Improving Neoadjuvant Strategies

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Disclosure Information

Employment:

Chair of Medical Oncology Department at Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain.
Full Professor of Medicine at Universidad Autónoma de Madrid, Spain.

Research Grants:

AstraZeneca, Roche, Bristol Myers Squibb, Boehringer-Ingelheim, Takeda.

Consultant or Advisory:

AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Celgene, Merck Sharp & Dohme, Roche, Takeda, Thermo-Fisher, Janssen, Amgen.

Stock Ownership:

None.

Improving Neoadjuvant Strategies: Key Directions

- Rational therapeutic combinations.
- Biomarker-guided optimization.
- Early monitoring and adaptive response.
- Innovative trial designs.
- Patient optimization.
- New advanced topics.

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Improving Neoadjuvant Strategies

How to improve pathological Complete Response (pCR) in the neoadjuvant setting?

Is it important to achieve pCR?

Rational combinations and Biomarker-Guided Personalization

Sci Rep. 2020 Apr 27;10(1):7078. doi: 10.1038/s41598-020-63796-w.

Effects of anti-PD-1 immunotherapy on tumor regression: insights from a patient-derived xenograft model

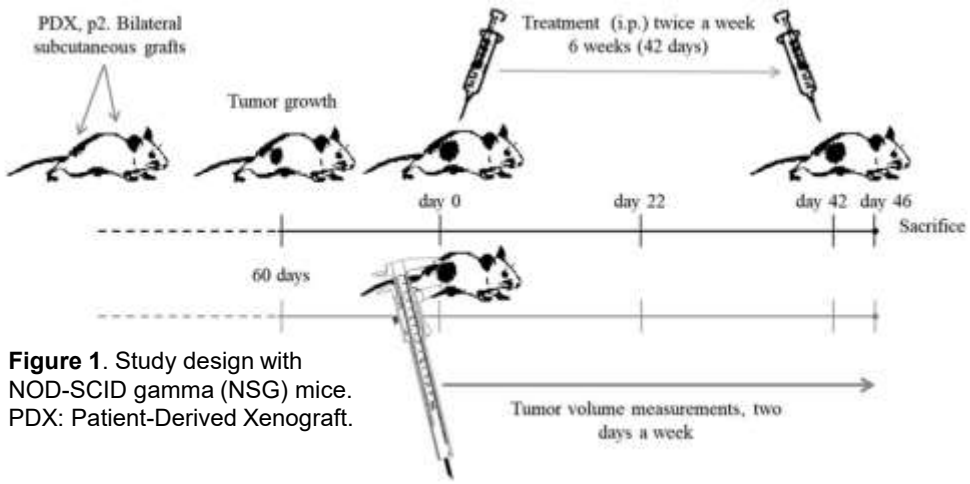


Figure 1. Study design with NOD-SCID gamma (NSG) mice. PDX: Patient-Derived Xenograft.

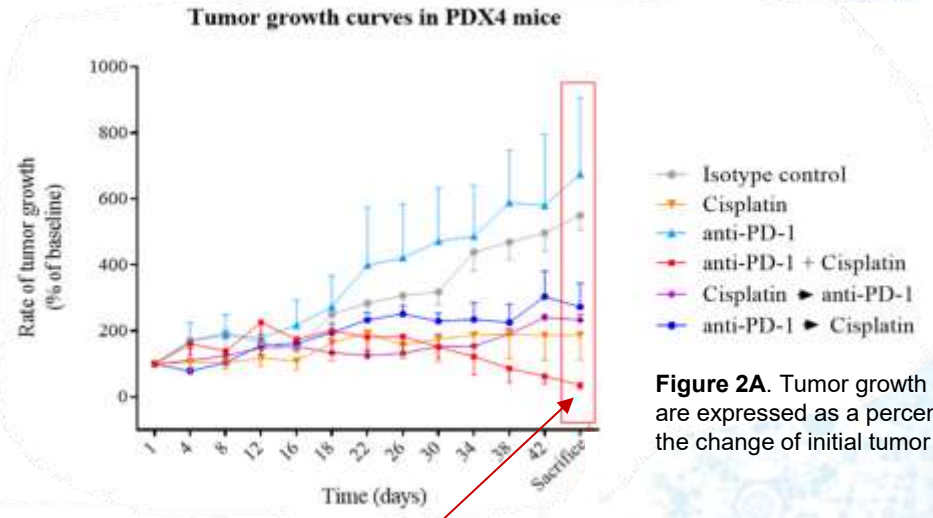


Figure 2A. Tumor growth curves are expressed as a percentage of the change of initial tumor volume.

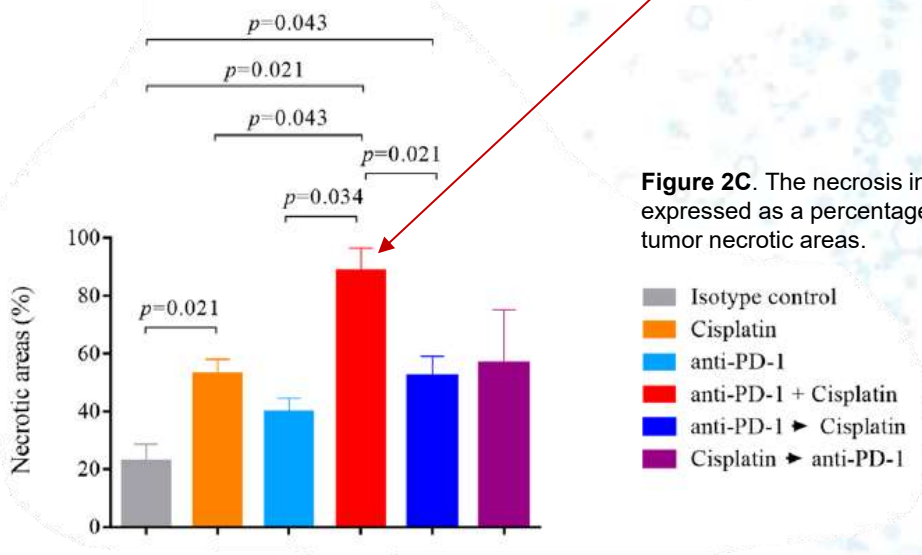


Figure 2C. The necrosis index is expressed as a percentage of tumor necrotic areas.

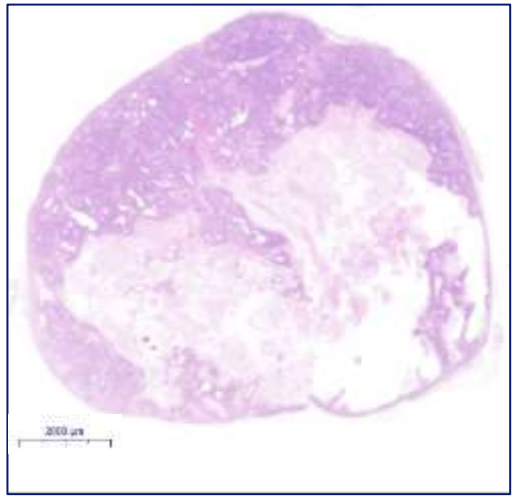
Rational combinations and Biomarker-Guided Personalization

Sci Rep. 2020 Apr 27;10(1):7078. doi: 10.1038/s41598-020-63796-w.

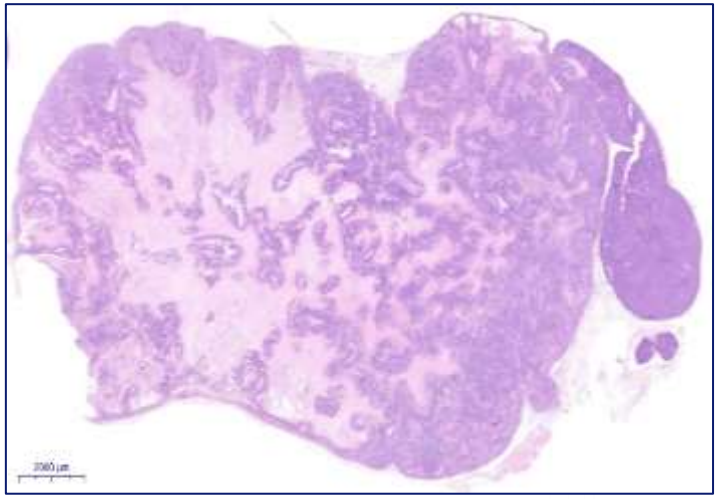
Effects of anti-PD-1 immunotherapy on tumor regression: insights from a patient-derived xenograft model

Resultados
Áreas necróticas

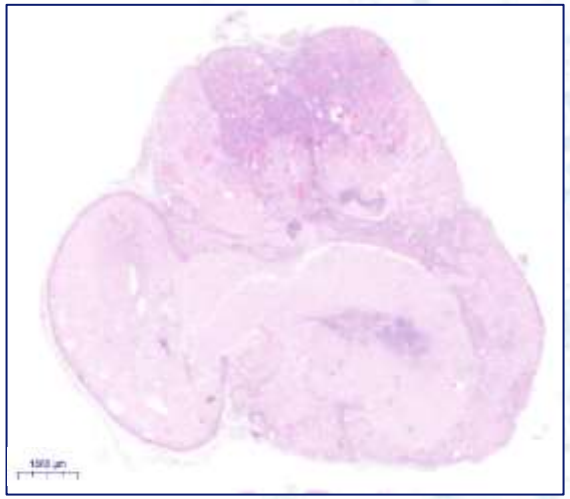
Respuesta a inmunoterapia en modelo PDX de carcinoma escamoso de pulmón. PDX4.



Cisplatino
53% necrosis

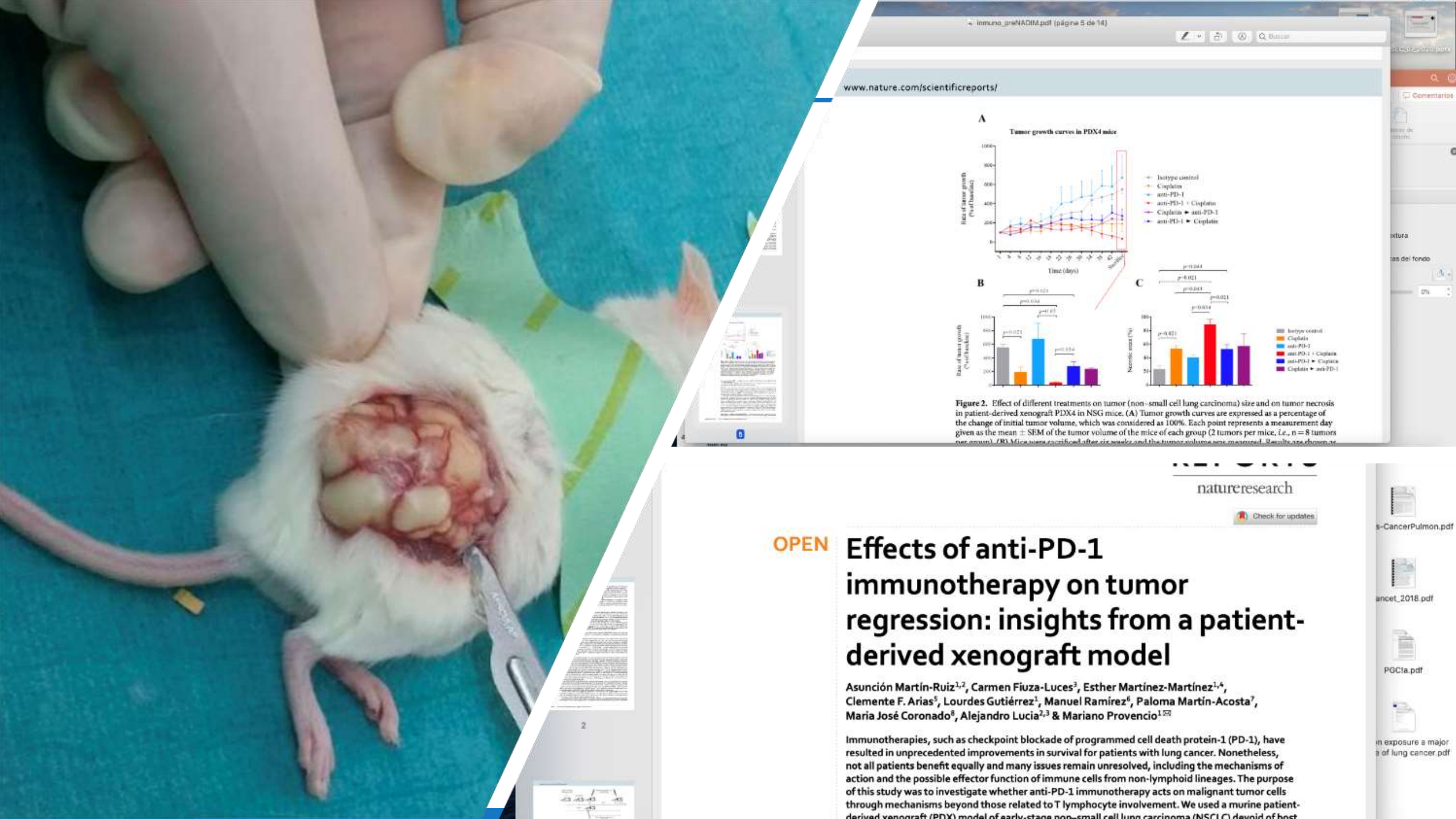


Nivolumab
40% necrosis



Cisplatino + Nivolumab (conco)
89% necrosis

Martín-Ruiz A. et. al., Sci Rep, 2020.



immuno_preNADIM.pdf (página 5 de 14)

www.nature.com/scientificreports/

Figure 2. Effect of different treatments on tumor (non–small cell lung carcinoma) size and on tumor necrosis in patient-derived xenograft PDX4 in NSG mice. (**A**) Tumor growth curves are expressed as a percentage of the change of initial tumor volume, which was considered as 100%. Each point represents a measurement day given as the mean ± SEM of the tumor volume of the mice of each group (2 tumors per mice, *i.e.*, n = 8 tumors per group). (**B**) Mice were sacrificed after six weeks and the tumor volume was measured. Results are shown as

nature research

Check for updates

OPEN

Effects of anti-PD-1 immunotherapy on tumor regression: insights from a patient-derived xenograft model

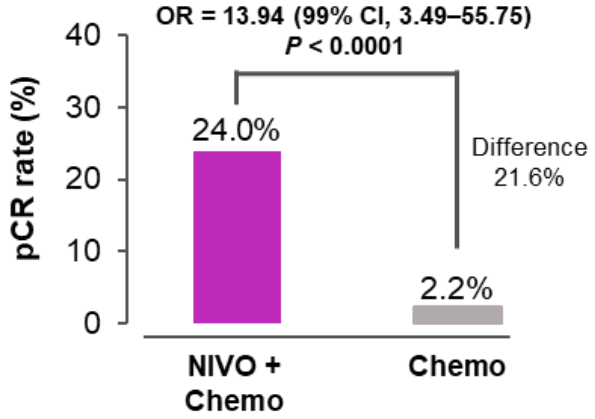
Asunción Martín-Ruiz[1,2], Carmen Fiuza-Luces[3], Esther Martínez-Martínez[1,4], Clemente F. Arias[5], Lourdes Gutiérrez[1], Manuel Ramírez[6], Paloma Martín-Acosta[7], María José Coronado[8], Alejandro Lucia[2,3] & Mariano Provencio[1]✉

Immunotherapies, such as checkpoint blockade of programmed cell death protein-1 (PD-1), have resulted in unprecedented improvements in survival for patients with lung cancer. Nonetheless, not all patients benefit equally and many issues remain unresolved, including the mechanisms of action and the possible effector function of immune cells from non-lymphoid lineages. The purpose of this study was to investigate whether anti-PD-1 immunotherapy acts on malignant tumor cells through mechanisms beyond those related to T lymphocyte involvement. We used a murine patient-derived xenograft (PDX) model of early-stage non–small cell lung carcinoma (NSCLC) devoid of host

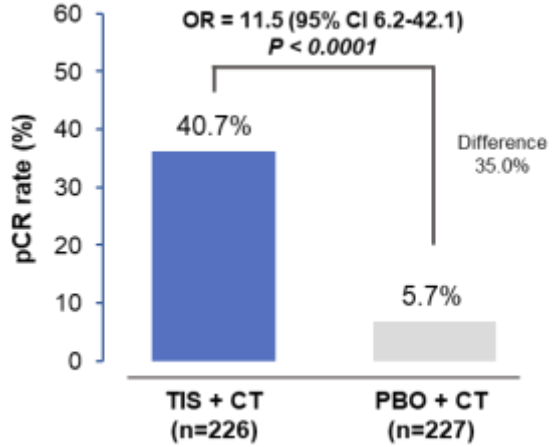
s-CancerPulmon.pdf
ancet_2018.pdf
PGC1a.pdf
n exposure a major
of lung cancer.pdf

Pathological Complete Response (pCR)

