New Developments for Locally Advanced Lung Cancer

March 6, 2022

Diana Saravia, MD

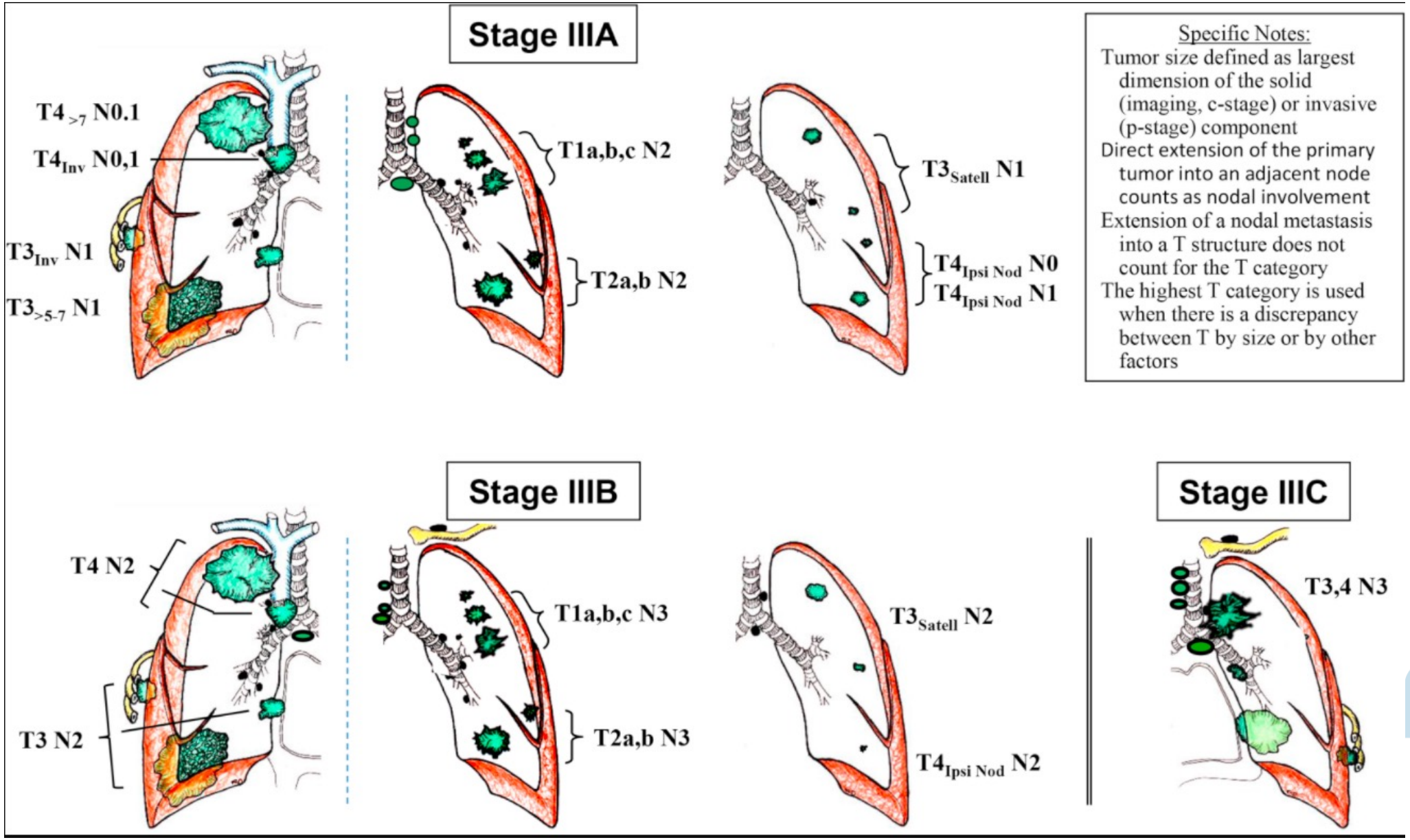
Department of Hematology/Oncology

Cleveland Clinic

What is locally advanced?

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

TNM classification 8th edition



Detterbeck, F; et al. The Eight Edition Lung Cancer Stage Classification. Chest Journal. Jan 2017.

PRETREATMENT EVALUATION

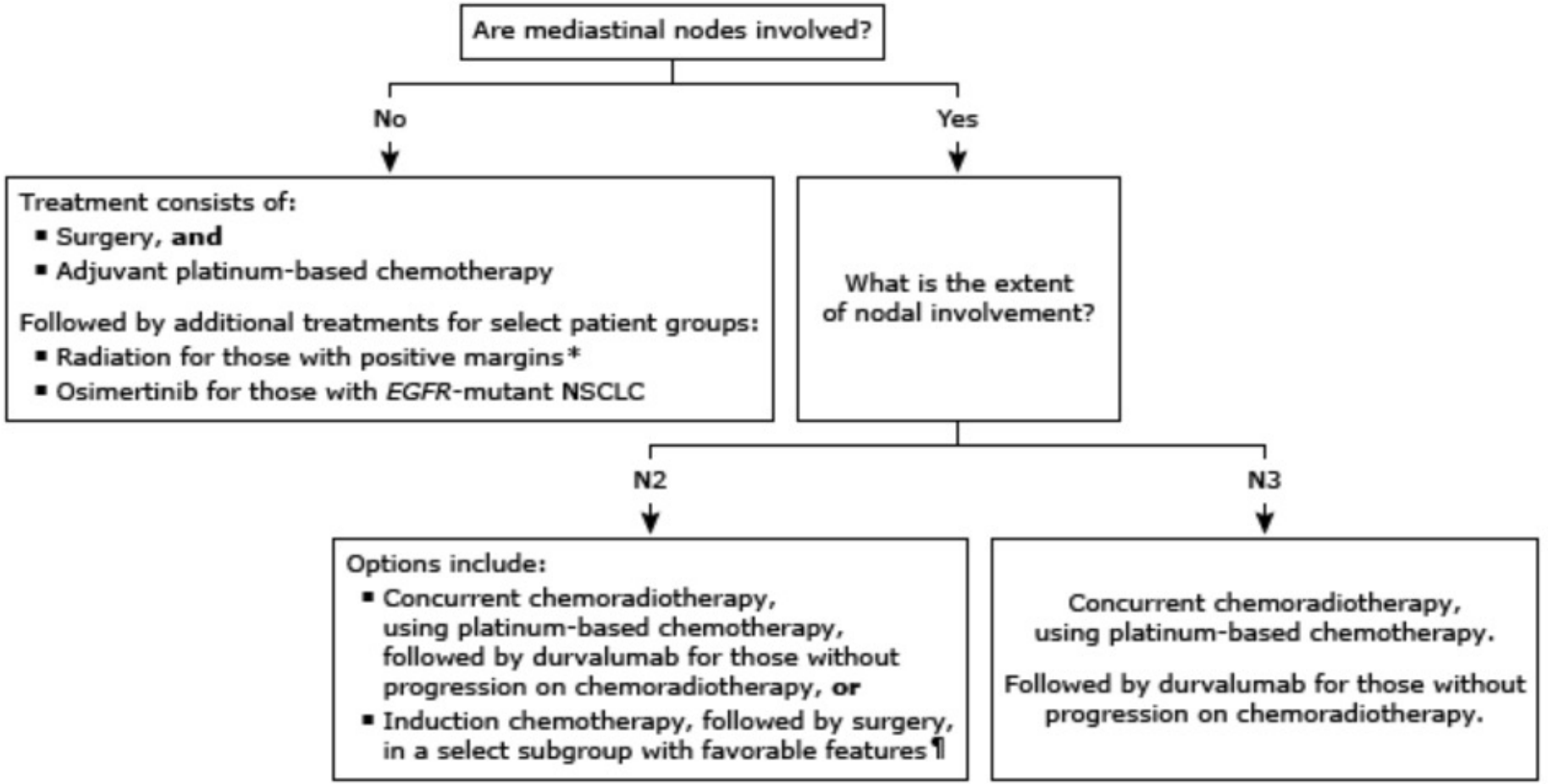
- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation[h]
- Brain MRI with contrast[o]
- MRI with contrast of spine + thoracic inlet for superior sulcus lesions abutting the spine, subclavian vessels, or brachial plexus
- FDG PET/CT scan[j] (if not previously done)

- Surgery
- Chemotherapy
- Radiation
- Immunotherapy
- Targeted therapy (osimertinib)

NCCN guidelines 2022

Current Approach

Management of stage III non-small cell lung cancer



IMMUNOTHERAPY
(for resectable disease)

Neoadjuvant

TABLE 3. Neoadjuvant Phase II Trials of Single-Agent Anti–PD-L1

Study	Stage (eighth edition)	No. of Participants	Anti–PD-L1 Agent	MPR/pCR
JHU/MSKCC[28]	IB-IIIA	21	Nivolumab × two doses	45%/15% (of 20 resected tumors)
NEOSTAR[30]	I-IIIA	23 21	Nivolumab × two doses (6 wk) Nivolumab-ipilimumab (6 wk)	22%/9% (ITT) 38%/29% (ITT)
LCMC3[31]	IB-IIIA	181	Neoadjuvant atezolizumab × two followed by adjuvant atezolizumab (if clinical benefit)	20%/7% (of 144 resected tumors without EGFR/ALK alterations)
Ready et al[32]	IB-IIIA/25	30	Neoadjuvant pembrolizumab × two (6 wk) and four cycles of adjuvant pembrolizumab	28%/8% (of 25 resected tumors)
Gao et al[33]	IA-IIIA	40	Neoadjuvant sintilimab × two doses (6 wk)	41%/16% (of 37 resected tumors)
PRINCEPS[34]	I-IIIA	30	Neoadjuvant atezolizumab × one dose (4 wk)	14%/0% (of 29 resected tumors)
IONESCO[35]	IB > 4 cm/IIIA	46	Neoadjuvant durvalumab × three doses (6 wk)	17.5%/7%

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ITT, intention-to-treat; MPR, major pathologic response; pCR, pathologic complete response; PD-L1, programmed death-ligand 1.

