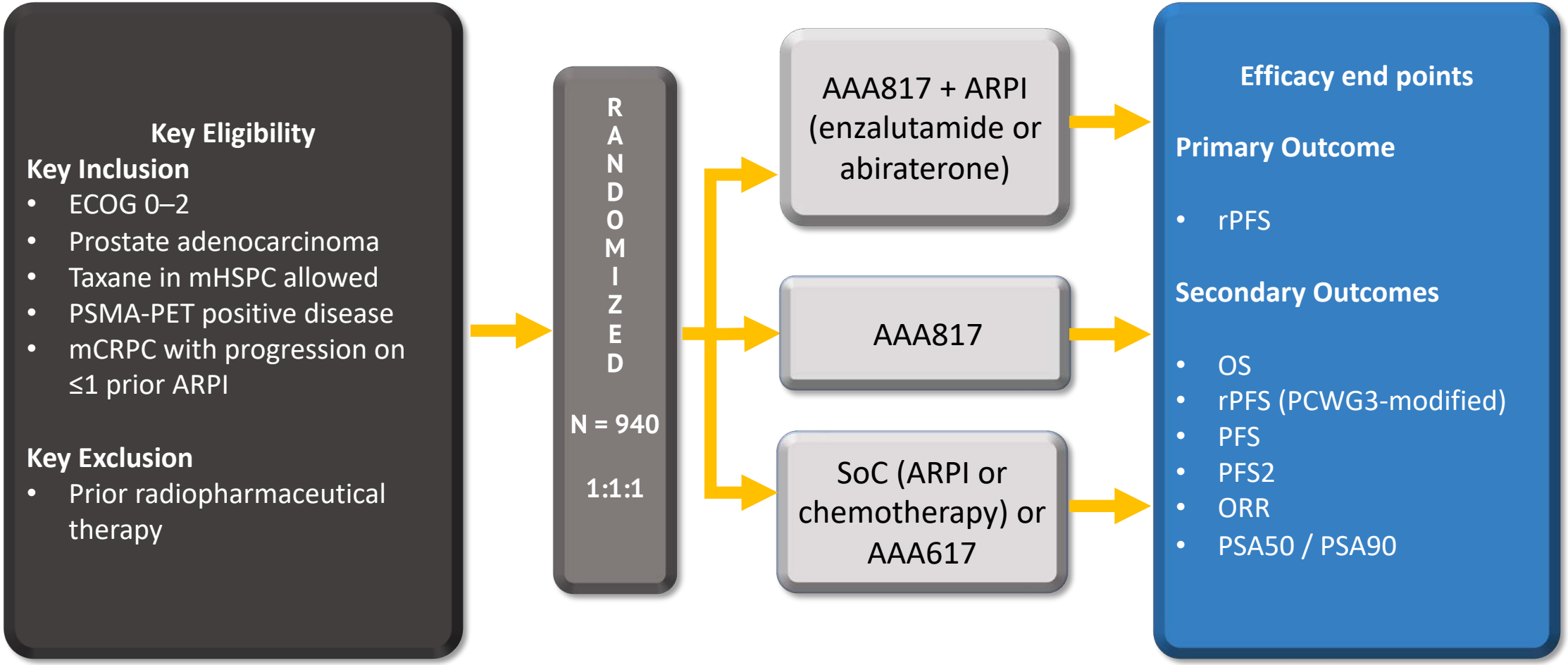
Phase 3 ProstACT Global: Lu-177-Rosopatamab Tetraxetan (Lu-TLX591) in mCRPC
(post ARPI mCRPC)



