Fourth Annual
National General Medical Oncology Summit

Sunday, March 2, 2025

Moderator

Neil Love, MD

Faculty

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Philip A Philip, MD, PhD
Kanwal Raghav, MD
Jonathan E Rosenberg, MD

Module 15: Immunotherapy and Other Nontargeted Approaches for NSCLC

Management of Nonmetastatic NSCLC without a Targetable Mutation — Dr Govindan

First- and Later-Line Therapy for Metastatic NSCLC without a Targetable Mutation — Dr Liu

Module 15: Immunotherapy and Other Nontargeted Approaches for NSCLC

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Immunotherapy and Other Nontargeted Approaches for NSCLC

Ramaswamy Govindan M.D.
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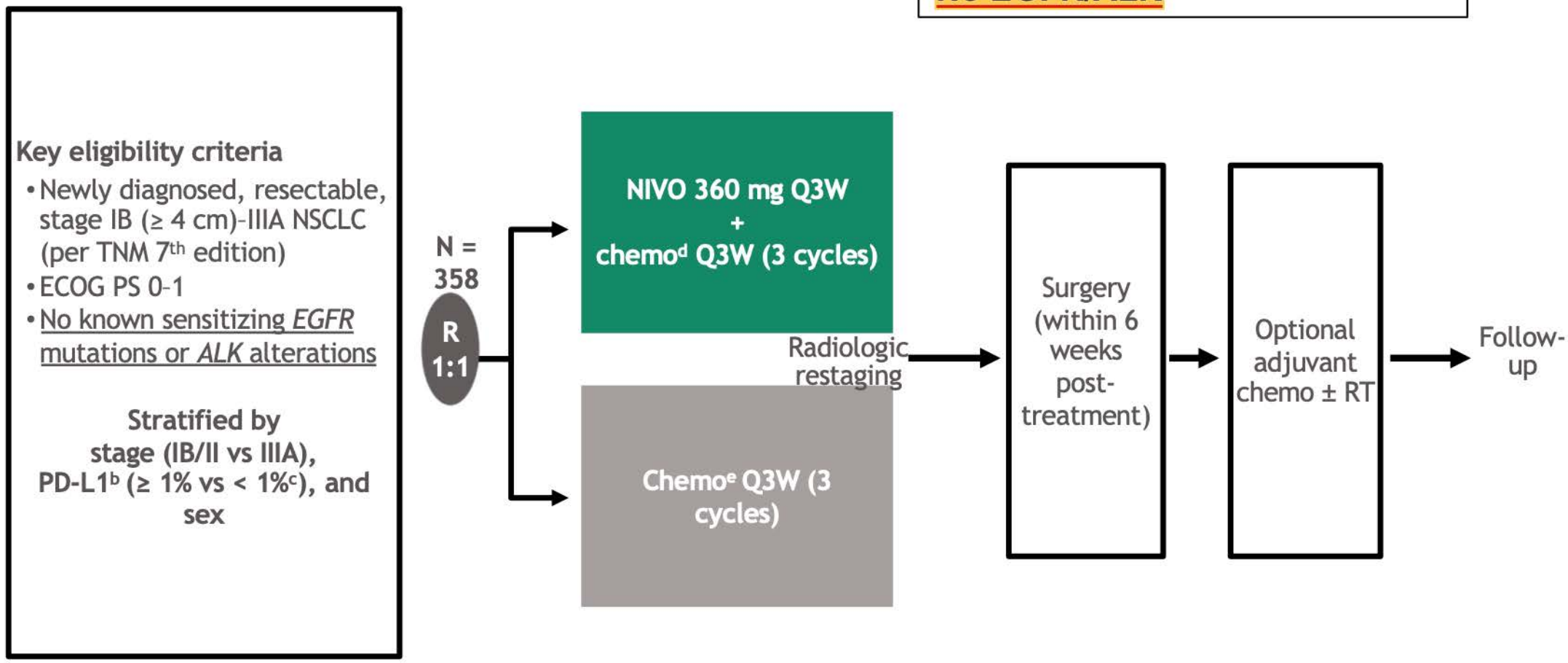
St. Louis

Disclosures

No relevant conflicts of interest to disclose.

First Phase III: CheckMate 816

37% stage IB/II; 63% Stage IIIA
50% PD-L1 >1%
No EGFR/ALK



MADRID 2023 ESMO congress

Spicer ASCO 2021 abstr: 8503, Forde NEJM

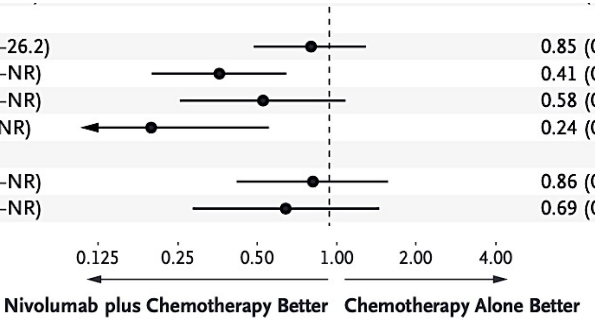
The NEW ENGLAND JOURNAL of MEDICINE

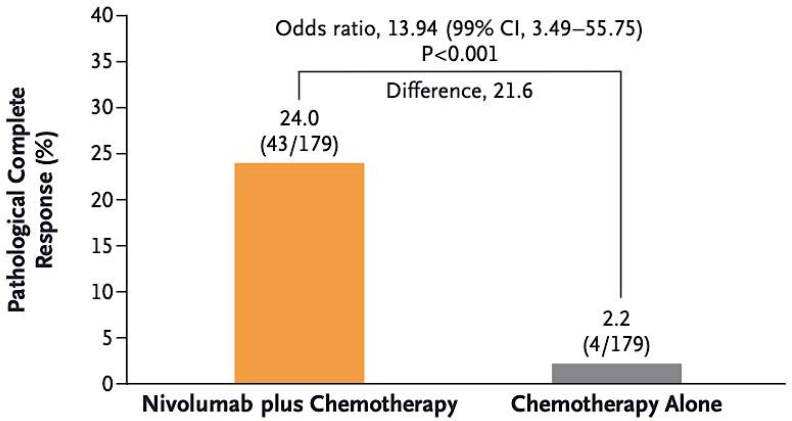
ESTABLISHED IN 1812 MAY 26, 2022 VOL. 386 NO. 21

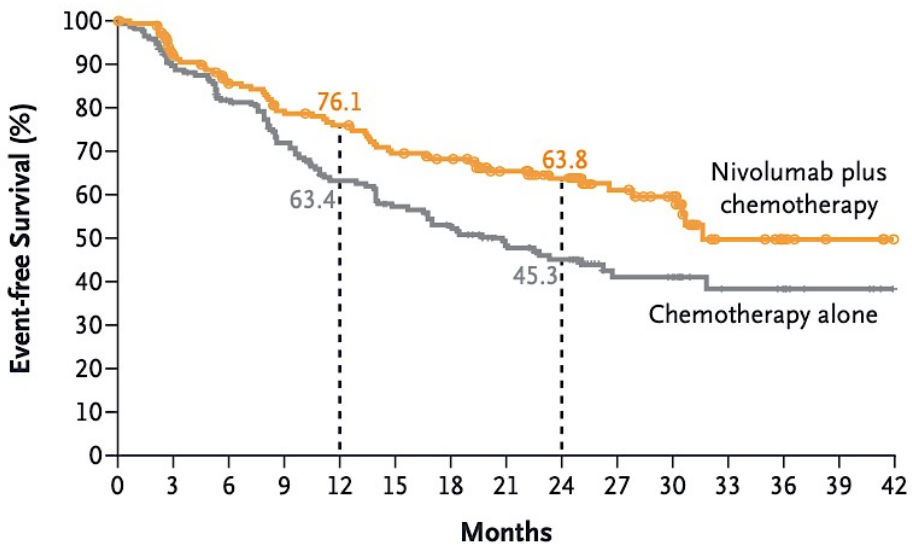
Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)
TMB				
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)	0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)	0.69 (0.33–1.46)







	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

No. at Risk

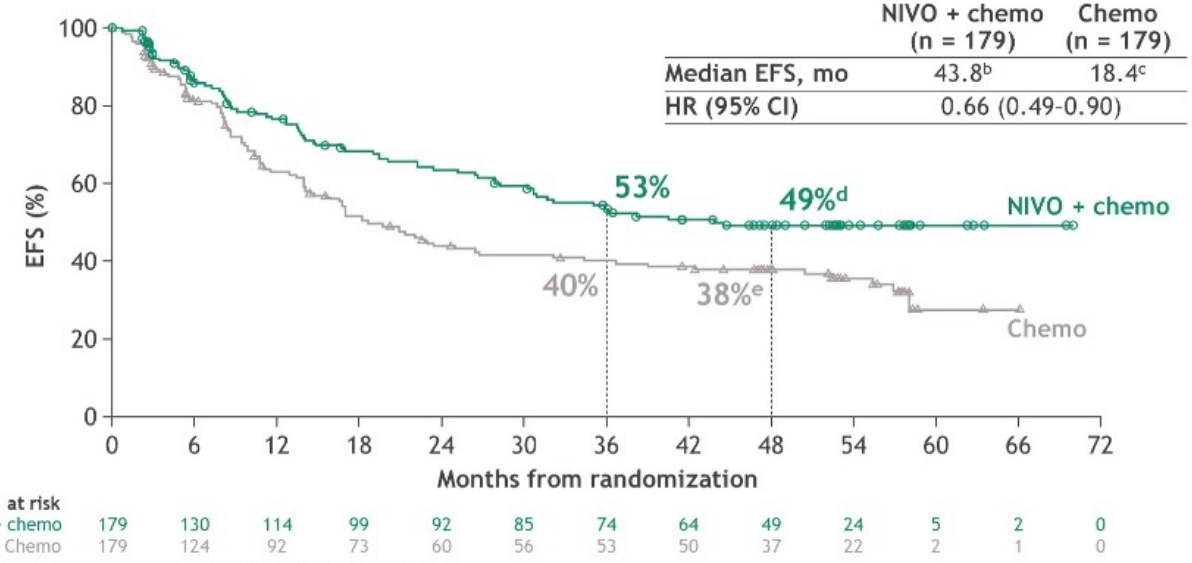
Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

CheckMate 816 Trial 4-Year Update: Event-Free Survival (EFS) and Overall Survival (OS) with Neoadjuvant Nivolumab and Chemotherapy versus Chemotherapy Alone

EFS

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

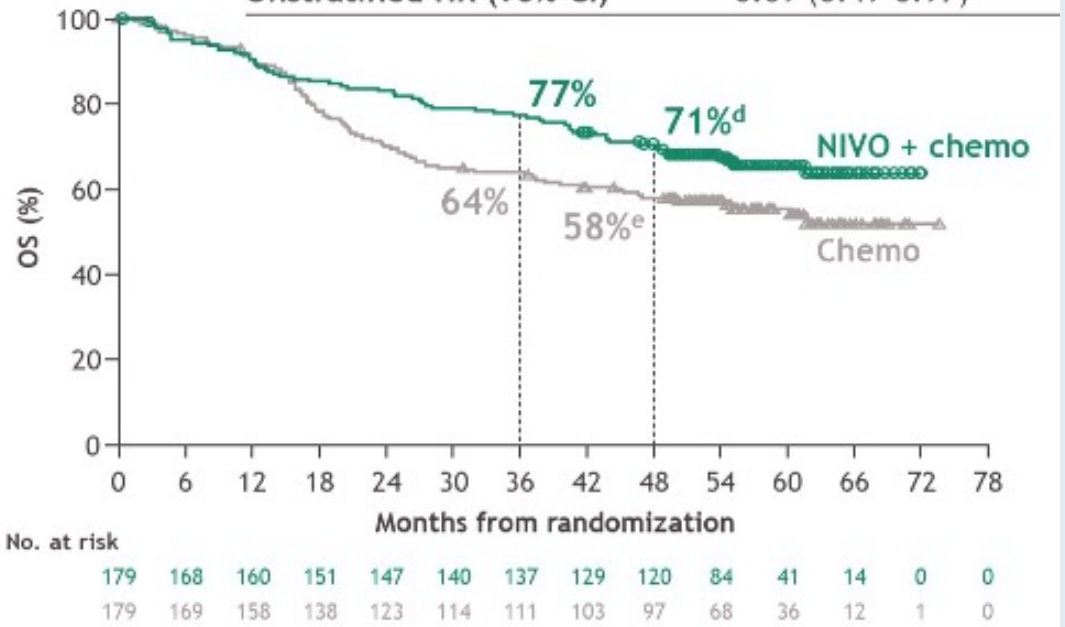
	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo	43.8[b]	18.4[c]
HR (95% CI)	0.66 (0.49-0.90)	



Database lock date, February 23, 2024; minimum/median follow-up, 49.1/57.6 months.
[a]Exploratory analysis. [b]95% CI: [c]30.6-NR; [d]14.0-26.7; [e]41-57; [c]30-46. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985. 2. Forde PM, et al. Oral presentation at European Lung Cancer Congress (ELCC); March 29-April 1 2023; Copenhagen, Denmark. Presentation 840.

OS

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



Spicer J et al. ASCO 2024;Abstract LBA8010.

RTP RESEARCH TO PRACTICE

Final Analysis of CheckMate 816 Demonstrates Statistically Significant and Clinically Meaningful OS Improvement for Patients with Resectable NSCLC

Press Release: February 19, 2025

The final analysis of overall survival (OS) from the Phase 3 CheckMate 816 study, which evaluated nivolumab in combination with platinum-doublet chemotherapy as a neoadjuvant treatment for adult patients with resectable NSCLC (tumors ≥4 cm or node-positive), demonstrated a statistically significant and clinically meaningful improvement in OS, a key secondary endpoint, in comparison to neoadjuvant chemotherapy alone. The results build on the previously reported primary endpoints of event-free survival and pathological complete response, which also met statistical significance.

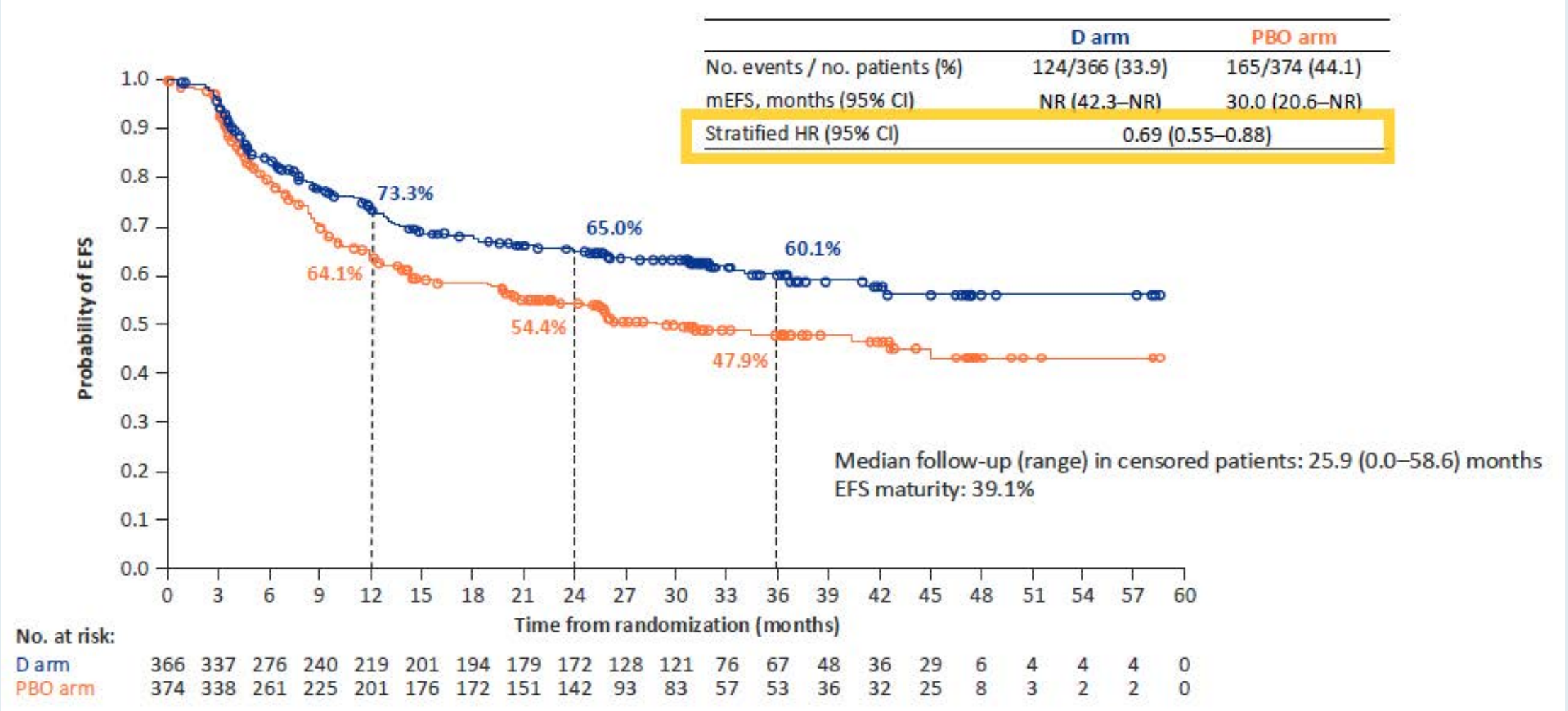
The safety profile of nivolumab in combination with chemotherapy was consistent with previously reported studies, with no new safety signals observed.

The manufacturer will conduct an analysis of the updated data and plans to provide a comprehensive update on the data in a future peer-reviewed setting.

https://news.bms.com/news/details/2025/Bristol-Myers-Squibb-Announces-Opdivo-Plus-Chemotherapy-as-the-First-and-Only-Neoadjuvant-Only-Immuno-Oncology-Therapy-to-Demonstrate-Statistically-Significant-and-Clinically-Meaningful-Overall-Survival-in-Resectable-Non-Small-Cell-Lung-Cancer/default.aspx

RTP RESEARCH TO PRACTICE

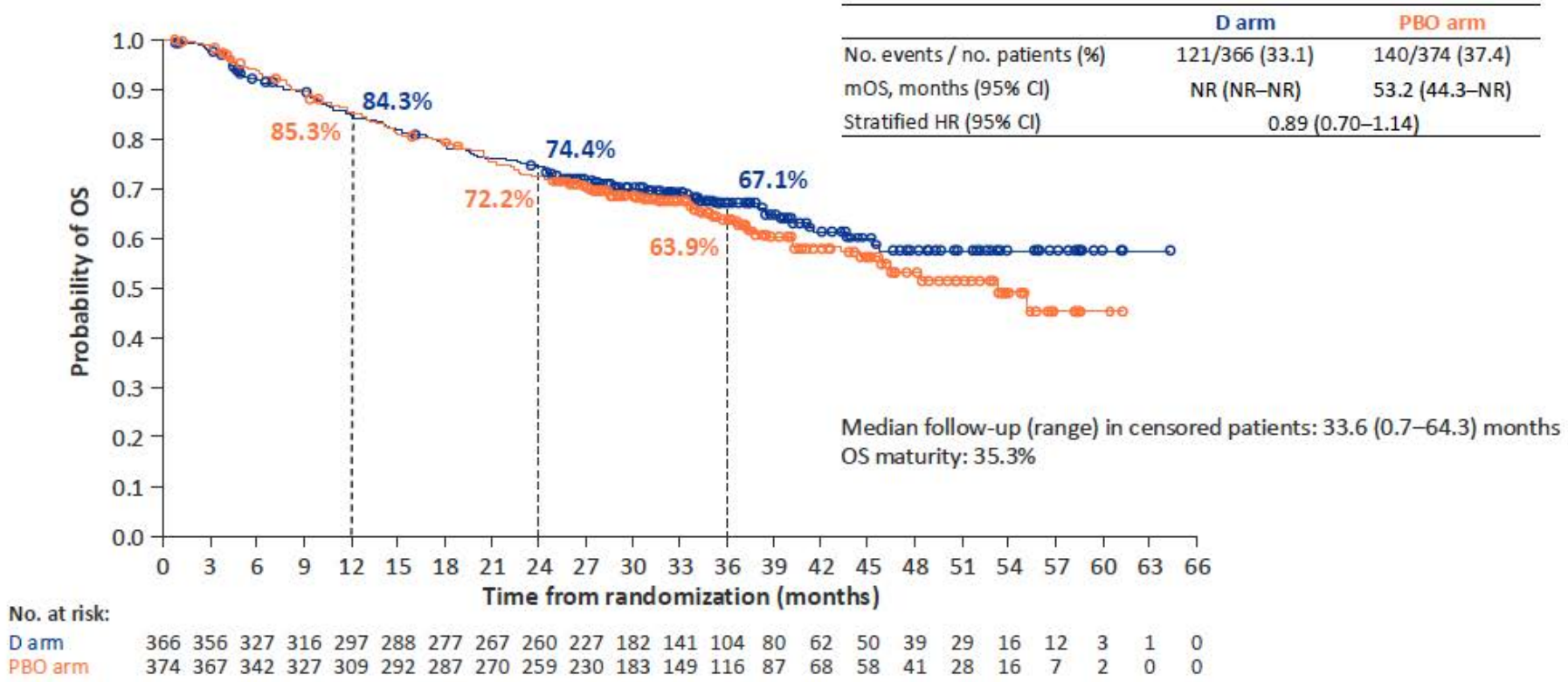
AEGEAN: Updated EFS Outcomes from a Phase III Trial of Perioperative Durvalumab for Resectable NSCLC



Heymach JV et al. World Conference on Lung Cancer 2024;Abstract OA13.03.

AEGEAN: Overall Survival with Perioperative Durvalumab for Resectable NSCLC

- Based on 35% maturity, an OS trend favoring the durvalumab arm was observed



	D arm	PBO arm
No. events / no. patients (%)	121/366 (33.1)	140/374 (37.4)
mOS, months (95% CI)	NR (NR–NR)	53.2 (44.3–NR)
Stratified HR (95% CI)	0.89 (0.70–1.14)	

Median follow-up (range) in censored patients: 33.6 (0.7–64.3) months
OS maturity: 35.3%

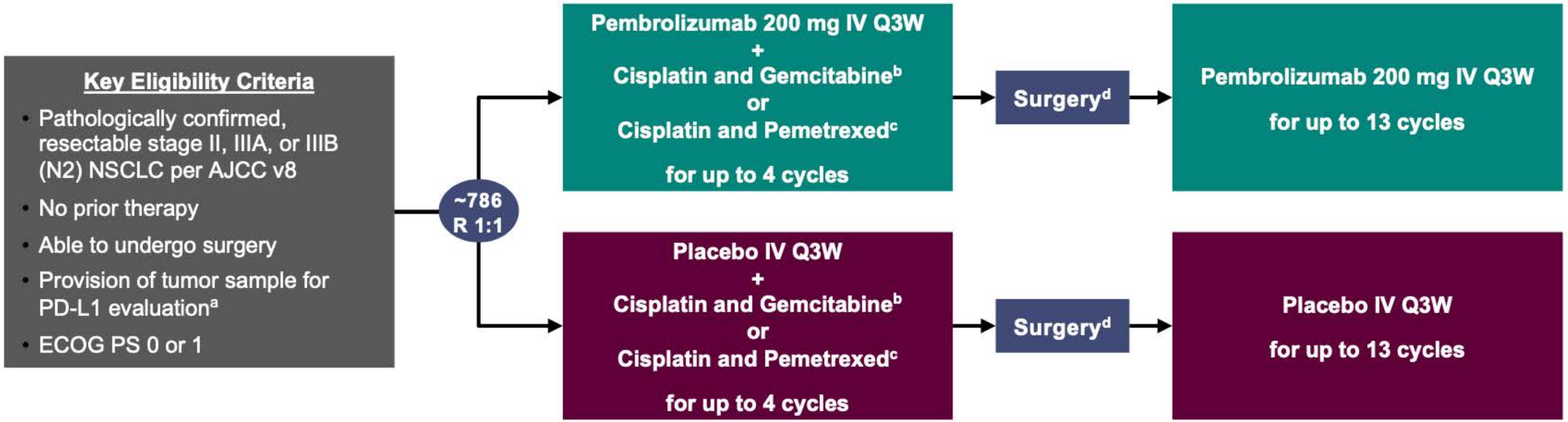
- Preplanned analysis censoring patients with cause of death due to COVID-19: OS HR = 0.84 (95% CI: 0.66–1.08)

Heymach JV et al. World Conference on Lung Cancer 2024;Abstract OA13.03.

RTP RESEARCH TO PRACTICE

KEYNOTE-671 Study Randomized, Double-Blind, Ph 3 Trial

~30% stage II; ~1/3 each PD-L1 group (<1, 1-49, 50+); ~5% EGFR/ALK



Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

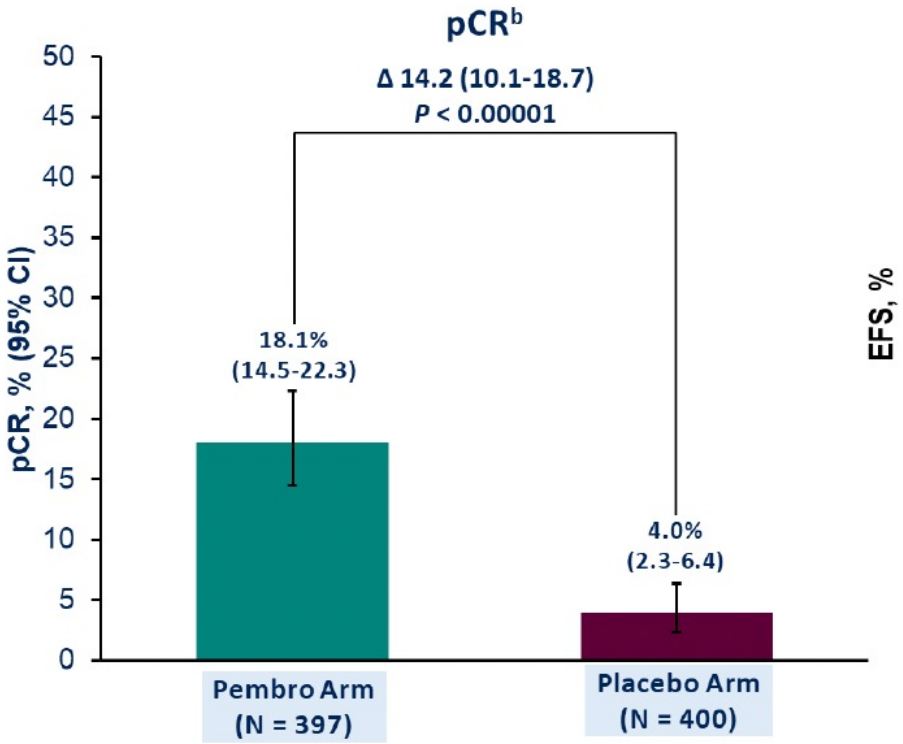
Dual primary end points: EFS per investigator review and OS

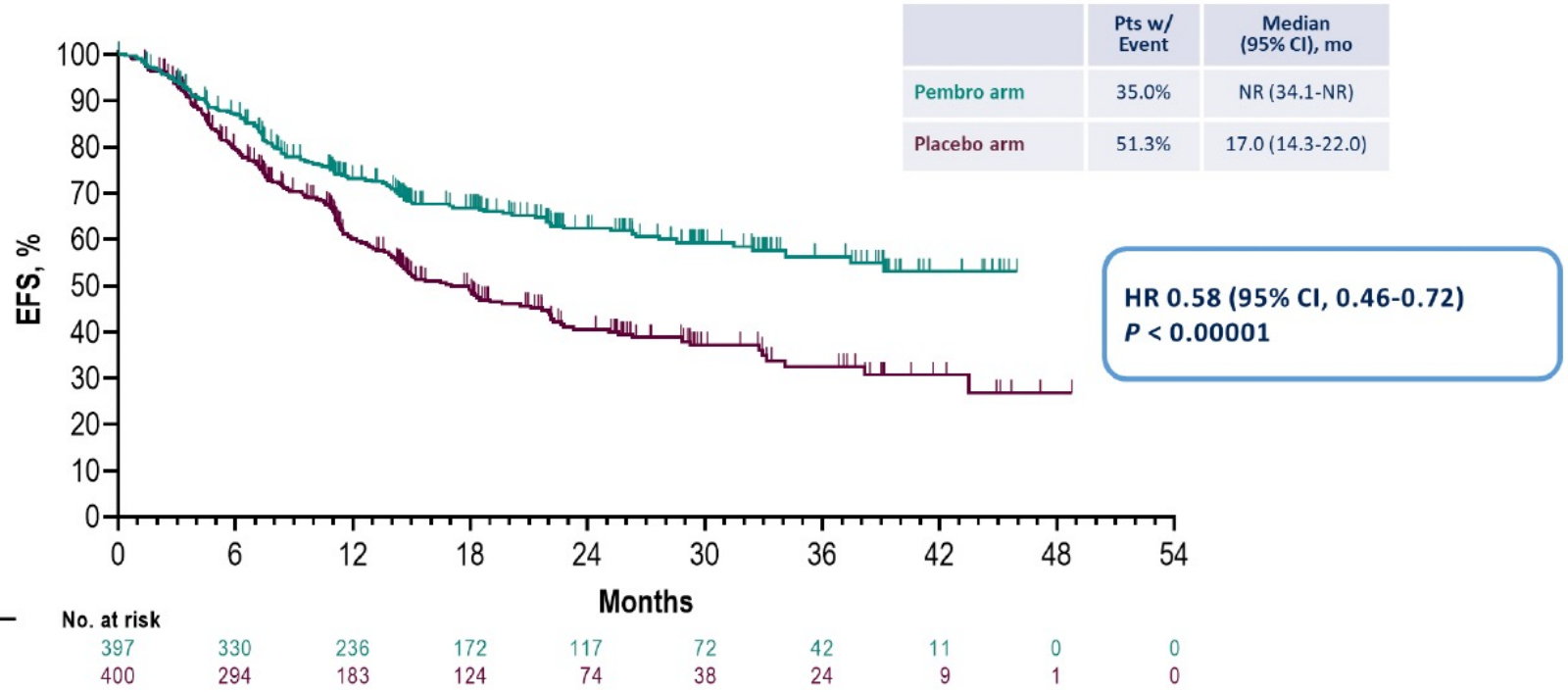
Key secondary end points: mPR and pCR per blinded, independent pathology review, and safety

[a] Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. [b] Cisplatin 75 mg/m^2 IV Q3W + gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W was permitted for squamous histology only. [c] Cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W was permitted for nonsquamous histology only. [d] Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease. ClinicalTrials.gov identifier: NCT03425643.

Wakelee, ASCO 2023, NEJM 2023

KEYNOTE-671 Perioperative Pembro + CT: pCR and EFS in stage II-IIIB NSCLC (AJCC 8th)





	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)

HR 0.58 (95% CI, 0.46-0.72)
P < 0.00001

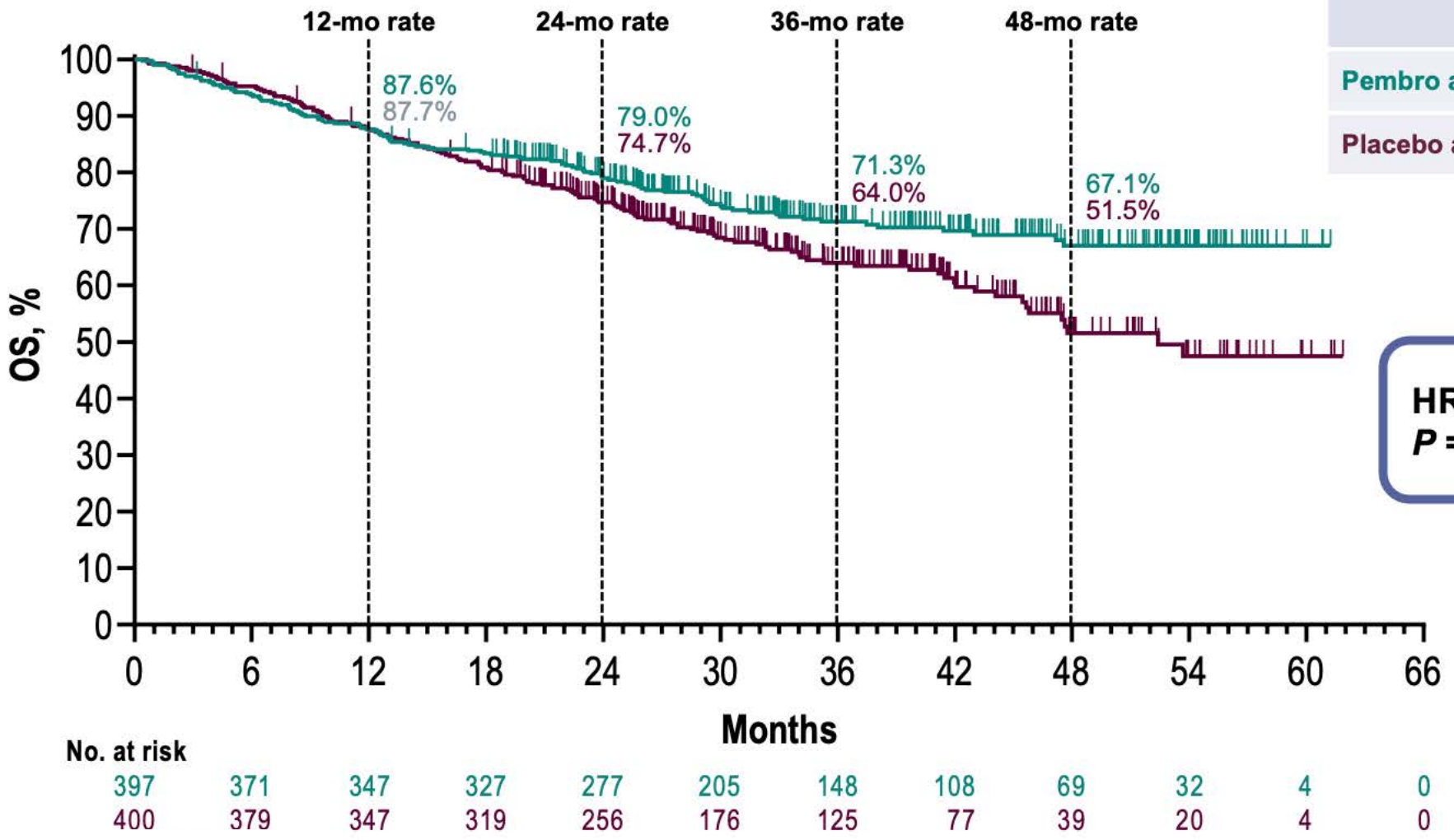
[b] Defined as absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0). Data cutoff date for IA1: July 29, 2022.

EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Wakelee H, Oral Presentation ASCO Annual Meeting 2023
Wakelee H et al. *N Engl J Med* 2023

KN671 Overall Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)



	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

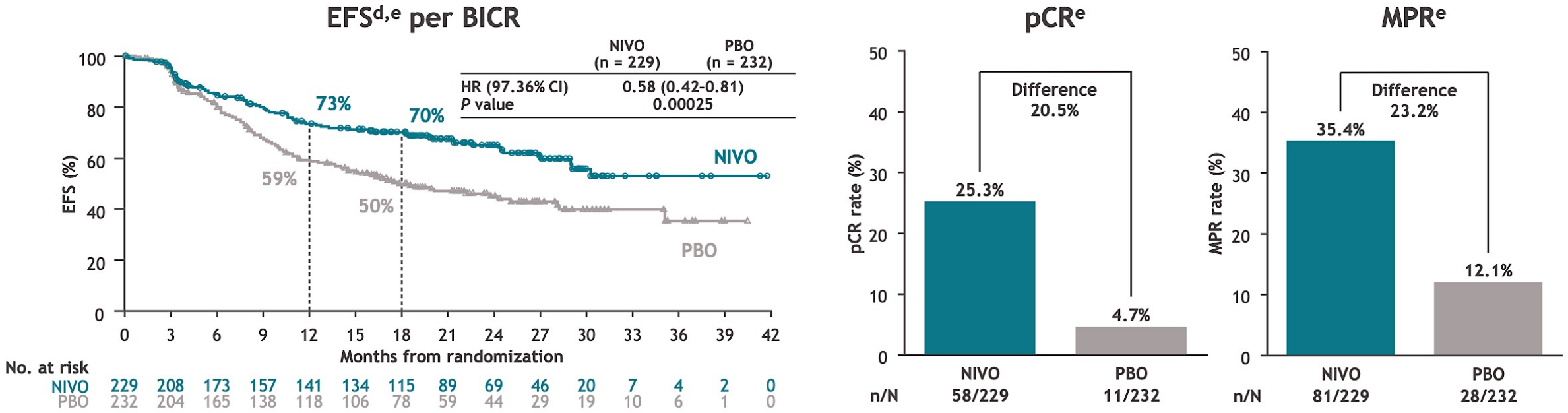
HR 0.72 (95% CI, 0.56-0.93)
***P* = 0.00517[a]**

Spicer JD, Lancet 2024
Spicer ESMO 2023

OS defined as time from randomization to death from any cause. [a] Significance boundary at IA2, *P* = 0.00543.
Data cutoff date for IA2: July 10, 2023.

Clinical outcomes with perioperative nivolumab in patients with resectable NSCLC from the phase 3 CheckMate 77T study

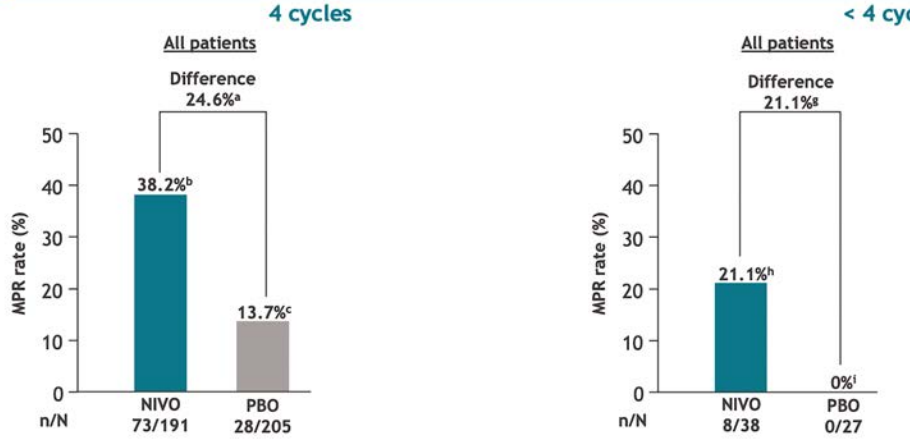
- In the randomized phase 3 CheckMate 77T study, neoadjuvant NIVO + chemo followed by adjuvant NIVO demonstrated statistically significant and clinically meaningful improvement in EFS[a] vs neoadjuvant chemo followed by adjuvant placebo (PBO) in patients with resectable NSCLC; pCR[b] and MPR[c] were also improved



Cascone T, N Engl J Med 2024, Awad ELCC 2024

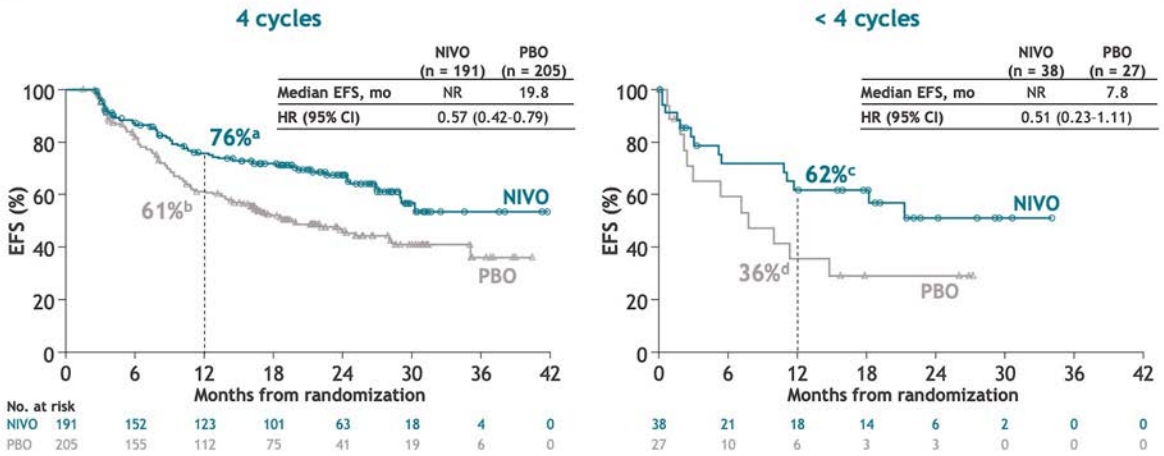
CheckMate 77T study

MPR by number of completed neoadjuvant treatment cycles



Follow-up, median (range): 25.4 (15.7-44.2) months.
[a-i]95% CI: [a]16.1-32.7; [b]31.3-45.5; [c]9.3-19.1; [d]19.6-38.7; [e]38.2-54.3; [f]11.4-23.2; [g]5.1-36.3; [h]9.6-37.3; [i]0-12.8; [j]6.9-61.3; [k]19.1-63.9; [l]0-30.8.

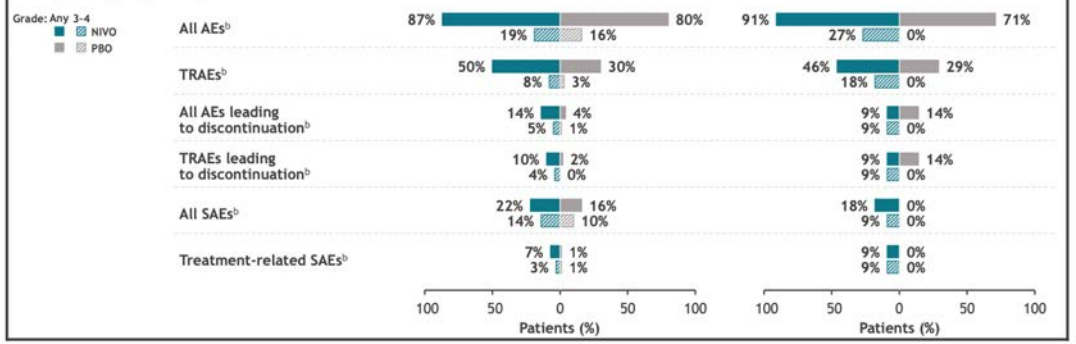
EFS by number of completed neoadjuvant treatment cycles



Follow-up, median (range): 25.4 (15.7-44.2) months.
[a-d]95% CI: [a]68-81; [b]54-68; [c]42-76; [d]15-57.

Adjuvant treatment and safety[a]

	Patients who completed 4 neoadjuvant cycles		Patients who could receive < 4 neoadjuvant cycles	
	NIVO (n = 191)	PBO (n = 205)	NIVO (n = 38)	PBO (n = 27)
Received adjuvant treatment, n (%)	131 (69)	145 (71)	11 (29)	7 (26)
Median number of adjuvant cycles (IQR)	13 (7-13)	13 (8-13)	13 (4-13)	11 (3-13)
Safety during adjuvant period				



Awad ELCC 2024

IMpower010 Study Design

12% stage 1, ~50% stage II, 40% stage III
55% PD-L1+; ~15% known driver mutation

Completely resected stage IB-IIIA[a] NSCLC

- Stage IB tumors ≥4 cm
- ECOG 0-1
- Lobectomy
- Tumor tissue for PD-L1 analysis

Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

1-4 cycles

N=1280

R 1:1

No crossover

Atezolizumab 1200 mg q21d x 16 cycles or 1 year

BSC

N = 1005

Survival follow-up

Hierarchical statistical testing of endpoints

DFS in PD-L1 TC ≥1% stage II–IIIA population[b]

If positive:

DFS in all-randomized stage II–IIIA population[b]

If positive:

DFS in ITT population (stage IB-IIIA)[b]

If positive:

OS in ITT population[b]

- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA and follow up is ongoing
- Endpoint was not formally tested

Stratification factors

- Sex | Stage | Histology | PD-L1 status

Key exploratory endpoints

- OS biomarker analyses

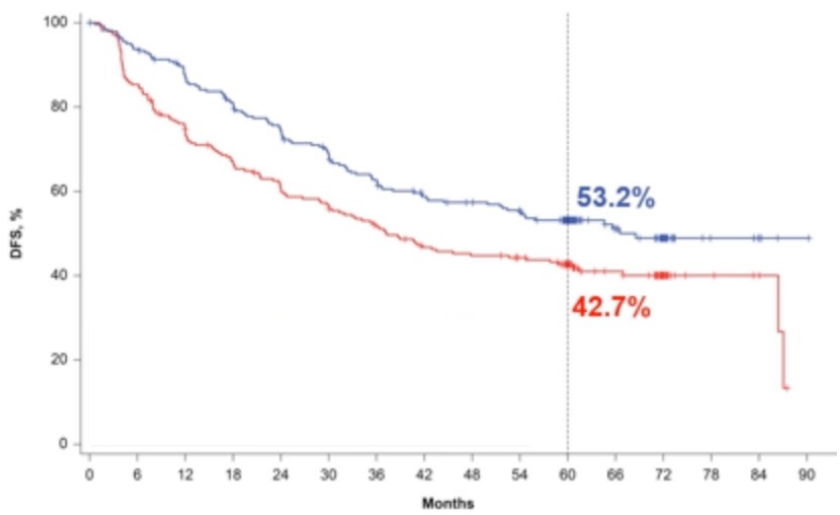
Key secondary endpoints

- OS in ITT | Safety | Exploratory OS biomarker analyses

Clinical cutoff: 18 April 2022. Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group, q21d, every 21 days.
[a] Per UICC/AJCC staging system, 7th edition. [b] Two-sided α=0.05.

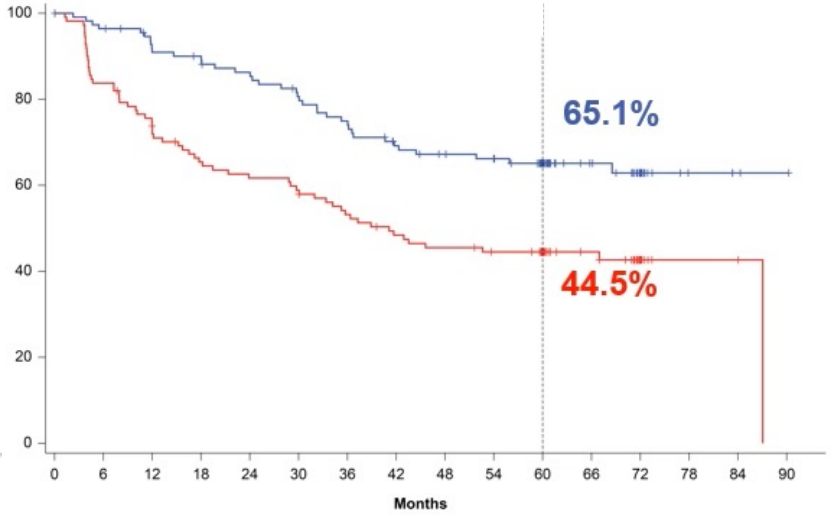
IMpower010 Trial: Final Disease-Free Survival (DFS) Analysis in Stage II-IIA NSCLC

PD-L1 TC ≥1%



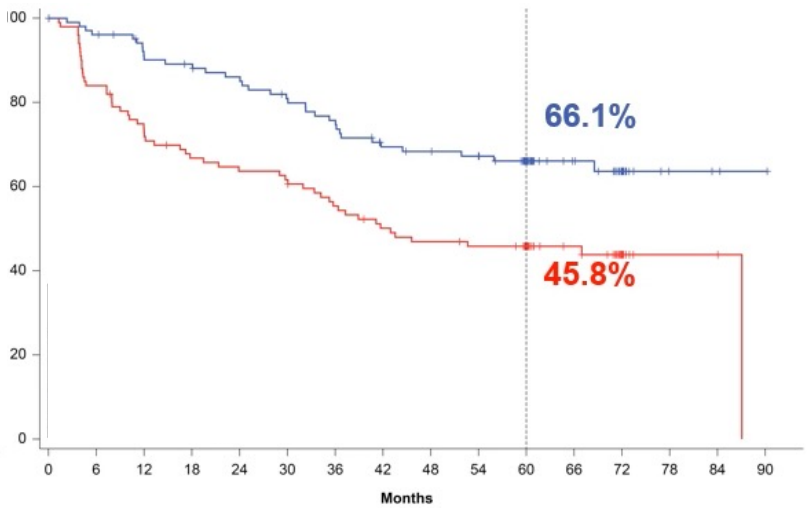
Median DFS
Atezo 68.5 mo
BSC 37.3 mo
HR 0.70

PD-L1 TC ≥50%



Median DFS
Atezo NE
BSC 41.1 mo
HR 0.48

PD-L1 TC ≥50%, no EGFR/ALK alt.



Median DFS
Atezo NE
BSC 42.9 mo
HR 0.49

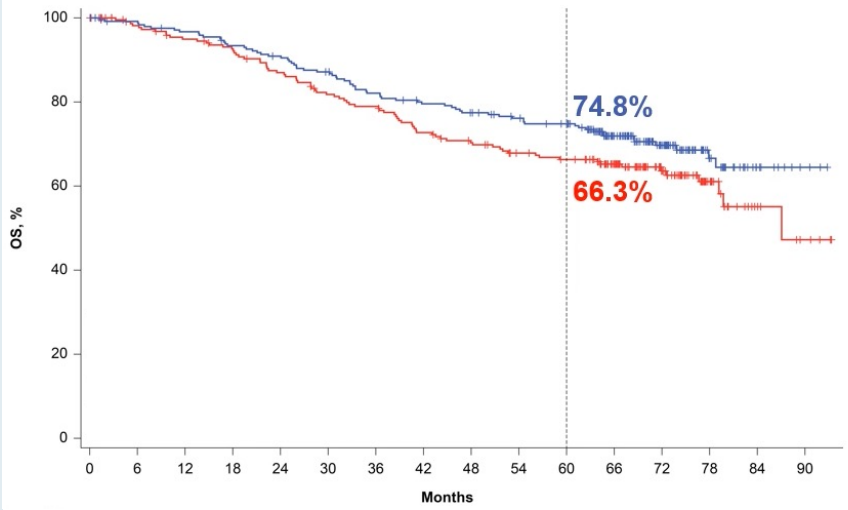
TC = tumor cells; BSC = best supportive care

Wakelee HA et al. ASCO 2024;Abstract LBA8035.

RTP RESEARCH TO PRACTICE

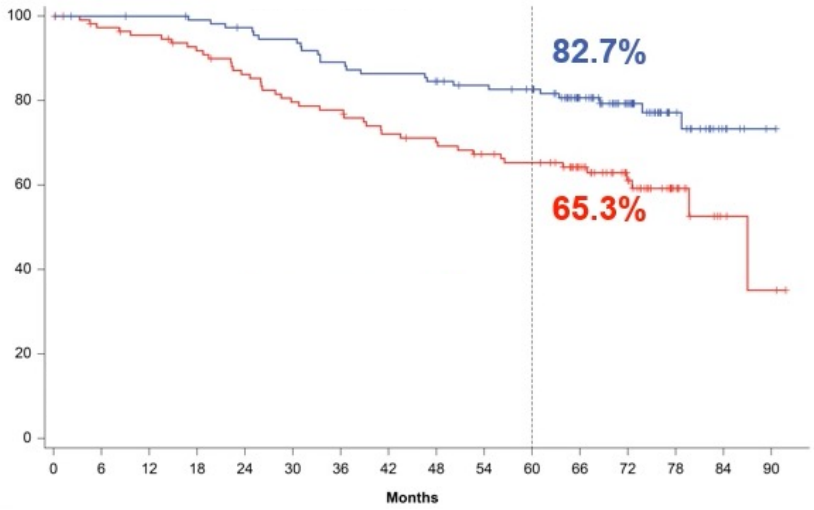
IMpower010: Second OS Interim Analysis in Stage II-IIA NSCLC

PD-L1 TC ≥1%



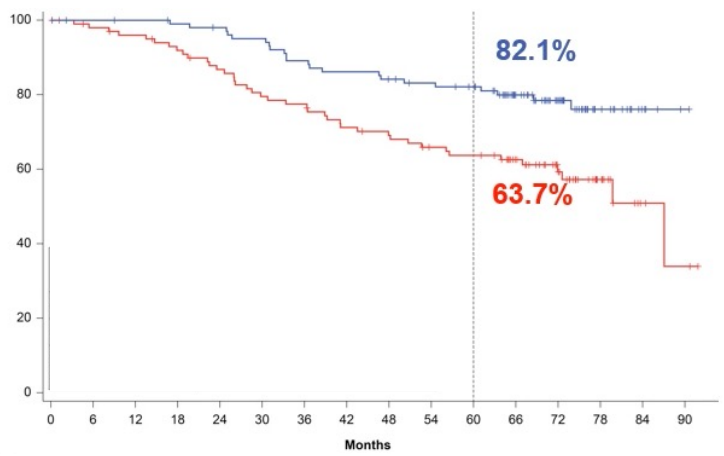
Median OS
Atezo NE
BSC 87.1 mo
HR 0.77

PD-L1 TC ≥50%



Median OS
Atezo NE
BSC 87.1 mo
HR 0.47

PD-L1 TC ≥50%, no EGFR/ALK alt.



Median OS
Atezo NE
BSC 87.1 mo
HR 0.44

Wakelee HA et al. ASCO 2024;Abstract LBA8035.

RTP RESEARCH TO PRACTICE

Safety summary - *(data cutoff: 18 Apr '22)*

Overall safety profile was consistent with previous analysis; no new safety signals were seen

	IMpower010 DFS IA (21 Jan '21)	IMpower010 OS IA (18 Apr '22)	
	Atezo (n=495)	Atezo (n=495)	BSC (n=495)
All-grade AE	92.7%	92.5%	70.9%
Treatment-related AE	67.7%	67.9%	0%
Grade 3-4 AE	21.8%	22.0%	11.5%
Treatment-related Grade 3-4 AE	10.7%	10.7%	0%
Serious Adverse Event	17.6%	17.8%	8.5%
Treatment-related SAE	7.5%	7.5%	0%
Grade 5 AE	1.6%	1.8%[a]	0.6%
Treatment-related Grade 5 AE	0.8%	0.8%	0%
AE leading to dose interruption of atezolizumab	28.7%	28.7%	0%
AE leading to any treatment withdrawal	18.2%	18.2%	0%
All-grade Atezo AESI[b]	51.7%	52.1%	9.5%
Grade 3-4 Atezo AESI	7.9%	7.9%	0.6%
All-grade atezo AESI requiring use of corticosteroids	12.1%	12.3%	0.8%

AESI, AE of special interest; SAE, serious AE. [a] No new deaths due to AEs occurred since the DFS IA clinical cutoff date; a previous 'other' death was updated to a Grade 5 AE.
[b] No new AESI medical concepts noted at OS IA vs DFS IA.

1. Felip, E et al Lancet 2021; 938; 1344-1357; 2. Wakelee. HA et al ASCO 2021; abs #8500.

Tan D, ESMO Singapore 2023

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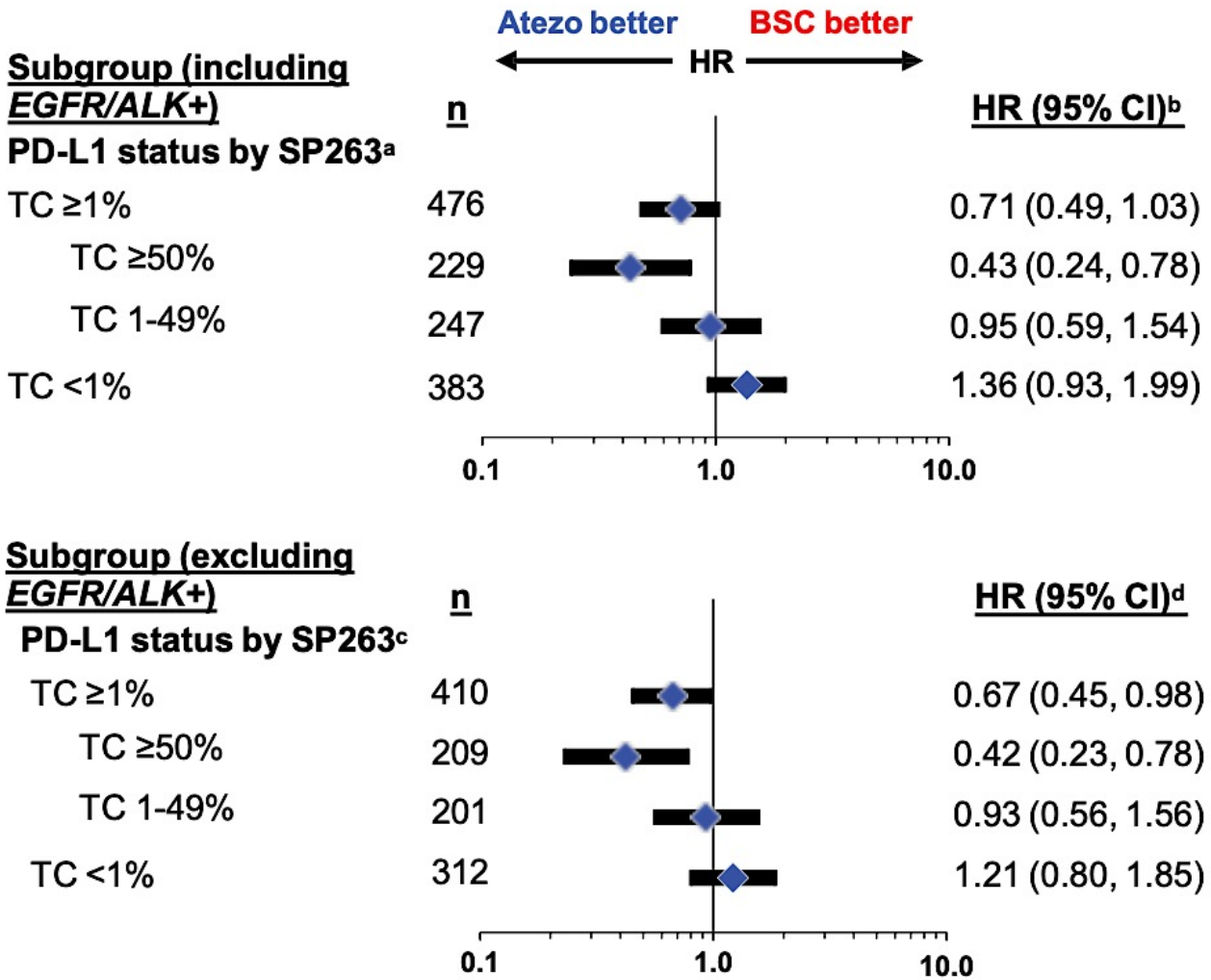
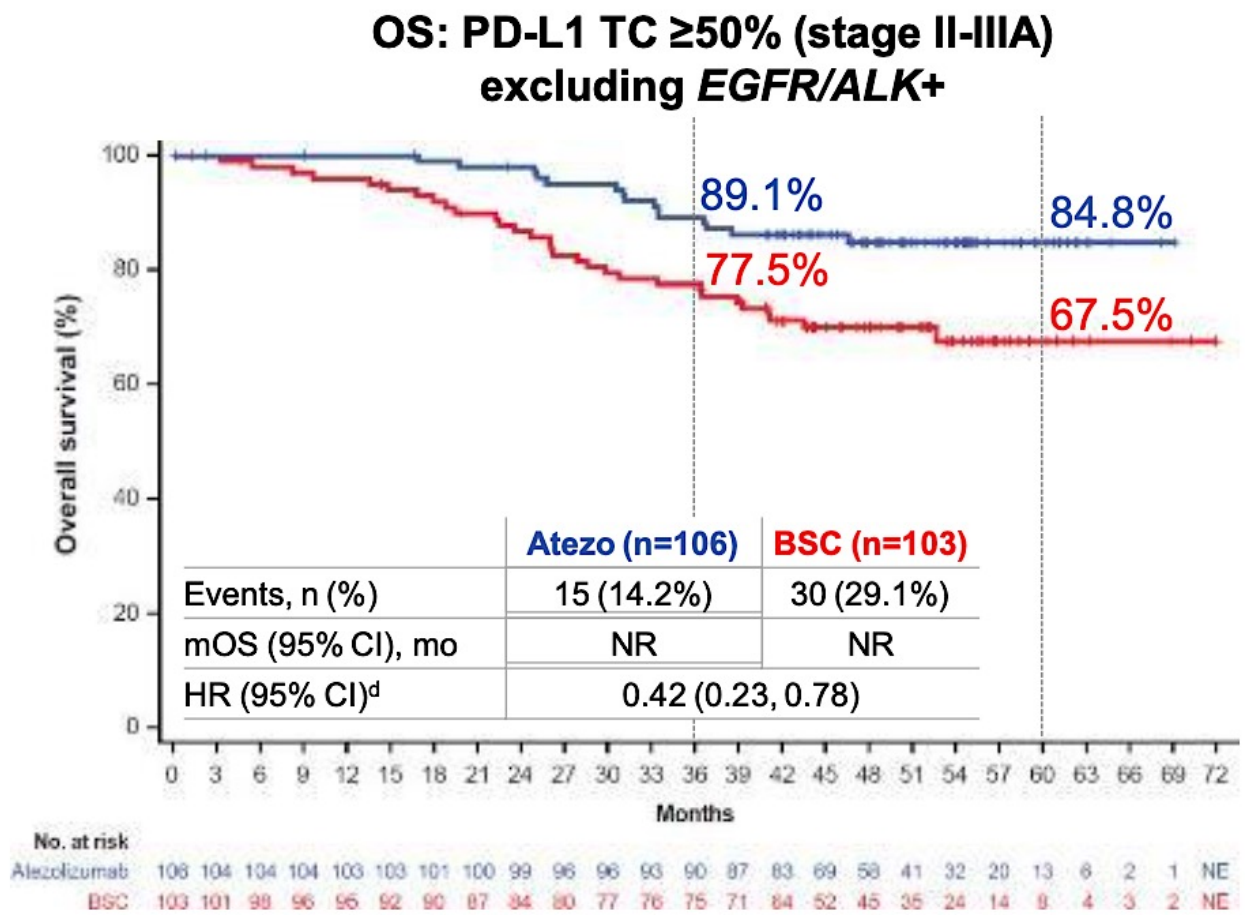
1. Felip, E et al Lancet 2021; 938; 1344-1357; 2. Wakelee. HA et al ASCO 2021; abs #8500.

Tan D, ESMO Singapore 2023

OS by biomarker status (stage II-IIIA)

(data cutoff: 18 Apr '22)

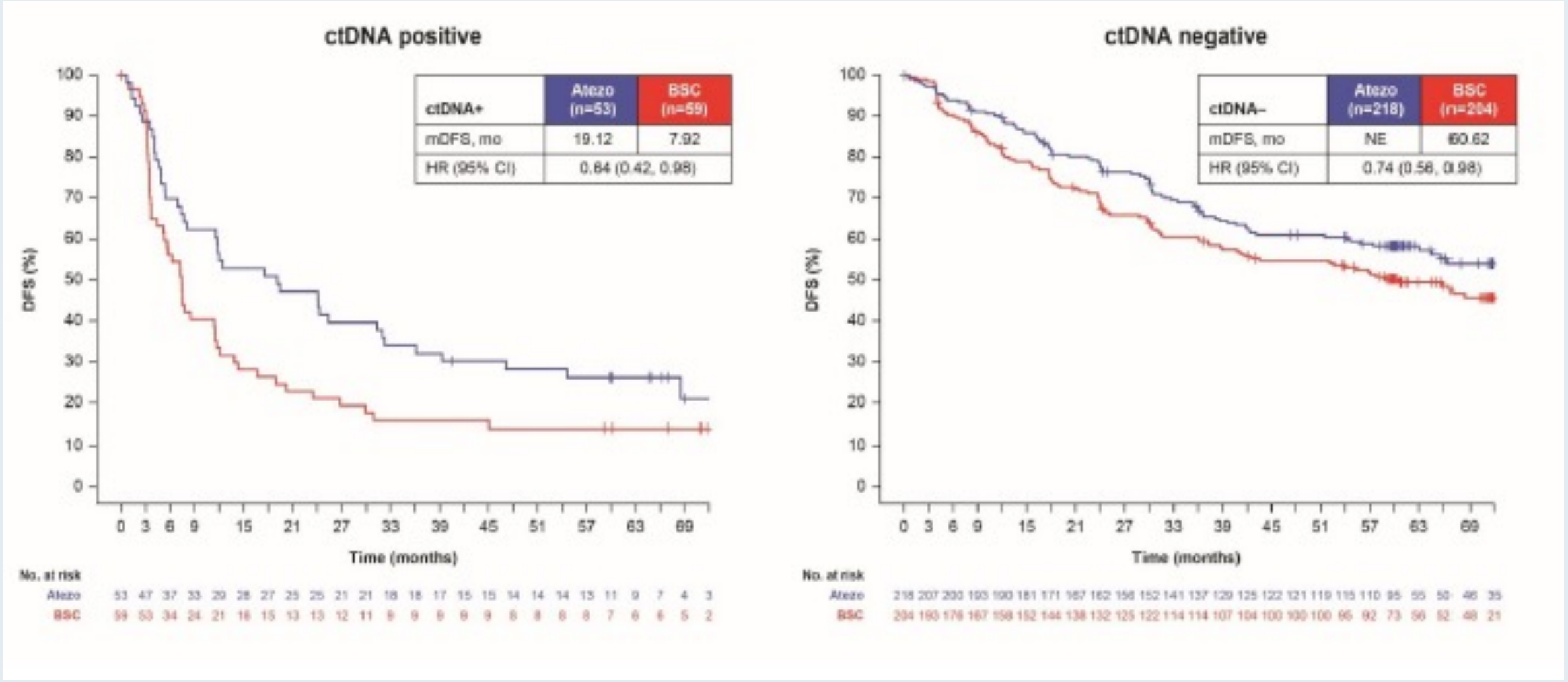




[a] 23 patients had unknown PD-L1 status. [b] Stratified for PD-L1 TC ≥1%; unstratified for all other subgroups. [c] 21 patients had unknown PD-L1 status. [d] Unstratified.