Chaft et al. JCO. Jan 2022.

Neoadjuvant

TABLE 4. Phase III Studies of Neoadjuvant Chemotherapy Plus PD-L1 Blockade in Resectable Non–Small-Cell Lung Cancer

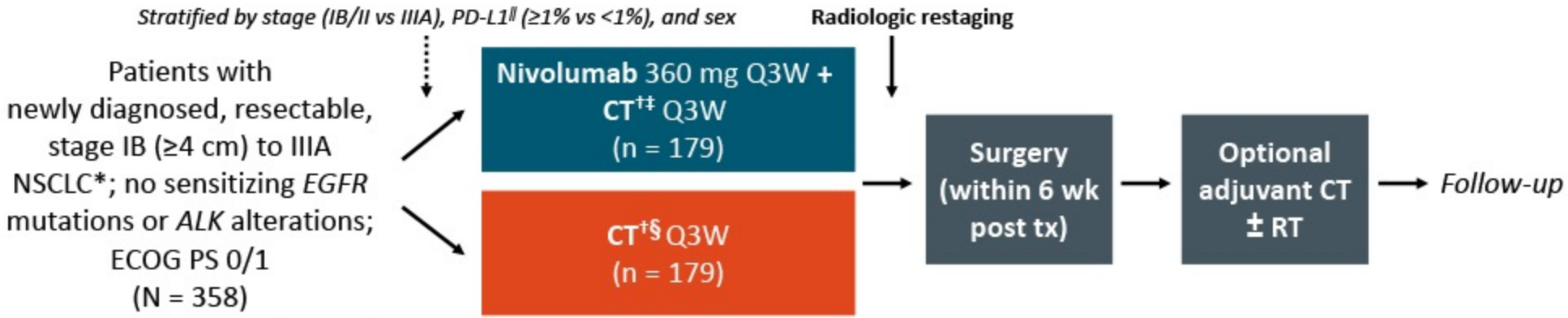
Trial Identifier and Status	Study Title (planned accrual)	Stage (edition)	Backbone	Intervention	Adjuvant IO Treatment	Primary End Points
NCT02998528 Completed accrual Q4 2019	CheckMate 816 (N = 358)	IB-IIIA (seventh)	Three cycles of cisplatin or carboplatin plus vinorelbine, pemetrexed, gemcitabine, docetaxel, or paclitaxel	With or without nivolumab	No	pCR EFS
NCT03425643 Accrual ongoing	KEYNOTE 671 (N = 786)	IIA-IIIA (eighth)	Four cycles of cisplatin plus pemetrexed or gemcitabine	Pembrolizumab or placebo	Adjuvant pembrolizumab or placebo	EFS OS
NCT03456063 Accrual ongoing	IMPOWER 030 (N = 450)	II-IIIB (eighth)	Four cycles of cisplatin or carboplatin plus pemetrexed, gemcitabine, or nab-paclitaxel	Atezolizumab or placebo	Adjuvant atezolizumab or best supportive care	EFS
NCT03800134 Accrual ongoing	AEGEAN (N = 800)	IIA-IIIB (eighth)	Four cycles of cisplatin plus gemcitabine or pemetrexed or carboplatin plus pemetrexed or paclitaxel	Durvalumab or placebo	Adjuvant durvalumab or placebo	pCR EFS
NCT04025879 Accrual ongoing	CheckMate 77T (N = 452)	II-IIIB (eighth)	Four cycles of cisplatin or carboplatin plus pemetrexed, docetaxel, or paclitaxel	Nivolumab or placebo	Adjuvant nivolumab or placebo	EFS

Abbreviations: EFS, event-free survival; IO, immunotherapy; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed death-ligand 1.

Chaft et al. JCO. Jan 2022.

CheckMate 816: Neoadjuvant Nivolumab + Platinum Chemotherapy for Resectable Stage IB-IIIA NSCLC

- Randomized, open-label phase III trial (data cutoff: September 16, 2020; min f/u: 7.6 mo)

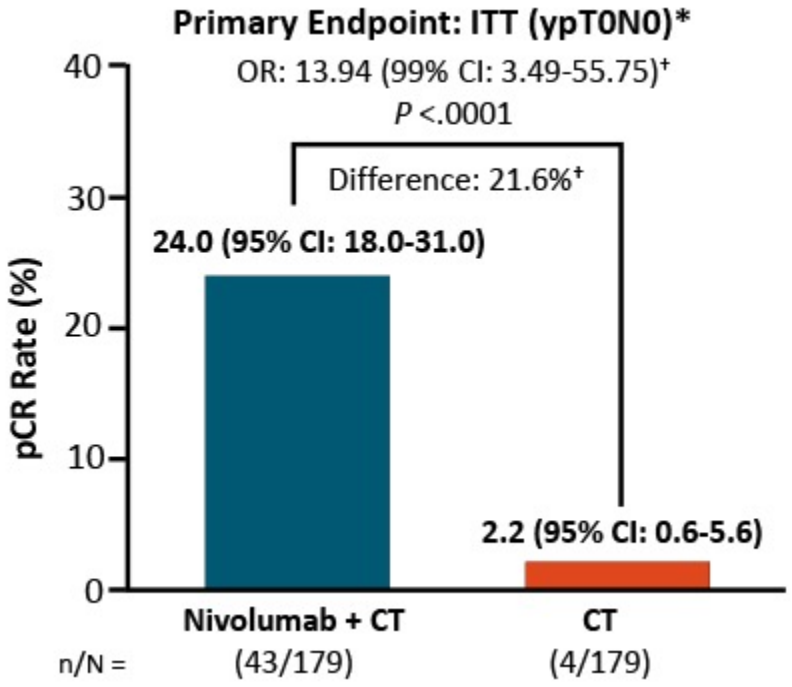


*By TNM 7th edition. †3 cycles. ‡NSQ: cisplatin/pemetrexed or carboplatin/paclitaxel; SQ: cisplatin/gemcitabine or carboplatin/paclitaxel. §NSQ: cisplatin/pemetrexed; SQ: cisplatin/vinorelbine, cisplatin/docetaxel, cisplatin/gemcitabine; both: carboplatin/paclitaxel. ‖PD-L1 28-8 pharmDx IHC assay. Arm evaluating nivolumab (3 mg/kg for 3 cycles) + ipilimumab (1 mg/kg for 1 cycle) not shown.

- **Primary endpoints:** pCR (by BIPR) and EFS (by BICR)
- **Key secondary endpoints:** OS, mPR (by BIPR), time to death or distant metastasis
- **Key exploratory endpoints:** ORR (by BICR), feasibility of surgery, peri- and postoperative surgery related AEs

Forde. AACR 2021. Abstr CT003. Spicer. ASCO 2021. Abstr 8503. NCT02998528.

