Fourth Annual
National General Medical Oncology Summit

Saturday, March 1, 2025

Moderator

Neil Love, MD

Faculty

Rahul Aggarwal, MD
Aditya Bardia, MD, MPH
Mitesh J Borad, MD
Virginia F Borges, MD, MMSc
Harold J Burstein, MD, PhD
Rashmi Chugh, MD
Christopher Flowers, MD, MS
Jonathan Goldman, MD
Nicole Lamanna, MD
Natasha B Leighl, MD, MMSc
Amit Mahipal, MD, MPH
William K Oh, MD
David M O'Malley, MD
Joyce O'Shaughnessy, MD
Krish Patel, MD
Richard F Riedel, MD
Kerry A Rogers, MD
Simron Singh, MD, MPH
Brian M Slomovitz, MD
Jonathan Strosberg, MD

Fourth Annual National General Medical Oncology Summit

Module 5: EGFR Mutation-Positive Non-Small Cell Lung Cancer

Current Management of Nonmetastatic and Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) — Dr Leighl

Promising Novel Agents in Clinical Development; EGFR Exon 20 Mutation-Positive NSCLC — Dr Goldman

Module 5: EGFR Mutation-Positive Non-Small Cell Lung Cancer

Current Management of Nonmetastatic and Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) — Dr Leighl

Promising Novel Agents in Clinical Development; EGFR Exon 20 Mutation-Positive NSCLC — Dr Goldman

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

Natasha Leighl MD MMSc FRCPC FASCO
Professor of Medicine, University of Toronto
Lung Medical Oncology Site Lead,
OSI Pharmaceuticals Foundation Chair
Princess Margaret Cancer Centre, Toronto, Canada

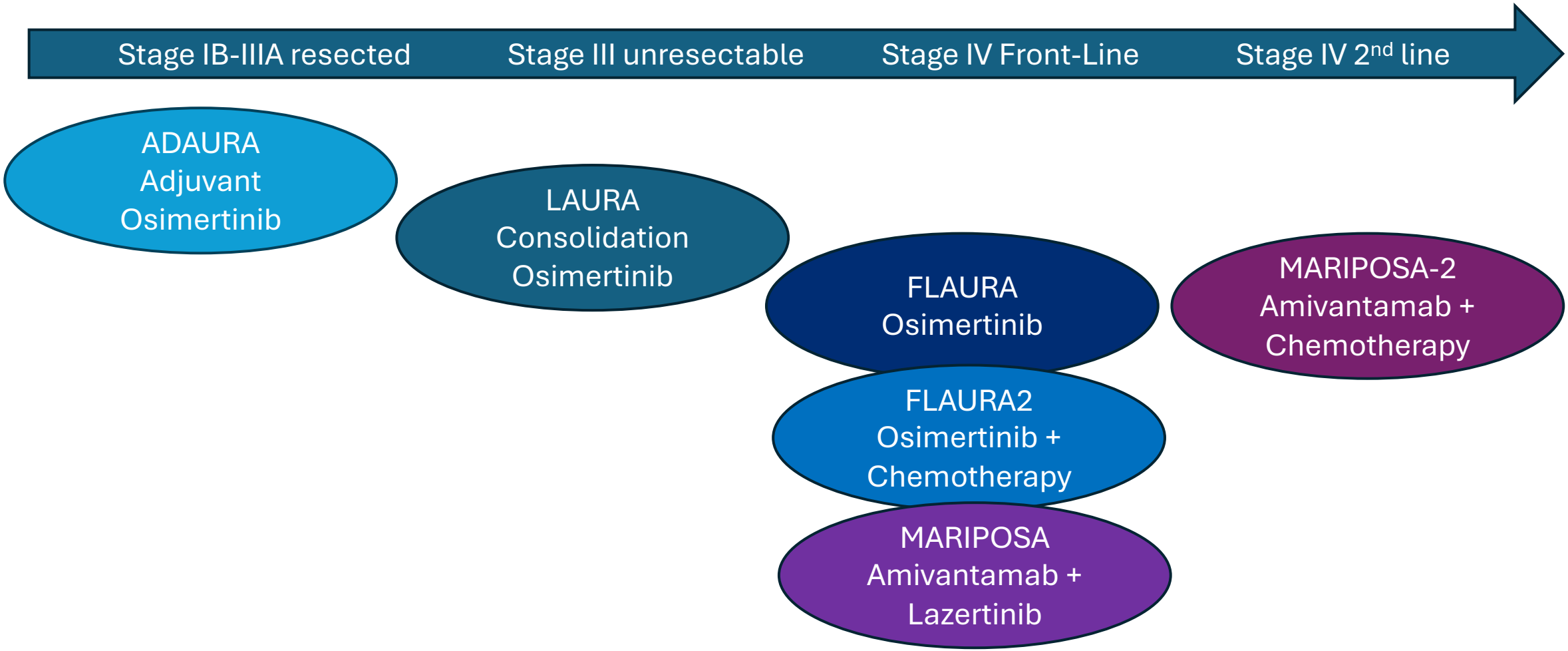
UHN Canada's #1 Hospital

TEMERTY FACULTY OF MEDICINE
UNIVERSITY OF TORONTO

Disclosures

No relevant conflicts of interest to disclose.

EGFR-directed therapy now appropriate across stages



ADAURA: adjuvant osimertinib x 3 years in patients with resected stage IB (≥3 cm, high risk)-IIIA EGFR-mutated lung cancer

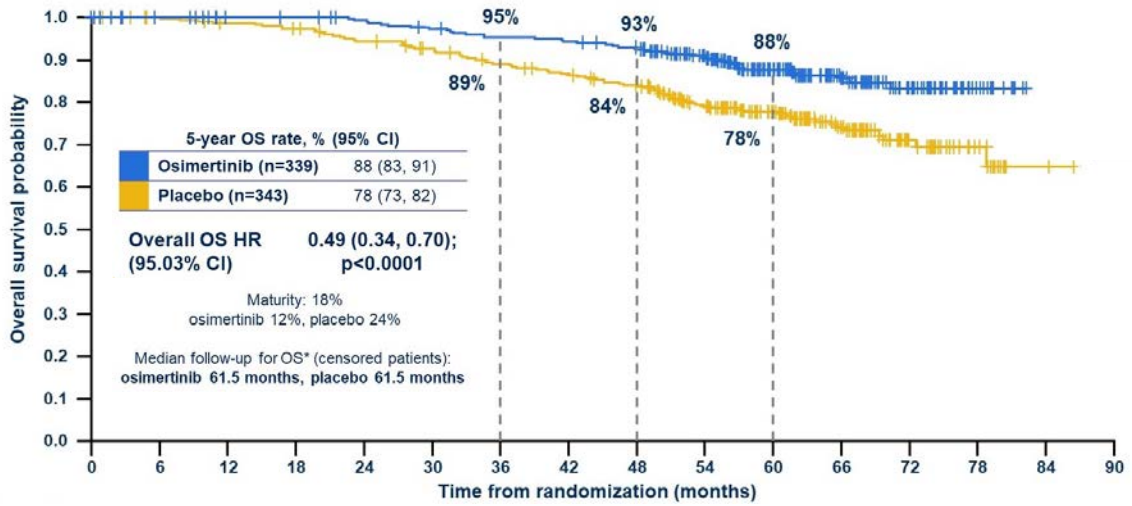
Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Maximum interval between surgery and randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
Stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
Race (Asian vs non-Asian)

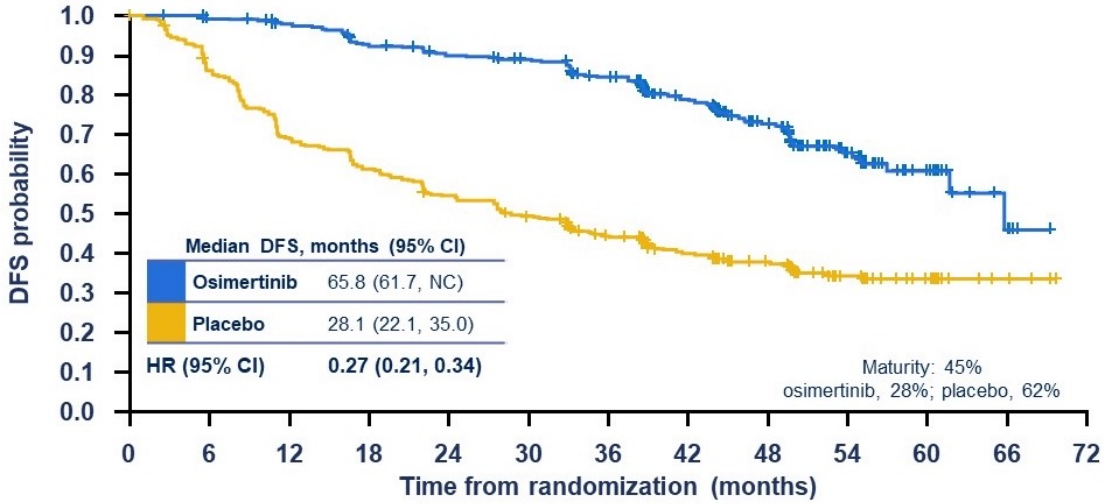
Randomization 1:1 (N=682)

- **Osimertinib 80 mg, once daily**
- **Placebo, once daily**



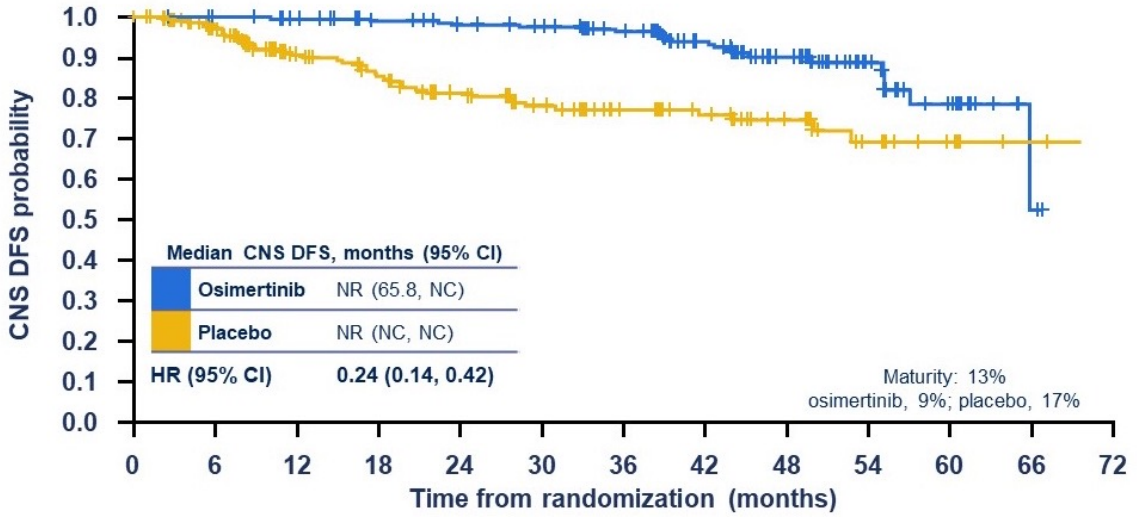
ADAURA updated DFS analysis[3,4] (stage IB–IIIA)†

JCO January 2023



ADAURA updated CNS DFS analysis[5,6] (stage II–IIIA)

JCO January 2023

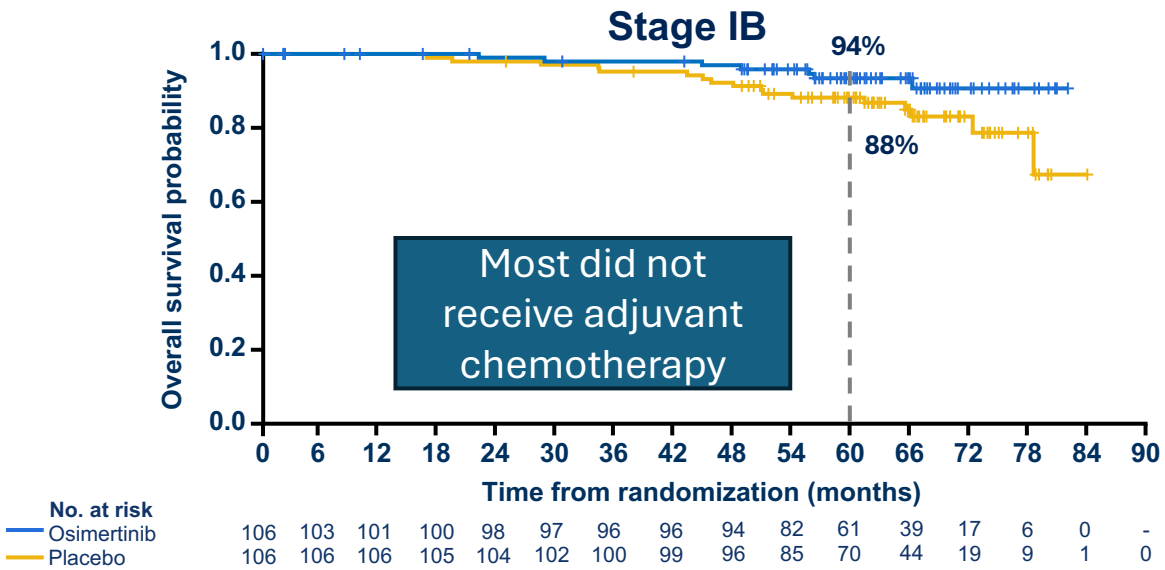


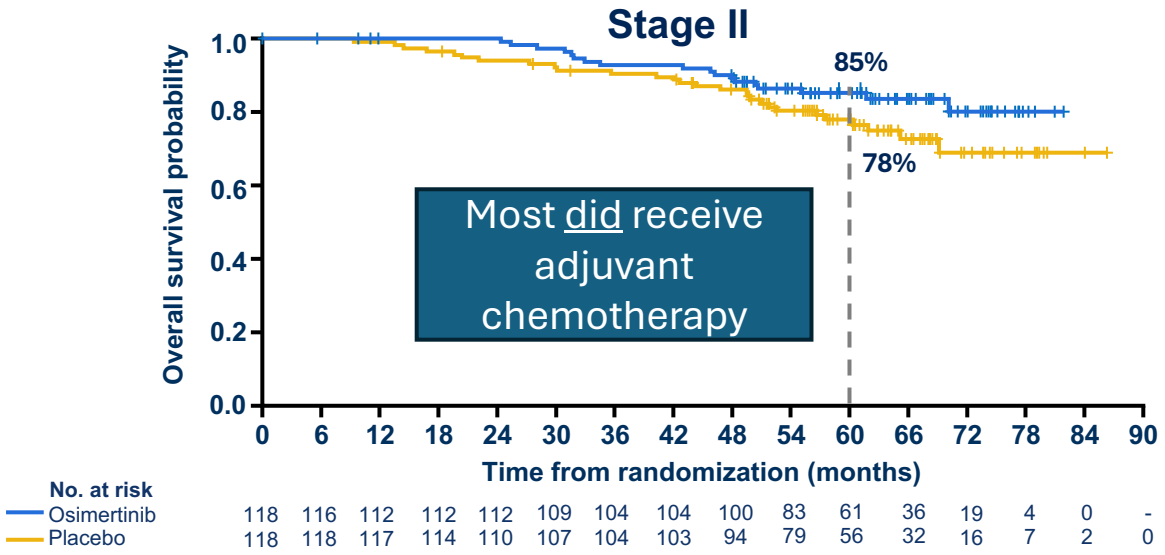
Herbst RS et al. ASCO 2023

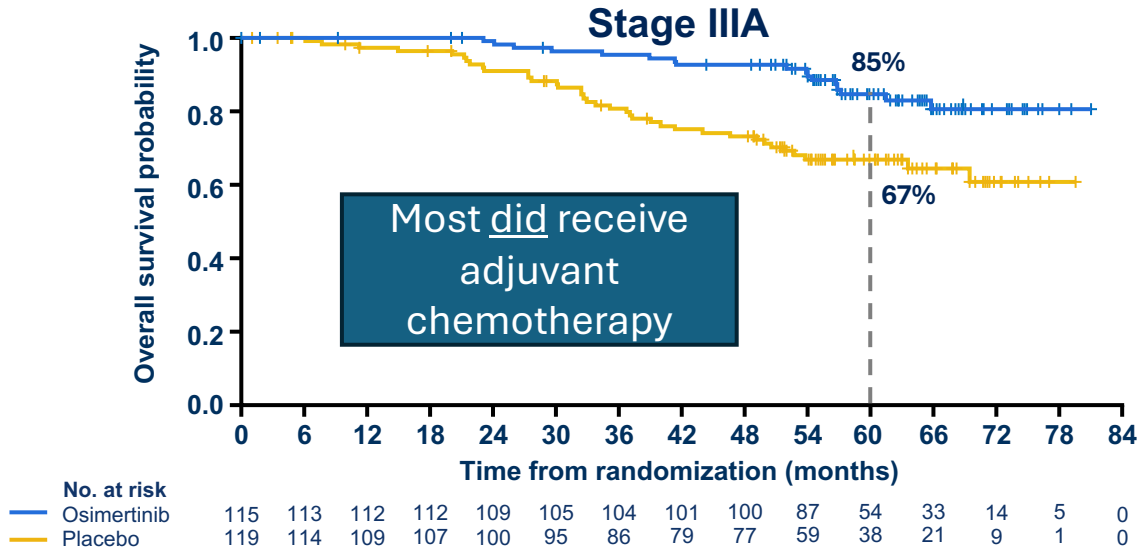
Overall survival by stage – can we omit chemotherapy in stage II-III? No…

Among Patients with Stage II-III NSCLC

Treatment	5 year OS
No Chemotherapy/placebo	66%
Chemotherapy/placebo	75%
No Chemotherapy/ 3 yrs osimertinib	80%
Chemotherapy/3 yrs osimertinib	87%







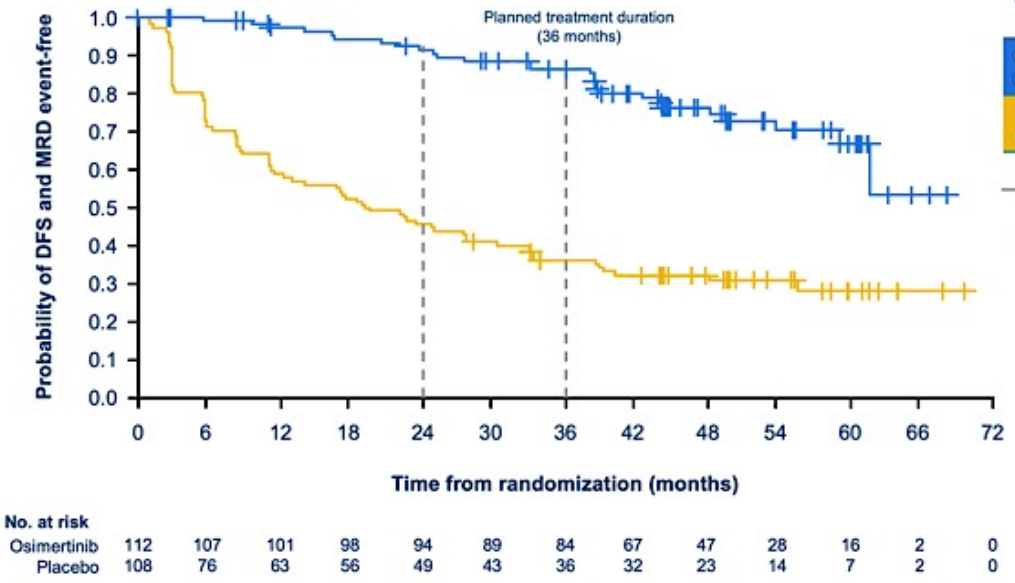
Data cut-off: January 27, 2023. Tick marks indicate censored data.
CI, confidence interval; HR, hazard ratio; OS, overall survival

Herbst RS et al. ASCO 2023

@ASCO2024: ADAURA MRD analysis - ctDNA unable to identify population for de-escalation but associated with DFS

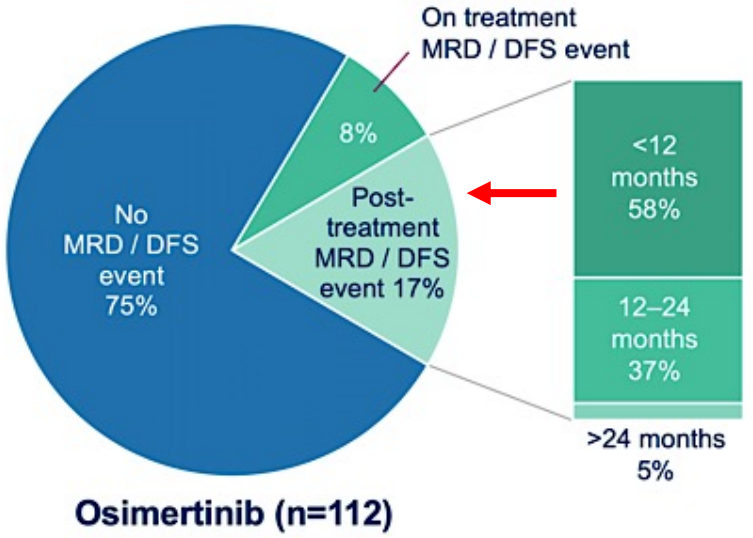
- 8% MRD post op; lead time to recurrence ~5 months

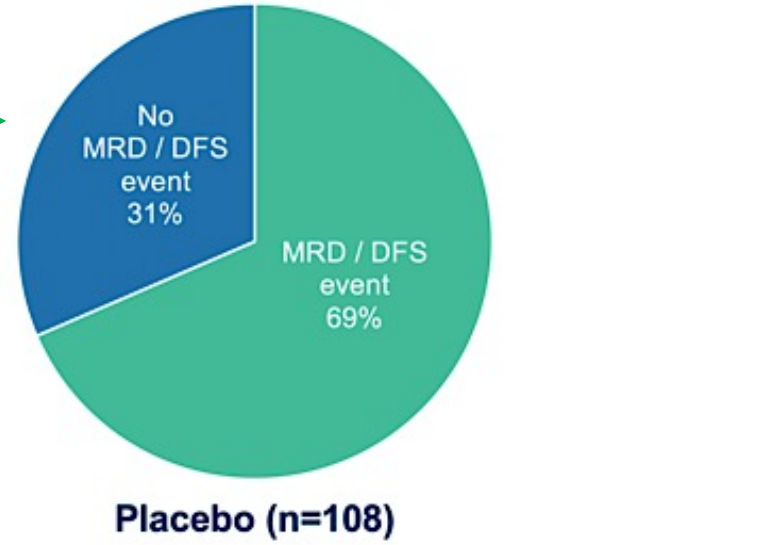
Patients receiving osimertinib were more likely to be DFS and MRD event-free* vs. placebo



% (95% CI)	DFS and MRD event-free rate	
	24 months	36 months
Osimertinib (n=112)	91 (84, 95)	86 (78, 92)
Placebo (n=108)	46 (36, 55)	36 (27, 45)
HR (95% CI) 0.23 (0.15, 0.36)†		

Median follow-up time, months (95% CI):
osimertinib 44.2 (42.4, 49.1), placebo 19.1 (11.1, 28.3





John T et al ASCO 2024

LAURA Phase 3 double-blind study design

Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT† treatment

Key inclusion criteria:
- ≥18 years (Japan: ≥20)
- WHO PS 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Maximum interval between last dose of CRT and randomization: 6 weeks

Osimertinib 80 mg, once daily

Randomization 2:1 (N=216)

Stratification by:
Concurrent vs sequential CRT
Stage IIIA vs stage IIIB/IIIC
China vs non-China

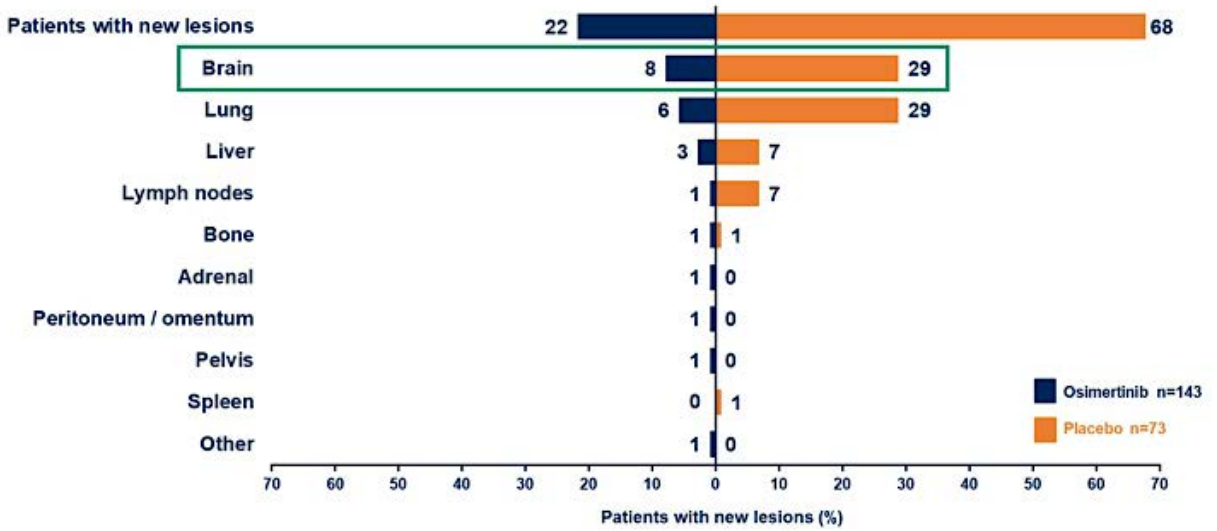
Placebo, once daily

Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria

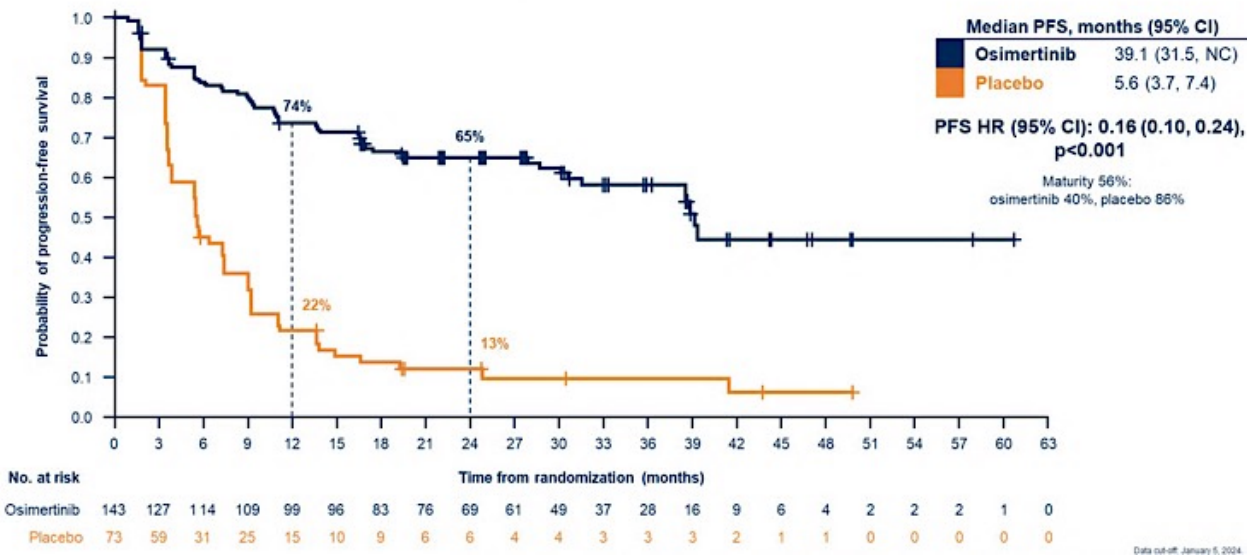
Open-label osimertinib after BICR-confirmed progression offered to both treatment arms§

Tumor assessments:
- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

Sites of new lesions by BICR

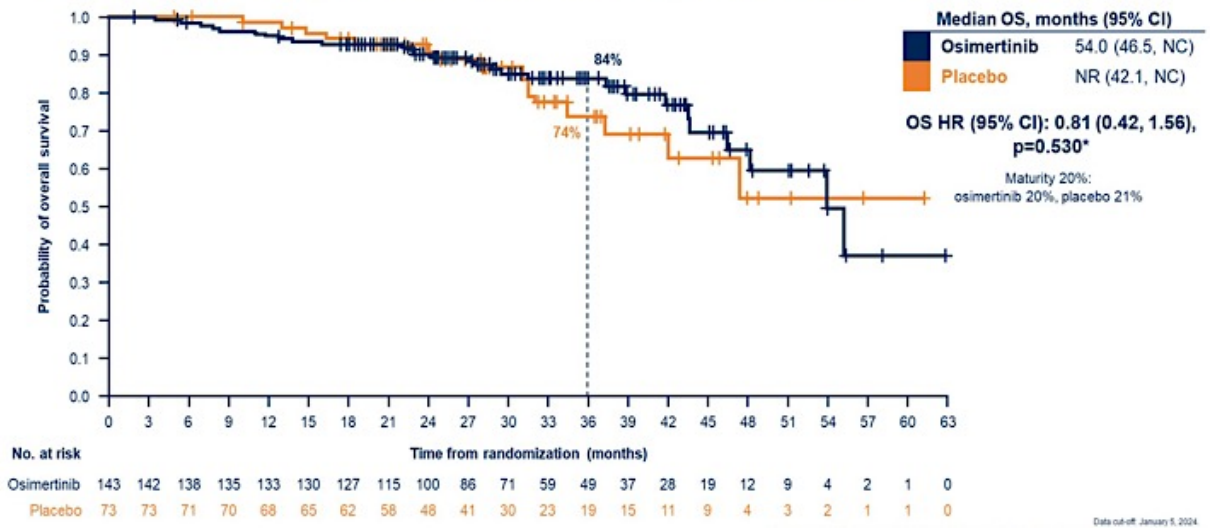


Progression-free survival by BICR



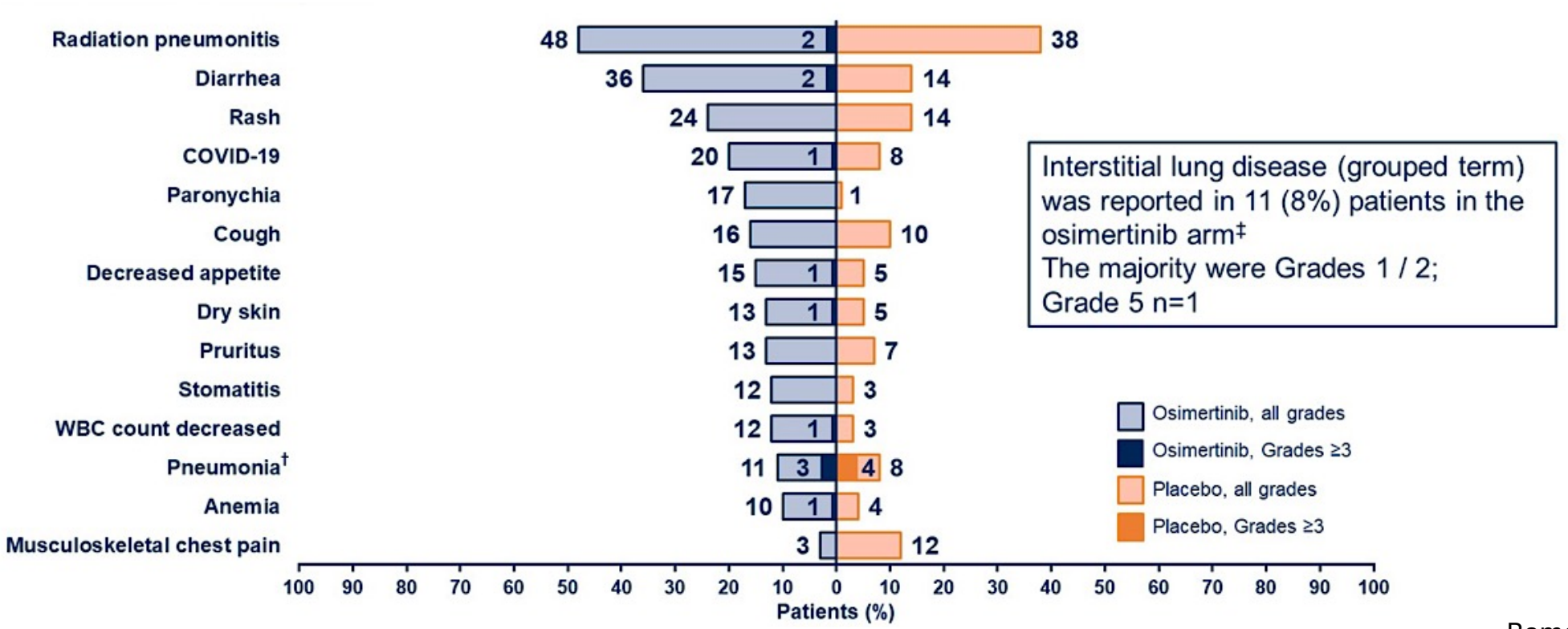
Interim analysis of overall survival

- In the placebo arm, 81% of patients with BICR-confirmed progression crossed over to osimertinib



Ramalingam et al ASCO 2024; Lu et al NEJM 2024

		Osimertinib (n=143)	Placebo (n=73)
Median duration of exposure, months*	Total	24.0	8.3
	Actual	23.7	7.9
AE, any cause,† n (%)			
Any AE		140 (98)	64 (88)
Any AE Grade ≥3		50 (35)	9 (12)
Any AE leading to death		3 (2)	2 (3)
Any serious AE		55 (38)	11 (15)
Any AE leading to discontinuation		18 (13)	4 (5)
Any AE leading to dose reduction		12 (8)	1 (1)
Any AE leading to dose interruption		80 (56)	18 (25)



Interstitial lung disease (grouped term) was reported in 11 (8%) patients in the osimertinib arm‡
The majority were Grades 1 / 2;
Grade 5 n=1

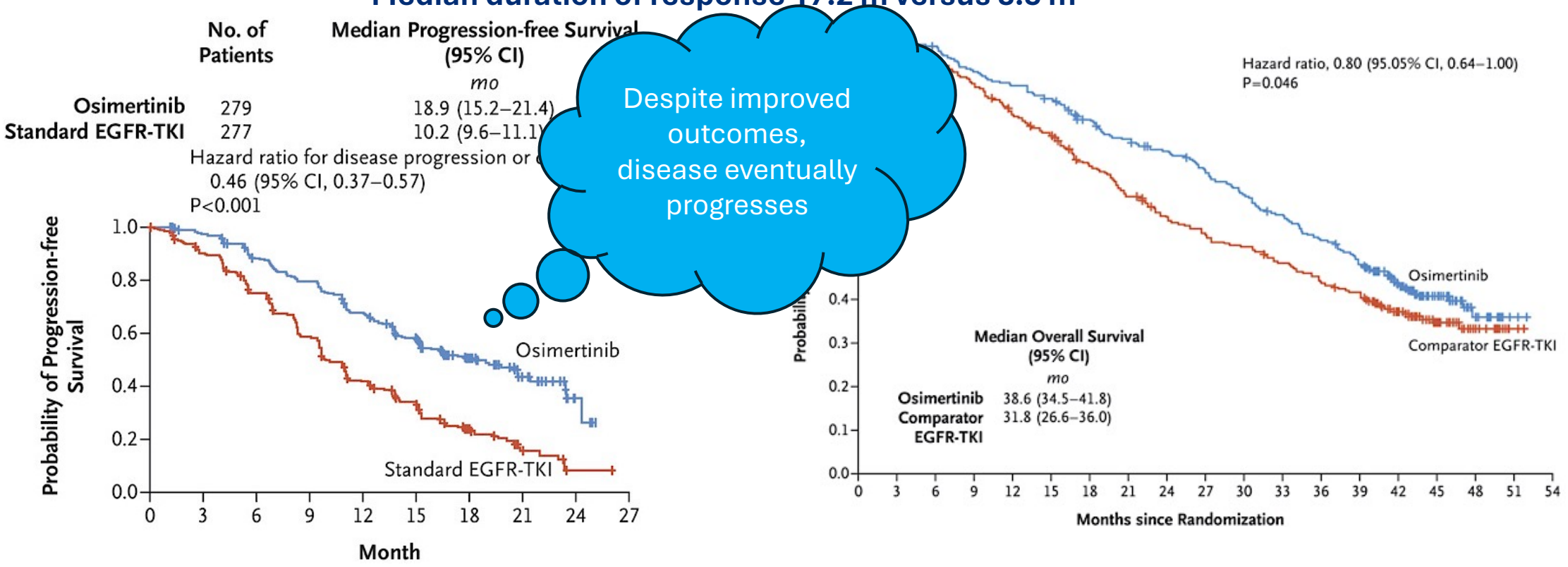
Ramalingam et al ASCO 2024

FLAURA: Osimertinib first-line in patients with advanced *EGFR* ex19del/L858R mutant lung cancer

Improved OS, CNS PFS, PFS versus erlotinib/gefitinib

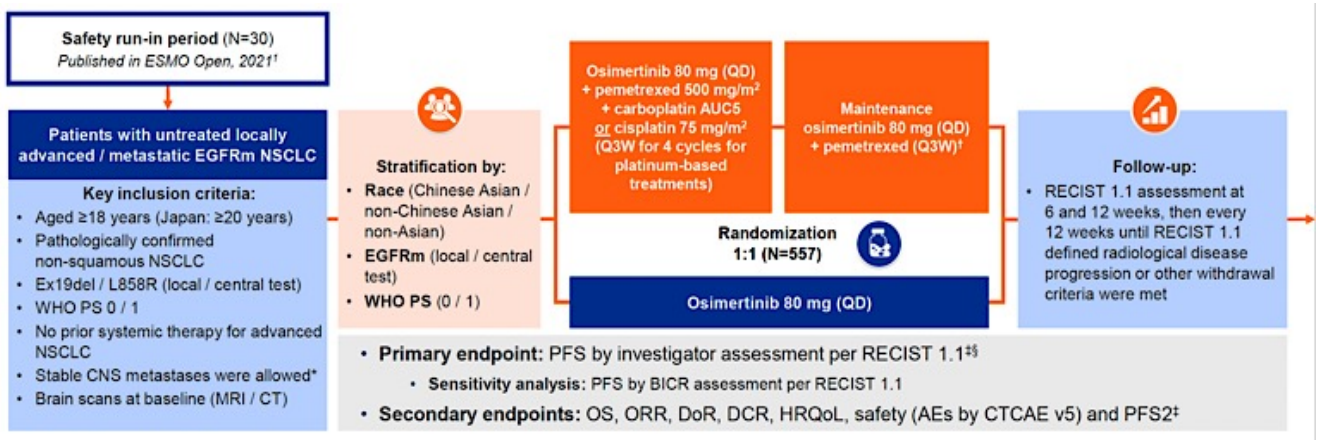
ORR 80% versus 76%

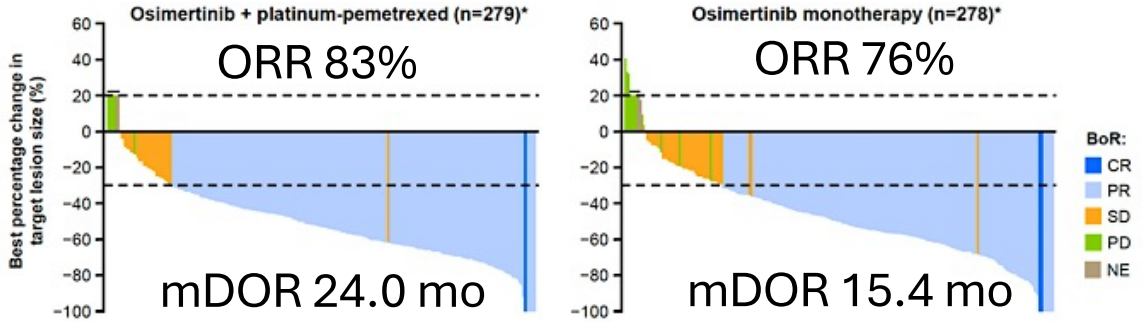
Median duration of response 17.2 m versus 8.5 m



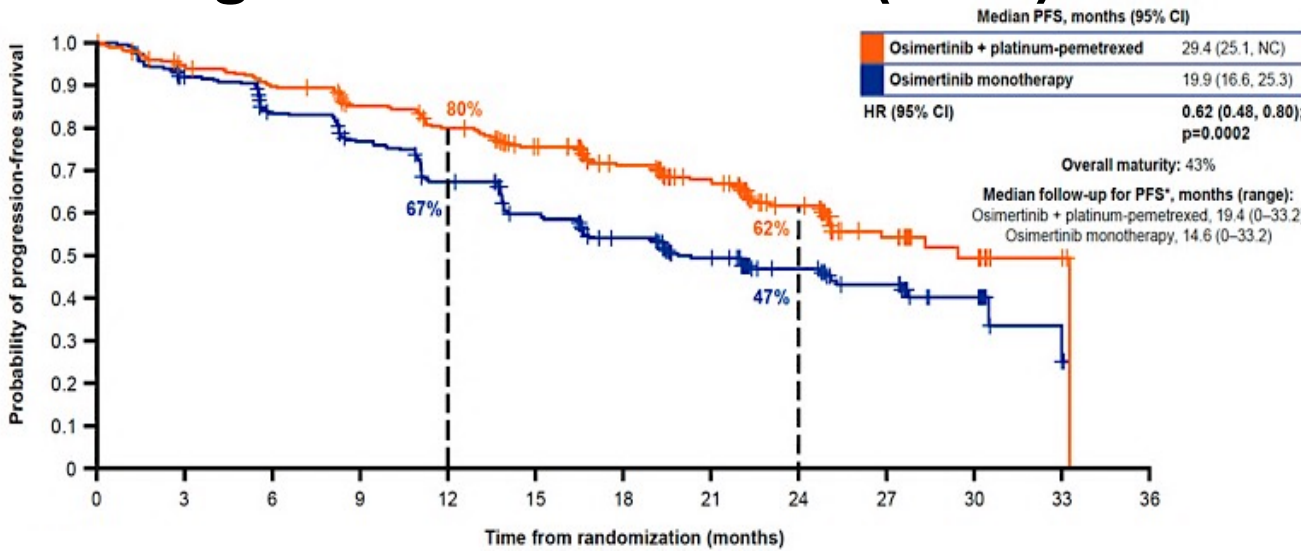
Soria JC et al New Engl J Med 2018;378:113-125; Ramalingam S et al New Engl J Med 2020;382:41-50; Hanna NH *et al. J Clin Oncol* 2021; 39:1040-1091; Planchard D, *et al. Ann Oncol* 2018; 29 (Suppl 4): iv192–iv237, 2018; National Comprehensive Cancer Network. Non-small Cell Lung Cancer. Version 4.2021, March 3, 2021; Melosky B et al. Curr Oncol 2020;27:e146-e155.

Beyond osimertinib - FLAURA2

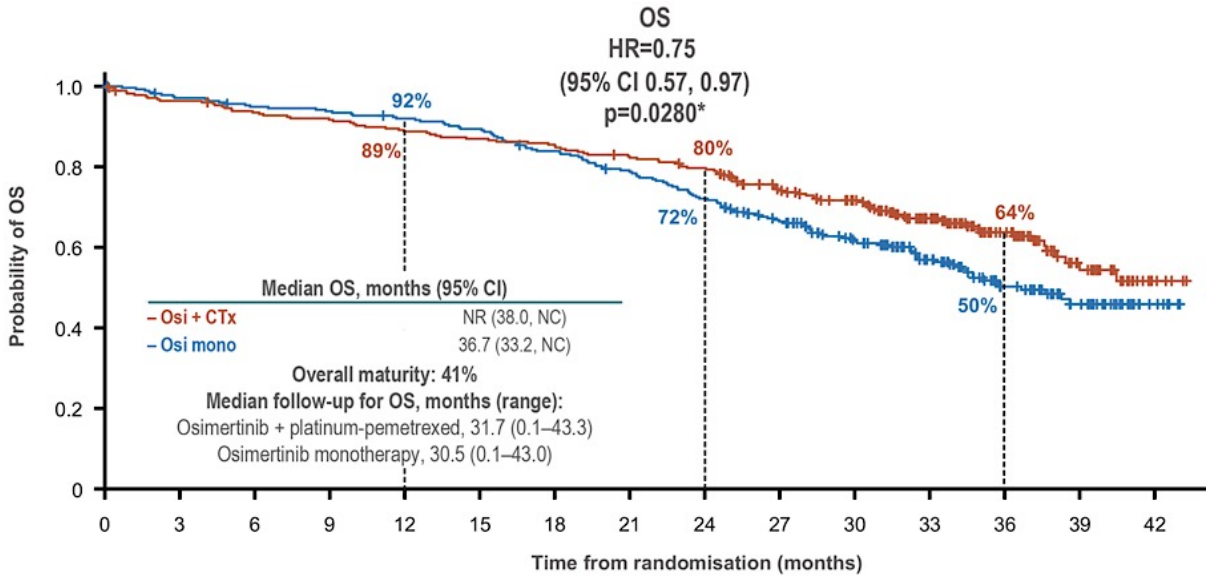




Progression-Free Survival (BICR)



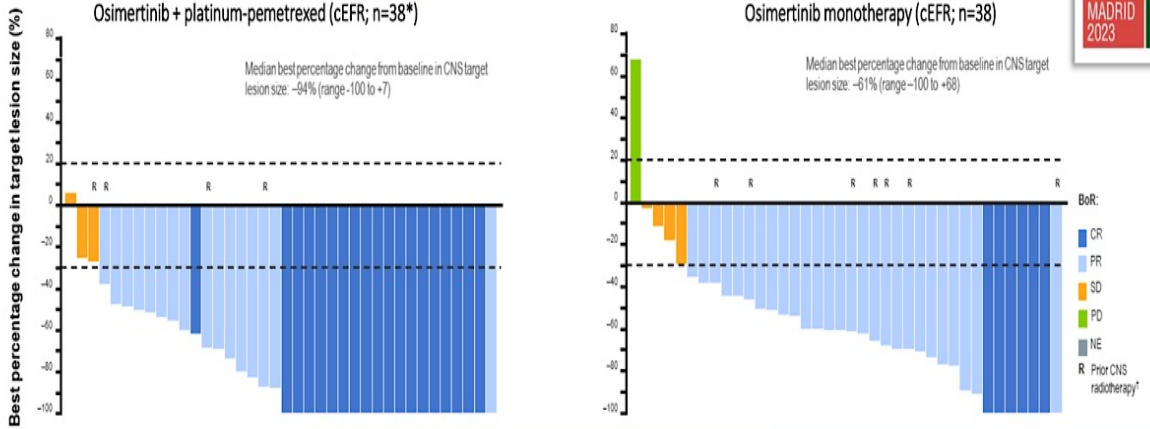
Overall Survival



Janne P, et al. WCLC 2023; Planchard D et al NEJM 2023; Valdiviezo Lama NI, et al ELCC 2024, Abstr 4O

FLAURA2 – CNS response, Safety

Osimertinib with the addition of CTx demonstrated a high proportion of complete responses in the CNS by CNS BICR



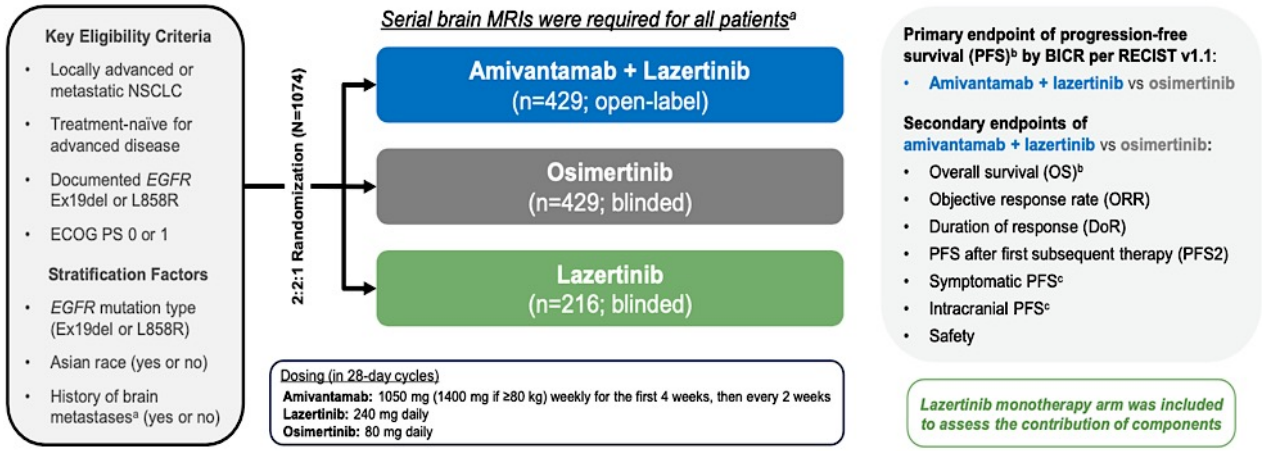
	cFAS (n=222) Measurable + non-measurable BM		cEFR (n=78) Measurable BM	
CNS response‡	Osi + CTx (n=118)	Osi mono (n=104)	Osi + CTx (n=40)	Osi mono (n=38)
CNS ORR, % (95% CI)	73 (64 to 81)	69 (59 to 78)	88 (73 to 96)	87 (72 to 96)
Complete response, n (%)	70 (59)	45 (43)	19 (48)	6 (16)
Partial response, n (%)	16 (14)	27 (26)	16 (40)	27 (71)
CNS DCR, % (95% CI)	91 (84 to 95)	93 (87 to 97)	95 (83 to 99)	97 (86 to 100)
Median DoR, months (95% CI)§	NR (23.8, NC)	26.2 (19.4, NC)	NR (21.6, NC)	20.9 (12.6, NC)

Patients with AEs, n (%)*	Osimertinib + platinum-pemetrexed (n=276)	Osimertinib monotherapy (n=275)
AE any cause	**276 (100)**	**268 (97)**
Any AE Grade ≥3	176 (64)	75 (27)
Any AE leading to death	18 (7)	8 (3)
Any serious AE	104 (38)	53 (19)
Any AE leading to discontinuation	**132 (48)**	**17 (6)**
Osimertinib / carboplatin or cisplatin / pemetrexed discontinuation	**30 (11) / 46 (17) / 119 (43)**	17 (6) / NA / NA

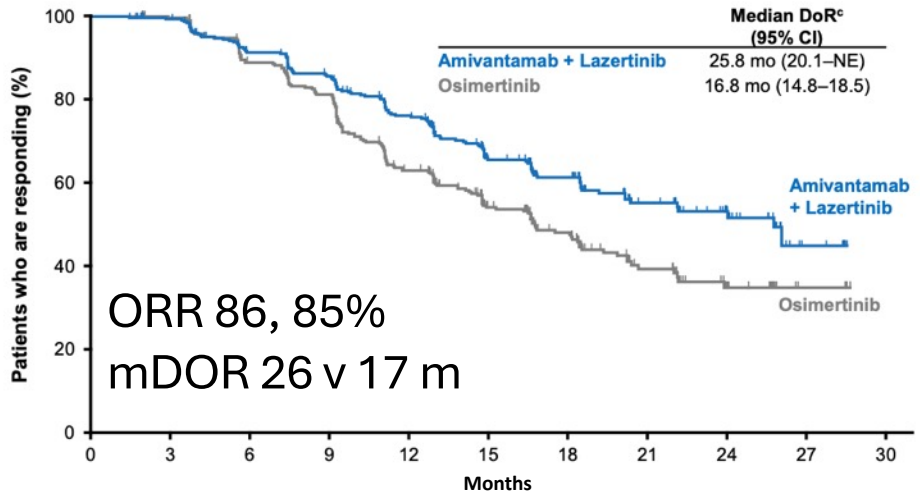
Increased hematologic toxicity,
Treatment discontinuation rates

Planchard NEJM 2024
Planchard ESMO 2024

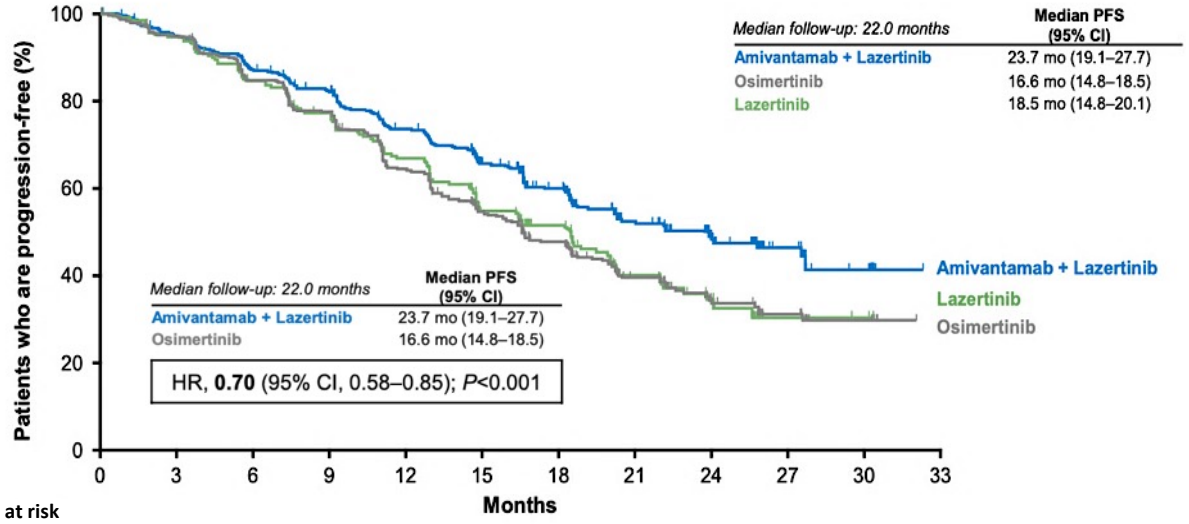
Beyond osimertinib - MARIPOSA



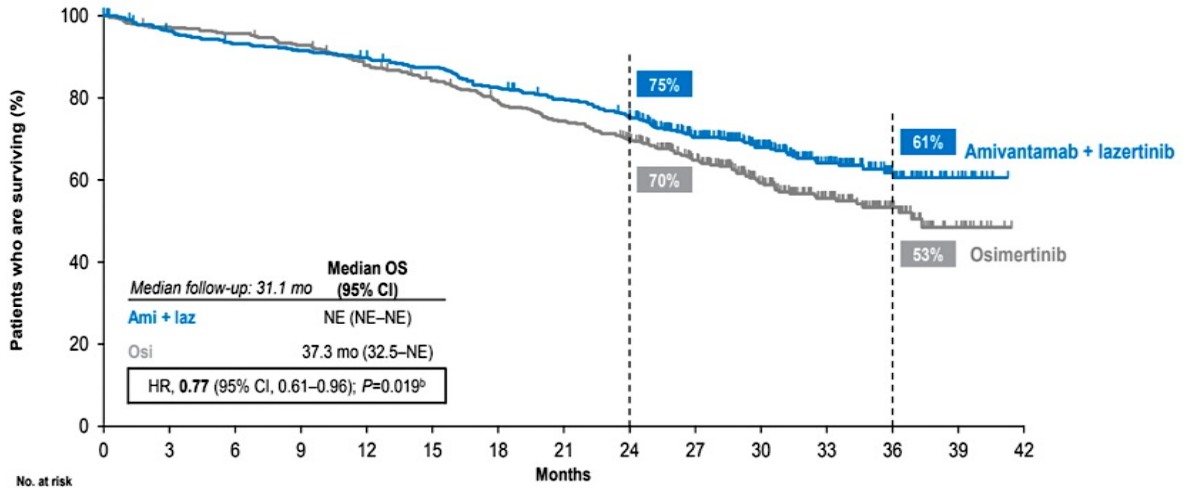
Median Duration of Response



Progression-Free Survival (BICR)

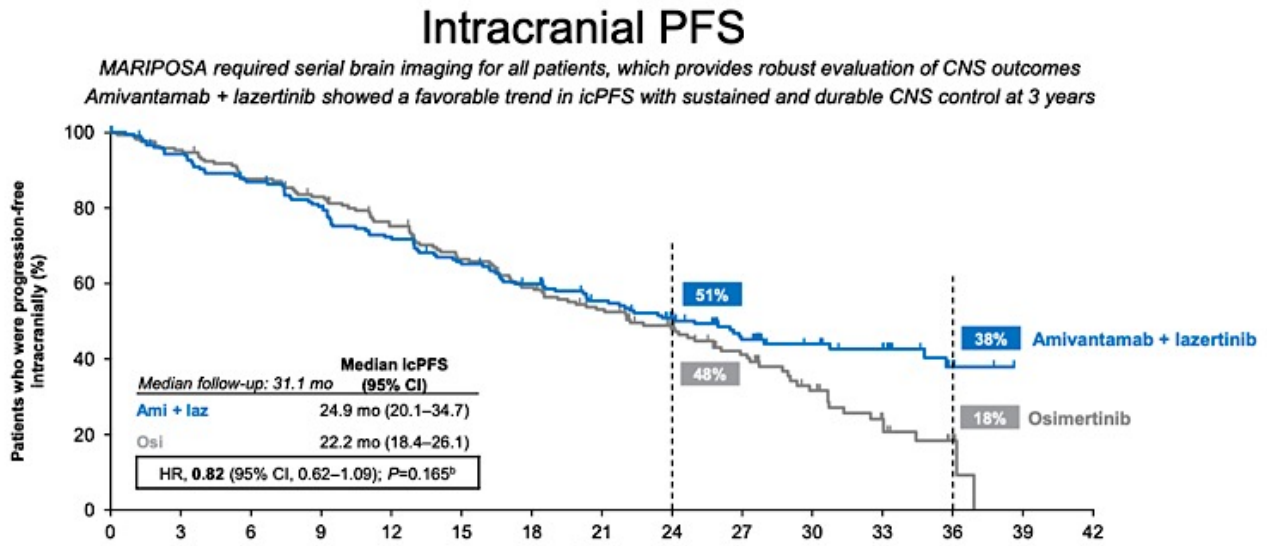


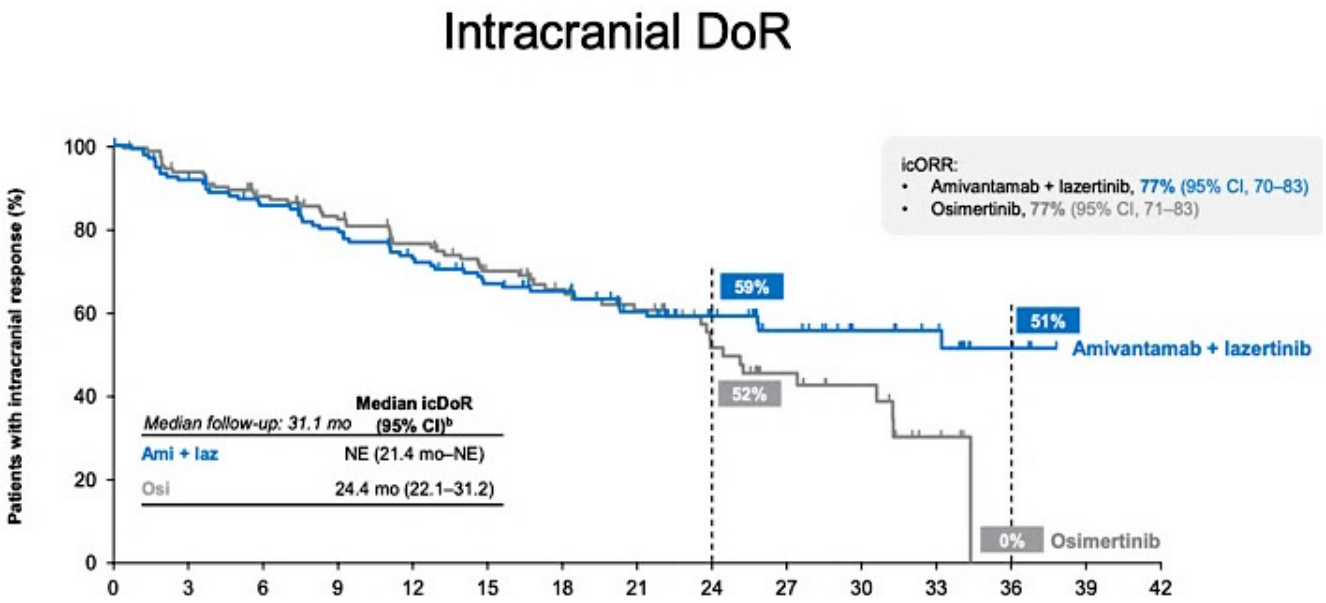
Interim Overall Survival



Cho BC et al ESMO 2023; Cho BC et al NEJM 2024; Gadgeel WCLC 2024

MARIPOSA – CNS response, Safety





TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)
AEs leading to death	34 (8)	31 (7)
Any AE leading to treatment:		
Interruptions of any agent	350 (83)	165 (39)
Reductions of any agent	249 (59)	23 (5)
Discontinuations of any agent	**147 (35)**	**58 (14)**
Discontinuation of all agents	**10%**	**3%**
Any VTE, n (%)	**157 (37)**	**39 (9)**
Median onset to first VTE	**84 days**	194 days
Within first 4 months, n (%)	**97 of 157 (62)**	13 of 39 (33)

Gadgeel et al WCLC 2024; Cho et al ESMO 2023; Cho et al NEJM 2024

Amivantamab-vmjw plus Lazertinib Shows Statistically Significant and Clinically Meaningful Improvement in Overall Survival versus Osimertinib

Press Release: January 7, 2025

“On January 7, 2025, The manufacturer announced positive topline results for the gold standard endpoint in cancer treatment of overall survival (OS) from the Phase 3 MARIPOSA study, evaluating amivantamab-vmjw plus lazertinib as a first-line therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions (ex19del) or L858R substitution mutations. The chemotherapy-free combination regimen met the final pre-specified secondary endpoint of OS and demonstrated clinically meaningful and statistically significant improvement in OS versus the current standard of care osimertinib. Improvement in median OS is expected to exceed one year.

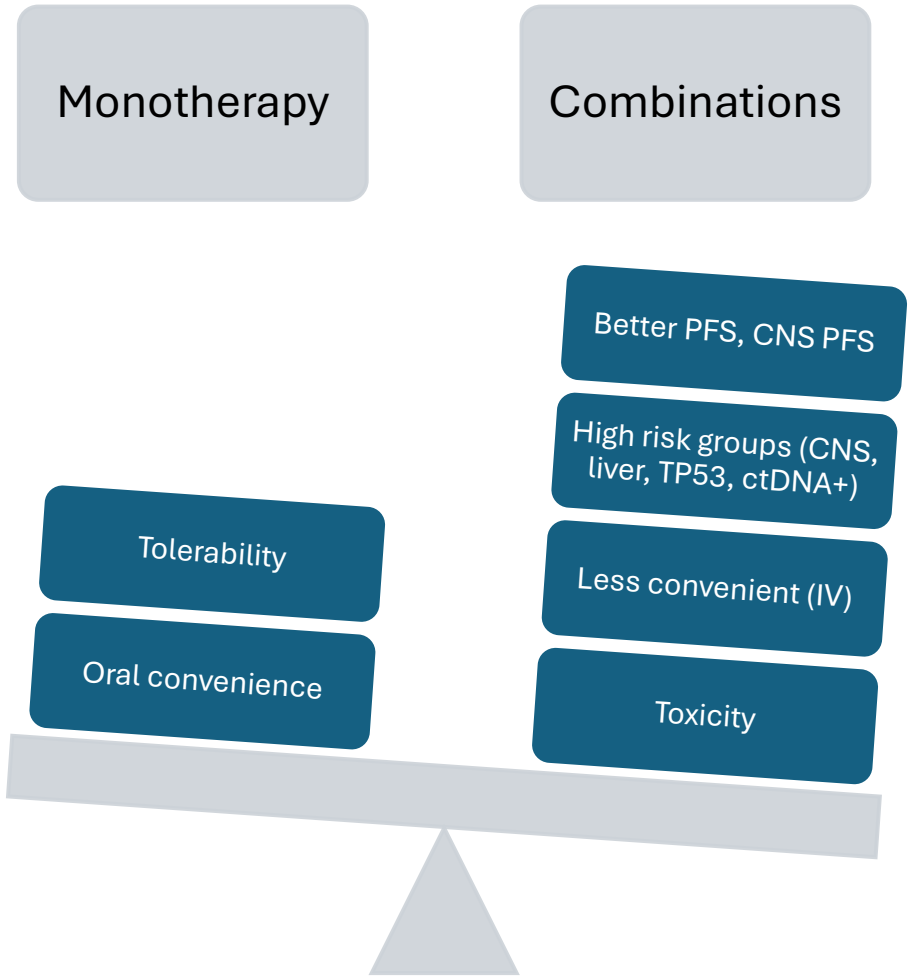
Results from the final overall survival analysis build upon previously reported data from the interim analysis and positive results from the progression-free survival analysis.

The safety profile was generally consistent with the profiles of the individual treatments. Adverse event rates were consistent in this arm as compared to other amivantamab-containing regimens. Venous thromboembolic events were observed with the combination. Subsequent studies showed that administering oral anticoagulant medicines prophylactically during the initial four months of the regimen significantly reduced the risk of thrombosis.”

https://www.jnj.com/media-center/press-releases/rybrevant-amivantamab-vmjw-plus-lazcluze-lazertinib-shows-statistically-significant-and-clinically-meaningful-improvement-in-overall-survival-versus-osimertinib

Who needs intensified therapy?

Benefit in high risk subgroup	FLAURA2	MARIPOSA
CNS mets	✓	✓
Liver mets	✓	✓
TP53 co-mutations	✓	✓
ctDNA baseline	✓	✓
ctDNA clearance	✓	✓
L858R	✓	✓



Felip et al ASCO 2024; Planchard et al WCLC 2024; Janne et al AACR 2024

PALOMA-3: SC v. IV amivantamab plus lazertinib in patients after failure of platinum and osimertinib in patients with advanced EGFRm NSCLC

Key eligibility criteria
- Locally advanced or metastatic NSCLC
- Disease had progressed on or after osimertinib and platinum-based chemotherapy, irrespective of order
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0–1

Stratification factors
- Brain metastases (yes or no)
- *EGFR* mutation type (Ex19del vs L858R)
- Race (Asian vs non-Asian)
- Type of last therapy (osimertinib vs chemotherapy)

1:1 randomization (N=418)

SC Amivantamab + Lazertinib (n=206)

IV Amivantamab + Lazertinib (n=212)

Dosing (in 28-day cycles)

SC Amivantamab[a,b] (co-formulated with rHuPH20 and administered by manual injection): 1600 mg (2240 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks thereafter

IV Amivantamab[b]: 1050 mg weekly (1400 mg if ≥80 kg) for the first 4 weeks, then every 2 weeks thereafter

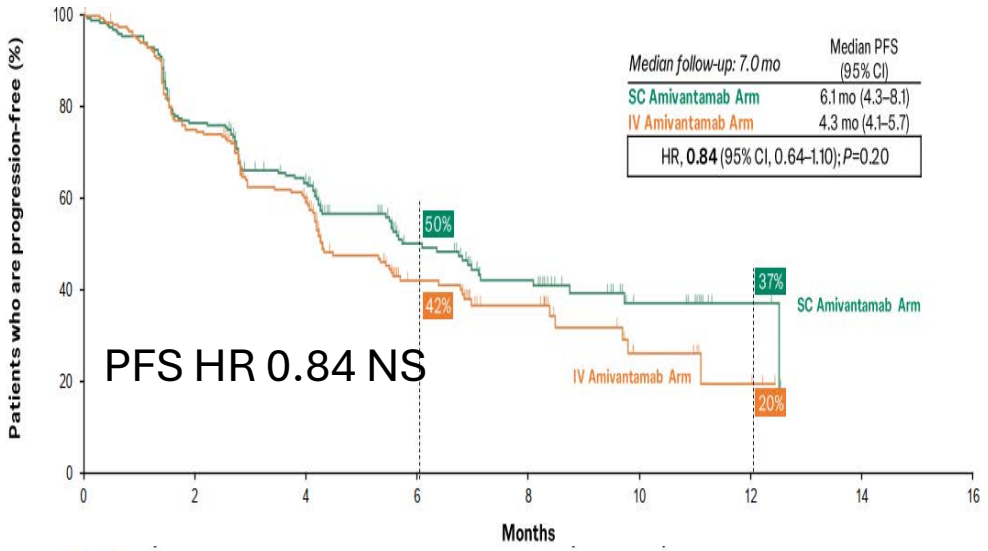
Lazertinib: 240 mg PO daily

Prophylactic anticoagulation recommended for the first 4 months of treatment

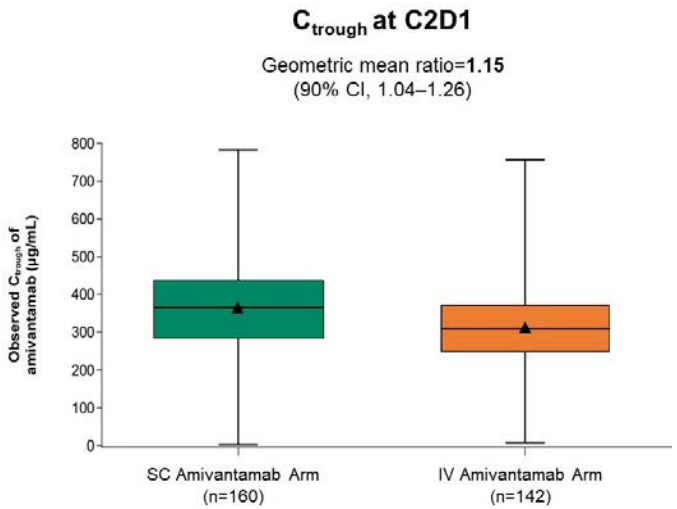
Co-primary endpoints[c]:
- C_{trough} (noninferiority)[d]
- C2 AUC (noninferiority)[e]

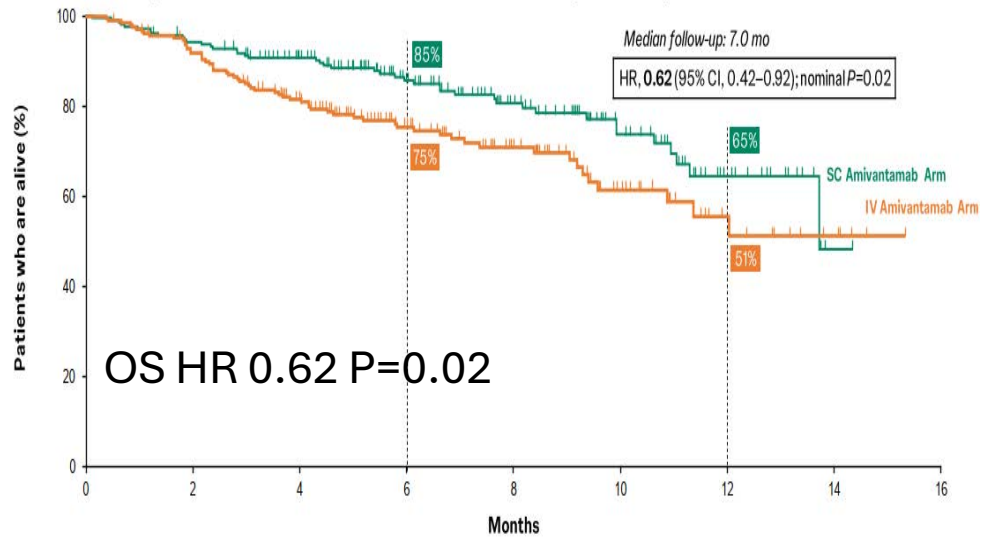
Secondary endpoints:
- ORR (noninferiority)
- PFS (superiority)
- DoR
- Patient satisfaction[f]
- Safety

Exploratory endpoints:
- OS



Non-inferior pharmacokinetics, ORR, trend to longer duration of response, PFS and improved OS

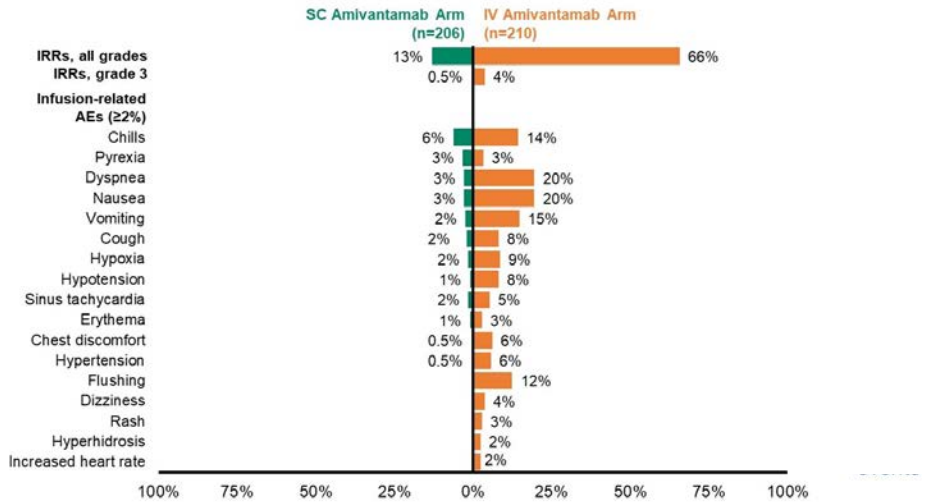




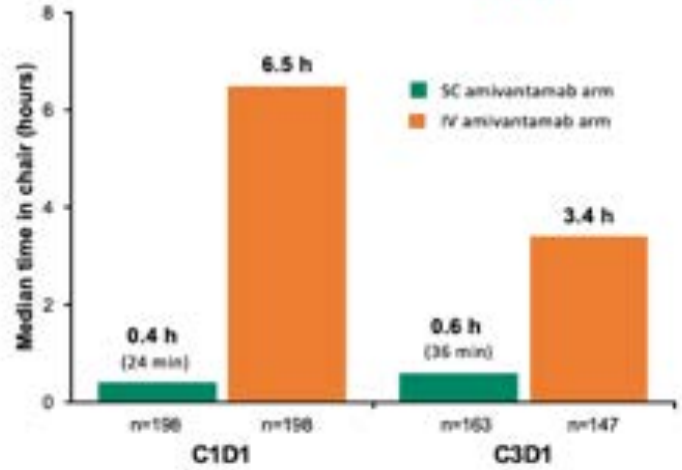
Leighl et al ASCO 2024; Leighl et al J Clin Oncol 2024

PALOMA-3: other benefits of amivantamab SC administration

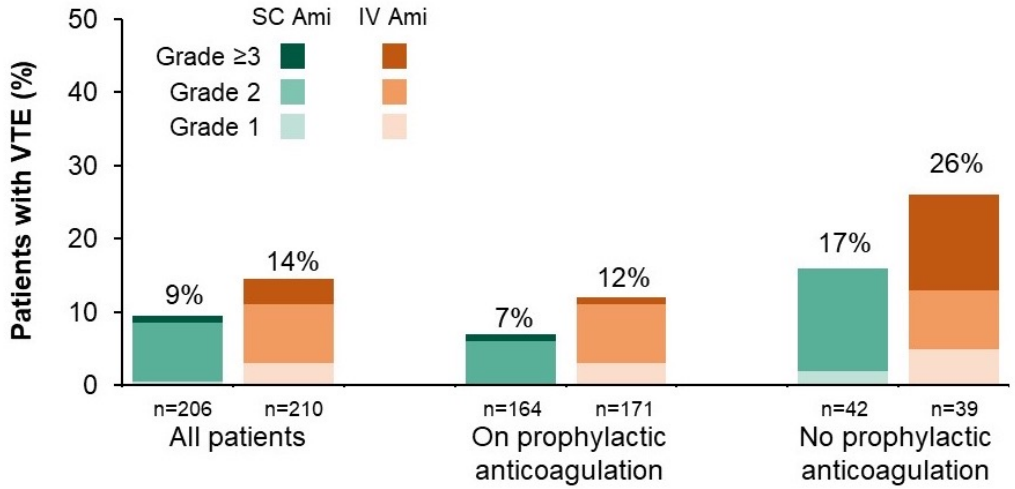
Incidence of IRR-related Symptoms



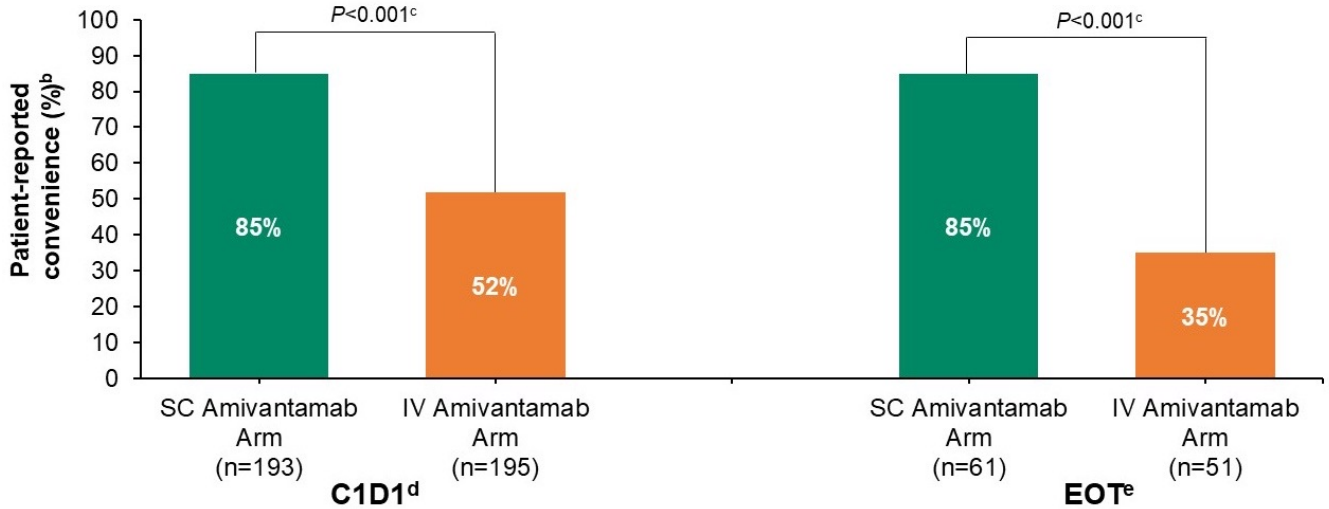
Patient Time in Chair[a]



Rates of VTE by Treatment Arm and Prophylaxis Status



Frequency of Patient-reported Convenience per Modified TASQ[a]

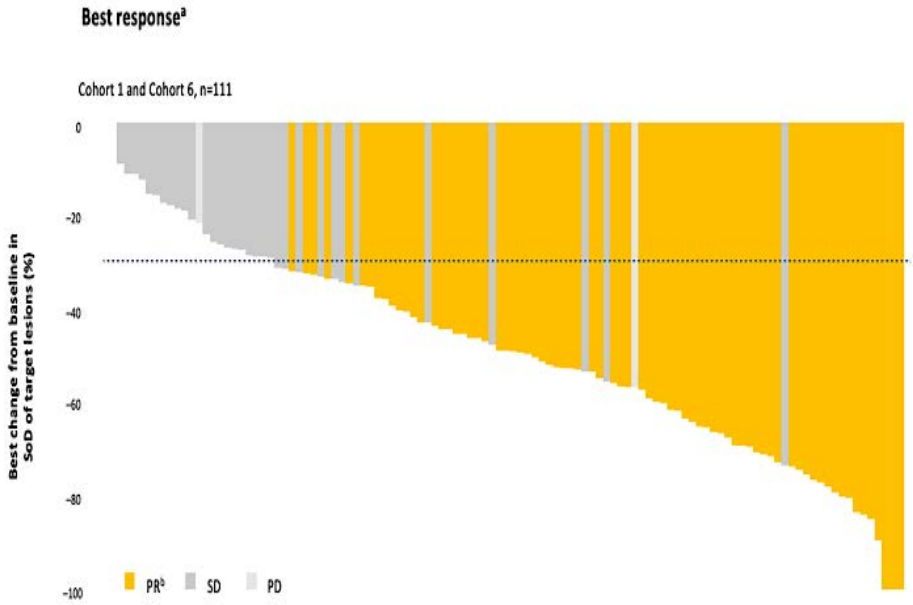


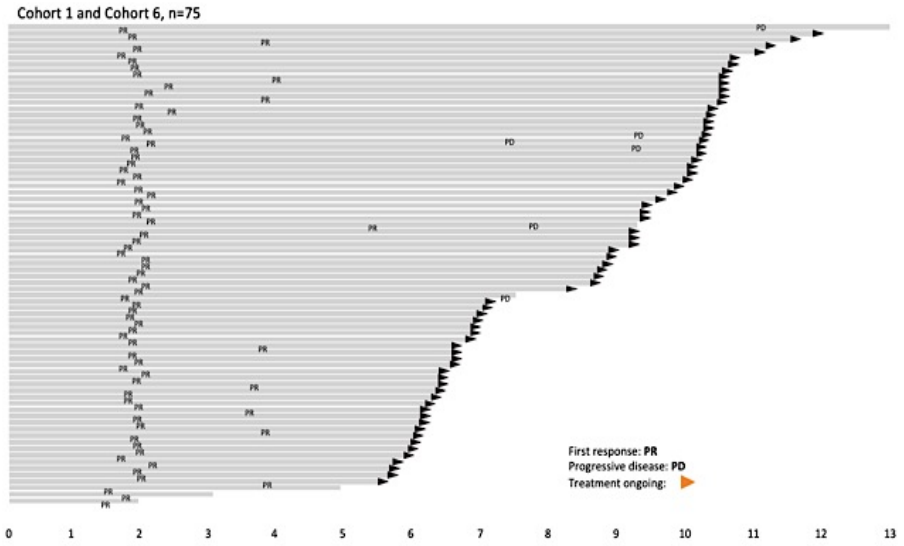
Leighl et al ASCO 2024; Leighl et al J Clin Oncol 2024

