

Updates in Thoracic Oncology

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Disclosure of Conflicts of Interest

Tom Stinchcombe, MD, has the following financial relationships to disclose:

Activity	Company
Advisory board or data monitoring committee	EMD Serono, Novartis, Janssen Oncology, Turning Point Therapeutics, Sanofi/Aventis, GlaxoSmithKline, Genentech/Roche, Daiichi Sankyo/Astra Zeneca, Takeda
Research Funding	AstraZeneca, Takeda, Takeda, Seattle Genetics, Mirati Therapeutics, Genentech/Roche (Institution)

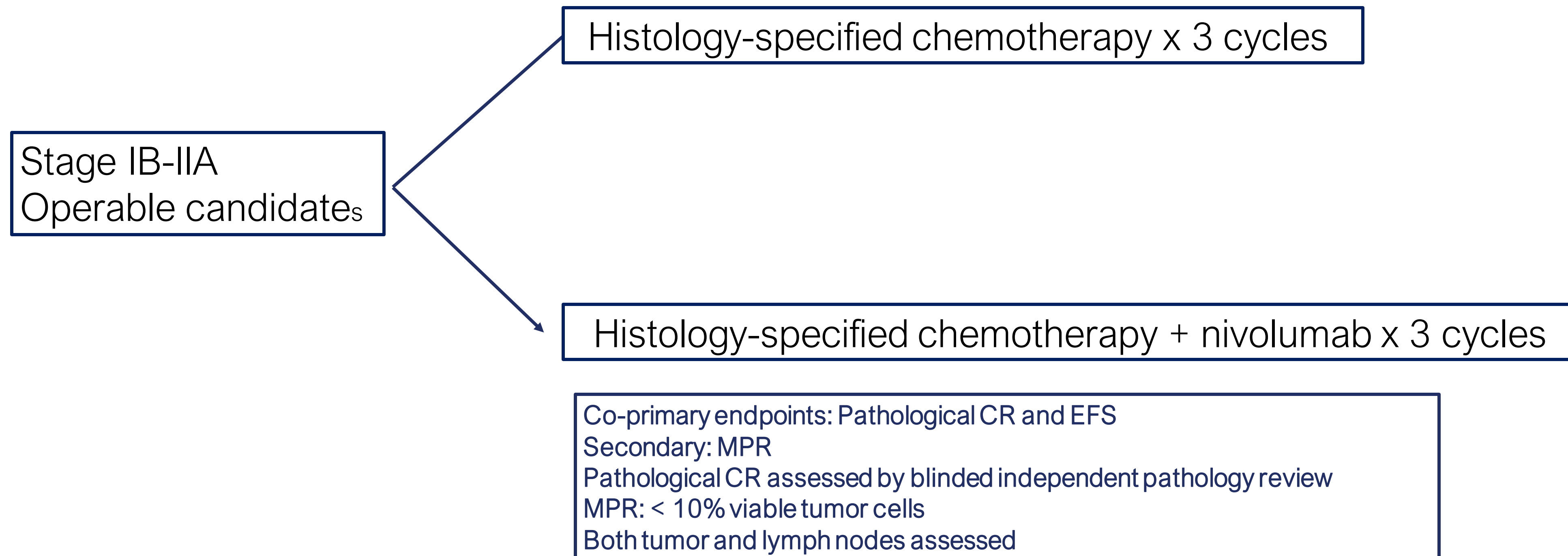
Learning Objectives

- Understand recent systemic therapy for surgically resectable non-small cell lung cancer
- Summarize the long-term benefit from chemoradiotherapy followed durvalumab
- Discuss recently approved targeted therapies for *KRAS* G12C and *EGFR* exon 20 insertions

Topics

- Integration of immunotherapy into resectable non-small cell lung cancer
 - Checkmate 0816: Phase 3 trial of pre-operative chemotherapy +/- nivolumab
 - Evaluation of prognostic markers
 - Follow-up on IMpower 010: Adjuvant atezolizumab
- Stage 3 NSCLC: Long-term follow-up of PACIFIC trial
- Targeted therapies:
 - *KRAS* G12C: novel agents and combination therapies
 - *EGFR* exon 20 insertions

Checkmate 816: Phase 3 trial of neoadjuvant chemotherapy +/- ICI



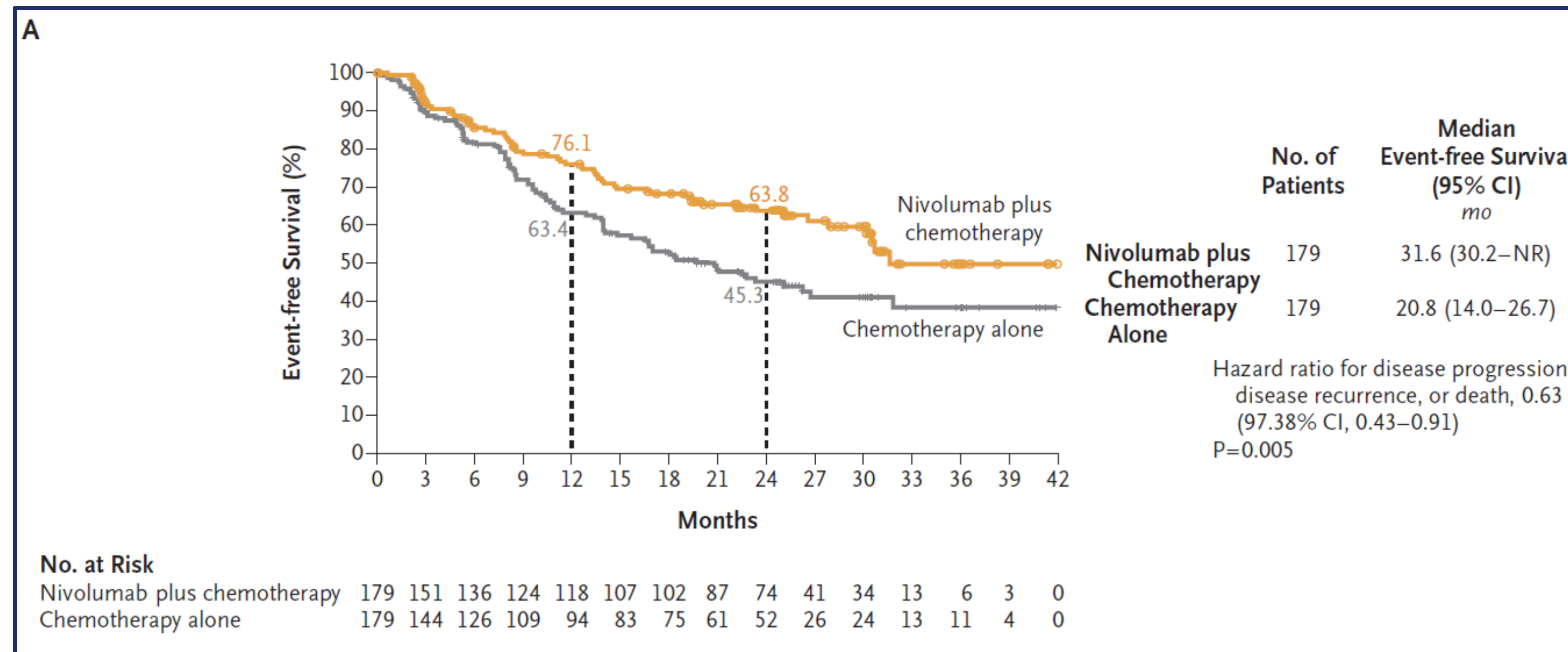
Forde et al NEJM 2022

Select patient characteristics and baseline demographics

Patient characteristics	Chemotherapy (n=179)	Chemotherapy + nivo (n=179)
Median age (range)	65 (34-84)	64 (41-82) years
Female sex	52 (29.1%)	51 (28.5%)
Histology		
Squamous	95 (53%)	87 (48.6%)
Non-squamous	84 (46.9%)	92 (51.4%)
ECOG 0/1	117 (65.4%)/62 (34.0%)	124 (69.3%)/55 (30.7%)
Smoking history		
Never	20 (11.2%)	19 (10.6%)
Current or former	115 (88.3%)	160 (89.4%)
Stage		
IB or II	62 (34.6%)	65 (36.3%)
IIIA	115 (64.2%)	113 (63.1%)
Platinum therapy		
Cisplatin	134 (74.9%)	124 (69.3%)
Carboplatin	33 (18.4%)	39 (21.8%)

