19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
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Nuevo estándar de tratamiento neoadyuvante en cáncer de pulmón no microcítico

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Declaration of Interests

Personal financial interests

Consultancy/honoraria from AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, BMS, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, J&J, Lilly, MSD, Novartis, Pfizer, Roche, Regeneron, Sanofi and Takeda. Direct funding from Medscape and Touch Medical.

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Non-financial interests

ESMO Faculty for lung and other thoracic tumors.

IASLC Academy and Educational Committee member.

Former President of Spanish Medical Oncology Society (SEOM) and Spanish Federation of Medical Societies (FACME).

Member of the Spanish National Health Advisory Board.

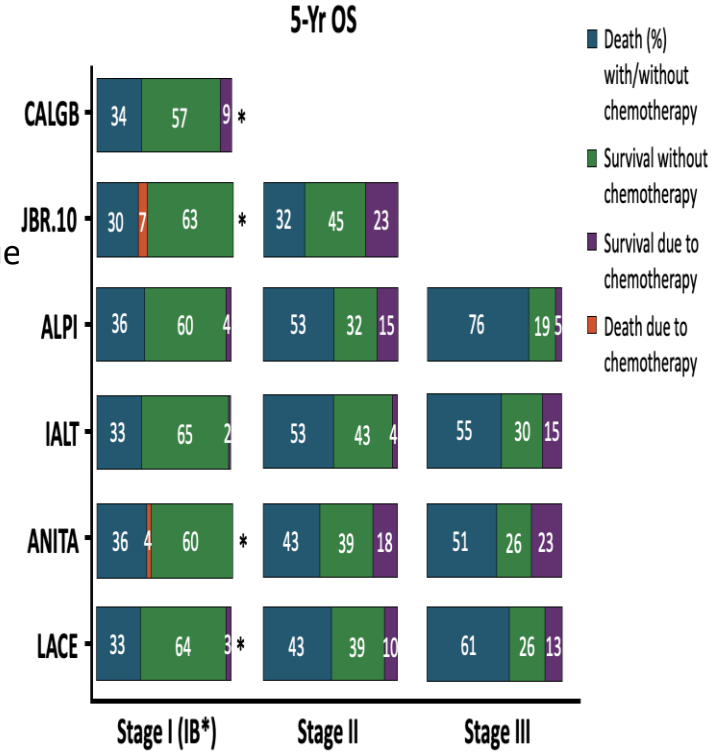
President of the National Technical Committee and Executive Board member of the the Spanish Patients Against Cancer Association (AECC) and Member of the Scientific Committee of their Research Foundation.

Member of the Scientific Committee of the Spanish Lung Cancer Patient's Advocacy Association (AECAP)

Introduction

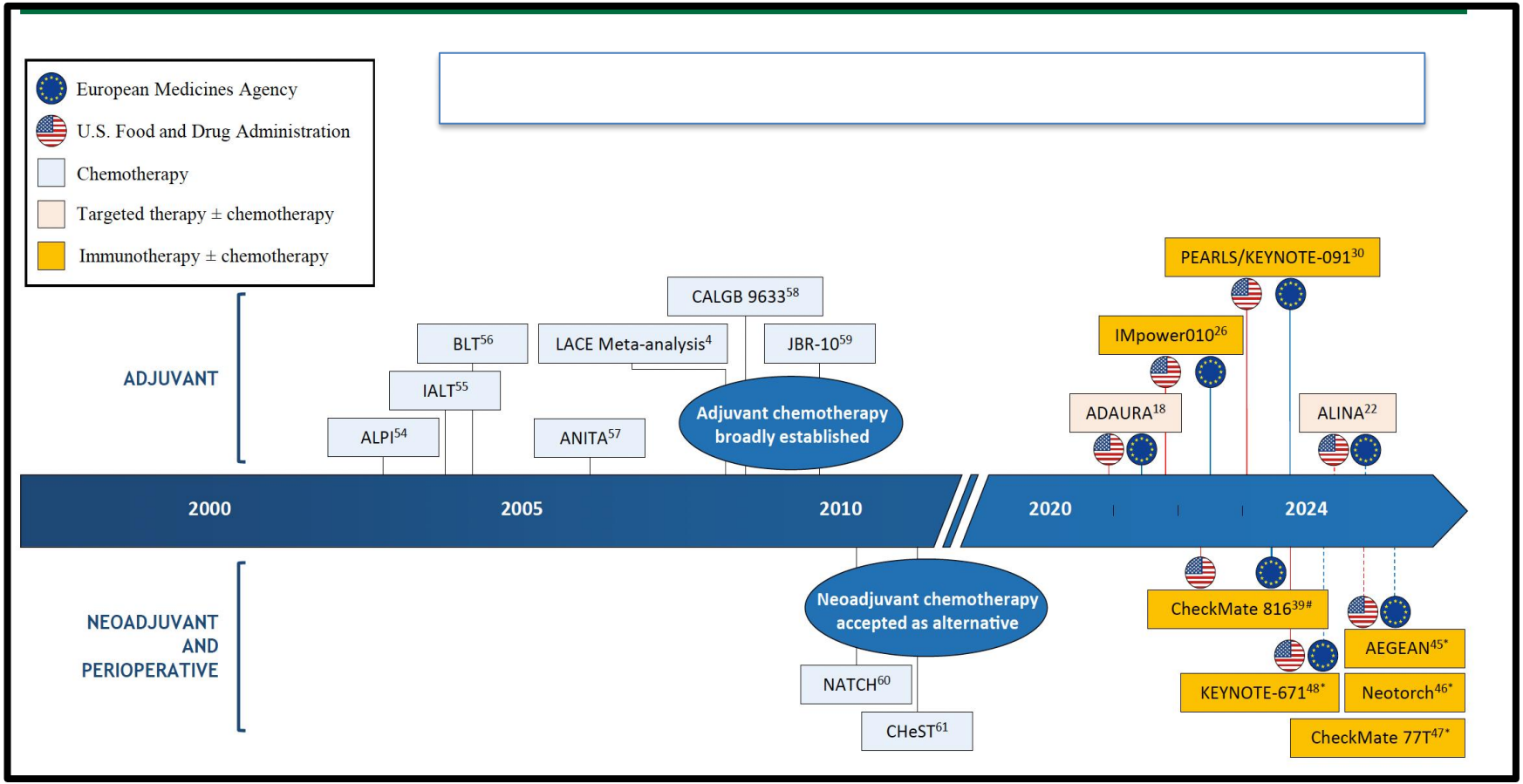
- For decades, early-stage NSCLC treatment remained largely unchanged.
- ~25% with stage IB, 35% - 50% with stage II, and a higher percentage with pathologic stage III NSCLC face disease recurrence and death due to their cancer despite curative-intent surgery.
- Platinum-based **chemotherapy** in stage II-IIIA NSCLC and selected stage IB cases **improved survival by approximately 5%** in both neoadjuvant and adjuvant.
- The **modest long-term survival is largely due to distant tumor relapse**, which is reported to

occur up to three times more frequently than local recurrences.



Kris M. JCO. 2017;35:2960.

Timeline of key studies influencing the treatment of resectable NSCLC



Houda et al. The Lancet Regional Health – Europe 2024

Considerations for Timing of Treatment for Early-Stage NSCLC

How Is the Decision Made?