www.clinicaltrials.gov: NCT06520345

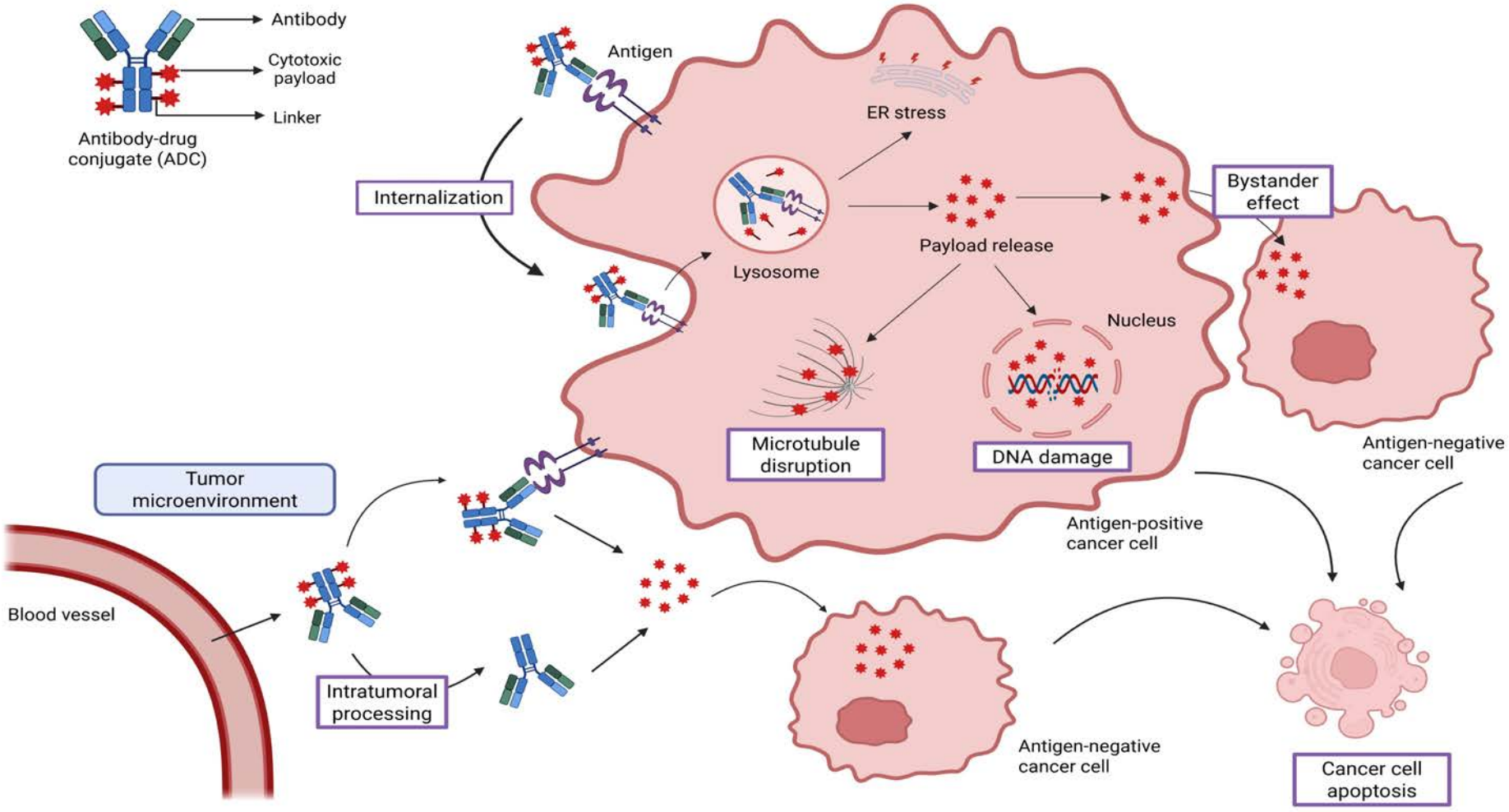
Tagawa..**Agarwal,** ASCO, 2025

Phase 3 AcTFirst: 225Ac-PSMA-617 (AAA817) + ARPI in PSMA-positive mCRPC
(post ARPI mCRPC)



www.clinicaltrials.gov: NCT06855277

Antibody Drug Conjugates: Mechanism of Action



Ozay ZI...**Agarwal N**. *Therapeutic Advances in Medical Oncology*, 2026

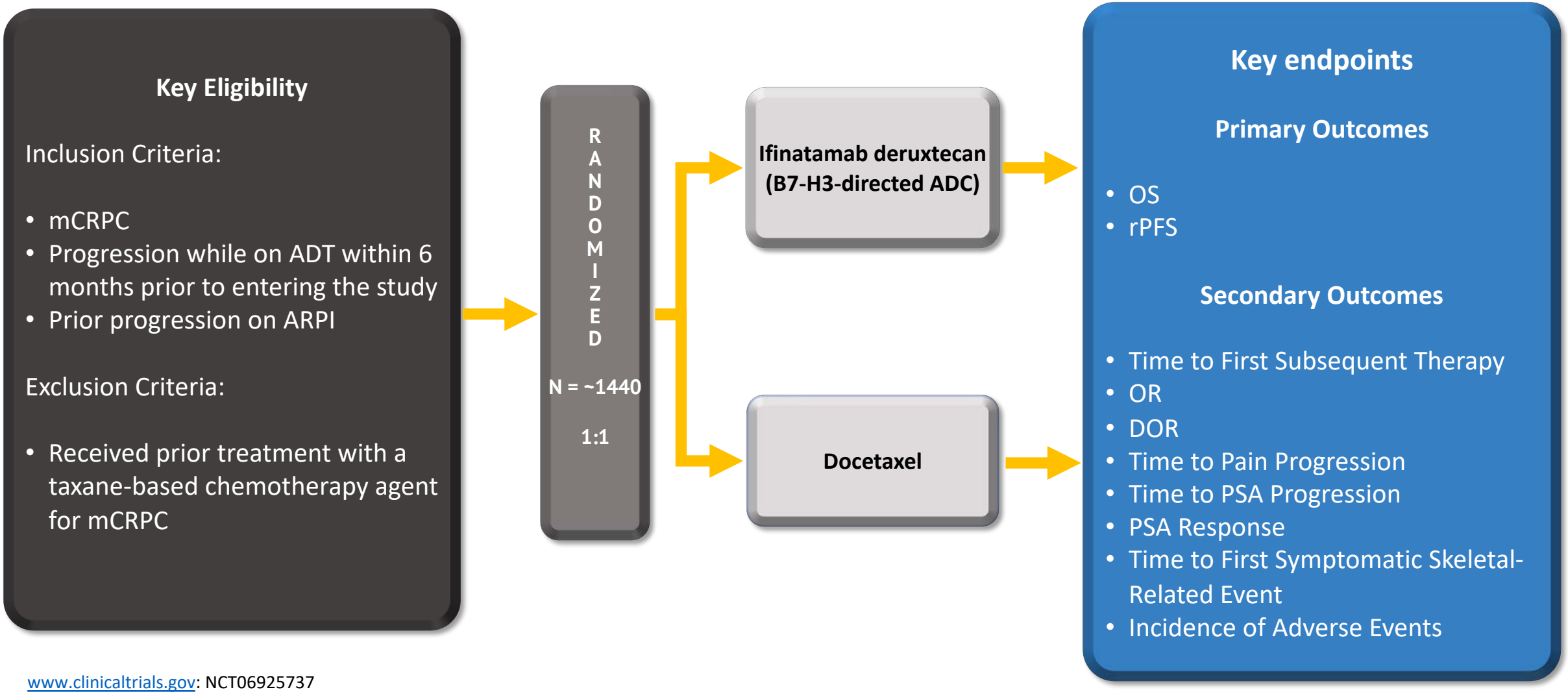
Phase I/II Prospective Studies of PSMA Targeting ADCs in Prostate Cancer