PALOMA2 RESULTS: 1L SC amivantamab + Lazertinib

	Overall (N=113)	
	INV	ICR
ORR, % (95% CI)	77 (68–84)	79 (70–86)

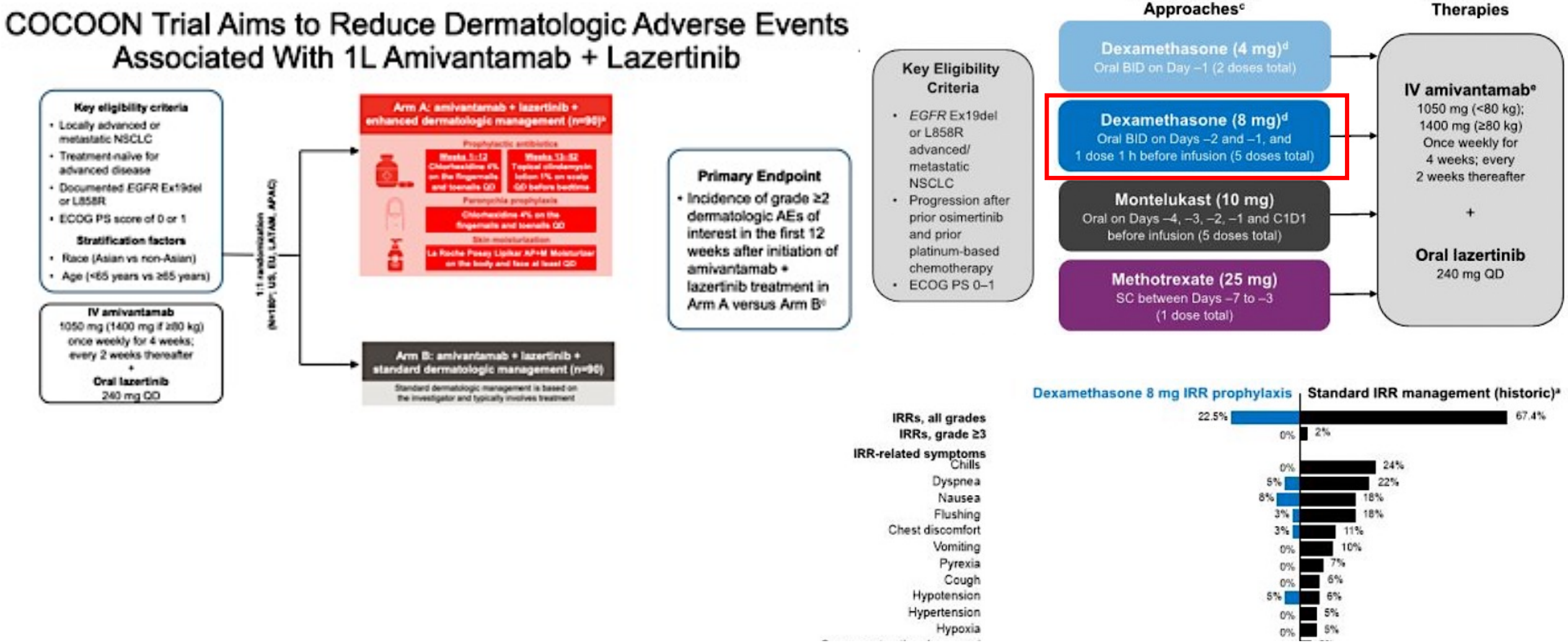
- Among all patients, the INV-assessed ORR was 77% and ICR-assessed ORR 79%
- A similar BICR-assessed ORR of 86% (95% CI, 83–89) was observed with IV amivantamab + lazertinib in MARIPOSA[1]
- Median time to response was 1.9 months (range, 1.4–5.3)
  - IRRs in 16%; VTE in 13%
  - PK (Ctrough) similar to IV ami Q2W





Scott et al ASCO 2024

Other ways to decrease toxicity with combinations



Cho et al P3.12D.04 WCLC 2024; Lopes et al WCLC 2024

Treatment Recommendations Post Osimertinib Progression

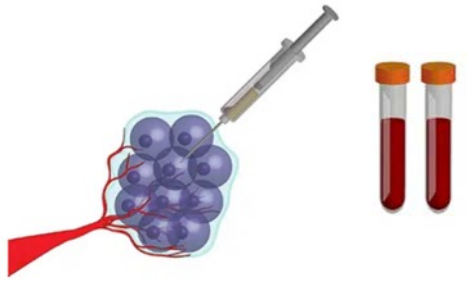
Oligoprogression/CNS Progression

Asymptomatic

- Local therapy (surgery or SABR) for limited lesions
- May continue osimertinib

CNS Progression

- Local therapy/SRS for limited lesions
- May continue osimertinib

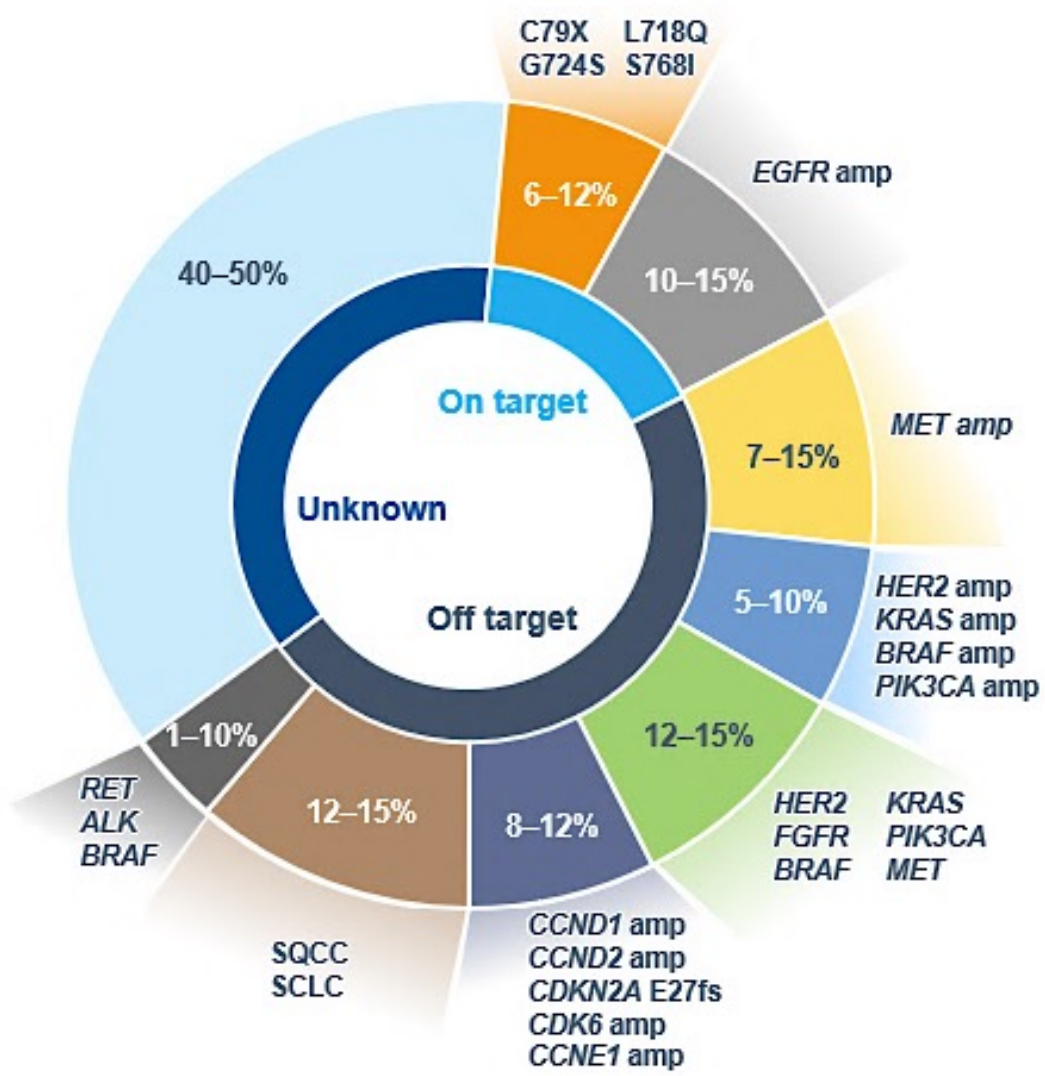


Systemic Progression

- **Platinum Doublet +/- Bevacizumab**
- **Amivantamab + Platinum Doublet**
- **Clinical Trial**

Biopsy to characterize molecular resistance

NCCN. Clinical practice guidelines in oncology: non-small cell lung cancer. v.5.2024. nccn.org. Image source: biochain.com



Adapted from Passaro et al. Nat Med 2021

On Target

EGFR combinations:
TKIs, mAbs, Bispecifics
Amivantamab + Lazertinib, Osimertinib + Necitumumab…

797S/4Gi: BLU945, BLU701, BBT176, JIN-A02, JBJ-09-063

Gen-omic

***MET* amplification:**
Osimertinib + savolitinib, capmatinib, tepotinib

Off Target

RET, ROS1, ALK, TRK fusions: dual TKI
BRAF V600E: BRAF/ MEK/EGFR TKI

Off Target Protein

MET protein expression:
Telisotuzumab vedotin + Osimertinib
Amivantamab + Lazertinib

Driver Agnostic

Driver agnostic:
HER3 ADC: Patritumab Deruxtecan
TROP2 ADCs: Dapotamab Deruxtecan, MK-2870
Chemotherapy + Ivonescimab (VEGFRi+PD-L1i)
Local therapy + Osimertinib
VEGF inhibitors + Osimertinib +/- Chemotherapy

SCLC SqC

Histologic Transformation:
Chemotherapy +/- Osimertinib

Impact of 1L Combinations on Resistance Mechanisms

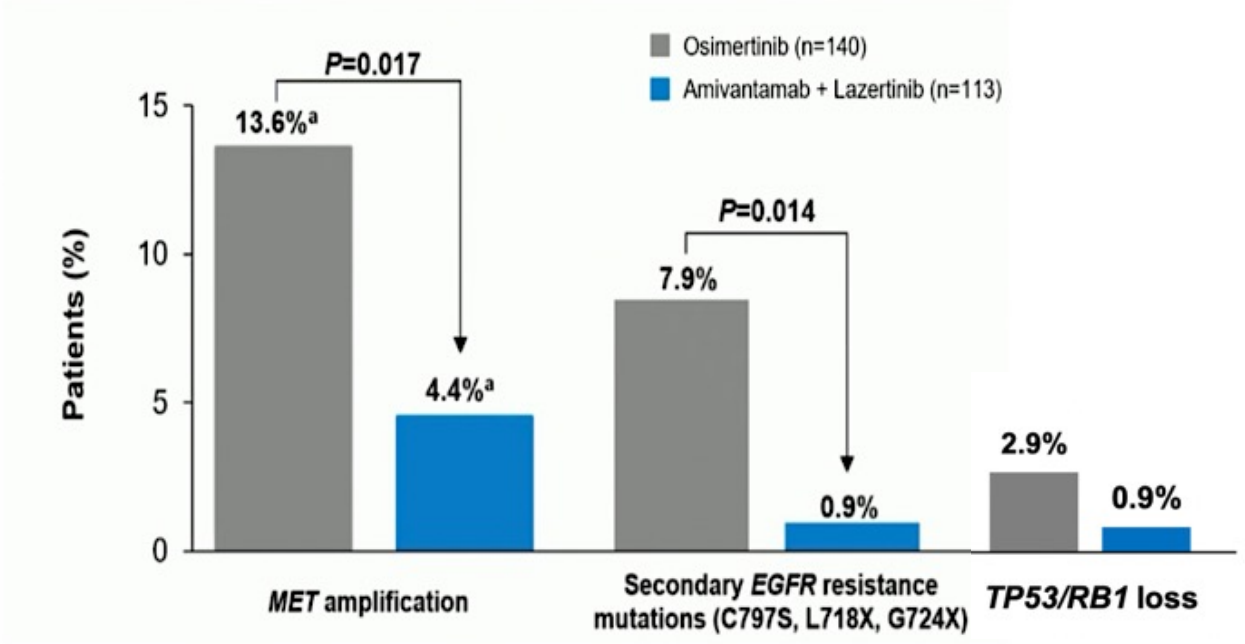
FLAURA2
Osimertinib + Chemo

ACQUIRED RESISTANCE MECHANISMS

Functional groups	Acquired gene alteration, n (%)	FLAURA osimertinib monotherapy (n=109)[1]	FLAURA2 osimertinib monotherapy (n=73)	FLAURA2 osimertinib + platinum-pemetrexed (n=53)[a]
EGFR mutations	C797S	7 (6)	9 (12)	2 (4)
	Other Uncommon	5 (5)	3 (4)	ND
RTK amplifications	*MET* amplification	17 (16)	10 (14)	5 (9)
	ERBB2 amplification	2 (2)	1 (1)	3 (6)
MAPK / PI3K mutations	*BRAF* V600E	3 (3)	4 (5)	ND
	KRAS mutation	3 (3)	6 (8)	3 (6)
	PIK3CA mutation	6 (6)	6 (8)	2 (4)
	ERBB2 mutation	ND	1 (1)	ND
Cell cycle gene amplifications	*CCND1 / E1* amplification	7 (6)	1 (1)	3 (6)
	CDK4 / 6 amplification	7 (6)	4 (5)	3 (6)
Fusions	*RET*	ND	3 (4)	1 (2)
	BRAF	ND	3 (4)	1 (2)
	ALK	1 (1)	2 (3)	ND
	Other	NR	5 (7)	2 (4)
RB1 loss (with *TP53*)		NR	4 (5)	ND
No known resistance alteration detected		NR	36 (49)	40 (75)

Acquired resistance mechanisms were broadly similar across treatment arms

MARIPOSA
Lazertinib + Amivantamab



Lee et al ESMO Asia 2023; Besse et al ESMO 2024

MARIPOSA-2: Amivantamab + Chemo ± Lazertinib vs Chemo in Patients with *EGFR*mut Adv NSCLC Post-Osimertinib

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)

Serial brain MRIs were required for all patients[a]

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]

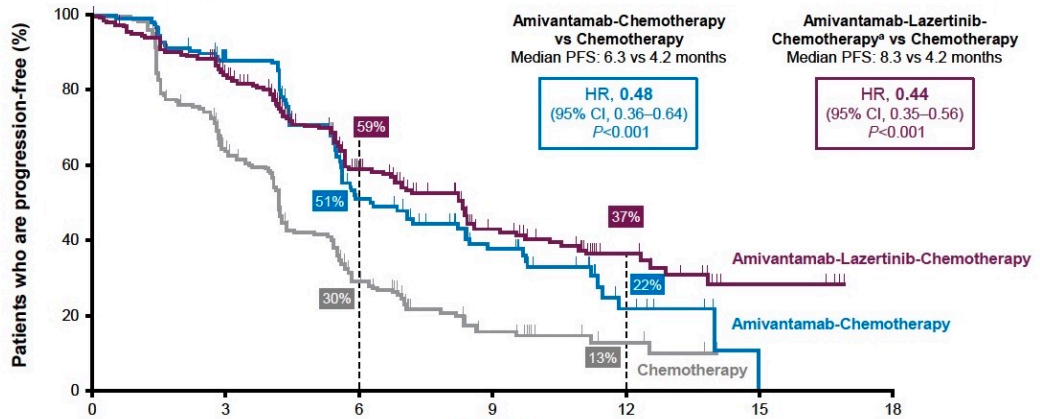
Chemotherapy administered at the beginning of every cycle:

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

- **Dual primary endpoint:** PFS[c] by BICR per RECIST 1.1
- **Secondary endpoints:** ORR[c], DoR, OS[c], intracranial PFS, safety

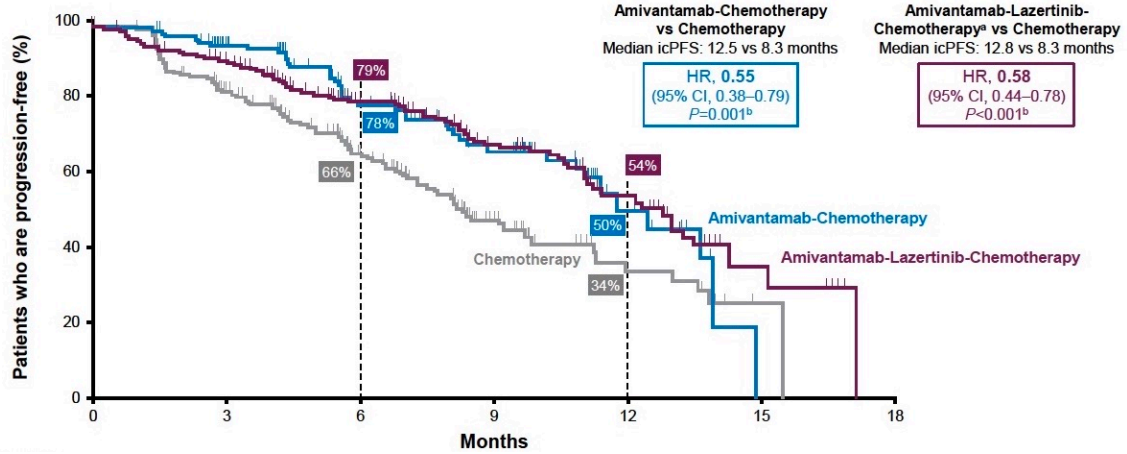
Primary Endpoint: Progression-free Survival by BICR

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



Intracranial Progression-free Survival by BICR

Amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of intracranial progression or death by 45% and 42%, respectively



Passaro et al ESMO 2023

Many potential journeys to improve patient outcomes

- First-line Therapy

Osimertinib

Osimertinib + Platinum

Amivantamab + Lazertinib

Second-line Therapy

Resistance targeting therapy (e.g. MET)

Amivantamab + Chemotherapy

Amivantamab + Lazertinib

ADCs (HER3, TROP2)

Chemotherapy +/- VEGF/PD-1i

Third-line Therapy…

Resistance targeting therapy (e.g. MET)

ADCs (HER3, TROP2)

Chemotherapy

Amivantamab + Lazertinib or Chemo

Take home points

- Important to test early for EGFR alterations in stage IB-IV NSCLC and target EGFR as early as possible
- Adjuvant, consolidation and 1L metastatic EGFR TKI now standard
- Intensified first-line regimens FLAURA2 (osimertinib/chemo), MARIPOSA (amivantamab/Lazertinib) new options to be discussed – preferable in high risk disease
- Second line MARIPOSA-2 (amivantamab/chemo) has replaced chemo alone as standard
- Many exciting options coming in second-line and beyond (ADCs, other novel agents)
- Need to optimize testing for resistance mechanisms
- Thoughtful sequencing will become more challenging as we have more options

Discussion Questions

- Regulatory and reimbursement issues aside, which first-line therapy would you generally recommend for a younger patient with metastatic nonsquamous non-small cell lung cancer (NSCLC) with an EGFR exon 19 deletion (PD-L1 tumor proportion score [TPS] 60%)?

- Regulatory and reimbursement issues aside, which first-line therapy would you generally recommend for a younger patient with metastatic nonsquamous NSCLC with an EGFR L858R mutation and TP53 and RB1 alterations (PD-L1 TPS 60%)?

Discussion Question

- A patient with metastatic nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 60% responds to first-line osimertinib and then experiences disease progression with no targetable secondary mutations. Regulatory and reimbursement issues aside, what is your most likely next systemic therapy?

Discussion Question

- A patient with metastatic nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 60% responds to first-line osimertinib/chemotherapy and then experiences disease progression with no targetable secondary mutations. Regulatory and reimbursement issues aside, what is your most likely next systemic therapy?

Module 5: EGFR Mutation-Positive Non-Small Cell Lung Cancer

Current Management of Nonmetastatic and Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) — Dr Leighl

Promising Novel Agents in Clinical Development; EGFR Exon 20 Mutation-Positive NSCLC — Dr Goldman

UCLA Health | David Geffen School of Medicine

EGFR Exon 20 Mutation-Positive NSCLC: Promising Novel Agents in Clinical Development

Jonathan Goldman, MD
Professor, UCLA Hematology & Oncology
Director of Clinical Trials in Thoracic Oncology
Associate Director of Drug Development

Disclosures

UCLA Health | David Geffen School of Medicine

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, Gilead Sciences Inc, Gritstone bio, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Pfizer Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc
Contracted Research	AbbVie Inc, Advaxis Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, GSK, Janssen Biotech Inc, Lilly, Merck, Pfizer Inc, Puma Biotechnology Inc, Spectrum Pharmaceuticals Inc, Vaccinex Inc

Update: Novel therapies for EGFR exon 20 Mutations in NSCLC

UCLA Health | David Geffen School of Medicine

- Structure and pathophysiology of EGFR exon 20 mutations
- First line therapy: Amivantamab and chemotherapy
- 3 TKI’s in trials
- 3 ADC’s in trials

EGFR Exon 20 Mutation-Positive NSCLC

UCLA Health | David Geffen School of Medicine

EGFR exon 20 insertions account for 4-10% of all EGFR mutations and are resistant to 1st, 2nd, and 3rd gen EGFR TKIs

Molecular testing for EGFR exon 20 insertion by NGS is the most sensitive and specific technique

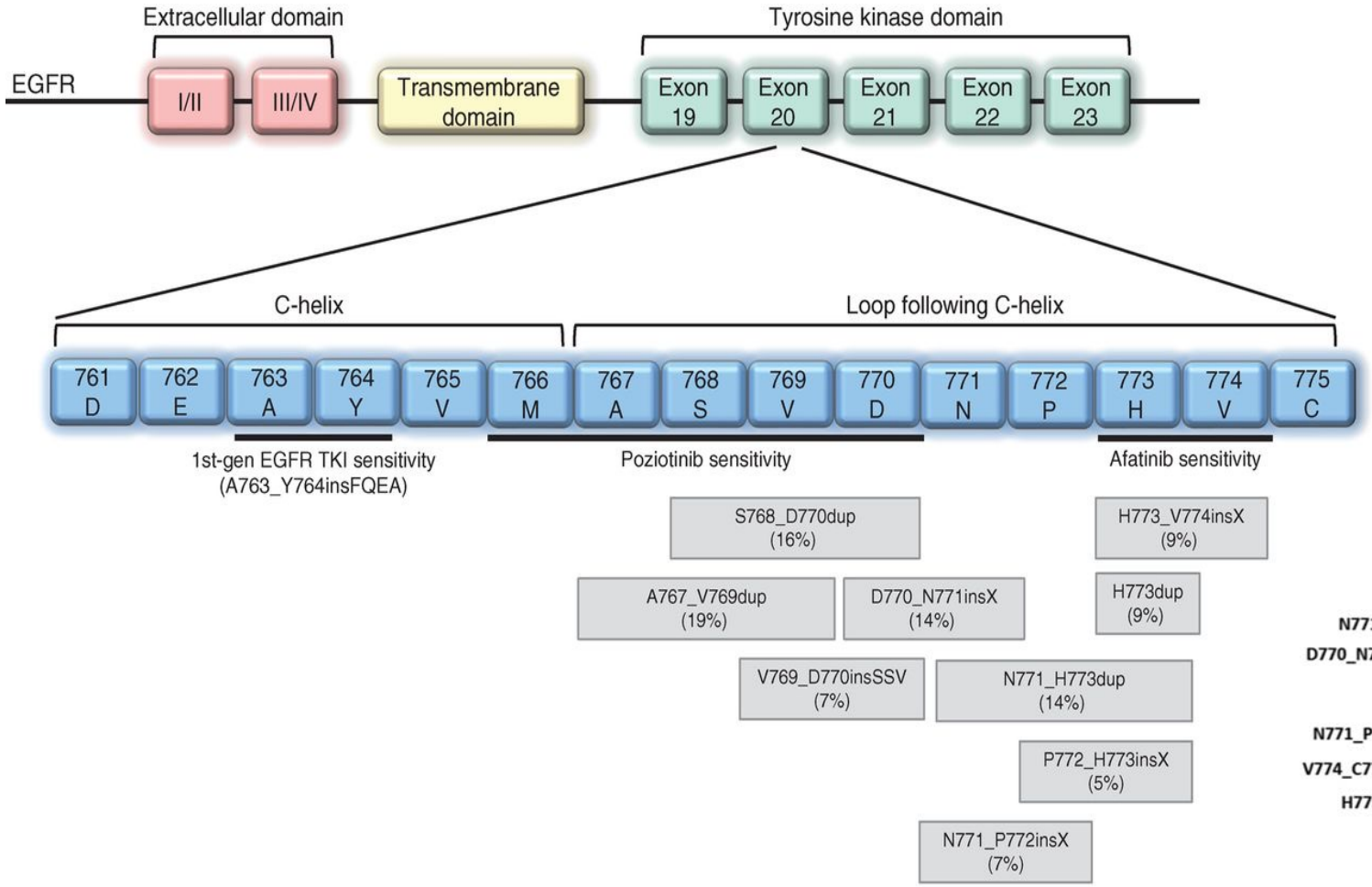
Poor prognosis (until recently):

Median OS of 16.2 months.

5-year survival rates of 8%.

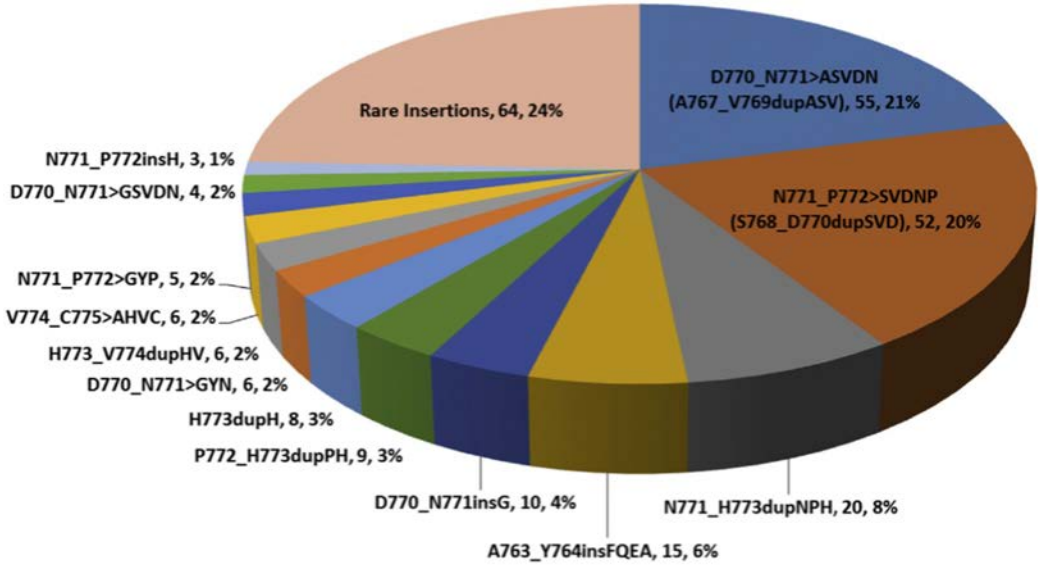
Park K, et al. *Lung Cancer*. 2023;178:166-171. Cho BC, et al. *Clin Lung Cancer*. 2023;24(2):89-97.
Viteri S, et al. *Mol Oncol.* 2023;17(2):230-237. Bazhenova L, et al. *Lung Cancer.* 2021;162:154–161.

Location of EGFR exon 20 insertions



Exon 20 mutations lead to constitutive activation without impacting the ATP pocket.

The C-helix is rotated inward, leading to an active state conformation and receptor dimerization.



Meador CB, et al. *Cancer Discov*. 2021;11(9):2145-2157.

Riess JW, et al. *J Thorac Oncol*. 2018;13(10):1560-1568.

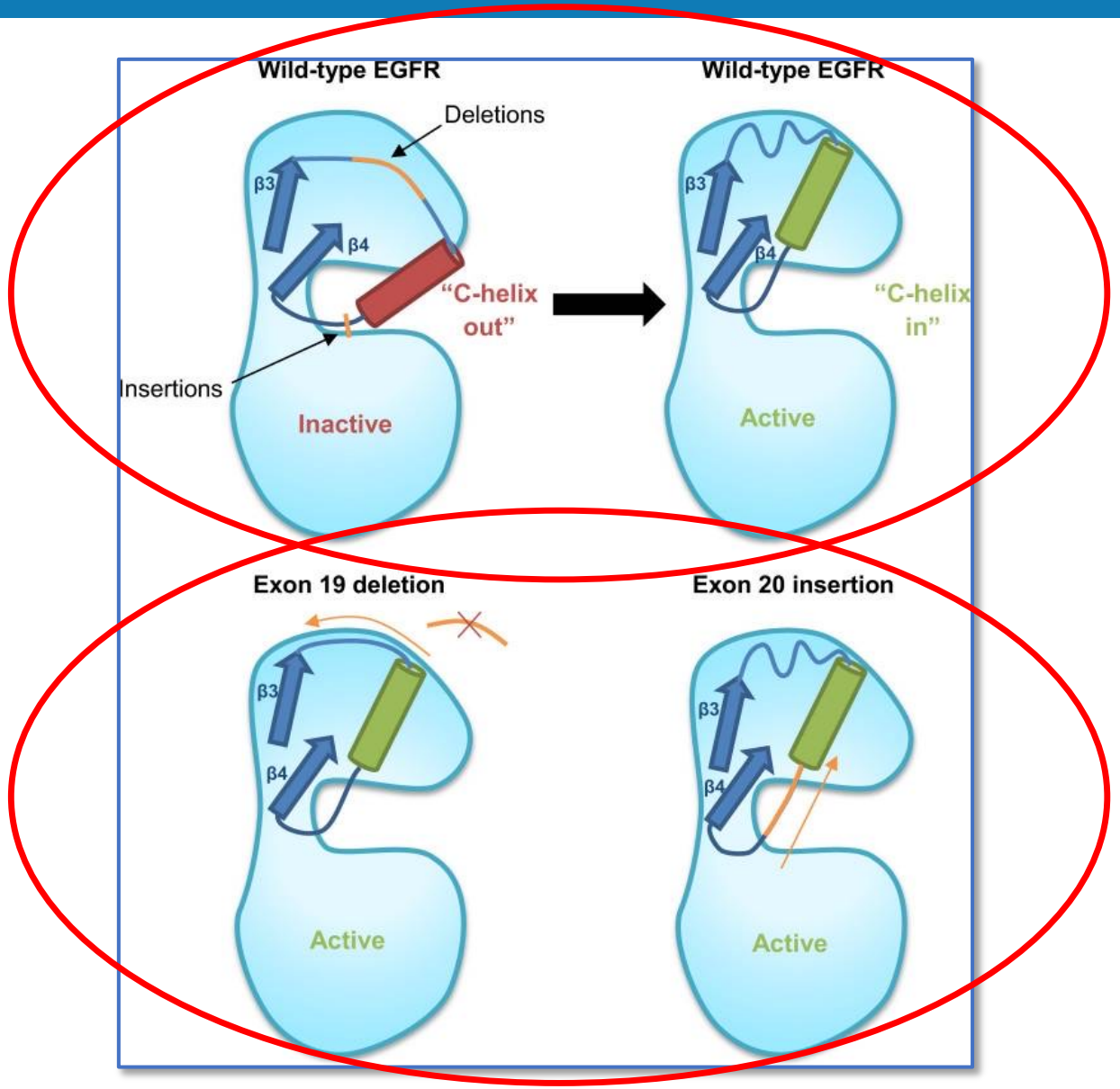
Structure of EGFR exon 20 insertions

UCLA Health | David Geffen School of Medicine

For wild type EGFR, ligand-binding and activation includes rotating the C helix inward and allowing key interactions in the cleft between the N and C lobes.

Oncogenic mutations favor the active conformation even in the absence of ligand.

- Exon 19 deletions “pull” the C-helix from the N-terminal side
- Exon 20 insertions “push” from the C-terminal side



Vyse S, et al. Signal Transduct Target Ther. 2019; 4: 5.

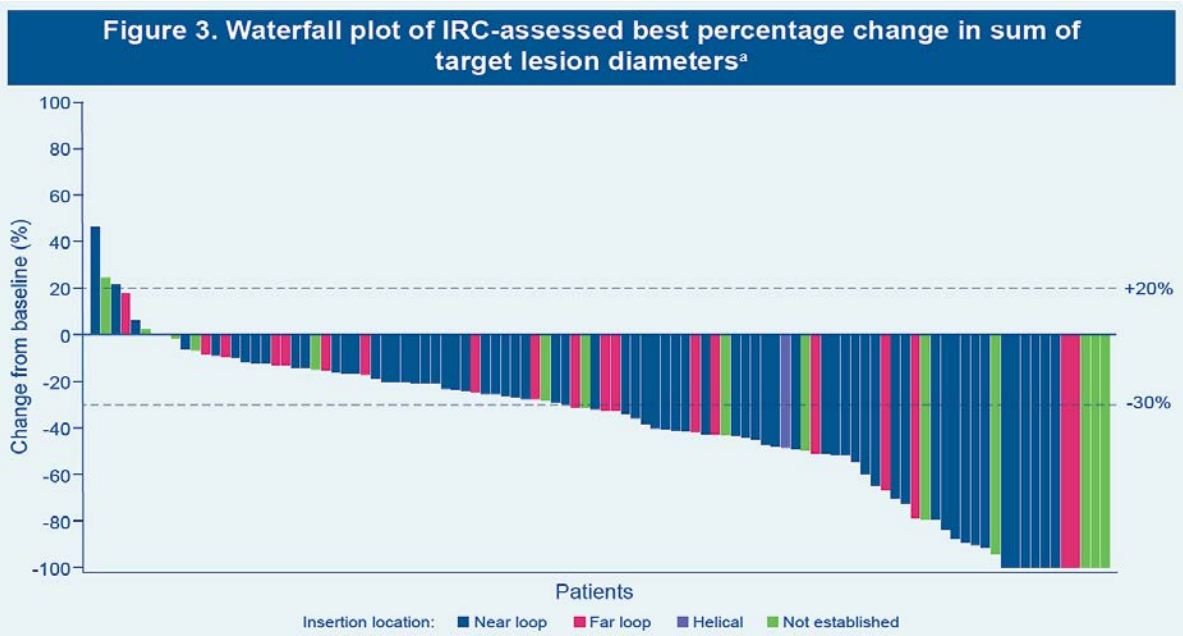
Anti-EGFR ex20ins Therapies

UCLA Health | David Geffen School of Medicine

Tyrosine kinase inhibitor:

Mobocertinib

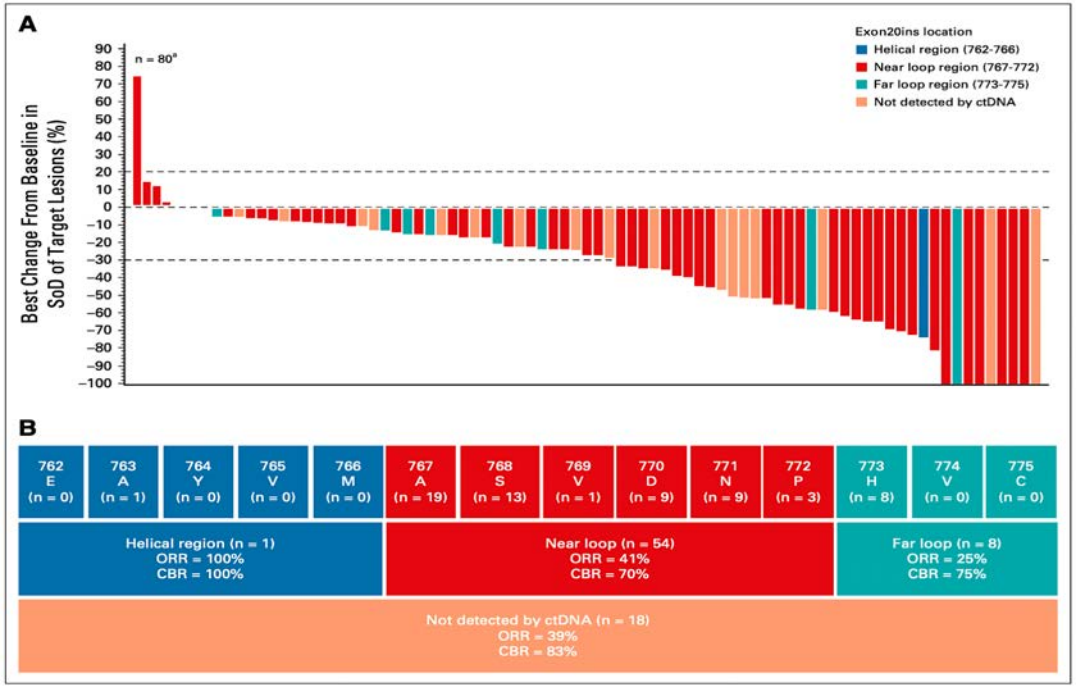
- ORR 28%, OS 24 m



Bispecific Antibody:

Amivantamab

- ORR 37%, OS 23 m



Ramalingam SS, et al. ESMO 2022, Poster 988P. Garrido Lopez P, et al. ELCC 2023, Abstract 3O.
Park K, et al. *J Clin Oncol* 2021;39(30):3391-3402.

Anti-EGFR ex20ins Therapies

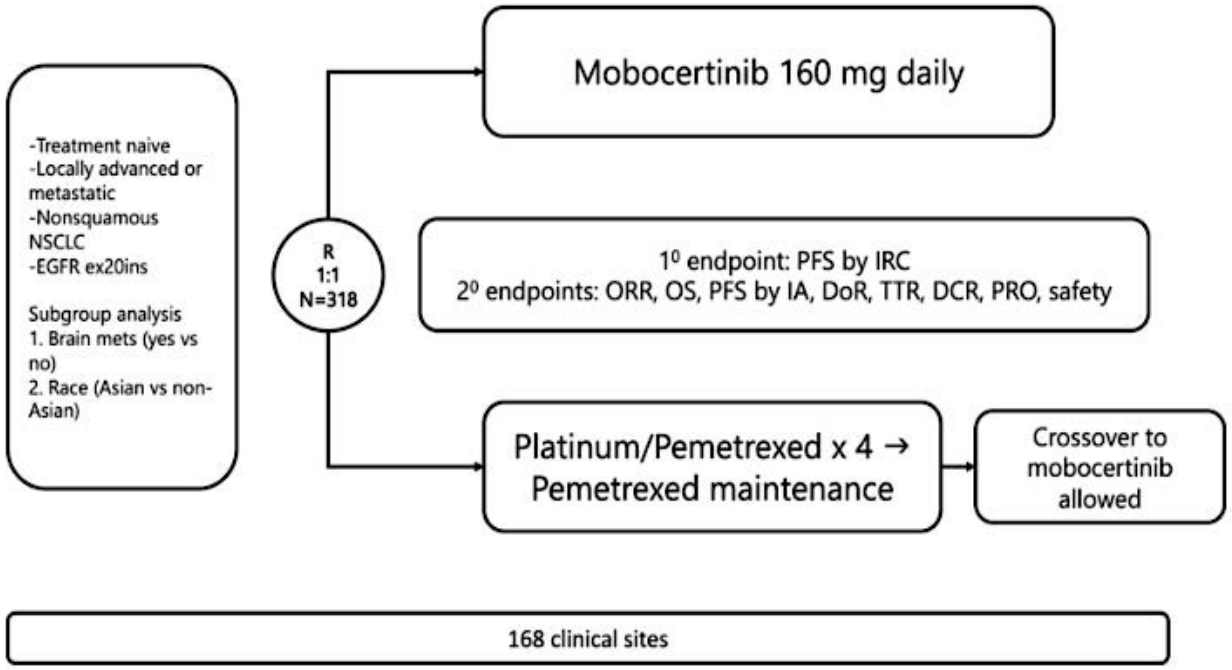
UCLA Health | David Geffen School of Medicine

Tyrosine kinase inhibitor:

Mobocertinib

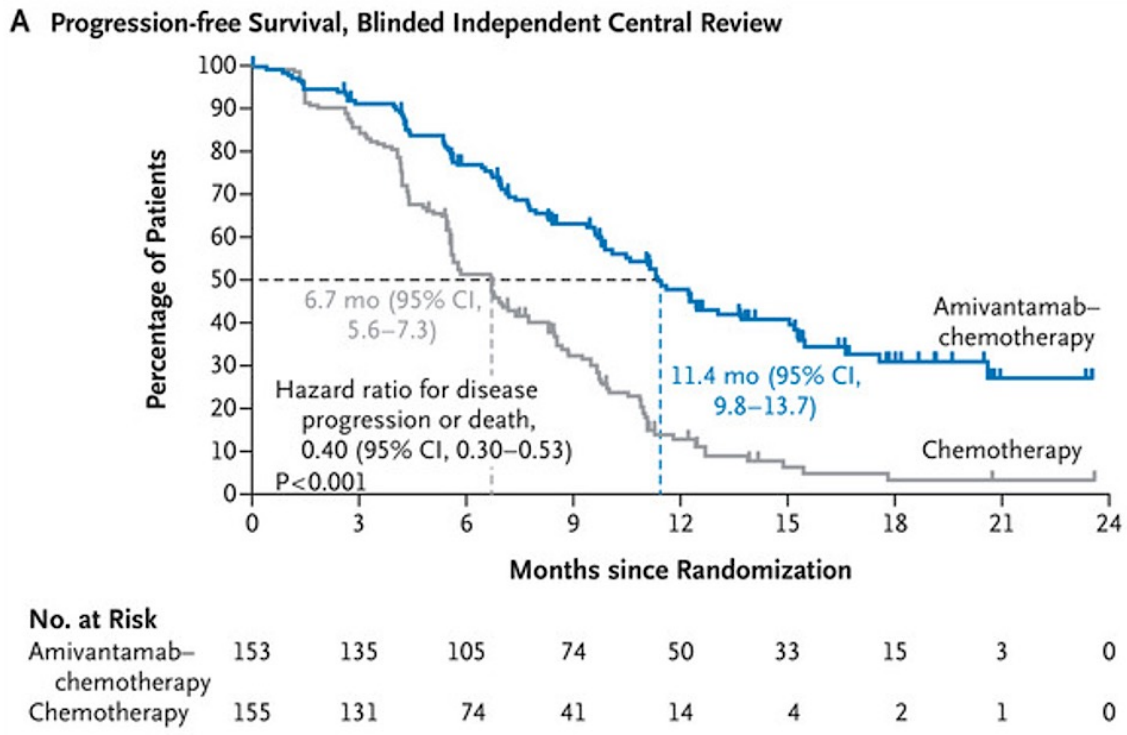
Missed Ph 3 endpoint

EXCLAIM-2 (NCT04129502) Phase 3 Trial Schema



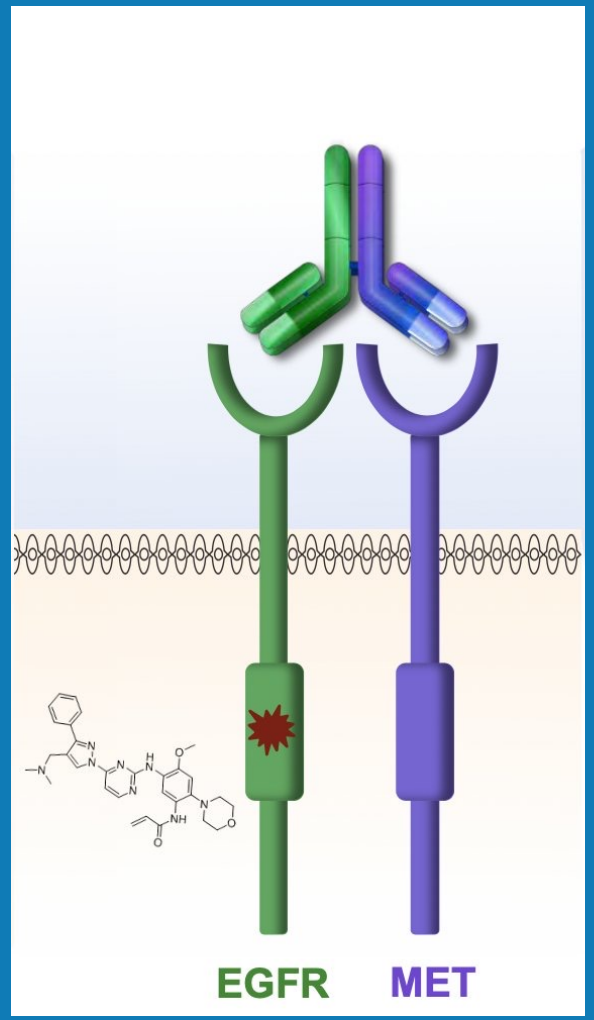
Bispecific Antibody:

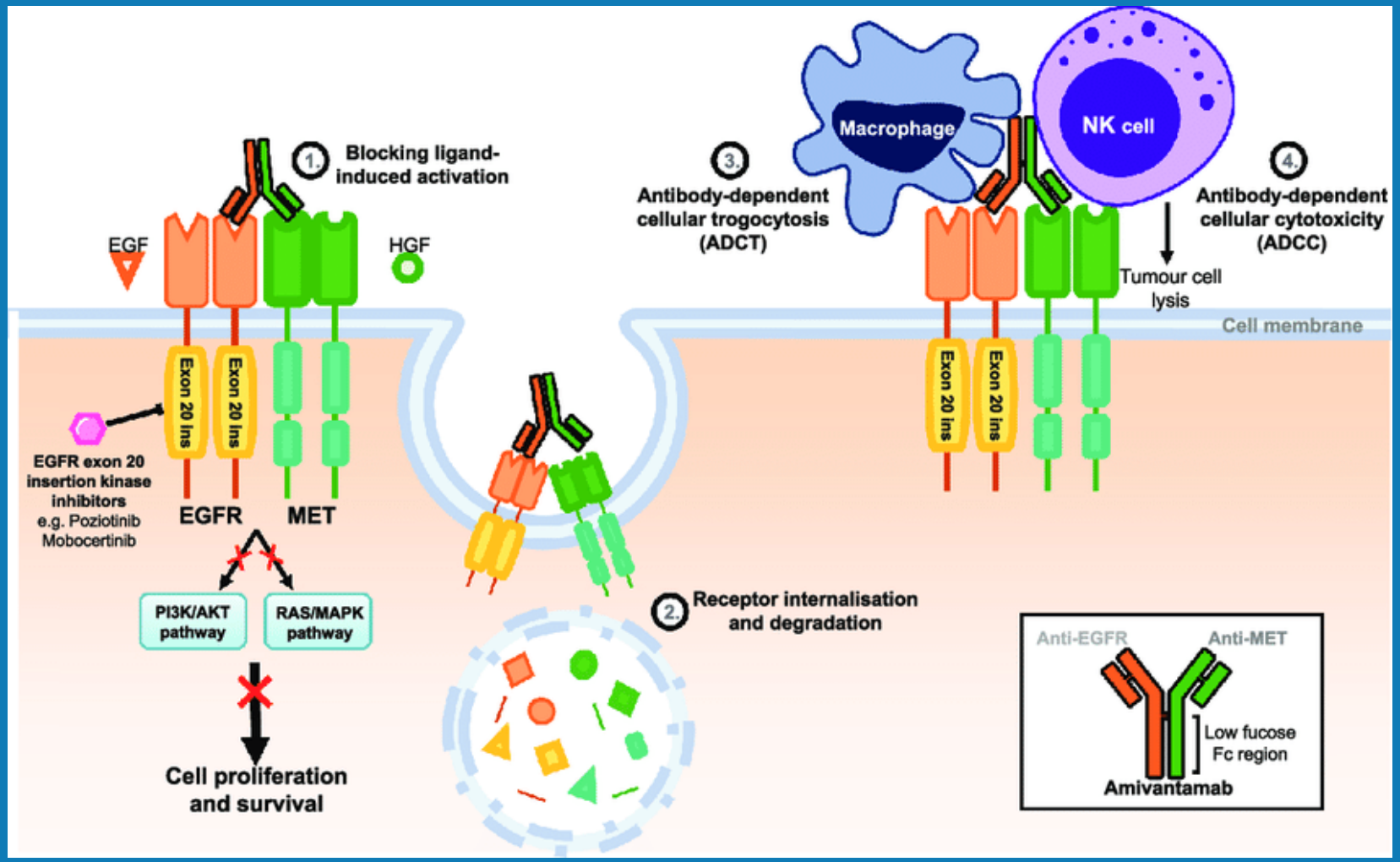
Amivantamab + chemo beat chemo alone



Zhou C, et al. *N Engl J Med*. 2023;NEJMoa2306441.

Amivantamab





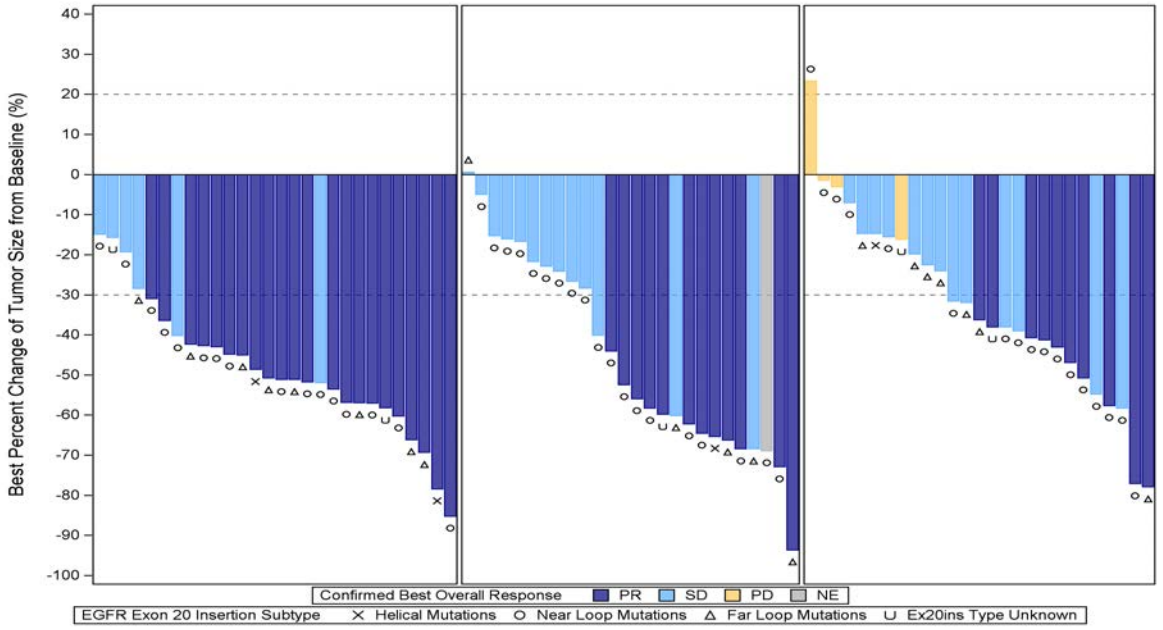
Vyse, et al, Exp Rev of Anti-infective Therapy, 2021.

Update: Novel therapies for EGFR exon 20 Mutations in NSCLC

UCLA Health | David Geffen School of Medicine

- Structure and pathophysiology of EGFR exon 20 mutations
- First line therapy: Amivantamab and chemotherapy
- 3 TKI's in trials
- 3 ADC's in trials

Soon to come: New TKI's



Efficacy by IRC	Treatment Naïve 240mg N=28	Previously Treated 240mg N= 26	Previously Treated 160mg N= 26
Confirmed ORR, % (95% CI)	78.6% (59.05%, 91.70%)	46.2% (26.59%, 66.63%)	38.5% (20.23%, 59.43%)
Best Response, n (%)			
Partial response (PR)	22 (78.6%)	12 (46.2%)	10 (38.5%)
Stable disease (SD)	6 (21.4%)	12 (46.2%)	12 (46.2%)
Progressive disease (PD)	0	0	4 (15.4%)
Not evaluable/Not done	0 / 0	1 (3.8%) / 1 (3.8%)	0 / 0
DoR, median (months) (95% CI)	15.2 (8.74, 24.84)	13.1 (5.62, 13.80)	9.7 (5.59, NA)
DCR (CR+PR+SD), % (95% CI)	100.0% (87.66%, 100.00%)	92.3% (74.87%, 99.05%)	84.6% (65.13%, 95.64%)

Firmonertinib

FAVOUR trial in EGFR exon 20

	Tx Naive	Pre-treated
Confirmed ORR	79%	46%
Grade 3 TRAE	13%	29%
Diarrhea (total/Gr3-4)	74% / 0%	86% / 0%
Anemia (total/Gr3-4)	43% / 0%	25% / 0%
Rash (total/Gr3-4)	23% / 0%	21% / 0%

Han B, et al. Presented at: WCLC, 2023.

Soon to come: New TKI's

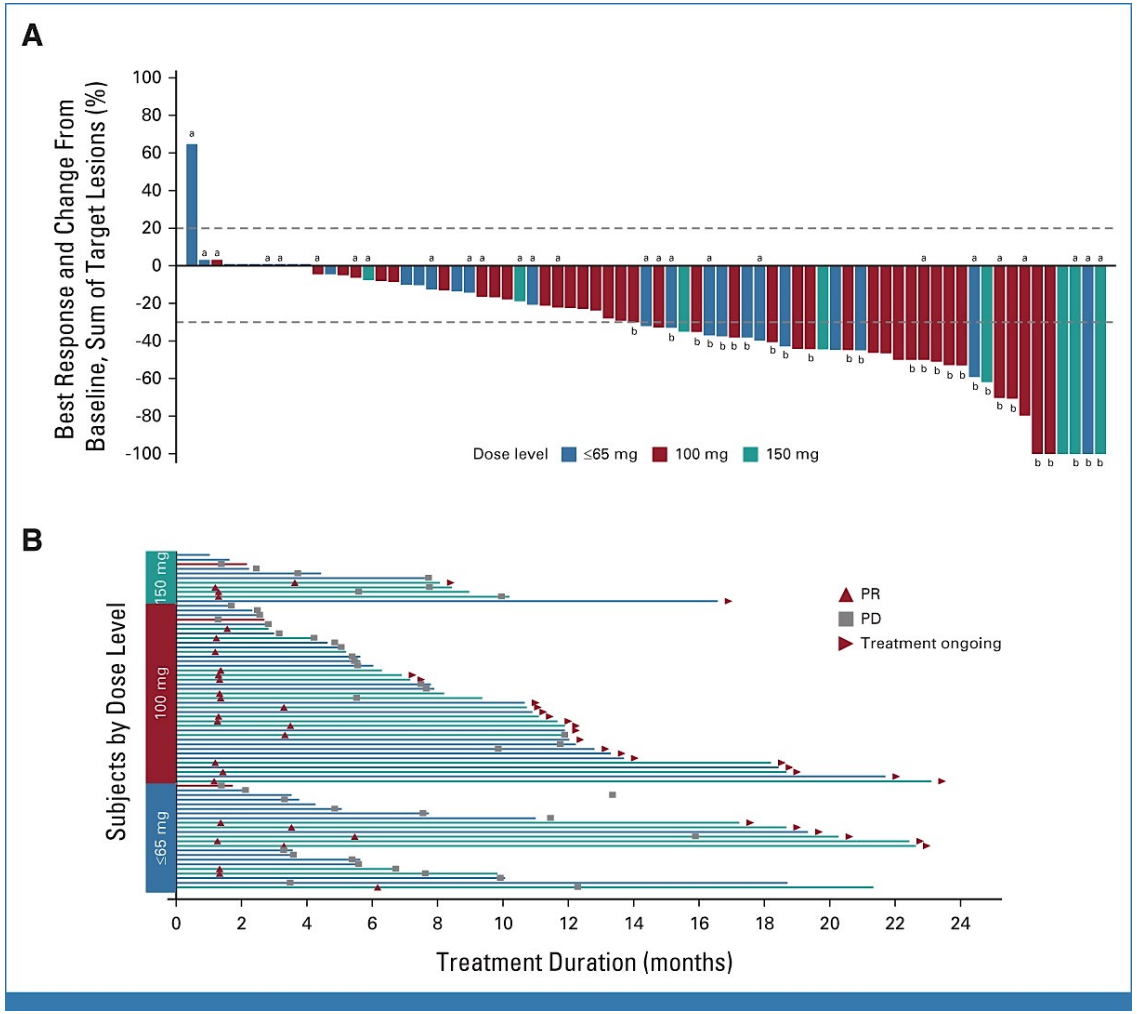
UCLA Health | David Geffen School of Medicine

Zipalertinib (CLN-081/TAS6417)

REZILIENT trials

- 73 patients, mostly pretreated but only 1/3 with prior TKI

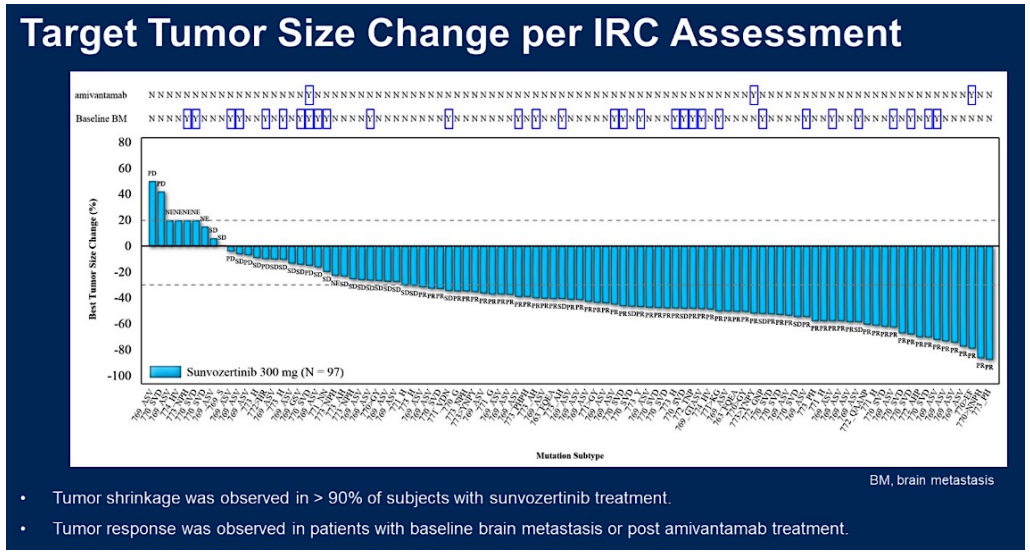
Confirmed ORR	38%
Grade 3 TRAE	13%
Rash (total/Gr3-4)	80% / 1%
Paronychia (total/Gr3-4)	32% / 0%
Diarrhea (total/Gr3-4)	30% / 3%

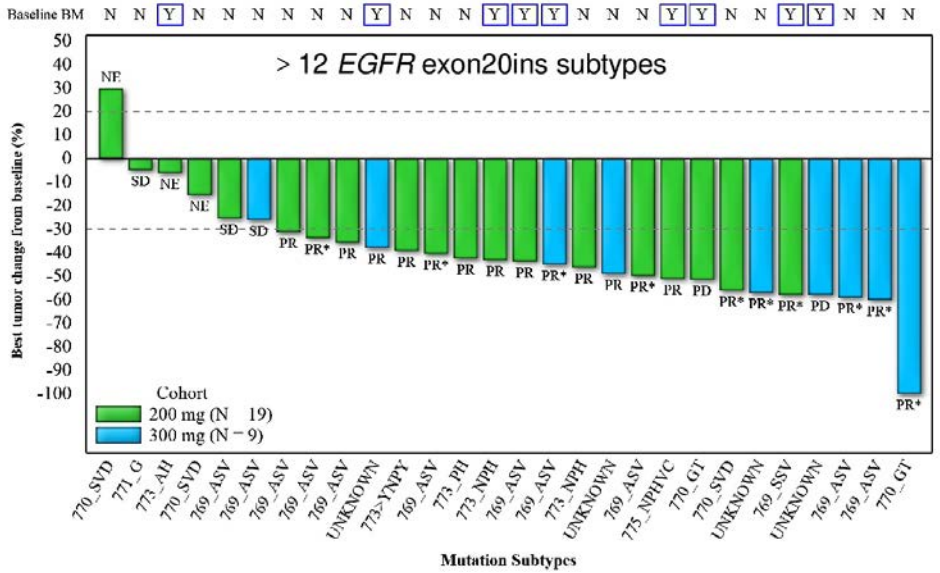


Piotrowska Z, et al. *J Clin Oncol*. 2023;41(26):4218-4225.

Soon to come: New TKI's

UCLA Health | David Geffen School of Medicine





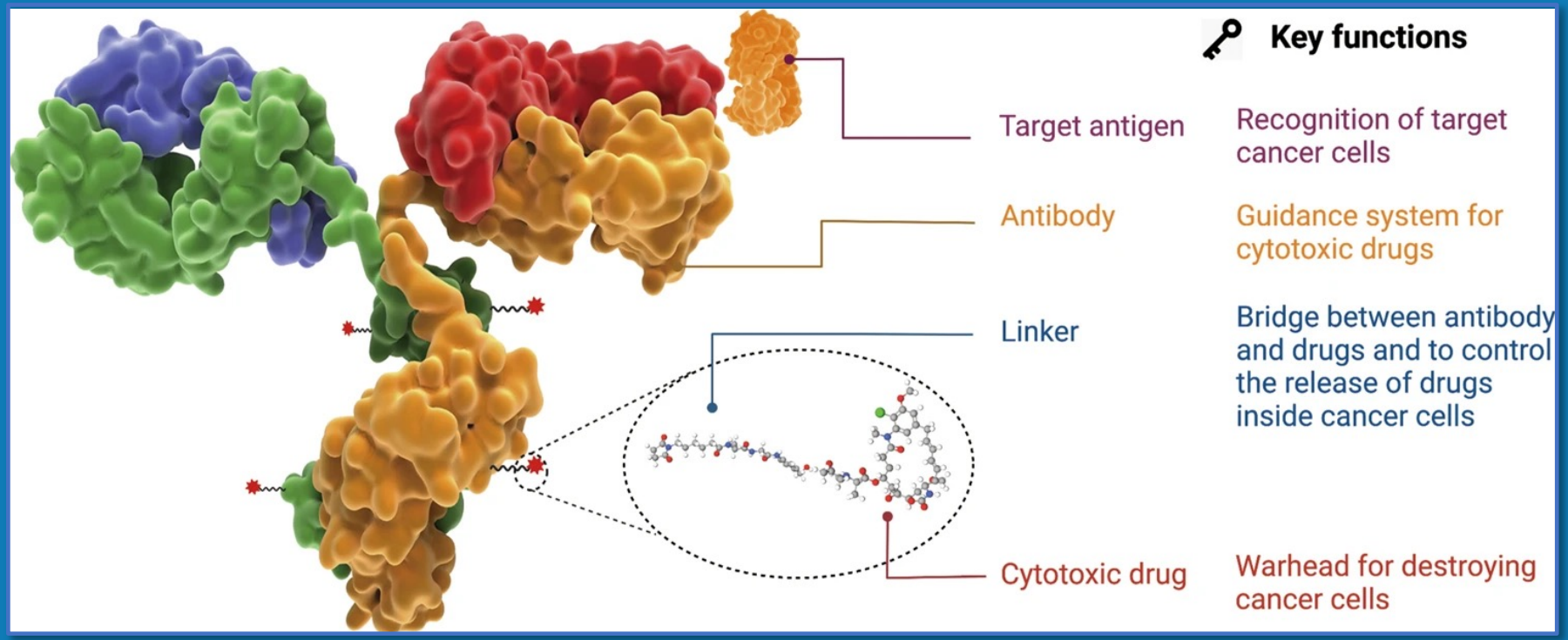
Sunvozertinib

WU-KONG trials

	Tx Naive	Pre-treated
Confirmed ORR	71%	61%
Grade 3 TRAE	NR	39%
Diarrhea (total/Gr3-4)	NR / 3.6%	67% / 7.7%
Rash (total/Gr3-4)	NR / 3.6%	54% / 1%
Paronychia		34% / 2%
Anemia		49% / 6%

Wang M, et al. *J Clin Oncol*. 2023;41(Suppl 16):9002. Xu Y, et al. *J Clin Oncol*. 2023;41(16_suppl):9073.

Antibody Drug Conjugates



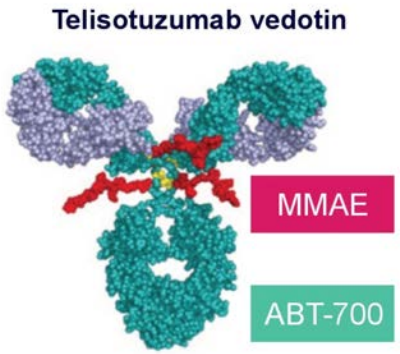
ADC COMPONENTS

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

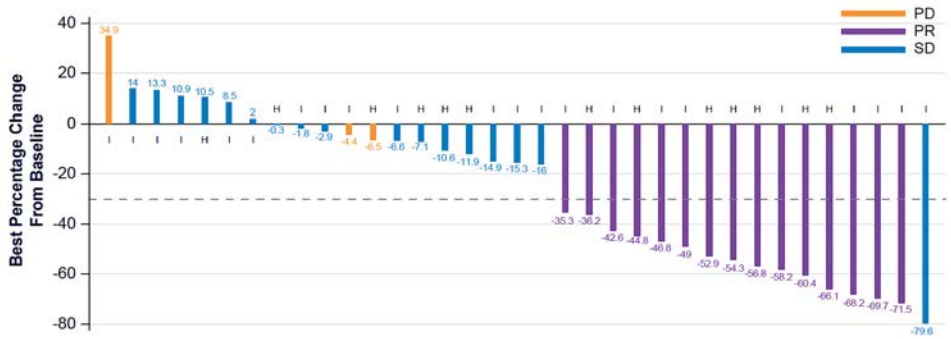
- Most data here focuses on canonical EGFR mutations (exon 19 deletions and L858R), and activity in atypical mutations is inferred.

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

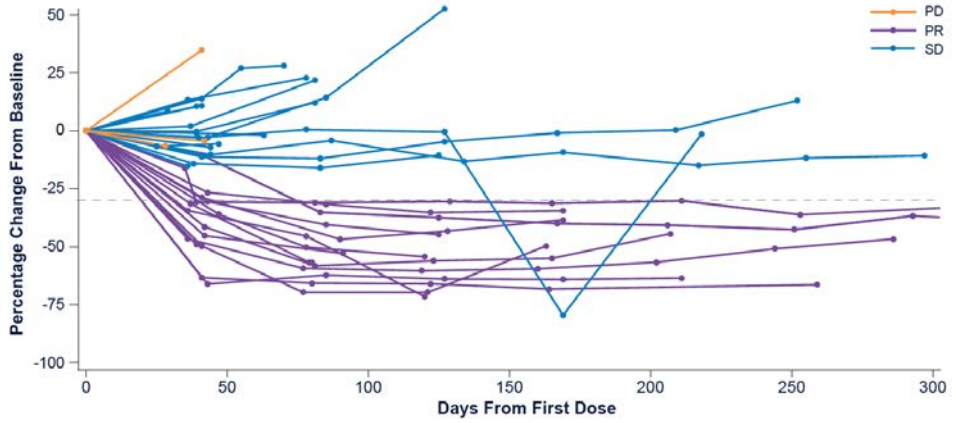
Telisotuzumab Vedotin in MET overexpressing NSCLC



Best Percent Change in Size of Target Lesion Nonsquamous *EGFR* WT



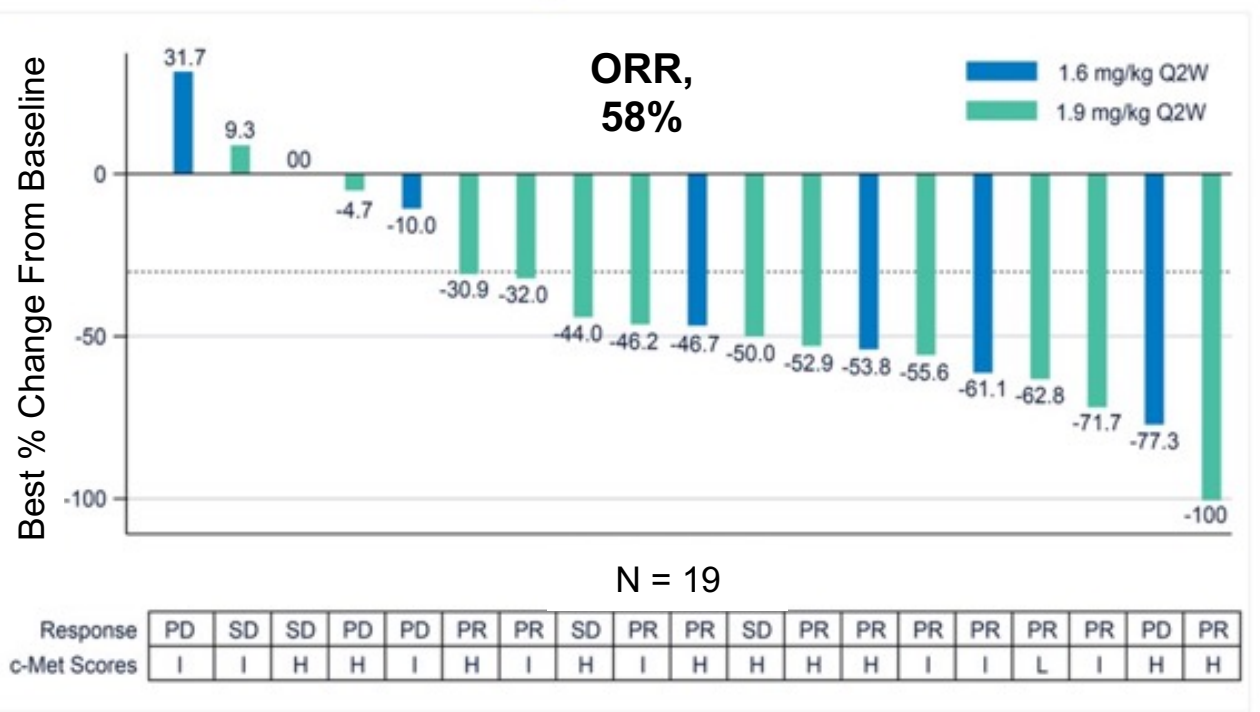
Nonsquamous *EGFR*-Mutant



TEAEs, n (%)	Nonsquamous *EGFR* WT (n = 47)	Nonsquamous *EGFR*-Mutant (n = 38)	Squamous (n = 28)
Any	44 (94)	37 (97)	27 (96)
Related to study drug	32 (68)	33 (87)	16 (57)
Grade ≥3	24 (51)	13 (34)	13 (46)
Serious	19 (40)	8 (21)	7 (25)
Leading to Teliso-V discontinuation	16 (34)	8 (21)	10 (36)
Leading to death possibly related to Teliso-V	1 (2)	0	2 (7)
Any-grade AEs [≥10% of patients], n (%)			
Nausea	**10 (21)**	**11 (29)**	**5 (18)**
Hypoalbuminemia	**12 (26)**	**5 (13)**	**5 (18)**
Decreased appetite	**9 (19)**	**9 (24)**	**2 (7)**
Peripheral edema	**10 (21)**	**7 (18)**	**3 (11)**
Peripheral sensory neuropathy	**10 (21)**	**8 (21)**	**2 (7)**
Vision blurred	7 (15)	7 (18)	3 (11)
Asthenia	6 (13)	7 (18)	3 (11)
Gamma-glutamyltransferase increased	6 (13)	4 (11)	6 (21)
Keratitis	4 (9)	10 (26)	2 (7)
Constipation	5 (11)	8 (21)	2 (7)
Fatigue	4 (9)	7 (18)	4 (14)
Anemia	7 (15)	4 (11)	3 (11)
Alanine aminotransferase increased	4 (9)	5 (13)	3 (11)
Diarrhea	3 (6)	6 (16)	3 (11)
Dizziness	4 (9)	5 (13)	3 (11)
Dyspnea	6 (13)	3 (8)	3 (11)
Grade ≥3 AEs [≥3 patients], n (%)			
Malignant neoplasm progression	3 (6)	3 (8)	1 (4)
Pneumonia	3 (6)	2 (5)	1 (4)
Hyponatremia	0	1 (3)	4 (14)
Anemia	2 (4)	1 (3)	0
Dyspnea	1 (2)	1 (3)	1 (4)
Fatigue	1 (2)	0	2 (7)
Gamma glutamyltransferase increased	0	2 (5)	1 (4)
Peripheral sensory neuropathy	2 (4)	0	1 (4)
Pneumonitis	1 (2)	1 (3)	1 (4)

Camidge DR et al. *Clin Cancer Res*. 2021;27:5781-5792.

Telisotuzumab Vedotin + Osimertinib: activity post osimertinib



Category	N	ORR,[a] %
Teliso-V dose, mg/kg		
1.6	7	43
1.9	12	67
Total	19	58
cMET level, 3+ staining		
High (≥50%)	10	50
Intermediate (25%-49%)	8	63
Total	18	56
EGFR mutation		
L858R	9	56
Del19	9	67
Total	18	58
Last prior regimen		
Contained osimertinib	8	50
Did not contain osimertinib	11	64
Total	19	58

Goldman JW et al. ASCO 2022. Abstract 9013.

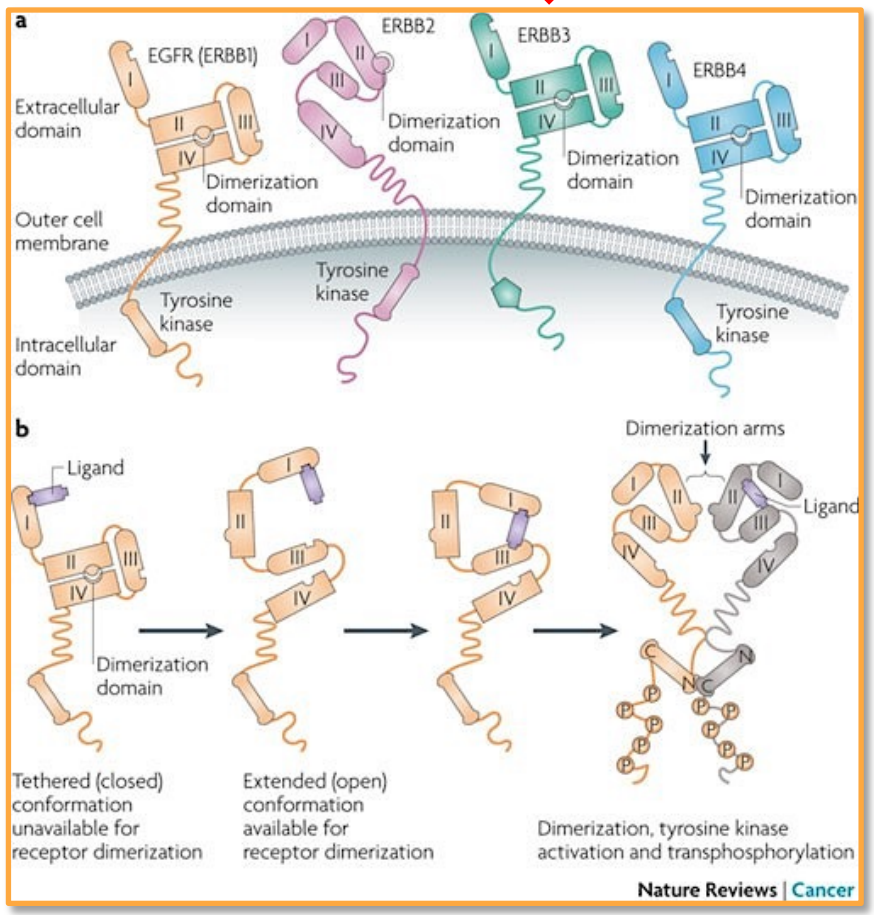
Post-Osimertinib Therapies With MET as a Target

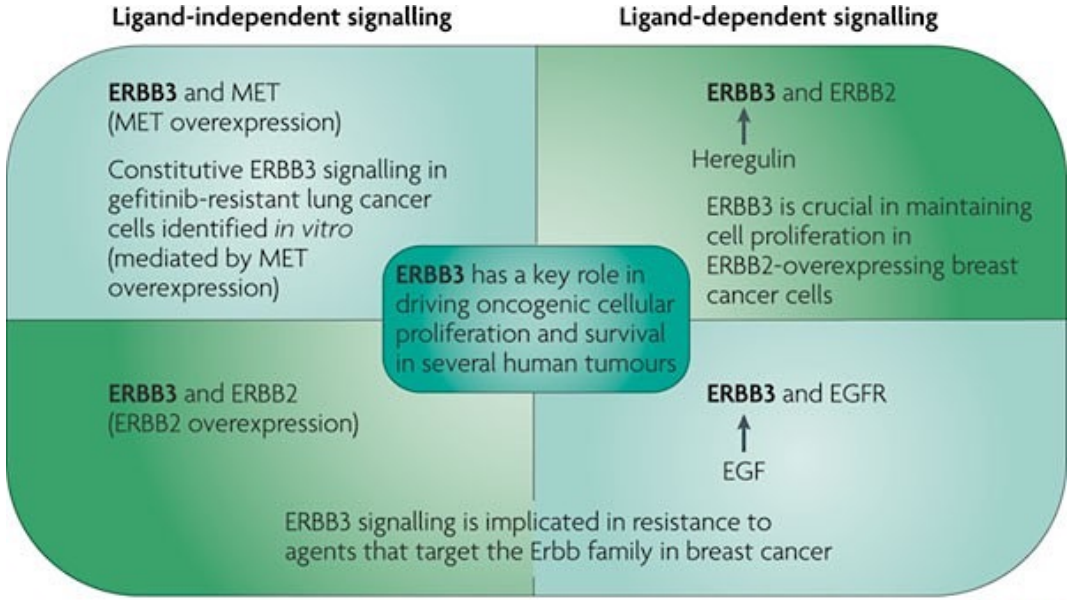
	Amivantamab + Lazertinib (N = 45)[1]	Amivantamab + Lazertinib PD Chemotherapy (N = 162)[2]	Osimertinib + Savolitinib (N = 69)[3]	Teliso-V + Osimertinib (N = 25)[4]
Study	CHRYSALIS	CHRYSALIS-2	TATTON (B1)	-
Target	*EGFR/MET*	*EGFR/MET*	*EGFR/MET*	*MET* Expression
ORR, %	36	33	30	58
Median DOR, mo	9.6	9.6	7.9	Not reported
Median PFS, mo	4.9	5.1	5.4	Not reported
Grade ≥3 TRAE, %	16	38	57	32

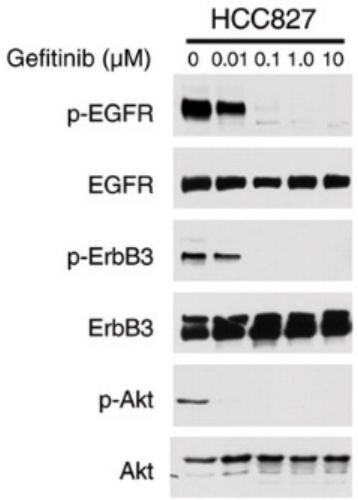
1. Sequist LV et al. *Lancet Oncol*. 2020;21:373-386. 2. Cho BC et al. ASCO 2021. Abstract 9006. 3. Shu CA et al. ASCO 2022. 4. Goldman JW et al. ASCO 2022. Abstract 9013.

