Neoadyuvancia en CPNCP

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GECP
lung cancer research

DISCLOSURES

Employment:
- Universidad Autónoma de Madrid.
- Chair of Medical Oncology Department at Puerta de Hierro Hospital

Research Grants:
AstraZeneca, Roche, BMS, Boerhringer-Ingelheim, Takeda

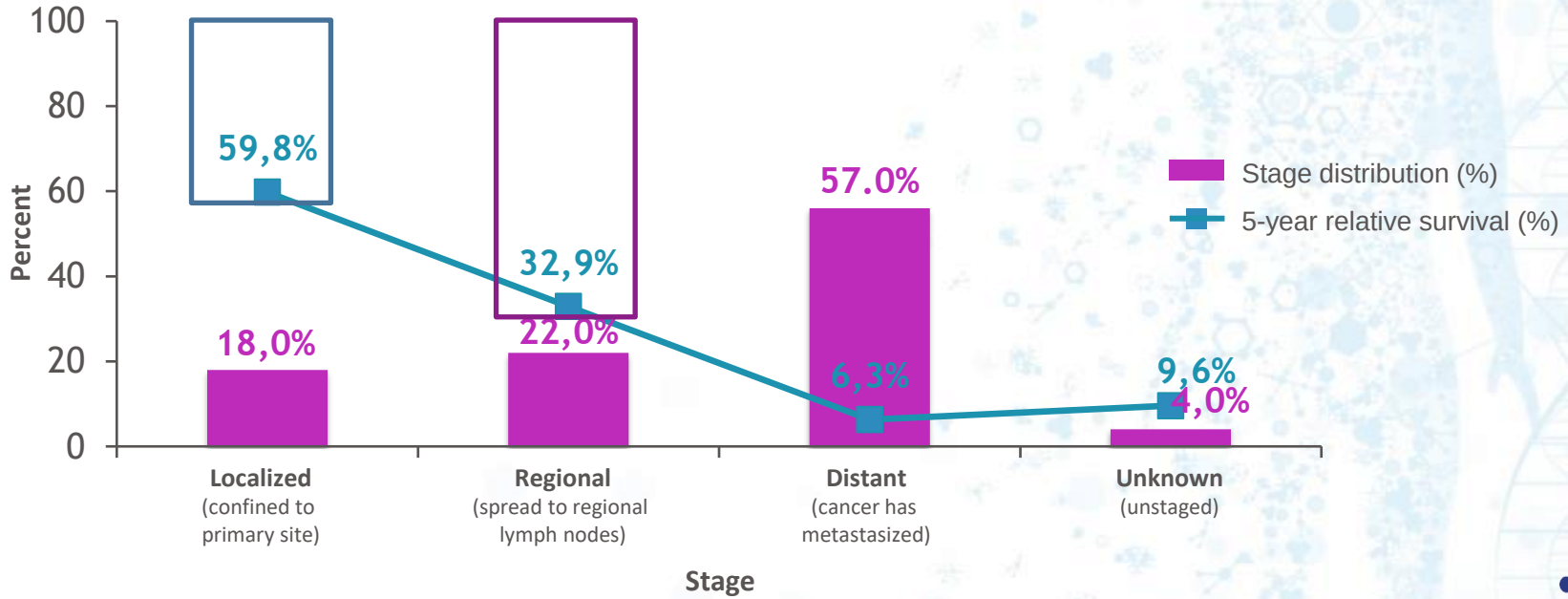
Consultant:
AstraZeneca, BMS, Boerhringer-Ingelheim, Celgene, MSD, Roche, Takeda, Thermo-Fisher

Stock holder:
- None

- **NADIM IP CM 816 investigator**

Disease burden and relative survival of patients with lung cancer by stage of disease at diagnosis in the United States

Stage distribution and 5-year relative survival of patients with lung cancer by stage at diagnosis for 2011–2017 in the US, all races, both sexes



US, United States.
Surveillance, Epidemiology, and End Results Program (SEER). Cancer Stat Facts: Lung and Bronchus Cancer. Accessed June 15, 2021. http://seer.cancer.gov/statfacts/html/lungb.html.

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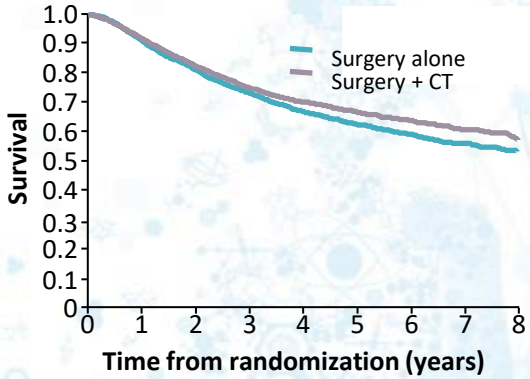
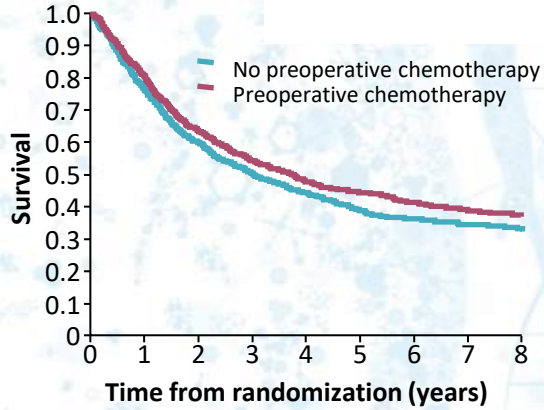
Stages I & II → Surgery & Adjuvant QT

Stage IIIA → Resectable → Surgical Multimodal treatment



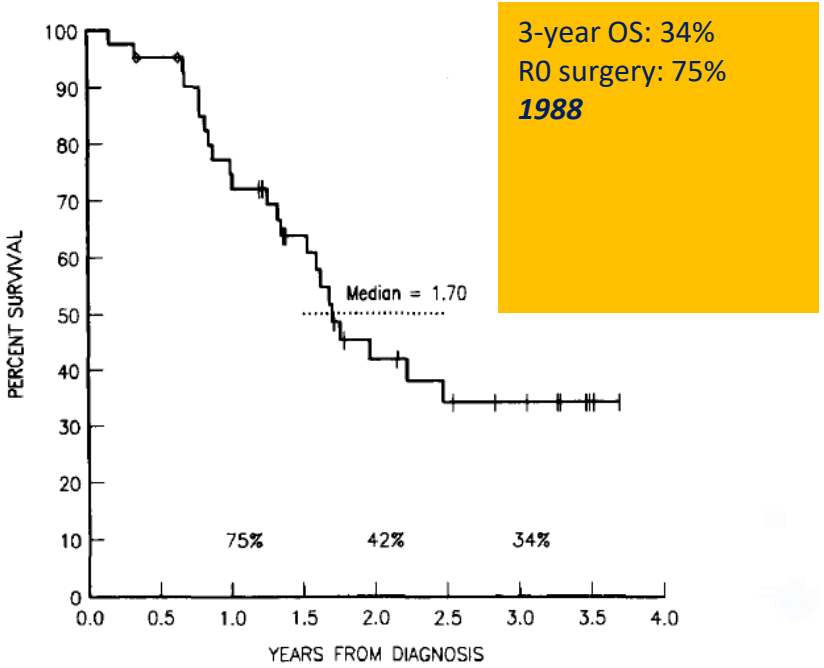


- **NEOADJUVANT and ADJUVANT therapies are treatment options that may improve outcomes in patients undergoing surgery**

NSCLC BMJ 1995; Lancet 2014

The Effects of Preoperative Chemotherapy on the Resectability of Non–Small Cell Lung Carcinoma with Mediastinal Lymph Node Metastases (N2 M0)

Nael Martini, M.D., Mark G. Kris, M.D., Richard J. Gralla, M.D., Manjit S. Bains, M.D., Patricia M. McCormack, M.D., Larry R. Kaiser, M.D., Michael E. Burt, M.D., and Muhammad B. Zaman, M.D.



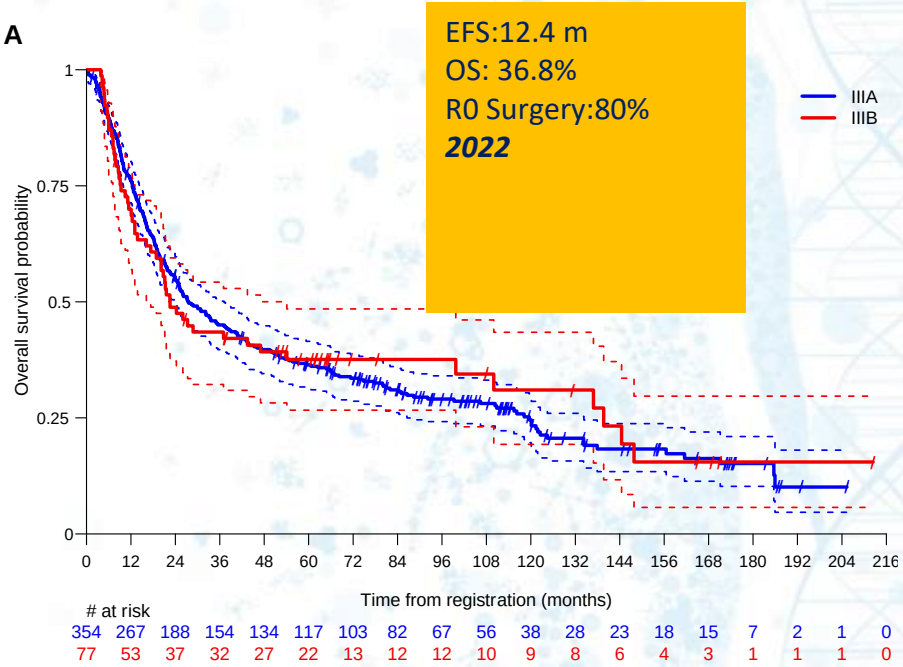
3-year OS: 34%
R0 surgery: 75%
1988

Fig 4. Survival from diagnosis for 41 patients treated with chemotherapy.

Martini N et al. The effects of preoperative chemotherapy on the resectability of non-small cell lung carcinoma with mediastinal lymph node metastases (N2 M0). Ann Thorac Surg. 1988 Apr;45(4):370-9.

Long-term outcomes of operable stage III NSCLC in the pre-immunotherapy era: results from a pooled analysis of the SAKK 16/96, SAKK 16/00, SAKK 16/01, and SAKK 16/08 trials

D. König, MD[1*], S. Schär[2], D. Vuong[3], M. Guckenberger[3], K. Furrer[4], I. Opitz[4], W. Weder[5], S. I. Rothschild[1], A. Ochsenbein[6], A. Zippelius[1], A. Addeo[7], M. Mark[8], E. I. Eboulet[2], S. Hayoz[2], S. Thierstein[2], D. C. Betticher[9], H.-B. Ris[10], R. Stupp[11], A. Curioni-Fontecedro[12], S. Peters[13], M. Pless[14] & M. Früh[15]



EFS:12.4 m
OS: 36.8%
R0 Surgery:80%
2022

König D et al. Corrigendum to 'Long-term outcomes of operable stage III NSCLC in the pre-immunotherapy era: results from a pooled analysis of the SAKK 16/96, SAKK 16/00, SAKK 16/01, and SAKK 16/08 trials': [ESMO Open Volume 7, Issue 2, (2022), 100455]. ESMO Open. 2022 Jun;7(3):100494.

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New data?
Where does the data come from?

IASLC	O.S. 60 m
IB	68%
IIA	60%
IIB	53%
IIIA	36%

Stages I & II → Surgery & Adjuvant Ch

Neoadjuvant: **CM 816** (IB-IIIA)

Stage IIIA → Resectable

Perioperative: **NADIM I** (IIIA)

Adjuvant (IB-IIIA)
IMpower010 Atezolizumab
KN 091 Pembrolizumab

Perioperative
AEGEAN: Durva + Chemo (Neo): surgery + Adjuvant Durva
NEOTORCH: toripalimab + platinum Surgery + Adjuvant Tori
KN 671: Pembro + Chemo (Neo) Surgery+ adjuvant pembro
CM 77T: Nivo+ Chemo (Neo). Surgery + Adjuvant Nivo

Perioperative IIIA
NADIM II: Nivo+ Chemo (Neo). Surgery + Adjuvant Nivo (**Stage IIIA**)

Studies bringing new data

NADIM I	IIIA (7th)
NADIM II N2- T4 N01	IIIA-IIIB (8th)
CM 816	Ib-IIIIA (7th)

NEOTORCH	II-IIIA-IIIB (8th)
AEGEAN	IIIA-IIA-IIIB (N2) (8th)
KN 671	IIA-IIIB (8th)
CM 77T	IIA-IIIB (8th)

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Studies bringing new data

NADIM I		IIIA (7th)
NADIM II	N2- T4 N01	IIIA-IIIB (8th)

CM 77T	IIA-IIIB (8th)