1. Felip, E et al Lancet 2021; 938; 1344-1357; 2. Wakelee. HA et al ASCO 2021; abs #8500.

IMpower010: DFS by Circulating Tumor DNA (ctDNA) Status in the Stage II-IIIA ctDNA-Evaluable Population

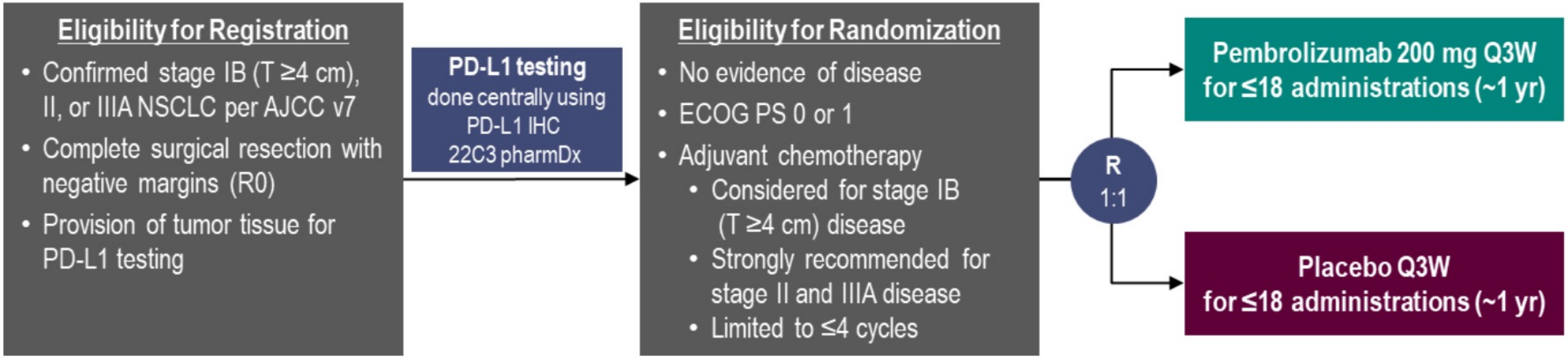


Wakelee HA et al. ESMO 2024;Abstract 1211P.

RTP RESEARCH TO PRACTICE

PEARLS/KEYNOTE-091 Study Design

14% stage 1, ~56% stage II, 30% stage III
60% PD-L1+; ~7% known driver mutation



Dual Primary End Points

- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

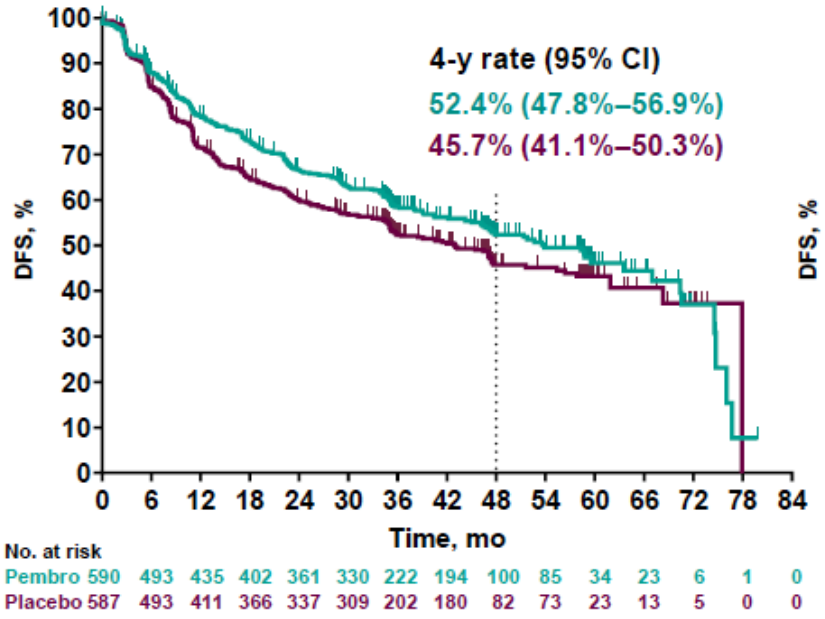
Paz-Ares ESMO plenary 2022, O'Brien ASCO 2022, Lancet Oncol 2023

KN091 Outcomes

ITT Population

HR,[a] 0.81 (95% CI, 0.68–0.96)

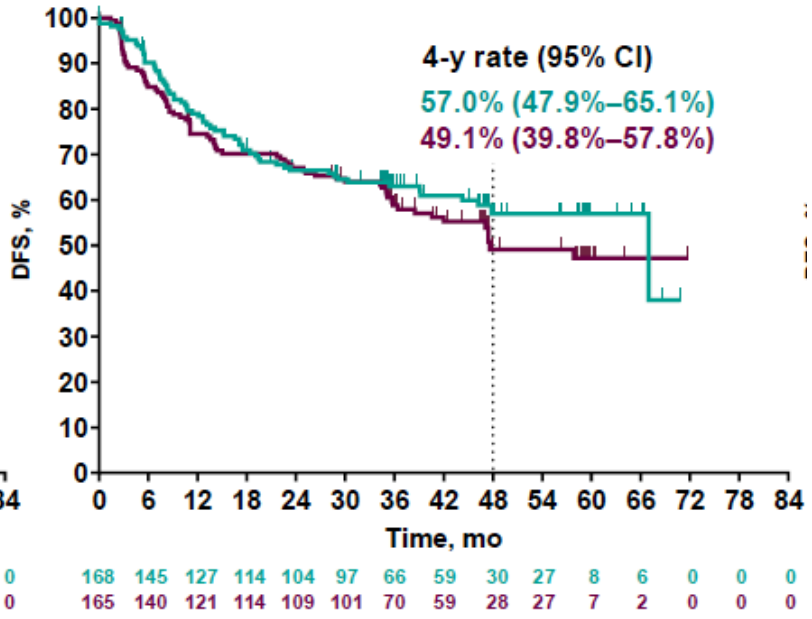
Median (95% CI), mo
Pembrolizumab: 53.8 (46.2–67.0)
Placebo: 43.0 (35.0–51.6)



PD-L1 TPS ≥50%

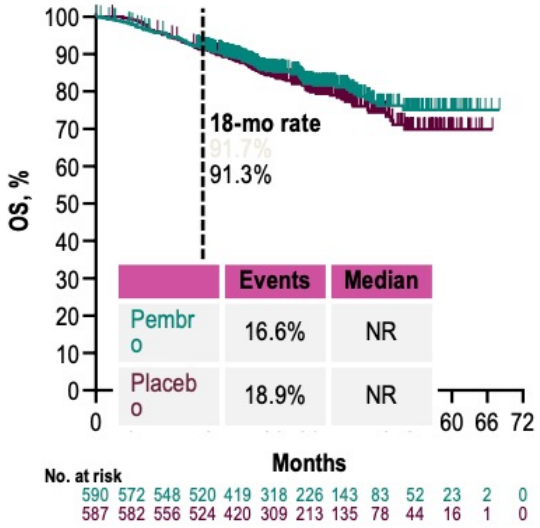
HR,[a] 0.83 (95% CI, 0.59–1.16); *P* = 0.13[b]

Median (95% CI), mo
Pembrolizumab: 67.0 (47.8–NR)
Placebo: 47.6 (36.4–NR)



OS, Overall Population

HR 0.87 (95% CI 0.67-1.15)
***P* = 0.170**



US FDA approval Jan 26, 2023

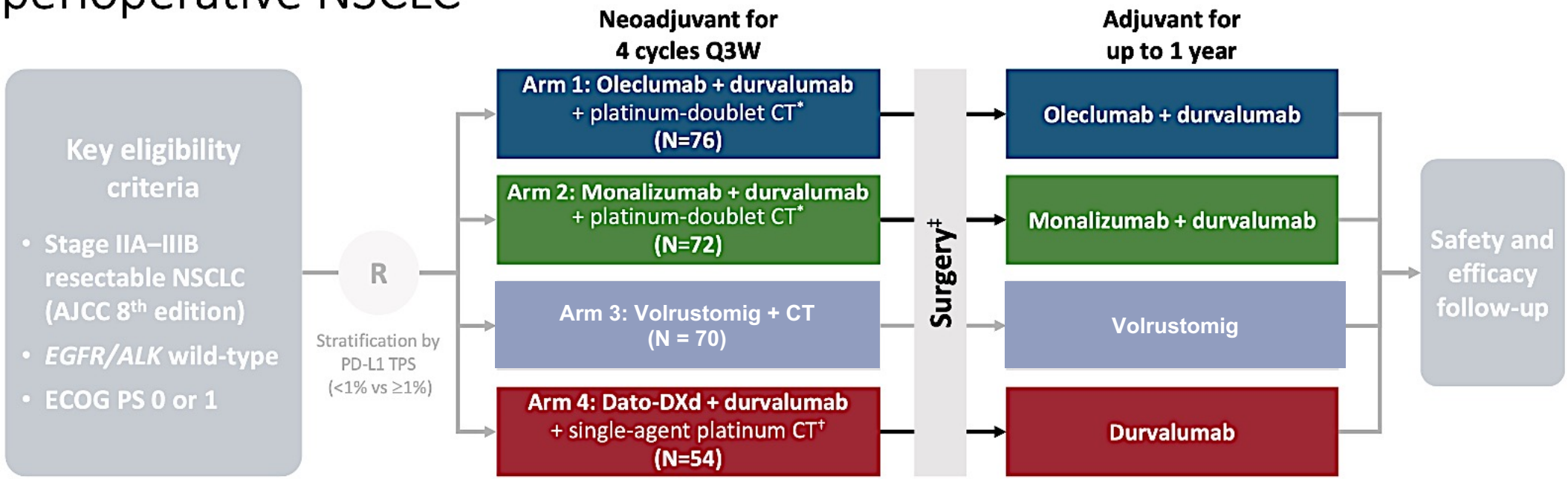
TPS = tumor proportion score

MADRID 2023 ESMO congress

Besse ESMO Immuno-oncology 2023, Paz-Ares ESMO plenary 2022, O'Brien ASCO 2022, Lancet Oncol 2022

NeoCOAST-2

NeoCOAST-2: Open-label, multi-arm platform study in perioperative NSCLC



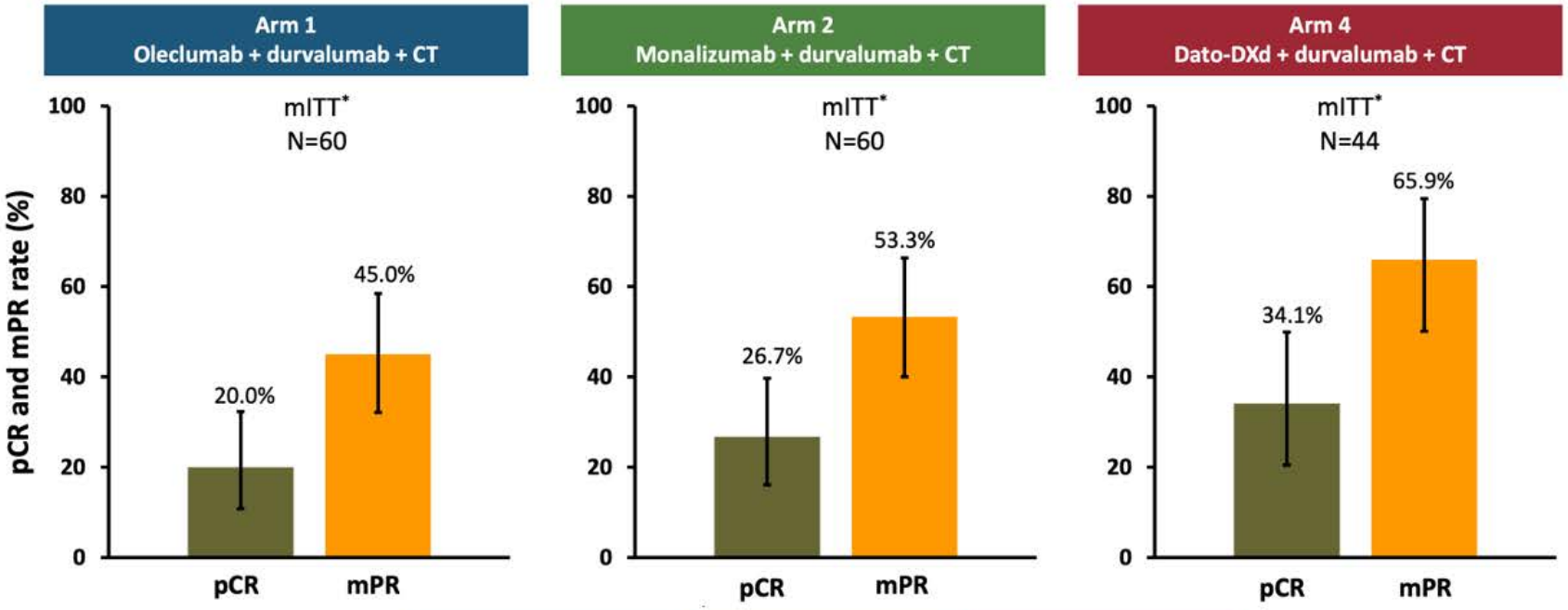
Primary endpoints
- pCR rate§
- Safety and tolerability

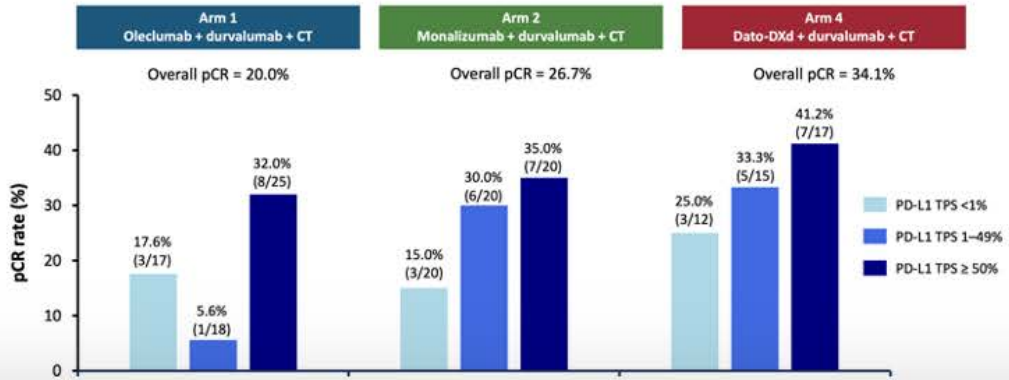
Key secondary endpoints
- mPR rate§ and EFS
- Feasibility of surgery

Statistical considerations
- This study was not powered to make direct statistical comparisons between arms.
- Descriptive statistics are summarised and presented.
- The primary intent was to look for preliminary efficacy signals by calculating pCR rates.

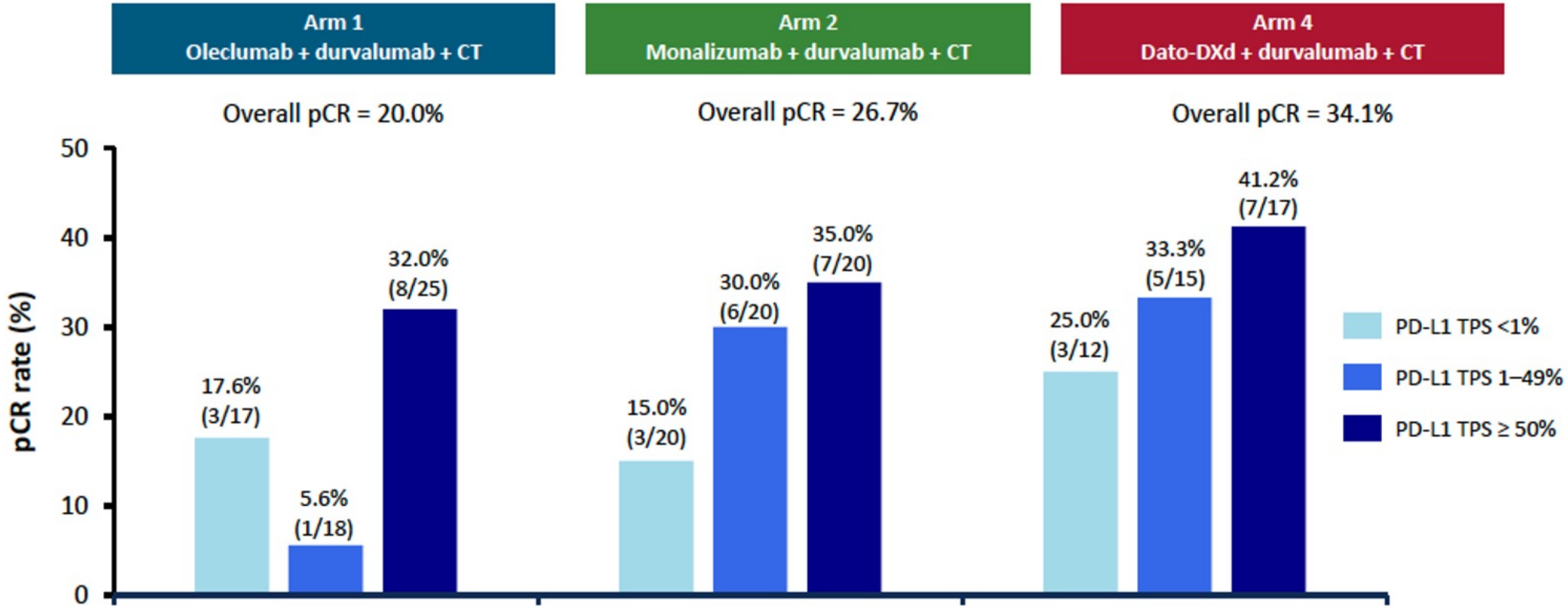
NeoCOAST-2: pCR; surgery in 92-95%

NeoCOAST-2: pCR and mPR rates across treatment arms





pCR rates across baseline PD-L1 expression subgroups



Data cut-off: 17 June 2024. Based on the modified intention-to-treat population which includes all randomised patients with confirmed NSCLC histology who received at least 1 dose of study treatment and had data available at data cut-off, including those who were unable to receive or complete surgery.
Baseline PD-L1 status is assessed using central (Ventana SP263) or local testing (Ventana SP263, pharmDx 28-8, or pharmDx 22C3). Proportion of central results were Arm 1: 12/60 (20%); Arm 2: 18/60 (30%); Arm 4: 13/44 (30%). Local results are reported for all other patients. CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; NSCLC, non-small-cell lung cancer; pCR, pathological complete response; PD-L1, programmed cell death ligand 1; TPS, tumour proportion score.

Cascone T| NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

Adjuvant Immunotherapy in completely resected NSCLC

Study	Treatment	Stage	Phase	n	Primary endpoint	mDFS (m)
IMpower-010	Atezolizumab vs placebo	IB-IIIA	3	1005	DFS in stage II-IIIA with PD-L1 ≥1%, then stage II-IIIA, then ITT	NR vs 35.3 NR vs 35.3 NR vs 37.2
PEARLS/KEYNOTE -091	pembrolizumab	IB-IIIA	3	1177	DFS in ITT and PD-L1 ≥ 50%	53.6 vs 42 NR vs NR
BR.31 (CCTG study) (NCT02273375)	Durvalumab plus or minus chemo	IB-IIIA	3	1415	DFS in PD-L1 ≥25%	69.9 months (95% CI, 57.6-not reached [NR]) vs 60.2 months

Felip E et al. Lancet 2021; O'Brien M et al. Lancet Oncol 2022; Goss G. ESMO 2024

Neoadjuvant Chemo-Immunotherapy

Chemoimmunotherapy → Surgery

Study	Neoadjuvant Therapy	Phase	n	Stage	Primary endpoint	MPR	pCR
NADIM	Nivolumab + Platinum doublet x 3 cycles	2	46	IIIA	PFS at 24 m	83%	63%
NeoTPD01	Toripalimab + Platinum doublet x 3 cycles	2	33	IIIA-IIIB(T3-4N2)	MPR	67%	50%
SAKK 16/14	Platinum-doublet x 3 cycles then Durvalumab x 2 cycles	2	68	IIIA	1 yr EFS	62%	18%
Columbia/MGH	Atezolizumab +Platinum doublet x 4 cycles	2	30	IB-IIIA	MPR	57%	33%
TD-FOREKNOW	Camrelizumab +Platinum doublet vs Platinum Doublet x 3 cycles	2	94	IIIA-IIIB (T3N2)	pCR	65% vs 16%	33% vs 9%
CheckMate 816	Nivolumab + Platinum-Doublet x 3 vs Platinum doublet x 3 cycles	3	773	IB (>4cm)-IIIA	EFS & pCR	37% vs 9%	24% vs 2%

Neoadjuvant chemotherapy: pCR 4.6-20% and MPR 27%

Neoadjuvant immunotherapy: pCR 6-38% and MPR 19-45%

Neoadjuvant chemo-immunotherapy: pCR 18-63% and MPR 37-83%

Provencio M et al Lancet Oncol 2020; Zhao Z et al. ASCO 2021; Rothschild SI et al. JCO 2021; Shu CA et al. Lancet Oncology 2020; Lei J et al. JAMA Oncology 2023; Forde PM et al. NEJM 2022

Perioperative Chemoimmunotherapy

Chemoimmunotherapy → Surgery → Immunotherapy

Study	Ph	Stage	Neoadjuvant Treatment	N	Adjuvant treatment	Primary Endpoint	MPR	pCR	2 yr-EFS	2 yr-OS
NADIM II	2	IIIA, IIIB	Nivolumab plus chemo x 3 Vs chemo x 3	86	Nivolumab x 6 m	pCR	57% vs 14%	37% vs 7%	-	67% vs 41%
KEYNOTE-671	3	II-IIIB (N2)	Pembrolizumab plus chemo x 4 vs chemo	797	Pembrolizumab x 13 cycles	EFS and OS	30% vs 11%	18% vs 4%	62.4% vs 40.6%	81% vs 78%
AEGEAN	3	II-IIIB (N2)	Durvalumab plus chemo vs placebo plus chemo	802	Durvalumab vs placebo x 12 cycles	EFS 12m and PCR	33% vs 12%	17% vs 4%	63.3% vs 52.4%	-
CheckMate 77T	3	IIA-IIIB (N2)	Nivolumab plus chemo x 4 vs chemo x 4	461	Nivolumab x 1 year	18 m EFS	35% vs 12%	25% vs 5%	18 m 70.2% vs 50%	-
NEOTORCH	3	II-III	Toripalimab plus chemo x 3 vs chemo x 3	501	Toripalimab x 13 cycles	EFS and MPR	49% vs 8%	25% vs 1%	65% vs 39%	NE vs 30.4m

Provencio M et al. NEJM 2024; Wakelee H et al NEJM 2023; Heymach J et al. NEJM 2023; Cascone T et al. NEJM 2024; Lu S et al. JAMA 2024

Advantages of Neoadjuvant, perioperative and adjuvant chemoimmunotherapy

Neoadjuvant or perioperative
Early access to systemic therapy, address micrometastatic disease earlier, better priming of immune system
May downstage tumor, improve resectability
Allows response assessment to systemic therapy
Pathologic endpoints- possible surrogates for improved EFS
Increased compliance to therapy with neoadjuvant approach

Adjuvant
No delay to curative intent surgery
Pathologic staging available prior to systemic therapy, extent of disease
Adequate tumor specimen and time for genomic testing
Less post-operative morbidity and mortality

PACIFIC

Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Study

- Patients with Stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks

All-comers population

1-42 days post-CRT

R

2:1 randomization, stratified by age, sex, and smoking history N=713

Durvalumab 10 mg/kg q2w for up to 12 months N=476

Placebo N=237

Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

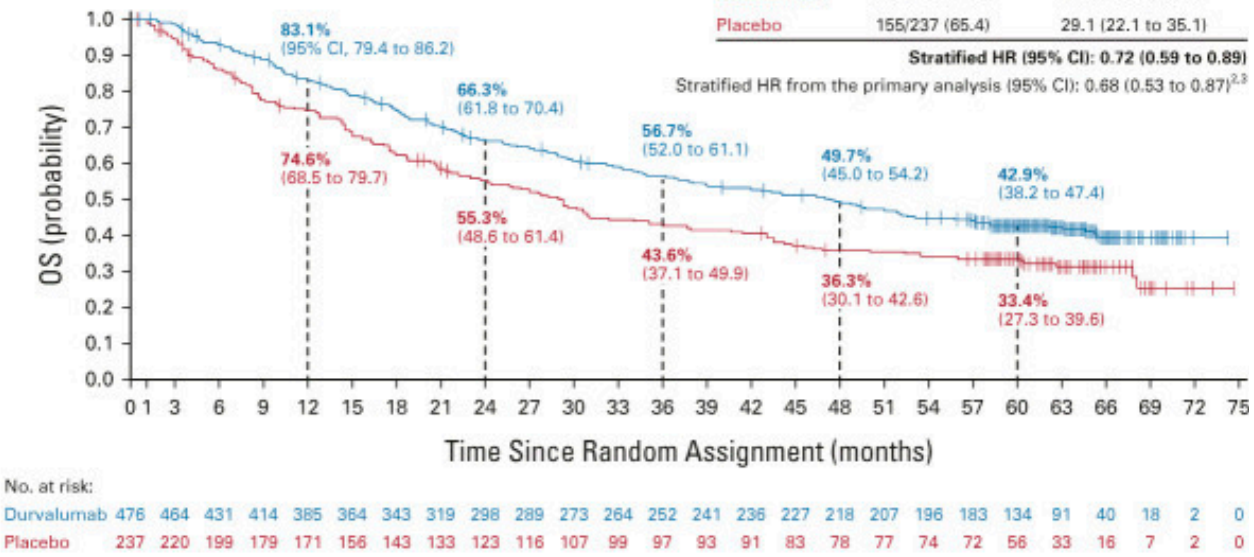
Key secondary endpoints

- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



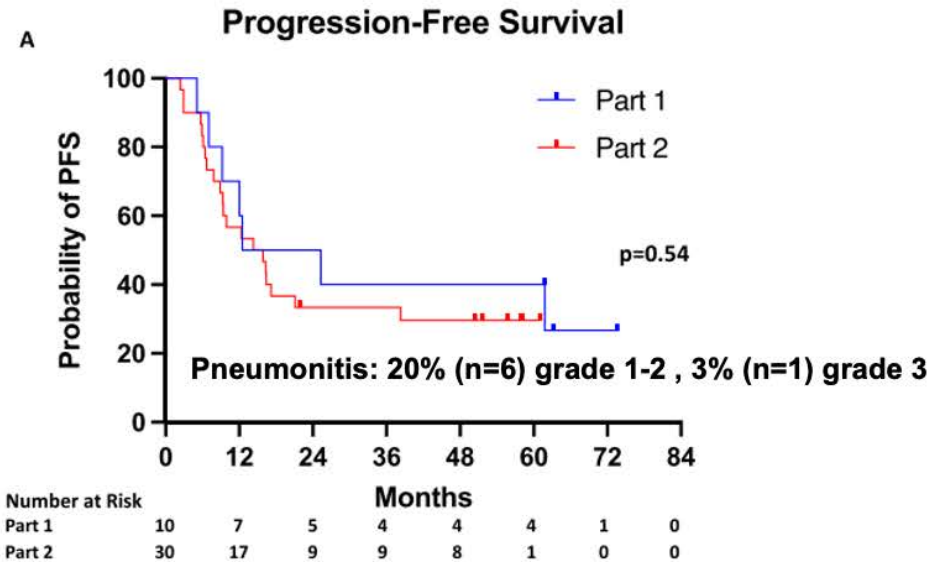
No. at risk:

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

Spigel DR et al, *J Clin Oncol* 2022

Concurrent CRT-IO trials in unresectable NSCLC

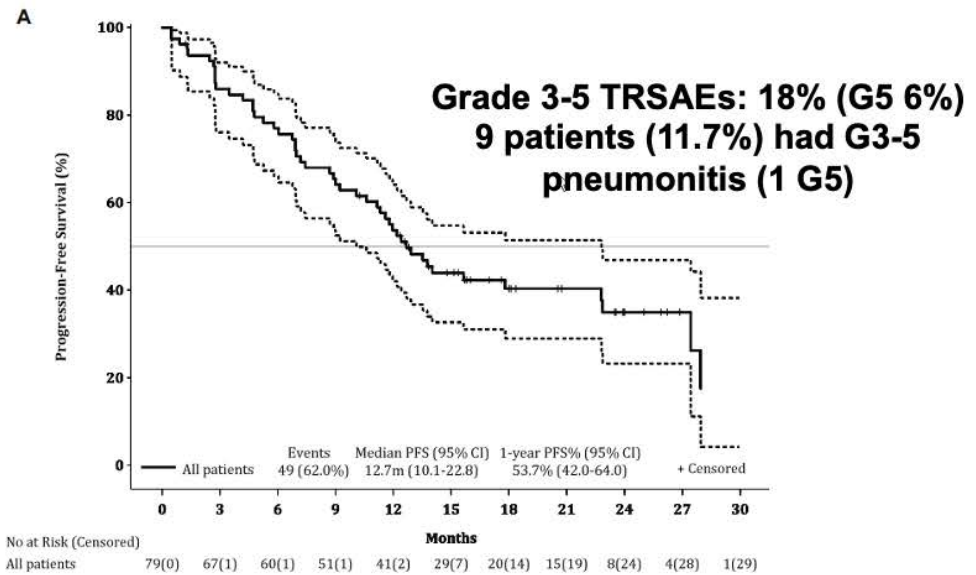
DETERRED P2 trial: CRT with concurrent and/or consolidative atezolizumab comparable efficacy as consolidative durvalumab in PACIFIC trial.



Median PFS: 15.1 mo Part 2
Median OS: NR Part 2

Liu et al., *Lung Cancer* 2022

NICOLAS V.3 P2 trial: CRT with concurrent nivolumab followed by nivolumab for 1 year

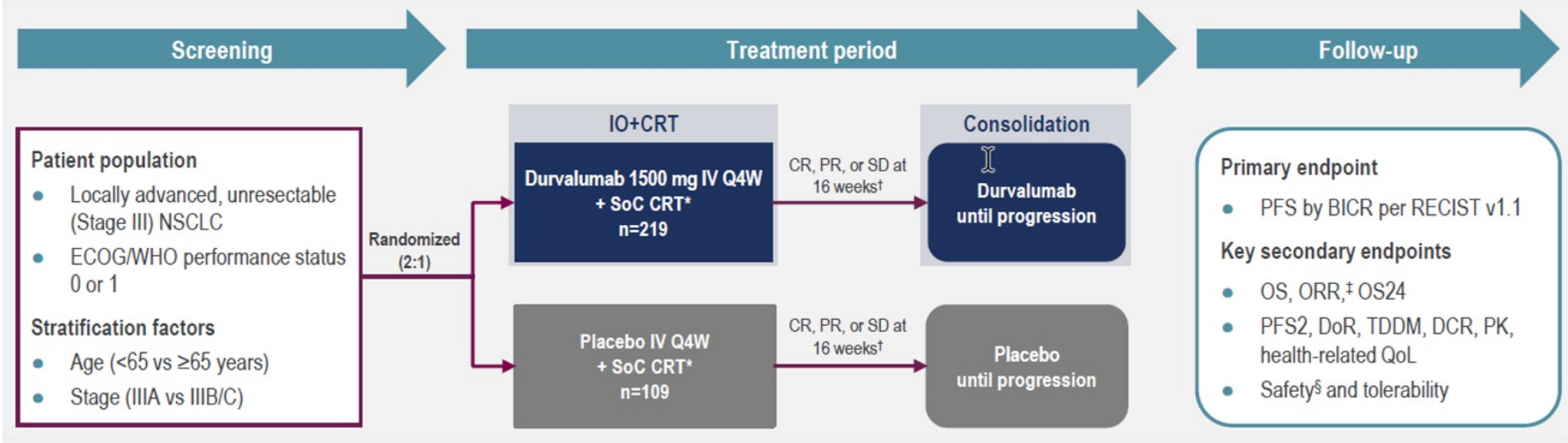


1-year PFS 53.7%; median PFS 12.7 mo
Median OS 38.8 mo; 2-year OS 63.7%

Peters et al., *J Thorac Oncol* 2021

PACIFIC-2: P3R durvalumab in combination with CRT for unresectable stage III NSCLC

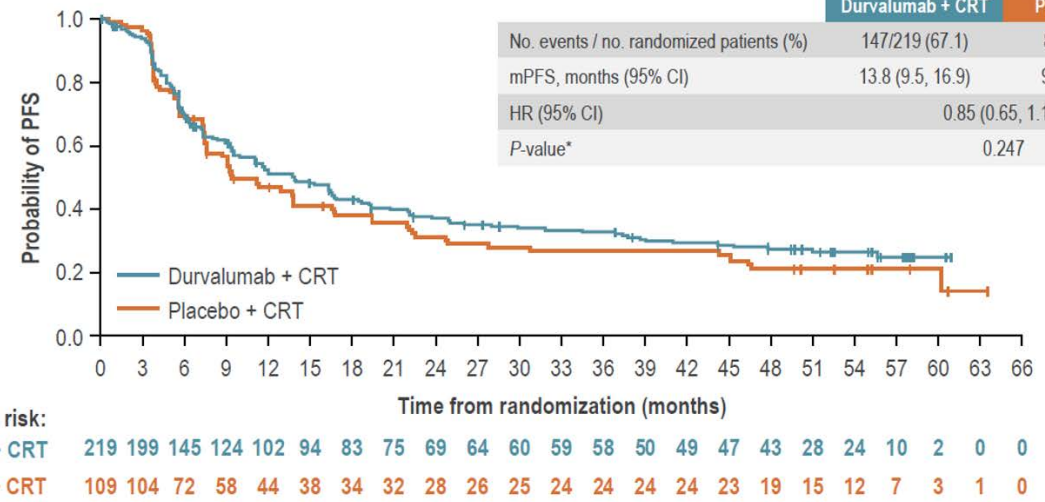
PACIFIC-2 (NCT03519971) is a phase 3, randomized, double-blind, placebo-controlled, multicenter, global study of durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo



Patients were recruited from **29 March 2018** through **24 June 2019** across 106 sites in Asia, Eastern Europe, and the Americas, including: Brazil, Czech Republic, Hungary, India, Japan, Mexico, Peru, Philippines, Poland, Republic of Korea, Russia, Turkey, Thailand, and Vietnam.

Bradley JD, ELCC 2024

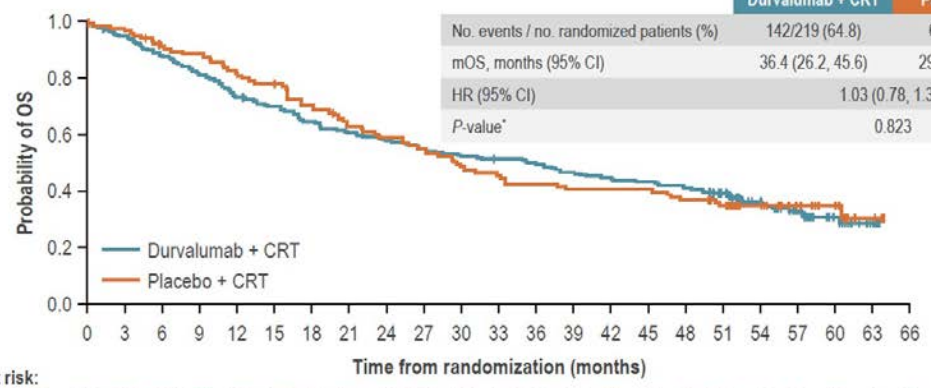
PACIFIC-2: PFS in ITT population



	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	147/219 (67.1)	80/109 (73.4)
mPFS, months (95% CI)	13.8 (9.5, 16.9)	9.4 (7.5, 16.6)
HR (95% CI)	0.85 (0.65, 1.12)	
P-value*	0.247	

No. at risk:																							
Durvalumab + CRT	219	199	145	124	102	94	83	75	69	64	60	59	58	50	49	47	43	28	24	10	2	0	0
Placebo + CRT	109	104	72	58	44	38	34	32	28	26	25	24	24	24	24	23	19	15	12	7	3	1	0

PACIFIC-2: OS, ORR in ITT and AEs in safety population



	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	142/219 (64.8)	69/109 (63.3)
mOS, months (95% CI)	36.4 (26.2, 45.6)	29.5 (23.2, 45.1)
HR (95% CI)	1.03 (0.78, 1.39)	
P-value*	0.823	

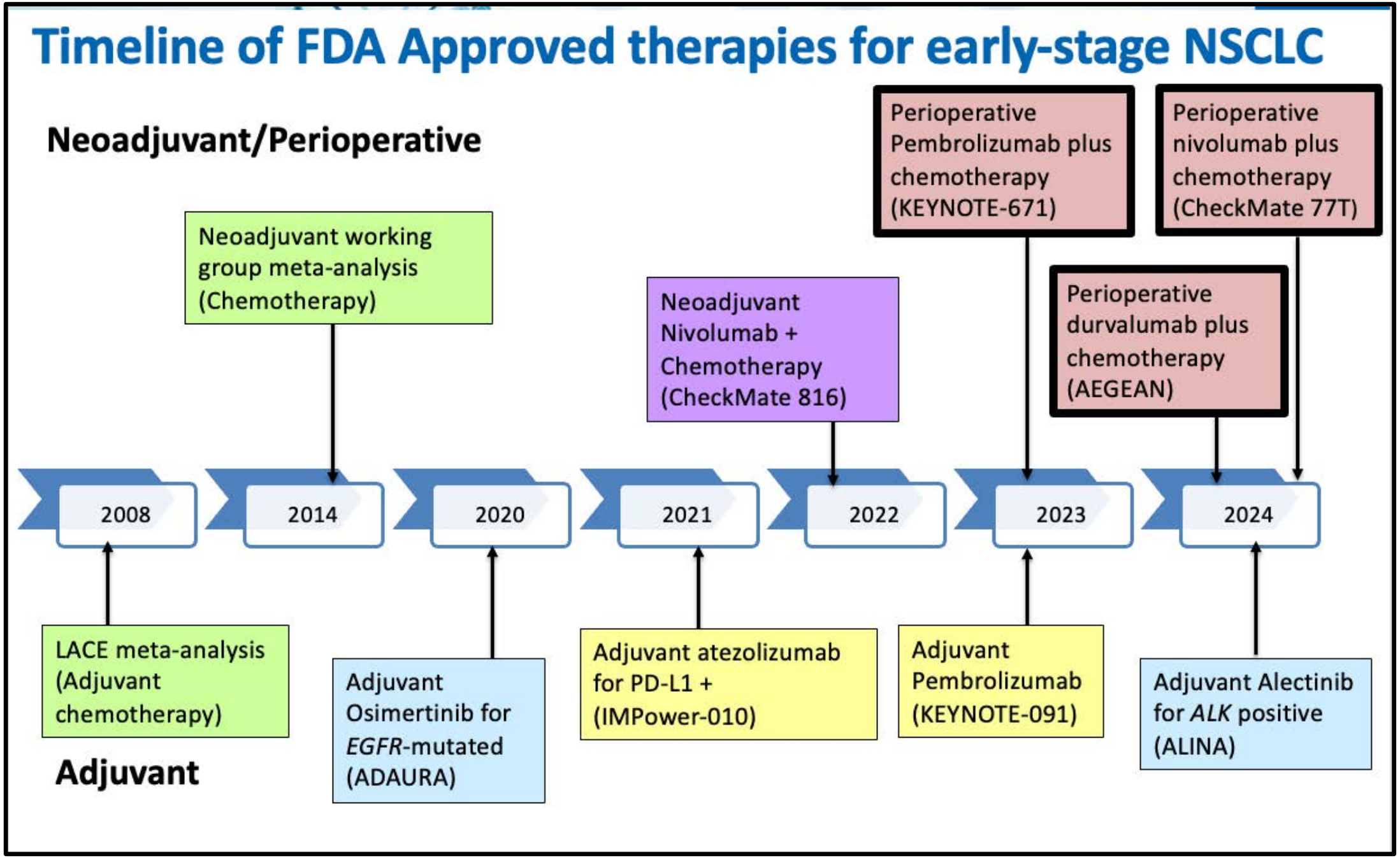
No. at risk:																							
Durvalumab + CRT	219	207	191	177	160	152	141	132	126	120	114	111	107	100	95	94	89	75	49	31	15	1	0
Placebo + CRT	109	106	98	95	87	83	75	66	62	57	51	47	45	43	43	43	39	35	27	17	9	2	0

There was no difference in ORR between the durvalumab (60.7%; 95% CI: 53.9, 67.2) and placebo (60.6%; 95% CI: 50.7, 69.8) arms (p=0.976).

In the first 4 months of IO+CRT, a higher number of AEs leading to discontinuation (14.2% vs 5.6%) or death (6.8% vs 4.6%) occurred in the durvalumab arm

Bradley JD, ELCC 2024

Timeline of FDA Approved therapies for early-stage NSCLC



Discussion Questions

- Regulatory and reimbursement issues aside, in general, which neoadjuvant/adjuvant treatment would you most likely recommend for an otherwise healthy 65-year-old patient with Stage IIB adenocarcinoma of the lung with no targetable tumor mutations and a PD-L1 TPS of 50%? How do you decide between neoadjuvant, perioperative and adjuvant immunotherapy for these patients?

Module 15: Immunotherapy and Other Nontargeted Approaches for NSCLC

Management of Nonmetastatic NSCLC without a Targetable Mutation — Dr Govindan

First- and Later-Line Therapy for Metastatic NSCLC without a Targetable Mutation — Dr Liu

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First- and Later-Line Therapy for Metastatic NSCLC without a Targetable Mutation

Stephen V. Liu, MD
Georgetown University

NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

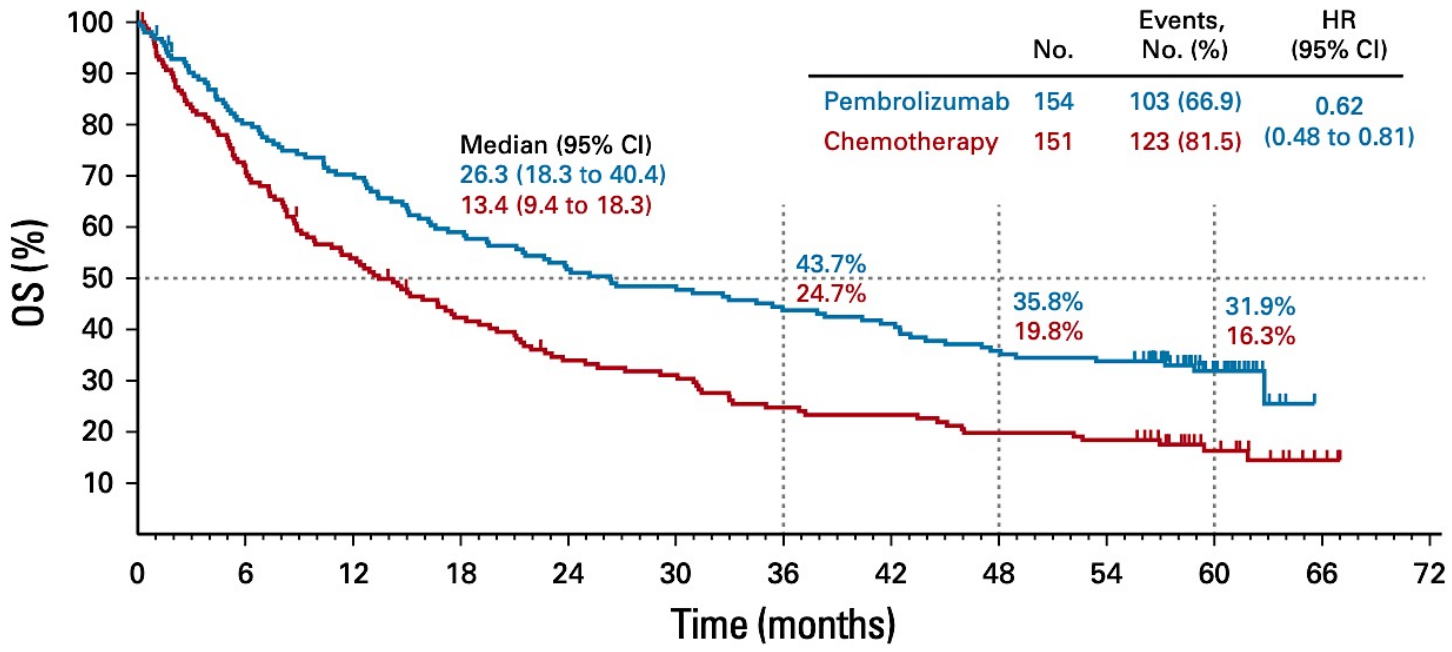
http://lombardi.georgetown.edu
Lombardi CancerLine: 202.444.4000

Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Jazz Pharmaceuticals Inc, Johnson & Johnson Pharmaceuticals
Consulting Agreements	AbbVie Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Guardant Health, Jazz Pharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Merus, Mirati Therapeutics Inc, Natera Inc, Novartis, OSE Immunotherapeutics, Pfizer Inc, Regeneron Pharmaceuticals Inc, Revolution Medicines, Takeda Pharmaceuticals USA Inc, Yuhan Corporation
Contracted Research	AbbVie Inc, Alkermes, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Cogent Biosciences, Duality Biologics, Elevation Oncology, Ellipses Pharma, Genentech, a member of the Roche Group, Gilead Sciences Inc, Merck, Merus, Nuvalent, OSE Immunotherapeutics, Puma Biotechnology Inc, RAPT Therapeutics, Synthekine, SystImmune Inc

NSCLC Without a Targetable Mutation

- Standard first-line treatment remains immunotherapy
- Value is durability – potential for long-term survival



Reck, JCO 2021

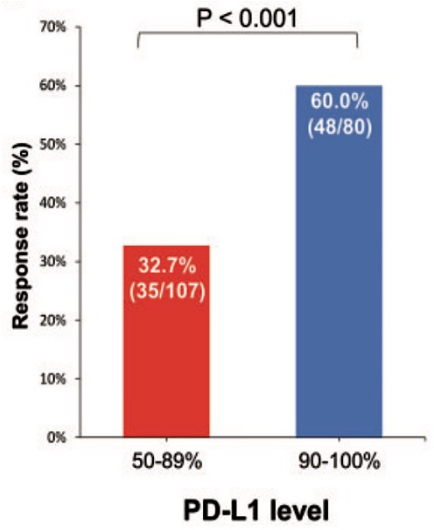
Georgetown | Lombardi

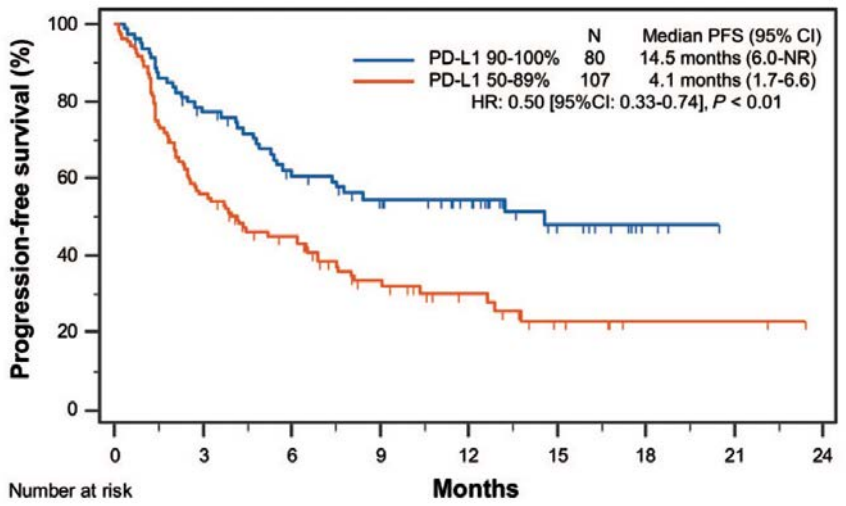
Multiple 1L Immunotherapy Strategies

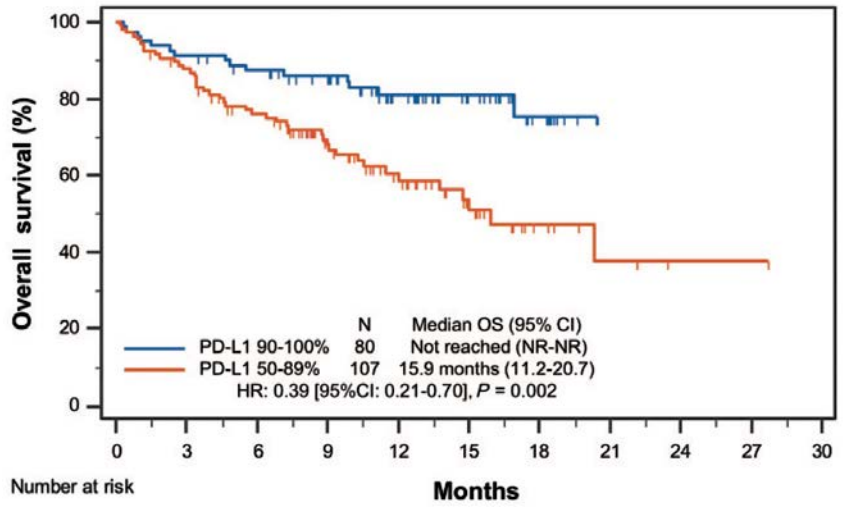
- PD(L)1 monotherapy – primarily for PD-L1 high
  - Pembrolizumab, atezolizumab, cemiplimab
- PD(L)1 + chemotherapy
  - Non-squamous: platinum + pemetrexed + pembrolizumab, carboplatin + nab-paclitaxel + atezolizumab, carboplatin + paclitaxel + bevacizumab + atezolizumab, cemiplimab + chemotherapy
  - Squamous: platinum + nab-paclitaxel/paclitaxel + pembrolizumab, cemiplimab + chemotherapy
- Dual checkpoint strategies
  - Nivolumab + ipilimumab +/- chemotherapy
  - Durvalumab + tremelimumab + chemotherapy

Choosing Immunotherapy Regimens

- Primary predictive marker remains PD-L1 expression
  - PD-L1 expression is a spectrum
    - PD-L1 TPS 50-89%: RR 32.7%, mPFS 4.1m, mOS 15.9m
    - PD-L1 TPS 90-100%: RR 60.0%, mPFS 14.5m, mOS not reached



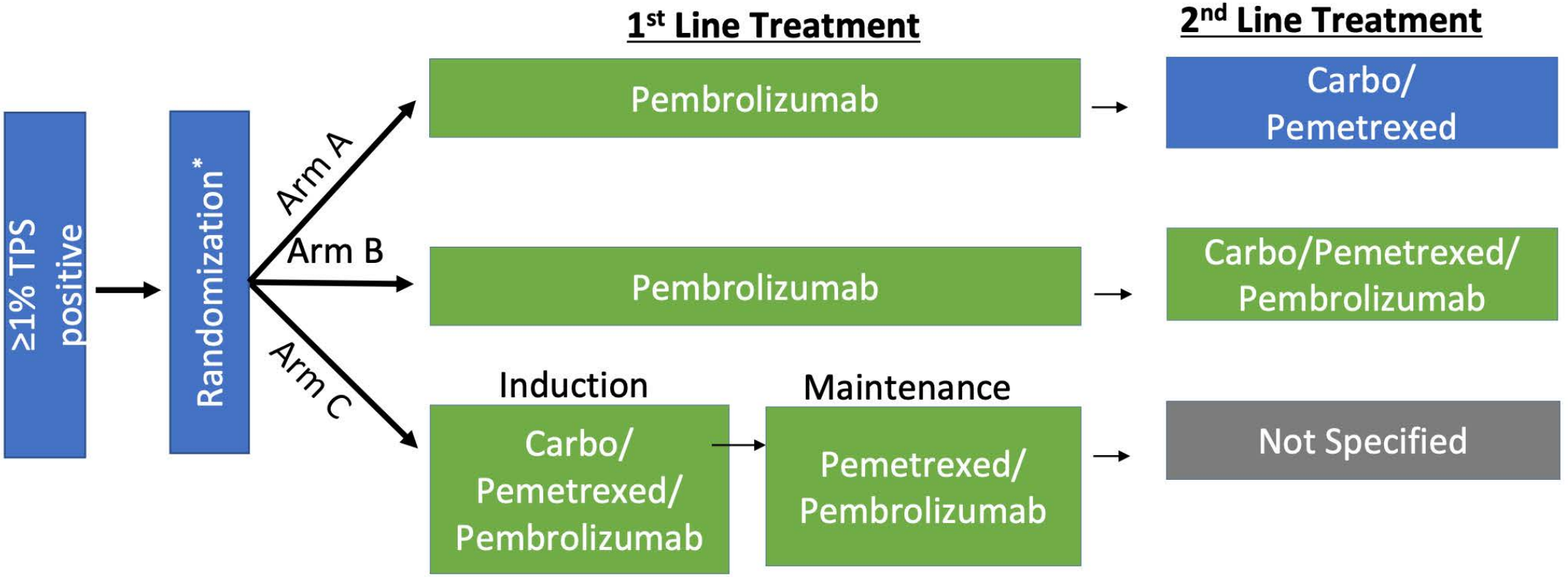




Aguilar, Ann Oncol 2019

Immunotherapy +/- Chemotherapy?

INSIGNA: A Randomized, Phase III Study of Firstline **I**mmunotherapy alone or in Combination with Chemotherapy in Induction/Maintenance or Post-progression in Advanced **N**onsquamous Non-Small Cell Lung Cancer (NSCLC) with Immunobiomarker **SIGN**ature-driven **A**nalysis



ECOG-ACRIN/SWOG: Borghaei/Chiang

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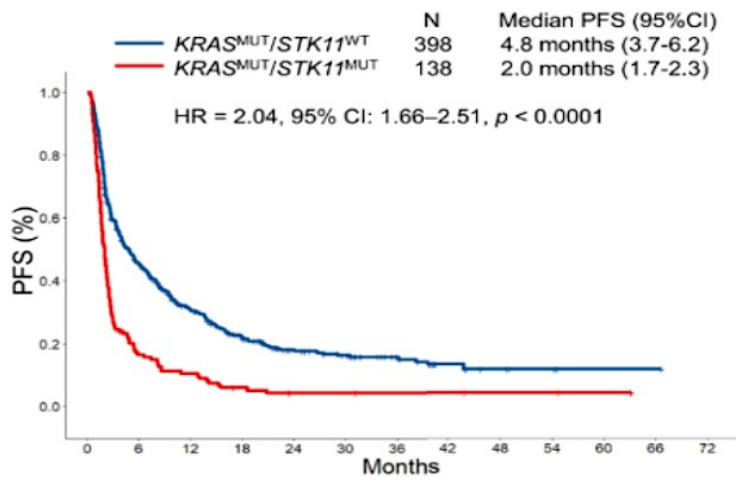
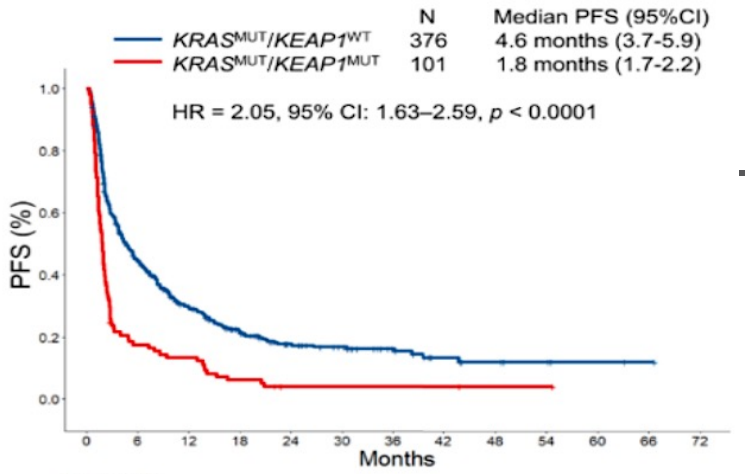
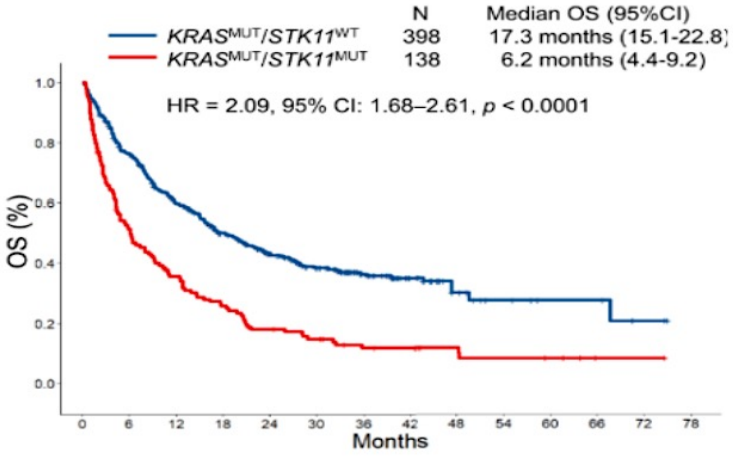
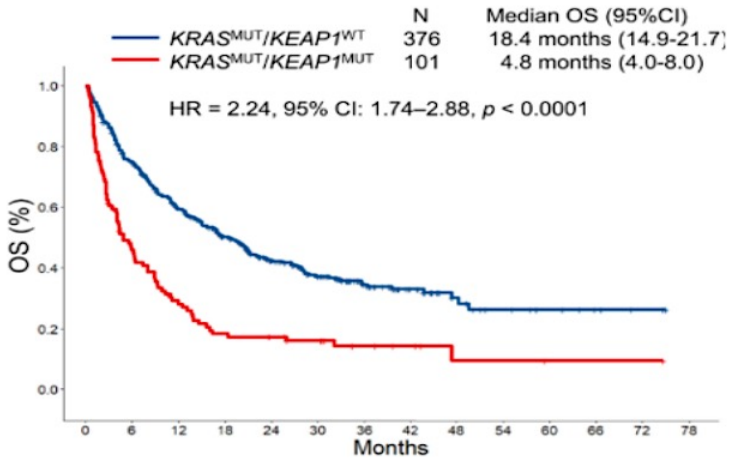
Possible Negative Predictors

- Mutations in STK11 and KEAP1









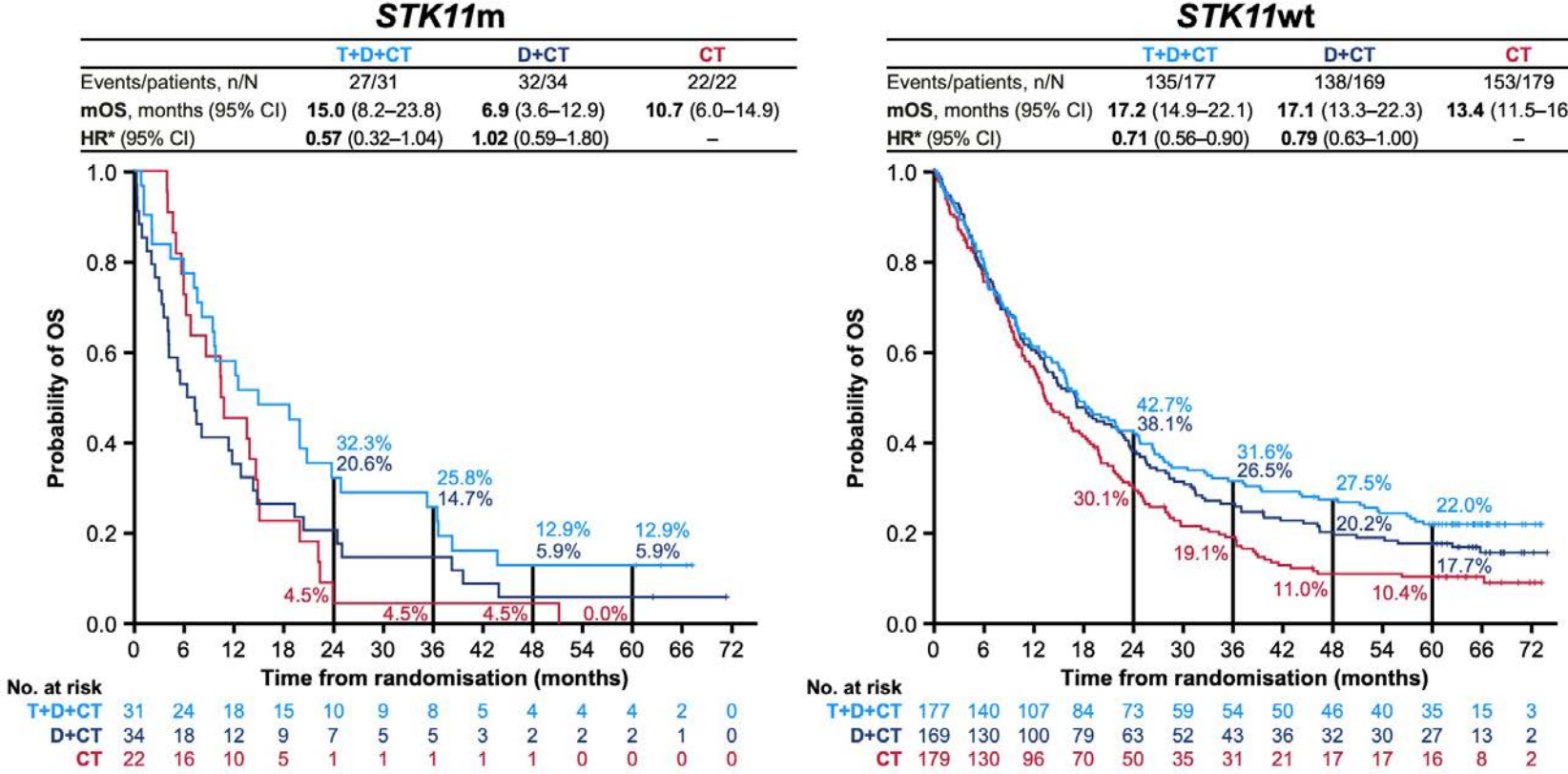
- Portend poor prognosis with PD(L)1 monotherapy in KRAS mutant NSCLC
- Supported by multiple datasets

Ricciuti, JTO 2021

Georgetown | Lombardi

Targeting CTLA-4 in STK11/KEAP1

- Benefit from PD(L)1/CTLA4 in STK11/KEAP1 mt
  - Subset data from CM 227, CM 9LA, POSEIDON

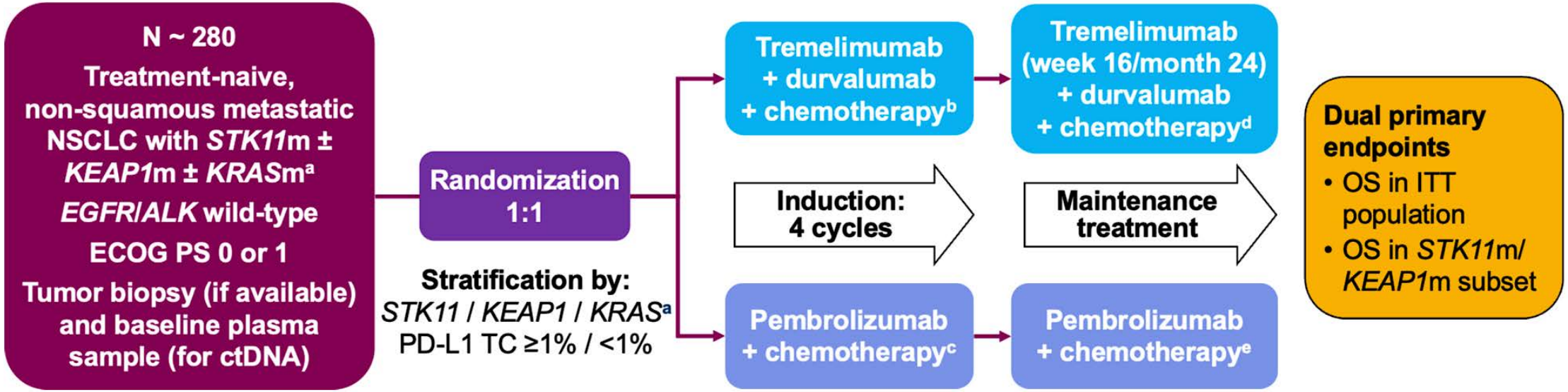


Peters, ESMO IO 2023

Georgetown | Lombardi

STK11 and KEAP1

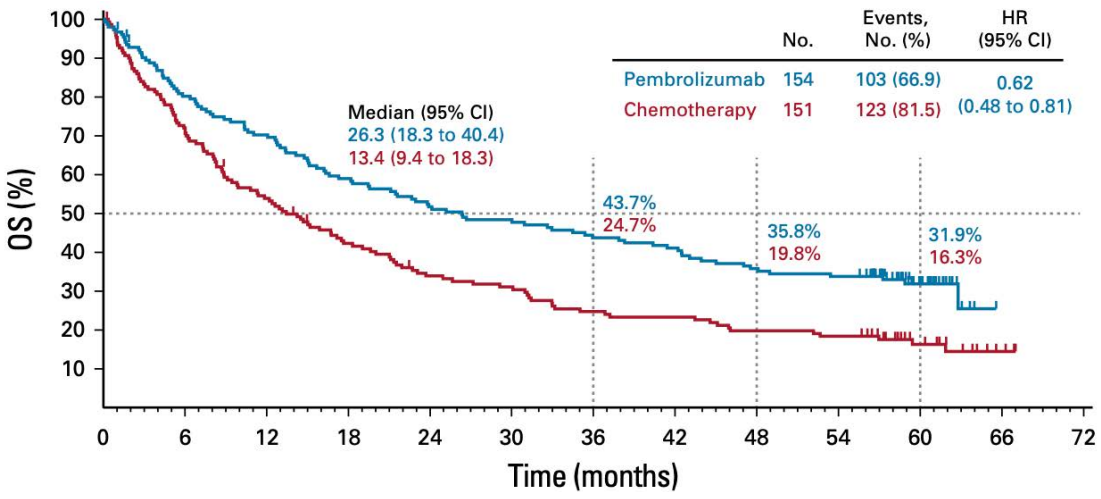
- Phase IIIb TRITON study
  - KEYNOTE-189 vs POSEIDON in KRAS, STK11, KEAP1 mt

