Stage III NSCLC – Surgical/Combined Modality

MA01.08, OA13.03, ES31.05

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5-Year Clinical Outcomes of Perioperative Nivolumab and Chemotherapy in Stage III NSCLC (NADIM trial)

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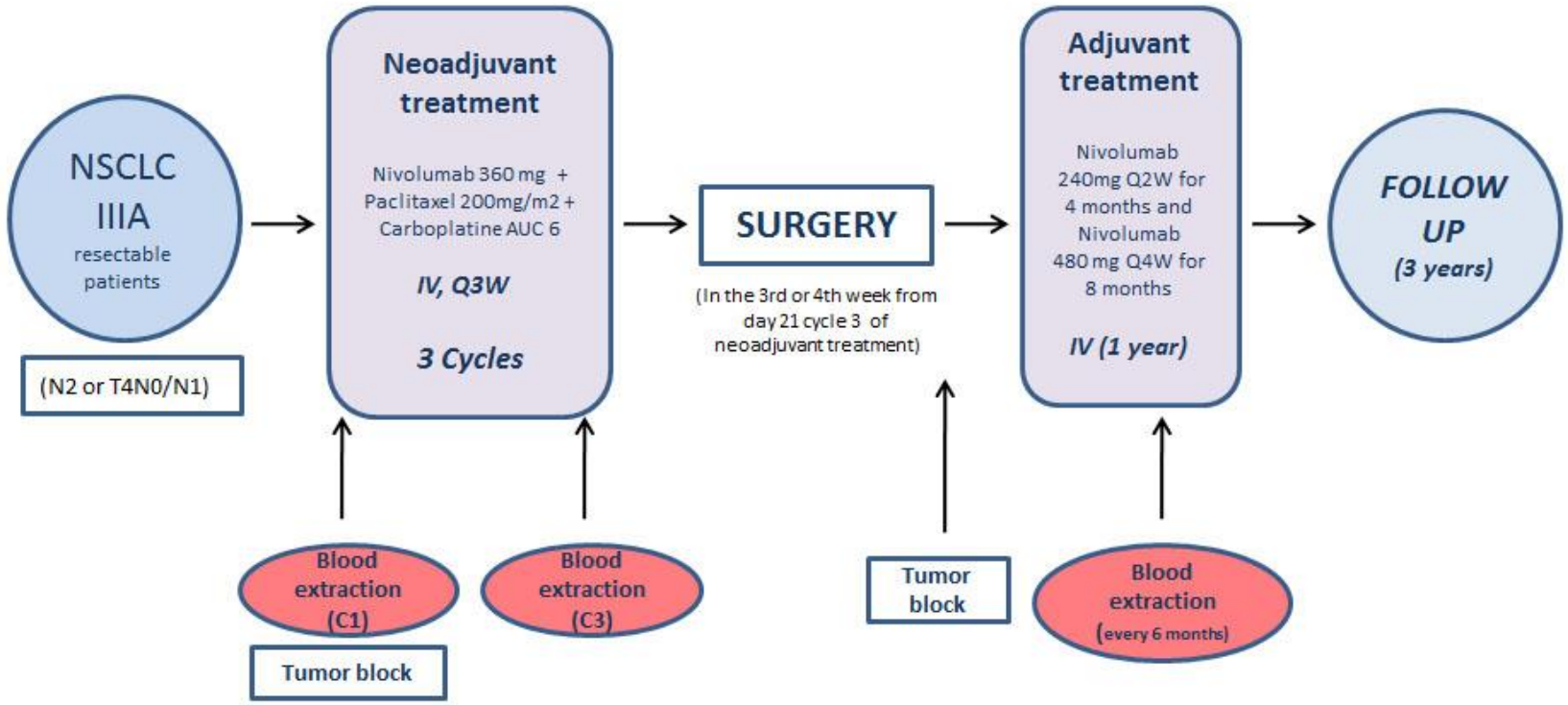
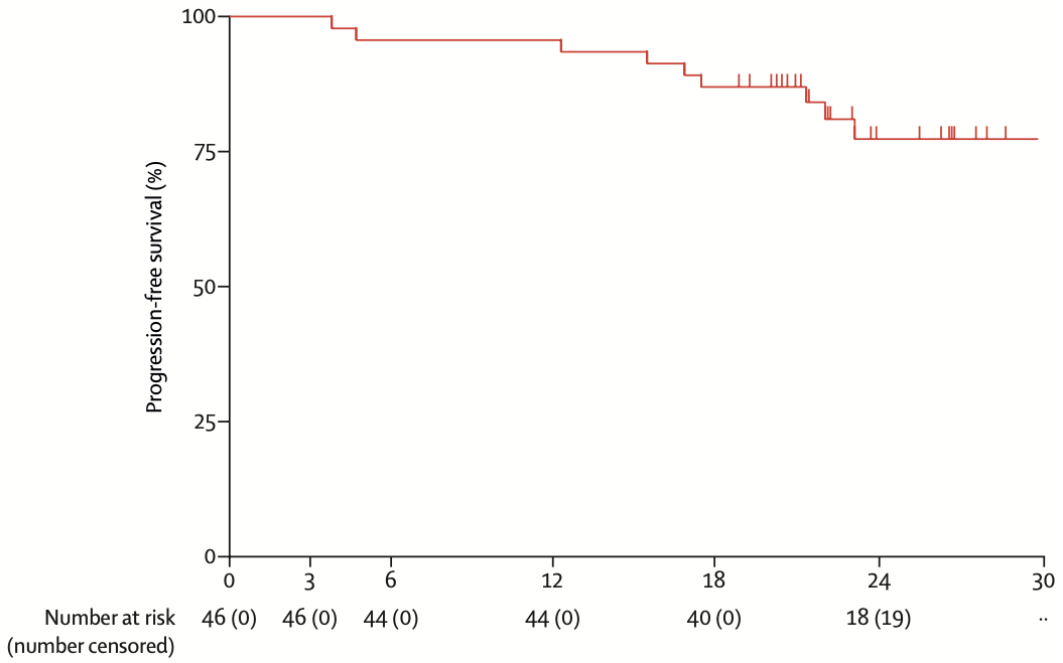
NADIM I Trial Design

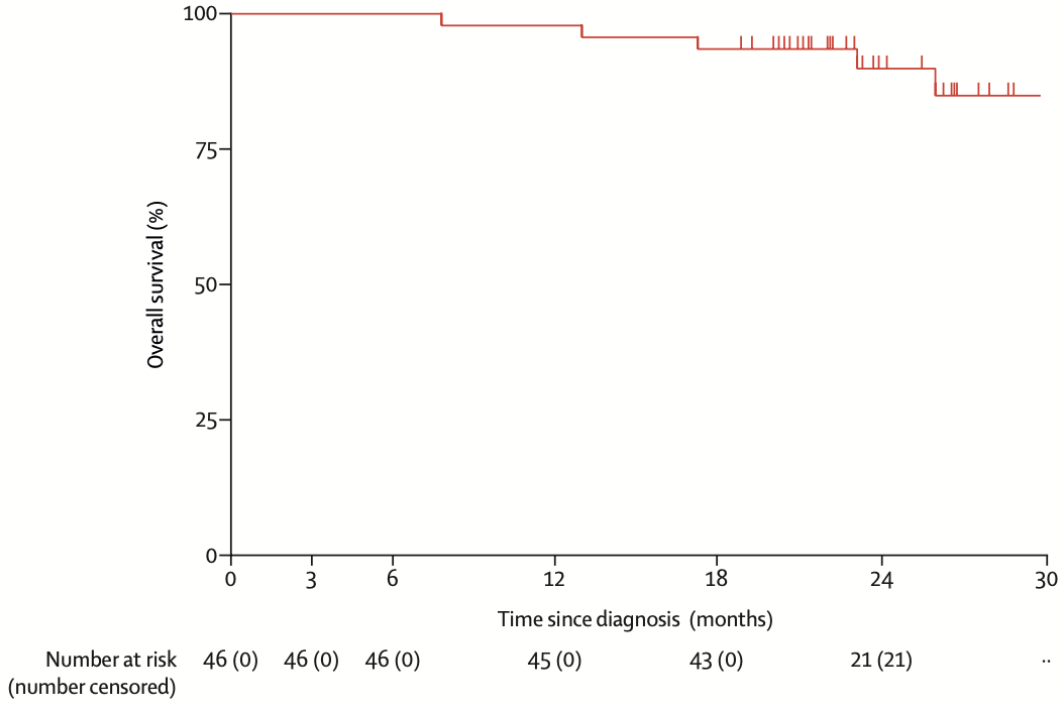
NADIM Patient baseline characteristics	N=46 (ITT)
Age (median, range)	63 (41-77)
Co-morbidities, N (%)	43 (93%)
N2	**33 (74%)**
Multiple station	**25 (54%)**