Neoadjuvant approaches provide rich research opportunities:

- **Rapid assessment of response to novel therapies within tumors and surrounding tissue, LNs**
- Platform for biomarker development

Neoadjuvant	Adjuvant
Better treatment compliance	
Can add further therapy postoperatively	More commonly used in routine practice (>95%)
In vivo test of drug sensitivity	No risk of surgical delay
Better antigen priming?	No increased perioperative risks due to preop therapy
Potential downstaging	Complete pathologic staging

→ **Multidisciplinary and Patient Discussion**

CheckMate 159: Pivotal phase II trial

- Pilot experience
  - N 21
  - 2 cycles Nivolumab neoadjuvant for resectable patients stage IB - IIIA
  - Results:
    - 45% MPR, 15% pCR
    - At 5-year follow-up:
      - 89% of patients with MPR were alive and disease-free
      - 60% recurrence-free survival
      - 89% OS

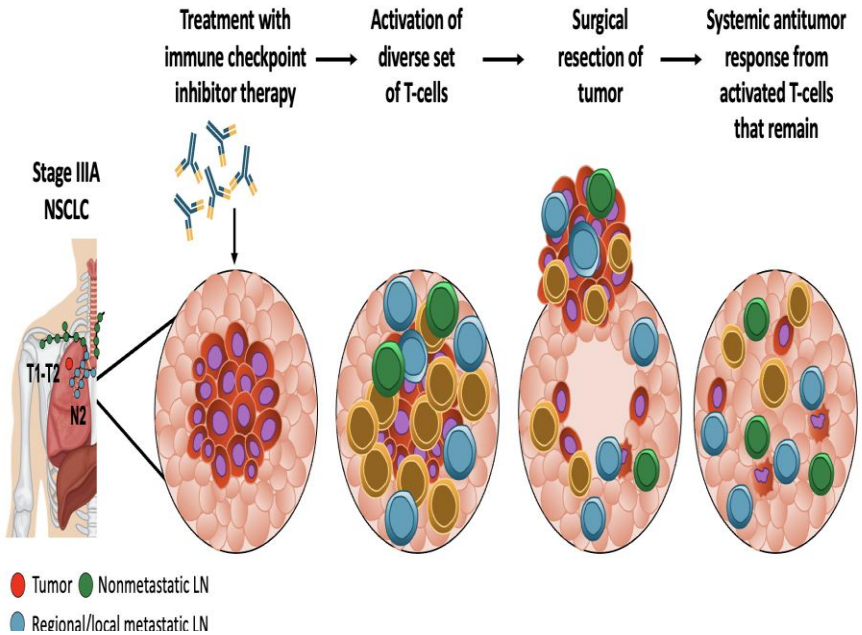
Forde, P.M. N. Engl. J. Med. 2018, Rosner, S Clin. Cancer Res. 2023

Immunotherapy in Resectable Cancer

Immunotherapy in early stages of cancer is biologically sound approach because[3-5]:

- Patients may have a more intact immune system
- Draining lymph nodes are in situ in neoadjuvant setting
- Potential for long-lasting immune priming against micrometastases
- Ideal opportunity for translational science in neoadjuvant setting

Chemotherapy is a rational partner for IO as it disrupts tumor architecture, resulting in antigen shedding and inducing rapid disease control

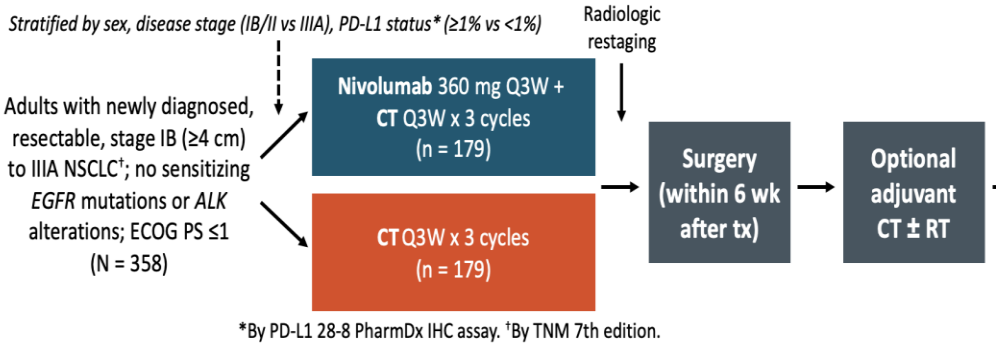


van Pul. Front Immunol. 2021;12:643291. Chaft. Nat Rev Clin Oncol. 2021;18:547; Versluis. Nat Med. 2020;26:475..

Perioperative approach

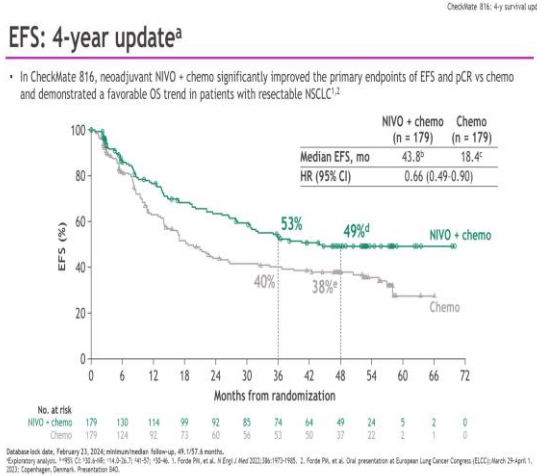
Neoadjuvant immunotherapy (with CT) followed by surgery and adjuvant immunotherapy (with or without CT)						
NADIM II NCT03838159	II	86	Stage IIIA-IIIB	CT + nivolumab *vs* neoadjuvant CT alone	pCR	Nivolumab: pCR 37% (21/57) CT: pCR 7% (2/29)
neoSCORE NCT04459611	II	60	Stage IB-IIIA	Neoadjuvant CT + sintilimab (2 cycles) then adjuvant CT (2 cycles) + sintilimab *vs* neoadjuvant CT + sintilimab (3 cycles) then adjuvant CT (1 cycle) + sintilimab	MPR	2 cycles: MPR 26.9% (7/26) 3 cycles: MPR 41.4% (12/29)
AEGEAN NCT03800134	III	740	Stage II-IIIB –IIIA/B: 71%	CT + durvalumab *vs* CT + placebo	EFS, pCR	HR 0.68 (95% CI 0.53–0.88) Durvalumab: pCR 17.2% (63/366), MPR 33.3% Placebo: pCR 4.3% (16/374), MPR 12.3%
CheckMate 77T NCT04025879	III	461	Stage II-IIIB –IIIA/B: 64%	CT + nivolumab *vs* CT + placebo	EFS	HR 0.58 (97.36% CI 0.42–0.81) Nivolumab: pCR 25.3%, MPR 35.4% Placebo: pCR 4.7%, MPR 12.1%
KEYNOTE-671 NCT03425643	III	797	Stage II-IIIB –IIIA/B: 70%	CT + pembrolizumab *vs* CT + placebo	EFS, OS	OS: HR 0.72 (95% CI 0.56–0.93) EFS: HR 0.59 (95% CI 0.48–0.72) Pembrolizumab: pCR 18.1%, MPR 30.2% Placebo: pCR 4.0%, MPR 11.0%
Neotorch NCT04158440	III	404[a]	Stage II-III	Neoadjuvant CT + toripalimab (3 cycles) then adjuvant CT (1 cycle) + toripalimab *vs* neoadjuvant CT + placebo (3 cycles) then adjuvant CT (1 cycle) + placebo	ÈFS, MPR	HR 0.40 (95% CI 0.28–0.57) Toripalimab: MPR 48.5% (98/202), pCR 24.8% Placebo: MPR 8.4% (17/202), pCR 1.0%
RATIONALE-315 NCT04379635	III	453	Stage II-IIIA –IIIA: 58%	CT + tislelizumab *vs* CT + placebo	ÈFS, MPR	Tislelizumab: MPR 56.2% (127/226), pCR 40.7% Placebo: MPR 15.0% (34/227), pCR 5.7%

