Adjuvant Treatment of Early-Stage NSCLC

Karen Kelly, MD
CEO, IASLC

The Data for Adjuvant EGFR TKIs

Trial	Regimen	Stage	Landmark DFS (%)		5-Year OS (%)		
			TKI	Control	TKI	Control	
ICTAN	**6 / 12 Month icotinib vs obs**	**II - IIIA (55-56% N2+)**	**5-yr 50% / 51% HR 0.41 (0.27-0.62)**	**25% 25%**	**74% / 75% HR 0.56 (0.32-0.98)**	**65%**	**DFS and OS Improved**
ADAURA	3 yrs osimertinib vs placebo	II-IIIA population	4-yr 70% HR 0.23 (0.18-0.30)	29%	85% HR 0.49 (0/33-0.73)	73%	**DFS and OS Improved**
RADIANT	2 years erlotinib vs chemo	IB-IIIA (48% Stage I)	2-yr 75% HR 0.61 (0.38-0.98)	54%	Immature		
EVIDENCE	2 years icotinib vs chemo	II - IIIA (57-62% N2+)	3-yr 64% HR 0.36 (02.4-0.55)	33%	Immature		DFS Improved
CTONG 1104	2 years gefitinib vs chemo	II - IIIA (64-65 N2+)	5-yr 23% HR 0.56 (0.40-0.79)	23%	53% HR 0.92 (0.62-1.36)	51%	DFS Improved
IMPACT	2 years gefitinib vs chemo	II-III (58-62% N2+)	5-yr 32% HR 0.92 (0.67-1.28)	34%	78% HR 1.03 (0.65-1.65)	75%	
EVAN	2 years erlotinib vs chemo	IIIA (94-100% N2+)	5-yr 48% HR 0.38 (0.20-0.70)	N/A	85% HR 0.37 (0.19-0.73)	51%	**DFS and OS Improved**

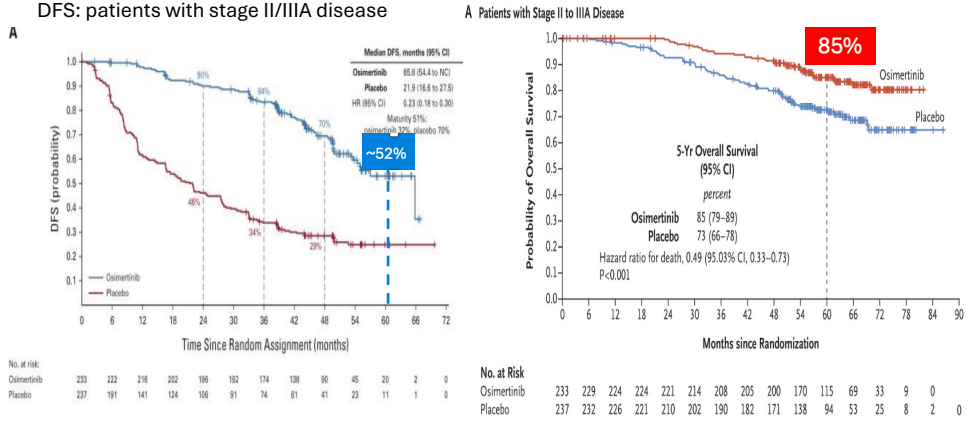
He et al. Lancet Resp Med. 2021;9(9):1021-1029; Tada et al. Clin Oncol. 2022;40(3):231-241; O'Brien et al. JCO 2015;33(15):suppl7540 Abstract #7540; Zhong et.al. JCO 2021;39(7):713-722; Yue et al. JCO 2022;40(34):3912-3917; Kelly et al. JCO 2015;33(34):4007-14; Tsuboi et al. NEJM 2023;389:137-147; Herbst et al. J Clin Oncol. 2023 Apr 1;41(10):1830-1840.

The Data for Adjuvant EGFR-TKIs

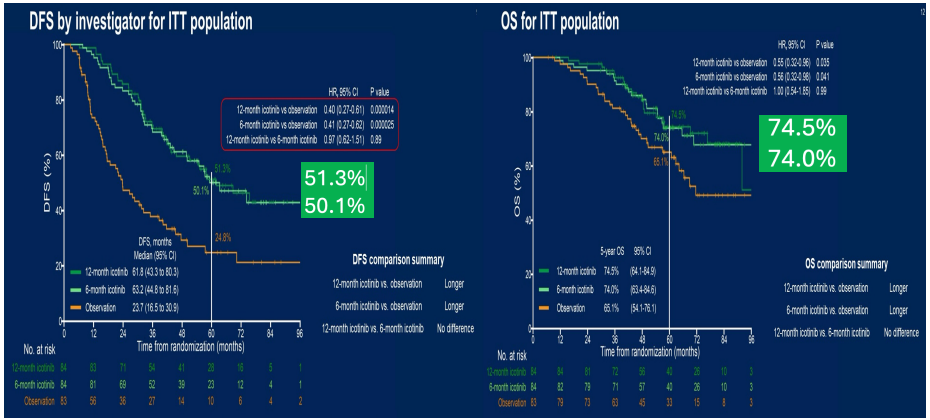
Trial	N	Treatment	Stage	Primary Endpoint	HR	Secondary Endpoint	HR
ADUARA (ASCO 2020, 2023) International	682	Osimertinib vs placebo for 3 years (Patient may or may not have had adjuvant chemotherapy)	IB (> 4cm) -IIIA (7th ed.)	DFS in Stage II-IIIA	0.20	OS	0.49 for Stage II-IIIA
ICTAN (ASCO 2024) China	318	Icotinib for 6 months or 12 months vs placebo (All patients had > 2 cycles of adjuvant chemotherapy)	II - IIIA (7th ed.)	DFS	0.41 (6 mos) 0.40 (12 mos)	OS	0.56 (6 mos) 0.55 (12 mos)

ADAURA

DFS: patients with stage II/IIIA disease

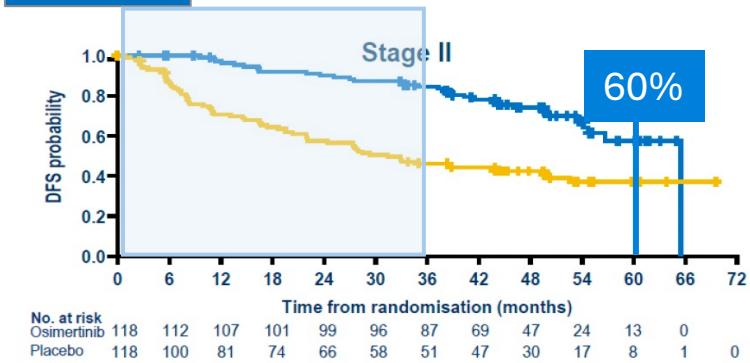


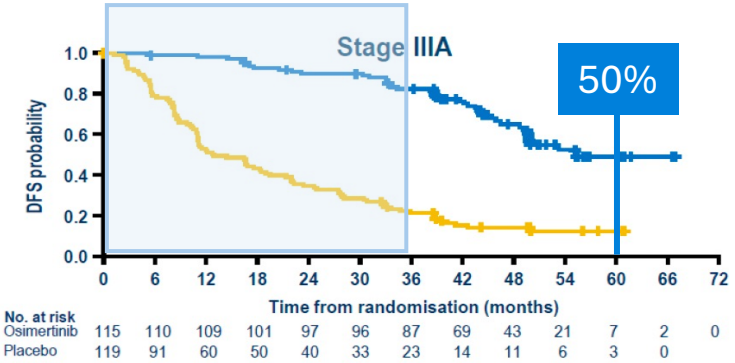
ICTAN



How long do you need systemic therapy?

