IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Best of IASLC WCLC 2022
Adjuvant/Neo-Adjuvant Systemic Therapy

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DISCLOSURES

Company	Relationship(s)
Mirati, Merck (uncompensated), Genentech/Roche (uncompensated)	Advisor
ACEA Biosciences, Arrys Therapeutics, AstraZeneca/Medimmune, BMS, Clovis Oncology, Genentech/Roche, Helsinn, Merck, Novartis, SeaGen, Xcovery	Research Funding (paid to Institution)
President – IASLC Executive Committee ECOG-ACRIN	Other Executive Role

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Early Stage NSCLC – Highlighted in Presidential Symposium

Neo-Adjuvant – NADIMII

Adjuvant – Updated IMpower010

First Step: Neo-Adjuvant Nivolumab

Feasibility N=21: Nivo 3 mg/kg x 2 doses

Did not delay or interfere with surgery

PR	**2 (10%)**
SD	18 (85%)
PD	1 (5%)

Major Pathologic Response (MPR)
9/21 pts = 43%

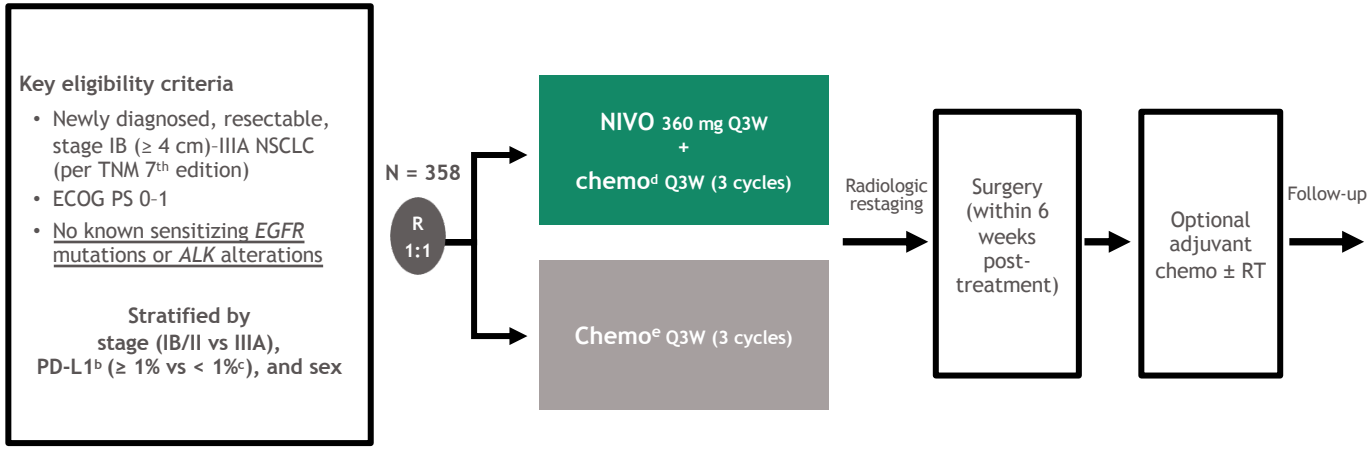
Toxicity

Drug-related Adverse Events N=22	Any Grade N(%)
Fever	1* (5)
Thyroid dysfunction	1 (5)
GI Anorexia/dysgeusia Vomiting/diarrhea LFT abnormality	 2 (9) 1 (5) 1 (5)
Pneumonia	0
Infusion reaction	1 (5)
CNS (delirium)	1 (5)

Subsequent Single Agent IO Neoadjuvant trials MPR ~20%

Chaft & Forde, et al.; NEJM 2018

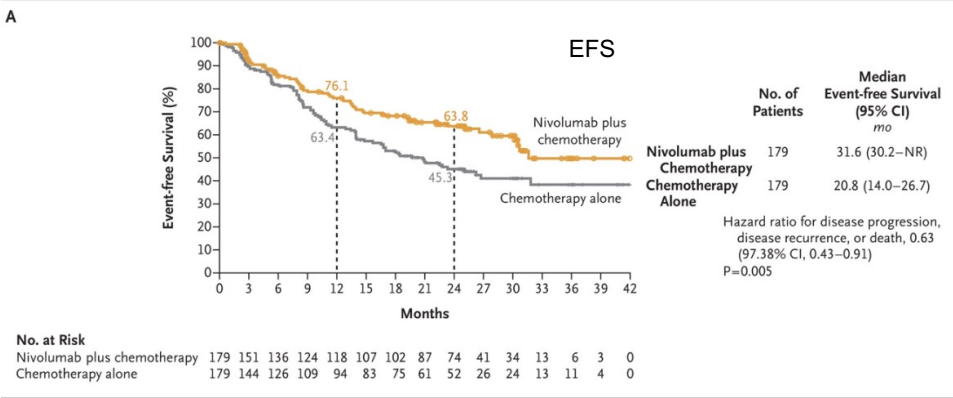
CM816

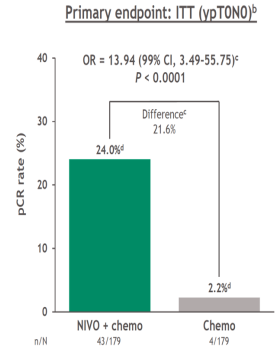


63% Stage IIIA
50% PD-L1 >1%
No EGFR/ALK
IO + Chemo

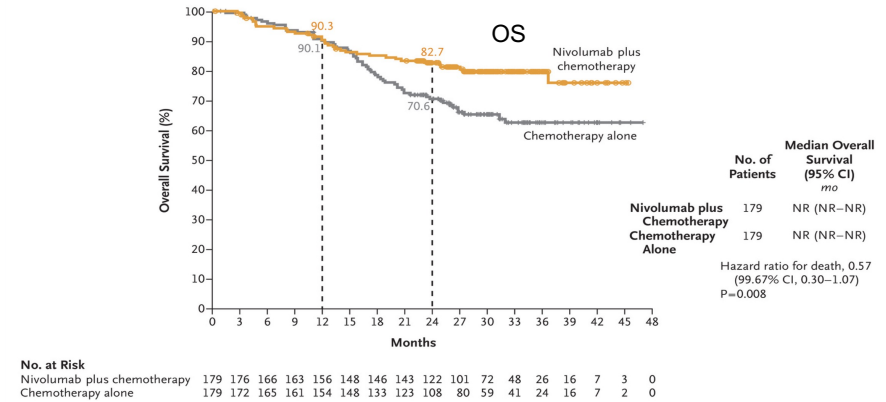
Spicer ASCO 2021 abstr: 8503, Forde NEJM

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

Forde NEJM

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NIVOLUMAB + CHEMOTHERAPY vs CHEMOTHERAPY AS NEOADJUVANT TREATMENT FOR RESECTABLE IIIA-B NSCLC

