Novinky z ASCO 2025

Svoboda T.

2025 ASCO ANNUAL MEETING

LBA1

LBA1: **Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair** (dMMR) **colon cancer** (Alliance A021502; ATOMIC)

Frank A. Sinicrope, Fang-Shu Ou, Dirk Arnold, Walter R. Peters, Robert J. Behrens, Christopher H. Lieu, Khalid Matin, Deirdre J. Cohen, Samara L. Potter, Wendy L. Frankel, Ardaman Shergill, Dennis Hsu, Anke C. Reinacher-Schick, Tyler Zemla, Clare A. Gatten, Eileen O'Reilly, Jeffrey A. Meyerhardt

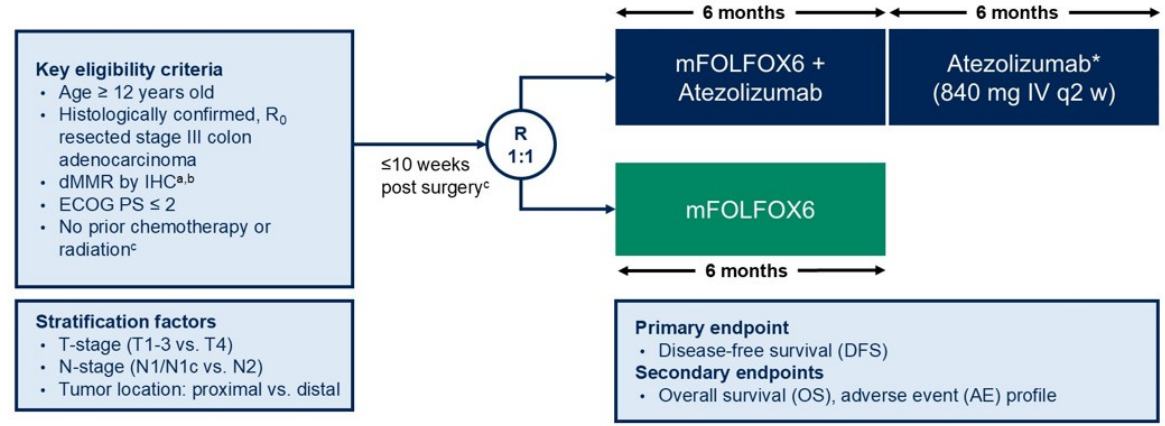
Background

- Standard adjuvant chemotherapy for stage III colon cancer (node positive) consists of a fluoropyrimidine + oxaliplatin regardless of mismatch repair (MMR) status
- ~ 15% of colon cancers have deficient MMR (dMMR) and may display resistance to fluoropyrimidines[1-5]
- Despite adjuvant chemotherapy, approximately 30% of stage III patients will experience recurrence of their cancer
- While approved for dMMR metastatic cancers, it is unknown if an immune checkpoint inhibitor will improve outcomes after surgical resection of dMMR stage III colon cancer

1. Grady & Markowitz. Dig Dis Sci 2015; 2. Boland & Goel. Gastroenterology 2010; 3. Roth et al. J Clin Oncol 2010;
4. Gutierrez et al. JCO Precis Oncol 2023; 5. Sinicrope FA, Sargent DJ. Clin Cancer Res. 2012;18:1506–1512

Study Design

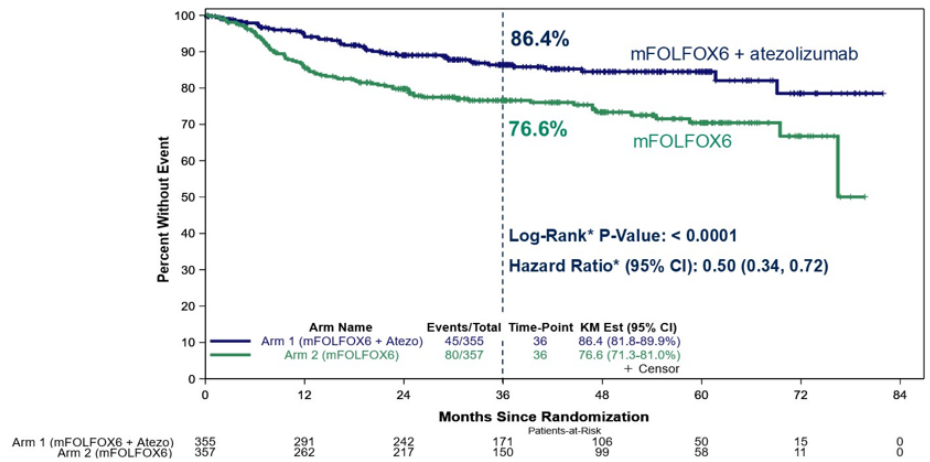
ATOMIC is a randomized, multicenter, open label phase 3 study



[a] **dMMR by immunohistochemistry (IHC) locally or at site-selected reference laboratory. Retrospective central confirmation of dMMR also performed.**
[b] Lynch syndrome included.
[c] One cycle of mFOLFOX6 prior to randomization permitted.

*Atezolizumab (anti-PD-L1)

Primary Endpoint: DFS



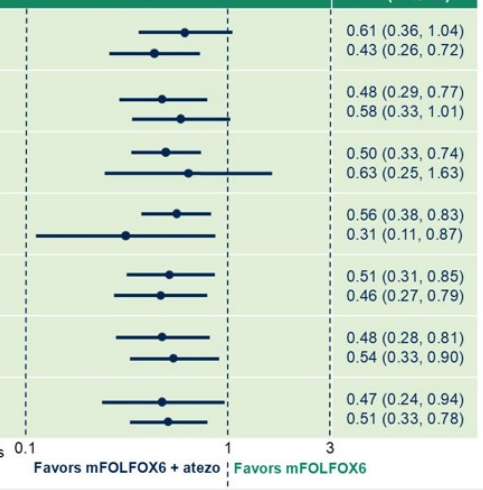
Confirmed dMMR by central reference laboratory: Log-Rank P-Value: 0.0007, Hazard Ratio (95% CI): 0.53 (0.36, 0.79)

*Stratified by randomization factors

Median follow-up = 37.2 mos

DFS by Subgroups

		mFOLFOX6 + Atezo	mFOLFOX6	HR (95% CI)
Age	< 65 year	22/173	36/187	0.61 (0.36, 1.04)
	≥ 65 year	23/182	44/170	0.43 (0.26, 0.72)
Sex	Female	24/186	50/206	0.48 (0.29, 0.77)
	Male	21/169	30/151	0.58 (0.33, 1.01)
Race	White	38/302	69/305	0.50 (0.33, 0.74)
	Other	7/53	11/52	0.63 (0.25, 1.63)
Tumor Location	Proximal	40/301	65/296	0.56 (0.38, 0.83)
	Distal	5/53	14/57	0.31 (0.11, 0.87)
T-Stage	Tx/T1-T3	23/243	44/243	0.51 (0.31, 0.85)
	T4	22/112	36/114	0.46 (0.27, 0.79)
N-Stage	$N1/N1_c$	21/226	41/225	0.48 (0.28, 0.81)
	N2	24/129	39/132	0.54 (0.33, 0.90)
Risk Group	Low*	12/164	25/164	0.47 (0.24, 0.94)
	High*	33/191	55/193	0.51 (0.33, 0.78)
		Events/Patients	Events/Patients	



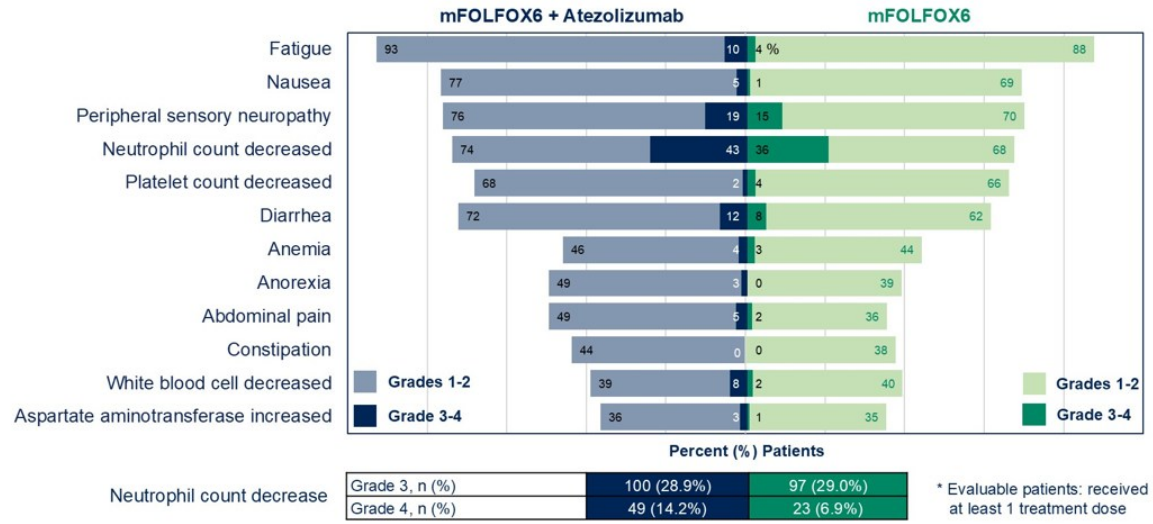
*Low (Tx-T3 and N1/N1c); High (T4 or N2)

Overall Survival

- OS data are not mature
- Median (Q1, Q3) OS follow-up is 42.5 (27.9, 60.5) months
- The OS comparison may be confounded by subsequent immunotherapy

Patient Safety

AEs Occurring in > 35% of Evaluable* Patients



Neutrophil count decrease	mFOLFOX6 + Atezolizumab	mFOLFOX6
Grade 3, n (%)	100 (28.9%)	97 (29.0%)
Grade 4, n (%)	49 (14.2%)	23 (6.9%)

* Evaluable patients: received at least 1 treatment dose

Conclusions

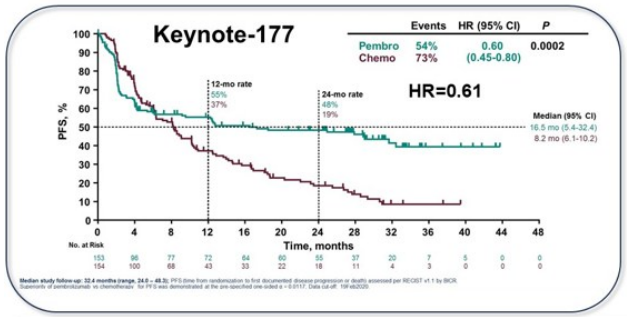
mFOLFOX6 + Atezolizumab demonstrated a statistically significant and clinically meaningful 50% risk reduction in recurrence or death over mFOLFOX6 alone

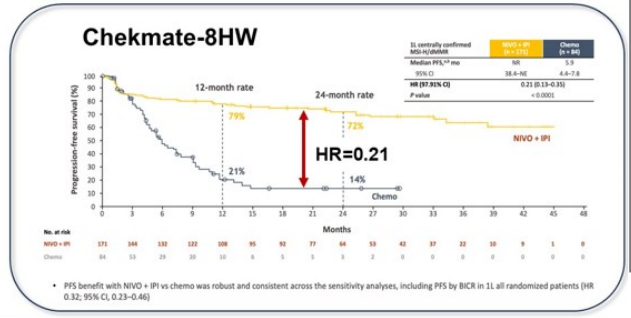
The safety of mFOLFOX6 + Atezolizumab was in line with the known safety profiles of each, with a manageable increase in non-febrile neutropenia

Atezolizumab plus mFOLFOX6 is a practice changing treatment for patients with dMMR stage III colon cancer

Immunotherapy for metastatic dMMR colorectal cancers

The current standard 1st line treatment for metastatic MMR-deficient colorectal cancers is either **pembrolizumab** monotherapy or **nivolumab/ipilimumab**: **without chemotherapy**

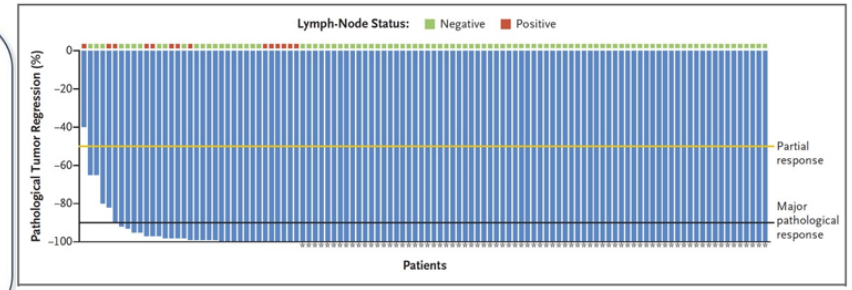


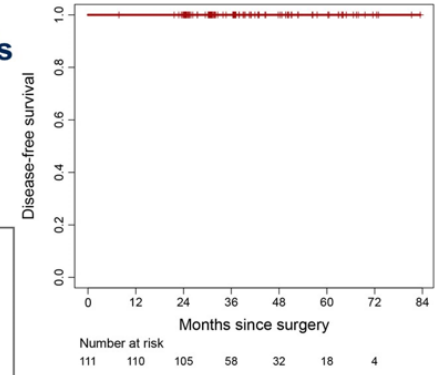


Andre et al, NEJM 2021; NEJM 2024; Lancet 2025

Neoadjuvant immunotherapy for dMMR colon cancer

- **NICHE-2: deep pathologic responses in 95% patients with two cycles of neoadjuvant immunotherapy**
  - **65% of patients with cT4 tumors**
- **3-year DFS 100%**

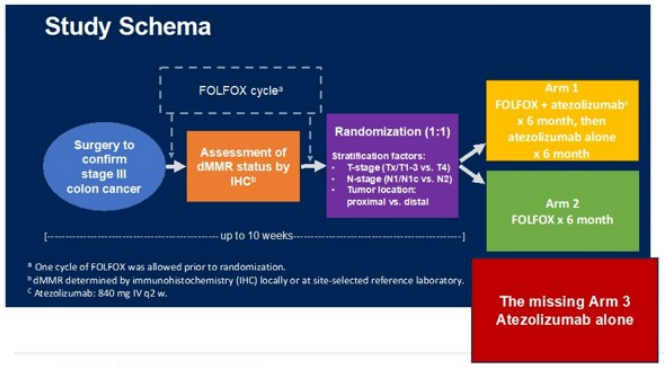




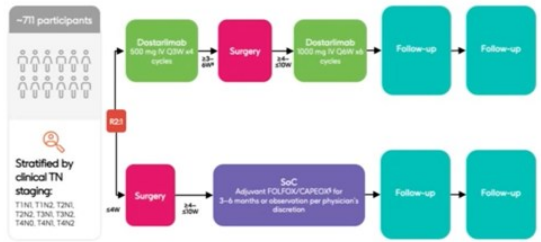
Chalabi et al, NEJM 2024; Chalabi et al, ESMO 2024

- **Chemotherapy has very limited efficacy in dMMR colon cancers**
- **Efficacy of adjuvant atezolizumab alone unknown after ATOMIC**

  Could chemo blunt the T-cell response?
- **Neoadjuvant immunotherapy is extremely effective, without chemotherapy, with limited toxicity**



AZUR-2 study ongoing → IO alone, neoadjuvant + adjuvant (**1 year total**) ***vs*** standard of care adjuvant chemotherapy



Post-ATOMIC questions and answers

- Can adjuvant immunotherapy cure more patients with dMMR colon cancers?
  - **YES!**
- Do patients with dMMR colon cancers need chemotherapy?

  ? **My take: probably not**
- Do patients need a full year of atezolizumab?

  ? **My take: probably not**

2025 ASCO ANNUAL MEETING

LBA2

GORTEC

NIVOPOSTOP (GORTEC 2018-01)

A phase III randomized trial of adjuvant nivolumab added to radio-chemotherapy in patients with resected head and neck squamous cell carcinoma at high risk of relapse

Jean Bourhis, Anne Aupérin, Christian Borel, Gautier Lefebvre, Severine Racadot, Lionnel Geoffrois, Xu Shan Sun, Esma Saada, Beatriz Cirauqui, Tomasz Rutkowski, Stephanie Henry, Anouchka Modesto, Alison Johnson, Benoit Calderon, Yoann Pointreau, Elisabeth Perez Ruiz, Joanna Kazmierska, Amanda Psyrri, Ricard Mesia, Yungan Tao

on behalf of GORTEC

Background

Resected locally advanced squamous-cell carcinoma of the head and neck (LA-SCCHN) with high risk of relapse:

High risk pathological features after surgery are **mainly** extra capsular extension in cervical nodes (ECE) and/or positive / close (< 1 mm) margin(s)

For over 20 years, the Standard of Care (SOC) has been adjuvant cisplatin-radiotherapy*

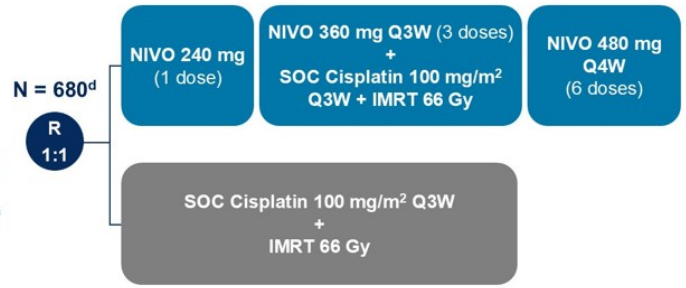
40-45% recurrence (local and/or distant)*: **unmet clinical need**

** Bernier J NEJM 2024 ; Cooper JS NEJM 2004*

NIVOPOSTOP study design

Key inclusion criteria:

- Adult patients <75 y/o
- ECOG PS 0-1
- SCC of the oral cavity, oropharynx, larynx, or hypopharynx with :
  - Complete macroscopic surgical resection
  - pStage III or IV[b] (AJCC 8th edition)
  - High-risk pathological features of relapse[c]



[a]Minimization factors : p16 (OPC p16+ versus OPC p16- and non-OPC) and centers . [b]pStage II p16+ oropharynx if pT3/T4 and tobacco ≥20 packs/year; [c]extra capsular extension (ECE) of lymph node, microscopically positive tumor margins (R1 or close margin ≤ 1 mm), ≥ 4 cervical nodal involvements without ECE, multiple peri-neural invasions; [d]total number of randomized patients between October 2018 and July 2024.

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Disease-free survival: (primary endpoint ; ITT)

Analysis based on **252 DFS events** at the data cutoff of April 30th 2024

Median follow-up: 30.3 months (IQR 16-44.9)

3-years DFS

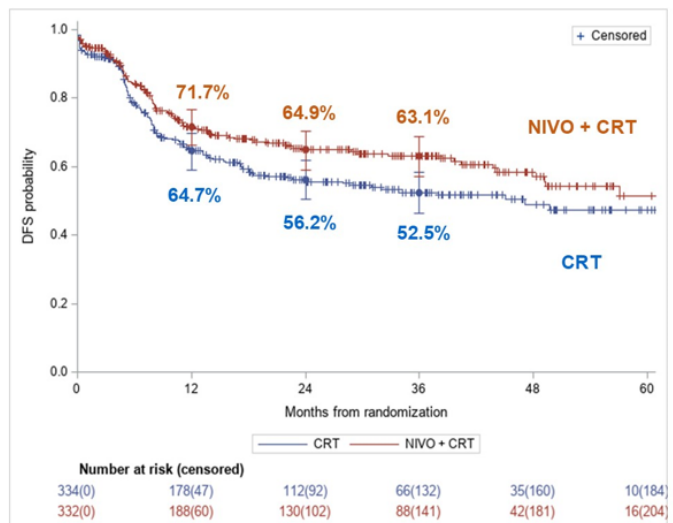
63.1% (95%CI 57.0%; 68.7%) with NIVO + CRT

versus

52.5% (95%CI 46.2%; 58.4%) with CRT

Stratified* HR (95%CI) = 0.76 (0.60; 0.98)
Stratified log-rank p-value=0.034

*HR stratified for p16 status (OPC p16 positive *versus* OPC p16 negative and non-OPC) in Cox model



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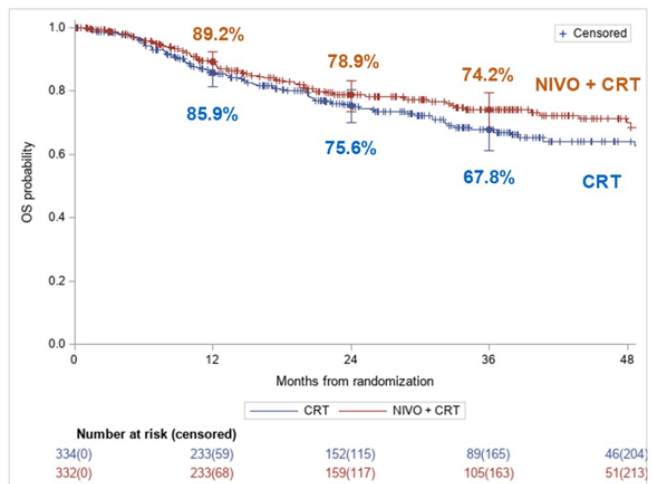
Overall survival (descriptive)

At the data cutoff, 158 patients died.

Results are in favor of NIVO + CRT but **OS could not be formally tested** since the pre-specified number of deaths was not reached.

The statistical analysis of OS requires more mature data according to the statistical plan.



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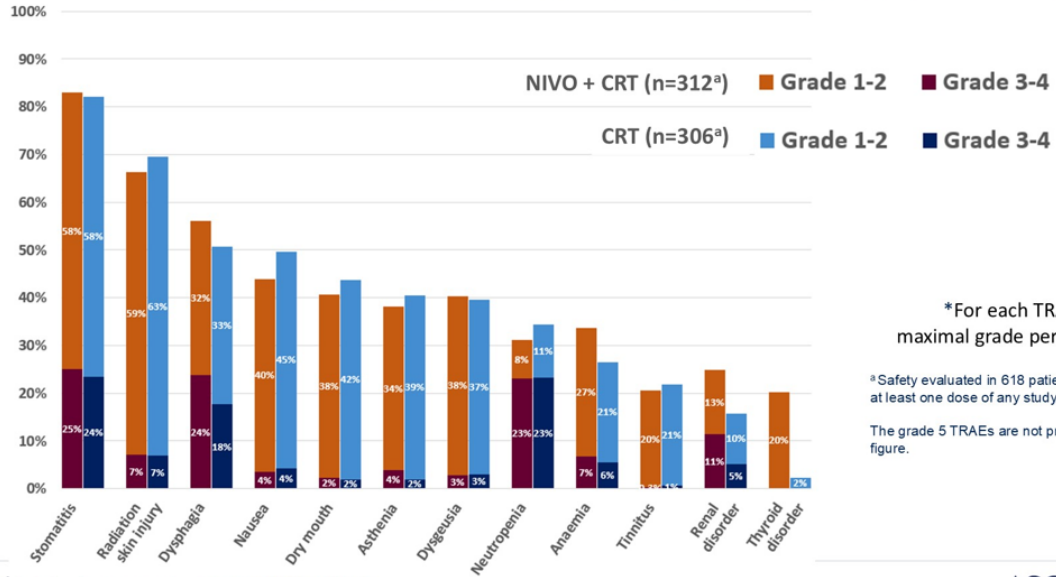
Common TRAEs* ≤ 9 months after CRT



*For each TRAE, maximal grade per patient

[a]Safety evaluated in 618 patients who received at least one dose of any study treatment.

The grade 5 TRAEs are not presented in this figure.

Summary

The benefit-risk ratio of adding nivolumab appeared favorable :

- The primary endpoint was met : DFS significantly improved (HR 0.76)
- Moderate increased toxicity, without increase in treatment-related deaths

Post-operative nivolumab added to SOC cisplatin-RT improved patient outcomes for resected high-risk LA-SCCHN, that could be proposed as a new standard treatment, … for the first time in two decades…

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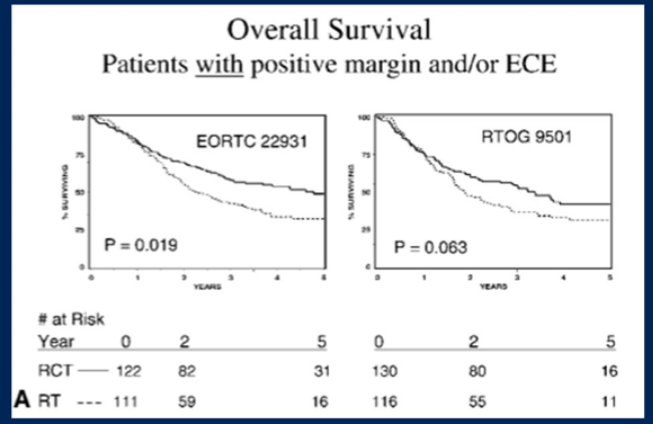
RTOG 9501 & EORTC 22931

- Both POSITIVE studies
- Joint Analysis Pooled data
- Conclusions: Post-Operative Radiation plus cisplatin improves overall survival for High-Risk patients (positive margin and/or ECE)
- DFS, OS benefit--local control

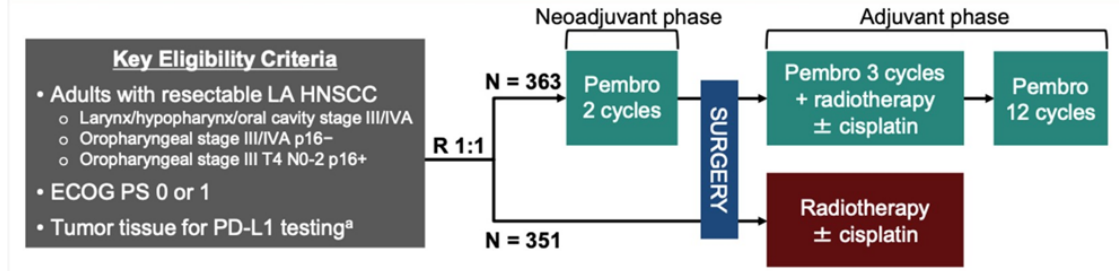


Cooper et al NEJM, 2004 PMID: 15128893
Bernier et al NEJM, 2004 PMID 15128894
Bernier et al, Head Neck, 2005, PMID 16161069

KEYNOTE-689 Study

NCT03765918

Courtesy of Merck



Stratification factors
- Primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx)
- Tumor stage (III vs IVA)
- PD-L1 TPS[a] (≥50% vs <50%)

Primary endpoint: EFS per RECIST 1.1 by BICR

Key secondary endpoints: Major pathological response (mPR; ≤10% residual invasive SCC in resected primary tumor and all sampled regional lymph nodes) by BIPR and OS

Other secondary endpoints include: Safety

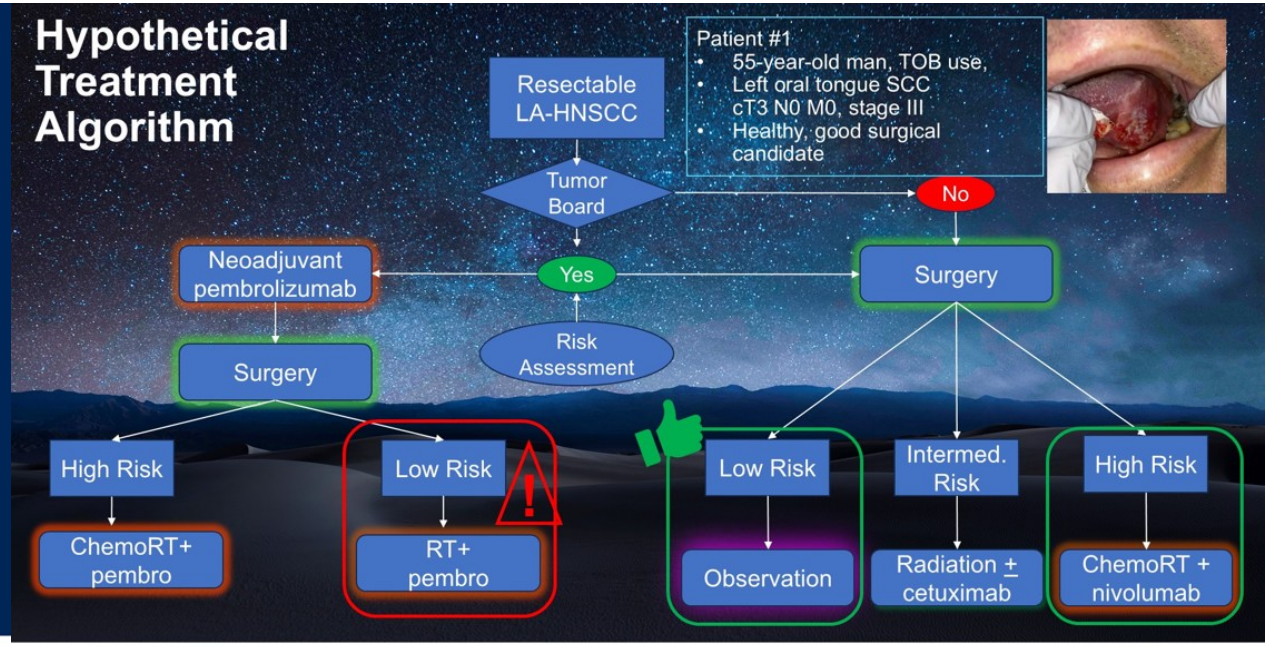
BICR, blinded independent central review; BIPR, blinded independent pathologist review; EFS, event-free survival; OS, overall survival.
[a]Assessed by PD-L1 IHC 22C3 pharmDx; TPS=% tumor cells with membranous PD-L1 staining; CPS=number of PD-L1–staining cells ÷ total # viable tumor cells × 100.

NIVOPOSTOP vs KEYNOTE 689

	NIVOPOSTOP	KEYNOTE 689
Population	Mostly oral cavity (few HPV)	Mostly oral cavity (few HPV)
Population	Pathologic High Risk (few Intermediate)	Clinical Intermediate & High Risk
Experimental Intervention	Adjuvant	Neoadjuvant
Primary Endpoint	DFS	EFS
Control Benefit	Locoregional	Distant metastatic

- Immune priming

Hypothetical Treatment Algorithm



2025 ASCO ANNUAL MEETING

LBA 3

Results From VERIFY, a Phase 3, Double-Blind, Placebo (PBO)-Controlled Study of Rusfertide for Treatment of Polycythemia Vera (PV)

Andrew T. Kuykendall[1], Naveen Pemmaraju[2], Kristen Pettit[3], Joseph Shatzel[4], Alessandro Lucchesi[5], Valentín García-Guitérrez[6], Jiri Mayer[7], Abdulraheem Yacoub[8], Harinder Gill[9], Antonin Hlusi[10], Daniel Sasca[11], Joseph M. Scandura[12], Marina Kremyanskaya[13], Phil Dinh[14], Sarita Khanna[14], Suneel Gupta[14], Arturo Molina[14], Aniket Bankar[15] on behalf of the VERIFY Investigators

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]University of Michigan, Ann Arbor, MI, USA; [4]Oregon Health & Science University, Portland, Oregon, USA; [5]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; [6]Hospital Universitario Instituto Ramón y Cajal de Investigación Sanitaria, Universidad de Alcalá, Madrid, Spain; [7]University Hospital and Masaryk University, Brno, Czech Republic; [8]University of Kansas Cancer Center, Westwood, Kansas, USA; [9]Department of Medicine, School of Clinical Medicine, LKS Faculty of Medicine, the University of Hong Kong, Hong Kong; [10]Palacky University and University Hospital Olomouc, Olomouc, Czech Republic; [11]Universitaetsmedizin der Johannes Gutenberg - Universitaet Mainz, Mainz, Germany; [12]New York Presbyterian Hospital/Weill Cornell Medical Center, New York, NY, USA; [13]Mount Sinai Medical Center, New York, NY, USA; [14]Protagonist Therapeutics, Inc., Newark, California, USA; [15]Princess Margaret Cancer Centre, Toronto, ON, Canada.

PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

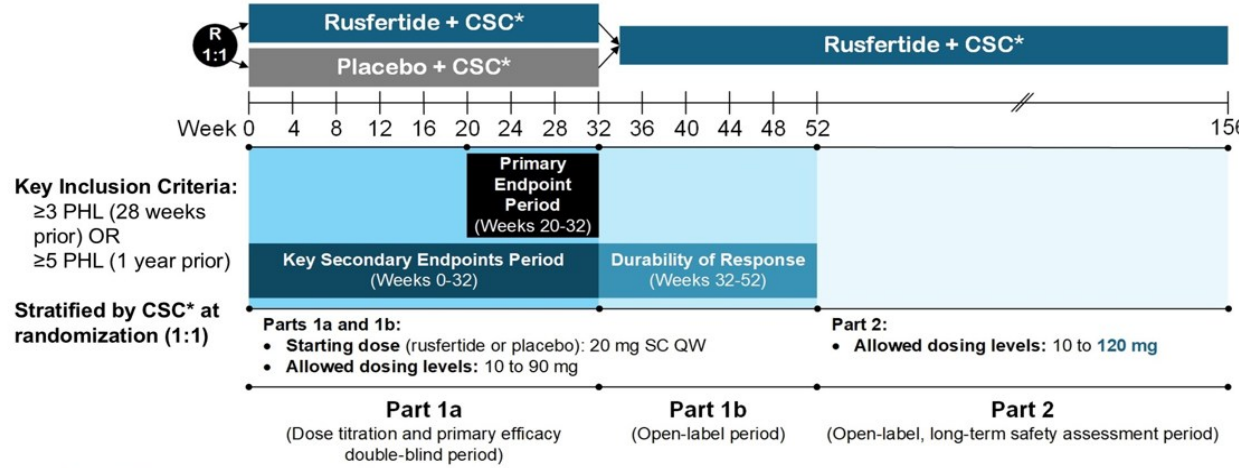
Background

- Polycythemia vera (PV) is a myeloproliferative neoplasm driven by acquired *JAK2* mutations[1-3]
- PV is characterized by excessive production of blood cells which contributes to an increased risk of cardiovascular and thrombotic events
- Primary goal of PV treatment aims to reduce thrombotic risk by achieving and maintaining Hct <45%[2,3]
- Current standard-of-care for PV: phlebotomy ± cytoreductive therapy
- Frequent phlebotomy is burdensome and often insufficient for durable Hct control <45%[4-6]

Hct, hematocrit; PHL, phlebotomy; PV, polycythemia vera.

1. Mora B, Passamonti F. *Clin Lymphoma Myeloma Leuk*. 2023;23(2):79-85; 2. Marchioli R, et al. *N Engl J Med*. 2013;368(1):22-33; 3. Tremblay D, et al. *JAMA*. 2025;333(2):153-60; 4. Alvarez-Larrán A, et al. *Haematologica*. 2016;102(1):103-9; 5. Verstovsek S, et al. Ann Hematol. 2023;102(3):571-81. 6. Ginzburg YZ, *Leukemia*. 2018;32(10):2105-16.

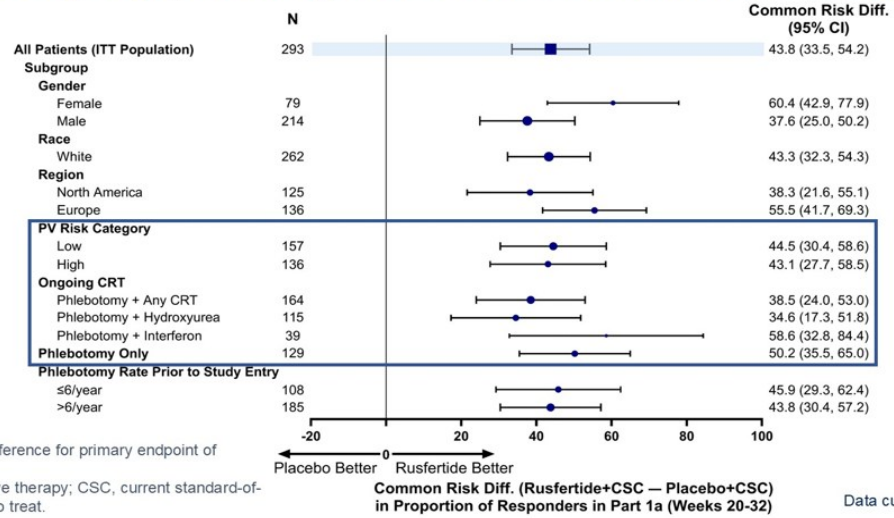
Phase 3 VERIFY Study (NCT05210790) Design in PV



*PHL ± CRT

CRT, cytoreductive therapy; CSC, current standard-of-care; PHL, phlebotomy; PV, polycythemia vera; QW, once-weekly; R, randomization; SC, subcutaneous.

Rusfertide + CSC Benefit Maintained vs. Placebo + CSC for Response* Across Subgroups, Including Risk Status and Concurrent Therapy



*Common risk difference for primary endpoint of response.

CRT, cytoreductive therapy; CSC, current standard-of-care; ITT, intent to treat.

Data cutoff: 7 January 2025

Conclusions

- Rusfertide is an investigational weekly subcutaneous injection for PV
- In the phase 3 VERIFY study that included patients with PV who were receiving CSC, rusfertide met its primary endpoint and all four key secondary endpoints vs. placebo
  - In VERIFY Part 1a, rusfertide:
    - Significantly reduced the PHL eligibility and improved Hct vs. placebo
    - Demonstrated a statistically significant improvement in symptoms (assessed using two PRO instruments)
- Rusfertide demonstrated a manageable safety profile consistent with prior studies
- **Rusfertide represents a potential new treatment option for PV**
  - These data will be used to file marketing authorizations throughout the world

CRT, cytoreductive therapy; CSC, current standard-of-care; Hct, hematocrit; PHL, phlebotomy; PRO, patient-reported outcome; PV, polycythemia vera.

2025 ASCO ANNUAL MEETING

SERENA-6

LBA4

Camizestrant + CDK4/6 inhibitor for the treatment of emergent *ESR1* mutations during first-line endocrine-based therapy and ahead of disease progression in patients with HR+/HER2– advanced breast cancer: Phase 3, double-blind ctDNA-guided SERENA-6 trial

Nicholas Turner*
Royal Marsden Hospital, London, UK

Additional authors:
Erica Mayer, Yeon Hee Park, Wolfgang Janni, Cynthia Ma, Massimo Cristofanilli, Giampaolo Bianchini, Kevin Kalinsky, Hiroji Iwata, Stephen Chia, Peter A. Fasching, Adam Brufsky, Zbigniew Nowecki, Javier Pascual, Lionel Moreau, Shin-Cheh Chen, Sasha McClain, Steven Fox, Cynthia Huang Bartlett, François-Clément Bidard*

*Contributed equally

*ESR1*m surveillance during first-line AI+CDK4/6i

SERENA-6

Screened, N=3325

Patients on first-line AI + CDK4/6i for ≥6 months

*ESR1*m testing (every 2–3 months)

***ESR1*m surveillance, n=3256**

Patients with *ESR1*m detected, n=548

Positive on first test: 51%*
Positive after 2-5 tests: 38%*
Positive after >5 tests 11%*

Randomized, n=315

Patients tested for *ESR1*m in ctDNA with Guardant360 CDx every 2–3 months at time of routine staging scans

Patients ongoing in surveillance when screening closed, n=1949

Discontinued (n=233) due to:
- Screen failure (n=200)
  - Concurrent disease progression (n=53)
  - Patient not meeting other eligibility criteria (n=48)
  - Reason not provided (n=99)
- Withdrew consent, lost to follow-up or unknown (n=33)

An estimate of the proportion of patients with emerging *ESR1*m during the study period is 42%, calculated from the 548 patients with a positive test/(the number of patients tested for *ESR1*m [n=3256] minus the number of patients that were still ongoing in surveillance when screening closed [n=1949]).

Number of tests to obtain a positive *ESR1*m test result based on n=521 patients who met all the eligibility criteria for the *ESR1*m surveillance step. Patients were screened for inclusion into the study from 264 sites in 23 countries.
Of the 3325 patients screened for inclusion, ctDNA from patient blood samples were tested for *ESR1*m using Guardant360CDx (Guardant Health, Redwood City, CA, US).

SERENA-6 study design

SERENA-6

Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

R 1:1
N=315

Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI

Stratification factors
- Visceral vs non-visceral
- *ESR1*m detection at first test vs at a subsequent test
- Time from initiation of AI + CDK4/6i to randomization: <18 vs ≥18 months
- Palbociclib vs ribociclib vs abemaciclib

Continuing AI (anastrozole/letrozole) + CDK4/6i + placebo for camizestrant

Treatment continued until disease progression, unacceptable toxicity, patient withdrawal or death

Primary endpoint

PFS by investigator assessment (RECIST v1.1)

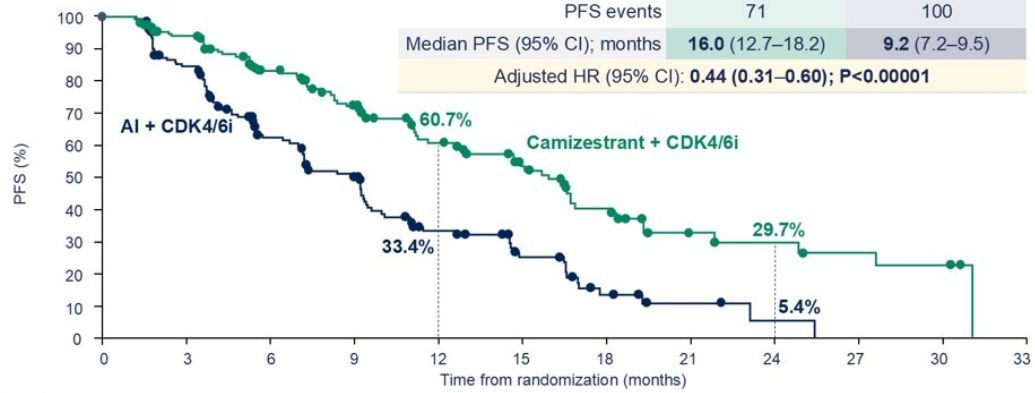
Secondary endpoints
- PFS2**
- OS**
- Safety
- Patient-reported outcomes

*Pre- or perimenopausal women, and men received a luteinizing hormone–releasing hormone agonist per clinical guidelines. **Key secondary endpoint.
OS, overall survival; PFS2, second progression-free survival; qd, once daily dose; R, randomized; RECIST, response evaluation criteria in solid tumors.

Primary endpoint: Investigator-assessed PFS

SERENA-6

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS events	71	100
Median PFS (95% CI); months	**16.0** (12.7–18.2)	**9.2** (7.2–9.5)
Adjusted HR (95% CI): **0.44 (0.31–0.60); P<0.00001**		



Number of patients at risk

Camizestrant + CDK4/6i	157	138	105	82	55	41	26	11	9	7	6	0
AI + CDK4/6i	158	124	73	55	29	17	7	3	1	0	0	0

P-value crossed the threshold for significance (P=0.0001). PFS was defined per RECIST v1.1. HR was estimated using the Cox proportional hazard model adjusted for stratification factors.
CI, confidence interval; HR, hazard ratio.

Investigator-assessed PFS by subgroup

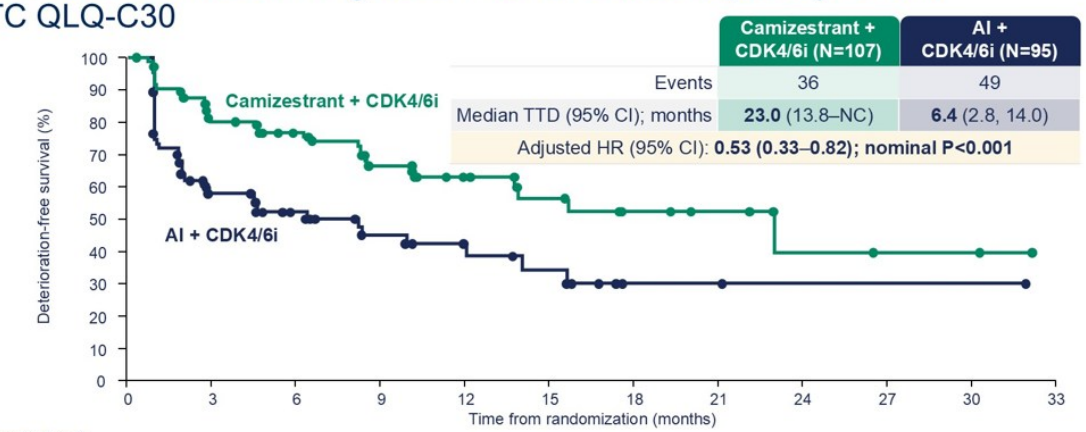
SERENA-6

	Subgroup	Camizestrant + CDK4/6i	AI + CDK4/6i	Hazard ratio (95% CI)
		no. of events/total no.		
	All patients	71/157	100/158	**0.44** (0.31–0.60)
Age	<65 years	44/95	67/104	**0.51** (0.34–0.74)
	≥65 years	27/62	33/54	**0.35** (0.21–0.59)
Race	Asian	22/39	25/34	**0.60** (0.33–1.07)
	White	37/97	61/102	**0.39** (0.26–0.59)
	Other	12/21	14/21	**0.39** (0.18–0.85)
Region	Asia	19/40	28/39	**0.46** (0.25–0.83)
	Europe	37/89	54/91	**0.41** (0.26–0.62)
	North America	15/28	18/28	**0.57** (0.28–1.13)
Menopausal status	Pre-/perimenopausal women, and men	14/34	18/31	**0.39** (0.19–0.79)
	Postmenopausal	57/123	82/127	**0.46** (0.32–0.65)
Disease site*	Visceral	32/65	37/64	**0.57** (0.35–0.92)
	Non-visceral	39/92	63/92	**0.38** (0.25–0.56)
Time from initiation of AI + CDK4/6i to randomization*	<18 months	28/50	29/46	**0.60** (0.35–1.01)
	>18 months	43/105	69/110	**0.39** (0.26–0.58)
CDK4/6i*	Palbociclib	57/117	78/118	**0.45** (0.32–0.64)
	Ribociclib	4/23	13/23	**0.27** (0.08–0.77)
	Abemaciclib	10/15	9/15	**0.63** (0.25–1.59)
Time of *ESR1*m detection*	First test	36/82	56/79	**0.32** (0.20–0.49)
	A subsequent test‖	35/75	44/79	**0.64** (0.41–0.99)
Type of *ESR1*m	D538G	29/70	52/82	**0.34** (0.21–0.53)
	Y537S	24/61	46/60	**0.29** (0.17–0.47)
	Y537N	13/29	18/25	**0.44** (0.21–0.90)

*Stratification factors at randomization. ‖Subsequent tests were performed every 2-3 months after the initial test. HRs and 95% CIs were not calculated for subgroups with <20 events, except for the CDK4/6i subgroup. HRs and 95% CIs were calculated from a Cox proportional hazards model with treatment, factor and treatment-by-factor as covariates.

Time to deterioration in global health status/quality of life

EORTC QLQ-C30



	Camizestrant + CDK4/6i (N=107)	AI + CDK4/6i (N=95)
Events	36	49
Median TTD (95% CI); months	**23.0** (13.8–NC)	**6.4** (2.8, 14.0)
Adjusted HR (95% CI): **0.53 (0.33–0.82); nominal P<0.001**		

Number of patients at risk

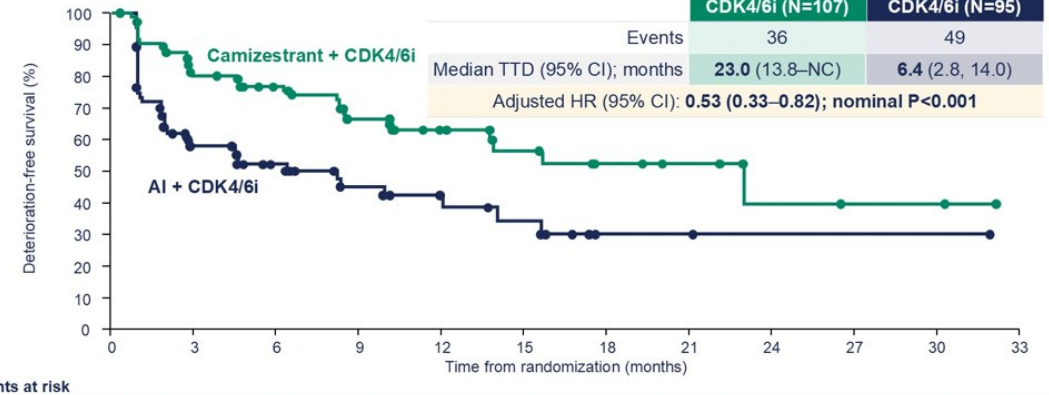
Camizestrant + CDK4/6i	107	72	59	40	24	16	9	6	3	2	2	0
AI + CDK4/6i	95	42	26	16	11	8	2	2	1	1	1	0

- Camizestrant + CDK4/6i also delayed the time to deterioration in pain compared with AI + CDK4/6i

Assessments were conducted at baseline, weeks 4, 8 and 12 and then every 8 weeks until PFS2. Analysis conducted in patients with a baseline score and at least one post-baseline assessment. TTD in global health status/quality of life, an exploratory endpoint, was defined as the time from randomization to first deterioration that was confirmed at a subsequent timepoint measured using the European Organization for Research and Treatment of Cancer 30-item quality-of-life questionnaire (**EORTC QLQ-30**). Deterioration was defined as a decrease from baseline ≥16.6. HR was estimated using the Cox proportional hazard model stratified by time of *ESR1*m detection (one test vs more than one test), and time from initiation of AI + CDK4/6i to randomization (<18 months vs. ≥18 months). NC, not calculable; TTD, time-to-deterioration.

Time to deterioration in global health status/quality of life

EORTC QLQ-C30



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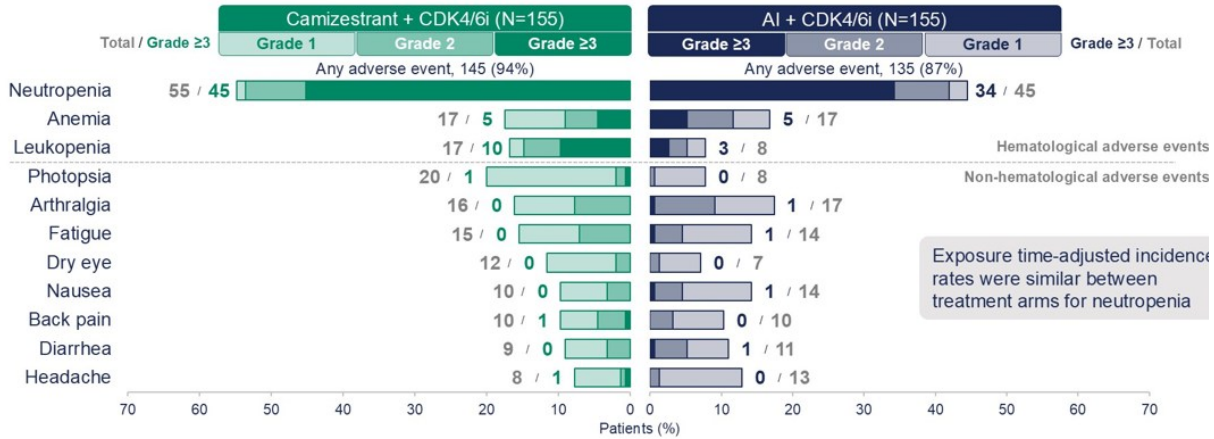
Adverse events (≥10% of patients)



Exposure time-adjusted incidence rates were similar between treatment arms for neutropenia

Photopsia (brief flashes of light in the peripheral vision) did not impact daily activities: If experienced, visual effects had no/minimal impact on daily activities, were typically ≤1 minute, ≤3 days/week, and reversible. There were no structural changes in the eye and no changes in visual acuity

Neutropenia is reported as a group term that includes neutropenia and decreased neutrophil count; anemia is reported as a group term that includes anemia and hemoglobin decreased; leukopenia is reported as a group term that includes leukopenia and white blood cell count decrease. Bradycardia and sinus bradycardia were reported in the camizestrant + CDK4/6i arm only, in 8 patients (5.2%) and 4 patients (2.6%), respectively. No (sinus) bradycardia AEs were grade ≥3, and none of these events required treatment discontinuation. Impact of visual effects was measured using the Visual Symptom Assessment Questionnaire.

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Conclusions

- Switching AI to camizestrant with continuation of CDK4/6i, guided by the emergence of *ESR1* mutations during first-line therapy ahead of disease progression, significantly improved PFS in patients with HR+/HER2– ABC
- PFS benefit was consistent across the CDK4/6i and clinically relevant subgroups
- Camizestrant + CDK4/6i delayed time to deterioration in quality of life versus continuing AI + CDK4/6i, and was well tolerated with a very low rate of treatment discontinuations due to adverse events
- SERENA-6 is the first global registrational phase 3 study to demonstrate the clinical utility of ctDNA monitoring to detect and treat emerging resistance in breast cancer

The findings from SERENA-6 have the potential to become a new treatment strategy in oncology to optimize first-line patient outcomes

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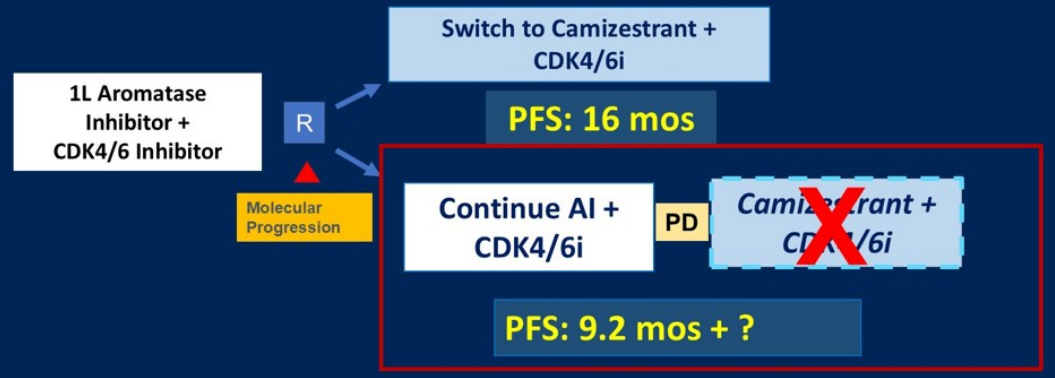
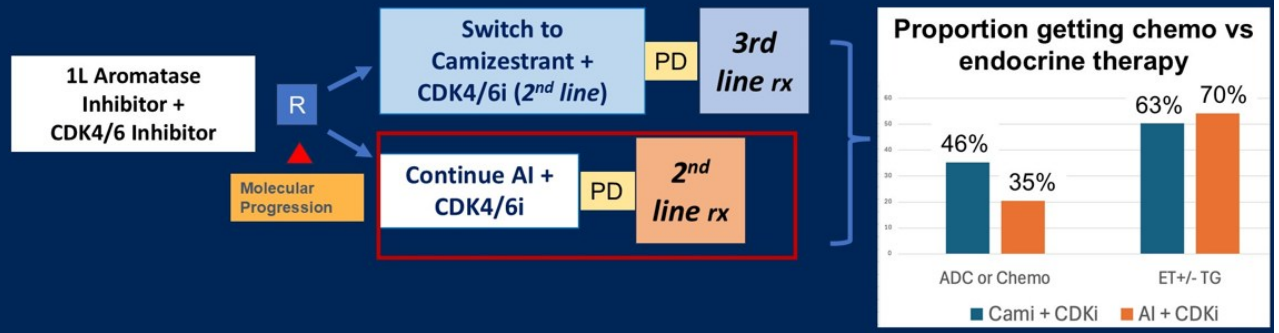
Lack of crossover limits clinical utility assessment



- No direct comparison of response time or overall strategy with switch at molecular vs. anatomic progression

Imbalance in post-progression treatment



~10% with more chemotherapy in the camizestrant switch group after first anatomic progression; 10% oral SERD in control

Key Take Aways from SERENA-6

- **ctDNA-guided switching to camizestrant at at emergence of *ESR1m* prolonged 1st line PFS**
  - Acceptable toxicity and QOL
  - Possible new regulatory approval path
- **Additional outcomes needed to determine clinical utility of the strategy**
  - Too early for PFS-2 and OS
  - Design creates challenges to clinical utility
  - Other tangible benefits (e.g., longer time to chemotherapy, delay to development of more aggressive metastases such as CNS involvement)
  - Full complement of financial, psychological and systemic costs

How to counsel Julia?

- **Next week: Cannot yet recommend the SERENA-6 strategy**
  - Camizestrant is not yet approved
  - Strategy not validated for other mutations or drugs
- **If camizestrant approved based on PFS and QOL**
  - "Is more time on this treatment worth going through the testing process if it doesn't help you live longer?"

2025 ASCO ANNUAL MEETING

LBA 5

Yelena Janjigian
Chief, Gastrointestinal Oncology at Memorial Sloan Kettering Cancer Center

Event-free Survival (EFS) in MATTERHORN: a Randomized, Phase 3 Study of Durvalumab plus 5-Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel Chemotherapy (FLOT) in Resectable Gastric / Gastroesophageal Junction Cancer (GC / GEJC)

Yelena Y. Janjigian,[1] Salah-Eddin Al-Batran,[2] Zev A. Wainberg,[3] Kei Muro,[4] Daniela Molena,[5] Eric Van Cutsem,[6] Woo Jin Hyung,[7] Lucjan Wyrwicz,[8] Do-Youn Oh,[9] Takeshi Omori,[10] Markus Moehler,[11] Marcelo Garrido,[12] Sulene C.S. Oliveira,[13] Moishe Liberman,[14] Victor Castro Oliden,[15] Elizabeth C. Smyth,[16] Olivier Serrano,[17] Eric Heilbron,[18] Alejandra Negro,[18] Josep Tabernero[19]

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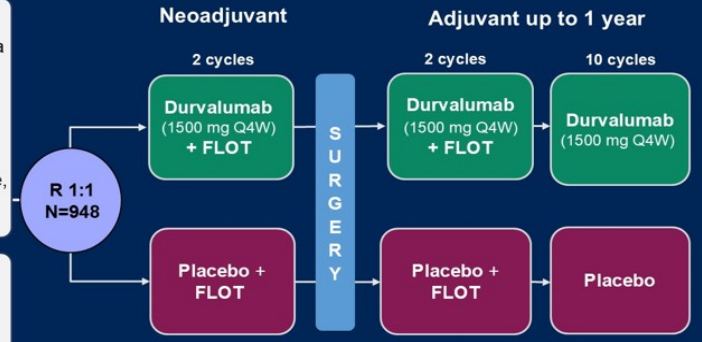
MATTERHORN Study Design

A global, Phase 3, randomized, double-blind, placebo-controlled study

Study population
- Gastric and GEJ adenocarcinoma
- Stage II to IVa
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrollment in Asia, Europe, North & South America

Stratification factors
- Asia vs non-Asia
- Clinical N+ vs N-
- PD-L1: TAP <1% vs TAP ≥1%*



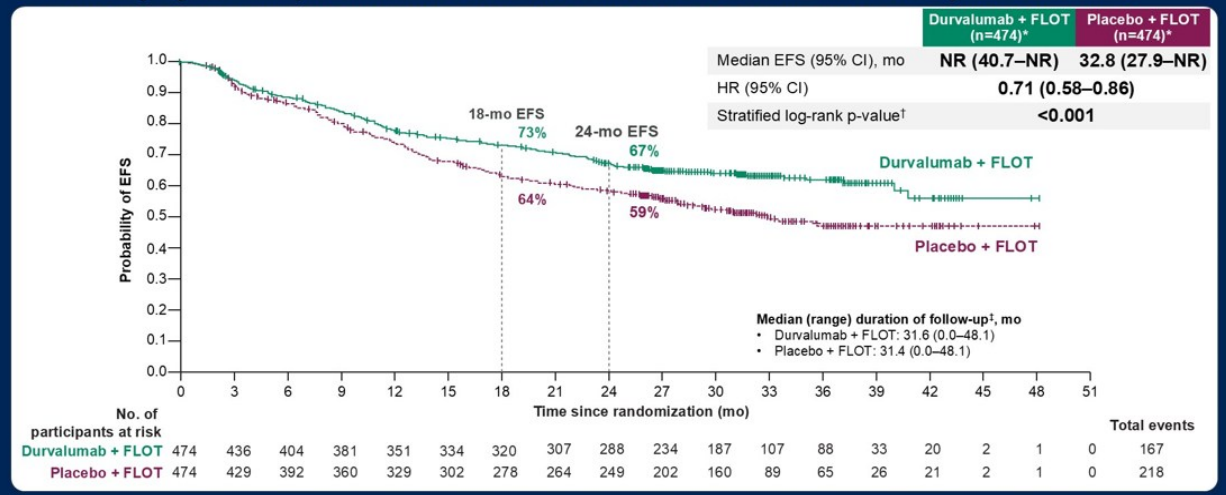
Primary endpoint:
- EFS

Secondary:
- OS
- pCR

FLOT: 5-fluorouracil 2600 mg/m², leucovorin 200 mg/m², oxaliplatin 85 mg/m², docetaxel 50 mg/m², on Days 1 and 15 Q4W. 4 doses (two cycles) pre- and post-operative; durvalumab: 1500 mg on Day 1 Q4W. 2 doses (two cycles) of durvalumab or placebo pre- and post-operative, followed by 10 doses of post-operative durvalumab or placebo monotherapy. Participants undenerent surgery 4–8 weeks after last dose of neoadjuvant therapy. Adjuvant therapy began 4–12 weeks post-surgery. Durvalumab / placebo monotherapy may be continued if FLOT is discontinued due to toxicity. *Measured by IHC using VENTANA PD-L1 (SP263) CDx Assay (Roche Diagnostics; IUO).
ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastroesophageal junction; IHC, immunohistochemistry; IUO, investigational use only; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1; PS, performance status; Q4W, every 4 weeks; R, randomized; TAP, Tumor Area Positivity.

Primary Endpoint of Event-Free Survival (EFS)

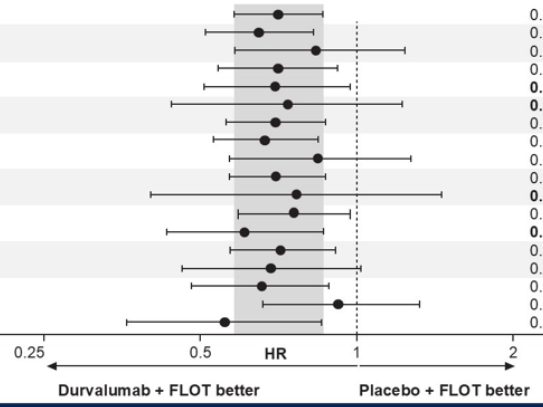
A statistically significant improvement in EFS was observed with durvalumab with FLOT vs placebo with FLOT



Events were defined as the earliest of RECIST v1.1 events, non-RECIST v1.1 events, or deaths of any cause. Analysis was based on BICR assessments and / or locally by pathology testing if clinically required. The HR and its CI were estimated from a Cox proportional hazards model, adjusted for geographic region, clinical lymph node status, and PD-L1 expression. The CI for the HR was calculated using a profile likelihood approach. The 2-sided p-value was calculated using a stratified log-rank test adjusted for geographic region, clinical lymph node status, and PD-L1 expression.*Full analysis set (all randomized participants, regardless of treatment received). †The threshold of significance for this analysis was 0.0239. ‡In censored participants.
BICR, blinded independent central review; CI, confidence interval; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; HR, hazard; mo, month; NR, not reached; PD-L1, programmed cell death ligand-1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

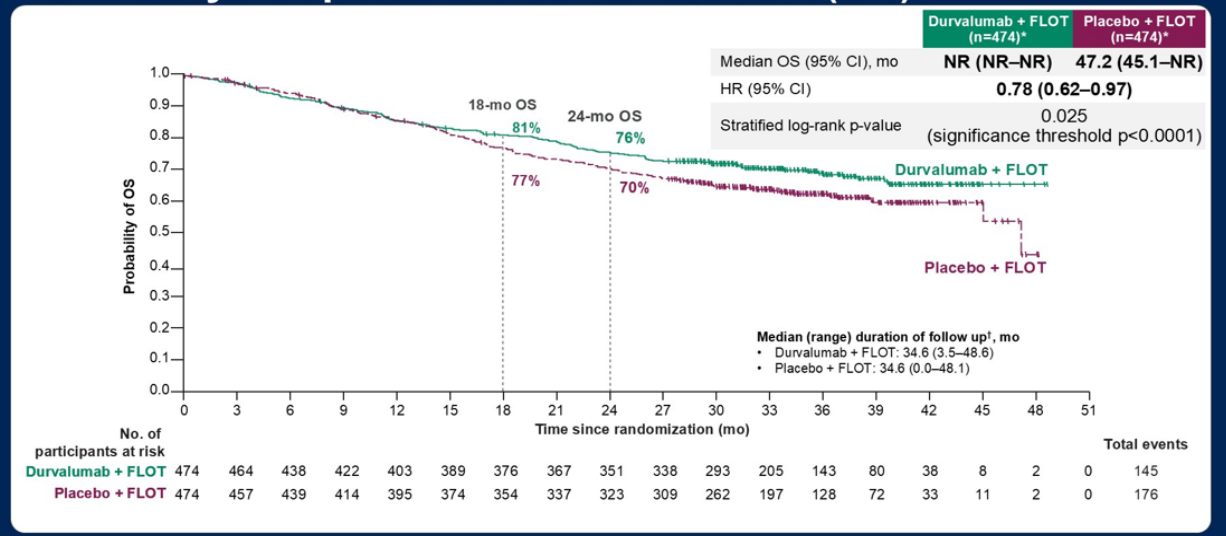
EFS in Key Subgroups: Consistent Benefit Observed

Subgroup	Category	N	HR for event (95% CI)
All participants		948	0.71 (0.58–0.86)
Sex*	Male	682	0.65 (0.51–0.83)
	Female	266	0.84 (0.58–1.24)
Age at randomization*	<65 years	556	0.71 (0.54–0.92)
	≥65 years	**392**	**0.70 (0.51–0.97)**
Geographic region*	**Asia**	**180**	**0.74 (0.44–1.22)**
	Non-Asia	768	0.70 (0.56–0.87)
Clinical lymph node status*	N+	667	0.67 (0.53–0.84)
	N-	277	0.85 (0.57–1.27)
PD-L1 expression*	TAP ≥1%	853	0.70 (0.57–0.87)
	TAP <1%	**95**	**0.77 (0.40–1.46)**
Primary tumor location*	Gastric	640	0.76 (0.59–0.97)
	GEJ	**308**	**0.61 (0.43–0.86)**
ECOG PS*	0	703	0.72 (0.57–0.91)
	1	245	0.69 (0.46–1.02)
Histology type†	Intestinal	483	0.66 (0.48–0.89)
	Diffuse	249	0.93 (0.66–1.32)
	Indeterminate	216	0.56 (0.36–0.86)



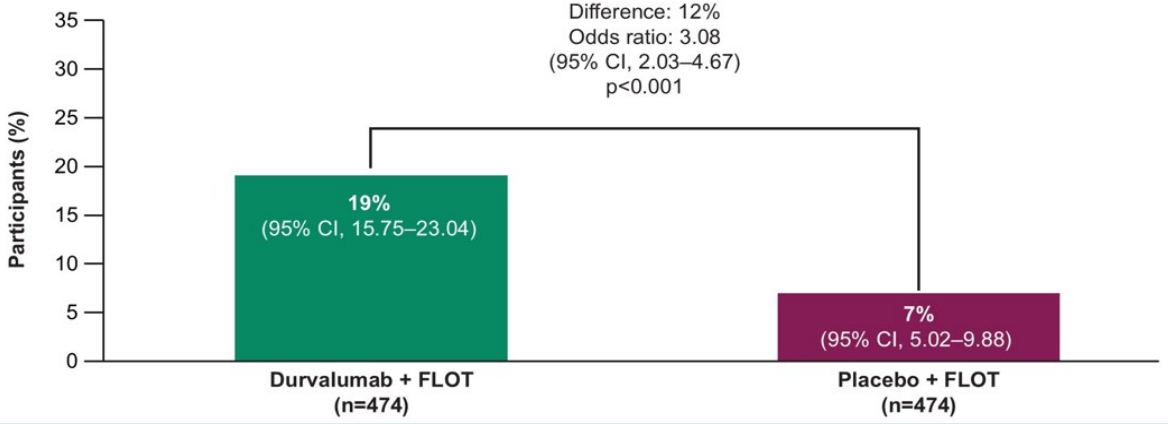
Gray band represents the 95% CI for the all-participants HR. The analysis was performed using a Cox proportional hazards model with treatment as the only covariate. The CI was calculated using a profile likelihood approach. Events were defined as the earliest of RECIST v1.1 events, non-RECIST v1.1 events, or deaths of any cause. Analysis was based on BICR assessment and / or locally by pathology testing if clinically required.*Pre-specified per protocol. †Assessed post hoc per local laboratory.
BICR, blinded independent central review; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastroesophageal junction; HR, hazard ratio; PD-L1, programmed cell death ligand-1; PS, performance status; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TAP, Tumor Area Positivity.

Secondary Endpoint of Overall Survival (OS)



MATTERHORN is ongoing for OS (33.9% maturity at this interim analysis). Events were defined as time from randomization until the date of death due to any cause. The HR and its CI were estimated from a Cox proportional hazards model, adjusted for geographic region, clinical lymph node status, and PD-L1 expression. The CI for the HR was calculated using a profile likelihood approach. The 2-sided p-value was calculated using a stratified log-rank test adjusting for geographic region, clinical lymph node status, and PD-L1 expression.
*Full analysis set (all randomized participants, regardless of treatment received). †In censored participants. CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; HR, hazard ratio; mo, month; NR, not reached; OS, overall survival; PD-L1, programmed cell death ligand-1.

pCR: A Statistically Significant Improvement With the Addition of Durvalumab to FLOT

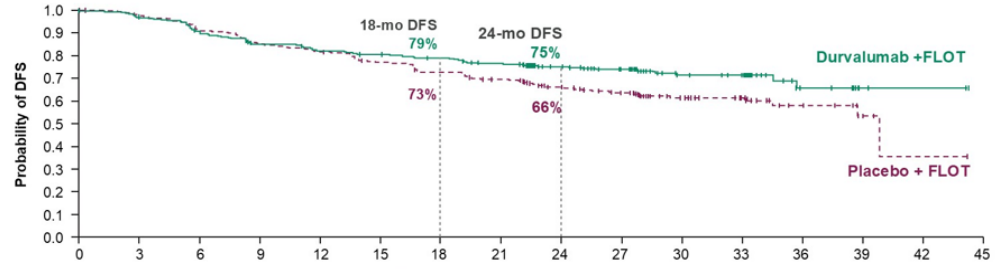


Full analysis set (all randomized participants, regardless of treatment received). Threshold of significance for this analysis was 0.001. Participants had pCR if there was no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathologic regression of 100%, based on central assessment. Central review of pCR was scored using modified Ryan criteria. The analysis was performed using a stratified Cochran-Mantel-Haenszel test. The stratification factors included geographic region, clinical lymph node status, and PD-L1 expression.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1.
Janjigan YY, et al. *Annal Oncol* 2023;34(suppl 2). Abs LBA73.

Secondary Endpoint of Disease-Free Survival (DFS)

DFS improved with durvalumab with FLOT vs placebo with FLOT in those with R0 resection

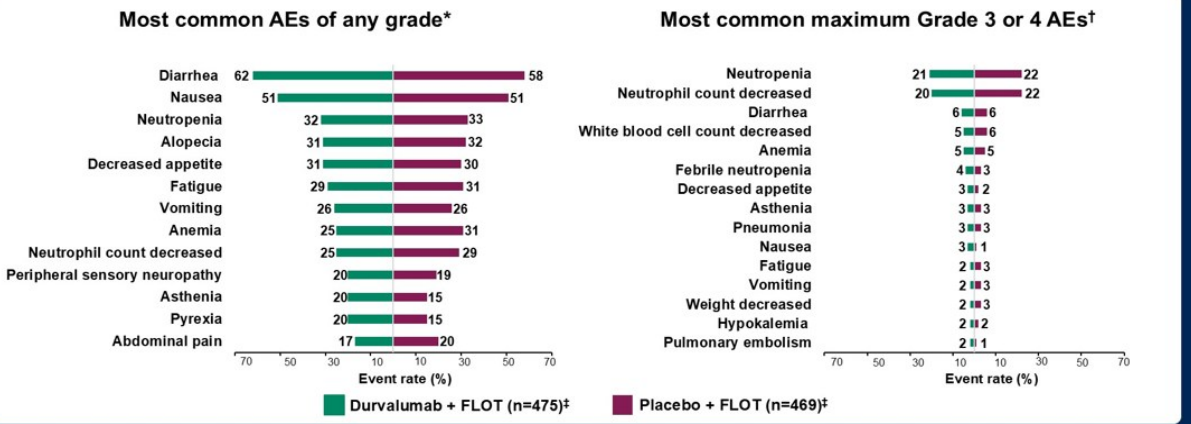
	Durvalumab + FLOT (n=339)	Placebo + FLOT (n=323)
Median DFS (95% CI), mo	NR (NR–NR)	39.8 (38.7–NR)
HR (95% CI)	0.70 (0.53–0.93)	



No. of participants at risk																Total events
Durvalumab + FLOT	339	327	305	283	272	265	258	244	184	168	81	74	19	3	2	0	90
Placebo + FLOT	323	315	293	275	262	245	230	217	157	142	72	56	23	4	2	0	119

DFS (defined by RECIST v1.1) was time from adjuvant baseline scan until the earliest of first evidence of disease recurrence or death due to any cause, in participants with R0 resection and no evidence of disease at the adjuvant baseline scan. Participants who were alive and disease free at the time of analysis were censored at date last known alive and without the DFS event. If a participant died between first post-surgery scan and next scheduled RECIST v1.1 scan, this was considered an event. The HR and its CI were estimated from a Cox proportional hazards model, adjusted for geographic region, clinical lymph node status, and PD-L1 expression. The CI for the HR was calculated using a profile likelihood approach. CI, confidence interval; DFS, disease-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; HR, hazard ratio; mo, month; NR, not reached; PD-L1, programmed cell death ligand-1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

Common AEs: Balanced Between Cohorts, Aligned With Known Profiles of Durvalumab and FLOT



*AEs occurring in ≥20% of participants in any treatment group. †AEs occurring in ≥2% of participants in any treatment group. ‡Safety analysis set (participants who received at least one dose of study treatment); one participant in the placebo + FLOT group received a single dose of durvalumab and is, therefore, included in the durvalumab + FLOT group for the safety analysis.
AE, adverse event; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Conclusions

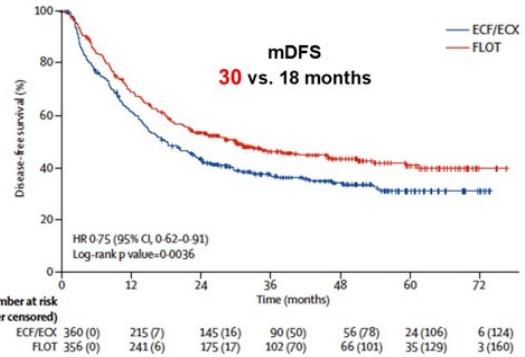
- **Durvalumab with FLOT significantly improved EFS** vs FLOT alone in resectable gastric and GEJ adenocarcinoma
- **EFS benefit was consistent** across subgroups and geographic regions
- No new safety concerns were identified
- OS data are encouraging; final OS analysis pending

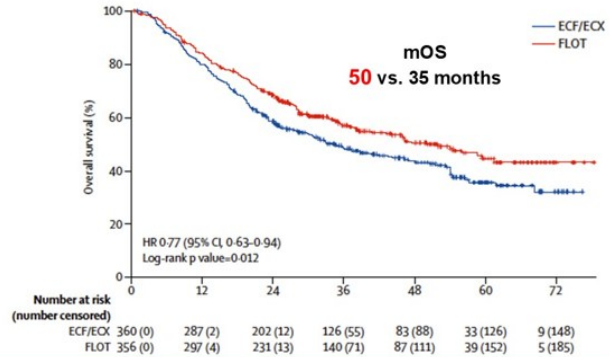
A copy of these slides and an infographic plain language summary of this presentation can be accessed via the QR code above

MATTERHORN supports global adoption of perioperative durvalumab with FLOT as a new standard for patients with localized gastric and gastroesophageal adenocarcinoma

EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastroesophageal junction; OS, overall survival.