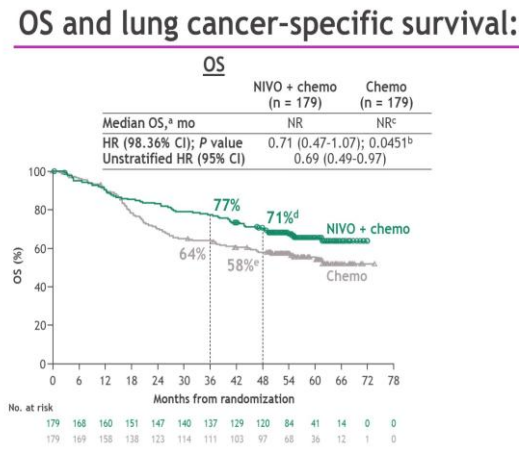
CheckMate 816



- EFS favored the combination arm (median 44 m vs. 18.4 m)
- EFS better, especially in stage IIIA, non-squamous histology, and PD-L1 ≥1% (HR 0.41). **No benefit in the PD-L1 negative group (HR 0.85).**
- pCR also favored the combination arm (24% vs 2.2% p < 0.001). MPR higher as well (36.9% vs 8.9%)
- 4-years:
  - EFS improved by 11% (49% vs. 38%; HR: 0.66
  - OS (4-year OS: 71% vs. 58%; HR: 0.71; 95% CI:0.47–1.07; p = 0.045)

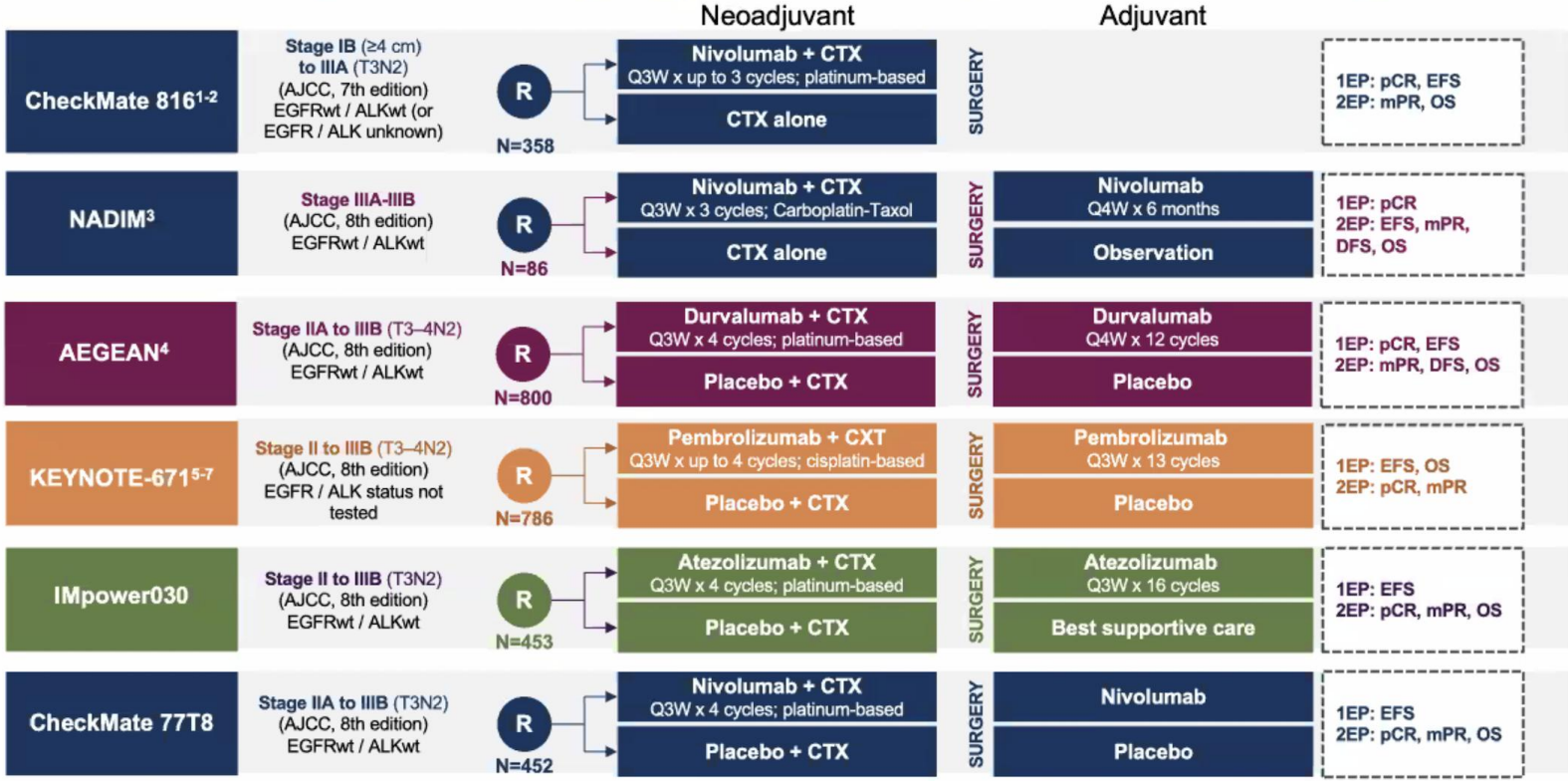
- **Primary endpoints:** pCR and EFS by BICR





J. Clin. Oncol. 2024, 42, LBA8010.

The Landscape is Changing with Neoadjuvant IO Strategies



1.-Forde PM, et al. NEJM 2022; 2.- Girard N, et al. ELCC 2023; 3.- Provencio M, et al, NEJM 2023; 4.- Heymach JV, et al. NEJM 2023; 5.- Wakelee H, et al. NEJM 2023; 6.- Wakelee, ASCO 2023. 7.- Spicer J, ESMO 2023; 8..-Cascone T. LBA ESMO 2023

Pooled results

All of these trials have reported the ICB arm

Significantly higher pCR compared with chemotherapy alone (~20% vs. ~5%, respectively),

Longer event-free survival (EFS), reducing the risk of recurrence by approximately 40%

OS: Only the KN 671 trial has reported significant improvement in OS (HR: 0.72); data for other phase III RCTS testing OS are not yet mature.

