Management of Borderline Resectable NSCLC

Gavitt Woodard, MD, FACS
Assistant Professor Thoracic Surgery
Yale School of Medicine

Charu Aggarwal, MD, MPH, FASCO
Leslye M Heisler Professor of Medicine
University of Pennsylvania

Disclosures

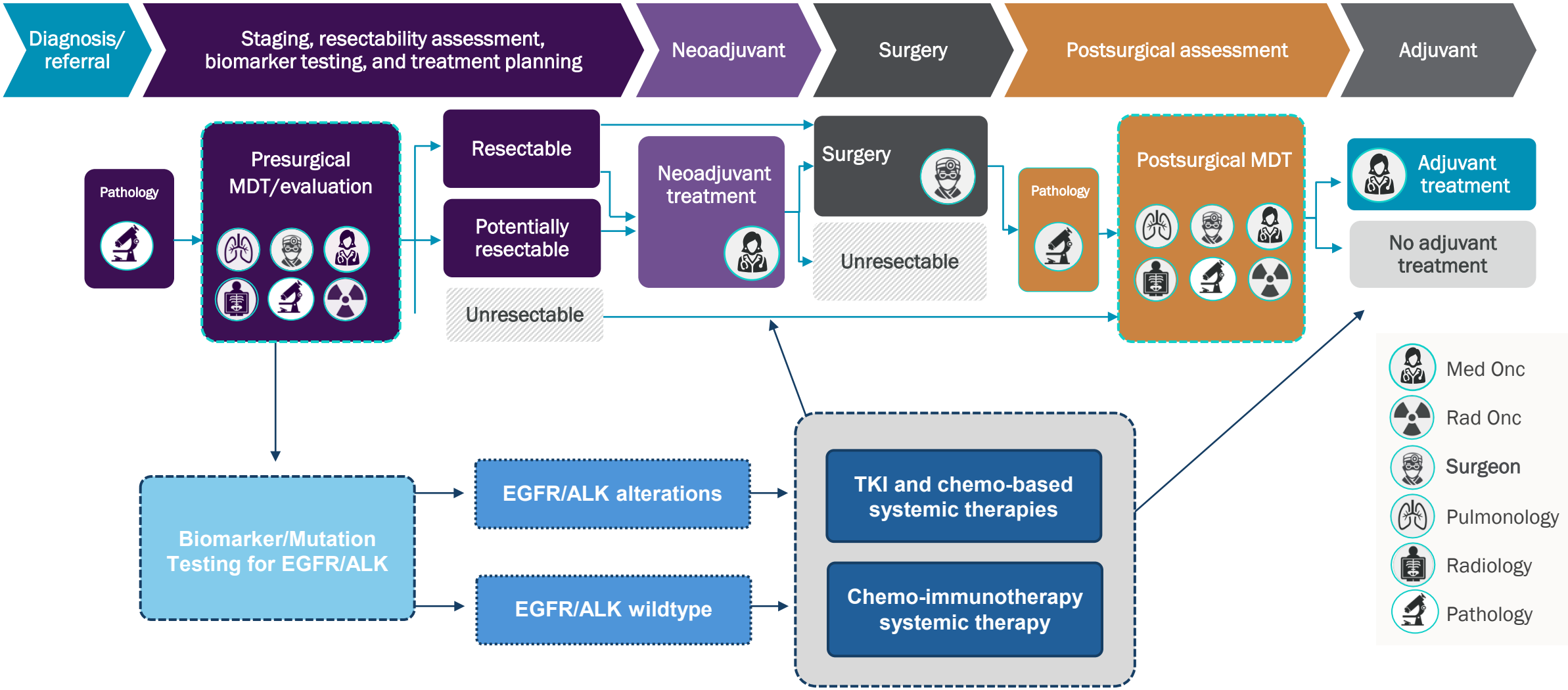
Gavitt Woodard

- Advisory board to AstraZeneca, Merck, Bristol Myers Squibb
- Joint patent holder on small molecule drug
- Research Funding Support: Braude Foundation Private Grant, Yale Cancer Center, #IRG 17-172-57 from the American Cancer Society, Yale SPORE in Lung Cancer (P50 CA196530), IASLC International Lung Cancer Foundation, Thoracic Surgery Foundation AstraZeneca Lung Cancer Research Grant, LUNGevity Career Development Award