ADAURA





ICTAN

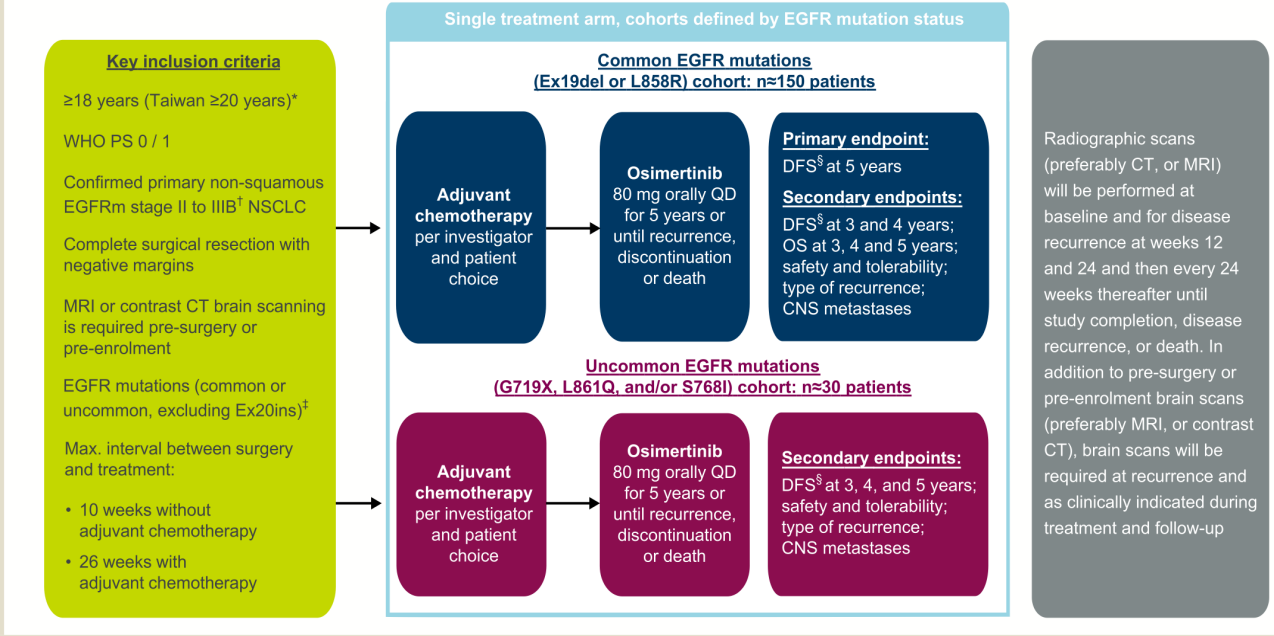
Most tumor progression occurs after stopping a TKI

Slide courtesy of Dr. Jay Lee

Soo RA, et al. Clin Lung Ca 2023

How long do you need systemic therapy?

Figure 1 TARGET Study Design.



Soo R, et al. Clin Lung Cancer 2024

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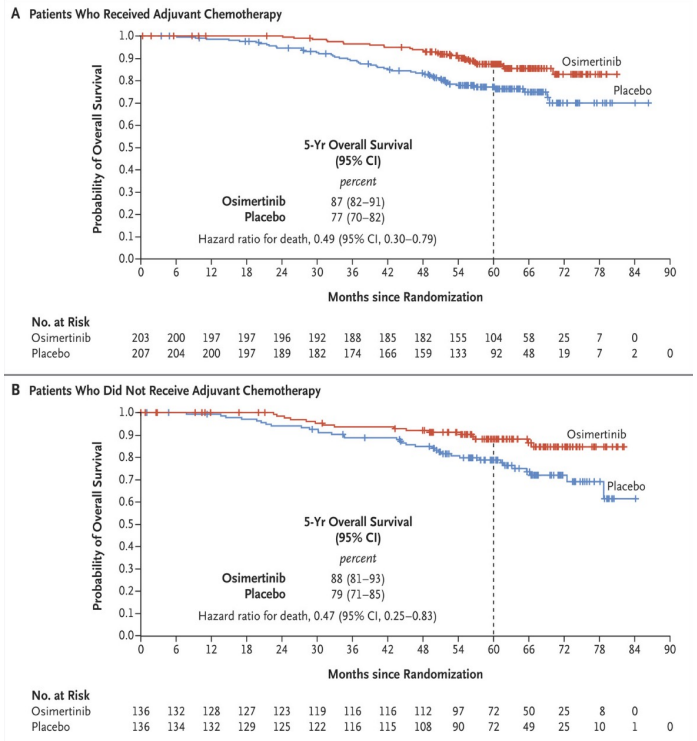
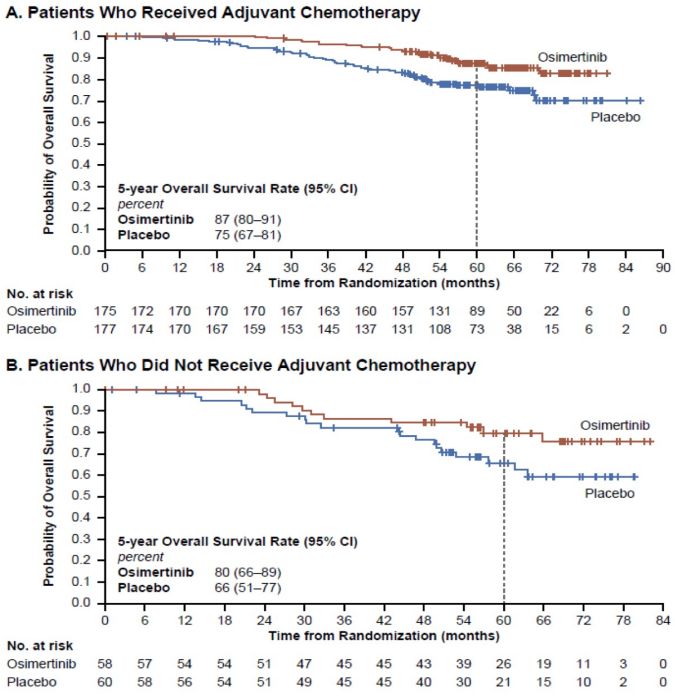
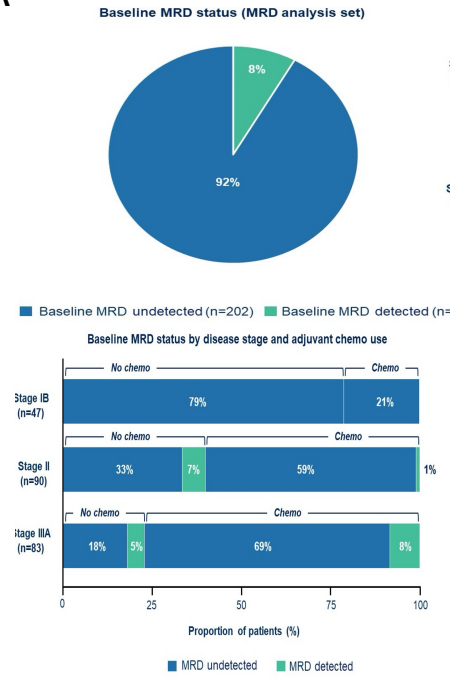
Do we need adjuvant chemotherapy?