	MLN2704	PSMA-MMAE	MEDI3726	ARX517
NCT#	NCT00070837	NCT01414283	NCT02991911	NCT04662580
Patient population	mCRPC	mCRPC with prior progression on abiraterone and/or enzalutamide	mCRPC with prior progression on taxane-based CT and abiraterone and/or enzalutamide	mCRPC
Study design	Phase I / II	Phase II	Phase I / Ib	Phase I
Tumor antigen target	PSMA	PSMA	PSMA	PSMA
Payload	Maytansinoid-1 (DM-1)	Monomethyl auristatin E(MMAE)	Pyrrolobenzodiazepine	Amberstatin-269
Primary endpoint	DLT, MTD, PSA50	Antitumor activity, safety, tolerability	Safety, DLT, MTD	Safety, PK and clinical efficacy
No. of patients	62	119	33	24
Median number of prior lines of therapy, n (range)	-	-	4 (NA)	4 (NA)
Prior Taxane, n (%)	33 (53)	-	33 (100)	12 (50)
Prior ARPI, n (%)	-	119 (100)	33 (100)	24 (100)
PSA50 responses, n (%)	5 of 62 (8)	16 of 113 (14)	-	0 of 24 (33.3)
ORR, n (%)	0 of 27 (0)	-	0 of 33 (0)	2 of 7 (28.5)
Peripheral neuropathy, any G – G ≥ 3 (%)	71 – 10	NA – 7.6	-	-
Neutropenia, any G – G ≥ 3 (%)	-	NA – 31.4	-	-
Nausea, any G – G ≥ 3 (%)	61 - NA	NA – 2.5	21.2 - 0	-
Fatigue, any G – G ≥ 3 (%)	60 - NA	NA – 16.8	30.3 – 6.1	33.3 - 0
Reference	Milowsky et al., *Urologic Oncology*, 2016	Petrylak et al., *The Prostate*, 2020	de Bono et al., *Clinical Cancer Research*, 2021	Shen et al., ESMO 2023

Phase I/II Prospective Studies of ADCs in Prostate Cancer (non-PSMA targets)

	DSTP3086S	Sacituzumab govitecan	FOR46	Ifinatamab Deruxtecan/DS-7300a	DB 1311/BNT324
NCT#	NCT01283373	NCT03725761	NCT03575819	NCT04145622	NCT05914116
Patient population	mCRPC	mCRPC with prior progression on ARPI	mCRPC previously treated with an ARPI but chemotherapy-naïve in the mCRPC setting	mCRPC	Advanced/metastatic solid tumors (including mCPRC)
Study design	Phase I	Phase II	Phase I	Phase I/II	Phase I / II
Tumor antigen target	STEAP-1	TROP-2	CD46	B7-H3	B7-H3
Payload	Monomethyl auristatin E	SN-38	Monomethyl auristatin E	DNA topoisomerase I	DNA topoisomerase 1
Primary endpoint	Safety, RP2D	PSA response rate	MTD	Safety and tolerability	ORR
No. of patients	77	30	56	29	73 (patients with mCRPC)
Median number of prior lines of therapy, n (range)	-	-	5 (2 – 14)	Part 1 (dose-escalation): Median 6.0 prior lines of therapy (range 2–10) Part 2 (dose-expansion): Median 5.0 prior lines of therapy (range 3–10)	4 (1 – 14)
Prior taxane, n (%)	Docetaxel: 43 (56) Cabazitaxel: 8 (10)	6 (30) in mHSPC	0 (0)	-	Docetaxel: 68 (93.2) Cabazitaxel: 29 (39.7)
Prior ARPI, n (%)	Abiraterone: 52 (68) Enzalutamide: 35 (45)	20 (100)	56 (100)	-	70 (95.9)
PSA50 response, n (%)	11 of 77 (14.3)	0 (0)	14 of 39 (36)	-	-
ORR, n (%)	1 of 46 (2.7)	-	5 of 25 (20)	6 of 29 (20.7)	22 of 52 (42.3)
Median rPFS, months (95% CI)	-	-	8.7 (NA)	5.5 (5.3 – NR)	NE (5.7 – NE)
Peripheral neuropathy, any G – G ≥ 3 (%)	51 – 4	-	32.1 - NA	-	-
Neutropenia, any G – G ≥ 3 (%)	-	85 - NA	41.1 - NA	-	13.2 – 7.9
Nausea, any G – G ≥ 3 (%)	38 – 1	-	-	-	44.7 - 0
Fatigue, any G – G ≥ 3 (%)	56 – 4	-	-	-	21.1 - 0
References	Danila et al., ASCO 2019	Lang et al., ESMO 2024	Aggarwal et al., *Journal of Clinical Oncology*, 2025	Patel MR, et al., ASCO 2022	Parsonson et al., ASCO 2025