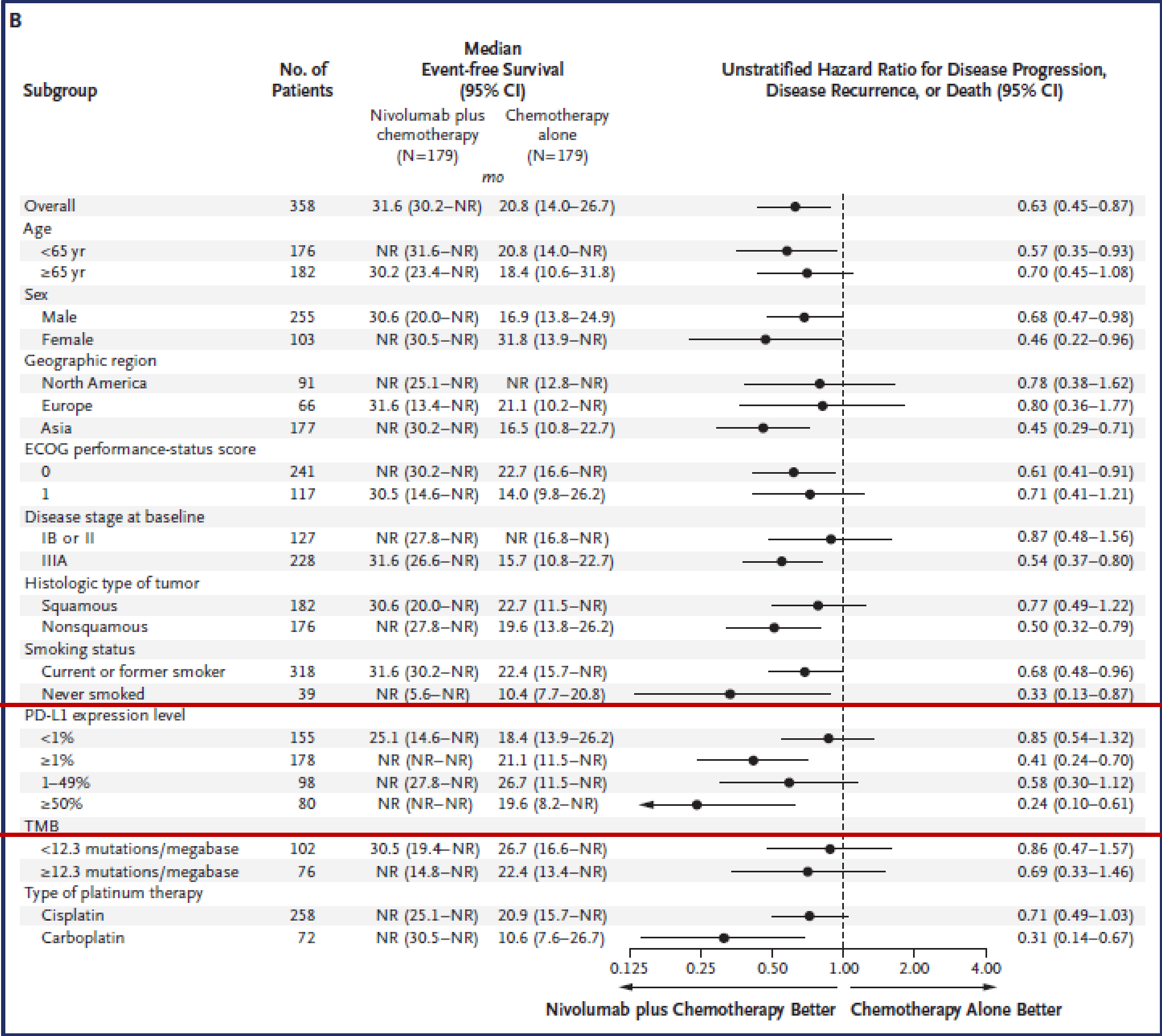
Forde et al NEJM 2022

KM for event-free survival



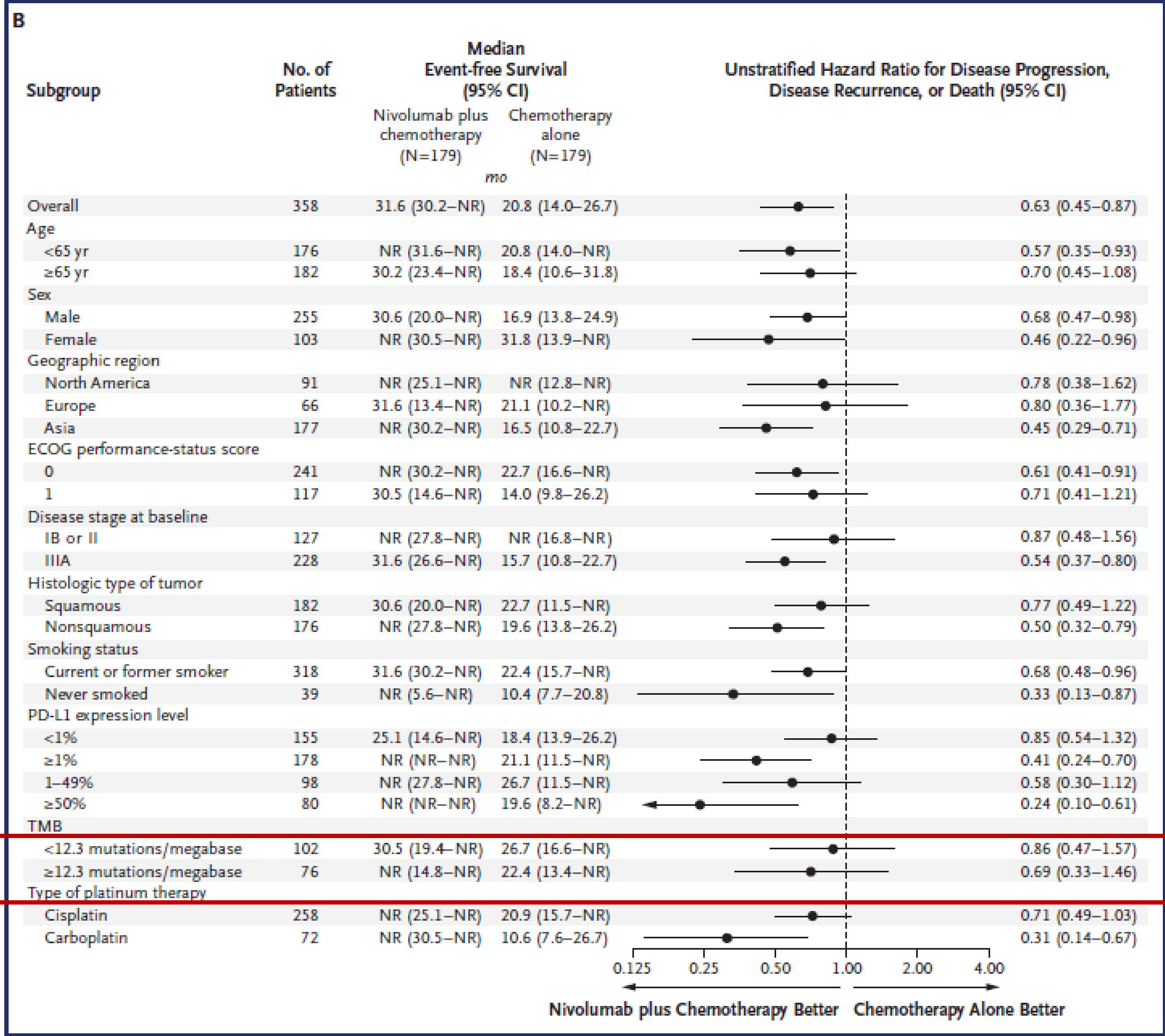
Forde et al NEJM 2022

EFS subgroup analyses



Forde et al NEJM 2022

EFS subgroup analyses



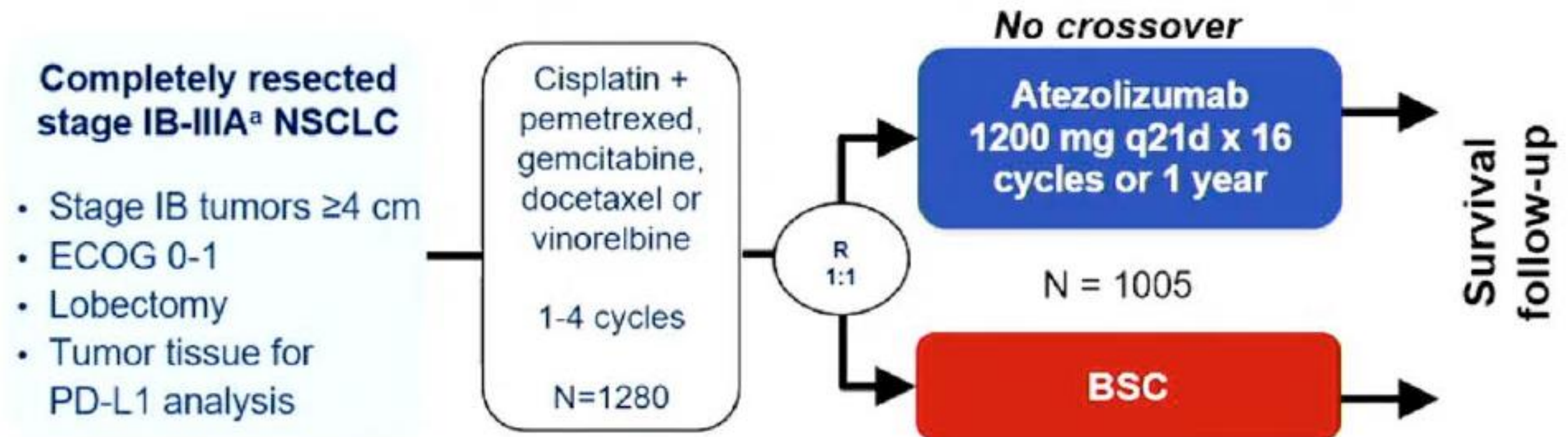
Forde et al NEJM 2022

BMS 816: secondary outcomes

	Chemotherapy (n=179)	Chemotherapy + nivolumab (n=179)	
Path CR	2.2%	24%	OR: 13.94 95% CI: 3.49-55.75, p<0.0001
MPR	8.9%	36.9%	OR: 5.79 95% CI: 3.16-10.26
Grade 3 or 4 AE	37%	34%	
Surgical resection	75%	83%	
R0 resection	78%	83%	

Forde et al NEJM 2022

IMpower010: Phase III: Randomised trial of atezolizumab vs BSC in early-stage NSCLC



Stratification factors

- Sex | Stage | Histology | PD-L1 status

Primary endpoint

- Investigator-assessed DFS tested hierarchically

Key secondary endpoints

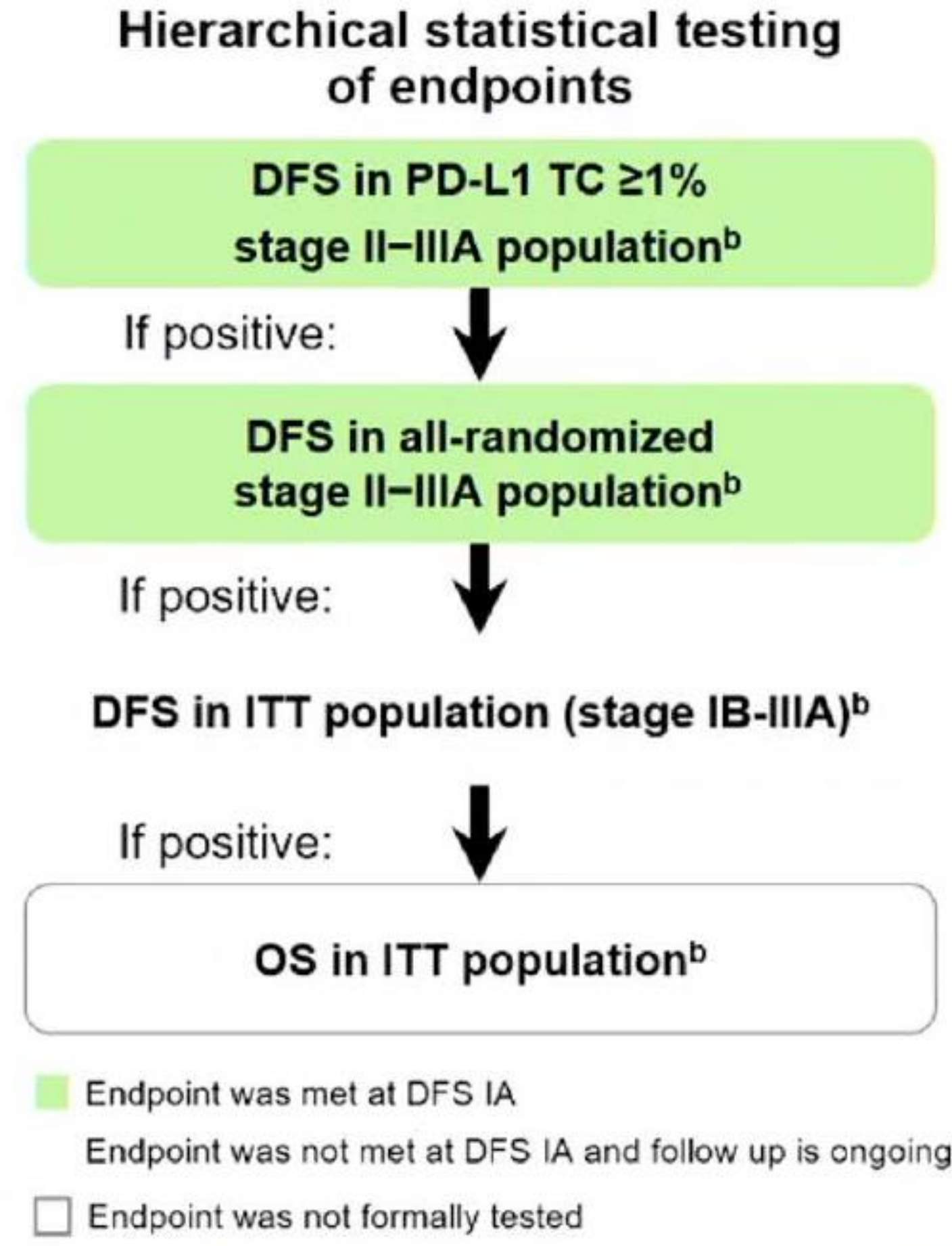
- OS in ITT | DFS in PD-L1 TC $\geq 50\%$ | 3-yr and 5-year DFS

Key exploratory endpoints

- OS biomarker analyses

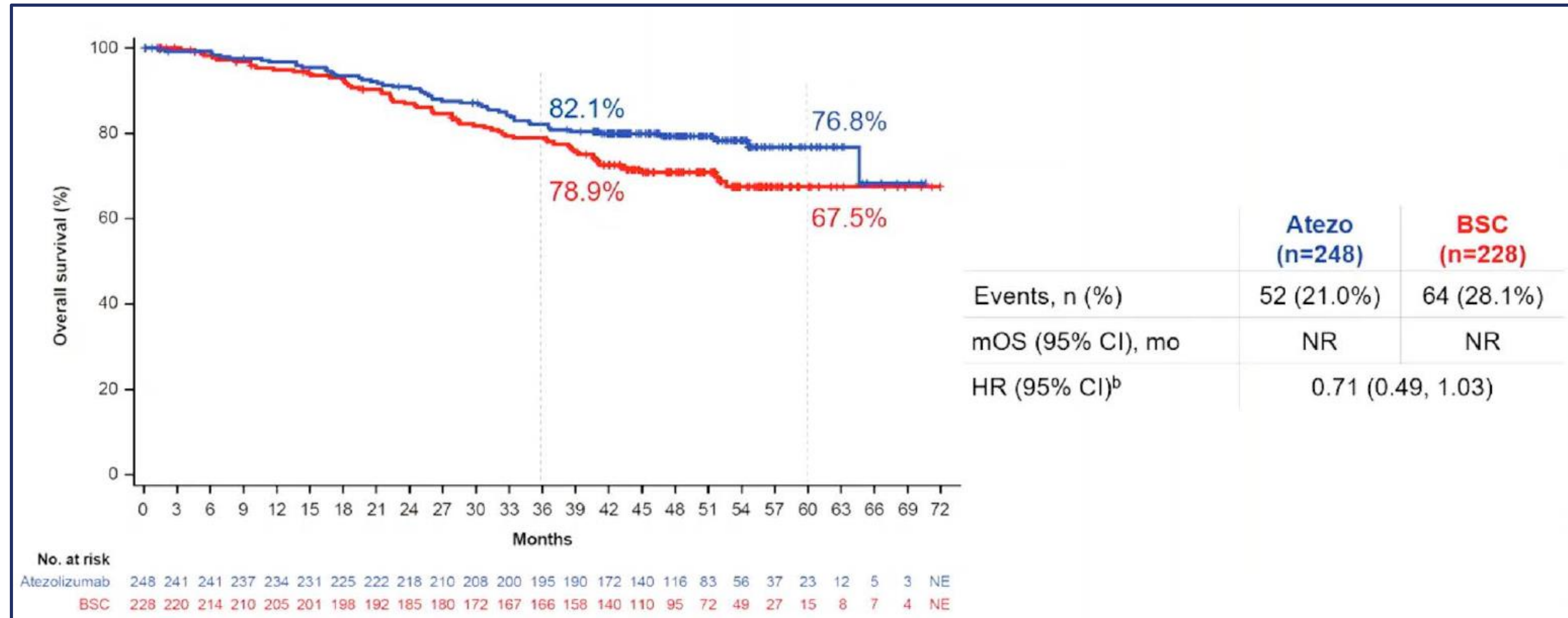
Clinical cutoff: 18 April 2022. Both arms included observation and regular scans for disease recurrence on the same schedule. ECOG, Eastern Cooperative Oncology Group, q21d, every 21 days.

^a Per UICC/AJCC staging system, 7th edition. ^b Two-sided $\alpha=0.05$.



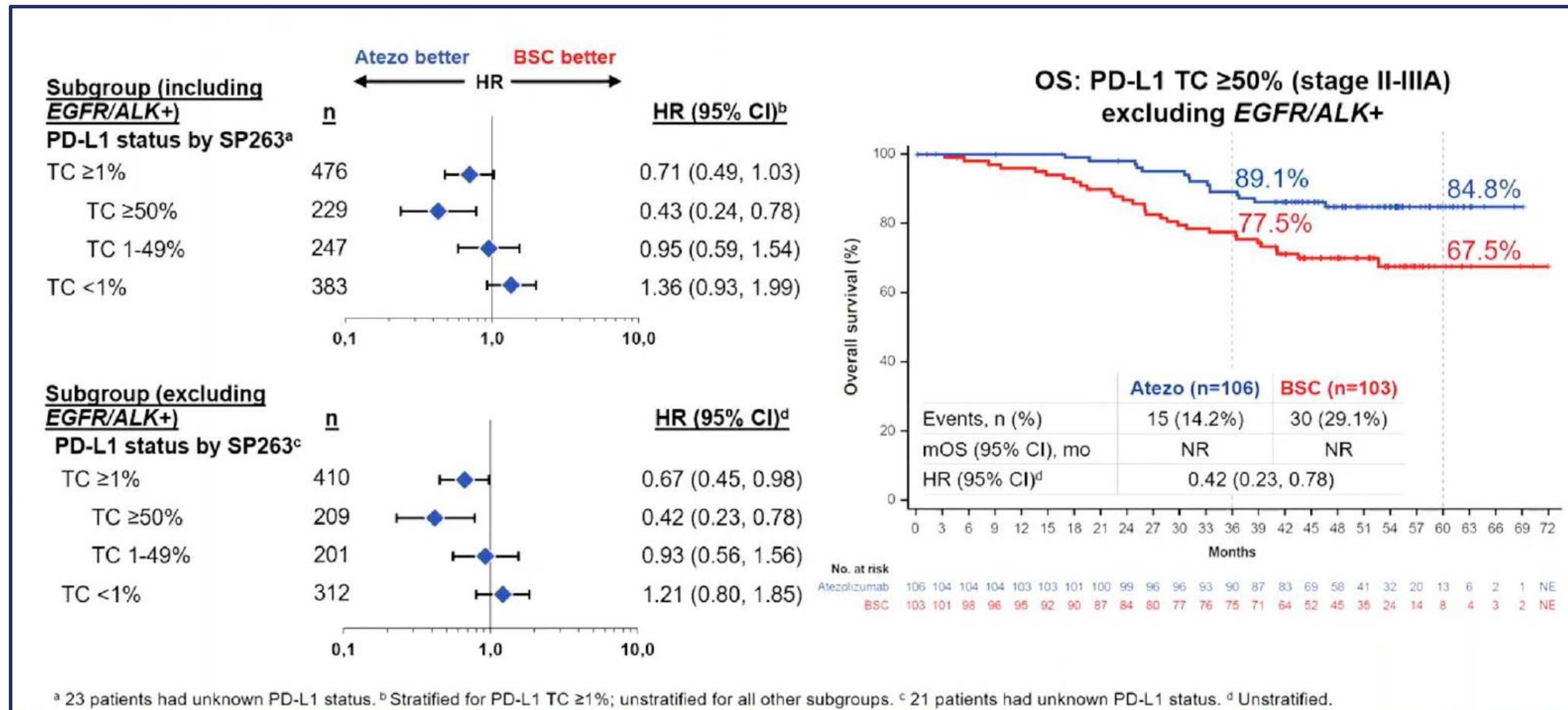
Felip et al WCLC 2022

Results of OS IA: PD-L1 TC \geq 1% (stage II-IIIa) (data cutoff: 18Apr '22, median follow-up: 46 months)