Perioperative Therapy Is A Global Option

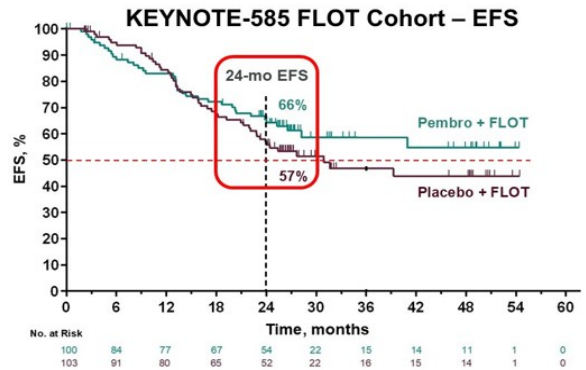


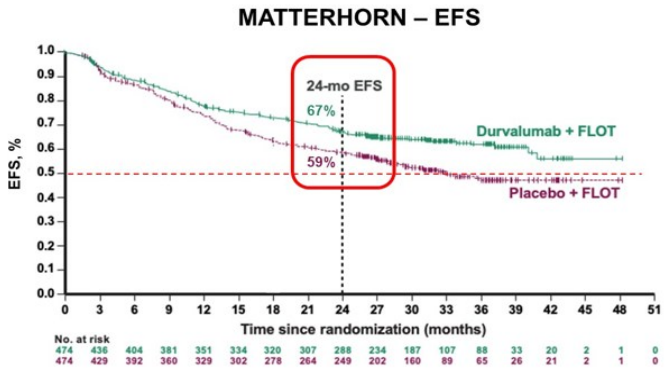


Guideline	Neoadjuvant/Periop Population	Endorsed Regimens	Key Trials
NCCN	High risk T2N0,cT1b-T2, N+, ≥cT3, any N	**FLOT**	AIO-FLOT4, ESOPEC
ESMO	Stage IB-III (>T1 and/or >N0)	**FLOT**	AIO-FLOT4, ESOPEC
Pan-Asian ESMO	cT4N+, Bulky Lymph Nodes	**FLOT** or DOS, or doublet	AIO- FLOT4, PRODIGY, RESOLVE, JCOG0501

Lancet Onc 2019

FLOT + ICI in MATTERHORN and KN-585



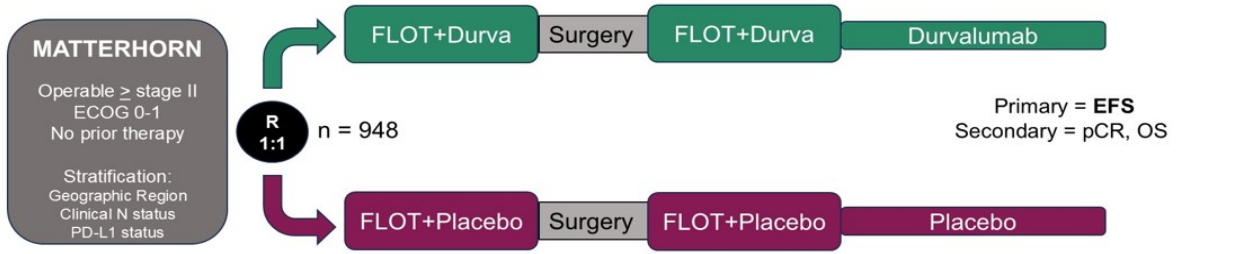


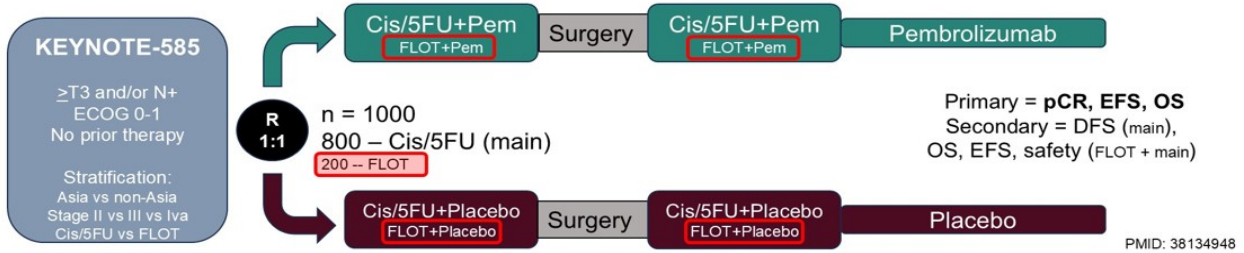
GI ASCO 2024

	Pembrolizumab + FLOT (n=100)	Placebo + FLOT (n=103)
Median EFS (95% CI), months	NR (28.2–NR)	30.9 (22.8–NR)
HR (95% CI)	**0.79 (0.52–1.22)**	
p-value	**NR**	

	Durvalumab + FLOT (n=474)	Placebo + FLOT (n=474)
Median EFS (95% CI), months	NR (40.7–NR)	32.8 (27.9–NR)
HR (95% CI)	**0.71 (0.58–0.86)**	
p-value	**<0.001**	

MATTERHORN In the Perioperative ICI Landscape





PMID: 38134948

Summarizing and Implementing MATTERHORN

Question	MATTERHORN Answer	My Answer	My Comments
Will it change practice?	YES	YES	• Met primary endpoint • Clear and meaningful EFS improvement
Is EFS enough?	YES	YES	• Clinically important, approvable • EFS displays OS surrogacy
Should we offer for all?	YES	YES	• No subgroup to exclude, yes to all PD-L1 strata • Oldest patient in MATTERHORN was 84
Will OS be positive?	TBD	YES	• Promising curve shape, p = 0.03 now • Strong design with p threshold 0.049 at FA

References, PMID: 38134948, 34252374, 39952264, 34133211, 38996201, 36652563, 39542422

2025 ASCO ANNUAL MEETING

Precision Oncology Changing the Tide in the First-Line Setting of Metastatic Colorectal Cancer

Gastrointestinal Cancers: Colorectal Cancer – Highlights of the Day

Christine Parseghian, MD
Associate Professor of Gastrointestinal Medical Oncology
UT MD Anderson Cancer Center

Key Takeaway Points/Conclusions

BRAF-directed therapy for mCRC (BREAKWATER): PFS, ORR, and now OS data support the **FDA approval of Encorafenib, Cetuximab, plus FOLFOX in the 1L setting**

- **Is this practice changing?** YES!

Immunotherapy for dMMR/MSI-H mCRC (CheckMate 8HW): NIVO + IPI combination checkpoint blockade has response and survival benefit over single-agent NIVO **across all lines of therapy**

- **Is this practice changing?** YES!

KRAS G12C-directed therapy for mCRC (CODEBREAK 101): With long-term follow up, sotorasib plus panitumumab plus FOLFIRI showed promising ORR, PFS and OS in 2L+.

- **Is this practice changing?** Not quite yet.

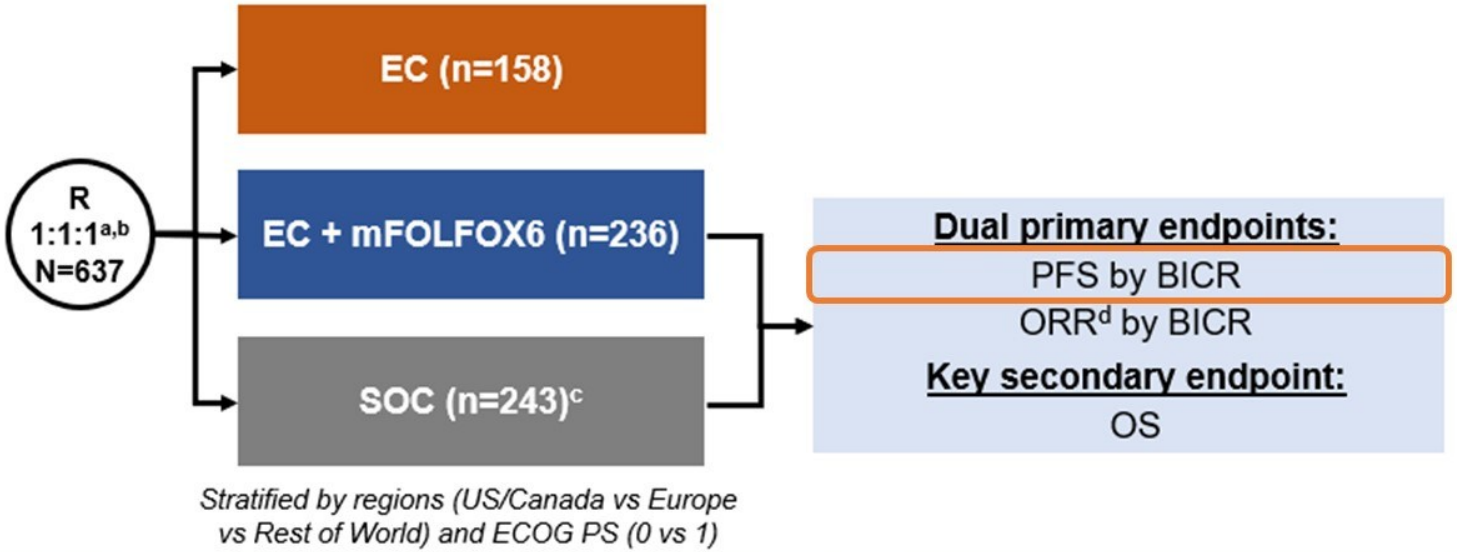
Abstract LBA3500: First-line encorafenib plus cetuximab and mFOLFOX6 in BRAF V600E MT mCRC (BREAKWATER): Survival updates

Inclusion criteria

- Age ≥16 years (or ≥18 years based on country)
- No prior systemic treatment for metastatic disease
- Measurable disease (RECIST 1.1)
- BRAF V600E-mutant mCRC by local or central laboratory testing
- ECOG PS 0 or 1
- Adequate bone marrow, hepatic, and renal function

Exclusion criteria

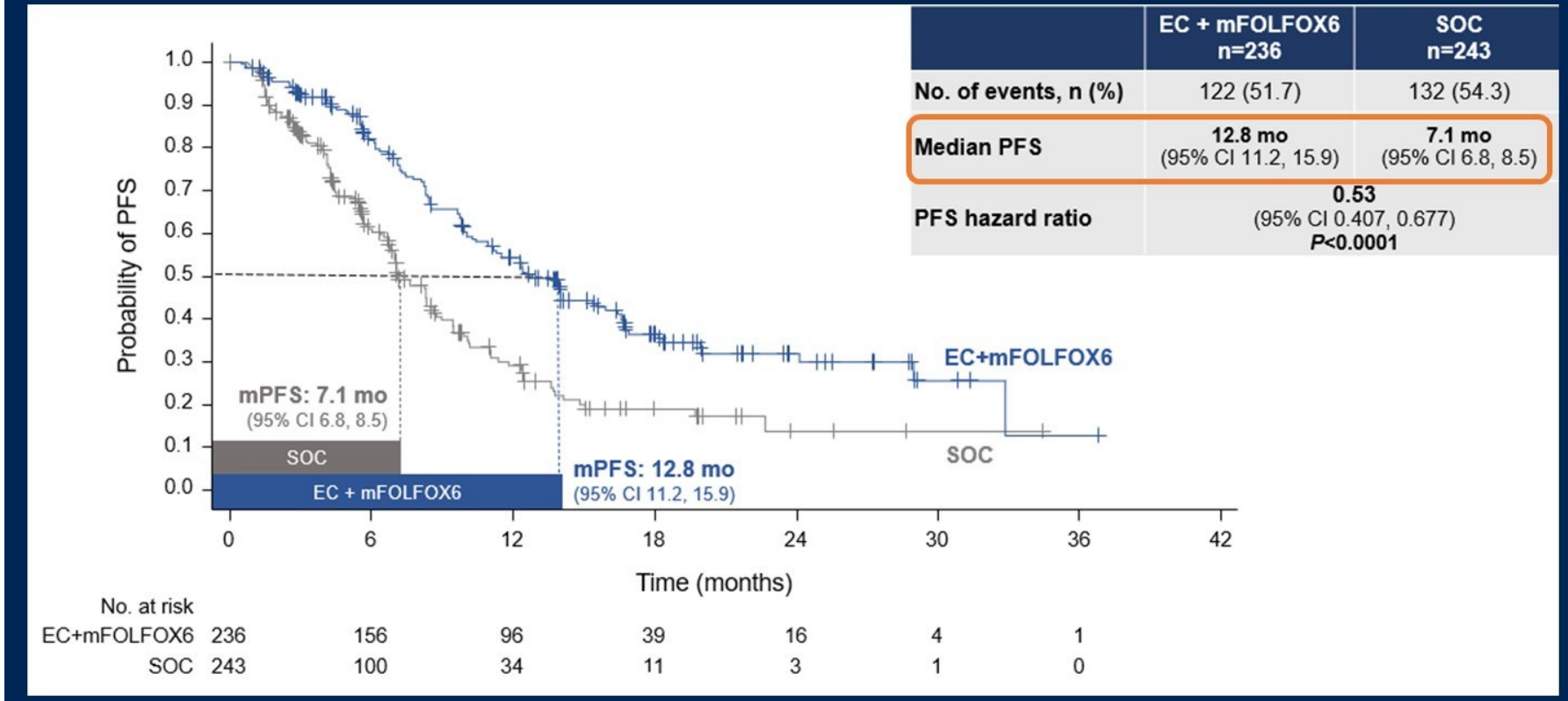
- Prior BRAF or EGFR inhibitors
- Symptomatic brain metastases
- MSI-H/dMMR tumors (unless patients were ineligible to receive immune checkpoint inhibitors due to a pre-existing medical condition)
- Presence of a *RAS* mutation



- As part of FDA Project FrontRunner, the **ORR** was previously read out and led to an accelerated approval that was contingent for full approval upon the **PFS** co-primary endpoint, now reported at ASCO.
- Here they present the primary analysis of **PFS** and a second interim analysis of **OS** in the EC + mFOLFOX and SOC arms, the efficacy data in the EC arm, and safety in all.

Elez et al., ASCO 2025

Abstract LBA3500: Primary Progression Free Survival Analysis (EC + mFOLFOX6 vs SOC)



	EC + mFOLFOX6 n=236	SOC n=243
No. of events, n (%)	122 (51.7)	132 (54.3)
Median PFS	**12.8 mo** (95% CI 11.2, 15.9)	**7.1 mo** (95% CI 6.8, 8.5)
PFS hazard ratio	**0.53** (95% CI 0.407, 0.677) ***P*<0.0001**	

✓ Second dual primary met

Striking improvement in PFS of nearly 6 months.

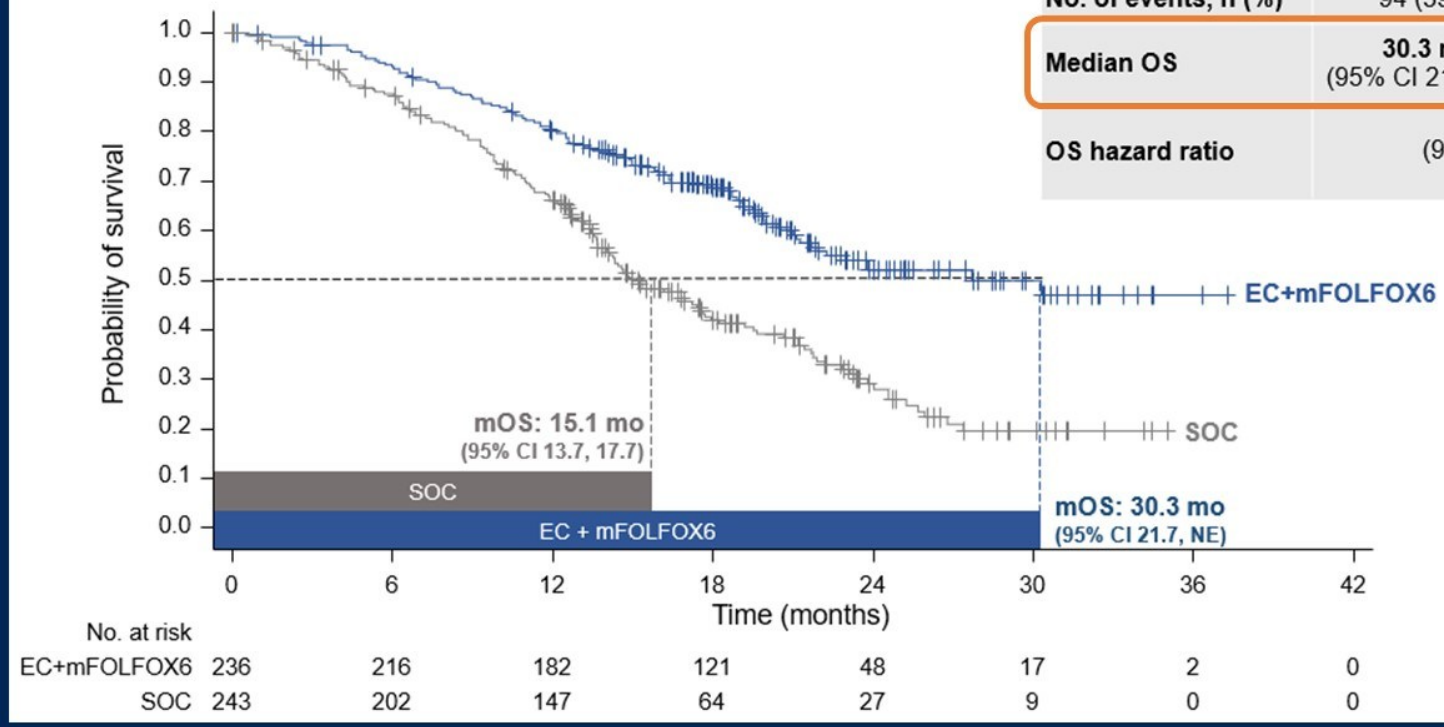
In a population where only half of patients survive to receive second-line, these results are incredibly clinically meaningful.

EC + mFOLFOX favored in all subgroup analyses of PFS including in pts with > 3 or more organs involved, including liver

Elez et al., ASCO 2025

Abstract LBA3500: Updated Overall Survival analysis (EC + mFOLFOX6 vs SOC)

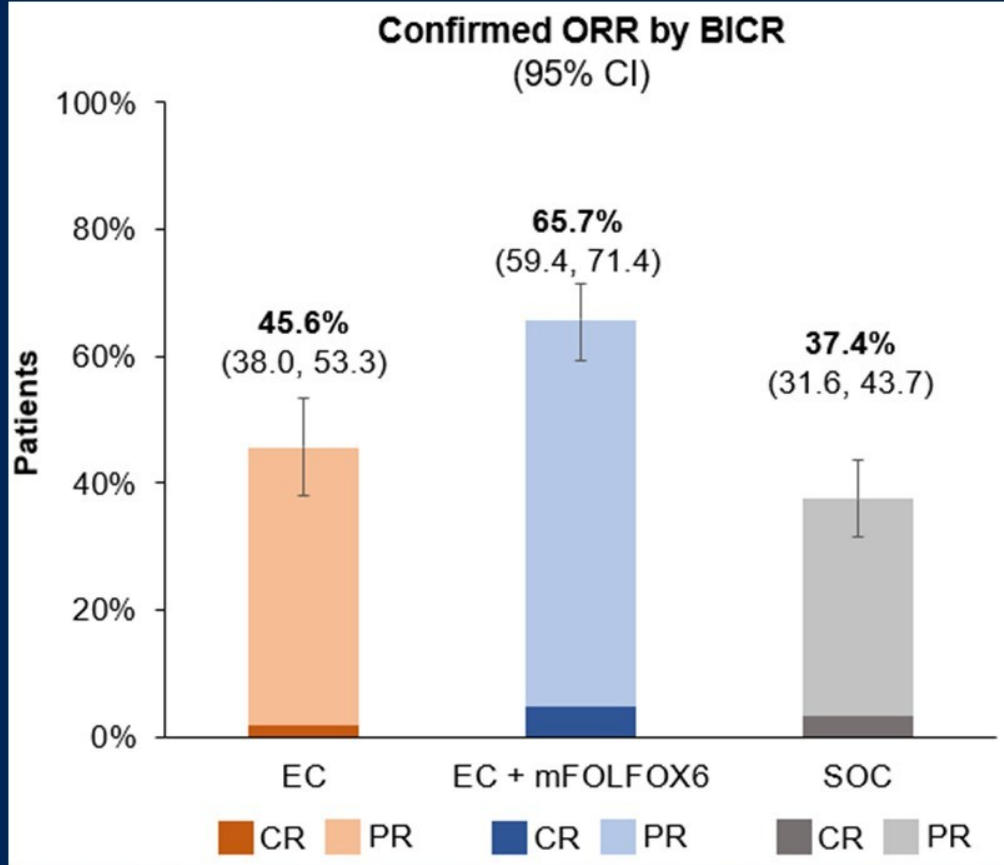
	EC + mFOLFOX6 n=236	SOC n=243
No. of events, n (%)	94 (39.8)	148 (60.9)
Median OS	**30.3 mo** (95% CI 21.7, NE)	**15.1 mo** (95% CI 13.7, 17.7)
OS hazard ratio	**0.49** (95% CI 0.375, 0.632) ***P*<0.0001**[a]	



- The second interim analysis of OS demonstrated statistically and clinically meaningful improvement, with a doubling of the OS in the EC + FOLFOX arm.
- EC + mFOLFOX favored in all subgroup analyses of OS

Elez et al., ASCO 2025

Abstract LBA3500: Updated Best Overall Response in all patients



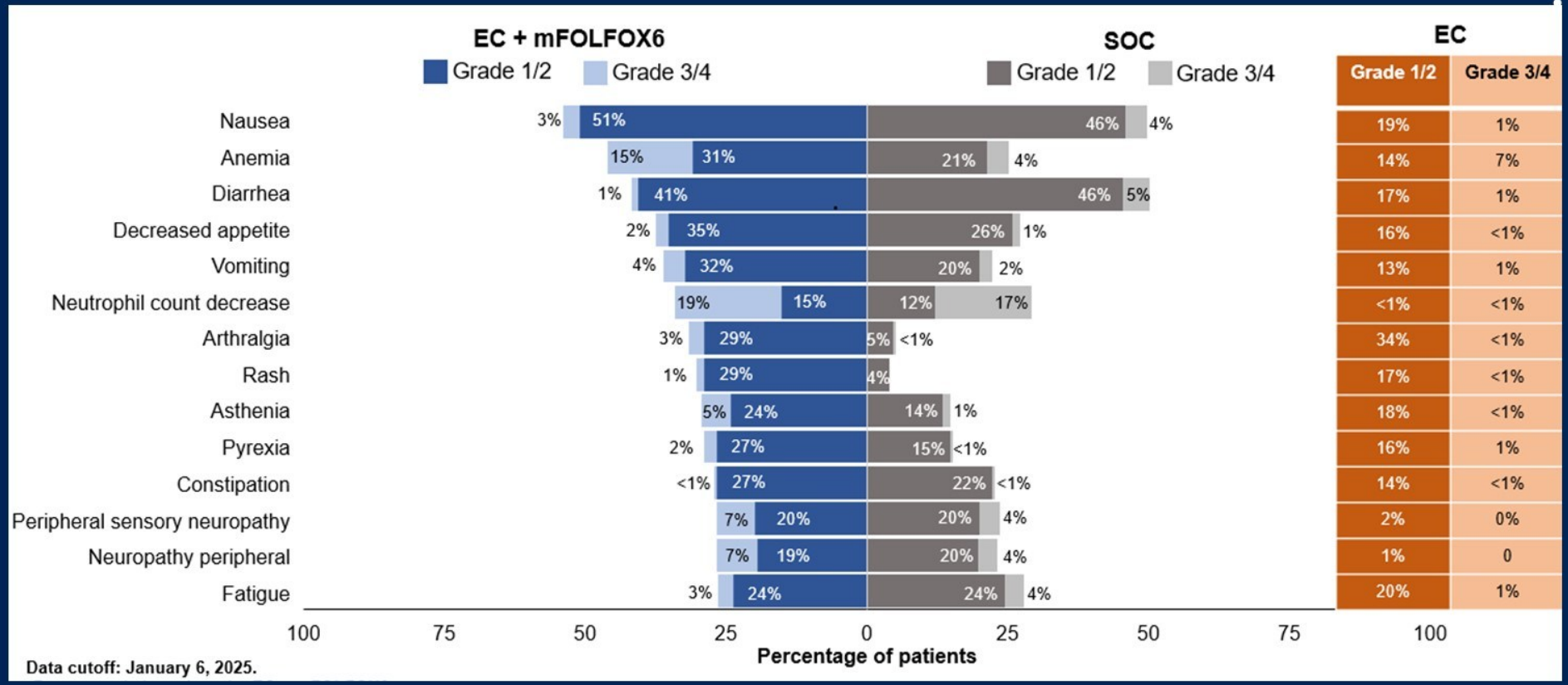
Confirmed Best Overall Response, TTR, and DOR by BICR

All randomized patients	EC n=158	EC + mFOLFOX6 n=236	SOC n=243
Confirmed best overall response, n (%)[a]			
CR	3 (1.9)	11 (4.7)	8 (3.3)
PR	69 (43.7)	144 (61.0)	83 (34.2)
SD	57 (36.1)	50 (21.2)	85 (35.0)
PD	12 (7.6)	8 (3.4)	21 (8.6)
Responders	**n=72**	**n=155**	**n=91**
TTR, median (range), weeks	6.6 (4.3 to 86.4)	7.0 (5.1 to 103.6)	7.3 (5.4 to 48.0)
DOR, median (95% CI), months	7.0 (4.2, 11.6)	13.9 (10.9, 18.5)	10.8 (7.6, 13.4)
Patients with a DOR of ≥6 months, n (%)	29 (40.3)	110 (71.0)	38 (41.8)
Patients with a DOR of ≥12 months, n (%)	15 (20.8)	54 (34.8)	16 (17.6)

Updated data now showing improvement in ORR by **28%.** Continued signs of doubling of the rate of durable responses

Elez et al., ASCO 2025

Abstract LBA3500: Most Frequent (≥25%) All Causality TEAEs



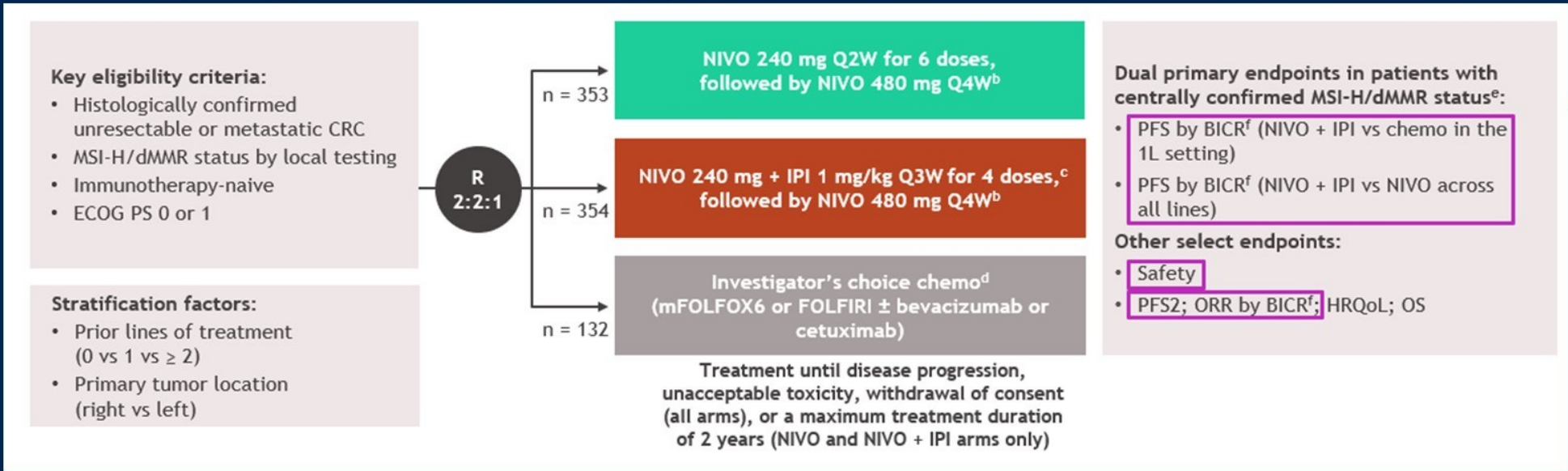
Mainly GI toxicities, slightly more prominent with EC + mFOLFOX

Significant differences seen in arthralgia, rash and asthenia which are known side effects of EC (class effect).

Cytopenias and asthenia differences not unexpected with mFOLFOX may also be related to extended time on treatment.

Elez et al., ASCO 2025

Abstract 3501: Nivolumab plus ipilimumab vs chemotherapy or nivolumab monotherapy for dMMR CRC: Expanded analysis from CheckMate 8HW



At data cutoff (8/2024), the median follow up was 47 months

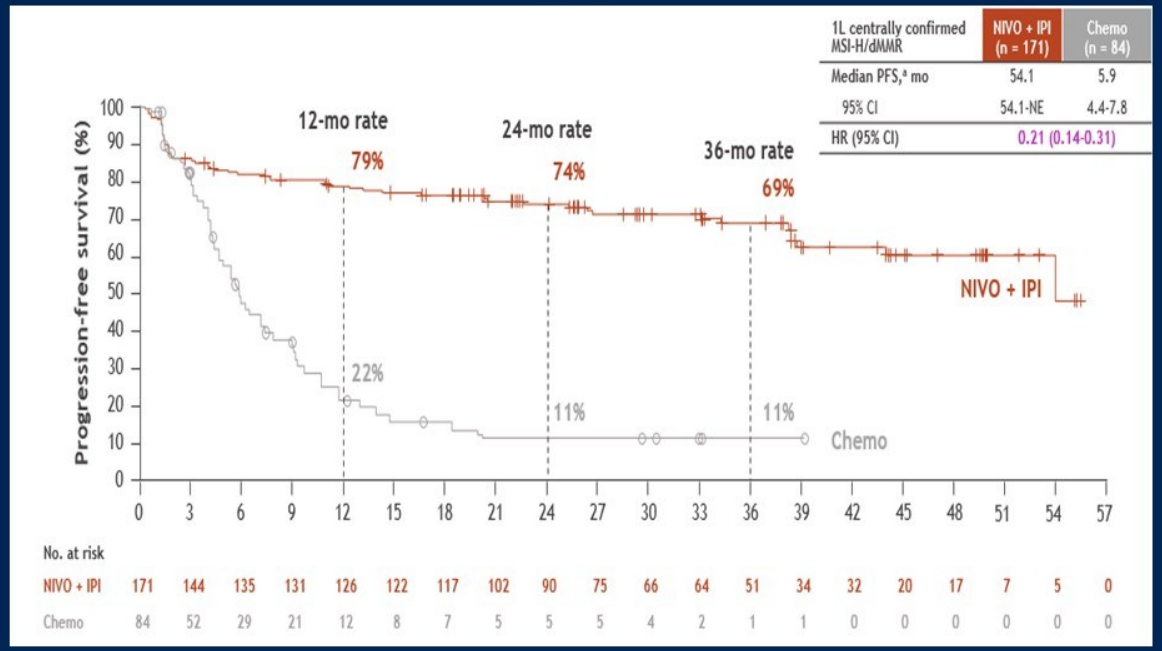
- NIVO + IPI already reported out as superior PFS vs chemo in 1L (HR 0.21; P < 0.0001) and superior PFS vs NIVO across all lines, (HR, 0.62; P = 0.0003).
- Here reporting expanded analyses of NIVO + IPI vs NIVO across all lines and longer follow up results for NIVO + IPI vs chemo in the 1L setting

André et al, Lancet 2025; Lenz et al., ASCO 2025

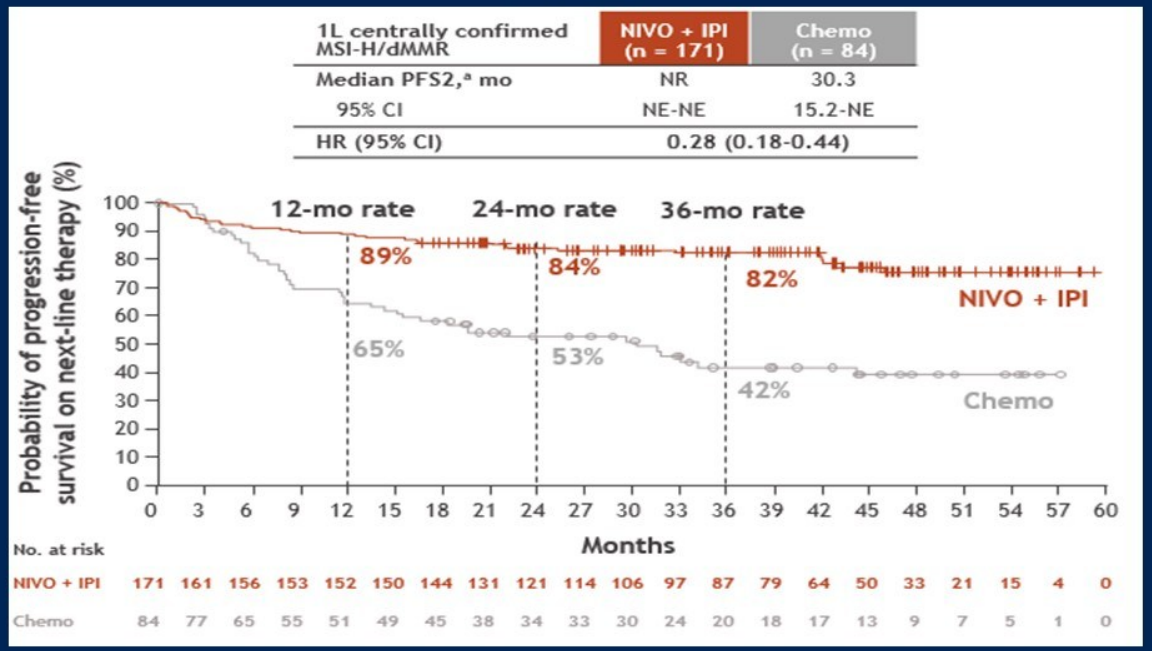
PRESENTED BY: Christine Parseghian, MD

Abstract 3501: PFS of NIVO + IPI vs chemo (1L)

PFS



PFS2



- NIVO + IPI continued to show clinically meaningful PFS benefit vs chemo with longer follow-up
- Early separation and flattening of curves
- PFS2 continued to favor NIVO + IPI vs chemo with a 72% reduction in the risk of death or disease progression after first subsequent therapy, **<u>despite a high rate of susbsequent immunotherapy in the chemo group (71%)</u>**

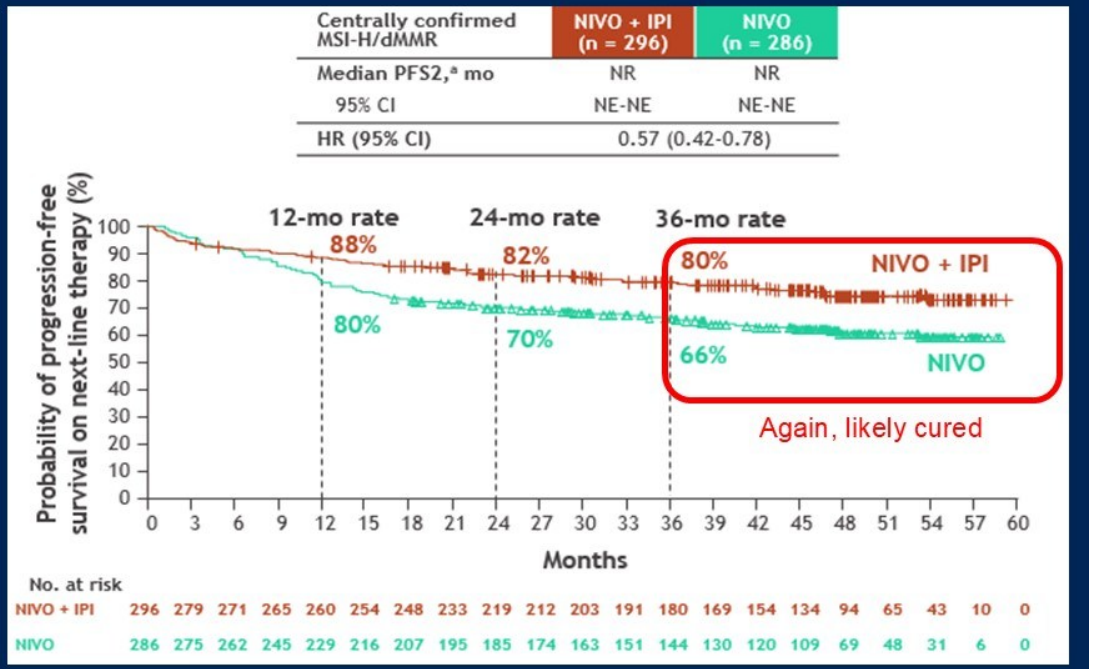
Lenz et al., ASCO 2025

Abstract 3501: PFS of Nivolumab/Ipilumumab vs Nivolumab (all lines)

PFS

Would consider these pts essentially cured

PFS2



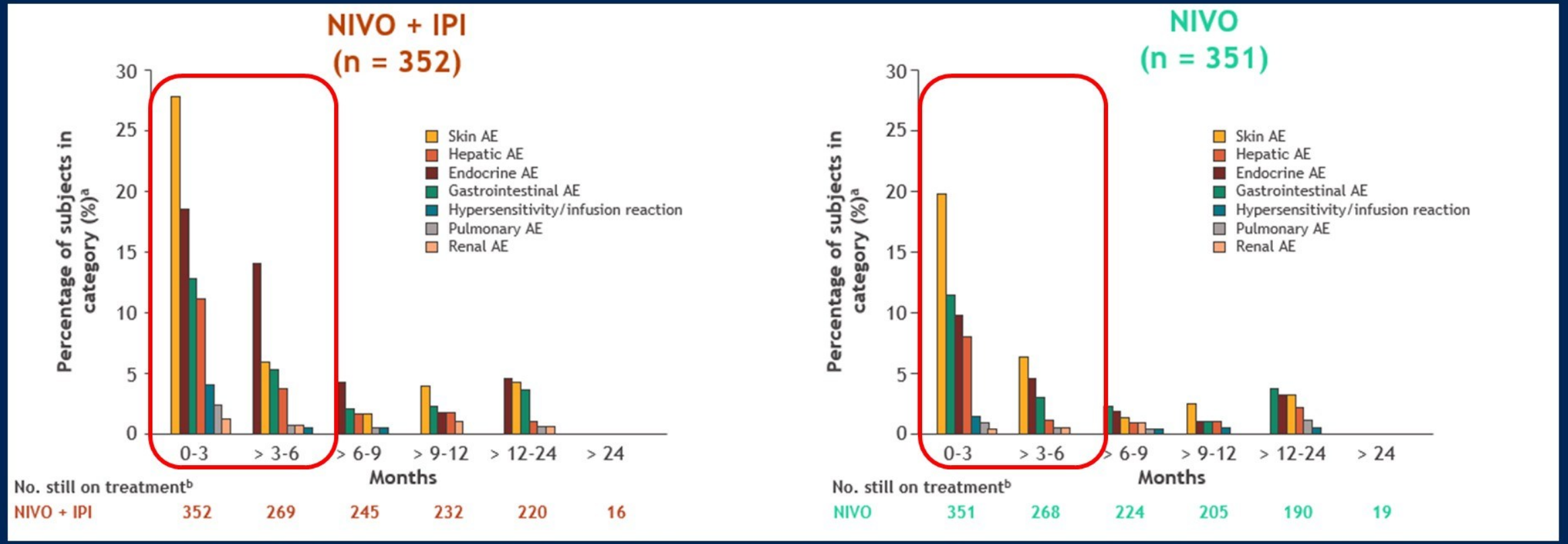
Again, likely cured

- NIVO + IPI demonstrated statistically significant and clinically meaningful PFS benefit vs NIVO (38% reduction in risk of death or progression to 1L)

- PFS2 data clearly favor upfront NIVO + IPI over NIVO alone
- Benefit of upfront IPI could not be fully matched by a 2L (early progression?).
- Sequencing matters!

Lenz et al., ASCO 2025

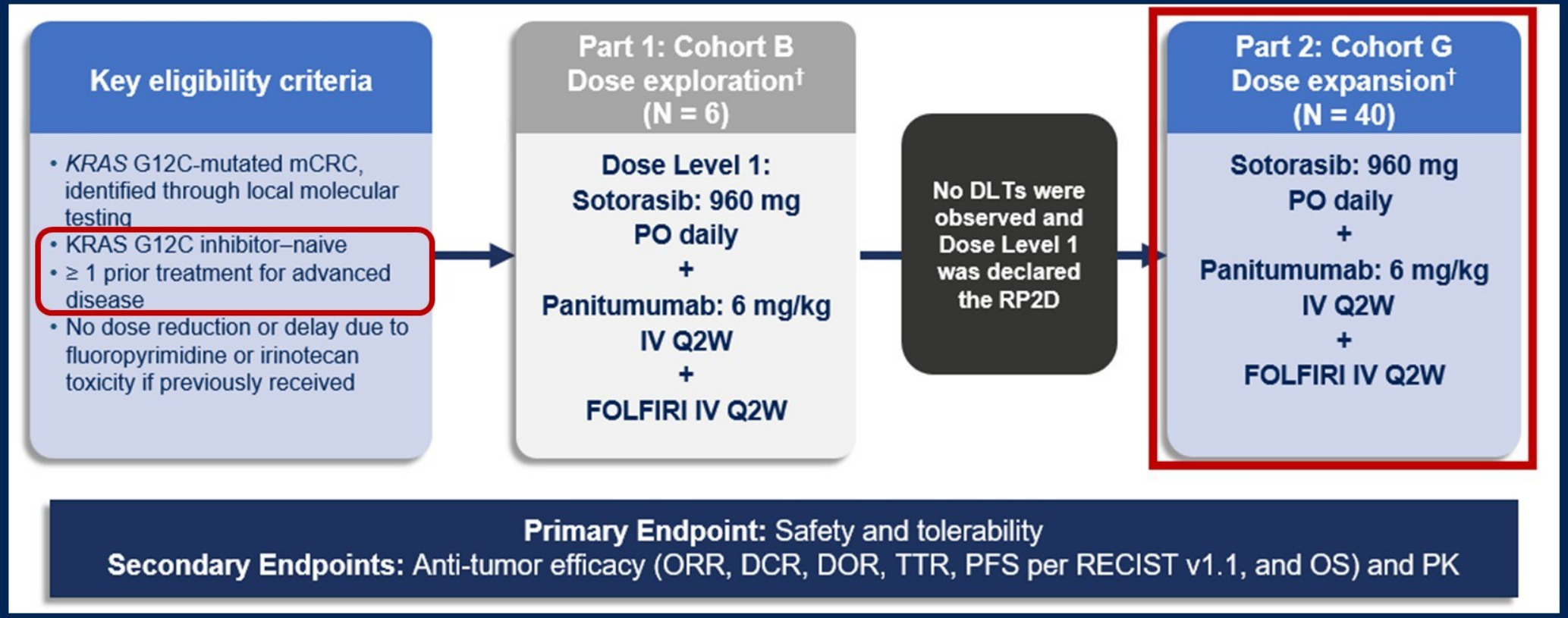
Abstract 3501: Emergency of immunologic TRAEs over time



- Majority of TRAEs occurring in the first 3-6 months of therapy. Side effects relatively comparable aside from endocrine and skin toxicities
- Timing predictability allows for proactive management of toxicities

Lenz et al., ASCO 2025

Abstract 3506: Long-term safety and efficacy of sotorasib plus panitumumab and FOLFIRI for previously treated KRAS G12C MT mCRC: CodeBreak 101 (phase 1b subprotocol)



Strickler et al, ASCO 2025

Abstract 3506: Baseline Characteristics

- All patients received prior 5-FU and oxaliplatin, 73% received prior irinotecan, and 50% progressed on prior irinotecan
- Heavily pretreated population (68% with ≥ 2 prior lines)

Characteristic	Part 2: Cohort G (N = 40)
Prior lines of therapy for metastatic disease	
1	13 (33)
2	12 (30)
≥ 3	15 (38)
Median (range)	2 (1-6)
Prior therapies	
Fluoropyrimidine	40 (100)
Oxaliplatin	40 (100)
Irinotecan	29 (73)
Anti-angiogenic biologic*	31 (78)
Regorafenib and/or trifluridine-tipiracil	9 (23)
Anti-PD-(L)1	2 (5)
Anti-EGFR antibody	2 (5)

Strickler et al, ASCO 2025

Abstract 3506: Efficacy

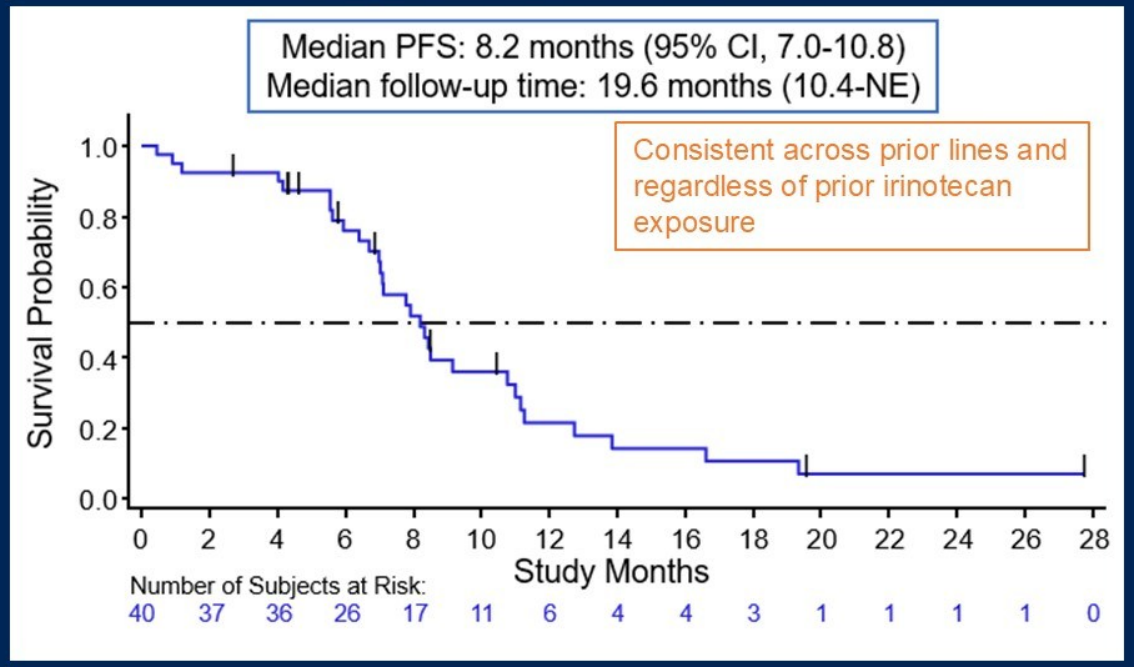
Response by investigator assessment	Part 2: Cohort G (N = 40)
ORR confirmed 95% CI	23 (57.5) 40.9-73.0
CR	0
PR	23 (57.5)
SD	14 (35.0)
PD	2 (5.0)
Unavailable	1 (2.5)
DCR 95% CI	37 (92.5) 79.6-98.4
DOR, median, mo (95% CI)	6.6 (5.5-9.7)

- Confirmed ORR 57.5%, with DCR of 92.5%
- Responses seen regardless of prior progression on irinotecan-based regimens

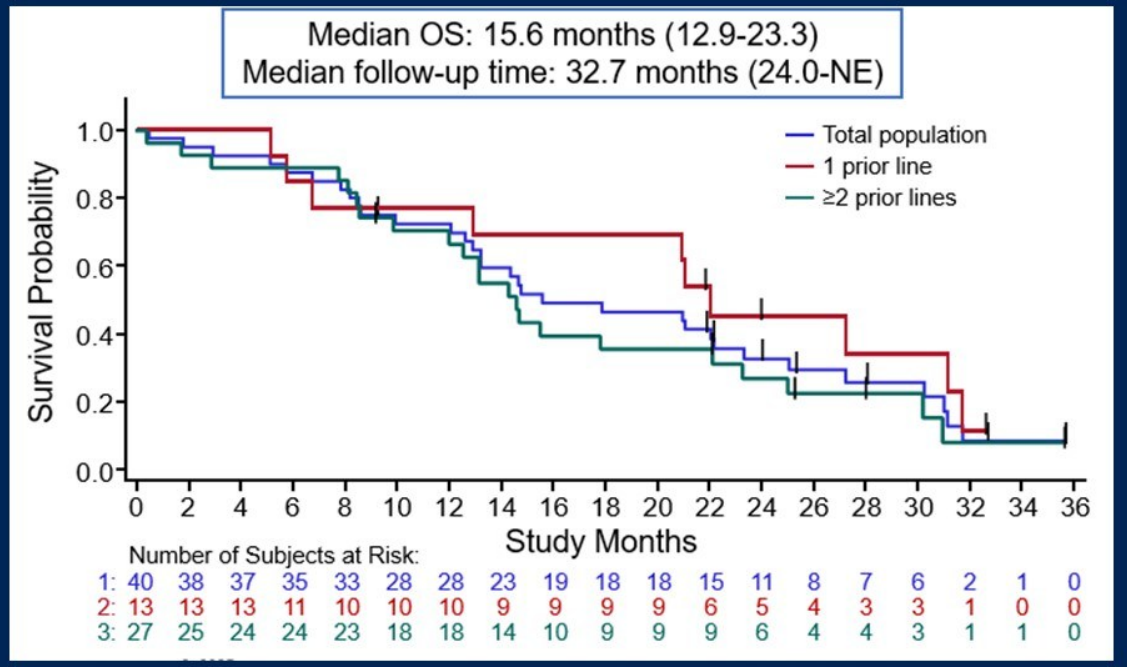
Strickler et al, ASCO 2025

Abstract 3506: Survival outcomes

Progression-free survival



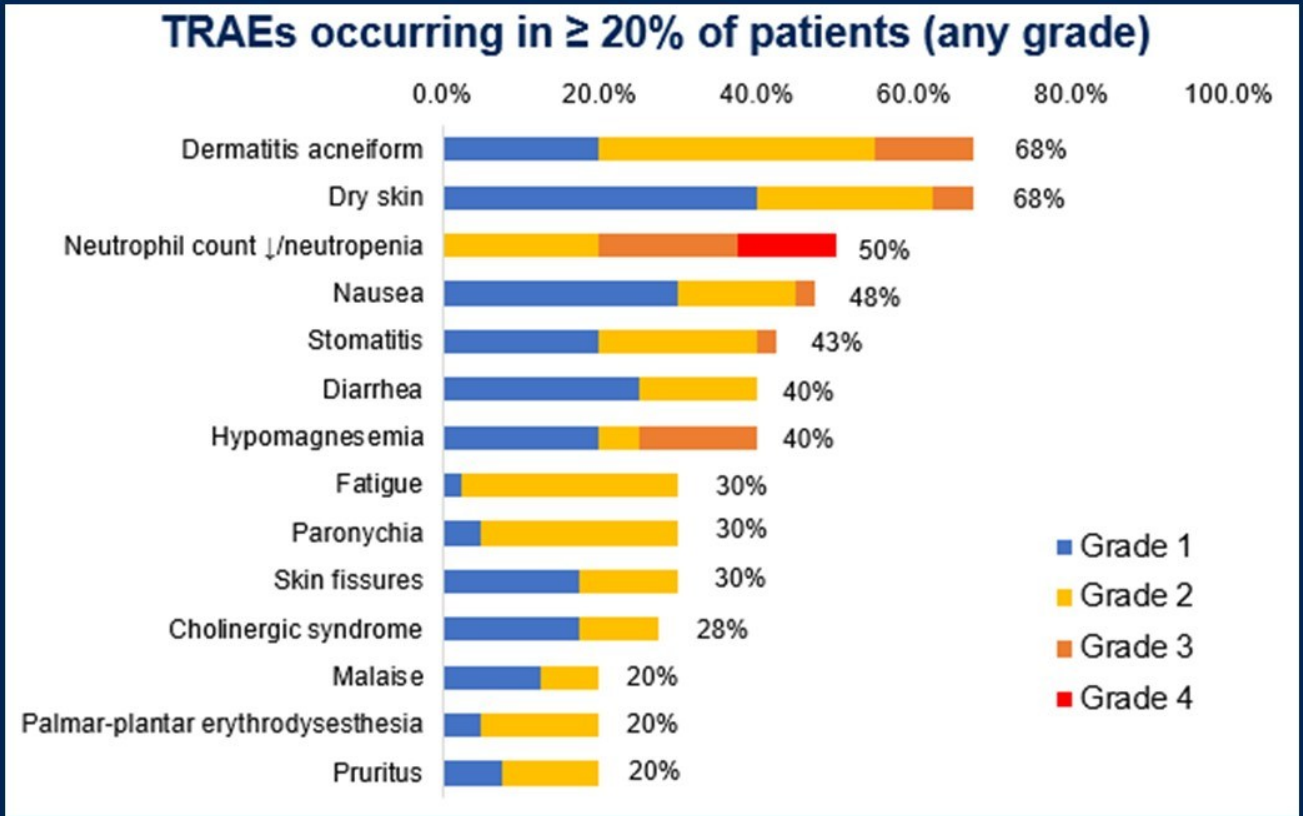
Overall survival by line



OS was numerically superior in those with only 1 line of prior therapy, but not statistically significant

Strickler et al, ASCO 2025

Abstract 3506: Safety



- Safety profile consistent with that known for each agent.
- Grade 4 TRAEs were neutropenia in n=5 (13%)
- 37.5% of patients required a component of FOLFIRI to be discontinued due to TRAE
  - FIRE-3 (FOLFIRI plus cetux) saw 14-20% of patients needing treatment modifications or discontinuation due to toxicity

Strickler et al, ASCO 2025

Key Takeaway Points/Conclusions

BRAF-directed therapy for mCRC: PFS, ORR, and now OS data support the **FDA approval of EC plus FOLFOX in the 1L setting**

- **Questions**: Will FOLFIRI backbone chemotherapy have similar efficacy? →Data to come. Is there a role for rechallenge with BRAF V600E inhibitors if fails frontline? → Not yet, but trials needed. Should I add EC if FOLFOX already started and NGS finds a BRAF V600E MT? YES! Sequencing matters!
- **Is this practice changing?** YES! EC + mFOLFOX is the new SOC for BRAF V600E MT mCRC in 1L.

Immunotherapy for dMMR/MSI-H mCRC: NIVO + IPI has response/survival benefit over single agent NIVO across all lines of therapy.

- **Questions:** Is cost and slightly worse toxicity of the dual checkpoint blockade justifiable in all patients? Need biomarkers for response to personalize immunotherapy type and duration. Is PD-1/CTLA-4 the optimal combination?
- **Is this practice changing?** YES! Nivo/Ipi now approved in1L dMMR mCRC. Sequencing matters! The long-term radiographic control likely represents **cure**, as highlighted by the rarity of disease progression after 2 years of therapy and case series of surgically resected residual radiographic disease with pathological CR. **Potential cure outweighs minimal increased risk of toxicity with the doublet.**

KRAS G12C-directed therapy for mCRC: Sotorasib plus panitumumab plus FOLFIRI showed promising ORR, PFS and OS in 2L+.

- **Questions**: Will outcomes improve in 1L? (ongoing phase 3 CodeBreak 301 study). Is there a role for rechallenge with KRAS G12C inhibitors if fails with first exposure? → Not yet. Trials needed.
- **Is this practice changing?** Not quite yet. Awaiting CodeBreak 301. Continue to use sotorasib plus panitumumab or cetuximab plus adagrasib for 2L+ per FDA approval.

2025 ASCO ANNUAL MEETING

Highlights of the Day

Gastrointestinal Cancer- Gastroesophageal, Pancreatic, and Hepatobiliary

Namrata (Neena) Vijayvergia, MD FACP

Fox Chase Cancer Center PA

Highlights of the Day: non colorectal GI

1. **PANOVA-3**: Phase 3 study of Tumor Treating Fields (TTFields) with gemcitabine and nab-paclitaxel (GnP) for locally advanced pancreatic adenocarcinoma (LAPC)

2. **DESTINY-Gastric04**: Trastuzumab deruxtecan vs ramucirumab plus paclitaxel in second-line treatment of patients with human epidermal growth factor receptor 2–positive (HER2+) unresectable and/or metastatic gastric cancer or gastroesophageal junction adenocarcinoma.

3. **CheckMate 577**: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: final analysis of overall survival

4. **IKF S662 GAIN**: Neoadjuvant chemotherapy with gemcitabine plus cisplatin followed by radical liver resection versus immediate radical liver resection alone followed adjuvant therapy in biliary tract cancer

PRESENTED BY: Namrata (Neena) Vijayvergia, MD FACP

Key Takeaway Points

1

- TTFields shows promise for LAPC with limited toxicity.
- OS benefit without PFS improvement: need for pause

2

- DFS benefit without OS gain from adjuvant nivolumab for esophageal cancer
- Use in ESCC and esophageal adenoCA PD-L1 +ve, not candidates for FLOT

3

- T-DXd is a new standard in 2L HER2+ Gastric Cancer over Paclitaxel/ Ramucirumab
- Need to reconfirm Her2 status

4

- Neoadjuvant gemcitabine/cisplatin is a promising approach in early-stage BTC
- Larger and adequately powered trials are needed

PRESENTED BY: Namrata (Neena) Vijayvergia, MD FACP

PANOVA-3: Phase 3 study of Tumor Treating Fields (TTFields) with gemcitabine and nab-paclitaxel (GnP) for locally advanced pancreatic adenocarcinoma (LA-PAC)

Vincent Picozzi, Hani Babiker, Sreenivasa Chandana, Bohuslav Melichar, Anup Kasi, Jin Gang, Javier Gallego, Andrea Bullock, Hao Chunyi, Lucjan Wyrwicz, Arsen Osipov, Christelle de la Fouchardiere, Tomislav Dragovich, Woojin Lee, Kynan Feeney, Philip Philip, Makoto Ueno, Eric Van Cutsem, Thomas Seufferlein, Teresa Macarulla on behalf of the PANOVA-3 study investigators

LAPC- a high unmet need

- The current SOC for unresectable LAPC is combination chemotherapy (GnP, FOLFIRINOX, NALIRIFOX) +/- radiation
- **Clinical evidence not promising**
  - **LAP-07 (2016)**
    - **No OS benefit** with CRT (16.5 vs. 15.2 months, *p* = 0.83).
  - **CONKO-007 (2022)**
    - **Improved local control and resectability**, but **no significant OS benefit** (15.0 vs. 15.1 months, *p* = 0.713).
  - **NEOPAN (PRODIGE 29-UCGI 26, 2024)**
    - **Improved PFS** with FOLFIRINOX but **no OS benefit**; higher toxicity.

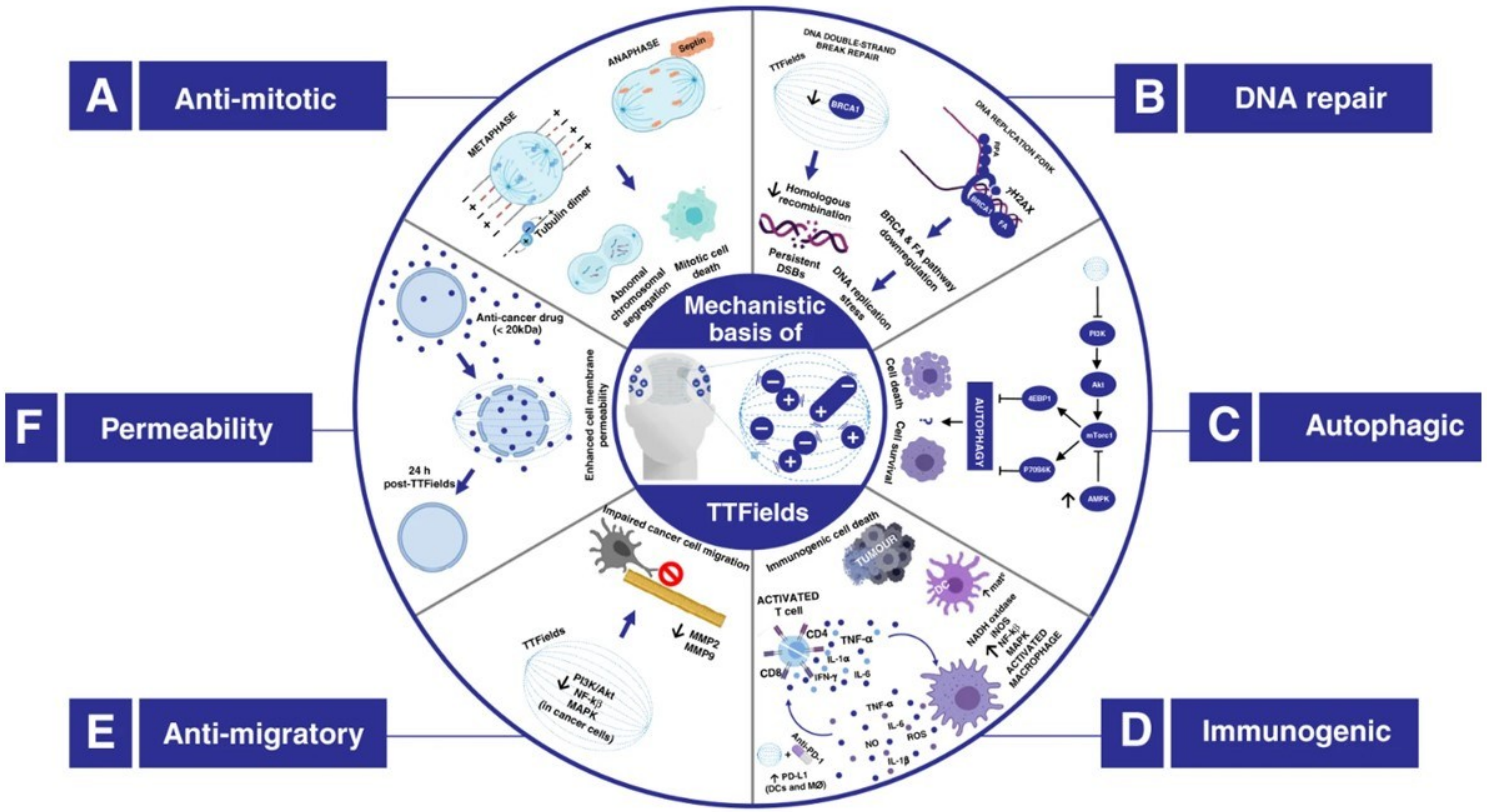
Tumor Treating Fields: the device

The Device

The Arrays

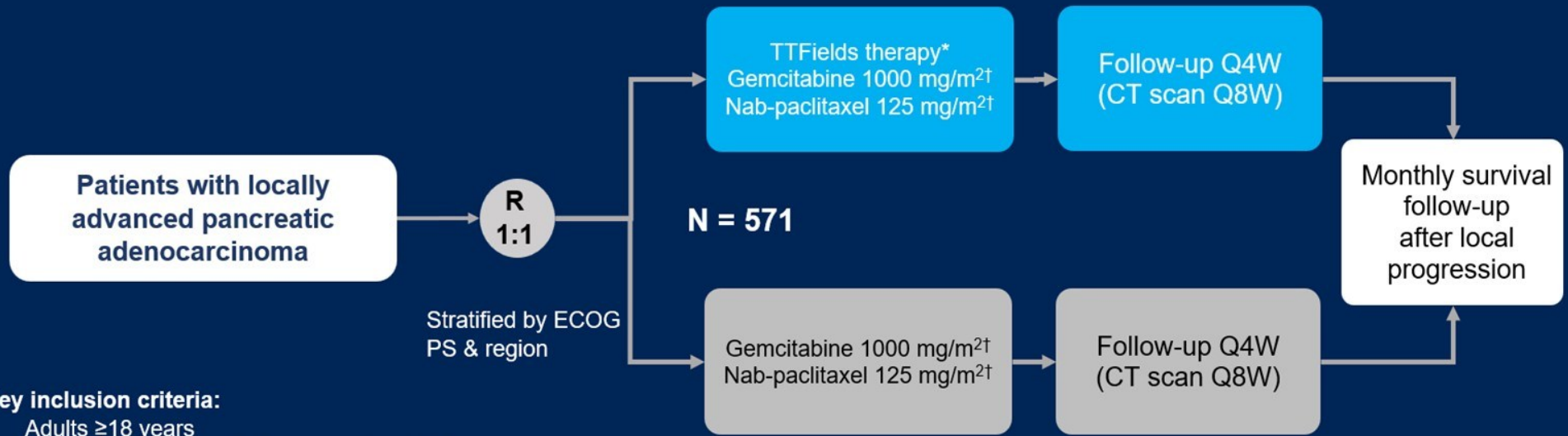
Currently approved for Glioblastoma multiforme, mesothelioma and NSCLC

Tumor Treating Fields : proposed mechanisms



Rominiyi et.al., *Br J Cancer* **124**, 697–709 (2021)

PANOVA-3 study design



Key inclusion criteria:
- Adults ≥18 years
- Previously untreated, biopsy confirmed disease
- Life expectancy ≥3 months
- ECOG PS 0-2

Key exclusion criteria:
- Prior palliative treatment to the tumor
- Implanted electronic medical device in torso
- Known allergies to medical adhesives, hydrogel or chemotherapies

Study sites: 198 across 20 countries (North and South America, Europe, Asia)‡
Enrollment: March 2018 – March 2023

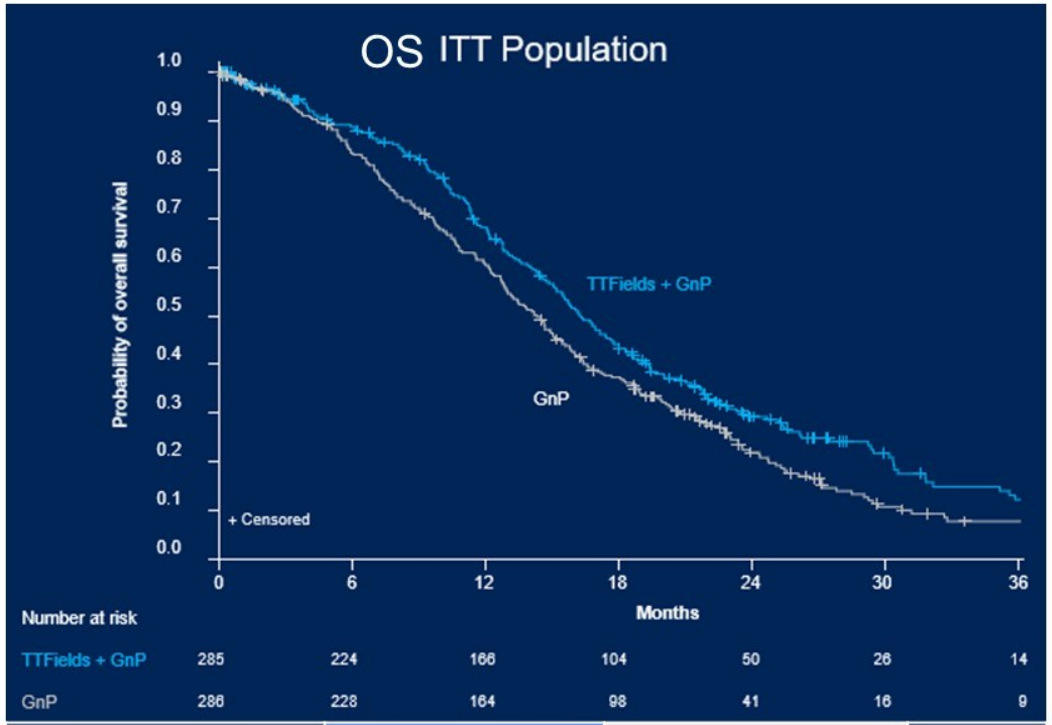
Data cut-off: October 16, 2024
Registration number: NCT03377491

1º endpoint: OS
2º endpoint: PFS, pain free survival

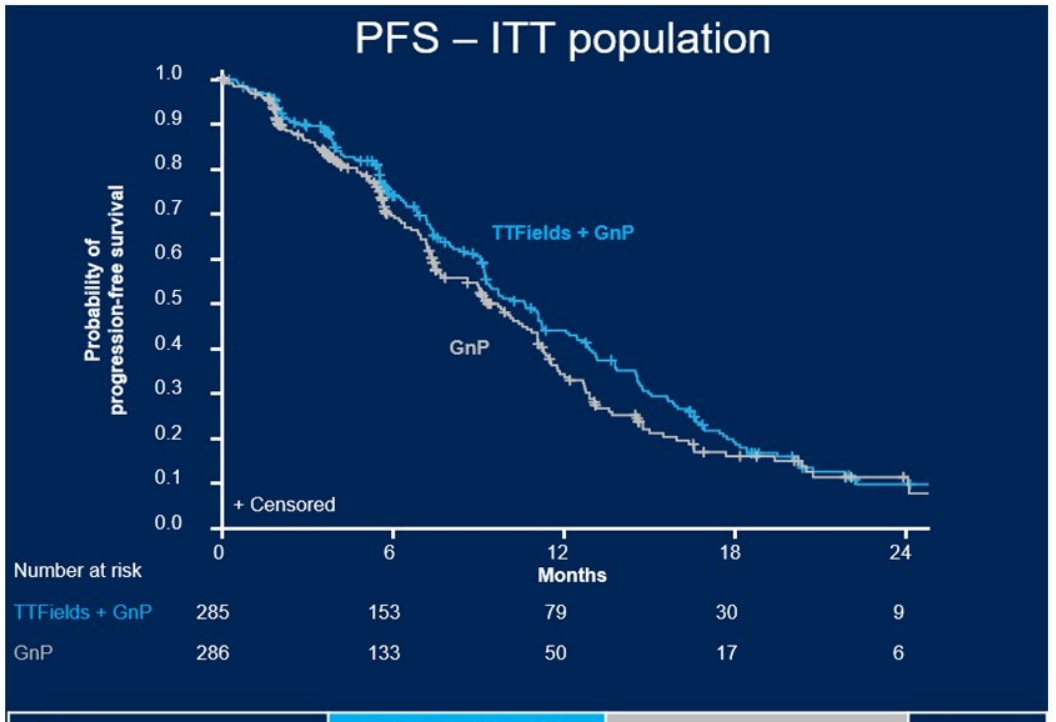
*150 kHz, 18h/day; †On days 1, 8, and 15 of each 28-day cycle; ‡ US, Mexico, Brazil, Canada; Spain, Hungary, Czech Republic, France, Poland, Germany, Austria, Switzerland, Italy, Israel, Belgium, Croatia; China, South Korea, Australia and Hong Kong;
ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICF, informed consent form; R, randomization; TTFields, Tumor Treating Fields; Q4W, every 4 weeks; Q8W, every 8 weeks

Picozzi et.al., ASCO 2025

PANOVA 3: Efficacy data



ITT	TTFields with GnP	GnP	P-val
Median OS (95% CI)	16.2 (15.0, 18.0)	14.2 (12.8, 15.4)	0.039
	HR = 0.82 (95% CI: 0.68, 0.99)		



ITT	TTFields with GnP	GnP	P-value
Median PFS (95% CI) Events	10.6 (9.2, 12.2) 176	9.3 (7.6, 11.1) 162	0.137
	HR = 0.85 (95% CI: 0.68, 1.05)		

Median pain free survival = 15.2 m vs 9.1 m, p 0.027

Picozzi et.al., ASCO 2025

Toxicity of TTFields : clinical and other

AEs occurring in ≥20% of patients overall, n (%)	TTFields with GnP (N=274)		GnP (N=273)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	268 (97.8)	243 (88.7)	270 (89.9)	230 (84.2)
Dermatitis	82 (29.9)	8 (2.9)	8 (2.9)	0
Rash	71 (25.9)	5 (1.8)	23 (8.4)	1 (0.4)
Pruritus	61 (22.3)	0	23 (8.4)	0

AE, n (%)	TTFields with GnP (N=274)		GnP (N=273)	
	All grades	Grade ≥3	All grades	Grade ≥3
Serious AE	147 (53.6)	143 (52.2)	131 (48.0)	130 (47.6)
AE leading to device discontinuation	23 (8.4)		NA	
AE leading to chemotherapy discontinuation	47 (17.2)		43 (15.8)	
AE leading to death	17 (6.2)		16 (5.9)	

7.7% of patients reported a grade 3 skin AE

The cost for TTFields therapy for GBM costs approximately $20,000/month

Picozzi et.al., ASCO 2025

Clinical implications

Take home point: TTFields in addition to GnP an emerging option for LAPC with limited systemic toxicity.

