Radicalità chirurgica e/o oncologica

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Stage III Treatment Strategies

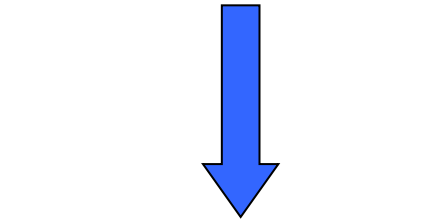
T and M	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a/b	IB/IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IV	IV	IV	IV
M1b	IV	IV	IV	IV

Resectable stage II and III:
chemo + surgery ± RT

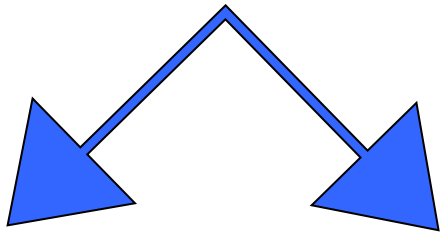
Unresectable stage III:
chemo/RT + immunotherapy

EORTC 08941

579 Pts “unresectable” N2 NSCLC (3 cycles CHT – cisplatin)



332 (57%) partial or complete response



RT 60 Gy
154 pts

Surgery 154 pts

EORTC 08941

RESULTS

- No difference in OS and in DFS
- Different pattern of relapse
  - **loco-regional - RT**
  - distant -
    - Surgery
      - Lobectomy 27%
      - Pneumonectomy 12%
- 5-y survival
  - N0 – N1 29%
  - N2 – N3 7%

EVALUATION OF OPERABILITY

- **RESECTABILITY IN LOCALLY ADVACED TUMORS:**
  - R0 resection
  - CT/PET, mediastinoscopy
  - Surgical expertise

- **FUNCTIONAL OPERABILITY:**
  - Cardiorespiratory function
  - Comorbidities

- **IMPACT OF SURGERY ON ONCOLOGICAL PROGNOSIS:**
  - Evaluation of expected oncological outcome-N2?
  - Definition of operability prior to treatment initation

RISK/BENEFIT

Complete Resection: definition

✓ Confirmation of negative surgical margins in the resected specimen

✓ Highest mediastinal node negativity at the time of surgery

✓ Systematic nodal dissection, with removal of at least 3 mediastinal lymphnode stations, always including subcarinal station 7.

Incomplete resection (R1, R2), uncertain resection

IASLC Rami-Porta R. Lung Cancer 2005;49:25-33

Resectable stage IIIA NSCLC: NCCN 2021

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SURGICAL THERAPY

The Role of Surgery in Patients with Stage IIIA (N2) NSCLC

- Repeat mediastinoscopy, while possible, is technically difficult and has a lower accuracy compared to primary mediastinoscopy. One possible strategy is to perform EBUS (± EUS) in the initial pretreatment evaluation and reserve mediastinoscopy for nodal restaging after neoadjuvant therapy.[5]
- Patients with a single lymph node smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.[1,6,7]
- Restaging after induction therapy is difficult to interpret, but CT +/- PET should be performed to exclude disease progression or interval development of metastatic disease.
- Patients with negative mediastinum after neoadjuvant therapy have a better prognosis.[7,8]
- Neoadjuvant chemoradiotherapy is used in 50% of the NCCN Member Institutions, while neoadjuvant chemotherapy is used in the other 50%. Overall survival appears similar provided RT is given postoperatively, if not given preoperatively.[5,9] Neoadjuvant chemoradiotherapy is associated with higher rates of pathologic complete response and negative mediastinal lymph nodes.[10] However, that is achieved at the expense of higher rates of acute toxicity and increased cost.