CheckMate 816

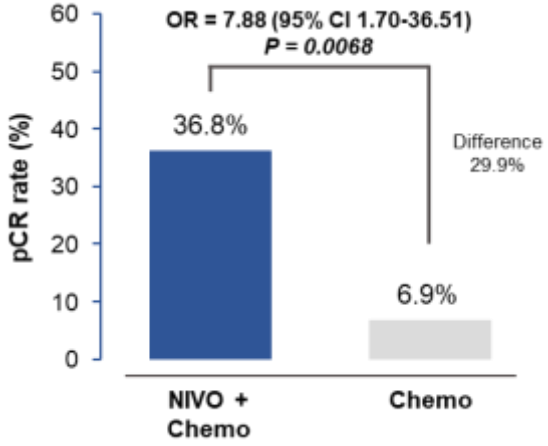


Rationale 315

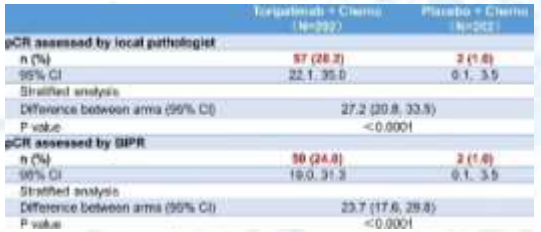


NADIM II
Primary endpoint-pCR

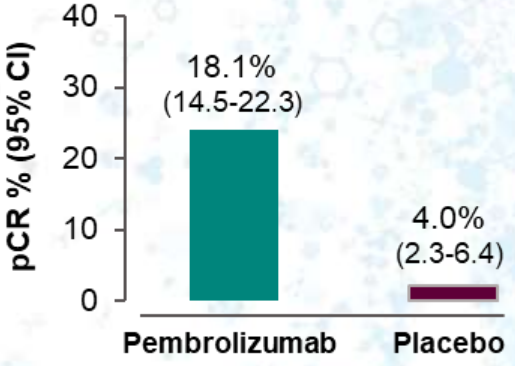
pCR rate in the ITT population



AEGEAN



	Toripalimab + Chemo (N=292)	Placebo + Chemo (N=202)
pCR assessed by local pathologist		
n (%)	57 (20.2)	2 (1.0)
95% CI	22.1, 35.0	0.1, 3.5
Stratified analysis		
Difference between arms (95% CI)	27.2 (20.8, 33.5)	
P value	<0.0001	
pCR assessed by GIPR		
n (%)	50 (24.8)	2 (1.0)
95% CI	19.0, 31.3	0.1, 3.5
Stratified analysis		
Difference between arms (95% CI)	23.7 (17.6, 29.8)	
P value	<0.0001	



Pathological Response

Nat Med. 2024 Jan;30(1):218-228. doi: 10.1038/s41591-023-02660-6. Epub 2023 Oct 30.

Association between pathologic response and survival after neoadjuvant therapy in lung cancer

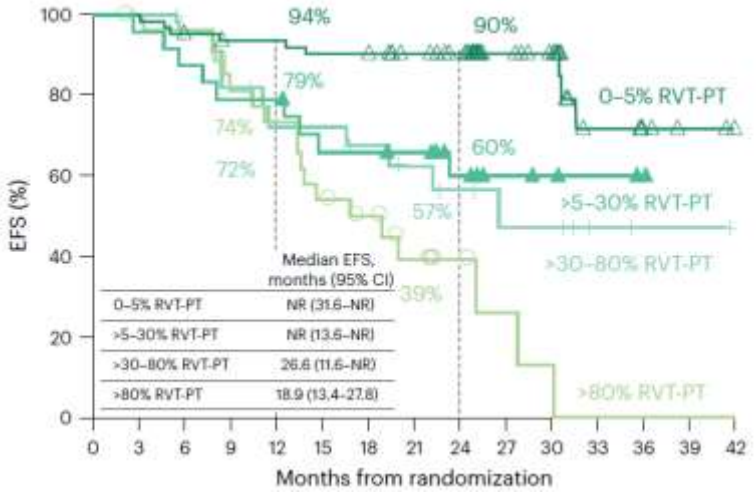
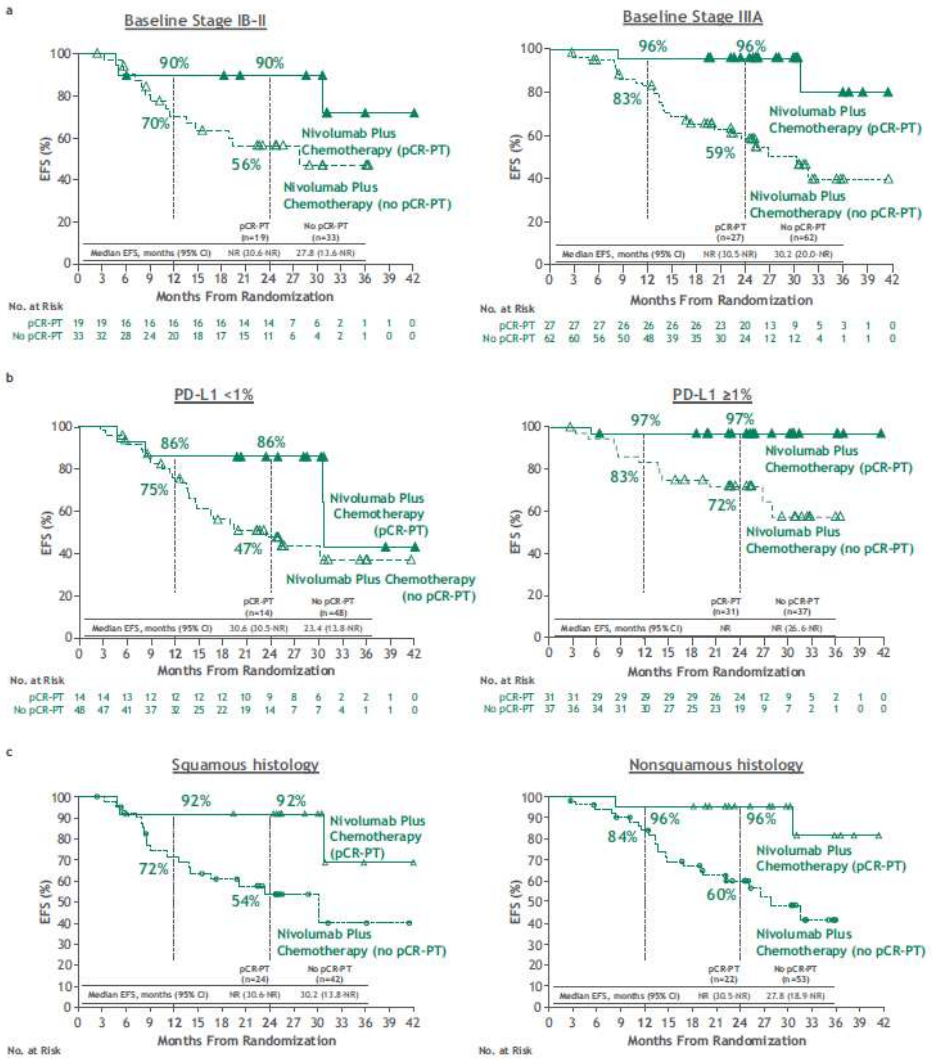


Figure 1. Kaplan-Meier curves of EFS by %RVT-PT categories for patients treated with nivolumab plus chemotherapy.



Extended Fig 2. Kaplan-Meier curves of EFS by pCR status and disease characteristics in the patient population from the nivolumab plus chemotherapy arm.

Pathological Response

Clinical Trial > Lancet Oncol. 2024 Nov;25(11):1453-1464. doi: 10.1016/S1470-2045(24)00498-4.
Epub 2024 Oct 14.

Perioperative chemotherapy and nivolumab in non-small-cell lung cancer (NADIM): 5-year clinical outcomes from a multicentre, single-arm, phase 2 trial

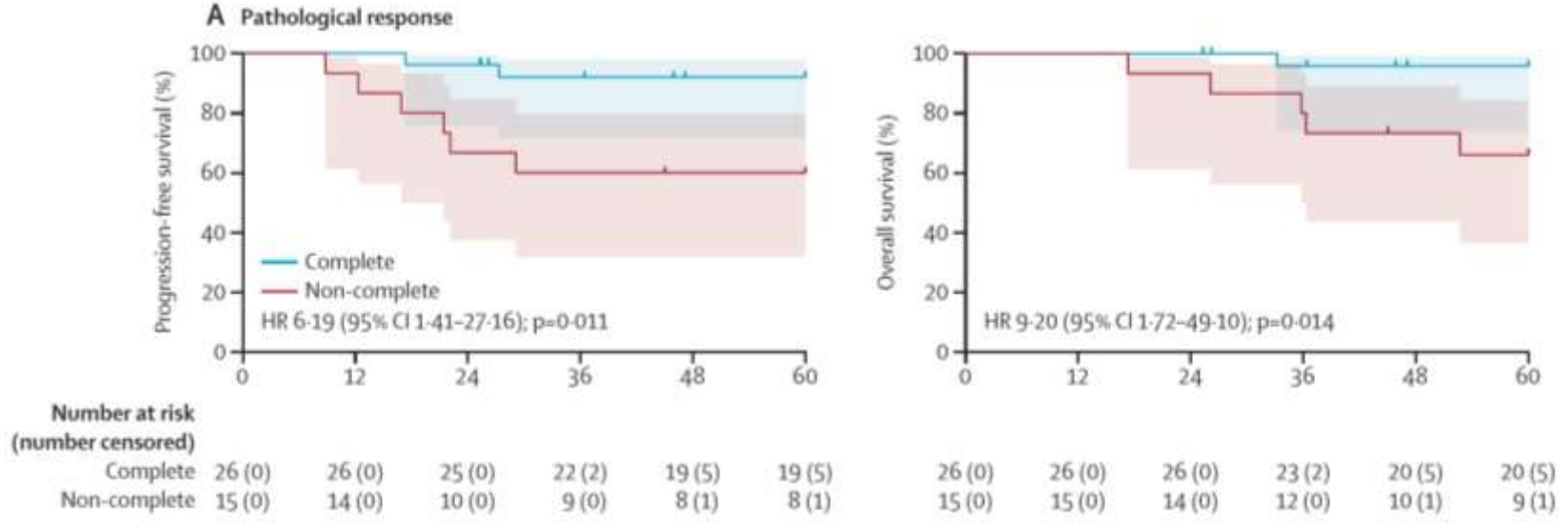


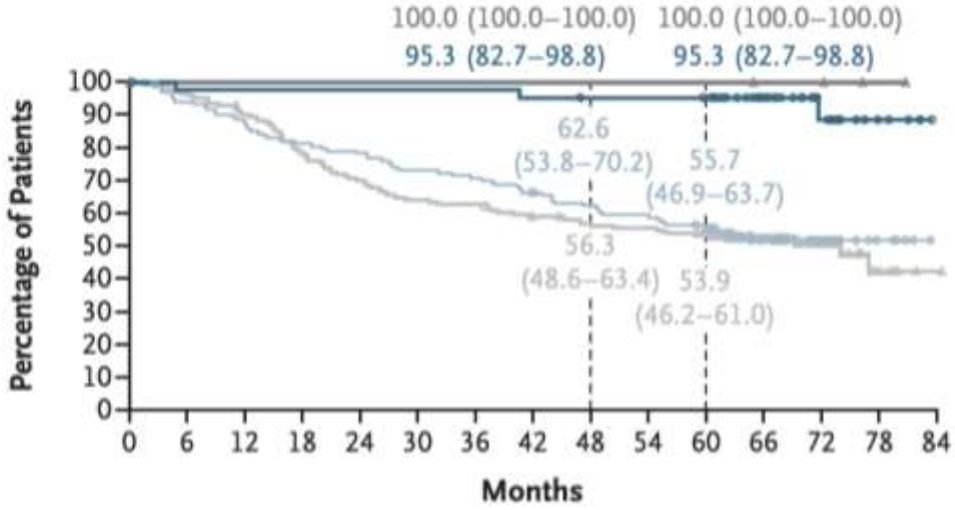
Figure 3. Post-hoc survival analyses by pathological response and adjuvant treatment adherence. Progression-free survival and overall survival Kaplan-Meier curves of patients who underwent tumor resection who had a complete pathological response versus those with a major or incomplete pathological response.

Provencio M. et. al., Lancet Oncol, 2024.

Pathological Complete Response (pCR)

Can patients be **cured** with only 3 cycles of chemo-immunotherapy followed by surgery?

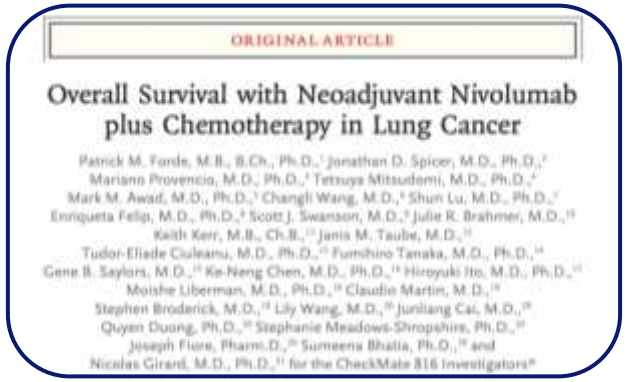
A Overall Survival in Patients with or without a Pathological Complete Response (pCR)



	Median Overall Survival (95% CI) *mo*
Nivolumab+Chemotherapy	
pCR (N=43)	NR (NR–NR)
No pCR (N=136)	NR (53.9–NR)
Hazard ratio for death, 0.11 (0.04–0.36)	
Chemotherapy Alone	
pCR (N=4)	NR (NR–NR)
No pCR (N=175)	73.7 (46.7–NR)

No. at Risk

Pathological complete response															
Nivolumab+chemotherapy	43	42	42	42	42	42	42	41	40	40	39	25	13	4	0
Chemotherapy alone	4	4	4	4	4	4	4	4	4	4	4	3	3	1	0
No pathological complete response															
Nivolumab+chemotherapy	136	126	117	109	105	98	95	88	82	77	72	42	16	5	0
Chemotherapy alone	175	166	155	135	120	110	108	100	94	93	87	55	26	5	1



ORIGINAL ARTICLE

Overall Survival with Neoadjuvant Nivolumab plus Chemotherapy in Lung Cancer

Patrick M. Forde, M.B., B.Ch., Ph.D.,[1] Jonathan D. Spicer, M.D., Ph.D.,[2] Mariano Provencio, M.D., Ph.D.,[3] Tetsuya Mitsudomi, M.D., Ph.D.,[4] Mark M. Awad, M.D., Ph.D.,[5] Changli Wang, M.D.,[6] Shun Lu, M.D., Ph.D.,[7] Enriqueta Felip, M.D., Ph.D.,[8] Scott J. Swanson, M.D.,[9] Julie R. Brahmer, M.D.,[10] Keith Kerr, M.B., Ch.B.,[11] Janis M. Taube, M.D.,[12] Tudor-Eliade Ciuleanu, M.D., Ph.D.,[13] Fumihiro Tanaka, M.D., Ph.D.,[14] Gene B. Saylors, M.D.,[15] Ke-Neng Chen, M.D., Ph.D.,[16] Hiroyuki Ito, M.D., Ph.D.,[17] Moishe Liberman, M.D., Ph.D.,[18] Claudie Martin, M.D.,[19] Stephen Broderick, M.D.,[20] Lily Wang, M.D.,[20] Junliang Cai, M.D.,[20] Quyen Duong, Ph.D.,[20] Stephanie Meadows-Shropshire, Ph.D.,[20] Joseph Fiore, Pharm.D.,[20] Sumeena Bhatia, Ph.D.,[20] and Nicolas Girard, M.D., Ph.D.,[21] for the CheckMate 816 Investigators*

Forde P.M. et. al., N Engl J Med, 2025.

Improving Neoadjuvant Strategies

Do we select the population better to have more complete answers, or do we try to get more complete answers from everyone?

Rational combinations and Biomarker-Guided Personalization

Clinical Trial > Lancet Oncol. 2020 Nov;21(11):1413-1422. doi: 10.1016/S1470-2045(20)30453-8.
Epub 2020 Sep 24.

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

PD-L1: CRP showed higher PD-L1 TPS.
TMB: No associated to pResponse.