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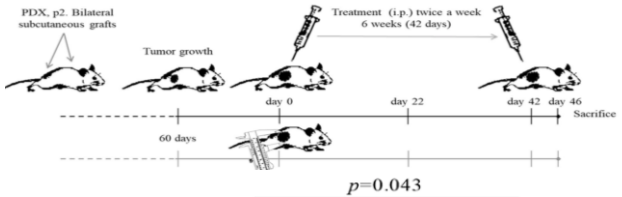
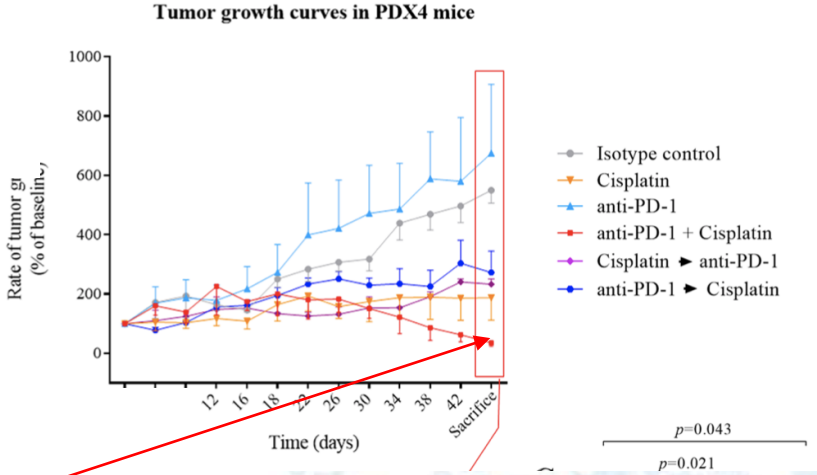
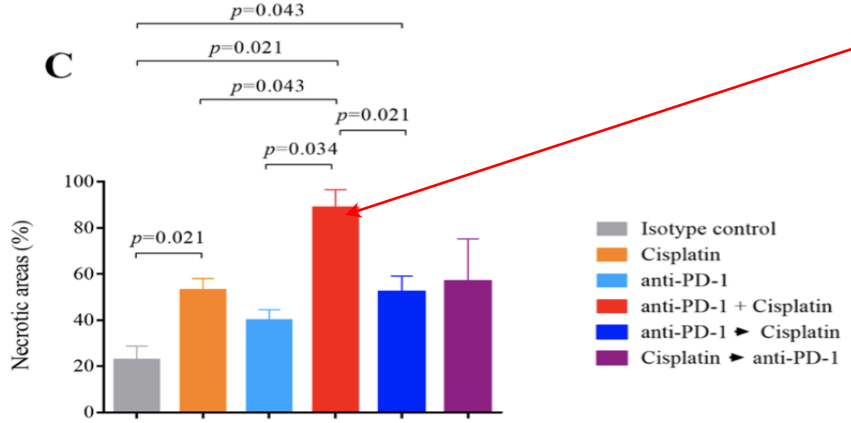
Effects of anti-PD-1 immunotherapy on tumor regression: insights from a patient-derived xenograft model

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], Maria José Coronado[8], Alejandro Lucia[2,3] & Mariano Provencio[1] ✉

NADIM Rational: How to improve







Martín-Ruiz A et al. Effects of anti-PD-1 immunotherapy on tumor regression: insights from a patient-derived xenograft model. Sci Rep. 2020 Apr 27;10(1):7078.

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

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RESPUESTA A INMUMOTERAPIA.

EN UN MODELO PDX DE CARCINOMA ESCAMOSO DE PULMÓN. PDX4

RESULTADOS
áreas necróticas

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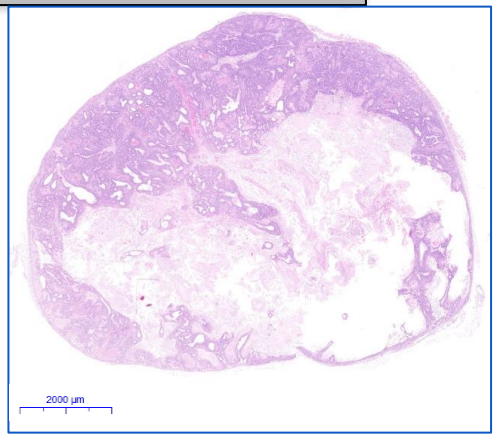

Cisplatino
53% necrosis

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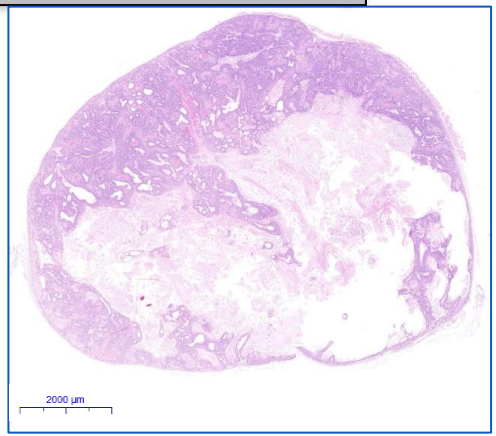
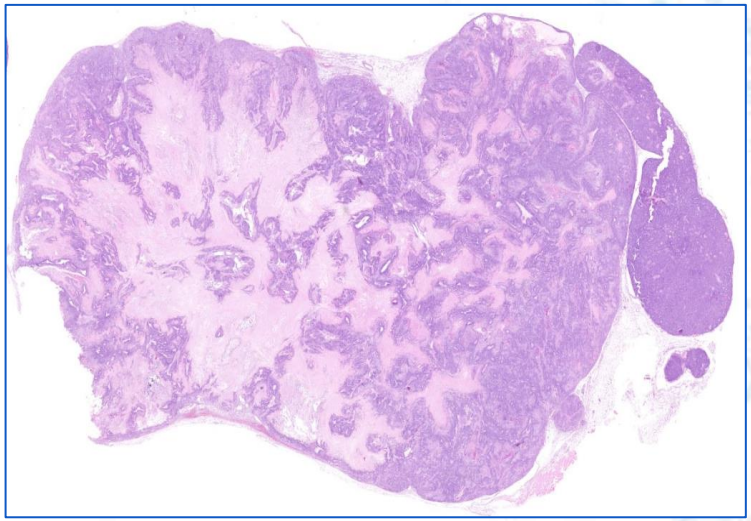


Cisplatino
53% necrosis



Nivolumab
40% necrosis

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

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EN UN MODELO PDX DE CARCINOMA ESCAMOSO DE PULMÓN. PDX4

RESULTADOS
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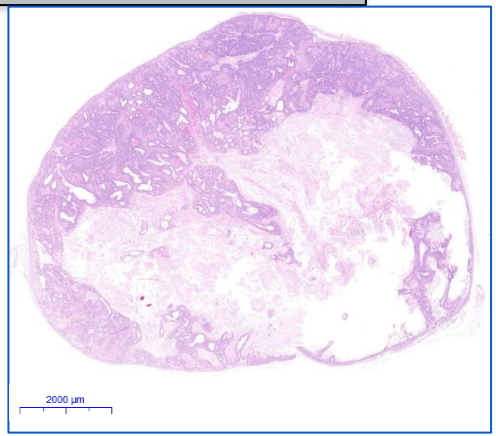
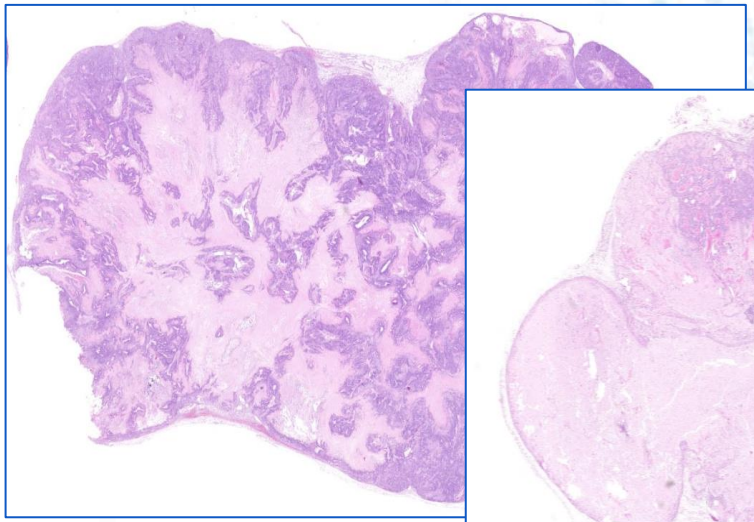
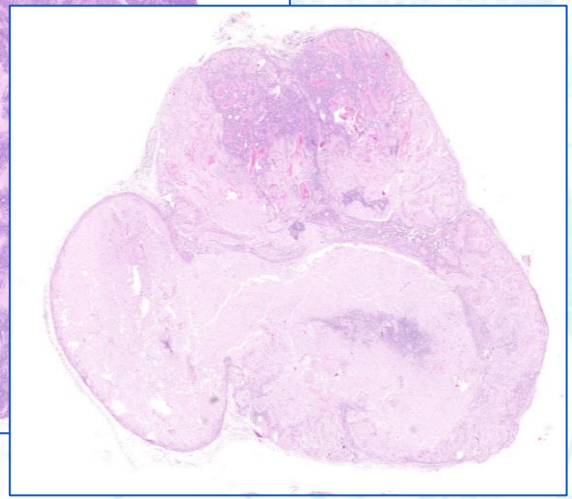


Cisplatino
53% necrosis



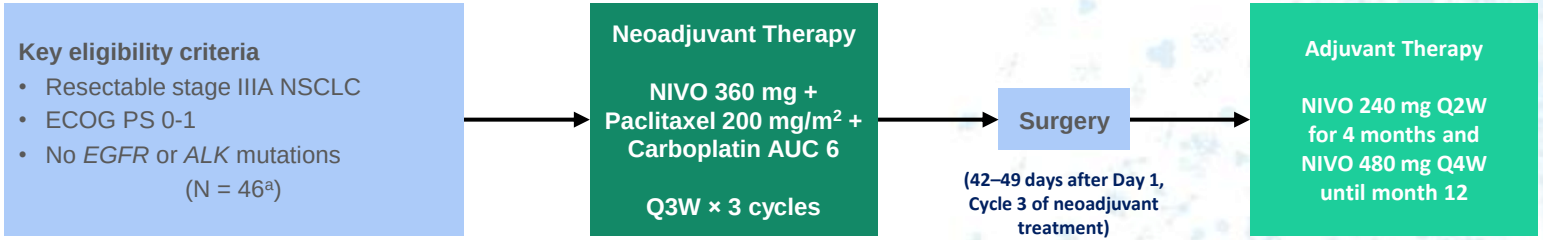
Nivolumab
40% necrosis



Cisplatino + Nivolumab (conco)
89% necrosis

NADIM (NCT03081689): study design

- NADIM was a phase 2, open-label study that assessed neoadjuvant NIVO in combination with chemotherapy in resectable stage IIIA NSCLC
- Patients received the combination prior to surgical resection, followed by adjuvant NIVO therapy



Primary endpoint:

- PFS at 24 months

Secondary endpoints:

- OS at 3 years
- Pathologic and imaging response
- Downstaging rate
- Complete resection rate
- PD rate at 3 years
- Surgical outcome
- Safety

Exploratory endpoint:

- ctDNA as a biomarker

[a]Modified ITT population, which included all patients who received neoadjuvant treatment. Per-protocol population (n = 37) included all patients who had tumor resection and received ≥ 1 cycle of adjuvant treatment.
AUC, area under the curve; ctDNA, circulating tumor DNA; NIVO, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status.
Provencio M et al. *Lancet Oncol.* 2020;21:1413–1422.

NADIM: Patient characteristics and surgical details

Patient characteristics	ITT[1] (N = 46)	Surgical group[2] (n = 41)
Age, years	median (IQR): 63 (58–70)	mean (SD): 63.8 (9.05)
Sex, n (%)		
Male	34 (74)	29 (70.7)
Female	12 (26)	12 (29.3)
ECOG PS, n (%)		
0	25 (54)	–
1	21 (46)	
Preoperative functional assessment, mean ± SD		
Forced expired volume in 1 second	–	87.80 ± 14.9
Diffusion capacity for carbon monoxide	–	75.74 ± 23.9
Maximal oxygen consumption test	–	87.33 ± 14.8
Smoking status		
Former smoker (≥ 1 year), n (%)	25 (54)	23 (56.1)
Current smoker, n (%)	21 (46)	18 (43.9)
Pack-years, median (IQR)	49 (39–61)	–
Histology, n (%)		
Adenocarcinoma	26 (57)	25 (61)
Squamous cell carcinoma	16 (35)	13 (31.7)
Not specified or undifferentiated	4 (9)	2 (4.9)
Large cell carcinoma	–	1 (2.4)
Comorbidities, n (%)		
Yes	43 (93)	–
No	3 (7)	–
Dyslipidemia	16 (35)	–
Hypertension	15 (33)	14 (34.1)
Diabetes	9 (20)	9 (22)
Chronic obstructive pulmonary disease	9 (20)	8 (19.5)
Heart disease	7 (15)	7 (17.1)
Hypercholesterolemia	4 (9)	18 (43.9)
Depressive disorder or anxiety	4 (9)	–
Nephropathy	2 (4)	2 (4.9)
Asthma	1 (2)	1 (2.4)
Vasculopathy	1 (2)	–

Clinical staging	ITT[1] (N = 46)	Surgical group[2] (n = 41)
Tumor lesion size, median (IQR), mm	35 (23–60)	–
Nodal stage, n (%)		
N0	9 (20)	8
N1	3 (7)	3
N2	**34 (74)**	30
Single	9 (20)	–
Multiple	25 (54)	–
TNM staging classification, n (%)		
T1N2M0	15 (33)	14[a]
T2N1M0	1 (2)	1[b]
T2N2M0	6 (13)	8[c]
T3N1M0	1 (2)	1
T3N2M0	13 (28)	7
T4N0M0	9 (20)	8
T4N1M0	1 (2)	1
T4N2M0	–	1

Type of resection[2]	n (%)
Lobectomy	35 (85.3)
Right upper	20 (48.8)
Bronchial sleeve	1 (2.4)
Left upper	3 (7.3)
Vascular sleeve	2 (4.9)
Right lower	5 (12.2)
Left lower	4 (9.7)
Bilobectomy	3 (7.3)
Pneumonectomy	3 (7.3)
Approach	
VATS	21 (51.2)
Conversion to open	4 (19)
Thoracotomy	20 (48.8)

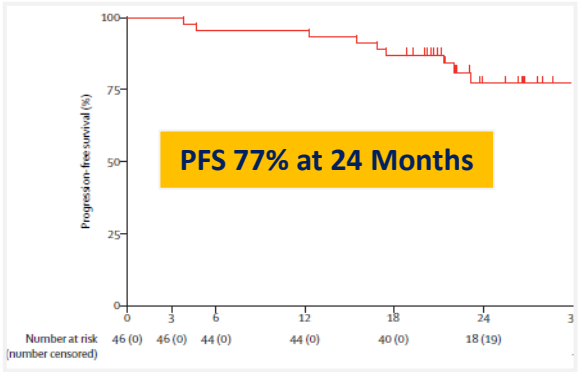
[a]T1a (n = 1), T1b (n = 7), T1c (n = 6). [b]T2b. [c]T2a (n = 5), T2b (n = 3).
IQR, interquartile range; PS, performance status; SD, standard deviation; TNM, tumor, node, metastasis; VATS, video-assisted thoracoscopic surgery.

