Perioperative Therapy in Early Stage NSCLC – Implications for Molecular Testing

Case

65 year-old Caucasian woman with no smoking history.
She was noted to have bronchiectasis on a coronary calcium screening scan.
A follow-up chest CT revealed two suspicious nodules in the RLL

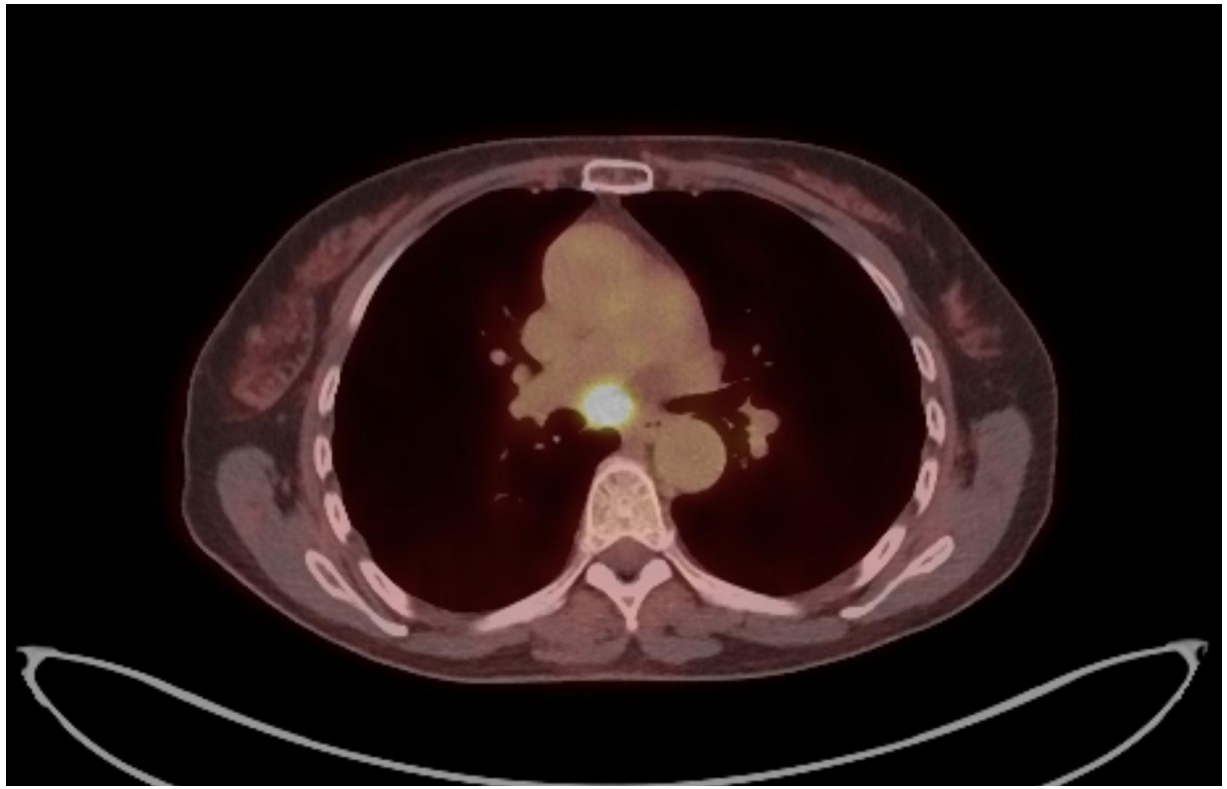
Past Medical History: Hypercholesteremia

Past Surgical History: Biopsy right breast stereotactic (9/22/2009) – benign

Social History:
Reports that she has never smoked. She has never used smokeless tobacco.
Pediatrician
Regular exercise

Imaging:

Case



Initial Evaluation

What should we our next step here?

Patterns of Referral, Discussion at Tumor Board, Staging, Molecular Testing

Staging Principles

- Accurate staging is the key to delivering outstanding multidisciplinary care
- Radiographic predictors may allow us to select patients for more or less extensive staging and lymph node assessment
- Clinical staging alone is often inaccurate
- Intraoperative lymph node assessment/resection is also often inadequate and poor assessment is associated with decreased survival

Staging has never been more complex

Proposed AJCC 9th Edition Lung Cancer Staging Guidelines

(January 2024)

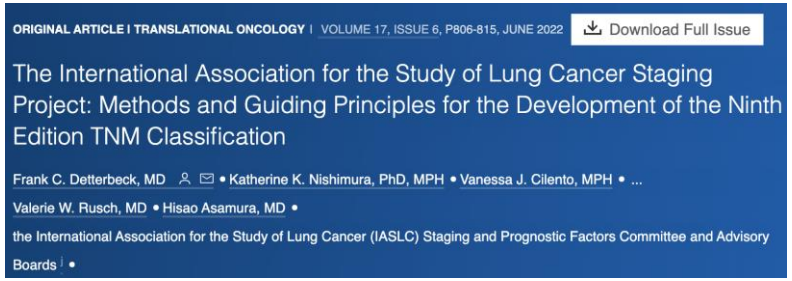
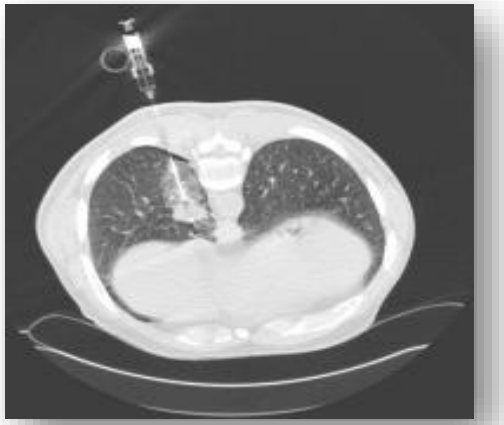


