IMMUNE CHECKPOINT INHIBITION IN RESECTABLE NSCLC:
Lessons learned from NEOPREDICT-Lung

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DISCLOSURES:

Commercial Interests

Bristol-Myers-Squibb, Advisory Board, Invited Speaker, Personal
Hoffmann-La Roche, Advisory Board, Invited Speaker, Personal
Pfizer, Advisory Board, Personal
Merck Sharp Dohme, Expert Testimony, Advisory Board, Invited Speaker, Personal
AstraZeneca, Expert Testimony, Advisory Board, Personal
Pierre-Fabre Oncology, Advisory Board, Personal
Amgen, Advisory Board, Personal
Daiichi Sankyo, Advisory Board, Personal
Janssen, Advisory Board, Invited Speaker, Personal
Iteos therapeutics, Advisory Board, Personal

Non-Commercial interest:

Chair WG oncology of Belgian Thoracic Society
Board member of Forum Vlaamse Longartsen
Member of All.Can Belgium – WG Lung Cancer

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Possible treatment strategies for resectable early stage NSCLC

Neoadjuvant, adjuvant, periadjuvant

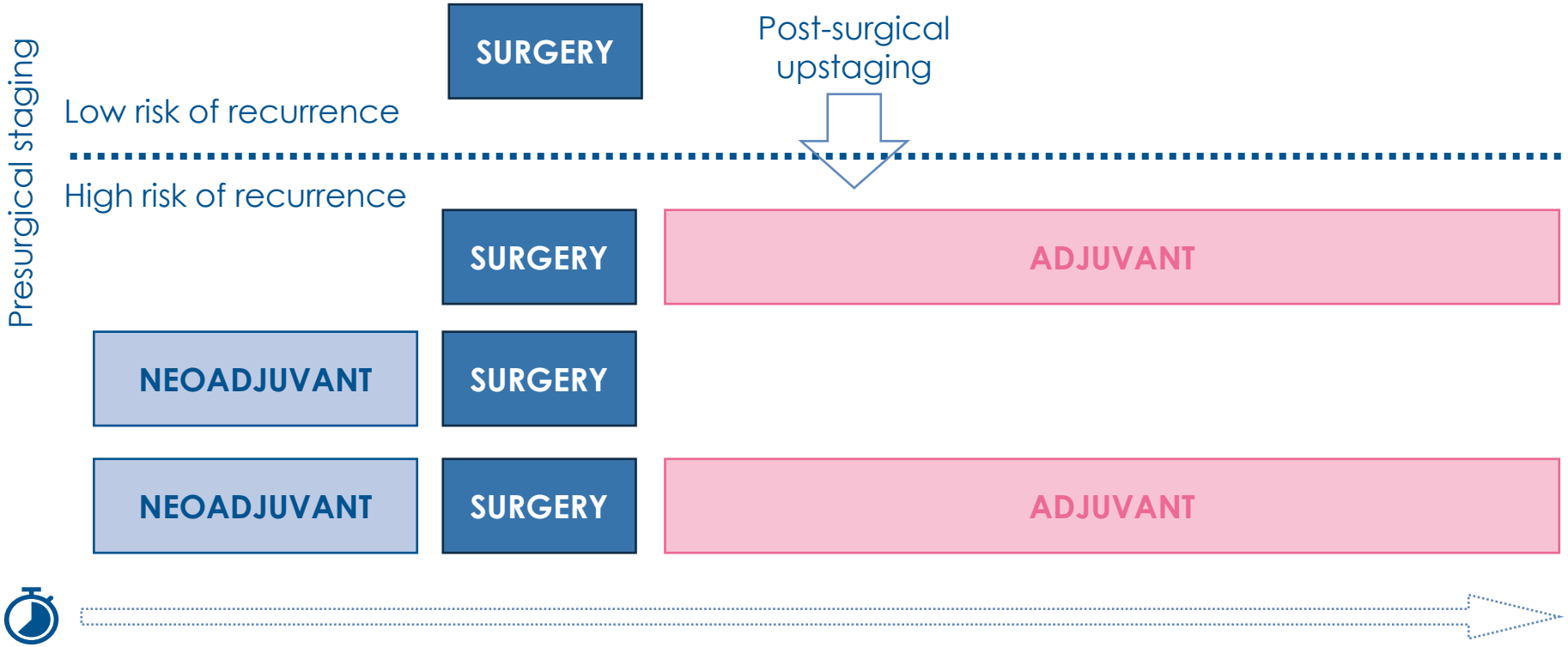


Table 1

Table 1: Overview of neoadjuvant ICI monotherapy or ICI combination therapy trials in resectable NSCLC.

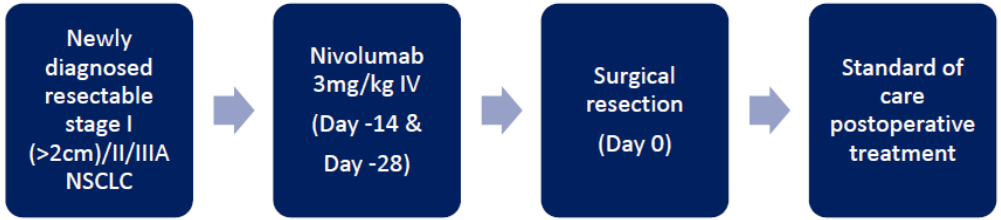
Name	N	Stage	Regimen	Primary Endpoint	Proportion of patients undergoing resection (%)	Proportion of patient with MPR (%)	Proportion of patients with pCR (%)	Proportion of patients undergoing R0 resection (%)	Post-operative 30-day mortality (%)
Forde et al. 2018* [28]	21	I-IIIA	nivolumab	safety	100	45.0	15.0	95	0
NCT02259621 NEOSTAR 2021 * [34]	44	I-IIIA	nivolumab +/- ipilimumab	MPR	91.0 77.0	24 50	10 38	100 100	4.3 0
NCT03158129 Gao et al. 2020 [30]	40	I-IIIB	sintilimab	MPR	92.5	40.5	16.2	97.3	5.4
ChiCTR-OIC-17013726 PRINCEPS* 2020 [31]	30	I-IIIA (no N2)	atezolizumab	toxicity	100	14.0	0	96.7	10
NCT02994576 LCMC3 2022 [32]	181	IB-IIIB	atezolizumab	MPR	89.1	20.4	6.8	92.0	1.3
NCT02927301 IONESCO 2022 [33]	46	IIB-IIIA	durvalumab	R0 resection	93.5	18.6	0	90.0	NA[#]
NCT03030131 NEOPREDICT 2022 [37]	60	IB-IIIA	Nivolumab +/-relatlimab	safety	100	27 30	14 17	100 97	0 0
NCT04205552 NEOCOAST 2023 [40] NCT03794544	83	I-IIIA (single level N2)	Durvalumab +/- oleclumab or monalizumab or danvatirsen	MPR	91.6	11.1 19.0 30.0 31.3	3.7 9.5 10.0 12.5	NA	NA

*: TNM 7th edition, all others 8th edition;
MPR = major pathological response; pCR = pathological complete response.
[#] IONESCO trial was discontinued due to high 90-day post-operative mortality (8.7%).

pCR rates vary from 3,2 to 38% ; surgical omission from 0% to 23%

Cuppens et al. Lung Cancer 2024

Setting the stage:
Forde et al. NEJM 2018



22 enrolled
1 withdrawn (pathology revision: SCLC)
21 resected (1 unresectable during VATS – tracheal invasion)

RECIST	**N (%)**
PR	2 (10%)
SD	18 (85%)
PD	1 (5%)
MPR	**N (%)**
20 resected	9 (45%)

Endpoints:
- Primary: Safety/Feasibility (AE (90 days) and >37 days delay preplanned surg date)
- Exploratory: Pathological response rate (MPR), immunological and genomic correlates

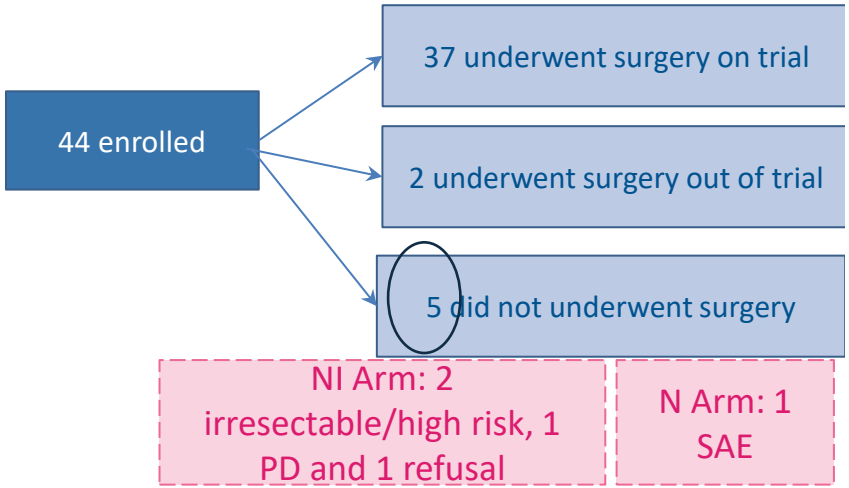
Neoadjuvant Nivolumab did not delay/interfere with surgery and was safe

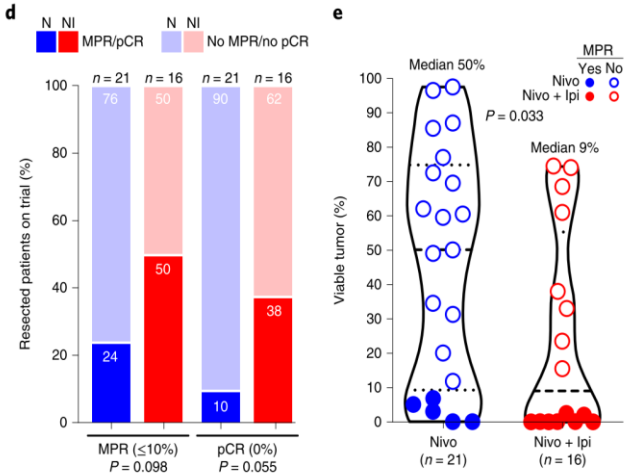
Too good to be true (?)