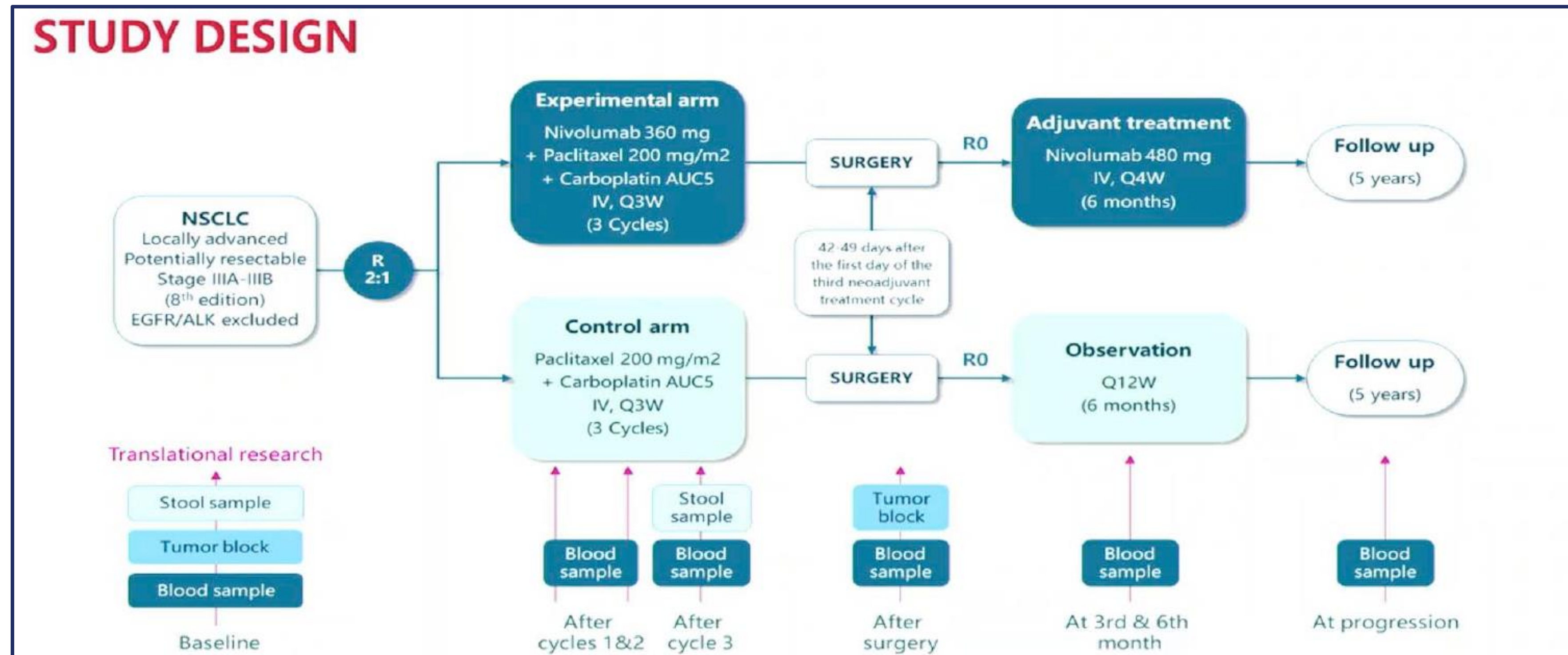
Felip et al WCLC 2022

OS by biomarker status (stage II-III A): (data cutoff: 18 Apr '22)



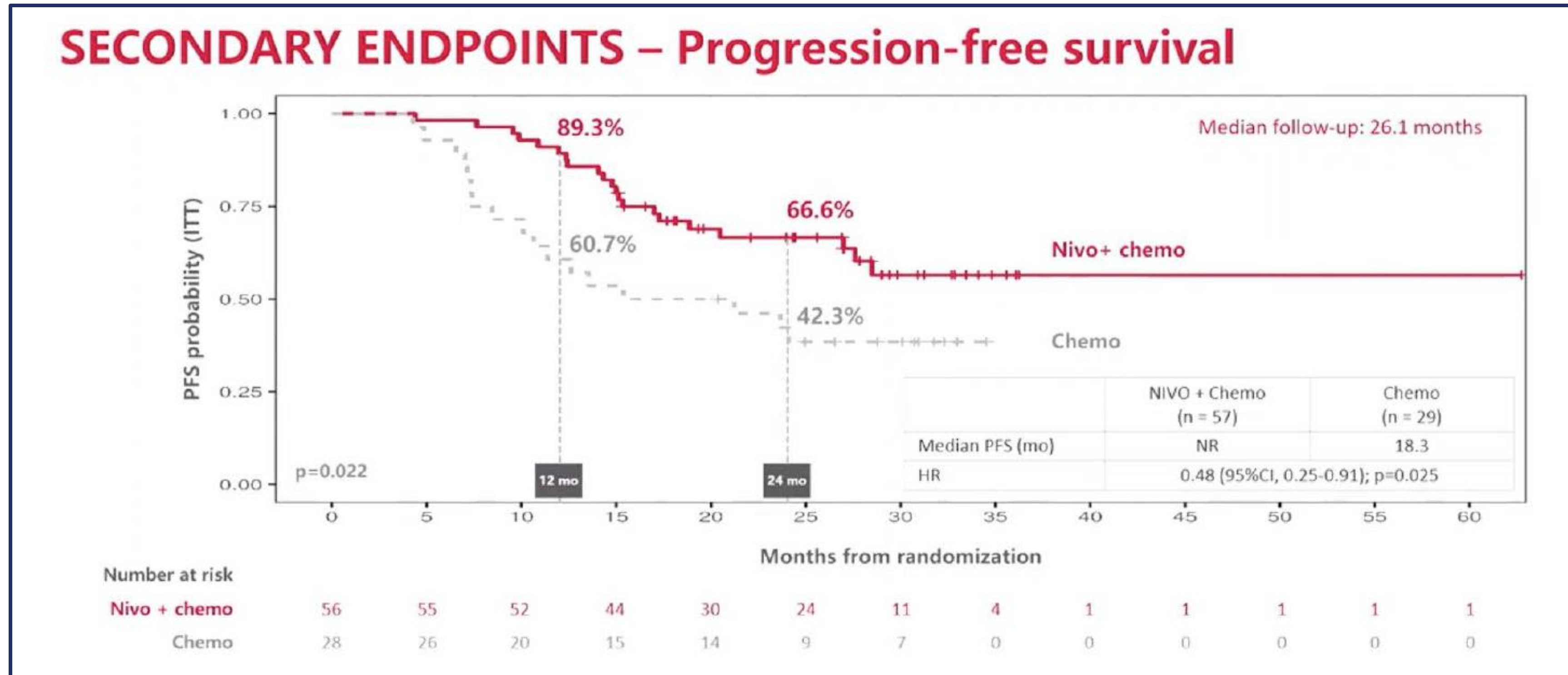
Felip et al WCLC 2022

Progression-free survival and overall survival results from the phase 2: NADIM II trial



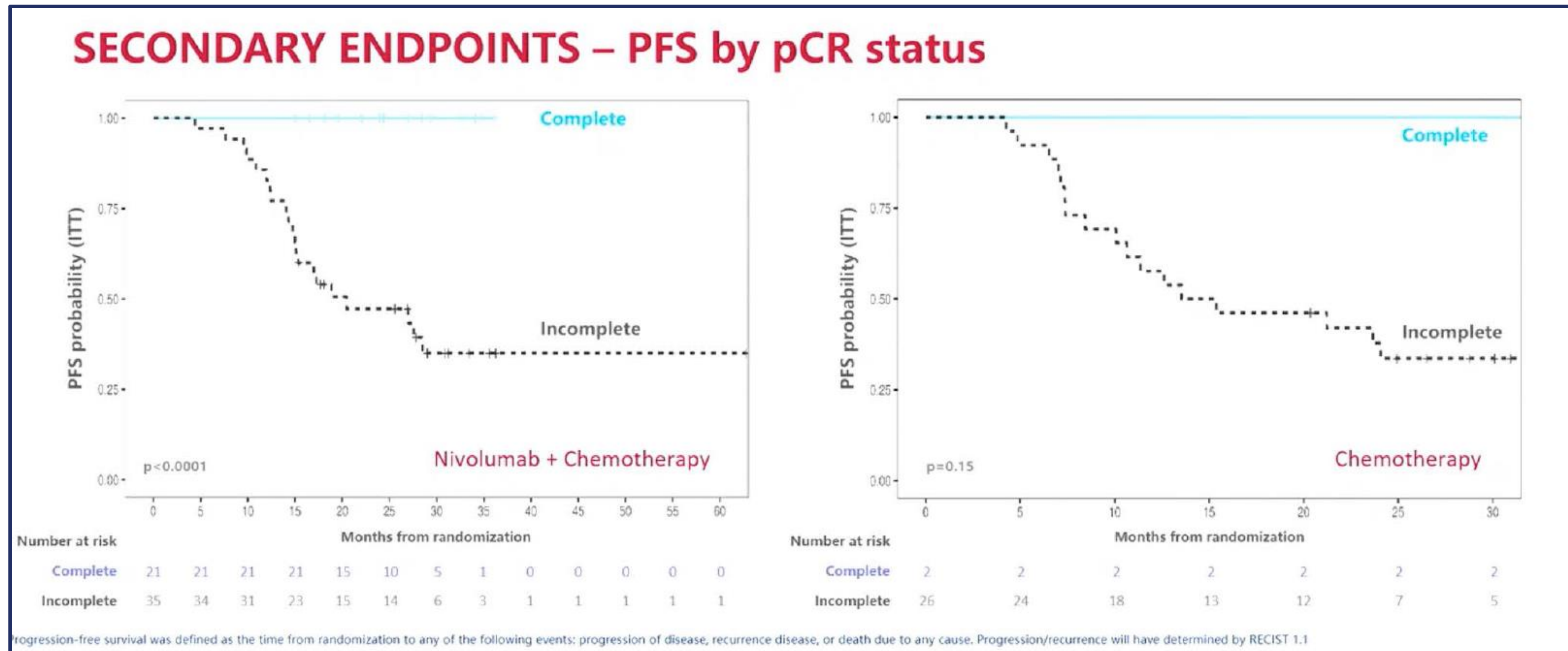
Provencio et al WCLC 2022

Progression-free survival and overall survival results from the phase 2: NADIM II trial



