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

Stage III NSCLC
Surgical/Combined Modality

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DISCLOSURES

Has no relevant financial relationships

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

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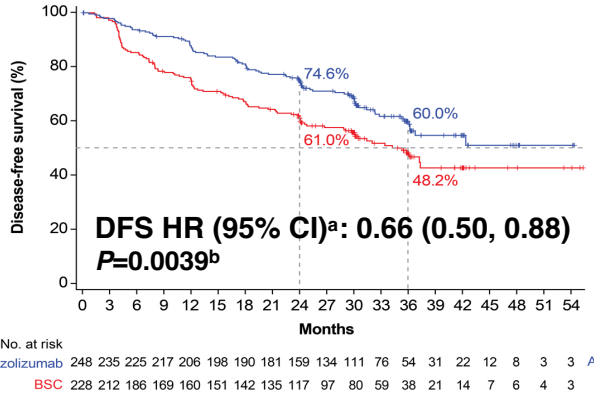
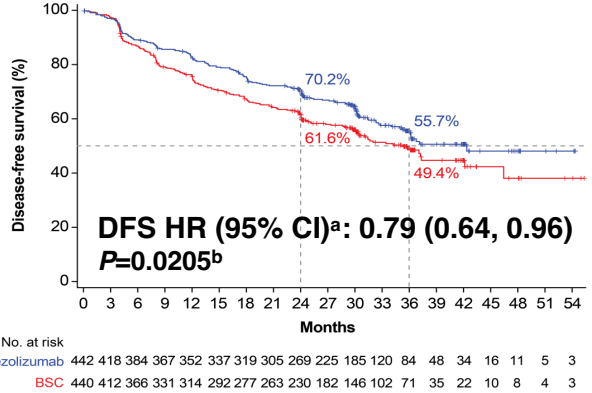
Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators*
Lancet 2021; 398: 1344–57

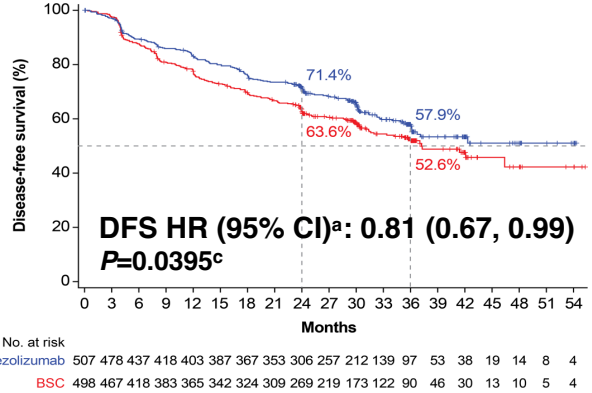
DFS: PD-L1 TC ≥1% stage II-IIIA population



DFS: All-randomised stage II-IIIA population



DFS: ITT (randomised stage IB-IIIA) population



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

Completely resected stage IB-IIIA[a] NSCLC

- Stage IB tumors ≥4 cm
- ECOG 0-1
- Lobectomy
- Tumor tissue for PD-L1 analysis

Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

1-4 cycles

N=1280

R 1:1

No crossover

Atezolizumab 1200 mg q21d x 16 cycles or 1 year

N = 1005

BSC

Survival follow-up

Stratification factors

- Sex | Stage | Histology | PD-L1 status

Primary endpoint

- Investigator-assessed DFS tested hierarchically

Key secondary endpoints

- OS in ITT I DFS in PD-L1 TC ≥50% I 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.

Hierarchical statistical testing of endpoints

DFS in PD-L1 TC ≥1% stage II–IIIA population[b]

If positive:

DFS in all-randomized stage II–IIIA population[b]

If positive:

DFS in ITT population (stage IB-IIIA)[b]

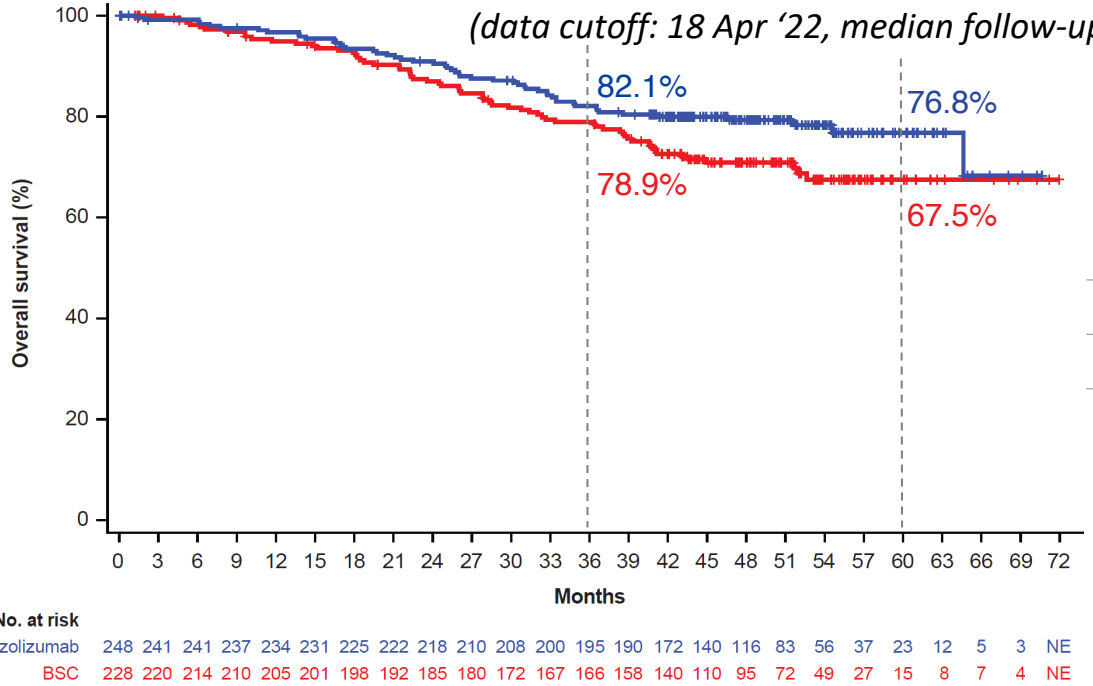
If positive:

OS in ITT population[b]

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

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

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



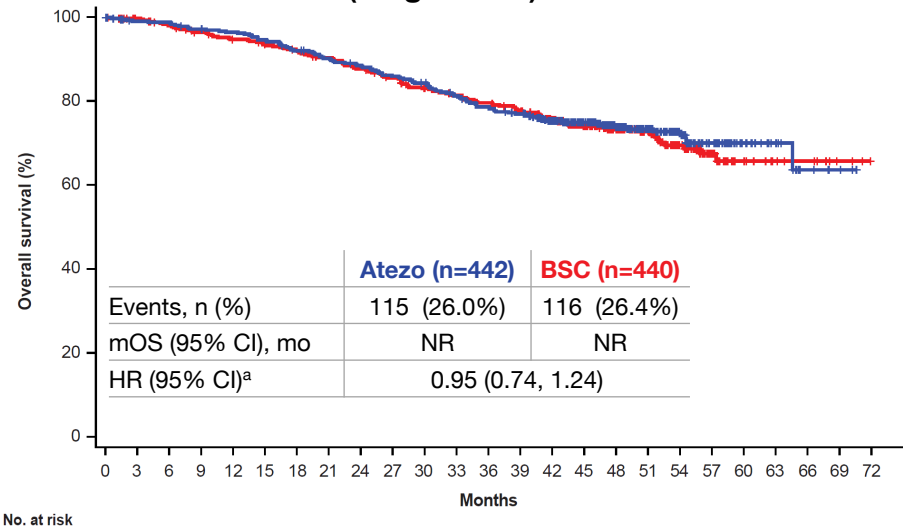
	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[b]	0.71 (0.49, 1.03)	

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)

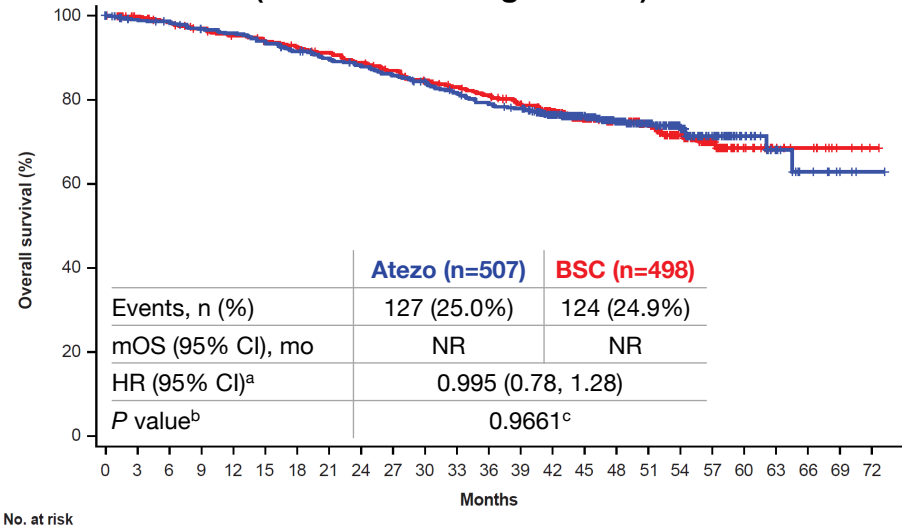


	Atezo (n=442)	BSC (n=440)
Events, n (%)	115 (26.0%)	116 (26.4%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.95 (0.74, 1.24)	

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]	