NEOSTAR

Primary hypothesis: Neoadjuvant Nivolumab or Nivolumab+Ipilimumab will produce MPR
Endpoints:

- Primary: MPR
- Secondary:
  - safety (toxicity, peri-operative morbidity and mortality)
  - ORR, RFS, OS
  - Complete resection rate, pCR
  - CD8+ TILs
- Exploratory endpoints





Percentage viable tumor	Total (*n* = 44) *n* (%)	Nivo (*n* = 23) *n* (%)	Nivo + Ipi (*n* = 21) *n* (%)	*P* value
MPR (≤10% viable tumor)[a+b]	13 (29%)	5 (22%) (95% CI: 7–44%)	8 (38%) (95% CI: 18–62%)	0.235
0% viable tumor (pCR)[a]	8 (18%)	2 (9%) (95% CI: 1–28%)	6 (29%) (95% CI: 11–52%)	0.126
1–10% viable tumor[b]	5 (11%)	3 (13%)	2 (10%)	
11–50% viable tumor	10 (23%)	6 (26%)	4 (19%)	
51–100% viable tumor	14 (32%)	10 (43%)	4 (19%)	
‡No surgery on trial	7 (16%)	2 (9%)	5 (23%)	

Cascone et al. Nature Medicine, 2021

nature medicine

Neoadjuvant nivolumab with or without relatlimab in resectable non-small-cell lung cancer: a randomized phase 2 trial

Martin Schuler, Kristof Cuppens, Till Plönes, Marcel Wiesweg, Bert Du Pont, Balazs Hegedus, Johannes Köster, Fabian Mairinger, Kaid Darwiche, Annette Paschen, Brigitte Maes, Michel Vanbockrijck, David Lähnemann, Fang Zhao, Hubertus Hautzel, Dirk Theegarten, Koen Hartemink, Henning Reis, Paul Baas, Alexander Schramm & Clemens Aigner

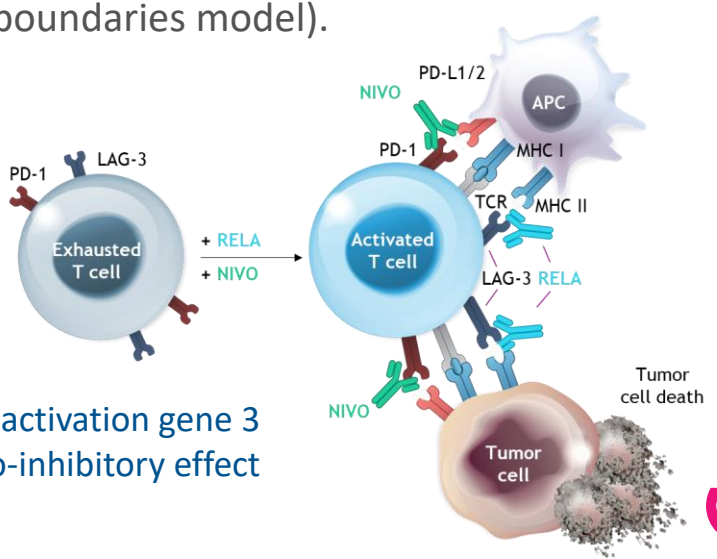
Nature Medicine **30**, 1602–1611 (2024) | Cite this article

Introduction

- **NEOPREDICT-Lung : multicentric, randomized, non-comparative** investigator initiated **phase II** study (NCT04205552) evaluating the feasibility of **short-course (2 cycles every 14 days) neoadjuvant** therapy, of PD1-inhibition, **nivolumab 240mg,** or combined PD-1 and LAG-3 inhibition, **nivolumab 240mg** and **relatlimab 80mg**. Study design does not allow formal comparison of treatment arms.

- Feasibility is defined as achieving **surgery within 43 days** after initiation of neoadjuvant therapy with continuous monitoring of feasibility boundaries (Pocock boundaries model).

- For arms A and B: FPI March 2020 ; LPI July 2022

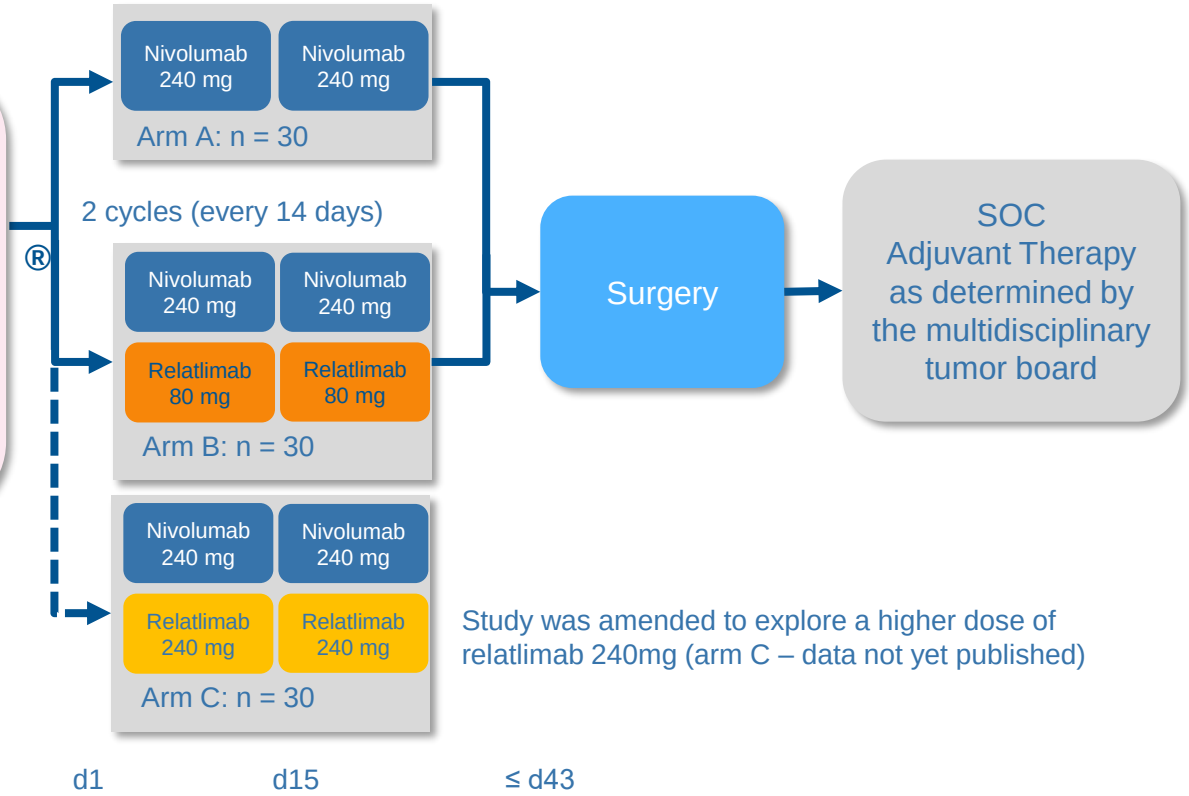


LAG3 (CD223) : Lymphocyte-activation gene 3
immune checkpoint recept; immuno-inhibitory effect

NEOPREDICT-Lung

Key Eligibility

- Histologically confirmed NSCLC
- Stage I B, II or III A (8th TNM edition)
- Curative resectability as determined by the multidisciplinary tumor board
- Sufficient organ function
- ECOG 0 and 1



Primary Endpoint: Feasibility of neoadjuvant short-course IO (Pockcock boundary model)

Secondary endpoints: ORR, MPR-rate, OS, DFS, …

Study was amended to explore a higher dose of relatlimab 240mg (arm C – data not yet published)

Baseline characteristics (arm A & B)

	Nivolumab 240mg (arm A)	Nivolumab 240mg plus Relatlimab 80mg (arm B) *
n (female, male)	30 (15, 15)	27 (11, 16)
Age in years, median (range)	64 (43–77)	67 (43–81)
Histology		
Adenocarcinoma	13 (43.3%)	14 (51.9%)
Squamous cell carcinoma	10 (33.3%)	8 (29.6%)
Other (LCNEC, adenosquamous, large cell NOS)	7 (23.3%)	5 (18.5%)
PD-L1 status (TPS – 22c3 PharmDx)		
<1%	6 (20.0%)	8 (26.7%)
1–49%	14 (46.7%)	15 (50.0%)
≥50%	10 (33.3%)	7 (23.3%)

* Three patients arm B were excluded for further analysis due to stage IV disease which had been undetected at baseline staging

