New Therapeutic Directions in Lung Cancer

UCDAVIS COMPREHENSIVE CANCER CENTER

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NCI CCC
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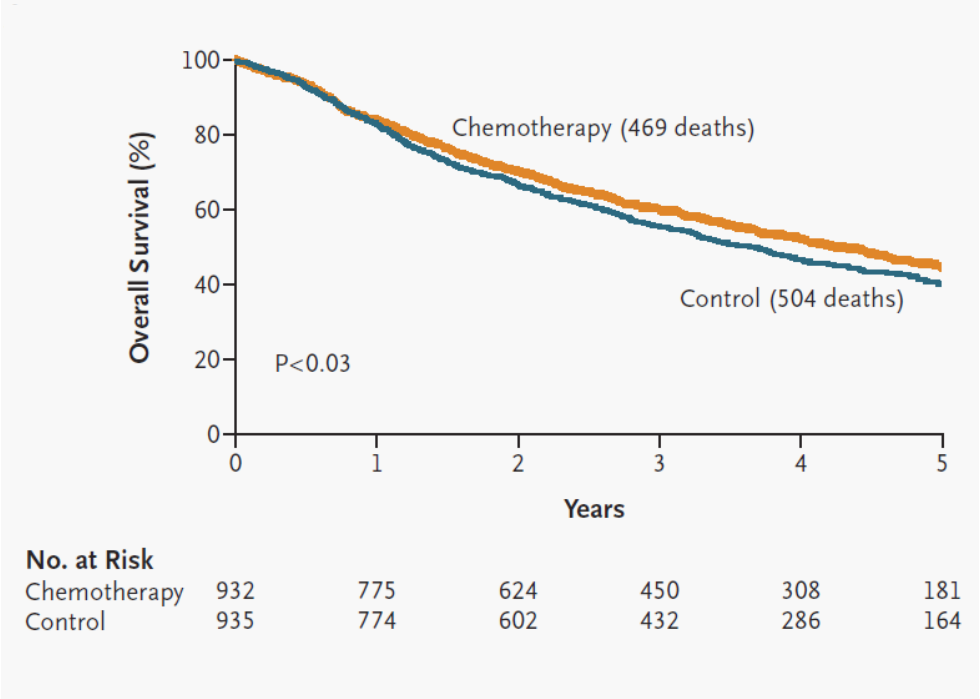
Adjuvant Chemotherapy Meta-analysis



