Neoadjuvant or Adjuvant Therapy For Lung Cancer. Does it Matter?

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Janakiraman Subramanian MD, MPH

Objectives

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- Chemotherapy's role in peri-operative setting
- Targeted therapy in the adjuvant setting
- Role of immunotherapy
    - Adjuvant vs Neoadjuvant
- Future landscape

Role of cytotoxic chemotherapy in resectable NSCLC

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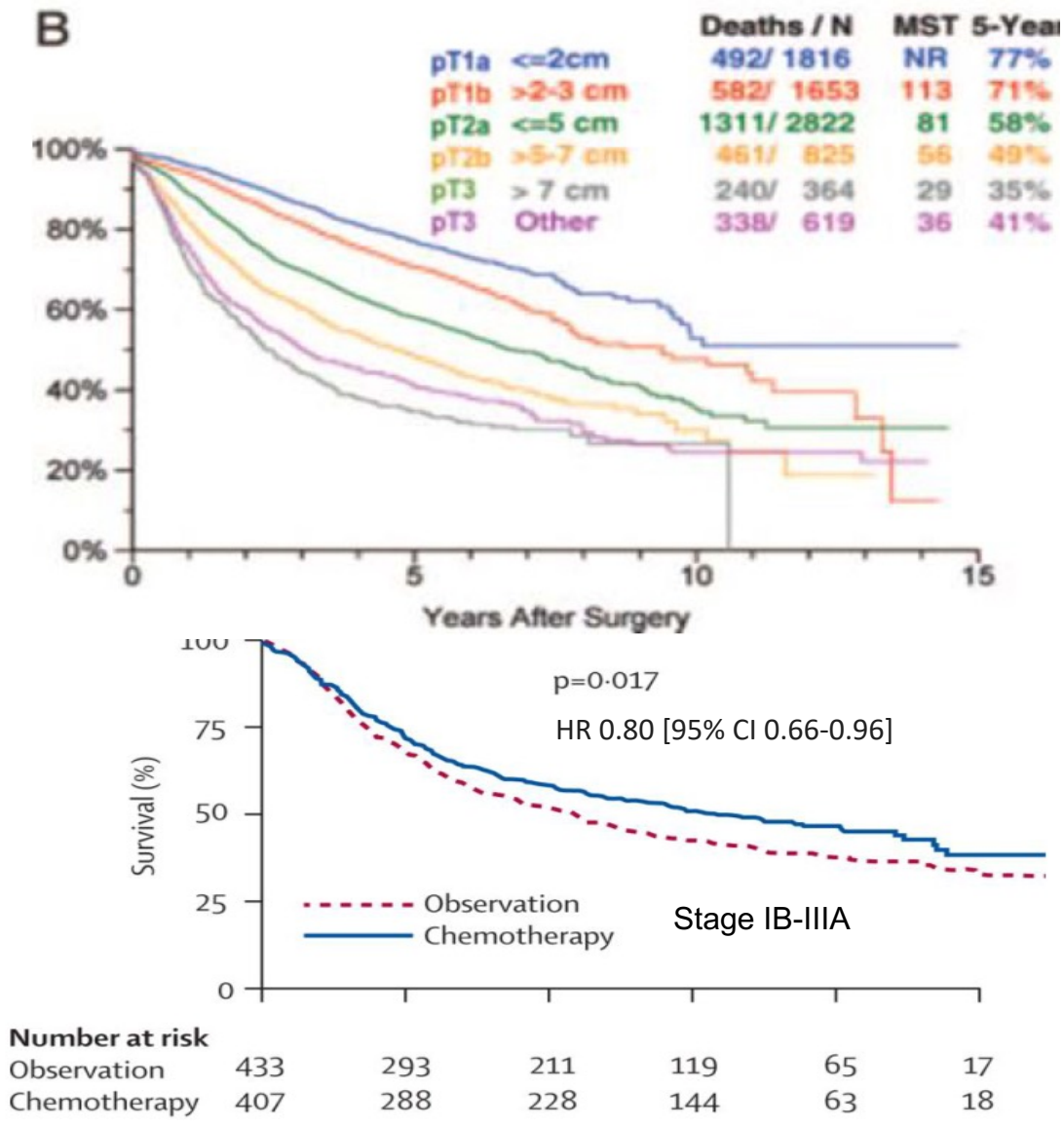

- 5-year OS rates
  - pT1a 77% v pT3 35%-41%
- Recurrence is primarily distant disease
- Platinum based chemotherapy does reduce disease recurrence & improve OS.

Detterbeck. Chest 2009, Douillard. Lancet Oncol 2006

Adjuvant vs Neoadjuvant Chemotherapy

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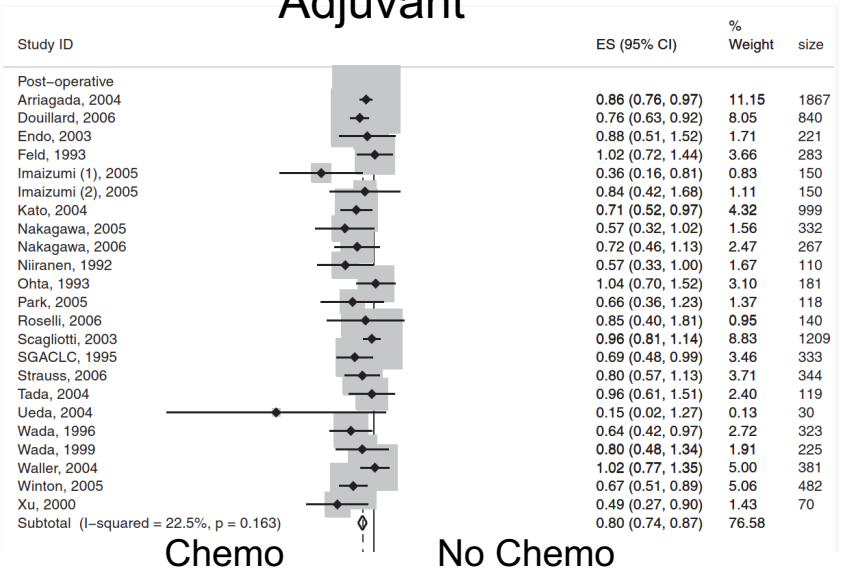
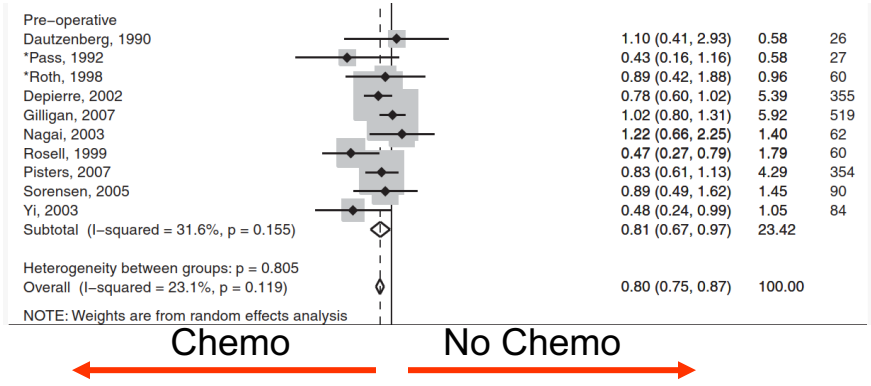
Meta – analysis of adjuvant and neo adjuvant chemotherapy

Adjuvant



HR 0.80 (0.74-0.87, p <0.001)

Neo-Adjuvant



HR 0.81 (0.68-0.97, p = 0.024)

- LACE Meta-analysis: 5-year OS increased by 5.4% ± 1.6%
- No significant different difference in OS benefit between adjuvant and neo-adjuvant chemotherapy.

Lim et al. J Thorac Oncol 2009, Pignon et al. JCO 2008

Adjuvant Treatment of EGFR mutation positive NSCLC

Peri-op EGFR TKI

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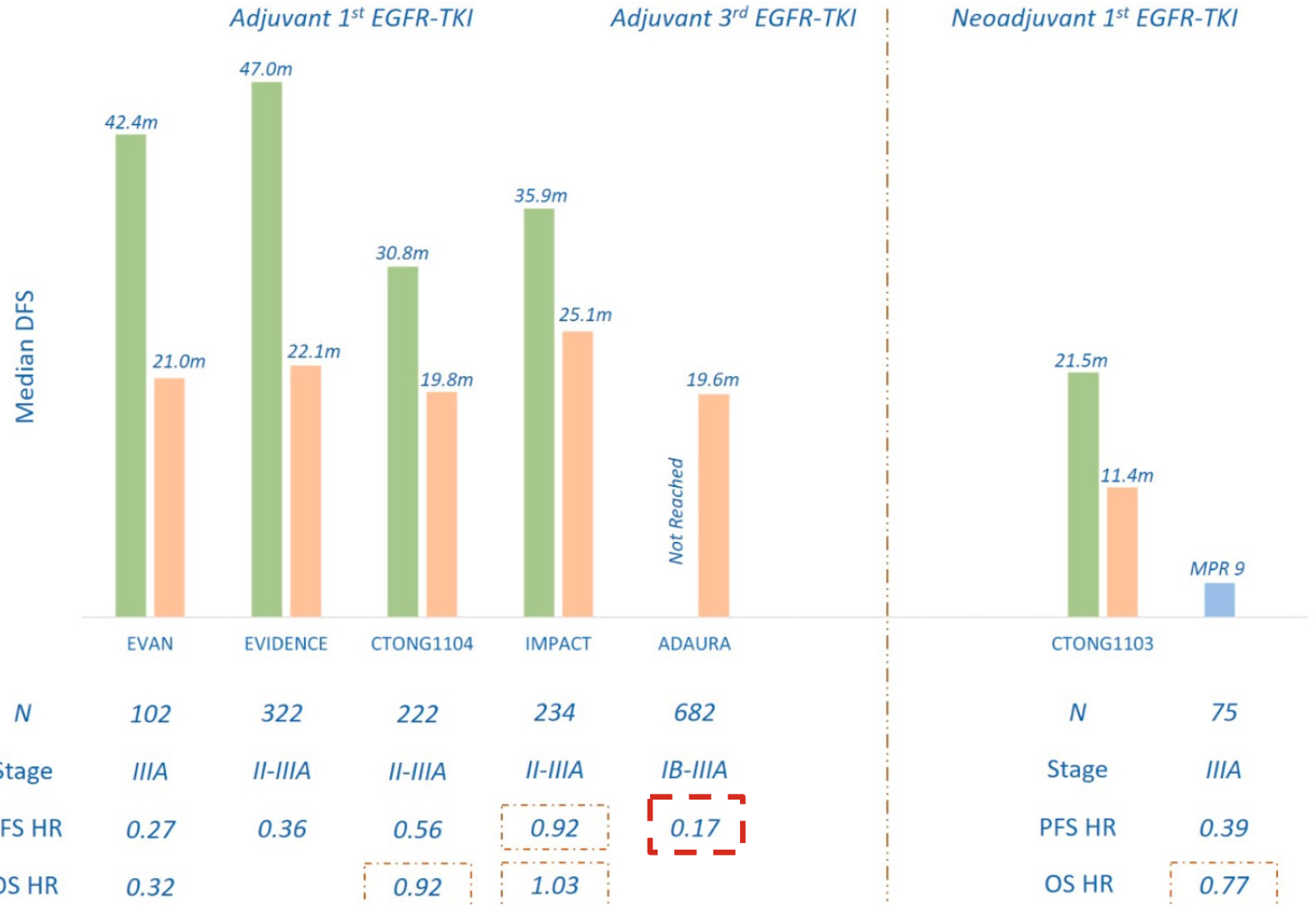

Liu et al. Lung Cancer 2023

The NEW ENGLAND JOURNAL of MEDICINE

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Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

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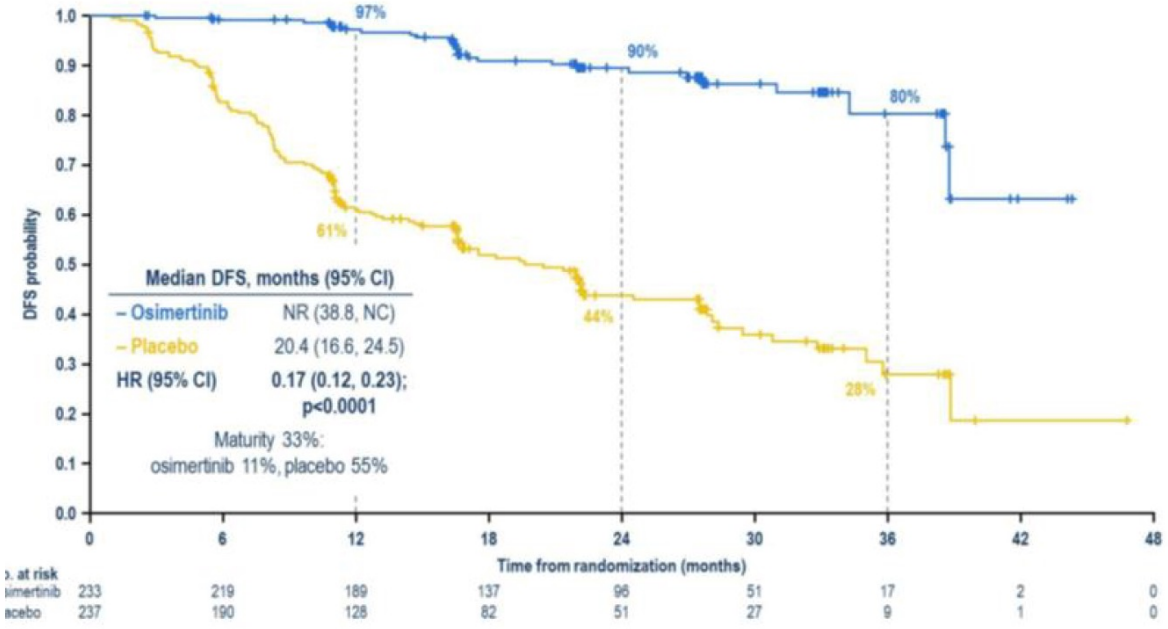

- ADAURA established the paradigm of adjuvant osimertinib for 3 years in resected stage IB-IIIA EGFR exon 19 or L858R NSCLC.
- Primary endpoint DFS; HR of 0.17 (0.12-0.23)
- Median DFS NR vs 19.6 mo
- CNS DFS NR vs 48.6 mo