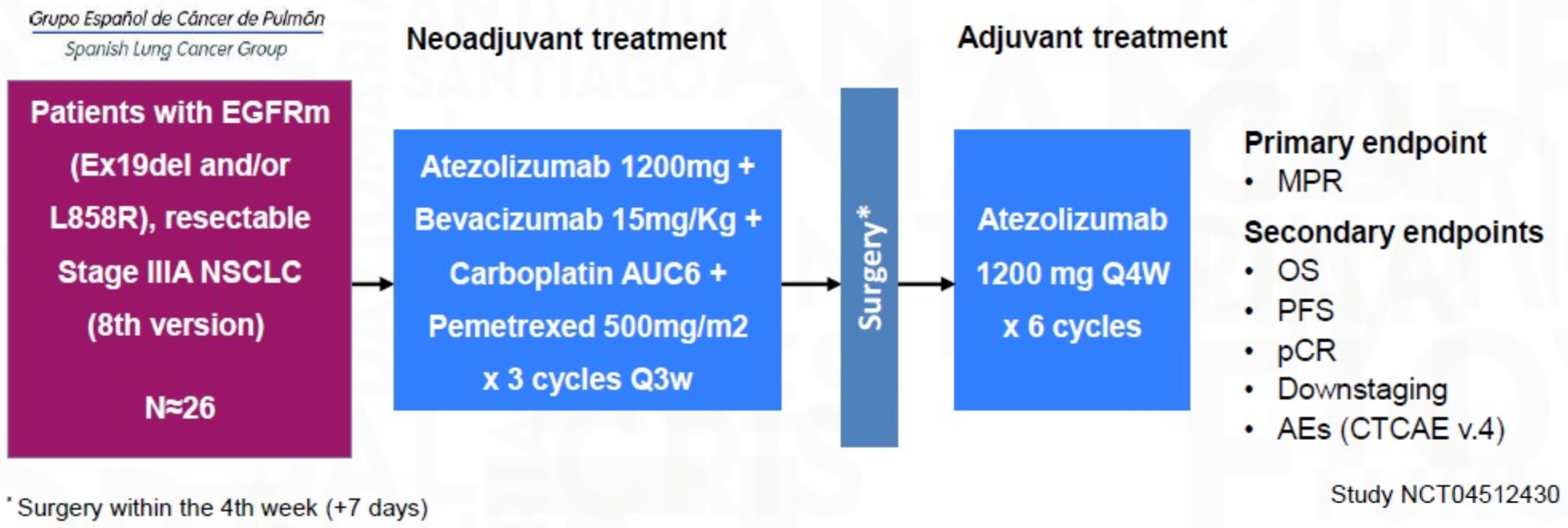
Checkmate 816



- Nivo + chemo did not delay surgery
- Did not increase surgical complications
- Tolerable AEs

Forde. AACR 2021. Abstr CT003.

neoDIANA: Phase II, Neoadjuvant Atezolizumab plus CT in resectable Stage IIIA (N2) EGFR+ NSCLC



Is neoadjuvant IO the right choice?

- Well tolerated
- Does not delay surgery
- No unexpected surgical complications
- MPR 14-45% (MPR after NAC15-20%)

Adjuvant

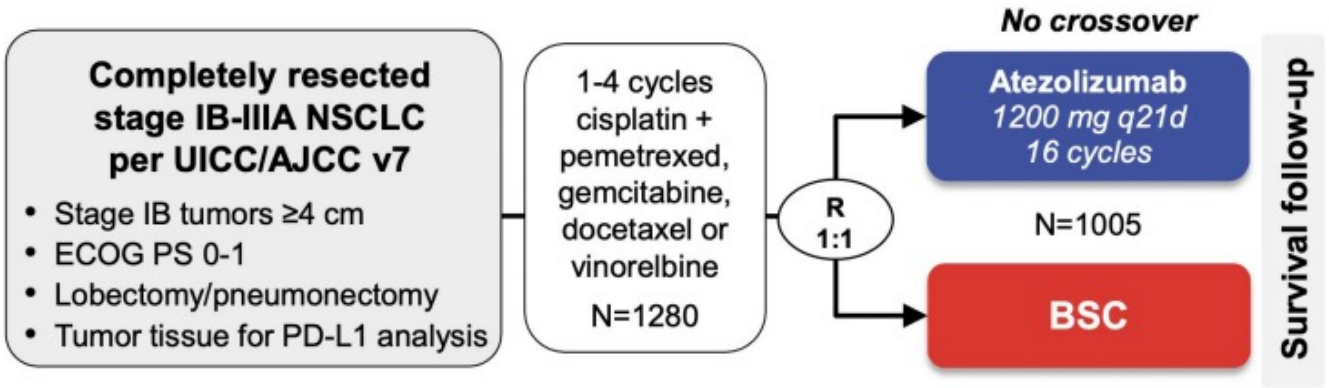
TABLE 2. Phase III Trials of Adjuvant anti–PD-L1 for Resected Non–Small-Cell Lung Cancer

Study	PD-1/PD-L1 Inhibitor	Sample Size	Chemotherapy-Specified	PORT	Placebo	Primary End Points	Status
EA5142/ANVIL (NCT02595944)	Nivolumab	903	No	Yes	No	DFS and OS DFS in PD-L1 ≥ 50% and in ITT	Completed accrual
IMpower010 (NCT02486718)	Atezolizumab	1,280	Yes	No	No	DFS in stage II/III PD-L1+ and all DFS in ITT PD-L1+ and all	Completed accrual
BR.31 (NCT02273375)	Durvalumab	1,360	No	No	Yes	DFS in PD-L1+	Completed accrual
EORTC141/PEARLS (NCT02504372)	Pembrolizumab	1,080	No	Yes	Yes	DFS in all DFS in PD-L1 high	Completed accrual
ACCIO/ALLIANCE (NCT04267848)	Pembrolizumab (concurrent and sequential arms)	1,263	Yes	No	No	DFS and OS in all	Accrual ongoing

Abbreviations: DFS, disease-free survival; ITT, intention to treat; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PORT, postoperative radiotherapy.

Chaft et al. JCO. Jan 2022.

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial



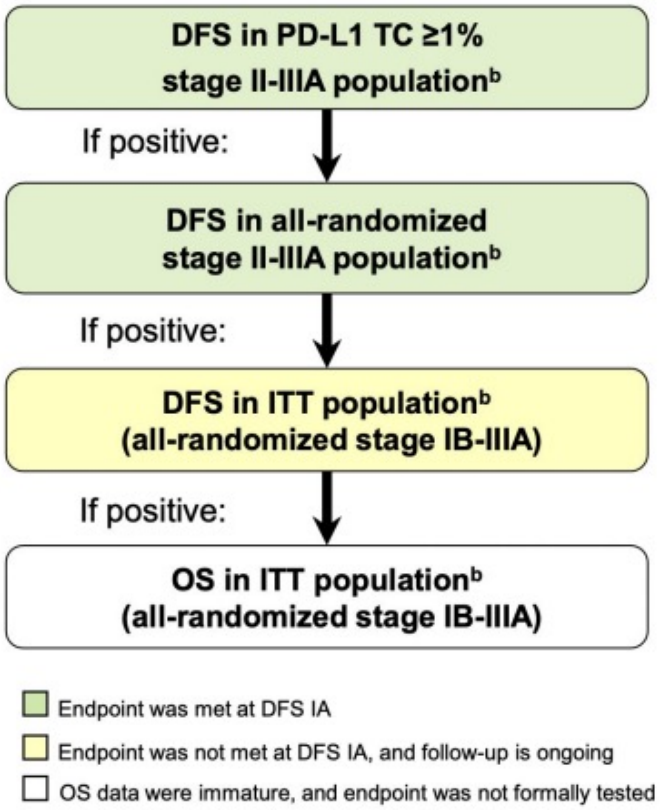
Stratification factors

- Male vs female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  1. PD-L1 TC ≥1% (SP263) stage II-IIIA population
  2. All-randomized stage II-IIIA population
  3. ITT (all-randomized stage IB-IIIA) population

