Lung Cancer UPDATES
ESMO HIGHLIGTHS
20-24 OCTUBRE 2023
Madrid, Spain

Iniciativa científica de:
GECP
lung cancer research

Estadios Iniciales

Manuel Dómine

Hospital Universitario Fundación Jiménez Díaz. IIS-FJD

ESTRATEGIAS EN ESTADIOS INICIALES NSCLC

ESTADIOS INICIALES

- NEOADYUVANCIA
  - Neoadjuvant Nivolumab + chemotherapy in the phase 3 CheckMate-816 study: 3 years results by PD-L1 expression. Mariano Provencio
  - Neoadjuvant nivolumab + ipilimumab vs chemotherapy in the phase 3 CheckMate-816 Trial Mark Awad

Neoadjuvant Nivolumab + chemotherapy in the phase 3 CheckMate-816 study: 3 years results by PD-L1 expression

Iniciativa científica de: GECP lung cancer research

MADRID 2023 ESMO congress

Neoadjuvant nivolumab plus chemotherapy in the phase 3 CheckMate 816 study: 3-year results by tumor PD-L1 expression

Mariano Provencio Pulla,[1] Patrick M. Forde,[2] Jonathan Spicer,[3] Changli Wang,[4] Shun Lu,[5] Tetsuya Mitsudomi,[6] Mark M. Awad,[7] Enriqueta Felip,[8] Stephen R. Broderick,[2] Scott J. Swanson,[7] Julie Brahmer,[2] Keith Kerr,[9] Gene B. Saylors,[10] Fumihiro Tanaka,[11] Ke-Neng Chen,[12] Phuong Tran,[13] Junliang Cai,[13] Javed Mahmood,[13] Stephanie Meadows-Shropshire,[13] Nicolas Girard[14]

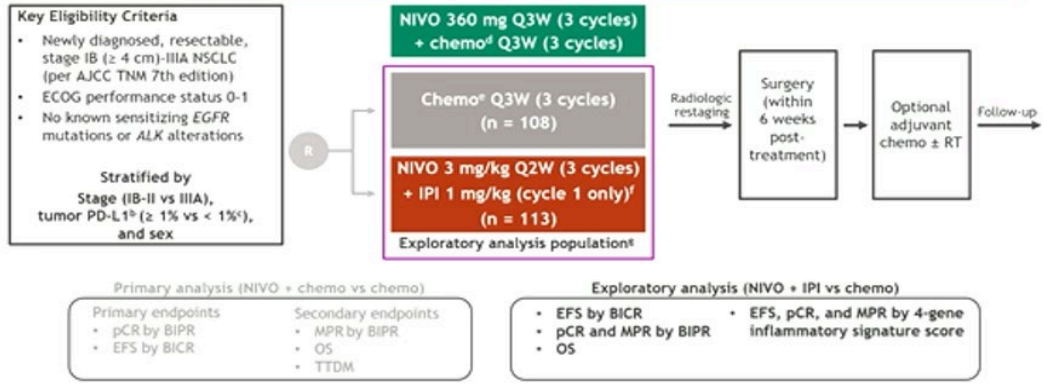
[1]Hospital Universitario Puerta de Hierro, Madrid, Spain; [2]The Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Medicine, The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [3]McGill University Health Centre, Montreal, Quebec, Canada; [4]Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [5]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [6]Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; [7]Dana-Farber Cancer Institute, Boston, MA, USA; [8]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [9]Aberdeen Royal Infirmary, Aberdeen, UK; [10]Charleston Oncology, Charleston, SC, USA; [11]University of Occupational and Environmental Health, Kitakyushu, Japan; [12]Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China; [13]Bristol Myers Squibb, Princeton, NJ, USA; [14]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France

Presentation number LBA57

Mariano Provencio Pulla

Neoadjuvant nivolumab (N) + chemotherapy (C) in the phase III CheckMate 816 study: 3-y results by tumor PD-L1 expression

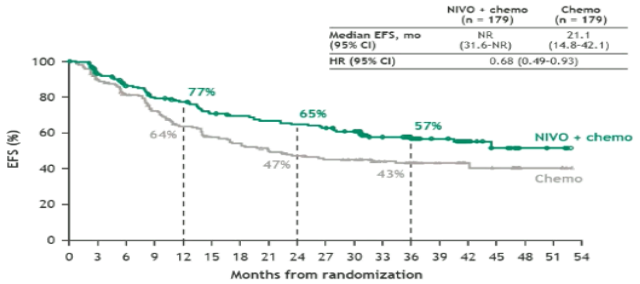
CheckMate 816[a] study design

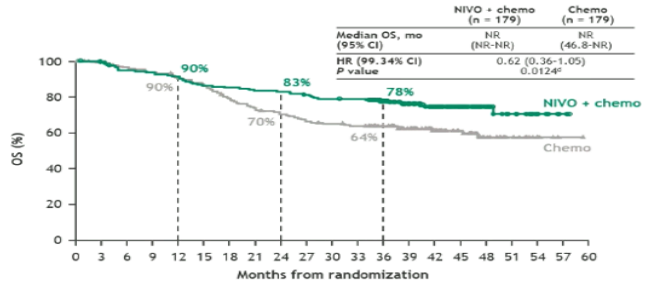


Database lock date: October 14, 2022. Minimum/median follow-up: 37.1/49.2 months.
[a]NCT02998528. [b]Determined using the PD-L1 IHC 28-8 pharmDx assay (Dako). [c]Included patients with PD-L1 expression status not evaluable and indeterminate. [d]Non-squamous: pemetrexed + cisplatin or paclitaxel + carboplatin. Squamous: gemcitabine + cisplatin or paclitaxel + carboplatin. [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pemetrexed + cisplatin (non-squamous only), or paclitaxel + carboplatin. [f]Enrollment to the NIVO + IPI arm closed early after the primary analysis population of the study was changed to patients concurrently randomized to NIVO + chemo vs chemo based on evolving external trial data.[1,2] [g]Only included patients concurrently randomized to the NIVO + IPI or chemo arms.
1. Cascone T, et al. *Nat Med* 2021;27:504-514. 2. Provencio M, et al. *Lancet Oncol* 2020;21:1413-1422.

Introduction

- Neoadjuvant NIVO + chemo has shown statistically significant and clinically meaningful improvements in EFS and pCR vs chemo in patients with resectable NSCLC in the phase 3 CheckMate 816 study[1]
  - NIVO + chemo continues to demonstrate long-term EFS benefit and favorable OS trend vs chemo[2,a]



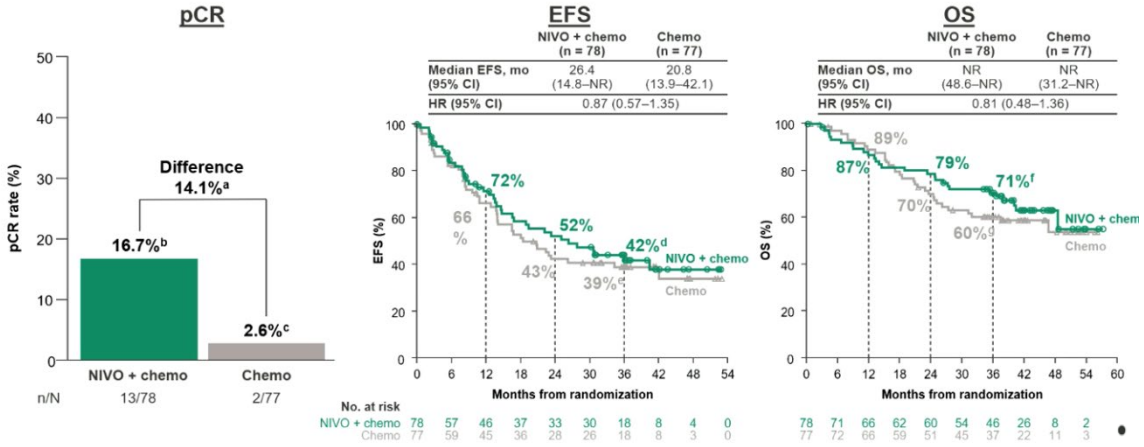


- NIVO + chemo is approved as a neoadjuvant therapy in the US and several other countries for adult patients with resectable NSCLC (tumors ≥ 4 cm or node-positive)[3] and in the EU for patients with resectable NSCLC at high risk of recurrence and tumor PD-L1 expression ≥ 1%[4]
- Here, we present prespecified exploratory subgroup analyses of efficacy, surgical, and safety outcomes with NIVO + chemo vs chemo in patients with tumor PD-L1 ≥ 1% or < 1% in CheckMate 816

[a]Database lock: October 14, 2022. Minimum/median follow-up: 32.9/41.4 months. EFS and OS curves adapted from reference 2 with permission from the author. [b]Significance boundary for OS was not crossed at this interim analysis. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985. 2. Forde PM, et al. Oral presentation at European Lung Cancer Congress; March 29-April 1, 2023; Copenhagen, Denmark. Presentation 840. 3. OPDIVO® (nivolumab) [package insert]. Princeton, NJ, USA: Bristol Myers Squibb; February 2023. 4. OPDIVO® (nivolumab) [summary of product characteristics]. Dublin, Ireland: Bristol Myers Squibb Pharma EEIG; September 2023.

