



Wake Forest University
School of Medicine



Atrium Health
Levine Cancer

NCI

Comprehensive
Cancer Center

Unveiling the Current State of Resectable Lung Cancer Treatment: Empowering Advances & Promising Innovations

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Disclosures

Consulting/Honoraria

Sanofi / BMS / Genzyme

Adjuvant in the immunotherapy era

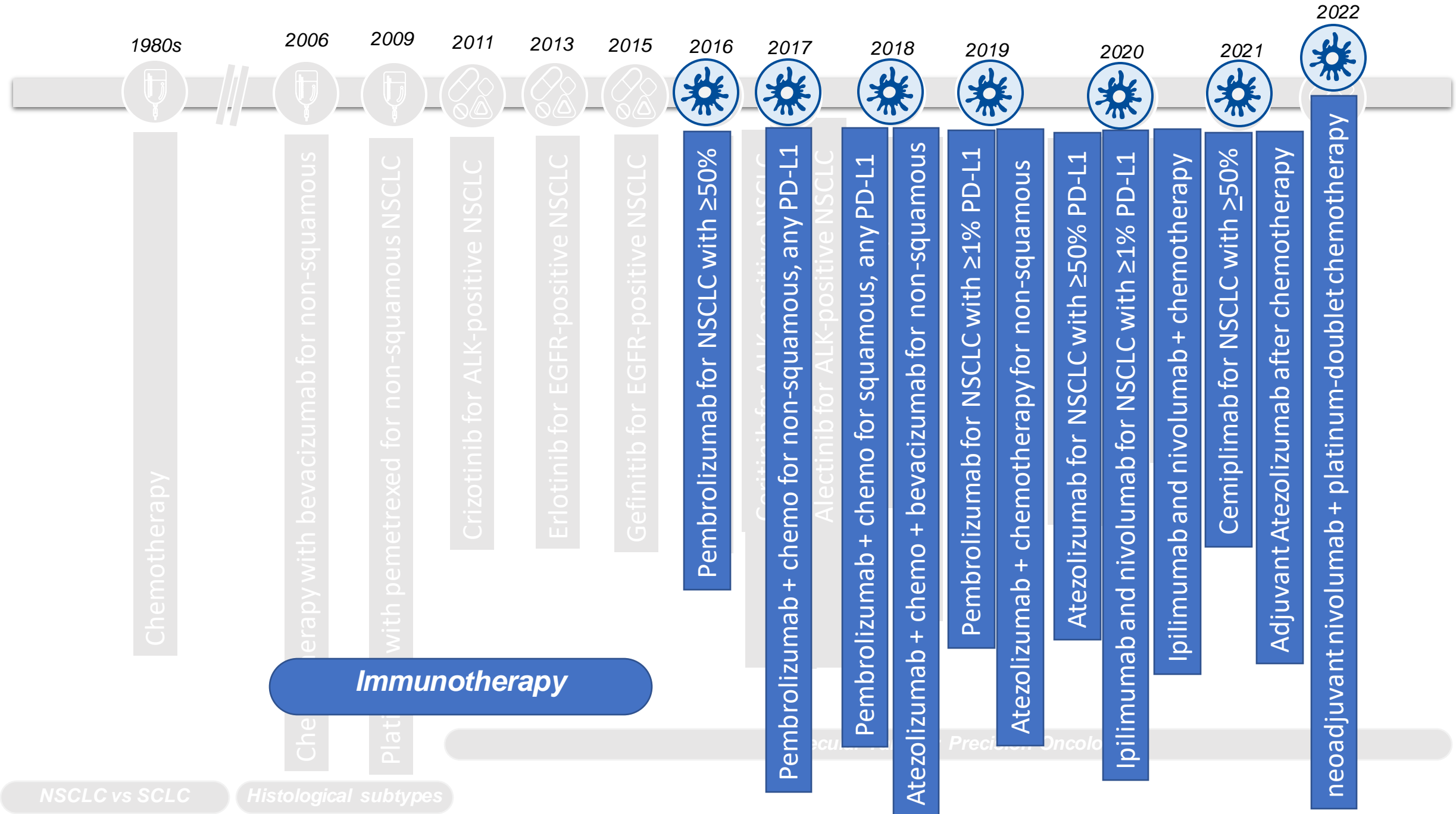
Adjuvant in the targeted therapy era

Neoadjuvant therapy in the immunotherapy era



NSCLC vs SCLC

Histological subtypes



Non-Small Cell Lung Cancer

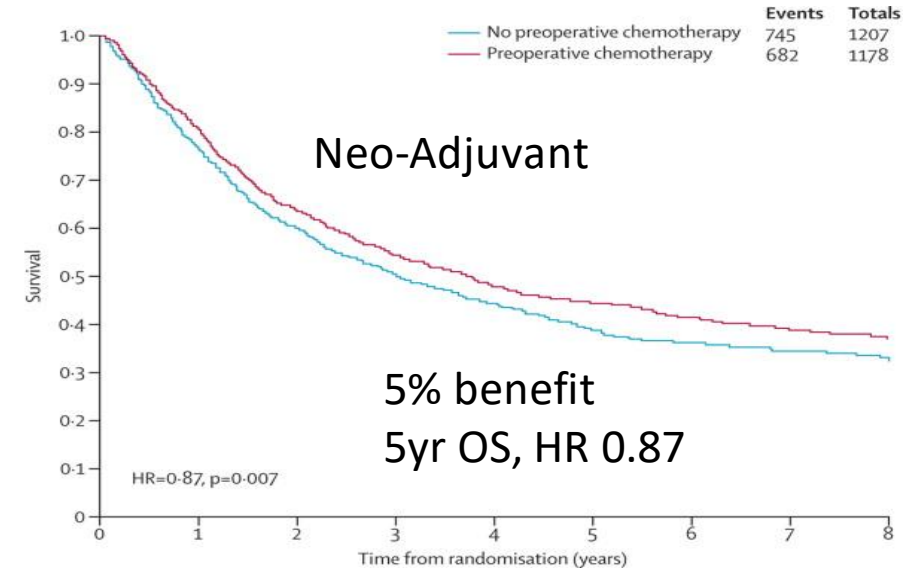
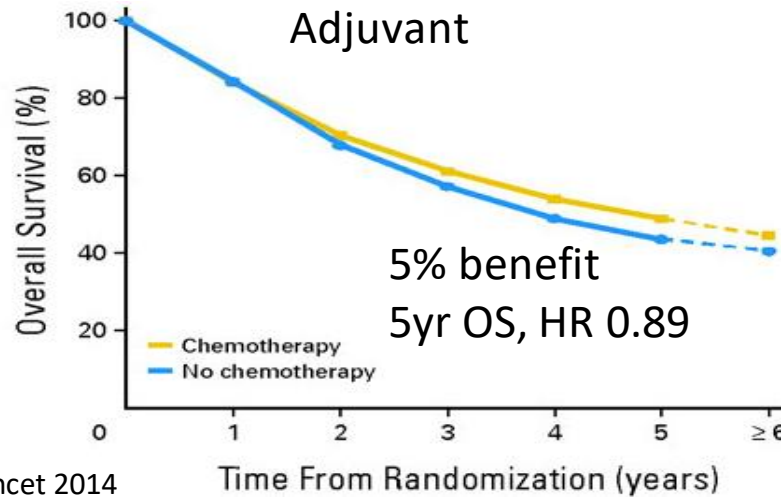
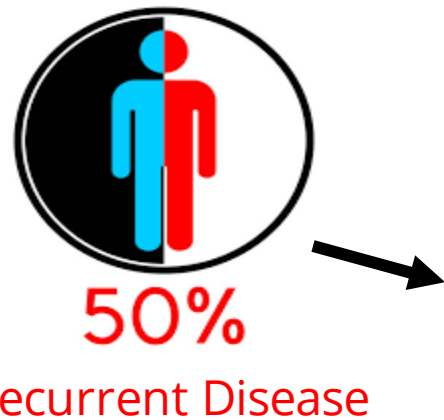
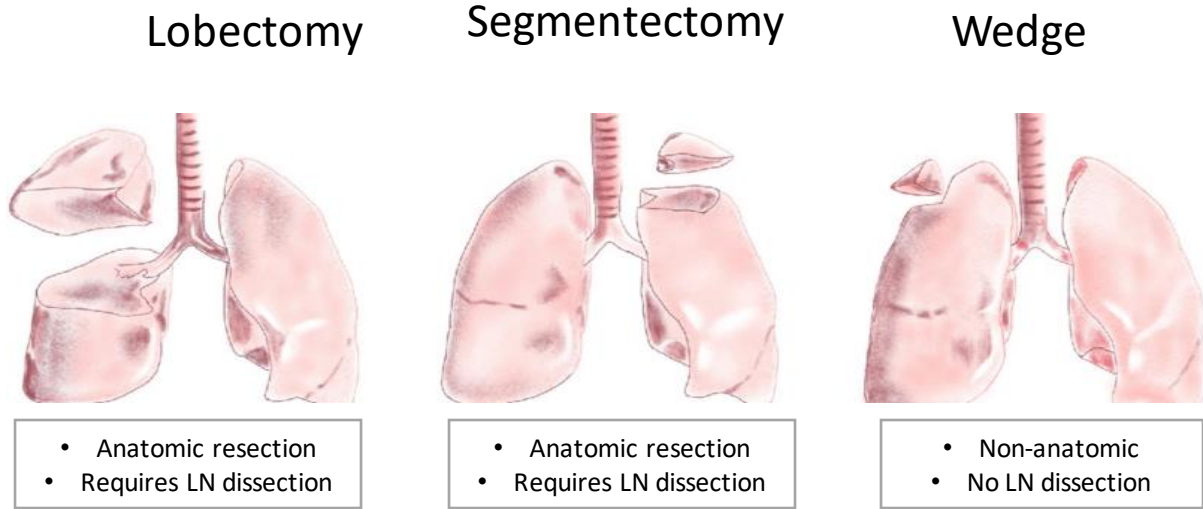
- Lung cancer accounts for the most deaths of any cancer worldwide
- Non-small cell lung cancers (NSCLCs) make up 85%
- Diagnosis is STILL made at a metastatic or locally advanced stage
- 25% to 30% have resectable disease
- Surgical resection alone is not curative in the majority of patients with resectable NSCLC
- The rate of recurrent disease increases with stage

Matsuyama R et al. J Clin Oncol 2006 / Le Chevalier T. Ann Oncol 2010/ Goldstraw P et al. Thorac Oncol 2016



