

Surgical Treatment of Locoregionally Advanced NSCLC in Era of Immunotherapy/Targeted Therapy

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Objectives

- To understand the benefits of neoadjuvant and perioperative chemoimmunotherapy for NSCLC
- To understand the risks of operation for lung cancer
- To understand the benefits and limitations of surgery for patients with mediastinal nodal spread.

Division of Thoracic and Esophageal Surgery



Philip Linden, MD

Chief, Division of Thoracic Surgery
Professor of Surgery
Surgical Director, Thoracic Oncology Program

Training : Brigham and Women's Hospital

Expertise: VATS/RATS Surgery, esophageal and lung cancer



Christopher Towe, MD

Director, Chest Wall Disease Program

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Expertise: VATS/RATS Surgery, chest wall surgery, database research

Locations: CMC and Parma



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Director, Thoracic Airway Program

Training : Massachusetts General Hospital

Expertise: VATS/RATS surgery, airway surgery

Locations: CMC and Lake West

Division of Thoracic and Esophageal Surgery



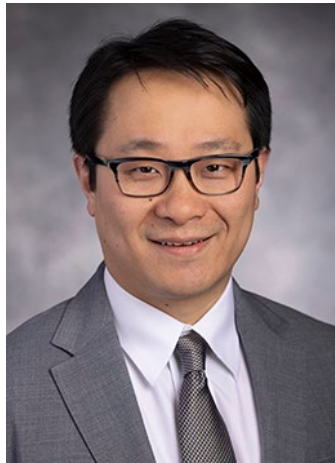
Jillian Sinopoli, DO

Director, Thoracic Education

Training : Brigham and Women's Hospital

Expertise: VATS/RATS Surgery, lung and esophageal surgery

Locations: Cleveland and Beachwood

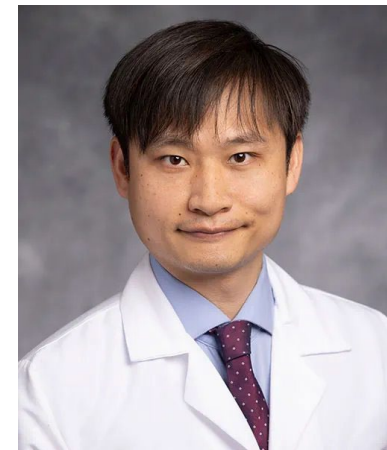


Bo Jiang MD

Training: Case Western, Cleveland Medical Center

Expertise: Minimally Invasive VATS/RATS

Locations: Elyria and Cleveland



Xun Luo MD

Training: UH CMC and West Virginia University

Expertise: Minimally Invasive Thoracic Surgery

Locations: Cleveland and Parma

UH CMC Thoracic Quality Data

- **Lobectomy – 3 star program**

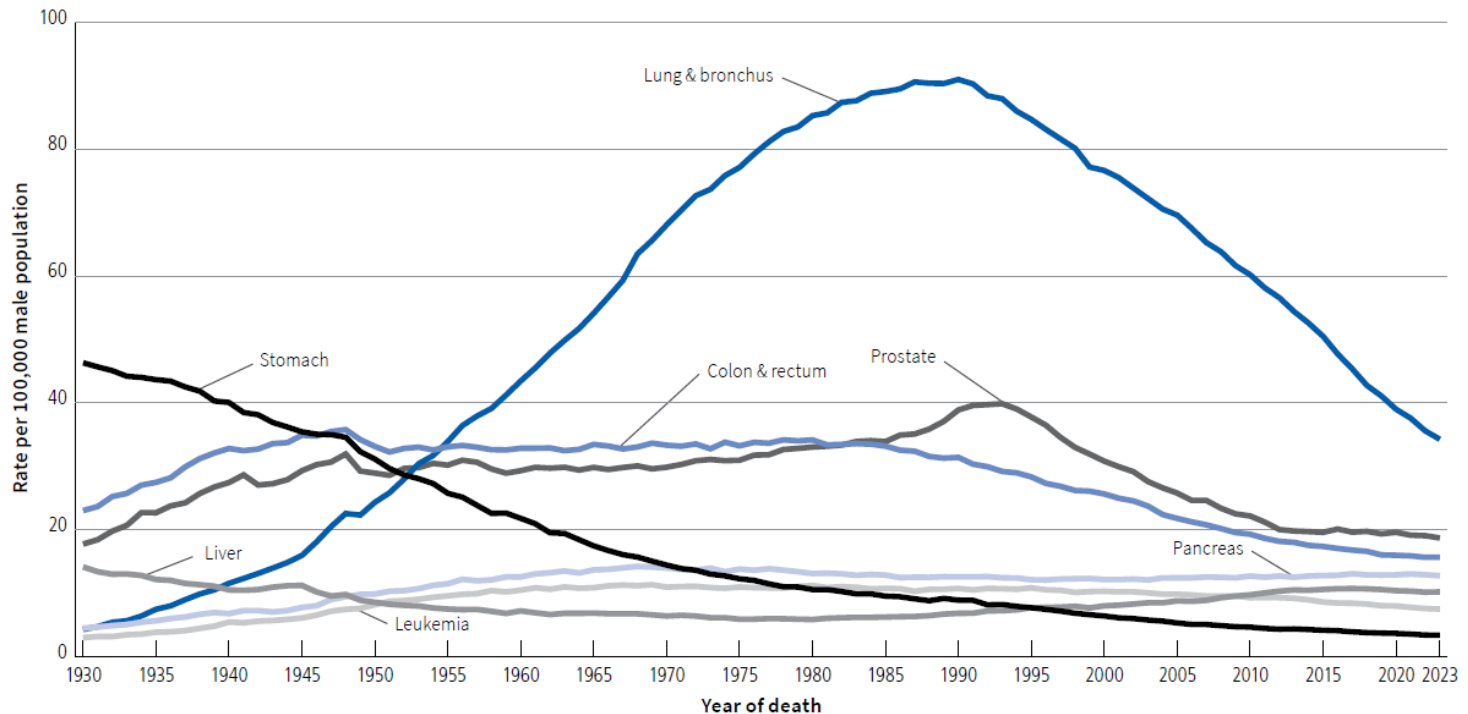
- Perioperative Mortality 0.4% CMC vs. 1.3% STS
- Median length of stay 3.0 days CMC vs. 4.0 days STS
- Stage I lobectomy performed minimally invasively
 - 94% CMC vs. 74% STS
- Risk Adjusted Combined mortality/major morbidity for lung resections:
 - 18% lower than STS average*