- Is this practice changing?
  May be for small subset of LAPC population, pain control better

- When you get back to the clinic next week
  Informed discussion with patients about relative benefit and toxicity, need to continuous therapy

- Additional research to evaluate its benefit
  PANOVA 4 in metastatic pancreas cancer, data on subsequent therapies, sham control arm?

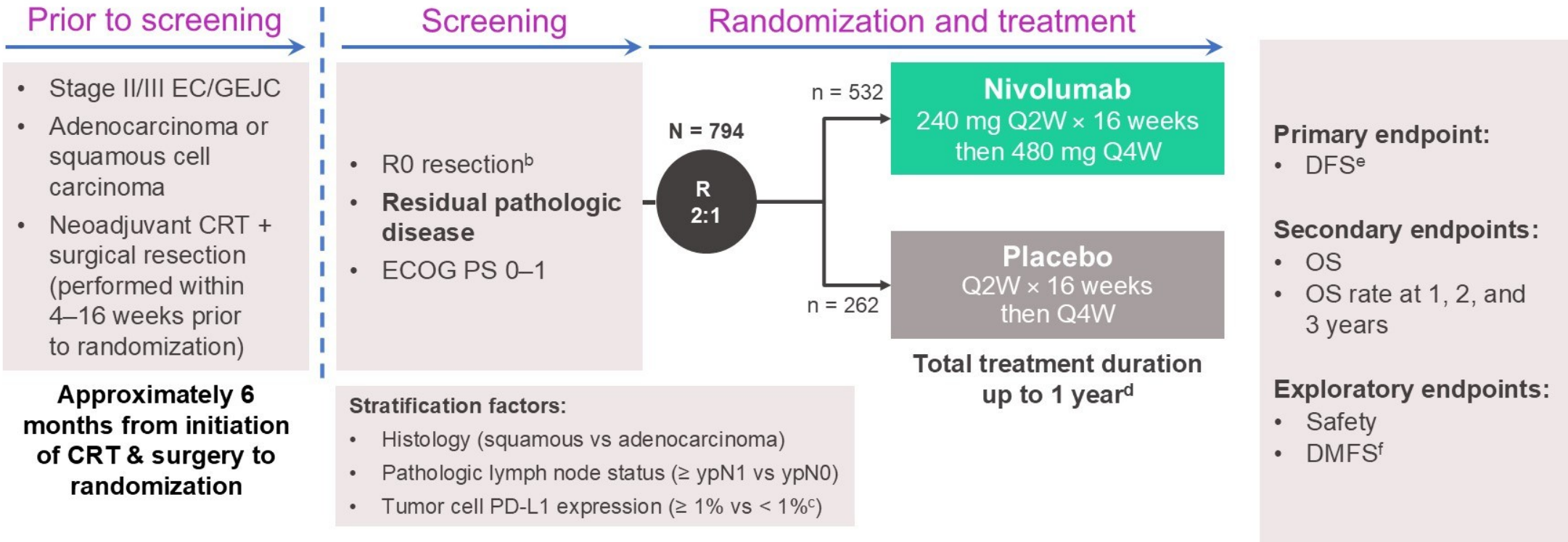
Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: final analysis of overall survival from CheckMate 577

Ronan J. Kelly,[1] Jaffer A. Ajani,[2] Jaroslaw Kuzdzal,[3] Thomas Zander,[4] Eric Van Cutsem,[5] Guillaume Piessen,[6] Guillermo Mendez,[7] Josephine Feliciano,[8] Satoru Motoyama,[9] Astrid Lièvre,[10] Hope Uronis,[11] Elena Elimova,[12] Cecile Grootscholten,[13] Karen Geboes,[14] Jenny Zhang,[15] Stephen McCraith,[15] Beilei He,[15] Ming Lei,[15] James M. Cleary,[16] Markus Moehler[17]

PRESENTED BY: Namrata (Neena) Vijayvergia MD FACP

CheckMate 577 study design

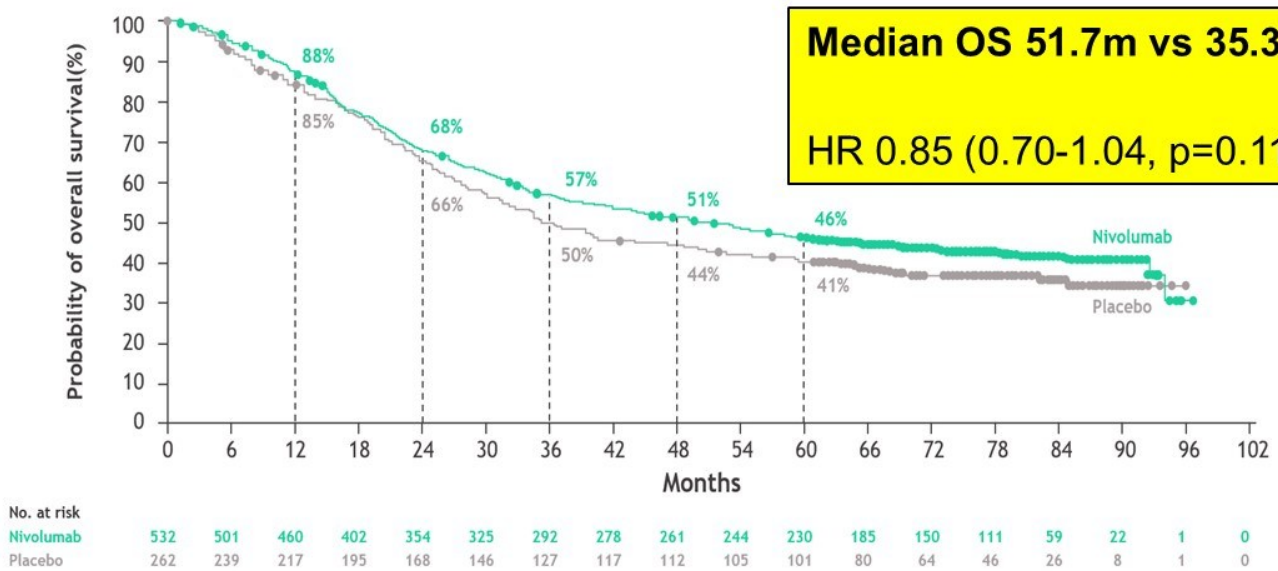
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]



- Median follow-up was 78.3 months (range, 60.1–96.6)

Kelly et.al., ASCO 2025

CM577: Updated Survival Analysis



- **DFS benefit preserved -**

  21.8m vs 10.8 m

  HR 0.76 (0.63 – 0.91)

- **OS numerically longer** by 16 months
- **OS significant** when **adjusted for subsequent therapies**

  OS 38.6 vs 20.2 months (HR 0.73, 0.58-0.95)

- **Subgroup analysis**: benefit
  - ESCC
  - CPS score>1

PRESENTED BY: Namrata (Neena) Vijayvergia MD FACP

Clinical implications

Take home point: Adjuvant Nivolumab continues to improve DFS with only numerical OS benefit in resected Esophageal Cancer

- Is this practice changing?
  Not really, but evolving landscape may restrict utilization to subgroups

- When you get back to the clinic next week
  Consider it for ESCC, patients not candidates for FLOT and possibly PD-L1+ve esophageal cancers

- Additional research to evaluate benefit
  Stay tuned for the MATTERHORN trial being presented today

Trastuzumab deruxtecan (TdXD) vs ramucirumab (RAM) plus paclitaxel (PTX) in second-line treatment of patients with human epidermal growth factor receptor 2–positive (HER2+) unresectable and/or metastatic gastric cancer or gastroesophageal junction adenocarcinoma: Primary analysis of the randomized, phase 3 DESTINY-Gastric04 study.

Kohei Shitara
National Cancer Center Hospital East, Kashiwa, Japan

Additional authors: Mahmut Gümüş, Filippo Pietrantonio, Sara Lonardi, Christelle de la Fouchardière, Clélia Coutzac, Jeroen Dekervel, Daniel Hochhauser, Lin Shen, Wasat Mansoor, Bo Liu, Lorenzo Fornaro, Min-Hee Ryu, Jeeyun Lee, Fabricio Souza, Lori Jukofsky, Yumin Zhao, Takahiro Kamio, Meredith Venerus, Aziz Zaanan, Eric Van Cutsem

Background

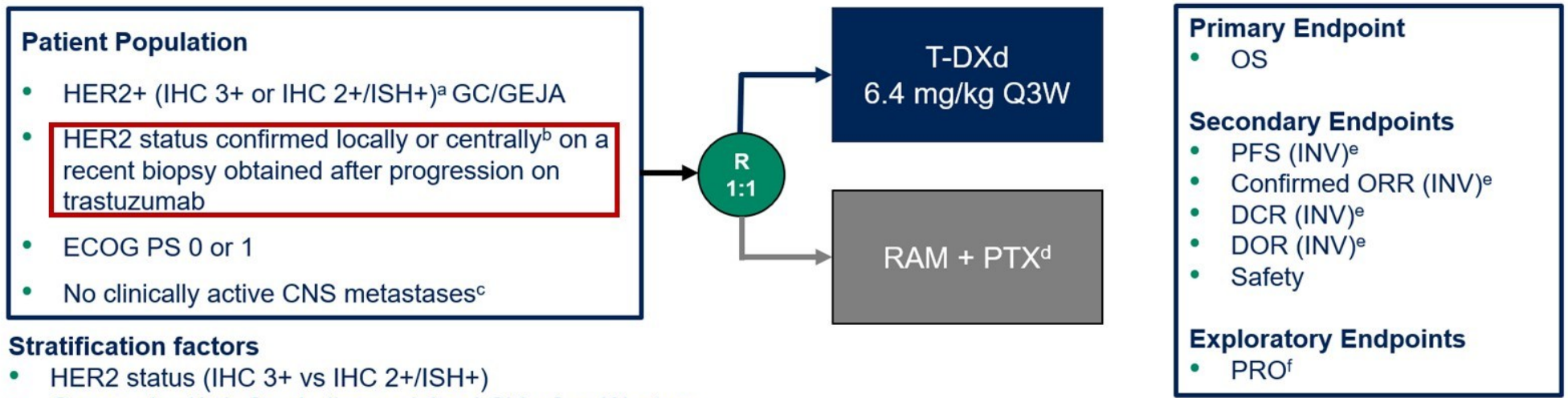
- Two options for second line therapy in Her2 +ve gastric and GE junction adenocarcinoma
  - T-DXd based on DESTINY-Gastric01/02/06
  - RAM + PTX per phase 3 RAINBOW trial

DESTINY-Gastric04 was conducted to evaluate T-DXd in a head-to-head phase 3 trial versus RAM + PTX in patients with HER2+ metastatic GC/GEJA

Shitara K et al. *N Engl J Med.* 2020;382:2419-30.
Van Cutsem E et al. *Lancet Oncol.* 2023;24:744-56.
Shen L et al. *Ann Oncol.* 2023;34:S1542-3.
Wilke H et al. *Lancet Oncol.* 2014;15:1224-35.

Study Design

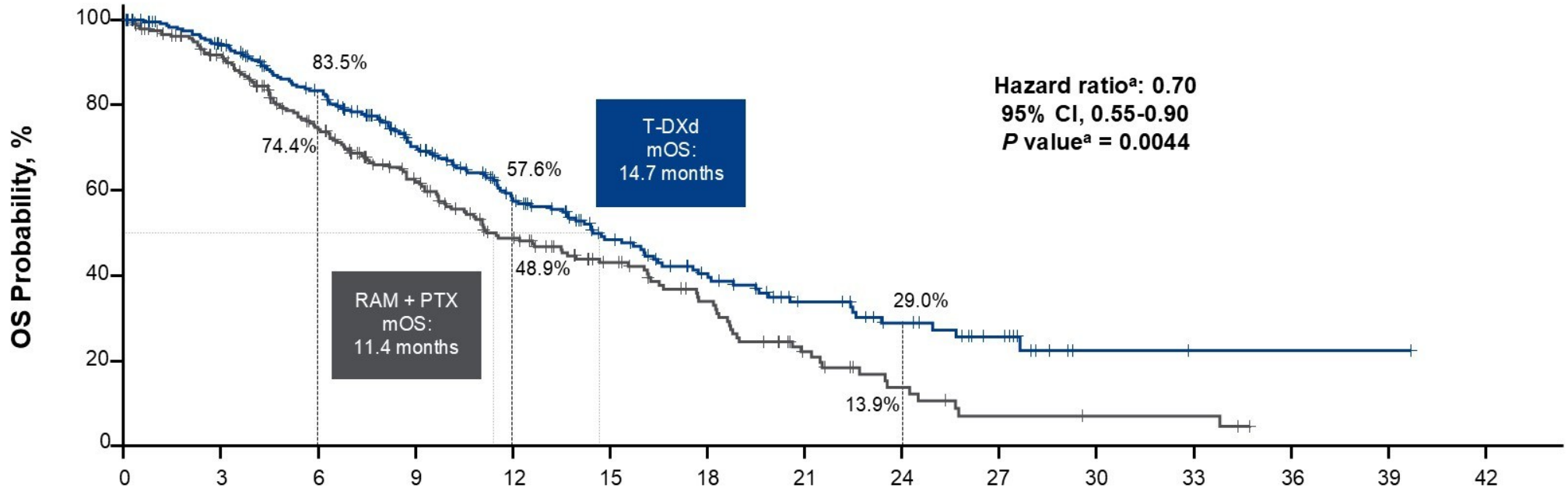
DESTINY-Gastric04: A Global, Multicenter, Randomized, Phase 3 Trial (NCT04704934)



Stratification factors

- HER2 status (IHC 3+ vs IHC 2+/ISH+)
- Geography (Asia [excluding mainland China] vs Western Europe vs mainland China/rest of world)
- Time to progression on 1L therapy (<6 months vs ≥6 months)

OS : Primary Endpoint

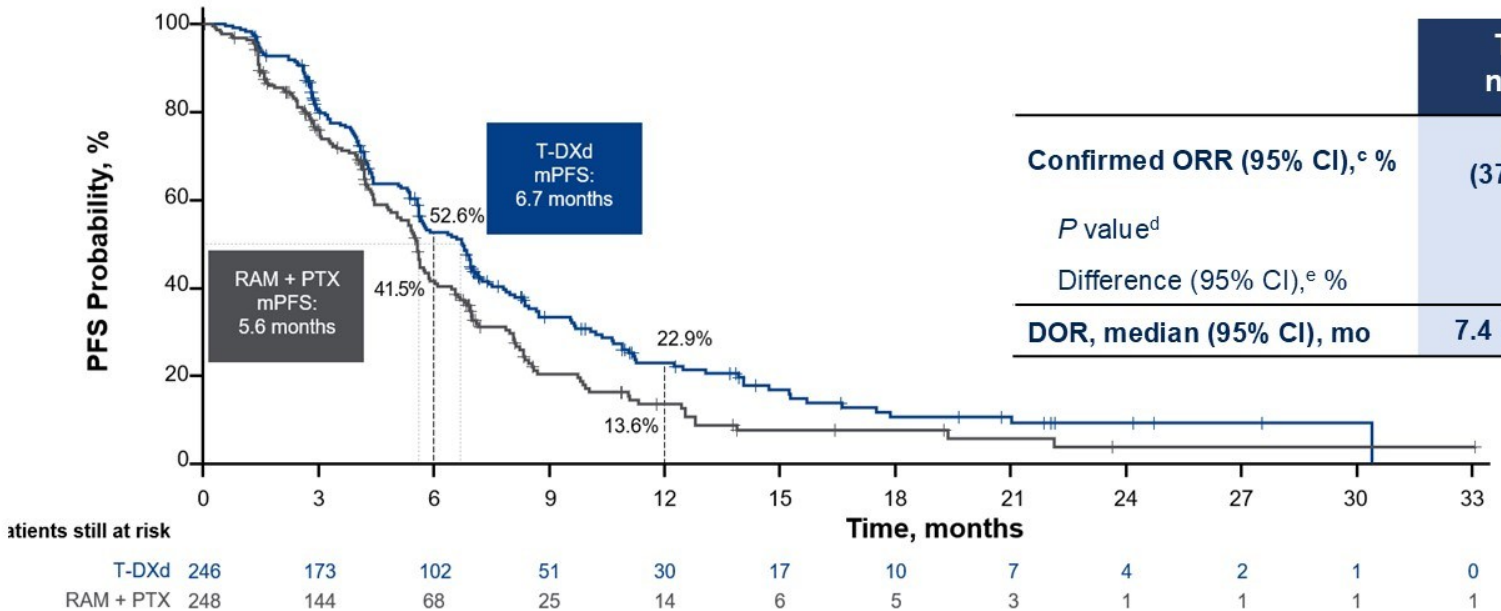


Patients still at risk

T-DXd	246	219	185	134	94	65	45	30	21	12	2	1	1	1	0
RAM + PTX	248	204	150	109	76	52	36	18	9	4	3	3	0		

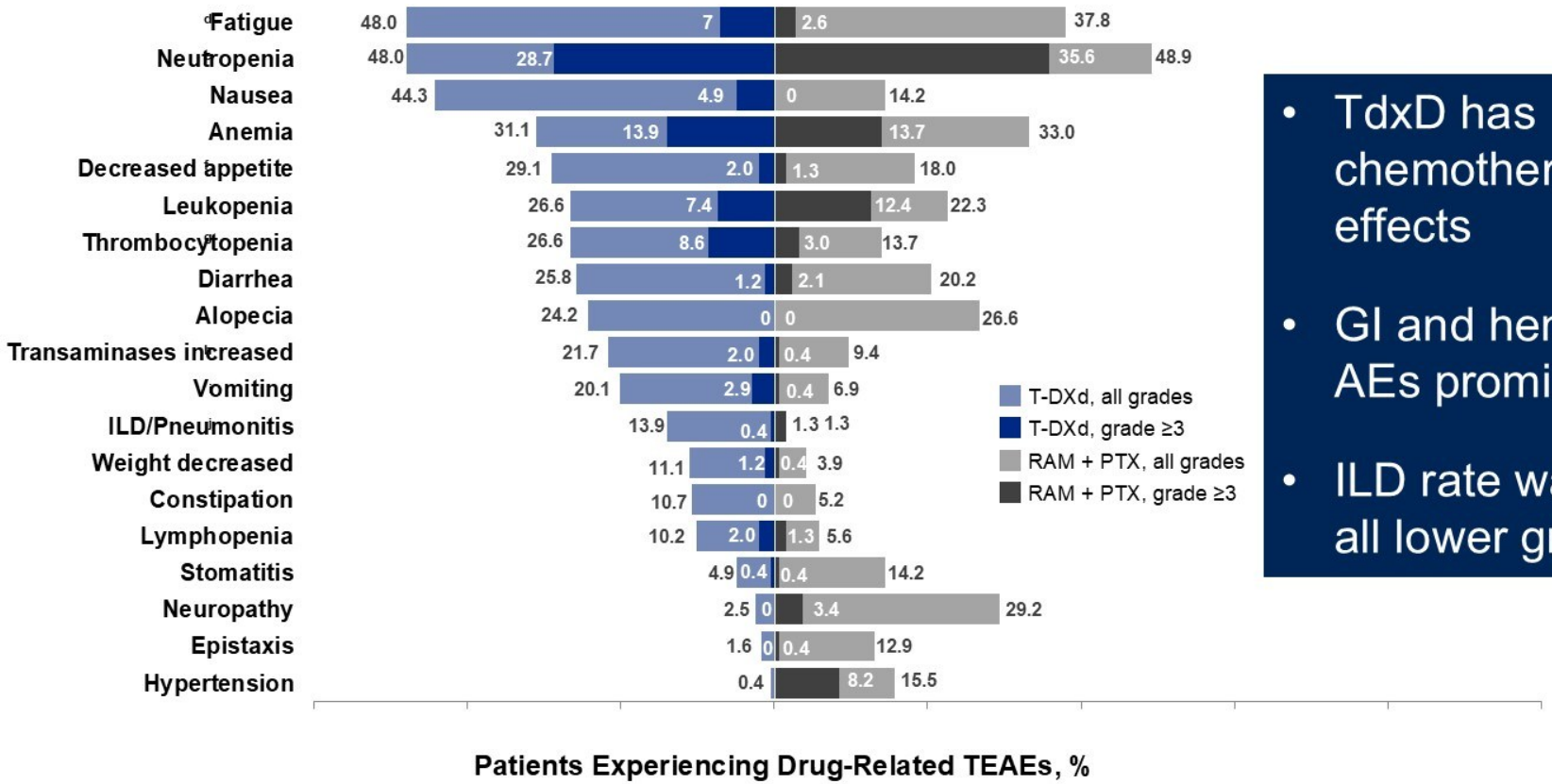
T-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with RAM + PTX in HER2+ GC/GEJA, showing a 30% reduction in risk of death

Secondary endpoints : PFS and ORR



	T-DXd n = 246	RAM + PTX n = 248
Confirmed ORR (95% CI),[c] %	**44.3 (37.8-50.9)**	**29.1 (23.4-35.3)**
P value[d]	0.0006	
Difference (95% CI),[e] %	15.1 (6.1-24.2)	
DOR, median (95% CI), mo	**7.4 (5.7-10.1)**	**5.3 (4.1-5.7)**

Adverse event profile[a]



- TdxD has chemotherapy side effects
- GI and hematologic AEs prominent
- ILD rate was 13.9% - all lower grade

Clinical implications

Take home point: T-DXd superior to RAM + paclitaxel in 2L+ Her2+ve Gastric/GE junction adenocarcinoma in terms of OS (14.7 vs 11.4 months; HR 0.70, *P*=0.0044)

- Is this practice changing?
  - Yes, globally this study validates efficacy of TDXd in 2L setting; Her2 reconfirmation must be standard
- When you get back to the clinic next week
  - Offer this to robust patients over RAM+ paclitaxel, but look out for ILD
- Additional research to evaluate benefit
  - Can availability of TDXd narrow the OS gap observed (only 21% received it in SOC arm)

The IKF S662 GAIN Trial

Neoadjuvant chemotherapy with gemcitabine plus cisplatin followed by radical liver resection versus immediate radical liver resection alone followed adjuvant therapy in biliary tract cancer
Final results from the phase III AIO/ CALGP/ ACO- GAIN-Trial

Thorsten O. Goetze, Arndt Vogel, Johann Pratschke, Matthias Behrend, Daniel Reim, Andreas A Schnitzbauer, Annalen Bleckmann, Silvan Becker, Nuh Rahbari, Stefan M. Brunner, Steffen Manekeller, Kim Barbara Luley, Sven Arke Lang, Kerstin Gutsche, Timorshah Habibzada, Jorge Klagges, Marina Schaaf, Claudia Pauligk, Ulli Simone Bankstahl, Salah-Eddin Al-Batran

Background: unmet need in early stage BTC

Neoadjuvant approach

PROS

- Can improve R0 resection rate
- Better compliance with therapy
- Early treatment of metastatic disease

CONS

- Delay of effective treatment of chemorefractory disease

Adjuvant approach

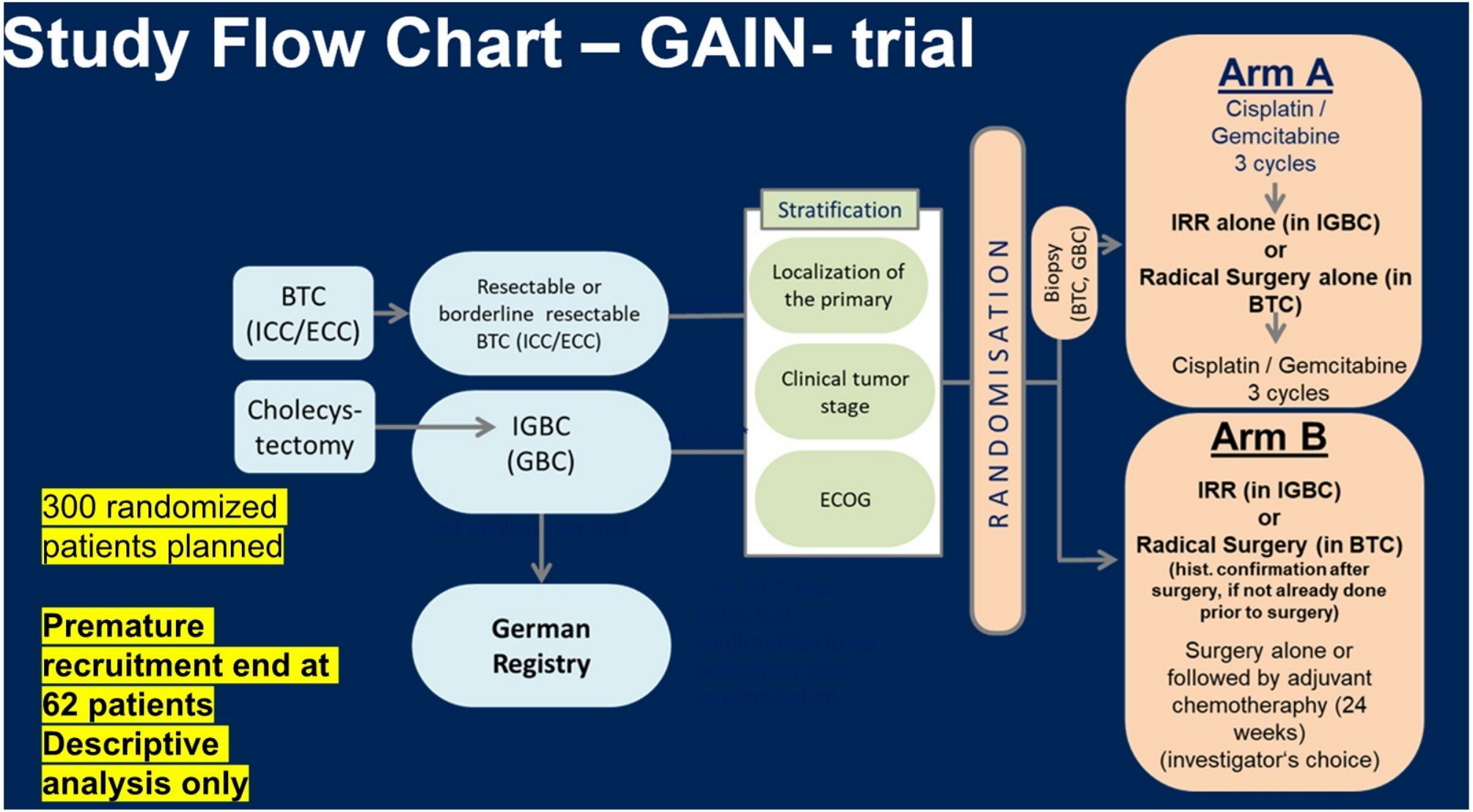
PROS

- Accurate staging information
- Allows for surgery first

CONS

- A subset of eligible patients cannot receive therapy
- Prospective studies with mixed results
  - JCOG1202: Positive but S-1 availability limited
  - BILCAP: OS benefit in per-protocol analysis
  - PRODIGE 12/BCAT: Negative

Study Flow Chart – GAIN- trial



300 randomized patients planned

Premature recruitment end at 62 patients
Descriptive analysis only

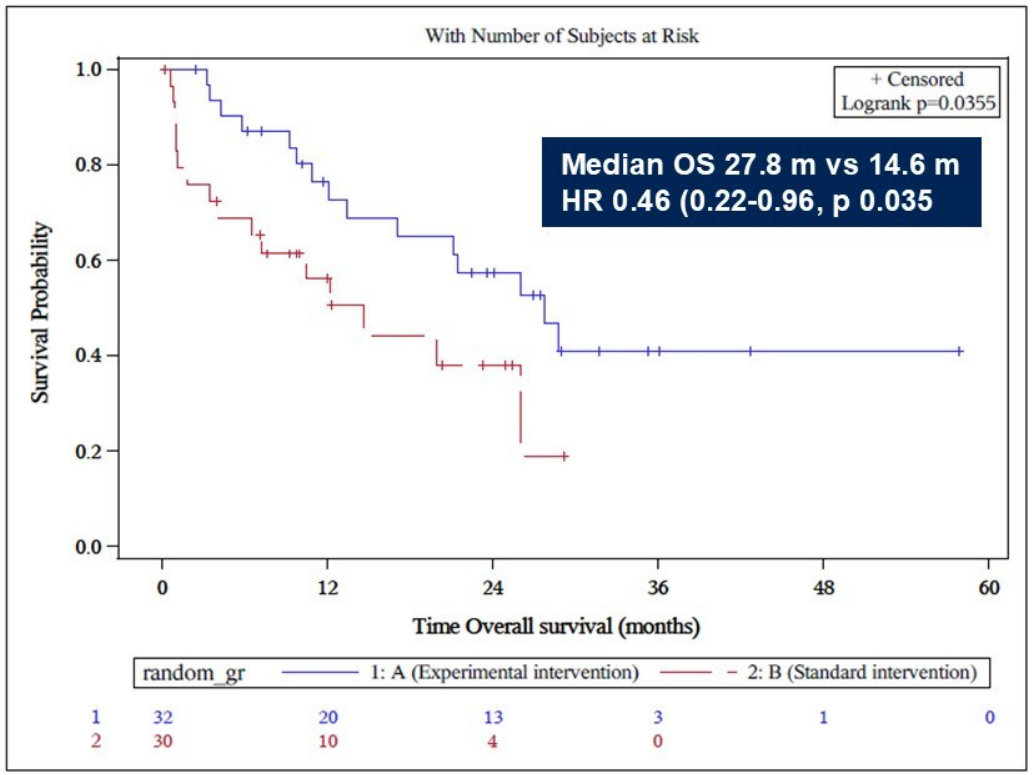
Baseline characteristics and drug exposure

	Arm A: Neo Gem/Cis (N=32)		Arm B: SOC (N=30)	
Tumor site				
Gallbladder Carcinoma (GBC)	9	28.1%	11	36.7%
Intrahepatic Cholangiocarcinoma	11	34.4%	12	40.0%
(ICC)	12	37.5%	7	23.3%
Extrahepatic Cholangiocarcinoma (ECC)				

- Arm A: >90% received neoadjuvant cycles and >40% received the adjuvant cycles
- Arm B: only 26% received any adjuvant therapy, 13% received >3 cycles.

Results

Overall Survival



- R0 resection rate improved in Gem/Cis group (83.3% vs 40%)
- Numerically similar rates of surgical complications between groups
- 6 deaths within 30 days in surgery first group, 1 in Cis/Gem

Clinical implications

Take home point: Supports the feasibility a **neoadjuvant therapy in BTC**, its limitations mean that **larger, more homogenous, and adequately powered trials** are needed before changing standard of care.

- Is this practice changing?
  No, but **nearly doubled OS** (27.8 vs 14.6 months) and **higher R0 resection rates** with **no added morbidity or toxicity** suggests the **biological advantage** of perioperative therapy in BTC

- When you get back to the clinic next week
  Consider neo-adjuvant therapy on a case by case basis- selection is key

- Additional research to evaluate benefit
  Doesn't change current standard, need for international collaboration to do successful trials – ACTICCA-1, ARTEMIDE-Biliary

2025 ASCO ANNUAL MEETING

HEAD AND NECK CANCER

Highlights of the Day

Barbara Burtness, MD

Yale Cancer Center

Key Takeaway Points/Conclusions

- Abstr 6001:Addition of cemiplimab after radiation improves DFS but not OS in resected cutaneous squamous cell cancer
- LBA 6003: Preliminary data regarding omission of cisplatin from chemoradiation after immunotherapy-containing induction for nasopharyngeal cancer
- Abstr 6007: Combined androgen blockade active in AR+ salivary gland cancer
- Abstr 6008: Combination Dabrafenib/Tremetinib/Pembrolizumab active in anaplastic thyroid cancer

2025 ASCO ANNUAL MEETING

Phase 3 trial of adjuvant cemiplimab versus placebo for high-risk cutaneous squamous cell carcinoma (C-POST)

Danny Rischin,[1] Sandro Porceddu,[2] Fiona Day,[3] Daniel P Brungs,[4,5] Hayden Christie,[6] James E Jackson,[7] Brian N Stein,[8] Yungpo Bernard Su,[9] Rahul Ladwa,[10] Gerard Adams,[11] Samantha E Bowyer,[12] Zulfiquer Otty,[13] Naoya Yamazaki,[14] Paolo Bossi,[15,16] Amarnath Challapalli,[17] Axel Hauschild,[18] Annette L Lim,[1] Vishal Patel,[19] Joanna Walker,[20] Maite De Liz Vassen Schurmann,[21] Paola Queirolo,[22] Javier Cañueto,[23] Flavio Augusto Ferreira da Silva,[24] Alexander Stratigos,[25] Alexander Guminski,[26] Charles Lin,[27,28] Fernanda Damian,[29] Lukas Flatz,[30] Anne E Taylor,[31] David R Carr,[32] Samuel Harris,[33] Dmitry Kirtbaya,[34] Gaëlle Quereux,[35] Piotr Rutkowski,[36] Nicole Basset-Seguin,[37] Nikhil I Khushalani,[38] Caroline Robert,[39] Haisong Ju,[40] Camryn Joseph,[40] Shikha Bansal,[40] Chieh-I Chen,[40] Dimple A Modi,[40] Frank Seebach,[40] Suk-Young Yoo,[40] Israel Lowy,[40] Priscila Goncalves,[40] Matthew G Fury[40]

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High-Risk Resected Cutaneous Squamous Cell Carcinoma

- TROG 05.01 added carboplatin to post-operative RT for non-immunosuppressed patients with high-risk resected cutaneous squamous cancers
- Lower risk population than anticipated with some imbalance between the arms
- 2-year locoregional FFS 88 vs. 89%
- Left the question unanswered for higher risk patients

Phase 3 Randomized Trial (KEYNOTE-630) of Adjuvant Pembrolizumab Versus Placebo for High-Risk Locally Advanced Cutaneous Squamous Cell Carcinoma Following Surgery and Radiation

Shlomo A. Koyfman[1]; Jenny H. Lee[2]; Laurent Mortier[3]; Ase Bratland[4]; Noel E. Luna-Romero[5]; Mitchell Chipman[6]; Marcin Dzienis[7]; Mikhail Klochikhin[8]; Jeremy E. H. Long[9]; Dmitry Kirtbaya[10]; Marcus Monroe[11]; Markus Gifoni[12]; John Kaczmar[13]; Jennifer DeSimone[14]; Ángela Zambrano Harvey[15]; Cecile Pages Laurent[16]; Juan Shen[17]; Jianda Yuan[17]; Burak Gumuscu[17]; Michael Schenker[18]

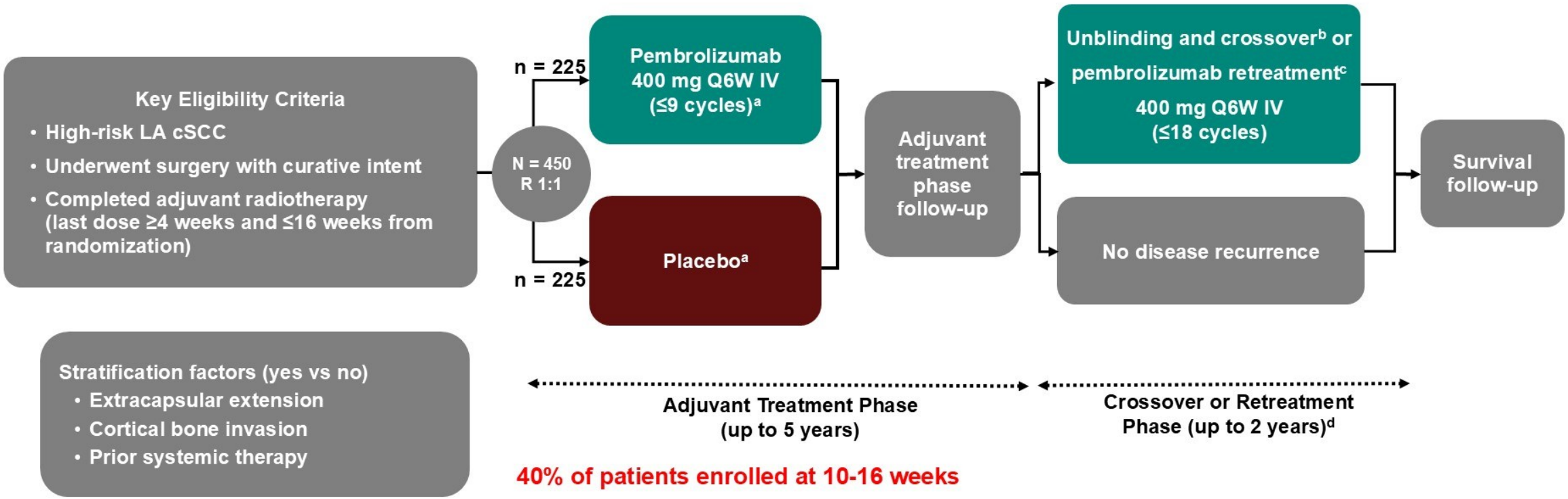
[1]Cleveland Clinic, Cleveland, OH, USA; [2]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [3]Hopital Claude Huriez, CHRU Lille, Lille, France; [4]Oslo University Hospital, Oslo, Norway; [5]Onco-Hematología de Occidente, Guadalajara, Jalisco, Mexico; [6]Alfred Health, Melbourne, Australia; [7]Gold Coast University Hospital, Southport, QLD, Australia; [8]Yaroslavl Regional SBIH Clinical Oncology Hospital, Yaroslavl, Russia; [9]Sunshine Coast University Private Hospital, Birtinya QLD 4575, Australia; [10]Oncological Dispensary #2 of Ministry of Health of Krasnodar Region, Sochi, Russia; [11]Huntsman Cancer Institute, UT, USA; [12]Instituto D'Or de Ensino e Pesquisa, Rio de Janeiro, Brazil; [13]MUSC Health University Medical Center, Charleston, SC, USA; [14]Inova Schar Cancer Institute, Fairfax, VA, USA; [15]Fundacion Valle del Lili, Cali, Colombia; [16]IUCT-Oncopole, Toulouse, France; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]University of Medicine and Pharmacy of Craiova, Craiova, Romania

ASCO L MEETING #ASCO25

PRESENTED BY:

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

KEYNOTE-630 (NCT03833167) Trial Design

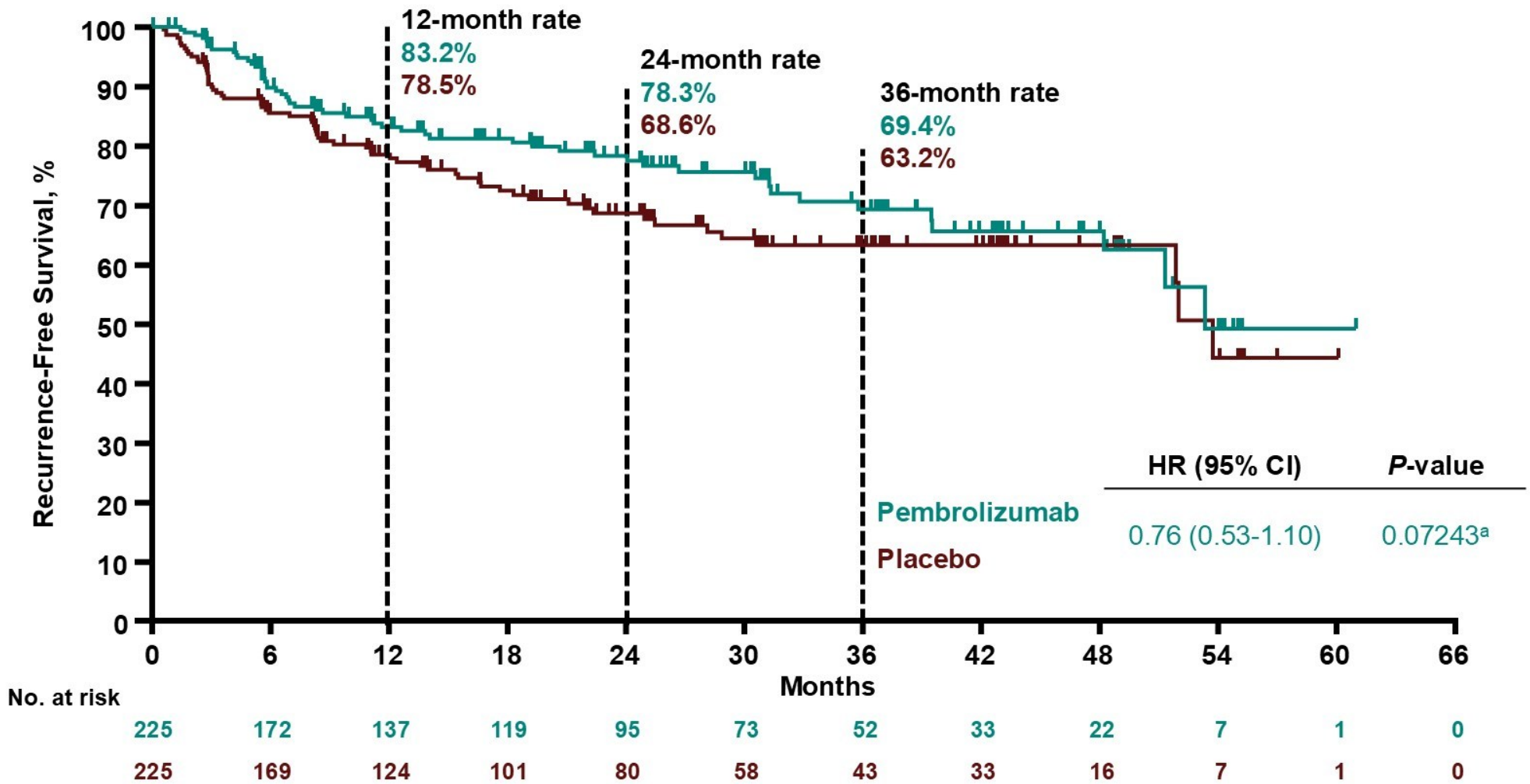


End points:

- **Primary:** Recurrence-free survival (RFS)[e] per investigator with biopsy confirmation
- **Secondary:** Overall survival (OS; key), safety and tolerability

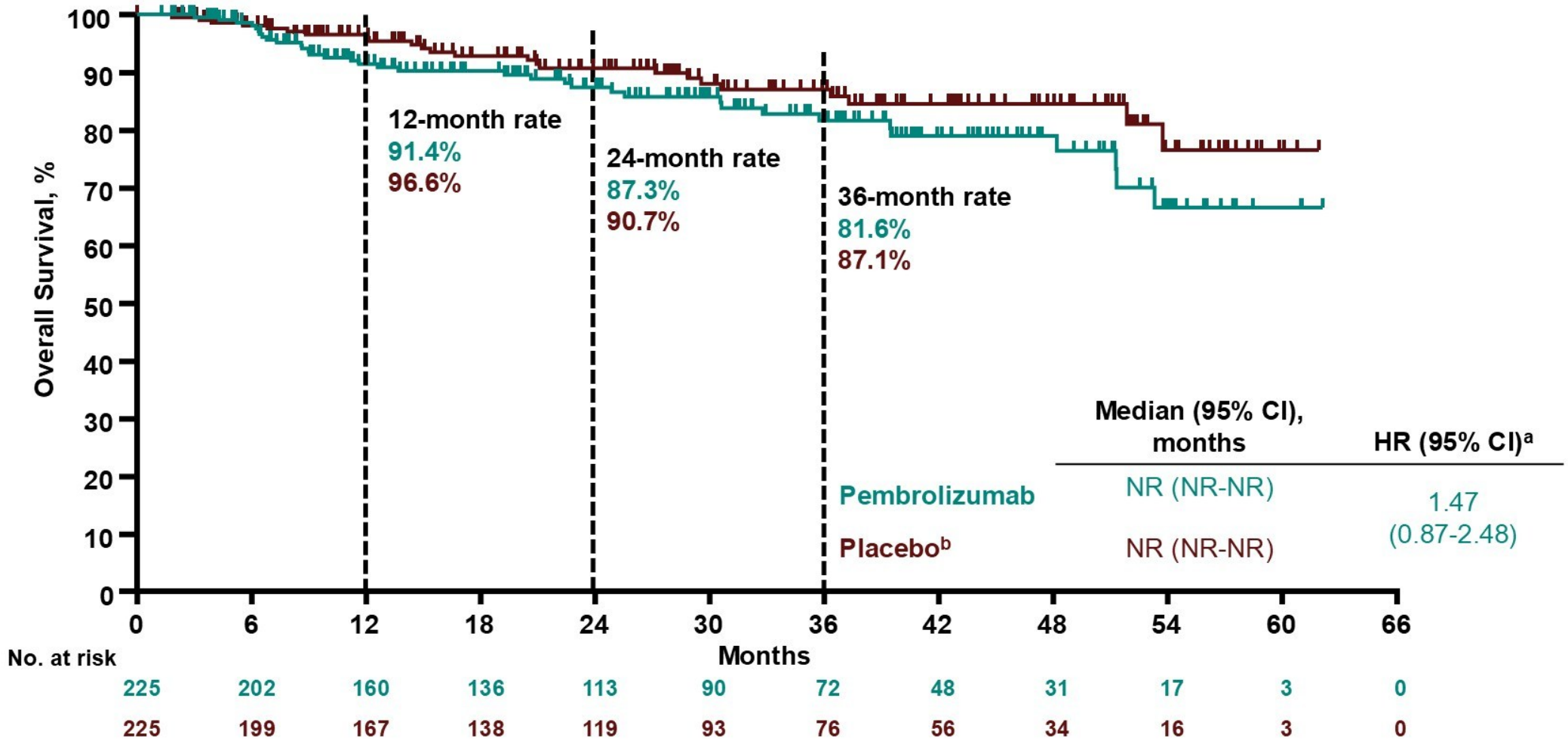
Median study follow-up[f]:
28.6 months (range, 2.0-62.5)

Recurrence-Free Survival per Investigator



[a]*P*-value boundary for statistical significance was 0.0160. Data cutoff date: June 28, 2024.

Overall Survival



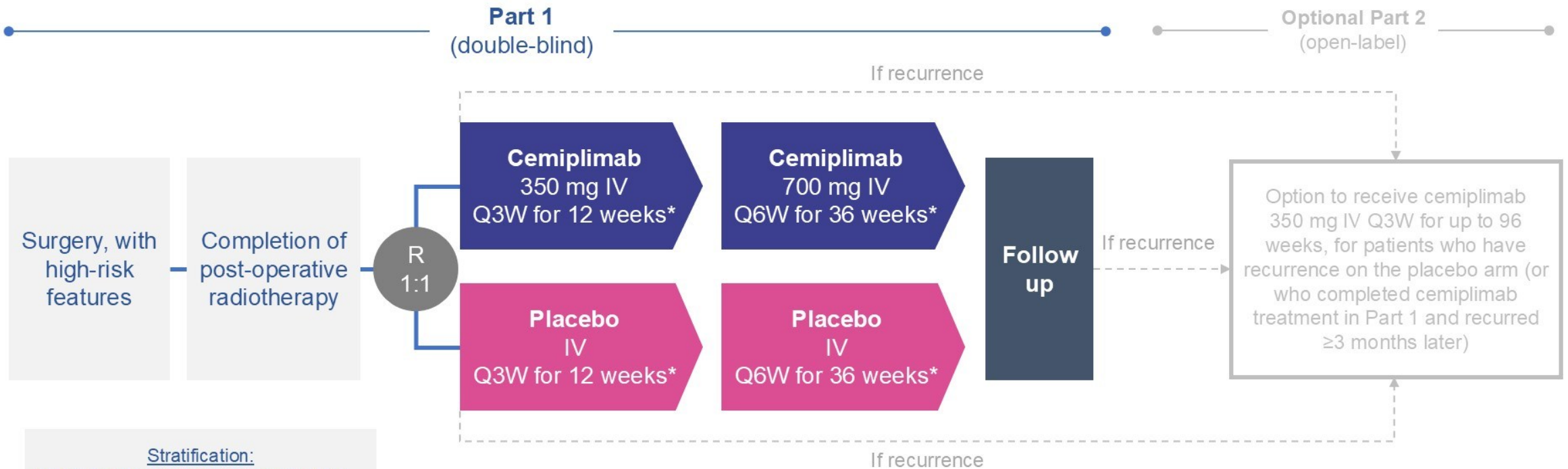
Reasons for Death and Proportion of All Deaths by Time From Randomization

	Pembrolizumab n = 225	Placebo n = 225
Total deaths, n (%)	35 (15.6)	24 (10.7)
Deaths <1 year from randomization, n (%)	17 (7.6)	7 (3.1)
Disease progression	6 (2.7)	4 (1.8)
Adverse event	11 (4.8)	3 (1.3)
COVID-19/COVID-19 pneumonia	2 (0.8)	1 (0.4)
Sepsis/septic shock	2 (0.8)	0
Other	7 (3.1)[b]	2 (0.9)[c]

	Pembrolizumab n = 225	Placebo n = 225
Deaths[d], n (%)	35 (15.6)	24 (10.7)
Time from randomization, n (%)		
<3 months	0	1 (0.4)
3-6 months	3 (1.3)	3 (1.3)
6 months-1 year	14 (6.2)	3 (1.3)
1-2 years	6 (2.7)	9 (4.0)
2-3 years	6 (2.7)	4 (1.8)
3-4 years	2 (0.9)	2 (0.9)
4-5 years	4 (1.8)	2 (0.9)

[b]Death from cardio-respiratory arrest, unknown death, dengue fever, hypovolemic shock, pneumonia, respiratory failure, and urinary tract infection. [c]Cerebrovascular accident and completed suicide. [d]During the COVID-19 pandemic, from March 1, 2020 to May 31, 2023, 18 deaths were reported as RFS events including 13 participants in the pembrolizumab group and 5 participants in the placebo group. Data cutoff date: June 28, 2024.

C-POST phase 3 trial



Stratification:

- Tumor location: Head & neck vs non-head & neck
- Geographic region: N. America vs AUS/NZ vs ROW
- High-risk category: nodal vs non-nodal
- ECOG performance score: 0 vs 1
- History of CLL: yes vs no

Treatment until disease progression, unacceptable toxicity, withdrawal of consent, or death

Median time to enrollment 1.4 months from RT

Primary endpoint: Disease-free survival (DFS)

*Original regimen was Q3W only. Starting with protocol amendment 2 (Jun 2021), the regimen was Q3W start / Q6W switch, as shown in the diagram.

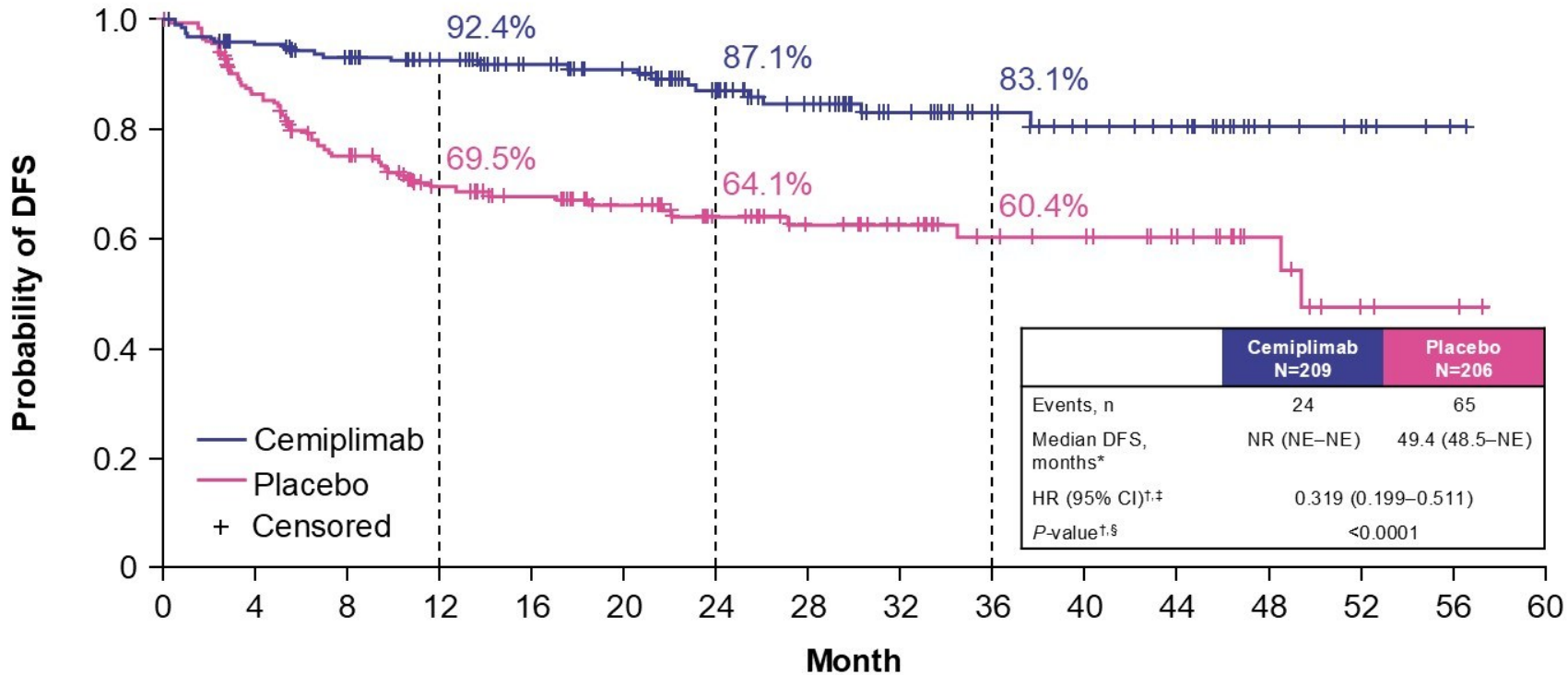
Nodal and **non-nodal** high-risk criteria*

Nodal disease	In-transit metastases	Perineural invasion	T4 lesions	Recurrent CSCC
ECE with ≥1 node ≥20 mm[1] OR ≥3 nodes regardless of ECE	Skin or subcutaneous metastases >20 mm from the primary lesion but not beyond the regional nodal basin	Clinical and/or radiologic involvement of named nerves	Invasion of cortical bone or skull base	CSCC that arises within the area of previously resected tumor, plus ≥1 additional feature: • ≥N2b disease associated with the recurrent lesion • Nominal ≥T3 • Poorly differentiated histology and recurrent lesion ≥20 mm diameter

*High-risk CSCC with both nodal and non-nodal features was categorized as high-risk nodal disease.

ECE, extracapsular extension.
1. Connolly et al. *Proc ESTRO 2025*. E25-1045.

Disease-free survival



	Cemiplimab N=209	Placebo N=206
Events, n	24	65
Median DFS, months*	NR (NE–NE)	49.4 (48.5–NE)
HR (95% CI)†,‡	0.319 (0.199–0.511)	
P-value†,§	<0.0001	

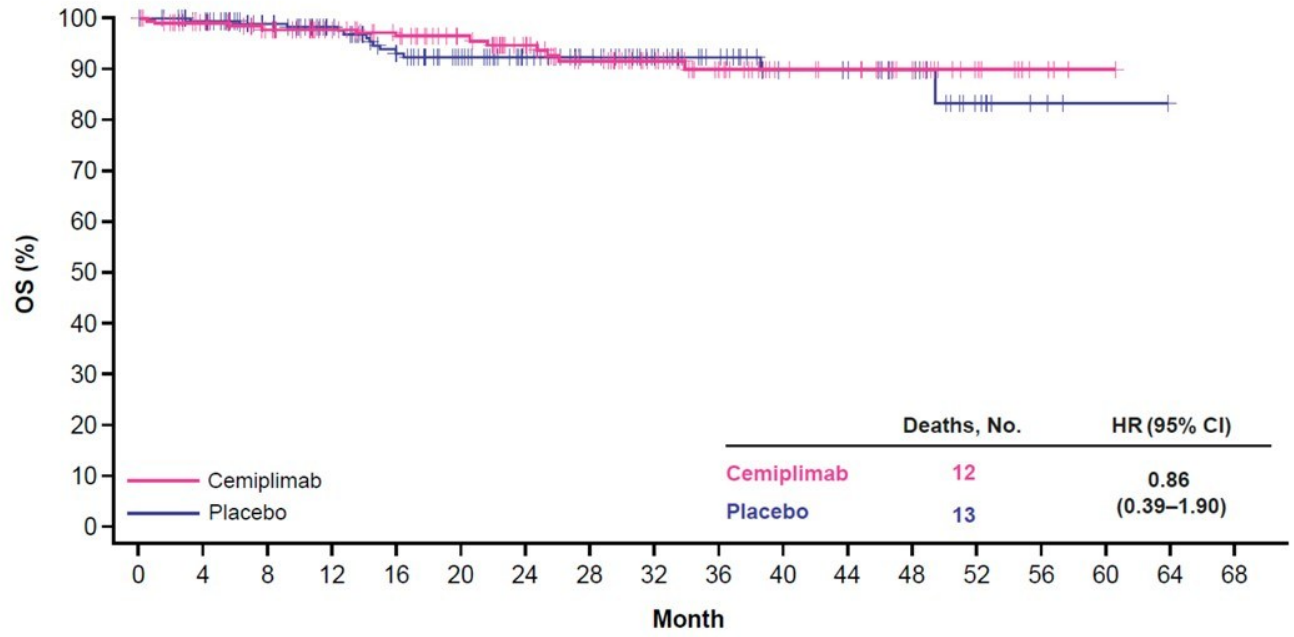
No. of patients at risk:

Cemiplimab	209	172	157	132	116	104	83	66	47	33	27	22	9	6	1	0
Placebo	206	161	130	94	82	69	53	42	36	26	24	18	10	4	2	0

NE, not evaluable; NR, not reached.
*Based on Kaplan–Meier method. †Stratified by anatomic region of resected high-risk tumor & geographical region. ‡Based on stratified proportional hazards model. §Two-sided *P*-value. Significance threshold set to 0.00455 using the O'Brien Fleming alpha spending function.

Overall Survival

Figure S5. Kaplan-Meier Curves of OS



Number of participants at risk

Cemiplimab	209	185	166	144	131	115	100	79	32	47	34	31	21	10	4	1	0	0
Placebo	206	191	168	141	120	102	83	69	32	44	32	29	18	8	3	1	0	0

Abbreviations: HR, hazard ratio.

	Deaths	Deaths due to disease	Other causes
Cem	12	4	8
Pbo	13	8	5

Rischin et al,
NEJM May 2025

Are these divergent study results?

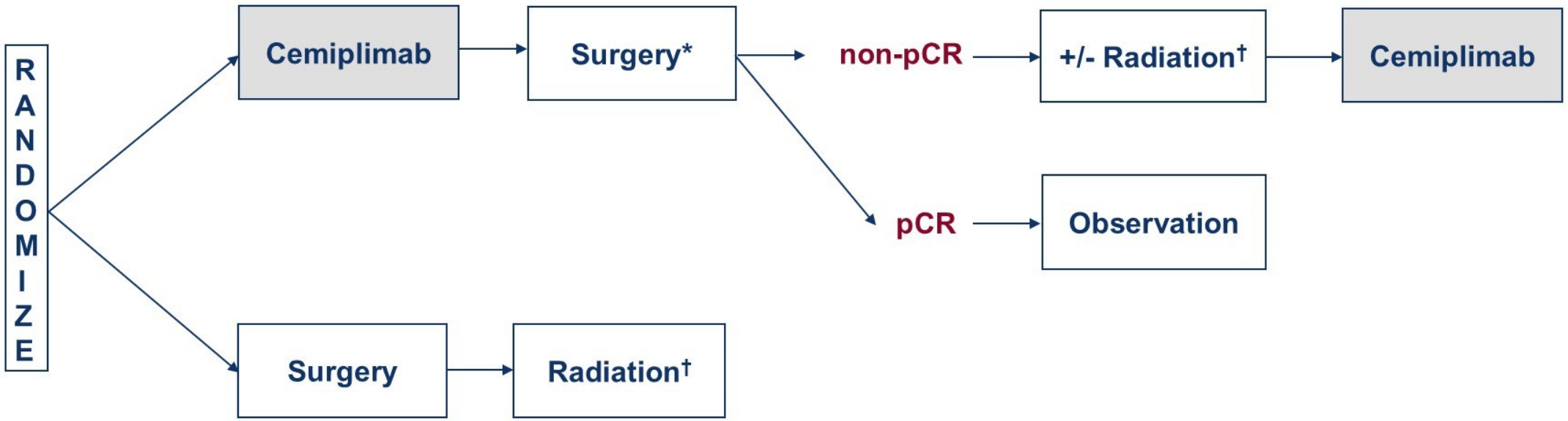
- In each case, improvement in DFS from PD-1 inhibition did not translate into an overall survival benefit in PD-L1 unselected patients, and does not seem likely to
- Is DFS the appropriate endpoint?
  - Older patients with co-morbidities have competing mortality risks
  - Cemiplimab is also highly active for recurrent disease
- Patient preference regarding post-radiation cemiplimab will be important given toxicities, cost, inconvenience and lack of survival benefit
- Neoadjuvant immunotherapy leads to 51% path CR rate and may, as in other cancers, provide greater benefit than post-radiation immunotherapy

Gross N et al, *NEJM* 2022

NRG-HN014

Randomized Phase 3 Trial

N=420



ClincalTrials.gov: NCT06568172

* Response-adapted oncologic surgery
† As indicated per protocol
pCR (pathologic complete response)

Primary Endpoint:
Event-free Survival (EFS)

Key Takeaway Points/Conclusions

Cemiplimab after radiation improves DFS but not OS in resected, high-risk PD-L1 unselected cutaneous squamous cell carcinoma.

Given competing causes of mortality, toxicity, expense, inconvenience and activity of cemiplimab for recurrent disease, patient preference should guide use of cemiplimab in this setting.

Neoadjuvant cemiplimab has promise and is studied in NRG HN014.

2025 ASCO ANNUAL MEETING

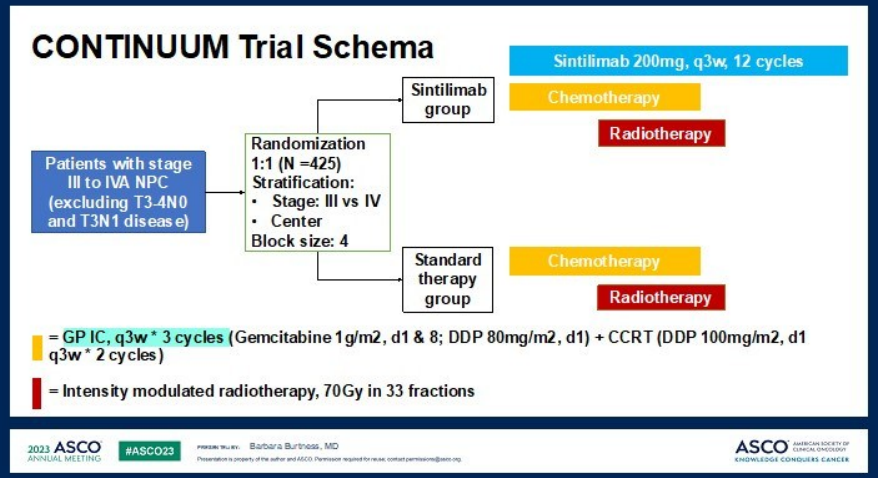
PD-1 blockade with toripalimab incorporated into induction chemotherapy and radiotherapy with or without concurrent cisplatin in locoregionally advanced nasopharyngeal carcinoma (DIAMOND): A multicenter, non-inferiority, phase 3, randomized controlled trial

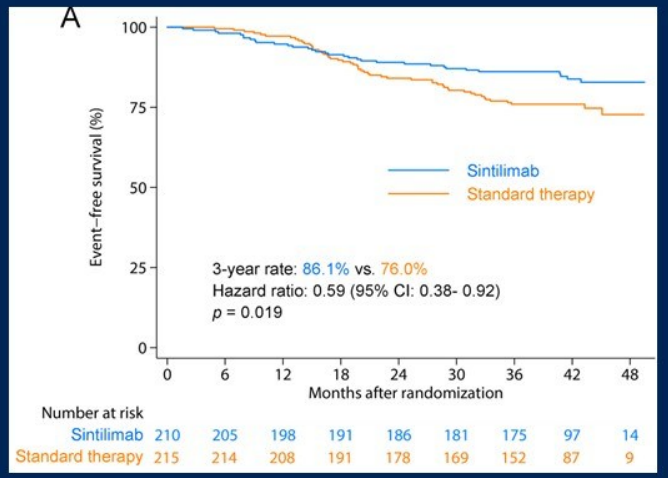
Jun Ma, Ying Sun, Cheng Xu, Liang-Fang Shen, Feng Jin, Kun-Yu Yang, Guang-Yuan Hu, Xiao-Dong Zhu, Ying Wang, Ning Zhang, De-Sheng Hu, Guo-Rong Zou, Xiao-Zhong Chen, Shao-Wen Xiao, Jin-Gao Li, Xin-Qiong Huang, Ying Huang, Ling Guo, Xiao-Yu Liang

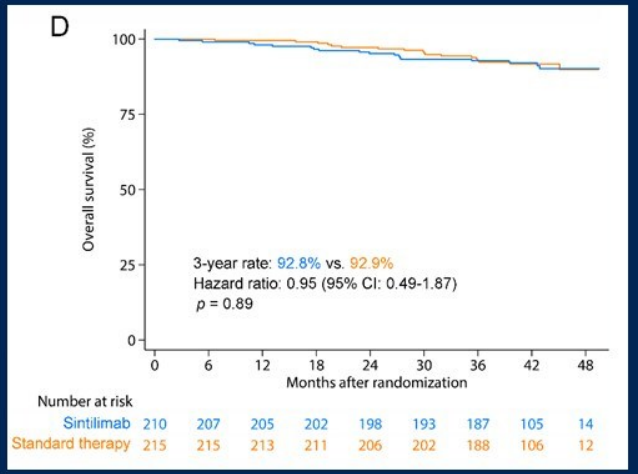
- Principal investigator: Prof. Jun Ma
- Sun Yat-sen University Cancer Center, Guangzhou, China
- majun2@sysu.edu.cn

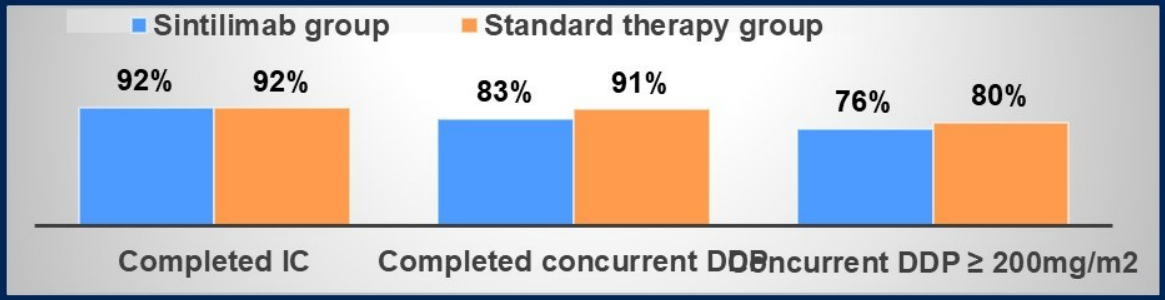
PRESENTED BY: Jun Ma (ORCID: 0000-0002-1137-93)

Addition of PD-1 Inhibition to Standard Therapy in Locally Advanced Nasopharyngeal Cancer





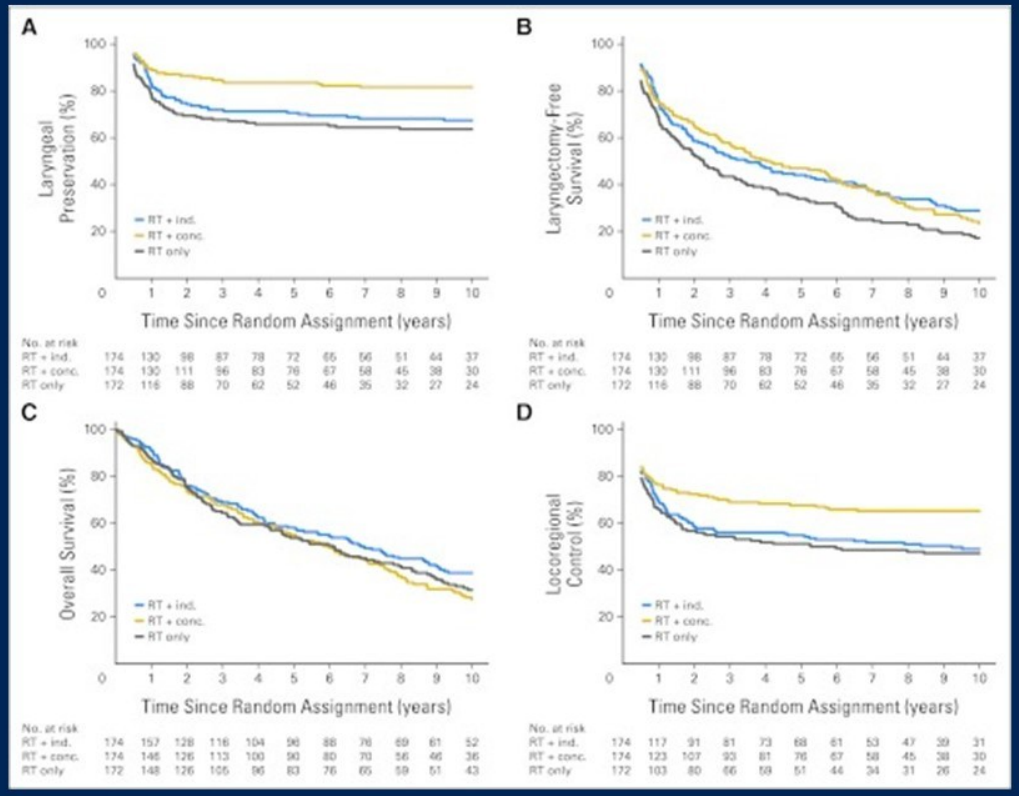




Lesser CDDP delivery
Short follow up for virally associated cancer
Not yet recommended SOC

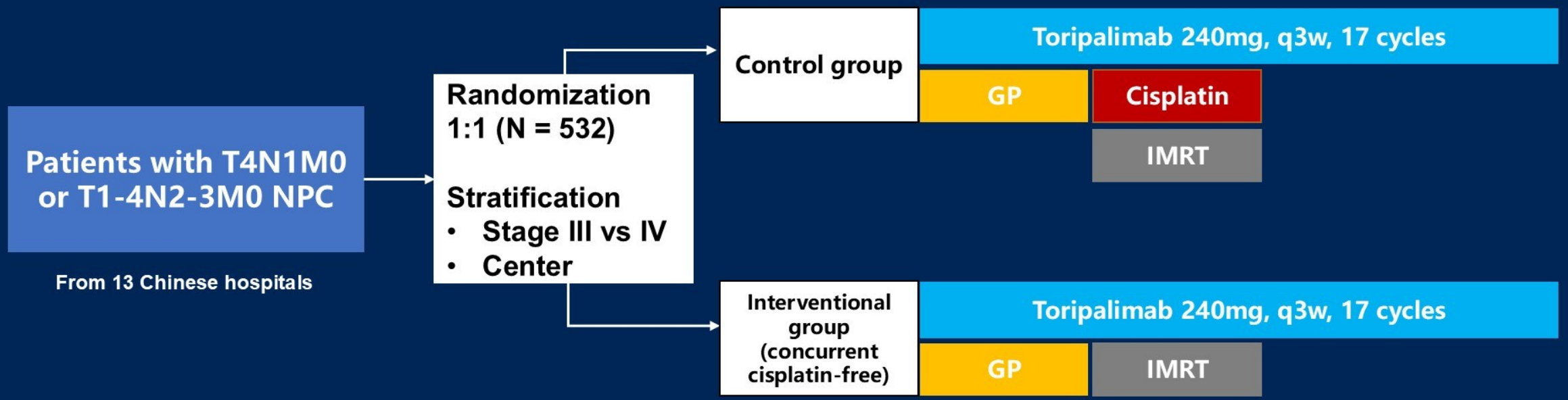
What if less cisplatin is a good thing?