A questionnaire was submitted to the NCCN Member Institutions in 2010 regarding their approach to patients with N2 disease. Their responses indicate the patterns of practice when approaching this difficult clinical problem.

a) Would consider surgery in patients with one N2 lymph node station involved by a lymph node smaller than 3 cm: (90.5%)
b) Would consider surgery with more than one N2 lymph node station involved, as long as no lymph node was bigger than 3 cm: (47.6%)
c) Uses EBUS (+/- EUS) in the initial evaluation of the mediastinum: (80%)
d) Uses pathologic evaluation of the mediastinum, after neoadjuvant therapy, to make a final decision before surgery: (40.5%)
e) Would consider neoadjuvant therapy followed by surgery when a patient is likely, based on initial evaluation, to require a pneumonectomy: (54.8%)

METHODS

- 13-item online survey with general and resectability questions
- Distribution to members of EORTC, ESTS, ETOP, ESTRO, ERS, and IASLC
- Definition of **consensus**: **75% agreement** among participants

- T-stage and N-stage according to the 8th TNM edition
- N2 (ipsilateral mediastinal and/or subcarinal nodes) working definition:
  - *N2 single*: single station, non-bulky (≤3cm), discrete*
  - *N2 multi*: multi-level, non-bulky (≤3cm), discrete
  - *N2 bulky*: bulky (>3cm) and discrete
  - *N2 invasive*: invasive growth#

** discrete = well defined/with identifiable borders*
 # invasive = infiltration in the surrounding tissues

Houda I. et al. An International EORTC Survey on Resectability of Stage III Non-small Cell Lung Cancer WCLC2023 OA06.03

SURVEY SUMMARY: Areas of controversy in resectable stage III NSCLC

	N0	N1	N2 SINGLE	N2 MULTI	N2 BULKY	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	POTENTIALLY RESECTABLE	?	UNRESECTABLE[2]	UNRESECTABLE	UNRESECTABLE
T3 size	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE	?	UNRESECTABLE	UNRESECTABLE	
T3 satellite	NOT STAGE III DISEASE	POTENTIALLY RESECTABLE	POTENTIALLY RESECTABLE	?	UNRESECTABLE	UNRESECTABLE	
T3 invasion	NOT STAGE III DISEASE	POTENTIALLY RESECTABLE	?[1]	?	UNRESECTABLE	UNRESECTABLE	
T4 size	POTENTIALLY RESECTABLE	POTENTIALLY RESECTABLE	?	UNRESECTABLE[2]	UNRESECTABLE	UNRESECTABLE	
T4 satellite	POTENTIALLY RESECTABLE	?[1]	?	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE	
T4 invasion	?[1]	?[1]	?	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE	

TN-subgroups for stage III NSCLC; Some results may deviate from the results in the final consensus; ?, no consensus achieved;
1, no consensus achieved but considered as potentially resectable by thoracic surgeons; 2, consensus unresectable but no consensus in the group of thoracic surgeons.

Houda I. et al. An International EORTC Survey on Resectability of Stage III Non-small Cell Lung Cancer WCLC2023 OA06.03

Consensus

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.

* Criteria for general thoracic surgery are defined in European Guidelines (Eur J Cardiothor Surg 45: 779- 86, 2014).

Brandão M. et al. Consensual definition of stage III NSCLC Resectability: EORTC-Lun Cancer Group initiative with other scientific society WCLC2023 OA06.05

Consensus

	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
§Some **T4 tumours by infiltration of major structures** are potentially resectable – see Table 1

Brandão M. et al. Consensual definition of stage III NSCLC Resectability: EORTC-Lun Cancer Group initiative with other scientific society WCLC2023 OA06.05

Stage IIIA – cT1-2 N2 tumors

Single-station N2

•Single-station N2, non-bulky and non-invasive, tumors are considered **resectable**

Multiple-station N2 – resectable?

•**Absence of consensus** between the results of the systematic review (frequently unresectable) *vs* the clinical case review (n=15, all unresectable) *vs* the survey (10-40% of the respondents answered that multiple N2 were potentially resectable, depending on the T stage)

•**Case-by-case discussion**: highly and carefully selected patients with non-bulky, non-invasive N2 multi- station involvement may be considered for resection; the *exact number of nodes/stations* for a tumor to be still considered resectable cannot be defined

Brandão M. et al. Consensual definition of stage III NSCLC Resectability: EORTC-Lun Cancer Group initiative with other scientific society WCLC2023 OA06.05

Stage IIIA – cT1-2 N2 tumors

Bulky N2

- No consensual definition of “bulky” N2
- Most cases are considered as **unresectable** in the survey and literature review
- During the clinical case review, 14% of N2 bulky tumors considered as ***resectable***
- In specific situations of highly selected patients, *inclusion of those patients in multidisciplinary trials* with surgery as local therapy **can be discussed**