NADIM I – 24 Month Outcomes



PFS in ITT population
77.1% (59.9-87.7) at 24 mo



OS in ITT population
89.9% (74.5-96.2) at 24 mo

Lancet Oncol 2020; 21: 1413–22

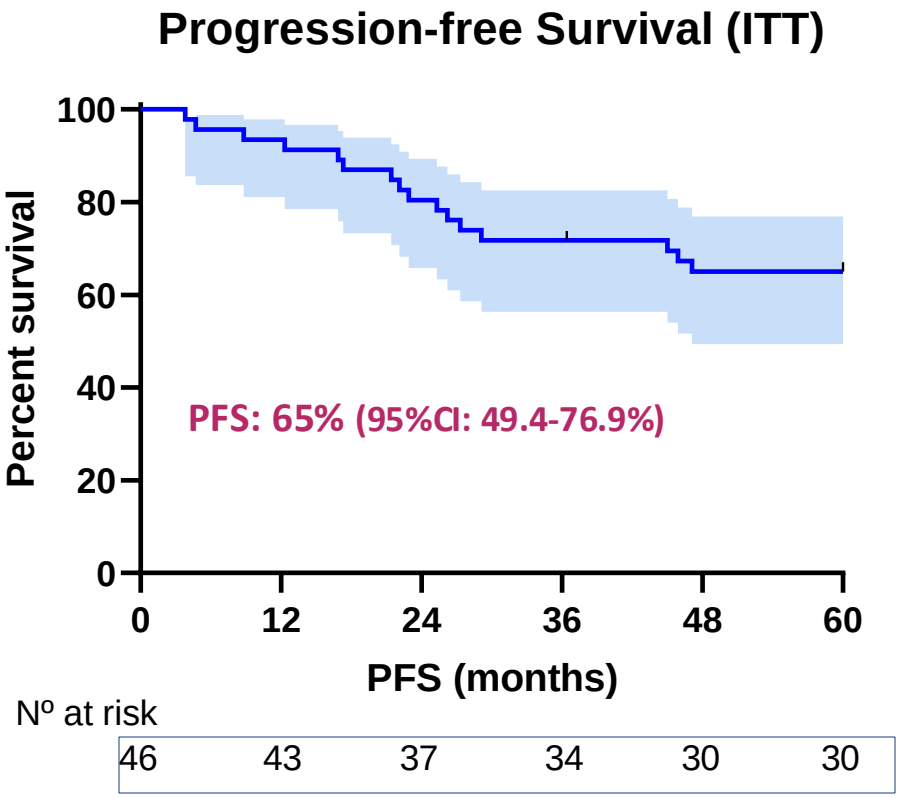
5-y NADIM

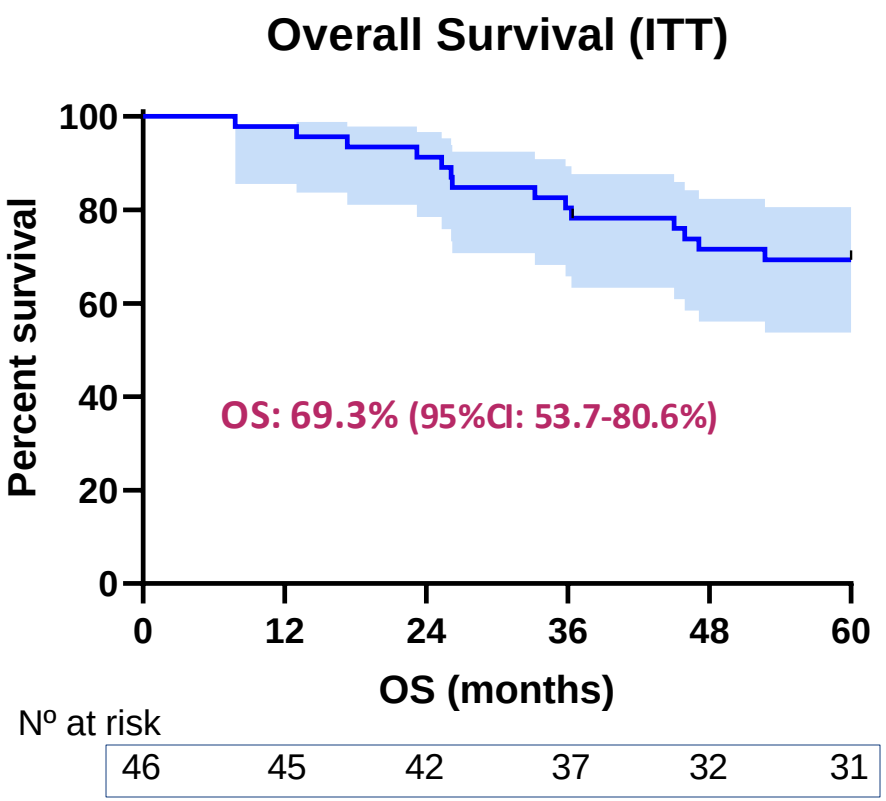
INTRODUCTION

- Neoadjuvant chemoimmunotherapy has been shown to be highly effective in resectable stage IIIA NSCLC.
- The significance of established immunotherapy biomarkers (PD-L1 TPS, TMB, ctDNA…) remains uncertain.
- We present the **5-year survival outcomes** of the NADIM I study.

5-y NADIM

PFS and OS at 5-y in ITT population (n= 46)