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

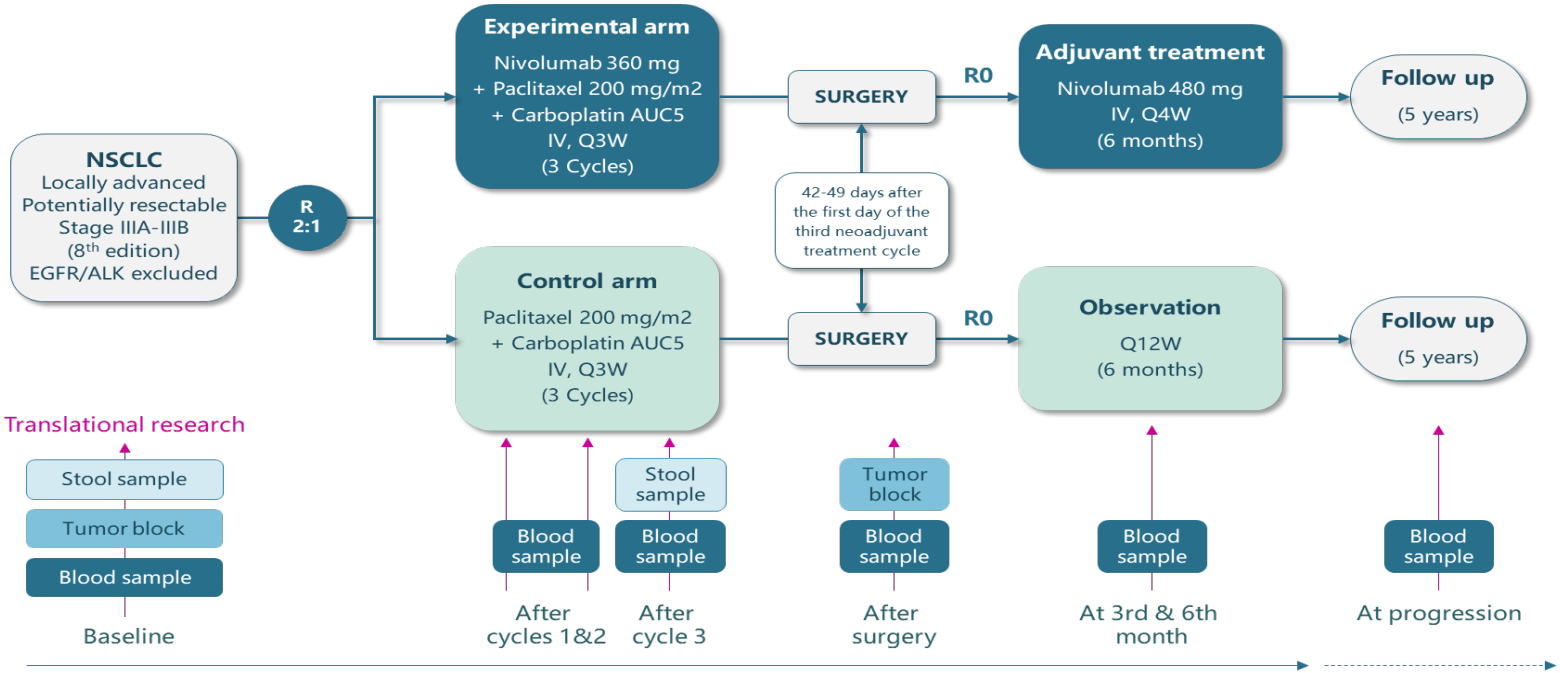
Dr. Mariano Provencio

Hospital Universitario Puerta de Hierro-Majadahonda, Madrid

SPAIN

NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

STUDY DESIGN



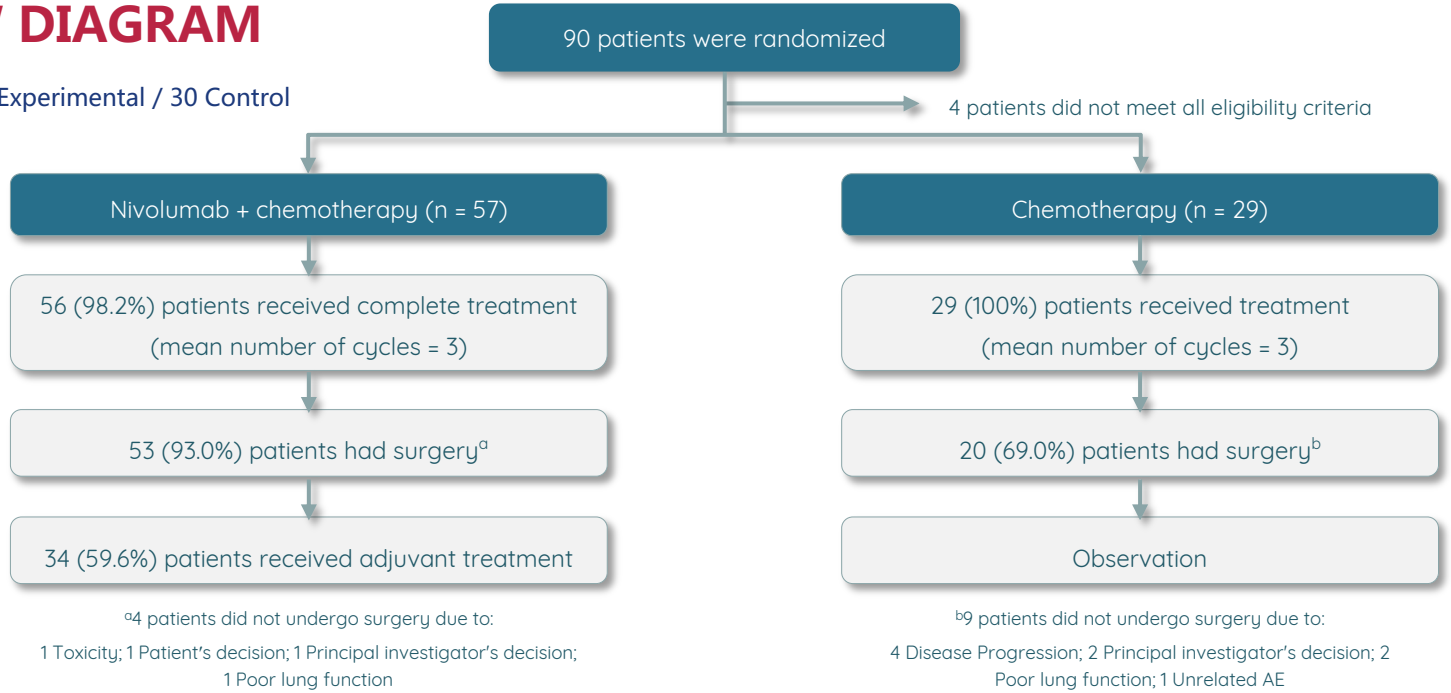
BASELINE CHARACTERISTICS (ITT)

Characteristic	NIVO + Chemo (n = 57)	Chemo (n = 29)
Age – median (range), years	63 (58-70)	62 (57-66)
Female – No. (%)	21 (36.8)	13 (44.8)
History of tobacco use – No. (%)		
Never smoker	5 (8.7)	0 (0.0)
Former smoker	23 (40.4)	10 (34.5)
Current smoker	29 (50.9)	19 (65.5)
ECOG PS – No. (%)		
0	31 (54.4)	16 (55.2)
1	26 (45.6)	13 (44.8)
Histology – No. (%)		
Adenocarcinoma	25 (43.9)	11 (37.9)
Adenosquamous	1 (1.8)	0 (0.0)
Squamous	21 (36.8)	14 (48.3)
Large Cell Carcinoma	2 (3.5)	1 (3.5)
NOS / Undifferentiated	7 (12.3)	2 (6.9)
Other	1 (1.8)	1 (3.5)

Characteristic	NIVO + Chemo (n = 57)	Chemo (n = 29)
TNM classification (AJCC 8th Ed.)		
T1N2M0	12 (21.1)	4 (13.8)
T2N2M0	16 (28.1)	7 (24.1)
T3N1M0	2 (3.5)	1 (3.5)
T3N2M0	13(22.8)	5 (19.3)
T4N0M0	6 (10.5)	9 (31.0)
T4N1M0	8 (14.0)	3 (10.3)
Tumor size – Median (range), mm	43 (29-54)	52 (39-75)
Nodal stage – No. (%)		
N0	6 (10.5)	9 (31.0)
N1	10 (17.5)	4 (13.8)
N2	41 (71.9)	16 (55.2)
N2 multiple station	21 (36.8)	10 (34.5)

FLOW DIAGRAM

Accrual: 60 Experimental / 30 Control



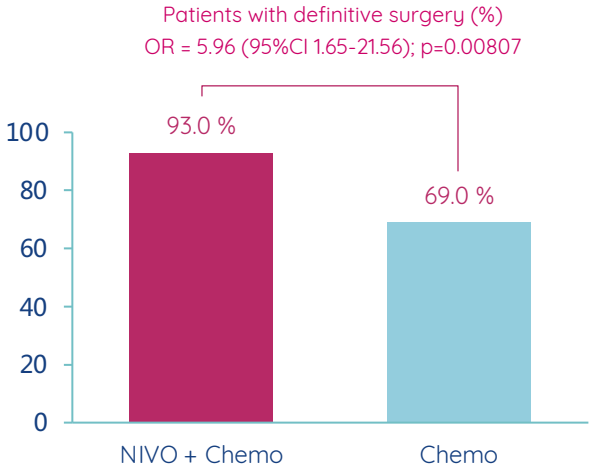
[a]4 patients did not undergo surgery due to:
1 Toxicity; 1 Patient's decision; 1 Principal investigator's decision; 1 Poor lung function