ADAURA – All Patients



ADAURA –Patients with Stage II/IIIA





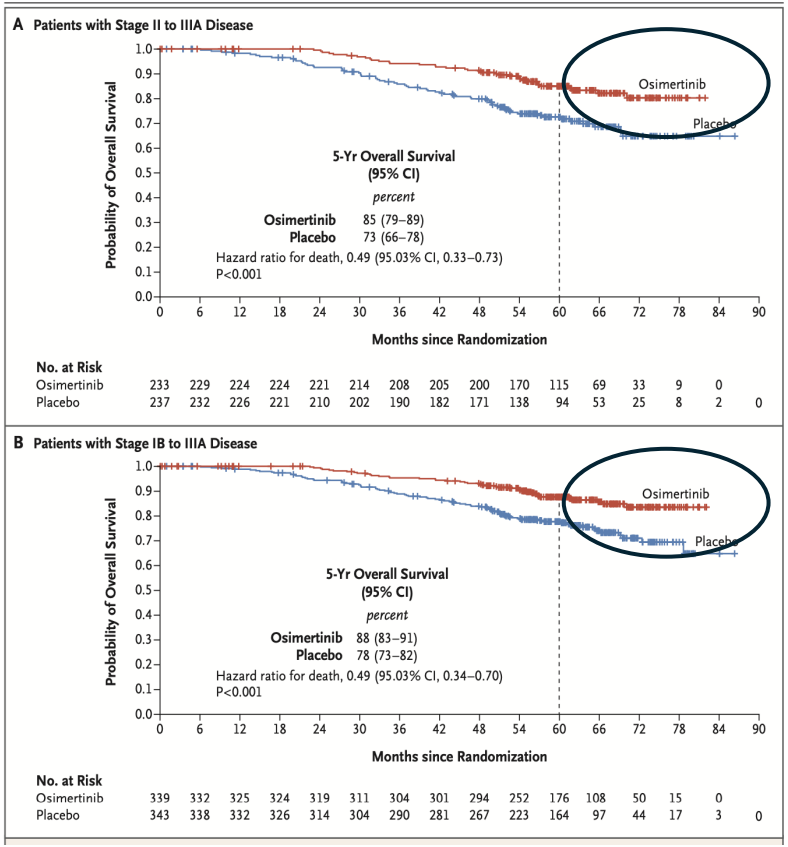
Patients with Stage II and III NSCLC who did not receive adjuvant chemotherapy were more likely to have baseline MRD positivity.
Stage II 1 7% vs 1%
Stage III 21% vs 10%

Tsuboi M, et al. NEJM 2023, John T, et al. ASCO 2024

Slide courtesy of Dr. Jay Lee

Soo RA, et al. Clin Lung Ca 2023

Are we curing patients with TKIs?



- More time is needed to definitively determine if we are curing a subset of patients.
- If so, who are these patients?
- What clinical and biological features are likely to predict cure?

Tsuboi M, et al. NEJM 2023

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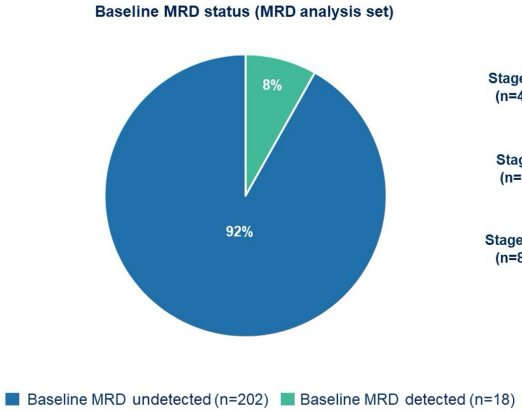
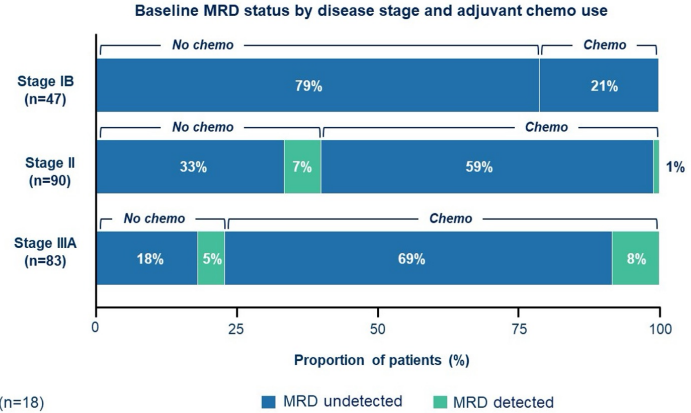
Soo RA, et al. Clin Lung Ca 2023

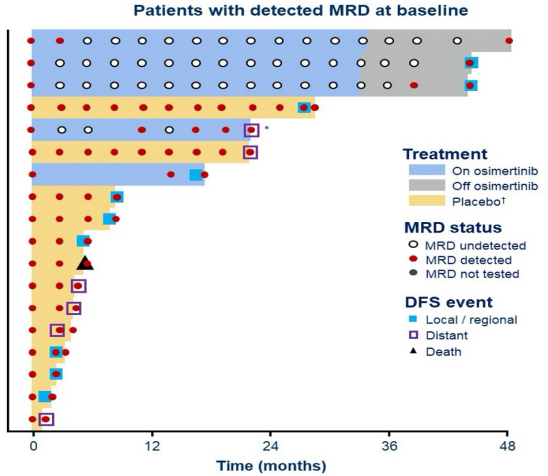
The Role of ctDNA

Molecular residual disease analysis from the ADAURA trial of adjuvant osimertinib in patients with resected EGFR-mutated stage IB–IIIA non-small cell lung cancer

Thomas John,[1] Christian Grohé, Jonathan Goldman, Terufumi Kato, Konstantin Laktionov, Laura Bonanno, Marcello Tiseo, Margarita Majem, Manuel Dómine, Myung-Ju Ahn, Maurice Pérol, Ryan Hartmaier, Jacqulyne Robichaux, Preetida Bhetariya, Aleksandra Markovets, Yuri Rukazenkov, Caitlin Muldoon, Roy S. Herbst, Masahiro Tsuboi, Yi-Long Wu







- Of 18 patients with detected MRD at baseline
  - 4 / 5 patients receiving osimertinib cleared MRD
  - 0 / 13 patients receiving placebo cleared MRD

17 of 18 patients progressed

ASCO 2024

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Additional Randomized Trials

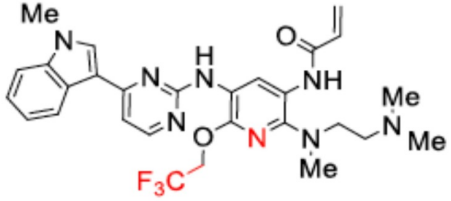
FORWARD

A Phase III, Double-blind, Randomized, Placebo-Controlled Multi-centre, Study to Assess the Efficacy and Safety of **Furmonertinib** (AST2818) Versus Placebo, in Patients With Epidermal Growth Factor Receptor Mutation Positive Stage II-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy NCT04853342

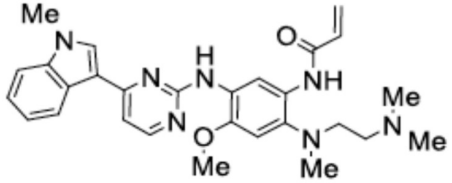
N = 318

Primary Endpoint: DFS

Furmonertinib 80 mg po daily for 3 years (?)



Furmonertinib



Osimertinib

Zhang SS and Ou SI. Lung Cancer: Targets and Therapy Oct 2022

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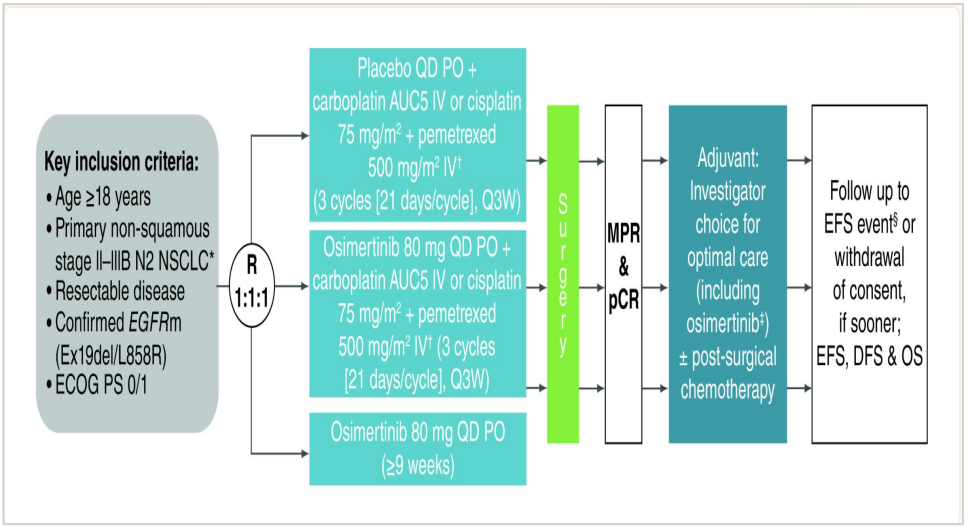
Soo RA, et al. Clin Lung Ca 2023

Building Upon the Results

NEOADAURA 2



Approximately 351 patients with resectable stage II–IIIB N2 *EGFR*m NSCLC will be enrolled. This sample size was based on an approximate 90% power to detect a statistically significant difference in MPR of 20%, with a two-sided overall significance level of 5% when assuming a 20% MPR in the control arm.

