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UNIVERSIDAD DE LAS PALMAS
DE GRAN CANARIA

# Neoadjuvant Immunotherapy and target therapy in Resectable NSCLC

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# Disclosure Information

**Consultant or Advisory Role:** BMS, MSD, ROCHE, ASTRA ZENECA, BOEHRINGER INGELHEIM, NOVARTIS, Lilly.

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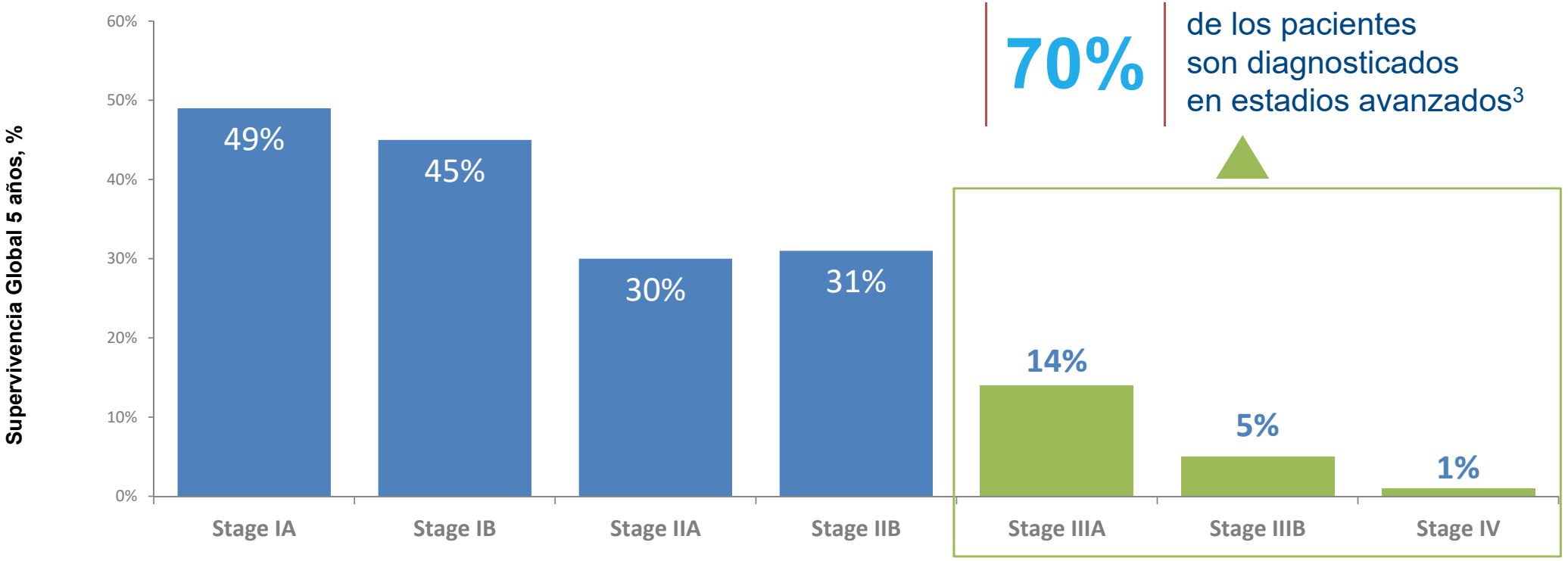
# SUPERVIVENCIA EN CANCER DE PULMÓN NO MICROCÍTICO

- **Las tasas de supervivencia** para los pacientes con CPNM **disminuyen** drásticamente en **etapas avanzadas de la enfermedad**




NSCLC=non-small cell lung cancer

**1**. American Cancer Society. Non small-cell survival rates by stage. May 2016. Available at: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-survival-rates. Accessed: Mar 2017; **2**. Carnio S *et al. Semin Oncol.* 2014;41(1):69–92; **3**. Molina JR *et al. Mayo Clin Proc.* 2008;83(5):584–94

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# Early detection through low-dose CT screening may reduce mortality in lung cancer

- The proportion of patients with stage I–III disease is expected to increase as low-dose CT screening becomes more common[1]

**NLST[2]**

Large trial of >50,000 patients

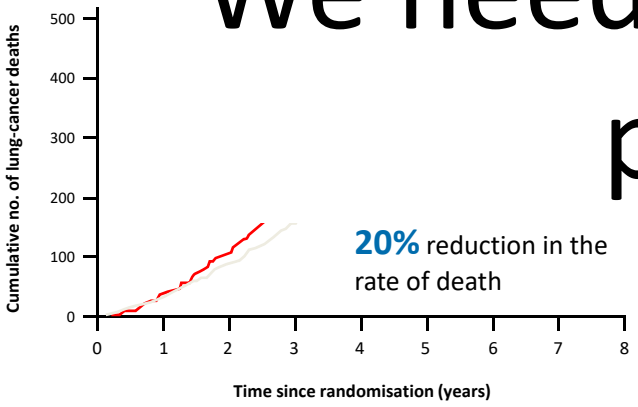
**NELSON[1]**

Medium trial of >15,000 patients

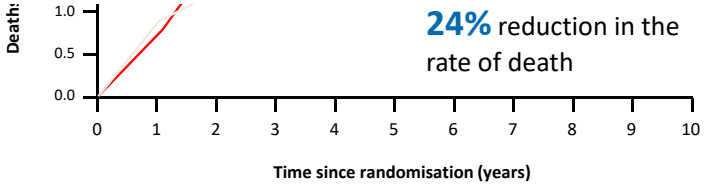
**MILD[3]**

Small trial of >4,000 patients

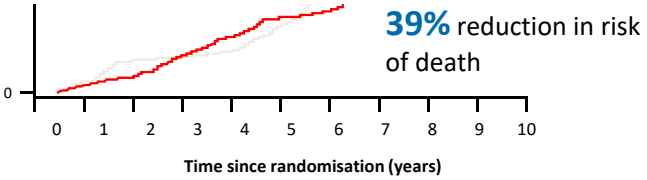
# We need a lung cancer screening program in Spain




**20%** reduction in the rate of death




**24%** reduction in the rate of death




**39%** reduction in risk of death

- By detecting more cancers at an earlier stage, where outcomes are better, lung cancer screening may improve long-term survival

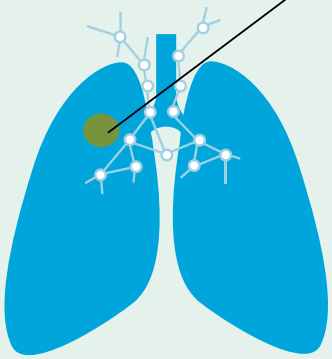
1. de Koning, et al. N Engl J Med 2020 2. National Lung Screening Trial Research Team. N Engl J Med 2011 3. Pastorino, et al. Ann Oncol 2019

# Disease staging terminology: what is early-stage and locally advanced NSCLC?

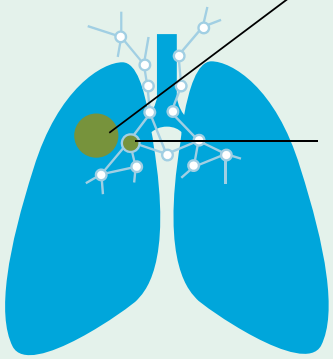
## Early-stage

**Stage I and II disease:** Vast majority is **resectable**
(Complete resection (R0) is possible)
Classification of early stage NSCLC is based on prognosis, however ESMO and NCCN guidelines have different definitions

**STAGE I**




**STAGE II**

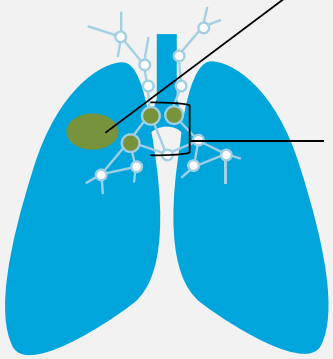



## Locally advanced

**Stage III disease**

| Resectable | Potentially resectable | Unresectable Complete resection (R0) is not possible |
|---|---|---|

**STAGE III**




For **CIT trials**, early-stage NSCLC refers to stage I and II disease plus selected stage III cases where **complete tumour resection** is feasible

*ESMO refer to UICC TNM classification while NCCN refer to AJCC TNM classification
An Asian expert group has similar definitions of NSCLC

Postmus, et al. Ann Oncol 2017; Ghysen and Vansteenkiste, Curr. Opin. Oncol. 2019; NCCN guidelines v1.2020
Tan, et al. J Thorac Oncol 2019

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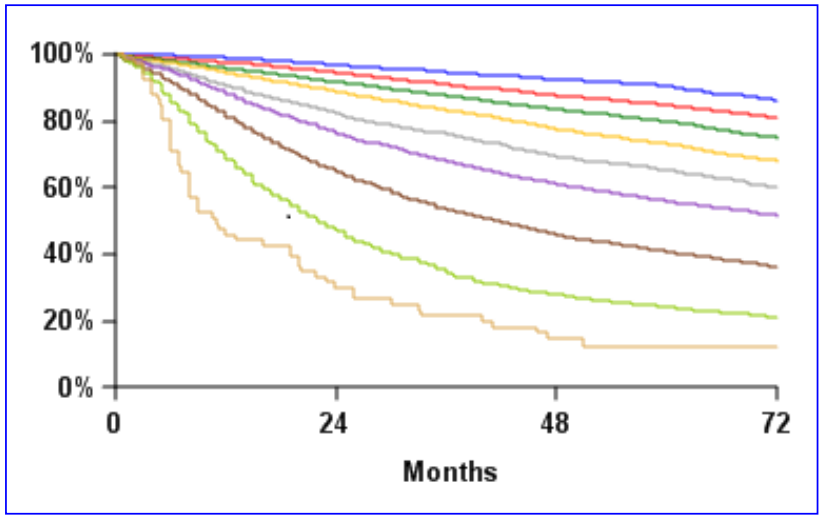
# IASLC dataset for stage grouping on the 8th edition

## Pathological stage




| | Events/N | MST | 2 years | 5 years |
|---|---|---|---|---|
| IA1 | 139/1389 | NR | 97% | 90% |
| IA2 | 823/5633 | NR | 94% | 85% |
| IA3 | 875/4401 | NR | 92% | 80% |
| IB | 1618/6095 | NR | 89% | 73% |
| IIA | 556/1638 | NR | 82% | 65% |
| IIB | 2175/5226 | NR | 76% | 56% |
| IIIA | 3219/5756 | 41.9 | 65% | 41% |
| IIIB | 1215/1729 | 22.0 | 47% | 24% |
| IIIC | 55/69 | 11.0 | 30% | 12% |

*Goldstraw P et al. J Thorac Oncol 2016; 11: 39-51.*

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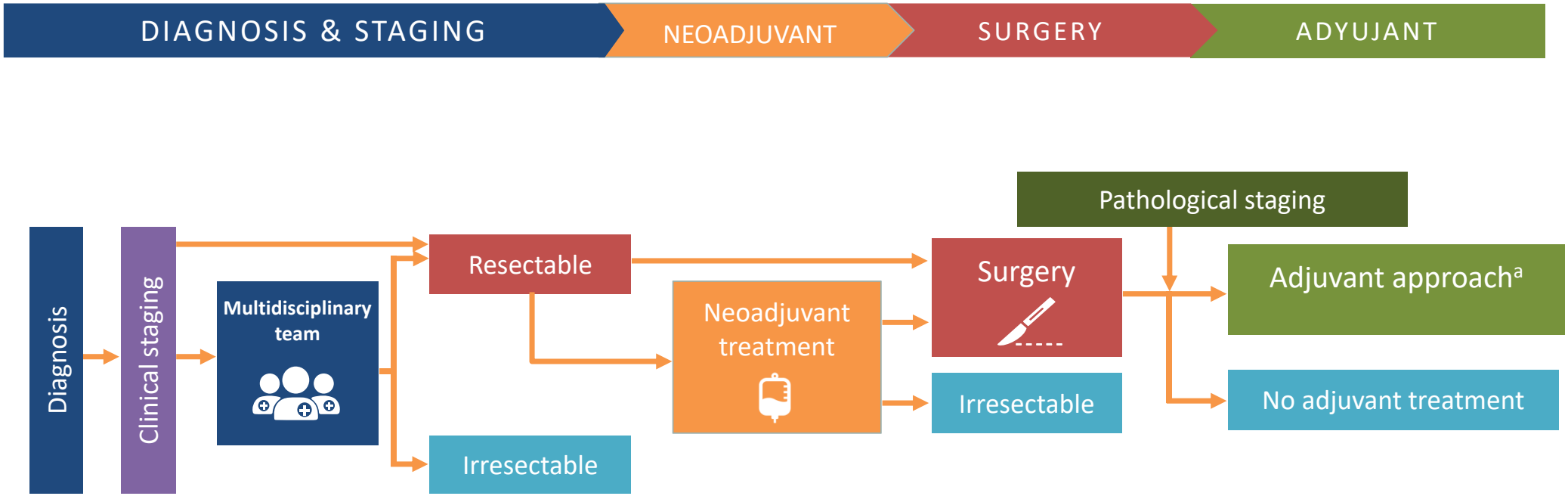
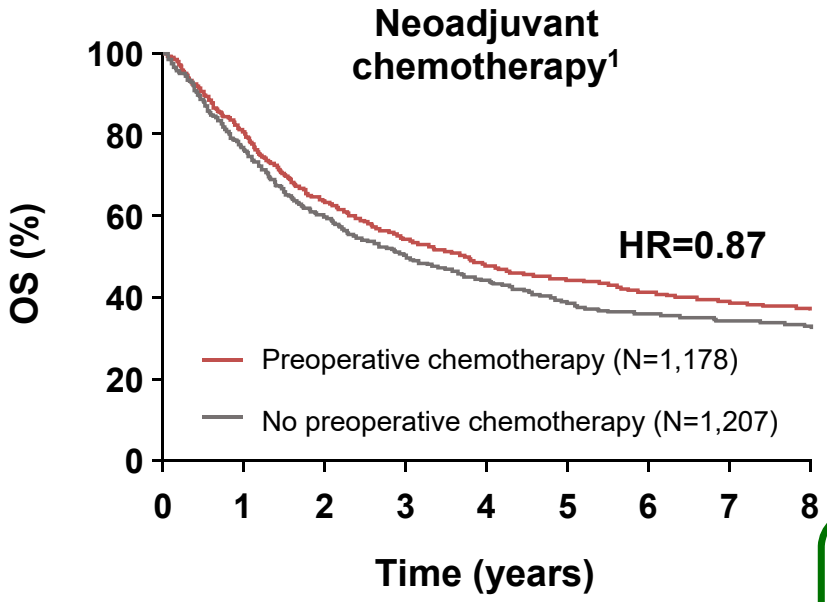


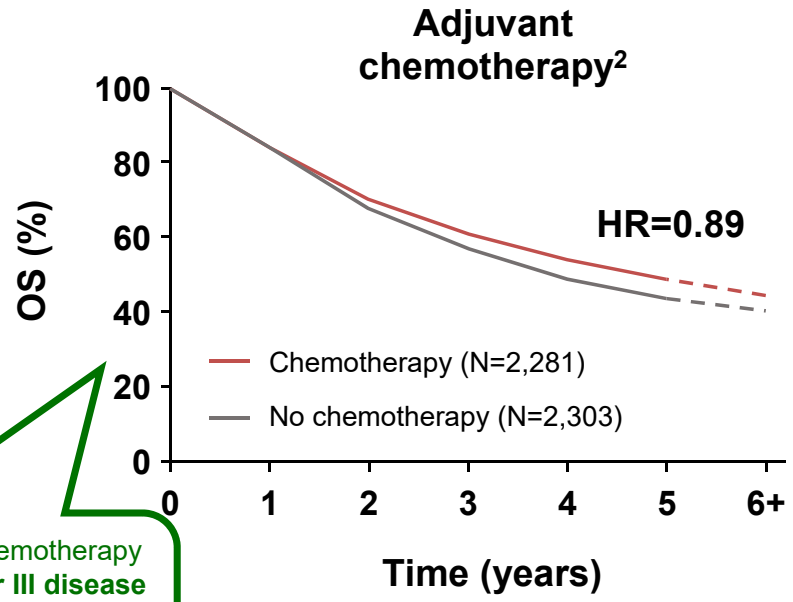

- [1] Mauguen A, Pignon J-P, Burdett S, Domerg C, Fisher D, Paulus R, et al. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data. Lancet Oncol. junio de 2013;14(7):619-26. [2] Postmus PE et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;28(suppl 4):iv1–iv21.
- [2] Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. julio de 2017;28:iv1-21.
- [A] Incluye radioterapia y terapia sistémica (generalmente quimioterapia con agentes a base de platino, como cisplatino y carboplatino )
- Abreviaturas: CPNM: cancer de pulmón no microcítico

# Neoadjuvant and adjuvant chemotherapy significantly improve OS in patients with stage I–III NSCLC;* both show a similar and modest benefit




**5%**

**improvement in 5-year OS[1,2]**




The greatest benefit with adjuvant chemotherapy was shown in patients with **stage II or III disease** (HR=0.83 for both stages)[2]
In stage I NSCLC, adjuvant chemotherapy mainly appears to benefit patients with tumours >4cm[3]

For stage I & II NSCLC, the greater evidence base and similar outcomes mean
**ESMO guidelines recommend adjuvant chemotherapy over neoadjuvant chemotherapy**

*Data from pooled analyses (analyses use earlier editions of staging guidelines)


1. NSCLC Meta-analysis Collaborative Group. Lancet 2014
2. Pignon, et al. J Clin Oncol 2008
3. Postmus, et al. Ann Oncol 2017

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# Why do we do Adjuvant Therapy?