[b]9 patients did not undergo surgery due to:
4 Disease Progression; 2 Principal investigator's decision; 2 Poor lung function; 1 Unrelated AE

SURGERY SUMMARY

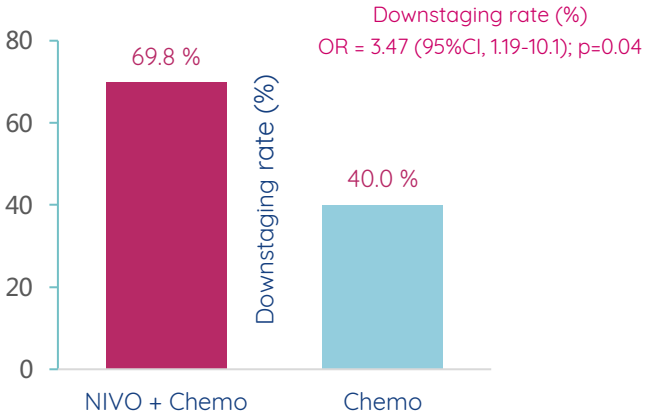
Type of surgery, No. (%)	NIVO + Chemo (n = 53)	Chemo (n = 20)	Total (n = 73)
Pneumonectomy	6 (11.3)	2 (10.0)	8 (11.0)
Lobectomy	40 (75.5)	17 (85.0)	57 (78.1)
Bilobectomy	4 (7.5)	1 (5.0)	5 (6.8)
Segmentectomy	2 (3.8)	0 (0.0)	2 (2.7)
Right Lower Lobectomy + Segmentectomy	1 (1.9)	0 (0.0)	1 (1.4)

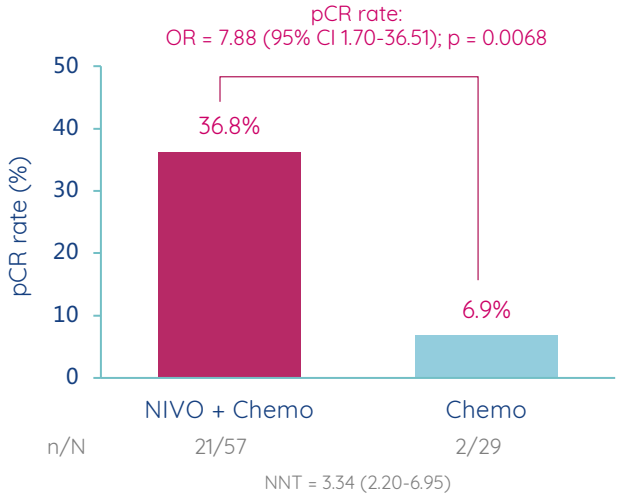
Resection degree, No (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)
R0	49 (92.5)	13 (65.0)
Odds Ratio: 6.60 (95% CI 1.67-26.02); p = 0.007		



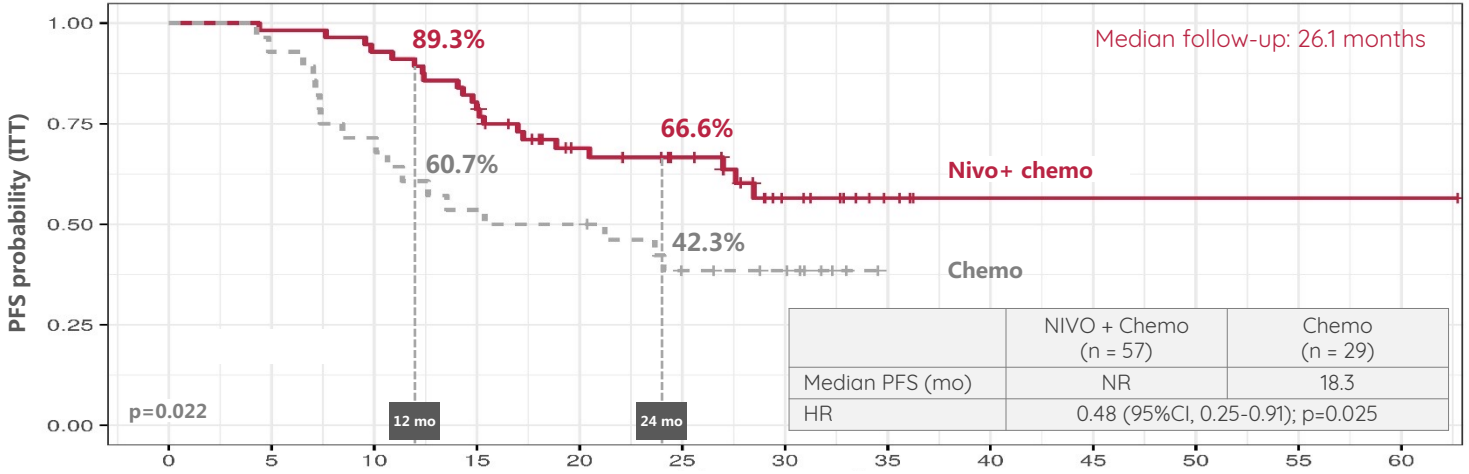
SECONDARY ENDPOINTS – Downstaging

Downstaging, No. (%)	Yes	No	Total
Nivolumab + chemotherapy	37 (69.8)	16 (30.2)	53
Chemotherapy	8 (40.0)	12 (60.0)	20
Total	45 (61.6)	28 (38.4)	73





SECONDARY ENDPOINTS – Progression-free survival

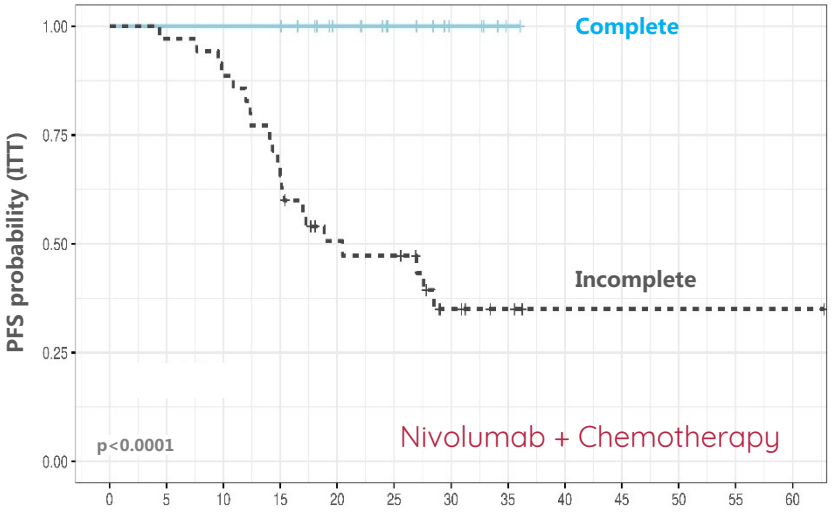


	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median PFS (mo)	NR	18.3
HR	0.48 (95%CI, 0.25-0.91); p=0.025	

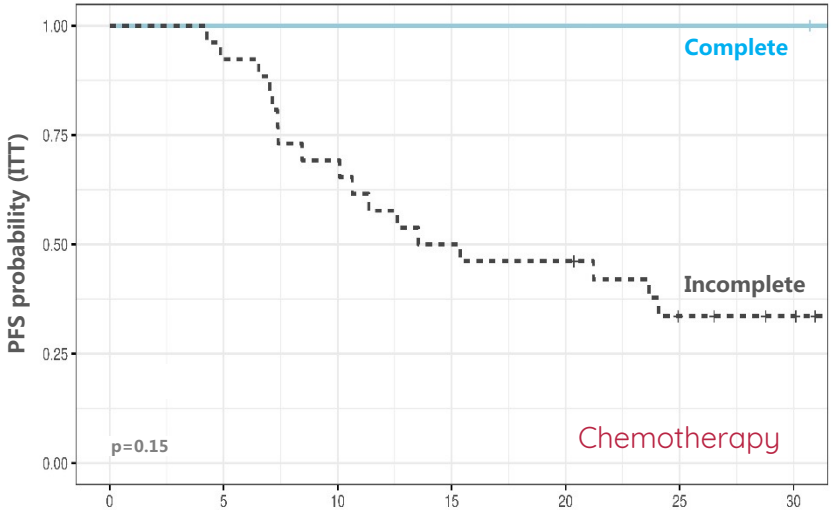
Number at risk													
Nivo + chemo	56	55	52	44	30	24	11	4	1	1	1	1	1
Chemo	28	26	20	15	14	9	7	0	0	0	0	0	0