ADAURA Update – ESMO 2022

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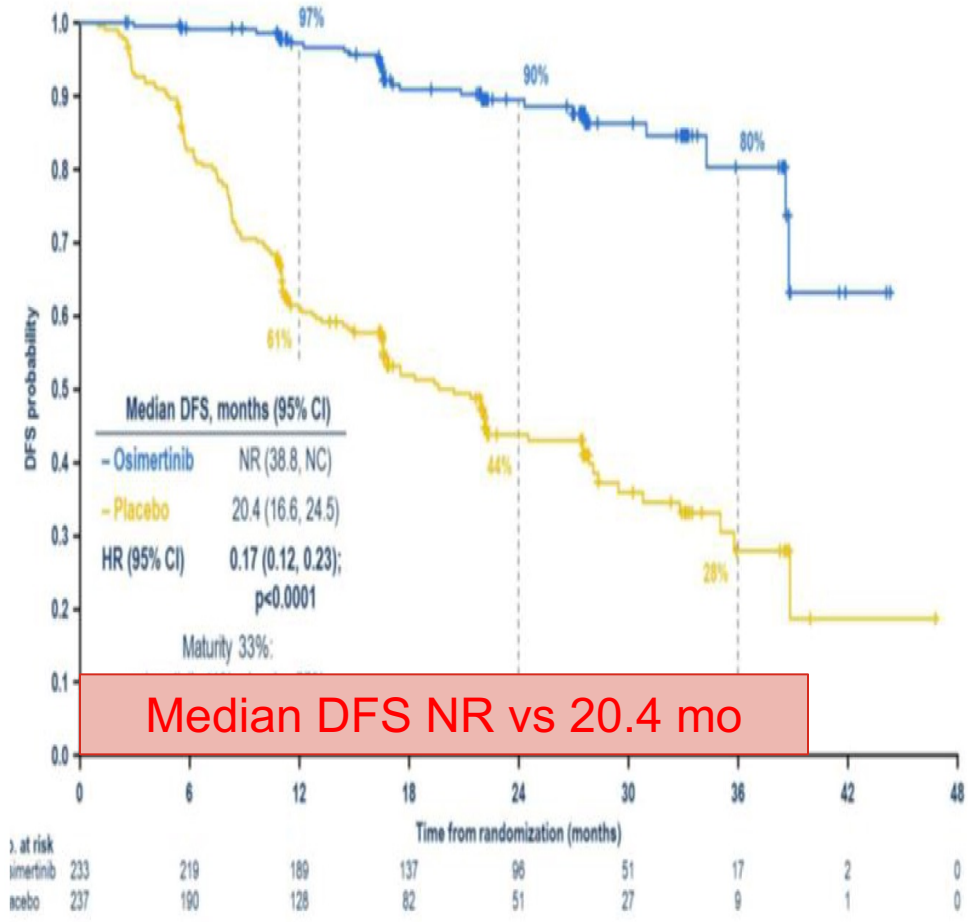
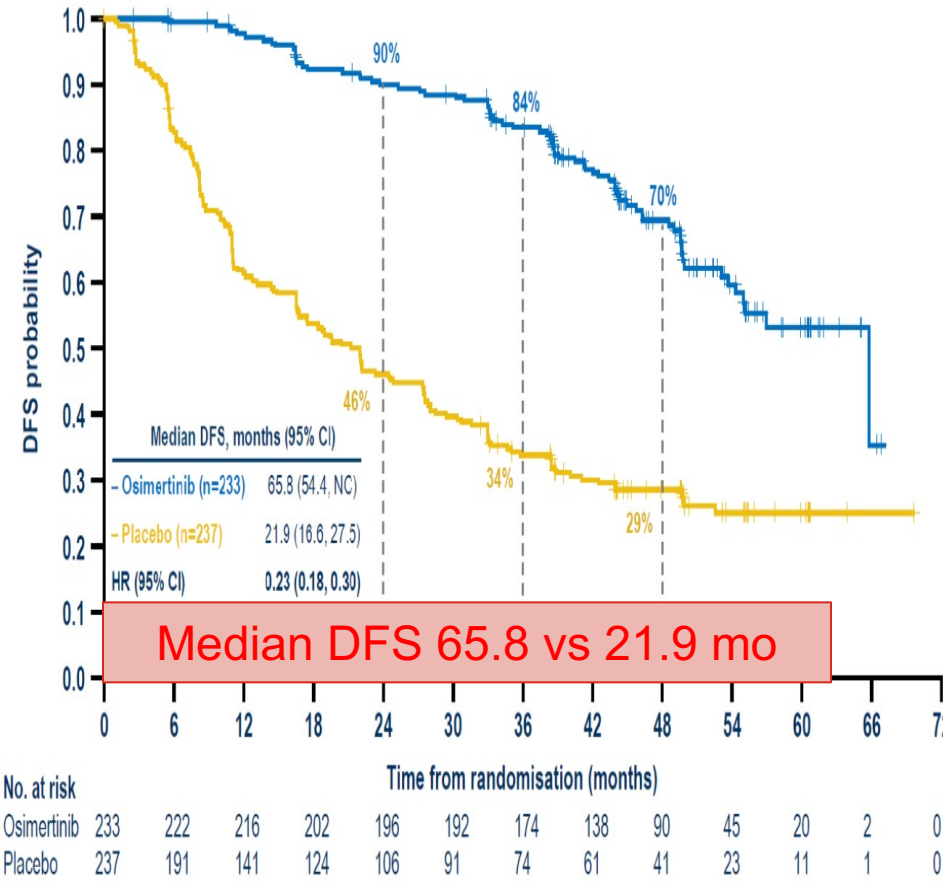
4-year Update – consistent DFS benefit HR 0.23 (0.18, 0.30) from 0.17 (0.12, 0.23)





Wu et al. NEJM 2020, Tsuboi et al ESMO 2022,

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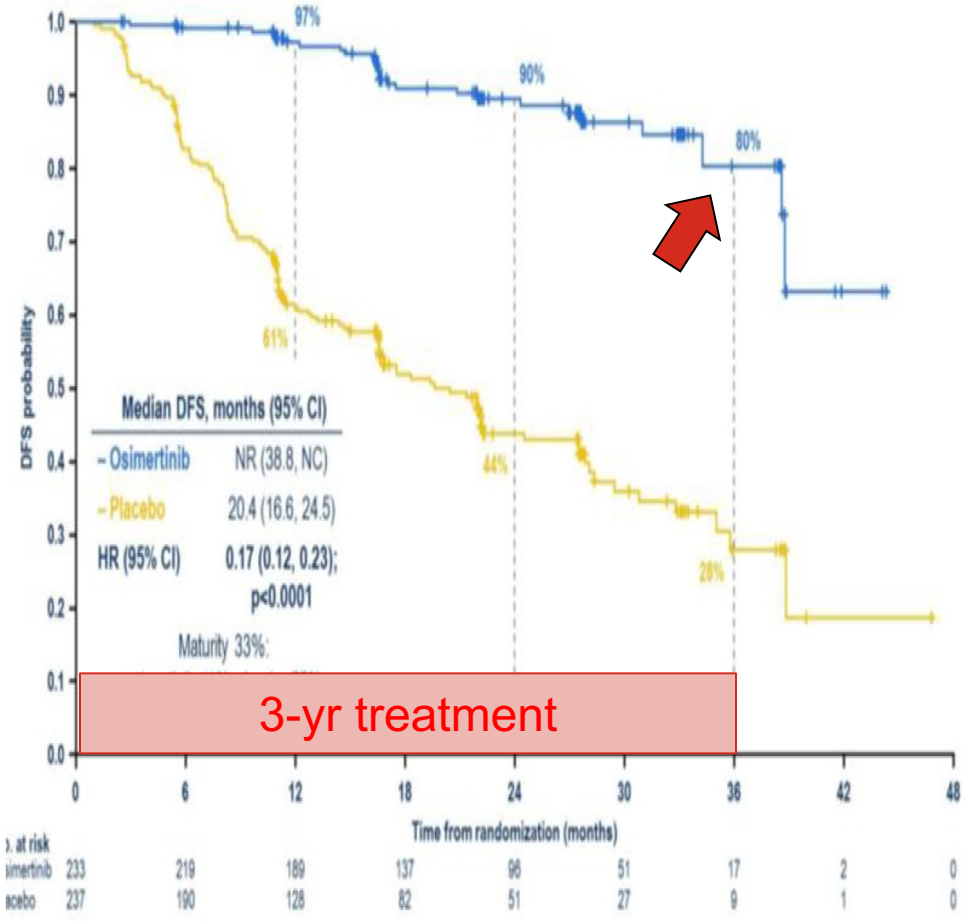
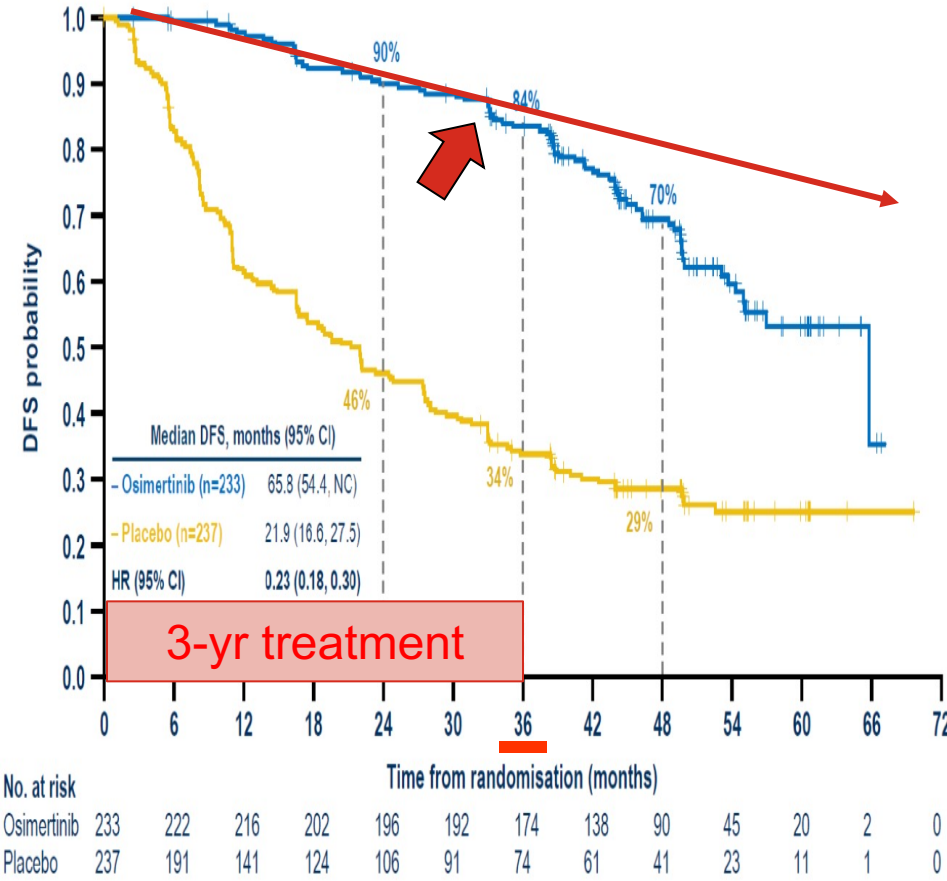
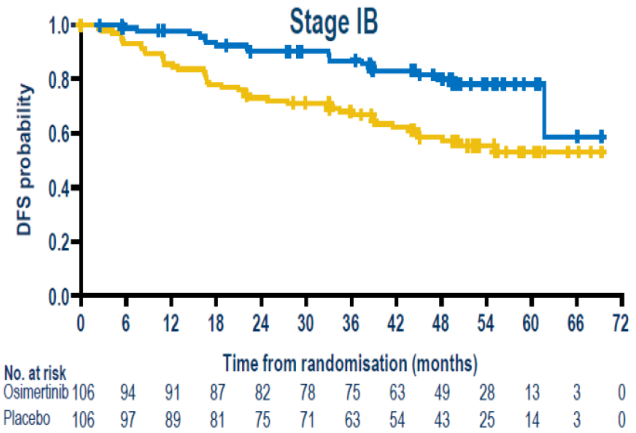
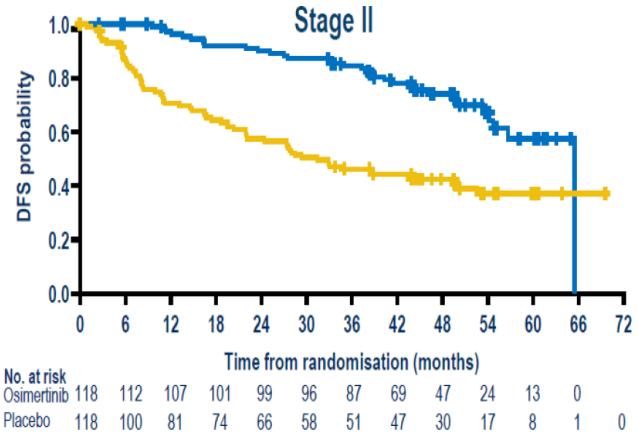


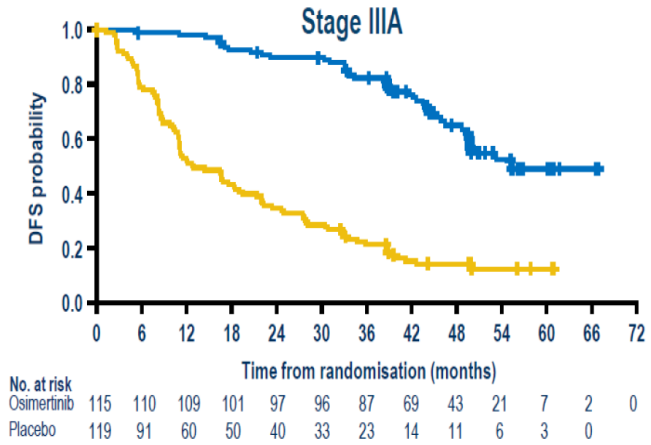


Wu et al. NEJM 2020, Tsuboi et al ESMO 2022,

DFS by stage: a waning effect for stage II and IIIA?