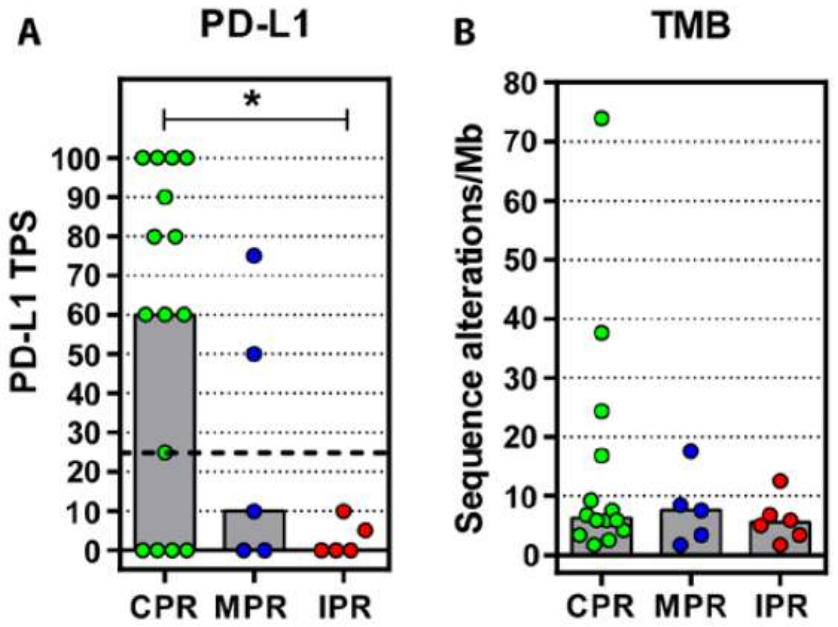


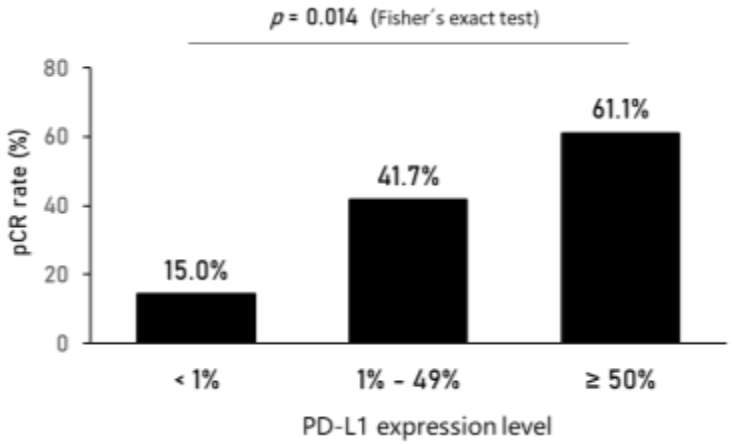
Figure S4. PD-L1, TMB and specific mutations versus pathologic response and PFS. *CPR, complete pathologic response; MPR, major pathologic response; IPR, incomplete pathologic response. TPS: tumor proportion score.*

Rational combinations and Biomarker-Guided Personalization

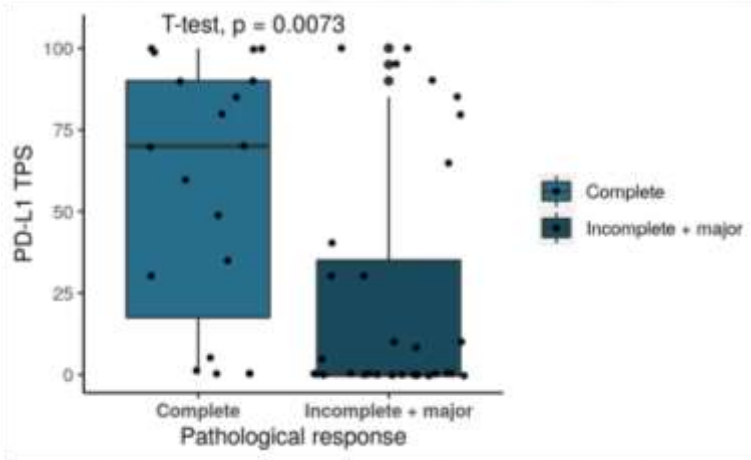
Meeting Abstract: 2022 ASCO Annual Meeting I
FREE ACCESS | Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers | June 02, 2022

Nivolumab + chemotherapy versus chemotherapy as neoadjuvant treatment for resectable stage IIIA NSCLC: Primary endpoint results of pathological complete response (pCR) from phase II NADIM II trial.

PD-L1



The pCR rate rises across increasing categories of PD-L1 TPS.



Patients with pCR had higher PD-L1 TPS compared to non-responders.

Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022).
DOI: 10.1200/JCO.2022.40.16_suppl.8501

Improving Neoadjuvant Strategies

More drugs that increase response?

Rational combinations and Biomarker-Guided Personalization

Clinical Trial > J Clin Oncol. 2025 Apr 20;43(12):1453-1462. doi: 10.1200/JCO-24-02239.
Epub 2025 Jan 8.

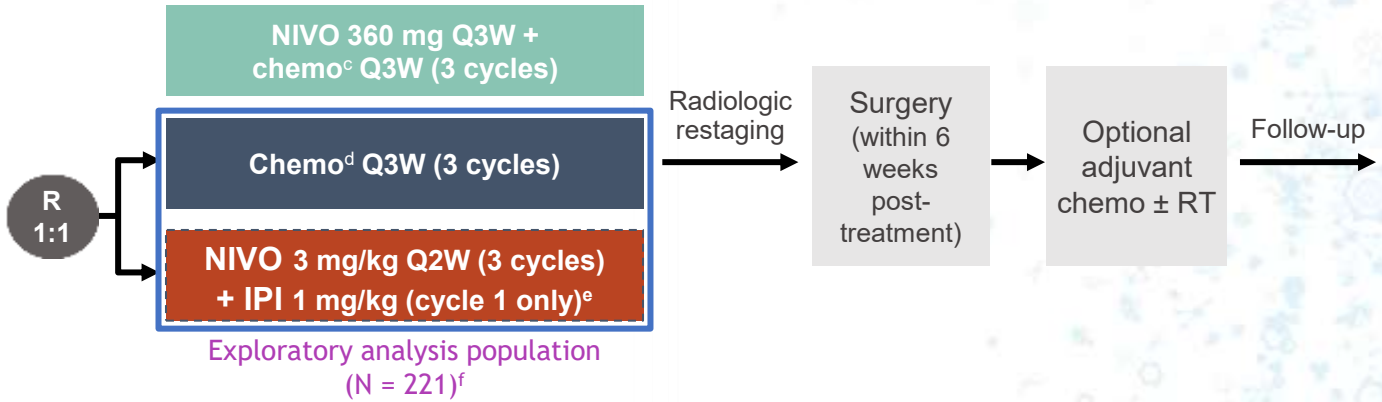
Neoadjuvant Nivolumab Plus Ipilimumab Versus Chemotherapy in Resectable Lung Cancer

CheckMate 816: Study Design

Key eligibility criteria

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

Stratified by stage (IB–II vs IIIA), tumor PD-L1[a] (≥ 1% vs < 1%[b]), and sex



Primary analyses (NIVO + chemo vs chemo)

Primary endpoints
- pCR by BIPR
- EFS by BICR

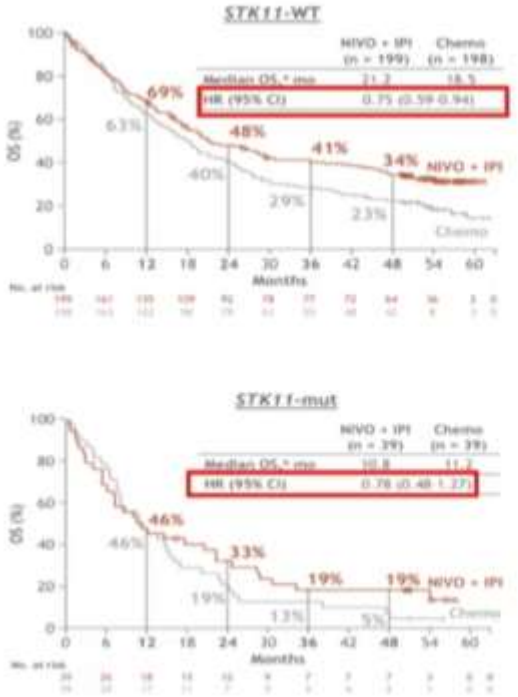
Secondary endpoints
- MPR by BIPR
- OS
- TTDM

Exploratory analyses (NIVO + IPI vs chemo)
- EFS by BICR
- pCR and MPR by BIPR
- OS
- EFS, pCR, and MPR by 4-gene inflammatory signature score

Rational combinations and Biomarker-Guided Personalization

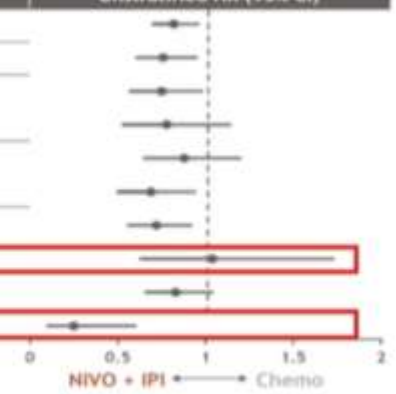
CheckMate-227: Nivolumab/Ipilimumab across STK11 & KEAP1 mutations

Overall Survival- STK11



Progression-Free Survival Across Subgroups

Subgroup, n[b]	4-y PFS rate, %		Median PFS, mo		Unstratified HR	Unstratified HR (95% CI)
	NIVO + IPI	Chemo	NIVO + IPI	Chemo		
NSQ (n = 419, 419)	14	3	5.2	5.6	0.82	
Mut-eval (n = 238, 237)	14	3	5.6	5.6	0.76	
KRAS-WT (n = 150, 162)	19	6	5.6	5.6	0.75	
KRAS-mut (n = 88, 75)	17	2	5.4	5.8	0.78	
TP53-WT (n = 111, 106)	10	5	5.4	5.6	0.88	
TP53-mut (n = 127, 131)	24	7	5.8	6.6	0.69	
STK11-WT (n = 199, 198)	19	6	8.1	6.1	0.72	
STK11-mut (n = 39, 39)	13	0	2.8	4.3	1.04	
KEAP1-WT (n = 218, 219)	16	6	5.5	5.8	0.83	
KEAP1-mut (n = 20, 18)	41	0	11.1	2.9	0.25	



KEAP1^{MUT}(N=38)
OS HR 0.31 (95% CI 0.14-0.70)
Ipi/Nivo: mOS 24.4m
Chemo: mOS 8.9m

Ramalingam S et al., ESMO Immuno-Oncology Congress, 2021.

Rational combinations and Biomarker-Guided Personalization

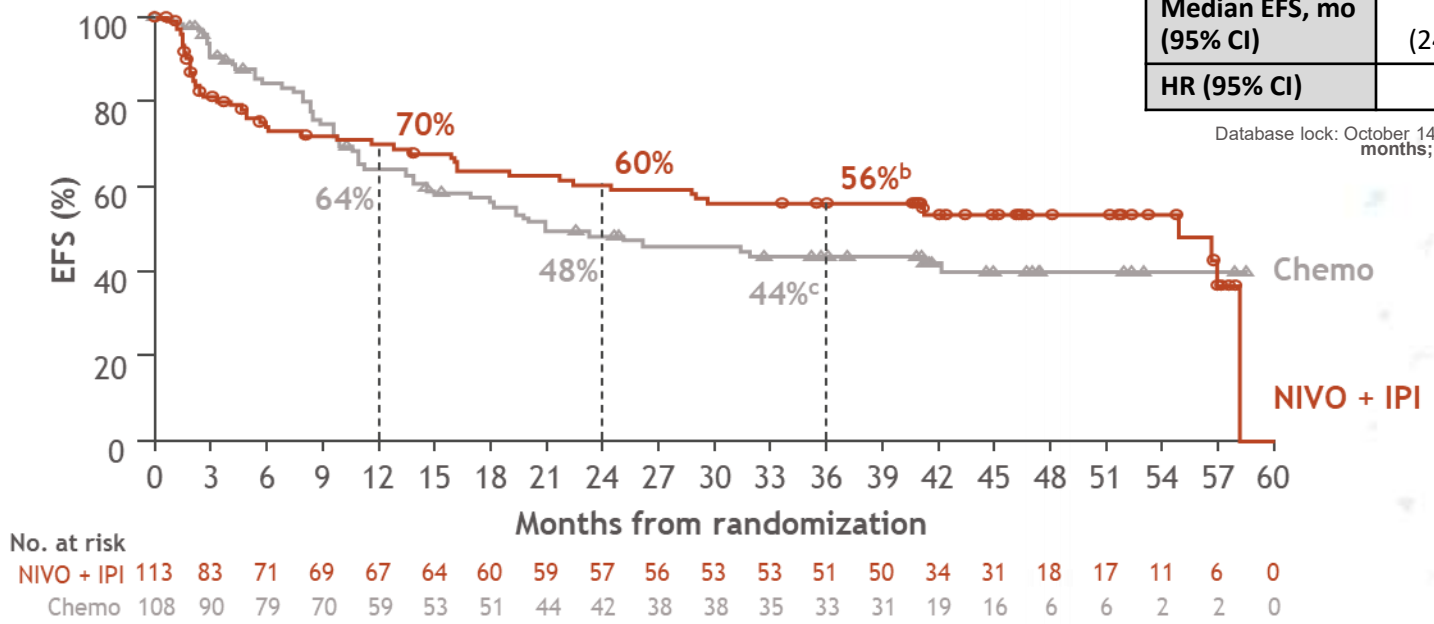
Clinical Trial > J Clin Oncol. 2025 Apr 20;43(12):1453-1462. doi: 10.1200/JCO-24-02239.
Epub 2025 Jan 8.

Neoadjuvant Nivolumab Plus Ipilimumab Versus Chemotherapy in Resectable Lung Cancer

CheckMate 816: EFS with neoadjuvant Nivo + IPO Vs. Chemo

	NIVO + IPI (n = 113)	Chemo (n = 108)
Median EFS, mo (95% CI)	54.8 (24.4–NR)	20.9 (14.2–NR)
HR (95% CI)	0.77 (0.51–1.15)	

Database lock: October 14, 2022; **minimum follow-up: 37.1 months; median follow-up: 49.2 months**.



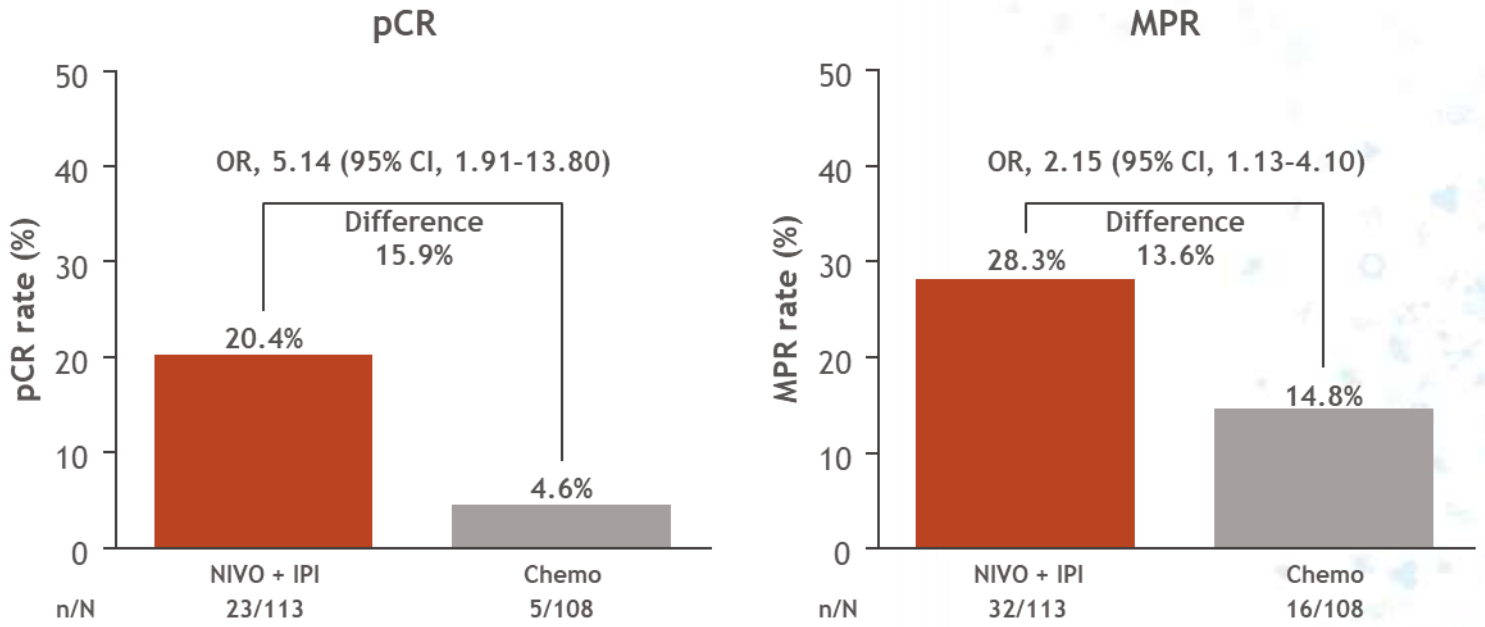
Awad MM. et. al., J Clin Oncol, 2025.
Adapted with permission.

Rational combinations and Biomarker-Guided Personalization

Clinical Trial > J Clin Oncol. 2025 Apr 20;43(12):1453-1462. doi: 10.1200/JCO-24-02239.
Epub 2025 Jan 8.

Neoadjuvant Nivolumab Plus Ipilimumab Versus Chemotherapy in Resectable Lung Cancer

CheckMate 816: pCR and MPR with neoadjuvant Nivo + IPO Vs. Chemo



Awad MM. et. al., J Clin Oncol, 2025.
Adapted with permission.