Brandão M. et al. Consensual definition of stage III NSCLC Resectability: EORTC-Lun Cancer Group initiative with other scientific society WCLC2023 OA06.05

Stage IIIA – cT4 N0-1 tumors

- **T4 by separate nodules or by size** are considered **resectable**
- **T4 by infiltration of major structures** (Table 1): frequently considered as **borderline resectable**; a *case-by-case discussion* must be performed including an experienced surgeon and frequently requires a *multidisciplinary approach* in dedicated specialized centres

Table 1	Unre-sectable	Potentially resectable
Pulmonary artery in the pericardium		✓
Superior vena cava		✓
Diaphragm		✓
Heart	✓*	
Carina		✓
Trachea	✓*	
Oesophagus	✓*	
Spinal cord	✓	
Vertebral body		✓
Recurrent laryngeal nerve		✓
Mediastinal fat		✓
Great vessels: aorta, inferior vena cava, pulmonary vein		✓

**Some locations as heart, trachea and oesophagus are generally considered unresectable while rare cases can be resected in case of minimal neoplastic infiltration*

Brandão M. et al. Consensual definition of stage III NSCLC Resectability: EORTC-Lun Cancer Group initiative with other scientific society WCLC2023 OA06.05

Stage IIIB – cT3-4 N2 tumors

- cT3N2 and cT4 (size or satellite) N2 are considered **resectable** if **single-station N2**
- **Case-by-case discussion:** highly and carefully selected patients with ***"limited" discrete N2 multi-station*** *involvement* (non bulky, non invasive), while the exact number of nodes/stations defining "limited" cannot be defined

Stage IIIB – cT1-2 N3 tumors

- cT1-2N3 tumors are considered **unresectable**

Stage IIIC – cT3-4 N3 tumors

- Tumors with major structures infiltration and N3 disease are considered **unresectable**

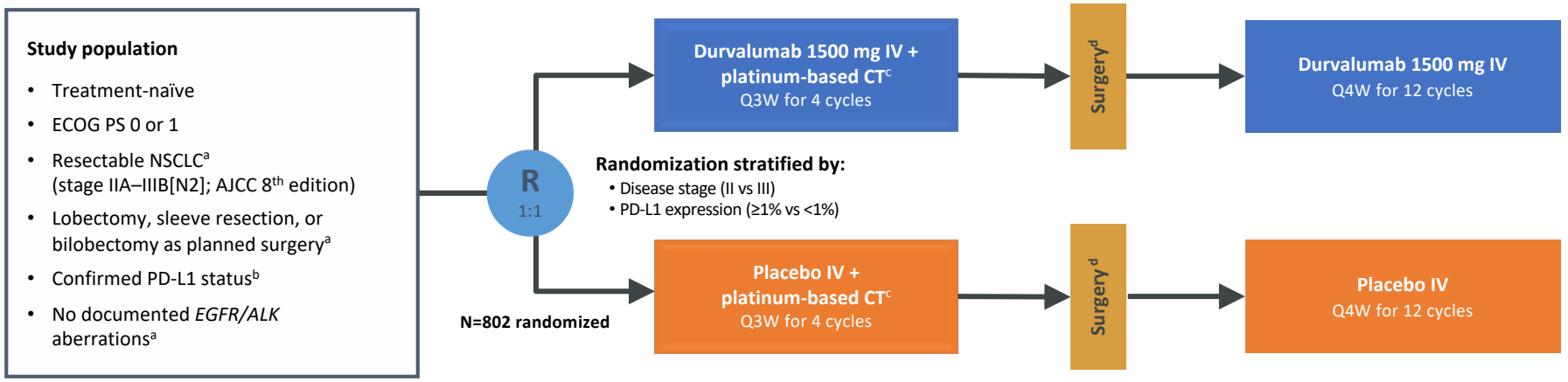
Brandão M. et al. Consensual definition of stage III NSCLC Resectability: EORTC-Lun Cancer Group initiative with other scientific society WCLC2023 OA06.05