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

SECONDARY ENDPOINTS – PFS by pCR status



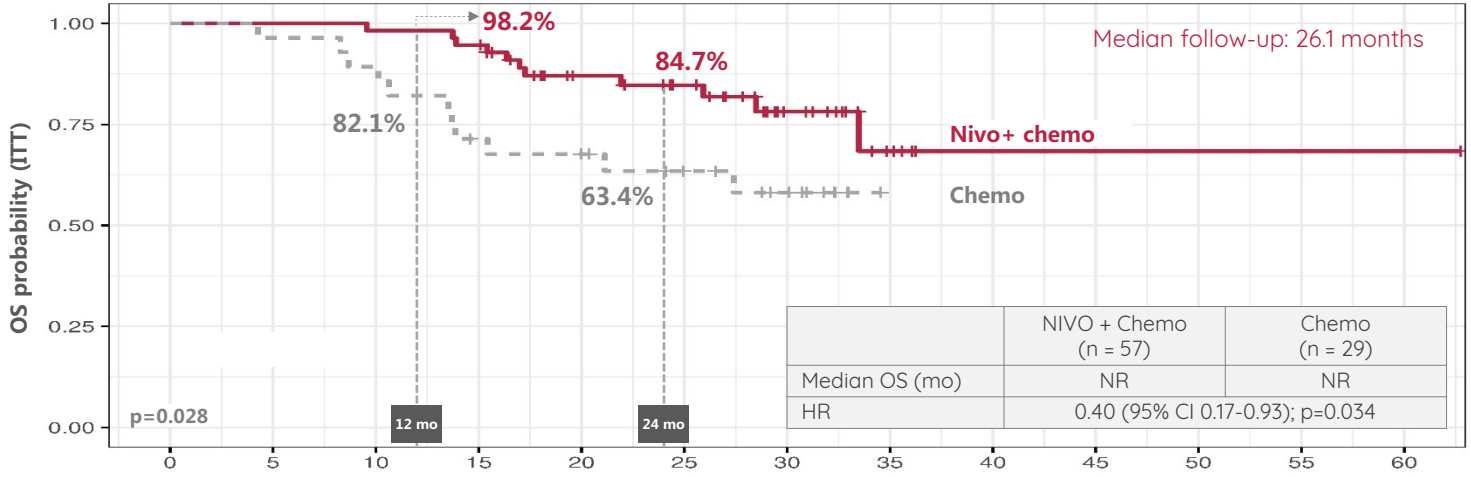
Number at risk													
Complete	21	21	21	21	15	10	5	1	0	0	0	0	0
Incomplete	35	34	31	23	15	14	6	3	1	1	1	1	1



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

SECONDARY ENDPOINTS – Overall survival

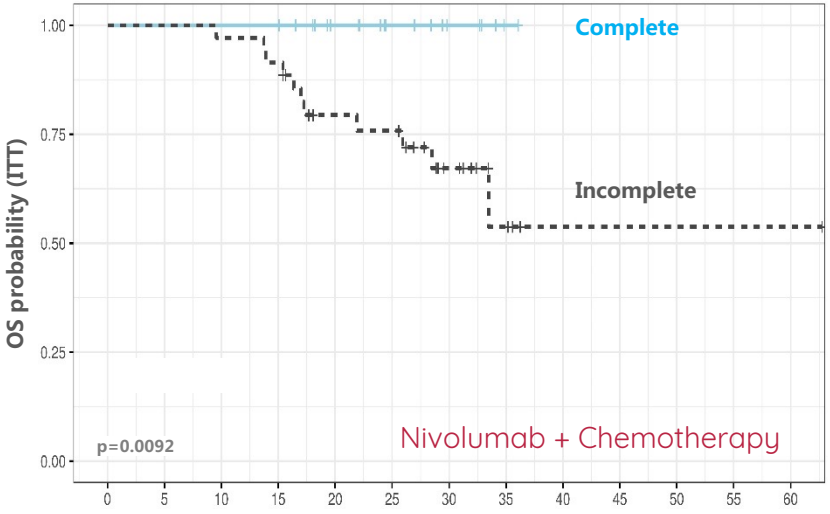


	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median OS (mo)	NR	NR
HR	0.40 (95% CI 0.17-0.93); p=0.034	

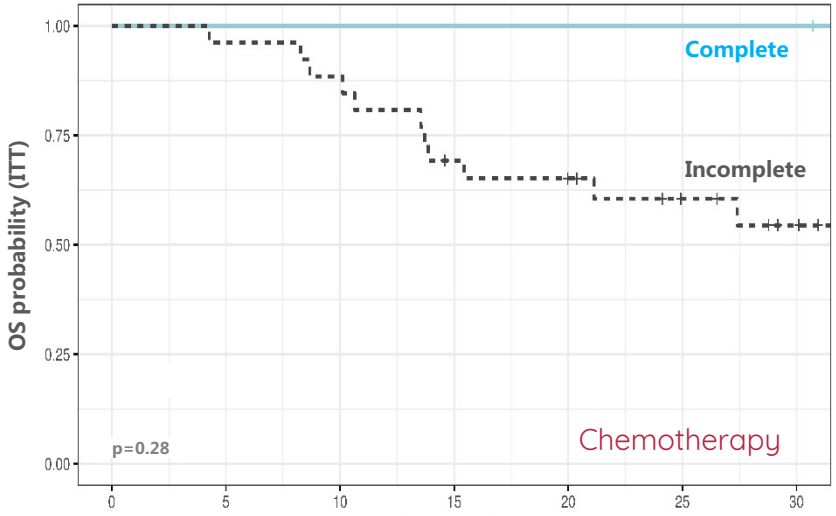
Number at risk													
Nivo + chemo	56	56	55	53	37	31	15	5	1	1	1	1	1
Chemo	28	27	25	19	17	13	9	0	0	0	0	0	0

Overall survival was defined as the time from randomization to death. OS was censored on the last date a participant was known to be alive

SECONDARY ENDPOINTS – OS by pCR status



Number at risk													
Complete	21	21	21	21	15	10	5	1	0	0	0	0	0
Incomplete	35	35	34	32	22	21	10	4	1	1	1	1	1



Number at risk							
Complete	2	2	2	2	2	2	2
Incomplete	26	25	23	17	15	11	7

Overall survival was defined as the time from randomization to death. OS was censored on the last date a participant was known to be alive

CONCLUSIONS

- **NADIM II confirms superiority of neoadjuvant nivolumab plus chemotherapy combination in patients with resectable stage IIIA-B NSCLC**
- **The addition of neoadjuvant nivolumab to chemotherapy:**
  - **→ Significantly improved pCR (OR = 7.88 [95% CI 1.70-36.51]) (Chi-squared test: p=0.0068)**
  - **→ Significantly improved PFS rate at 12 (89.3% vs 60.7%, p=0.001) and 24 months (66.6% vs 42.3%, p=0.012)**
  - **→ Significantly improved OS rate at 12 (98.2% vs 82.1%, p=0.007) and 24 months (84.7% vs 63.4%, p=0.014)**
  - **→ Maintained a tolerable safety profile, with a moderate increase in grade 3-4 toxicity**
  - **→ Did not impede the feasibility of surgery**
- **NADIM II is the first clinical trial with a neoadjuvant immunotherapy-based combination (nivolumab + chemotherapy) for resectable stage IIIA-B NSCLC to show improved OS**