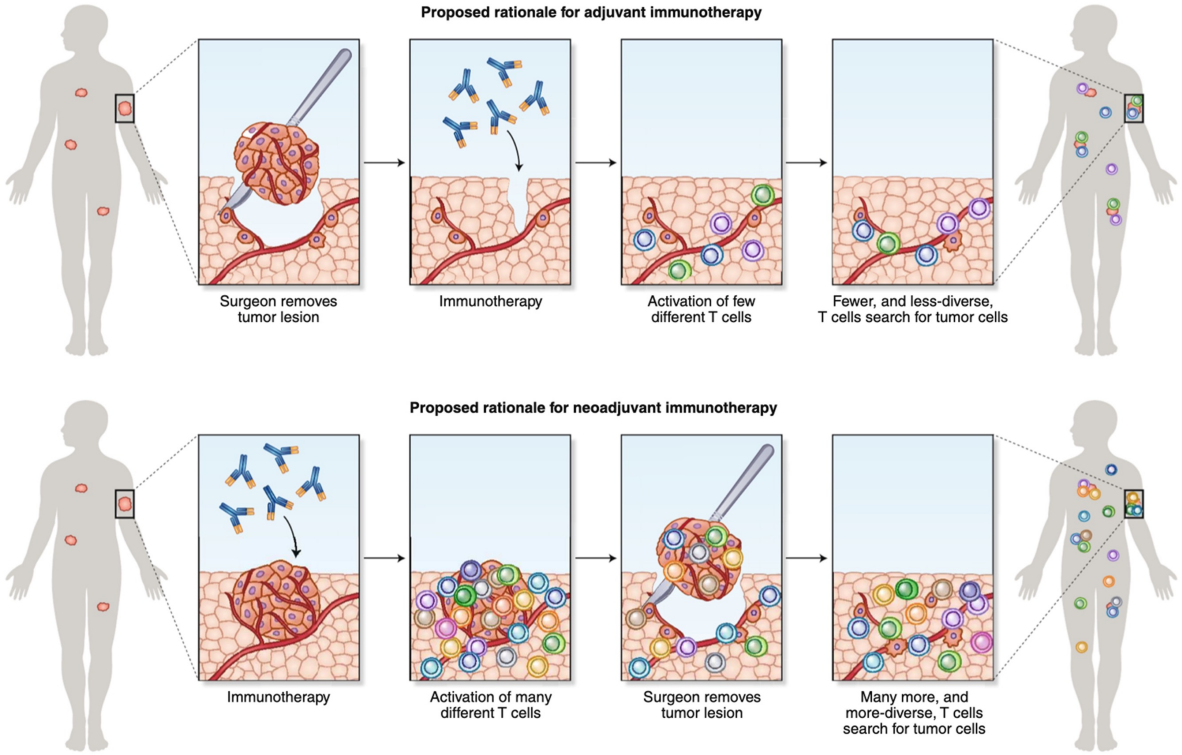
HR 0.86
95%CI (0.76-0.98) p=0.03

Median f/u 56 months

IALT Collaborative Group. *NEJM*. 2004;350:351-60

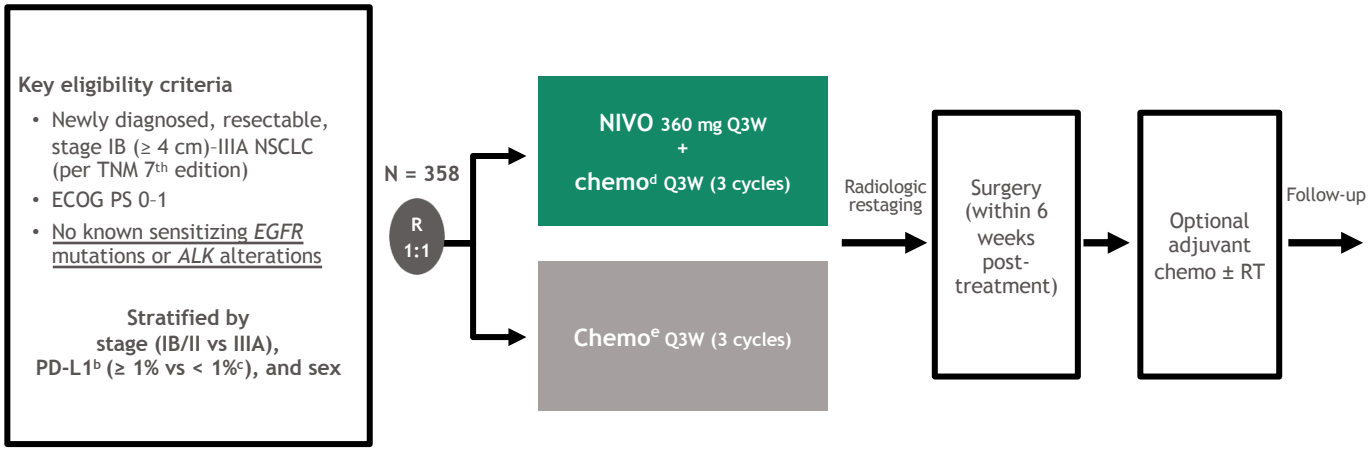
Neo-Adjuvant

What about neoadjuvant immunotherapy approaches? Checkmate 816 as a Paradigm



Versluis, Long, and Blank
Nat Med 2020

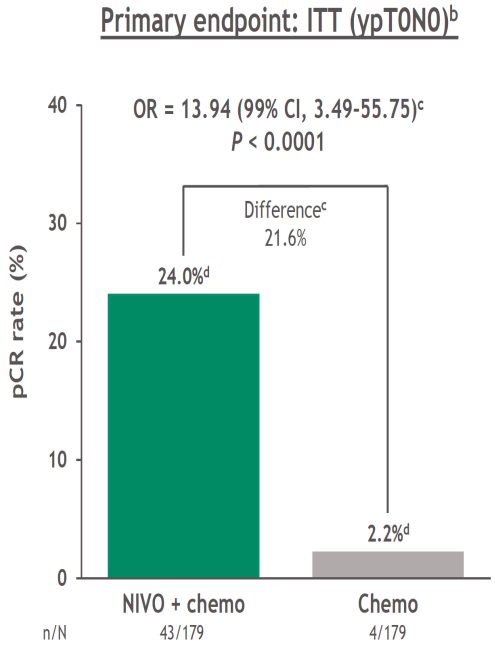
CM816

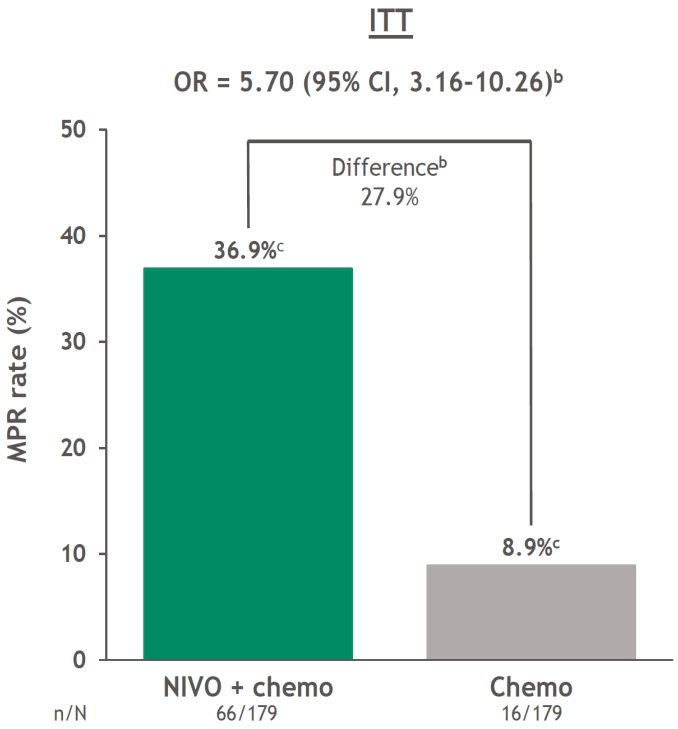


63% Stage IIIA
50% PD-L1 >1%
No EGFR/ALK
IO + Chemo

Spicer ASCO 2021 abstr: 8503, Forde NEJM

CM816 – pCR and MPR in ITT population

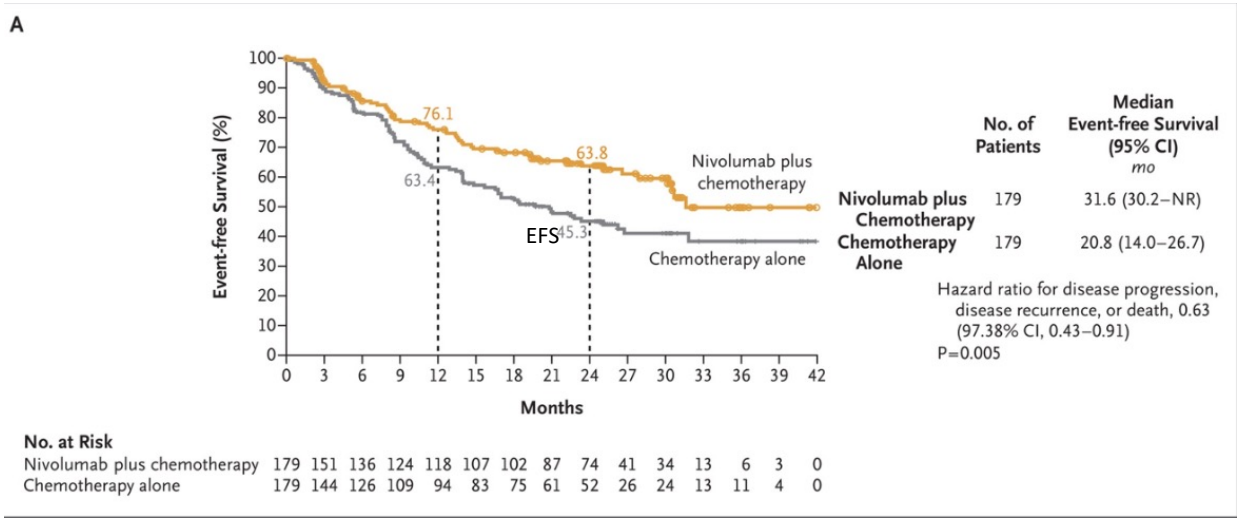


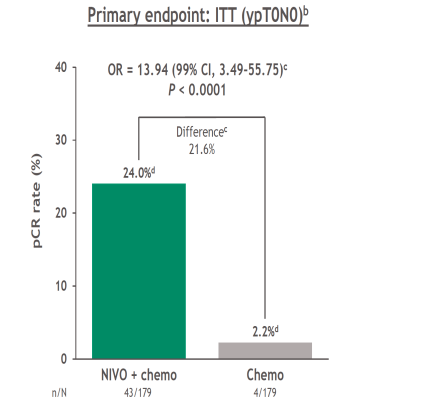


- pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4-29.0)

Forde CM816, AACR2021, NEJM

CM816 EFS + OS



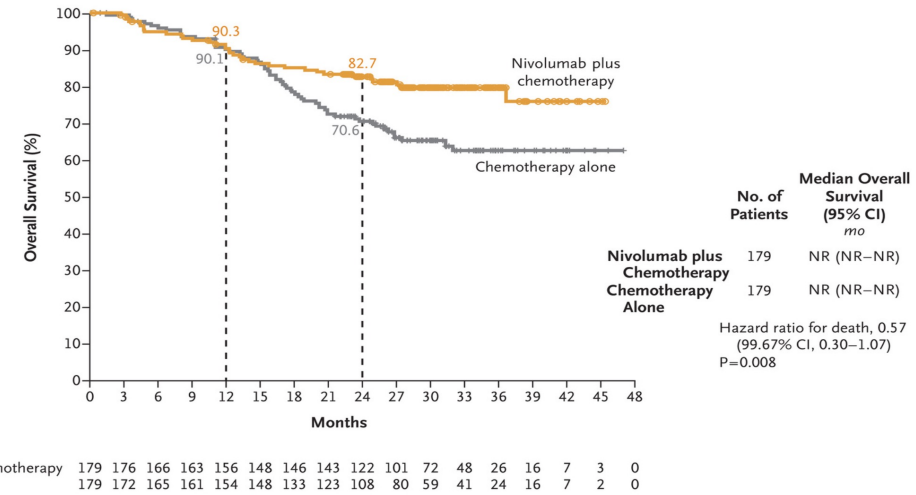


• pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4-29.0)