Treatment-related adverse events

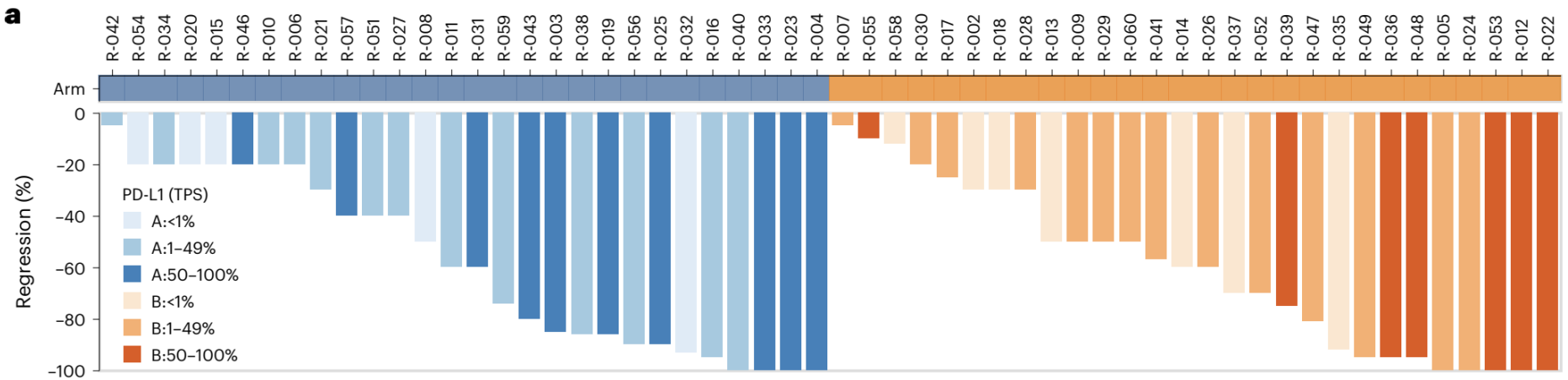
	Nivolumab 240mg (arm A)		Nivolumab 240mg plus Relatlimab 80mg (arm B)	
	all	grade ≥ 3	all	grade ≥ 3
Anemia	2 (7%)	-	-	-
Atrial fibrillation	1 (3%)	1 (3%)	-	-
Hyperthyroidism	5 (17%)	1 (3%)	4 (13%)	-
Hypothyroidism	2 (7%)	-	3 (10%)	-
Gastrointestinal	1 (3%)	-	2 (7%)	-
Hepatic	1 (3%)	1 (3%)	1 (3%)	1 (3%)
Proteinuria	1 (3%)	-	-	-
Pneumonitis	-	-	2 (7%)	-
Chills/fever	2 (3%)	-	-	-
Rash	1 (3%)	-	-	-

Primary and secondary endpoints

	Nivolumab 240mg (arm A)	Nivolumab 240mg plus Relatlimab 80mg (arm B) *
Primary Endpoint: surgery≤ 43 days	100%	100%
Secondary Endpoints:		
ORR (RECIST version 1.1)	10%	27%
ORR (PERCIST version 1.0)*	38%	38%
Major pathological response	26,7%	33,3%
Pathological complete response	13,3%	18,5%
R0-resection rate	100%	97%

Primary endpoint of feasibility, defined as surgery within 43 days after start neoadjuvant therapy, was met by all patients (100%) in both arms.

Key finding 1:
Short course and closely monitored neoadjuvant IO is safe and does not increase the risk of surgical omission

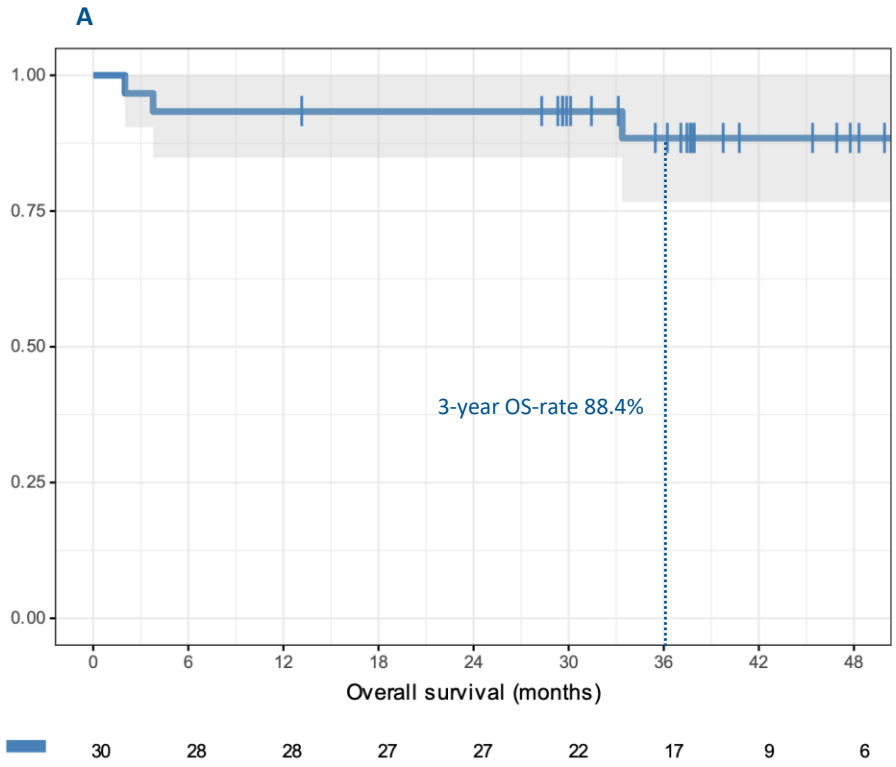


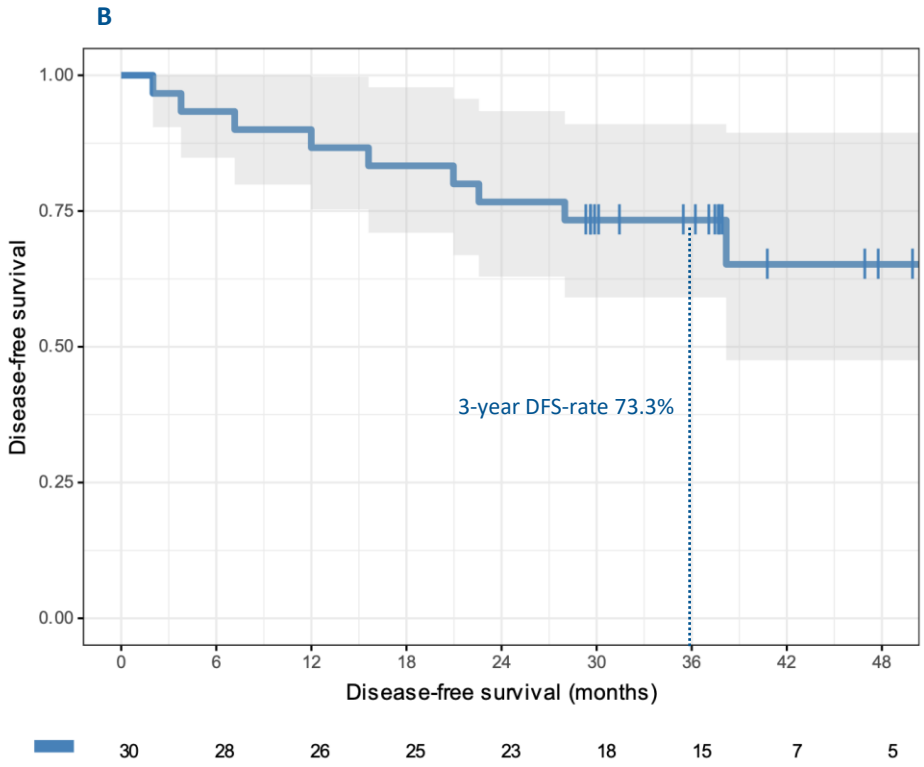
Secondary endpoint:

Arm A (N)	**MPR 26,7%**	**pCR 13,3%**
Arm B (N+R)	**MPR 33,3%**	**pCR 18,5%**

* MPR = major pathological response (<10% residual viable tumor)
* pCR = pathological complete response (0% residual viable tumor)