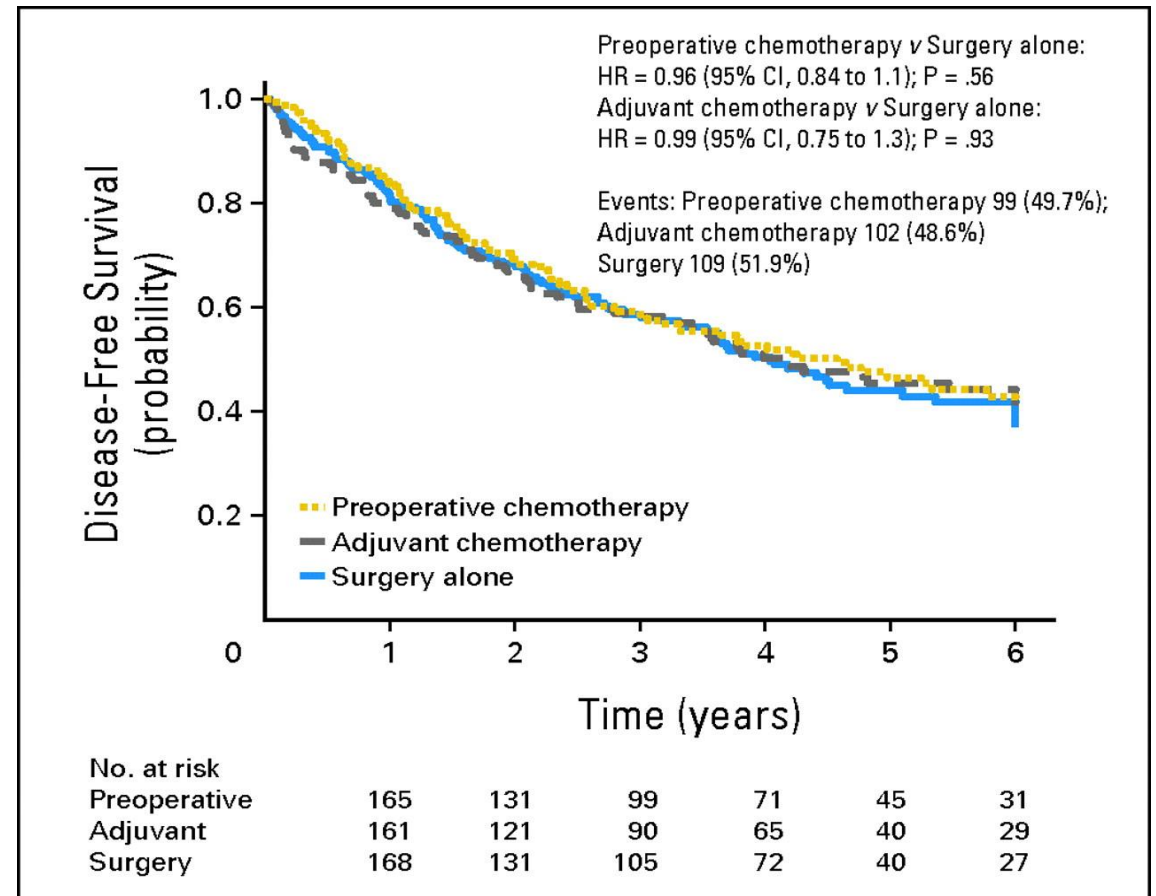
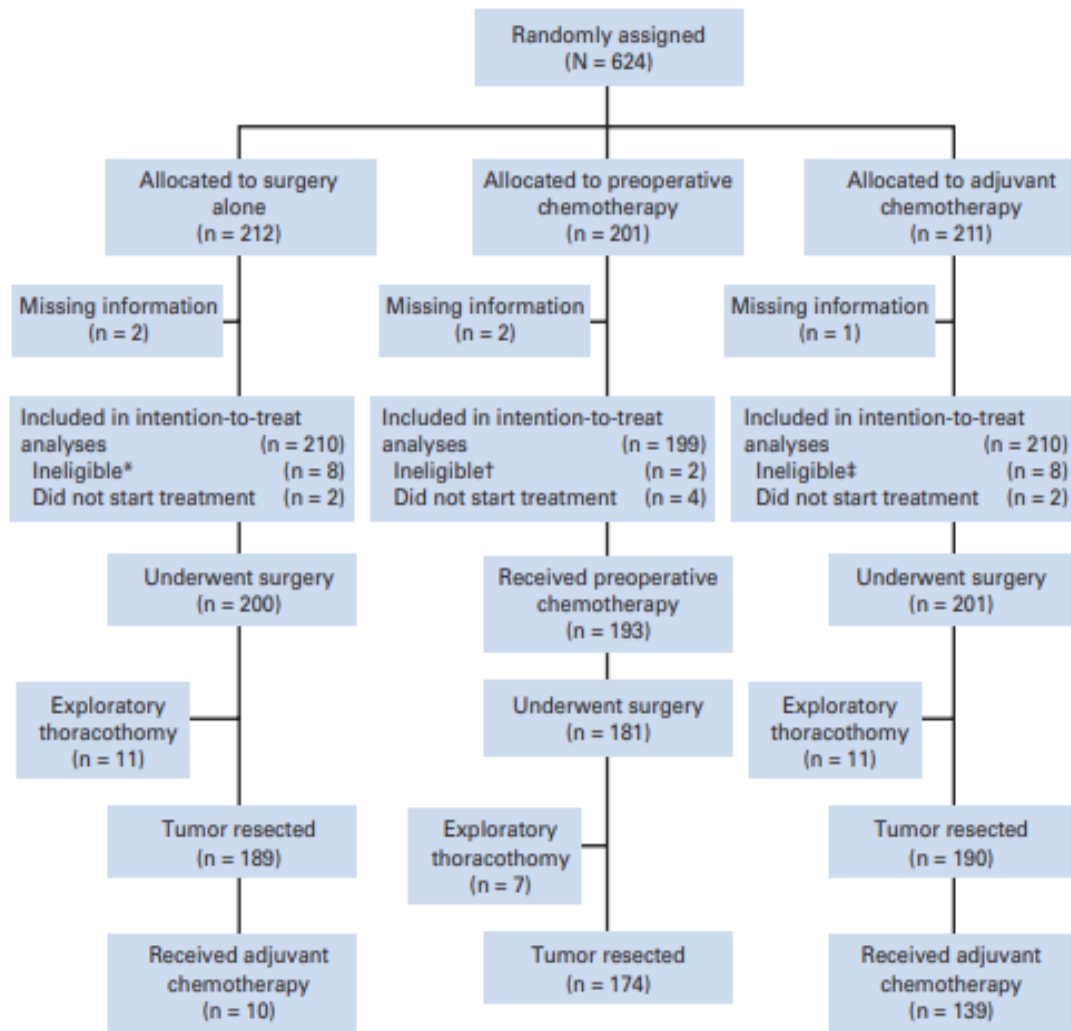
20-30% of patient with NSCLC have early-stage disease

Definitive Surgical Therapy



Pignon et al. J Clin Oncol 2008

NSCLC Meta-analysis collaborative group et al. Lancet 2014

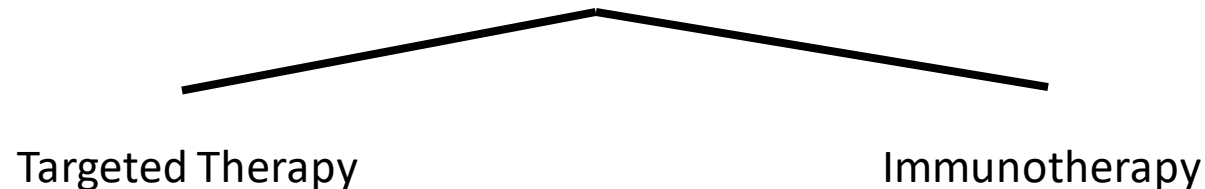


No statistically significant differences in disease-free survival with the addition of preoperative or adjuvant chemotherapy to surgery.

Treatment for resectable NSCLC

- Platinum based CT in the adjuvant and neoadjuvant are interchangeable and part of SOC for 20 yrs+
- Nuances to Adjuvant v. Neoadjuvant therapy
 - A – definitive surgical therapy goes first and prioritized, 30% do not complete adjuvant therapy
 - N – systemic therapy is prioritized and 15% do not have tumor resected

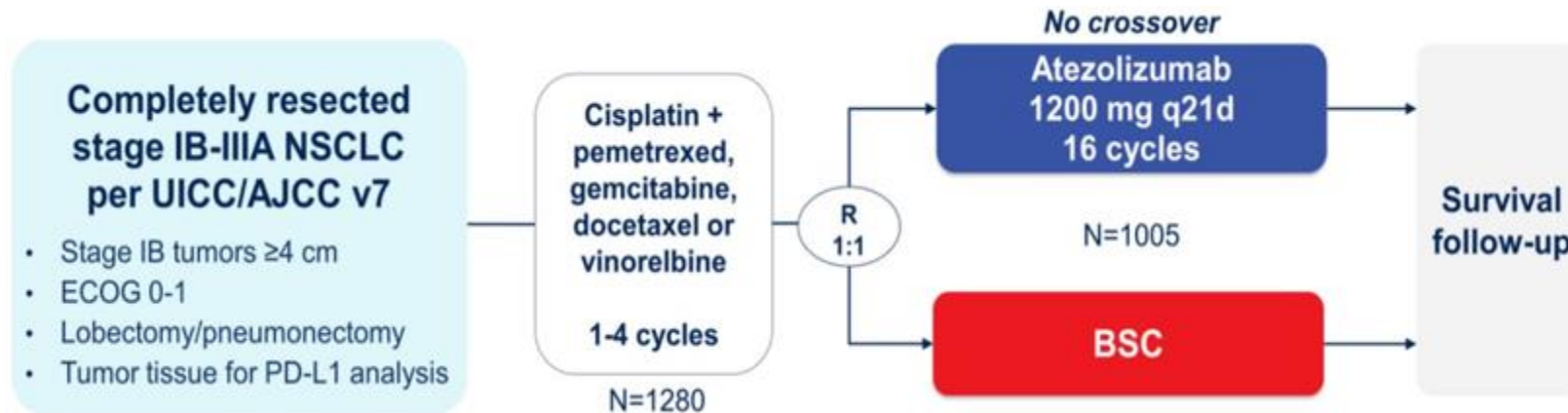
How does this change in the ERA of better systemic therapy?