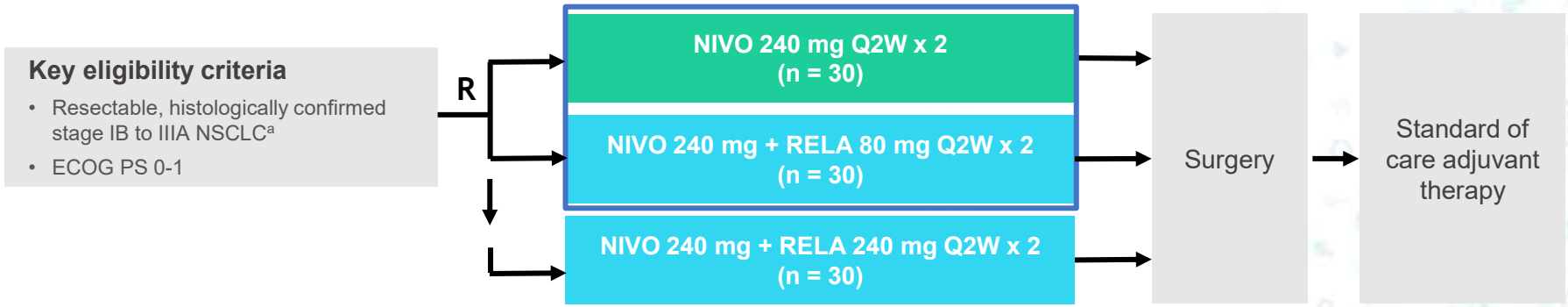
Rational combinations and Biomarker-Guided Personalization

Clinical Trial > Nat Med. 2024 Jun;30(6):1602-1611. doi: 10.1038/s41591-024-02965-0.
Epub 2024 Apr 30.

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

NCT04205552: Phase 2, randomized, open-label study assessing neoadjuvant NIVO with or without RELA in resectable NSCLC.

NEOpredict-Lung: Study Design



Primary endpoint
- Feasibility of curatively intended surgery within 43 days

Key secondary endpoints
- Radiographic and pathologic response rates
- R0 resection rate
- DFS and OS
- Safety

Schuler M. et. al., Nat Med, 2024.

Cuppens K. et. al., Oral presentation at WCLC, 2024. Abstract OA01.05.

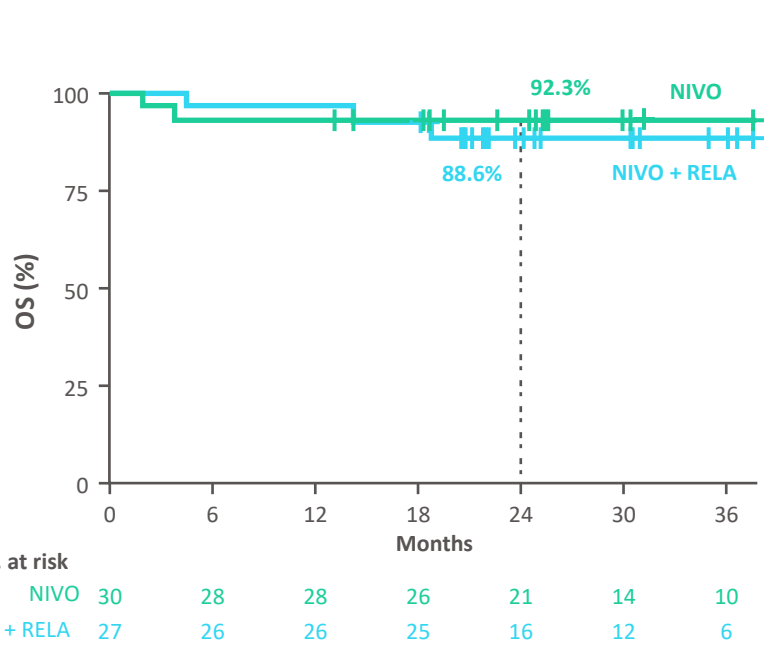
Rational combinations and Biomarker-Guided Personalization

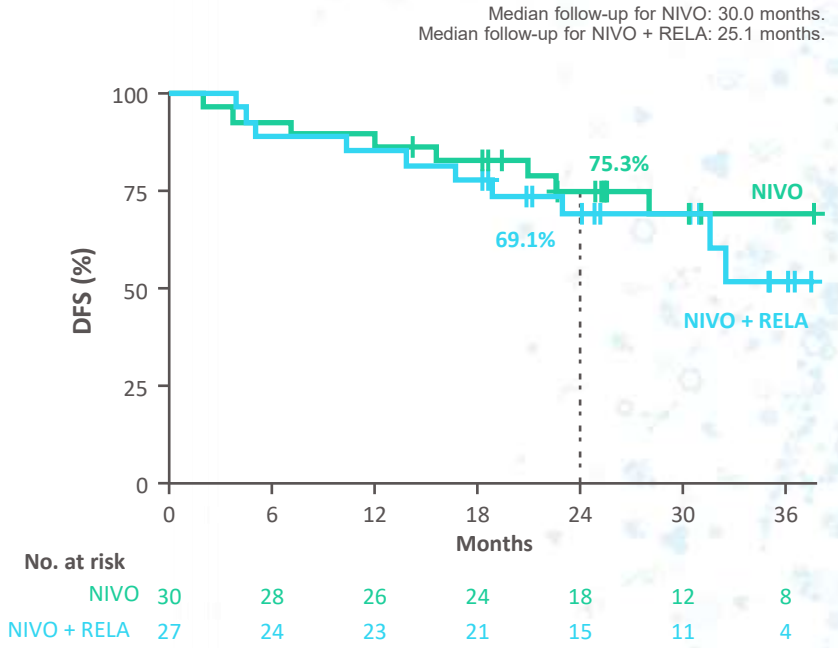
Clinical Trial > Nat Med. 2024 Jun;30(6):1602-1611. doi: 10.1038/s41591-024-02965-0.
Epub 2024 Apr 30.

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

NCT04205552: Phase 2, randomized, open-label study assessing neoadjuvant NIVO with or without RELA in resectable NSCLC.

NEOpredict-Lung: Survival outcomes





Schuler M. et. al., Nat Med, 2024.

Cuppens K. et. al., Oral presentation at WCLC, 2024. Abstract OA01.05.

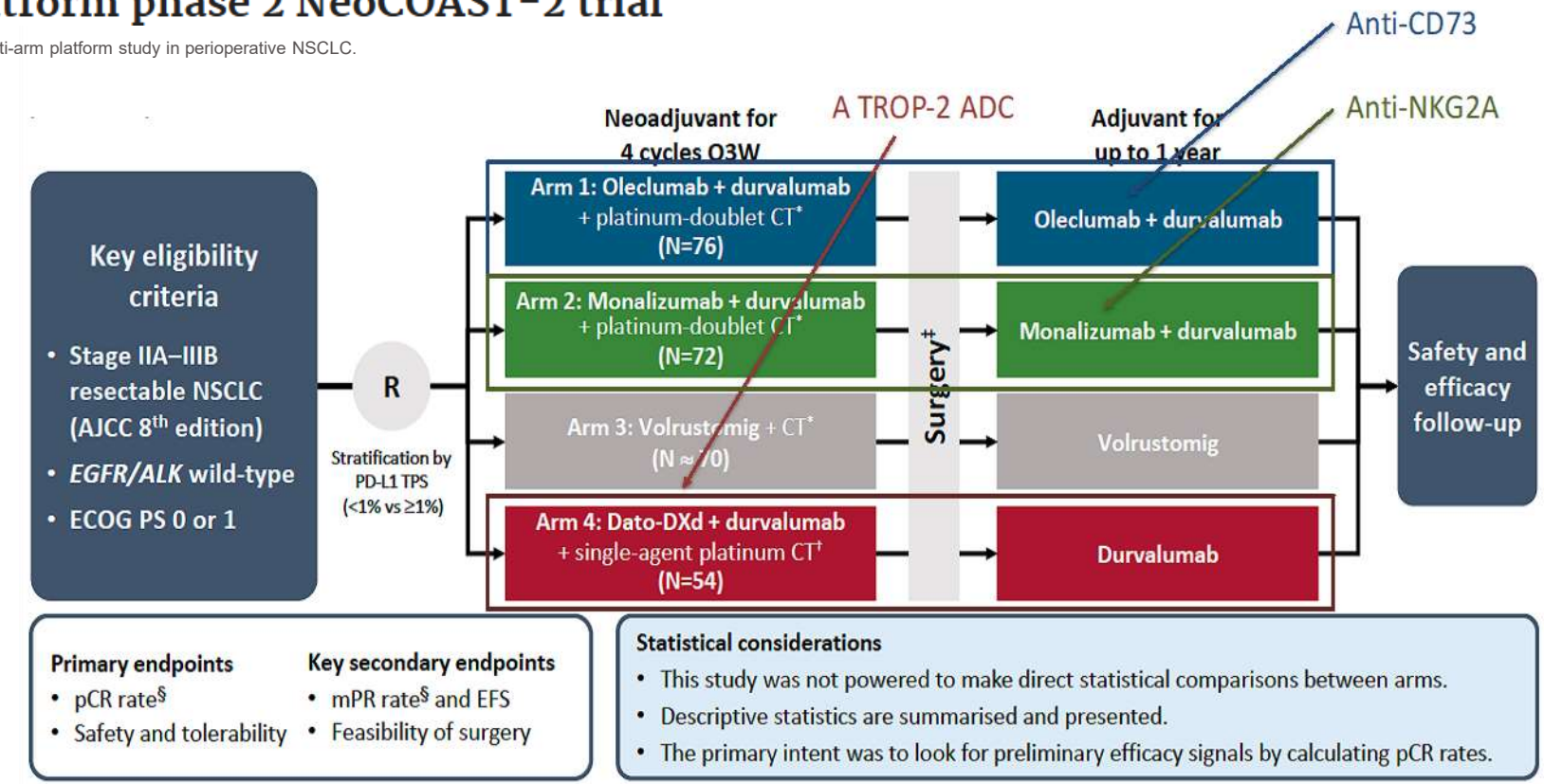
Rational combinations and Biomarker-Guided Personalization

Clinical Trial > Nat Med. 2025 Aug;31(8):2788-2796. doi: 10.1038/s41591-025-03746-z.
Epub 2025 May 31.

Perioperative durvalumab plus chemotherapy plus new agents for resectable non-small-cell lung cancer: the platform phase 2 NeoCOAST-2 trial

Phase 2, randomized, open-label, multi-arm platform study in perioperative NSCLC.

NeoCOAST-2: Study Design



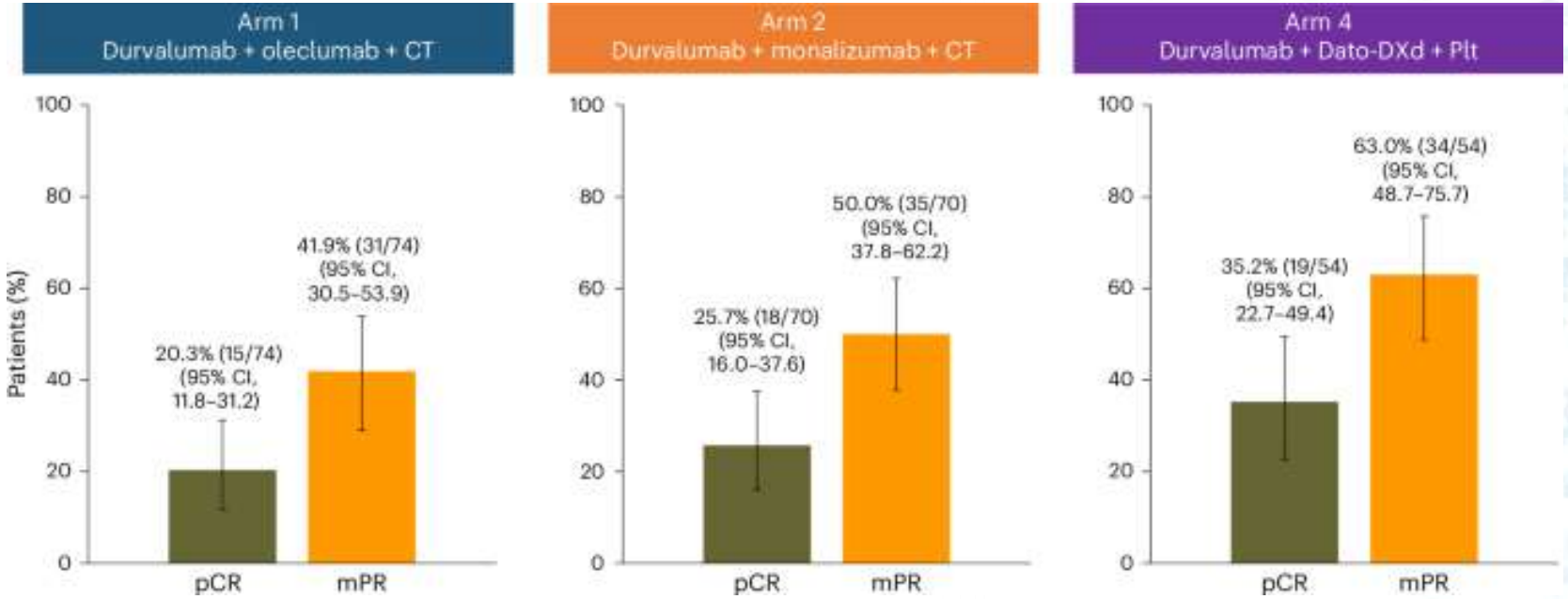
Cascone T. et. al., Nat Med, 2025.

Rational combinations and Biomarker-Guided Personalization

Clinical Trial > Nat Med. 2025 Aug;31(8):2788-2796. doi: 10.1038/s41591-025-03746-z.
Epub 2025 May 31.

Perioperative durvalumab plus chemotherapy plus new agents for resectable non-small-cell lung cancer: the platform phase 2 NeoCOAST-2 trial

NeoCOAST-2: Proportion of patients with pCR or mPR



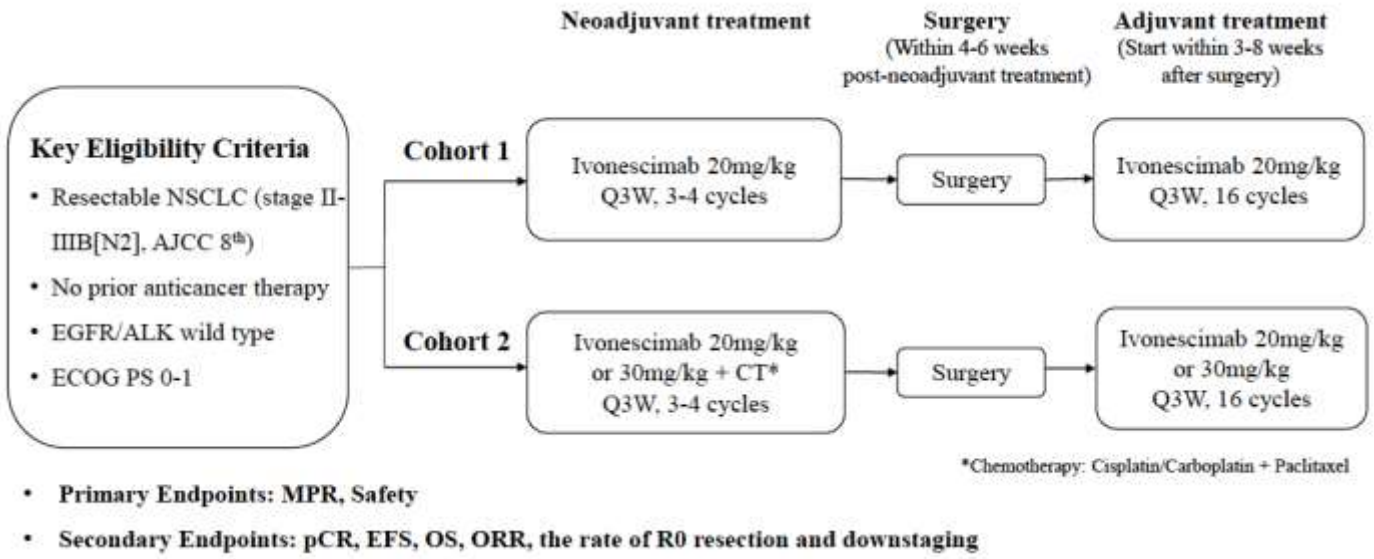
Cascone T. et. al., Nat Med, 2025.

Rational combinations and Biomarker-Guided Personalization

Perioperative Ivonescimab alone or combined with chemotherapy in resectable NSCLC.

NCT05247684: Reports the efficacy and safety of a phase II study of perioperative ivonescimab alone or combined with chemotherapy in resectable NSCLC.

Ivonescimab is a first-in-class anti-PD-1/VEGF bispecific antibody that both as monotherapy and in combination with chemotherapy, showed promising antitumor activity and manageable safety profile in patients with advanced NSCLC.



Wang C. et. al., Oral presentation at WCLC, 2024. Abstract OA01.06.