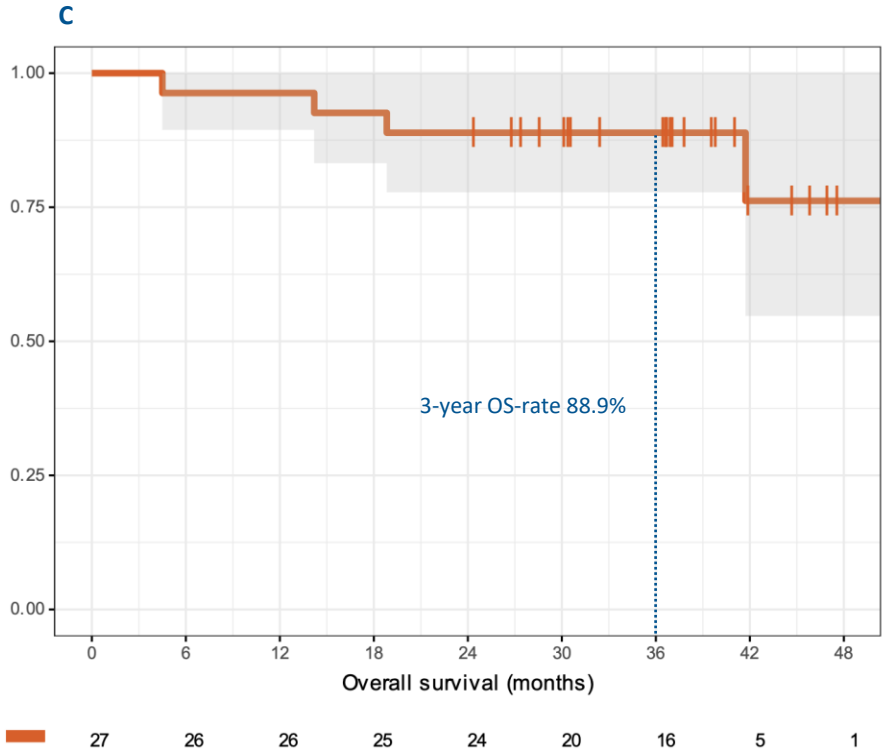
Survival Arm A: Nivolumab

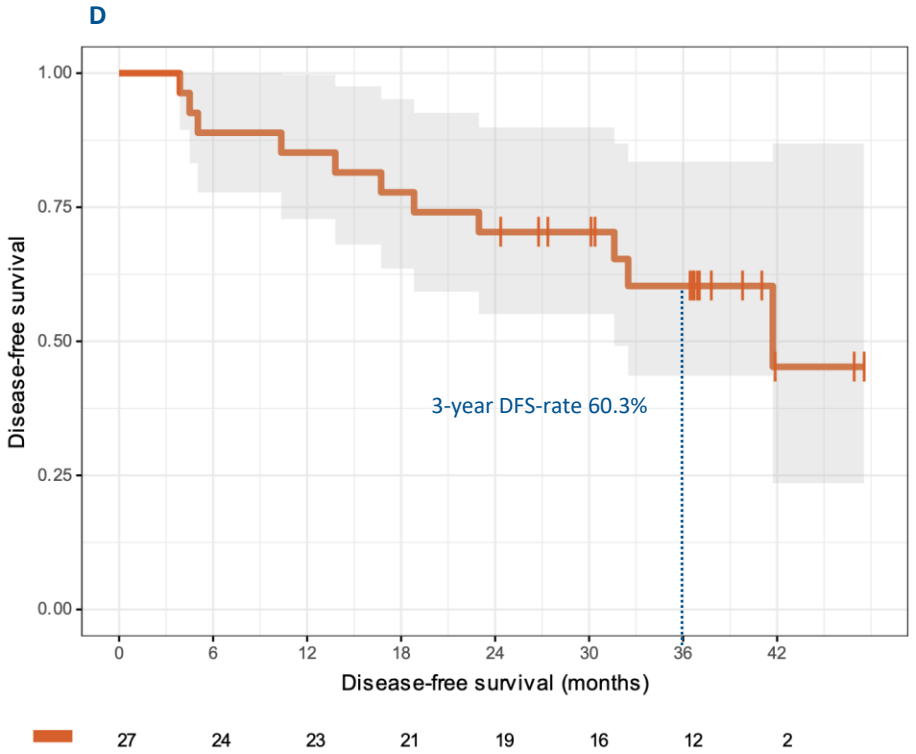




* Median follow up: 37.6 months (35.4 - 46.8)
* Data not yet published – please do not share

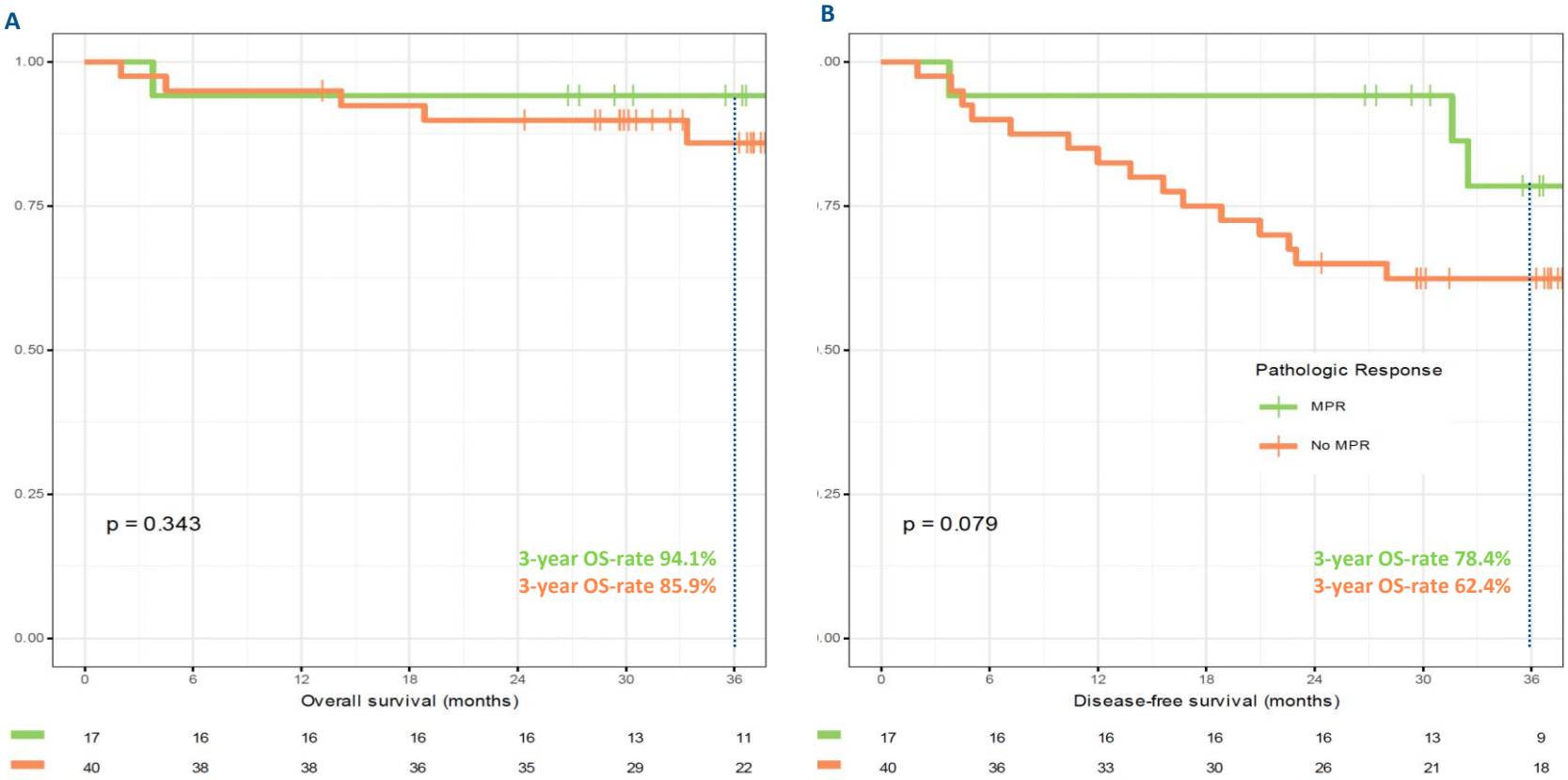
Survival Arm B: Nivolumab + Relatlimab





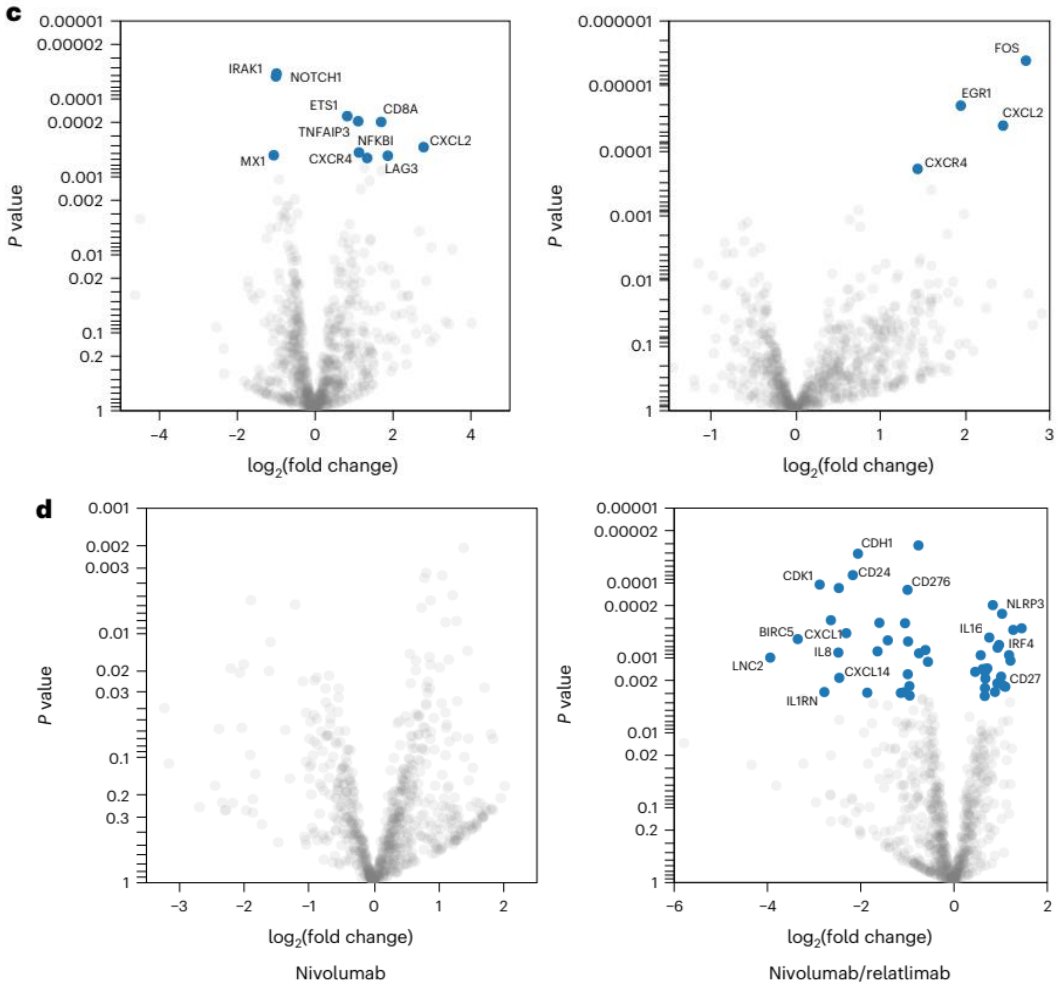
* Median follow up: 36.8 months (32.4 - 41.8)
* Data not yet published – please do not share

Survival: MPR versus non-MPR



* Median follow up: 37.4 months (36.4- 40.7)
* Data not yet published – please do not share

Key finding 2:
Short course neoadjuvant IO can induce a significant number of pathological responses which correlates with improved clinical outcome



Inflammation-associated chemokines and receptors, were strongly induced in both arms.