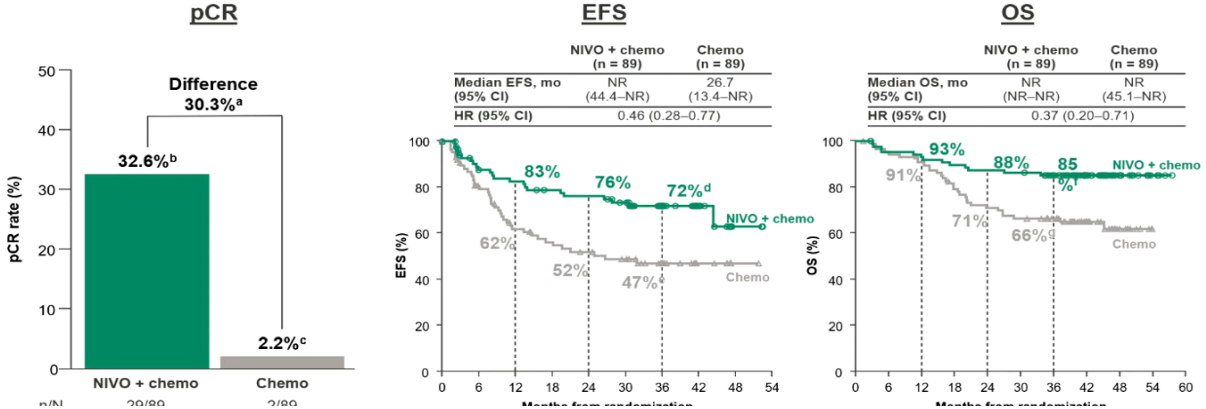
Neoadjuvant Nivolumab + chemotherapy in the phase 3 CheckMate-816 study: 3 years results by PD-L1 expression

Efficacy outcomes in patients with tumor PD-L1 < 1%



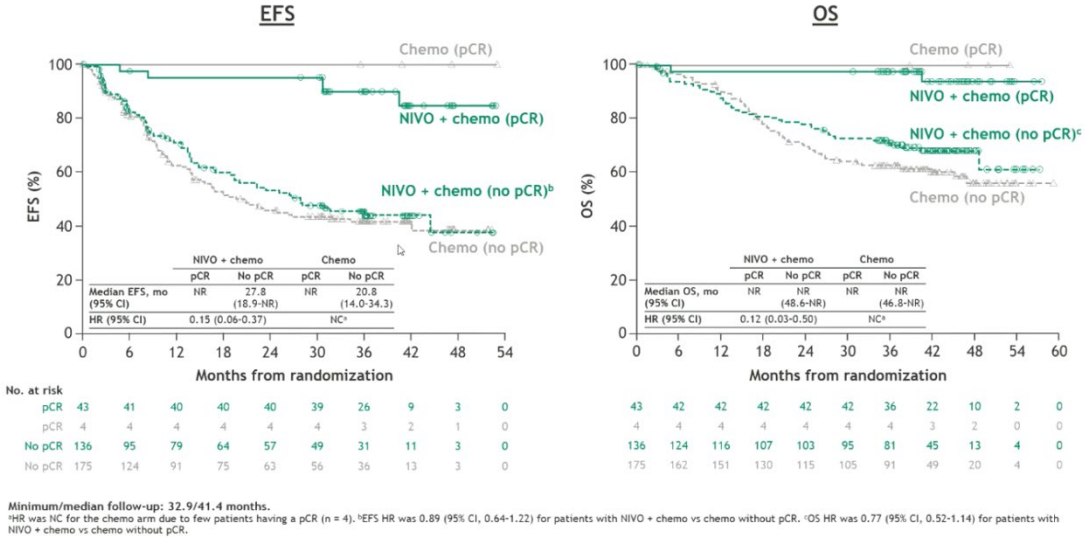
- Median TTDM[h] (95% CI) was 48.6 mo (36.6–NR) vs 27.4 mo (21.4–NR) for NIVO + chemo vs chemo (HR, 0.72; 95% CI, 0.45–1.15); 3-year TTDM rates were 63% vs 46%[i]
- Baseline characteristics were generally similar between tumor PD-L1 subgroups and treatment arms, although a higher proportion of patients

Efficacy outcomes in patients with tumor PD-L1 ≥ 1%



- In these exploratory analyses from CheckMate 816, neoadjuvant NIVO + chemo provided clinical benefit vs chemo in patients with resectable NSCLC, regardless of tumor PD-L1 expression
- A greater magnitude of benefit with NIVO + chemo vs chemo was seen for patients with tumor PD-L1 ≥ 1% compared with those with tumor PD-L1 < 1%

Efficacy outcomes by pCR status in concurrently randomized patients



Minimum/median follow-up: 32.9/41.4 months.
[a]HR was NC for the chemo arm due to few patients having a pCR (n = 4). [b]EFS HR was 0.89 (95% CI, 0.64-1.22) for patients with NIVO + chemo vs chemo without pCR. [c]OS HR was 0.77 (95% CI, 0.52-1.14) for patients with NIVO + chemo vs chemo without pCR.

Conclusiones

- **En este análisis exploratorio del CheckMate- 816: Nivo-QT ofrece un beneficio clínico independientemente de la expresión de PD-L-1,**
- **La magnitud de l beneficio fue mayor en los pacientes que expresan PD-L1 ≥ 1%**
- **Estos reultados refuerzan el papel de Nivo-QT como tratamiento estándar en NSCLC resecables**

Neoadjuvant nivolumab + ipilimumab vs chemotherapy in the phase 3 CheckMate-816 Trial

Iniciativa científica de: GECP

14:00 - 15:45 Proffered Paper session - Non-metastatic NSCLC and other thoracic malignancies

CHAIRS: FIONA BLACKHALL, RAFAL DZIADZIUSZKO

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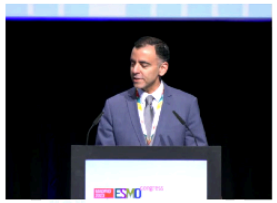
Neoadjuvant nivolumab plus ipilimumab vs chemotherapy in the phase 3 CheckMate 816 trial

Mark M. Awad,[1] Patrick M. Forde,[2] Nicolas Girard,[3] Jonathan Spicer,[4] Changli Wang,[5] Shun Lu,[6] Tetsuya Mitsudomi,[7] Enriqueta Felip,[8] Stephen R. Broderick,[2] Scott J. Swanson,[1] Julie Brahmer,[2] Keith Kerr,[9] Gene B. Saylors,[10] Ke-Neng Chen,[11] Junliang Cai,[12] Javed Mahmood,[12] Jaclyn Neely,[12] David Balli,[12] Nan Hu,[12] Mariano Provencio Pulla[13]

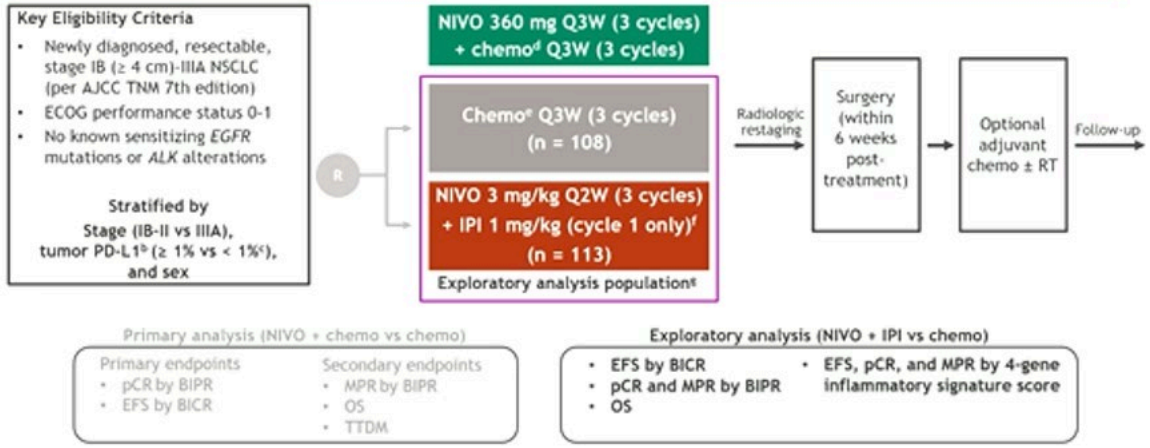
[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]The Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Medicine, The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [3]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France; [4]McGill University Health Centre, Montreal, Quebec, Canada; [5]Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [6]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai JiaoTong University, Shanghai, China; [7]Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; [8]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [9]Aberdeen Royal Infirmary, Aberdeen, UK; [10]Charleston Oncology, Charleston, SC, USA; [11]Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China; [12]Bristol Myers Squibb, Princeton, NJ, USA; [13]Hospital Universitario Puerta de Hierro, Madrid, Spain

Presentation number 1261O



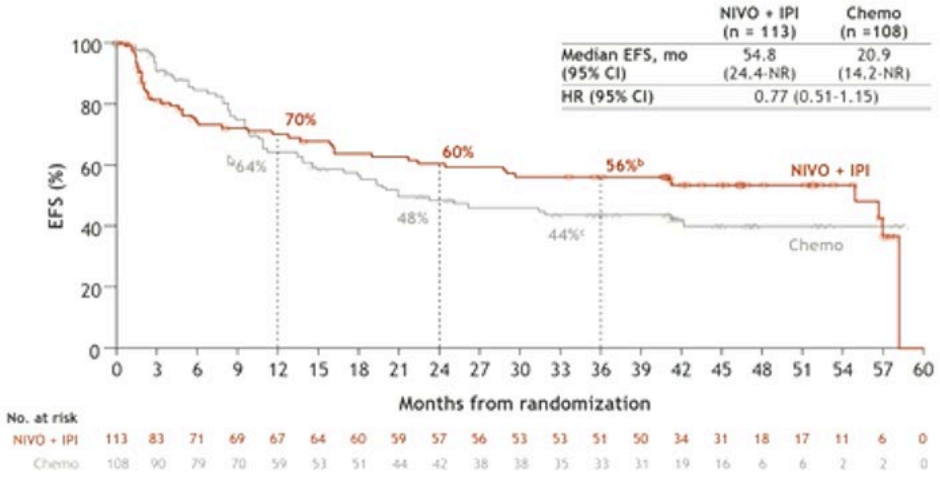
Mark Awad
Neoadjuvant nivolumab (N) + ipilimumab (I) vs chemotherapy (C) in the phase III CheckMate 816 trial