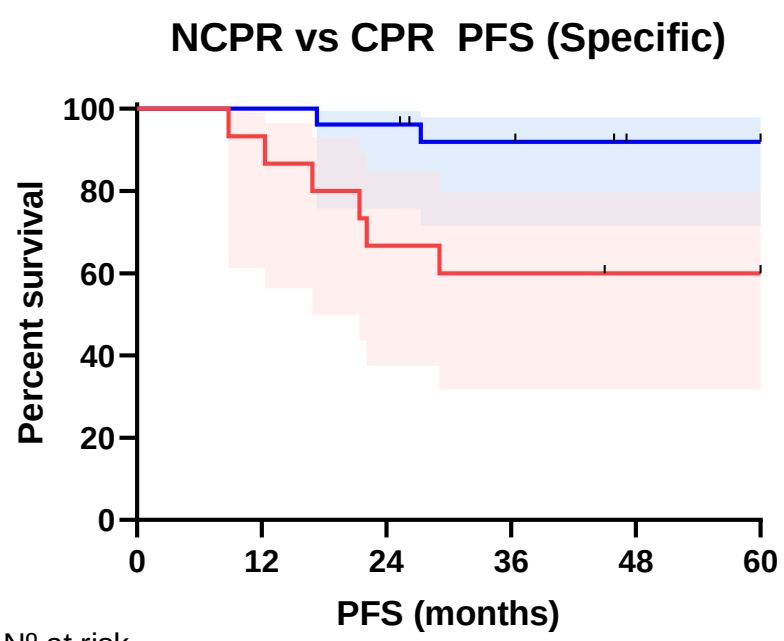


97.8% maturity at 60 months

ITT, intention to treat

5-y NADIM

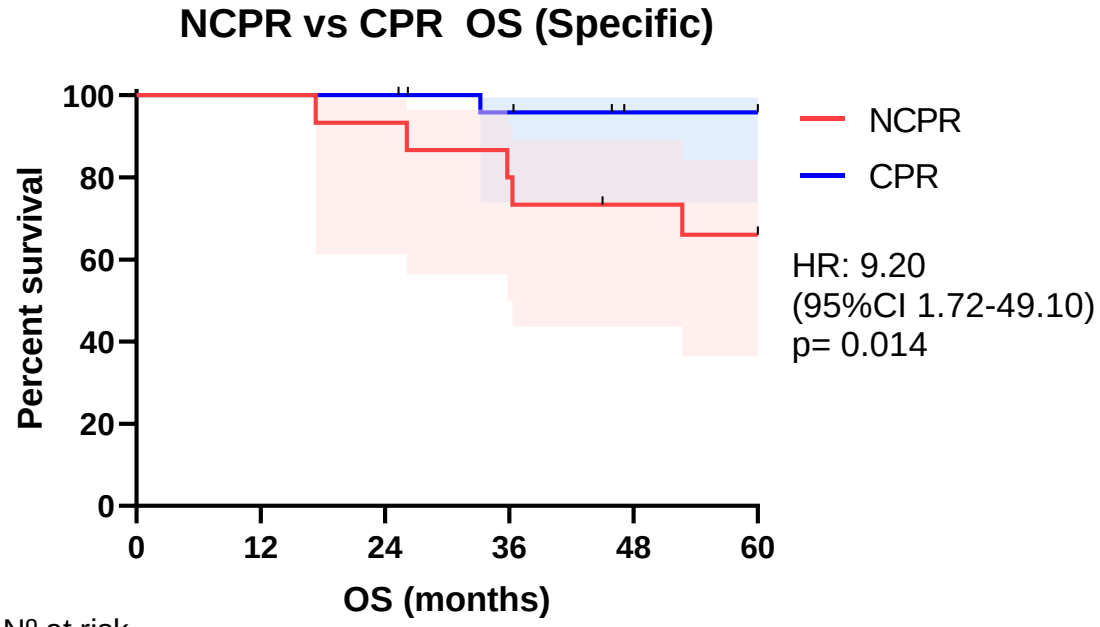
LONG-TERM SURVIVAL FOR RESECTED PATIENTS



Nº at risk						
CPR	26	26	25	22	19	19
NCPR	15	14	10	9	8	8

NCPR PFS: 60% (95%CI: 31.8-79.7%)

CPR PFS: 92% (95%CI: 70.5-97.9%)



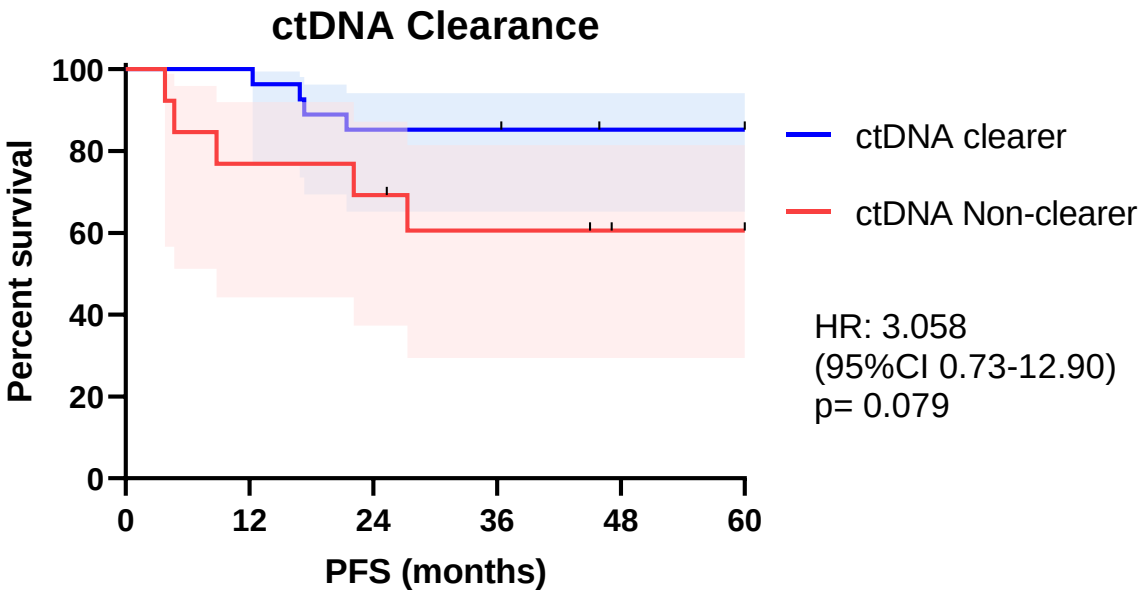
Nº at risk						
CPR	26	26	26	23	20	20
NCPR	15	15	14	12	10	9

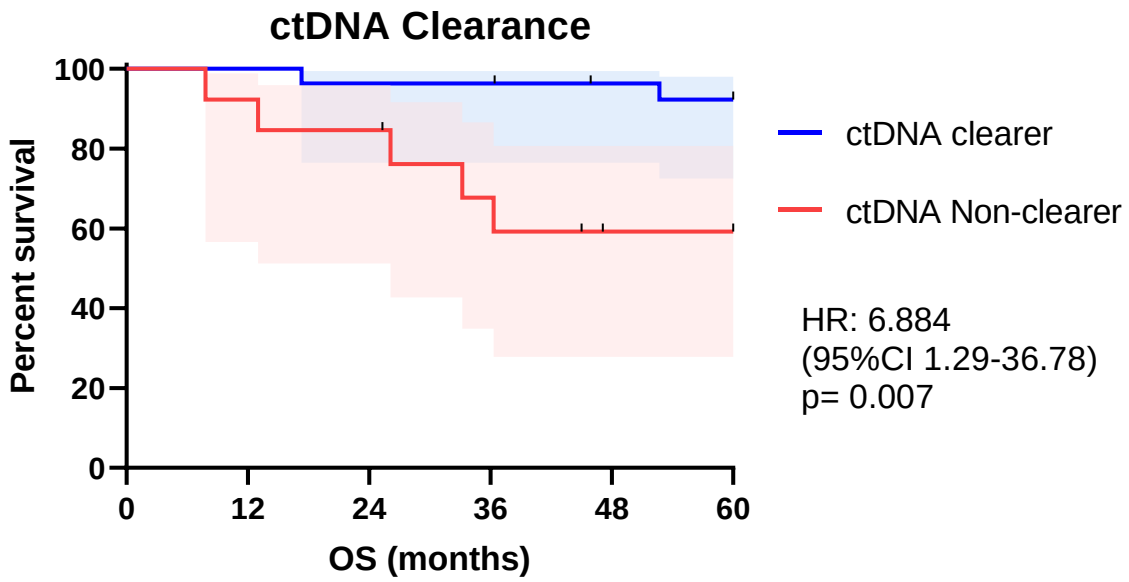
NCPR OS: 66% (95%CI: 36.5-84.3%)

CPR OS: 95.8% (95%CI: 73.9-99.4%)

5-y NADIM

PREDICTIVE BIOMARKERS (III)





PFS Non-ctDNA clearer: 60.6% (95%CI: 29.4-81.4%)

PFS ctDNA clearer: 85.2% (95%CI: 65.2-94.2%)

OS Non-ctDNA clearer: 59.2% (95%CI: 27.9-80.7%)