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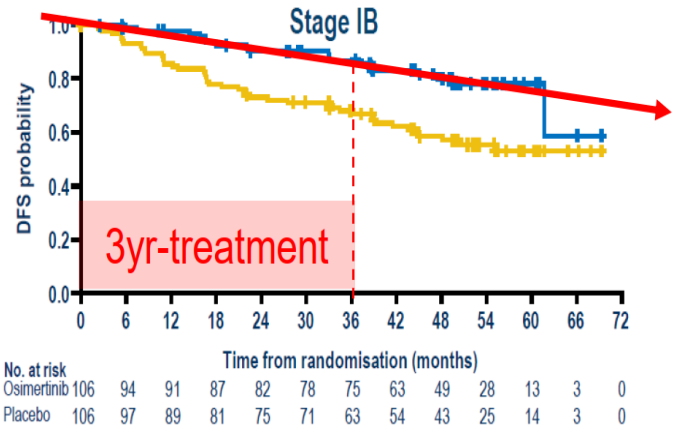
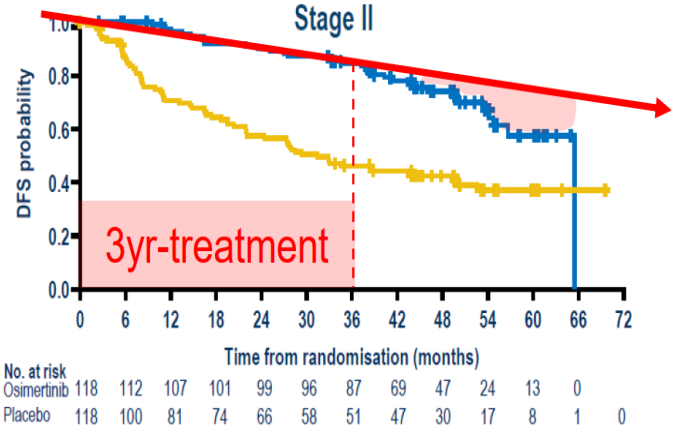
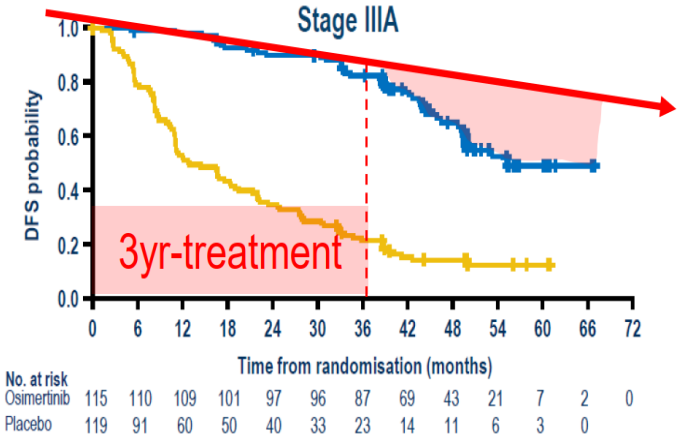
Tsuboi et al. ESMO (2022)

DFS by stage: a waning effect for stage II and IIIA?

A potential excess of DFS events for stage







Questions

1. For stage IB: are more patients cured with 3yr osimertinib than stage II/IIIA, or are there simply not enough events post treatment discontinuation?
2. For stage II/IIIA:
   - what is the optimal duration of osimertinib – is 3 years enough?
   - is osimertinib simply delaying relapse & if so, is the huge DFS difference meaningful to patients and payers?
   - how does this change adjuvant chemotherapy decision-making?
3. If stopping osimertinib at 3yr, what's the optimal imaging frequency post treatment discontinuation?

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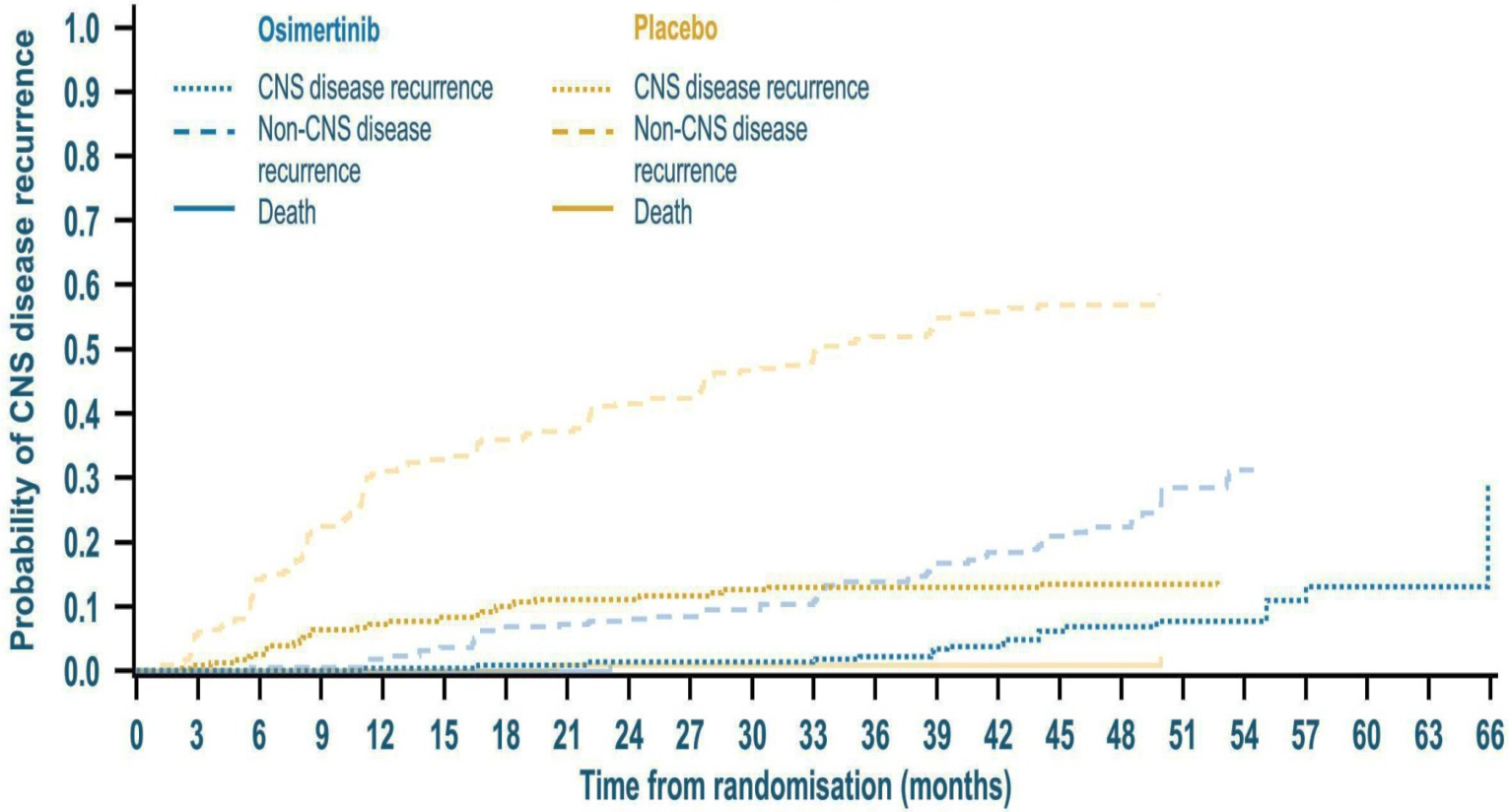
Tsuboi et al. ESMO (2022)

CONDITIONAL PROBABILITY OF CNS* AND NON-CNS RECURRENCE IN PATIENTS WITH STAGE II / IIIA DISEASE

- The estimated probability of observing CNS recurrence (in the absence of non-CNS recurrence or death) at 36 months was 2% (95% CI: 0.9%, 5.0%) with osimertinib versus 13% (95% CI: 8.5%, 18.5%) with placebo
- The cumulative incidence† of CNS recurrence was consistently lower in the osimertinib arm than in the placebo arm



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Masahiro Tsuboi, MD

*Defined as the probability of observing CNS as the first recurrence event, conditional on the patient not experiencing a competing risk event (non-CNS recurrence and death by any cause) by time t; †Cumulative incidence function calculated using a Fine and Gray model.

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CI, confidence interval; CNS, central nervous system; DFS, disease-free survival

Data cut-off: April 11, 2022.

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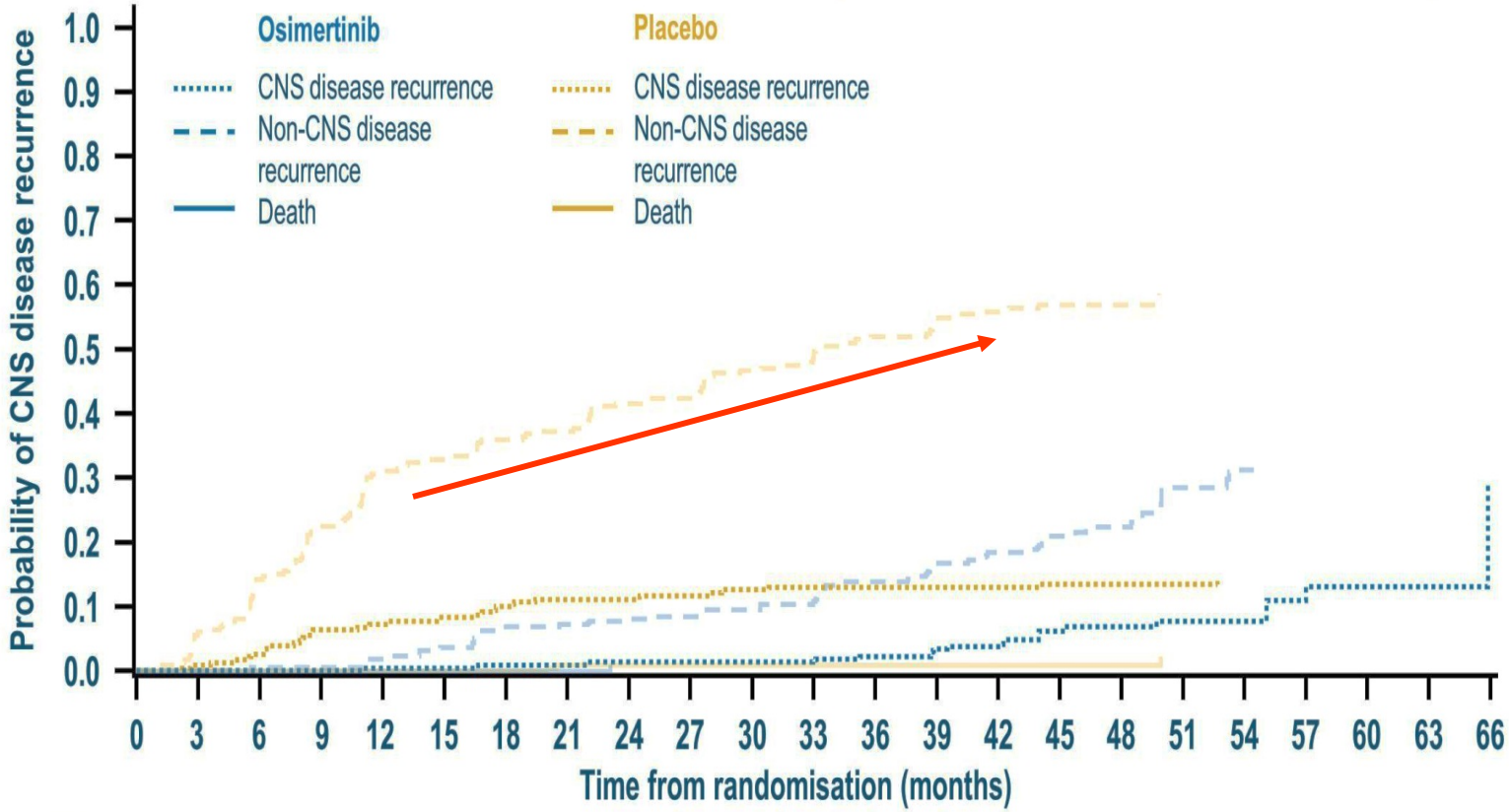

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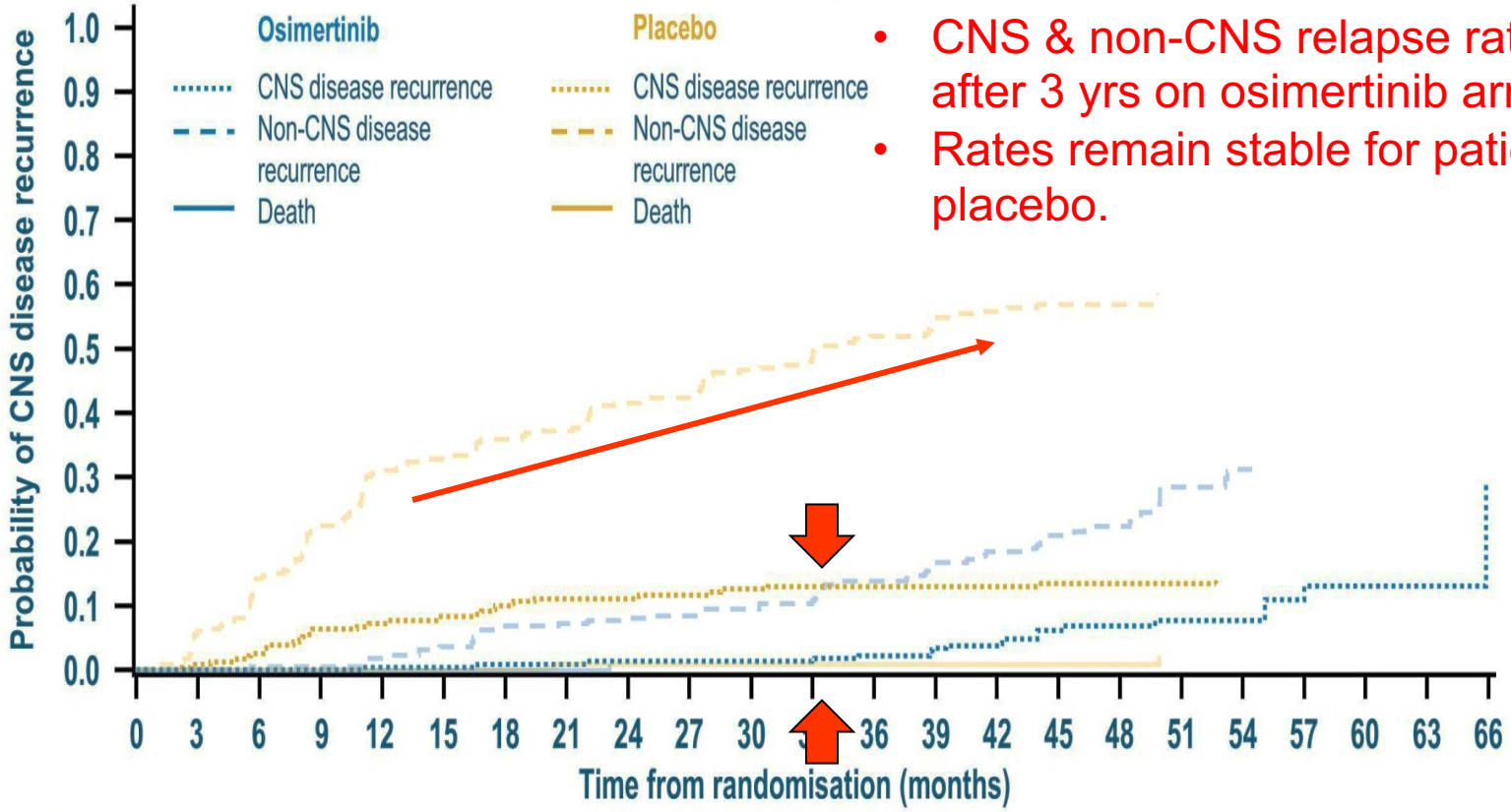

- CNS & non-CNS relapse rates rise after 3 yrs on osimertinib arm.
- Rates remain stable for patients on placebo.