LAG-3 was only induced in the nivolumab arm.

More homogenous suppression of gene programs linked to granulocytes, monocytes and macrophages in N+R treated patients with MPR.

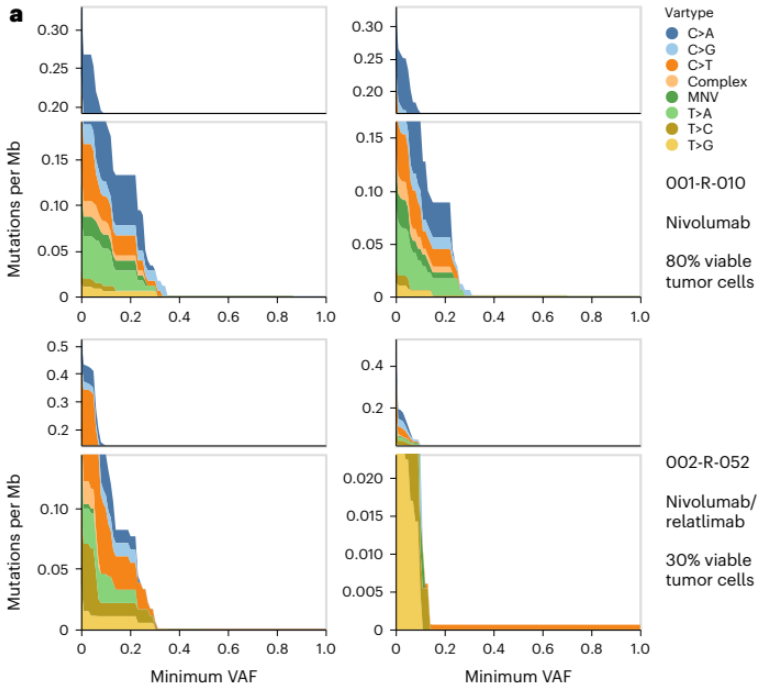
More consistent and directed immune activation by combined treatment with nivolumab plus relatlimab, may provide opportunities for rational triplet combinations.

Schuler & Cuppens et al. Nature Medicine, 2024

Key finding 3:
Changes in gene expression after therapy differ between nivolumab and nivolumab+relatlimab treated patient

Potential for rational triplet combinations?

Longitudinal genomic sequencing of pre-versus post-treatment specimens:



ICI rapidly induced genomic changes (with merely 4 weeks of therapy): 3 subgroups

1. Subgroup who failed to reinvigorate an immune response, significantly impacting on clonally diverse tumors . 'Non-Responders"

2. Subgroup of patients in who four weeks of nivolumab with or without relatlimab were sufficient to empower complete immune eradication of lung cancers (no meaningful longitudinal genomic analyses possible). "Complete path. responders"

3. Subgroup of patients who achieved substantial but not complete histopathological responses, in whom already clonal selection/enrichment of apparently resistant clones and depletion of sensitive clones was observed (copy number gain of MYC and KRAS, and pathogenic variants of IDH1 and STK11). "Clonal selectors"

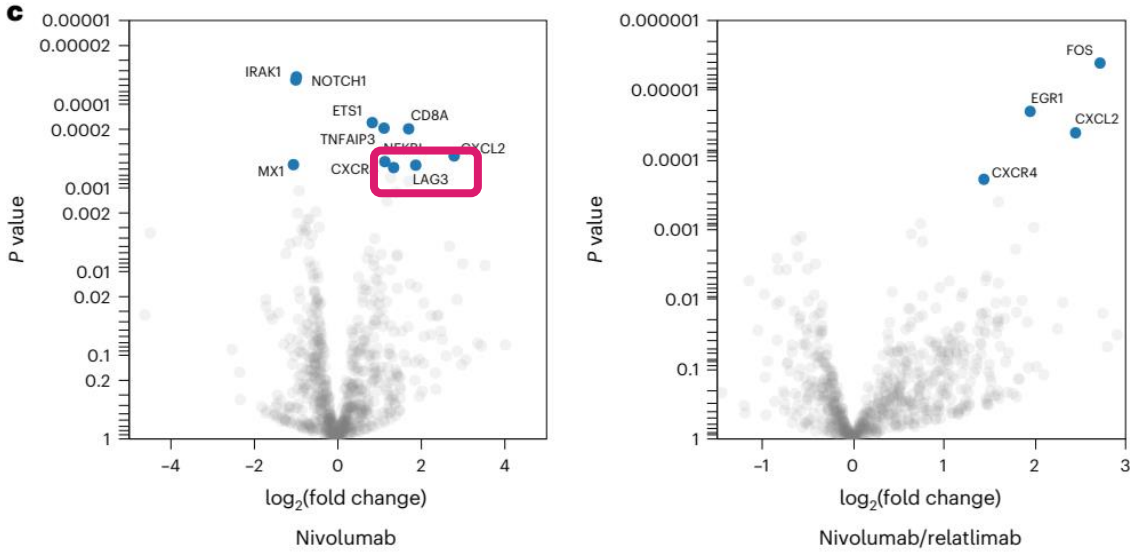
Future potential role for cfDNA monitoring to detect emergence of resistant clones and implement targeted strategies?

Schuler & Cuppens et al. Nature Medicine, 2024

Key finding 4:

Rapidly ICI-induced immune activation may shape the individual genomic landscapes of NSCLC

Potential role for early detection (eg. cfDNA) of resistant clones and targeted strategies?

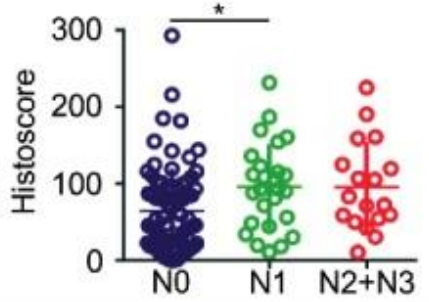


C. Differential expression of immune-related and cancer pathway-related genes in response to treatment with nivolumab (left) and nivolumab and relatlimab (right) are presented as volcano plots. Significantly (FDR ≤ 0.05) upregulated (right of 0 line on x axes) and downregulated (left of 0 line on x axes) genes are depicted as blue closed circles. Selected significantly regulated genes are indicated. P values on the y axes were calculated using the two-sided quasi-likelihood F-test approach of EdgeR.

Schuler & Cuppens et al. Nature Medicine, 2024

Deng et al. Onco Immunology, 2016

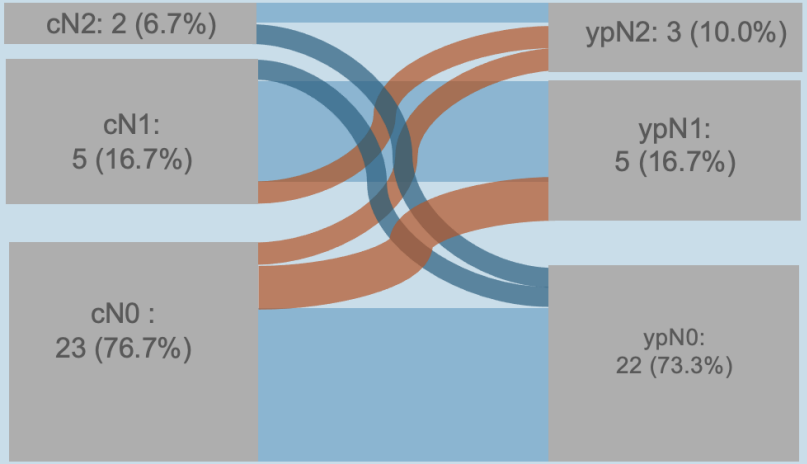
B. The quantitative analysis of LAG-3 histoscore is performed in lymph node status (negative, N0; positive, N1, N2+N3, right panel), One-way ANOVA with post Tukey test, *$p < 0.05$.



Nodal evolution

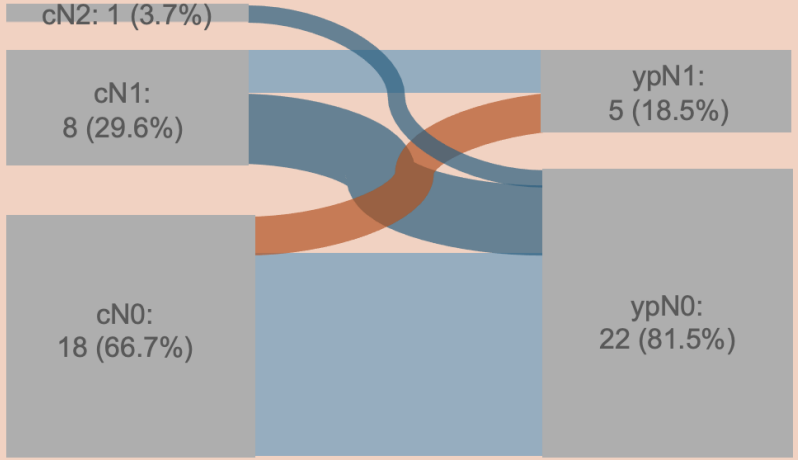
Mediastinal staging cfr. ESTS guidelines: All cN1 and cN2 confirmed at randomization by EBUS (13), mediastinoscopy (1) or both (2). Of 41 cN0 patients, 27 EBUS, 5 mediastinoscopy and 2 both.