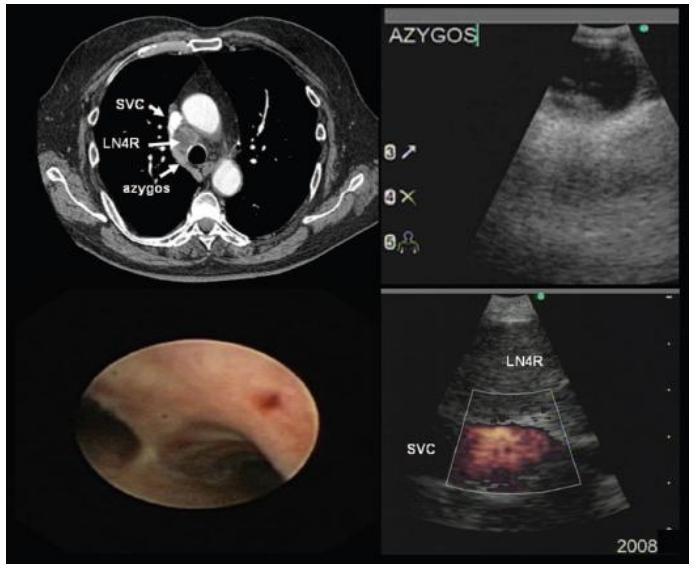
TABLE TNM stage grouping according to the proposed 9th edition of the TNM classification of lung cancers

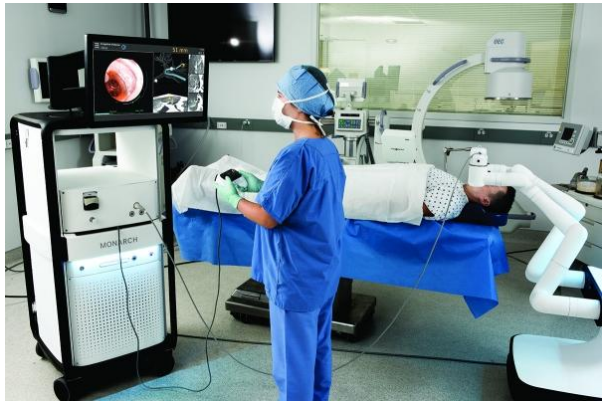
T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b > 1 to ≤ 2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c > 2 to ≤ 3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a > 3 to ≤ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b > 4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 > 5 to ≤ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Satellite nodules	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral nodules	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Contralateral nodules	IVA	IVA	IVA	IVA	IVA
	M1a Pleural, pericardial effusion	IVA	IVA	IVA	IVA	IVA
	M1b Single extra-thoracic lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple extra-thoracic lesions in a single organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple extra-thoracic lesions in multiple organ systems	IVB	IVB	IVB	IVB	IVB

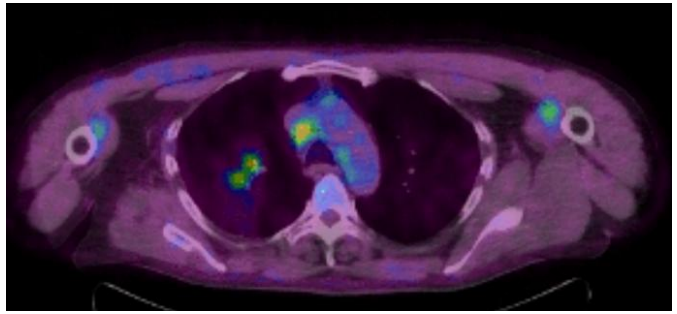
Multiple Tools Available for Pre-Treatment Staging and Diagnosis of Lung Cancer

- CT scan
- Tissue diagnosis by bronchoscopy/EBUS, CT-FNA, or surgery
- PET scan









Case

65 year-old Caucasian woman with no smoking history.
She was noted to have bronchiectasis on a coronary calcium screening scan.
A follow-up chest CT revealed two suspicious nodules in the RLL

Initial Evaluation….

- **PET CT scan shows no evidence of distant metastatic disease**
- **MRI brain is negative**
- **EBUS Bronch Bx is performed, and dx is NSCLC, adenocarcinoma in RLL, and 12R and 7 LN are positive for adenocarcinoma.**

Molecular:
PD-L1 40%

- **How are decisions being made for surgery?**

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- How are decisions being made for surgery?
- Who decides chemoradiation or surgery?
- If surgery, do you do neoadjuvant or perioperative?
- Which is the preferred regimen?

Summary of Select Neoadjuvant and Perioperative IO Trials

Neoadjuvant Immunotherapy (Approved)	
CheckMate -816	Nivolumab + chemo x 3 cycles

→ SURGERY — FDA approved

SURGERY → (FDA approved)

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

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

Summary of Select Neoadjuvant and Perioperative IO Trials: Inclusion and Exclusion Criteria

Criteria		AEGEAN[1] (Perioperative)	CheckMate 816[2] (neoadjuvant only)	KEYNOTE-671[3,4] (Perioperative)	CheckMate 77T[5,6] (Perioperative)
N		740	358	797	451
Stage		Stage II, IIIA, and IIIB (N2) *By AJCC 8th ed*	Stage IB (≥4 cm), II, IIIA *By AJCC 7th ed*	Stage II, IIIA, and IIIB (N2) *By AJCC 8th ed*	Stage IIA (>4 cm) to IIIB (N2) *By AJCC 8th ed*
Regimen	Neoadjuvant	Durva + CT (Q3W x 4 cycles)	Nivo + CT (Q3W x 3 cycles)	Pembro + CT (Q3W up to 4 cycles)	Nivo + CT (Q3W x 4 cycles)
	Adjuvant	Durva (Q4W x 12 cycles)	N/A	Pembro (Q4W x 13 cycles)	Nivo (Q4W X 12 cycles)
Platinum backbone		Cisplatin/carboplatin	Cisplatin/carboplatin	Cisplatin	Cisplatin/carboplatin
Planned pneumonectomy permitted at baseline?		Amended to exclude	Yes	Yes	No specified
T4 invasion		Excluded	Included	Included	Excluded
EGFRm/ALK alterations		Excluded from mITT analysis	Excluded patients with known EGFR/ALK alterations	Included	No EGFRm/no known ALK alterations

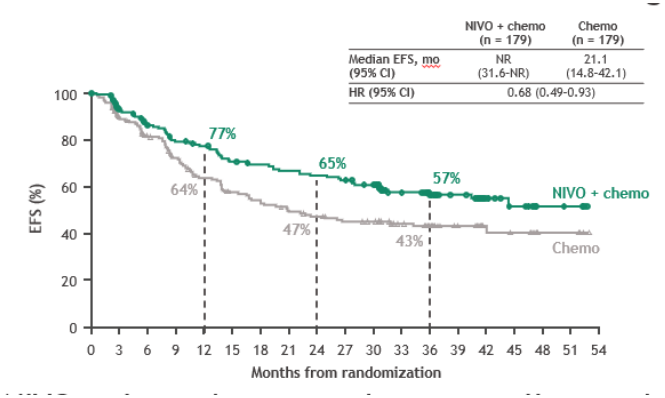
1. Heymach J, et al. AACR 2023. Abs CT005; 2. Forde PM, et al. *N Engl J Med*. 2022; 3. Wakelee HA, et al. ASCO 2023. Abs LBA500; 4. Wakelee HA, et al. *N Engl J Med*. 2023; 5. Cascone T, et al. ESMO 2023. Abs LBA1; 6. Cascone T, et al. ASCO 2020. Abs TPS9076.