Tsuboi M, et al. Future Oncology 2022

Study	Phase	N	Stage	Therapy	Results
Aredo 2023 NCT03433469	II	27	I-IIIA	Osimertinib x 8wks → sx	MPR 5 % (4/15).
NEOS Lv 2023 ChiCTR1800016948	IIb	38	IIA-IIIB	Osimertinib x 6wks → sx	ORR 71.1 % (27/38). MPR 10.7%

Ongoing clinical trials with combination neoadjuvant *EGFR*-TKI and chemotherapy.

Study	Phase	Stage	N	Therapy	Primary endpoint (s)
NCT04470076 [46]	II	IIa-IIIb	30	Platin-based/pemetrexed x 3 21-day cycles with concurrent afatinib during cycles → sx → afatinib x 2 yrs	MRP, ORR
NOCE01 NCT05011487 [47]	II	III	30	Cisplatin/pemetrexed x 2 21-day cycles with concurrent osimertinib x 60 days → sx	Complete LN clearance
Neolpower NCT05104788 [48]	II	II-IIIB	27	Platin-based/pemetrexed x 2 21-day cycles with concurrent icotinib x 6 wks → sx	MPR
FORSEE NCT05430802 [49]	II	IIIA-IIIB	40	Cisplatin/pemetrexed x 3 21-day cycles with concurrent furmonertinib x 9 wks → sx	ORR
NeoADAURA (NCT04351555) [50]	III	II-IIIB (N2)	328	neoadjuvant chemo + placebo vs chemo + osimertinib vs osimertinib 9 wks → sx → investigator choice (osimertinib x 3yrs +/- chemo)	MPR
NCT05132985 [51]	II	II-IIIB N2	45	Platin-based/pemetrexed x 2 21-day cycles with concurrent icotinib → sx → platin-based doublet chemotherapy x 2 21-day cycles with icotinib x 2 yrs	MPR

Grant C and Nagasaka M. Cancer Treatment Review March 2024

Slide courtesy of Dr. Jay Lee

Soo RA, et al. Clin Lung Ca 2023

Building Upon the Results
High Risk Stage I NSCLC

- Prospectively collected data
- Pathological Stage I (8th ed)
- N=1298

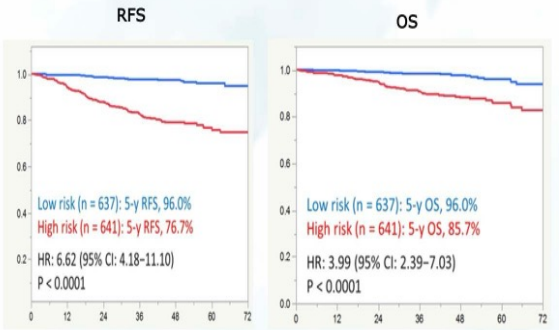
Multivariable Cox Analysis for RFS

Variables	HR	95% CI	P value
Age (> 70 y)	2.14	1.50–3.09	<0.0001
Gender (Female)	0.71	0.48–1.05	0.089
Invasive component size (> 2 cm)	1.60	1.09–2.36	0.016
Histology (Adenocarcinoma)	0.92	0.62–1.40	0.698
Lymphatic permeation	1.67	1.13–2.43	0.008
Vascular invasion	2.78	1.84–4.22	<0.0001
Visceral pleural invasion	1.81	1.22–2.68	0.003

High-risk group (n = 641): Invasive component size > 2 cm or Lymphatic permeation or Vascular invasion or Visceral pleural invasion

Low-risk group (n = 637): Invasive component size ≤ 2 cm and No lymphatic permeation and No vascular invasion and No visceral pleural invasion

Tsutani Y, et al. Ann Thoracic Surg 2022

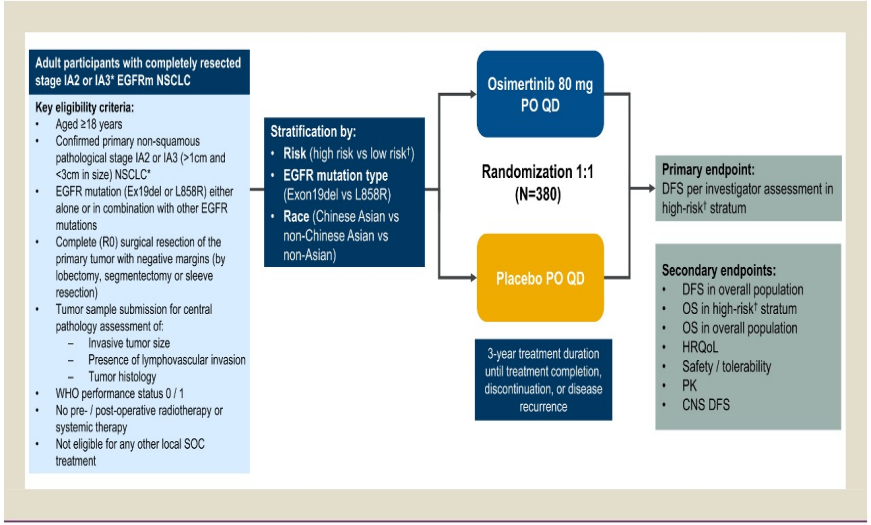


Osimertinib Therapy After Resection in High-risk Stage I EGFRm NSCLC (OSTAR)

- Single arm, single institution (Tianjin University
- 65 patients receiving Osimertinib for 3 years
- Primary endpoint: 3 YR DFS

Slide courtesy of Dr. Jay Lee

ADAURA 2

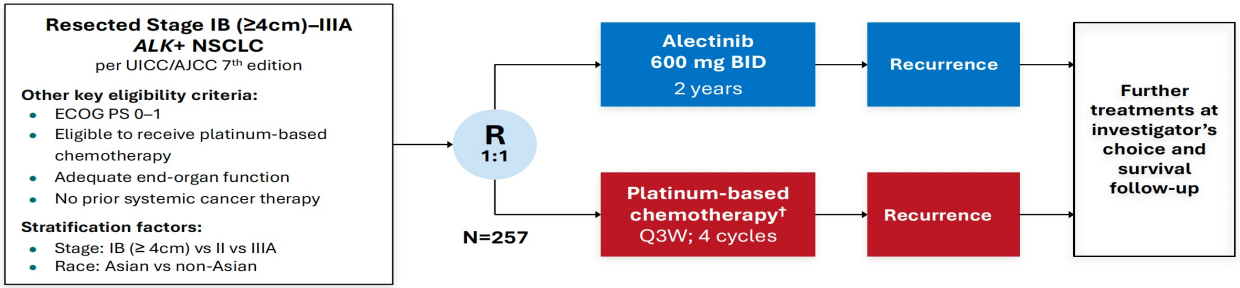


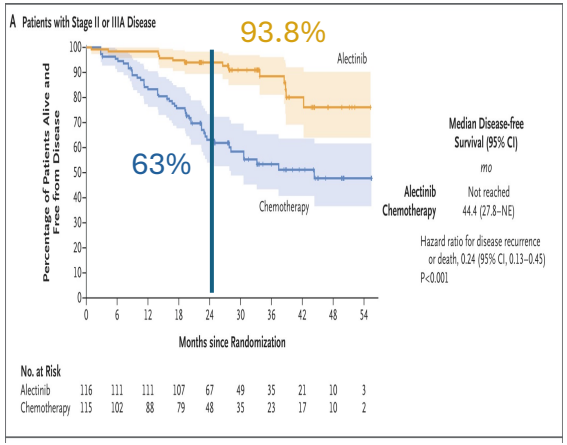
†High-risk defined as presence of ≥1 of the following factors based on central pathology review: largest diameter of invasive component of primary tumor >2 cm, lymphovascular invasion, and/or high- grade histology (≥20% micropapillary, solid, or complex gland adenocarcinoma).