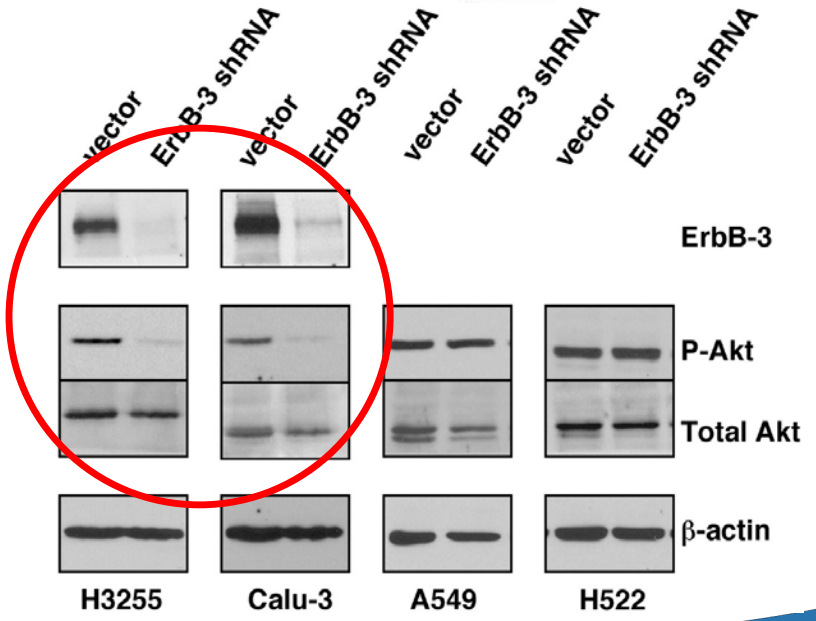
Targeting HER3: mechanism of action

UCLA Health | David Geffen School of Medicine







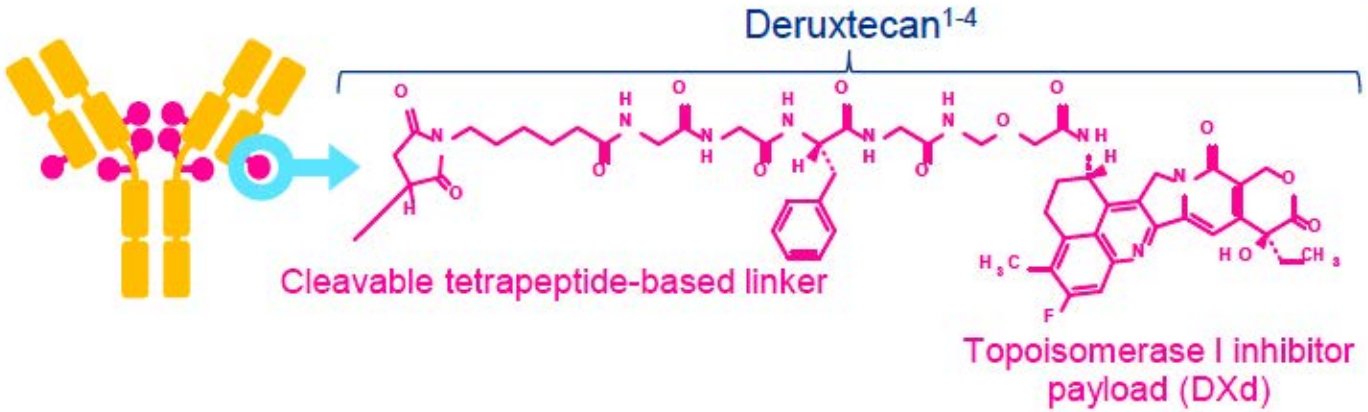


Baselga, J., Swain, S. *Nat Rev Cancer* **9**, 463–475 (2009).
J.A. Engelman, P.A. Jänne, C. et al. PNAS 102(10) 3788-3793.
Jeffrey A. Engelman et al, MET Amplification Leads to Gefitinib Resistance in Lung Cancer by Activating ERBB3 Signaling. Science 316,1039-1043(2007).

Patritumab Deruxtecan (HER3-DXd)

HER3-DXd is an ADC composed of 3 parts[1-4]:

- A fully human anti-HER3 IgG1 mAb (patritumab)
- A topoisomerase I inhibitor payload (DXd)
- A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



Payload mechanism of action: topoisomerase I inhibitor[1-4,a]
High potency of payload[1-4,a]
High drug to antibody ratio ≈8[1,2,a]
Payload with short systemic half-life[2,3,a,b]
Stable linker-payload[2-4,a]
Tumor-selective cleavable linker[1-5,a]
Bystander antitumor effect[2,6,a]

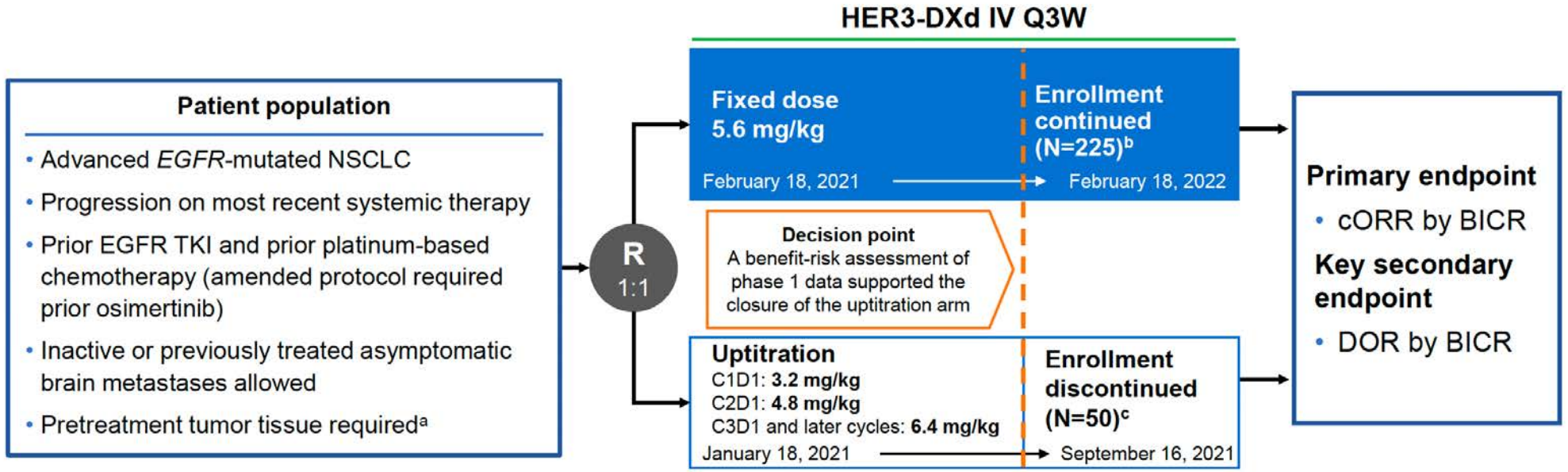
Yu, H. 2023 WCLC.

Patritumab: HER3-DXd

UCLA Health | David Geffen School of Medicine

Patritumab Deruxtecan
HERTHENA-Lung01

HERTHENA-Lung01 Study Design[1]



Primary data cutoff, 21 Nov 2022[d]
Snapshot data cutoff, 18 May 2023 (additional 6 months follow-up)
Data are presented for the 5.6-mg/kg fixed-dose arm

- Efficacy from snapshot data cutoff—median study follow-up, 18.9 (range, 14.9-27.5) months
- Safety from primary data cutoff—median treatment duration, 5.5 (range, 0.7-18.2) months

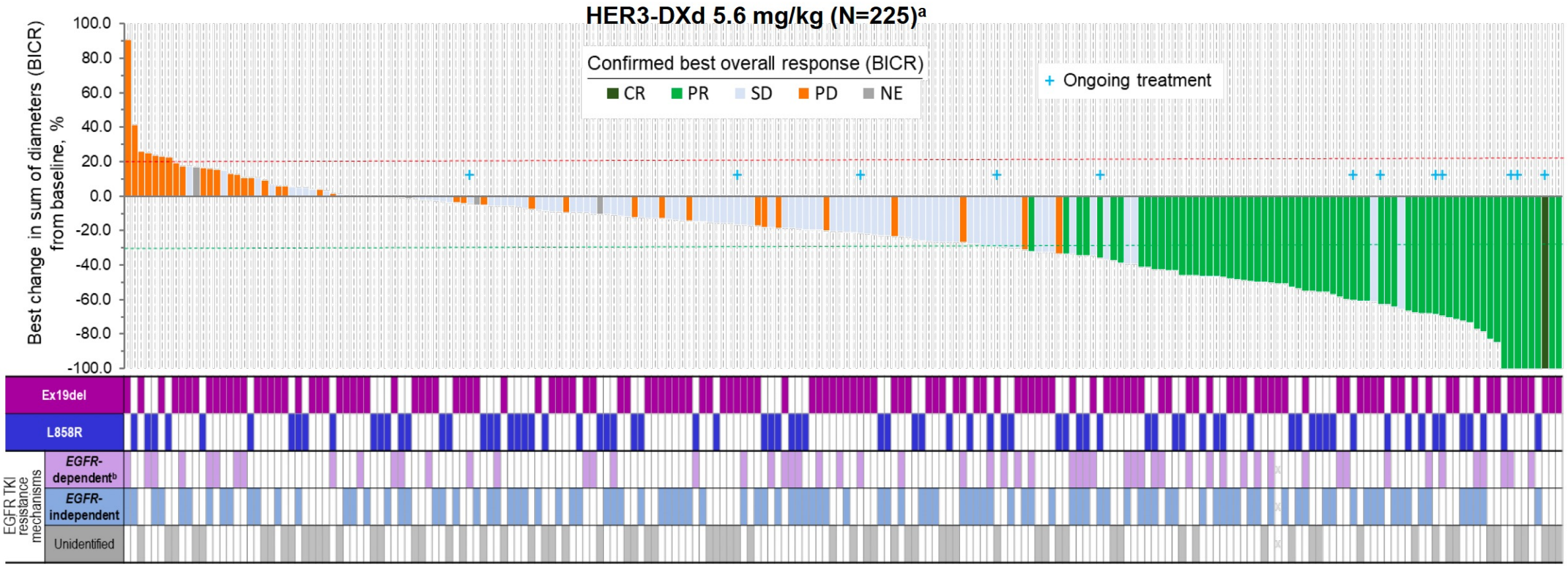
BICR, blinded independent central review; C, cycle; cORR, confirmed objective response rate (complete or partial response confirmed ≥4 weeks after initial response [RECIST version 1.1]); D, day; DOR, duration of response; HER, human epidermal growth factor receptor; IV, intravenous; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.
[a] Inclusion not based on detection of HER3 expression. [b] 226 patients were enrolled; 225 received ≥1 dose. [c] 51 patients were enrolled; 50 received ≥1 dose. [d] Data cutoff for the primary analysis occurred when all enrolled patients had either ≥9 months of follow-up or had discontinued from the study earlier.

1. Yu HA, et al. *Future Oncol*. 2023;19:1319-1329.

Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance

Patritumab Deruxtecan
HERTHENA-Lung01

Patritumab (HER3-DXd)



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

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

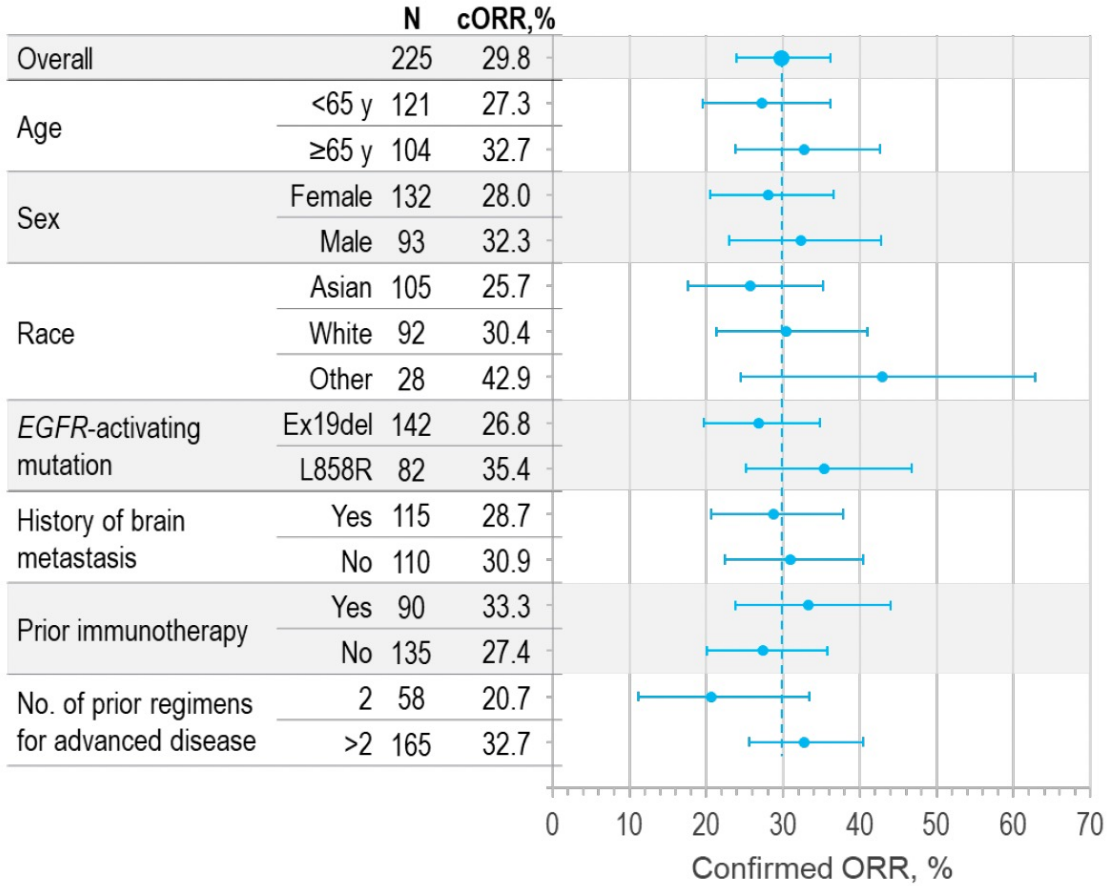
Clinically Meaningful Efficacy Was Observed in the Overall Population and Across Subgroups

Confirmed responses and survival		Prior EGFR TKI (any) and PBC (N=225)	Subset with prior 3G EGFR TKI and PBC (n=209)
cORR (95% CI), %		**29.8 (23.9-36.2)**	**29.2 (23.1-35.9)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	66 (29.3)	60 (28.7)
	SD[a]	99 (44.0)	91 (43.5)
	PD	43 (19.1)	41 (19.6)
	NE[b]	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), mo		6.4 (4.9-7.8)	6.4 (5.2-7.8)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.2-13.1)	11.9 (10.9-13.1)

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

Patritumab (HER3-DXd)

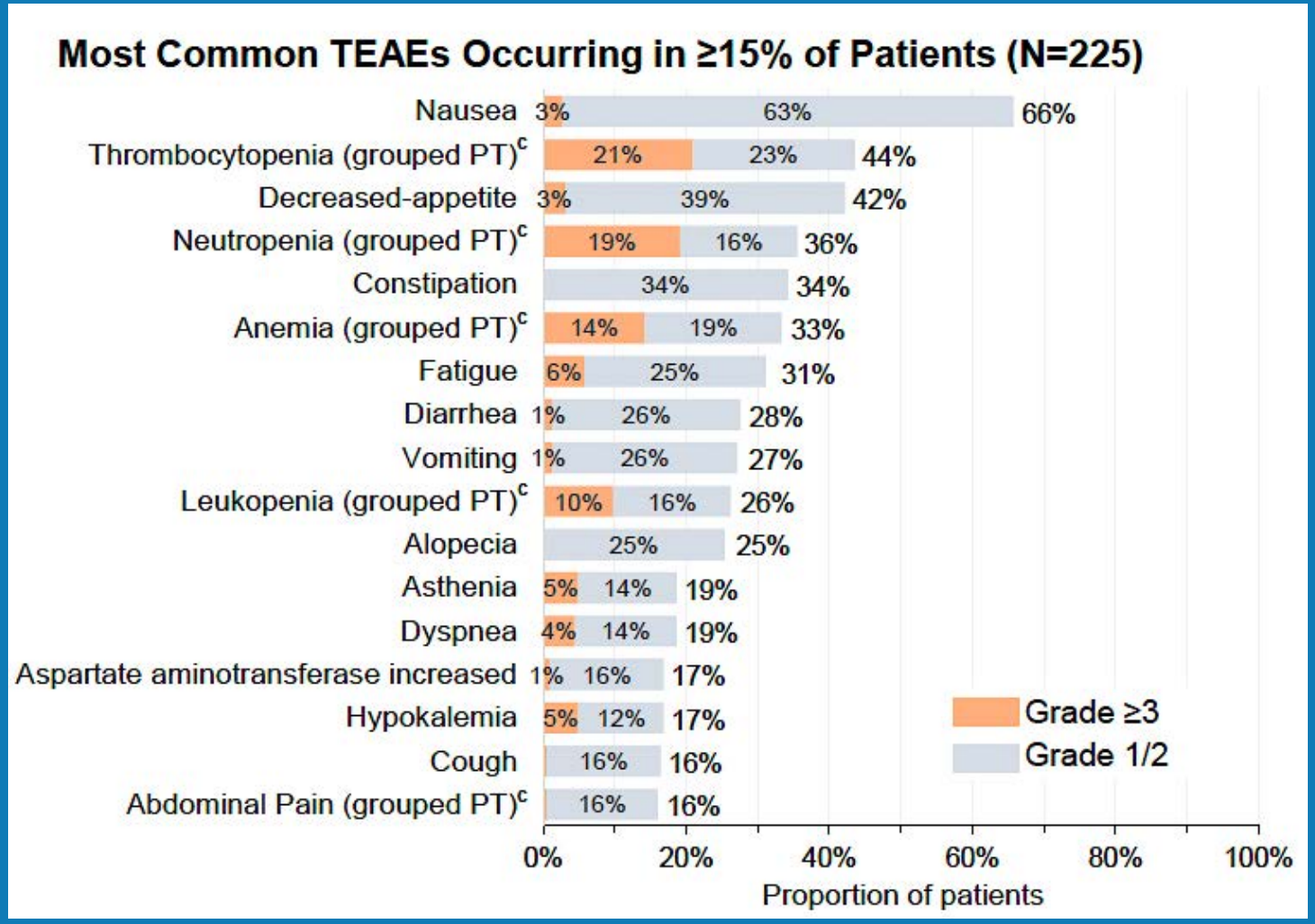
cORR by Patient and Disease Characteristics at Study Entry



3G, third generation; BICR, blinded independent central review; cORR, confirmed objective response rate (CR or PR confirmed ≥4 weeks after initial response [RECIST v1.1]); CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] Includes non-CR/non-PD. [b] No adequate postbaseline tumor assessment (n=12); SD too early (SD <5 weeks after start of study treatment [n=4]).

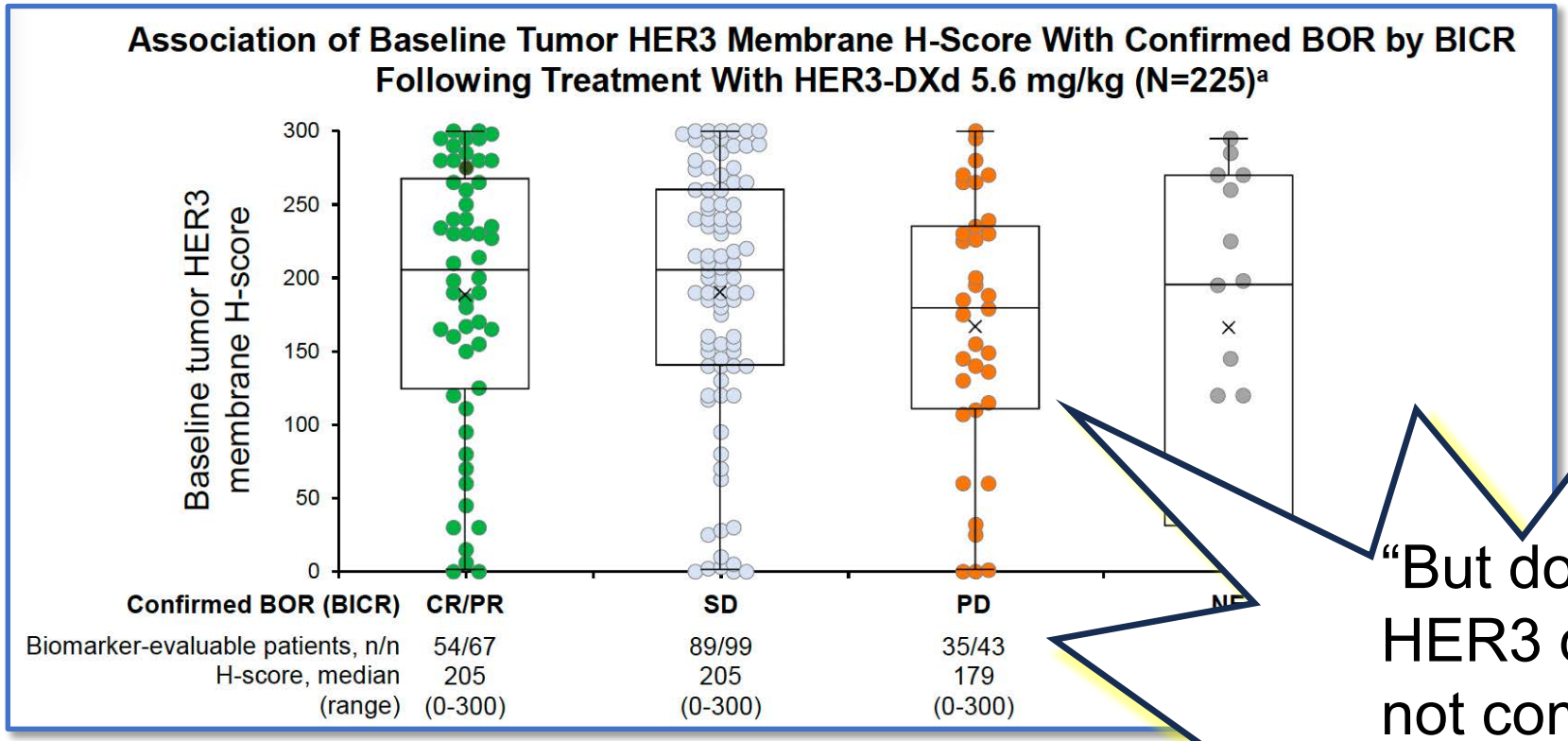
Patritumab DXd Adverse Events

- Tolerated better than many ADCs
- Toxicities primarily grade 1/2 nausea, diarrhea and anorexia and cytopenias
- Adjudicated ILD rate 5.3% (1.3 % Gr 3-5)
- Tox-related treatment discontinuation 7.1%



Patritumab activity: target dependent?

UCLA Health | David Geffen School of Medicine

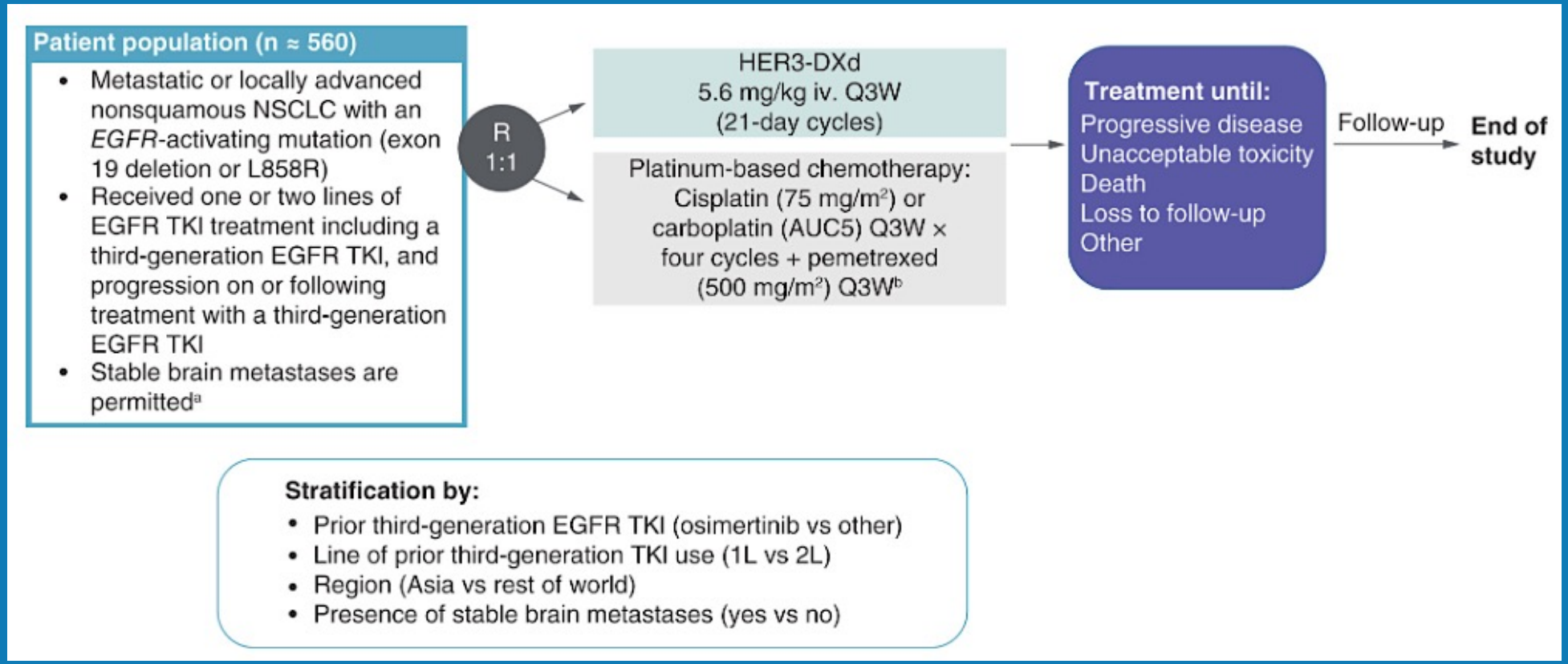


"But doc, HER3 did not come up on my NGS report!"

Activity not dependent on target H score:

- Potentially can benefit a large proportion of patients
- Do we understand the mechanism of action?

HERTHENA-Lung02

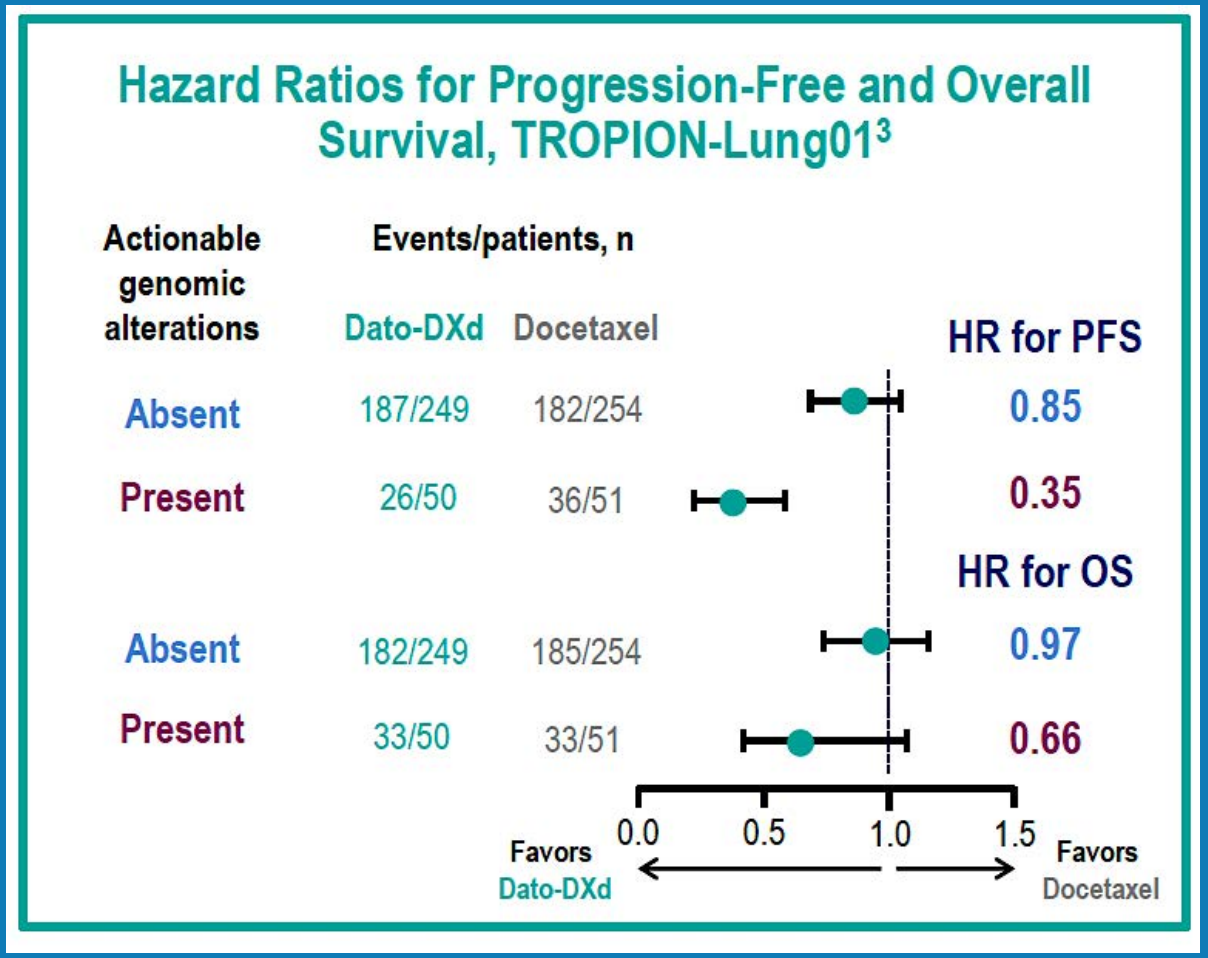


- 586 subjects enrolled
- 9/17/24 Press release: statistically significant improvement in PFS. OS data are immature.
- No new safety signals. 2 grade 5 ILD events.

Mok, T., Jänne, P. A., Yu, H, et al. Future Oncology 2024, 20(15), 969–980.

Datopotamab deruxtecan (Dato-DXd)

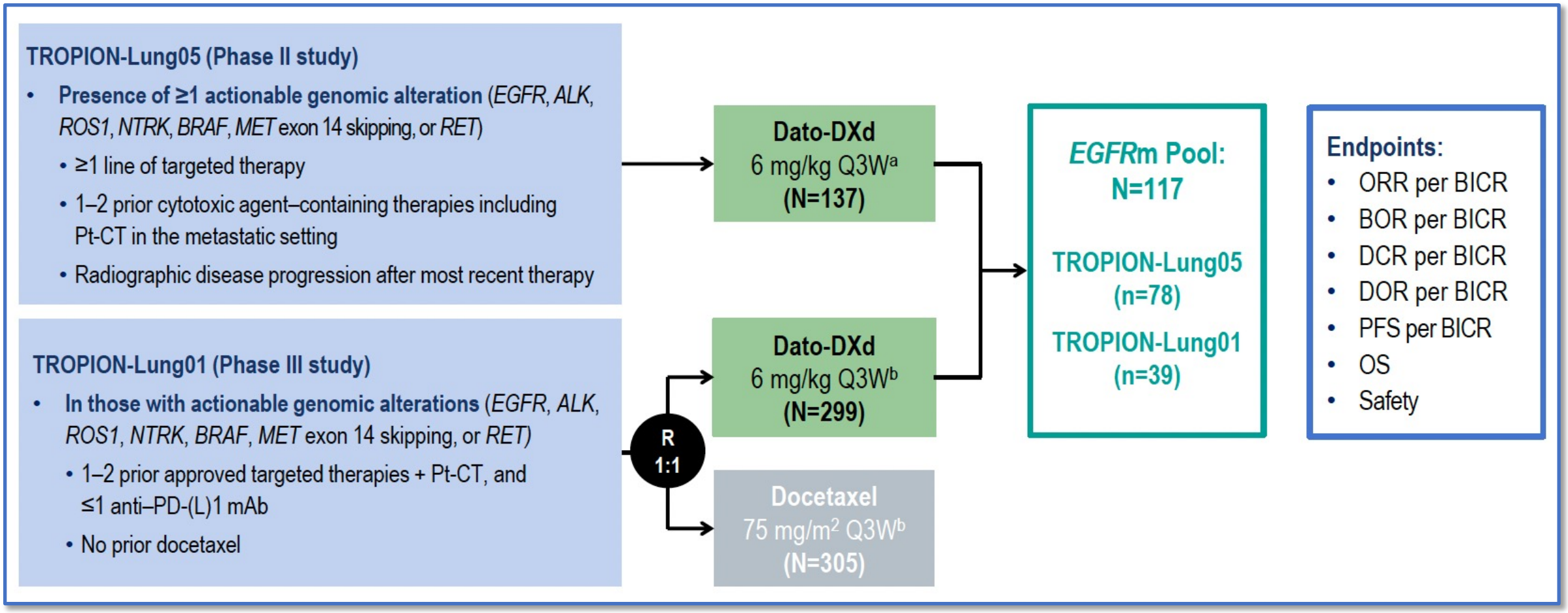
- Trop2-directed ADC
- Topoisomerase I inhibitor payload



Ahn, M-J, ESMO Asia, 2024.

Dato-DXd in EGFRm NSCLC

Pooled Analysis from TROPION-Lung05 and 01



Ahn, M-J, ESMO Asia, 2024.

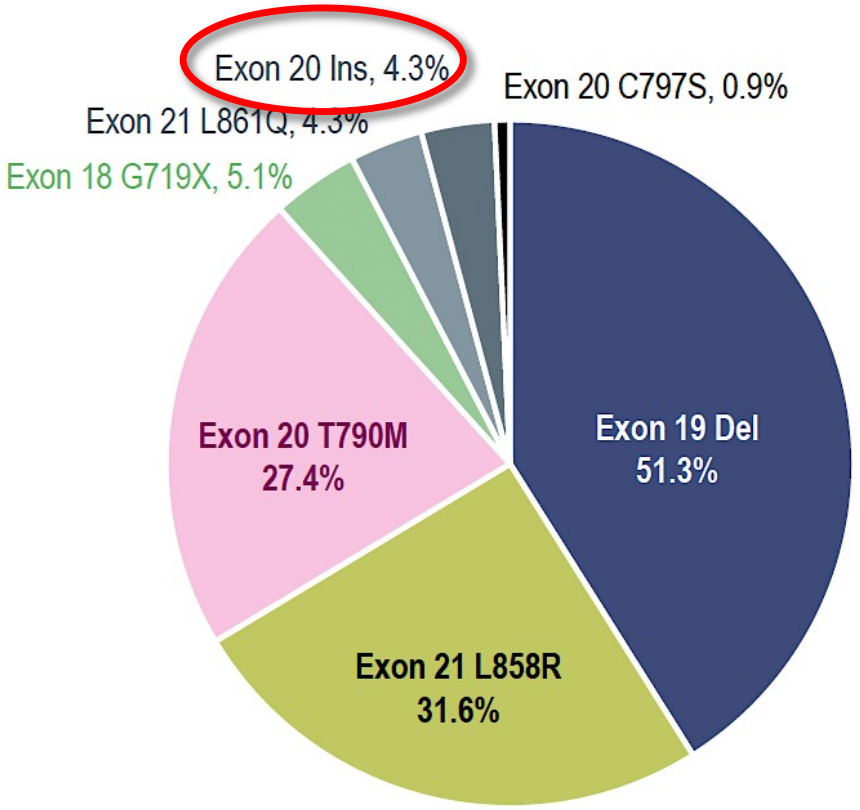
TROPION-Lung01 & 05 EGFRm cohort

UCLA Health | David Geffen School of Medicine

Demographics and Baseline Characteristics

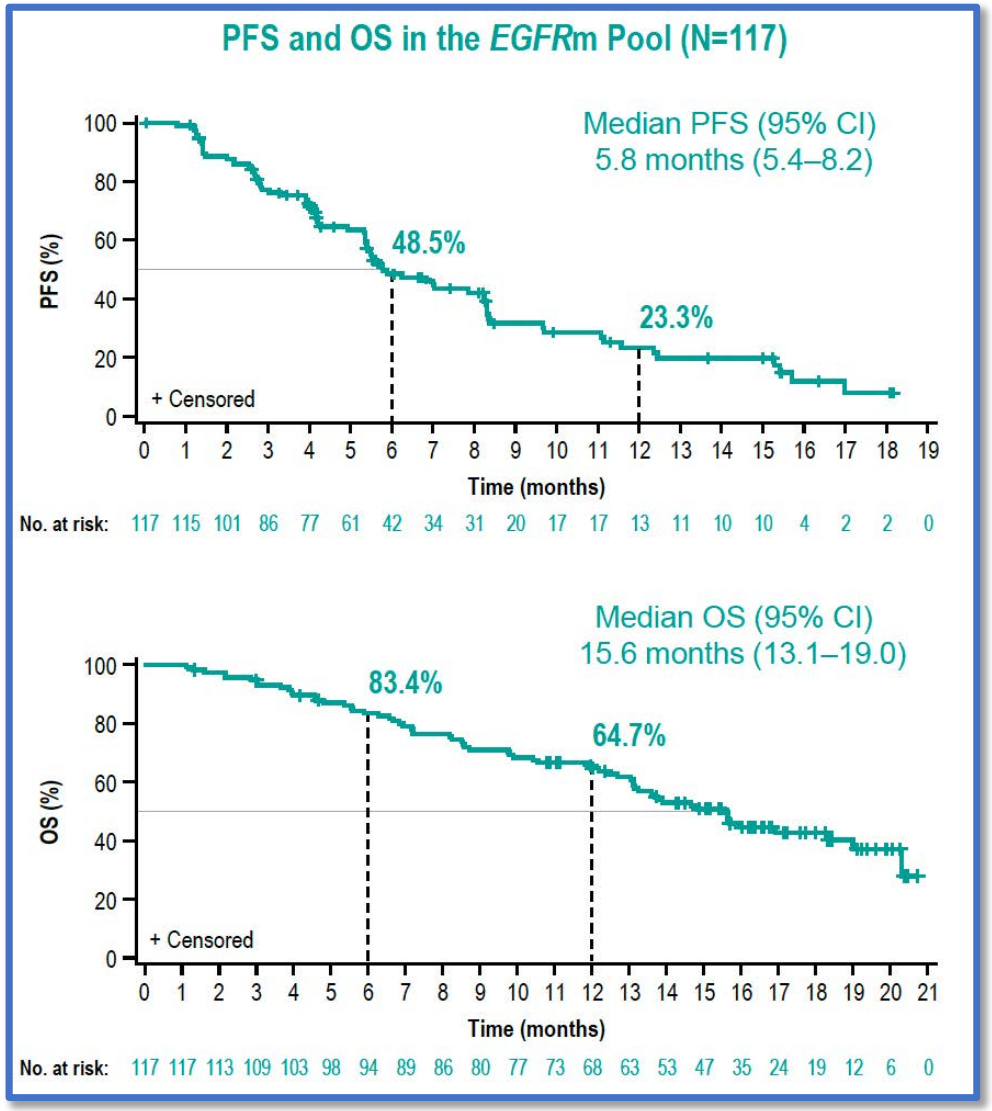
Characteristic	*EGFR*m Pool (N=117)	TROPION-Lung05 (N=78)	TROPION-Lung01 (N=39)
Median age (range), years	63 (36–81)	63 (36–77)	62 (39–81)
Sex, female, n (%)	73 (62.4)	52 (66.7)	21 (53.8)
Race, n (%)			
Asian	81 (69.2)	55 (70.5)	26 (66.7)
White	27 (23.1)	20 (25.6)	7 (17.9)
Black or African American	1 (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



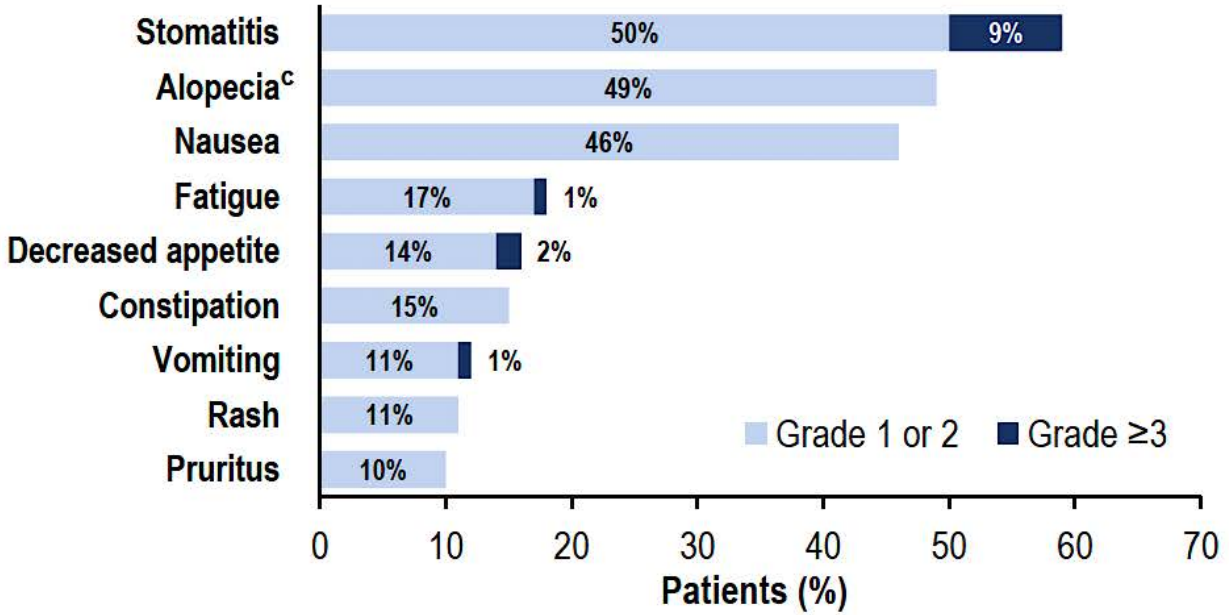
- Confirmed ORR 42.7%
- CR rate 4.3%
- mDOR 7.0 m
- DCR 86.3%

Ahn, M-J, ESMO Asia, 2024.

Safety Summary Dato-DXd

	*EGFR*m Pool (N=117)
TRAEs, n (%)	111 (95)
Grade ≥3	27 (23)
Associated with dose reduction	26 (22)
Associated with dose delay	27 (23)
Associated with treatment discontinuation	6 (5)
Associated with death	0 (0)
Serious TRAEs	9 (8)
AESIs[a], n (%)	
Stomatitis/oral mucositis	81 (69)
Grade 3[b]	11 (9)
Ocular surface events	38 (32)
Grade 3[b]	3 (3)
Adjudicated drug-related ILD	5 (4)
Grade 3[b]	1 (1)

TRAEs Occurring in ≥10% of *EGFR*m Pool (N=117)



- Median Dato-DXd treatment duration: **6.1 months**

- Overall safety profile consistent with TROPION-Lung01 and 05
- No grade 4 or 5 adjudicated drug-related ILD
- Ocular surface events[a] were primarily dry eye (12%), vision blurred and keratitis (each 7%)
- No TRAEs associated with death

[a]AESIs listed are treatment emergent and include all preferred terms that define the medical concept. Some patients may have had >1 event. [b]No grade 4 or 5 events occurred. [c]Includes an event incorrectly reported as grade 3 per CTCAE grades.
AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; *EGFR*m, *EGFR* mutated; ILD, interstitial lung disease; TRAE, treatment-related adverse event.

Datopotamab deruxtecan granted Priority Review in the US for patients with previously treated advanced EGFR-mutated non-small cell lung cancer Press Release: January 13, 2025

The Biologics License Application (BLA) for datopotamab deruxtecan (Dato-DXd) has been accepted and granted Priority Review in the US for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor-mutated (*EGFR*m) non-small cell lung cancer (NSCLC) who have received prior systemic therapies, including an *EGFR*-directed therapy.

In a pooled analysis of patients with previously treated advanced or metastatic EGFRm NSCLC in the TROPION-Lung05 and TROPION-Lung01 trials presented at the European Society for Medical Oncology (ESMO) Asia 2024 Congress, datopotamab deruxtecan demonstrated a confirmed objective response rate (ORR) of 42.7% (95% confidence interval [CI] 33.6-52.2) as assessed by blinded independent central review (BICR) and a median duration of response (DoR) of 7.0 months (95% CI 4.2-9.8). The safety profile of datopotamab deruxtecan was consistent with previous reports from the TROPION-Lung05 and TROPION-Lung01 trials, with no new safety concerns identified.

https://www.astrazeneca.com/media-centre/press-releases/2025/datopotamab-deruxtecan-granted-priority-review-in-the-us-for-patients-with-previously-treated-advanced-egfr-mutated-non-small-cell-lung-cancer.html

Update: Novel therapies for EGFR exon 20 Mutations in NSCLC

UCLA Health | David Geffen School of Medicine

- Structure and pathophysiology of EGFR exon 20 mutations
- First line therapy: Amivantamab and chemotherapy
- 3 TKI's in trials
- 3 ADC's in trials
- There may be a role for all of the above.

Discussion Questions

- Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with metastatic nonsquamous NSCLC with an EGFR exon 20 insertion mutation and a PD-L1 TPS of 10%?

- A patient with metastatic nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 60% responds to first-line amivantamab/lazertinib and then experiences disease progression with no targetable secondary mutations. Regulatory and reimbursement issues aside, what is your most likely next systemic therapy?

Discussion Question

- A patient with metastatic nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 60% experiences disease progression on first-line osimertinib and second-line amivantamab/chemotherapy with no targetable secondary mutations. Regulatory and reimbursement issues aside, what is your most likely next systemic therapy?

Module 6: Gynecologic Cancers

Ovarian Cancer; HER2-Directed Therapy for Advanced Gynecologic Cancers — Dr O'Malley

Endometrial Cancer and Cervical Cancer — Dr Slomovitz

Module 6: Gynecologic Cancers

Ovarian Cancer; HER2-Directed Therapy for Advanced Gynecologic Cancers — Dr O'Malley

Endometrial Cancer and Cervical Cancer — Dr Slomovitz

Ovarian Cancer

David O'Malley, MD

Director & Professor, Division of Gynecologic Oncology in Obstetrics and Gynecology
John G. Boutselis Chair in Gynecologic Oncology
GOG-P Clinical Trial Advisor (Ovarian Cancer)

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

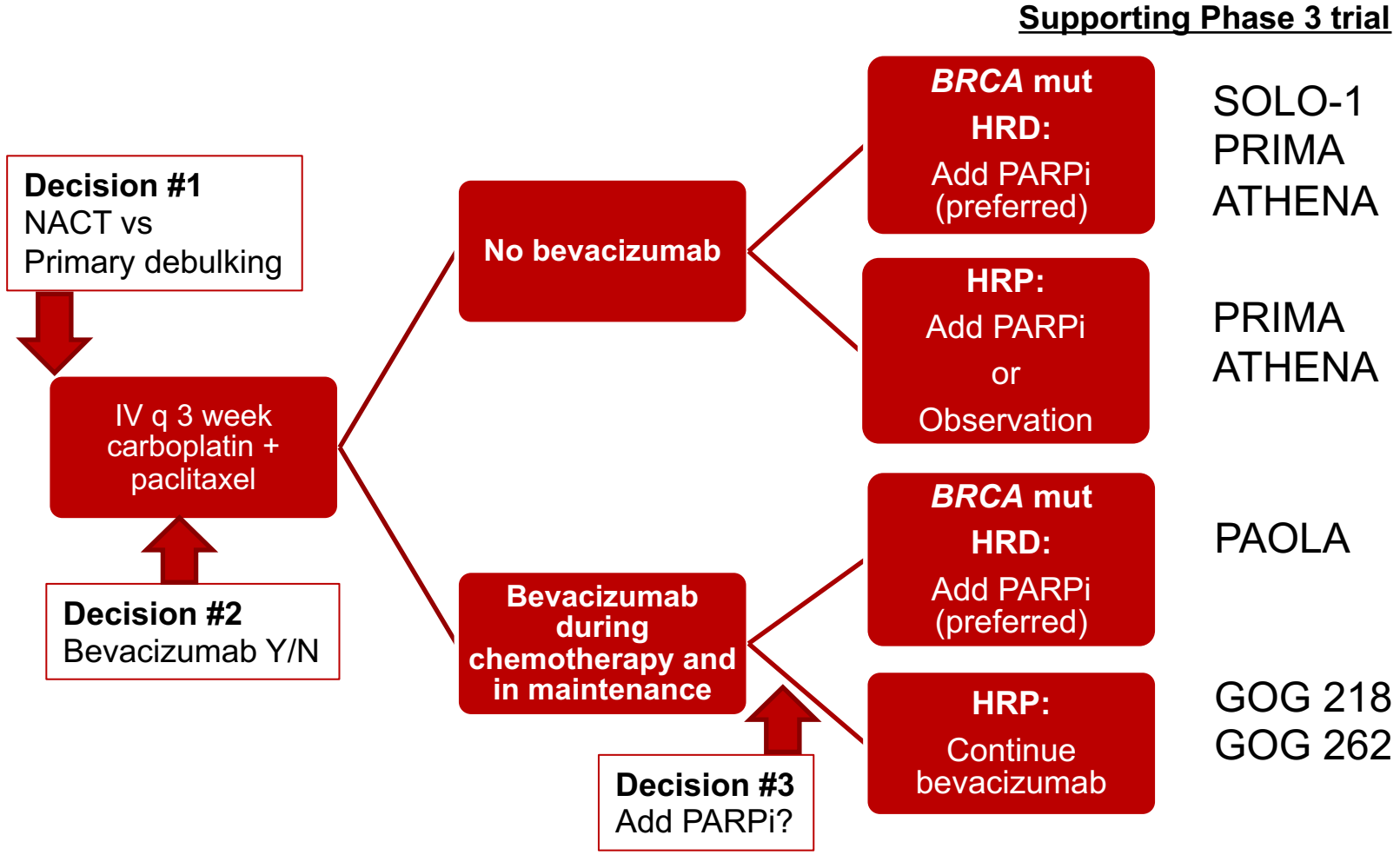
Creating a cancer-free world. One person, one discovery at a time.




Disclosures

Advisory Committees and Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Corcept Therapeutics, Duality Biologics, Genmab US Inc, GSK, Merck, MSD, Regeneron Pharmaceuticals Inc, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Sutro Biopharma, Verastem Inc
Contracted Research	AbbVie Inc, Adaptimmune, Advaxis Inc, Agenus Inc, Alkermes, Aravive Inc, Arcus Biosciences, Arquer Diagnostics, AstraZeneca Pharmaceuticals LP, Atossa Therapeutics, BeiGene Ltd, Bristol Myers Squibb, Cardiff Oncology, Celcuity, Clovis Oncology, Corcept Therapeutics, Deciphera Pharmaceuticals Inc, Duality Biologics, Eisai Inc, Elevar Therapeutics, EMD Serono Inc, Exelixis Inc, Genelux Corporation, Genentech, a member of the Roche Group, Genmab US Inc, GSK, ImmunoGen Inc, Imvax Inc, Incyte Corporation, InterVenn Biosciences, InxMed, Iovance Biotherapeutics, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Laekna Therapeutics, Leap Therapeutics Inc, Luzsana Biotechnology, Merck, Mersana Therapeutics Inc, MSD, Myriad Genetic Laboratories Inc, Novartis, Novocure Inc, Onconova Therapeutics Inc, OncoQuest Inc, Pfizer Inc, Predictive Oncology Inc, Prelude Therapeutics, Regeneron Pharmaceuticals Inc, Replimune, Roche Laboratories Inc, R-Pharm US, Rubius Therapeutics, Seagen Inc, Sorrento Therapeutics, Sumitomo Dainippon Pharma Oncology Inc, Sutro Biopharma, Tarveda Therapeutics, Tesaro, A GSK Company, Toray Industries Inc, Trillium Therapeutics Inc, Umoja Biopharma, VBL Therapeutics, Verastem Inc, Vincerx Pharma, Xencor, Zentalis Pharmaceuticals
Nonrelevant Financial Relationships	Amarex Clinical Research, GOG Foundation, Ludwig Institute for Cancer Research Ltd, National Cancer Institute, NRG Oncology, RTOG Foundation, SWOG

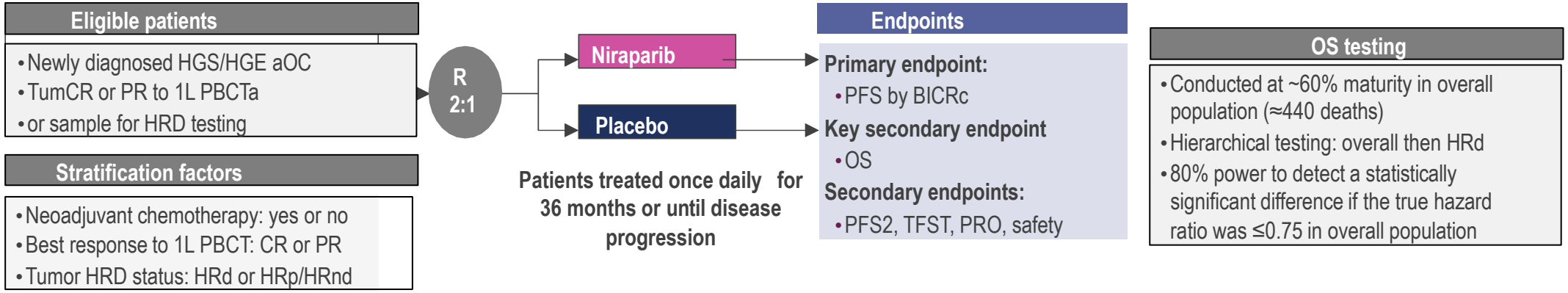
Integrated Maintenance Treatment Paradigm for Use in 1-L Ovarian Cancer



1. NCCN guidelines. Ovarian Cancer Nov, 2024.

PRIMA/ENGOT-OV26/GOG-3012 Trial of Niraparib 1L Maintenance

Phase 3 PRIMA trial enrolled patients with newly diagnosed aOC at a high risk for disease recurrence



Disease stage

35.1% stage IV disease at diagnosis

Initial treatment

66.7% received neoadjuvant chemotherapy

30.6% achieved partial response to 1L PBCT

Residual disease

>99% stage III disease at diagnosis with residual disease after primary debulking surgery

47.5% postoperative visible residual disease or no debulking surgery

Tumor HRD/*BRCA* status

50.9% HRd

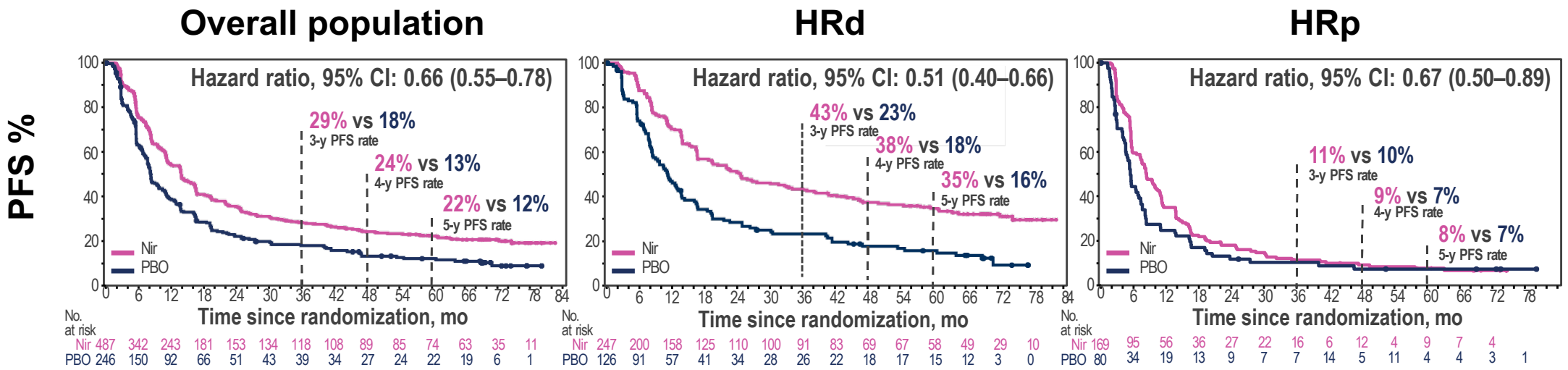
30.4% HRd/*BRCA*m

34.0% HRp

NCT02655016

González-Martín A, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain

Updated long-term PFS (investigator-assessed) PRIMA/ENGOT-OV26/GOG-3012 Trial of Niraparib 1L Maintenance



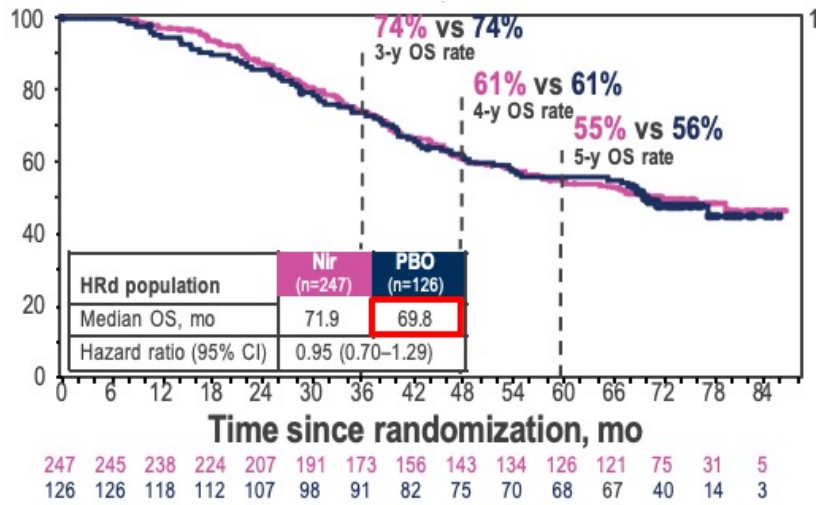
- Data cutoff date, 8 April 2024; median follow-up, 6.2 years
- Among patients alive at 5 years in the HRd population, patients who received niraparib were twice as likely to be progression free (35%) than patients who received placebo (16%)
- Delaying progression is critical to maintain health-related quality of life[1]

NCT02655016

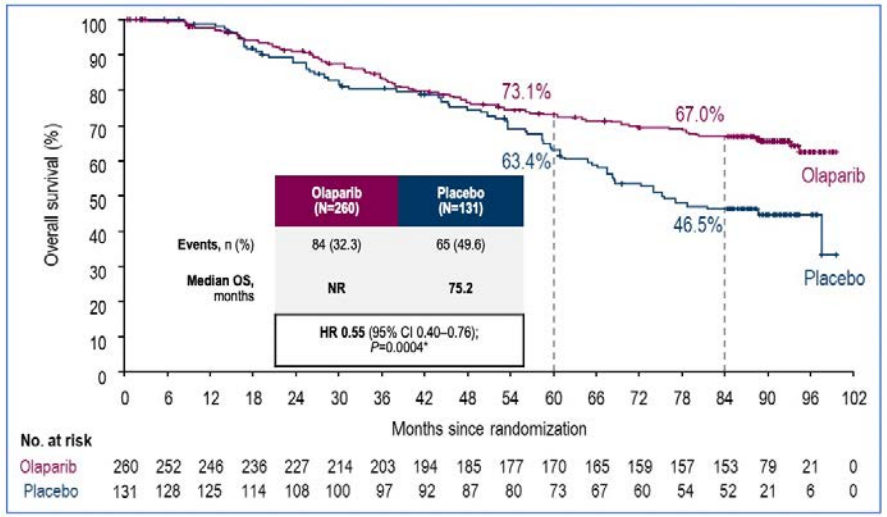
aAt study start, patients were monitored for disease progression (CT/MRI) every 12 weeks (3 cycles); in August 2019, the protocol was amended to monitor patients who stayed on study treatment for more than 2 years for disease progression every 24 weeks (6 cycles).
bPFS hazard ratios and associated 95% CI calculated using stratified Cox proportional hazards model. For all analyses, stratification factors were those used in randomization. CT, computed tomography; HRd, homologous recombination deficient; HRp, homologous recombination proficient; MRI, magnetic resonance imaging; Nir, niraparib; PBO, placebo; PFS, progression-free survival.

1. Chase DM, et al. Gynecol Oncol. 2022;166(3):494–502.
2. González-Martín A, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain

BRCA+/HRD+: PRIMA OS

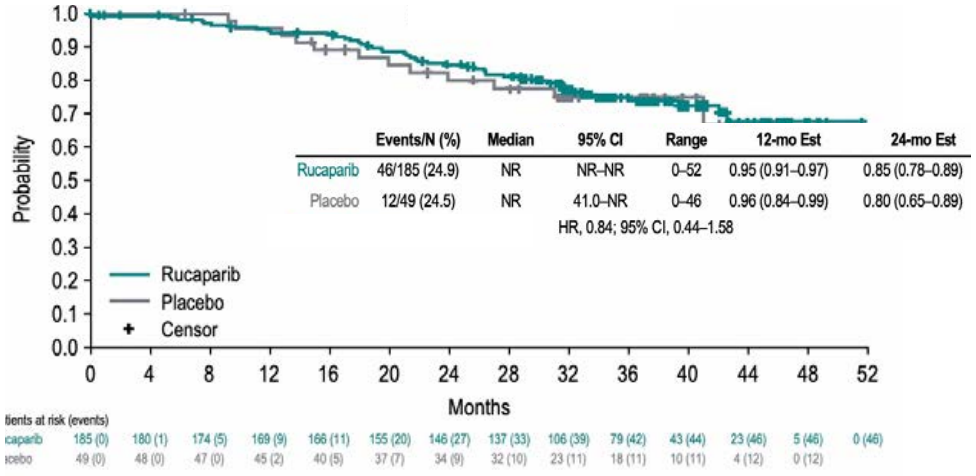


BRCA+: SOLO-1 OS



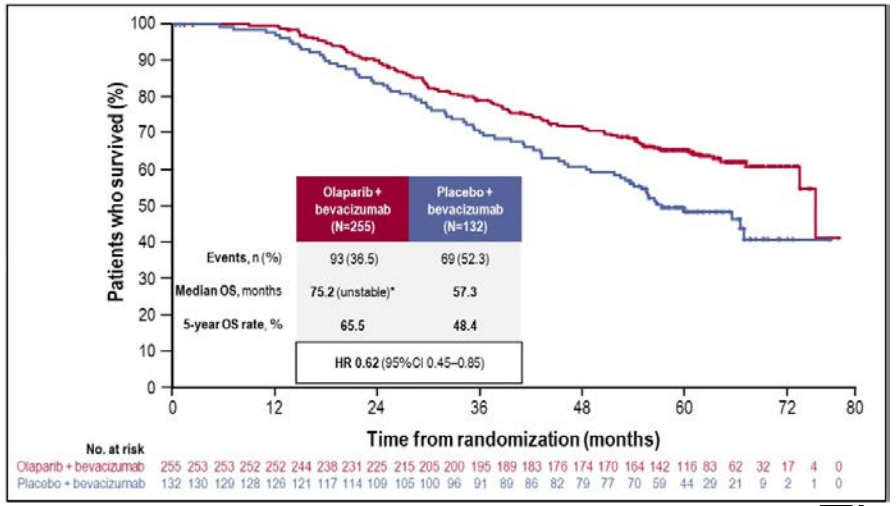
Di Silvestro P, et al. J Clin Oncol 2023

BRCA+/HRD+: ATHENA MONO OS



Kristeleit R, et al. SGO 2024

BRCA+/HRD+: PAOLA OS

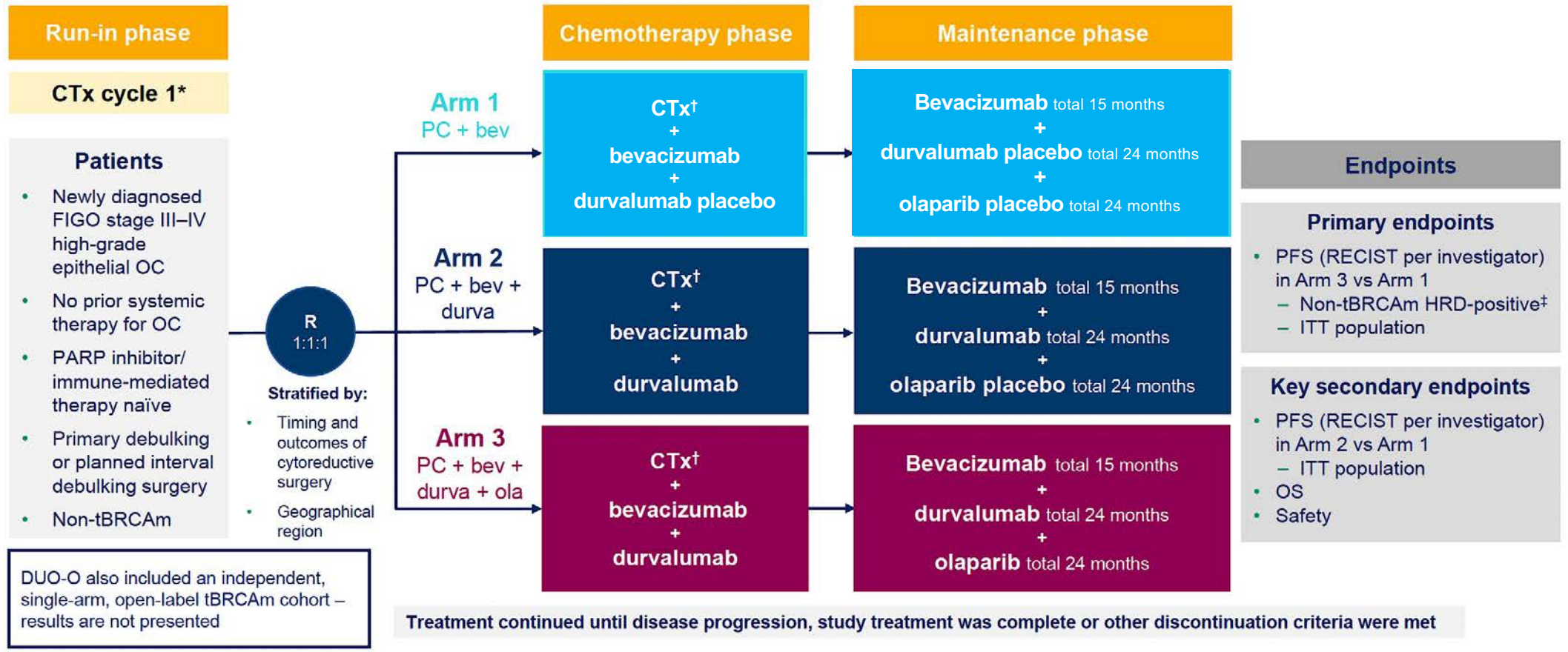


Ray-Coquard I, et al. Ann Oncol 2023

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

GOG 3025 DUO-O : C/T/Bev +/- Durva +/- Olaparib



Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m² IV q3w and carboplatin at AUC5 or AUC6 IV q3w. PFS interim analysis DCO: December 5, 2022.
*With or without bevacizumab according to local practice; †Cycles 2–6; ‡Genomic instability score ≥42 assessed prospectively by Myriad MyChoice CDx assay.
AUC, area under the curve; bev, bevacizumab; bid, twice daily; CTx, chemotherapy; DCO, data cutoff; durva, durvalumab; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; ola, olaparib; OS, overall survival; PC, paclitaxel/carboplatin; po, by mouth; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria for Solid Tumors.

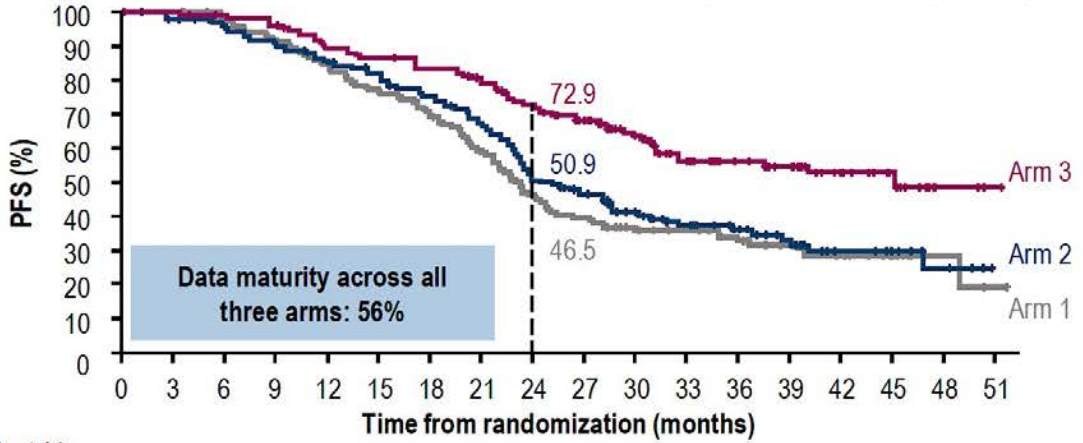
P Harter, et al. Presented at ASCO 2023, Chicago, IL

GOG 3025 DUO-O: C/T/Bev +/- Durva +/- Olaparib

Final PFS

Non-tBRCAm HRD-positive

	Arm 1 CP + B N=143	Arm 2 CP + B + D N=148	Arm 3 CP + B + D + O N=140
Median follow-up,* months	38.4	33.1	34.6
Events, n (%)	94 (66)	89 (60)	57 (41)
mPFS,† months	23.3	25.1	45.1
HR (95% CI) vs Arm 1‡		0.89 (0.67–1.19)	0.46 (0.33–0.65)

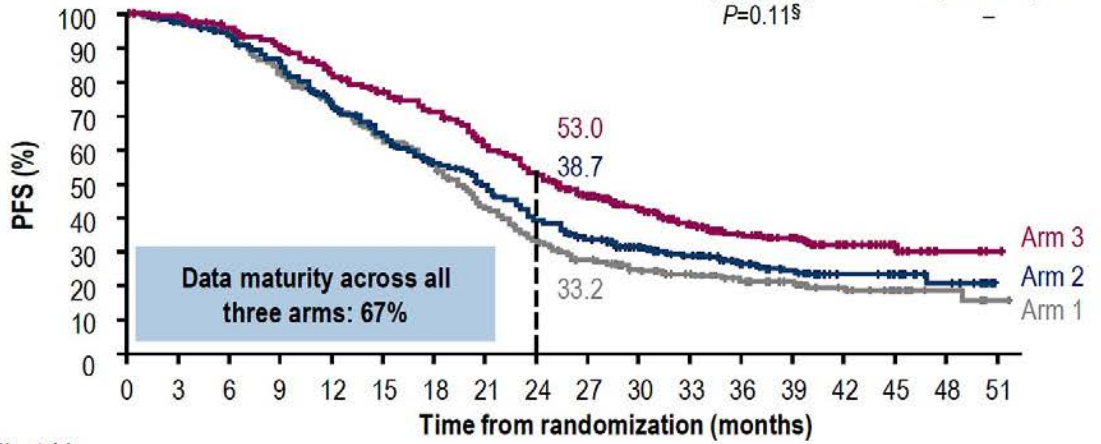


No. at risk:

Arm 1	143	141	136	126	116	105	95	80	63	54	45	42	33	27	16	9	3	1
Arm 2	148	142	136	128	118	112	102	89	68	59	45	36	29	22	13	9	5	0
Arm 3	140	138	135	131	120	116	111	103	94	82	66	50	41	35	22	13	3	1

Non-tBRCAm ITT

	Arm 1 CP + B N=378	Arm 2 CP + B + D N=374	Arm 3 CP + B + D + O N=378
Median follow-up,* months	34.5	33.1	32.0
Events, n (%)	283 (75)	257 (69)	221 (58)
mPFS,† months	19.3	20.6	25.1
HR (95% CI) vs Arm 1‡		0.87 (0.74–1.03) *P*=0.11§	0.61 (0.51–0.73) –



No. at risk:

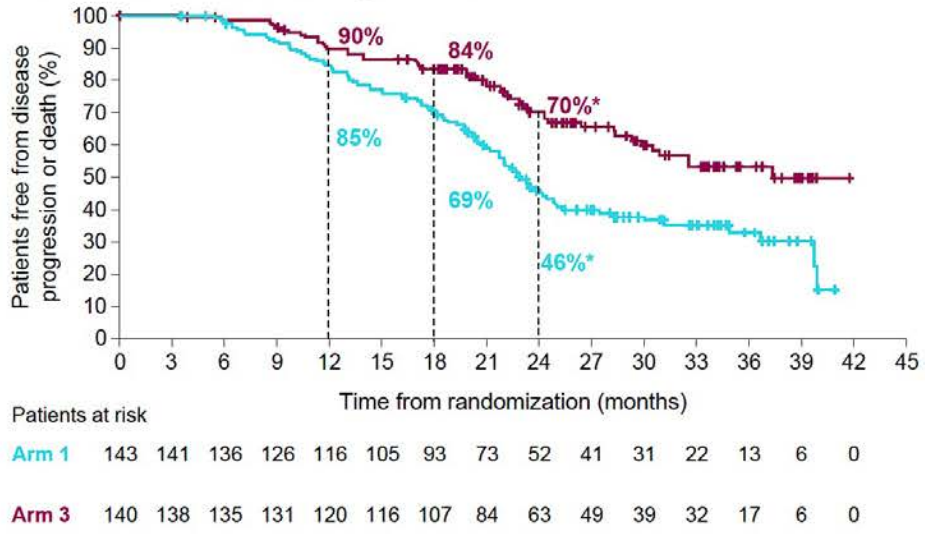
Arm 1	378	363	341	297	260	223	196	150	117	95	77	65	50	42	27	15	6	1
Arm 2	374	354	335	302	255	222	190	161	130	109	87	71	54	43	27	16	8	0
Arm 3	378	367	352	324	287	267	244	205	178	144	116	87	70	56	35	18	5	1

Trillsch F et al. ESMO Gyn Congress 2024;Abstract 43O.

GOG 3025 DUO-O : C/T/Bev +/- Durva +/- Olaparib

Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

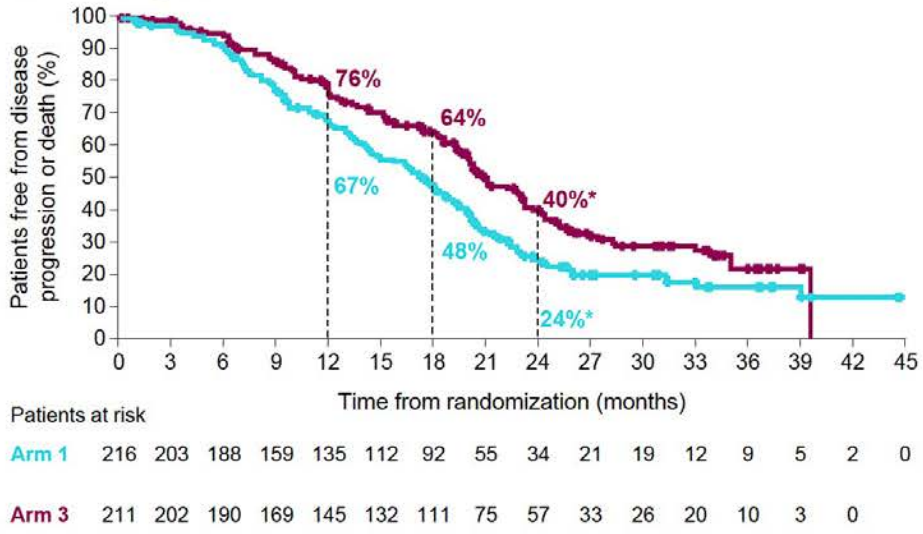


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	49 (35)
Median PFS, months†	23.0	37.3‡
HR (95% CI) vs Arm 1		**0.51** (0.36–0.72)§

HRD-negative



Patients at risk

Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0

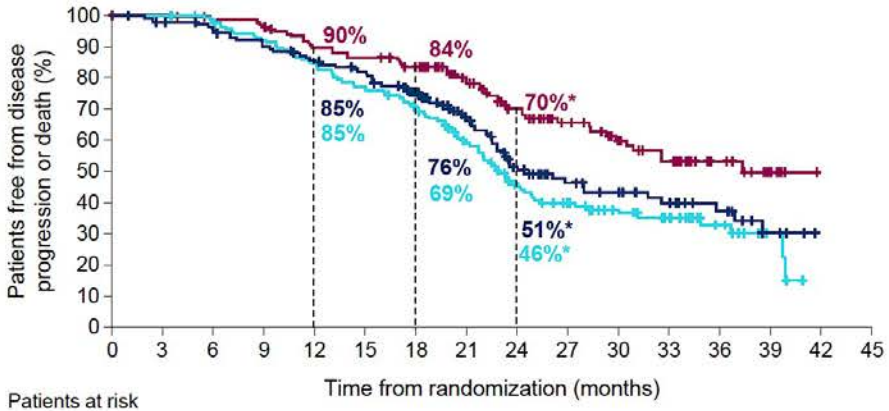
	Arm 1 PC + bev N=216	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	127 (60)
Median PFS, months†	17.4	20.9
HR (95% CI) vs Arm 1		**0.68** (0.54–0.86)§

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 2 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

GOG 3025 DUO-O : C/T/Bev +/- Durva +/- Olaparib

Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

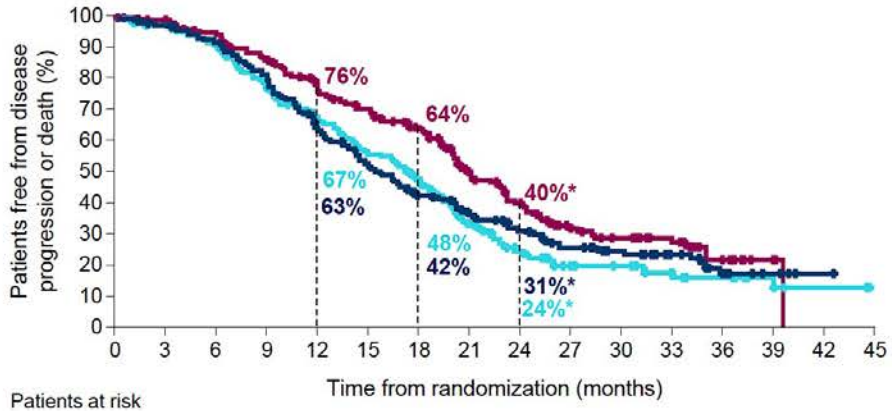


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

HRD-negative



Patients at risk

Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 2	199	189	177	153	120	97	76	59	45	33	25	17	8	4	1	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 2 PC + bev + durva N=199	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	142 (71)	127 (60)
Median PFS, months†	17.4	15.4	20.9
HR (95% CI) vs Arm 1		**0.94** (0.75–1.18)§	**0.68** (0.54–0.86)§

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 1 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

P Harter, et al. Presented at ASCO 2023, Chicago, IL

ATHENA/GOG-3020 Study Schema

Key Patient Eligibility

- Newly diagnosed, stage III–IV, advanced, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Completed frontline platinum-doublet chemotherapy and surgery
  - Achieved investigator-assessed CR or PR
  - Received cytoreductive surgery (primary or interval; complete resection permitted)
- ECOG PS 0 or 1
- No prior frontline maintenance treatment for ovarian cancer

Randomization 4:4:1:1

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm C (n≈100)
placebo PO + nivolumab 480 mg IV

Arm D (n≈100)
placebo PO + placebo IV

Randomization Stratification Factors

- Tumor HRD test status[a]
- Disease status post-chemotherapy
- Timing of surgery

Treatment for 24 months,[b] with a 4-week lead-in of rucaparib; study drugs could be discontinued independently

Study Analyses

ATHENA-COMBO

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

ATHENA-MONO

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm D (n≈100)
placebo PO + placebo IV

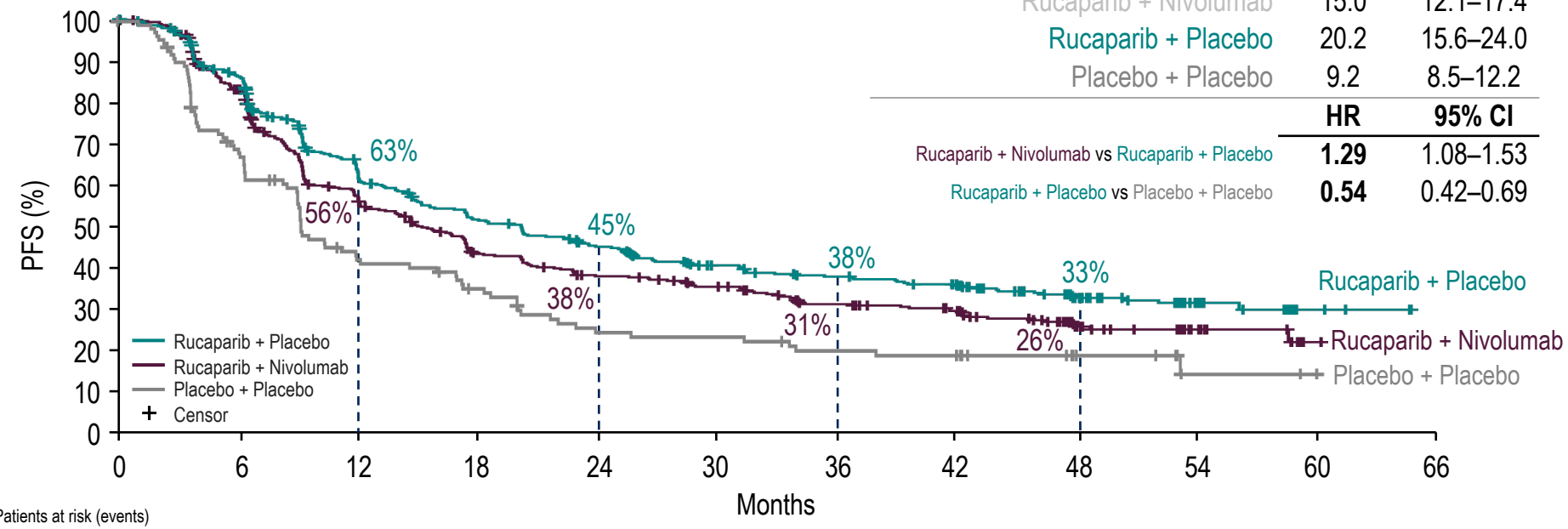
Primary endpoint: Investigator-assessed PFS in the ITT population

NCT03522246

NCT03522246. [a]Centrally assessed, determined by FoundationOne CDx next-generation sequencing assay (BRCA mutation, BRCA wild-type/LOH high [LOH ≥16%], BRCA wild-type/LOH low [LOH <16%], BRCA wild-type/LOH indeterminate). [b]Treatment for 24 months or until radiographic progression, unacceptable toxicity, or other reason for discontinuation. IV placebo was intended to commence on Day 1 of Cycle 2 and treatment cap defined as 24 months after the start of IV placebo; 28-day cycles.
BID, twice daily; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; LOH, loss of heterozygosity; PFS, progression-free survival; PO, by mouth; PR, partial response.
Monk B, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.