- **Esophagectomy – 3 star program**

- Perioperative mortality 0.7% CMC vs. 3.5% STS
- Median length of stay 7.0 days CMC vs. 10.0 days STS
- Risk Adjusted Combined mortality/major morbidity
 - 35% lower than STS average

NSCLC Death Rate

Figure 1. Trends in Age-adjusted Cancer Death Rates by Site, Males, US, 1930-2023



Rates are age adjusted to the 2000 US standard population. Due to historical improvements in classification, lung & bronchus includes pleura, trachea, mediastinum, and other respiratory organs; colon & rectum includes small intestine; and liver includes intrahepatic bile duct, gallbladder, and other biliary sites.

Data source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2023, National Center for Health Statistics, Centers for Disease Control and Prevention.

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NSCLC Regional Disease Survival

Table 8. Five-year Relative Survival Rates (%) by Stage at Diagnosis, US, 2015-2021

	All stages	Local	Regional	Distant		All stages	Local	Regional	Distant
Breast (female)	92	>99	87	33	Non-Hodgkin lymphoma	74	87	78	67
Colon & rectum ^a	65	91	74	15	Oral cavity & pharynx	69	88	69	37
Colon ^a	63	91	74	13	Ovary	52	92	71	32
Rectum	67	90	74	18	Pancreas	13	44	17	3
Esophagus	22	49	28	5	Prostate	98	>99	>99	38
Kidney & renal pelvis	79	93	76	19	Stomach	38	77	37	8
Larynx	62	79	49	35	Thyroid	98	>99	98	50
Liver ^b	22	38	13	3	Urinary bladder ^c	79	73	41	9
Lung & bronchus	28	65	37	10	Uterine cervix	68	91	62	20
Melanoma of the skin	95	>99	76	35	Uterine corpus	81	95	70	19

Rates are adjusted for normal life expectancy and based on cases diagnosed in the SEER 21 areas, excluding Illinois, with follow-up through 2022.

^aExcludes appendix. ^bIncludes intrahepatic bile duct. ^cRate for in situ carcinoma is 98%. Stage classification based on Combined Summary Stage. **Local:** invasive cancer confined entirely to the organ of origin. **Regional:** cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

Data source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2025.