Summary of Select Neoadjuvant and Perioperative IO Trials: Clinical Outcomes

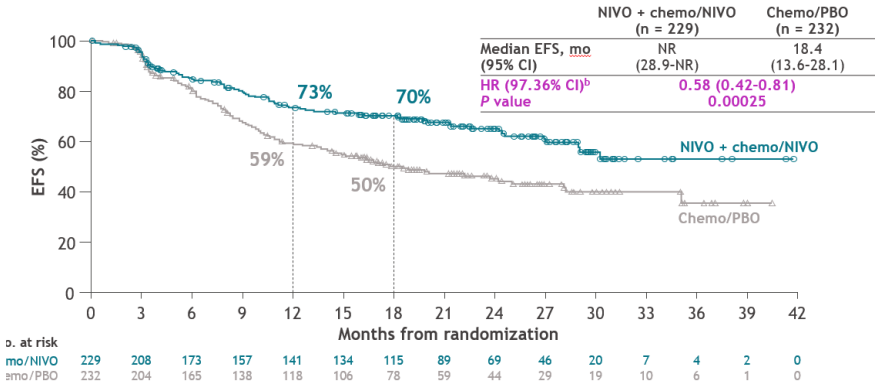
Criteria	AEGEAN[1] (Perioperative)		CheckMate 816[2-4] (neoadjuvant only)		KEYNOTE-671[5-7] (Perioperative)		CheckMate 77T[8] (Perioperative)	
Parameter	Durva + CT	PBO + CT	Nivo + CT	CT alone	Pembro + CT	PBO + CT	Nivo + CT	PBO + Nivo
Nodal status: N0/N1/N2, %	30/21/50	27/23/50	N/A		37/20/42	36/18/47	36/23/40	
CT regimens	**NSQ:** cisplatin or carboplatin + pemetrexed **SQ: c**isplatin + gemcitabine or carboplatin + paclitaxel		**Any histology:** carboplatin + paclitaxel **NSQ**: cisplatin + pemetrexed **SQ:** cisplatin + gemcitabine **CT only arm:** vinorelbine or docetaxel + cisplatin		**NSQ:** cisplatin + pemetrexed **SQ: c**isplatin + gemcitabine		**NSQ:** cisplatin or carboplatin + pemetrexed, or carboplatin + paclitaxel **SQ: c**isplatin + docetaxel or carboplatin + paclitaxel	
pCR, %	17.2	4.3	24.0	2.2	18.1	4.0	25.3	4.7
MPR	33.3	12.3	N/A	N/A	30.2	11.0	35.4	12.1
Median follow-up (mEFS & mOS), months	11.7		41.4		36.6		25.4	
mEFS, months (95% CI)	NR (31.9-NR)	25.9 (18.9-NR)	43.8	18.4	47.2	18.3	NR (28.9-NR)	18.4 (13.6-28.1)
HR for mEFS (95% CI)	0.68 (95% CI: 0.53-0.88)		0.66 (95% CI: 0.49-0.90)		0.59 (95% CI: 0.48-0.72)		0.58 (97.36% CI: 0.42-0.81)	
mOS, months (95% CI)	Not yet tested		NR Est 4-yr: 71%	NR Est 4-yr: 58%	NR (NR-NR)	52.4 (45.7-NR)	Not yet tested	
HR for mOS (95% CI)	N/A		0.71 (98.36% CI: 0.47-1.07)		0.72 (95% CI: 0.56-0.93)		N/A	

CT, chemotherapy; durva, durvalumab; HR, hazard ratio; IO, immuno-oncology; mEFS, median EFS; mOS, median overall survival; MPR, major pathologic response; N/A not available; Nivo, nivolumab; NR, not reached; pCR, pathologic complete response; Pembro, pembrolizumab

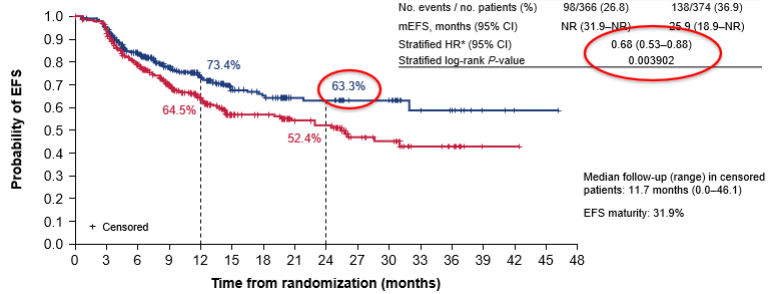
EFS Outcomes by Trial



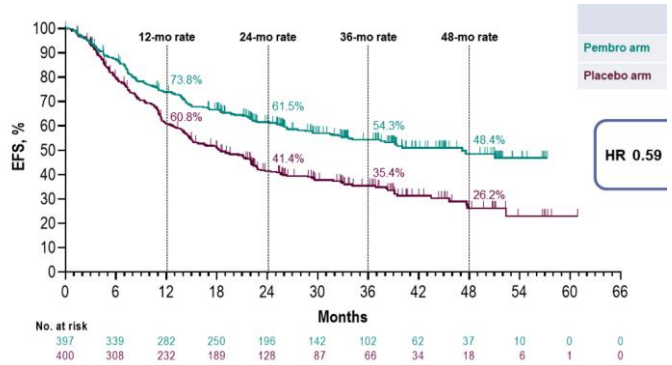
CM816 – 9 wks neoadj chemo-IO
2 yr EFS – 65%