ATHENA-Combo: Investigator Assessed PFS *(ITT)*

	Median	95% CI
Rucaparib + Nivolumab	15.0	12.1–17.4
Rucaparib + Placebo	20.2	15.6–24.0
Placebo + Placebo	9.2	8.5–12.2
	HR	**95% CI**
Rucaparib + Nivolumab vs Rucaparib + Placebo	**1.29**	1.08–1.53
Rucaparib + Placebo vs Placebo + Placebo	**0.54**	0.42–0.69



Patients at risk (events)

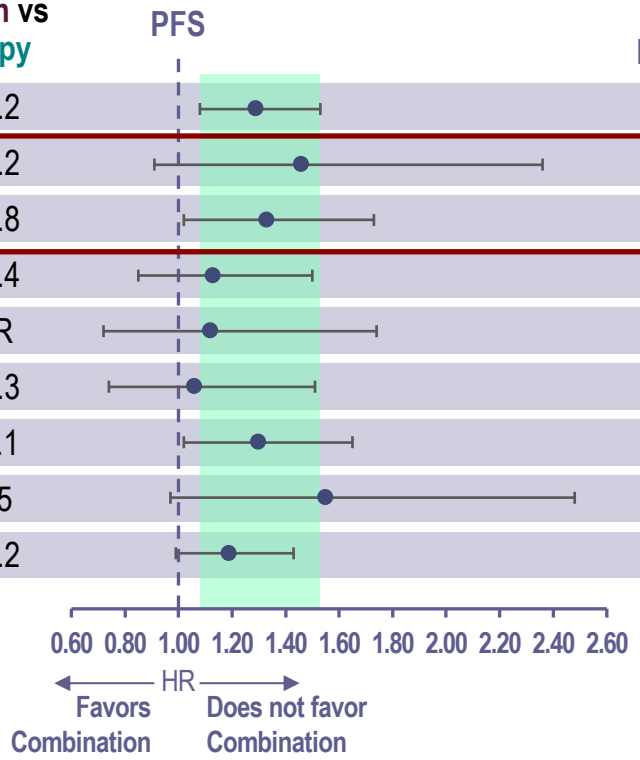
Ruca+Nivo	436 (0)	333 (69)	218 (174)	159 (224)	136 (244)	122 (253)	98 (267)	87 (272)	44 (280)	14 (282)	1 (283)	0 (283)
Ruca+Plac	427 (0)	352 (57)	246 (149)	197 (193)	166 (218)	136 (234)	123 (243)	113 (249)	68 (258)	24 (260)	4 (261)	0 (261)
Plac+Plac	111 (0)	73 (34)	43 (61)	33 (69)	23 (78)	21 (80)	17 (83)	16 (84)	8 (84)	2 (85)	1 (85)	0 (85)

NCT03522246

Data cutoff date: May 17, 2024.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Nivo, nivolumab; PFS, progression-free survival; Plac, placebo; Ruca, rucaparib.
Monk B, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.

ATHENA-Combo: Investigator Assessed PFS *(Exploratory Subgroups)*

Population	Rucaparib + Nivolumab (n)	Rucaparib + Placebo (n)	Median, months Combination vs Monotherapy	HR (95% CI)
ITT	436	427	15.0 vs 20.2	1.3 (1.1–1.5)
PD-L1 ≥5%	69	72	22.8 vs 52.2	1.5 (0.9–2.4)
PD-L1 ≥1%	199	197	18.3 vs 25.8	1.3 (1.0–1.7)
HRD	193	185	28.9 vs 31.4	1.1 (0.9–1.5)
BRCA mutation	94	91	48.0 vs NR	1.1 (0.7–1.7)
BRCA wild-type/LOH^{high}	99	94	17.3 vs 22.3	1.1 (0.7–1.5)
BRCA wild-type/LOH^{low}	188	189	11.0 vs 12.1	1.3 (1.0–1.7)
BRCA wild-type/LOH^{indeterminate}	55	53	9.2 vs 17.5	1.6 (1.0–2.5)
No BRCA mutation	357	336	12.1 vs 15.2	1.2 (1.0–1.4)



NCT03522246

Data cutoff: May 17, 2024.
Populations in bold are stratification factors.
BRCA wild-type/LOH high (LOH cutoff, ≥16%), BRCA wild-type/LOH low (LOH cutoff, <16%).
BRCA, BRCA1 or BRCA2; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; LOH, loss of heterozygosity; NR, not reached; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Monk B, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.

Right When You Thought IO Was Done in 1L OC…

FIRST Study Design

20 December 2024

Issued: London, UK

For media and investors only

Manufacturer announces FIRST trial met its primary endpoint of progression free survival in first line advanced ovarian cancer

KEYLYNK-001 Study Design | non-BRCAm

Manufacturer Announces Phase 3 KEYLYNK-001 Trial Met Primary Endpoint of Progression-Free Survival (PFS) in Patients with Advanced Epithelial Ovarian Cancer

December 9, 2024 6:45 am ET

FIRST Study Design

FIRST is a randomised, double-blind Phase III study

- Histologically confirmed diagnosis of FIGO Stage III–IV non-mucinous epithelial ovarian cancer
- All Stage IV
- Stage III disease are eligible if they are:
  - Stage IIIC CC0 with ≥5 cm extra-pelvic disease following PDS
  - inoperable Stage III disease,
  - macroscopic residual tumour following PDS
  - NACT is planned
- People who undergo PDS or receive NACT are eligible
- ECOG PS 0–1
- People must provide blood and tumour tissue samples

CTX ± bev (1 cycle) → R 1:2 N=1405

Treatment duration: 41 months

Cycles 2–6 | Maintenance Phase

Chemotherapy

Optional: **Bevacizumab** 7.5 or 15 mg/kg Q3W (up to 15 months)

Placebo Q3W | Placebo Q6W (up to 36 months)

Niraparib 200 or 300 mg QD (up to 36 months)

Chemotherapy

Optional: **Bevacizumab** 7.5 or 15 mg/kg Q3W (up to 15 months)

Dostarlimab (500 mg Q3W) | Dostarlimab (1000 mg Q6W up to 36 months)

Niraparib 200 or 300 mg QD (up to 36 months)

Stratification by:

- *Concurrent bevacizumab use*
- *HRRm status*
- *Disease burden*

Primary endpoints

- **PFS in PD-L1+ pts.** TAP >5% ???
- **PFS in ITT**

Secondary endpoints

- PFS (BICR RECIST v1.1 & irRECIST)
- OS
- TFST
- TSST
- PFS2
- ORR
- Safety and tolerability
- HRQoL

Study start date: October 2018
Estimated primary completion date: July 2023

Bev=bevacizumab; BICR=blinded independent central review; CC=complete cytoreductive; CTX=chemotherapy; ECOG PS=Eastern Cooperative Oncology Group performance status; FIGO=International Federation of Gynecology and Obstetrics; HRRm=homologous recombination repair mutation; HRQoL=health-related quality of life; (ir)RECIST=(immune-related) Response Evaluation Criteria in Solid Tumors; ITT=intent-to-treat; NACT=neoadjuvant chemotherapy; ORR=overall response rate; OS=overall survival; PD-L1=programmed death ligand 1; PDS=primary debulking surgery; PFS=progression-free survival; PFS2=time to progression on subsequent therapy; Q3W=every 3 weeks; Q6W=every 6 weeks; QD=once daily; R=randomised; TFST=time to first subsequent therapy; TSST=time to start of second subsequent therapy or death.

1. FIRST. Available at: https://clinicaltrials.gov/ct2/show/NCT03602859. Accessed November 2022.

KEYLYNK-001 Study Design | non-BRCAm

KEYLYNK-001 is a randomised, double-blind Phase III study

- Histologically confirmed diagnosis of FIGO Stage III–IV epithelial ovarian cancer
- BRCAwt
- Candidate for primary or interval debulking surgery
- ECOG PS 0–1
- Biopsy of a tumour lesion for prospective testing of *BRCA1/2* and PD-L1 tumour markers status prior to randomisation

CTX (1 cycle) → R 1:1:1 N=1284

Treatment duration: 35 months

Cycles 2–6 | Maintenance Phase

Chemotherapy

Optional: **Bevacizumab**

Placebo (Q3W up to 35 cycles)

Placebo Q6W (up to 36 months)

Chemotherapy

Optional: **Bevacizumab**

Pembrolizumab (200 mg Q3W up to 35 cycles)

Placebo Q6W (up to 36 months)

Chemotherapy

Optional: Bevacizumab

Pembrolizumab (200 mg Q3W up to 35 cycles)

Olaparib (300 mg BID up to 2 years)

Stratification by:

- *Surgery status (residual tumour after PDS [yes/no] or planned interval debulking)*
- *Planned bevacizumab use (yes/no)*
- *PD-L1 combined positive score (CPS; <10 or ≥10)*

Primary endpoints

- **PFS in PD-L1+ people CPS ≥10**
- **PFS in ITT**

Secondary endpoints

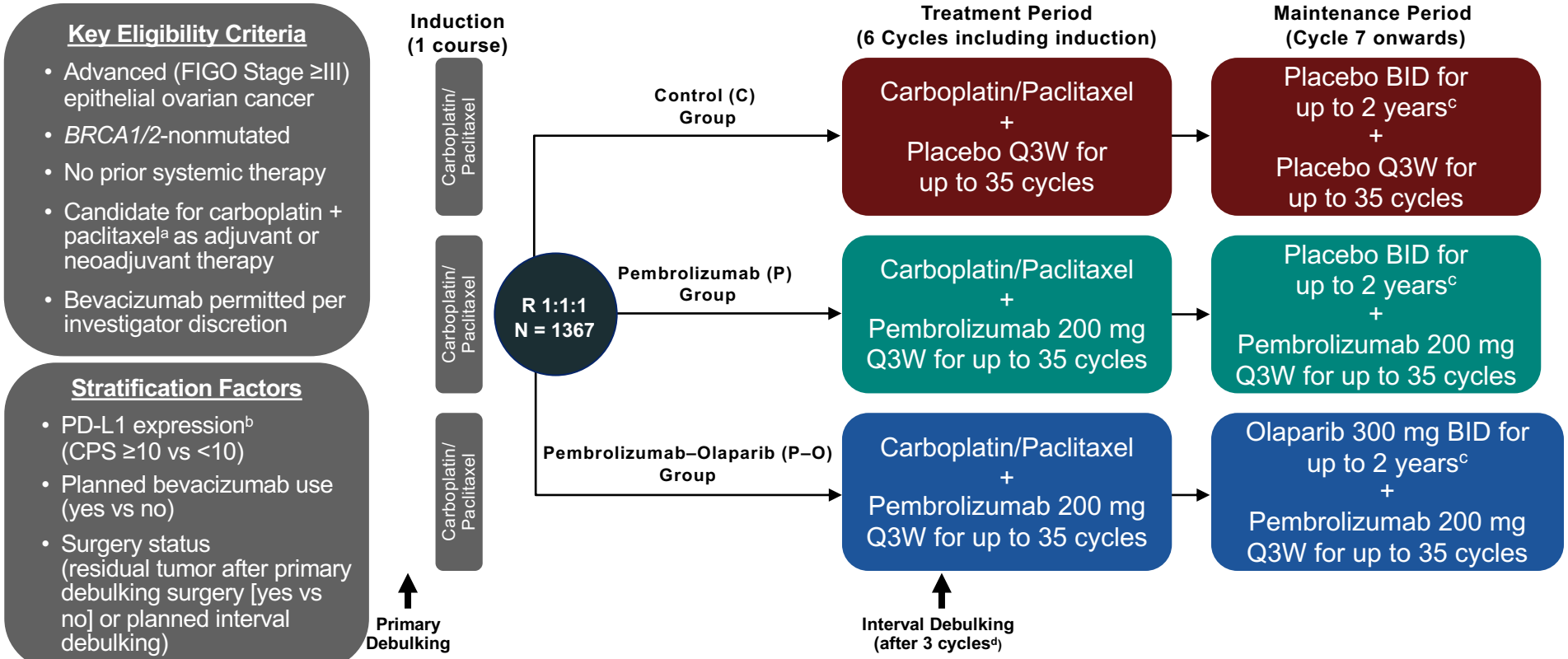
- OS
- PFS (BICR) in PD-L1+
- PFS (BICR) in ITT
- PFS2 in PD-L1+
- PFS2 in ITT
- Safety and tolerability
- HRQoL
- TFST, TSST, TDT
- pCR
- TWiST

Study start date: December 2018
Estimated primary completion date: October 2023

aOC=advanced ovarian cancer; BICR=blinded independent central review; BID=twice daily; BRCAm=BRCA mutated; CPS=combined positive score; CTX=chemotherapy; ECOG PS=Eastern Cooperative Oncology Group performance status; FIGO=International Federation of Gynecology and Obstetrics; HRQoL=health-related quality of life; ITT=intent-to-treat; OS=overall survival; pCR=pathological complete response; PD-L1=programmed death ligand 1; PDS=primary debulking surgery; PFS=progression-free survival; PFS2=time to progression on subsequent therapy; R=randomised; TDT=time to treatment discontinuation; TFST=time to first subsequent therapy; TSST=time to start of second subsequent therapy or death; TWiST=time without symptoms of disease progression or toxicity; Q3W=every 3 weeks; Q6W=every 6 weeks

1. KEYLYNK-001. Available at: https://clinicaltrials.gov/ct2/show/NCT03740165. Accessed November 2022; 2. Fujiwara K, et al. *Ann Oncol*. 2019;30(suppl_9):ix77–ix90.

ENGOT-OV43/GOG-3036/KEYLYNK-001 Study Design (NCT03740165)



[a]Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an adverse event requiring discontinuation of paclitaxel. [b]Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100). [c]Only participants with no evidence of disease at start of maintenance and no progression stopped after 2 years. [d]Including induction cycle.

Vergote et al, ESGO 2025

Baseline Characteristics

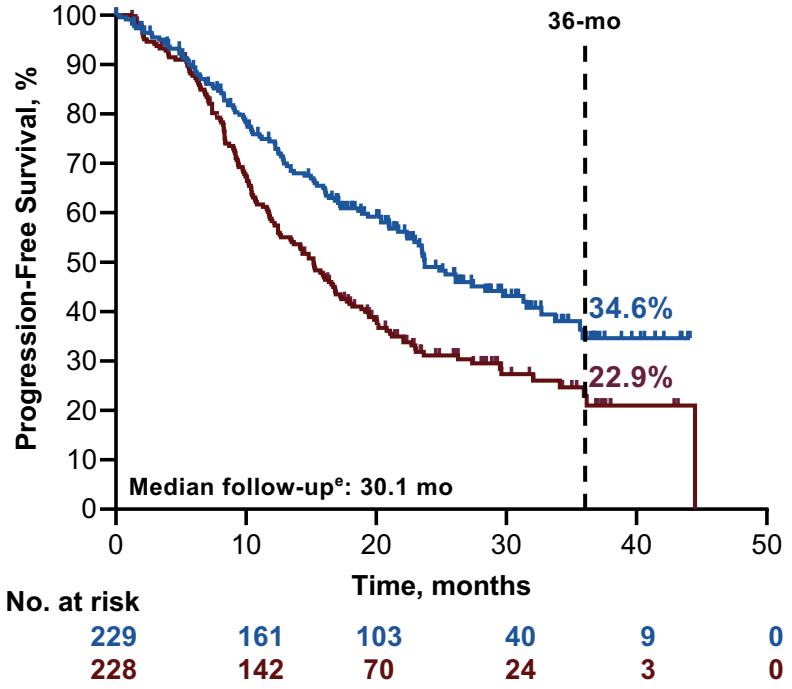
	P–O Group (N = 455)	P Group (N = 458)	C Group (N = 454)
PD-L1 CPS ≥10	229 (50.3%)	230 (50.2%)	228 (50.2%)
Histology			
High grade serous	389 (85.5%)	398 (86.9%)	383 (84.4%)
Clear cell	28 (6.2%)	25 (5.5%)	28 (6.2%)
Endometrioid	20 (4.4%)	11 (2.4%)	15 (3.3%)
Carcinosarcoma	9 (2.0%)	6 (1.3%)	10 (2.2%)
Low grade serous	8 (1.8%)	17 (3.7%)	16 (3.5%)
Other	1 (0.2%)	1 (0.2%)	2 (0.4%)
Surgery Performed			
R0 primary debulking	92 (20.2%)	98 (21.4%)	93 (20.5%)
R1 primary debulking	155 (34.1%)	151 (33.0%)	151 (33.3%)
Interval debulking	166 (36.5%)	174 (38.0%)	170 (37.4%)
None	42 (9.2%)	35 (7.6%)	40 (8.8%)
Started bevacizumab			
Yes	199 (43.7%)	205 (44.8%)	206 (45.4%)
No	256 (56.3%)	253 (55.2%)	248 (54.6%)

[a]3 participants had missing information for race, 2 (0.4%) in the P group and 1 (0.2%) in the C group. [b]1 participant (0.2%) in the P–O group had FIGO stage IIB disease at screening.
Data cutoff date: August 26, 2024.

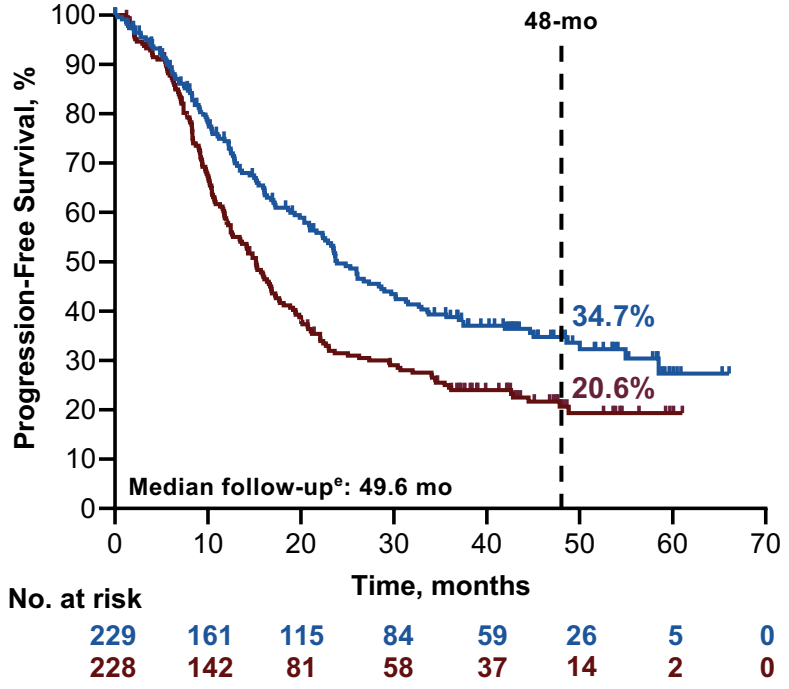
Vergote et al, ESGO 2025

Progression-Free Survival P–O vs C, CPS ≥10 Population

IA1[a]	Median, months	Events	HR (95% CI)	*P*-value
P–O Group	23.7	48.9%	0.63[c] (0.49-0.80)	<0.0001[d]
C Group	15.2	66.2%		



FA[b]	Median, months	Events	HR (95% CI)
P–O Group	23.9	58.5%	0.66[c] (0.53-0.83)
C Group	15.2	72.4%	

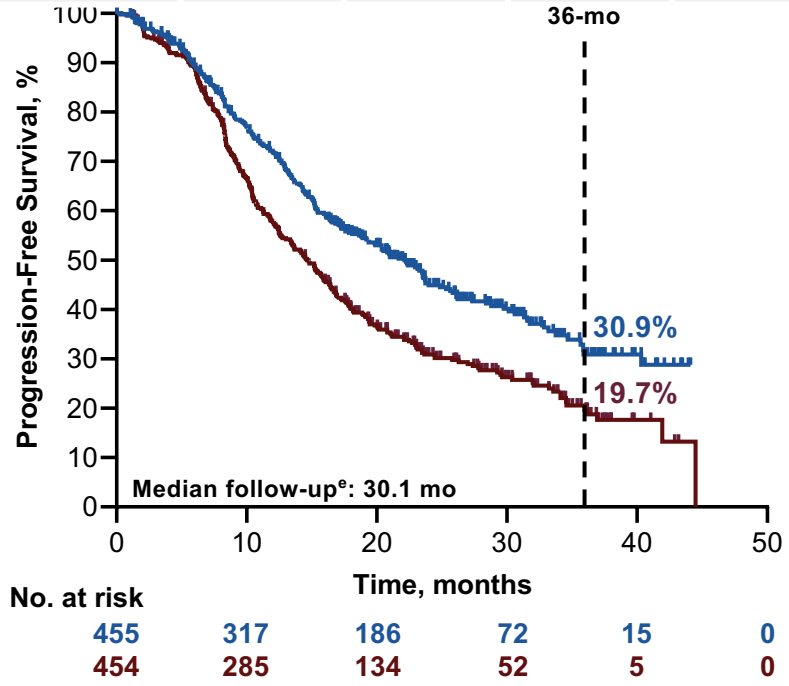


Response assessed per RECIST v1.1 by investigator review. [a]Data cutoff date: January 9, 2023. [b]Data cutoff date: August 26, 2024. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary met. [e]Defined as the time from randomization to the data cutoff date.

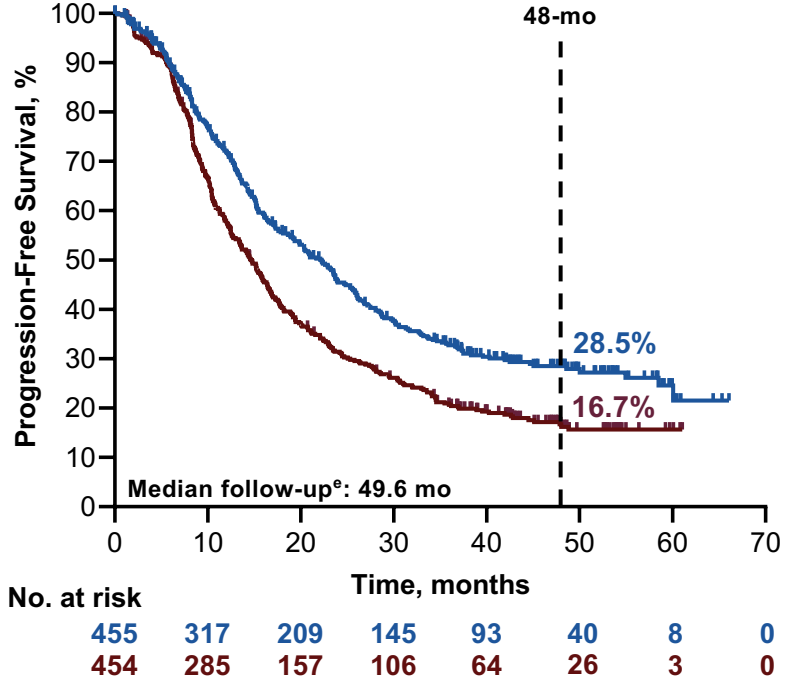
Vergote et al, ESGO 2025

Progression-Free Survival P–O vs C, Total ITT Population

IA1[a]	Median, months	Events	HR (95% CI)	*P*-value
P–O Group	22.1	53.0%	0.68[c] (0.58-0.81)	<0.0001[d]
C Group	14.6	69.2%		



FA[b]	Median, months	Events	HR (95% CI)
P–O Group	22.2	64.0%	0.71[c] (0.61-0.84)
C Group	14.6	77.5%	



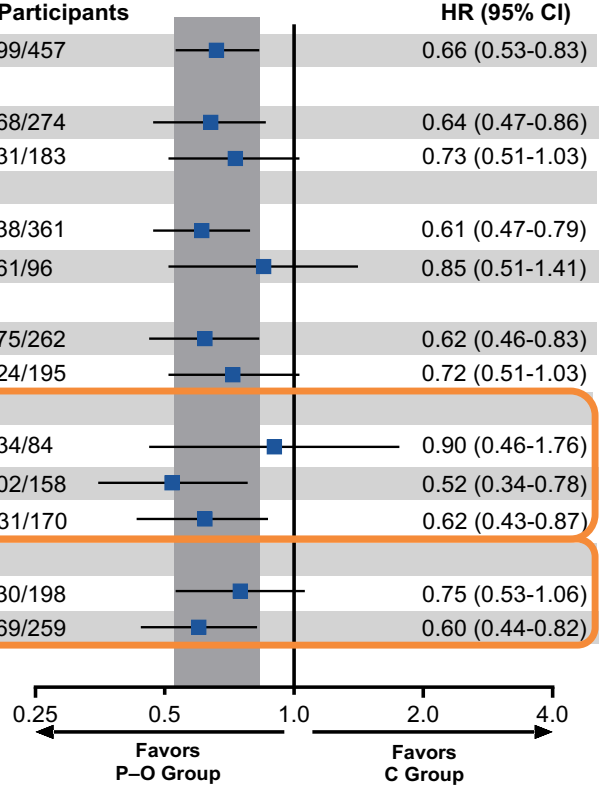
Response assessed per RECIST v1.1 by investigator review. [a]Data cutoff date: January 9, 2023. [b]Data cutoff date: August 26, 2024. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary met. [e]Defined as the time from randomization to the data cutoff date.

Vergote et al, ESGO 2025

Progression-Free Survival in Subgroups P–O vs C at FA

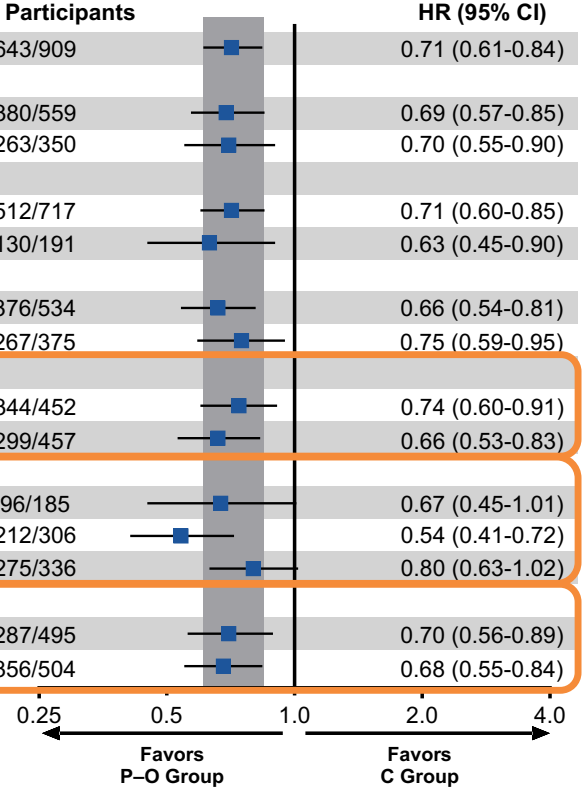
CPS ≥10 Population

Subgroup	No. of Events/ No. of Participants	HR (95% CI)
Overall	299/457	0.66 (0.53-0.83)
Age		
<65 years	168/274	0.64 (0.47-0.86)
≥65 years	131/183	0.73 (0.51-1.03)
Race		
White	238/361	0.61 (0.47-0.79)
All others	61/96	0.85 (0.51-1.41)
ECOG PS score		
0	175/262	0.62 (0.46-0.83)
1	124/195	0.72 (0.51-1.03)
Debulking surgery		
R0 primary	34/84	0.90 (0.46-1.76)
R1 primary	102/158	0.52 (0.34-0.78)
Interval	131/170	0.62 (0.43-0.87)
Bevacizumab use		
Yes	130/198	0.75 (0.53-1.06)
No	169/259	0.60 (0.44-0.82)



Total ITT Population

Subgroup	No. of Events/ No. of Participants	HR (95% CI)
Overall	643/909	0.71 (0.61-0.84)
Age		
<65 years	380/559	0.69 (0.57-0.85)
≥65 years	263/350	0.70 (0.55-0.90)
Race		
White	512/717	0.71 (0.60-0.85)
All others	130/191	0.63 (0.45-0.90)
ECOG PS score		
0	376/534	0.66 (0.54-0.81)
1	267/375	0.75 (0.59-0.95)
PD-L1 status[a]		
CPS <10	344/452	0.74 (0.60-0.91)
CPS ≥10	299/457	0.66 (0.53-0.83)
Debulking surgery		
R0 primary	96/185	0.67 (0.45-1.01)
R1 primary	212/306	0.54 (0.41-0.72)
Interval	275/336	0.80 (0.63-1.02)
Bevacizumab use		
Yes	287/495	0.70 (0.56-0.89)
No	356/504	0.68 (0.55-0.84)

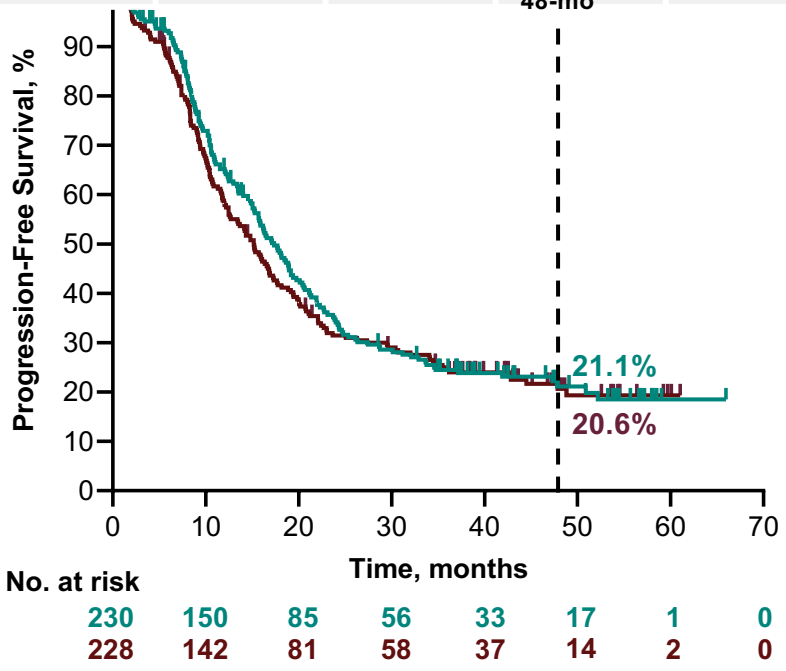


Response assessed per RECIST v1.1 by investigator review. [a]The subgroup results shown in the forest plot were based on an unstratified Cox model, so the results for CPS ≥10 may differ slightly compared with those of the primary analysis, which were based on a stratified Cox model. Data cutoff date: August 26, 2024.

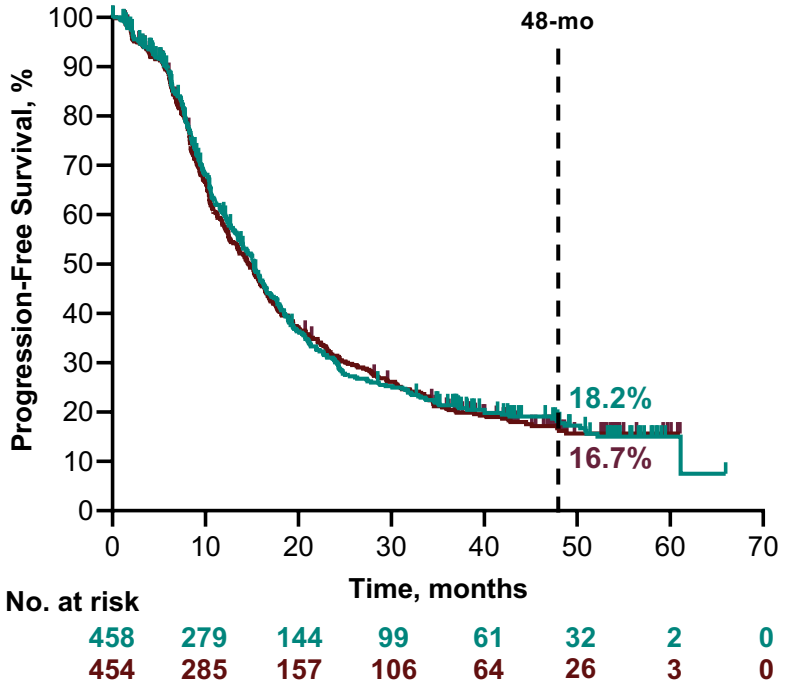
Vergote et al, ESGO 2025

Progression-Free Survival P vs C at FA

CPS ≥10 Population	Median, months	Events	HR (95% CI)	*P*-value
P Group	17.3	69.6%	0.95[a] (0.77-1.19)	0.3339[b]
C Group	15.2	72.4%		



Total ITT Population	Median, months	Events	HR (95% CI)
P Group	15.2	73.8%	1.01[a] (0.87-1.18)
C Group	14.6	77.5%	

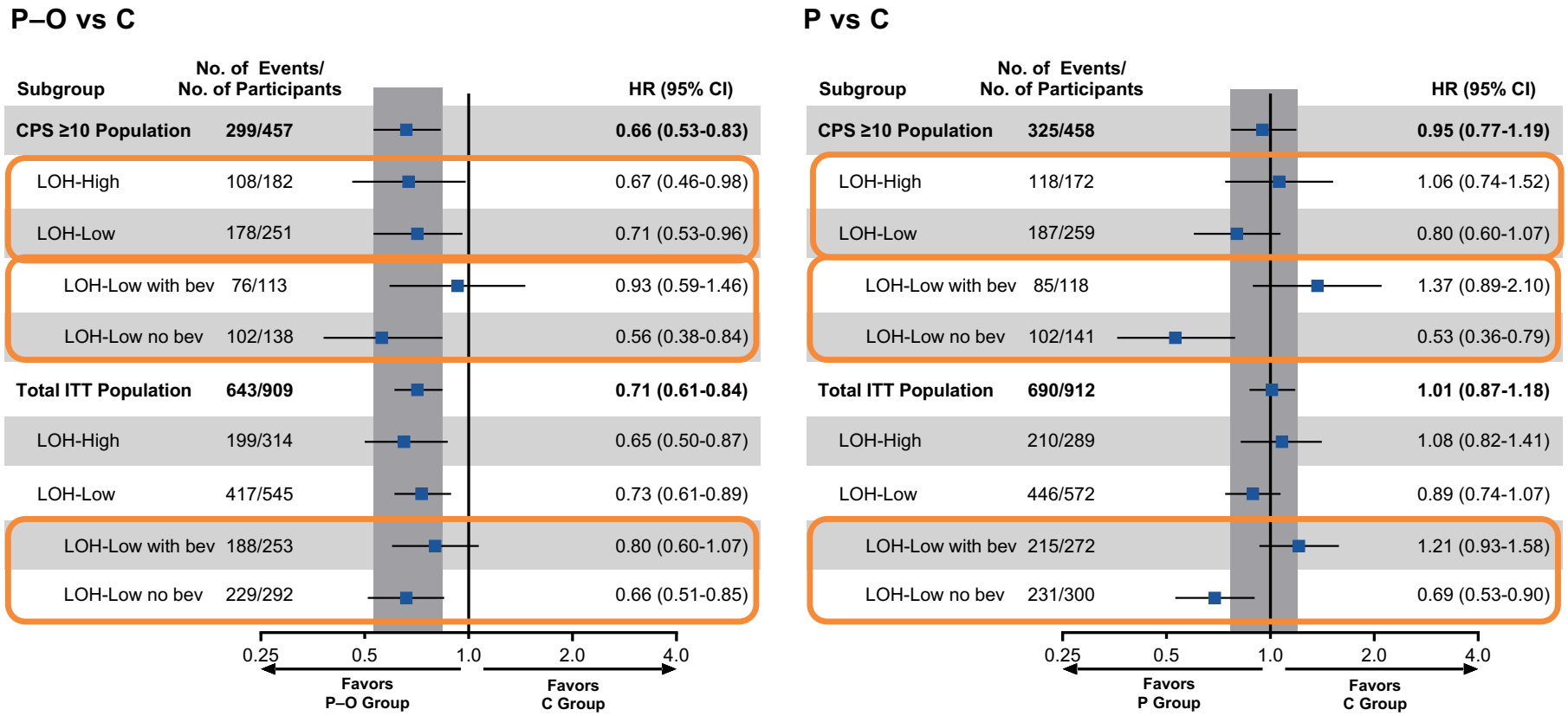


Median follow-up[c]: 49.6 mo

Response assessed per RECIST v1.1 by investigator review. [a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary not met. [c]Defined as the time from randomization to the data cutoff date. Data cutoff date: August 26, 2024.

Vergote et al, ESGO 2025

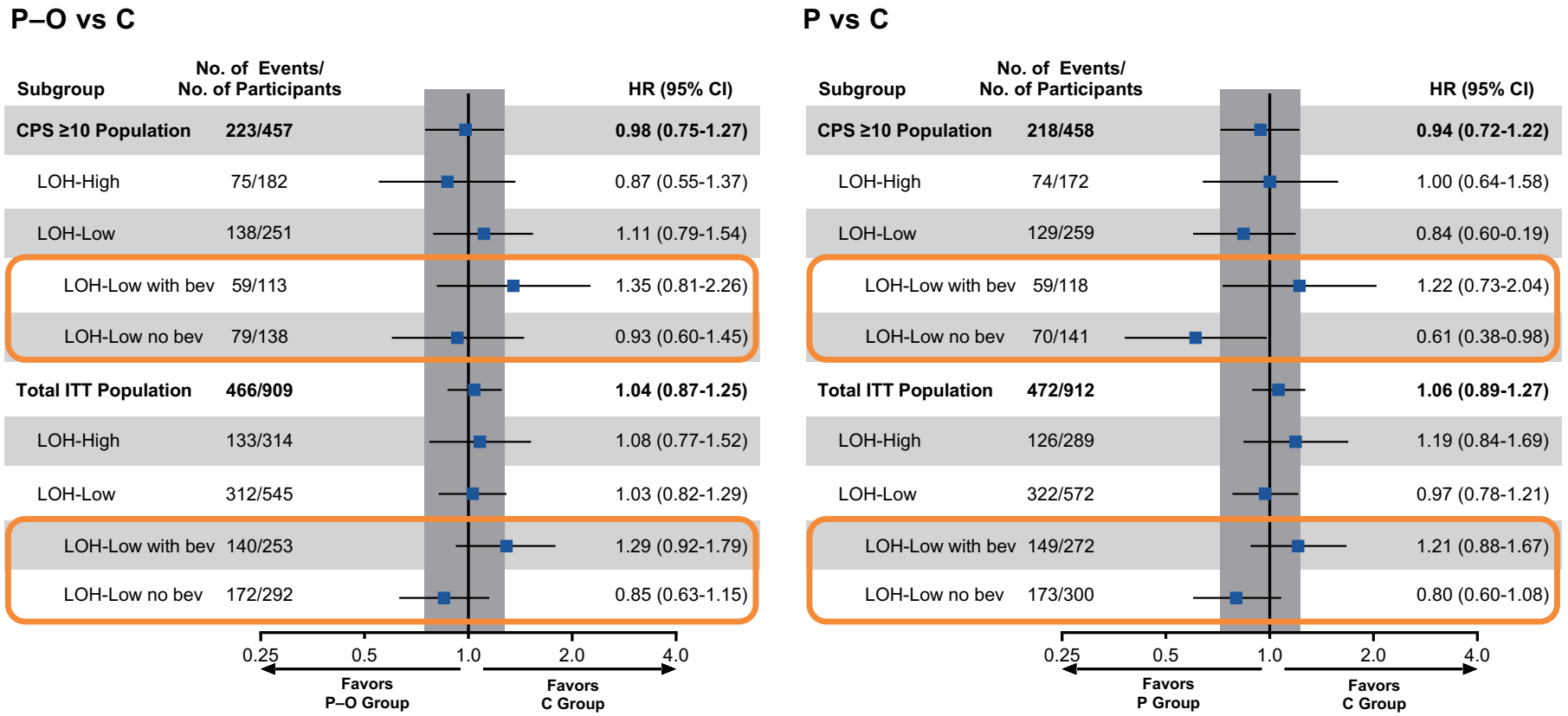
Progression-Free Survival in **FMI-LOH** Subgroups at FA



Response assessed per RECIST v1.1 by investigator review. FMI-LOH and bev subgroups based on post-hoc, exploratory, unstratified analysis. FMI, Foundation Medicine Inc.
LOH, loss of heterozygosity. Bev, bevacizumab. Data cutoff date: August 26, 2024.

Vergote et al, ESGO 2025

Overall Survival in **FMI-LOH** Subgroups at FA



FMI-LOH and bev subgroups based on post-hoc, exploratory, unstratified analysis. FMI, Foundation Medicine Inc. LOH, loss of heterozygosity. Bev, bevacizumab.
Data cutoff date: August 26, 2024.

Vergote et al, ESGO 2025

Recurrent - New Therapeutic Targets

The James

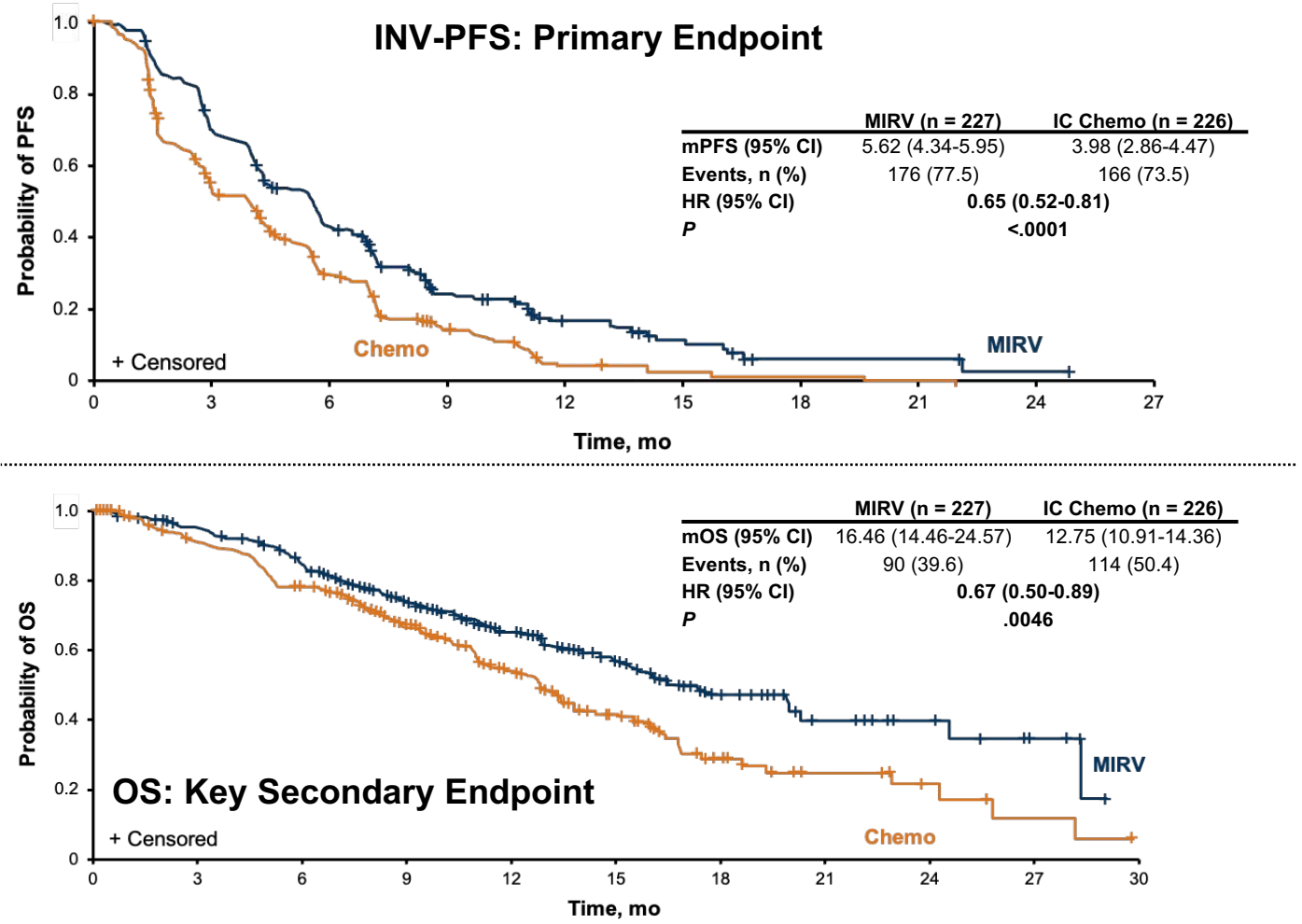
The Ohio State University
Wexner Medical Center

Folate Receptor alpha

The James

The Ohio State University
Wexner Medical Center

Mirvetuximab Soravtansine Improved PFS and OS[1]



MIRASOL

- 35% improvement in PFS with MIRV vs chemotherapy
- 33% improvement in OS with MIRV vs chemotherapy
- ORR more than doubled: 42% vs 16% with MIRV vs chemotherapy (P < .0001; 12 CRs vs 0 CRs)

FDA Approval April 2024

1. Moore KN et al. *N Engl J Med.* 2023;389:2162-2174.

PICCOLO (NCT05041257) – Study Design[1-3]

A single-arm, open-label, phase 2 trial of MIRV in patients with ≥3L platinum-sensitive ovarian cancer with FRα-high expression

PICCOLO Patient Population (N=79)

Enrollment and Key Eligibility

- Platinum-sensitive disease (defined as radiographic progression >6 months from last dose of most recent platinum therapy)
- FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells[a]
- At least 2 prior platinum-containing regimens[b]
- Prior PARPi required if *BRCA*+
- Prior BEV not required
- Appropriate for single-agent therapy

Treatment Regimen

MIRV
(6 mg/kg AIBW Q3W)

Primary Endpoint

ORR by INV

Key Secondary Endpoint

DOR by INV

Other Secondary Endpoints

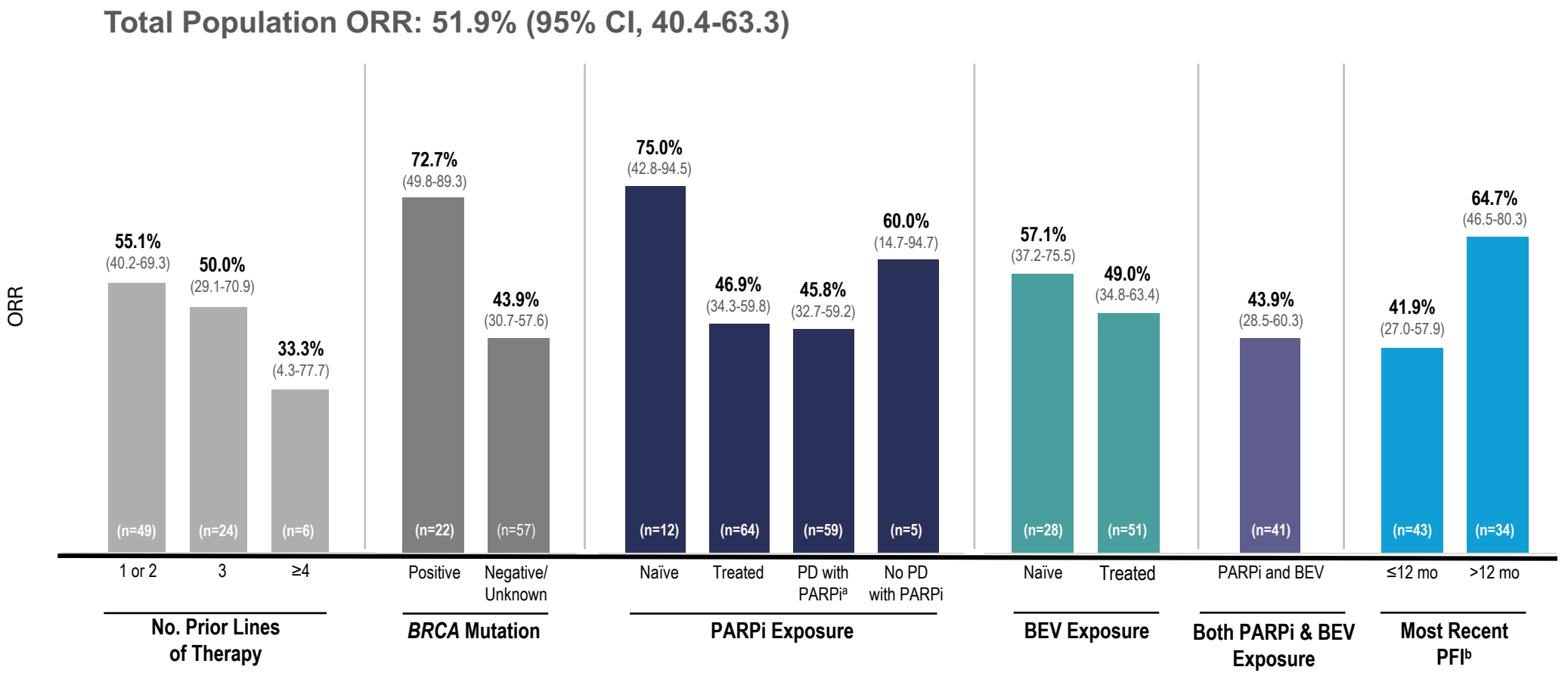
- Safety and tolerability
- CA-125 response (GCIG criteria)
- PFS
- OS
- Sensitivity analyses[c]

[a]FRα expression measured by the VENTANA FOLR1 (FOLR1-2.1 RxDx) Assay. [b]1 prior line if documented platinum allergy. [c]ORR, DOR, and PFS by BICR will be summarized as sensitivity analyses.

3L, third-line; AIBW, adjusted ideal body weight; BEV, bevacizumab; BICR, blinded independent central review; *BRCA*, BReast CAncer gene; CA-125, cancer antigen 125; DOR, duration of response; FRα, folate receptor alpha; GCIG, Gynecological Cancer InterGroup; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine-gynx; ORR, objective response rate; OS, overall survival; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor; PFS, progression-free survival; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.

1. ClinicalTrials.gov identifier: NCT05041257. Updated April 22, 2024. Accessed July 29, 2024.; 2. Alvarez Secord A, et al. Poster presented at: International Gynecologic Cancer Society (IGCS) Annual Global Meeting; 29 September-1 October 2022; New York City, NY USA [Abstract 1556]. 3. Alvarez Secord A, et al. Poster presented at: Society of Gynecologic Oncology's (SGO) Annual Meeting on Women's Cancer; 18-21 March,2022; Phoenix, AZ USA. [Abstract 300].

ORR by Subgroups



NCT05041257

Data cutoff: January 17, 2024. ORR presented with 95% CI.
Half the participants had progression of disease within 30 days after the last dosing of a PARPi or progression was listed as the reason for treatment discontinuation of a PARPi, the participant was defined as having progressive disease on prior PARPi and was included in this category. bPlatinum-free interval is defined as time from last dose of the latest line platinum therapy to the date of disease progression and/or relapse following that line of therapy (time rounded to whole number).
BEV, bevacizumab; BRCA, Breast Cancer gene; CI, confidence interval; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor; PD, progressive disease; PFI, platinum-free interval; ORR, objective response rate.

HER2

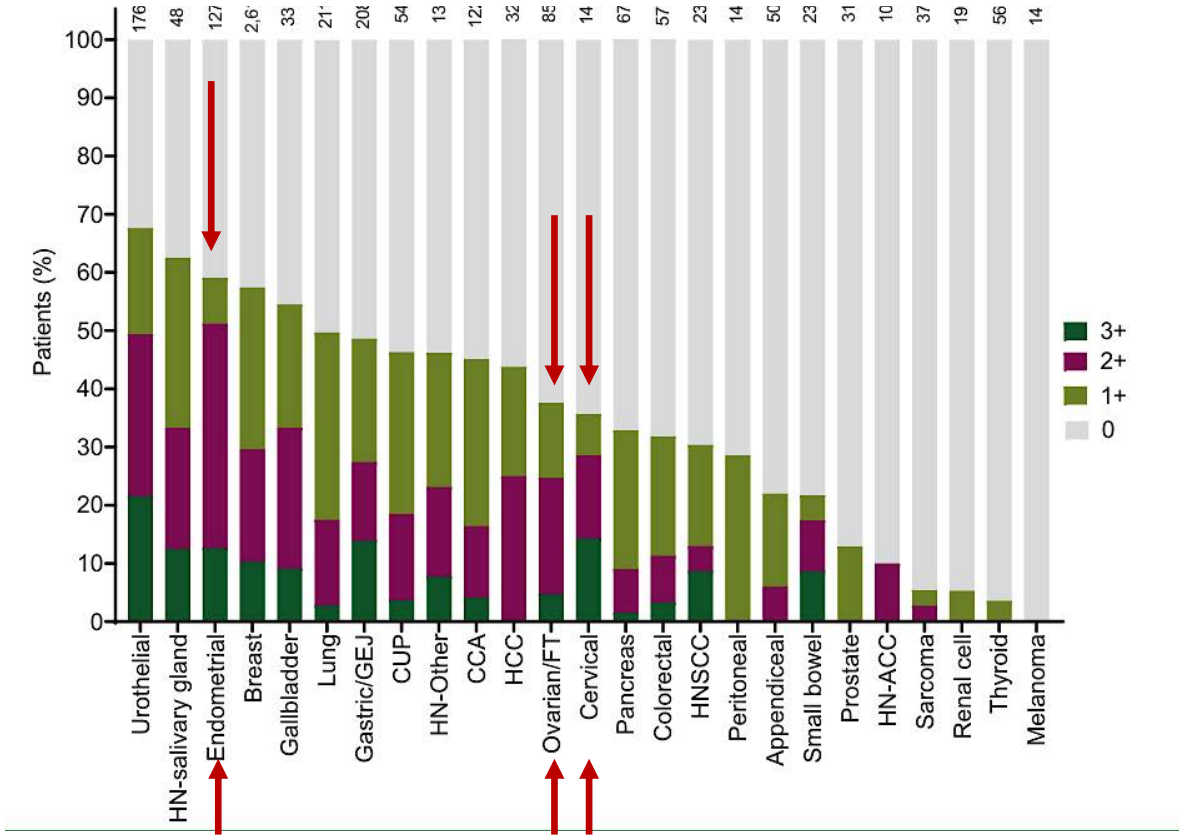
The James

The Ohio State University
Wexner Medical Center

HER2 expression

Distribution of HER2 IHC scores across cancers

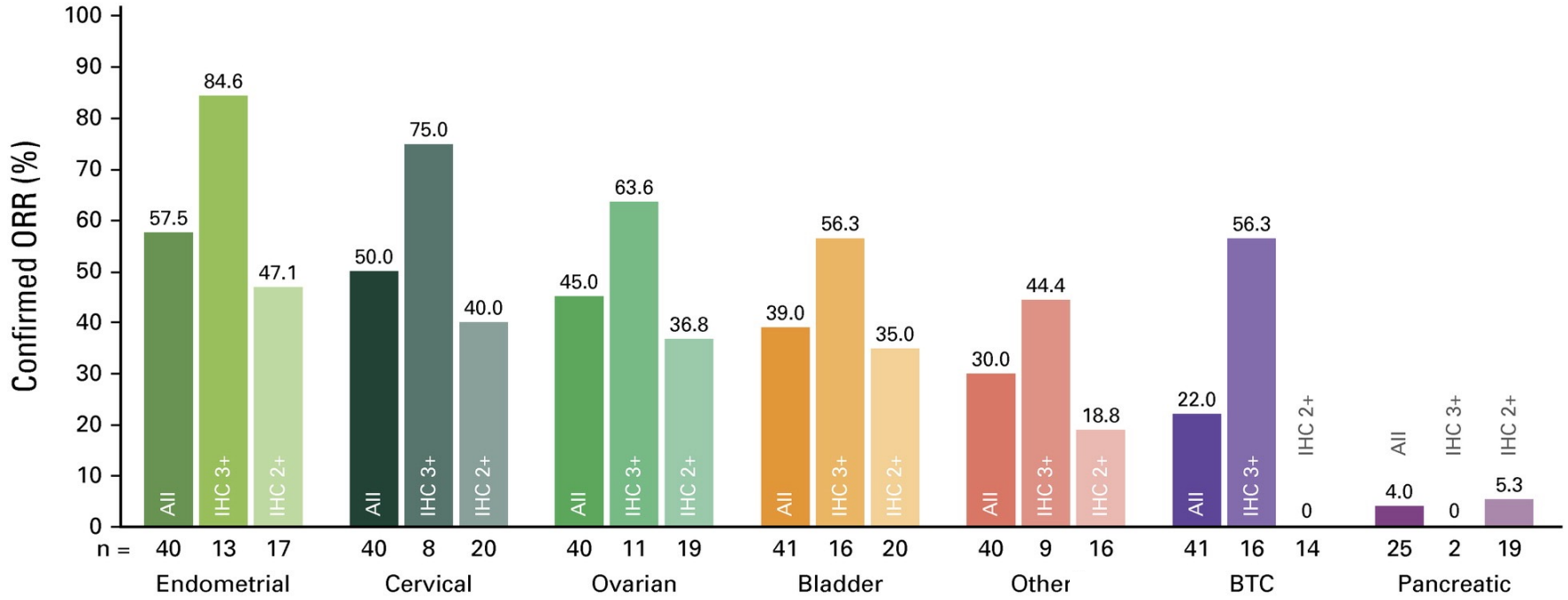
Cancer types	HER2 IHC expression levels				
	0	1+	2+	3+	Total
Gynecological					
Endometrial	52 (40.9)	10 (7.9)	49 (38.6)	16 (12.6)	127
Ovarian/FT	53 (62.4)	11 (12.9)	17 (20.0)	4 (4.7)	85
Peritoneal	10 (71.4)	4 (28.6)	0 (0)	0 (0)	14
Cervical	9 (64.3)	1 (7.1)	2 (14.3)	2 (14.3)	14
Vaginal	2 (100.0)	0 (0)	0 (0)	0 (0)	2
Vulvar	2 (28.6)	1 (14.3)	3 (42.9)	1 (14.3)	7



B. Uzunparmak et al, Annals of Oncology; Volume 34 - Issue 11 - 2023

Phase 2 DESTINY-PanTumor02 Study: Objective Response Rate by HER2 Status—Primary Analysis (N = 267)

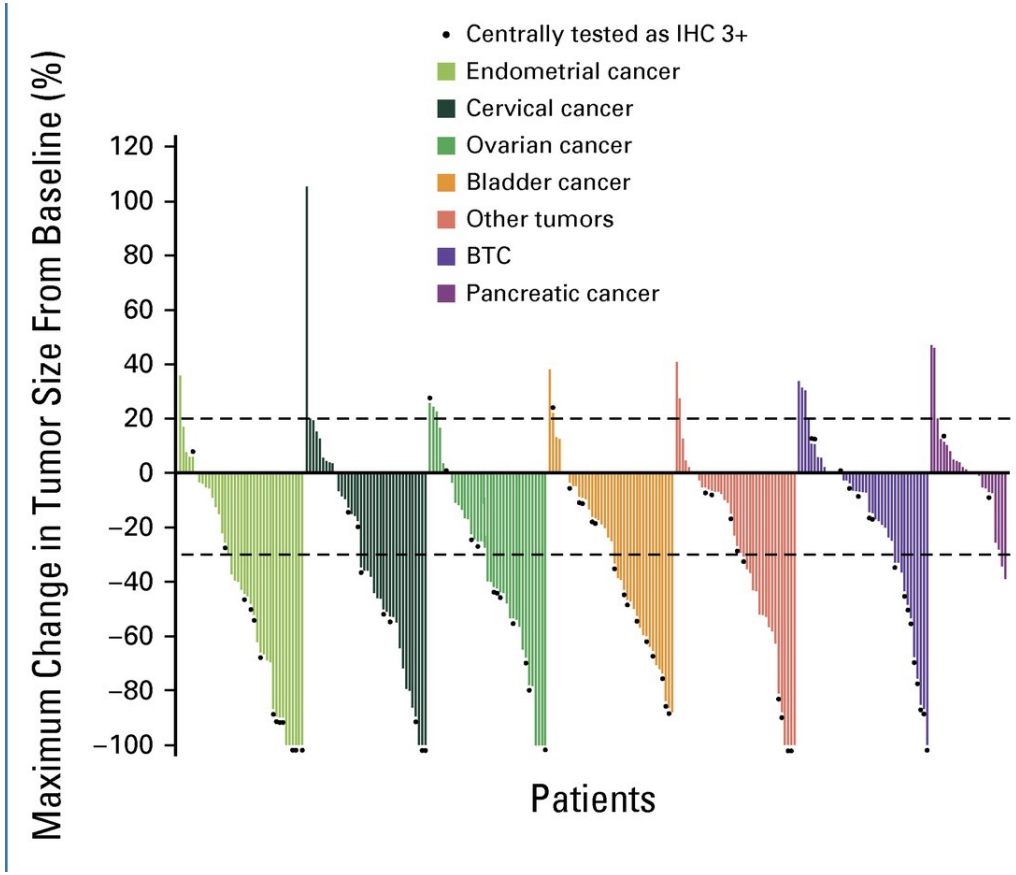
Median follow-up: 12.75 months



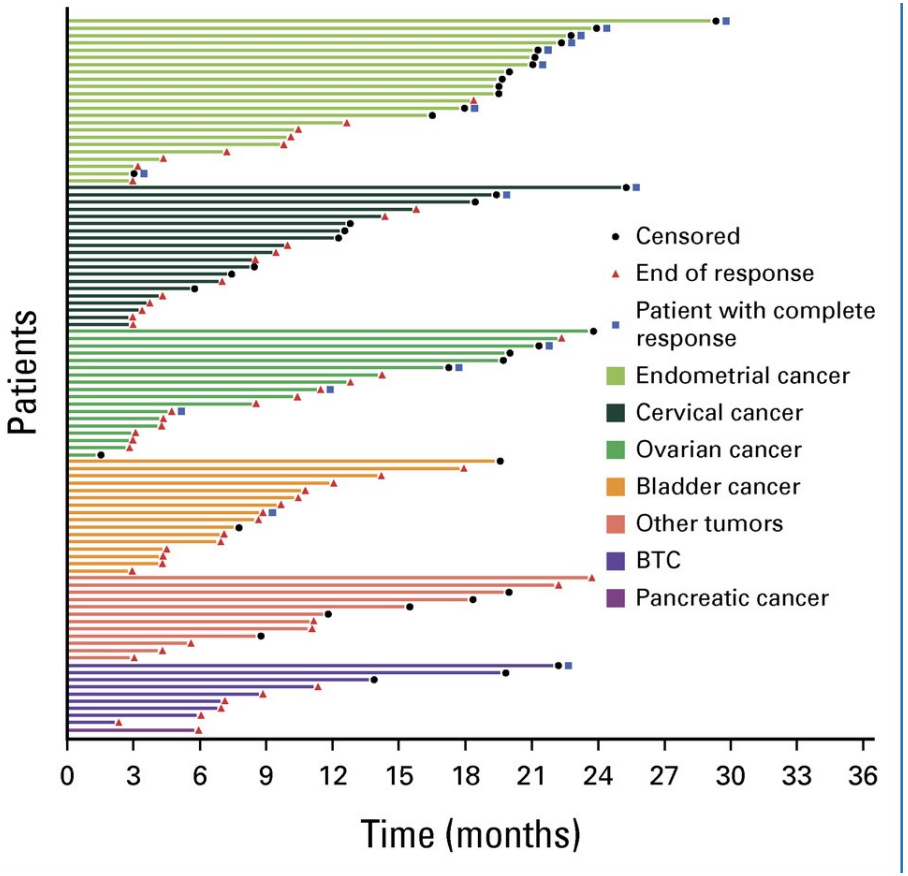
Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58.

Phase 2 DESTINY-PanTumor02 Study: Best Percentage Change in Target Lesion From Baseline

Maximum Change From Baseline

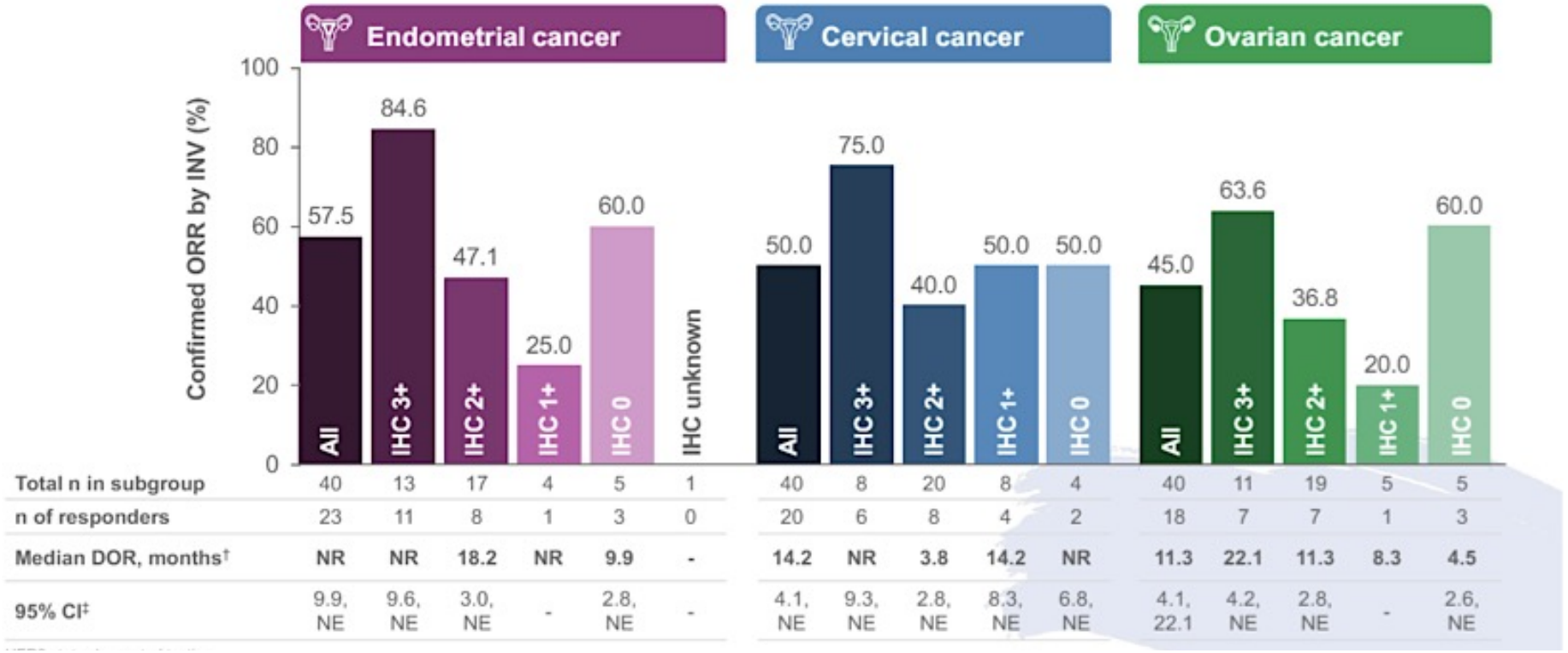


Duration of Response



Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58.

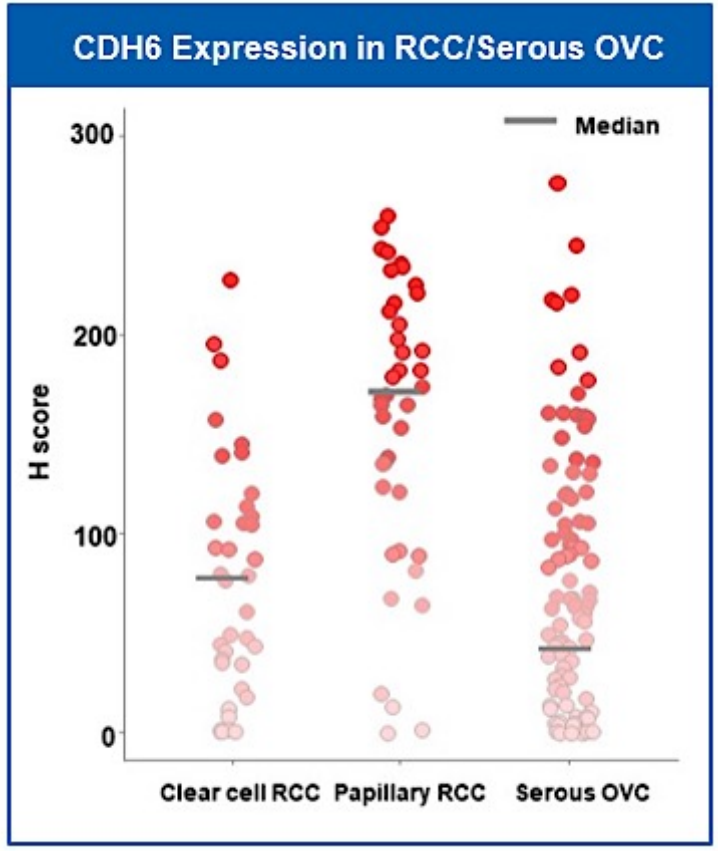
DESTINY-PanTumor02: Response (INV) by HER2 Expression Level—GynOnc Cohorts

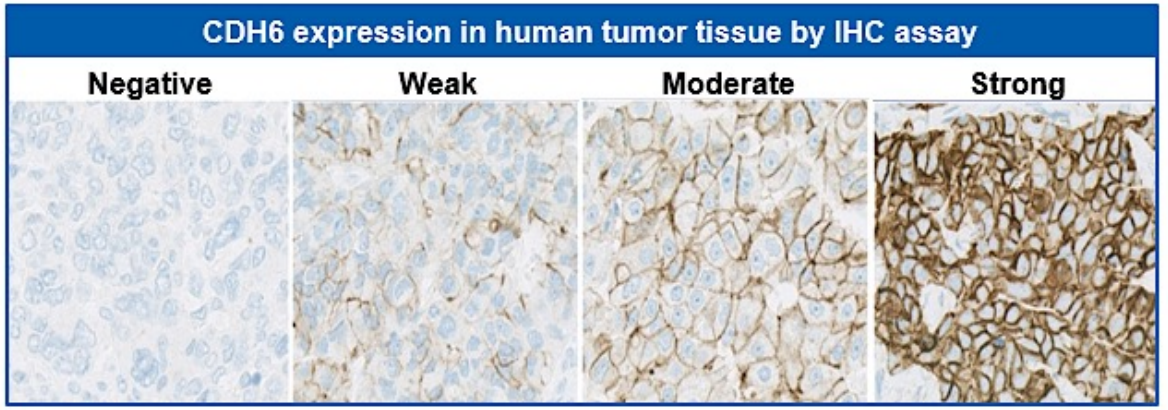


Lee JY, et al. International Gynecological Cancer Society 2023; November 5-7, 2023; Seoul, Korea..

Targeting Cadherin 6 (CDH6)

Targeting Cadherin 6 (CDH6) in Ovarian Cancer: Why?





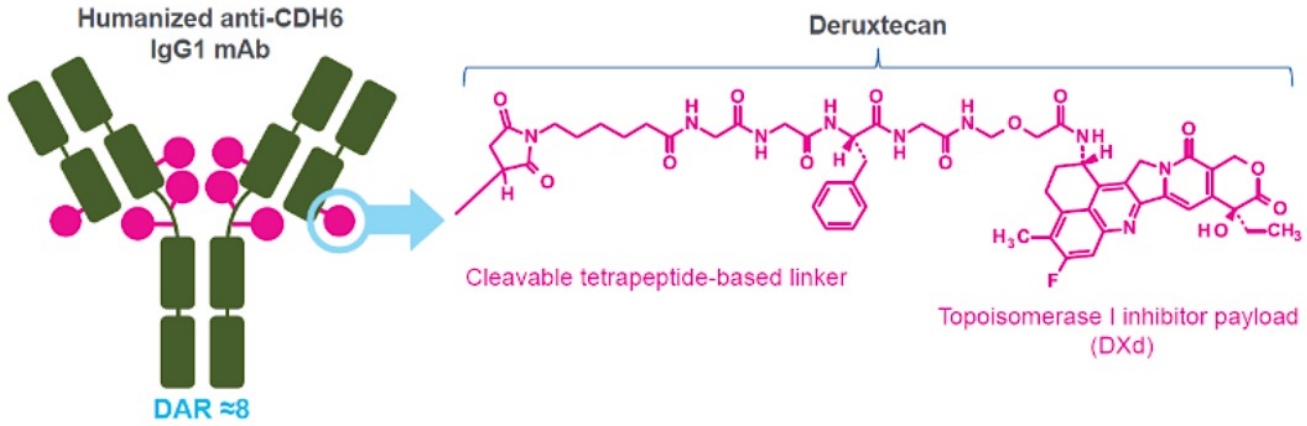
Tumor type	n	CDH6 H-score (n ,%)							
		0		1-100		101-200		201-300	
Clear cell RCC	39	0	0%	25	64%	13	33%	1	3%
Papillary RCC	41	1	2%	9	22%	18	44%	13	32%
Serous OVC	118	18	15%	71	60%	24	20%	5	4%

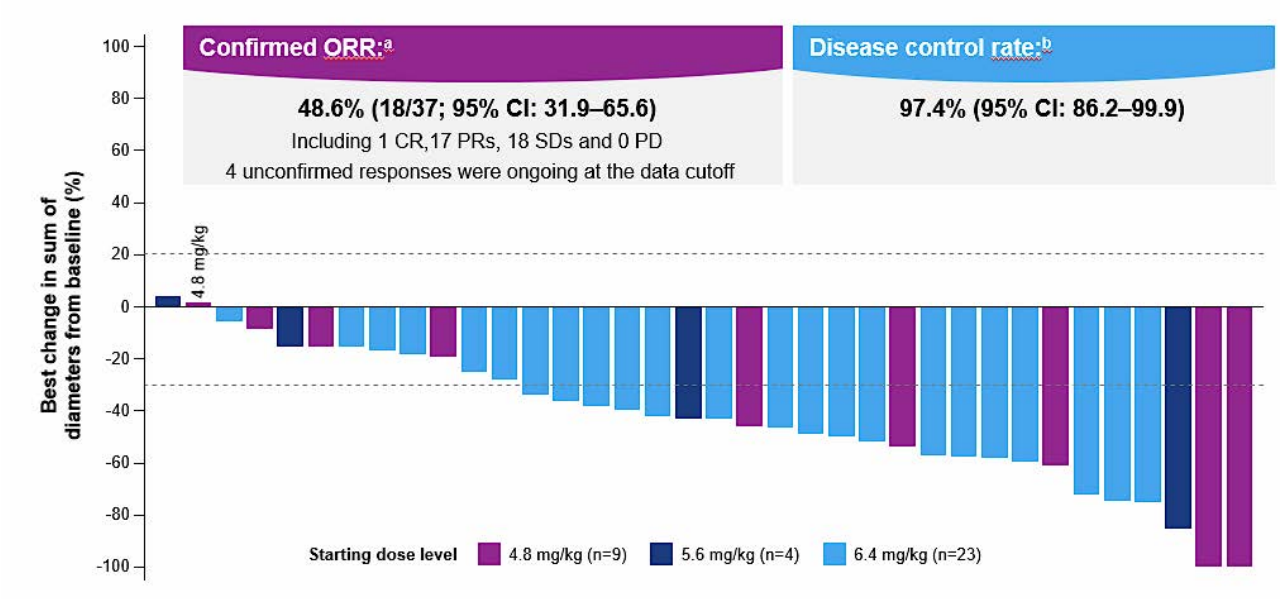
- CDH6 is part of the cadherin family, which is involved with cell-cell adhesion, organ development, and epithelial-mesenchymal transition
- Function of CDH6 has yet to be fully elucidated
- CDH6 is overexpressed in various cancers, particularly EOC

Hirokazu S, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 16-21 September 2021; Paris, France. [Abstract 10P].

Targeting CDH6 in OC

	Raludotatug deruxtecan (DS-6000)[1,2]
Payload	Topoisomerase 1 inhibitor (DXd)
DAR	8
Linker	Cleavable tetrapeptide based linker
Trial	**NCT04707248**





Median DOR:[a]

11.2 months (95% CI: 3.1–NE)
Median (range) FU: 6.7 months (1.4–16.8)

Median TTR:[a]

5.7 weeks (95% CI: 5.3–11.4)

Median PFS:[b]

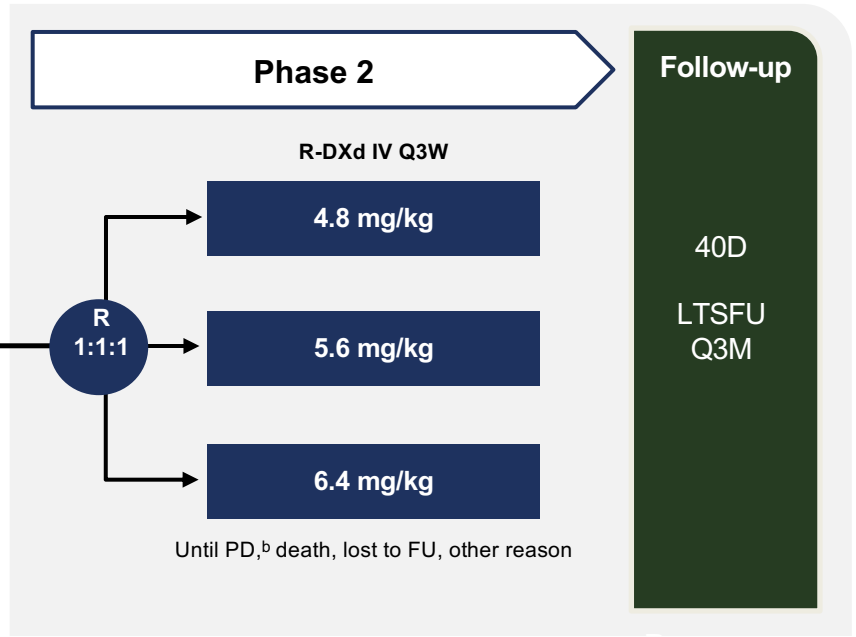
8.1 months (95% CI: 5.3–NE)
Median (range) FU: 4.0 months (0–25.1)

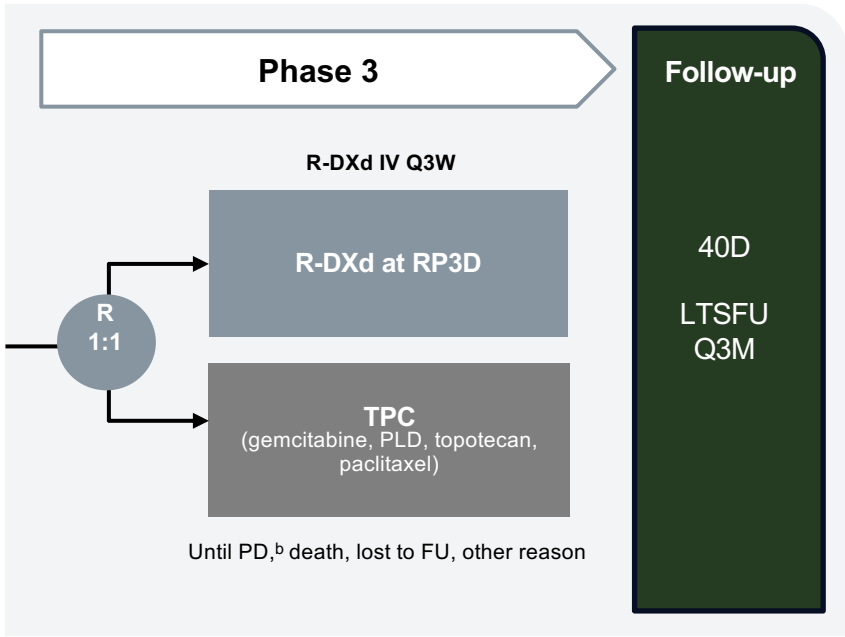
1. Moore K, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 20-24 October 2023; Madrid, Spain.;
2. NCT04707248. Accessed from: https://clinicaltrials.gov/study/NCT04707248?cond=NCT04707248&rank=1.