Arm A: N=30
Nivolumab 240mg



Nodal downstaging cN2 > ypN1/0 or cN1 > ypN0	2/7 (28.6%)
Nodal upstaging cN0 > ypN1/2 or cN1 > ypN2	5/28 (17.8%)
Post-operative TNM downstaging	16/30 (53.3%)
Post-operative TNM upstaging	8/30 (26.7%)

Arm B: N=27
Nivolumab 240mg plus Relatlimab 80mg



Nodal downstaging cN2 > ypN1/0 or cN1 > ypN0	6/9 (66.7%)
Nodal upstaging cN0 > ypN1/2 or cN1 > ypN2	2/26 (7.7%)
Post-operative TNM downstaging	18/27 (66.7%)
Post-operative TNM upstaging	6/27 (22.2%)

Key finding 5:
Dual PD1/LAG3 checkpoint inhibition can potentially improve nodal clearance

Potential role for dual PD1/LAG3 inhibition in stage III/N2 patients

HOW DOES NEOPREDICT-Lung FIT IN THE LANDSCAPE OF NEOADJUVANT ICI REGIMENS

Table 2

Table 2: Overview of ICI and chemotherapy combination trials in resectable NSCLC.

Name Year of first outcome publication	Phase	N	Stage	Primary Endpoint	Regimen	Proportion of patients undergoing resection (%)	Proportion of patient with MPR (%)	Proportion of patients with pCR (%)	Proportion of patients undergoing R0 resection (%)	Post-operative 30-day mortality (%)
Shu et al. 2020* [41] NCT02716038	2	30	IB-IIIA	MPR	Atezolizumab + chemotherapy	97.0	57.0	33.0	87.0	3.0
NADIM #* 2020 [50] NCT03081689	2	46	IIIA	PFS	Nivolumab + chemotherapy	89.0	83.0	63.0	100	0
SAKK 16/14 #* 2021 [52] NCT02572843	2	68	IIIA (N2)	EFS	Durvalumab + chemotherapy	81.0	62.0	10.0	93.0	2.0
NEOSTAR* 2023 [46] NCT03158129	2	44	IB-IIIA	MPR	Nivolumab + chemotherapy +/- ipilimumab	100 91.0	32.1 50.0	18.2 18.2	90.0 95.0	0 0
NADIM-II # 2023 [53] NCT03838159	2	86	IIIA – IIIB (N2)	pCR	Nivolumab +/- chemotherapy	93.0 69.0	52.6 13.8	36.8 6.9	NA	NA
Checkmate 816* 2021 [42] NCT02998528	3	358	IB-IIIA	EFS pCR	Nivolumab or placebo + chemotherapy	83.2 75.4	36.9 8.9	24.0 2.2	83.2 77.8	NA
Keynote-671 # 2023 [54] NCT03425643	3	797	II-IIIB (N2)	EFS MPR	Pembrolizumab or placebo + chemotherapy	82.1 79.4	30.2 11.0	18.1 4.0	92.0 84.2	1.8 0.6
AEGEAN # 2023 [56] NCT03800134	3	802	IIA-IIB (N2)	EFS pCR	Durvalumab or placebo + chemotherapy	80.6 80.7	33.3 12.3	17.2 4.3	94.7 91.3	NA
Checkmate 77T # 2023 [58] NCT04025879	3	461	IIA-IIB (N2)	EFS	Nivolumab or placebo + chemotherapy	78.0 77.0	35.4 12.1	25.3 4.7	89.0 90.0	NA
NEOTORCH # 2024 [57] NCT04158440	3	404	II-III	EFS MPR	Toropalimab or placebo + chemotherapy	82.2 73.3	48.5 8.4	8.4 1.0	95.8 92.6	NA
RATIONALE-315 # 2024 [59] NCT04379635	3	453	II-IIIA	EFS MPR	Tislelizumab or placebo + chemotherapy	84.1 76.2	56.2 15	40.7 5.7	95.3 93.1	1.3 1.8

#: Perioperative chemo-immunotherapy.

*: TNM 7th edition, all others 8th edition

MPR = major pathological response; pCR = pathological complete response; EFS = event free survival; PFS = progression free survival; NSCLC = non-small cell lung cancer.

pCR rates vary from 8,4 to 63% ; surgical omission from 0% to 22%

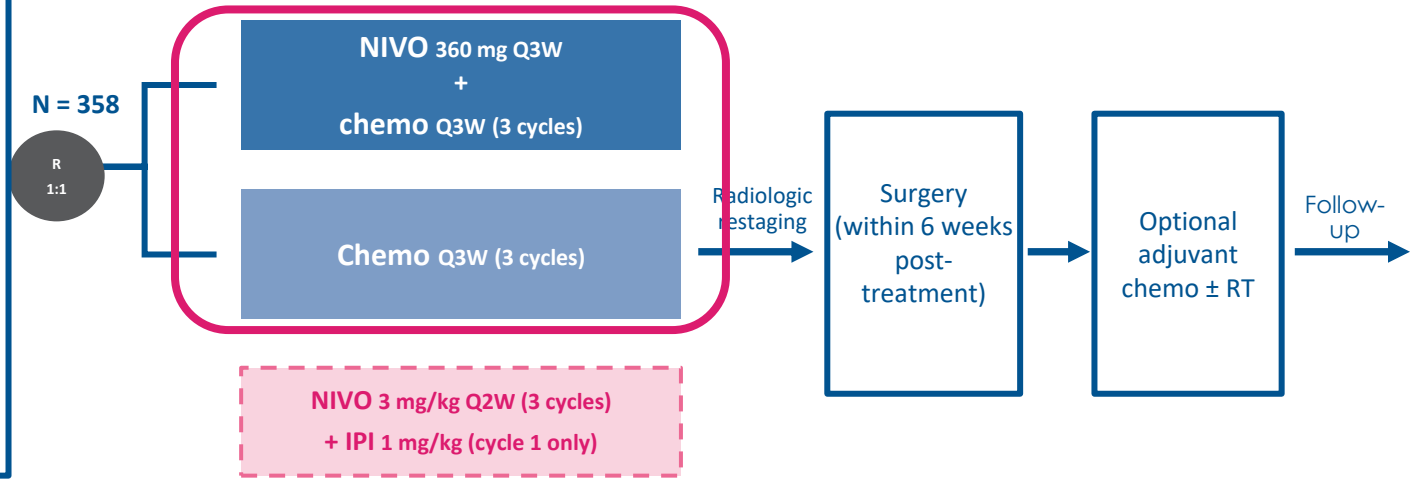
Cuppens et al. Lung Cancer 2024

CheckMate 816

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)–IIIA NSCLC (per **TNM 7th** edition)
- ECOG performance status 0–1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by
Stage (IB–II vs IIIA), PD-L1 (≥ 1% vs < 1%), and sex



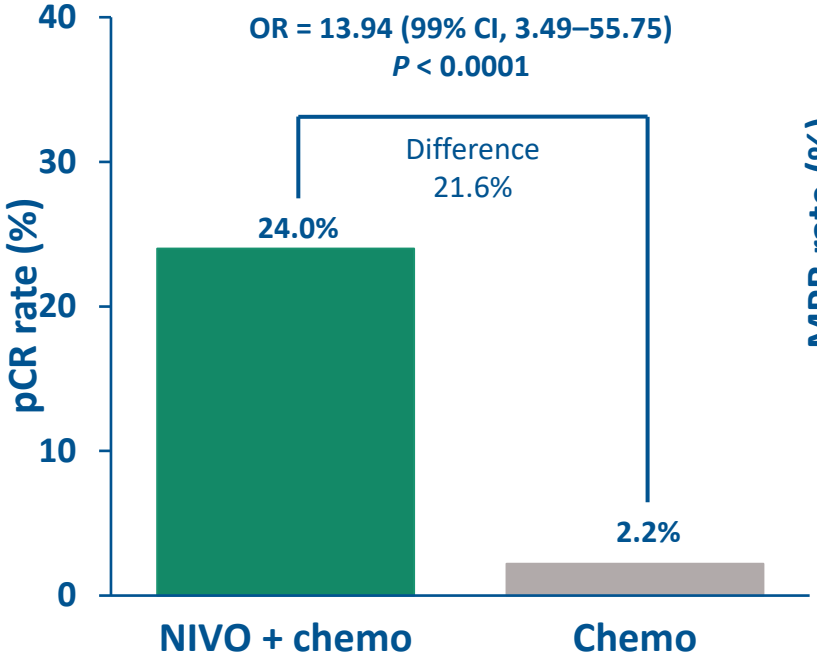
Primary endpoints
- pCR by BIPR
- EFS by BICR