Neo-Adjuvant Studies

Drug	N	Stages	Description	Primary Endpoint
Nivo + platinum chemo (**ipi/nivo closed**) CM816	350	Stage IB–IIIA, resectable NSCLC	Neo-adjuvant, no adjuvant	MPR / RFS
Atezo + platinum chemo Impower030	374	Stage II–IIIB (T3N2), resectable NSCLC	Neo-adjuvant chemo-ICI, then adjuvant IO	MPR / RFS
Pembro + platinum chemo KN671	786	Stage IIB–IIIA, resectable NSCLC	Neo-adjuvant chemo-ICI then adjuvant IO	RFS / OS
Durva + platinum chemo Aegean	300	Stage II–IIIA, resectable NSCLC	Neo-adjuvant chemo-ICI then adjuvant IO	MPR

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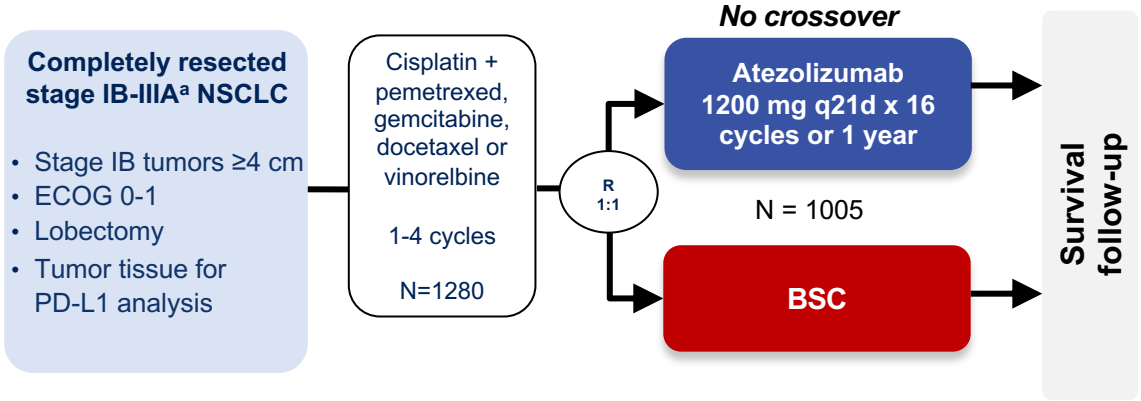
IMpower010: Overall survival interim analysis of a phase III study of atezolizumab vs best supportive care in resected NSCLC

Enriqueta Felip,[1] Nasser Altorki,[2] Eric Vallieres,[3] Ihor O. Vynnychenko,[4] Andrey Akopov,[5] Alex Martinez-Marti,[1] Antonio Chella,[6] Igor Bondarenko,[7] Shunichi Sugawara,[8] Yun Fan,[9] Hirotsugu Kenmotsu,[10] Yuh-Min Chen,[11] Yu Deng,[12] Meilin Huang,[12] Virginia McNally,[13] Elizabeth Bennett,[12] Barbara J. Gitlitz,[12] Caicun Zhou,[14] Heather A. Wakelee[15]

[1]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]NewYork-Presbyterian Hospital, Weill Cornell Medicine, New York, NY, USA; [3]Swedish Cancer Institute, Seattle, WA, USA; [4]Regional Municipal Institution Sumy Regional Clinical Oncology Dispensary, Sumy State University, Sumy, Ukraine; [5]Pavlov State Medical University, Saint Petersburg, Russia; [6]Pneumology Unit, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; [7]Dnipro State Medical University, Dnipro, Ukraine; [8]Sendai Kousei Hospital, Miyagi, Japan; [9]Zhejiang Cancer Hospital, Hanzhou, China; [10]Shizuoka Cancer Center, Shizuoka, Japan; [11]Taipei Veterans General Hospital and National Yang Ming Chiao Tung University, Taipei, Taiwan; [12]Genentech Inc, South San Francisco, CA, USA; [13]Roche Products Ltd, Welwyn Garden City, United Kingdom; [14]Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai, China; [15]Stanford University School of Medicine/Stanford Cancer Institute, Stanford, CA, USA.

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

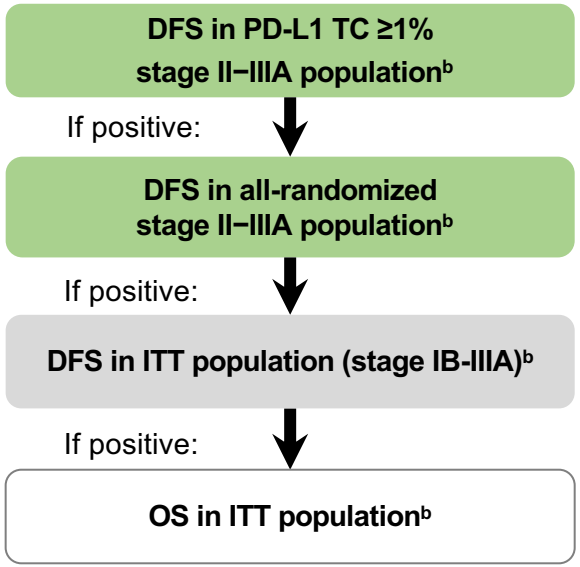


Stratification factors
- Sex | Stage | Histology | PD-L1 status

Key secondary endpoints
- OS in ITT | Safety | Exploratory OS biomarker analyses

Key exploratory endpoints
- OS biomarker analyses

Hierarchical statistical testing of endpoints



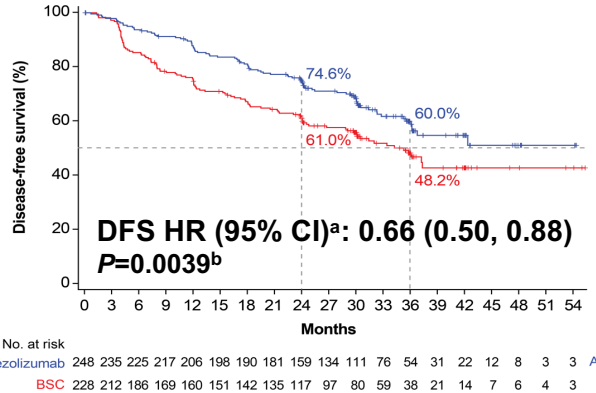
Endpoint was met at DFS IA
Endpoint was not met at DFS IA and follow up is ongoing
Endpoint was not formally tested

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.

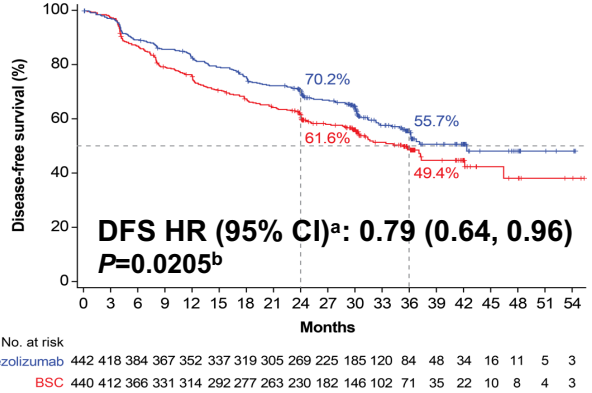
Recap of DFS and OS data from the DFS IA[1,2]

(data cutoff: 21 Jan '21, median follow-up: 32 months)

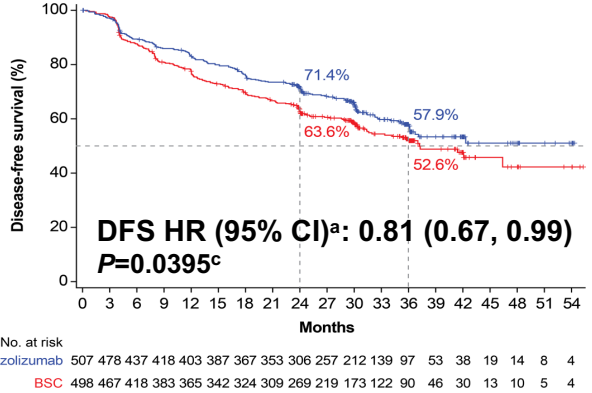
DFS: PD-L1 TC ≥1% stage II-IIIA population