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Global Phase III Trials Neoadjuvant and Perioperative ChIO Stage II-III NSCLC

Trial	pCR	Event Free Survival (HR)	Overall Survival (HR)
Checkmate 816-Neo Nivo+Chemo vs. Chemo (3 cycles)	24.0% vs. 2.2%	HR 0.68 5 yr 49% vs. 34% Median 60 vs 21 months	5 yr 65% vs. 55% (HR 0.72)
Checkmate 77T Periop nivo + chemo (4 cycles) vs. Chemo	25.3% vs. 4.7%	HR 0.61 Median 46.6 vs. 17months	Not mature
AEGEAN (Durvalumab)	17.2% vs. 4.3%	HR 0.68	Not mature
KEYNOTE 671 (Pembrolizumab)	18.1% vs. 4.0%	HR 0.58 Median 57 vs. 18 months	5 yr 65% vs. 54% (HR0.74)

Checkmate 816 : Neoadjuvant ChIO

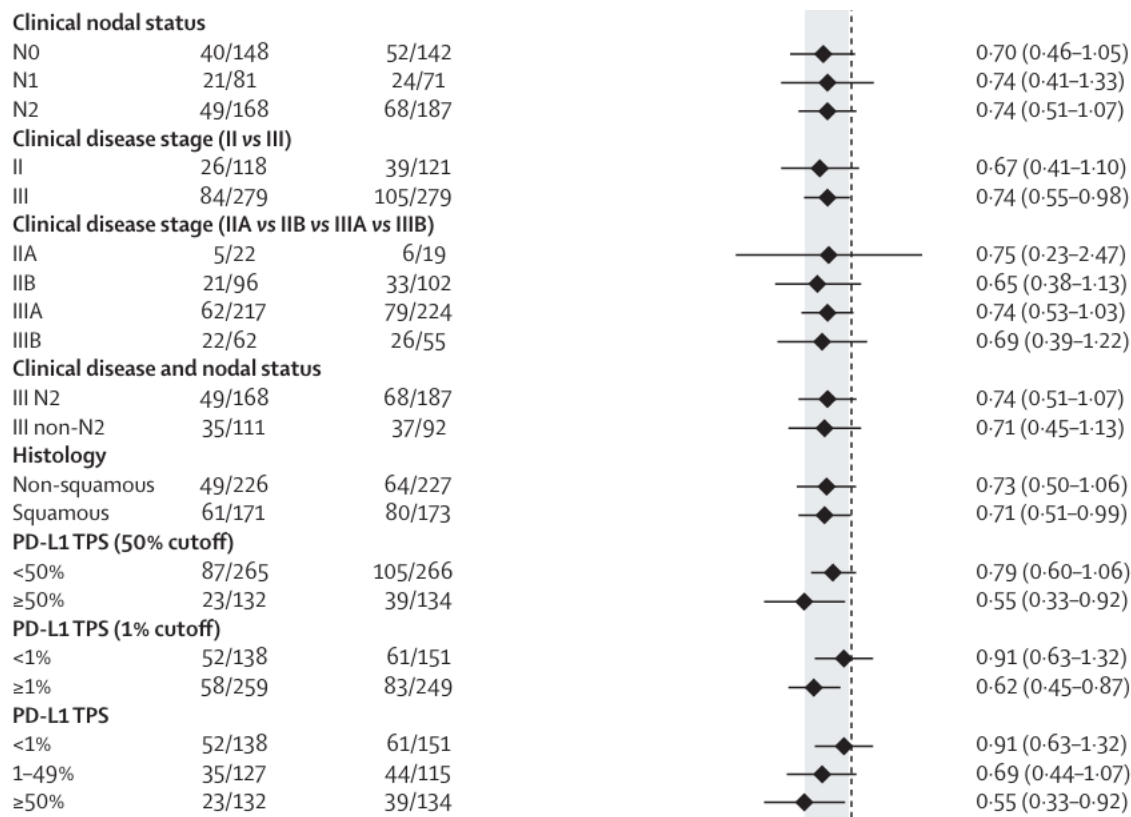
- 3 cycles neo Nivo/Chemo vs Chemo alone (also nivo/ipi arm)
- 50% squamous, 43% PDL1<1%, 63% stage IIIA
- pCR 24.0% vs. 2.2%
- **5 yr OS 65.4% vs 55.0% (HR 0.72)** (NEJM 2025;393(8):741)
- In **pCR group, 5 yr OS 95.3%** / Non pCR group, 5 yr OS 55.7%
- Greatest benefit in PDL 1 $\geq 50\%$, (HR 0.33 vs. 0.60)
- PDL <1% OS HR 0.89
- OS HR 0.39 with carboplatin, 0.81 cisplatin
- stage II OS HR 0.77 / stage III OS HR 0.70
- Squamous / non squamous HR identical