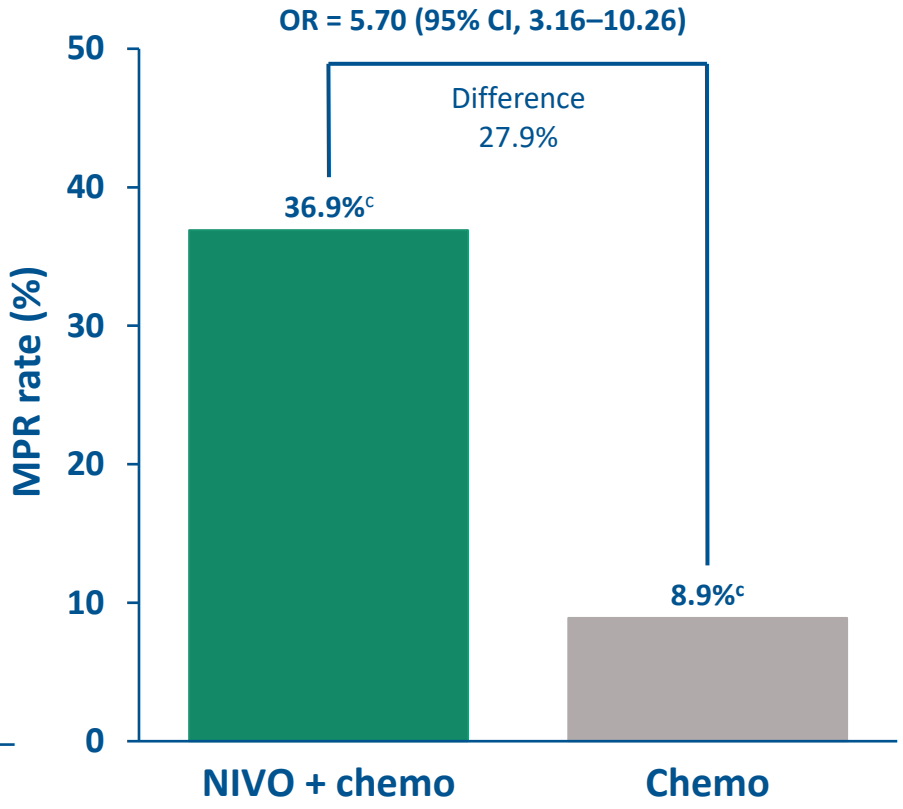
Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA)

Forde et al. AACR, 2021

Chekmate 816

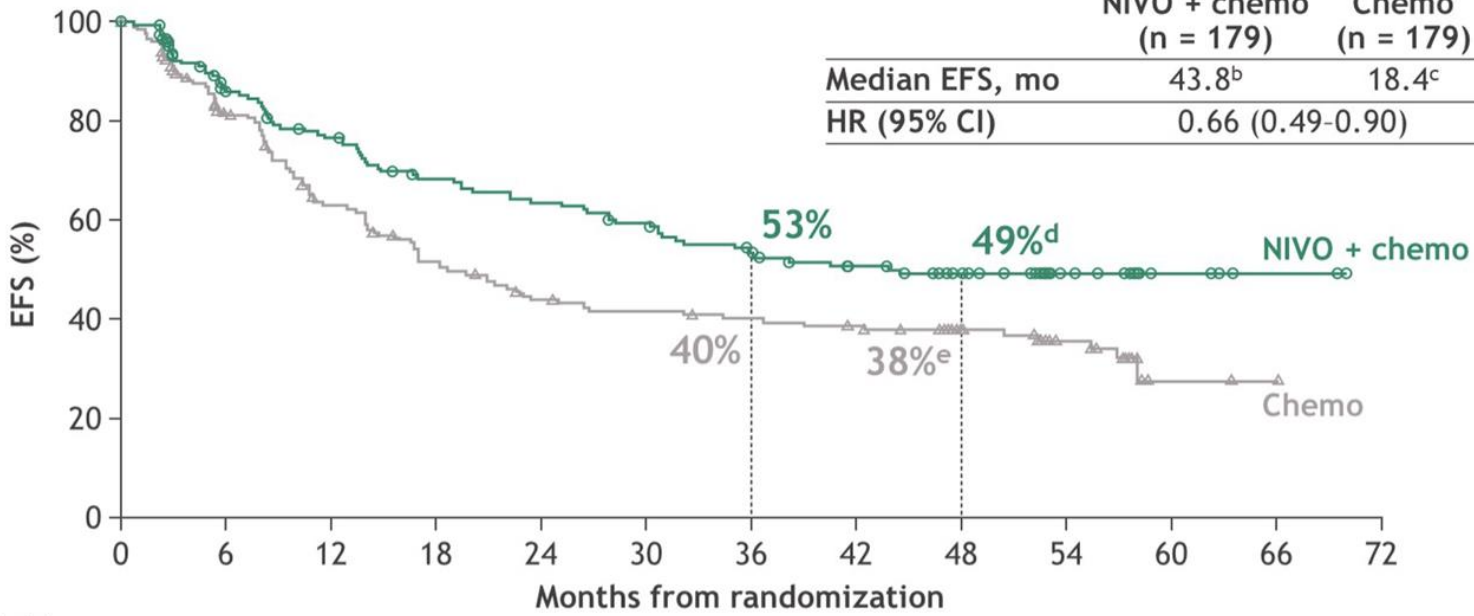




Forde et al. AACR, 2021

Primary endpoint:
EFS with neoadjuvant NIVO + chemo vs chemo

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo	43.8[b]	18.4[c]
HR (95% CI)	0.66 (0.49-0.90)	



No. at risk												
NIVO + chemo	179	130	114	99	92	85	74	64	49	24	5	2	0
Chemo	179	124	92	73	60	56	53	50	37	22	2	1	0

Database lock date, February 23, 2024; minimum/median follow-up, 49.1/57.6 months.
[a]Exploratory analysis. [b-e]95% CI: [b]30.6-NR; [c]14.0-26.7; [d]41-57; [e]30-46. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985. 2. Forde PM, et al. Oral presentation at European Lung Cancer Congress (ELCC); March 29-April 1, 2023; Copenhagen, Denmark. Presentation 840.

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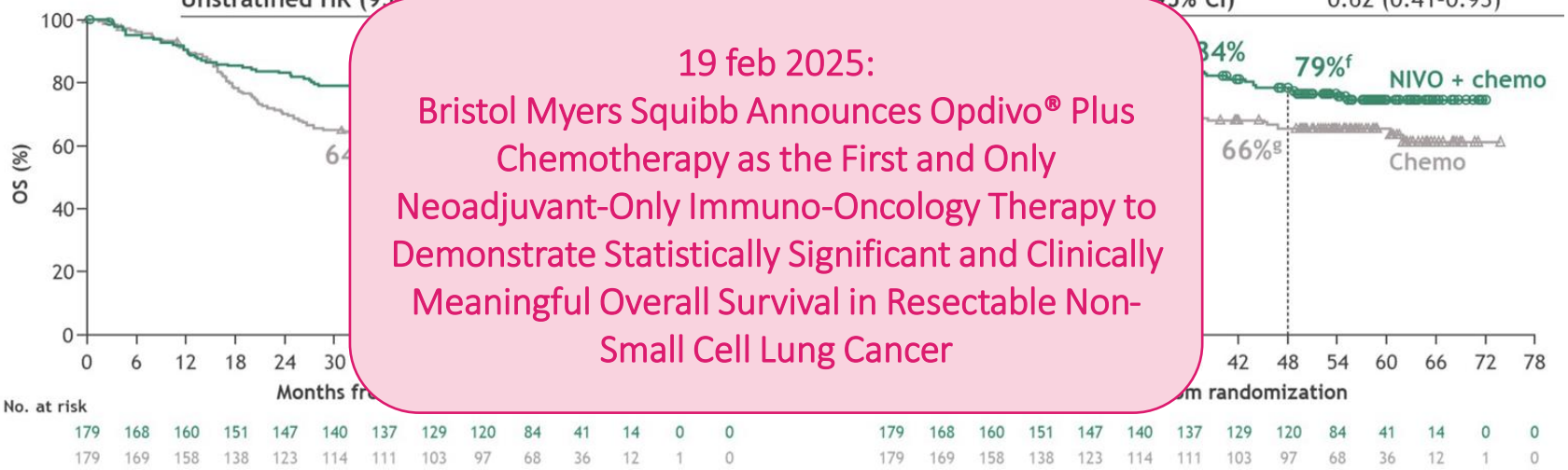
OS

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR[c]
HR (98.36% CI); *P* value	0.71 (0.47-1.07); 0.0451[b]	
Unstratified HR (95% CI)		

Lung cancer-specific survival[h]

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median lung cancer-specific survival, mo	NR	NR
Unstratified HR (95% CI)	0.62 (0.41-0.93)	



19 feb 2025:
Bristol Myers Squibb Announces Opdivo® Plus Chemotherapy as the First and Only Neoadjuvant-Only Immuno-Oncology Therapy to Demonstrate Statistically Significant and Clinically Meaningful Overall Survival in Resectable Non-Small Cell Lung Cancer

- Patients in the NIVO + chemo arm who had pCR continued to have improved OS vs those who did not (HR [95% CI], 0.08 [0.02-0.34]; **4-year OS rates, 95% vs 63%**)

Minimum/median follow-up, 49.1/57.6 months.
[a]Reasons for OS events (deaths) in all treated patients in the NIVO + chemo vs chemo arms (N = 176 in each arm) were disease (23% vs 33%), study drug toxicity (0% vs 2%), unknown (3% vs 3%), and other (7% vs 5%). [b]Significance boundary for OS (0.0164) was not met at this interim analysis. [c-g]95% CI: [c]50.4-NR; [d]63-77; [e]50-65; [f]72-84; [g]58-72. [h]Exploratory analysis; events were deaths with noted reason of "disease" per investigator assessment.