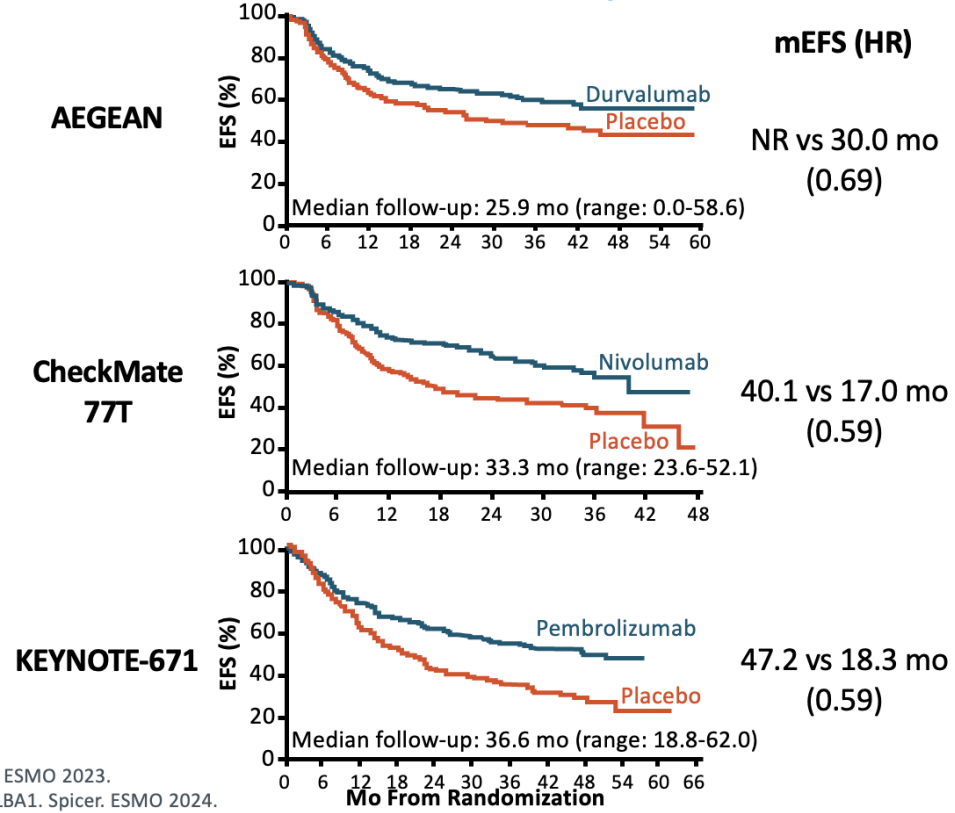
Study	Perioperative /Neoadjuvant	N	Percentage of PD-L1 > 1%	Percentage of Stage III %	Percentage of Surgery	pCR CT-ICB vs. CT	EFS HR [95% CI, *p*]	OS HR [95% CI, *p*]
CheckMate 816 [33,49]	Neoadjuvant	358	50%	63%	83%	24% vs. 2.2%	0.66 [0.49–0.9]	0.71 [0.47–1.07, $p = 0.045$] *
CheckMate 77T [34]	Perioperative	461	56%	64%	77%	25% vs. 5%	0.58 [0.42–0.81, $p < 0.00025$)	NR
KEYNOTE671 [35,47]	Perioperative	797	65%	70%	82%	18% vs. 4%	0.59 [0.48–0.72]	0.72 [0.56–0.93, $p < 0.01$)
AEGEAN [36]	Perioperative	802	67%	71%	81%	17% vs. 4%	0.68 [0.53–0.88, $p < 0.01$]	NR
NEOTORCH [37]	Perioperative	501	66%	100%	82%	25% vs. 1.0%	0.40 [0.28–0.57, $p < 0.01$]	0.62 [0.38–1.0, $p = 0.05$]
RATIONALE 315 [38]	Perioperative	453	58%	58%	84%	41% vs. 5.7%	0.56 [0.40–0.79, p <0.01]	0.62 [0.39–0.98, $p = 0.02$]

Lavaud P, Cancers 2024

Phase III Perioperative Studies in Resectable NSCLC: pCR and EFS

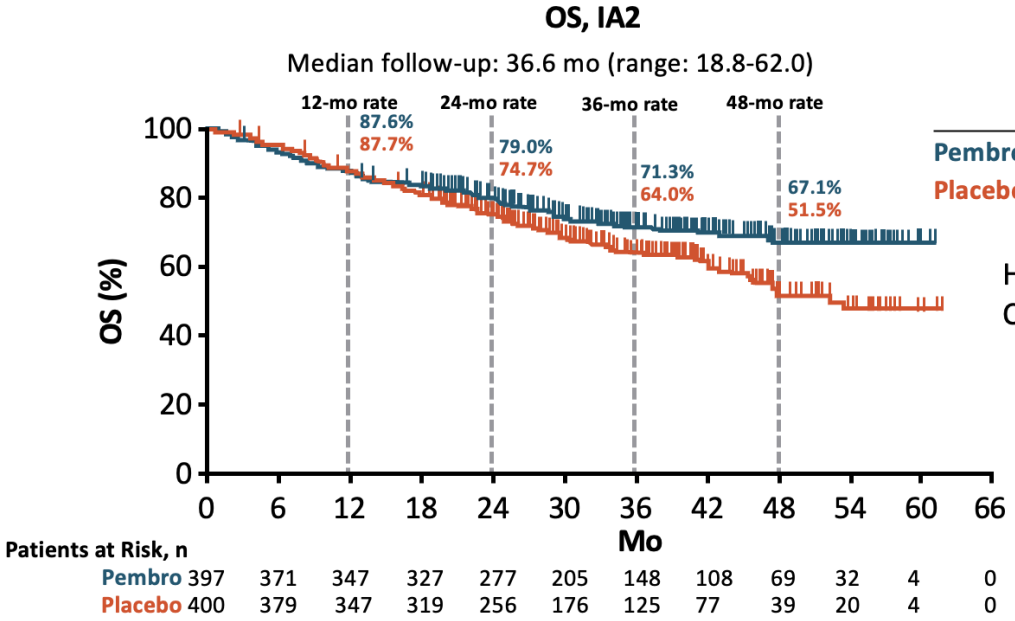
pCR Rate, %

Trial	IO + CT	Pbo + CT
AEGEAN (durvalumab)	17.2	4.3
CheckMate 77T (nivolumab)	25.3	4.7
KEYNOTE-671 (pembrolizumab)	18.1	4.0



Wakelee. ASCO 2023. Abstr LBA100. Wakelee. NEJM. 2023;389:491. Spicer. ESMO 2023. Abstr LBA56. Cascone. NEJM. 2024;390:1756. Cascone. ESMO 2023. Abstr LBA1. Spicer. ESMO 2024.