REJOICE-Ovarian01/GOG-3096: Phase 2/3 Randomized Study of R-DXd in Platinum-Resistant EOC

Key eligibility criteria:

- High-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer
- 1−3 prior LOT (inc. bevacizumab)
- Platinum-resistant disease
- Prior MIRV if high FRα[a]
- ECOG PS 0−1
- No prior CDH6-targeting agents or ADCs with linked TOPO I inhibitor
- Patients with primary platinum-refractory disease are not eligible





Stratification:

- Number of prior LOT (1 vs 2/3)
- CDH6 expression (high vs low)
- TPC (paclitaxel vs others; *Ph 3 only*)

Primary endpoint:

- ORR per BICR[b]

Key secondary endpoints:

- ORR per inv[b]
- DOR

Primary endpoints:

- ORR per BICR[b]
- PFS per BICR[b]

Key secondary endpoints:

- OS
- QOL

NCT06161025

NCT06161025. Accessed from: https://clinicaltrials.gov/study/NCT06161025?term=NCT06161025&rank=1.

Discussion Question

- A 65-year-old woman with no comorbidities presenting with OC with extensive intra-abdominal disease and ascites (clinical Stage IIIC) receives neoadjuvant carboplatin/paclitaxel/bevacizumab with good response and proceeds to surgery with R0 resection. Regulatory and reimbursement issues aside, what would you most likely recommend as maintenance therapy (and for what duration) based on BRCA and HRD status?

Discussion Questions

- What are your preferred first- and second-line systemic therapy for HER2-positive (IHC 3+) metastatic cervical cancer?

- For which clinical scenarios, if any, would you like to be able to administer trastuzumab deruxtecan to a patient with HER2-low (IHC 1+ or 2+) gynecologic cancers?

Module 6: Gynecologic Cancers

Ovarian Cancer; HER2-Directed Therapy for Advanced Gynecologic Cancers — Dr O'Malley

Endometrial Cancer and Cervical Cancer — Dr Slomovitz

Endometrial Cancer (EC) and Cervical Cancer (CC)

Brian M Slomovitz, MD
Professor, OB-GYN, Florida International University
Director, Gynecologic Oncology
Co-Chair, Cancer Research Committee
Mount Sinai Medical Center
Miami, Florida

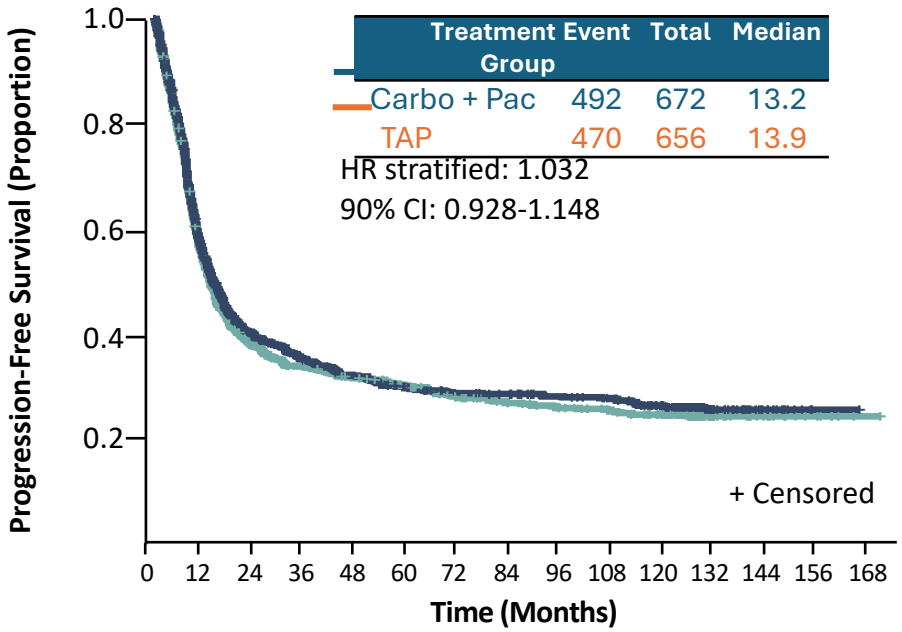
Disclosures

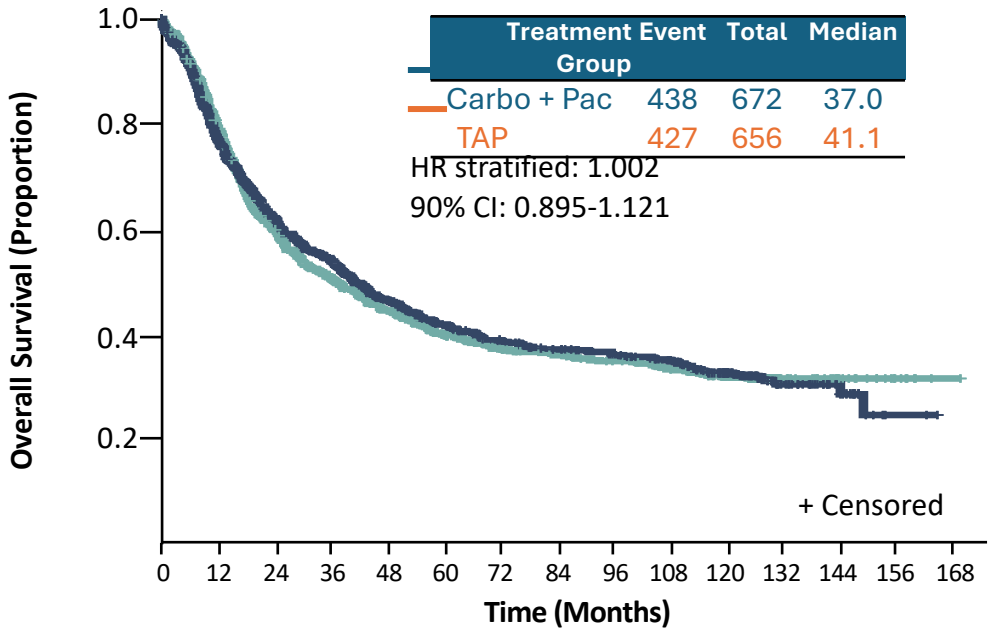
Consulting Agreements	Aadi Bioscience, AstraZeneca Pharmaceuticals LP, Eisai Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Incyte Corporation, Merck, Novartis, Regeneron Pharmaceuticals Inc, Seagen Inc

GOG0209: Carboplatin + Paclitaxel in Advanced Endometrial Cancer
Final Survival Analysis

- 2000s: chemotherapy was the standard of care
- 2019: carboplatin + paclitaxel became the preferred regimen (GOG0209)

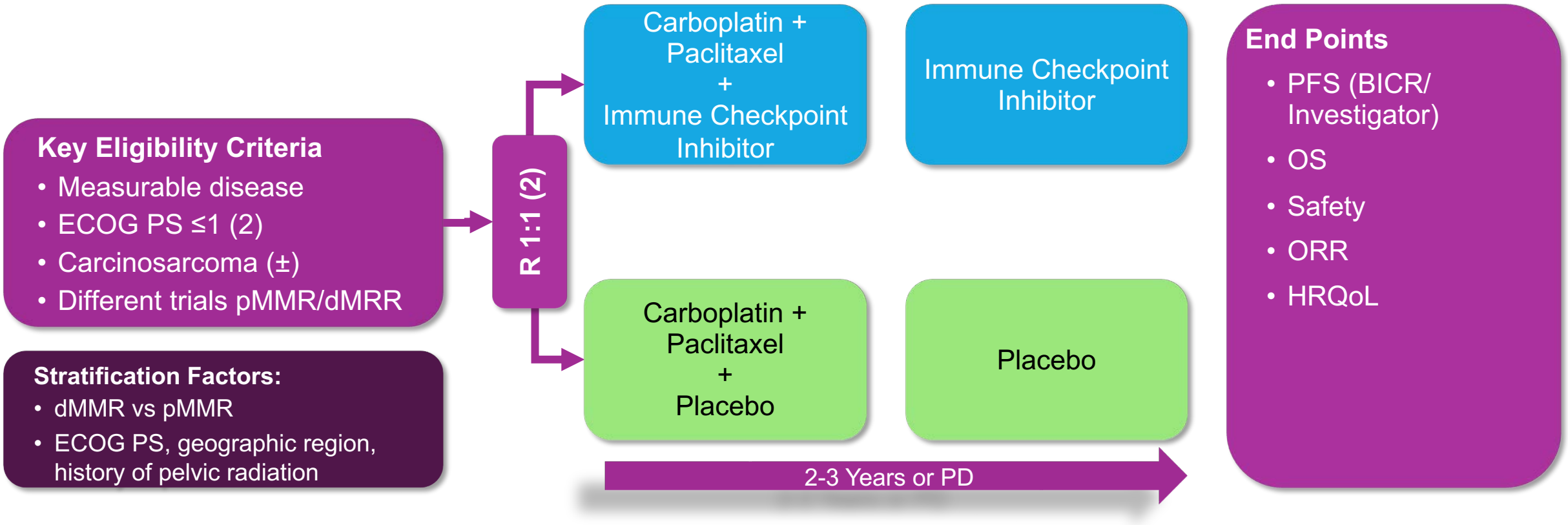
PFS ~13 months, OS ~20 months, response rate 52%





Carbo, carboplatin; OS, overall survival; pac, paclitaxel; TAP, paclitaxel-doxorubicin-cisplatin.
Miller DS, et al. *J Clin Oncol*. 2020;38:3841-3850.

Benefit of IO + Chemo in EC: 1L studies in patients with advanced stage or recurrent EC

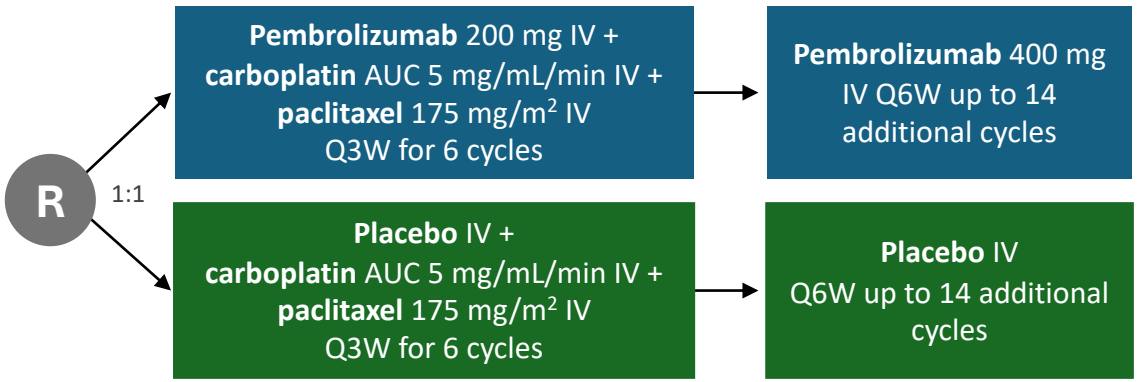


BICR=blinded independent central review; dMMR=deficient mismatch repair; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HRQoL=health-related quality of life; ORR=overall response rate; OS=overall survival; pMMR=proficient mismatch repair; PD=progressive disease; PFS=progression-free survival; R=randomized.

Mirza M et al. NEJM March 2023
Eskander et al. NEJM March 2023
Colombo N, et al. Lancet Oncol Sept 2024
Marth C, et al. SGO 2024 Annual Meeting

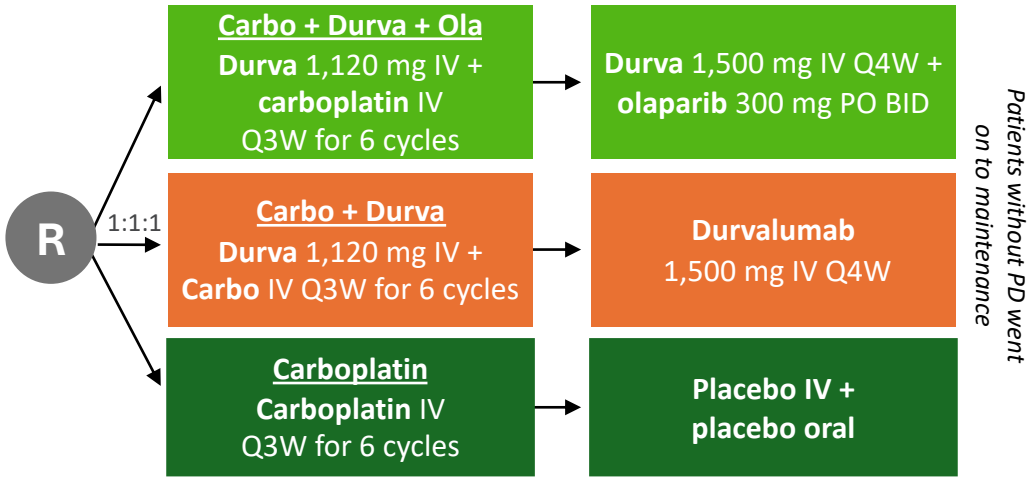
Transformative Clinical Trials in the Advanced Stage and Recurrent Setting

NRG-GY018



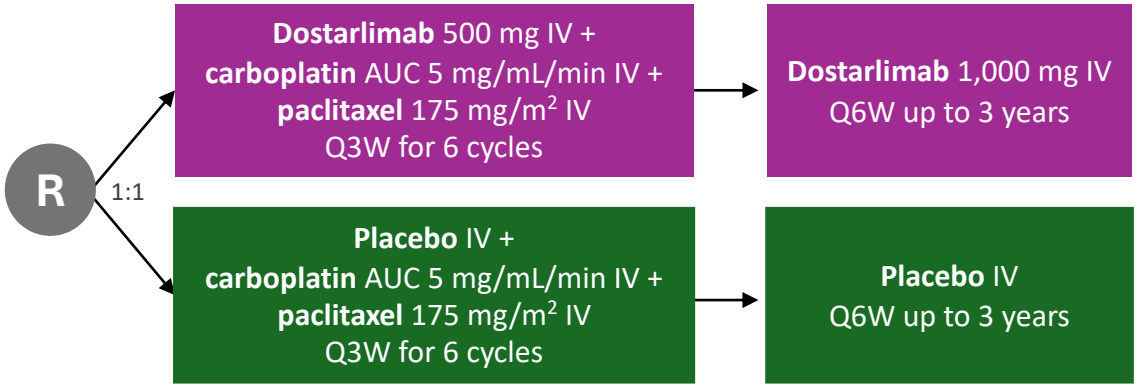
Stratified by MMR status (pMMR vs dMMR), ECOG status, and prior adjuvant chemo

DUO-E/GOG-3041



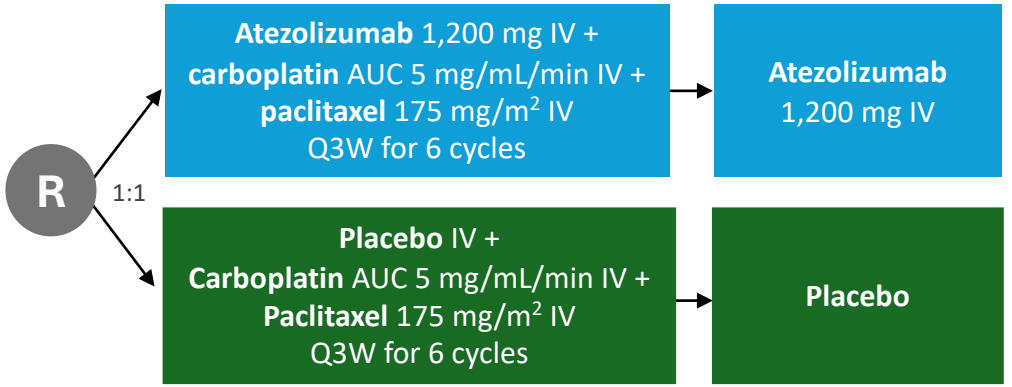
Stratified by MMR status, disease status, region of world

GOG-3031/RUBY



Stratified by MMR/MSI status, prior external pelvic radiotherapy, and disease status

AtTEnd



Stratified by MMR status, disease status, region of world, histology

BID, twice a day; Carbo, carboplatin; Durva, durvalumab; Ola, Olaparib; PO, orally.

Eskander RN, et al. *N Engl J Med*. 2023;388:2159-2170; Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158; Westin SN, et al. *J Clin Oncol.* 2024;42:283-299; Colombo N, et al. *Ann Oncol*. 2023;34(suppl 2):S1281-S1282.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

M.R. Mirza, D.M. Chase, B.M. Slomovitz, R. dePont Christensen, Z. Novák, D. Black, L. Gilbert, S. Sharma, G. Valabrega, L.M. Landrum, L.C. Hanker, A. Stuckey, I. Boere, M.A. Gold, A. Auranen, B. Pothuri, D. Cibula, C. McCourt, F. Raspagliesi, M.S. Shahin, S.E. Gill, B.J. Monk, J. Buscema, T.J. Herzog, L.J. Copeland, M. Tian, Z. He, S. Stevens, E. Zografos, R.L. Coleman, and M.A. Powell, for the RUBY Investigators*

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

ASCO Journal of Clinical Oncology®

Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial

Shannon N. Westin, MD, MPH[1]; Kathleen Moore, MD[2]; Hye Sook Chon, MD[3]; Jung-Yun Lee, MD[4]; Jessica Thomes Pepin, MD[5]; Michael Sundborg, MD[6]; Ayelet Shai, MD, PhD[7]; Joseph de la Garza, MD[8]; Shin Nishio, MD[9]; Michael A. Gold, MD[10]; Ke Wang, MD[11]; Kristi McIntyre, MD[12]; Todd D. Tillmanns, MD[13]; Stephanie V. Blank, MD[14]; Ji-Hong Liu, MD[15]; Michael McCollum, MD[16]; Fernando Contreras Mejia, MD[17]; Tadaaki Nishikawa, MD[18]; Kathryn Pennington, MD[19]; Zoltan Novak, MD, PhD[20]; Andreia Cristina De Melo, MD[21]; Jalid Sehouli, MD[22]; Dagmara Klasa-Mazurkiewicz, MD[23]; Christos Papadimitriou, MD[24]; Marta Gil-Martin, MD[25]; Birute Brasiuniene, MD, PhD[26]; Conor Donnelly, PhD[27]; Paula Michelle del Rosario, MD[28]; Xiaochun Liu, MD, PhD[29]; and Els Van Nieuwenhuysen, MD[30]; on behalf of the DUO-E Investigators

DOI https://doi.org/10.1200/JCO.23.02132

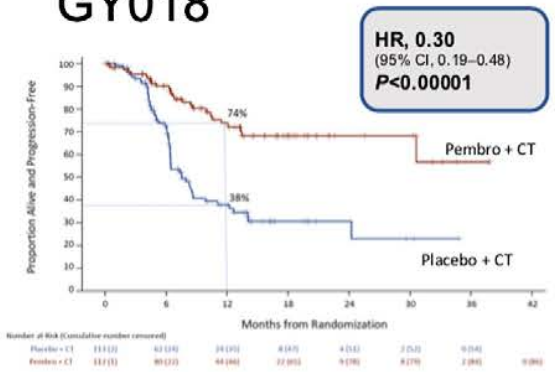
Atezolizumab and chemotherapy for advanced or recurrent endometrial cancer (AtTEnd): a randomised, double-blind, placebo-controlled, phase 3 trial

*Nicoletta Colombo, Elena Biagioli, Kenichi Harano, Francesca Galli, Emma Hudson, Yoland Antill, Chel Hun Choi, Manuela Rabaglio, Frederic Marmé, Christian Marth, Gabriella Parma, Lorena Fariñas-Madrid, Shin Nishio, Karen Allan, Yeh Chen Lee, Elisa Piovano, Beatriz Pardo, Satoshi Nakagawa, John McQueen, Claudio Zamagni, Luis Manso, Kazuhiro Takehara, Giulia Tasca, Annamaria Ferrero, Germana Tognon, Andrea Alberto Lissoni, Mariacristina Petrella, Maria Elena Laudani, Eliana Rulli, Sara Uggeri, M Pilar Barretina Ginesta, and AtTEnd study group**

1. Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145-2158. doi:10.1056/nejmoa2216334; 2. Eskander RN, et al. *N Engl J Med.* 2023;388(23):2159-2170. doi:10.1056/NEJMoa2302312; 3. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. doi: 10.1200/JCO.23.02132; 4. Colombo N, et al. *Lancet Oncol.* 2024,Sep;25(9):1135-1146. doi: 10.1016/S1470-2045(24)00334-6.

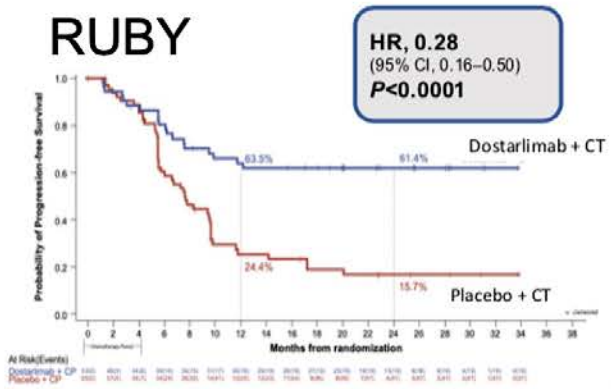
Benefit of IO + Chemo in the dMMR EC population

GY018



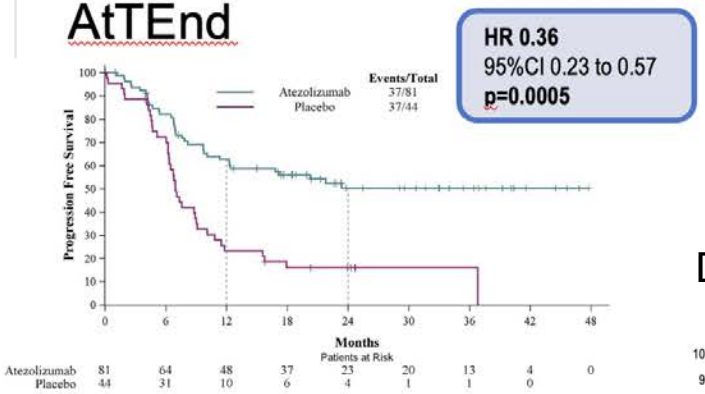
	No with events%	Median
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)

RUBY



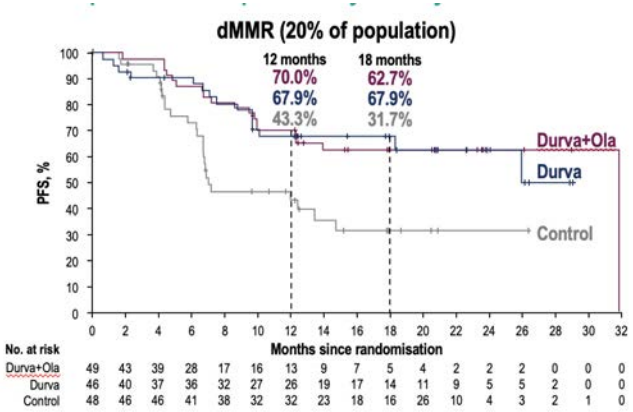
	No with events%	Median
Dostar + CT	35.8	NR (11.8-NR)
Placebo + CT	72.3	7.7 (5.6-9.7)

AtTEnd



	No with events%	Median
Atezo + CT	45.7	NR (12.3-NR)
Placebo + CT	84.1	6.9 (6.2-9.0)

DUO-E

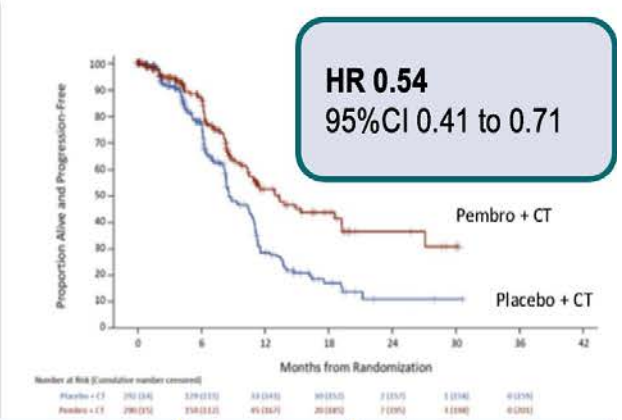


	No with events %	Median
Durva + CT	32.6	NR (NR-NR)
Durva + O + CT	37.5	31.8 (12.4-NR)
Placebo + CT	51	7.0 (6.7-14.8)

Slide courtesy of Dr. David Tan ESMO 2023. Revised

Benefit of IO + Chemo in the pMMR EC population

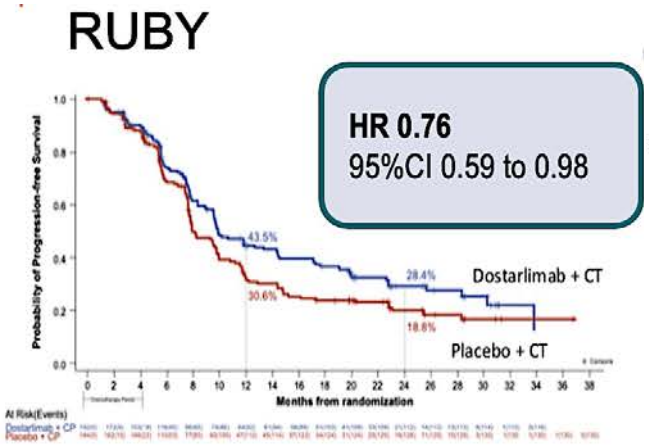
GY018



	No with events%	Median
Pembro + CT	30.6	13.1 (10.5-18.8)
Placebo + CT	45.5	8.7 (8.4-10.7)
Maturity	38.1%	

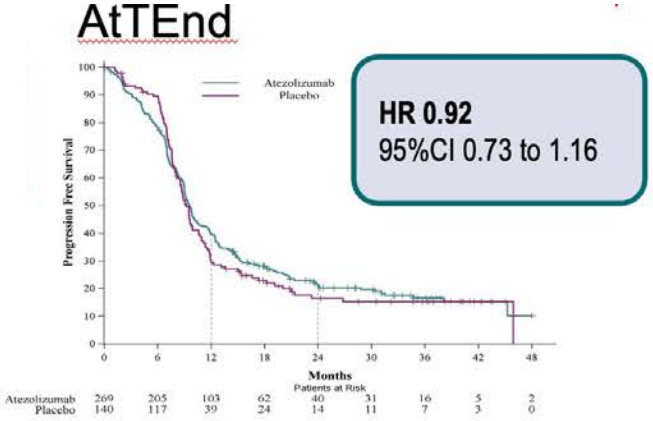
Only trial with prespecified alpha allocated analysis in pMMR EC cohort as primary endpoint

RUBY



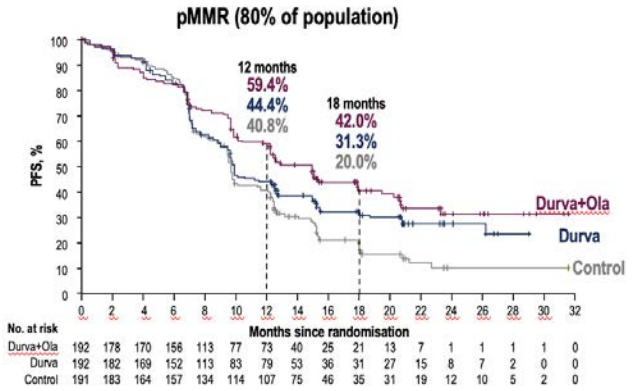
	No with events%	Median
Dostar + CT	60.4	9.9 (9.0-13.3)
Placebo + CT	70.7	7.9 (7.6-9.8)
Maturity	65.4%	

AtTEnd



	No with events%	Median
Atezo + CT	78	9.5 (9.0-10.4)
Placebo + CT	77	9.2 (8.5-9.9)
Maturity	78%	

DUO-E



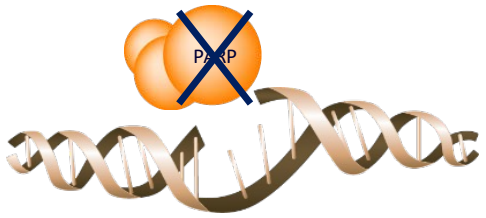
	No with events %	Median
Durva + CT	64.6	9.9 (9.4-12.5)
Durva + O + CT	56.5	15 (12.4-18)
Placebo + CT	77.1	9.7 (9.2-10.1)

Slide courtesy of Dr. David Tan ESMO 2023. Revised

Mechanism of Action of PARP Inhibitors

DNA SSBs occur all the time in cells and PARP detects and repairs them

During the replication process unrepaired SSBs are converted into DSBs



PARPi

Trapped PARP on single-strand breaks

Replicating cells

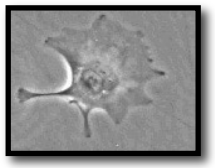
Normal cell

Cancer cell with HRD

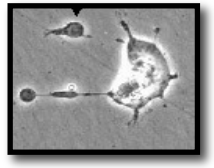
Repair by homologous recombination

No effective repair (No HR pathway)

Survival



Tumor-specific killing by PARP inhibitors

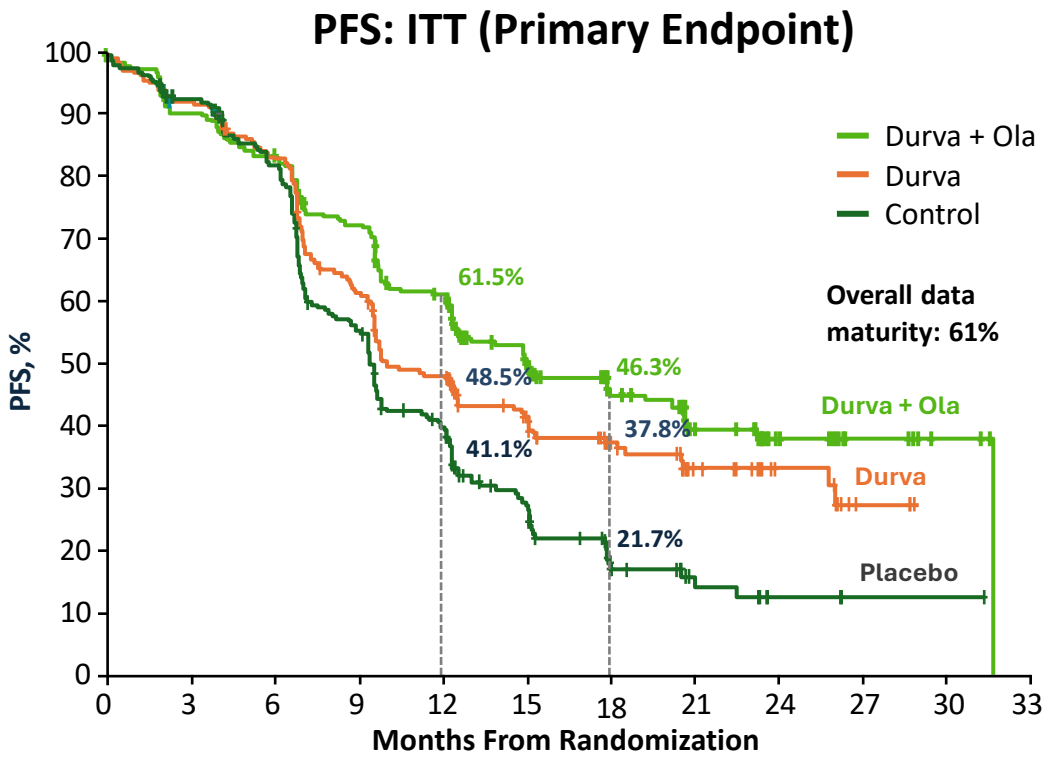


Cell death

DSB, double-strand break; HR, homologous recombination; HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; SSB, single-strand break.

O'Connor MJ, et al. *Mol Cell*. 2015;60:547-560.

DUO-E: Maintenance Durvalumab ± Olaparib on PFS in ITT Population



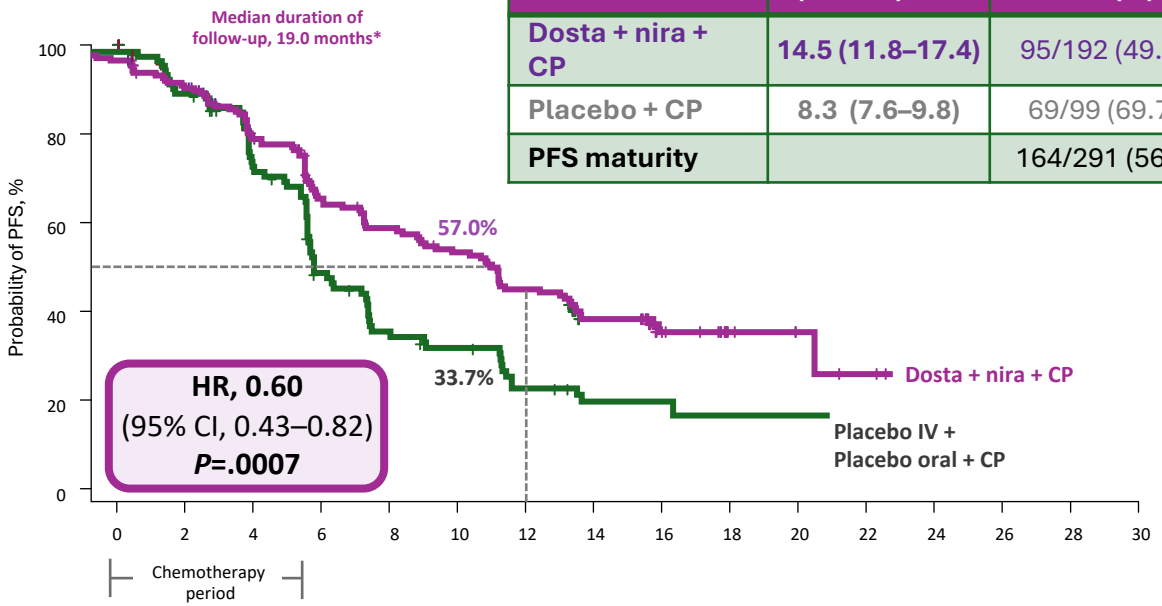
	Control (n = 241)	Durva (n = 238)	Durva + Ola (n = 239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS, mo (95% CI)	9.6 (9.0-9.9)	10.2 (9.7-14.7)	15.1 (12.6-20.7)
HR (95% CI) vs control		**0.71 (0.57-0.89); *P* = .003**	**0.55 (0.43-0.69); *P* < .0001**
HR (95% CI) vs durva			**0.78 (0.61-0.99)**

ITT, intention to treat; Ola, olaparib.
Westin SN, et al. *J Clin Oncol.* 2024;42:283-299.

RUBY Part 2: Maintenance Dostarlimab ± Niraparib on PFS in Overall and pMMR Populations

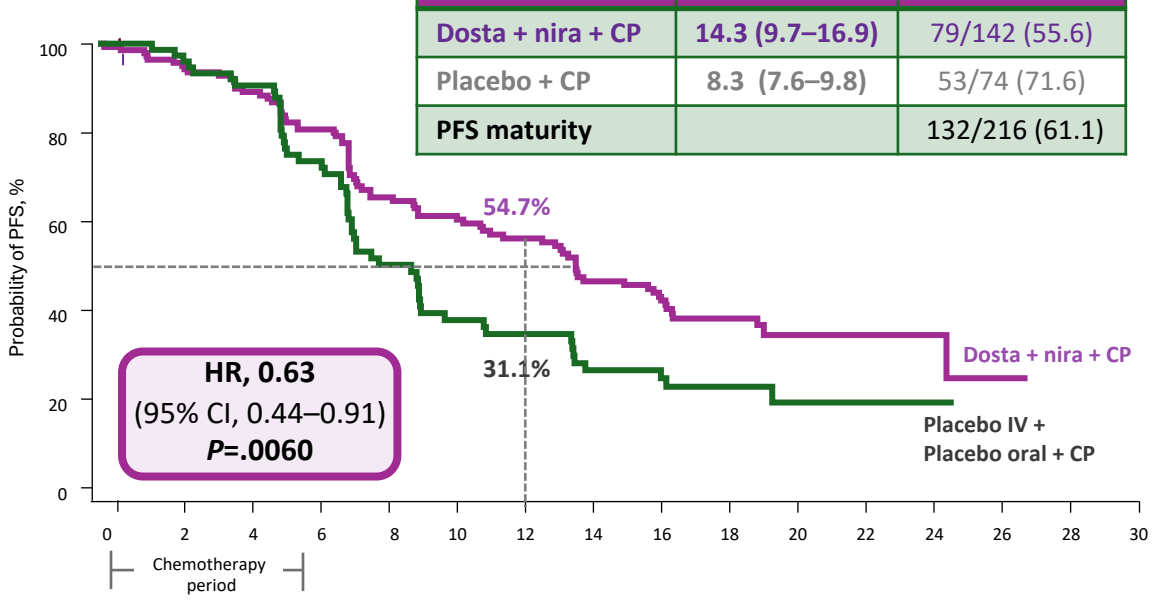
Overall

	Median (95% CI), mo	Events, n/N (%)
Dosta + nira + CP	14.5 (11.8–17.4)	95/192 (49.5)
Placebo + CP	8.3 (7.6–9.8)	69/99 (69.7)
PFS maturity		164/291 (56.4)



pMMR

	Median (95%CI), mo	Events, n/N (%)
Dosta + nira + CP	14.3 (9.7–16.9)	79/142 (55.6)
Placebo + CP	8.3 (7.6–9.8)	53/74 (71.6)
PFS maturity		132/216 (61.1)



Maintenance dostarlimab + niraparib resulted in a statistically significant improvement in PFS in the overall and pMMR populations

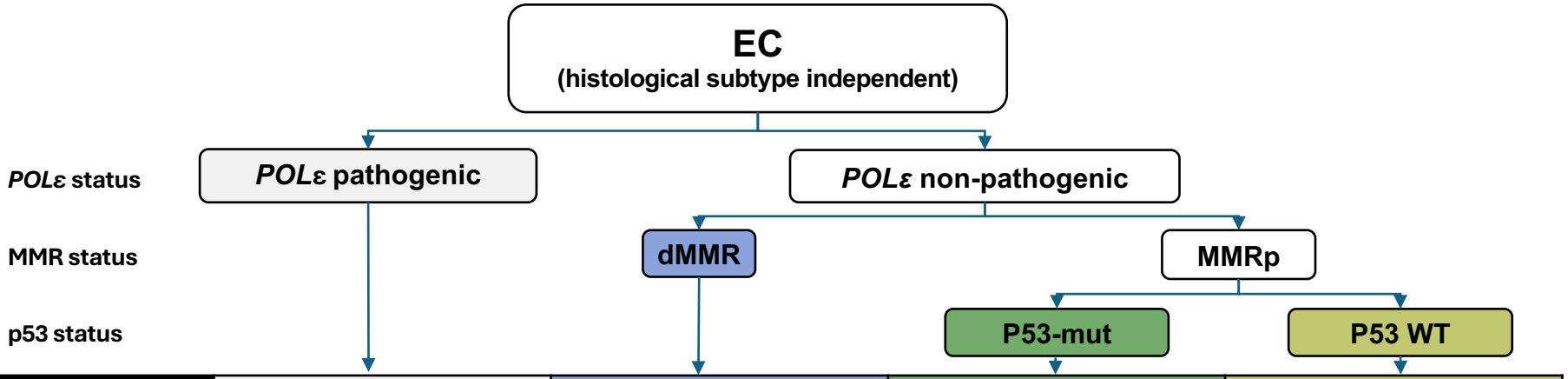
*Median expected duration of follow-up.

Nira, niraparib.

Mirza MR, et al. Presented at: 2024 ESMO Gynecological Cancers Congress; June 20-22, 2024; Florence, Italy. Oral abstract 38M0.

GOG-3031/RUBY: Molecular Classification Algorithm

- In RUBY Part 1, molecular classification was performed for all participants with WES results – 400 of 494 patients

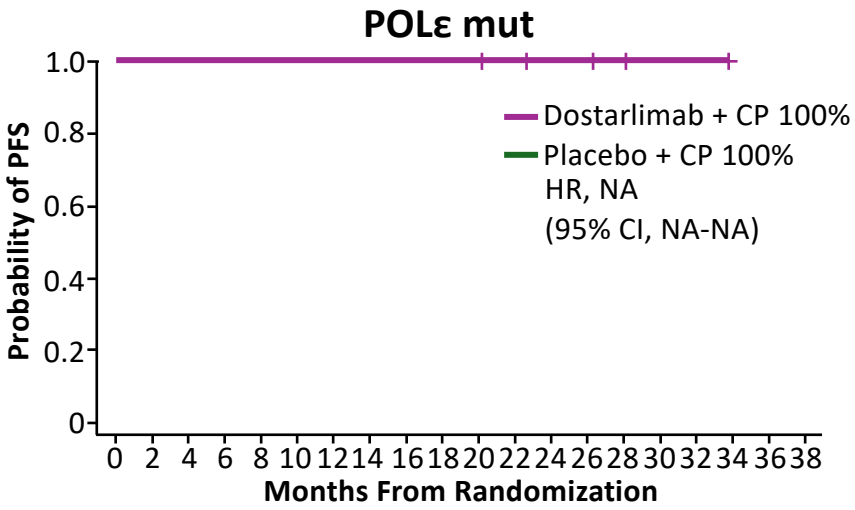


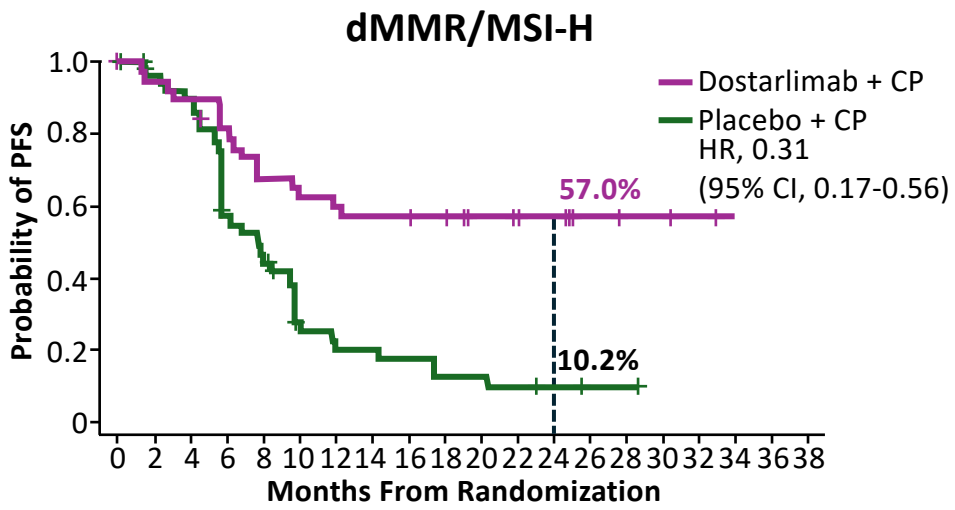
Integrated diagnosis	POLεmut (EDM)	dMMR (or MSI-H)	TP53 aberrant	NSMP
Prevalence in RUBY, % (n/N)	**1.25%** (5/400)	**22.75%** (91/400)	**22%** (88/400)	**54%** (216/400)
Diagnostic test	WES	Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization	WES	

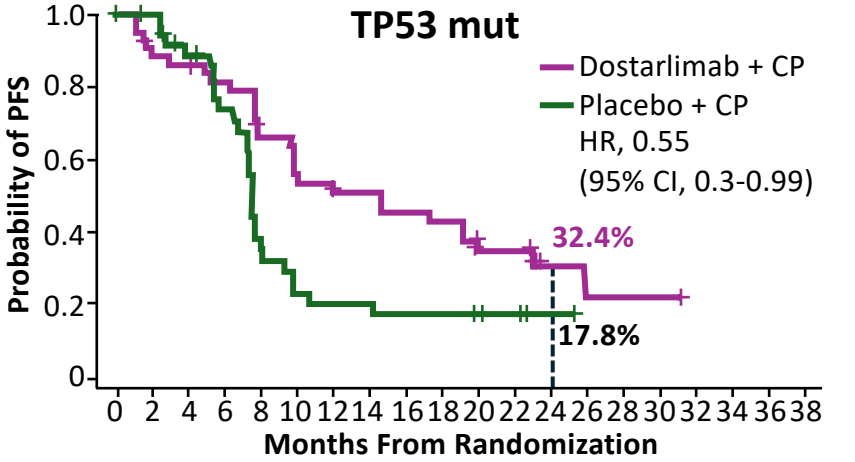
Efficacy per molecular classification was an exploratory analysis.
dMMR, mismatch repair deficient; EC, endometrial cancer; EDM, exonuclease domain; IHC, immunohistochemistry; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; mut, mutated; NGS, next generation sequencing; NSMP, no specific molecular profile; PCR, polymerase chain reaction; POLε, polymerase epsilon; TP53, tumor protein 53; WES, whole exome DNA sequencing; WT, wild type.

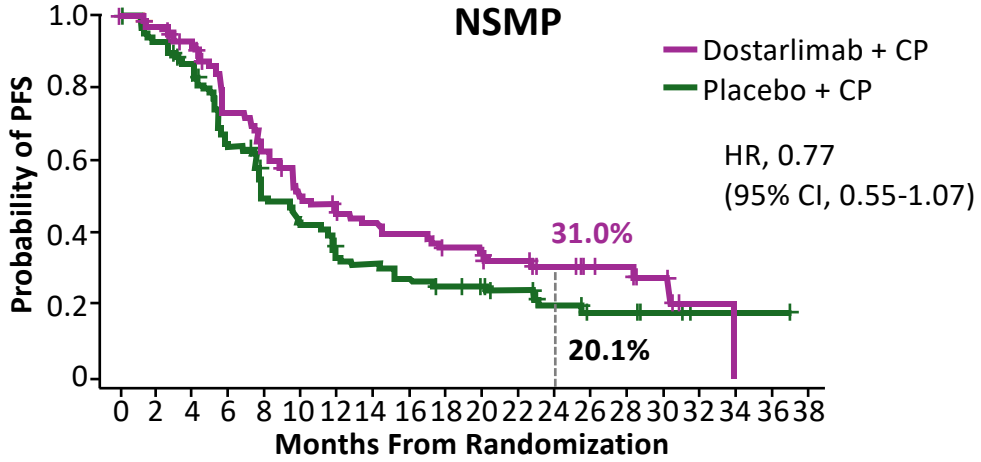
Mirza MR, et al. ESMO 2023.

RUBY: PFS According to Molecular Subgroup







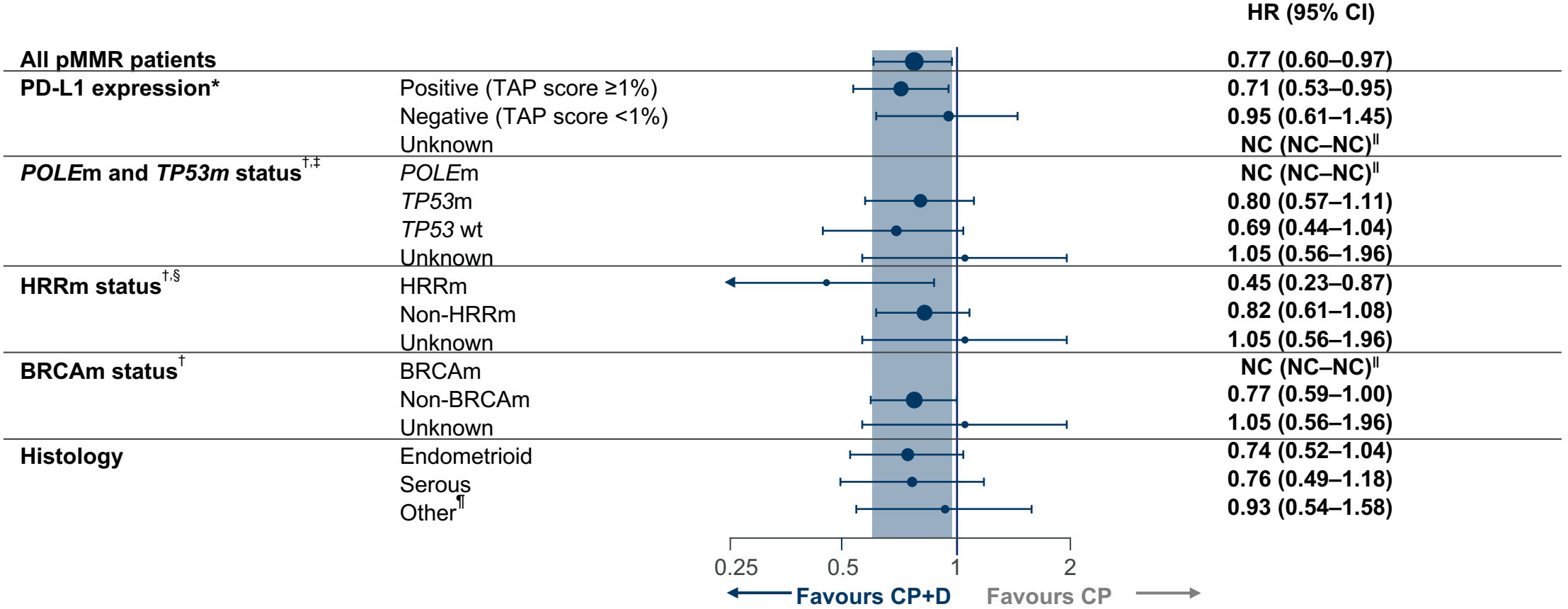


Data based on exploratory analysis based on 400 patients from the RUBY trial with known molecular classification with WES.
Mirza MR, et al. Presented at: 2023 Annual Global Meeting of the International Gynecologic Cancer Society; November 5-7, 2023; Seoul, Korea. Abstract SE008.

pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab versus CP

Post hoc exploratory analysis

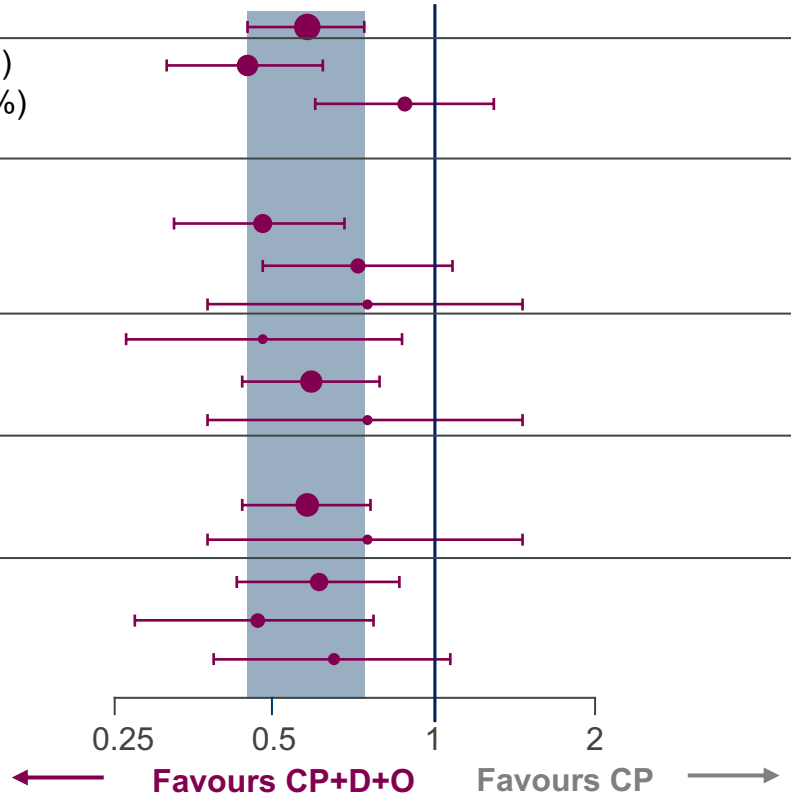


DCO: 12 April 2023. *PD-L1 expression was evaluated using the VENTANA PD-L1 (SP263) assay. PD-L1 positive defined as TAP ≥1%, PD-L1 negative defined as TAP <1%, and unknown included patients who withdrew consent or due to sample unavailability; †Status determined retrospectively in two ways: from tissue samples (FoundationOne®CDx assay; Foundation Medicine, Inc.), and by molecular profiling of ctDNA (FoundationOne®Liquid CDx; Foundation Medicine, Inc.) from blood samples; ‡*TP53*m status defined as a sample with a deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; *TP53* wt status defined as a sample with no deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; and unknown *TP53*m status included patients recruited in China, where *TP53* and/or *POLE* testing was not performed, patients who withdrew consent and patients for whom no sample was available; §Positive HRRm status defined as a sample with a deleterious or suspected deleterious mutation in any of the following prespecified genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* and *RAD54L*; negative HRRm status (non-HRRm) defined as a sample with no deleterious or suspected deleterious mutations in any of the prespecified genes; and unknown HRRm status included patients recruited in China, where HRR testing was not performed, patients who withdrew consent and patients for whom no sample was available; ‖Not calculated due to low event numbers; ¶'Other' includes carcinosarcoma, mixed epithelial, clear cell, undifferentiated, mucinous, and other.
DCO, data cutoff; NC, not calculable.

pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab + olaparib versus CP

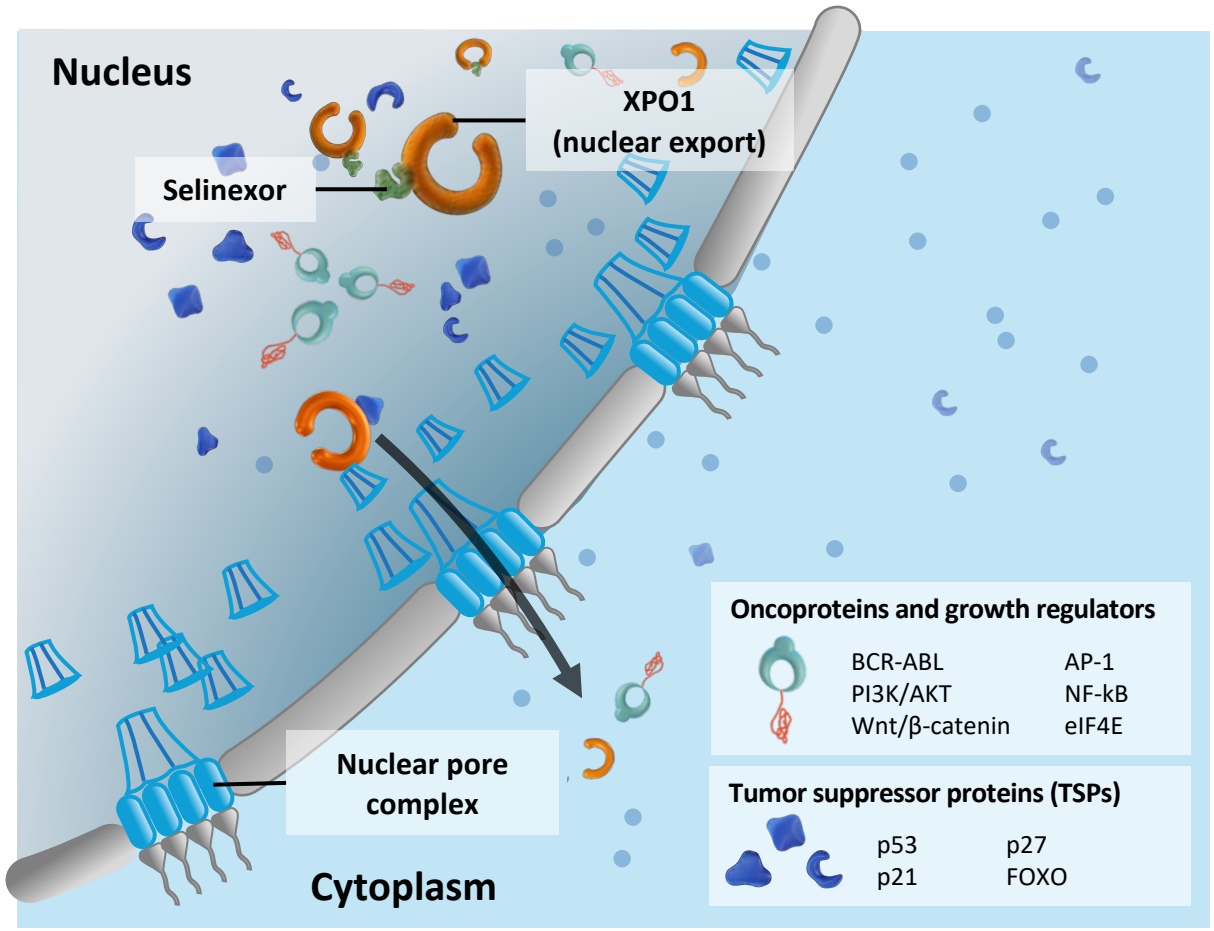
Post hoc exploratory analysis



		HR (95% CI)
All pMMR patients		**0.57 (0.44–0.73)**
PD-L1 expression*	Positive (TAP score ≥1%)	**0.44 (0.31–0.61)**
	Negative (TAP score <1%)	**0.87 (0.59–1.28)**
	Unknown	**NC (NC–NC)[§]**
***POLE*m and *TP53m* status**[†,‡]	*POLE*m	**NC (NC–NC)[‖]**
	*TP53*m	**0.47 (0.32–0.67)**
	TP53 wt	**0.71 (0.47–1.07)**
	Unknown	**0.74 (0.37–1.45)**
HRRm status[†,§]	HRRm	**0.47 (0.26–0.86)**
	Non-HRRm	**0.58 (0.43–0.78)**
	Unknown	**0.74 (0.37–1.45)**
BRCAm status[†]	BRCAm	**NC (NC–NC)[‖]**
	Non-BRCAm	**0.57 (0.43–0.75)**
	Unknown	**0.74 (0.37–1.45)**
Histology	Endometrioid	**0.60 (0.42–0.85)**
	Serous	**0.46 (0.27–0.76)**
	Other[¶]	**0.64 (0.38–1.06)**

DCO: 12 April 2023. *PD-L1 expression was evaluated using the VENTANA PD-L1 (SP263) assay. PD-L1 positive defined as TAP ≥1%, PD-L1 negative defined as TAP <1%, and unknown included patients who withdrew consent or due to sample unavailability; †Status determined retrospectively in two ways: from tissue samples (FoundationOne®CDx assay; Foundation Medicine, Inc.), and by molecular profiling of ctDNA (FoundationOne®Liquid CDx; Foundation Medicine, Inc.) from blood samples; ‡*TP53*m status defined as a sample with a deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; *TP53* wt status defined as a sample with no deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; and unknown *TP53*m status included patients recruited in China, where *TP53* and/or *POLE* testing was not performed, patients who withdrew consent and patients for whom no sample was available; §Positive HRRm status defined as a sample with a deleterious or suspected deleterious mutation in any of the following prespecified genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* and *RAD54L*; negative HRRm status (non-HRRm) defined as a sample with no deleterious or suspected deleterious mutations in any of the prespecified genes; and unknown HRRm status included patients recruited in China, where HRR testing was not performed, patients who withdrew consent and patients for whom no sample was available; ‖Not calculated due to low event numbers; ¶'Other' includes carcinosarcoma, mixed epithelial, clear cell, undifferentiated, mucinous, and other.
DCO, data cutoff; NC, not calculable.

Selinexor Is a Targeted Oral XPO1 Inhibitor

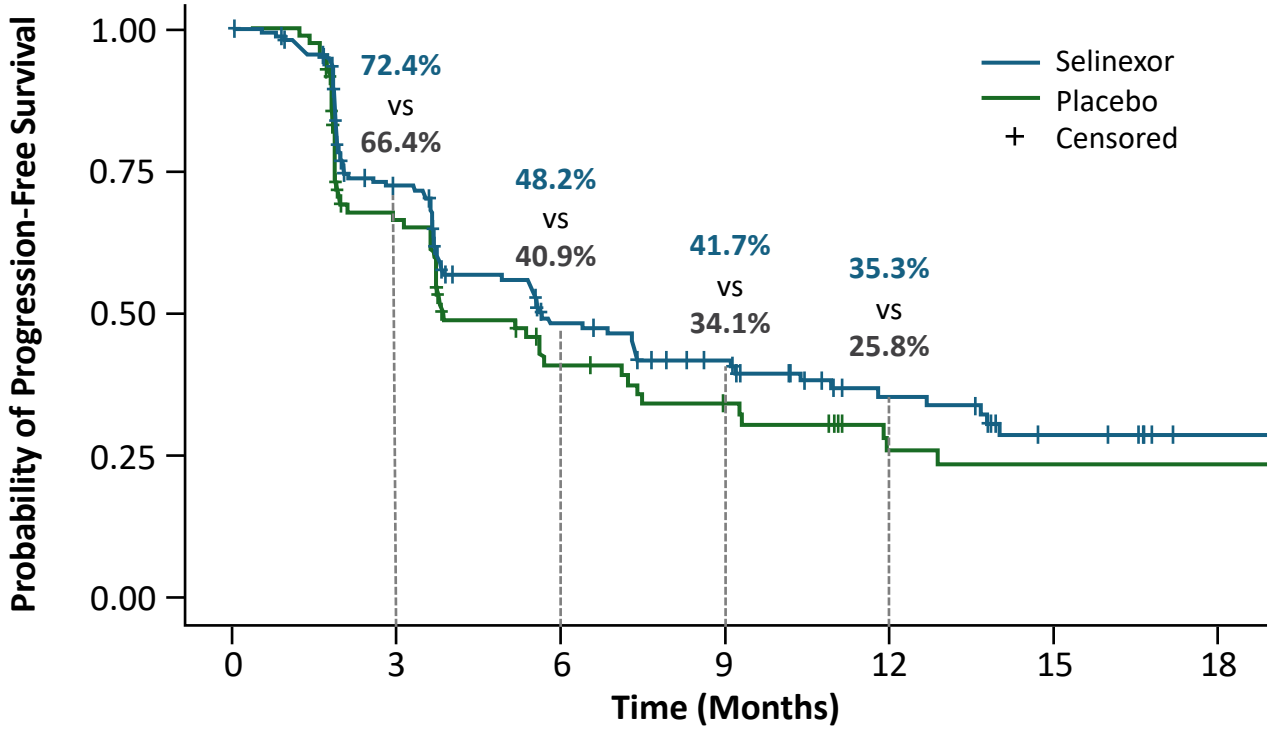


XPO1 inhibition by selinexor results in:

- Nuclear retention and functional reactivation of TSPs (eg, p53), which selectively kills cancer cells and largely spares normal cells
- Inhibition of mRNA export of select oncogenes, thus decreasing subsequent translation and synthesis of oncoproteins
- Simultaneous targeting of several oncogenic pathways involved in cancer development, maintenance, and progression

- Tai Y-T, et al. *Leukemia*. 2014;28:155-165; Gandhi UH, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:335-345; Sun Q, et al. *Signal Transduct Target Ther*. 2016;1:16010.

ENGOT-EN5/GOG-3055/SIENDO: PFS in ITT Population



Median follow-up: 10.2 months (95% CI 8.97, 13.57)

Median PFS

Selinexor (n = 174): 5.7 mo (95% CI, 3.81-9.20)

Placebo (n = 89): 3.8 mo (95% CI, 3.68-7.39)

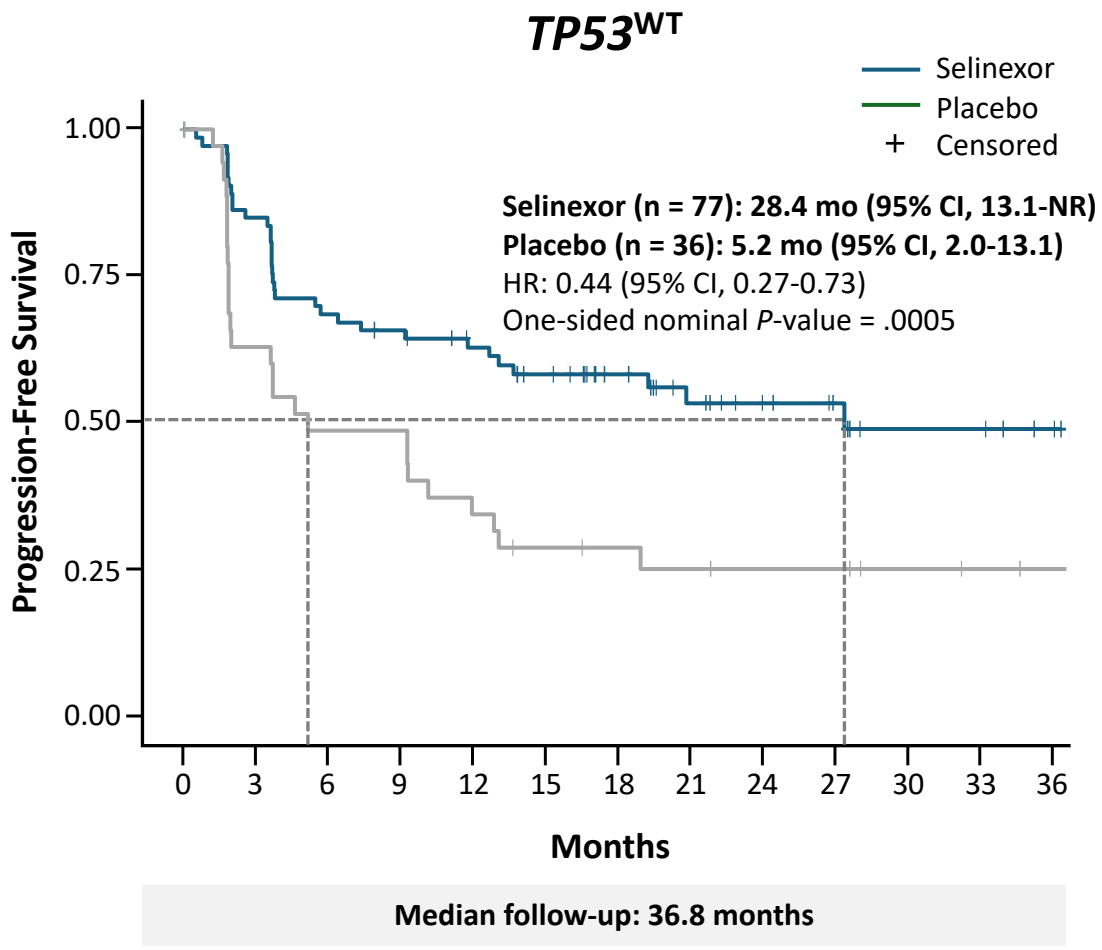
- Audited* (by electronic case report form)
  - HR = 0.71 (95% CI, 0.50-0.99)
  - Two-sided *P*-value = .05
- Unaudited* (by interactive response technology)
  - HR = 0.76 (95% CI, 0.54-1.08)
  - Two-sided *P*-value = .13

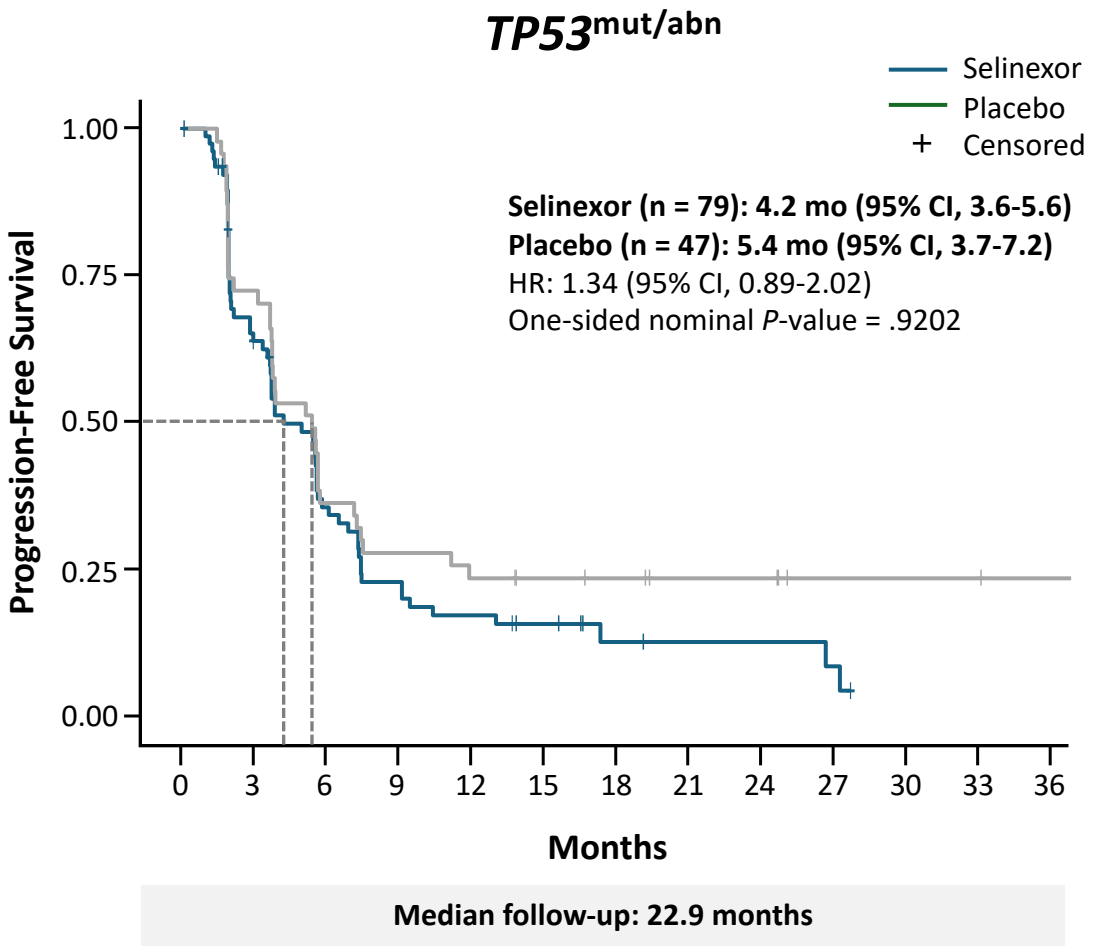
*In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the investigators prior to database lock and unblinding. The statistical analysis was validated by the independent ENGOT statistician and approved by the IDMC.

CR, complete response; IDMC, independent data safety monitoring committee; PR, partial response.

Vergote I, et al. *J Clin Oncol*. 2023;41:5400-5410.

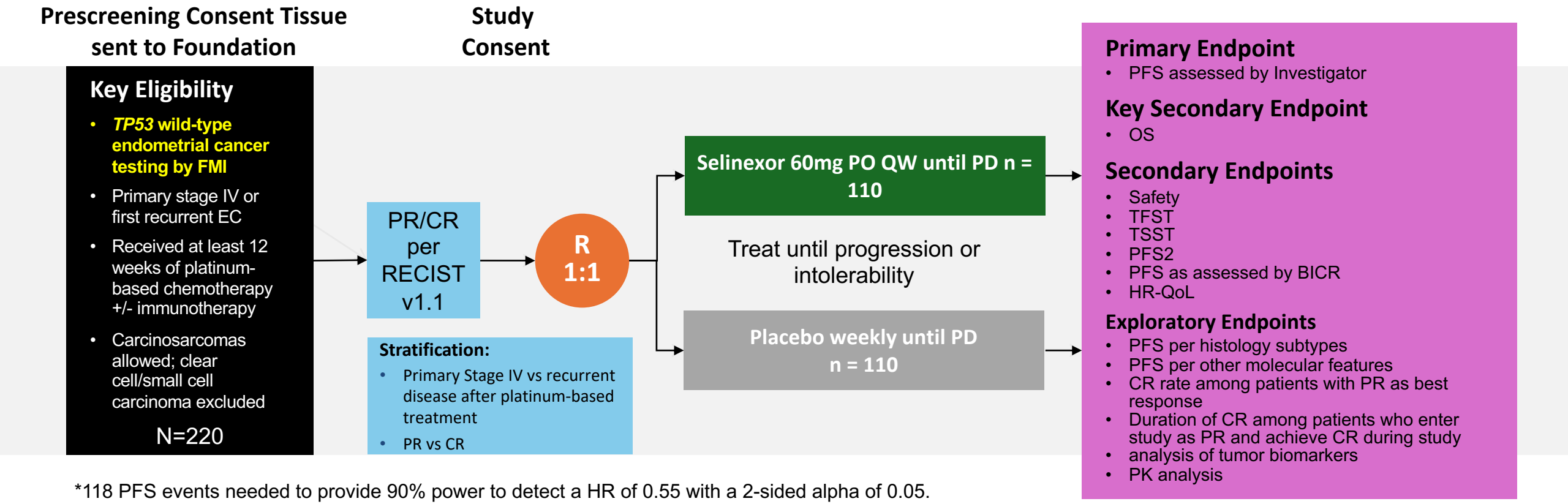
ENGOT-EN5/GOG-3055/SIENDO: Long-Term Follow-Up of PFS in Prespecified Exploratory *TP53*^{WT} and *TP53*$^{mut/abn}$ Subgroups





- Makker V, et al. *Gynecol Oncol*. 2024;185:202-211; Slomovitz BM, et al. *J Clin Oncol*. 2023;41(suppl 36):427956.

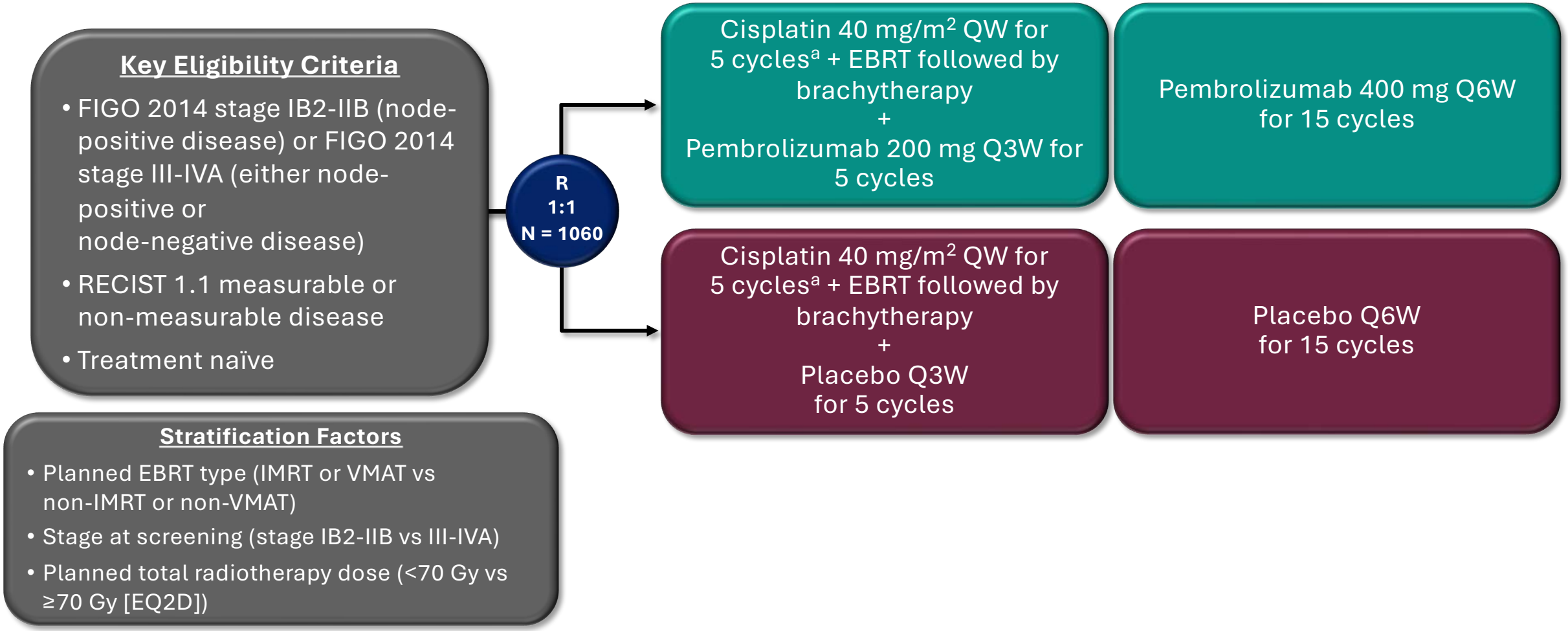
XPORT-EC-042 (NCT05611931): A Phase 3, Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial of Selinexor in Maintenance Therapy After Systemic Therapy for Patients With *TP53* Wild-type, Advanced, or Recurrent EC



*118 PFS events needed to provide 90% power to detect a HR of 0.55 with a 2-sided alpha of 0.05.

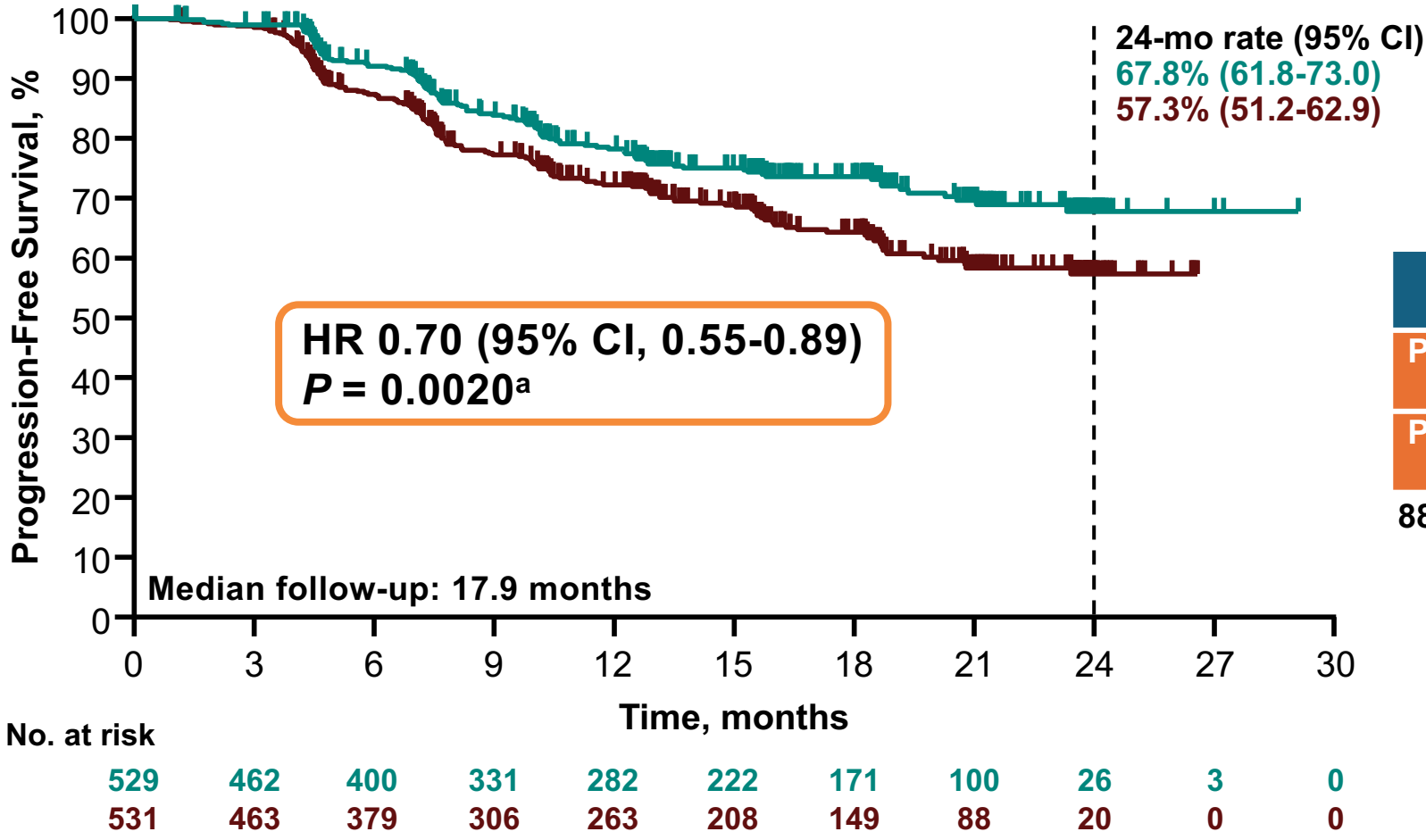
- EC, endometrial cancer; FMI, Foundation Medicine; BICR, blinded independent central review; CR, complete response; DCR, disease control rate; EC, endometrial cancer; HR-QoL, health-related quality of life; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PFS2, time from randomization until the second progression event; PD, progressive disease; PK, pharmacokinetics; PR, partial response; R, randomized; RECIST, Response Evaluation Criterial in Solid Tumors; TFST, time to first subsequent treatment; TSST, time to second subsequent treatment; QW, every week.