- Surgical outcome for early-staged NSCLC except stage IA is still disappointing.
- Most of recurrences are systemic disease
- To eliminate micro-metastases and probably cure patients
- Patients have a more intact immune system
- Suppresses remaining cells and delay recurrence

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# Why not to do Adjuvant Therapy?

- Surgical can cure a numbers of early-staged NSCLC.
- Overtreatment of patient cured by surgery
- Adverse events (early and late)
- Cost of therapy

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# Why do we do Neo-Adjuvant Therapy?

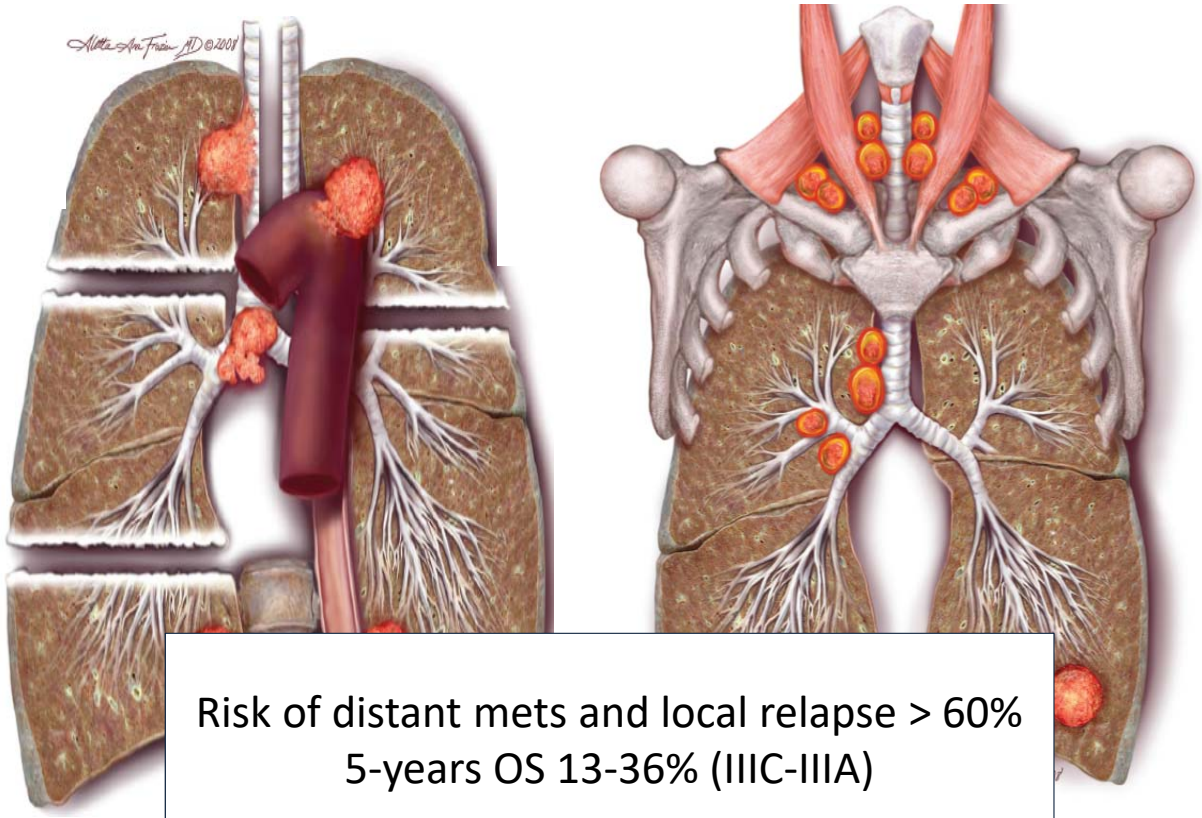
- Treat micrometastases at the earliest time point
- Increase compliance with therapy prior to surgery.
- Assess treatment efficacy prior to surgery.
- Evaluate biomarkers and surrogate endpoints (MPR and pCR).

# Stage III NSCLC Includes Multiple Diseases

Stage III heterogeneity

T3/T4 disease

N2/N3 disease



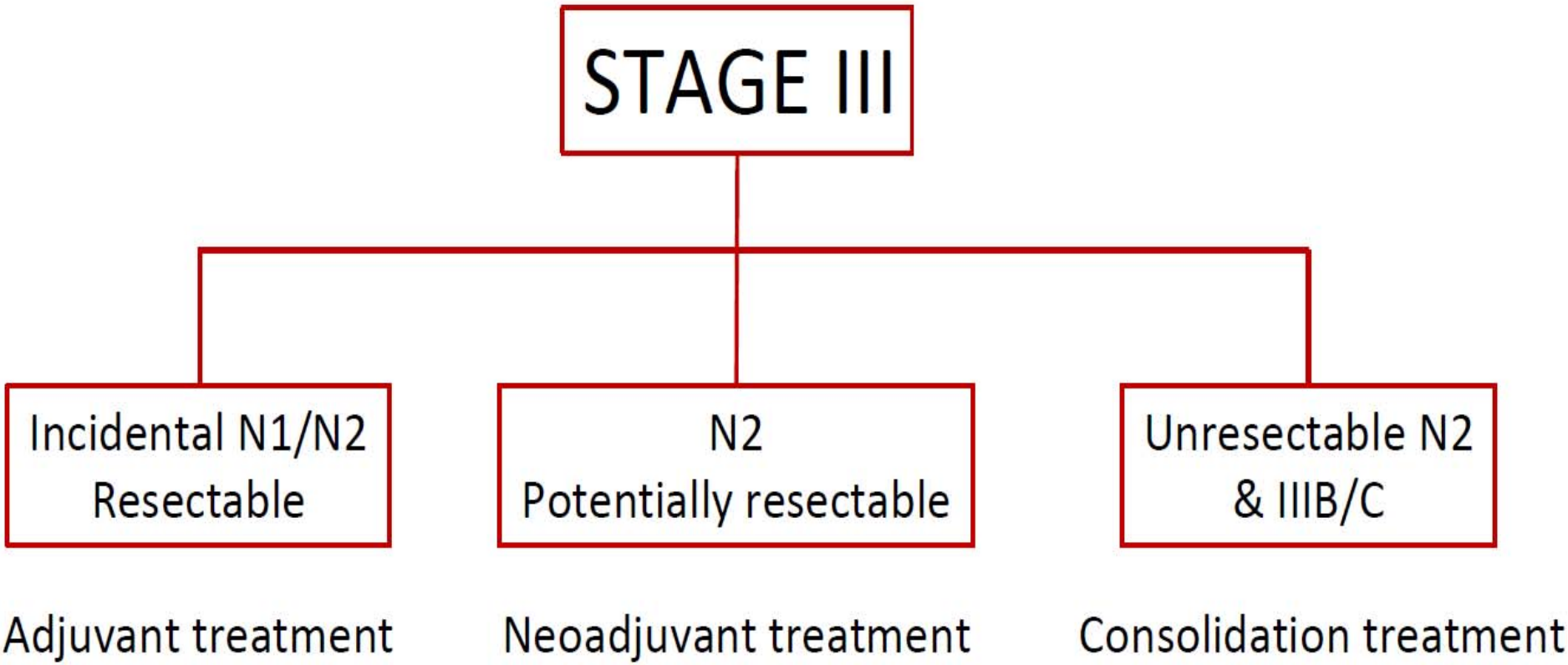
Risk of distant mets and local relapse > 60%
5-years OS 13-36% (IIIC-IIIA)

## Stage III NSCLC
Includes multiple diseases

**STAGE IIIA**
- >7 cm no nodes
- 5 cm with N1
- Any N2
- Surgery as part of multimodality treatment

**STAGE IIIB**
- >5 cm with N2
- Or any N3
- Nonoperative treatment

1. Goldstraw P, et al. *J Thorac Oncol*. 2016;11:39-51. 2. NCCN® Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 2.2019. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.


STAGE III
Incidental N1/N2
Resectable
N2
Potentially resectable
Unresectable N2
& IIIB/C
Adjuvant treatment
Neoadjuvant treatment
Consolidation treatment

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# Neoadjuvant approach
# Role of Immunotherapy

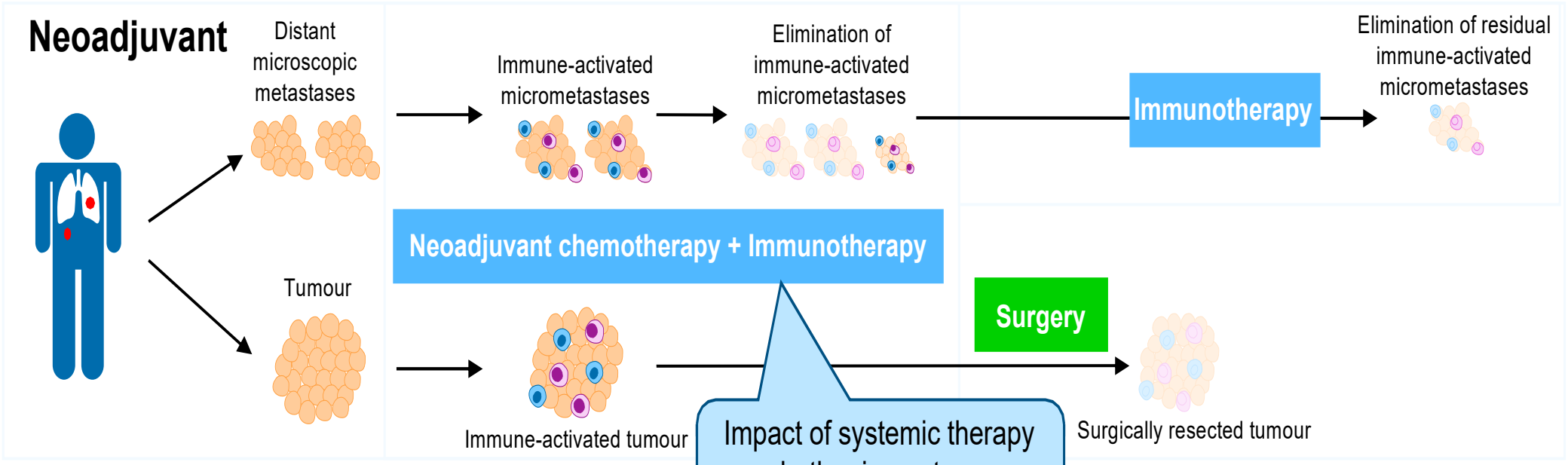


Figure adapted from Robert Nat Med 2018

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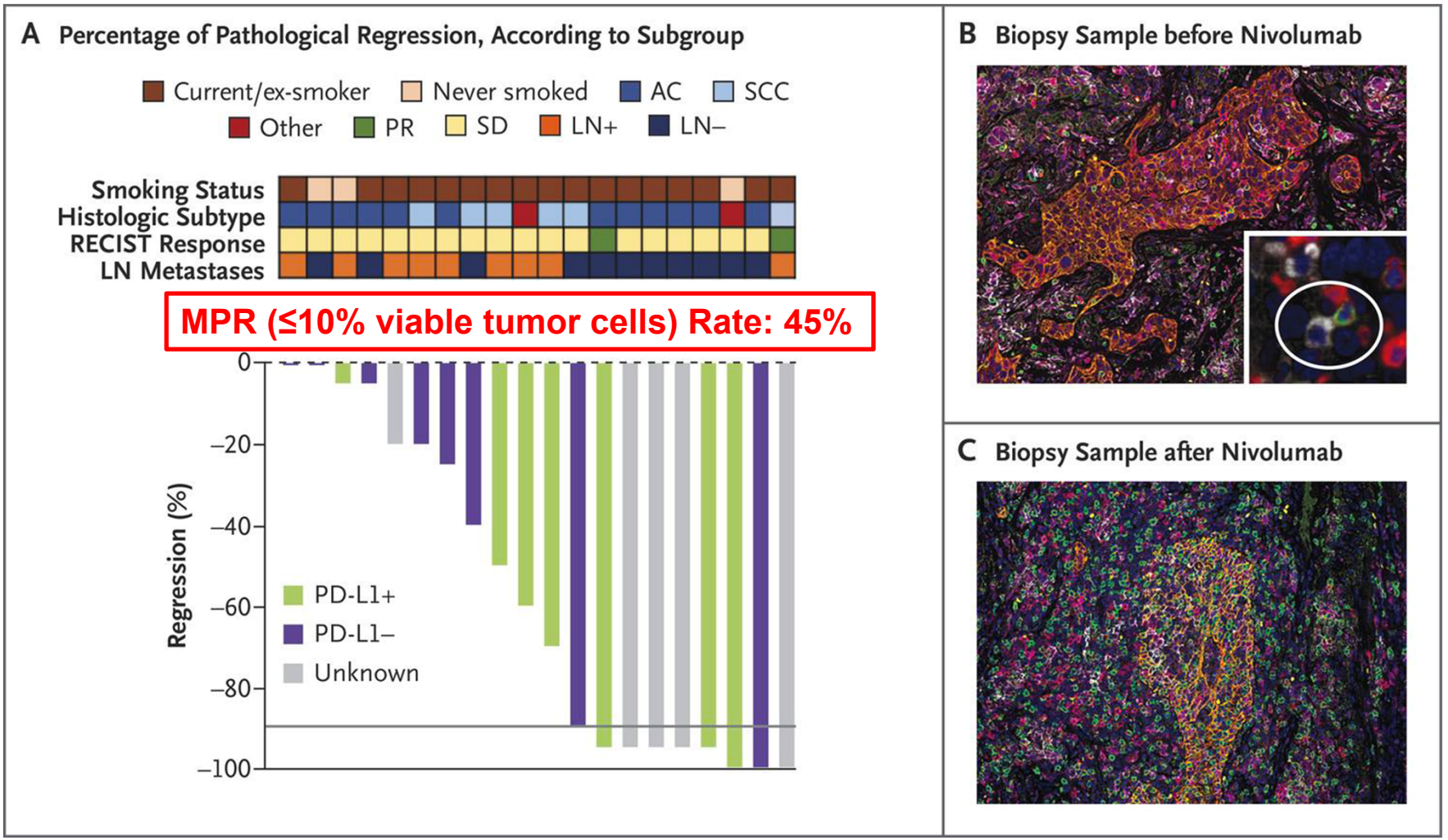
# Neoadjuvant nivolumab is feasible, safe and active in resectable NSCLC

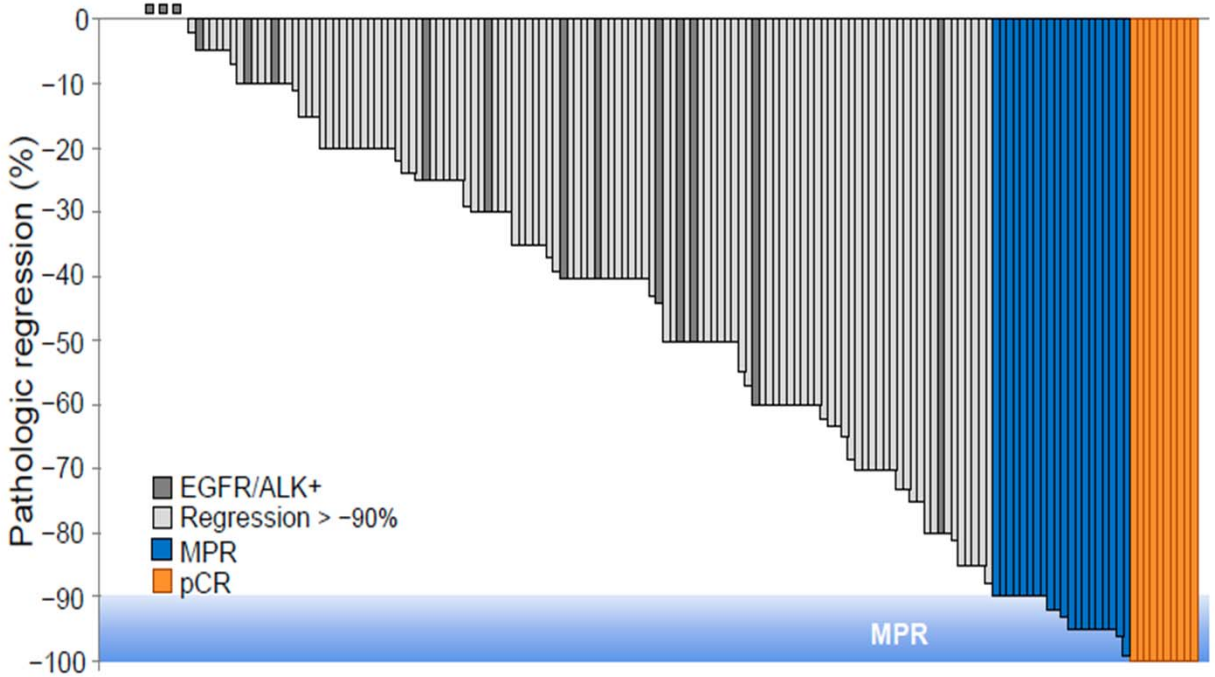
**MPR 45%**
**pCR: 15%**



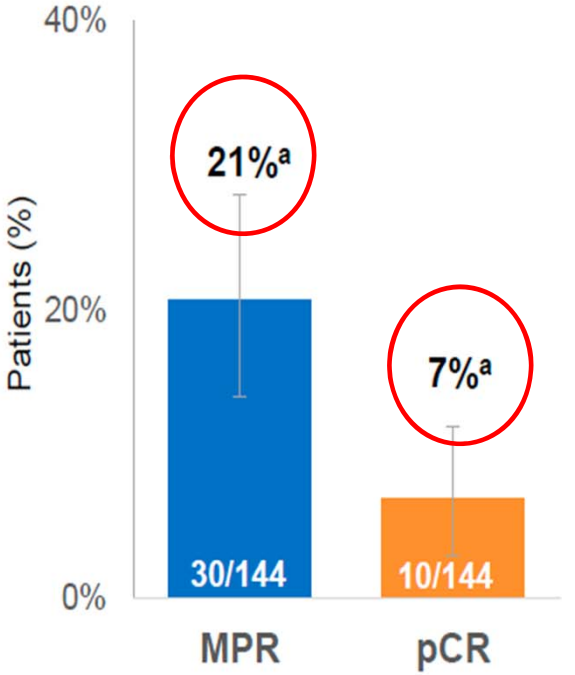

Forde, PM et al. N Engl J Med. 2018

# MPR to neoadjuvant atezolizumab in the LCMC3 study

**Pathologic response in surgery population (n=159)**




**Major pathologic response in primary efficacy population (n=144)**




Pathologic regression defined as % viable tumor cells – 100%.
MPR, major pathologic response; pCR, pathologic complete response.
[a] Error bars indicate 95% CI.

