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Susan Scott, MD

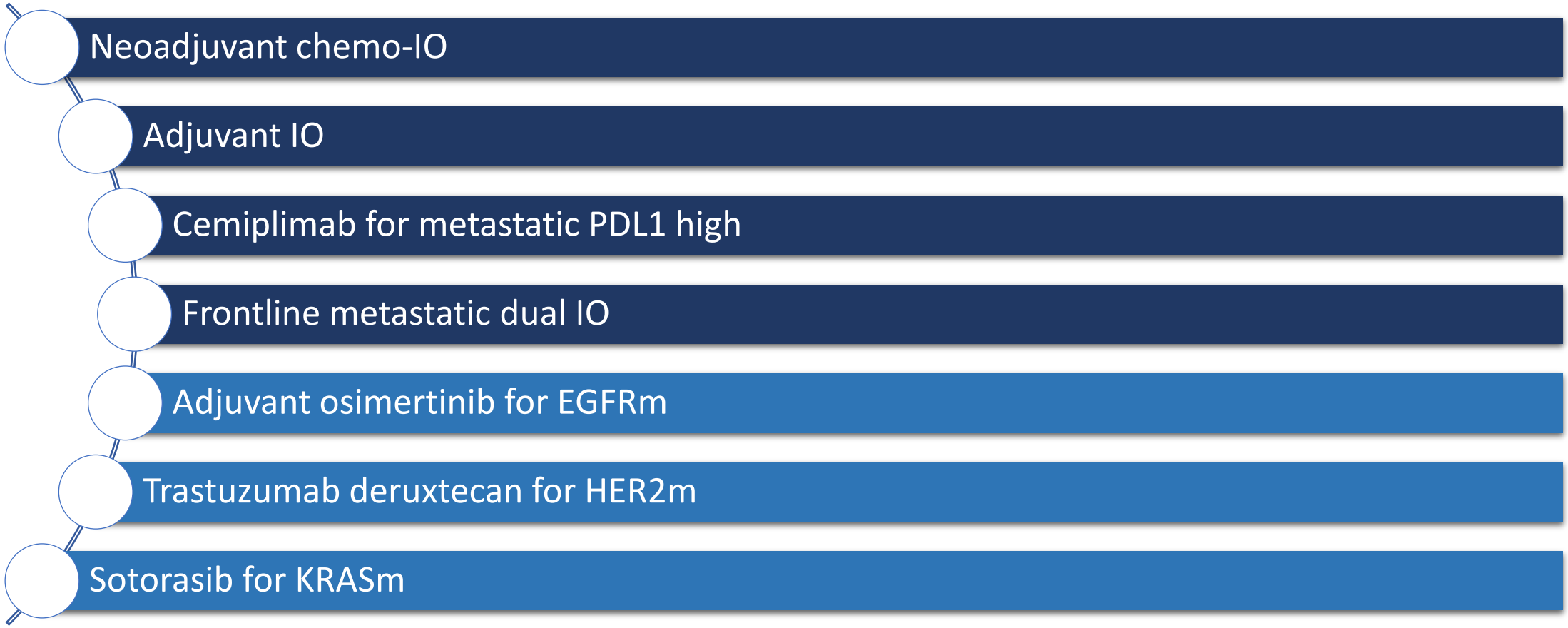
Dr. Susan Scott is a thoracic medical oncologist with the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center at Sibley Memorial Hospital and Assistant Professor of Oncology at the Johns Hopkins University School of Medicine. Dr. Scott is board certified in Medical Oncology and Internal Medicine and has expertise in thoracic malignancies, including non-small cell lung cancer, small cell lung cancer and pulmonary carcinoid tumors, as well as thymic malignancies.

Dr. Scott received her undergraduate education at the University of Oxford, UK and medical doctorate from Yale University. She completed residency at the Cleveland Clinic where she also served as Chief Resident in Internal Medicine. Dr. Scott joined Johns Hopkins Oncology for fellowship training in Baltimore and was recruited to the thoracic oncology program to continue work as a physician and clinical scientist focused in lung cancer.

Most important advances in LUNG CANCER

Susan C. Scott, MD
Johns Hopkins University

What's new in NSCLC?



Who should get **neoadjuvant chemo-immunotherapy**?

	TNM 7th EDITION	TNM 8th EDITION
T	-	Tis
	-	Tmi
	-	Tss
	T1a (≤2 cm) →	T1a (≤1 cm)
	T1b (>2 -3 cm)	T1b (>1-2cm)
		T1c (>2-3cm)
	T2a (>3-5 cm) →	T2a (>3cm but ≤4cm)
	T2b (>5-7 cm)	T2b (>4cm but ≤5cm)
	T3 (>7 cm) →	T4
	T3 - atelectasis/pneumonitis involving whole lung)	T2 atelectasis/pneumonitis irrespective of involving lobe or whole lung
	T3 tumor involving the main bronchus <2cm distance to carina →	T2 -tumor involving the main bronchus irrespective of distance to carina
	T3 -invasion of the diaphragm →	T4 (invasion of the diaphragm)
N	No changes	
M	M1b - distant metastasis →	M1b - single extrathoracic metastasis
		M1c - multiple extrathoracic metastases

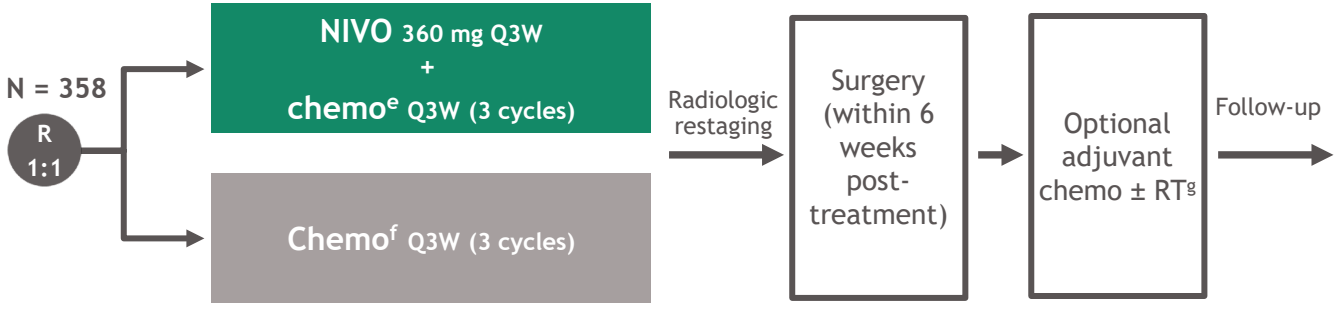
T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Neoadjuvant chemo-immunotherapy: CheckMate 816

Key eligibility criteria

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

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



Primary endpoints
- pCR by BIPR
- EFS[h] by BICR

Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

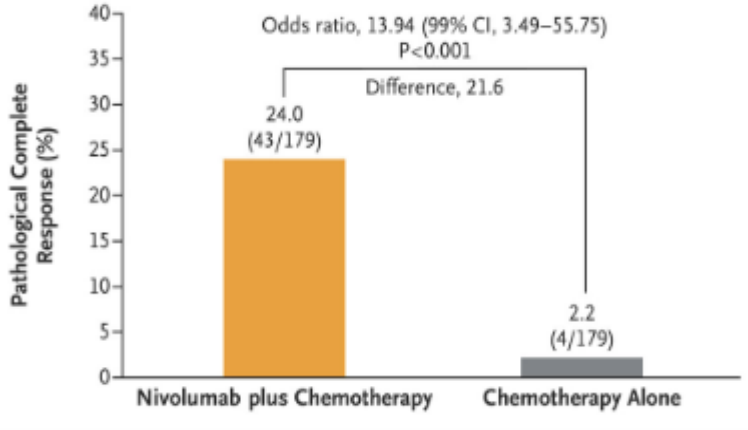
Key exploratory analysis
- **EFS by pCR status**

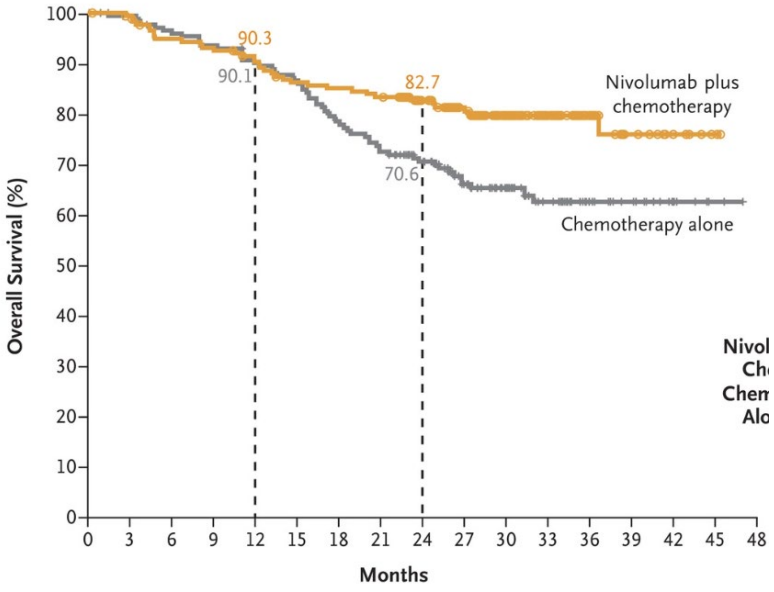
[a]NCT02998528; [b]TNM Classification of Malignant Tumors 7th edition; [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [d]Included patients with PD-L1 expression status not evaluable and indeterminate; [e]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [f]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; [g]Per healthcare professional choice; [h]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy.

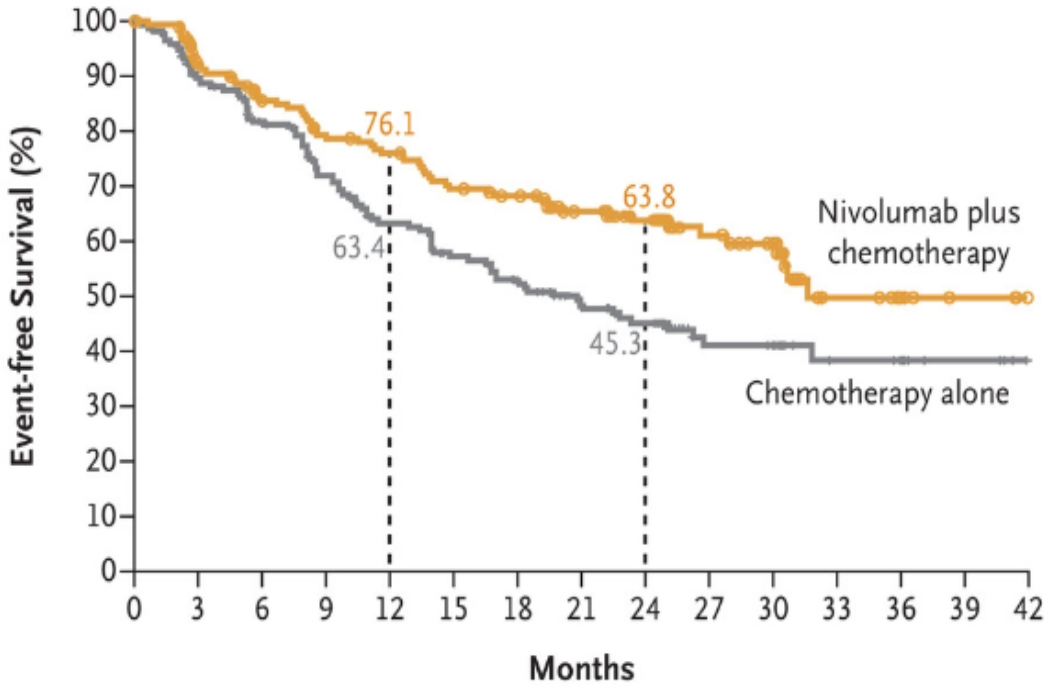
Enrolled	Stage	Histology	Smoking	Platinum chemo
358	IB/II 36%	Nonsquam 49%	Ever 89%	Cisplatin 72%
	IIIA 65%	Squamous 51%	Never 11%	Carboplatin 28%

Forde PM et al AACR 2021
Forde PM et al NEJM 2022

Neoadjuvant chemo-immunotherapy: CheckMate 816







	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

Forde PM et al NEJM 2022

Neoadjuvant chemo-immunotherapy: CheckMate 816

No signal for inferior surgical outcomes with pre-operative chemo-IO

	Nivolumab + chemotherapy (149 patients)	Chemotherapy (135 patients)
Delayed surgery, number of patients (%)	31 (21)	24 (18)
Length of delay of surgery (weeks), median (IQR)	2.0 (0.6-3.0)	2.4 (1.0-3.7)
Surgical approach % of patients		
Thoracotomy	59%	63%
Minimally invasive	30%	22%
Minimally invasive → open	11%	16%
Type of surgery, % of patients		
Lobectomy	77%	61%
Pneumonectomy	17%	25%
Completeness of resection, % of patients		
R0	83%	78%
R1	11%	16%
R2	3%	3%
Rx	3%	4%
Hospital stay (days), median (IQR)	135 patients 10.0 (7.0-14.0)	124 patients 10.0 (7.0-14.5)
Surgery-related adverse events, % of patients[a]		
Any grade	41%	47%
Grades 3-4	11%	15%

Spicer J et al ASCO 2021

Who should get **neoadjuvant chemo-immunotherapy**?

- Resectable *at dx*
- Stage II-IIIA
  - Tumors >4 cm
  - N0 or N1
  - Single station N2
- EGFR/ALK negative

T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Neoadjuvant Systemic Therapy

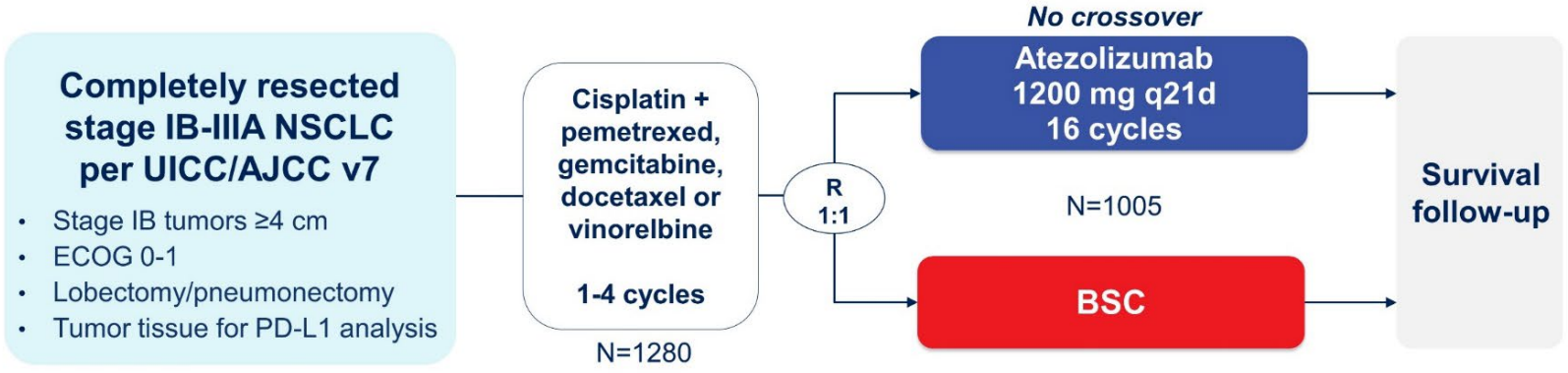
- **Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for 3 cycles[10,*]**
  - **Platinum-doublet chemotherapy options include:**
    - ◊ **Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)**
    - ◊ **Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (non-squamous histology)**
    - ◊ **Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)**
    - ◊ **Cisplatin 75 mg/m² day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)**
  - **Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin**
    - ◊ **Carboplatin AUC 5 or AUC 6 day 1, pemetrexed 500 mg/m² day 1 (non-squamous histology)**
    - ◊ **Carboplatin AUC 5 or AUC 6 day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)**

Bottom line:

Neoadjuvant chemo-nivolumab for resectable NSCLC w/o driver

Who should get **adjuvant immunotherapy?**

Adjuvant immunotherapy: IMpower010



Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

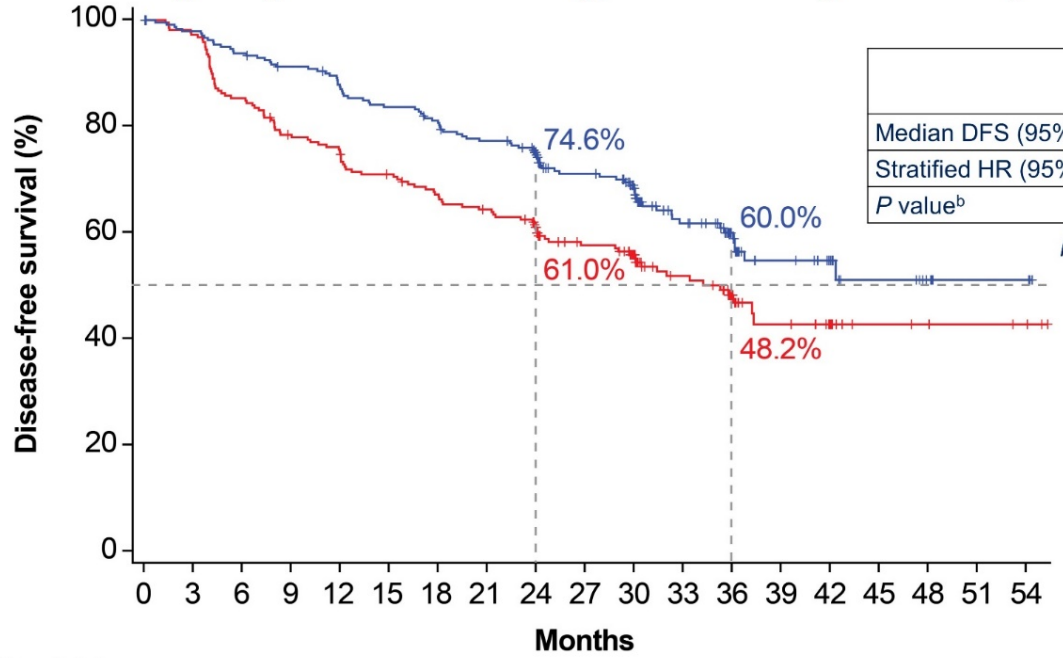
Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

Enrolled	Stage	Histology	PDL1	Smoking	Mutations
1005	IB/II 59%	Nonsquam 66%	>1% 55%	Ever 78%	EGFR 11.6%
	IIIA 41%	Squamous 34%	<1% 45%	Never 22%	ALK 3.3%

Wakelee HA et al ASCO 2021

Adjuvant immunotherapy: IMpower010

IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA population (primary endpoint)



	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

Median follow-up: 32.8 mo (range, 0.1-57.5)

No. at risk

Atezolizumab	248	235	225	217	206	198	190	181	159	134	111	76	54	31	22	12	8	3	3
BSC	228	212	186	169	160	151	142	135	117	97	80	59	38	21	14	7	6	4	3

Clinical cutoff: January 21, 2021. CI, confidence interval; HR, hazard ratio; NE, not evaluable. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.