NEOADJUVANT/PERIOPERATIVE vs ADJUVANT IO

STUDY	NEOADJUVANT	N	EGFR or ALK	ADJUVANT	STAGE	DFS or EFS HR	OS HR	DFS or EFS	OS
CHEKMATE 816	Nivolumab + CT vs CT (3 cycles)	358	excluded if known	none	IB-IIIA (7˚) II-IIIB (8°)	0.68	0.62	65% 2y 57% 3y	83% 2y 78% 3y
AEGEAN	Durvalumab + CT vs CT (4 cycles)	802	excluded	Durvalumab vs supportive care	IIA –IIIB (8°)	0.68	NR	63% 2y	NR
KEY-NOTE 671	Pembrolizumab + CT vs CT (up to 4 cycles)	786	included	Pembrolizumab vs placebo	II –IIIB (8°)	0.58	0.73	62% 2y	81% 2y
ADJUVANT									
IMPOWER 010	N/A		included	CT mandatory ATEZOLIZUMAB	II –IIIA (8°)	0.66	NR	75% 2y	NR
KEY-NOTE 091	N/A		included	CT optional PEMBROLIZUMAB	II –IIIA (8°)	0.76	0.87	73% 1.5y	92%

	CM816 (Chemo-Nivolumab)	AEGEAN (Chemo-Durvalumab)	Neotorch (Chemo-Toripalimab)	Keynote 671 (Chemo-Pembro)
Randomized	358	802	404	797
Endpoints	PCR, EFS	PCR, EFS	MPR, EFS (by stage groups)	EFS, OS
Stages	IB-IIIA (AJCC7) or II-IIIB (AJCC8)	II-IIIB (Possible pneumonectomy excluded)	III (stage II results not yet presented)	II-IIIB
Systemic plan	Neoadj (3 cycles)	Periadj (4+12 cycles)	Periadj (3-4+13 cycles)	Periadj (4+13 cycles)
Surgery	83%	81%	82%	82%
Impact on surgical outcomes	Grade 3/4 AE = 11.4% 3.4% 90-day mortality	N/A	N/A	Grade 3-4 AE = 18.2% 4% 90-day mortality
R0 rate	83%	95%	96%	92%
EFS @ 2 years	65%	63.3%	67%	62.4%
OS @ 2 years	82.7% (HR 0.57, 95% CI 0.38-0.87)	N/A	81.2%	80.9% (HR 0.73, 95% CI 0.54-0.99)

AEGEAN: Study Design



Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented EGFR/ALK aberrations[e]

Primary:

- pCR by central lab (per IASLC 2020)
- EFS using BICR (per RECIST v1.1)

Key secondary:

- MPR by central lab (per IASLC 2020)
- DFS using BICR (per RECIST v1.1)
- OS

[a]The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented *EGFR/ALK* aberrations; [b]Ventana SP263 immunohistochemistry assay; [c]Choice of CT regimen determined by histology and at the investigator's discretion. For non-squamous: cisplatin + pemetrexed or carboplatin + pemetrexed. For squamous: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment); [d]PORT was permitted where indicated per local guidance; [e]All efficacy analyses reported in this presentation were performed on the mITT population, which includes all randomized patients who did not have documented *EGFR/ALK* aberrations. AJCC = American Joint Committee on Cancer; ALK =anaplastic lymphoma kinase; BICR = blinded independent central review; CT = chemotherapy; DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; EGFR= epidermal growth factor receptor; IASLC = International Association for the Study of Lung Cancer; IV = intravenous; mITT = modified intent-to-treat; MPR = major pathologic response; NSCLC = non-small cell lung cancer; OS = overall survival; pCR, = pathologic complete response; PD-L1 = programmed cell death ligand-1; PORT = post-operative radiotherapy; PS = performance status; Q*W = every * weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1. Heymach JV et al. Presented at AACR; April 14-19, 2023; Orlando, FL.