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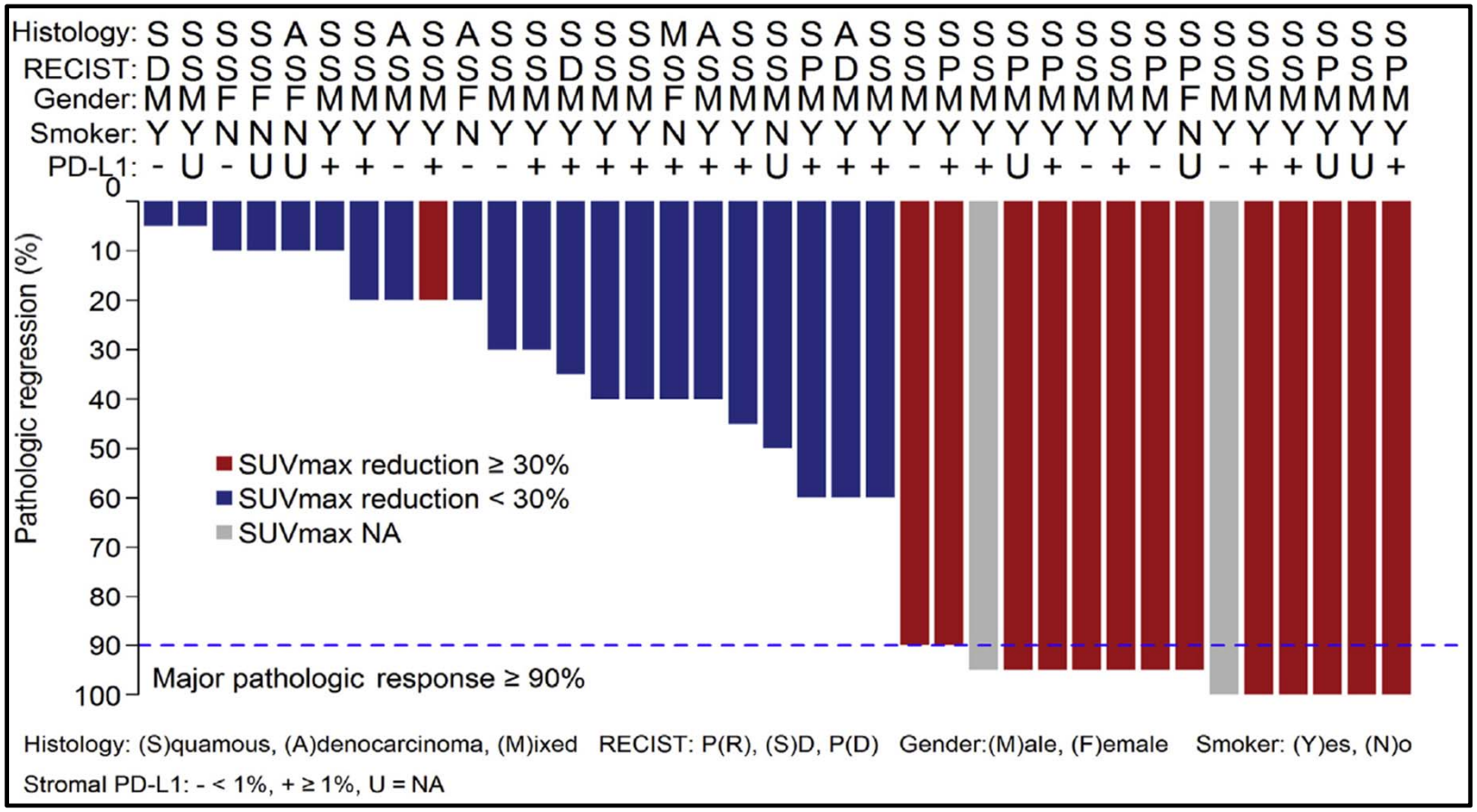
# MPR to neoadjuvant sintilimab in resectable NSCLC

**MPR rate: 40.5%**
**pCR rate: 16%**




Gao, S et al. J Thorac Oncol. 2020

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# MPR to neoadjuvant durvalumab with or without SBRT for resectable NSCLC

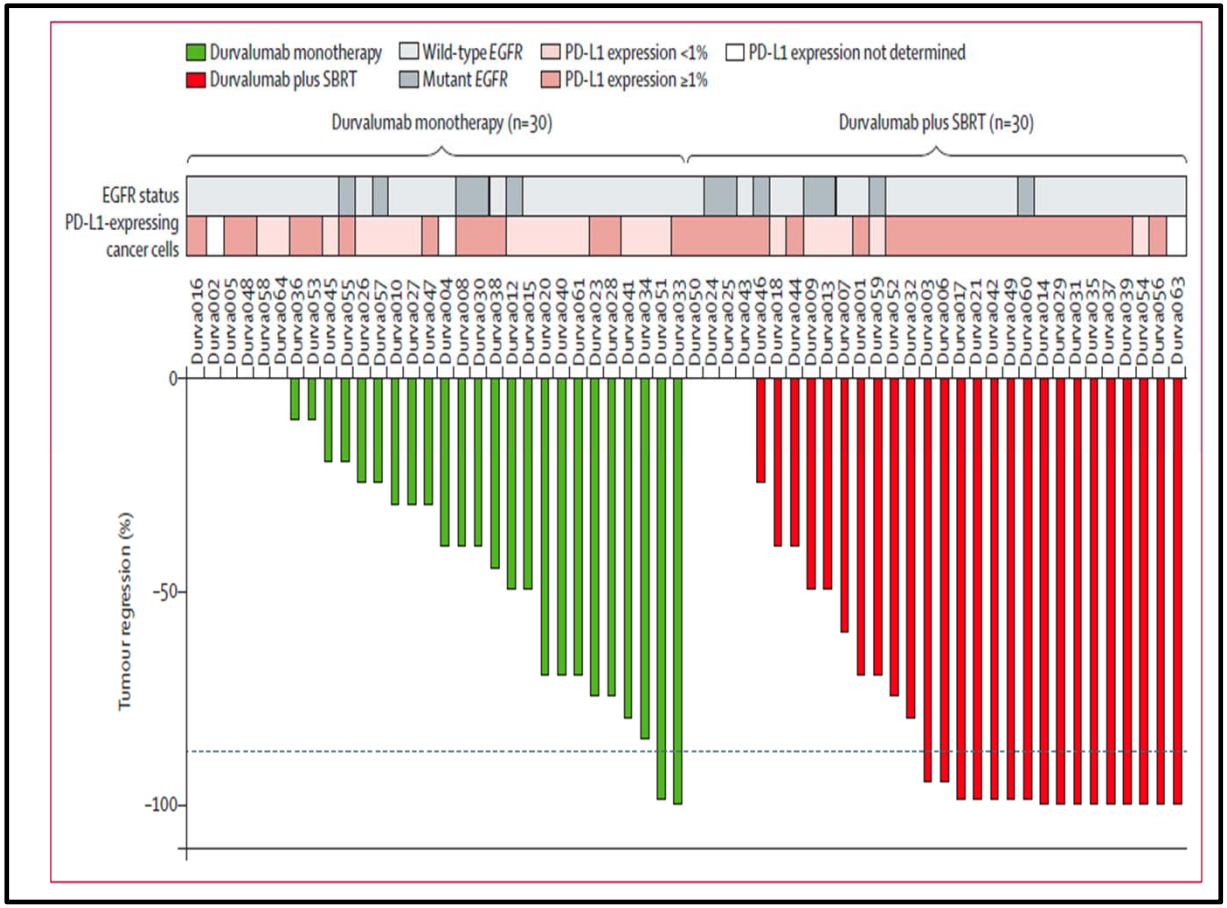
Resection rate: 87% in both arms

**MPR in primary tumors**

- Durva mono: 6.7% (2/30)

- Durva + SBRT 53.7% (16/30)

**[pCR 27%** (8/30)]




Altorki NK et al, Lancet Oncol 2021

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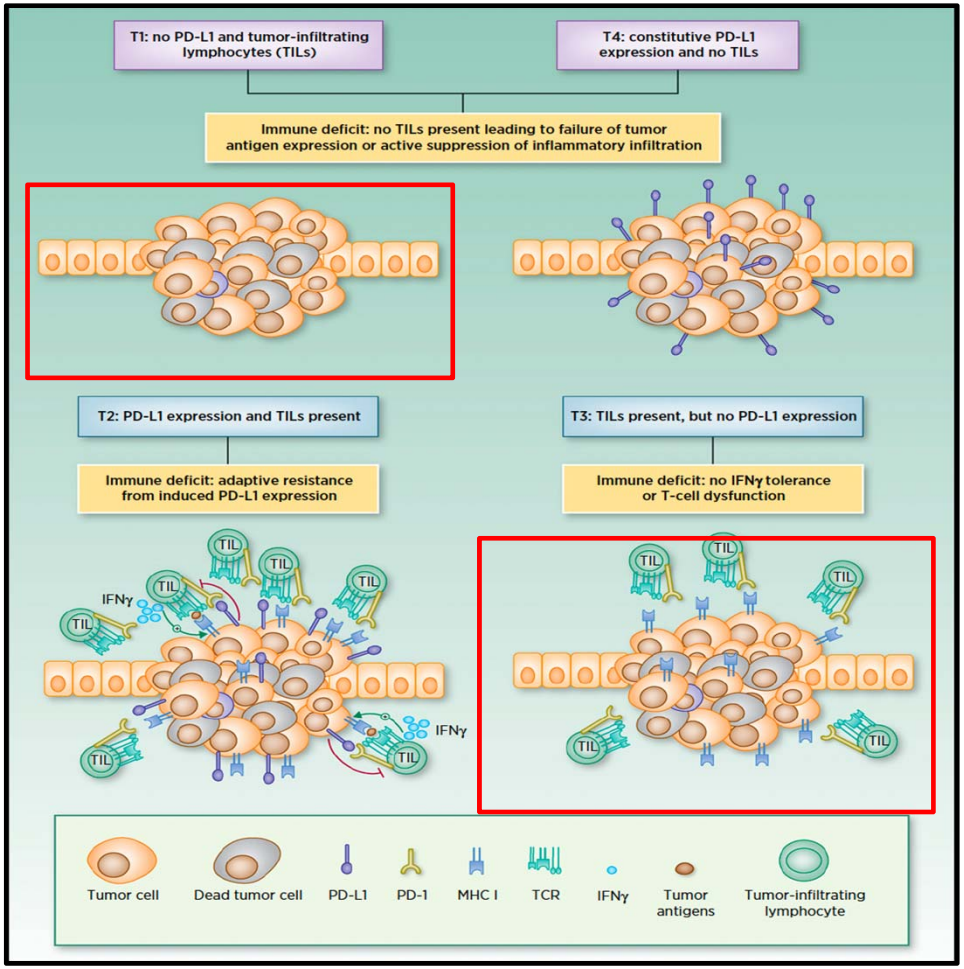


# Neoadjuvant CT/IO and IO-IO combination trials

The enhancement of PD-L1 expression through chemotherapy and T cell with anti CTLA4

Janice M. Mehnert. Clin Cancer Res, 2017

Fournel L. Cancer Lett. 2019. Curran MA. Proc Natl AcadSci U S A. 2010. Shin J. Cancer Res Treat. 2019.

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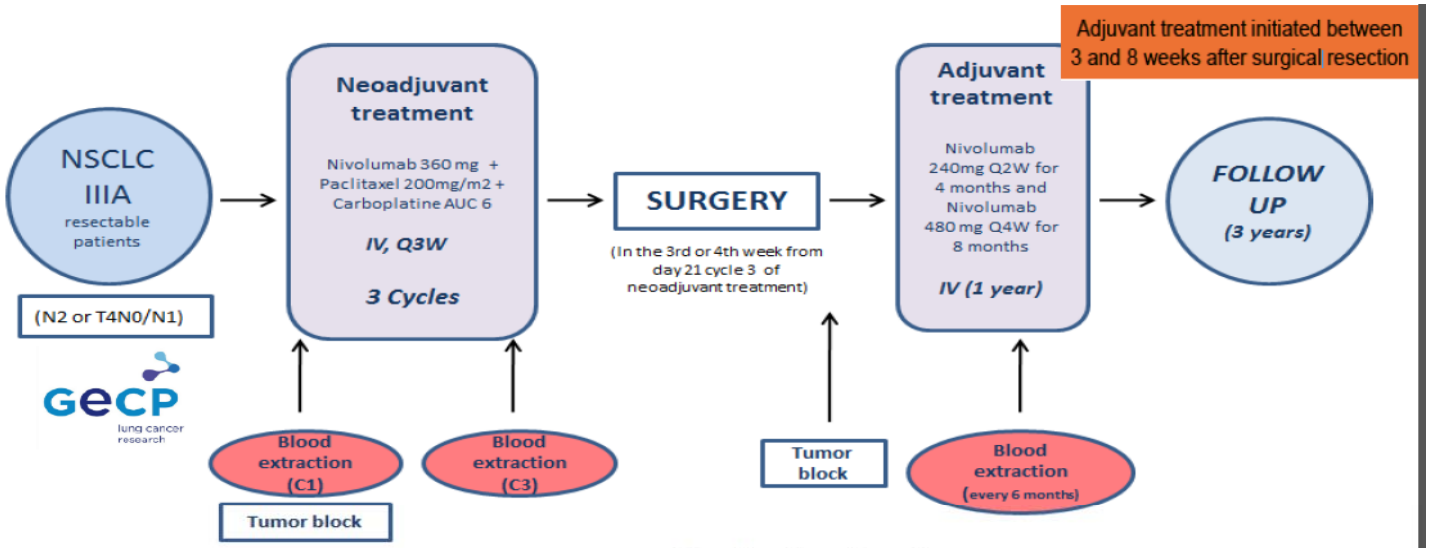
# NADIM trial




## Surgery

| Type of surgery | N | % |
|---|---|---|
| Lower bi-lobectomy | 2 | 6.7 |
| Left upper lobectomy | 2 | 6.7 |
| Left lower lobectomy | 3 | 10 |
| Right upper lobectomy | 15 | 50 |
| Right lower lobectomy | 5 | 16.6 |
| Right pneumonectomy | 2 | 6.7 |
| Left pneumonectomy | 1 | 3.3 |

≈ 90%

| Resection type | N | % |
|---|---|---|
| R0 | 29 | 96.5 |

## Pathological response

| | N | % |
|---|---|---|
| Major response[1] | 24 | 80.0 |
| Complete response | 18 | 75.0 |
| Less < 90% | 6 | 20.0 |
| Total | 30 | 100.0 |

[1]Major pathological response defined as <10% viable tumor cells in the resected specimen.