EFS HR 0.63
97.38% CI (0.43-0.91), p.005

OS HR 0.57
(99.67% CI 0.30-1.07), p.008

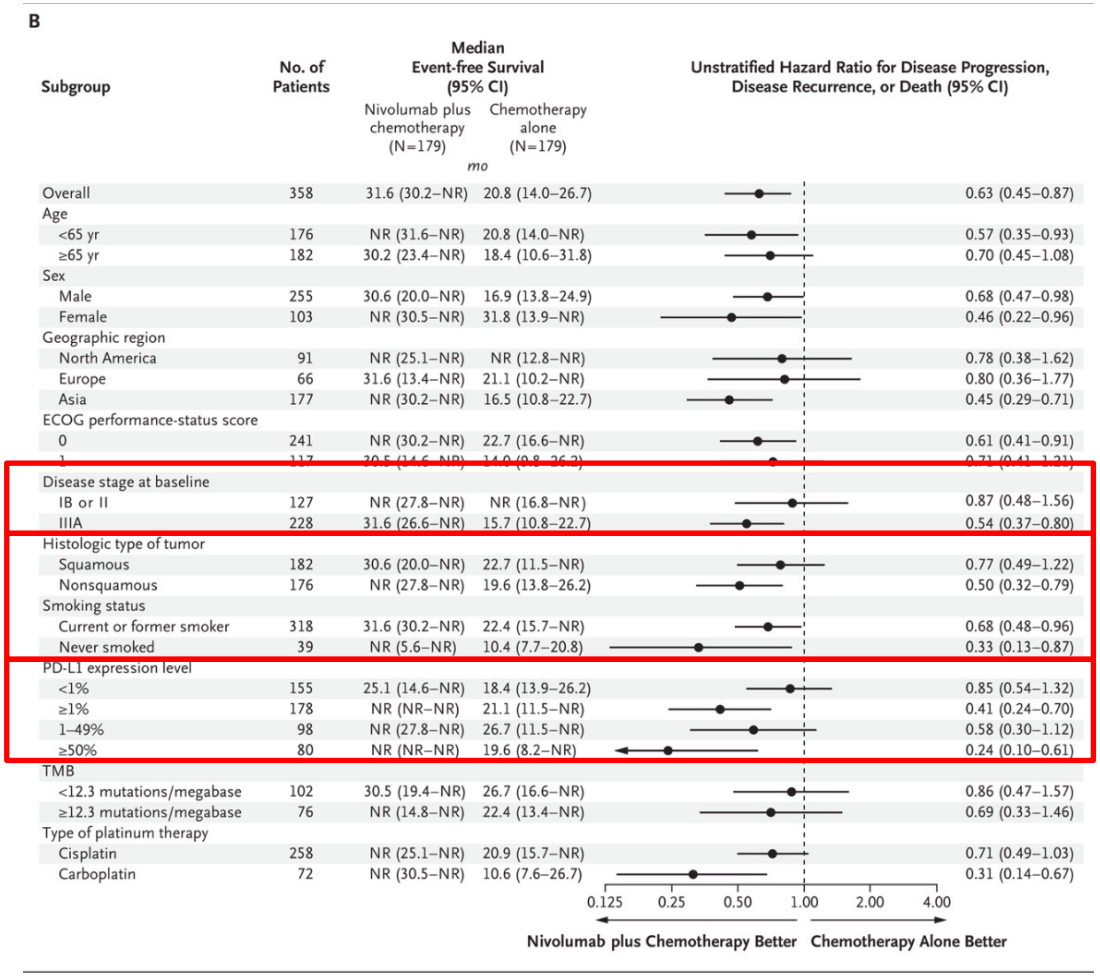
OS



Forde NEJM

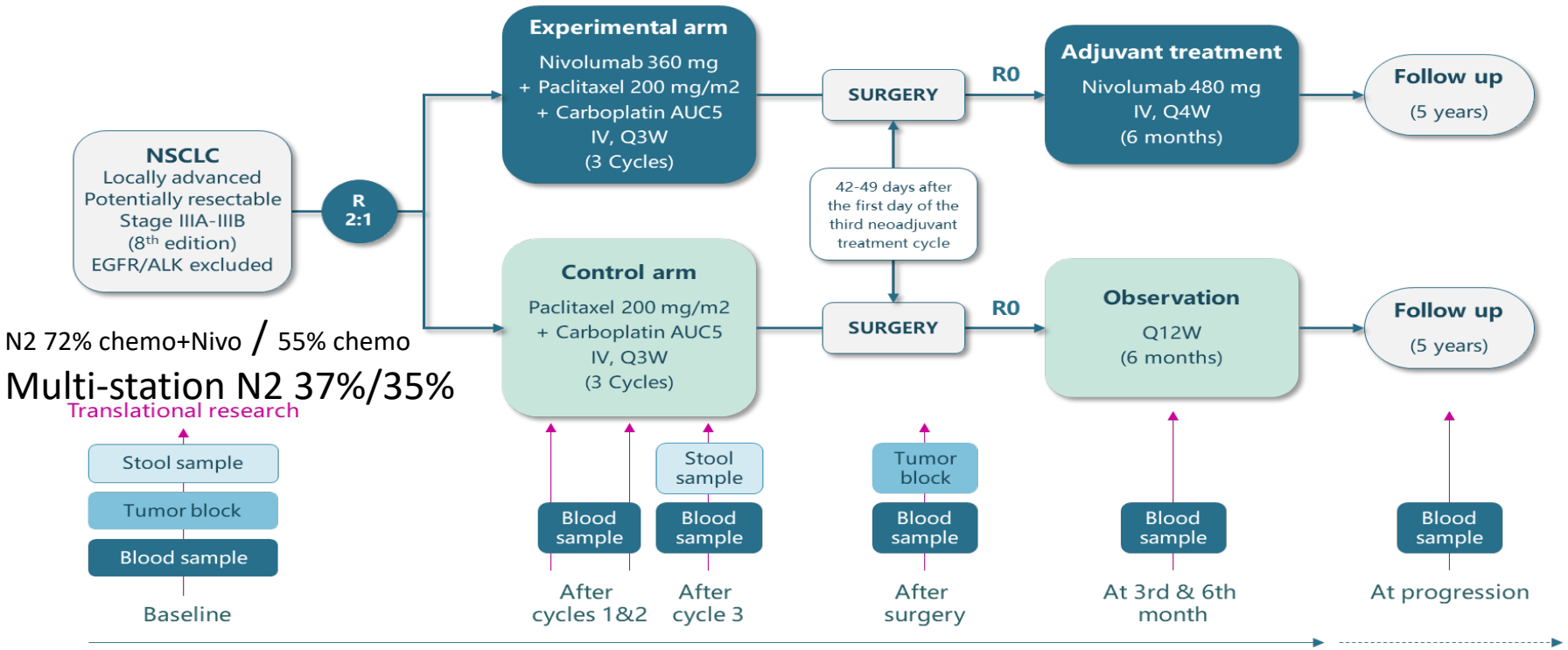
CM816 subsets

Nivo best:
Asia
Stage IIIA
Non-Sq
Never-smokee
PD-L1≥50%



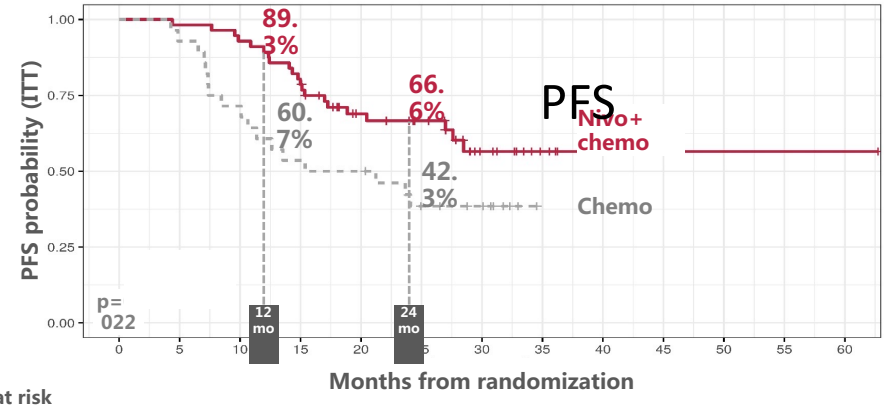
Forde NEJM 2022

NADIM II STUDY DESIGN – Phase II



Provencio, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

NADIM II
2nd ENDPOINTS – PFS and OS



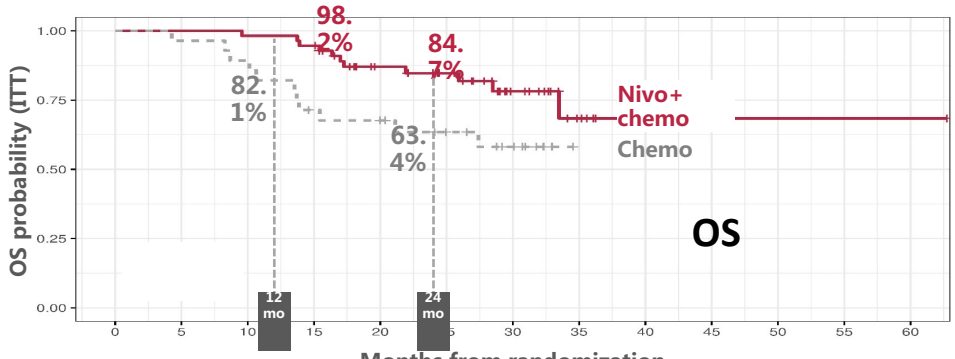
umber at risk

Nivo + chemo	56	55	52	44	30	24	11	4	1	1	1	1	1
Chemo	28	26	20	15	14	9	7	0	0	0	0	0	0

	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median PFS (mo)	NR	18.3
HR	0.48 (95%CI, 0.25-0.91); p=0.025	

Median follow-up: 26.1 months

	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median OS (mo)	NR	NR
HR	0.40 (95% CI 0.17-0.93); p=0.034	



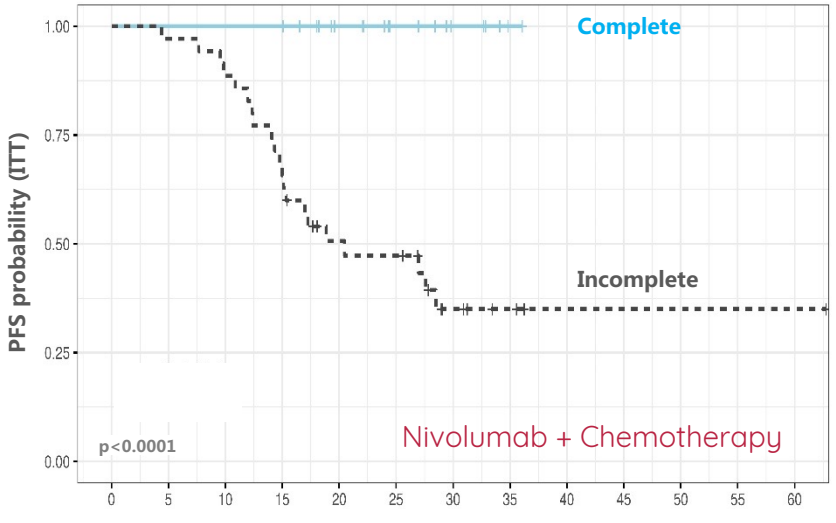
Number at risk

Nivo + chemo	56	56	55	53	37	31	15	5	1	1	1	1	1
Chemo	28	27	25	19	17	13	9	0	0	0	0	0	0

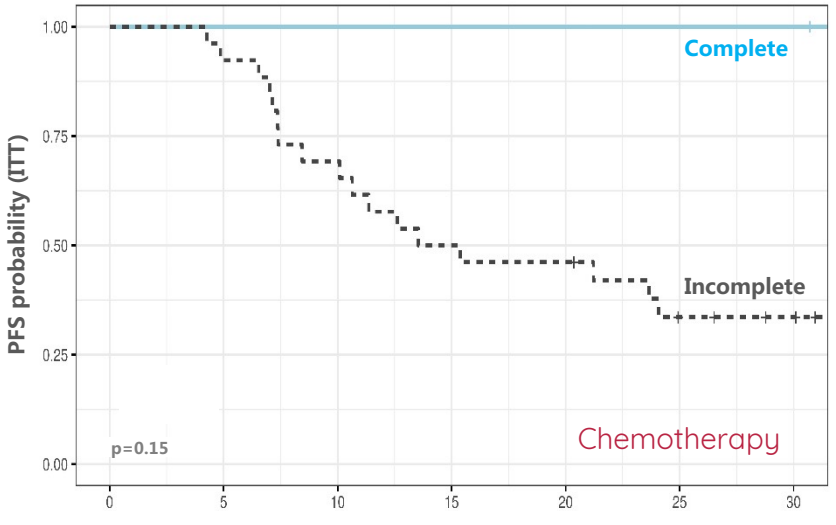
Progression-free survival was defined as the time from randomization to any of the following events: progression of disease, recurrence disease, or death due to any cause. Progression/recurrence will have determined by RECIST 1.1