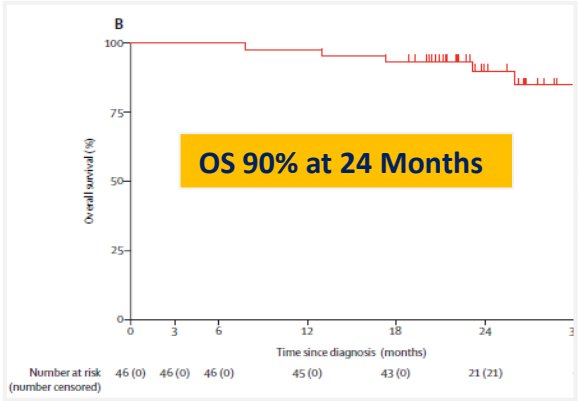
1. Provencio M et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020 Nov;21(11):1413-1422.

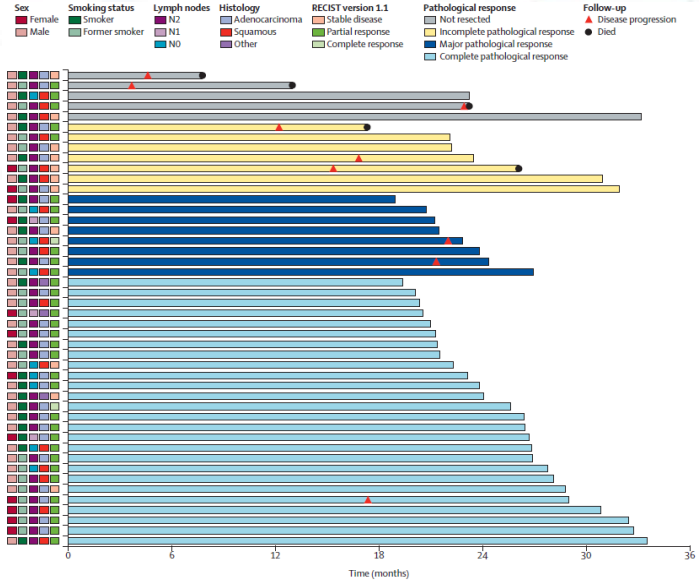
Adapted with permission.[1,2]

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

Mariano Provencio, Ernest Nadal, Amelia Insa, María Rosario García Campelo, Joaquín Casal-Rubio, Manuel Dómine, Margarita Majem, Delvys Rodríguez-Abreu, Alex Martínez-Martí, Javier De Castro Carpeño, Manuel Cobo, Guillermo López Vivanco, Edel Del Barco,







Incomplete Pathologic Response	7 (17·1 %)
Major Pathologic Response	34 (82·9 %)
Complete Pathologic Response	26 (63·4 %)

Provencio M et al. Lancet Oncol. 2020

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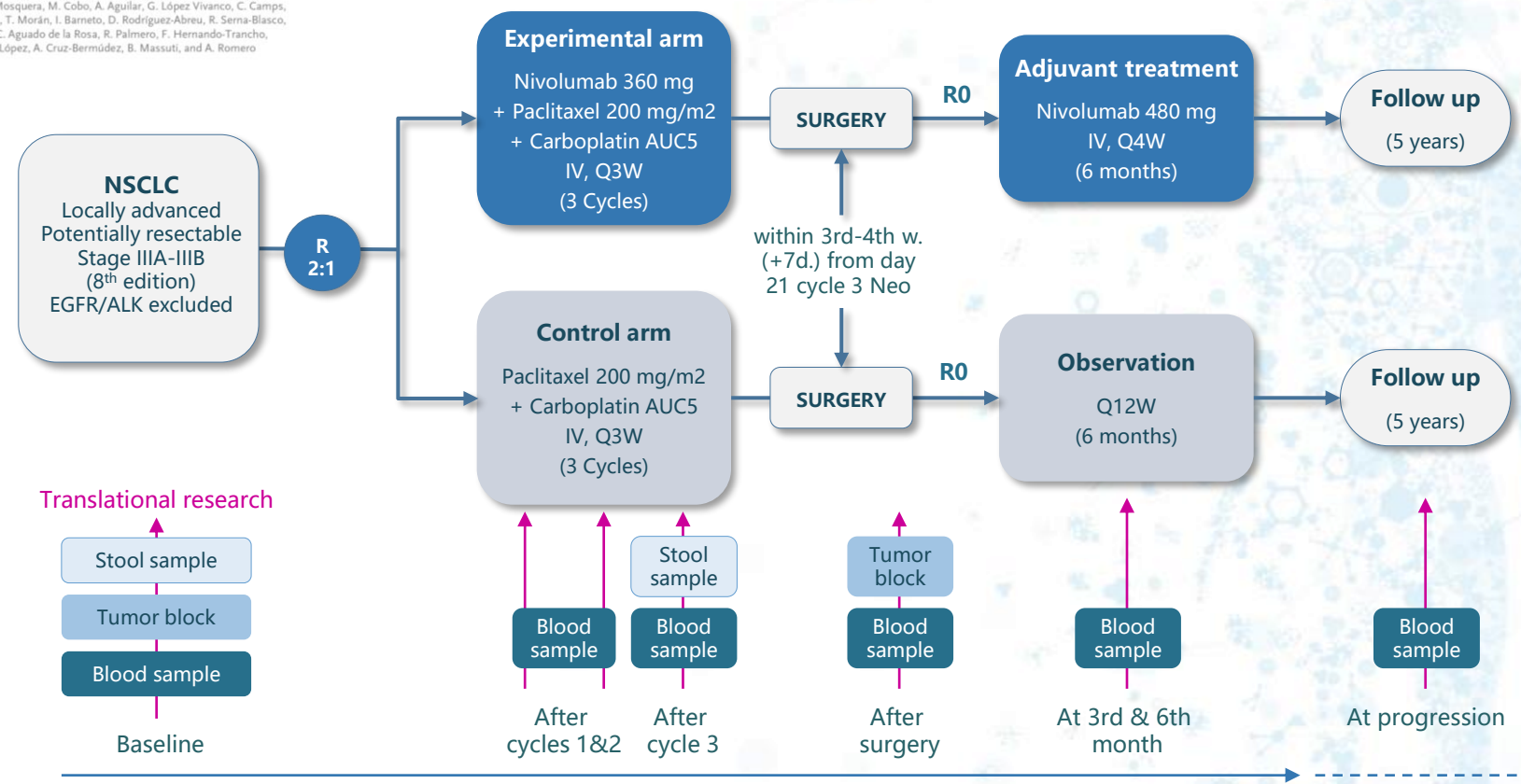
ORIGINAL ARTICLE

Perioperative Nivolumab and Chemotherapy in Stage III Non–Small-Cell Lung Cancer

M. Provencio, E. Nadal, J.L. González-Larriba, A. Martínez-Martí, R. Bernabé, J. Bosch-Barrera, J. Casal-Rubio, V. Calvo, A. Insa, S. Ponce, N. Reguart, J. de Castro, J. Mosquera, M. Cobo, A. Aguilar, G. López Vivanco, C. Camps, R. López-Castro, T. Morán, I. Barneto, D. Rodríguez-Abreu, R. Serna-Blasco, R. Benítez, C. Aguado de la Rosa, R. Palmero, F. Hernando-Trancho, J. Martín-López, A. Cruz-Bermúdez, B. Massuti, and A. Romero

NADIM II (NCT03838159): study design



Provencio M et al. Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2023 Aug 10;389(6):504-513.

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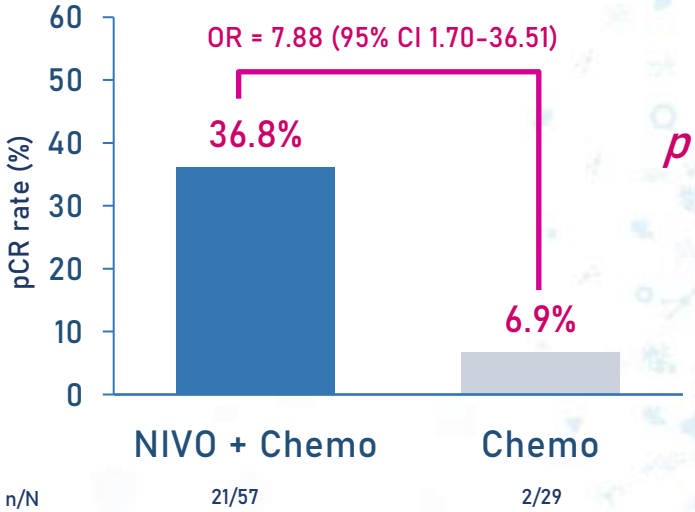
NADIM II. Primary endpoint - pCR

pCR[a] rate in the ITT population[b]

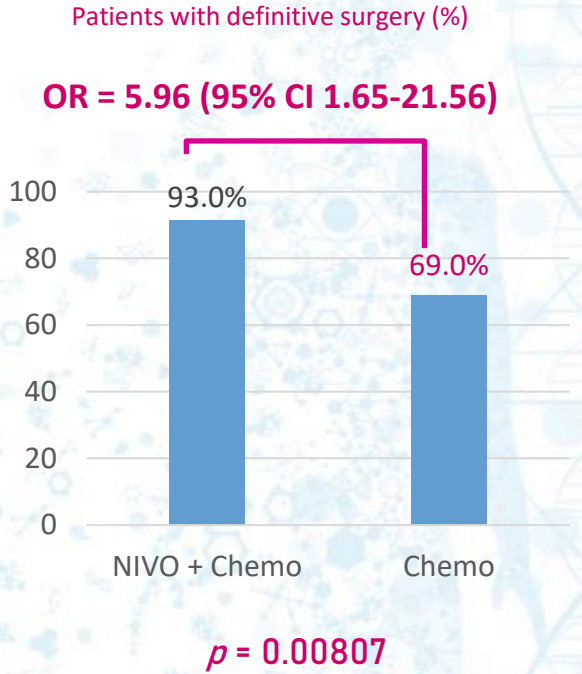


$p = 0.0068$

NNT: 3.34 (2.2—6.95)

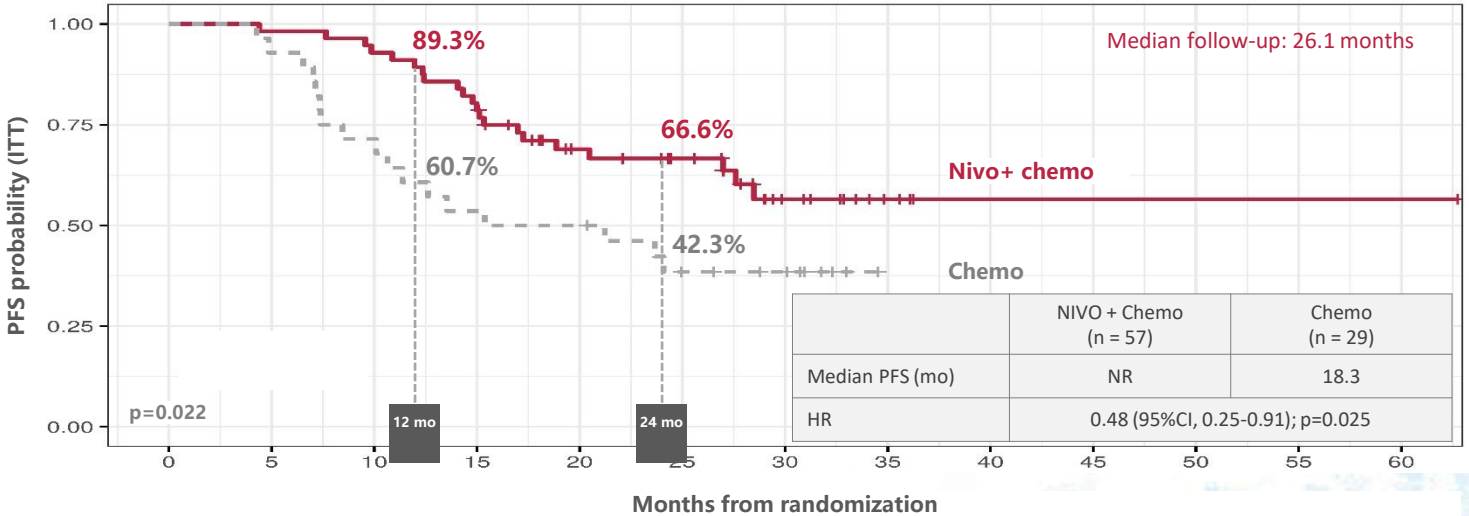
NADIM II-Surgery summary

Surgery summary			
Patients, No. (%)	**NIVO + chemo (n = 57)**	**Chemo (n = 29)**	**Total**
Patients with definitive surgery	53 (93.0)	20 (69.0)	73
Patients with cancelled definitive surgery	4 (7.0)	9 (31.0)	13
Due to adverse events	1 (1.7)	0 (0.0)	1
Due to disease progression	0 (0.0)	4 (13.7)	4
Not suitable for surgery	3 (5.2)	5 (17.2)	8