Provencio et al, WCLC 2018

Single-arm
Open-label
Multicenter
Resectable IIIA NSCLC (7th ed. AJCC)

N = 46 patients
30 patients underwent surgery

## Clinical response

| | N | % |
|---|---|---|
| Complete response (CR) | 3 | 10.0 |
| Partial response (PR) | 18 | 60.0 |
| Stable disease (SD) | 9 | 30.0 |
| Total | 30 | 100.0 |

*No progressive disease has been observed.*

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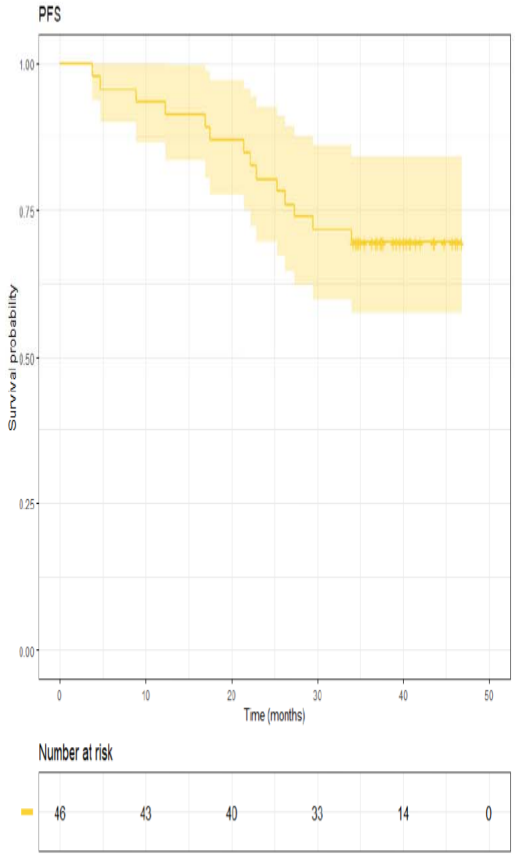
# NADIM TRIAL: PFS (primary endpoint)




**ITT population:**

- **PFS 69.6%** (95%CI: 54.1-80.7%) **at 36 and 42 months.**

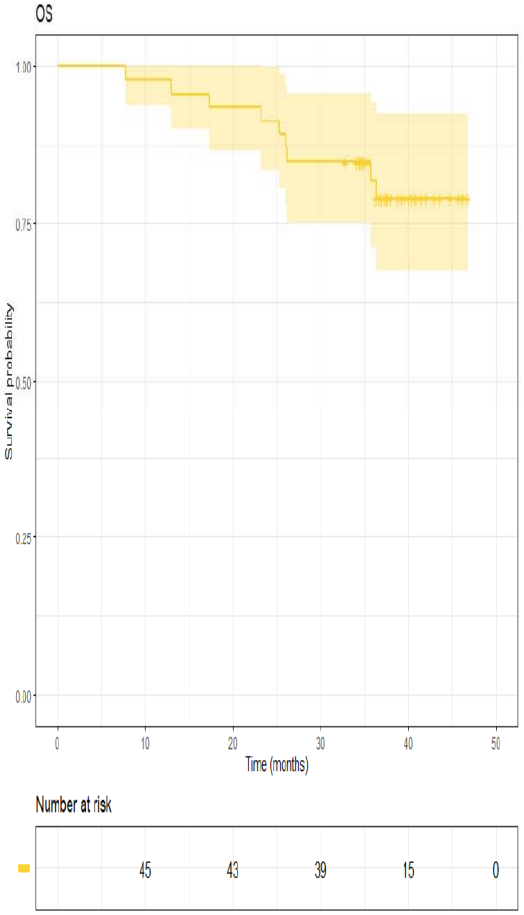
**PP population:**

- **PFS 81.1%** (95%CI: 64.4-90.5%) **at 36 and 42 months.**

The median PFS for patients who had progressive disease was 21.4 months (95% CI: 8.8–26.2 months)

Provencio et al, WCLC 2021

# NADIM TRIAL: OS




**ITT population:**

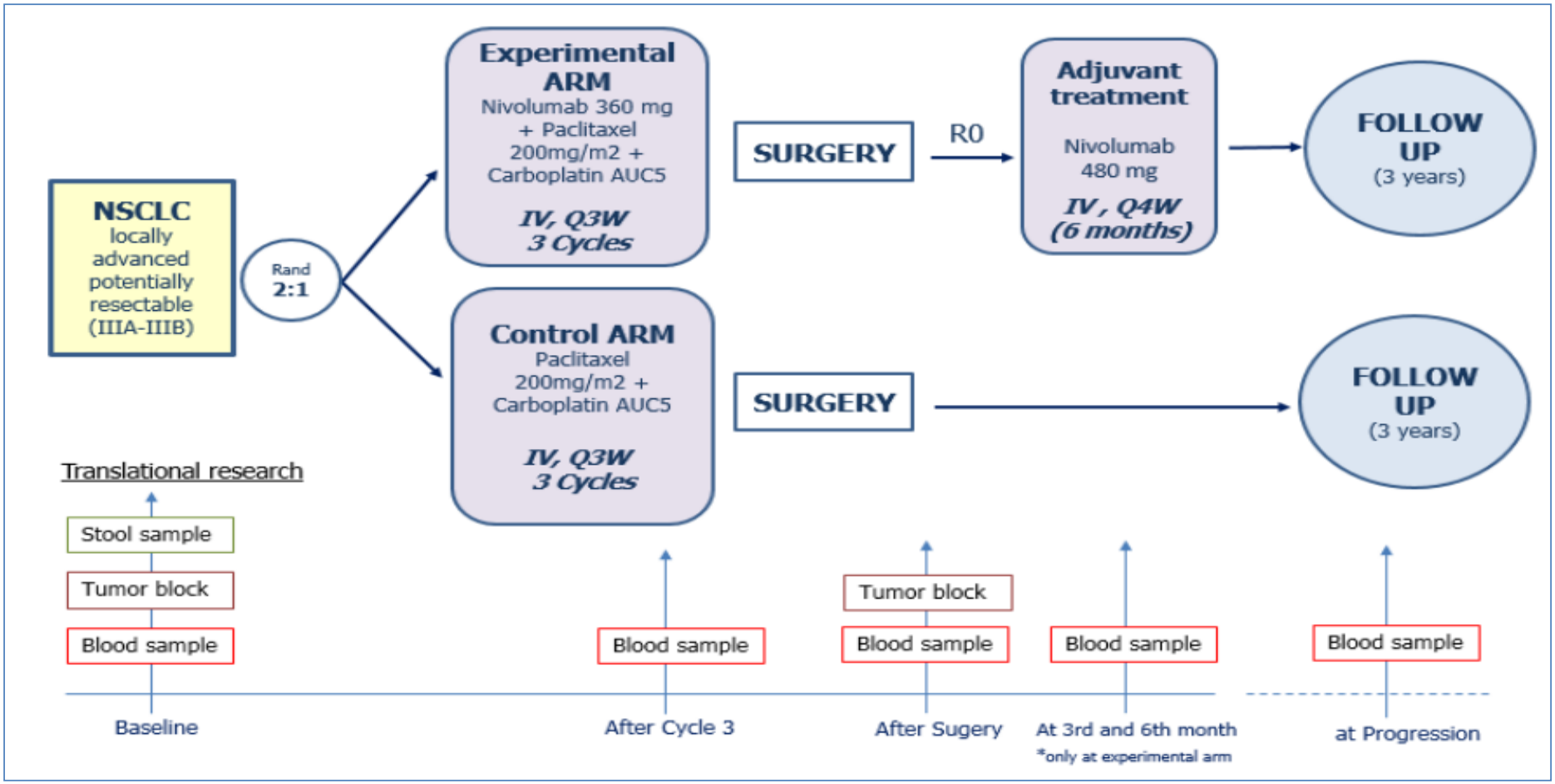
- **OS 81.9%** (95% CI: 66.8-90.6%) **at 36 months.**
- **OS 78.9%** (95%CI: 63.1-88.6%) **at 42 months.**

**PP population:**

- **OS 91.0%** (95%CI: 74.2-97.0%) **at 36 months**
- **OS 87.3%** (95%CI: 69.3-95.1%) **at 42 months.**

Provencio et al, WCLC 2021

# NADIM II trial: Nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for resectable stage IIIA non-small cell lung cancer (NSCLC)



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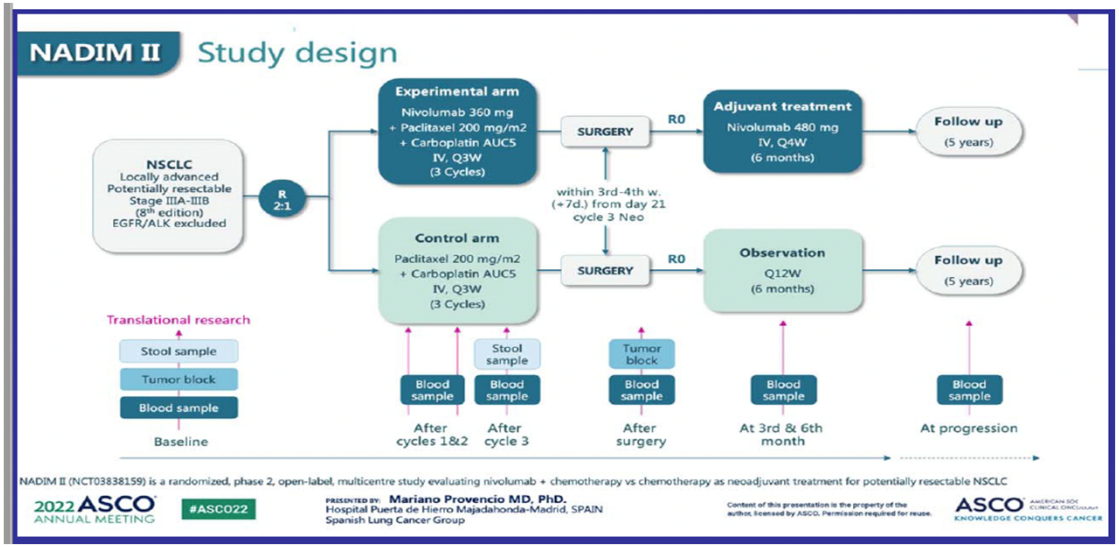
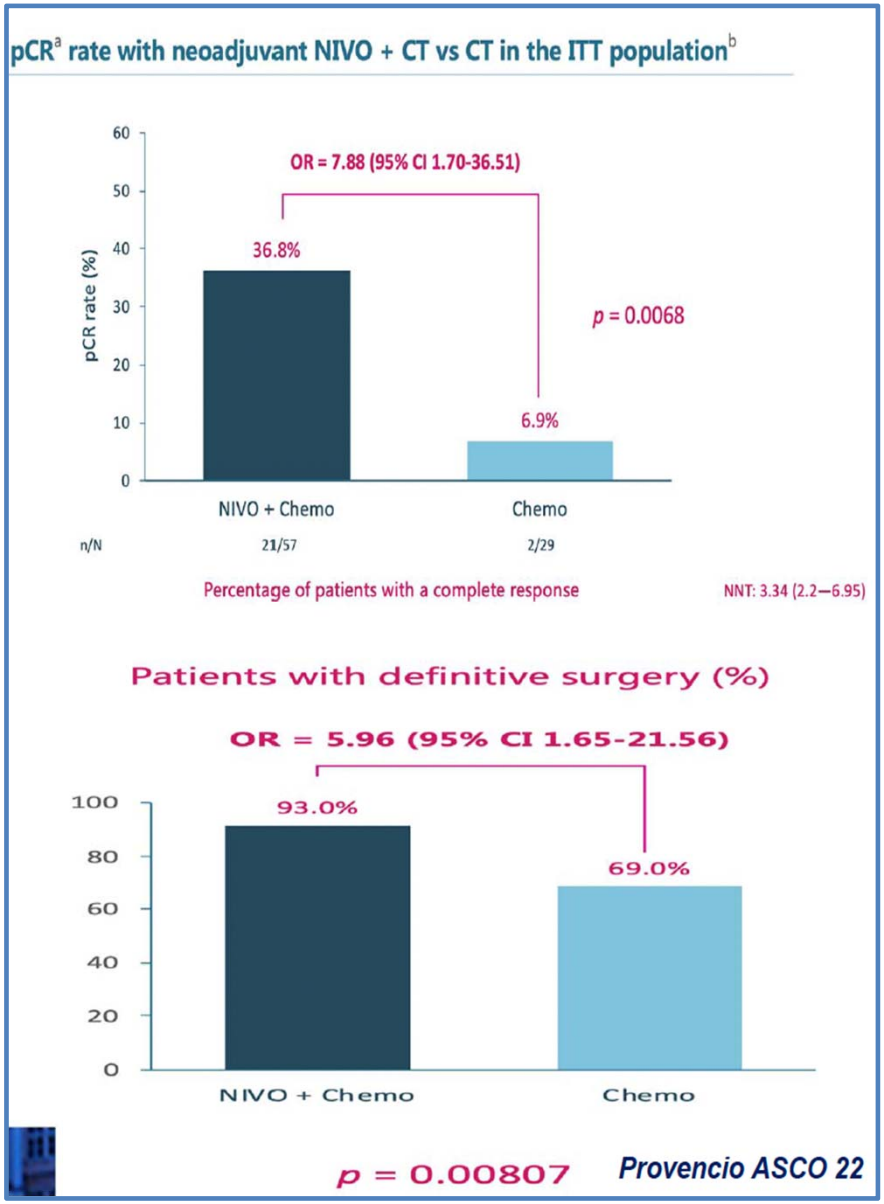
# NADIM II trial




**Baseline characteristics - ITT population**

| Characteristic | NIVO + Chemo (n = 57) | Chemo (n = 29) |
|---|---|---|
| TNM classification (AJCC 8th edition) | | |
| T1N2M0 | 12 (21.1) | 4 (13.8) |
| T2N2M0 | 16 (28.1) | 7 (24.1) |
| T3N1M0 | 2 (3.5) | 1 (3.5) |
| T3N2M0 | 13(22.8) | 5 (19.3) |
| T4N0M0 | 6 (10.5) | 9 (31.0) |
| T4N1M0 | 8 (14.0) | 3 (10.3) |
| Tumor size – Median (range), mm | 43 (29-54) | 52 (39-75) |
| Nodal stage – No. (%) | | |
| N0 | 6 (10.5) | 9 (31.0) |
| N1 | 10 (17.5) | 4 (13.8) |
| N2 | 41 (71.9) | 16 (55.2) |
| N2 multiple station | 21(36.8) | 10 (34.5) |



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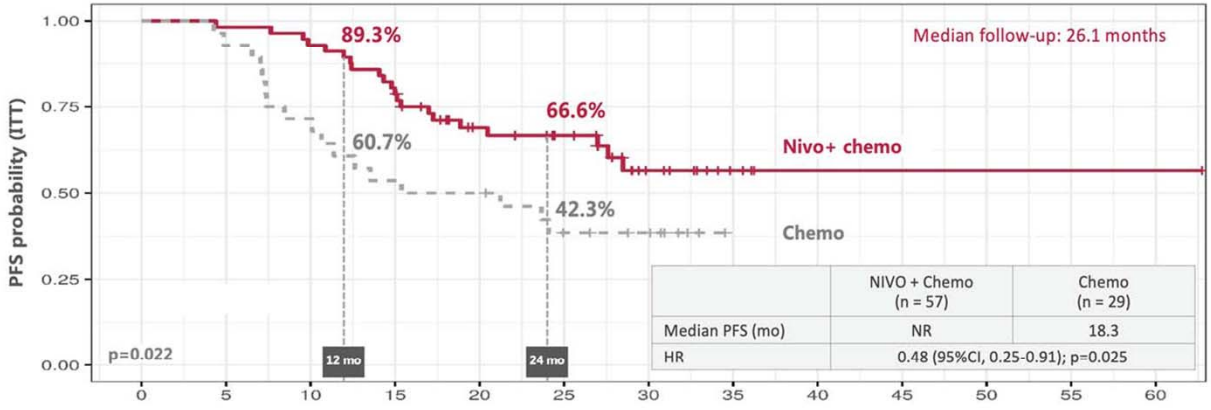
## SECONDARY ENDPOINTS – Progression-free survival




| | 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

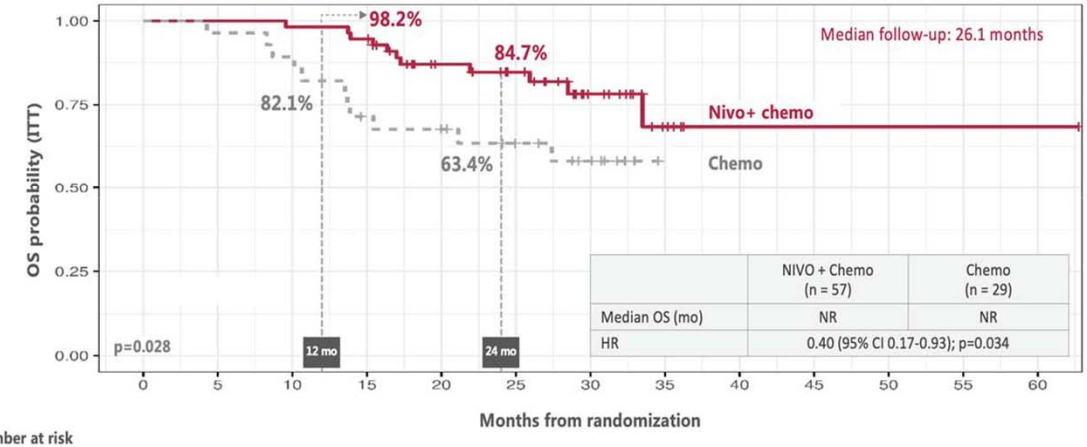
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Nivo + chemo | 56 | 55 | 52 | 44 | 30 | 24 | 11 | 4 | 1 |
| Chemo | 28 | 26 | 20 | 15 | 14 | 9 | 7 | 0 | 0 |

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/

Dr. Mariano Provencio, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

**2-year OS 85% vs 63% (HR 0.40)**

## SECONDARY ENDPOINTS – Overall survival



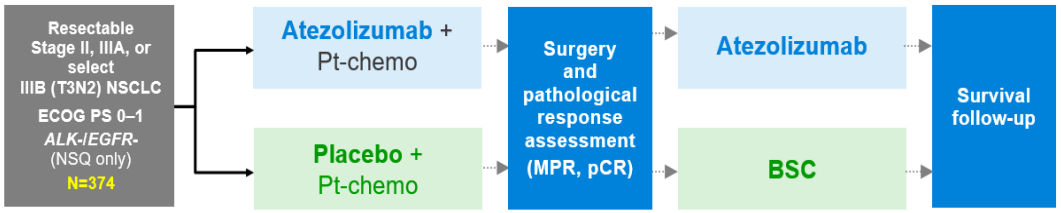

| | NIVO + Chemo (n = 57) | Chemo (n = 29) |
|---|---|---|
| Median OS (mo) | NR | NR |
| HR | 0.40 (95% CI 0.17-0.93); p=0.034 | |