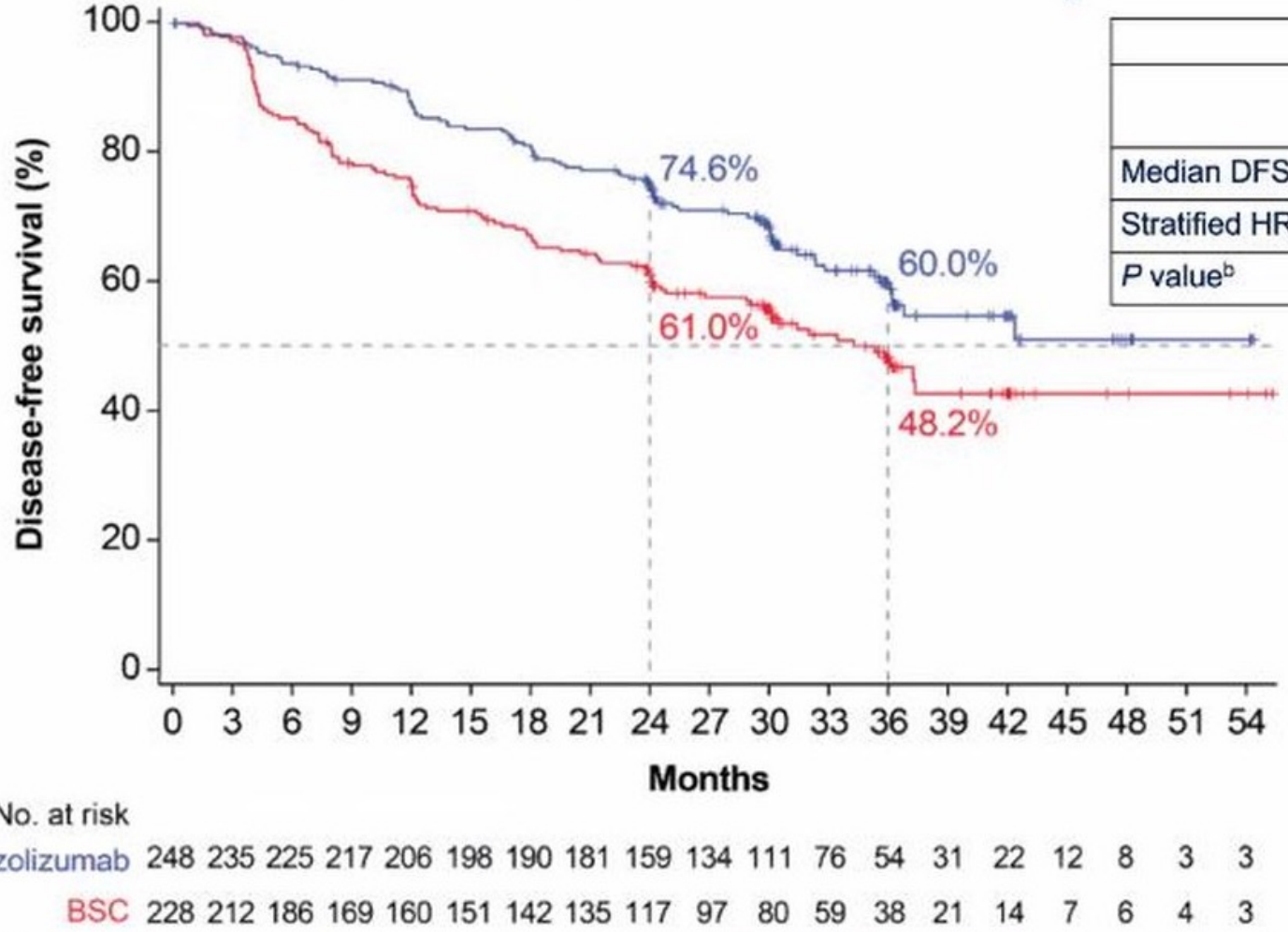
Hierarchical statistical testing



Both arms included observation and regular scans for disease recurrence on the same schedule.
IC, tumor-infiltrating immune cells. [a] Per SP142 assay. [b] Two-sided α=0.05.

Felip E et al. *Lancet*. 2021;398(10308):1344-1357.

Atezolizumab following surgery and chemotherapy reduced the risk of disease recurrence or death by 34% in people with stage II-IIIA NSCLC whose tumors express ≥1% PD-L1[a]



	PD-L1 TC ≥1% stage II-IIIA	
	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

Median follow-up: 32.8 mo (range, 0.1-57.5)

Felip E et al. *Lancet*. 2021;398(10308):1344-1357.

NCCN Guidelines

Previous Adjuvant Chemotherapy

- **Osimertinib 80 mg daily[10]**
  - **Osimertinib for patients with completely resected stage IB–IIIA *EGFR* (*exon 19* deletion, *L858R*) NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.**
- **Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[11]**
  - **Atezolizumab for patients with completely resected stage IIB–IIIA or high risk stage IIA PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.**

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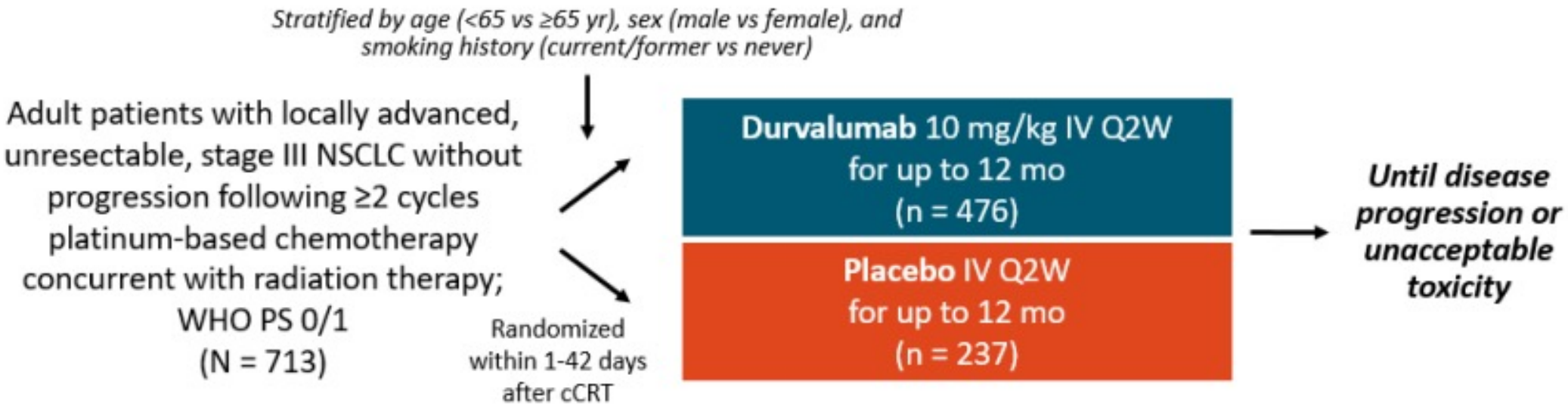
Is adjuvant IO the right choice?

- Tolerable
- Data is encouraging
- OS data is immature
- IMpower010 defines new SOC and need for comprehensive biomarker testing earlier in the time line of management (PDL1!)

IMMUNOTHERAPY
(for *un*resectable disease)

PACIFIC

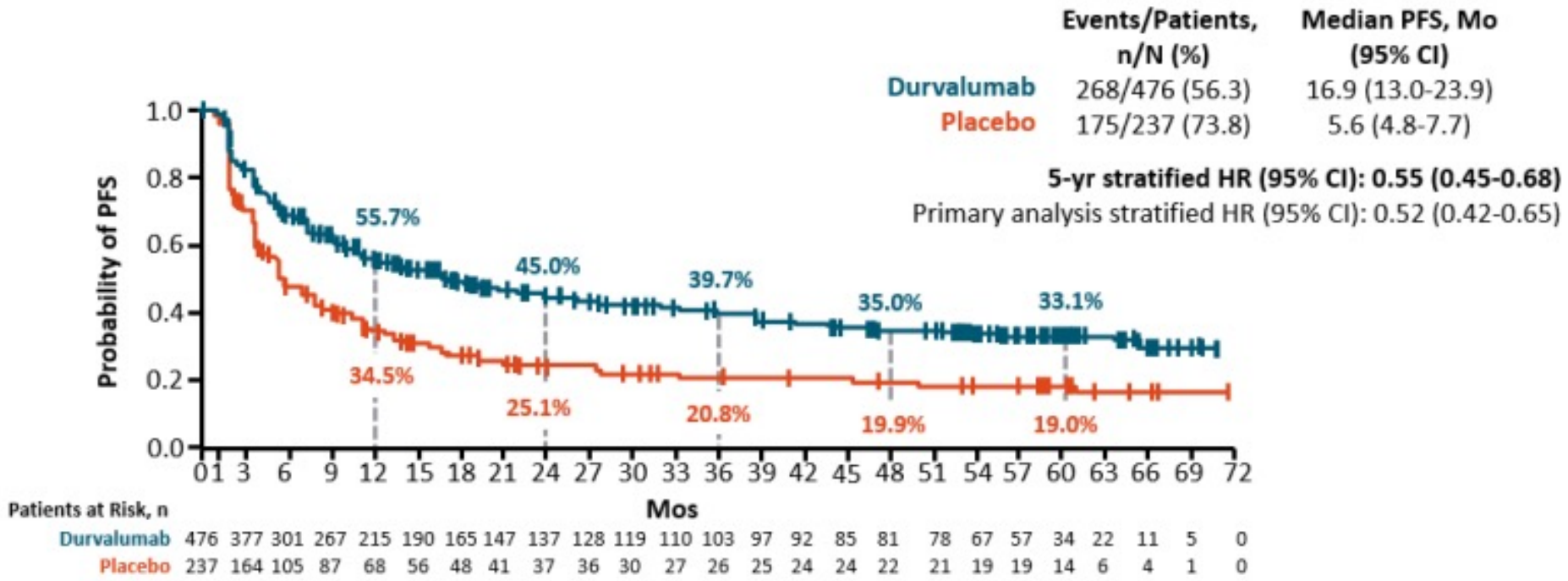
- Randomized, double-blind, placebo-controlled phase III trial



Patients enrolled regardless of PD-L1 status. If available, pre-cCRT tumor tissue archived for PD-L1 testing.