CheckMate 816[a] study design



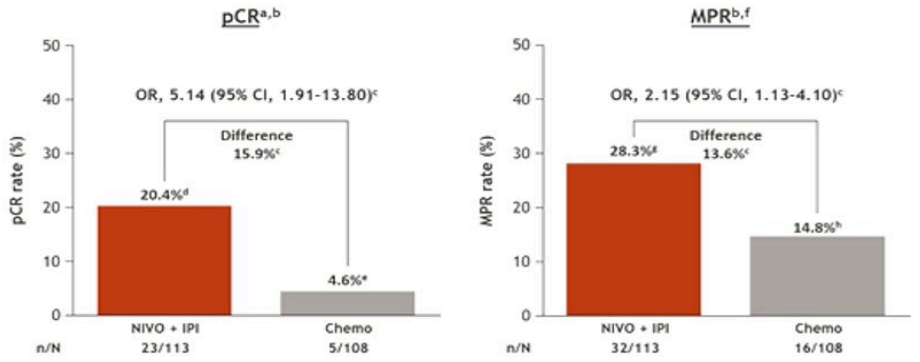
Database lock date: October 14, 2022. Minimum/median follow-up: 37.1/49.2 months.
[a]NCT02998528. [b]Determined using the PD-L1 IHC 28-8 pharmDx assay (Dako). [c]Included patients with PD-L1 expression status not evaluable and indeterminate. [d]Non-squamous: pemetrexed + cisplatin or paclitaxel + carboplatin. Squamous: gemcitabine + cisplatin or paclitaxel + carboplatin. [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pemetrexed + cisplatin (non-squamous only), or paclitaxel + carboplatin. [f]Enrollment to the NIVO + IPI arm closed early after the primary analysis population of the study was changed to patients concurrently randomized to NIVO + chemo vs chemo based on evolving external trial data.[1,2] [g]Only included patients concurrently randomized to the NIVO + IPI or chemo arms.
1. Cascone T, et al. *Nat Med* 2021;27:504-514. 2. Provencio M, et al. *Lancet Oncol* 2020;21:1413-1422.

EFS[a] with neoadjuvant NIVO + IPI vs chemo



Minimum/median follow-up: 37.1/49.2 months.
[a]Time from randomization to any disease progression precluding surgery, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause per BICR. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b]95% CI: [c]46-65; [d]33-54.

pCR and MPR with neoadjuvant NIVO + IPI vs chemo

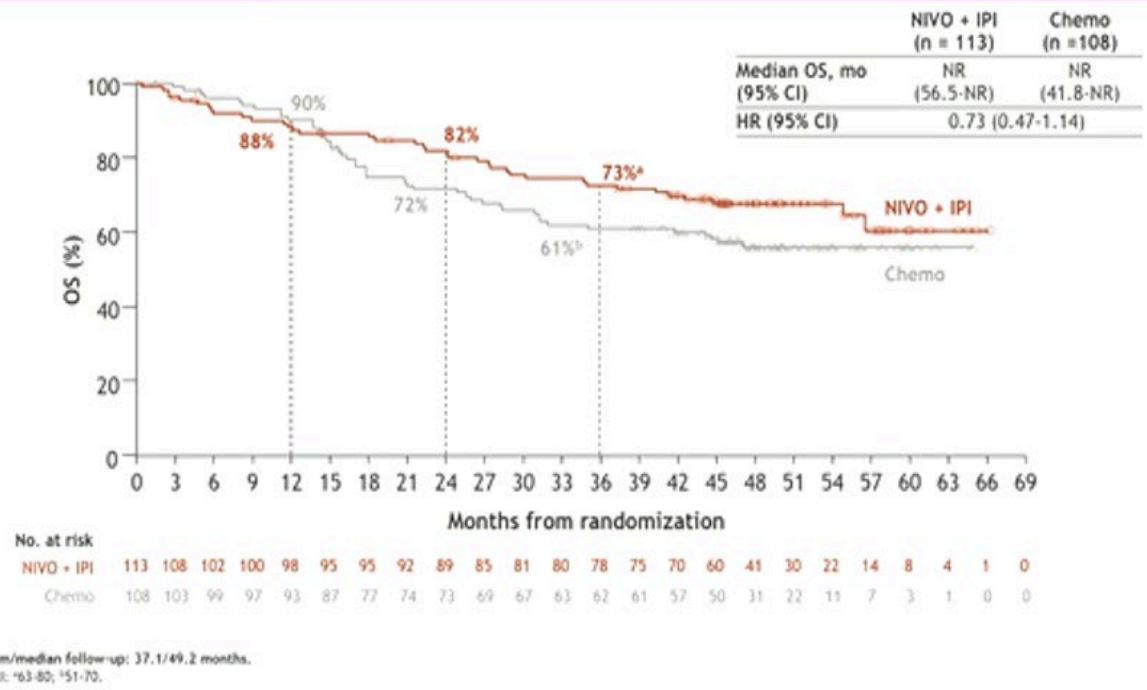


Database lock date: September 16, 2020.
[a]0% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per BIPR. [b]Patients who did not undergo surgery were classified as nonresponders. [c]Calculated using stratified Cochran-Mantel-Haenszel method. [d]95% CI: [e]13.4-29.0; [f]1.5-10.5. [g]≤ 10% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per BIPR. [h]95% CI: [i]20.2-37.6; [j]8.7-22.9.

Neoadjuvant nivolumab + ipilimumab vs chemotherapy in the phase 3 CheckMate-816 Trial

Iniciativa científica de: GECP lung cancer research

OS with neoadjuvant NIVO + IPI vs chemo



Minimum/median follow-up: 37.1/49.2 months.
[a]95% CI: [a]63-80; [b]51-70.

- In this exploratory analysis from CheckMate 816, neoadjuvant NIVO + IPI showed potential clinical benefit vs chemo in patients with resectable NSCLC
  - pCR and MPR rates were higher with NIVO + IPI vs chemo
  - Both EFS and OS appeared to favor NIVO + IPI vs chemo after 1 year
- NIVO + IPI had a tolerable safety profile and similar rate of definitive surgery as chemo
- NIVO + chemo remains the standard neoadjuvant treatment for eligible patients with resectable NSCLC

ESTADIOS INICIALES

Iniciativa científica de: GECP lung cancer research

- TRATAMIENTO PERIOPERATORIO CON QUIMIOTERAPIA + INMUNOTERAPIA
  - CheckMate 77T: Ph III study comparing neoadyuvant nivolumab + chemotherapy with neoadyuvant placebo + chemotherapy folloved by surgery and adjuvant nivolumab o placebo for previously untreated stage II-IIIB NSCLC. Tina Cascone et al.
  - Overall Survival in the Keynote -671 Study of perioperative Pembrolizumab for Early Stage NSCLC. Jonathan Spicer, et al.
  - Association of ctDNA clearance and Pathological Response with Neoadyuvant treatment in patients with resectable NSCLC from Phase III AEGEAN trial. Martin Reck et al

CheckMate 77T: Ph III study comparing neoadyuvant nivolumab + chemotherapy with neoadyuvant placebo + chemotherapy folloved by surgery and adjuvant nivolumab o placebo for previously untreated stage II-IIIB NSCLC

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CheckMate 77T: Phase 3 study comparing neoadjuvant nivolumab plus chemotherapy with neoadjuvant placebo plus chemotherapy followed by surgery and adjuvant nivolumab or placebo for previously untreated, resectable stage II-IIIB NSCLC

Tina Cascone,[1] Mark M. Awad,[2] Jonathan Spicer,[3] Jie He,[4] Shun Lu,[5] Boris Sepesi,[1] Fumihiro Tanaka,[6] Janis M. Taube,[7] Robin Cornelissen,[8] Libor Havel,[9] Jaroslaw Kuzdzal,[10] Lubos B. Petruzelka,[11] Lin Wu,[12] Jean-Louis Pujol,[13] Hiroyuki Ito,[14] Cinthya Coronado Erdmann,[15] Padma Sathyanarayana,[15] Stephanie Meadows-Shropshire,[15] Mariano Provencio Pulla[16]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]McGill University Health Centre, Montreal, Québec, Canada; [4]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [5]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [6]University of Occupational and Environmental Health, Kitakyushu, Japan; [7]The Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [8]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [9]Thomayer Hospital, Prague, Czech Republic; [10]John Paul II Hospital, Krakow, Poland; [11]Charles University, Prague, Czech Republic; [12]Hunan Cancer Hospital, Changsha, China; [13]Montpellier Regional University Hospital, Montpellier, France; [14]Kanagawa Cancer Center, Yokohama, Japan; [15]Bristol Myers Squibb, Princeton, NJ, USA; [16]Hospital Universitario Puerta de Hierro, Madrid, Spain

Tina Cascone

CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II–IIIB NSCLC

GECP lung cancer research

CheckMate 77T[a] study design

Key eligibility criteria
- Resectable, stage IIA (> 4 cm)-IIIB (N2) NSCLC (per AJCC 8th edition)
- No prior systemic anti-cancer treatment
- ECOG PS 0-1
- No *EGFR* mutation/known *ALK* alterations[b]