Charu Aggarwal

- Consultant: AbbVie, AstraZeneca, Daiichi Sankyo / AstraZeneca, Gilead Sciences, Novocure, Pfizer
- Research funding, paid to University of Pennsylvania: AstraZeneca / MedImmune, Candel Therapeutics,Daiichi Sankyo / AstraZeneca, Genmab, Loxo@Lilly, Merck Sharp & Dohme

Importance of an MDT discussion and biomarker testing in NSCLC treatment planning



Factors that Determine Surgical Resectability

- **Surgical (technical) resectability**
  - Feasibility of R0 resection
  - Extent of reconstruction
  - Predicted postoperative functional reserve/ quality of life
- **Medial operability**
  - PFTs
  - Performance status / frailty / age
  - Baseline physiology (VO_2, 5-min walk test, quantitative V/Q, ECOG, nutritional status, overall exercise tolerance, lifestyle, comorbidities, etc)
- Surgeon / hospital experience and risk tolerance (highly variable)
- Patient wishes and risk tolerance (highly variable)
- Understanding of alternatives and competing cancer control/risk profile characteristics

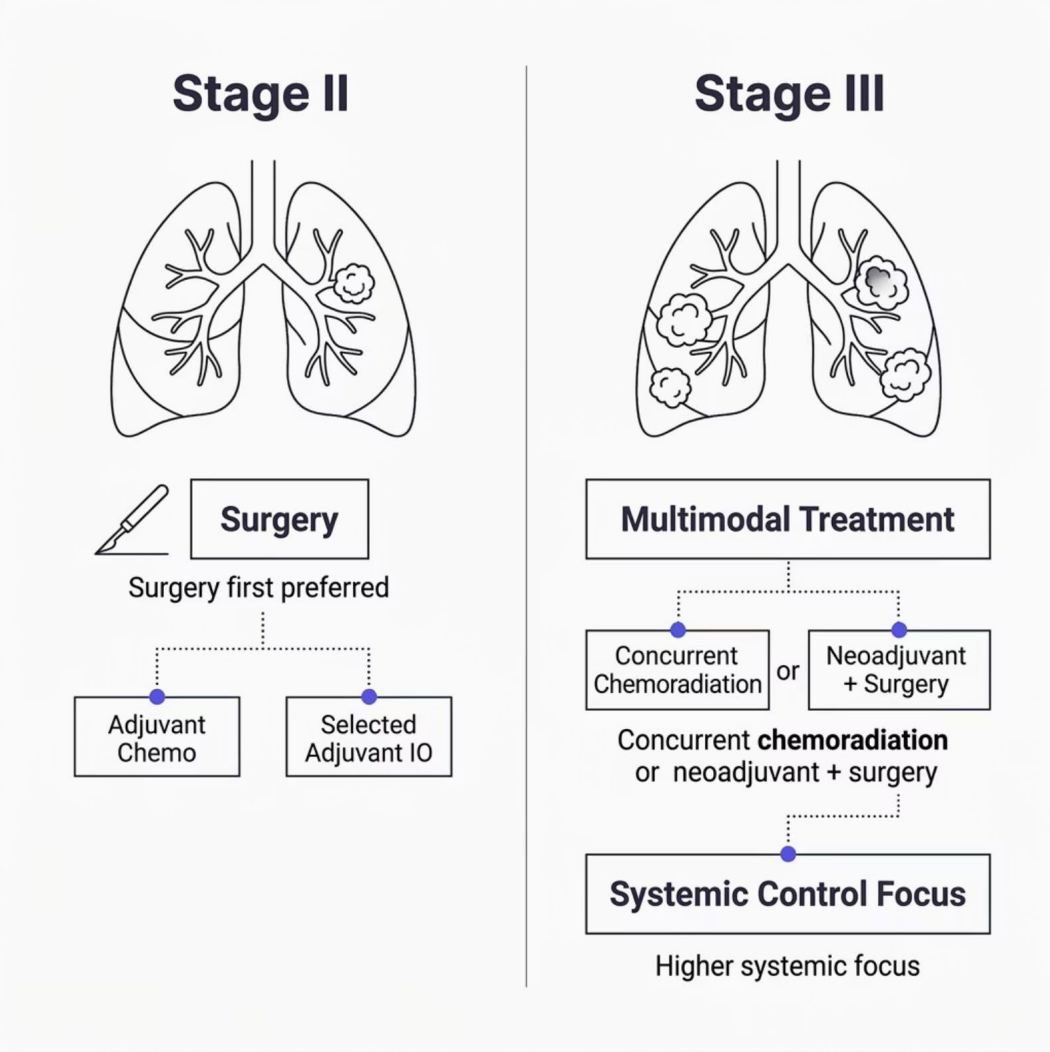
EORTC-Lung Group Initiative Consensus Definition of Stage III NSCLC Resectability