Adjuvant in the immunotherapy era

Impower-010

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial



Stratification factors

- Male vs female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status^a: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints

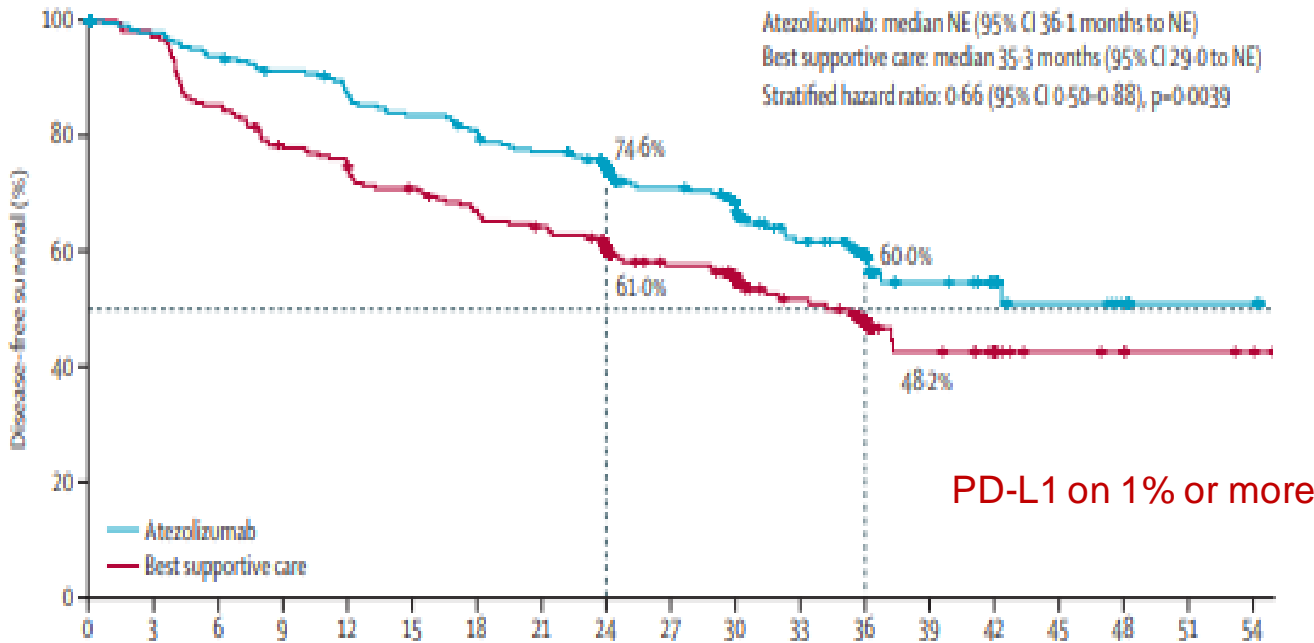
- Investigator-assessed DFS tested hierarchically:
 1. PD-L1 TC ≥1% (SP263) stage II-IIIa population
 2. All-randomized stage II-IIIa population
 3. ITT (all-randomized stage IB-IIIa) population

- 66% Non-Squam
- Stage IB = 12.2%
- Stage II = 46.7%
- Stage III = 41%
- 55% PDL1 ≥ 1% (SP263)

Felip E et al. Lancet. 2021

Impower-010

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomized, multicenter, open-label, phase 3 trial



DFS benefit across all groups and enrichment for those with Increased PDL1

PD-L1 on 1% or more

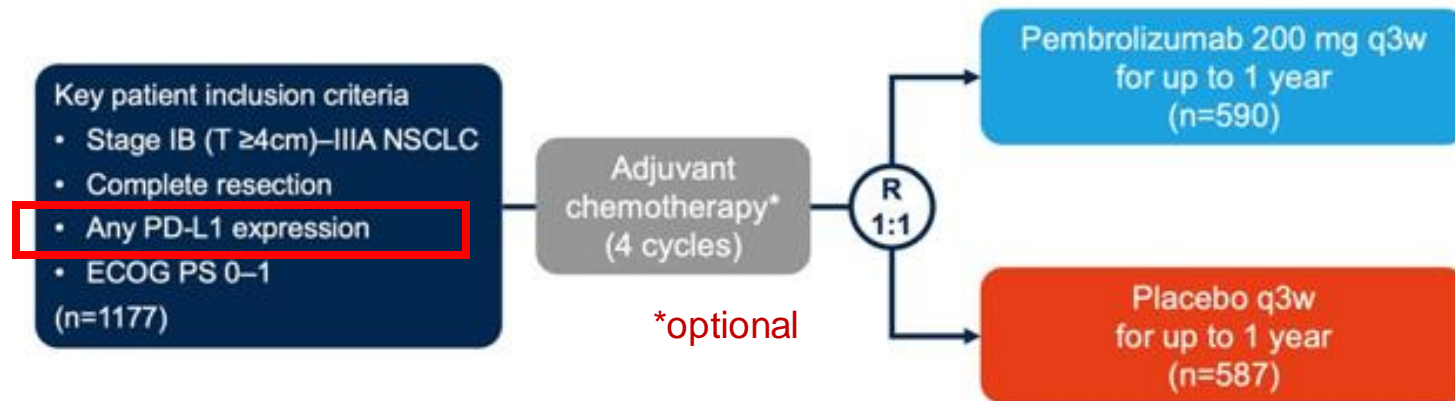
PD-L1 status by SP263

PD-L1 status	n/N	Median NE (95% CI)	n/N	Median NE (95% CI)	Hazard Ratio (95% CI)
TC <1%	181/383	36.1 (30.2-NE)	202/383	37.0 (28.6-NE)	0.97 (0.72-1.31)
TC ≥1%	248/476	NE (36.1-NE)	228/476	35.3 (29.0-NE)	0.66 (0.49-0.87)
TC 1-49%	133/247	32.8 (29.4-NE)	114/247	31.4 (24.0-NE)	0.87 (0.60-1.26)
TC ≥50%	115/229	NE (42.3-NE)	114/229	35.7 (29.7-NE)	0.43 (0.27-0.68)

Felip E et al. Lancet. 2021

Keynote 091/PEARLS Study

Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer: randomized, triple-blind, phase 3 trial



Dual Primary End Points

- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

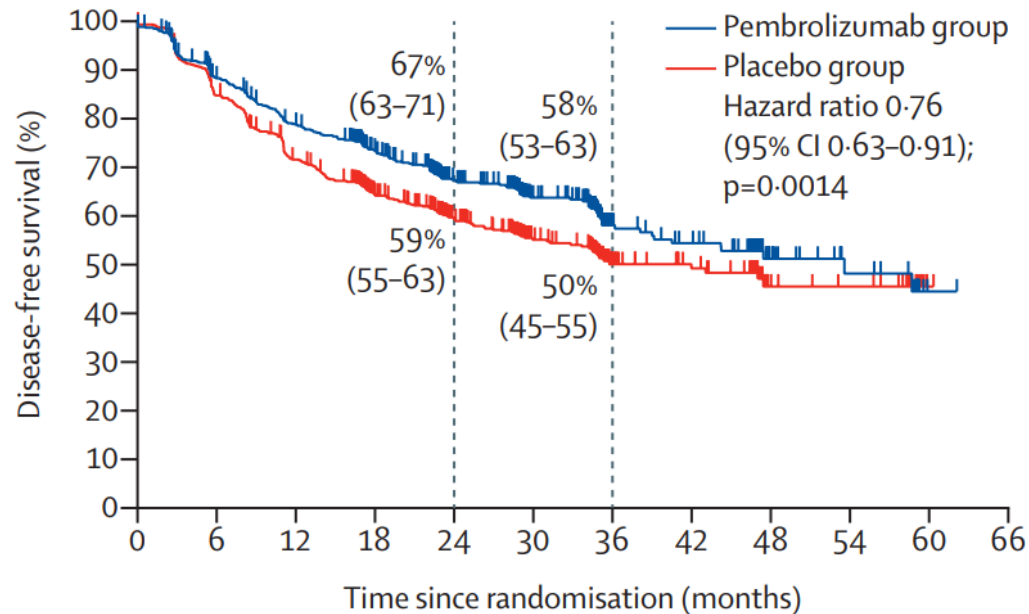
- N=1177
- 68% Non-Squam
- Stage IB = 14%
- Stage II = 55%
- Stage III = 30%
- 28% PDL1 ≥ 50% each arm

O'Brien M et al. Lancet. 2022

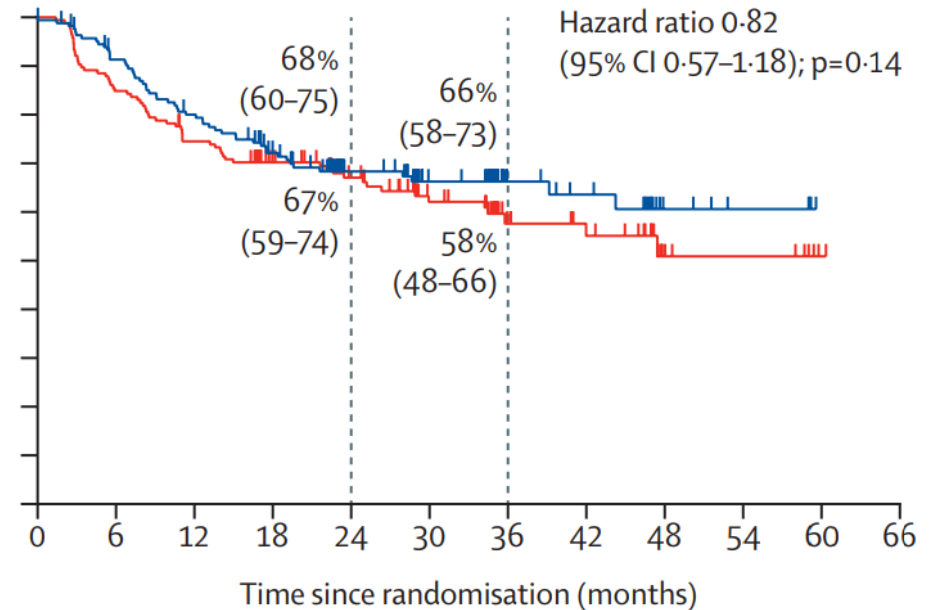
Keynote 091/PEARLS Study

Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer: randomized, triple-blind, phase 3 trial

Overall population



PD-L1 TPS ≥ 50%



PD-L1 TPS

<1%	89/233	106/232
1-49%	69/189	91/190
≥50%	54/168	63/165



DFS benefit in overall population, irrespective of PDL1 expression

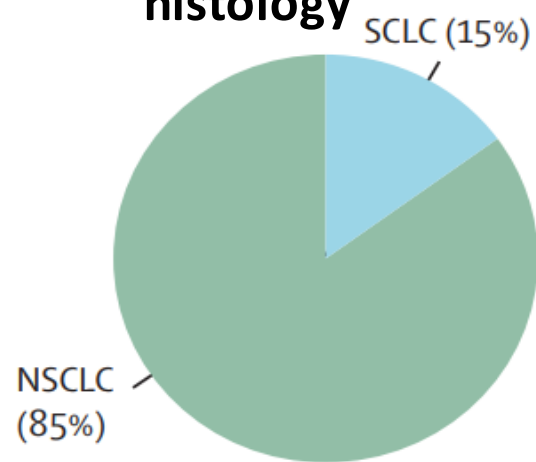
Adjuvant Immunotherapy CT in NSCLC

Stay Tuned.....