Checkmate 816 : Surgical Results

- About 80% progressed to resection; similar in both groups
- 60% Thoracotomy rate same with ChIO vs. Ch
- Duration of surgery shorter with ChIO vs. Ch
- Lower conversion rate with stage III, but higher with stage II
- Lower pneumonectomy rate ChIO group

Keynote 671 : Stage II/III patients : Pembro / cis-gem 4 cycles preop with yr adj pembro vs. chemo alone

- OS HR 0.72 (Spicer et al. Lancet 2024;404:1240)



Keynote 671: Surgical Results

- 30 d mortality 1.8% ChIO vs. 0.6% Ch
- 90 d mortality 4% ChIO, vs. 1.6% Ch
- R0 92% ChIO vs. 84% Ch

AEGEAN: Periop Durvalumab

Heymach. JCO.2026 Update. Median F/U 26 months

- 740 stage II/III randomized to 4 cycles preop and 1 yr postop
- 50% N2, 24% IIIB, 9% multistation N2
- OS not available
- EFS HR 0.69
 - Stage IIIA 0.60
 - Identical HR (0.69-0.71) for PDL1 <1%, 1-50 and >50

AEGAEN : Surgical Results

- 80% both arms progressed to surgery
- R0 92-95% both groups
- Mortality 1-2% both groups
- Similar 9% grade 3-4 complications

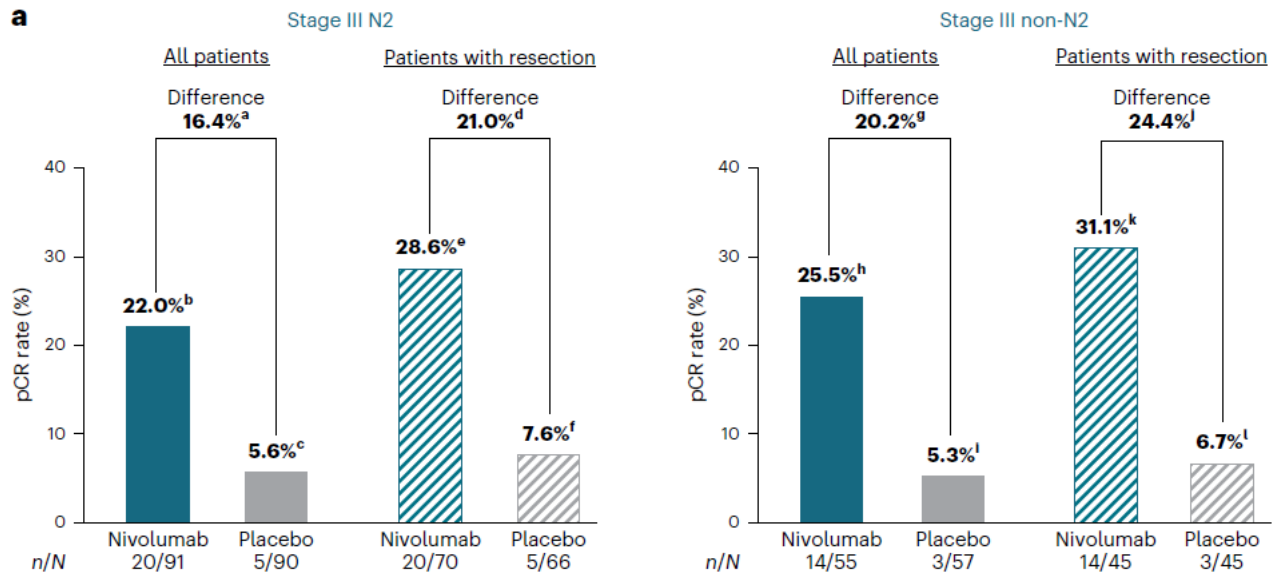
Checkmate 77T : Periop Nivolumab

- 461 patients, stage II-III, 4 cycles
- EFS HR 0.58 (no OS data yet)
- pCR 25% vs. 5%, MPR 35% vs. 12%
- R0 resection 90% in both groups
- EFS HR (0.43-0.49) similar for single and multistation N2
- EFS HR better with higher PDL1 status