	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

***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

Brandao, M et al. WCLC 2023.

Stage II vs Stage III NSCLC



- **Stage II:** Surgery-first was the dominant paradigm when resectability is unambiguous; **neoadjuvant strategies are increasingly considered**
- **Stage IIIA:** Requires multidisciplinary input; neoadjuvant chemo-IO gaining traction
- **Stage IIIB/C:** Typically unresectable; concurrent chemoradiation ± durvalumab is standard

The boundary between "resectable" and "borderline "borderline resectable" Stage III remains one of the of the most contested decisions in thoracic oncology oncology

Neoadjuvant, Adjuvant, and Perioperative Immunotherapy

FDA Approved Immunotherapy Approaches in Resectable NSCLC

Neoadjuvant Immunotherapy	
CheckMate -816	Nivolumab + chemo x 3 cycles

→ **SURGERY**

SURGERY →

Adjuvant Immunotherapy	
IMpower010	Chemo → atezolizumab ~1 y (PD-L1 ≥1%)
KEYNOTE-091	Chemo (optional) → pembrolizumab ~1 year

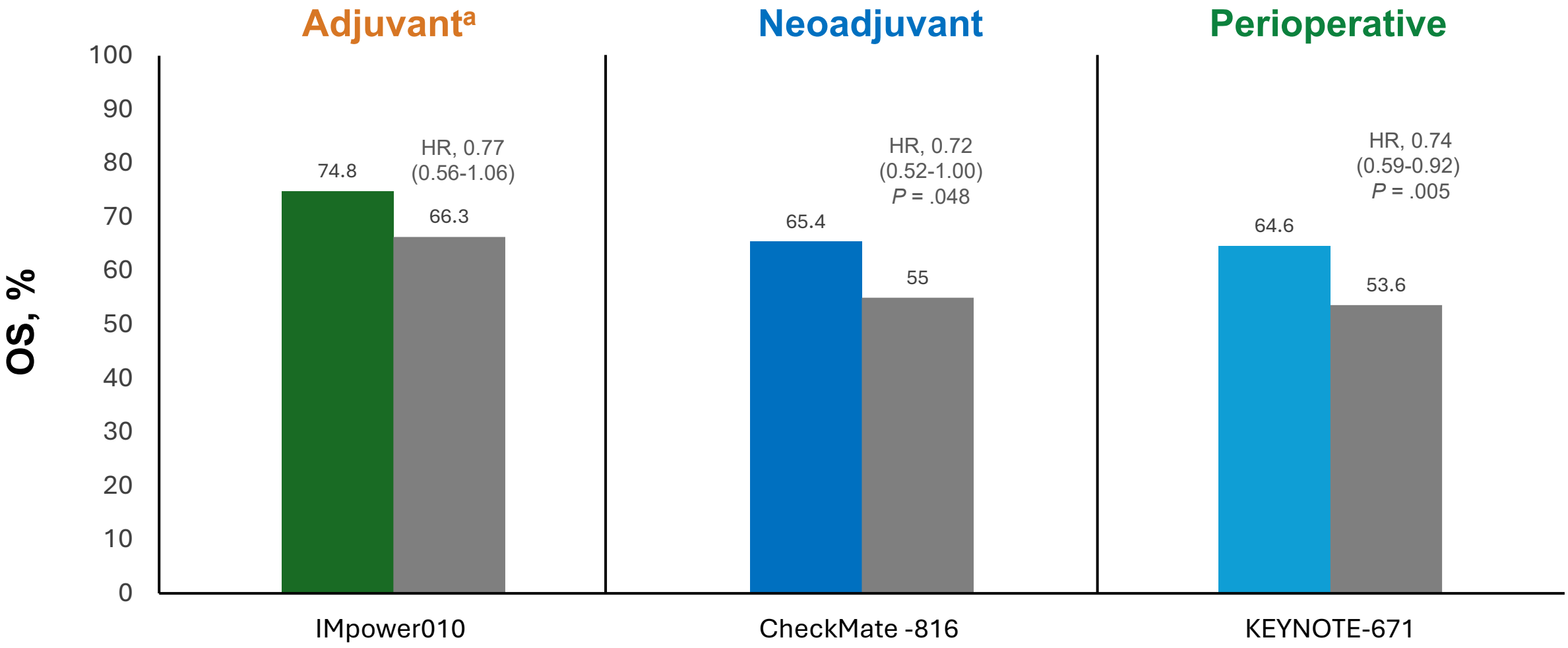
Study	Neoadjuvant Regimen		Adjuvant Regimen
AEGEAN	Durvalumab + chemo x 4 cycles		Durvalumab ~1 year
CheckMate -77T	Nivolumab + chemo x 4 cycles	→ **SURGERY** →	Nivolumab ~1 year
KEYNOTE-671	Pembrolizumab + chemo x 4 cycles		Pembrolizumab ~1 year