Number at risk

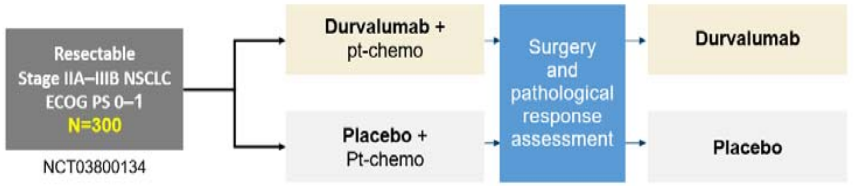
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivo + chemo | 56 | 56 | 55 | 53 | 37 | 31 | 15 | 5 | 1 | 1 | 1 | 1 | 1 |

# Neoadjuvant phase III trials in NSCLC

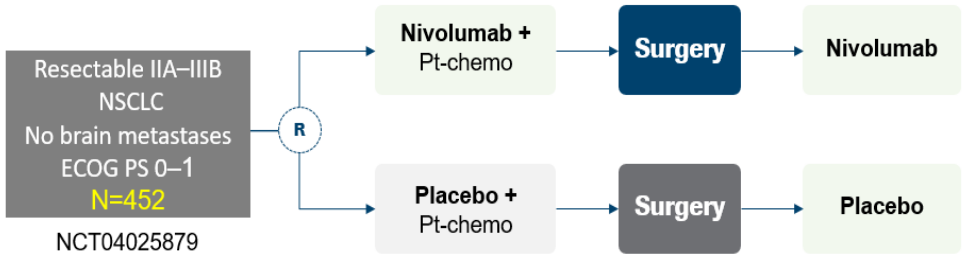
## IMpower030 (primary endpoint: MPR/EFS)



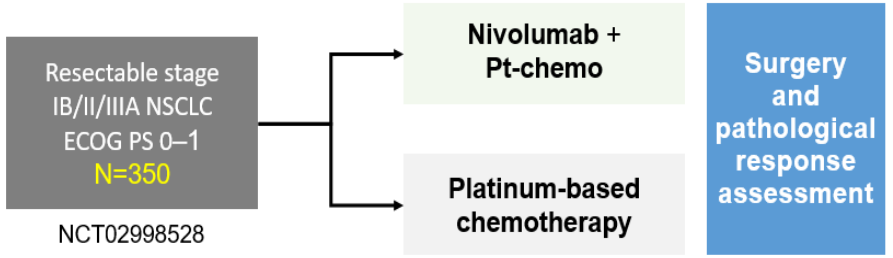

## AEGEAN (primary endpoint: MPR)



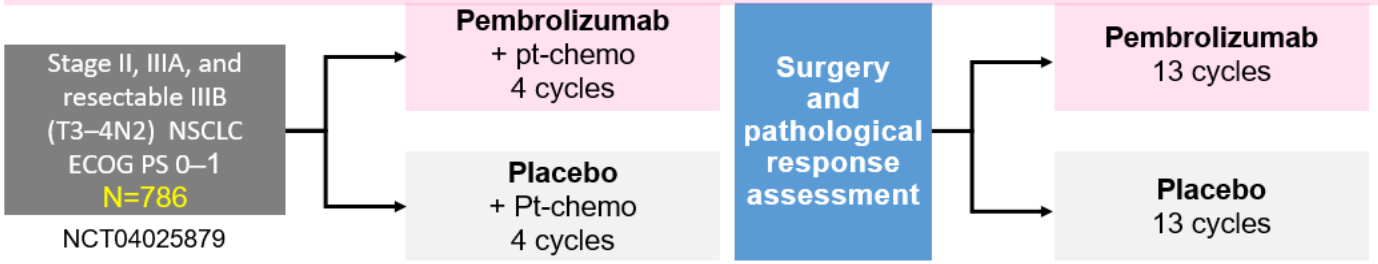

## NCT03456063 CHECKMATE 77T (primary endpoint: EFS)




## CHECKMATE 816 (primary endpoint: EFS/CPR)




## KEYNOTE-671 (primary endpoint: EFS/OS)



# CheckMate 816 study design[a]

**Key Eligibility Criteria**

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

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

**N = 358**

R 1:1

- **NIVO** 360 mg Q3W + **chemo**[d] Q3W (3 cycles)
- **Chemo**[e] Q3W (3 cycles)
- **NIVO** 3 mg/kg Q2W (3 cycles) + **IPI** 1 mg/kg (cycle 1 only)[f]

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± RT[g] → Follow-up

**Primary endpoints**
- pCR by BIPR
- EFS by BICR

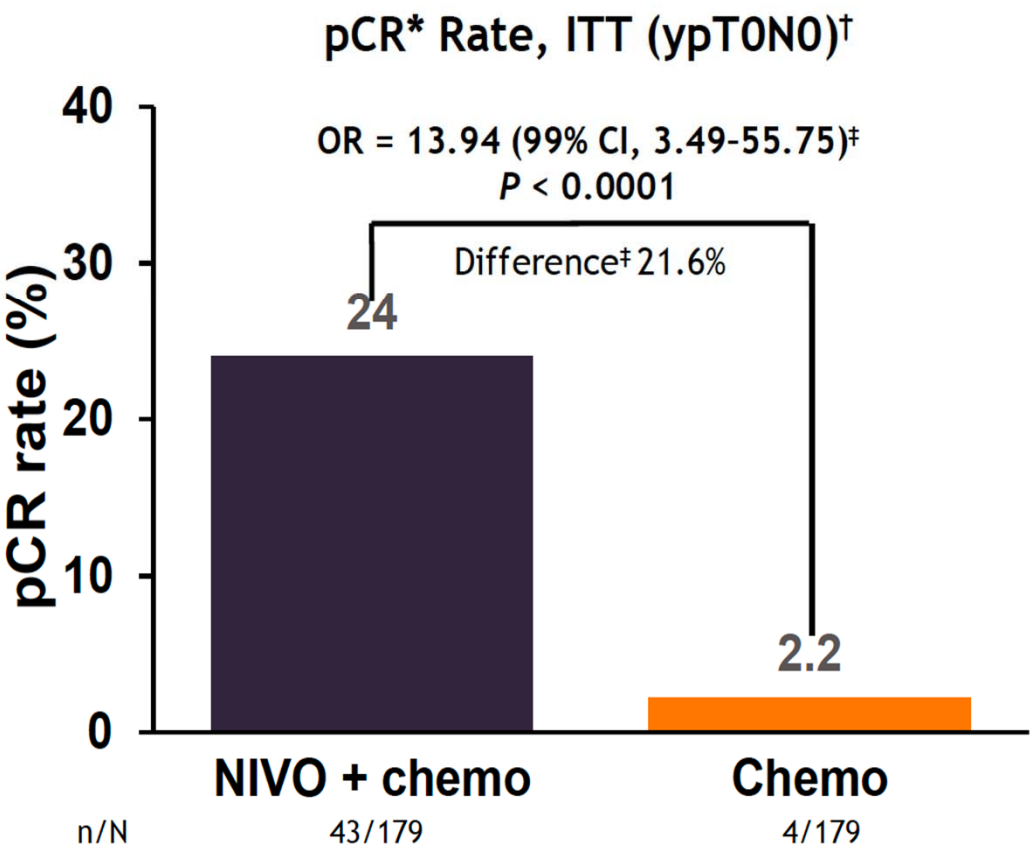
**Secondary endpoints**
- MPR by BIPR
- OS
- Time to death or distant metastases

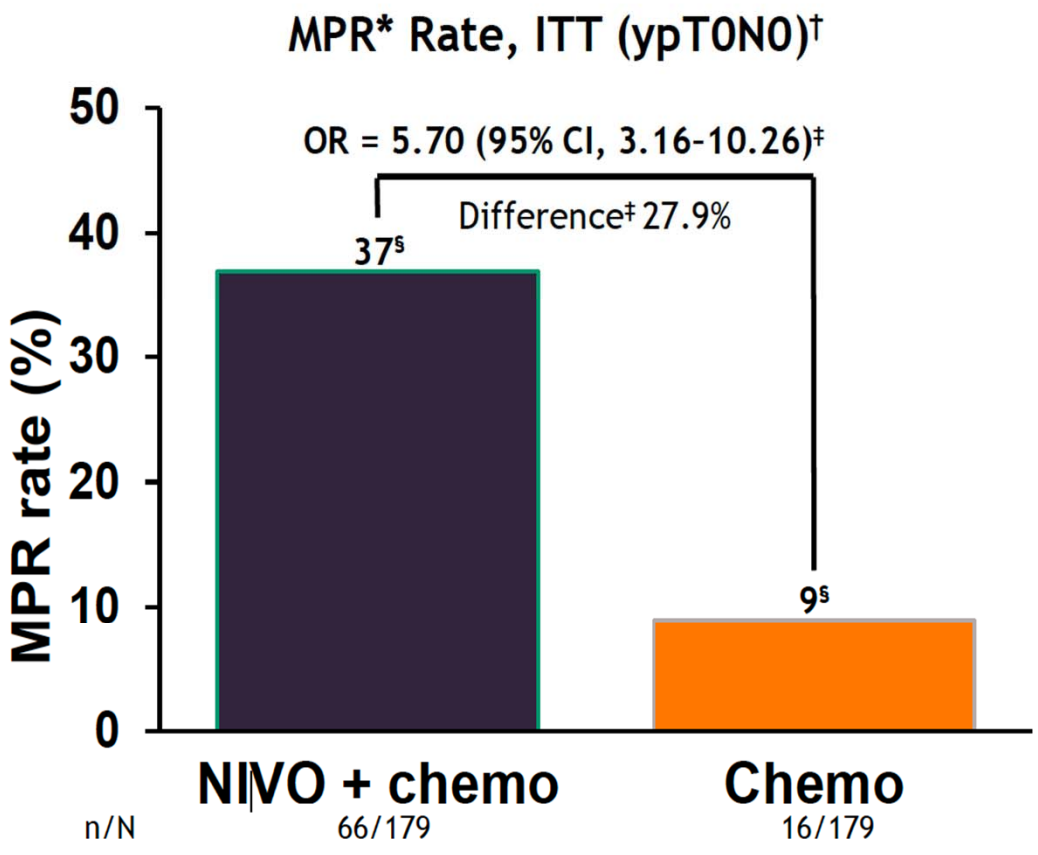
**Exploratory endpoints**
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

**Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.**

[a]NCT02998528; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; [f]Randomized exploratory arm (enrollment closed early); [g]Per healthcare professional choice.

# CheckMate 816: pCR and MPR rates were higher with neoadjuvant nivolumab + chemo vs chemo




- pCR rate in the exploratory nivolumab + ipilimumab arm (ITT) was 20.4% (95% CI: 13.4-29.0)

Forde PM et al. Oral presentation at AACR 2021. Abstract CT003.

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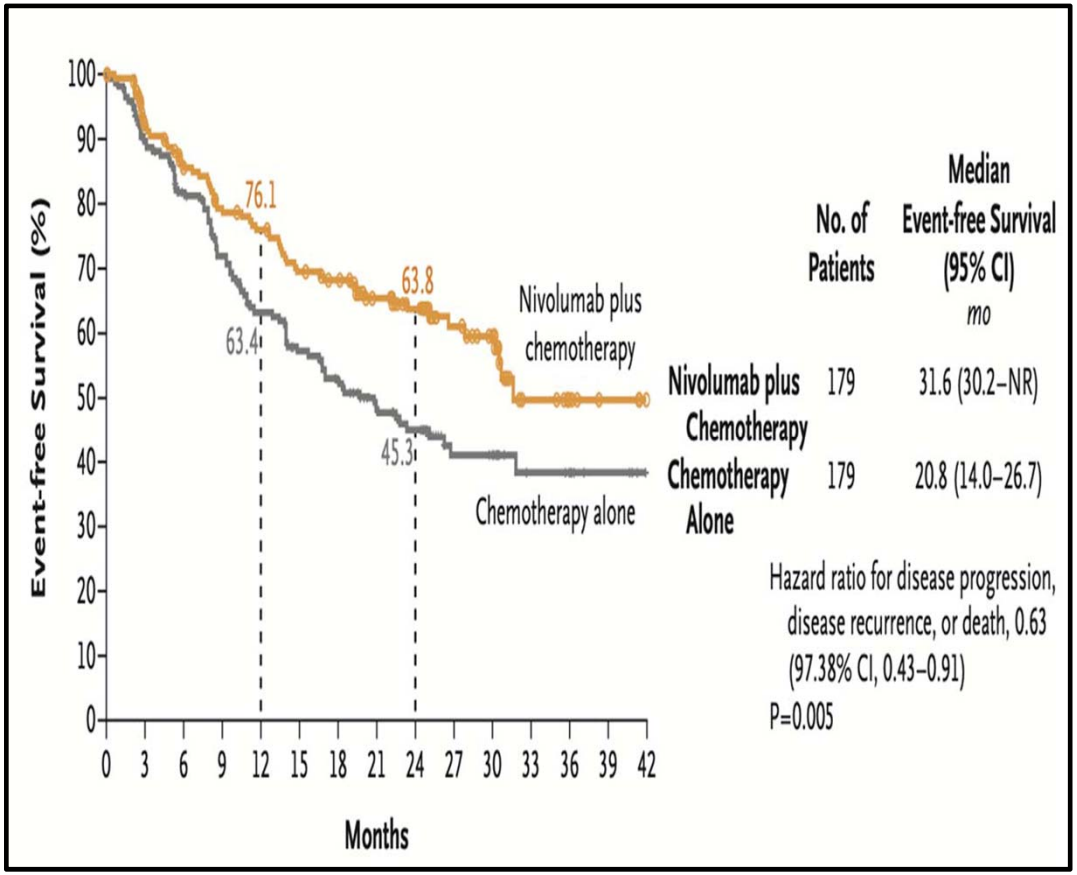
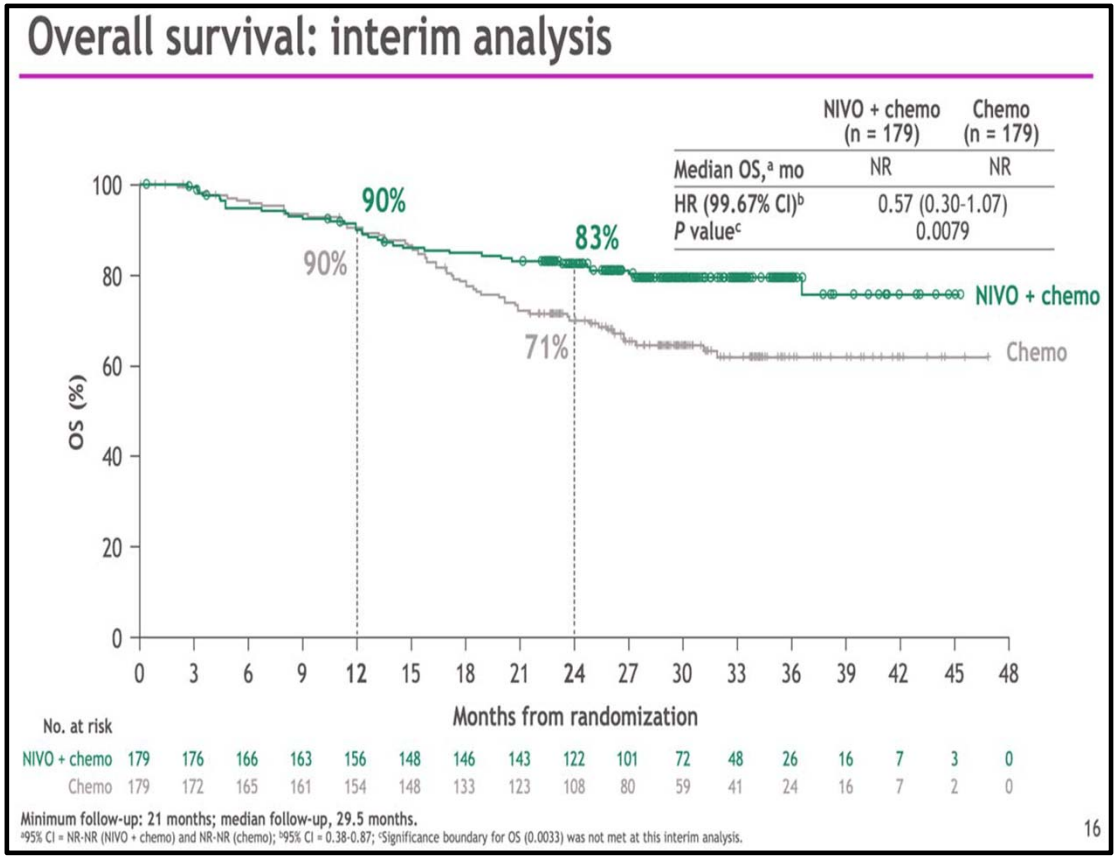
# *Neoadjuvant immunotherapy: CheckMate 816*