CM77T – 12 wks neoadj chemo-IO + 52 wks adjuvant IO
2 yr EFS – ~65%



AEGEAN – 12 wks neoadj chemo-IO + 52 wks of adj IO
2 yr EFS – 63.3%



KN671 – 12 wks neoadj chemo-IO + 39 wks adj IO
2 yr EFS – 61.5%

Summary of Select Neoadjuvant and Perioperative IO Trials: Safety

Criteria	AEGEAN[1] (Perioperative)		CheckMate 816[2] (neoadjuvant only)		KEYNOTE-671[3] (Perioperative)		CheckMate 77T[4] (Perioperative)	
Safety Parameter	Durva + CT (n=400)	PBO + CT (n=399)	Nivo + CT (n=179)	CT alone (n=179)	Pembro + CT (n=396)	PBO + CT (n=399)	Nivo + Chemo (n=229)	Pbo + Chemo (n=232)
TRAEs								
Any Grade, %	86.8	80.7	84	90	96.7	95.0	89	87
Grade 3/4, %	32.4	32.9	36	38	45.2	37.8	32.5	25.2
Severe	37.5*	31.6*	12	10	18.4	14.5	19.3	9.2
Leading to TD	12.0	6.0	11	10	13.6	5.3	19.3	7.4
Immune-related AEs								
Any Grade, %	23.7	9.3	-	-	26	9	-	-
Grade 3/4, %	4.2	2.5	-	-	6.6	1.5	-	-

**Any cause severe adverse event*
CT, chemotherapy; durva, durvalumab; IO, immuno-oncology; Nivo, nivolumab; Pembro, pembrolizumab; TD, treatment discontinuation

1. Heymach J, et al. AACR 2023. Abs CT005; 2. Spicer J, et al. ASCO 2024. Abs LBA 8010; 3. Spicer JD, et al. ESMO 2023. Abs LBA56; 4. Cascone T, et al. *N Engl J Med.* 2024;390(19):1756-1769.

Summary of Select Neoadjuvant and Perioperative IO Trials: Surgical Outcomes

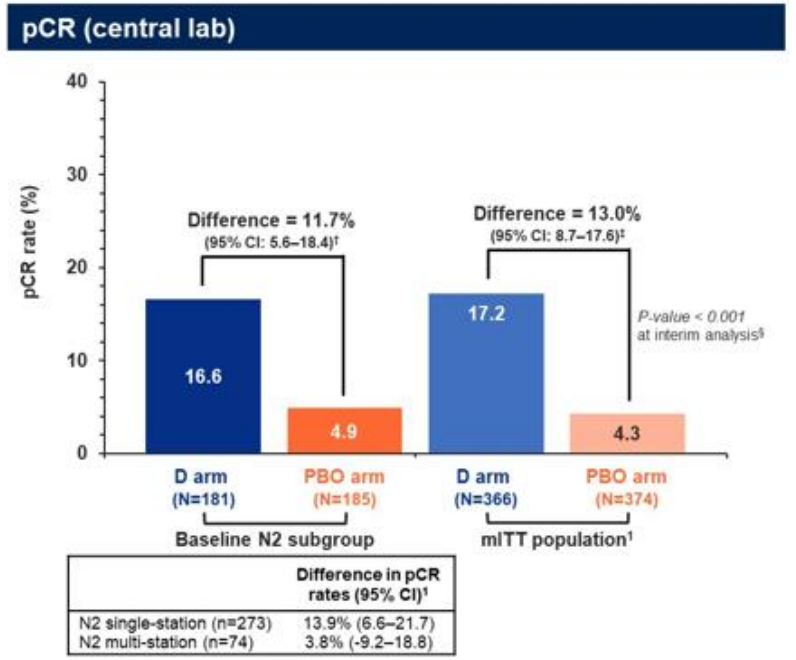
Criteria	AEGEAN[1] (Perioperative)		CheckMate 816[2-4] (neoadjuvant only)		KEYNOTE-671[5-7] (Perioperative)		CheckMate 77T[8] (Perioperative)	
Parameter	Durva + CT (n=366)	PBO + CT (n=374)	Nivo + CT (n=179)	CT alone (n=179)	Pembro + CT	PBO + CT	Nivo + Chemo (n=229)	Pbo + Chemo (n=232)
Patient underwent surgery, %	80.6	80.7	85 (Stage IB/II) 83 (Stage IIIA)	82(Stage IB/II) 72 (Stage III)	82.1	79.4	78	78
Definitive surgery cancelled, %	19.4	19.3	12 (Stage IB/II) 17 (Stage IIIA)	13 (Stage IB/II) 25 (Stage IIIA)	-	-	20	22
Did not undergo surgery due to AEs, %	1.4	1.1	1.1	0.6	6.3	4.2	3.0	2.0
R0 resection, %	94.7	91.3	83.2	77.8	92.0	84.2	89	90
R1/R2 resection, n(%)	-	-	-	-	-	-	11	10
HR disease recurrence, progression, or death (95% CI)	0.68 (0.53-0.88; *P* =.004)		0.68 -		0.63 (0.43-0.91; *P* =.005)		0.58 (0.42-0.81; *P* =.00025)*	
RR disease recurrence, progression, or death; %	32		32		37		42	

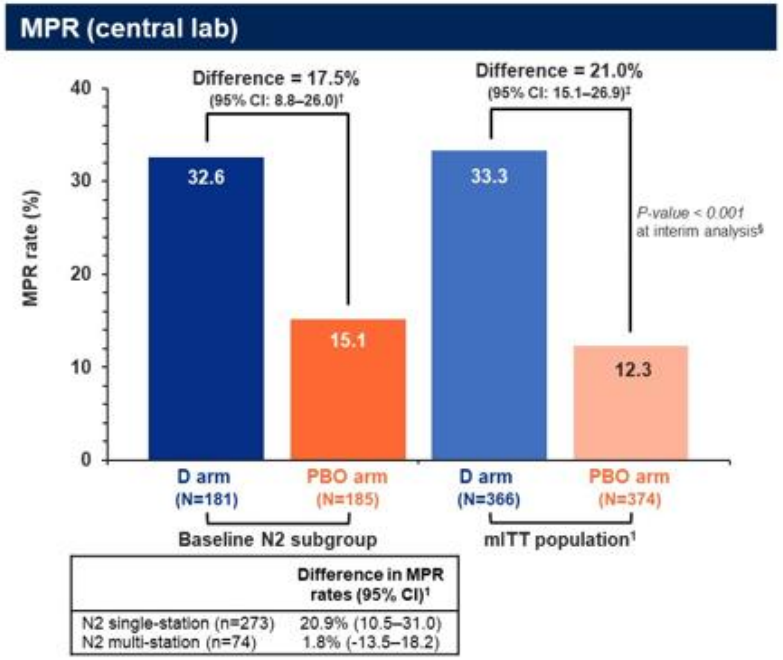
**97.36% confidence interval*
CT, chemotherapy; durva, durvalumab; IO, immuno-oncology; Nivo, nivolumab; Pembro, pembrolizumab