ENGOT-cx11/GOG-3047/KEYNOTE-A18: Randomized, Double-Blind, Phase 3 Study



[a]A 6th cycle was allowed per investigator discretion. EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; Gy, grays; IMRT, intensity-modulated radiotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; VMAT, volumetric-modulated arc therapy. ENGOT-cx11/GOG-3047/KEYNOTE-A18 ClinicalTrials.gov identifier, NCT04221945.

Progression-Free Survival at IA1



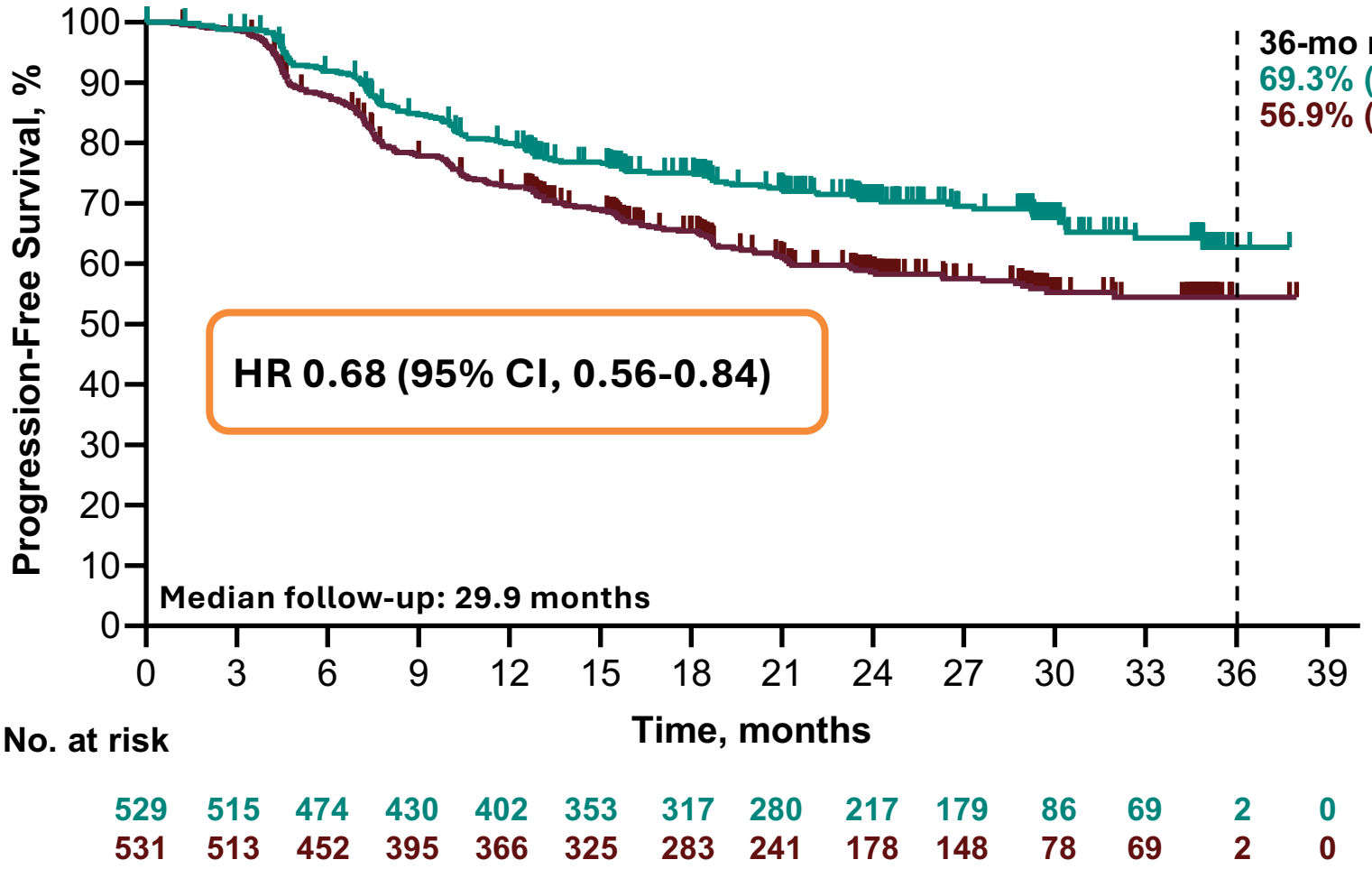
	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	21.7%	NR (NR-NR)
Placebo Arm	29.0%	NR (NR-NR)

88.5% information fraction[a]

Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. [a]With 269 events (88.5% information fraction), the observed *P* = 0.0020 (1-sided) crossed the prespecified nominal boundary of 0.0172 (1-sided) at this planned first interim analysis. The success criterion of the PFS hypothesis was met, and thus no formal testing of PFS will be performed at a later analysis. Data cutoff date: January 9, 2023.

Lorusso D et al Lancet. 2024 Apr 6;403(10434):1341-1350.

Updated Progression-Free Survival at IA2

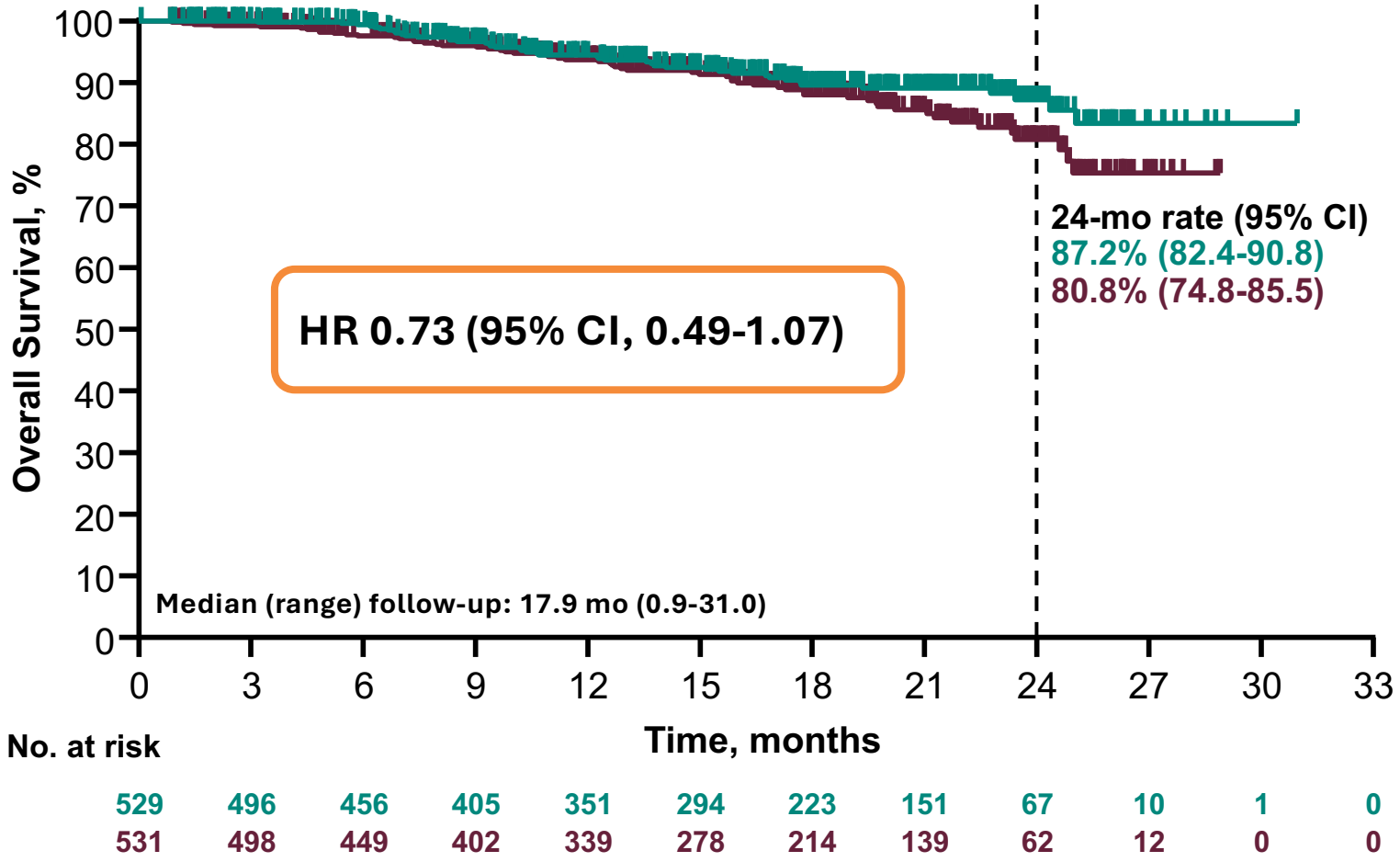


	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	29.3%	NR (NR-NR)
Placebo Arm	39.5%	NR (32.0-NR)

Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. Since the success criterion of the PFS hypothesis was met at IA1, no formal testing of PFS was performed at IA2.
Data cutoff date: January 8, 2024.

Lorusso D, et al. Lancet. 2024 Oct 5;404(10460):1321-1332.

KN-A18/GOG-3047 Primary Endpoint: Overall Survival (Immature, IA1)



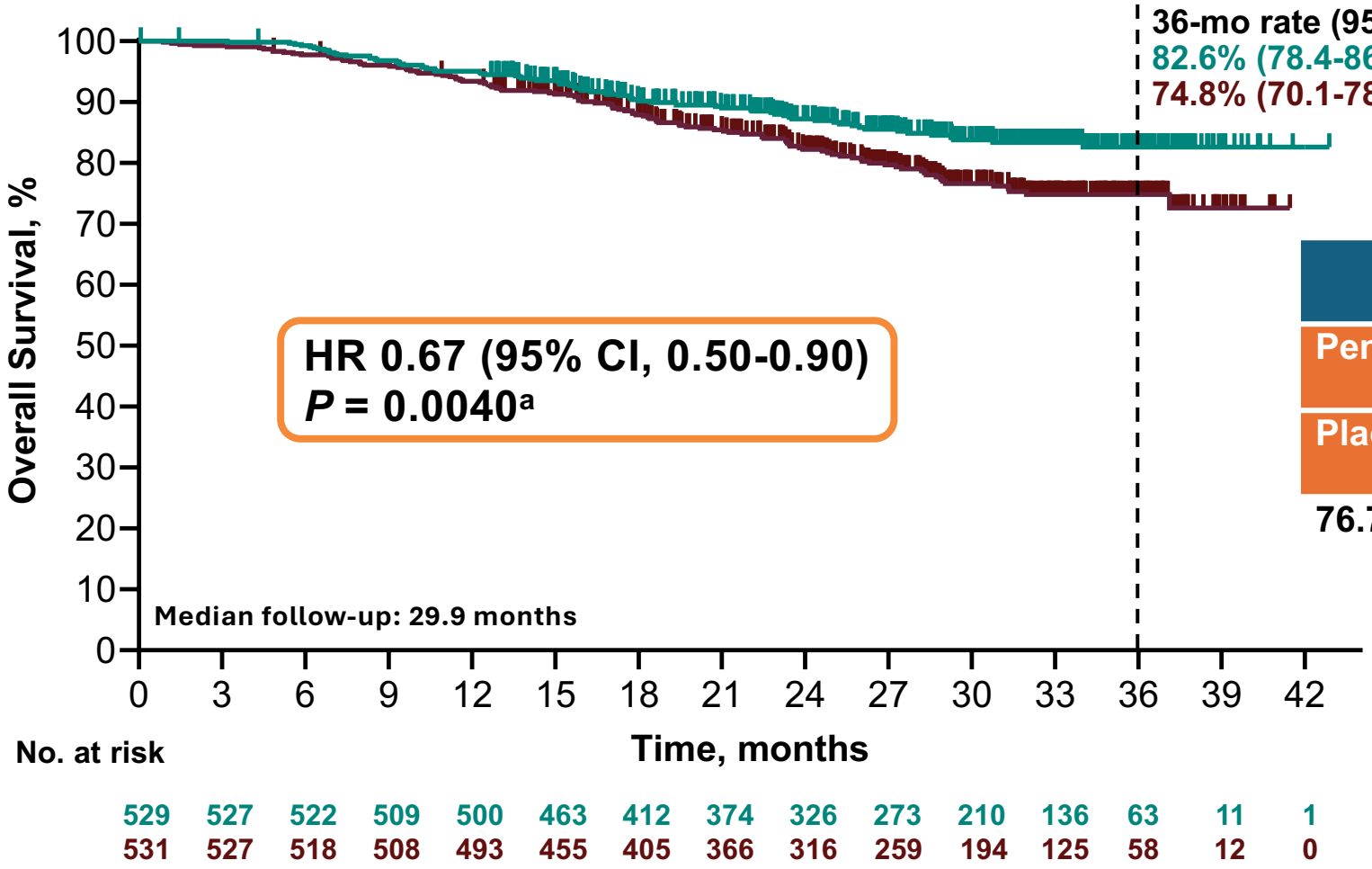
	Pts w/ Event *	Median, mo (95% CI)
Pembro Arm	8.3%	NR (NR-NR)
Placebo Arm	11.1%	NR (NR-NR)

*42.9% information fraction[a]

[a]At this analysis, 103 of the 240 deaths expected at the final analysis had occurred.
Data cutoff date: January 9, 2023.

Lorusso D et al Lancet. 2024 Apr 6;403(10434):1341-1350.

Primary Endpoint: Overall Survival at IA2



	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	14.2%	NR (NR-NR)
Placebo Arm	20.5%	NR (NR-NR)

76.7% information fraction[a]

[a]With 184 of the 240 deaths expected at the final analysis (76.7% information fraction), the observed *P* = 0.0040 (1-sided) crossed the prespecified nominal boundary of 0·01026 (1-sided) at this planned second interim analysis. At this time, 66 patients had received immunotherapy as post-progression treatment, including 15/138 patients (10.9%) in the pembro arm and 51/193 patients (26.4%) in the placebo arm; of those, 10 (7.2%) and 41 (21.2%), respectively, had received pembro. Data cutoff date: January 8, 2024.

KEYNOTE-A18

Lorusso D, et al. Lancet. 2024 Oct 5;404(10460):1321-1332.

Incremental Improvements in Survival (OS) in First-Line Cervical Cancer with Combinations and Biomarkers

Chemotherapy backbone (platinum + taxane) [2009]

Adding bevacizumab [2014]

Adding pembrolizumab [2021 IA1 / 2023 Final]

GOG-204 established the global standard with a median OS of 12.9 months[1]

ORR = 29%

GOG-240 added bevacizumab in eligible patients with a median OS of 17.5 months[2]

ORR = 48%

KEYNOTE-826 added pembrolizumab in PD-L1 positive (CPS ≥1%) median OS 28.6 months [3]

ORR = 69%

1. Monk BJ et al J Clin Oncol. 2023 Dec 20;41(36):5505-5511.
2. Tewari KS et al Lancet. 2017 Oct 7;390(10103):1654-1663.
3. Monk BJ et al KEYNOTE-826 Final analysis. Presented at ASCO, 2023.

ESGO European Society of Gynaecological Oncology | 24th European Congress on Gynaecological Oncology | Sept 28-Oct 1, 2023 | Istanbul, Türkiye

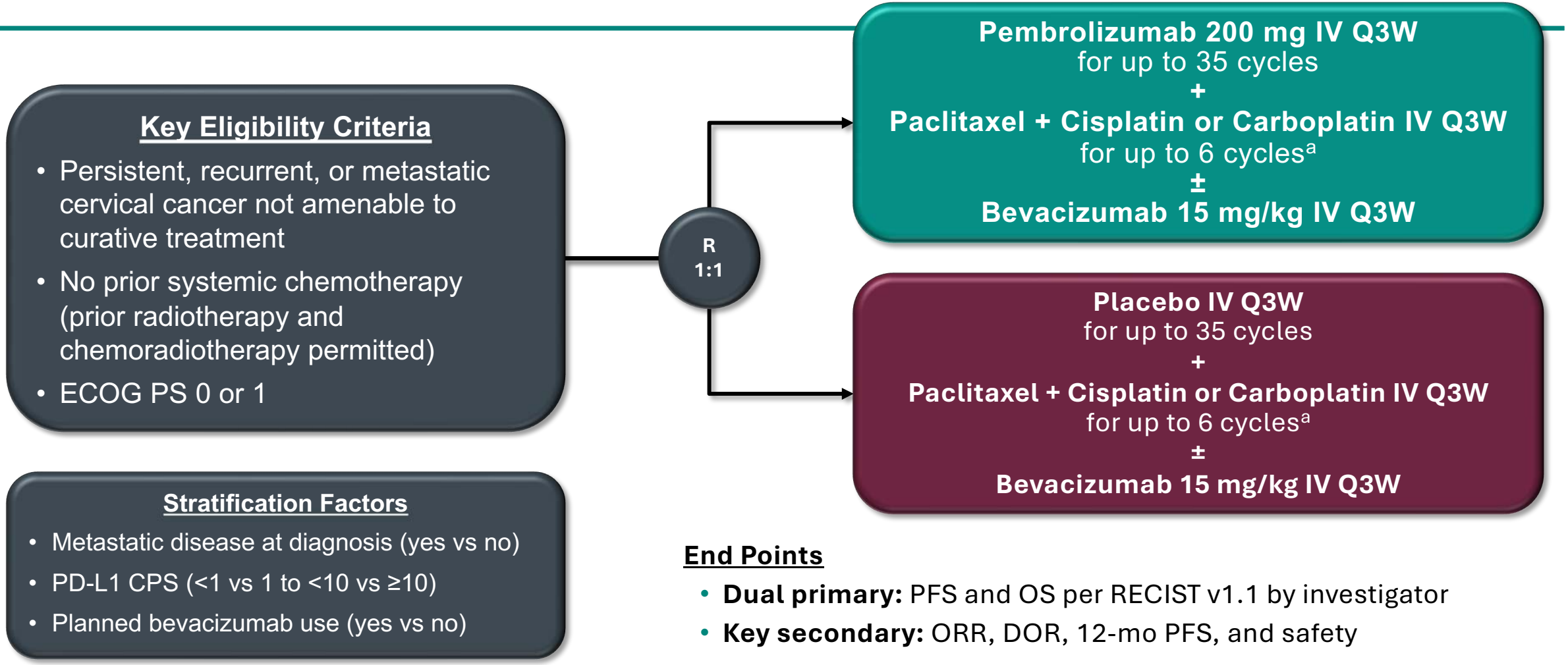
Pembrolizumab + Chemotherapy for First-Line Treatment of Patients With Persistent, Recurrent, or Metastatic Cervical Cancer: Final Overall Survival Results and Bevacizumab Subgroup Analysis of KEYNOTE-826

Domenica Lorusso[1], Nicoletta Colombo[2,3], Krishnansu S. Tewari[4], Coraline Dubot[5], Valeria Cáceres[6], Kosei Hasegawa[7], Ronnie Shapira-Frommer[8], Pamela Salman[9], Eduardo Yañez[10], Mahmut Gümüs[11], Mivael Olivera Hurtado de Mendoza[12], Vanessa Samouëlian[13], Vincent Castonguay[14], Alexander Arkhipov[15], Kan Li[16], Sarper Toker[16], Cumhur Tekin[16], Bradley J. Monk[17]

[1]Gynaecology Oncology Unit, Fondazione Policlinico Universitario A Gemelli IRCCS and Catholic University of Sacred Heart, Rome, Italy; [2]Gynecologic Oncology Program, European Institute of Oncology IRCCS, Milan, Italy; [3]Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy [4]Obstetrics & Gynecology, University of California, Irvine, Orange, California, United States; [5]Oncologie Gynécologique et Mammaire, Centre François Baclesse, Caen, France; [6]Medical Oncology, Instituto de Oncologia Angel H. Roffo, Buenos Aires, Argentina; [7]Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka, Japan; [8]Ella Lemelbaum Institute for Immuno-Oncology, Sheba Medical Center, Ramat Gan, Israel; [9]Medical Oncology, Oncovida Cancer Center, Providencia, Santiago, Chile; [10]Medical Oncology, Universidad de la Frontera, Temuco, Chile; [11]Medical Oncology, Istanbul Medeniyet University Hospital, Istanbul, Turkey; [12]Medical Oncology, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; [13]Gynecologic Oncology, Centre Hospitalier de l'Université de Montréal (CHUM), Centre de Recherche de l'Université de Montréal (CRCHUM), Université de Montréal, Montreal, Canada; [14]Medical Oncology, Centre Hospitalier Universitaire de Québec, Université Laval, Quebec City, Canada; [15]Oncology and Chemical Therapy, Medical Rehabilitation Center under the Ministry of Health of Russian Federation, Moscow, Russia; [16]Oncology, Merck & Co., Inc., Rahway, New Jersey, United States; [17]Gynecologic Oncology, HonorHealth Research Institute, University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, Arizona, United States

Ann Oncol. 2024 Oct 9:S0923-7534(24)04033-X. doi: 10.1016/j.annonc.2024.10.002. Online ahead of print.

KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study



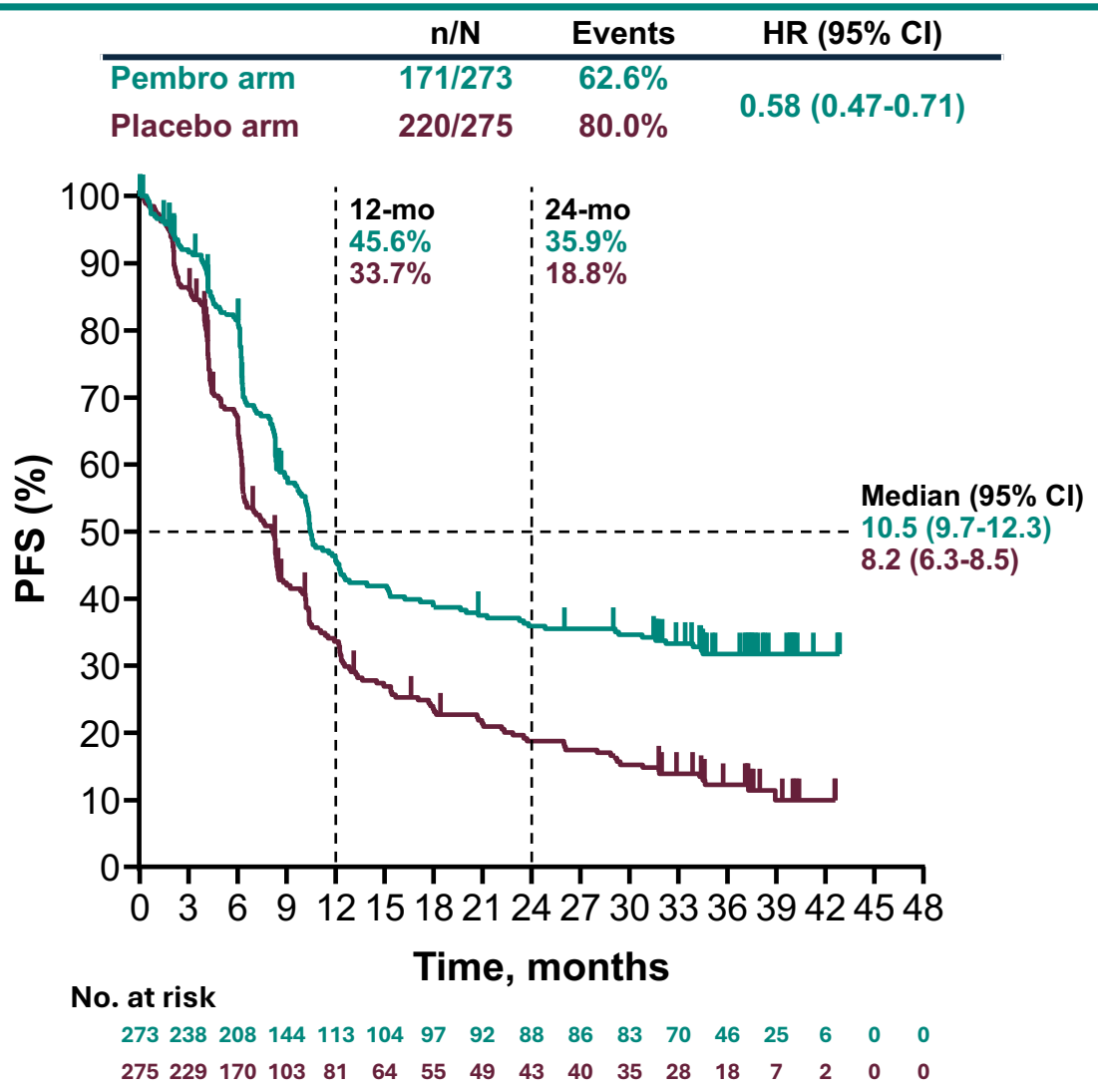
End Points

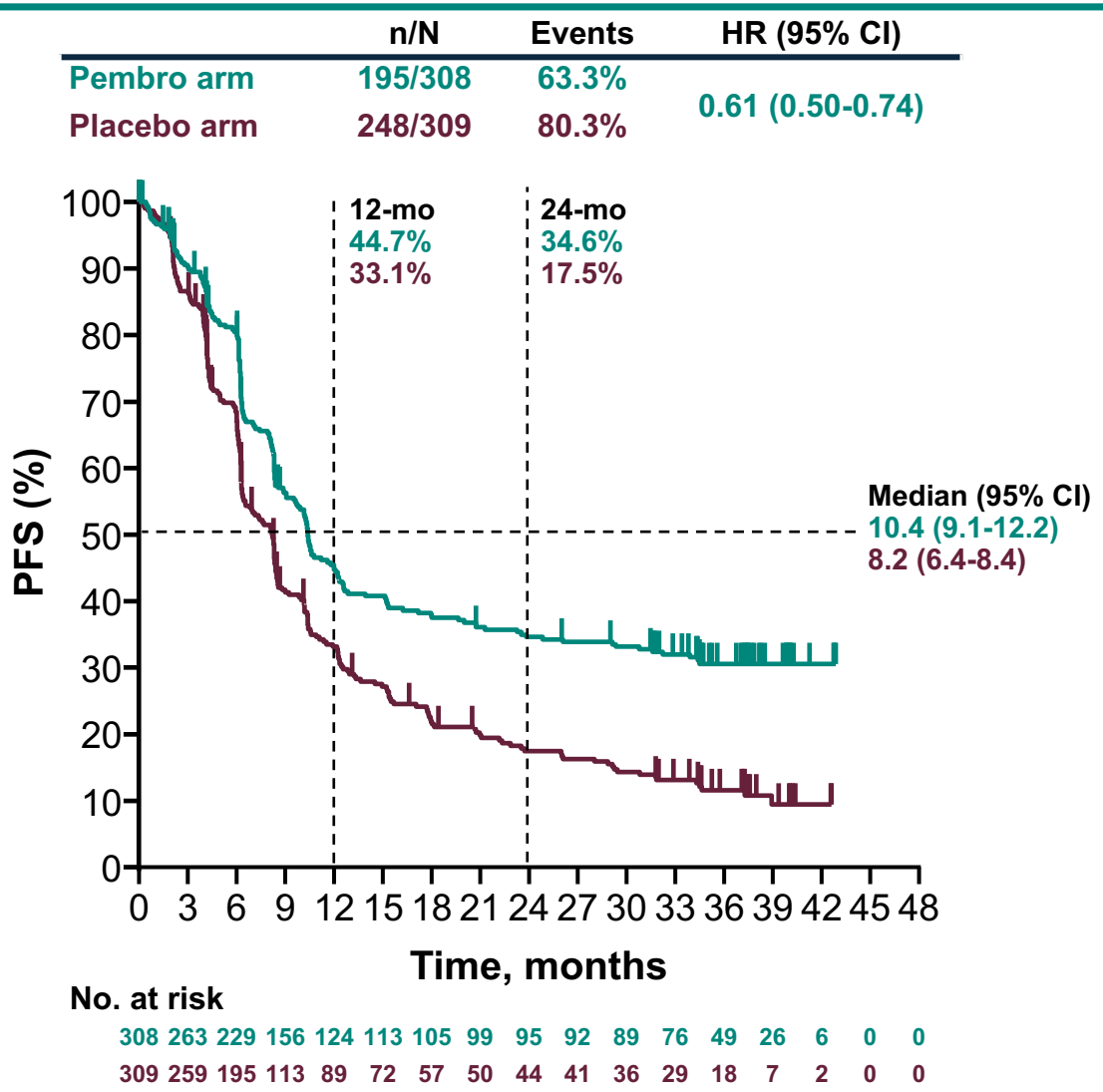
- **Dual primary:** PFS and OS per RECIST v1.1 by investigator
- **Key secondary:** ORR, DOR, 12-mo PFS, and safety

[a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although patients with ongoing clinical benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation. CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100. KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

Ann Oncol. 2024 Oct 9:S0923-7534(24)04033-X. doi: 10.1016/j.annonc.2024.10.002. Online ahead of print.

KEYNOTE-826: Protocol-Specified Final PFS





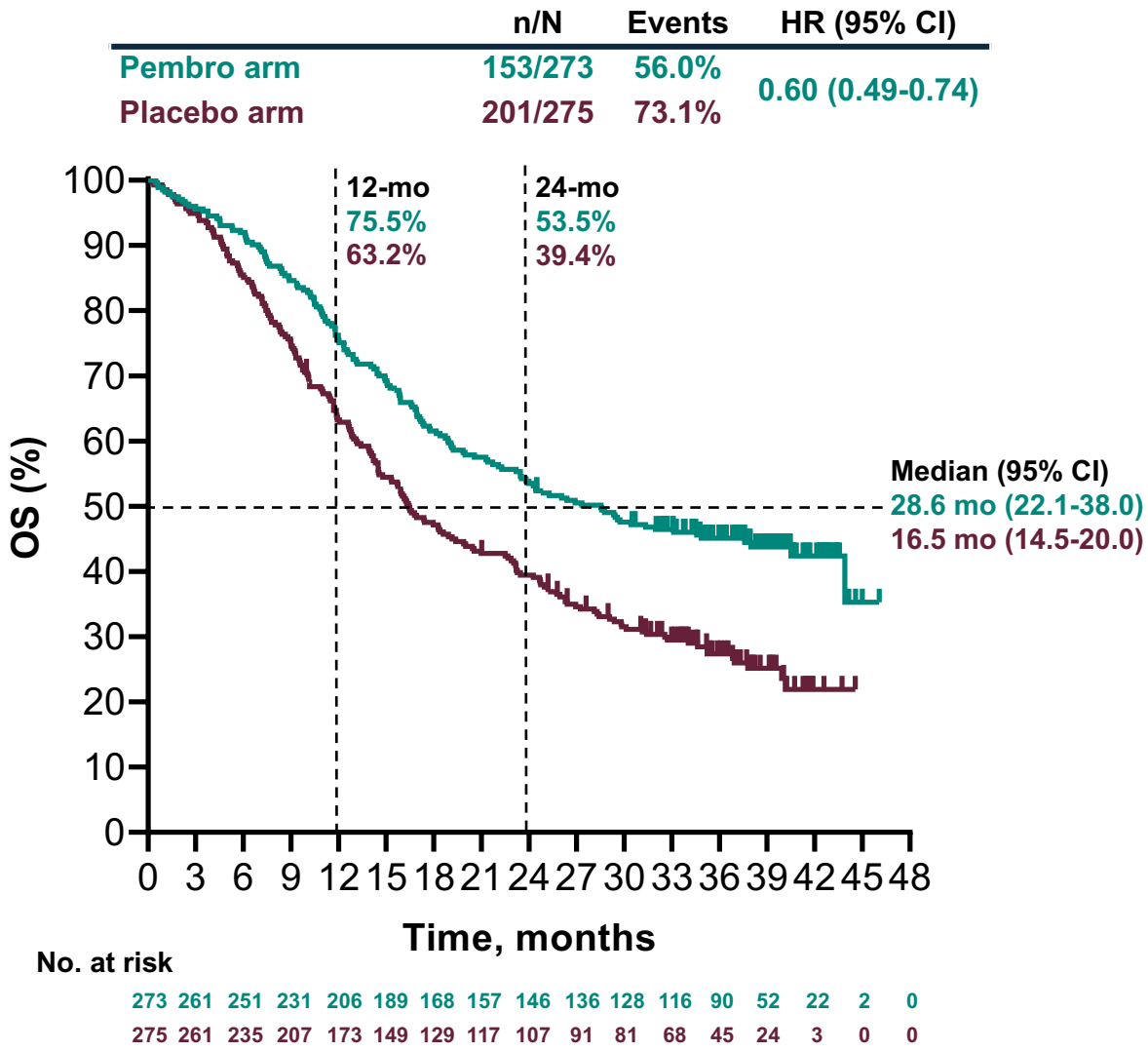
Response assessed per RECIST v1.1 by investigator review. Data cutoff date: October 3, 2022.

PD-L1 CPS ≥1 Population

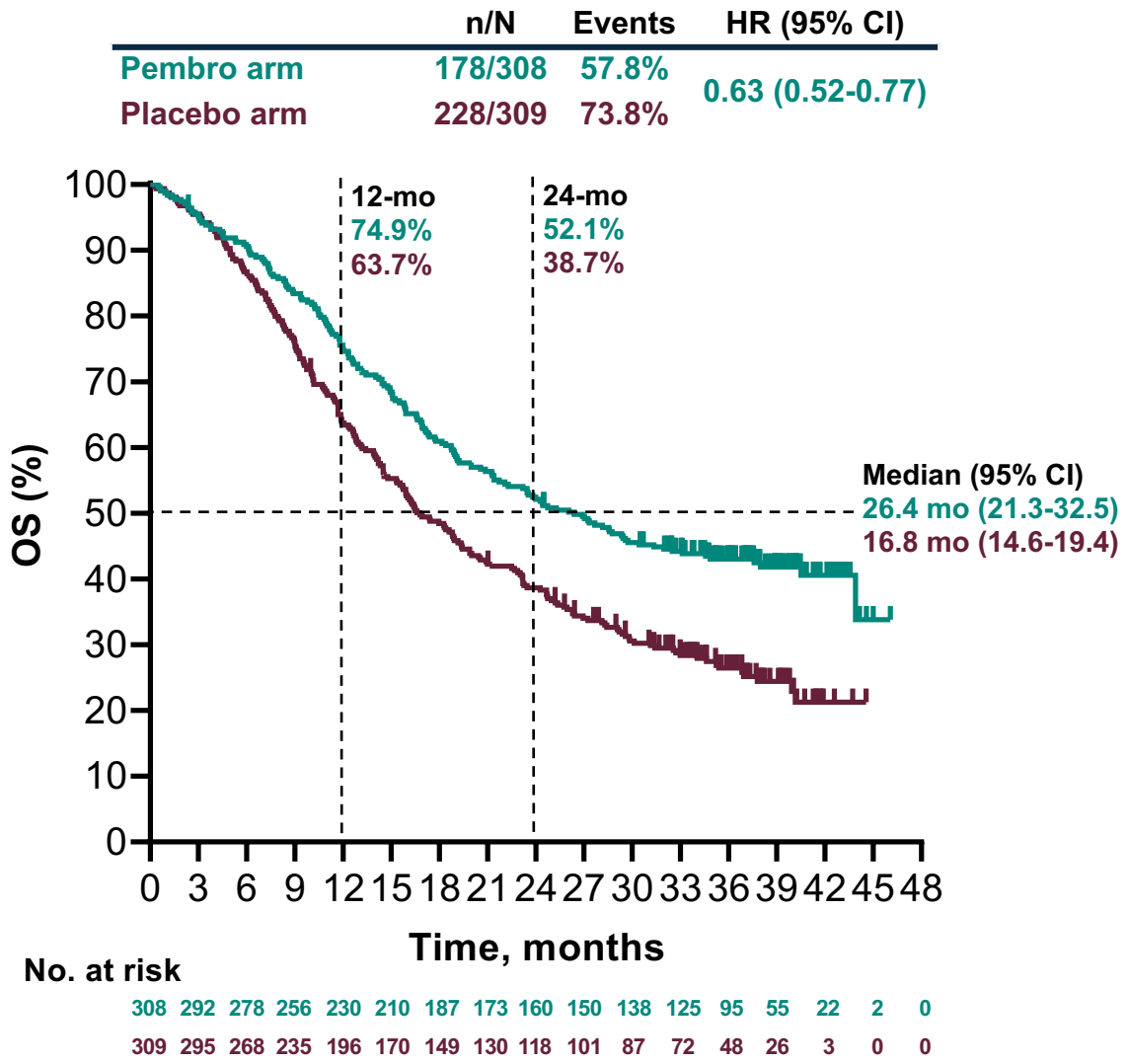
All-Comer Population

Monk BJ et al J Clin Oncol. 2023 Dec 20;41(36):5505-5511

KEYNOTE-826: Protocol-Specified Final OS



PD-L1 CPS ≥1 Population



All-Comer Population

Data cutoff date: October 3, 2022.

Monk BJ et al J Clin Oncol. 2023 Dec 20;41(36):5505-5511

Discussion Questions

- Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a patient with microsatellite-stable/mismatch repair-proficient metastatic endometrial cancer (EC)?
- For which clinical scenarios, if any, would you prefer to use chemoimmunotherapy followed by combined anti-PD-1/PD-L1 antibody and PARP inhibitor maintenance for patients with EC?
- Do you have a hypothesis as to why TP53 mutation status predicts for treatment benefit with selinexor?

Module 7: Prostate Cancer

Hormonal Therapy for Patients with Prostate Cancer — Dr Oh

Other Available and Emerging Therapeutic Approaches — Dr Aggarwal

Module 7: Prostate Cancer

Hormonal Therapy for Patients with Prostate Cancer — Dr Oh

Other Available and Emerging Therapeutic Approaches
— Dr Aggarwal

Prostate Cancer GMO 2025

William K. Oh, MD
Director, Precision Medicine
Yale Cancer Center and Smilow Cancer Hospital

Service Line Medical Director
Smilow Cancer Hospital at Greenwich Hospital

Chair, National Prostate Cancer Roundtable
American Cancer Society

YaleNewHavenHealth
Smilow Cancer Hospital

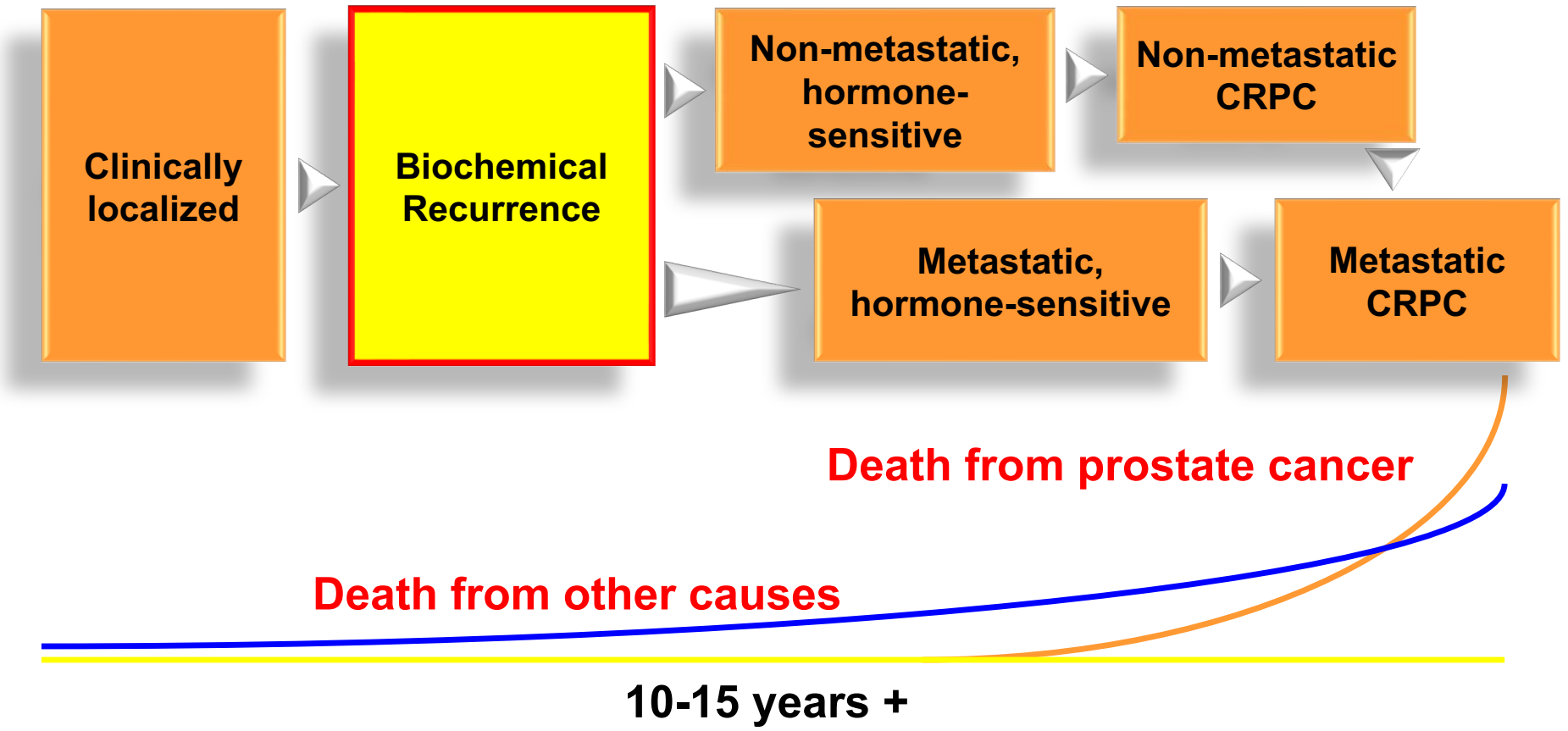
Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Disclosures

Advisory Committees	Pfizer Inc
Consulting Agreements	Abbott Laboratories, AstraZeneca Pharmaceuticals LP, Cytogen Corporation, Nature's Toolbox Inc, Novartis, Sumitomo Dainippon Pharma Oncology Inc
Stock Options — Private Companies	Nature’s Toolbox Inc
Stock Options/Stock —Public Companies	GeneDx

- Major efficacy and safety findings from the Phase III EMBARK trial evaluating enzalutamide plus leuprolide versus enzalutamide or leuprolide alone in patients with nonmetastatic hormone-sensitive PC (nmHSPC) and high-risk biochemical recurrence
- Published data from the Phase III PRESTO trial evaluating the role of ADT intensification with apalutamide with or without abiraterone in patients with high-risk biochemically recurrent nmHSPC
- Extended follow-up with abiraterone, enzalutamide and apalutamide in combination with ADT for patients with metastatic HSPC (mHSPC)
- Key outcomes from the Phase III ARANOTE study evaluating the addition of darolutamide to ADT for patients with mHSPC
- Key data from the Phase III ARASENS trial evaluating darolutamide in combination with docetaxel and ADT for mHSPC
- Biologic justification for targeting the PI3K/AKT/mTOR pathway in PC, particularly in PTEN-deficient disease; mechanism of action of capivasertib
- Emerging results from the Phase III CAPItello-281 trial assessing capivasertib plus abiraterone/ADT in patients with de novo mHSPC and PTEN deficiency
- Design, eligibility criteria and primary and secondary endpoints of the ongoing Phase III CAPItello-280 trial evaluating capivasertib in combination with docetaxel/ADT for patients with mCRPC

Clinical States of Prostate Cancer

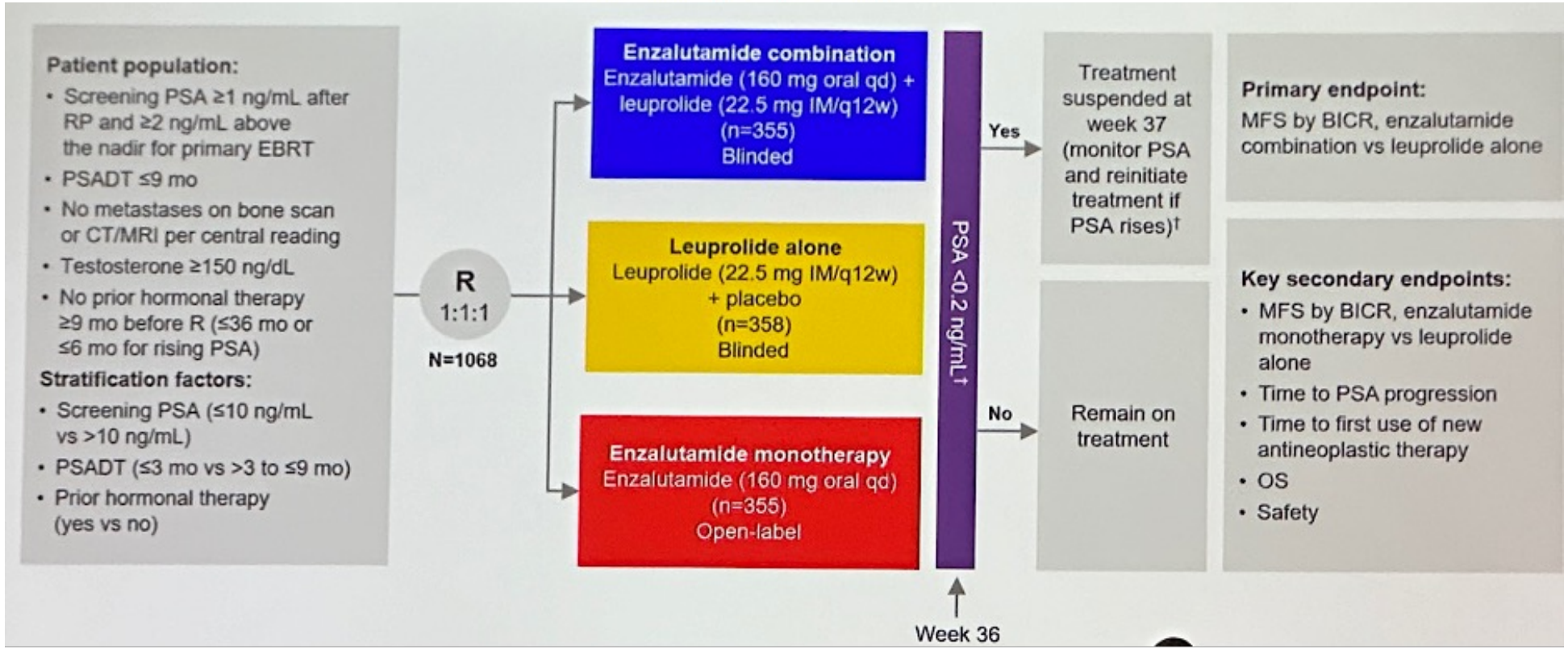


The NEW ENGLAND JOURNAL of MEDICINE

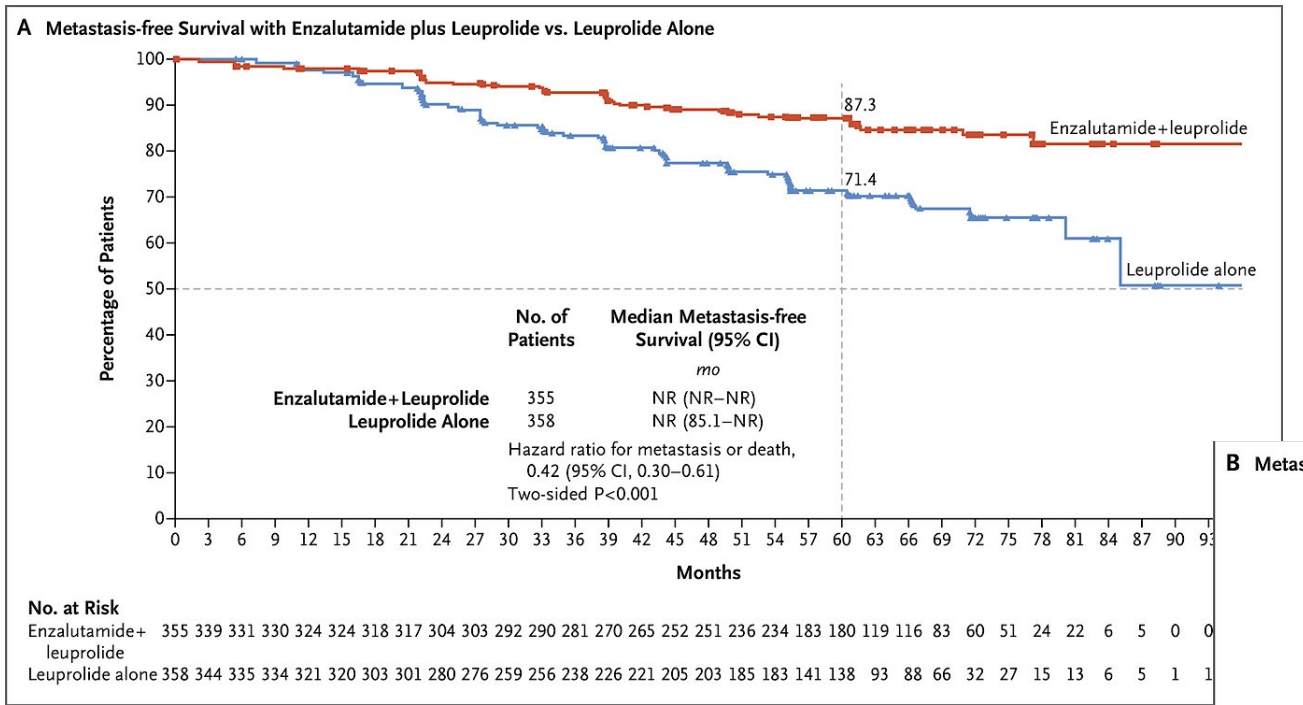
ESTABLISHED IN 1812 OCTOBER 19, 2023 VOL. 389 NO. 16

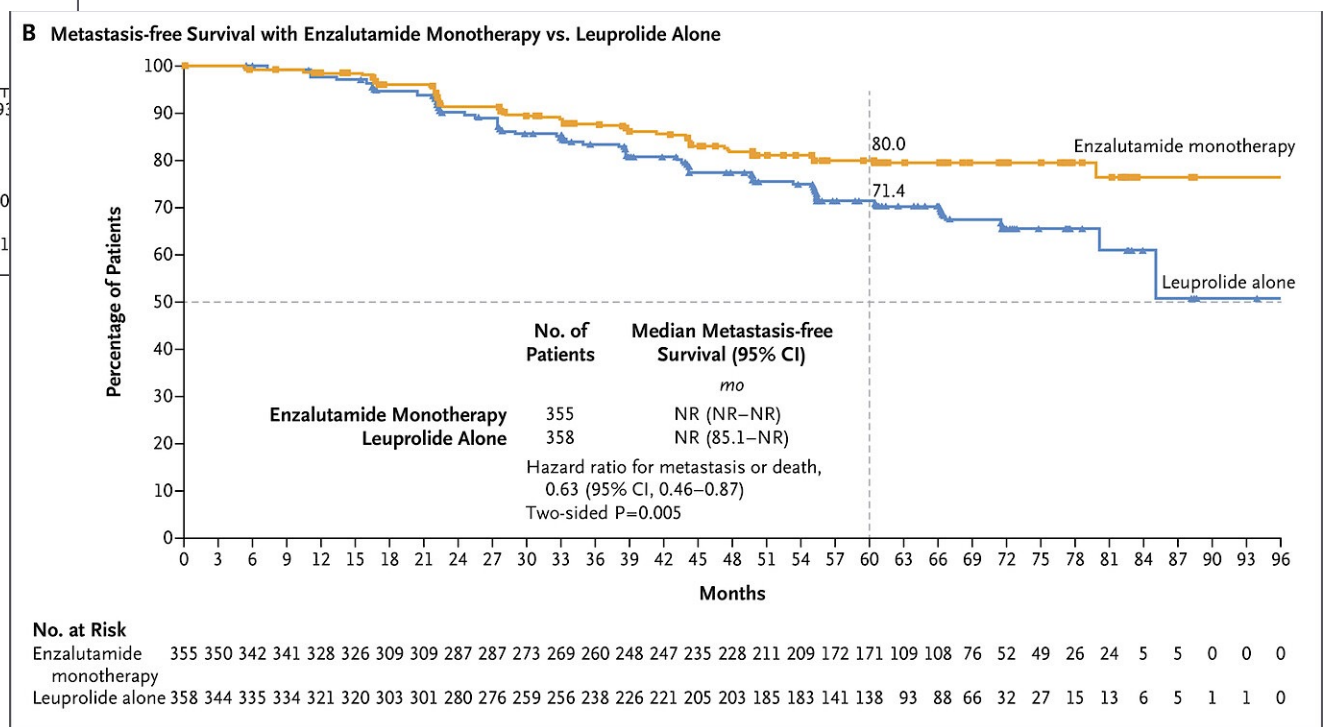
Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

S.J. Freedland, M. de Almeida Luz, U. De Giorgi, M. Gleave, G.T. Gotto, C.M. Pieczonka, G.P. Haas, C.-S. Kim, M. Ramirez-Backhaus, A. Rannikko, J. Tarazi, S. Sridharan, J. Sugg, Y. Tang, R.F. Tutrone, Jr., B. Venugopal, A. Villers, H.H. Woo, F. Zohren, and N.D. Shore



EMBARK: LHRH+ENZA > ENZA Monotherapy > LHRH Alone in BCR



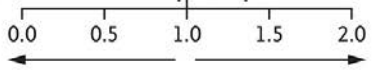


Freedland SJ, de Almeida Luz M, De Giorgi U, et al. *N Engl J Med*. 2023;389(16):1453-1465

EMBARK: Secondary End Points

A Secondary End Points, Enzalutamide plus Leuprolide vs. Leuprolide Alone

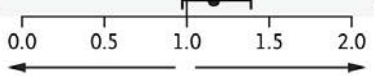
End Point	Enzalutamide+ Leuprolide (no. of patients)	Leuprolide Alone (no. of patients)	Enzalutamide+ Leuprolide (no. of events)	Leuprolide Alone (no. of events)	Hazard Ratio (95% CI)	Two-Sided P Value
Metastasis-free survival (primary end point)	355	358	45	92	0.42 (0.30–0.61)	<0.001
Overall survival	355	358	33	55	0.59 (0.38–0.91)	0.02
PSA progression	355	358	8	93	0.07 (0.03–0.14)	<0.001
First use of new antineoplastic therapy	355	358	58	140	0.36 (0.26–0.49)	<0.001
Distant metastasis	355	358	30	59	0.44 (0.28–0.69)	
Resumption of any hormonal therapy	321	240	256	217	0.69 (0.58–0.83)	
Castration resistance	355	358	14	120	0.09 (0.05–0.16)	
Symptomatic progression	355	358	104	169	0.55 (0.43–0.70)	
First symptomatic skeletal event	355	358	9	32	0.26 (0.13–0.55)	
First deterioration in FACT-P total score	355	358	257	248	1.14 (0.95–1.36)	



Enzalutamide+Leuprolide Better Leuprolide Alone Better

B Secondary End Points, Enzalutamide Monotherapy vs. Leuprolide Alone

End Point	Enzalutamide Monotherapy (no. of patients)	Leuprolide Alone (no. of patients)	Enzalutamide Monotherapy (no. of events)	Leuprolide Alone (no. of events)	Hazard Ratio (95% CI)	Two-Sided P Value
Metastasis-free survival	355	358	63	92	0.63 (0.46–0.87)	0.005
Overall survival	355	358	42	55	0.78 (0.52–1.17)	0.23
PSA progression	355	358	37	93	0.33 (0.23–0.49)	<0.001
First use of new antineoplastic therapy	355	358	84	140	0.54 (0.41–0.71)	<0.001
Distant metastasis	355	358	40	59	0.61 (0.41–0.92)	
Resumption of any hormonal therapy	304	240	279	217	1.66 (1.38–1.98)	
Symptomatic progression	355	358	117	169	0.62 (0.49–0.79)	
First symptomatic skeletal event	355	358	14	32	0.42 (0.23–0.79)	
First deterioration in FACT-P total score	355	358	263	248	1.17 (0.98–1.39)	



Enzalutamide Monotherapy Better Leuprolide Alone Better

Freedland SJ et al. *N Engl J Med* 2023;389:1453-1465.

EMBARK: Safety

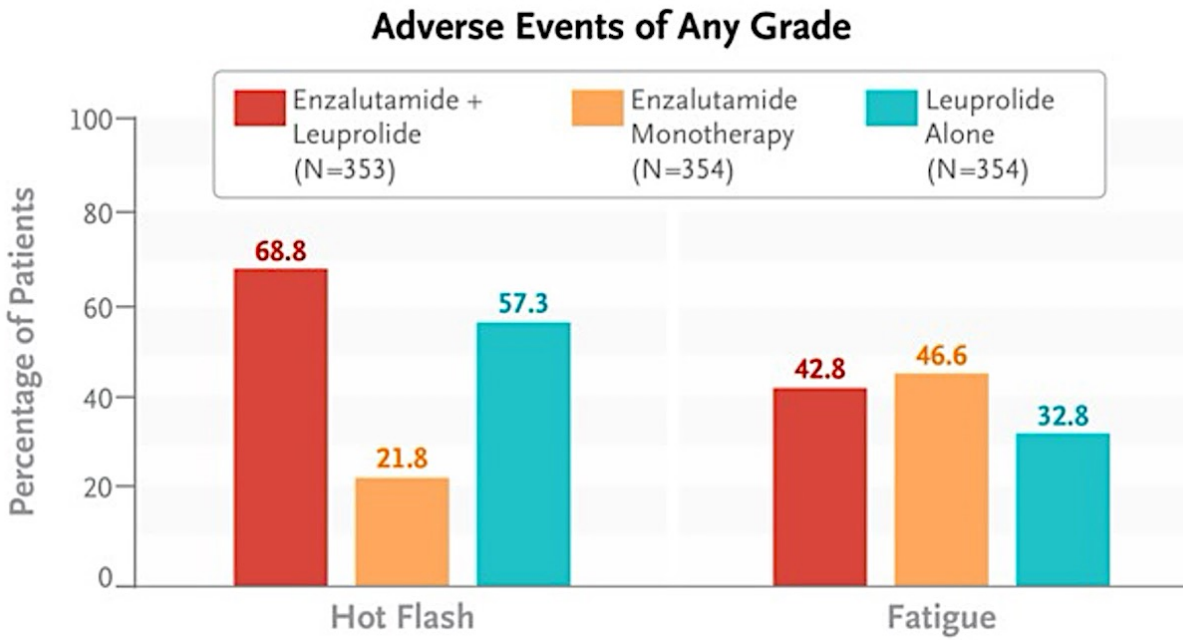


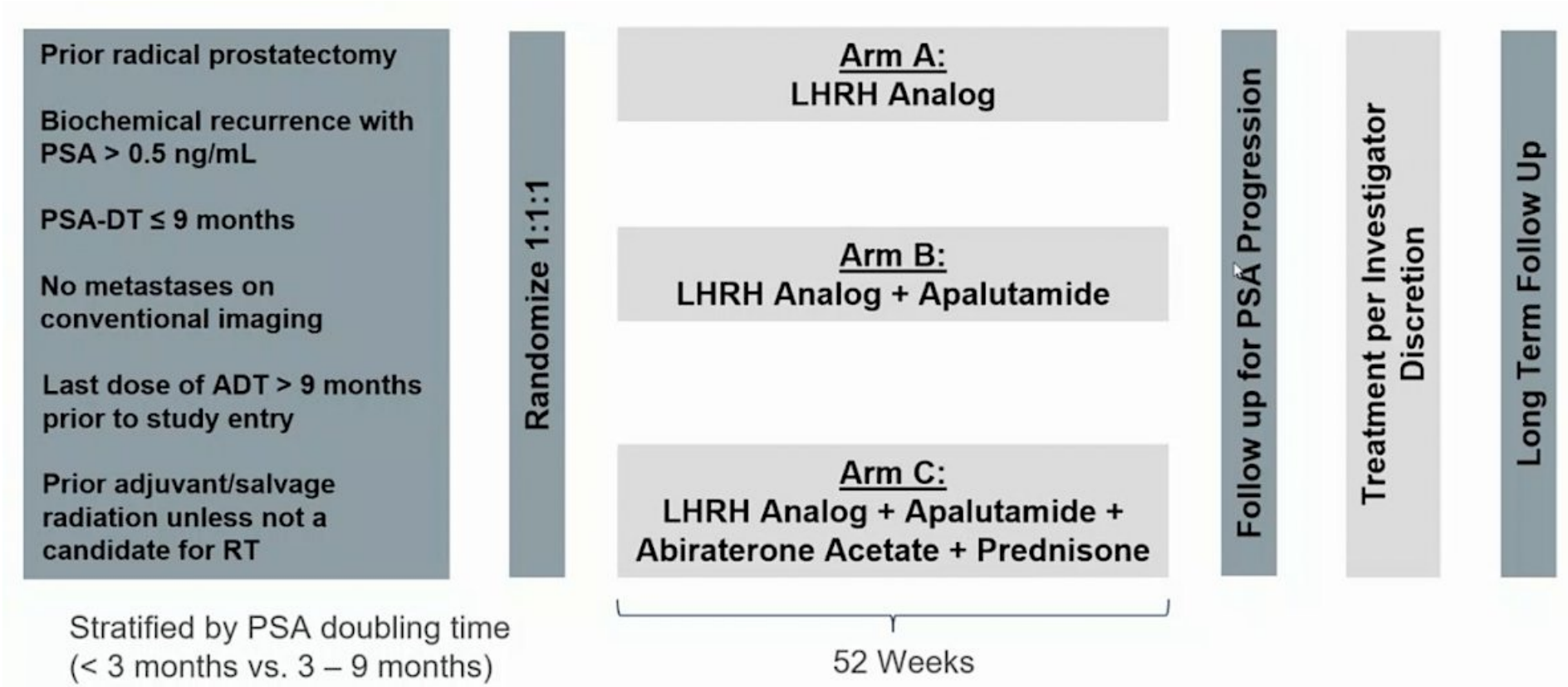
Table 2. Adverse Events (Safety Population).*

Event	Enzalutamide + Leuprolide (N=353)		Leuprolide Alone (N=354)		Enzalutamide Monotherapy (N=354)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)					
Any adverse event	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related adverse event	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious adverse event	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious adverse event	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
Adverse event leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
Adverse event leading to permanent discontinuation of treatment	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)
Adverse event leading to death†	6 (1.7)	—	3 (0.8)	—	8 (2.3)	—
Most common adverse events‡						
Hot flash	243 (68.8)§	2 (0.6)	203 (57.3)§	3 (0.8)	77 (21.8)	1 (0.3)
Fatigue	151 (42.8)§	12 (3.4)	116 (32.8)	5 (1.4)	165 (46.6)§	14 (4.0)
Arthralgia	97 (27.5)	7 (2.0)	75 (21.2)	1 (0.3)	81 (22.9)	2 (0.6)
Hypertension	82 (23.2)	24 (6.8)	69 (19.5)	18 (5.1)	67 (18.9)	19 (5.4)
Fall	74 (21.0)	4 (1.1)	51 (14.4)	4 (1.1)	56 (15.8)	7 (2.0)
Back pain	60 (17.0)	3 (0.8)	54 (15.3)	1 (0.3)	62 (17.5)	3 (0.8)
Diarrhea	49 (13.9)	2 (0.6)	31 (8.8)	1 (0.3)	46 (13.0)	1 (0.3)
Constipation	46 (13.0)	1 (0.3)	31 (8.8)	0	34 (9.6)	1 (0.3)
Hematuria	42 (11.9)	8 (2.3)	44 (12.4)	4 (1.1)	45 (12.7)	9 (2.5)
Insomnia	42 (11.9)	2 (0.6)	37 (10.5)	0	25 (7.1)	0
Nausea	42 (11.9)	1 (0.3)	29 (8.2)	1 (0.3)	54 (15.3)	2 (0.6)
Pain in arm or leg	41 (11.6)	3 (0.8)	36 (10.2)	2 (0.6)	40 (11.3)	1 (0.3)
Asthenia	39 (11.0)	2 (0.6)	21 (5.9)	1 (0.3)	39 (11.0)	3 (0.8)
Dizziness	39 (11.0)	2 (0.6)	37 (10.5)	2 (0.6)	41 (11.6)	3 (0.8)
Headache	39 (11.0)	3 (0.8)	32 (9.0)	0	41 (11.6)	1 (0.3)
Urinary incontinence	34 (9.6)	4 (1.1)	28 (7.9)	3 (0.8)	36 (10.2)	6 (1.7)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)§	3 (0.8)
Coronavirus disease 2019	27 (7.6)	2 (0.6)	36 (10.2)	4 (1.1)	44 (12.4)	2 (0.6)
Peripheral edema	27 (7.6)	1 (0.3)	37 (10.5)	1 (0.3)	31 (8.8)	1 (0.3)
Urinary tract infection	27 (7.6)	1 (0.3)	26 (7.3)	2 (0.6)	37 (10.5)	7 (2.0)
Weight decreased	24 (6.8)	1 (0.3)	12 (3.4)	0	39 (11.0)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0
Breast tenderness	5 (1.4)	0	4 (1.1)	0	51 (14.4)	0

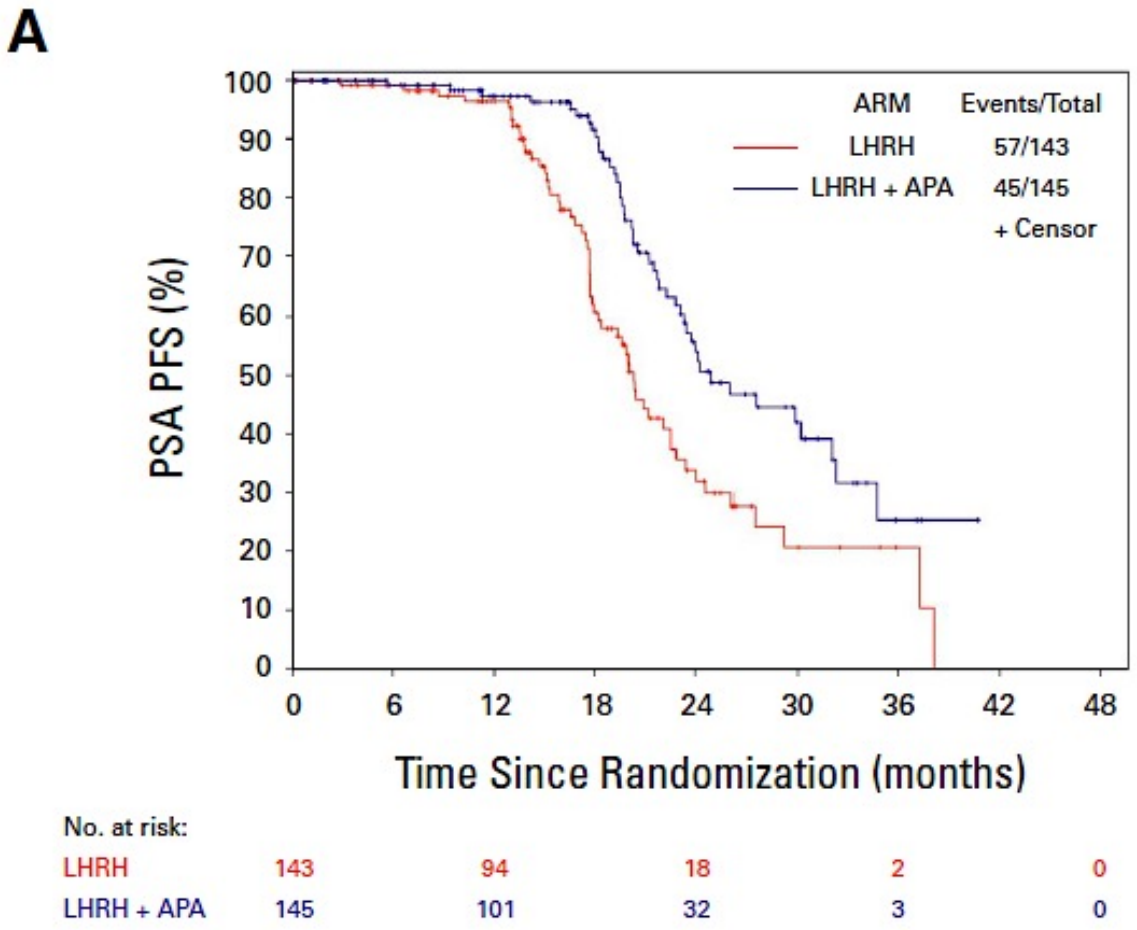
Freedland SJ et al. *N Engl J Med* 2023;389:1453-1465.

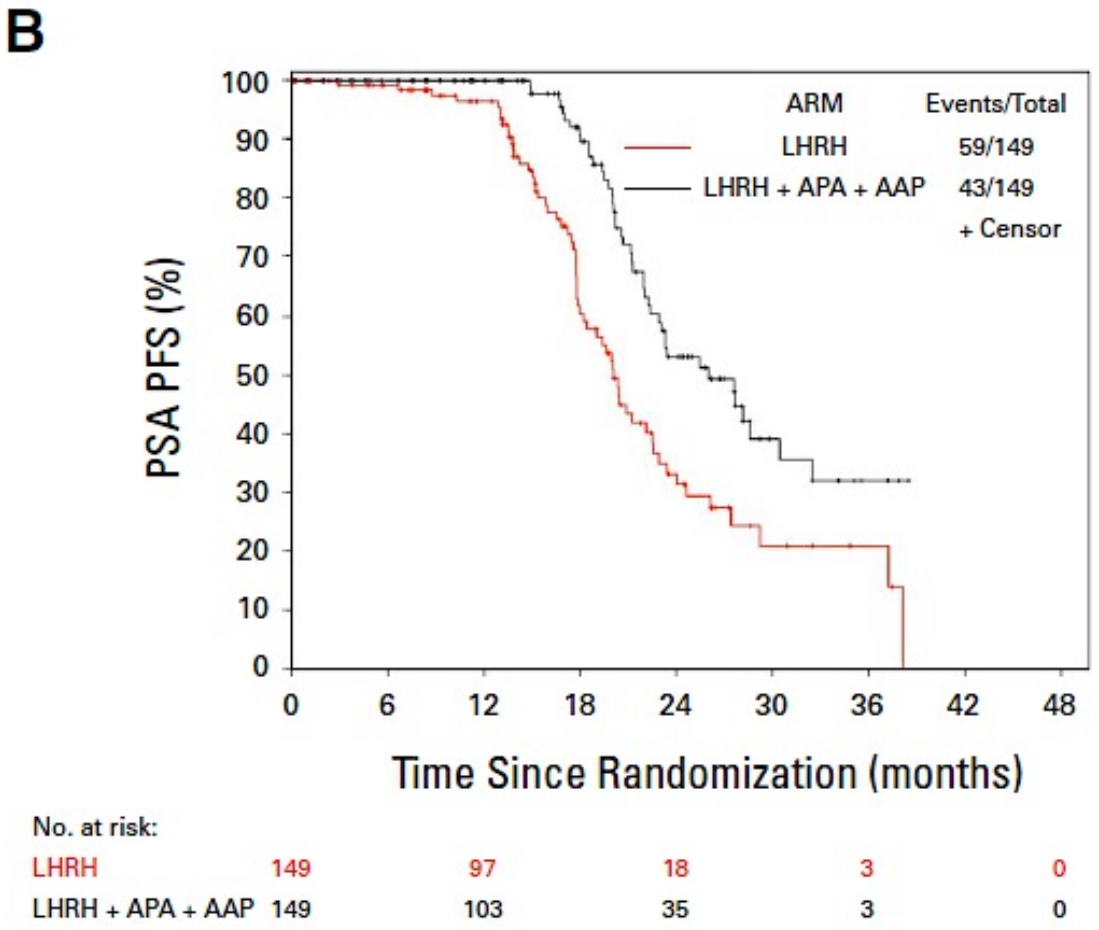
PRESTO: A Phase III, Open-Label Study of Intensification of Androgen Blockade in Patients With High-Risk Biochemically Relapsed Castration-Sensitive Prostate Cancer (AFT-19)

Rahul Aggarwal, MD[1]; Glenn Heller, PhD[2]; David W. Hillman, MS[3]; Han Xiao, MD[2]; Joel Picus, MD[4]; Mary-Ellen Taplin, MD[5]; Tanya Dorff, MD[6]; Leonard Appleman, MD[7]; Douglas Weckstein, MD[8]; Akash Patnaik, MD[9]; Alan Bryce, MD[10]; Daniel Shevrin, MD[11]; James Mohler, MD[12]; Daniel Anderson, MD[13]; Arpit Rao, MD[14]; Scott Tagawa, MD[15]; Alan Tan, MD[16]; Susan Halabi, PhD[17]; Katharine Dooley, MPH[3]; Patrick O'Brien, BS[3]; Ronald Chen, MD, MPH[18]; Charles J. Ryan, MD[19]; Scott E. Eggener, MD[9] and Michael J. Morris, MD[2]; on behalf of the PRESTO Study Investigators



PRESTO: rPFS Improved with APA But No Better with APA/AAP



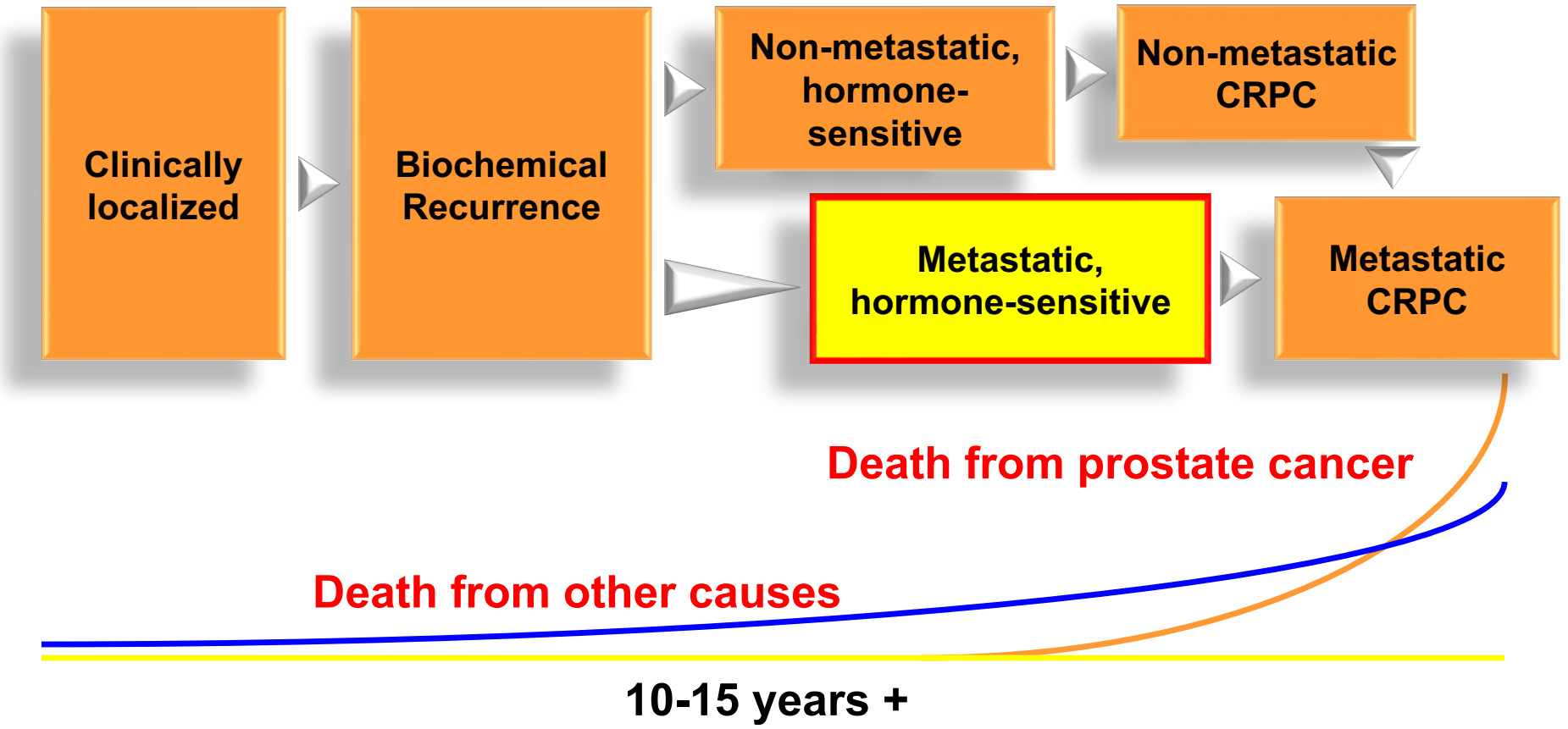


Aggarwal R, Heller G, Hillman DW, et al. *J Clin Oncol*. 2024;42(10):1114-1123.