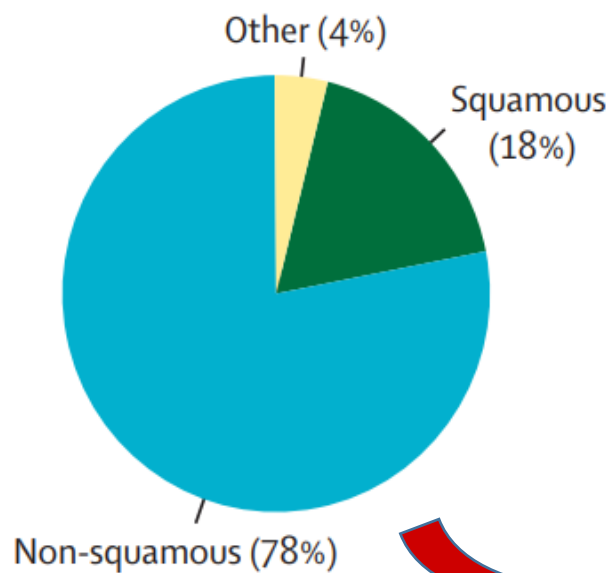
Clinical Trial	IO agent	Primary endpoints	Accrual Status	Stage	Target Accruals	Adjuvant Chemo
ACCIO (Alliance)	Pembro	DFS	Recruiting (Dec 2024)	IB-III A	1210	1-4 cycles Platin db
ANVIL (Alliance)	Nivo	DFS, OS	Active (July 2024)	IB-III A	903	CT and/or RT
CCTG BR.31	Durva	DFS	Active (Jan 2024)	IB-II A	1415	CT permitted

Adjuvant in the targeted therapy era

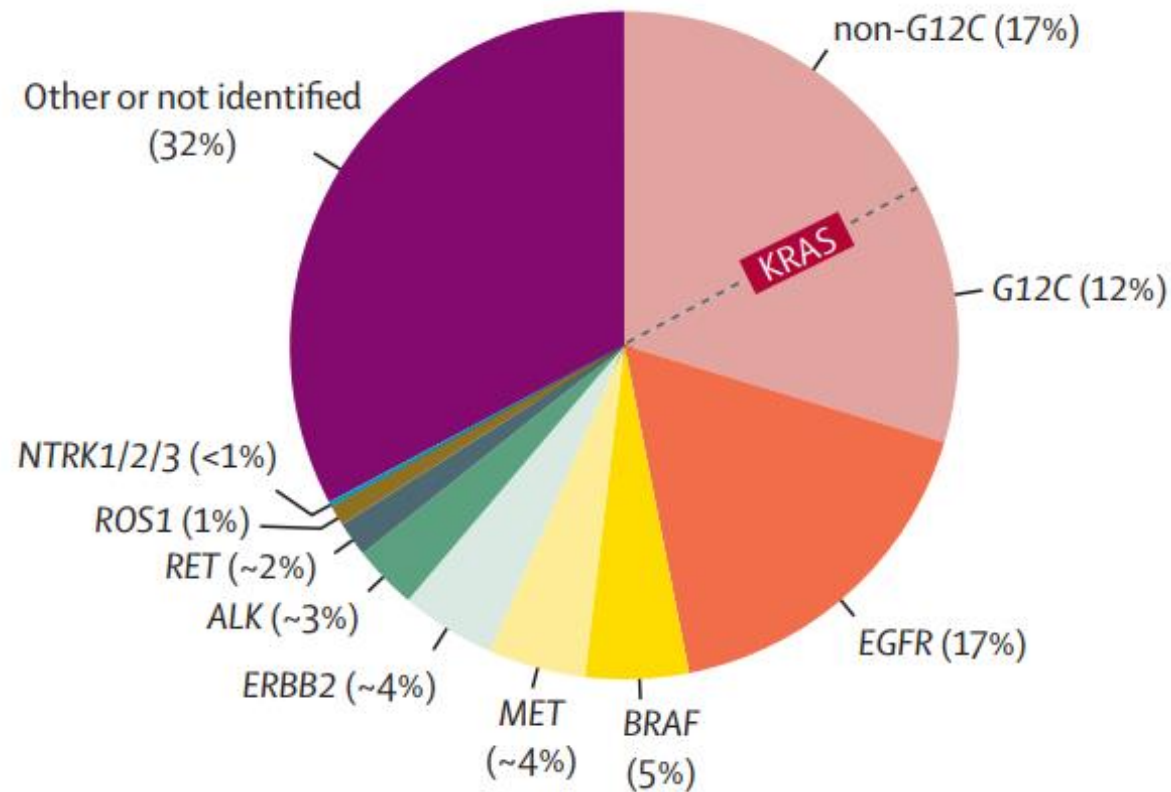
Lung cancer histology



NSCLC histology



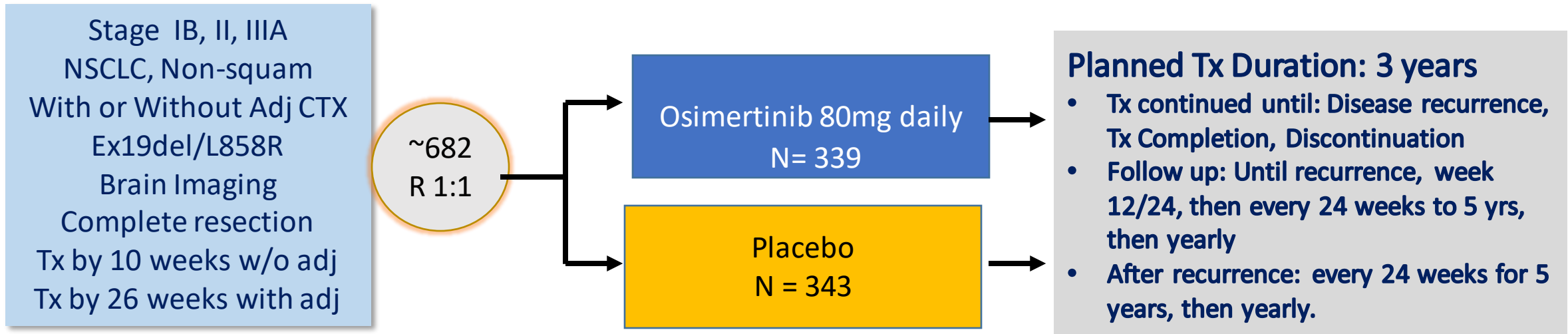
Oncogenic mutations in NSCLC



Thai AA et al. Lung cancer. Lancet. 2021 Aug 7;398(10299):535-554.

ADAURA

Overall survival analysis of adjuvant osimertinib in patients with resected EGFR-mutated stage IB–IIIA NSCLC