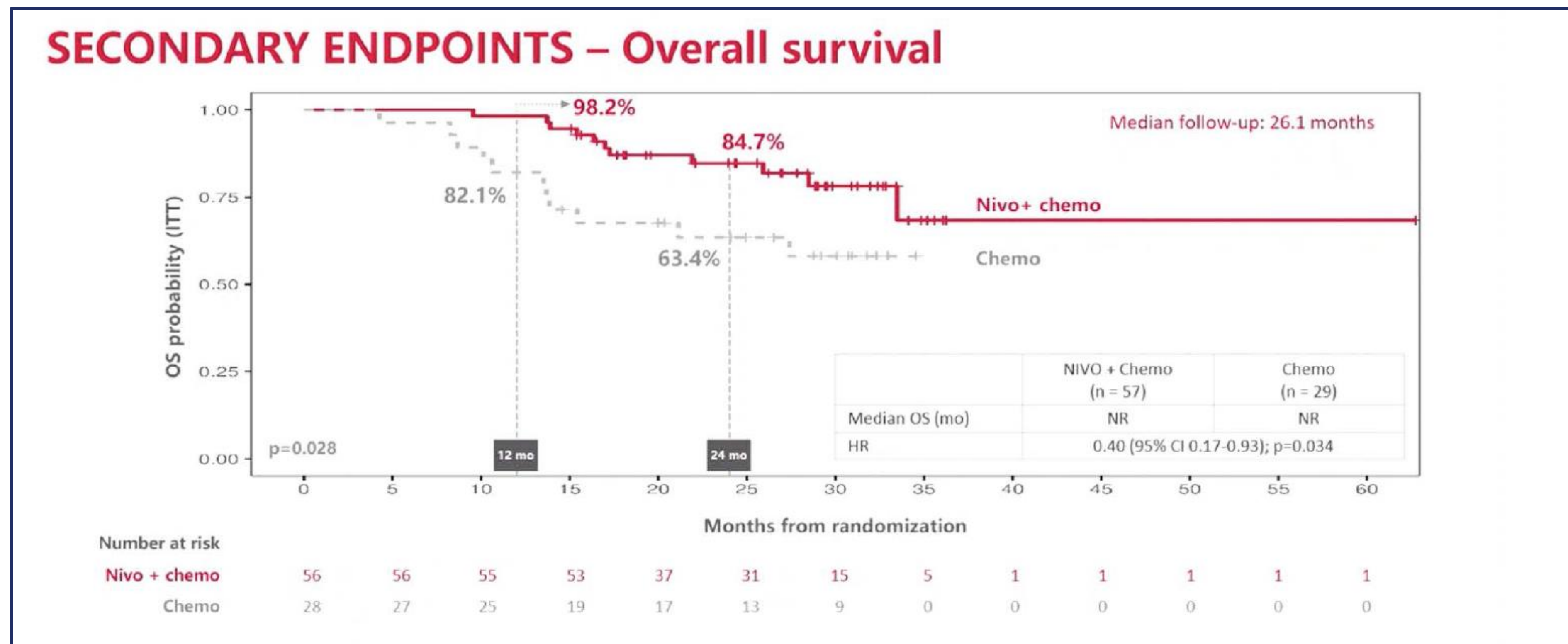
Provencio et al WCLC 2022

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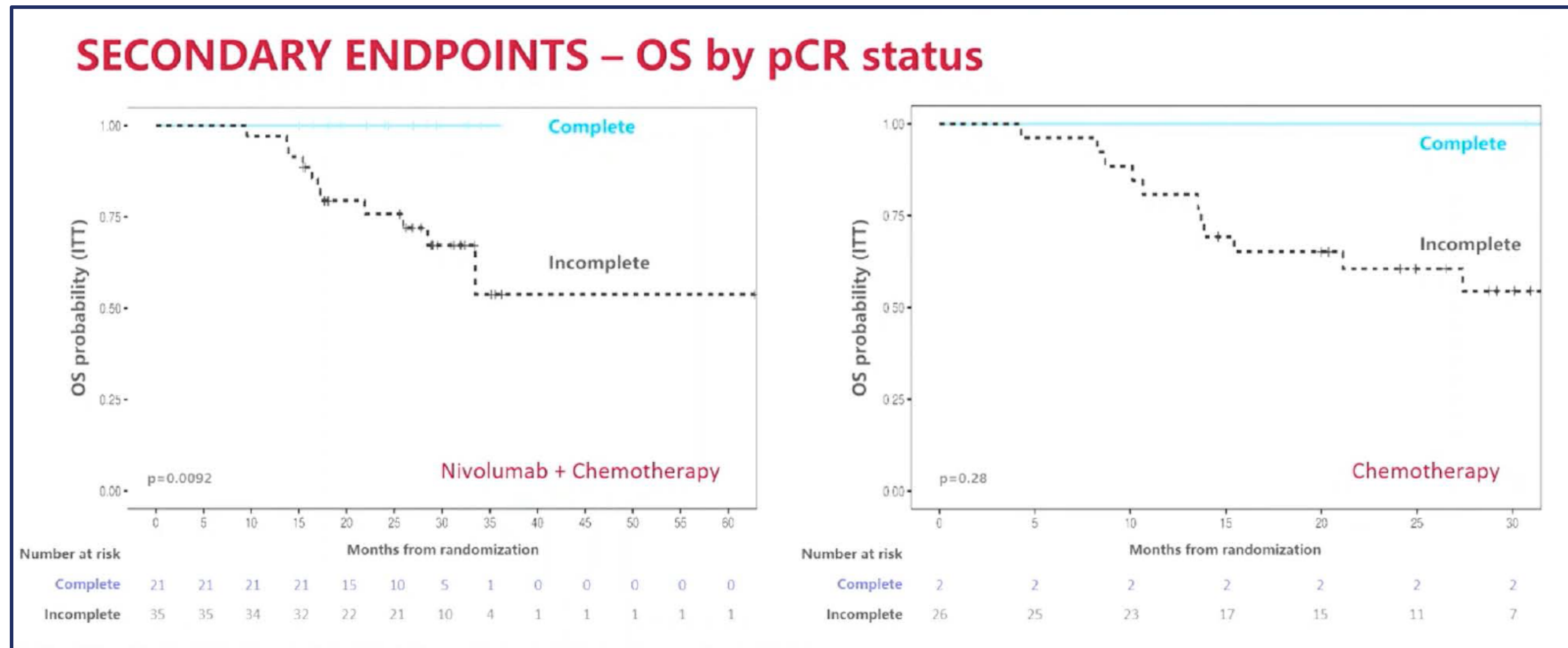
Provencio et al WCLC 2022

Progression-free survival and overall survival results from the phase 2: NADIM II trial



Provencio et al WCLC 2022

Progression-free survival and overall survival results from the phase 2: NADIM II trial

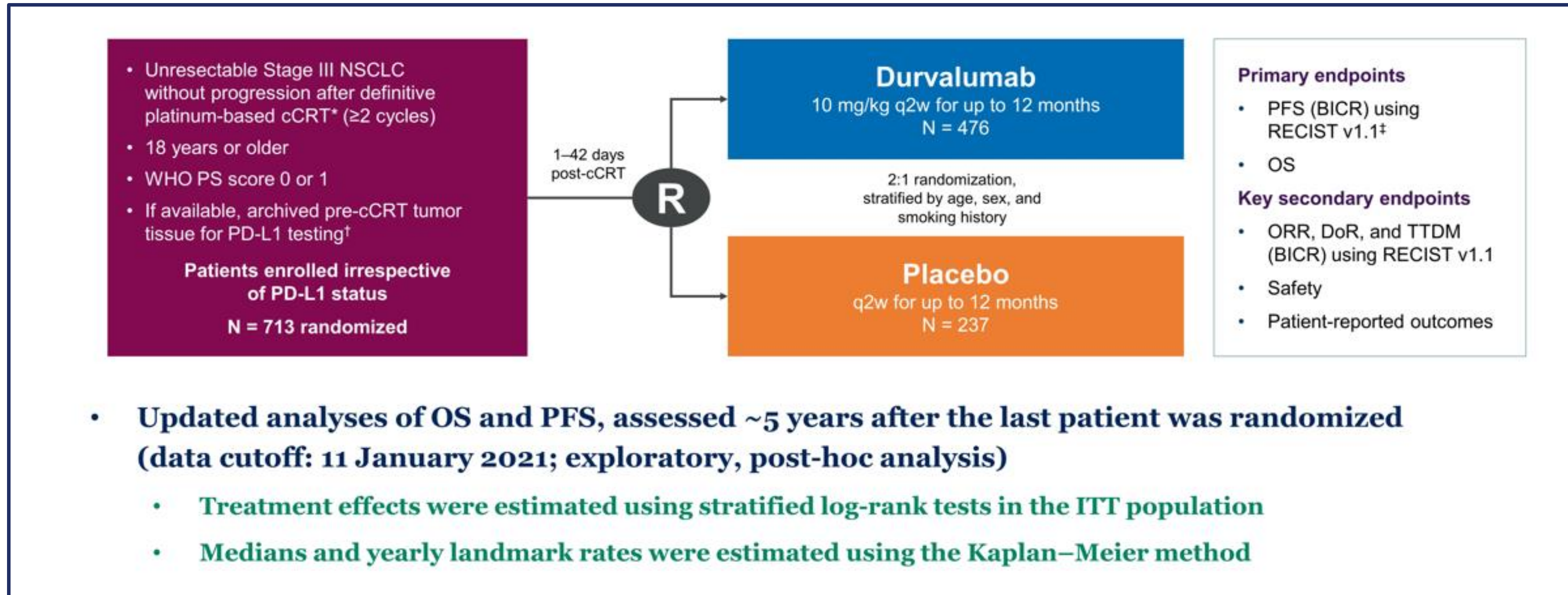


Provencio et al WCLC 2022



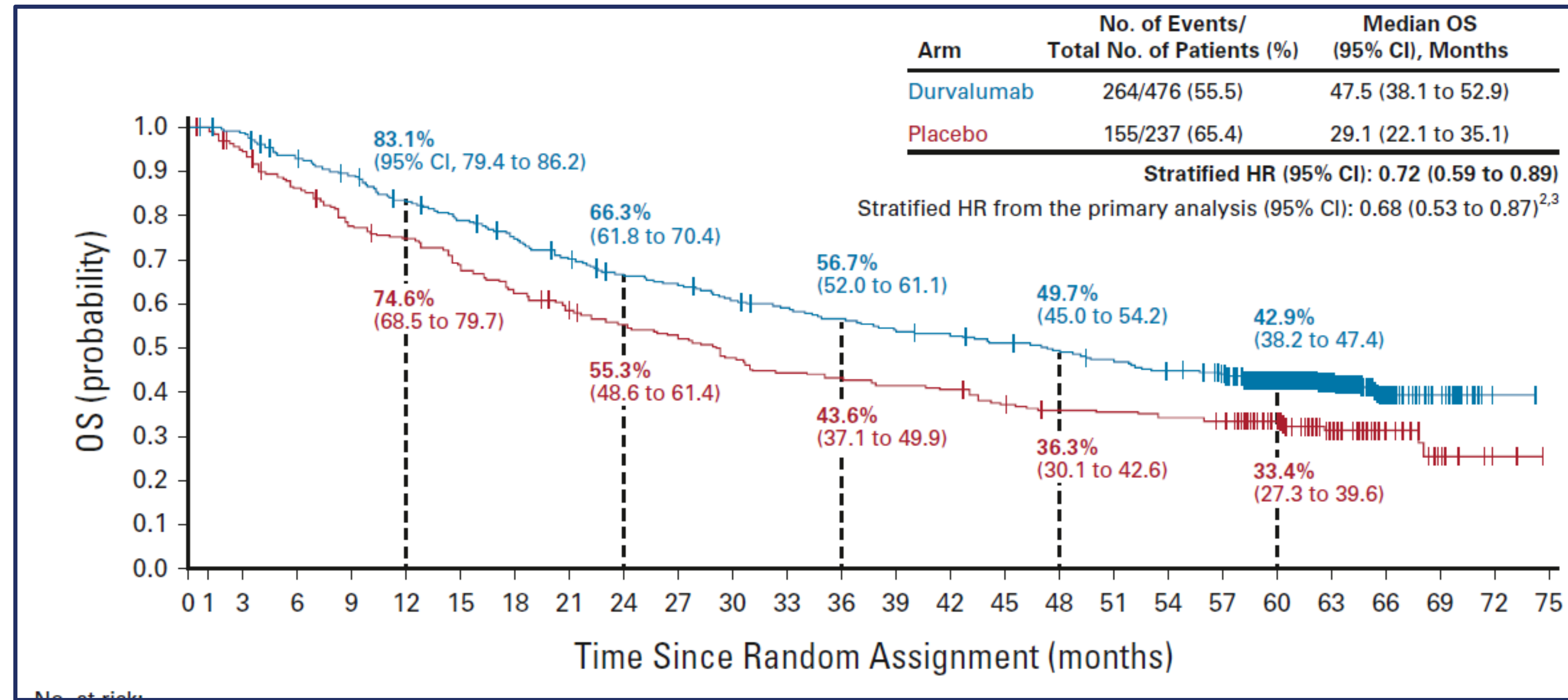
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PACIFIC: Study schema