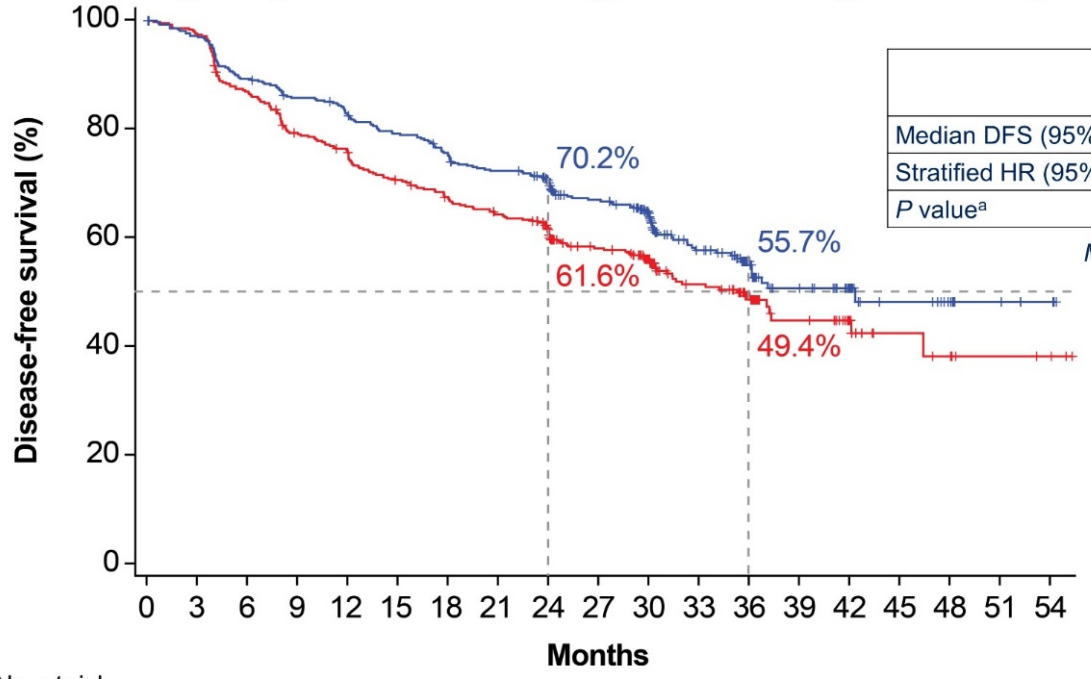
Presented By: Dr. Heather A. Wakelee
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

2021 ASCO ANNUAL MEETING

Wakelee HA et al ASCO 2021

Adjuvant immunotherapy: IMpower010

IMpower010: DFS in the all-randomized stage II-IIIA population (primary endpoint)



	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

Median follow-up: 32.2 mo (range, 0-57.5)

No. at risk

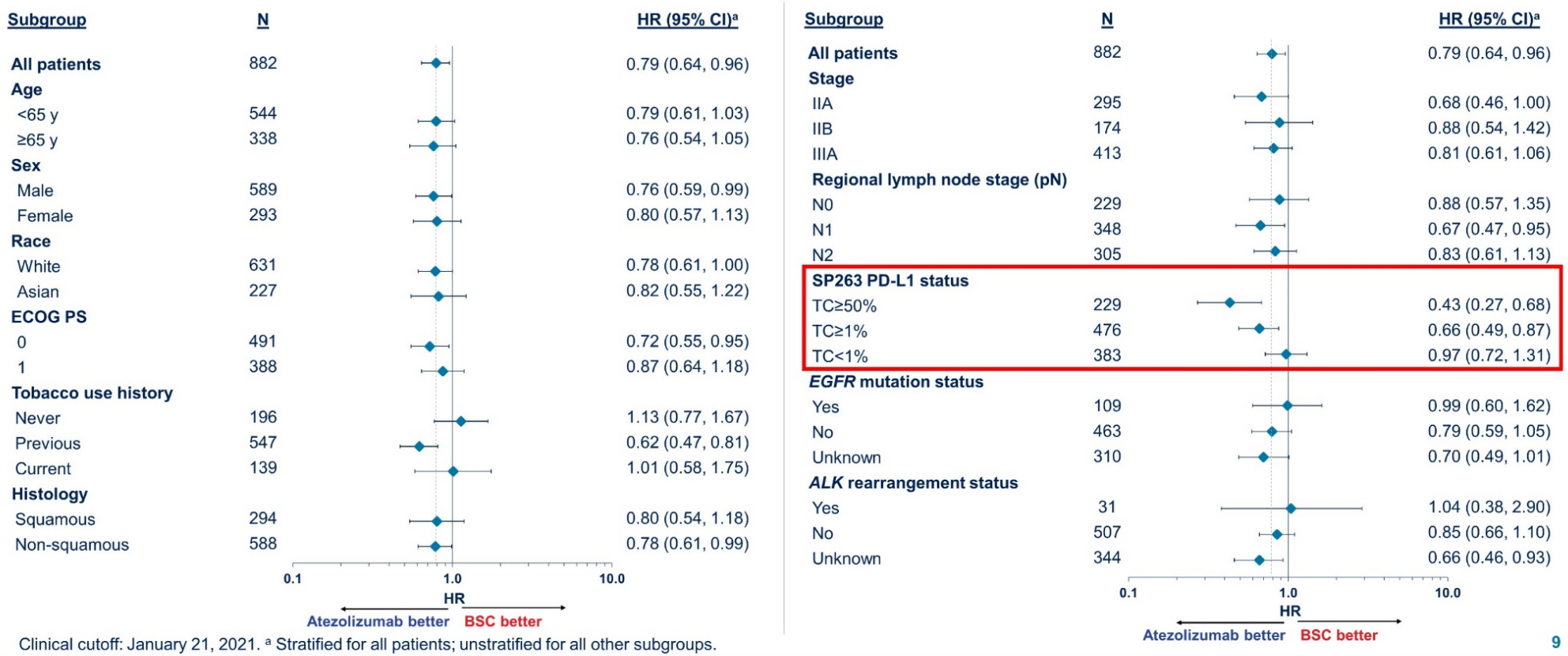
Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] Crossed the significance boundary for DFS.

Wakelee HA et al ASCO 2021

Adjuvant immunotherapy: IMpower010

IMpower010: DFS in key subgroups of the all-randomized stage II-IIIA population



Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.

Presented By: Dr. Heather A. Wakelee
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

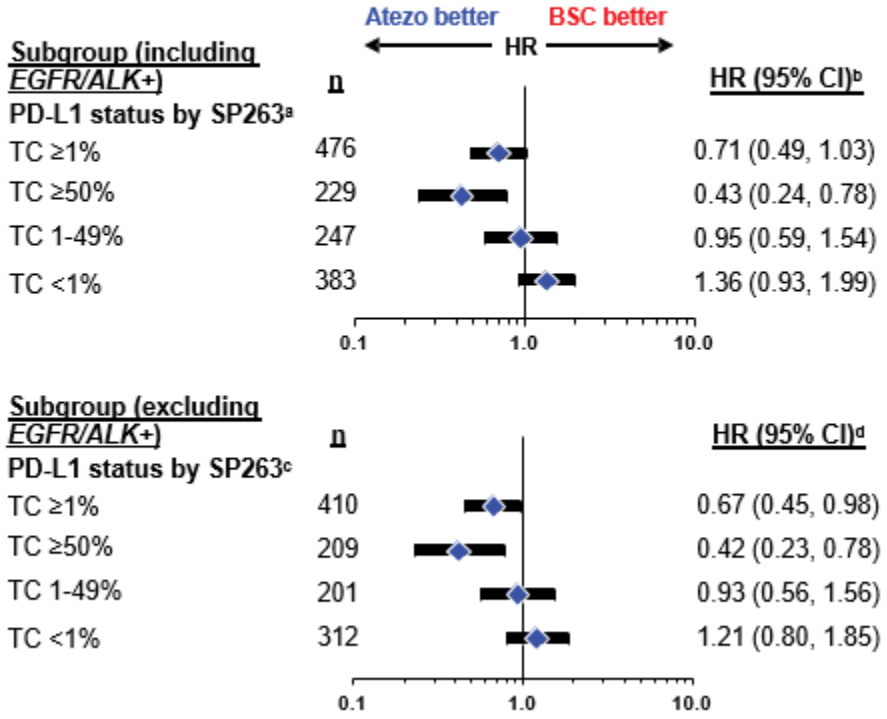
2021 ASCO ANNUAL MEETING

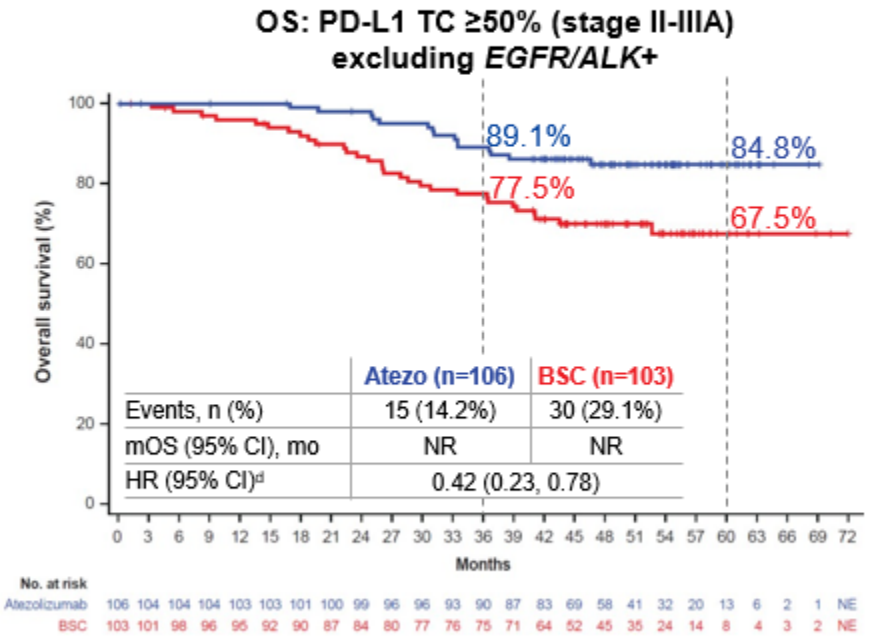
Wakelee HA et al ASCO 2021

Adjuvant immunotherapy: IMpower010

OS by biomarker status (stage II-IIIA)

Data cutoff: 18 Apr 2022



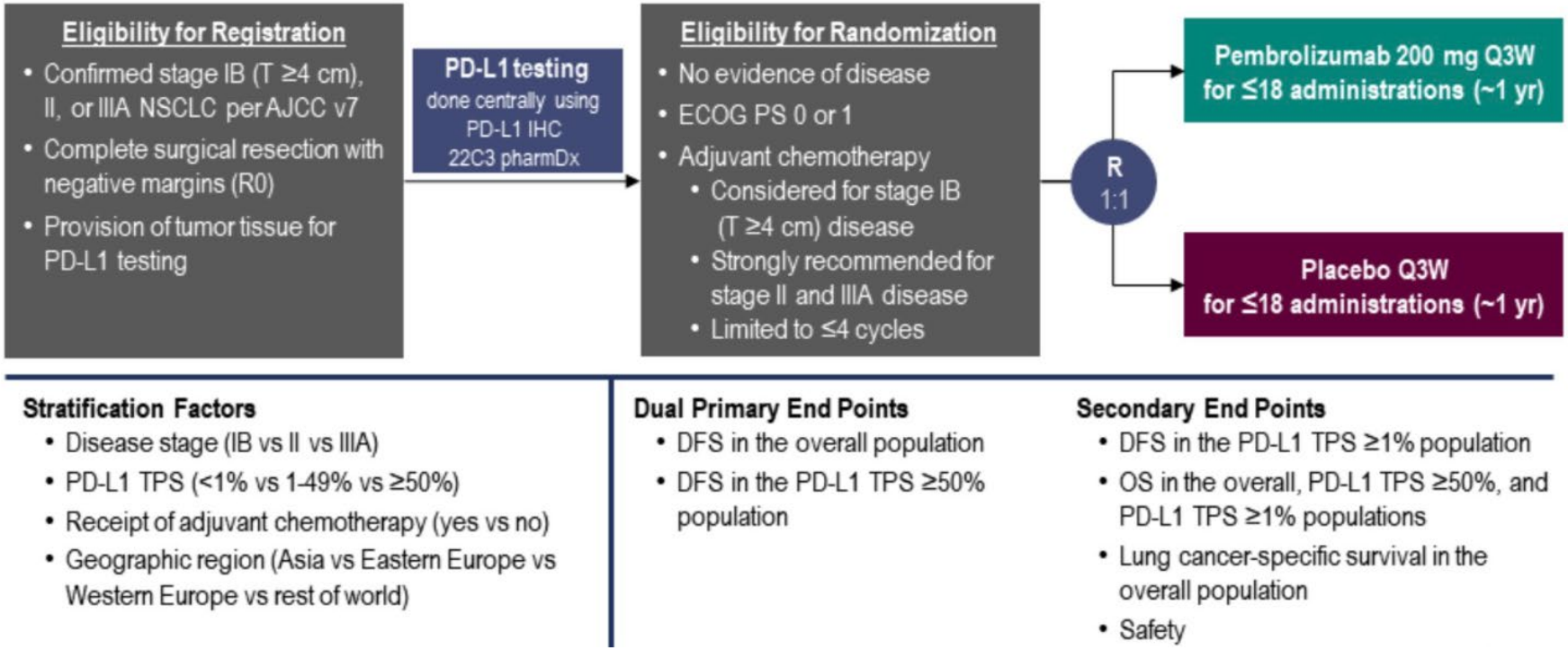


a 23 patients had unknown PD-L1 status. b Stratified for PD-L1 TC ≥1%; unstratified for all other subgroups. c 21 patients had unknown PD-L1 status. d Unstratified.