Checkmate 77T : Surgical Results

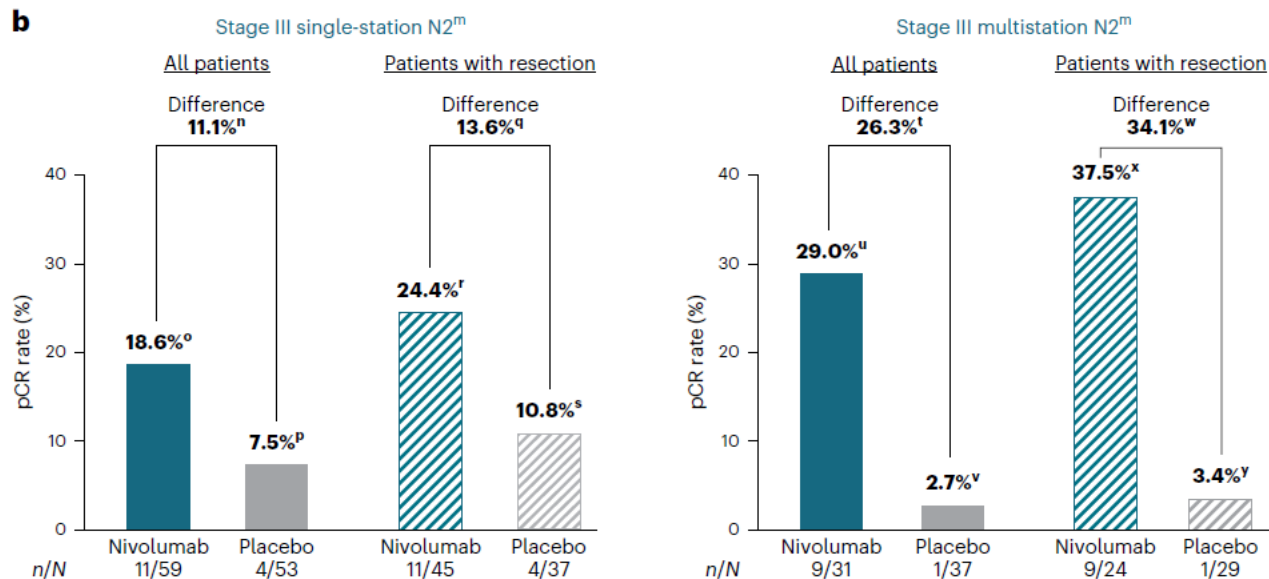
- R0 resection rate 90% in both groups
- Surgery AE 40% in both groups, grade III/IV 12% both groups
- Pneumonectomy rate, N2 disease
 - 1% with perioperative Nivo
 - 14% with placebo

N2 vs. non N2 stage III disease



Multistation N2

- CHECKMATE 77T – 38% of N2 multistation (13% of study group)



T4N2, Stage IIIB

- T4 : size >7cm, ipsilateral multilobar, invasion (heart, spine, aorta, trachea, esophagus, vagus, diaphragm, SVC)
- KEYNOTE 671: 28% T4, 15% IIIB, no difference in OS IIIA and IIIB (HR 0.69-0.74)
- AEGEAN: 25% T4, 24% IIIB
- Checkmate 77T: T4N2 included but not reported separately
- R0 resection rate 90% in patients above
- T4N2 by size >7cm – resection reasonable
- T4N2 invasion : resection reasonable for left atrium, SVC, diaphragm, vagus, portion of vertebral body, but *not* for aorta, esophagus, spinal canal invasion.