Nivo, nivolumab; Chemo, chemotherapy

NADIM II-SECONDARY ENDPOINTS – Progression-free survival

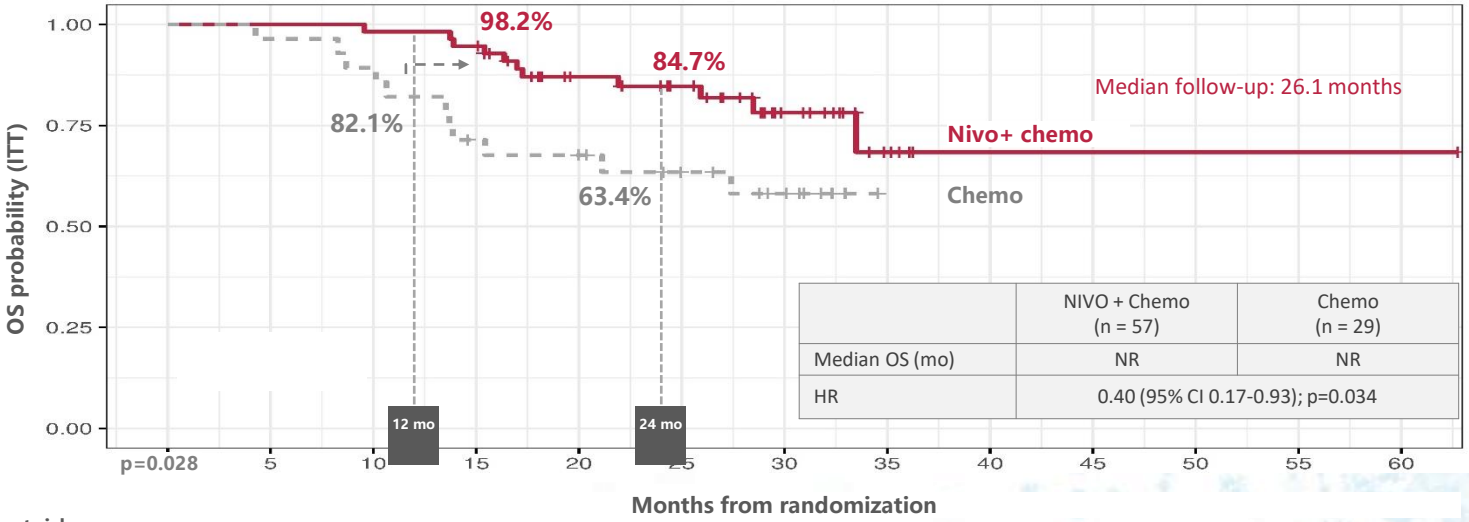


	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median PFS (mo)	NR	18.3
HR	0.48 (95%CI, 0.25-0.91); p=0.025	

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

Progression-free survival was defined as the time from randomization to any of the following events: progression of disease, recurrence disease, or death due to any cause. Progression/recurrence will have determined by RECIST 1.1

NADIM II– Overall survival



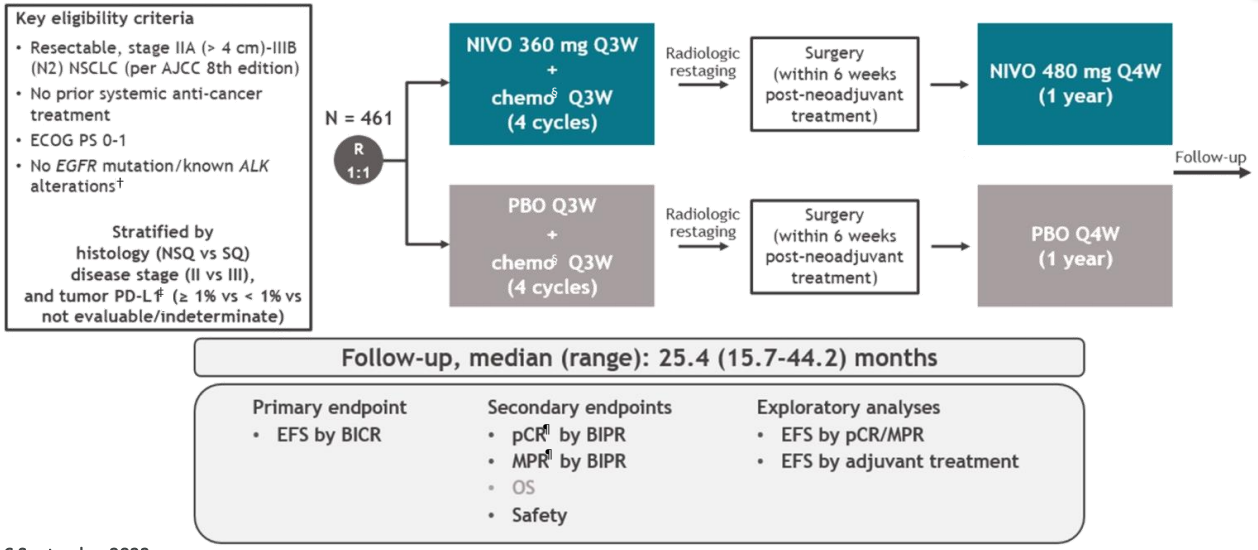
	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median OS (mo)	NR	NR
HR	0.40 (95% CI 0.17-0.93); p=0.034	

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

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

Mariano Provencio, Puerta de Hierro University Hospital, Madrid,Spain.

CheckMate 77T: Phase 3 study of neoadjuvant nivolumab + chemo and adjuvant nivolumab in patients with resectable Stage II–IIIB NSCLC*[1]



Database lock date: 6 September 2023

*NCT04025879; †*EGFR* testing was mandatory in all patient with NSQ histology. *ALK* testing was done in patients with a history of *ALK* alterations. *EGFR*/*ALK* testing done using US FDA/local health authority-approved assays; ‡Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); §NQS: cisplatin + pemetrexed, carboplatin + pemetrexed, or carboplatin + paclitaxel; SQ: cisplatin + docetaxel or carboplatin + paclitaxel; ¶Assessed per immune-related pathologic response criteria[2]

AJCC, American Joint Committee on Cancer; *ALK*, anaplastic lymphoma kinase; BICR, blinded independent central review; BIPR, blinded independent pathological review; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; *EGFR*, epidermal growth factor receptor; MPR, major pathological response; NIVO, nivolumab; NSCLC, non-small cell lung cancer; NQS, non-squamous; OS, overall survival; pCR, pathological complete response; PBO, placebo; PD-L1, programmed cell death ligand-1; QXW, every X weeks; R, randomised; SQ, squamous

1. Cascone T, et al. Presented at ESMO 2023 (Abstract LBA1); 2. Cottrell TR, et al. Ann Oncol 2018;29:1853–60

Introduction

- Nivolumab (NIVO) + chemotherapy (chemo) is the standard-of-care neoadjuvant treatment for eligible patients with resectable NSCLC

- A perioperative treatment approach including adjuvant NIVO could potentially further reduce the risk of relapse and improve clinical benefit in patients with resectable NSCLC[1,2]

- CheckMate 77T is a global, randomized, double-blind, phase 3 study evaluating neoadjuvant NIVO + chemo followed by adjuvant NIVO (NIVO + chemo/NIVO) vs chemo/placebo (PBO) in patients with resectable stage II–IIIB NSCLC

  – Here, we present results from the first prespecified EFS interim analysis

1. Provencio M, et al. *Lancet Oncol* 2020;21:1413–1422 2. Provencio M, et al. *N Engl J Med* 2023;389:504–513.

CheckMate 77T: Phase 3 study of neoadjuvant nivolumab + chemo and adjuvant nivolumab in patients with resectable Stage II–IIIB NSCLC

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Baseline characteristics

	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)*
Median age, years (range)	66 (37-83)	66 (35-86)
Male, n (%)	167 (73)	160 (69)
Geographic region, n (%)		
North America	23 (10)	21 (9)
Europe	123 (54)	127 (55)
Asia	65 (28)	50 (22)
Rest of the world[†]	18 (8)	34 (15)
ECOG PS, n (%)		
0	147 (64)	141 (61)
1	82 (36)	91 (39)
Disease stage,[‡] n (%)		
IIA-B[§]	81 (35)	81 (35)
IIIA-B[¶]	146 (64)	149 (64)
Histology, n (%)		
Squamous	116 (51)	118 (51)
Non-squamous	113 (49)	114 (49)

	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)*
Smoking status, n (%)		
Current/former	212 (93)	205 (88)
Never	17 (7)	27 (12)
Tumor PD-L1 expression,[#] n (%)		
Not evaluable	8 (4)	11 (5)
< 1%	93 (41)	93 (40)
≥ 1%	128 (56)	128 (55)
1-49%	83 (36)	76 (33)
≥ 50%	45 (20)	52 (22)
Platinum therapy type, n (%)		
Cisplatin	55 (24)	42 (18)
Carboplatin	167 (73)	180 (78)

Percentages may not total 100 due to rounding. *1 (<1%) patient with squamous histology had reported *EGFR* mutation; this was tested locally and could not be confirmed due to site closure; [†]Includes only Argentina, Australia, Brazil, and Mexico; [‡]Disease stage (per AJCC 8th edition) as reported in case report forms. 2 (1%) patients in the NIVO + chemo/NIVO arm had Stage IIIC disease, and 2 (1%) patients in the chemo/PBO arm had Stage IV disease; [§]Stage IIA was reported in 15 (7%) patients in the NIVO + chemo/NIVO arm and 18 (8%) patients in the chemo/PBO arm; Stage IIB disease was reported in 66 (29%) and 63 (27%) patients, respectively; [¶]Stage IIIA was reported in 103 (45%) patients in the NIVO + chemo/NIVO arm and 114 (49%) patients in the chemo/PBO arm; Stage IIIB disease was reported in 43 (19%) and 35 (15%) patients, respectively, [#]Determined using the PD-L1 IHC 28-8 pharmDx assay (Dako)

AJCC, American Joint Committee on Cancer; Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; NIVO, nivolumab; NSCLC, non-small cell lung cancer; PBO, placebo; PD-L1, programmed cell death ligand-1

Cascone T, et al. Presented at ESMO 2023 (Abstract LBA1)

CheckMate 77T: Phase 3 study of neoadjuvant nivolumab + chemo and adjuvant nivolumab in patients with resectable Stage II–IIIB NSCLC

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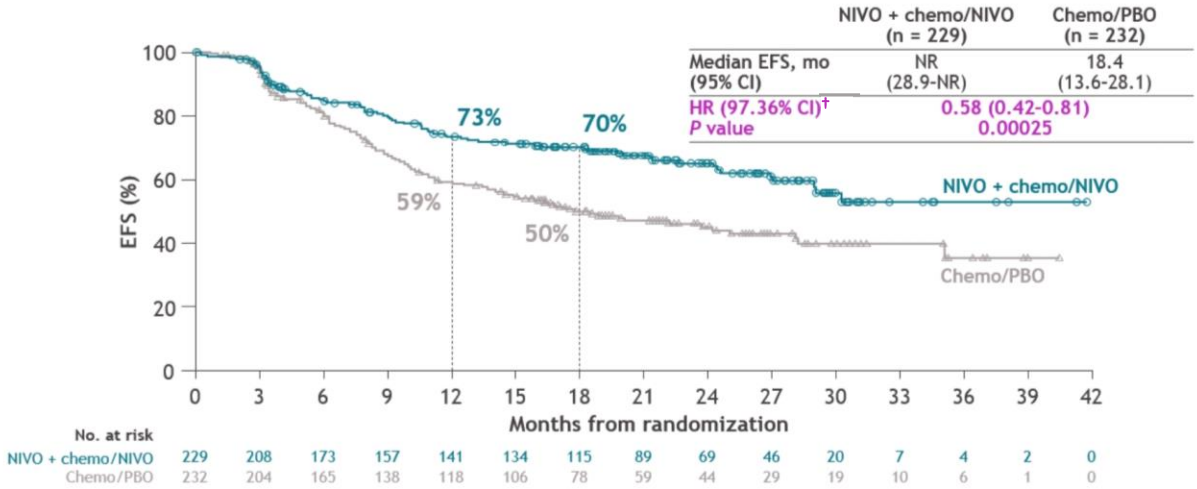
Primary endpoint: EFS* per BICR with neoadjuvant NIVO + chemo/adjuvant NIVO vs chemo/PBO



- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41–0.76

Median follow-up (range): 25.4 months (15.7-44.2). *Time from randomisation to any disease progression precluding surgery, abandoned surgery due to unresectability or disease progression, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause. Patients who received subsequent therapy were censored at the last evaluable tumour assessment on or prior to the date of subsequent therapy. †Unstratified HR (95% CI), 0.59 (0.44–0.79)