Bottom line:

Adjuvant atezolizumab approved in PDL1 >1%, appears most benefit in >50%

Adjuvant immunotherapy: PEARLS

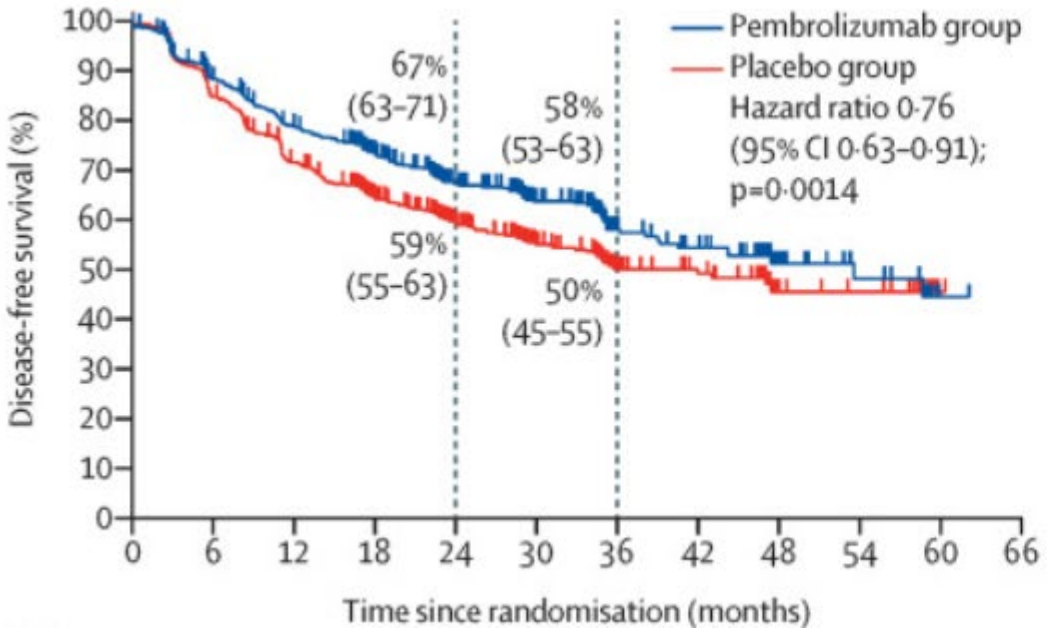


Enrolled	Stage	Histology	PDL1	Chemo	Mutations
1177	IB/II 71%	Nonsquam 65%	>1% 60%	No 14%	EGFR 6.2%
	IIIA 29%	Squamous 35%	<1% 40%	Yes 86%	ALK 1%

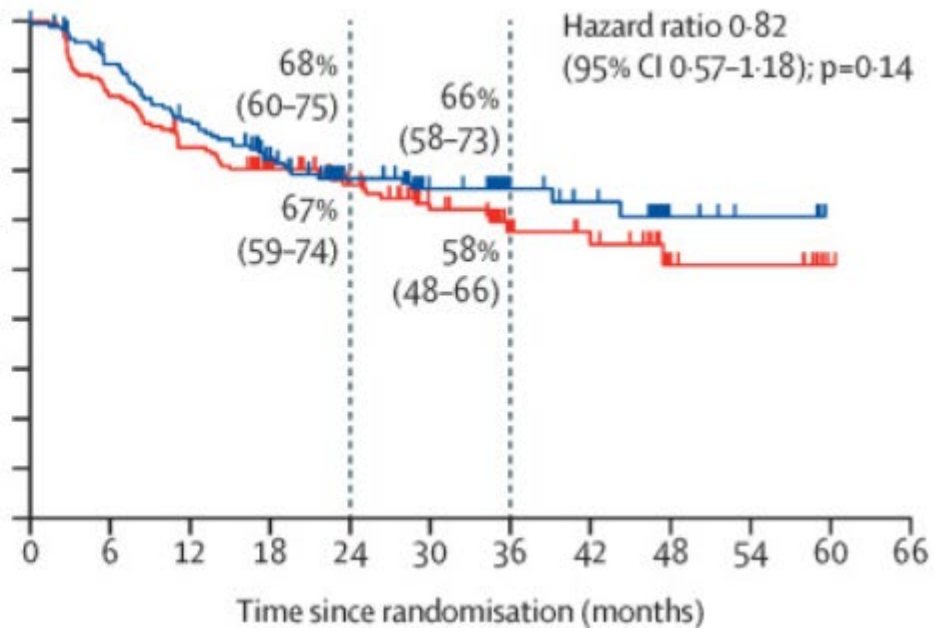
Pas-Ares L, et al ESMO Virtual 2022

Adjuvant immunotherapy: PEARLS

Overall Population

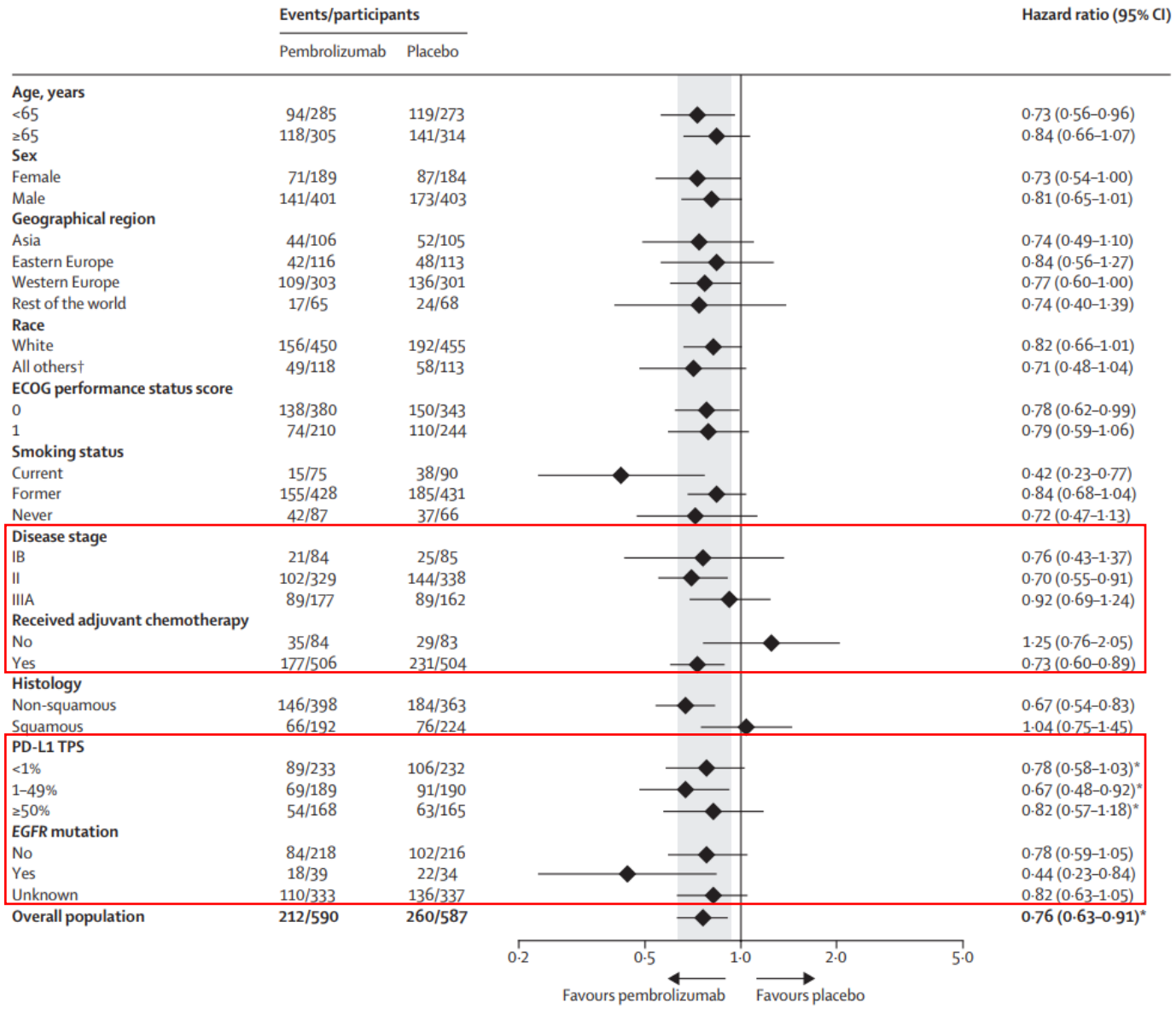


PDL1 TPS ≥50%



O'Brien M, et al Lancet 2022

Adjuvant immunotherapy: PEARLS



O'Brien M, et al Lancet 2022

Who should get **adjuvant immunotherapy?**

If no neoadjuvant IO:

- PD-L1 >50% – YES
- PD-L1 1-49% – Maybe, approved
- PD-L1 <1% – Probably no, not approved

If yes neoadjuvant IO: ?

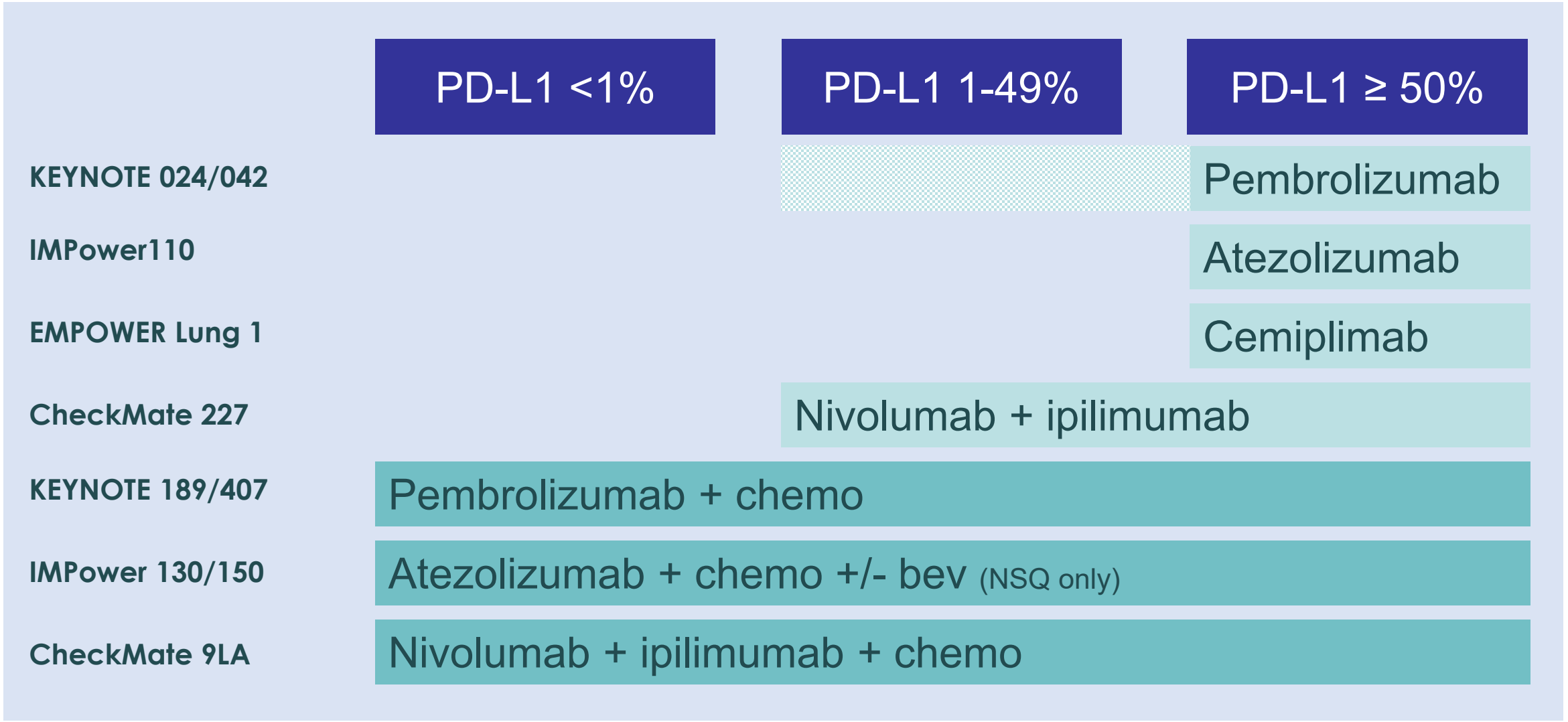
THE JURY IS STILL OUT

Factors to consider

- Stage/risk of recurrence
- PD-L1
- Pathologic response
- Prior chemotherapy
- Tolerance to neoadjuvant
- Risk of toxicity

What are the options for **advanced NSCLC PDL1 ≥50%?**

Frontline immunotherapy in advanced NSCLC



Scott SC 2022

Frontline immunotherapy: EMPOWER Lung-1

Key Eligibility Criteria
- Treatment-naïve advanced NSCLC
- PD-L1 ≥50%
- No *EGFR*, *ALK* or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

Stratification Factors:
- Histology (squamous vs non-squamous)
- Region (Europe, Asia or ROW)

N=710

Five interim analyses were prespecified per protocol

Second interim analysis (1 March 2020) presented here

R 1:1

Arm A
Cemiplimab monotherapy IV
350 mg Q3W
Treat until PD or 108 weeks

PD → **Optional continuation of cemiplimab + 4 cycles of chemotherapy**

Arm B
4–6 cycles of investigator's choice chemotherapy

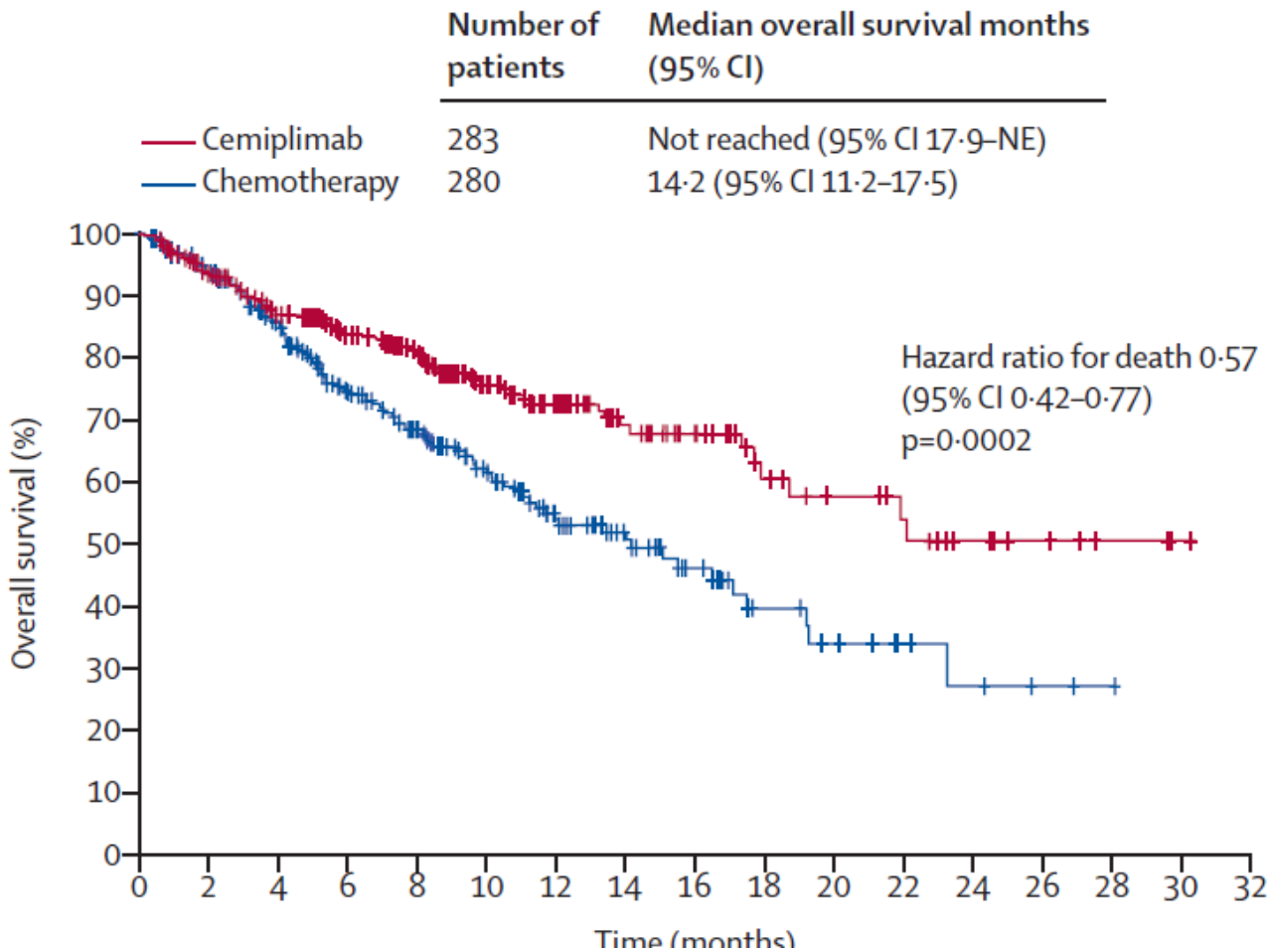
PD → **Optional crossover to cemiplimab monotherapy**