Adjuvant, Neoadj, and Periop Immunotherapy Trials

Trial	IMpower010[1]	KEYNOTE-091[2]	CheckMate -816[3]	AEGEAN[4]	Neotorch[5]	KEYNOTE-671[6]	CheckMate -77T[7]	RATIONALE-315[8]
Timing	Adjuvant	Adjuvant	Neoadjuvant	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative
Size	1005	1177	358	802	500	797	461	453
Agent I/O	Atezolizumab (PD-L1)	Pembrolizumab (PD-1)	Nivolumab (PD-1)	Durvalumab (PD-L1)	Toripalimab (PD-1)	Pembrolizumab (PD-1)	Nivolumab (PD-1)	Tislelizumab (PD-1)
No. cycles	16	18	3	16	17	13	16	12
Inclusion	Completely resected IB (≥ 4cm)-IIIA (7^{th})	Completely resected IB (≥4cm)-IIIA (7^{th}); R0	Resectable IB (≥4cm)-IIIA (7^{th})	Resectable IIA-IIIB [N2] (8^{th}) by lobectomy	Resectable II-IIIB (8^{th})	Resectable II-IIIB [N2] (8^{th})	Resectable IIA (>4 cm)-IIIB [N2] (8^{th})	Resectable II-IIIA (8^{th})
Stage IB+II/III, %	59 / 41	72 / 28	36 / 64	29 / 71	20 / 80*	30 / 70	35 / 65	41 / 59
Primary endpoint	DFS hierarchical	DFS, DFS (PD-L1 ≥50%)	pCR, EFS	pCR, EFS	MPR, EFS	EFS, OS	EFS	EFS, MPR
Chemotherapy	Cisplatin doublet	Platinum doublet encouraged	Platinum doublet	Platinum-based	Platinum-based	Cisplatin doublet	Platinum doublet	Platinum doublet
EGFR/ALK	Included (15%)	Included (7.4%)	No documented mutation (WT: Asia)	No documented mutation	WT	Included (7%)	No *EGFR*, no documented *ALK*	WT