Cisplatin is associated with hearing loss, vomiting, and increased late mortality



Forastiere et al *JCO* 2013

DIAMOND Trial Schema



= GP induction chemotherapy, q3w * 3 cycles (gemcitabine 1g/m², day 1 & 8; cisplatin 80mg/m², day 1)

= Concurrent cisplatin (100mg/m², day 1, q3w * 2 cycles)

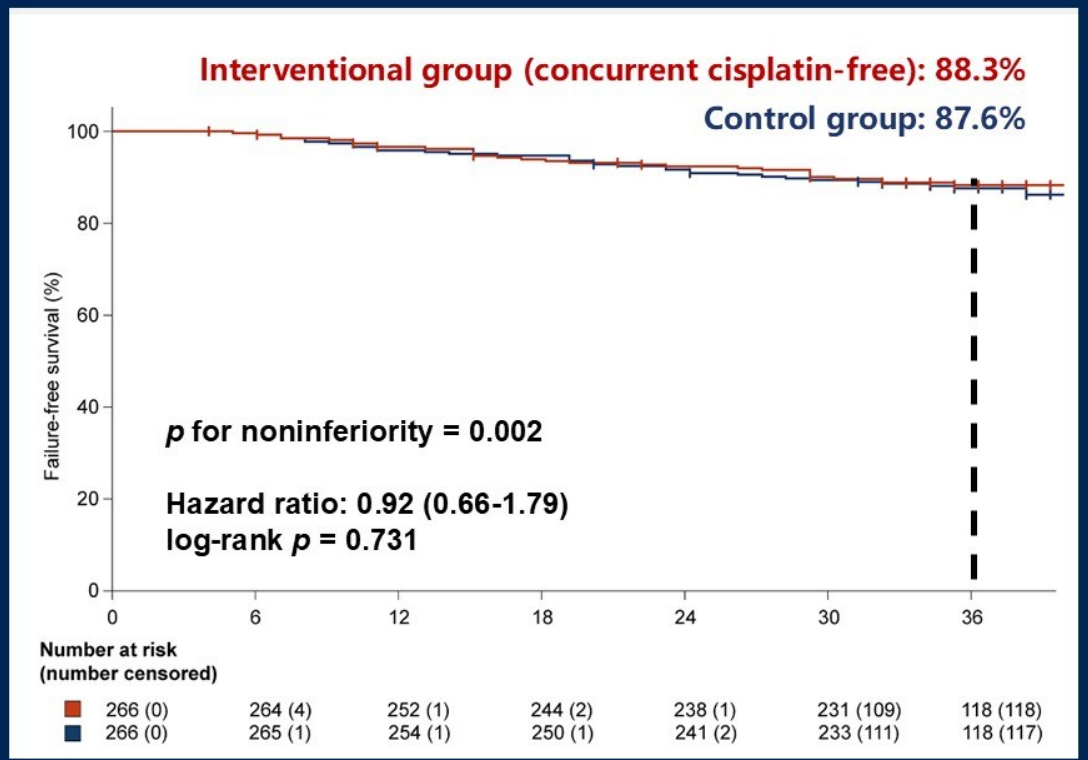
= Intensity-modulated radiotherapy (70Gy in 33 fractions, once daily, Monday–Friday weekly)

PRESENTED BY: Jun Ma (ORCID: 0000-0002-1137-93)

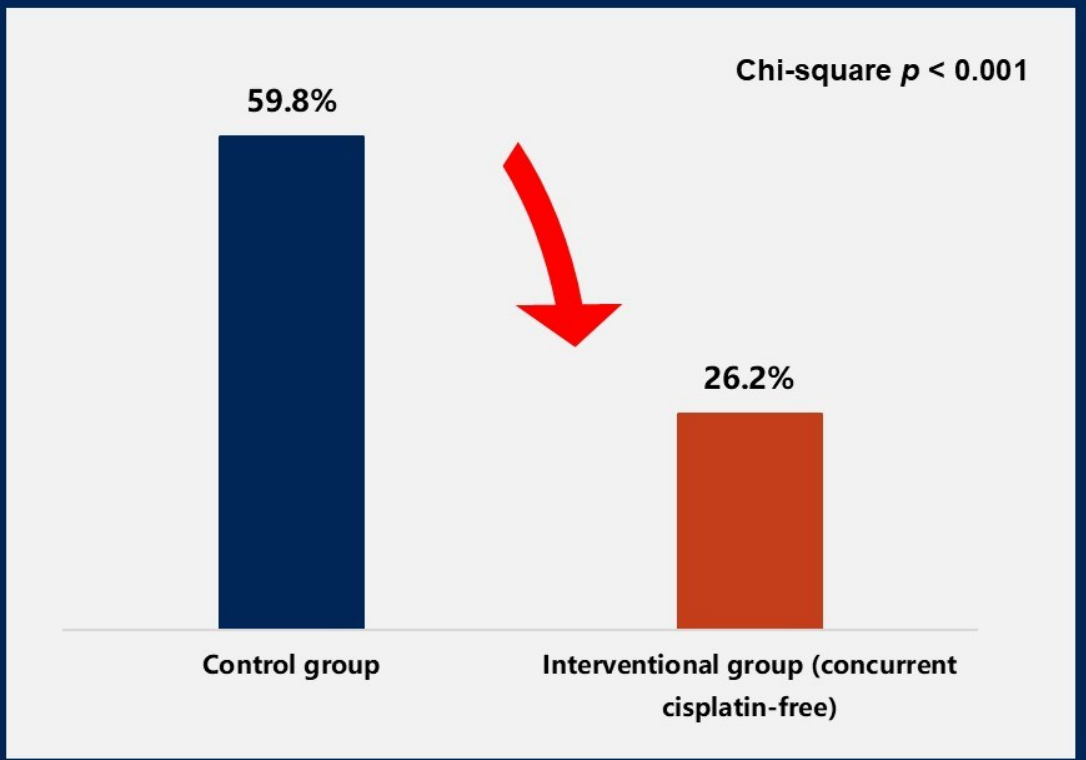
ClinicalTrials.gov: NCT04907370

Primary endpoints: FFS and all-grade vomiting

1-sided 95% CI for 3-yr FFS difference: -4.8% (lower limit) > non-inferiority margin of -8%



Incidence of all-grade vomiting: decreased by 33.6%



PRESENTED BY: Jun Ma (ORCID: 0000-0002-1137-93)

ClinicalTrials.gov: NCT04907370

Conclusions

- Induction chemoimmunotherapy is active in locoregionally advanced nasopharynx cancer
- No survival advantage is evident to date
  - Consistent with need for longer follow up in virally mediated cancers
  - May also reflect high activity of PD-1 inhibition at the time of relapse
- Additional benefit beyond survival might come from reduction in intensity of definitive therapy
  - However, given natural history of nasopharynx cancer, longer follow up is needed before this can be accepted outside a clinical trial

Darolutamide plus Goserelin for Androgen Receptor-Positive Salivary Gland Cancers: Results of Phase 2 Study (DISCOVARY)

Susumu Okano[1], Makoto Tahara[1], Kiyoaki Tsukahara[2], Tomoyuki Otsuka[3], Satoshi Kano[4], Masato Nagaoka[5], Hideoki Uryu[6], Daisuke Sano[7], Naoki Nishio[8], Kazuchika Ono[9], Akira Ohkoshi[10], Toyoyuki Hanazawa[11], Satoru Shinoda[12], Yuriko Takeda[12], Kouji Yamamoto[12], Naomi Kiyota[13]

[1]National Cancer Center Hospital East, Kashiwa, Japan; [2]Tokyo Medical University, Shinjyuku, Japan; [3]Osaka International Cancer Institute, Osaka, Japan; [4]Hokkaido University Hospital, Sapporo, Japan; [5]Jikei University Hospital, Minato, Japan; [6]National Hospital Organization Kyushu Medical Center, Fukuoka, Japan; [7]Yokohama City University Hospital, Yokohama, Japan; [8]Nagoya University Hospital, Nagoya, Japan; [9]Institute of Science Tokyo Hospital, Bunkyo, Japan; [10]Tohoku University Hospital, Sendai, Japan; [11]Chiba University Hospital, Chiba, Japan; [12]Yokohama City University, Yokohama, Japan; [13]Kobe University Hospital, Kobe, Japan

2025 ASCO ANNUAL MEETING

#ASCO25

PRESENTED BY: Susumu Okano, MD, PhD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Trial Design

Key eligibility criteria

- AR-positive SGC (≥1% IHC-positive tumor cells)
- Unresectable locally advanced or recurrent/metastatic disease
- Evaluable tumor lesion by enhanced CT or MRI
- No carcinomatous meningitis or symptomatic brain metastasis
- Performance status (ECOG) of 0-2
- Adequate organ function
- Written informed consent

NCT05694819

Monotherapy phase (N=24)

Darolutamide 1200mg/day

Registration: Apr/2020-Feb/2021

Combination phase (N=33)

Darolutamide 1200mg/day
Goserelin acetate 3.75mg q4w

Registration: Sep/2022-Aug/2023

Primary endpoint: ORR per RECIST by ICR

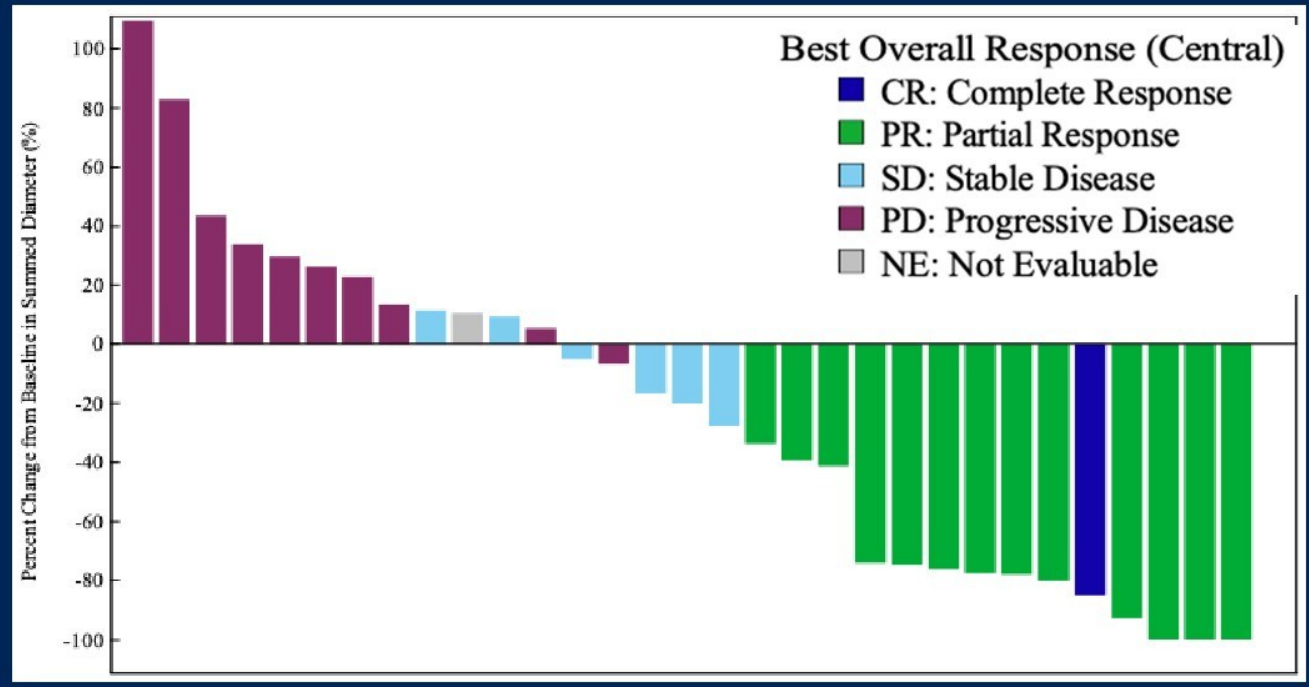
Secondary endpoints: ORR by investigator, DCR, CBR, PFS, OS, Safety, CBD, DOR, BOR, QOL (EQ-5D-5L)

ORR, objective response rate; ICR, independent central review; DCR, disease control rate; CBR, clinical benefit rate; PFS, progression-free survival; OS, overall survival; CBD, clinical benefit duration; DOR, duration of response; BOR, best overall response; QOL, quality of life

PRESENTED BY: Susumu Okano, MD, PhD

Primary Endpoint: Objective Response Rate by ICR (n=31)

	n	%	95%CI
CR	1	3.2	0.1-16.7
PR	13	41.9	24.5-60.9
SD	6	19.4	7.5-37.5
PD	10	32.3	16.7-51.4
NE	1	3.2	0.1-16.7
ORR	14	45.2	27.3-64.0
DCR	20	64.5	45.4-80.8
CBR	16	51.6	33.1-69.8



ORR was 45.2% (90% CI, 29.7- 61.3), which met the predetermined hypothesis*

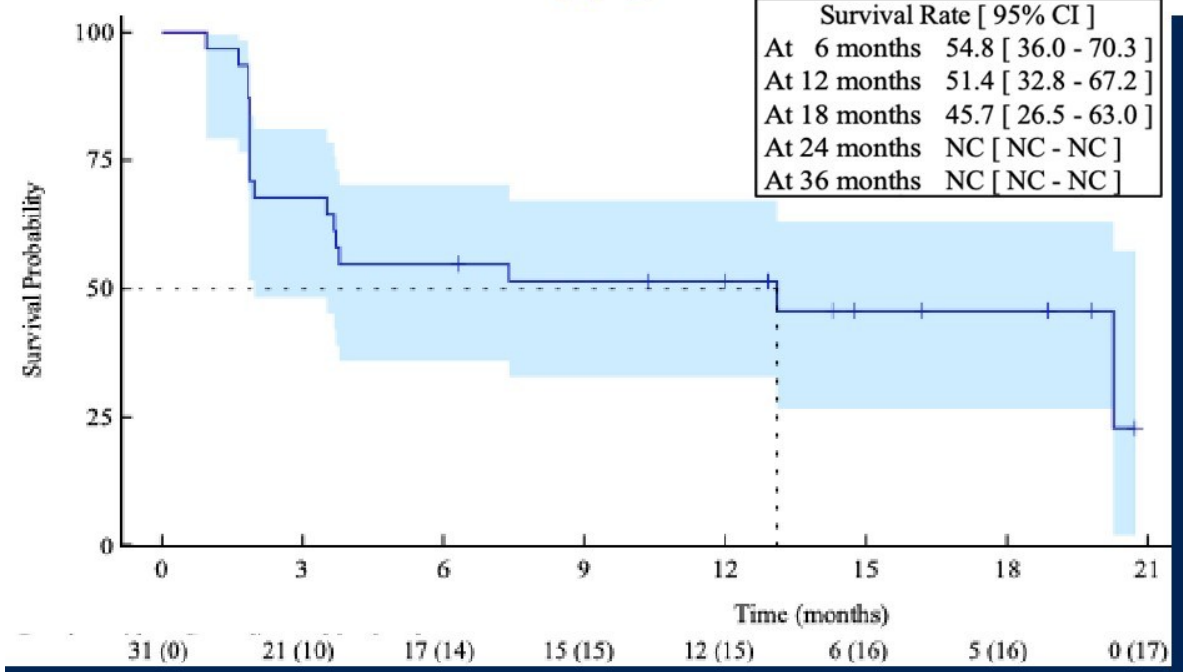
Data cutoff date: 9 August 2024

*Expected value 40%, threshold 15%, alpha = 0.05 (one-sided), power 90%

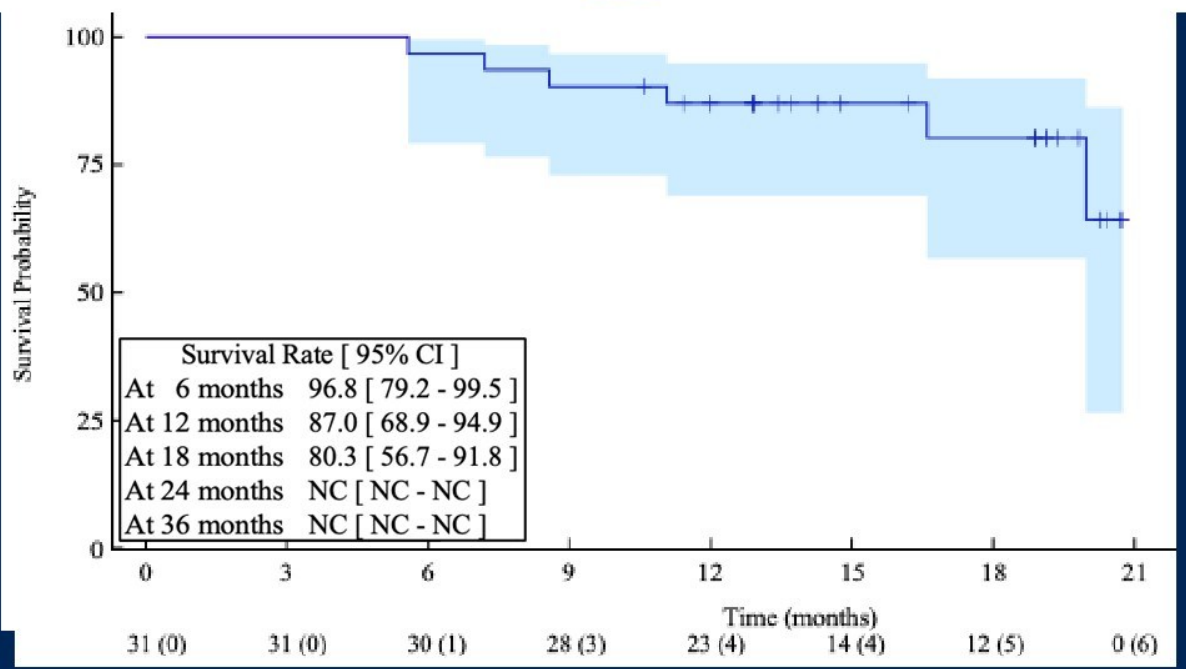
PRESENTED BY: Susumu Okano, MD, PhD

PFS and OS (n=31)

PFS



OS



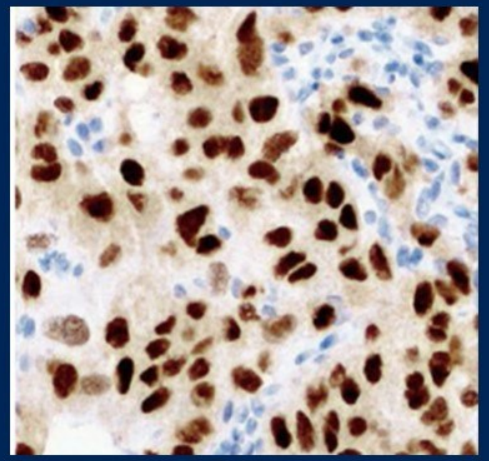
Median PFS: 13.1 months (95%CI, 2.0-NC)

Median OS: Not reached (95%CI, 20.0-NC)

PRESENTED BY: Susumu Okano, MD, PhD

Conclusions

- Adds to the evidence for combined androgen blockade in AR+ salivary gland cancer
- Heavily weighted to AR 70% + subset
- Some HER2+ patients



Key Takeaway Points/Conclusions

Complete androgen blockade is an option for treatment of androgen receptor expressing salivary gland cancers.

CAB has not yet been demonstrated to be superior to chemotherapy for first-line therapy in the AR 70%+ /HER2- population.

2025 ASCO ANNUAL MEETING

Neoadjuvant pembrolizumab in combination with dabrafenib and trametinib (DTP) for *BRAF V600E*-mutated anaplastic thyroid cancer (*BRAF*m-ATC): a multicenter phase 2 trial

Mark Zafereo, Rui Jennifer Wang, Naifa Lamki Busaidy, Ramona Dadu, Priyanka C. Iyer, Steven G. Waguespack, Li Xu, Anastasios Maniakas, Victoria E. Banuchi, Stephen Lai, Steven B. Chinn, Jessica Lyn Geiger, Kathleen Claire Kerrigan, Saad A. Khan, Eric J. Moore, Mabel M. Ryder, Joseph Scharpf, Francis P. Worden, Michelle D. Williams, Maria E. Cabanillas

Speaker: Mark Zafereo, MD

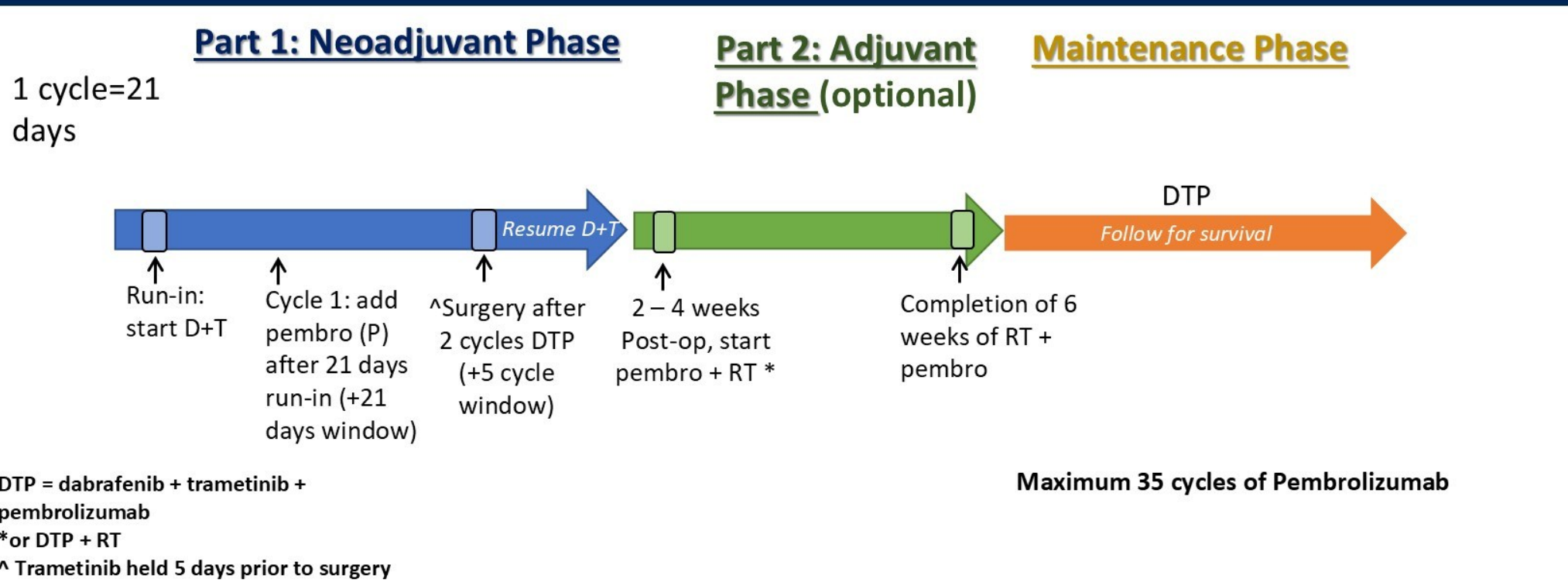
Anaplastic Thyroid Cancer

- Dabrafenib/trametinib (DT) is FDA approved for *BRAFV600E*-mutated ATC
  - Median PFS 6.7 months and OS 14.5 months in phase 2 ROAR trial
  - Most patients develop resistance to DT

Subbiah et al, *Ann Oncol* 2022

Methods: trial schema

Single-arm open-label multicenter phase II clinical trial



	Total *n* = 40
Age (yrs), median (range)	68 (47–86)
Overall stage, *n* (%)	
IVB	15 (38%)
IVC	25 (62%)
ECOG performance status, *n* (%)	
0	23 (58%)
1	17 (42%)
Previous therapy for ATC, *n* (%)	
Surgery	3 (8%)
Radiotherapy	2 (5%)
Chemotherapy	3 (8%)

Surgical resection status			
R0	**R1**	**R2**	**No surgery**
23 (59%)	6 (15%)	1 (3%)	9 (23%)

2/3s of resected patients had no remaining ATC component on pathology

Key Takeaway Points/Conclusions

Despite small sample size, given the difficulty of randomized clinical trials in this rare and rapidly fatal malignancy, phase II data have guided management. DTP appears more active than DT and is an appropriate regimen for use in BRAF-mutated ATC

2025 ASCO ANNUAL MEETING

Highlights of the Day

Breast Cancer: Local/Regional/Adjuvant Tract

Jacqueline S. Jeruss, MD, PhD, FACS
Alfred E. Chang, MD Professor of Surgical Oncology
University of Michigan

Four Studies Selected From Outstanding Session

- Predicting pathologic complete response (pCR) from clinicopathologic variables and HER2DX genomic test in stage II & III HER2+ breast cancer treated with taxane, trastuzumab, and pertuzumab (THP): secondary results from EA1181 (CompassHER2 pCR) trial. Nadine Tung et al.

- Predicting nodal burden after neoadjuvant chemotherapy (NAC) with circulating tumor (ct)DNA for surgical planning: results from the I-SPY2 trial. Rita A Mukhtar et al.

- Comparison of marking techniques for target lymph nodes in 2,596 patients with node-positive breast cancer treated with neoadjuvant chemotherapy: Results from the prospective multicenter AXSANA / EUBREAST-03 / AGO-B-053 study (NCT04373655). Maggie Banys-Paluchowski, et al.

- 15-year Outcomes for Women with Premenopausal Hormone Receptor-positive Early Breast Cancer in the SOFT and TEXT Trials Assessing the Benefits from Adjuvant Exemestane (E)+ Ovarian Function Suppression (OFS) or Tamoxifen (T)+OFS. Prudence A Francis, et al.

Predicting pathologic complete response (pCR) from clinicopathologic variables and HER2DX genomic test in stage II & III HER2+ breast cancer treated with taxane, trastuzumab, and pertuzumab (THP): secondary results from EA1181 (CompassHER2 pCR) trial. Nadine Tung et al.

Clinical Question

- Standard of care stage II/III HER2+ breast cancer: neoadjuvant multi-agent chemotherapy & HP (e.g., TCHP, AC-THP)
  - pCR rates: ~60%[1,2] (~70% ER-, ~40% ER+), 3yr iDFS ~92%[3]
- EA1181: Primary aim, future analysis: Is 3yr RFS with pCR after THP equivalent to pCR after multi-agent chemo + HP?
- **Secondary aims: (current presentation)**
  - **pCR rate with THP ? Predictors of pCR ?: clinical factors & HER2DX pCR score**

Research Findings

- pCR rate with THP: 44% overall; 64% for ER-/HER2+, 33% for ER+/HER2+
- Clinicopathologic factors significantly associated with higher pCR rate:
  - ER 0 or ER+ ≤70%, HER2 IHC 3+ (vs HER2 IHC 2+/ISH positive)
  - Weekly paclitaxel (vs q3wk docetaxel)
- HER2Dx pCR score provided complementary assessment re possibility of pCR; clinical stage: no

Notable Strengths/ Weaknesses

- Operable HER2+ breast cancer: clinicopathologic factors & molecular tools can help identify patients appropriate for less intensive chemotherapy
- Primary Aim data- 3y RFS among patients with pCR maturing
  - Additional data may add to this perspective

PRESENTED BY: Jacqueline Jeruss, MD, PhD, FACS
[1] Hurvitz et al Lancet Oncol 2018, [2] Schneeweiss et al Annals Oncol 2013, [3] Minckwitz NEJM 2017

Conclusions/Take Home Points

Clinical Relevance:
- De-escalation highly relevant to support personalize patient care and possible help minimize treatment-related morbidity

Immediately practice changing?
- Data supports rational use THP regimen, esp. ER-/HER2+ pts

Impact on value/cost of care
- More streamlined chemotherapy regimens could translate to fewer side effects, decreased expenditure

Predicting nodal burden after neoadjuvant chemotherapy (NAC) with circulating tumor (ct)DNA for surgical planning: results from the I-SPY2 trial. Rita A Mukhtar et al.

Clinical Question	• Goal: Better prediction, after neoadjuvant therapy, of low or high residual nodal burden to facilitate optimal axillary surgery • Specifically, could a maching learning algorithm with clinical factors and circulating tumor DNA status after NAC (+ or -) help predict residual nodal burden? • Potentially help to avoid unnecessary axillary lymph node dissection, as low volume disease likely removed by sentinel node surgery alone
Research Findings	• ctDNA after NAC can predict residual nodal burden (ypN2-3 disease) • Test performance accuracy differed based on clinical nodal status, HR subtype • For certain patients with aggressive subtypes, ctDNA could predict residual nodal burden to help tailor axillary surgery
Notable Strengths/ Weaknesses	• Novel approach for possible personalized surgical de-escalation • Analysis based on retrospective data • Prospective outcomes data needed following omission of ALND in low vs. high nodal burden setting • Implementation of axillary imaging information could strengthen model prediction

PRESENTED BY: Jacqueline Jeruss, MD, PhD, FACS

Conclusions/Take Home Points

Clinical Relevance:
- De-escalation highly relevant to support personalize patient care and possibly help minimize surgical morbidity

Immediately practice changing?
- Novel approach with ongoing validation underway

Impact on value/cost of care
- More streamlined surgical care could result in fewer complications, lower expenditures

Comparison of marking techniques for target lymph nodes in 2,596 patients with node-positive breast cancer treated with neoadjuvant chemotherapy: Results from the prospective multicenter AXSANA / EUBREAST-03 / AGO-B-053 study (NCT04373655). Maggie Banys-Paluchowski, et al.

Clinical Question	• Last several years, significant initiative to de-escalate axillary surgery • Options: ALND, SLNB, TLNB, TAD • Goal: Examine TLN detection rate using different pre-NACT marking techniques: international prospective AXSANA study
Research Findings	• Pre-NACT use probe-guided detection markers resulted significantly higher TLN detection rate vs. clip alone • TLN detection rate associated with surgeon's learning curve, BMI, & axillary response to therapy
Notable Strengths/ Weaknesses	• Findings provide clear guidance re use probe guided detection markers • Analysis surgical endpoints ongoing- several opinions re best practice • Availability/use different markers varies with clinical environment/ resource access

PRESENTED BY: Jacqueline Jeruss, MD, PhD, FACS

Conclusions/Take Home Points

Clinical Relevance:
- Study provides supportive data to guide approach to TAD with probe-guided detection

Immediately practice changing?
- Clinical settings where probe-guided detection possible should consider this approach

Impact on value/cost of care
- More streamlined surgical care could result in decreased morbidity/treatment accuracy, lower expenditures, clip costs a factor

15-year Outcomes for Women with Premenopausal Hormone Receptor-positive Early Breast Cancer in the SOFT and TEXT Trials Assessing the Benefits from Adjuvant Exemestane (E)+ Ovarian Function Suppression (OFS) or Tamoxifen (T)+OFS. Prudence A Francis, et al.

Clinical Question	• Premenopausal patients- chemotherapy induced amenorrhea= lower risk HR+ BC recurrence • Young women < 35 yrs HR+ BC, higher risk recurrence vs. older premenopausal patients • **Premenopausal HR+ pts, value of adding OFS to adjuvant tamoxifen uncertain ?** • **Postmenopausal pts, aromatase inhibitors reduced recurrence compared to tamoxifen- for premenopausal pts given AI + OFS would result overlap ?**
Research Findings	• Adding OFS to antihormonal therapy reduced recurrence with 15-yr BCFI: E+OFS (78.6%) > T+OFS (75.7%) > T (72.1%) yet clinically meaningful OS benefit limited to high-risk subgroups • E+OFS vs T+OFS reduced Distant Recurrence (HR=0.75; 0.63-0.90), with OS, smaller reduction in deaths (HR=0.89; 0.74-1.06) • OFS + oral E vs T substantially reduced recurrence young/high grade pts, durable Overall Survival benefit
Notable Strengths/ Weaknesses	• High risk young and high grade patients, comprehensive findings: OFS/antihormonal therapy resulted in decreased BC events, improved overall survival • Yet, BC events continued beyond 15 yrs, regardless ET assignment, especially patients < 40 yrs • Impact quality of life/comorbidities critical nuanced discussion re therapeutic recommendations • Elinzanetant (EZN) tx for vasomotor symptoms, presented/pub yest NEJM, Dr. Cardoso

PRESENTED BY: Jacqueline Jeruss, MD, PhD, FACS

Pagani et al, Eur J Cancer 1998;Aebi et al, Lancet 2000; Goldhirsch et al, JNCI Monogr 2001
Prudence A. Francis, et al., ASCO 2025.

Conclusions/Take Home Points

Clinical Relevance:
- 15 year outcomes SOFT/TEXT trials support use OFS and E over T in particular for high grade or exquisitely young pts

Immediately practice changing?
- Data supports recommendation for OFS/E for highest risk pts

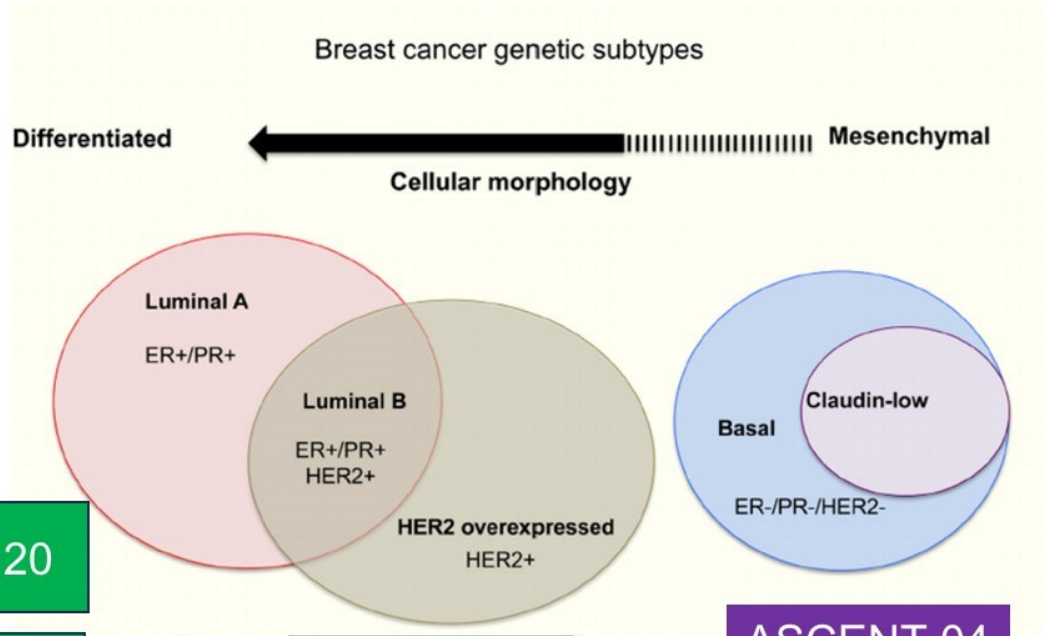
Impact on value/cost of care
- Data driven, long term OFS/antihormonal therapy for selected pts could result in decreased morbidity, mortality, lower expenditures

2025 ASCO ANNUAL MEETING

Metastatic breast cancer highlights

Maryam Lustberg MD MPH
Yale Cancer Center
New Haven, CT USA

Abstracts Highlighted



INAVO-120

VERITAC-2

Destiny -09

ASCENT-04

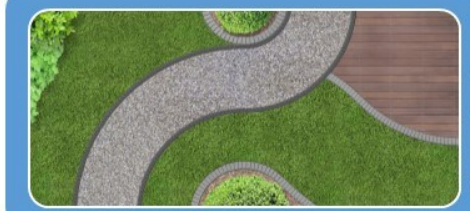
Updates in Hormone Receptor Positive MBC

INAVO-120

VERITAC-2

PRESENTED BY: Maryam Lustberg MD MPH

Key takeaways HR+ MBC #ASCO25



Treatment landscape in HR+ MBC is rapidly evolving.

- Many new targeted drugs
- Triplet therapy (PI3Ki+ fulvestrant/CDK4/6i) promising PFS and OS in first line endocrine resistant tumors (INAVO120)
- All show modest improvements in PFS in second line and beyond

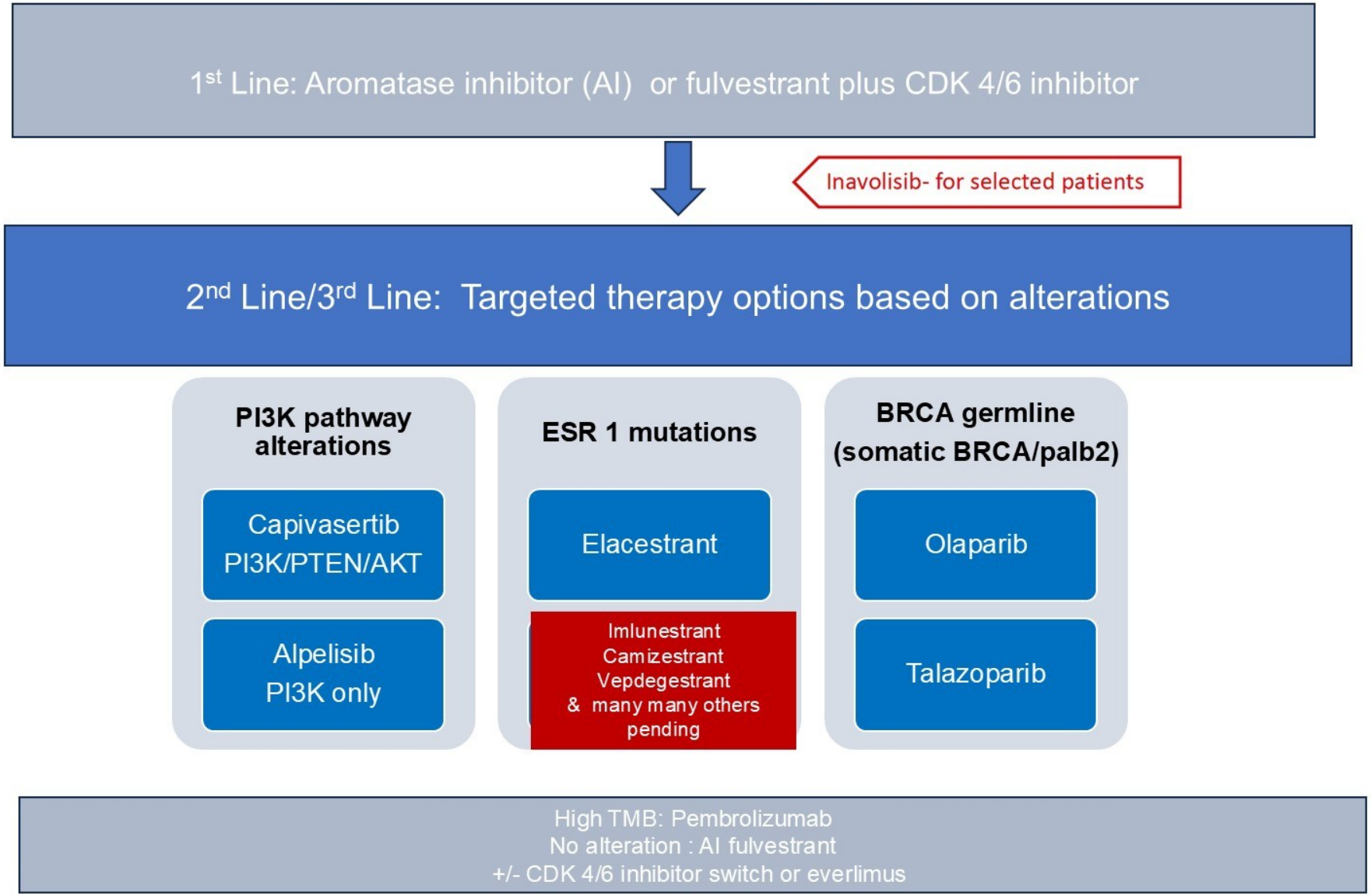
Biomarker driven therapy selection of targeted therapies is happening now.

- PIK3CA pathway as part of triple combination with CDK4/6 in patients with endocrine resistant tumors.
- ESR1 alteration as a biomarker of endocrine resistance (VERITAC-2)
- Dynamic monitoring for ESR1 alterations is important in deciding on optimal systemic therapy approaches.

Optimal sequencing of targeted therapies remains unclear

- Safety, tolerability, and quality of issue may be differentiators.
- Predictors of benefit and resistance are to be determined still.

Treatment algorithm for HR+ HER neg/low/ultralow MBC



PRESENTED BY: Maryam Lustberg MD MPH

Ongoing questions in HR+ positive MBC

- Can we safely and effectively improve systemic therapy for patients with early rapid progression ?
- How can we best optimize post CDK 4/6 inhibitor systemic therapy options with new targeted therapy/endocrine therapy options?
- How to best use dynamic biomarker monitoring to inform therapy switches?
- When to incorporate ADCs and in what sequence?

PRESENTED BY: Maryam Lustberg MD MPH

INAVO120 Phase III trial final overall survival (OS) analysis of first-line inavolisib (INAVO)/placebo (PBO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with *PIK3CA*-mutated, hormone receptor-positive (HR+), HER2-negative (HER2–), endocrine-resistant advanced breast cancer (aBC).

Nicholas Turner, Seock-Ah Im, Cristina Saura, Dejan Juric, Sibylle Loibl, Kevin Kalinsky, Peter Schmid, Sherene Loi, Eirini Thanopoulou, Noopur Shankar, Yanling Jin, Thomas J. Stout, Tiffany D. Clark, Chunyan Song, Komal L. Jhaveri

Takeaways:

1. Overall survival has been shown with triplet combination of inavolisib plus palbociclib-fulvestrant
2. Median progression to subsequent chemotherapy was significantly delayed
3. Significantly higher rates of hyperglycemia, stomatitis and vision changes were reported with inovolisib. On clinical trial discontinuation rates were low.

PRESENTED BY: Maryam Lustberg MD MPH

INAVO120: A Phase III, randomized, double-blind, placebo-controlled study[1,2]

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2– aBC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **No prior therapy for aBC**
- **Fasting glucose <126 mg/dL and HbA_{1c} <6.0%**

Enrollment period: January 2020 to September 2023

N = 325

R 1:1

- **Inavolisib (9 mg PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)†**
- **Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)†**

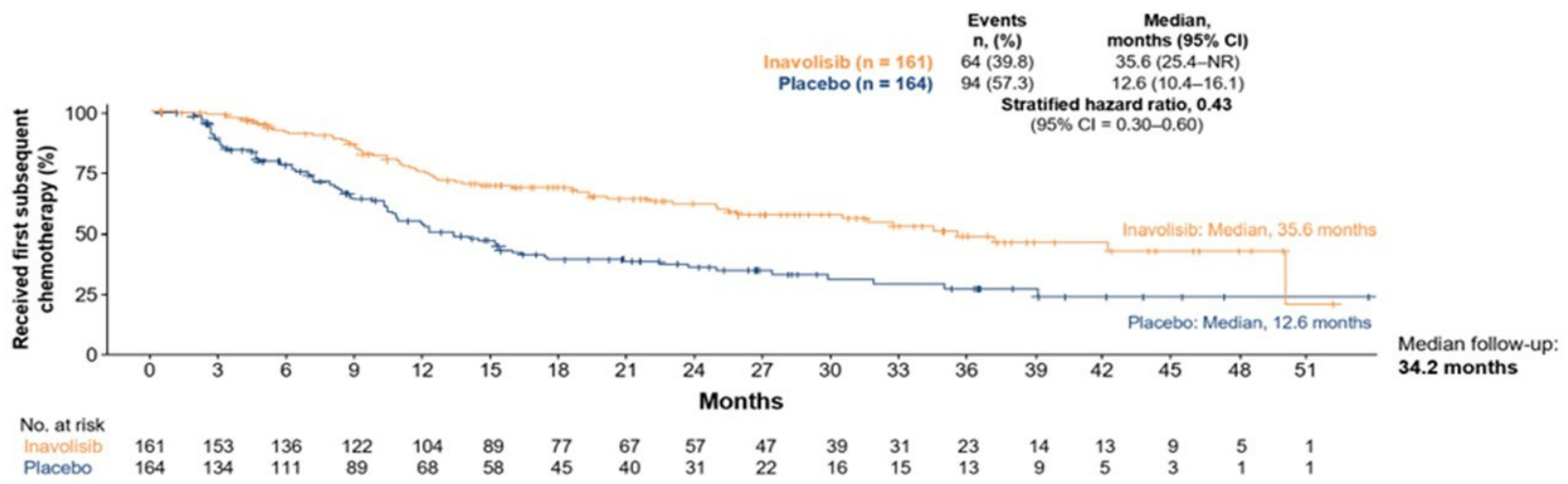
Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

- Visceral disease (yes vs. no)
- Endocrine resistance (primary vs. secondary)‡
- Region (North America/Western Europe vs. Asia vs. Other)

INAVO120 time to first subsequent chemotherapy



Median follow-up: **34.2 months**

Time to first subsequent chemotherapy was substantially delayed (by ~2 years) by the addition of inavolisib to palbociclib and fulvestrant (improvement in median time: 23 months)

Median follow-up: **34.2 months**

Patients, n (%) with at least one:	Inavolisib (n = 161)	Placebo (n = 163)
Any-grade AE	161 (100)	163 (100)
Grade 3–4 AE	146 (90.7)	138 (84.7)
Grade 5 AE*	6 (3.7)	2 (1.2)
Serious AE	44 (27.3)	22 (13.5)
AE leading to discontinuation of treatment		
Inavolisib/placebo	11 (6.8)	1 (0.6)
Palbociclib	10 (6.2)	0
Fulvestrant	6 (3.7)	0
AE leading to dose reduction of treatment		
Inavolisib/placebo	24 (14.9)	6 (3.7)
Palbociclib	65 (40.4)	56 (34.4)

INAVO120 selected AEs*

	Inavolisib (n = 161)		Placebo (n = 163)	
Patients, n (%)	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	147 (91.3)	133 (82.6)	148 (90.8)	131 (80.4)
Thrombocytopenia	80 (49.7)	22 (13.7)	75 (46.0)	8 (4.9)
Stomatitis or mucosal inflammation	89 (55.3)	9 (5.6)	47 (28.8)	0
Anemia	64 (39.8)	11 (6.8)	62 (38.0)	3 (1.8)
Hyperglycemia	102 (63.4)	11 (6.8)	22 (13.5)	0
Diarrhea†	84 (52.2)	6 (3.7)	26 (16.0)	0
Nausea	47 (29.2)	0	32 (19.6)	0
Rash	43 (26.7)	0	32 (19.6)	1 (0.6)
Ocular toxicities‡	47 (29.2)	1 (0.6)	26 (16.0)	0
Aspartate transaminase/ alanine transaminase increase	34 (21.1)	7 (4.3)	37 (22.7)	4 (2.5)
Vomiting	26 (16.1)	2 (1.2)	10 (6.1)	2 (1.2)
Lymphopenia	6 (3.7)	1 (0.6)	15 (9.2)	3 (1.8)
Pneumonitis§	5 (3.1)	1 (0.6)	2 (1.2)	0

Better prophylaxis /mitigation approaches are needed as this combination expands in real world setting.

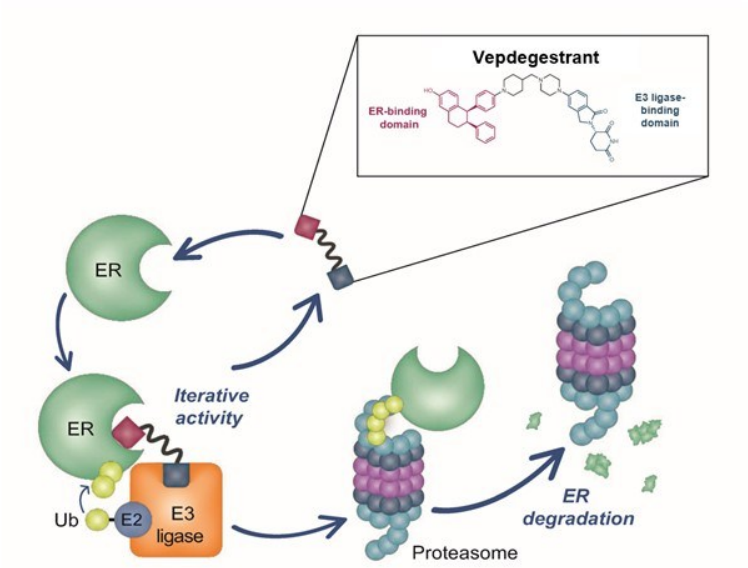
Future less toxic combination with other agents in this class?

Ongoing questions in HR+ positive MBC

- Can we safely and effectively improve systemic therapy for patients with early rapid progression ?
- How can we best optimize post CDK 4/6 inhibitor systemic therapy options with new targeted therapy/endocrine therapy options?
- How to best use dynamic biomarker monitoring to inform therapy switches?
- When to incorporate ADCs and in what sequence?

Vepdegestrant, a PROTAC ER Degrader, vs Fulvestrant in ER+/HER2- Advanced Breast Cancer: Results of the Global, Randomized, Phase 3 VERITAC-2 Study

Erika P Hamilton[1], Michelino De Laurentiis[2], Komal Jhaveri[3], Xichun Hu[4], Sylvain Ladoire[5], Anne Patsouris[6], Claudio Zamagni[7], Jiuwei Cui[8], Marina Cazzaniga[9], Timucin Cil[10], Katarzyna Jerzak[11], Christian Fuentes[12], Tetsuhiro Yoshinami[13], Alvaro Rodriguez-Lescure[14], Olga Valota[15], Dongrui R Lu[16], Marcella Martignoni[15], Janaki Parameswaran[17], Xin Zhi[17], Mario Campone[18]



Vepdegestrant has a unique MOA that directly harnesses the ubiquitin-proteasome system to degrade ER[8]

Key Takeaways

Vepdegestrant is the first PROTAC to be evaluated in a phase 3 study

Oral vepdegestrant was well tolerated and demonstrated statistically significant and clinically meaningful improvement in PFS vs fulvestrant in patients with *ESR1*m

Results of the phase 3 VERITAC-2 study support vepdegestrant as a potential treatment option for previously treated *ESR1*m ER+/HER2- advanced breast cancer

VERITAC-2: Global Phase 3 Trial of Vepdegestrant

Key Eligibility Criteria

- Age ≥18 years old
- ER+/HER2- advanced or metastatic breast cancer
- Prior therapy:
  - 1 line of CDK4/6i + ET
  - ≤1 additional ET
  - Most recent ET for ≥6 months
  - No prior SERD (eg, fulvestrant, elacestrant)
  - No prior chemotherapy for advanced or metastatic disease
- Radiological progression during or after the last line of therapy

Randomization (1:1)

28-day Treatment Cycles

Vepdegestrant (n=313)
200 mg orally (once daily)

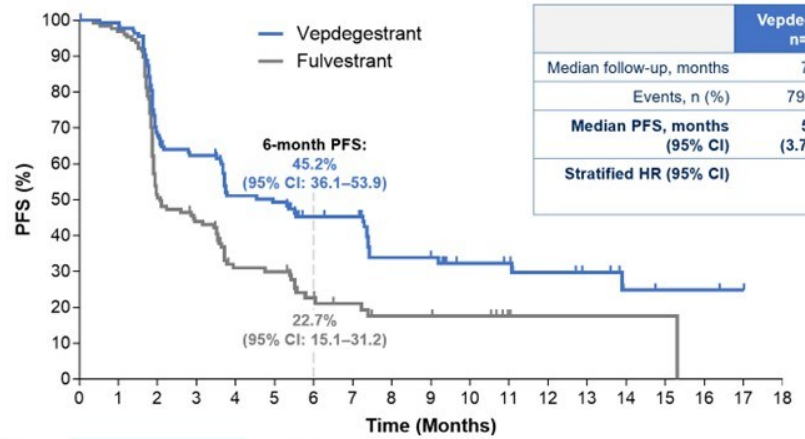
Fulvestrant (n=311)
500 mg IM
(days 1 and 15 of cycle 1; day 1 of subsequent cycles)

Stratification Factors:
- *ESR1* mutation[a] (yes vs no)
- Visceral disease (yes vs no)

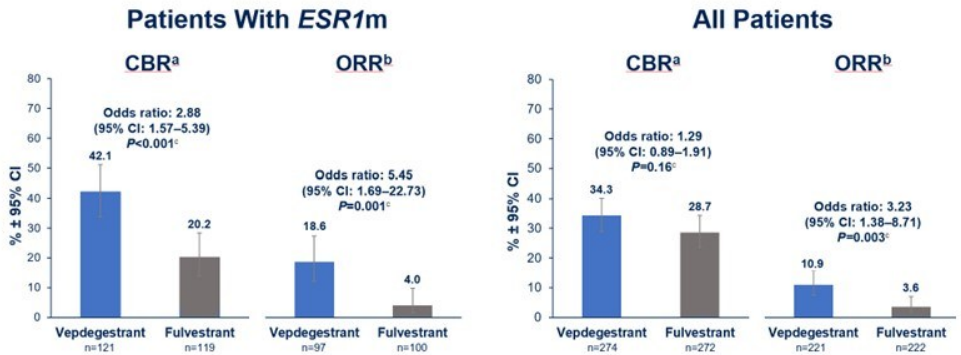
Primary Endpoints:
- PFS by BICR in
  - *ESR1*m population
  - All patients

Secondary Endpoints:
- OS (key secondary)
- CBR and ORR by BICR
- AEs

VERITAC-2 Primary Endpoint: PFS by BICR in Patients With *ESR1*m



	Vepdegestrant n=136	Fulvestrant n=134
Median follow-up, months	7.4	6.0
Events, n (%)	79 (58)	95 (71)
Median PFS, months (95% CI)	**5.0 (3.7–7.4)**	**2.1 (1.9–3.5)**
Stratified HR (95% CI)	**0.57 (0.42–0.77)**	
	2-sided *P*<0.001	



Ongoing questions in HR+ positive MBC

- Can we safely and effectively improve systemic therapy for patients with early rapid progression ? Efficacy shown in INAVO120 data. However, toxicity experience in real world will need to be carefully monitored and additional mitigation strategies are needed.
- How can we best optimize post CDK 4/6 inhibitor systemic therapy options with new targeted therapy/endocrine therapy options? Still a work in progress and as new targeted approvals enter the scene, we will need to use robust real world data, symptom toxicities, and overall patient experience to help determine how best use these agents.
- How to best use dynamic biomarker monitoring to inform therapy switches? SERENA-6 ASCO25 and multiple other studies in progress
- When to incorporate ADCs and in what sequence? Multiple studies in progress

Updates in Her2 Positive MBC

Destiny -09

PRESENTED BY: Maryam Lustberg MD MPH

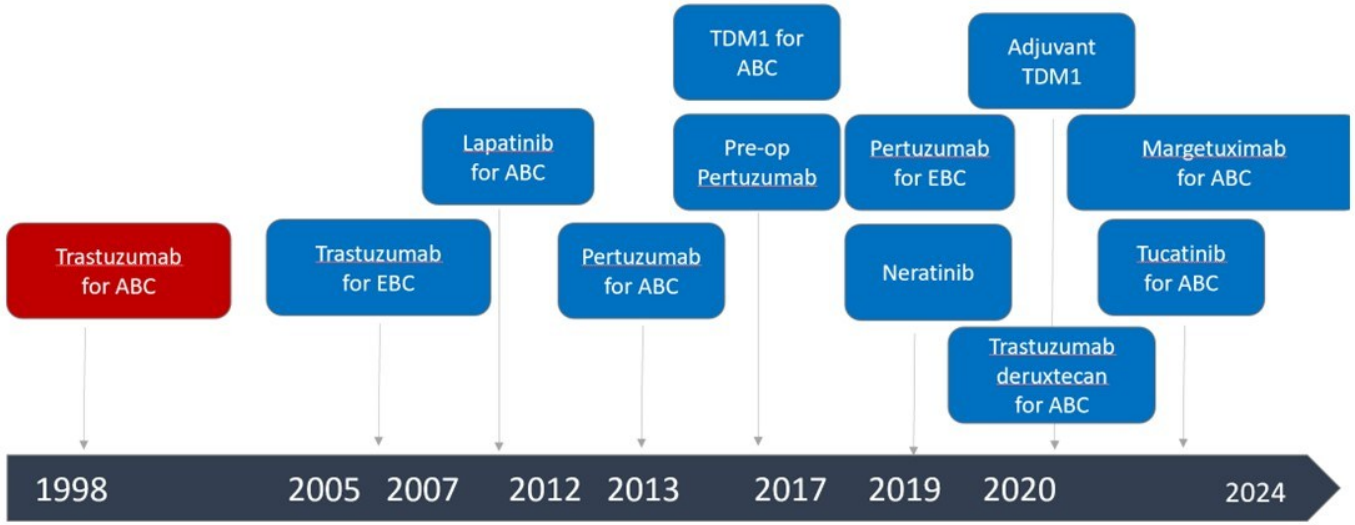
Key takeaways in HER2 positive MBC #ASC025:

TDXd + P showed a statistically significant improvement PFS vs taxane plus HP

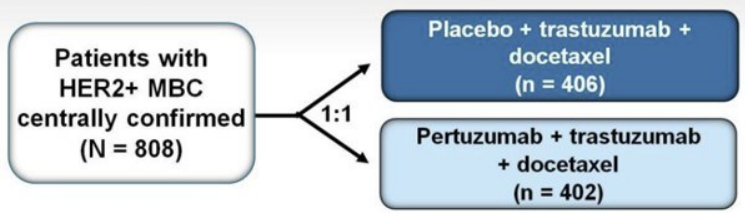
This is likely a new first line standard of care for patients with HER2 positive MBC

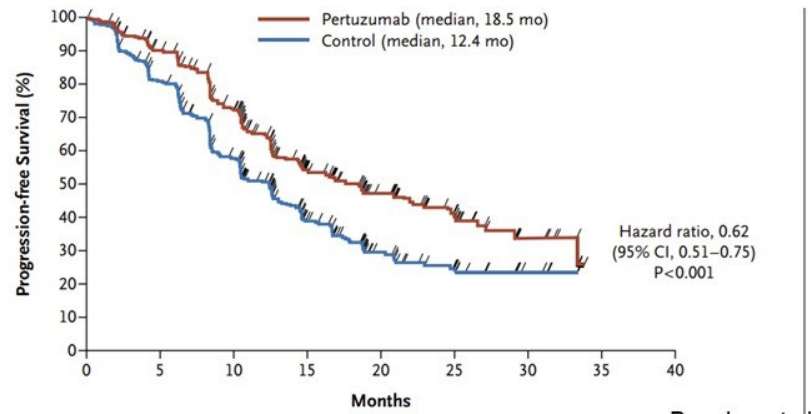
Many unanswered questions remain including de-escalation strategies for the right patient population and role of CDK 4/6 inhibitor plus endocrine therapy /HP in HR+ HER2 positive tumors

Milestones in HER2+ Breast Cancer



CLEOPATRA Study Design





Bacelga et al NEJM, 2012

Ongoing questions in HER2 positive MBC

- Can we do better than the CLEOPATRA regimen?
- How to optimize maintenance therapy particularly in HR + HER2 positive breast cancer: Role of CDK 4/6 inhibitors
- Are chemo free regimens possible for selected patients?
- When can therapy be safety stopped in patients in with long term disease stability ?
- How can we reduce risk of CNS metastasis and progression?
- Can we achieve a long term cure in Her2 positive MBC?

2025 ASCO ANNUAL MEETING

DESTINY Breast09

Trastuzumab deruxtecan (T-DXd) + pertuzumab vs taxane + trastuzumab + pertuzumab (THP) for first-line treatment of patients with human epidermal growth factor receptor 2–positive (HER2+) advanced/metastatic breast cancer: interim results from DESTINY-Breast09

Sara M Tolaney, MD
Dana-Farber Cancer Institute, Boston, MA, US

Key takeaways

44%
Reduction in risk of disease progression or death with T-DXd + P vs THP (by BICR)

- **T-DXd + P** demonstrated a **PFS improvement** vs the established first-line standard of care (THP) in HER2+ a/mBC
- Safety was consistent with known profiles of individual treatments; no new safety signals identified

T-DXd + P demonstrated a statistically significant and clinically meaningful PFS benefit vs THP that was consistently observed across all subgroups and may represent a new first-line standard of care for patients with HER2+ a/mBC

PRESENTED BY: Maryam Lustberg MD MPH

DESTINY-Breast09 study design

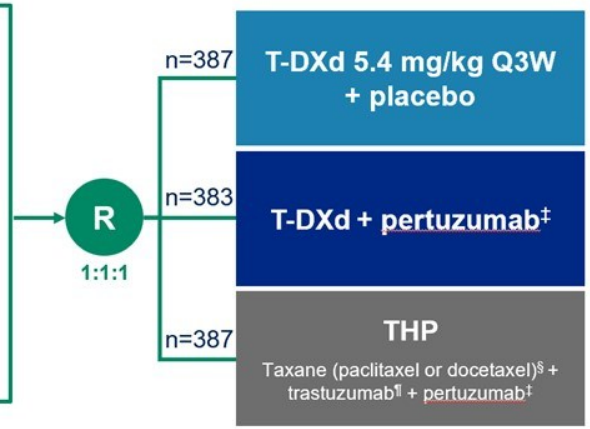
A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)

Eligibility criteria

- HER2+ a/mBC
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant / adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic† treatment for mBC**

Stratification factors

- De-novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA* Mut (detected vs non-detected)



Endpoints

Primary
- PFS (BICR)

Key secondary
- OS

Secondary
- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR)
- Safety and tolerability

- If T-DXd was discontinued due to AEs, patients could switch to trastuzumab‖
- Concurrent use of ET (AI or tamoxifen) was allowed after six cycles of T-DXd or discontinuation of taxane in THP arm

DESTINY-Breast09 study design

A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)

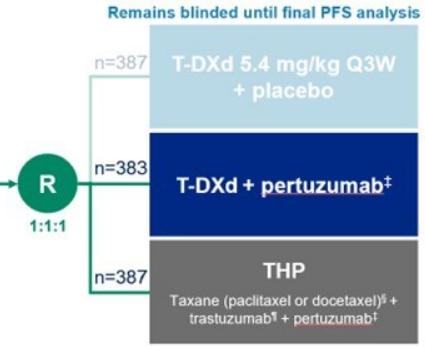
Remains blinded until final PFS analysis

Eligibility criteria

- HER2+ a/mBC
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant / adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic† treatment for mBC**

Stratification factors

- De-novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA* Mut (detected vs non-detected)



Endpoints

Primary
- PFS (BICR)

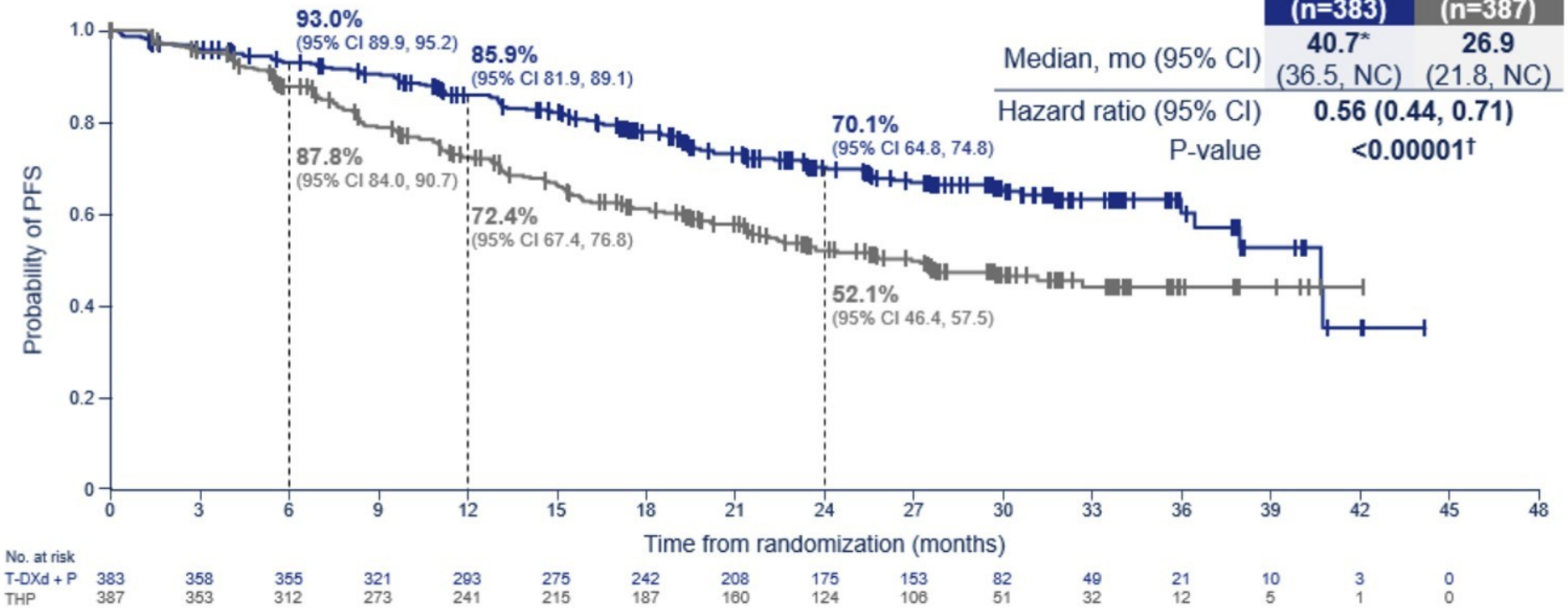
Key secondary
- OS

Secondary
- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR)
- Safety and tolerability

Interim analysis: At this DCO (Feb 26, 2025), the criterion for **PFS superiority** (**P-value <0.00043**) was met for **T-DXd + P** vs **THP**

DESTINY-Breast09

PFS (BICR): primary endpoint



	T-DXd + P (n=383)	THP (n=387)
Median, mo (95% CI)	40.7* (36.5, NC)	26.9 (21.8, NC)
Hazard ratio (95% CI)	0.56 (0.44, 0.71)	
P-value	<0.00001†	

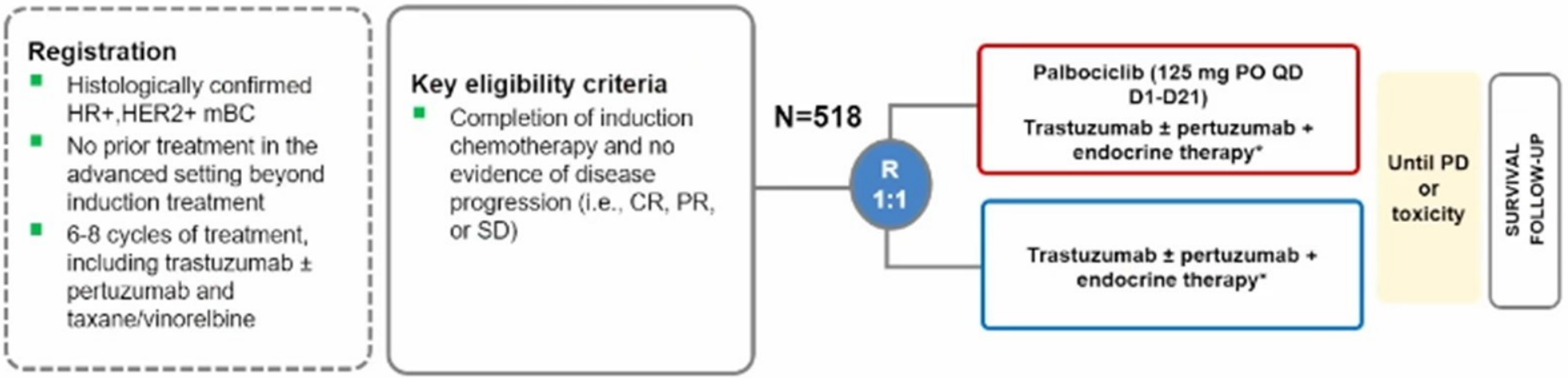
Median PFS
THP 18.5 mts
CLEOPATRA

Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

Ongoing questions in HER2 positive MBC

- Can we do better than the CLEOPATRA regimen?
- How to optimize maintenance therapy particularly in HR + HER2 positive breast cancer: Role of CDK 4/6 inhibitors
- Are chemo free regimens possible for selected patients?
- When can therapy be safety stopped in patients in with long term disease stability ?
- How can we reduce risk of CNS metastasis and progression?
- Can we achieve a long term cure in Her2 positive MBC?

AFT-38 PATINA Study Design

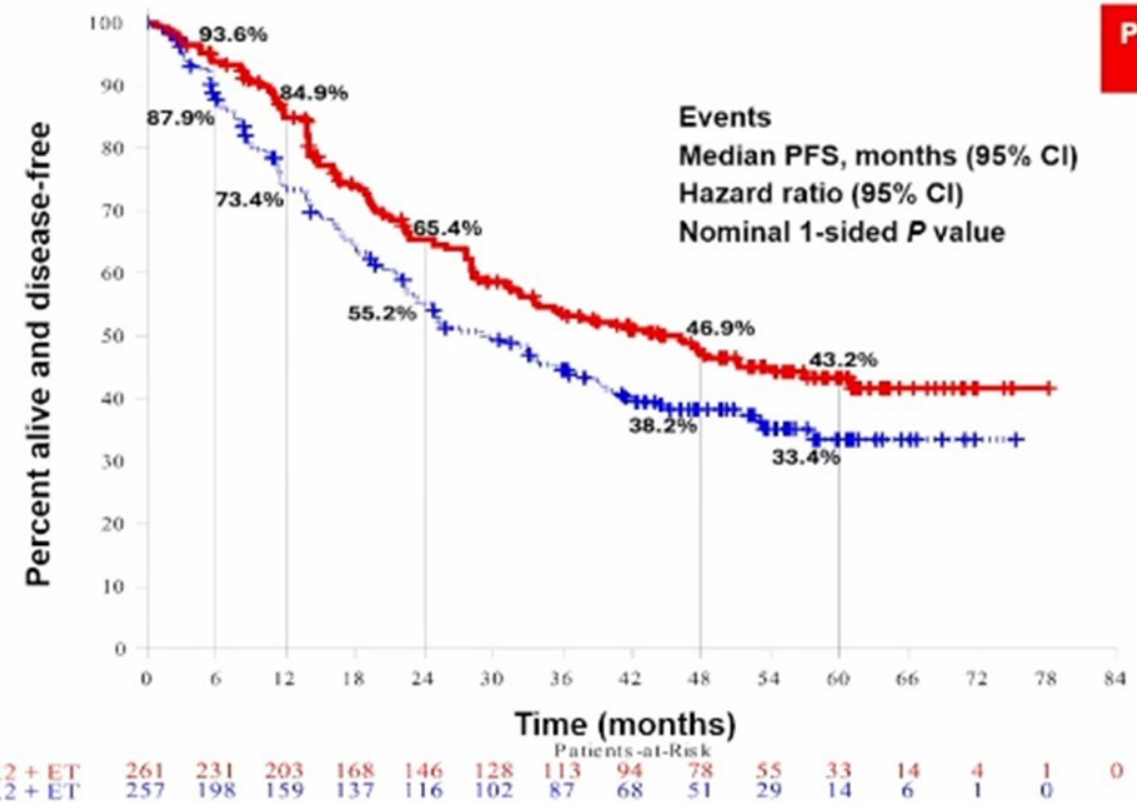


Stratification factors

- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)†
- Response to induction therapy (CR or PR vs SD) by investigator assessment†
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)

*Trastuzumab and pertuzumab were administered per SOC. Endocrine therapy options include an aromatase inhibitor or fulvestrant. †Factors used in stratified analyses.
CR=complete response; D=day; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer; PD=progressive disease; PO=orally; PR=partial response; QD=once a day; R=randomization; SD=stable disease; SOC=standard of care.

Primary Endpoint: PFS (Investigator-Assessed)



	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; palbo=palbociclib.

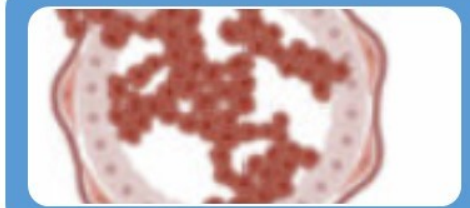
Play

Updates in Triple Negative MBC

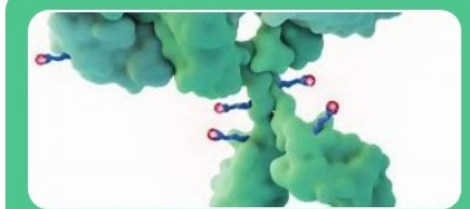
ASCENT-04

PRESENTED BY: Maryam Lustberg MD MPH

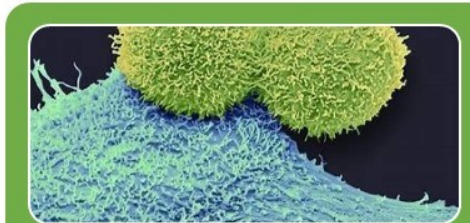
Key Takeaways Metastatic TNBC #ASCO25



Progress is urgently needed for patients with metastatic TNBC; with almost half of patients not receiving 2nd line treatment and a third dying before receiving 2nd line therapy.



SG + pembro led to a significant improvement in PFS vs chemo + pembro.These results will likely lead a change to current first line standard of care.



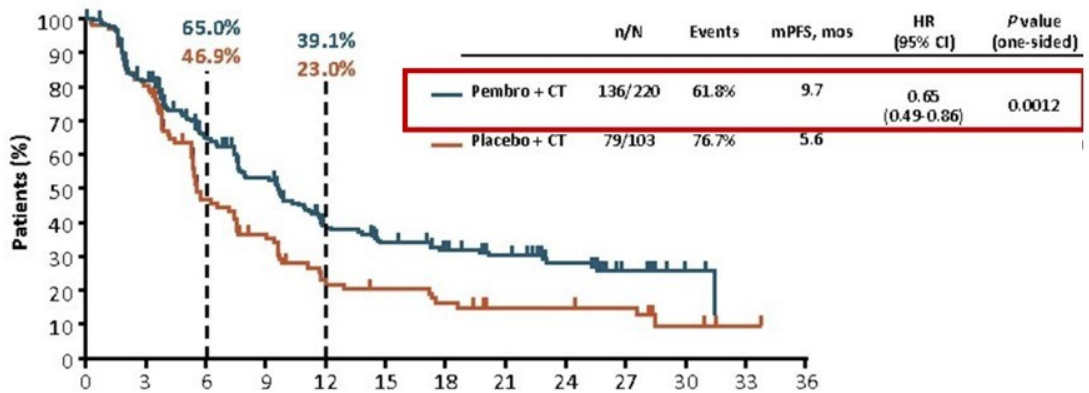
Additional ADC immunotherapy combinations and emerging therapeutic strategies are currently under investigation.

Some unanswered questions in TNBC MBC

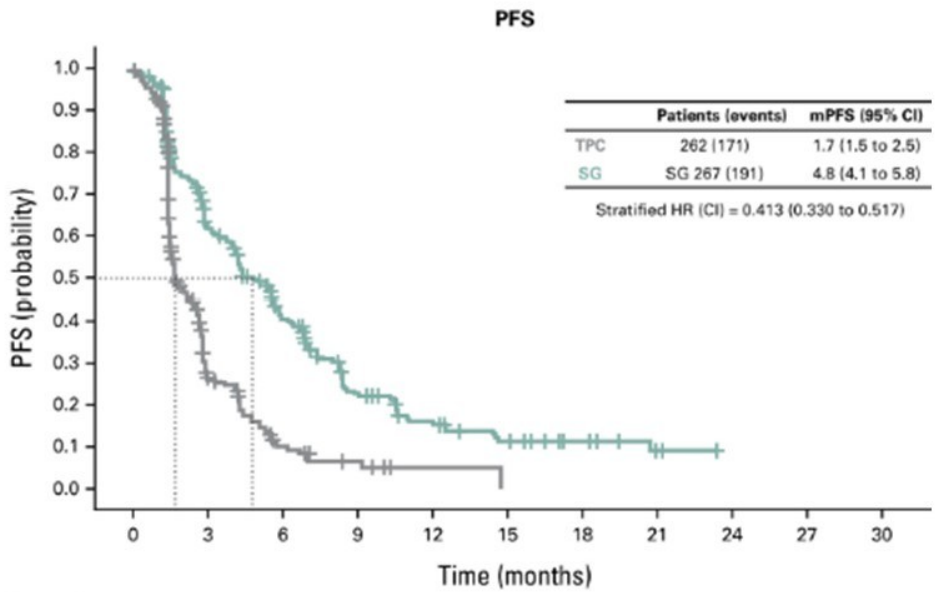
- How can we improve our current first line therapy with traditional chemotherapy /immunotherapy backbone in PDL+ MBC
- What is the optimal regimen for PDL negative MBC?
- How to deliver sustainable effective therapies in 2nd line and beyond?
- How can reduce the risk of brain metastases and improve their management?