BICR, blinded independent central review; CI, confidence interval; Chemo, chemotherapy; EFS, event-free survival; HR, hazard ratio; NIVO, nivolumab; NSCLC, non-small cell lung cancer; PBO, placebo

Cascone T, et al. Presented at ESMO 2023 (Abstract LBA1)

CheckMate 77T: Phase 3 study of neoadjuvant nivolumab + chemo and adjuvant nivolumab in patients with resectable Stage II–IIIB NSCLC

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EFS analysis by key subgroups

	Median EFS*, mo		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)		
Overall (N = 461)	NR	18.4		0.59 (0.44-0.79)
< 65 years (n = 202)	NR	16.7		0.55 (0.36-0.85)
≥ 65 years (n = 259)	NR	20.1		0.61 (0.41-0.91)
Male (n = 327)	NR	16.7		0.53 (0.37-0.75)
Female (n = 134)	30.2	18.8		0.71 (0.41-1.20)
North America (n = 44)	30.2	9.4		0.59 (0.25-1.38)
Europe (n = 250)	NR	23.7		0.61 (0.40-0.92)
Asia (n = 115)	NR	13.9		0.47 (0.26-0.86)
ECOG PS 0 (n = 288)	NR	20.1		0.57 (0.39-0.83)
ECOG PS 1 (n = 173)	29.0	17.3		0.61 (0.39-0.97)
Stage II (n = 162)	NR	NR		0.81 (0.46-1.43)
Stage III (n = 297)	30.2	13.4		0.51 (0.36-0.72)
N0 (n = 167)†	NR	NR		0.80 (0.48-1.32)
N1 (n = 108)†	NR	28.1		0.58 (0.29-1.16)
N2 (n = 182)†‡	30.2	10.0		0.46 (0.30-0.70)
Single-station (n = 112)	30.2	10.0		0.49 (0.29-0.84)
Multi-station (n = 69)	NR	10.0		0.43 (0.21-0.88)
Squamous (n = 234)	NR	17.0		0.46 (0.30-0.72)
Non-squamous (n = 227)	28.9	18.4		0.72 (0.49-1.07)
Current/former smoker (n = 417)	NR	17.0		0.54 (0.40-0.74)
Never smoker (n = 44)	19.7	25.0		1.32 (0.54-3.20)
PD-L1 < 1% (n = 186)§	29.0	19.8		0.73 (0.47-1.15)
PD-L1 ≥ 1% (n = 256)§	NR	15.8		0.52 (0.35-0.78)
PD-L1 1-49% (n = 159)¶	30.2	28.1		0.76 (0.46-1.25)
PD-L1 ≥ 50% (n = 97)	NR	8.0		0.26 (0.12-0.55)
Cisplatin (n = 97)	27.0	15.8		0.61 (0.35-1.08)
Carboplatin (n = 347)	NR	17.3		0.53 (0.37-0.75)

Median follow-up (range): 25.4 months (15.7-44.2). *Per BICR; †Nodal status was N3 in 4 patients; ‡N2 subcategory was not reported in 1 patient. Baseline characteristics were similar across treatment arms in the N2 nodal status subgroup, which comprised ~40% of patients; §Tumour PD-L1 expression was not evaluable/indeterminate in 19 patients; ¶Most patients in this subgroup had low PD-L1 expression (median 10% across both arms)
BICR, blinded independent central review; CI, confidence interval; Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; HR, hazard ratio; NIVO, nivolumab; NSCLC, non-small cell lung cancer; PBO, placebo; PD-L1, programmed cell death ligand-1
Cascone T, et al. Presented at ESMO 2023 (Abstract LBA1)

CheckMate 77T: Phase 3 study of neoadjuvant nivolumab + chemo and adjuvant nivolumab in patients with resectable Stage II–IIIB NSCLC

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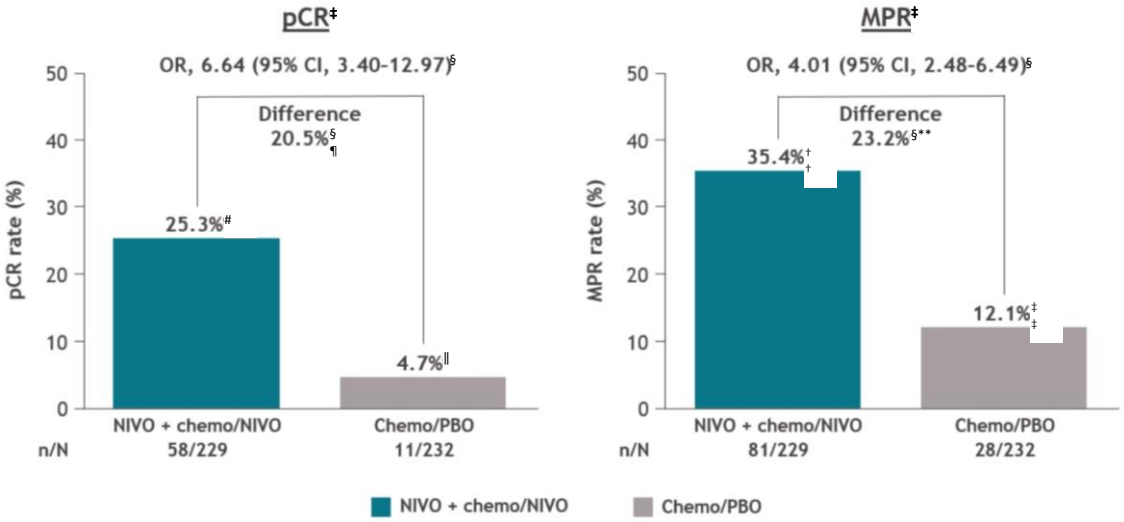
pCR* and MPR† per BIPR



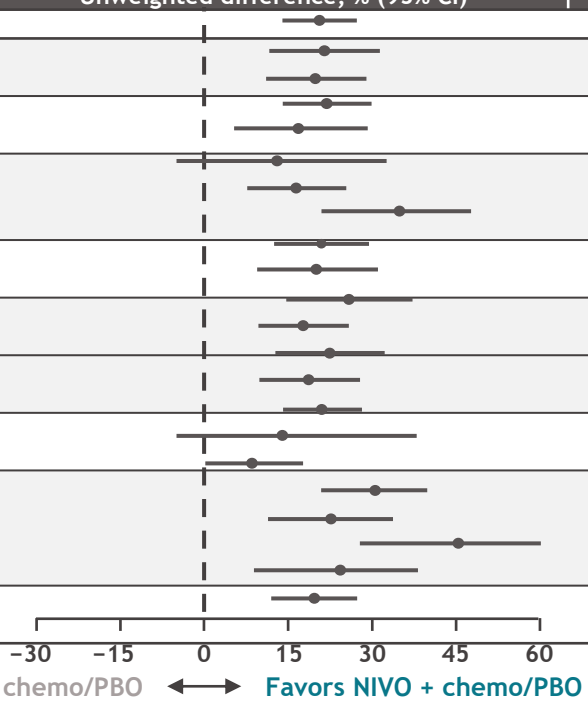
*0% residual viable tumour cells post-surgery in both primary tumour (lung) and sampled lymph nodes per immune-related pathologic response criteria; †≤10% residual viable tumour cells post-surgery in both primary tumour (lung) and sampled nodes per immune-related pathologic response criteria; ‡Patients who did not undergo surgery or received alternative anti-cancer treatment prior to surgery were classified as non-responders; §Calculated using the stratified Cochran-Mantel-Haenszel method; ¶–‡‡95% CI: ¶14.3–26.6; #19.8–31.5; ‖2.4–8.3; **15.8–30.6; ††29.2–41.9; ‡‡8.2–17.0

Chemo, chemotherapy; CI, confidence interval; MPR, major pathological response; NIVO, nivolumab; NSCLC, non-small cell lung cancer; OR, odds ratio; PBO, placebo; pCR, pathological complete response

Cascone T, et al. Presented at ESMO 2023 (Abstract LBA1)

pCR subgroup analysis

	pCR rate,[a] %		Unweighted difference, % (95% CI)	Unweighted difference, %
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)		
Overall (N = 461)	25.3	4.7		20.6
< 65 years (n = 202)	25.5	4.0		21.5
≥ 65 years (n = 259)	25.2	5.3		19.9
Male (n = 327)	26.9	5.0		21.9
Female (n = 134)	21.0	4.2		16.8
North America (n = 44)	13.0	0		13.0
Europe (n = 250)	22.0	5.5		16.4
Asia (n = 115)	36.9	2.0		34.9
ECOG PS 0 (n = 288)	25.9	5.0		20.9
ECOG PS 1 (n = 173)	24.4	4.4		20.0
Stage II (n = 162)	29.6	3.7		25.9
Stage III (n = 299)[b]	23.0	5.3		17.7
Squamous (n = 234)	28.4	5.9		22.5
Non-squamous (n = 227)	22.1	3.5		18.6
Current/former smoker (n = 417)	25.9	4.9		21.1
Never smoker (n = 44)	17.6	3.7		13.9
PD-L1 < 1% (n = 186)[c]	12.9	4.3		8.6
PD-L1 ≥ 1% (n = 256)[c]	35.2	4.7		30.5
PD-L1 1–49% (n = 159)[c]	26.5	3.9		22.6
PD-L1 ≥ 50% (n = 97)[c]	51.1	5.8		45.3
Cisplatin (n = 97)	29.1	4.8		24.3
Carboplatin (n = 347)	24.6	5.0		19.6



[a]Per BIPR. [b]Included 2 patients with stage IV disease. [c]Tumor PD-L1 expression was not evaluable/indeterminate in 19 patients.

CheckMate 77T: Phase 3 study of neoadjuvant nivolumab + chemo and adjuvant nivolumab in patients with resectable Stage II–IIIB NSCLC

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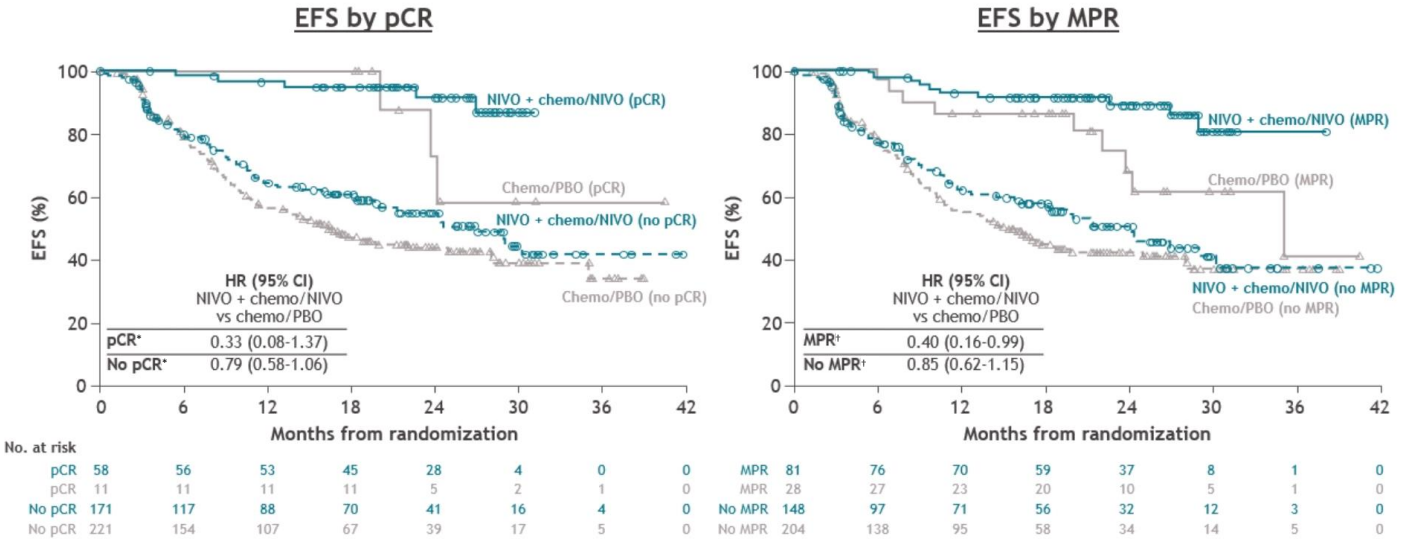
Exploratory analysis: EFS by pCR and MPR status



Median follow-up (range): 25.4 months (15.7-44.2). *HR (95% CI) 0.14 (0.06-0.35) in patients with pCR vs those without in the NIVO + chemo/NIVO arm and 0.32 (0.10-1.00) in the chemo/PBO arm; †HR (95% CI) 0.18 (0.09-0.35) in patients with MPR vs those without in the NIVO + chemo/NIVO arm and 0.40 (0.20-0.78) in the chemo/PBO arm

Chemo, chemotherapy; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; MPR, major pathological response; NIVO, nivolumab; NSCLC, non-small cell lung cancer; PBO, placebo; pCR, pathological complete response

Cascone T, et al. Presented at ESMO 2023 (Abstract LBA1)

CheckMate 77T: Phase 3 study of neoadjuvant nivolumab + chemo and adjuvant nivolumab in patients with resectable Stage II–IIIB NSCLC