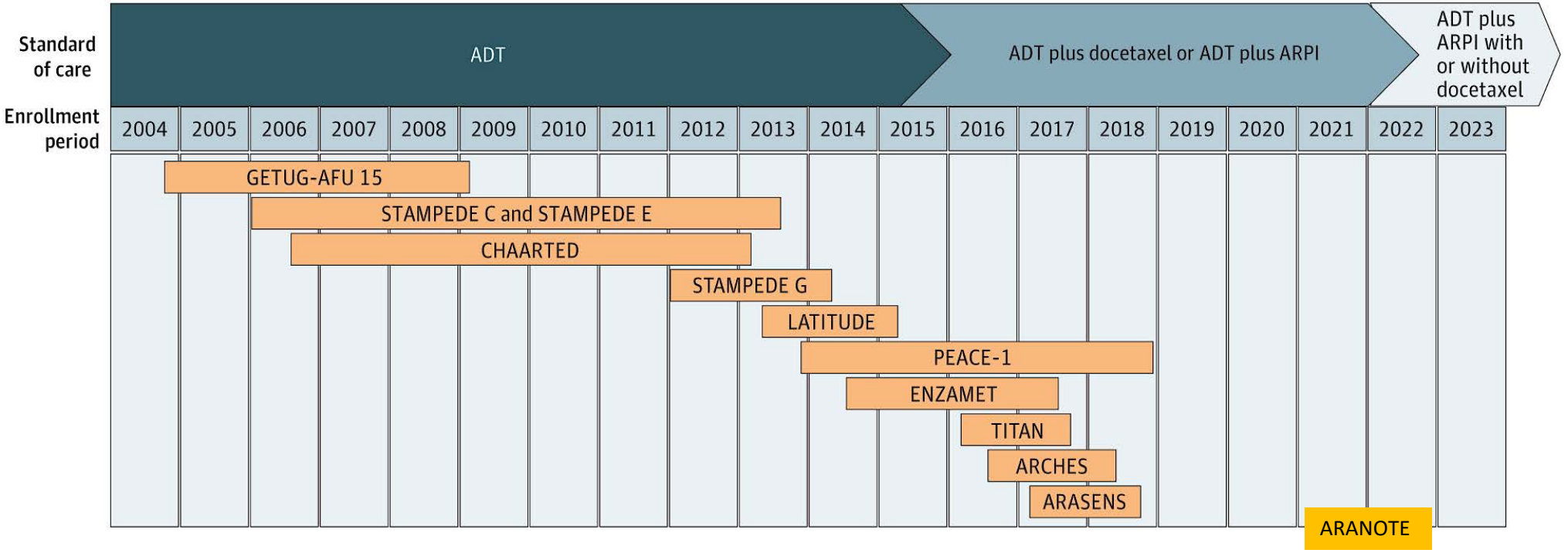
YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Clinical States of Prostate Cancer



11 Prospective RCTs Demonstrate Significant Survival Benefit for Combination Therapy in mHSPC



"Doublet" Therapies

[ADT] *vs* [ADT + ARPI]

HR for OS: 0.63-0.81

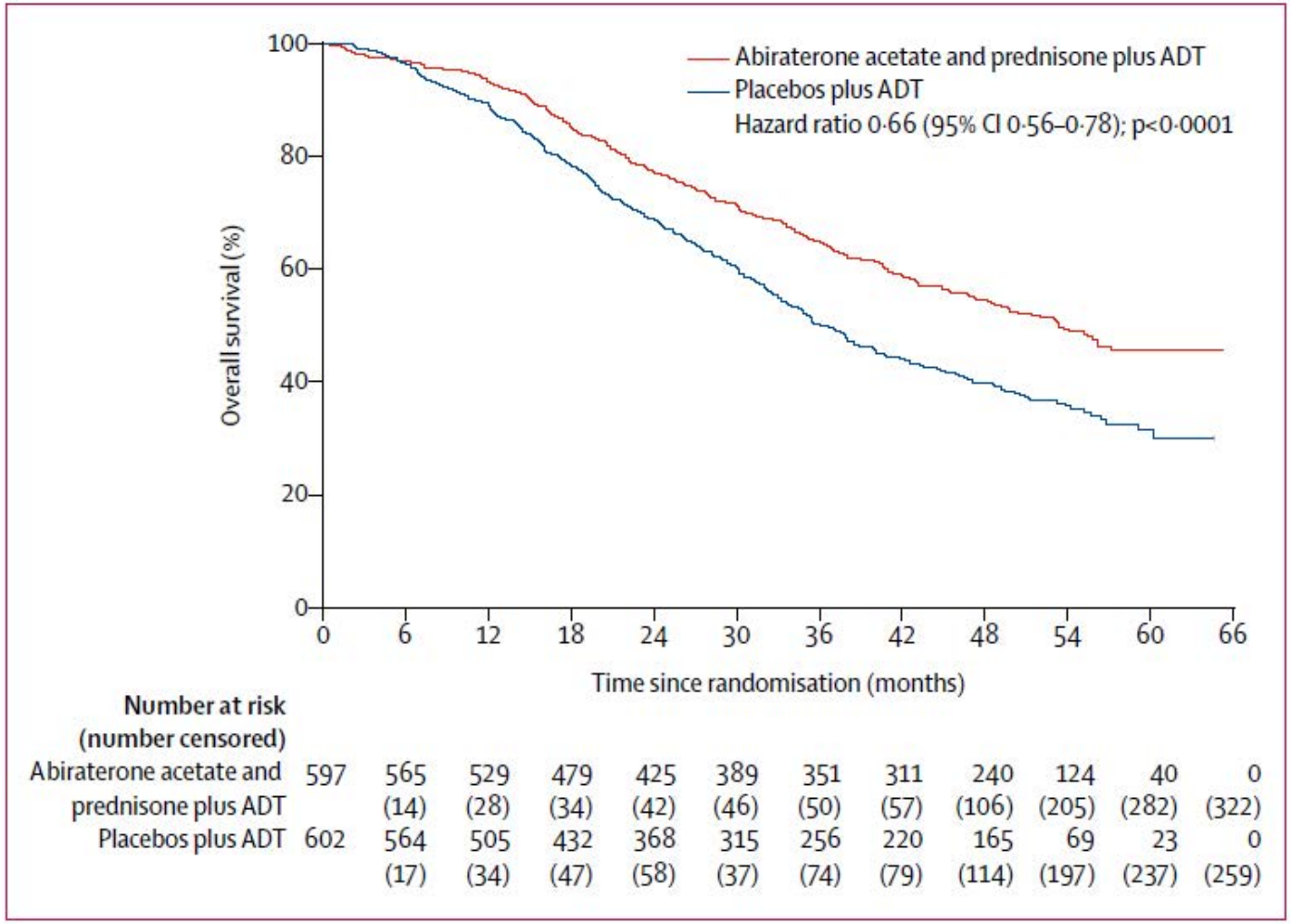
"Triplet" Therapies

[ADT + Doce] *vs* [ADT + Doce + ARPI]

HR for OS: 0.68-0.75

Hussain. JAMA Onc 10:807, 2024

Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial

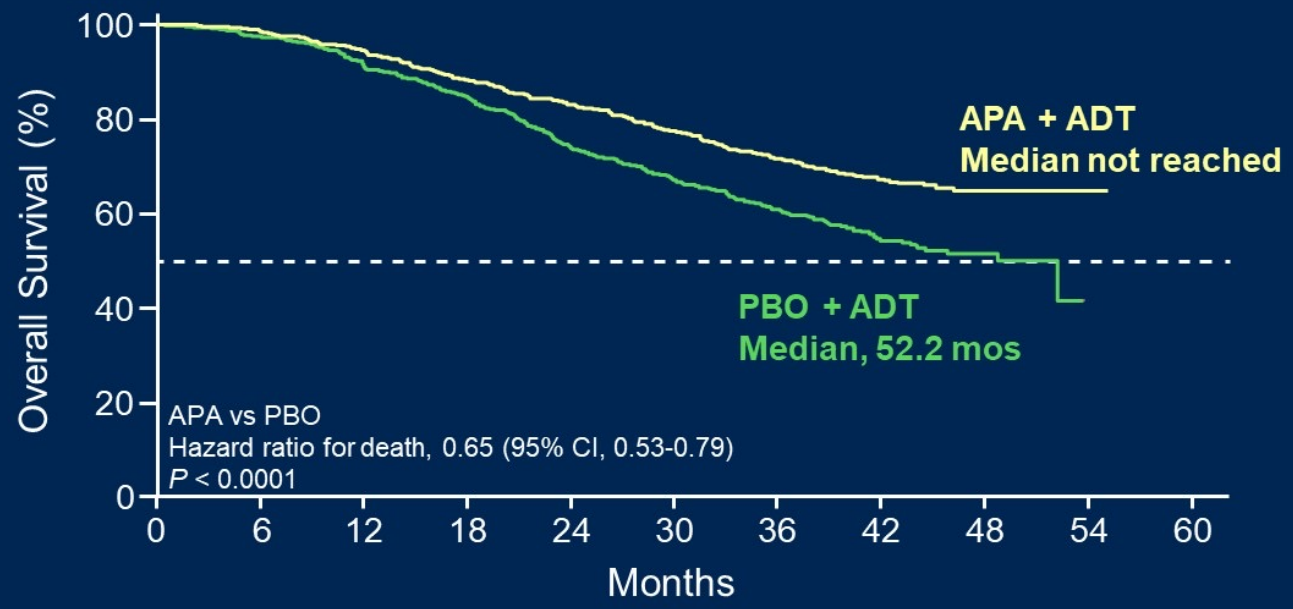


Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597	565 (14)	529 (28)	479 (34)	425 (42)	389 (46)	351 (50)	311 (57)	240 (106)	124 (205)	40 (282)	0 (322)
Placebos plus ADT	602	564 (17)	505 (34)	432 (47)	368 (58)	315 (37)	256 (74)	220 (79)	165 (114)	69 (197)	23 (237)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

Figure 2: Kaplan-Meier curve of overall survival in the intention-to-treat population
ADT=androgen deprivation therapy.

Fizazi K, Tran N, Fein L, et al
Lancet Oncol. 2019;20(5):686-700.

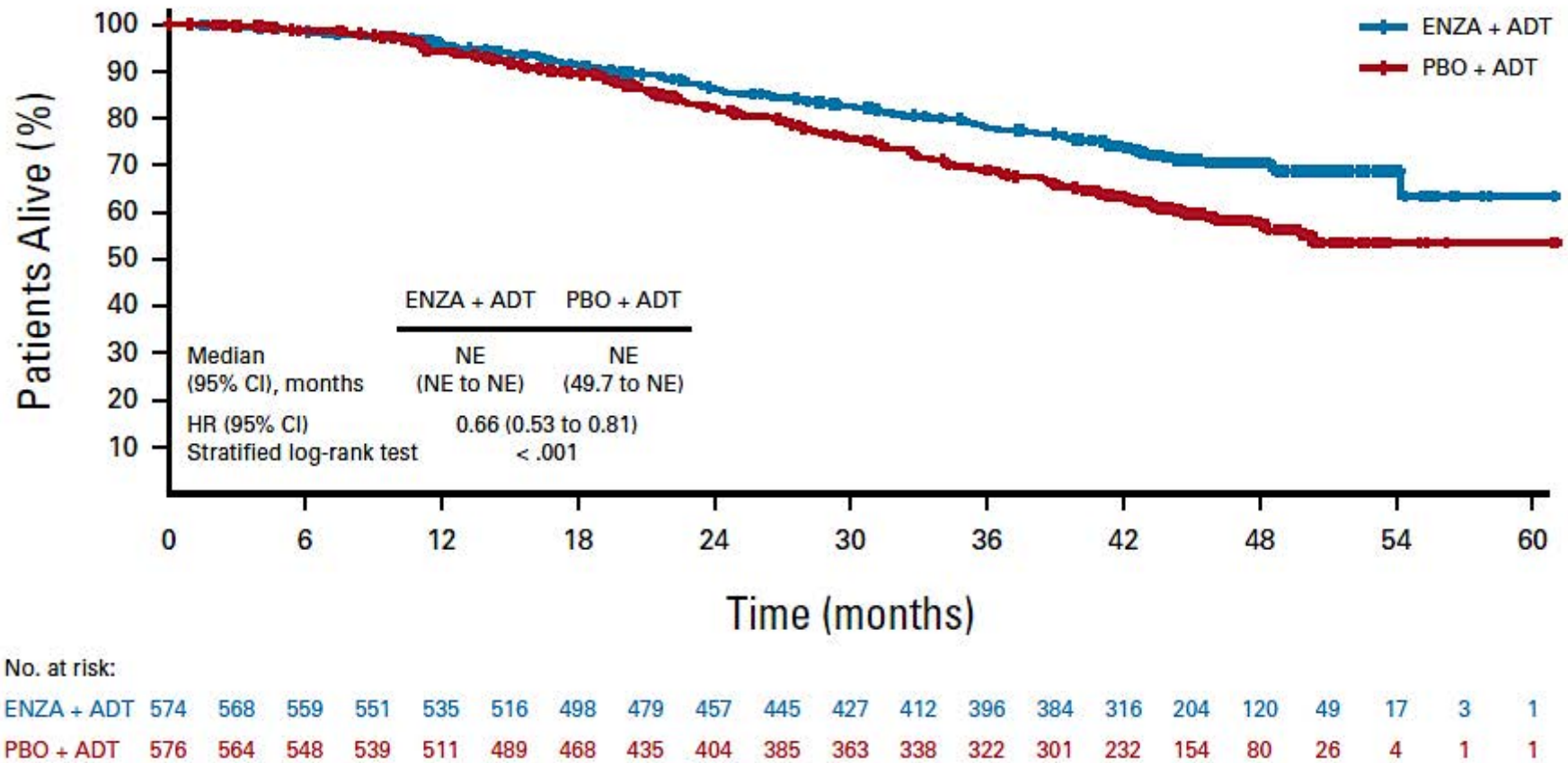
With Median Follow-up 44.0 Months, APA Plus ADT Reduced Risk of Death by 35%



No. at risk:											
APA + ADT	525	513	489	452	425	394	362	227	52	3	0
PBO + ADT	527	510	474	436	374	339	301	181	43	0	0

Chi KN et al, ASCO GU 2021; Abstract 11.

Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer

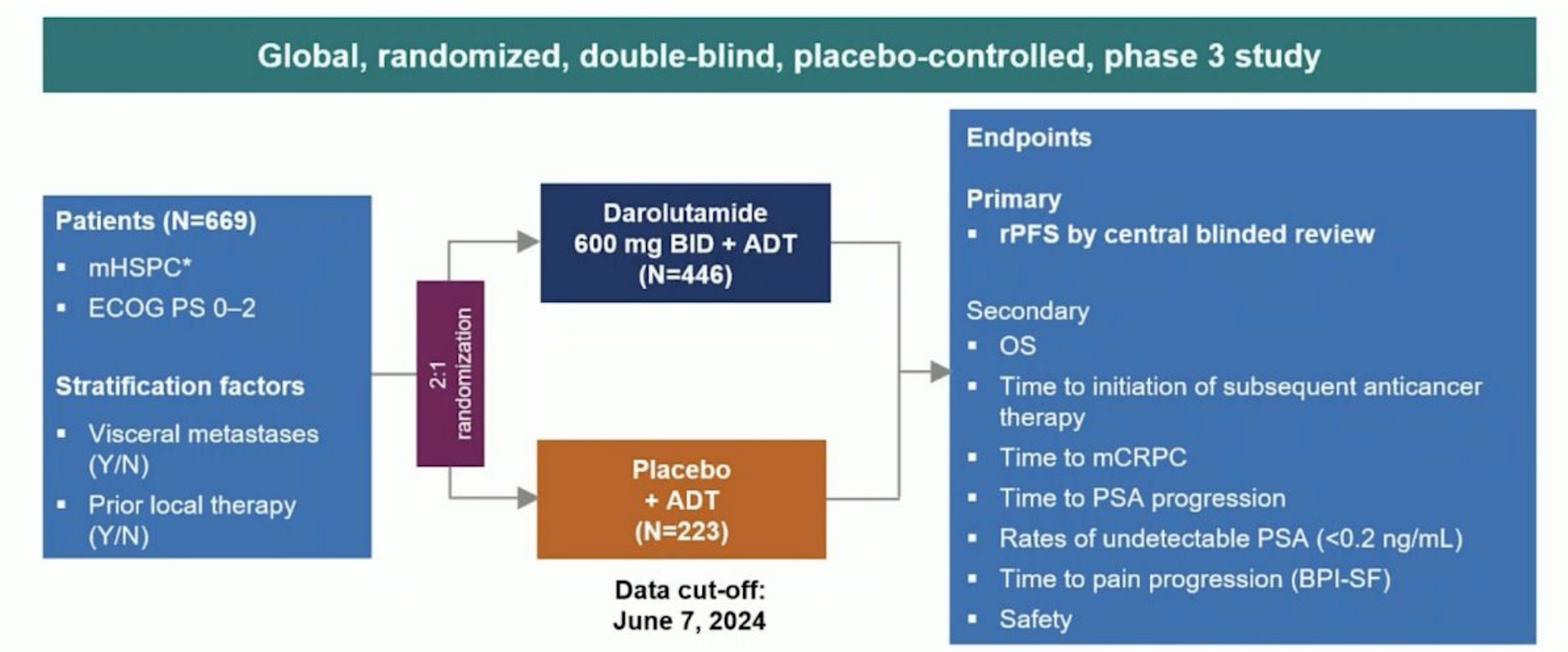


Armstrong AJ, Azad AA, Iguchi T, et al. *J Clin Oncol*. 2022;40(15):1616-1622.

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

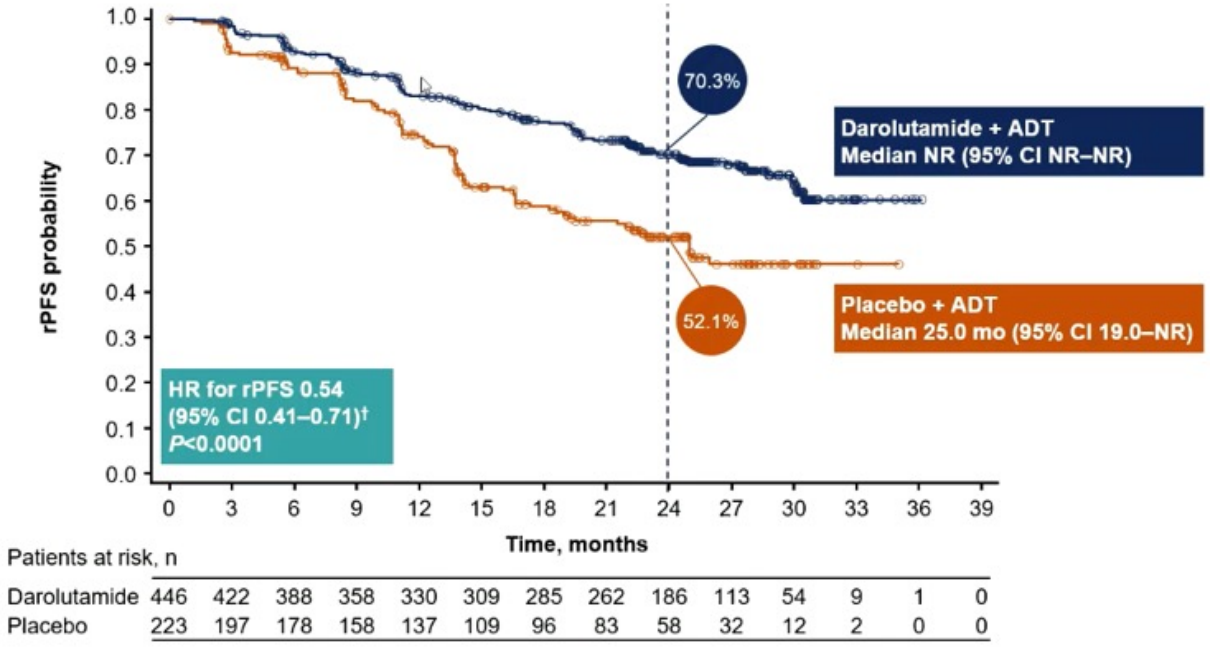
Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial

Fred Saad, MD[1]; Egils Vjaters, MD[2]; Neal Shore, MD, FACS[3]; David Olmos, MD, PhD[4]; Nianzeng Xing, MD[5]; Andrea Juliana Pereira de Santana Gomes, MD[6]; Augusto Cesar de Andrade Mota, MD, PhD[7]; Pamela Salman, MD, PhD[8]; Mindaugas Jievaltas, MD, PhD[9]; Albertas Ulys, MD, PhD[10]; Maris Jakubovskis, MD[11]; Evgeny Kopyltsov, MD, PhD[12]; Weiqing Han, MD, PhD[13]; Liina Nevalaita, PhD[14]; Isabella Testa, MD[15]; Marie-Aude Le Berre, MSc[16]; Iris Kuss, MD[17]; and Kunhi Parambath Haresh, MD[18]



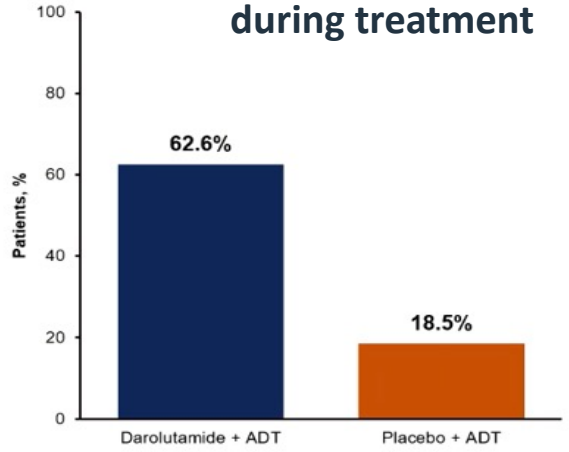
ARANOTE (Phase 3): Radiological PFS and PSA

Primary endpoint: Radiological PFS

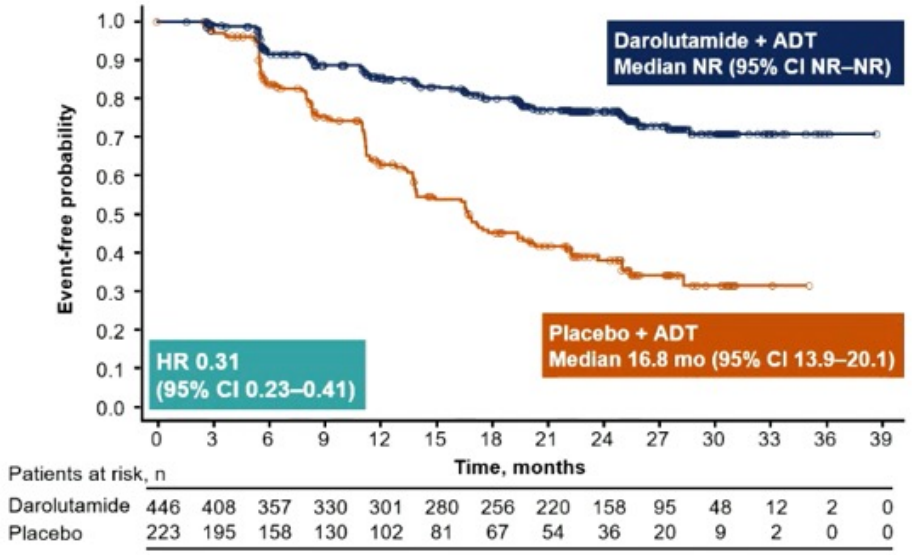


- Benefit of darolutamide was consistent across all subgroups

PSA <0.2 ng/mL at any time during treatment



Time to PSA progression



ADT, androgen-deprivation therapy.

Saad F, et al. ESMO 2024. Abstract LBA68
Saad F, Vjaters E, Shore N, et al. *J Clin Oncol*. 2024;42(36):4271-4281.

ARANOTE (Phase 3): Safety

Most common TEAEs

TEAEs	Darolutamide + ADT (n=445)		Placebo + ADT (n=221)	
	Incidence, %	EAIR/ 100 PY	Incidence, %	EAIR/ 100 PY
Fatigue	5.6	3.2	8.1	5.7
Mental impairment	1.6	0.9	0.5	0.3
Hypertension	9.4	5.5	9.5	6.7
Cardiac arrhythmias	8.8	5.1	6.8	4.7
Coronary artery disorders	3.6	2.0	1.4	0.9
Heart failure	0.9	0.5	0.9	0.6
Falls, including accident	1.3	0.8	0.9	0.6
Bone fracture	4.0	2.3	2.3	1.5
Vasodilation/flushing	9.2	5.6	7.2	5.0
Diabetes mellitus and hyperglycemia	9.0	5.3	9.5	6.7
Rash	4.3	2.4	3.6	2.4

ADT, androgen-deprivation therapy.

Incidence of TEAEs

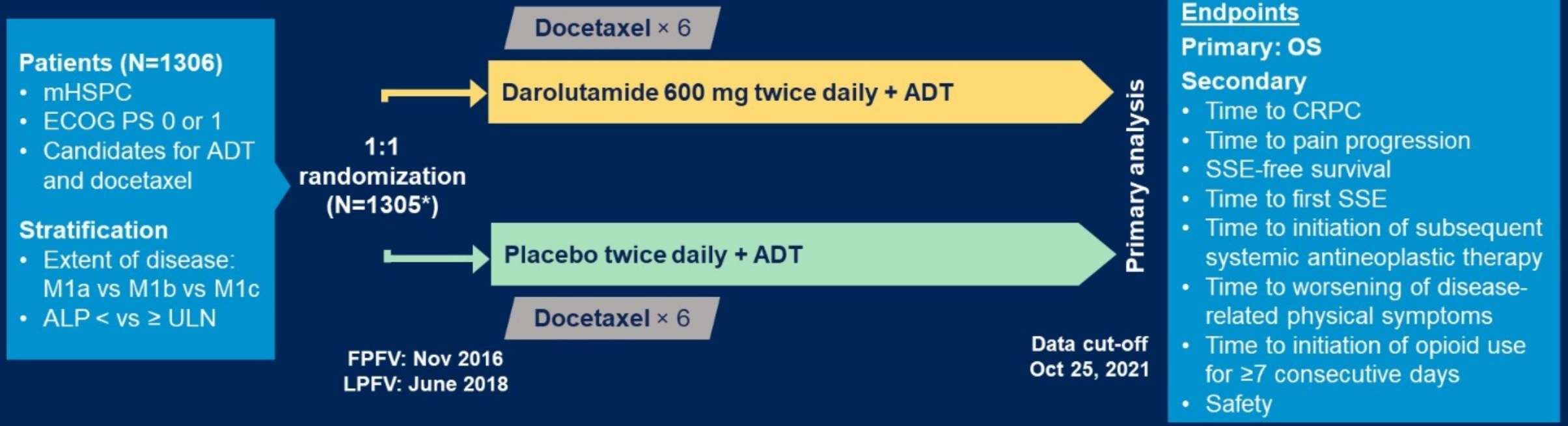
TEAEs, %	Darolutamide + ADT (n=445)	Placebo + ADT (n=221)
Any	91.0	90.0
Worst grade		
Grade 3 or 4	30.8	30.3
Grade 5	4.7	5.4
Serious	23.6	23.5
TEAEs leading to permanent discontinuation of study drug	6.1	9.0

- Median treatment duration: Darolutamide, 24.2 months; Placebo, 17.3 months

Saad F, et al. ESMO 2024. Abstract LBA68
Saad F, Vjaters E, Shore N, et al. *J Clin Oncol*. 2024;42(36):4271-4281.

ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)

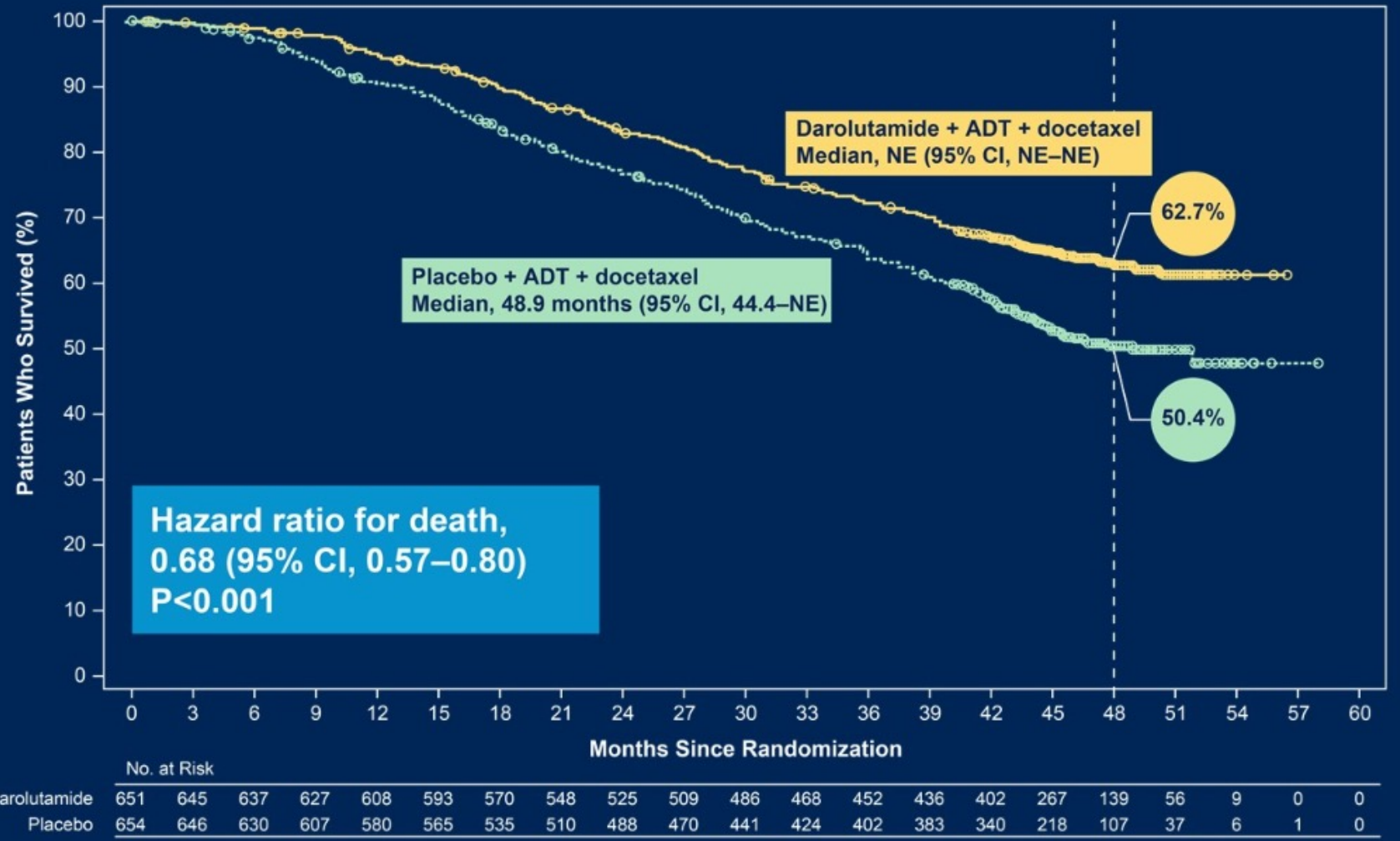


- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

*One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations. ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.

ARASENS Primary Endpoint*: Overall Survival

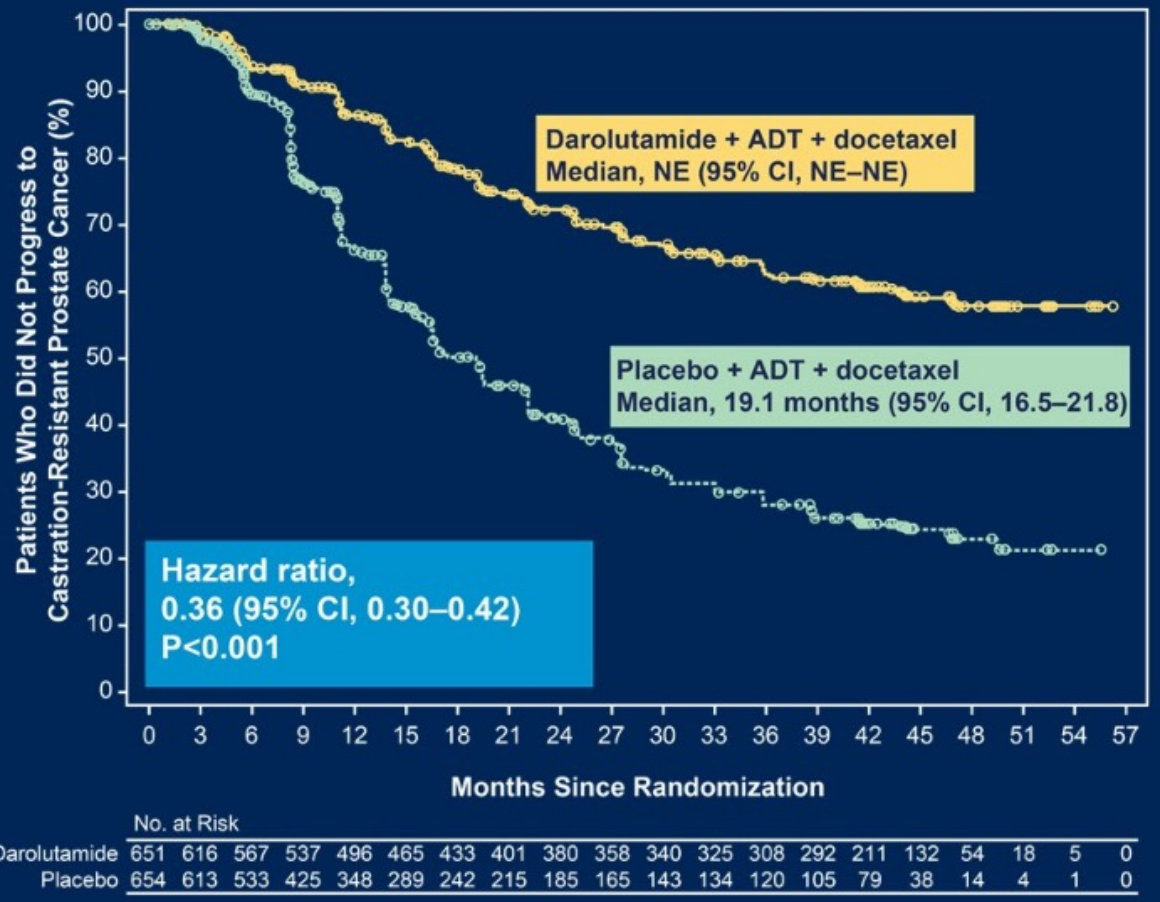
Darolutamide significantly reduced the risk of death by 32.5%



*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

Key Secondary Endpoints

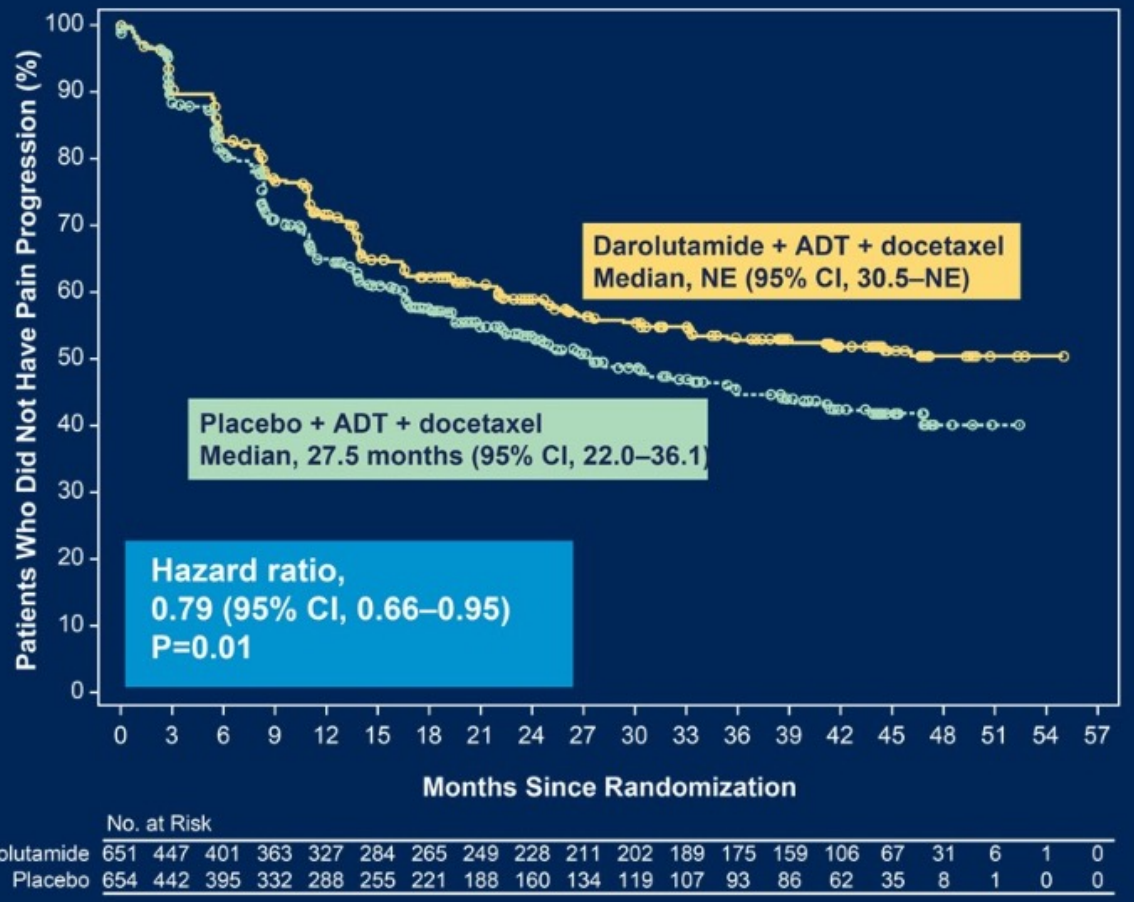
Time to CRPC



No. at Risk

Darolutamide	651	616	567	537	496	465	433	401	380	358	340	325	308	292	211	132	54	18	5	0
Placebo	654	613	533	425	348	289	242	215	185	165	143	134	120	105	79	38	14	4	1	0

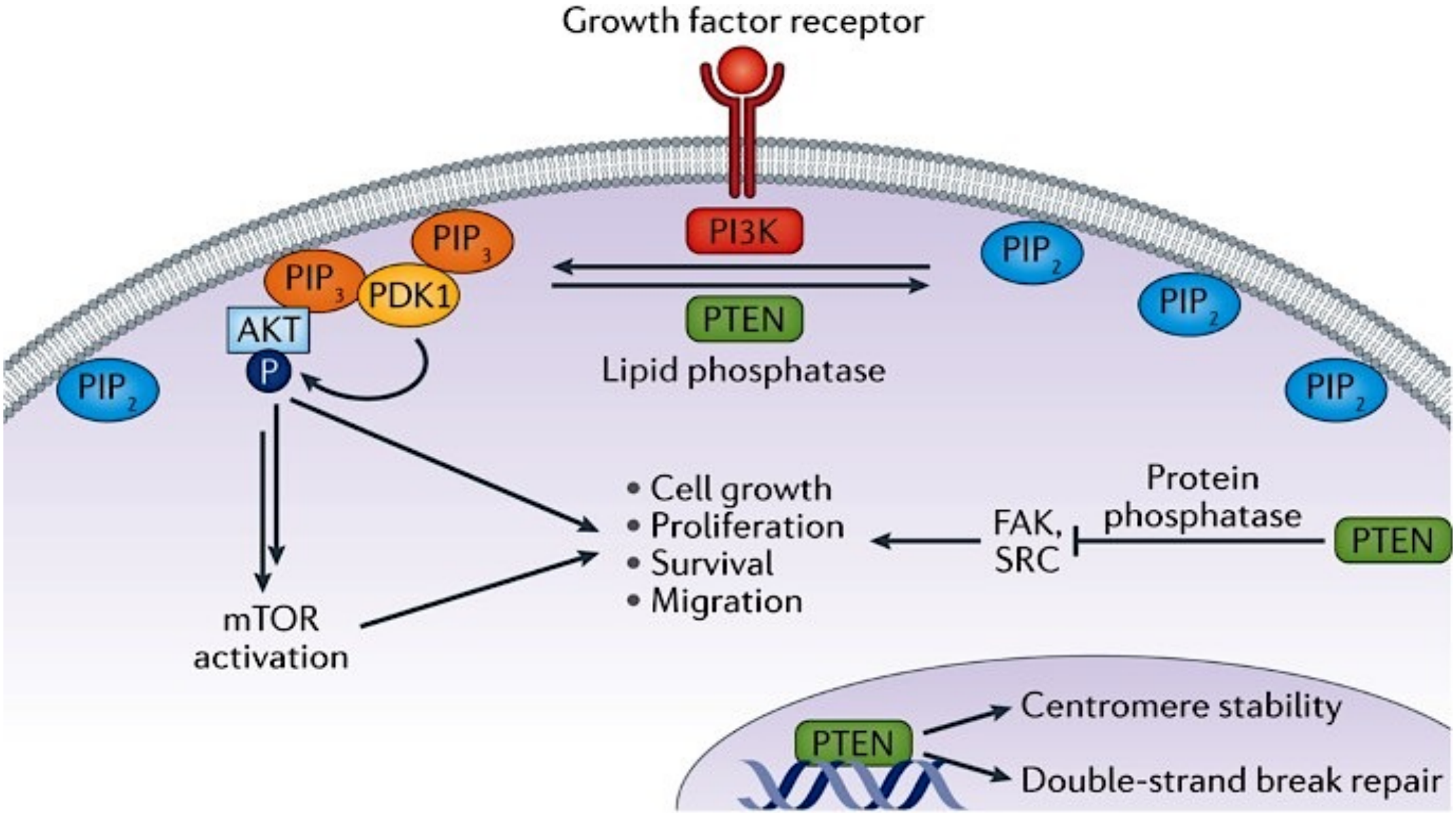
Time to pain progression*



No. at Risk

Darolutamide	651	447	401	363	327	284	265	249	228	211	202	189	175	159	106	67	31	6	1	0
Placebo	654	442	395	332	288	255	221	188	160	134	119	107	93	86	62	35	8	1	0	0

*Pain progression was defined by change in the Brief Pain Inventory–Short Form questionnaire worst pain score or initiation of opioid therapy for ≥7 days.


Growth factor receptor
PI3K
PTEN
Lipid phosphatase
PIP3
PIP3
PDK1
AKT
P
PIP2
PIP2
PIP2
PIP2
• Cell growth
• Proliferation
• Survival
• Migration
mTOR
activation
FAK,
SRC
Protein
phosphatase
PTEN
PTEN
Centromere stability
Double-strand break repair

Abstract number: TPS 178

Presented at ASCO-GU Virtual Congress 2021 (February 11–13, 2021)

A phase 3 trial of capivasertib and abiraterone versus placebo and abiraterone in patients with *de novo* metastatic hormone-sensitive prostate cancer characterized by PTEN deficiency (CAPItello-281)

Karim Fizazi,[1] Daniel George,[2] Maria De Santis,[3] Noel Clarke,[4] Andre Fay,[5] Hirotsugu Uemura,[6] Lynda Grinsted,[7] Claire Rooney,[7] Remy B Verheijen,[7] Rana Anjum,[8] Andrew Foxley,[7] Thomas Morris[7]

[1]Department of Medical Oncology, Gustave Roussy, Paris Saclay University, Villejuif Cedex, France; [2]Duke University Medical Center, Duke Cancer Institute, Durham, NC, USA; [3]Department of Urology, Charité Universitätsmedizin, Berlin, Germany, and Department of Urology, Medical University of Vienna, Vienna, Austria; [4]The Christie NHS Foundation Trust, Manchester, UK; [5]PUCRS School of Medicine, Porto Alegre, Brazil; [6]Department of Urology, Kindai University Faculty of Medicine, Osaka, Japan; [7]R&D Oncology, AstraZeneca, Cambridge, UK; [8]R&D Oncology, AstraZeneca, Boston, MA, USA

Objective

- CAPItello-281 (NCT04493853) is a global, phase 3 trial to evaluate the efficacy and safety of capivasertib in combination with abiraterone (plus prednisone/prednisolone) on a background of ADT versus placebo plus abiraterone (plus prednisone/prednisolone) on a background of ADT in patients with *de novo* mHPSC with PTEN-deficient tumors.

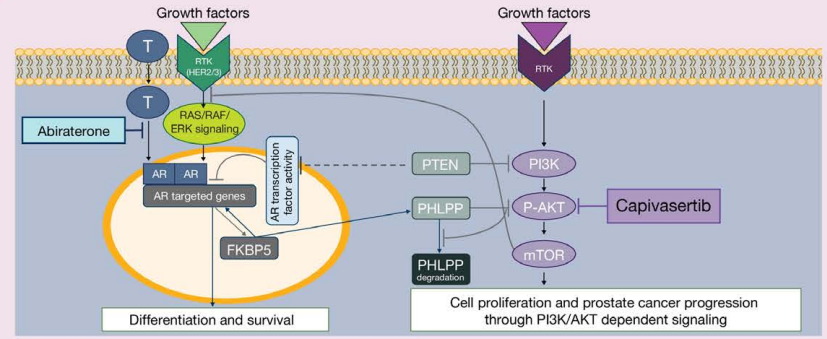
Key study features

- CAPItello-281 is a randomized, double-blind, placebo-controlled, multicenter phase 3 trial.
- Patients receive either oral capivasertib (400 mg) or placebo (twice daily; 4 days on, 3 days off on a 28-day treatment cycle) in combination with abiraterone (1000 mg once daily) and androgen deprivation therapy until radiographic disease progression or unacceptable toxicity.
- The primary endpoint is radiographic progression-free survival (rPFS).
- The trial is being conducted at around 350 study sites in Europe, North America, South America, Australia and Asia (including China and Japan).
- Patient enrollment began in July 2020 and is ongoing.

Background

- Prostate cancer is the most prevalent form of cancer in men and is associated with considerable morbidity and mortality. With an estimated 358 989 deaths in 2018, prostate cancer is the fifth leading cause of death from cancer in men worldwide.[1]
- In patients with metastatic hormone-sensitive prostate cancer (mHSPC), androgen deprivation therapy (ADT) is highly effective in improving clinical outcomes.[2]
- Recent studies demonstrated the benefits of adding the androgen biosynthesis inhibitor, abiraterone, or non-steroidal antiandrogens, e.g. enzalutamide, to ADT.[3,4]
- However, mHSPC inevitably progresses to a castration-resistant phenotype.[5,6] Patients with *de novo* mHSPC are at higher risk of progressing to a castration-resistant disease state than those with prostate cancer that has progressed to metastasis after treatment for localized or locally advanced disease.[7]
- Aberrant activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway, predominately due to PTEN loss, is common in prostate cancer, especially at later disease stages.[8]
- There is an important unmet medical need for treatments in the *de novo* mHSPC setting, particularly in patients whose tumors are characterized by PTEN deficiency.
- The androgen receptor signaling and AKT pathway are reciprocally cross-regulated, so that inhibition of one leads to upregulation of the other (**Figure 1**).[9,10] Therefore, combining abiraterone therapy with AKT inhibition may be beneficial in patients with mHSPC with tumors characterized by PTEN deficiency.
- In the IPATential150 phase 3 study (NCT03072238), an AKT inhibitor, ipatasertib, prolonged radiographic progression-free survival (rPFS) when combined with abiraterone, compared with abiraterone alone in patients with metastatic castration-resistant prostate cancer with tumors characterized by PTEN loss.[11]
- Capivasertib (AZD5363) is a potent, selective inhibitor of AKT1, -2 and -3 that has shown activity in preclinical models of hormone-sensitive and castration-resistant prostate cancer with PTEN loss.[12]
- Capivasertib in combination with abiraterone exhibited an acceptable safety and tolerability profile in a phase 1 study (NCT04087174) in mCRPC patients.[13]

Figure 1. The PI3K/AKT/mTOR pathway and crosstalk with AR signaling[a]



[a]Modified from Mulholland *et al.* 2011, and Carver *et al.* 2011
PTEN loss suppresses AR transcription factor activity leading to reduced prostate epithelial differentiation and survival. Collaboratively, PTEN loss activates the PI3K/AKT signaling pathway and reduces the AR-regulated FKBP5–PHLPP negative feedback loop to AKT activation, further enhancing AKT activation, leading to androgen/AR-independent prostate epithelial proliferation. Simultaneous inhibition of androgen biosynthesis by abiraterone and AKT signaling by capivasertib results in inhibition of prostate cancer cell proliferation[10]
AKT, protein kinase B; AR, androgen receptor; FKBP5, FKBP5 scaffold protein; HER2/3, human epidermal growth factor receptors 2/3; mTOR, mammalian target of rapamycin; P-AKT, phosphorylated AKT; PHLPP, PHLPP phosphatase; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; RAS/RAF/ERK, Ras-Raf-ERK pathway; RTK, receptor tyrosine kinase; T, testosterone

Methods

Study design and participants

- CAPItello-281 is a randomized, double-blind, placebo-controlled, multicenter phase 3 trial.
- The global trial is being conducted in over 30 countries and around 350 study sites (**Figure 2**). Enrollment began in July 2020 and is ongoing.
- Participants will be enrolled and screened according to the two-part screening procedure (**Figure 3**) to achieve a total of 1000 randomized participants in a 1:1 ratio to the two treatment arms. The PTEN status of a tumor sample is tested in Screening Part 1; most of the remaining assessments are carried out in Screening Part 2.
- Key inclusion and exclusion criteria for patient participation in CAPItello-281 are shown in **Table 1**.
- Following screening, patients receive either oral capivasertib (400 mg) or placebo (twice daily; 4 days on, 3 days off on a 28-day treatment cycle) in combination with abiraterone (1000 mg once daily) and ADT until radiographic disease progression or unacceptable toxicity (**Figure 4**).

Efficacy

- The primary endpoint is rPFS: the time from randomization to radiographic disease progression, as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for soft tissue and/or Prostate Cancer Working Group 3 (PCWG3) for bone, or death due to any cause.
- Key secondary endpoints are shown in **Figure 4**.

Safety

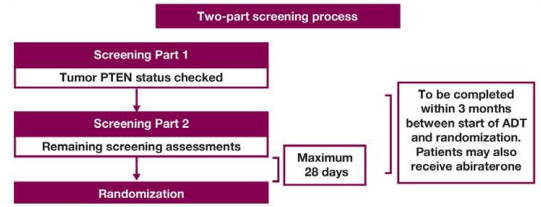
- Adverse events (AEs) and serious AEs (SAEs) are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
- Safety and tolerability data will be evaluated in terms of AEs/SAEs, vital signs, clinical chemistry/hematology/glucose metabolism parameters and electrocardiogram parameters and summarized using appropriate descriptive statistics.

Figure 2. Map of the countries with planned enrollment for CAPItello-281

Statistical analyses of primary and secondary endpoints

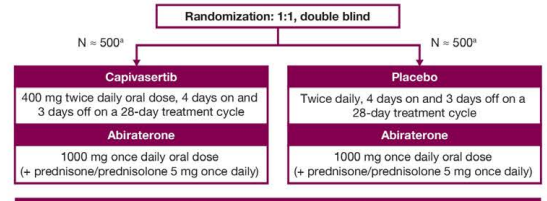
- The effect of capivasertib versus placebo on rPFS will be tested using a log-rank test stratified by the randomization stratification factors.
- Analysis of secondary endpoints will follow a multiple test procedure to preserve the overall type 1 error (family-wise error rate) in the strong sense.

Figure 3. Two-part screening process for CAPItello-281



ADT, androgen deprivation therapy; PTEN, phosphatase and tensin homolog

Figure 4. Trial design and outcome measures for CAPItello-281



All participants receive continuous ADT

Objectives and endpoints

Primary
- Radiographic progression-free survival (rPFS) by investigator assessment

Safety
- Safety and tolerability of capivasertib + abiraterone versus placebo + abiraterone in patients with PTEN-deficient mHSPC

Key secondary
- Overall survival (OS)
- Time to start of first subsequent anticancer therapy (TFST)
- Symptomatic skeletal event-free survival (SSE-FS)
- Time to pain progression (TTTP)

[a]Estimated number to achieve appropriate statistical power
ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer; PTEN, phosphatase and tensin homolog

Table 1. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Adult males ≥ 18 years of age (≥ 20 years of age in Japan), with asymptomatic or mildly symptomatic mHSPC	• Radiotherapy with a wide field of radiation or major surgery within 4 weeks before the start of study treatment
• ECOG/WHO performance status of 0 or 1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks	• Brain metastases or spinal cord compression
• Histologically confirmed *de novo* (i.e., diagnosed within 3 months of randomization) mHSPC; adenocarcinoma must be the primary histological pattern and patients with small-cell tumors are not eligible	• Past medical history or any evidence of clinically active of interstitial lung disease • Clinically significant heart disease • Clinically significant abnormalities of glucose metabolism
• Consent to provide a FFPE tissue block (preferred) or slides	• Refractory nausea and vomiting, malabsorption syndrome, chronic gastrointestinal diseases or other condition that would preclude adequate absorption of capivasertib
• Valid PTEN IHC result indicating PTEN deficiency (centralized testing)	• History of hypersensitivity to active or inactive excipients of capivasertib, abiraterone or drugs with a similar chemical structure or class
• Metastatic disease documented prior to randomization by clear evidence of ≥ 1 bone lesion and/or ≥ 1 soft tissue lesion	• Any evidence of severe or uncontrolled systemic diseases, including active bleeding diatheses, or known active infection including hepatitis B, hepatitis C and HIV
• Candidate for abiraterone and steroid therapy. Previous treatment with abiraterone and/or a steroid for *de novo* disease is allowed up to a maximum of 3 months (93 days) prior to randomization	• Any other chemotherapy, immunotherapy, immunosuppressant medication (other than corticosteroids) or anticancer agents within 3 weeks of the first dose of study treatment
• Ongoing ADT with GnRH analog (combination with first-generation androgen receptor antagonists, e.g., bicalutamide is allowed), or LHRH antagonist or bilateral orchiectomy	• Nitrosourea or mitomycin C within 6 weeks of the first dose of study treatment • Drugs known to prolong the QT interval

ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin embedded; GnRH, gonadotropin-releasing hormone; HIV, human immunodeficiency virus; IHC, immunohistochemistry; LHRH, luteinizing hormone-releasing hormone; mHSPC, metastatic hormone-sensitive prostate cancer; PTEN, phosphatase and tensin homolog; WHO, World Health Organization

References

1. International Agency for Research on Cancer. GLOBOCAN database (September 2018). Available from: http://gco.iarc.fr/. (Accessed November 1, 2020).
2. Heleen C *et al. Endocr Relat Cancer* 2014;21:T105–18.
3. Fizazi K *et al. Lancet Oncol* 2019;20:686–700.
4. Armstrong AJ *et al. J Clin Oncol* 2019;37:2974–86.
5. Scher HI *et al. PLoS One* 2015;10:e0139445.
6. Caltirini C *et al. Cancers (Basel)* 2019;11:1355.
7. Francini E *et al. Prostate* 2018;78:889–95.
8. Jamaspishvili T *et al. Nat Rev Urol* 2018;15:222–34.
9. Carver BS *et al. Cancer Cell* 2011;19:575–86.
10. Mulholland DJ *et al. Cancer Cell* 2011;19:792–804.
11. de Bono JS *et al. Ann Oncol* 2020;31:S1142–1215. Presented at ESMO Virtual Congress 2020.
12. Marques RB *et al. Eur Urol* 2015;67:1177–85.
13. Shore N *et al.* Presented at ASCO GU Virtual Symposium 2021.

Funding

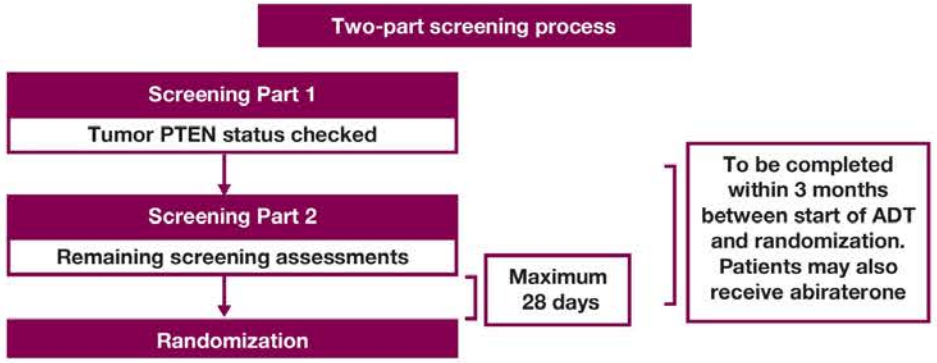
This study (NCT04493853) was funded by AstraZeneca.

Acknowledgments

We thank the patients already enrolled in this trial and their families, our co-investigators and Julia Grigorieva, PhD, of Oxford PharmaGenesis, Philadelphia, USA, who provided medical writing assistance.

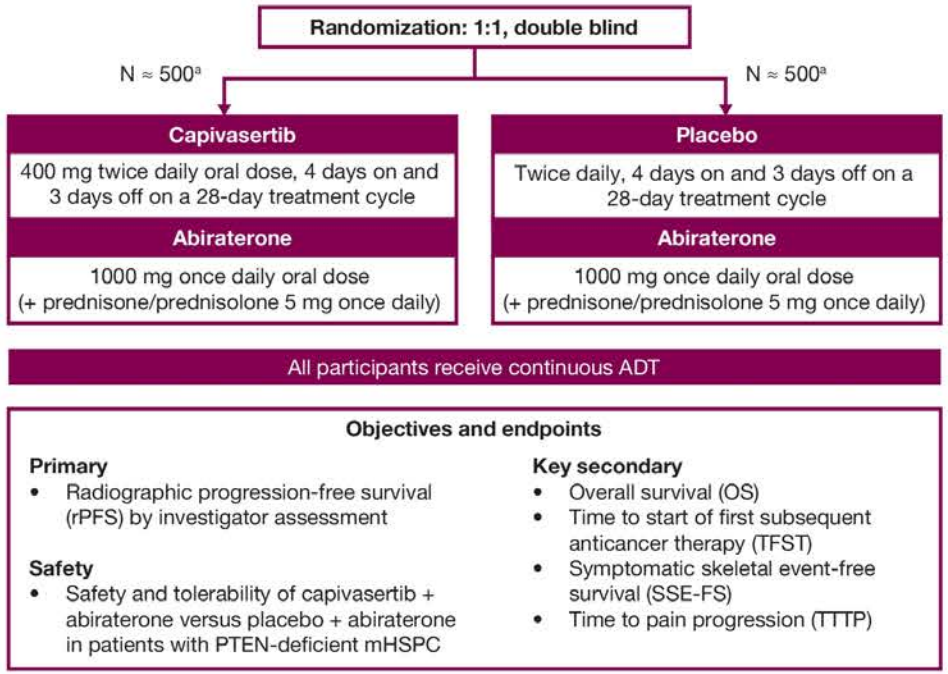
AZD5363 was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

Figure 3. Two-part screening process for CAPItello-281



ADT, androgen deprivation therapy; PTEN, phosphatase and tensin homolog

Figure 4. Trial design and outcome measures for CAPItello-281



[a]Estimated number to achieve appropriate statistical power
ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer; PTEN, phosphatase and tensin homolog

Fizazi K et al, ASCO GU 2021; Abstract TPS178.

Capivasertib combination in PTEN-deficient metastatic hormone-sensitive prostate cancer demonstrated statistically significant and clinically meaningful improvement in radiographic progression-free survival in CAPItello-281 Phase III trial

PUBLISHED 25 November 2024

First and only AKT inhibitor combination to demonstrate benefit in this specific subtype of prostate cancer

Positive high-level results from the CAPItello-281 Phase III trial showed that capivasertib in combination with abiraterone and androgen deprivation therapy (ADT) demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of radiographic progression-free survival (rPFS) versus abiraterone and ADT with placebo in patients with PTEN-deficient *de novo* metastatic hormone-sensitive prostate cancer (mHSPC).
Overall survival (OS) data were immature at the time of this analysis; however, the capivasertib combination showed an early trend towards an OS improvement versus abiraterone and ADT with placebo. The trial will continue as planned to further assess OS as a key secondary endpoint.
Prostate cancer is the second most prevalent cancer in men and the fifth leading cause of male cancer death globally.[1] Only one third of patients with metastatic prostate cancer survive five years after diagnosis.[2] Newly diagnosed mHSPC is an aggressive form of the disease associated with poor outcomes and survival.[3,4] Approximately 200,000 patients are diagnosed with mHSPC each year, and one in four have PTEN-deficient tumours.[5] Patients with a tumor biomarker of PTEN deficiency have a particularly poor prognosis.[6]

https://www.astrazeneca.com/media-centre/press-releases/2024/truqap-improved-rpfs-in-advanced-prostate-cancer.html

CAPItello-280: a Phase III study of capivasertib and docetaxel versus placebo and docetaxel in metastatic castration-resistant prostate cancer

Simon J Crabb,[1] Ding-Wei Ye,[2] Hirotsugu Uemura,[3] Thomas Morris,[4] Christopher Gresty,[4] Jill Logan,[4] Claire Rooney,[4] Andrew Foxley,[4] Michael Carducci[5]

[1]Southampton Clinical Trials Unit, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK; [2]Fudan University Shanghai Cancer Center, Shanghai, China; [3]Department of Urology, Kindai University Faculty of Medicine, Ōsakasayama, Osaka, Japan; [4]Oncology R&D, AstraZeneca, Cambridge, UK; [5]Johns Hopkins, Baltimore, MD, USA

Abstract number: TPS287

Key inclusion criteria

- Adults ≥18 years of age with metastatic CRPC
- No prior chemotherapy for metastatic CRPC
- Prior ARTA (abiraterone, enzalutamide, apalutamide, or darolutamide) for HSPC or CRPC for at least 3 months and evidence of disease progression (radiological or via PSA assessment) whilst on treatment
- Serum testosterone level ≤50 ng/dL
- Eligible for docetaxel treatment (investigator assessment)
- Ongoing ADT
- ECOG PS 0 or 1

Key exclusion criteria

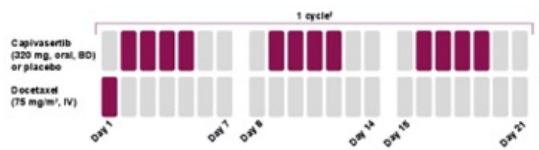
- Radiotherapy to ≥30% of bone marrow within 4 weeks of the start of study treatment
- Major surgery within 4 weeks of the start of study treatment
- Brain metastases or spinal cord compression
- Cardiac abnormalities
- Clinically significant glucose metabolism abnormalities (e.g. Type I or II diabetes mellitus requiring insulin treatment)
- Inadequate bone marrow reserve or organ function
- History of another primary malignancy except for malignancy treated with curative intent with no known active disease within the past 5 years and of a low potential risk of recurrence
- Specified prior or concomitant therapy, including chemotherapy or exposure to inhibitors of the PI3K/AKT/PTEN signaling pathway

N≈790 randomized 1:1*

Capivasertib (320 mg orally, BD, 4 days on, 3 days off) plus docetaxel (75 mg/m² IV on Day 1 of each 21-day cycle for 6–10 cycles)†

Matching placebo (320 mg orally, BD, 4 days on, 3 days off) plus docetaxel (75 mg/m² IV on Day 1 of each 21-day cycle for 6–10 cycles)†

Schedule of each 21-day dosing cycle



*Stratification factors: the patient has received two or more lines of prior next-generation hormonal agents, with at least one line of next-generation hormonal agent used in CRPC setting (yes/no); the patient has visceral metastases (yes/no); geographic region (1. North America, Western Europe, and Australia; 2. Latin America and Eastern Europe; 3. Asia).
†Plus prednisone or prednisolone 5 mg BD or 10 mg QD, and a background of continued ADT.

Study endpoints

Primary

- **OS** defined as the time from randomization until the date of death due to any cause

Secondary

- **rPFS** defined as the time from randomization to radiographic progression according to RECIST v1.1 or PCWG3 criteria (investigator-assessed)
- **TTPP** defined as the time from randomization to clinically meaningful pain progression (2-point increase from baseline in BPI-SF Item 3 'worst pain' and/or the initiation of, or increase in, opioid use)
- **SSRE** defined as the time from randomization to use of radiation therapy for skeletal symptoms, new symptomatic pathological bone fractures, spinal cord compression, or surgical intervention for bone metastasis
- **Safety and tolerability**
- **Patient-reported outcomes** including physical functioning, urinary symptoms, pain, and HRQoL
- **Pharmacokinetic analysis**

Discussion Questions

- A 60-year-old man undergoes radical prostatectomy for Gleason 7 prostate adenocarcinoma followed by external beam radiation therapy for early PSA recurrence. Eighteen months later his PSA rises to 1.2 ng/mL and over the next 12 months continues to rise to 2.4 ng/mL. What treatment, if any, would you recommend?

- What is your usual treatment approach for a patient who develops bone-only metastatic prostate cancer after receiving ADT for M0 disease? How does the volume of disease affect your thinking?

Discussion Questions

- What systemic therapy would you typically recommend for a patient presenting de novo with Gleason 8 prostate cancer and 6 moderately symptomatic bone metastases? How, if at all, does your decision change based on patient age?

- What is your understanding of and/or experience with the efficacy and tolerability of capivasertib in combination with ADT and abiraterone for patients with metastatic hormone-sensitive prostate cancer (mHSPC) and PTEN deficiency?

Module 7: Prostate Cancer

Hormonal Therapy for Patients with Prostate Cancer — Dr Oh

Other Available and Emerging Therapeutic Approaches — Dr Aggarwal

UCSF Helen Diller Family Comprehensive Cancer Center

Available and Emerging Therapeutic Approaches for mCRPC

Rahul Aggarwal, MD
Professor of Medicine
University of California San Francisco

Disclosures

No relevant conflicts of interest to disclose.

Outline

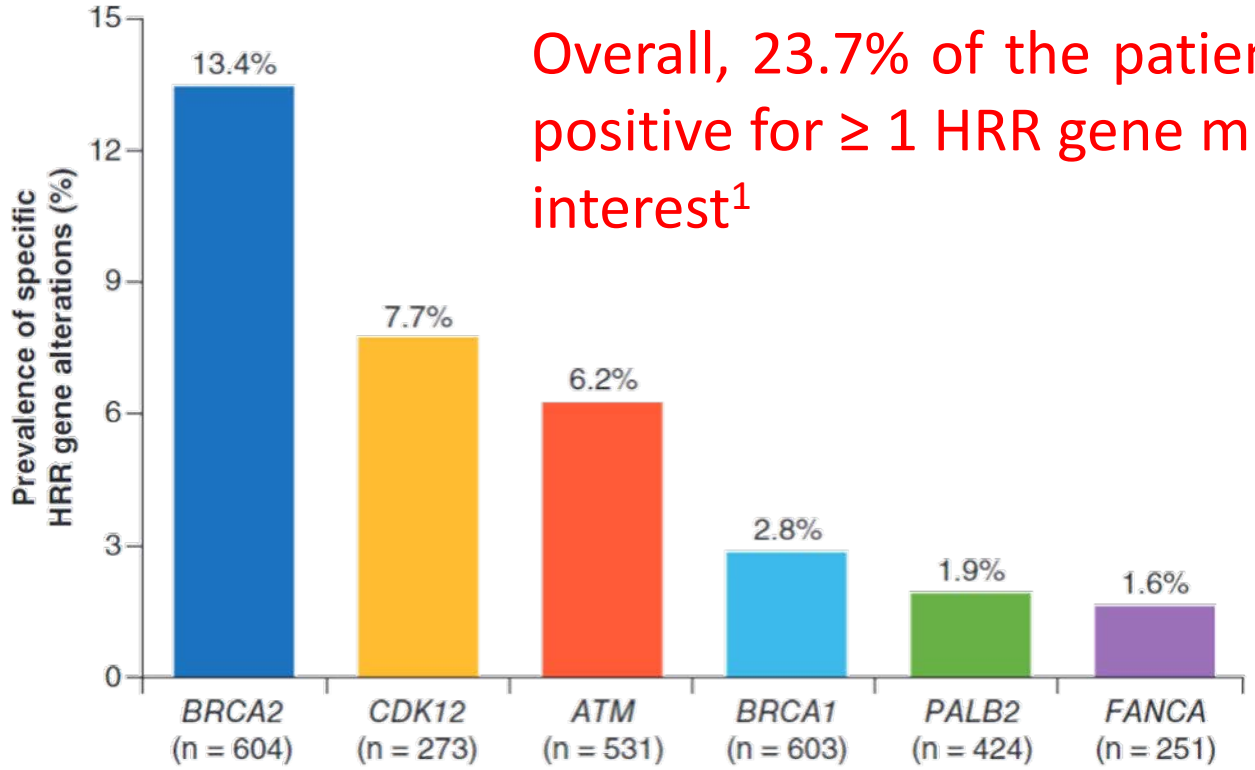
- Combining AR Pathway + PARP Inhibition in mCRPC
- Radiopharmaceuticals for the treatment of mCRPC
- Emerging Treatment Options
  - Immune checkpoint inhibition (CONTACT-02)
  - EZH2 Inhibition
  - Bi-specific T-cell engagers

Outline

- Combining AR Pathway + PARP Inhibition in mCRPC
- Radiopharmaceuticals for the treatment of mCRPC
- Emerging Treatment Options
  - Immune checkpoint inhibition (CONTACT-02)
  - EZH2 Inhibition
  - Bi-specific T-cell engagers

Prevalence of Homologous Repair Recombination Mutations in Advanced Prostate Cancer

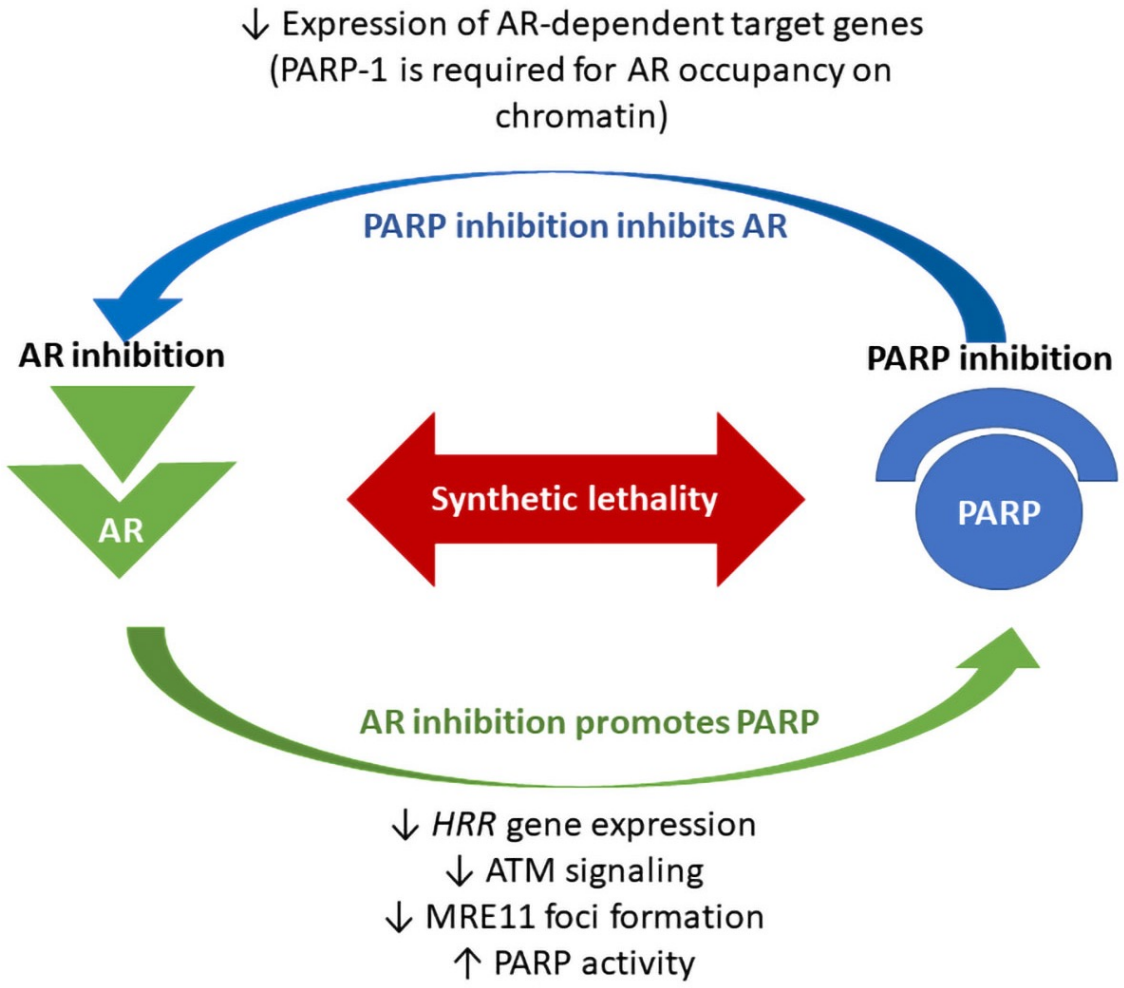
- Retrospective multicenter observational cohort study of advanced prostate cancer in the US from 2013-2019
- 674 patients were tested for 1 or more of 6 HRR mutations of interest: BRCA1, BRCA2, CDK12, ATM, FANCA, PALB2



Overall, 23.7% of the patients tested positive for ≥ 1 HRR gene mutation of interest[1]

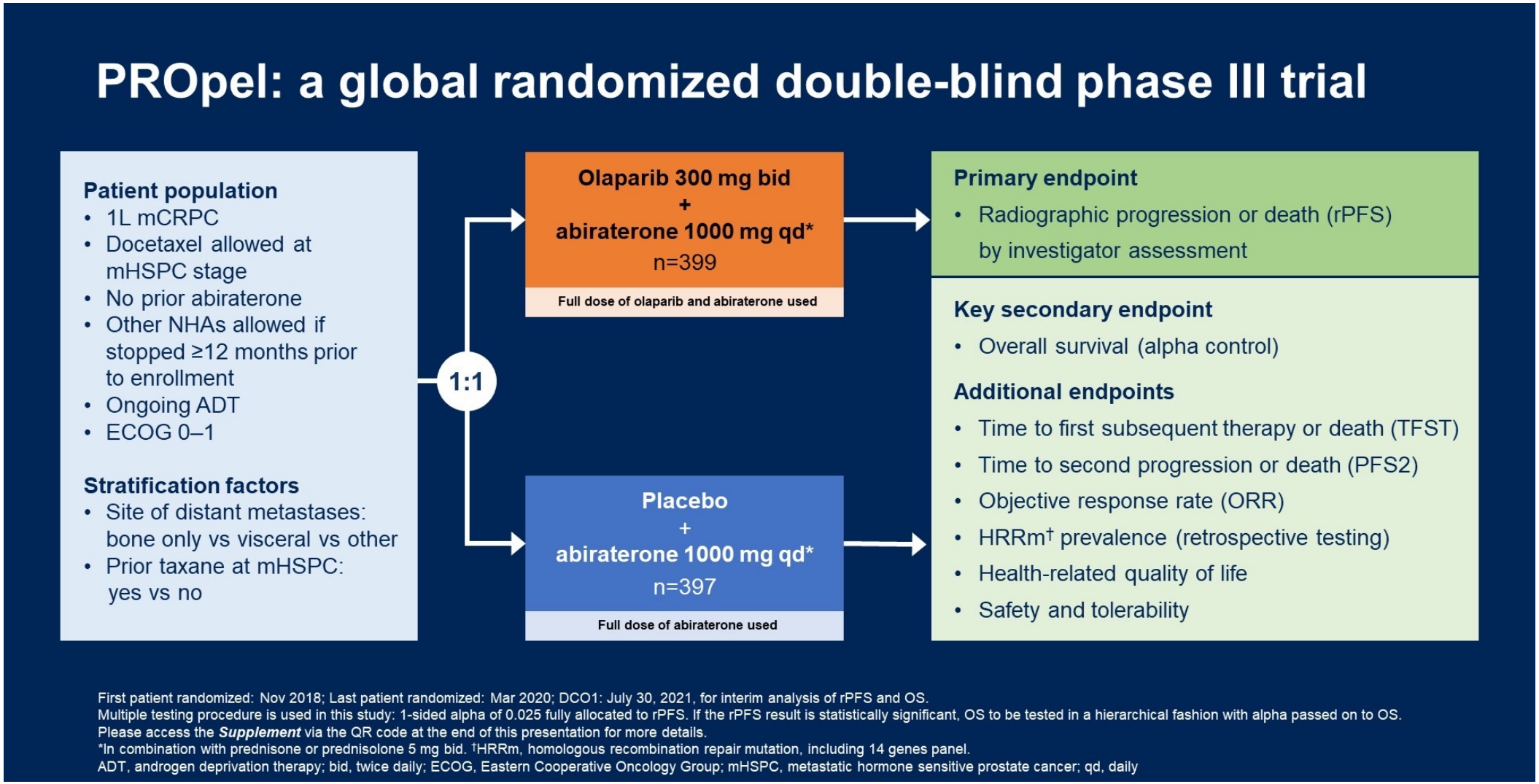
Shore N et al. Future Oncology, 2021

Rationale for Dual Androgen Receptor + PARP Blockade



Panebianco M, et al. Explor Target Antitumor Ther, 2024

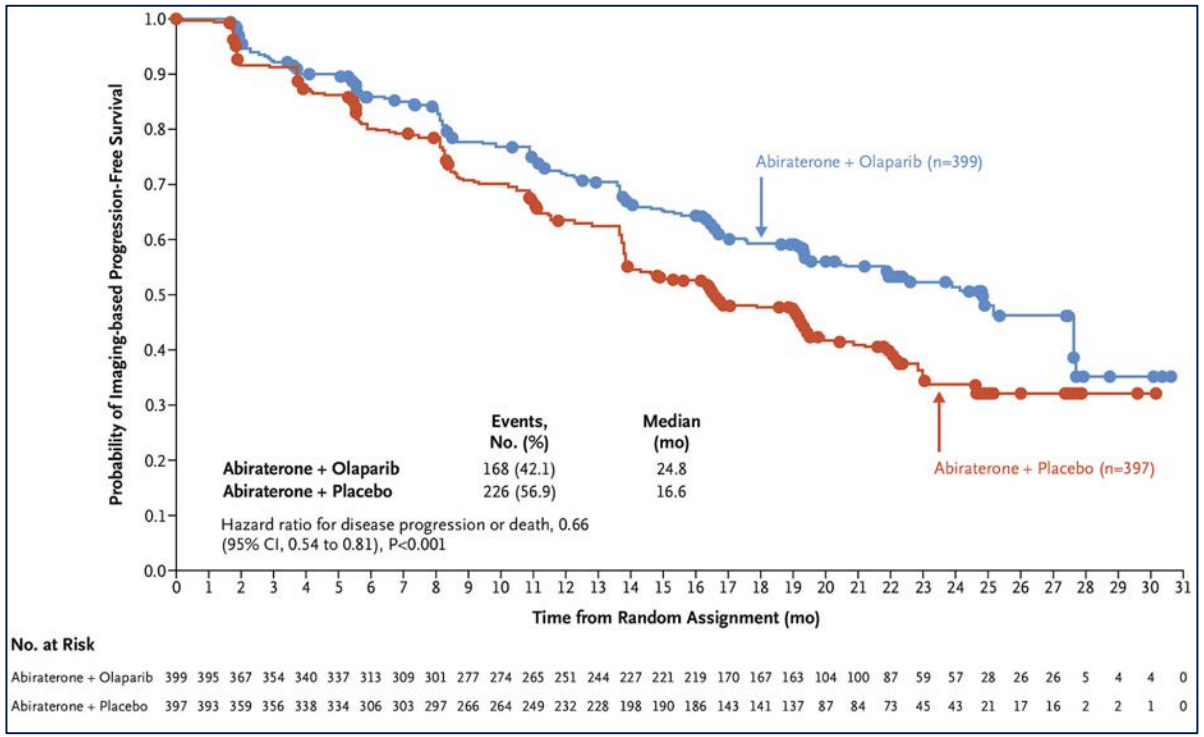
PROpel Randomized Phase 3 Study



Saad F, et al. ASCO 2022

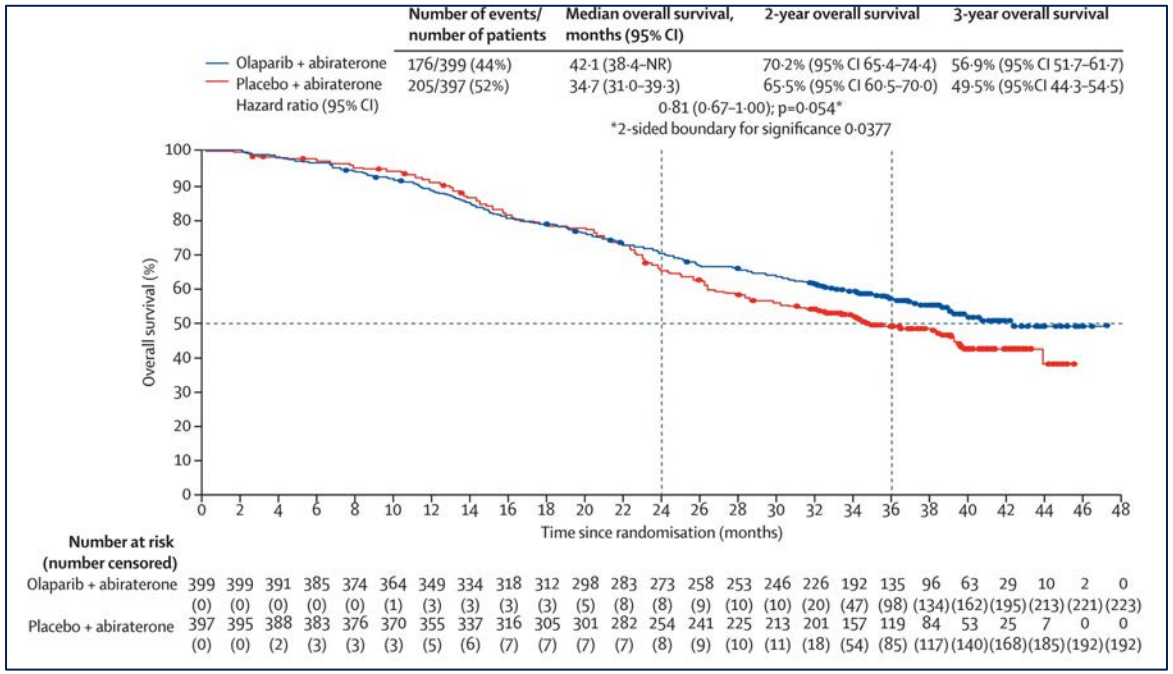
PROpel Randomized Phase 3 Study

Radiographic PFS by Investigator Assessment



All-comer population
(HRR-mutant + wild type + unknown)
Median rPFS 24.8 vs. 16.6 months
HR = 0.66, p < 0.001

Overall Survival at Final Analysis

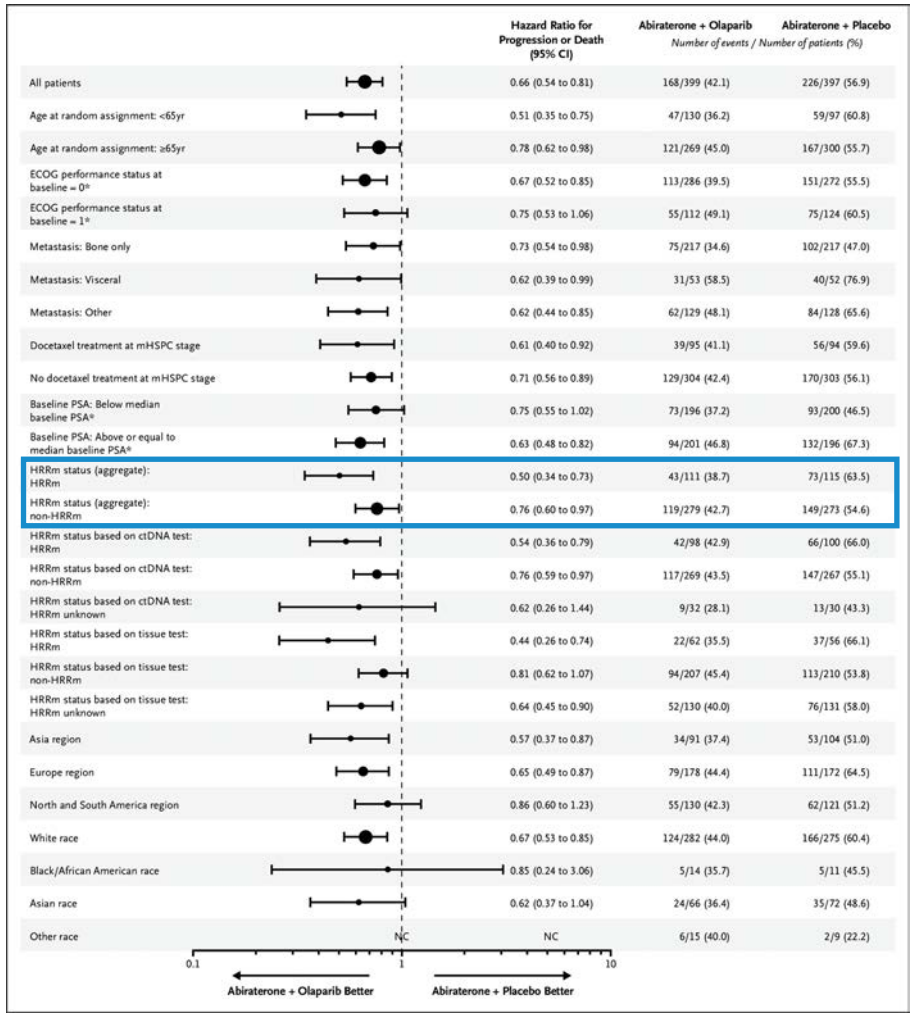


All-comer population
(HRR-mutant + wild type + unknown)
Median OS 42.1 vs. 34.7 months,
HR = 0.81, p = 0.054