DFS: All-randomised stage II-IIIA population



DFS: ITT (randomised stage IB-IIIA) population



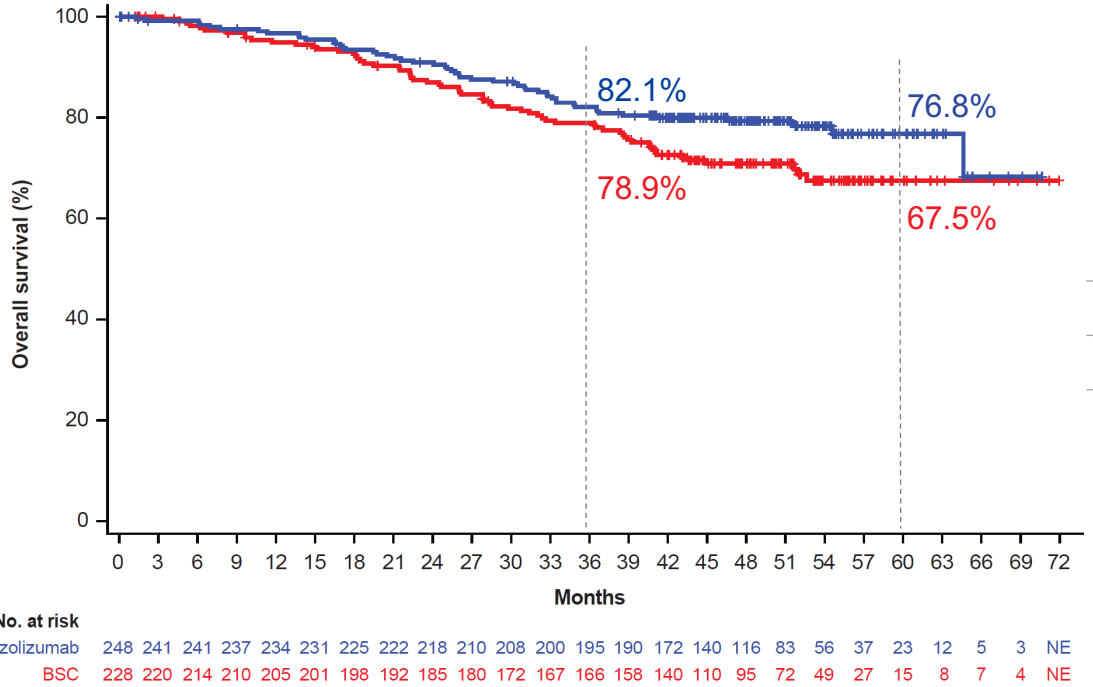
- **OS data** were not mature (event to patient ratio in ITT was 19% in atezolizumab arm, 18% in BSC arm)
  - PD-L1 TC ≥1% stage II-IIIA population: OS HR, 0.77 (95% CI: 0.51, 1.17)[a]
  - All-randomised stage II-IIIA population: OS HR, 0.99 (95% CI: 0.73, 1.33)[a]
  - ITT (randomised stage IB-IIIA) population: OS HR, 1.07 (95% CI: 0.80, 1.42)[a]

Clinical cutoff: 21 Jan 2021. [a] Stratified. [b] Statistical significance boundary for DFS crossed. [c] Statistical significance boundary for DFS not crossed.

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

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

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



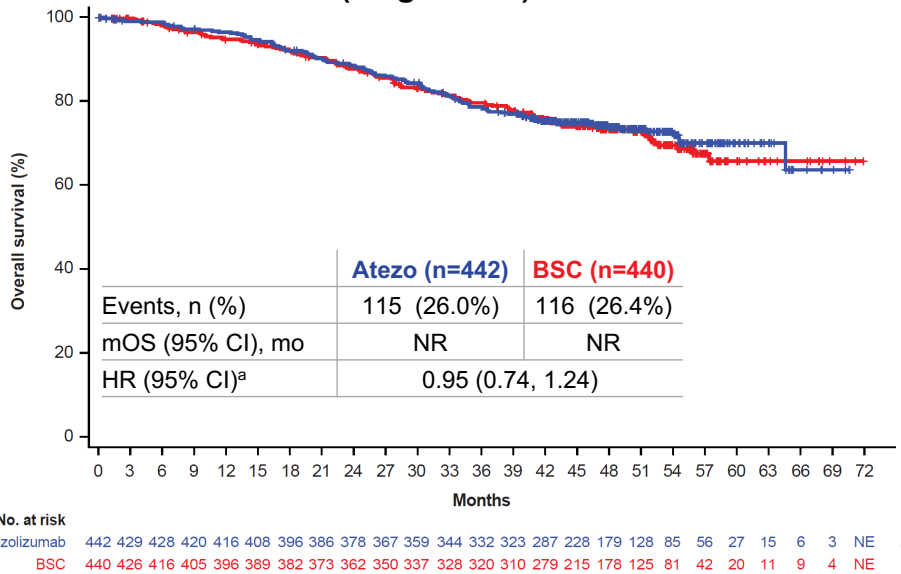
	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[b]	0.71 (0.49, 1.03)	

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

Results of OS IA: other primary populations

(data cutoff: 18 Apr '22, median follow-up: 45 months)

All randomised (stage II-IIIA)

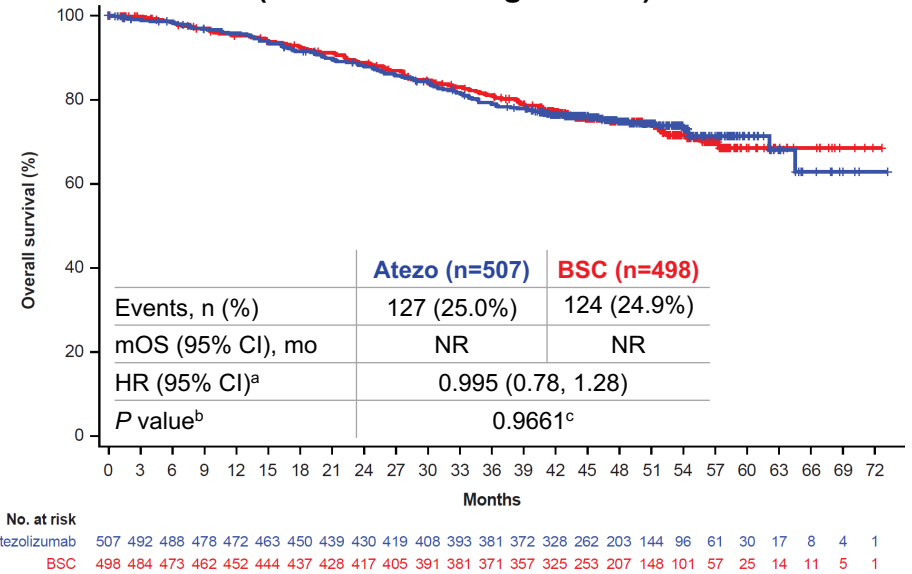


	Atezo (n=442)	BSC (n=440)
Events, n (%)	115 (26.0%)	116 (26.4%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.95 (0.74, 1.24)	

No. at risk

Atezolizumab	442	429	428	420	416	408	396	386	378	367	359	344	332	323	287	228	179	128	85	56	27	15	6	3	NE
BSC	440	426	416	405	396	389	382	373	362	350	337	328	320	310	279	215	178	125	81	42	20	11	9	4	NE

ITT (randomised stage IB-IIIA)



	Atezo (n=507)	BSC (n=498)
Events, n (%)	127 (25.0%)	124 (24.9%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.995 (0.78, 1.28)	
P value[b]	0.9661[c]	