Metastatic TNBC regimens currently in use. Can we do better?

KN-355 1st line



ASCENT 2nd line



1.Cortes et al NEJM, 2022 2. Bardia et al

Sacituzumab Govitecan Plus Pembrolizumab vs Chemotherapy Plus Pembrolizumab in Patients With Previously Untreated, PD-L1 Positive, Advanced or Metastatic Triple-Negative Breast Cancer: Primary Results From the Randomized, Phase 3 ASCENT-04/KEYNOTE-D19 Study

Sara M Tolaney[1], Evandro de Azambuja[2], Kevin Kalinsky[3], Sherene Loi[4], Sung-Bae Kim[5], Clinton Yam[6], Bernardo Rapoport[7,8], Seock-Ah Im[9], Barbara Pistilli[10], Wassim McHayleh[11], David W Cescon[12], Junichiro Watanabe[13], Manuel Alejandro Lara Banuelas[14], Ruffo Freitas-Junior[15], Javier Salvador Bofill[16], Maryam Afshari[17], Dianna Gary[17], Lu Wang[17], Catherine Lai[17], Peter Schmid[18]

Key take aways: SG + pembro led to a significant improvement in PFS vs chemo + pembro.These results will likely lead a change to current first line standard of care

ASCENT-04/KEYNOTE-D19 Study Design

Previously untreated, locally advanced unresectable, or metastatic TNBC[a]:

- PD-L1-positive (CPS ≥ 10 by the 22C3 assay[b])
- ≥ 6 months since treatment in curative setting (prior anti-PD-[L]1 use allowed)

N = 443

R 1:1

SG + pembro[d]
(SG 10 mg/kg IV, days 1 and 8 of 21-day cycles; pembro 200 mg, day 1 of 21-day cycles)
n = 221

Chemo* + pembro[d]
(paclitaxel 90 mg/m² OR nab-paclitaxel 100 mg/m² on days 1, 8, & 15 of 28-day cycles, OR gemcitabine 1000 mg/m² + carboplatin AUC 2 on days 1 & 8 of 21-day cycles; pembro 200 mg on day 1 of 21-day cycles)
n = 222

**Eligible patients who experienced BICR-verified disease progression were allowed to cross-over to receive 2L SG monotherapy*

All treatment, including SG or chemo, was continued until BICR-verified disease progression or unacceptable toxicity

End points

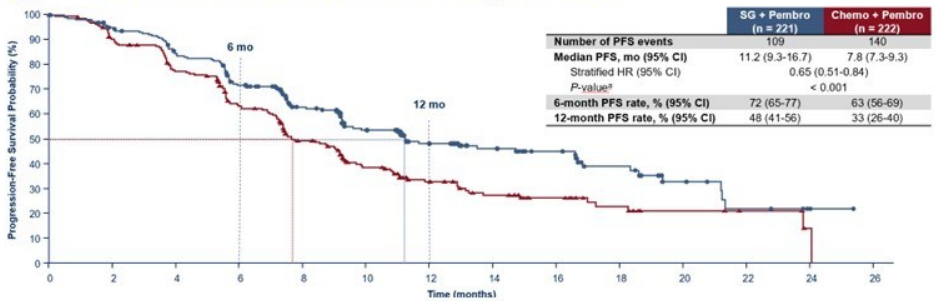
Primary
- PFS by BICR[e]

Secondary
- OS
- ORR, DOR by BICR[e]
- Safety
- QoL

Stratification factors:
- De novo mTNBC[c] vs recurrent within 6 to 12 months from completion of treatment in curative setting vs recurrent > 12 months from completion of treatment in curative setting
- US/Canada/Western Europe vs the rest of the world
- Prior exposure to anti-PD-(L)1 (yes vs no)

ITT Population	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Female sex, n (%)	221 (100)	222 (100)
Median age, (range) yr	54 (23-88)	55 (27-82)
≥ 65 yr, n (%)	58 (26)	57 (26)
Race or ethnic group,[a] n (%)		
White	139 (63)	118 (53)
Black	13 (6)	11 (5)
Asian	43 (19)	63 (28)
Other/not specified	26 (12)	30 (14)
Geographic region, n (%)		
North America/Western Europe	85 (38)	85 (38)
Rest of the world[b]	136 (62)	137 (62)
ECOG PS at baseline,[c] n (%)		
0	156 (71)	154 (69)
1	65 (29)	67 (30)
Curative treatment-free interval, n (%)		
De novo	75 (34)	75 (34)
Recurrent within 6-12 mo	40 (18)	40 (18)
Recurrent > 12 mo	106 (48)	107 (48)

Progression-Free Survival by BICR



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of PFS events	109	140
Median PFS, mo (95% CI)	11.2 (9.3-16.7)	7.8 (7.3-9.3)
Stratified HR (95% CI)	0.65 (0.51-0.84)	
P-value[a]	< 0.001	
6-month PFS rate, % (95% CI)	72 (65-77)	63 (56-69)
12-month PFS rate, % (95% CI)	48 (41-56)	33 (26-40)

Subgroup Analysis of Progression-Free Survival by BICR

	SG + Pembro n	SG + Pembro Median PFS, mo (95% CI)	Chemo + Pembro n	Chemo + Pembro Median PFS, mo (95% CI)	Unstratified HR (95% CI)
ITT population	221	**11.2** (9.3-16.7)	222	**7.8** (7.3-9.3)	0.66 (0.51-0.85)
Age group					
< 65 yr	163	**11.3** (9.3-16.8)	165	**7.5** (7.0-9.2)	0.61 (0.45-0.82)
≥ 65 yr	58	**11.1** (7.5-NR)	57	**9.3** (7.3-13.2)	0.85 (0.52-1.39)
ECOG PS					
0	156	**12.9** (9.3-16.8)	154	**8.7** (7.3-9.9)	0.65 (0.48-0.88)
≥ 1	65	**9.2** (7.5-18.3)	67	**7.5** (5.6-9.3)	0.66 (0.43-1.03)
Geographic region					
US/Canada/Western Europe	85	**11.7** (7.5-19.4)	85	**7.4** (5.7-9.9)	0.65 (0.43-0.98)
Rest of the world	136	**11.2** (9.3-16.7)	137	**8.4** (7.4-9.3)	0.66 (0.48-0.91)
Curative treatment-free interval					
De novo	75	**8.1** (7.3-18.6)	75	**7.7** (6.1-11.9)	0.89 (0.59-1.34)
Recurrent 6-12 mo	40	**9.9** (5.7-16.8)	40	**7.2** (4.4-9.1)	0.62 (0.36-1.08)
Recurrent > 12 mo	106	**16.6** (11.0-NR)	107	**8.7** (7.3-10.8)	0.52 (0.35-0.76)
Prior (neo)adjuvant anti-PD-(L)1 therapy					
Yes	9	**7.5** (0.9-NR)	11	**6.6** (2.1-NR)	1.08 (0.31-3.75)
No	212	**11.7** (9.3-16.8)	211	**7.8** (7.4-9.3)	0.65 (0.50-0.84)
Chemo selected prior to randomization					
Taxane	116	**11.1** (8.6-16.7)	114	**9.2** (7.2-12.9)	0.82 (0.58-1.17)
Gemcitabine/Carboplatin	105	**11.3** (9.2-21.2)	108	**7.4** (6.9-9.0)	0.52 (0.36-0.75)

PFS benefit was observed for SG + pembro vs chemo + pembro across most prespecified subgroups

2025 ASCO ANNUAL MEETING

Genitourinary Oncology Highlights of the Day

Practice Reinforcing for the Trials of Tomorrow

Bradley A McGregor, MD
Marra Lochiatto Investigatorship in Kidney Cancer
Dana Farber Cancer Institute, Boston MA

Selected Abstracts

- Metastatic RCC
  - Role of Nivolumab and Ipilimumab
  - Novel combinations and drugs
- Adjuvant RCC
  - Biomarkers?
  - Updated Survival for Adjuvant Pembrolizumab
- Perioperative Urothelial
  - Role of ctDNA
- Metastatic Urothelial
  - Continued benefit from EV-Pembro

Abstract 4505,4516
Abstract 4506, 4515

Abstract 4510
Abstract 4514

Abstract 4503

Abstract 4502

Study design: CheckMate 214

N = 1096

Key inclusion criteria[1]

- ≥ 18 years old
- Treatment-naïve aRCC
- Clear cell component
- Measurable disease per RECIST v1.1
- KPS ≥ 70%

Stratification factors:

- IMDC risk score
- Geographic region

R 1:1

Nivolumab 3 mg/kg IV
+ **Ipilimumab** 1 mg/kg IV Q3W (× 4 doses)
followed by **Nivolumab** 3 mg/kg Q2W

Patients receiving NIVO monotherapy could switch to NIVO 240 mg Q2W or 480 mg Q4W flat dosing

Sunitinib 50 mg PO QD
for 4 weeks on, 2 weeks off
(6-week cycles)

Crossover from SUN to NIVO+IPI was permitted for IMDC intermediate/poor-risk patients

Median (range) OS follow-up, 9.3 years (111.1 [103.0-119.3] months)

Primary endpoints: OS, PFS and ORR (both per IRRC) in IMDC intermediate/poor-risk patients

Secondary endpoints: OS, PFS and ORR (both per IRRC) in ITT patients; safety in all treated patients

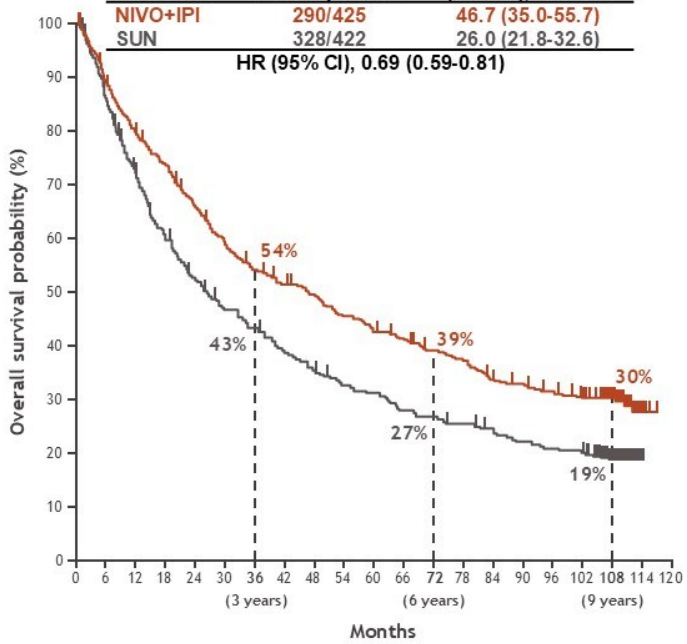
Exploratory endpoints: OS, PFS and ORR (both per IRRC) in IMDC favorable-risk patients

OS, PFS, and DOR in the IMDC intermediate/poor-risk population

OS

Treatment	Events/patients	Median OS (95% CI), months
NIVO+IPI	290/425	46.7 (35.0-55.7)
SUN	328/422	26.0 (21.8-32.6)

HR (95% CI), 0.69 (0.59-0.81)



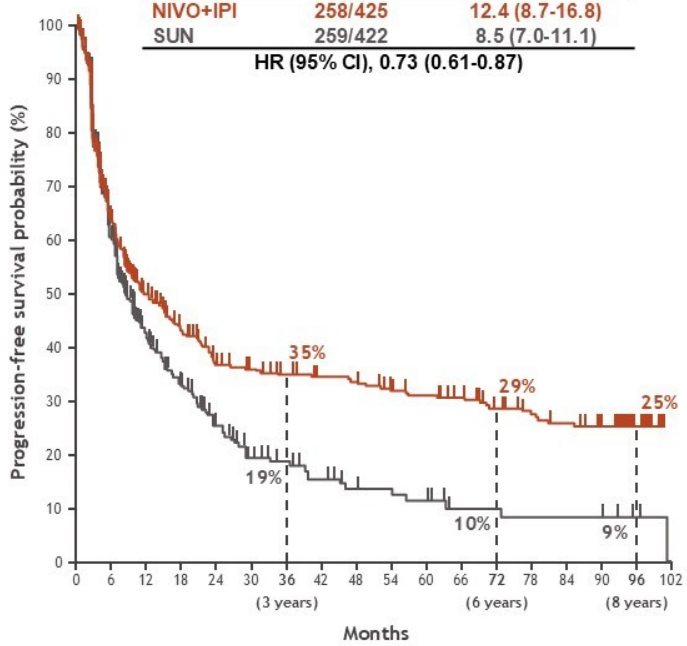
No. at risk

NIVO+IPI	425	377	336	309	273	244	223	210	200	184	172	165	153	146	131	126	119	111	70	7	0
SUN	422	358	296	243	210	187	173	154	140	128	121	109	105	97	90	83	78	76	45	2	0

PFS per IRRC

Treatment	Events/patients	Median PFS (95% CI), months
NIVO+IPI	258/425	12.4 (8.7-16.8)
SUN	259/422	8.5 (7.0-11.1)

HR (95% CI), 0.73 (0.61-0.87)



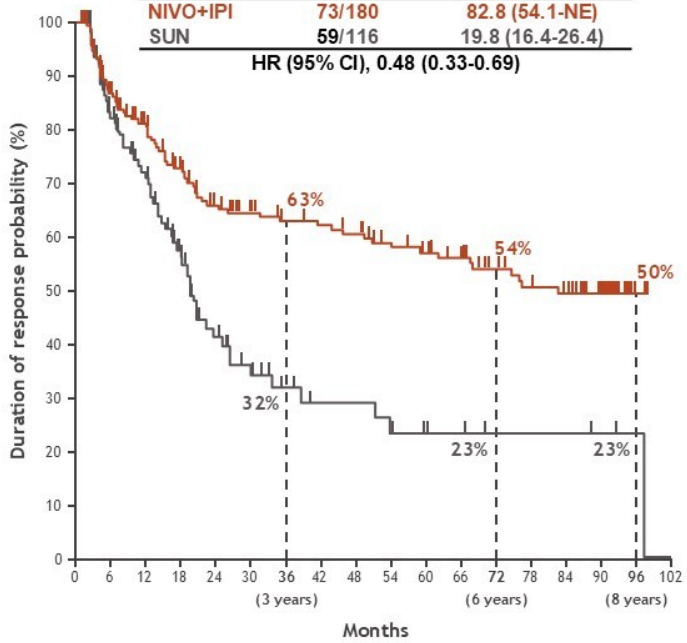
No. at risk

NIVO+IPI	425	237	168	135	107	100	90	84	82	74	70	65	56	50	46	38	11	0			
SUN	422	194	110	77	50	33	26	19	14	13	11	6	6	5	5	5	2	0			

DOR per IRRC

Treatment	Events/patients	Median DOR (95% CI), months
NIVO+IPI	73/180	82.8 (54.1-NE)
SUN	59/116	19.8 (16.4-26.4)

HR (95% CI), 0.48 (0.33-0.69)



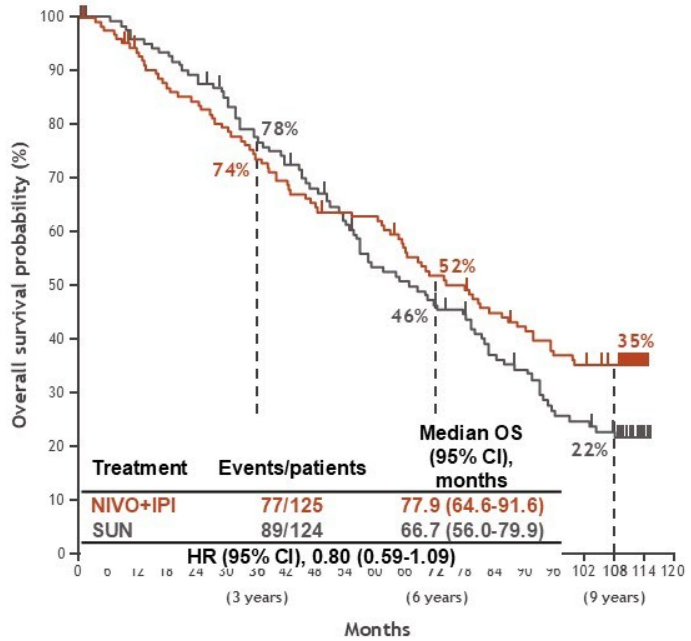
No. at risk

NIVO+IPI	180	147	127	109	94	87	79	77	74	67	63	59	50	45	42	28	2	0			
SUN	116	78	61	42	26	19	13	10	10	7	6	5	3	3	3	2	1	0			

- With a median follow-up of > 9 years, long-term benefits were sustained with NIVO+IPI vs SUN in patients with IMDC intermediate/poor risk, including improved OS and PFS and more durable responses

OS, PFS, and DOR in the IMDC favorable-risk population

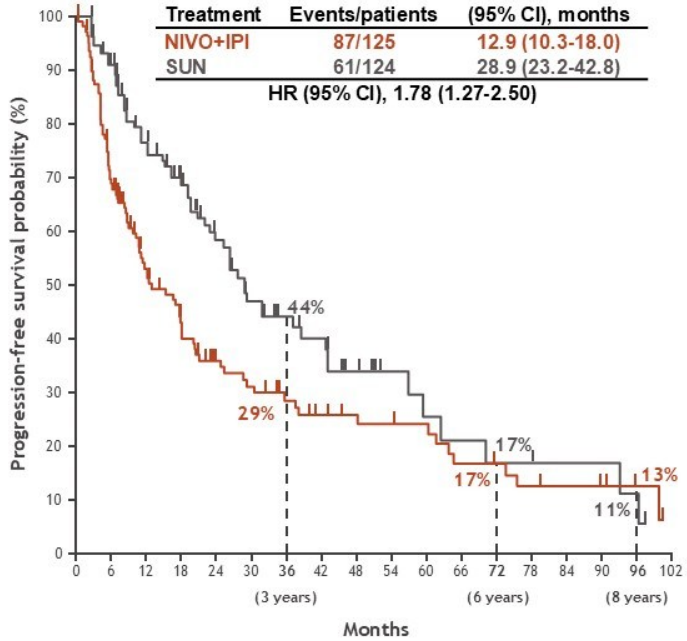
OS



No. at risk

NIVO+IPI	125	121	113	105	102	96	89	84	78	76	75	66	61	58	52	48	42	40	35	4	0
SUN	124	121	116	113	107	101	92	86	80	71	61	58	52	48	40	36	28	26	21	5	0

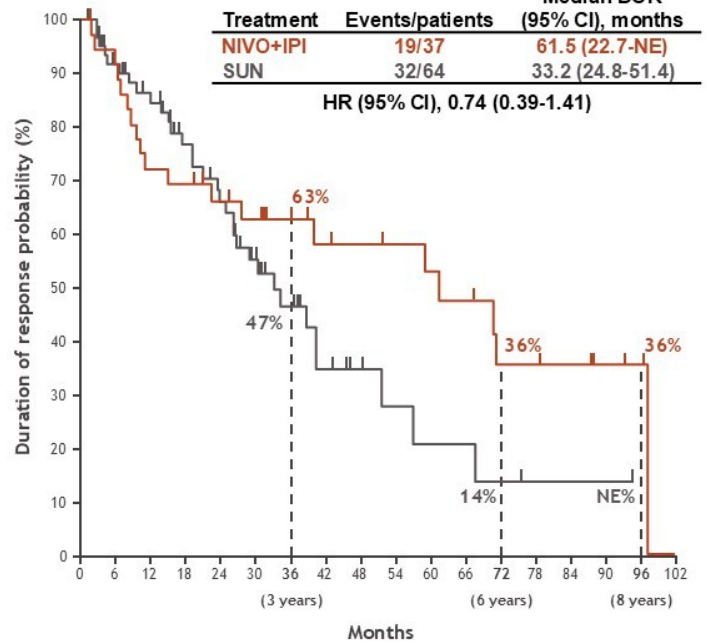
PFS per IRRC



No. at risk

NIVO+IPI	125	82	55	41	30	26	21	17	15	14	13	9	8	6	5	4	2	0			
SUN	124	99	74	58	42	32	23	20	13	8	6	5	4	4	3	3	2	0			

DOR per IRRC

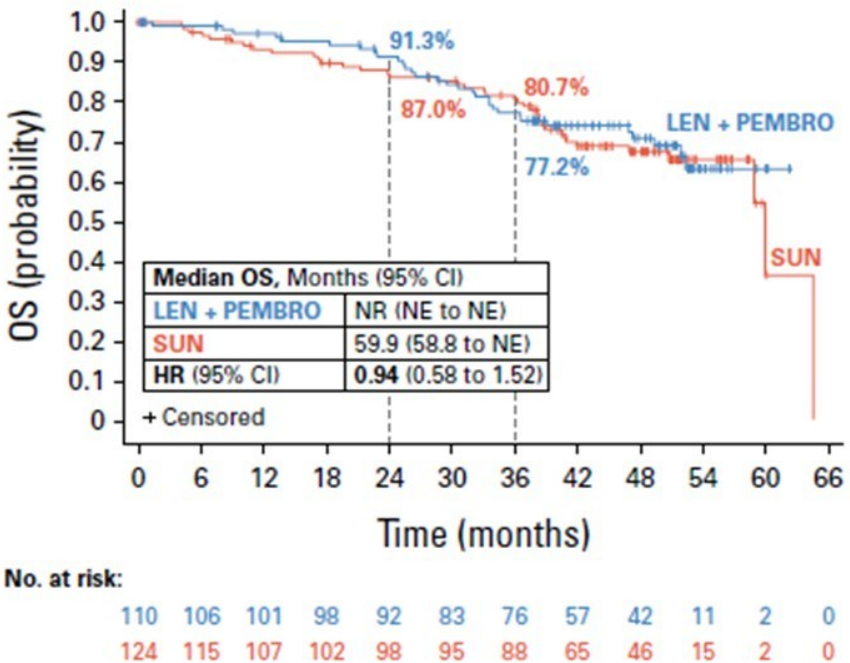


No. at risk

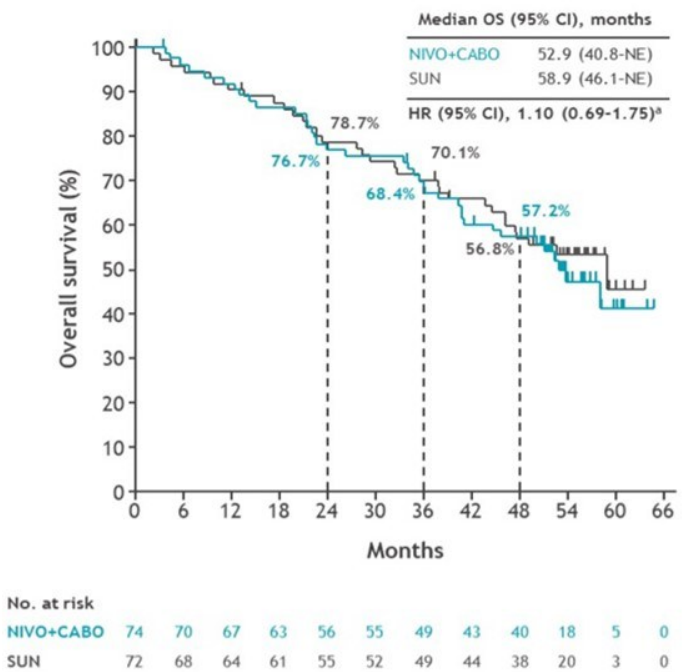
NIVO+IPI	37	33	26	25	21	19	16	13	12	11	10	9	6	6	5	3	2	0			
SUN	64	53	46	37	31	23	15	9	6	4	3	3	2	1	1	1	0	0			

- Long-term OS results in patients with IMDC favorable risk trended in favor of NIVO+IPI over SUN, with more durable responses

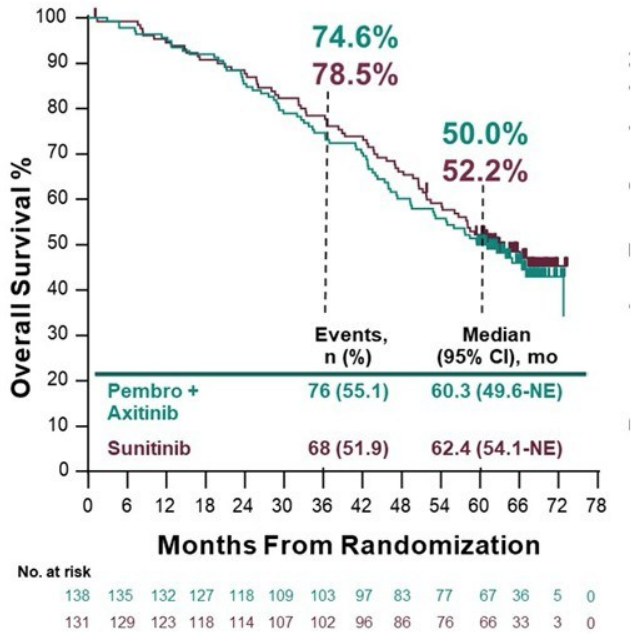
IO/TKI in Favorable Risk Disease



CLEAR



CM 9ER



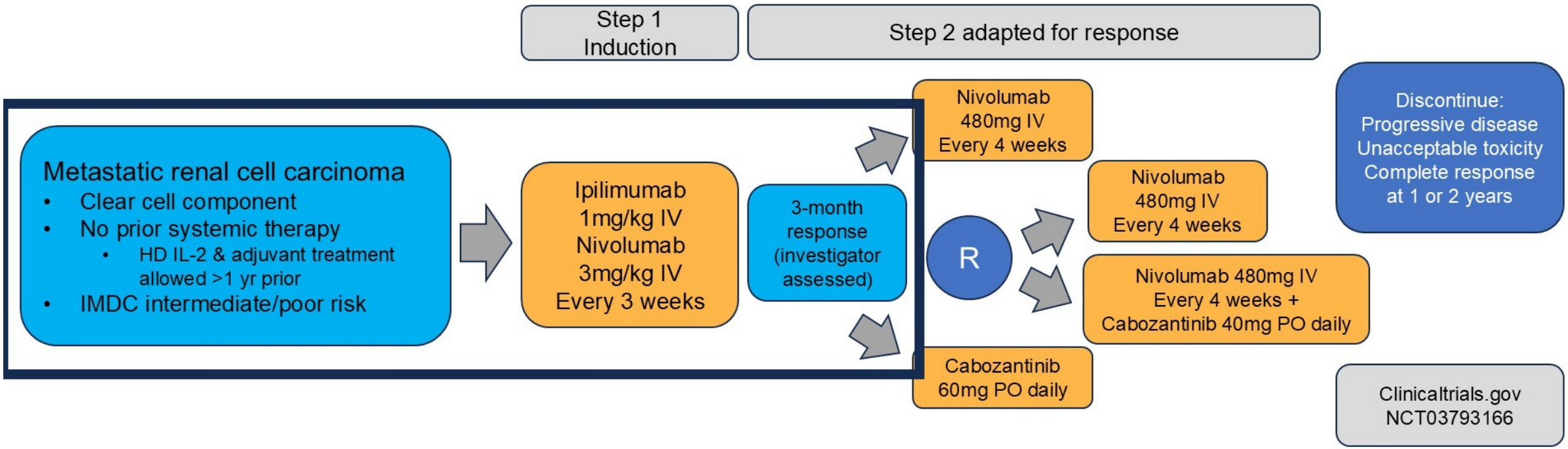
KN 426

Rini et al, ASCO 2023, Bouron et al ASCO GU 2024, Motzer RJ, et al. *J Clin Oncol*. 2024;

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0) OR RELAPSED DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b,c] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Ipilimumab + nivolumab[b,d]	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Pazopanib • Sunitinib	• Active surveillance[1,2,3] • Axitinib (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b,c] (category 1) • Ipilimumab + nivolumab[b,d] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B)

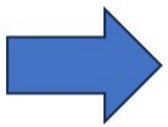
PDIGREE (A031704): Phase 3 Adaptive Trial



Primary endpoint: Overall Survival of randomized cohort

Step 1 Analysis (Data Cutoff January 2025)

- 1111 patients enrolled into Step 1 between May 2019 and May 2024
  - 747 (67%) enrolled into step 2
    - 597 randomized
    - 299 nivo, 298 nivo-cabo
    - PD cohort: 141 cabozantinib
    - CR cohort: 9 nivolumab



- Patient characteristics did not differ in step 2 registration
- Disease characteristics differed in step 2 registration
  - Fewer poor risk disease (21% vs 23%)
  - Fewer bone mets (24% vs 27%)
- 37 deaths total in step 1
  - Majority from progressive disease

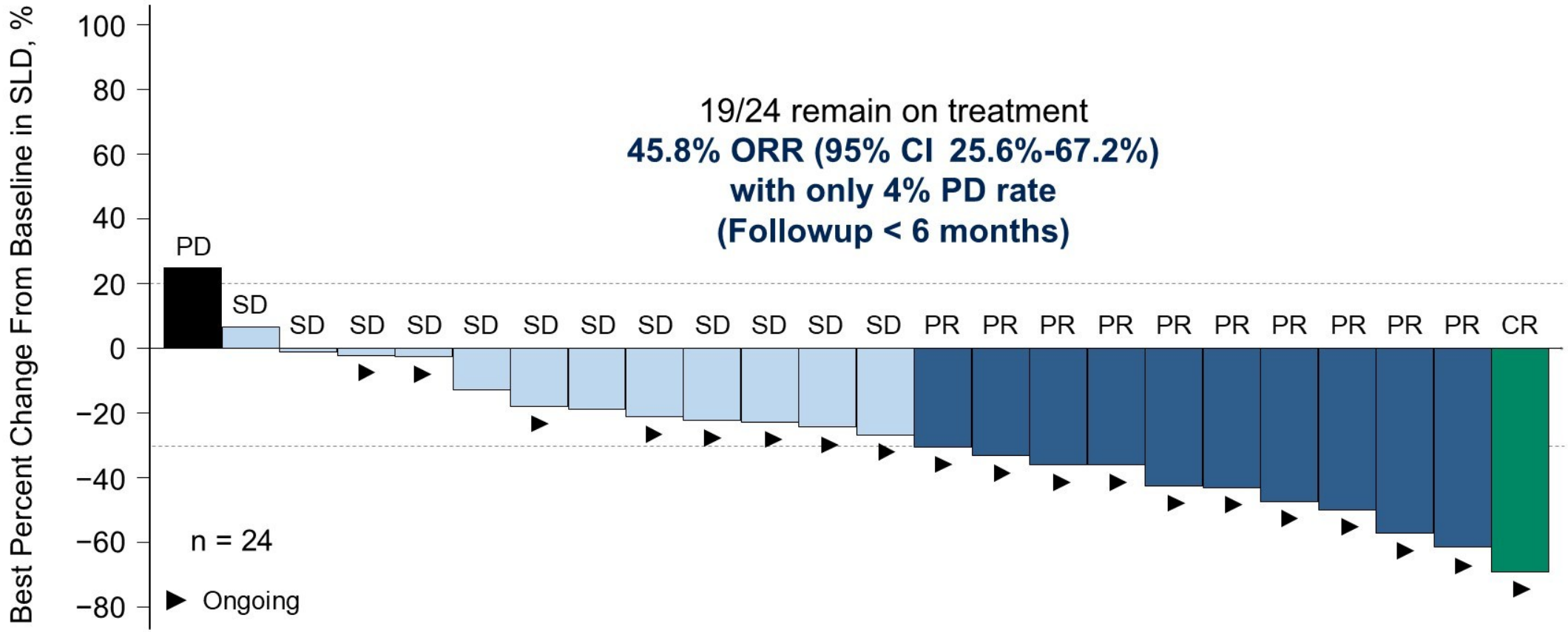
15 grade 5 events at least possibly due to AEs – cardiac, liver, respiratory failure

Key Takeaway Points/Conclusions

Long term follow-up confirms benefit of nivolumab and ipilimumab in metastatic clear cell renal cell carcinoma independent of risk group

Patient selection is critical to optimize outcomes

Cabozantinib and Casdatifan (HIF2α inhibitor)



Treatment-Related AEs (Any Grade)

	Safety Population n (%) (N = 42)		
	AE Related to		
	Casdatifan	Cabozantinib	Any Study Drug
Follow-up, months, median (range)		3.7 (1.1–9.1)	
Patients with any treatment-related AE, n (%)	41 (98%)	39 (93%)	41 (98%)
Anemia	**29 (69%)**	**18 (43%)**	**29 (69%)**
Fatigue	20 (48%)	23 (55%)	23 (55%)
Alanine aminotransferase increased	8 (19%)	16 (38%)	16 (38%)
Diarrhea	6 (14%)	15 (36%)	15 (36%)
Aspartate aminotransferase increased	6 (14%)	14 (33%)	14 (33%)
Platelet count decreased	5 (12%)	12 (29%)	12 (29%)
Nausea	5 (12%)	10 (24%)	10 (24%)
Dizziness	7 (17%)	6 (14%)	8 (19%)

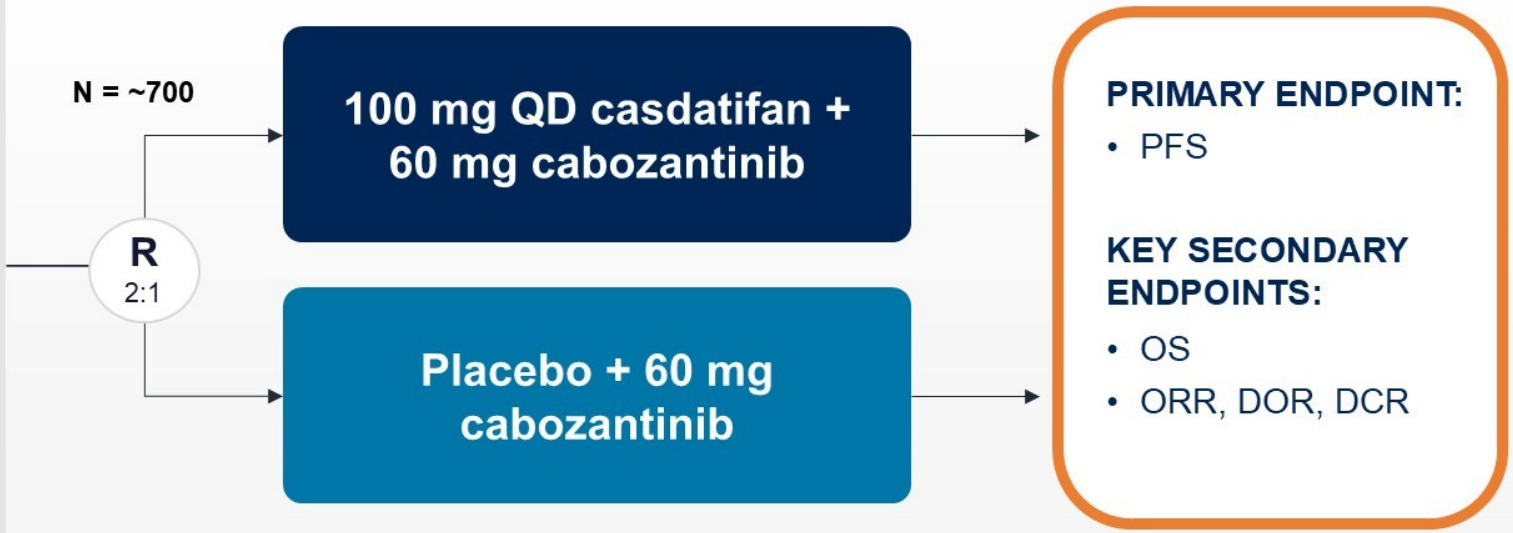
- Most cases of anemia and fatigue did not require a dose change and resolved

PRESENTED BY: Toni Choueiri, MD

PEAK-1

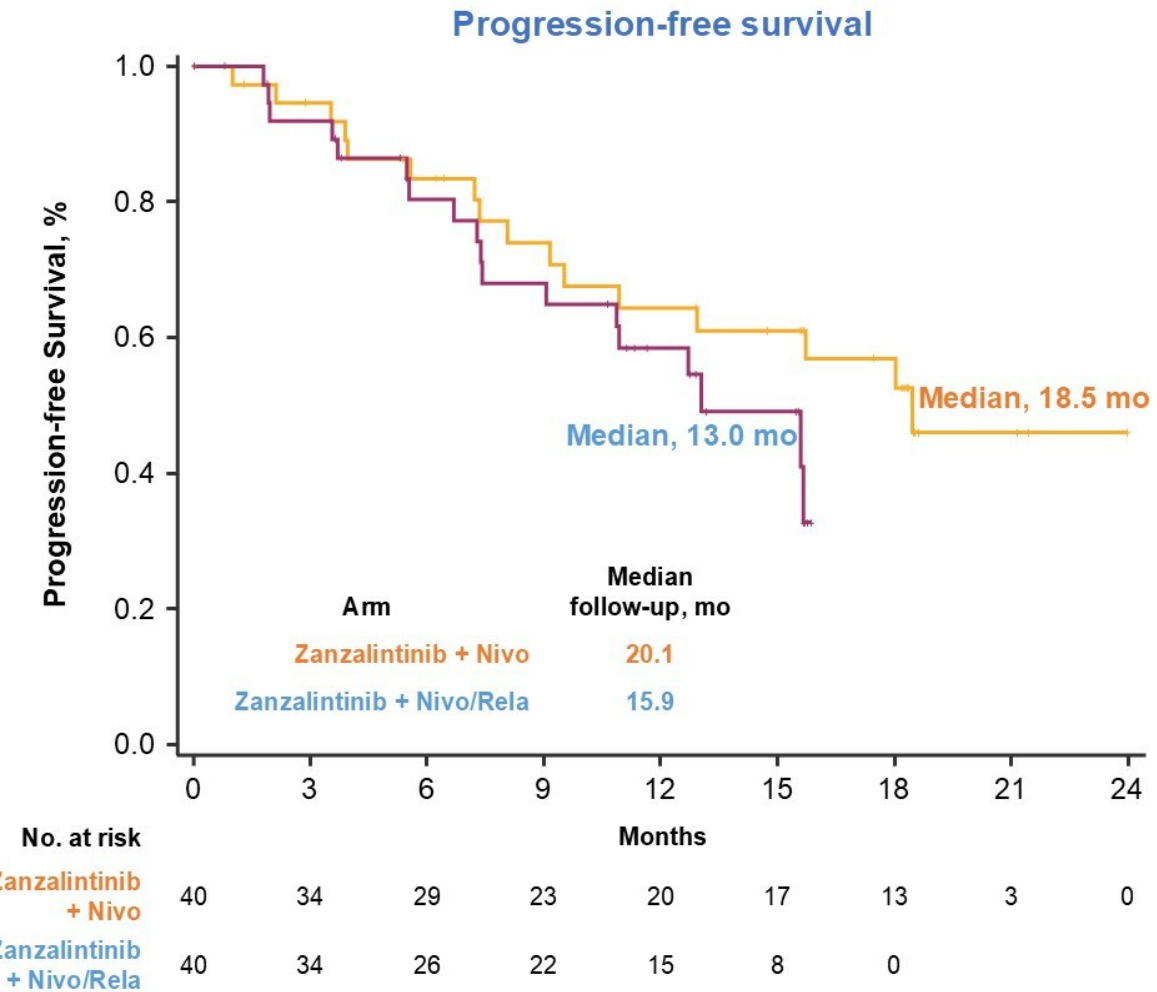
PATIENT POPULATION:

- Unresectable, locally advanced or metastatic ccRCC
- Measurable disease per RECIST v1.1
- Have had prior anti–PD-1/PD-L1
- Have not received cabozantinib
- HIF-2α–inhibitor naive



Zanzalintinib (new TKI)

	Zanzalintinib + Nivo (n=40)	Zanzalintinib + Nivo/Rela (n=40)
ORR (95% CI), %	**63 (46–77)**	**40 (25–57)**
Confirmed CR, n (%)	3 (8)	1 (3)
Confirmed PR, n (%)	22 (55)	15 (38)
SD, n (%)	11 (28)	20 (50)
PD, n (%)	2 (5)	3 (8)
Median DOR (95% CI), months	**NE (11.1–NE)**	**NE (4.0–NE)**
12-month DOR (95% CI), %	73.4 (50.0–87.1)	74.1 (39.1–90.9)
Median PFS (95% CI), months	**18.5 (9.5–NE)**	**13.0 (7.4–NE)**
6-month PFS (95% CI), %	83.4 (66.8–92.2)	80.4 (63.1–90.2)
12-month PFS (95% CI), %	64.4 (45.7–78.1)	58.4 (39.9–73.0)
DCR (95% CI), %	**90 (76–97)**	**90 (76–97)**
Median TTR (range), months	**2.1 (1.7–11.0)**	**3.6 (1.7–12.8)**



Per RECIST v1.1. CI, confidence interval; DOR, duration of response; NE, not estimable; TTR, time to objective response.

PRESENTED BY: Jad Chahoud, MD

Zanzalintinib Toxicity Summary

Safety Overview

	Zanzalintinib + Nivo (n=40)	Zanzalintinib + Nivo/Rela (n=40)
Median exposure (range), months	16.1 (0.5–24.8)	10.9 (0.5–17.1)
Zanzalintinib	16.1 (0.5–25.1)	7.6 (0.5–18.0)
Nivo or nivo/rela	10.5 (0–24.0)	6.3 (0.0–17.1)
TEAE (any grade / grade 3/4),[a] n	40 / 33	40 / 32
Related to any study treatment	40 / 32	40 / 30
Serious TEAE, n	21	24
Related to any study treatment	10	13
Dose modification due to TEAEs, n		
Zanzalintinib dose reductions	34	31
Zanzalintinib dose holds	39	39
Nivo or nivo/rela dose delays	30	27
Immune-related TEAE (any grade / grade 3),[b] n	32 / 12	34 / 12
AST/ALT increase[c]	23 / 7	25 / 6
Rash maculo-papular	9 / 3	10 / 4

Grade 3/4 TEAEs Occurring in >2 Patients

Zanzalintinib + Nivo (n=40)		
TEAE, n	**Any grade**	**Grade 3/4***
Hypertension	24	13
Diarrhea	31	6
AST increase	20	5
ALT increase	17	5
PPE	11	4
Decreased appetite	22	3
Fatigue	18	3
Rash, maculo-papular	11	3
Urinary tract infection	6	3

Zanzalintinib + Nivo/Rela (n=40)		
TEAE, n	**Any grade**	**Grade 3/4***
Hypertension	19	6
Rash, maculo-papular	13	6
Lipase increase	11	4
Pulmonary embolism	4	4
ALT increase	19	3
Fatigue	13	3
Hypertransaminasemia	5	3
Other AE of interest		
PPE	2	0

***Most severe AEs were grade 3 events. Only 2 patients in each arm experienced grade 4 AEs.**

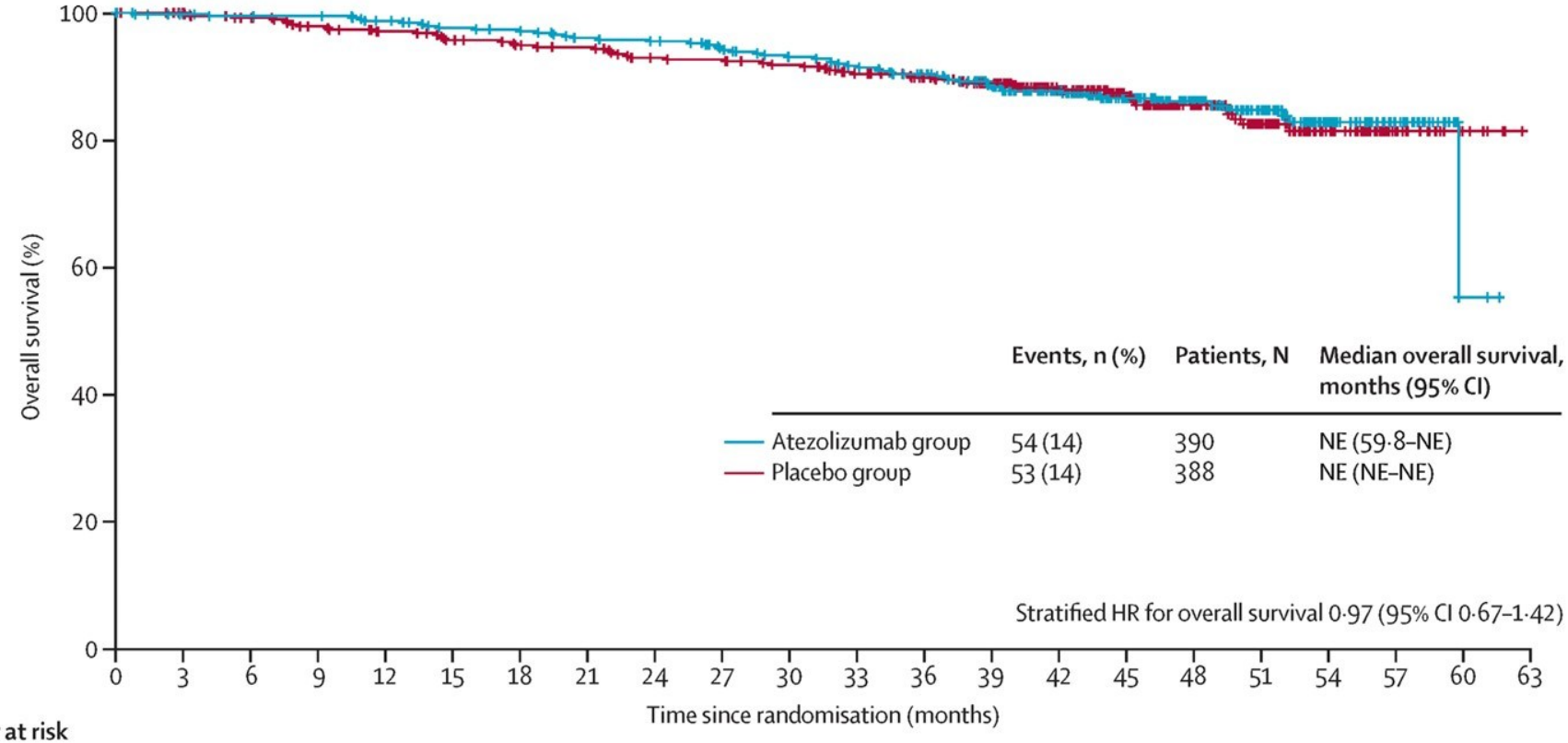
PRESENTED BY: Jad Chahoud, MD

Key Takeaway Points/Conclusions

Encouraging efficacy for novel combination (Cabozantinib and Casdatifan) supports ongoing phase 3 trials

Zanzalintinib is TKI with activity and favorable toxicity profile in combination with immune checkpoint blockade

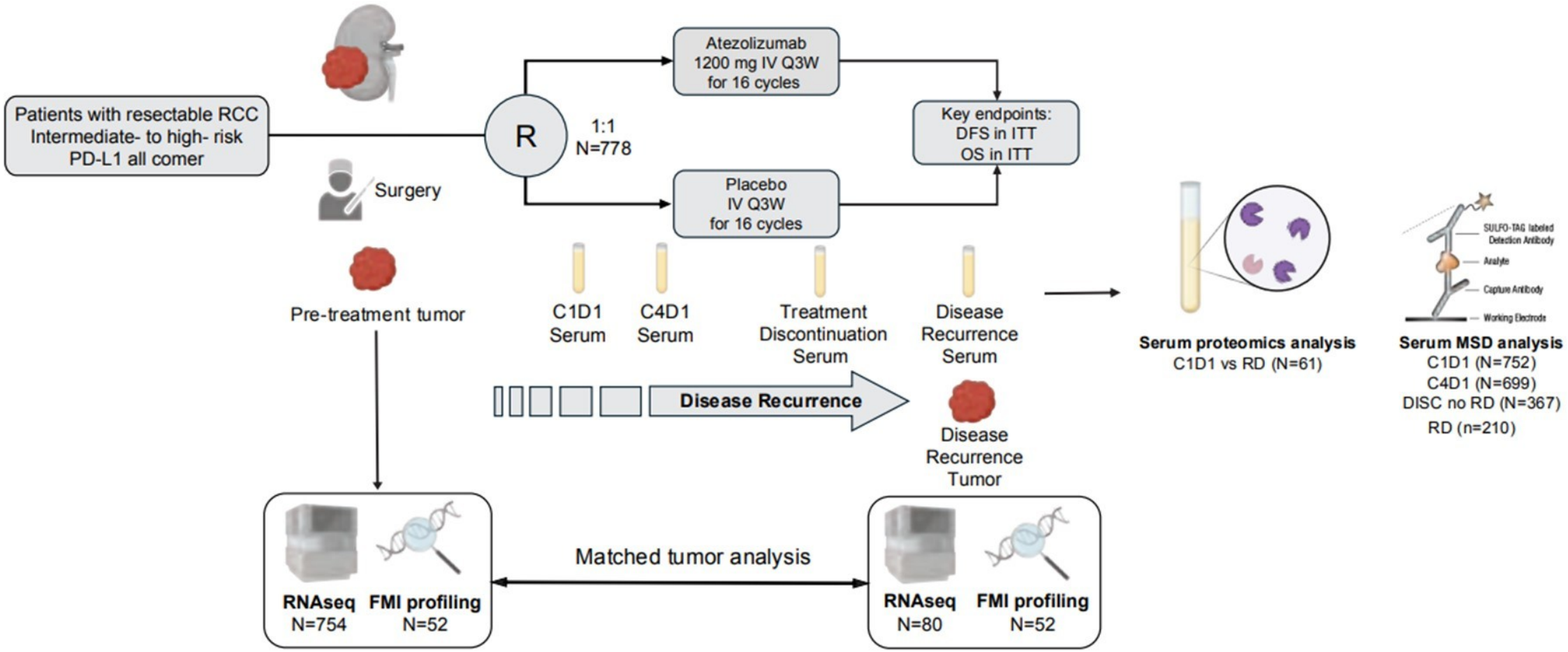
Investigator-assessed DFS in the ITT population



Number at risk (number censored)																					
Atezolizumab group	390 (0)	383 (6)	379 (9)	378 (10)	371 (14)	365 (16)	363 (17)	357 (18)	355 (18)	347 (22)	341 (23)	336 (23)	326 (28)	300 (48)	250 (95)	196 (146)	144 (197)	103 (236)	58 (279)	28 (309)	2 (334)	NE
Placebo group	388 (0)	379 (9)	372 (13)	363 (17)	355 (22)	349 (23)	343 (26)	340 (28)	331 (31)	330 (31)	325 (33)	314 (39)	304 (47)	287 (61)	226 (119)	181 (163)	138 (202)	92 (244)	49 (286)	20 (315)	6 (329)	NE

Pal SK *et al* Lancet 2022;400:359-68.

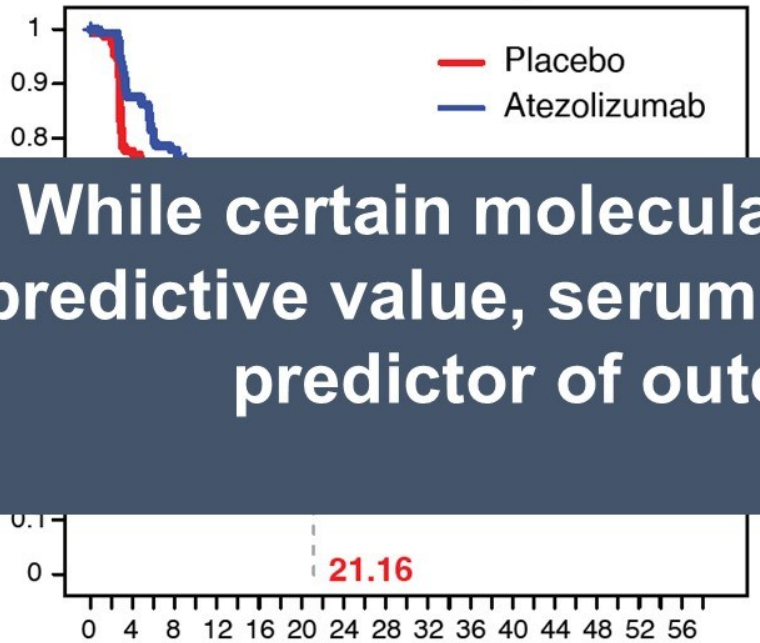
Correlative studies



Atezolizumab improved DFS vs placebo in the baseline KIM-1^{High} subgroup

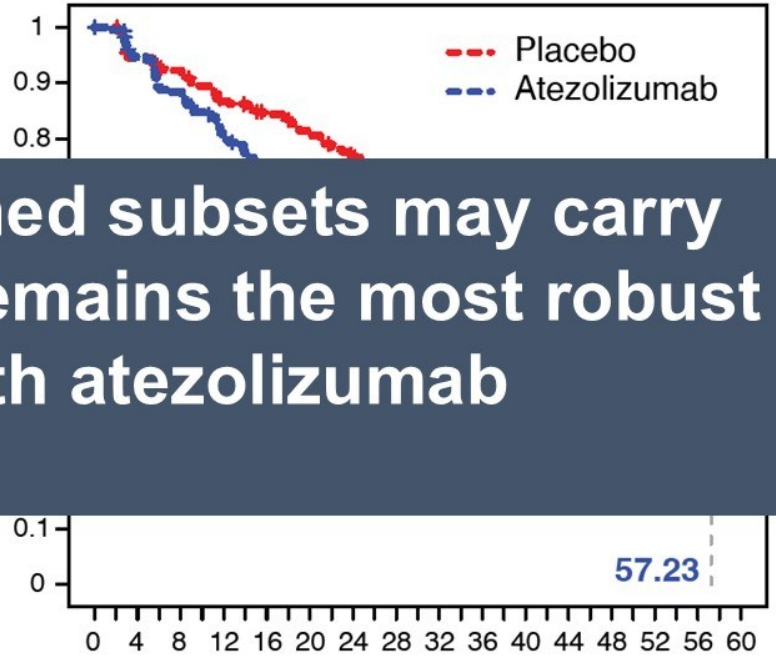
While certain molecularly defined subsets may carry predictive value, serum KIM-1 remains the most robust predictor of outcome with atezolizumab

KIM-1^{High} subgroup



	n	Median DFS	HR (95% CI)
Atezolizumab	151	NE	0.72 (0.52, 0.99)
Placebo	149	21.16	

KIM-1^{Low} subgroup



	n	Median DFS	HR (95% CI)
Atezolizumab	229	57.23	1.12 (0.88, 1.63)
Placebo	223	NE	

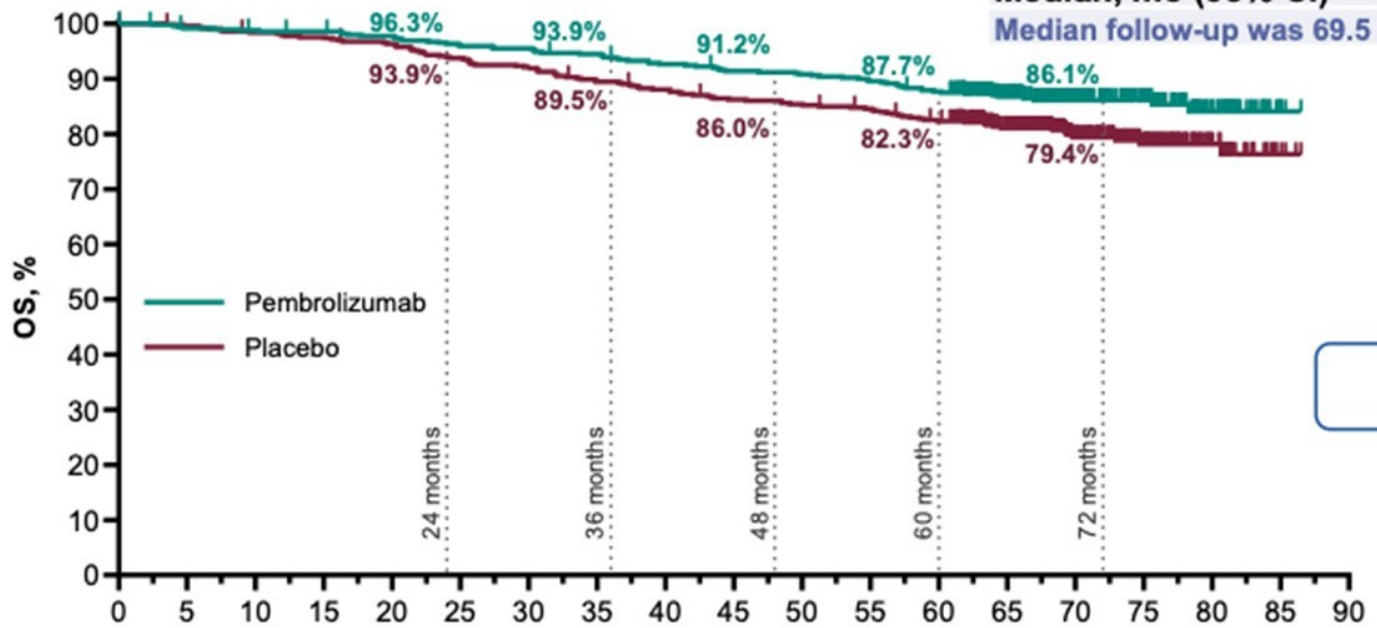
[a] HR stratified by pathologic disease stage and geographic region.

PRESENTED BY: Sumanta Kumar Pal, MD, FASCO

KN 564 Updated Overall Survival- Adjuvant Pembrolizumab

	Pembro (N = 496)	Placebo (N = 498)
Events, n	68	99
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)

Median follow-up was 69.5 months (range, 60.2–86.9)



No. at Risk																			
Pembrolizumab	496	489	486	484	479	470	468	462	452	445	442	436	426	310	198	121	50	3	0
Placebo	498	494	487	483	476	463	455	441	433	423	419	413	400	284	177	111	46	4	0

HR 0.66 (95% CI 0.48–0.90)

Key secondary OS endpoint was met at IA3 and was not formally statistically tested thereafter.

Data cutoff date: September 25, 2024.

PRESENTED BY: Naomi Haas, MD

A032201

Key Eligibility Criteria

- ccRCC
  - pT2, grade 4
  - ≥pT3 any grade
  - TxN1
  - M1 NED within year of nephrectomy (ablative therapy allowed)
- No prior systemic therapy for RCC
- ECOG PS 0-1

N=1040+

R
1:1

Tivozanib 1.34 mg D1-21 q28D for 6 months*

+

Pembrolizumab For 12 months

Pembrolizumab For 12 months

*Reductions to 0.89 D1-21, 0.89 mg every other day; no limits on dose interruptions
Primary Endpoint – DFS
Key Secondary Endpoint - OS
Secondary Endpoints – QOL, Toxicities, Biomarkers

+ Stratify by T2/T3, T4/N1 or M1NED

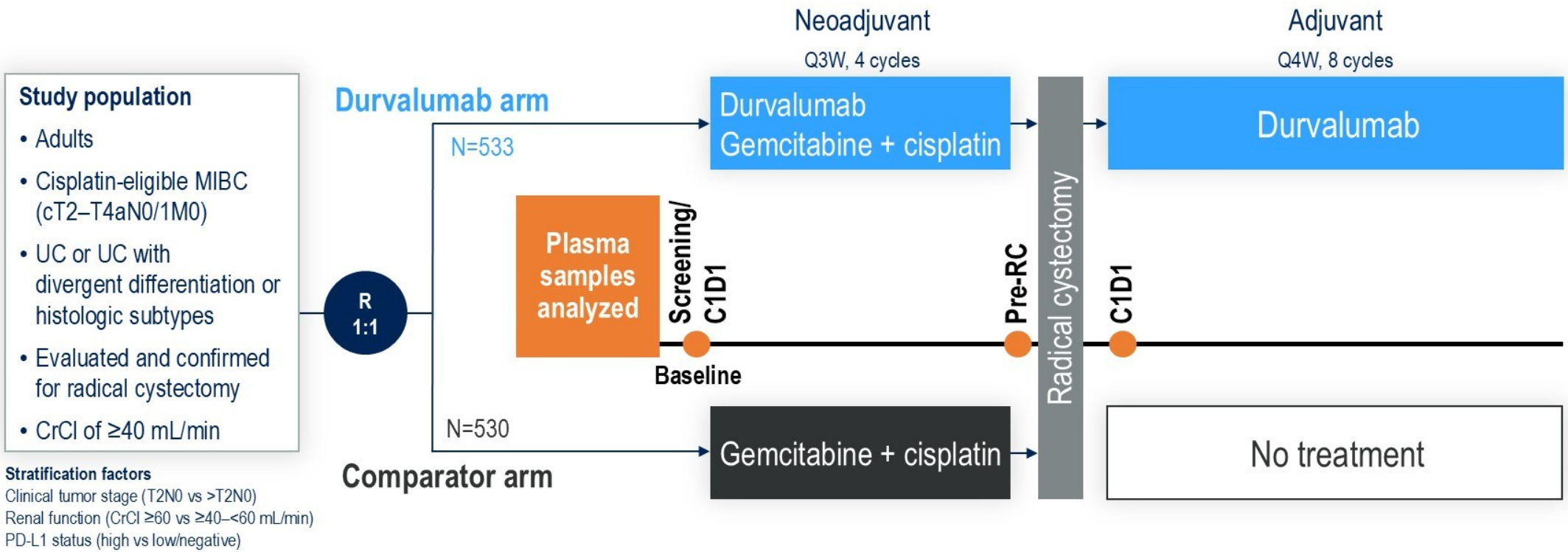
Key Takeaway Points/Conclusions

At this time there is no biomarker to guide treatment in the adjuvant setting for high-risk renal cell carcinoma

Extended follow-up confirms benefit of adjuvant pembrolizumab for resected clear cell RCC

(T2G4, ≧T3, N+ or M1NED within 12 months)

NIAGARA: Study Design



- Plasma ctDNA was assessed using the Signatera™ personalized, tumor-informed MRD assay (Natera, Inc, Austin, TX, USA)
- Patients were asked at screening to provide pretreatment tumor tissue and blood samples, longitudinal blood samples, and consent for germline sequencing

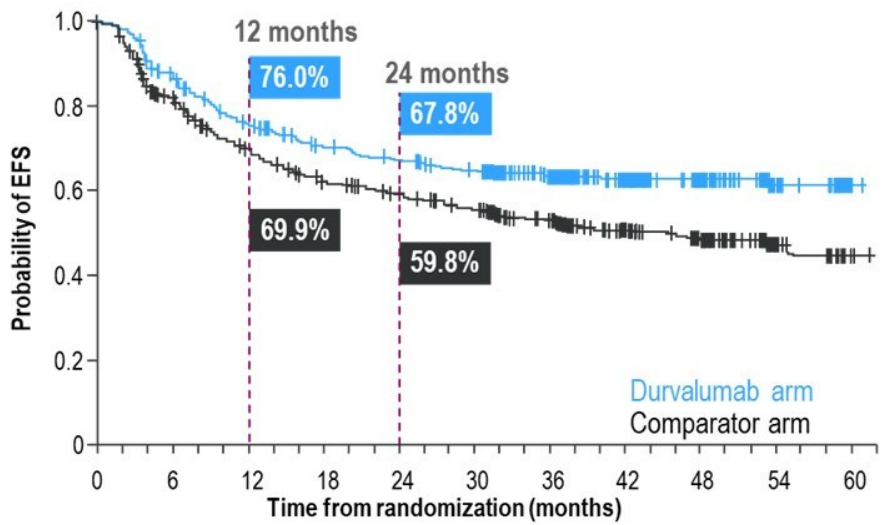
NIAGARA: Clear benefit to perioperative durvalumab

For perioperative durvalumab + NAC with radical cystectomy vs NAC with radical cystectomy alone:

- **Event-free survival**: HR, 0.68 (95% CI 0.56-0.82), ***P*<0.0001**
- **Overall survival**: HR, 0.75 (95% CI 0.59-0.93), ***P*=0.0106**
- **pCR rate**: 37.3% vs 27.5%
- **Safety**[1]: addition of durvalumab to NAC was tolerable and manageable, with no new safety signals

FDA APPROVED

Event-free survival



No. of patients at risk

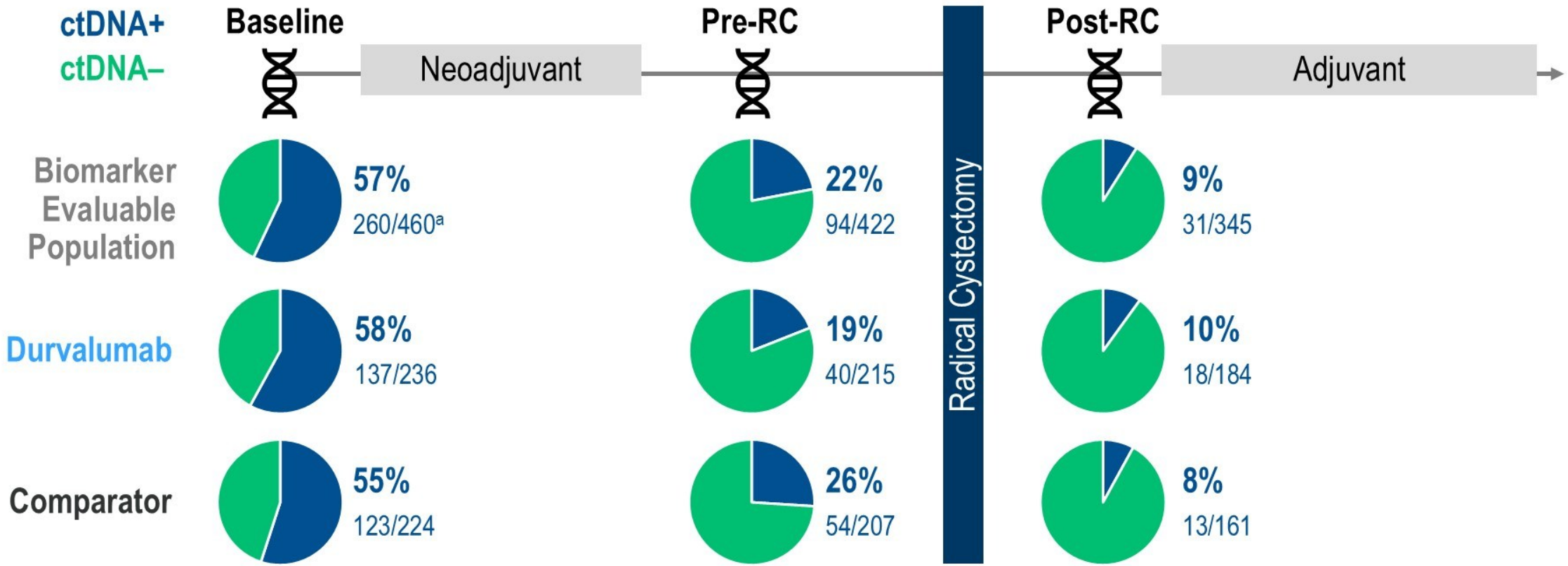
Durvalumab arm	533	454	386	348	330	312	255	180	115	32	1
Comparator arm	530	416	343	300	281	259	214	159	94	24	2

Median EFS follow-up in censored patients: 42.3 months (range, 0.03–61.3)

From *N Engl J Med*, Powles T, Catto JWF, Galsky MD, et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer, 391:1773–86. Copyright © (2024) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

NIAGARA: ctDNA Detection Rates

ctDNA+ rates decreased after neoadjuvant treatment and radical cystectomy

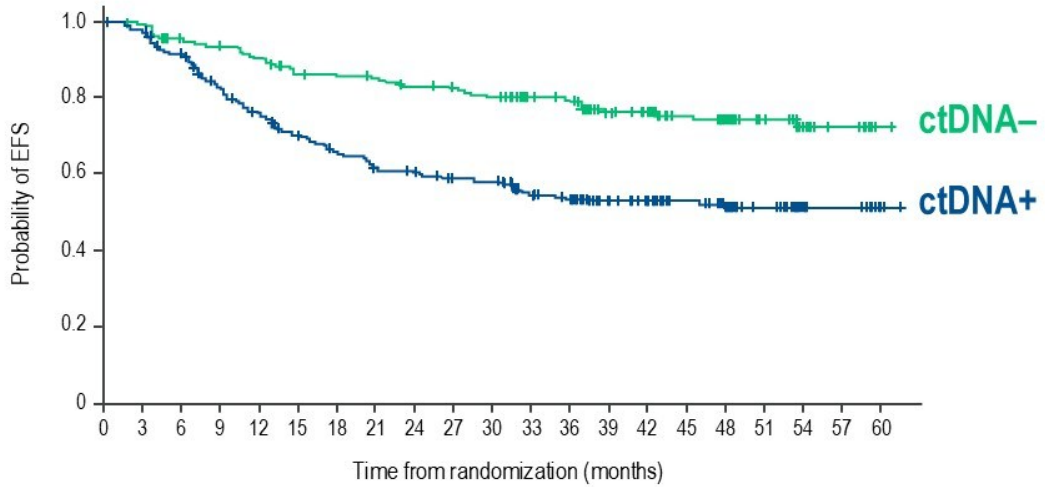


[a]The overall BEP was 462 patients, however, 2 patients did not have a baseline ctDNA assessment available.
BEP, biomarker evaluable population; ctDNA, circulating tumor DNA; RC, radical cystectomy.