Stratified by histology (NSQ vs SQ) disease stage (II vs III), and tumor PD-L1[c] (≥ 1% vs < 1% vs not evaluable/indeterminate)

N = 461 → R 1:1

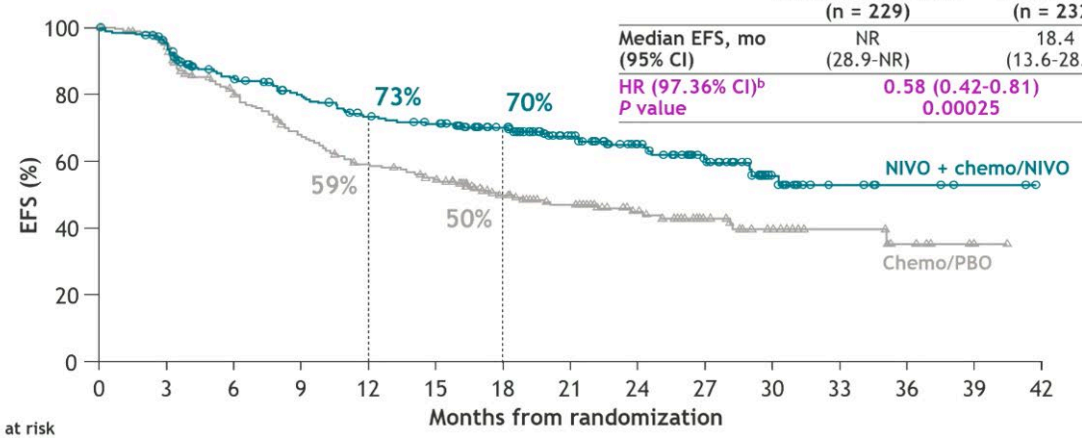
- NIVO 360 mg Q3W + chemo[d] Q3W (4 cycles) → Radiologic restaging → Surgery (within 6 weeks post-neoadjuvant treatment) → NIVO 480 mg Q4W (1 year)
- PBO Q3W + chemo[d] Q3W (4 cycles) → Radiologic restaging → Surgery (within 6 weeks post-neoadjuvant treatment) → PBO Q4W (1 year)

Follow-up

Follow-up, median (range): 25.4 (15.7-44.2) months

Primary endpoint	Secondary endpoints	Exploratory analyses
• EFS by BICR	• pCR[e] by BIPR • MPR[e] by BIPR • OS • Safety	• EFS by pCR/MPR • EFS by adjuvant treatment

Primary endpoint: EFS[a] per BICR with neoadjuvant NIVO + chemo/adjuvant NIVO vs chemo/PBO



	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)
Median EFS, mo (95% CI)	NR (28.9-NR)	18.4 (13.6-28.1)
HR (97.36% CI)[b]	0.58 (0.42-0.81)	
P value	0.00025	

No. at risk

NIVO + chemo/NIVO	229	208	173	157	141	134	115	89	69	46	20	7	4	2	0
Chemo/PBO	232	204	165	138	118	106	78	59	44	29	19	10	6	1	0

Median follow-up (range): 25.4 months (15.7-44.2).
[a]Time from randomization 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 tumor assessment on or prior to the date of subsequent therapy. [b]Unstratified HR (95% CI), 0.59 (0.44-0.79).

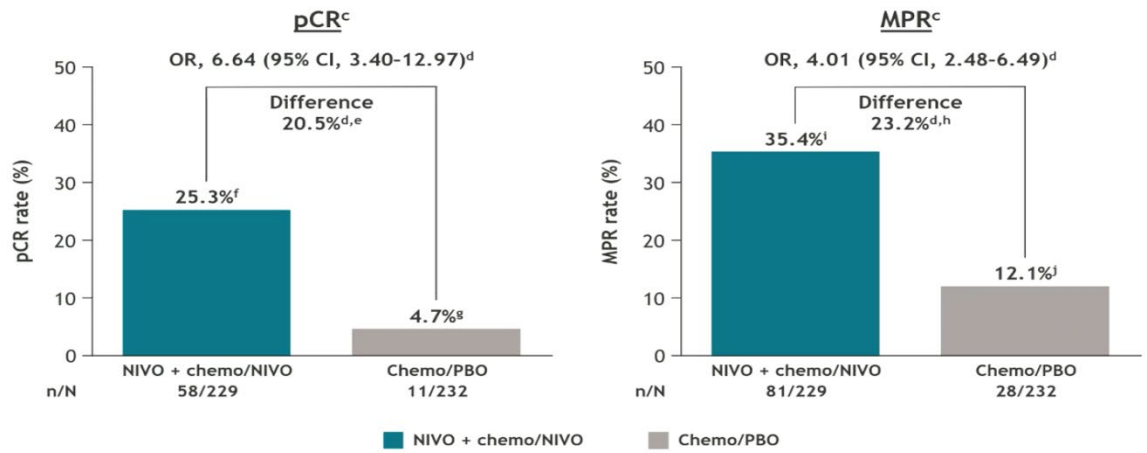
EFS analysis by key subgroups

	Median EFS,[a] mo		Unstratified HR (95% CI)
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)	Unstratified HR (95% CI)
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)[b]	NR	NR	0.80 (0.48-1.32)
N1 (n = 108)[b]	NR	28.1	0.58 (0.29-1.16)
N2 (n = 182)[b,c]	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)[d]	29.0	19.8	0.73 (0.47-1.15)
PD-L1 ≥ 1% (n = 256)[d]	NR	15.8	0.52 (0.35-0.78)
PD-L1 1-49% (n = 159)[e]	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).
[b]Per BICR. [c]Nodal status was N3 in 4 patients. [c]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. [d]Tumor PD-L1 expression was not evaluable/indeterminate in 19 patients. [e]Most patients in this subgroup had low PD-L1 expression (median 10% across both arms).

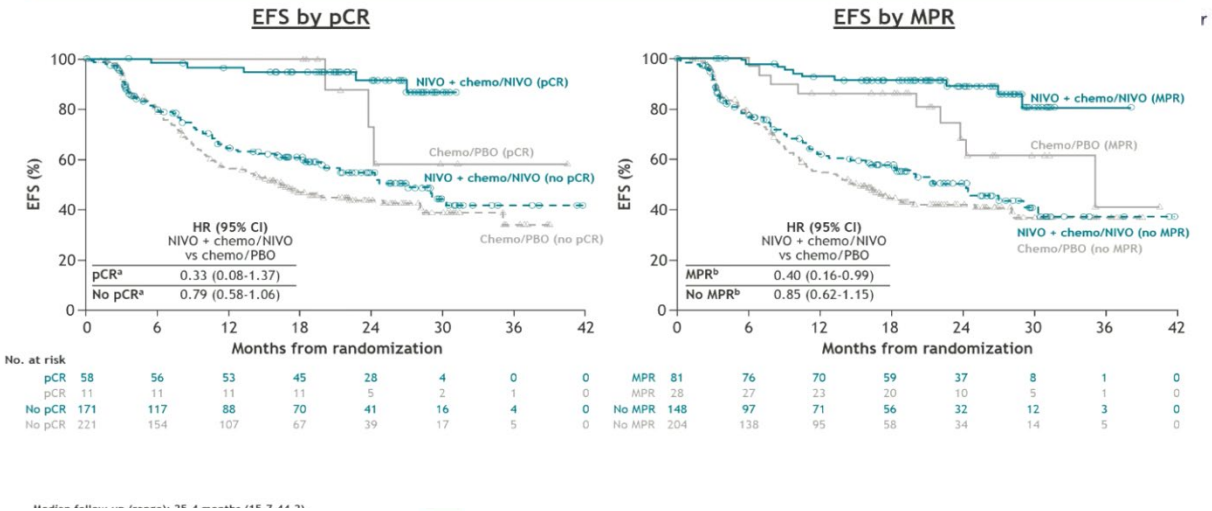
CheckMate 77T: Ph IIIstudy comparing neoadyuvant nivolumab + chemotherapy with neoadyuvant placebo + chemotherapy folloved by surgery and adjuvant nivolumab o placebo for previously untreated stage II-IIIB NSCLC

pCR[a] and MPR[b] per BIPR

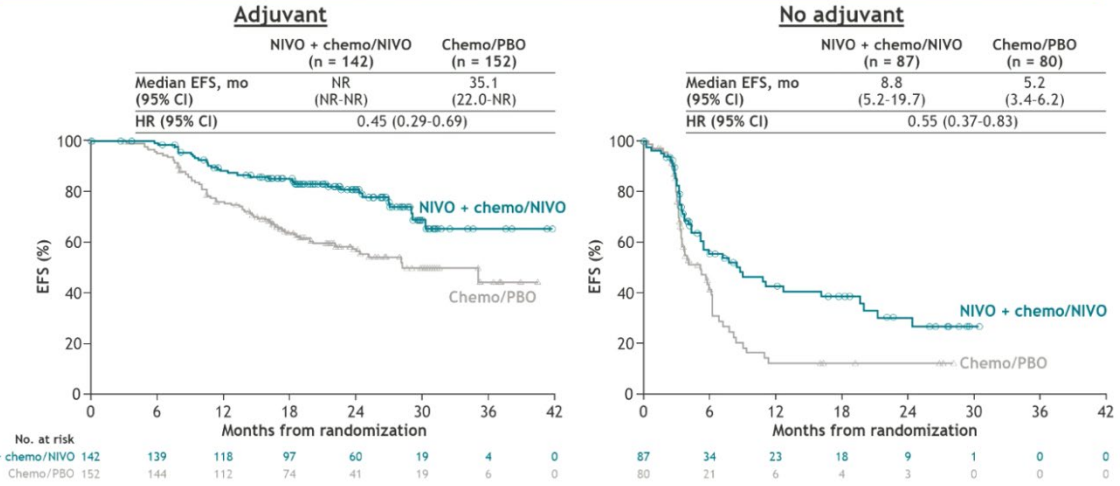


[a]0% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per immune-related pathologic response criteria. [b]≤ 10% residual viable tumor cells post-surgery in both primary tu (lung) and sampled lymph nodes per immune-related pathologic response criteria. [c]Patients who did not undergo surgery or received alternative anti-cancer treatment prior to surgery were classified as non-respond [d]Calculated using the stratified Cochran-Mantel-Haenszel method. [e-j]95% CI: [e]14.3-26.6; [f]19.8-31.5; [g]2.4-8.3; [h]15.8-30.6; [i]29.2-41.9; [j]8.2-17.0. BIPR, blinded independent pathological review.