1. Felipe E et al. *Lancet*. 2021;398:1344-1357. 2. O'Brien M et al. *Lancet Onc*. 2022;23:1274-1286. 3. Forde P et al. *N Engl J Med*. 2022;386:1973-1985.
4. Heymach J et al. AACR 2023. Abstract CT005. 5. Lu S et al. ASCO 2023. Abstract 8501. 6. Wakelee H et al. *N Engl J Med.* 2023;389:491-503.
7. Cascone T et al. ESMO 2023. Abstract LBA1. 8. Yue D et al. ELCC 2024. Abstract 1080.

Adjuvant, Neoadjuvant, Perioperative Overall Survival[1-3]



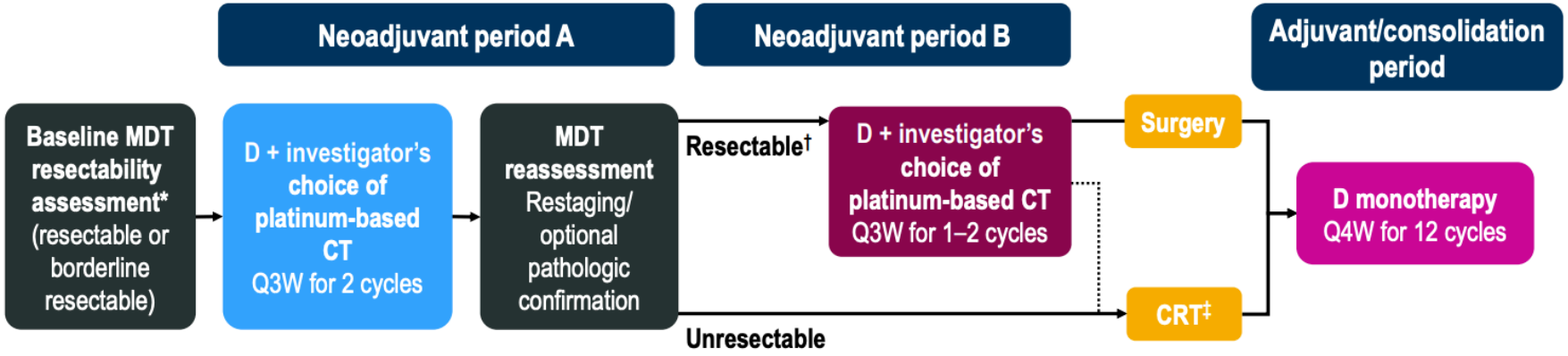
[a] Stage II-IIIA PD-L1 TC 50%, excluding patients with known *EGFR/ALK* alterations.

1. Wakelee HA et al. ASCO 2024. Abstract LBA8035. 2. Forde PM et al. ASCO 2025. Abstract LBA8000. 3. Wakelee. H, et al. ESMO 2025. Abstract LAB67.