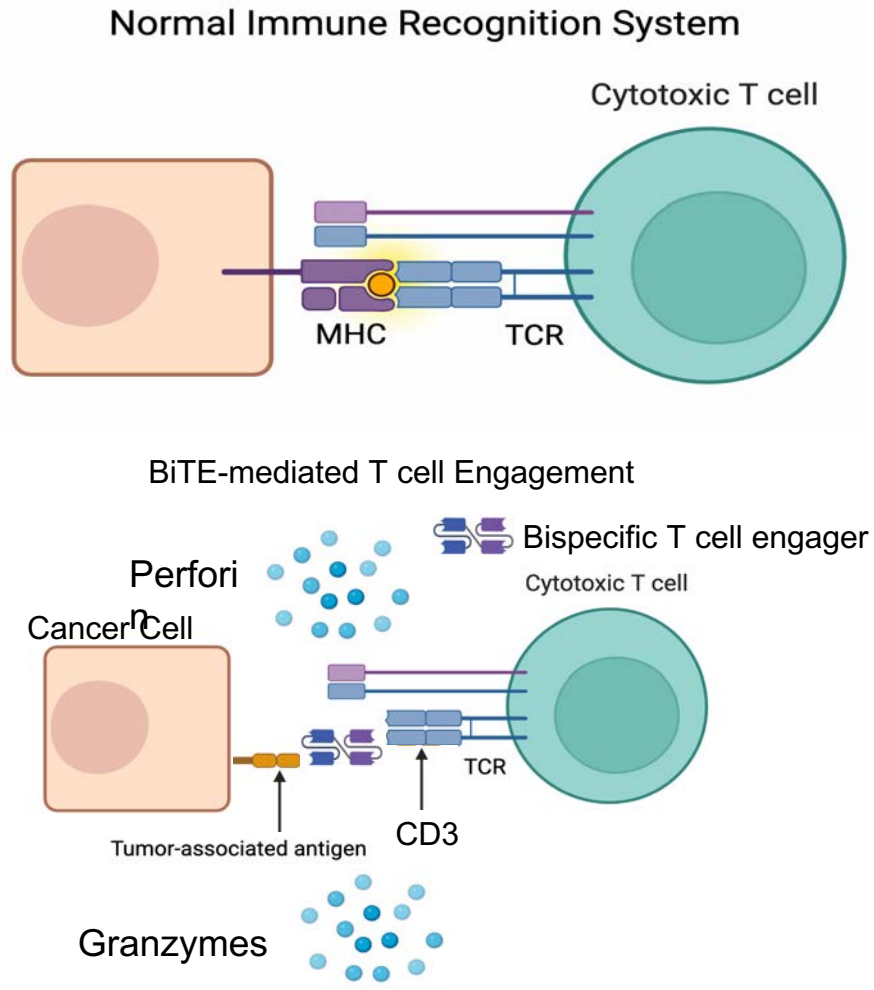
Phase 3 IDeate-Prostate01 trial: B7-H3-directed ADC vs Docetaxel



www.clinicaltrials.gov: NCT06925737

T-cell Engagers: Mechanism of Action

- MHC-TCR engagement (and co-stimulation) is required for T-cell stimulation in normal circumstances
- MHC expression is downregulated in cancer cells
- TCEs bypass the steps needed for MHC-TCR-dependent T-cell activation
- TCEs engage both CD3 on T-cells and a tumor-associated antigen on cancer cells, leading to T-cell mediated killing of cancer cells