Exploratory analysis: EFS by pCR and MPR status



Exploratory analysis: EFS by adjuvant treatment status

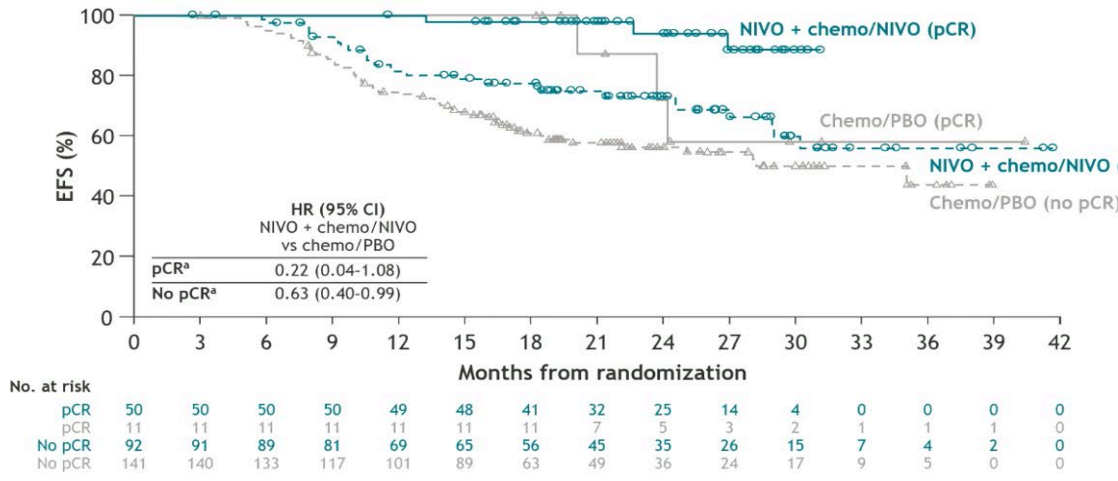


- NIVO + chemo/NIVO improved EFS vs chemo/PBO with numerically higher benefit in patients who received adjuvant treatment (HR [95% CI], 0.45 [0.29-0.69]) vs those who did not (HR [95% CI], 0.55 [0.37-0.83])[a]

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

CheckMate 77T: perioperative NIVO in resectable NSCLC

Exploratory analysis: EFS by pCR status in patients who received adjuvant treatment



Median follow-up (range): 25.4 months (15.7-44.2).
[a]HR (95% CI), 0.17 (0.05-0.57) in patients with pCR vs those without in the NIVO + chemo/NIVO arm and 0.45 (0.14-1.45) in the chemo/PBO arm.

CheckMate 77T: Ph IIIstudy comparing neoadyuvant nivolumab + chemotherapy with neoadyuvant placebo + chemotherapy folloved by surgery and adjuvant nivolumab o placebo for previously untreated stage II-IIIB NSCLC

entífica de: GECP lung cancer research

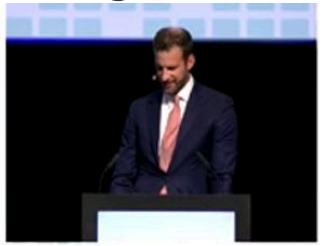
CONCLUSIONES

- Tratamiento perioperatorio con Nivo+ QT seguido de cirugía y Nivo adyuvante produce un aumento significativo en EFS (HR 0.58)
- Este beneficio es en todos los subgrupos
- Entre los pacientes elegibles para tratamiento adyuvante nivo perioperatorio mejoró EFS independiente de estatus de pCR.
- Nivo + quimio neoadyuvante continua obteniendo beneficio en pacientes que no pueden recibir adyuvancia
- Este estudio confirma esta estrategia perioperatoria como nueva opción de tratamiento par NSCLC resecables

Overall Survival in the Keynote -671 Study of perioperative Pembrolizumab for Early Stage NSCLC

Overall Survival in the KEYNOTE-671 Study of Perioperative Pembrolizumab for Early-Stage NSCLC

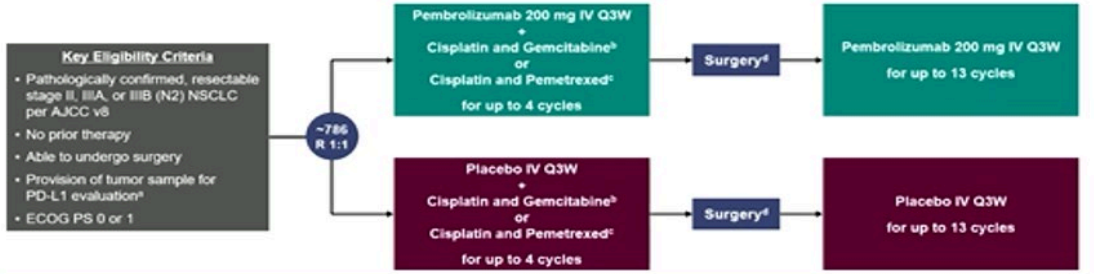
Jonathan D Spicer,[1] Shugeng Gao,[2] Moishe Liberman,[3] Terufumi Kato,[4] Masahiro Tsuboi,[5] Se-Hoon Lee,[6] Ke-Neng Chen,[7] Christophe Dooms,[8] Margarita Majem,[9] Ekkehard Eigendorff,[10] Gastón L Martinengo,[11] Olivier Bylicki,[12] Marina C Garassino,[13] Delvys Rodriguez-Abreu,[14] Jamie Chaft,[15] Silvia Novello,[16] Jing Yang,[17] Steven M Keller,[17] Ayman Samkari,[17] Heather Wakelee,[18] on behalf the KEYNOTE-671 Investigators



Jonathan Spicer

Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage non-small-cell lung cancer

KEYNOTE-671 Study Design
Randomized, Double-Blind, Phase 3 Trial



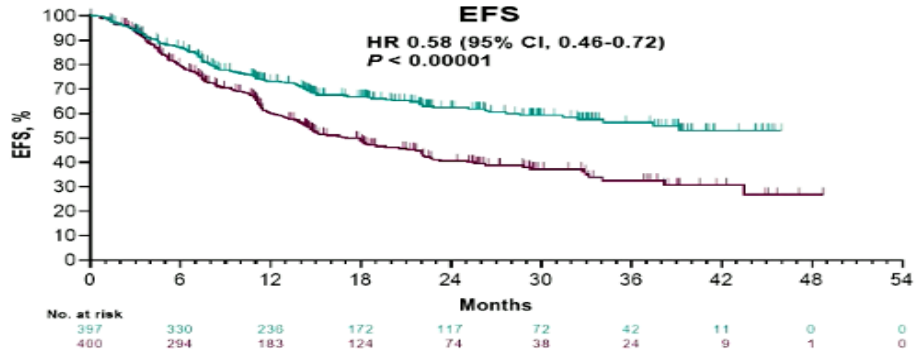
Stratification Factors
- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

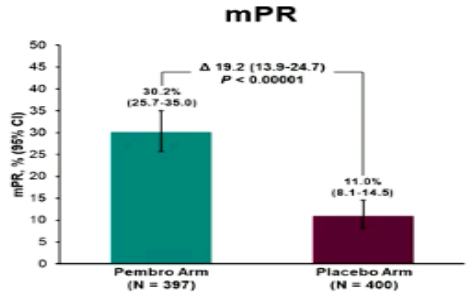
Dual primary end points: EFS per investigator review and OS

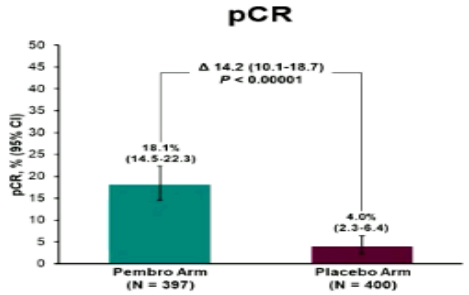
Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

KEYNOTE-671 Results: Interim Analysis 1
Median Follow-Up[a]: 25.2 months (range, 7.5-50.6)

- Neoadjuvant pembrolizumab + chemotherapy followed by surgery and adjuvant pembrolizumab significantly improved EFS, mPR, and pCR compared with neoadjuvant chemotherapy and surgery alone
- AE profile was as expected based on the known profiles of the individual treatment components







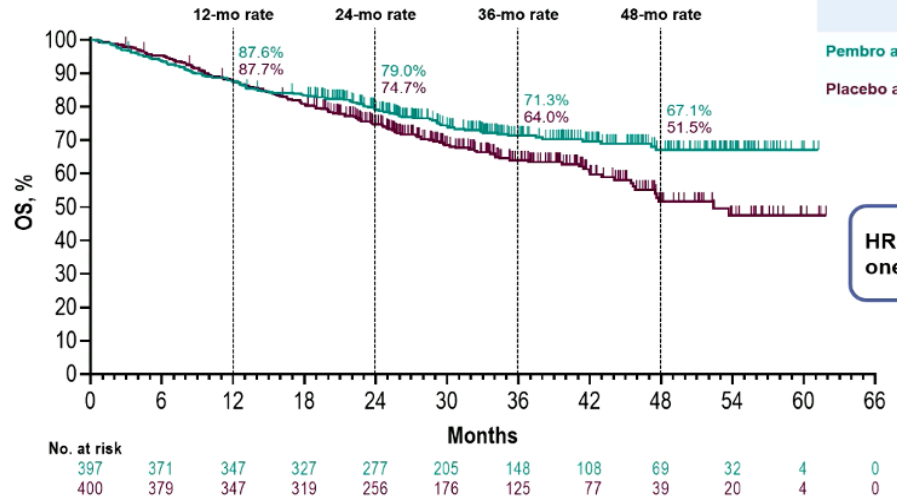
[a] Defined as time from randomization to data cutoff date of July 29, 2022.
Wakelee H et al. *N Engl J Med* 2023;389:491-503.