MDT-BRIDGE: Neoadjuvant Durva + CT and MDT Could Allow More Patients to Receive Curative-Intent Treatment (Surgery or CRT)

Key inclusion criteria and study requirements

- Aged ≥18 years
- Previously untreated and pathologically confirmed, resectable or borderline resectable, stage IIB–IIIB NSCLC (per AJCC 8th edition[2])
- *EGFR*/*ALK*wt (per local test)
- WHO/ECOG PS 0–1
- At least 1 target lesion not previously irradiated
- Pre-operative RT not allowed



Primary endpoint

- Resection rate, defined as proportion of all patients who underwent definitive surgery

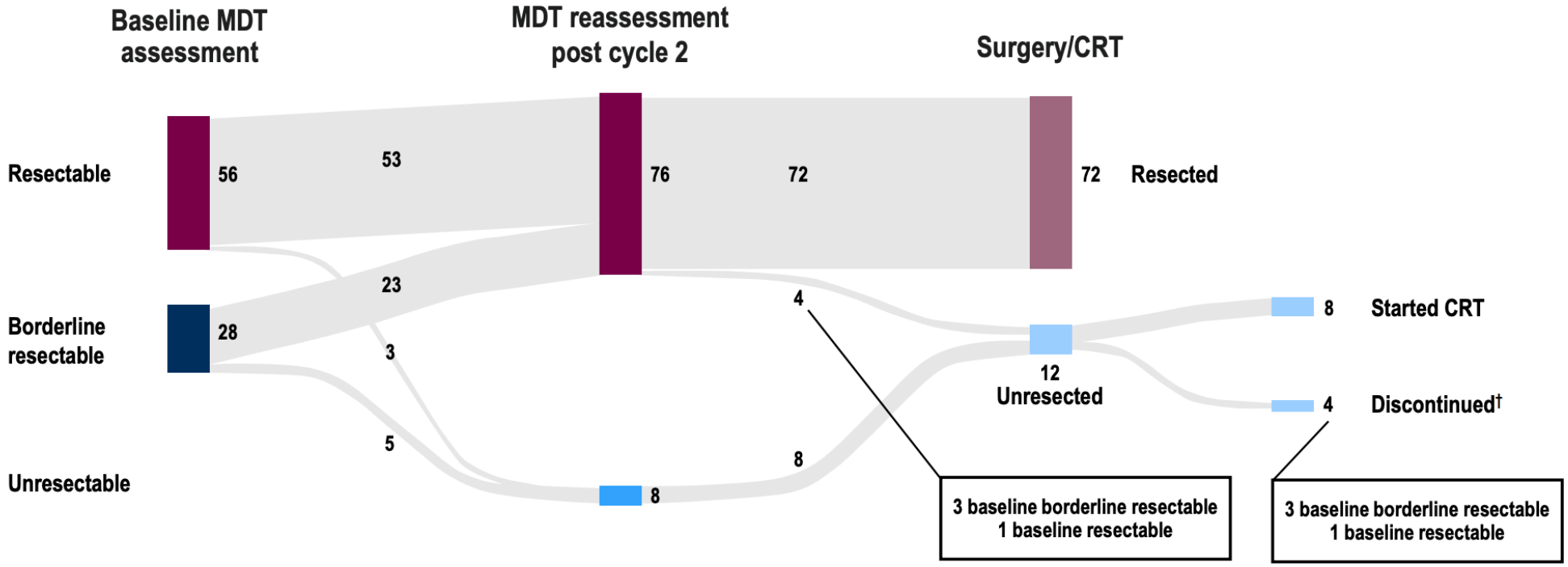
Secondary endpoints

- Resection rate in patients deemed resectable/borderline resectable at baseline
- Surgical outcomes in patients who underwent surgery
- ORR in patients deemed resectable/unresectable at reassessment
- pCR in patients deemed resectable at reassessment
- Safety

- This planned interim analysis (DCO 8 May 2025) was conducted in the subset with sufficient follow-up, defined as patients who have had the opportunity to be followed up for 6 months or undergo definitive surgery, including patients who discontinued the study for any reason or died (**efficacy subset, N=84**)
- Safety was analysed in all patients who had received ≥1 dose of study treatment at the time of the DCO (**safety population, N=131**)

Reck M, et al. ESMO 2025. Abstract LAB65.