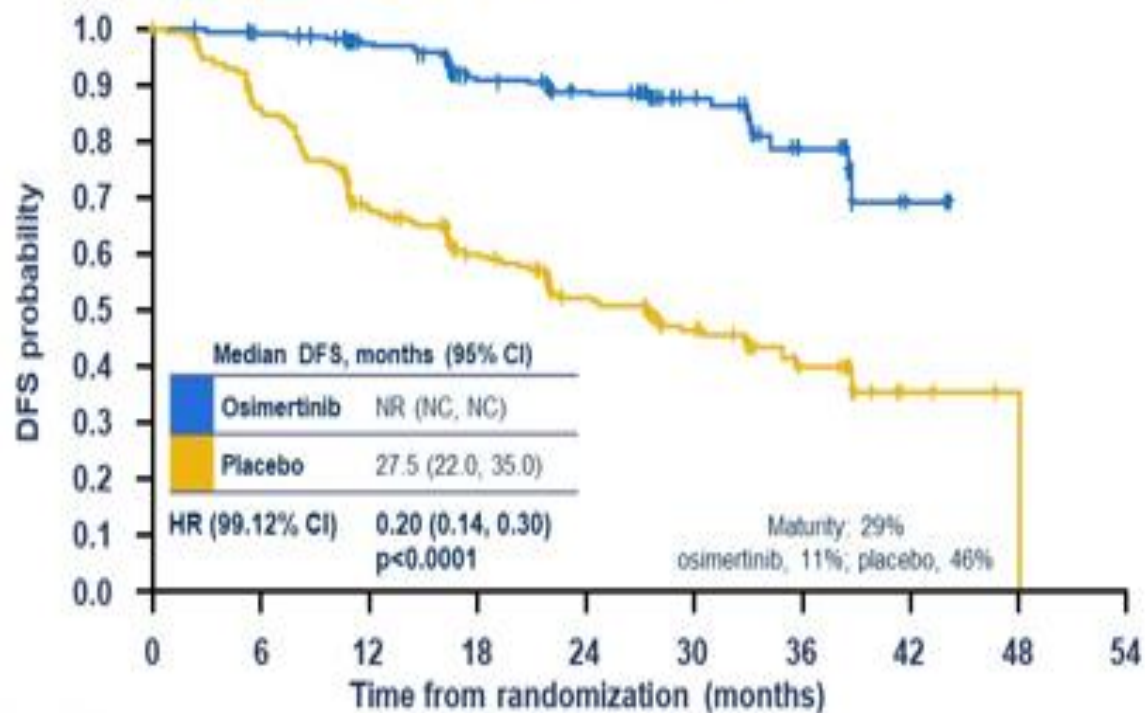
Primary Endpoint: DFS in stage II-III A

Secondary Endpoints: DFS in overall population (stage IB-III A), OS, Safety, QoL

Previous Updates

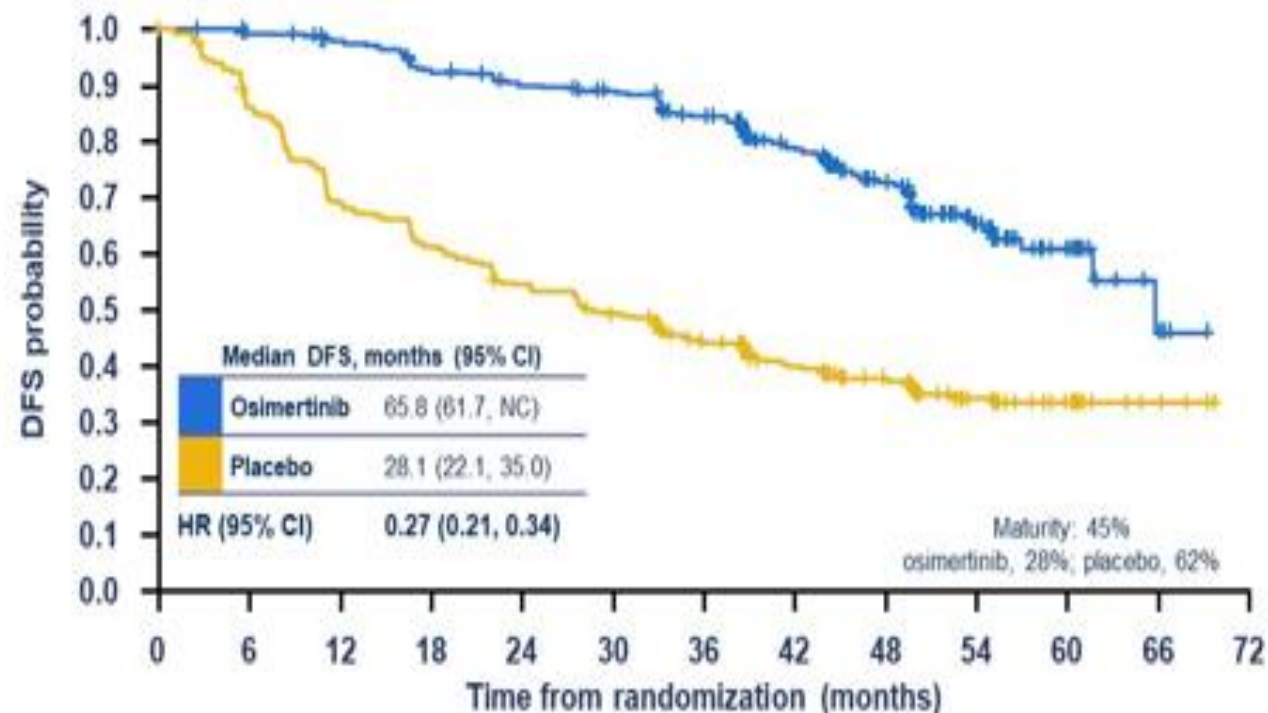
ADAURA primary DFS analysis (stage IB–IIIA)

NEJM October 2020



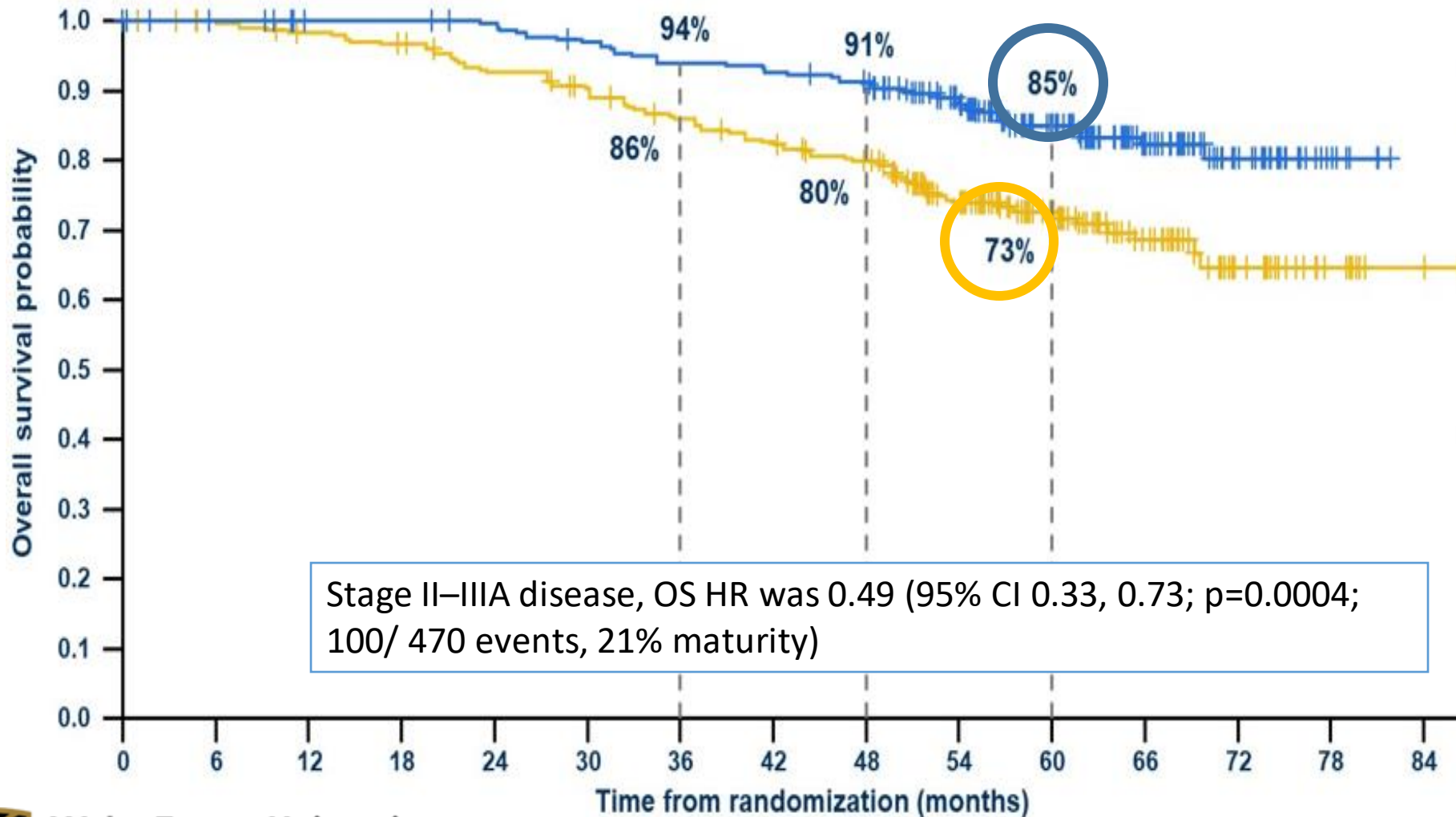
ADAURA updated DFS analysis (stage IB–IIIA)

JCO January 2023



Osimertinib Improves OS

5-year OS



Stage II–IIIA disease, OS HR was 0.49 (95% CI 0.33, 0.73; p=0.0004; 100/ 470 events, 21% maturity)

Stage IB–IIIA:
OS HR was 0.49
p=0.0001; 124/682
events, 18%
maturity)

5-year OS rate was
88% vs 78%

Median OS was not
reached in either
group

Expanding role in molecular profiling in non-metastatic NSCLC

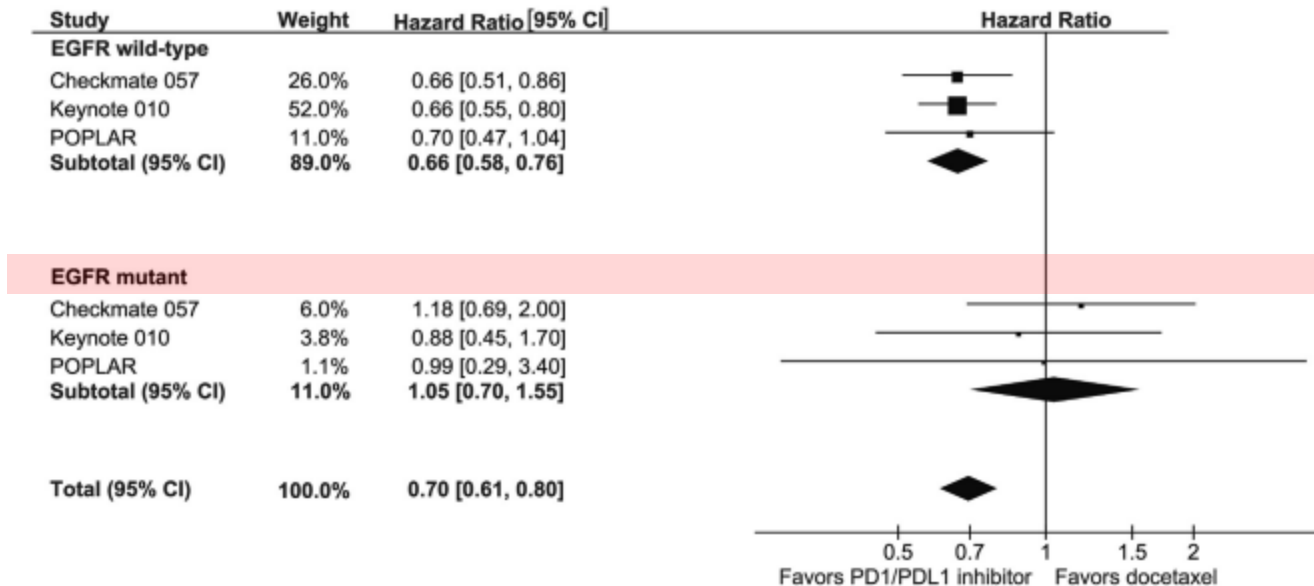
- Molecular testing allows for clear treatment options in the neoadjuvant/adjuvant therapies
- Identify situations where ICI may not be as safe or effective
- Provides prognostic and predictive information
- Provides opportunities for clinical trials
- Provides information which may save time and money at disease recurrence

Obtain tumor molecular profiling using NGS during the initial work up of all patients with non-squamous NSCLC.