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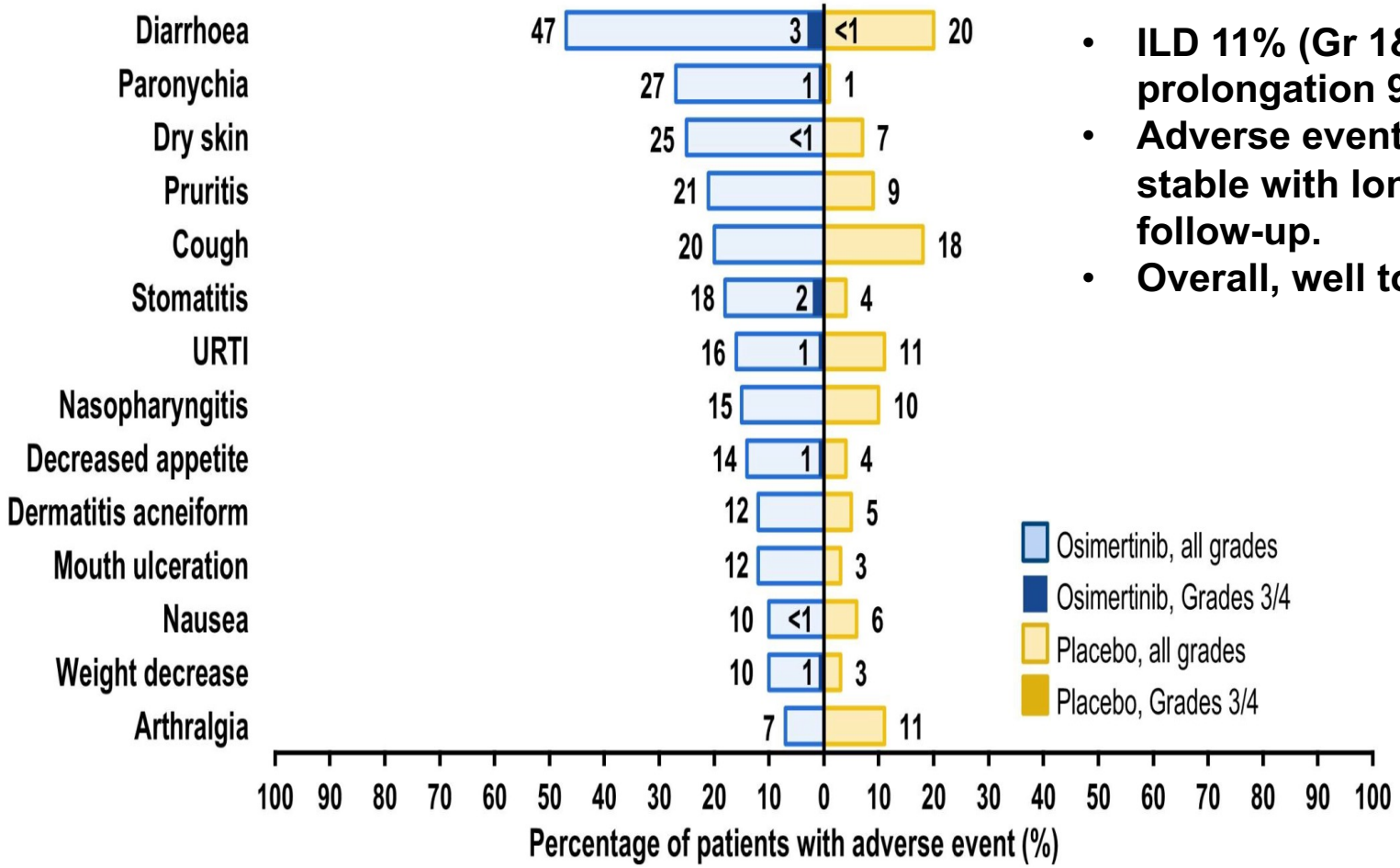
ALL CAUSALITY ADVERSE EVENTS (≥10% OF PATIENTS)



- **ILD 11% (Gr 1&2) QTc prolongation 9%.**
- **Adverse events remain stable with long term follow-up.**
- **Overall, well tolerated.**

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*Compared with the January 17, 2020 data cut-off, one additional patient reported interstitial lung disease (grouped term): pneumonitis, Grade 2; †Grade 1, n=6; Grade 2, n=5; Grade 3, n=0; ‡Osimertinib: Grade 1, n=16; Grade 2, n=10; Grade 3, n=4; placebo: Grade 1, n=7; Grade 2, n=0; Grade 3, n=1.

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QTc, electrocardiogram QT; URTI, upper respiratory tract infection
Data cut-off: April 11, 2022.

Targeted Therapy Futurescape

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Target	A/ Neo A	Study	Phase	Stage	Regimen	Primary Endpoint
EGFR	A	ICTAN	III	IIA-IIA	C v C + Icotinib	DFS
		CORIN	II	IB	Obs v Icotinib	OS
		ALCHEMIST	III	IB-IIIA	C v C + Erlotinib	OS
		APEX	III	II-IIIA	C v C + Almo vs Almonertinib	DFS
	NeoA	NEOADAURA	III	II-IIIB	Osi v Osi + C v P + C	MPR
		ANSWER	II	IIIA	Almo v Erlot/C	ORR
		NeoIpower	II	II-IIIB	Icotinib + C	MPR
ALK	A	ALCHEMIST	III	IB-IIIA	C v C + crizotinib	OS
	NeoA	ALINA	III	IB-IIIA	C v alectinib	MPR
RET	A	LIBRETTO-432	III	IB-IIIA	Selpercatinib v P	EFS
MET	NeoA	GEOMETRY-N	II	IB-IIIB	Capmatinib	MPR
ALK/ROS1/ BRAF/RET/ NTRK	NeoA	NAUTIKA1	II	II-III	TKI x 2 cycles	MPR

Conclusions

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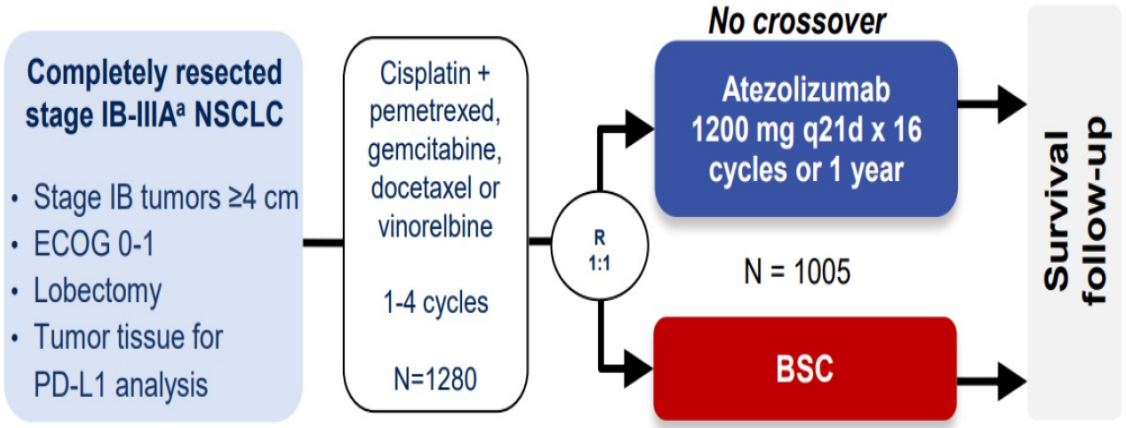
- Adjuvant osimertinib improves DFS in patients with resected EGFRm+ NSCLC. Reduces risk of recurrence particularly CNS mets.
- Well tolerated, no new AEs on 4-yr follow-up
- But questions remain,
  - Is 3 years of adjuvant osimertinib enough?
  - Will there be an OS benefit?
  - Is treatment waning effect specific to stages II & III?
  - How long do we surveil patients? Is 5 years enough?
- Expecting data on other targets including ALK, RET, MET, ROS1, BRAF & NTRK

Immunotherapy in Resectable NSCLC

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

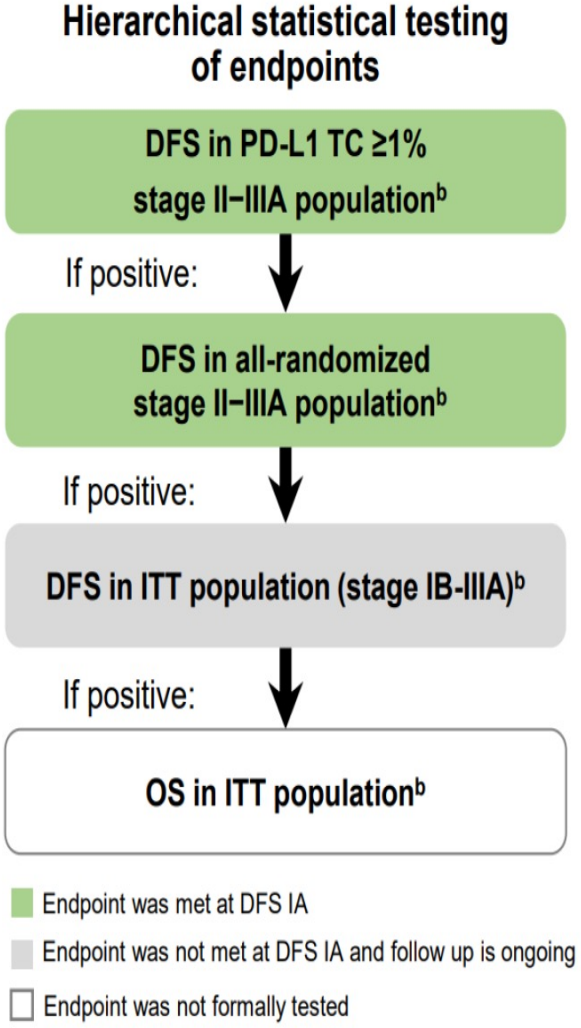
Key secondary endpoints

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

Key exploratory endpoints

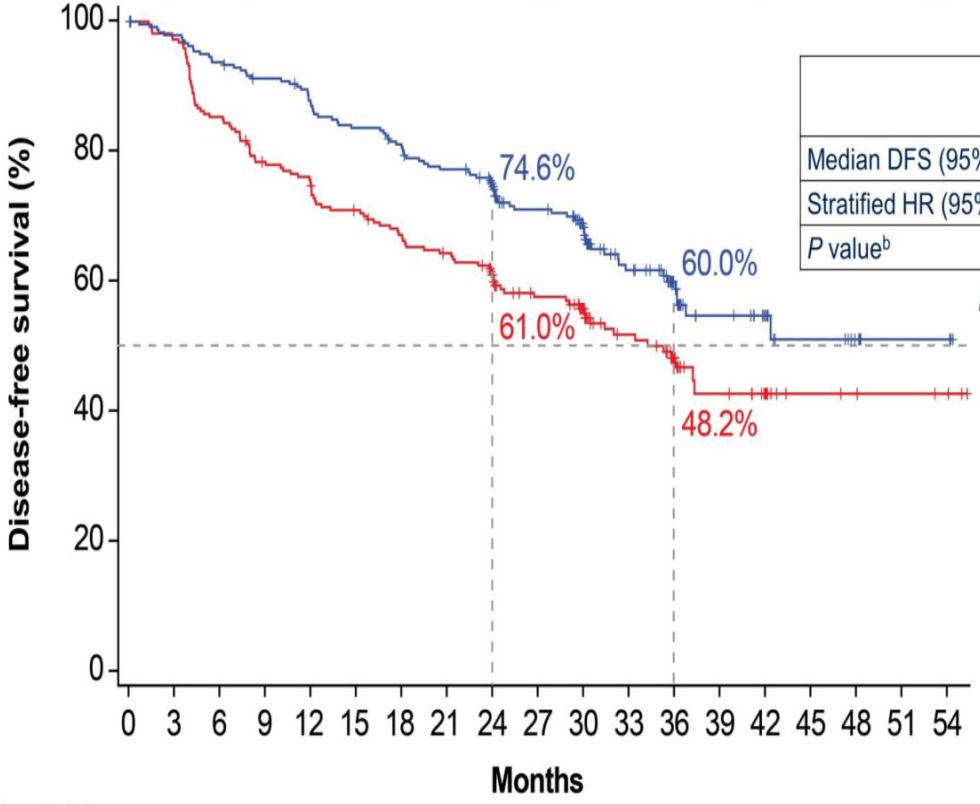
- OS biomarker analyses

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 α=0.05.