MHC, Major Histocompatibility Complex; TCR, T-Cell Receptor

Hage Chehade C…Agarwal N, ***EU***, 2025

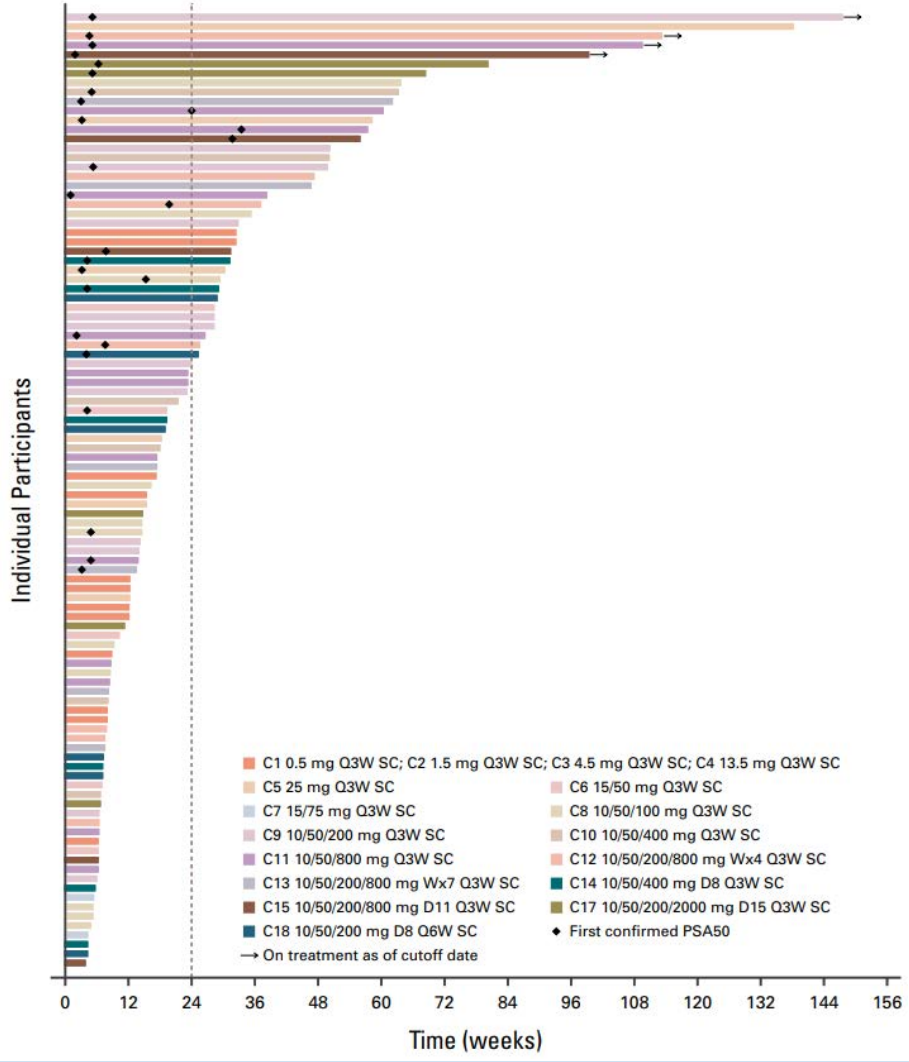
Bispecific T-Cell Engagers in Prostate Cancer

	Pasotuxizumab	JNJ-63898081	AMG 160	LAVA-1207	Xaluritamig	Tarlatamab	Pasritamig
Patient Population	mCRPC with prior progression on ≥ 1 taxane and abiraterone and/or enzalutamide	mCRPC with prior progression on taxane or ARPI	mCRPC with prior progression on 1 to 2 taxane-based regimens and ARPI	Treatment refractory mCRPC	mCRPC with prior progression on ARPI and 1 – 2 taxane regimens	Metastatic de novo or treatment-emergent NEPC with prior progression on ≥ 1 platinum CT or ARPI	mCRPC with prior receipt of ARPI and/or chemotherapy
Study Design	Phase 1 Dose escalation	Phase 1 Dose escalation + dose expansion	Phase 1 Dose escalation + dose expansion	Phase 1/2a Dose escalation + dose expansion	Phase 1 Dose escalation	Phase 1b Dose expansion	Phase 1 Dose escalation + dose expansion
Tumor Antigen Target	PSMA	PSMA	PSMA	PSMA	STEAP-1	DLL3	KLK2
Primary Endpoint	Safety, MTD	Safety, anti-tumor response	Safety, MTD, RP2D	Safety, RP2D	Safety, MTD, RP2D	Safety	Safety, RP2D
No. of Patients	47	39	133	20	97	40	174
Visceral Metastases, n (%)	-	-	22 (16.5)	-	51 (53)	-	42 (24.3)
Median number of prior lines of therapy, n (range)	-	-	-	4 (3 – 10)	4 (1 – 9)	3 (2 – 4)	4 (1 – 13)
Prior Taxane, n (%)	-	30 (76.9)	128 (96.2)	-	82 (85)	-	136 (78.2)
Prior ARPI, n (%)	-	38 (97.4)	132 (99.2)	-	96 (99)	-	173 (99.4)
PSA50 Responses, n (%)	12 of 39 (30.7)	2 of 26 (7.7)	42 of 133 (31.6)	-	43 of 87 (49)	-	14 of 33 (42.4)
ORR, n (%)	0 of 18 (0)	0 of 23 (0)	7 of 59 (10.6)	0	16 of 67 (24)	4 of 38 (10.5) in all pts, 4 of 18 (22.2) in DLL3+ pts	7 of 84 (8.3)
Median rPFS, months (95% CI)	-	-	3.8 (3.5 – 4.9)	-	-	2.1 for all pts, 3.7 for DLL3+ pts	7.9 (2.9 – NE)
Antidrug antibodies, n (%)	30 of 31 (96.7%) in SC cohort 0 of 16 (0) in IV cohort	17 of 27 (63%) in SC cohort 2 of 12 (16.7%) in IV cohort	30 of 81 (37%) in dose escalation 29 of 53 (55%) in dose expansion	-	49 of 90 (54%)	-	-
CRS, any G – G ≥ 3 (%)	6 – 2.1	66.7 – 0	97.7 – 20.3	~ 10 - 0	72 – 2	75 – 2.5	8.9 - 0
Fatigue, any G – G ≥ 3 (%)	34 – 2.1	41 – 0	53.2 – 23.4% of dose exploration cohort (n = 77)	~ 45 - 0	45 – 11	-	15 - 0