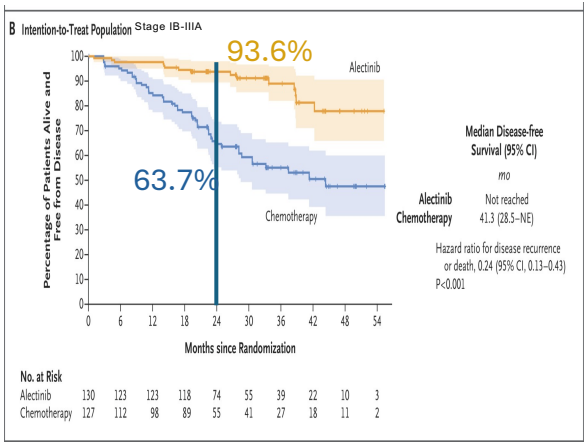
Tsutani Y, et al. Clin Lung Cancer 2023

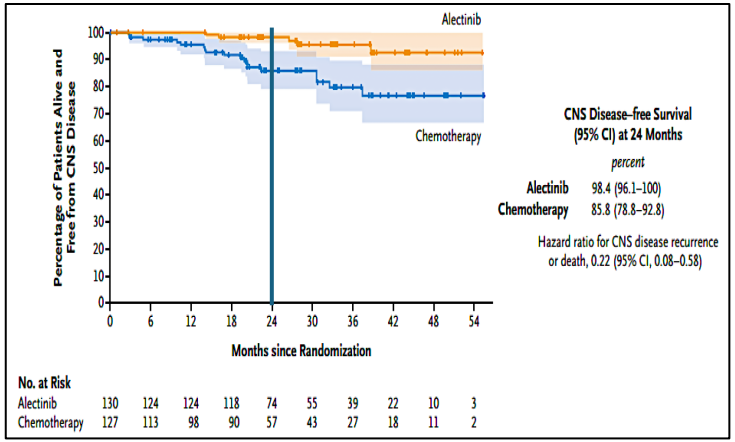
Soo RA, et al. Clin Lung Ca 2023

The Data for Adjuvant ALK-TKIs - ALINA





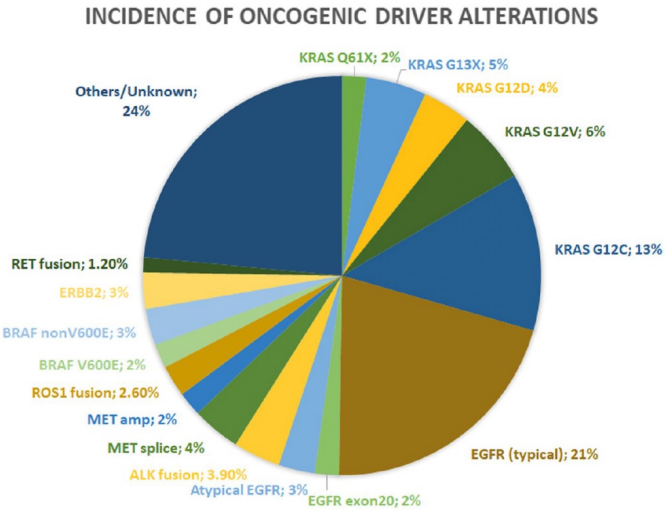




Median FU = 27.8 months

Wu Y, et al NEJM 2024.

Can Patients with Other Oncogenic Drivers Benefit from an Adjuvant TKI?



Friedleander A, et al. Biomarker Research 2024

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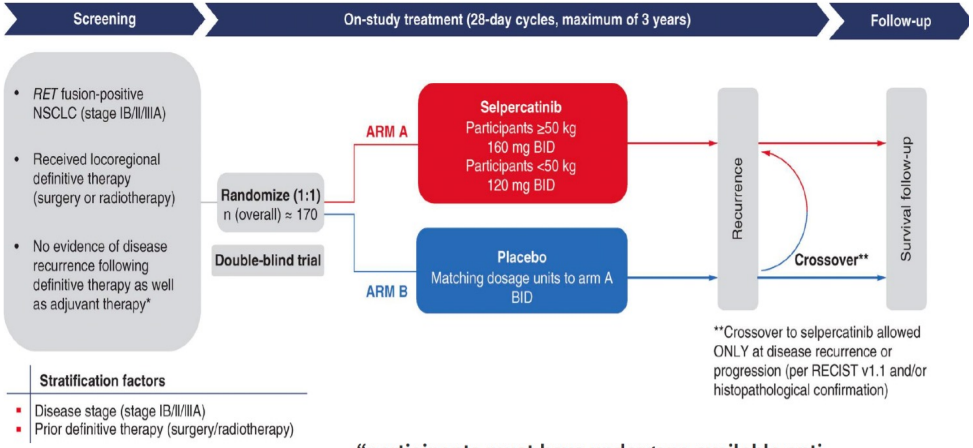


Tsuboi et al, Future Oncology 2022

"participants must have undergone available anti-cancer therapy (including chemotherapy or durvalumab) or not be suitable for it"

IASLC Consensus Recommendations

Recommendation 6: For patients being considered for neoadjuvant or adjuvant systemic therapy, at a minimum, determination of *EGFR* and *ALK* alteration status is required. Tumor proportion score measurement for determination of PD-L1 status should also be considered.

Agreement: 100%

Recommendation 19: For patients with stage II/IIIA disease with *EGFR*-sensitizing mutations, adjuvant Osimertinib is recommended. Adjuvant platinum-based chemotherapy prior to Osimertinib is encourage. For patients with stage IB (T3-4cmN0) disease, adjuvant Osimertinib alone is recommended.

Agreement: 94%

Recommendation 20: For patients with stage IB (tumors ≥ 4 cm) – IIIA disease with ALK alterations, adjuvant alectinib is recommended. Adjuvant chemotherapy prior to alectinib can be considered at the discretion of the treating providers.

Agreement: 95%

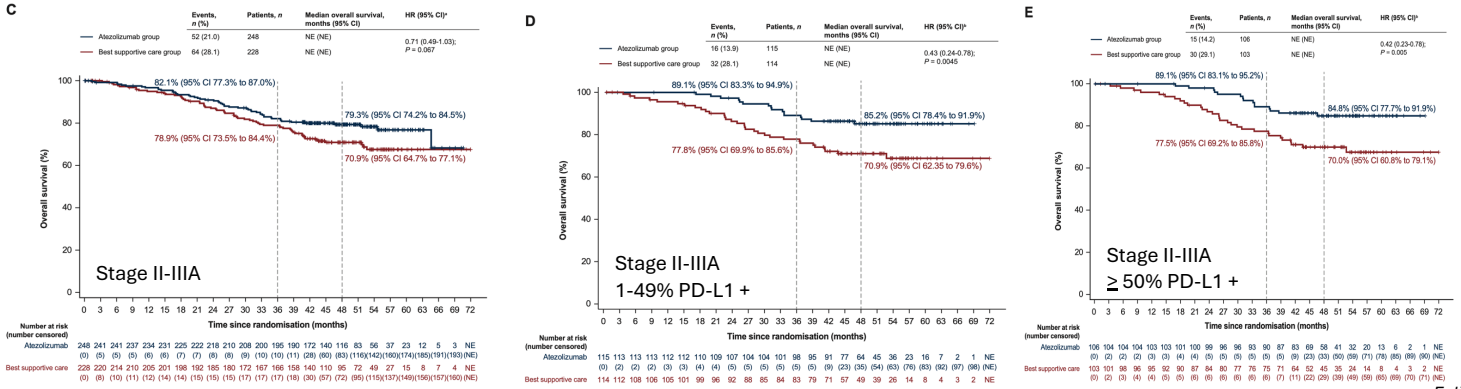
The Data for Adjuvant Immune Checkpoint Inhibitors

Surgery ⟶ Chemotherapy ⟶ ICI

FDA Approved Adjuvant Immunotherapy for NSCLC

	PD-L1 <1%	PD-L1 1-49%		PD-L1 >50%	
IB (>4cm)	Pembrolizumab		Pembrolizumab		Pembrolizumab
II	Pembrolizumab	Atezolizumab	Pembrolizumab	Atezolizumab	Pembrolizumab
IIIA	Pembrolizumab	Atezolizumab	Pembrolizumab	Atezolizumab	Pembrolizumab