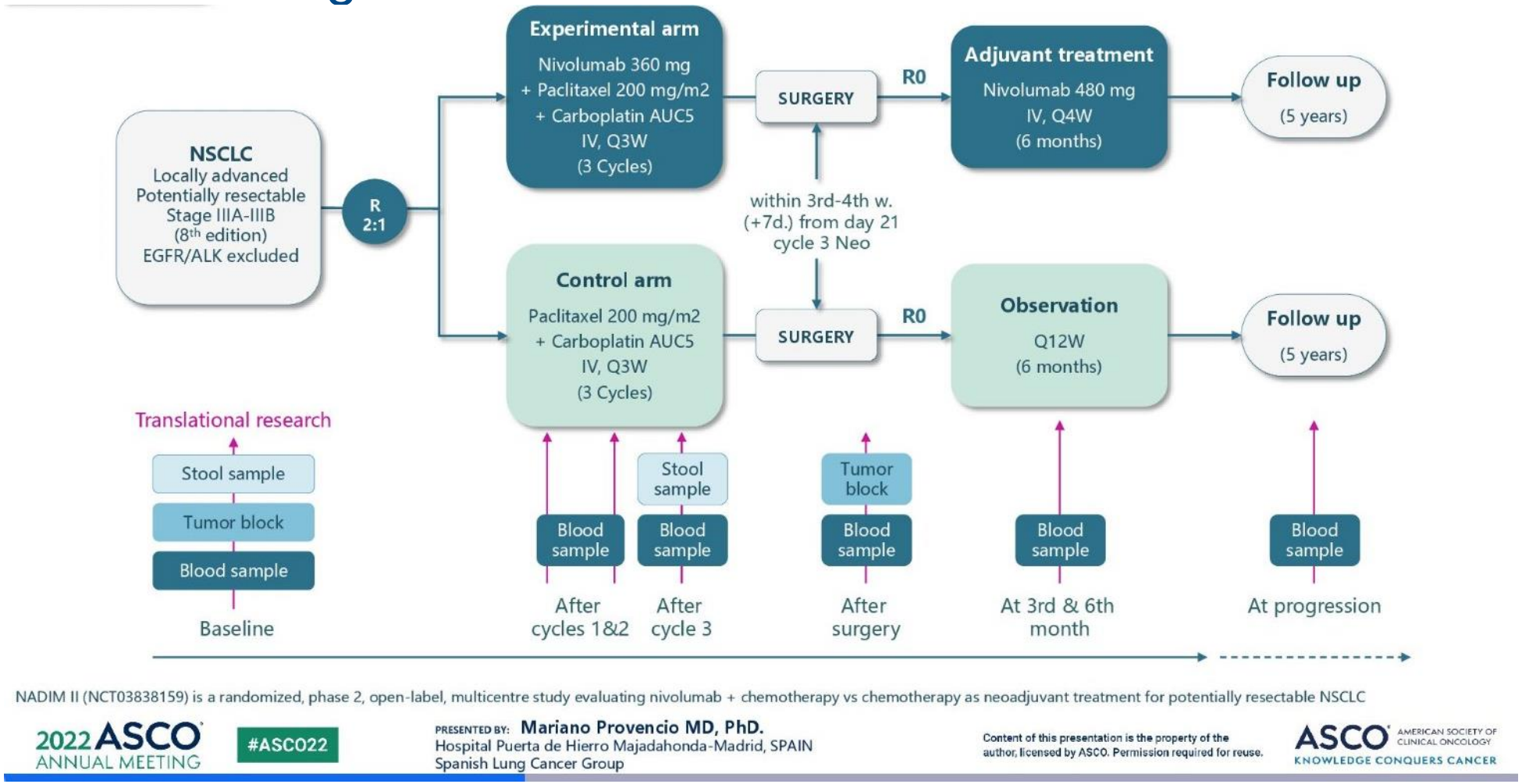
OS ctDNA clearer: 92.3% (95%CI: 72.5-98%)

5-y NADIM

CONCLUSIONS

- NADIM I **confirms the robust clinical benefit** of perioperative chemo-immunotherapy **at 5 years**, reinforcing its use in resectable stage IIIA NSCLC.
  - → **5-years PFS (ITT): 65.0% (95% CI 49.4-76.9)**
  - → **5-years OS (ITT): 69.3% (95% CI 53.7-80.6)**
- There are **no signs of late toxicity nor of treatment-related deaths**.
- Particular **benefit** is observed in **patients who achieved CPR** and might serve as good surrogates for survival.
  - → **5-years PFS: 92.0% (95% CI 70.5-97.9) with CPR vs 60.0% (95% CI 31.8-79.7) with non-CPR**
  - → **5-years OS: 95.8% (95% CI 73.9-99.4) with CPR vs 66.0% (95% CI 36.5-84.3) with non-CPR**
- **ctDNA clearance** after neoadjuvant treatment showed a **good prediction of PFS and OS** (especially valuable in patients with a worse prognosis).
- **Neither PD-L1 tumor proportion score nor TMB are markers of PFS or OS**.

NADIM II Trial Design



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

2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY: Mariano Provencio MD, PhD.
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NADIM II – 24 Month Outcomes

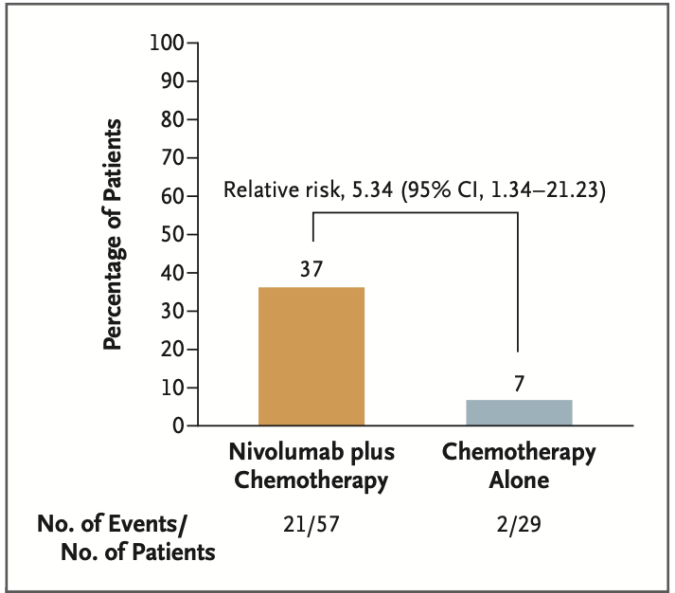

Figure 1. Pathological Complete Response (Intention-to-Treat Population).

The intention-to-treat population included all the patients who had undergone randomization and received at least one cycle of neoadjuvant treatment. All the patients who underwent surgery (73 patients) had a valid assessment of pathological response. A pathological complete response was defined as 0% residual viable tumor cells in both the primary tumor (lung) and sampled lymph nodes. Patients who did not undergo surgery were considered to have not had a response.

PCR
37% vs. 7%
HR 5.34 (1.34-21.23)

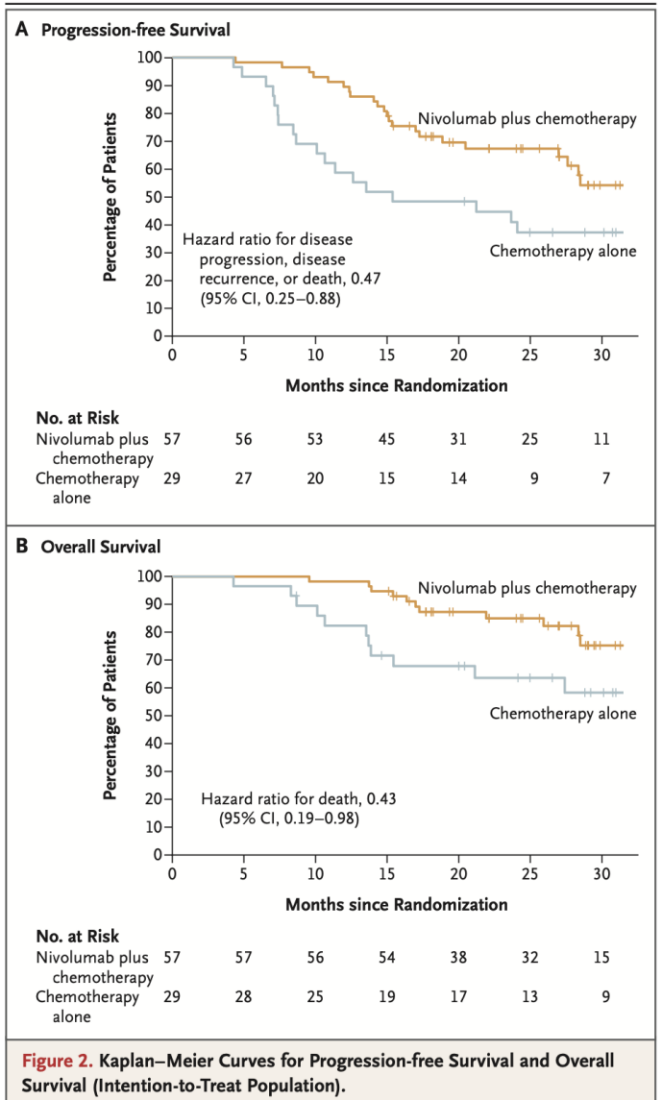

Figure 2. Kaplan–Meier Curves for Progression-free Survival and Overall Survival (Intention-to-Treat Population).