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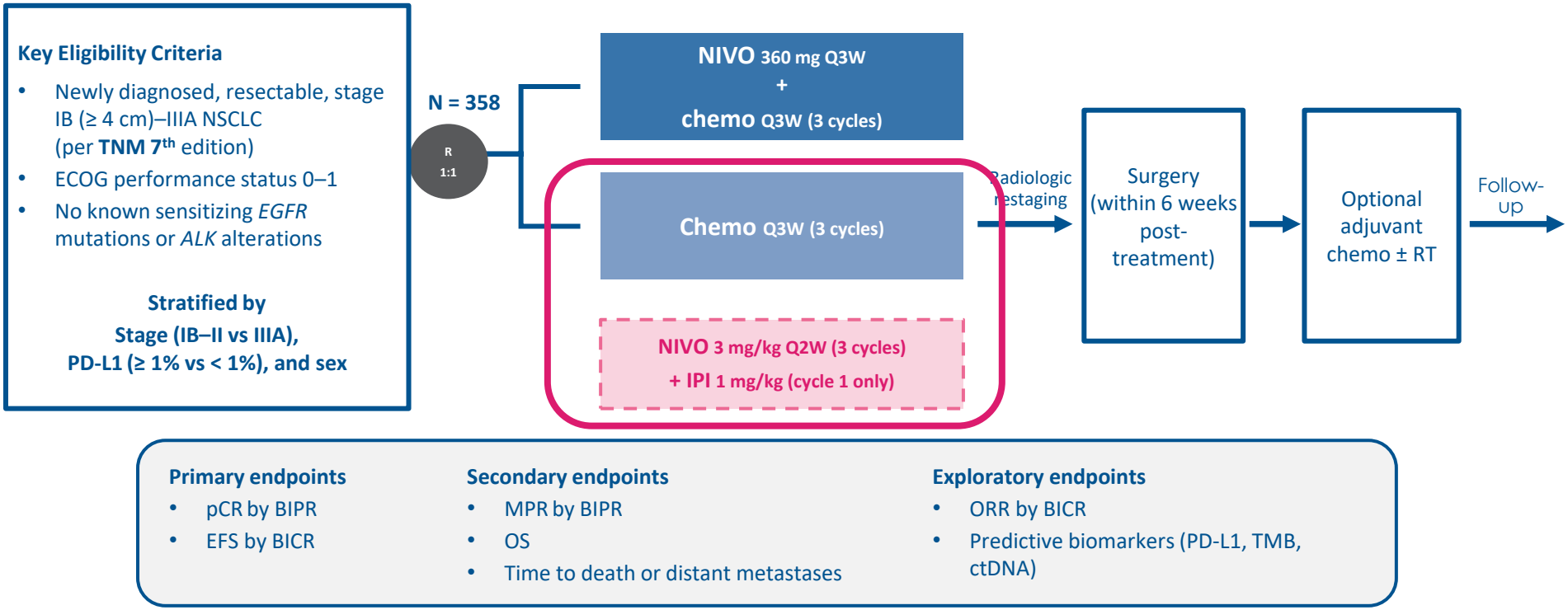
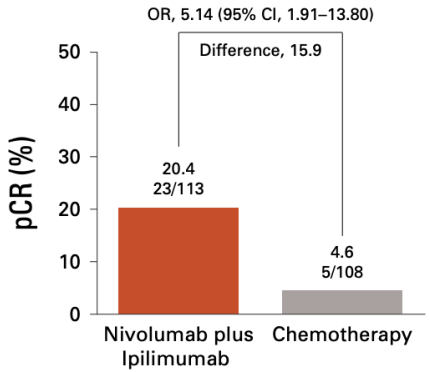
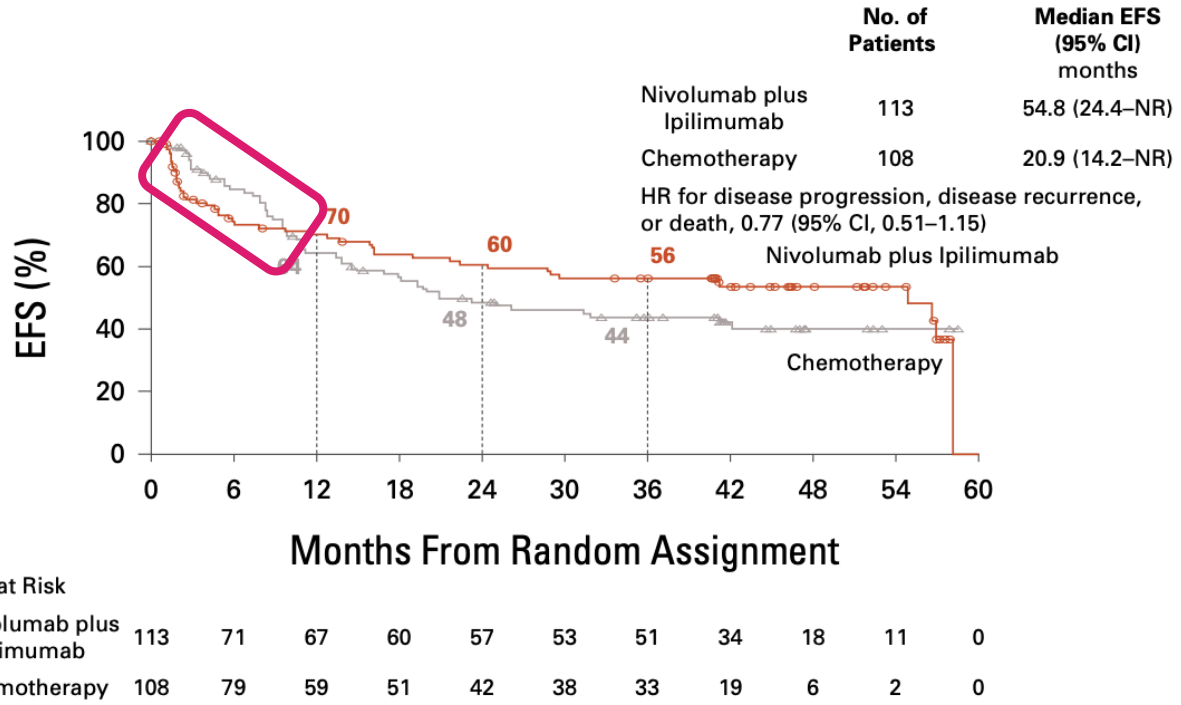
CheckMate 816

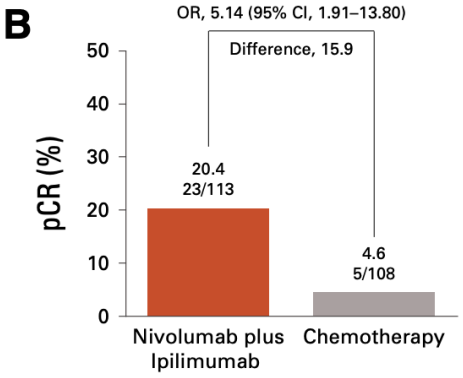


Forde et al. AACR, 2021





Awad et al. JCO 2025



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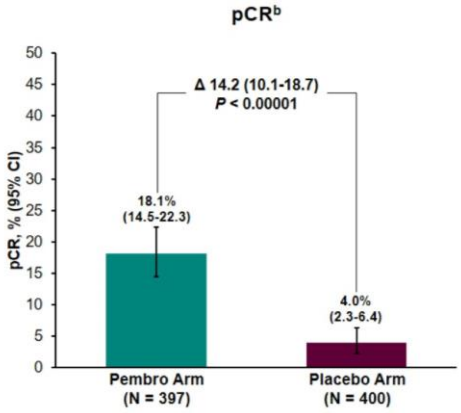
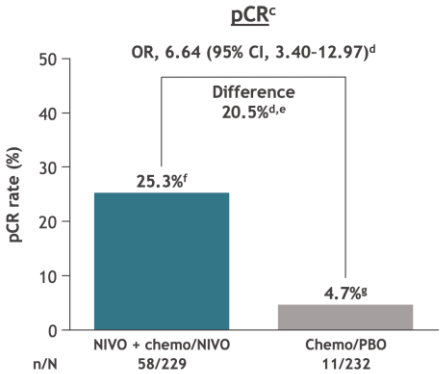


Keynote 671



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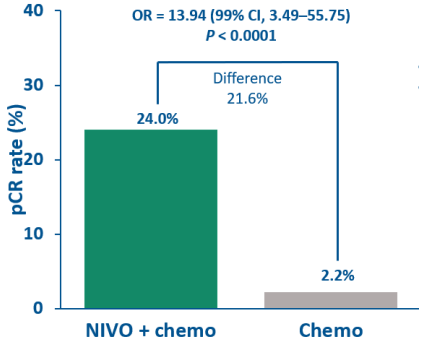

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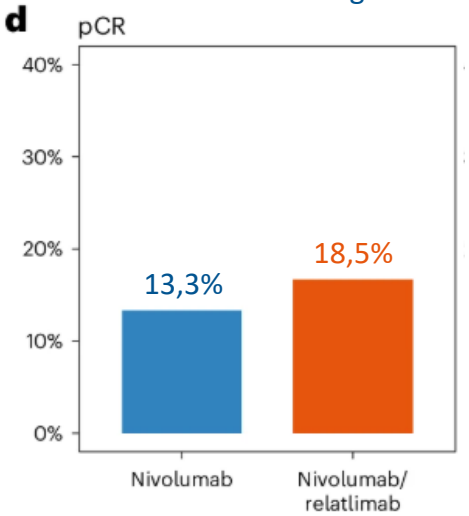
NEOPREDICT-Lung



short course of neoadjuvant (dual) IO can induce significant responses.

Are we overtreating patients by prolonging the neoadjuvant treatment course?

Lack of a robust biomarker to identify patients who do not require chemotherapy and could benefit of an IO solely based strategy.

In summary

- NEOPREDICT-Lung is the first study to evaluate dual PD1 and LAG3 inhibition in resectable lung cancer.
- Short course and closely monitored neoadjuvant nivolumab +/- relatlimab is safe and does not increase the risk of surgical omission
- Neoadjuvant neoadjuvant nivolumab +/- relatlimab can induce a significant number of pathological responses which correlates with improved clinical outcome
- More consistent and directed immune activation was induced with nivolumab + relatlimab and holds potential for rational triplet combinations.
- The individual genomic landscapes of NSCLC changes rapidly under ICI pressure and potentially resistant clones can be identified early, creating opportunities for early individualized targeted intervention.
- Dual PD1/LAG3 checkpoint inhibition can potentially improve nodal clearance