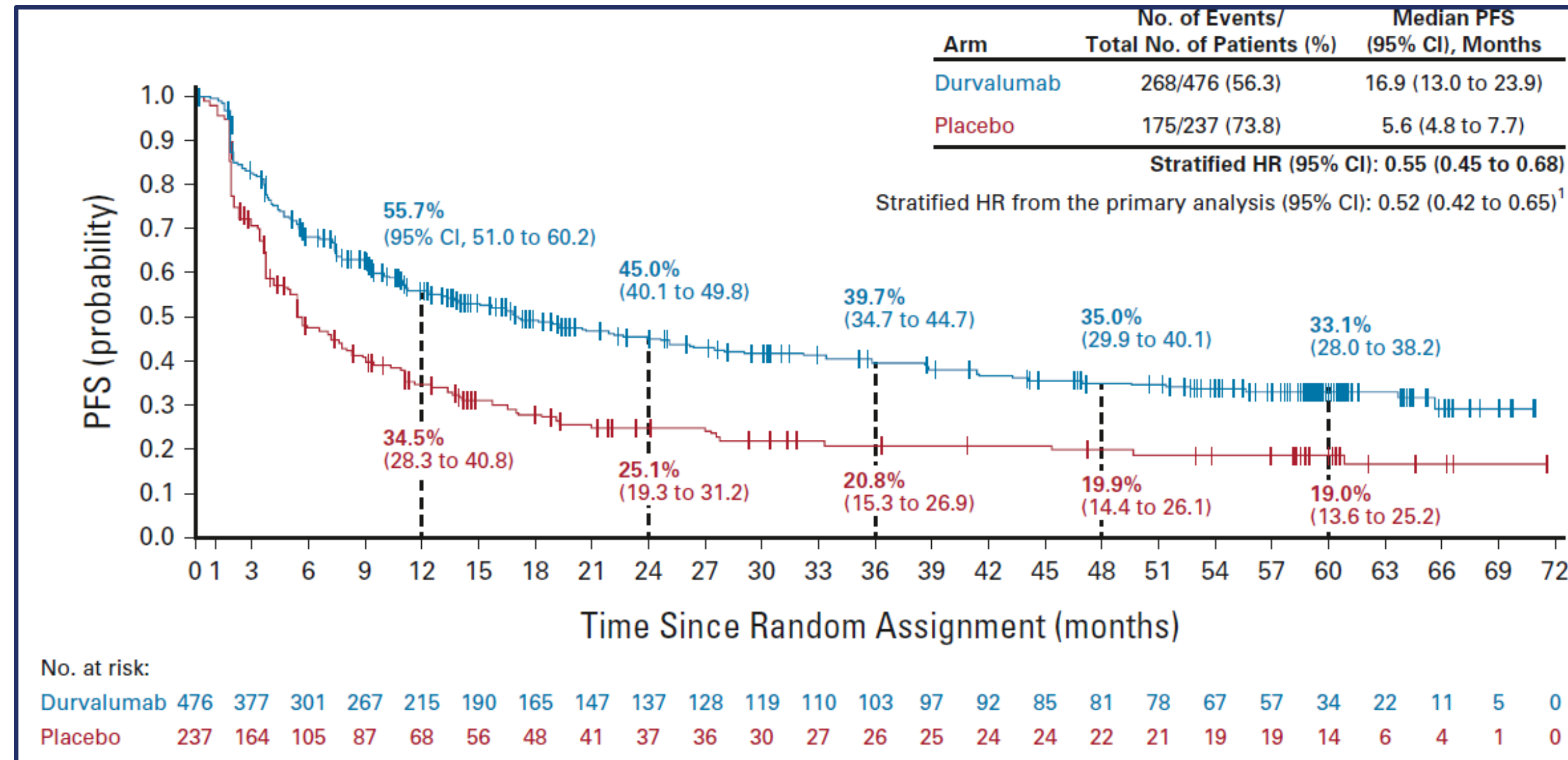
Spigel et al JCO 2022

PACIFIC trial: 5-year follow-up: PFS



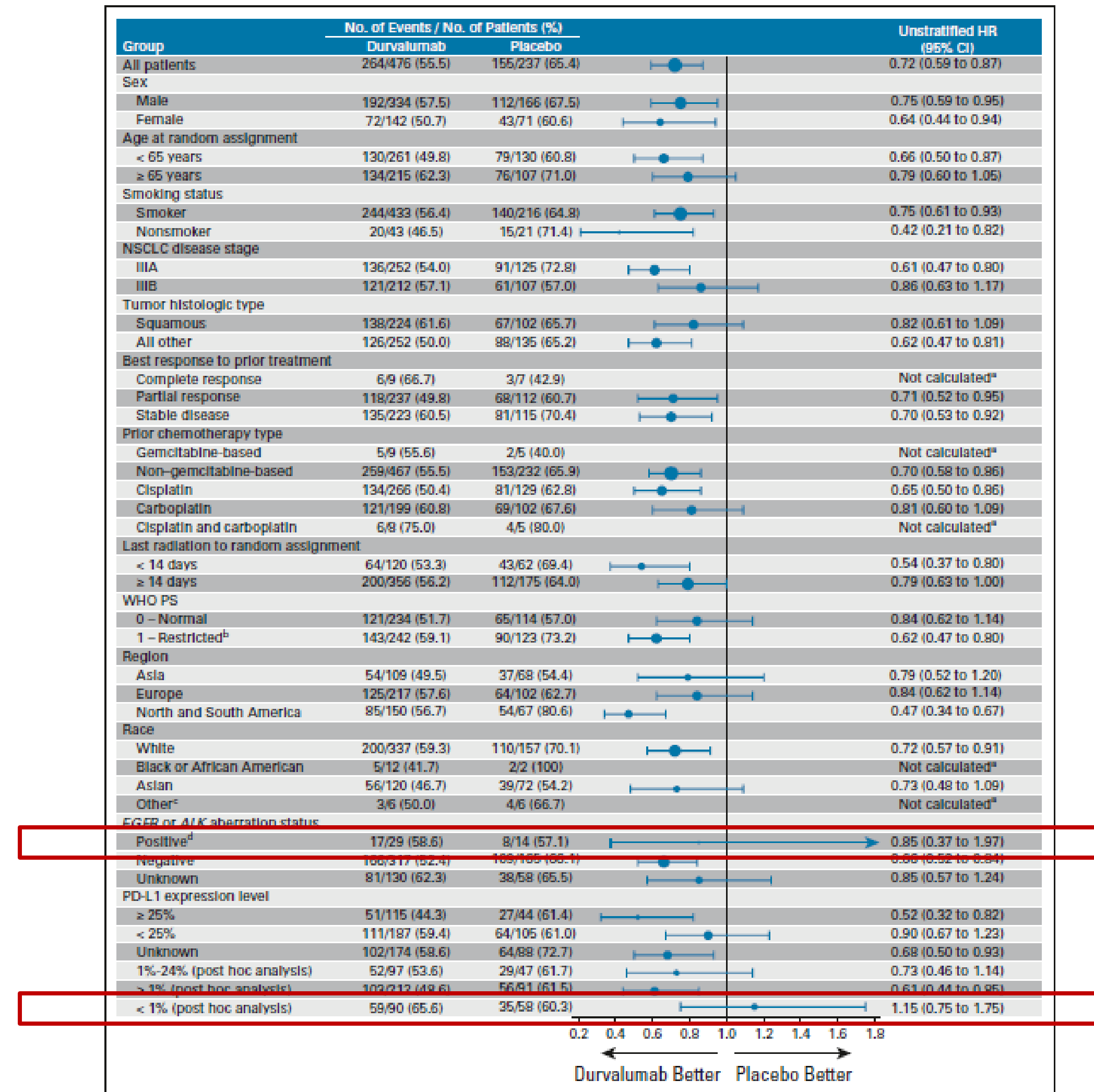
Spigel et al JCO 2022

PACIFIC trial: 5-year follow-up: PFS



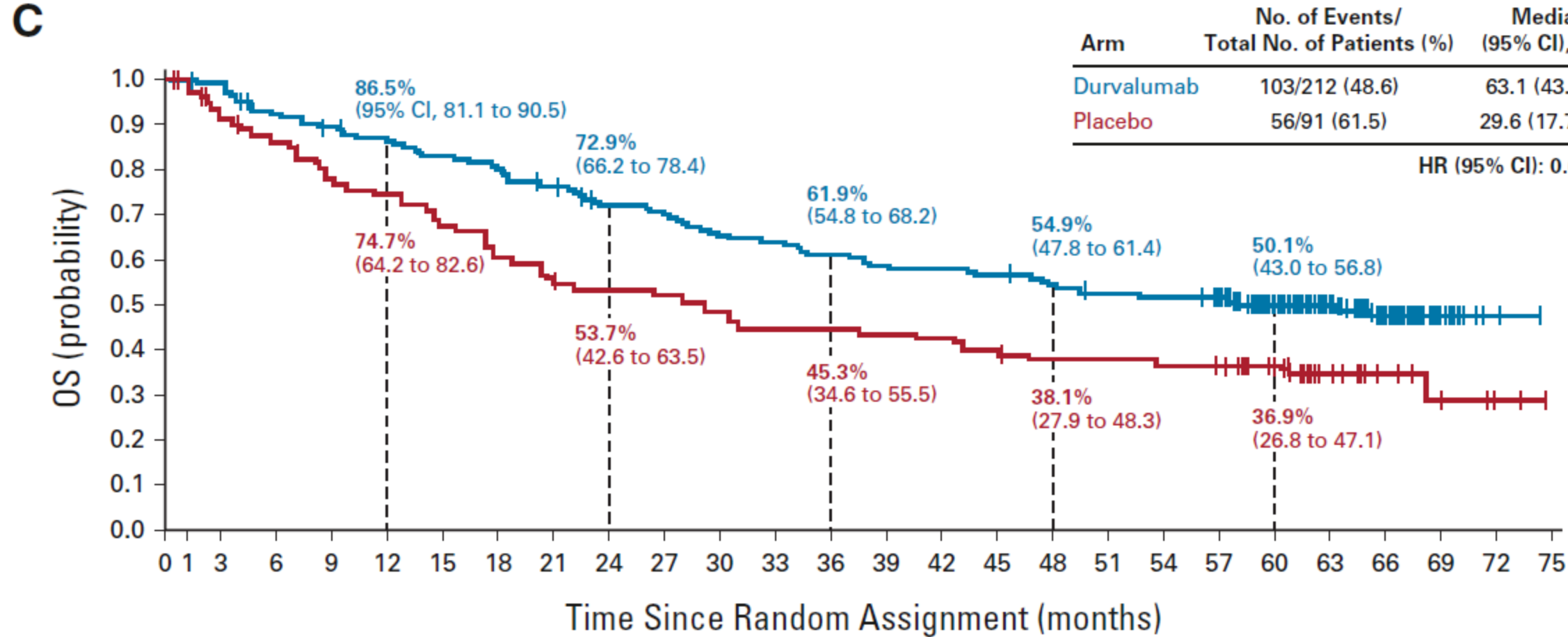
Spigel et al JCO 2022

Overall survival analysis: subgroups



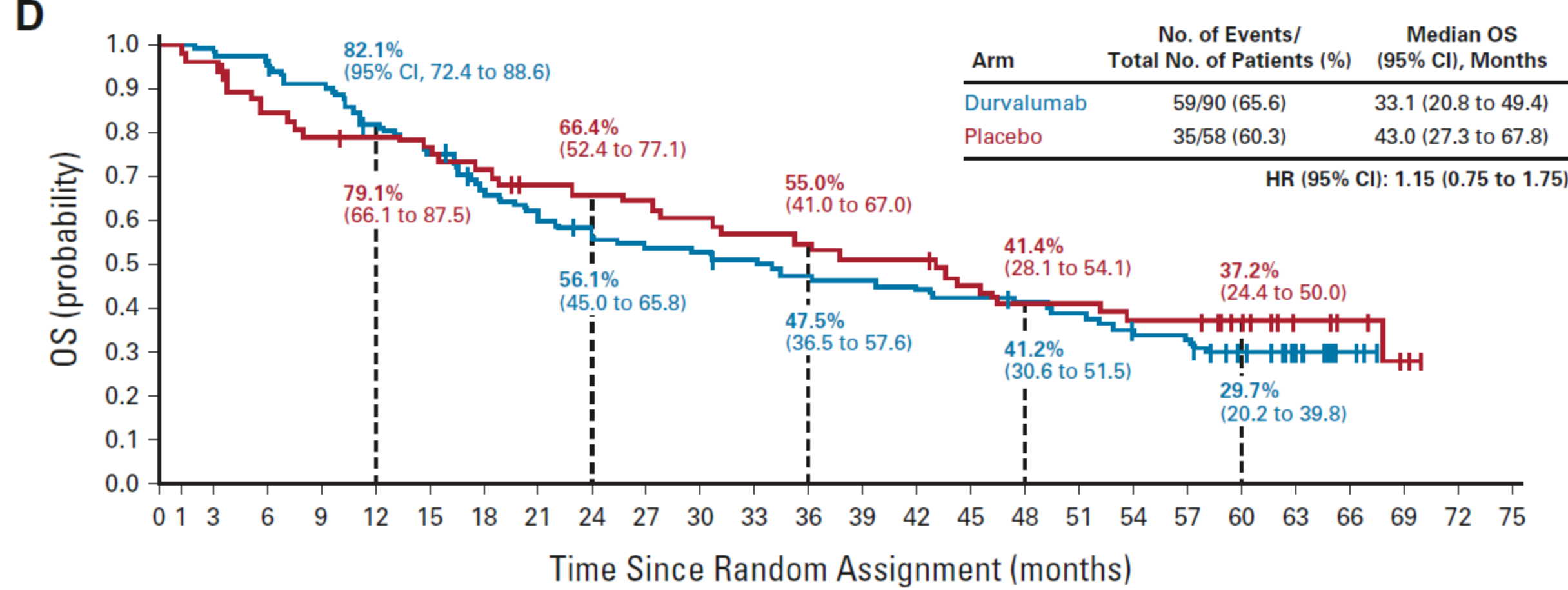
Spigel et al JCO 2022

KM for PD-L1 <1% and ≥ 1%



No. at risk:

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
Durvalumab	212	208	193	186	178	171	165	156	146	141	132	129	124	118	117	114	109	105	103	98	74	52	29	14	1	0
Placebo	91	81	75	67	64	58	52	47	45	44	41	38	38	37	36	33	31	31	30	29	24	14	8	5	2	0



No. at risk:

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
Durvalumab	90	88	84	81	72	65	56	50	46	44	43	41	38	37	35	34	33	31	27	25	18	11	3	0	0	0
Placebo	58	56	48	45	44	43	40	36	35	34	32	30	29	27	27	23	20	20	18	18	14	7	5	2	0	0