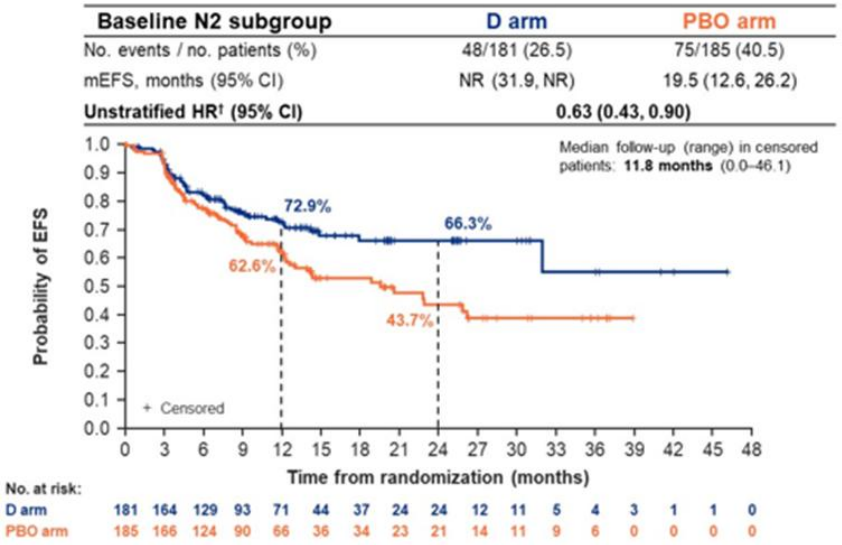
1. Heymach J, et al. N Engl J Med. 2023;389(18):1672-1684; 2. Forde PM, et al. *N Engl J Med*. 2022; 3. Forde PM, et al. ELCC 2023. Abs 54O; 4. Spicer J, et al. ASCO 2024. Abs LBA8010; 5. Wakelee HA, et al. ASCO 2023. Abs LBA500; 6. Wakelee HA, et al. *N Engl J Med*. 2023; 7. Spicer JD, et al. ESMO 2023. Abs LBA56; 8. Cascone T, et al. ESMO 2023. Abs LBA1.

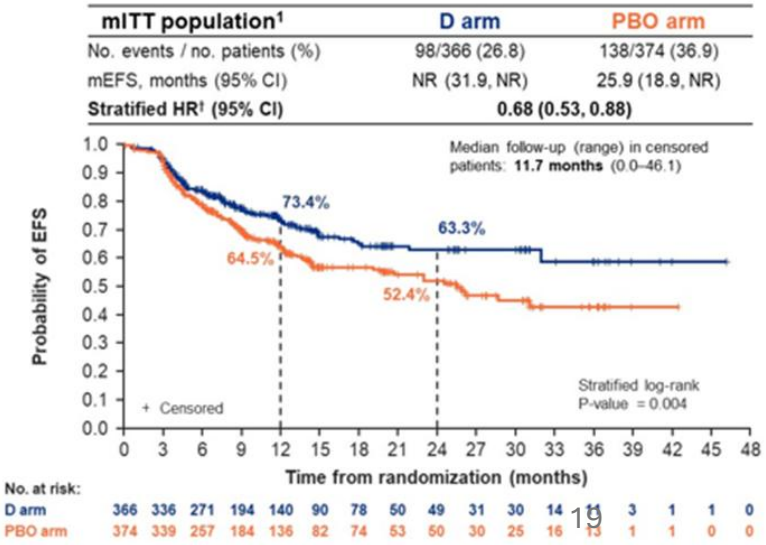
What to do with N2 disease?