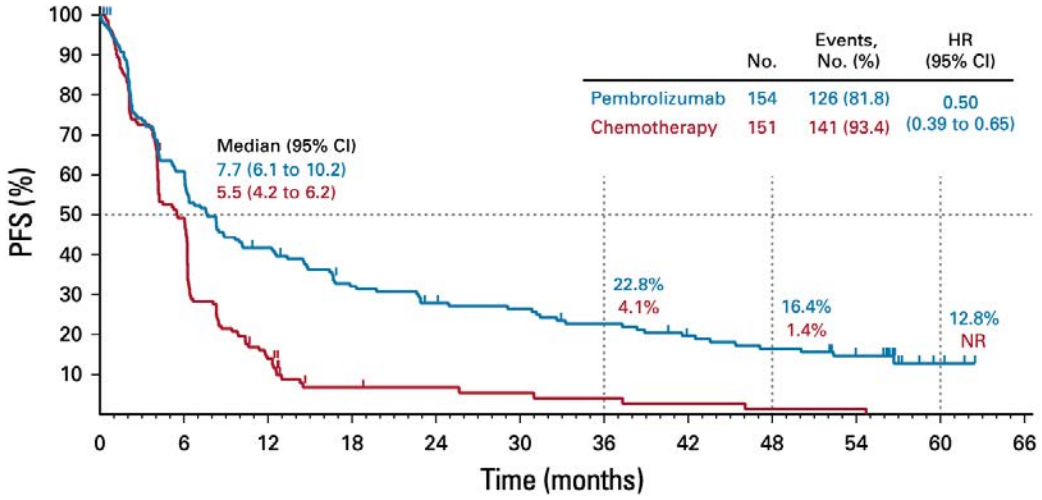


Skoulidis, ASCO 2024

Resistance and Immunotherapy

- Long-term survival is possible, but most pts progress
  - Heterogeneous and poorly understood mechanisms
  - Intrinsic vs acquired resistance

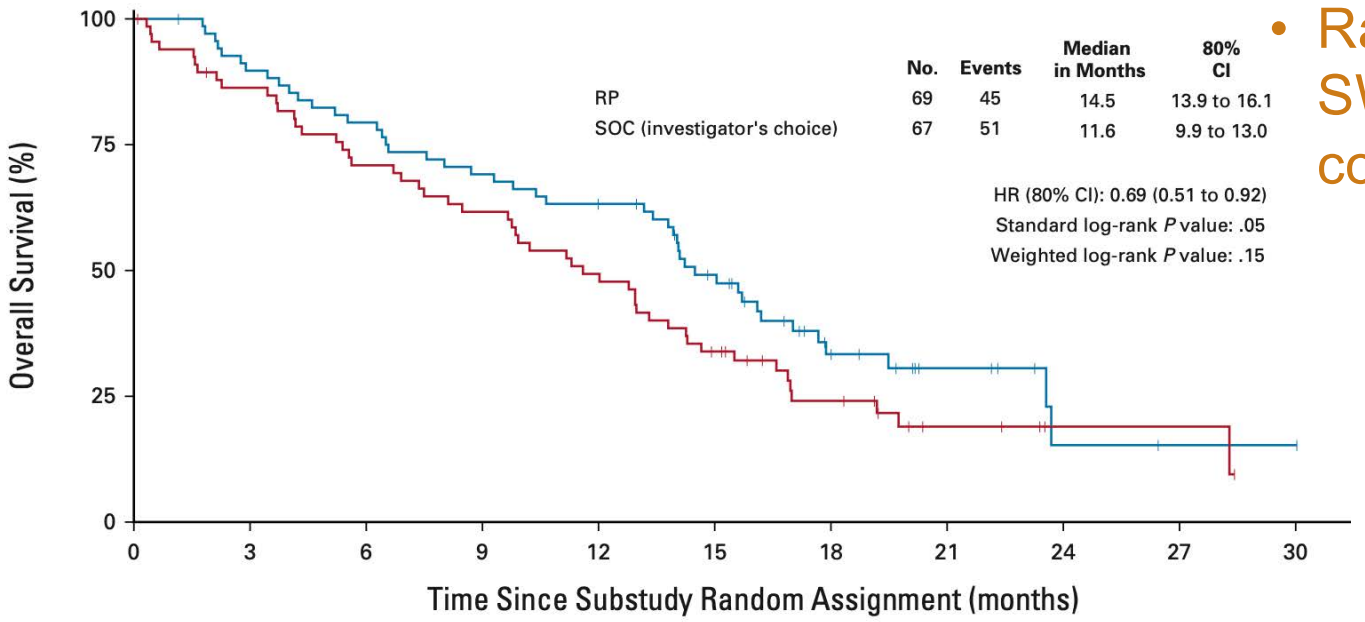




Reck, JCO 2021

Later-Line Therapy

- Lung-MAP S1800A
  - Pembrolizumab + ramucirumab vs standard of care
    - Similar RR and PFS between arms
    - Survival favored pembro/ram (14.5m vs 11.6m, HR 0.69)



- Randomized Phase III SWOG Pragmatica completed enrollment

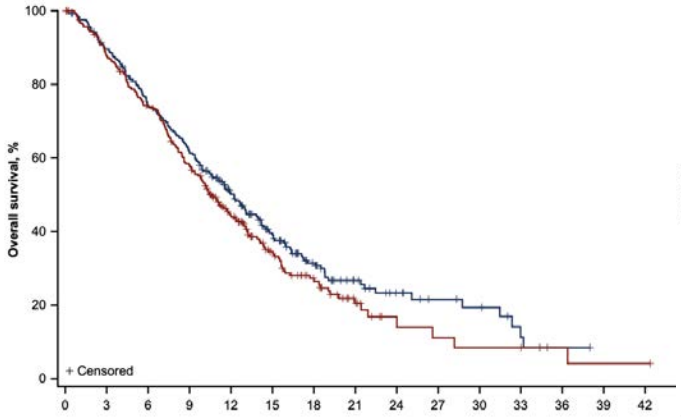
Reckamp, JCO 2022

Georgetown | Lombardi

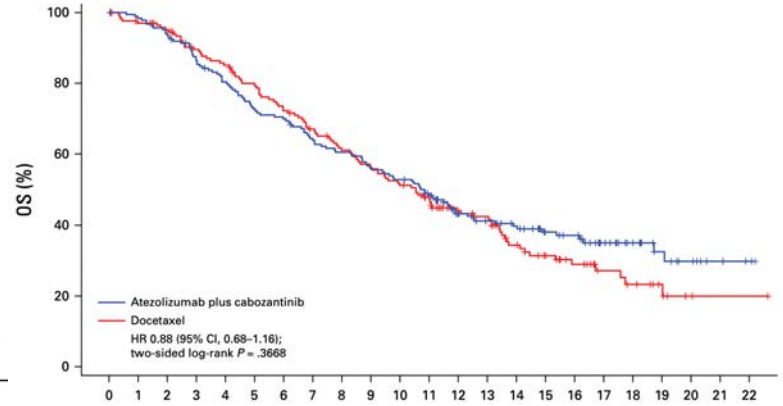
Later-Line Therapy

- Multikinase TKIs added to PD(L)1
  - Promising rationale and early studies, negative phase III trials

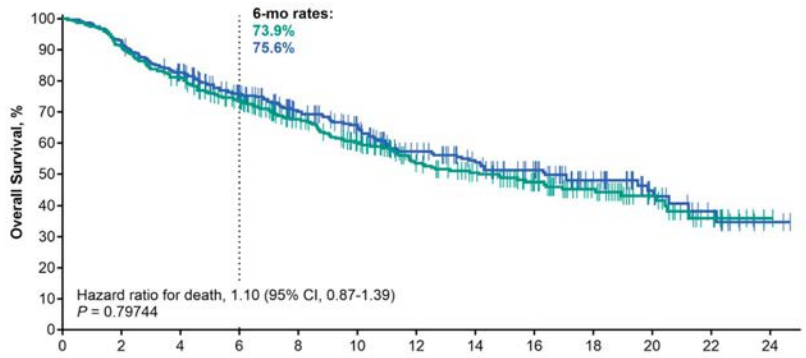
SAPPHIRE
Sitravatinib + Nivolumab



CONTACT-01
Cabozantinib + Atezolizumab



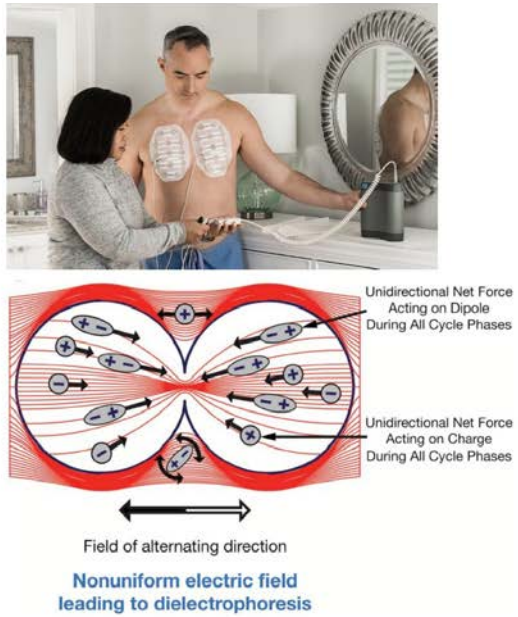
LEAP 007
Lenvatinib + Pembrolizumab

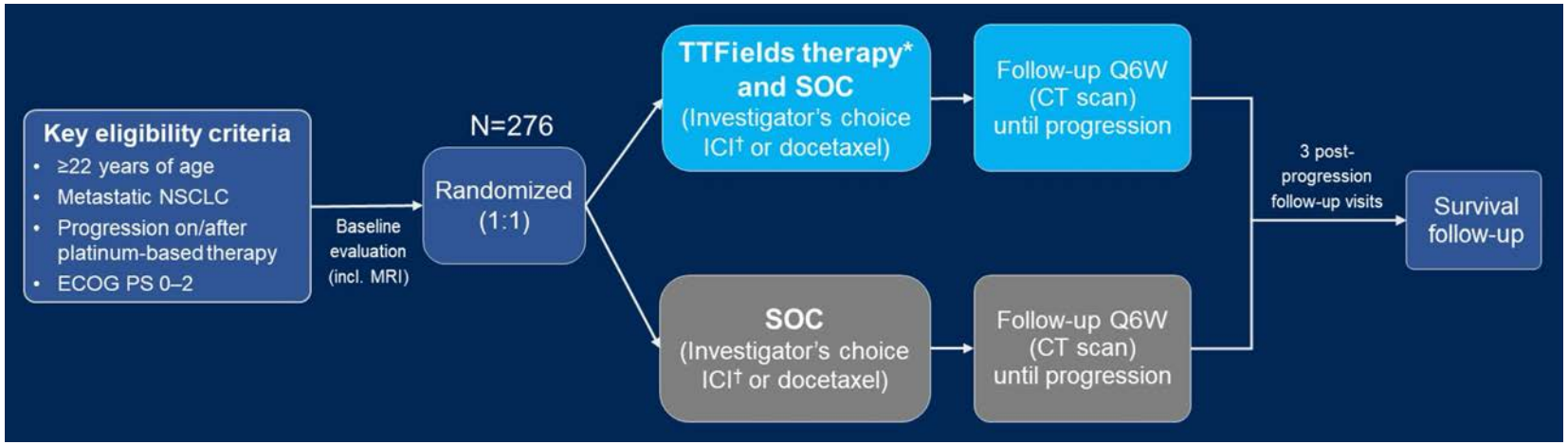


Borghaei, Ann Oncol 2023; Neal, JCO 2024; Yang, JTO 2023

Tumor Treating Fields

- LUNAR (EF-24)
  - Phase III trial of PD(L)1 or docetaxel +/- TTFields



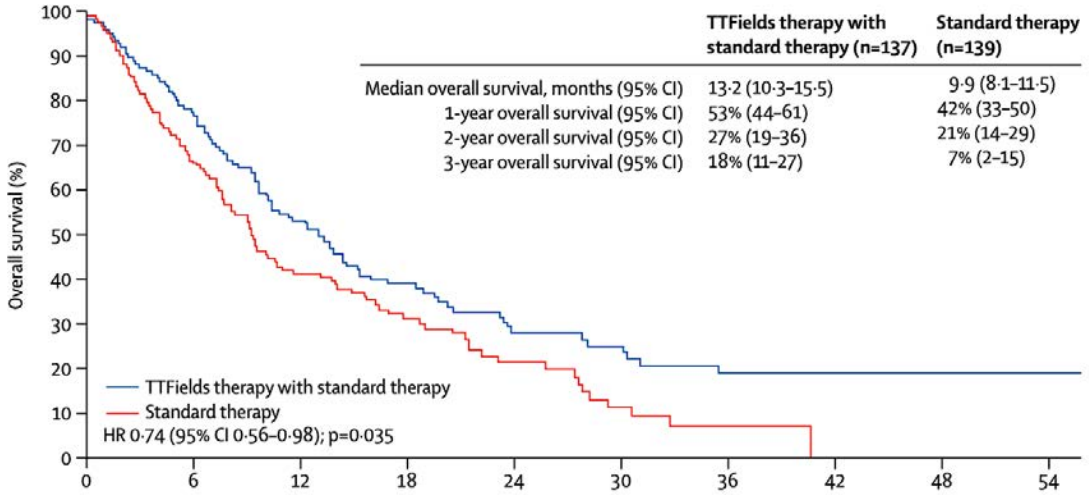


Leal, ASCO 2023; Leal, Lancet Oncol 2023

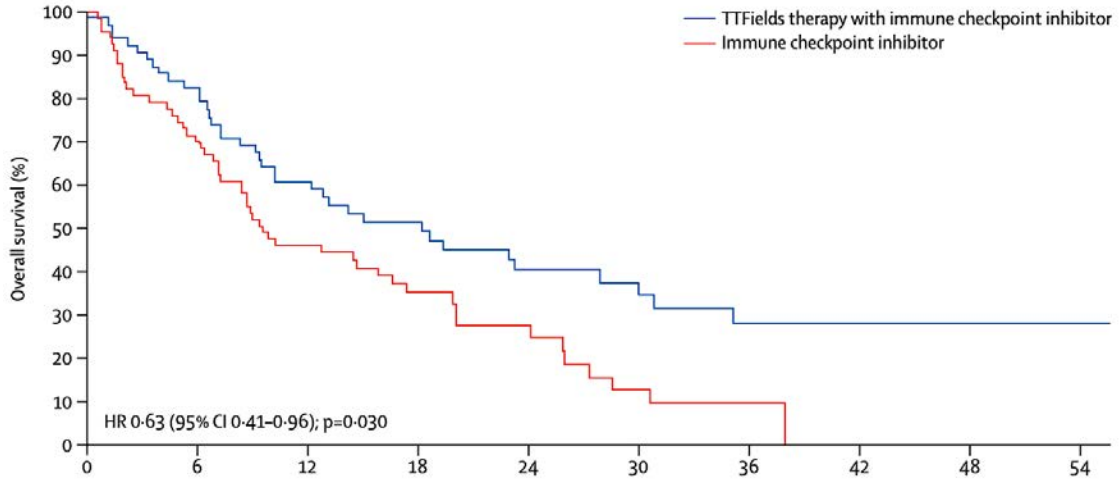
Georgetown | Lombardi

Tumor Treating Fields

- LUNAR (EF-24)
  - Phase III trial of PD(L)1 or docetaxel +/- TTFields
  - Adding TTFields improved OS (13.2m vs 9.9m, HR 0.74)
    - In ICI group, TTFields improved OS (18.5m vs 10.8m, HR 0.63)



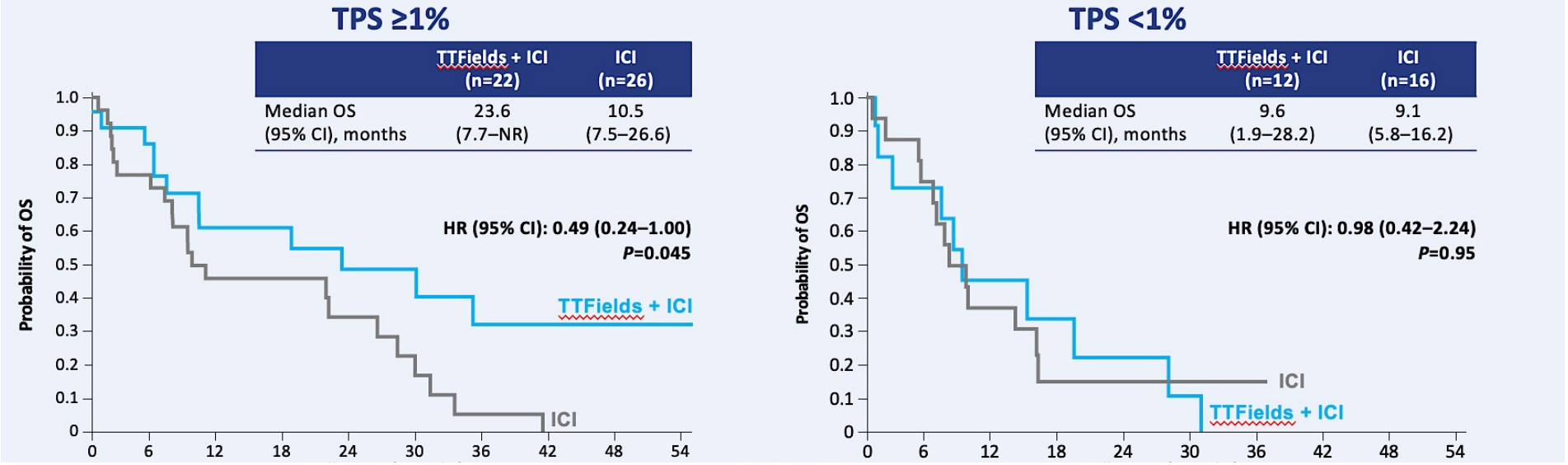
	TTFields therapy with standard therapy (n=137)	Standard therapy (n=139)
Median overall survival, months (95% CI)	13·2 (10·3–15·5)	9·9 (8·1–11·5)
1-year overall survival (95% CI)	53% (44–61)	42% (33–50)
2-year overall survival (95% CI)	27% (19–36)	21% (14–29)
3-year overall survival (95% CI)	18% (11–27)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



Leal, Lancet Oncol 2023

Tumor Treating Fields

- LUNAR (EF-24)
  - Phase III trial of PD(L)1 or docetaxel +/- TTFields
  - Greater degree of benefit with ICI in PD-L1 positive NSCLC

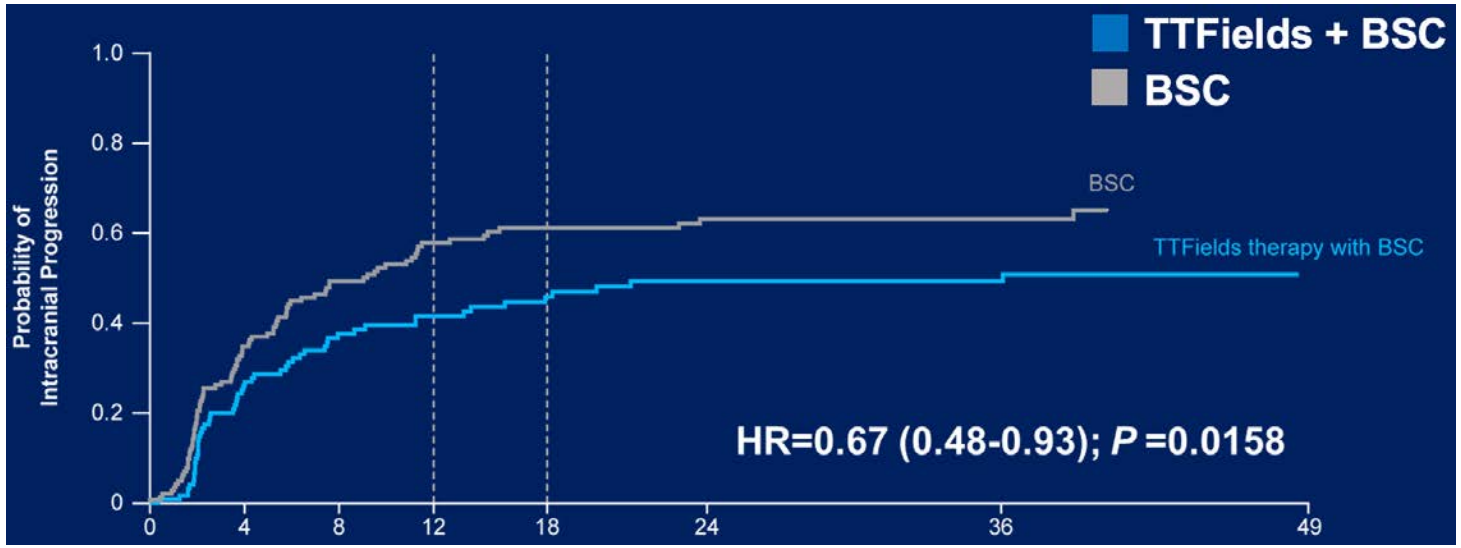


Leal, WCLC 2023

Georgetown | Lombardi

Tumor Treating Fields

- METIS
  - Phase III trial of TTFields in pts with NSCLC and brain mets
    - Patients with brain metastases received SRS and systemic therapy and randomized to adding TTFields vs BSC
    - Prolonged time to intracranial progression: 21.9 vs 11.3m, HR 0.67

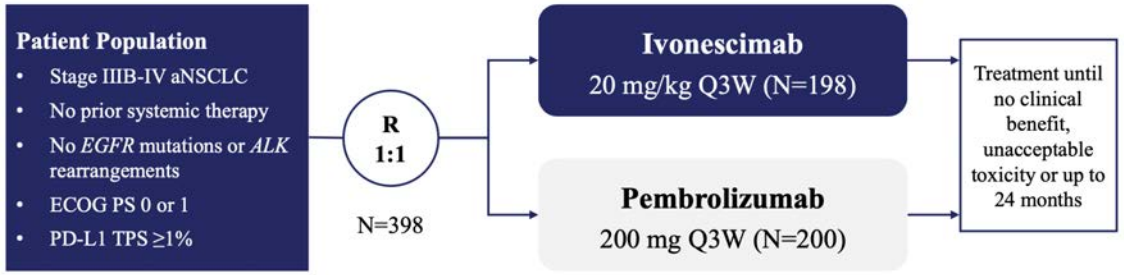


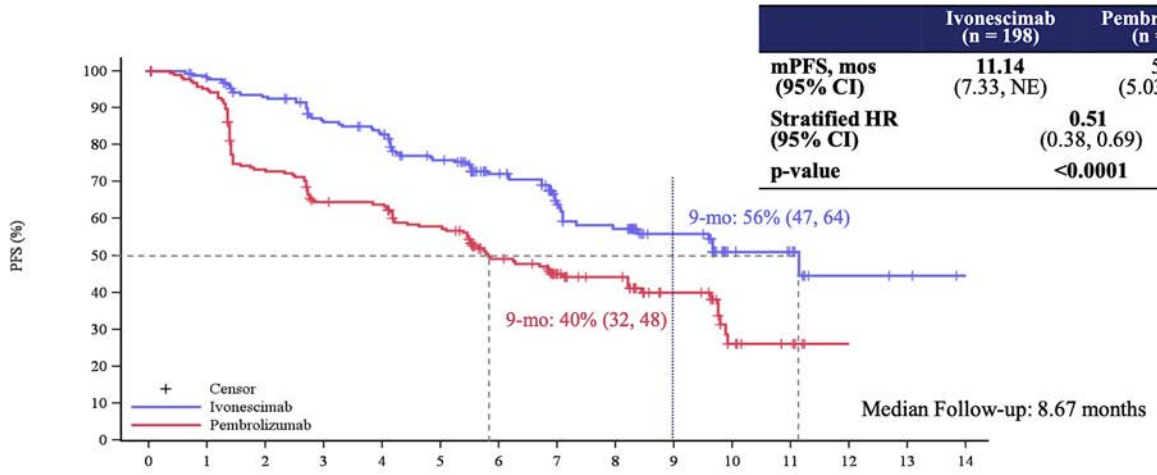
Mehta, ASCO 2024

Georgetown | Lombardi

Promising Future Strategies

- Ivonescimab: VEGF-PD1 bispecific antibody
- HARMONi-2: Phase III pembrolizumab vs ivonescimab





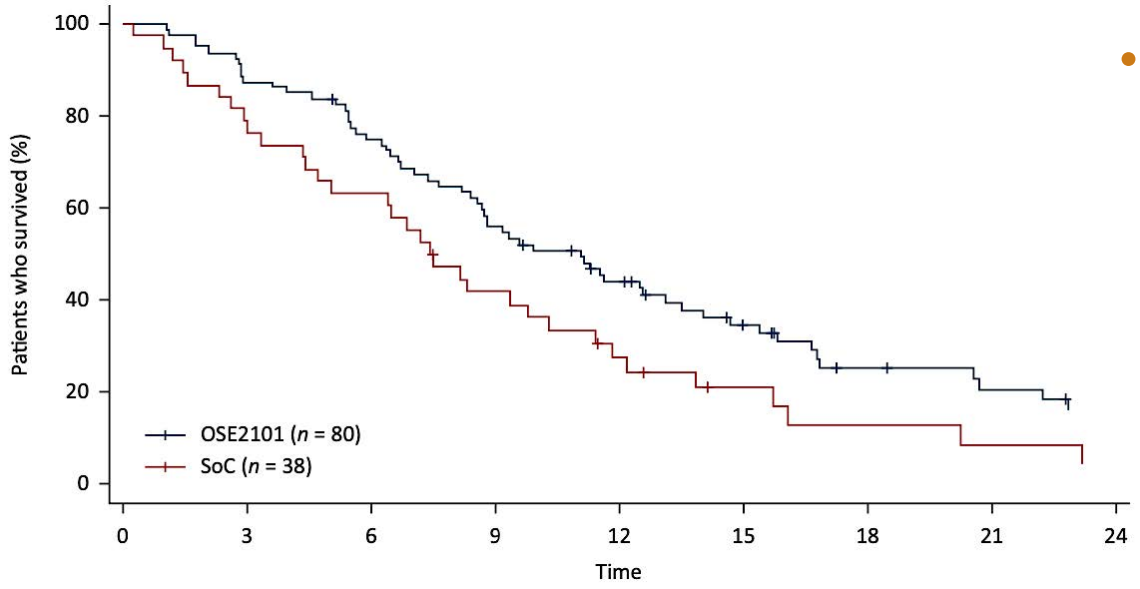
	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	11.14 (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	0.51 (0.38, 0.69)	
p-value	<0.0001	

- Improvements in PFS
  - 11.14 vs 5.82m, HR 0.51
  - PD-L1 low HR 0.54
  - PD-L1 high HR 0.46
  - Squamous HR 0.48
  - Non-squamous HR 0.54
- RR 50.0% vs 38.5%

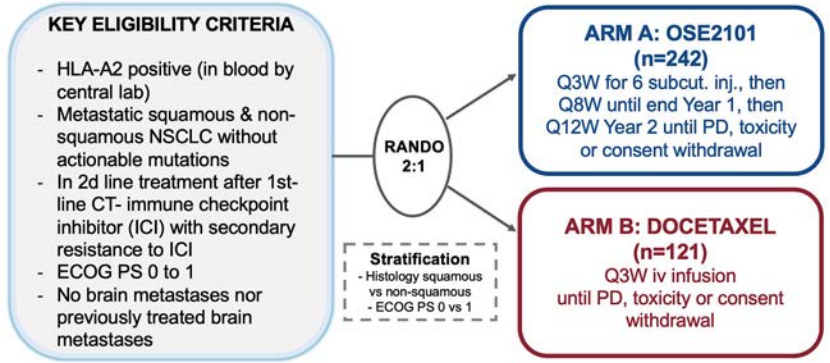
Zhou, WCLC 2024

Choosing Immunotherapy Regimens

- OSE2101
  - Vaccine targeting 5 tumor associated antigens
    - HER2, CEA, MAGE 2, MAGE 3, p53
  - ATALANTE-1: OSE2101 vs docetaxel
    - OS benefit in pts with secondary resistance to ICI (OS HR 0.59)



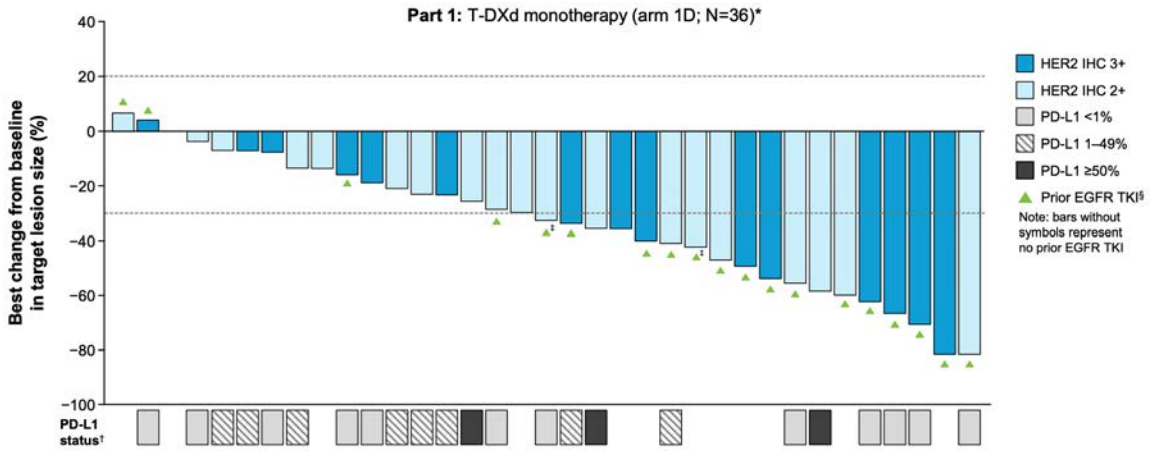
- Phase III ARTEMIA trial underway



Besse, Ann Oncol 2023; Liu, WCLC 2023

Antibody Drug Conjugates

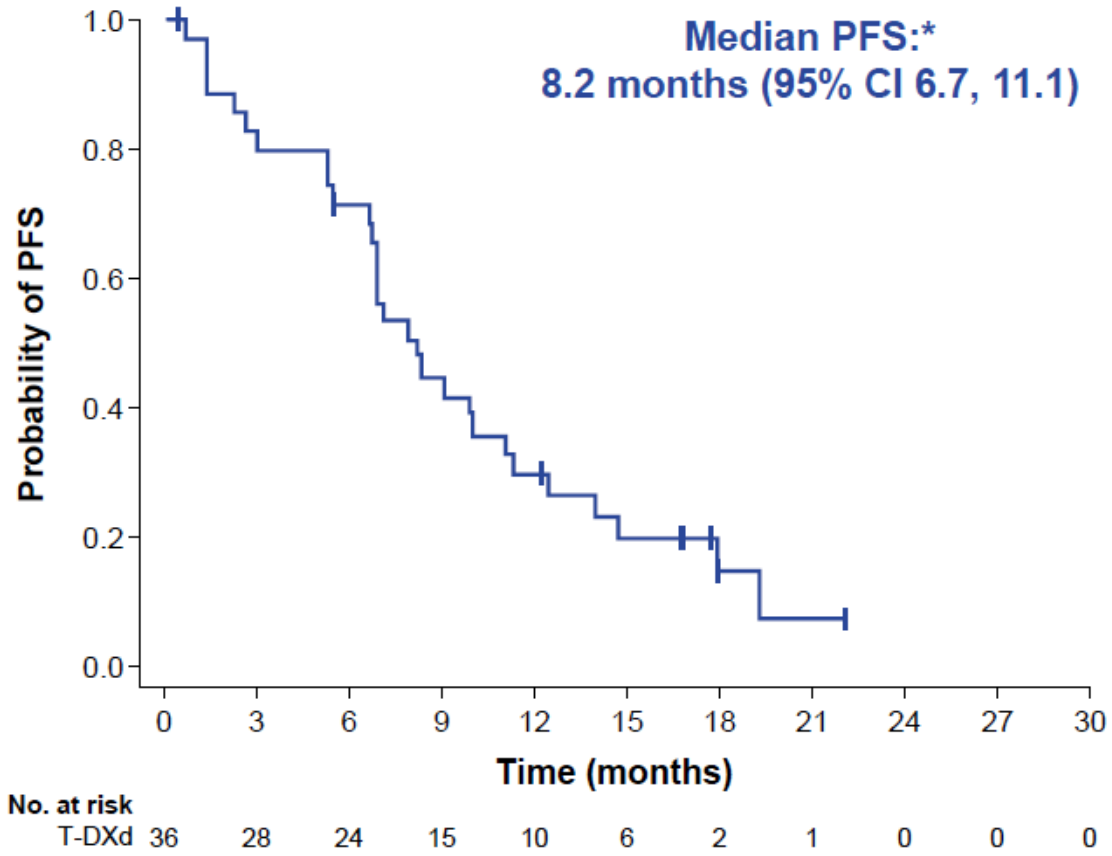
- Trastuzumab deruxtecan (T-DXd)
  - FDA approved for HER2 mutant NSCLC August 11, 2022
  - FDA approved for HER2 IHC3+ cancers April 5, 2024
- DESTINY-Lung03
  - T-DXd 5.4mg/kg in HER2 IHC 3+/2+
    - RR 44.4% (56.3% in IHC 3+)

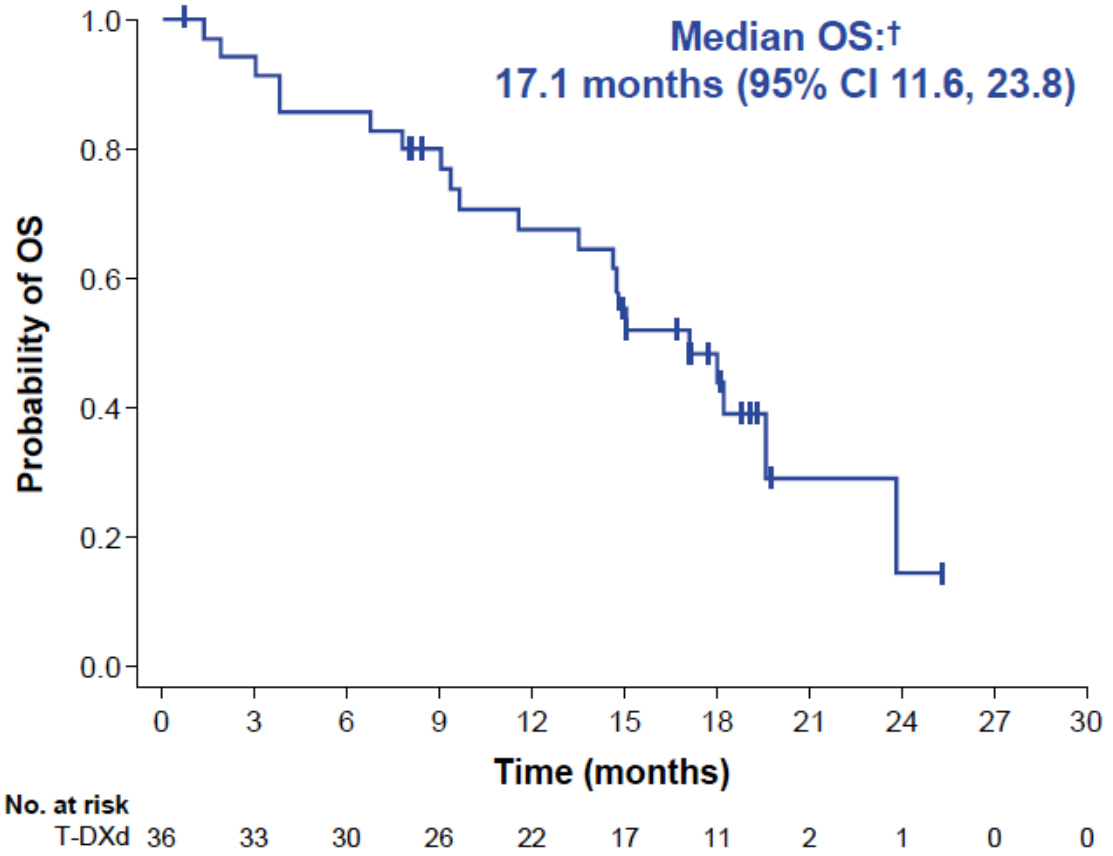


Planchard, WCLC 2024

Georgetown | Lombardi

DESTINY-Lung03: Survival Outcomes



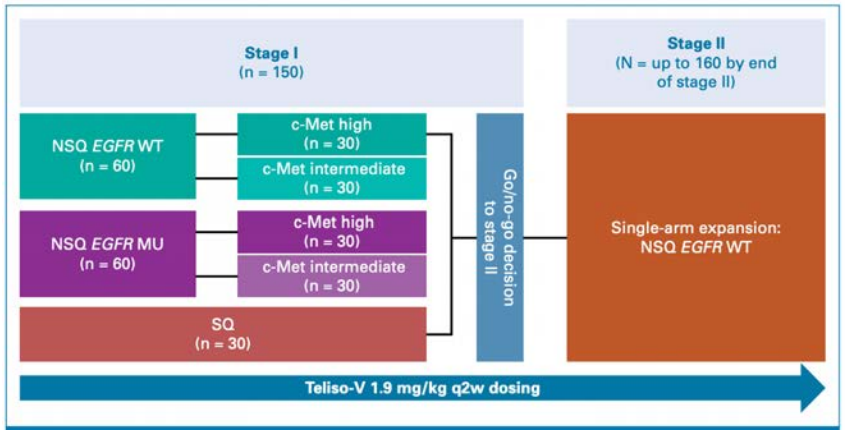


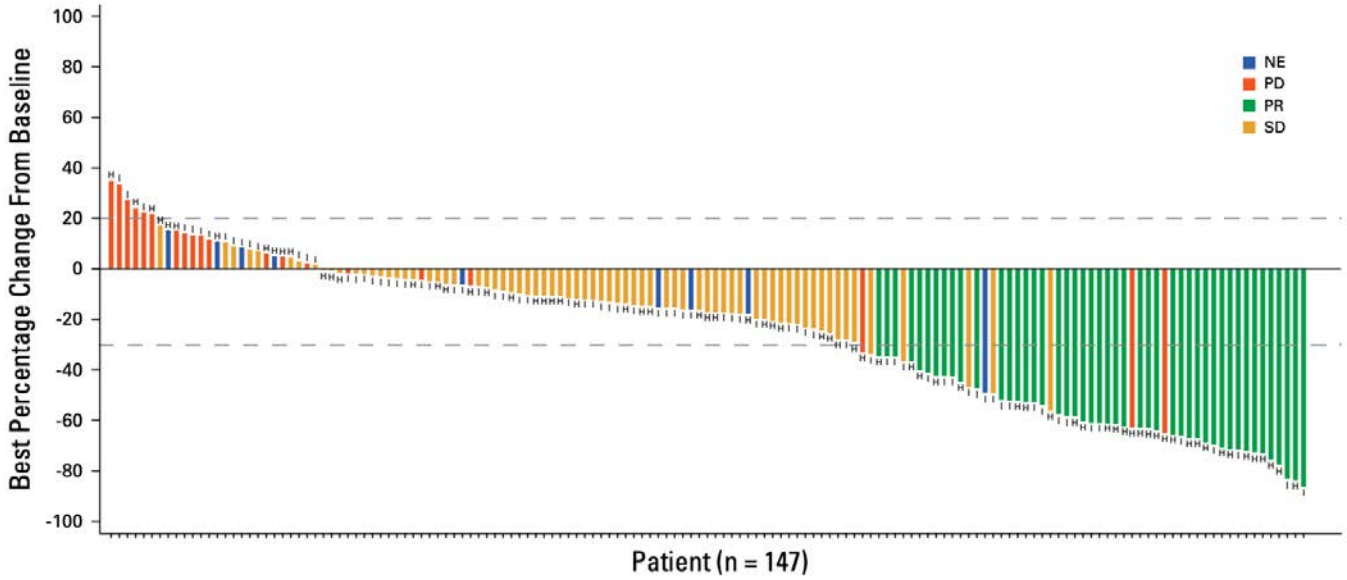
Symbols indicate a censored observation; PFS was assessed by investigator using RECIST v1.1. *Patients without disease progression or who had died, or who had disease progression or died after two or more missed visits, were censored at the last evaluable RECIST v1.1 assessment, or at the date of first dose if there were no evaluable visits or no baseline assessment (unless the patient died within 13 weeks of baseline); †any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive; if the date of death occurred after the data cutoff date, the patient was censored at the date of data cutoff

Planchard D et al. World Congress on Lung Cancer 2024;Abstract OA16.05.

Antibody Drug Conjugates

- Telisotuzumab vedotin: cMet directed ADC
- LUMINOSITY



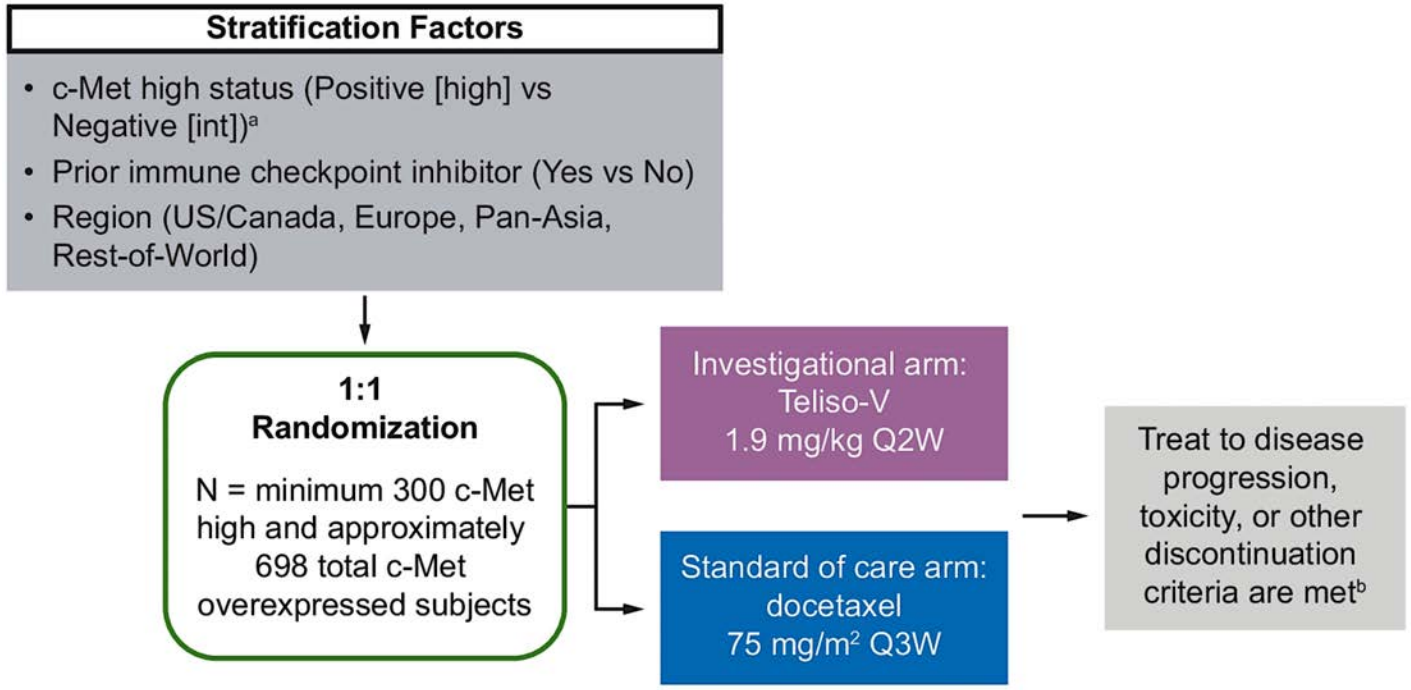


  - EGFR wt non-squamous
    - RR 28.6%
      - cMet high RR 34.6%, intermediate RR 22.9%
    - DOR 8.3m, PFS 5.7m, OS 14.5m

Camidge, JCO 2024

Antibody Drug Conjugates

- Telisotuzumab vedotin: cMet directed ADC
- Phase III TeliMET NSCLC-01 Study
  - cMet overexpressing, EGFR wt, non-squamous NSCLC

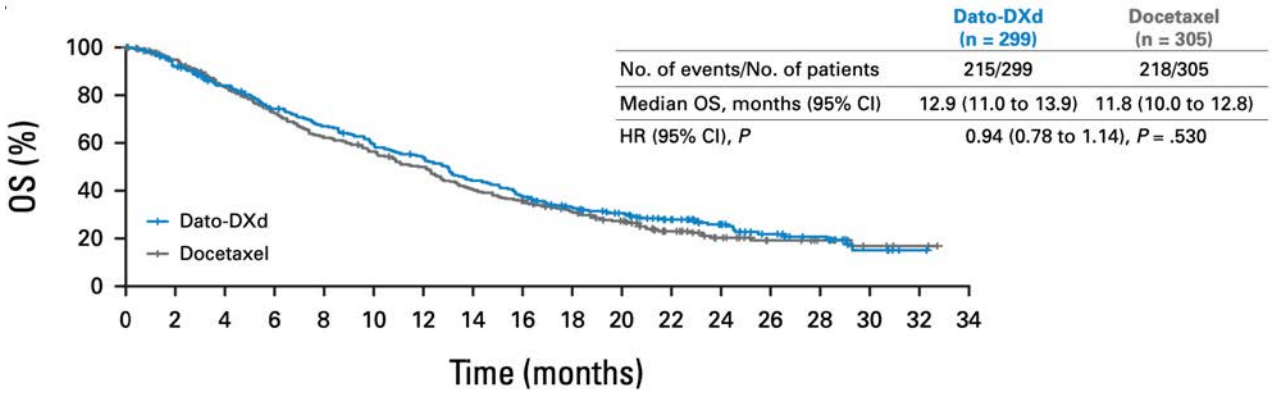


Lu, ASCO 2024

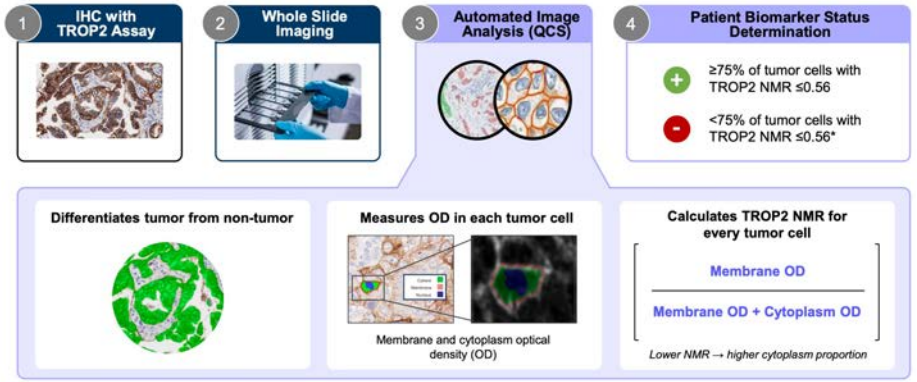
Georgetown | Lombardi

Antibody Drug Conjugates

- Datopotamab deruxtecan
- TROPION-Lung01: Dato-DXd vs docetaxel
  - PFS benefit (esp in non-sq) but no improvement in OS
  - Being explored in EGFR+ but new biomarker needed?



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



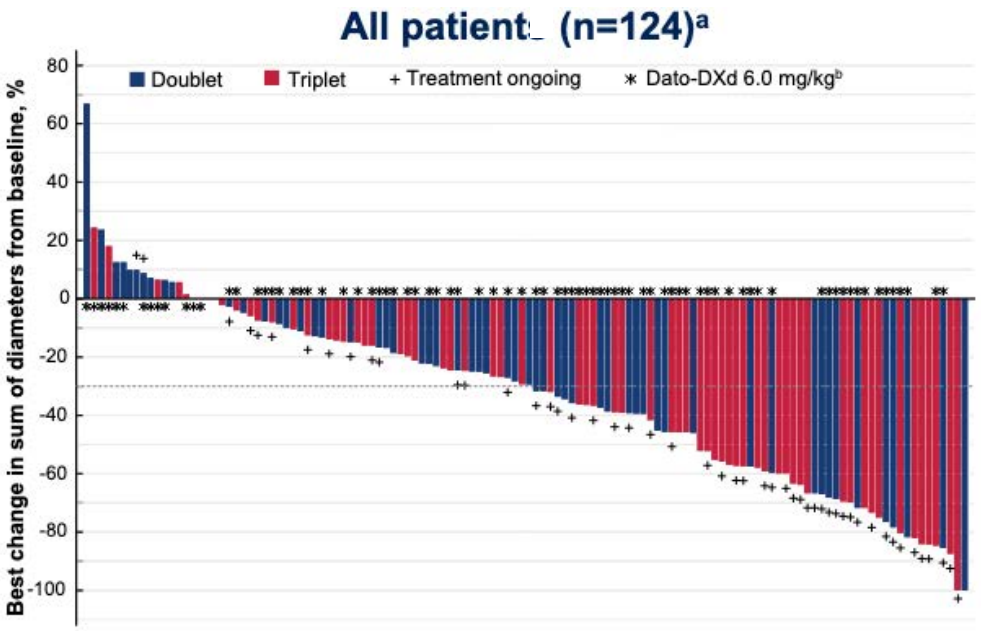
Ahn, JCO 2024; Garassino, WCLC 2024

Georgetown | Lombardi

Datopotamab Deruxtecan with Immune Checkpoint Inhibitors for Advanced NSCLC without Actionable Mutations

Phase Ib TROPION-Lung02

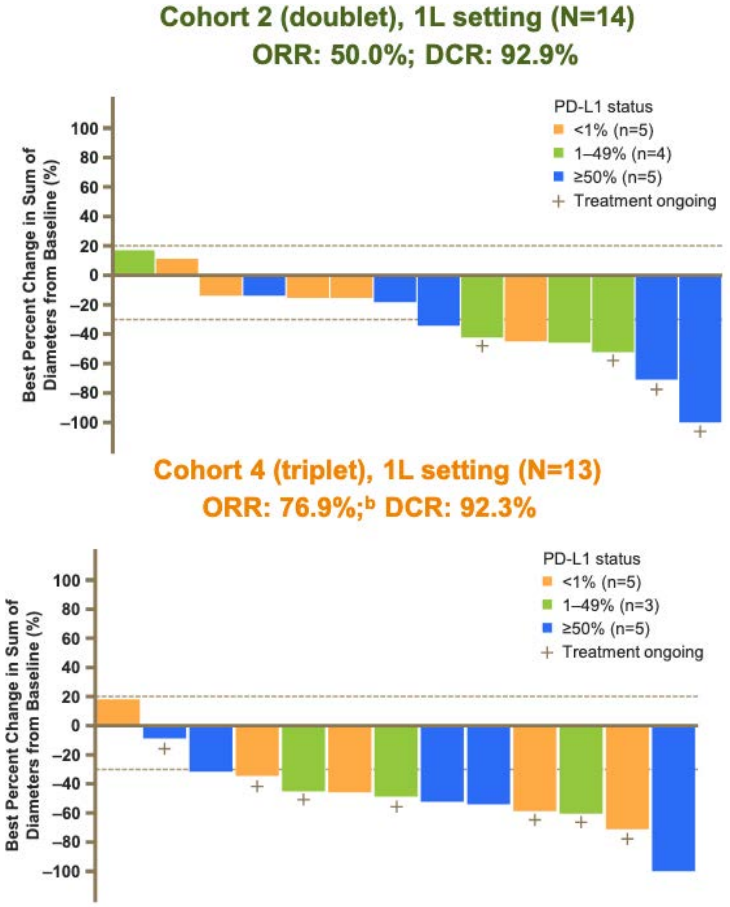
Dato-DXd + pembro ± platinum chemo



Antitumor activity with doublet and triplet in patients in the 1L and 2L+ settings

Phase Ib TROPION-Lung04

Dato-DXd + durvalumab ± carboplatin



Goto Y et al. ASCO 2023;Abstract 9004; Papadopoulos KP et al. World Congress on Lung Cancer 2023;Abstract OA05.06.

Select Ongoing Phase III Trials of First-Line Datopotamab Deruxtecan Combined with Immunotherapy in Advanced or Metastatic NSCLC without Actionable Mutations

Study	Patient population	Intervention	Estimated completion date
TROPION-Lung08 (NCT05215340)	Advanced/ Metastatic PD-L1 High (TPS ≥50%) NSCLC	Dato-DXd + pembrolizumab vs pembrolizumab	February 2028
AVANZAR (NCT05687266)	Advanced/ metastatic NSCLC	Dato-DXd + durvalumab + carboplatin vs chemotherapy + pembrolizumab	November 2027
TROPION-Lung07 (NCT05555732)	Advanced/ Metastatic PD-L1 High (TPS ≥50%) NSCLC	Dato-DXd + pembrolizumab ± chemotherapy vs pembrolizumab + chemotherapy	August 2027
TROPION-Lung10 (NCT06357533)	Advanced/ Metastatic PD-L1 High (TPS ≥50%) NSCLC	Rilvegostomig ± Dato-DXd vs pembrolizumab	April 2028

www.clinicaltrials.gov. Accessed February 2025.

NSCLC Without a Targetable Mutation

- Immunotherapy is the standard of care for patients without a targetable mutation
  - Many different strategies for delivery
  - Ongoing studies to provide further insights into personalization
- Effective options against resistance remain an unmet need
- Novel strategies being developed
  - TTFields, bispecifics, vaccines, antibody-drug conjugates
- Goal is long-term survival for all patients with NSCLC

Discussion Questions

- Which first-line treatment regimen would you recommend for a 65-year-old patient with symptomatic, high-volume metastatic nonsquamous NSCLC, no identified targetable mutations and a PD-L1 tumor proportion score of 0%?

- Do you believe that community-based oncologists should be testing for STK11/KEAP1 mutations in their patients with metastatic NSCLC and considering them when making decisions regarding first-line therapy?

Discussion Questions

- Based on your knowledge of available data, would you like to be able to access datopotamab deruxtecan for patients with metastatic NSCLC without targetable tumor mutations who have experienced disease progression on first-line chemoimmunotherapy?

- How would you approach the prevention and management of oral mucositis/stomatitis associated with datopotamab deruxtecan?

Discussion Questions

- Regulatory and reimbursement issues aside, in which line of therapy would you offer trastuzumab deruxtecan to a patient with HER2-positive (IHC 3+) metastatic NSCLC and a PD-L1 TPS of 10%? What about to a patient with HER2-mutant disease?

Module 16: Pancreatic Cancer

Selection and Sequencing of Therapy for Patients with Metastatic Pancreatic Adenocarcinoma (PAD) — Dr Oberstein

Biomarker-Based Strategies for Metastatic PAD; Novel Investigational Approaches — Dr Philip

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NYU Langone Health

Perlmutter Cancer Center

An NCI-designated Comprehensive Cancer Center

Selection and Sequencing of Therapy for Patients with Metastatic Pancreatic Adenocarcinoma (PAD)

Paul Oberstein, MD, MS
Section Chief, GI Medical Oncology
NYU Langone Health

March, 2025

Disclosures

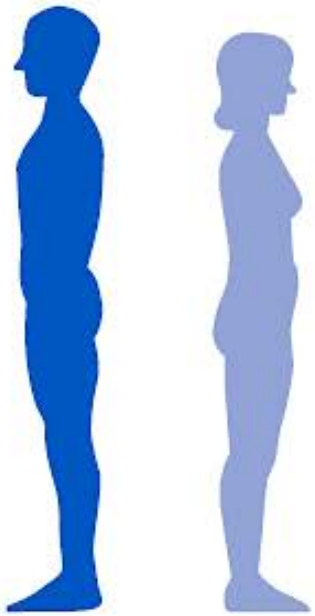
Advisory Committees	Boehringer Ingelheim Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Merck
Consulting Agreements	Ipsen Biopharmaceuticals Inc
Speakers Bureaus	Ipsen Biopharmaceuticals Inc, Jazz Pharmaceuticals Inc

Treatment in Metastatic Pancreatic Cancer Outline

- Review the scope of this challenge in 2025
- Treatment options based on stage
- Consideration of patient factors and treatment sequencing in treatment decisions
- Data for agents in metastatic pancreatic cancer
- New data from NAPOLI-3 and impact on treatment decisions
- Other factors to consider in treatment of metastatic pancreatic cancer

Estimated number of new cancer deaths in the US in 2025

Male		
Lung & bronchus	64,190	20%
Prostate	35,770	11%
Colon & rectum	28,900	9%
Pancreas	27,050	8%
Liver & intrahepatic bile duct	19,250	6%
Leukemia	13,500	4%
Esophagus	12,940	4%
Urinary bladder	12,640	4%
Non-Hodgkin lymphoma	11,060	3%
Brain & other nervous system	10,170	3%
All sites	**323,900**	



Female		
Lung & bronchus	60,540	21%
Breast	42,170	14%
Pancreas	24,930	8%
Colon & rectum	24,000	8%
Uterine corpus	13,860	5%
Ovary	12,730	4%
Liver & intrahepatic bile duct	10,840	4%
Leukemia	10,040	3%
Non-Hodgkin lymphoma	8,330	3%
Brain & other nervous system	8,160	3%
All sites	**294,220**	

Cancer Statistics 2025- American Cancer Society

Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.
Source: Cancer Facts & Figures 2025.

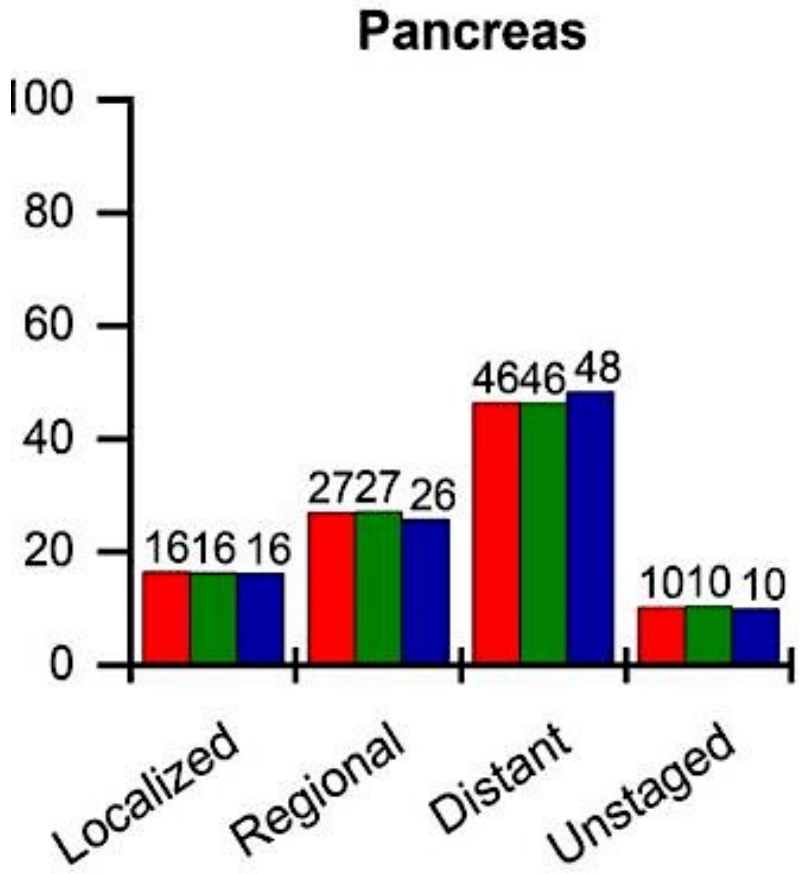
Trends in five-year relative survival (%), US, 1975-2020

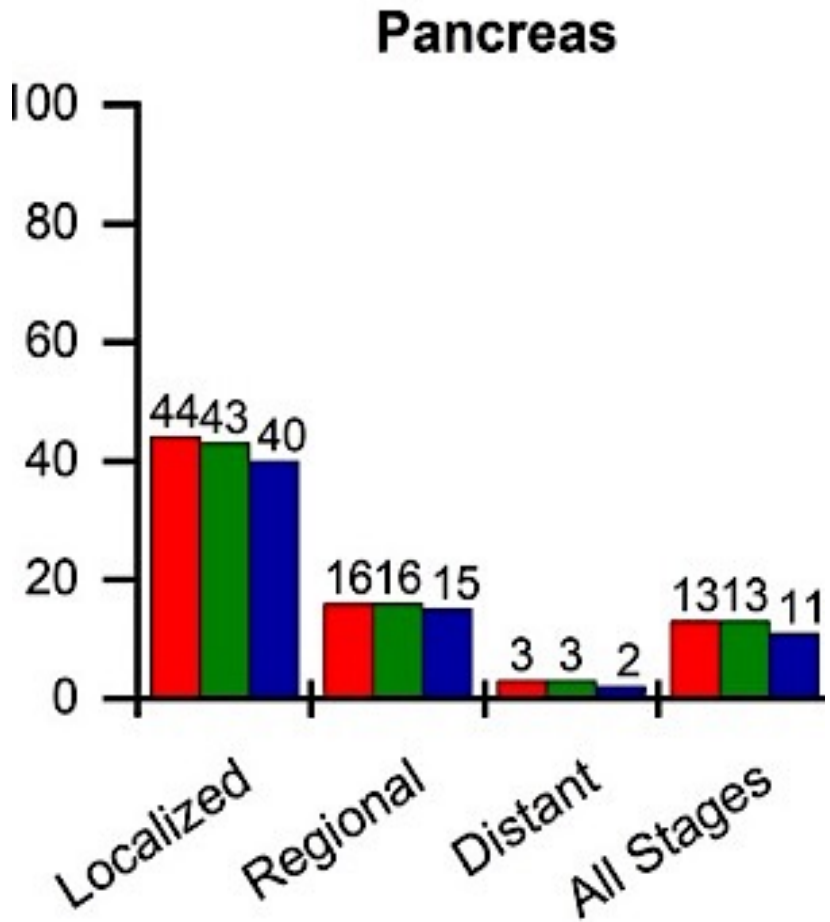
Site	1975-77	1995-97	2014-2020
All sites	49	63	69
Breast (female)	75	87	91
Colon & rectum	50	61	64
Leukemia	34	48	67
Liver & intrahepatic bile duct	3	7	22
Lung & bronchus	12	15	27
Melanoma of the skin	82	91	94
Non-Hodgkin lymphoma	47	56	74
Ovary	36	43	51
Pancreas	3	4	13
Prostate	68	97	97
Uterine cervix	69	73	67
Uterine corpus	87	84	81

Cancer Statistics 2025

Survival is age adjusted for normal life expectancy and are based on cases diagnosed in the Surveillance, Epidemiology, and End Results (SEER) 9 areas for 1975-1977 and 1995-1997 and in the SEER 22 areas for 2014-2020; cases followed through 2021.
Data source: Surveillance, Epidemiology, and End Results program, National Cancer Institute, 2025.

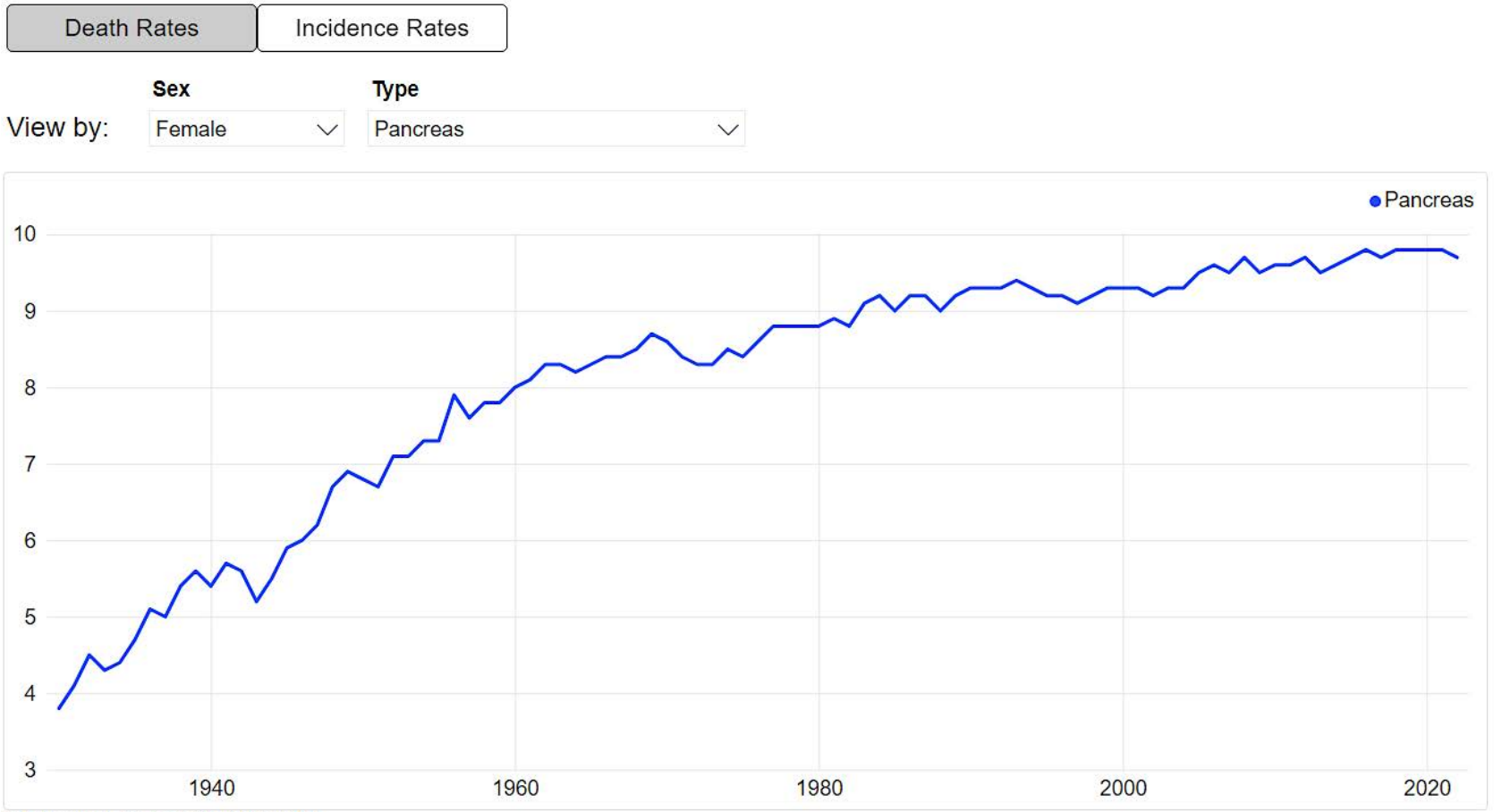
However outcomes for pancreatic cancer vary greatly by stage





American Cancer Society data, Siegel et al 2025

Despite this the number of people dying of pancreatic cancer is not decreasing (yet)

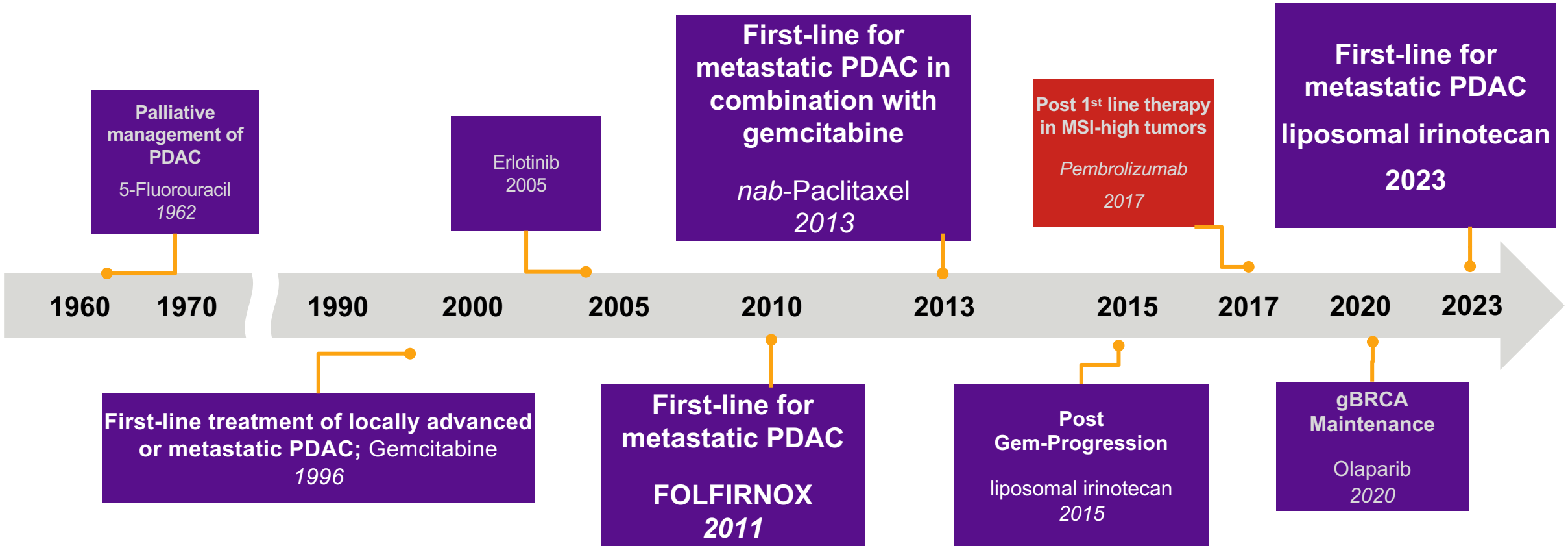


©American Cancer Society, 2025
Data Souce: National Center for Health Statistics, Centers for Disease Contol and Prevention, 2024
Average annual rate per 100,000, age-adjusted to the 2000 US standard population.