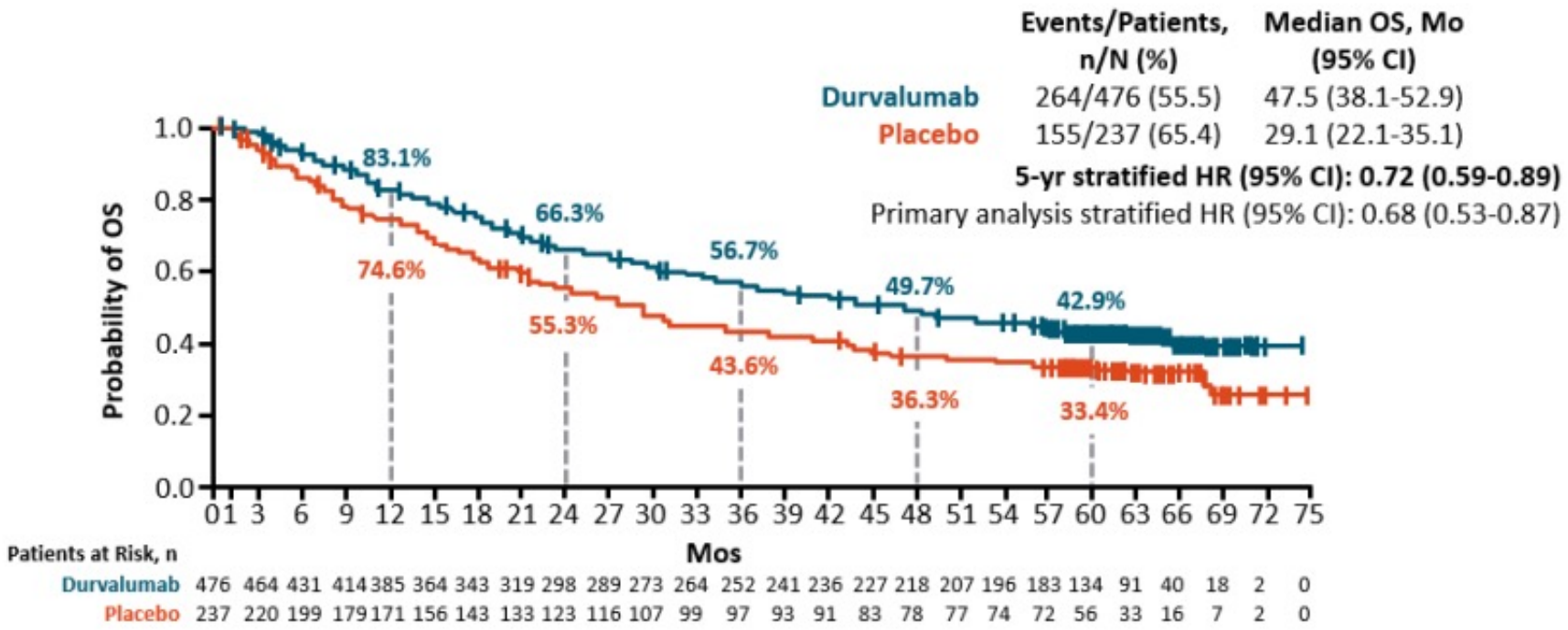
Spigel DR eat al. ASCO 2021.

PACIFIC: 5 yr PFS



Spigel DR et al. ASCO 2021.

PACIFIC: 5 yr OS



Spigel DR et al. ASCO 2021.

PACIFIC: outcomes

	PACIFIC	PACIFIC
Arm	CCRT	CCRT→durva
Median follow up	5.0 yrs	5.0 yrs
OS (median)	29.1 mos	47.5 mos
5-year OS	33.4%	42.9%
5-year PFS	19%	33.1%

Spigel DR et al. ASCO 2021.

FDA expands approval of durvalumab to reduce the risk of non-small cell lung cancer progressing

For Immediate Release: February 16, 2018

The U.S. Food and Drug Administration today approved durvalumab for the treatment of patients with stage III non-small cell lung cancer (NSCLC) whose tumors are not able to be surgically removed (unresectable) and whose cancer has not progressed after treatment with chemotherapy and radiation (chemoradiation).

NCT03840902: Phase II, Bintrafusp alfa (M7824) With cCRT Followed by M7824 vs cCRT Plus Plb Followed by Durvalumab

NCT03745222: Phase III, Tislelizumab (BGB-A317) Plus cCRT Followed by Tislelizumab Monotherapy in Unresectable Stage III NSCLC

DUART (NCT04249362): Phase II, treated with RT and ineligible for chemotherapy followed by Durvalumab x 1 year in Unresectable Stage III NSCLC

PACIFIC 2 (NCT03745222): Phase III, Durvalumab plus cCRT vs plb plus cCRT folowed by durvalumab or plb in Unresectable Stage III NSCLC

PACIFIC 5 (NCT03706690): Phase III, either concurrent or sequential CRT followed by durvalumab or plb until PD in Unresectable Stage III NSCLC

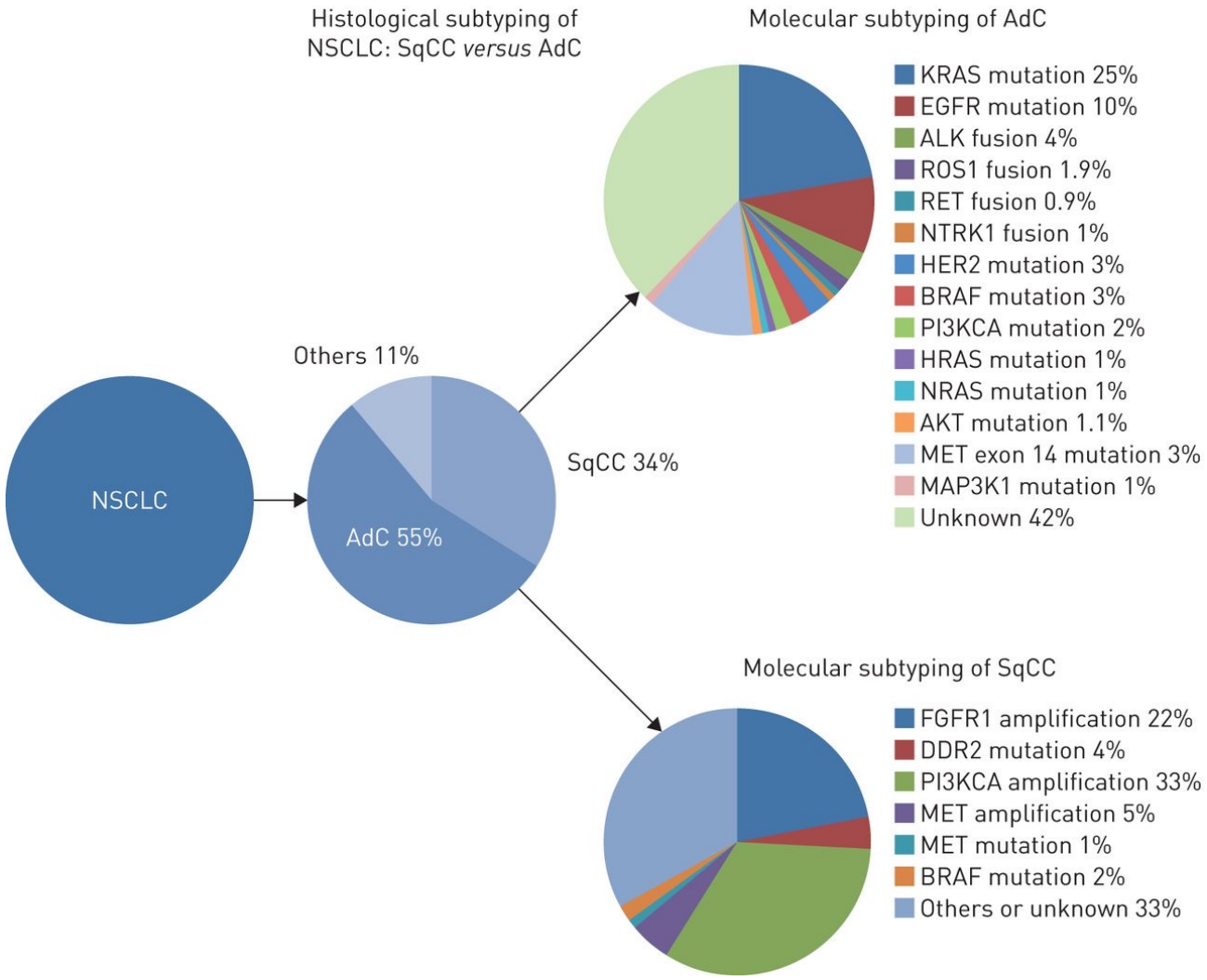
PACIFIC 6 (NCT03693300): Phase II, of durvalumab x 1 year after sequential CRT in patients with ECOG 0-1 and ECOG 2 and Unresectable Stage III NSCLC

COAST (NCT03822351): Phase II multidrug platform study (Durvalumab, Durvalumab plus Oleclumab, Durvalumab plus Monalizumab) as consolidation after cCRT in Unresectable Stage III NSCLC

Future Directions

Hales Russell. 19th Annual Winter Lung Cancer Conference. February 5, 2022

TARGETED THERAPY



Lukas Bubendorf et al. Eur Respir Rev 2017;26:170007

ADAURA

ORIGINAL ARTICLE

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., et al., for the ADAURA Investigators*

Patients with completely resected stage IB/II/IIIA NSCLC with negative margins; primary nonsquamous NSCLC with *EGFR* ex19del or L858R*; aged ≥ 18 yrs (≥ 20 yrs in Japan/Taiwan); WHO PS 0/1; brain imaging done; adj CT permitted; maximum time from surgery to randomization: 10 wks without adj CT, 26 wks with adj CT (N = 682)

Stratified by stage (IB vs II vs IIIA), EGFR mutation (ex19del vs L858R), race (Asian vs non-Asian)