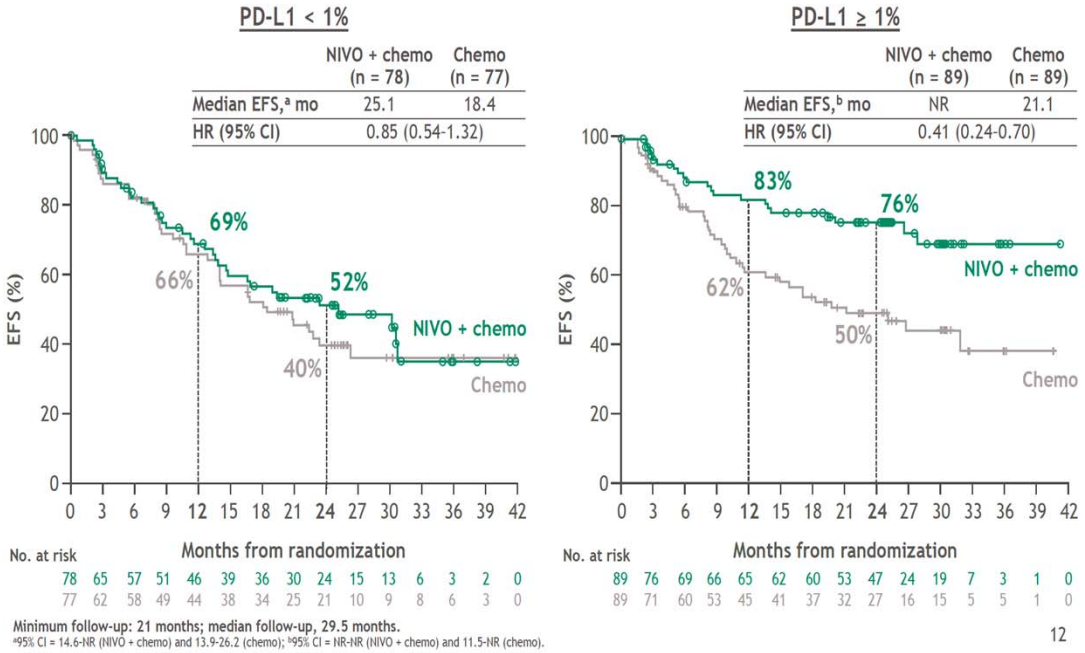
## Primary endpoint: EFS




*Forde NEJM 22*

# EFS by tumor PD-L1 expression







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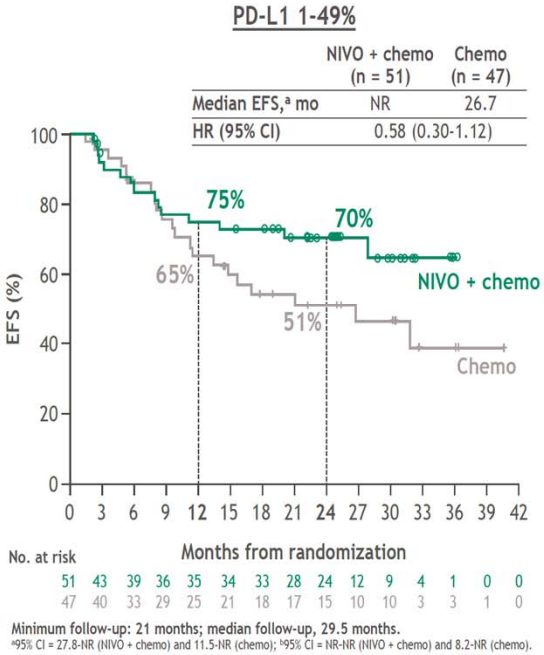
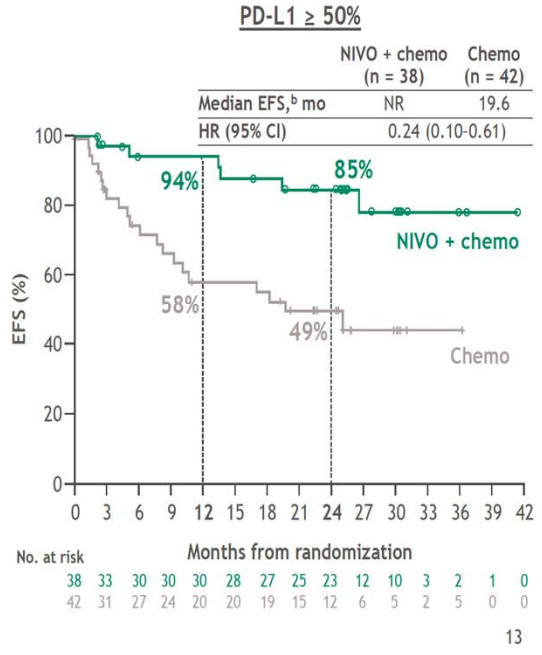
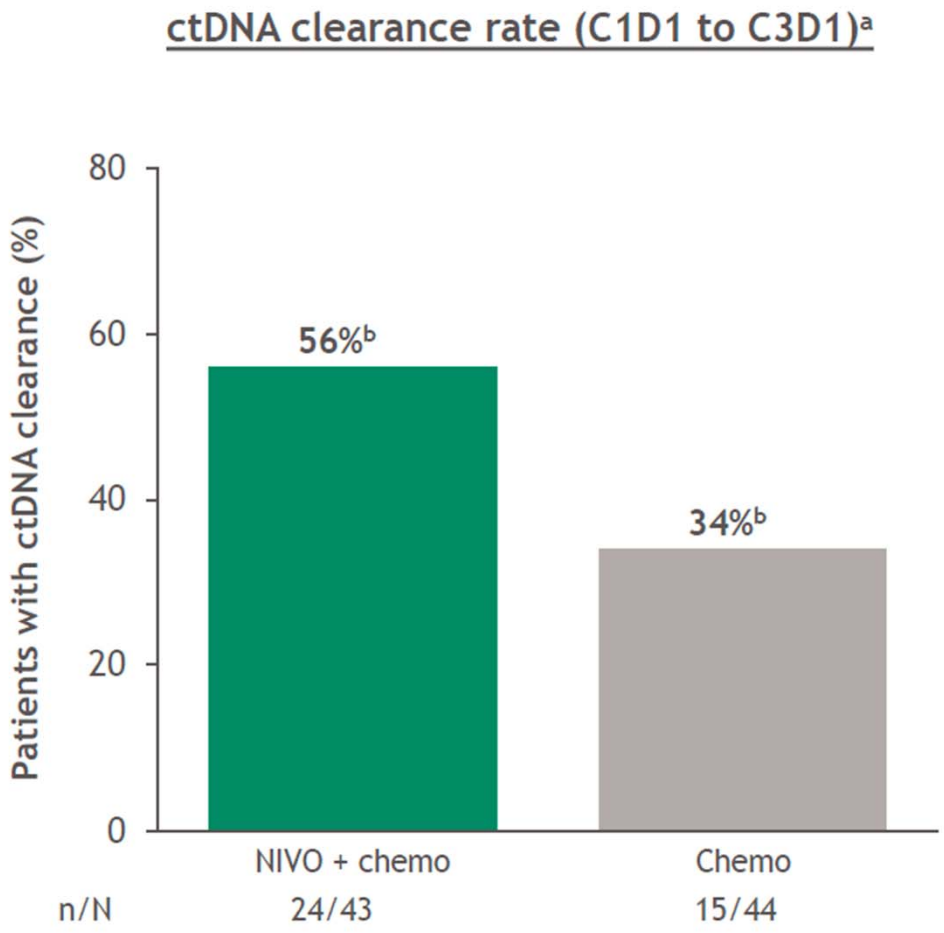


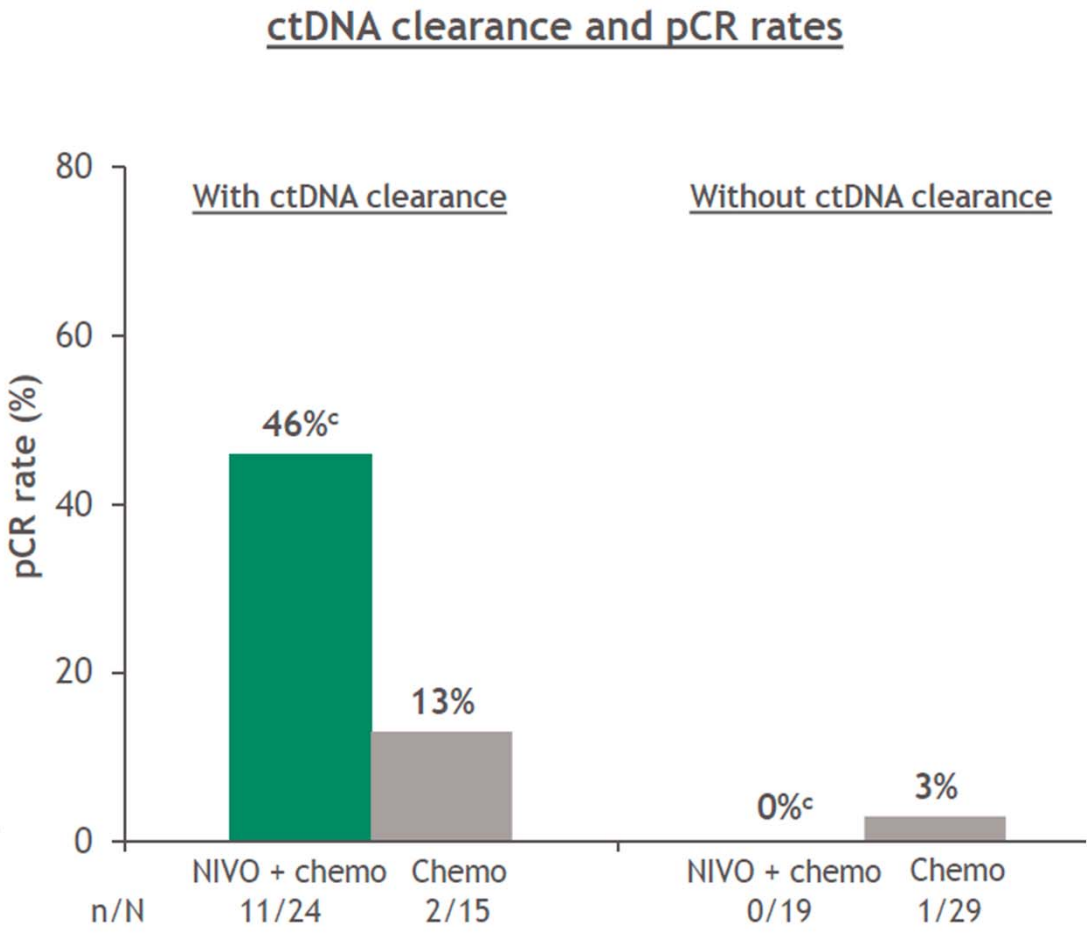




13

Girard et al, AACR 2022

# ctDNA clearance and association with pathological response in CheckMate 816




Forde PM et al. Oral presentation at AACR 2021. Abstract CT003.

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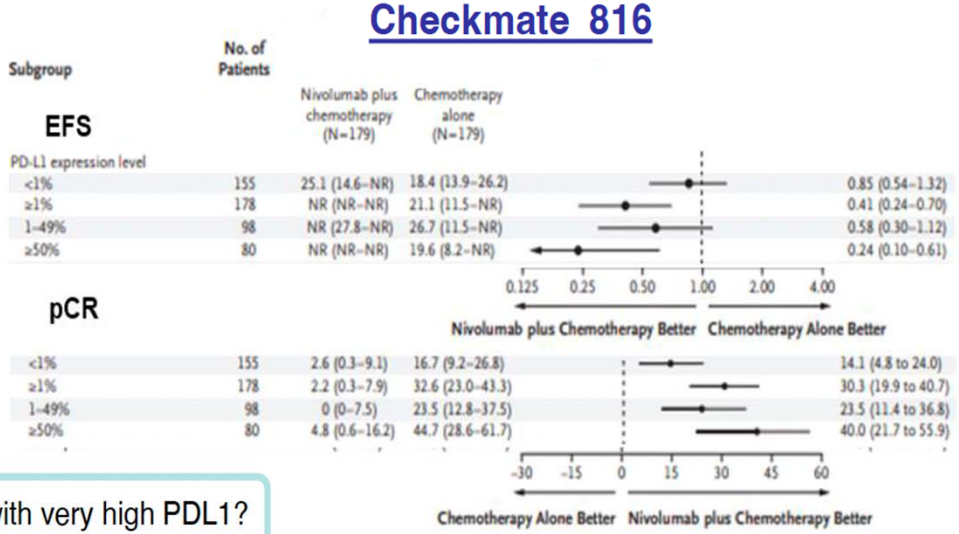
# Which patients benefit from neoadjuvant chemo-IO?

PDL1

## Checkmate 816




Outcome in pts with very high PDL1?

## NADIM II

pCR

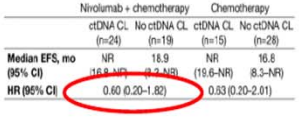

OR for pCR in the PD-L1 ≥1%: **16.0** (95% CI 1.86-137.61; p = 0.007)

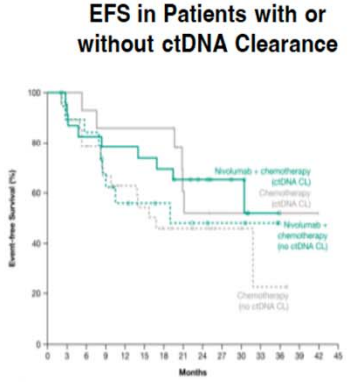
PFS

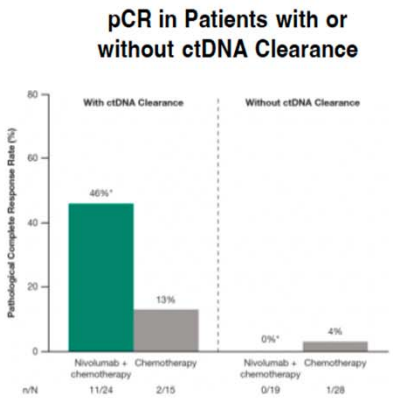

OS

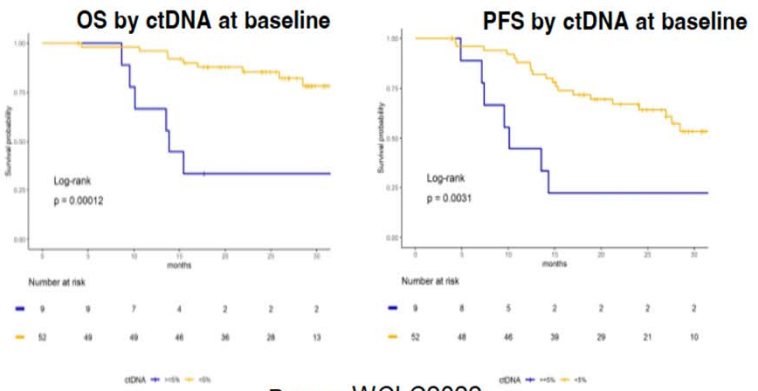

Favors Nivo + Chemo ⟷ Favors Chemo

ctDNA




Forde. NEJM 2022

Romero WCLC2022

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- **Front-line attack of micrometastases**

## Compliance

| | SAKK16/14 (IIIa TNM 7) n=68 | Shu (II-IIIa TNM 7) n=30 | NADIM (IIIa TNM 7) n=46 | CM 816 (Ib-IIIa TNM 7) n=358 | NADIM 2 (IIIa/IIIb TNM8) n=90 |
|---|---|---|---|---|---|
| No surgery | 19% | 3% | 10% | 17%<br>12% Ib/II; 17% IIIa | 7% |
| Progressive disease | 10% | 7% | 0% | 6.9%<br>5% Ib/II; 8% IIIa | 0% |
| Incomplete resection R1/R2 | 7% | 13% | 0% | 17% | 7.5% |

Rothschild JCO 2021 , Shu Lancet Oncol 2020, Provencio Lancet Oncol 2020, Forde NEJM 2022, Provencio ASCO&WCLC 2022

**NADIM**: 100% completed Neoadjuvant Ch-IO treatment

Chouaid C Lung Cancer 2018; Kelh K JAMA Oncol 2022; Felip R Lancet 2021; Forde P NEJM; Provencio M Lancet Onc 2020

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# Combinationts IO-IO

## Neoadjuvant Nivolumab plus Ipilimumab in Stage II-IIIA NSCLC (JHU & MSKCC)

**START**
Screening; baseline PET/CT; pre-treatment research core biopsy; Research Bronch

**Key Eligibility**
- Stage II-IIIA NSCLC
- Resectable disease
- ECOG 0-1

***Nivolumab monotherapy arm (n=15)***
Nivolumab 240mg IV on D-42, -28, -14 prior to planned surgery (D0) → Repeat PET/CT, Research Bronch, surgery on D0 → Adjuvant combination chemotherapy*

***Nivolumab + Ipilimumab combination arm (n=15)***
Nivolumab 3mg/kg IV + Ipilimumab 1 mg/kg on D-42, followed by Nivolumab 3mg/kg IV on D-28 & D-14 prior to planned surgery (D0) → Repeat PET/CT, Research bronch, surgery on D0 → Adjuvant combination chemotherapy*

*investigator choice chemotherapy +/- radiation therapy at discretion of treatment team

**Primary Endpoints**
- Feasibility: delay in surgery of <24d from pre-planned surgery date
- Safety: adverse events (AEs) up to 100 days post-treatment (or 30d post-surgery)