MDT-BRIDGE: Neoadjuvant Durva + CT and MDT Could Allow More Patients to Receive Curative-Intent Treatment (Surgery or CRT)

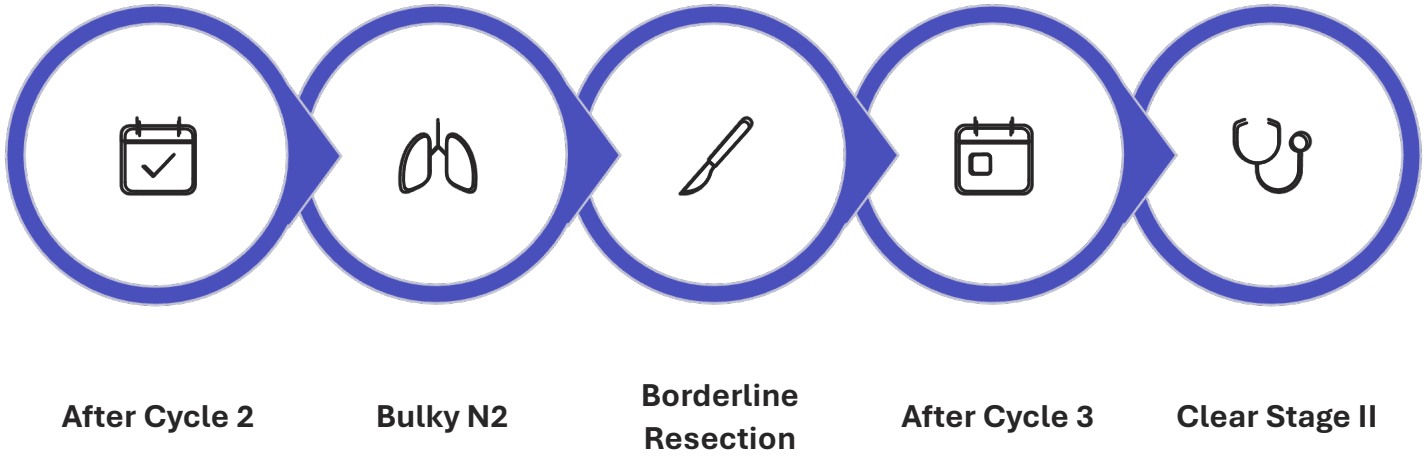


Most baseline borderline resectable were reassessed as resectable after 2 cycles

95.2% had either surgery or CRT after neoadjuvant D + CT

Reck M, et al. ESMO 2025. Abstract LAB65.

Response Assessment: Who Gets Scans and When?