Overall Survival in the Keynote -671 Study of perioperative Pembrolizumab for Early Stage NSCLC

Iniciativa científica de: GECP lung cancer research

Overall Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)

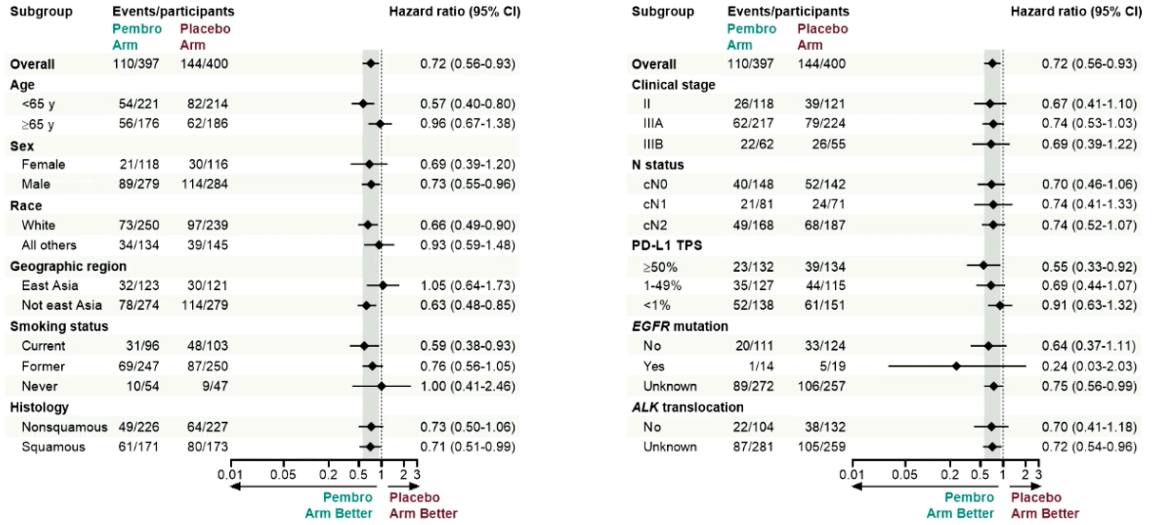


	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

HR 0.72 (95% CI, 0.56-0.93)
one-sided *P* = 0.00517[a]

OS defined as time from randomization to death from any cause. [a] Significance boundary at IA2, one-sided *P* = 0.00543.
Data cutoff date for IA2: July 10, 2023.

Overall Survival in Subgroups, IA2



Per the prespecified analysis plan, subgroups with <30 participants are excluded from the forest plot. Subgroups for stage IIIA and IIIB and pN status were post hoc; all other subgroups were prespecified.
Data cutoff date for IA2: July 10, 2023.

Overall Survival in the Keynote -671 Study of perioperative Pembrolizumab for Early Stage NSCLC

Iniciativa científica de: GECP lung cancer research

Overall Survival, IA2

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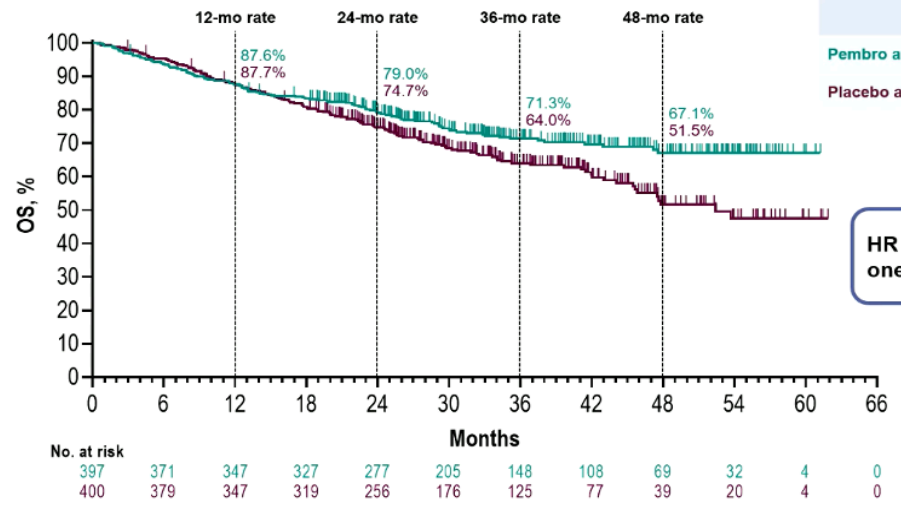

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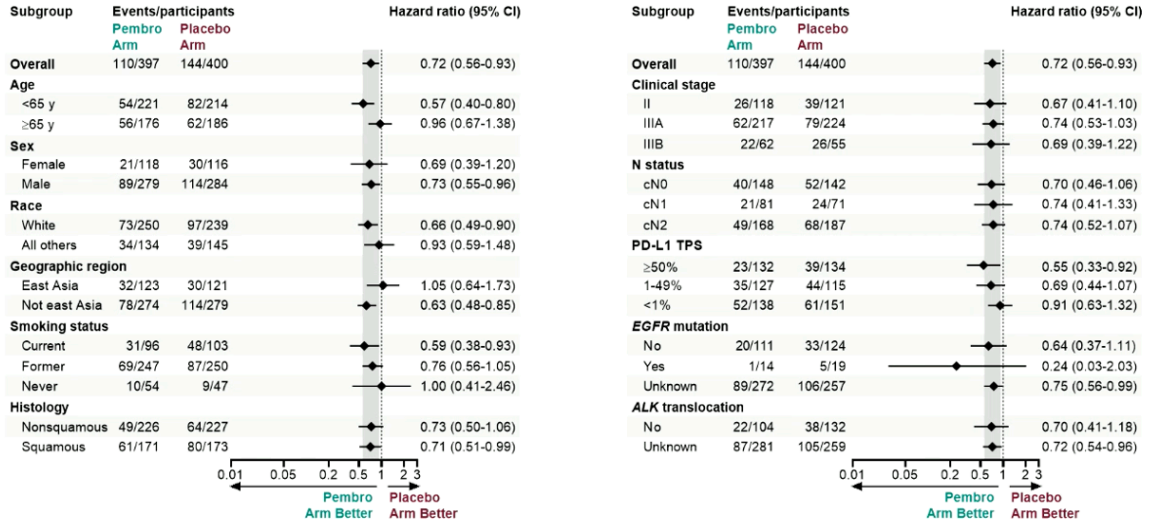

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- **The significant OS improvement in the absence of new safety signals establishes the perioperative pembrolizumab regimen as a new standard of care for resectable stage II, IIIA, or IIIB (N2) NSCLC**
  - **On October 16, 2023, the US FDA granted pembrolizumab approval for the treatment of resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery**

Tratamiento con inmunoterapia + quimioterapia perioperatoria

Iniciativa científica de:
GECP
lung cancer research

Tratamiento con inmunoterapia + quimioterapia perioperatoria

Iniciativa científica de: GECP lung cancer research

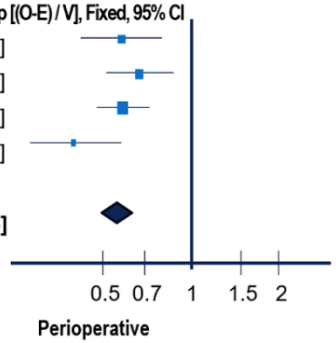
Are all the perioperative regimens the same?

YES!

	Placebo				Hazard Ratio
	Events	Total	Events	Total	Exp [(O-E) / V], Fixed, 95% CI
77T	52	229	90	232	0.58 [0.42, 0.81]
Aegean	98	366	138	374	0.67 [0.51, 0.86]
Keynote 671	174	397	248	400	0.68 [0.53, 0.88]
Neotorch	47	202	97	202	0.40 [0.28, 0.57]
Total (95% CI)		**1194**		**1208**	**0.58 [0.50, 0.66]**
Total events	371		573		

Heterogeneity: $Chi^2 = 5.31$, df = 3 (P = 0.15); $I^2 = 43\%$

Test for overall effect: Z = 8.15 (P < 0.00001)



Tratamiento con inmunoterapia + quimioterapia perioperatoria

Iniciativa científica de: GECP lung cancer research

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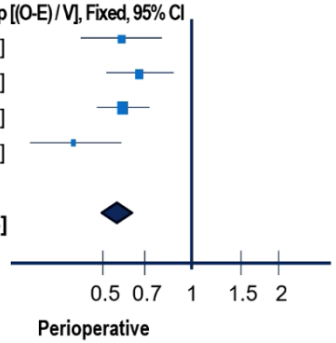


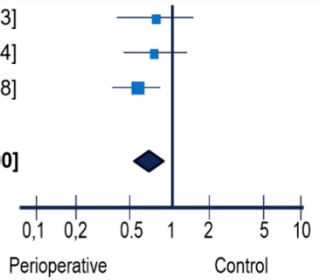
Should we treat also patients with Stage II?