Follow-up

Endpoints:
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL and safety

Sezer et al, ESMO 2020

Frontline immunotherapy: EMPOWER Lung-1

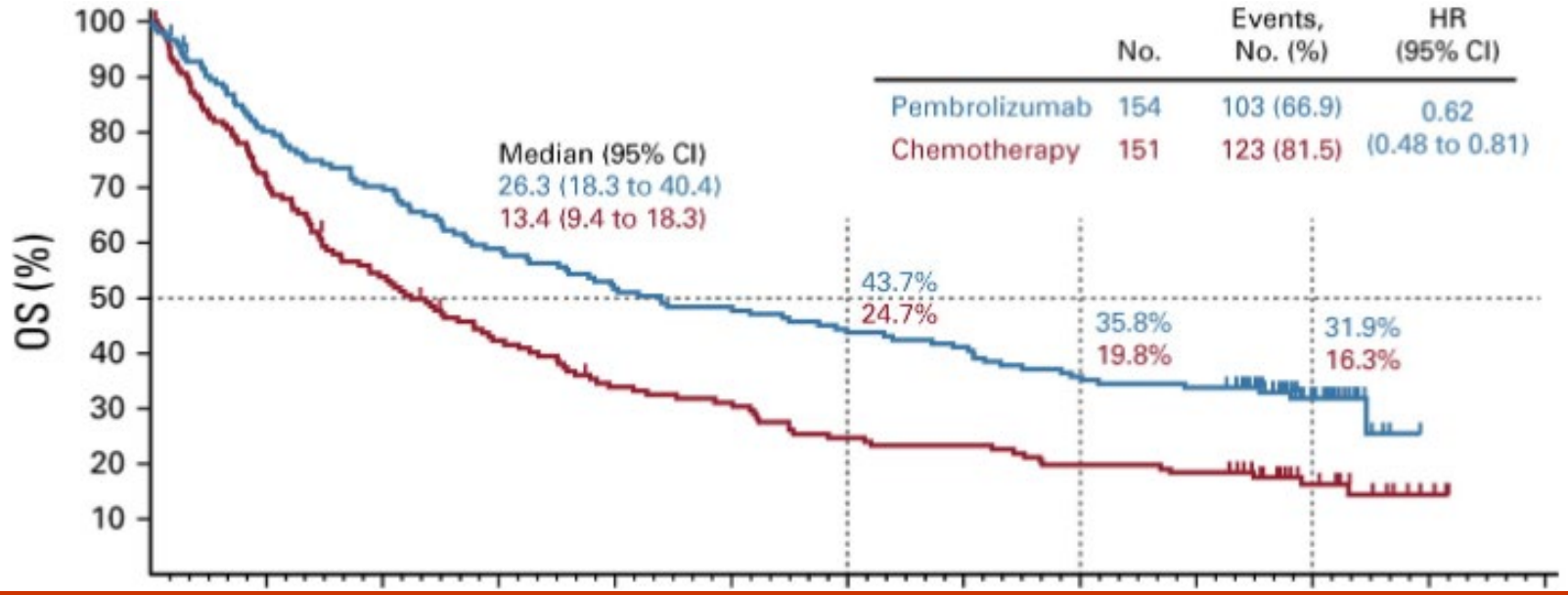


Sezer *et al*, Lancet 2021

What are the options for **advanced NSCLC PDL1 ≥50%?**

	ORR	mOS	HR-OS	% 2 year OS	Gr ≥3 AE
Keynote 024	46%	26.3 vs 13.4	0.62 (0.48-0.81)	51.5 vs 34.5	27%
IMPower110	38%	20.2 vs 14.7	0.76 (0.54-1.09)	Not reported	34%
EMPOWER Lung 1	39%	NR vs 14.2	0.57 (0.42-0.77)	50.4 vs 27.1	14%

Keynote-024

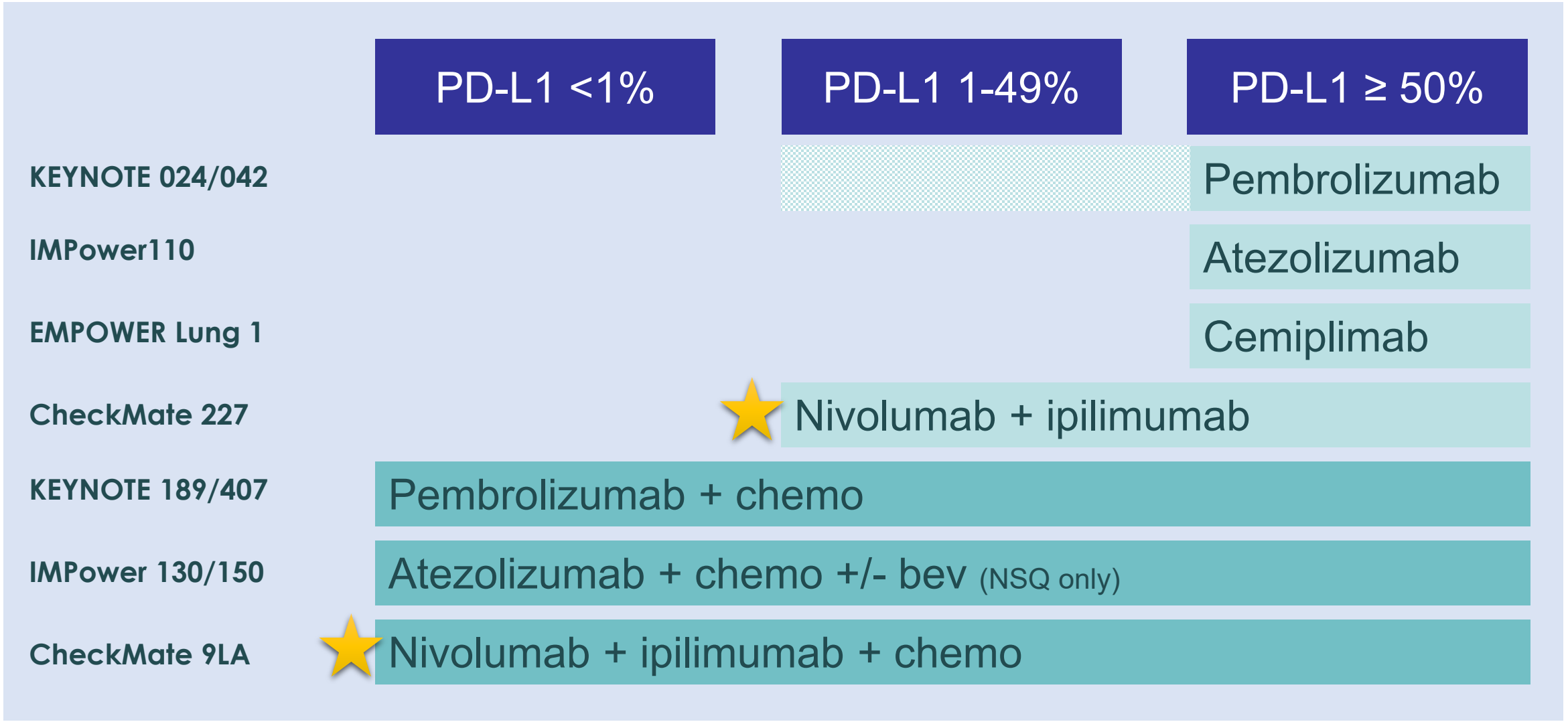


Bottom line:

Cemiplimab is an approved alternative for advanced NSCLC PDL1 >50%

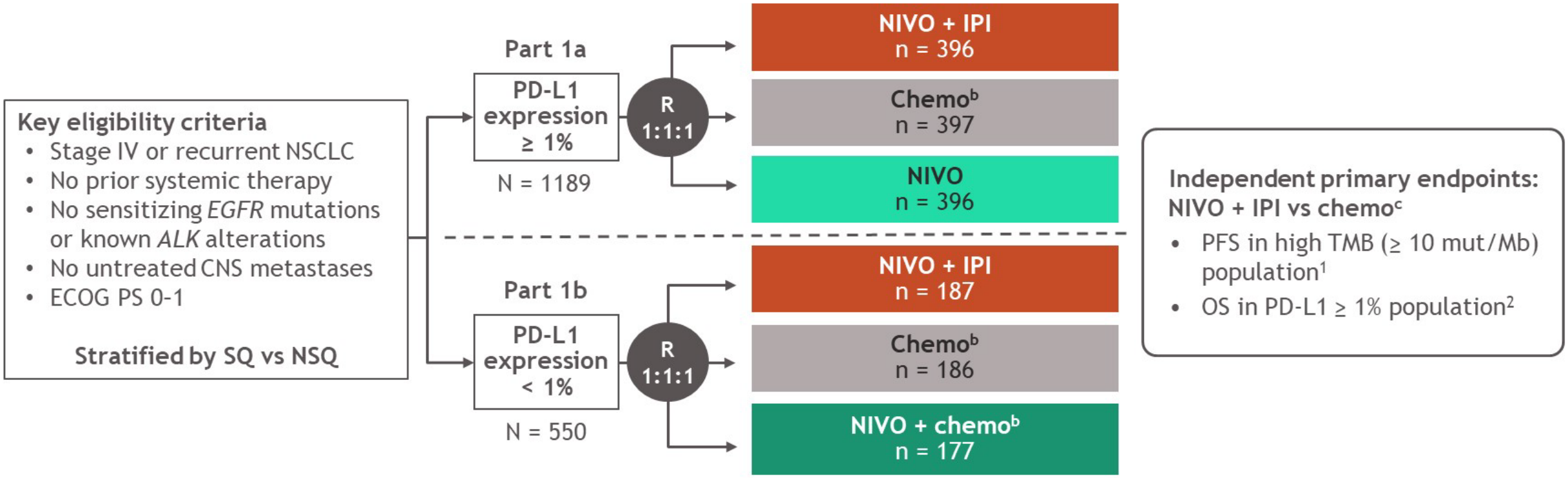
What are the options for **advanced NSCLC PDL1 0%?**

Frontline immunotherapy in advanced NSCLC



Scott SC 2022

Dual immunotherapy in advanced NSCLC: CheckMate 227

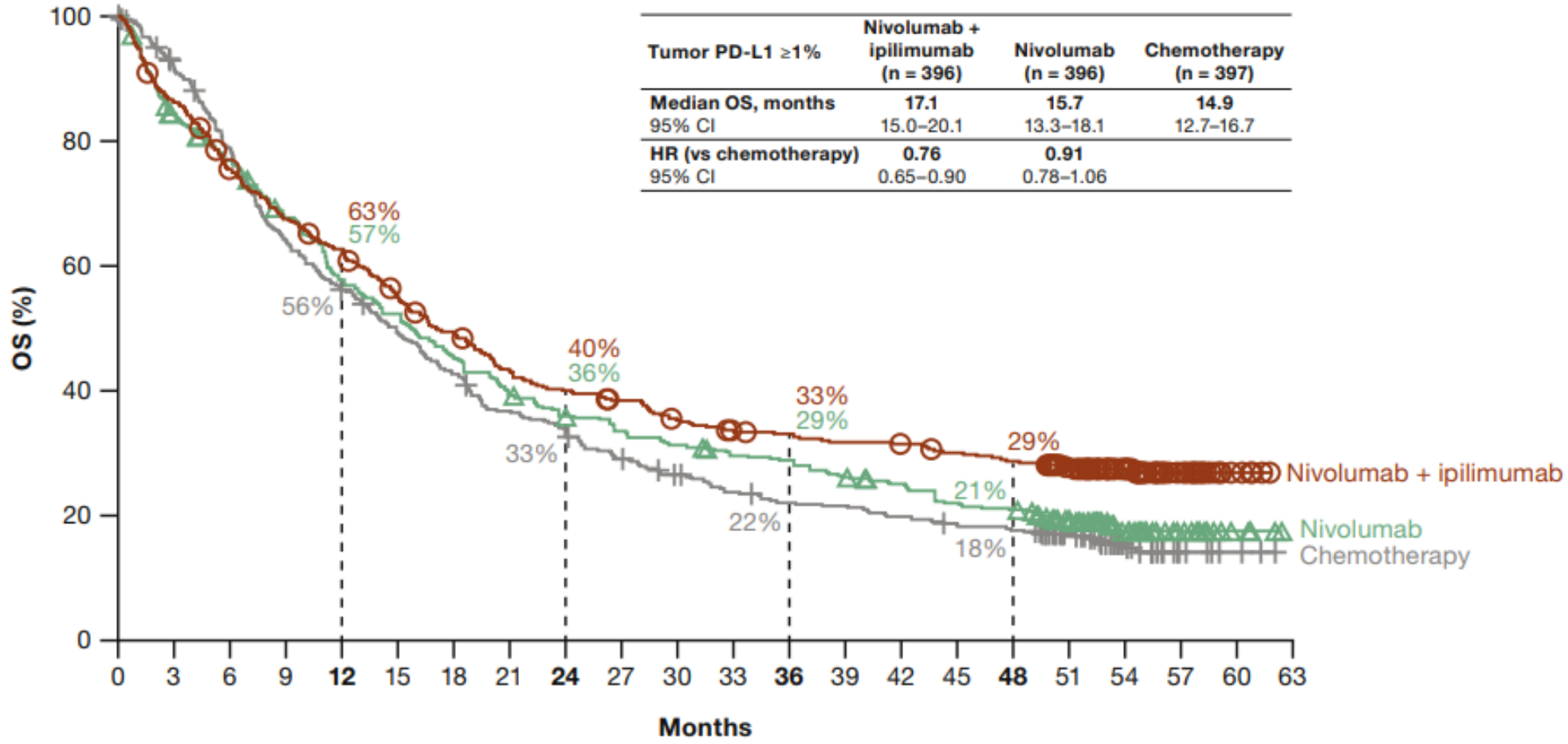


Paz-Ares L *et al*, ASCO 2021

Dual immunotherapy in advanced NSCLC: CheckMate 227

PD-L1 ≥1%

Tumor PD-L1 ≥1%	Nivolumab + ipilimumab (n = 396)	Nivolumab (n = 396)	Chemotherapy (n = 397)
Median OS, months	**17.1**	**15.7**	**14.9**
95% CI	15.0–20.1	13.3–18.1	12.7–16.7
HR (vs chemotherapy)	**0.76**	**0.91**	
95% CI	0.65–0.90	0.78–1.06	

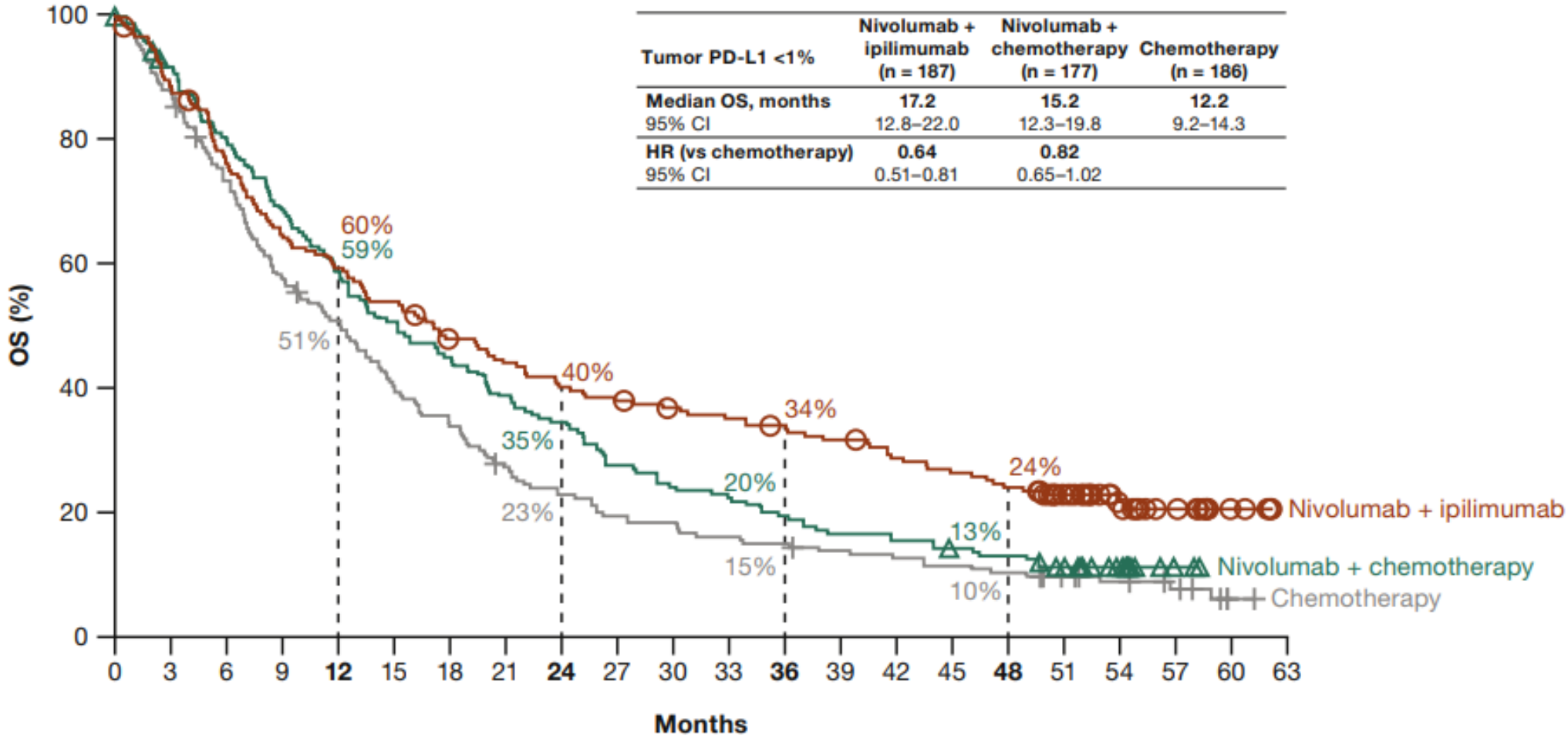


Paz-Ares *et al*, J Thoracic Onc 2022

Dual immunotherapy in advanced NSCLC: CheckMate 227

PD-L1 <1%

Tumor PD-L1 <1%	Nivolumab + ipilimumab (n = 187)	Nivolumab + chemotherapy (n = 177)	Chemotherapy (n = 186)
Median OS, months	**17.2**	**15.2**	**12.2**
95% CI	12.8–22.0	12.3–19.8	9.2–14.3
HR (vs chemotherapy)	**0.64**	**0.82**	
95% CI	0.51–0.81	0.65–1.02	