Atezolizumab Overall Survival



Felip E, et al.Ann Oncol 2023

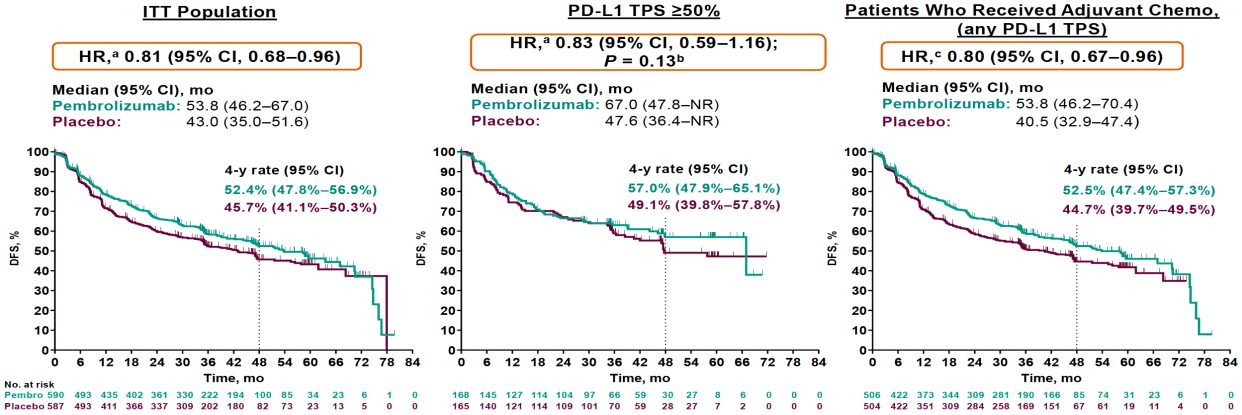
The Data for Adjuvant Immune Checkpoint Inhibitors

Surgery ⟶ Chemotherapy ⟶ ICI

FDA Approved Adjuvant Immunotherapy for NSCLC

	PD-L1 <1%	PD-L1 1-49%		PD-L1 >50%	
IB (>4cm)	Pembrolizumab		Pembrolizumab		Pembrolizumab
II	Pembrolizumab	Atezolizumab	Pembrolizumab	Atezolizumab	Pembrolizumab
IIIA	Pembrolizumab	Atezolizumab	Pembrolizumab	Atezolizumab	Pembrolizumab

Pembrolizumab Disease Free Survival



Besse B, et.al. ESMO Immuo Oncology 2023

Adjuvant Immune Checkpoint Inhibitors

Surgery → Chemotherapy → ICI

Trial	NCT Number	Sponsor	Start Date	Phase	Stage	Participants (*n*)	EGFR mutation/ALK rearrangement	Intervention following surgery	Primary Endpoint	Completion Date
BR31/IFCT1401	NCT02273375	Canadian Cancer Trials Group	2014	3	IB-IIIA AJCC 7th	1415	Included	**Arm A:** (optional chemotherapy and RT if N2) Durvalumab (1 year); **Arm B:** (optional chemotherapy and RT if N2) placebo (1 year) Did not meet primary endpoint 6/2024	DFS	2024
ANVIL	NCT02595944	National Cancer Institute (NCI)	2016	3	IB-IIIA AJCC 7th	903	Excluded	**Arm A:** (optional chemotherapy and RT) nivolumab (1 year, Q4W); **Arm B:** (optional chemotherapy and RT) observation (1 year)	DFS, OS	2024
ALCHEMIST Chemo-IO	NCT04267848	National Cancer Institute (NCI)	2020	3	IIA-IIIB AJCC 8th	1210	Excluded (applicable to non-squamous NSCLC)	**Arm A:** platinum doublet (4 cycles, Q3W) then observation; **Arm B:** platinum doublet (4 cycles, Q3W) then pembrolizumab 17 cycles (Q3W) or 16 cycles (Q6W, after 10/14/2020); **Arm C:** platinum doublet plus pembrolizumab (4 cycles, Q3W), then pembrolizumab 13 cycles (Q3W) or 12 cycles (Q6W, after 10/14/2020)	DFS	2024
NADIMADJUVANT	NCT04564157	Fundación GECP	2021	3	IB-IIIA AJCC 8th	210	Excluded	**Arm A:** Paclitaxel+carboplatin+nivolumab (4 cycles, Q3W) then nivolumab (6 cycles, Q4W); **Arm B:** Paclitaxel+carboplatin (4 cycles, Q3W) then observation	DFS	2028
LungMate-008	NCT04772287	Shanghai Pulmonary Hospital	2021	3	II-IIIB AJCC 8th	341	Excluded	**Arm A:** platinum doublet (4 cycles, Q3W) then toripalimab (4 cycles, Q3W); **Arm B:** platinum doublet (4 cycles, Q3W) then placebo (4 cycles, Q3W)	DFS	2027

Felip E, et al.Ann Oncol 2023

Adjuvant Immune Checkpoint Inhibitors

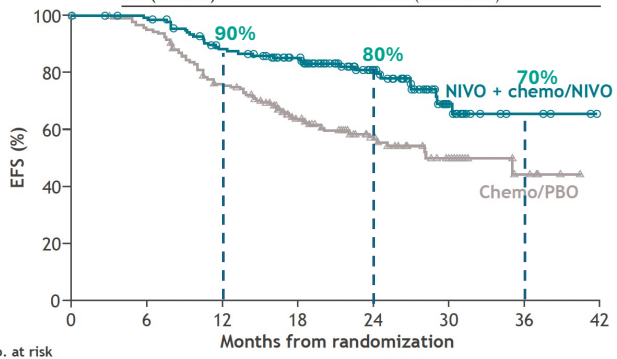
Neoadjuvant Therapy → Surgery → ICI

What is the contribution of the adjuvant component?

CM 77T

Adjuvant

	NIVO + chemo/NIVO (n = 142)	Chemo/PBO (n = 152)
Median EFS, mo (95% CI)	NR (NR-NR)	35.1 (22.0-NR)
HR (95% CI)	0.45 (0.29-0.69)	

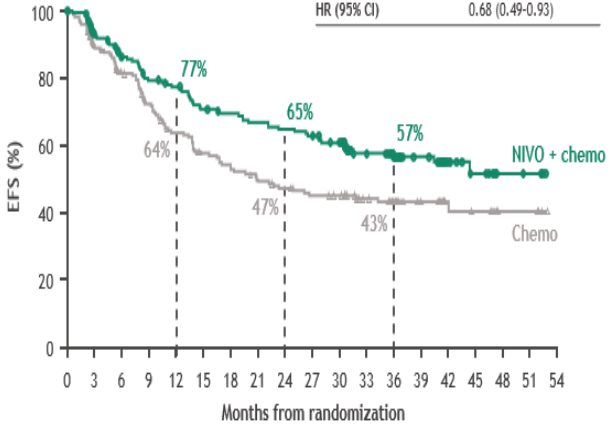


No. at risk

NIVO + chemo/NIVO	142	139	118	97	60	19	4	0
Chemo/PBO	152	144	112	74	41	19	6	0

CM 816

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo (95% CI)	NR (31.6-NR)	21.1 (14.8-42.1)
HR (95% CI)	0.68 (0.49-0.93)	



- NIVO + chemo/NIVO improved EFS vs chemo/PBO with numerically higher benefit in patients who received adjuvant treatment (HR [95% CI], 0.45 [0.29-0.69]) vs those who did not (HR [95% CI], 0.55 [0.37-0.83])[a]

Median follow-up (range): 25.4 months (15.7-44.2).

[a]HR (95% CI), 0.17 (0.11-0.27) in those who received adjuvant treatment vs those who did not in the NIVO + chemo/NIVO arm and 0.15 (0.10-0.22) in the chemo/PBO arm.