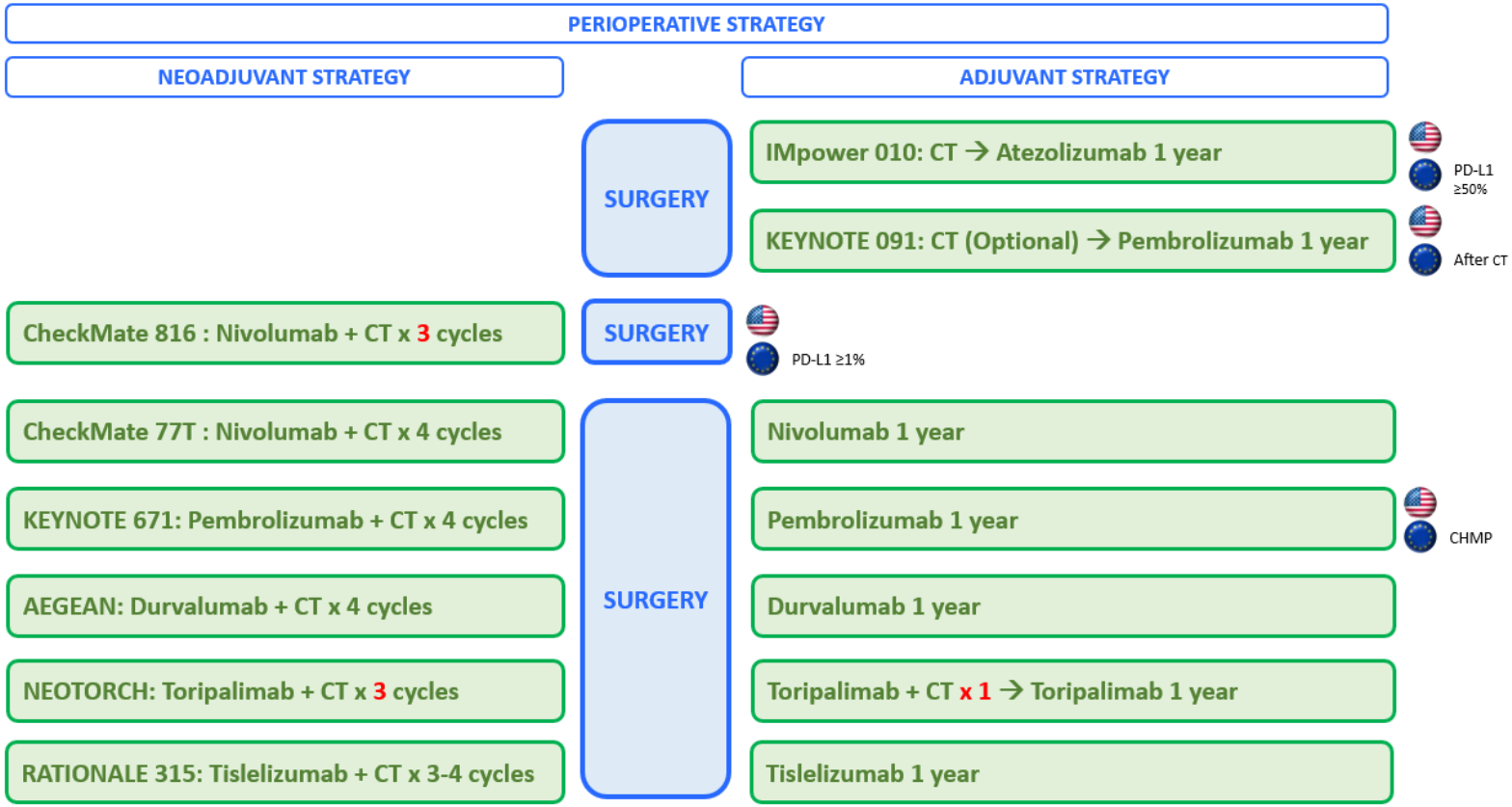
KEYNOTE 671: OS



	Patients With Event	Median, Mo (95% CI)
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* = .00517

Spicer. ESMO 2023. Abstr LBA56.



Lavaud P, Cancers 2024.

Key methodological issues

- Including varied patient groups, characterized by disease stages ranging from stages I to IIIC, and differences in inclusion of patients with EGFR and ALK alterations.

- Lack of a clear definition of resectability in all current studies, particularly concerning stage III disease.

- Consistent use of chemotherapy as the control arm treatment across all stages of NSCLC from IB to IIIC, which may not reflect the actual standard of care.

  In routine clinical practice, patients presenting with stages IB and II typically undergo initial surgery, followed by adjuvant chemotherapy, rather than the reverse.

  For stage IIIA, and especially for stages IIIB and IIIC, there is no clear standard treatment, as surgery has not been shown to be superior to chemoradiotherapy.

Houda I. Lancet 2024

Greater impact benefit according to PD-L1

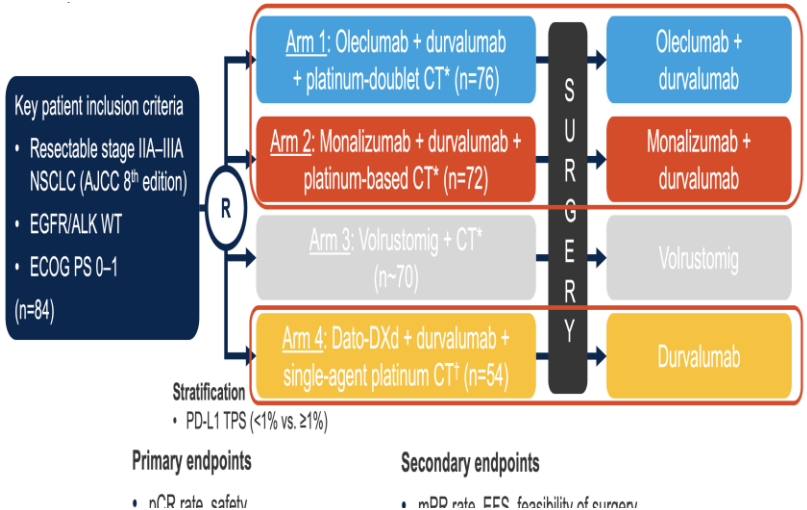
STUDY	PD-L1 ≥50%	PD-L1 1-49%	PD-L1 ≤1%	ALL
CheckMate 816 HR for EFS	0.29	0.63	0.87	0.68
AEGEAN HR for EFS	0.60	0.70	0.76	0.68
KN671 HR for EFS	0.42	0.51	0.59	0.58
NEOTORCH HR for EFS	0.31	0.31	0.59	0.50
CheckMate 77T HR for EFS	0.26	0.76	0.73	0.58