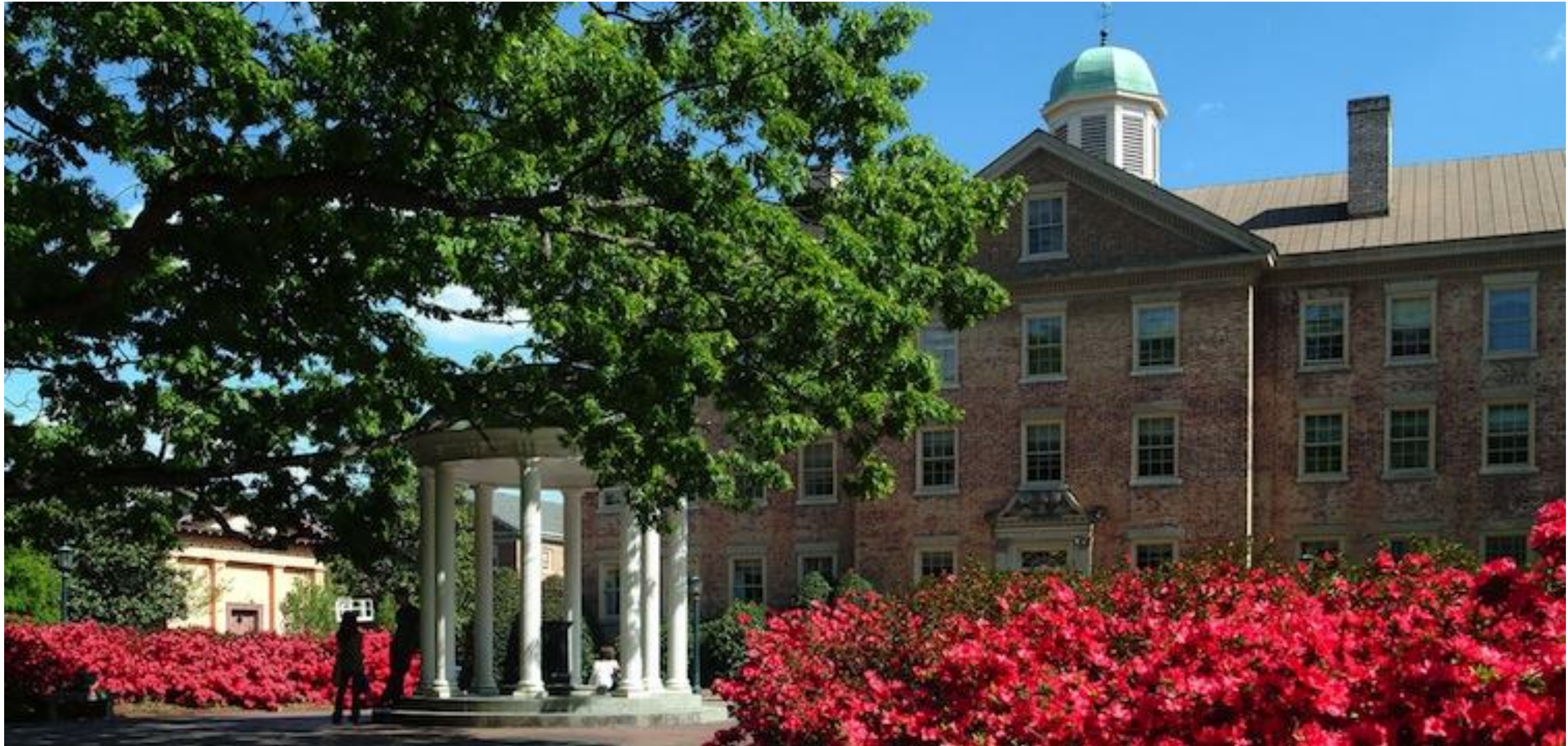
PD-L1 ≥ 1%

PD-L1 < 1%

Samples unavailable on 37% of patients

Spigel et al JCO 2022

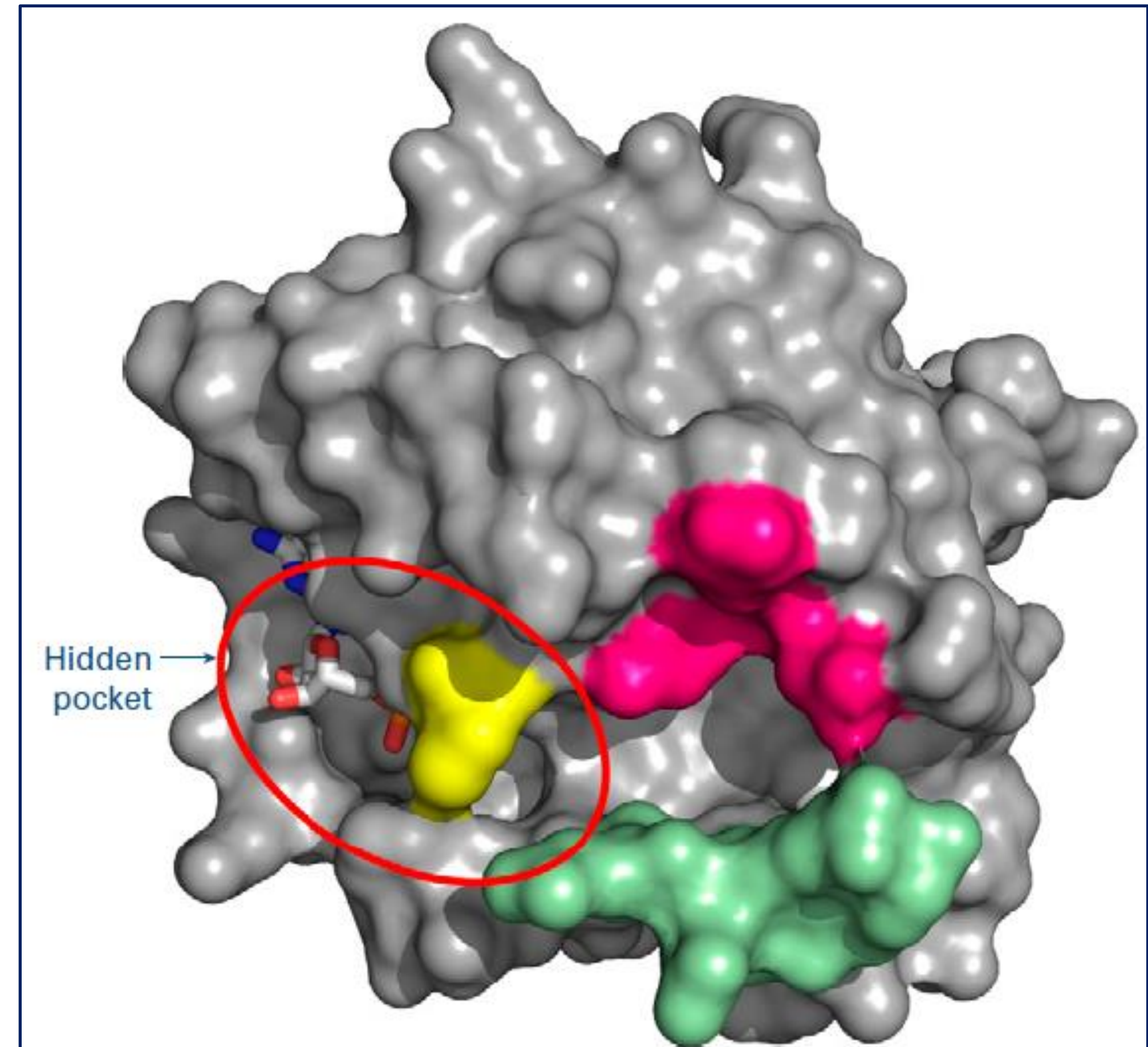




Targeted therapies

KRAS G12C mutations

- *KRAS* mutations 30% of mutations in NSCLC adenocarcinoma
- *KRAS* G12C 40-50% of *KRAS* mutations
- Covalent binding to cysteine residue in hidden pocket only present in inactive state
- Maintains *KRAS* protein in GDP bound inactive state
- Multiple agents in development



Burns et al JCO 2020

Krystal-1: Phase 2 Non-Small Cell Lung Cancer

- Stage 4 NSCLC
- KRAS G12C mutation
- Previous treatment PD-1/L-1



Adagrasib 600 mg BID
(capsule, fasted)

Primary objective: ORR by BICR
Secondary: DoR, PFS, safety and OS

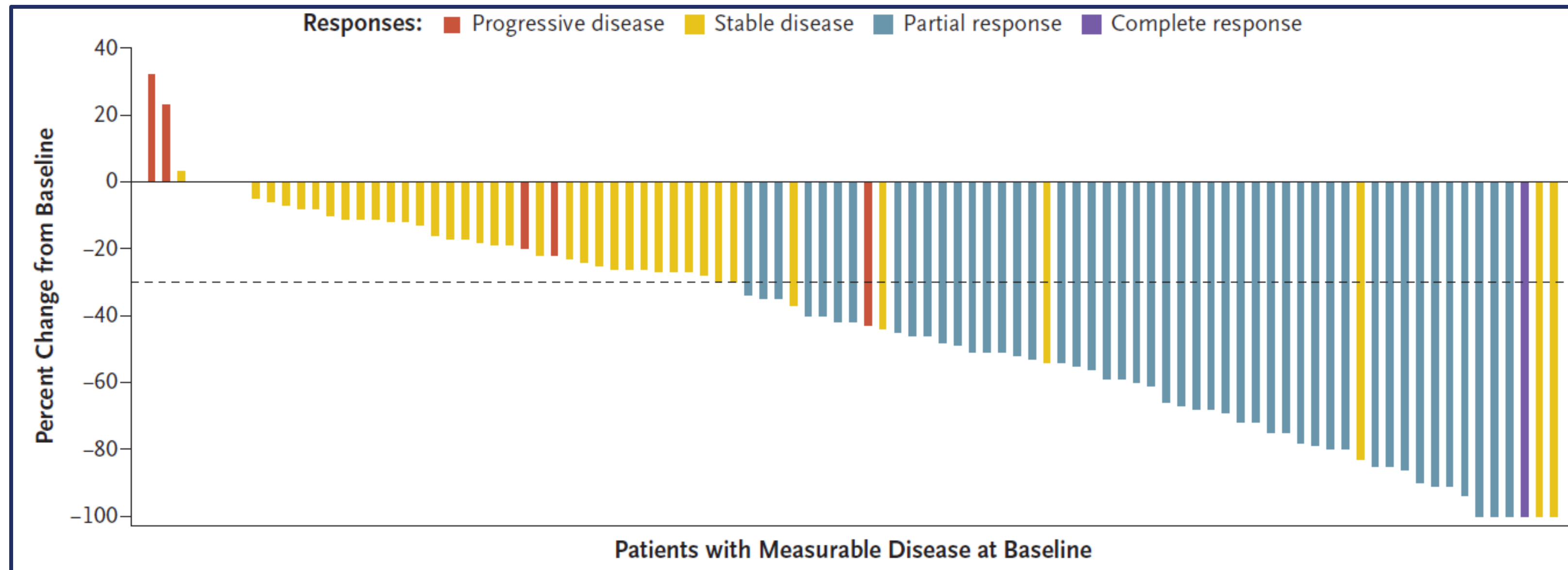
Janne et al NEJM 2022

Select patient characteristics and baseline demographics

Patient characteristics	Total =116
Median age (range)	64 (25-89) years
Female sex	65 (56%)
Race	
White	97(84%
Black or African American	9 (8%)
Asian o other	5 (4%)/5 (4%)
ECOG 0/1	18 (16%)/ 97 (84%)
Smoking history	
Never	5(4%)
Current or former	11(10%)/97 (84%)
Prior lines of therapy	
1	50 (43%)
2	40 (35%)
3	26 (22%)
Prior platinum therapy and ICI	
Prior platinum alone	2(2%)
Both	114 (98%)

Janne et al NEJM 2022

Objective response rate

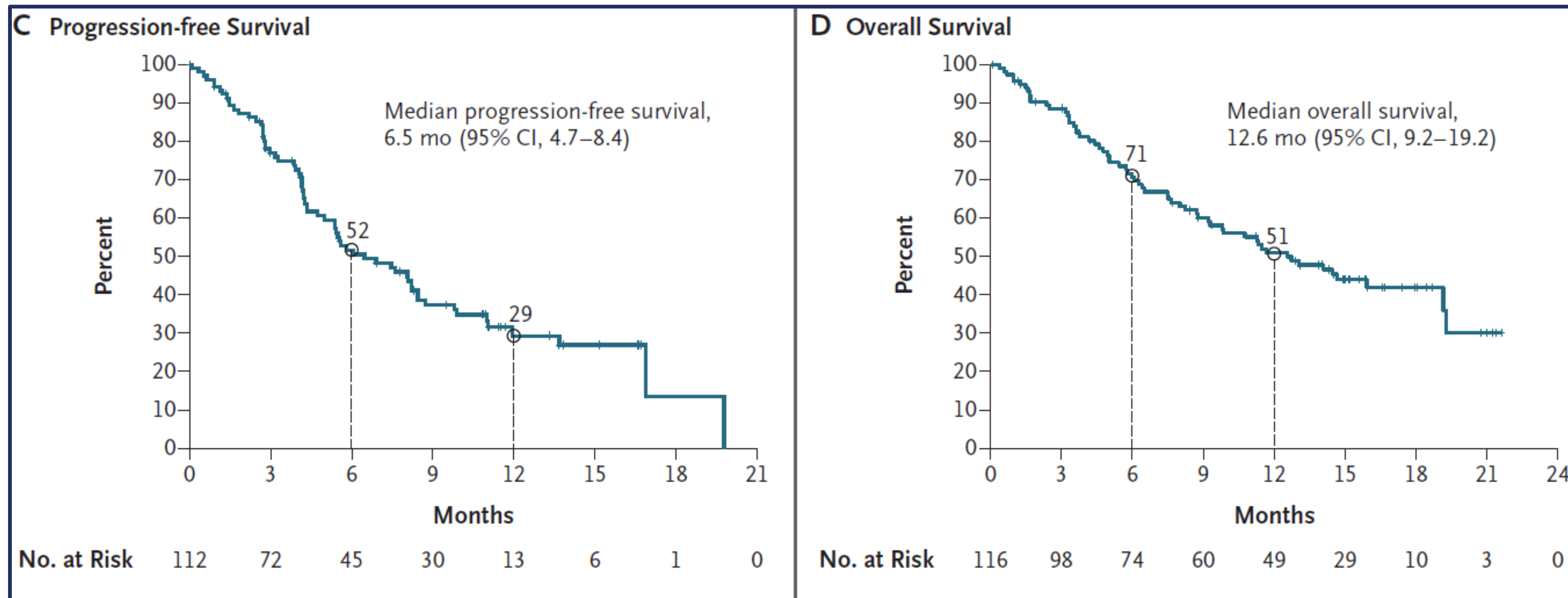


ORR: 42.9% (95% CI: 33.5-52.6)

DoR: 8.5 months (95% CI: 6.2-13.8)

Janne et al NEJM 2022

KM curves for PFS and OS



Janne et al NEJM 2022

Sotorasib and adagrasib efficacy

Efficacy parameter	Sotorasib	Adagrasib
ORR	37.1% (95% CI: 28.6-46.1)	43% (95% CI: 33.5-52.6)
DoR	11.1 (6.9-NE) (n=46)	8.5 (95% CI: 6.2-13.8) (n=48)
PFS (median)	6.8 (95% CI: 5.1-8.2)	6.5 (95% CI: 4.7-8.4)

Janne et al NEJM 2022, Skoulidis et al NEJM 2021

Select Adverse Events for adagrasib and sotorasib

Adverse event	Adagrasib		Sotorasib	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any adverse event	116 (100)	95 (81.9%)	125 (99.2%)	See below
Treatment dose reduction or interruption	96 (82.8%)	----	28 (22.2%)	20 (15.9%)
Treatment discontinuation	18 (15.5%)	-----	9 (7.1%)	5 (4%)
Diarrhea	82 (70.7%)	1 (0.9%)	40 (31.7%)	5 (4%)
Nausea	81 (69.8%)	5 (4.3%)	24 (19.0%)	0
ALT increase	33 (28.4%)	6 (5.2%)	19 (15.1%)	8 (6.3%)
AST increase	31 (26.7%)	6 (5.2%)	19 (15.1%)	7 (5.6%)
Fatigue	14 (11.1%)	0	14 (11.1%)	0
QT prolongation	23 (19.8%)	7 (6.0%)	3 (2.4%)	

The worst grade of adverse event was grade 3 in 53 patients (42.1%), grade 4 in 4 patients (3.2%), and grade 5 in 20 patients (15.9%).