ACS data from CRC. Annual rate per 100,000, age adjusted to 2000 US standard population

So how do we treat metastatic pancreatic cancer?

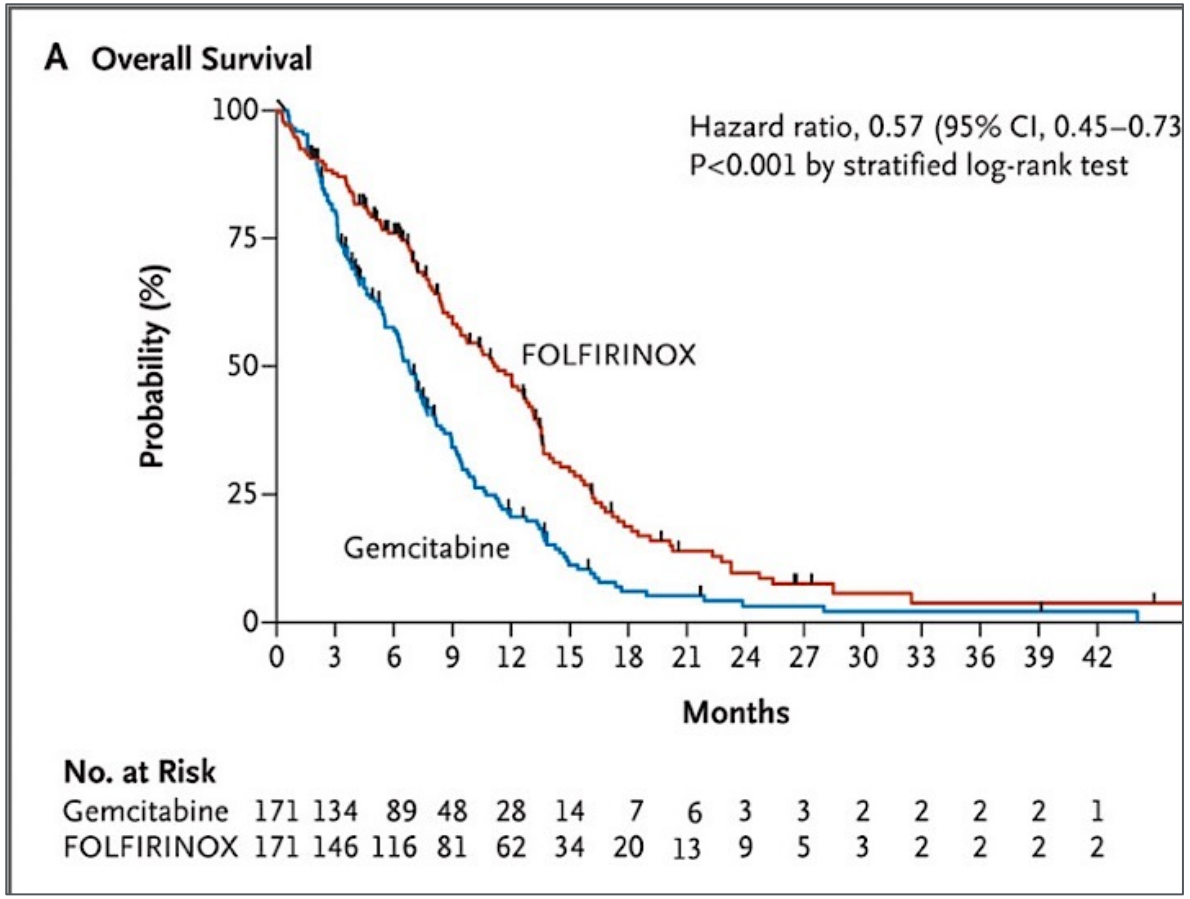
Key Milestones in the Treatment of Pancreatic Cancer



Cytotoxic

Immunotherapy

FOLFIRINOX compared to Gemcitabine
Impressive improvement in OS but with toxicity



Conroy et al 2011 NEJM

Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

* Events listed are those that occurred in more than 5% of patients in either group. NS denotes not significant.

Gem/*nab*-paclitaxel compared to Gemcitabine

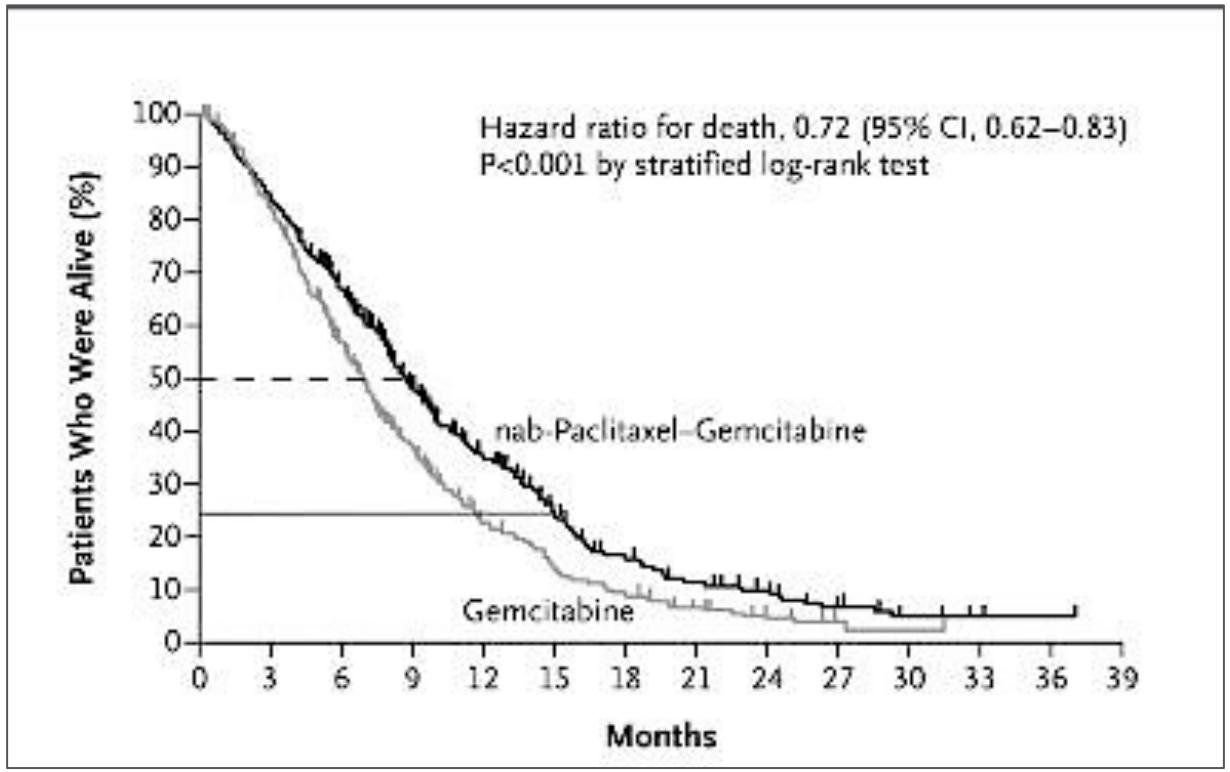


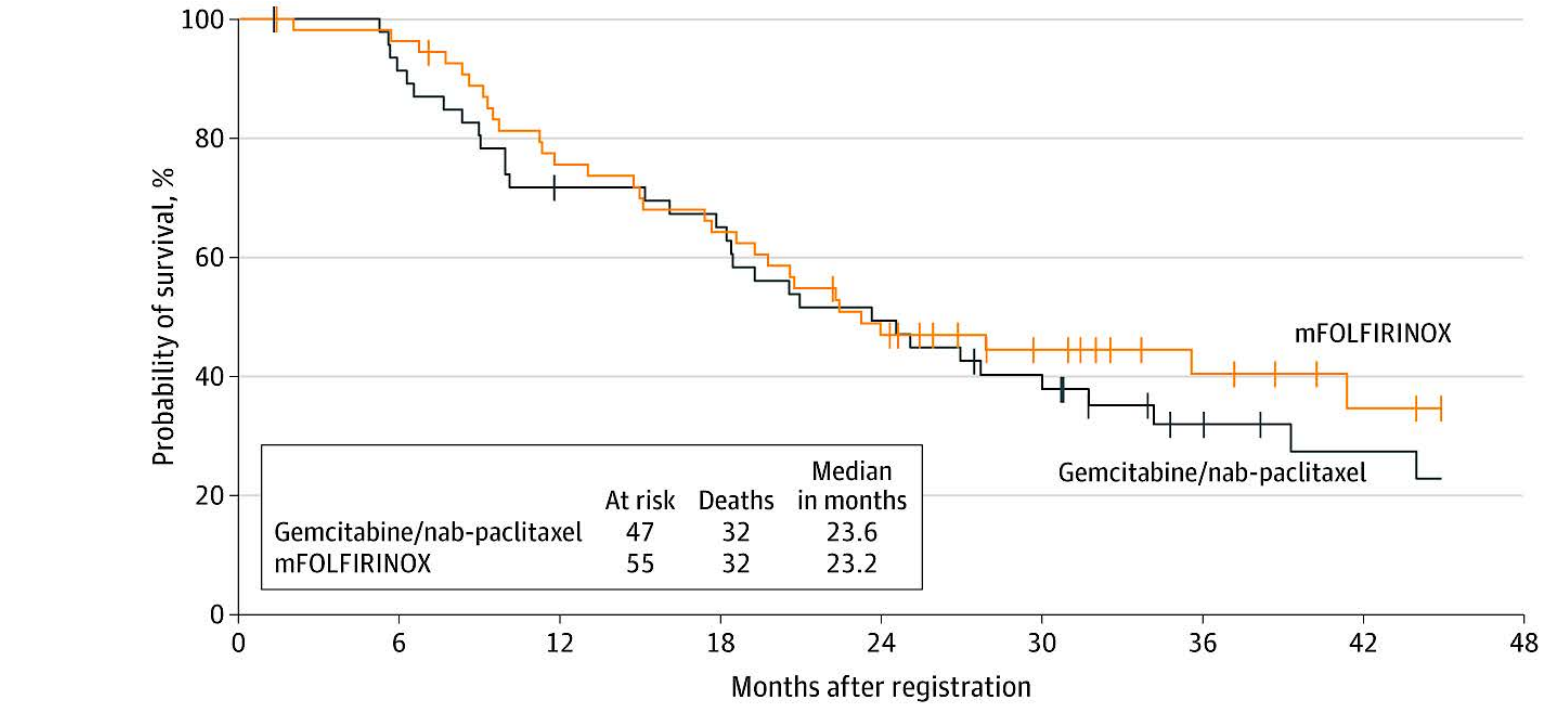
Table 3. Common Adverse Events of Grade 3 or Higher and Growth-Factor Use.*

Event	nab-Paclitaxel plus Gemcitabine (N=421)	Gemcitabine Alone (N=402)
Adverse event leading to death — no. (%)	18 (4)	18 (4)
Grade ≥3 hematologic adverse event — no./total no. (%)†		
Neutropenia	153/405 (38)	103/388 (27)
Leukopenia	124/405 (31)	63/388 (16)
Thrombocytopenia	52/405 (13)	36/388 (9)
Anemia	53/405 (13)	48/388 (12)
Receipt of growth factors — no./total no. (%)	110/431 (26)	63/431 (15)
Febrile neutropenia — no. (%)‡	14 (3)	6 (1)
Grade ≥3 nonhematologic adverse event occurring in >5% of patients — no. (%)‡		
Fatigue	70 (17)	27 (7)
Peripheral neuropathy§	70 (17)	3 (1)
Diarrhea	24 (6)	3 (1)
Grade ≥3 peripheral neuropathy		
Median time to onset — days	140	113
Median time to improvement by one grade — days	21	29
Median time to improvement to grade ≤1 — days	29	NR
Use of nab-paclitaxel resumed — no./total no. (%)	31/70 (44)	NA

Von Hoff et al 2013 NEJM

But we had no direct comparison of these regimens

- In other settings, like neoadjuvant there are smaller studies such as SWOG S1505 that didn't show a difference but we don't know if that translates into the metastatic setting



Sohal et al 2021 JAMA Oncology

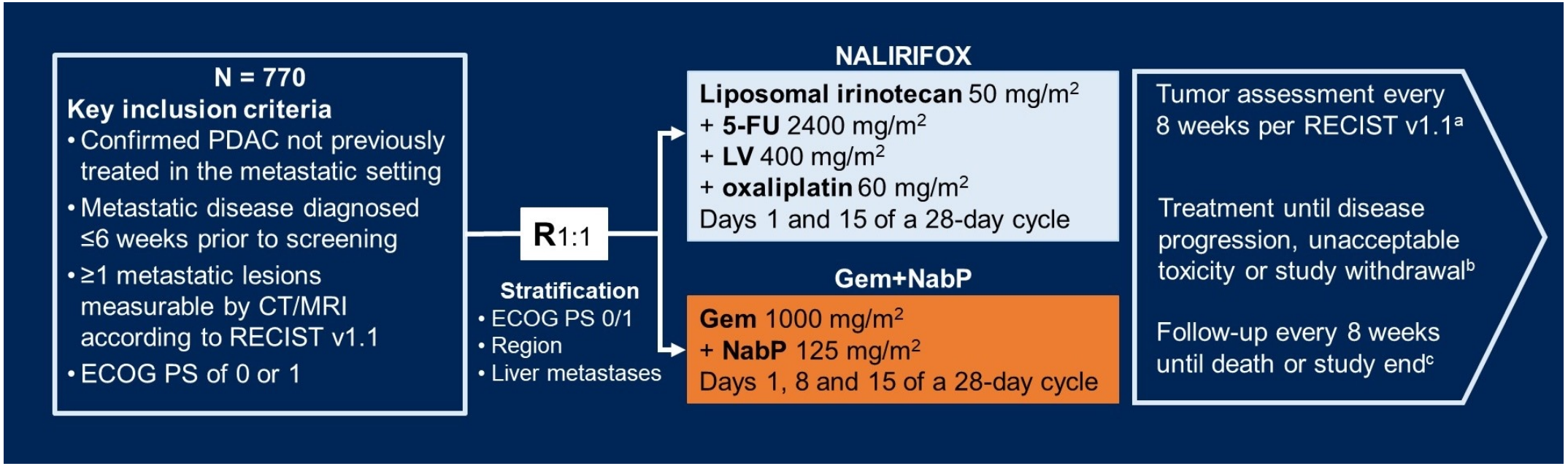
But we had no direct comparison of these regimens

- In the absence of clear head to head comparison we have to take many other factors into account
  - Stage of disease
    - For adjuvant treatment, the best data to date supports use of mFOLFIRINOX but there are other efficacious regimens
    - For neoadjuvant and metastatic, we have less guidance
  - Consideration of sequencing
    - We want to make sure every patient has the opportunity to receive every potentially effective therapy
  - Consideration of side effect profiles
    - Many patients with pancreatic cancer have comorbidities that may impact their ability to tolerate a particular therapy

Conroy et al, NEJM 2018

NAPOLI-3 trial directly addressed the best regimen for metastatic pancreatic cancer

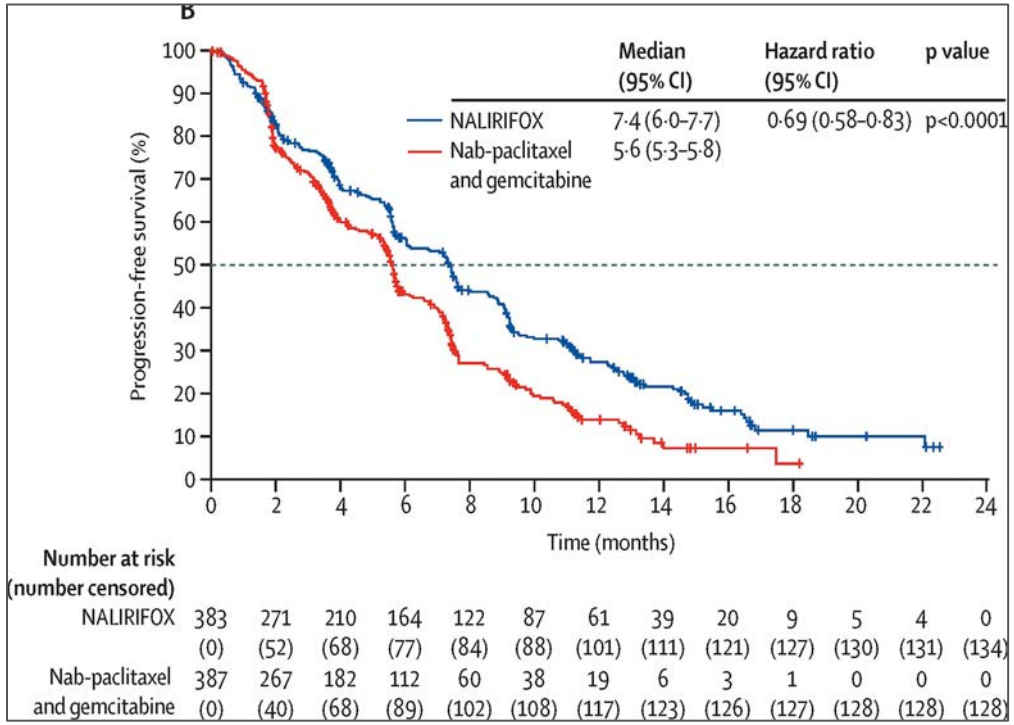
- This trial did not utilize the same dosing and regimen as the initial FOLFIRINOX study
- They utilized nano-liposomal irinotecan which was previously approved in combination with 5-FU in the 2nd line setting
- They also modified the Oxaliplatin dosing and removed bolus 5-FU

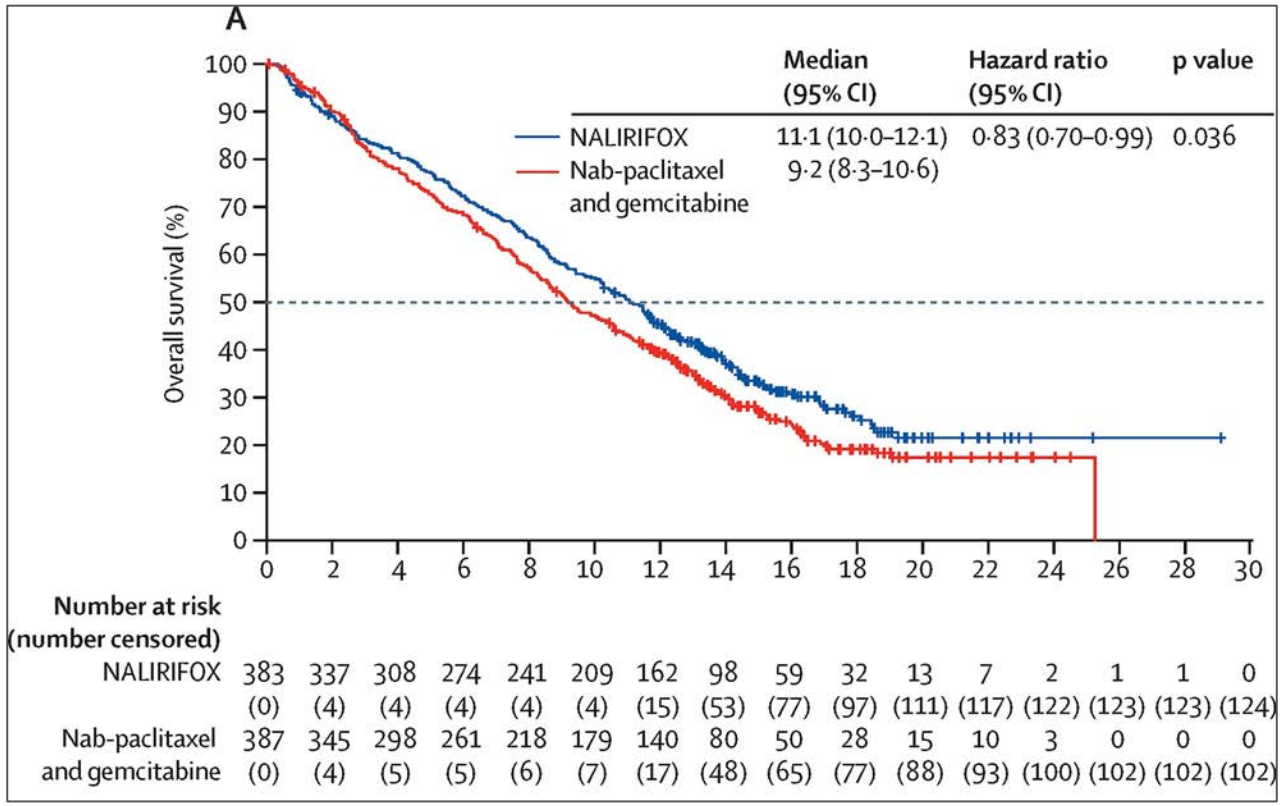


From Wainberg et al GI ASCO 2023

NAPOLI-3 results

- Overall NALIRIFOX was superior to gem/*nab*-p in prolonging OS

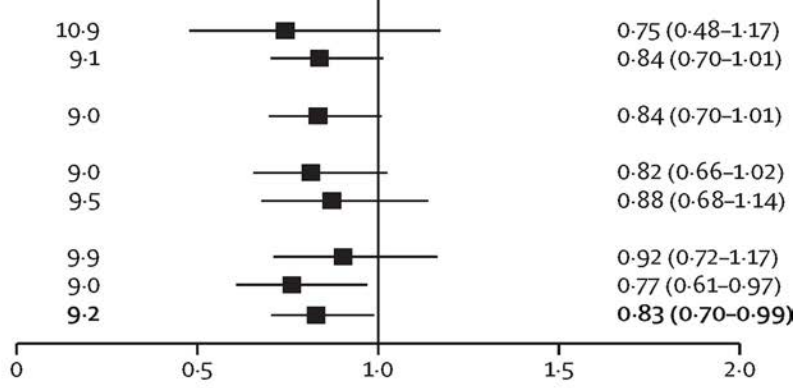




Wainberg et al 2023 Lancet

Subgroup analysis of NAPOLI-3 revealed benefit across many conditions

	Events/patients		NALIRIFOX, median (months)	Nab-paclitaxel and gemcitabine, median (months)	Hazard ratio (95% CI)
	NALIRIFOX	Nab-paclitaxel and gemcitabine			
Presence of liver metastases at baseline					
Yes	220/309	242/309	10·3	8·6	0·82 (0·68–0·98)
No	39/74	43/78	15·0	13·8	0·89 (0·57–1·37)
Number of metastatic sites					
1	75/114	92/138	11·5	11·3	0·98 (0·72–1·32)
2	87/120	83/108	11·5	10·1	0·89 (0·65–1·20)
≥3	97/149	110/141	10·9	7·7	0·69 (0·52–0·90)
Baseline ECOG performance status					
0	97/168	112/171	13·9	11·4	0·75 (0·57–0·98)
1	162/215	173/216	8·5	7·6	0·91 (0·73–1·13)
Region					
North America	85/120	94/122	11·2	9·1	0·79 (0·59–1·06)
Rest of the world	174/263	191/265	11·1	9·3	0·86 (0·70–1·05)
Main pancreatic tumour location					
Head	97/147	116/156	10·2	9·1	0·86 (0·65–1·12)
Other	162/236	169/231	11·7	9·2	0·83 (0·67–1·02)
Baseline CA 19–9					
<37 U/mL	34/60	45/71	13·2	10·9	0·75 (0·48–1·17)
≥37 U/mL	223/321	240/316	11·1	9·1	0·84 (0·70–1·01)
Race					
White	218/315	240/324	10·7	9·0	0·84 (0·70–1·01)
Sex					
Male	139/204	175/230	10·9	9·0	0·82 (0·66–1·02)
Female	120/179	110/157	11·6	9·5	0·88 (0·68–1·14)
Age, years					
<65	127/193	130/191	11·5	9·9	0·92 (0·72–1·17)
≥65	132/190	155/196	11·0	9·0	0·77 (0·61–0·97)
Overall	**259/383**	**285/387**	**11·1**	**9·2**	**0·83 (0·70–0·99)**



Wainberg et al 2023 Lancet

Updated survival data and toxicity data for NAPOLI-3

- At 29 month follow up
- mOS remained longer in the NALIRIFOX group (11.1 v 9.2 months, p= 0.026)
- 12 month OS was:
  45.6% vs 26.6%
- 18 month OS was:
  39.6% vs 20.0%

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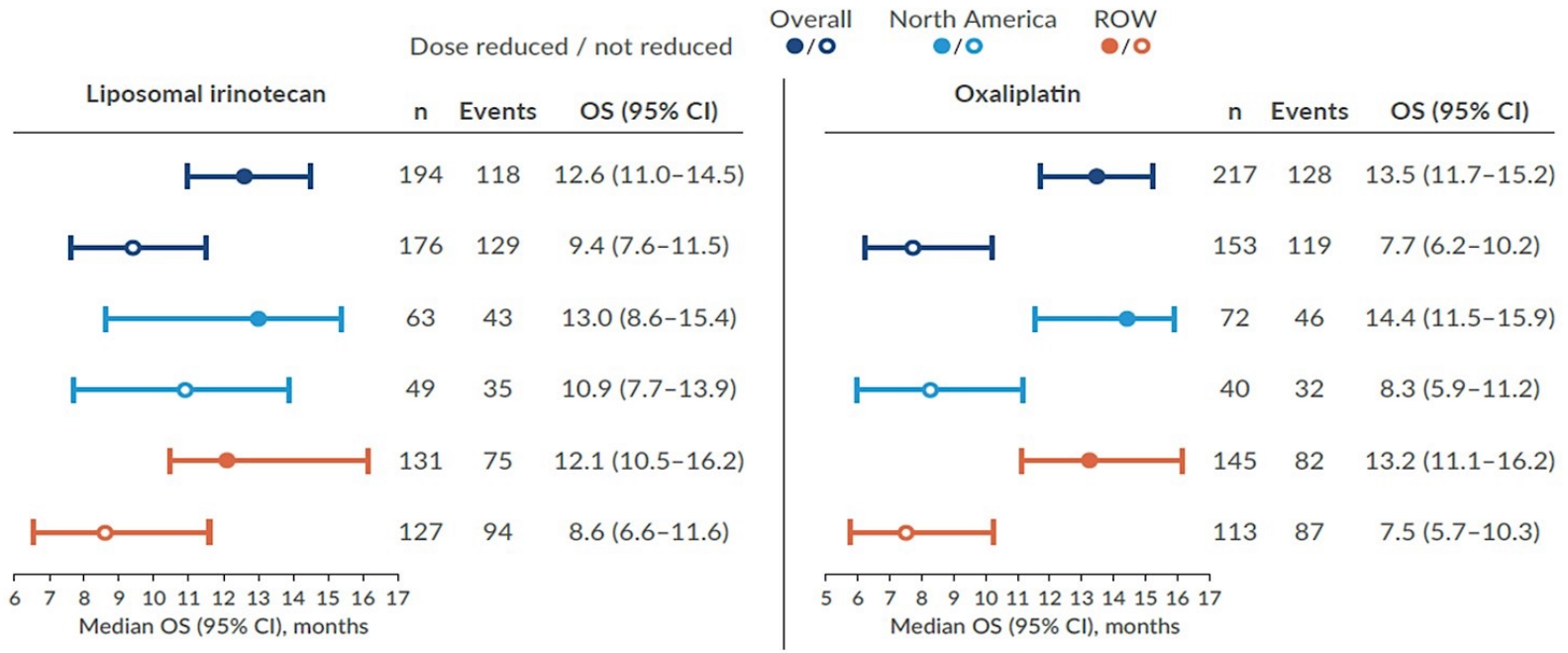
NAPOLI-3: Selected any-cause TEAEs

	NALIRIFOX (n = 370)		Gem+NabP (n = 379)	
Any-cause TEAEs in ≥10% of patients, %[a]	Any grade	Grade 3–4	Any Grade	Grade 3–4
Hematologic				
Neutropenia[b] / febrile neutropenia	50.0 / 2.4	23.8 / 2.4	50.6 / 2.6	38.0 / 2.4
Anemia	26.2	10.5	40.4	17.4
Thrombocytopenia[c]	24.0	1.6	40.6	6.1
Non-hematologic				
Diarrhea	70.5	20.3	36.7	4.5
Nausea	59.5	11.9	42.7	2.6
Vomiting	39.7	7.0	26.4	2.1
Hypokalemia	31.6	15.1	12.9	4.0
Peripheral neuropathy[d]	32.9	6.7	30.9	8.7
Paresthesia	11.9	0.3	8.7	0.5
Pyrexia	10.5	0.8	23.0	1.6

Presented by O'Reilly ASCO 2023 and Hussein et al GI ASCO 2025

Efficacy of dose adjustments on OS in patients with mPDAC treated with NALIRIFOX

- Of the patients who received NALIRIFOX (safety population, n = 370), 194 and 217 experienced ≥ 1 dose reduction of liposomal irinotecan and oxaliplatin, respectively.
- Patients with dose reductions of liposomal irinotecan or oxaliplatin had longer OS than those without dose reductions.



CI, confidence interval; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival; RoW, rest of the world.

- The most common any-grade AE leading to dose reduction of liposome irinotecan and oxaliplatin was diarrhea (40% and 36% patients with dose reductions, respectively).
- Longer OS in patients with dose reductions may be related to longer time on therapy and an increased likelihood of dose adjustment.
- Data suggest a path forward to further optimize the OS of patients with mPDAC receiving NALIRIFOX.

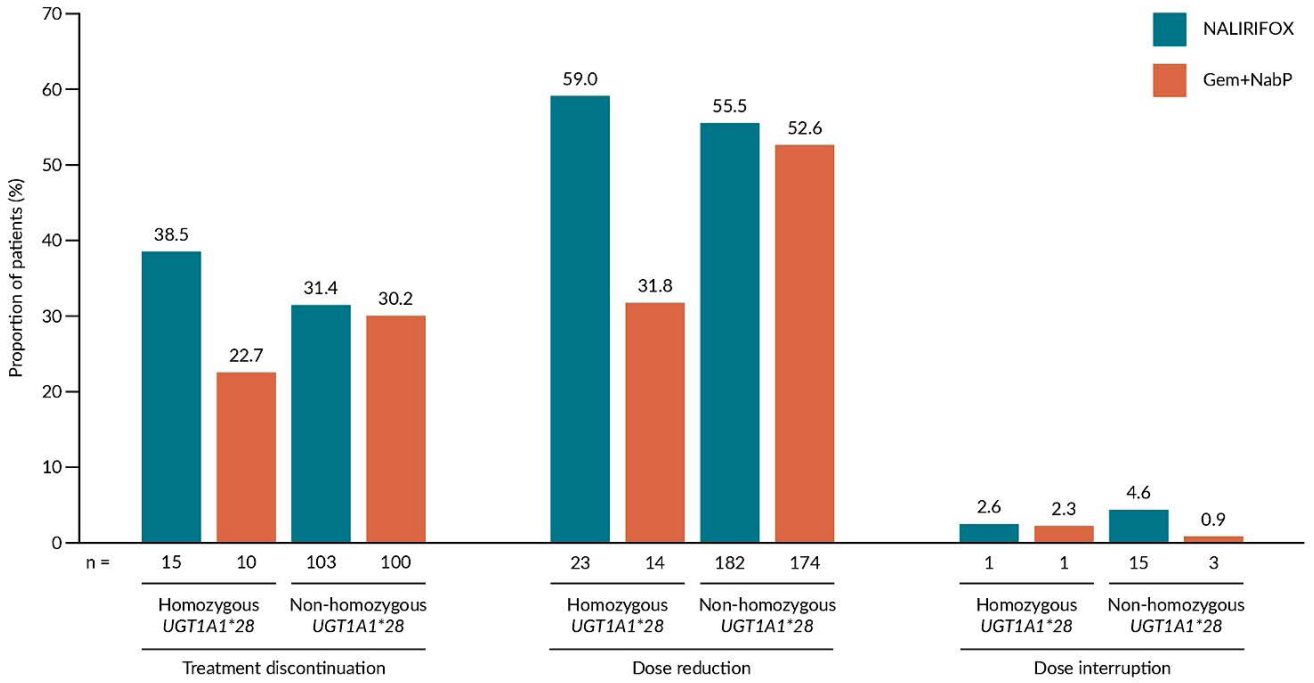
Patel A et al. ASCO GI 2025; Abstract 716.

Impact of UGT1A1*28 polymorphism on treatment tolerability in patients with mPDAC treated with NALIRIFOX in NAPOLI-3

Variable, n (%)	Randomized population	
	NALIRIFOX (n = 383)	Gem+NabP (n = 387)
Sex		
Female	179 (46.7)	157 (40.6)
Male	204 (53.3)	230 (59.4)
ECOG PS		
0	160 (41.8)	168 (43.4)
1	223[a] (58.3)	219 (56.6)
2	1 (0.3)	0 (0.0)
No. of metastatic sites		
1	114 (29.8)	138 (35.7)
2	120 (31.3)	108 (27.9)
≥ 3	149 (38.9)	141 (36.4)
Liver metastases		
Yes	307 (80.2)	311 (80.4)
No	76 (19.8)	76 (19.6)
***UGT1A1*28* allele status**		
Homozygous	40 (10.4)	45 (11.6)
Non-homozygous	339 (88.5)	338 (87.3)
Missing	4 (1.0)	4 (1.0)

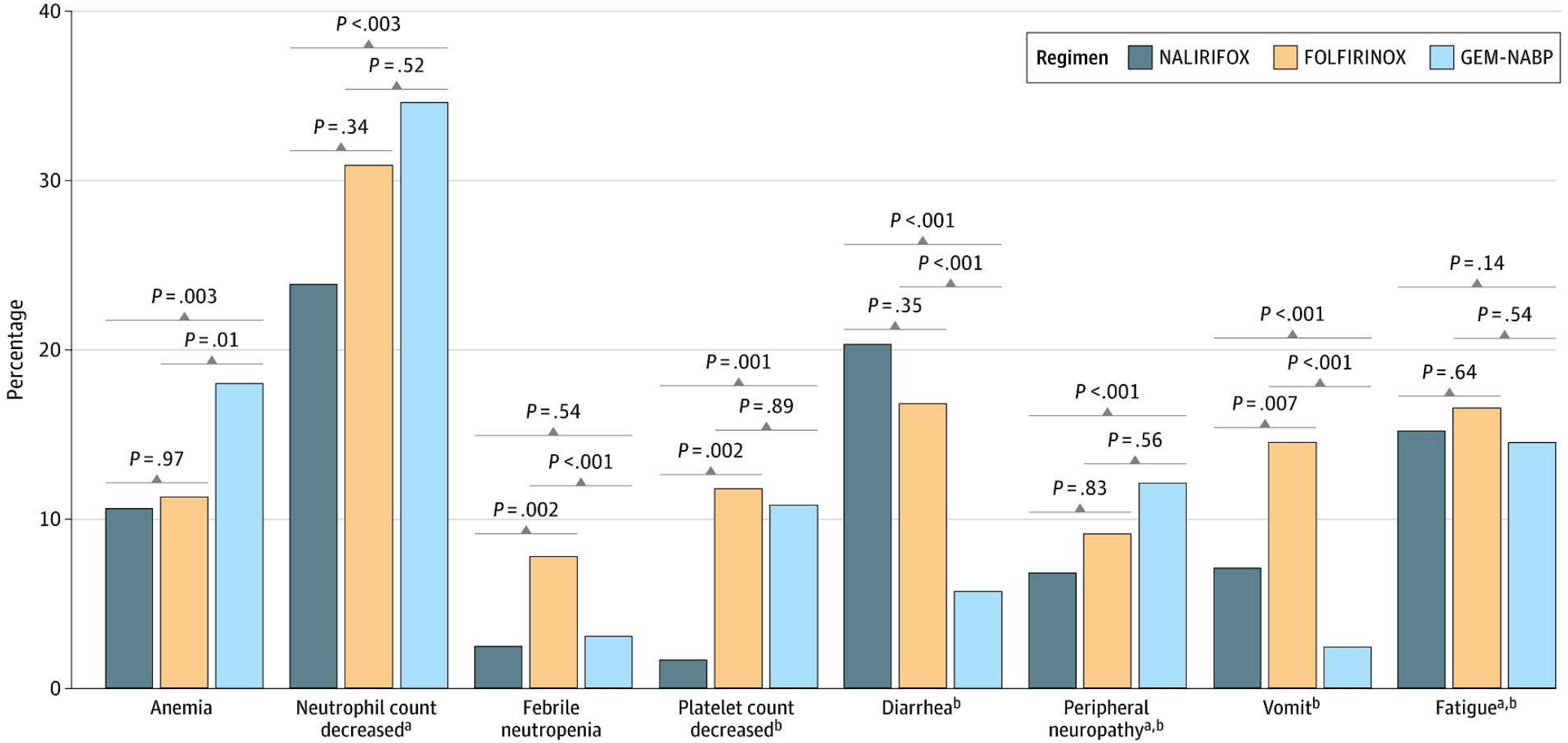
[a]For one patient, ECOG PS 1 was reconsidered to be ECOG PS 2 at randomization.
ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin.

TEAE, n (%)	*UGT1A1*28* homozygous		*UGT1A1*28* non-homozygous	
	NALIRIFOX (n = 39)	Gem+NabP (n = 44)	NALIRIFOX (n = 328)	Gem+NabP (n = 331)
Any	39 (100.0)	44 (100.0)	327 (99.7)	328 (99.1)
Related to any drug	39 (100.0)	41 (93.2)	310 (94.5)	308 (93.1)
Grade ≥ 3	31 (79.5)	34 (77.3)	288 (87.8)	288 (87.0)
Related to any drug	27 (69.2)	30 (68.2)	232 (70.7)	226 (68.3)
Serious	24 (61.5)	24 (54.5)	176 (53.7)	168 (50.8)
Leading to death	2 (5.1)	4 (9.1)	20 (6.1)	19 (5.7)



Abdelrahim M et al. ASOC GI 20-25; Abstract 717.

Systemic review of toxicity seen in published studies



JAMA Netw Open. 2024;7(1):e2350756

Choosing treatment in metastatic pancreatic cancer

- So now we utilize the same data to inform our treatment decisions:
- Superior efficacy seen with the NALIRIFOX regimen over G/A
- Different toxicity with overall similar numbers of overall toxicity but significant differences in the details
- Ability to sequence and provide subsequent therapy after as well as consideration of longer term toxicity that may impact future therapy

What to do after first line therapy Chemotherapy

- This is the recommended option right now but doesn't always happen

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Subsequent anti-cancer therapy

	NALIRIFOX (n = 383)	Gem+NabP (n = 387)
Any further subsequent anti-cancer therapy, %	50.5	54.4
Systemic anti-neoplastic therapy[a]	50.5	54.1
Surgery	0.3	0.5
Radiotherapy	0.5	1.1

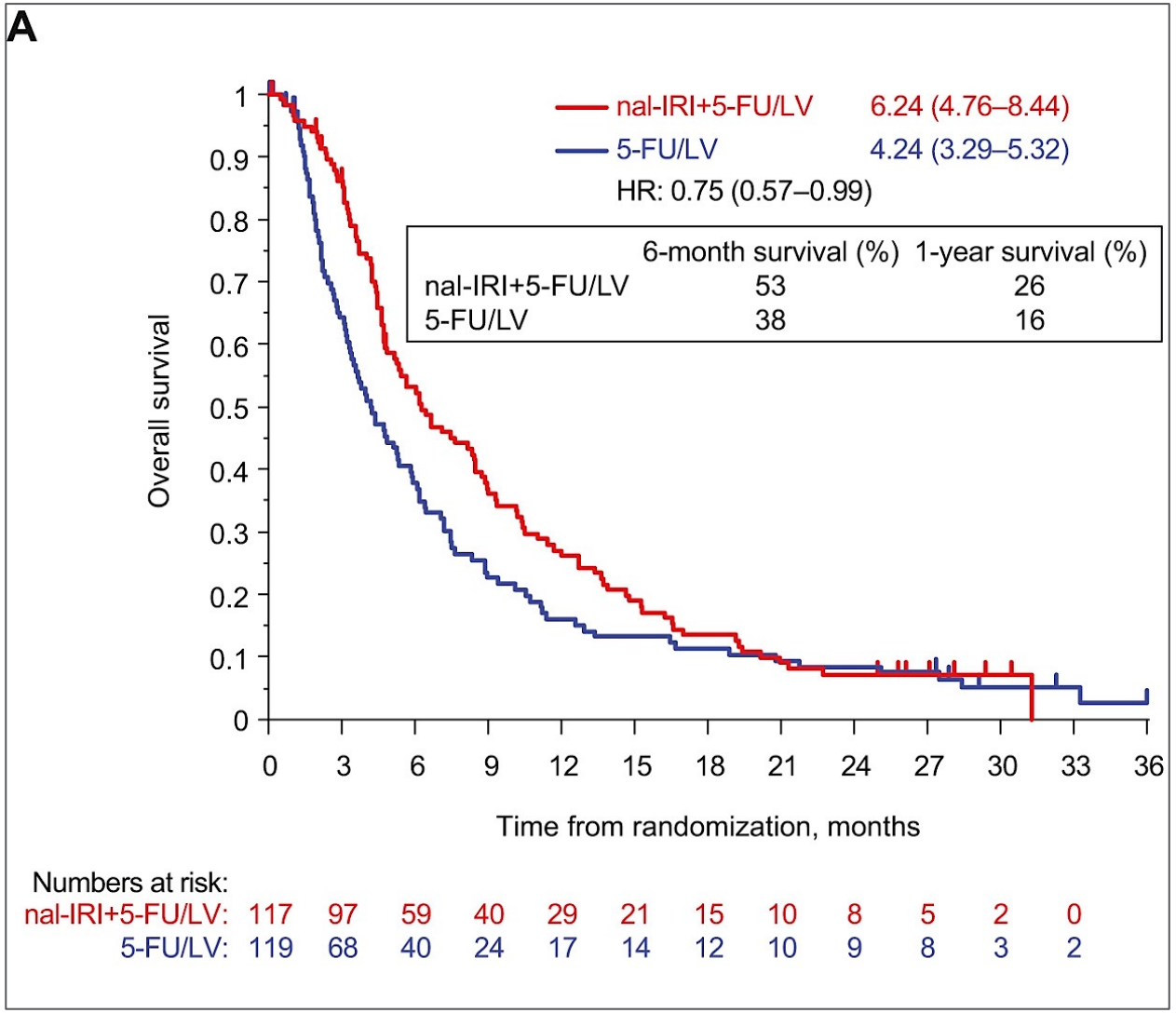
Most patients (41.4%) in the NALIRIFOX group received gemcitabine-based therapy and most patients (35.4%) in the Gem+NabP group received 5-FU-based therapy

Data presented at ASCO 2023 (Eileen O'Reilly)

What to do after first line therapy Chemotherapy

We generally think of 3 major pathways in 2nd line therapy

1. Identifiable targets
   - MMR, high TMB
   - NTRK fusion
   - BRAF
   - HER2
   - NRG1
   - KRAS G12C
2. Prior 5-FU based therapy
   - Gem based regimen
3. Prior Gemcitabine based therapy



Wang Gillam et al, European J of Cancer 2019

Summary
Treatment of metastatic pancreatic cancer

- Treatment has advanced and can prolong life including benefit to a large number of patients for 18 months and beyond
- There are 2 general backbones (5-FU and Gem) with NALIRIFOX showing improved efficacy compared to Gem based chemo in first line
- Patient factors are very important as the toxicity of each regimen differs and we want to give each patient the **best regimen** with the **least toxicity** to improve **quality of life**
- Second line therapy can improve outcomes and should be utilized
- Targeted therapies and clinical trials are ongoing and we expect these will have a big impact on future options for patients

Discussion Questions

- A 65-year-old patient with BRCA wild-type pancreatic adenocarcinoma (PDAC) and no significant comorbidities achieves a good response to neoadjuvant FOLFIRINOX and undergoes resection but is found to have metastatic disease 18 months later. Regulatory and reimbursement issues aside, what would you generally recommend as first-line therapy?

Discussion Questions

- Regulatory and reimbursement issues aside, what would you generally recommend as first-line therapy for a 65-year-old patient with no significant comorbidities and moderately symptomatic BRCA wild-type metastatic PDAC (mPDAC) to the liver, bone and lungs? Would this change if the patient had significant diabetes-related peripheral neuropathy? What if the patient were older (eg, age 80)?

Discussion Questions

- Based on your personal clinical experience and knowledge of available data, in general, how would you compare the global efficacy (likelihood and duration of response, survival) and tolerability of first-line NALIRIFOX to that of gemcitabine/*nab* paclitaxel?

- How do dose reductions of liposomal irinotecan or oxaliplatin affect outcomes with first-line NALIRIFOX? Does UGT1A1*28 status affect the incidence of treatment-emergent adverse events?

Discussion Questions

- Regulatory and reimbursement issues aside, what would you generally recommend as second-line therapy for a 65-year-old patient with BRCA wild-type mPDAC and no significant comorbidities who received first-line gemcitabine/*nab* paclitaxel?

Module 16: Pancreatic Cancer

Selection and Sequencing of Therapy for Patients with Metastatic Pancreatic Adenocarcinoma (PAD) — Dr Oberstein

Biomarker-Based Strategies for Metastatic PAD; Novel Investigational Approaches — Dr Philip

Pancreatic Cancer

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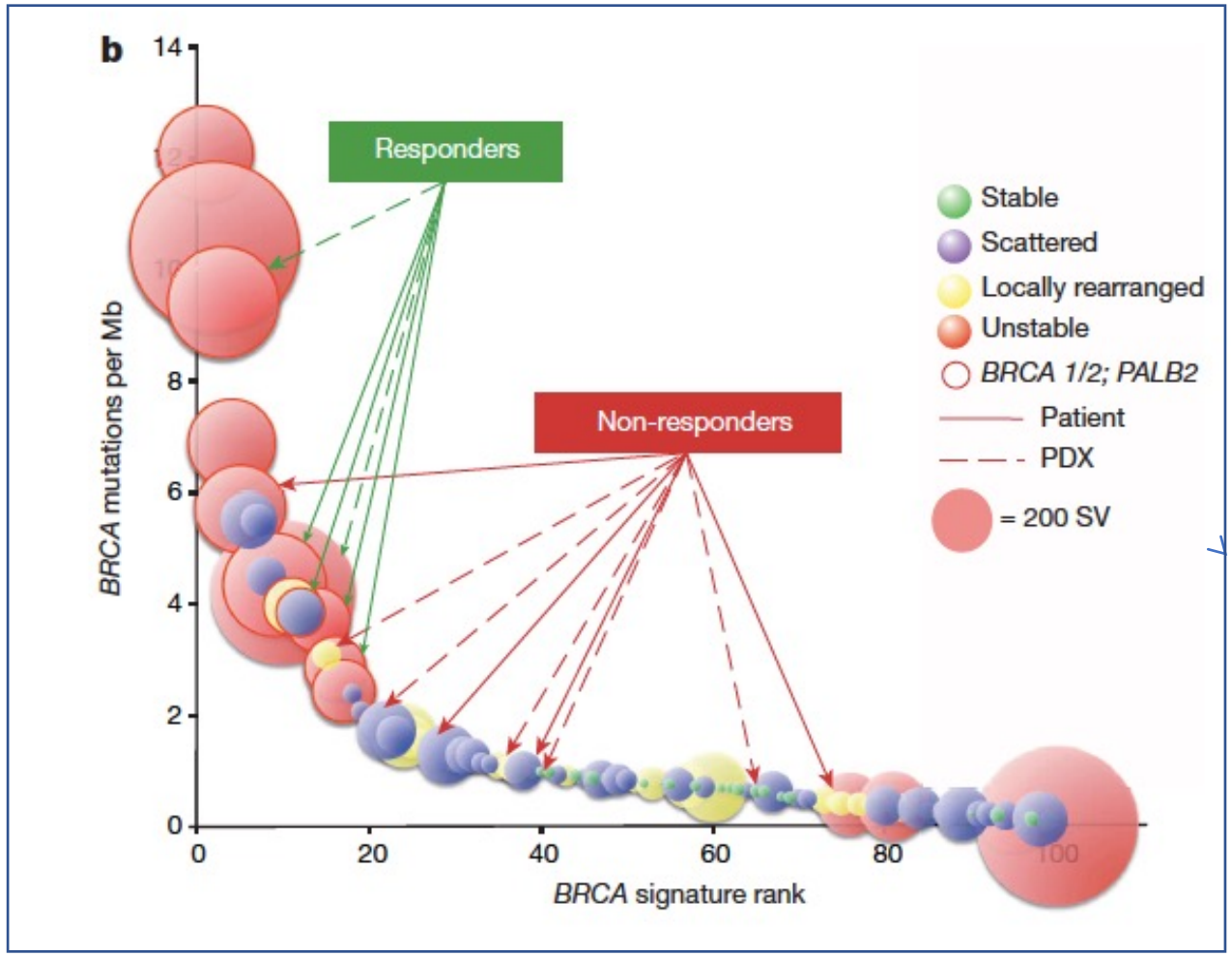
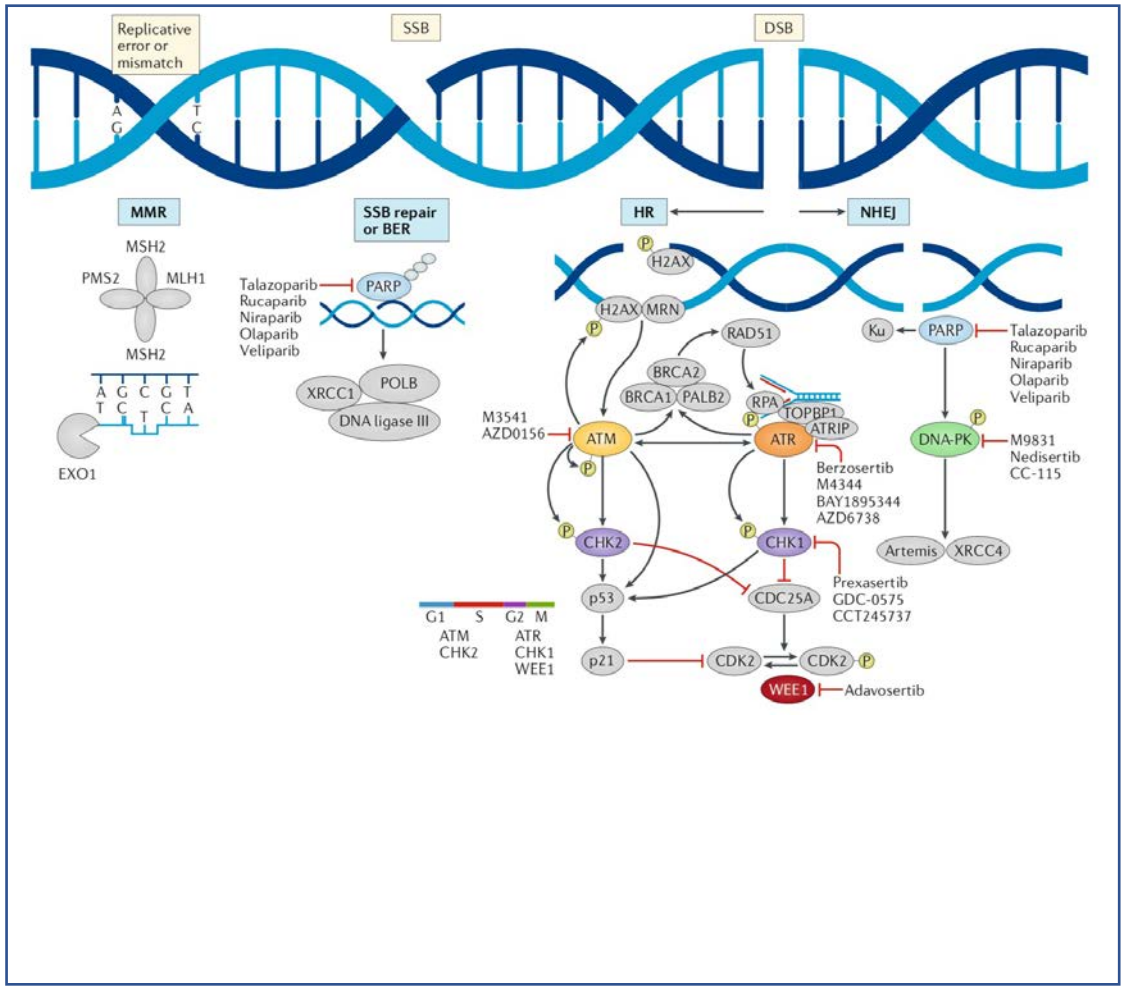
Disclosures

Advisory Committees	Agenus Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Daiichi Sankyo Inc, Gilead Sciences Inc, HUYA Bioscience International, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Jazz Pharmaceuticals Inc, Novocure Inc, Pfizer Inc, Processa Pharmaceuticals Inc, Seagen Inc, Takeda Pharmaceuticals USA Inc
Contracted Research	Amgen, BioNTech SE, Moderna, Novocure Inc
Data and Safety Monitoring Boards/Committees	Cyclacel Pharmaceuticals Inc, Oncolytics Biotech Inc
Speakers Bureaus	Astellas, Incyte Corporation

DNA Repair Defects in Pancreatic Cancer in Up to 25% of patients: Opportunities in Complex System





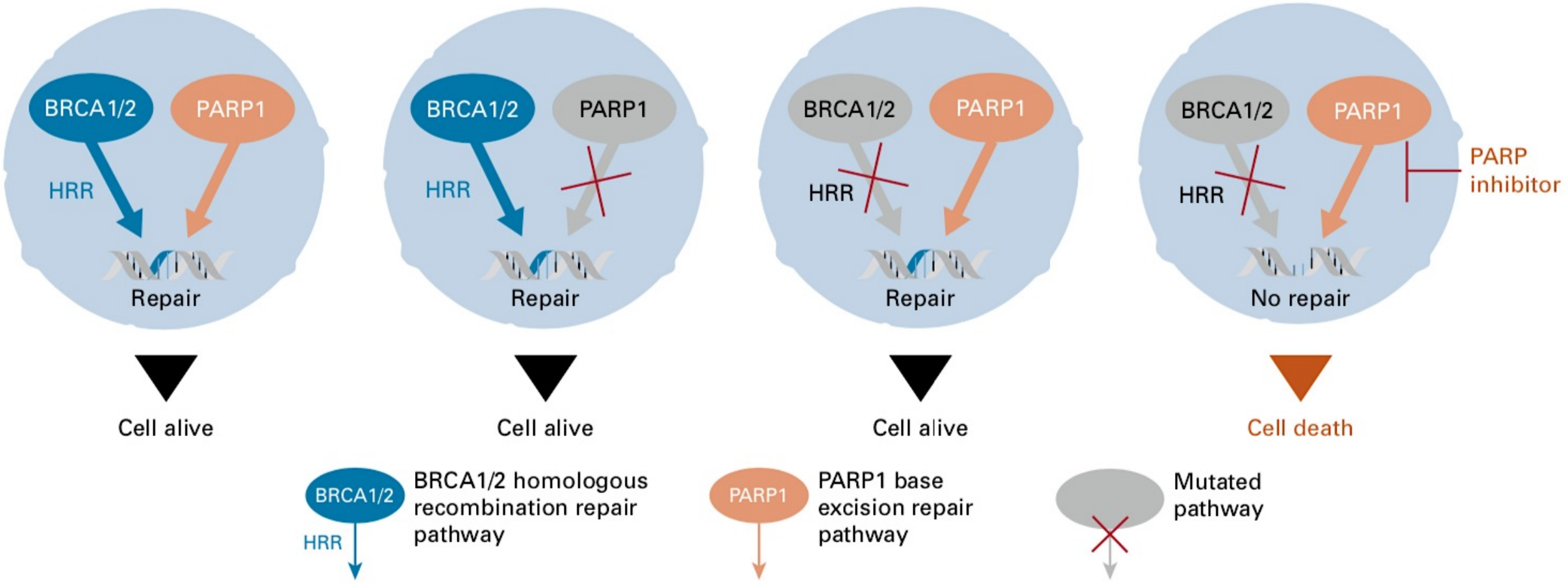
Waddell et al, Nature, 518:495, 2015; Pilie et al, Nature Reviews, 2019

BRCA1/2 Germline Mutations in Pancreatic Cancer

- 5% to 7% of patients with pancreatic cancer have germline *BRCA1/2* mutations
  - Ashkenazi Jewish heritage: 5% to 16%
  - Familial pancreatic cancer: 5% to 19%
  - Familial breast/ovarian cancer: 5% to 10%
- **40% of patients who are germline *BRCA1/2* mutation carriers do NOT have a family history of breast/ovarian cancer**

Hahn. Gastroenterology. 2003;124:544. Murphy. Cancer Res. 2002;62:3789. Ozçelik. Nat Genet. 1997;16:17. Lal. Cancer Res. 2000;60:409. Lucas. Clin Cancer Res. 2013;19:3396. Ferrone. JCO 2009;27:433. Stadler. Cancer. 2012;118:493. Brose. J Natl Cancer Inst. 2002;94:1365. Holter. JCO. 2015;33:3124. Chaffee. Genet Med. 2018;20:119. Petersen. Semin Oncol. 2016;43:548.

Induction of Cell Death in BRCA Deficient Vulnerable Cancer Cells by PARP Inhibitors: Synthetic Lethality

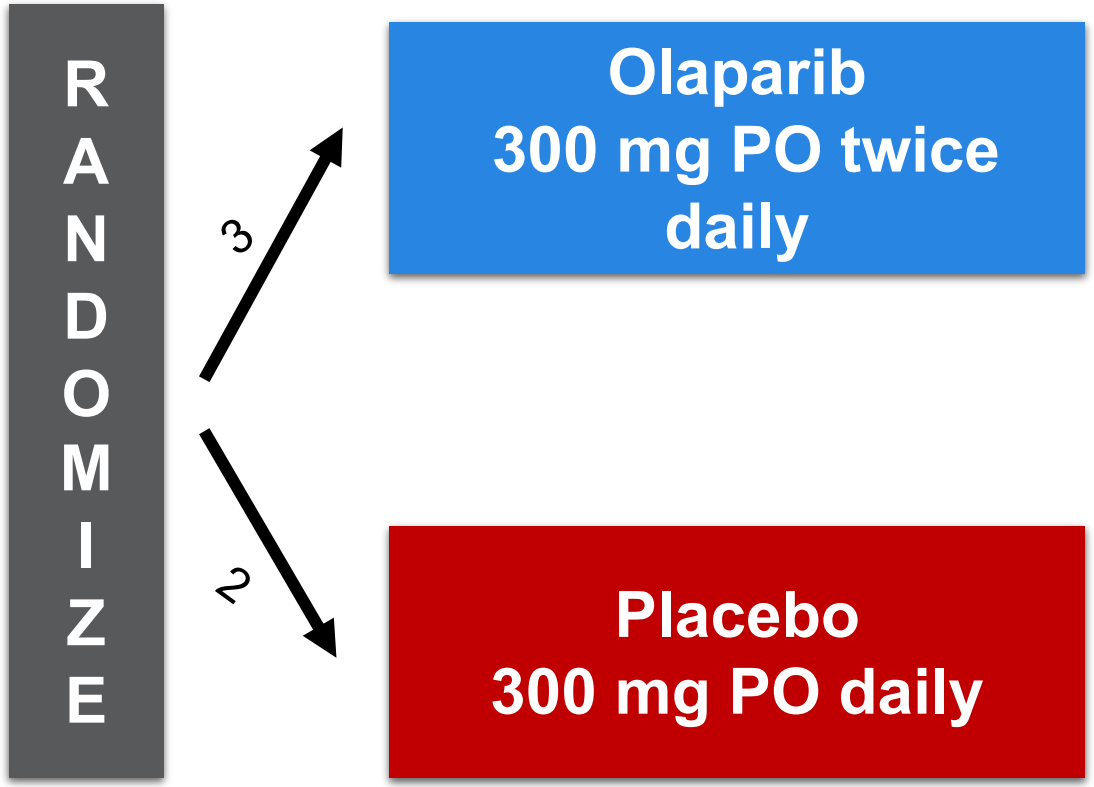


Gourley C, et al. *J Clin Oncol.* 2019.

POLO: A Phase 3 International PARPi Maintenance Study in Patients Who Have *Germline BRCA* Mutation

- Metastatic disease
- Stable or better on prior platinum therapy (≥ 4 months)
- ECOG 0-1

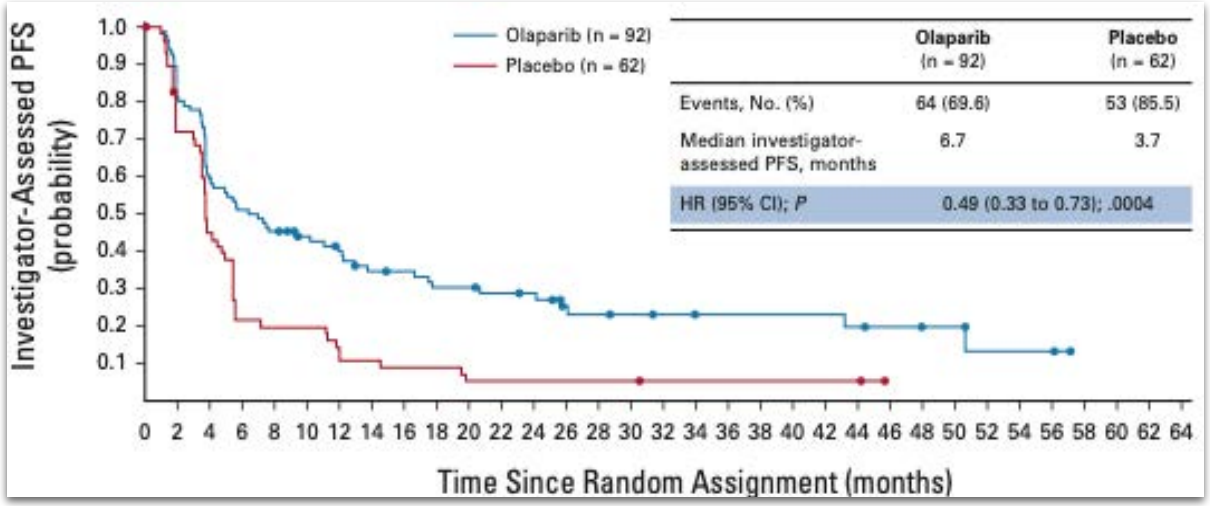
N = 154
Primary endpoint = PFS



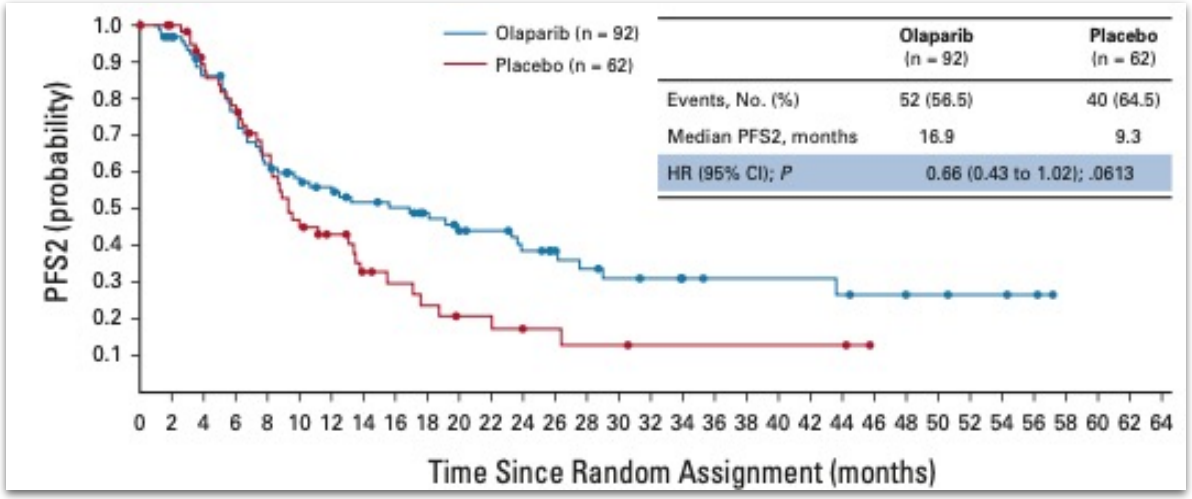
mPCA = metastatic pancreatic cancer; PARPi = PARP inhibitor; PFS = progression-free survival.