Adjuvant ChIO Trials

- IMPOWER 010 (Felip.JCO 2025;43(21):2343) 5 year outcomes
 - 1280 resected II-IIIa chemo then atezolizumab or supportive care
 - No improvement in DFS HR in intention to treat population, DFS HR 0.83 (0.69-1.00), considered not statistically significant
 - PDL >1% **DFS HR 0.70**, median 68.5 months vs. 37.3 months
 - PDL >50%, no EGFR/ALK, **DFS HR 0.49**
 - OS HR 0.94, yet still immature
 - PDL >1%, no EGFR/ALK, **HR 0.44** (0.26-0.74)
- Keynote 091 / PEARLS chemo allowed, adj Pembro 3yr outcomes
 - DFS HR 0.76 (0.63-0.91) median 54 vs. 42 months, no update since 2022
 - No clear benefit in PDL>50% population

The 2026 American Association for Thoracic Surgery Expert Consensus Document: Evaluation and management of N2+ non-small cell lung cancer



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N2 Consensus Document : Staging

- In patients with CT2a or greater, cN1, or cN2, pathologic mediastinal staging (EBUS [preferred] or mediastinoscopy) is recommended pre treatment to verify nodal disease and rule out N3 disease, 100% consensus
- Routine pathologic restaging after neoadjuvant ChIO should not be performed unless new N3 or M1 disease is suspected, 100% consensus

N2 Consensus Document:

Resectability

- The Determination of resectability, involving a thoracic oncologic surgeon, should be made before initiation of treatment, 83% consensus
- Resection can be beneficial in select T4N2 patients, multidisciplinary discussion needed, 100% consensus
- Direct extension of tumor in continuity with bulky mediastinal nodal involvement should be considered unresectable, 80% consensus
- Multistation N2 disease with nodes >3cm or with nodal invasion into adjacent structures is unresectable, 80% consensus

Comparison of Surgical Outcomes in Neoadjuvant N2 NSCLC ChIO Trials

Trial	Neoadjuvant strategy	N	Resection rate	Number (%) of participants that are N2+	Approach			Duration (minutes) or frequency of reported surgical difficulty	Type of Resection		R0 resection %	LOS (days)	Mortality		Clavien-Dindo complications ≥3
					MIS	Converted	Thoracotomy		Lobectomy	Pneumectomy			30 d	90 d	
NADIM 2021 ¹⁰⁶	3 cycles platinum + nivolumab	41	41/46 (89%)	30/41 (73%)	41%	10%	49%	195	78%	7%	100%	5	0%	0%	2.4%
NEOSTAR 2024 ¹⁰⁷	3 cycles platinum + nivolumab + ipilimumab	42	42/44 (95%)	NR	12%	NR	88%	152; 52%	83%	7%	93%	3.75	0%	0%	19.0%
AEGEAN 2025 ¹⁰⁸	4 cycles platinum + durvalumab	366	284/366 (78%)	133/284 (47%)	49%	NR	49%	210	88%	9%	95%	NR	1.4%	4.6%	6.1%
CHIO3 2026 ¹⁰⁹	4 cycles platinum + durvalumab	30	30/37 (81%)	30/30 (100%)	63%	7%	30%	47%	93%	7%	93%	3.5	0%	0%	6.7%
KEYNOTE-671 2026 ⁹⁸	4 cycles platinum + pembrolizumab	397	325/397 (82%)	168/325 (52%)	NR	NR	NR	NR	79%	11%	92%	8	1.8%	4%	NR
Checkmate 77T N2+ subset 2026 ⁹⁷	3 cycles platinum + nivolumab	91	70/91 (77%)	91/91 (100%)	26%	4%	70%	213	84%	1%	86%	9	0%	NR	NR

Surgical Results : NeoChIO

Trial	30d Mort	90 d Mort	Minimal invasive	R0	Grade III/IV	Operative Time	Pneum
CHECK 816							
Nivo					11%		
Placebo					15%		
AEGEAN							
Durva	1.4	4.6	49%	95%	8%	210 min	9.4%
Placebo	2.8	3.8	47%	91%	9%	198 min	11.2%
KEY671							
Pembro	1.8	4.0		92%			11%
Placebo	0.6	1.6		84%			12%
CHECK 77T							
Nivo				89%		217 min	9%
Placebo				90%		223 min	14%