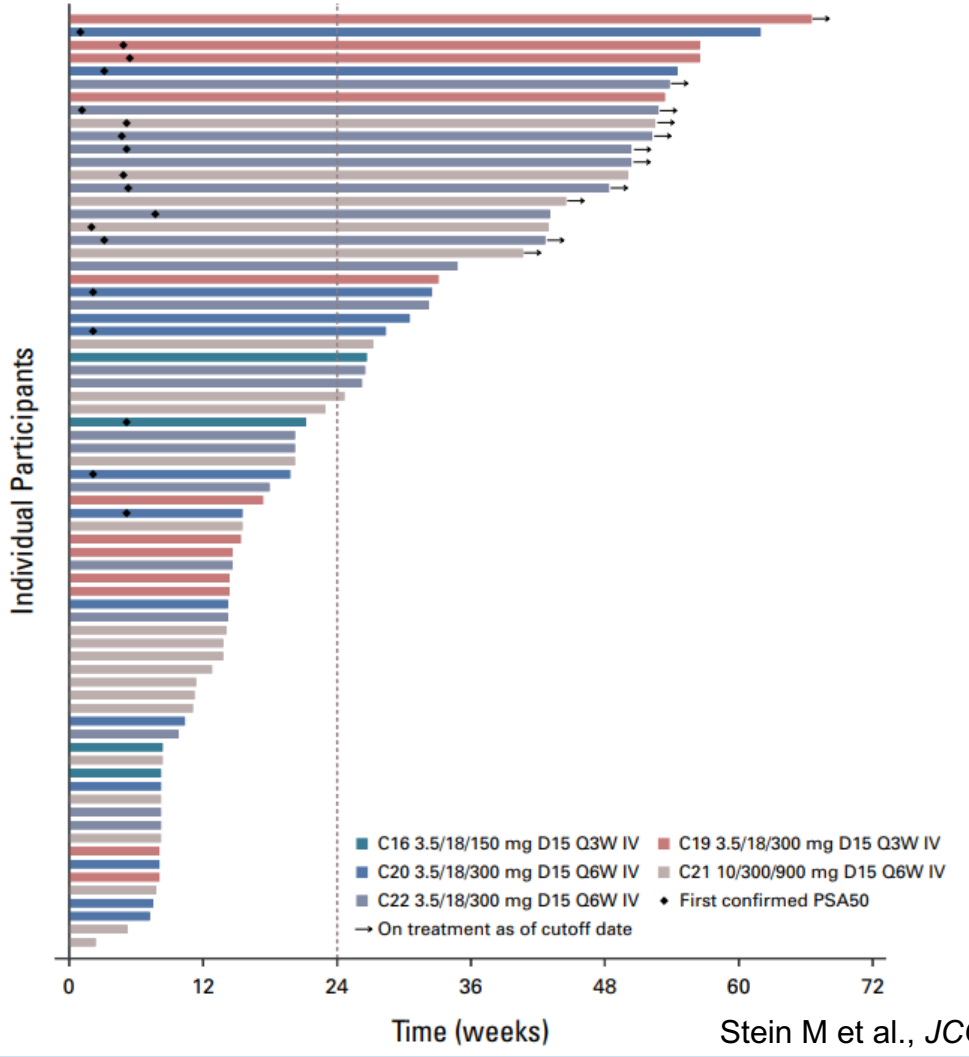
Hummel H et al., ***Immunotherapy***, 2020; Lim E et al., ***CGUC***, 2023; Dorff T et al., ***CCR***, 2024; Mehra N et al., ***ASCO 2023***; Kelly W et al., ***Cancer Discovery***, 2023; Aggarwal R et al., ***ASCO 2024; Baldini et al., ASCO 2025***
Hage Chehade C…Agarwal N, ***EU***, 2025

PSA Response with Pasritamig in mCRPC (phase 1 study)