Mariano Provencio, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

NADIM II
SECONDARY ENDPOINTS
PFS by pCR status



Number at risk													
Complete	21	21	21	21	15	10	5	1	0	0	0	0	0
Incomplete	35	34	31	23	15	14	6	3	1	1	1	1	1



Number at risk							
Complete	2	2	2	2	2	2	2
Incomplete	26	24	18	13	12	7	5

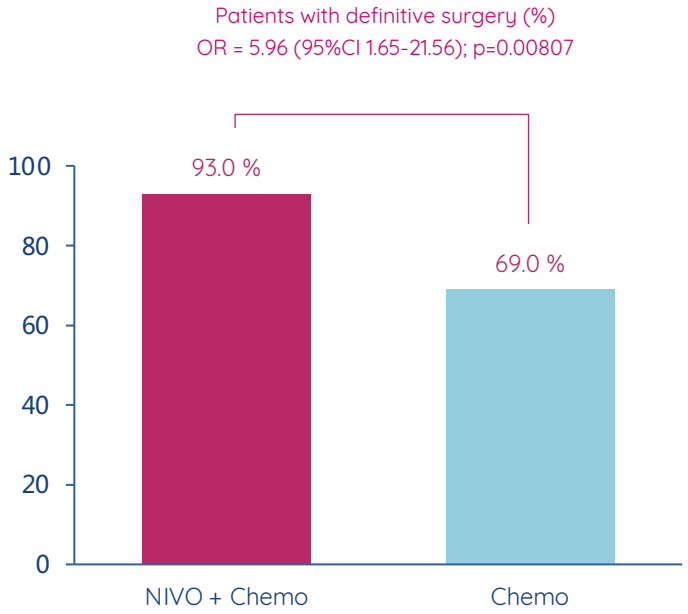
Progression-free survival was defined as the time from randomization to any of the following events: progression of disease, recurrence disease, or death due to any cause. Progression/recurrence will have determined by RECIST 1.1

Provencio, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

NADIM II
SURGERY SUMMARY

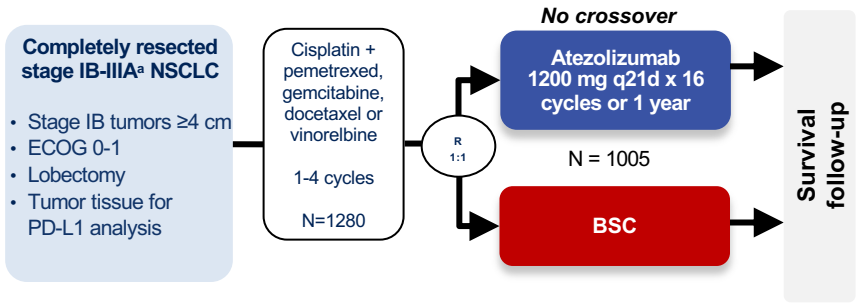
Type of surgery, No. (%)	NIVO + Chemo (n = 53)	Chemo (n = 20)	Total (n = 73)
Pneumonectomy	6 (11.3)	2 (10.0)	8 (11.0)
Lobectomy	40 (75.5)	17 (85.0)	57 (78.1)
Bilobectomy	4 (7.5)	1 (5.0)	5 (6.8)
Segmentectomy	2 (3.8)	0 (0.0)	2 (2.7)
Right Lower Lobectomy + Segmentectomy	1 (1.9)	0 (0.0)	1 (1.4)

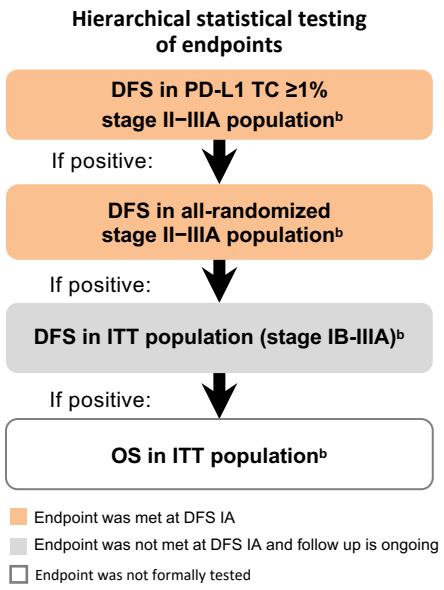
Resection degree, No (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)
R0	49 (92.5)	13 (65.0)
Odds Ratio: 6.60 (95% CI 1.67-26.02); p = 0.007		



Adjuvant

IMpower010





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

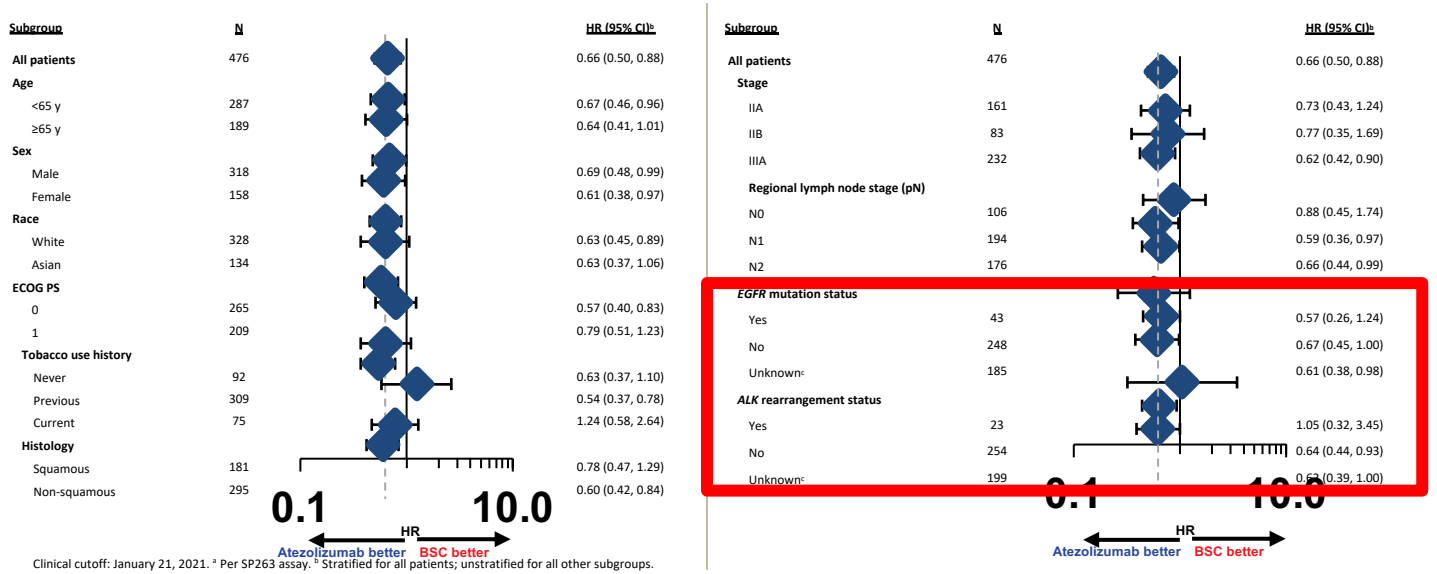
Clinical cutoff: 18 April 2022. Both arms included observation and regular scans for disease recurrence on the same schedule. ECOG, Eastern Cooperative Oncology Group, q21d, every 21 days.
[a] Per UICC/AJCC staging system, 7th edition. [b] Two-sided α=0.05.