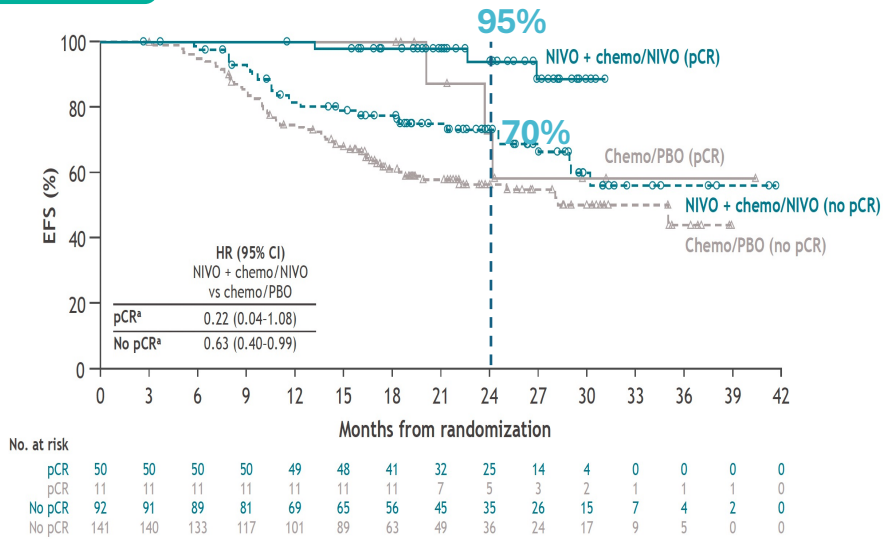
Cascone T, et al. ESMO 2023

Adjuvant Immune Checkpoint Inhibitors

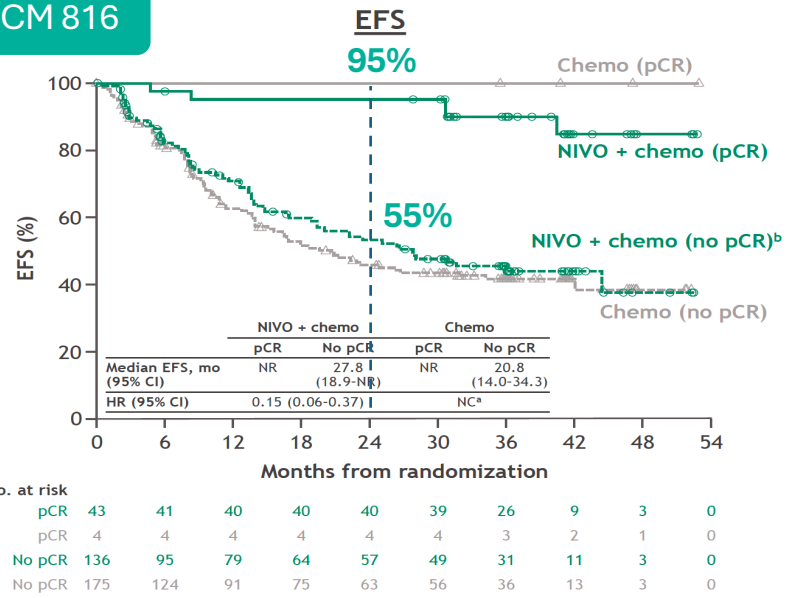
Neoadjuvant Therapy ⟶ Surgery ⟶ ICI

What is the contribution of the adjuvant component according to pathological response?

CM 77T



CM 816



Forde P, et al. NEJM 2022; Cascone T, et al. ESMO 2023

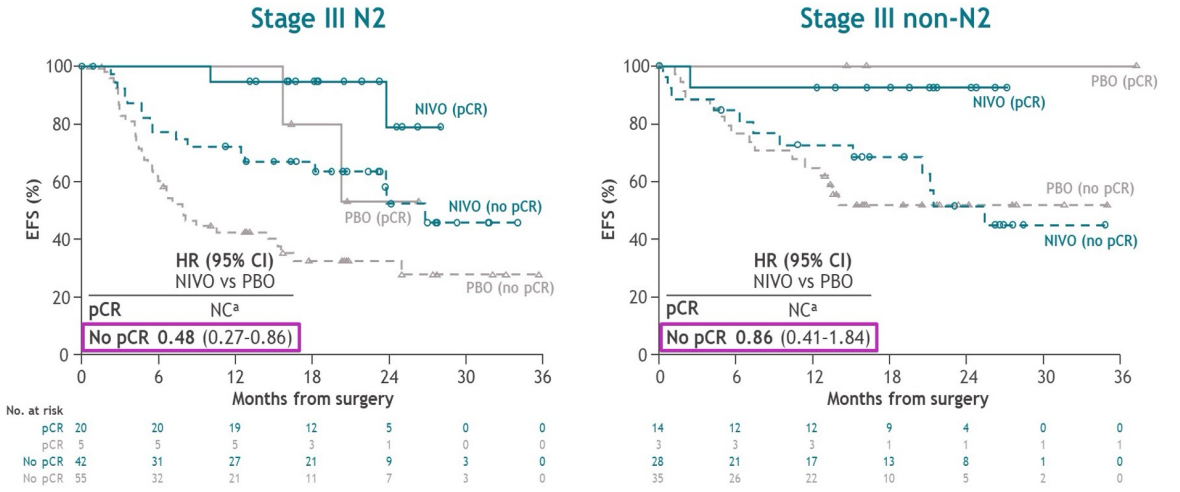
Adjuvant Immune Checkpoint Inhibitors

Neoadjuvant Therapy ⟶ Surgery ⟶ ICI

What is the contribution of the adjuvant component according to N status and pathological response?

CM 77T

Landmark EFS from definitive surgery by pCR status



Landmark EFS HRs for no pCR[a]: 0.59[b] (single-station N2) and 0.36[c] (multi-station N2)[d]

Median follow-up (range): 25.4 months (15.7-44.2). [a]HRs were NC for patients with pCR as there were < 10 patients in either treatment arm. [b,c]95% CI: [b]0.29-1.20; [c]0.12-1.09. [d]N2 subcategory was not reported in 1 patient in the NIVO arm.

Cascone T, et al. ASCO 2024

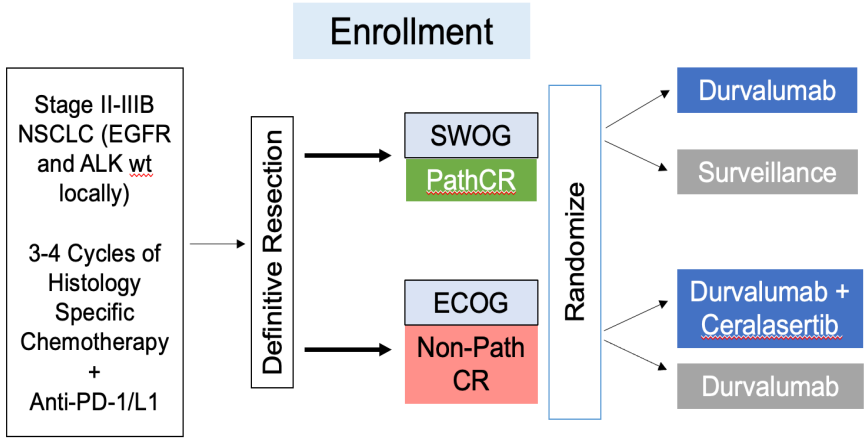
Adjuvant Immune Checkpoint Inhibitors

Neoadjuvant Therapy → Surgery → ICI

Prospective Evaluation of the Role of Adjuvant Therapy

Study	Regimen	N	pCR	No pCR
Neoadjuvant				
Checkmate 816 (ELCC 2023	Nivolumab + CT (3 cycles)	179	43 pts 24%	136 pts 76%
Perioperative (neoadjuvant + adjuvant)				
AEGEAN (AACR 2023)	Durvalumab + CT	366	63 pts 17.2%	303 pts 82.8%
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CT	397	72 pts 18.1%	325 pts 81.2%
CheckMate 77T (ESMO 2023)	Nivolumab + CT	229	58 pts 25.3%	171 pts 74.7%
RATIONALE-315 (ESMO 2023)	Tislelizumab + CT	226	92 pts 40.7%	134 pts 59.3%