Kindler HL, et al. ASCO 2019. Abstract LBA4; Golan T, et al. *N Engl J Med.* 2019 Jun 2. [Epub ahead of print]; ClinicalTrials.gov. NCT02184195.

Maintenance olaparib significantly prolonged PFS and PFS2 in updated results



	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	64 (69.6)	53 (85.5)
Median investigator-assessed PFS, months	6.7	3.7
HR (95% CI); *P*	0.49 (0.33 to 0.73); .0004	

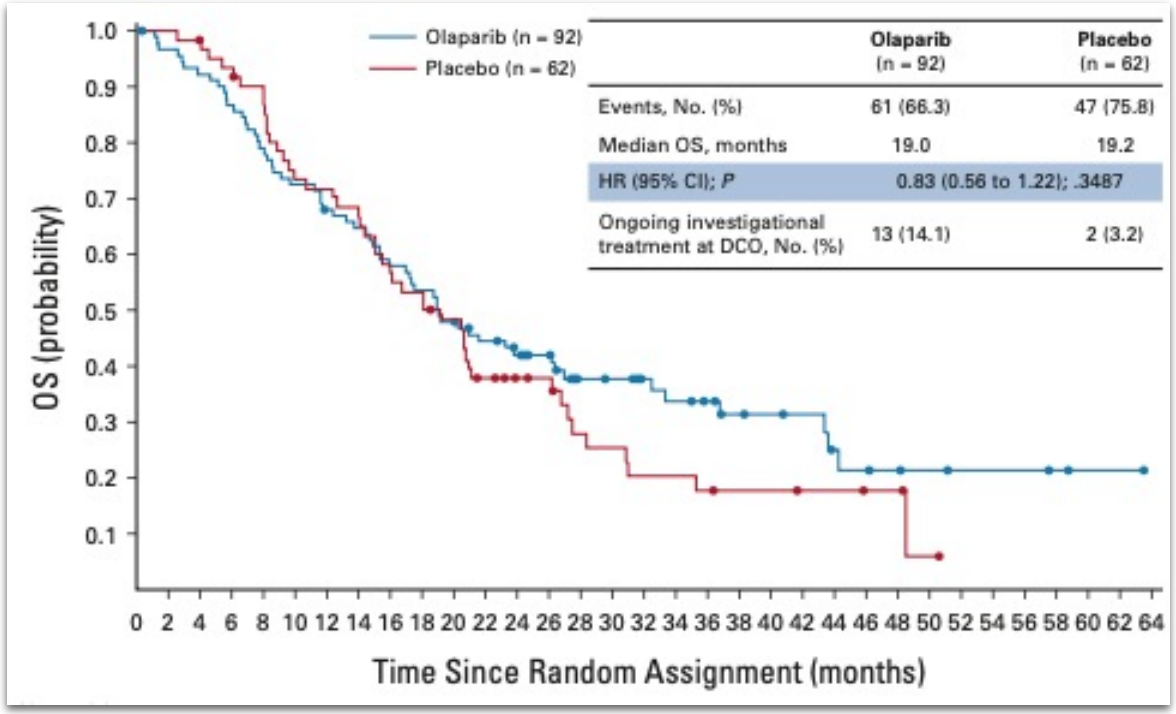


	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	52 (56.5)	40 (64.5)
Median PFS2, months	16.9	9.3
HR (95% CI); *P*	0.66 (0.43 to 1.02); .0613	

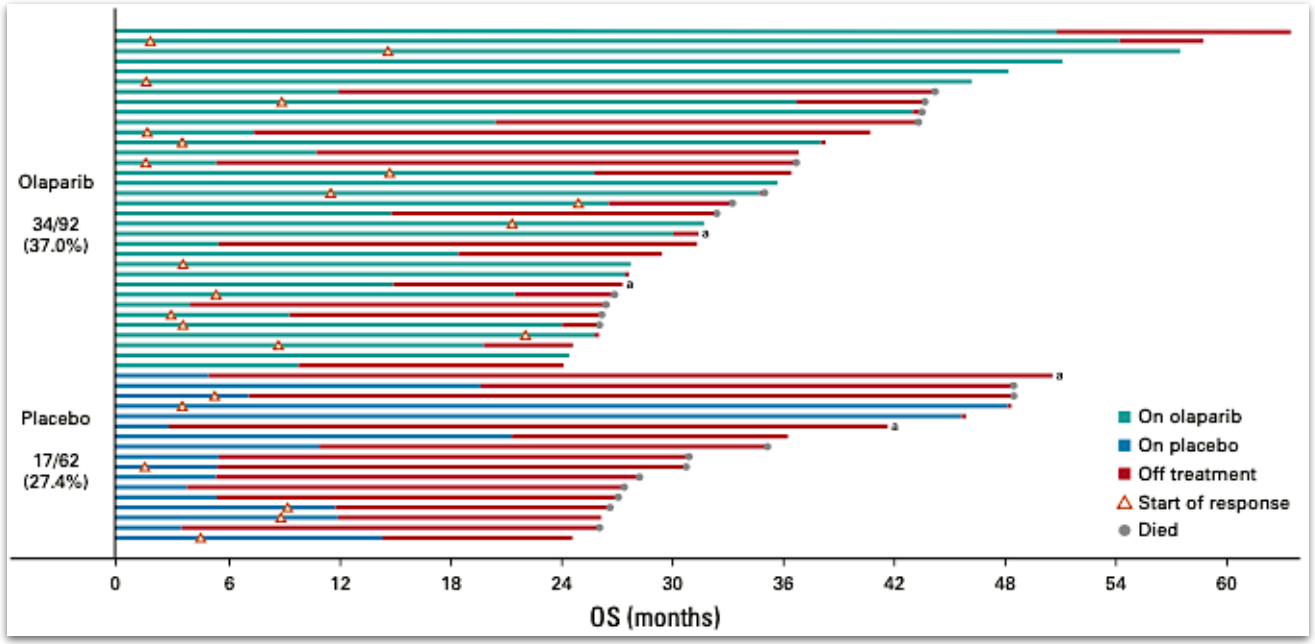
Patients With Measurable Disease at Baseline	Olaparib (n = 78)	Placebo (n = 52)
Objective response n (%)	18 (23.1)	6 (11.5)
Median time to response, mos	5.4	3.6
Median duration of response, mos	24.9	3.7

Kindler et al, JCO, 2022

Impact of olaparib on overall survival



	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	61 (66.3)	47 (75.8)
Median OS, months	19.0	19.2
HR (95% CI); *P*	0.83 (0.56 to 1.22); .3487	
Ongoing investigational treatment at DCO, No. (%)	13 (14.1)	2 (3.2)



Kindler et al, JCO, 2022

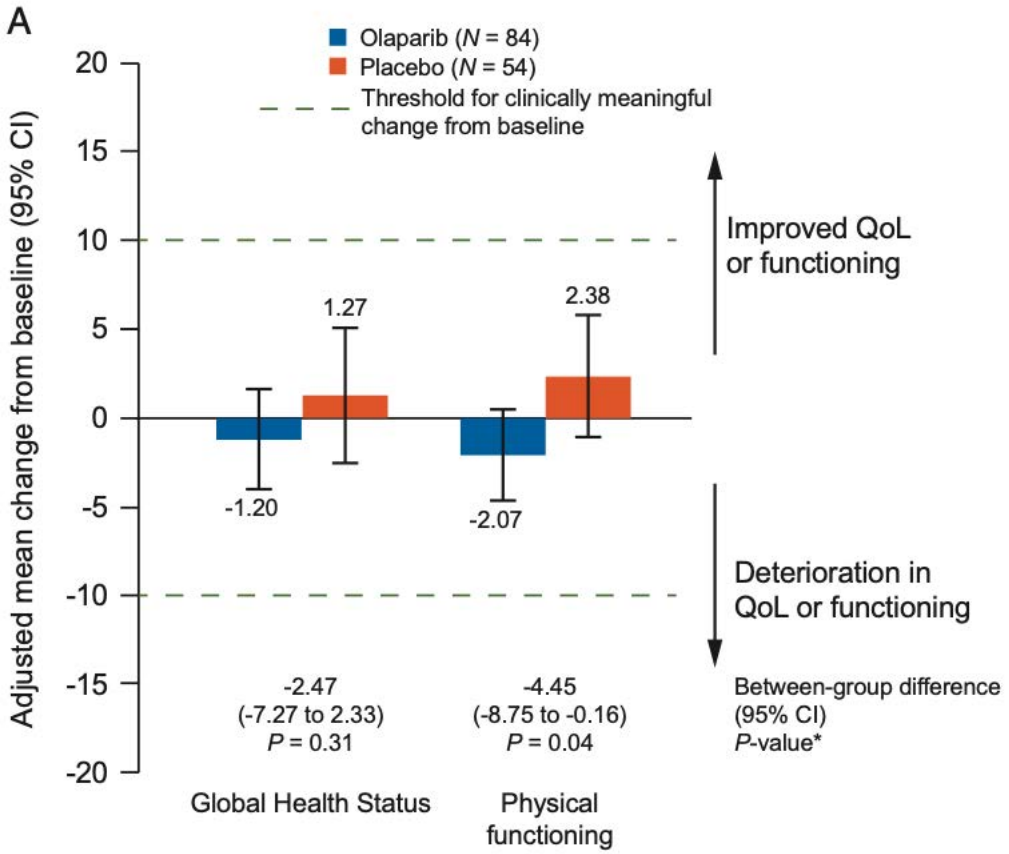
Grade 3 adverse events occurring in at least 15%

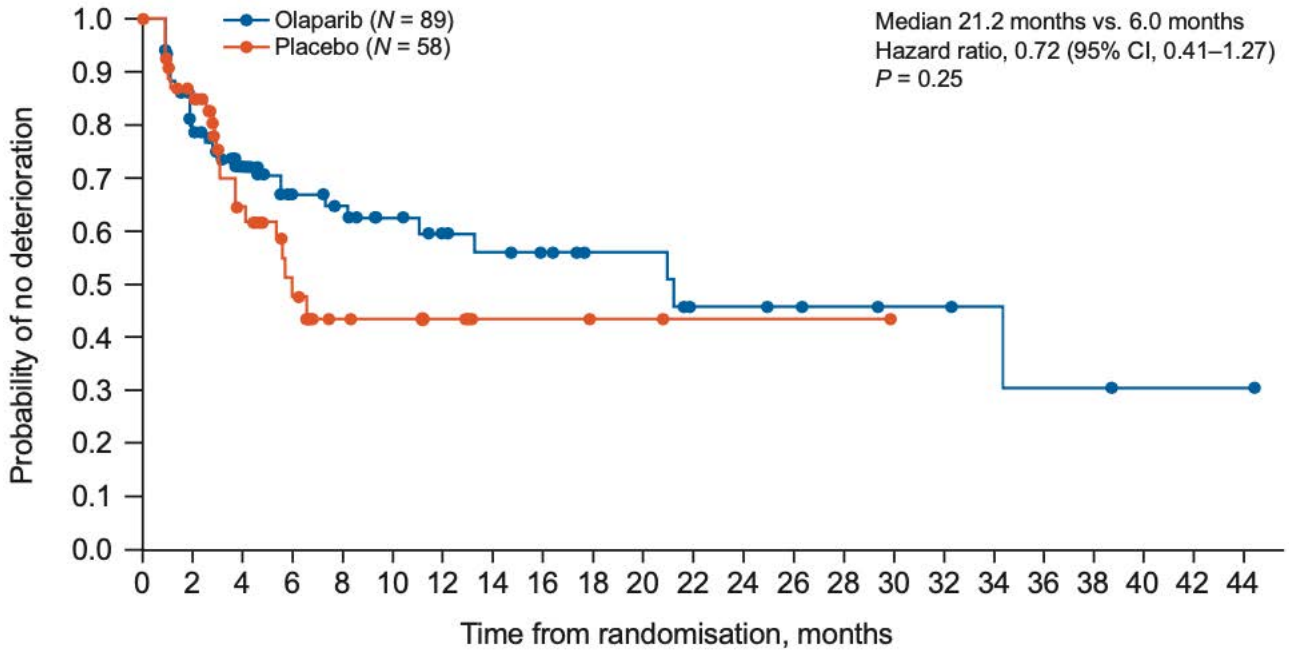
Event	Olaparib (%)	Placebo (%)
Nausea	1.1	1.6
Fatigue	5.6	0
Diarrhea	1.1	0
Anemia	12.2	3.3
Decreased appetite	3.3	0
Vomiting	2.2	1.6
Arthralgia	1.1	0
Asthenia	1.1	1.6
Treatment related	24.4	3.3
Discontinuation because of AE	8.9*	1.6*

*Only Grade1-2

Kindler et al, JCO, 2022

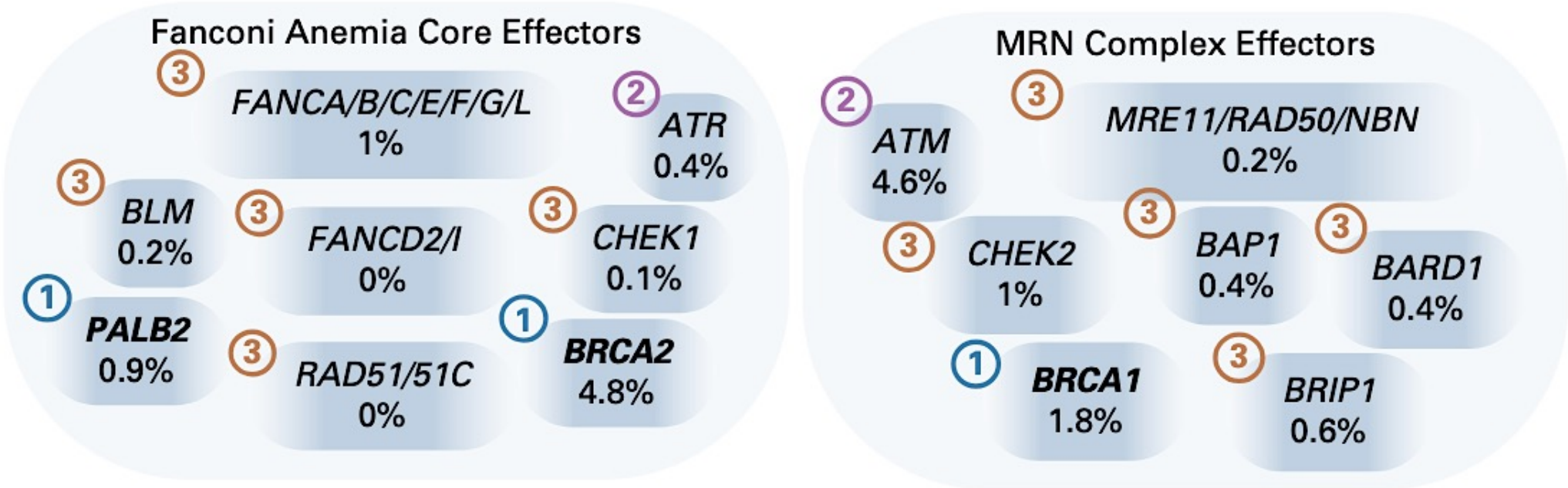
Health-related quality of life data support slowing of deterioration with olaparib





Hammel et al, Ann Oncol, 2019

Best evidence of PARP inhibition in DDR is in *BRCA/PALB* germline mutations



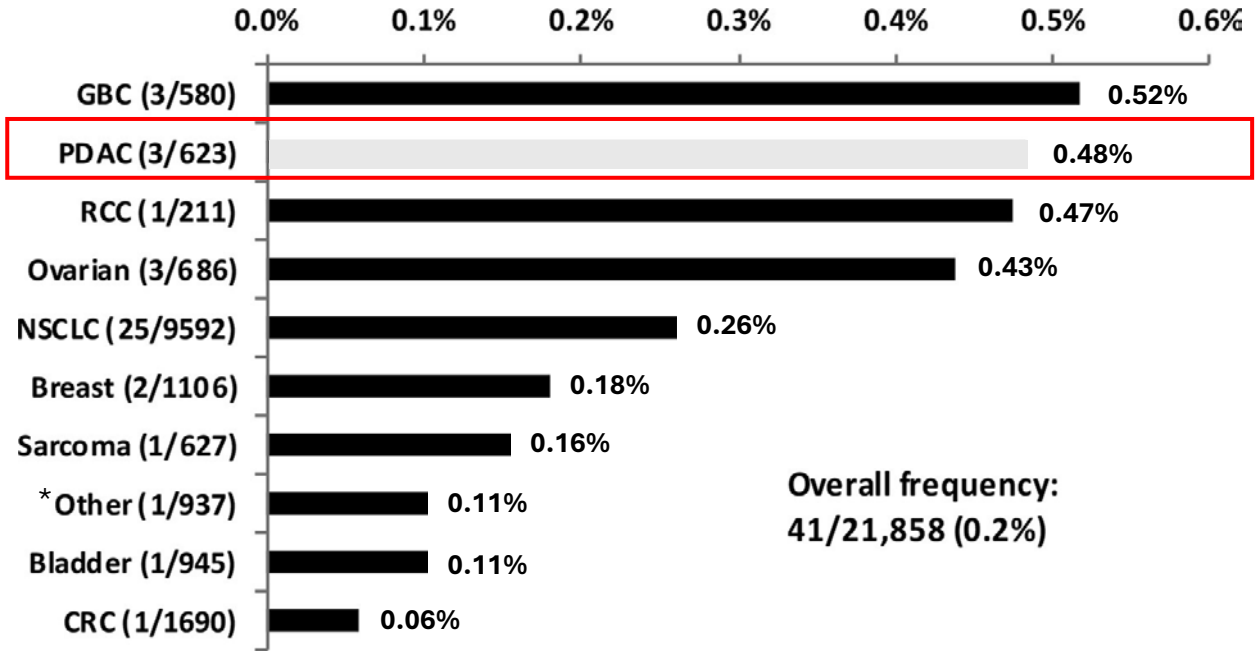
Pishvaian, et al, JCO Precision Oncology, October, 2019

Germline Testing in Pancreatic Cancer: Guidelines Recommendation

Germline testing is recommended for *any* patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes

NRG-1 fusions: rare but targetable

- Wide array fusion partners across and in different tumor types
- PDAC Frequency reported in 0.5-1.8%[1,2], and up to 6%[3] when enriched for *KRAS*^{WT}
- Younger than 60
- Similar disease characteristics

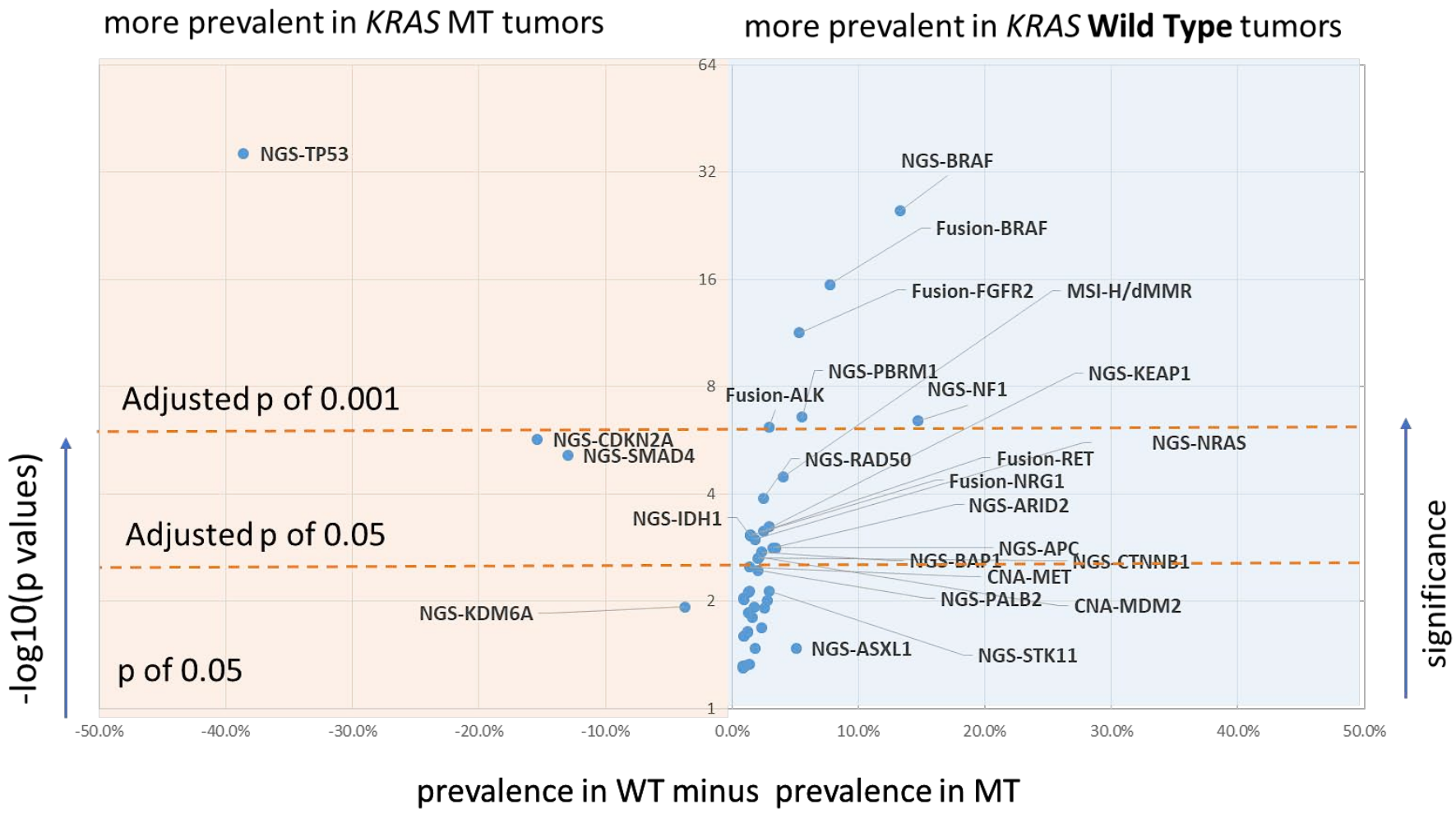


CRC, colorectal cancer; GBC, gallbladder cancer (cholangiocarcinoma); PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell carcinoma.

*Other category is a neuroendocrine tumor of the nasopharynx

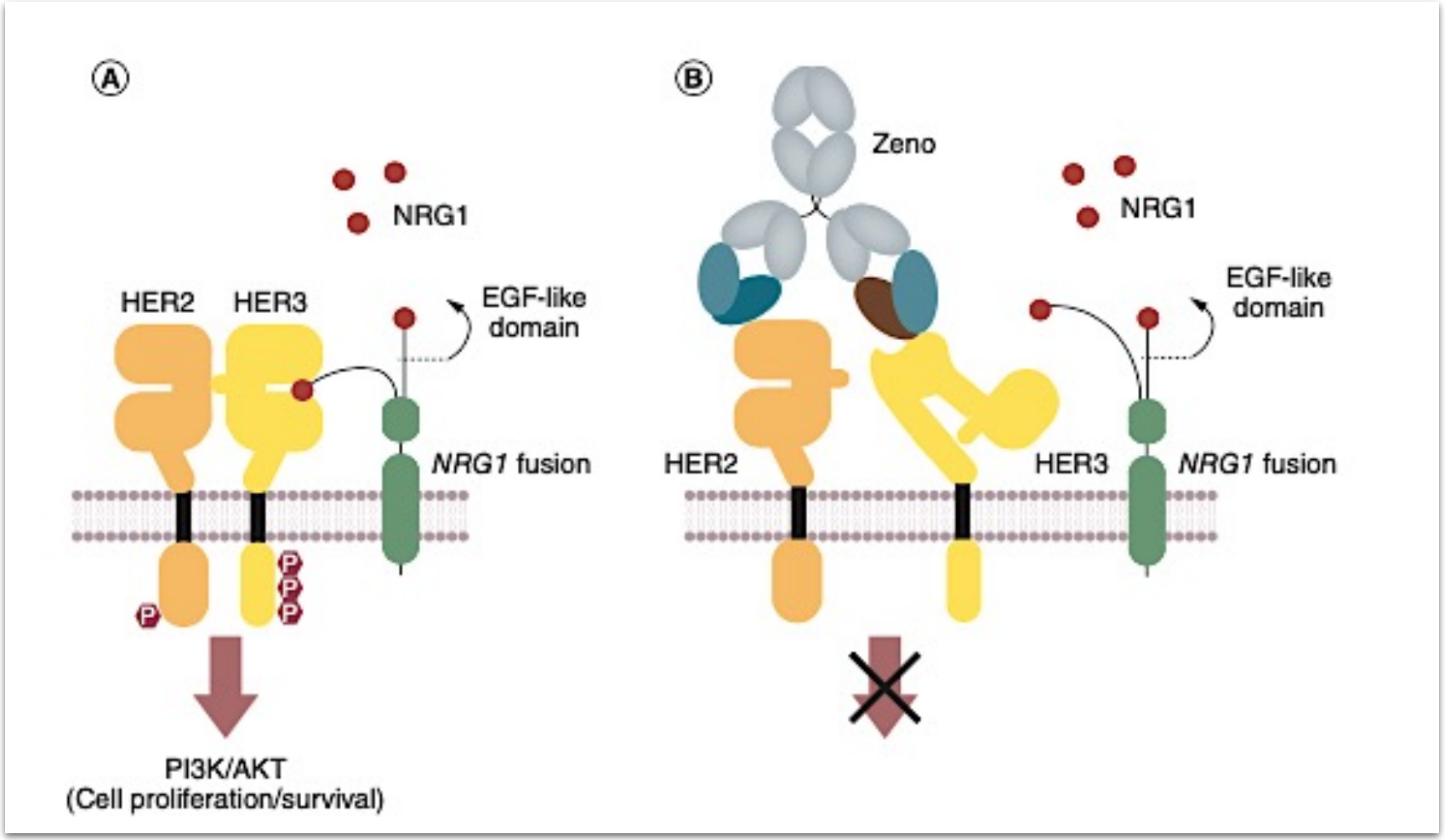
1. Jonna S et al. Clin Cancer Res. 2019;25(16):4966-49723.
2. Knepper TC et al. J Clin Oncol. 2022;40(16 suppl):4155.
3. Jones MR et al. Clin Cancer Res. 2019;25(15):4674-4681.

The *RAS* wild type (~10%) may offer druggable targets in including *NRG-1* fusions



Philip et al Clinical Cancer Research, 2022

Zenocutuzumab: a novel bispecific antibody targeting both HER2 and HER3



Kim et al, Future Oncology, 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Zenocutuzumab in *NRG1* Fusion–Positive Cancer

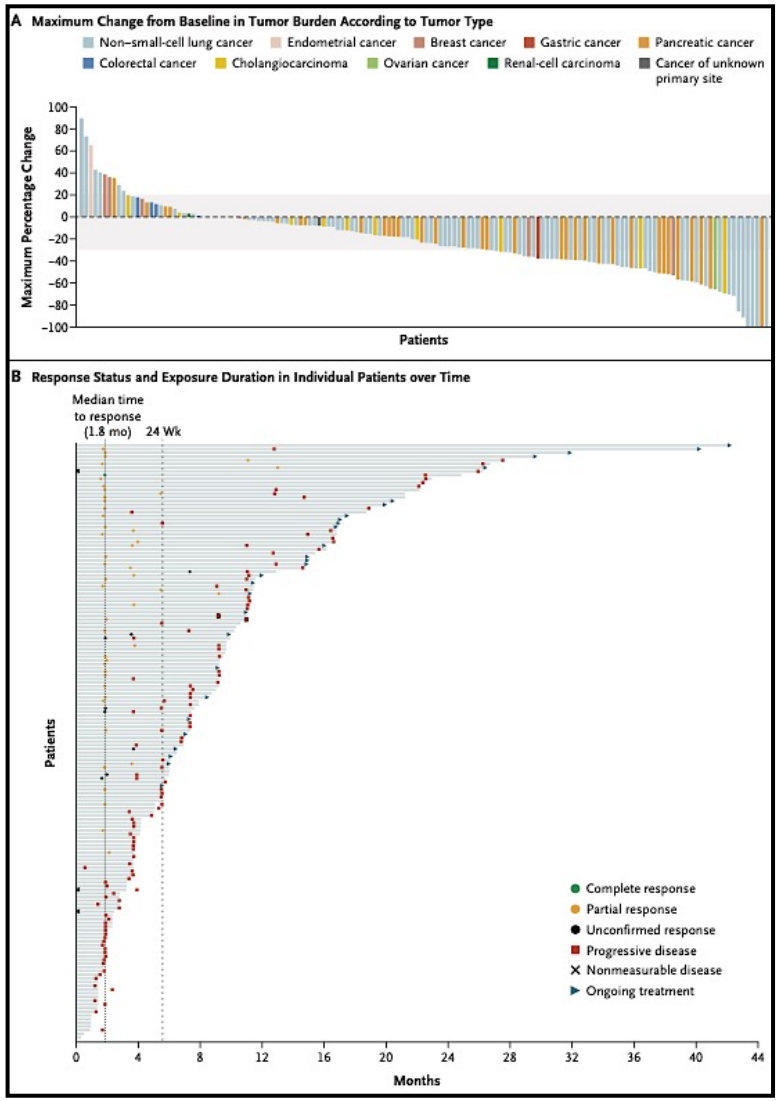
A.M. Schram,[1] K. Goto,[2] D.-W. Kim,[3] T. Macarulla,[4] A. Hollebecque,[5] E.M. O'Reilly,[1] S.-H.I. Ou,[6] J. Rodon,[7] S.Y. Rha,[8] K. Nishino,[9] M. Duruisseaux,[10,11,12] J.O. Park,[13] C. Neuzillet,[14] S.V. Liu,[15] B.A. Weinberg,[15] J.M. Cleary,[16,17] E. Calvo,[18] K. Umemoto,[19] M. Nagasaka,[19,20] C. Springfeld,[21] T. Bekaii-Saab,[22] G.M. O'Kane,[23] F. Opdam,[24] K.A. Reiss,[25] A.K. Joe,[26] E. Wasserman,[26] V. Stalbovskaya,[26] J. Ford,[26] S. Adeyemi,[26] L. Jain,[26] S. Jauhari,[26] and A. Drilon,[1] for the eNRGy Investigators*

NEJM February 6, 2025

Efficacy of zenocutuzumab in 32 patients with previously treated pancreatic cancers

- Total 204 patients/Pancreatic cancer = 32 (22%)

	Investigator Assessed		Central review	
	ORR, %	Med Duration of Response, mon	ORR, %	Med Duration of Response, mon
All *NRG-1* fusion tumors	30	11.1	31	11.5
Pancreatic cancer	42 (25-59)	7.4 (2.1 – 20.7)	44 28 -62)	9.1 (1.9 – 16.6)



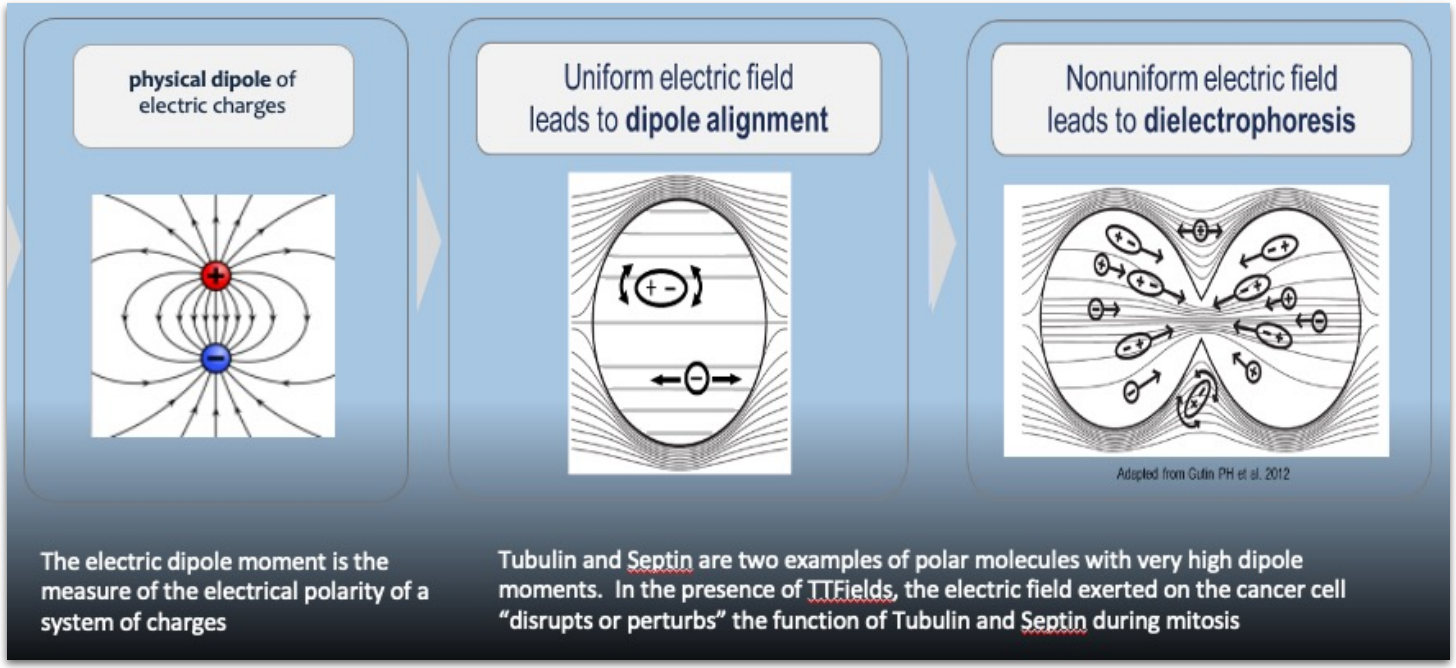
Schram et al, NEJM, 2025

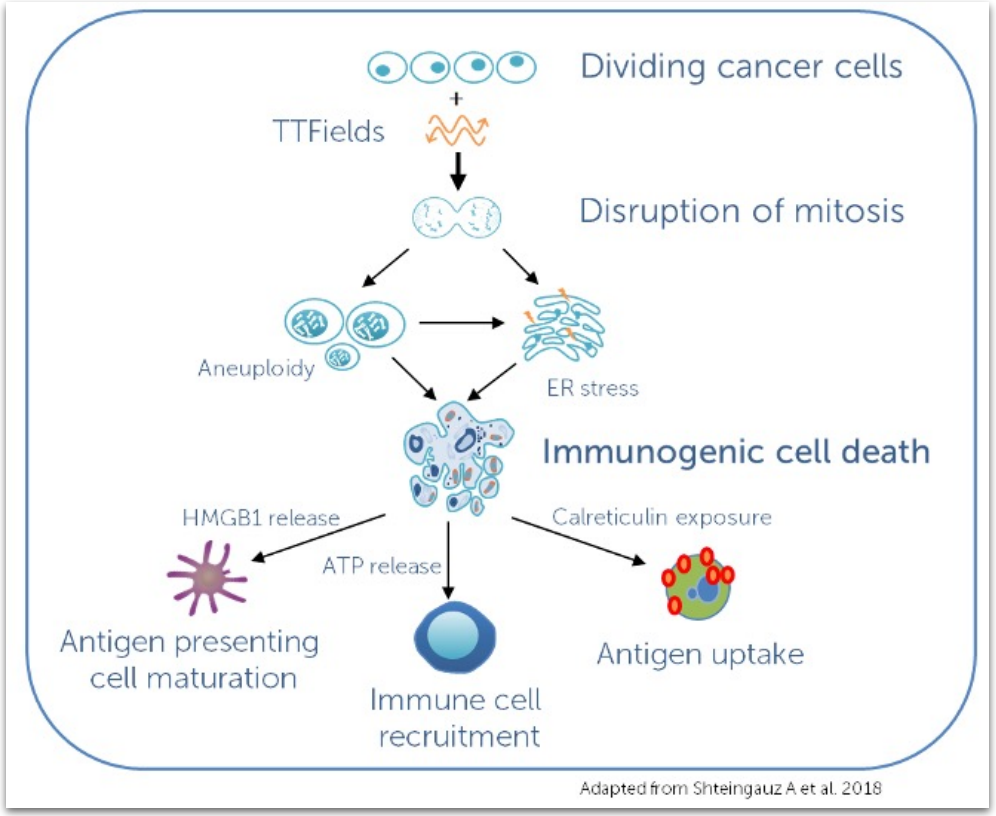
Treatment related adverse events in 204 pts

	Any grade, %	Grade 3-4, %
Diarrhea	18	1
Fatigue	12	0
Nausea	11	1
Anemia	4	1
Dyspnea	2	0
Constipation	3	0
Vomiting	6	<1
ALT	3	<1
Cough	1	0
Hypomagnesemia	2	0
Arthralgia	3	0
AST	3	1
Decreased appetite	2	<1

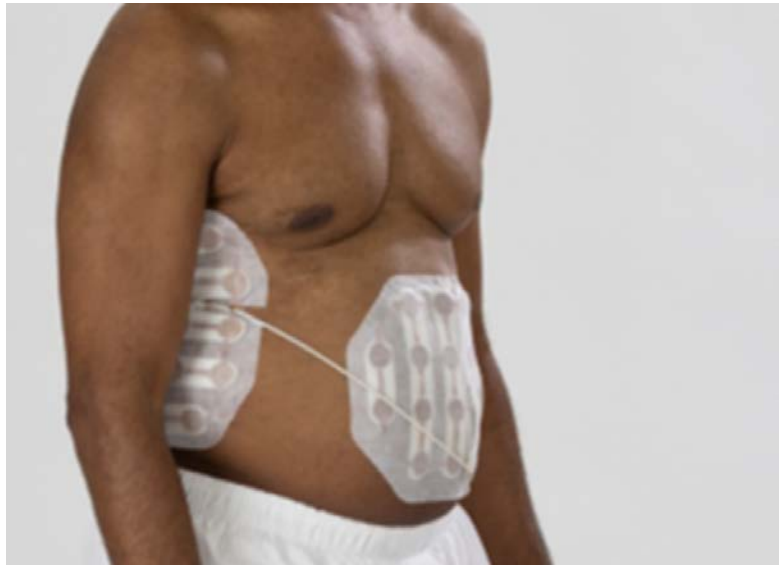
Schram et al, NEJM, 2025

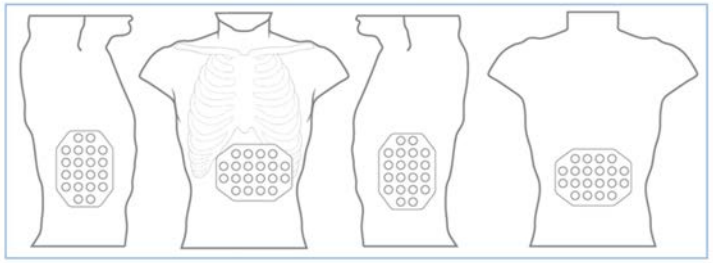
TTFields Disrupt Localization and Orientation of Polar Molecules and Organelles and May Lead to Immunogenic Cell Death





TTFields in the treatment of pancreatic cancer





- Two pairs of transducer arrays are applied to the patient's skin (AP & lateral) and connected to field generating device

EF-20: Phase 2 European Study of TTFields plus Chemotherapy in Patients with Advanced Pancreatic Cancer

TTFields applied ≥ 18 hours per day

- LAPC & metastatic
- No prior therapy
- ECOG 0-1

N = 40

Primary endpoint = safety

RANDOMIZE

1

TTFields + Gemcitabine

1

TTFields + Gemcitabine /nab-paclitaxel

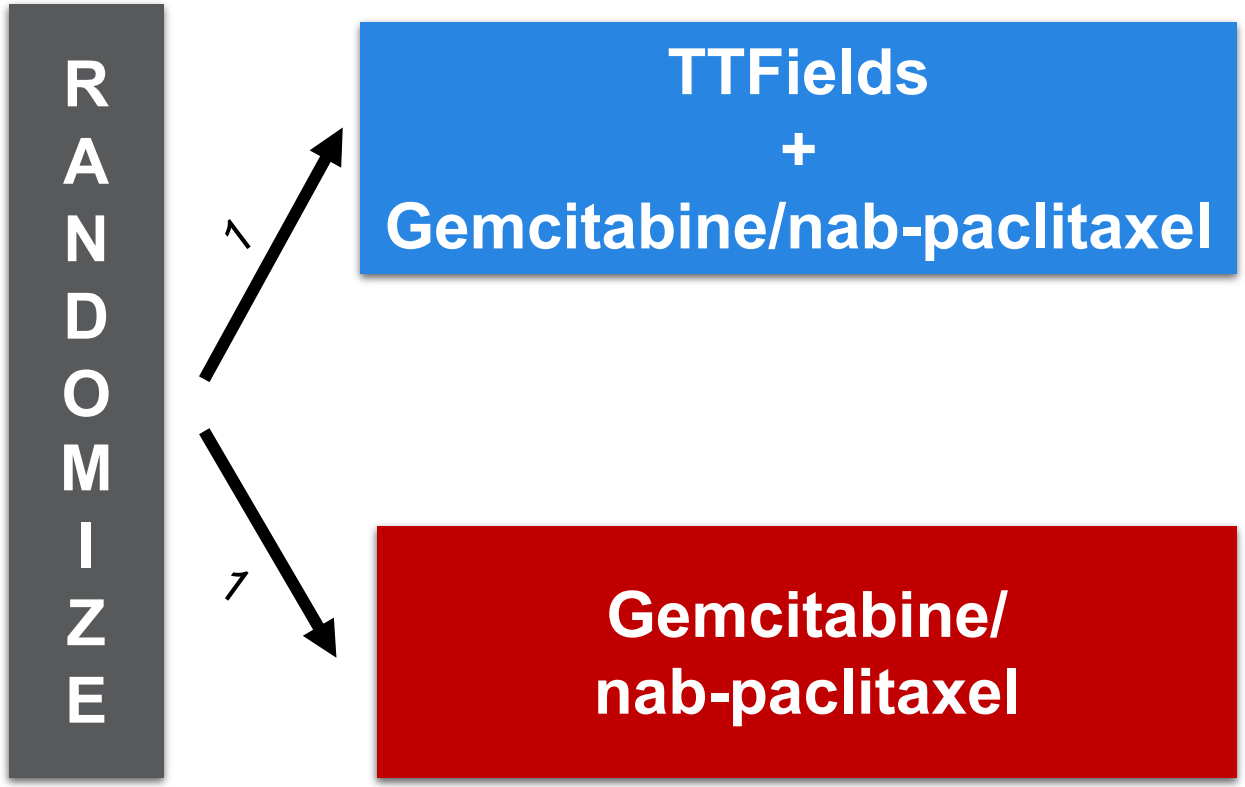
Grade 3-4 toxicity	TTF/ G (%)	TTF/ AG (%)
Neutropenia	20	35
Thrombocytopenia	0	15
Skin toxicity	**10**	**25**
Fatigue	10	15
PE	0	10
Diarrhea	10	5

Rivera F et al, Pancreatology, 2019

PANOVA-3: Phase 3 International Study of TTFields plus Chemotherapy in Patients with Locally Advanced Pancreatic Cancer

- LAPC
- No prior therapy
- ECOG 0-1

N = 556
Primary endpoint = Overall Survival

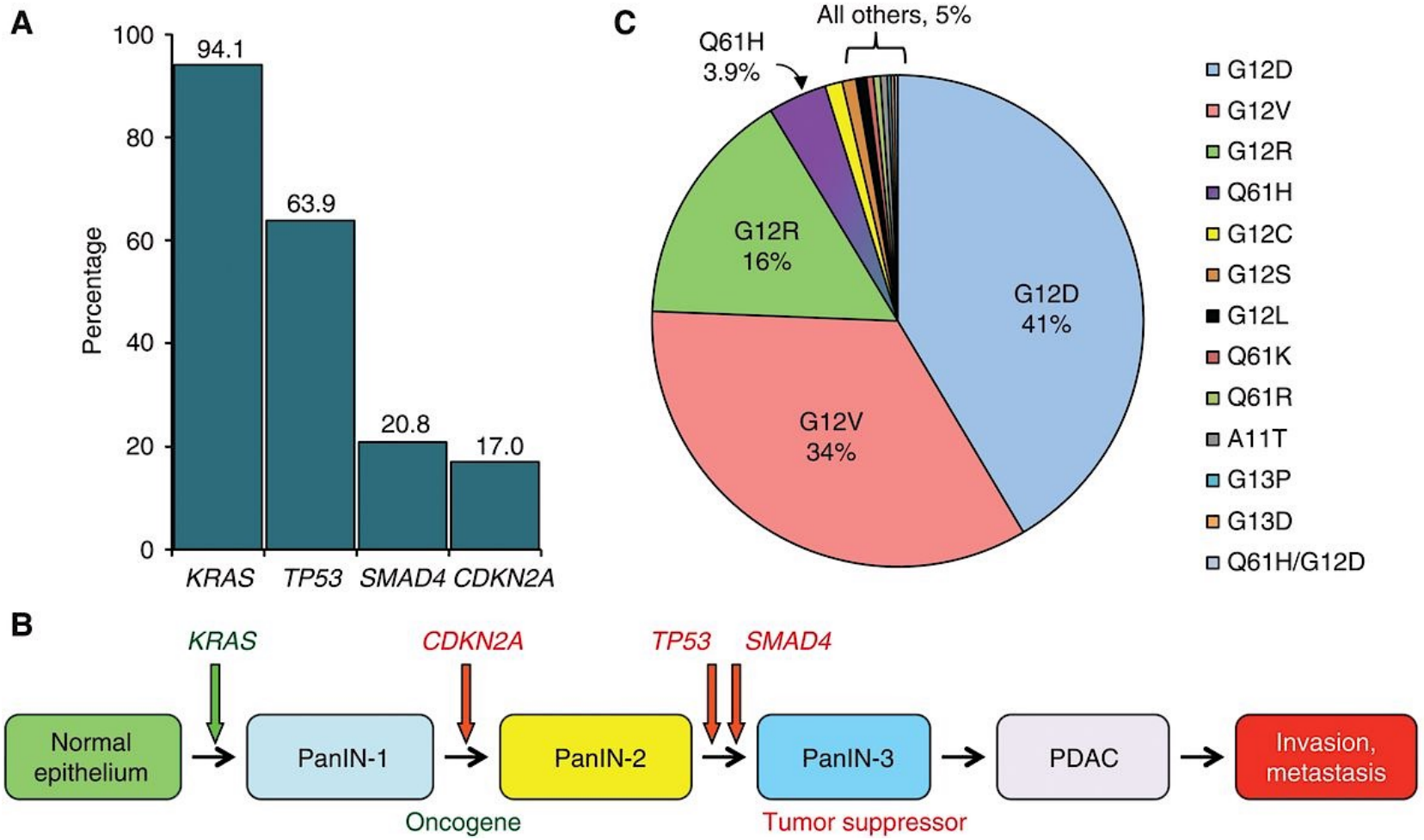


NCT03377491

12/02/2024: **Positive Topline Results from Phase 3 PANOVA-3 Clinical Trial of Tumor Treating Fields (TTFields) Therapy for Pancreatic Cancer**

- PANOVA-3 met its primary endpoint with a statistically significant improvement in overall survival
- Median OS 16.20 versus 14.16 months, HR 0.819, *p*=0.039
- Survival benefit increased over time
  - 13% improvement at 12 months
  - 33% improvement at 24 months

~90% of pancreatic adenocarcinomas have *KRAS* mutations and multiple tumor suppressor gene mutations

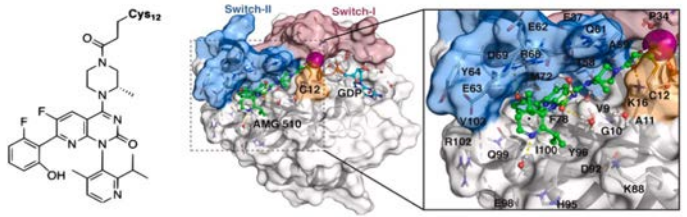


Andrew M. Waters, and Channing J. Der Cold Spring Harb Perspect Med 2018;8:a031435

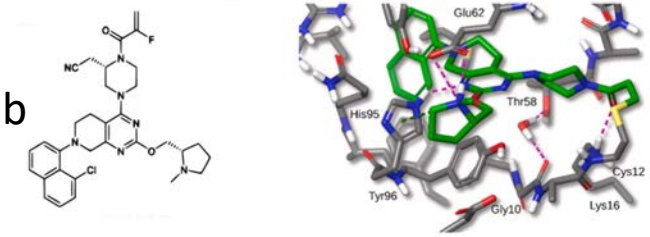
Direct and indirect strategies to target RAS signaling: need for better drugs

- Mutant-specific KRAS inhibitors
- Pan-KRAS inhibitors (*includes wild type*)
- SHP2 inhibitors
- SOS1 inhibitors

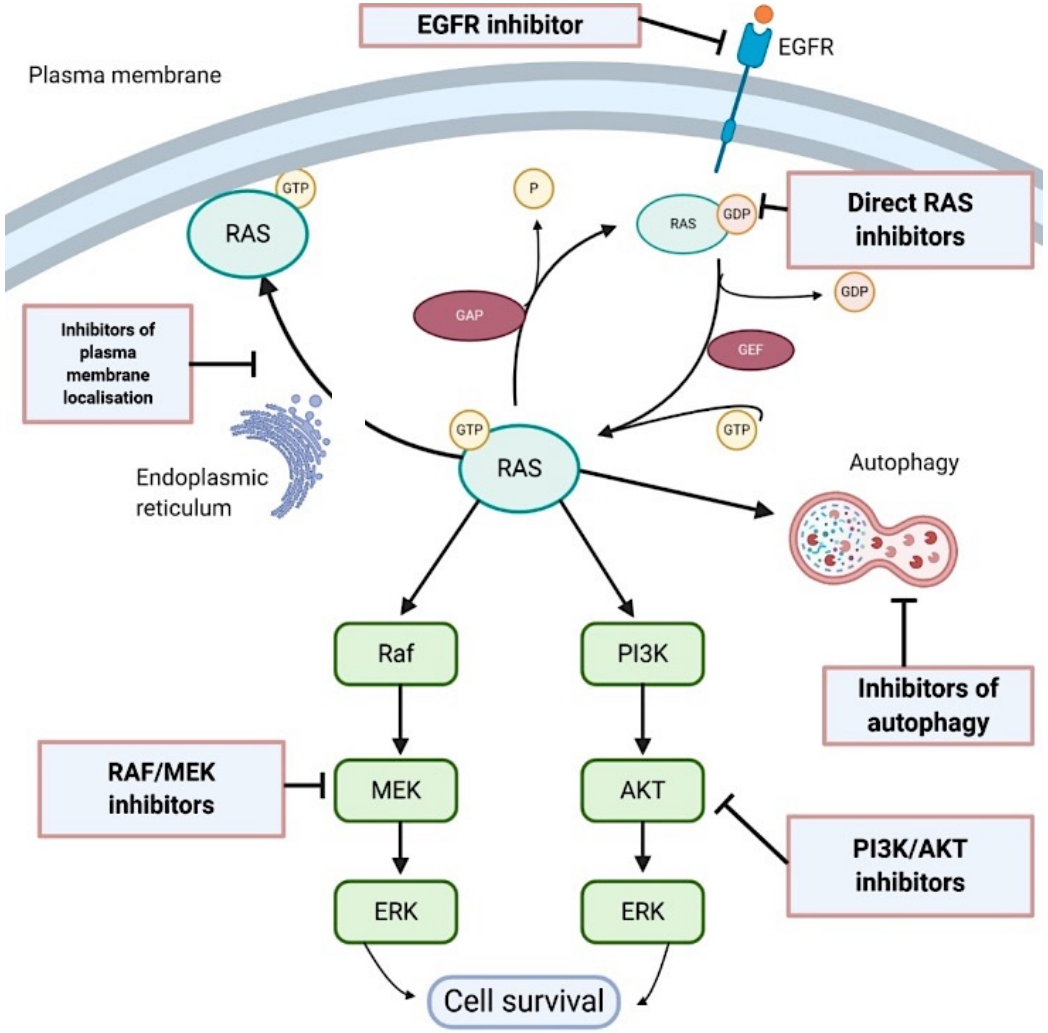
Sotorasib



Adagrasib



Targeting G12C

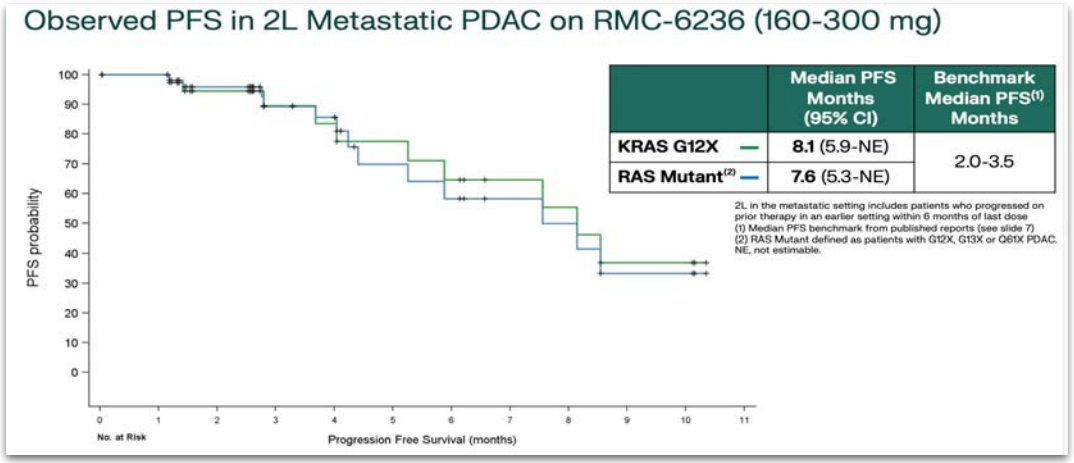


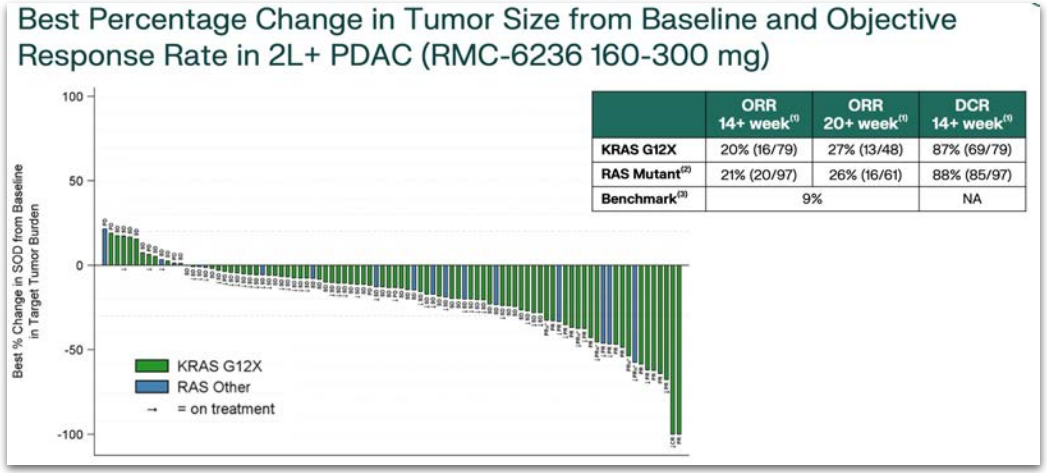
Conroy et al, Cancer Drug Resist, 2021; Lindsay et al, Lung Cancer, 2021

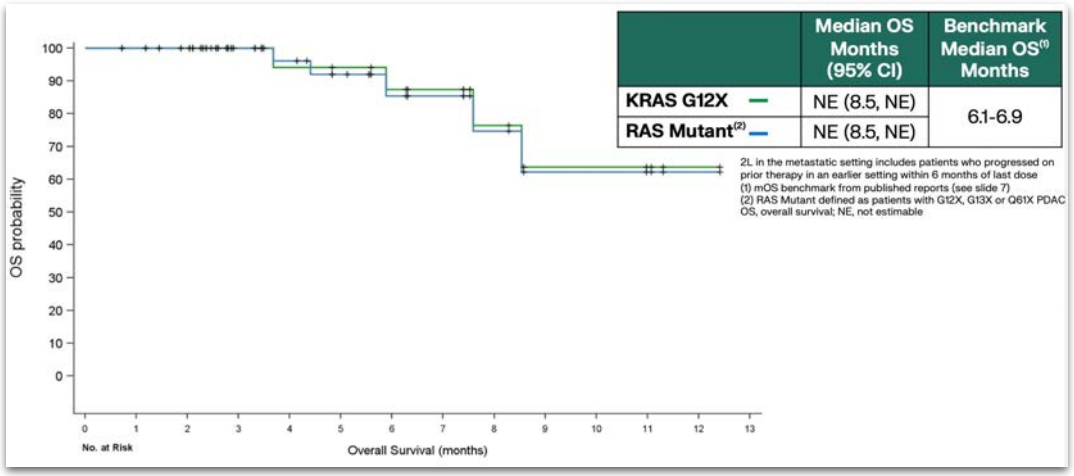
Select RAS inhibitors in pancreatic cancer

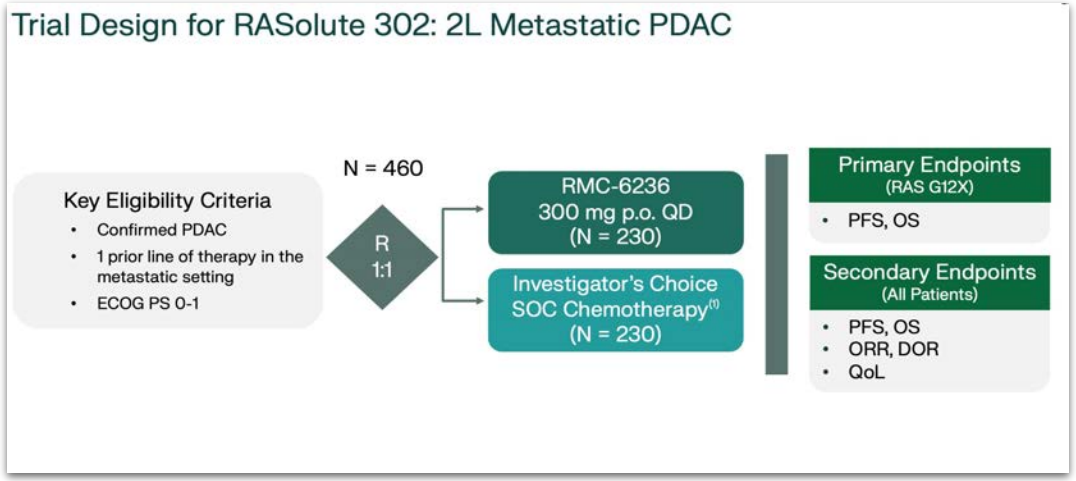
KRAS G12D inhibitors				
MRTX1133 Mirati Therapeutics	NCT05737706 Phase 1/2	KRAS G12D	OFF state inhibitor	No data
RMC-9805 Revolution Medicines	NCT06040541 Phase 1	KRAS G12D	ON state, tri-complex inhibitor	No data
HRS-4642 Jiangsu HengRui Medicine	NCT05533463 Phase 1[66]	KRAS G12D	Unknown	NSCLC (n=10) ORR: 10%, DCR: 90% Other solid tumors (n=8) ORR: 0%, DCR: 62%
ASP3082 Astellas	NCT05382559 Phase 1	KRAS G12D	PROTAC	No data
Pan/multi-RAS inhibitors				
RMC-6236 Revolution Medicines	NCT05379985 Phase 1 (ref. 76)	Pan-RAS RAS wild type	RAS-multi, ON state, tri-complex inhibitor	NSCLC (n=40) ORR: 38%, DCR: 85% PDAC (n=46) ORR: 20%. DCR: 87%
BI-3706674	NCT06056024 Phase 1	Pan-KRAS KRAS wild type	Pan-KRAS, OFF state inhibitor	No data

Early encouraging results in pretreated pancreas cancer using Pan-KRAS inhibitor RMC-6236









https://ir.revmed.com/static-files/eeeb0690-0ef4-44b8-b5fe-8d11d8df3c9a

Engineered Personalized Antitumor Vaccines May Overcome Tumor Heterogeneity

Article

Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer

https://doi.org/10.1038/s41586-023-06063-y

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Check for updates

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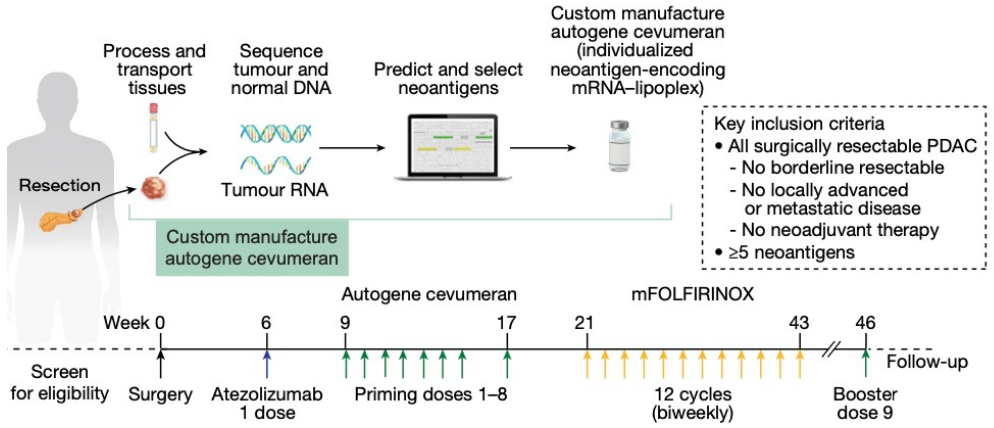
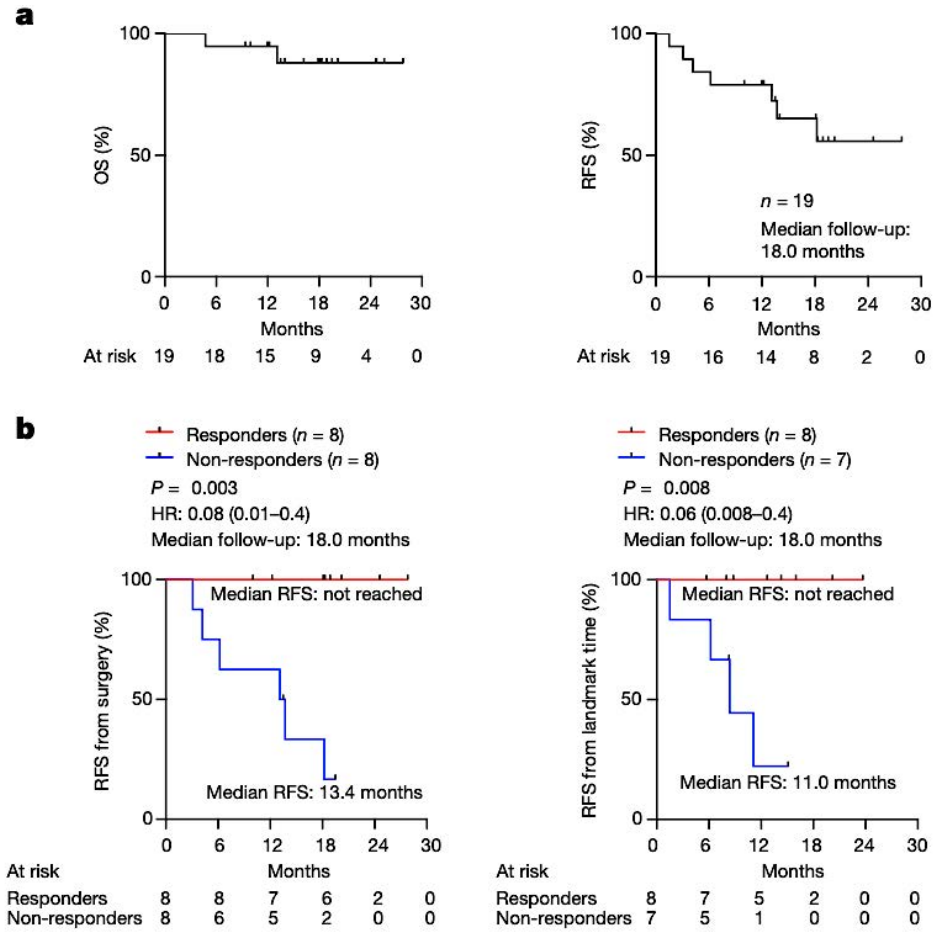




Nature **volume 618**, pages 144–150 (2023)

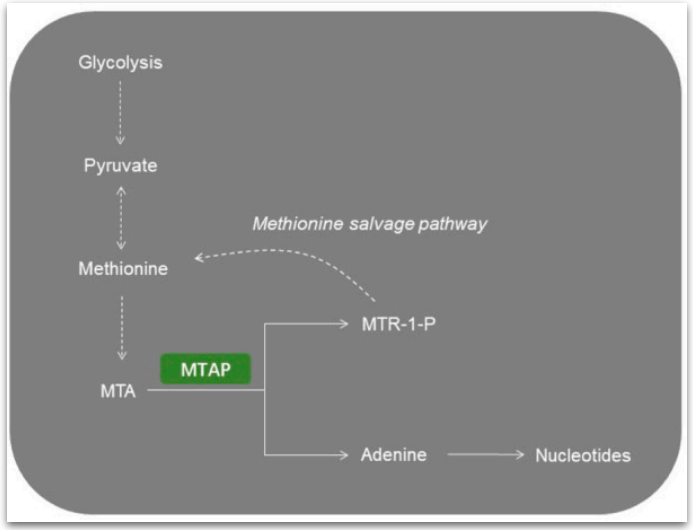
Expanding vaccine trials in pancreatic cancer