NIAGARA Baseline: ctDNA Detection Was Prognostic for EFS

Perioperative D+NAC provided EFS benefit to patients with ctDNA+ or ctDNA– status

EFS (combined arms)

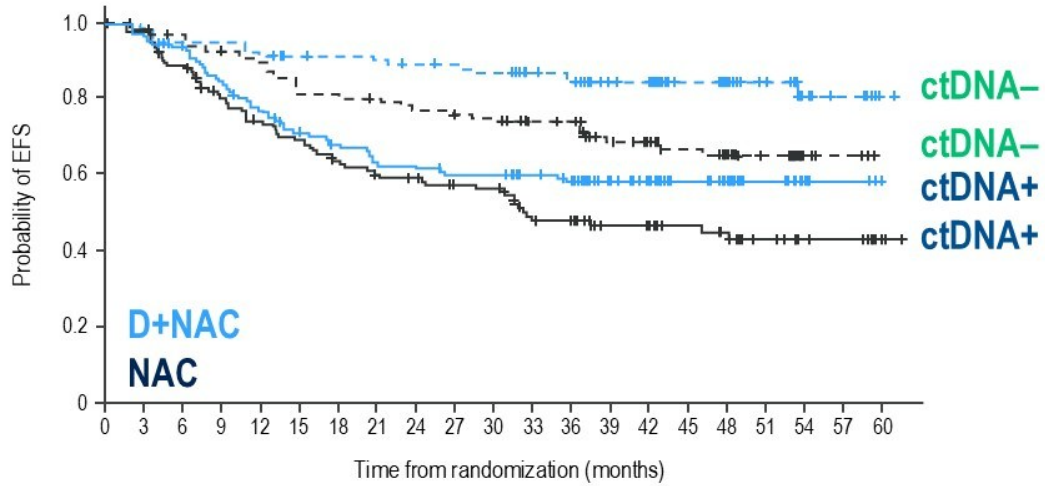


No. of patients at risk

ctDNA–	200	197	185	180	174	162	160	158	153	150	146	131	127	104	95	76	60	48	20	10	1
ctDNA+	260	253	233	206	188	170	156	145	143	135	134	114	105	83	72	61	47	33	16	13	2

ctDNA– vs ctDNA+	**HR, 0.42** (95% CI, 0.30–0.60)

EFS (per arm)



No. of patients at risk

ctDNA– D+NAC	99	99	91	91	88	84	83	82	80	79	77	69	66	55	51	39	35	29	14	7	1
ctDNA– NAC	101	98	94	89	86	78	77	76	73	71	69	62	61	49	44	37	25	19	6	3	0
ctDNA+ D+NAC	137	133	126	113	103	91	85	79	78	75	75	69	63	49	42	35	26	17	7	5	0
ctDNA+ NAC	123	120	107	93	85	79	71	66	65	60	59	45	42	34	30	26	21	16	9	8	2

ctDNA–: D+NAC vs NAC	**HR, 0.45** (95% CI, 0.24–0.84)
ctDNA+: D+NAC vs NAC	**HR, 0.73** (95% CI, 0.51–1.05)

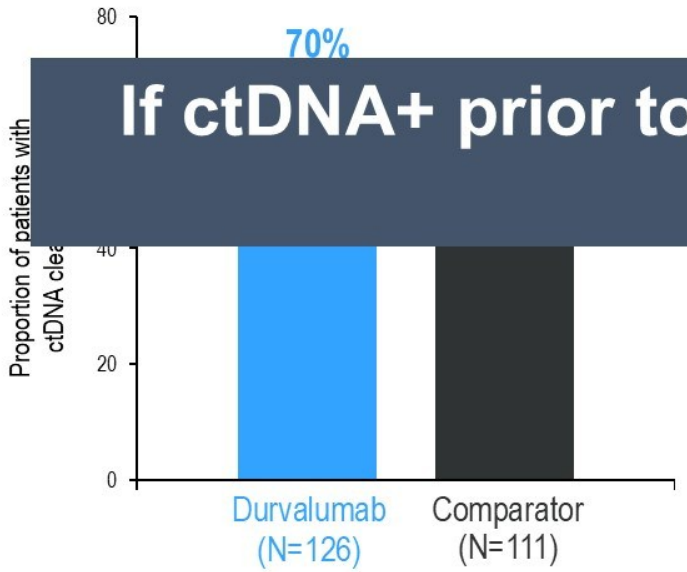
Durvalumab arm = D+NAC; Comparator arm = NAC

- **BEP baseline ctDNA+ = 57%**

NIAGARA Neoadjuvant Treatment: ctDNA Clearance Was Higher in the Durvalumab Arm and Prognostic for EFS

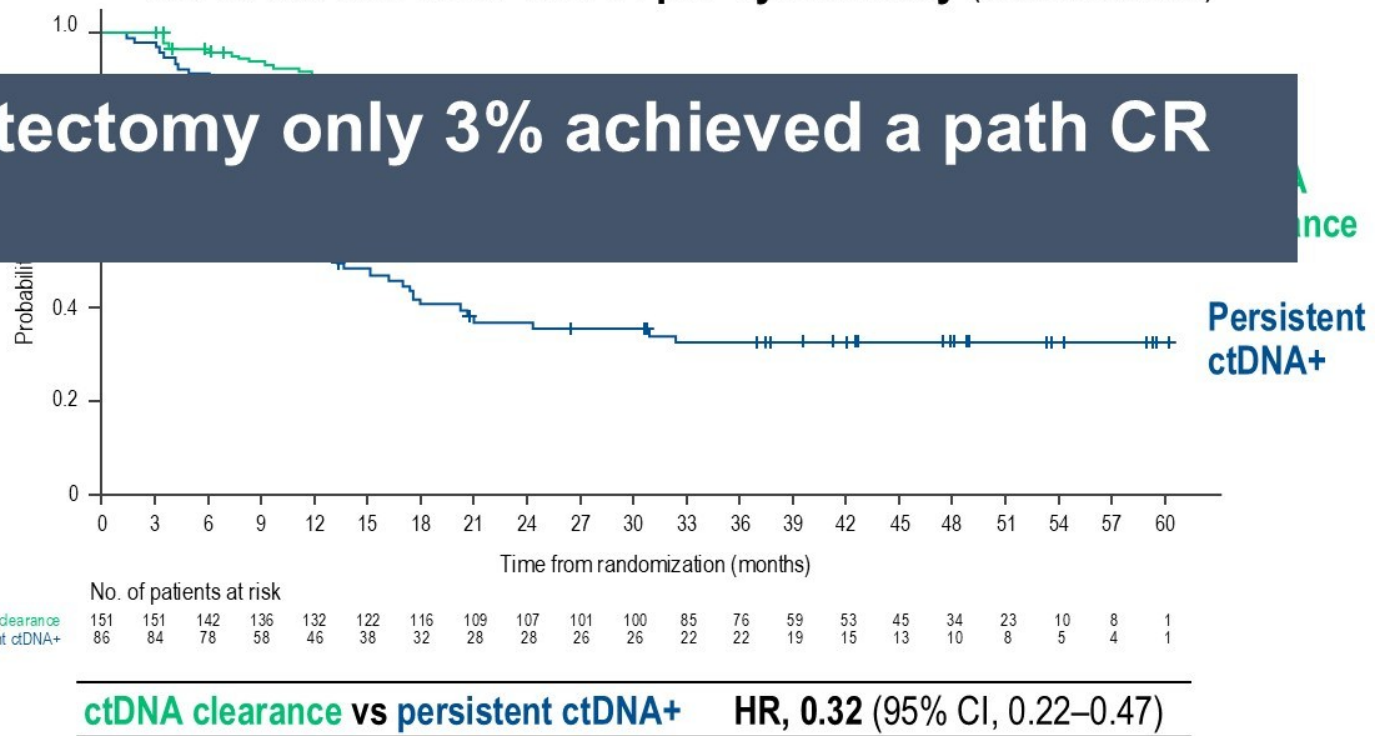
If ctDNA+ prior to cystectomy only 3% achieved a path CR

ctDNA clearance from baseline to pre-cystectomy



Patients that were ctDNA+ at baseline and had a pre-RC ctDNA sample

EFS in the baseline ctDNA+ population that did or did not clear ctDNA pre-cystectomy (combined arms)

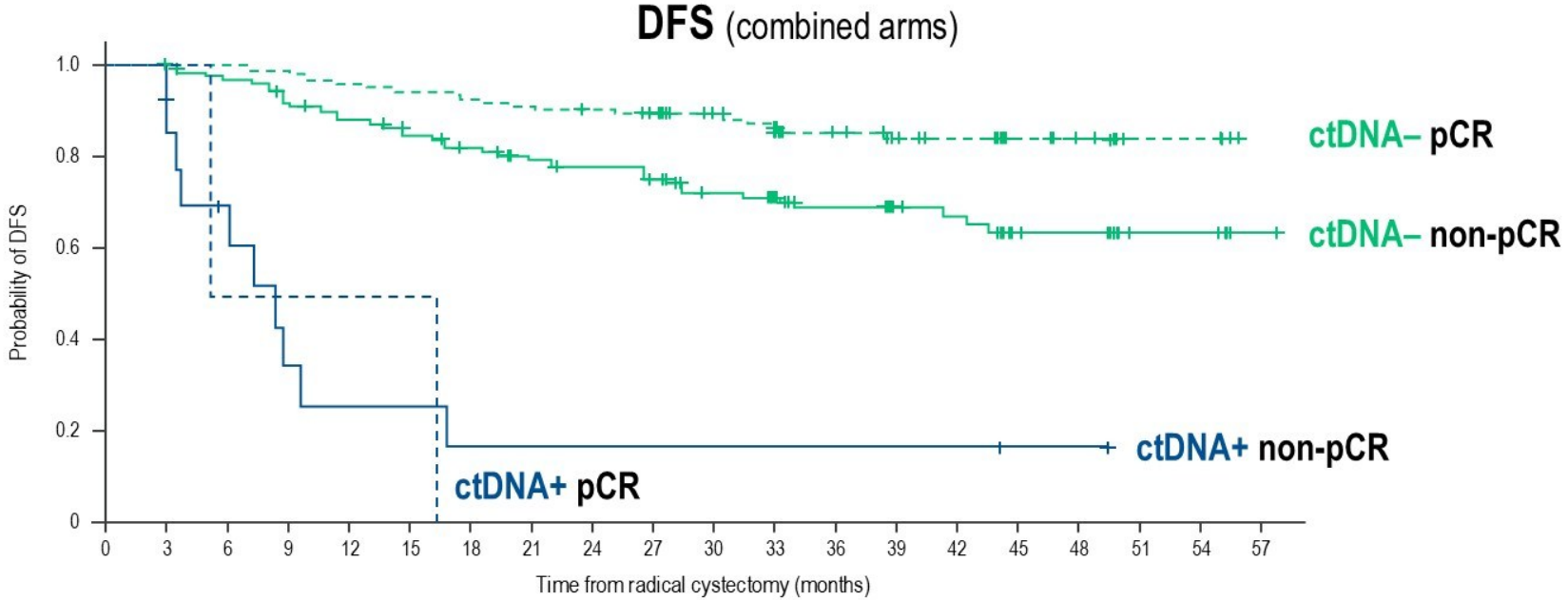


ctDNA clearance vs persistent ctDNA+ **HR, 0.32** (95% CI, 0.22–0.47)

PRESENTED BY: Thomas Powles, MD

NIAGARA Post-Cystectomy: DFS by ctDNA Detection and pCR

In the ctDNA– population, patients with pCR had better DFS prognosis



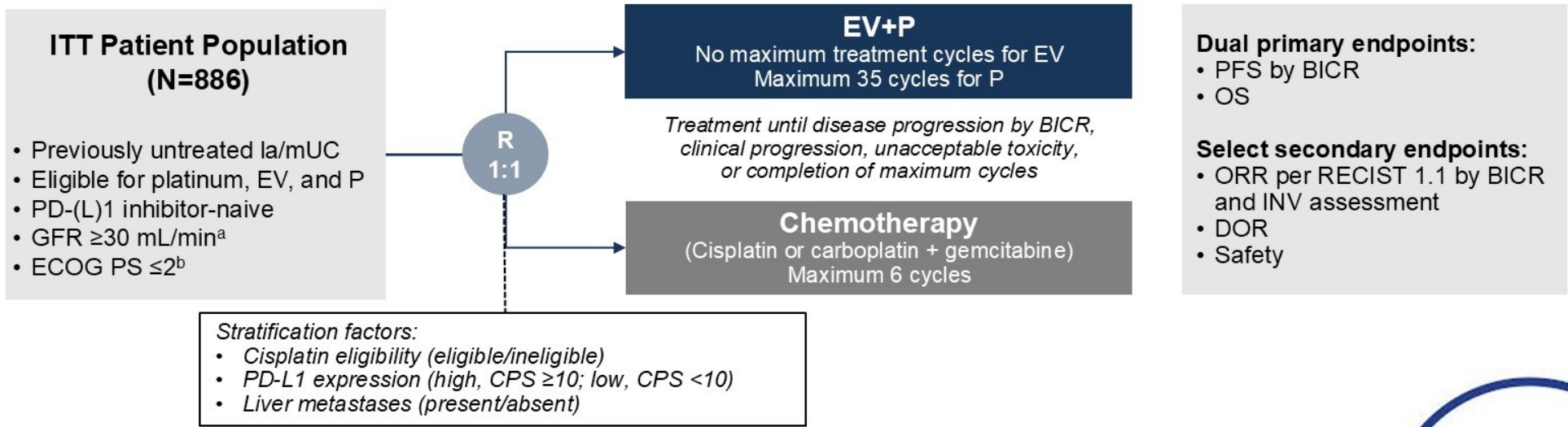
ctDNA–: pCR vs non-pCR	**HR, 0.41** (95% CI, 0.23–0.72)
ctDNA+: pCR vs non-pCR	HR not calculated

Key Takeaway Points/Conclusions

Cisplatin/Gemcitabine/Durvalumab is a new standard of care in perioperative setting for urothelial carcinoma

Detection of ctDNA is a prognostic biomarker; predictive role is unknown

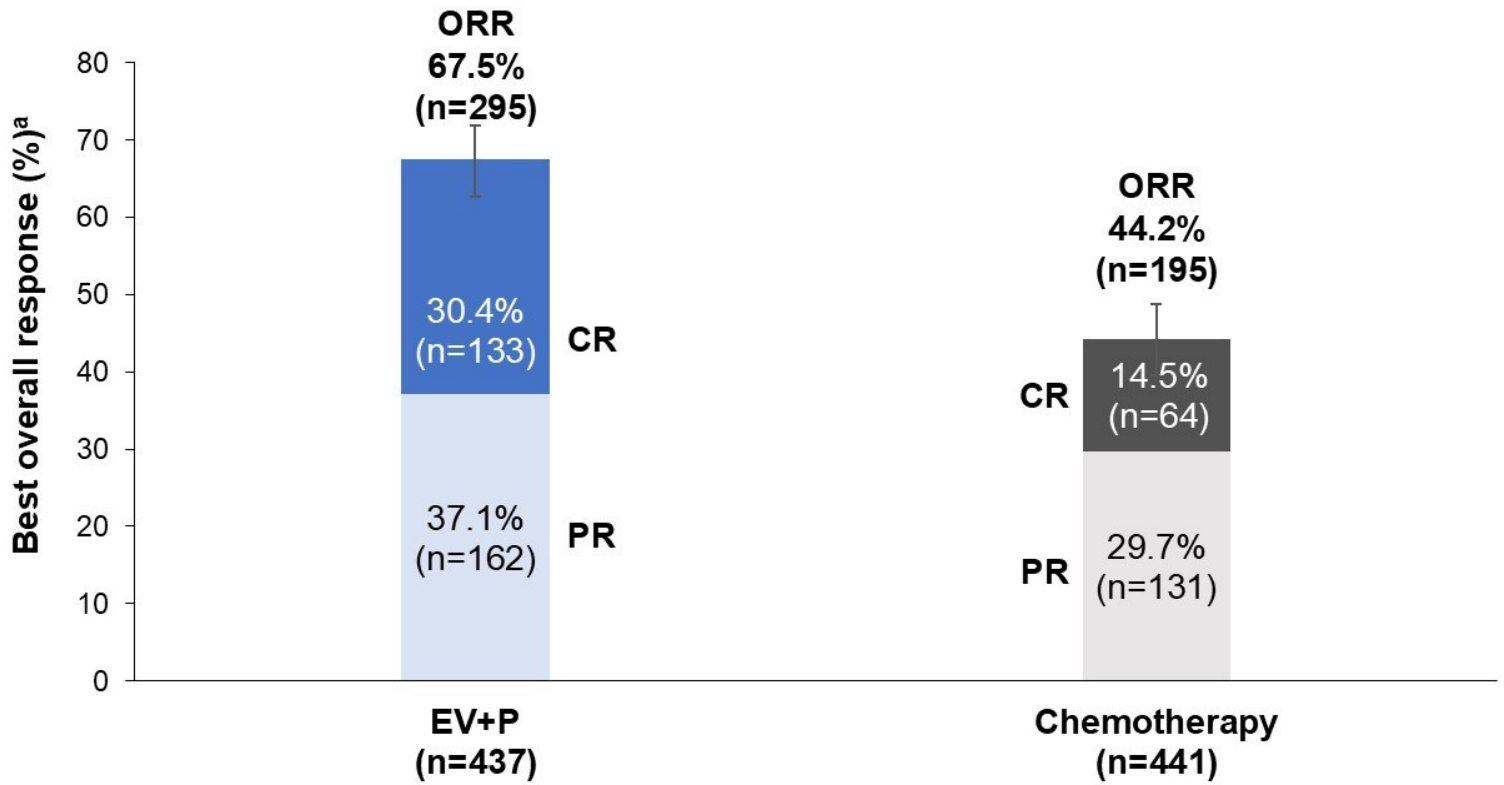
EV-302/KEYNOTE-A39 design



- This exploratory analysis evaluated outcomes in confirmed responders (CR+PR) with longer follow up (ITT population median follow up, ~2.5 y)

Confirmed objective response rate (CR+PR) by BICR

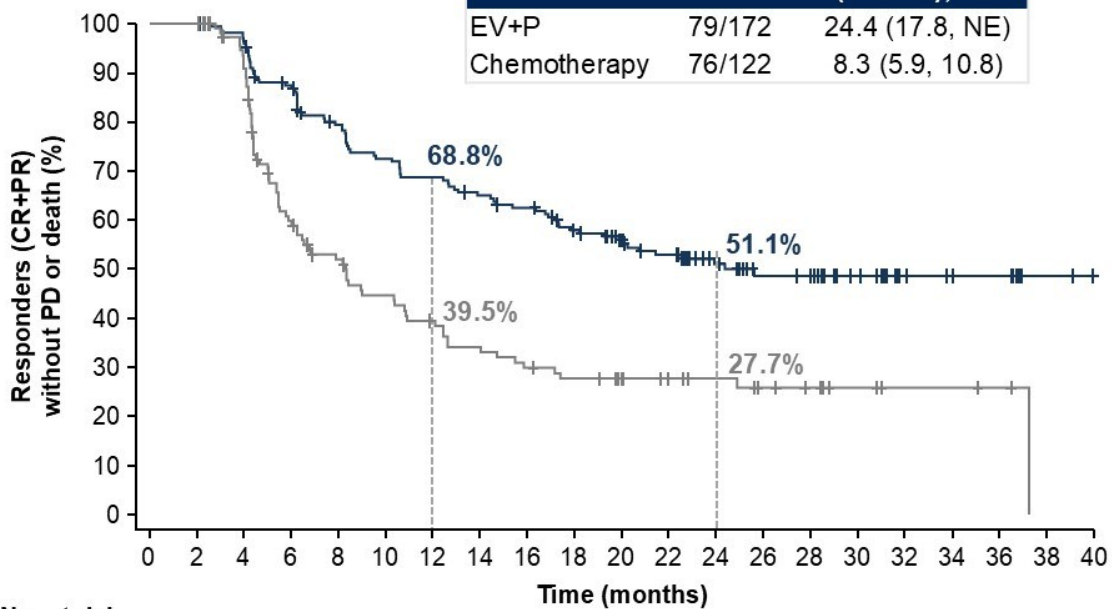
CR rate in the EV+P arm was twice that in the chemotherapy arm



Duration of response 23.3 months vs 7 months

Cisplatin-eligible patients

	Events/N	Median DOR (95% CI), mo
EV+P	79/172	24.4 (17.8, NE)
Chemotherapy	76/122	8.3 (5.9, 10.8)

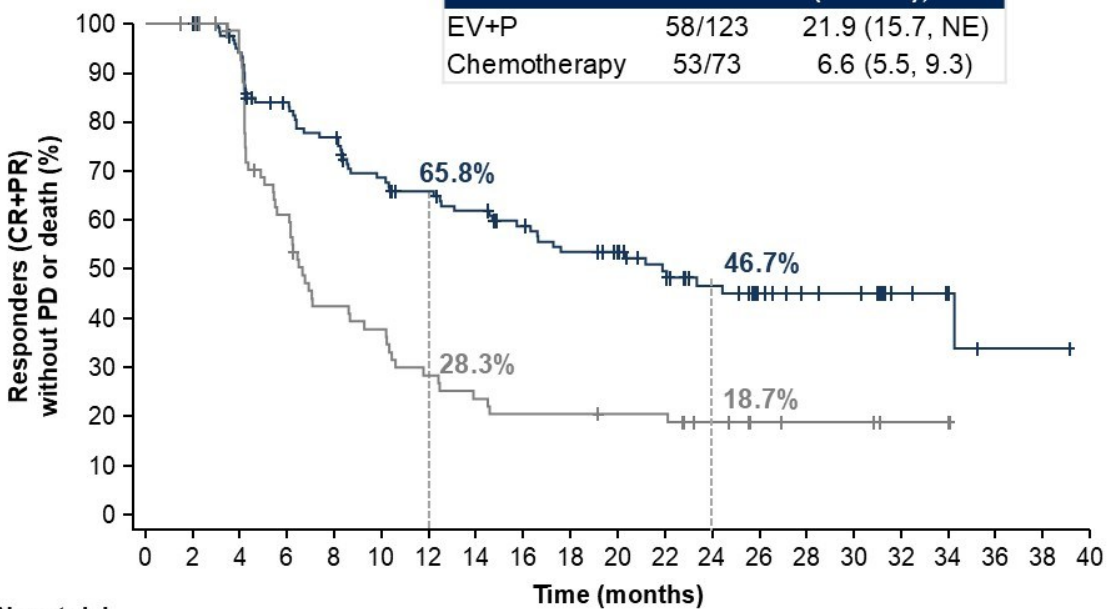


No. at risk

EV+P	172	172	162	144	127	116	110	103	98	87	78	70	48	36	35	23	12	9	8	2
Chemotherapy	122	122	99	62	51	43	37	32	28	25	22	18	15	11	9	5	3	3	2	

Cisplatin-ineligible patients

	Events/N	Median DOR (95% CI), mo
EV+P	58/123	21.9 (15.7, NE)
Chemotherapy	53/73	6.6 (5.5, 9.3)



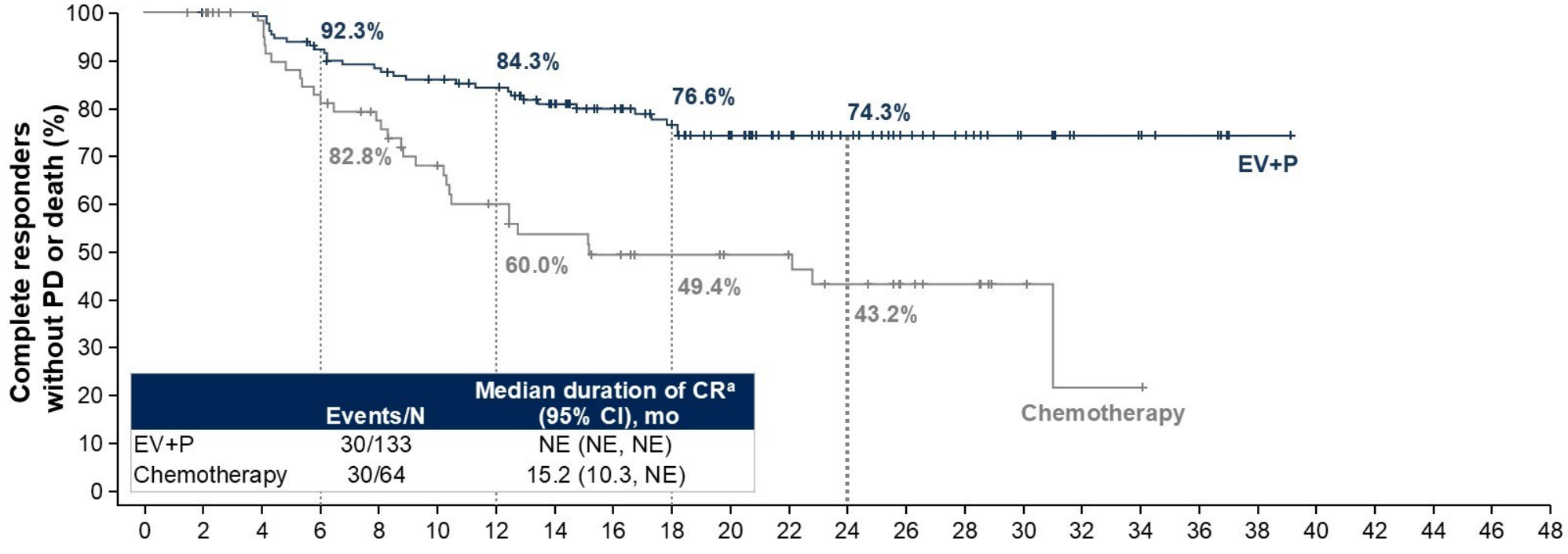
No. at risk

EV+P	123	123	112	94	86	74	67	62	56	50	47	37	30	22	18	17	8	5	2	2
Chemotherapy	73	72	63	40	27	24	18	15	13	13	12	12	8	5	4	4	2	2		

Data cutoff: August 8, 2024. NCT04223856. EV, enfortumab vedotin; NE, not estimable; P, pembrolizumab.

Duration of CR

Probability of maintained CR at 2 years was 74.3% with EV+P with 2 year 95.% survival rate



No. at risk

EV+P	133	132	129	118	112	107	101	89	78	68	55	44	36	27	23	16	8	7	5	1
Chemotherapy	64	63	57	48	42	35	29	25	22	19	17	16	13	9	7	3	1	1		

- 60.2% of patients with CR in the EV+P arm and 64.1% in the chemotherapy arm were cisplatin eligible

PRESENTED BY: Shiilpa Gupta, MD

Key Takeaway Points/Conclusions

Enfortumab Vedotin with Pembrolizumab is the standard of care for metastatic urothelial carcinoma with unprecedented duration of response and survival independent of cisplatin eligibility

Dose reductions pivotal to optimize toxicity profile

2025 ASCO® ANNUAL MEETING

Highlights of the Day III

Cornelia Kolberg-Liedtke

Department of Nursing, Midwifery and Therapy Sciences
Bochum University of Applied Sciences (*Hochschule Bochum*)
Bochum, Germany

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD

cornelia.kolberg-liedtke@hs-bochum.de

TRUST: This presentation is an ASCO highlight because …

… it adresses an important question **with high relevance to daily clinical practice**

… reports data from a surgical therapy trial with **comprehensive quality assurance** emphasizing the competence and experience of the surgeons involved.

… it gives information as that may be used in a **personalized treatment approach** regarding tumor stage and potential risks of therapy.


2025 ASCO ANNUAL MEETING

AGO STUDY GROUP

TRUST: Trial of radical upfront surgical therapy in advanced ovarian cancer (ENGOT ov33 / AGO-OVAR OP7)

Sven Mahner[1], Florian Heitz[2], Sahar Salehi[3], Alexander Reuss[4], Frederic Guyon[5], Andreas du Bois[2], Philipp Harter[2], Christina Fotopoulou[6], Denis Querleu[7], Berit Jul Mosgard[8], Bernhard Krämer[9], Francesco Raspagliesi[10], Björn Lampe[11], Alexander Burges[1], Barbara Schmalfeldt[12], Pauline Wimberger[13], Holger Bronger[14], Dennis Chi[15], Jalid Sehouli[16], Giovanni Aletti[17] and the TRUST investigators

[1]AGO Study Group & Department of Obstetrics and Gynecology, LMU University Hospital, Munich, Germany; [2]AGO Study Group & Department for Gynecology and Gynecologic Oncology; Kliniken Essen Mitte, Essen, Germany; [3]NSGO & Department of Women's and Children's Health, Karolinska Institutet and Department of Pelvic Cancer, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden; [4]AGO Study Group & KKS Marburg, Marburg, Germany; [5]GINECO & Institut Bergonié Bordeaux, Bordeaux, France; [6]AGO Study Group & Division of Cancer, Department of Surgery and Cancer, Imperial College London, London, UK; [7]GINECO & UOC ginecologia oncologica, dipartimento di scienze della donna, del bambino e di sanità pubblica, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; [8]NSGO & Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; [9]AGO Study Group & University Hospital Tuebingen, Tuebingen, Germany; [10]MaNGO & Istituto Tumori di Milano, Milano, Italy; [11]AGO Study Group & Kaiserswerther Diakonie, Duesseldorf, current address: Staedtische Kliniken, Moenchengladbach, Germany; [12]AGO Study Group & University Medical Center Hamburg Eppendorf, Hamburg, Germany; [13]AGO Study Group & Dresden University Hospital, Dresden, Germany; [14]AGO Study Group & TUM School of Medicine and Health, Technical University of Munich (TUM), Munich, Germany; [15]AGO Study Group & MSKCC, New York, USA; [16]AGO Study Group & Charite University Hospital, Berlin, Germany; [17]MaNGO & Istituto Europeo di Oncologia, IRCCS, Milano, Italy

2025 ASCO ANNUAL MEETING #ASCO25 PRESENTED BY: Sven Mahner, MD Sven.Mahner@med.uni-muenchen.de

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD

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TRUST: Trial Rationale

- The **optimal timing of surgical intervention** (i.e. prior to or after systemic therapy) in seemingly operable pts with advanced ovarian cancer, **remains controversial** (e.g. CHORUS, SCORPION; EORTC 55971, JGOG0602)
- TRUST was designed to evaluate the optimal timing of maximal effort cytoreductive surgery in patients with advanced ovarian cancer
  - With **seemingly resectable** tumor
  - **Fit enough** to sustain radical surgery
  - Treated in accredited gynecologic cancer centers with defined **surgical quality assurance** criteria

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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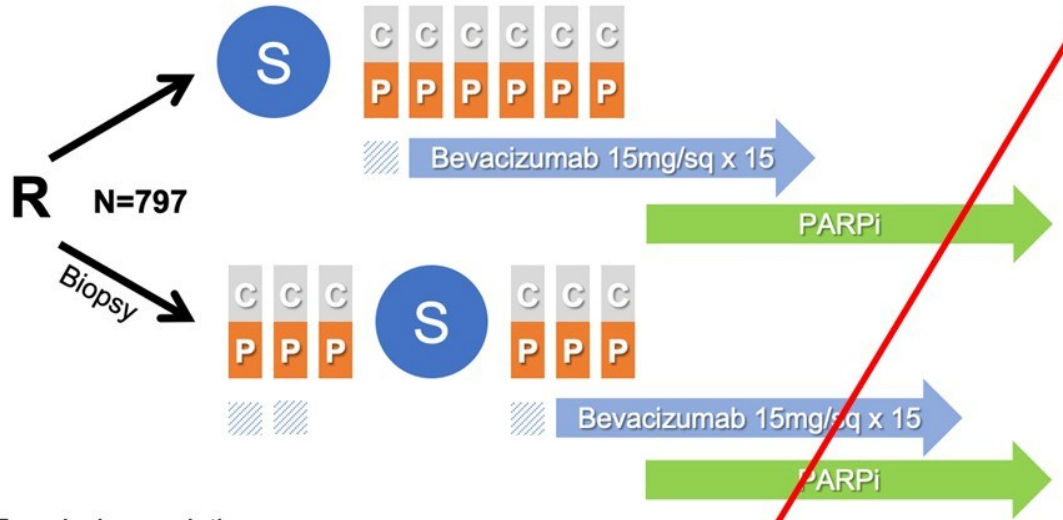
TRUST: Trial Design

ESGO certification and additional criteria

Pts. with ovarian-, fallopian-tube or peritoneal-cancer FIGO stage IIIB, IIIC and resectable stage IV



- *Primary Endpoint OS ITT analysis population.*
- *Key secondary Endpoints PFS, QoL, safety*
- *Strata: center, age, ECOG combination (ECOG 0 and age < 65yrs vs ECOG >0 or age ≥ 66yrs)*
- ***Qualification process for participating centers to ensure high surgical quality***

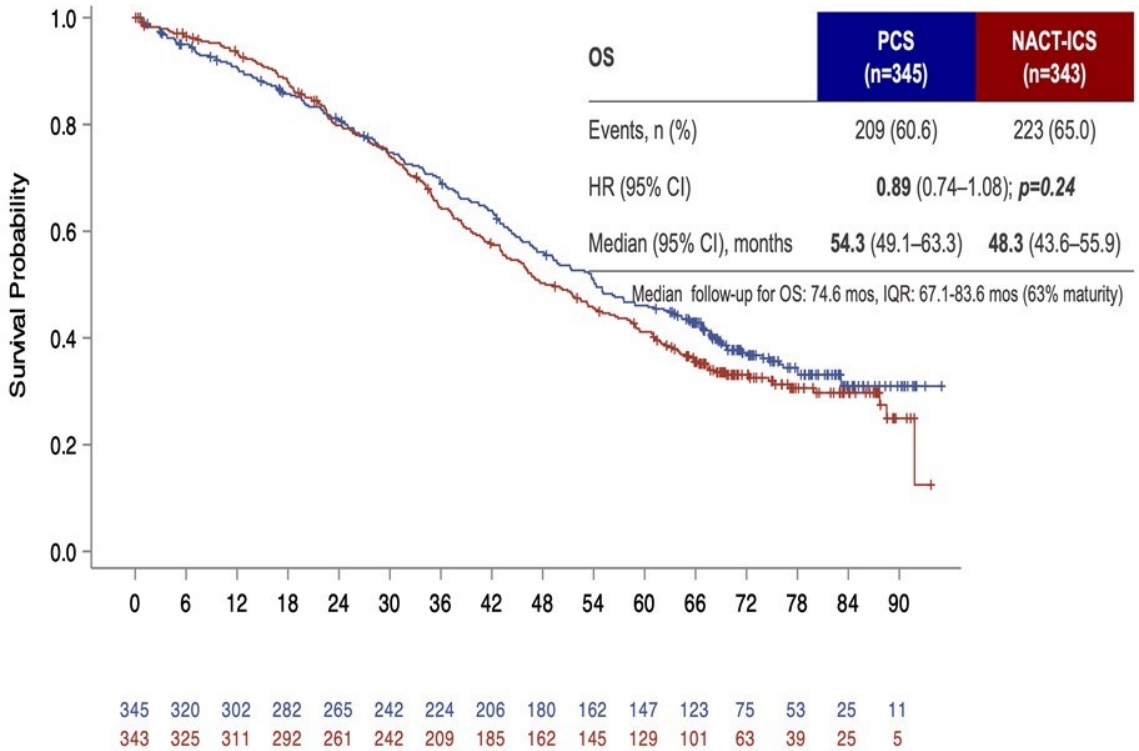
S surgery C Carboplatin AUC5 P Paclitaxel 175 mg/sq → Bev. 15mg 15 mon → PARPi

suggested therapy, also weekly paclitaxel possible / or omission of Bev, PARP or study treatment, as long as both TRUST arms can equally be recruited

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
cornelia.kolberg-liedtke@hs-bochum.de

TRUST: Results

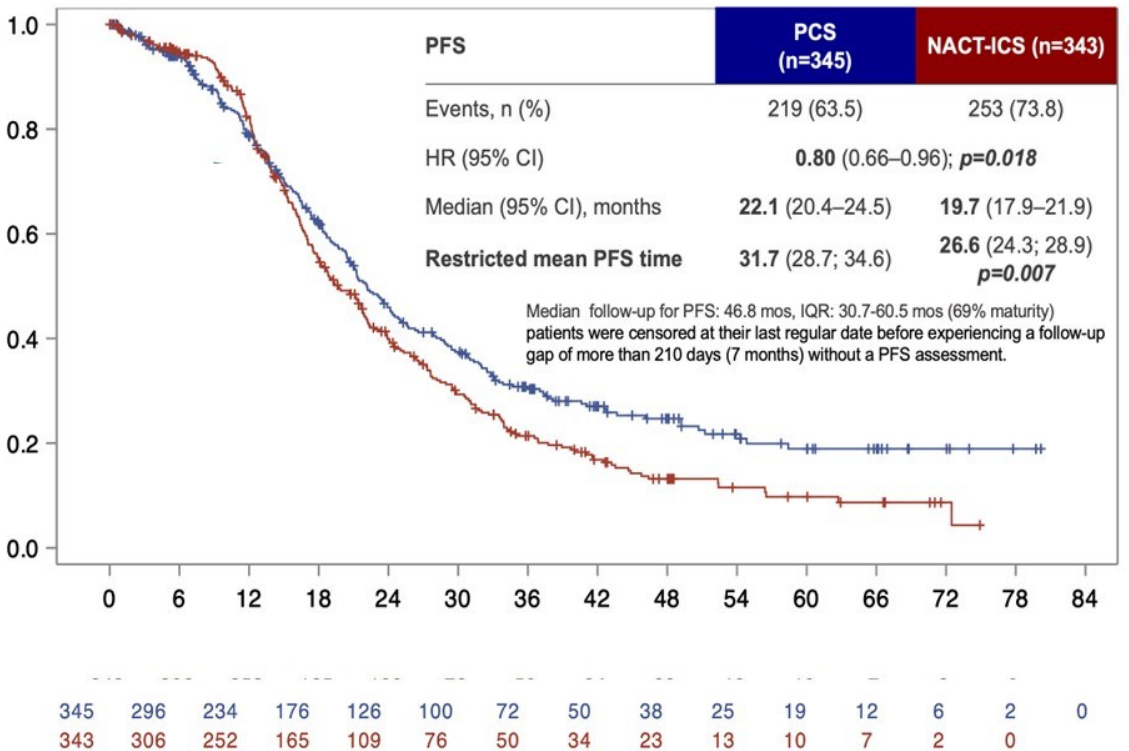
Primary Endpoint: OS (ITT) not met



OS	PCS (n=345)	NACT-ICS (n=343)
Events, n (%)	209 (60.6)	223 (65.0)
HR (95% CI)	**0.89** (0.74–1.08); ***p=0.24***	
Median (95% CI), months	**54.3** (49.1–63.3)	**48.3** (43.6–55.9)

Median follow-up for OS: 74.6 mos, IQR: 67.1-83.6 mos (63% maturity)

Secondary Endpoint: PFS (ITT)



PFS	PCS (n=345)	NACT-ICS (n=343)
Events, n (%)	219 (63.5)	253 (73.8)
HR (95% CI)	**0.80** (0.66–0.96); ***p=0.018***	
Median (95% CI), months	**22.1** (20.4–24.5)	**19.7** (17.9–21.9)
Restricted mean PFS time	**31.7** (28.7; 34.6)	**26.6** (24.3; 28.9) ***p=0.007***

Median follow-up for PFS: 46.8 mos, IQR: 30.7-60.5 mos (69% maturity)
patients were censored at their last regular date before experiencing a follow-up gap of more than 210 days (7 months) without a PFS assessment.

Benefit associated with primary surgery larger in patients with FIGO III (vs. FIGO IV) and/or complete gross tumor resection

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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TRUST: Conclusions

- Patients with advanced ovarian cancer had **excellent PFS and OS** after maximal effort cytoreduction with high complete resection rates – and those were **better than in previous trials** with similar research question (better surgery?! improved systemic therapy?!)
- The **primary endpoint** of the study, a statistically significant improvement in overall survival was **not met**, however, median OS was numerically longer after primary cytoreductive surgery.
- **Median PFS (secondary endpoint) was significantly improved** with an absolute improvement of five moths.
- **Extent of surgery and complications** were **higher** in patients undergoing primary surgery.
- TRUST results emphasize the **importance of defined surgical quality assurance criteria** and the treatment of advanced ovarian cancer patients in **accredited gynaecologic cancer centres**.

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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FIRST: This presentation is an ASCO highlight because …

… it adds another piece to the puzzle of optimal systemic combination therapy (particularly targeted agents) for patients with first-line advanced OC

FIRST: Rationale

- Preclinical evidence suggested **PD-(L)1 inhibitors** may result in improved activity **when combined** with chemotherapy, bevacizumab, or PARPi irrespective of HRD status.

- Clinical evidence supports this. For instance, the **DUO-O phase III trial** showed that adding durvalumab and olaparib to standard first-line therapy improved PFS in advanced ovarian cancer without BRCA mutations, especially in HRD-positive patients. There was no data regarding the benefit of either durvalumab or olaparib to chemotherapy and bevacizumab.

- The FIRST/ENGOT-OV44 (NCT03602859) trial was **designed to evaluate the addition of dostarlimab, a PD-1 inhibitor,** to first-line platinum-based chemotherapy and niraparib maintenance, ± bevacizumab, in patients with newly diagnosed aOC irrespective

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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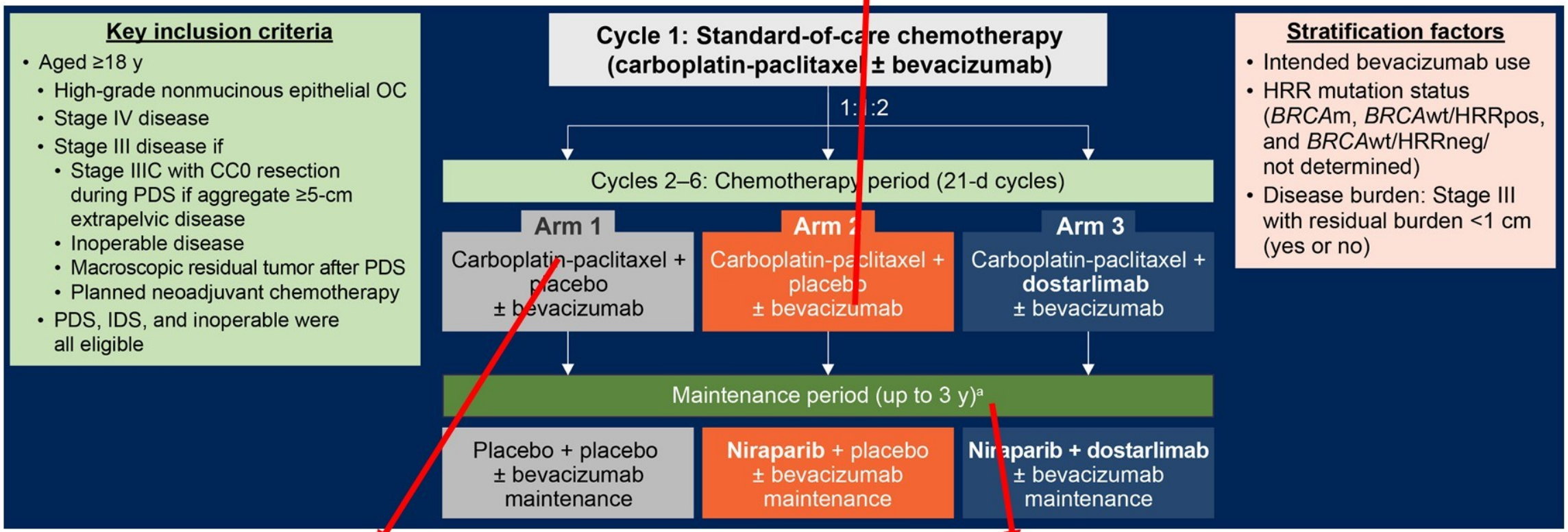
FIRST: Trial design

a bevacizumab applied in approx. 50%



b Following approvals of olaparib and niraparib as first-line maintenance therapy,1,2 enrollment into arm 1 was terminated (a priori planned)

c May continue treatment beyond 3 years in consultation with the medical monitor.

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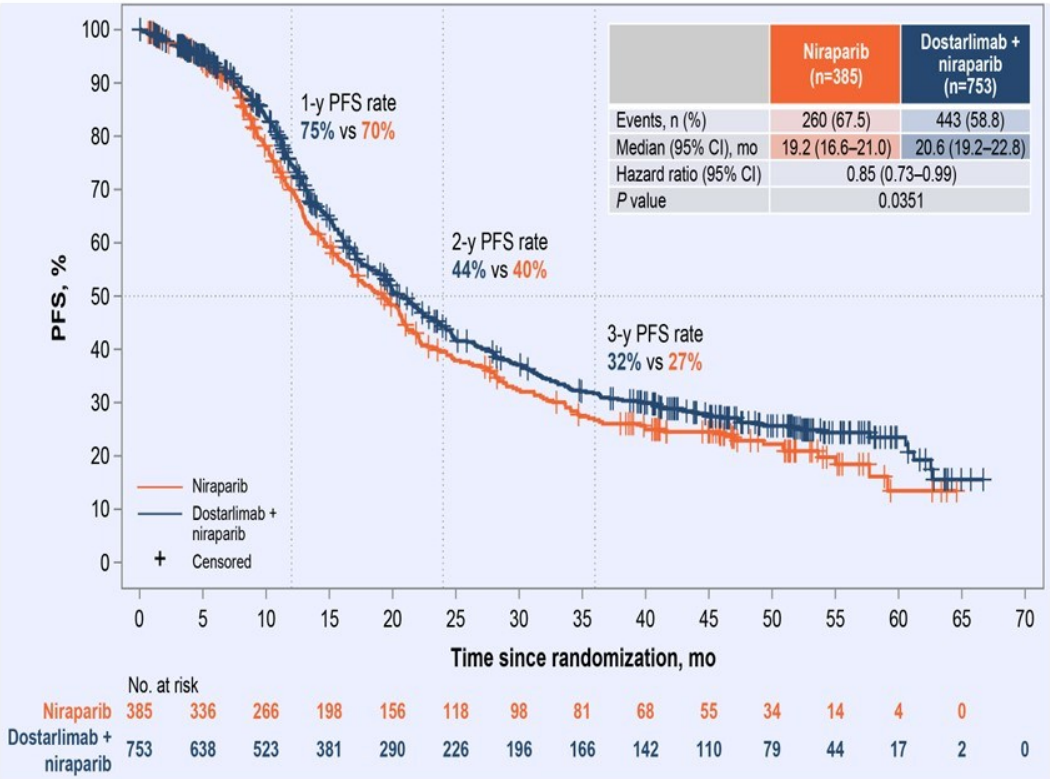
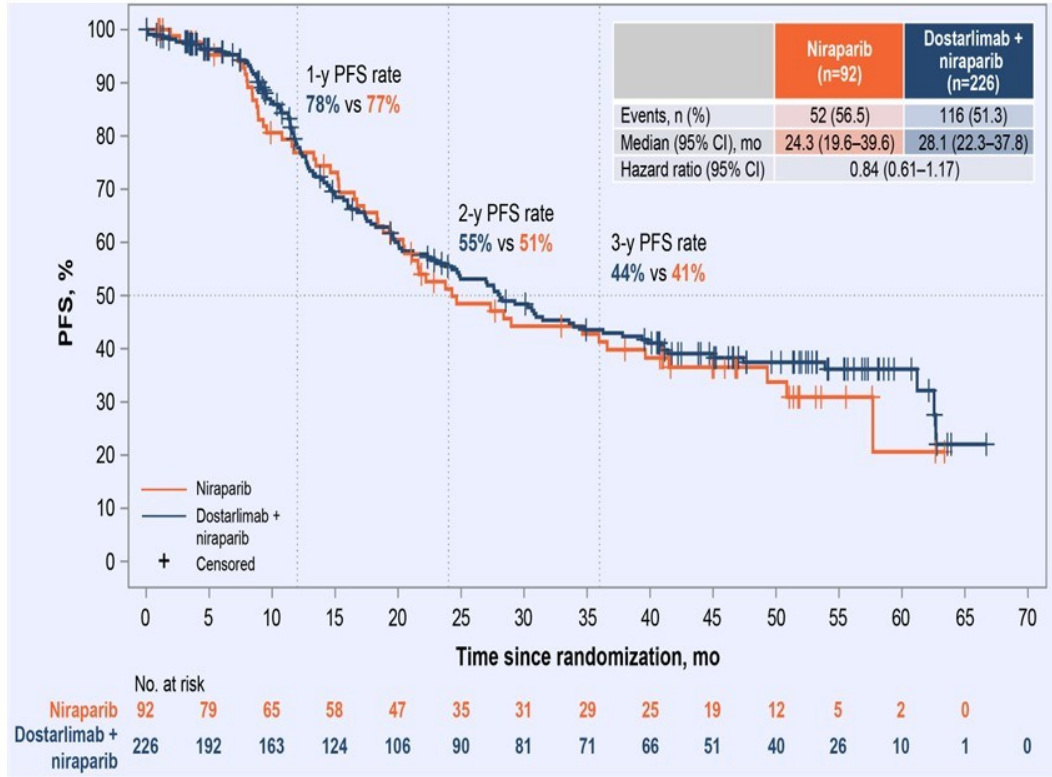
FIRST: Results (PFS)

PFS (ITT)



PFS (PD-L1 positive, 23.9 vs. 30%)



PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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FIRST: Conclusions

- FIRST **met ist primary endpoint** and demonstrated that for patients with newly diagnosed aOC, the addition of dostarlimab to first-line platinum-based chemotherapy and maintenance niraparib was associated with statistically significant.
- However, the improvement in PFS was **very modest** (absolute benefit approx. 1 month). PD-L1 status did not significantly alter results
- There was **no observed difference in OS**.
- Safety results were consistent with known individual safety profiles of the agents used in the study.

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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ROSELLA: This presentation is an ASCO highlight because …

… it introduces a **novel mechanism of action** into the treatment of patients with ovarian cancer (**selective glucocorticoid receptor antagonists, SGRA**)

… it demonstrates a **significant and clinically relevant improvement in PFS and particularly OS (though 50% immaturity)** among patients with high clinical need (i.e. patients with platinum-resistant ovarian cancer)

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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ROSELLA: Study rationale

- Patients with platinum-resistant ovarian cancer have a particularly unfavorable prognosis (i.e. median OS of approx. 1 year)
- Targeting of the **glucocorticoid receptor (GR)-2** in ovarian cancer is supported by several lines of research and may restore chemotherapy sensitivity.
- **Phase-II data** in patients with platinum-resistant OC show improvements in PFS and OS in association with the anti-GR-2 antibody relacorilant in combination with nab-paclitaxel and **support the evaluation in a phase-III** context.

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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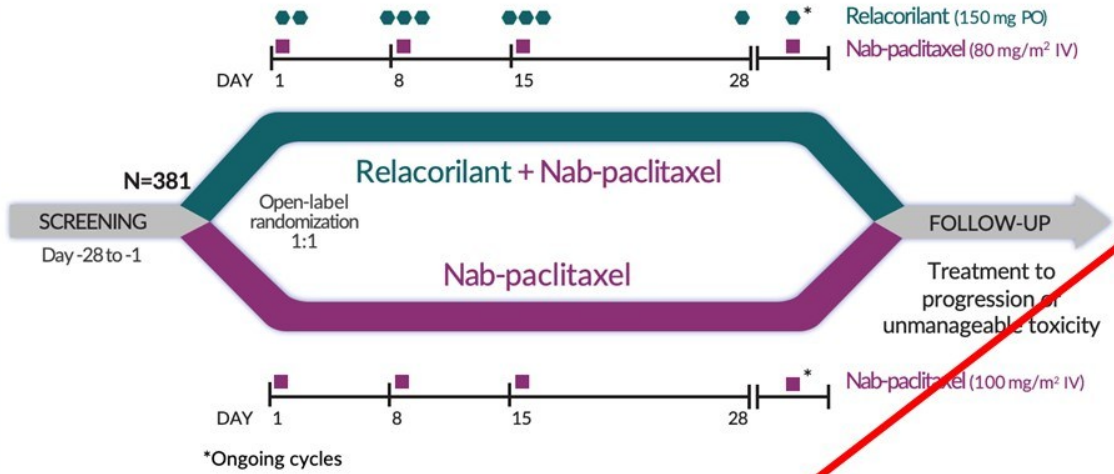
ROSELLA: Study design

Population

- Epithelial ovarian, primary peritoneal or fallopian tube cancer
- ECOG performance status 0 or 1
- Progression <6 months after the last dose of platinum therapy (excluding no response to, or progression in <1 month of primary platinum)
- 1–3 prior lines of therapy
- Must have received prior bevacizumab

NCT05257408



Stratification Factors
- Prior lines of therapy (1 vs >1)
- Region (North America vs Europe vs Korea, Australia, & Latin America)

Dual Primary Endpoints

- Progression-free survival (PFS) by RECIST v1.1 per blinded independent central review
- Overall survival

Secondary Endpoints

- PFS by RECIST v1.1 per Investigator
- ORR, DoR, CBR (RECIST v1.1)
- Response by CA-125 GCIG criteria
- Combined response (RECIST v1.1 and CA-125 GCIG criteria)
- Safety

First patient enrolled: 5th January 2023
Last patient enrolled: 8th April 2024
Data cutoff: 24th February 2025
Conducted at 117 sites in 14 countries.

If the P-value (stratified log-rank test) for either PFS-BICR (alpha=0.04) or OS (alpha=0.01) is less than the respective, pre-specified alpha boundary, the trial was considered positive.

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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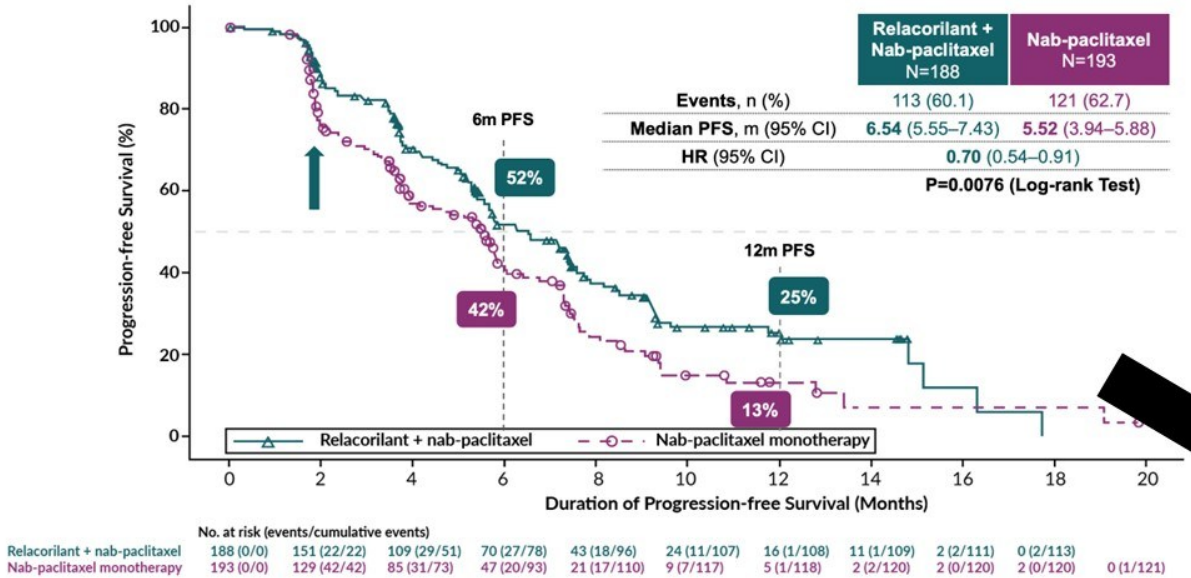
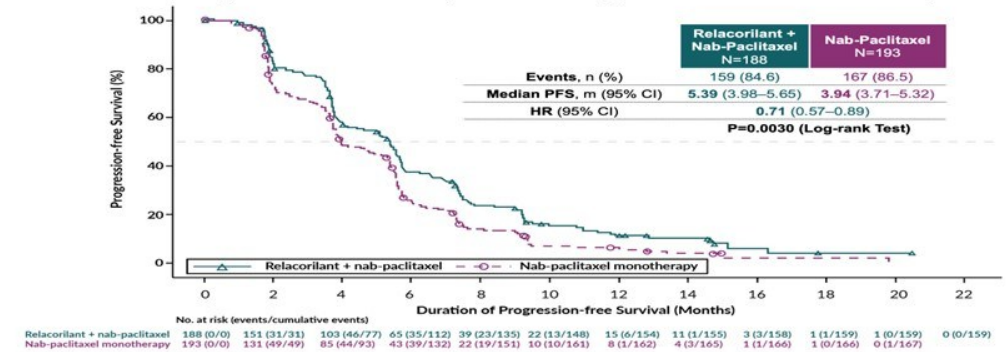
ROSELLA: Study results

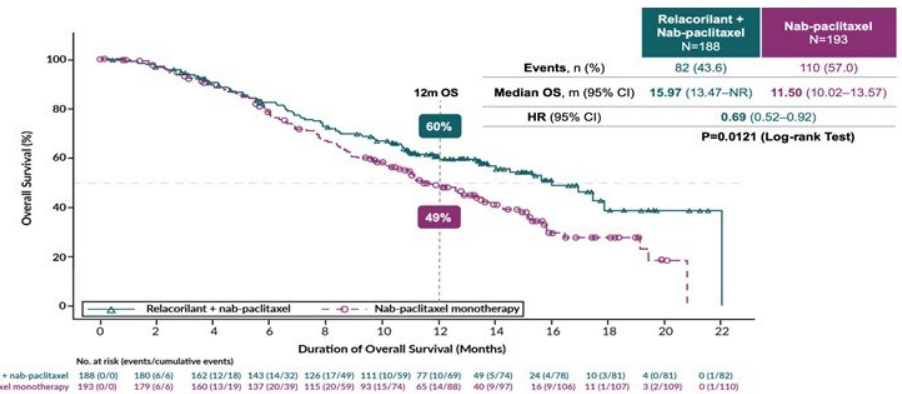
Primary EP: PFS (blinded indept. central review)



Secondary EP: PFS (investigator assessed)



Co-Primary EP: OS (only 50% maturity)



PFS and OS particularly improved in pts. ≥65 years, BRCA wt and/or no prior PARPi!

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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ROSELLA: Conclusions

- Relacorilant is a **first-in-class, oral, selective glucocorticoid receptor antagonist (SGRA)** for patients with ovarian cancer.
- The addition of relacorilant to nab-paclitaxel **statistically and clinically significantly extended PFS** in patients with platinum-resistant ovarian cancer.
- The hazard ratio was **similar to** that seen in **MIRASOL** (anti-folate-receptor-α-(FRα)-ADC), while **toxicity profiles differed (no ocular toxicity).**
- At this interim overall survival analysis, the addition of relacorilant to nab-paclitaxel showed a **clinically meaningful improvement in overall survival** (HR 0.69, median 16.0 vs 11.5 months, P=0.0121)
- Relacorilant plus nab-paclitaxel was **well-tolerated**, with a favorable safety profile consistent with previously reported data; **no new safety signals** were identified.

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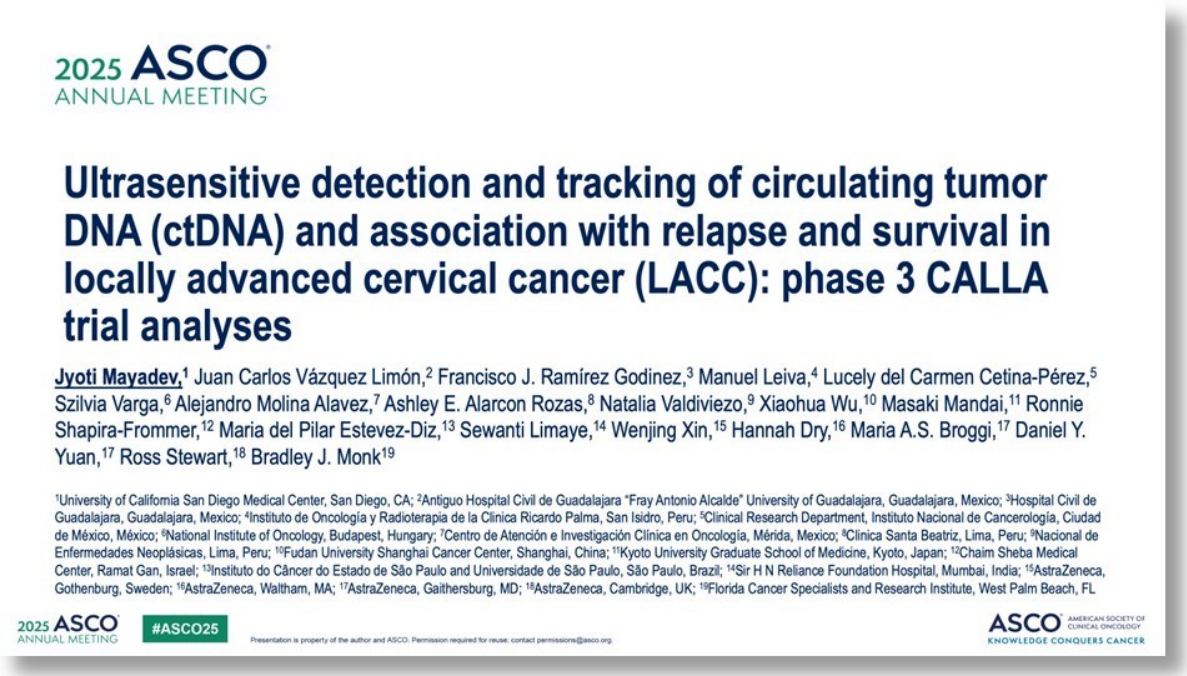
ctDNA in CALLA: This presentation is an ASCO highlight because …

… it adds significantly to the existing body of evidence that ctDNA analysis may represent an **important prognostic marker in patients with malignant tumors.**

…it may represent an important step to include ctDNA in the **treatment algorithm of patients with LACC**.



2025 ASCO ANNUAL MEETING

Ultrasensitive detection and tracking of circulating tumor DNA (ctDNA) and association with relapse and survival in locally advanced cervical cancer (LACC): phase 3 CALLA trial analyses

Jyoti Mayadev,[1] Juan Carlos Vázquez Limón,[2] Francisco J. Ramírez Godinez,[3] Manuel Leiva,[4] Lucely del Carmen Cetina-Pérez,[5] Szilvia Varga,[6] Alejandro Molina Alavez,[7] Ashley E. Alarcon Rozas,[8] Natalia Valdiviezo,[9] Xiaohua Wu,[10] Masaki Mandai,[11] Ronnie Shapira-Frommer,[12] Maria del Pilar Estevez-Diz,[13] Sewanti Limaye,[14] Wenjing Xin,[15] Hannah Dry,[16] Maria A.S. Broggi,[17] Daniel Y. Yuan,[17] Ross Stewart,[18] Bradley J. Monk[19]

[1]University of California San Diego Medical Center, San Diego, CA; [2]Antiguo Hospital Civil de Guadalajara "Fray Antonio Alcalde" University of Guadalajara, Guadalajara, Mexico; [3]Hospital Civil de Guadalajara, Guadalajara, Mexico; [4]Instituto de Oncología y Radioterapia de la Clinica Ricardo Palma, San Isidro, Peru; [5]Clinical Research Department, Instituto Nacional de Cancerología, Ciudad de México, México; [6]National Institute of Oncology, Budapest, Hungary; [7]Centro de Atención e Investigación Clínica en Oncología, Mérida, Mexico; [8]Clinica Santa Beatriz, Lima, Peru; [9]Nacional de Enfermedades Neoplásicas, Lima, Peru; [10]Fudan University Shanghai Cancer Center, Shanghai, China; [11]Kyoto University Graduate School of Medicine, Kyoto, Japan; [12]Chaim Sheba Medical Center, Ramat Gan, Israel; [13]Instituto do Câncer do Estado de São Paulo and Universidade de São Paulo, São Paulo, Brazil; [14]Sir H N Reliance Foundation Hospital, Mumbai, India; [15]AstraZeneca, Gothenburg, Sweden; [16]AstraZeneca, Waltham, MA; [17]AstraZeneca, Gaithersburg, MD; [18]AstraZeneca, Cambridge, UK; [19]Florida Cancer Specialists and Research Institute, West Palm Beach, FL

2025 ASCO ANNUAL MEETING #ASCO25

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

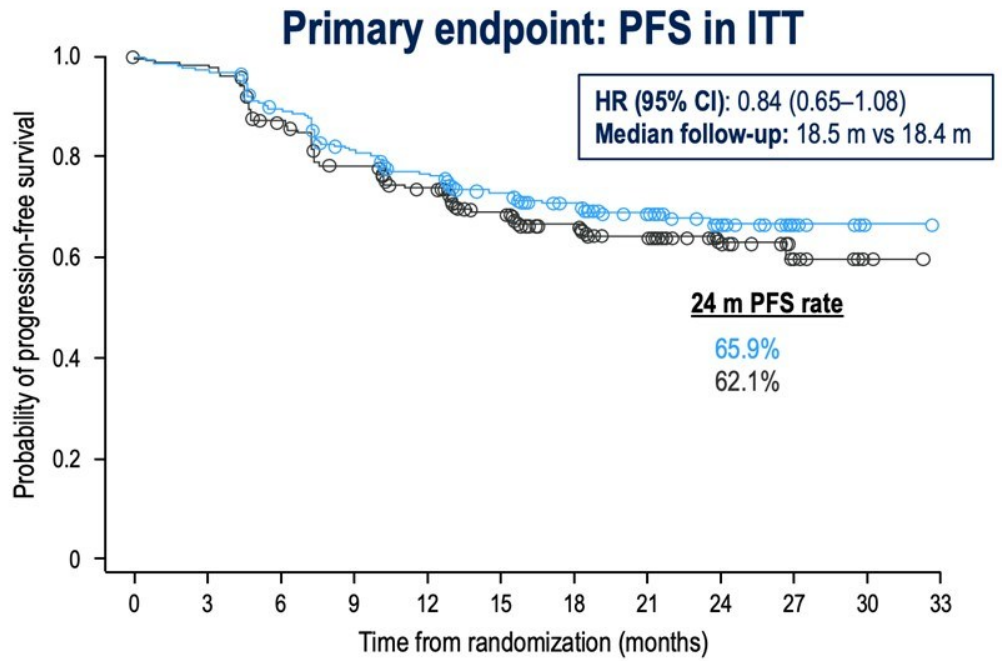
PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD

cornelia.kolberg-liedtke@hs-bochum.de

ctDNA in CALLA: Trial Rationale

- **30–50%** of patients with LACC have **recurrent disease within 5 years** after standard of care CRT
- **ctDNA** represents a **promising prognostic marker of relapse** in various cancers including cervical cancer

- The CALLA trial
  - analyzed whether **durvalumab + chemotherapy** could provide a PFS benefit compared to chemotherapy alone vs CRT in a biomarker unselected LACC population
  - did not meet its primary endpoint
  - showed a PFS benefit with durvalumab + CRT vs CRT for patients with PD-L1 TAP ≥20% in post hoc analyses



PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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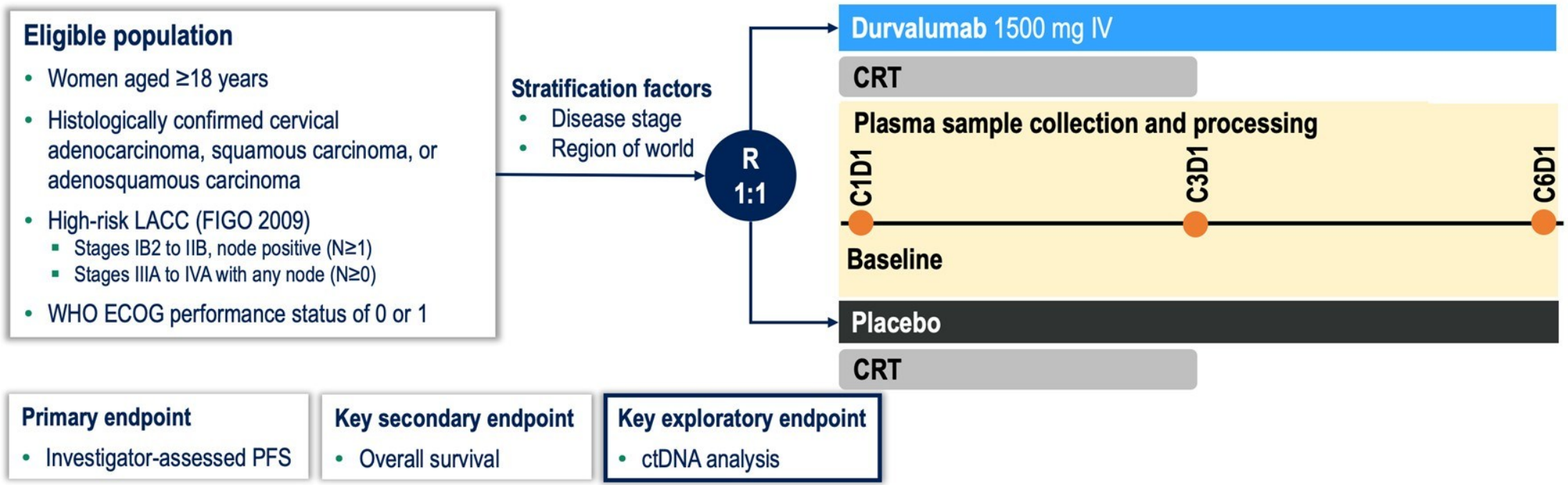
ctDNA in CALLA: Trial Design



At ASCO 2025, the authors presented an analysis of the association of ultrasensitive ctDNA detection with relapse and survival

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
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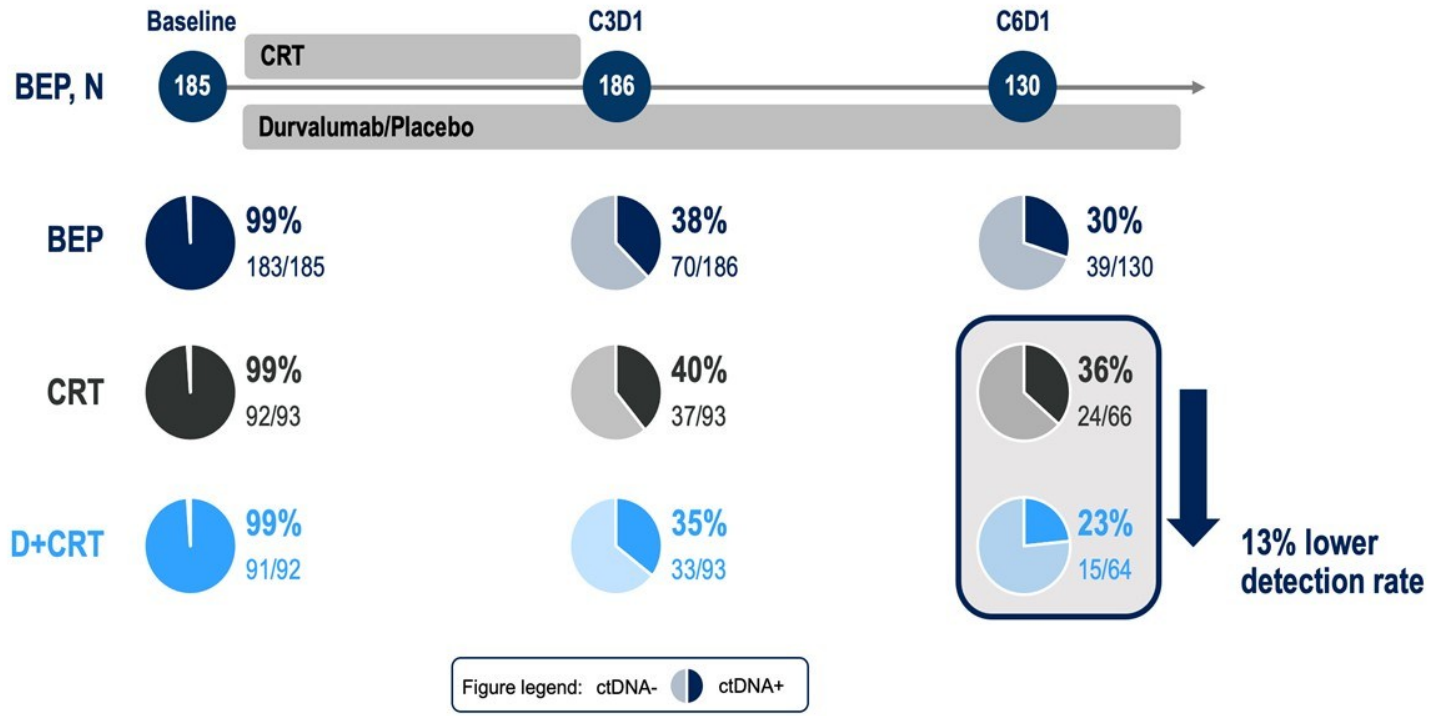
ctDNA in CALLA: Trial Results

- ctDNA+ rates decreased after treatment and **appeared lower with D+CRT** vs CRT **at C6D1**.
- Reduction in ctDNA+ rate in D+CRT vs CRT arm appeared to be greater in the PD-L1 TAP ≥20% subgroup (not shown here).