Background

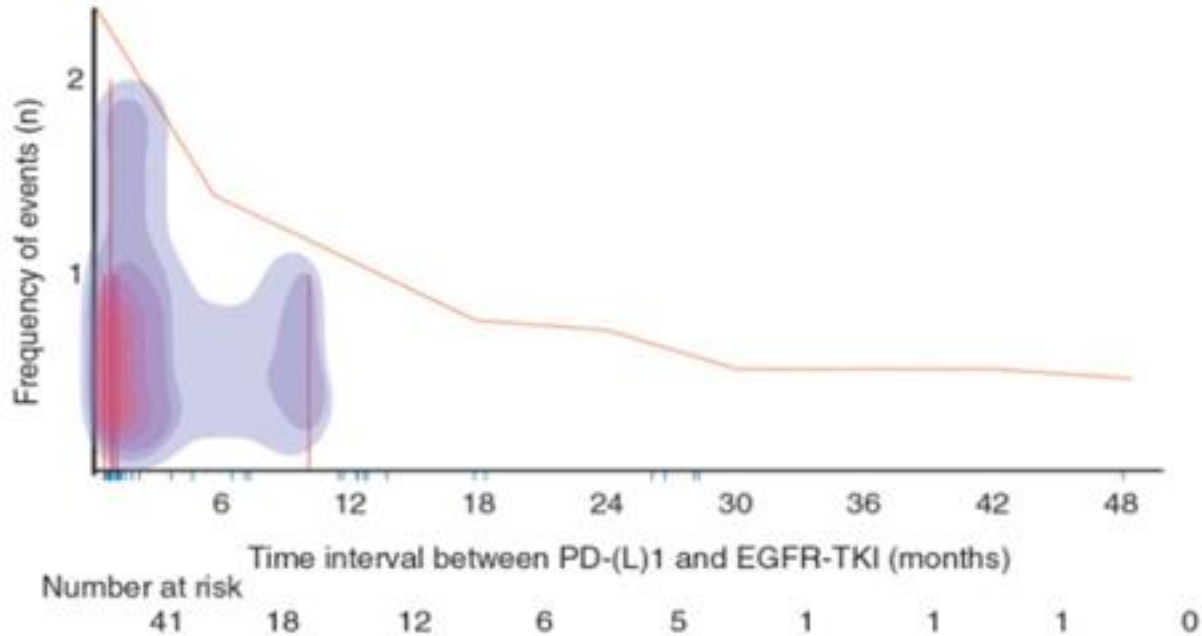
- Efficacy ICI in EGFR NSCLC is no better than chemo

- EGFR mutations were excluded in pivotal 1st line studies with ICI



CK Lee. JTO. 2017

ICIs are associated with excess toxicity if given in proximity to EGFR TKIs



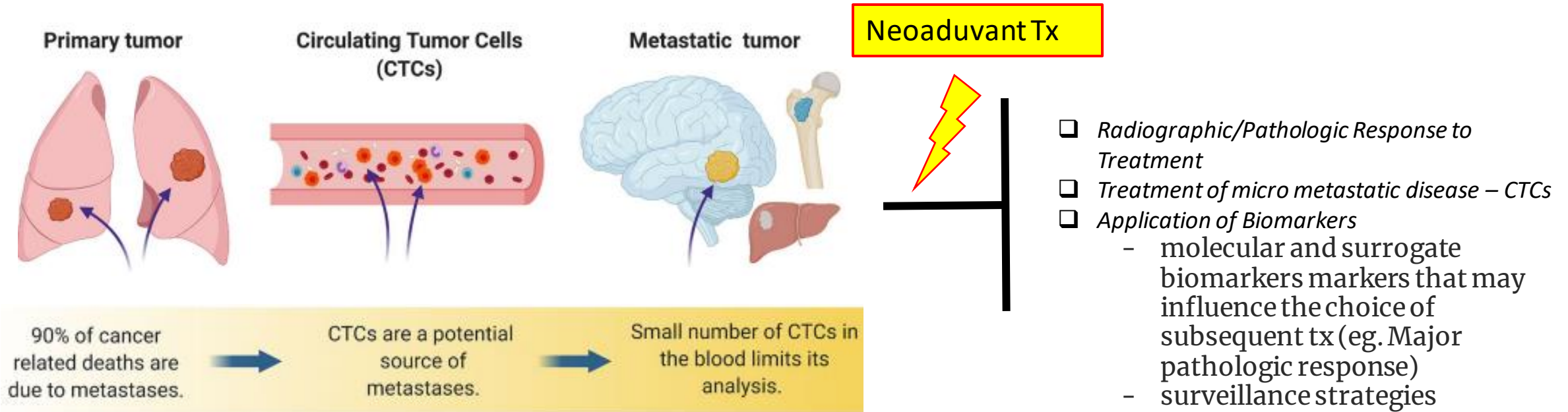
- Excess risk with Osimertinib + ICI (TATTON study)
- 35% rate of ILD/pneumonitis
- Osimertinib sequenced in the months after ICI therapy likely also carries increased risk of irAEs

Ahn et al. J Thorac Oncol. 2022

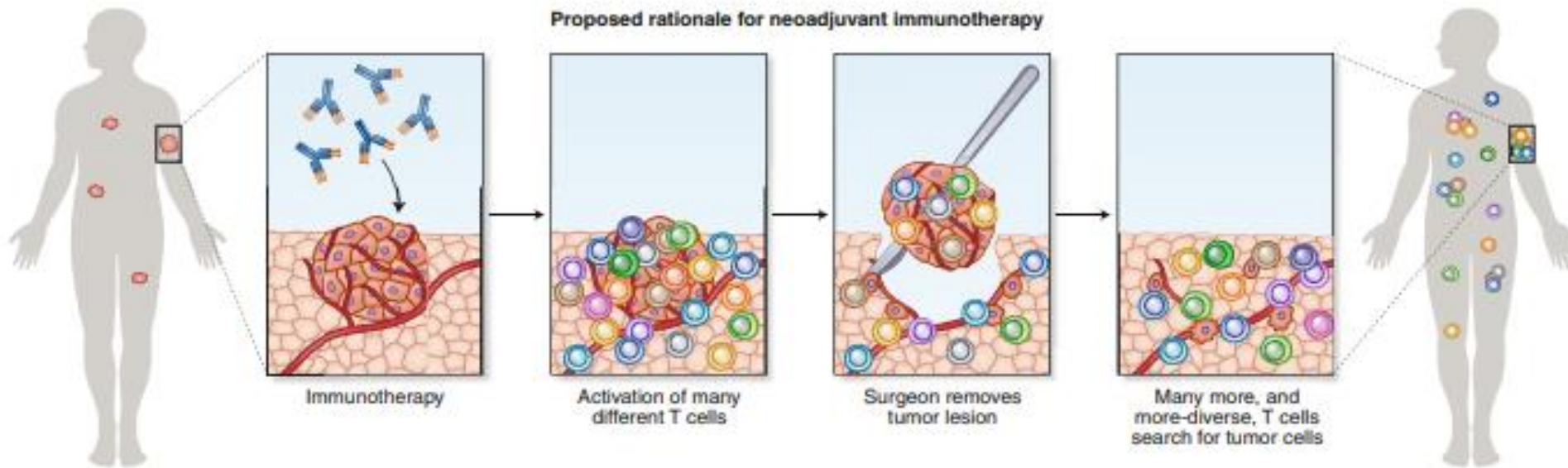
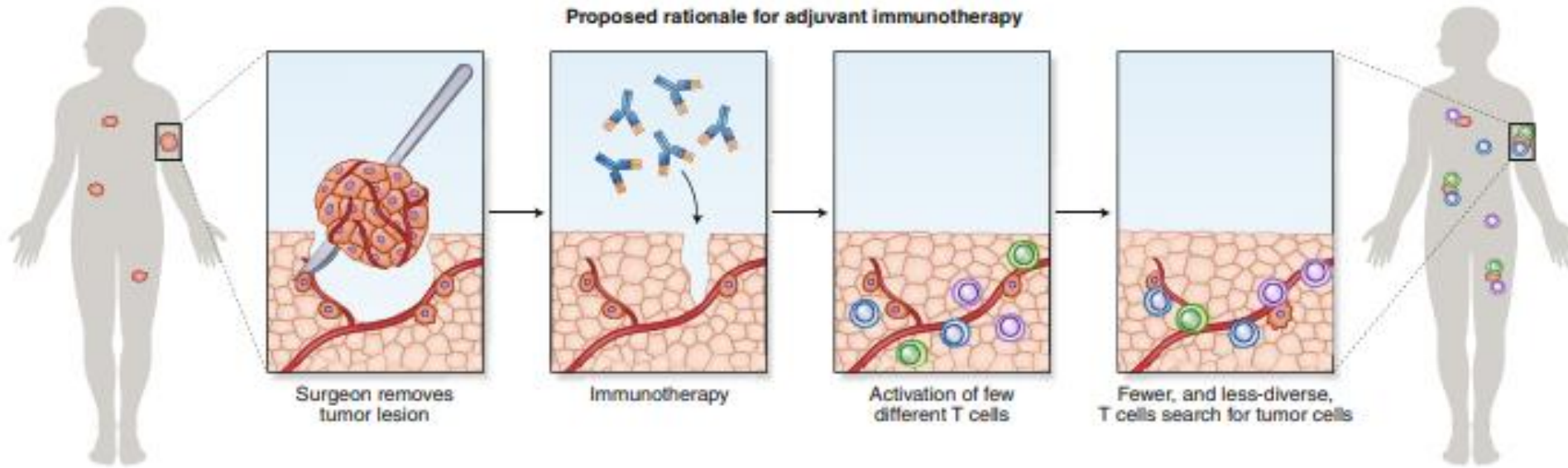
Schoenfeld et al. Annals of Oncology. 2019;30:839-44