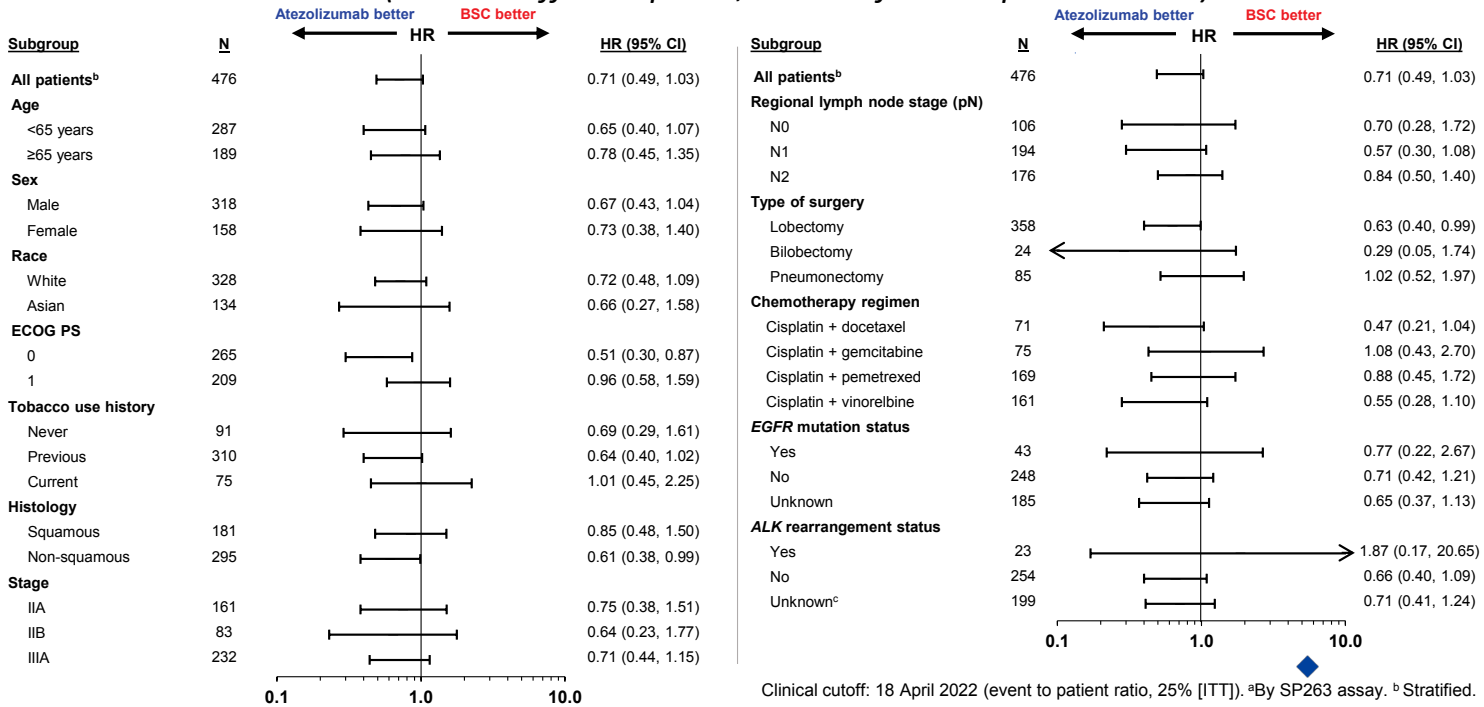
No. at risk

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)