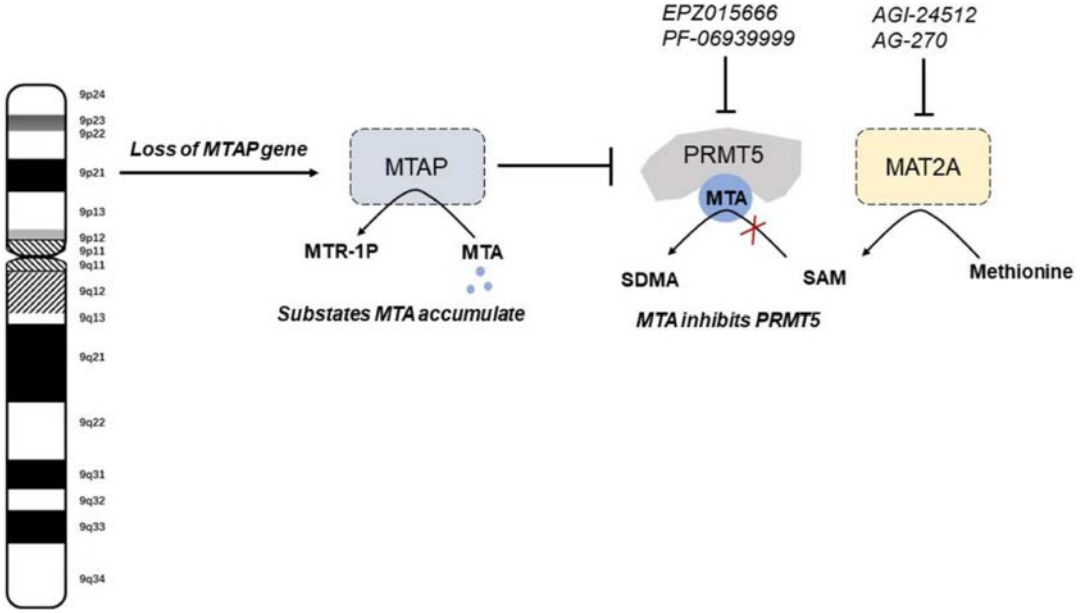
NCT	Setting/stage	Type of vaccine	Study Phase
03558945	Post-resection	Personalized neoantigen vaccine	I
06496373	Post resection	XP-004 mRNA + PD-I blocker	I
06326736	Post resection	mRNA + camrelizumab	I
06344156	Post-resection	Personalized + anti-PD-1	I
05916261	Advanced cancer	mRNA + pabolizumab	I
06353846	Post resection	XH001 neoantigen cancer vaccine + ipilimumab + chemo	1
05111353	Pre- vs post-resection	Synthetic long peptide + poly ICLC	I (randomized)
02600949	Advanced	custom peptide-based vaccine + imiquimod + pembro, and/or sotigalimab (APX005M)	I
04810910	Post resection	iNeo-Vac-P01 + GM-CSF	I
04117087	Post resection	KRAS-Targeted Long Peptide Vaccine With Nivolumab/ Ipilimumab	I
06411691	Advanced cancer	Synthetic long peptide KRAS vaccine + Balstilimab + Botensilimab	I
06015724	Advanced cancer	Anti-CD38 Antibody With KRAS Vaccine and Anti-PD-1 Antibody	I
04627246	Post resection	Dendritic cell vaccine with personalized peptides + SOC + Nivo	I
05964361	Advanced	IL-15-transpresenting WT-1 autologous Dendritic Cell Vaccination	I/II
05721846	Advanced	Nivo + Ipi + TGFβ-15 Peptide Vaccine + SBRT	I
02451982	Post Resection	GVAX + nivo	I

CLINCIALTRIALS.GOV – accessed Feb 15, 2025

Targeting tumors with methylthioadenosine phosphorylase (MTAP) loss

- 20% of pancreatic cancers
- Elevated ornithine decarboxylase (ODC)
- Adaptation to glycolytic pathways and *de novo* purine synthesis
- Vulnerability to targeting of the MAT2A/PRMT5/RIOK1 axis
  - EZP015556
  - AMG193
  - TNG908





Fan et al, Front Cell Dev Biol. 2023; 11: 1173356

CONCLUSIONS

- All newly diagnosed patients with pancreatic cancer should undergo germline and tumor profiling
- Olaparib is a standard of care as a maintenance treatment following favorable response to platinum-based therapy
- Zeno is effective in patients with pancreatic cancer who are previously treated with chemo and harbor somatic *NRG-1* fusion
- TTFields prolong survival in patients with locally advanced pancreatic cancer
- Promising therapies that target KRAS, claudin 18.2, MTAP deletion are in development phase
- Many mRNA and other vaccine trials are in progress with encouraging early signals

Module 17: Gastroesophageal Cancer

Role of Immune Checkpoint Inhibitors in the Management of Gastroesophageal Cancers — Dr Janjigian

Available and Emerging Targeted Therapeutic Approaches for Gastroesophageal Cancers — Dr Klempner

Module 17: Gastroesophageal Cancer

Role of Immune Checkpoint Inhibitors in the Management of Gastroesophageal Cancers — Dr Janjigian

Available and Emerging Targeted Therapeutic Approaches for Gastroesophageal Cancers — Dr Klempner

Memorial Sloan Kettering Cancer Center

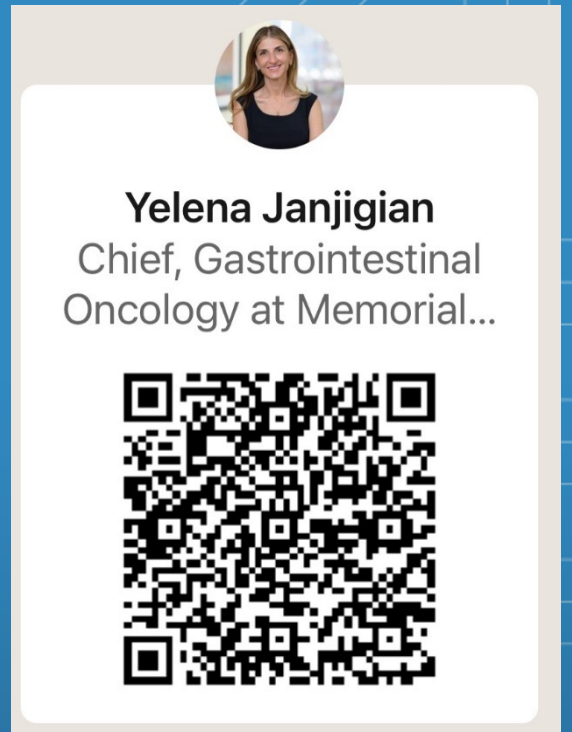
Role of Immune Checkpoint Inhibitors in the Management of Gastroesophageal Cancers

Yelena Y. Janjigian, MD
Chief Attending Physician

Gastrointestinal Oncology Service
Memorial Sloan Kettering Cancer Center

Email: janjigiy@mskcc.org

Sunday, March 2nd | 10 minutes
2:40 PM-3:30 PM



Disclosures

Advisory Committees	AbbVie Inc, AmerisourceBergen, Arcus Biosciences, ARS Pharmaceuticals, AskGene Pharma, Astellas, AstraZeneca Pharmaceuticals LP, Basilea Pharmaceutica Ltd, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Daiichi Sankyo Inc, eChinaHealth, Eisai Inc, Geneos Therapeutics, GSK, Guardant Health, HC Wainwright & Co, Imugene, Inspirna, Lilly, Lynx Health, Merck, Merck Serono, Mersana Therapeutics Inc, PeerMD, Pfizer Inc, Sanofi, Seagen Inc, Silverback Therapeutics, Suzhou Liangyihui Network Technology Co Ltd, Zymeworks Inc
Contracted Research	Arcus Biosciences, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Genentech, a member of the Roche Group, Inspirna, Lilly, Merck, Transcenta
Stock Options — Private Companies	Inspirna
Nonrelevant Financial Relationships	Clinical Care Options, Cycle for Survival, ED Medresources Inc, Fred's Team, Imedex, Master Clinician Alliance, MJH Life Sciences, National Cancer Institute, Paradigm Medical Communications, PeerView Institute, Physician Education Resource (PER), Stand Up 2 Cancer, Talem Health, TotalCME, US Department of Defense, Veda Life Sciences Inc (stock options), WebMD

2024 GEC updates

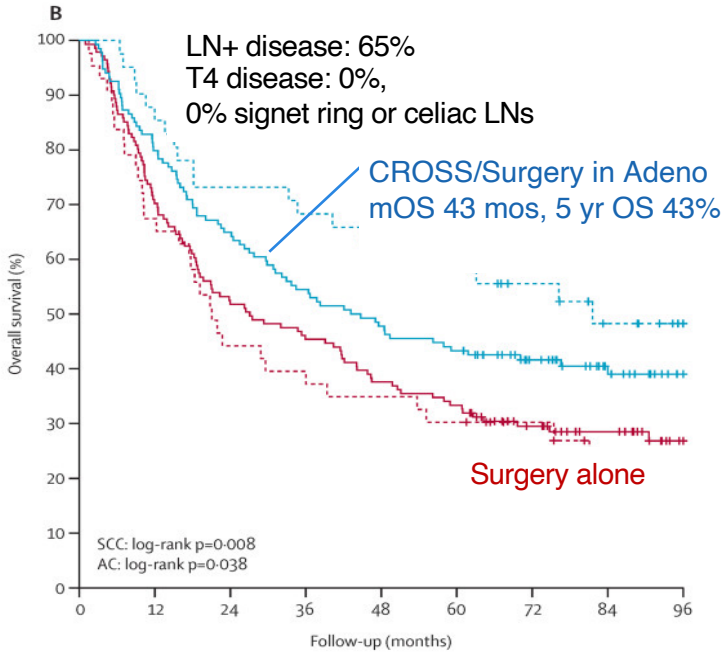
- FLOT is the preferred regimen--radiation does not improve outcomes in localized adenocarcinoma
- Final OS analysis from dual HER2/PD-1 blockade KN 811 in HER2+ GE
- Approval of first-line zolbetuximab in CLD18.2+
- Restriction of FDA approval to CPS $\geq$1 for first line immunotherapy

Treating systemic disease and micro-metastasis
~90 % of recurrences are distant (not local)

CROSS (PC/RT) vs Surgery

Surgery alone not enough
CROSS best in SCC>> Adeno

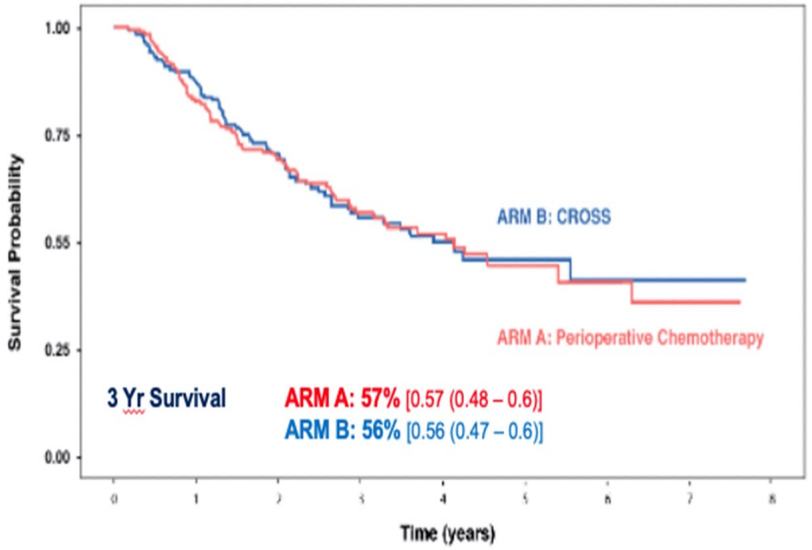
Adeno HR 0.75 CROSS /surgery vs. surgery alone



Neo-AEGIS-ECX vs. CROSS

ECX alone non inferior to CROSS
3-year OS 57% ; R0 82% vs 95%

14% (n=27) FLOT; T4 disease: 0%; LN+ 60%

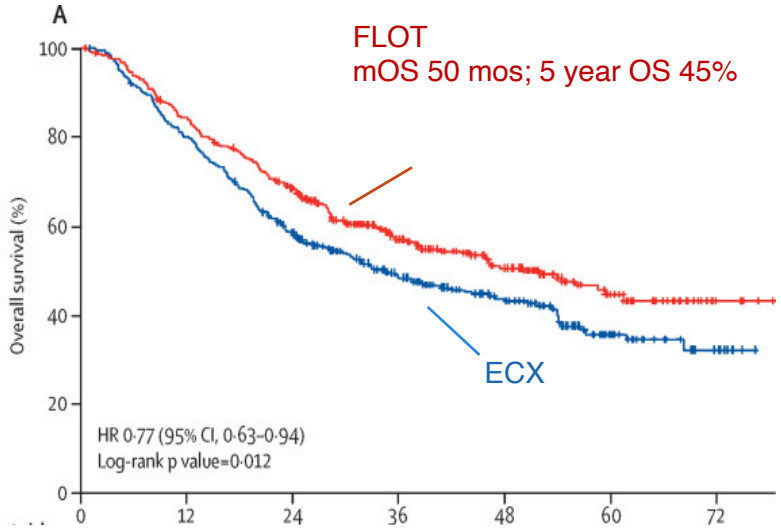


FLOT vs ECX

FLOT is preferred (not ECX)

LN+ disease: 78%; T4 disease: 8%
27% signet ring/PD

Adeno HR 0.76 FLOT vs ECX for GEJ adeno



Al-Batran et al. Phase III FLOT4. *Lancet 2019;* Van Hagen et al. Phase III CROSS, NEJM 2012; Shapiro et al. *Lancet Oncol 2015;* Reynolds, et al. *ASCO 2021*

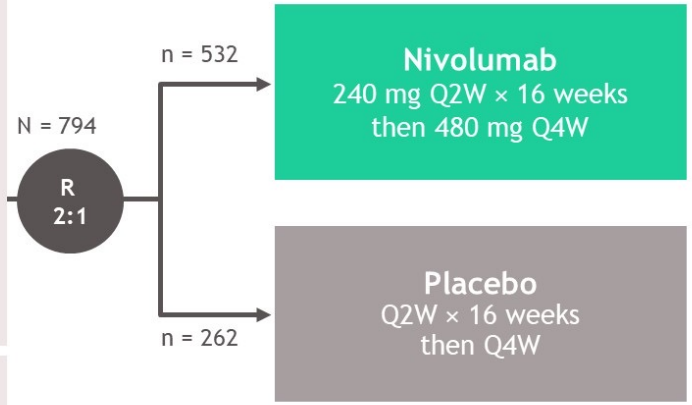
Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

Kelly RJ et al. DOI: 10.1056/NEJMoa2032125

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

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous versus adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 versus ypN0)
- Tumor-cell PD-L1 expression (≥ 1% versus < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

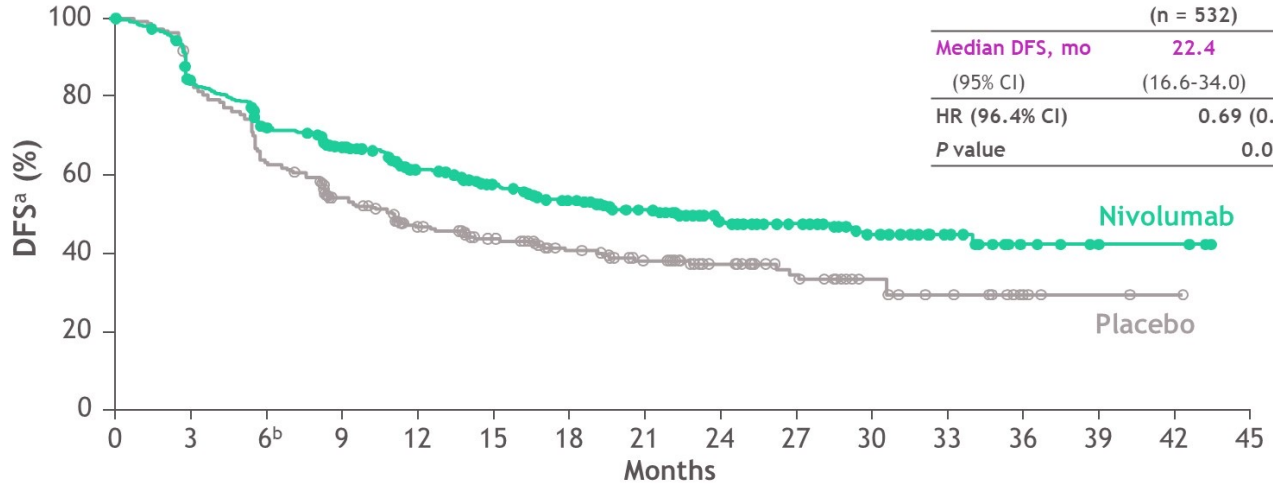
Exploratory endpoints included:
- Safety
- DMFS[g]
- PFS2[h]
- QoL

- Median follow-up was 24.4 months (range, 6.2–44.9)[i]
- Geographical regions: Europe (38%), United States and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov. NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a prespecified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]DMFS is defined as the time between randomization and the first distant recurrence or death, whichever occurs first; [h]PFS2 is defined as the time from randomization to progression after the first subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever is earlier; [i]Time from randomization date to clinical data cutoff (May 12, 2020).
Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Kelly RJ et al. ASCO 2021;Abstract 4003.

Disease-free survival (DFS)



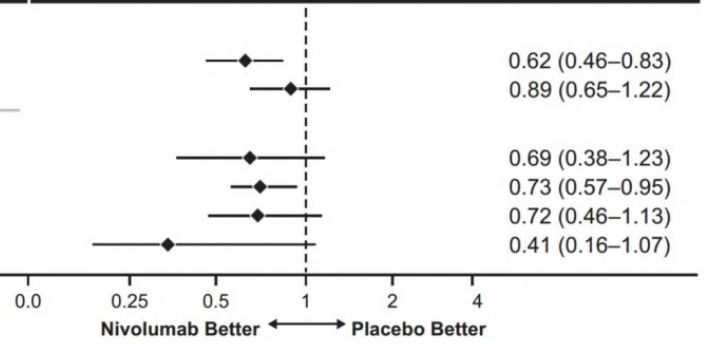
	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6-34.0)	(8.3-14.3)
HR (96.4% CI)	0.69 (0.56-0.86)	
P value	0.0003[c]	

No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

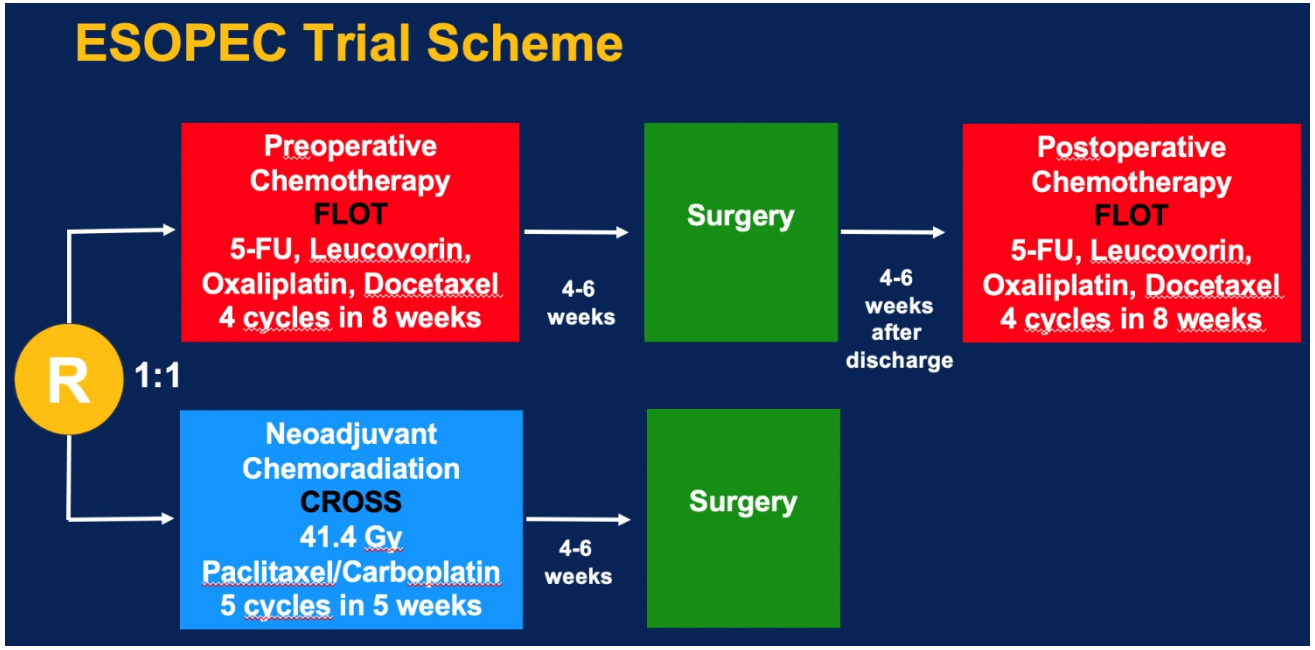
[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the prespecified interim analysis required the *P* value to be less than 0.036.
Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Subgroup	Median Disease-free Survival, months	
	Nivolumab	Placebo
PD-L1 CPS expression		
≥5 (n = 371)	29.4	10.2
<5 (n = 295)	16.3	11.1
Radiotherapy dosage		
<41.4 Gray (n = 92*)	19.7	13.8
41.4–50.4 Gray (n = 504)	24.0	11.1
>50.4 Gray (n = 152)	21.4	8.3
Not reported (n = 41)	14.4	6.1



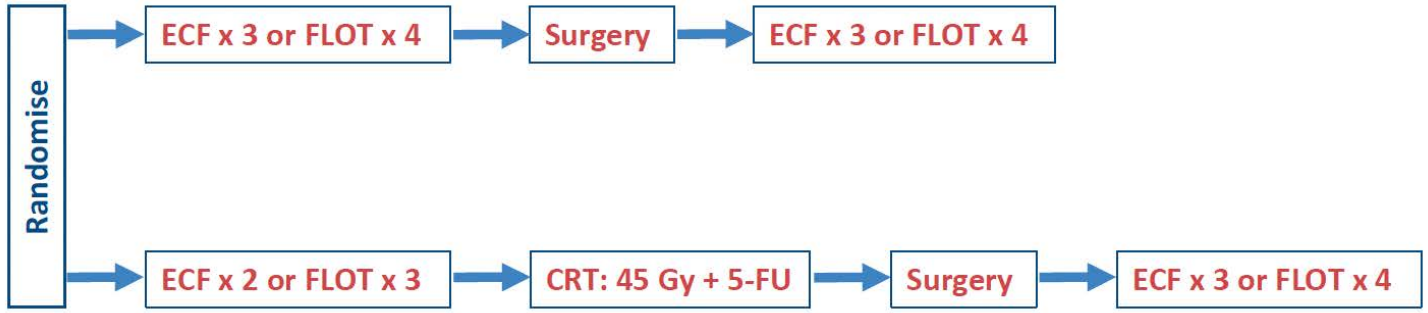
Kelly ASCO 2021, Kelly NEJM 2021

ESOPEC Overall Survival – FLOT is preferred

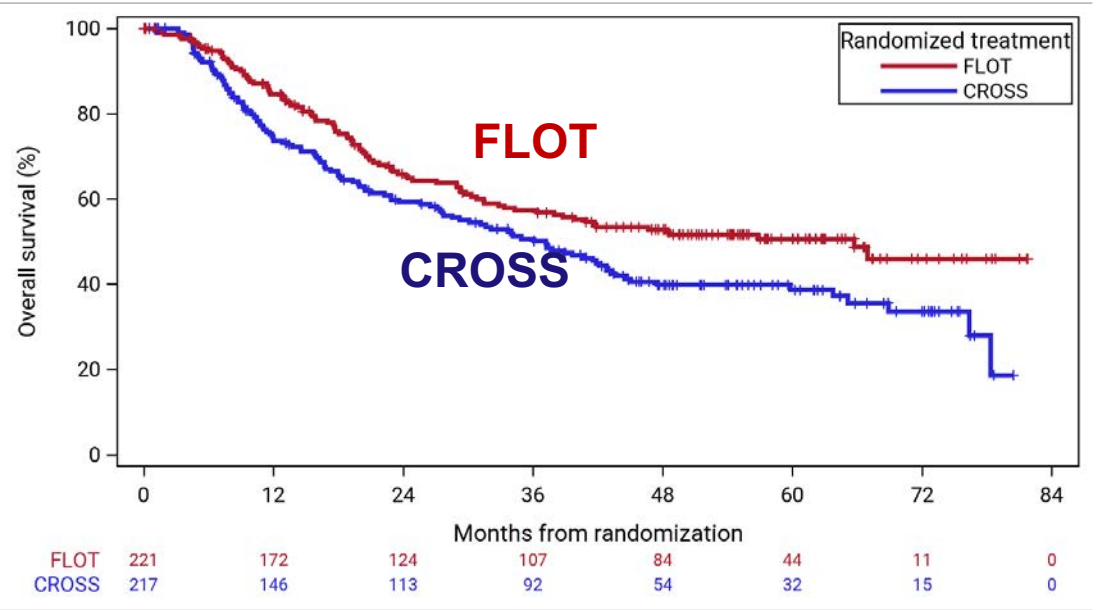


TOPGEAR No OS benefit for addition of CHEMO/RT to perioperative chemotherapy alone

Key eligibility criteria: resectable adenocarcinoma of stomach or GOJ (Siewert type II ≤ 2cm oesophageal involvement, and Siewert type III); stage IB–IIIC, ie.T3–T4 and/or N-positive



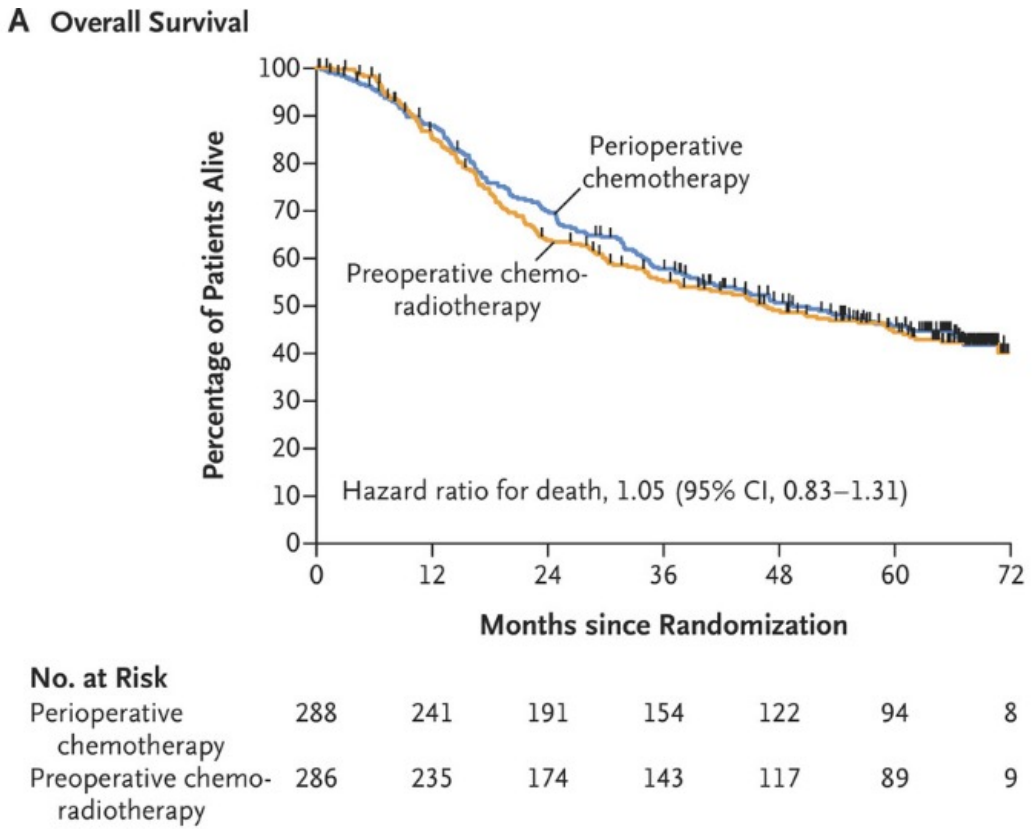
ESOPEC Overall Survival – FLOT is preferred



	FLOT	CROSS
Events	97	121
Median OS	66 mos	37 mos
3-year OS	57.4%	50.7%
5-year OS	50.6%	38.7%

Hoeppner ASCO 2024, Leung, NEJM 2024

TOPGEAR No OS benefit for addition of CHEMO/RT to perioperative chemotherapy alone



	Chemo	Chemo+Chemo/RT
Median OS	49 mos	46 mos
3-year OS	58%	55%
5-year OS	46%	44%

ASCO® Gastrointestinal Cancers Symposium

Pathological complete response to 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) with or without durvalumab in resectable gastric and gastroesophageal junction cancer: subgroup analysis by region from the Phase 3, randomized, double-blind MATTERHORN study

Yelena Y. Janjigian, MD

Yelena Y. Janjigian[1], Salah-Eddin Al-Batran[2], Zev A. Wainberg[3], Eric Van Cutsem[4], Daniela Molena[5], Kei Muro[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], Mehmet Bilici[16], John F. Kurland[17], Ioannis Xynos[18], Helen Mann[18], Josep Tabernero[19]

[1]Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Institute of Clinical Cancer Research, Krankenhaus Nordwest, University Cancer Center, Frankfurt, Germany; [3]Department of Gastrointestinal Medical Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [4]Department of Gastroenterology/Digestive Oncology, University Hospitals Leuven and KU Leuven, Leuven, Belgium; [5]Division of Thoracic Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [7]Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea; [8]Department of Oncology and Radiotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [9]Division of Medical Oncology, Department of Internal Medicine, Seoul National University Hospital; Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [10]Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan; [11]Research Center for Immunotherapy (FZI), Johannes Gutenberg-University Clinic, Mainz, Germany; [12]Hemato-Oncology Department, SAGA Clinical Trial Centre and Universidad Mayor, Santiago, Chile; [13]Clinical Oncology, The Clinical Research Center, Northern Riograndense League Against Cancer, Natal, Rio Grande do Norte, Brazil; [14]Division of Thoracic Surgery, Department of Surgery, Centre Hospitalier de l'Université de Montréal, Centre de Recherche du CHUM, Montréal, QC, Canada; [15]National Institute of Neoplastic Diseases (INEN), Lima, Peru; [16]Department of Medical Oncology, Atatürk University Faculty of Medicine, Erzurum, Turkey; [17]Oncology R&D, Late-Stage Development, AstraZeneca, Gaithersburg, MD, USA; [18]Oncology R&D, Late-Stage Development, AstraZeneca, Cambridge, UK; [19]Medical Oncology Department, Vall d'Hebron Hospital Campus & Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain

Methods

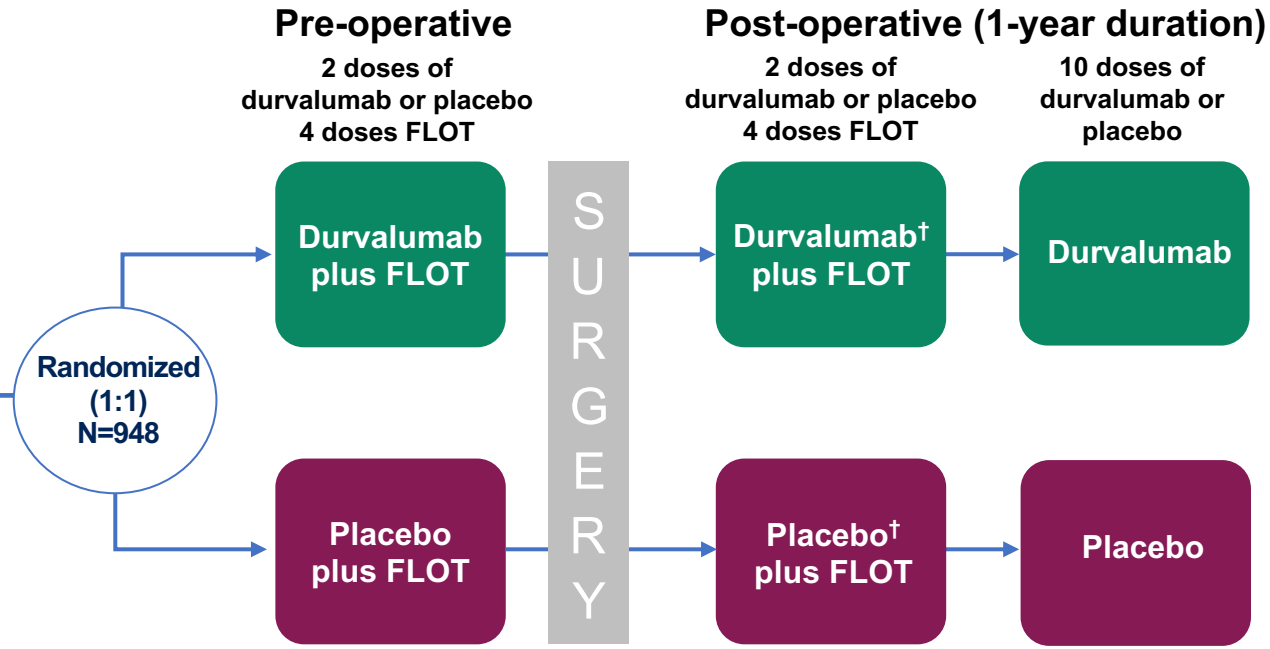
MATTERHORN is a global, Phase 3, randomized, double-blind, placebo-controlled study

Study population

- Gastric and GEJ adenocarcinoma
- Stage II, III and IVA (>T2 N0-3 M0 or T0-4 N1-3 M0)
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment from Asia, Europe, North America, and South America

Stratification factors

- Geographic region: Asia versus non-Asia
- Clinical lymph node status: positive versus negative
- PD-L1 status: TAP <1% versus TAP ≥1%*



Primary objective:

- EFS

Key secondary objectives:

- Central review of pathological complete response by modified Ryan criteria
- OS

Durvalumab 1500 mg or placebo Q4W (Day 1) plus FLOT Q2W (Days 1 and 15) for 4 cycles (2 doses of durvalumab or placebo plus 4 doses of FLOT pre- and post-operative), followed by durvalumab or placebo Q4W (Day 1) for 10 further cycles

FLOT: 5-fluorouracil 2600 mg/m^2, oxaliplatin 85 mg/m^2, docetaxel 50 mg/m^2, leucovorin 200 mg/m^2 on Days 1 and 15 of a 4-week cycle for 2 cycles (4 doses) pre- and post-operative; durvalumab: 1500 mg on Day 1 of a 4-week cycle, 2 cycles (2 doses) of durvalumab or placebo pre- and post-operative, followed by 10 cycles (10 doses) of durvalumab or placebo on Day 1 of a 4-week cycle.
*Measured by VENTANA PD-L1 (SP263) assay. †Durvalumab or placebo monotherapy may be continued if post-operative FLOT is discontinued due to toxicity.
ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GEJ, gastrooesophageal junction; OS, overall survival; PD-L1, programmed cell death ligand-1; PS, performance status; Q2W, every 2 weeks; Q4W, every 4 weeks; TAP, tumor area positivity.

Baseline characteristics

		Durvalumab plus FLOT (n=474)	Placebo plus FLOT (n=474)
Age (years), median (range)		62 (26–84)	63 (28–83)
Male, n (%)		326 (69)	356 (75)
ECOG PS, n (%)	0	337 (71)	366 (77)
Primary tumor location, n (%)	Gastric	324 (68)	316 (67)
	GEJ	150 (32)	158 (33)
Siewert status, n (%)	Type 1	44 (9)	55 (12)
	Type 2	72 (15)	68 (14)
	Type 3	34 (7)	35 (7)
Primary tumor stage, n (%)	T0–T2	50 (11)	36 (8)
	T3	307 (65)	321 (68)
	T4	117 (25)	117 (25)
Clinical lymph node status,* n (%)	Positive	329 (69)	330 (70)
PD-L1 expression status by TAP,† n (%)	<1%*	48 (10)	47 (10)
	≥1%*	426 (90)	427 (90)
	<5%	236 (50)	230 (49)
	≥5%	238 (50)	244 (51)
	<10%	372 (78)	373 (79)
	≥10%	102 (22)	101 (21)
MSI status,‡ n / N (%)	MSI-high	25 / 326 (8)	24 / 334 (7)
	Non-MSI-high	301 / 326 (92)	310 / 334 (93)
Histology type, n (%)	Intestinal	174 (37)	168 (35)
	Diffuse	104 (22)	85 (18)
	Unspecified adenocarcinoma or other	196 (41)	221 (47)

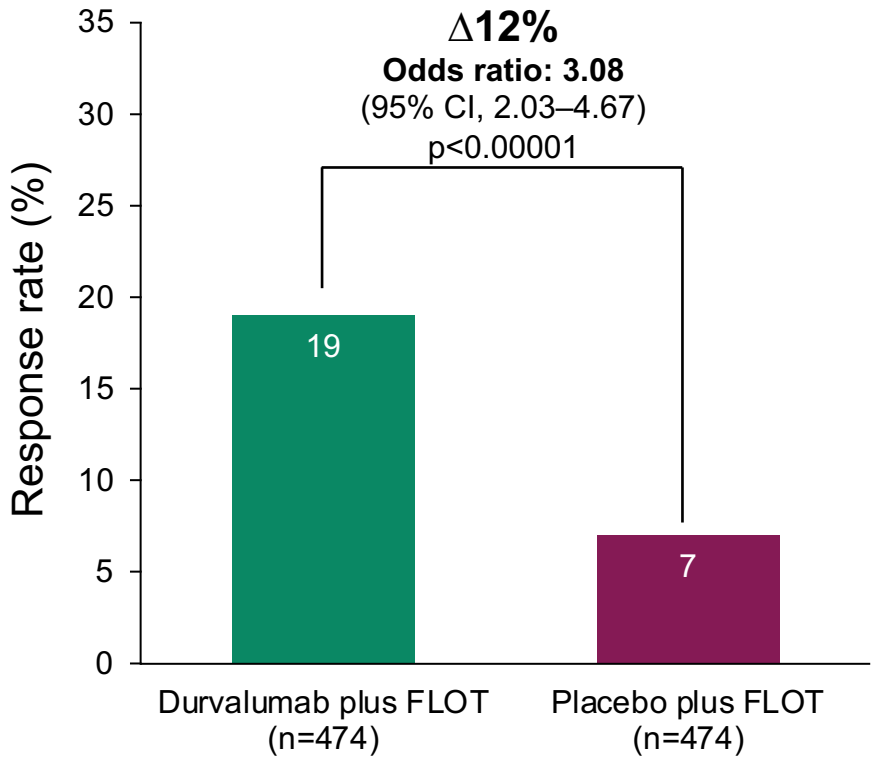
*Stratification factor data. †Measured by VENTANA PD-L1 (SP263) assay. ‡Measured by FoundationOne RUO assay for solid tumors. Out of 948 participants randomized in MATTERHORN, 781 participants were eligible for MSI testing based on consent, local laws, and submission of sufficient tissue; 660 participants (326 participants in the durvalumab plus FLOT arm and 334 participants in the placebo plus FLOT arm) were evaluable per Foundation Medicine Inc criteria. MSI status could not be determined for samples from 250 participants. MSI-high = fraction unstable loci >0.0124. Non-MSI-high includes those with MSS, MSI-equivocal, and MSI-unknown.

ECOG, Eastern Cooperative Oncology Group; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GEJ, gastroesophageal junction; MSI, microsatellite instability; MSS, microsatellite stable; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

Janjigian YY, et al. Presented at: European Society for Medical Oncology (ESMO) Congress 2023; October 20–24, 2023; Madrid, Spain. FPN (Final Publication Number): LBA73.

Pathological complete response

Durvalumab plus FLOT showed statistically significant improvement in pathological complete response



Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria.

CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

Janjigian YY, et al. *Annal Oncol* 2023;34:S1315-S1316.

Exposure

At DCO, 45% of participants in the durvalumab plus FLOT arm and 43% in the placebo plus FLOT arm were ongoing treatment*

	Durvalumab plus FLOT (n=474)		Placebo plus FLOT (n=474)†	
	Durvalumab	FLOT	Placebo	FLOT
Number of pre-operative cycles of durvalumab or placebo plus FLOT (Day 1 and 15), n (%)				
≥1 cycle	474 (100)	474 (100)	470 (99)	470 (99)
2 cycles	458 (97)	461 (97)	448 (95)	453 (96)
Participants with completed surgery, n (%)	411 (87)		399 (84)	
Number of post-operative cycles of durvalumab or placebo ± FLOT (Day 1 and 15 for first 2 cycles), n (%)				
≥1 cycle	348 (73)	342 (72)	340 (72)	337 (71)
≥2 cycles (2 cycles for FLOT‡)	325 (69)	299 (63)	314 (66)	297 (63)

*Including participants that have completed surgery but not yet received post-operative treatment. †One placebo participant received a single dose of durvalumab but is retained in the placebo plus FLOT group for exposure analysis.
‡At DCO, not all participants had the opportunity to complete post-operative FLOT.
DCO, data cut-off; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

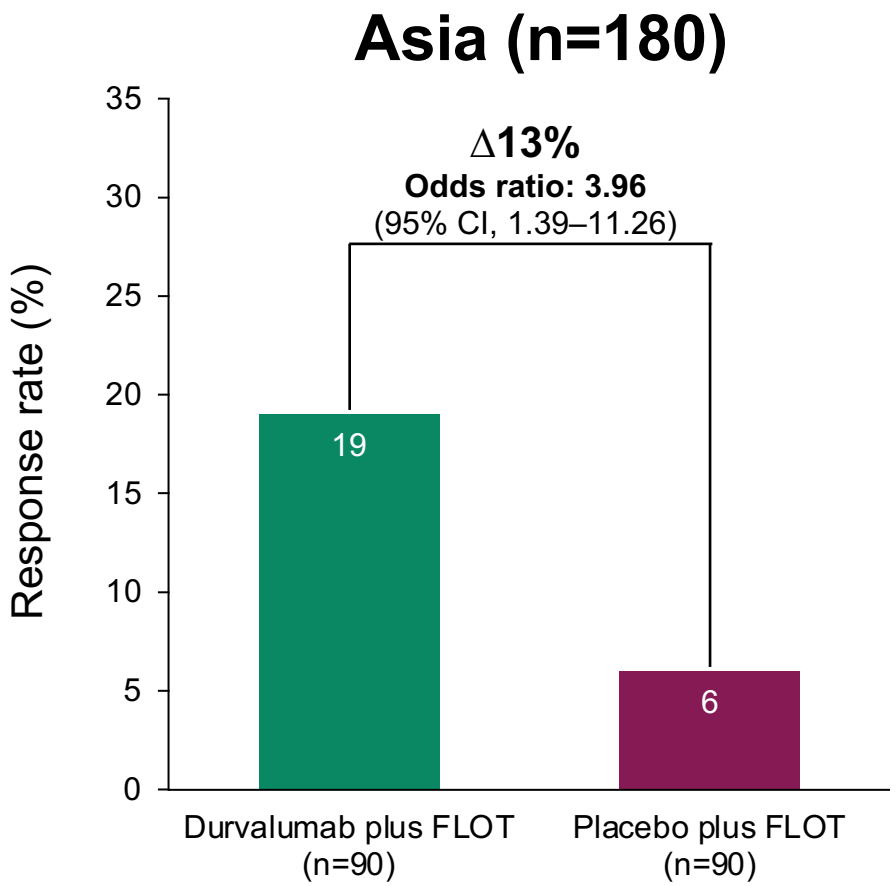
Pathological staging of participants who underwent surgery

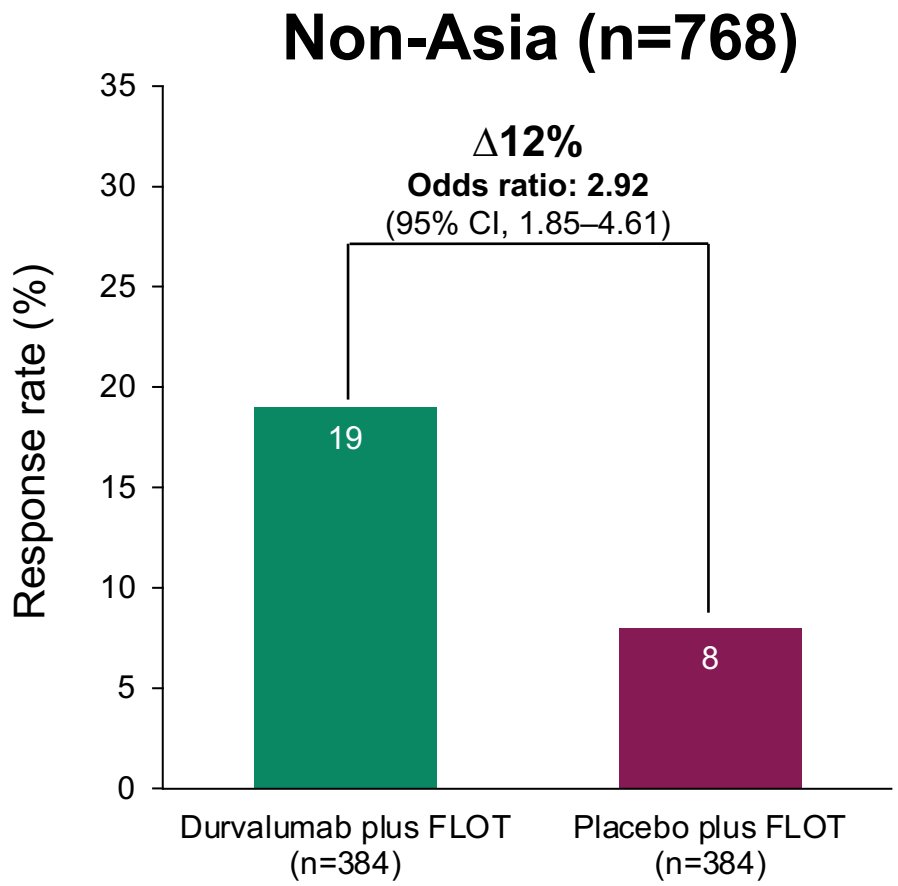
A higher percentage of participants achieved T0 and N0 with durvalumab plus FLOT versus placebo plus FLOT

Stage	Durvalumab plus FLOT (n=430)	Placebo plus FLOT (n=422)
T0, n (%)	98 (23)	45 (11)
N0, n (%)	223 (52)	154 (36)
T stage, n (%)		
≤T1	153 (36)	98 (23)
T2	54 (13)	46 (11)
T3	131 (30)	165 (39)
T4	48 (11)	65 (15)
M1, n (%)	4 (1)	7 (2)
Missing, n (%)	40 (9)	47 (11)

Pathological staging assessed by central review.
FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.
Janjigian YY, et al. Presented at: European Society for Medical Oncology (ESMO) Congress 2023; October 20–24, 2023; Madrid, Spain. FPN (Final Publication Number): LBA73.

Pathological complete response in Asia and non-Asia

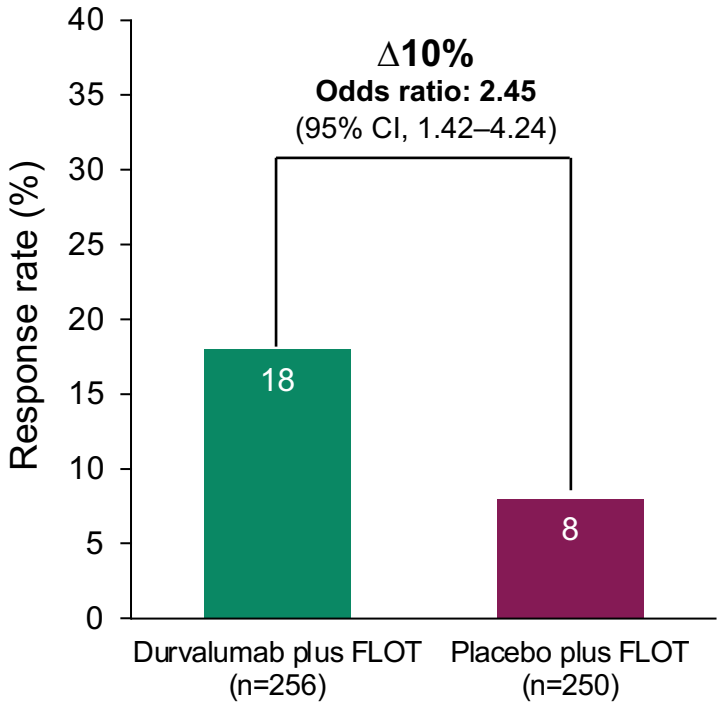




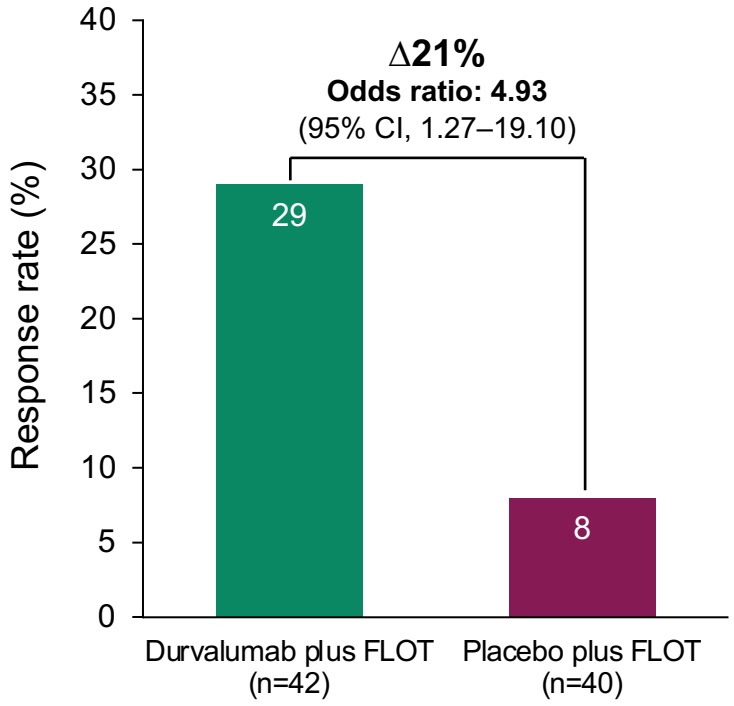
Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

Pathological complete response by region (non-Asia)

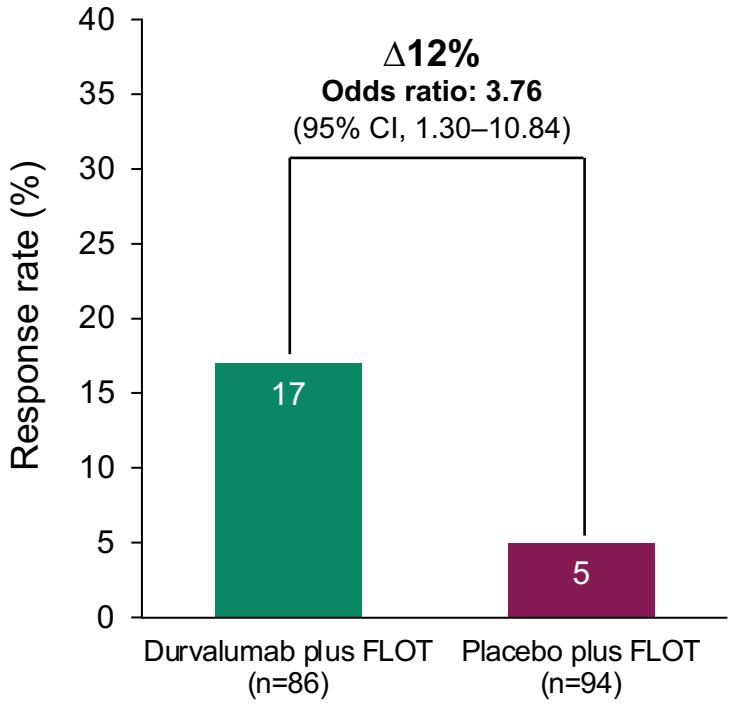
Europe (n=506)



North America (n=82)



South America (n=180)



Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

KEYNOTE-585 Study Design

Randomized, Double-Blind, Phase 3 Trial of Neoadjuvant and Adjuvant Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in G/GEJ Adenocarcinoma (Main Cohort)

Key Eligibility Criteria

- Localized G/GEJ adenocarcinoma defined by T3 or greater primary lesion or presence of N+ nodes
- No prior therapy
- Able to undergo surgery
- Provision of tumor sample for PD-L1 testing[a]
- ECOG PS 0-1

R 1:1
N = 804[b,c]

Pembrolizumab 200 mg IV Q3W + Cisplatin and Capecitabine/XP or Cisplatin and 5-FU/FP for up to 3 cycles
→ Surgery
→ **Pembrolizumab IV Q3W + Chemotherapy for up to 3 cycles**
→ **Pembrolizumab IV Q3W for up to 11 cycles**

Placebo IV Q3W + Cisplatin and Capecitabine/XP or Cisplatin and 5-FU/FP for up to 3 cycles
→ Surgery
→ **Placebo IV Q3W + Chemotherapy for up to 3 cycles**
→ **Placebo IV Q3W for up to 11 cycles**

Stratification factors
- Geographic region (Asia versus non-Asia)
- Tumor staging (II vs III vs IVa)
- Chemotherapy backbone (XP/FP vs FLOT)

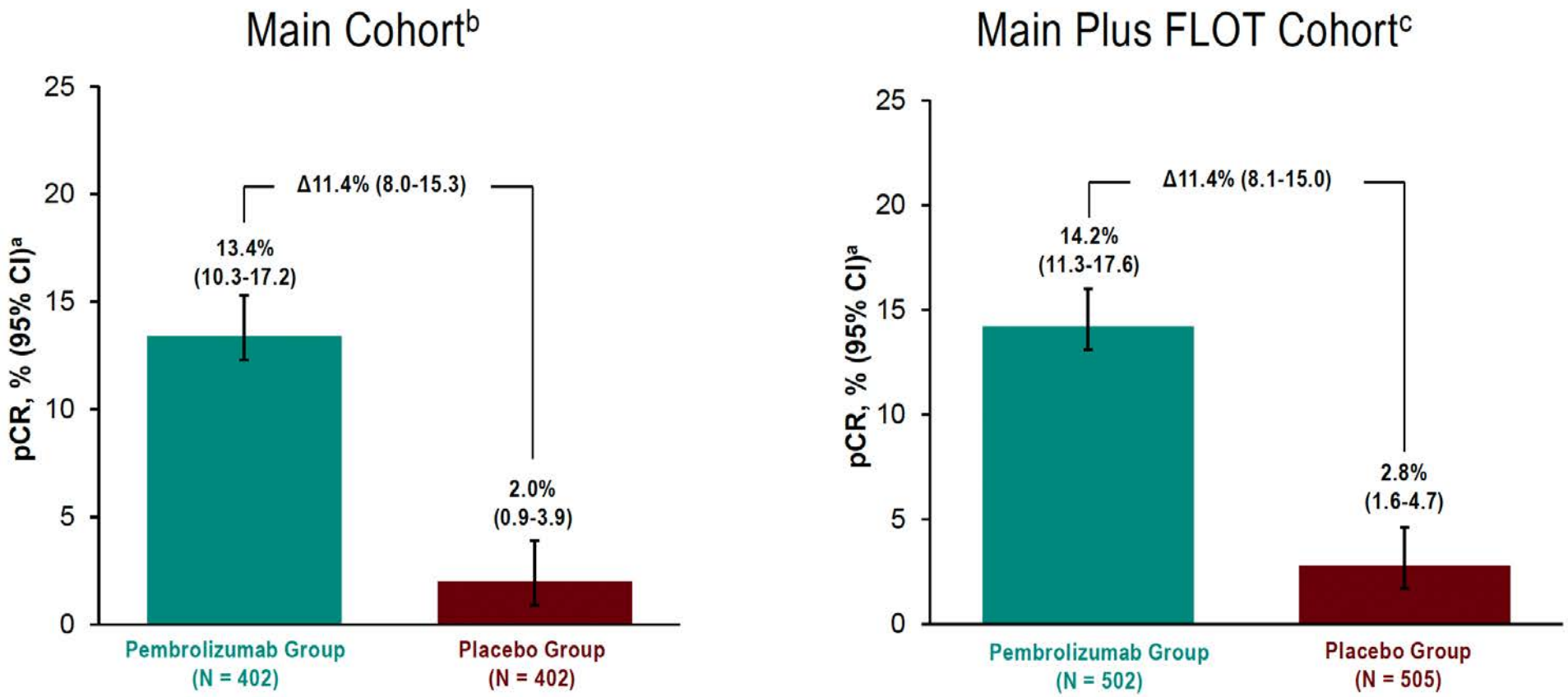
Endpoints:
- Primary: pathCR rate per BICR, EFS per investigator, OS (main cohort), safety (FLOT)
- Key secondary: safety (main cohort), safety, OS, EFS (main plus FLOT cohort)

Al-Batran SE et al. ASCO 2024;Abstract 247.

[a]PD-L1 status was centrally assessed; [b]Main cohort. [c]An additional 203 patients were randomized 1:1 to a separate FLOT cohort evaluating pembrolizumab + FLOT vs placebo + FLOT (5-FU 2600 mg/m^2, leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, docetaxel 50 mg/m^2) Q2W for up to 4 cycles in the neoadjuvant and adjuvant phases. XP: cisplatin 80 mg/m^2 IV on d1 and capecitabine 1000 mg/m^2 orally BID from d1 – d14. FP: cisplatin 80 mg/m^2 IV on d1 and 5-FU 800 mg/m^2 IV from d1 – d5 up to 4000 mg/m^2.

Pathological Complete Response

Assessed by Blinded, Independent Central Review



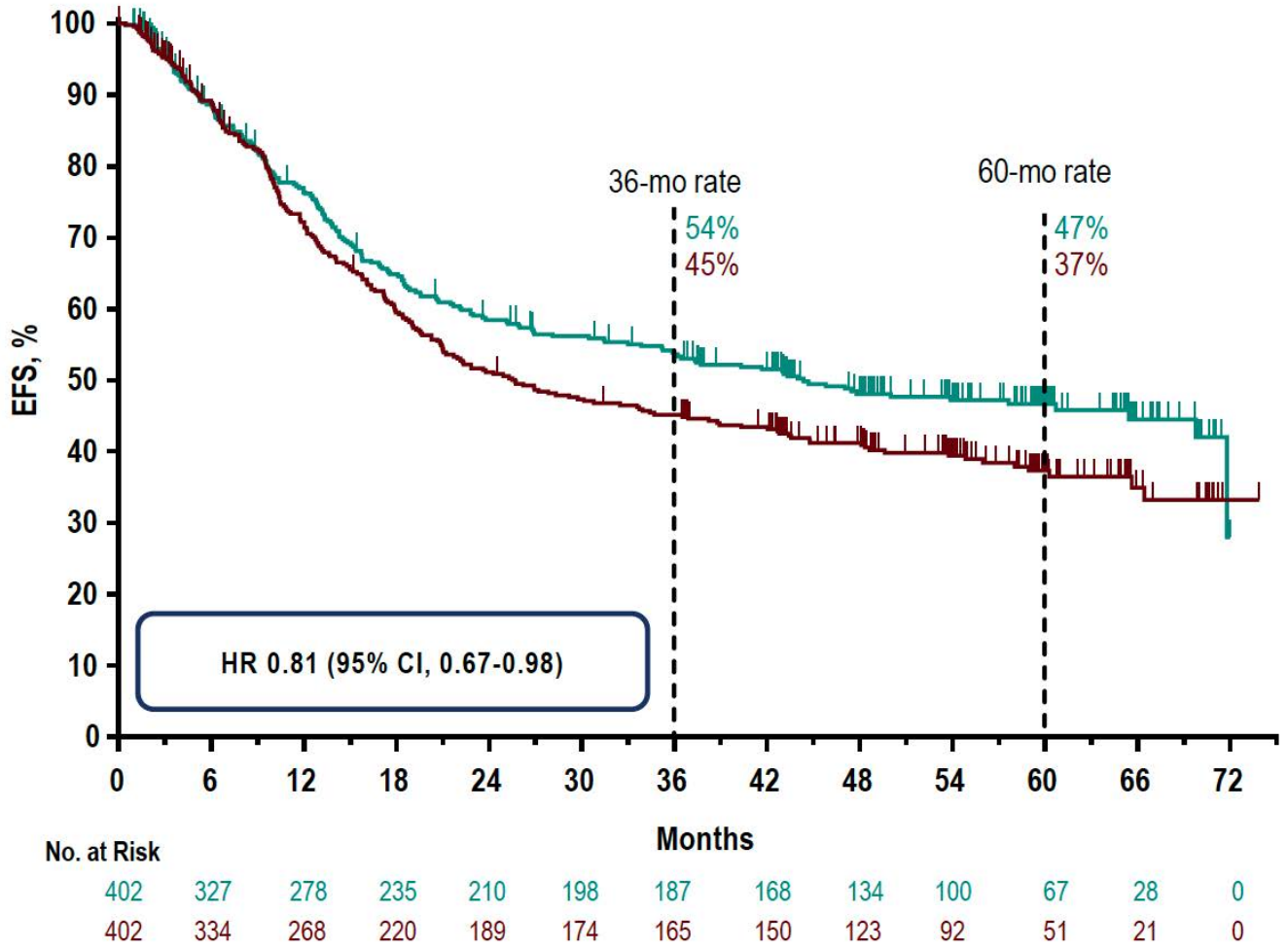
2024 ESMO GASTROINTESTINAL CANCERS

Data cutoff date: 01 Jun 2021. [a]Defined as no invasive disease within an entirely submitted and evaluated gross lesion and histologically defined nodes. [b]Based on first 804 patients randomized in the main cohort (ITT) at least 6 months before data cutoff (IA1). [c]Based on first 987 patients randomized in the main plus FLOT cohort (ITT) at least 6 months before data cutoff (IA1).

Shitara K et al. ESMO GI 2024;Abstract LBA3.

Event-Free Survival: Main Cohort

	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	194 (48%)	44.4 (33.0-69.8)
Placebo group	230 (57%)	25.7 (20.8-36.5)



Data cutoff date: 16 Feb 2024.

Shitara K et al. ESMO GI 2024;Abstract LBA3.

Immunotherapy in esophageal & gastric adenocarcinoma

- Nivolumab, pembro and tisle with chemotherapy initially approved in the United States for 1st-line treatment initially irrespective of PD-L1 status[1] **now restricted to PDL CPS1 ≥1**
- Pembrolizumab, trastuzumab, and chemotherapy approved in the United States for HER2-positive **PDL CPS1 ≥1** disease[2]
- Nivolumab approved in Asia irrespective of PD-L1 status for ≥ 3rd-line treatment[3]
- Pembrolizumab approval for ≥ 3rd-line treatment in the United States to be withdrawn (announced in July 2021)[4]
- Pembrolizumab approved in TMB ≥ 10 mut/Mb (United States) or MSI-H tumors (United States and Japan)[2,5]

1. Nivolumab [package insert]. 2. Pembrolizumab [package insert]. 3. Högner A, Thuss-Patience P. *Pharmaceuticals (Basel).* 2021;14:151.
4. Manufacturer press release, July 1, 2021 5. Manufacturer press release, August 24, 2020.

KEYNOTE-811 Study Design (NCT03615326)

Phase 3 Randomized, Placebo-Controlled

Key Eligibility Criteria

- Advanced, unresectable G/GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2+ by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

Stratification Factors

- Geographic region
- PD-L1 CPS <1 vs CPS ≥1
- Chemotherapy choice

R 1:1
N=698

Pembrolizumab 200 mg IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Placebo IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Endpoints

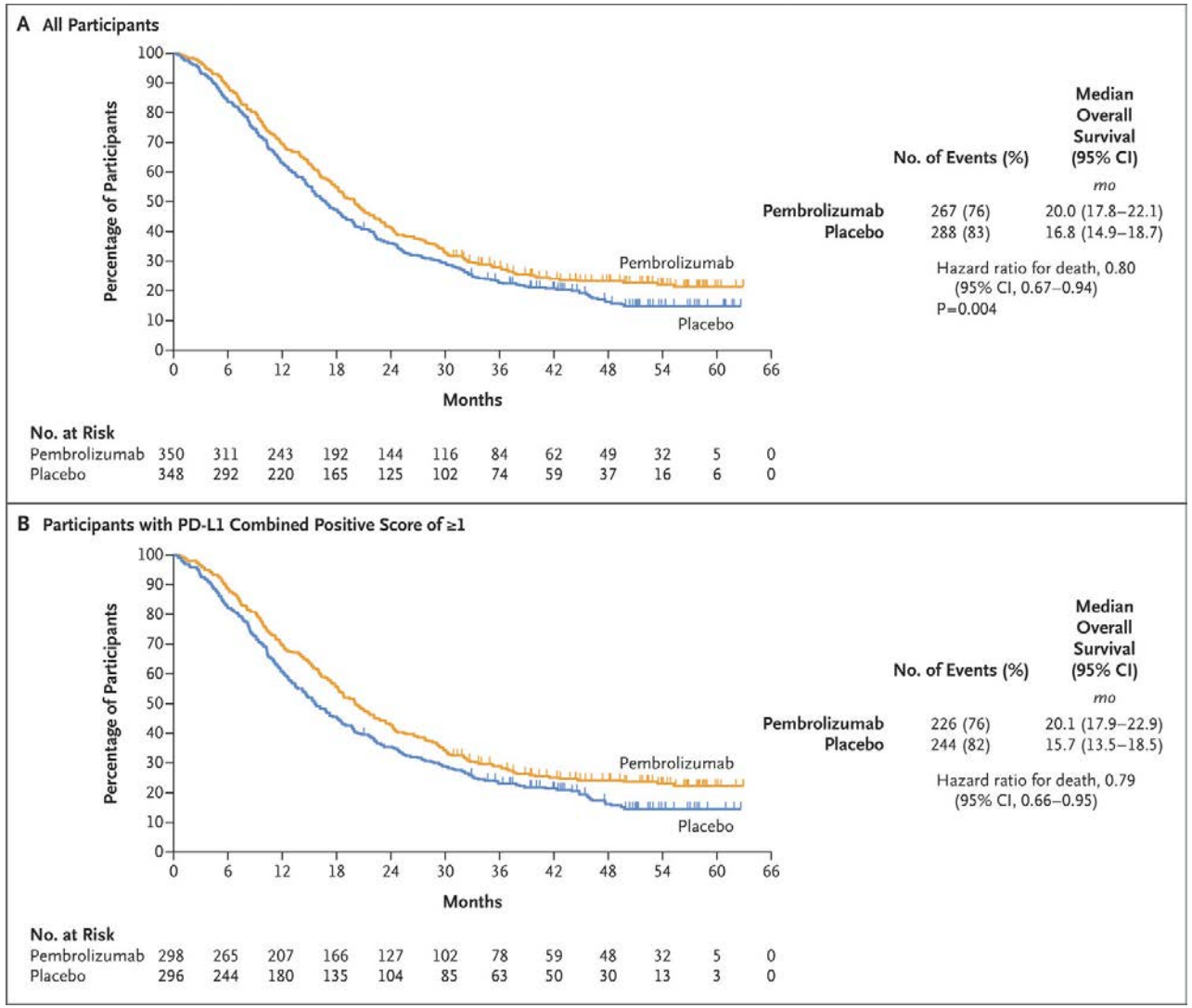
- Dual primary: OS, PFS
- Secondary: ORR, DOR , safety

[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. PFS, ORR, DOR per RECIST by BICR.