Felip E, WCLC 2022

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)

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

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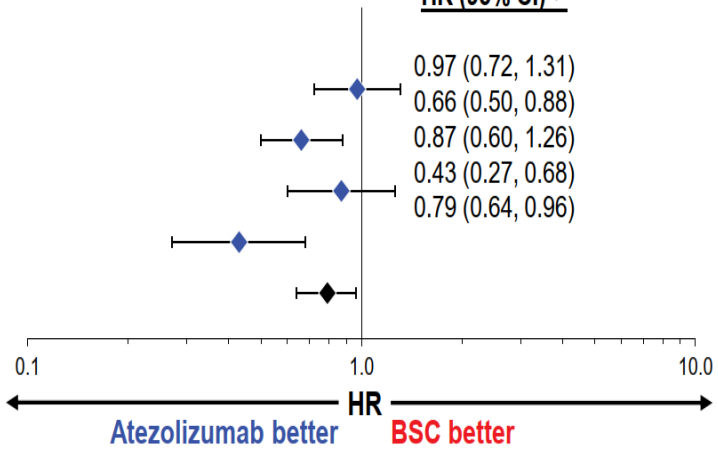
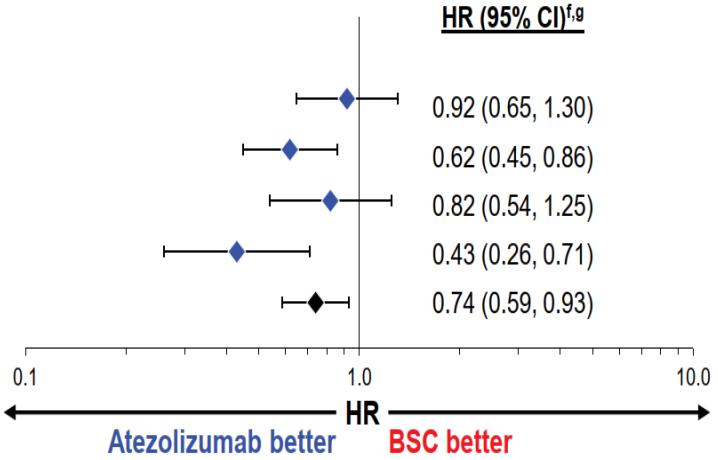
DFS by PD-L1 status[a]

All-randomised stage II-IIIA population (with and without known EGFR/ALK+ disease)

Subgroup *(including EGFR/ALK+)*	n	HR (95% CI)[b,c]
PD-L1 status by SP263		
TC <1%	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
TC 1-49%	247	0.87 (0.60, 1.26)
TC ≥50%	229	0.43 (0.27, 0.68)
All patients[d]	882	0.79 (0.64, 0.96)



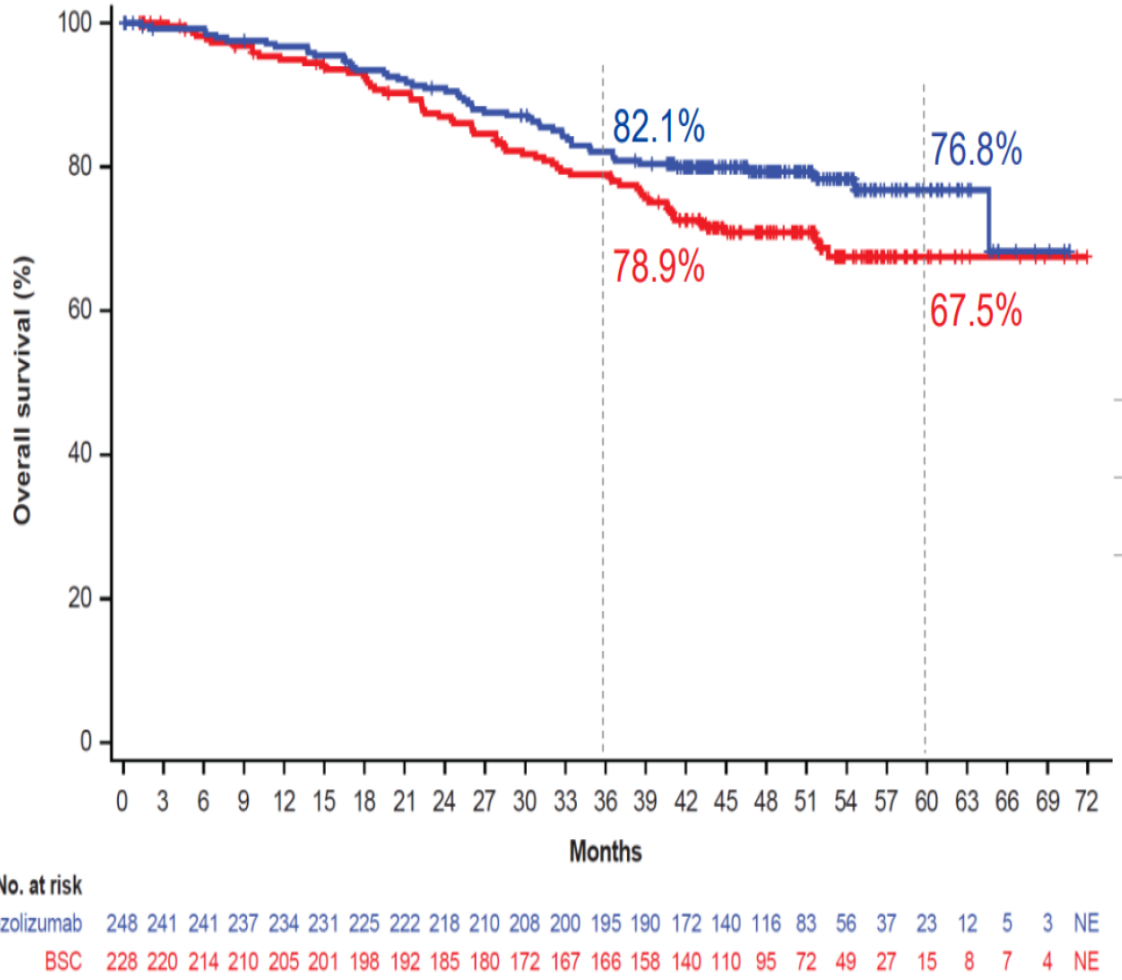
Subgroup *(excluding EGFR/ALK+)*[e]	n	HR (95% CI)[f,g]
PD-L1 status by SP263		
TC <1%	312	0.92 (0.65, 1.30)
TC ≥1%	410	0.62 (0.45, 0.86)
TC 1-49%	201	0.82 (0.54, 1.25)
TC ≥50%	209	0.43 (0.26, 0.71)
All patients[h]	743	0.74 (0.59, 0.93)



Clinical cutoff: 21 January 2021. [a] Per SP263 assay.
[b] Stratified for all patients and PD-L1 TC ≥1%; unstratified for all other subgroups. [c] DFS analyses in the PD-L1 TC <1% and TC 1-49% subgroups were exploratory. [d] 23 patients had unknown PD-L1 status as assessed by SP263. [e] Excluding patients with known *EGFR/ALK*+ NSCLC. [f] Unstratified for all subgroups. [g] EGFR/ALK+ exclusion analyses were post hoc. [h] 21 patients had unknown PD-L1 status as assessed by SP263.

Results of OS IA: PD-L1 TC ≥1%[a] (stage II-IIIA)

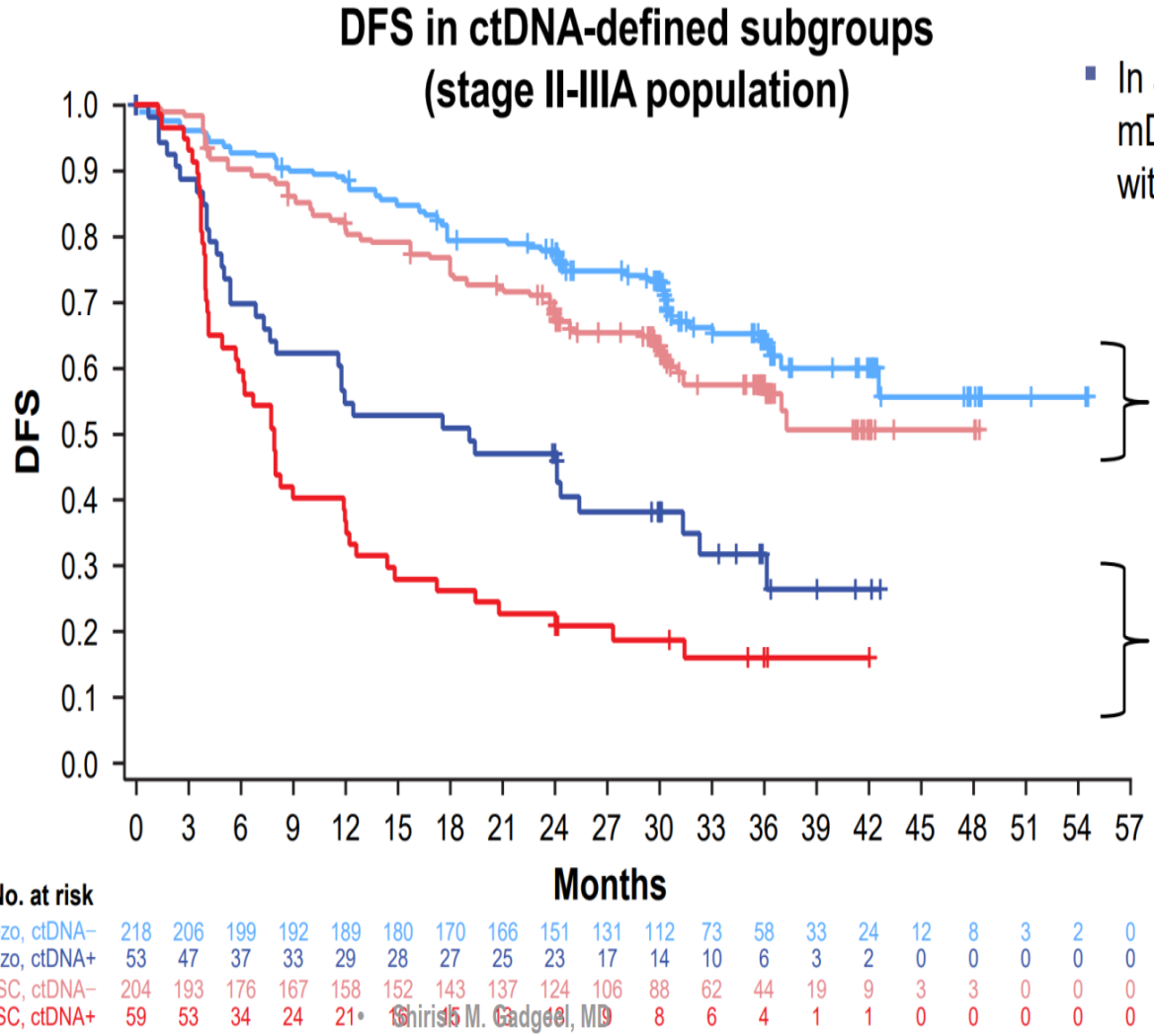
(data cutoff: 18 Apr '22, median follow-up: 46 months)



	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[b]	0.71 (0.49, 1.03)	

mOS, median overall survival; NR, not reached. [a]By SP263 assay. [b]Stratified.

ctDNA positivity was strongly prognostic, with DFS favouring atezo in both ctDNA+ and ctDNA– patients



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

Zhou, ESMO Immuno-Oncology

Clinical cutoff: 21 January 2021. Unstratified HRs are shown.

Shirish M. Gadgeel, MD

Zhou et al. IMpower010 biomarkers. https://bit.ly/3F2KriO
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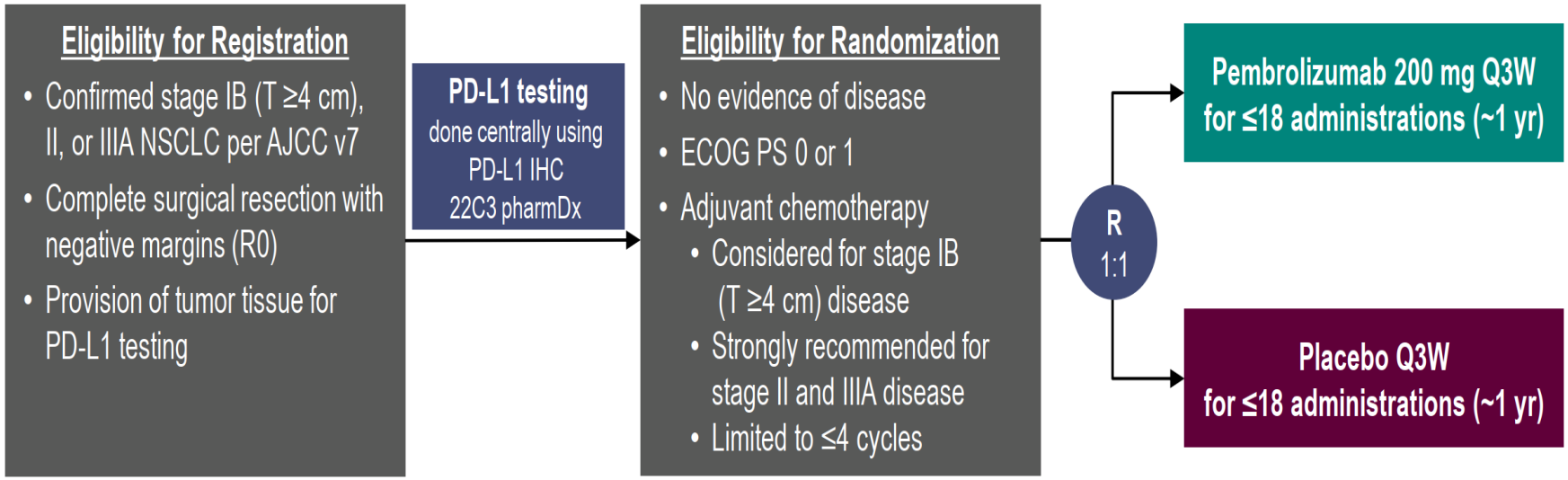
PEARLS/KEYNOTE-091 Study Design

Randomized, Triple-Blind, Phase 3 Trial



Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

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

ClinicalTrials.gov number, NCT02504372.