UNIVERSITY OF TEXAS MD Anderson

- Terminated early after 9/15 pts enrolled: 67% (6/9) TRAEs and 33% (3/9) grade ≥3 TRAEs.
- 3 of 9 patients (33%) had PD and no definitive surgery; 6 pts underwent resection (67%): 2 pCR (33%)
- 6 pts (67%) had tumor *STK11* mutations with or without *KRAS* or *KEAP1* co-mutations

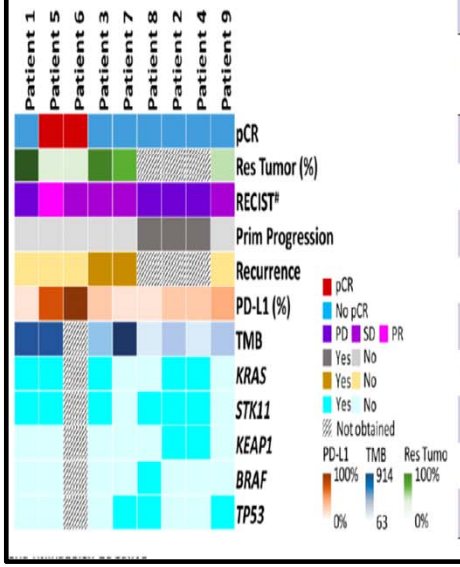
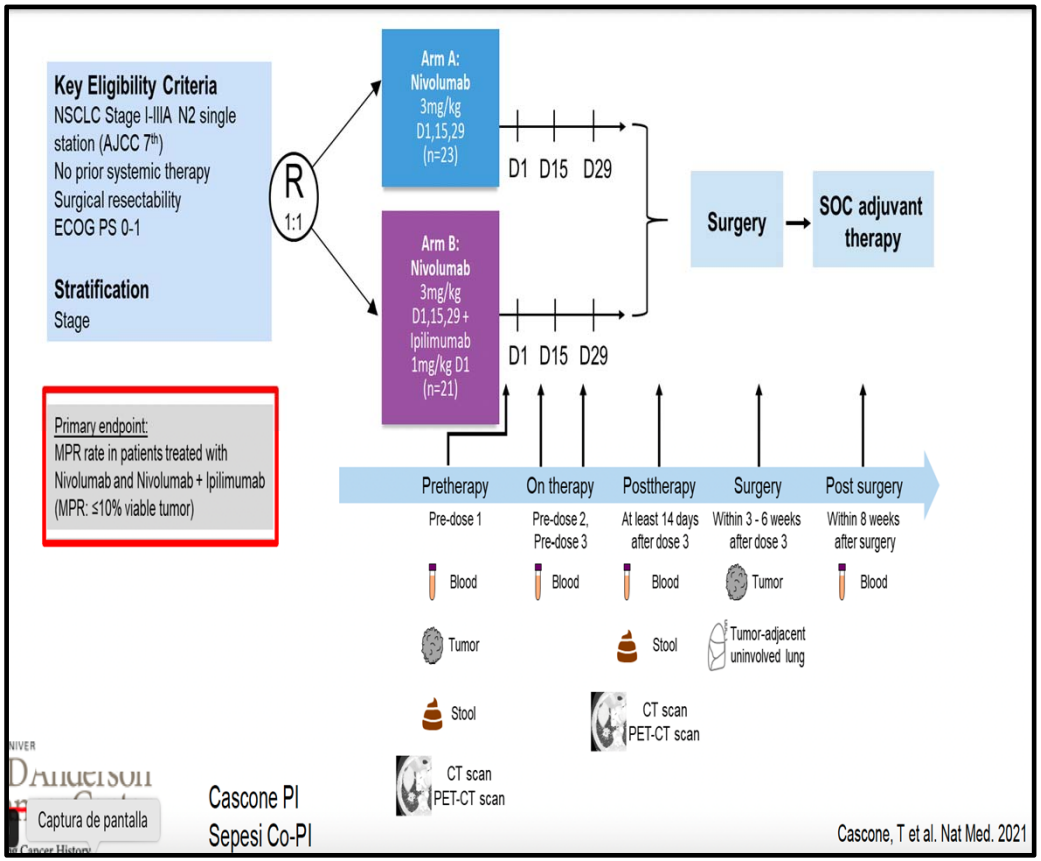



**Table 3** Radiographic, pathologic and molecular response characteristics

| Patient number | Radiographic response* | Residual tumor (%) | Pre-treatment PD-L1 (%) | Normalized tumor mutation burden | Driver genes with sequence alterations |
|---|---|---|---|---|---|
| 1 | PD | 100 | 0 | 344 | *KRAS, STK11* |
| 2 | PD† | N/A | 1 | 109 | *KRAS, KEAP1, STK11* |
| 3 | SD | 90 | 10 | 147 | *KRAS, STK11, TP53* |
| 4 | PD | N/A | 1 | 63 | *KRAS, KEAP1, STK11* |
| 5 | PR | 0 (pCR) | 75 | 554 | *KRAS, STK11* |
| 6 | SD | 0 (pCR) | 95 | Undeterminable‡ | Undeterminable‡ |
| 7 | SD | 70 | 0 | 914 | *TP53* |
| 8 | PD | N/A | 0 | 78 | *BRAF, STK11, TP53* |
| 9 | SD | 20 | 30 | 99 | *TP53* |

Reuss JE et al, JITC 2020

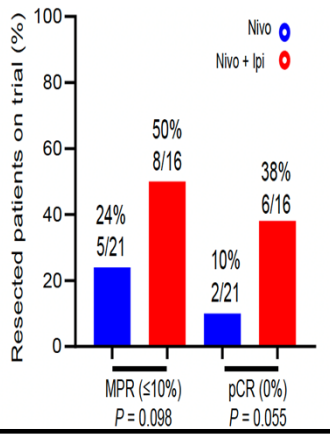
# NEOSTAR: phase II study of induction checkpoint blockade for untreated stage I-IIIA NSCLC amenable for surgical resection

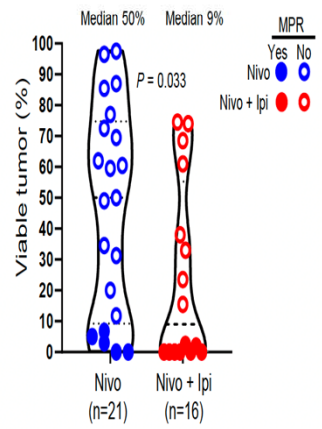



## Combined PD-1/CTLA-4 blockade meets the trial prespecified MPR efficacy boundary to be considered promising

| MPR RATE (%) | | |
|---|---|---|
| Percentage viable tumor | Nivo n=23 | Nivo + Ipi n=21 |
| 0-10 (MPR) | 22 (5/23) | 38 (8/21) |
| 0 (pCR) | 9 (2/23) | 29 (6/21) |

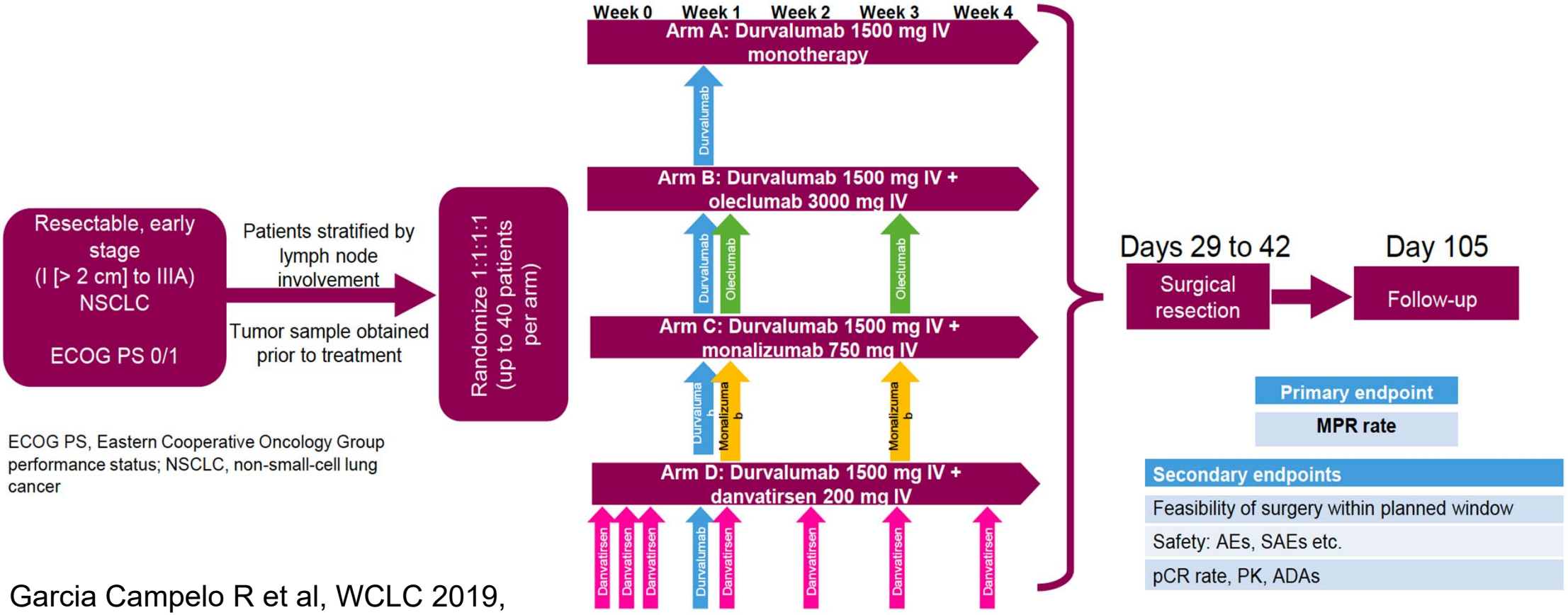
Prespecified trial efficacy boundary: ≥ 6 MPR




Cascone, T et al. Nat Med. 2021

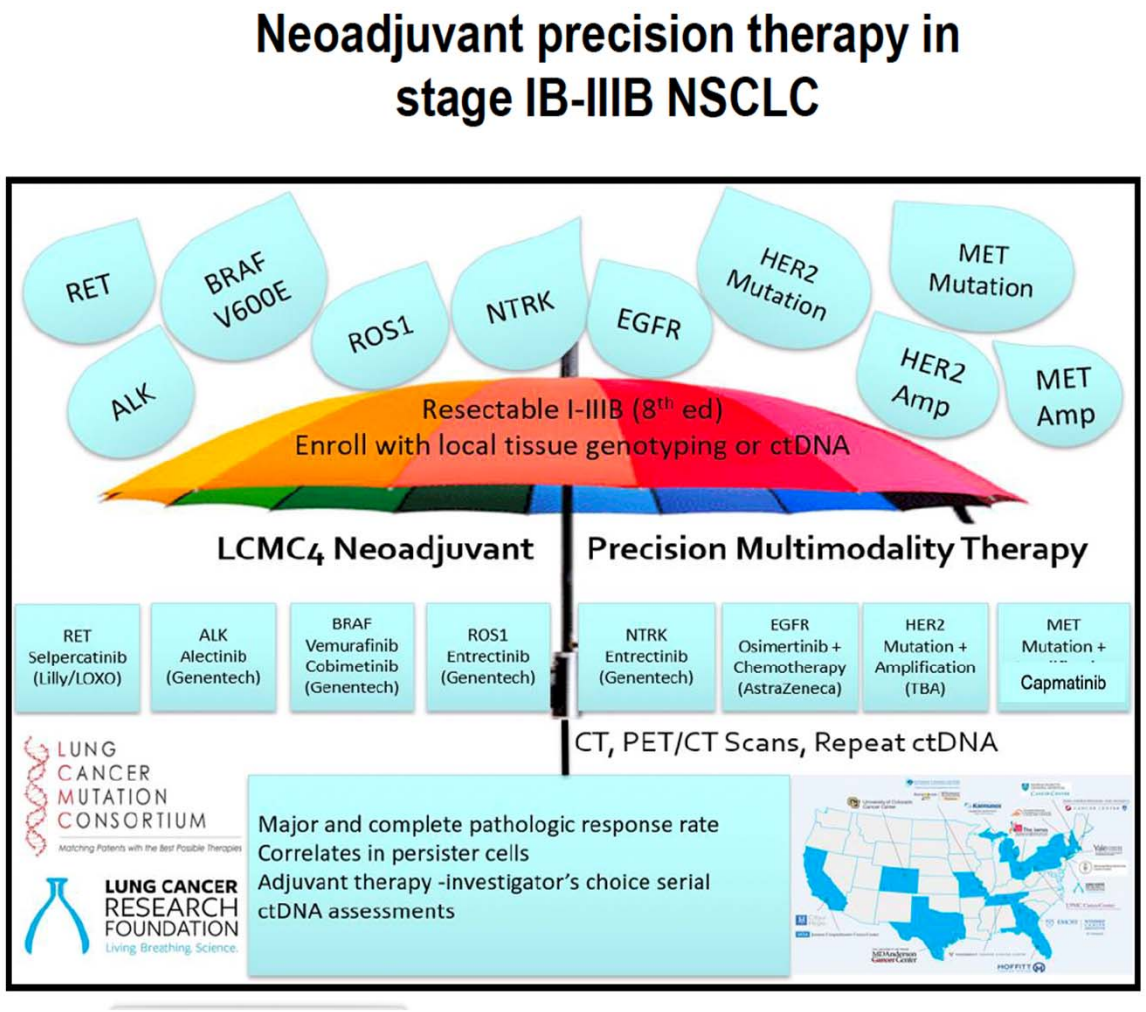
# NeoCOAST: P2R platform trial of neoadjuvant durva alone or combined with novel IO agents in NSCLC




ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small-cell lung cancer

Garcia Campelo R et al, WCLC 2019,

# Adjuvant and Neoadjuvant use of genotype directed therapy




## Adjuvant

**ALK**

Crizotinib vs. observation (NCT02194738)

Alectinib vs. chemotherapy (NCT03456076)

**RET**

Selpercatinib vs. placebo ( NCT04819100)

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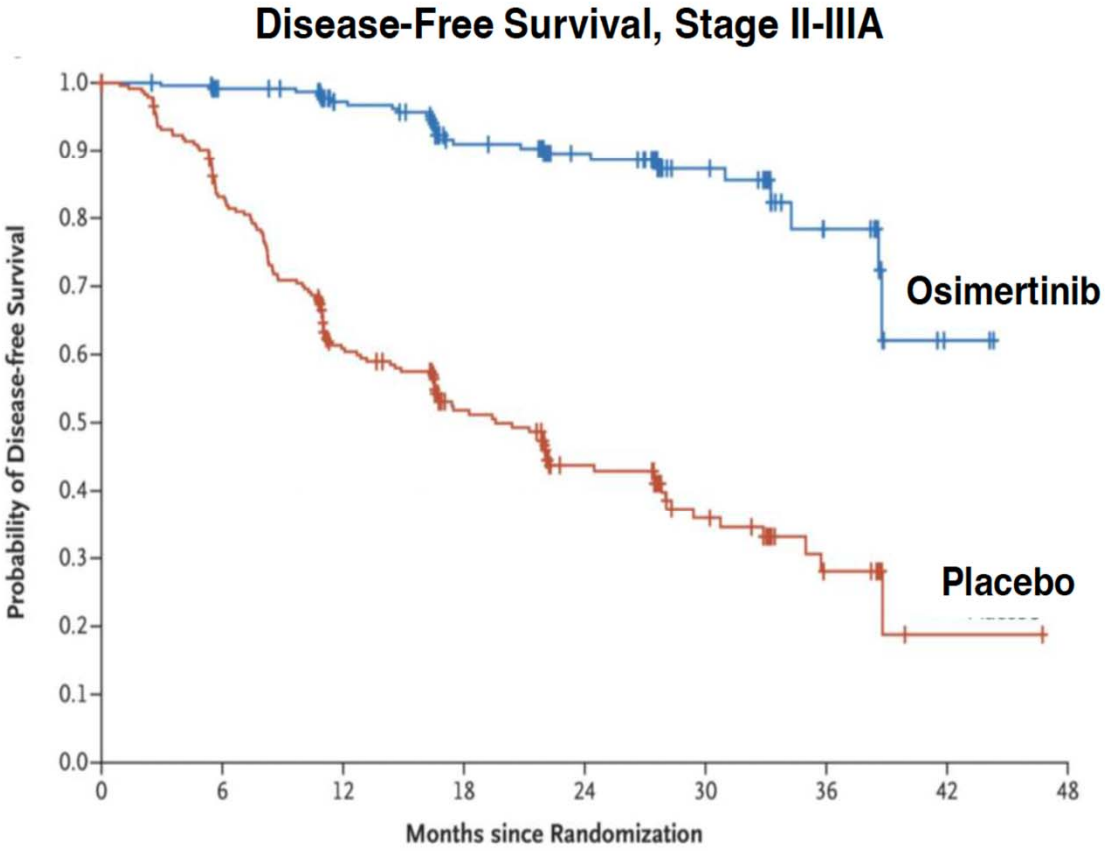
# Adjuvant Osimertinib Therapy Improves Disease-Free Survival
# ADAURA




- Randomized, 3 years adjuvant osimertinib versus placebo in resected stage IB-IIIA NSCLC
- Primary Endpoint DFS in stage II- IIIA
- DFS: NR vs 19.6 months (HR 0.17, 0.11-0.26)
- Impact on overall survival not yet known