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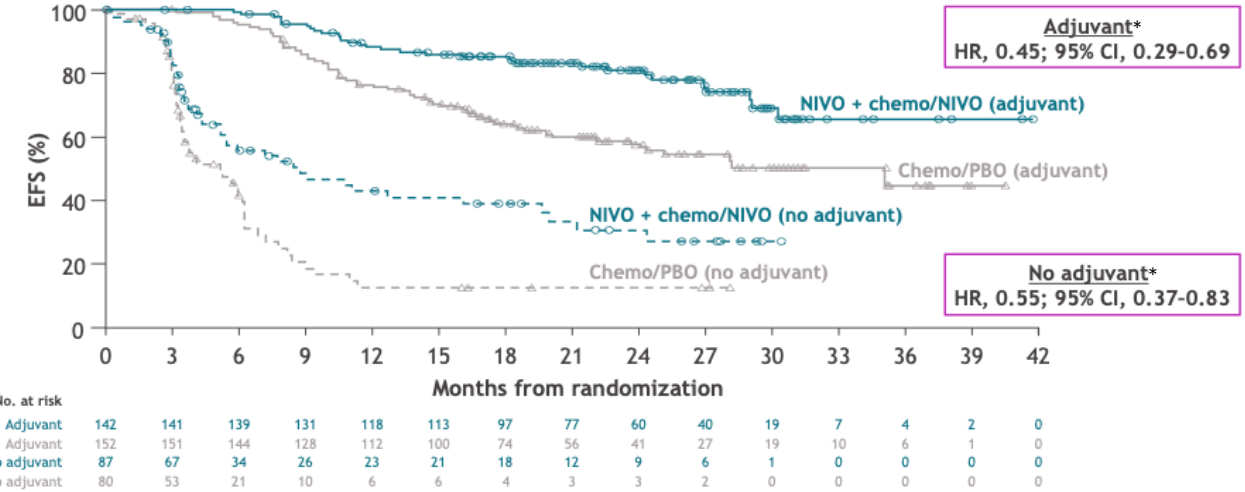
Exploratory analysis: EFS by adjuvant treatment status



- NIVO + chemo/NIVO improved EFS versus chemo/PBO with numerically higher benefit in patients who received adjuvant treatment (HR [95% CI], 0.45 [0.29, 0.69]) vs those who did not (HR [95% CI], 0.55 [0.37, 0.83])†

Median follow-up (range): 25.4 months (15.7–44.2). *HR (95% CI) with NIVO + chemo/NIVO vs chemo/PBO; †HR (95% CI), 0.17 (0.11, 0.27) in patients who received adjuvant treatment versus those who did not in the NIVO + chemo/NIVO arm and 0.15 (0.10, 0.22) in the chemo/PBO arm

Chemo, chemotherapy; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; NIVO, nivolumab; NSCLC, non-small cell lung cancer; PBO, placebo

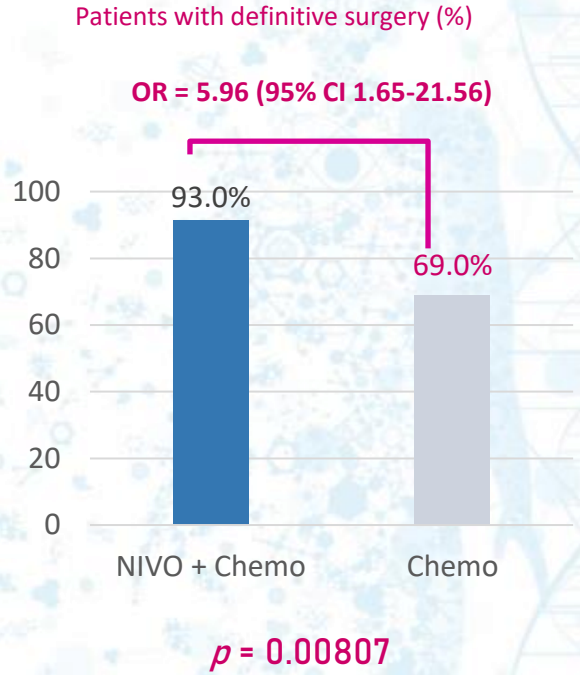
Cascone T, et al. Presented at ESMO 2023 (Abstract LBA1) and information provided Professor Provencio

Neoadjuvant treatment

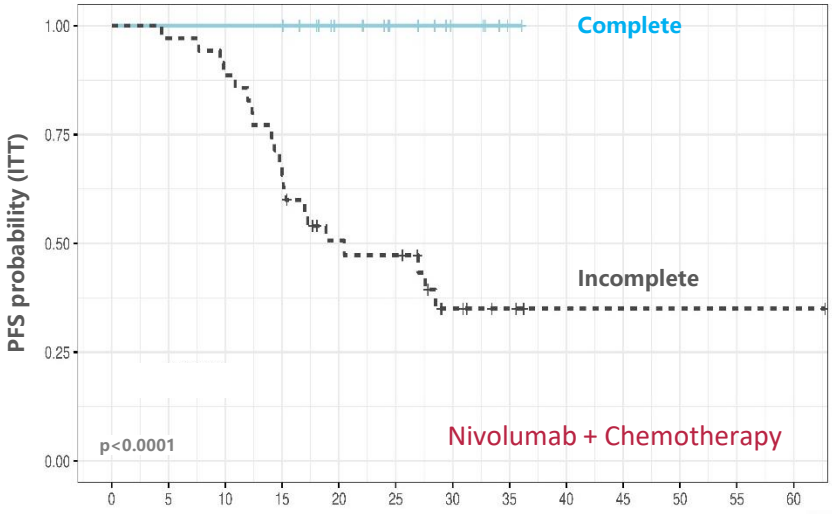
- Introduction
  - Old fashion neoadjuvant treatments
- New data, new trials
  - Design
  - Primary end points
- New Key aspects
  - Surgery aspects
  - Pathologic response
  - Biomarkers

NADIM II-Surgery summary

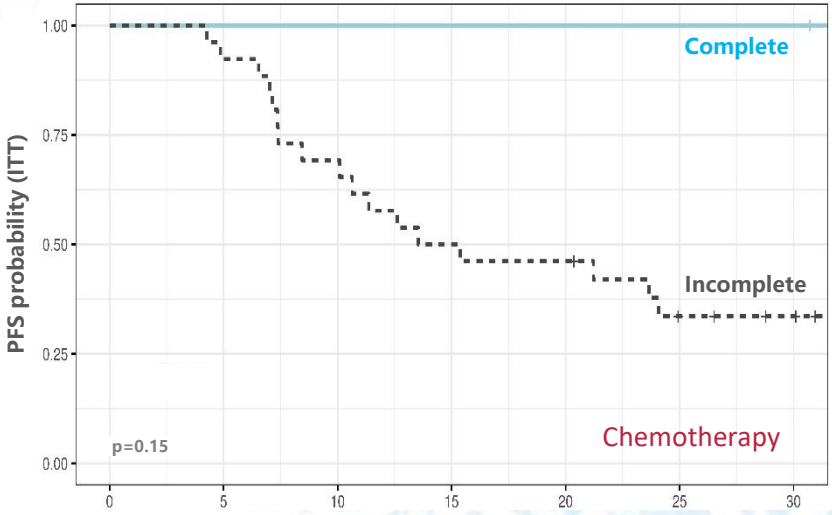
	NIVO + chemo (n = 57)	Chemo (n = 29)	Total
Patients with definitive surgery	53 (93.0)	20 (69.0)	73
Patients with cancelled definitive surgery	4 (7.0)	9 (31.0)	13
Due to adverse events	1 (1.7)	0 (0.0)	1
Due to disease progression	0 (0.0)	4 (13.7)	4
Not suitable for surgery	3 (5.2)	5 (17.2)	8



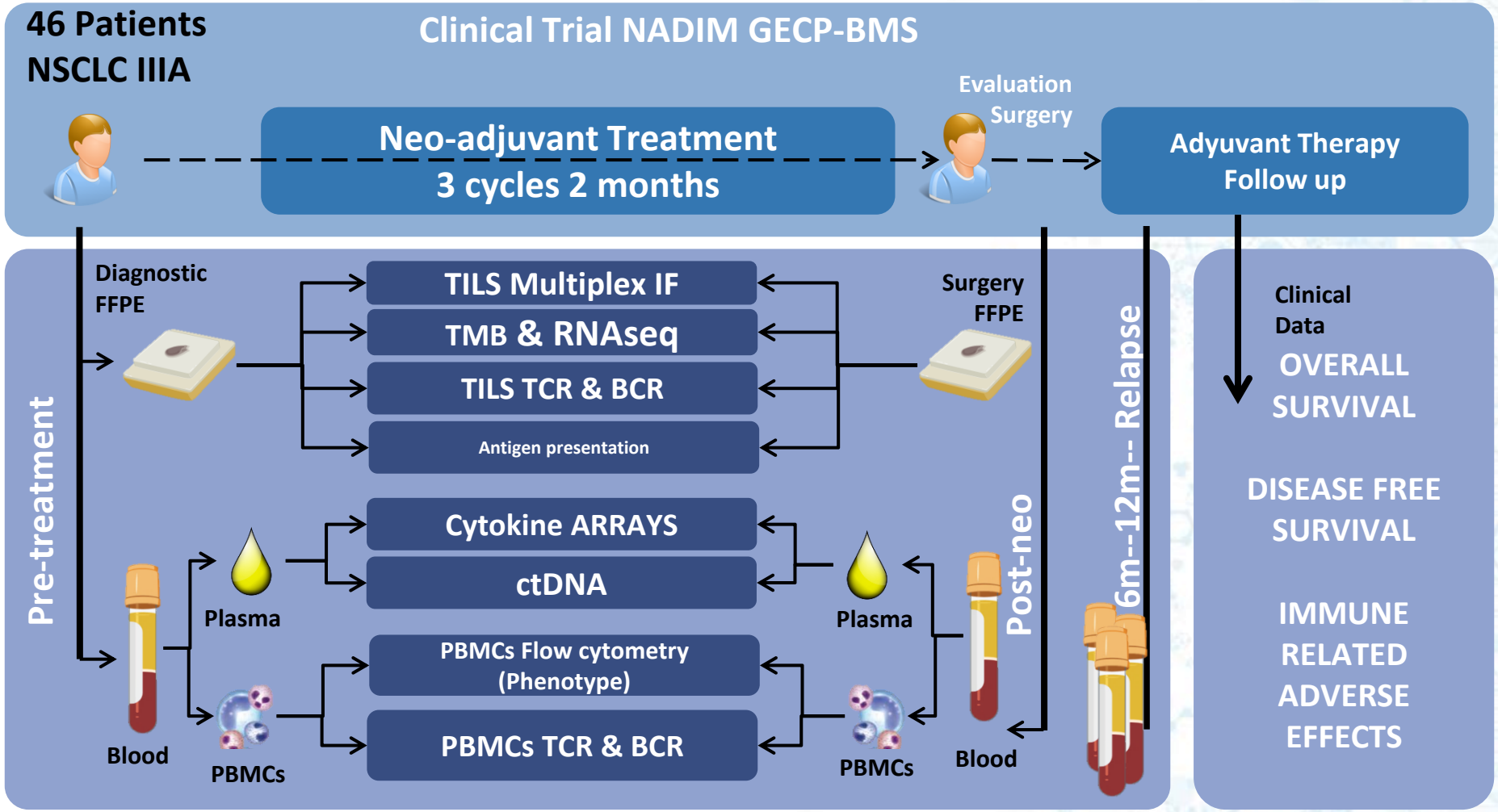
Secondary Endpoints – PFS by pCR status (NADIM II)

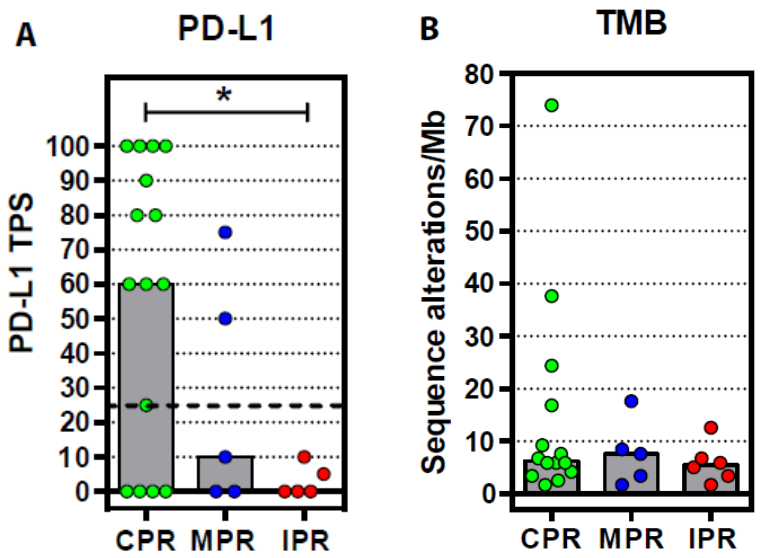


Number at risk													
Complete	21	21	21	21	15	10	5	1	0	0	0	0	0
Incomplete	35	34	31	23	15	14	6	3	1	1	1	1	1