BEP, biomarker evaluable population

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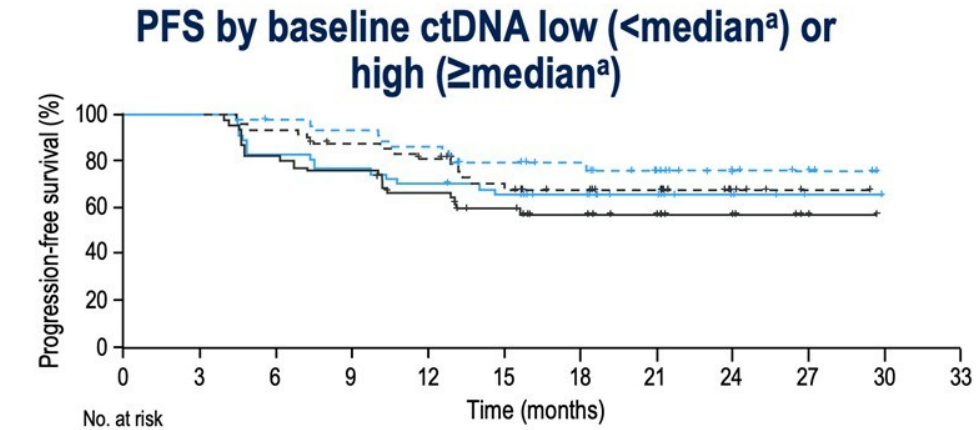
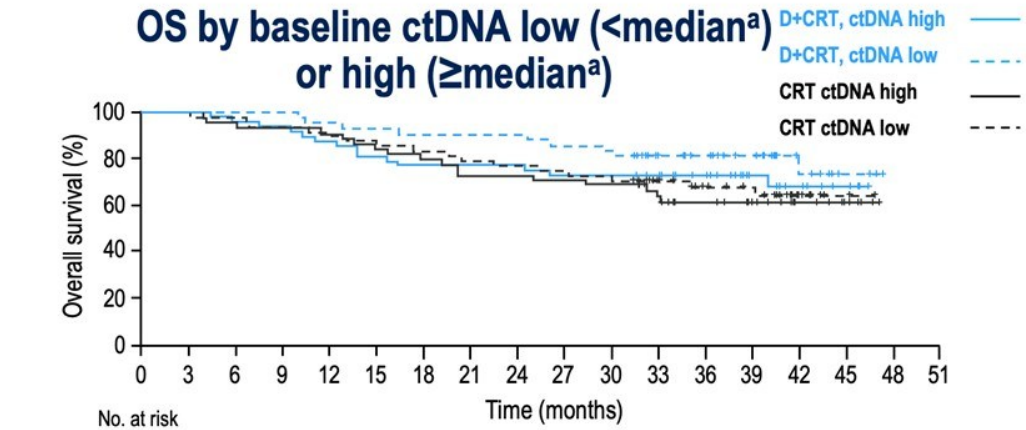
ctDNA in CALLA: Trial Results

- Low ctDNA at baseline was associated with reduced risk of progression and death



HR (95% CI)	D+CRT	CRT
ctDNA low vs ctDNA high	0.60 (0.27–1.33)	0.62 (0.31–1.23)
D+CRT vs CRT ctDNA high	0.75 (0.39–1.46)	
D+CRT vs CRT ctDNA low	0.72 (0.32–1.63)	



HR (95% CI)	D+CRT	CRT
ctDNA low vs ctDNA high	0.63 (0.27–1.45)	0.85 (0.43–1.69)
D+CRT vs CRT ctDNA high	0.77 (0.38–1.56)	
D+CRT vs CRT ctDNA low	0.55 (0.24–1.25)	

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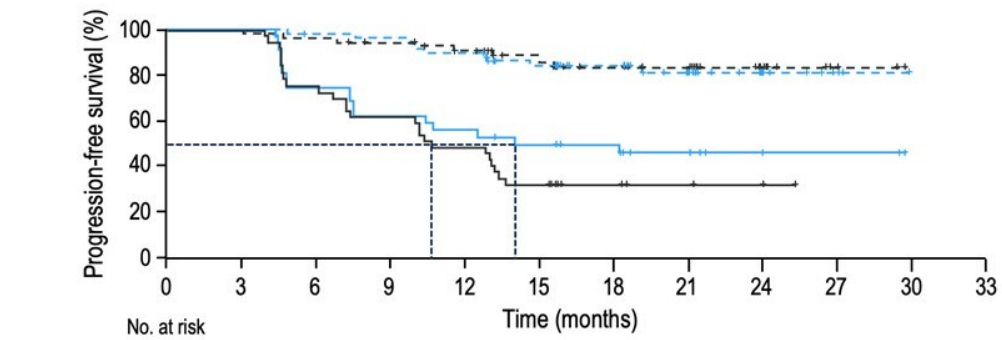
ctDNA in CALLA: Trial Results

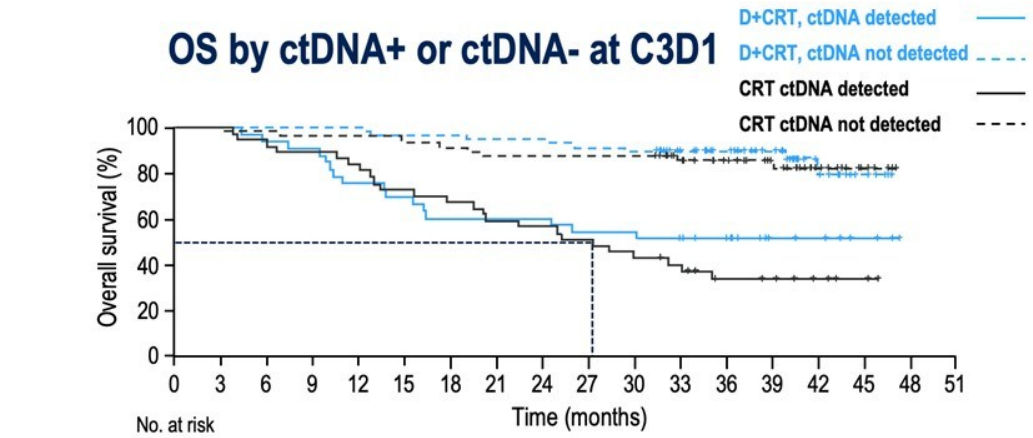
- ctDNA+ post chemotherapy was a negative prognostic factor for PFS and OS (results were similar at C6D1)
- Risk was independent of treatment arm

PFS by ctDNA+ or ctDNA- at C3D1



HR (95% CI)	D+CRT n/N=33/93	CRT n/N=37/93
Detected vs not detected	0.23 (0.11–0.50)	0.15 (0.07–0.33)

OS by ctDNA+ or ctDNA- at C3D1



HR (95% CI)	D+CRT n/N=33/93	CRT n/N=37/93
Detected vs not detected	0.20 (0.09–0.47)	0.18 (0.08–0.38)

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
cornelia.kolberg-liedtke@hs-bochum.de

ctDNA in CALLA: Conclusions

- This preplanned exploratory ctDNA analysis of a large, global LACC population from CALLA
  demonstrates the **high sensitivity of a personalized assay for ctDNA detection**
- Risk of progression and death were reduced by at least 95% in both treatment arms for patients with no ctDNA detected at C6D1
- **Baseline high ctDNA level** (≥ median) was associated with **higher risk of progression and death**
- Continued detection of ctDNA following CRT was independently prognostic of outcome

PRESENTED BY: Cornelia Kolberg-Liedtke, MD PhD
cornelia.kolberg-liedtke@hs-bochum.de

2025 ASCO ANNUAL MEETING

Highlights of the Day: Lung Cancer

NSCLC (local/regional) and SCLC

Eric K. Singhi, MD

University of Texas MD Anderson ~~Cancer~~ Center

Important clinical updates in NSCLC & SCLC

Resectable NSCLC

ES-SCLC

Important clinical updates in NSCLC & SCLC

	Study	Phase
Resectable NSCLC	CheckMate 816	3
	NeoADAURA	3
ES-SCLC	IMforte	3
	DeLLphi-304	3

Important clinical updates in NSCLC & SCLC

	Study	Phase	Practice-Changing?
Resectable NSCLC	CheckMate 816	3	Yes ✅
	NeoADAURA	3	No ❌
ES-SCLC	IMforte	3	Yes ✅
	DeLLphi-304	3	Yes ✅

Singhi Summary

PRESENTED BY: Eric K. Singhi, MD @lungoncdoc

Important clinical updates in NSCLC & SCLC

	Study	Phase	Practice-Changing?
Resectable NSCLC	CheckMate 816	3	Yes ✅
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ES-SCLC	IMforte	3	Yes ✅
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Singhi Summary

Let's review each study to answer:

Important clinical updates in NSCLC & SCLC

	Study	Phase	Practice-Changing?
Resectable NSCLC	CheckMate 816	3	Yes ✅
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Singhi Summary

Let's review each study to answer:

Who?
was studied

Important clinical updates in NSCLC & SCLC

	Study	Phase	Practice-Changing?
Resectable NSCLC	CheckMate 816	3	Yes ✅
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Singhi Summary

Let's review each study to answer:

Who? was studied

What? did the study show

PRESENTED BY: Eric K. Singhi, MD @lungoncdoc

Important clinical updates in NSCLC & SCLC

	Study	Phase	Practice-Changing?
Resectable NSCLC	CheckMate 816	3	Yes ✅
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ES-SCLC	IMforte	3	Yes ✅
	DeLLphi-304	3	Yes ✅

Singhi Summary

Let's review each study to answer:

Who? was studied

What? did the study show

Why? or why not practice-changing

PRESENTED BY: Eric K. Singhi, MD @lungoncdoc

Resectable NSCLC:
WITHOUT Actionable Genomic Alterations (AGAs)

PRESENTED BY: Eric K. Singhi, MD @lungoncdoc

Current Landscape

FDA Approved Regimens: *Resectable NSCLC*

Neoadjuvant

Trial	Stage Disease Characteristics	Regimen	Approval Endpoint
CheckMate 816 March 2022	IB-IIIA Irrespective PD-L1	Nivolumab + chemotherapy x 3 cycles	EFS HR 0.63, p = 0.005 OS HR 0.72, p = 0.0479 pCR 24%

Perioperative

Trial	Stage Disease Characteristics	Regimen	Approval Endpoint
KEYNOTE-671 October 2023	II-IIIB (N2) Irrespective PD-L1	Pembrolizumab + chemotherapy x 4 cycles -> S -> pembrolizumab x ~9 months	EFS HR 0.58, p <0.00001 OS HR 0.72, p=0.00517
AEGEAN August 2024	IIA-IIIB (N2) Irrespective PD-L1	Durvalumab + chemotherapy x 4 cycles -> S -> durvalumab x 1 year	EFS HR 0.68, p=0.0039 pCR 17%
CheckMate 77T October 2024	IIA-IIIB Irrespective PD-L1	Nivolumab + chemotherapy x 4 cycles -> S -> nivolumab x 1 year	EFS HR 0.58, p = 0.00025 pCR = 25%

Adjuvant

Trial	Stage Dz characteristics	Regimen	Approval Endpoint
IMpower010 October 2021	II-IIIA PD-L1 positive (>/=1%)	Adjuvant chemotherapy -> atezolizumab x 1 year	DFS HR 0.66; p = 0.004
PEARLS/ KEYNOTE-091 January 2023	IB-IIIA Irrespective PDL1	Adjuvant chemotherapy -> pembrolizumab x 1 year	DFS HR 0.73
ADAURA December 2020	IB-IIIA EGFR exon 21 L858R or exon 19 deletion positive	Osimertinib x 3 years (regardless of adjuvant chemotherapy)	DFS HR 0.20; p < 0.0001 OS HR 0.49; p <0.001
ALINA April 2024	IB-IIIA ALK-positive	Alectinib x 2 years	DFS HR 0.24; p<0.0001

X: @lungoncdoc

Current Landscape

FDA Approved Regimens: *Resectable NSCLC*

Neoadjuvant

Trial	Stage Disease Characteristics	Regimen	Approval Endpoint
CheckMate 816 March 2022	IB-IIIA Irrespective PD-L1	Nivolumab + chemotherapy x 3 cycles	EFS HR 0.63, p = 0.005 OS HR 0.72, p = 0.0479 pCR 24%

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PEARLS/ KEYNOTE-091 January 2023	IB-IIIA Irrespective PDL1	Adjuvant chemotherapy -> pembrolizumab x 1 year	DFS HR 0.73

Several approaches to choose from for our patients without AGAs

2025 ASCO ANNUAL MEETING

Overall survival with neoadjuvant nivolumab + chemotherapy in patients with resectable NSCLC in CheckMate 816

Patrick M. Forde,[1] Jonathan D. Spicer,[2] Mariano Provencio,[3] Tetsuya Mitsudomi,[4] Mark M. Awad,[5] Changli Wang,[6] Shun Lu,[7] Enriqueta Felip,[8] Stephen Broderick,[9] Scott J. Swanson,[10] Julie Brahmer,[9] Keith Kerr,[11] Tudor-Eliade Ciuleanu,[12] Fumihiro Tanaka,[13] Gene B. Saylors,[14] Ke-Neng Chen,[15] Lily Wang,[16] Quyen Duong,[16] Nicolas Girard[17]

[1]Trinity St. James's Cancer Institute, Trinity College Dublin, Dublin, Ireland; [2]McGill University Health Centre, Montreal, Quebec, Canada; [3]Hospital Universitario Puerta de Hierro, Madrid, Spain; [4]Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [7]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [8]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain; [9]The Bloomberg–Kimmel Institute for Cancer Immunotherapy, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine, Baltimore, MD, USA; [10]Brigham and Women's Hospital, Boston, MA, USA; [11]Aberdeen Royal Infirmary, Aberdeen, United Kingdom; [12]Institutul Oncologic Prof Dr Ion Chiricuță and University of Medicine and Pharmacy Iuliu Haţieganu, Cluj-Napoca, Romania; [13]The University of Occupational and Environmental Health, Kitakyushu, Japan; [14]Charleston Oncology, Charleston, SC, USA; [15]State Key Laboratory of Molecular Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France

Abstract number LBA8000

Who? was studied

CheckMate 816 study design[a]

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by
Stage (IB-II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex

N = 358

R 1:1

Primary analysis population
(Concurrently randomized)

- NIVO 360 mg Q3W + chemo[d] Q3W (3 cycles)
- Chemo[e] Q3W (3 cycles)

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo and/or RT → Follow-up

Minimum/median follow-up: 59.9/68.4 months

Primary endpoints
- pCR by BIPR
- EFS by BICR

Key secondary endpoints
- MPR by BIPR
- OS
- TTDM

Exploratory analyses
- OS by pCR, ctDNA clearance
- Lung cancer-specific survival

Database lock: January 23, 2025. From *The New England Journal of Medicine*, Forde PM, et al, Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer, 2022;386:1973–1985. Copyright © 2022 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society. [a]NCT02998528. [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [c]Included patients with PD-L1 expression status not evaluable and indeterminate. [d]Nonsquamous: pemetrexed + cisplatin or paclitaxel + carboplatin; squamous: gemcitabine + cisplatin or paclitaxel + carboplatin. [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pemetrexed + cisplatin (nonsquamous only), or paclitaxel + carboplatin.

Who? was studied

CheckMate 816 study design[a]

Primary analysis population
(Concurrently randomized)

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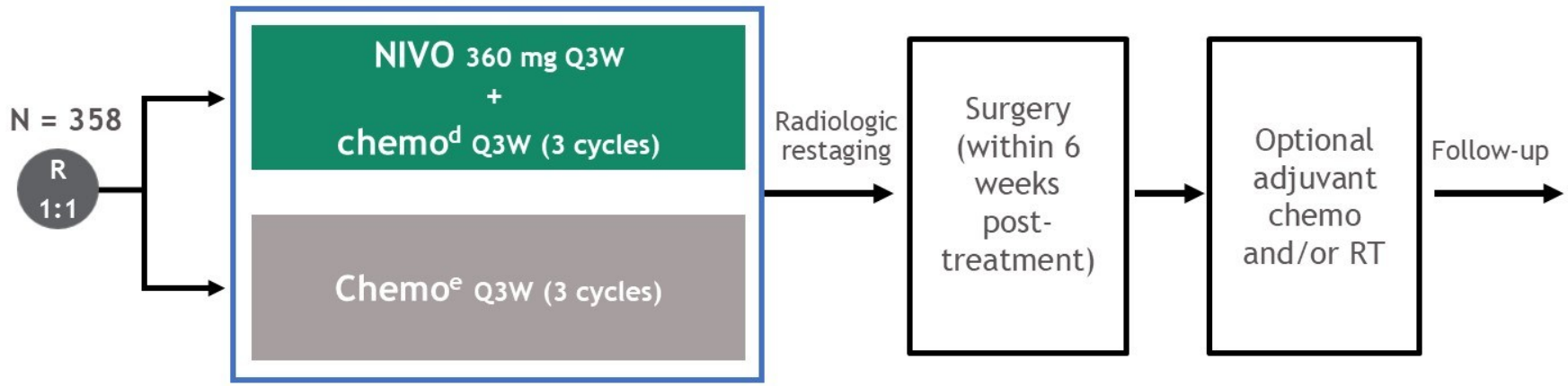
Stage (IB-II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex



Minimum/median follow-up: 59.9/68.4 months

Primary endpoints
- pCR by BIPR ✓
- EFS by BICR ✓

Key secondary endpoints
- MPR by BIPR
- OS ?
- TTDM

Exploratory analyses
- OS by pCR, ctDNA clearance
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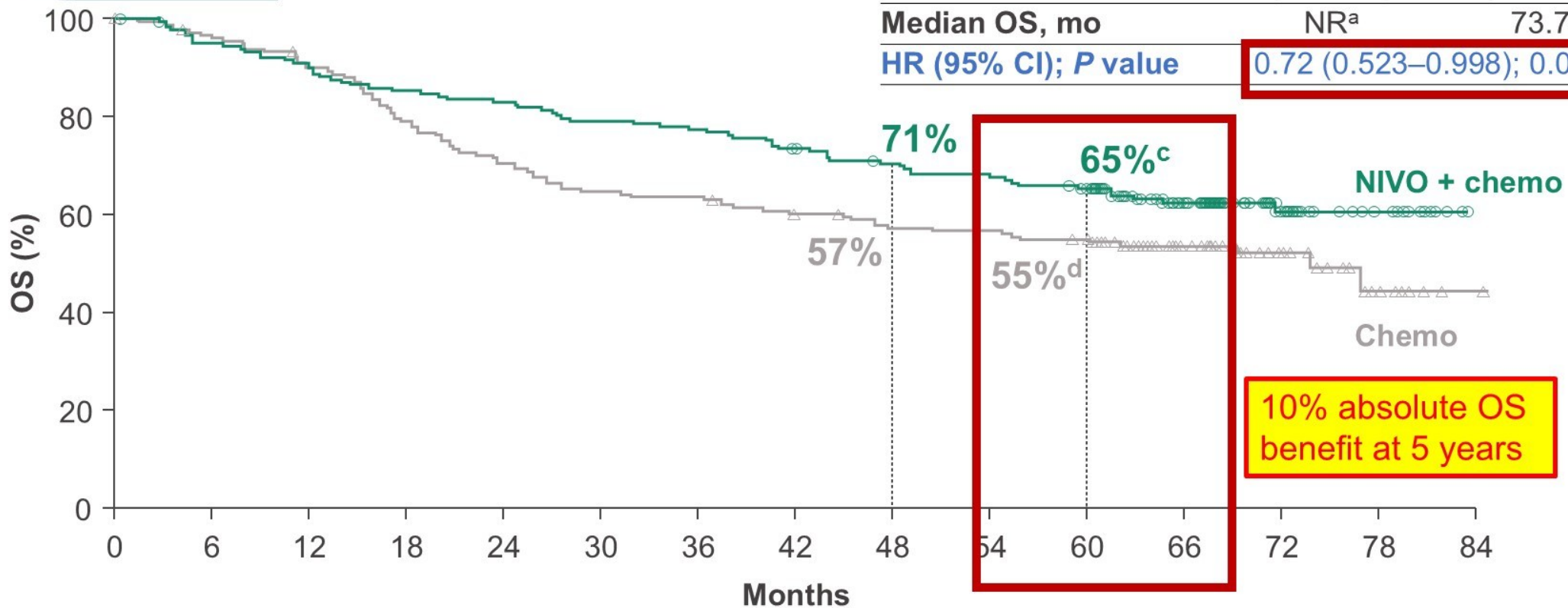
What? did the study show

Final analysis: OS with neoadjuvant NIVO + chemo vs chemo

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS, mo	NR[a]	73.7[b]
HR (95% CI); *P* value	0.72 (0.523–0.998); 0.0479	



No. at risk														
NIVO + chemo	179	168	159	151	147	140	137	129	122	117	111	67	29	9	0
Chemo	179	170	159	139	124	114	112	104	98	97	91	58	29	6	1

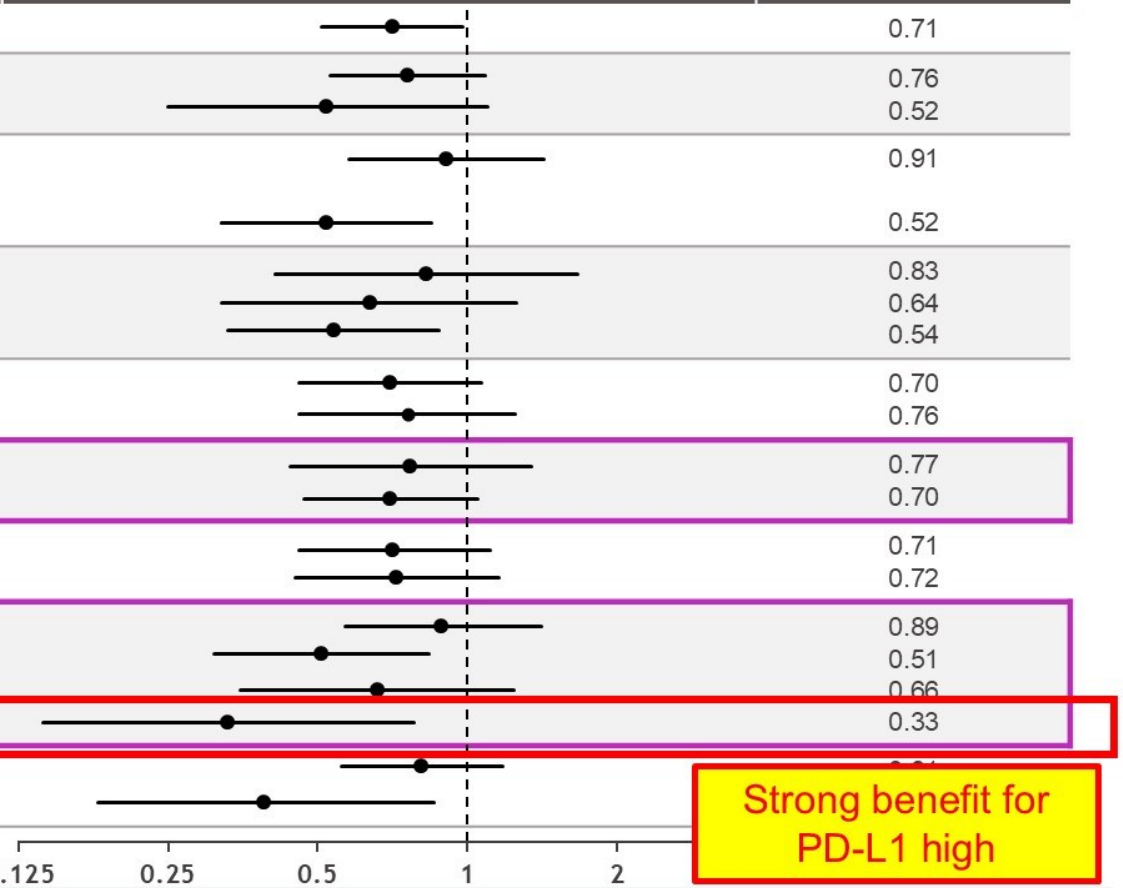
Minimum/median follow-up: 59.9/68.4 months.

[a]95% CI, NR; 47.3–NR. [b]95% CI, 47.4–62.

What? did the study show

OS analysis by key subgroups

	Median OS, mo		Unstratified HR (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	NR	73.7		0.71
Male (n = 255)	NR	61.8		0.76
Female (n = 103)	NR	NR		0.52
White (n = 169)	NR	73.7		0.91
Black or African American (n = 7)	NR	20.9		
Asian (n = 179)	NR	76.8		0.52
North America (n = 91)	NR	73.7		0.83
Europe (n = 66)	NR	38.3		0.64
Asia (n = 177)	NR	76.8		0.54
ECOG PS 0 (n = 241)	NR	76.8		0.70
ECOG PS 1 (n = 117)	71.6	45.3		0.76
Stage IB-II (n = 126)	NR	76.8		0.77
Stage IIIA (n = 229)	NR	73.7		0.70
Squamous (n = 182)	NR	73.7		0.71
Nonsquamous (n = 176)	NR	NR		0.72
PD-L1 < 1% (n = 155)	NR	61.8		0.89
PD-L1 ≥ 1% (n = 178)	NR	73.7		0.51
PD-L1 1%–49% (n = 98)	NR	73.7		0.66
PD-L1 ≥ 50% (n = 80)	NR	76.8		0.33
Cisplatin (n = 258)	NR	76.8		
Carboplatin (n = 72)	NR	37.2		



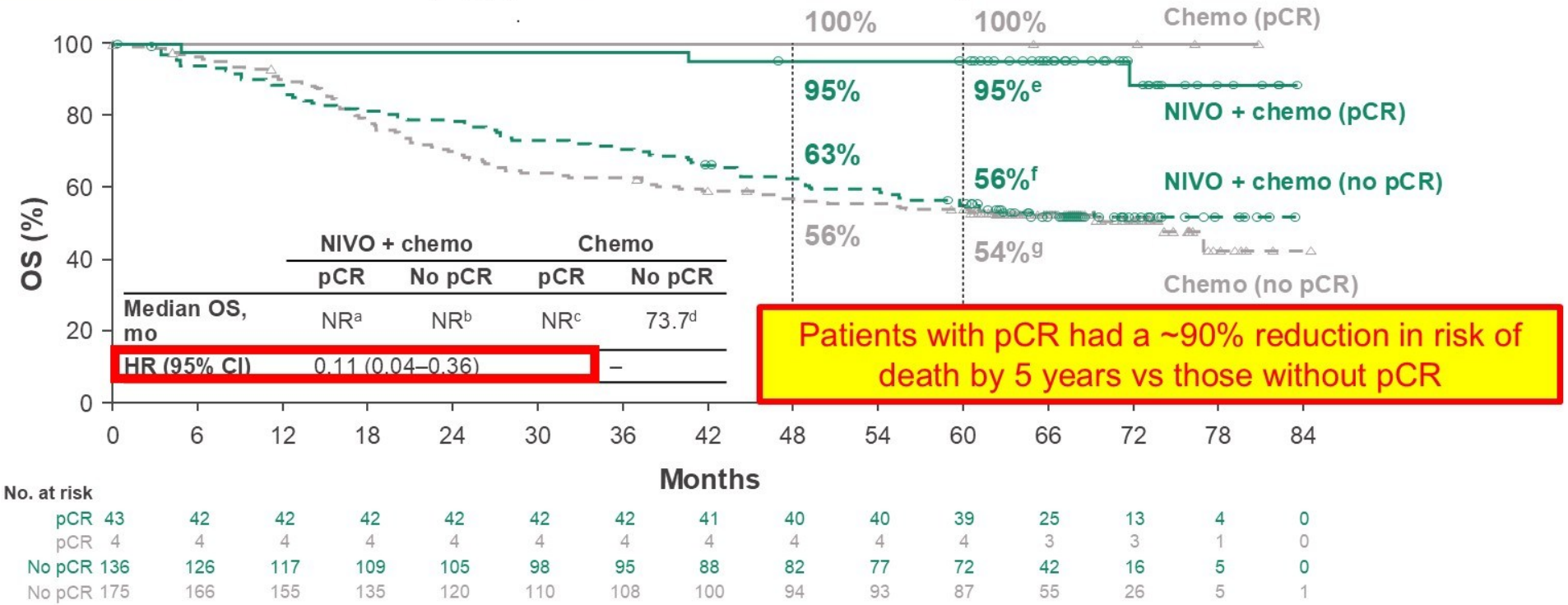
Strong benefit for PD-L1 high

Minimum/median follow-up: 59.9/68.4 months.
HRs were NC if there was an insufficient number of events (< 10 per arm).

What? did the study show

Exploratory analysis: OS by pCR status

- Among concurrently randomized patients, 43/179 (24%) patients in the NIVO + chemo arm and 4/179 (2%) patients in the chemo arm had pCR[1]



In the NIVO + chemo arm:

- Among patients with pCR, death occurred in 3 patients; none were due to disease[h]
- Among patients with no pCR, there were a total of 62 (46.6%) deaths; 44 (33.1%) were due to disease[i]

Minimum/median follow-up: 59.9/68.4 months.

HRs were NC if there was an insufficient number of events (< 10 per arm). [a-g]95% CI: [a]NR; [b]53.9–NR; [c]NR; [d]46.7–NR; [e]83–99; [f]47–64; [g]46–61. [h]In the chemo arm, there were no deaths in patients with pCR. [i]In the chemo arm, there were 82 (47.7%) deaths; 58 (33.7%) were due to disease. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973–1985.

CM816: Why? practice-changing?

- First (and only) exclusively neoadjuvant chemoimmunotherapy regimen to show significant OS benefit
- Proven pCR (24%) & EFS (HR 0.63) benefit
- Strong benefit for PD-L1 positive disease
  High reassurance if pCR achieved
- Lower time and financial toxicity compared to other strategies

Resectable NSCLC:
WITH Actionable Genomic Alteration: +EGFR

PRESENTED BY: Eric K. Singhi, MD @lungoncdoc

Current Landscape

FDA Approved Regimens: *Resectable NSCLC*

Neoadjuvant

Trial	Stage Disease Characteristics	Regimen	Approval Endpoint
CheckMate 816 March 2022	IB-IIIA Irrespective PD-L1	Nivolumab + chemotherapy x 3 cycles	EFS HR 0.63, p = 0.005 OS HR 0.72, p = 0.0479 pCR 24%

Perioperative

Trial	Stage Disease Characteristics	Regimen	Approval Endpoint
KEYNOTE-671 October 2023	II-IIIB (N2) Irrespective PD-L1	Pembrolizumab + chemotherapy x 4 cycles -> S -> pembrolizumab x ~9 months	EFS HR 0.58, p <0.00001 OS HR 0.72, p=0.00517
AEGEAN August 2024	IIA-IIIB (N2) Irrespective PD-L1	Durvalumab + chemotherapy x 4 cycles -> S -> durvalumab x 1 year	EFS HR 0.68, p=0.0039 pCR 17%
CheckMate 77T October 2024	IIA-IIIB Irrespective PD-L1	Nivolumab + chemotherapy x 4 cycles -> S -> nivolumab x 1 year	EFS HR 0.58, p = 0.00025 pCR = 25%

Adjuvant

Trial	Stage Dz characteristics	Regimen	Approval Endpoint
IMpower010 October 2021	II-IIIA PD-L1 positive (>/=1%)	Adjuvant chemotherapy -> atezolizumab x 1 year	DFS HR 0.66; p = 0.004
PEARLS/ KEYNOTE-091 January 2023	IB-IIIA Irrespective PDL1	Adjuvant chemotherapy -> pembrolizumab x 1 year	DFS HR 0.73
ADAURA December 2020	IB-IIIA EGFR exon 21 L858R or exon 19 deletion positive	Osimertinib x 3 years (regardless of adjuvant chemotherapy)	DFS HR 0.20; p < 0.0001 OS HR 0.49; p <0.001
ALINA April 2024	IB-IIIA ALK-positive	Alectinib x 2 years	DFS HR 0.24; p<0.0001

X: @lungoncdoc

PRESENTED BY: Eric K. Singhi, MD @lungoncdoc

2024 ASCO ANNUAL MEETING

Neoadjuvant osimertinib ± chemotherapy vs chemotherapy alone in resectable epidermal growth factor receptor-mutated (EGFRm) NSCLC: NeoADAURA

Jamie E. Chaft[1], Walter Weder, Jianxing He, Ke-Neng Chen, Maximilian J. Hochmair, Jin-Yuan Shih, Sung Yong Lee, Kang-Yun Lee, Nguyen Viet Nhung, Somcharoen Saeteng, Carlos H.A. Teixeira, Carles Escriu, Alex Martinez-Marti, Collin M. Blakely, Yasushi Yatabe, Sanja Dacic, Xiangning Huang, Yuri Rukazenkov, Anupriya Dayal, Masahiro Tsuboi

[1]Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; Department of Medicine, Weill Cornell Medical College, New York, NY, USA

NeoADAURA: global, randomized, Phase 3 controlled study

Who?
was studied

Patients with completely resectable EGFRm stage II–IIIB NSCLC*

Key inclusion criteria:

- Aged ≥18 years
- Histologically / cytologically confirmed non-squamous NSCLC
- Ex19del / L858R†
- WHO PS 0 / 1

N=358

R
1:1:1

Stratification by:
Stage II / III
Chinese‡ / other Asian / non-Asian
Ex19del / L858R

- Osi 80 mg QD (≥9 weeks)§¶ + carboplatin AUC5 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 (Q3W for 3 cycles)
- Osi mono 80 mg QD (≥9 weeks)¶#
- PBO QD (≥9 weeks)§¶ + carboplatin AUC5 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 (Q3W for 3 cycles)

Surgery

Investigator choice of adjuvant treatment

Post-surgery follow-up visits**

Sponsor-supplied osi was available for eligible patients who completed surgery in all arms††

Endpoints:

- **Primary: major pathological response (MPR; by blinded central pathology review)**
- Secondary: event-free survival, pathological complete response, nodal downstaging, and safety

NCT04351555. Figure borrowed from "*Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for EGFR-mutated resectable non-small-cell lung cancer: NeoADAURA*", Tsuboi M et al. Published online July 19, 2021 in *Future Oncology* and reprinted by permission of the publisher Informa UK Limited trading as Taylor & Francis Ltd, http://www.tandfonline.com .The figure was adapted with permission from the authors.

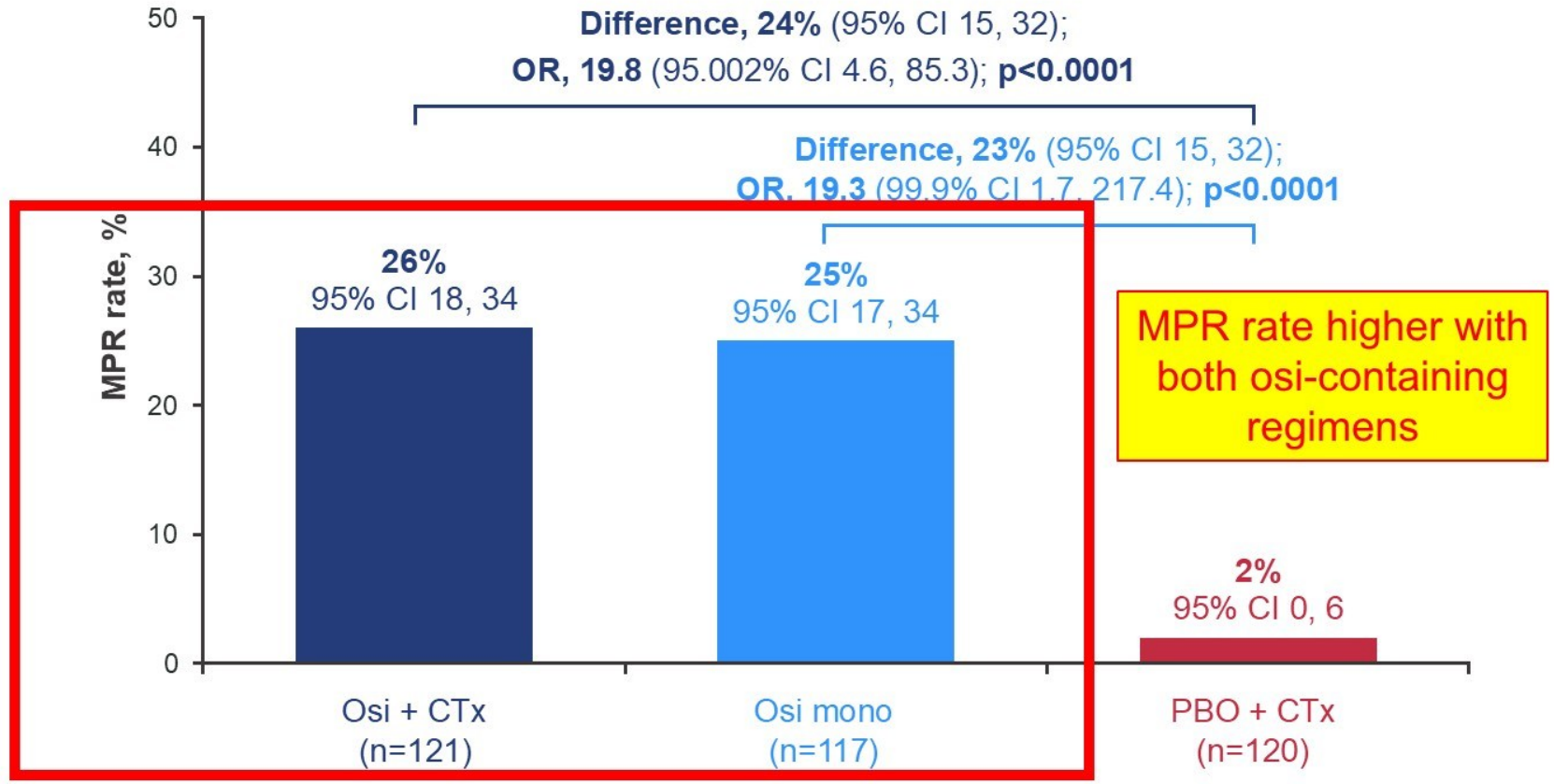
*AJCC Staging Manual 8th edition.†Confirmed by sponsor pre-approved local or central tissue testing. ‡Chinese living in mainland China. §Double-blind; ¶Osi or PBO could be continued up to the date of surgery, at the discretion of the investigator. #Open-label, sponsor-blinded. **At weeks 12 and 24 post-surgery, then every 24 weeks until 5 years, and then every 48 weeks until disease recurrence or other withdrawal criteria were met. ††Adjuvant osi could be given for a maximum 3-year treatment period, or until unacceptable toxicity or disease recurrence.

PRESENTED BY: Dr Jamie E. Chaft

AJCC, American Joint Committee on Cancer; AUC, area under the curve; CTx, chemotherapy; del, deletion; EGFRm, epidermal growth factor receptor-mutated; Ex19del, Exon 19 deletion; mono, monotherapy; NSCLC, non-small cell lung cancer; osi, osimertinib; PBO, placebo; Q3W, once every 3 weeks; QD, once daily; R, randomization; WHO PS, World Health Organisation performance status

What?
did the study show

MPR



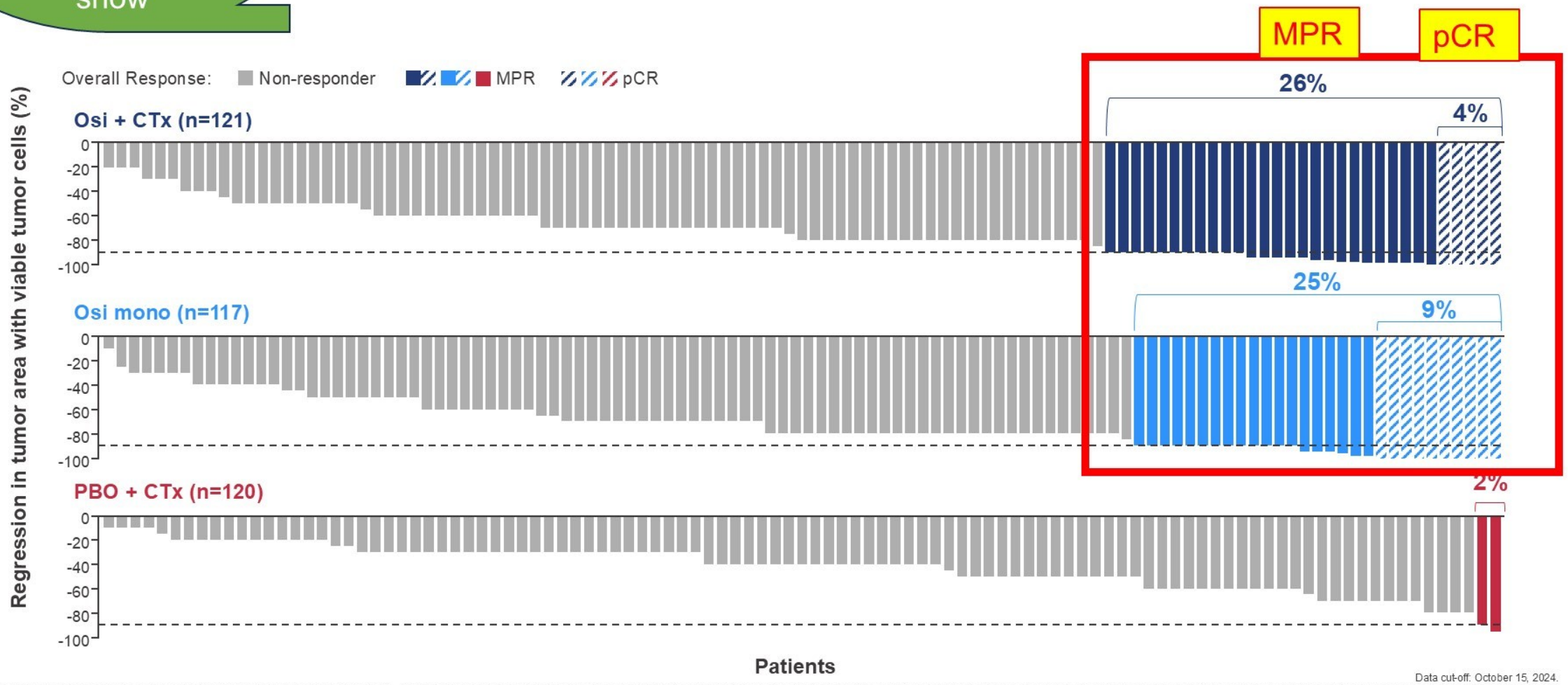
MPR defined as ≤10% residual viable tumor cells in the lung primary tumor at resection. Patients had to have an R0 result to be classified as responders. MPR assessed using the IASLC method. MPR was analyzed using the Cochran–Mantel–Haenszel test stratified by disease stage (II vs III), race (Chinese vs other Asian vs non-Asian) and EGFR mutation type (Ex19del vs L858R).

Data cut-off: October 15, 2024.

CI, confidence interval; CTx, chemotherapy; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; IASLC, International Association for the Study of Lung Cancer; mono, monotherapy; MPR, major pathological response; OR, odds ratio; osi, osimertinib; PBO, placebo

What?
did the study show

Depth of pathological response



MPR defined as ≤10% residual viable tumor cells in the lung primary tumor at resection. pCR defined as no residual viable tumor in surgical specimens including primary tumors and lymph nodes. Patients had to have an R0 result to be classified as responders. MPR and pCR assessed using the IASLC method. Pathological regression is summarized based on patients with evaluable % residual viable tumor, osi + CTx: n=109; osi mono: n=110; PBO + CTx: n=105.

Data cut-off: October 15, 2024.

CTx, chemotherapy; mono, monotherapy; IASLC, International Association for the Study of Lung Cancer; MPR, major pathological response; osi, osimertinib; PBO, placebo

NeoADAURA: Why? NOT practice-changing?

- Osimertinib (+/- chemo) w/ pCR rates of only 4-9%
- Surprisingly, neoadjuvant chemo adds little (MPR ~25%)
- ADAURA (adjuvant osimertinib) already shows OS benefit in resectable EGFR+ disease

Extensive-Stage Small Cell Lung Cancer: First-Line Treatment

PRESENTED BY: Eric K. Singhi, MD @lungoncdoc

2024 ASCO® ANNUAL MEETING

Lurbinectedin + atezolizumab as first-line maintenance treatment in patients with extensive-stage small cell lung cancer: Primary results of the Phase 3 IMforte trial

Luis Paz-Ares,[1] Hossein Borghaei,[2] Stephen V. Liu,[3] Solange Peters,[4] Roy S. Herbst,[5] Katarzyna Stencel,[6] Margarita Majem,[7] Grzegorz Czyżewicz,[8] Reyes Bernabé Caro,[9] Ki Hyeong Lee,[10] Melissa L. Johnson,[11] Nuri Karadurmuş,[12] Christian Grohé,[13] Vaikunth Cuchelkar,[14] Vilma Graupner,[15] Monika Kaul,[14] Ya-Chen Lin,[14] Debasis Chakrabarti,[16] Kamalnayan Bhatt,[16] Martin Reck[17]

[1]Hospital Universitario 12 de Octubre, H12O-CNIO Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain; [2]Fox Chase Cancer Center, Philadelphia, PA, USA; [3]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA; [4]University Hospital CHUV, Lausanne, Switzerland; [5]Yale School of Medicine, New Haven, CT, USA; [6]Wielkopolska Center of Pulmonology and Thoracic Surgery of Eugenia and Janusz Zeyland, Poznan, Poland; [7]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [8]The John Paul II Specialist Hospital, Kraków, Poland; [9]Hospital Universitario Virgen del Rocío, Seville, Spain; [10]Chungbuk National University Hospital, Cheongju, South Korea; [11]Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN, USA; [12]University of Health Sciences, Gülhane Training and Research Hospital, Ankara, Türkiye; [13]Klinik für Pneumologie, Evangelische Lungenklinik Berlin, Berlin, Germany; [14]Genentech Inc, South San Francisco, CA, USA; [15]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [16]Jazz Pharmaceuticals plc, Dublin, Ireland; [17]Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany

IMforte study design

Who?
was studied

First screening

Eligibility criteria
- No prior systemic treatment for ES-SCLC
- No CNS metastases
- ECOG PS 0/1

N=660

ENR

Induction phase

Atezo + carboplatin + etoposide (4 cycles q3w)[a]

Second screening

Eligibility criteria
- Ongoing CR/PR or SD following induction therapy
- ECOG PS 0/1

N=483[b]

Maintenance phase

R 1:1

Lurbi (3.2 mg/m²) + atezo (1200 mg) IV q3w[c]

Atezo (1200 mg) IV q3w

Treat until PD or unacceptable toxicity

No crossover allowed

Follow-up

Efficacy endpoint assessments started from randomization into the maintenance phase; safety analyses were from MC1D1

Stratification factors for randomization
- ECOG PS (0/1)
- LDH (≤ULN/>ULN)
- Presence of liver metastases (Y/N) at induction BL
- Prior receipt of PCI (Y/N)

Primary endpoints
IRF-PFS and OS

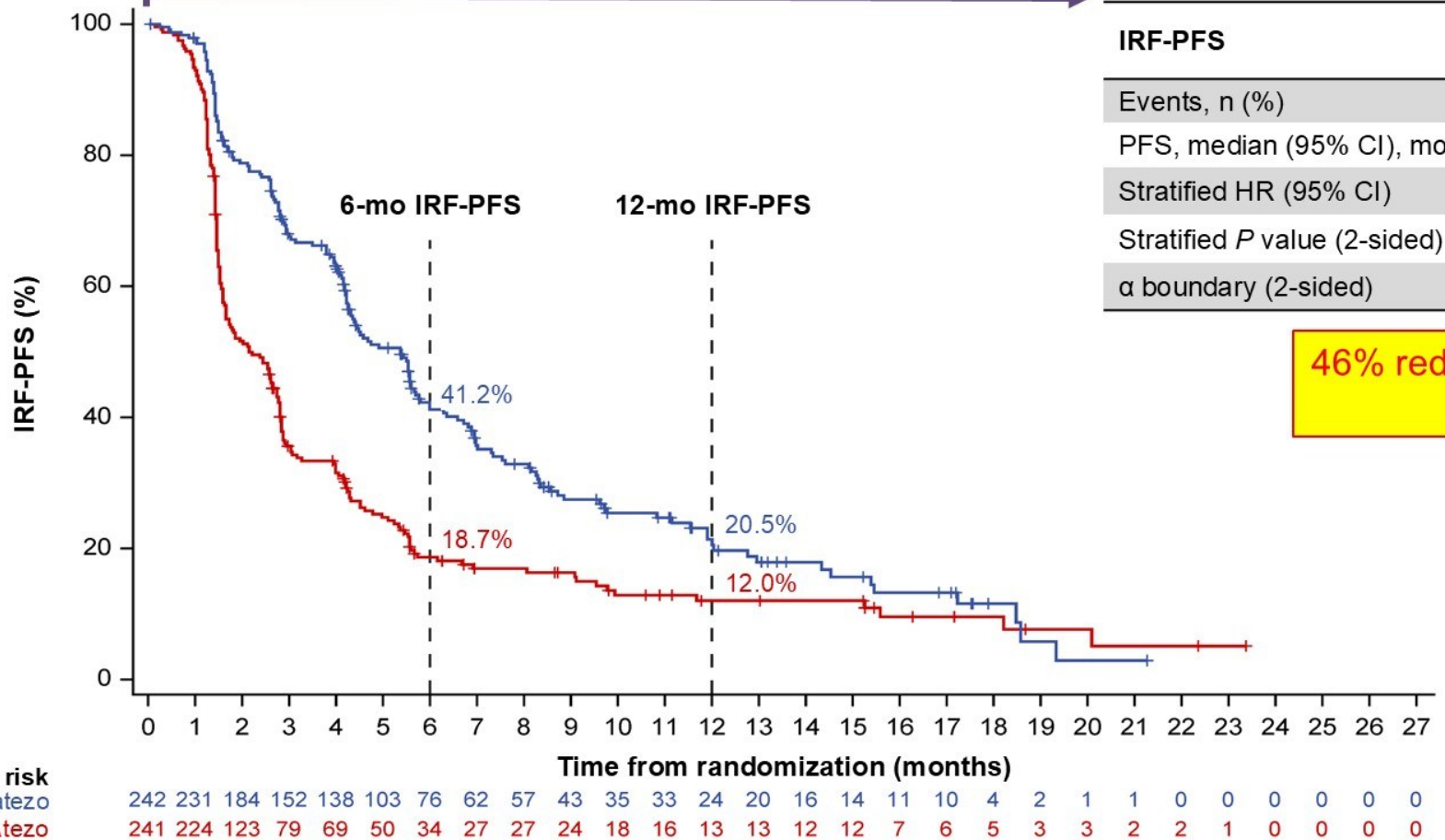
Secondary endpoints included
INV-PFS, ORR, DOR, and safety

Last patient randomized: April 30, 2024
Clinical cutoff: July 29, 2024

ClinicalTrials.gov ID: NCT05091567.
[a] Administered per standard dose. [b] 73% of patients continued from induction to maintenance. [c] With **prophylactic granulocyte colony-stimulating factor** and anti-emetics.
atezo, atezolizumab; BL, baseline; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ENR, enrollment; INV-PFS, investigator-assessed PFS; IRF-PFS, independent review facility-assessed PFS; IV, intravenously; LDH, lactate dehydrogenase; lurbi, lurbinectedin; MC1D1, maintenance Cycle 1 Day 1; PCI, prophylactic cranial irradiation; q3w, every 3 weeks; R, randomization; ULN, upper limit of normal; Y/N, yes/no.

What?
did the study show

IRF-PFS from randomization into maintenance phase



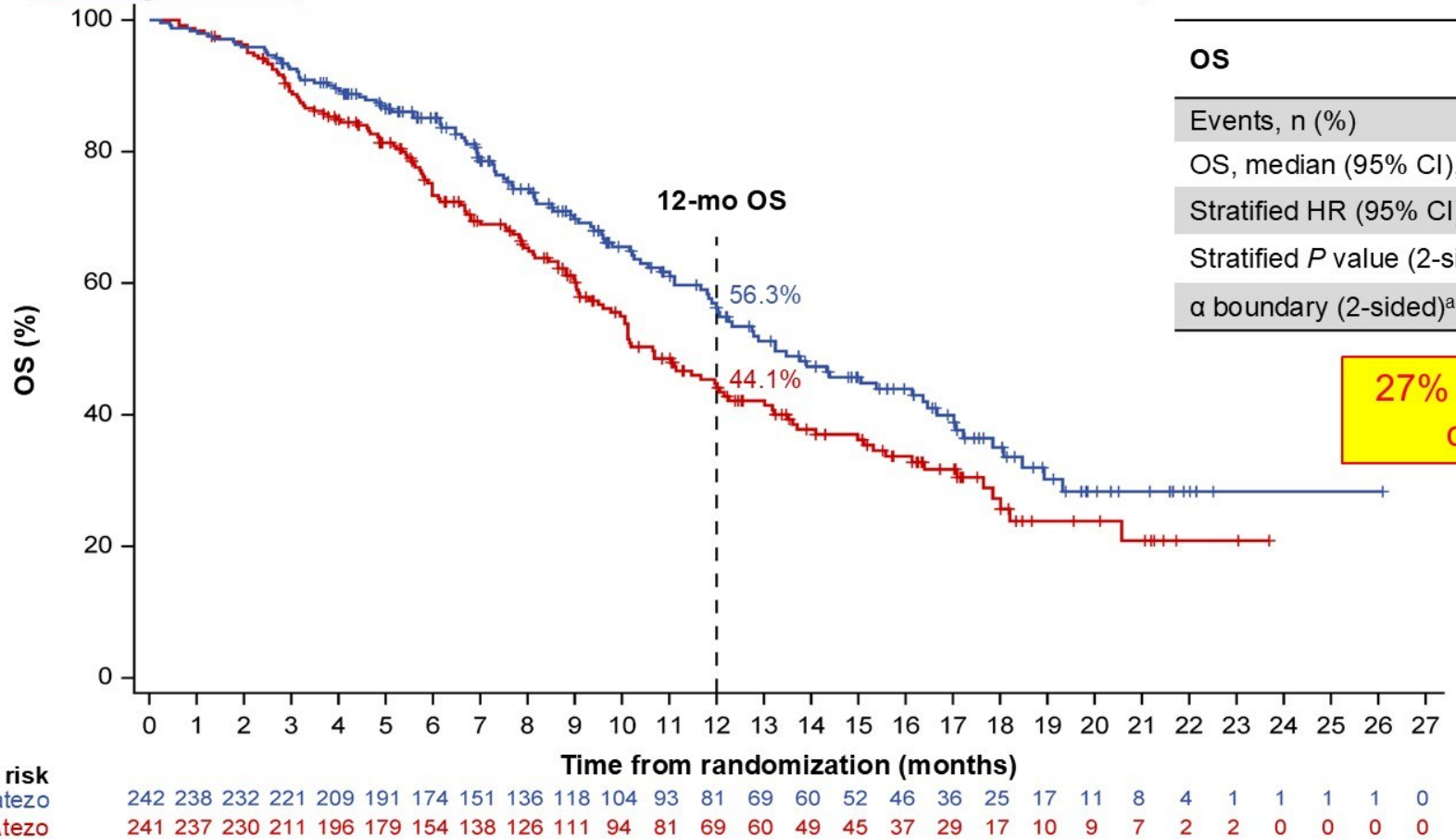
IRF-PFS	Lurbi + atezo (n=242)	Atezo (n=241)
Events, n (%)	174 (71.9)	202 (83.8)
PFS, median (95% CI), mo	5.4 (4.2, 5.8)	2.1 (1.6, 2.7)
Stratified HR (95% CI)	**0.54 (0.43, 0.67)**	
Stratified *P* value (2-sided)	<0.0001	
α boundary (2-sided)	0.001	

46% reduction in the risk of progression or death

Clinical cutoff: July 29, 2024; median survival follow-up: 15.0 mo (minimum follow-up: 3.0 mo).
CI, confidence interval; HR, hazard ratio.

What?
did the study show

OS from randomization into maintenance phase



OS	Lurbi + atezo (n=242)	Atezo (n=241)
Events, n (%)	113 (46.7)	136 (56.4)
OS, median (95% CI), mo	13.2 (11.9, 16.4)	10.6 (9.5, 12.2)
Stratified HR (95% CI)	**0.73 (0.57, 0.95)**	
Stratified *P* value (2-sided)	0.0174	
α boundary (2-sided)[a]	0.0313	

27% reduction in the risk of death compared to atezo alone

Clinical cutoff: July 29, 2024; median survival follow-up: 15.0 mo (minimum follow-up: 3.0 mo).
[a] As determined by the Hwang-Shih-Decani alpha spending function with the gamma parameter of −1.5.

IMforte: Why? Practice-changing

- First recent successful study to show maintenance benefit in aggressive SCLC
- OS benefit
- PFS benefit

Extensive-Stage Small Cell Lung Cancer: Second-Line Treatment

PRESENTED BY: Eric K. Singhi, MD @lungoncdoc

Extensive-Stage Small Cell Lung Cancer: Second-Line Treatment

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2025
Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[g]
Consider dose reduction or growth factor support for patients with PS 2

CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS

Preferred Regimens
- Clinical trial enrollment
- Re-treatment with platinum-based doublet[h,15-19]

Other Recommended Regimens
- Lurbinectedin[20,21]
- Topotecan oral (PO) or intravenous (IV)[22-25]
- Irinotecan[i,25,26]
- Tarlatamab-dlle[j,28]

CTFI ≤6 MONTHS

Preferred Regimens
- Clinical trial enrollment
- Lurbinectedin[20,21]
- Topotecan oral (PO) or intravenous (IV)[17,22-25]
- Irinotecan[i,25,26]
- Tarlatamab-dlle[j,28]
- Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[h,17-19]

Other Recommended Regimens
- Nivolumab[k] or pembrolizumab (if not previously treated with an ICI)[d,29-33]
- Paclitaxel[34,35]
- Temozolomide[36,37]
- Cyclophosphamide/doxorubicin/vincristine (CAV)[22]
- Docetaxel[38]
- Gemcitabine[27,39,40]
- Oral etoposide[41,42]

- Trial enrollment preferred
- Options remain limited
- Tarlatamab a new option

How best to sequence?

Ganti, Apar Kishor P., et al. "Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology." *Journal of the National Comprehensive Cancer Network*, vol. 19, no. 12, 2021, pp. 1441–1464. https://doi.org/10.6004/jnccn.2021.0058

2024 ASCO® ANNUAL MEETING

Tarlatamab versus chemotherapy as second-line treatment for small cell lung cancer (SCLC): primary analysis of the phase 3 DeLLphi-304 study

Charles M. Rudin, Giannis S. Mountzios, Longhua Sun, Byoung Chul Cho, Umut Demirci, Sofia Baka, Mahmut Gumus, Antonio Lugini, Tudor-Eliade Ciuleanu, Myung-Ju Ahn, Pedro Rocha, Bo Zhu, Fiona Blackhall, Tatsuya Yoshida, Taofeek K. Owonikoko, Luis Paz-Ares, Shuang Huang, Diana Gauto, Gonzalo Recondo, Martin Schuler

Speaker: **Charles M. Rudin, MD, PhD,** Fiona and Stanley Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York, USA.

Who?
was studied

Randomized, controlled, phase 3 DeLLphi-304 study (NCT05740566)

DeLLphi 304

Key inclusion criteria

- Histologically or cytologically confirmed SCLC
- Progression after 1L platinum-based chemotherapy +/- anti-PD-(L)1
- ECOG PS 0 or 1
- Asymptomatic, treated or untreated brain metastases

Randomization stratified by

- Prior anti-PD-(L)1 exposure (yes/no)
- Chemotherapy-free interval (< 90 days vs ≥ 90 and < 180 days vs ≥ 180 days)
- Presence of (previous/current) brain metastases (yes/no)
- Intended chemotherapy (topotecan/amrubicin vs lurbinectedin)

R
1:1
(N = 509)

Tarlatamab (n = 254)

Chemotherapy* (n = 255)

Topotecan (n = 185); Lurbinectedin (n = 47); Amrubicin (n = 23)

~18% received lurbi

Primary Endpoint: Overall survival
Key Secondary Endpoints: Progression-free survival, patient-reported outcomes
Other Secondary Endpoints: Objective response, disease control, duration of response, safety

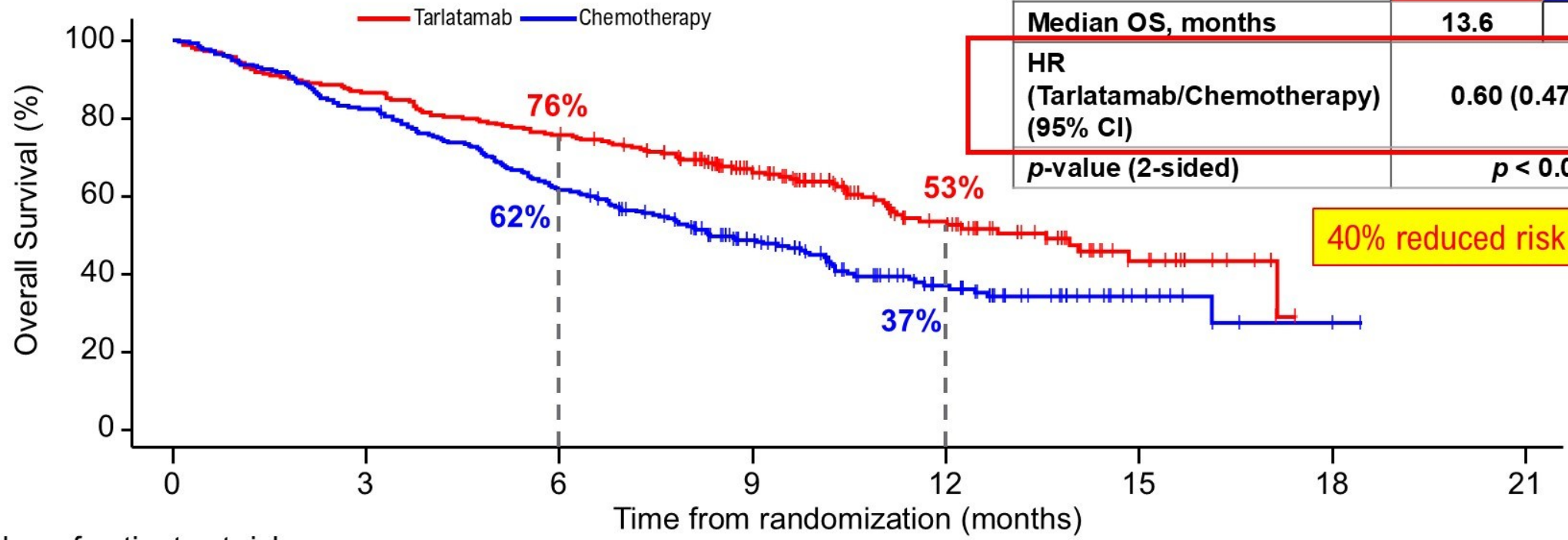
*Topotecan was used in all countries except Japan, lurbinectedin in Australia, Canada, Republic of Korea, Singapore and the US. Amrubicin was used in Japan.
1L, first-line; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **PD-(L)1,** programmed death (ligand)-1; **R,** randomization; **SCLC,** small cell lung cancer.

What?
did the study show

DeLLphi-304 met its primary endpoint with tarlatamab demonstrating superior overall survival over chemotherapy

	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median OS, months	13.6	8.3
HR (Tarlatamab/Chemotherapy) (95% CI)	0.60 (0.47, 0.77)	
p-value (2-sided)	$p < 0.001$	

40% reduced risk of death



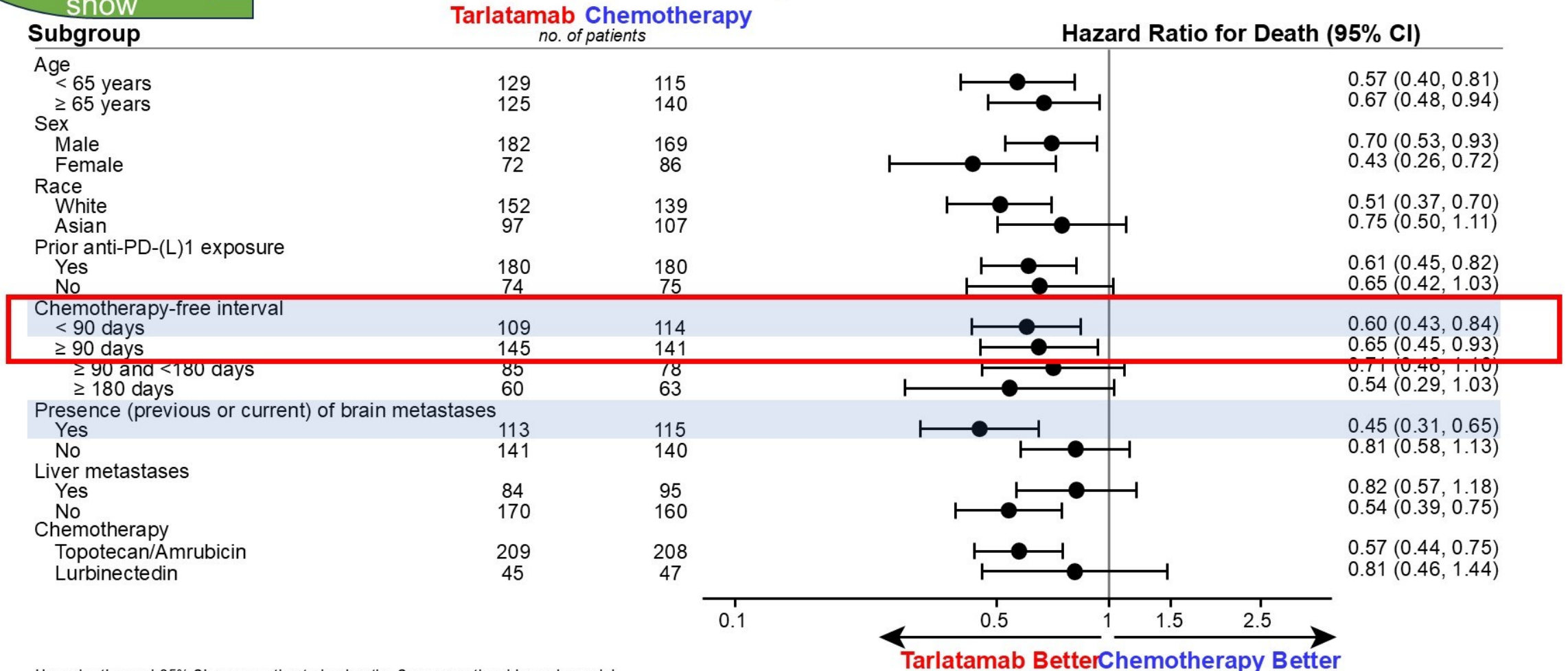
Number of patients at risk:

Tarlatamab	254	220	192	131	60	17	0
Chemotherapy	255	210	156	97	42	9	2	0

Median follow-up time: 11.2 months for the tarlatamab group and 11.7 months for the chemotherapy group. *p*-value was calculated using a stratified log-rank test.
HR, hazard ratio; **OS**, overall survival.

What? did the study show

Survival benefit with tarlatamab was consistent across prespecified patient subgroups



Hazard ratios and 95% CIs were estimated using the Cox proportional hazards model.
PD-(L)1, programmed cell death (ligand)-1.

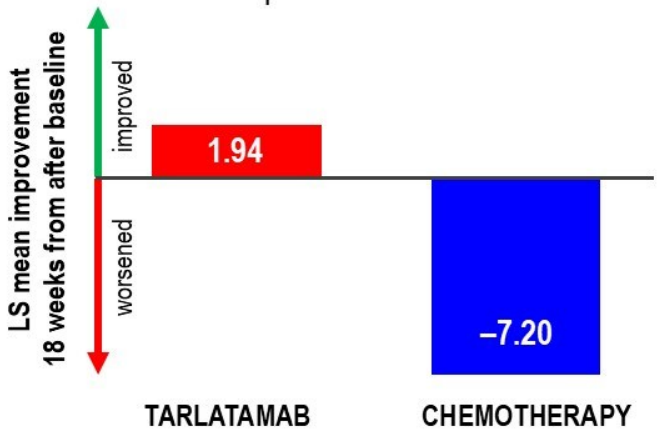
What? did the study show

Tarlatamab improved symptoms of dyspnea and cough after 18 weeks from baseline

Significantly improves patient-reported outcomes v chemotherapy

Dyspnea

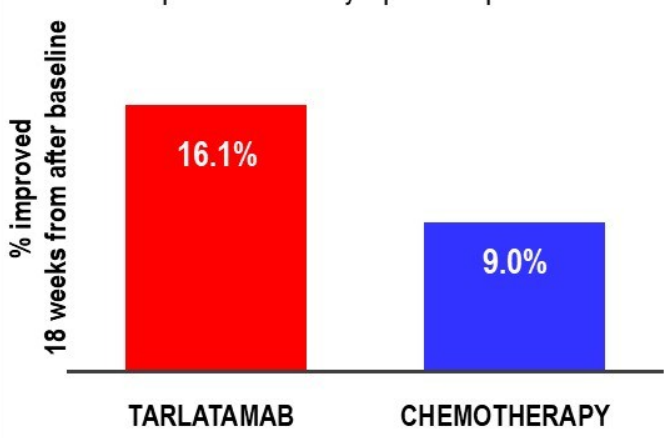
mean improvement from baseline



LS mean difference = -9.14*
95%CI (-12.64, -5.64)
***p*<0.001**

Cough

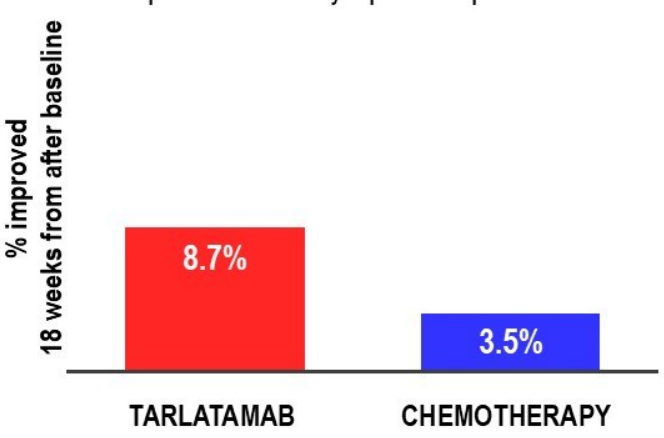
% patients with symptom improvement



Odds ratio = 2.04*
95%CI (1.17, 3.55)
***p*=0.012**

Chest Pain

% patients with symptom improvement



Odds ratio = 1.84*
95%CI (0.89, 3.81)
***p*=0.1**
(Did not meet statistical significance)

*Similar results were observed when the sensitivity analyses were carried out incorporating a more conservative estimand (i.e., treatment policy strategy) for change from baseline after 18 weeks in **dyspnea** (mean difference, -6.19; [95% CI, -8.88 to -3.49]), **cough** (odds ratio, 1.48 [95% CI, 1.08 to 2.02]), **chest pain** (odds ratio, 1.21 [95% CI, 0.80 to 1.82]), **physical functioning** (mean difference, 5.98 [95% CI, 2.75 to 9.22]), and **global health status** (mean difference, 5.04 [95% CI, 2.46 to 7.62]).

The change from baseline after 18 weeks in symptoms of chest pain, cough, and dyspnea were measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and the supplementary symptom scores for Lung Cancer (QLQ-LC13). Change from baseline after 18 weeks in chest pain and cough were analyzed using generalized linear mixed model (GLMM) with a cumulative logit link. Change from baseline after 18 weeks in dyspnea was analyzed using mixed effects model with repeated measures (MMRM) with a restricted maximum likelihood estimator method (REML). A hypothetical estimand strategy was pre-specified for these key seocondary PRO endpoints. Clinically meaningful improvement in chest pain and cough was defined as improving at least 1 level in the response categories. Difference in dyspnea score between groups with more than 9 points is considered clinically meaningful.
LS, least squares.

Tarlatamab had a more favorable safety profile

	Tarlatamab (n = 252)*	Chemotherapy (n = 244)*
Median duration of treatment, months, (range)	4.2 (< 1–17)	2.5 (< 1–15)
All grade, TEAEs, n (%)	249 (99)	243 (100)
All grade, TRAEs n (%)	235 (93)	223 (91)
Grade ≥ 3 TRAEs, n (%)	67 (27)	152 (62)
Serious TRAEs, n (%)	70 (28)	75 (31)
TRAEs leading to dose interruption and/or dose reduction, n (%)	48 (19)	134 (55)
TRAEs leading to discontinuation, n (%)	7 (3)	15 (6)
Treatment-related grade 5 events†, n (%)	1 (0.4)	4 (2)

Tarlatamab w/ LOWER rate of:
- High-grade AEs
- AEs leading to treatment discontinuation

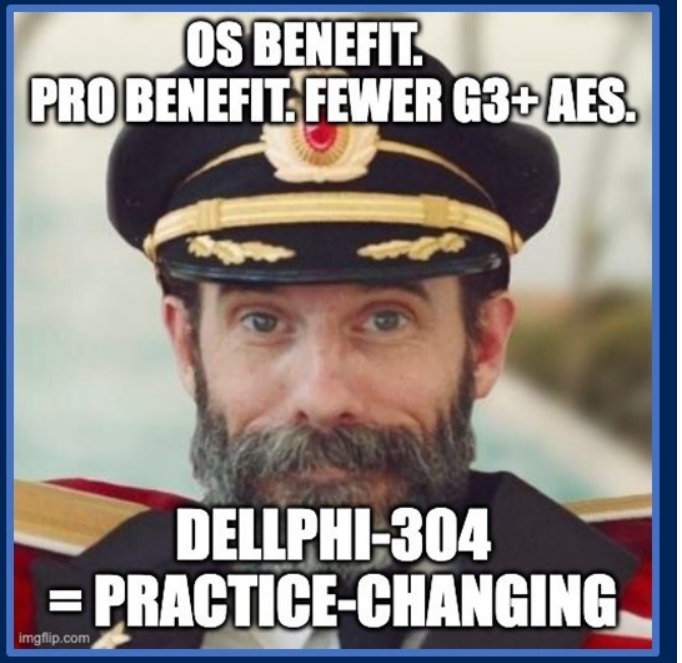
*Safety analysis set (all patients who received at least one dose of study treatment. †The single grade 5 TRAE observed with tarlatamab was attributed to ICANS in the setting of progressive neurological decline concurrent with persistent fever, hypoxemia, and hypotension. Grade 5 TRAEs observed with chemotherapy were attributed to general physical health deterioration (n = 1), pneumonia (n = 1), respiratory tract infection (n = 1), and tumor lysis syndrome (n = 1).
TEAE, treatment-emergent adverse event; **TRAE,** treatment-related adverse event.

DeLLphi-304

Why?

Practice-changing

- OS benefit
- Symptom improvement
- Benefits both platinum-sensitive & platinum-refractory disease
- Lower rate of high-grade AEs v chemotherapy



Conclusions

- Neoadjuvant therapy for resectable NSCLC:
  - Without AGA: CM816 (3 cycles of chemoIO) is a strong option, now with proven OS benefit.
  - With EGFR mutation: Neoadjuvant osimertinib (+/- chemo) improves MPR, however, pCR rates are low; adjuvant osimertinib (ADAURA) is (my) preferred regimen with proven OS benefit.