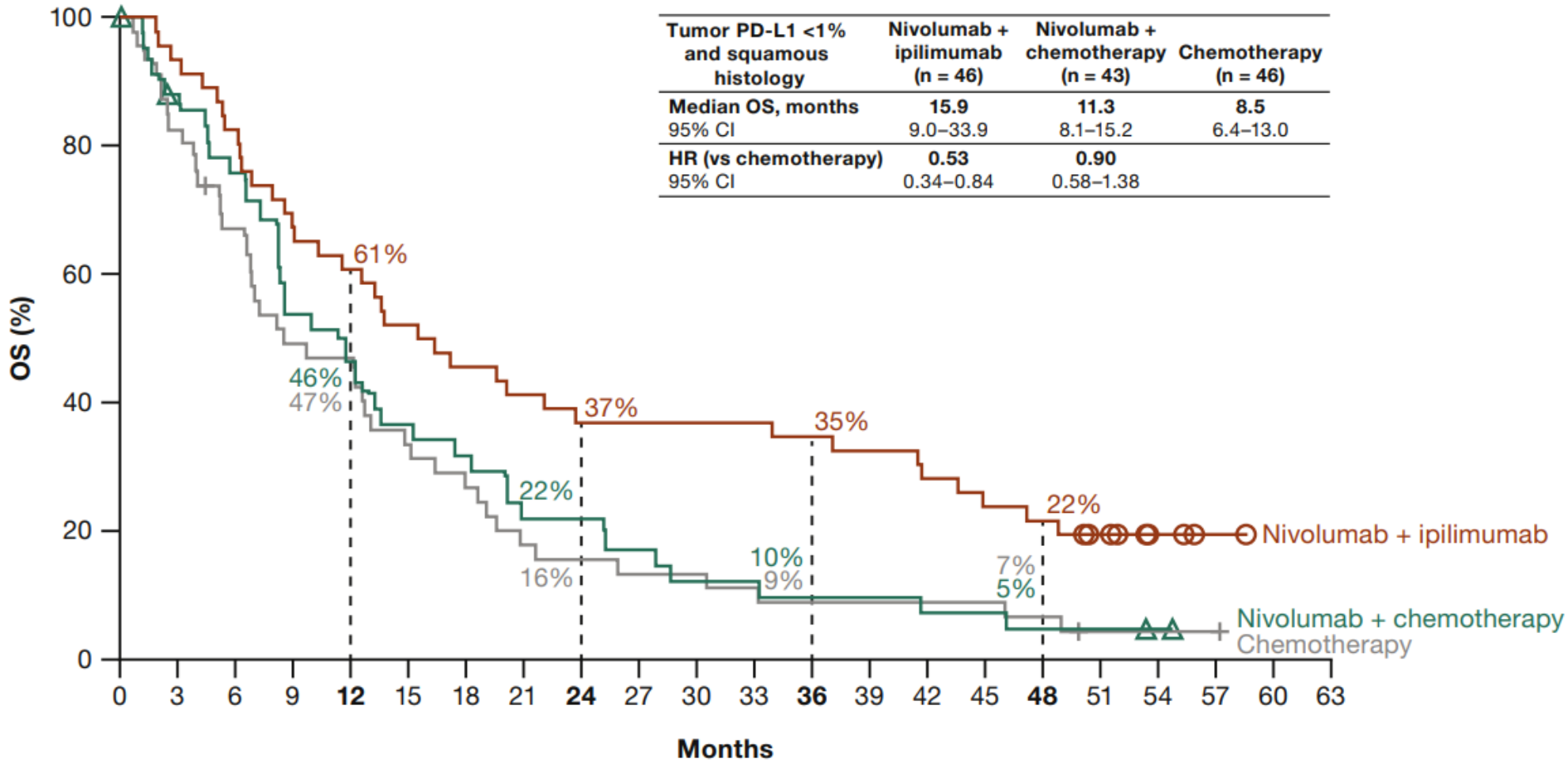


Paz-Ares *et al*, J Thoracic Onc 2022

Dual immunotherapy in advanced NSCLC: CheckMate 227

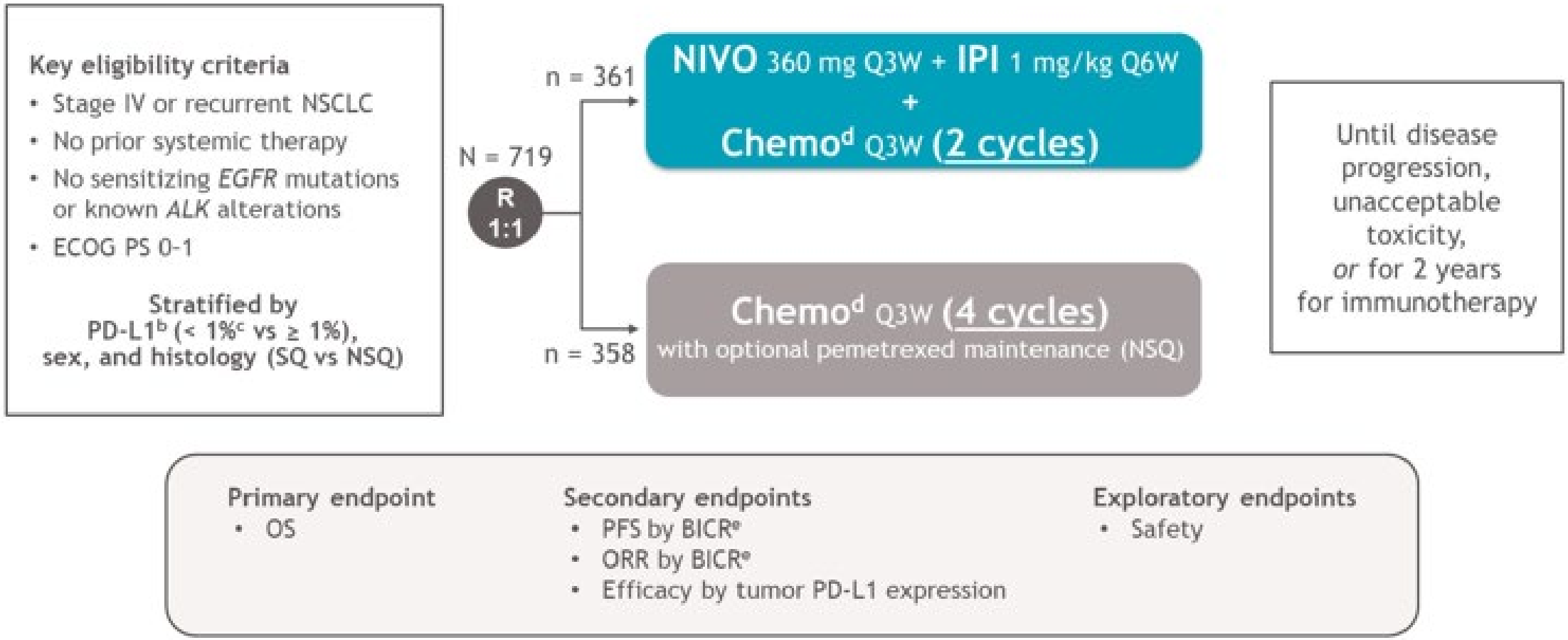
PD-L1 <1% Squamous

Tumor PD-L1 <1% and squamous histology	Nivolumab + ipilimumab (n = 46)	Nivolumab + chemotherapy (n = 43)	Chemotherapy (n = 46)
Median OS, months	**15.9**	**11.3**	**8.5**
95% CI	9.0–33.9	8.1–15.2	6.4–13.0
HR (vs chemotherapy)	**0.53**	**0.90**	
95% CI	0.34–0.84	0.58–1.38	



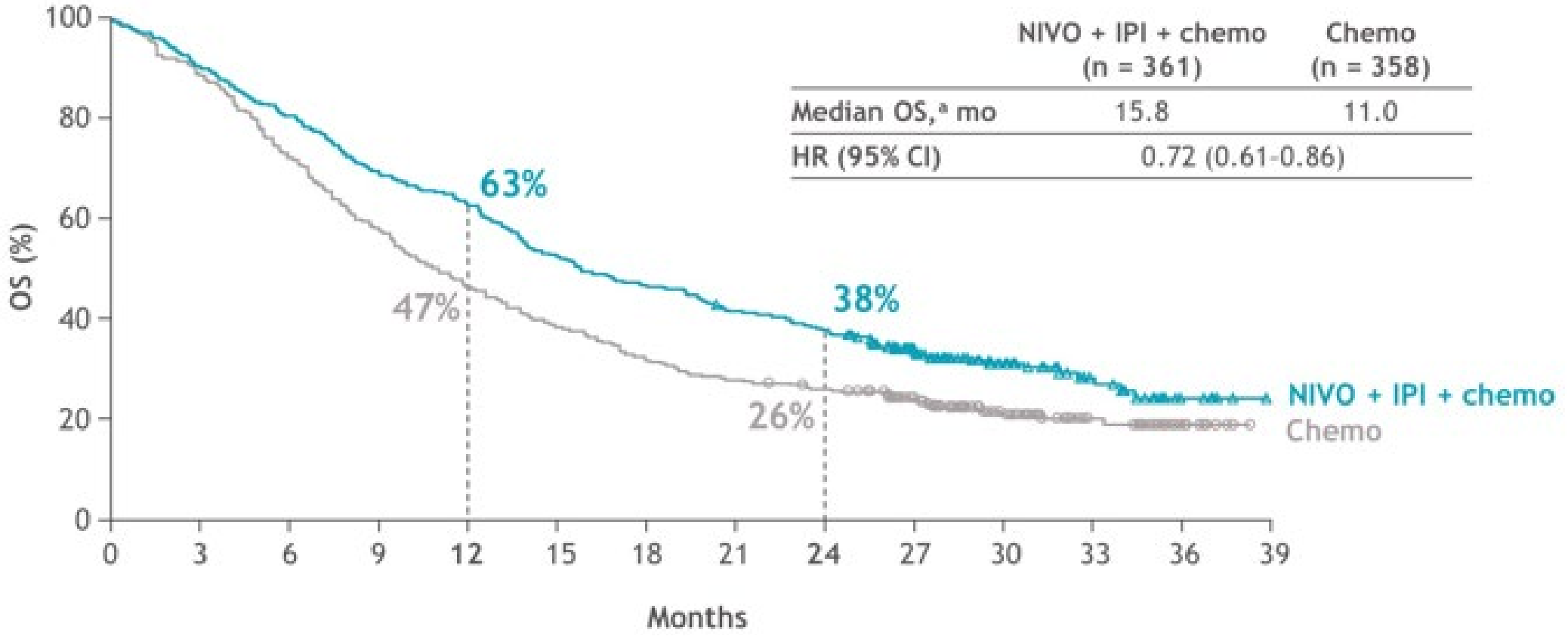
Paz-Ares *et al*, J Thoracic Onc 2022

Dual immunotherapy in advanced NSCLC: CheckMate 9LA



Reck M et al, ASCO 2021

Dual immunotherapy in advanced NSCLC: CheckMate 9LA

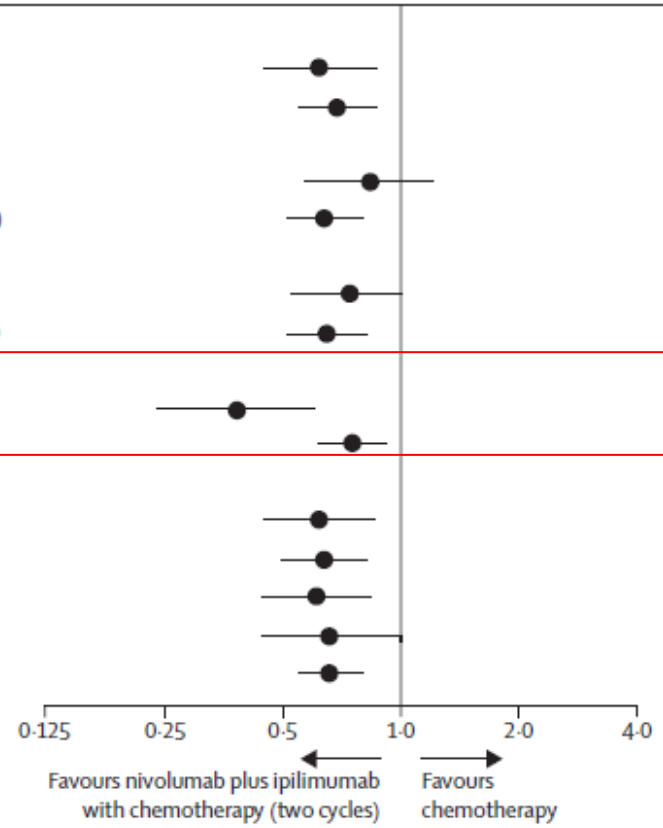


	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS,[a] mo	15.8	11.0
HR (95% CI)	0.72 (0.61-0.86)	

Reck M et al, ASCO 2021

Dual immunotherapy in advanced NSCLC: CheckMate 9LA

	Nivolumab plus ipilimumab with chemotherapy (two cycles)		Chemotherapy		Unstratified hazard ratio for death (95% CI)
	Events/ patients	Median overall survival, months (95% CI)	Events/ patients	Median overall survival, months (95% CI)	
Tumour histological type					
Squamous	66/115	14·5 (13·1-19·4)	83/112	9·1 (7·2-11·6)	0·62 (0·45–0·86)
Non-squamous	124/246	17·0 (14·0-NR)	159/246	11·9 (9·9-14·1)	0·69 (0·55–0·87)
Liver metastases					
Yes	50/68	10·2 (7·4-12·4)	67/86	8·1 (6·6-9·8)	0·83 (0·57–1·20)
No	140/293	19·4 (15·3-NR)	175/272	12·4 (10·4-14·4)	0·64 (0·51–0·80)
Bone metastases					
Yes	66/97	11·9 (8·6-15·0)	85/110	8·3 (6·7-9·8)	0·74 (0·53–1·01)
No	124/264	20·5 (15·5-NR)	157/248	12·4 (10·6-15·2)	0·65 (0·51–0·82)
CNS metastases					
Yes	29/64	NR (12·3-NR)	48/58	7·9 (5·0-10·7)	0·38 (0·24–0·60)
No	161/297	15·4 (13·8-19·4)	194/300	11·8 (10·0-13·7)	0·75 (0·61–0·92)
PD-L1 expression subgroups					
<1%	69/135	16·8 (13·7-NR)	89/129	9·8 (7·7-13·7)	0·62 (0·45–0·85)
≥1%	105/203	15·8 (13·8-NR)	139/204	10·9 (9·5-13·2)	0·64 (0·50–0·82)
1–49%	68/127	15·4 (12·6-NR)	78/106	10·4 (8·7-12·4)	0·61 (0·44–0·84)
≥50%	37/76	18·0 (13·1-NR)	61/98	12·6 (9·4-16·9)	0·66 (0·44–0·99)
All randomly assigned patients	**190/361**	**15·6 (13·9-20·0)**	**242/358**	**10·9 (9·5-12·6)**	**0·66 (0·55–0·80)***



Paz-Ares *et al*, Lancet Oncol 2021

What are the options for **advanced NSCLC PDL1 0%?**

- Pembrolizumab + chemo
- Atezolizumab + chemo +/- bev (NSQ only)
- Nivolumab + ipilimumab + chemo
- Nivolumab + ipilimumab

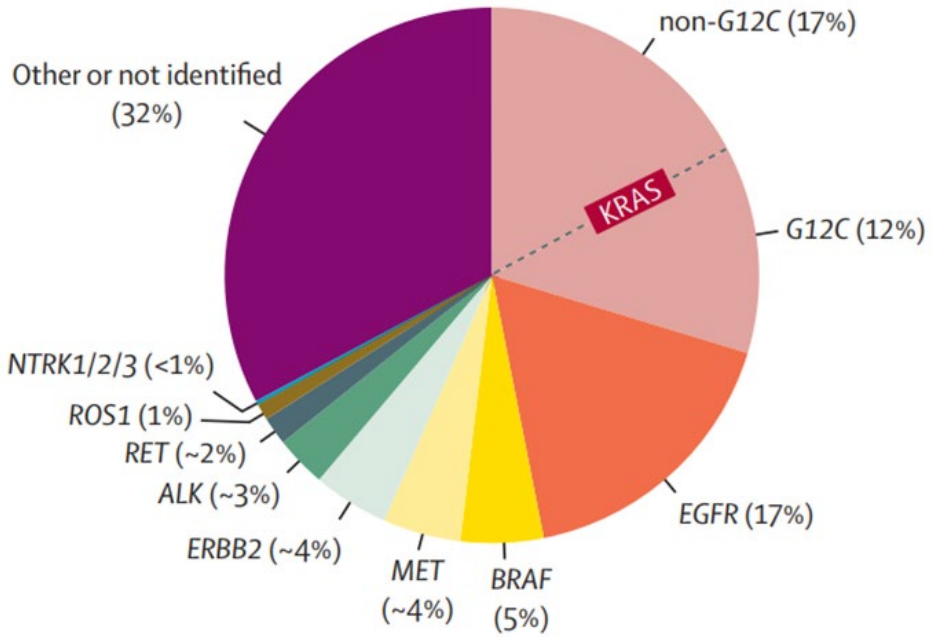
		CheckMate 227 Nivo/Ipi v Chemo	CheckMate 9LA Nivo/Ipi/Chemo vs Chemo
PD-L1 **≥1%**	Nonsquamous	**0.81** (0.67-0.99)	**0.71** (0.53-0.95)
	Squamous	**0.68** (0.51-0.89)	**0.70** (0.48-1.01)
PD-L1 **<1%**	Nonsquamous	**0.69** (0.53-0.89)	**0.75** (0.54-1.04)
	Squamous	**0.53** (0.34-0.84)	**0.48** (0.28-0.81)

	CheckMate 227		CheckMate 9LA	
All AE	**Nivo/Ipi**	**Chemo**	**Nivo/Ipi/Chemo**	**Chemo**
Treatment-related Gr 3-4	33%	36%	47%	38%
Treatment-related SAE	25%	14%	30%	18%

Bottom line:

Consider dual IO (ipi/nivo) regimens for PDL1 0 squamous. Beware toxicity.