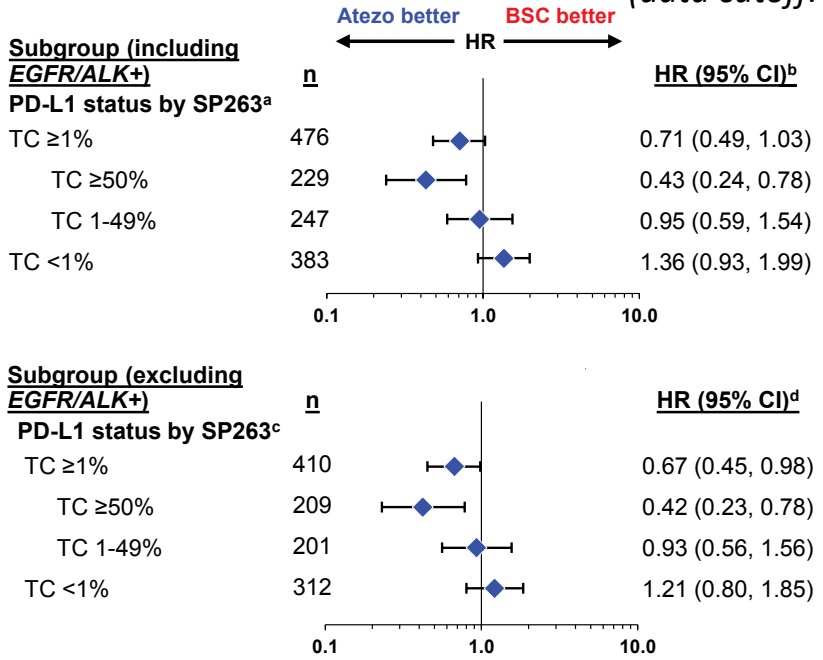


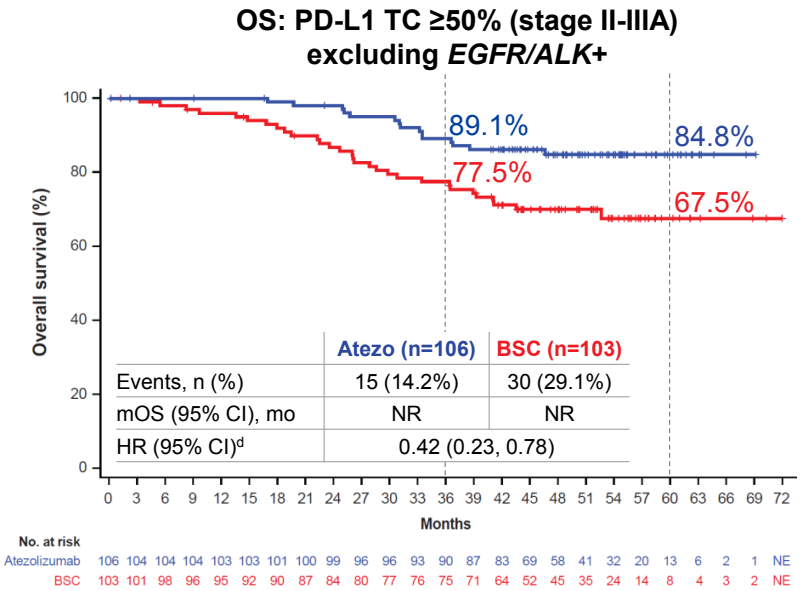
Subgroup	N	HR (95% CI)
All patients[b]	476	0.71 (0.49, 1.03)
Age		
<65 years	287	0.65 (0.40, 1.07)
≥65 years	189	0.78 (0.45, 1.35)
Sex		
Male	318	0.67 (0.43, 1.04)
Female	158	0.73 (0.38, 1.40)
Race		
White	328	0.72 (0.48, 1.09)
Asian	134	0.66 (0.27, 1.58)
ECOG PS		
0	265	0.51 (0.30, 0.87)
1	209	0.96 (0.58, 1.59)
Tobacco use history		
Never	91	0.69 (0.29, 1.61)
Previous	310	0.64 (0.40, 1.02)
Current	75	1.01 (0.45, 2.25)
Histology		
Squamous	181	0.85 (0.48, 1.50)
Non-squamous	295	0.61 (0.38, 0.99)
Stage		
IIA	161	0.75 (0.38, 1.51)
IIB	83	0.64 (0.23, 1.77)
IIIA	232	0.71 (0.44, 1.15)
Regional lymph node stage (pN)		
N0	106	0.70 (0.28, 1.72)
N1	194	0.57 (0.30, 1.08)
N2	176	0.84 (0.50, 1.40)
Type of surgery		
Lobectomy	358	0.63 (0.40, 0.99)
Bilobectomy	24	0.29 (0.05, 1.74)
Pneumonectomy	85	1.02 (0.52, 1.97)
Chemotherapy regimen		
Cisplatin + docetaxel	71	0.47 (0.21, 1.04)
Cisplatin + gemcitabine	75	1.08 (0.43, 2.70)
Cisplatin + pemetrexed	169	0.88 (0.45, 1.72)
Cisplatin + vinorelbine	161	0.55 (0.28, 1.10)
***EGFR* mutation status**		
Yes	43	0.77 (0.22, 2.67)
No	248	0.71 (0.42, 1.21)
Unknown	185	0.65 (0.37, 1.13)
***ALK* rearrangement status**		
Yes	23	1.87 (0.17, 20.65)
No	254	0.66 (0.40, 1.09)
Unknown[c]	199	0.71 (0.41, 1.24)

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.

- 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=495)
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
  - 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

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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

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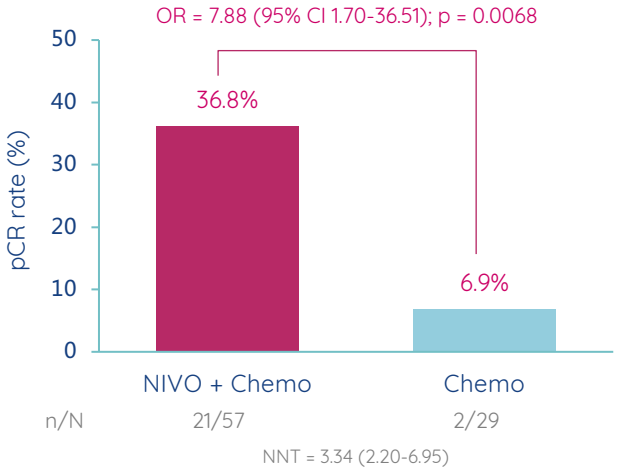
SPAIN