Baseline characteristics and planned treatment[1]

- Baseline characteristics were largely balanced between arms
- The planned neoadjuvant CT doublet was carboplatin-based for >70% of patients

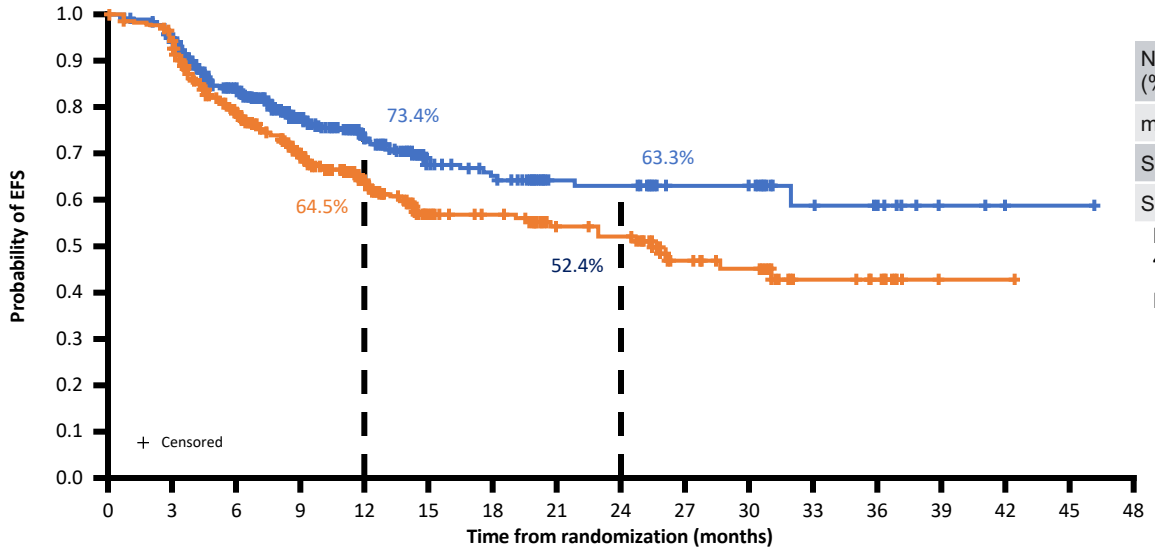
TNM classification‡		D arm (N=366)	PBO arm (N=374)
Primary tumor, %	T1	12.0	11.5
	T2	26.5	28.9
	T3	35.0	34.5
	T4	26.5	25.1
Regional lymph nodes, %	N0	30.1	27.3
	N1	20.5	23.3
	N2	49.5	49.5
	Single-station	38.5	35.3
	Multi-station	9.3	10.7

DCO = Nov 10, 2022. *Characteristics with missing/other responses were histology (0.3% in the D arm and 1.1% in PBO arm had 'other' histology), disease stage (0.3% in D arm had stage IV disease, and 0.3% in the PBO arm had stage III [NOS] disease, as reported per the eCRF), and N2 lymph node station status (1.6% in the D arm and 3.5% in the PBO arm had N2 disease with missing data on single-station versus multi-station classification). †Race was self-reported per the eCRF. ‡All patients were M0 except one patient in the D arm who was classified as M1 (NOS). eCRF, electronic case report form; NOS, not otherwise specified; TC, tumor cells.

Characteristics*		D arm (N=366)	PBO arm (N=374)
Age	Median (range), years	65.0 (30–88)	65.0 (39–85)
	≥75 years, %	12.0	9.6
Sex, %	Male	68.9	74.3
ECOG PS, %	0	68.6	68.2
	1	31.4	31.8
Race†, %	Asian	39.1	43.9
	White	56.3	51.1
	Other	4.6	5.1
Region	Asia	38.8	43.6
	Europe	38.5	37.4
	North America	11.7	11.5
	South America	10.9	7.5
Smoking status, %	Current	26.0	25.4
	Former	60.1	59.6
	Never	13.9	15.0
Disease stage (AJCC 8th ed.), %	II	28.4	29.4
	IIIA	47.3	44.1
	IIIB	24.0	26.2
Histology, %	Squamous	46.2	51.1
	Non-squamous	53.6	47.9
PD-L1 expression, %	TC <1%	33.3	33.4
	TC 1–49%	36.9	38.0
	TC ≥50%	29.8	28.6
Planned neoadjuvant platinum agent, %	Cisplatin	27.3	25.7
	Carboplatin	72.7	74.3

[1]Heymach JV, et al. *Cancer Res* 2023; 83 (8_Supplement):CT005.