PSA response in patients treated by SC administration

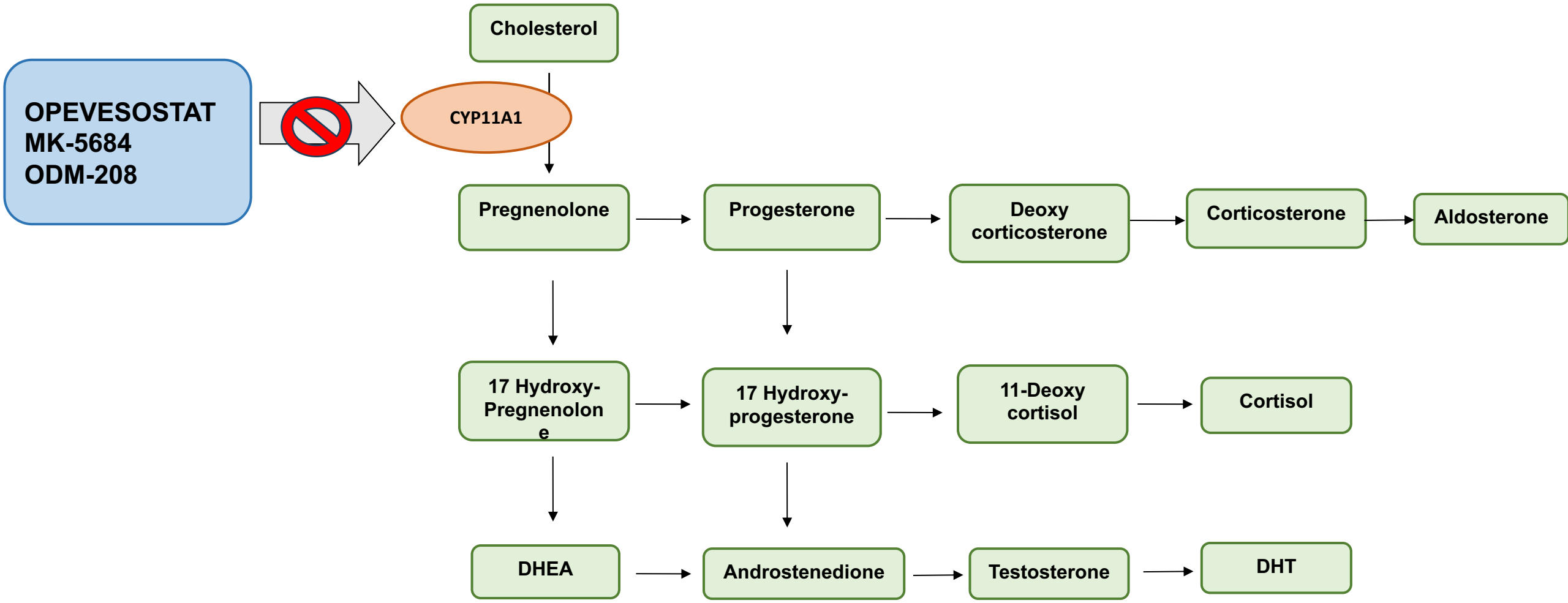


PSA response in patients treated by IV administration



Stein M et al., *JCO*, 2025

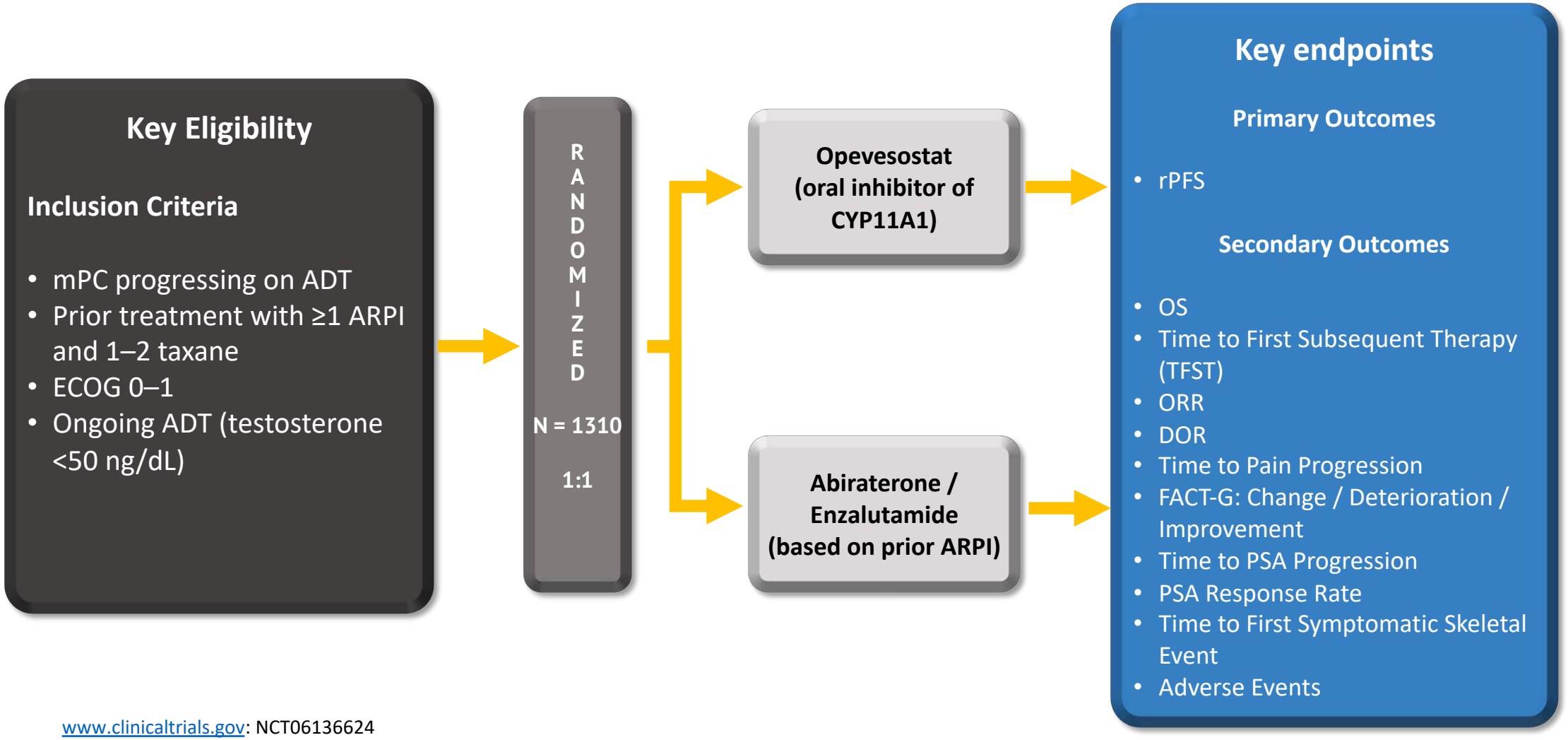
Mechanism of Action of Opevesostat (CYP11A1 inhibitor)