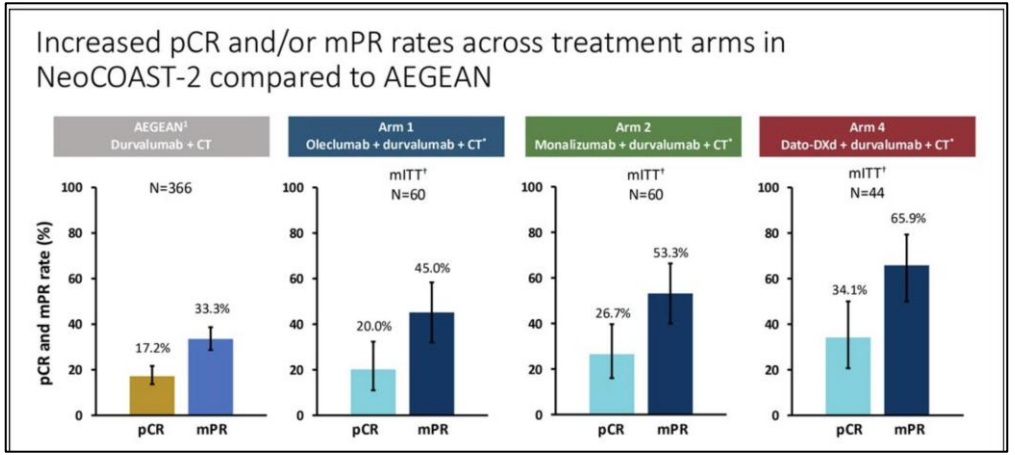
Neoadjuvant

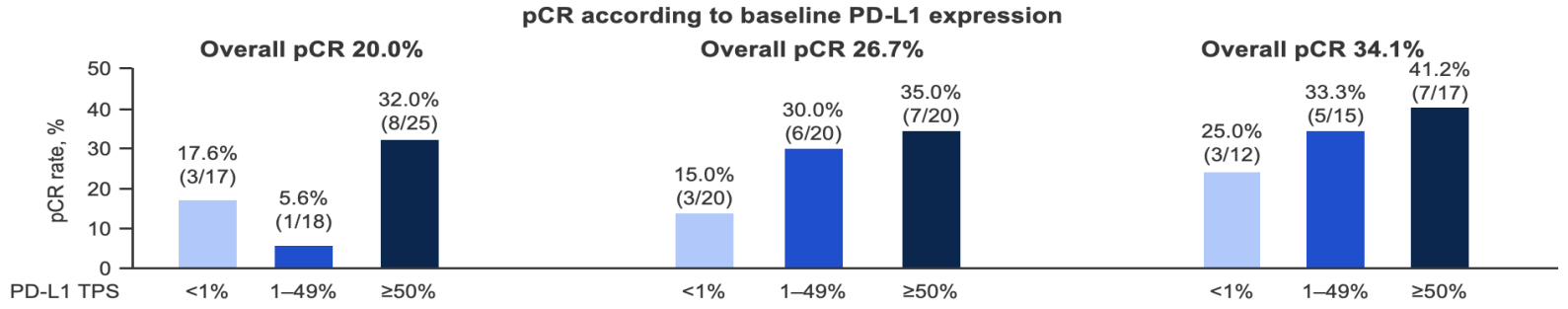
Perioperative

Forde P, ELCC 2023; Provencio et al, ESMO 2023; Heymach JV; AACR 2023; Wakelee H, ASCO 2023; Lu S, ASCO 2023; Cascone T ESMO 2023

NeoCOAST-2: Intensifying perioperative treatment for all patients







Cascone T, et al. J Thorac Oncol 2024;19(suppl):Abstr PL02.07

The issue of the resectability

All cases of early-stage NSCLC must be discussed in an MTB to define the best treatment approach

In all phase III RCTs, only resectable early-stage NSCLC but, the **definition of resectable disease is not homogeneous, especially for stage III NSCLC**

Consensus definition

Mandatory Work-up
Contrast enhanced chest CT scan
^{18}F-FDG-PET-CT with/without contrast
Brain imaging, preferably a brain MRI
Invasive mediastinal/nodal staging (EBUS, EUS, combined EBUS-EUS and/or mediastinoscopy)
Additional tests may be required if suspicion of invasion of any neighboring structures

Medical specialties involved in the treatment decision:
Thoracic surgeon*
Radiation oncologist
Medical oncologist and/or Pneumo-oncologist
Pulmonologist
Imaging specialist
Pathologist
Decision on technical resectability is made by the thoracic surgeon*, informed by the multidisciplinary team (MDT). The **final clinical decision** on the local treatment strategy should be placed in the oncological context by the MDT.

INTERNATIONAL EORTC SURVEY ON RESECTABILITY OF STAGE III NSCLC

	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY¶	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE*§	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

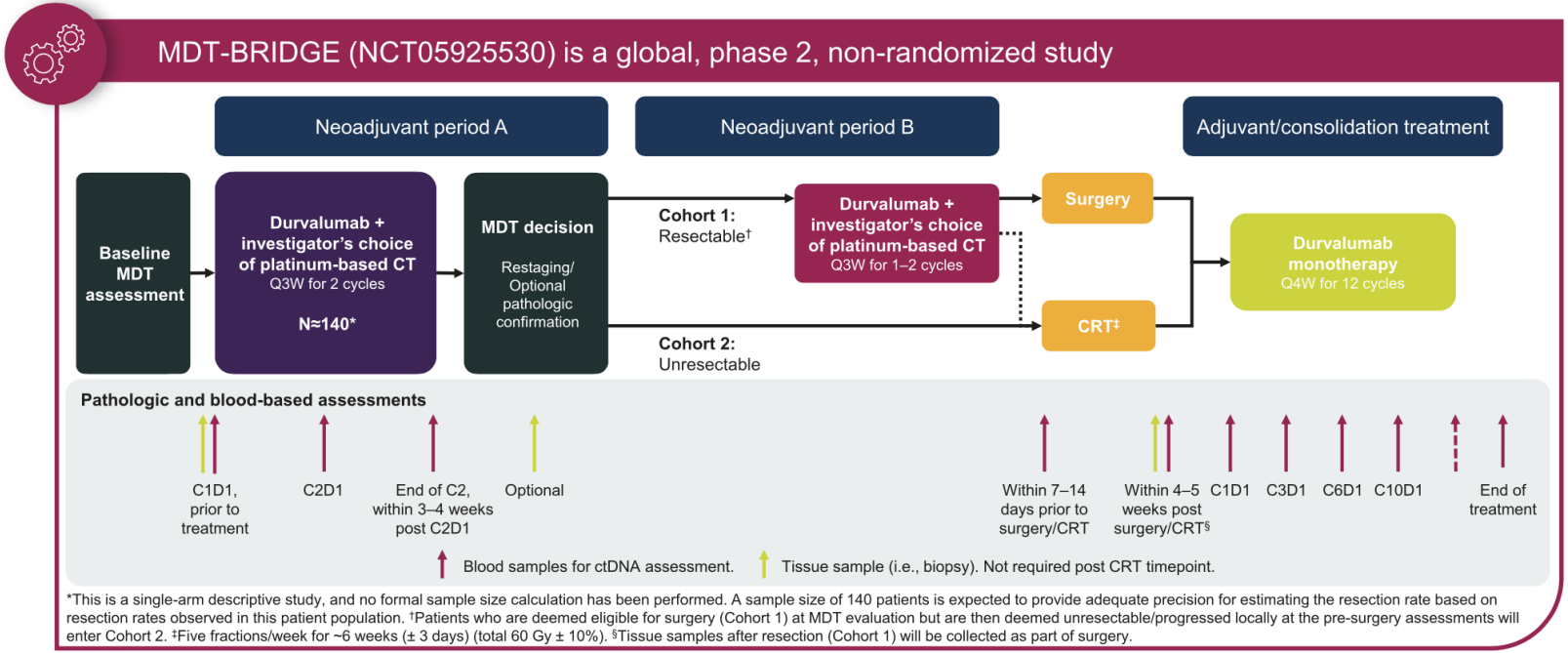
- In most instances considered as unresectable (multi-station N2, bulky N2 or T4 by invasion)
- Multiple-station N2 tumors is a field for further research

***Multiple station N2**: case-by-case discussion; the exact number of nodes/stations cannot be defined
¶Bulky N2: lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of highly selected patients, including those patients in multidisciplinary trials with surgery as local therapy can be discussed
§Some T4 tumours by infiltration of major structures are potentially resectable –see Table 1
11.