Combined ECOG/SWOG CLEAR-INSIGHT SCHEMA



Highlights importance of evaluating novel adjuvant regimens

Summary of the Phase III Results in Resectable NSCLC

Study	Neoadjuvant (CT-IO vs. CT)	N	EGRF/ ALK	Adjuvant (IO 1Y vs. Placebo)	Stage	Primary Endpoint	DFS/EFS HR	DFS/EFS Rate	OS Rate	OS HR
Neoadjuvant										
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	358	Excluded (if known)	None	IB-IIIA (7th ed.) II-IIIB (8th ed.)	pCR EFS	0.68	65% 2Y 57% 3Y	83% 2Y 78% 3Y	0.62
Perioperative (neoadjuvant + adjuvant)										
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	802	Excluded	Durvalumab	IIA-IIIB (8th ed.)	pCR EFS	0.68	63% 2Y	NR	NR
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CB (4 cycles)	786	Included	Pembrolizumab	II-IIIB (8th ed.)	EFS OS	0.59	62% 2Y	79% 2Y 71% 3Y 67% 4Y	0.72
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)	461	Excluded (if known)	Nivolumab	II-IIIB (8th ed.)	EFS	0.58	70% 1.5Y	NR	NR
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)	500	Excluded	Toripalimab + CT (1 cycle), Toripalimab	II-III	EFS MPR	0.40 (stage 3)	65% 2Y (stage 3)	NR	NR
RATIONALE -315 (ESMO 2023/24)	Tislelizumab + CT (3-4 cycles)	453	Excluded	Tislelizumab (8 cycles)	II-IIIA	pCR	0.56	68.3% 2Y	88.6 2Y	0.62
Adjuvant. (different patient population)										
IMpower 010 (WCLC 2022) (ESMO 2023)	N/A	1280	Included	CT mandatory Atezolizumab	II-IIIA (8th ed.)	DFS	0.66 (PD-L1≥1%)	75% 2Y	79% 4Y	0.71* (PDL1-≥1%)
Keynote-091 (ESMO 2022)	N/A	1177	Included	CT optional Pembrolizumab	II-IIIA (8th ed.)	DFS	0.76	73% 1.5Y	82% 3Y	0.87*

* Not significant

IASLC Consensus Recommendations

Recommendation 1: Patients should be evaluated by a multidisciplinary team to devise an individual treatment plan, ideally in a tumor board setting consisting of surgeons, medical oncologists, radiation oncologists, pathologists, pulmonologists, radiologists, and supportive care staff.

Agreement: 100%

Recommendation 7: Neoadjuvant chemoimmunotherapy is strongly preferred to upfront surgery for medically operation patients with resectable clinical stage IIIA or IIIB NSCLC at first presentation, irrespective of PD-L1 expression level.

Agreement: 94%

Recommendation 15: Neoadjuvant chemoimmunotherapy followed by surgery is preferred to upfront surgery for medically operable patients in technically resectable clinical stage II NSCLC at first presentation, regardless of PD-L1 expression

Agreement: 65% ***Nonconsensus Recommendations***

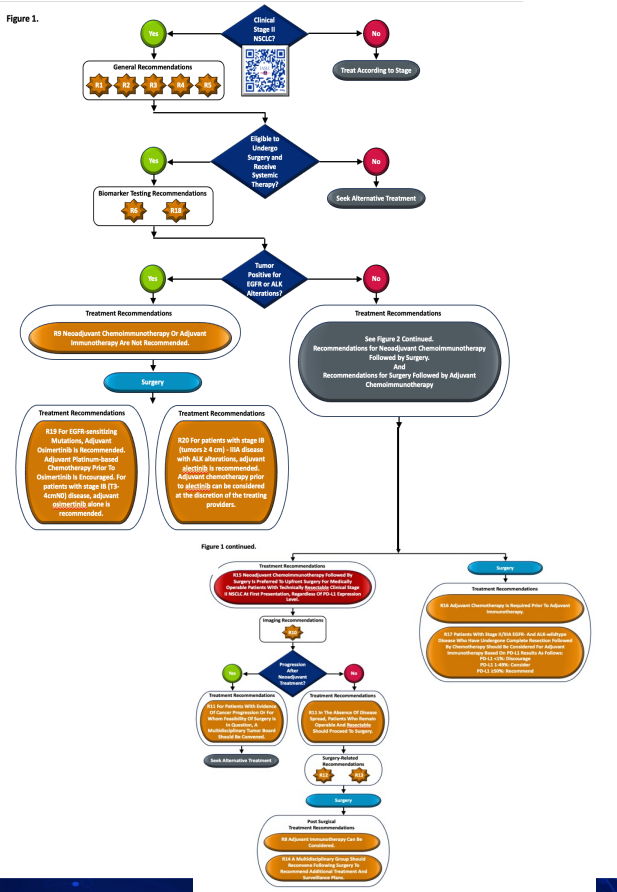
Recommendation 8: Following surgery in patients who receive neoadjuvant chemoimmunotherapy, adjuvant immunotherapy can be considered.

Agreement: 94%

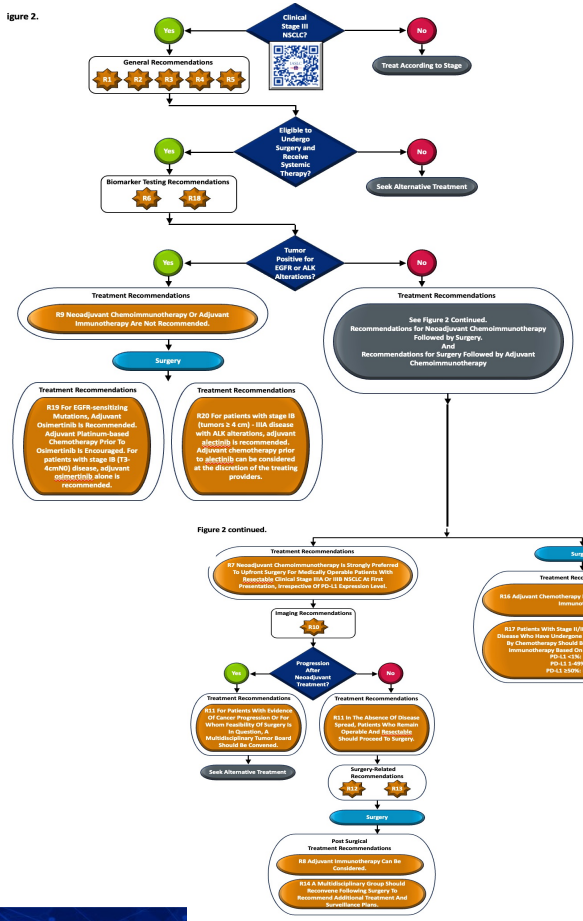
IASLC Consensus Recommendations


Neoadjuvant and Adjuvant Treatment for Early-Stage Resectable Non-small Cell Lung Cancer (NSCLC): Consensus Recommendations from the International Association for the Study of Lung Cancer (IASLC)

Figure 1.



igure 2.



Take Home Message

1. Adjuvant osimertinib is the standard of care for patients with resectable early-stage NSCLC.

2. Adjuvant alectinib is the standard of care for patients with resectable early-stage NSCLC.

3. Important questions regarding duration of treatment, the role of adjuvant chemotherapy and determining the benefit of TKIs for patients who have other types of oncogenic driven disease are being addressed.

4. Adjuvant immune checkpoint inhibitors after surgical resection and chemotherapy is an option for patients with early-stage resectable NSCLC.

5. Adjuvant immune checkpoint inhibitors after neoadjuvant chemotherapy plus immune checkpoint inhibitors and surgical resection (perioperative regimen) is increasing as the preferred regimen for the treatment of patients with early-stage resectable NSCLC.

6. Important questions addressing who needs adjuvant immune checkpoint inhibitors after neoadjuvant chemotherapy + immune checkpoint inhibitors and strategies to enhance the efficacy of adjuvant treatment are being tackled.

CONQUERING LUNG AND OTHER THORACIC CANCERS WORLDWIDE IN THE 21ST CENTURY

CELEBRATING 50 YEARS IASLC

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