Lonardi S et al. ESMO 2024;Abstract 1400O.

Pembrolizumab in HER2-Positive Gastric Cancer

Published September 13, 2024 | N Engl J Med 2024;391:1360-1362 | DOI: 10.1056/NEJMc2408121

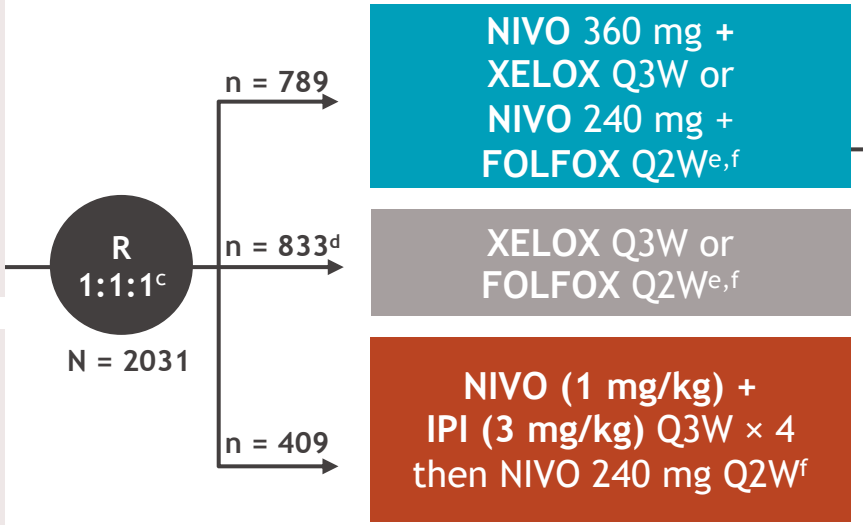


CheckMate 649 study design

- CheckMate 649 is a randomized, open-label, global phase 3 study[1,a]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0–1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints:
- **OS** and **PFS**[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- **OS** (PD-L1 CPS ≥ 1, all randomized)
- **OS** (PD-L1 CPS ≥ 10)
- **PFS**[g] (PD-L1 CPS ≥ 10, ≥ 1, all randomized)
- **ORR**[g]

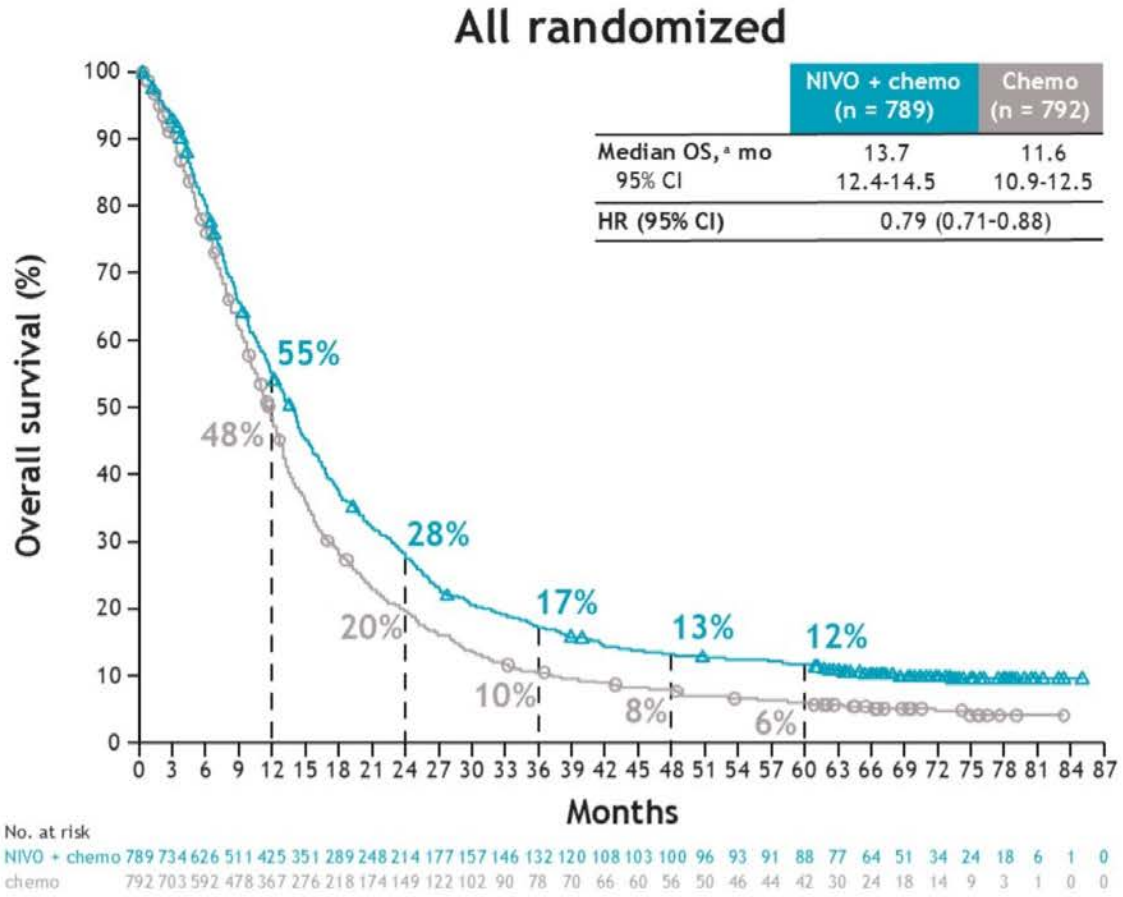
Exploratory endpoints:
- **Safety**
- **QoL**
- **Biomarkers**

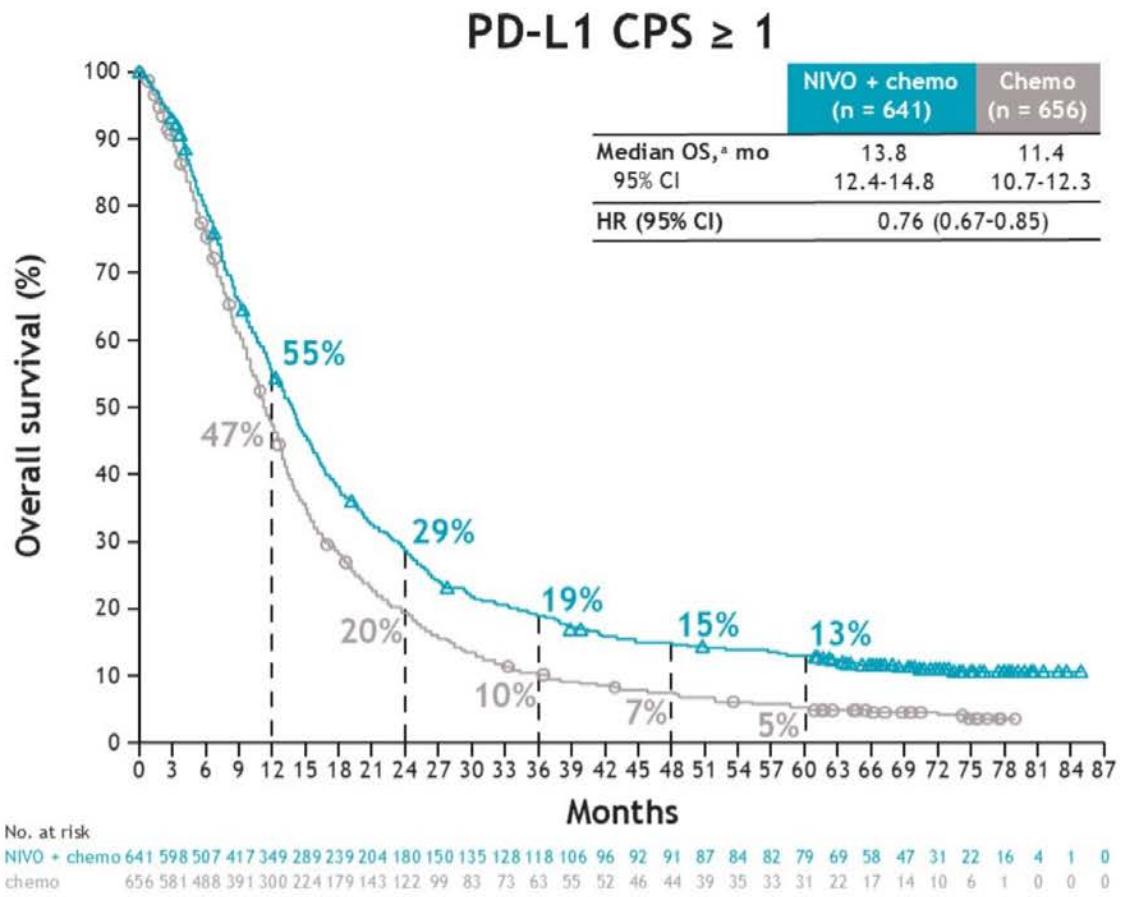
- At data cutoff (May 31, 2022), the minimum follow-up[h] was 47.9 months

[a]ClinicalTrials.gov. NCT02872116; [b]Less than 1% includes indeterminate tumor cell PD-L1 expression; [c]During concurrent randomization period; [d]Includes patients concurrently randomized to chemo vs NIVO + IPI (October 2016–June 2018) and to NIVO + chemo (April 2017-April 2019); [e]XELOX: oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14); FOLFOX: oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2); [f]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo or NIVO + IPI), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [g]BICR assessed; [h]Time from concurrent randomization of the last patient to clinical data cutoff.

1. Janjigian YY, et al. *Lancet* 2021;398:27-40.

Overall survival: FOLFOX/Nivolumab





- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up in all randomized, PD-L1 CPS ≥ 1, PD-L1 CPS ≥ 5, and PD-L1 CPS ≥ 10 populations (**Figure 2**)

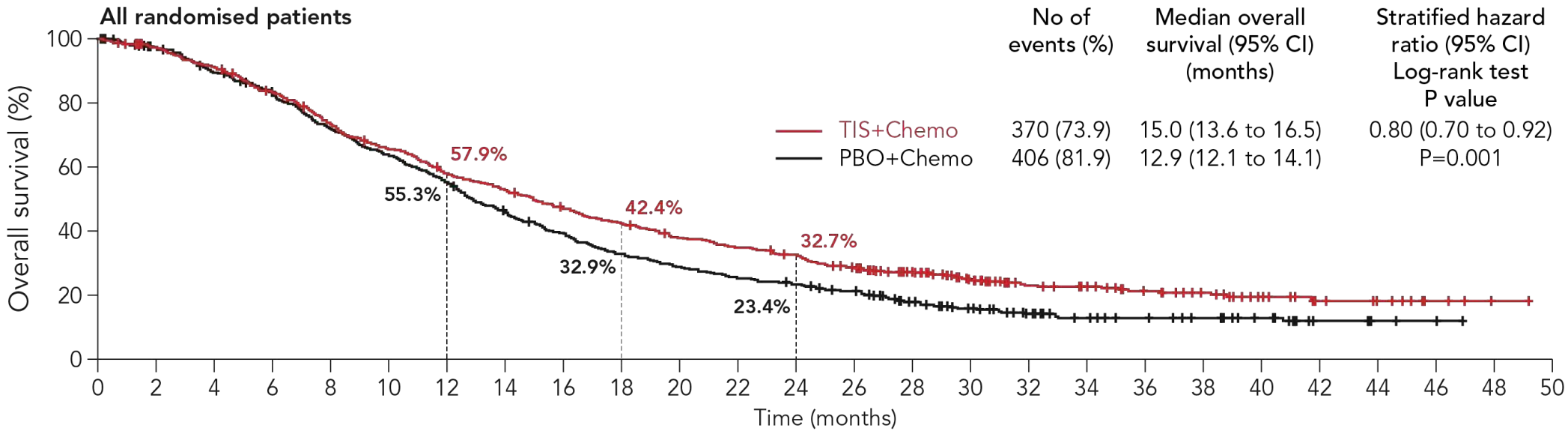
[a]Minimum follow-up, 60.1 months. CI, confidence interval; HR hazard ratio.

Janjigian Y et al. ASCO GI 2025;Abstract 398.

Overall survival

RATIONALE-305

ITT Population



No at Risk

TIS+Chemo	501	477	445	404	355	316	278	254	226	202	179	165	152	130	107	77	59	53	43	31	22	13	10	4	1	0
PBO+Chemo	496	472	431	398	344	304	264	218	186	155	136	119	109	96	73	52	39	29	25	20	15	6	3	2	0	0

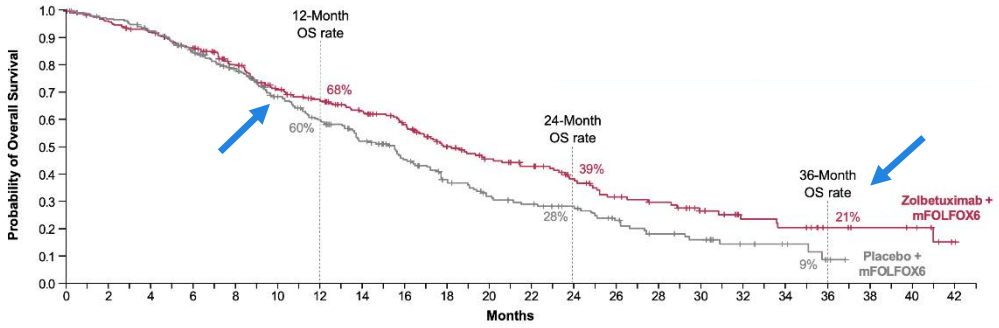
- Tislelizumab + chemo as first-line treatment of advanced GC/GEJC demonstrated a statistically significant and clinically meaningful improvement in OS over placebo + chemo in the ITT population at the final analysis

Data cutoff: 28 February 2023.
*Log-rank and Cox regression models were stratified by regions (Asia vs Europe/North America), PD-L1 expression (ITT population analysis only), and presence of peritoneal metastasis. P-values are one-sided and based on the stratified log-rank test. P-value boundary at final analysis is 0.0226.
Medians were estimated by the Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. OS rates were estimated by the Kaplan-Meier method.
Chemo=chemotherapy, CI=confidence interval, GC/GJEC=gastric or gastro-esophageal junction adenocarcinoma, HR=hazard ratio, ITT=intent-to-treat, OS=overall survival, PBO=placebo, PD-L1=programmed death-ligand 1, TIS=tislelizumab.
Qiu M-Z, et al. BMJ 2024; 385:e078876.

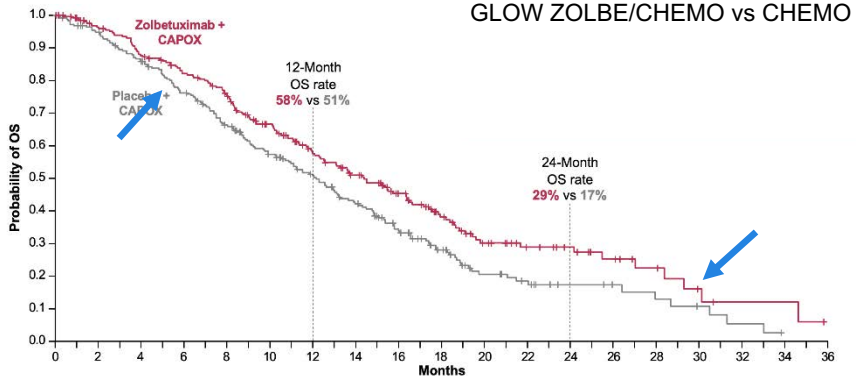
OS KM Curves: early & sustained separation are important

CLD18.2 +

SPOTLIGHT ZOLBE/CHEMO vs CHEMO

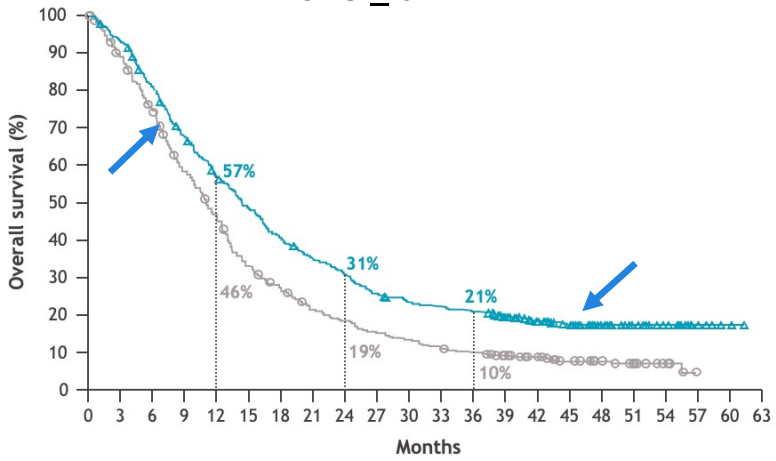


GLOW ZOLBE/CHEMO vs CHEMO

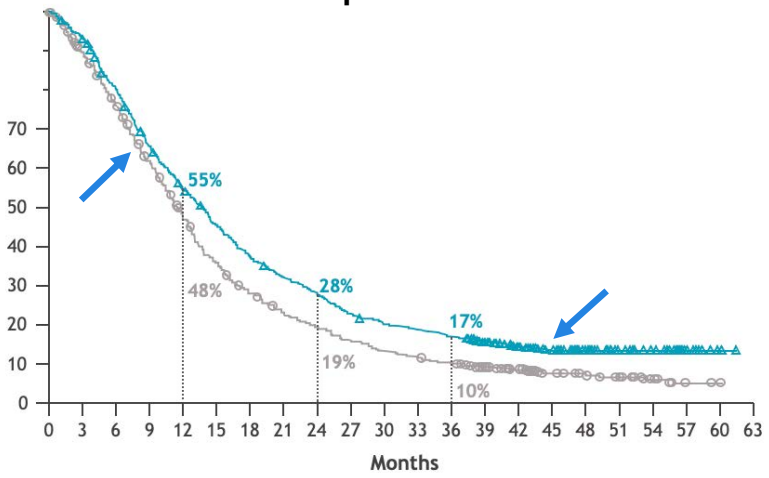


CheckMate 649 NIVO/CHEMO vs CHEMO

CPS ≥ 5

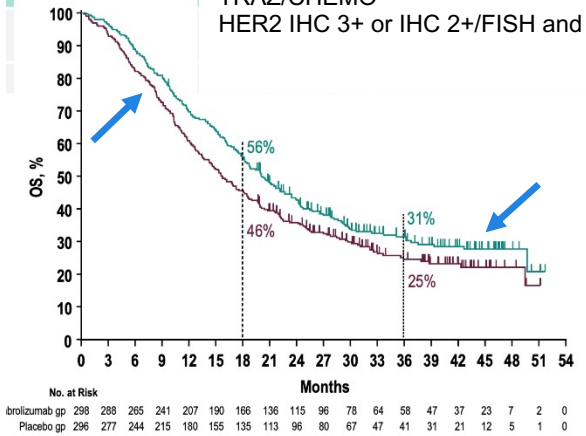


All patients



HER2 +

KEYNOTE-811 PEMBRO/TRAZ/CHEMO vs TRAZ/CHEMO
HER2 IHC 3+ or IHC 2+/FISH and CPS≥1



Bang *et al* Lancet 2010; Janjigian YY, *et al 2023 ASCO GI*;
Shitara 2023 ASCO GI; Xu RH 2023 ASCO Plenary Series Virtual

Better ORR Benefit with Anti-PD-1 vs Anti-CLDN18.2

Target	Trial	Design	ORR delta
PD-1	CheckMate 649	NIVO + chemo vs chemo	ITT: **12%** CPS ≥5: **15%**
PD-1	KEYNOTE-859	PEMBRO + chemo vs chemo	ITT: **9%** CPS ≥10: **17%**
PD-1	ORIENT-16	SINTI + chemo vs chemo	ITT: **9.6%** CPS ≥5: **13.9%**
PD-1	RATIONALE-305	TISLE + chemo vs chemo	ITT: **7.4%**
CLDN18.2	SPOTLIGHT	ZOLBE + FOLFOX vs FOLFOX	**0%**
CLDN18.2	GLOW	ZOLBE + CAPOX vs CAPOX	**2.2%**

Minimal/no improvement in ORR with zolbetuximab

ITT = intention to treat.

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40. Rha SY, et al. ASCO 2024;Abstract 4045. Xu J, et al. *JAMA*. 2023;330(21):2064-2074. Moehler MH, et al. *J Clin Oncol*. 2023;41(Suppl 4):286.

FDA ODAC Meeting on PD-L1 Thresholds (Sept 26, 2024)

- The FDA Oncologic Drugs Advisory Committee (ODAC) convened to evaluate PD-L1 thresholds for first-line immune checkpoint inhibitors in HER2-negative gastroesophageal cancers.
- The committee voted 10-2 (1 abstention) against a favorable risk-benefit profile of PD-1 inhibitors for patients with PD-L1 expression <1.
- Key discussion points:
  - Impact on accessibility and ongoing clinical trials.
- More details: FDA ODAC Meeting Announcement: https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-26-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-09262024

Prioritization biomarker based therapy

1. MSI-H
2. HER2
3. PDL1 CPS ≥1 or 5
4. CLD18.2 high

Janjigian YY, 2023 ASCO GI; Janjigian YY Nature 2021;
Shitara 2023 ASCO GI; Xu RH 2023 ASCO Plenary Series

Conclusion

- Biomarker testing for MSI, HER2, PDL1 and CLD18.2
- FLOT is the preferred regimen--radiation does not improve outcomes in localized adenocarcinoma
- Pembrolizumab/Trastuzumab/chemotherapy in HER2+ GE
- Approval of first-line zolbetuximab in CLD18.2+
- Upcoming data PD-L1 FLOT perioperative

Discussion Questions

- Outside of a clinical trial, have you or would you attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy for a patient with MSI-high gastroesophageal cancer?

- Regulatory and reimbursement issues aside, which additional therapy, if any, would you add to chemotherapy as first-line treatment for a 65-year-old patient presenting with metastatic claudin 18.2-negative, HER2-negative, MSS gastric adenocarcinoma, and how does level of PD-L1 expression affect your decision?

Module 17: Gastroesophageal Cancer

Role of Immune Checkpoint Inhibitors in the Management of Gastroesophageal Cancers — Dr Janjigian

Available and Emerging Targeted Therapeutic Approaches for Gastroesophageal Cancers — Dr Klempner

Available and Emerging Targeted Approaches in Gastroesophageal Cancers

Samuel J. Klempner, MD

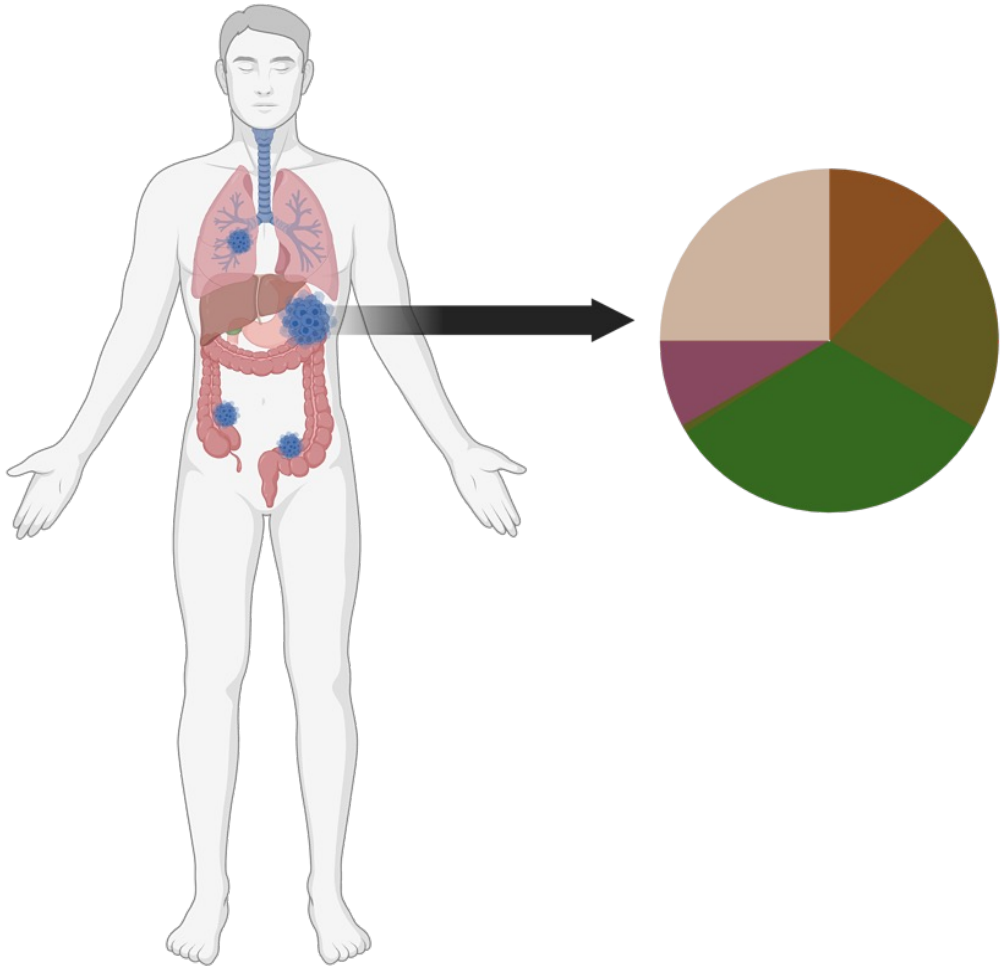
MGH Cancer Center

Boston, MA

Disclosures

Advisory Committees	Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology, Gilead Sciences Inc, I-Mab Biopharma, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Pfizer Inc, Taiho Oncology Inc
Consulting Agreements	Astellas, Novartis (ended 2023)
Stock Options — Private Companies	MBrace Therapeutics
Nonrelevant Financial Relationships	Debbie's Dream Foundation, Degregorio Family Foundation, Gastric Cancer Foundation, Gateway for Cancer Research, National Cancer Institute/National Institutes of Health, NCCN (member of Gastric and Esophageal Guidelines Committees), Stand Up 2 Cancer/AACR, Torrey Coast Foundation

Overview



1. Target Expression and Overlap in GC/GEJ
2. CLDN18.2 Directed Therapies in GC/GEJ
3. CLDN18.2 Toxicity Management
4. ADCs for Other Antigens and New Targets

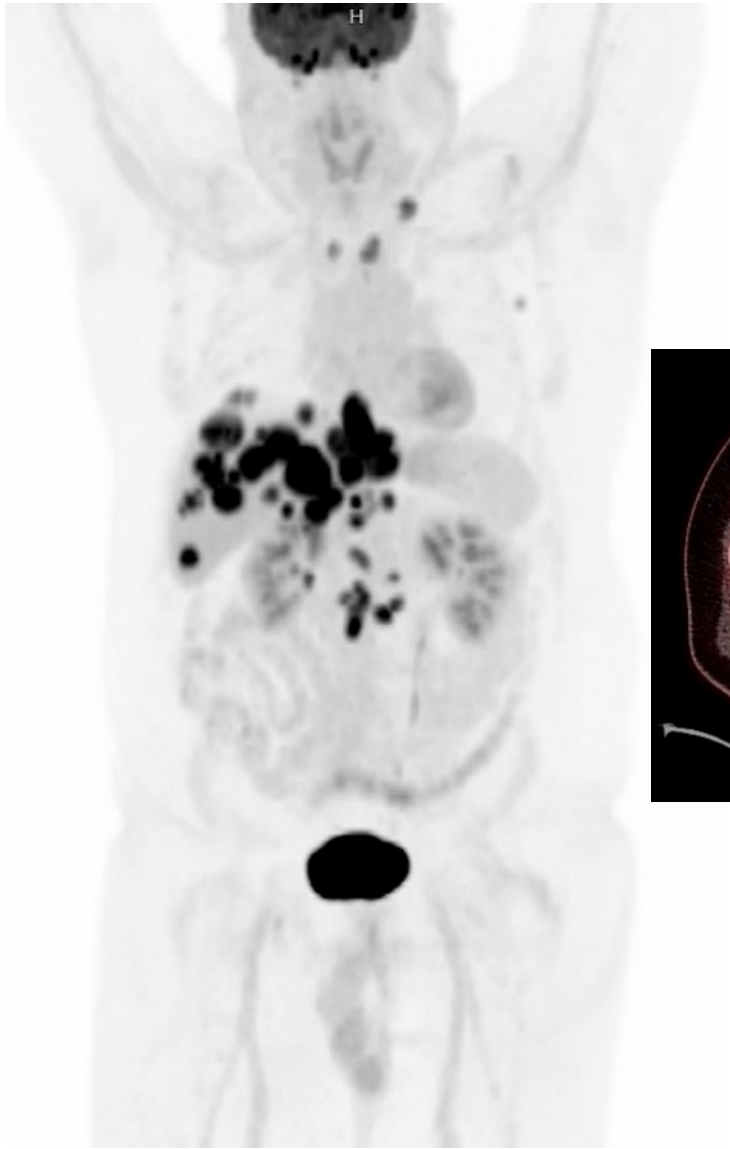
Made on Biorender.com

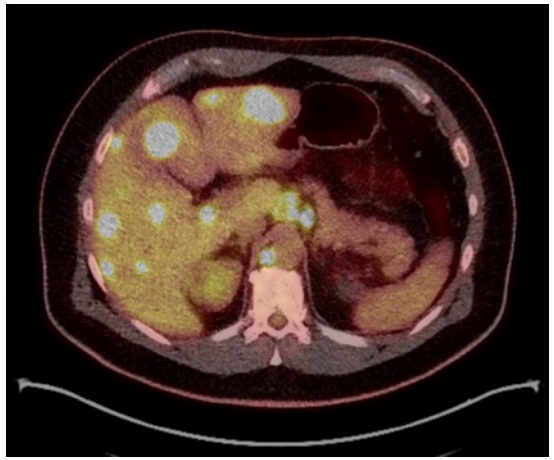
Starting in the Clinic

- HPI: 67M with limited PMH presents with increasing food sticking and 10lb weight loss.

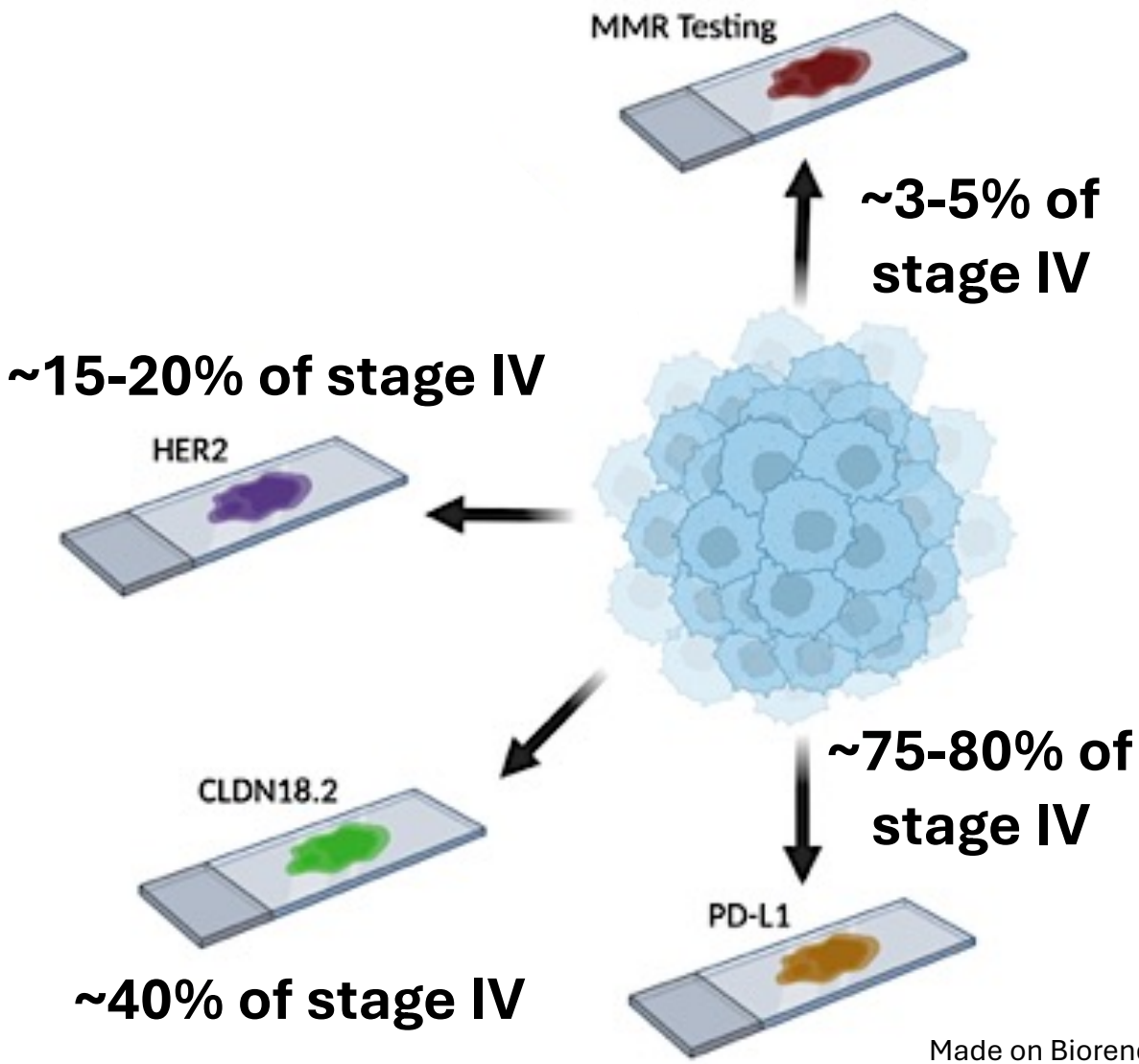
- PET-CT: Diffuse bilobar hepatic mets, widespread lymphadenopathy

- PATHOLOGY: Liver biopsy with mod-diff adenocarcinoma, pMMR, HER2 IHC 1+, PD-L1+ (CPS = 4), CLDN18.2 2+/3+ in 80% tumor cells

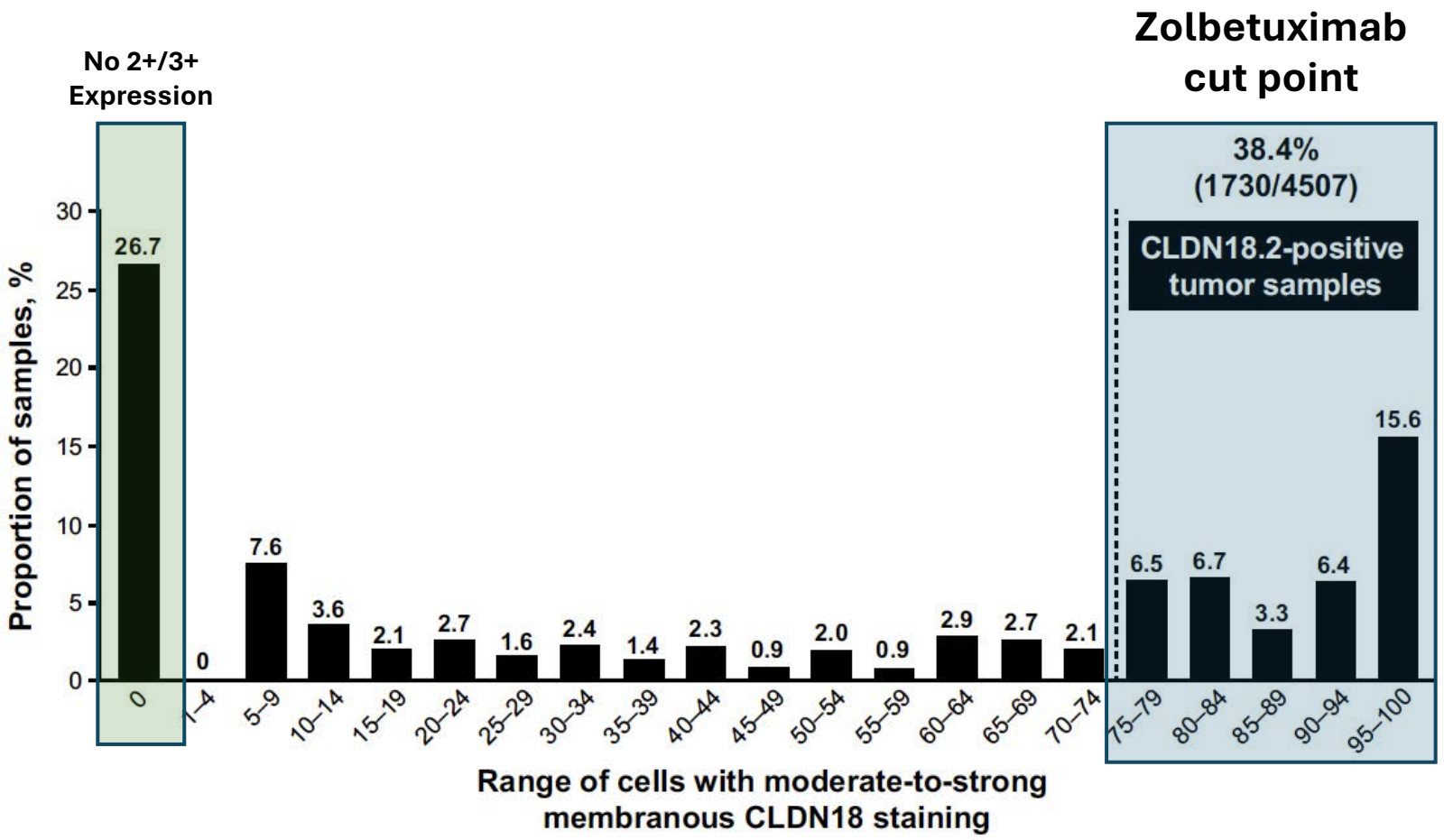




Biomarker Prevalence and Overlap



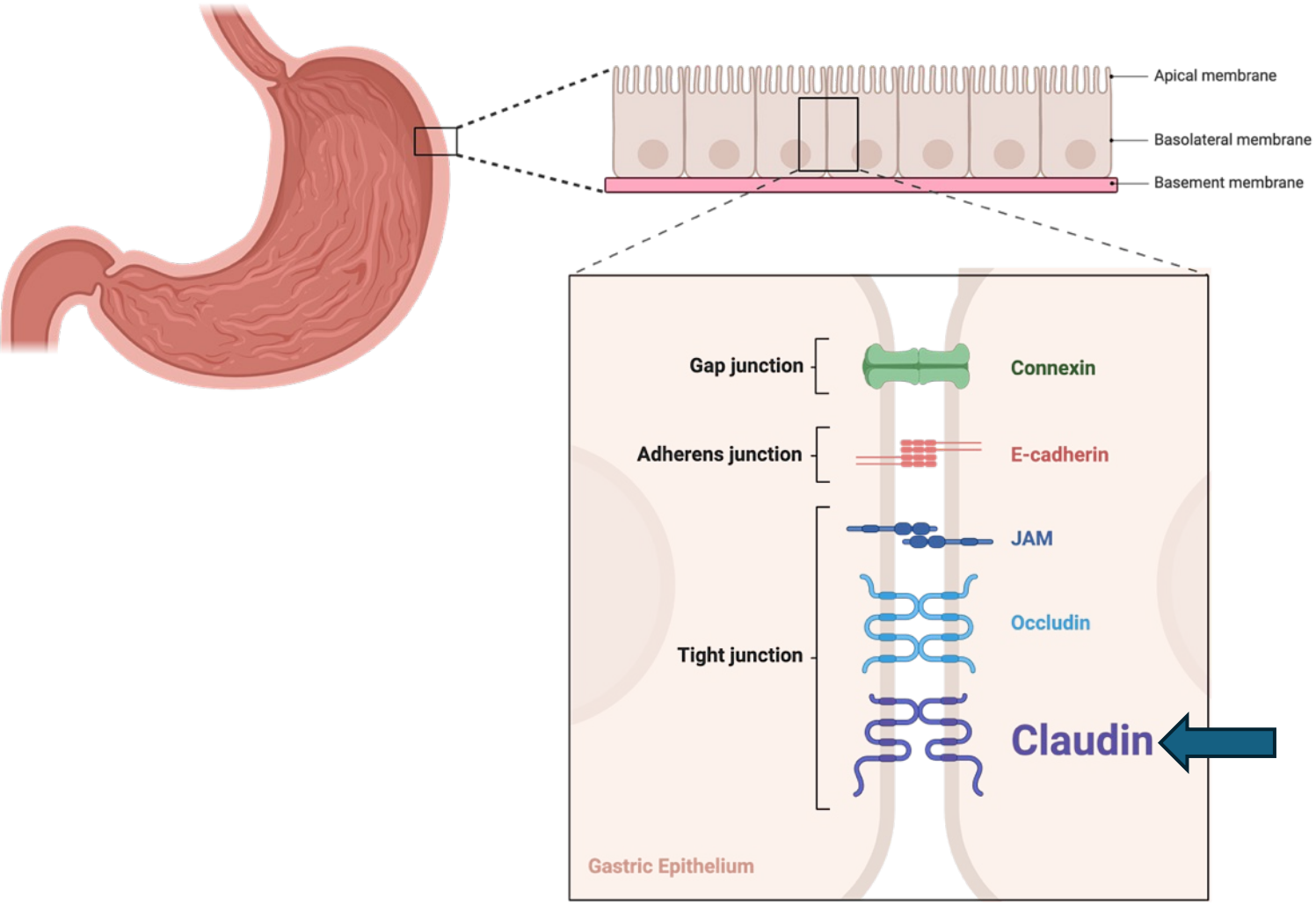
CLDN18.2 Prevalence and Overlap

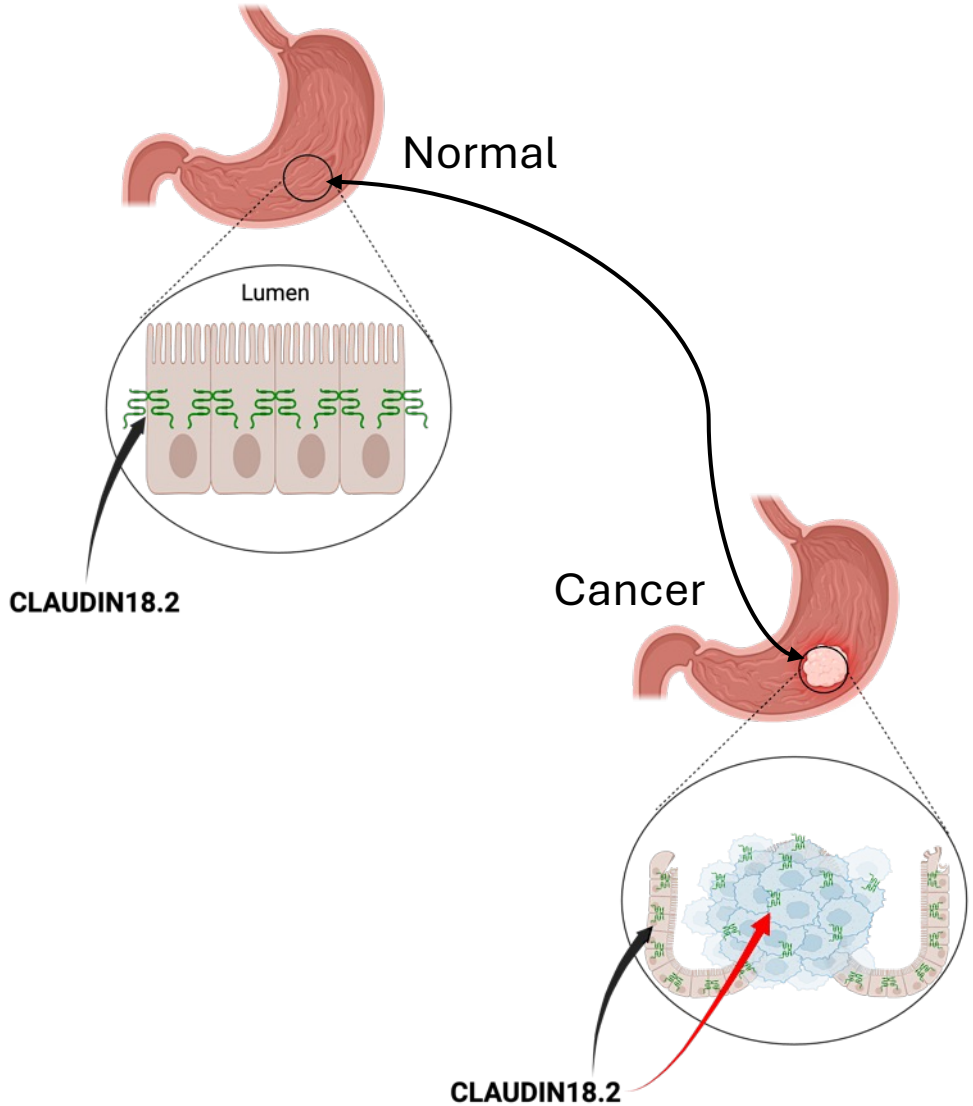


Biomarker	CLDN 18.2+	CLDN 18.2-
HER2-	85%	86%
HER2+	15%	14%
FGFR2b+	?	?
FGFR2b-	?	?
MSS	95%	94%
MSI	5%	6%
EBV+	4%	4%
EBV-	96%	96%
PD-L1- (CPS < 1)	26%	23%
PD-L1+ (CPS ≥ 1)	74%	77%
PD-L1+ (CPS < 5)	58%	49%
PD-L1+ (CPS ≥ 5)	42%	51%

Shitara K et al. Gastric Cancer. 2024 Sep;27(5):1058-1068; Kim TY et al. ESMO Open 2024

CLDN18.2 Biology: Location, Location, Location





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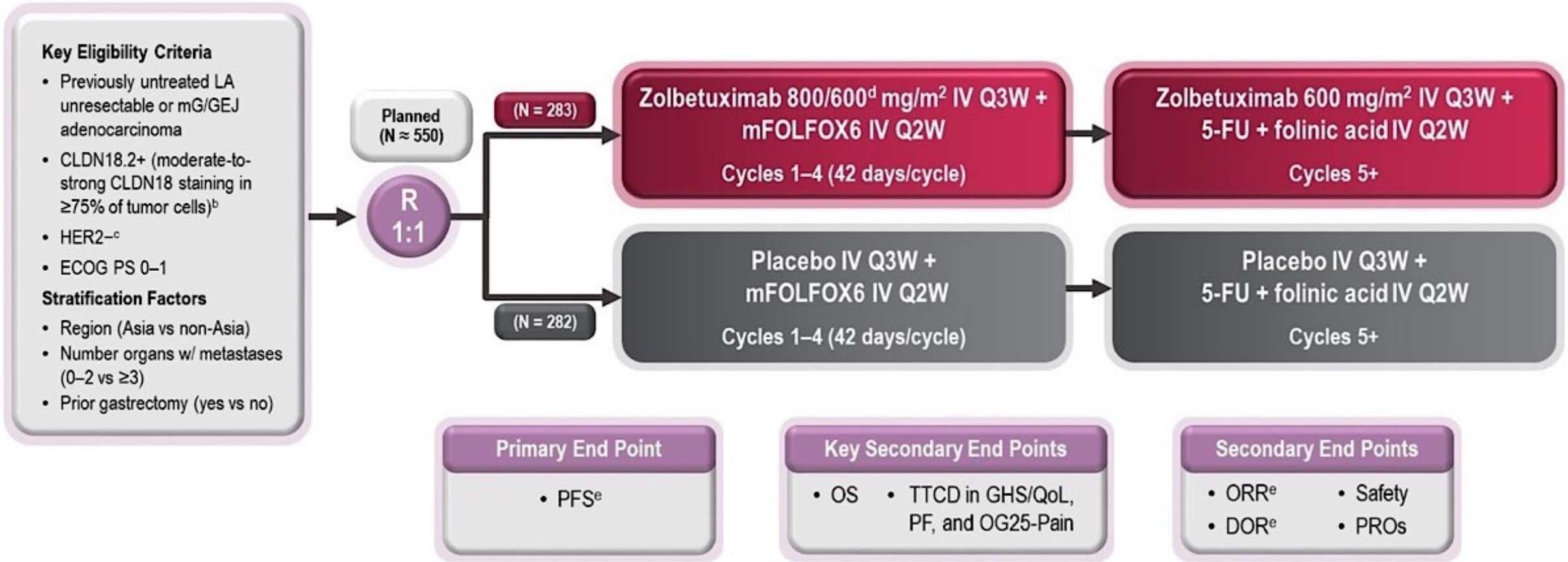
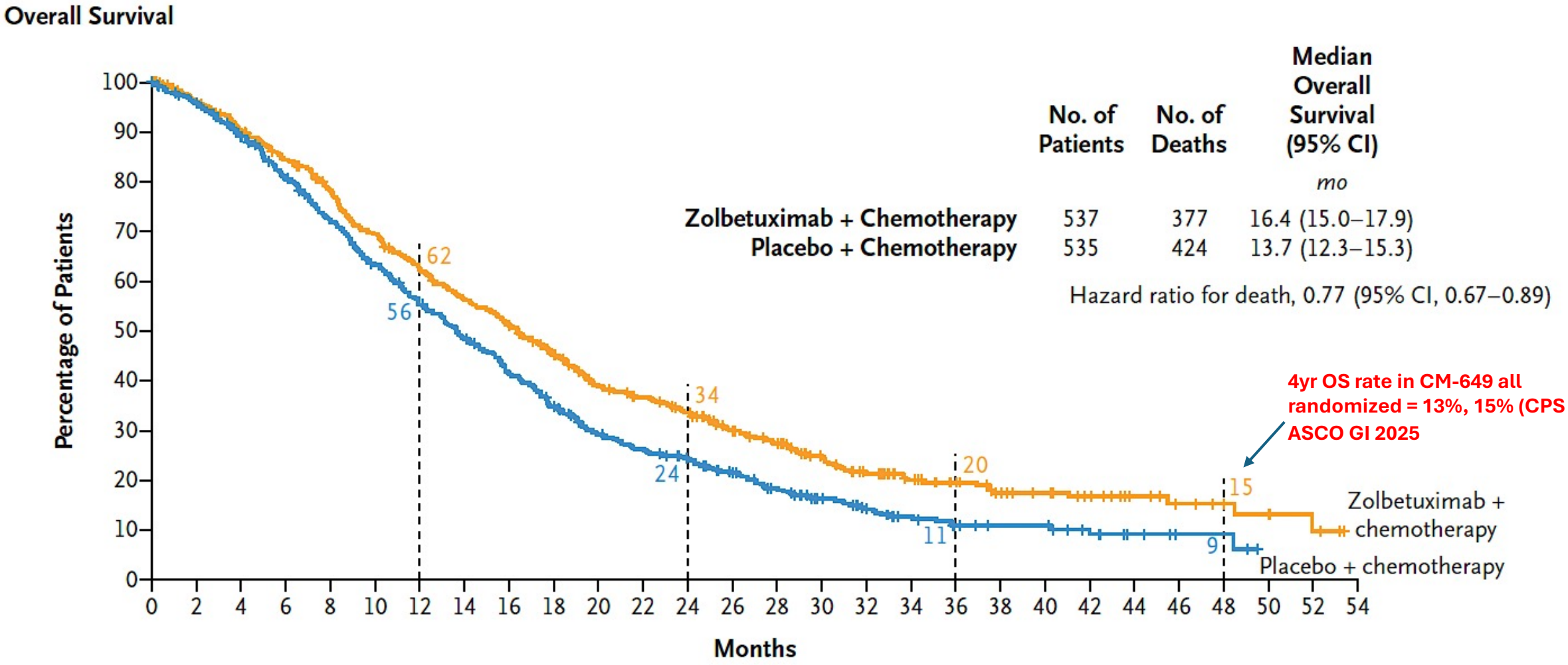
Zolbetuximab in 1L CLDN18.2+ GC/GEJ



ASCO GI 2023;Abstract LBA292

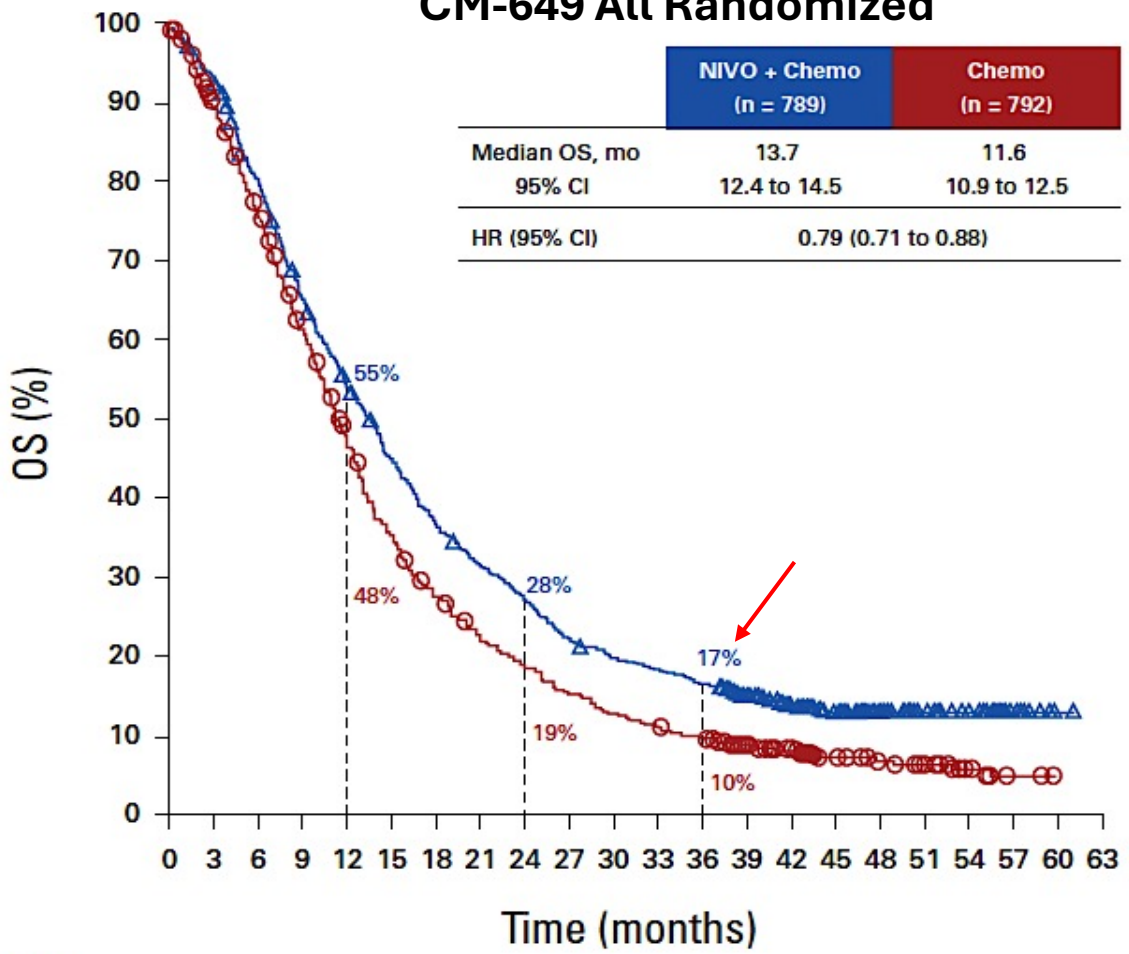
Zolbetuximab in 1L CLDN18.2+ GC/GEJ



Shitara K et al. NEJM 2024

Zolbetuximab Context in Other 1L Trials

CM-649 All Randomized

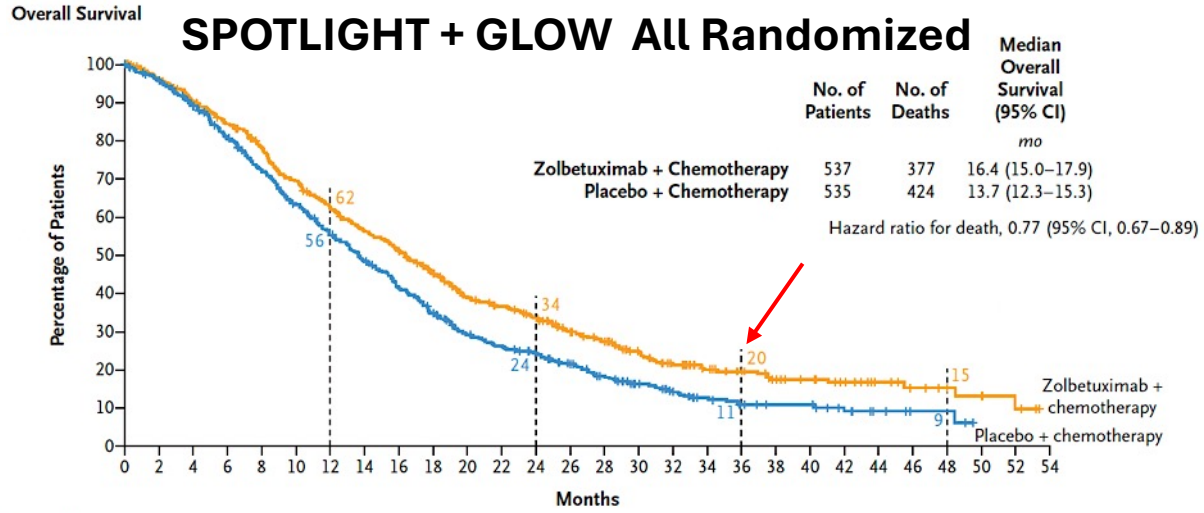


	NIVO + Chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.7	11.6
95% CI	12.4 to 14.5	10.9 to 12.5
HR (95% CI)	0.79 (0.71 to 0.88)	

No. at risk:

NIVO + chemo	789	733	625	509	422	349	287	246	212	175	154	143	129	106	87	67	48	30	23	9	2	0
Chemo	792	701	591	475	364	273	215	170	144	118	98	87	75	57	45	27	21	17	9	3	1	0

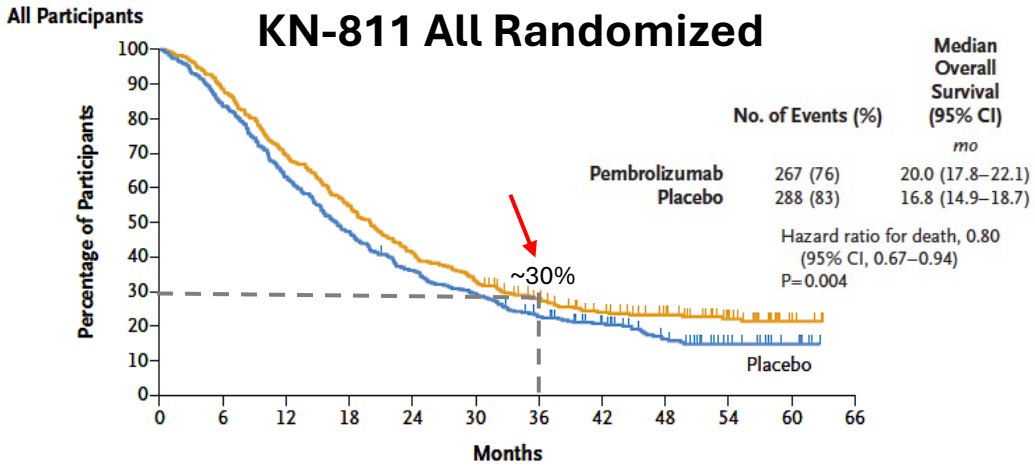
SPOTLIGHT + GLOW All Randomized



No. at Risk

Zolbetuximab	537	497	462	427	387	343	303	273	249	213	174	159	140	109	96	75	60	47	39	30	25	20	14	10	7	6	3	0
Placebo	535	506	463	409	362	317	278	239	204	169	135	119	102	85	65	50	38	28	21	17	17	11	6	3	3	0	0	0

KN-811 All Randomized

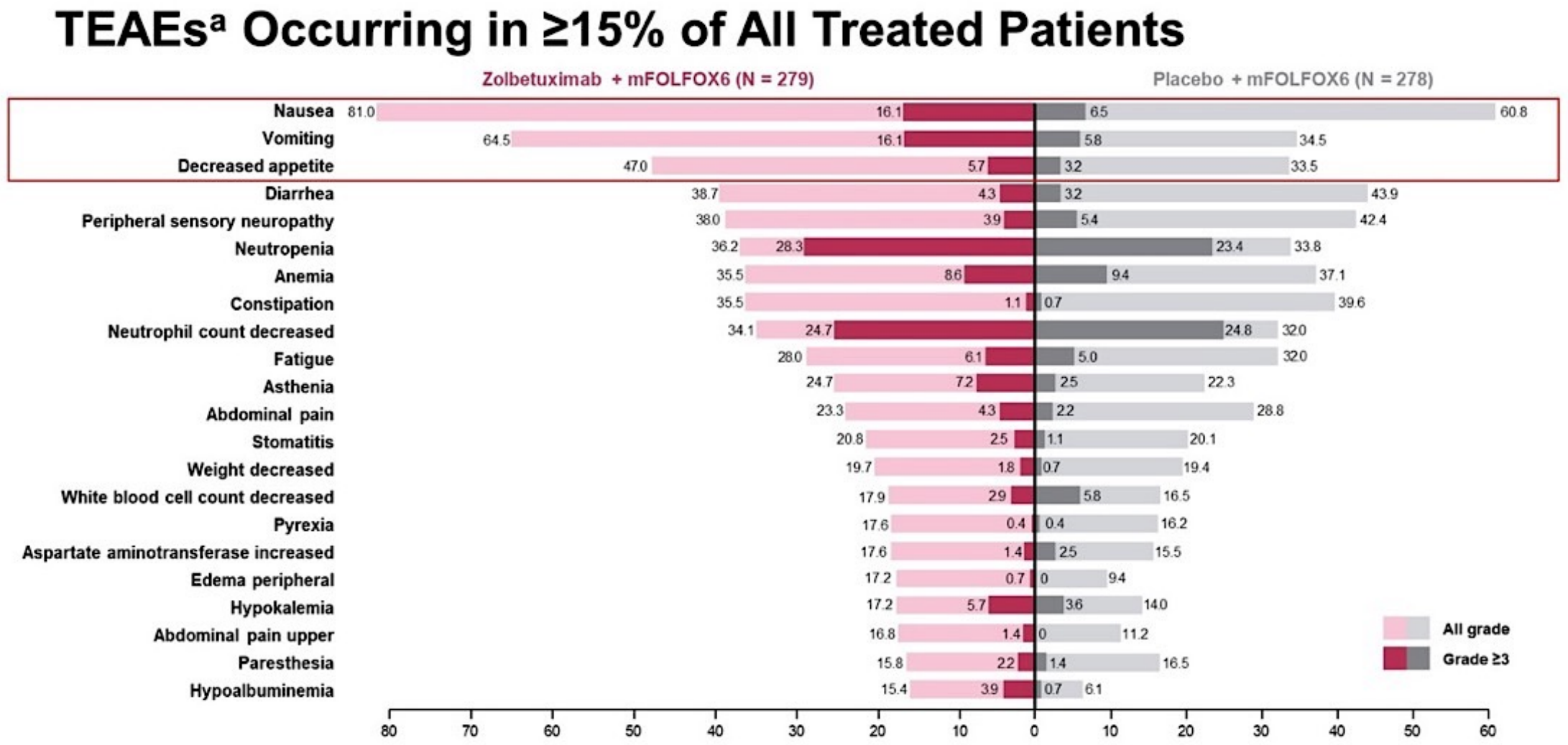


No. at Risk

Pembrolizumab	350	311	243	192	144	116	84	62	49	32	5	0
Placebo	348	292	220	165	125	102	74	59	37	16	6	0

Janjigian YY et al. JCO 2024; Shitara K et al. NEJM 2024; Janjigian YY et al. NEJM 2024

Zolbetuximab Toxicity

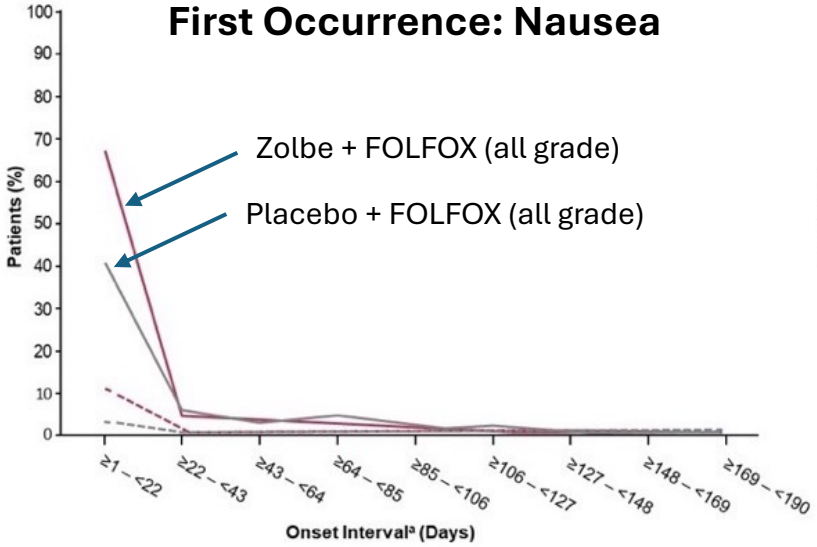


- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

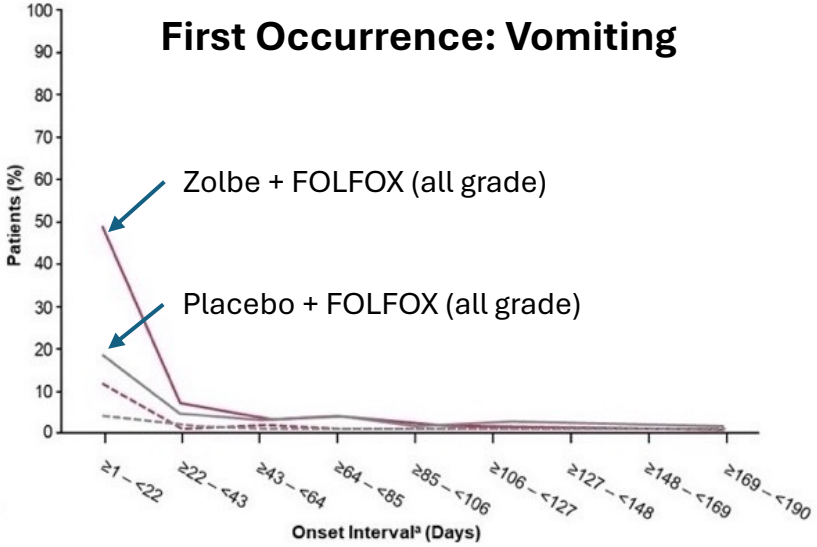
ASCO GI 2023;Abstract LBA292

Zolbetuximab Toxicity Management

First Occurrence: Nausea



First Occurrence: Vomiting



Prophylaxis before first infusion[a]