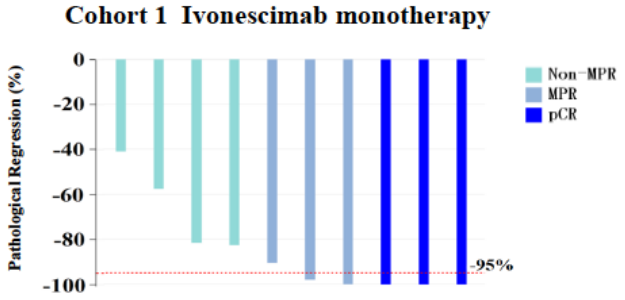
Rational combinations and Biomarker-Guided Personalization

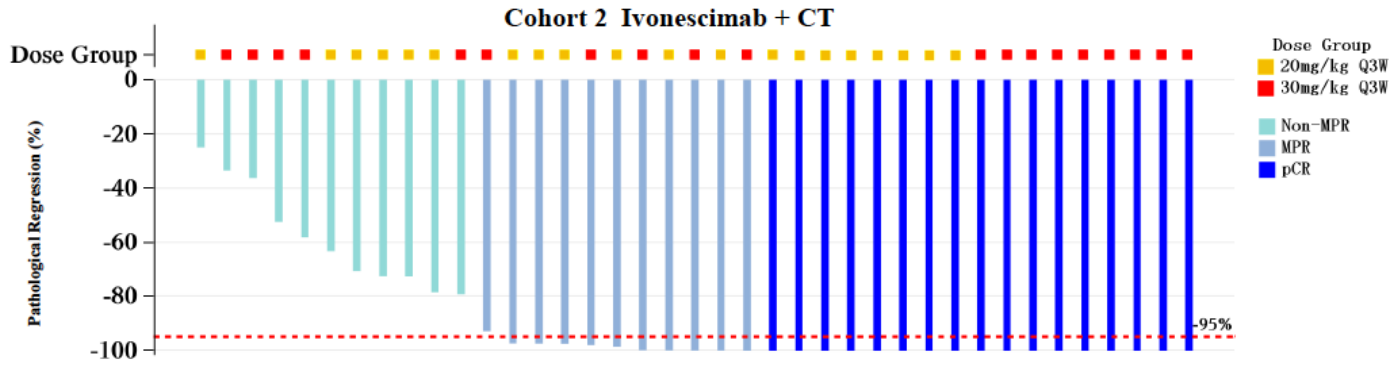
Perioperative Ivonescimab alone or combined with chemotherapy in resectable NSCLC.

NCT05247684: Reports the efficacy and safety of a phase II study of perioperative ivonescimab alone or combined with chemotherapy in resectable NSCLC.

Pathological Response

	Cohort 1 (N=10)	Cohort 2 (N=39)
MPR (RVT≤10%)	60.0%	71.8%
- RVT* < 5%	50.0%	69.2%
pCR	30.0%	43.6%



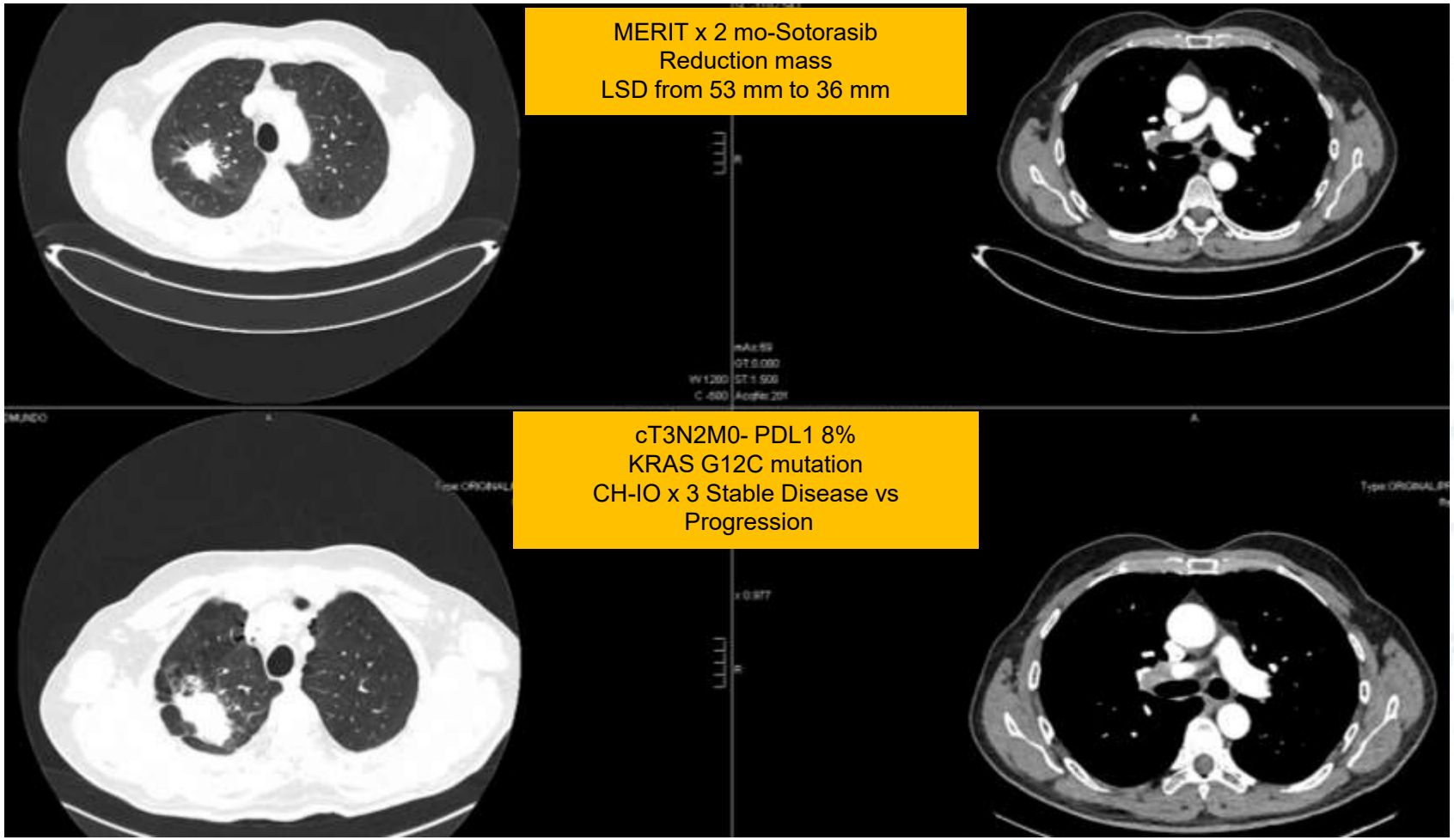


*RVT : residual viable tumor cells in both primary tumor and lymph nodes.

Wang C. et. al., Oral presentation at WCLC, 2024. Abstract OA01.06.

Mariano Provencio MD, PhD; Puerta de Hierro University Hospital, Madrid, Spain.

Rational combinations and Biomarker-Guided Personalization



Improving Neoadjuvant Strategies: Key Directions

- Rational therapeutic combinations.
- Biomarker-guided optimization.
- Early monitoring and adaptive response.
- Innovative trial designs.
- Patient optimization.
- New advanced topics.

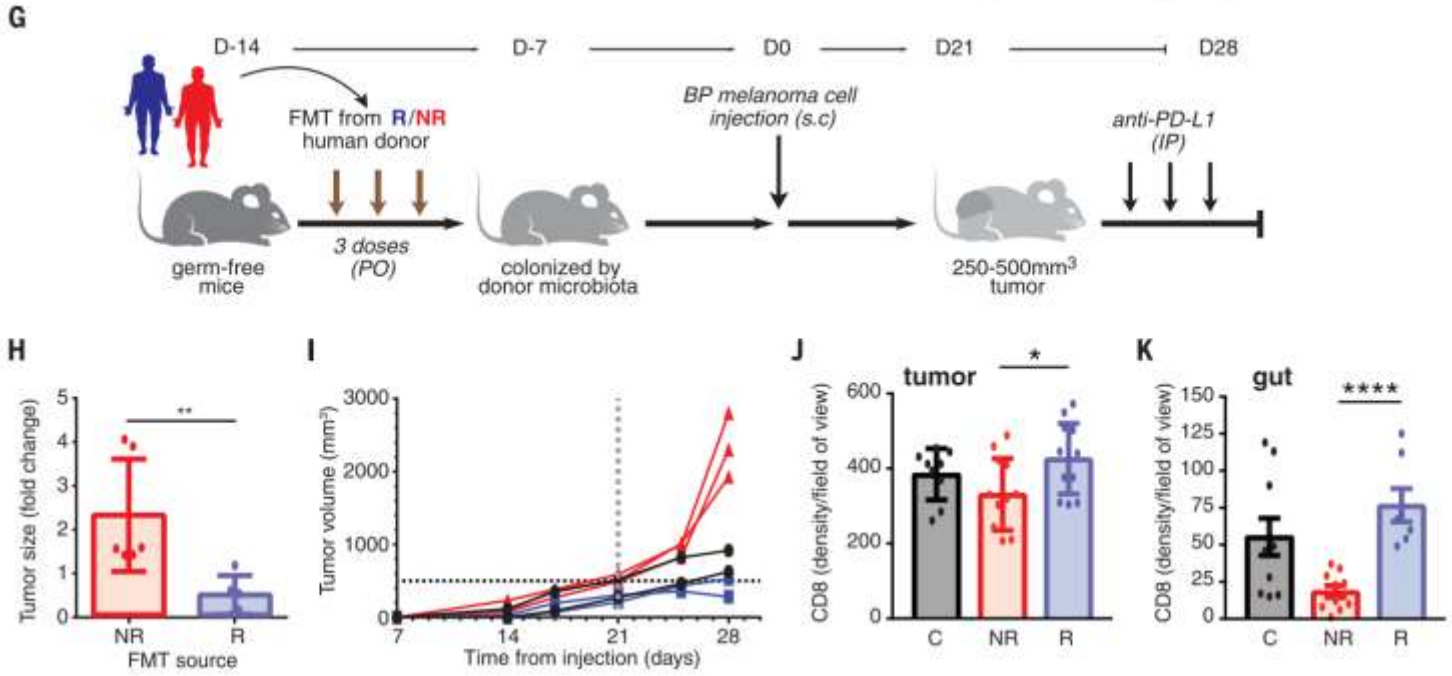
Microbiome and Immune Response

Science. 2018 Jan 5;359(6371):97-103. doi: 10.1126/science.aan4236. Epub 2017 Nov 2.

Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients

Evidence of FMT impact in immune antitumor response

Tumors of mice receiving R-FMT stool had a higher density of CD8+ T cells than mice receiving NR-FMT.



R-FMT: Responders-Fecal microbiome transplant. *NR-FMT*: Nonresponders-Fecal microbiome transplant.

Gopalakrishnan V. et. al., Science, 2018.

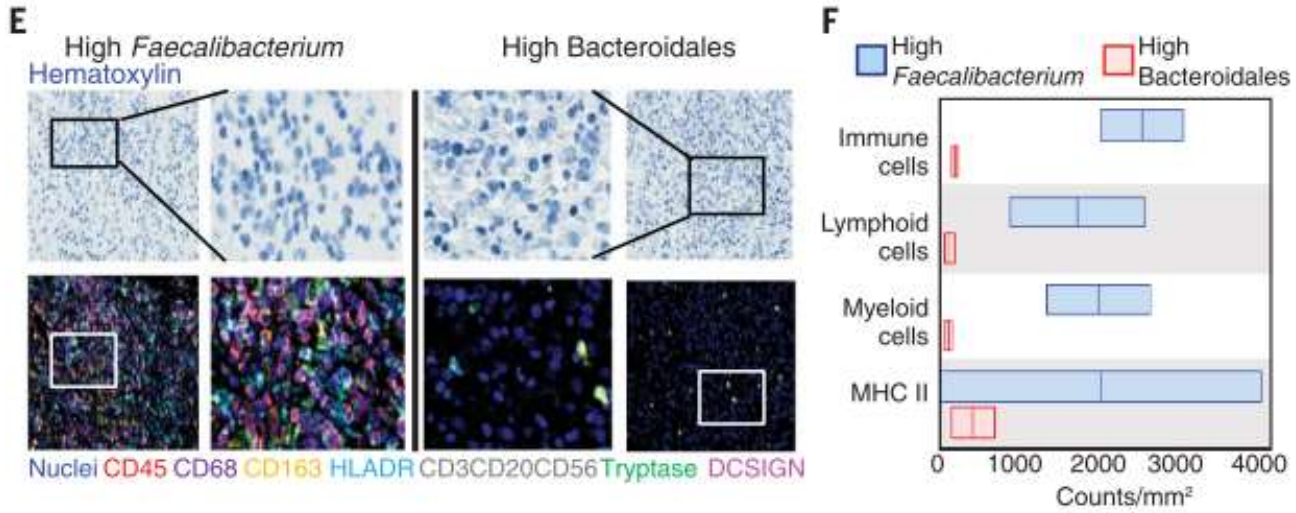
Microbiome and Immune Response

Science. 2018 Jan 5;359(6371):97-103. doi: 10.1126/science.aan4236. Epub 2017 Nov 2.

Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients

Evidence of microbiome association with TILs

Differential composition of the gut microbiome may influence therapeutic responses to anti–PD-1 therapy at the level of the tumor microenvironment.

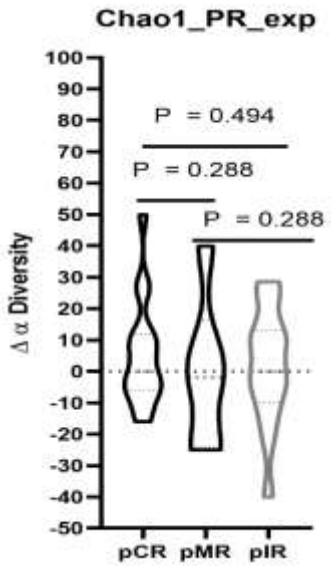


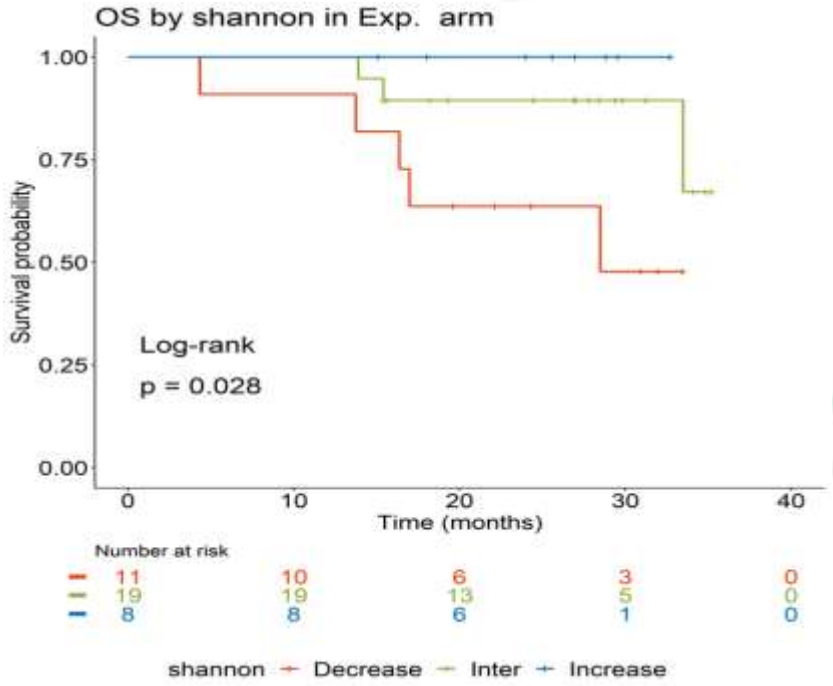
Gopalakrishnan V. et. al., Science, 2018.

Microbiome and Immune Response

NADIM preliminary results in microbiota analysis.