EFS using RECIST v1.1 (BICR) (mITT) (First Planned Interim Analysis of EFS)



No. at risk:																	
D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

	D arm	P arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank P-value	0.003902	

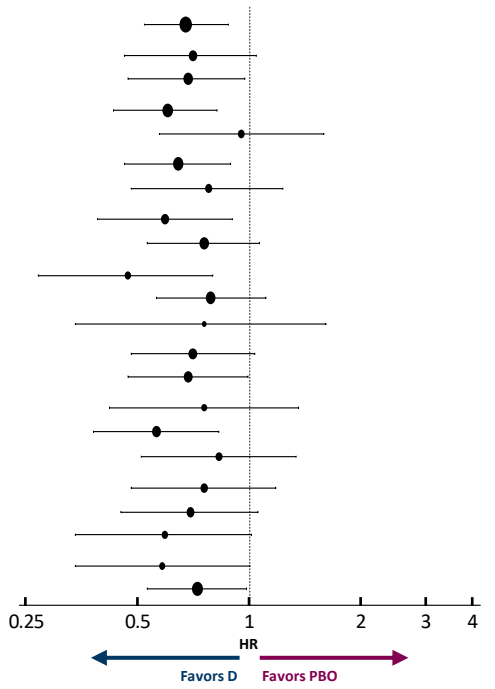
Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

DCO = November 10, 2022. EFS is defined as time from randomization to the earliest of: (A) PD that precludes surgery; (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; (C) local/distant recurrence using BICR per RECIST v1.1; or (D) death from any cause.
*HR <1 favors the durvalumab arm versus the placebo arm.
Median and landmark estimates calculated using the Kaplan–Meier method; HR calculated using a stratified Cox proportional hazards model; and *P*-value calculated using a stratified log rank test. Stratification factors: disease stage (II vs III) and PD-L1 expression status (<1% vs ≥1%). Significance boundary = 0.009899 (based on total 5% alpha), calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary.
D = durvalumab; DCO = data cut-off; BICR = blinded independent central review; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; mITT = modified intent-to-treat; NR = not reached; PBO = placebo; PD = progressive disease; PD-L1 = programmed cell death ligand-1; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.
Heymach JV et al. Presented at AACR; April 14-19, 2023; Orlando, FL.

EFS using RECIST v1.1 (BICR) by Subgroup (mITT)

Subgroup		n	Median EFS, months (95% CI) D arm (N=366)	Median EFS, months (95% CI) PBO arm (N=37	HR (95% CI)
All patients		740	NR (31.9–NR)	25.9 (18.9	0.68 (0.53–0.88)
Age at randomization	<65 years	358	NR (NR–NR)	NR (18.9-	0.71 (0.47–1.04)
	≥65 years	382	NR (17.9–NR)	24.5 (13.6-	0.69 (0.48–0.97)
Sex	Male	530	NR (31.9–NR)	22.9 (14.3-	0.61 (0.44–0.82)
	Female	210	NR (17.5–NR)	NR (13.6-	0.95 (0.58–1.56)
ECOG PS	0	506	NR (31.9–NR)	25.4 (14.3	0.65 (0.47–0.89)
	1	234	NR (21.8–NR)	25.9 (14.3	0.78 (0.49–1.22)
Race[a]	Asian	307	NR (NR–NR)	25.4 (13.9	0.60 (0.40–0.90)
	Non-Asian	433	31.9 (21.8–NR)	26.2 (14.3	0.76 (0.54–1.06)
Smoking	Current	190	NR (NR–NR)	14.3 (8.1-	0.48 (0.28–0.80)
	Former	443	NR (31.9–NR)	25.9 (19.5	0.79 (0.57–1.10)
	Never	107	NR (NR–NR)	24.5 (14.3	0.76 (0.35–1.58)
Histology	Squamous	360	NR (31.9–NR)	26.2 (13.0	0.71 (0.49–1.03)
	Non-squamous	375	NR (NR–NR)	25.4 (14.3	0.69 (0.48–0.99)
Disease stage (AJCC 8th edition)	Stage II	214	NR (NR–NR)	31.1 (25.4	0.76 (0.43–1.34)
	Stage IIIA	338	NR (NR–NR)	19.5 (11.7	0.57 (0.39–0.83)
	Stage IIIB	186	31.9 (11.7–NR)	18.9 (11.8	0.83 (0.52–1.32)
PD-L1 expression at baseline[b]	TC <1%	247	NR (14.9–NR)	20.6 (13.9	0.76 (0.49–1.17)
	TC 1–49%	277	NR (31.9–NR)	25.4 (12.2	0.70 (0.46–1.05)
	TC ≥50%	216	NR (NR–NR)	26.2 (14.3	0.60 (0.35–1.01)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR–NR)	31.1 (14.3	0.59 (0.35–1.00)
	Carboplatin	544	NR (31.9–NR)	25.4 (14.3	0.73 (0.54–0.98)