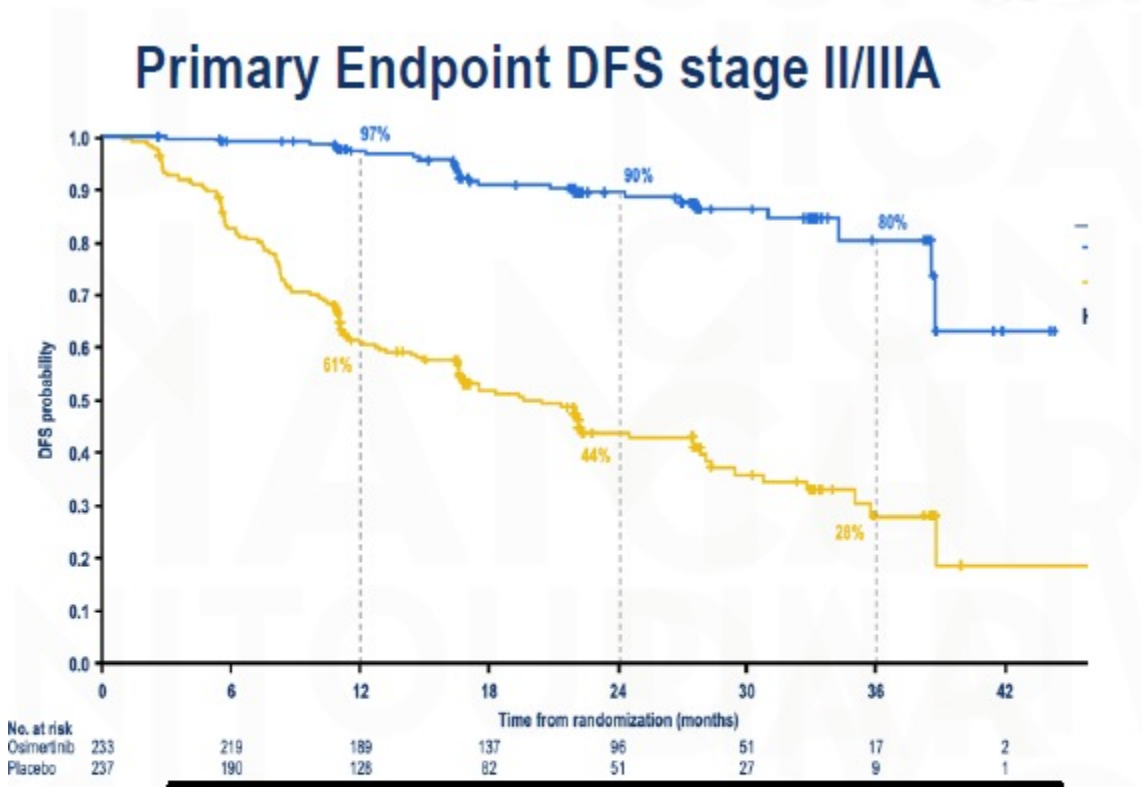
*Confirmed centrally in tissue. †Follow-up: until recurrence, Wks 12 and 24, then Q24W to 5 yrs, then yearly; after recurrence, Q24W for 5 yrs, then yearly.

- Primary endpoint: investigator-assessed DFS in patients with stage II/ IIIA disease
  - Trial designed to test superiority with assumed DFS HR of 0.70
- Secondary endpoints: DFS in overall population; landmark DFS rates at Yrs 2, 3, 4, and 5; OS; HRQoL; safety

Herbst. ASCO 2020. Abstr LBA5.

Slide credit: clinicaloptions.com

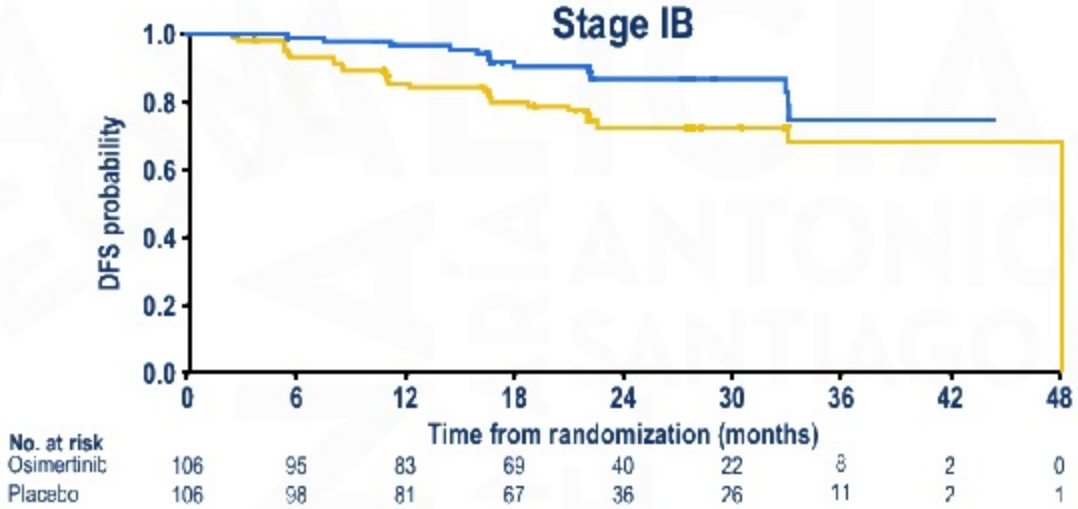
ADAURA

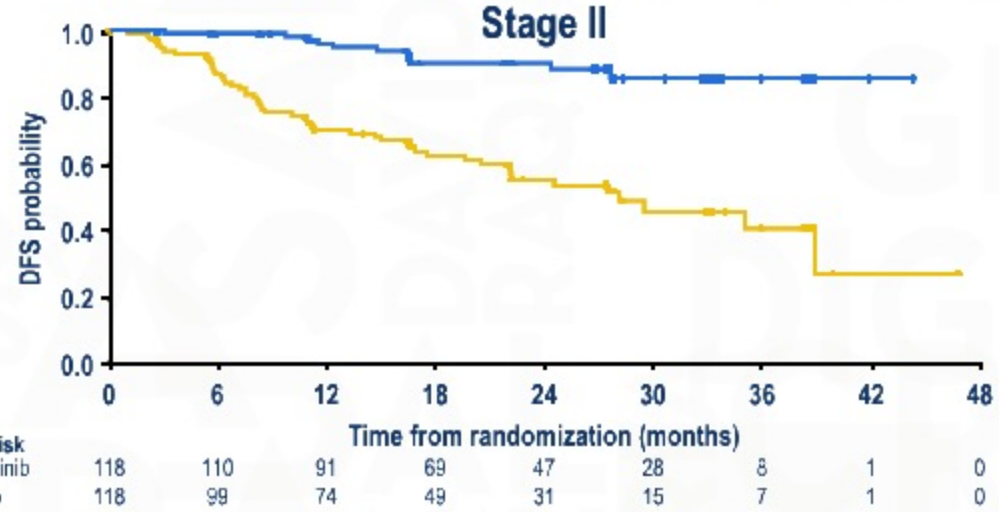


Median DFS, months (95% CI)	
– Osimertinib	NR (38.8, NC)
– Placebo	20.4 (16.6, 24.5)
HR (95% CI)	0.17 (0.12, 0.23); p<0.0001