Increase in gut microbiome diversity (alpha diversity) **after ICI treatment may be an independent predictor of survival outcomes** (data not published)

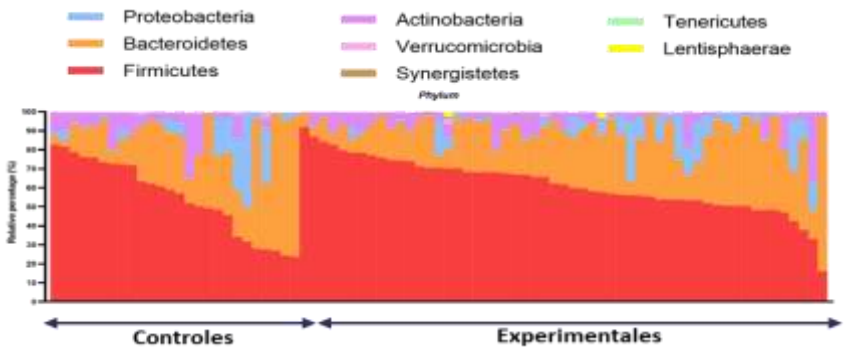


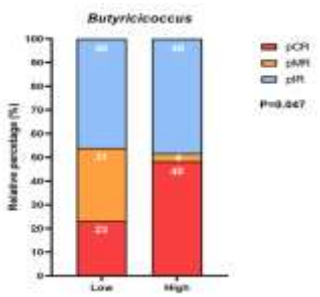


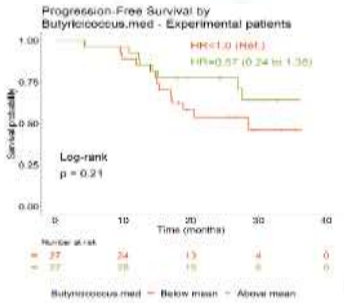
Microbiome and Immune Response

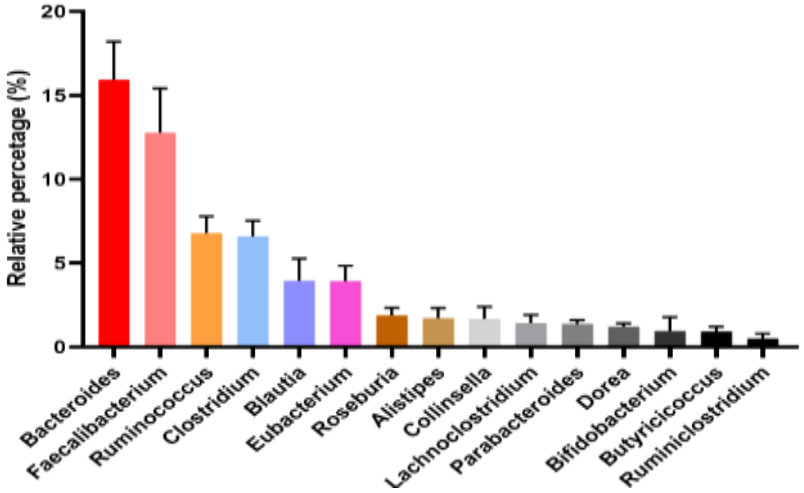
NADIM preliminary results in microbiota analysis.

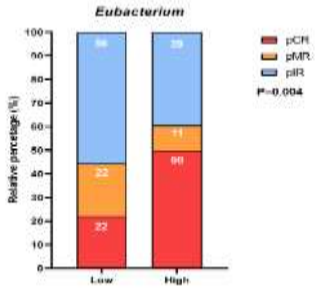
A higher abundance of Genera Butyricicoccus, and Eubacterium are associated with improved outcomes.

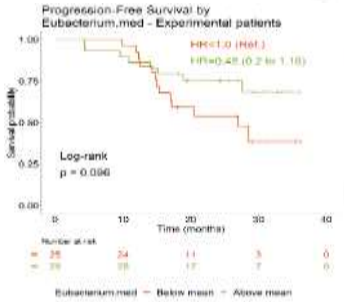


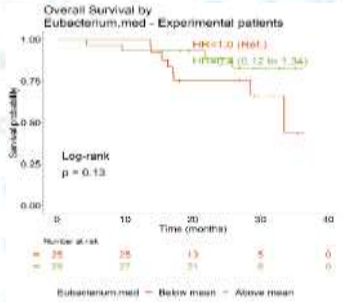












Microbiome and Immune Response

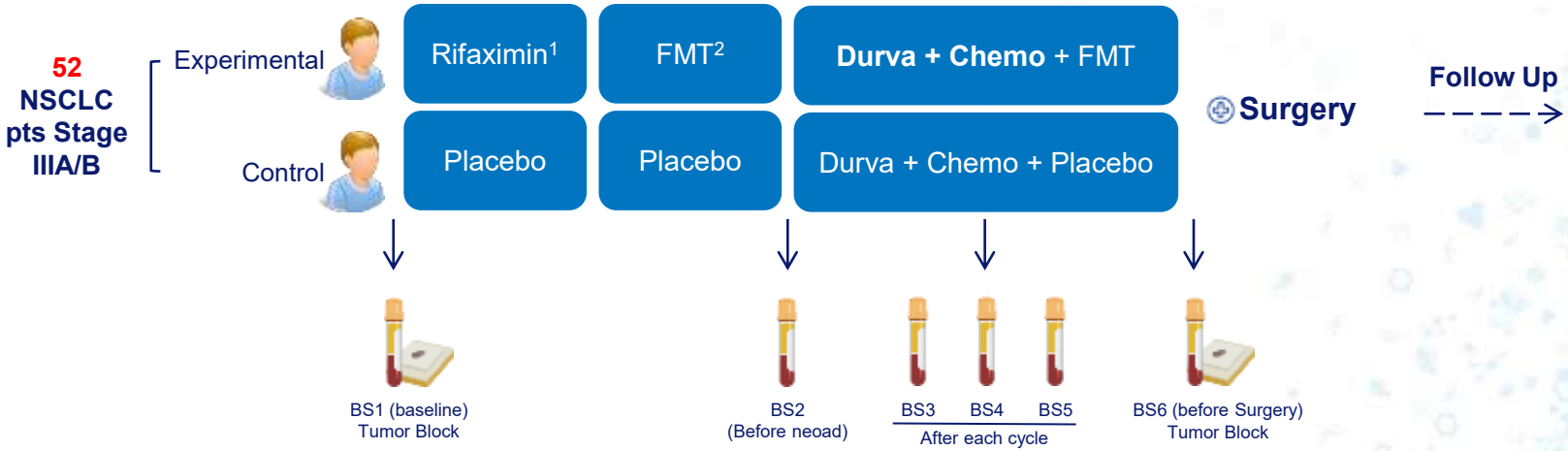
The gut microbiota modulate innate and adaptative immunity, as well as tumor antigens to improve immunotherapy responses.

Timeline of gut microbiota and ICI efficacy

Microbiome and Immune Response

Phase II randomized clinical trial for evaluating the safety, feasibility and efficacy of FMT in stage III NSCLC patients, using ICI-responders as donors.

New Study: Design of the study



Objective: To characterize the antitumor immune response and its association with fecal microbiome composition in the context of neoadjuvant chemo-immunotherapy.

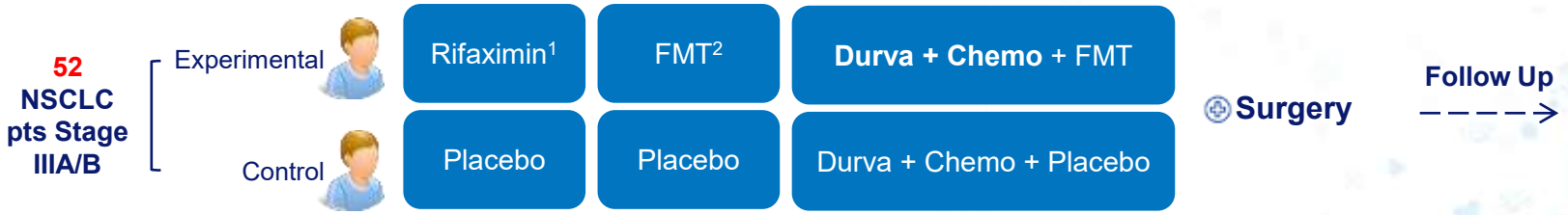
Basal + Surgery FFPE Tumor→ Spatial Transcriptomics to study TILs

Blood Samples (BS1-BS6)→ PBMCs Immunophenotype + cytokines

Microbiome and Immune Response

Phase II randomized clinical trial for evaluating the safety, feasibility and efficacy of FMT in stage III NSCLC patients, using ICI-responders as donors.

New Study: Design and objectives



Primary Objective: pCR rate

Secondary Objectives:

- Tumor resecability
- R0 rate
- PFS at 2 years
- Microbiota Changes
- Safety

[1]Rifaximin is a non-absorbable antibiotic suitable for intestinal decontamination for 3 days at a dose of 1,200 g/day in 2 doses.

[2]Patients will be treated with 5 capsules on the day of FMT and daily reminders for 15 days (1 capsule per day in a single dose).

Additional exploratory Objectives:

- Characterize the composition of the intestinal microbiota in a cohort of NSCLC patients treated with neoadjuvant chemo-immunotherapy and fecal transplantation.
- Identify species that predispose to achieving a pCR after neoadjuvant treatment.
- Investigate whether there is an association between the occurrence of adverse effects and the composition of the intestinal microbiota.
- Determine whether there is an association between BMI and the response rate to the combination of chemo-immunotherapy and FMT.
- Examine the patient's initial and final microbiota composition after surgery, whether there were changes and their relationship to response, toxicity and side effects.
- To characterize de antitumor immune response and its association with fecal microbiome composition in the context of neoadjuvant chemo-immunotherapy.

Innovative trial designs

Clinical Trial > Lancet. 2023 Sep 9;402(10405):871-881. doi: 10.1016/S0140-6736(23)01384-3.
Epub 2023 Jul 18. NCT03110978

Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial

I-SABR: Study Design

Key eligibility criteria

- Early-stage NSCLC
  - Stage IA-B (tumor size ≤ 4 cm, N0M0)
  - Stage IIA (tumor size ≤ 5 cm, N0M0)
  - Stage IIB (tumor size > 5 cm & ≤ 7 cm, N0M0)
- Isolated lung-parenchymal recurrent or persistent NSCLC suitable for SABR
- Patients with operable disease who choose to have SABR
- ECOG PS 0-2
- No lymph node involvement or distant metastasis
- No prior immunotherapy

N = 140

R 1:1

Stratified by PS, tumor size, histology and lung cancer history

SABR (50 gy in 4 fx or 70 Gy in 10 fx)

I-SABR: NIVO 480 mg Q4W x 4[c] + SABR (50 gy in 4 fx or 70 Gy in 10 fx)

Primary endpoint
- 4-year EFS

Secondary endpoints
- OS
- Toxiciy related to SABR and immunotherapy
- Exploratory analyses of predictive biological/radiomic markers

EFS, event-free survival; fx, fraction; Gy, gray; I-SABR; SABR with immunotherapy; NIVO, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PS, performance status; R, randomized; SABR, stereotactic ablative radiotherapy.

Chang JY. et. al., Oral presentation at WCLC, 2023. Abstract OA12.04.
Chang JY. et. al., Lancet, 2023.
Adapted with permission.

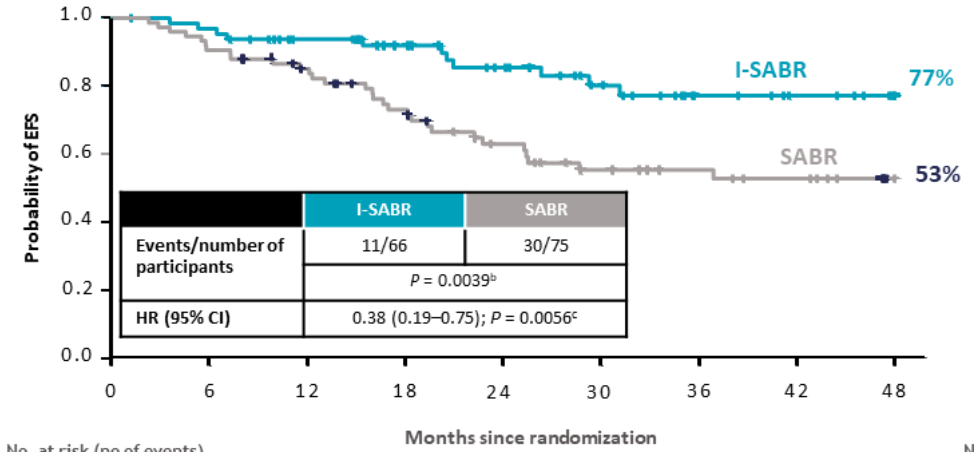
Innovative trial designs

Clinical Trial > Lancet. 2023 Sep 9;402(10405):871-881. doi: 10.1016/S0140-6736(23)01384-3.
Epub 2023 Jul 18. NCT03110978

Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial

I-SABR: Event-free survival

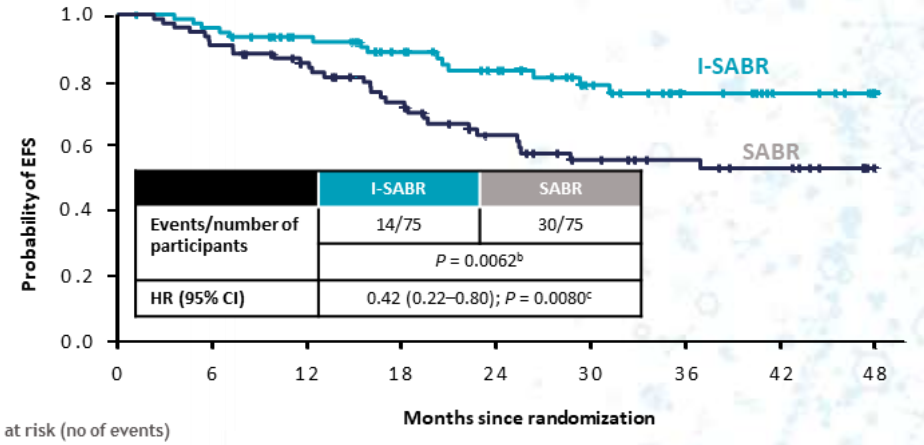
Per protocol



No. at risk (no of events)

I-SABR	66 (0)	54 (4)	38 (4)	18 (3)	7 (0)	
SABR	75 (0)	59 (11)	34 (14)	22 (4)	11 (1)	

Per ITT



No. at risk (no of events)

I-SABR	75 (0)	62 (5)	43 (6)	22 (3)	9 (0)	
SABR	75 (0)	59 (11)	34 (14)	22 (4)	11 (1)	

EFS, event-free survival; I-SABR; SABR with immunotherapy; ITT, intention to treat.

Chang JY. et. al., Oral presentation at WCLC, 2023. Abstract OA12.04.
Chang JY. et. al., Lancet, 2023.
Adapted with permission.

CASTER

“Phase II clinical trial of induction treatment with Carboplatin + Paclitaxel plus Cemiplimab followed by Stereotactic Body Radiation Therapy (SBRT) for NSCLC patients Stage I-II”

Nº Pacientes previstos: 34
Centros participantes: 15
Protocolo en preparación

Key eligibility criteria

- Histologically confirmed IA, IB, IIA or IIB NSCLC per 9th edition TNM Classification for Malignant Tumors
- Isolated parenchymal recurrences (tumour size ≤7 cm) of initially TanyNanyM0 disease
- Patient candidates for SBRT
- ECOG PS 0-2
- PD-L1 ≥1%
- No lymph node involvement or distant metastasis
- No prior immunotherapy

Primary endpoint
- PFS at 24 months

Secondary endpoints
- OS at 24 months
- Sites of first failure
- ORR according to RECIST v 1.1 after induction
- Translational research
- Toxicity/Safety