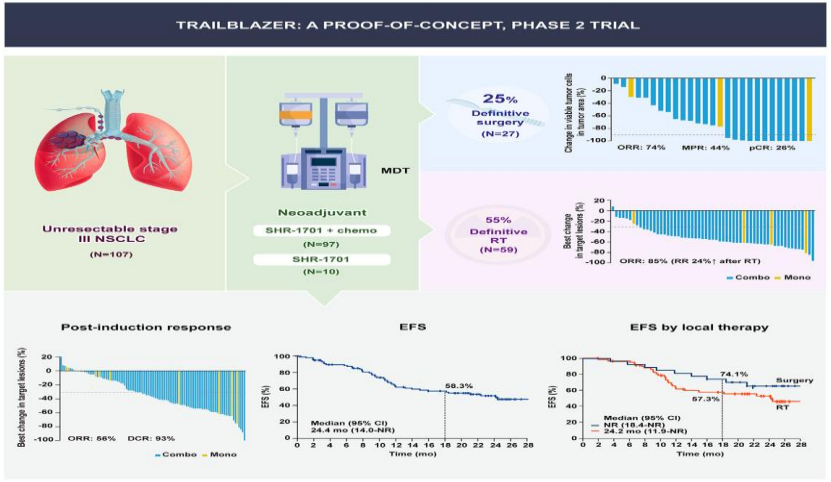
Domenghino, A.Nat. Med. 2023,
Dingemans, A.-M. J. Thorac. Oncol. 2023, 18, S57–S58.

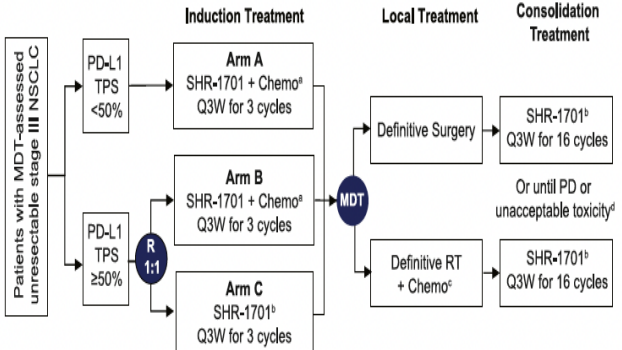
What about *borderline* resectability?

Several clinical trials launched to assess the feasibility and potential benefits of **surgical conversion** with neoadjuvant immune-based therapy



Neoadjuvant SHR-1701 with or without chemotherapy in *unresectable* stage III NSCLC: A proof-of-concept, phase 2 trial





SHR-1701 is a bifunctional agent composed of an IgG4 monoclonal antibody targeting PD-L1 fused with extracellular domain of the TGF-bII receptor

Design:

Neoadjuvant SHR-1701 ± chemo, then surgery/RT

Primary cohort (neoadjuvant combo):

Post-induction ORR 58%; 18-month EFS 56.6%

Surgery conversion: 25%, all R0 resection

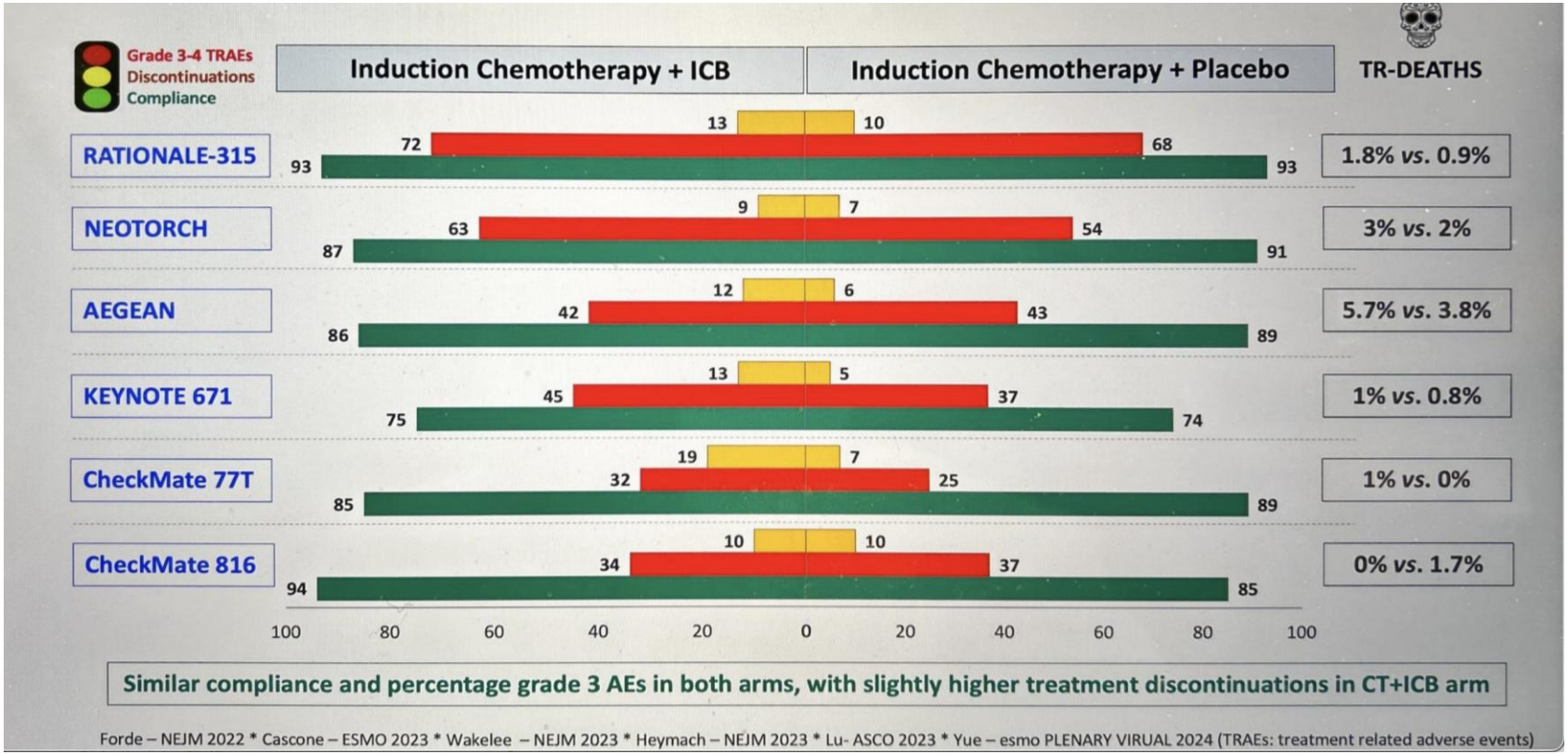
Surgical set: MPR 44%; pCRP 26%;

18-month EFS 74.1% (vs. 57.3% in RT set)

***Conclusion**: **Surgical conversion is feasible** and associated with better survival outcomes.*

Zhou et al., 2024, Cancer Cell 42, 1258–1267

TOXICITY CT+ IO vs CT ALONE



Forde – NEJM 2022 * Cascone – ESMO 2023 * Wakelee – NEJM 2023 * Heymach – NEJM 2023 * Lu- ASCO 2023 * Yue – esmo PLENARY VIRUAL 2024 (TRAEs: treatment related adverse events)