- Systemic therapy for ES-SCLC
  - 1L: Atezolizumab plus lurbinectedin maintenance should be new standard of care, offering PFS and OS benefits.
  - 2L: Tarlatamab outperforms standard chemotherapy with proven OS benefit, presenting a key option for all patients, despite delivery challenges

2025 ASCO ANNUAL MEETING

Highlights of the Day

Metastatic Non-small cell Lung Cancer

Sarah B. Goldberg, MD
Associate Professor of Medicine (Medical Oncology)
Yale School of Medicine

Abstracts to highlight

NSCLC with common EGFR mutations progressing on TKI therapy

- Patritumab deruxtecan (HERTHENA-Lung02 study)
- Savolitinib plus osimertinib (SACHI study)

Previously-treated EGFR exon 20 insertion-mutant NSCLC

- Zipalertinib (REZILIENT1 study)

HER2-mutant NSCLC without prior TKI

- Sevabertinib (SOHO-01 study)

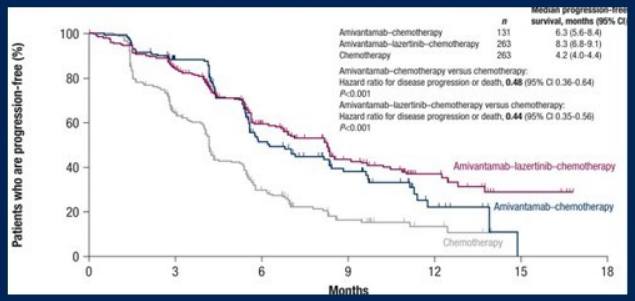
PRESENTED BY: Sarah B. Goldberg, MD

Treatment options in patients with common EGFR mutations after first-line EGFR TKI

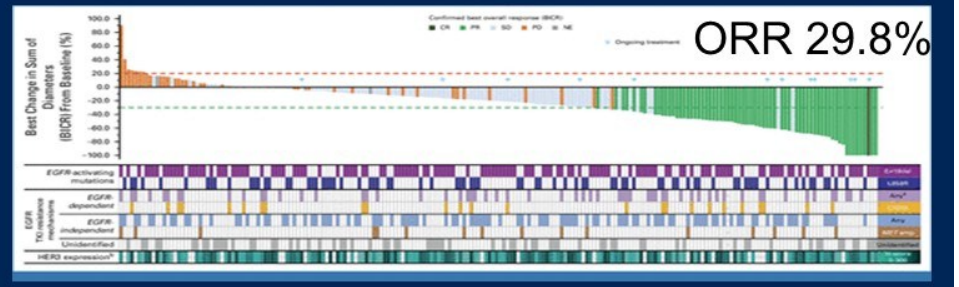
- After progression on a third-generation EGFR TKI, standard second-line treatment is platinum-based chemotherapy with amivantamab

- Patritumab deruxtecan (HER3 DXd) is an antibody drug conjugate directed against HER3 with activity in patients with EGFR-mutant lung cancer

MARIPOSA-2



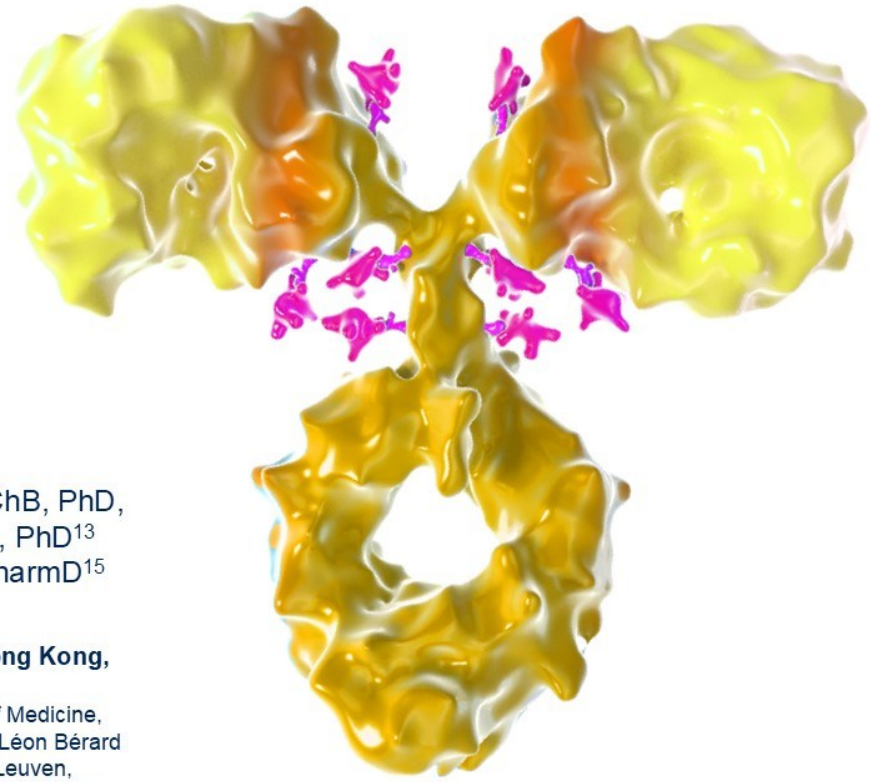
HERTHENA-Lung01



Passaro A, Ann Oncol 2024
Yu HA, et al. J Clin Oncol 2023

2025 ASCO ANNUAL MEETING

Patritumab Deruxtecan (HER3-DXd) in Resistant *EGFR*-Mutated Advanced NSCLC After a Third-Generation EGFR TKI: The Phase 3 HERTHENA-Lung02 Study



Tony S. K. Mok, MD, FRCPC, FASCO[1]

Helena A. Yu, MD[2] Sun Min Lim, MD, PhD[3] Isamu Okamoto, MD, PhD[4] Maurice Pérol, MD[5] Silvia Novello, MD, PhD[6] Christophe Dooms, MD, PhD[7] Jong-Mu Sun, PhD[8] Steven Kao, BHB, MBChB, PhD, FRACP[9] Pasi A. Jänne, MD, PhD[10] Martin Reck, MD, PhD[11] Conor Steuer, MD[12] Makoto Nishio, MD, PhD[13] Yi-Long Wu, MD[14] Ronan Fougeray, MS[15] Ragini Kudchadkar, MD[15] Jian Yu Wu[16] Stephen Esker, PharmD[15] Antonio Passaro, MD, PhD[17]

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Study design

HERTHENA-Lung02: A phase 3, global, multi-center, randomized, open-label study[1]

Select Eligibility Criteria

- **Advanced nonsquamous NSCLC with an *EGFR*-activating mutation (exon 19 deletion or L858R)**
- **1 or 2 prior line(s) of an approved EGFR TKI (must include a third-generation EGFR TKI)**
  - Non-osimertinib third-generation TKIs ≤20% in each arm
- **Disease progression while receiving or after a third-generation EGFR TKI**
- **No other prior systemic therapies for advanced disease**
- **Pretreatment tumor biopsy or archived tumor tissue since progression was required**
- **Stable brain metastases (asymptomatic and not requiring corticosteroids or anticonvulsants) were permitted**

586 patients; study start date, 08 July 2022

Randomized 1:1

HER3-DXd (N=293)
Patritumab deruxtecan
5.6 mg/kg IV Q3W

No crossover

PBC (N=293)
Cisplatin 75 mg/m^2
or carboplatin AUC5
Q3W (× 4 cycles)
+ Pemetrexed 500 mg/m^2 Q3W[a]

Final analysis of primary endpoint, PFS

Interim analysis 2 for OS; data not mature

End of study

Stratification

- Third generation EGFR TKI (osimertinib, other)
- Line of third generation EGFR TKI (first, second)
- Region (Asia, Non-Asia)
- Stable brain metastases (Present, Absent)

Primary Endpoint

- PFS (by BICR per RECIST)

Secondary Endpoints

- Key secondary: OS
- Other Secondary:
  - Safety
  - Intracranial PFS in patients with baseline brain metastases (by CNS BICR per CNS RECIST)[b]
  - HER3 protein expression and its relationship with efficacy
    (Analysis of the potential role of HER3 expression by IHC as a predictive biomarker of response to HER3-DXd in HERTHENA-Lung02 is ongoing)

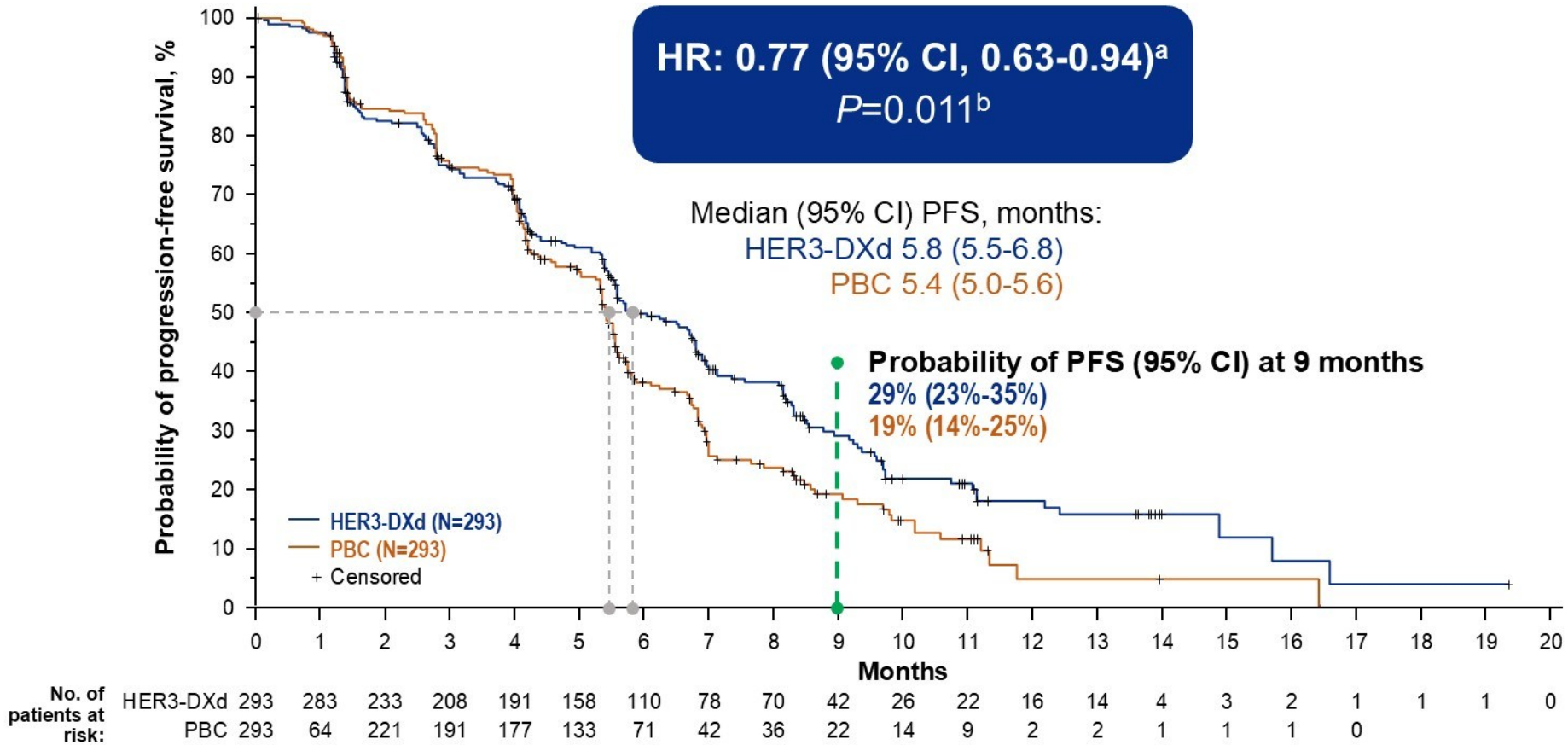
AUC5, area under curve of 5 mg/mL•min; BICR, blinded independent central review; CNS, central nervous system; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors v1.1; TKI, tyrosine kinase inhibitor.
[a] No limit to number of pemetrexed cycles as it is given as maintenance as per labeling. [b] Brain imaging was centrally assessed by a separate, blinded group of neuro-oncologists (CNS BICR) according to the CNS RECIST criteria.[2]

1. Mok TSK, et al. *Future Oncol.* 2024;20(15):969-980. 2. Yu HA, et al. *J Clin Oncol.* 2023;41(35):5363-5375.

PRESENTED BY: Prof. Tony S. K. Mok, MD, FRCPC, FASCO

ClinicalTrials.gov Identifier: NCT05338970
Eudra Clinical Trial Identifier: 2021-005879-40
Japan Clinical Trial Identifier: jRCT2021220002

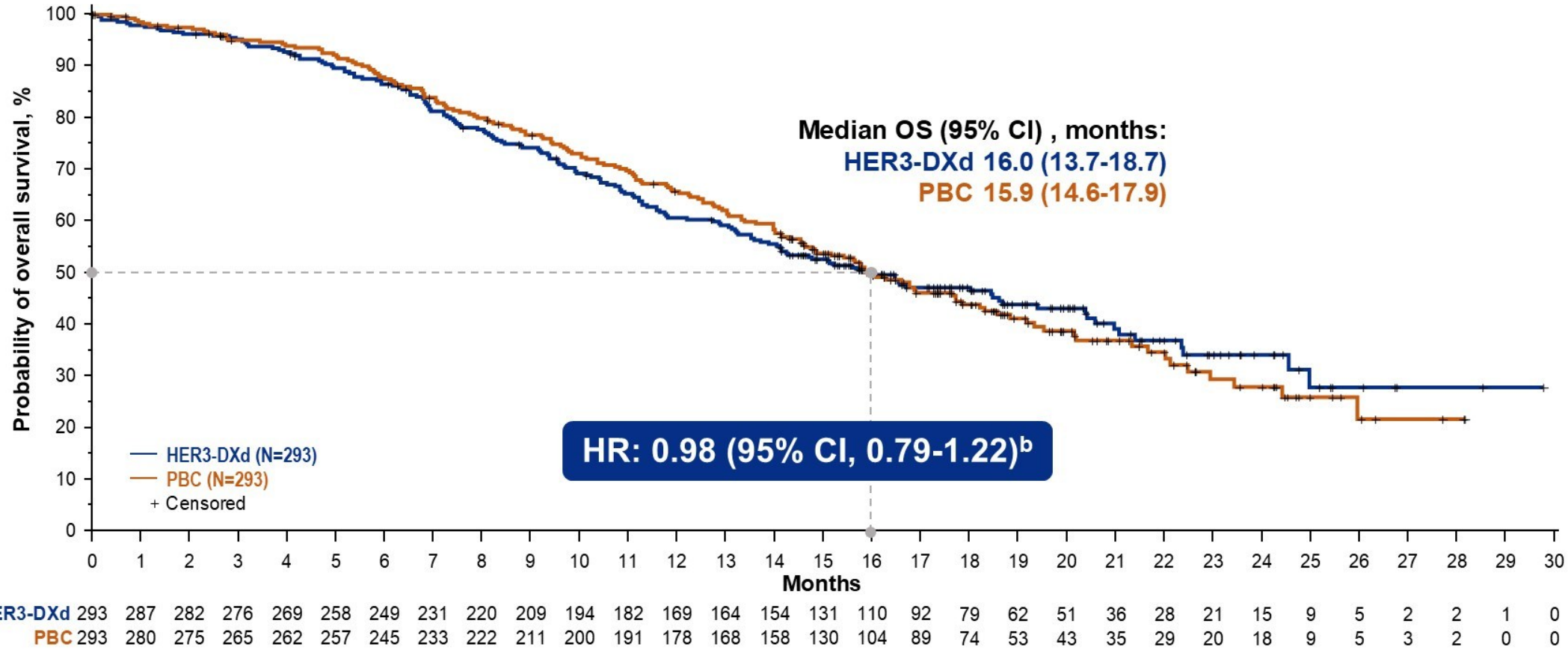
HER3-DXd significantly reduced the risk of disease progression (by BICR per RECIST) or death vs PBC



Median study duration: HER3-DXd, 10.7 (range, 5.2-21.5) months; PBC, 10.7 (range, 5.2-21.9) months.
BICR, blinded independent central review; HR, hazard ratio; ITT, intention to treat; PBC, platinum-based chemotherapy; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors v1.1.
[a] For disease progression or death. [b] Stratified log-rank test, ITT population; efficacy boundary for superiority, $P<0.04998$.

Newly available mature data from extended follow-up (data cutoff: Feb 28, 2025)[a]

OS for patients treated with HER3-DXd compared to PBC



Median follow-up: HER3-DXd, 18.7 months (95% CI, 17.9-19.9 months); PBC, 18.6 months (95% CI, 17.9-19.6 months).

HR, hazard ratio; OS, overall survival; PBC, platinum-based chemotherapy.

[a] 327 of 393 events had occurred; information fraction, 83%. [b] For death from any cause. Cox proportional hazards model stratified by randomization stratification factors.

Take home points

- HER3-DXd has acti… improvement in PFS and ORR comp… however there was no OS benefit
- HER3-DXd was mo… apy
- There are many oth… nt lung cancer and I anticipate tha… ctice in the future – but not this…

Patritumab Deruxtecan Biologics License Application for Patients With Previously Treated Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer Voluntarily Withdrawn

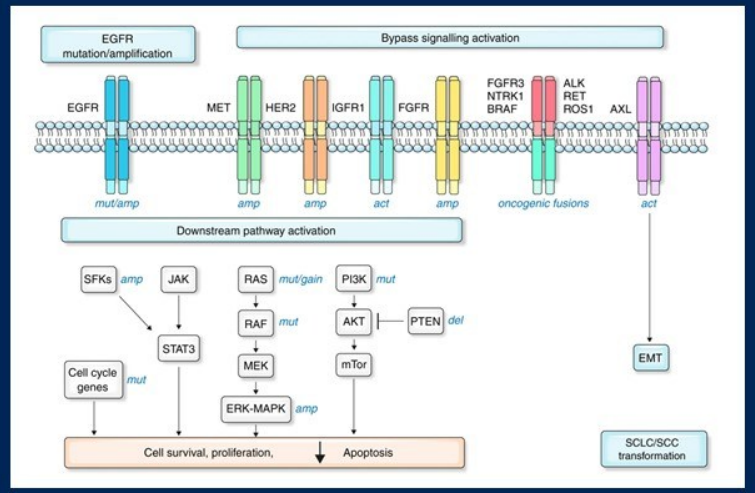
May 29, 2025 7:00 am ET

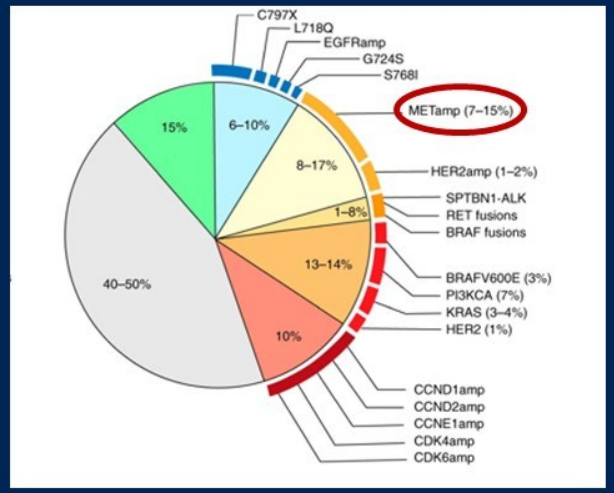
BASKING RIDGE, N.J. & RAHWAY, N.J., May 29, 2025 – The Biologics License Application (BLA) seeking accelerated approval in the U.S. for Daiichi Sankyo (TSE: 4568) and Merck's (NYSE: MRK), known as MSD outside of the United States and Canada, patritumab deruxtecan (HER3-DXd), based on the HERTHENA-Lung01 Phase 2 trial for the treatment of adult patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) previously treated with two or more systemic therapies, has been voluntarily withdrawn.

The decision to withdraw the BLA is based on topline overall survival (OS) results from the confirmatory HERTHENA-Lung02 Phase 3 trial where OS did not meet statistical significance, as well as discussions with the U.S. Food and Drug Administration. The decision is unrelated to the

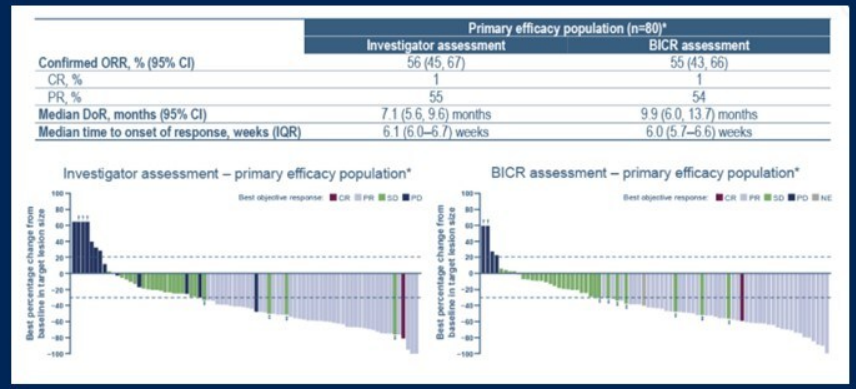
Targeting MET in EGFR TKI-resistant disease

- MET amplification is a known mechanisms of resistance to osimertinib
- Targeting MET with a MET TKI has demonstrated benefit in several trials





Osimertinib plus savolitinib in patients with EGFR-mutant NSCLC with MET amplification or overexpression (SAVANNAH)



	Primary efficacy population (n=80)*	
	Investigator assessment	BICR assessment
Confirmed ORR, % (95% CI)	56 (45, 67)	55 (43, 66)
CR, %	1	1
PR, %	55	54
Median DoR, months (95% CI)	7.1 (5.6, 9.6) months	9.9 (6.0, 13.7) months
Median time to onset of response, weeks (IQR)	6.1 (6.0–6.7) weeks	6.0 (5.7–6.6) weeks

Leonetti A, et al. BJC 2019
Ahn M-J, et al. ELCC 2025

2025 ASCO ANNUAL MEETING

Savolitinib combined with osimertinib versus chemotherapy in EGFR-mutant and MET-amplified advanced NSCLC after disease progression on EGFR tyrosine kinase inhibitor: results from a randomized phase 3 SACHI study

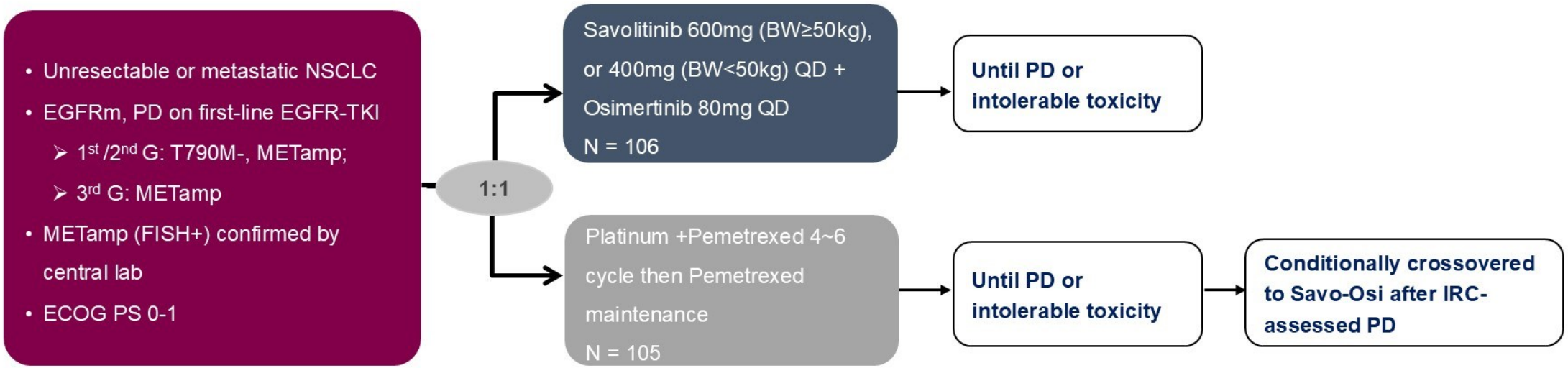
Shun Lu[1], Jie Wang[2], Nong Yang[3], Dongqing Lv[4], Lijuan Chen[5], Lin Wu[3], Xingya Li[6], Longhua Sun[7], Yongfeng Yu[1], Bo Jin[8], Lin Yang[9], Yubiao Guo[10], Haipeng Xu[11], Tienan Yi[12], Aiping Zeng[13], Xiaorong Dong[14], Jianhua Chen[3], Ziping Wang[15], Tony Mok[16], Weiguo Su[17]

1. Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; 2. Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China: 3. Hunan Cancer Hospital, Changsha, China; 4. Taizhou Hospital of Zhejiang Province, Taizhou, China; 5. Henan Cancer Hospital, Zhengzhou, China; 6. First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; 7. First Affiliated Hospital of Nanchang University, Nanchang, China; 8. The First Hospital of China Medical University, Shenyang, China; 9. Shenzhen People's Hospital, Shenzhen, China; 10. The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; 11. Fujian Provincial Cancer Hospital, Fuzhou, China; 12. Xiangyang Central Hospital, Xiangyang, China; 13. The Cancer Hospital Affiliated to Guangxi Medical University, Nanning, China; 14. Union Hospital Tongji Medical College Huazhong University of Science and Technology, Wuhan, China; 15. Beijing Cancer Hospital, Beijing, China; 16. Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong, Hongkong, China; 17. HUTCHMED, Shanghai, China

PRESENTED BY: Shun Lu, MD, PhD

SACHI Phase 3 Study Design

Randomized, open-label, multi-center phase 3 study conducted across 68 centers in China.



METamp:

- **Post 1st /2nd G:** MET copy number ≥5 or MET/CEP7 ≥2
- **Post 3rd G:** MET copy number ≥ 10

Stratification factors:

- **Brain metastasis**: (yes or no)
- **Prior 3rd G EGFR-TKI**: (yes or no)
- **EGFR mutation**: (ex19del vs L858R vs others)

Primary endpoint: PFS by investigator

Secondary endpoints: PFS by IRC, ORR, DCR, DoR, TTR, PFS, OS, safety

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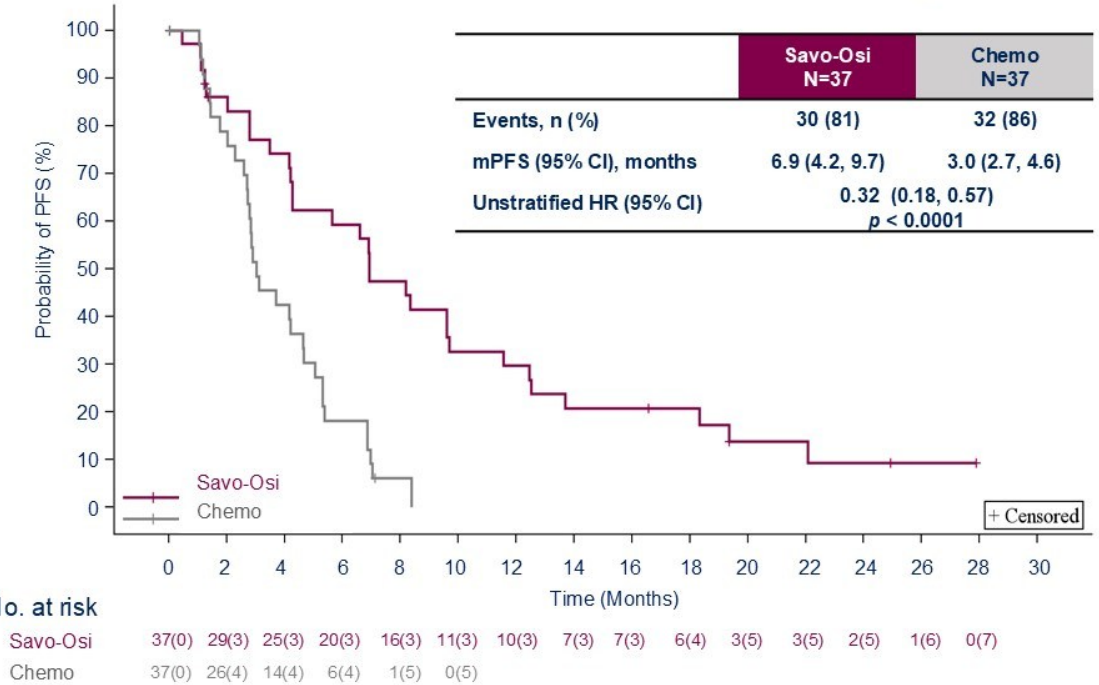
1st /2nd G: first or second generation; 3rd G: third generation; BW: body weight; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EGFRm, EGFR mutant; FISH, fluorescence in situ hybridization; IRC, independent review committee; METamp, MET amplification; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progression disease; PFS, progression-free survival; QD, once daily; Savo-Osi, Savolitinib-Osimertinib; TKI, tyrosine kinase inhibitor; TTR, time to response.

Progression-free Survival

Investigator assessed

Prior 3rd G EGFR-TKI treated subgroup

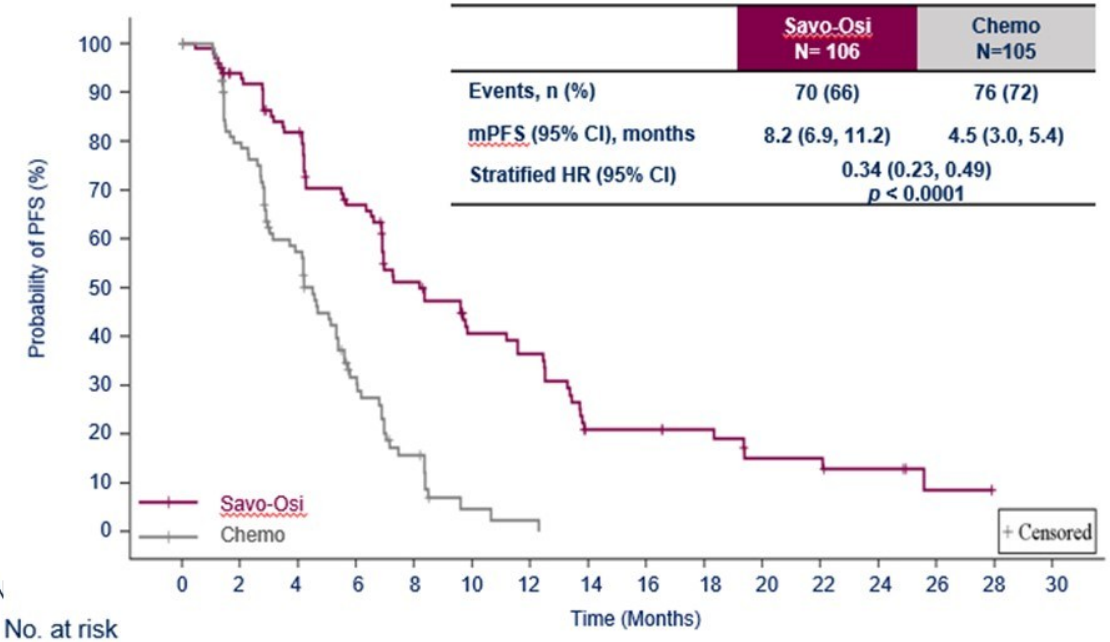


	Savo-Osi N=37	Chemo N=37
Events, n (%)	30 (81)	32 (86)
mPFS (95% CI), months	6.9 (4.2, 9.7)	3.0 (2.7, 4.6)
Unstratified HR (95% CI)	0.32 (0.18, 0.57) $p < 0.0001$	

No. at risk

Savo-Osi	37(0)	29(3)	25(3)	20(3)	16(3)	11(3)	10(3)	7(3)	7(3)	6(4)	3(5)	3(5)	2(5)	1(6)	0(7)
Chemo	37(0)	26(4)	14(4)	6(4)	1(5)	0(5)									

ITT population



	Savo-Osi N= 106	Chemo N=105
Events, n (%)	70 (66)	76 (72)
mPFS (95% CI), months	8.2 (6.9, 11.2)	4.5 (3.0, 5.4)
Stratified HR (95% CI)	0.34 (0.23, 0.49) $p < 0.0001$	

No. at risk

Savo-Osi	106(0)	86(14)	73(16)	57(19)	41(22)	29(26)	26(26)	13(28)	13(28)	11(30)	7(31)	7(31)	5(32)	2(34)	0(36)
Chemo	105(0)	69(18)	47(21)	22(26)	10(27)	2(29)	1(29)	0(29)							

PFS benefits in the population progressing on prior 3rd G EGFR-TKI treatment were comparable to those in ITT and prior 1st /2nd G EGFR-TKI treated populations.

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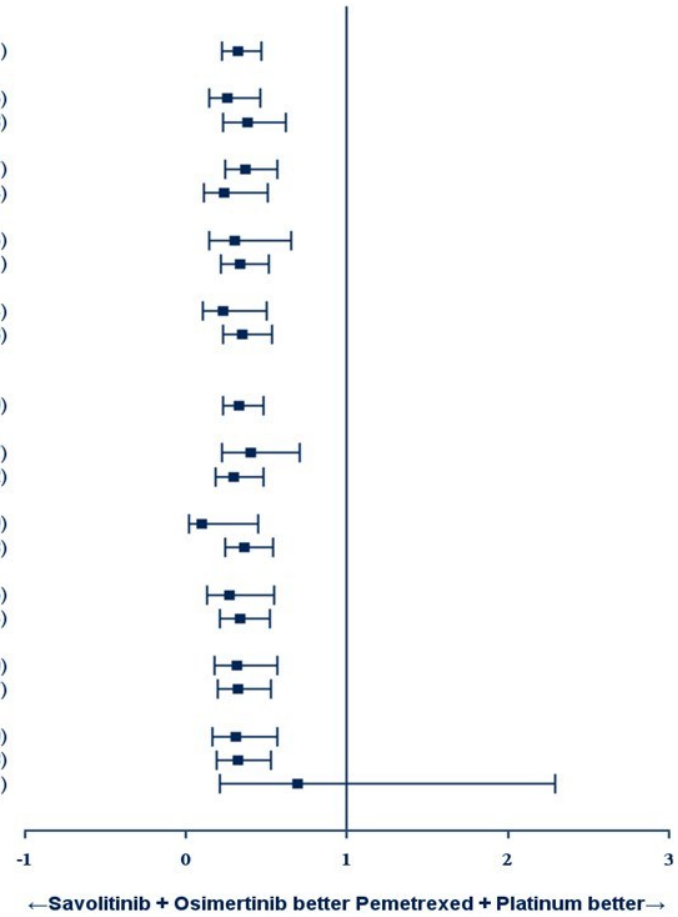
Median duration of PFS follow-up: 24.9 months (95%CI: 6.6, NE) for investigator assessment, and 19.4 months (95%CI: 11.1, NE) for IRC assessment.
3rd G: third generation; chemo, chemotherapy; CI: confidence interval; EGFR, epidermal growth factor receptor; HR: hazard ratio; ITT, intent to treat; (m)PFS, (median) progression-free survival; Savo-Osi, Savolitinib-Osimertinib; TKI, tyrosine kinase inhibitor.

Progression-free Survival: Subgroups in ITT

Investigator

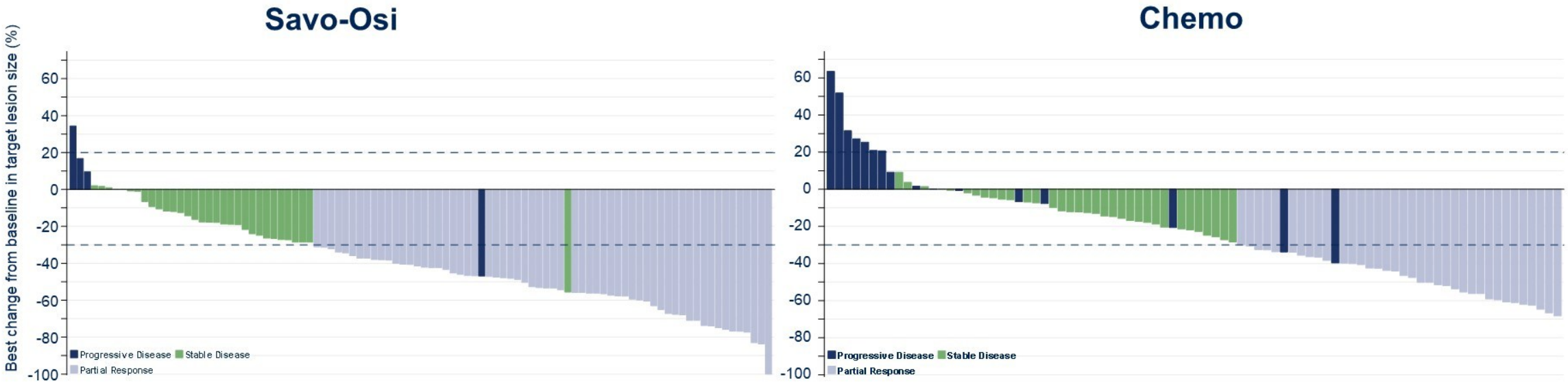
Subgroup	Savolitinib + Osimertinib Event/N	Pemetrexed + Platinum Event/N	HR (95%CI)
Overall	70/106	76/105	0.325 (0.224, 0.471)
Sex			
Male	26/44	39/50	0.259 (0.145, 0.463)
Female	44/62	37/55	0.379 (0.232, 0.618)
Age at randomization			
< 65	54/77	49/65	0.369 (0.240, 0.567)
>= 65	16/29	27/40	0.234 (0.108, 0.504)
Baseline ECOG performance status			
0	20/28	18/27	0.304 (0.142, 0.653)
1	50/78	58/78	0.333 (0.217, 0.511)
Smoking status			
Current/Previous smoker	17/28	21/27	0.230 (0.105, 0.504)
Nonsmoker (Never)	53/78	55/78	0.349 (0.228, 0.536)
Current tumor stage			
IIIB/IIIC	0/1	3/6	
IV/IVA/IVB	70/105	73/99	0.330 (0.228, 0.479)
Brain metastases			
Yes	28/38	31/39	0.399 (0.225, 0.707)
No	42/68	45/66	0.297 (0.183, 0.482)
Liver metastases			
Yes	9/11	13/15	0.097 (0.021, 0.449)
No	61/95	63/90	0.362 (0.244, 0.538)
Number of metastases sites			
< 3	19/35	24/31	0.269 (0.133, 0.545)
>= 3	51/70	49/68	0.333 (0.212, 0.524)
Previous use of 3rd generation EGFR-TKI			
Yes	30/37	32/37	0.316 (0.175, 0.569)
No	40/69	44/68	0.324 (0.199, 0.527)
Type of EGFR mutations			
Exon 19 Deletion	24/40	33/41	0.307 (0.166, 0.570)
L858R	38/54	37/52	0.319 (0.193, 0.528)
Other	8/12	6/12	0.694 (0.210, 2.291)



PRESENTED BY: Shun Lu, MD, PhD

chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR: hazard ratio; IRC, independent review committee; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Tumor Response in ITT: Investigator



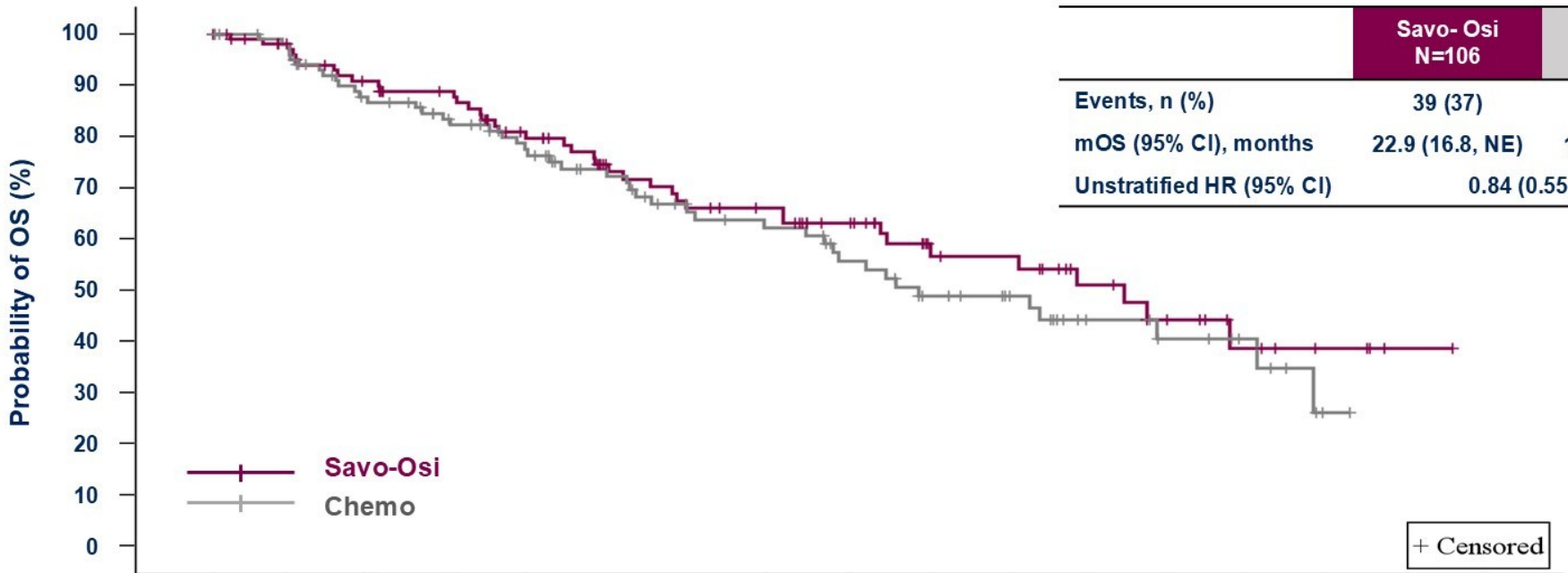
	Savo-Osi N=106	Chemo N=105	Stratified OR (95% CI)
ORR, % (95% CI)	58 (49-68)	34 (25-44)	2.74 (1.50-4.98) *p*=0.0004
DCR, % (95% CI)	89 (81-94)	67 (57-76)	3.98 (1.81-8.82) *p*=0.0001
Median DoR, month (95% CI)	8.4 (5.9-11.1)	3.2 (2.8-4.2)	-

chemo, chemotherapy; CI, confidence interval; DCR, disease control rate; DoR, duration of response; OR, odd ratio; ORR, objective response rate; Savo-Osi, Savolitinib-Osimertinib.

PRESENTED BY: Shun Lu, MD, PhD

Overall Survival-ITT

- OS data were still evolving, with overall maturity of 40%. 55 (52%) patients in Chemo group received subsequent MET inhibitor treatment (including 45 patients receiving study crossover treatment and 10 patients receiving other MET inhibitors).



	Savo- Osi N=106	Chemo N=105
Events, n (%)	39 (37)	45 (43)
mOS (95% CI), months	22.9 (16.8, NE)	17.7 (14.9, 26.3)
Unstratified HR (95% CI)	0.84 (0.55, 1.29)	

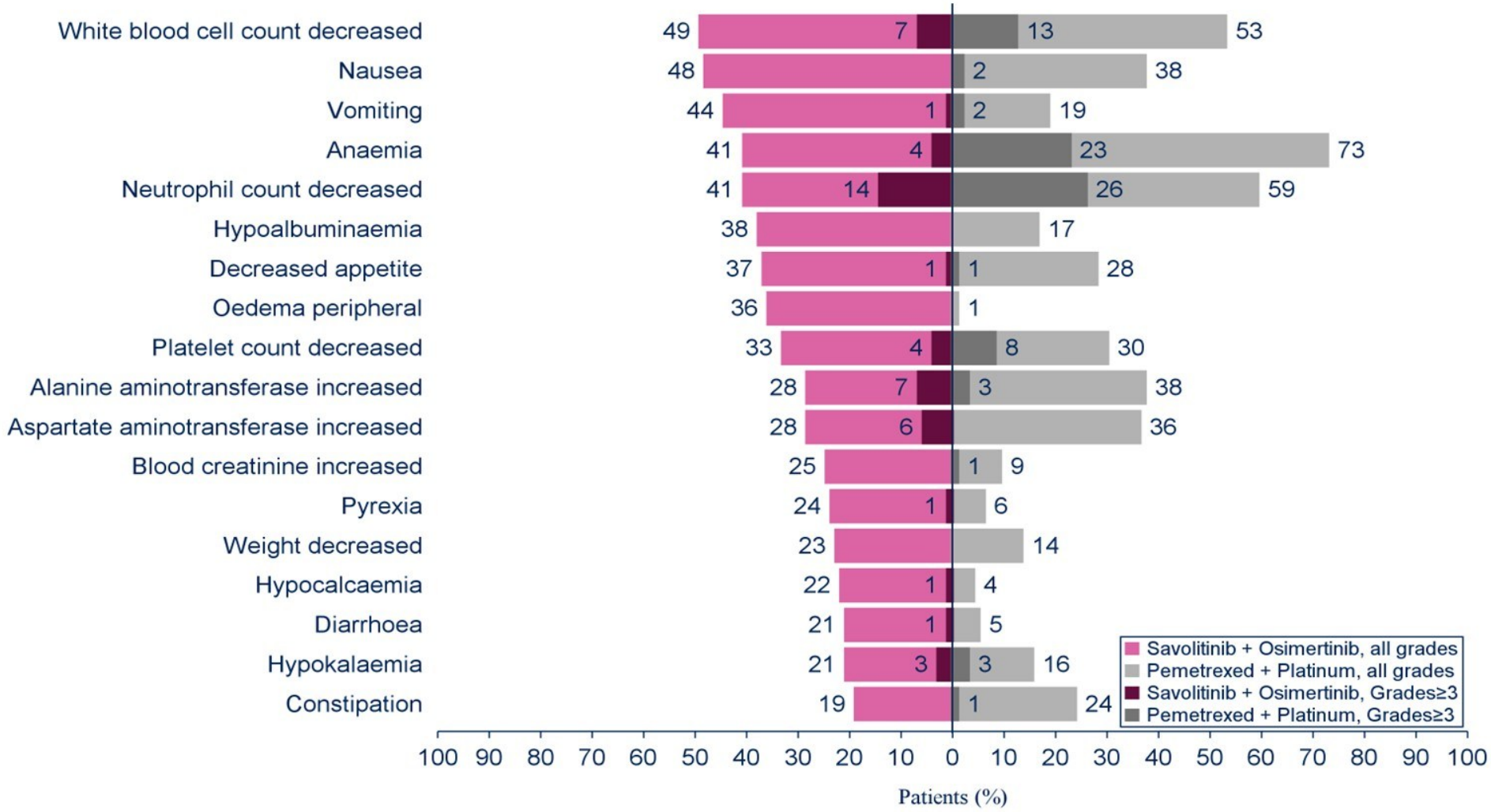
No. at risk

Savo-Osi	106(0)	96(7)	87(10)	80(15)	65(22)	52(30)	47(30)	44(33)	36(39)	25(48)	23(49)	16(54)	11(57)	7(60)	4(63)	1(66)	0(67)
Chemo	105(0)	96(4)	82(10)	72(16)	63(20)	53(27)	43(32)	40(33)	33(36)	26(39)	22(43)	13(50)	10(52)	7(55)	1(59)	0(60)	

PRESENTED BY: Shun Lu, MD, PhD

Median duration of OS follow-up: 17.7 months (95%CI: 15.3, 19.8) for ITT population.
chemo, chemotherapy; CI, confidence interval; HR: hazard ratio; ITT, intent to treat; (m)OS, (median) overall survival; NE, not estimable; Savo-Osi, Savolitinib-Osimertinib; TKI, tyrosine kinase inhibitor.

Adverse Events in ≥ 20% of Patients in Either Group

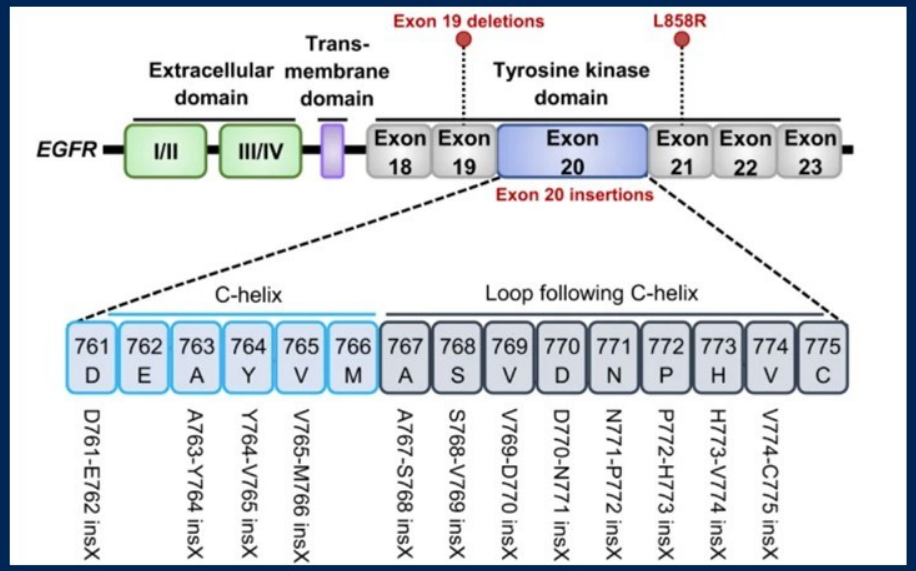


Take home points

- Targeting MET after progression on an EGFR TKI is a viable strategy
- Appropriately testing for MET amplification at resistance to EGFR TKIs is critical
- Osimertinib plus savolitinib has toxicity but is manageable
- Caveats:
  - What is the best cut-off to determine MET amplification?
  - Is platinum/pemetrexed the appropriate comparator for a 2nd line EGFR trial?
  - OS data is immature
  - This study was conducted in China so may not represent a global population
    - Results from the global phase 3 SAFFRON trial are eagerly awaited

EGFR exon 20 mutant NSCLC

- EGFR exon 20 insertion mutations comprise ~10% of all EGFR mutations
- Treatment options include first-line carboplatin/pemetrexed plus amivantamab or second-line amivantamab after progression on chemotherapy
- Despite many efforts, no TKIs are currently approved for this subset of EGFR
- Zipalertinib is an EGFR TKI that with activity against EGFR exon 20 mutations



Zhou C, et al NEJM 2023
Park K, et al. JCO 2021
Vyse S and Huang P. Sig Transduct Targeted Ther. 2019
Piotrowska Z, et al. JCO 2023

2025 ASCO ANNUAL MEETING

Efficacy of zipalertinib in NSCLC patients with EGFR exon 20 insertion mutations who received prior platinum-based chemotherapy with or without amivantamab

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REZILIENT1 Phase 2b study design

- REZILIENT1 is a phase 1/2, open-label, multicenter trial (NCT04036682)

- Safety analysis population: all patients who received ≥1 dose of zipalertinib 100 mg BID (N=244)
- Primary efficacy population: all patients who received ≥1 dose of zipalertinib 100 mg BID with ~8 months of minimum follow-up before data cutoff (December 10, 2024) (N=176)
- Patients were assigned to a cohort based on previous therapy (ie, platinum-based chemotherapy only or amivantamab)

BID, twice daily; CBR, clinical benefit rate; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertions; ICR, independent central review; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors.

Prior therapies

Characteristic	Platinum-based chemotherapy without ex20ins-targeted therapy (n=143)	Prior ex20ins-targeted therapy (n=101)	Safety population (N=244)
Median number of prior systemic regimens, No. (range)	1 (0–6)	2 (1–7)	2 (0–7)
Prior chemotherapy, No. (%)	132 (92)	96 (95)	228 (93)
Prior anti–PD-(L)1, No. (%)	67 (47)	46 (46)	113 (46)
Prior targeted therapy, No. (%)	37 (26)	101 (100)	138 (57)
Amivantamab	0	84 (83)	84 (34)
Mobocertinib	0	40 (40)	40 (16)
Bevacizumab	14 (10)	16 (16)	30 (12)
Osimertinib	13 (9)	7 (7)	20 (8)
BLU-451	0	5 (5)	5 (2)
Cetuximab	4 (3)	0	4 (2)
Poziotinib	0	3 (3)	3 (1)
Sunvozertinib	0	3 (3)	3 (1)
Other[a]	17 (12)	9 (9)	26 (11)
Prior brain radiation, No. (%)	18 (13)	15 (15)	33 (14)
Brain metastasis untreated, No. (%)	30 (21)	40 (40)	70 (29)

[a]Includes first/second generation EGFR tyrosine kinase inhibitors, ALK inhibitors, CDK4/6 inhibitors, NTRK/ROS1 inhibitors, angiokinase inhibitors.
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertions; PD-(L)1, programmed death-(ligand) 1.

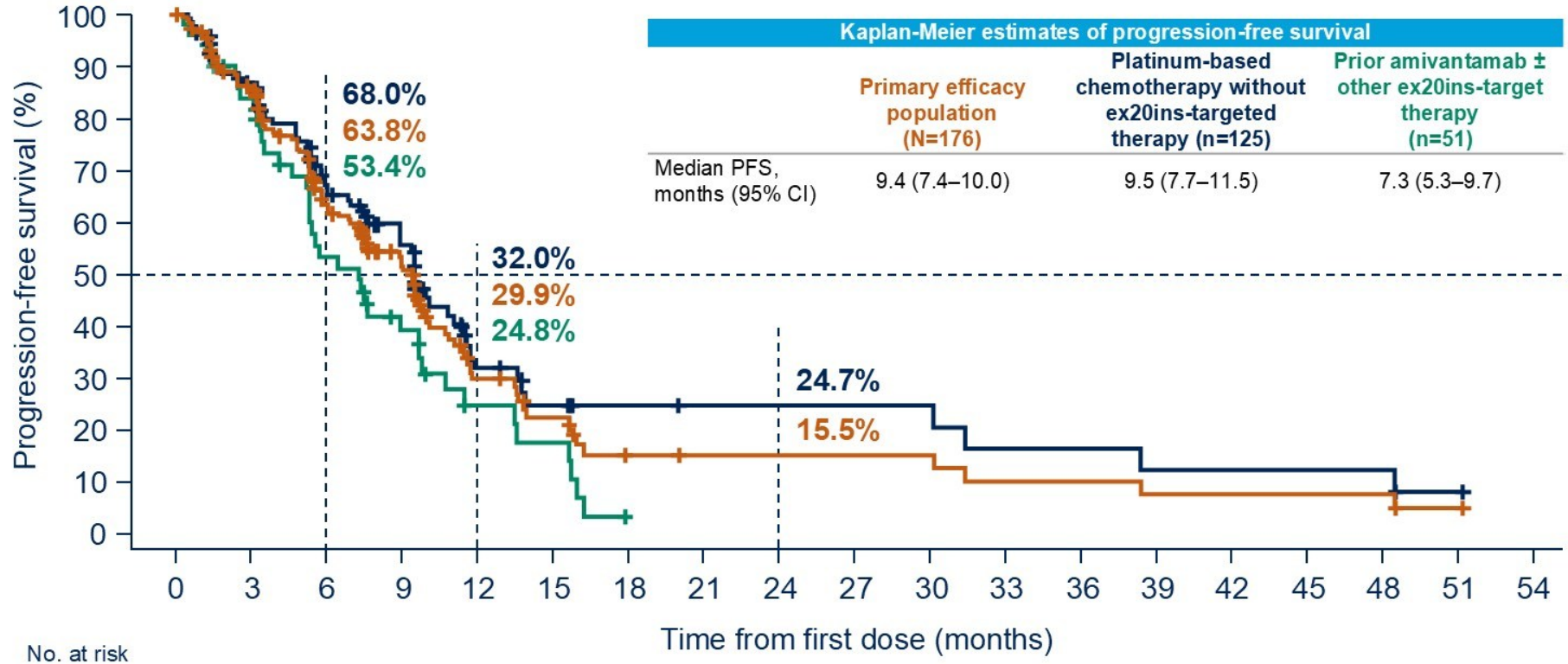
Efficacy per ICR in all patients and subgroups

Median follow-up: 9.3 months

Outcome	Primary efficacy population (N=176)	Platinum-based chemotherapy without ex20ins-targeted therapy (n=125)	Prior amivantamab ± other ex20ins-target therapy (n=51)[a]
BOR, No. (%)[b]			
CR	1 (1)	0	1 (2)
PR	61 (35)	50 (40)	11 (22)
Unconfirmed PR[c]	7 (4)	6 (5)	1 (2)
SD	88 (50)	55 (44)	33 (65)
PD	11 (6)	8 (6)	3 (6)
Not evaluable[d]	8 (5)	6 (5)	0
Confirmed ORR, No. (%) [95% CI][e]	62 (35) [28–43]	50 (40) [31–49]	12 (24) [13–38]
DCR, No. (%) [95% CI][f]	157 (89) [84–93]	111 (89) [82–94]	46 (90) [79–97]
CBR, No. (%) [95% CI][g]	113 (64) [57–71]	85 (68) [59–76]	28 (55) [40–69]
Median time to response, days (range)	44 (31–295)	44 (39–232)	44 (39–232)
Median DOR, months (95% CI)	8.8 (8.3–12.7)	8.8 (8.3–12.7)	8.5 (4.2–14.8)

Patients were evaluable for response if they had received at least one dose of zipalertinib and had at least one post-dose tumor assessment or had discontinued prior to the first efficacy assessment due to clinical disease progression or toxicity. [a]Including 30 patients who received prior amivantamab without and 21 patients with other ex20ins-targeted therapy. [b]Response confirmed ≥4 weeks after response first noted. [c]Patients had PR but confirmatory scan had not yet been performed. [d]No post-baseline imaging. [e]Proportion of patients with confirmed CR or PR. [f]Proportion of patients with CR, PR, or SD. [g]Proportion of patients with CR, PR, or with SD lasting ≥24 weeks.
BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ex20ins, exon 20 insertions; ICR, independent central review; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Progression-free survival per ICR



Kaplan-Meier estimates of progression-free survival

	Primary efficacy population (N=176)	Platinum-based chemotherapy without ex20ins-targeted therapy (n=125)	Prior amivantamab ± other ex20ins-target therapy (n=51)
Median PFS, months (95% CI)	9.4 (7.4–10.0)	9.5 (7.7–11.5)	7.3 (5.3–9.7)

No. at risk

Total	176	144	95	57	22	15	7	6	6	6	6	4	4	3	3	3	3	1	0
Platinum-based chemotherapy only	125	103	71	42	15	10	7	6	6	6	6	4	4	3	3	3	3	1	0
Prior amivantamab ± other ex20ins	51	41	24	15	7	5	0	0	0	0	0	0	0	0	0	0	0	0	0

Progression-free survival was defined as the time between the day of the first dose of zipalertinib and the first documentation of progressive disease or death, whichever occurred earlier.
CI, confidence interval; ex20ins, exon 20 insertions; ICR, independent central review; PFS, progression-free survival.

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Most common treatment-related adverse events

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

- Anemia was the most common grade 3 TRAE
- Other grade ≥3 TRAEs reported in ≥5 patients included pneumonitis and rash (6 patients [2.5%] each), and alanine aminotransferase increased, diarrhea, and platelet count decreased (5 patients [2.0%] each)
- Twelve patients (4.9%) had treatment-related pneumonitis, 5 of whom had received prior immunotherapy
  - Grade 1, n=3; grade 2, n=3; grade 3, n=5; grade 5, n=1

TRAE, treatment-related adverse event.

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Take home points

- Zipalertinib is an active drug against EGFR exon 20 insertion mutations, including in patients who received prior amivantamab
- Less activity in those who received prior EGFR TKIs
- Appears more tolerable than amivantamab
- Phase 3 trial is ongoing in combination with chemotherapy versus chemotherapy alone in patients with previously-untreated disease
- We may soon have several EGFR exon 20 TKIs available for use including zipalertinib, sunvozertinib and furmonertinib which have all received Breakthrough Therapy Designation by the FDA

HER2-mutant NSCLC

- HER2 mutations occur in 2-4% of NSCLC
  - Most commonly insertion mutations in the tyrosine kinase domain in exon 20
  - Less common are point mutations in the TKD and mutations in the extracellular and transmembrane domains
- Trastuzumab deruxtecan is the only HER2-targeted therapy available for patients with HER2 mutant lung cancer
- Sevabertinib is a TKI that targets both EGFR and HER2 exon 20 mutations with efficacy demonstrated in patients with previously treated HER2-mutant lung cancer

Girard N et al. *J Clin Oncol* 2024

2025 ASCO ANNUAL MEETING

SOHO-01: Safety and efficacy of BAY 2927088 in patients with advanced *HER2*-mutant non-small cell lung cancer (NSCLC) who were pretreated but naïve to HER2-targeted therapy or had not received any treatment for advanced disease

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June 1, 2025

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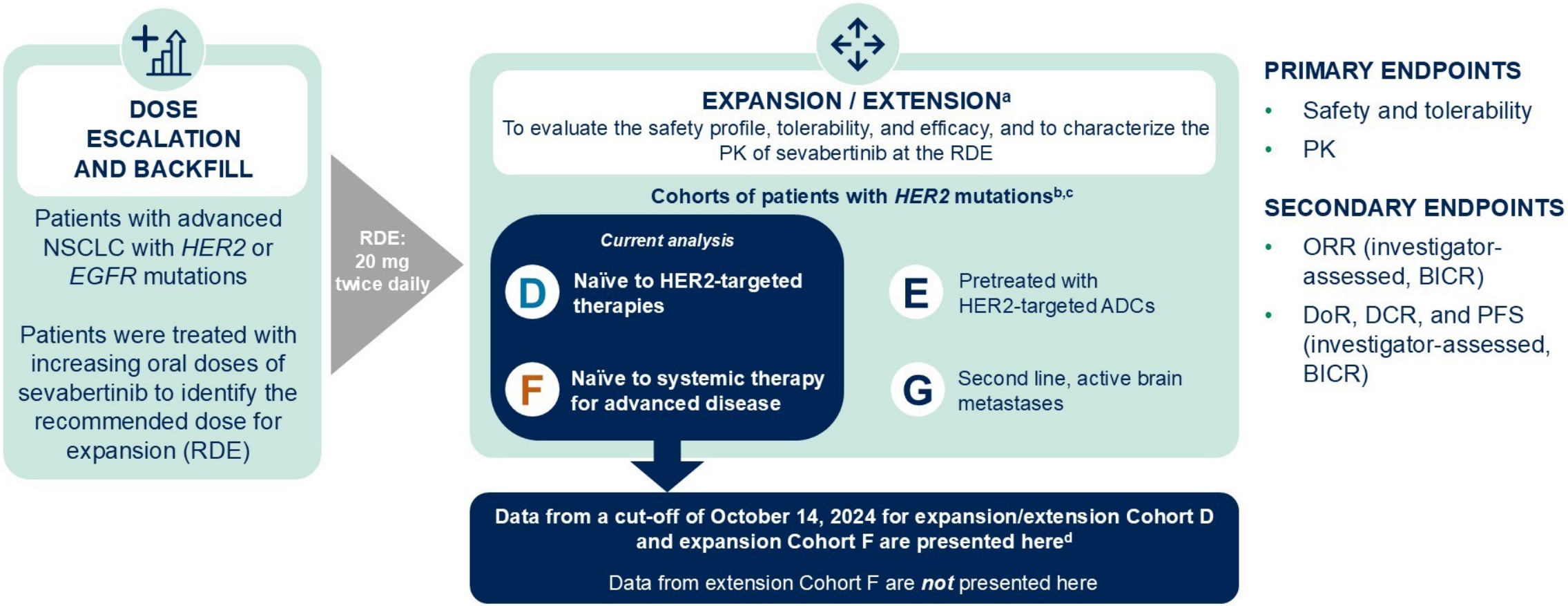
PRESENTED BY: Dr Herbert H. Loong

SOHO-01 study design (NCT05099172)



PRIMARY ENDPOINTS

- Safety and tolerability
- PK

SECONDARY ENDPOINTS

- ORR (investigator-assessed, BICR)
- DoR, DCR, and PFS (investigator-assessed, BICR)

[a]Patients enrolled in the dose escalation, backfill, and dose expansion phases who were treated at the same dose level (ie, RDE of 20 mg twice daily) and who met the same eligibility criteria as patients in the extension phase were combined into the corresponding subpopulation for statistical analysis; [b]Extension phase is ongoing in selected cohorts; [c]Cohorts of patients with *EGFR* mutations not shown here; [d]Includes patients treated with the RDE of study drug from the dose escalation and backfill phases

ADC, antibody-drug conjugate; BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics

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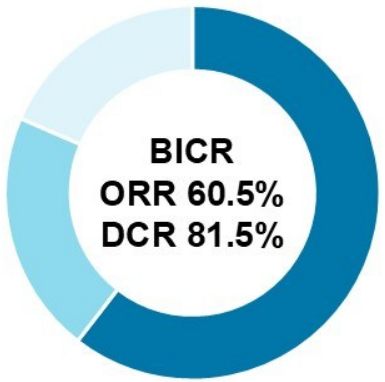
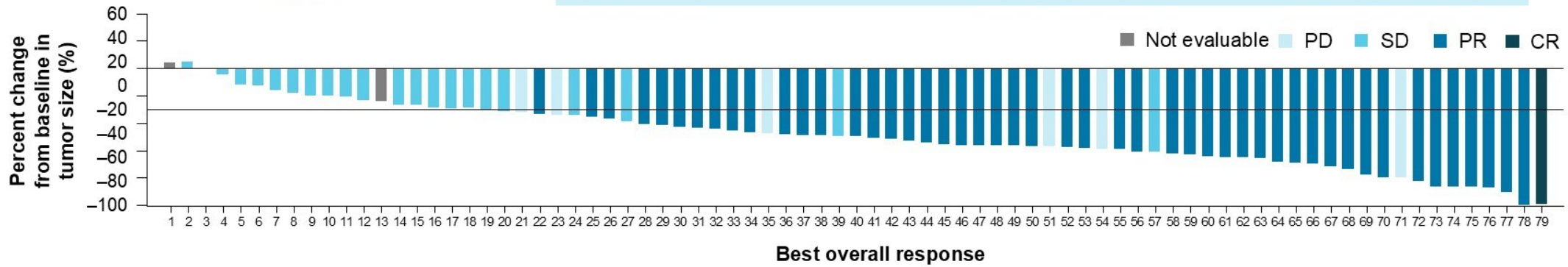
Sevabertinib in pretreated *HER2*-mutant NSCLC (Cohort D): Tumor response by blinded independent central review (BICR)

Cohort D (*n*=81), naïve to HER2-targeted therapy

Median follow-up: 7.3 months[a]



n (%)	INV	BICR
CR	1 (1.2)	1 (1.2)
PR	47 (58.0)	48 (59.3)
SD	22 (27.2)	22 (27.2)
PD	10 (12.3)	7 (8.6)
Not evaluable[b]	1 (1.2)	3 (3.7)
ORR[c] [95% CI]	**48 (59.3)** [47.8, 70.1]	**49 (60.5)** [49.0, 71.2]
DCR[d] [95% CI]	**68 (84.0)** [74.1, 91.2]	**66 (81.5)** [71.3, 89.2]

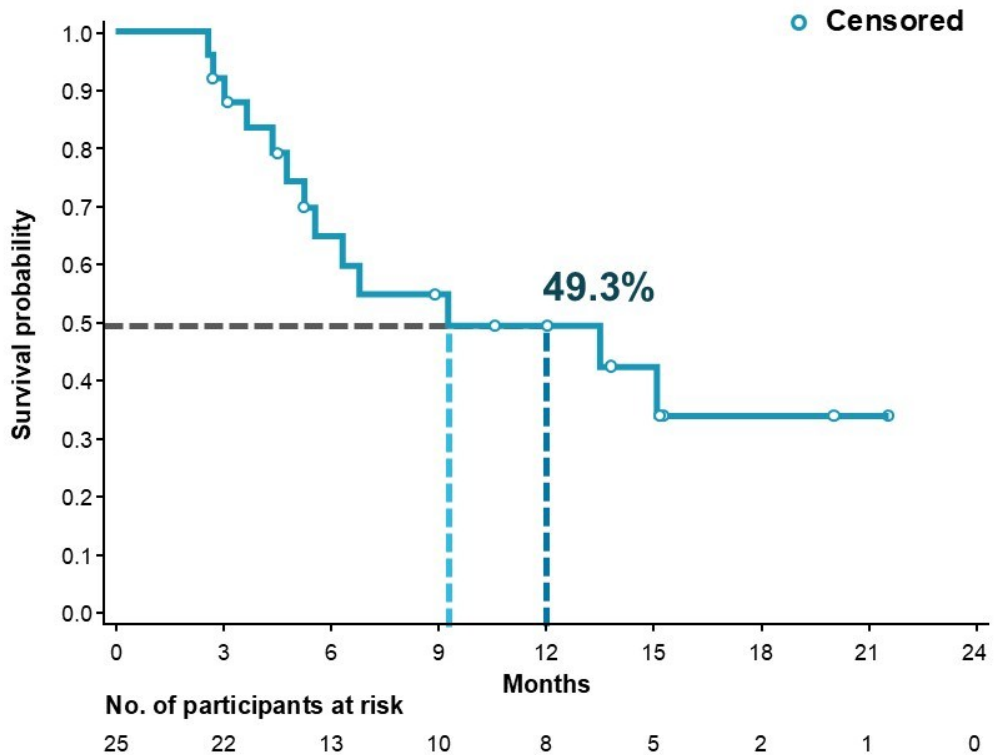


Data for patients without target lesion measurements are not shown in the waterfall plot

[a]Data for Extension Cohort D are immature as of the October 14, 2024, cut-off; [b]Requirement for CR / PR / SD or PD was not met; [c]Confirmed CR or PR; [d]Confirmed CR / PR or SD for ≥12 weeks

CR, complete response; DCR, disease control rate; INV, investigator assessed; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

Sevabertinib in pretreated *HER2*-mutant NSCLC (Expansion Cohort D): Duration of response (DoR) by BICR



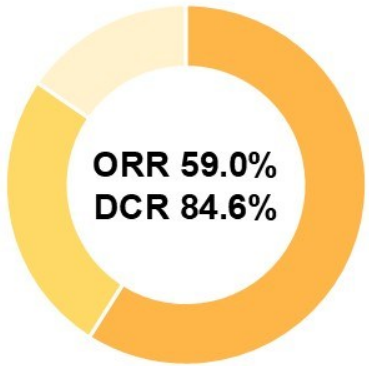
In Expansion Cohort D (*n*=44)[a]:

- **Median DoR (95% CI) was 9.2 months (5.2, not estimable); range 2.6-21.5[b] months**
- **12-month DoR rate was 49.3%**
- **48.0% of patients were censored**

[a]Data for Extension Cohort D are immature as of the October 14, 2024, cut-off; [b]Censored observation

BICR, blinded independent central review; CI, confidence interval

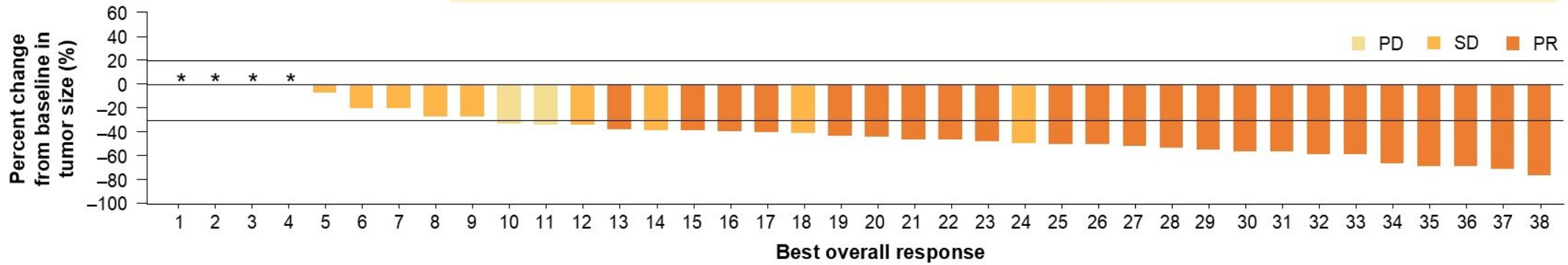
Sevabertinib in first-line *HER2*-mutant NSCLC (Expansion Cohort F): Preliminary tumor response



Cohort F (*n*=39): naïve to systemic therapy for advanced disease

Median follow-up: 5.6 months[a]

n (%)	INV
CR	0
PR	23 (59.0)
SD	12 (30.8)
PD	3 (7.7)
NA[b]	1 (2.6)
ORR[c] [95% CI]	**23 (59.0)** [42.1, 74.4]
DCR[d] [95% CI]	**33 (84.6)** [69.5, 94.1]



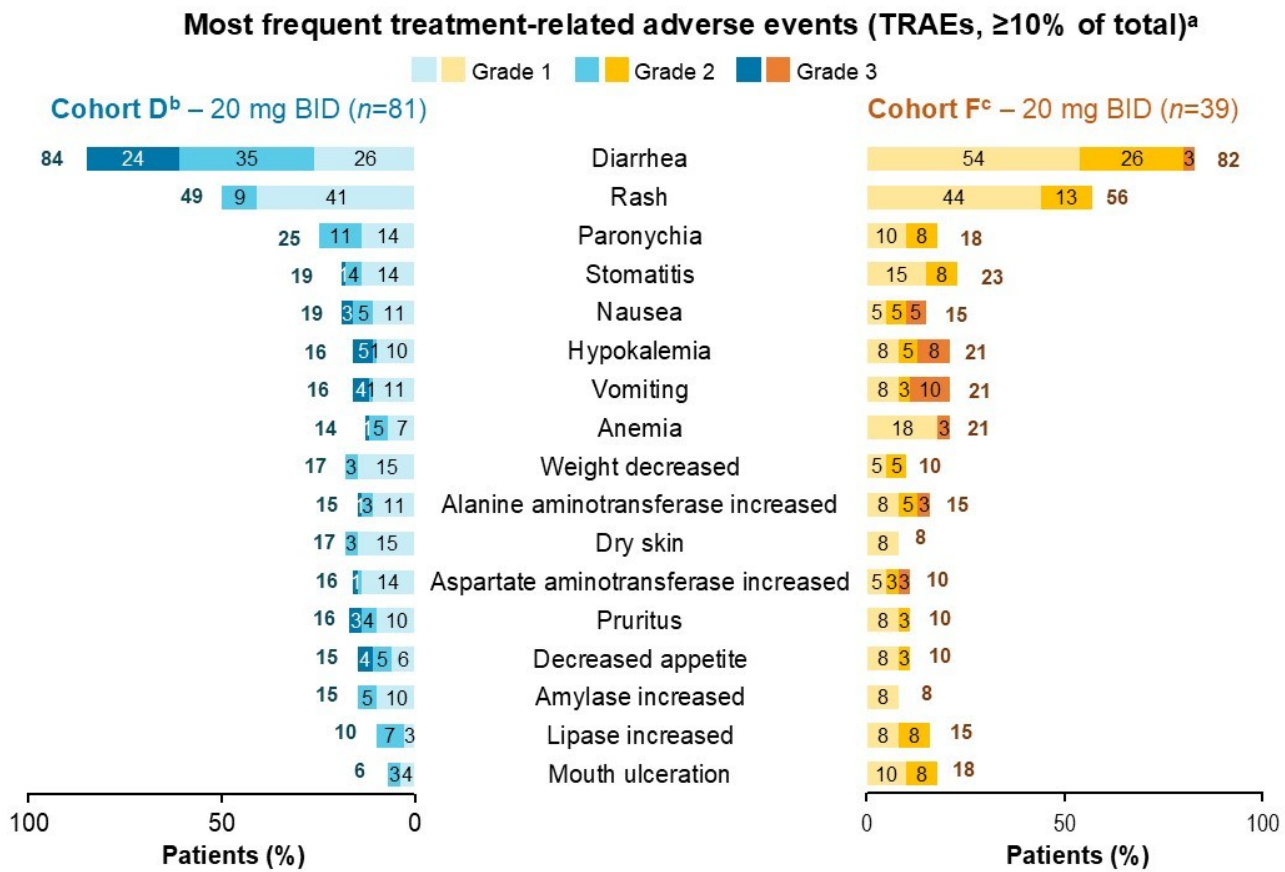
Date for patients without a target lesion measurement are not shown in the waterfall plot. Tumor response was assessed by RECIST v1.1.

*Patients exhibited a 0% tumor reduction

[a]Data for Extension Cohort F are immature as of the October 14, 2024, cut-off; [b]Not available: post-baseline tumor assessment, but discontinued due to a drug-related toxicity, death, or progression by clinical judgment before disease was re-evaluated and was therefore considered evaluable (considered as non-responder); [c]Patients with confirmed CR or PR; [d]Patients with confirmed CR or confirmed PR or SD for ≥12 weeks

CI, confidence interval; CR, complete response; DCR, disease control rate; INV, investigator assessed; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

Sevabertinib safety and tolerability



- **In pretreated patients (Cohort D), the safety profile was consistent with previous reports**
  - Grade 3 treatment-related diarrhea occurred in 24% of patients
  - Exploratory analysis showed a median of 1 episode (IQR 1, 1) and a median time to onset of 1.3 months (IQR 0.5, 3.6)
- **In first-line patients (Cohort F), treatment-related grade 3 diarrhea was reported in only 1 patient (3%)**
- **Overall, there were no cases of grade 4 diarrhea**
- **There were no reported cases of interstitial lung disease or pneumonitis**
- **4 patients (4.9%) in Cohort D and 1 patient (2.6%) in Cohort F had TRAEs leading to treatment discontinuation[d]**

[a]MedDRA v27.1, CTCAE v5.0; [b]Patients naïve to HER2-targeted therapies; [c]Patients naïve to systemic therapy for advanced disease; [d]Abnormal hepatic function (D: *n*=1), corneal epithelial microcysts and reduced visual acuity (D: *n*=1), dyspnea (D: *n*=1), electrocardiogram QT prolonged (D: *n*=1), and renal failure (F: *n*=1)

CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; IQR, interquartile range; MedDRA v27.1, Medical Dictionary for Regulatory Activities version 27.1

Take home points

- Sevabertinib is an active drug against HER2-mutant lung cancer
- Caveats:
  - Toxicity may be an issue for some patients
  - Activity in different HER2 mutations is unknown
  - Confirmatory trials is ongoing for first-line use
- This is an exciting time for HER2-mutant disease:
  - Several TKIs have demonstrated activity and may be available for patients in the near future
  - Both sevabertinib and zongertinib granted Breakthrough Therapy designation and Priority Review by the FDA