Number at risk							
Complete	2	2	2	2	2	2	2
Incomplete	26	24	18	13	12	7	5

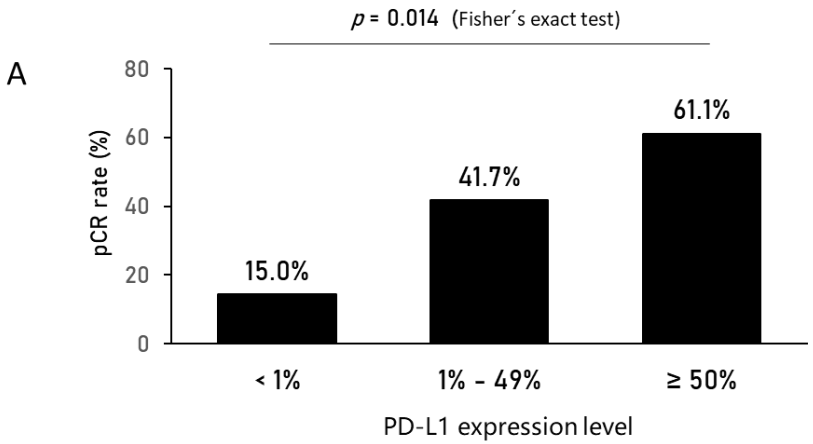

46 Patients
NSCLC IIIA
Clinical Trial NADIM GECP-BMS
Neo-adjuvant Treatment
3 cycles 2 months
Evaluation
Surgery
Adyuvant Therapy
Follow up
Pre-treatment
Diagnostic
FFPE
Surgery
FFPE
TILS Multiplex IF
TMB & RNAseq
TILS TCR & BCR
Antigen presentation
Cytokine ARRAYS
ctDNA
Plasma
Plasma
Blood
PBMCs
PBMCs Flow cytometry
(Phenotype)
PBMCs TCR & BCR
PBMCs
Blood
Post-neo
6m--12m-- Relapse
Clinical
Data
OVERALL
SURVIVAL
DISEASE FREE
SURVIVAL
IMMUNE
RELATED
ADVERSE
EFFECTS



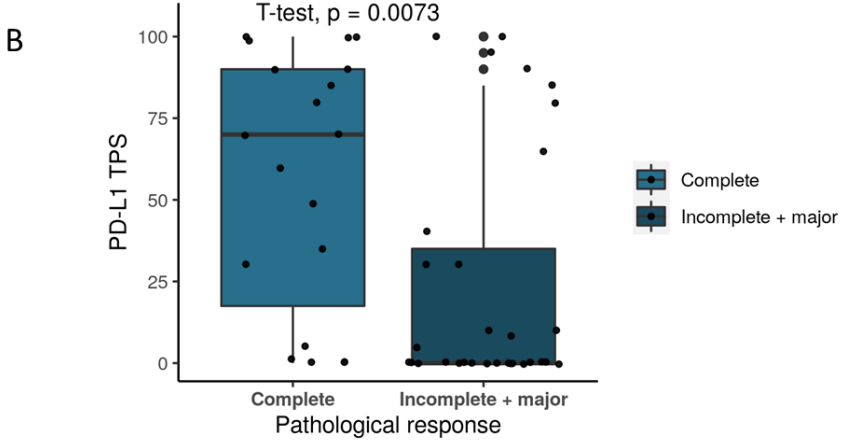
PD-L1: CPR showed higher PD-L1 TPS
TMB no associated to pResponse

Provencio et. al., Lancet Oncology 2020.

PD-L1



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

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

Received: 13 April 2021 | Revised: 17 June 2021 | Accepted: 21 June 2021 | Published online: 14 July 2021

DOI: 10.1002/ctm2.491

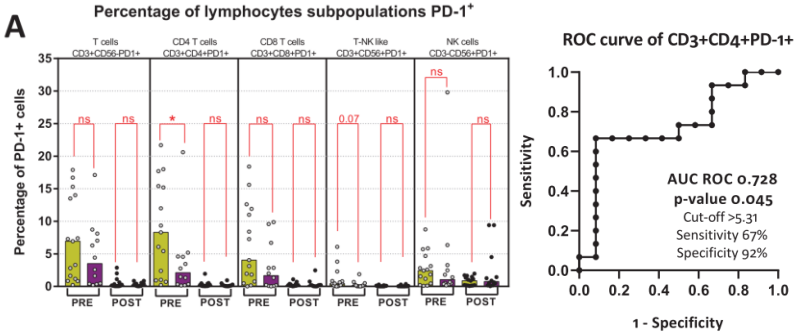
CLINICAL AND TRANSLATIONAL MEDICINE | WILEY

RESEARCH ARTICLE

Blood biomarkers associated to complete pathological response on NSCLC patients treated with neoadjuvant chemoimmunotherapy included in NADIM clinical trial

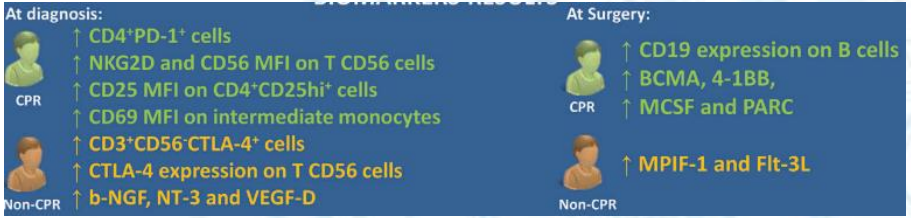
BIOMARKER

Level of PD1+ cells Pre-treatment associated to CPR



MECHANISM

Differential impact of treatment in CPR at peripheral level



1. Non-small cell lung cancer (NSCLC) patients achieving complete pathologic response (CPR) after neoadjuvant chemoimmunotherapy seem to have a distinctive peripheral blood immune status at diagnosis and surgery.
2. At diagnosis, CPR patients are characterized by a stronger previously induced immune response with a higher cytotoxic profile and lower levels of inhibitory cytokines and cells.

Open access Original research

Journal for ImmunoTherapy of Cancer

Tumor microenvironment gene expression profiles associated to complete pathological response and disease progression in resectable NSCLC patients treated with neoadjuvant chemoimmunotherapy

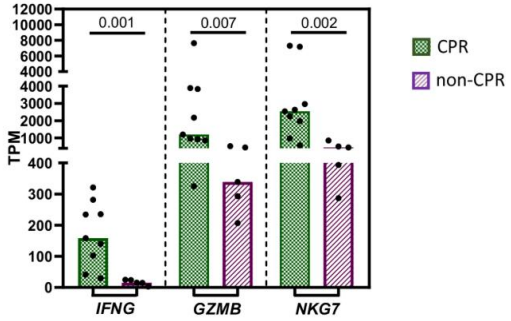
BIOMARKER

Pre-treatment IFNγ levels

MECHANISM

Preset immune response: Differential basal tumor microenvironment in CPR patients
+
Greater changes in CPR patients

B



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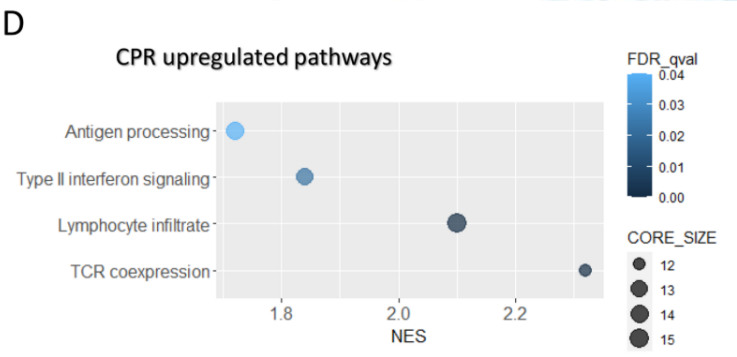

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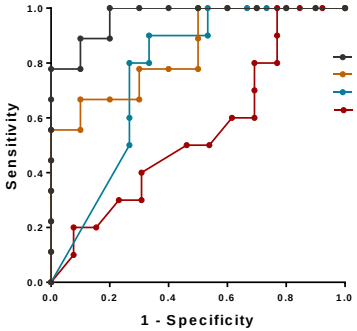
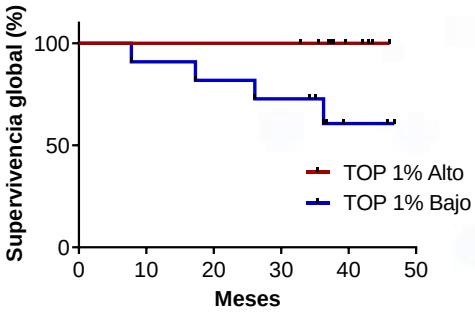
Research Article

Pre-treatment tissue TCR repertoire evenness is associated with complete pathological response in patients with NSCLC receiving neoadjuvant chemoimmunotherapy

BIOMARKER

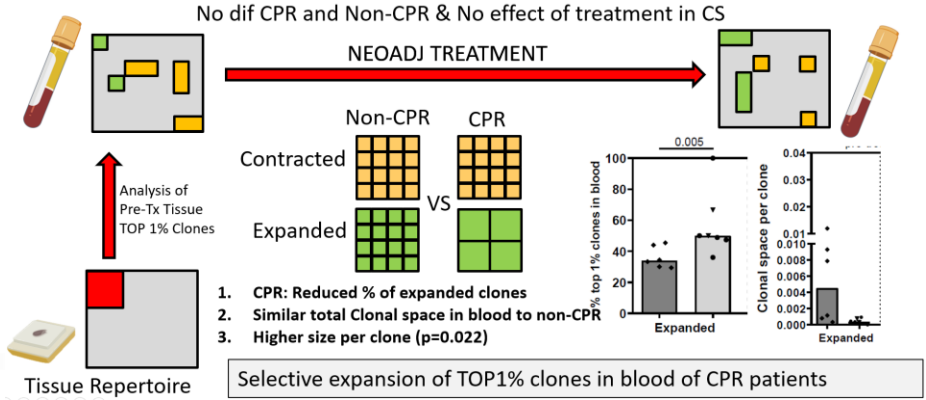
POSITIVE ASSOCIATION BETWEEN TCR REPERTOIRE AND CPR AT DIAGNOSIS
Most ranked clones (top 1%)
Occupied greater frequency in total clonal space





MECHANISM

PERIPHERAL IMMUNOSURVILLANCE
+
DIFFERENTIAL TUMOR IMMUNOGENICITY



Selective expansion of TOP1% clones in blood of CPR patients

Role of ctDNA in the Neoadjuvant setting

original reports

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

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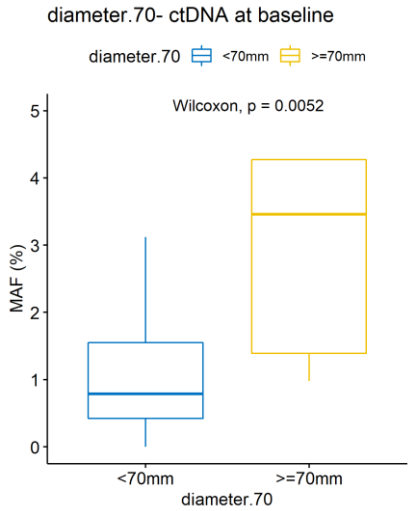
TABLE 2. Prognostic Value of Tumor Response to Treatment Assessments on the Basis of CT Scans, Pathologic Evaluation, and ctDNA (landmark analysis)

Survival surrogate	No.	HR (PFS)[a]	95% CI[a]	P[a]	C-index (PFS)	95% CI	HR (OS)[a]	95% CI[a]	P[a]	C-index (OS)	95% CI
Clinical response (CR plus PR *v* SD)	46	0.79	0.24 to 2.59	.698	0.62	0.47 to 0.77	0.87	0.20 to 3.75	.848	0.72	0.51 to 0.90
Pathologic response (pCR *v* major plus incomplete)	41	0.38	0.12 to 1.25	.111	0.63	0.47 to 0.78	0.24	0.04 to 1.33	.102	0.65	0.43 to 0.86
Undetectable ctDNA after treatment	40	0.26	0.07 to 0.93	.038	0.63	0.45 to 0.81	0.04	0.00 to 0.55	.015	0.82	0.61 to 1.00

Baseline ctDNA is of prognostic significance

Pre-treatment ctDNA levels were significantly associated with tumor size (maximum diameter ≥ 70mm)



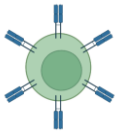
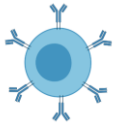
Median follow up time was 26.1 (IQR: 17.6-30.9) months

Pre-treatment ctDNA levels were significantly associated with progression free survival (PFS) and overall survival (OS) and regardless of the cutoff used (Table 1).