Resectability/Operability

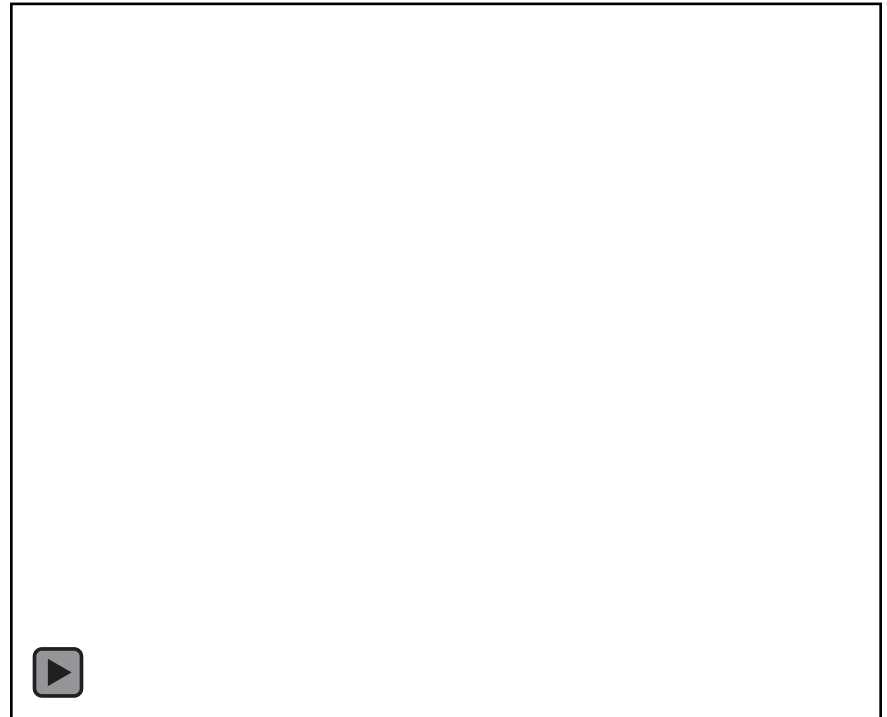
- **Medically Operable** is defined by :
 - Comorbidities (heart ischemia and function, pulmonary hypertension, severe organ dysfunction, frailty)
 - Lung function
- **Resectable** defined by likelihood of R0 resection
 - In context of cardiopulmonary reserve

What is Unresectable

- T4 invasion into esophagus, aorta, spinal canal, extensive invasion of heart
- N3
- Direct extension into mediastinum with bulky N2
- N2 disease that is multistation and bulky (>3cm) or surrounding vital structures

Not Resectable or Operable

- 80F
 - HTN, DM, CAD
 - DLCO 48%
 - Chest wall invasion
 - Requires pneumonectomy
 - Not *medically operable* due to poor lung function
 - Not *resectable* due to extensive chest wall involvement and need for pneumonectomy



Restaging/Assessment after NeoChIO

- CCT with IV contrast useful for surgical planning
- PET restaging used by some, though progression to metastatic disease is uncommon
- We do not routinely restage the mediastinum
 - Redo mediastinoscopy lower sensitivity and potentially higher risk
 - EBUS sensitivity :no induction 89%, post induction 64%
 - Would still recommend resection even for persistent N2 disease

MDT Bridge Study

- International phase 2 Trial
- Borderline resectable NSCLC stage IIB-IIIB
- Multidisciplinary discussion involving thoracic oncologic surgeons (primary practice in oncologic surgery)
- Primary endpoints: pCR and resection rate
- 2 cycles neo chemo/Durva, then re-evaluation
 - If resectable additional 1-2 cycles ChIO
 - If unresectable, converted to definitive chemoradiation
- **Preliminary Results: 71% of borderline patients resected with R0 resection rate of 85%**

Is there a Role for Preop CRT

- Radiation may be critical when sterilization of peripheral margin is critical, less important to see pCR.
 - Pancoast Tumors
 - Vertebral body / spine

Ongoing Adjuvant vs. Neo/Perioperative

- NATCH-ICI (JCOG 2317) Neoadjuvant vs. Adjuvant
 - Resectable stage II/III, EGF-R and ALK negative
 - Adjuvant ChIO, 1 year (no IO for PDL1<1%) vs.
 - Neo ChIO, 3 cycles, surgery then observation
 - Endpoints: OS, PFS, R0, site of relapse
- PROSPECT (Alliance) Perioperative vs. Adjuvant
 - Resectable Stage IIA – IIIB, EGF-R ALK negative
 - Neo Ch/IO 4 cycles then 1 yr adjuvant IO vs.
 - Adjuvant ChIO 4 cycles and 1 yr IO