PFS at 12 mo
89.5% vs. 58.6%
HR 0.47 (0.25-0.88)

OS at 12 mo
98.2% vs. 82.1%
HR 0.43 (0.19-0.98)

Perioperative Durvalumab for Resectable NSCLC

Updated Outcomes from the Phase 3 AEGEAN Trial

John V. Heymach,[1] David Harpole,[2] Tetsuya Mitsudomi,[3] Janis M. Taube,[4] Shugeng Gao,[5] Laszlo Urban,[6] Jin Hyoung Kang,[7] Francisco J. Orlandi,[8] Jeronimo Rodriguez-Cid,[9] Bartomeu Massuti,[10] Luis Leon Mateos,[11] Giulia Pasello,[12] Quincy Chu,[13] Jaroslaw Kolb-Sielecki,[14] Masao Nakata,[15] Mike Aperghis,[16] Helen Mann,[16] Tamer M. Fouad,[17] Gary J. Doherty,[16] Martin Reck[18]

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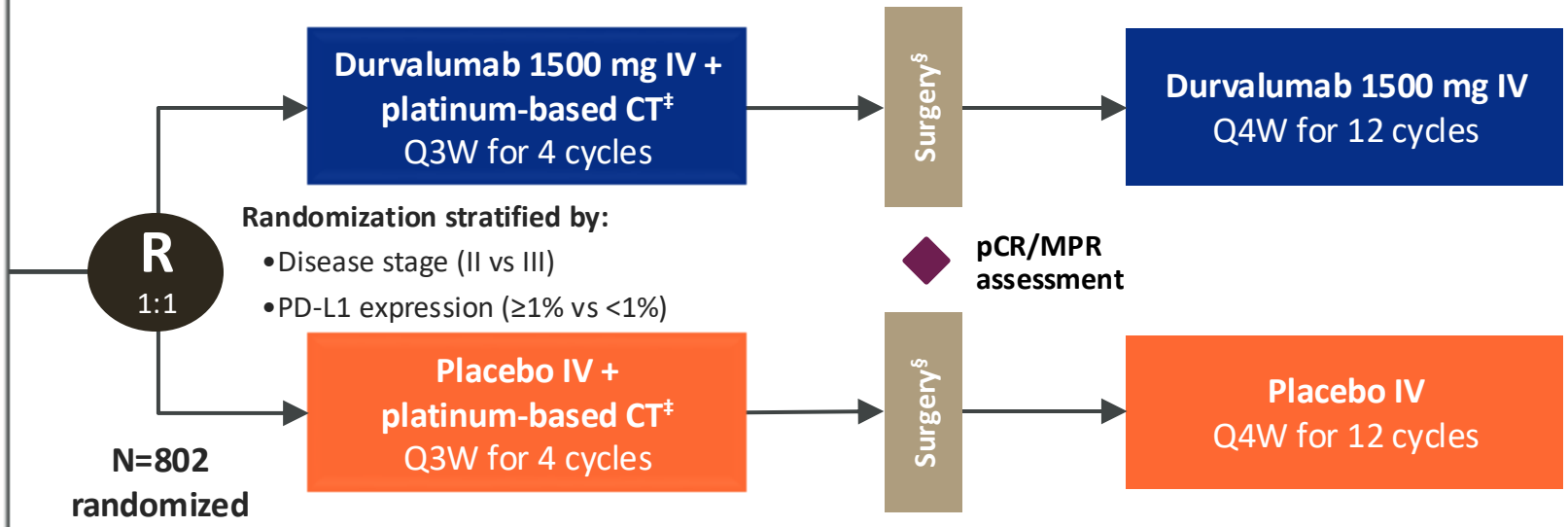
AEGEAN study design

Study population

- Resectable NSCLC* (stage IIA–IIIB[N2]; AJCC 8th ed)
- Treatment-naïve
- ECOG PS 0 or 1
- Lobectomy, sleeve resection, or bilobectomy as planned surgery*
- Confirmed PD-L1 status†
- No documented *EGFR/ALK* aberrations*



Efficacy analyses were performed in the mITT population (or its resected subpopulation), which excluded patients with documented EGFR/ALK *aberrations*¶

Primary endpoints: pCR, evaluated centrally (IASLC 2020[1]), and EFS per BICR (RECIST v1.1)

Key secondary endpoints: MPR, evaluated centrally (IASLC 2020[1]), DFS per BICR (RECIST v1.1) in the resected subpopulation, and OS

	EFS interim analysis #1	EFS interim analysis #2 (reported here)
Data cutoff	November 10, 2022	May 10, 2024
Median EFS follow-up	11.7 months (censored patients)	25.9 months (censored patients)
Data maturity	31.9%	39.1%

[1]Travis WD, et al. *J Thorac Oncol* 2020;15:709–40.

Background

- In the global phase 3 AEGEAN trial in patients with R-NSCLC, perioperative durvalumab + neoadjuvant CT, vs neoadjuvant CT alone, significantly improved the primary endpoints of EFS and pCR, with a safety profile consistent with the individual agents,[1] leading to recent FDA approval
  - EFS HR = 0.68 (95% CI: 0.53–0.88); P=0.004
  - Difference in pCR rate = 13.0% (95% CI: 8.7–17.6); P<0.001*

12 mo median follow-up

- Benefit in EFS was achieved at the first planned interim analysis, when ~23% of patients were still receiving adjuvant Tx
- Here, we present updated EFS and other results from the second planned interim analysis, based on 25.9 months median follow-up (censored patients) and 39.1% maturity

24 mo median follow-up

[1]Heymach JV, et al. *N Engl J Med* 2023;389:1672–84.

Baseline disease characteristics and planned treatment (mITT)

- Baseline characteristics were largely balanced between arms in the mITT population
  - The resected subpopulation for DFS analysis, which had R0/R1 margins and no evidence of progression in their first post-surgery scan,‡ had baseline characteristics broadly similar to the overall mITT population
- The planned neoadjuvant CT doublet was carboplatin-based for >70% of patients