H. Wakelee ASCO 2021, abstr 8500:IMpower010 Interim Analysis; Felip Lancet 2021, Felip IASLC WCLC 2022

IMpower010 Patient Characteristics

Characteristic	All patients (N=1005)	PD-L1 TC ≥1% (SP263) (stage II-IIIA)		All randomized (stage II-IIIA)		ITT (stage IB-IIIA)	
		Atezo (n=248)	BSC (n=228)	Atezo (n=442)	BSC (n=440)	Atezo (n=507)	BSC (n=498)
Median (range) age,	**62 (26-84)**	61 (34–82)	62 (26–84)	62 (33–82)	62 (26–84)	62 (33–83)	62 (26–84)
Age ≥65 y, n (%)	**382 (38.0)**	92 (37.1)	97 (42.5)	161 (36.4)	177 (40.2)	184 (36.3)	198 (39.8)
Sex, male, n (%)	**672 (66.9)**	171 (69.0)	147 (64.5)	295 (66.7)	294 (66.8)	337 (66.5)	335 (67.3)
Race, n (%)							
White	**738 (73.4)**	162 (65.3)	166 (72.8)	307 (69.5)	324 (73.6)	362 (71.4)	376 (75.5)
Asian	**242 (24.1)**	78 (31.5)	56 (24.6)	121 (27.4)	106 (24.1)	130 (25.6)	112 (22.5)
Other	**25 (2.5)**	8 (3.2)	6 (2.6)	14 (3.2)	10 (2.3)	15 (3.0)	10 (2.0)
Histology, non-SQ	**659 (65.6)**	152 (61.3)	143 (62.7)	292 (66.1)	296 (67.3)	328 (64.7)	331 (66.5)
Stage, n (%)							
IB	**123 (12.2)**	–	–	–	–	65 (12.8)	58 (11.6)
IIA	**295 (29.4)**	85 (34.3)	76 (33.3)	147 (33.3)	148 (33.6)	147 (29.0)	148 (29.7)
IIB	**174 (17.3)**	46 (18.5)	37 (16.2)	90 (20.4)	84 (19.1)	90 (17.8)	84 (16.9)
IIIA	**413 (41.1)**	117 (47.2)	115 (50.4)	205 (46.4)	208 (47.3)	205 (40.4)	208 (41.8)
Tobacco use, n (%)							
Never	**222 (22.1)**	51 (20.6)	41 (18.0)	100 (22.6)	96 (21.8)	114 (22.5)	108 (21.7)
Current/previous	**783 (77.9)**	197 (79.4)	187 (82.0)	342 (77.4)	344 (78.2)	393 (77.5)	390 (78.3)
PD-L1 by SP263, TC≥1%, n (%)[a]	**535 (54.6)**	248 (100)	228 (100)	248 (57.8)	228 (53.0)	283 (57.4)	252 (51.9)

IMpower010: DFS in key subgroups of the PD-L1 TC ≥1%[a] stage II-IIIA population



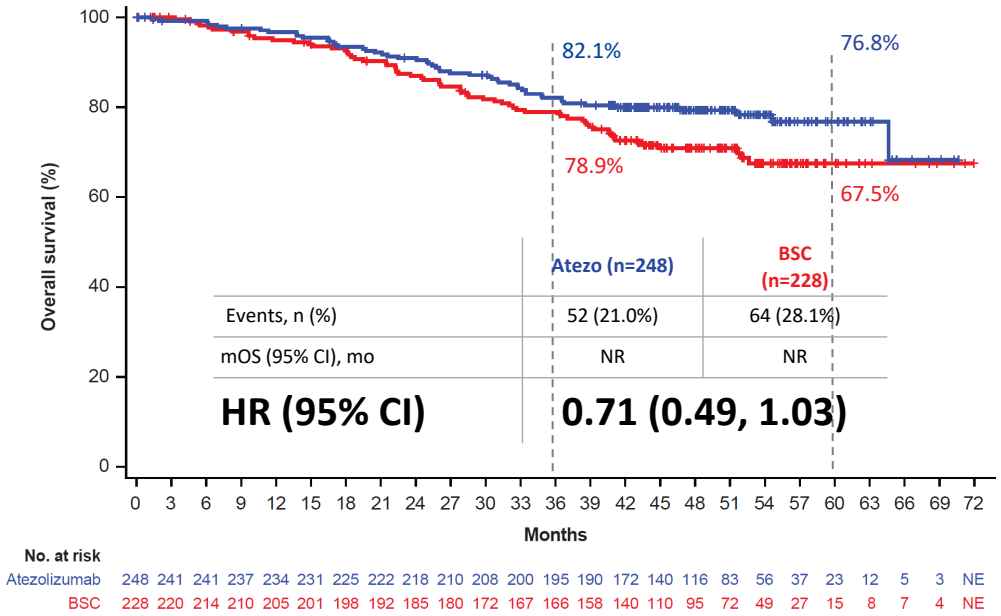
Clinical cutoff: January 21, 2021. [a] Per SP263 assay. [b] Stratified for all patients; unstratified for all other subgroups.
[c] 89.2% and 80.7% of patients in the ITT population with unknown *EGFR* or *ALK* status, respectively, had squamous NSCLC and were not required to undergo local or central testing.

Dr. Heather A. Wakelee ASCO 2021, abstr 8500

IMpower010: OS IA

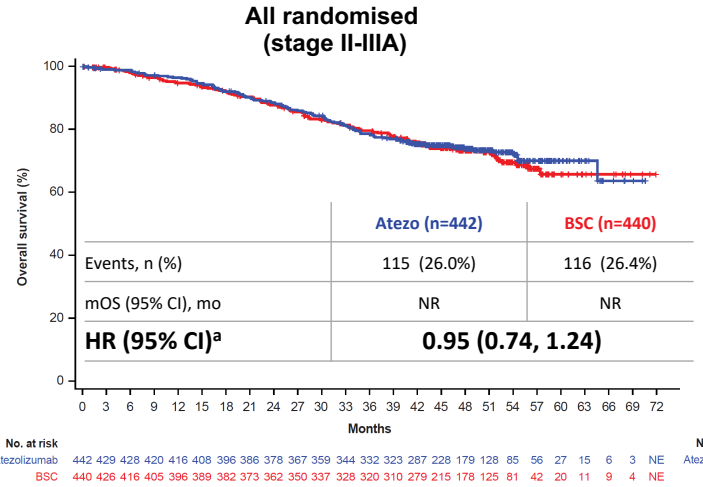
(data cut 4/18/22: 46 mo med) f/up)

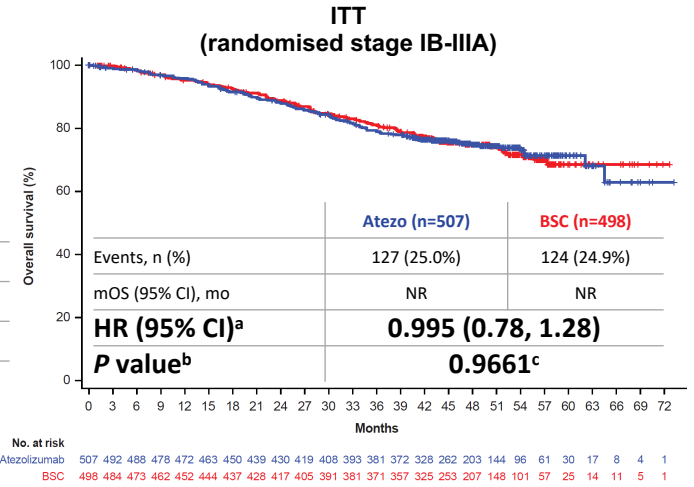
PD-L1 TC ≥1%[a] (stage II-IIIA)



- **At Initial Data Cut 1/21/21**
  - **PD-L1 TC ≥1% stage II-IIIA OS HR: 0.77 (95% CI: 0.51, 1.17)**

IMpower010: Results of OS IA (data cut 4/18/22: 46 mo med f/up) Other primary populations

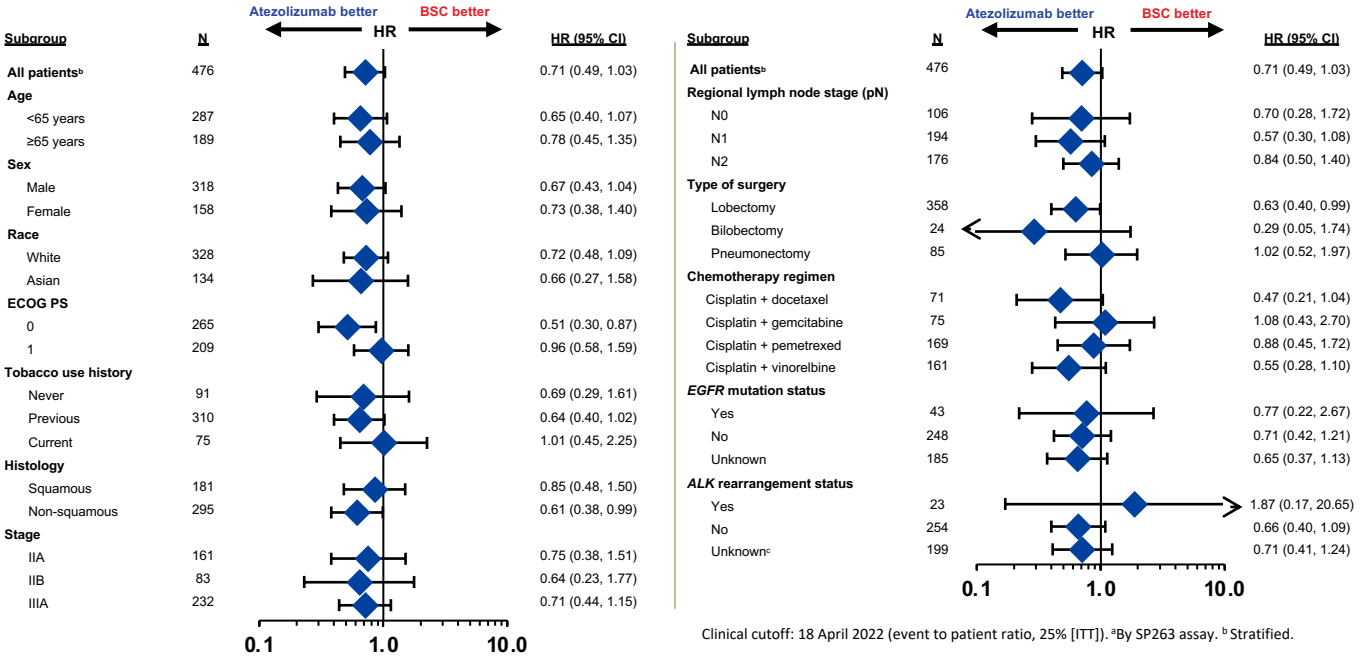




Clinical cutoff: 18 April 2022.[a] Stratified. [b] No formal testing until statistical significance observed for DFS in the ITT population due to the prespecified testing hierarchy.
[c] Descriptive purposes only.