Targetable molecular alterations in NSCLC



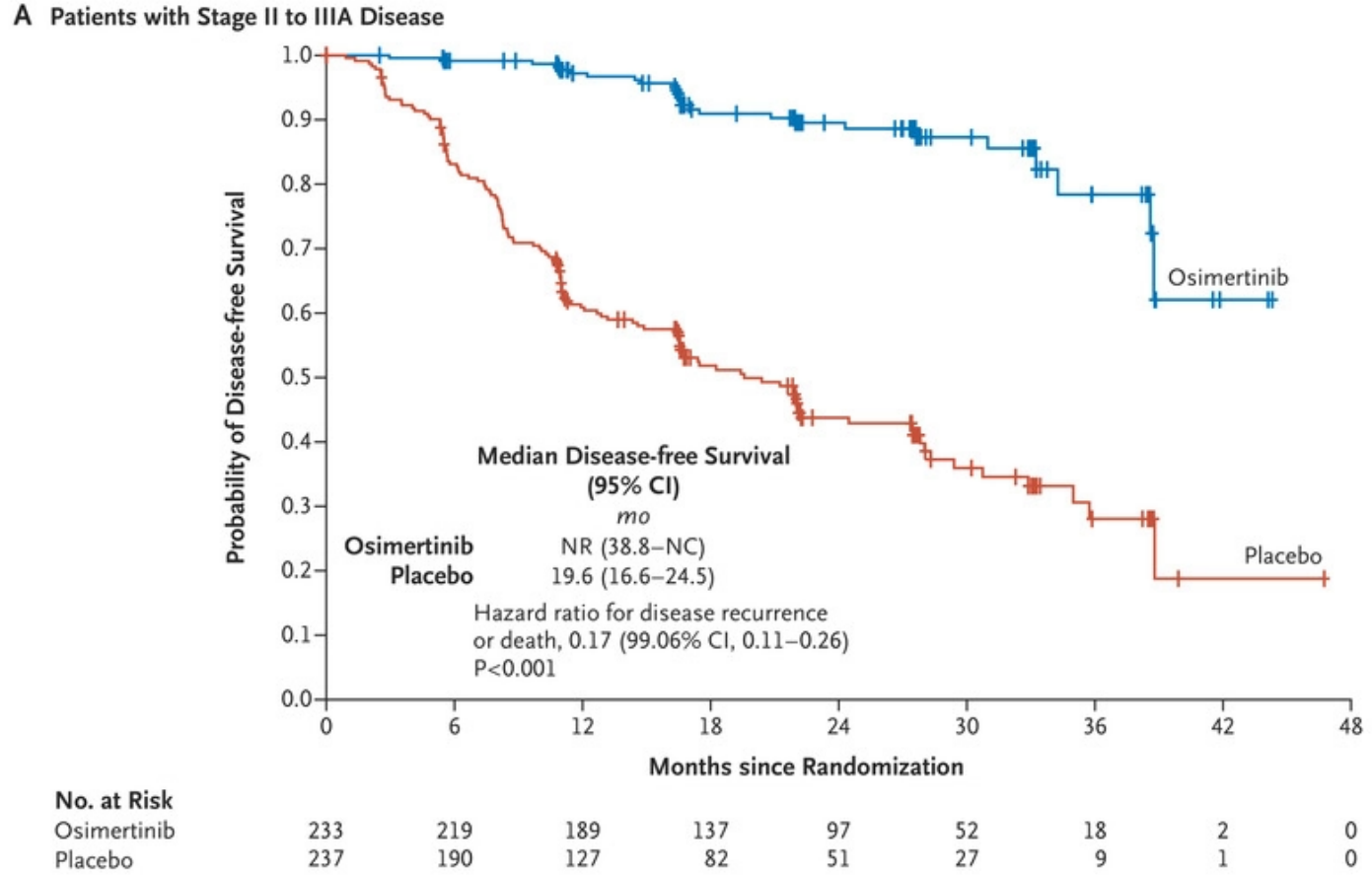
Molecular target	Approved drugs	
EGFR exon 19, 21	Osimertinib Erlotinib Erlotinib+ ramucirumab Erlotinib + bevacizumab	Afatinib Gefitinib
EGFR exon 20	Amivantamab	Mobocertinib
ALK	Alectinib Brigatinib Lorlatinib	Ceritinib Crizotinib
BRAF V600E	Dabrafenib + Trametinib	
NTRK fusion	Entrectinib	Larotrectinib
MET exon 14	Capmatenib Tepotenib	Crizotinib
ROS1	Entrectinib Crizotinib	Ceritinib Lorlatinib
RET	Selpercatinib Pralsetinib	
HER2	Trastuxumab deruxtecan	
KRAS G12C	Sotorasib	

Thai AA et al, Lancet 2021.

How to manage **EGFRm NSCLC after resection?**

- Who will benefit?
- Chemo before osi?
- How long to continue osi?
- What to do on relapse?

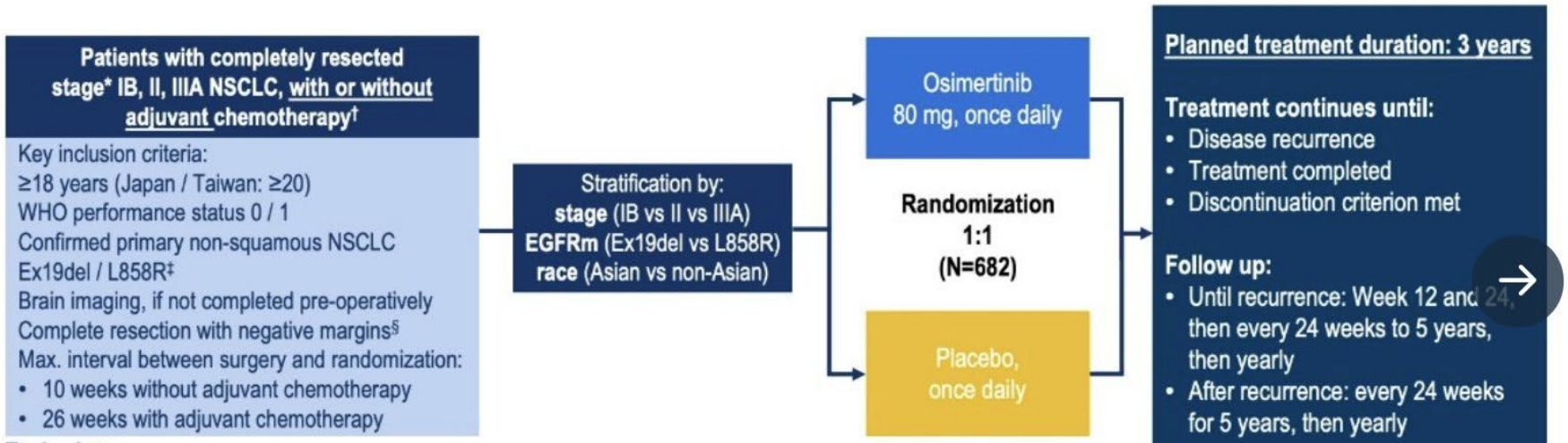
Adjuvant osimertinib



Wu Y et al, NEJM 2020

EGFR: Adjuvant osimertinib ADAURA

ADAURA Phase III double-blind study design



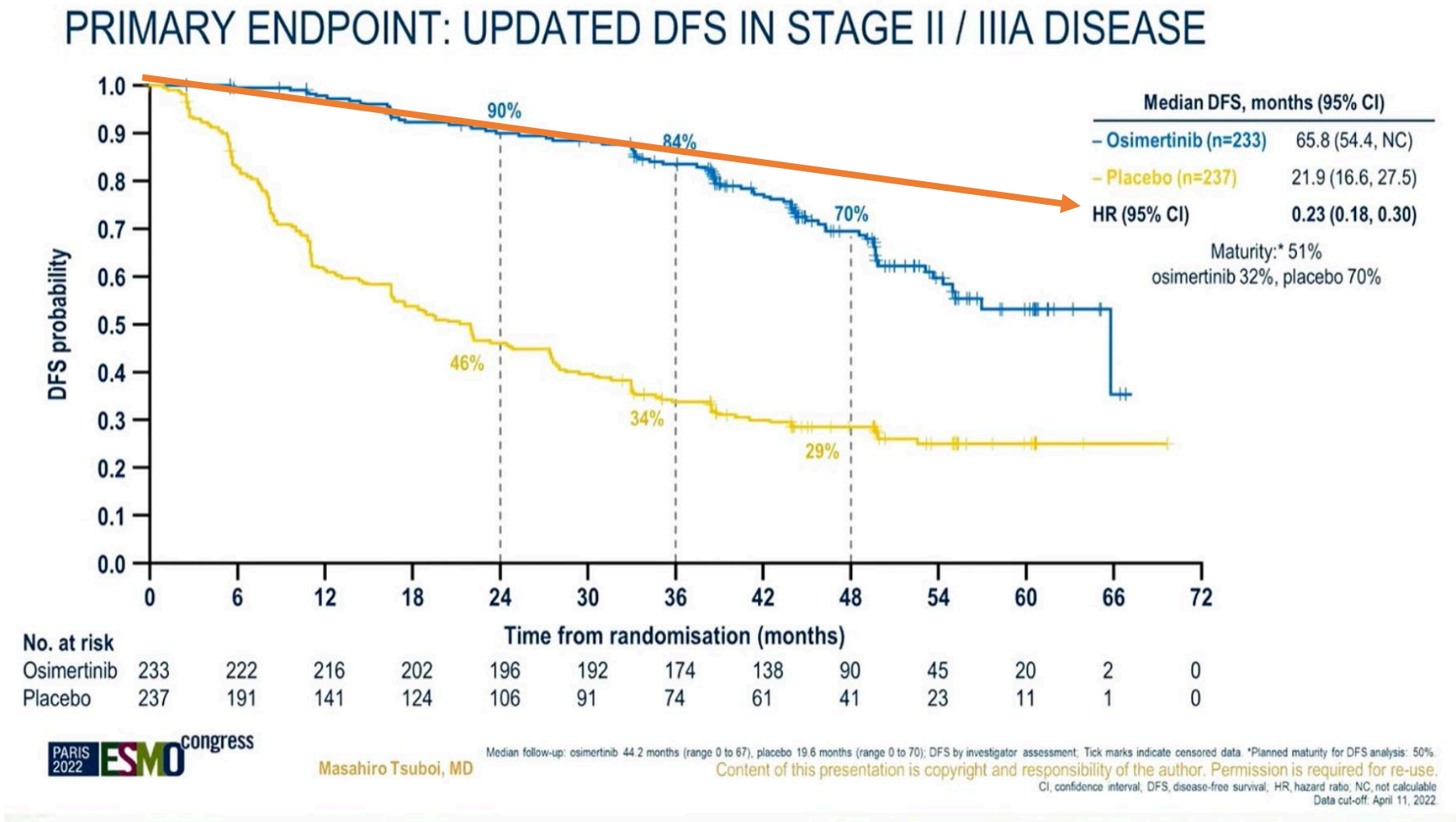
Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70

Enrolled	Race	Mutations	Stage	Node	Chemo
682	Asian 60%	Ex19del 55%	IB/II 65%	N0 40%	No 40%
	Non-Asian 40%	L858R 45%	IIIA 35%	N1/N2 60%	Yes 60%

Herbst R et al, ASCO 2020
Wu Y et al, NEJM 2020

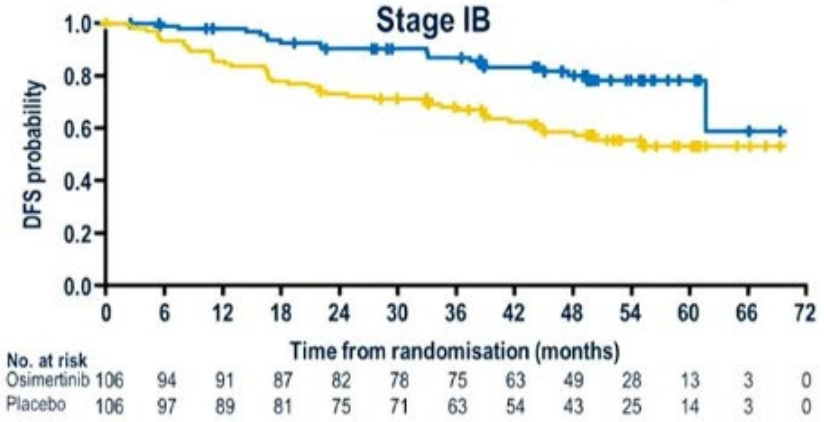
EGFR: Adjuvant osimertinib ADAURA

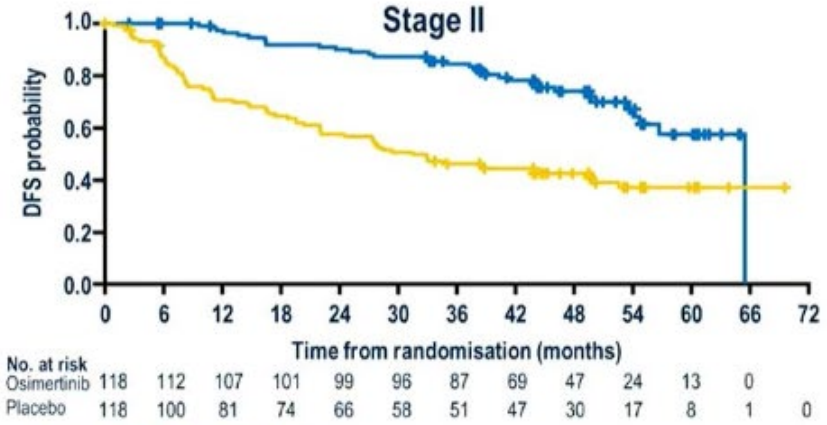


Tsuboi M et al, ESMO 2022

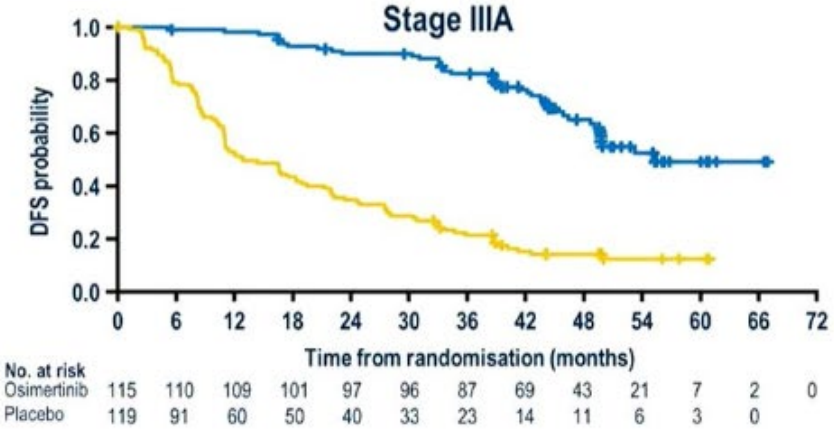
EGFR: Adjuvant osimertinib ADAURA

UPDATED DFS BY STAGE (AJCC / UICC 7TH EDITION)





	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (70, 87)	74 (64, 82)	65 (54, 74)
– Placebo	59 (48, 68)	42 (33, 51)	14 (8, 22)
Overall HR (95% CI)	0.41 (0.23, 0.69)	0.34 (0.23, 0.52)	0.20 (0.14, 0.29)



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DFS by investigator assessment; Tick marks indicate censored data.

AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio

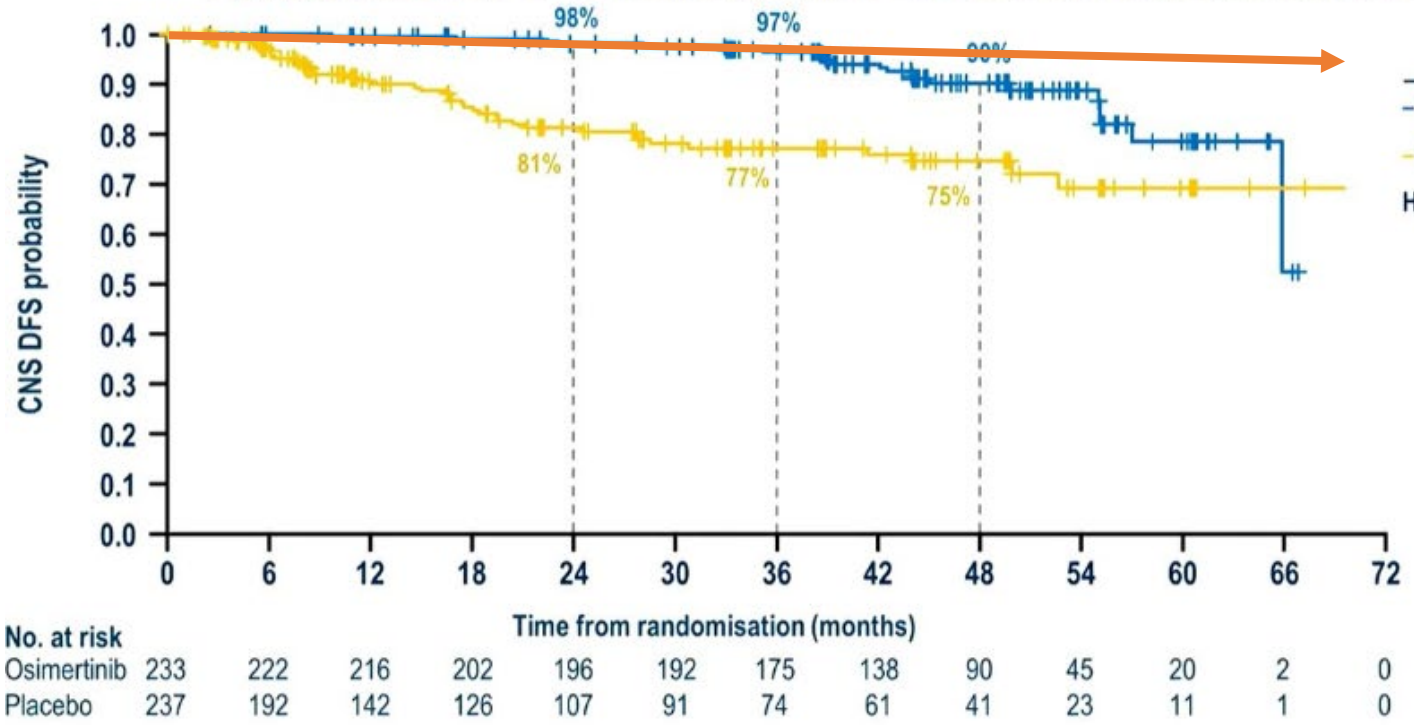
Data cut-off: April 11, 2022

Tsuboi M et al, ESMO 2022

EGFR: Adjuvant osimertinib ADAURA

UPDATED CNS DFS IN PATIENTS WITH STAGE II / IIIA DISEASE

- Overall, 63 patients (osimertinib n=22, placebo n=41) had CNS DFS events:*
  - 3 (14%) patients were on treatment at the time of CNS recurrence with osimertinib, versus 29 (71%) with placebo



Median CNS DFS, months (95% CI)	
– Osimertinib	NR (65.8, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	0.24 (0.14, 0.42)

Maturity 13%:
osimertinib 9%, placebo 17%

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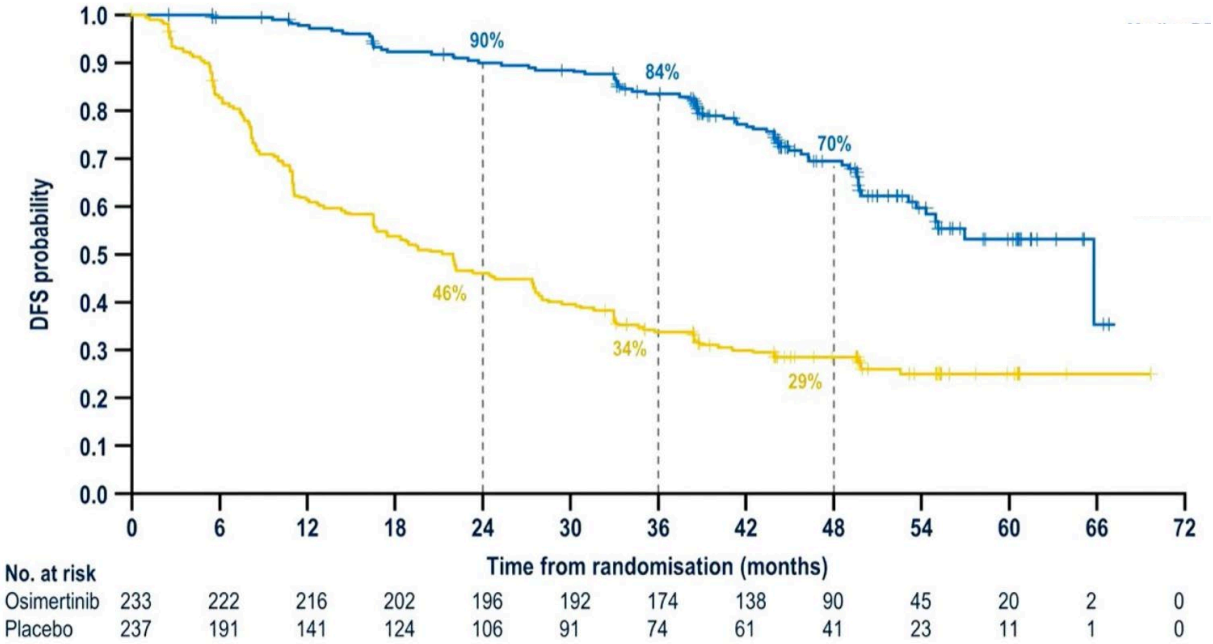
Median follow-up: osimertinib 44.2 months, placebo 20.4 months; DFS by investigator assessment; Tick marks indicate censored data
*Defined as CNS as the first site of disease recurrence, or death without any disease recurrence

CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; HR, hazard ratio; NC, not calculable; NR, not reached
Data cut-off: April 11, 2022

Tsuboi M et al, ESMO 2022

How to manage
EGFRm NSCLC after resection?

Adjuvant osimertinib

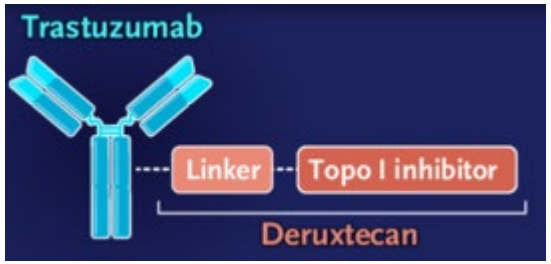


- Most benefit in highest risk
  - Osi after CRT? (LAURA trial)
- Use **chemo** first when indicated
- OFF: Close surveillance including MRI brain
- ON: Continue osi beyond 3 years?
  - Monitor closely after d/c
- Relapse on osi:
  1. Repeat NGS
  2. Treat: local tx, chemo, trial

Tsuboi M et al, ESMO 2022

How to manage advanced NSCLC with **HER2 mutation**?

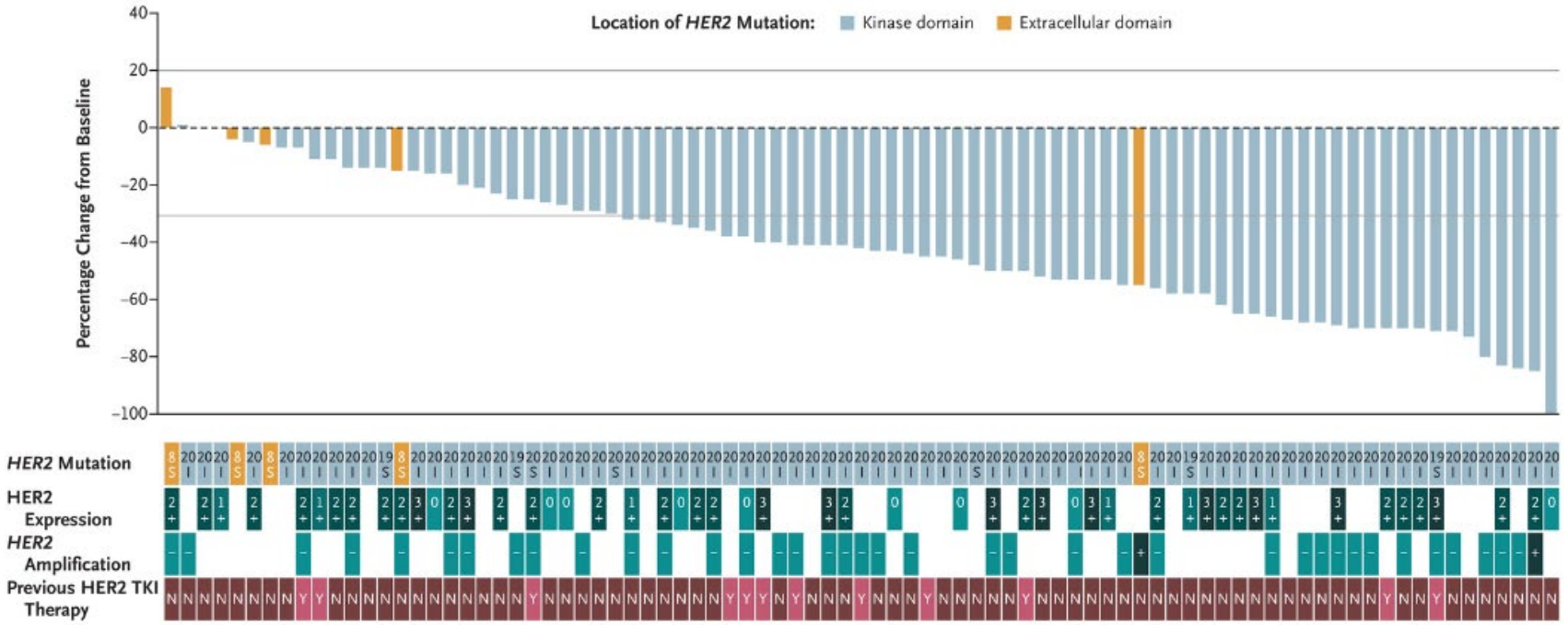
1. **Chemo +/- IO**
2. **Trastuzumab deruxtecan**



HER2 Alterations
Mutation (ex20ins)
Amplification (CNV)
Overexpression (IHC 3+)

DESTINY-Lung01 (2L)
- ORR 55%
- DCR 92%
- mPFS 8.2m
- mOS 18.6m

Gr ≥3 TRAE 46%
ILD 26%, 2 deaths



Li BT et al, NEJM 2022

HER2: T-DXd dosing
Destiny-Lung02

DESTINY-Lung02

Response by BICR

Response Assessment by BICR	Prespecified early cohort	
	T-DXd 5.4 mg/kg n = 52	T-DXd 6.4 mg/kg n = 28
Confirmed ORR,[a] n (%) [95% CI]	28 (53.8) [39.5, 67.8]	12 (42.9) [24.5, 62.8]
Best overall response, n (%)		
CR	1 (1.9)	1 (3.6)
PR	27 (51.9)	11 (39.3)
SD	19 (36.5)	14 (50.0)
PD	2 (3.8)	1 (3.6)
Not evaluable[b]	3 (5.8)	1 (3.6)
DCR,[c] n (%) [95% CI]	47 (90.4) [79.0, 96.8]	26 (92.9) [76.5, 99.1]
Median DoR, months [95% CI]	NE [4.2, NE]	5.9 [2.8, NE]
Median TTIR, months [range]	1.4 [1.2-5.8]	1.4 [1.2-3.0]
Median follow-up, months [range]	5.6 (1.1-11.7)	5.4 (0.6-12.1)

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Data cutoff: Mar 24, 2022.

[a]Proportion of patients with confirmed CR or PR assessed by BICR per RECIST v1.1. [b]3 patients were not evaluable at 5.4 mg/kg (1 patient never received treatment due to Covid; 2 patients discontinued before first tumor assessment); 1 not evaluable at 6.4 mg/kg (discontinued due to adverse event before first tumor assessment). [c]Proportion of patients with confirmed CR, PR, or SD assessed by BICR.

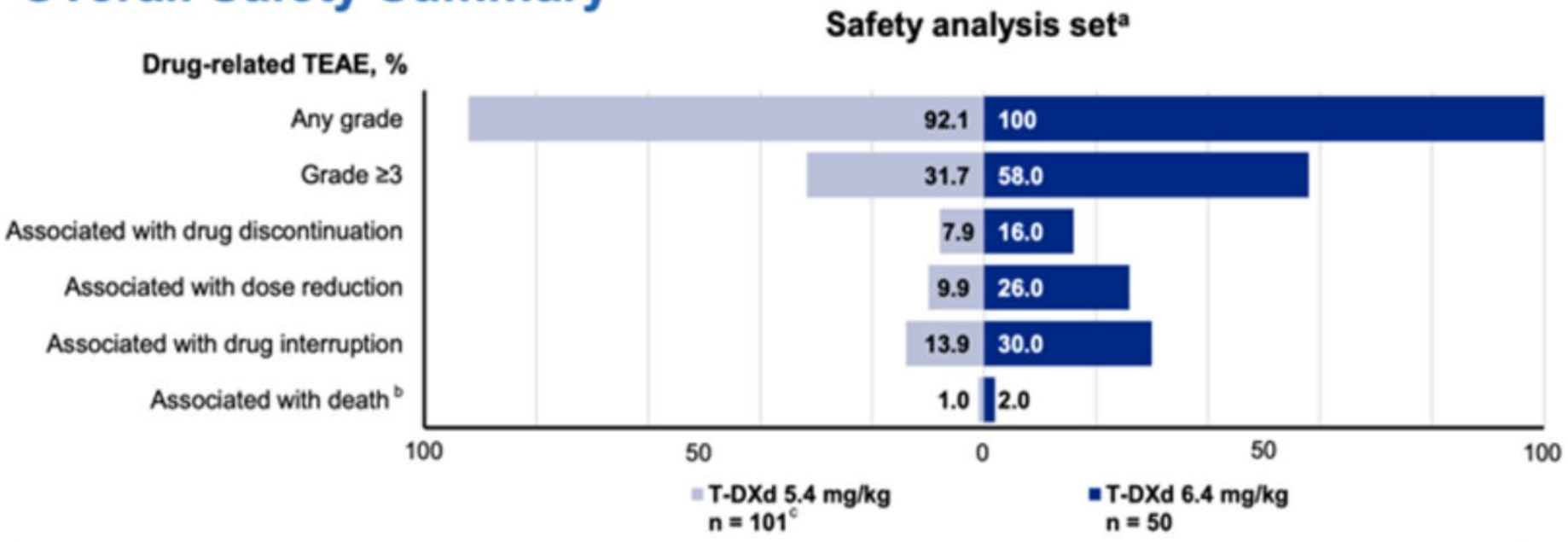
CR, complete response; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; TTIR, time to initial response.