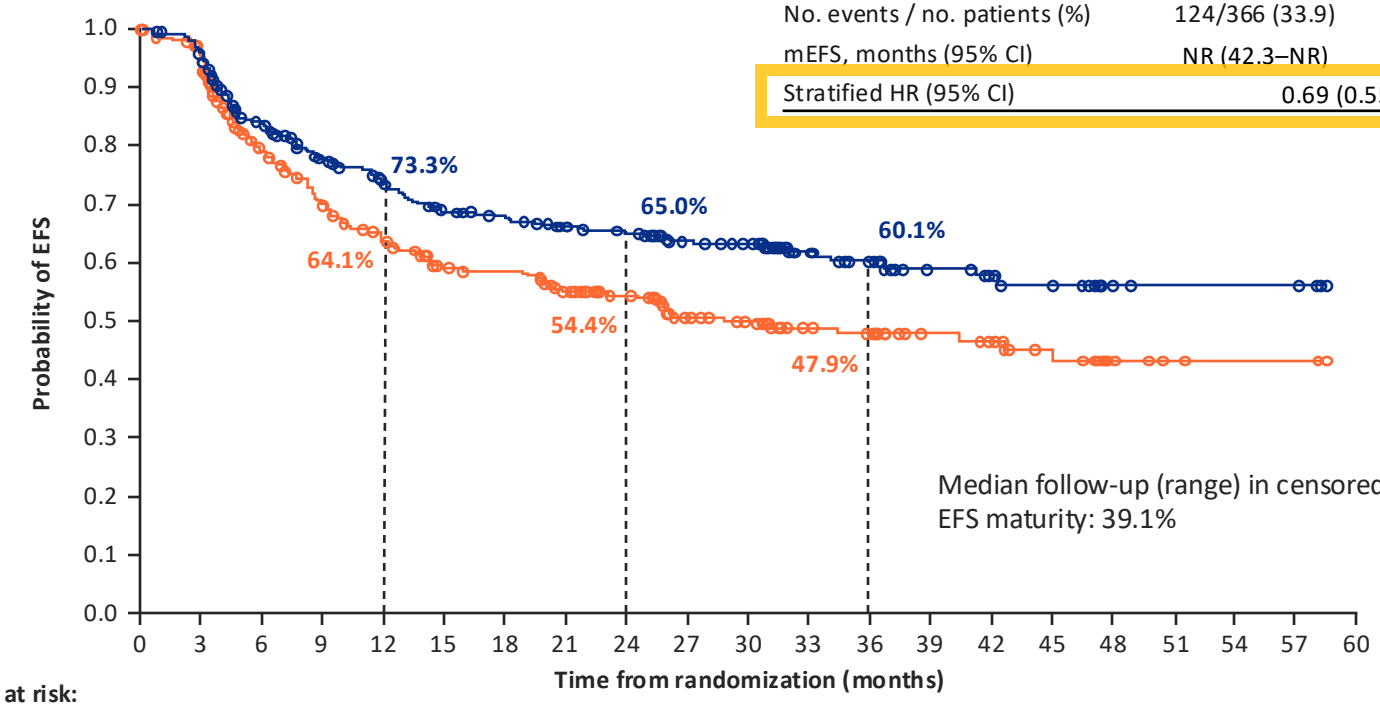
Characteristics		mITT population*[1] D arm (N=366)	mITT population*[1] PBO arm (N=374)
Age	Median (range), years	65.0 (30–88)	65.0 (39–85)
	≥75 years, %	12.0	9.6
Sex, %	Male	68.9	74.3
ECOG PS, %	0	68.6	68.2
	1	31.4	31.8
Race†, %	Asian	39.1	43.9
	White	56.3	51.1
	Other	4.6	5.1
Region, %	Asia	38.8	43.6
	Europe	38.5	37.4
	North America	11.7	11.5
	South America	10.9	7.5
Smoking status, %	Current	26.0	25.4
	Former	60.1	59.6
	Never	13.9	15.0
Disease stage (AJCC 8th ed.), %	II	28.4	29.4
	IIIA	47.3	44.1
	IIIB	24.0	26.2
Histology, %	Squamous	46.2	51.1
	Non-squamous	53.6	47.9
PD-L1 expression, %	TC <1%	33.3	33.4
	TC 1–49%	36.9	38.0
	TC ≥50%	29.8	28.6
Planned neoadjuvant platinum agent, %	Cisplatin	27.3	25.7
	Carboplatin	72.7	74.3

[1]Heymach JV, et al. *N Engl J Med* 2023;389:1672–84.

Updated EFS (second planned interim analysis; mITT)

- EFS benefit favoring the durvalumab arm was maintained and consistent with that reported previously[1]

	D arm	PBO arm
No. events / no. patients (%)	124/366 (33.9)	165/374 (44.1)
mEFS, months (95% CI)	NR (42.3–NR)	30.0 (20.6–NR)
Stratified HR (95% CI)	0.69 (0.55–0.88)	



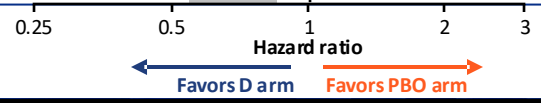
Median follow-up (range) in censored patients: 25.9 (0.0–58.6) months
EFS maturity: 39.1%

No. at risk:																					
D arm	366	337	276	240	219	201	194	179	172	128	121	76	67	48	36	29	6	4	4	4	0
PBO arm	374	338	261	225	201	176	172	151	142	93	83	57	53	36	32	25	8	3	2	2	0

Updated EFS by subgroup (mITT)

- EFS benefit was maintained across predefined subgroups

Subgroup		n	Median EFS, months (95% CI) D arm (N=366)	Median EFS, months (95% CI) PBO arm (N=374)	HR (95% CI)
All patients		740	NR (42.3–NR)	30.0 (20.6–NR)	0.69 (0.55–0.88)
Age at randomization	<65 years	358	NR (NR–NR)	34.4 (19.8–NR)	0.69 (0.48–0.97)
	≥65 years	382	NR (31.9–NR)	25.9 (15.1–NR)	0.71 (0.52–0.97)
Sex	Male	530	NR (41.2–NR)	25.9 (19.8–NR)	0.66 (0.50–0.88)
	Female	210	NR (33.2–NR)	40.4 (15.1–NR)	0.80 (0.52–1.23)
ECOG PS	0	506	NR (42.3–NR)	31.1 (19.5–NR)	0.66 (0.50–0.88)
	1	234	NR (21.8–NR)	28.6 (18.9–NR)	0.79 (0.52–1.20)
Race*	Asian	307	NR (42.3–NR)	25.9 (19.5–NR)	0.66 (0.45–0.95)
	Non-Asian	433	NR (33.2–NR)	31.1 (15.7–NR)	0.73 (0.54–0.99)
Smoking	Current	190	NR (33.2–NR)	20.4 (8.1–NR)	0.52 (0.32–0.82)
	Former	443	NR (41.2–NR)	30.0 (20.7–NR)	0.75 (0.56–1.02)
	Never	107	NR (13.0–NR)	34.4 (14.7–NR)	0.88 (0.47–1.61)
Histology	Squamous	360	NR (41.2–NR)	40.4 (15.1–NR)	0.70 (0.49–0.98)
	Non-squamous	375	NR (36.6–NR)	28.6 (19.8–NR)	0.73 (0.53–1.00)
Disease stage (AJCC 8th ed.)	Stage II	214	NR (41.2–NR)	NR (34.4–NR)	0.82 (0.49–1.34)
	Stage IIIA	338	NR (42.3–NR)	25.8 (11.7–45.0)	0.60 (0.42–0.84)
	Stage IIIB	186	36.6 (12.7–NR)	19.8 (11.7–42.6)	0.81 (0.53–1.23)
Lymph node station	N2 single	273	NR (NR–NR)	22.8 (13.9–42.6)	0.58 (0.39–0.85)
	N2 multi	74	31.9 (9.3–NR)	12.2 (7.2–NR)	0.78 (0.40–1.49)
PD-L1 expression at baseline†	TC <1%	247	NR (24.7–NR)	20.6 (14.3–NR)	0.69 (0.46–1.02)
	TC 1–49%	277	NR (31.9–NR)	25.9 (12.3–NR)	0.73 (0.50–1.05)
	TC ≥50%	216	NR (41.2–NR)	NR (24.5–NR)	0.71 (0.44–1.12)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR–NR)	45.0 (13.9–NR)	0.58 (0.35–0.93)
	Carboplatin	544	NR (36.6–NR)	26.2 (20.6–NR)	0.75 (0.57–0.97)

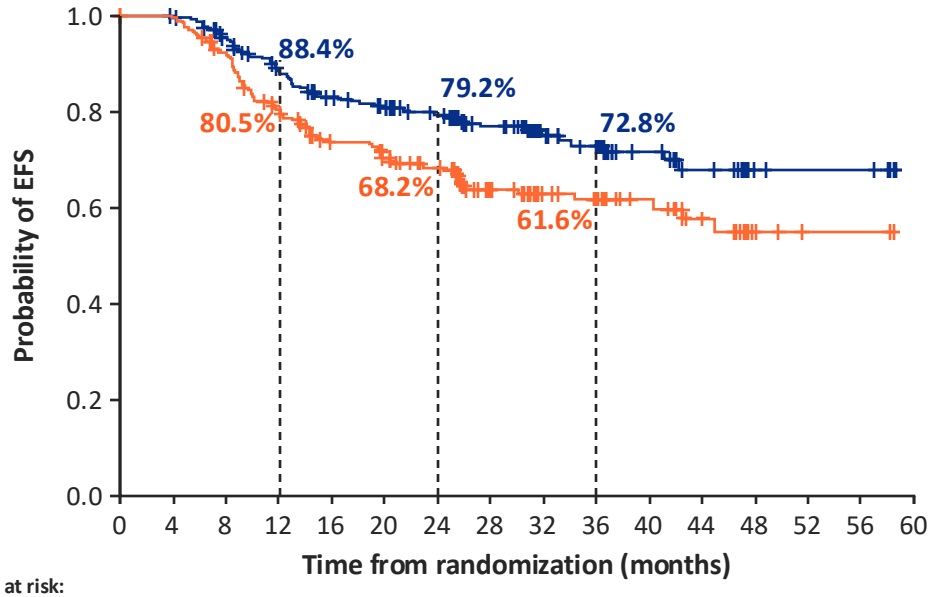


EFS by adjuvant treatment status (exploratory analysis, mITT)