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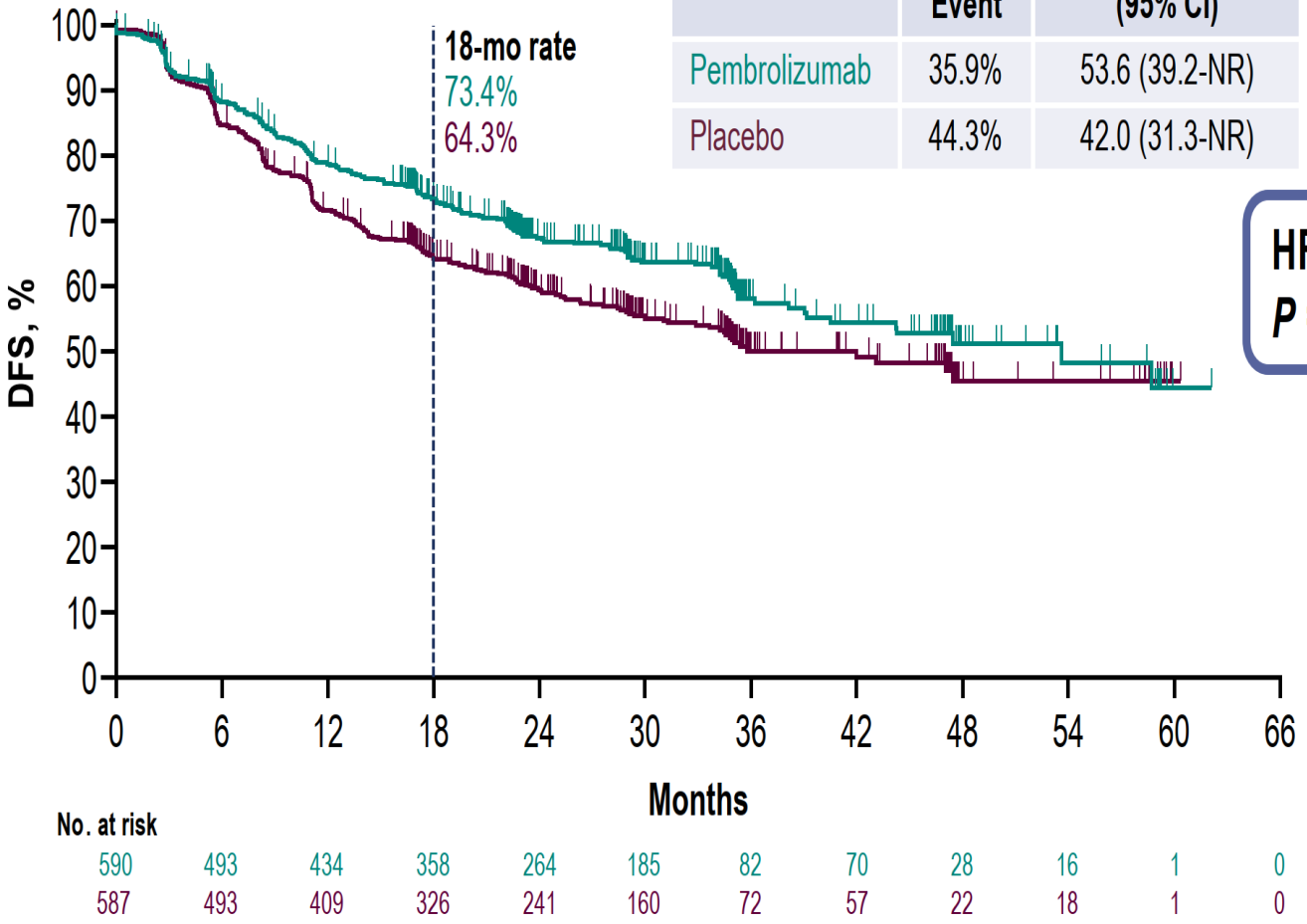
DFS, Overall Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)



HR 0.76 (95% CI, 0.63-0.91)
***P* = 0.0014**

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

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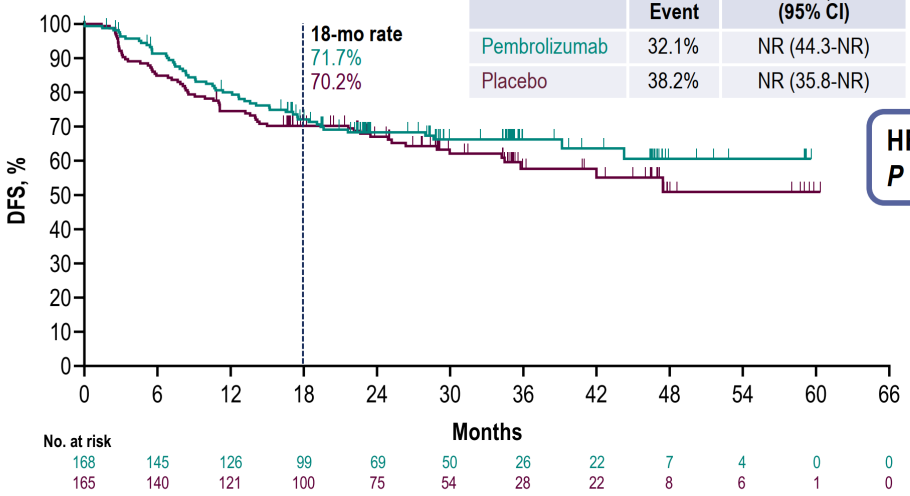
DFS, PD-L1 TPS ≥50% Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	32.1%	NR (44.3-NR)
Placebo	38.2%	NR (35.8-NR)



HR 0.82 (95% CI, 0.57-1.18)
***P* = 0.14**

- Did not meet co-primary endpoint DFS in PD-L1 ≥ 50% but trend in favor of pembrolizumab

ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

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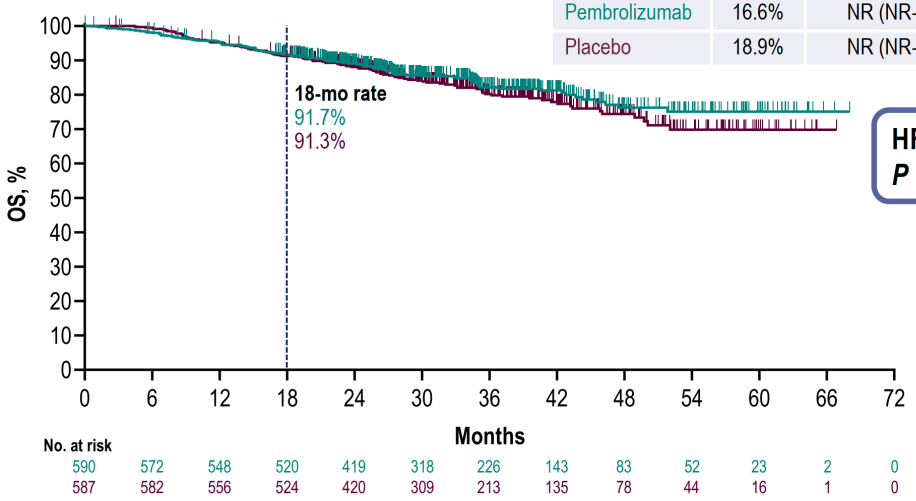
OS, Overall Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	16.6%	NR (NR-NR)
Placebo	18.9%	NR (NR-NR)



HR 0.87 (95% CI, 0.67-1.15)
***P* = 0.17**

- Secondary endpoint OS did not reach statistical significance, but immature data and longer follow-up needed

ESMO VIRTUAL PLENARY

Data cutoff date: September 20, 2021

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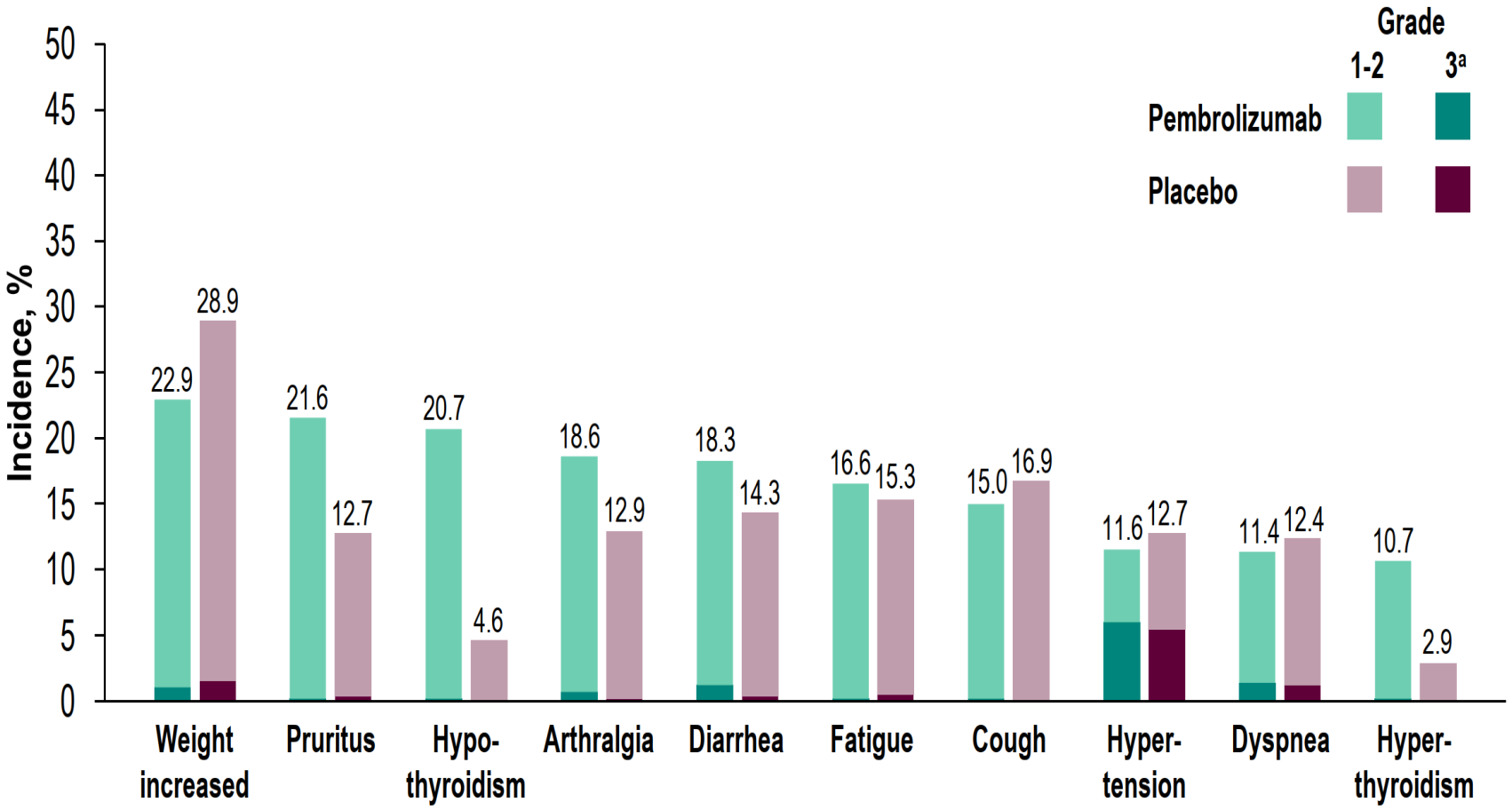
All-Cause AEs, Incidence ≥10%



[a] There were no AEs with incidence ≥10% that were of grade 4 or 5 severity.

Data cutoff date: September 20, 2021

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Neoadjuvant IO & Chemo IO

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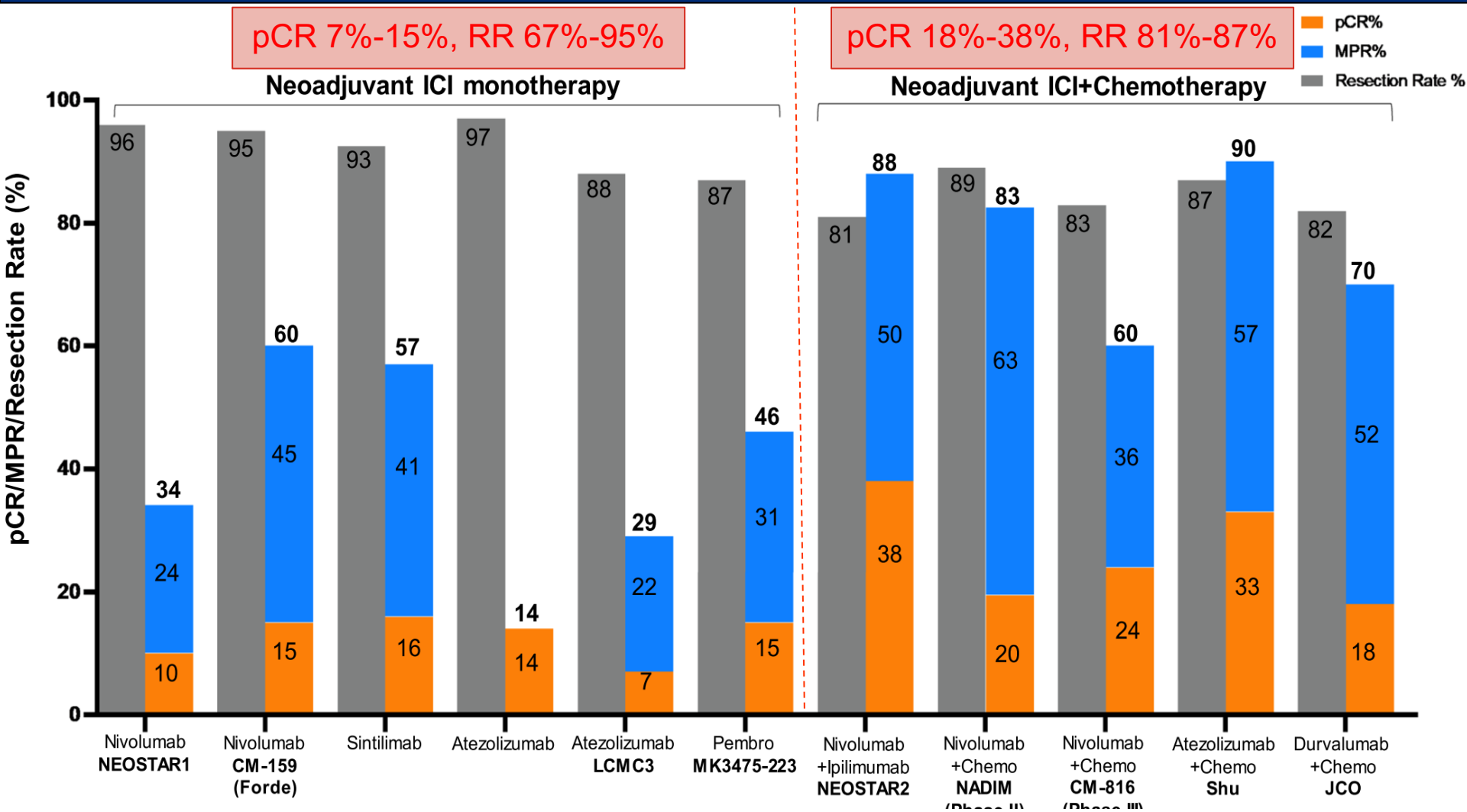