Neoadjuvant therapy in the immunotherapy era

Rationale for neoadjuvant therapy

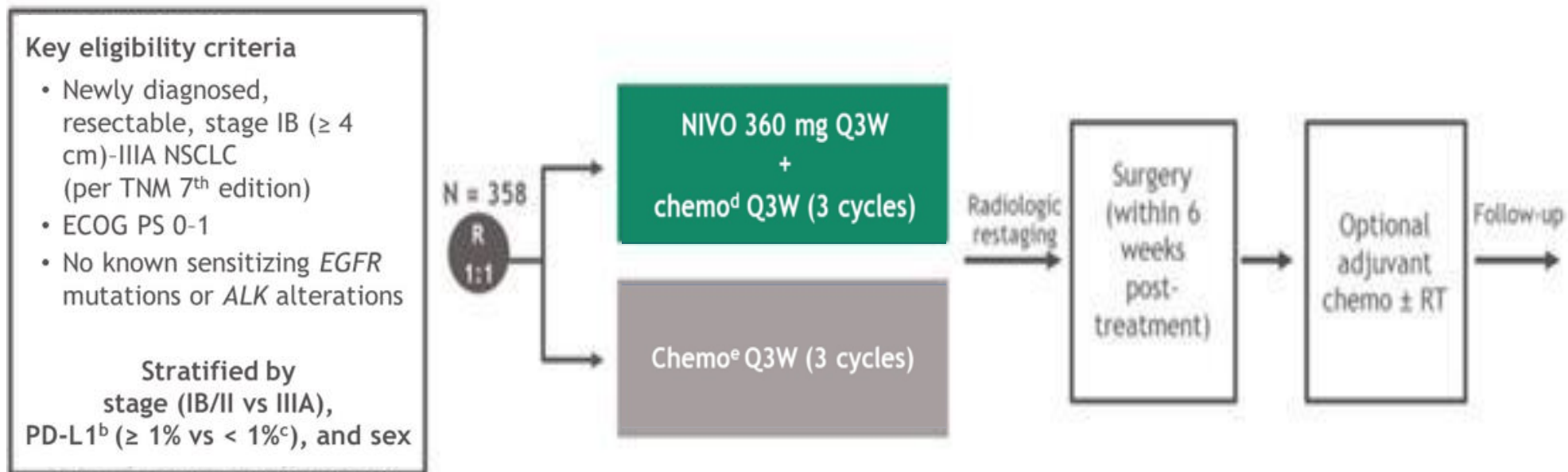


- (1) Tumor downsizing and better R0 resection rates
- (2) Micro metastatic disease improvements in DFS and OS
- (3) Intact tumor and primary lymphatics allow better T-cell priming (antigen source for T cell expansion)



Checkmate 816

Neoadjuvant nivolumab plus chemotherapy



Primary Endpoints:

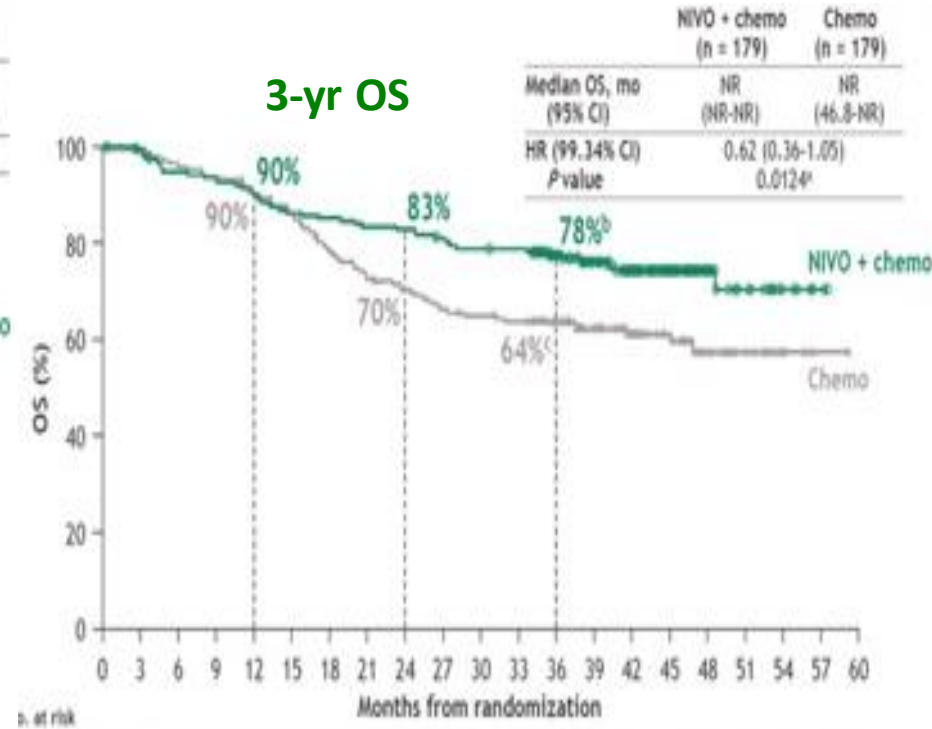
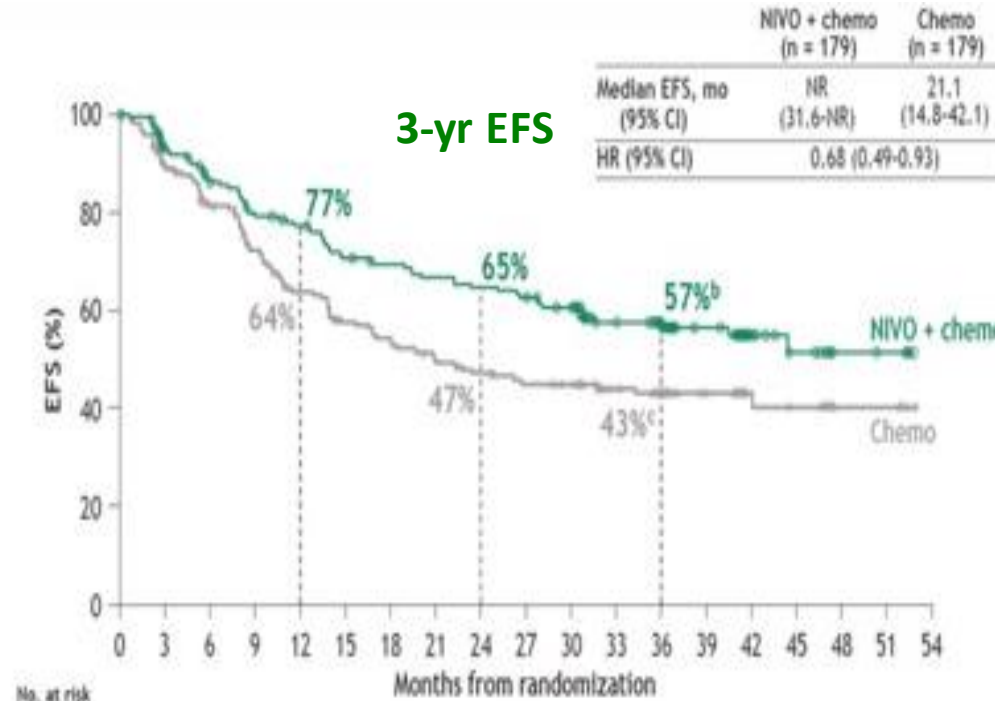
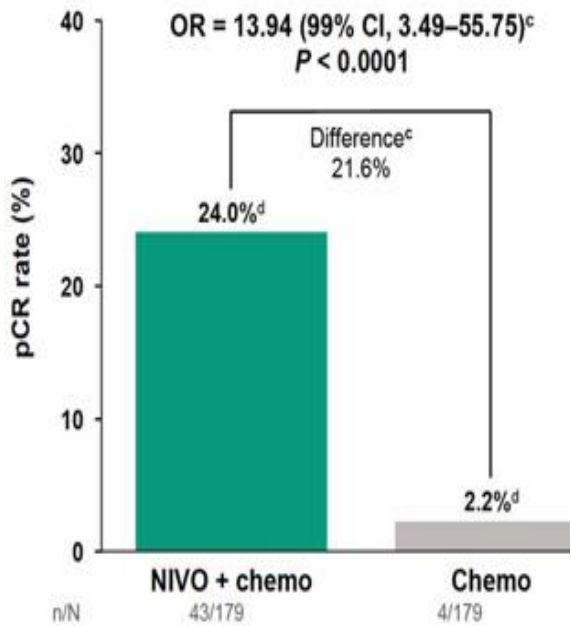
- MPR rate (<10% residual tumor) in PD-L1 expressors (≥1%) at definitive surgery

- Secondary: EFS, OS, and pCR in PD-L1 expressors (≥1%)

Checkmate 816

Neoadjuvant nivolumab plus chemotherapy – 3-year results

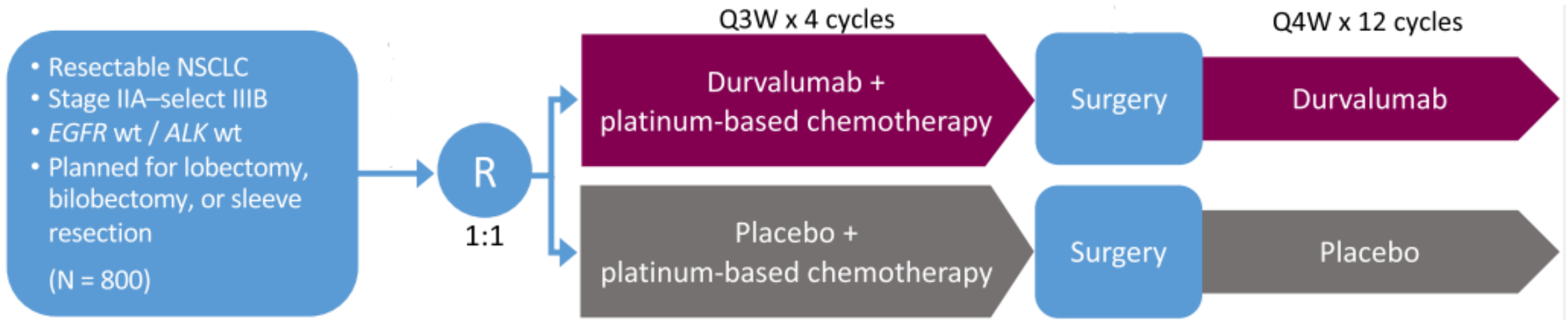
Primary endpoint: ITT (ypT0N0)



EFS benefit in overall population, increased benefit in PDL1 expression and with increased stage

AEGEAN

A phase 3 trial of neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in patients with resectable NSCLC