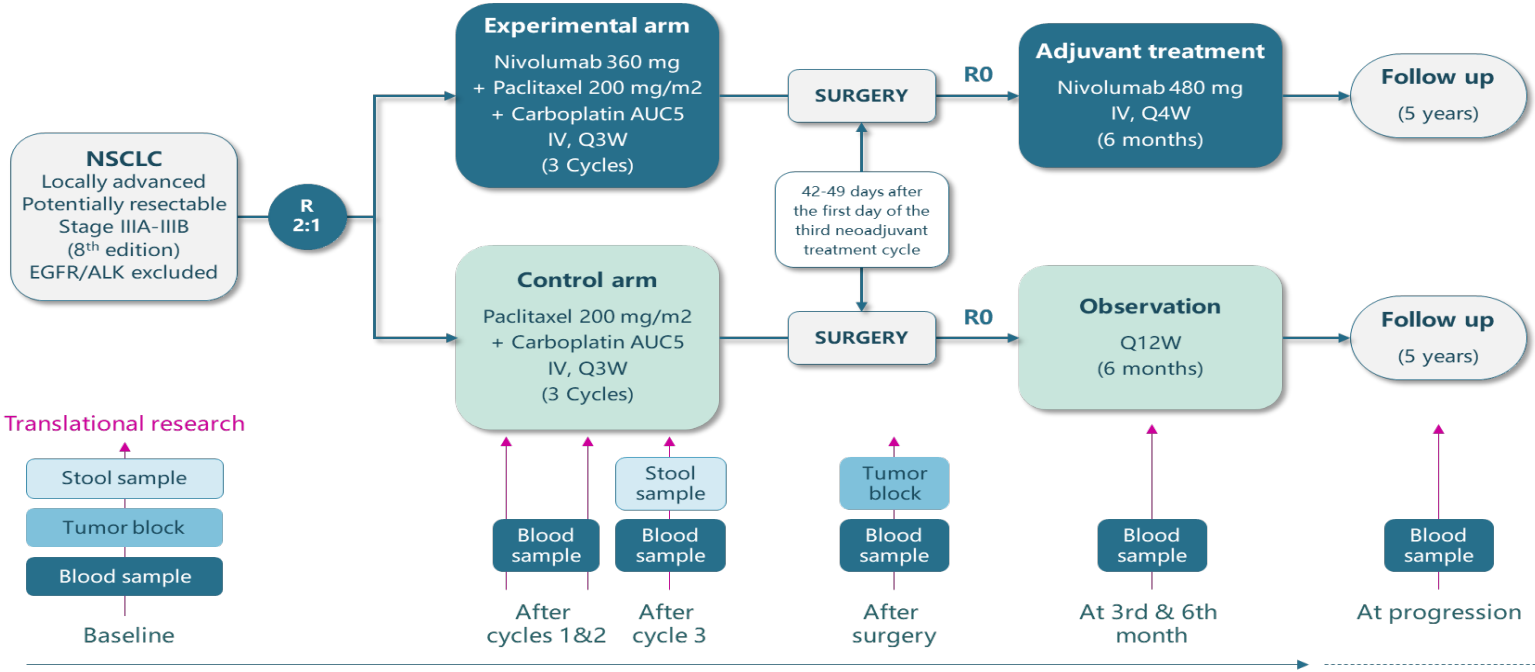
INTRODUCTION

- Results from the single-arm, phase 2 NADIM trial (NCT03081689), evaluating neoadjuvant nivolumab plus chemotherapy, showed unprecedentedly high survival rates in patients with resectable stage IIIA NSCLC —with an OS almost three times that reported in the historical series —, and improved percentage of patients with pCR[1,2].
- In the randomized phase 3 CheckMate 816 trial (NCT02998528), neoadjuvant nivolumab plus CT significantly improved the median event-free survival (HR 0.63 [97.38% CI, 0.43-0.91]; p=0.0052) and the pCR rate (OR 13.94 [99% CI, 3.49-55.75]; p<0.0001) versus CT alone in patients with resectable NSCLC[3].
- In the randomized phase 2 NADIM II study, neoadjuvant nivolumab plus chemotherapy significantly improved the primary endpoint of pCR vs Chemo in patients with resectable stage IIIA-B NSCLC (36.8% vs 6.9%, OR 7.88 [95% CI 1.70-36.51]; p = 0.0068)[4].
- Here we present the results of the secondary endpoints of PFS and OS rates at 24 months.



1. Provencio M. et al. Lancet Oncol 2020;21:1413-22; 2. Provencio M, et al. J Clin Oncol 2022; doi: 10.1200/JCO.21.02660; 3. Forde P, et al. Clinical Trial NEJM 2022;386:1973-1985; Provencio M, et al. J Clin Oncol 40, 2022 (suppl 16; abstr 8501)

STUDY DESIGN



ENDPOINTS

Primary endpoint

- **Pathological complete response in the ITT population**

Secondary endpoints

- **Major pathological response (MPR)**
- **Portion of delayed/canceled surgeries, length of hospital stays, surgical approach, incidence of AE/SAE related to surgery**
- **Safety and tolerability: Adverse events graded according to CTCAE v5.0**
- **OS at 12, 18 and 24 months**
- **PFS at 12, 18 and 24 months**
- **Potential predictive biomarkers (ctDNA, TCR)**
- **Other:** (i) Downstaging; (ii) Mortality at 90 days after surgery; (iii) Association between clinical baseline characteristics and ORR, pathological response, adverse events, PFS and OS; (iv) Association between pathological response and PFS or OS; (v) Association between MPR and histology; (vi) Association between histology and PFS at 18 months.

CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumor DNA; ORR, objective response rate; TCR, T-cell receptor

STATISTICAL ANALYSIS PLAN

- The analysis was conducted according to the intention-to-treat (ITT) principle: patients who did not undergo surgery were considered as non-responders for final analysis
- The ITT population was the primary population for efficacy analysis, which included those patients who had received at least one dose of study treatment
- Pathological complete response was defined as the absence of any viable tumor cell in the resected lung specimen and all regional lymph nodes
- Referring to the results of previous phase 2 NADIM trial (NCT03081689)[1], we assumed a proportion of pCR of 10% in the Control Arm (chemotherapy [CT] + surgery) and 40% in the Experimental Arm (CT+ immunotherapy + surgery + immunotherapy)
- An alpha level of 5%, a statistical power of 80%, and a drop-out rate of 15% was set
- A sample size of 90 patients (60 in the Experimental Arm and 30 in the Control Arm) was estimated to show the difference between both groups
- An independent data monitoring committee evaluated the superiority of nivolumab + CT vs CT for pCR at the preplanned analysis