Goto K et al, ESMO 2022

HER2: T-DXd dosing
Destiny-Lung02

DESTINY-Lung02

Overall Safety Summary



Median treatment duration, months (range)	3.7 (0.7-11.8)	3.3 (0.7-12.6)
Median follow-up, months (range)	3.8 (0-11.7)	3.9 (0.5-12.1)

Bottom line:

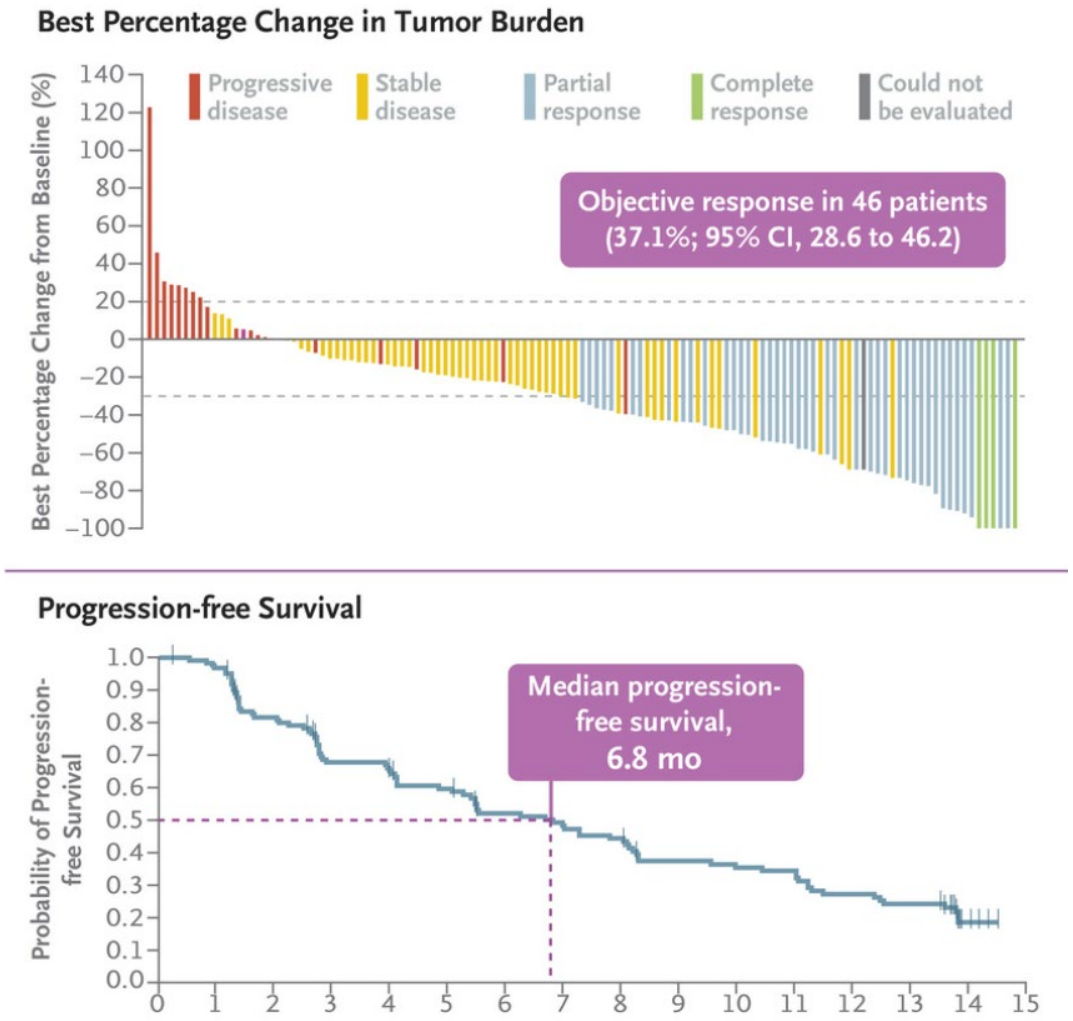
Consider TDXd at 5.4 mg/kg for HER2 mutated NSCLC.

How to manage advanced NSCLC with **$KRAS^{G12C}$ mutation?**

1. **Chemo +/- IO**
2. **Sotorasib or docetaxel**

CodeBreak 100

- ORR 37%
- DCR 81%
- mPFS 6.8m
- mOS 12.5m

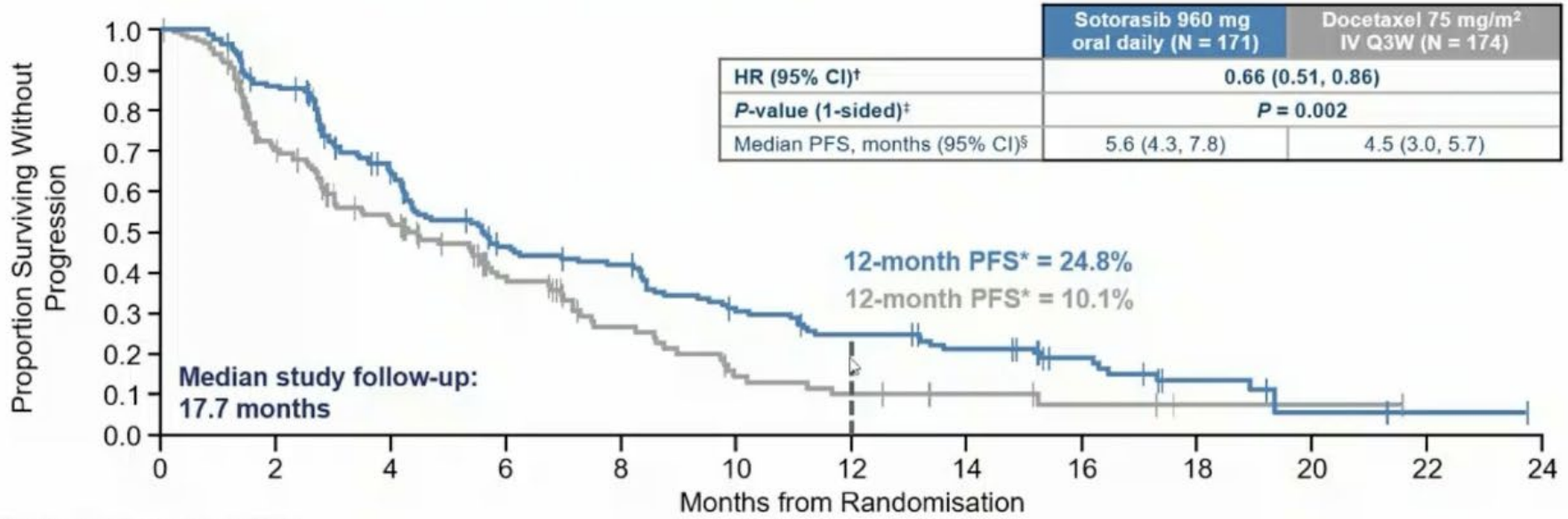


Skoulidis F et al, NEJM 2021

KRAS: Sotorasib (CodeBreaK 200)

Primary Endpoint: PFS by BICR

	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)



Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model.
‡*P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

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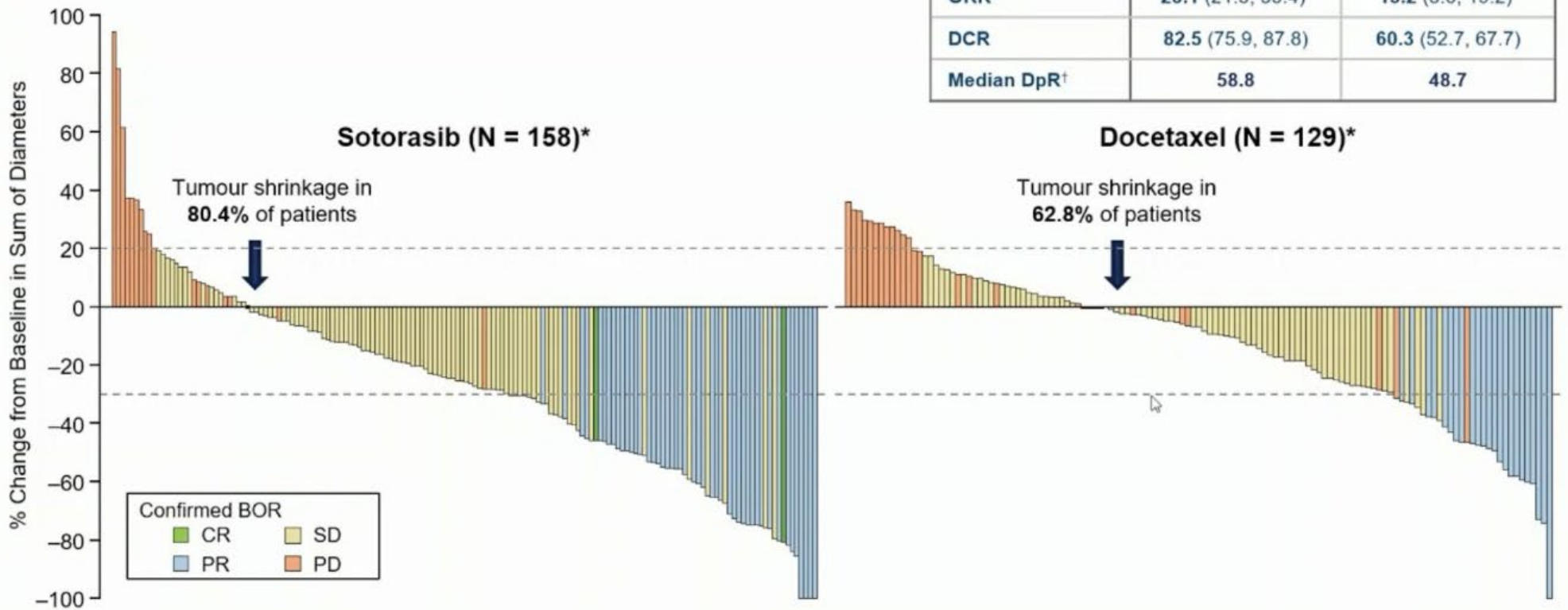
Johnson ML et al, ESMO 2022

KRAS: Sotorasib (CodeBreaK 200)

Tumour Response by BICR

% (95% CI)	Sotorasib	Docetaxel
ORR	**28.1** (21.5, 35.4)	**13.2** (8.6, 19.2)
DCR	**82.5** (75.9, 87.8)	**60.3** (52.7, 67.7)
Median DpR†	**58.8**	**48.7**



Response rate was significantly higher with sotorasib versus docetaxel ($P < 0.001$)

*Patients without baseline target lesions or post-baseline percent changes, or with BOR of NE are not shown.
†Median of best percent change from baseline in sum of diameters for confirmed responders.

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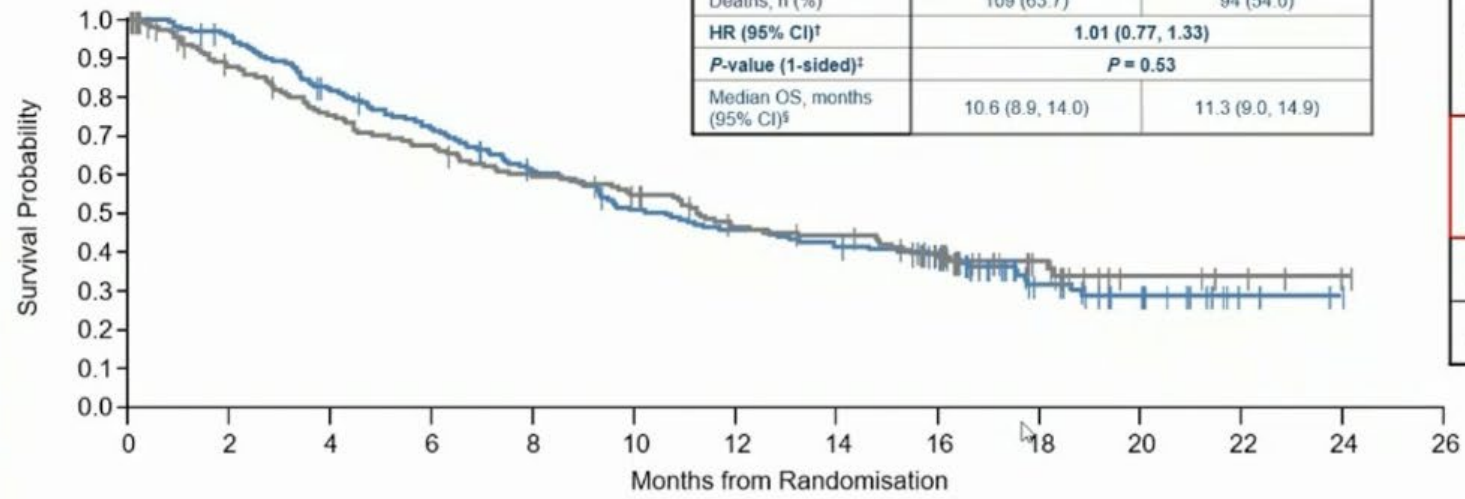
Johnson ML et al, ESMO 2022

KRAS: Sotorasib (CodeBreaK 200)

OS: Sotorasib vs Docetaxel*

	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)



Number of Patients at Risk:

Sotorasib	171	162	137	119	98	81	73	66	56	25	15	3	0
Docetaxel	174	135	115	103	90	81	65	61	44	20	7	4	1	0

	Sotorasib	Docetaxel
Any subsequent treatment, including crossover**	36%	42%
Subsequent $KRAS^{G12C}$ inhibitor, including crossover	4%	34%
Subsequent chemo	21%	12%
Subsequent IO	9%	6%

*OS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model
‡ *P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.
**Patients (16.4% in sotorasib arm, 5.2% in docetaxel arm) were treated beyond progression

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Johnson ML et al, ESMO 2022

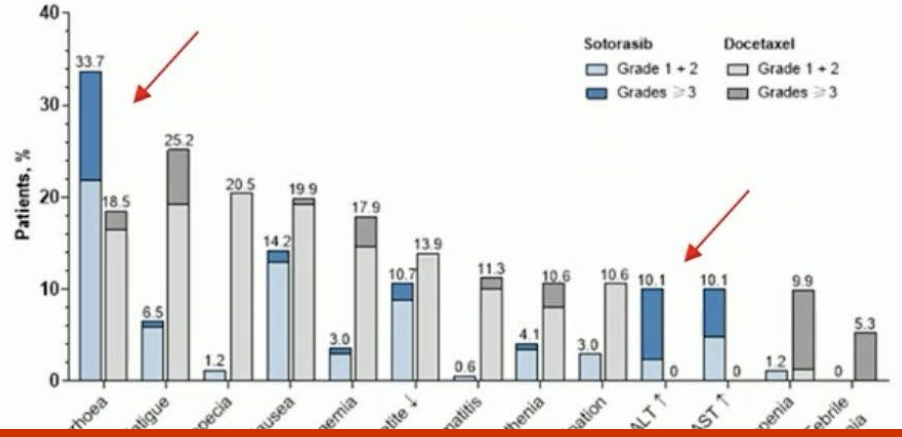
KRAS: Sotorasib (CodeBreaK 200)

Are there any drawbacks to 2nd line sotorasib?

- ✓ Sotorasib arm had fewer treatment-related adverse events, especially severe (10.5% v 22.7%)
- ✓ Similar rate of discontinuation for toxicity, toxic deaths
- ✓ Convenience of oral agent versus IV

What about financial toxicity?

Drug costs/month:	US	Canada
Sotorasib	>$17,900 USD.	$13,488 CAD
Docetaxel	~$ 1,700 USD.	~$ 300 CAD

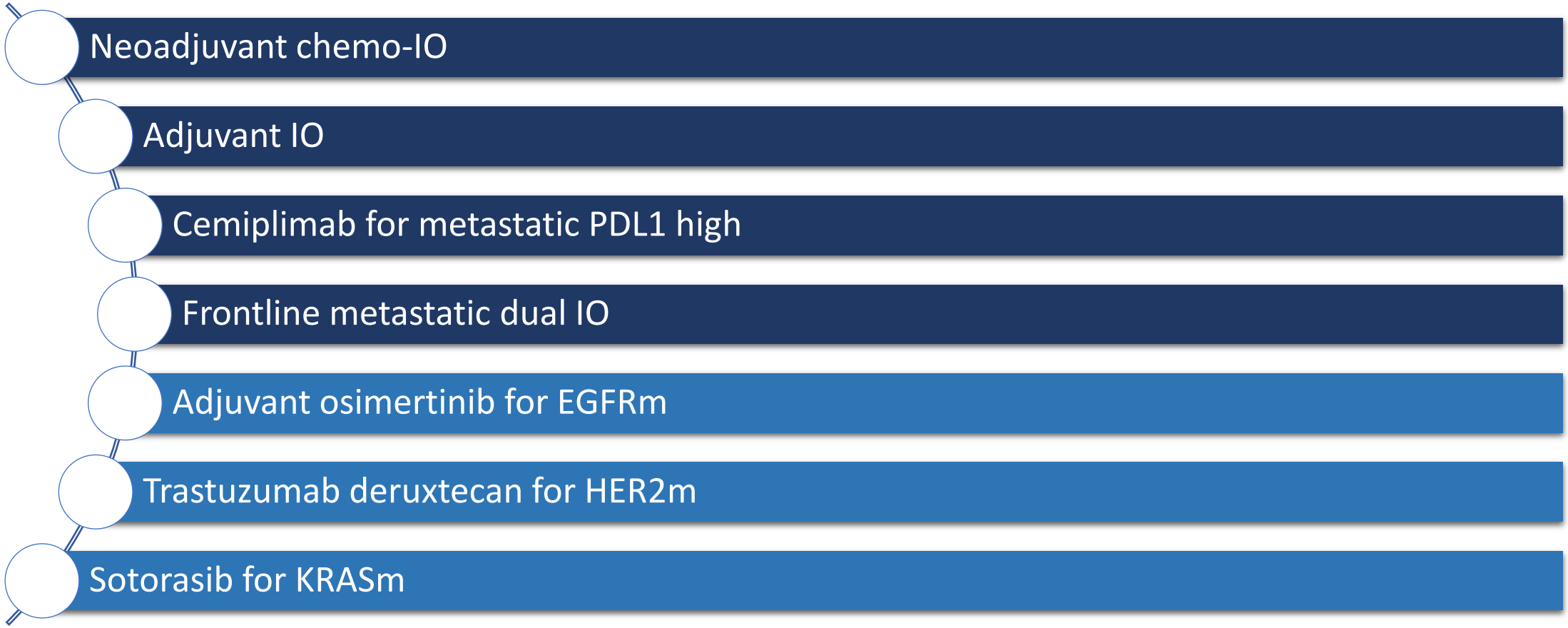


HR PFS >0.65; better QOL, >10% 1 yr PFS improvement

Bottom line:

Try sotorasib after chemo-IO for KRASm. Need more data on tx combinations and sequencing.

What's new in NSCLC?



Q&A