Saad F, et al. Lancet Oncol 2023

PROpel Randomized Phase 3 Study: Subgroup Analysis

Radiographic PFS by Investigator Assessment

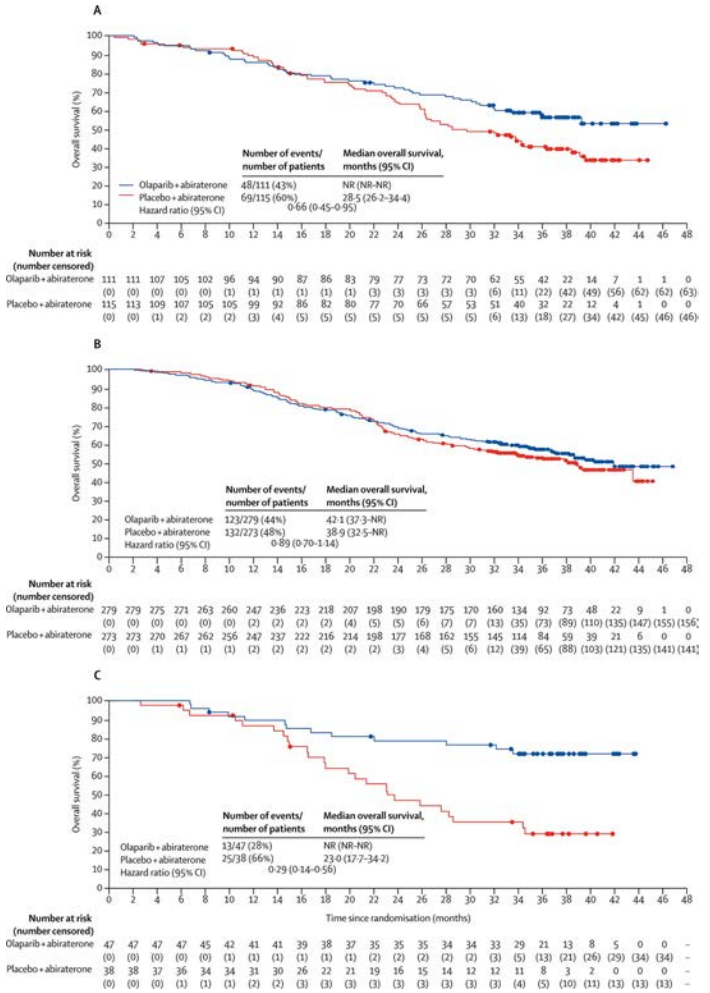


	Hazard Ratio for Progression or Death (95% CI)	Abiraterone + Olaparib *Number of events / Number of patients (%)*	Abiraterone + Placebo *Number of events / Number of patients (%)*
All patients	0.66 (0.54 to 0.81)	168/399 (42.1)	226/397 (56.9)
Age at random assignment: <65yr	0.51 (0.35 to 0.75)	47/130 (36.2)	59/97 (60.8)
Age at random assignment: ≥65yr	0.78 (0.62 to 0.98)	121/269 (45.0)	167/300 (55.7)
ECOG performance status at baseline = 0*	0.67 (0.52 to 0.85)	113/286 (39.5)	151/272 (55.5)
ECOG performance status at baseline = 1*	0.75 (0.53 to 1.06)	55/112 (49.1)	75/124 (60.5)
Metastasis: Bone only	0.73 (0.54 to 0.98)	75/217 (34.6)	102/217 (47.0)
Metastasis: Visceral	0.62 (0.39 to 0.99)	31/53 (58.5)	40/52 (76.9)
Metastasis: Other	0.62 (0.44 to 0.85)	62/129 (48.1)	84/128 (65.6)
Docetaxel treatment at mHSPC stage	0.61 (0.40 to 0.92)	39/95 (41.1)	56/94 (59.6)
No docetaxel treatment at mHSPC stage	0.71 (0.56 to 0.89)	129/304 (42.4)	170/303 (56.1)
Baseline PSA: Below median baseline PSA*	0.75 (0.55 to 1.02)	73/196 (37.2)	93/200 (46.5)
Baseline PSA: Above or equal to median baseline PSA*	0.63 (0.48 to 0.82)	94/201 (46.8)	132/196 (67.3)
HRRm status (aggregate): HRRm	0.50 (0.34 to 0.73)	43/111 (38.7)	73/115 (63.5)
HRRm status (aggregate): non-HRRm	0.76 (0.60 to 0.97)	119/279 (42.7)	149/273 (54.6)
HRRm status based on ctDNA test: HRRm	0.54 (0.36 to 0.79)	42/98 (42.9)	66/100 (66.0)
HRRm status based on ctDNA test: non-HRRm	0.76 (0.59 to 0.97)	117/269 (43.5)	147/267 (55.1)
HRRm status based on ctDNA test: HRRm unknown	0.62 (0.26 to 1.44)	9/32 (28.1)	13/30 (43.3)
HRRm status based on tissue test: HRRm	0.44 (0.26 to 0.74)	22/62 (35.5)	37/56 (66.1)
HRRm status based on tissue test: non-HRRm	0.81 (0.62 to 1.07)	94/207 (45.4)	113/210 (53.8)
HRRm status based on tissue test: HRRm unknown	0.64 (0.45 to 0.90)	52/130 (40.0)	76/131 (58.0)
Asia region	0.57 (0.37 to 0.87)	34/91 (37.4)	53/104 (51.0)
Europe region	0.65 (0.49 to 0.87)	79/178 (44.4)	111/172 (64.5)
North and South America region	0.86 (0.60 to 1.23)	55/130 (42.3)	62/121 (51.2)
White race	0.67 (0.53 to 0.85)	124/282 (44.0)	166/275 (60.4)
Black/African American race	0.85 (0.24 to 3.06)	5/14 (35.7)	5/11 (45.5)
Asian race	0.62 (0.37 to 1.04)	24/66 (36.4)	35/72 (48.6)
Other race	NC	NC	6/15 (40.0)	2/9 (22.2)

0.1 — 1 — 10

Abiraterone + Olaparib Better | Abiraterone + Placebo Better

Overall Survival at Final Analysis

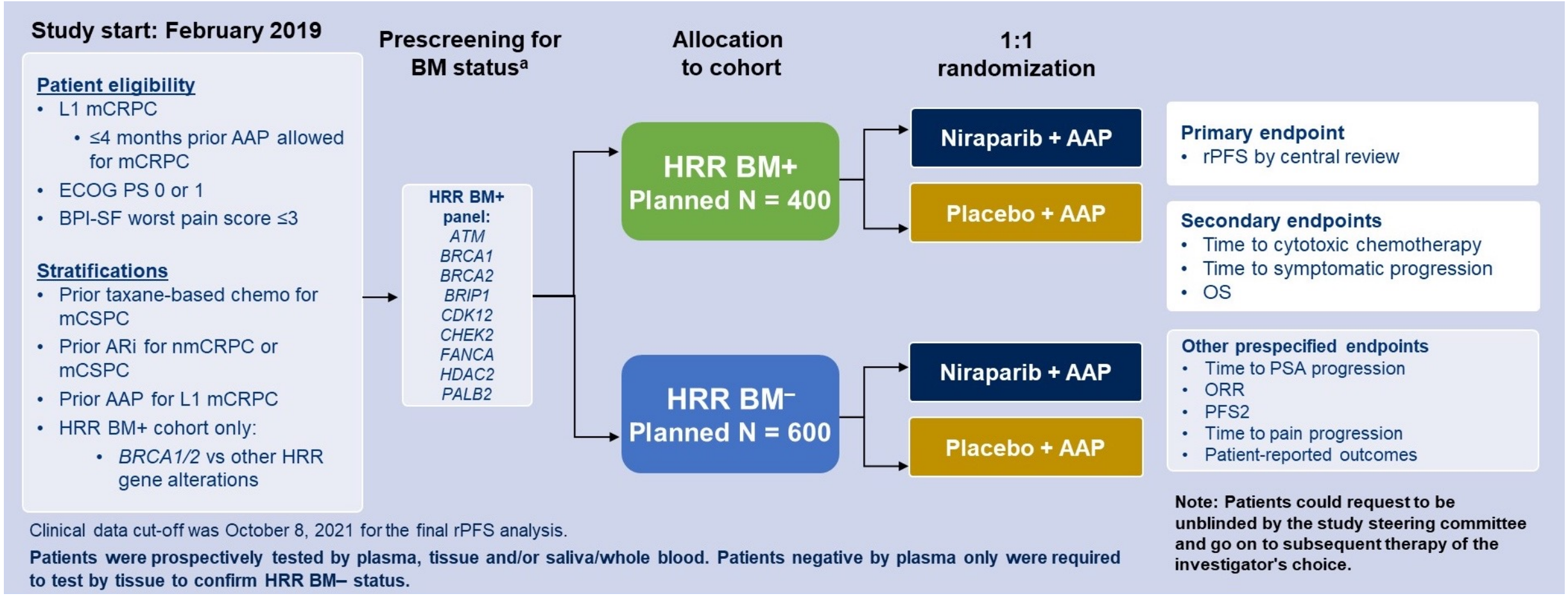


HRR-Mutant
HR = 0.66

HRR-wild type
HR = 0.89

BRCAm
HR = 0.29

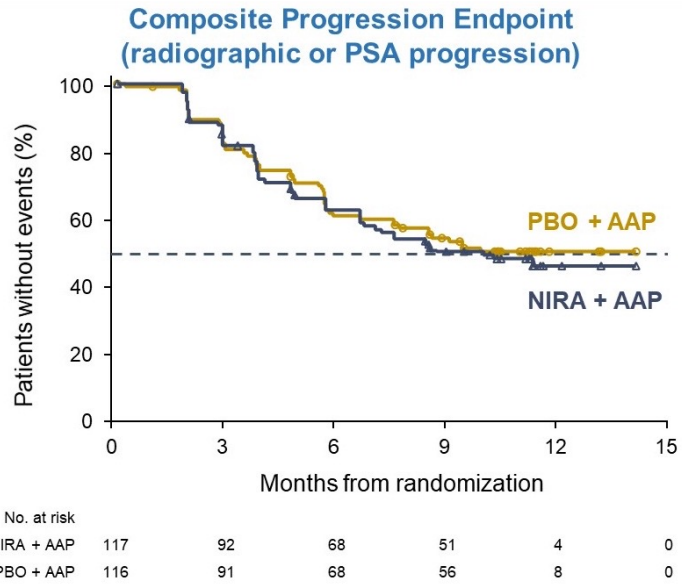
MAGNITUDE Phase 3 Trial



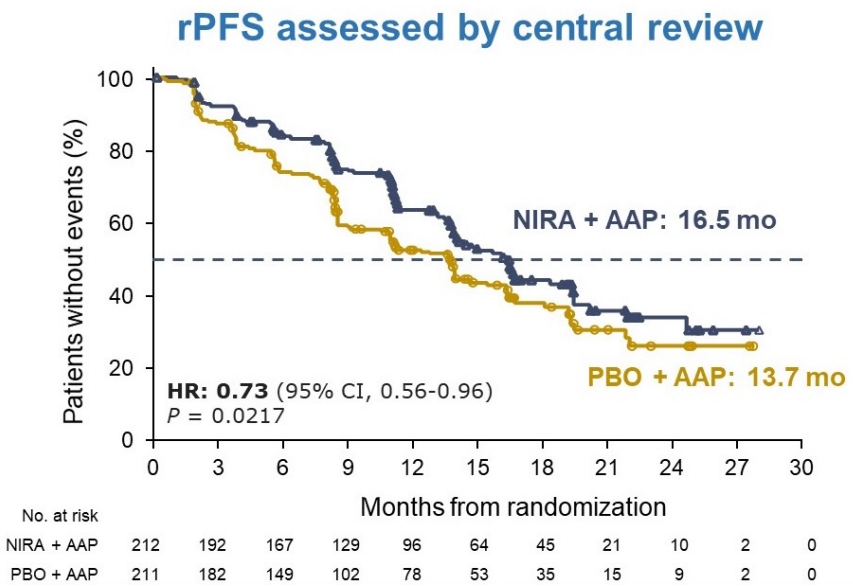
Chi K, et al. ASCO GU 2022

MAGNITUDE Phase 3 Trial

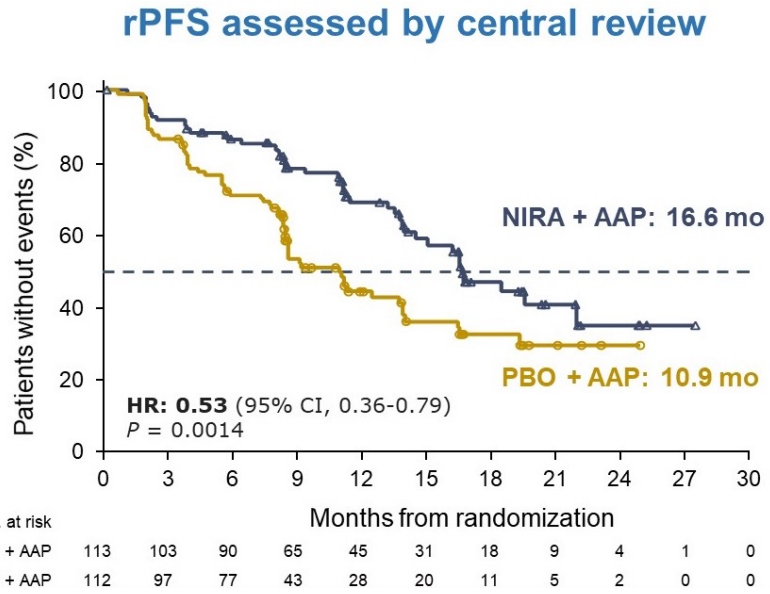
HRR negative:
Stopped for futility



HRR-mutated

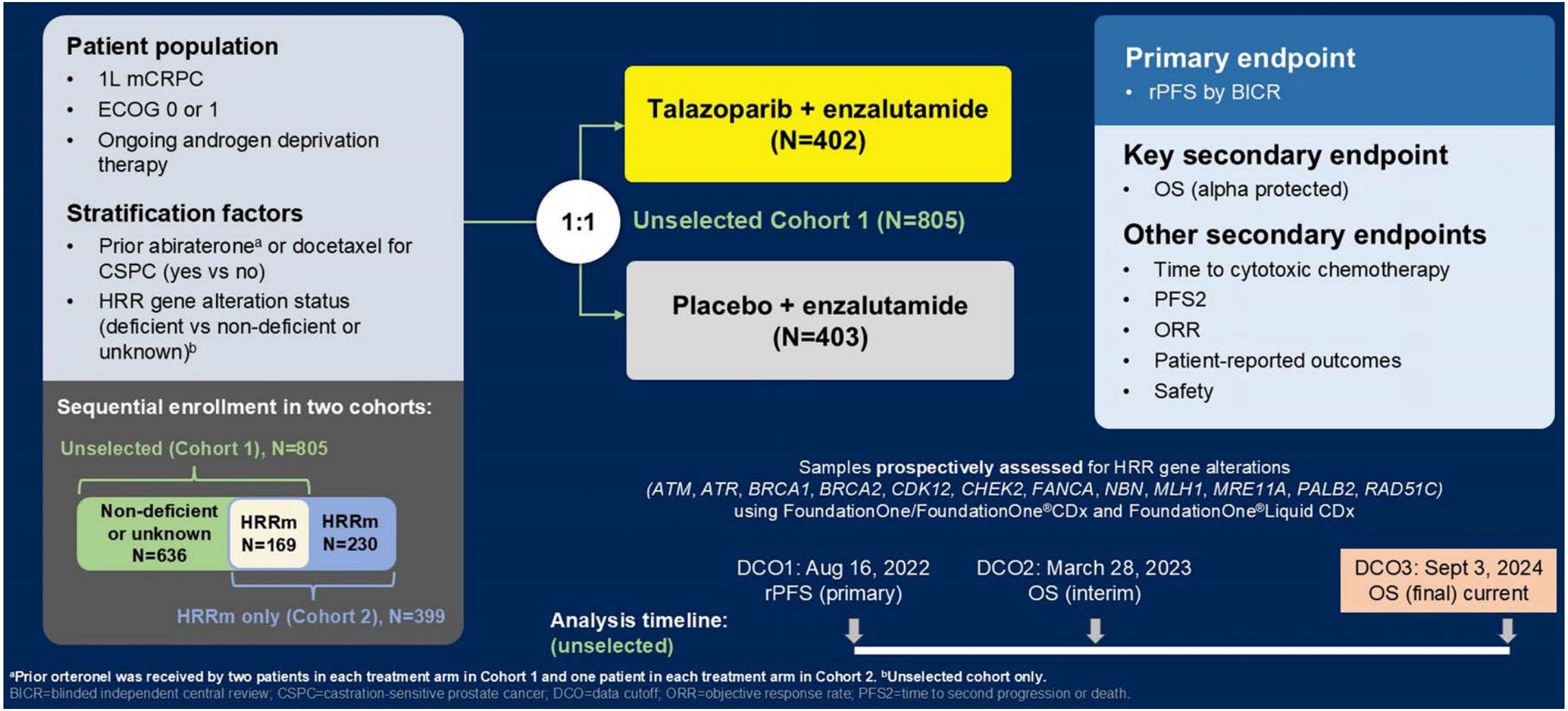


BRCA1/2-mutant



Chi K, et al. ASCO GU 2022

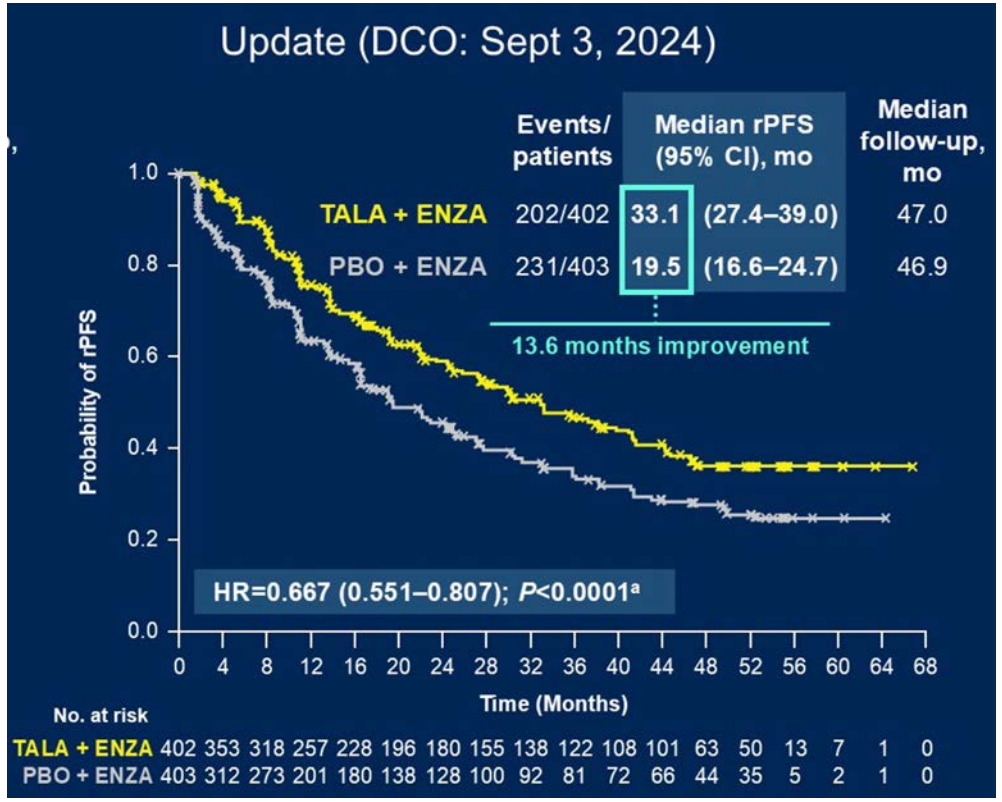
TALAPRO-2



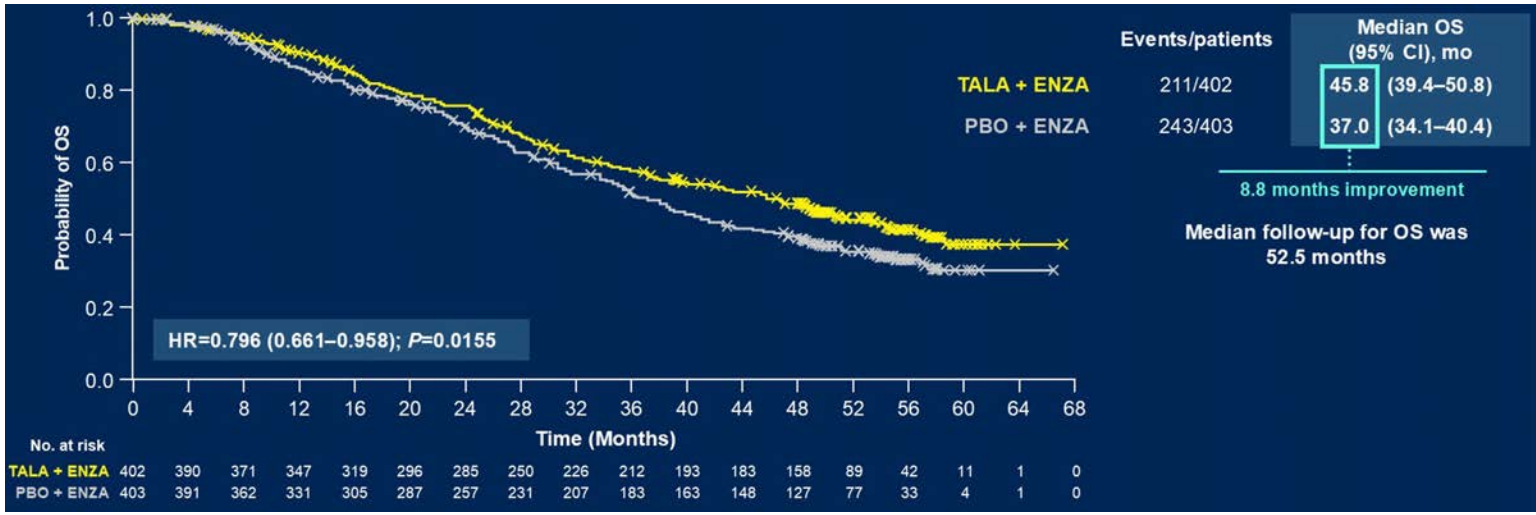
Agarwal N, et al. ASCO GU 2025

TALAPRO-2: Unselected Cohort (HRR wild type + mutant + unknown)

Radiographic PFS by Central Review



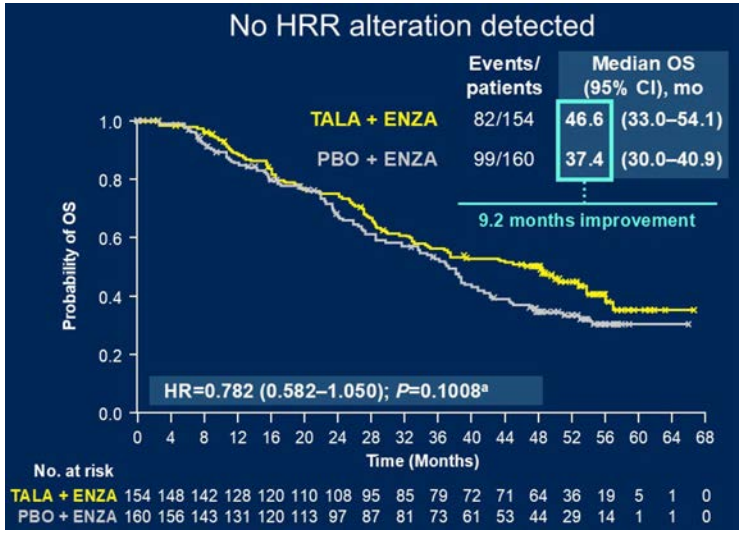
Overall Survival – Updated Analysis



Agarwal N, et al. ASCO GU 2025

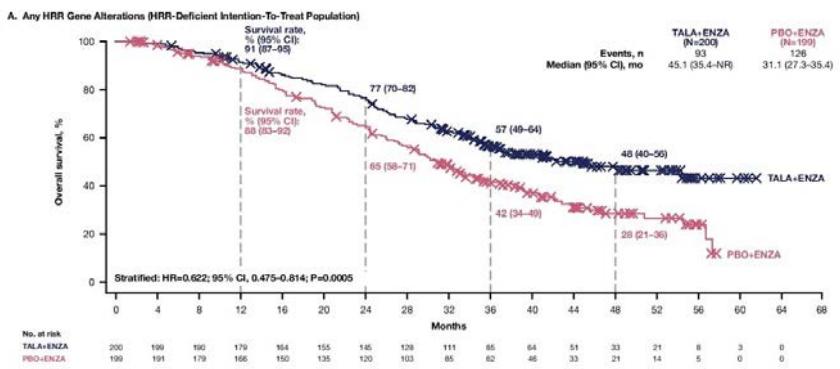
TALAPRO-2: Subgroup Analyses for OS Endpoint

Known Wild Type[1] (ctDNA AND Tissue)



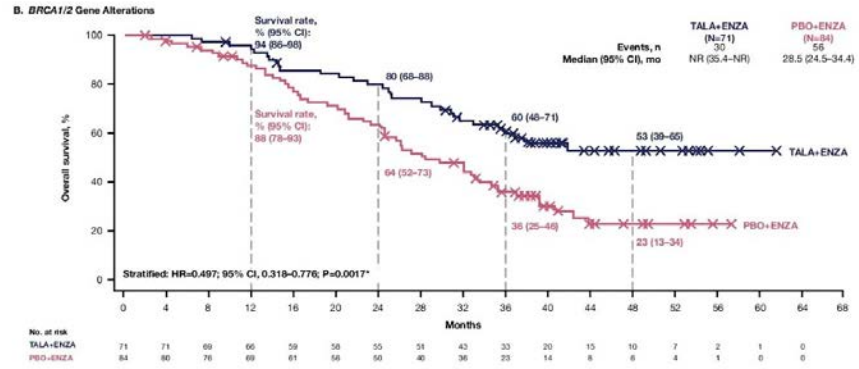
HR = 0.782, nominal p = 0.10

Any HRR alteration[2]



HR = 0.622, p = 0.0005

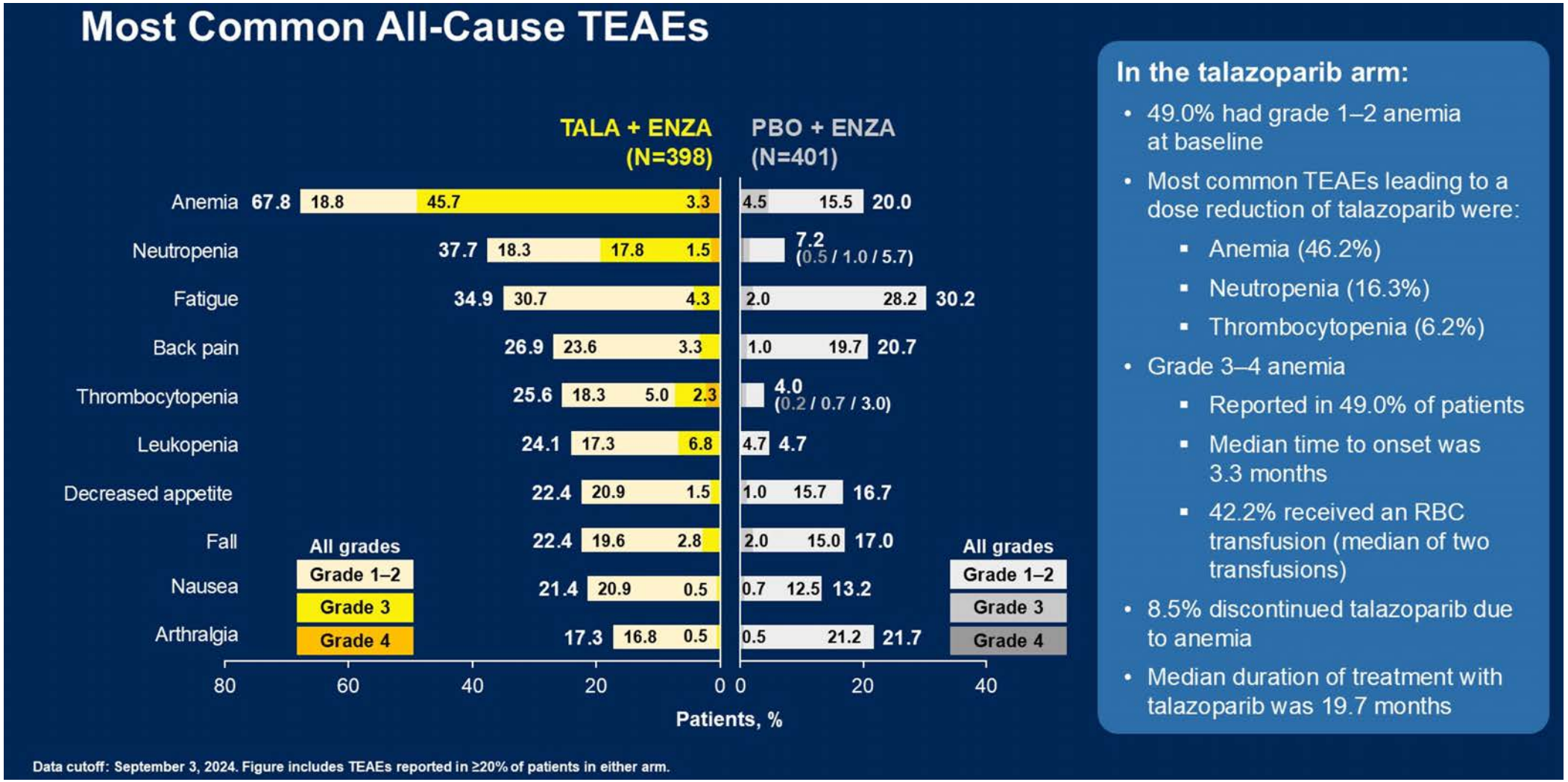
BRCA1/2 Mutated[2]



HR = 0.497, nominal p = 0.0017

1. Agarwal N, et al. ASCO GU 2025; 2. Fizazi K et al. ASCO GU 2025

TALAPRO-2: Safety



Agarwal N, et al. ASCO GU 2025

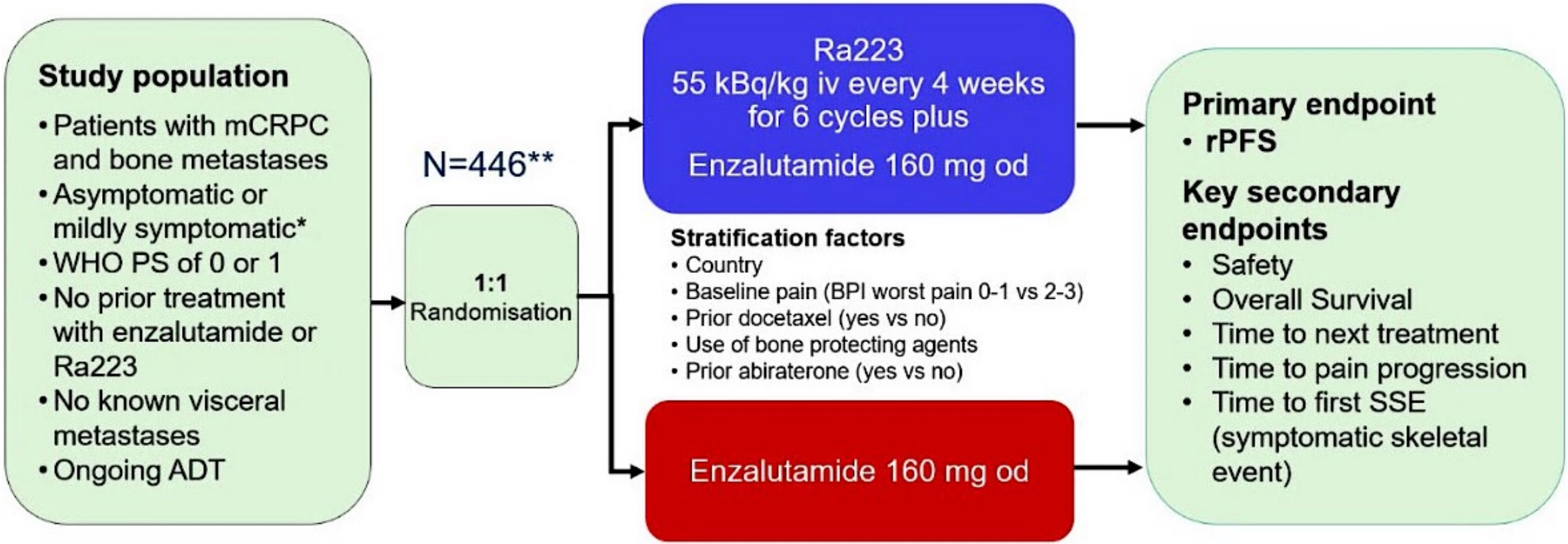
Summary: AR + PARP inhibition

- Both germline + somatic genomic testing is necessary to optimally identify *HRR*-mutant mCRPC
- AR + PARP inhibition improves PFS and OS in first-line HRR-mutant mCRPC
  - *BRCA/PALB2 > CDK12 >> ATM, CHEK2*
- Updated results of TALAPRO-2 first to demonstrate potential OS benefit in HRR-wild type mCRPC, but caveats:
  - Smaller magnitude of benefit
  - Need to carefully weigh risks/benefits of treatment

Outline

- Combining AR Pathway + PARP Inhibition in mCRPC
- Radiopharmaceuticals for the treatment of mCRPC
- Emerging Treatment Options
  - Immune checkpoint inhibition (CONTACT-02)
  - EZH2 Inhibition
  - Bi-specific T-cell engagers

PEACE-3



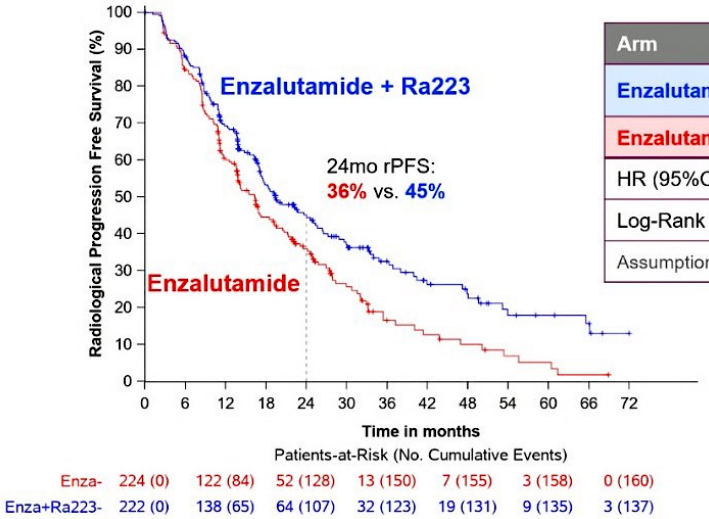
*defined as brief pain inventory WP24 score < 4
** original target accrual N=560, adapted for slow accrual

Use of bone protecting agents (BPA) made mandatory
(after inclusion of 119 patients)

Gillessen S, et al. ESMO 2024

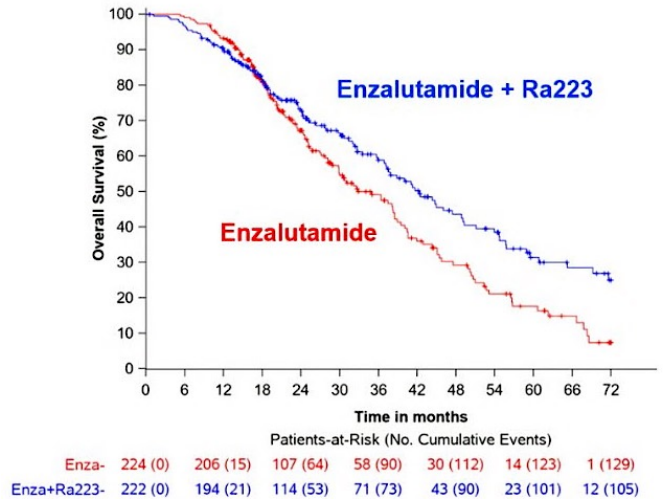
PEACE-3

Radiographic PFS



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	139/222	**19.4** (17.1-25.3) mo
Enzalutamide	160/224	**16.4** (13.8-19.2) mo
HR (95%CI)	**0.69** (0.54-0.87)	
Log-Rank p-value	**0.0009**	
Assumption of proportional hazard achieved		

Overall Survival



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	110/222	**42.3** (36.8-49.1) mo
Enzalutamide	129/224	**35.0** (28.8-38.9) mo
HR (95%CI)	**0.69** (0.52-0.90)	
Log-Rank p-value	**0.0031**	<0.0034

- Pre-set level of significance for interim analysis was ≤ 0.0034
- Due to non-proportional hazards plus lack of unequivocal significance for RMST (restricted mean survival time) sensitivity analysis, study will continue to final OS analysis

Gillessen S, et al. ESMO 2024

PEACE-3

Most common grade 3-5 treatment emergent AE (TEAE)	Enza+Ra223 (N=218) N (%)	Enza (N=224) N (%)
All		
Hypertension	73 (33.5)	77 (34.4)
Fatigue	12 (5.5)	4 (1.8)
Fracture	11 (5.1)	3 (1.3)
Anaemia	10 (4.6)	5 (2.2)
Neutropenia	10 (4.6)	0
Bone Pain	9 (4.1)	11 (4.9)
Weight Decreased	7 (3.2)	1 (0.4)
Spinal Cord Compression	6 (2.8)	8 (3.6)
Treatment related		
Hypertension	25 (11.5)	27 (12.1)
Fatigue	9 (4.1)	3 (1.3)
Anaemia	6 (2.8)	0
Neutropenia	7 (3.2)	0

Side effects of special interest: 1 MDS, 1 AML and 1 CML in the combination arm

Gillessen S, et al. ESMO 2024

VISION

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

2:1

Protocol-permitted SOC + ^{177}Lu-PSMA-617
7.4 GBq (200 mCi) every 6 weeks
4 cycles, increasable to 6

Protocol-permitted SOC alone

Treatment → Follow-up → Final analysis

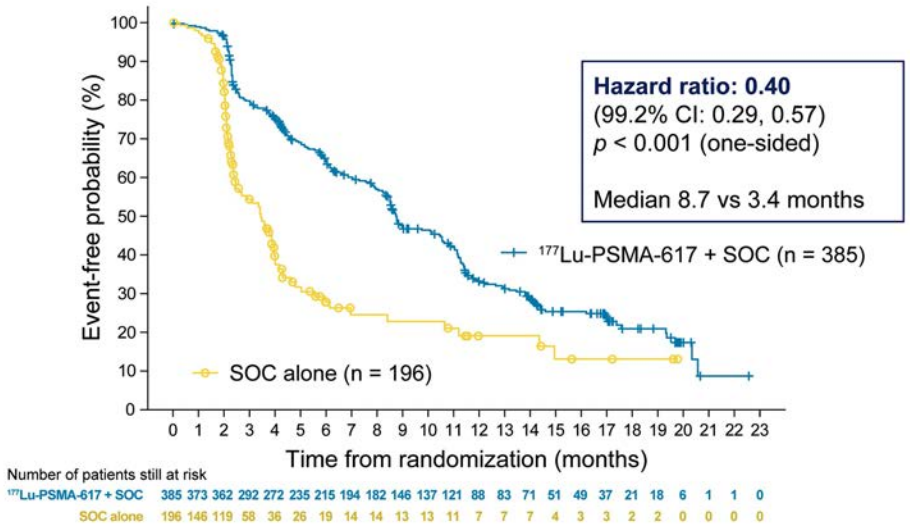
- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

Morris M, et al. ASCO 2021

VISION

Radiographic PFS

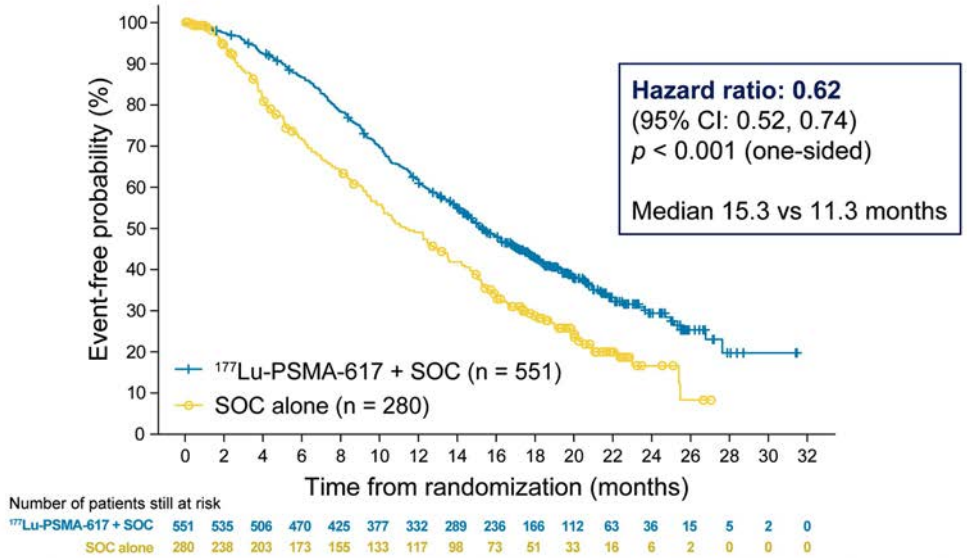
Primary analysis
rPFS analysis set (n = 581)



HR = 0.40, p < 0.001

Overall Survival

Primary analysis
All randomized patients (N = 831)



HR = 0.62, p < 0.001

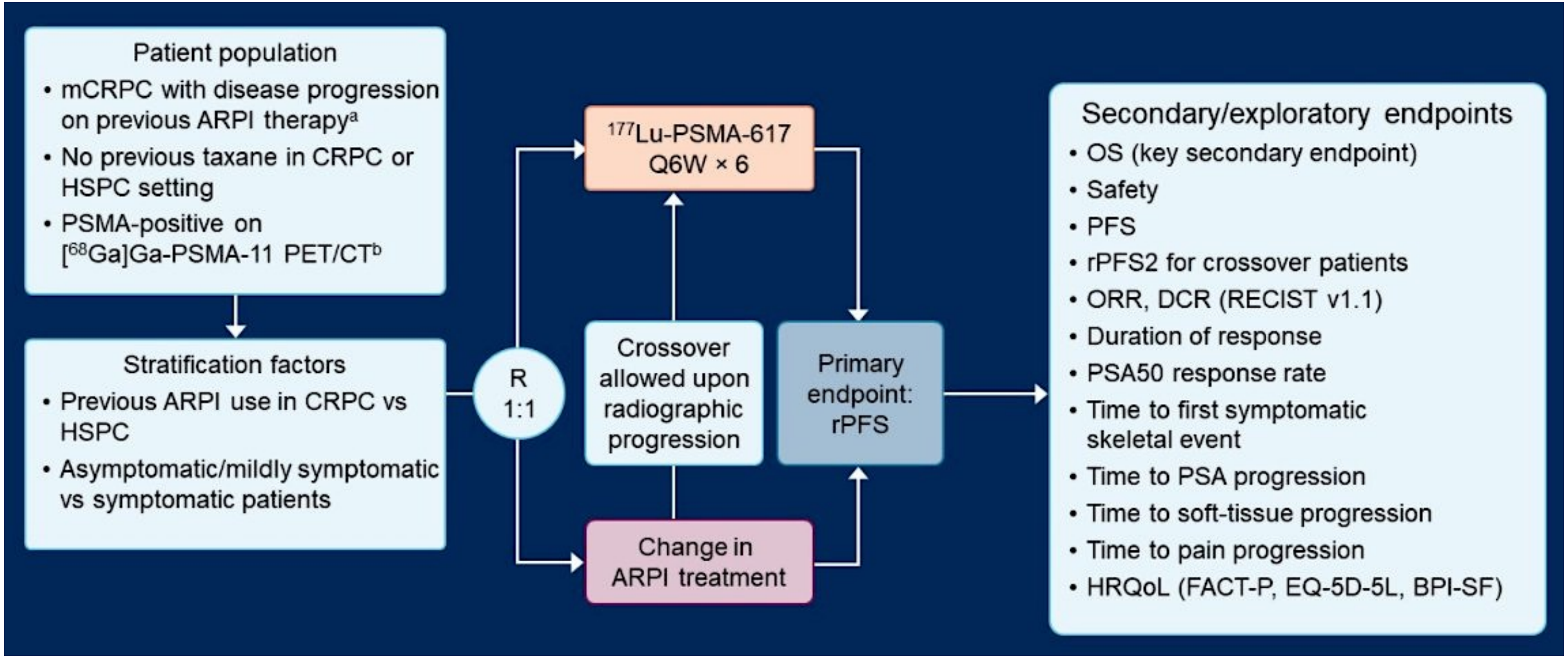
Morris M, et al. ASCO 2021

VISION

Patients, n (%)	All grades		Grade 3–5	
	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

Morris M, et al. ASCO 2021

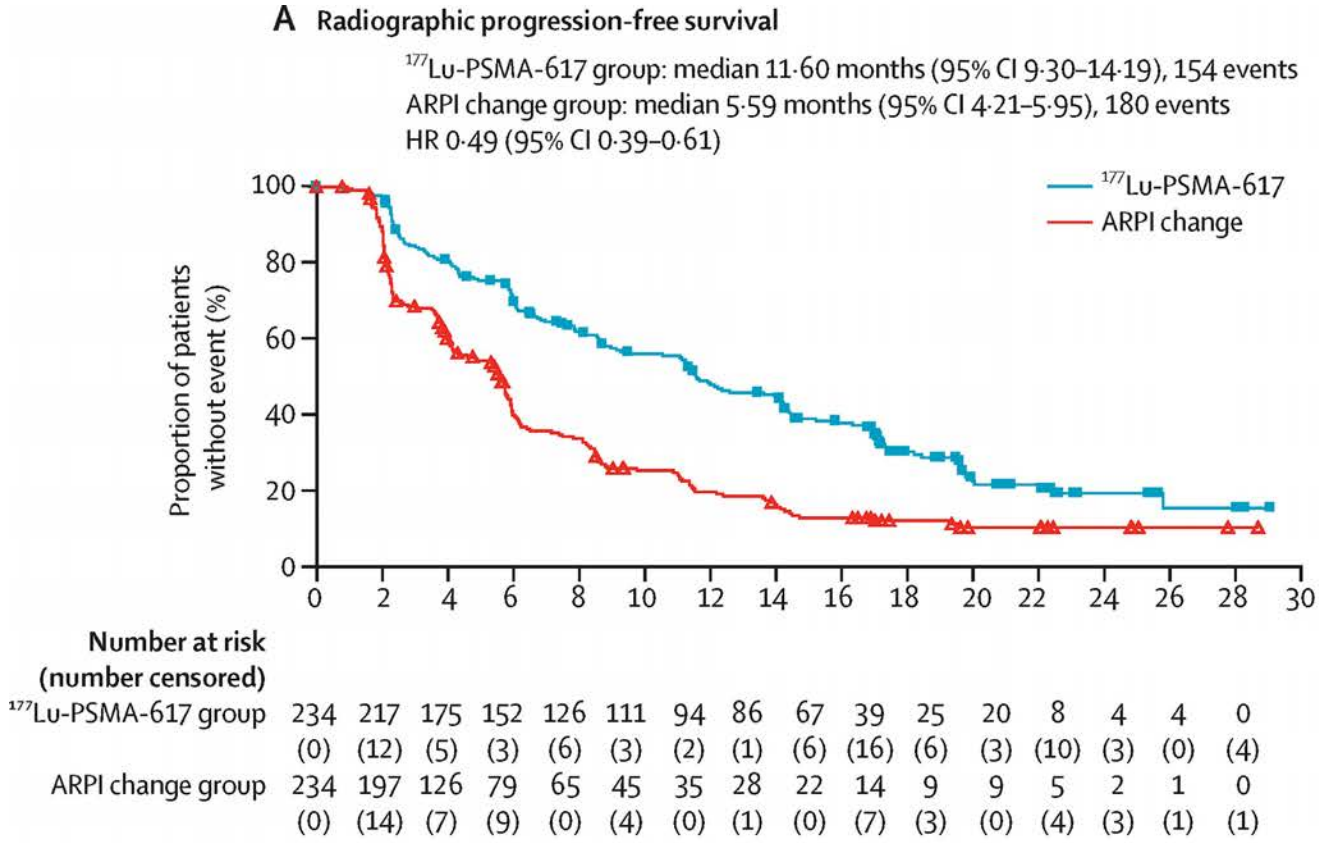
PSMAfore



Sartor O, et al. ESMO 2023

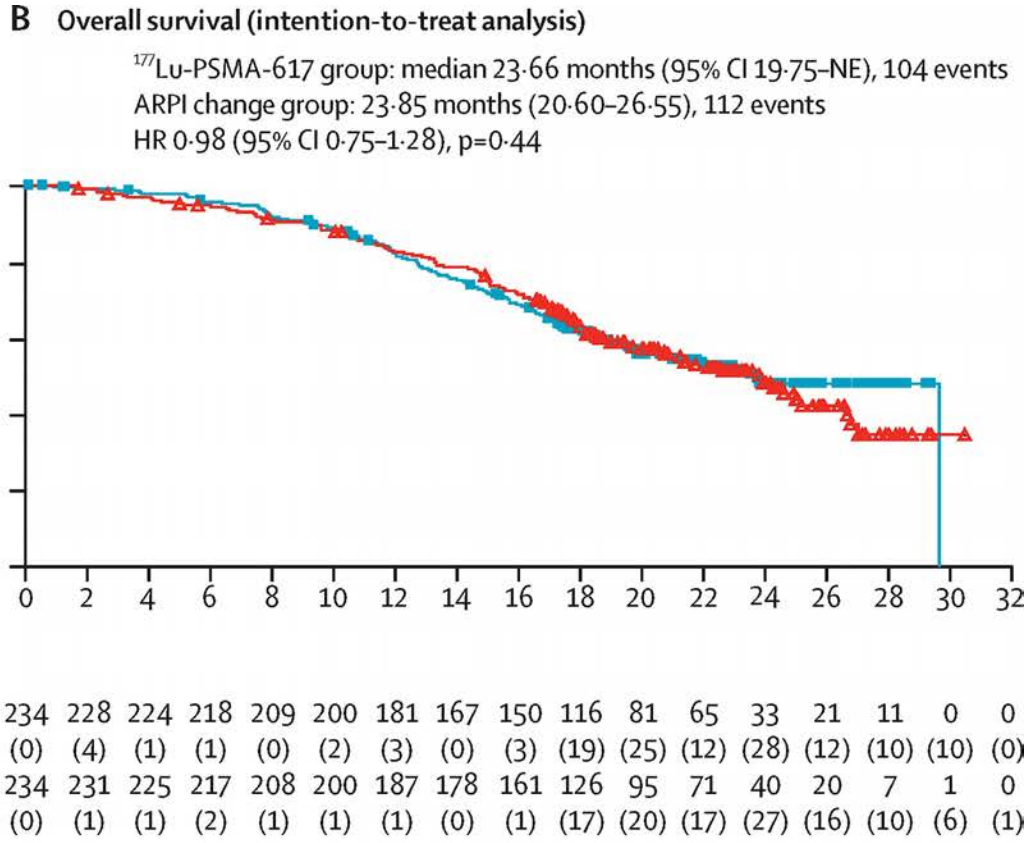
PSMAfore

Radiographic PFS



HR = 0.49 (95% CI: 0.39–0.61)
Median 11.6 versus 5.6 months

Overall Survival



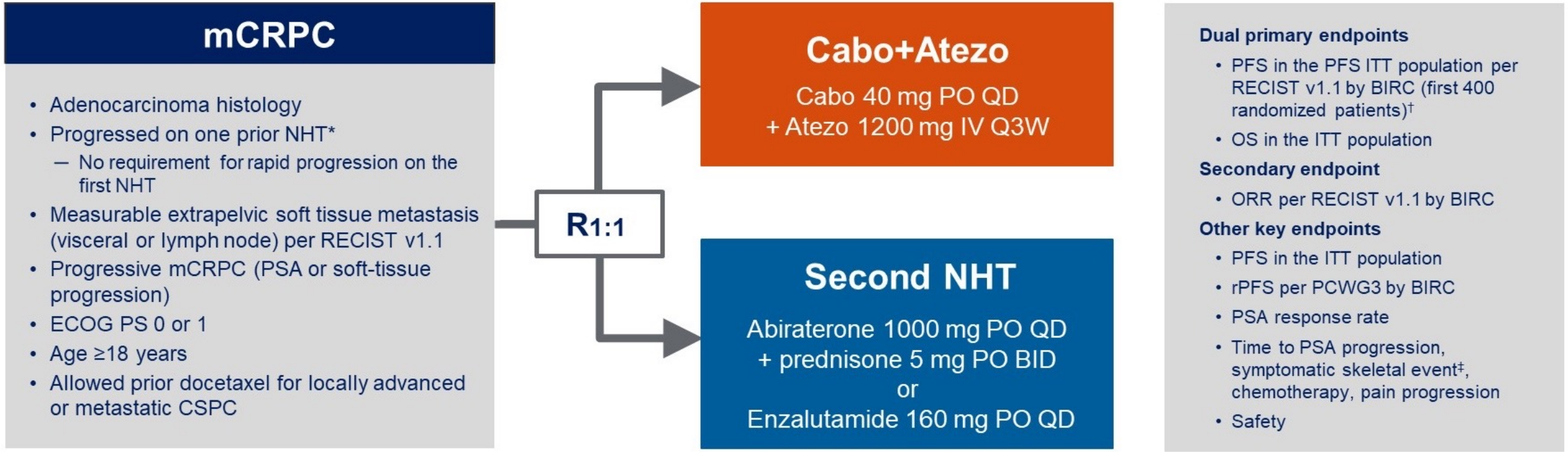
HR = 0.98 (95% CI: 0.75–1.28)
Median 23.7 versus 23.9 months

Morris M, et al. Lancet 2024

Outline

- Combining AR Pathway + PARP Inhibition in mCRPC
- Radiopharmaceuticals for the treatment of mCRPC
- Emerging Treatment Options
  - Immune checkpoint inhibition (CONTACT-02)
  - EZH2 Inhibition
  - Bi-specific T-cell engagers

CONTACT-02

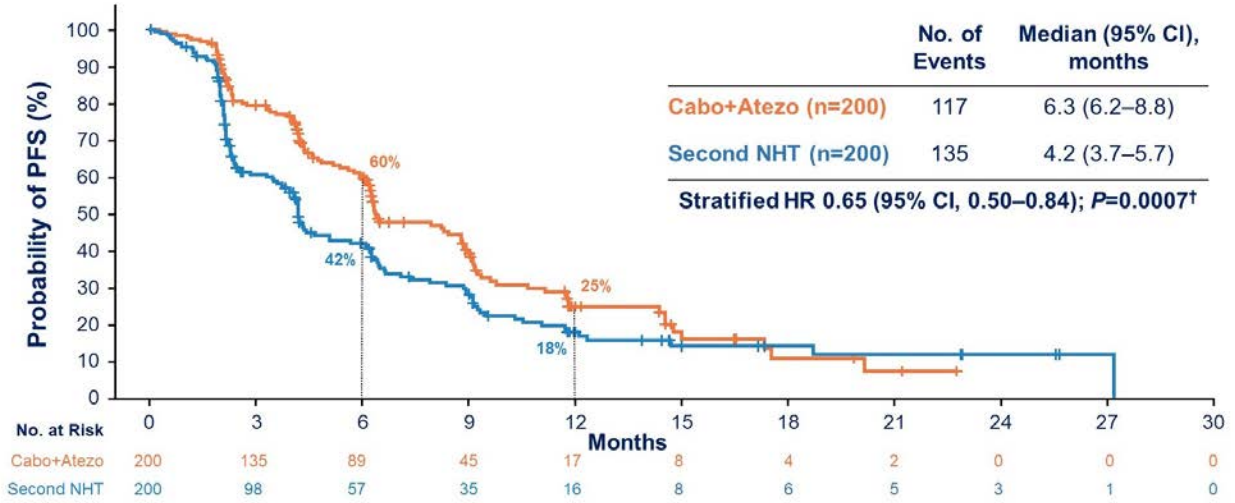


NHT = novel hormonal therapy

Agarwal N, et al. ASCO GU 2024

CONTACT-02

Radiographic PFS

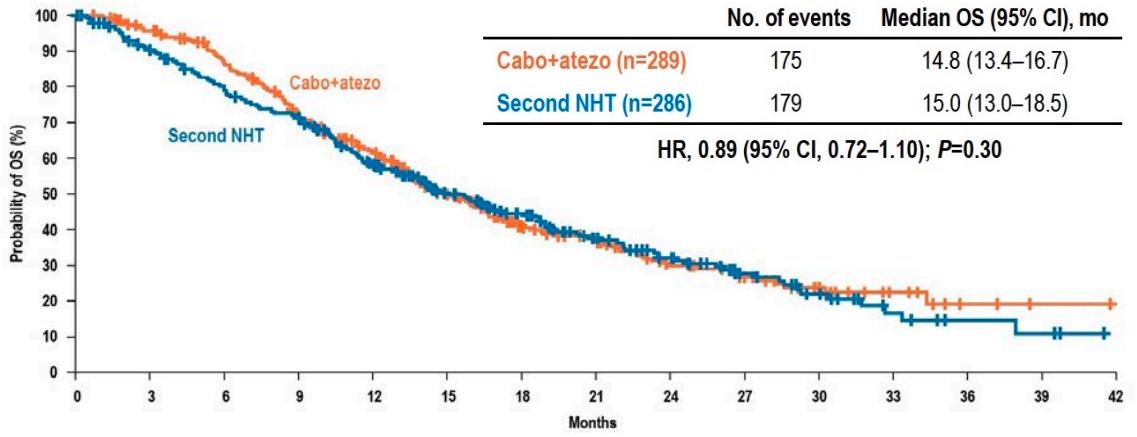


	No. of Events	Median (95% CI), months
Cabo+Atezo (n=200)	117	6.3 (6.2–8.8)
Second NHT (n=200)	135	4.2 (3.7–5.7)

Stratified HR 0.65 (95% CI, 0.50–0.84); *P*=0.0007†

- **Median PFS per BIRC (ITT): 6.3 vs 4.2 mo (HR 0.64 [95% CI, 0.50–0.81]; *P*=0.0002)**
- Median rPFS per PCWG3 in PFS ITT population: 6.3 vs 4.1 mo (HR, 0.62 [95% CI, 0.48–0.81])

Final Overall Survival

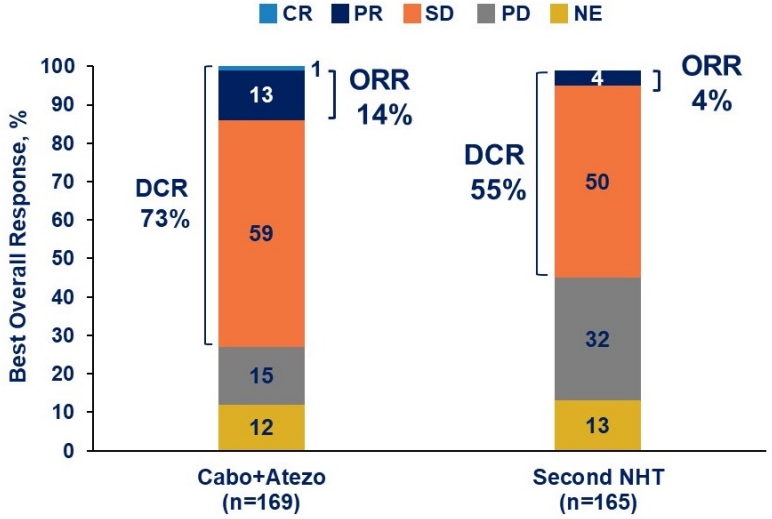


	No. of events	Median OS (95% CI), mo
Cabo+atezo (n=289)	175	14.8 (13.4–16.7)
Second NHT (n=286)	179	15.0 (13.0–18.5)

HR, 0.89 (95% CI, 0.72–1.10); *P*=0.30

Median follow-up (range): 24.0 (9.8–42.0) months

Objective Response Rate



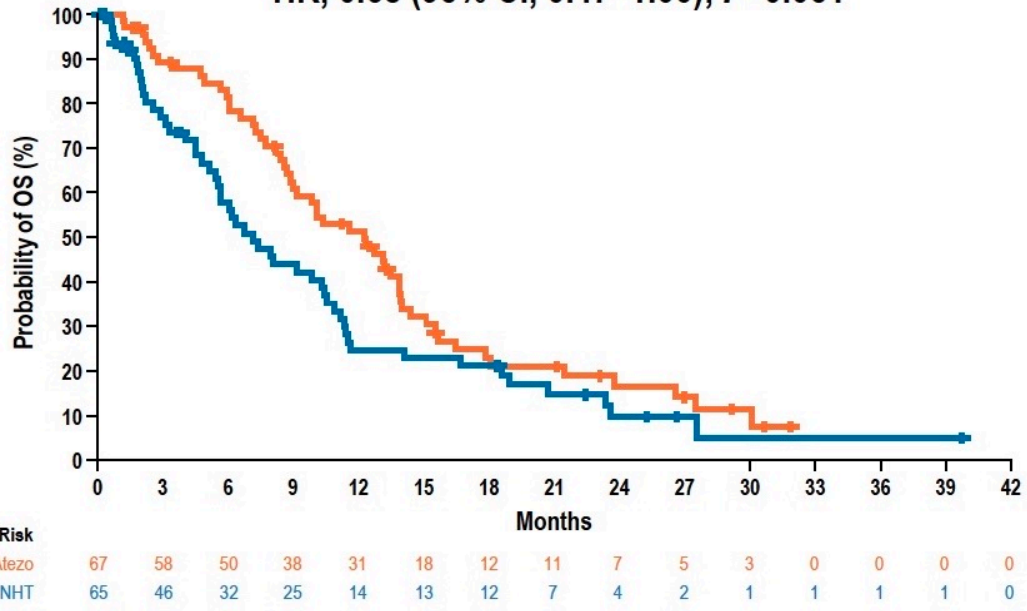
Agarwal N, et al. ASCO GU 2024
Agarwal N, et al. ESMO 2024

CONTACT-02: Final OS for Patients with Metastases

Liver Metastasis

Reduction in risk of death –32%

HR, 0.68 (95% CI, 0.47–1.00); *P*=0.051



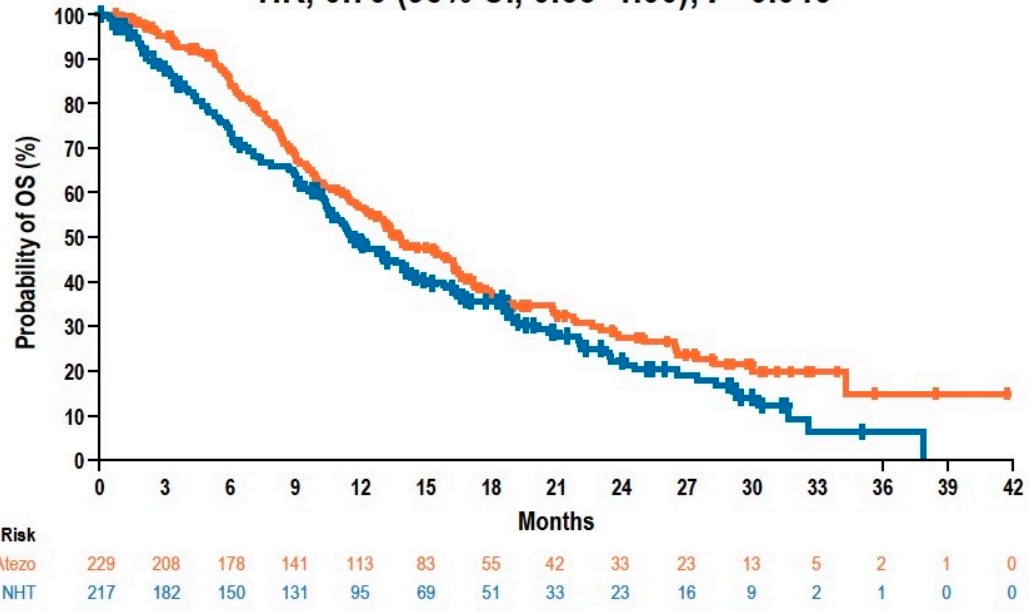
No. at Risk															
Cabo+Atezo	67	58	50	38	31	18	12	11	7	5	3	0	0	0	0
Second NHT	65	46	32	25	14	13	12	7	4	2	1	1	1	1	0

	No. of Events	Median OS mo (95% CI)
Cabo+Atezo (n=67)	53	12.2 (8.8–13.8)
Second NHT (n=65)	52	7.1 (5.3–10.4)

Bone Metastasis

Reduction in risk of death –21%

HR, 0.79 (95% CI, 0.63–1.00); *P*=0.046



No. at Risk															
Cabo+Atezo	229	208	178	141	113	83	55	42	33	23	13	5	2	1	0
Second NHT	217	182	150	131	95	69	51	33	23	16	9	2	1	0	0

	No. of Events	Median OS mo (95% CI)
Cabo+Atezo (n=229)	146	13.8 (11.9–16.3)
Second NHT (n=217)	156	11.6 (10.5–14.1)

Agarwal N, et al. ESMO 2024

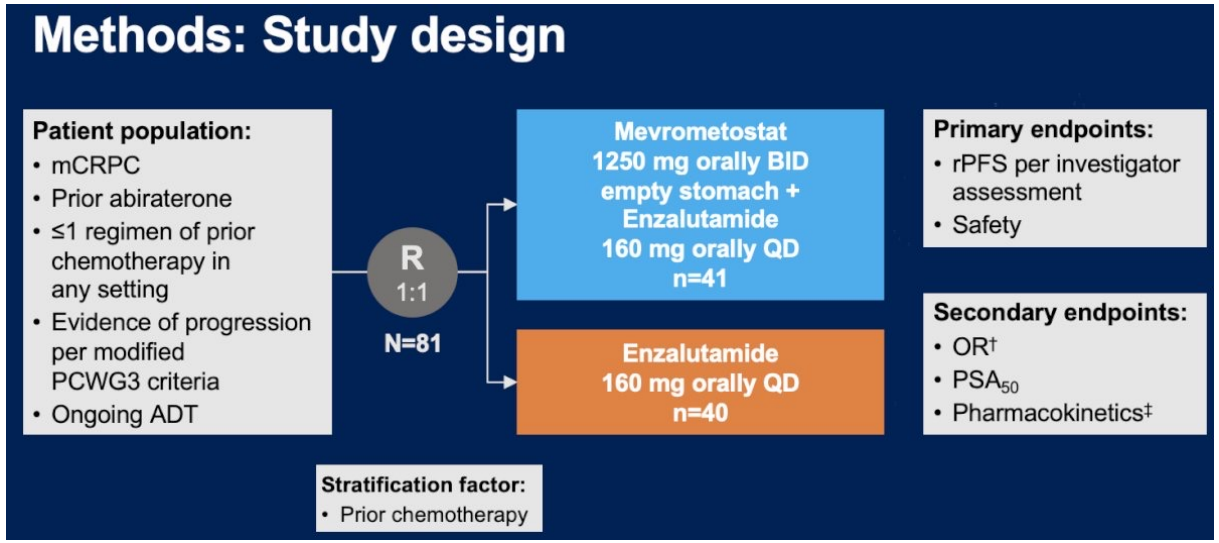
CONTACT-02: Safety

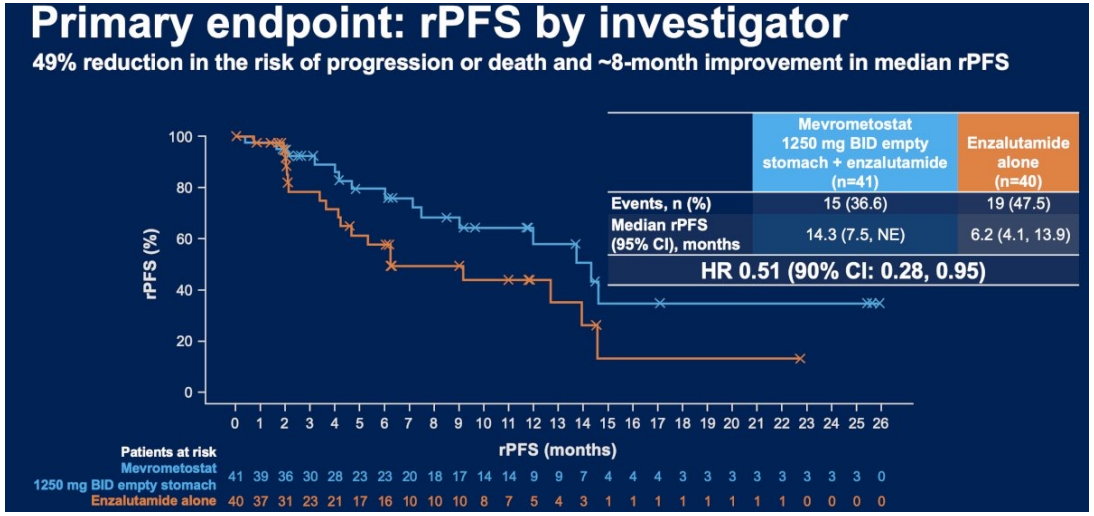
	Cabo+Atezo (n=284)		Second NHT (n=284)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any treatment-emergent AE	100%	56%	92%	26%
Any treatment-related AE	94%	40%	45%	8%
Treatment-emergent AEs occurring in ≥20%				
Diarrhea	48%	5%	7%	1%
Decreased appetite	40%	1%	15%	1%
Fatigue	30%	6%	20%	2%
Anemia	28%	8%	19%	6%
Nausea	28%	<1%	13%	<1%
Asthenia	28%	4%	14%	1%
Aspartate aminotransferase increased	25%	3%	6%	1%
Alanine aminotransferase increased	24%	3%	4%	1%
Hypothyroidism	23%	0%	1%	0%
Hypertension	21%	8%	7%	2%
Stomatitis	20%	2%	1%	0%

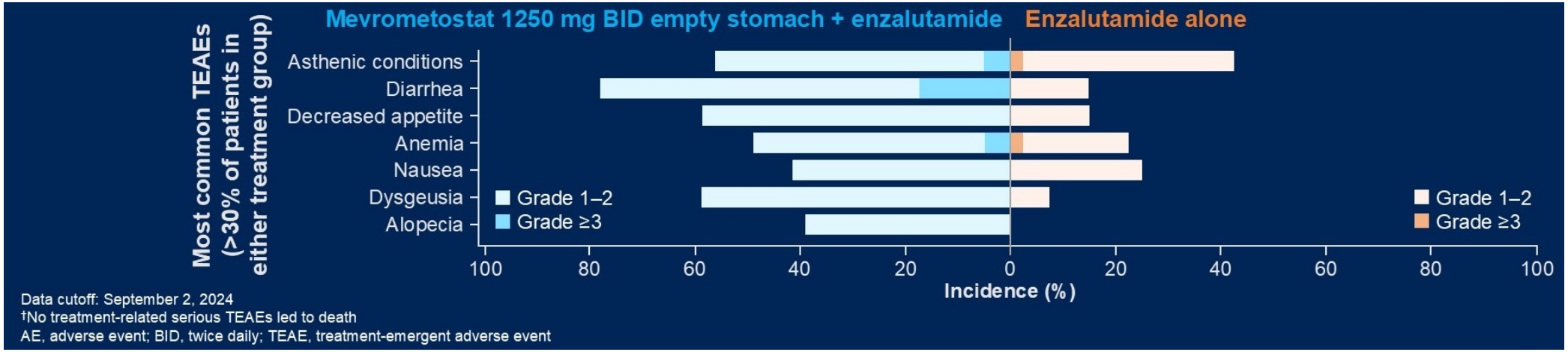
No treatment-related grade 5 adverse events occurred in either treatment arm.

Agarwal N, et al. ESMO 2024

Mevrometostat: EZH2 inhibitor



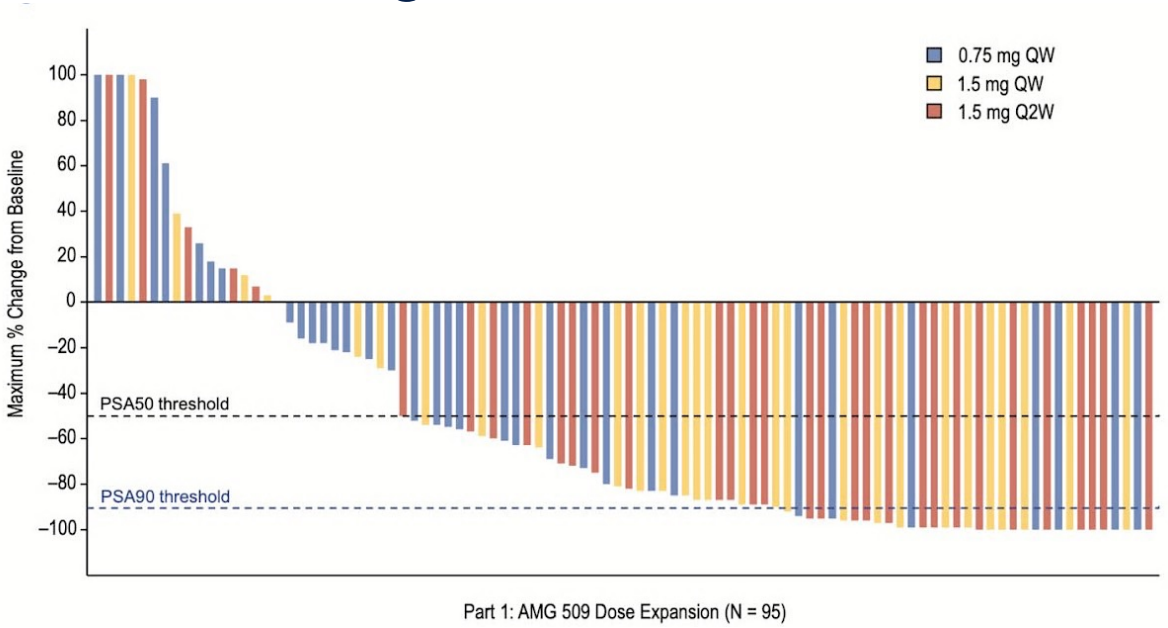


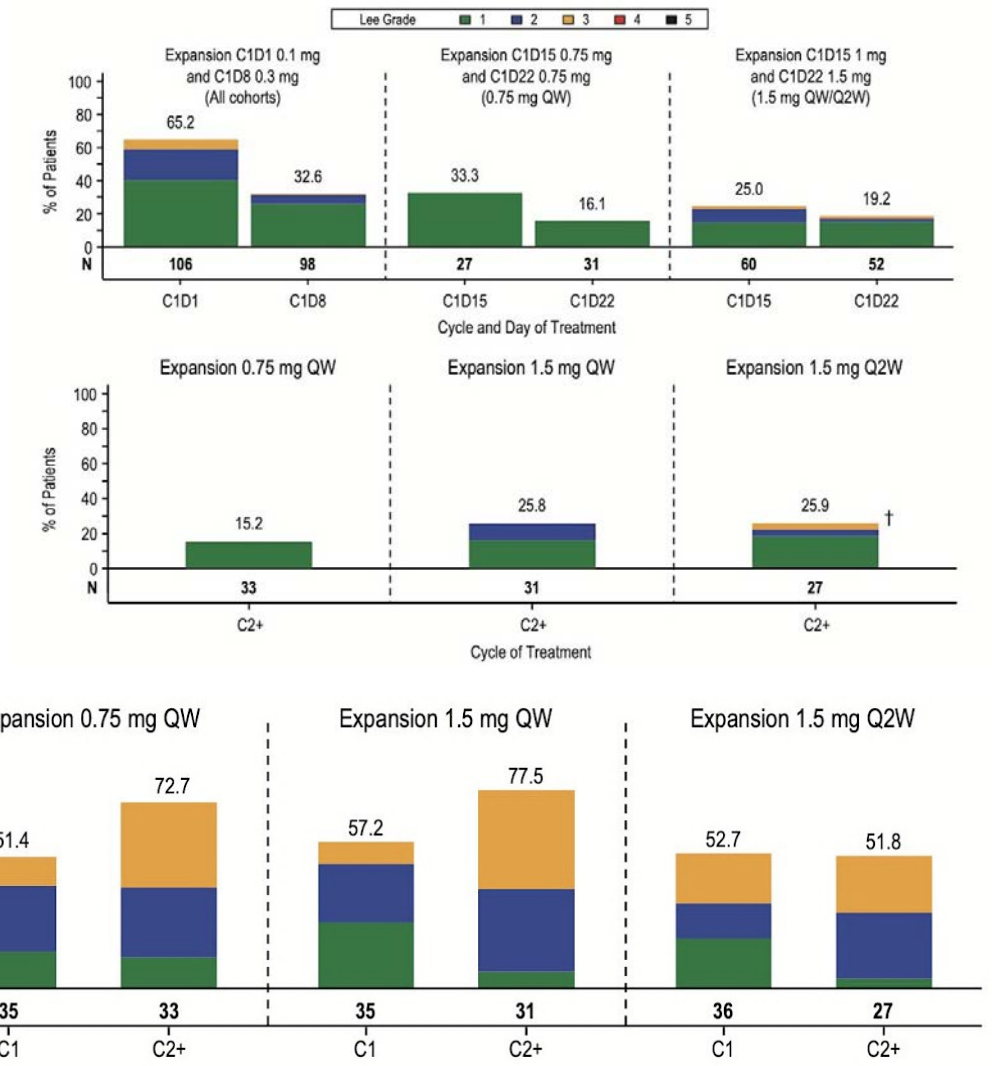


Schweizer M, et al. ASCO GU 2025

Xaluritamig: A Bispecific T-cell Engager Targeting STEAP1

PSA Change from Baseline





Kelly WK, et al. ESMO 2024

Summary: Emerging Treatment Options

- Atezolizumab + cabozantinib improves progression-free survival versus second ARPI in high-risk, taxane-naïve mCRPC
  - Caveats: ARPI switch comparator arm, modest PFS benefit, OS data immature

- Multiple promising therapeutic modalities and strategies for the treatment of mCRPC
  - Epigenetic modifiers: Polycomb repressor complex 2 (PRC2)
  - AR pathway inhibition (CYP11 inhibitor, AR degraders)
  - Homologous recombination repair pathway (PARP1 selective, pol theta inhibitors)
  - Antibody-drug conjugates: PSMA, STEAP1, B7-H3, CD46, DLL3
  - Bi-specific T-cell engagers
  - Novel radio-isotopes: ^{225}Ac, ^{212}Pb, ^{67}Cu

Discussion Question

- A 65-year-old man with a germline BRCA2 mutation undergoes external beam radiation therapy followed by 2 years of ADT and abiraterone for locally advanced (N1) prostate cancer. Five years later he is found to have widespread, moderately symptomatic bone metastases (PSMA-positive). What systemic treatment would you most likely recommend?

- A 65-year-old man with a germline BRCA2 mutation presents with mHSPC to the bone and receives apalutamide and ADT with response then progression (PSMA-positive). What systemic treatment would you most likely recommend?

-

Discussion Questions

- A 65-year-old man with mHSPC to the bone and lungs receives ADT and abiraterone but experiences disease progression 18 months later (PSMA-positive, HRR-negative). What systemic treatment would you most likely recommend?

We are taking a short break!

The program will resume at 3:50 PM ET

Up Next…

Drs Mitesh J Borad and Amit Mahipal discuss the management of biliary tract cancers

RTP
RESEARCH
TO PRACTICE