YES!

Study or Subgroup	Perioperative Immunothery		Placebo		Hazard Ratio
	Events	Total	Events	Total	Exp [(O-E) / V], Fixed, 95% CI
77T	22	81	26	81	0.81 [0.46, 1.43]
Aegean	21	104	27	110	0.76 [0.43, 1.34]
Keynote671	37	118	62	121	0.59 [0.40, 0.88]
Total (95% CI)		**303**		**312**	**0.68 [0.51, 0.90]**
Total events	80		115		

Heterogeneity: $Chi^2 = 1.01$, df = 2 (P = 0.60); $I^2 = 0\%$

Test for overall effect: Z = 2.70 (P = 0.007)



Tratamiento con inmunoterapia + quimioterapia perioperatoria

Iniciativa científica de: GECP lung cancer research

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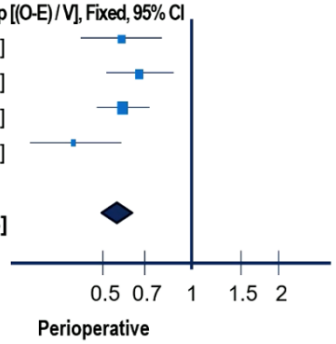
Total events	371		573		

Heterogeneity: Chi² = 5.31, df = 3 (P = 0.15); I² = 43%

Test for overall effect: Z = 8.15 (P < 0.00001)



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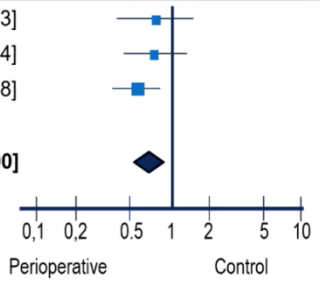


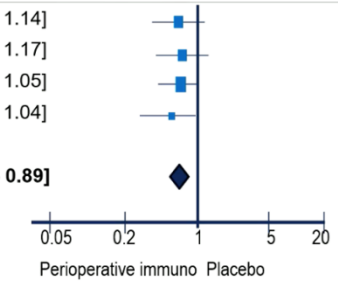
Should we treat also when PD-L1 is negative?

YES!

Study or Subgroup			Placebo		Hazard Ratio
	Events	Total	Events	Total	Exp [(O-E) / V], Fixed, 95% CI
77T	33	93	44	93	0.73 [0.47, 1.14]
Aegean	35	122	46	125	0.76 [0.49, 1.17]
Keynote 671	58	138	77	151	0.75 [0.54, 1.05]
Neotorch	17	69	30	70	0.59 [0.33, 1.04]
Total (95% CI)		**422**		**439**	**0.72 [0.58- 0.89]**
Total events	143		197		

Heterogeneity: Chi² = 0.59, df = 3 (P = 0.90); I² = 0%

Test for overall effect: Z = 2.99 (P = 0.003)



Association of ctDNA clearance and Pathological Response with Neoadyuvant treatment in patients with resectable NSCLC from Phase III AEGEAN trial

Iniciativa científica de: ecp lung cancer research

MADRID 2023 ESMO congress

LBA59

Associations of ctDNA Clearance and Pathological Response with Neoadjuvant Treatment in Patients with Resectable NSCLC from the Phase 3 AEGEAN Trial

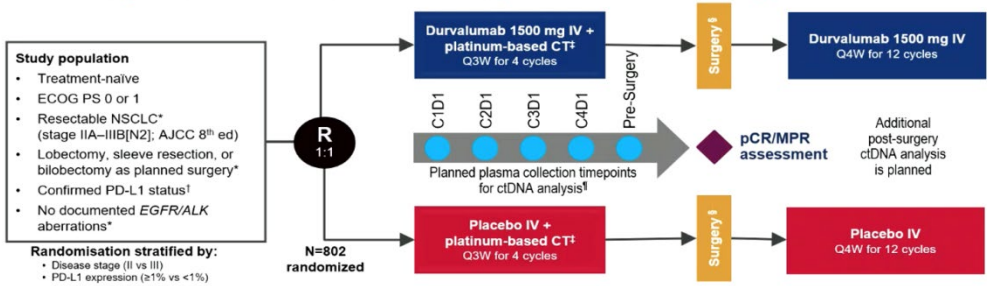
Martin Reck,[1] Davina Gale,[2] David Harpole,[3] Janis M. Taube,[4] Tetsuya Mitsudomi,[5] Maximilian Hochmair,[6] Thomas Winder,[7] Zhou Zhu,[8] Zhongwu Lai,[9] Ross Stewart,[2] Darren Hodgson,[2] Gary J. Doherty,[2] John V. Heymach[10]

[1]Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [2]AstraZeneca, Cambridge, UK; [3]Department of Surgery, Duke University Medical Center, Durham, NC, USA; [4]Bloomberg–Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA; [5]Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan; [6]Department of Respiratory and Critical Care Medicine, Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Klinik Floridsdorf, Vienna, Austria; [7]Internal Medicine II, Landeskrankenhaus Feldkirch, Feldkirch, Austria; [8]AstraZeneca, Gaithersburg, MD, USA; [9]AstraZeneca, Waltham, MA, USA; [10]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas, M.D. Anderson Cancer Center, Houston, TX, USA

Martin Reck
Associations of ctDNA clearance and pathological response with neoadjuvant treatment in patients with resectable NSCLC from the phase III AEGEAN trial

AEGEAN Study Design

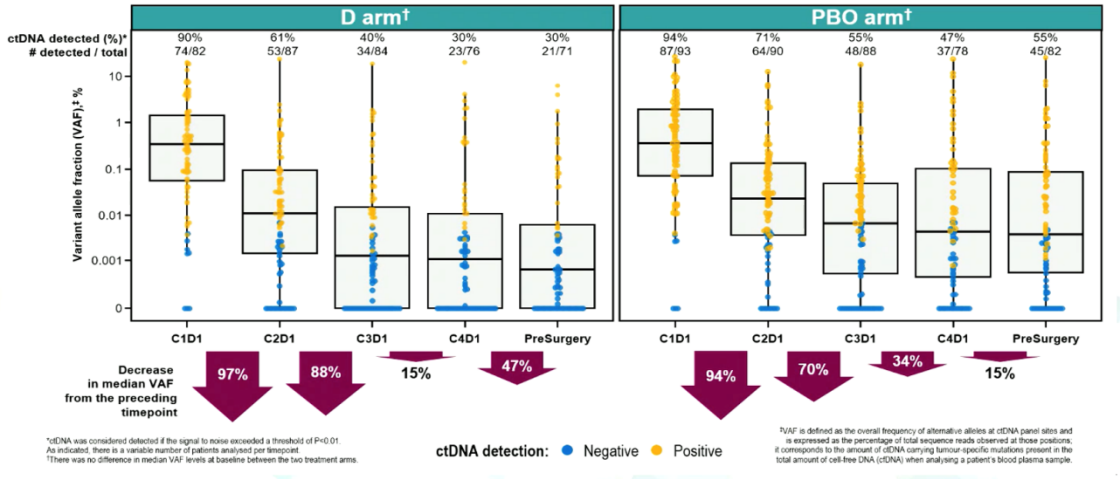
Phase 3, global, randomised, double-blind, placebo-controlled study



- Plasma samples were collected at protocol-specified timepoints, including prior to each neoadjuvant treatment cycle and before surgery
- Analysis was performed using Invitae Personalized Cancer Monitoring™, a tumour-informed MRD assay[1]
  - Patient-specific tumour-informed panels were designed to include 16-50 variants, identified by whole exome sequencing of treatment-naïve diagnostic biopsies only (rather than on-study surgical resections) to avoid selection bias

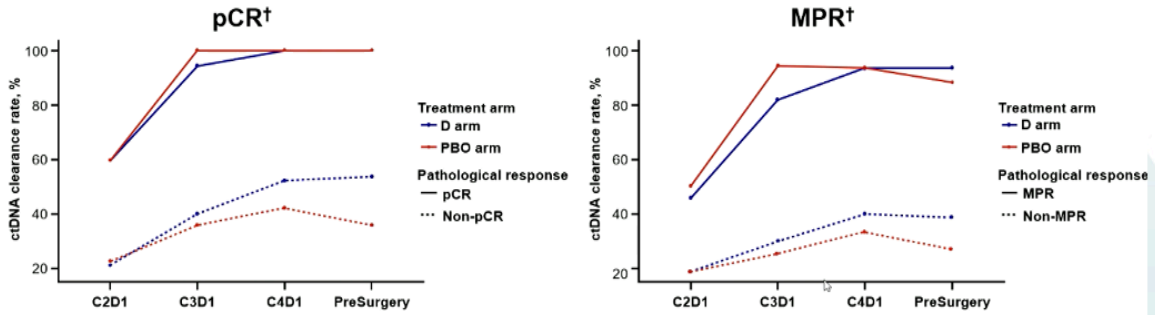
VAF Levels during Neoadjuvant Treatment

- There was a deeper reduction in median VAF levels in the D arm vs the PBO arm, with the largest decrease observed after the 1st cycle



Association of ctDNA Clearance with pCR/MPR and Its Predictive Utility

- Among patients who were ctDNA-positive at baseline (C1D1), all patients achieving pCR and >90% of all patients achieving MPR had ctDNA clearance at C4D1*



El tratamiento neoadyuvante mostró una disminución mayor de niveles de ctDNA y “clearance” en la rama de D + QT que en la de Pcbo + QT. Ente los pacientes que fueron + en la visita basal que alcazaron una pCR el 100% y el 90% de los MPR presentaron “clearance” de ctDNA y puede ser un posible biomarcador para identificar los pacientes que mas se pueden beneficiar previamente a la cirugía.