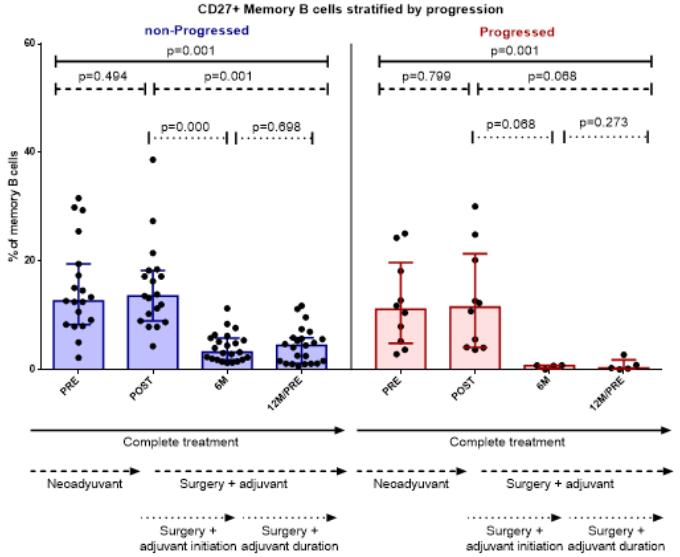
PFS				*OS*			
Cut-off	**HR (95% CI for HR)**	**P-value**	**P-value LogRank**	***Cut-off***	**HR (95% CI for HR)**	**P-value**	**P-value LogRank**
MAF 3%	0.43 (0.19-0.96)	0.039	0.033	MAF 3%	0.32 (0.11-0.91)	0.032	0.024
MA F3.5%	0.34 (0.15-0.79)	0.012	0.008	MA F3.5%	0.23 (0.079-0.64)	0.005	0.002
MAF 4%	0.28 (0.12-0.66)	0.003	0.002	MAF 4%	0.19 (0.067-0.55)	0.002	0.001
MAF 4.5%	0.29 (0.12-0.69)	0.005	0.003	MAF 4.5%	0.16 (0.058-0.47)	0.001	<0.001
MAF 5%	0.29 (0.12-0.69)	0.005	0.003	MAF 5%	0.16 (0.058-0.47)	0.001	<0.001
MAF 5.5%	0.35 (0.14-0.87)	0.024	0.018	MAF 5.5%	0.21 (0.071-0.62)	0.005	<0.001
MAF 6%	0.28 (0.11-0.76)	0.012	0.007	MAF 6%	0.21 (0.065-0.67)	0.008	0.004
MAF 6.5%	0.28 (0.11-0.76)	0.012	0.007	MAF 6.5%	0.21 (0.065-0.67)	0.008	0.004
MAF 7%	0.28 (0.11-0.76)	0.012	0.007	MAF 7%	0.21 (0.065-0.67)	0.008	0.004
MAF 7.5%	0.28 (0.11-0.76)	0.012	0.007	MAF 7.5%	0.21 (0.065-0.67)	0.008	0.004
MAF 8%	0.29 (0.1-0.86)	0.025	0.017	MAF 8%	0.16 (0.05-0.52)	0.002	<0.001
MAF 8.5%	0.29 (0.1-0.86)	0.025	0.017	MAF 8.5%	0.16 (0.05-0.52)	0.002	<0.001
MAF 9%	0.29 (0.1-0.86)	0.025	0.017	MAF 9%	0.16 (0.05-0.52)	0.002	<0.001
MAF 9.5%	0.29 (0.1-0.86)	0.025	0.017	MAF 9.5%	0.16 (0.05-0.52)	0.002	<0.001
MAF 10%	0.29 (0.1-0.86)	0.025	0.017	MAF 10%	0.16 (0.05-0.52)	0.002	<0.001
MAF 15%	0.12 (0.024-0.56)	0.007	0.001	MAF 15%	0.084 (0.017-0.41)	0.002	<0.001

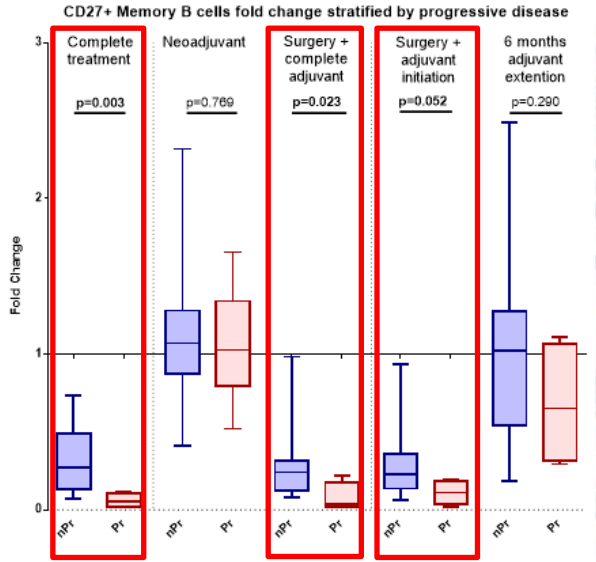
Table 1. Hazard ratio (HR), 95% confidence interval (95%CI), and P-values for PFS and OS according to ctDNA levels at baseline. Abbreviations: MAF, mutant allele fraction; OS, overall survival; PFS, progression-free survival.

NADIM ONGOING PROJECTS

	NADIM I		NADIM II
	NEOADJUVANT	ADJUVANT	
 T-cell	Clin&TransMed (PR…) CCR (TC…) JITC (…seq) PUBLICATIONS	TCR + PBMCs + Cytokines	Single-Cell/Visium & Validation of Results
 B-cell	BCR + Fenotipo PBMCs + TLS + (RNAseq reanalysis) +Spatial transcriptomics		
 MHC	HLA LOH + (Reanalysis with tissue data Multiplex, RNAseq)		

Changes in CD27+ Memory B cells throughout treatment



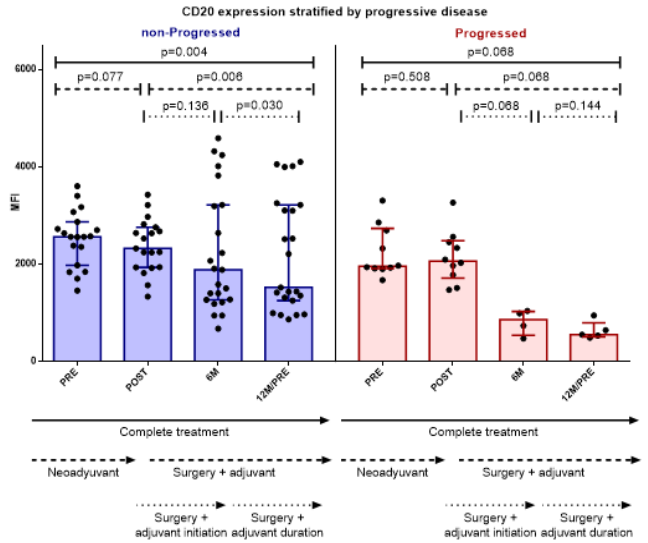


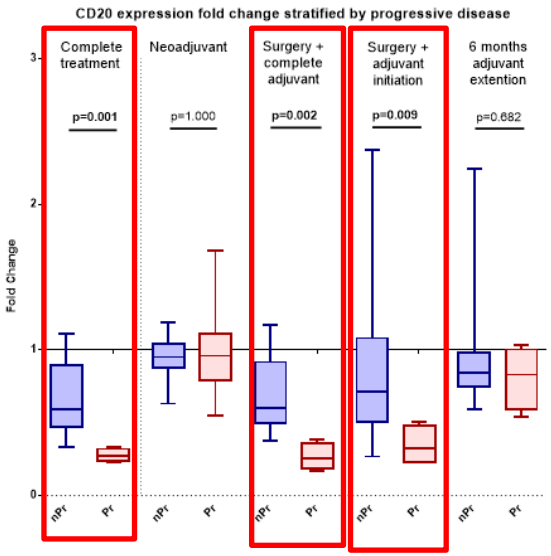
The magnitude of the memory B cell percentage **reduction was significantly more pronounced in patients whose disease progress** thereafter.

Immunosurveillance during adjuvant therapy at NADIM

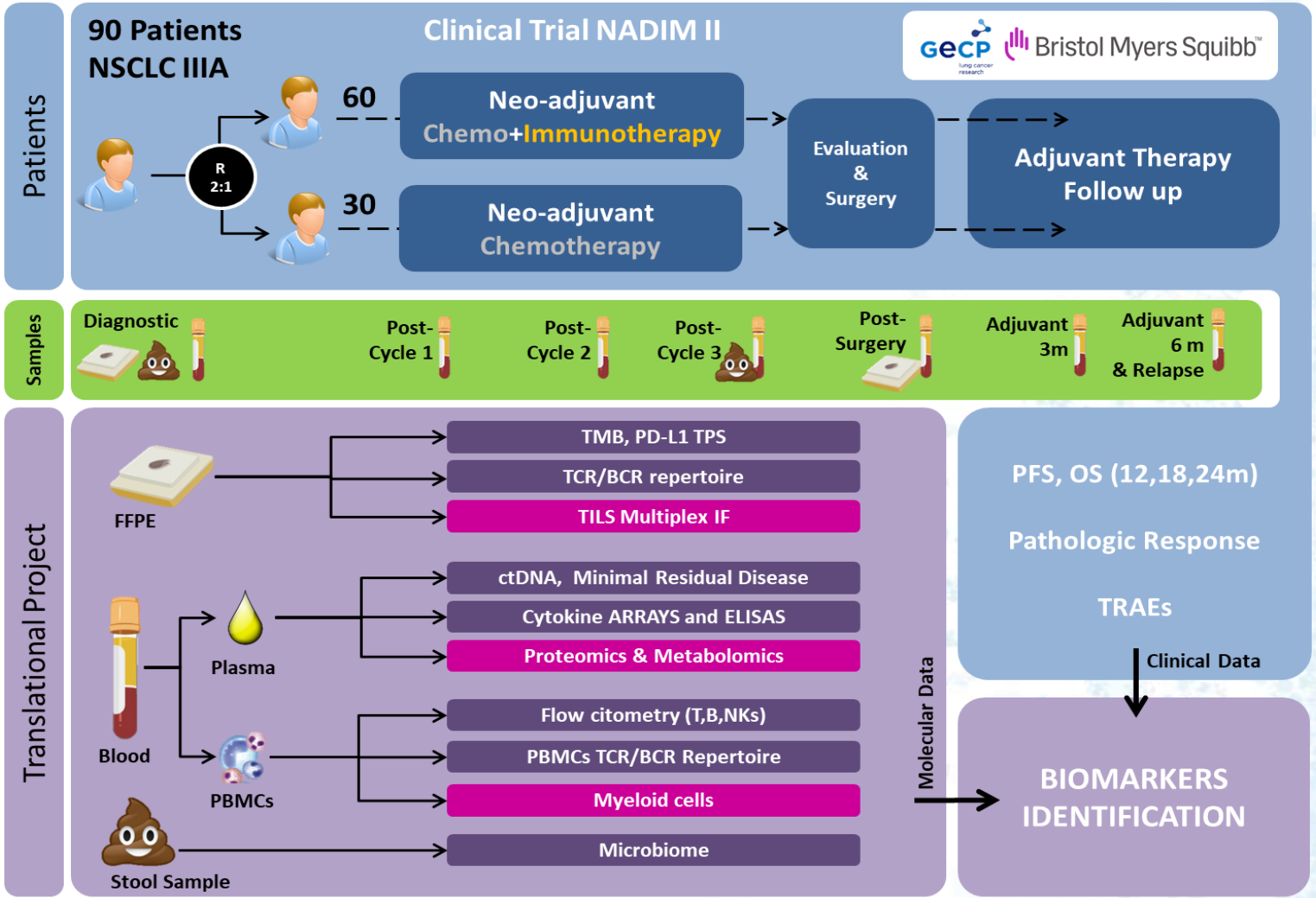
Flow cytometry: B cells

Changes in CD20 expression in B cells throughout treatment





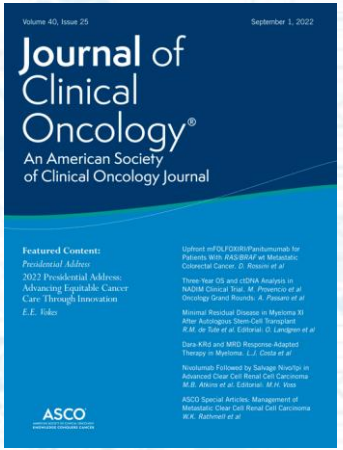
The magnitude of CD20 levels **reduction was significantly more pronounced in patients whose disease progress** thereafter.


Patients
90 Patients
NSCLC IIIA
Clinical Trial NADIM II
GECP
Bristol Myers Squibb
R
2:1
60
Neo-adjuvant
Chemo+Immunotherapy
30
Neo-adjuvant
Chemotherapy
Evaluation
&
Surgery
Adjuvant Therapy
Follow up
Samples
Diagnostic
Post-
Cycle 1
Post-
Cycle 2
Post-
Cycle 3
Post-
Surgery
Adjuvant
3m
Adjuvant
6 m
& Relapse
Translational Project
FFPE
TMB, PD-L1 TPS
TCR/BCR repertoire
TILS Multiplex IF
Blood
Plasma
ctDNA, Minimal Residual Disease
Cytokine ARRAYS and ELISAS
Proteomics & Metabolomics
PBMCs
Flow citometry (T,B,NKs)
PBMCs TCR/BCR Repertoire
Myeloid cells
Stool Sample
Microbiome
Molecular Data
PFS, OS (12,18,24m)
Pathologic Response
TRAEs
Clinical Data
BIOMARKERS
IDENTIFICATION

NADIM I

PUBLICATIONS

1. *Provencio et al 2020.* **Lancet Oncology.**
2. *Sierra et. al. 2021.* **Journal for immunotherapy of cancer.**
3. *Casarrubios et. al. 2021.* **Clinical Cancer Research.**
4. *Laza et. al. 2021.* **Clinical and translational Medicine.**
5. *Romero-Roman et. al.* 2021. **European Journal of Cardiothoracic Surgery**
6. *Rocha et. al. 2022* (*Collab with I.Wistuba Lab*). **Clinical Cancer Research**
7. *Casarrubios et. al. 2022.* **Journal for immunotherapy of cancer.**
8. *Provencio et. al. 2022.* **Journal of Clinical Oncology**
9. *Provencio M et al*. 2023**. NEJM**



FUTURE DIRECTIONS

- Single cell aproach & Spatial Transcriptomics
- Validation in REAL NADIM 100 patients
- Adjuvant treatment NADIN I and II
- NADIM ADJUVANT
- SUPER NADIM-ATHENEA- ARIAN

Conclusions

- Ch-IO should be the standard as induction treatment.
- It will be difficult to compare studies as not all of them specify who are N2 or not.
- The clinical approach of N2 or N3 is crucial.
- Less information if they are single or multiple N2.
- In any case, the results are much better and very consistent compared with the standard treatment.
- The question of adjuvant treatment after surgery remains to be resolved.

Thank you!

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GECP lung cancer research