Godoy et al Biomarker Res 2023

Checkmate 816

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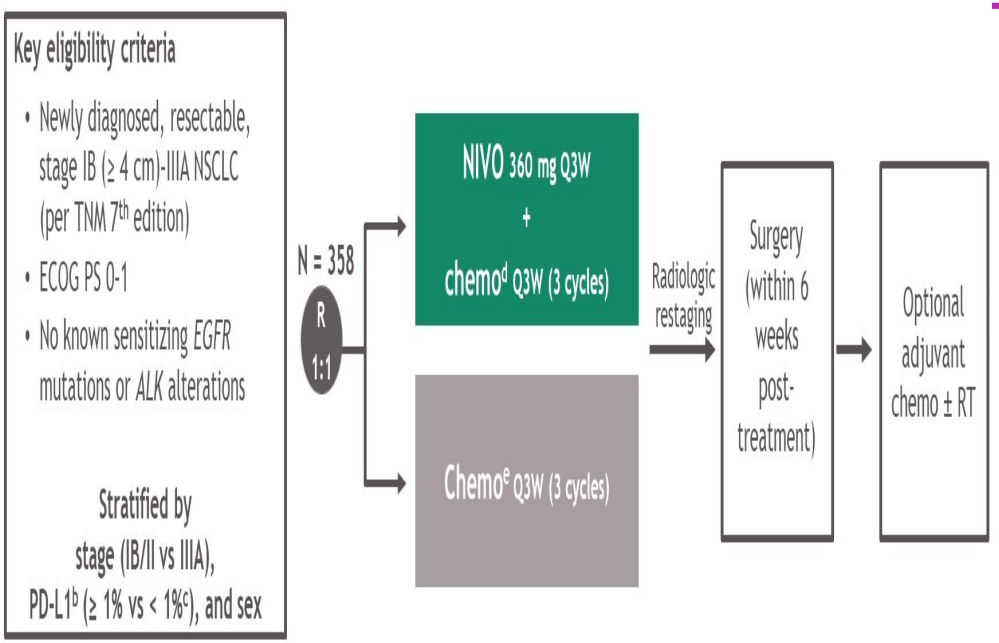


Primary endpoints
- pCR by BIPR
- EFS by BICR

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

Key exploratory endpoints included
- ORR by BICR
- Feasibility of surgery; peri- and post-operative surgery-related AEs

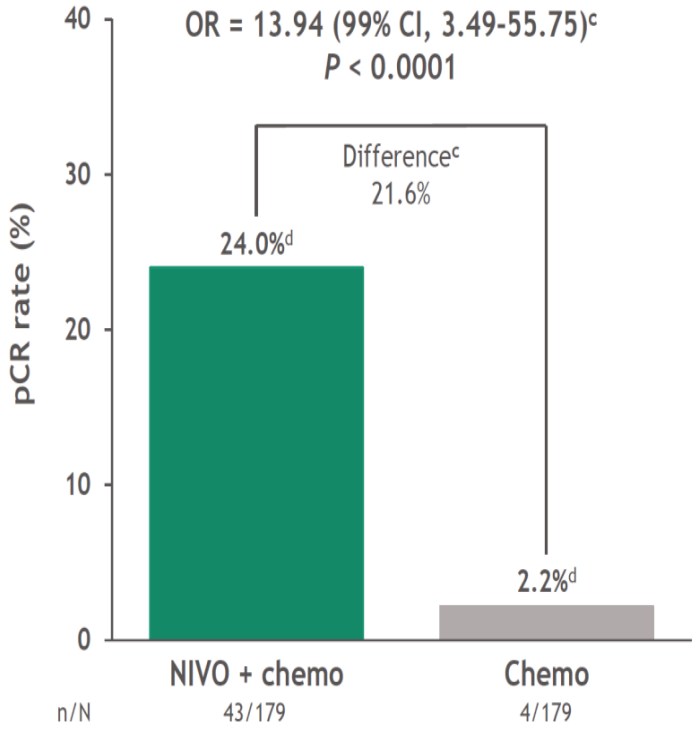
Baseline characteristics

	NIVO + chemo (n = 179)	Chemo (n = 179)
Age, median (range), years	64 (41-82)	65 (34-84)
Female, %	28	29
ECOG PS		
0	69	65
1	31	35
Smoking status,[a] %		
Current/former	89	88
Never	11	11
Histology, %		
Squamous	49	53
Non-squamous	51	47
Stage,[b,c] %		
IB/II (A & B)	36	35
IB	6	4
IIA	17	18
IIB	14	13
IIIA	**63**	**64**
Region,[d] %		
North America	23	28
Europe	23	14
Asia	48	51
Tumor PD-L1 expression,[c] %		
Not evaluable	7	7
< 1%	44	43
≥ 1%	50	50

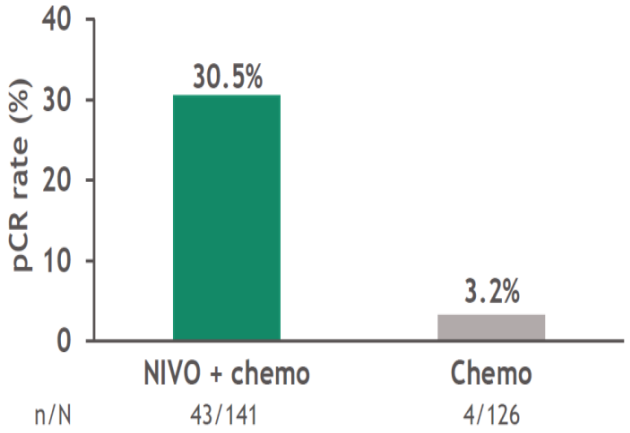
Tsuboi ASCO 2022

Neoadjuvant Nivolumab + CT in Resectable Stage IB-IIIA (CheckMate 816): pCR[a] Rate

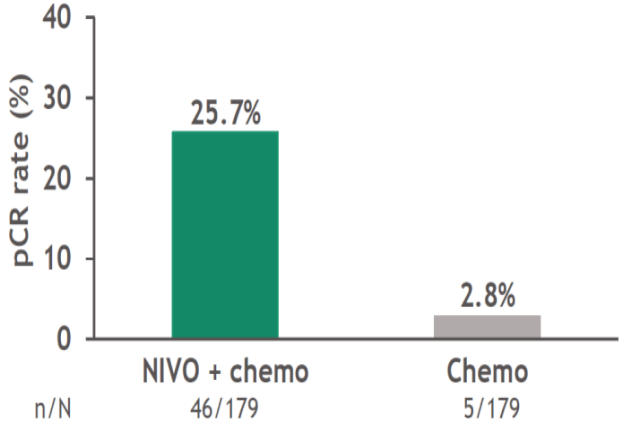
PRIMARY ENDPOINT: ITT (ypT0N0)[b]



PATIENTS WITH RESECTION[e] (ypT0N0)



PRIMARY TUMOR ONLY IN ITT (ypT0)



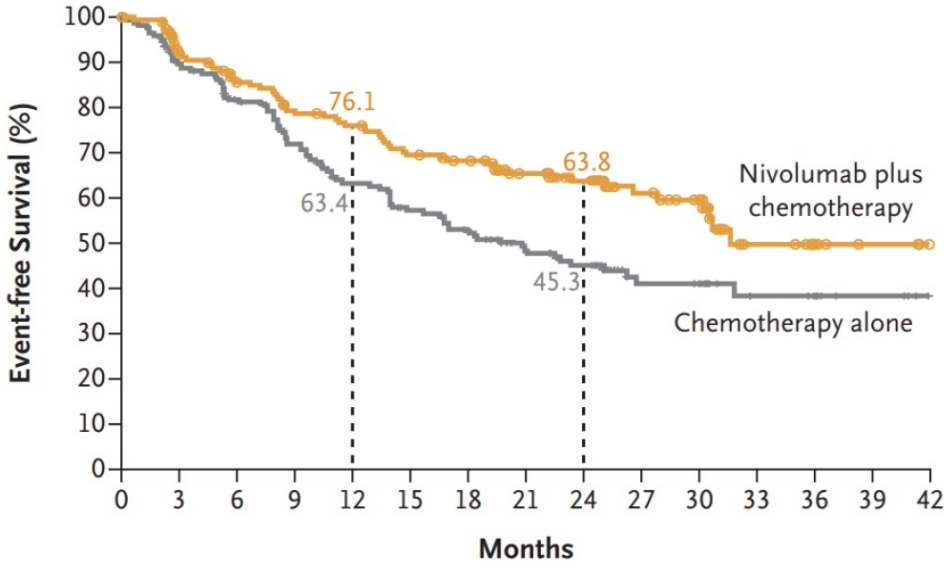
- **pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4 29.0)**

CT, chemotherapy.
[a]Per BIPR; pCR: 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]ITT principle: patients who did not undergo surgery counted as non responders for primary analysis; [c]Calculated by stratified Cochran Mantel Haenszel method; [d]pCR rates 95% CI: NIVO + chemo, 18.0 31.0; chemo, 0.6 5.6; [e]Patients who underwent definitive surgery with an evaluable pathology sample for BIPR.
Forde P, et al. American Association for Cancer Research Annual Meeting 2021. Presentation CT003.

Checkmate 816 Results

INOVA Schar Cancer Institute

A



	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

Forde et al. NEJM 2022

Checkmate 816 Results

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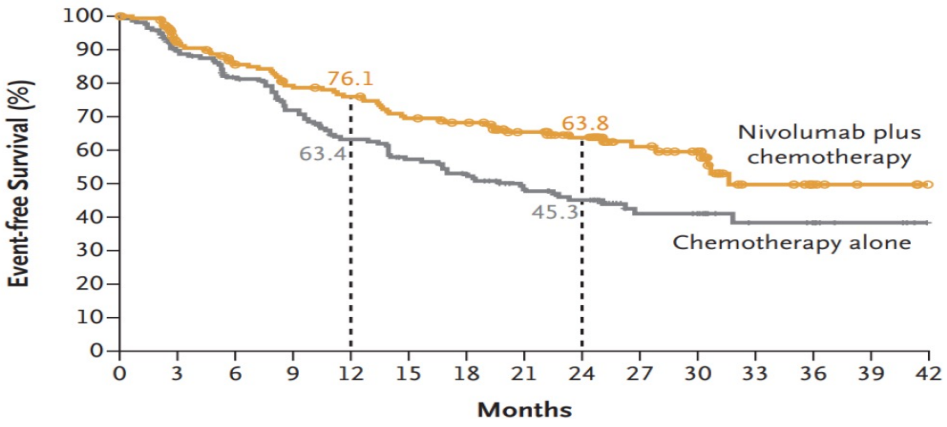
A



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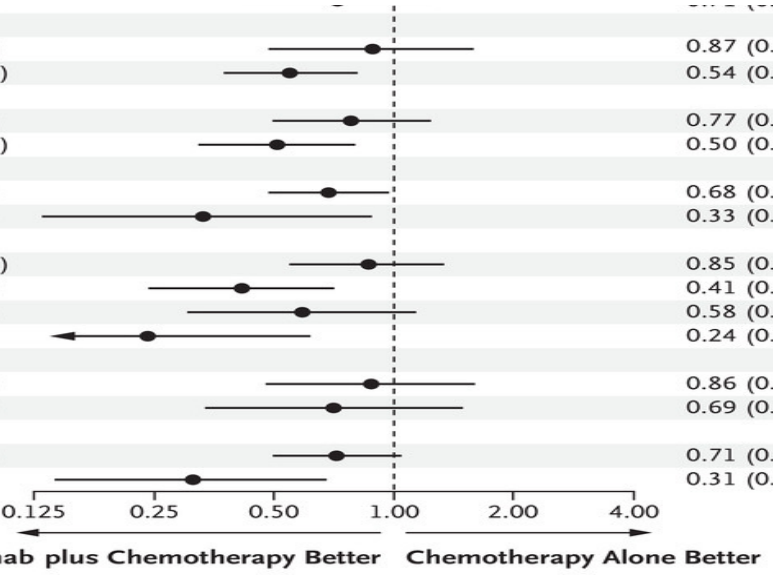
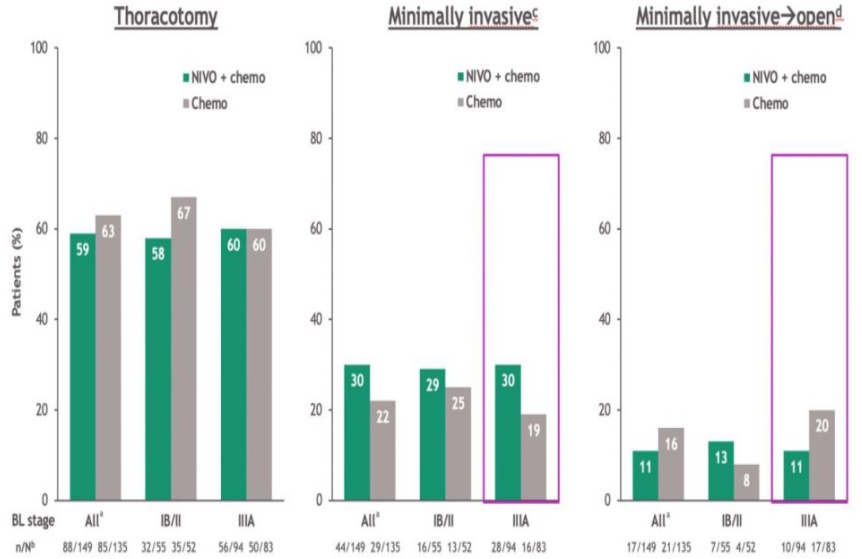
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