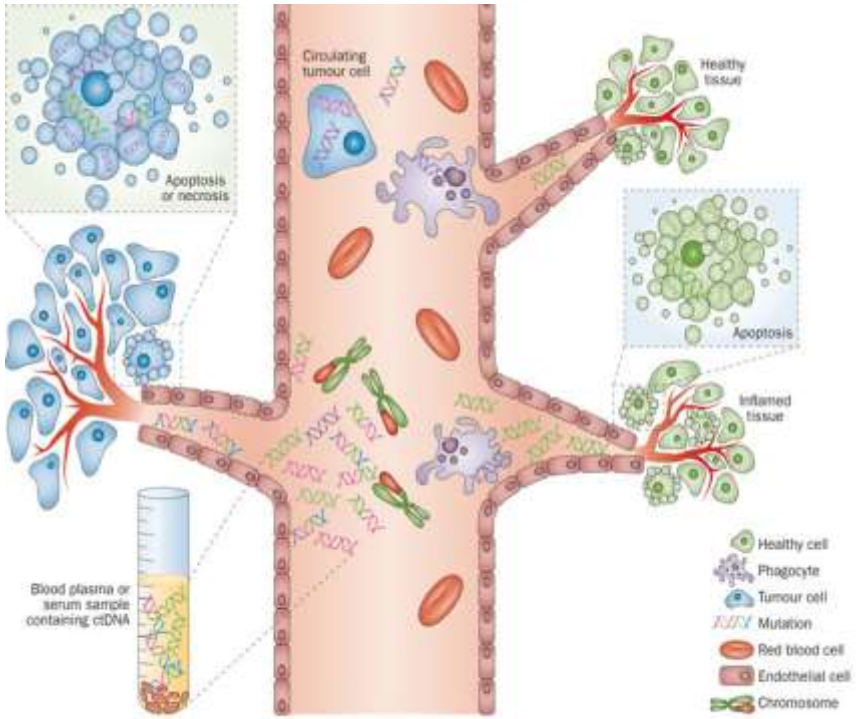
PET-CT/ Brain MRI or CT

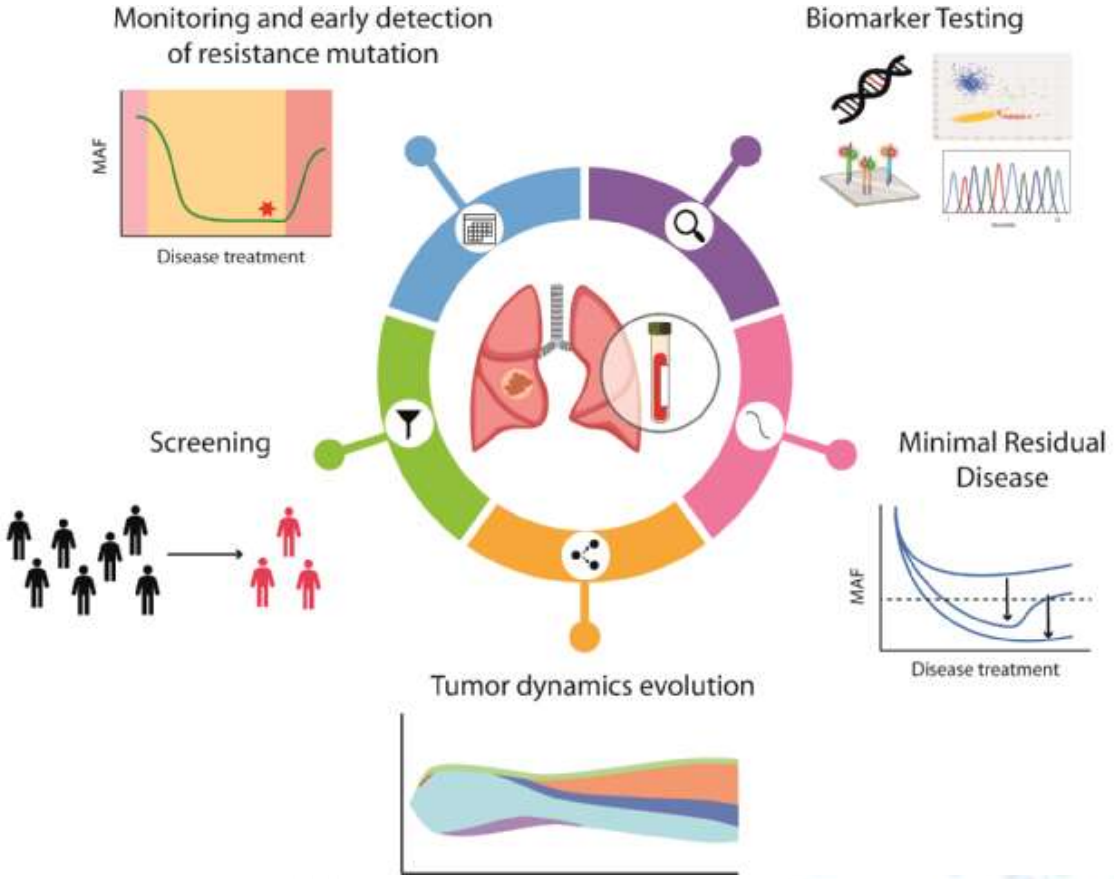
BLOOD SAMPLES (PD-L1)

NSCLC, non-small cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography. progression free survival; OS, overall survival; fx, fraction; Gy, gray; SBRT, stereotactic body radiation therapy.

Predictive Biomarkers

Circulating tumor DNA (ctDNA)





Crowley E. et. al., *Nat Rev Clin. Oncol,* 2013.

Predictive Biomarkers

Circulating tumor DNA (ctDNA)

Clinical Trial > J Clin Oncol. 2022 Sep 1;40(25):2924-2933. doi: 10.1200/JCO.21.02660.
Epub 2022 May 16. NCT03081689

Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non–Small–Cell Lung Cancer (NADIM phase II trial)

OS at 36 months was 81.9% (95% CI, 66.8 to 90.6) in the ITT population, rising to 91% (95% CI, 74.2 to 97.0) in the per-protocol population.

Biomarker	No.	Deaths	Progressions	HR (PFS)[a]	95% CI[a]	P[a]	HR (OS)[a]	95% CI[a]	P[a]
Basal ctDNA < 1%	43	9	12	0.20	0.06 to 0.63	.006	0.07	0.01 to 0.39	.002

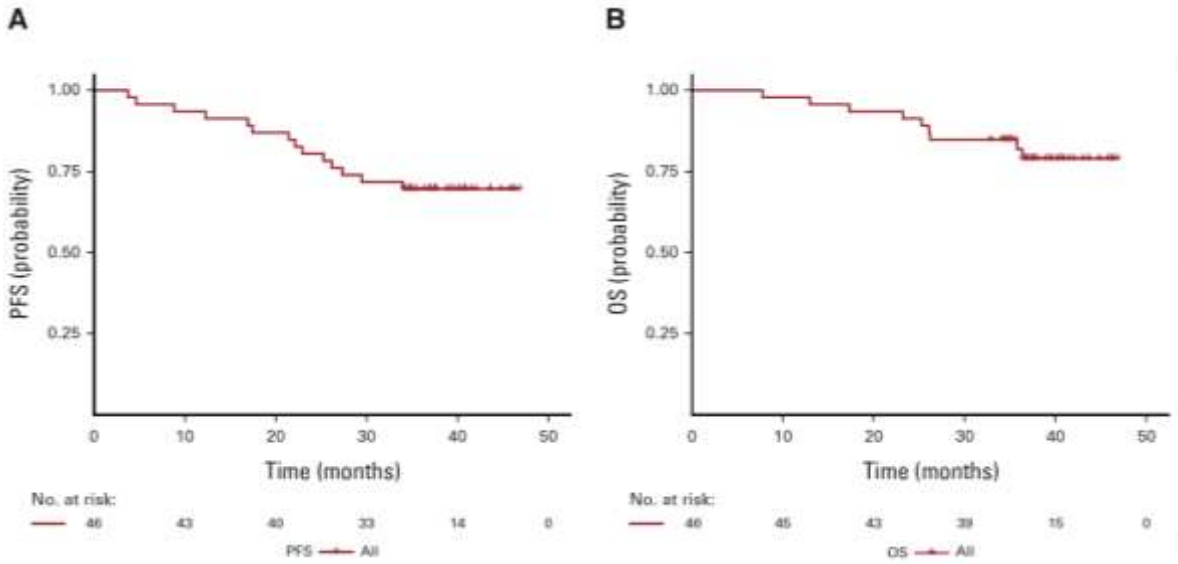


Fig 1. Kaplan-Meier curves for (A) PFS and (B) OS in the ITT population (N = 46). *ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.*

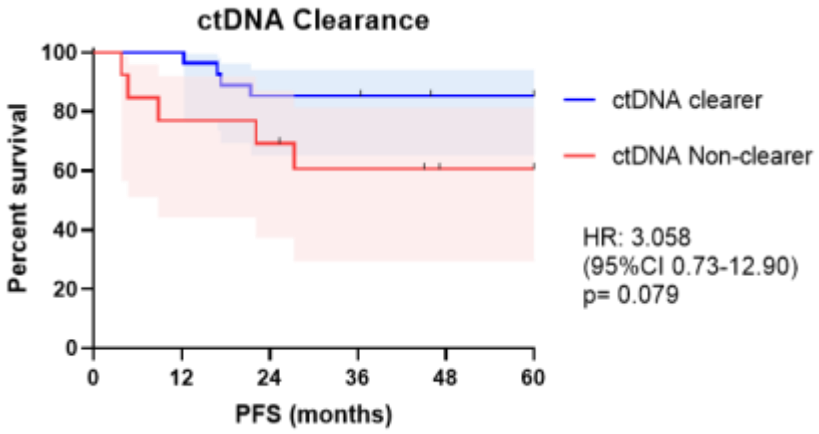
Provencio M. et. al., J Clin Oncol, 2022.

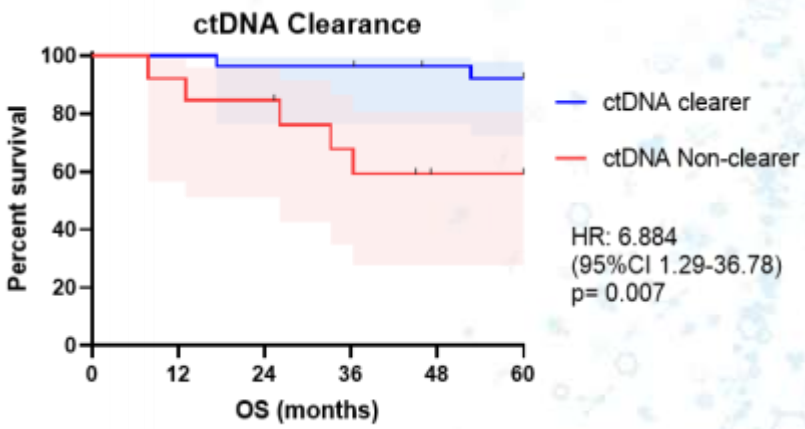
Predictive Biomarkers

Circulating tumor DNA (ctDNA)

Clinical Trial > Lancet Oncol. 2024 Nov;25(11):1453-1464. doi: 10.1016/S1470-2045(24)00498-4. Epub 2024 Oct 14.

Perioperative chemotherapy and nivolumab in non-small-cell lung cancer (NADIM): 5-year clinical outcomes from a multicentre, single-arm, phase 2 trial





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

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

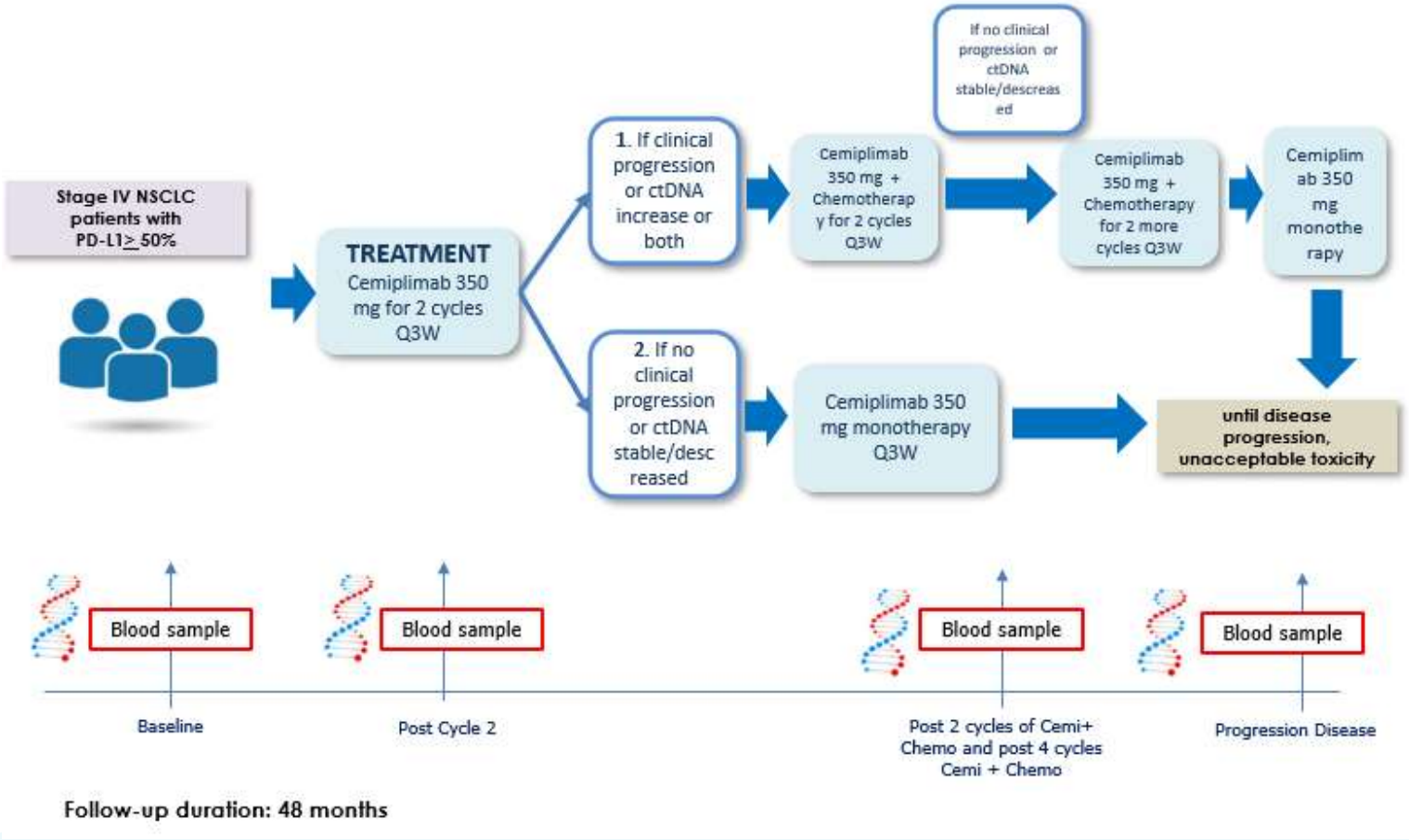
OS Non-ctDNA clearance: 59.2% (95%CI: 27.9-80.7%)

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

Provencio M. et. al., Lancet Oncol, 2024.

PALACE

"Phase II clinical trial with an adaptive design according to response to cemiplimab monotherapy using ctDNA and subsequent treatment with chemotherapy (CT) and cemiplimab or cemiplimab monotherapy in first line stage IV NSCLC patients" PALACE



20 centers
63 p planned
26 p recruited
Open July 2025

Improving Neoadjuvant Strategies: Key Directions

- Rational therapeutic combinations.
- Biomarker-guided optimization.
- Early monitoring and adaptive response.
- Innovative trial designs.
- **Patient optimization.**
- New advanced topics.

Improving Neoadjuvant strategies

Patient Optimization

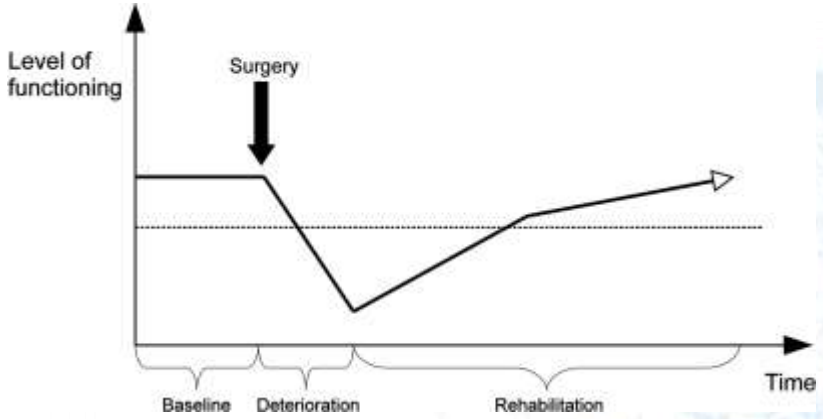
Prehabilitation before surgery

- Nutrition.
- Exercise: moderate aerobic + resistance.
- Smoking cessation.
- Vaccines

Evaluation of response

Multidisciplinary teams (MDT)

- Expertise.



Lee L. et. al., Surgery, 2014.

Improving Neoadjuvant strategies

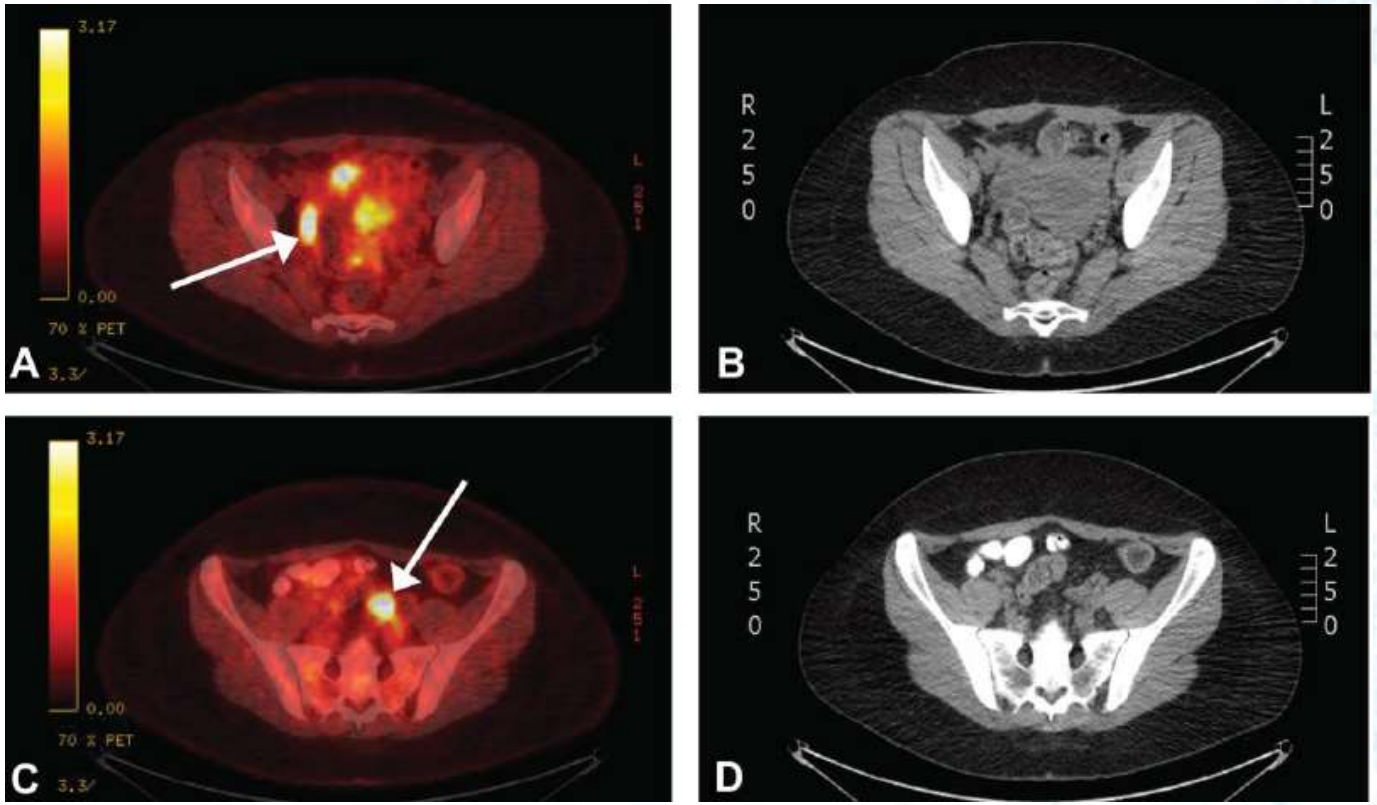
Patient Optimization - Evaluation of response

Case Reports > Obstet Gynecol. 2015 Jul;126(1):182-5. doi: 10.1097/AOG.0000000000000701.