1. Provencio M, et al. Lancet Oncol 2020;21:1413–1422

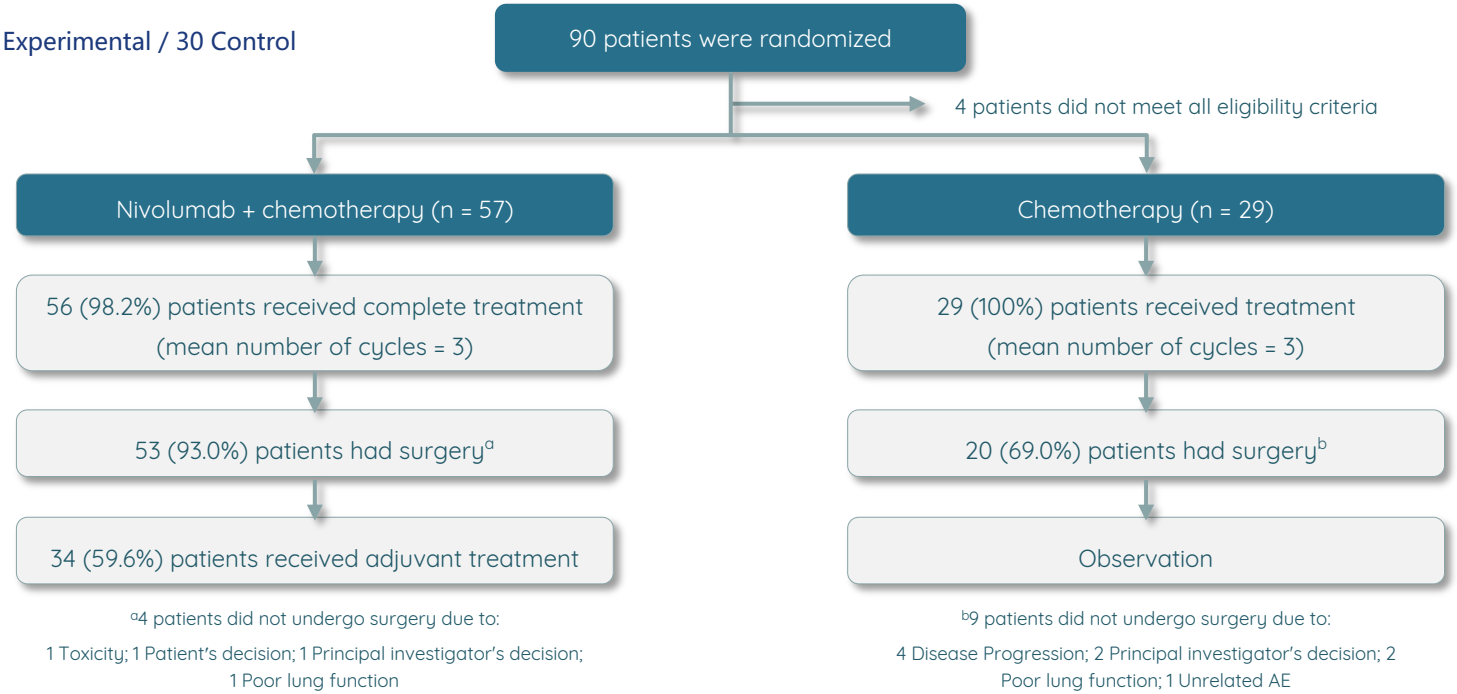
BASELINE CHARACTERISTICS (ITT)

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

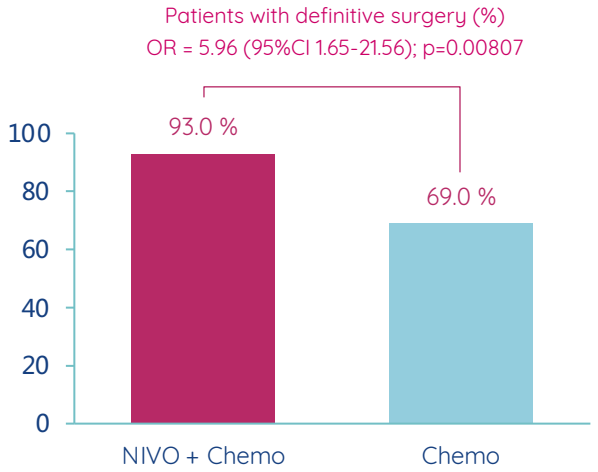
[b]9 patients did not undergo surgery due to:

4 Disease Progression; 2 Principal investigator's decision; 2 Poor lung function; 1 Unrelated AE

SURGERY SUMMARY

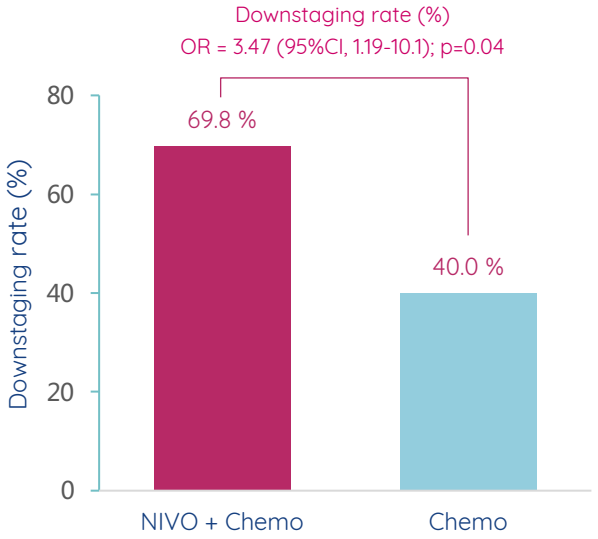
Type of surgery, No. (%)	NIVO + Chemo (n = 53)	Chemo (n = 20)	Total (n = 73)
Pneumonectomy	6 (11.3)	2 (10.0)	8 (11.0)
Lobectomy	40 (75.5)	17 (85.0)	57 (78.1)
Bilobectomy	4 (7.5)	1 (5.0)	5 (6.8)
Segmentectomy	2 (3.8)	0 (0.0)	2 (2.7)
Right Lower Lobectomy + Segmentectomy	1 (1.9)	0 (0.0)	1 (1.4)