DCO = Nov 10, 2022; median EFS follow-up in censored patients: 11.7 months (range: 0.0–46.1); EFS maturity: 31.9%. Median calculated using the Kaplan–Meier method; HR for all patients (mITT) calculated using a stratified Cox proportional hazards model. HRs for subgroups calculated using unstratified Cox proportional hazards models. The size of circles is proportional to the number of events for each subgroup, and the horizontal bars represent the 95% CIs. [a]Race was self-reported per the electronic case report form; [b]Determined using the Ventana SP263 immunohistochemistry assay. AJCC = American Joint Committee on Cancer; BICR = blinded independent central review; CI = confidence interval; D = durvalumab; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; HR = hazard ratio; mITT = modified intent-to-treat; NR = not reached; PBO = placebo; PD-L1 = programmed cell death ligand-1; PS = performance status; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; TC = tumor cell. Heymach JV et al. Presented at AACR; April 14-19, 2023; Orlando, FL.

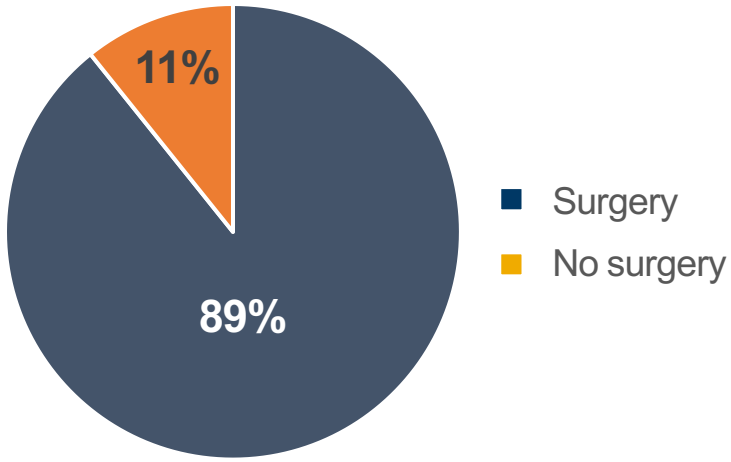
PREOPERATIVE ATTRITION TO SURGERY

STUDY	PHASE	NEOADJUVANT THERAPY	N OF CYCLES	PREOP ATTRITION (study group)	PREOP ATTRITION (control group)	Time from last dose neoadjuvant therapy to surgery
LCMC3	II	ATEZOLIZUMAB MONOTHERAPY	2	12%	N/A	22 (11-74 days)
CHECK-MATE 816	III	CT+NOVOLUMAB	3	16%	21%	5.3 (4.6-6) weeks)
NEOTORCH	III	CT+TORIPALIMAB	3	18%	27%	NR
AEGEAN	III	CT+DURVALUMAB	4	19%	19%	NR
KEY-NOTE 671	III	CT+PEMBROLIZUMAB	4	18%	21%	NR

Additional question

SURGERY AFTER DOWNSTAGING WITH NEOADJUVANT CHEMO-IO IN BORDERLINE RESECTABLE CASES

The **majority (89%) would recommend surgery**
after downstaging with neoadjuvant chemo-IO, assumed to be available.



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