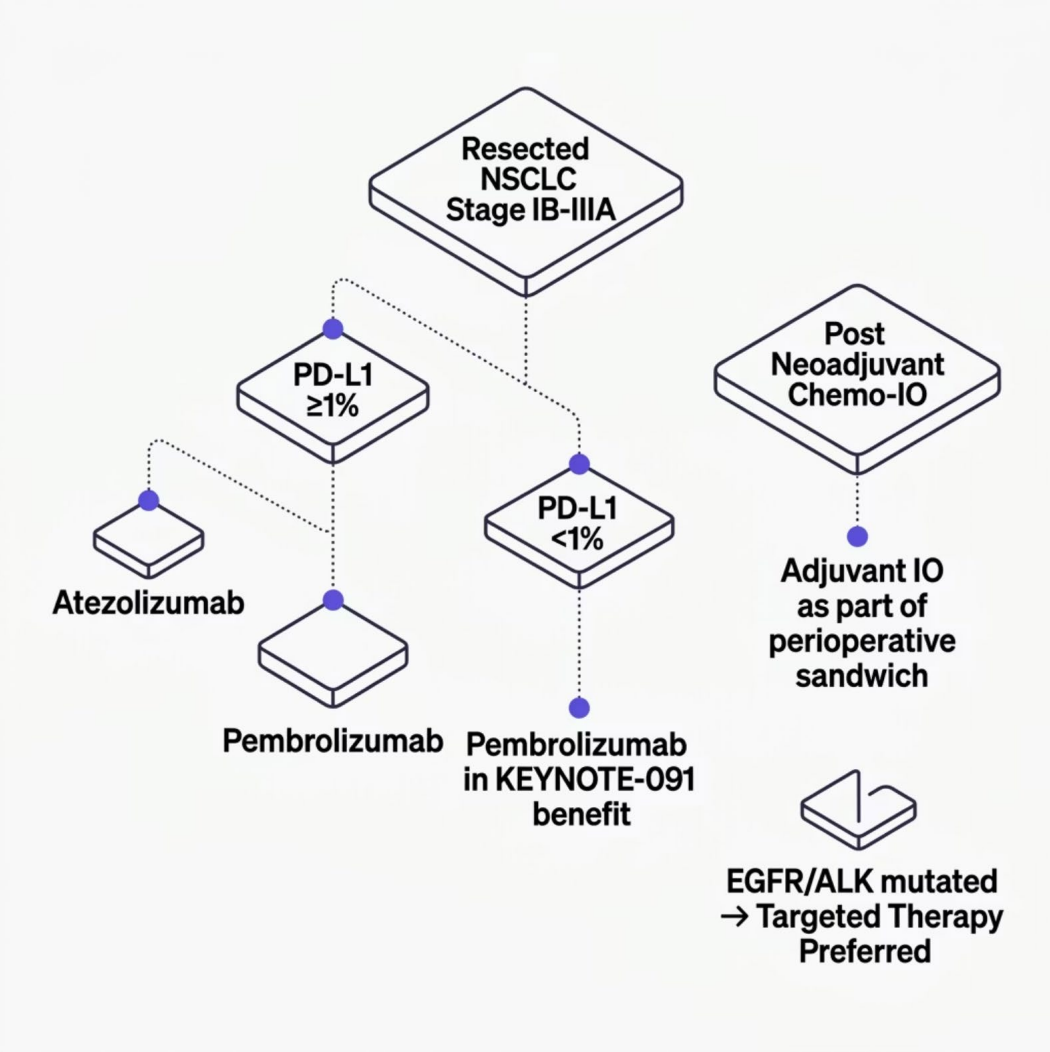


Clinical Rationale

- **After 2 cycles:** Warranted when resectability is uncertain — early identification of progression avoids delays to surgery or a pivot in strategy
- **After 3 cycles:** Acceptable in clearly resectable disease with low radiologic risk; allows fuller systemic exposure before reassessment
- Neither approach is uniformly codified — institutional protocols vary widely

An algorithmic, MDT-driven scan protocol reduces variability and ensures timely surgical planning.

Who Gets Adjuvant Immunotherapy?



Key Principles

- Adjuvant IO is most clearly indicated in **PD-L1 ≥1%, Stage II–IIIA** resected NSCLC
- Avoid adjuvant IO in **EGFR/ALK-positive** tumors — targeted therapy is preferred
- In the perioperative sandwich model, adjuvant IO completes systemic coverage initiated pre-operatively
- Benefit in PD-L1-negative patients remains less robust — individualize decision

Key Takeaways for the MDT

01

Stage II vs III: Individualize

Don't default to surgery-first in all Stage II — assess tumor biology, nodal risk, and systemic therapy readiness at MDT.

02

Perioperative Is the New Standard

Both CheckMate 816 and AEGEAN support chemo-IO sandwiching surgery. Select regimen based on histology, PD-L1, and institutional experience.

03

Standardize Scan Timing

Build a protocol: scan at Cycle 2 for high-risk/borderline cases, Cycle 3 for clearly resectable disease. Reduce variability with MDT governance.

04

Adjuvant IO: Biomarker-Driven

Prioritize PD-L1 ≥1%, Stage II–IIIA, EGFR/ALK-negative patients. In perioperative protocols, adjuvant IO completes the treatment arc.