AEGEAN: ASCO 2024 Update – Efficacy in Stage III N2 NSCLC



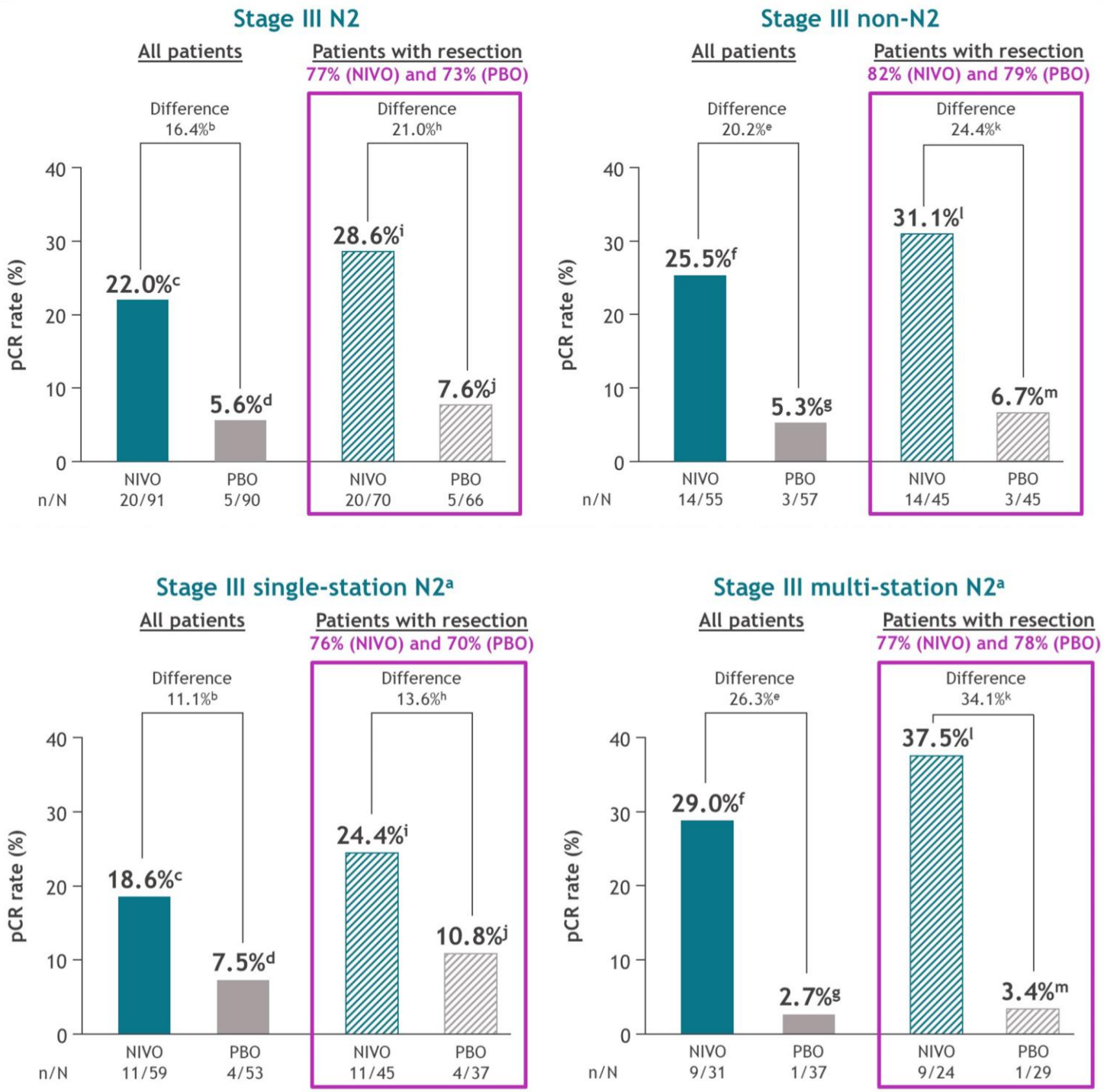






Heymach J, et al. ASCO 2024. Abstract 8011.

CheckMate 816: ASCO 2024 Update – pCR in Stage III N2 NSCLC



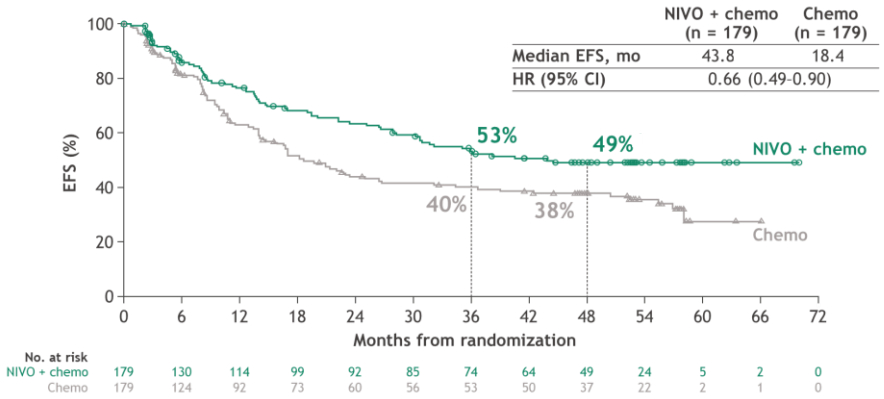
Spicer J, ASCO 2024. Abs LBA 8010.

Neoadjuvant alone or Perioperative?

Perioperative IO Compared With Neoadjuvant IO

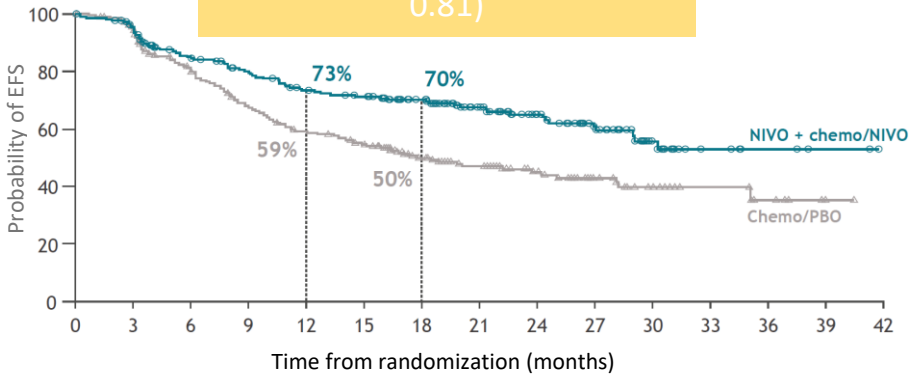
CheckMate 816 (Neoadjuvant Treatment)

HR: 0.66 (95% CI: 0.49, 0.90)



CheckMate 77T (Perioperative Treatment)

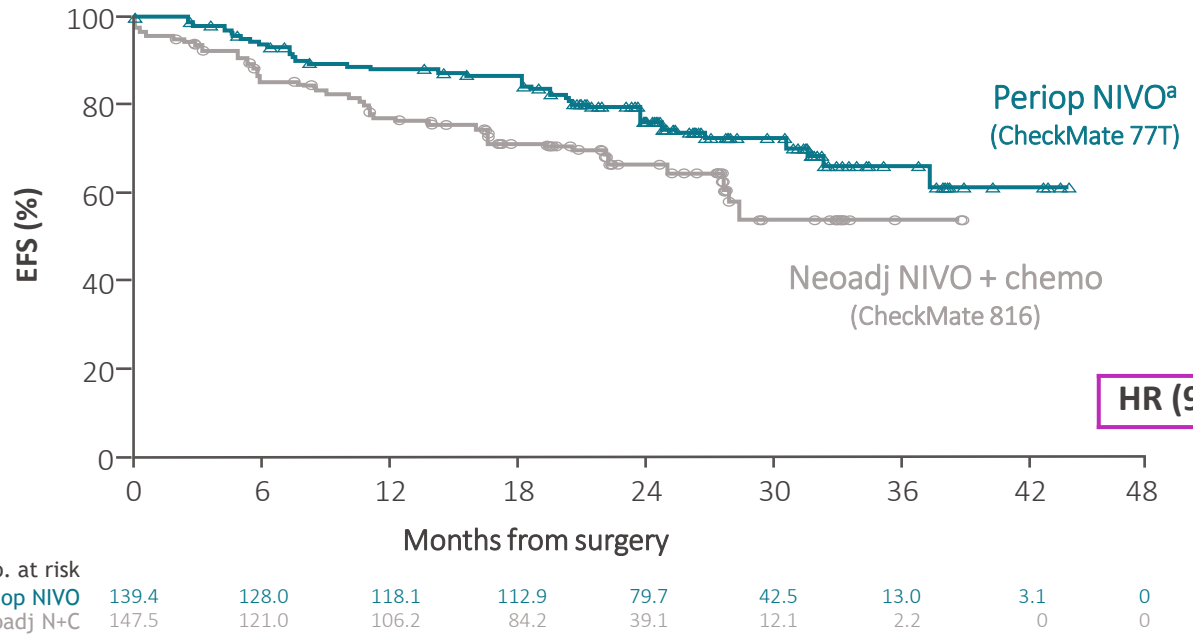
HR: 0.58 (97.36% CI: 0.42, 0.81)



Really Need ANVIL – study of adjuvant nivolumab

Spicer JD, et al. ASCO 2024. Abstract LBA8010. Cascone T, et al. NEJM 2024 390(19), 1756-1769.