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		

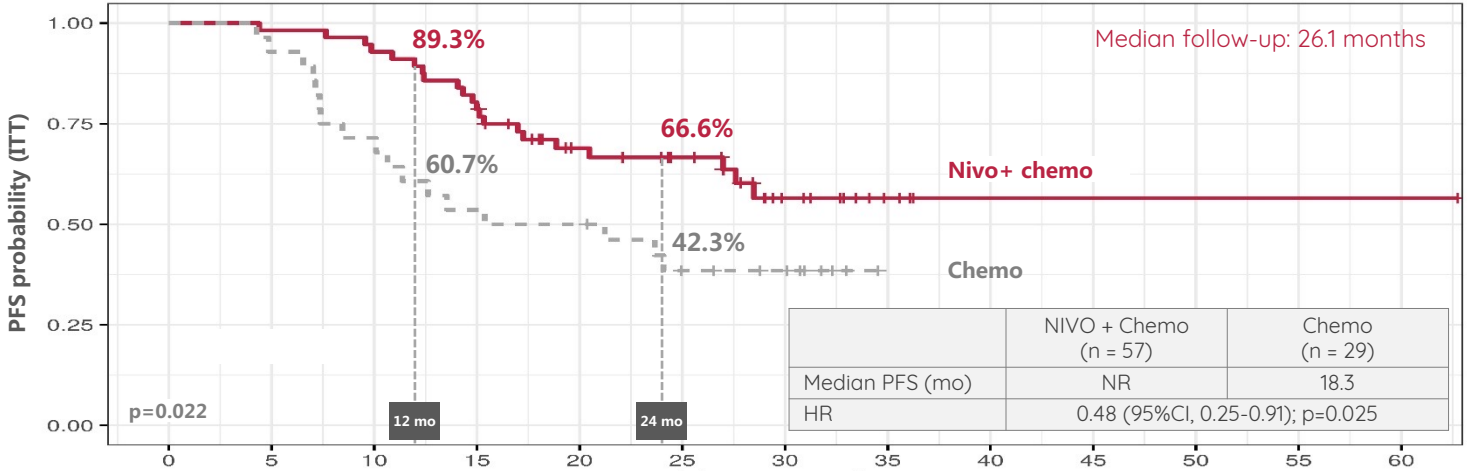


SECONDARY ENDPOINTS – Downstaging

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

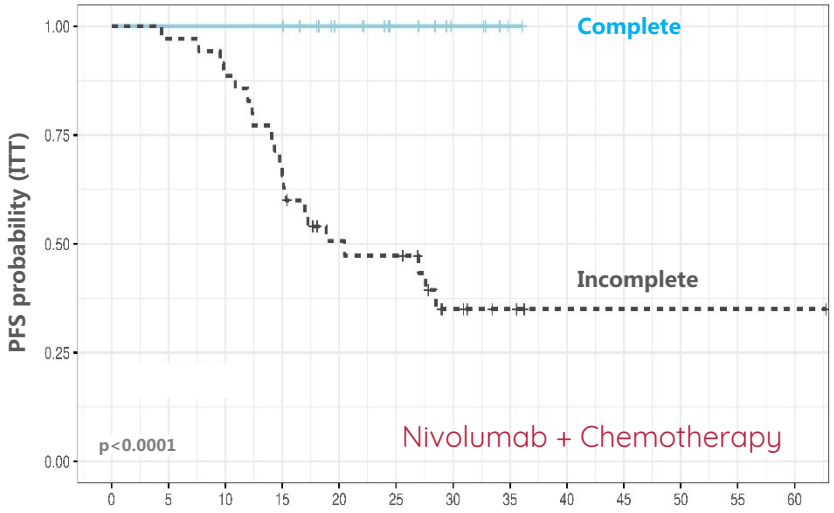


	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median PFS (mo)	NR	18.3
HR	0.48 (95%CI, 0.25-0.91); p=0.025	

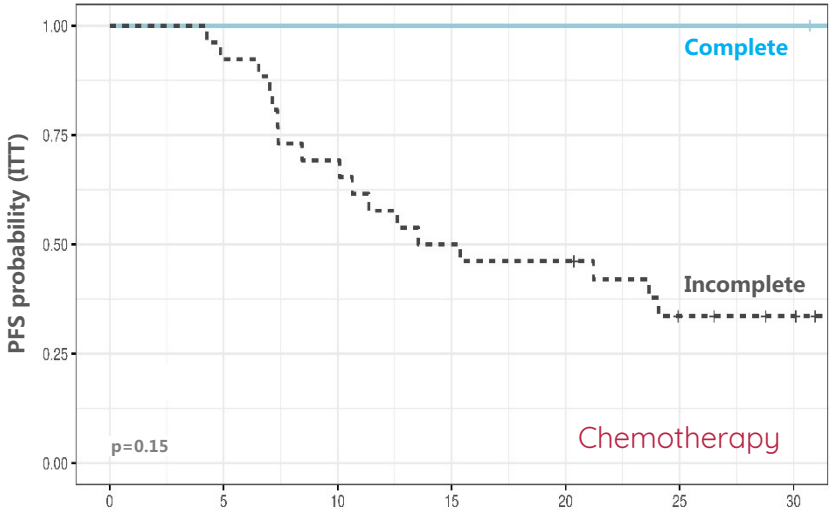
Number at risk													
Nivo + chemo	56	55	52	44	30	24	11	4	1	1	1	1	1
Chemo	28	26	20	15	14	9	7	0	0	0	0	0	0