Adapted from Agarwal N, *Future Oncology*, 2010

Phase 3 OMAHA-003: Opevesostat (CYP11A1 inhibitor) in mCRPC

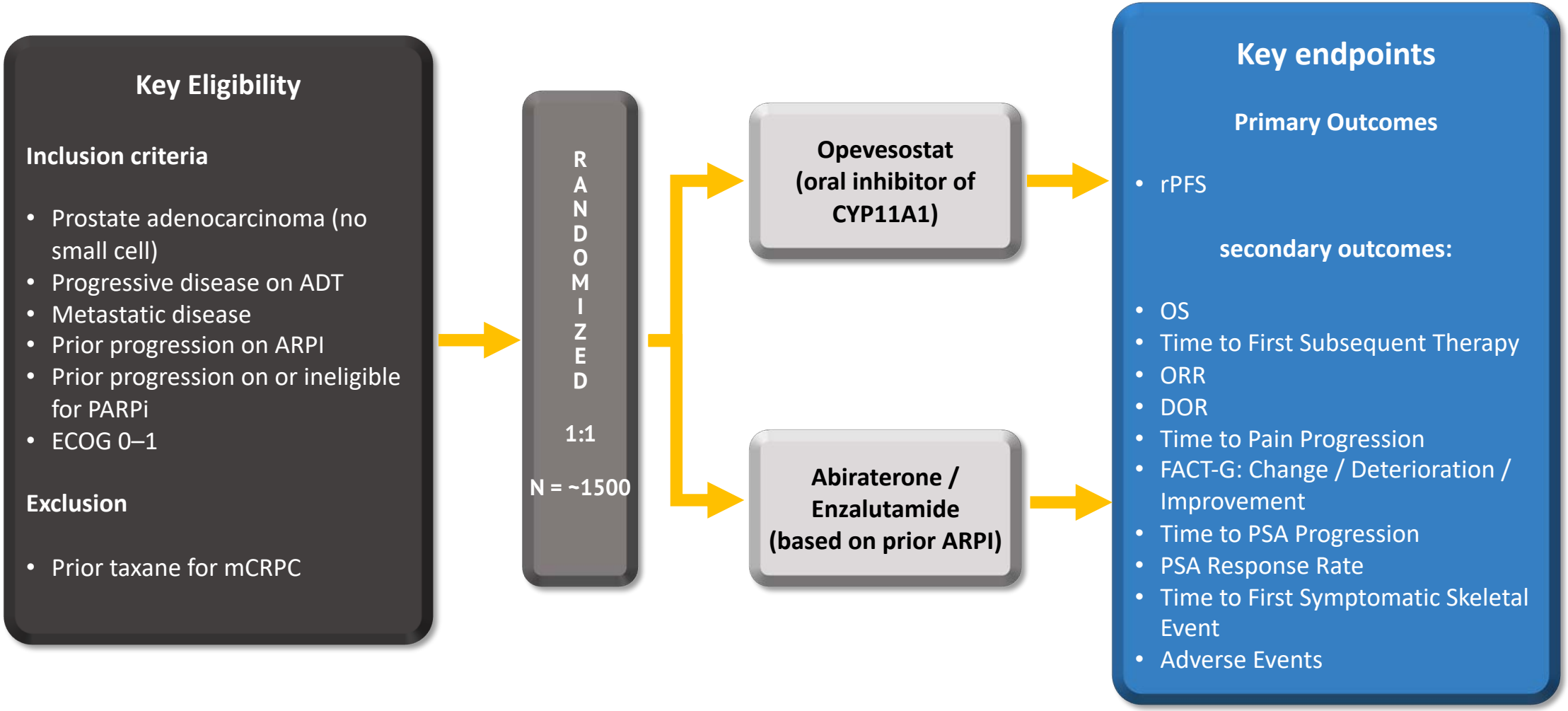
(post prior ARPI and taxane in mCRPC)



www.clinicaltrials.gov: NCT06136624

Yu E..Antonarakis E. 2025 ASCO GU symposium.

Phase 3 OMAHA-004: Opevesostat (CYP11A1 inhibitor) in mCRPC
(post prior ARPI in mCRPC)



www.clinicaltrials.gov: NCT06136650

Gratzke C..Fizazi K. 2025 ASCO GU symposium.

Conclusions

- ***Treatment of metastatic prostate cancer has undergone a revolution in the last decade leading to approval of multiple novel agents, and more coming soon***
- ***However, disease eventually progresses and remains lethal***
- ***Identification of new molecular targets and biomarkers of response remains critical to improve our patients' lives***

QUESTIONS?

We are taking a short break!

The program will resume at 1:15 PM ET

Up Next…

Drs Anthony M Hunter and Abdulraheem Yacoub discuss the management of myelofibrosis and systemic mastocytosis

RTP
RESEARCH
TO PRACTICE