Extensive Tattoos Mimicking Lymphatic Metastasis on Positron Emission Tomography Scan in a Patient With Cervical Cancer

Patient with **stage IB Cervical Cancer** and extensive tattoos in the lower extremities.

Preoperative PET-CT scan identified **ileac lymph nodes suspicious for metastatic disease**.



Grove N. et. al., Obstet Gynecol, 2015.

Improving Neoadjuvant strategies

Patient Optimization - Evaluation of response

Case Reports > Obstet Gynecol. 2015 Jul;126(1):182-5. doi: 10.1097/AOG.0000000000000701.

Extensive Tattoos Mimicking Lymphatic Metastasis on Positron Emission Tomography Scan in a Patient With Cervical Cancer

At the time of surgical resection, bilateral pigmented **lymph nodes** were identified with histologic examination showing **deposition of tattoo ink** and no malignant cells.

Physicians should be aware of the **possible effects of tattoos on PET-CT findings** while counseling patients and formulating a treatment.

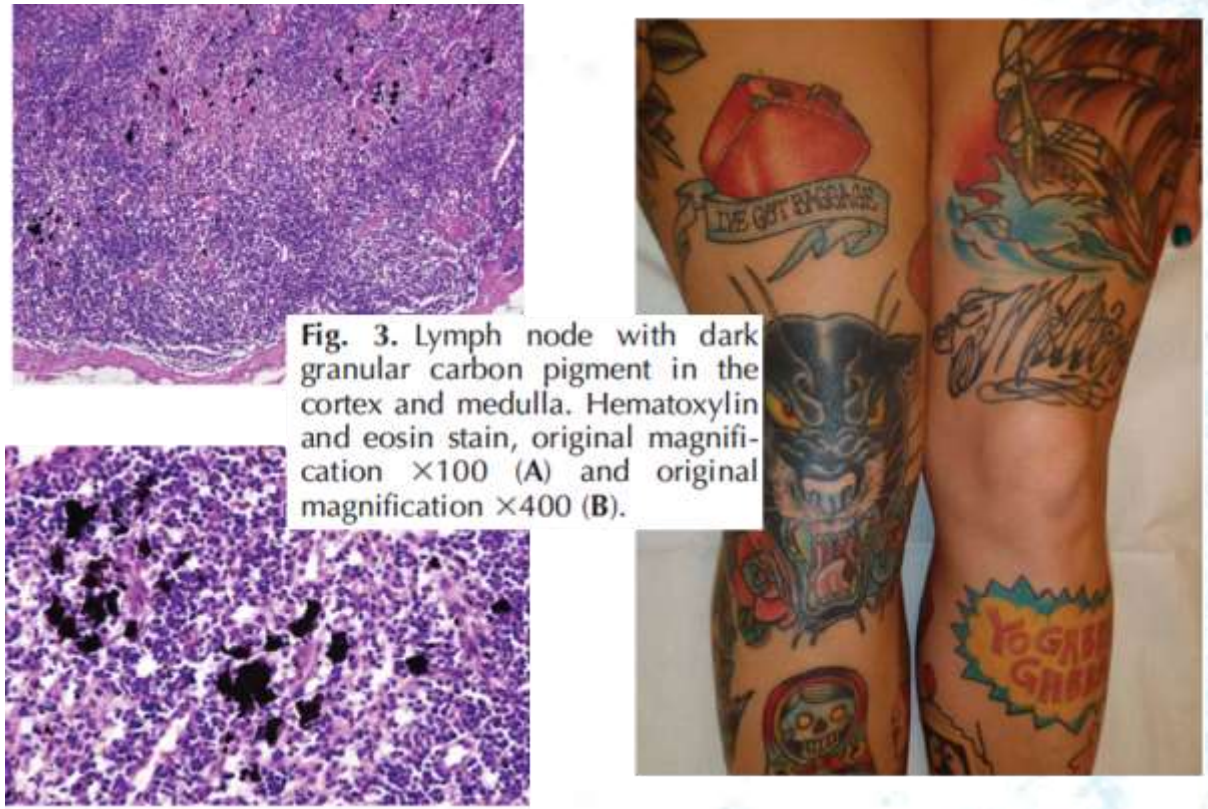


Fig. 3. Lymph node with dark granular carbon pigment in the cortex and medulla. Hematoxylin and eosin stain, original magnification ×100 (**A**) and original magnification ×400 (**B**).

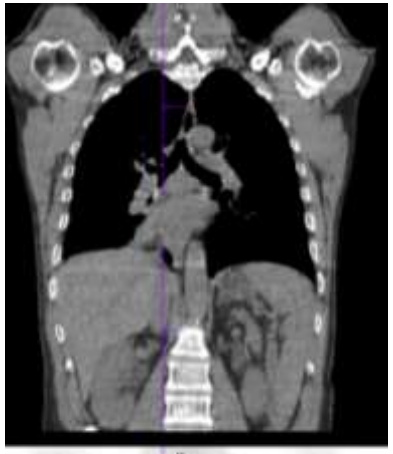
Grove N. et. al., Obstet Gynecol, 2015.

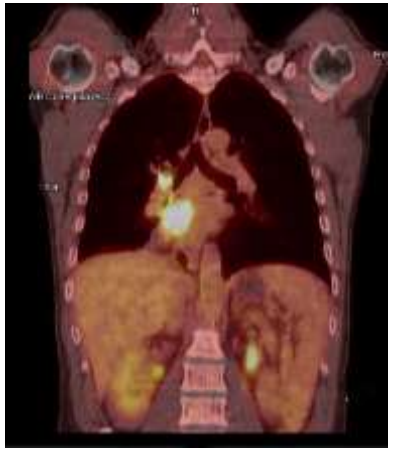
Improving Neoadjuvant strategies

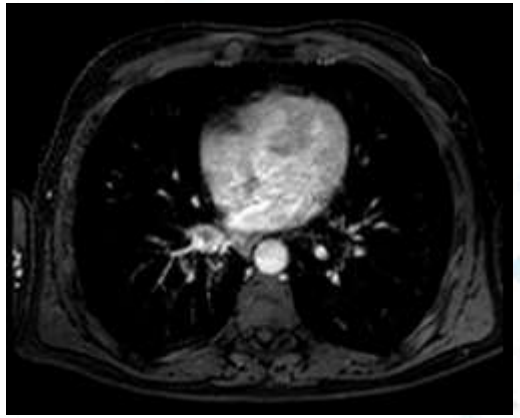
Patient Optimization - Evaluation of response

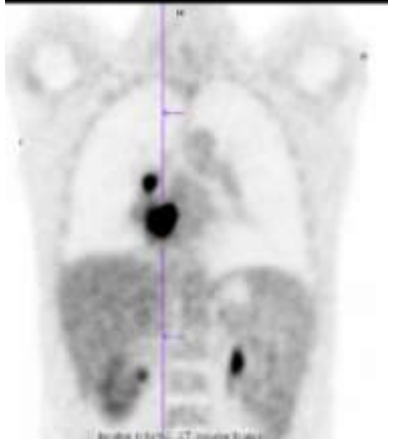
Radiologic response does not always match the true pathologic response. It highlights the need to confirm response histologically, not rely solely on scans.

“Assume nothing, prove everything” – Dr. V. Rusch









*n(%)		Pathologic Response		
		IPR (n=7)	MPR (n=8)	CPR (n=26)
Clinical Response *	Stable Disease (n=9)	5 (55·6)	1 (11·1)	3 (33·3)
	Partial Response (n=30)	2 (6·7)	6 (20·0)	22 (73·3)
	Complete Response (n=2)	0 (0)	1 (50·0)	1 (50·0)

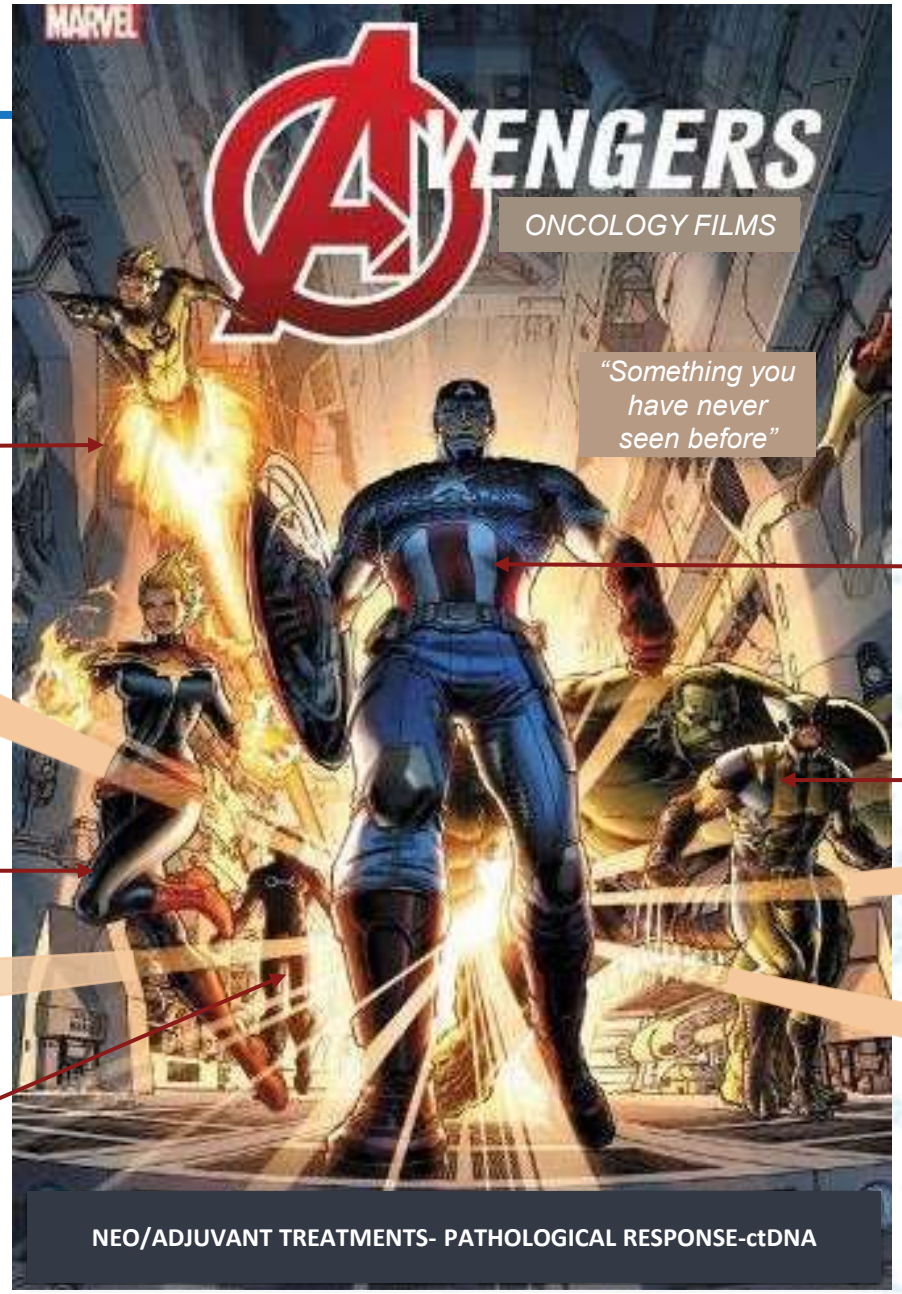
Table S5. Clinical response versus pathologic response in patients who underwent surgery. *IPR, incomplete pathological response; MPR, major pathological response; CPR, complete pathologic response.*

Provencio M. et. al., Lancet Oncol, 2020.

Improving Neoadjuvant strategies

Patient Optimization – Multidisciplinary teams (MDT)

IN THE ERA OF IMMUNOTHERAPY, NO HERO WORKS ALONE… WE NEED THE WHOLE TEAM.



TKIs

EGFR ALK

Immunotherapy

IA-Radiomics

Surgeon

Chemotherapy

ct-DNA

Biomarkers

Conclusions

1- Rational therapeutic combinations
2- Pathological complete response (pCR) is emerging as a strong surrogate marker for long-term survival, potentially allowing for reduced treatment intensity in selected patients.
3- Biomarker-guided optimization is essential for tailoring treatment strategies. Molecular profiling and immune-related markers can better predict response and personalize therapy.
4- Innovative trial designs like platform studies (e.g., NeoCOAST-2, NEOpredict-Lung) allow for rapid evaluation of novel combinations and accelerate the adoption of effective therapies.
5- The role of the microbiome is increasingly recognized in modulating immune response. Fecal microbiota transplantation (FMT) is a promising approach being investigated to enhance immunotherapy efficacy.
6- Early monitoring and adaptive response assessment—especially using ctDNA—offers a non-invasive and real-time method to evaluate treatment response and guide further decisions.
7- Patient optimization and multidisciplinary team (MDT) involvement are critical to improving outcomes. Integrated care enhances decision-making and survival across all lung cancer stages.

The **future of neoadjuvant strategies** lies in a personalized, dynamic, and multidisciplinary approach that combines scientific innovation with clinical precision.

Thank you!

GECP lung cancer research

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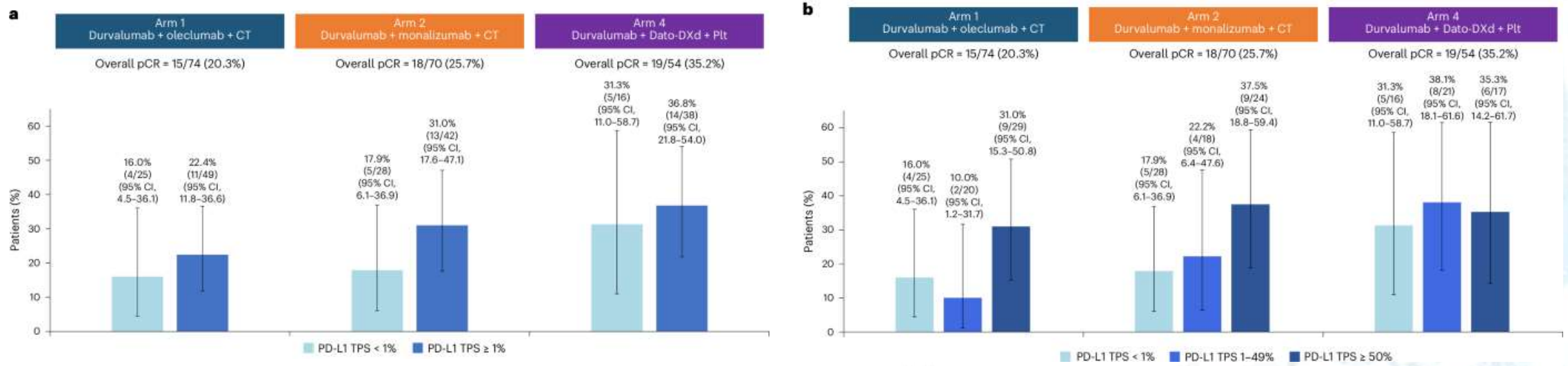
Rational combinations and Biomarker-Guided Personalization

Clinical Trial > Nat Med. 2025 Aug;31(8):2788-2796. doi: 10.1038/s41591-025-03746-z.
Epub 2025 May 31.

Perioperative durvalumab plus chemotherapy plus new agents for resectable non-small-cell lung cancer: the platform phase 2 NeoCOAST-2 trial

NeoCOAST-2: PD-L1 TPS in patients with pCR



Cascone T. et. al., Nat Med, 2025.