ESTADIOS INICIALES

Iniciativa científica de: GECP lung cancer research

- TRATAMIENTO ADYUVANTE
  - ALINA: Efficacy and safety of adjuvant alectinib vs chemotherapy in patients with early-stage ALK + NSCLC. Benjamin Solomon et al.

ALINA: Efficacy and safety of adjuvant alectinib vs chemotherapy in patients with early-stage ALK + NSCLC

Iniciativa científica de:

MADRID 2023 ESMO congress

ALINA: efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage *ALK*+ NSCLC

Benjamin J. Solomon[1], Jin Seok Ahn[2], Rafal Dziadziuszko[3], Fabrice Barlesi[4], Makoto Nishio[5], Dae Ho Lee[6], Jong-Seok Lee[7], Wenzhao Zhong[8], Hidehito Horinouchi[9], Weimin Mao[10], Maximilian Hochmair[11], Filippo de Marinis[12], Maria Rita Migliorino[13], Igor Bondarenko[14], Tania Ochi Lohmann[15], Tingting Xu[16], Andres Cardona[17], Walter Bordogna[18], Thorsten Ruf[19], Yi-Long Wu[8]

Ben Solomon
ALINA: Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC)

ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R 1:1

N=257

- **Alectinib 600 mg BID** 2 years → **Recurrence**
- **Platinum-based chemotherapy†** Q3W; 4 cycles → **Recurrence**

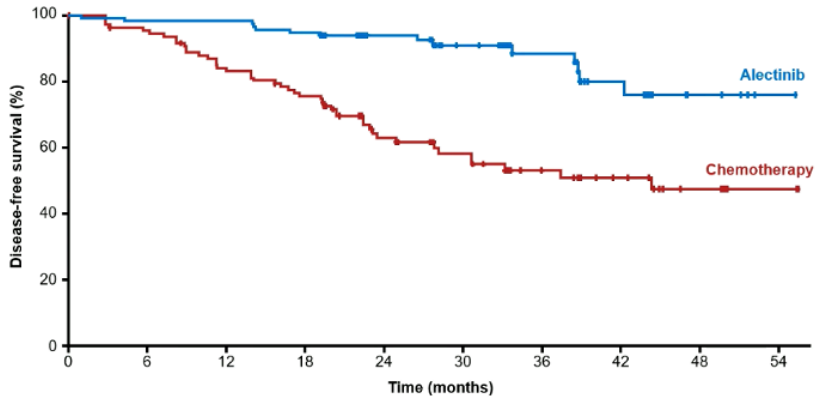
→ **Further treatments at investigator's choice and survival follow-up**

Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

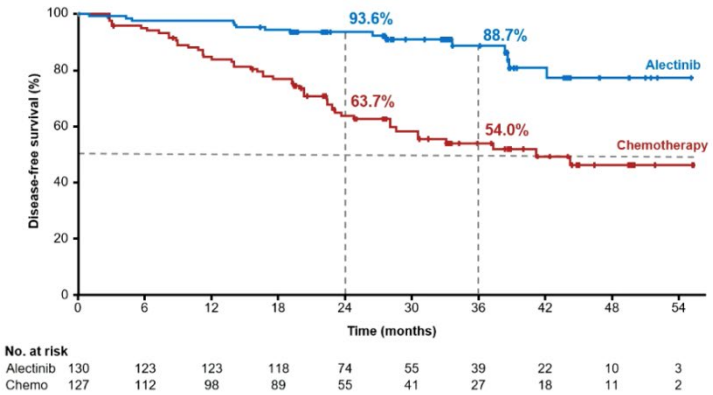
Disease-free survival: stage II–IIIA*



	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

Disease-free survival: ITT (stage IB–IIIA)*



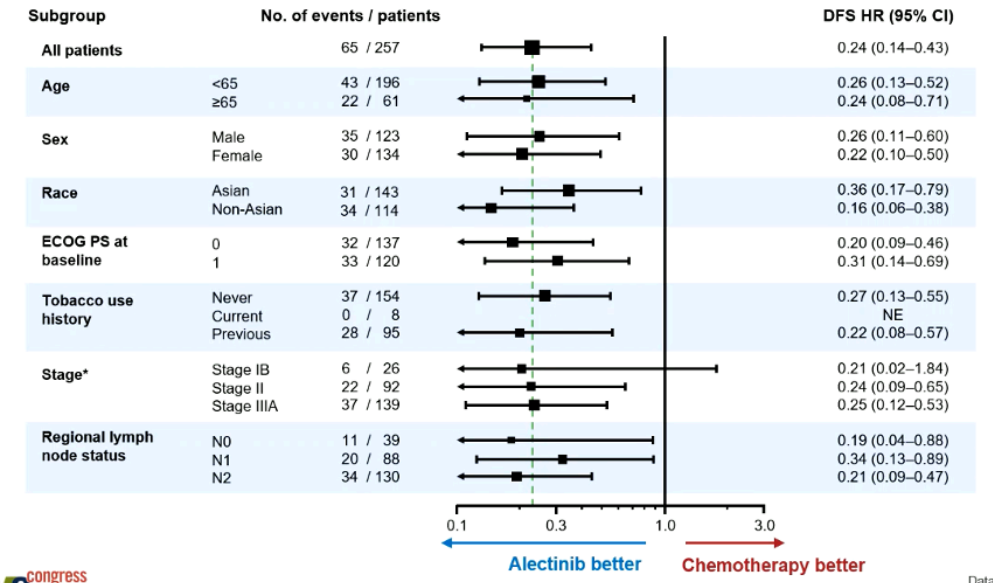
	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p†<0.0001	

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

MADRID 2023 ESMO congress

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months
*Per UICC/AJCC 7th edition; †Stratified log rank; ‡2 events in the alectinib arm, 4 events in the chemo arm; one additional patient in the chemo arm died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

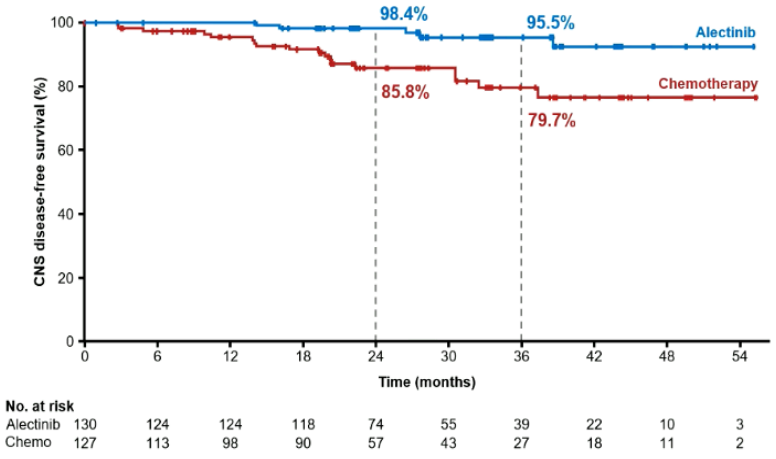
Disease-free survival subgroup analysis (ITT)



Data cut-off: 26 June 2023

Arrows indicate lower bound of the CI<0.1; *Per UICC/AJCC 7th edition

CNS disease-free survival in the ITT population



	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	5	18
Death	1	4
Brain recurrence	4	14
CNS-DFS HR* (95% CI)	0.22 (0.08, 0.58)	

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

CONCLUSIONES

- ALINA es el primer estudio que muestra el beneficio de un inhibidor ALK en pacientes ALK resecados
- Alectinib adjuvante produce un beneficio estadísticamente significativo en SLP vs QT (HR 0.24) que se reflejó en todos los subgrupos
- Se observó un beneficio significativo en la SLP en SNC
- El perfil de seguridad fue excelente en línea con la toxicidad mostrada en estadios IV
- Alectinib adyuvante es una nueva estrategia estándar para NSCLC estadios IB-IIIA completamente resecados

RESUMEN

- Nivolumab + QT en estadios IB-IIIA continua siendo el tratamiento neoadyuvante estándar, independientemente de la expresión de PD-L1, aunque se benefician mas los pacientes PD-L1 +
- El tratamiento perioperatorio cuyo estudio pionero fue el estudio NADIM se consolida como tratamiento estándar en estadio II-IIIB resecables, con datos positivos de supervivencia en el estudio KN-671
- Es necesario realizar a todos los pacientes el tratamiento adyuvante?
  - Quizás se podría evitar en pacientes con pCR o aclaramiento de ct DNA, aunque son cuestiones pendientes que se están investigando
  - El estudio ChecMate 77T demostró que el tratamiento adyuvante mejoró la EFS independientemente del estatus de pCR

- El estudio ALINA con alectinib adyuvante en NSCLC estadios I-III ALK + completamente resecados es el nuevo tratamiento estándar