Landmark EFS (BICR) from Definitive Surgery



	Weighted (ATE)[b]	
	Periop NIVO[a] (n = 139.4[c])	**Neoadj NIVO + chemo (n = 147.5[c])**
HR (95% CI)	**0.61 (0.39–0.97)**	

- HR (95% CI): ATT[d] weighted analysis, 0.56 (0.35–0.90); unweighted analysis, 0.59 (0.38–0.92)

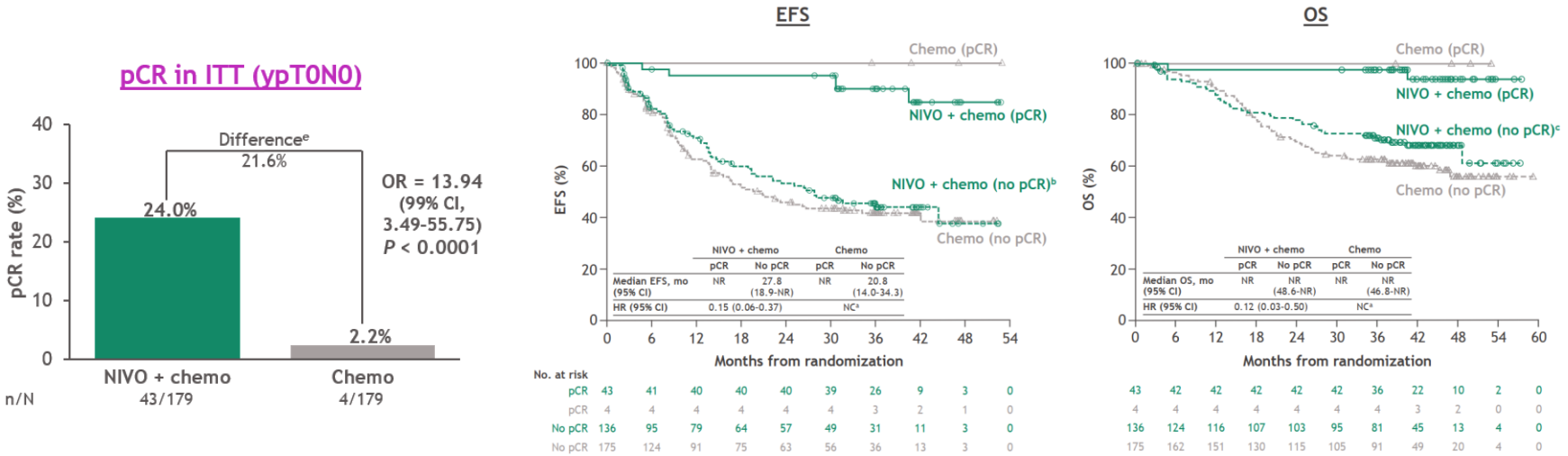
Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. [a]Includes only patients who received ≥ 1 dose of adjuvant NIVO. [b]ATE: varying weights were applied to all patients in both neoadjuvant NIVO + chemo arm (CheckMate 816) and perioperative NIVO (CheckMate 77T) to make them comparable to one another. [c]N values fractional due to weighting. [d]ATT: varying weights were applied to patients in the neoadjuvant NIVO + chemo arm (CheckMate 816) to make them comparable to those in the perioperative NIVO arm (CheckMate 77T).

In the unweighted analysis population, 89 patients (64%) completed adjuvant therapy, and median number of doses (range) was 13.0 (1-13). Unweighted landmark EFS from surgery among all patients who had surgery (regardless of whether they received adjuvant NIVO in CheckMate 77T) for periop NIVO vs neoadj NIVO + chemo: HR = 0.82 (95% CI, 0.55-1.21).

Slide Courtsey of Forde, P etal WCLC 2024

What to do with pCR?

Outcomes by Path CR in NSCLC: CheckMate 816 Nivolumab plus Chemotherapy

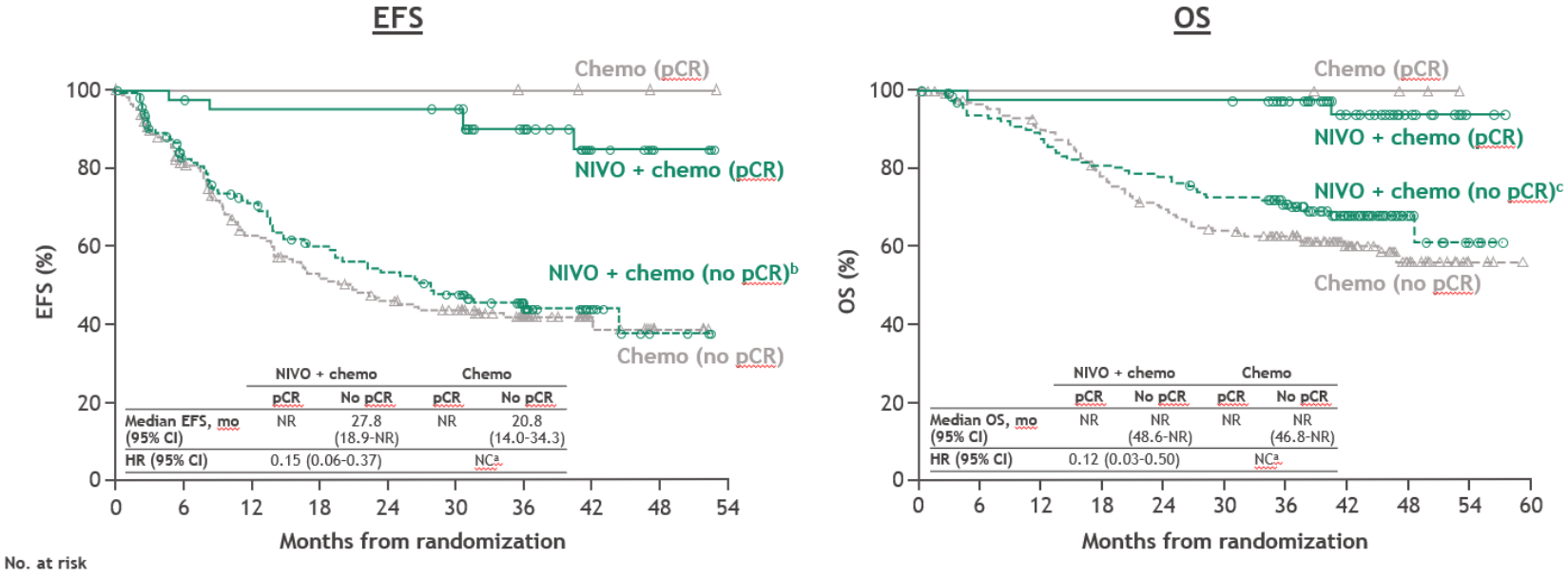


pCR=0% residual viable tumor cells in both primary tumor (lung) and sampled LN (≥ 5 stations, including ≥ 3 mediastinal, were recommended)