- EFS benefit in the durvalumab arm was more pronounced in patients who received adjuvant treatment

Received adjuvant treatment

	D arm	PBO arm
No. events / no. patients (%)	58/242 (24.0)	83/237 (35.0)
mEFS, months (95% CI)	NR (NR–NR)	NR (42.6–NR)
Unstratified HR (95% CI)	0.62 (0.44–0.86)	

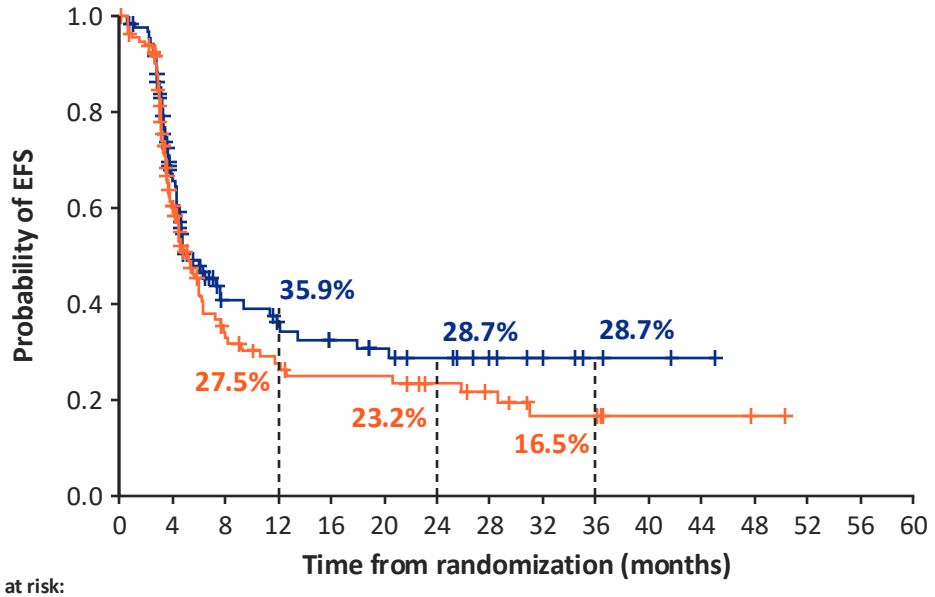


No. at risk:

D arm	242	239	222	198	181	173	159	118	73	64	46	29	6	4	4	0
PBO arm	237	234	212	181	155	145	129	77	53	47	33	24	7	2	2	0

Did not receive adjuvant treatment

	D arm	PBO arm
No. events / no. patients (%)	66/124 (53.2)	82/137 (59.9)
mEFS, months (95% CI)	5.1 (4.5–9.3)	5.2 (4.1–6.3)
Unstratified HR (95% CI)	0.83 (0.60–1.14)	

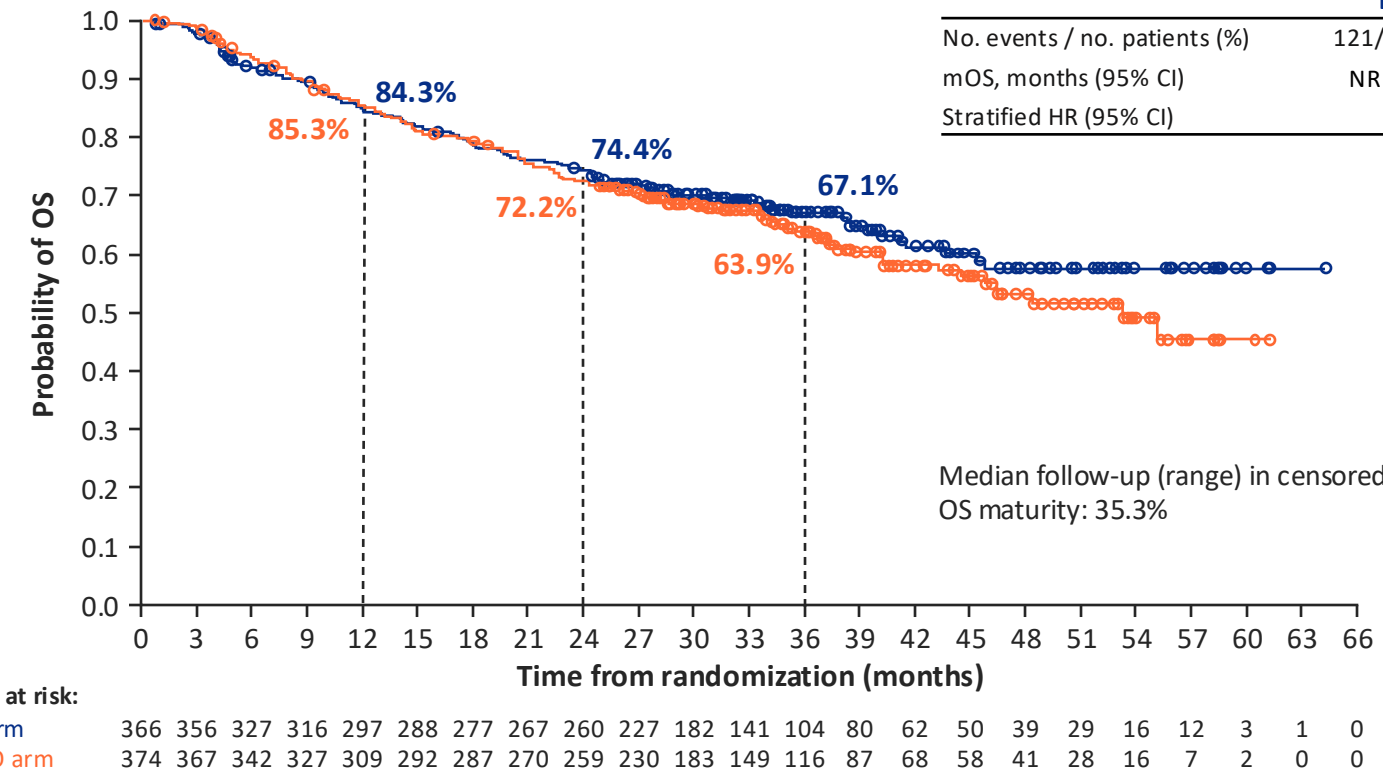


No. at risk:

D arm	124	62	26	21	18	16	13	8	5	3	2	1	0	0	0	0
PBO arm	137	62	26	20	17	17	13	10	6	6	3	3	1	0	0	0

OS (mITT)

- Based on 35% maturity, an OS trend favoring the durvalumab arm was observed



	D arm	PBO arm
No. events / no. patients (%)	121/366 (33.1)	140/374 (37.4)
mOS, months (95% CI)	NR (NR–NR)	53.2 (44.3–NR)
Stratified HR (95% CI)	0.89 (0.70–1.14)	

Median follow-up (range) in censored patients: 33.6 (0.7–64.3) months
OS maturity: 35.3%

- Preplanned analysis censoring patients with cause of death due to COVID-19: OS HR = 0.84 (95% CI: 0.66–1.08)

Conclusions

- EFS benefit in favor of the durvalumab arm remained consistent with that reported previously[1]
  - **Updated EFS HR = 0.69 (95% CI: 0.55–0.88)**
  - EFS benefit was maintained across predefined subgroups, including within the planned neoadjuvant platinum subgroups
  - In separate exploratory analyses, EFS benefit in the durvalumab arm was more pronounced in patients who received adjuvant treatment and favored the durvalumab arm regardless of pCR status
- Clinically meaningful DFS improvement and an OS trend favoring the durvalumab arm were observed
  - In separate exploratory analyses, the magnitude of DFS benefit with durvalumab was larger in patients with pCR and improvement in lung cancer-specific survival also favored the durvalumab arm
- Perioperative durvalumab + neoadjuvant CT was associated with a manageable AE profile, with no new safety signals observed at this update

These findings, with additional follow-up, further support FDA-approved perioperative durvalumab as a new treatment option for patients with R-NSCLC

Resection After IO or Targeted Therapies: How Hard Is It?