IMpower010 Subgroup analysis of OS in PD-L1 TC ≥1% (stage II-IIIA) population

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

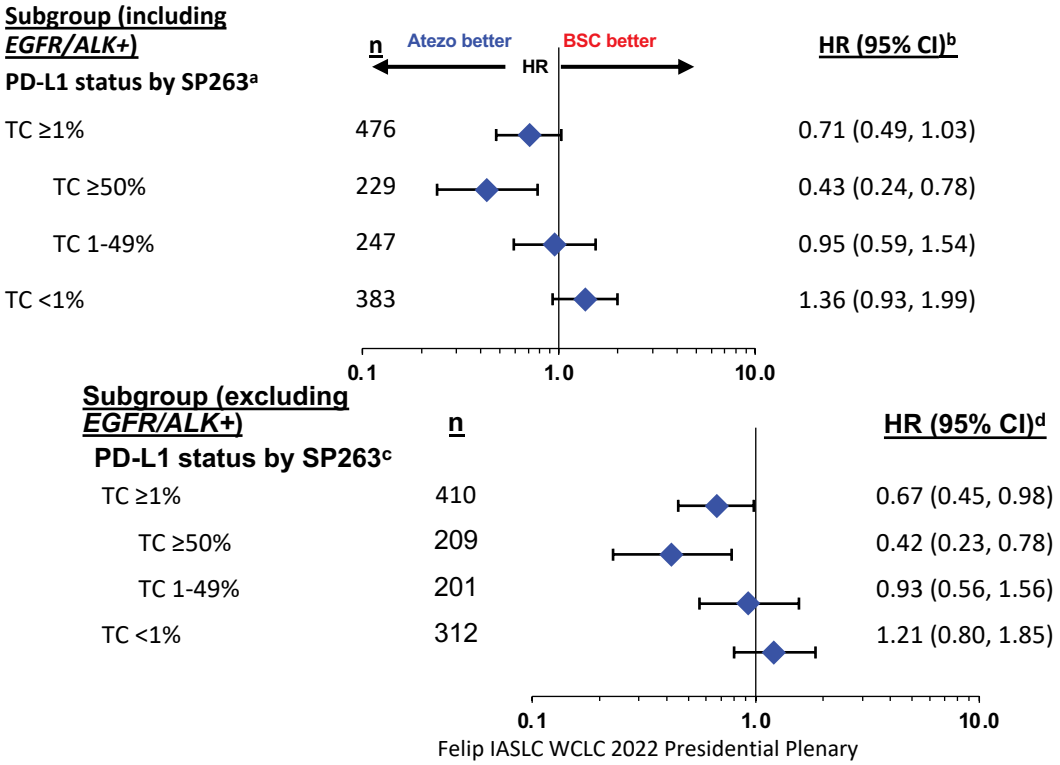


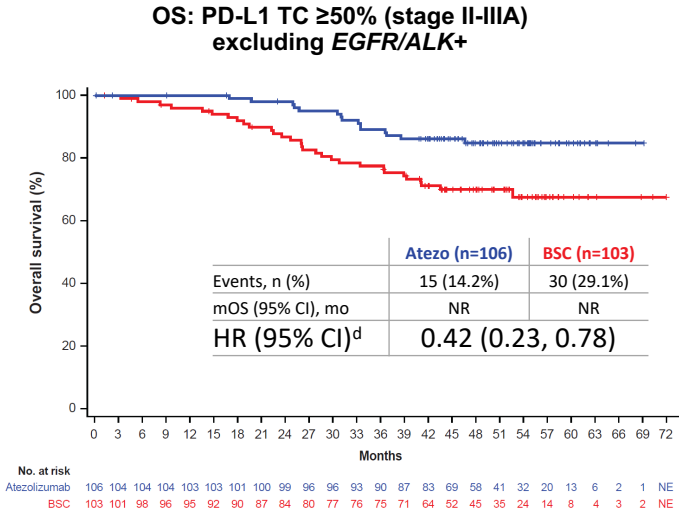
Clinical cutoff: 18 April 2022 (event to patient ratio, 25% [ITT]). [a]By SP263 assay. [b] Stratified.

Felip IASLC WCLC 2022 Presidential Plenary

Impower010 OS by Biomarkers (stage II-IIIA)

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





IMpower010 Safety summary

(data cutoff: 18 Apr '22)

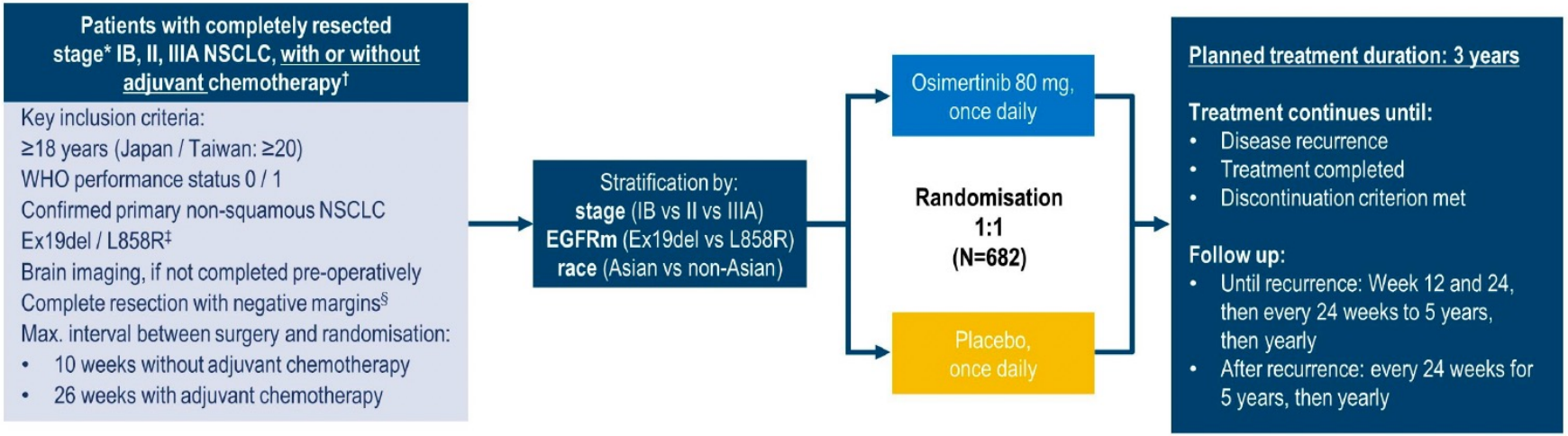
- Overall safety profile was consistent with previous analysis; no new safety signals were seen

	IMpower010 DFS IA (21 Jan '21)	IMpower010 OS IA (18 Apr '22)	
	Atezo (n=495)	Atezo (n=495)	BSC (n=508)
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.