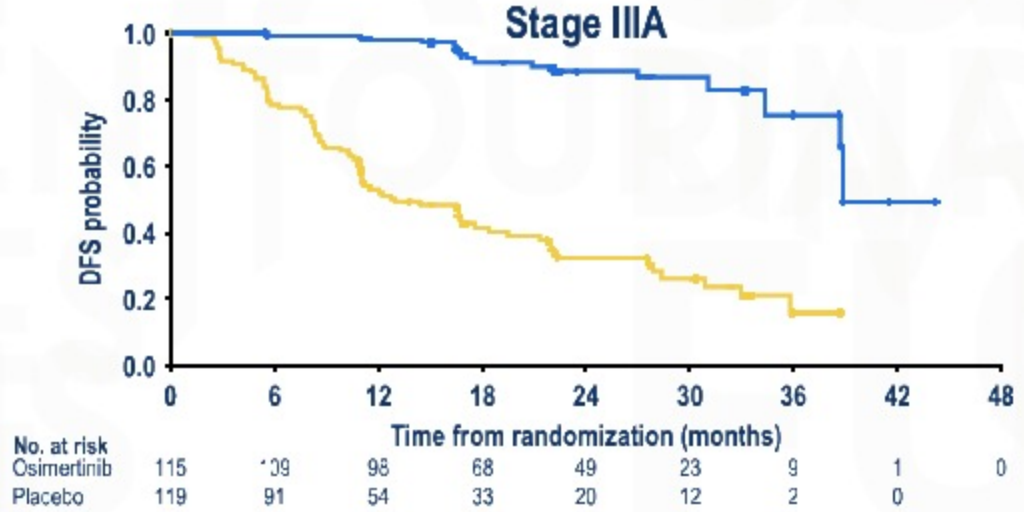
Roy S. Herbst, ASCO 2020

ADAURA



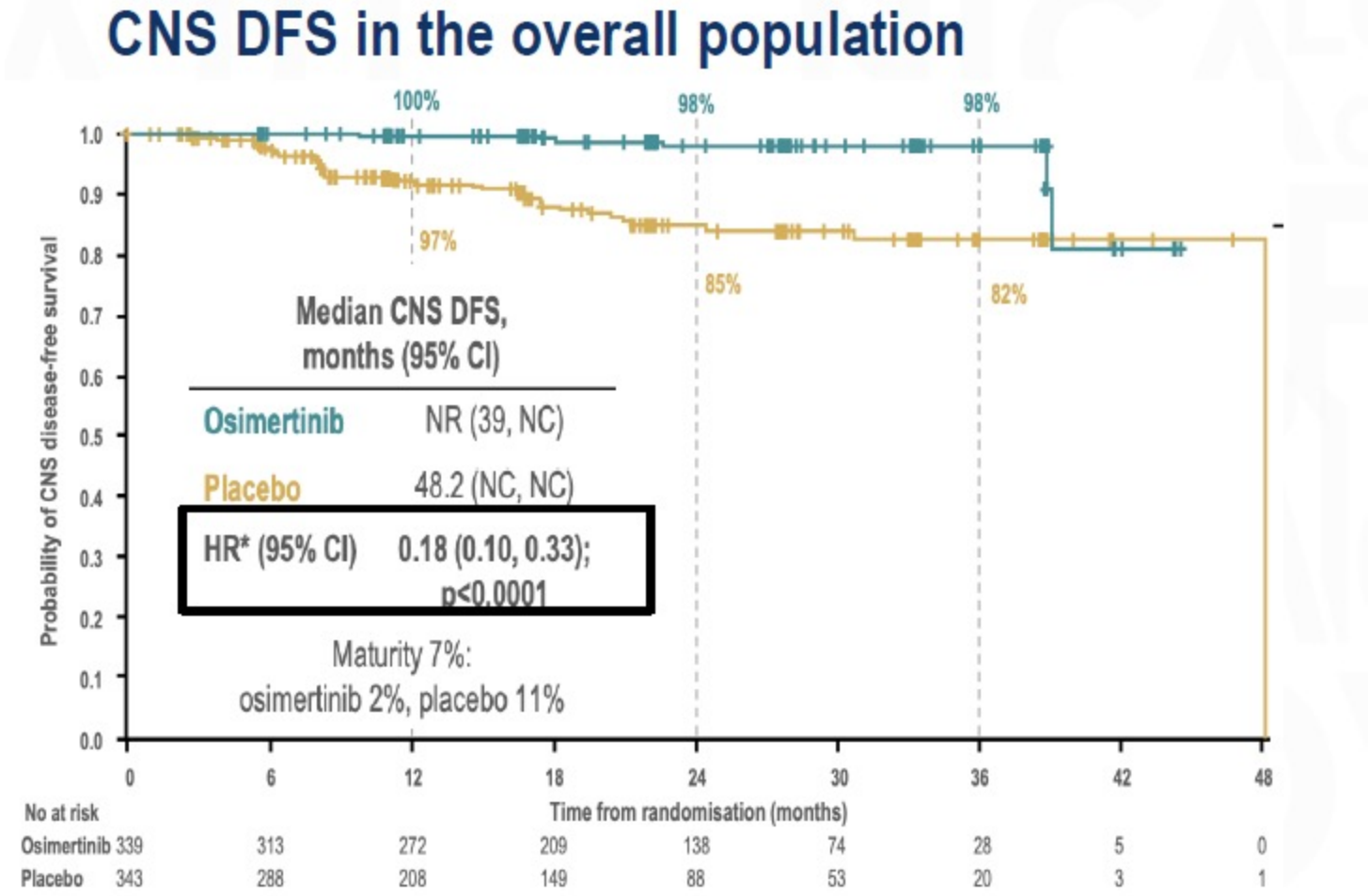


	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	**0.50 (0.25, 0.96)**	**0.17 (0.08, 0.31)**	**0.12 (0.07, 0.20)**



Roy S. Herbst, ASCO 2020

ADAURA


CNS DFS in the overall population
100%
98%
98%
97%
85%
82%
Probability of CNS disease-free survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Median CNS DFS, months (95% CI)
Osimertinib NR (39, NC)
Placebo 48.2 (NC, NC)
HR* (95% CI) 0.18 (0.10, 0.33); p<0.0001
Maturity 7%: osimertinib 2%, placebo 11%
0 6 12 18 24 30 36 42 48
Time from randomisation (months)
No at risk
Osimertinib 339 313 272 209 138 74 28 5 0
Placebo 343 288 208 149 88 53 20 3 1

FDA NEWS RELEASE

FDA Approves First Adjuvant Therapy for Most Common Type of Lung Cancer

Share | Tweet | Linkedin | Email | Print

For Immediate Release: December 18, 2020

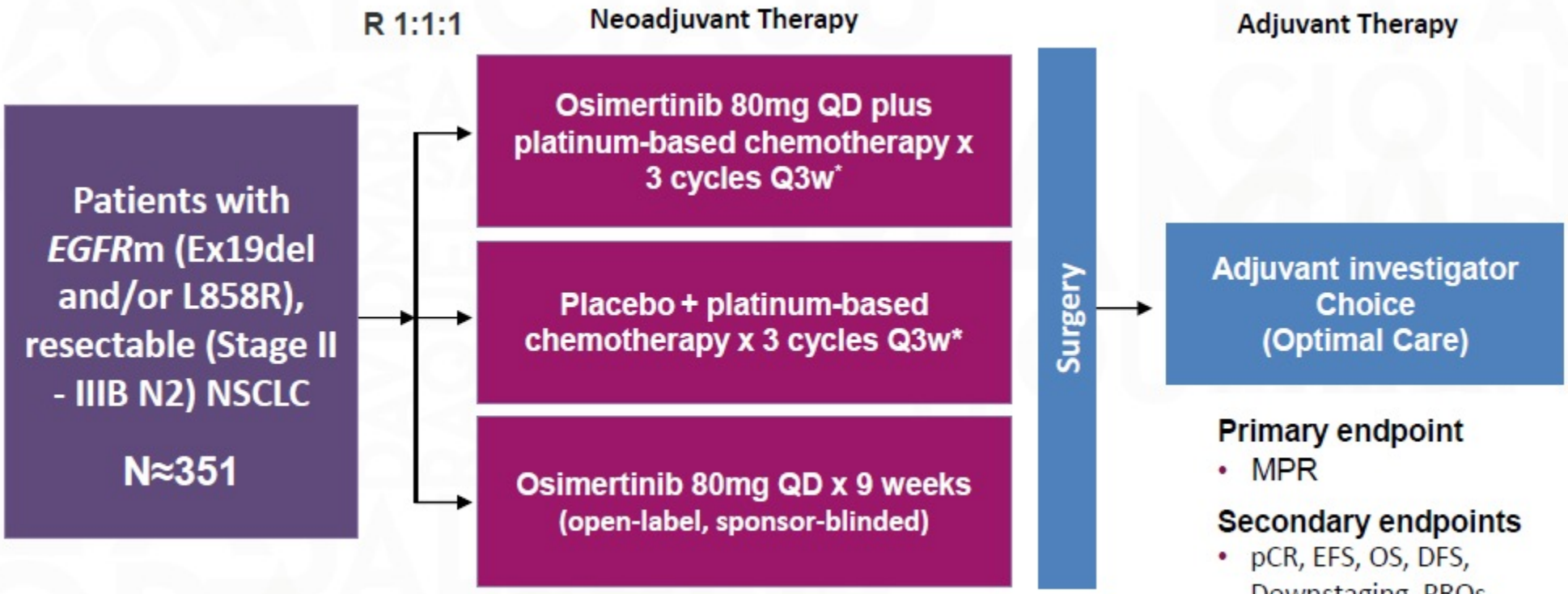
Today, the U.S. Food and Drug Administration approved Tagrisso (osimertinib) as the first adjuvant treatment for patients with non-small cell lung cancer whose tumors have a specific type of genetic mutation.