Sotorasib pharmacokinetics and dose study

Dose (mg)	N	T _{max} (hr)	C _{max}	AUC _{0-24hr}	T _{1/2}
180	6	0.73	6.44	31.7	5.13
360	24	1.0	6.31	38.9	5.53
720	11	1.1	5.45	42.1	4.75
960	24	1.1	5.39	32.4	5.07

KRAS G12C
Stage 4
PD-L1 <1% and/or STK11 mutation

240 mg daily

960 mg daily

Primary endpoint: ORR
Secondary: safety, tolerability
Sample size: 170

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214665Orig1s000TOC.cfm

<https://clinicaltrials.gov/ct2/show/NCT04933695>

Sotorasib and ICI (pembrolizumab or atezolizumab)

CodeBreakK 100/101: First report of safety/efficacy of sotorasib in combination with pembrolizumab or atezolizumab in advanced KRAS p.G12C NSCLC

IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

CodeBreakK 100/101 Study Design

- Phase 1b multicenter, open-label studies

Key Eligibility

- Advanced KRAS p.G12C-mutated NSCLC
- Received (or refused) prior standard therapies
- No prior KRAS^{G12C} inhibitor
- No active brain mets

Screening/Enrollment

Sotorasib* (oral daily) at:

960 mg

720 mg

360 mg

240 mg

120 mg

+

Sotorasib lead-in 21d or 42d then combination (N = 29)

Atezolizumab 1200 mg Q3W (N = 10)

OR

Pembrolizumab 200 mg Q3W (N = 19)

Concurrent treatment (N = 29)

Atezolizumab 1200 mg Q3W (N = 10)

OR

Pembrolizumab 200 mg Q3W (N = 19)

Primary endpoints: safety
Key secondary endpoints: ORR, DOR, DCR, PK

*Not all doses were tested for each cohort.
DCR, disease control rate; PK, pharmacokinetics; Q3W, every 3 weeks.


Snapshot: April 15, 2022

Here we present first data of lead-in and concurrent sotorasib with pembrolizumab or atezolizumab from CodeBreakK 100/101 with median follow-up time of 12.8 months (range: 1.6, 29.9)

Li et al WCLC 2022

Sotorasib and ICI (pembrolizumab or atezolizumab)

CodeBreak 100/101: First report of safety/efficacy of sotorasib in combination with pembrolizumab or atezolizumab in advanced KRAS p.G12C NSCLC

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Safety by Dose: Pembrolizumab Concurrent

TRAE, n (%)	Sotorasib 120 mg (N = 5)		Sotorasib 360 mg (N = 8)		Sotorasib 720 mg (N = 2)		Sotorasib 960 mg (N = 4)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	5 (100)	4 (80)	7 (88)	6 (75)	2 (100)	2 (100)	3 (75)	3 (75)
Hepatotoxicity	2 (40)	2 (40)	3 (38)	2 (25)	2 (100)	2 (100)	3 (75)	3 (75)
ALT increased	2 (40)	1 (20)	3 (38)	1 (13)	2 (100)	2 (100)	3 (75)	3 (75)
AST increased	2 (40)	2 (40)	3 (38)	0	2 (100)	2 (100)	3 (75)	1 (25)


- Higher rate of TRAEs than with either monotherapy⁶⁻⁸, with no fatal TRAEs
- At lower doses of sotorasib, there was a trend towards less liver enzyme elevations, although sample sizes were limited
- Given the safety data for this combination, sotorasib lead-in was explored

Hepatotoxicity included autoimmune hepatitis, ALT increased, AST increased, ALP increased, bilirubin increased, and GGT increased.
ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

Li et al WCLC 2022

Sotorasib and ICI (pembrolizumab or atezolizumab)

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Safety for Sotorasib Lead-in + Pembrolizumab

TRAE*, n (%)	Sotorasib 120 mg (N = 3)		Sotorasib 240 mg (N = 5)		Sotorasib 360 mg (N = 11)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	3 (100)	3 (100)	3 (60)	1 (20)	9 (82)	6 (55)
ALT increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	3 (27)
AST increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	2 (18)
ALP increased	2 (67)	0	0	0	3 (27)	2 (18)
Diarrhea	1 (33)	0	1 (20)	0	6 (55)	1 (9)
Arthralgia	1 (33)	0	0	0	2 (18)	0
Nausea	0	0	0	0	4 (36)	0
Fatigue	0	0	0	0	4 (36)	0
Hypokalemia	0	0	0	0	3 (27)	2 (18)
Decreased appetite	0	0	0	0	3 (27)	0
Headache	0	0	0	0	2 (18)	0
Hepatotoxicity	2 (67)	2 (67)	2 (40)	1 (20)	6 (55)	5 (45)

Overall safety data from lead-in and concurrent cohorts support lower dose sotorasib and lead-in administration for better tolerability

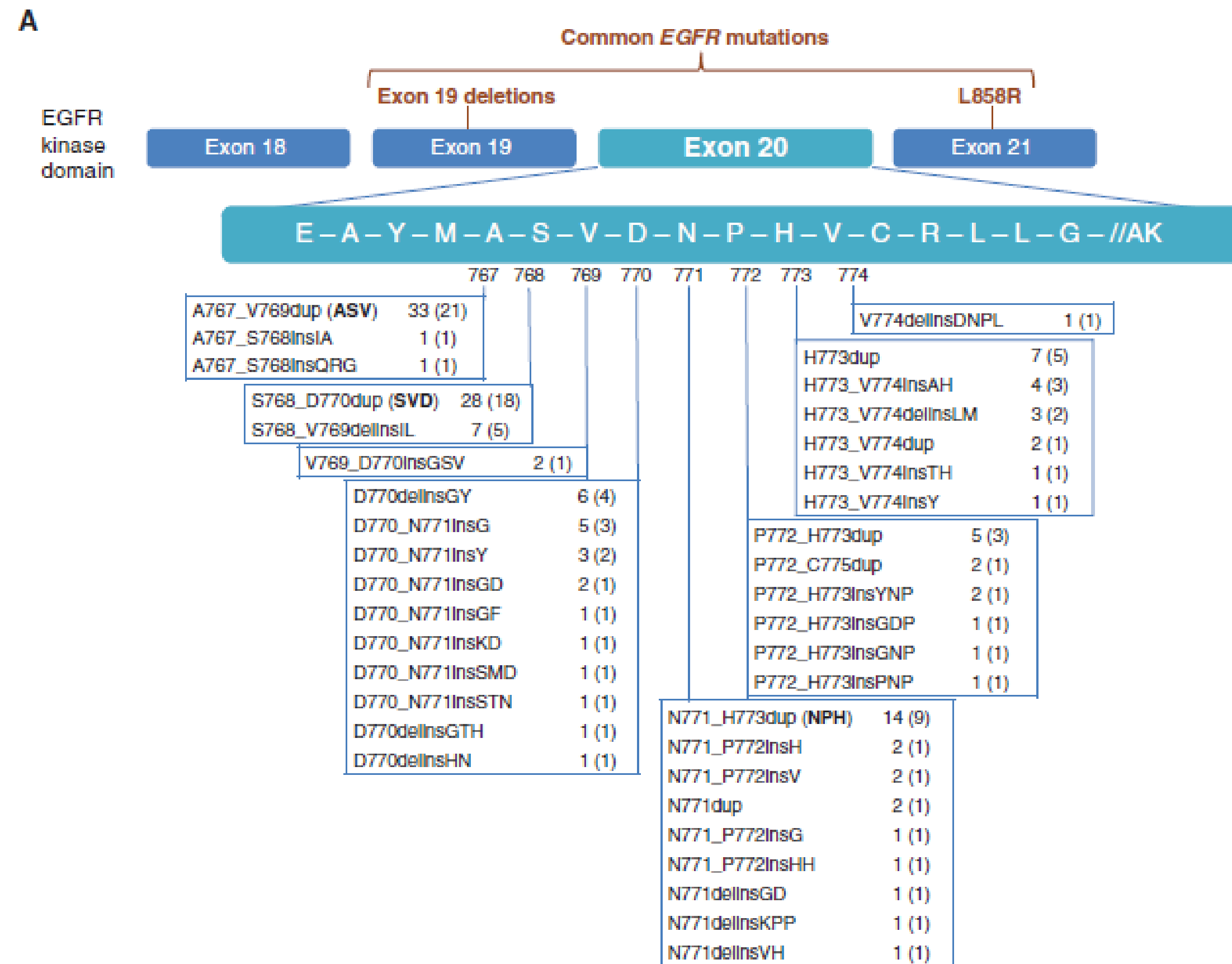
*Any grade TRAE or grade ≥ 3 TRAE occurring in ≥ 1 patient in any dose cohort.

Li et al WCLC 2022



EGFR exon 20 insertions

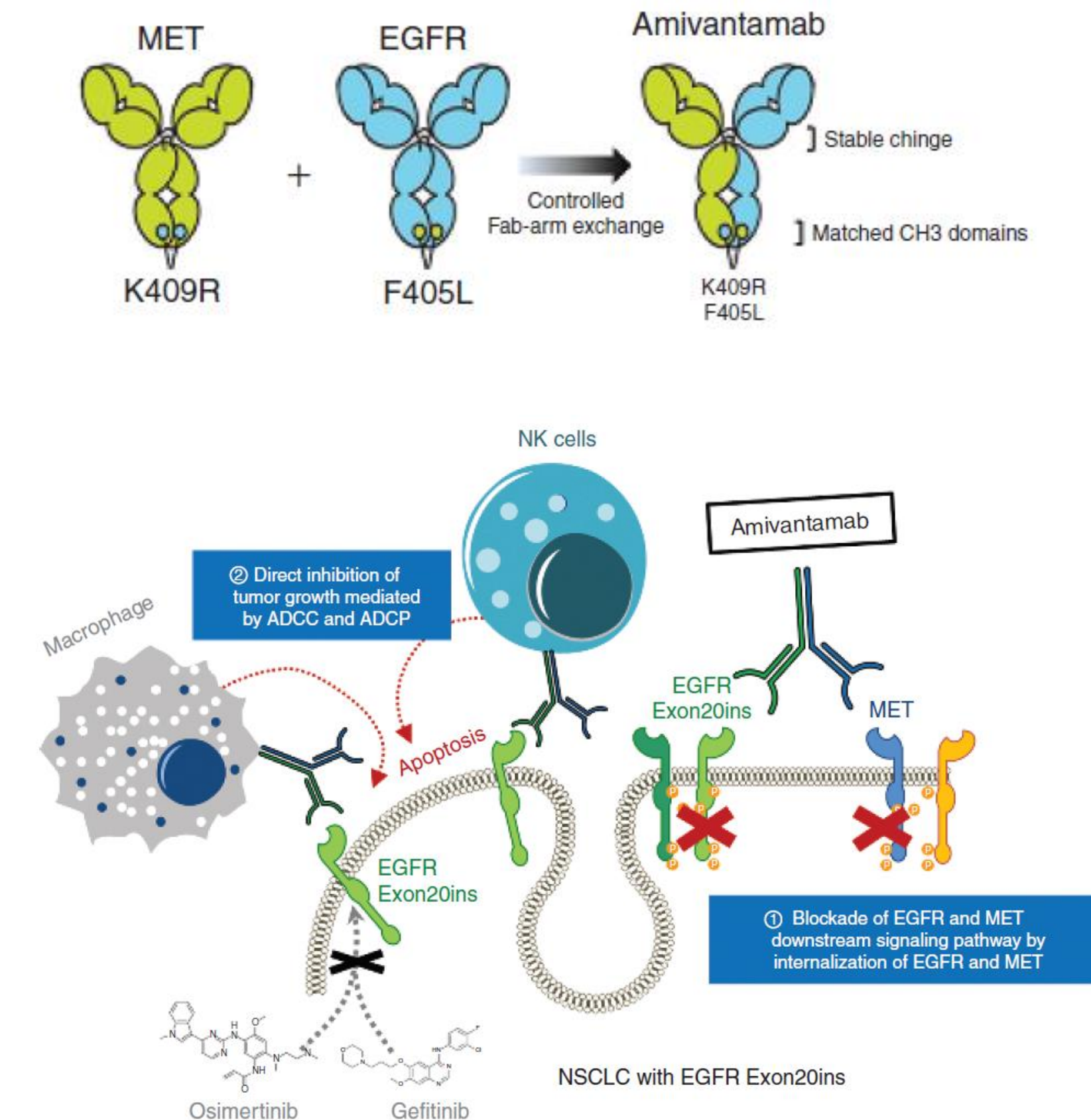
EGFR exon 20 insertion mutations



Gonzalez et al Cancer Discovery 2021

Amivantamab

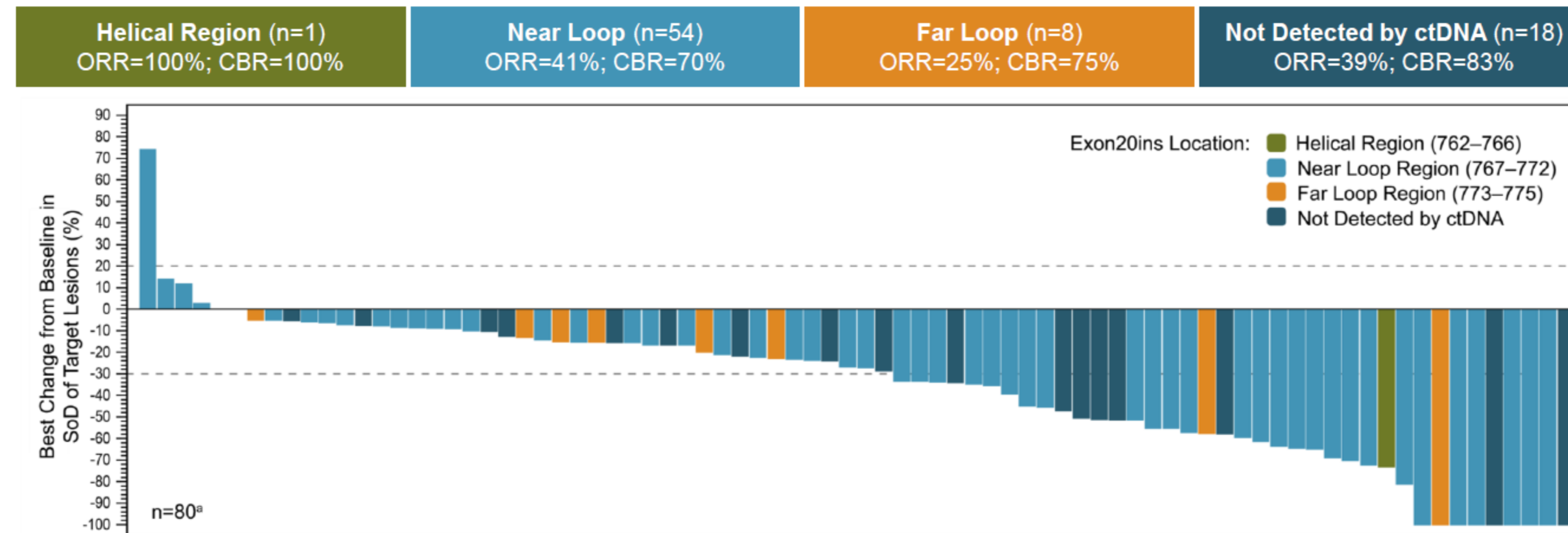
- Bi-specific antibody targeting EGFR-MET
- Preclinical models demonstrated activity in EGFR exon 20 insertions
- MOA: inhibition of signal pathways, ADCC, and anti-body cellular phagocytosis