EGFR TKIs in Early Stage Lung Cancer

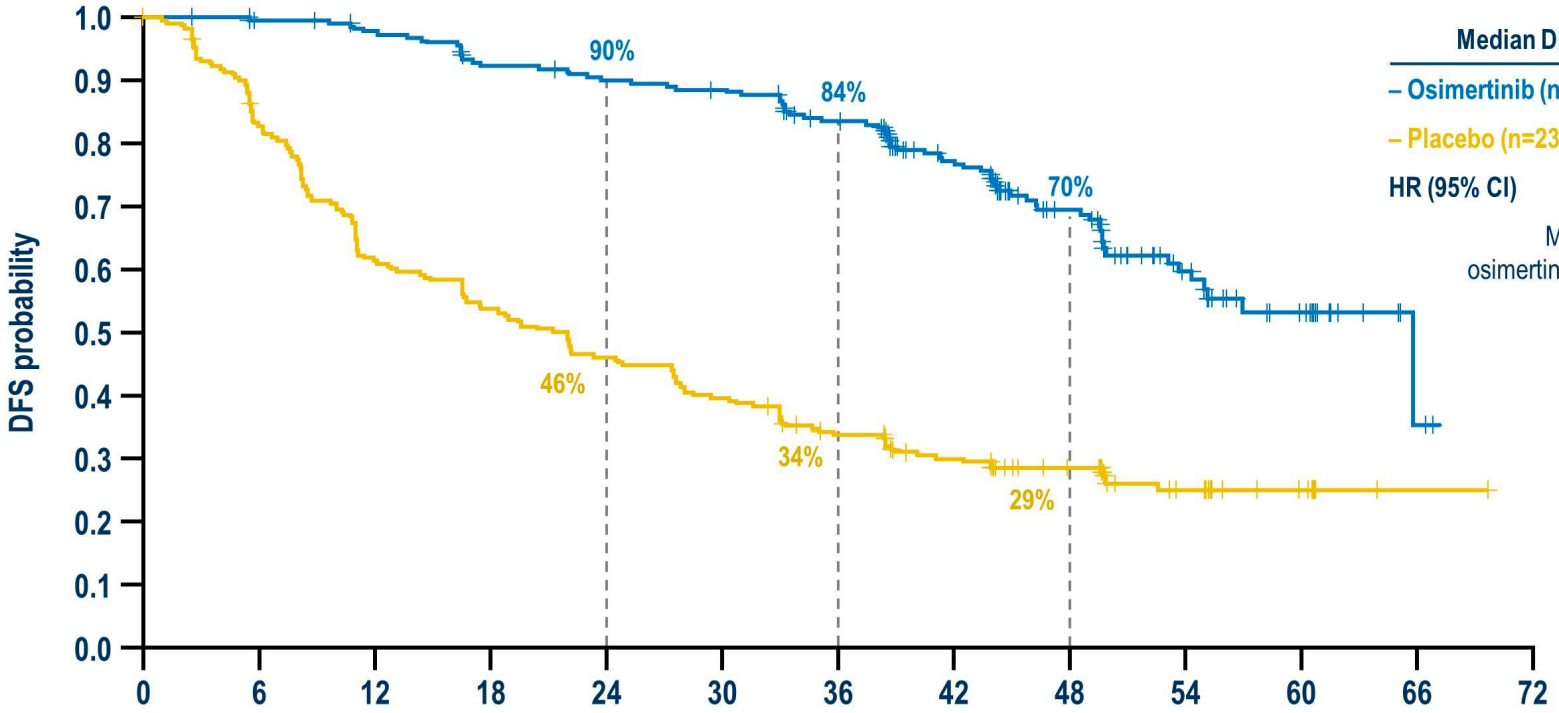
PHASE III ADAURA STUDY DESIGN



Endpoints

- **Primary endpoint:** DFS by investigator assessment in stage II / IIIA patients, designed for superiority under the assumed DFS HR of 0.70
- **Key secondary endpoints:** DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life
- **Pre-specified exploratory endpoints:** Patterns of recurrence, time to CNS disease recurrence or death (CNS DFS)

PRIMARY ENDPOINT: UPDATED DFS IN STAGE II / IIIA DISEASE



Median DFS, months (95% CI)	
– Osimertinib (n=233)	65.8 (54.4, NC)
– Placebo (n=237)	21.9 (16.6, 27.5)
HR (95% CI)	0.23 (0.18, 0.30)

Maturity:* 51%
osimertinib 32%, placebo 70%

No. at risk												
Osimertinib	233	222	216	202	196	192	174	138	90	45	20	2	0
Placebo	237	191	141	124	106	91	74	61	41	23	11	1	0

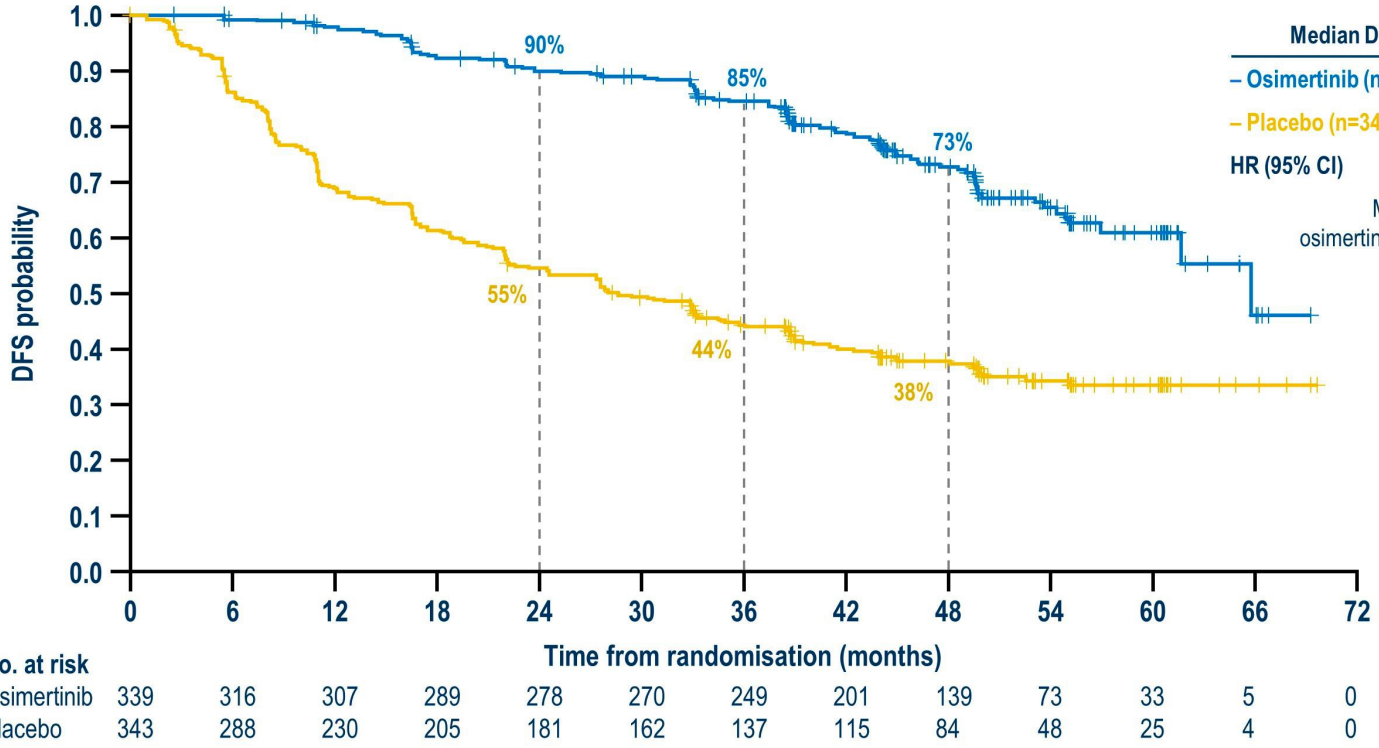
PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

Median follow-up: osimertinib 44.2 months (range 0 to 67), placebo 19.6 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data. *Planned maturity for DFS analysis: 50%.

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable
Data cut-off: April 11, 2022.

UPDATED DFS IN THE OVERALL POPULATION (STAGE IB / II / IIIA DISEASE)



No. at risk												
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

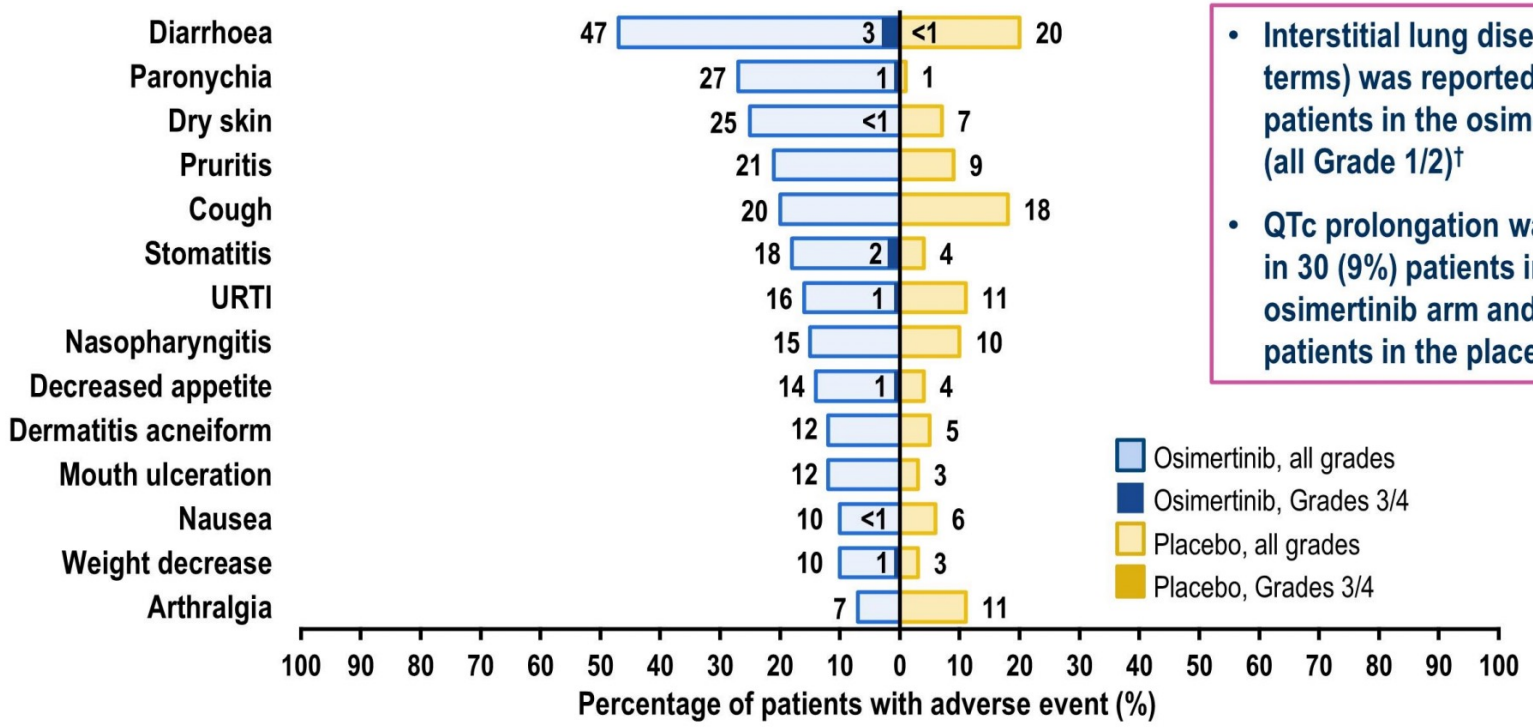
Median follow-up: osimertinib 44.2 months (range 0 to 69), placebo 27.7 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data.