Costs

Drug	Trial	Treatment costs (€[a])	EMA indication	Least expensive scenario (estimated minimum total costs, €)			Most expensive scenario (estimated maximum total costs, €)		
				Mean	Minimum[b]	Maximum[c]	Mean	Minimum[b]	Maximum[c]
Osimertinib	ADAURA	224,486	Three years of adjuvant treatment (80 mg once daily) in stage IB-IIIA, *EGFR* mutation-positive (ex19del or ex21L858R) NSCLC	19,754,768	15,714,020	23,795,516	19,754,768	15,714,020	23,795,516
Atezolizumab	IMpower010	64,528	One year of adjuvant treatment (1200 mg every three weeks) following chemotherapy in stage II-IIIA, *EGFR* wildtype, and *ALK*-negative NSCLC with PD-L1 ≥50%	Not included[d]	N/A	N/A	Not included[e]	N/A	N/A
Nivolumab	CheckMate-816	11,920	Three cycles (360 mg every three weeks) of neoadjuvant treatment combined with chemotherapy in stage II-IIIA NSCLC with PD-L1 ≥1%	6,007,680	5,816,960	6,198,400	2,622,400	2,538,960	2,705,840
Pembrolizumab	PEALRS/ KEYNOTE-091	102,981	One year of adjuvant treatment (200 mg every three weeks) following chemotherapy in stage IB(≥4 cm)-IIIA NSCLC regardless of PD-L1 expression	14,211,378	9,680,214	18,742,542	34,704,597	23,685,630	45,723,564
Total				39,973,826	31,211,194	48,736,458	57,081,765	41,938,610	72,224,920

Patients receive only one treatment. TNM staging is according to the seventh edition of the TNM classification system. *Abbreviations*: EMA, European Medicines Agency; NSCLC, non-small cell lung cancer. [a]Based on the list prices in the Netherlands including VAT. [b]Based on the proportion of patients who completed treatment in each trial. [c]Based on a 100% treatment completion rate. [d]Atezolizumab is not included in this scenario because, theoretically, nivolumab may also be indicated in the same population but is less expensive. [e]Atezolizumab is not included in this scenario because, theoretically, pembrolizumab may also be indicated in the same population but is more expensive.

Table 4: **An overview of cost estimates of the novel adjuvant and neoadjuvant treatments based on the NSCLC incidence in the Netherlands.**

Houda I. The Lancet Regional Health – Europe 2024;

Costs

Drug	Trial	Treatment costs (€[a])	EMA indication	Least expensive scenario (estimated minimum total costs, €)			Most expensive scenario (estimated maximum total costs, €)		
				Mean	Minimum[b]	Maximum[c]	Mean	Minimum[b]	Maximum[c]
Osimertinib	ADAURA	224,486	Three years of adjuvant treatment (80 mg once daily) in stage IB-IIIA, EGFR mutation-positive (ex19del or	19,754,768	15,714,020	23,795,516	19,754,768	15,714,020	23,795,516
Atezolizumab	IMpower010								N/A
Nivolumab	CheckMate-816							50	2,705,840
Pembrolizumab	PEALRS/ KEYNOTE-091							530	45,723,564
Total								510	72,224,920

Patients receive only one treatment … mall cell lung cancer.
[a]Based on the list prices in the Neth… Atezolizumab is not
included in this scenario because, t… se, theoretically,
pembrolizumab may also be indica…

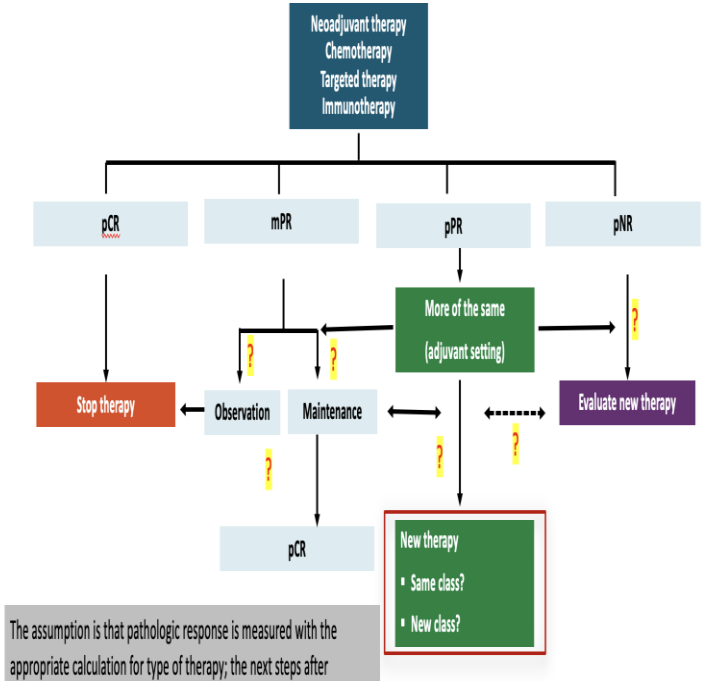
Table 4: An overview of cost e…

In resectable NSCLC, where the conclusive benefits of adjuvant immunotherapy following neoadjuvant chemoimmunotherapy are not fully established, particularly without mature survival data, *countries must balance innovative care with budgetary constraints*

Houda I. The Lancet Regional Health – Europe 2024;

Open questions

- Who could avoid adjuvant treatment after induction?
- Who can benefit the most?
- How to modulate treatment in patients MRD-positive and do not achieve pCR?
    - Continuing with the same adjuvant ICB used in the neoadjuvant treatment,
    - Intensifying adjuvant treatment with dual ICBS,
    - Exploring other strategies such as adjuvant vaccines.
- The role of induction ICB in patients with oncogenic addicted diseases other than EGFR and ALK
- The best treatment approach for patients who do not proceed to surgery after induction therapy
- The optimal duration of adjuvant ICB therapy to balance efficacy and long-term toxicity, particularly in patients who have received neoadjuvant ICBs plus chemotherapy.



Challenges for the next generation of clinical trials

- **Universal consensus on resectability criteria in stage III** NSCLC is lacking and should therefore be consensually defined, at least for research purposes.
- Studies **should be tailored to reflect the actual standard** of care for each substage of NSCLC, especially for stage III substages involving radiotherapy.
- Study designs should consider **incorporating ctDNA clearance and pCR for stratification** of adjuvant therapy, as the role of these biomarkers for guiding adjuvant therapy still needs more clarification.
- Surgical study designs should encompass **surgical quality metrics**, enhancing the evaluation of surgical methods employed and optimizing resection quality and survival rates.

Conclusions

- New treatment strategies have shifted the treatment landscape of early-stage NSCLC, but several relevant clinical questions remain unresolved, such as the role of adjuvant ICB after an induction approach or the optimal duration of the postoperative treatment.
- Upfront molecular diagnosis, accurate stage, and MTB decisions about resectability are crucial.
- Other health measures, such as increased screening programs, selection of predictive markers, and residual disease detection assays, hold great potential to continue to improve outcomes in this setting **but** the next challenges will be to avoid excessive treatment and exposure to unnecessary toxicity and to try to minimize healthcare costs.