Mara B. Antonoff, MD
UT MD Anderson Cancer Center
USA

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Role of Neoadjuvant Therapy: Historical

- Recommended for patients with
  - T3 or T4 tumors
  - IIIA-N2 disease
  - Superior sulcus tumors
- Agents
  - Platinum-based doublets +/- radiation
- *More recent:*
  - *Anti PD-1 and PDL-1 immunotherapies*
  - *Ongoing trials: targeted therapies*

	IA + small IB: SURGERY alone	II + non-N2 IIIA: SURGERY + adjuvant chemo	N2-IIIA: Neoadj + surgery + PORT	IIIB/C: definitive CXRT
	N0	N1	N2	N3
T1	IA	IIA	IIIA	IIIB
T2a/b	IB / IIA	IIA/IIB	IIIA	IIIB
T3	IIB	IIIA	IIIA	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1	IV	IV	IV	IV
	chemotherapy			

NSCLC treatment – Now

	IA	IB-IIIA		Unresectable IIIB–IIIC
	SURGERY – extend depends on size and location	*Neoadjuvant IO ± chemo + SURGERY ± adjuvant IO/targeted tx/chemo ± XRT*		*ChemoXRT ± IO ± targeted tx*
	N0	N1	N2	N3
T1	IA	IIA	IIIA	IIIB
T2a/b	IB / IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1	IV	IV	IV	IV

Chemo, IO, targeted tx ± LCT via SURGERY and/or XRT

NCCN guidelines for NSCLC v5.2024; Postmus PE, et al. *Ann Oncol.* 2017;28(suppl 4):iv1–21; Remon J, et al. *Ann Oncol.* 2021;32(12):1637–1642.

Oncologic & Post-Op Outcomes of Surgery

- **R0 resection:** *Similar or better after chemo-IO than chemo alone*
  - AEGEAN, durva + chemo→ 95% R0
  - KEYNOTE-671, pembrolizumab + chemo → 92% R0
  - CheckMate 816, nivolumab + chemo → 83% R0

- **Surgical complications:** *Similar or better after chemo-IO than chemo alone*
  - KEYNOTE-671:
    - 90-day mortality[a]: 4.0% vs 1.6% (chemo-IO vs chemo alone)
  - CheckMate 816:
    - Surgery-related AEs: 42% vs 47%; Grade 3/4: 11% vs 15% (chemo-IO vs chemo alone)
    - 90-day mortality[a]: 3.4% vs 1.5% (chemo-IO vs chemo alone)

Spicer JD, et al. Presented at STS 2024; Dunne et al, Ann Thorac Surg 2024; Heymach JV et al, N Eng J Med 2024; Forde PM, et al, N Engl J Med. 2022

Impact of IO on Operative Conduct

- Bott et al, neoadjuvant nivolumab in resectable I-IIIA NSCLC
  - 20 patients underwent surgery 1 after 2 cycles of IO
  - 15 lobectomy, 1 bilobe, 2 pneumonectomy, 1 sleeve, 1 wedge
  - 1/3 started open, and **over ½ of minimally invasive cases required conversion due to hilar inflammation/fibrosis**
- Sepesi et al, Neostar
  - Surgeons judged **40% of operations to be more complex than usual**
  - 19% lasted > 4 hours

Bott MJ et al, J Thorac Cardiovasc Surg 2019; Sepesi et al, IASLC WCLC 2019

Neoadjuvant Impact on cN1 Challenges

Intraoperative challenges after induction therapy for non–small cell lung cancer: Effect of nodal disease on technical complexity

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	Neoadjuvant Treatment (38) N (%)	Up Front Surgery (41) N (%)	*P*
Node unable to be removed from PA	6 (15.8)	2 (4.8)	0.145
Node stuck to PA causing tear	1 (2.6)	1 (2.4)	1.000
Node forces change in approach to vasculature	8 (21.0)	3 (7.3)	0.107
Intrapericardial PA control due to node	4 (10.5)	0	**0.049**
Proximal PA control due to lymph node	8 (21.0)	2 (4.9)	**0.043**
Extent of surgery changed due to node	2 (5.2)	2 (4.9)	1.000
Arterioplasty/sleeve due to lymph node	7 (18.4)	0	**0.004**

Feldman HA et al, JTCVS Open 2022

Surgical Complexity after Targeted Therapy

- Evaluation of NORTHSTAR and BRIGHTSTAR
- Aim: to characterize intraoperative nuances of pulmonary resection in stage IV NSCLC following treatment with targeted therapy in patients with oligo- and polymetastatic disease
- Patients identified who underwent lung resection from 2 prospective trials of LCT (surgery and/or radiation) after targeted therapy (N = 21)
- All operations took place from 06/2018-04/2022
- Intraoperative findings of complexity were systematically collected immediately postoperatively in 4 domains using 4-point scales

Overall global case complexity	• 1: Easier than normal dissection • 2: Normal tissue planes, e.g. typical stage I upfront resection • 3: Moderate difficulty in dissection • 4: Severe difficulty in dissection
Severity of adhesions	• 1: None • 2: Minimal • 3: Moderate • 4: Severe
Difficulty of mediastinal nodal dissection	• 1: Easier than normal • 2: Normal dissection • 3: Moderately more difficult dissection • 4: Severely more difficult nodal dissection
Difficulty of hilar vascular dissection	• 1: Easier than normal • 2: Normal dissection • 3: Moderately more difficult dissection • 4: Severely more difficult hilar dissection

Antonoff M, et al NACLC 2022

Surgical Complexity after Targeted Therapy

- Mean OR time (255 min) and EBL (200 mL) were typical; 1 (4.8%) patient needing PRBCs
- 0 operative mortalities, 0 ICU admissions, median chest tube duration typical at 2.48 days
- **Procedures were minimally invasive in 2 (9.5%)**
  - 17 (81.0%) lobectomies
  - 2 (9.5%) wedges
  - 2 (9.5%) segmentectomies
- **Surgeons reported cases as severely difficult in 16 (76.2%)**
- **Adhesions were reported as severe in 6 cases (28.6%)**
- **Mediastinal nodal dissection was severely impacted in 11 (52.4%)**
- **Severe hilar fibrosis complicated the vascular dissection in 17 (81.0%)**
- These challenges led to ***frequent need for advanced maneuvers***:
  - Chest wall resection, 23.8%
  - Change in surgical approach, 4.8%
  - Proximal PA control, 4.8%
  - Extended resection, 4.8%

Surgery is more difficult after neoadj tx of any kind, whether chemo, IO, or targeted tx!

Antonoff M, et al NACLC 2022

Oncologic & Post-Op Outcomes of Surgery

Baylor College of Medicine
Hanley Center — Help becomes hope.
Mayo Clinic
Origins Behavioral Healthcare
Beth Israel Deaconess Medical Center
Hospital for Special Surgery
The University of Texas MD Anderson Cancer Center
UCLA Health
caron — Comprehensive Addiction Treatment, Recovery For Life
Johns Hopkins Medicine
Memorial Sloan Kettering Cancer Center
UCSF Medical Center
Cleveland Clinic
Joslin Diabetes Center
National Jewish Health
UHealth — University of Miami Health System
University of Miami Miller School of Medicine

Feasibility does not equate to "easibility" or generalizability!

Summary

Multimodality options rapidly expanding

- Pathologic endpoints are pivotal in assessing efficacy
- Huge potential impact on patient experience

Surgeons need to step it up!

- Implications for case complexity
- Nuances for planning, informed consent, and resident training