Previous Adjuvant Chemotherapy

- **Osimertinib 80 mg daily[10]**
  - **Osimertinib for patients with completely resected stage IB–IIIA *EGFR* (*exon 19* deletion, *L858R*) NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.**
- **Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[11]**
  - **Atezolizumab for patients with completely resected stage IIB–IIIA or high risk stage IIA PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.**

NCCN guidelines 2022

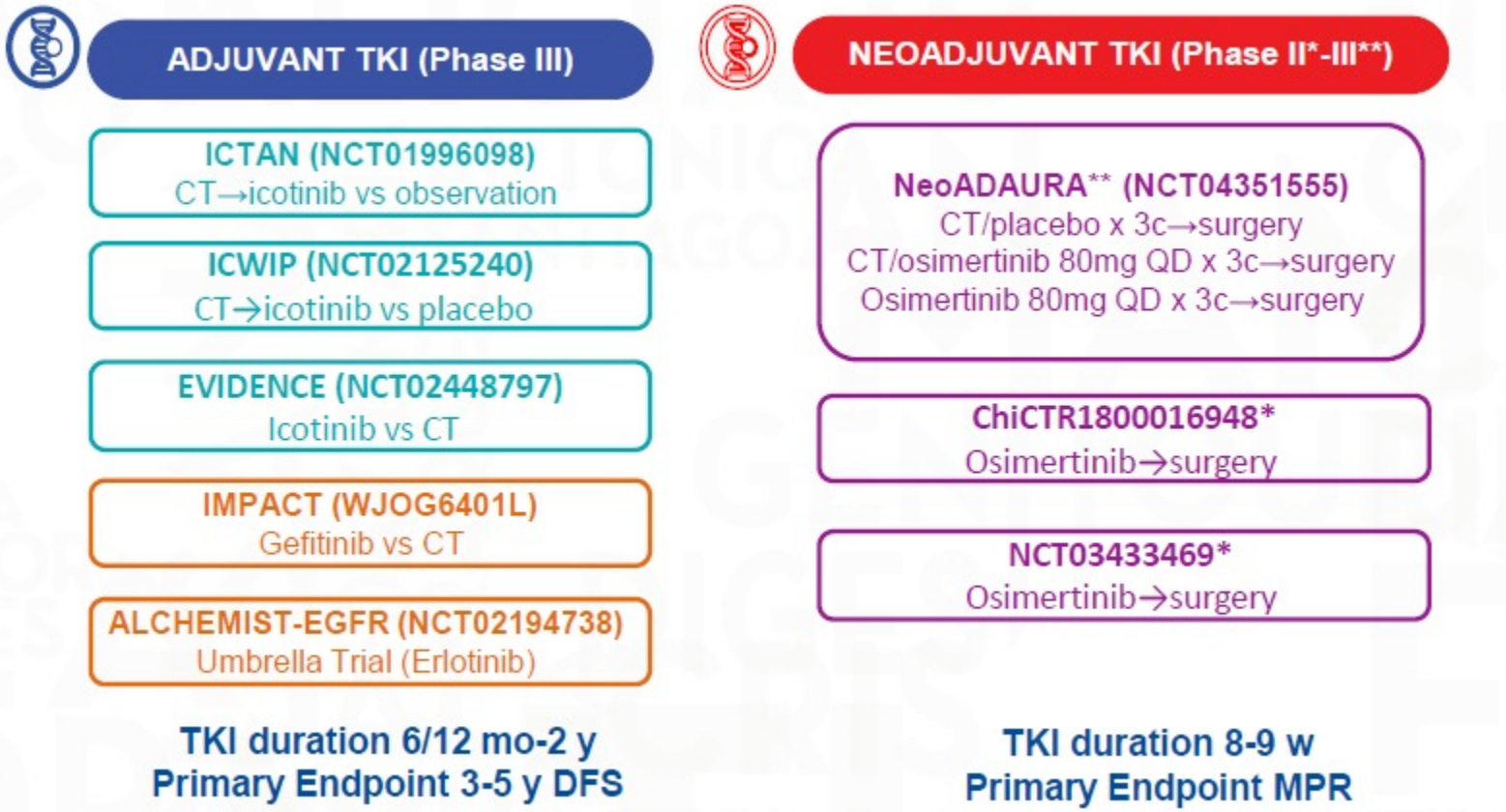
NeoADAURA: Phase III, Neoadjuvant Osimertinib in resectable stage II-IIIB(N2) EGFR+ NSCLC



* Cisplatin (75 mg/m^2) / Carboplatin (AUC5) with Pemetrexed (500 mg/m^2) x 3 cycles

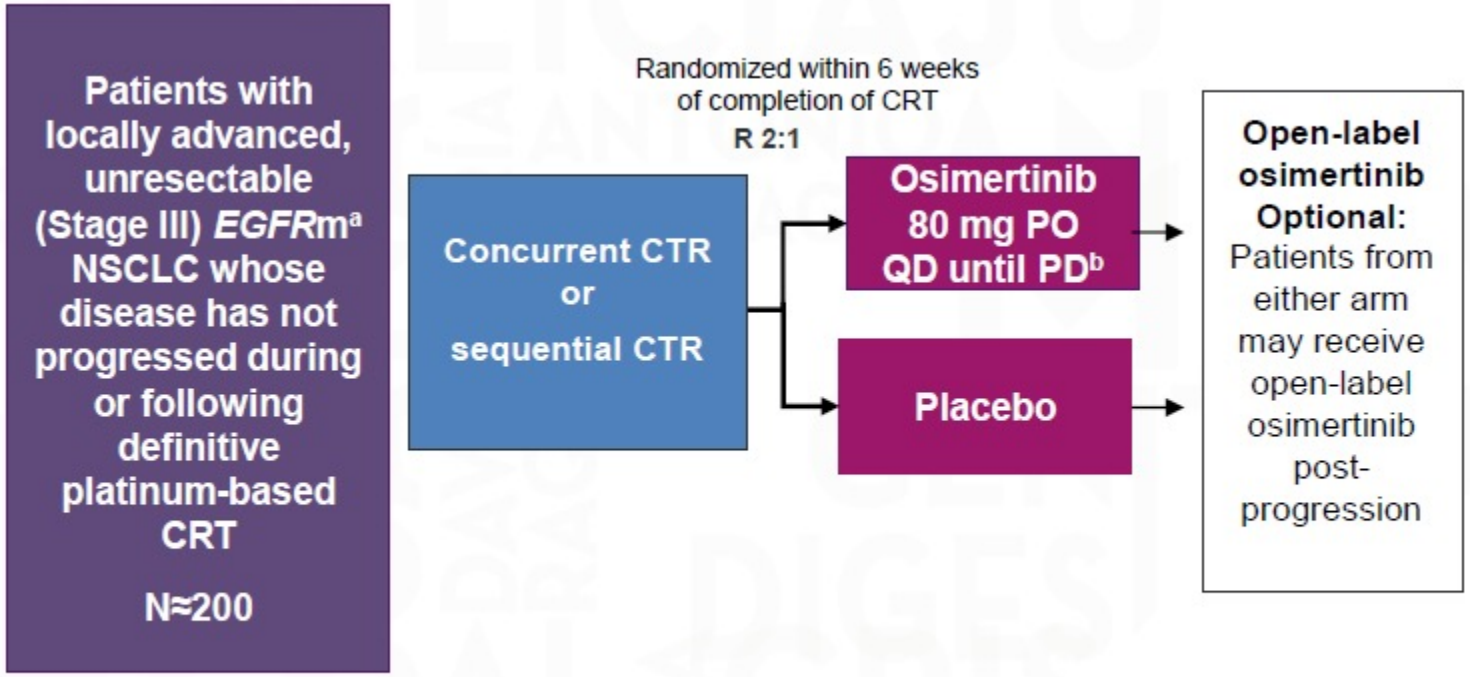
Study NCT04351555

Other perioperative trials with TKIs in EGFR + NSCLC



Reyes R and Reguart N, TLCR 2020

LAURA: Phase III, Osimertinib Consolidation in Unresectable Stage III EGFR+ NSCLC



Primary endpoint

- PFS

Secondary endpoints

- PFS in patients with EGFR Ex19del or L858R mutation
- PFS in patients with EGFRm Ex19del or L858R detectable in ctDNA
- Time to CNS PFS
- OS, ORR, DoR, DCR, tumor shrinkage, TTDM, TTD, PFS2, TFST, TSST
- PROs and HRQoL
- Incidence of AEs
- PK

[a]**Ex19del or L858R either alone or in combination with other EGFR mutations**

[b]Treatment will be continued until disease progression, unacceptable toxicity or other discontinuation criteria are met

Study NCT03521154

Ongoing trials

Active, not recruiting Has Results	AZD9291 Versus Gefitinib or Erlotinib in Patients With **Locally Advanced** or Metastatic **Non-small Cell Lung Cancer**	• **Locally Advanced** or Metastatic EGFR Sensitising Mutation Positive **Non Small Cell Lung Cancer**
Recruiting	HERTHENA-**Lung**01: Patritumab Deruxtecan in Subjects With Metastatic or **Locally Advanced** EGFR-mutated **Non-Small Cell Lung Cancer**	• **Non-Small Cell Lung Cancer** Metastatic • **Non-Small Cell Lung Cancer** With Mutation in Epidermal Growth Factor Receptor
Recruiting	Study of Osimertinib With and Without Ramucirumab in **Locally Advanced** or Metastatic **Non-Small Cell Lung Cancer** (NSCLC)	• **Non Small Cell Lung Cancer** • EGFR Gene Mutation • **Advanced Cancer** • Metastatic **Cancer**

Clinicaltrials.gov

Conclusions

- Locally advanced NSCLC represents a highly heterogeneous group of patients
- No consensus on treatment with increasing number of options for selected patients (IO, TT)
- Molecular profiling should be performed at the time of diagnosis to help guide therapy
  - Tissue testing should be performed whenever feasible
  - Plasma-based testing may complement tissue testing and should also be considered at the time of diagnosis

Cleveland Clinic

Every life deserves world class care.