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



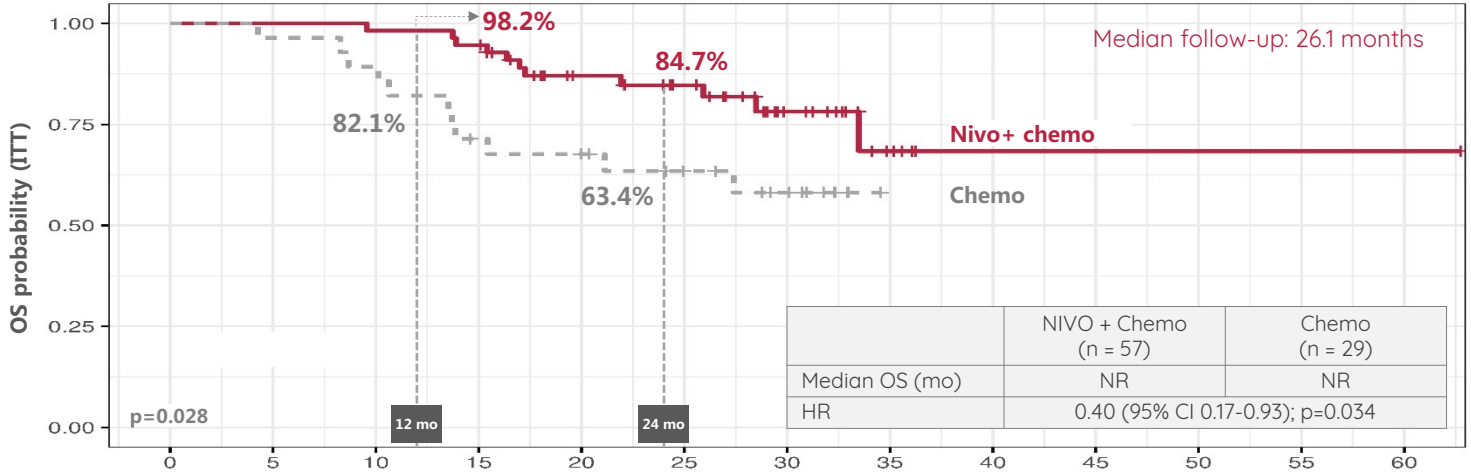
Number at risk													
Complete	21	21	21	21	15	10	5	1	0	0	0	0	0
Incomplete	35	34	31	23	15	14	6	3	1	1	1	1	1



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

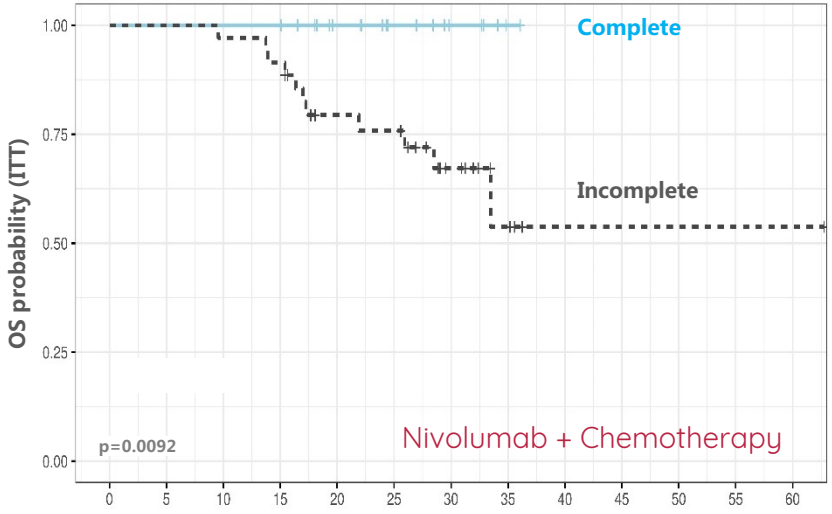


	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median OS (mo)	NR	NR
HR	0.40 (95% CI 0.17-0.93); p=0.034	

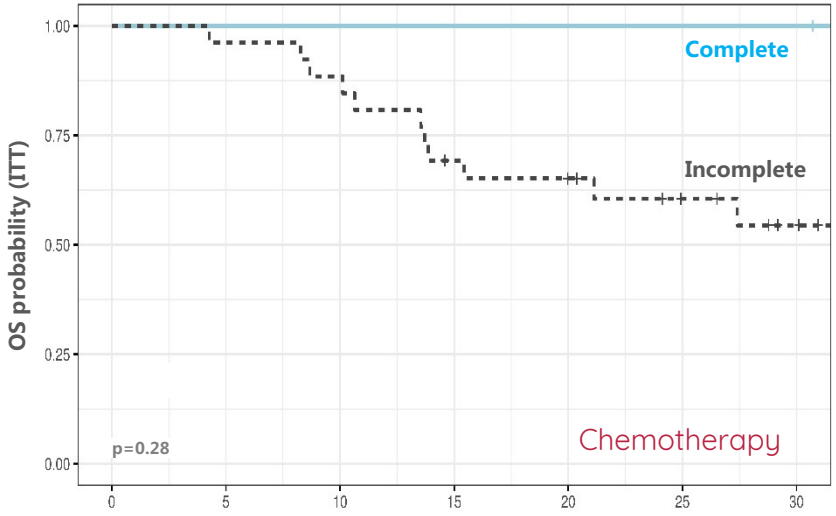
Number at risk													
Nivo + chemo	56	56	55	53	37	31	15	5	1	1	1	1	1
Chemo	28	27	25	19	17	13	9	0	0	0	0	0	0

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