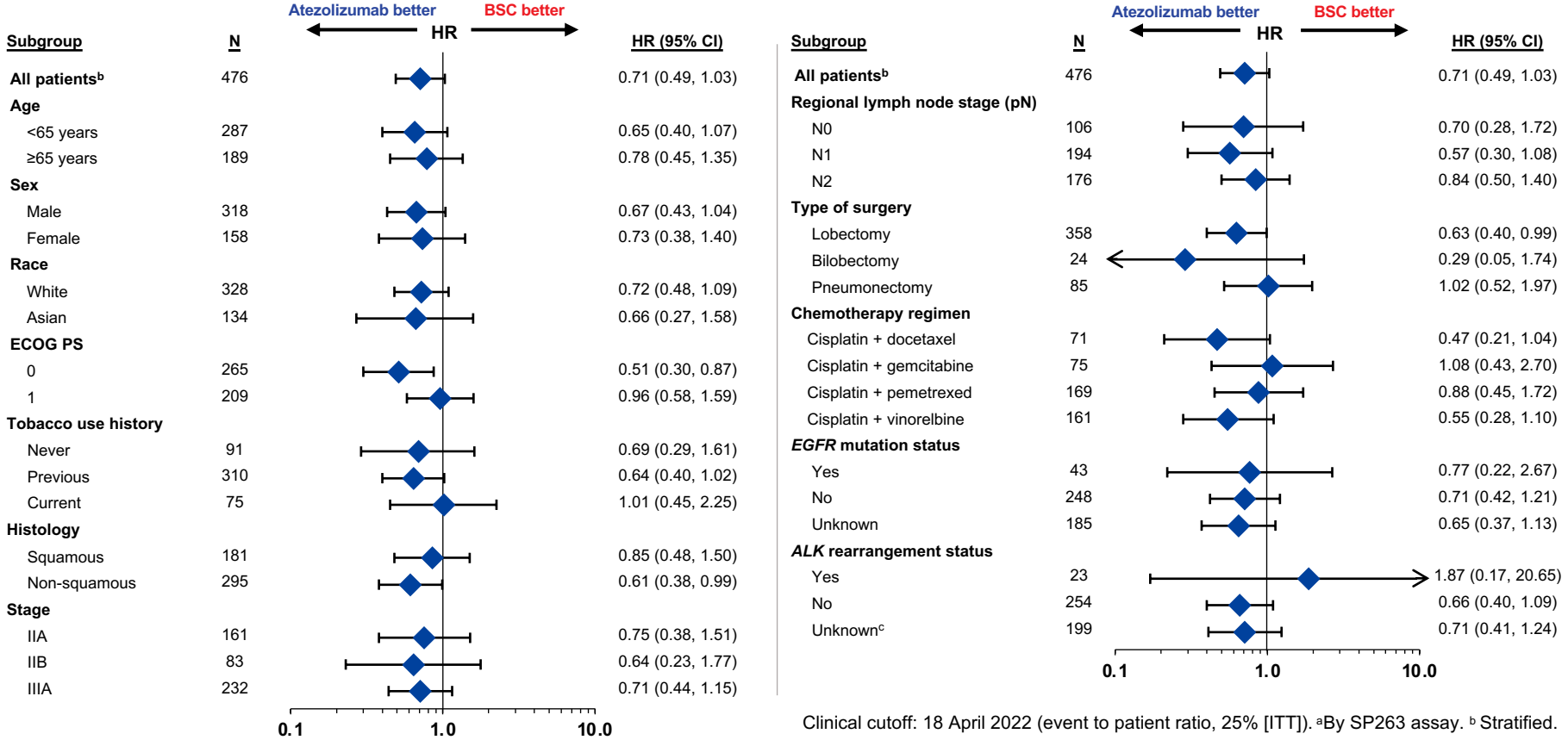
No. at risk

Atezolizumab	507	492	488	478	472	463	450	439	430	419	408	393	381	372	328	262	203	144	96	61	30	17	8	4	1
BSC	498	484	473	462	452	444	437	428	417	405	391	381	371	357	325	253	207	148	101	57	25	14	11	5	1

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.

Subgroup analysis of OS in PD-L1 TC ≥1%[a] (stage II-IIIA)

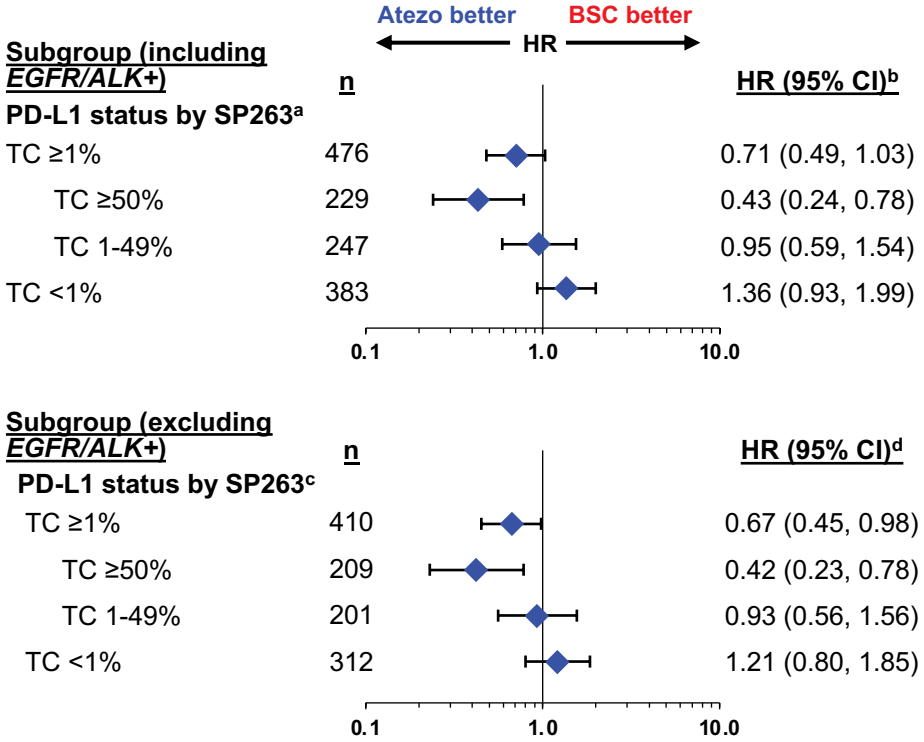
(data cutoff: 18 Apr '22, median follow-up: 46 months)

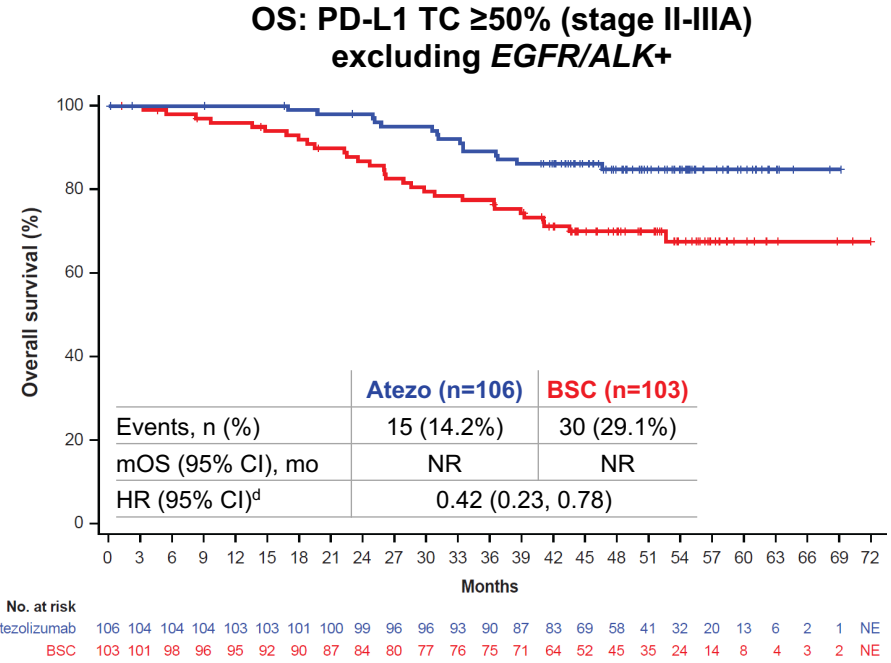


Clinical cutoff: 18 April 2022 (event to patient ratio, 25% [ITT]). [a]By SP263 assay. [b] Stratified.