Provide one of the following NCCN-recommended **high-risk antiemetic agents[b]**

- NK-1 + 5-HT3 + dexamethasone + olanzapine
- or
- NK-1 + 5-HT3 + dexamethasone
- or
- 5-HT3 + dexamethasone + olanzapine

During first infusion, if patient is experiencing

- Nausea alone → Consider either making no modifications, or stopping the infusion for 30-60 min and restarting it at the same rate before the stop if symptoms improve; and After the first hour (when the infusion is running at 200-265 mg/m²/h), also consider slowing the infusion without stopping it first[d]
- Any vomiting[c] → Consider adding antiemetic treatment (e.g. rescue medications) → Stop the infusion for 30-60 min and restart it at a slower rate if symptoms improve[d]

When planning for second or subsequent infusions, if patient in the prior infusion experienced[e]

- Nausea alone or 1 episode of vomiting[c] → Rate recommended in PI; and Make no change or escalate from previous infusion
- Repeated vomiting[c] → Slower than rate recommended in PI[d]; and Escalate from previous infusion

During second and subsequent infusions, if patient is experiencing[f,g]

- Nausea alone → Make no modifications
- Any vomiting[c] → Stop the infusion for 30-60 min and restart it at a slower rate if symptoms improve[d]

KEY

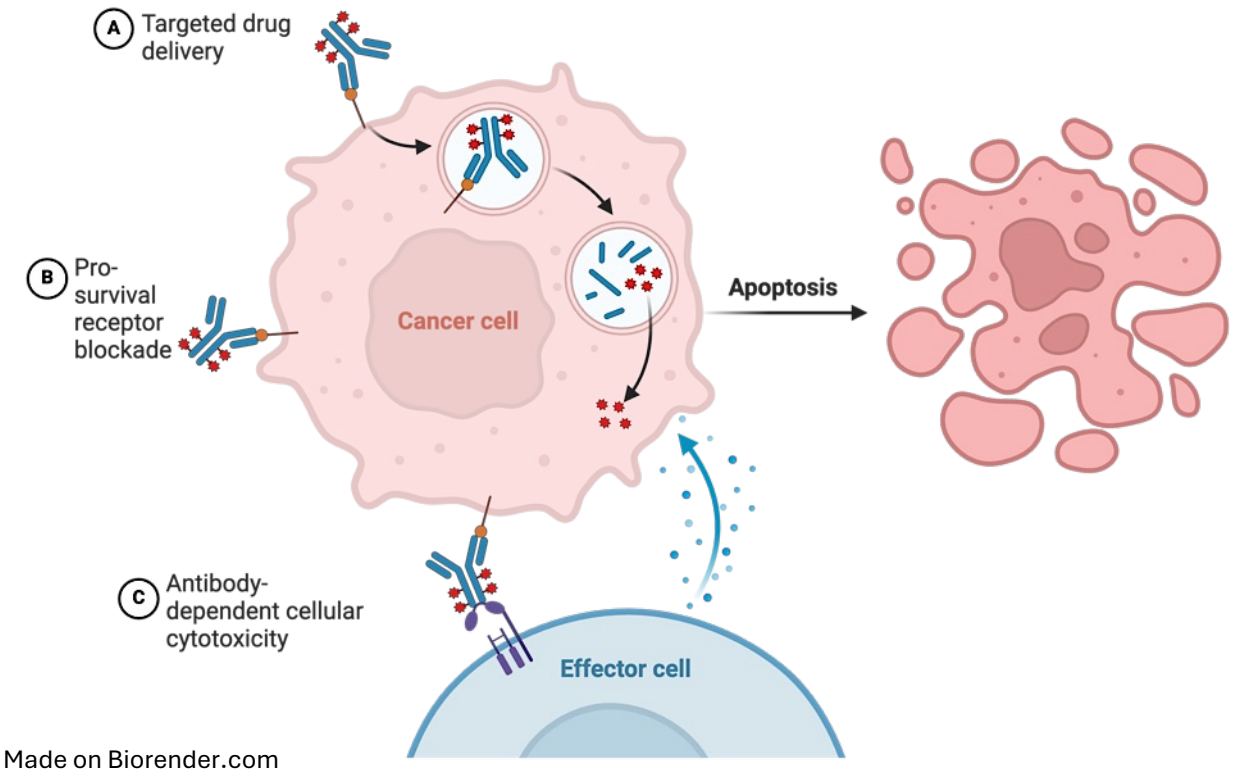
- Antiemetic regimens
- Patient symptoms
- Zolbetuximab infusion rate

ASCO GI 2023;Abstract LBA292

Klempner SJ et al. ESMO GI 2025

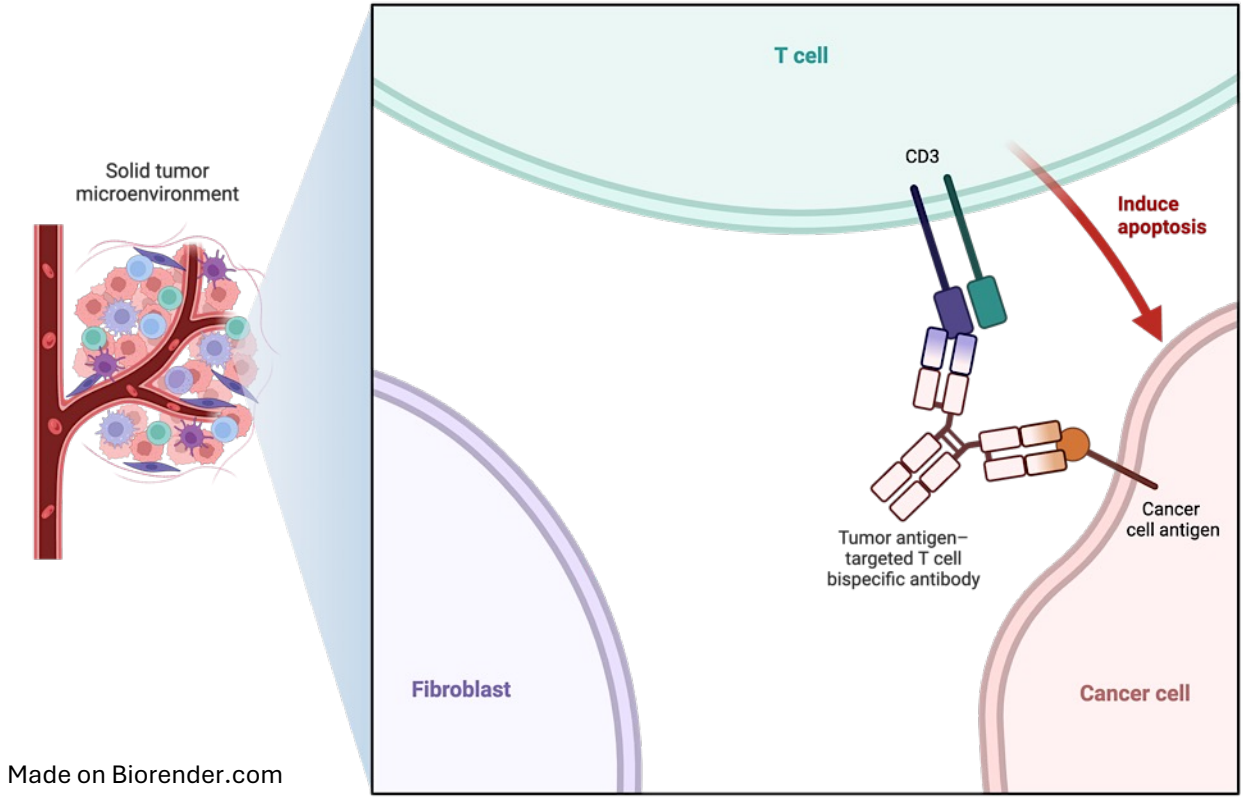
Expanding Beyond Zolbetuximab

Antibody Drug Conjugates



AZD0901 – CLDN18.2 ADC with **MMAE** Payload
EO-3021 – CLDN18.2 ADC with **MMAE** Payload
IBI343 -- CLDN18.2 ADC with **TOPO1** Payload
SHR-A1904 -- CLDN18.2 ADC with **TOPO1** Payload

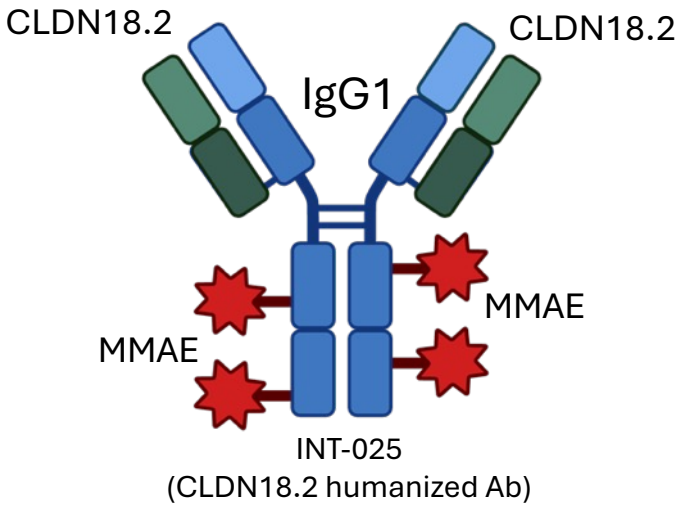
Bispecific Antibodies and BiTEs



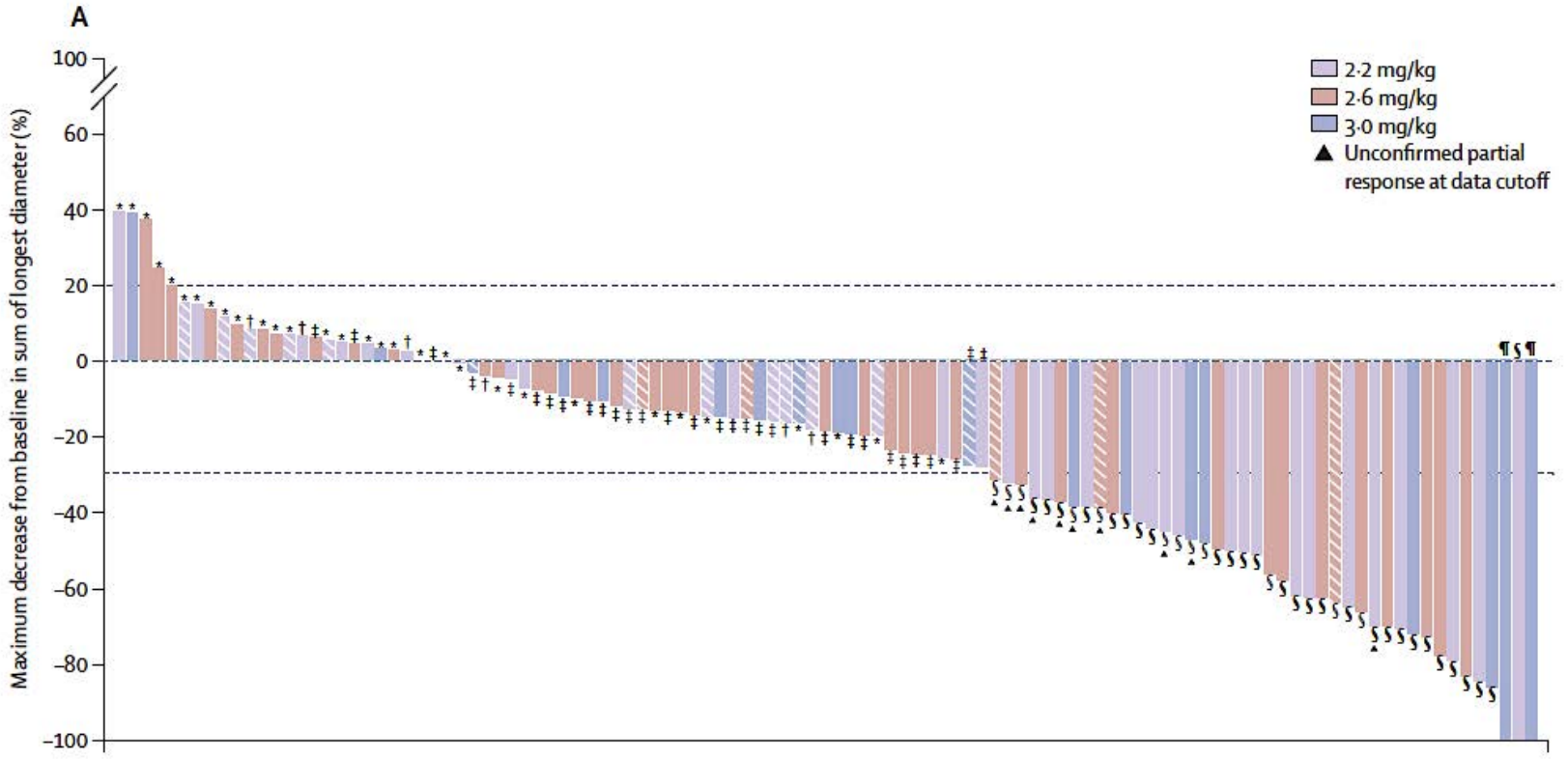
Givastomig – CLDN18.2 x 4-1BB bispecific
PT886 – CLDN18.2 x CD47 bispecific
ASP2138 – CLDN18.2 x CD3 BiTE
AZD5863 -- CLDN18.2 x CD3 BiTE

CLDN18.2 ADC Activity in GC/GEJ: AZD0901

AZD0901 (CMG901)



Global phase III 2L+ CLARITY trial examining AZD0901 vs investigator-choice chemotherapy in CLDN18.2+ GC/GEJ is ongoing (NCT06346392)



Feature	CLDN18.2-high 2.2mg/kg (n = 32)	CLDN18.2-high 2.6mg/kg (n = 45)	CLDN18.2-high 3.0mg/kg (n = 15)	CLDN18.2-high Total (n = 93)
cORR	47%	22%	38%	33%
mPFS	4.8 months	3.3 months	9.9 months	4.8 months
mOS	11.8 months	11.5 months	11.1 months	11.8 months

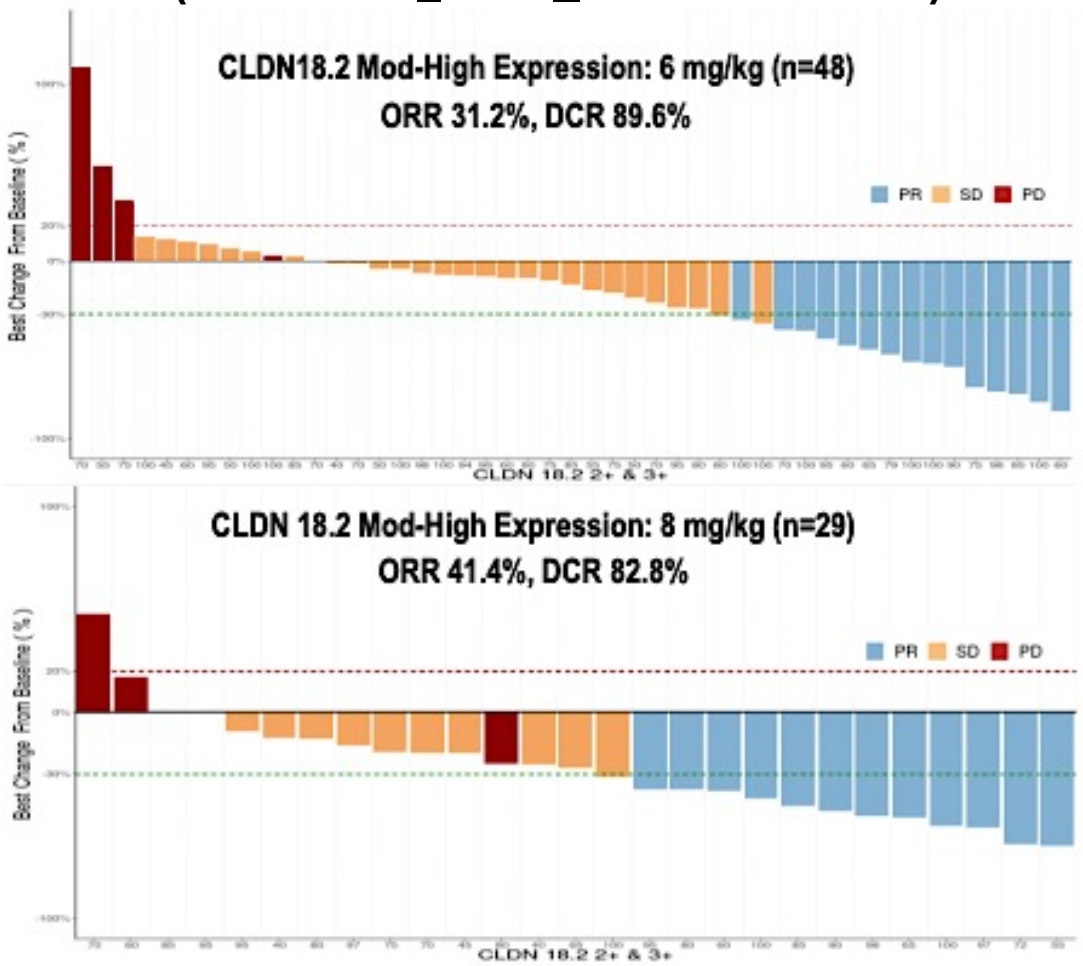
CLDN18.2 ≥2+ in 20% tumor cells = CLDN18.2-high

Ruan DY et al. Lancet Oncology 2025

Other CLDN18.2 ADCs: IBI343 and SHR-A1904

IBI343

(CLDN18.2 ≥2+ in ≥40% tumor cells)

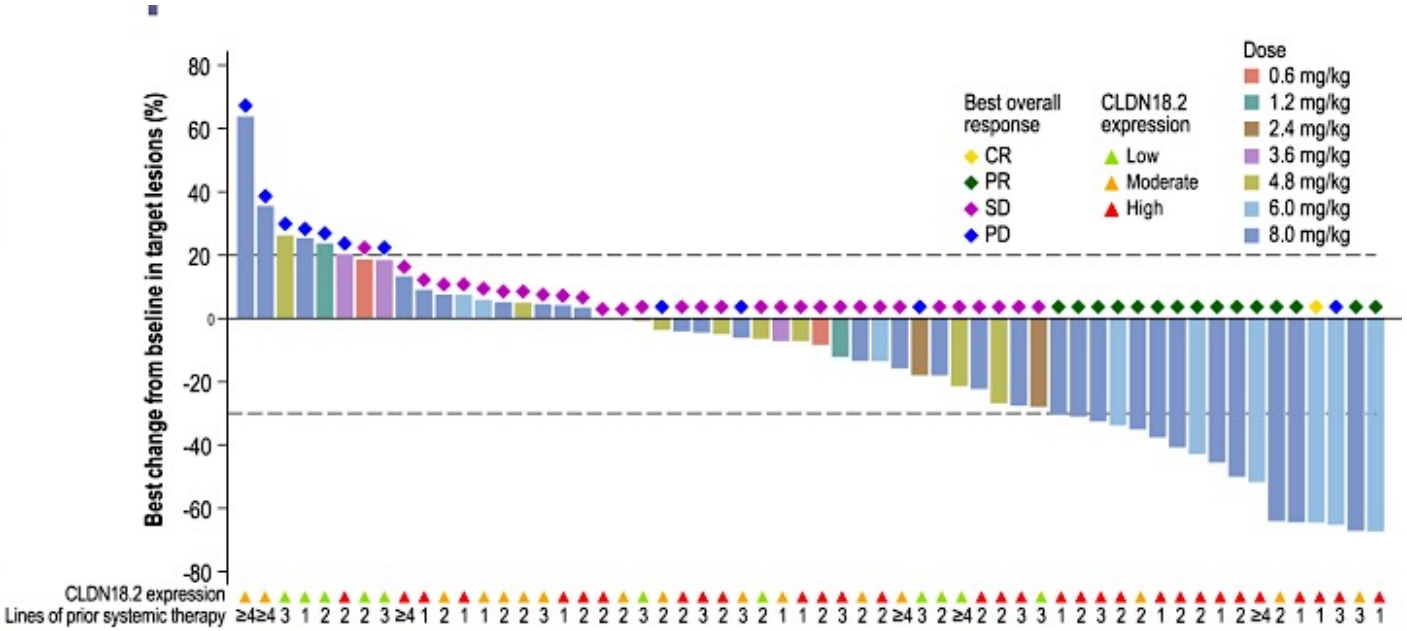


ESMO GI 2024;Abstract 396MO

SHR-A1904

(low = CLDN18.2 ≥1+ in 1-49% tumor cells)

(mod = CLDN18.2 ≥2+ in 50-69% tumor cells)



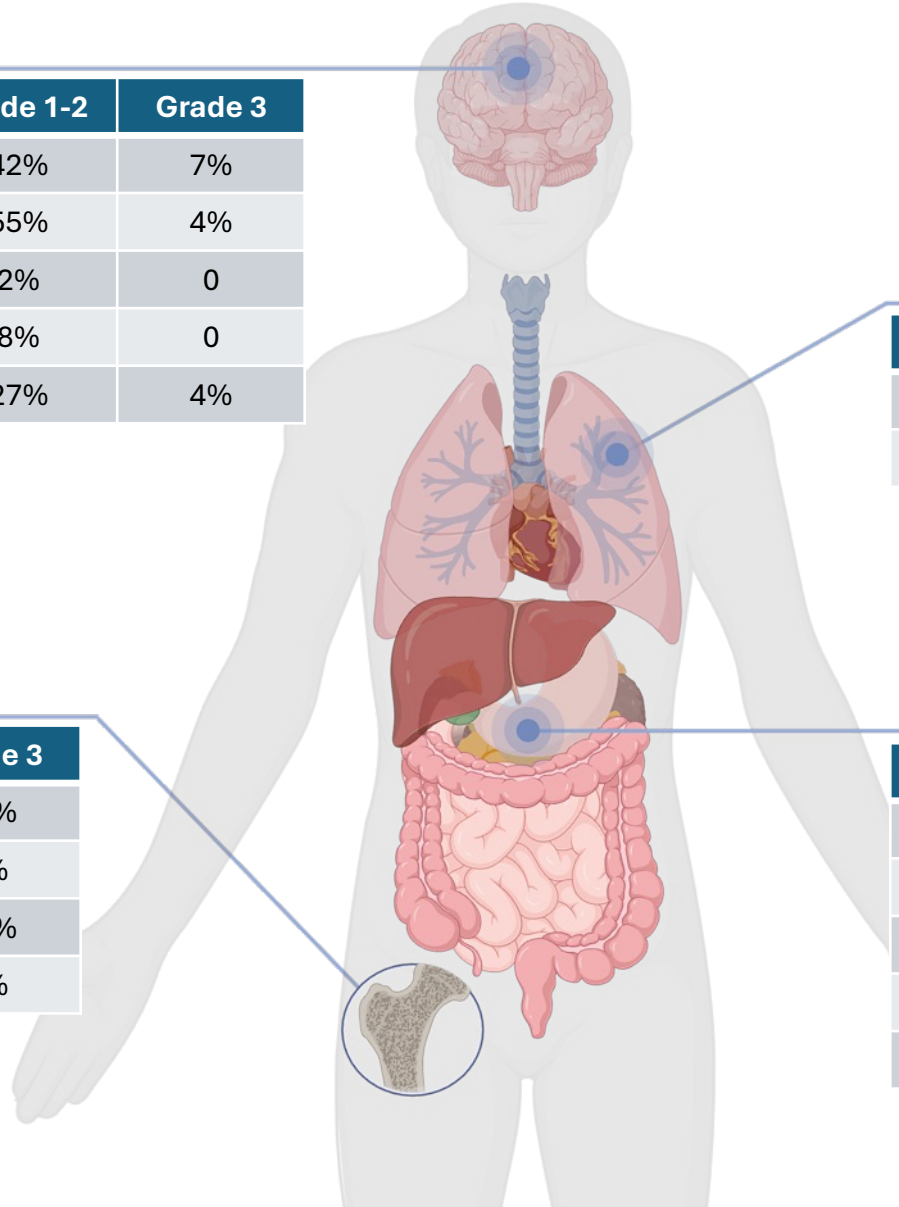
	6.0 mg/kg (N=9)	8.0 mg/kg (N=30)	All (N=58)
ORR, n (%; 95% CI)	5 (**55.6**; 21.2–86.3)	11 (**36.7**; 19.9–56.1)	16 (27.6; 16.7–40.9)
DCR, n (%; 95% CI)	8 (**88.9**; 51.8–99.7)	26 (**86.7**; 69.3–96.2)	47 (81.0; 68.6–90.1)

ESMO 2024;Abstract 609O

CLDN18.2 ADC Toxicity in GC/GEJ: AZD0901

General

Toxicity	Grade 1-2	Grade 3
Decr. Appetite	42%	7%
Weight Loss	55%	4%
Fatigue	2%	0
Alopecia	8%	0
Asthenia	27%	4%



Pulmonary

Toxicity	Grade 1-2	Grade 3
Pneumonitis	6%	0
URI	6%	1%

Bone Marrow

Toxicity	Grade 1-2	Grade 3
Anemia	52%	13%
Low PLTs	10%	2%
Neutropenia	33%	16%
Leukopenia	43%	7%

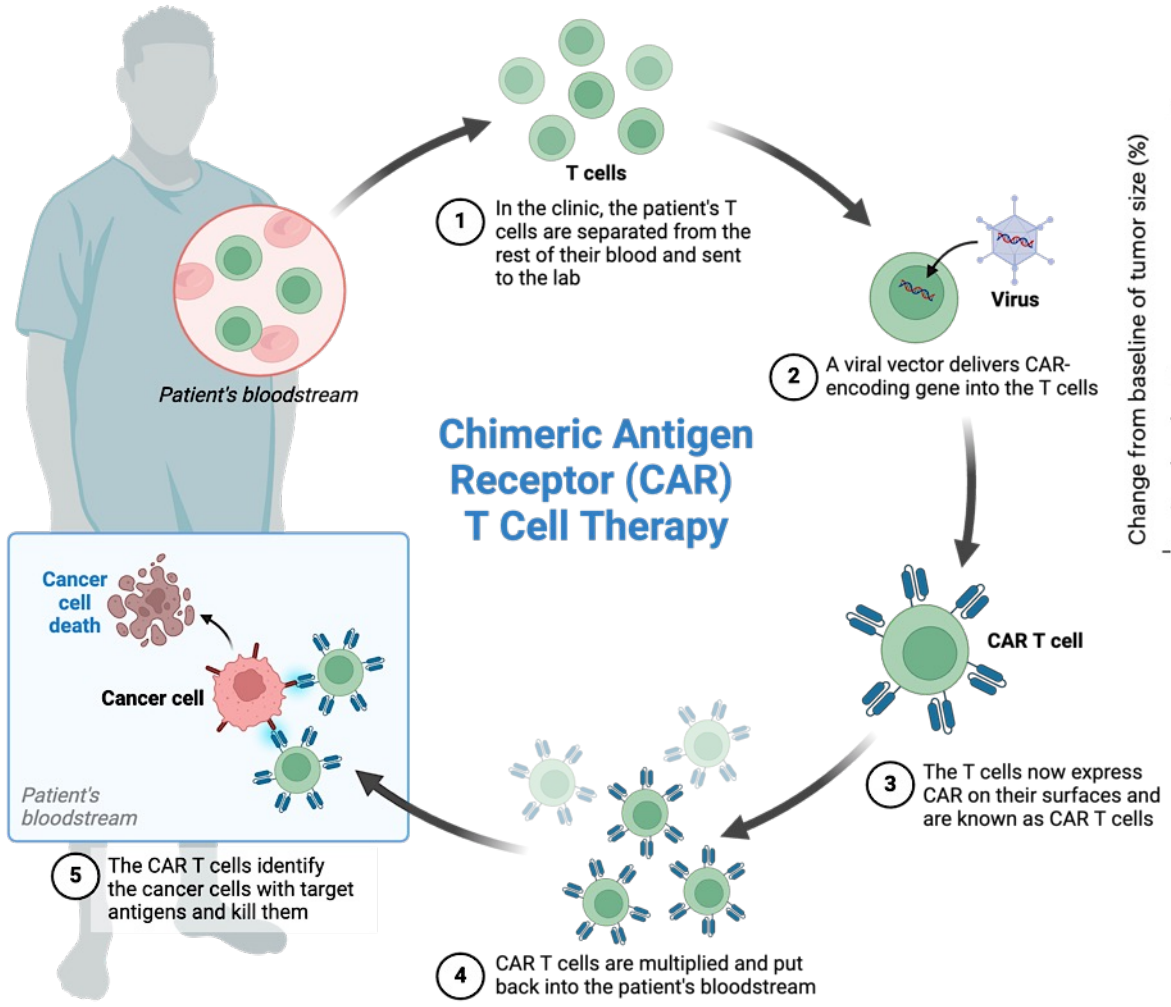
Gastrointestinal

Toxicity	Grade 1-2	Grade 3
Vomiting	46%	10%
Nausea	53%	4%
Diarrhea	19%	1%
Abd. Pain	16%	3%
Constipation	21%	0%

Made on Biorender.com

Ruan DY et al. Lancet Oncology 2025

The First Positive Randomized CAR-T in Solid Tumors?



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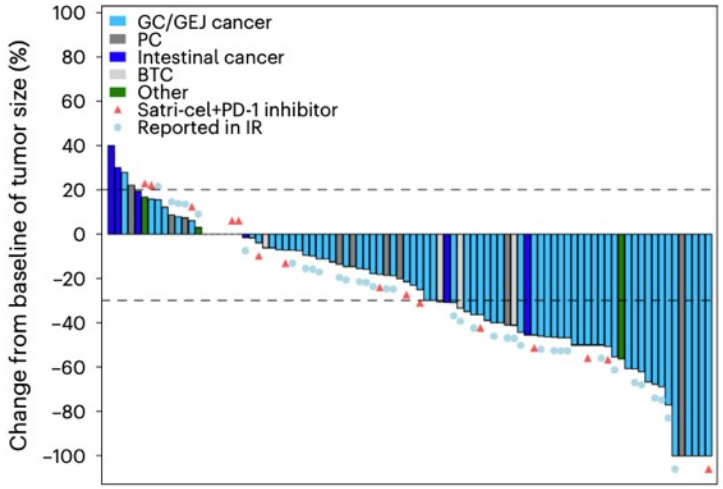
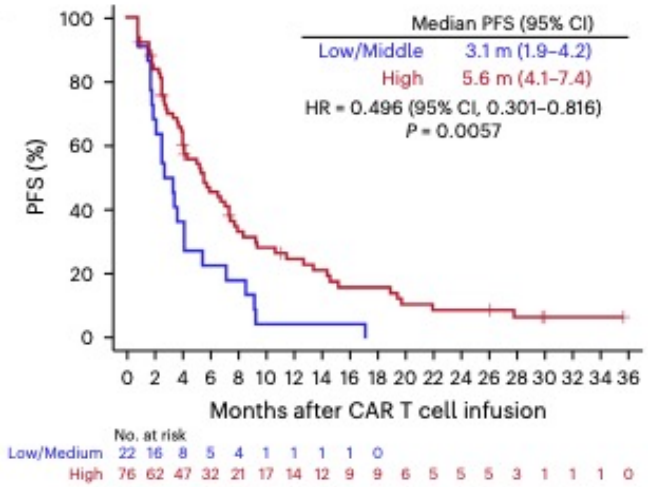
CT041 CLDN18.2 CAR-T in previously treated CLDN18.2+

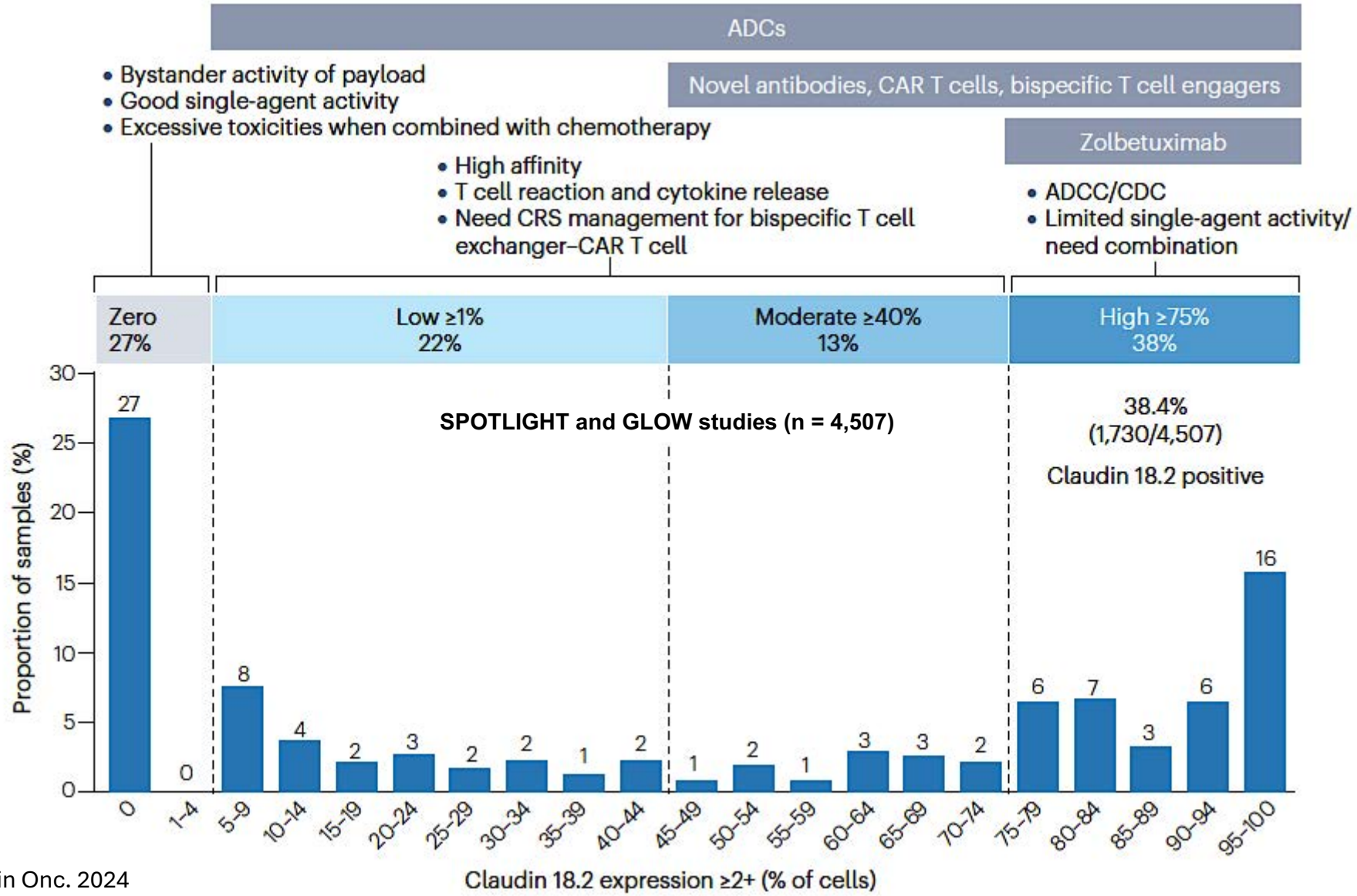




Qi C et al. Nature Med 2024

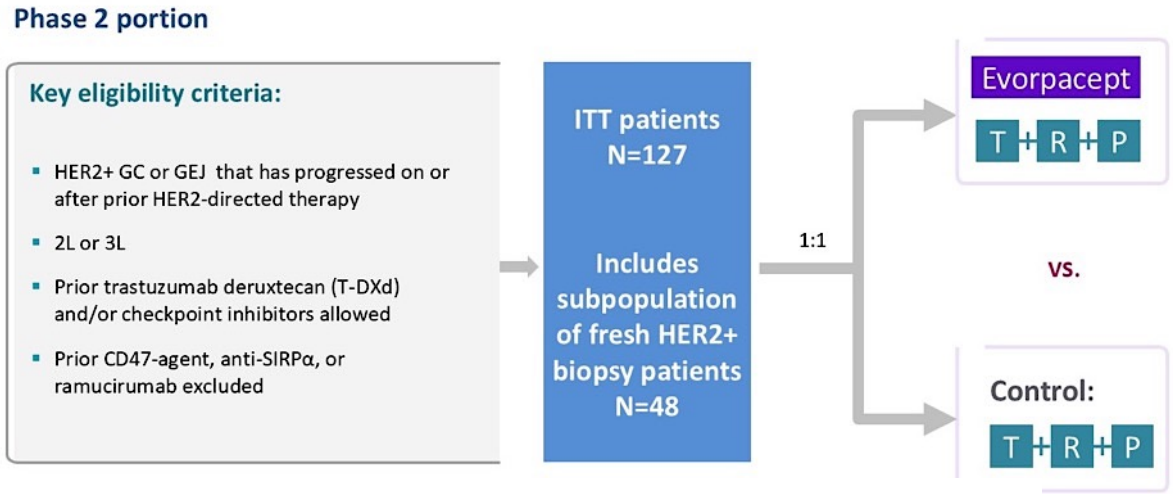
<u>Manufacturer Press Release (12/30/2024)</u>: positive results from the pivotal Phase II clinical trial CT041-ST-01(NCT04581473) in patients with Claudin18.2 expression-positive, advanced gastric/gastroesophageal junction cancers that have failed at least 2 prior lines therapy. Patients were 2:1 randomly assigned to receive treatment of satricabtagene autoleucel (satri-cel) versus physician's choice (including paclitaxel, docetaxel, irinotecan, apatinib, or nivolumab). The primary endpoint of the trial is progression-free survival (PFS) assessed by the Independent Review Committee (IRC).

Spectrum of CLDN18.2 Therapies



Nakayama I et al. Nat Rev Clin Onc. 2024

Other Targets in Advanced GC/GEJ: HER2



	Evo +T+R+P	T+R+P
N evaluable	63	64
Confirmed ORR, n (%) [95% CI]	**26 (41.3%) [29.0%; 54.4%]**	**17 (26.6%) [16.3%; 39.1%]**
CR (Complete Response)	1 (1.6%)	1 (1.6%)
PR (Partial Response)	25 (39.7%)	16 (25.0%)
SD (Stable Disease)	21 (33.3%)	35 (54.7%)
PD (Progressive Disease)	9 (14.3%)	7 (10.9%)
NE (Not Evaluable)	2 (3.2%)	1 (1.6%)
No Post baseline assessment	5 (7.9%)	4 (6.3%)
Median DOR (months) [95% CI]	**15.7 [7.7; NR]**	**9.1 [5.3; NR]**
Number of events	12 (46.2%)	9 (52.9%)

ASCO GI 2025;Abstract 332

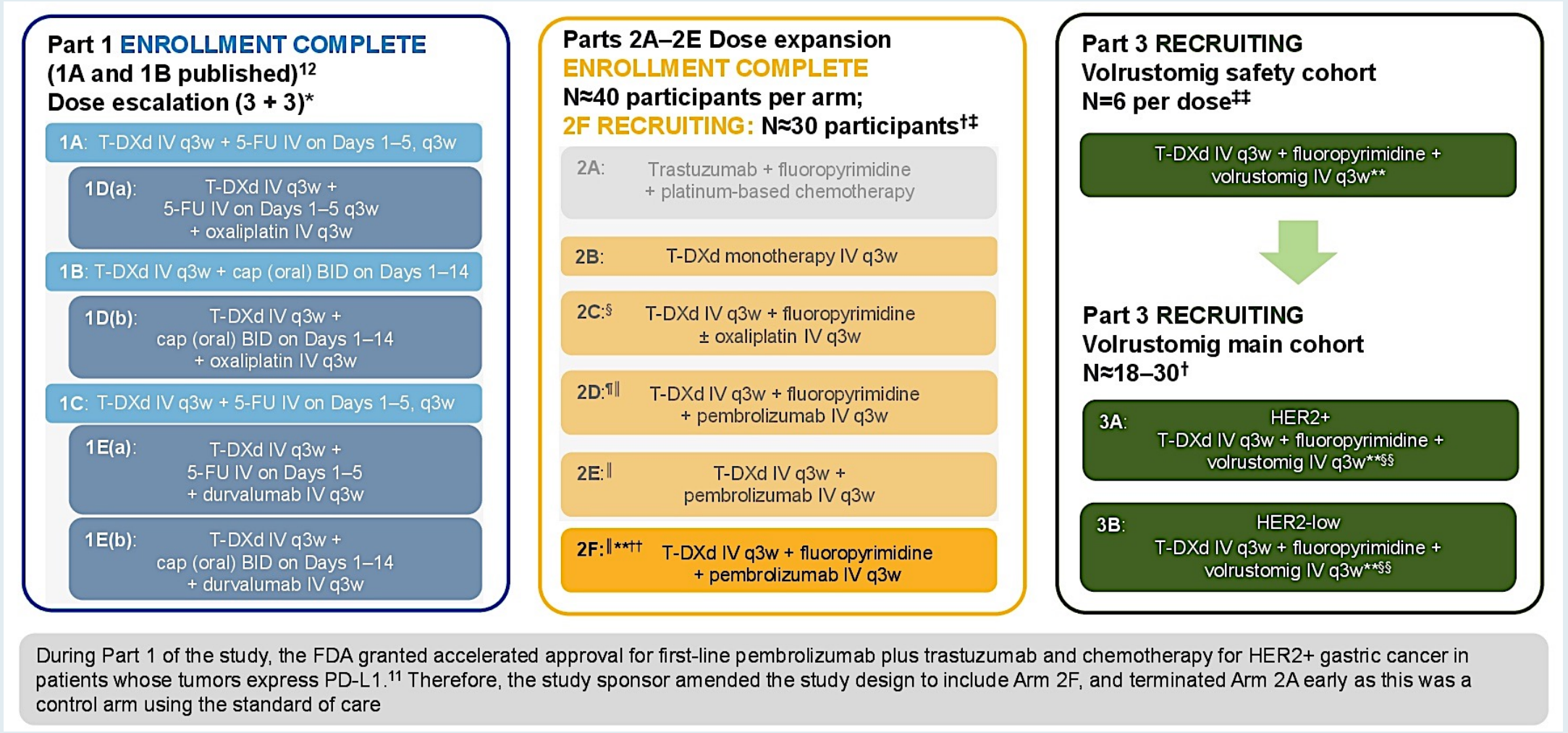
Current Standard Option after trastuzumab: T-DXd

Feature	DG-01 (3L+)	DG-02 (2L)
ORR Experimental	**51%**	**42%**
ORR Control (Paclitaxel or Irinotecan)	14%	N/A
PFS Experimental	**5.6 months**	**5.6 months**
PFS Control (Paclitaxel or Irinotecan)	3.5 months	N/A
OS Experimental	**12.5 months**	**12.1 months**
OS Control (Paclitaxel or Irinotecan)	8.4 months	N/A

Any Grade Toxicity with T-DXd	DG-01 (3L+)	DG-02 (2L)
Nausea	63%	67%
Neutrophil Decrease	63%	17%
Anemia	58%	38%
Malaise and/or Decreased Appetite	34%	33%
Vomiting	26%	45%
Diarrhea	32%	36%
Fatigue	22%	42%
Alopecia	22%	24%
ILD/pneumonitis	10%	10%

Shitara K et al. N Engl J Med. 2020; Van Cutsem E et al. Lancet Oncol. 2023

Phase Ib/II DESTINY-Gastric03 Study Design



During Part 1 of the study, the FDA granted accelerated approval for first-line pembrolizumab plus trastuzumab and chemotherapy for HER2+ gastric cancer in patients whose tumors express PD-L1.[11] Therefore, the study sponsor amended the study design to include Arm 2F, and terminated Arm 2A early as this was a control arm using the standard of care

Janjigian YY et al. ASCO GI 2024;Abstract TPS424.

Phase Ib/II DESTINY-Gastric03: Efficacy

Figure 2. Best percentage change in target lesion size from baseline

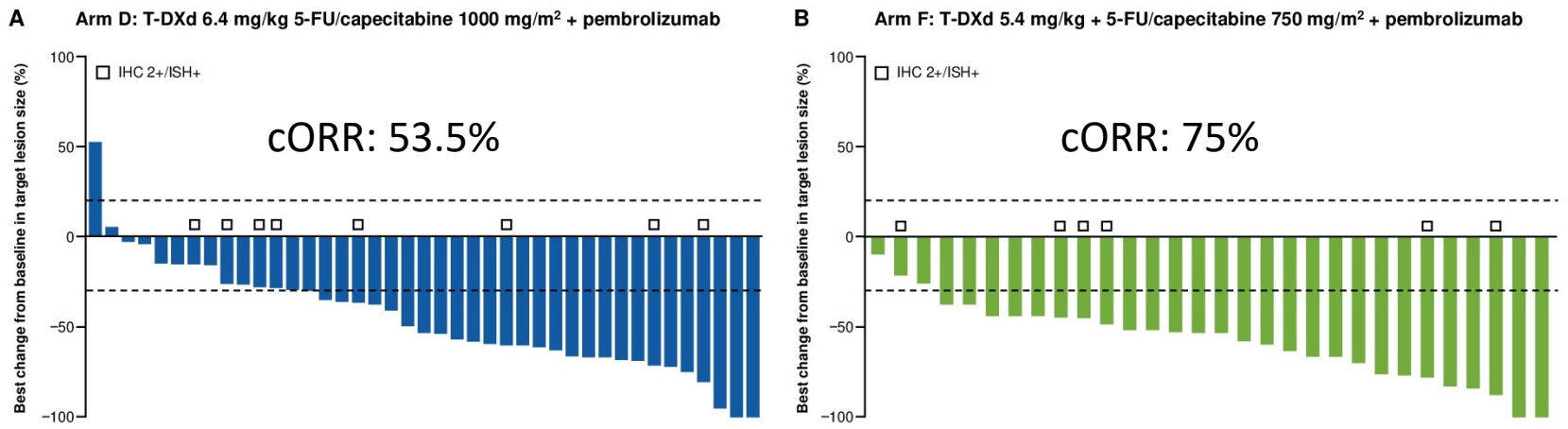
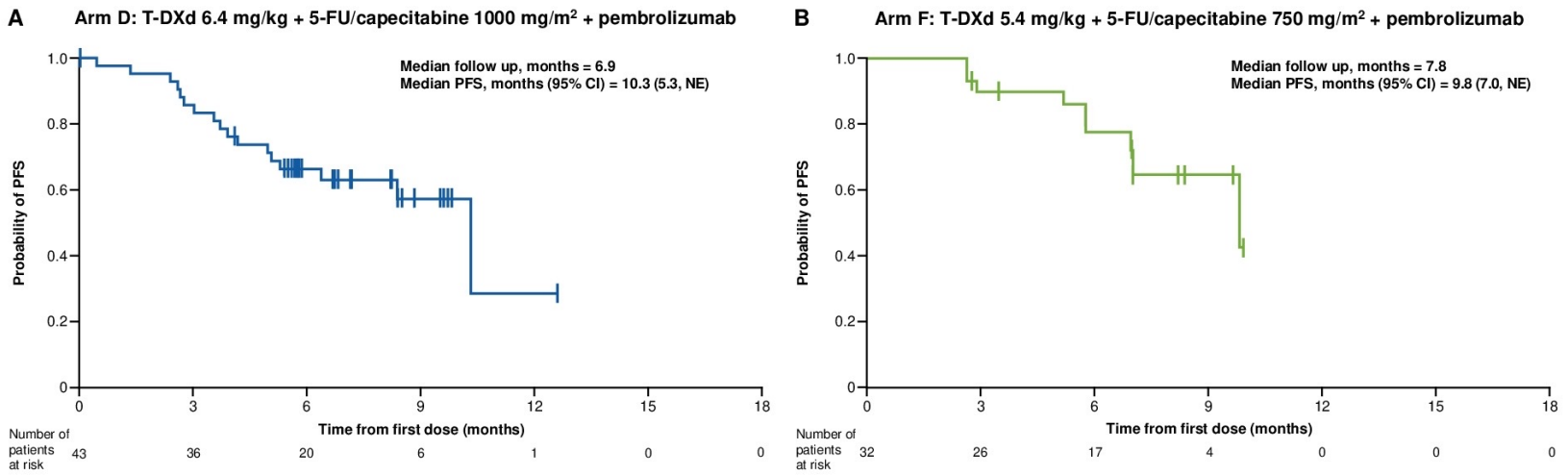


Figure 3. Kaplan-Meier estimates of PFS



Janjigian YY et al. ASCO GI 2025;Abstract 448.

RTP RESEARCH TO PRACTICE

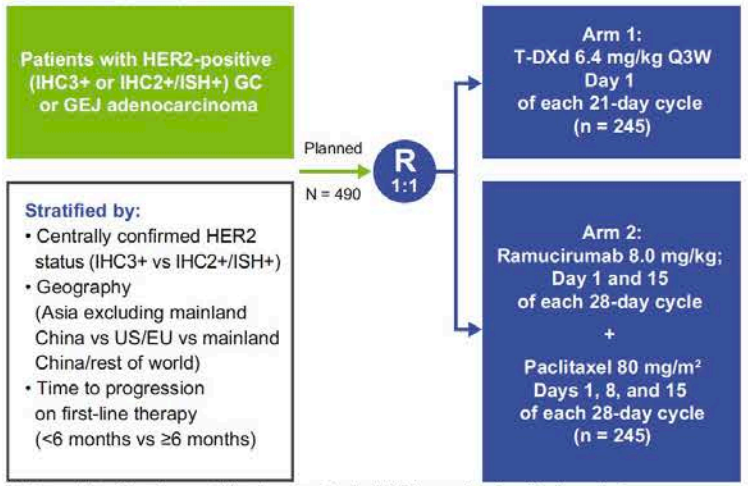
Phase III DESTINY-Gastric04 Study Design

Methods

Study Design and Population

- DESTINY-Gastric04 is a global, multicenter, 2-arm, randomized, open-label phase 3 study (**Figure 2**)

Figure 2. Study Design



EU, European Union; GC, gastric cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; US, United States.

Key Inclusion Criteria

- Adults (according to local regulation) and able to provide informed consent
- Unresectable, locally advanced, or metastatic GC or GEJ adenocarcinoma
- Progression on or after previous first-line treatment including trastuzumab-containing therapy
- Centrally confirmed HER2-positive status (IHC3+ or IHC2+/ISH+) on a tumor biopsy obtained after progression on or after a trastuzumab-containing regimen
- ECOG PS of 0 or 1
- LVEF ≥50% within 28 days before randomization

Key Exclusion Criteria

- Anticancer therapy after trastuzumab-containing therapy
- Myocardial infarction ≤6 months before randomization or symptomatic CHF
- History of ILD/pneumonitis that required steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disease

CHF, congestive heart failure; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; LVEF, left ventricular ejection fraction.

Study Endpoints

Primary	• **OS**		
Secondary	Efficacy by investigator-assessed RECIST v1.1 • PFS • ORR • DOR • DCR	Safety • AEs, including TEAEs, SAEs, and AEs of special interest, graded according to NCI-CTCAE v5.0 • ECOG PS, vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA, and radiological findings	Pharmacokinetics • Serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA 1181a Immunogenicity • Incidence of antidrug antibodies and neutralizing antibodies
Exploratory	Health economics and outcomes research • EORTC EQ-5D-5L, FACT-Ga, and global anchor (PGIS, PGIC, and PGI-TT) questionnaires		

AE, adverse event; DCR, disease control rate; DOR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC EQ-5D-5L, European Organization for Research and Treatment of Cancer EuroQoL-5 dimensions-5 levels of severity; FACT-Ga, functional assessment of cancer therapy–gastric; HER2, human epidermal growth factor receptor 2; MAAA 1181a, released drug; MUGA, multigated acquisition; NCI-CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PGIC, Patient Global Impression–Change; PGIS, Patient Global Impression–Severity; PGI-TT, Patient Global Impression–Treatment Tolerability; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

NCT04704934

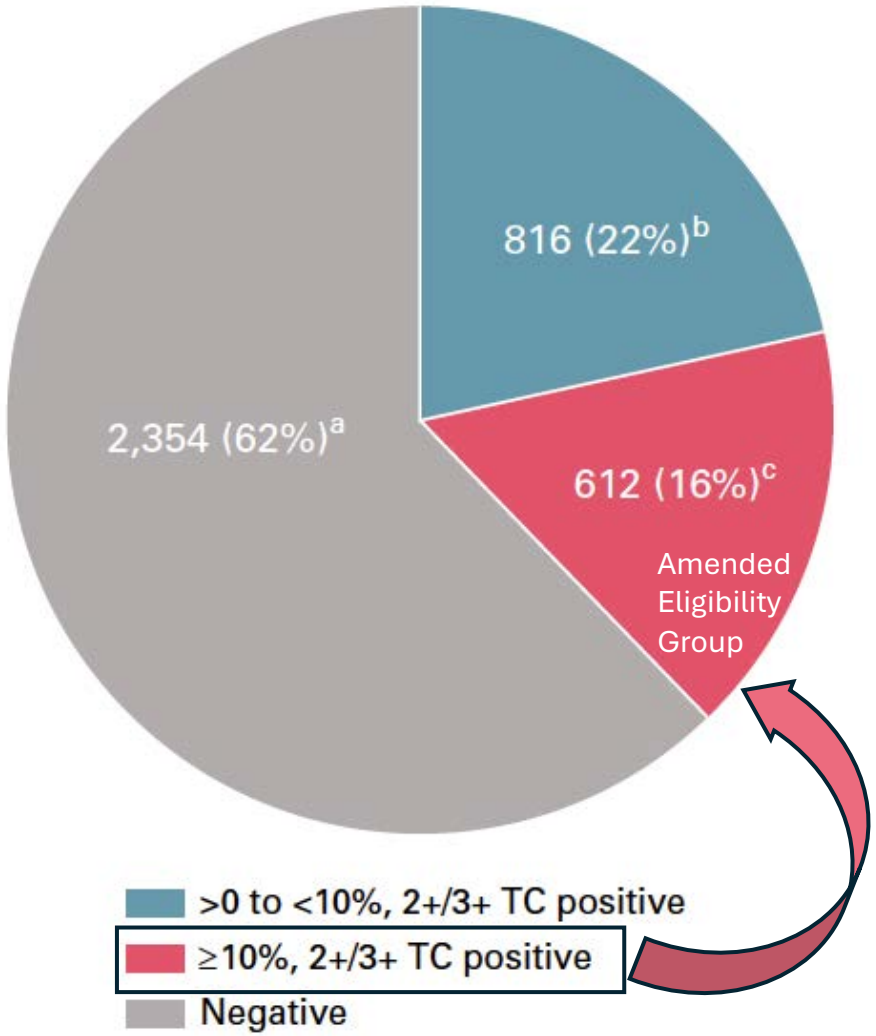
Shitara K et al. ESMO 2021;Abstract 1436TiP.

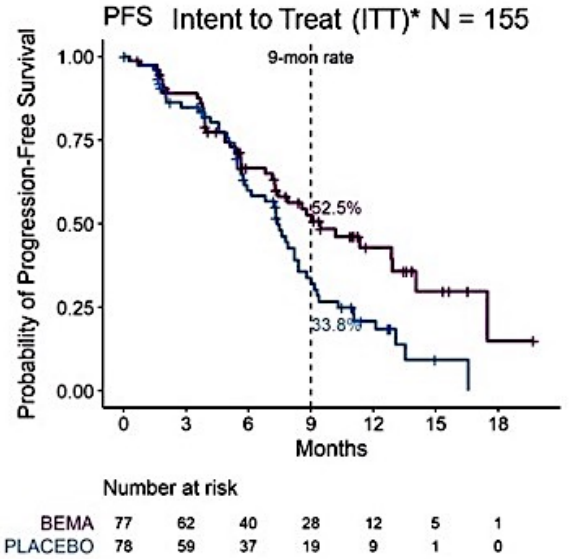
Other Targets in Advanced GC/GEJ: FGFR2b

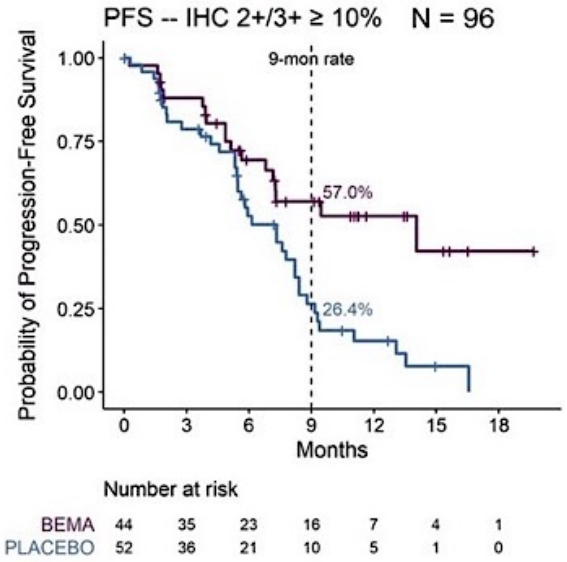
TABLE 1. Patient and Sample Characteristics

Characteristics	Patients (N = 3,782), No. (%)
Sex	
Female	1,217 (32)
Male	2,565 (68)
Region	
APAC	1,988 (53)
EMEA	1,360 (36)
Latin America	362 (10)
United States/Canada	72 (2)
Age, years	
<65	2,023 (53)
≥65	1,759 (47)
Tissue collection site	
Metastatic site	548 (14)
Primary site	3,234 (86)
Tissue collection method	
Biopsy	3,396 (90)
Resection	364 (10)
Unknown	22 (1)
Location of primary tumor	
GC	2,512 (66)
GEJC	455 (12)
Unspecified[a]	815 (22)

FORTITUDE-101 Screening





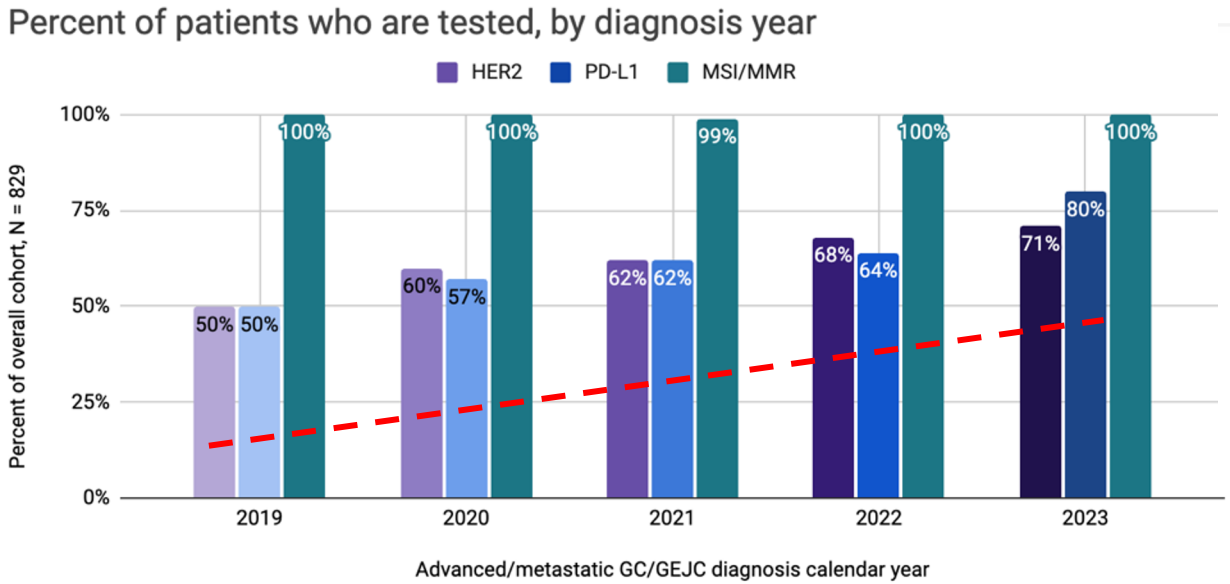


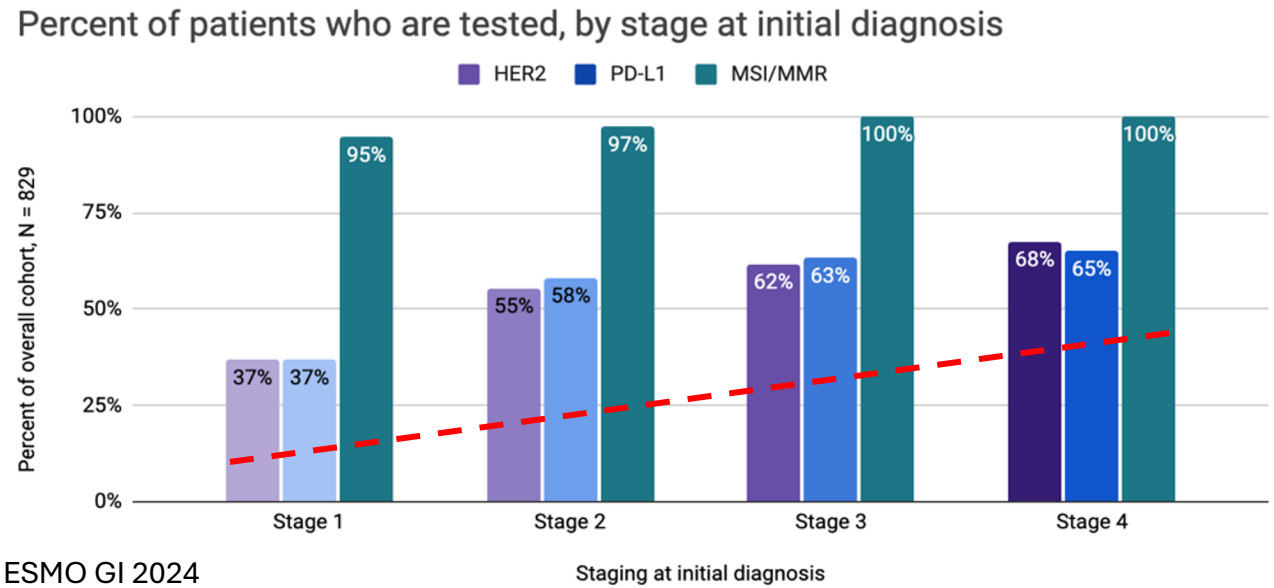
Rha SY et al. JCO PO 2025; Wainberg ZA et al. Lancet Onc 2022

Other Targets in Advanced GC/GEJ

Target/Mechanism	Approach(es)	Rationale
VEGF	PD-1 x VEGF bispecific, small molecule TKIs	Remodel TME (reduce Treg, MDSC)
YAP/TEAD, FAK	Oral Small molecules	Hippo pathway activation common in GC FAK activation in DGC
T-cell Exhaustion	TIGIT mAb in combo with PD-1, combo with chemo + PD-1 (e.g., STAR-221 phase III), TIGIT x PD-L1 bispecific	Dual checkpoint targeting (synergy, resensitization)
T-cell Stimulating	IL-2 + PD-1, etc	CD8+ T-cell expansion (IL-2) + T-cell reinvigoration (PD-1)
Myeloid Targeting (TLR8, STING, etc.)	Combos with PD-1, combo with ADC	Reprogram TME
EGFR, MET, HER2	ADCs (bispecific EGFR x MET, etc.), mAb, biparatopic (Zanidatamab)	Targeted ADC payload delivery, improved ADCC/CDC, receptor internalization
Other cellular therapies (TILs, CAR-T, CAR-NK, etc.)	Multiple	Multiple
Personalized neoantigen vaccines	Combo with FLOT, maintenance, etc	Enhance immune recognition

A Final Message on Biomarker Testing





NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
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Discussion

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

Endoscopy has become an important tool in the diagnosis, staging, treatment, and surveillance of patients with esophageal and EGJ cancers.

Multiple forceps biopsies, 6-8 should be performed to provide sufficient material for histologic and molecular interpretation.

Graham DY Schwartz JT, Cain GD, Gyorkey F. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. Gastroenterology 1982;82:228-231

- We can press the message for adequate tissue sampling, including during serial re-assessments.
- We can do better communicating biomarker needs to pathology colleagues

ESMO GI 2024

Discussion Questions

- Regulatory and reimbursement issues aside, which additional therapy, if any, would you add to chemotherapy as first-line treatment for a 65-year-old patient presenting with metastatic claudin 18.2-positive, HER2-negative, MSS gastric adenocarcinoma, and how does level of PD-L1 expression affect your decision?

- What would you recommend for a patient who is experiencing nausea and vomiting during the initial infusion of zolbetuximab?

Discussion Questions

- Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with newly diagnosed metastatic HER2-positive, MSS gastric adenocarcinoma, and how does level of PD-L1 expression affect your decision?

- Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-positive, MSS gastric adenocarcinoma (PD-L1 CPS ≥1) who experiences disease progression on FOLFOX/trastuzumab/pembrolizumab?

Discussion Questions

- What results do you expect to see from the Phase III DESTINY-Gastric04 study comparing trastuzumab deruxtecan to ramucirumab/paclitaxel as second-line treatment for HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma?

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