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable

Data cut-off: April 11, 2022.

– **Median DFS was 65.8 months in the osimertinib arm and 21.9 months in the placebo arm**

ALL CAUSALITY ADVERSE EVENTS (≥10% OF PATIENTS)

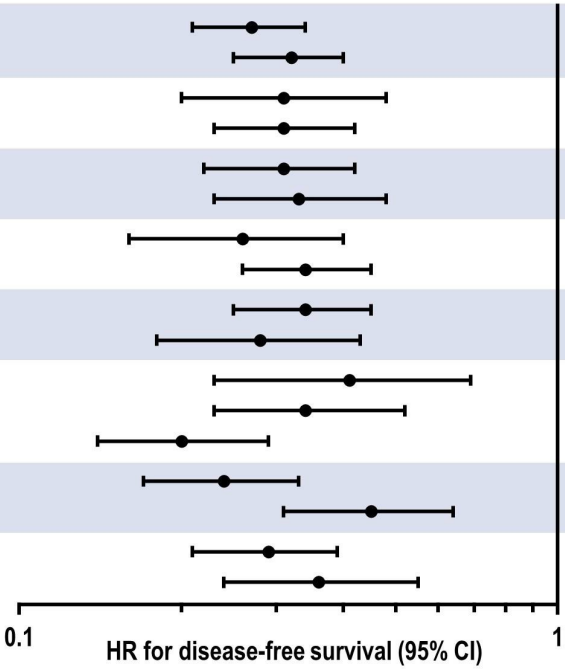


- Interstitial lung disease (grouped terms) was reported in 11 (3%)* patients in the osimertinib arm (all Grade 1/2)†
- QTc prolongation was reported in 30 (9%) patients in the osimertinib arm and 8 (2%) patients in the placebo arm‡

UPDATED DFS ACROSS SUBGROUPS IN THE OVERALL POPULATION

- A DFS benefit with osimertinib was observed across all predefined subgroups

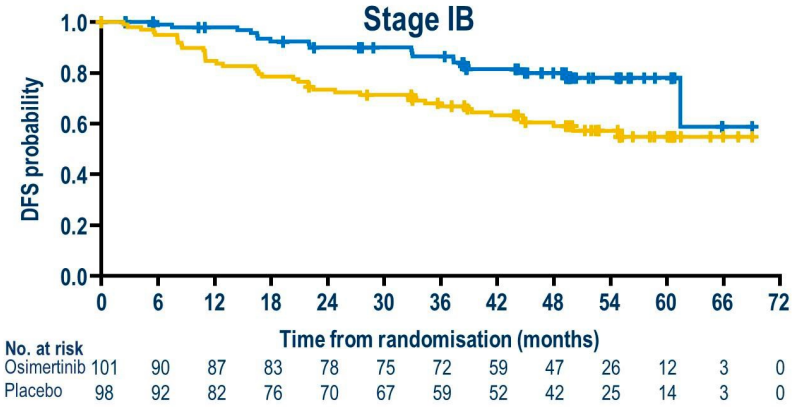
Subgroup		HR	95% CI
Overall (N=682)	Stratified log-rank	0.27	0.21, 0.34
	Unadjusted Cox PH	0.32	0.25, 0.40
Sex	Male (n=204)	0.31	0.20, 0.48
	Female (n=478)	0.31	0.23, 0.42
Age	<65 yr (n=380)	0.31	0.22, 0.42
	≥65 yr (n=302)	0.33	0.23, 0.48
Smoking history	Yes (n=194)	0.26	0.16, 0.40
	No (n=488)	0.34	0.26, 0.45
Race	Asian (n=434)	0.34	0.25, 0.45
	Non-Asian (n=248)	0.28	0.18, 0.43
Stage*	IB (n=212)	0.41	0.23, 0.69
	II (n=236)	0.34	0.23, 0.52
	IIIA (n=234)	0.20	0.14, 0.29
EGFR mutation	Ex19Del (n=378)	0.24	0.17, 0.33
	L858R (n=304)	0.45	0.31, 0.64
Adjuvant chemotherapy	Yes (n=410)	0.29	0.21, 0.39
	No (n=272)	0.36	0.24, 0.55

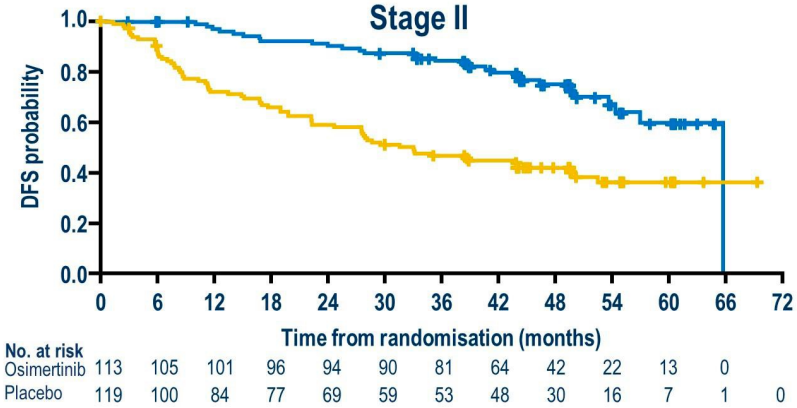


Overall population: stage IB / II / IIIA; DFS by investigator assessment. *AJCC / UICC 7th edition.

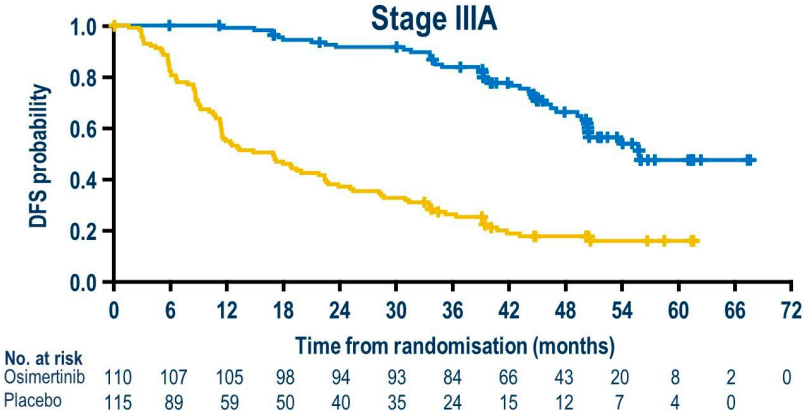
AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; HR, hazard ratio; yr, year.
Data cut-off: April 11, 2022.

UPDATED DFS BY STAGE (AJCC / UICC 8TH EDITION*)





	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (69, 87)	75 (65, 83)	66 (55, 75)
– Placebo	60 (49, 69)	43 (34, 52)	16 (10, 24)
Overall HR (95% CI)	**0.44 (0.25, 0.76)**	**0.33 (0.21, 0.50)**	**0.22 (0.15, 0.31)**



DFS by investigator assessment; Tick marks indicate censored data.

*Re-staging based on data captured in the Pathology at Diagnosis AJCC / UICC 8th edition manual, per investigator assessment requested before the primary analysis.

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.

Conclusions

Neo-Adj Chemo-IO

1)Achieves high pCR

2)Requires treating every patient

3)Risks ~10% loss of surgery

4) What about adjuvant therapy after?

5) Why operate if pCR?

Adjuvant IO

1) Atezo Improves DFS in patients with PD-L1+ stage II-IIIA NSCLC

2) How do we select? Can potentially be limited to those with ctDNA after resection?

3) How can we improve probability of efficacy (DFS HR 0.43 even at PD-L1 level of 50%)?

4) Can adjuvant IO alone be sufficient to avoid chemotherapy?

Adjuvant TKI

1) Importance of molecular testing in early stage disease
2) Impressive DFS but are we curing patients?