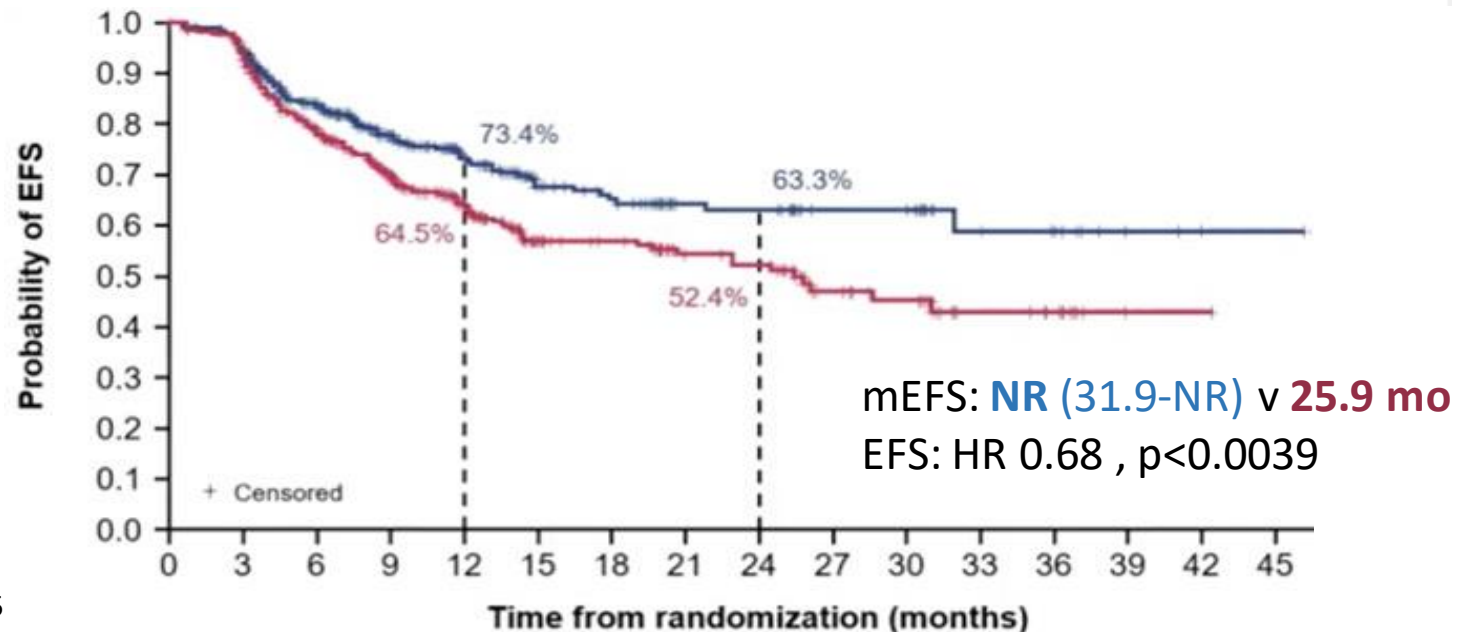


Primary endpoints

- pCR
- EFS

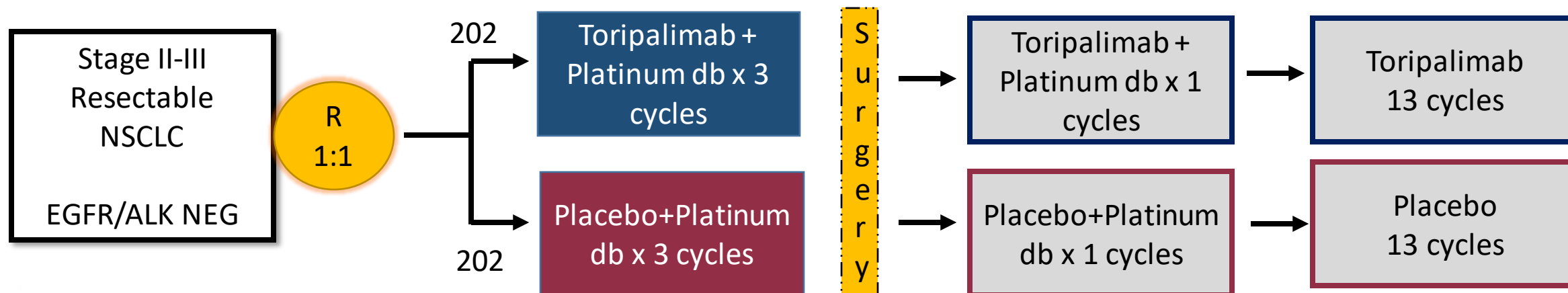
Secondary endpoints

- mPR
- DFS
- OS
- pCR, mPR, EFS, DFS, OS (PD-L1 TC $\geq 1\%$ group)



NEOTORCH

Perioperative toripalimab + platinum-doublet chemotherapy vs chemotherapy in resectable stage II/III non-small cell lung cancer (NSCLC): Interim event-free survival (EFS) analysis of the phase III Neotorch study



Primary endpoints:

- EFS by Investigator (stage III)
- EFS by Investigator (stage II-III)
- MPR by BIPR (stage III)
- MPR by BIPR (stage II-III)

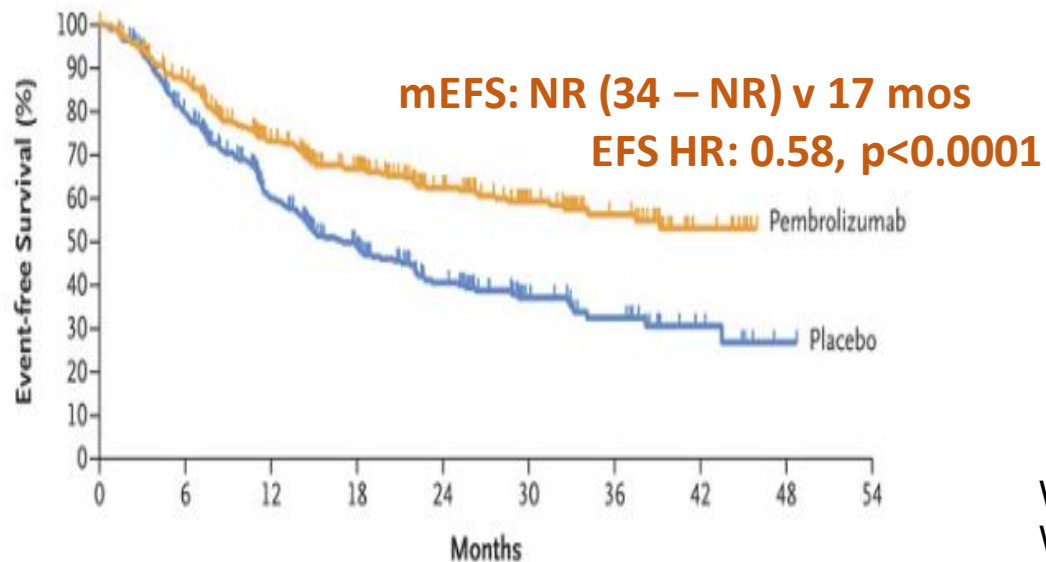
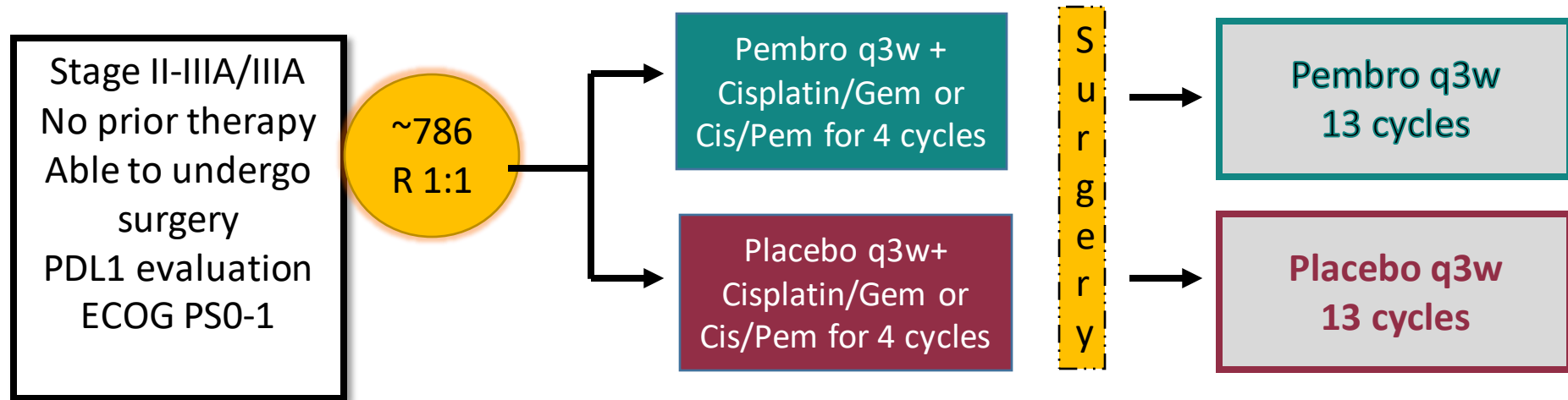
Secondary Endpoints:

- Overall survival
- pCR by BIPR/site pathologist for stage III and stage II-III

- Toripalimab is an anti-PD-1 monoclonal antibody
- 1/3 Stage IIIB disease
- Median follow-up = 18.3 months
- 2 yr EFS 64.7 v. 38.7
- EFS HR=0.40, 95% CI (0.277-0.565); P<0.0001
- mEFS NR vs 15.1 months
- pCR 57% vs 2%

KEYNOTE

Randomized, double-blind, phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC



- 70% stage III, 15% stage IIIB (N2)
- Major pathological response = 30.2% v 11%; P<0.0001
- Pathological complete response = 18.1% v 4.0%, P<0.0001

Wakelee H et al. JCO. ASCO Abstract 2023 (LBA100)

Wakelee H et al. NEJM. 2023

Operative Immunotherapy

Neoadjuvant



Checkmate 816
(IB-III A)



Perioperative

KN-671
(IIB-III A)



AEGEAN
(IIA-IIIB)



Neotorch
(IIA-IIIB)



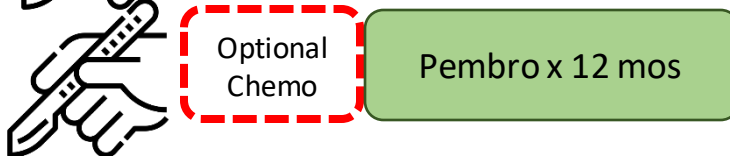
Adjuvant



IMpower010
(IB-III A)



Keynote 091
(IB-III A)



In Conclusion

Advances have been made in resectable NSCLC

Selection and sequencing of multimodality therapy for early-stage lung cancer will require multidisciplinary review

Immunotherapy

Adjuvant and Neoadjuvant chemo-IO have changed the management strategy of resectable NSCLC

Tailored approach Needed

- **PDL1 score**
- **Stage**
- **Other Biomarkers**
- **pCR**
- **CTC or other biomarkers**

Precision Oncology

Upfront tumor molecular profiling is critical for treatment decision making in early-stage NSCLC

Extra Slides

Targeted Therapies for Biomarker-Positive NSCLC