OS by biomarker status (stage II-IIIA)

(data cutoff: 18 Apr '22)





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

Safety summary
(data cutoff: 18 Apr '22)

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

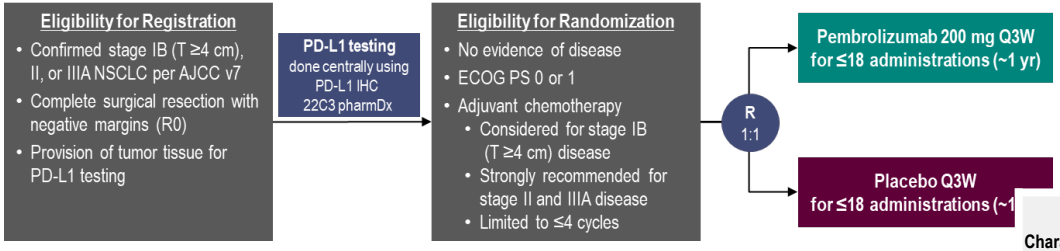
	IMpower010 DFS IA (21 Jan '21)	IMpower010 OS IA (18 Apr '22)	
	Atezo (n=495)	Atezo (n=495)	BSC (n=508)
All-grade AE	92.7%	92.5%	70.9%
Treatment-related AE	67.7%	67.9%	0%
Grade 3-4 AE	21.8%	22.0%	11.5%
Treatment-related Grade 3-4 AE	10.7%	10.7%	0%
Serious Adverse Event	17.6%	17.8%	8.5%
Treatment-related 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.

Summary

- An OS trend in favor of atezolizumab was seen in the PD-L1 TC ≥1% stage II-IIIA population (OS HR, 0.71 [95% CI: 0.49, 1.03]) at the time of this first pre-specified IA OS analysis
  - OS HR in this population improved numerically with longer follow-up
  - In the PD-L1 TC ≥50% stage II-IIIA subpopulation, a clinically meaningful OS trend in favor of atezolizumab was observed (OS HR, 0.43 [95% CI: 0.24, 0.78])
- OS benefit favouring atezolizumab was not seen in the all-randomised stage II-IIIA or ITT populations
- After an additional 13 months of follow-up, the safety profile remains broadly unchanged, with no new or unexpected safety signals, and is consistent with the known safety profile of atezolizumab
- These data support the previously reported positive benefit-risk profile of adjuvant atezolizumab in PD-L1+ resected NSCLC and contribute to evidence supporting standard of care use
- IMpower010 will continue to the final DFS analysis, with further OS follow-up and analyses

PEARLS/KEYNOTE-091 Study Design



Dual Primary End Points
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

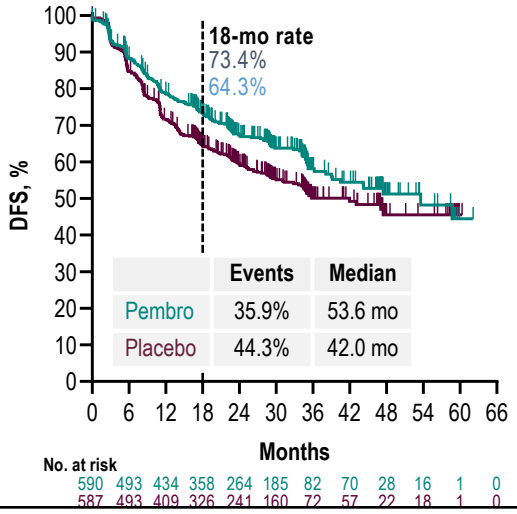
Secondary End Points
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population

Characteristic	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Age, median (range), y	65.0 (31-87)	65.0 (37-85)	64.5 (38-82)	65.0 (37-85)
Male sex	68.0%	68.7%	72.0%	70.3%
Geographic region				
Asia	18.0%	17.9%	17.3%	17.6%
Eastern Europe	19.7%	19.3%	18.5%	18.2%
Western Europe	51.4%	51.3%	53.6%	53.9%
Rest of world	11.0%	11.6%	10.7%	10.3%
ECOG PS 1	35.6%	41.6%	31.0%	38.8%
Current/former smoker	85.3%	88.8%	91.7%	92.1%
Nonsquamous histology	67.5%	61.8%	61.3%	63.6%
Received adjuvant chemotherapy	85.8%	85.9%	85.1%	85.5%
Pathologic stage[a]				
IB	14.2%	14.5%	12.5%	13.3%
II	55.8%	57.6%	56.5%	56.4%
IIIA	30.0%	27.6%	31.0%	30.3%
EGFR mutation[b]	6.6%	5.8%	3.6%	3.0%
ALK translocation[c]	1.2%	1.2%	1.8%	0.0%

[b]*EGFR* mutation status was unknown for 670 (63.5%) in the overall population and 198 (59.5%) in the TPS ≥50% population.
[c]ALK translocation status was unknown for 747 (63.5%) in the ITT and 217 (65.2%) in the TPS ≥50% population.

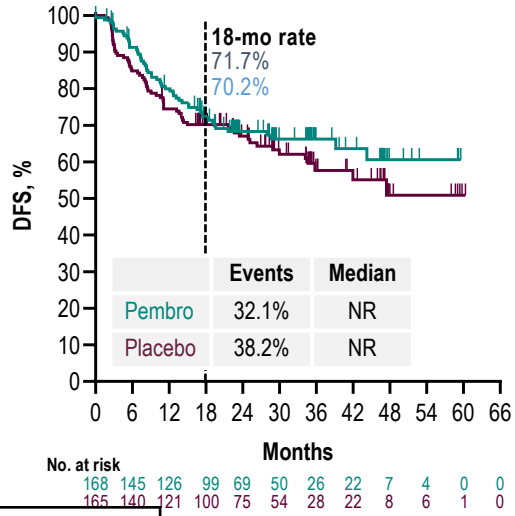
PEARLS/KN-091:
Results Second Interim Analysis

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



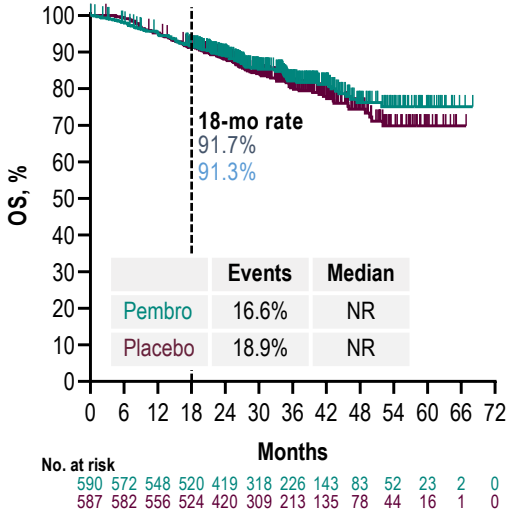
	Events	Median
Pembro	35.9%	53.6 mo
Placebo	44.3%	42.0 mo

DFS, PD-L1 TPS ≥50% Population
HR 0.82 (95% CI 0.57-1.18)
***P* = 0.14**



	Events	Median
Pembro	32.1%	NR
Placebo	38.2%	NR

OS, Overall Population
HR 0.87 (95% CI 0.67-1.15)
***P* = 0.170**



	Events	Median
Pembro	16.6%	NR
Placebo	18.9%	NR

Impower010 DFS HR: all comer 0.81, PD-L1 ≥50% 0.43

- DFS benefit generally consistent across most protocol-specified subgroups, including PD-L1 TPS <1% (HR 0.78, 95% CI 0.58-1.03) and 1-49% (HR 0.67, 95% CI 0.48-0.92)
- Overall safety profile generally as expected for pembrolizumab monotherapy

Paz-Ares L et al. *Ann Oncol* 2022; 2022-4;33:451-453 (Abstr VP3-2022).

Adjuvant PD-1/PD-L1 IO trials

Drug/Trial	Description	Stages entered	Description	Primary endpoint
Nivolumab ANVIL arm of ALCHEMIST	US, NCI (ECOG), Observational control	IB (4cm)-IIIA After Adj Chemo +/- radiation	Phase 3 Allows PD-L1 +/-	OS/DFS
Atezolizumab IMPOWER010	Global, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS
Durvalumab	Global, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS
Pembrolizumab PEARLS KN-091	ETOP/EORTC, Placebo Controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS

Conclusions

NADIMII- further data supporting Neo-adjuvant chemo-IO as a standard in stage III NSCLC as a standard of care

IMpower010- survival trend promising and curves separating, best results with PD-L1>50%