*Wu et al. NEJM. 2020;383:1711-23.*

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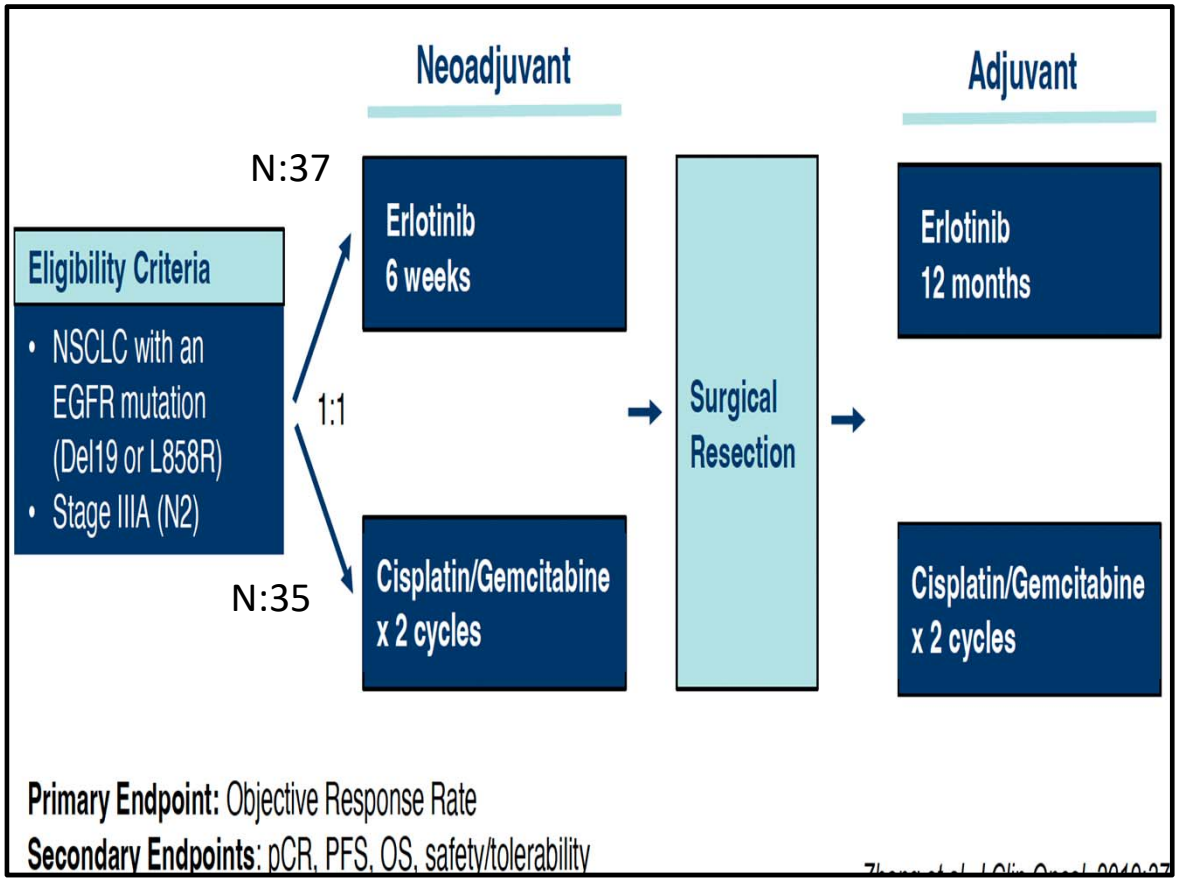
# CTONG 1103 (EMERGING), Perioperative Erlotinib vs Cisplatin/Gemcitabine




**Trend towards better surgical outcomes**

| | Erlotinib | Gem/Cis | P-value |
|---|---|---|---|
| Resection Rate | 84% | 69% | 0.129 |
| R0 Rate | 73% | 63% | |
| LN Downstaging | 11% | 3% | 0.185 |
| N2 → N0 | 8% | 3% | |

*Zhong et al. J Clin Oncol. 2019;37:2235-45*

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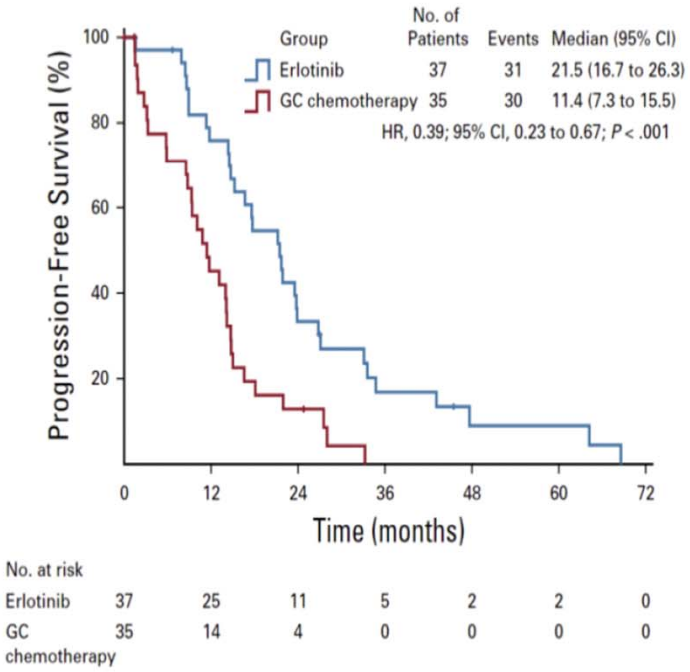
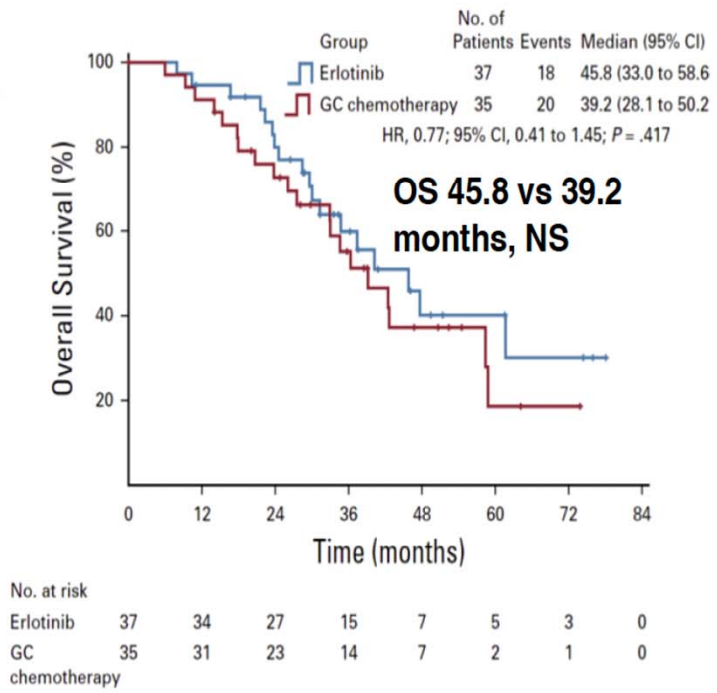
# CTONG 1103 (EMERGING), Perioperative Erlotinib vs Cisplatin/Gemcitabine

## Improved PFS, OS not significantly improved

### Progression-Free Survival




### Overall Survival




| | Erlotinib (n=37) | Cis/Gem (n=35) | |
|---|---|---|---|
| **ORR** | 54.1% | 34.3% | OR 2.26 (0.87-5.84) |
| **pCR** | 0% | 0% | |
| **MPR** | 9.7% | 0% | |
| **PFS** | 21.5 months | 11.4 months | HR 0.39 (0.23-0.67) |

ORR, Objective Response Rate; pCR, Pathologic Complete Response Rate; MPR, Major Pathologic Response Rate; PFS, Progression Free Survival; Cis/Gem, Cisplatin/Gemcitabine

*Zhong et al. J Clin Oncol. 2019;37:2235-45*

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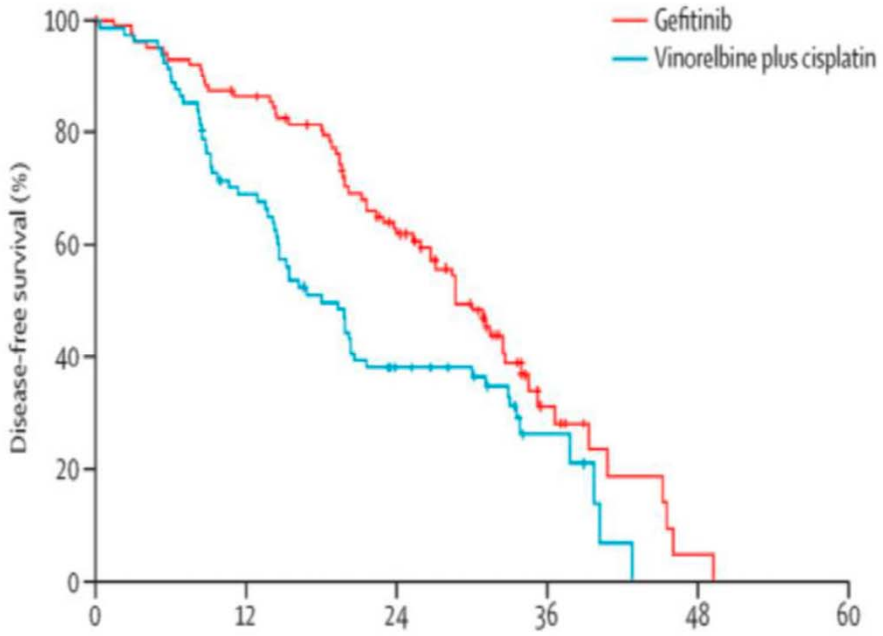
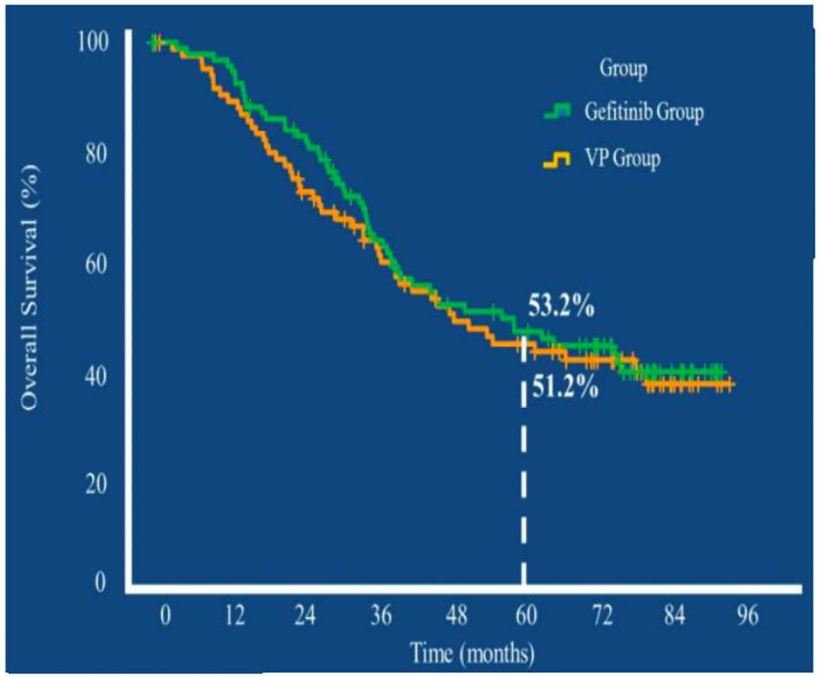
# Adjuvant EGFR TKI 1/2

## Adjuvant 1st/2nd Generation TKI Therapy Improve DFS but not OS




**Disease Free Survival 28.8 vs 18.00 months**
HR 0.60, 95% CI 0.42-0.87




**Overall Survival 75.5 vs 62.8 months**
HR 0.92, 95% CI 0.62-1.36

*Zhong et al. Lancet. 2018; 19(1): 139-48; Wu et al. ASCO 2020. Abstract 9005.*

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# Neoadjuvant Osimertinib

## Neoadjuvant osimertinib

NEOS – Phase II Single-Arm, 6 weeks neoadjuvant osimertinib

**Eligibility Criteria**
- NSCLC with an EGFR mutation (del19 or L858R)
- Stage II-IIIB

→ **Neoadjuvant**
Osimertinib
6 weeks
(n = 40)

→ **Surgical Resection**

**Primary Endpoint:**
Objective Response Rate

**Secondary Endpoints:**
R0 rate, MPR rate, pCR rate
N2 downstaging rate, safety

**Objective Response Rate** 71.1%
**MPR Rate** 10.7%
**pCR Rate:** 3.6%

*Lyuet al. Annals Oncol. 2022;23(2):571-2.*

## Neoadjuvant osimertinib

Phase II Single Arm, 1-2 months Neoadjuvant Osimertinib

**Eligibility Criteria**
- NSCLC with an EGFR mutation (del19 or L858R)
- Stage I-IIIA Resectable

→ **Neoadjuvant**
Osimertinib
8 weeks
(n=13, interim)

→ **Surgical Resection**

**Primary Endpoint:**
Major Pathologic Response Rate

**Secondary Endpoints:**
Pathologic response rate, pCR rate, LN downstaging, PFS, OS, safety, resection rate, surgical complication rate

**Objective Response Rate** 46%
**MPR Rate** 15%
**pCR Rate:** 0%

*Blakely et al. IASLC WCLC 2021. P26.02*

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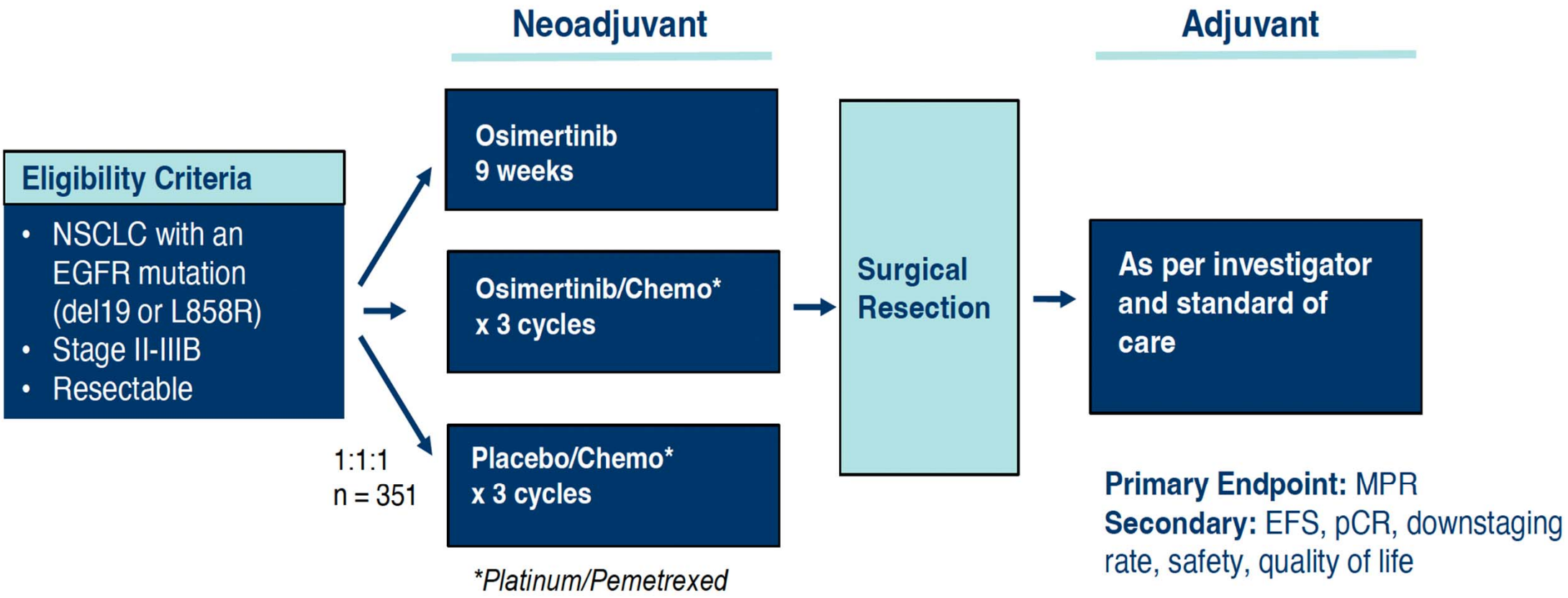
# NeoADAURA: A randomized study of neoadjuvant osimertinib/chemotherapy




**Primary Endpoint:** MPR
**Secondary:** EFS, pCR, downstaging rate, safety, quality of life

*Tsuboi et al. Future Oncol. 2021.17(31):4045-55.*

## But….

- TKIs inhibit cell proliferation, hindering tumor rather than eradicate the disease.
- Does TKI adjuvant treatment have the same long-term survival impact than at disease recurrence?
- Tumors are heterogeneous and under pharmacological pressure by TKI, clones with different biological behaviors emerge.

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# Take Home Messages

- Neoadjuvant IO + chemo SOC in resectable NSCLC without impairing surgery feasibility
- Patient and tumor specific biomarkers necessary to predict benefit: improve upon PD-L1
- ADJ CT followed by immunotherapy or ADJ CT+immunotherapy?
- Neo adjuvant CT+immunotherapy follow ADJ IO?
- ctDNA/MRD technology may help to individualize therapy

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# THANK YOU!!

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