Forde P et al AACR 2020; Provencio M et al ESMO 2023

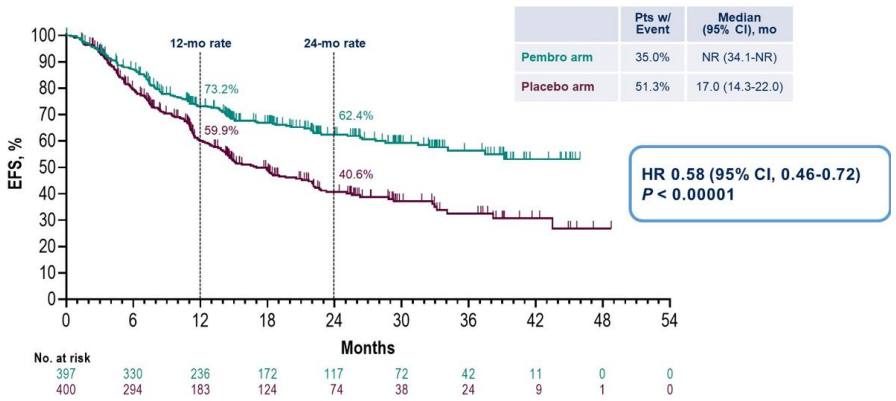
What does adjuvant IO add after neoadjuvant IO?

If pCR occurs it portends a >90% 3 yr EFS and >95% likelihood of being alive at 3 years - *without* adjuvant IO



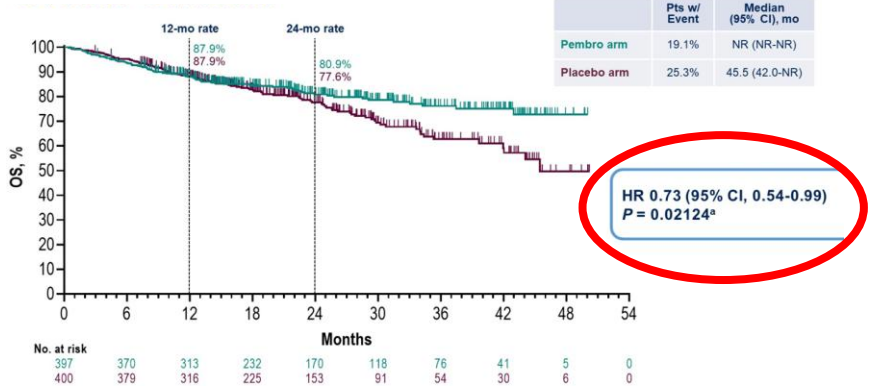
CheckMate 816 - 3 year outcomes by pCR status

Outcomes:
KeyNote 671 Pembrolizumab + Chemotherapy



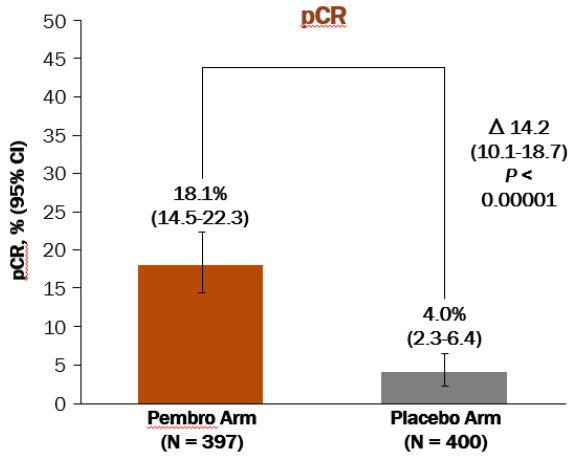
	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)

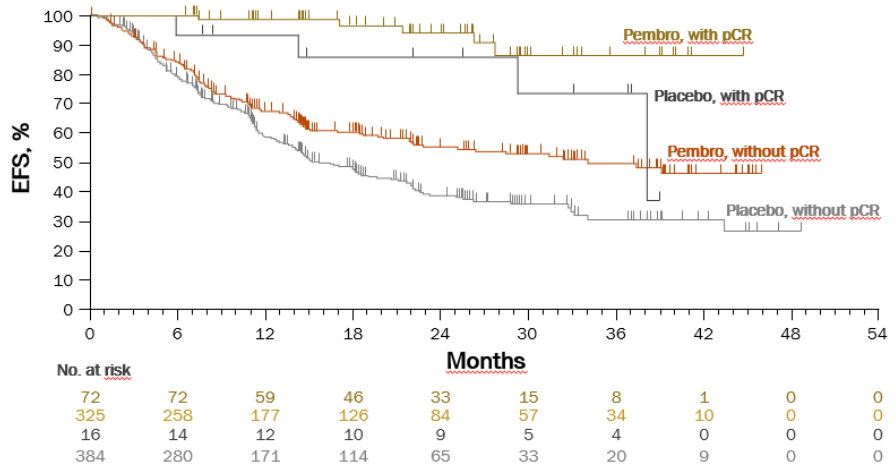
HR 0.58 (95% CI, 0.46-0.72)
P < 0.00001



	Pts w/ Event	Median (95% CI), mo
Pembro arm	19.1%	NR (NR-NR)
Placebo arm	25.3%	45.5 (42.0-NR)

HR 0.73 (95% CI, 0.54-0.99)
P = 0.02124[a]





With pCR
HR 0.33
(95% CI, 0.09-1.22)

Without pCR
HR 0.69
(95% CI, 0.55-0.85)

Wakelee H et al ASCO 2023

Case – Post Surgical Evaluation

- Stage IIIB (T3N2) NSCLC
  - PDL-1 40%
  - No molecular alterations