Yun et al Cancer Discovery 2020

Amivantamab Efficacy

Best ORR by Insertion Region of Exon 20 (detected by ctDNA)



25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360[®]) from 63 evaluable patient samples

ORR: 40% (95% CI: 29-51)

DoR: 11.1 months (95% CI: 6.9-NR)

Median PFS: 8.3 (95% CI: 6.5-10.9)

Park et al JCO 2021

Amivantamab: Treatment-related AE

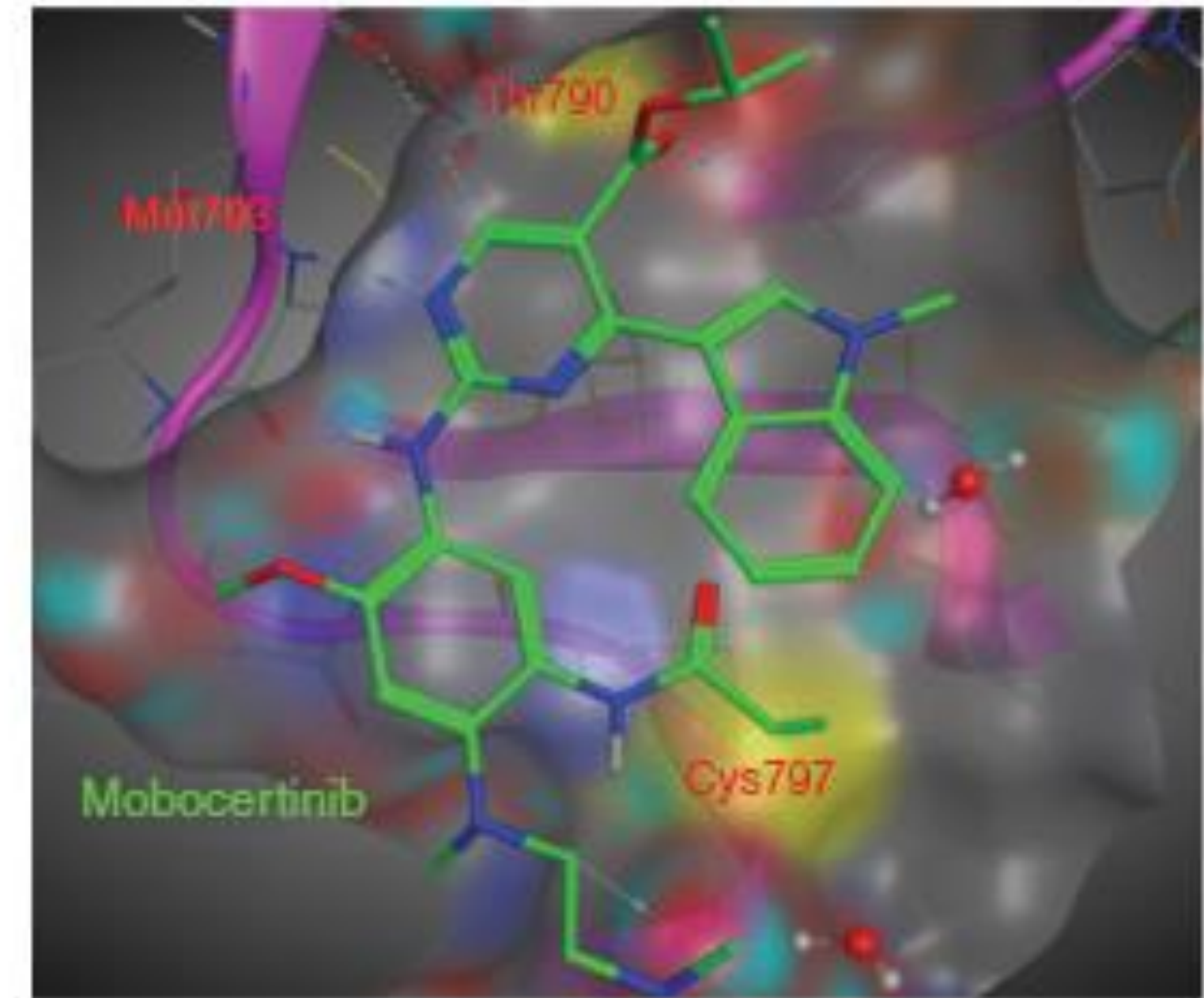
Safety	Total	Grade ≥ 3
Rash	98 (86%)	4(4%)
Paronychia	48 (42%)	1 (1%)
Stomatitis	21 (18%)	0
Pruritus	19 (17%)	0
Hypoalbuminemia	17 (15%)	2 (2%)
Peripheral edema	11 (10%)	0
IRR*	75 (66%)	3 (3%)
Nausea	13 (11%)	0
Fatigue	14 (12%)	1 (1%)
Increased ALT	14 (12%)	1 (1%)

IRR: Cycle 1 day split over 2 days, with premedication (dexamethasone, benadryl, tylenol), and slow infusion

Park et al JCO 2021

Mobocertinib

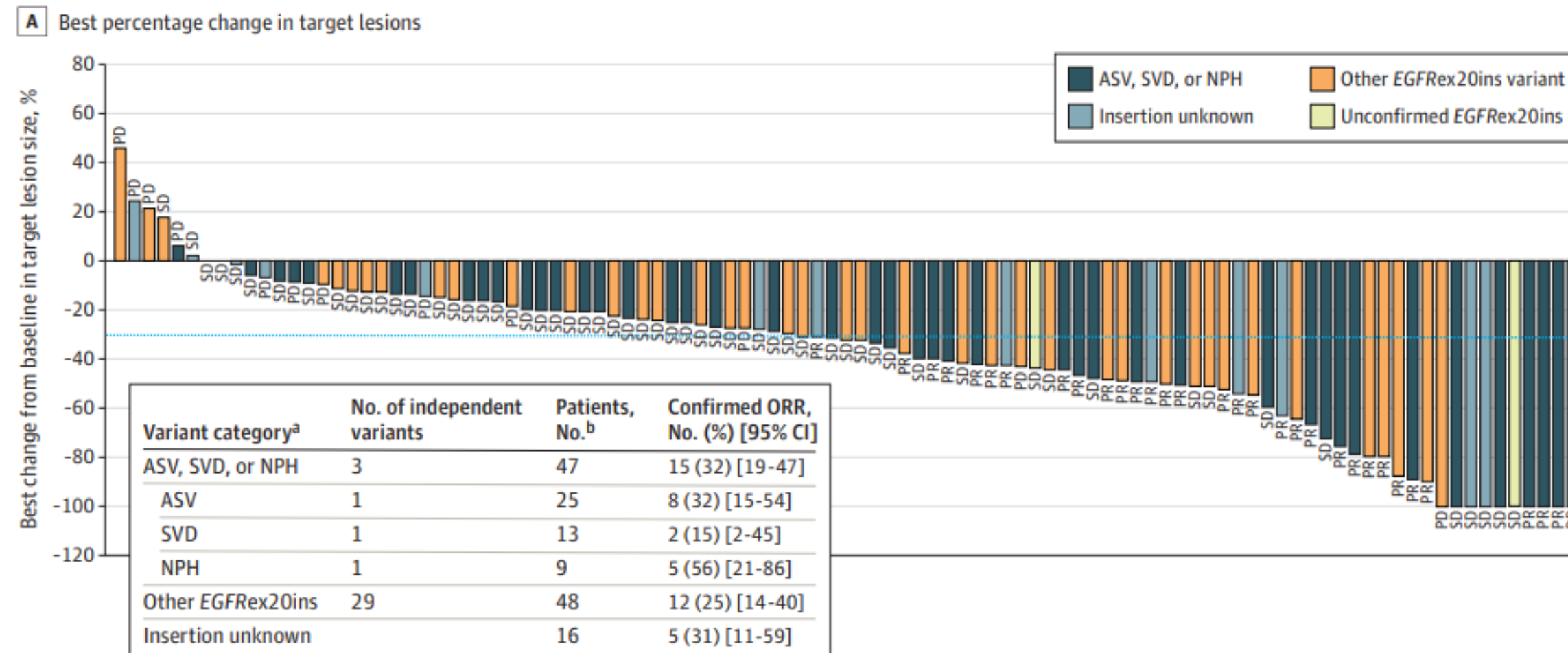
- EGFR TKI: levels high enough to inhibit EGFR exon 20 insertion mutations had significant side effects on EGFR wildtype
- Difficult to maintain therapeutically effective doses
- Mobocertinib specifically designed to potently inhibit oncogenic variants containing activating *EGFR* exon 20 insertion mutations with selectivity over wild-type EGFR
- Phase 2 study prior platinum pretreatment cohort (n = 114)



Zhou et al JAMA Oncology 2021

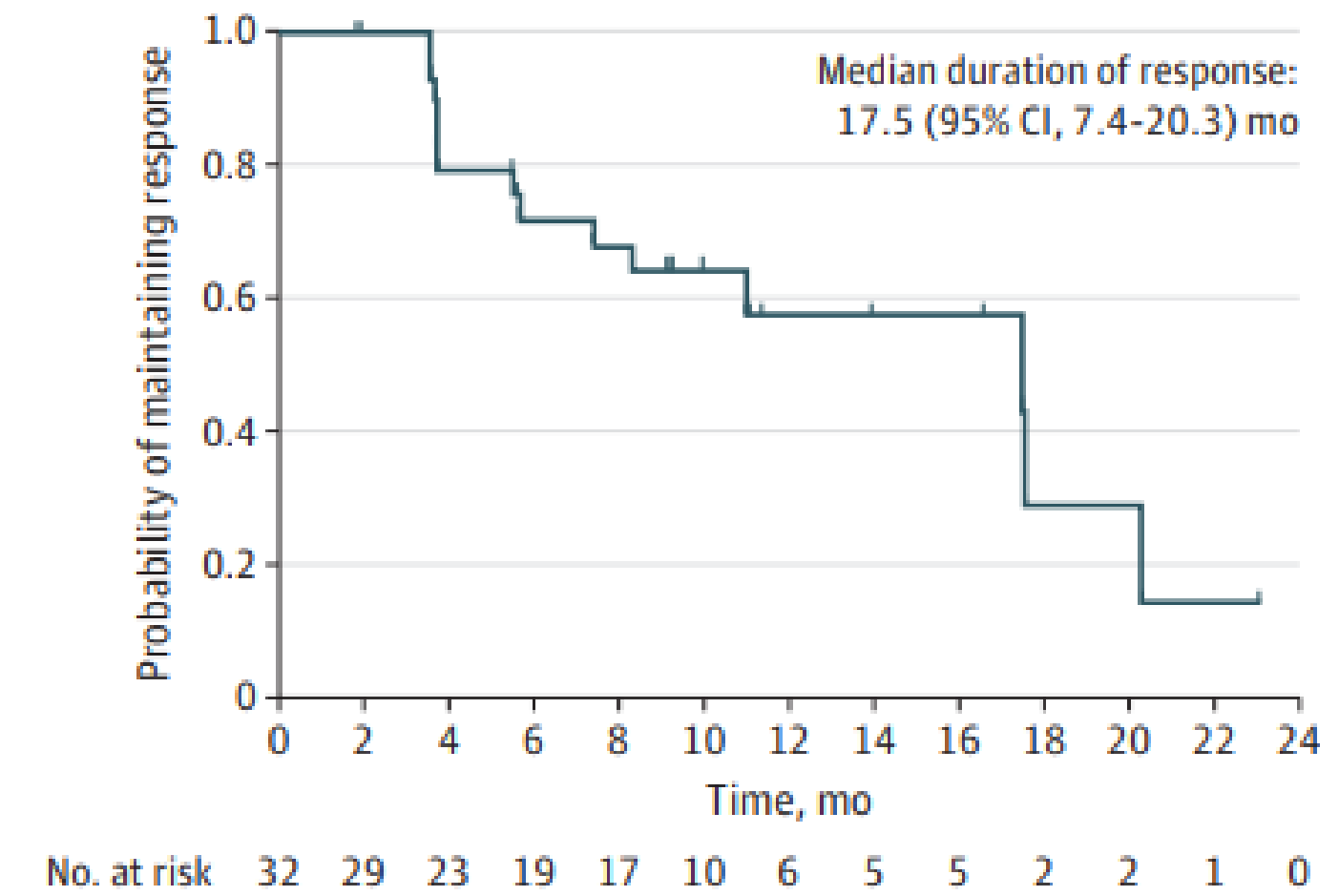
Mobocertinib efficacy

Figure 2. Mobocertinib Activity in Platinum-Pretreated Patients With *EGFR*Ex20ins Mutation-Positive Metastatic NSCLC (PPP Cohort)



ORR: 32% (95% CI: 20-37)

C Median duration of confirmed response



Median PFS 7.3 (95% CI: 5.5-9.2)

Zhou et al JAMA Oncology 2021

Moborcertinib : Treatment-related AE

Safety	All grade	Grade \geq 3
Diarrhea	91%	21%
Rash	45%	0%
Paronychia	38%	<1%
Stomatitis	24%	4%
Pruritus	21%	<1%
QT prolonged	11%	3%
Nausea	34%	4%
Fatigue	14%	3%
Increased AST	8%	<1%

Zhou et al JAMA Oncology 2021

Final thoughts

- Immunotherapy a standard of care for resectable patients
 - Debate will be about pre-operative chemotherapy and ICI vs adjuvant ICI
 - Optimal duration not defined
 - Identification of biomarkers critical
- PACIFIC: long term benefit for consolidation durvalumab
- Debate about pre-operative chemotherapy and ICI vs PACIFIC
- *KRAS* G12C and *EGFR* exon 20 insertions now “actionable mutations”
 - Combination therapy trials ongoing

Men's Basketball Championship - Final Four

8 North Carolina
29-9



81



Final

77



2 Duke
32-7