Disease stage at baseline				
IB or II	127	NR (27.8–NR)	NR (16.8–NR)	0.87 (0.48–1.56)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)	0.54 (0.37–0.80)
Histologic type of tumor				
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)	0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)	0.50 (0.32–0.79)
Smoking status				
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)	0.68 (0.48–0.96)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)	0.33 (0.13–0.87)
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)
Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)	0.31 (0.14–0.67)



Forde et al. NEJM 2022

Surgical approach by baseline stage of disease



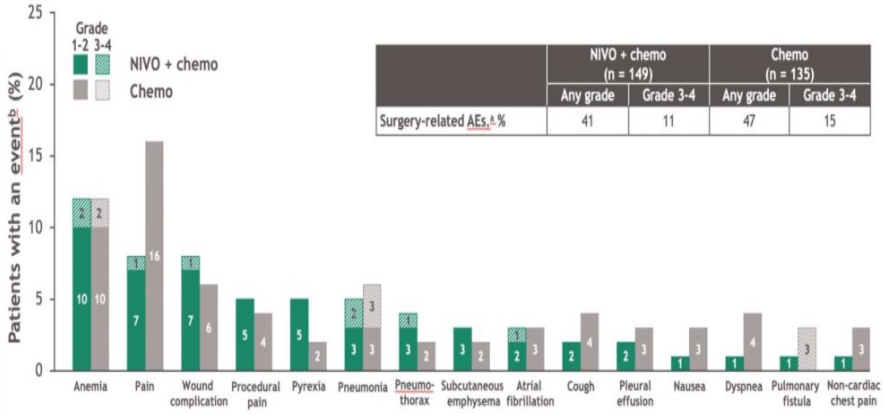
Nivo + chemo resulted in more minimally invasive surgeries and fewer pneumonectomies

Nivo+ chemo did not increase surgery related AEs

Jonathan Spicer, abstract 8503

90-Day surgery-related complications summary[a]

	NIVO + chemo (n = 149)		Chemo (n = 135)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Surgery-related AEs,[a] %	41	11	47	15



- Grade 5 surgery-related AEs (within 24 hours of AE onset) were reported in 2 patients in the NIVO + chemo arm and were deemed unrelated to study drug per investigator (1 each due to pulmonary embolism and aortic rupture)[c]
- 30-day and 90-day mortality rates are planned to be evaluated when survival endpoints are available

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Safety

Patients (%)	All treated		pCR (primary tumor)[b]		No pCR (primary tumor)[b]		MPR (primary tumor)[b]		No MPR (primary tumor)[b]	
	NIVO + chemo (n = 176)	Chemo (n = 176)	NIVO + chemo (n = 46)	Chemo (n = 5)	NIVO + chemo (n = 95)	Chemo (n = 121)	NIVO + chemo (n = 72)	Chemo (n = 22)	NIVO + chemo (n = 69)	Chemo (n = 104)
Any grade TRAEs[a]	82	89	85	100	84	88	79	96	90	86
Grade 3-4 TRAEs[a]	34	37	30	40	37	35	31	32	39	36

- Incidence of TRAEs in the NIVO + chemo arm was similar in patients with or without pCR/MPR and consistent with all treated patients

[a]Includes events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose as per Common Terminology Criteria for Adverse Events Version 4.0; Medical Dictionary for Regulatory Activities Version 24.0; [b]pCR and MPR assessed in path-evaluable patient population.

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Neoadjuvant IO vs Adjuvant IO

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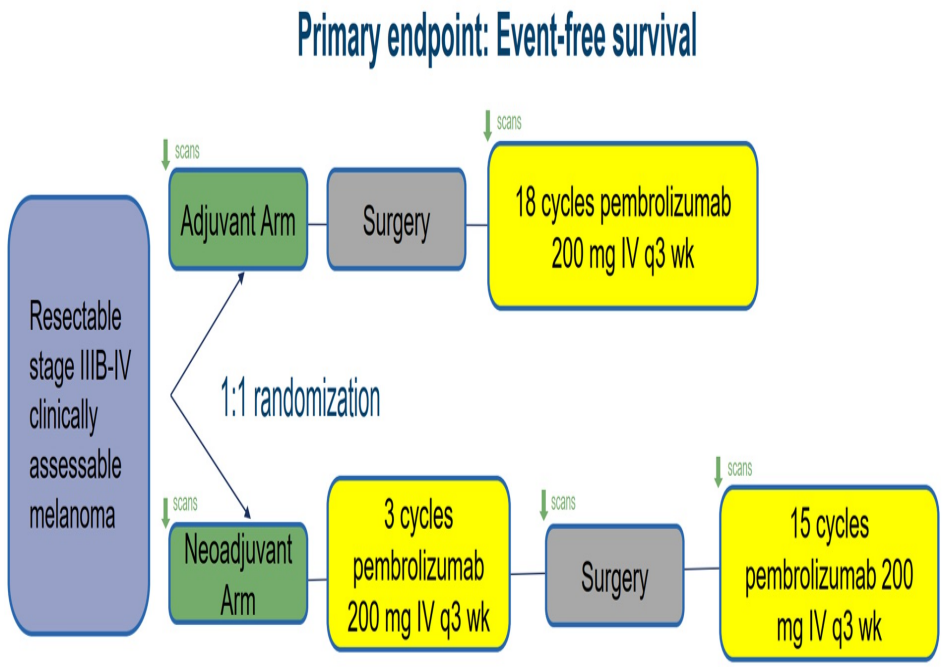
S1801 Study Schema



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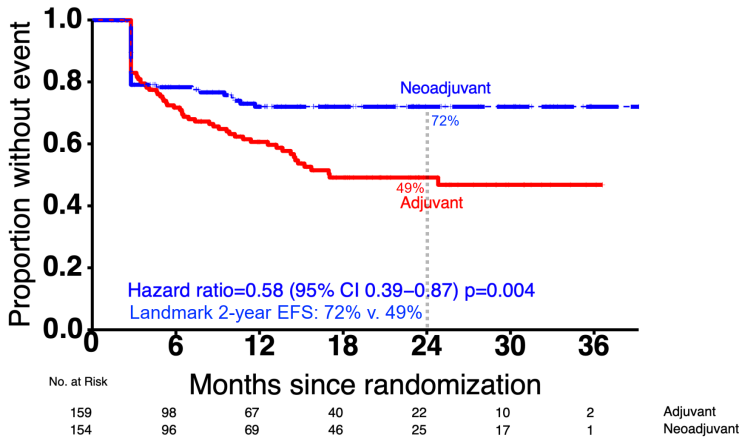
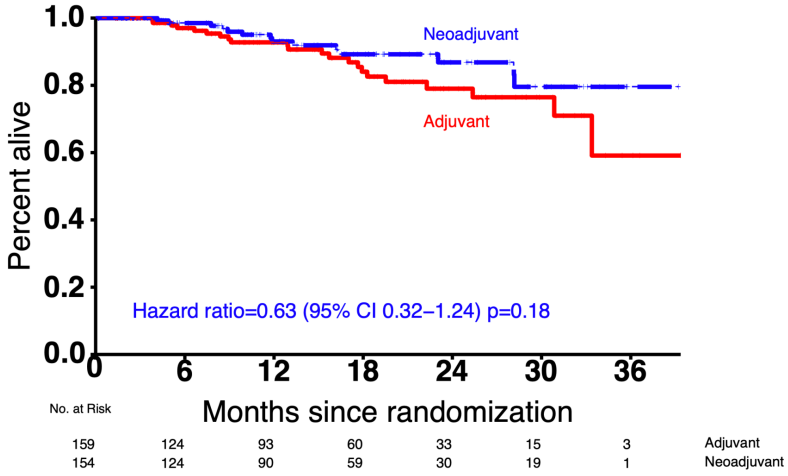
S1801 primary endpoint: Event-free survival



Overall survival



Patel et al. ESMO 2022

Why Neoadjuvant vs Adjuvant IO in NSCLC?

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- Pros
  - Higher neoantigen load
  - Early treatment of micro-metastatic disease
  - Intact tumor vasculature
- Cons
  - Delay in resection
  - Treatment related adverse events
  - Risk of delayed/cancelled surgery (CM 816 83% vs 75%; NADIM II 93% v 69%)

Futurescape

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Neo A/A	Study	Phase	Stage	Regimen	Primary Endpoint
Neo A	KN-671	III	IIB, IIIA	C+Pem v C	EFS, OS
	IMp-030	III	II,IIIA & *IIIB*	Atezo+C v C	MPR
	AEGEAN	III	II,IIIA & *IIIB*	C+Durva v C	pCR, EFS
	NCT04379635	III	II,IIIA	Tisle+C v C	MPR, EFS
	NCT04025879	III	IIA-*IIIB*	Nivo+C > Surg > Nivo	EFS
	NCT04158440	III	IIIA	Tori+C	MPR, EFS
A	NCT02273375	III	IB-IIIA	Adj Durva v Placebo	DFS
	ALVIN	II/III	IB-IIIA	Adj Nivo v Obs	DFS, OS
	MERMAID 1 & 2	II/III	II-III	C+Durva > Durva	DFS
	NADIM-ADJ	II/III	IB-IIIA	C+Nivo>Nivo	DFS

Conclusions

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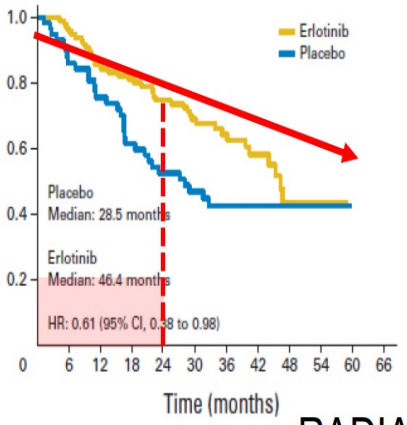
- IO agents in peri-op treatment of NSCLC is a key breakthrough, but questions remain,
  - Neo-adjuvant v adjuvant? It maybe a function of patient selection: ?cfDNA ?imaging
  - Is 3 cycles of neo-adjuvant chemo IO enough?
  - Do we need both neo-adjuvant & adjuvant IO? Is there an optimal regimen?
- Pre-treatment molecular testing is essential!
- Results from ongoing trials would guide patient & treatment selection.

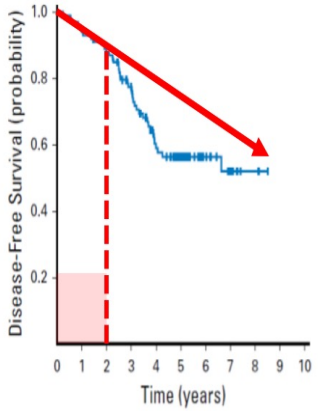
Waning treatment effect of TKIs after discontinuation

Identified in other adjuvant EGFR TKI trials

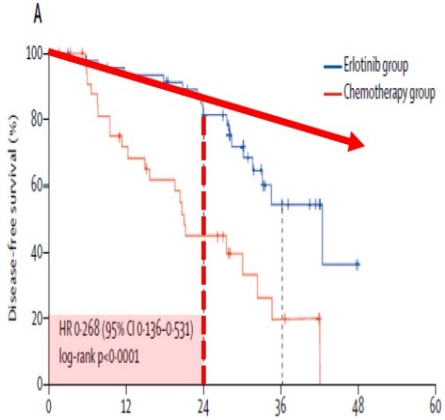


Treatment Duration

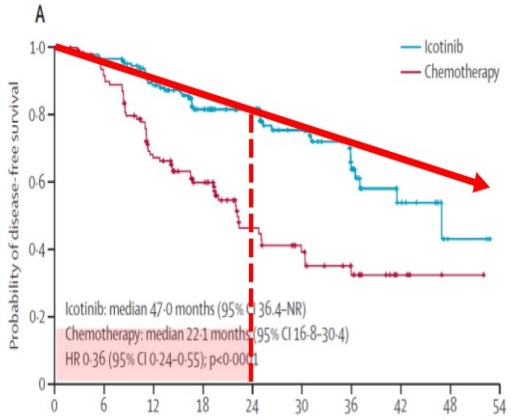
RADIANT[1]
erlotinib



SELECT[2]
erlotinib

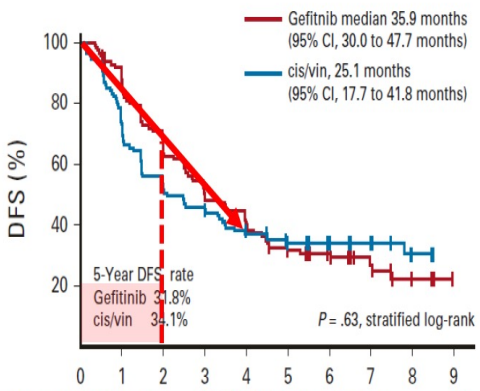


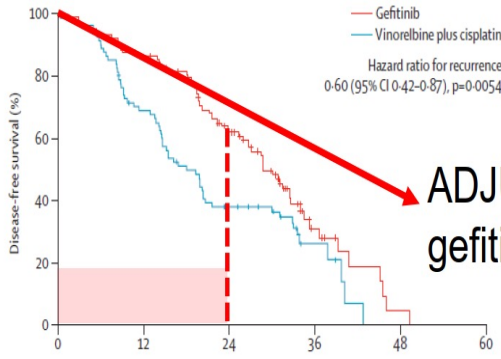
EVAN[3]
erlotinib



EVIDENCE[4]
icotinib

IMPACT[5]
gefitinib





ADJUVANT[6]
gefitinib

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Sanjay Popat FRCP PhD @DrSanjayPopat

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1, Kelly et al. JCO (2015); 2, Pennell et al. JCO (2018);3, Yue et al. Lancet Rep Med (2018); 4, He et al. Lancet Resp Med (2021); 5, Tada et al. JCO (2021); 6; Zhong et la. Lancet Oncol (2017)