Adjuvant & Neo-Adjuvant Therapy of NSCLC: Novel Concepts & Approaches

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Disclosures

Commercial Interest	Relationship(s)
Amgen	Research Grant (Institutional)
Astex	Research Grant (Institutional)
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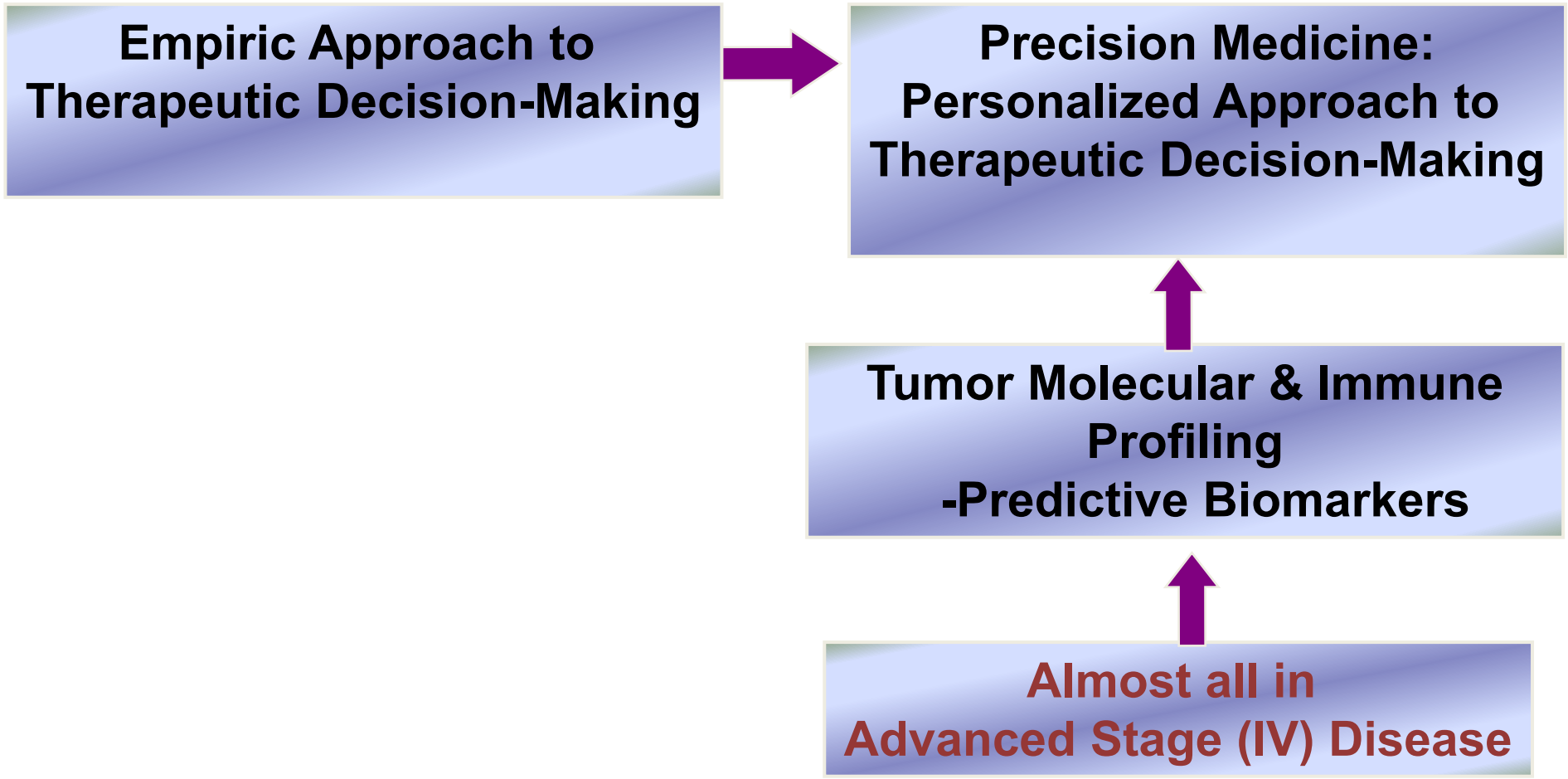
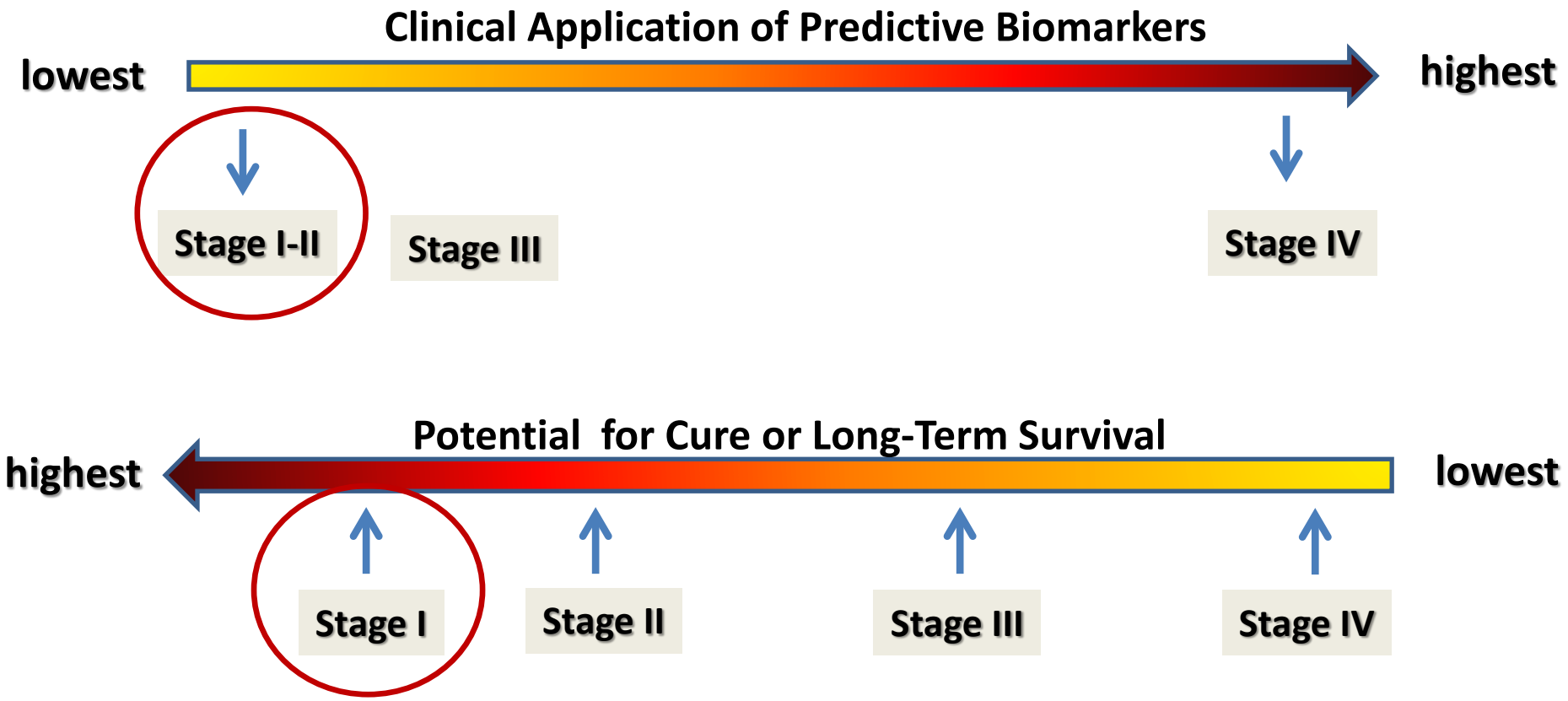
Adagene	Consultant (Institutional)
Astra Zeneca	Consultant (Institutional)
IO Biotech	Consultant (Institutional)
Guardant Health	Consultant (Institutional)
Oncocyte	Consultant (Institutional)
Roche Genentech	Advisory Board
Merck	Advisory Board
Novartis	Advisory Board
Boehringer Ingelheim	Advisory Board
Regeneron	Advisory Board
Sanofi	Advisory Board
Amgen	Advisory Board

Transition from Empiric to Precision Medicine: Rationally Selected & Personalized Therapy of NSCLC



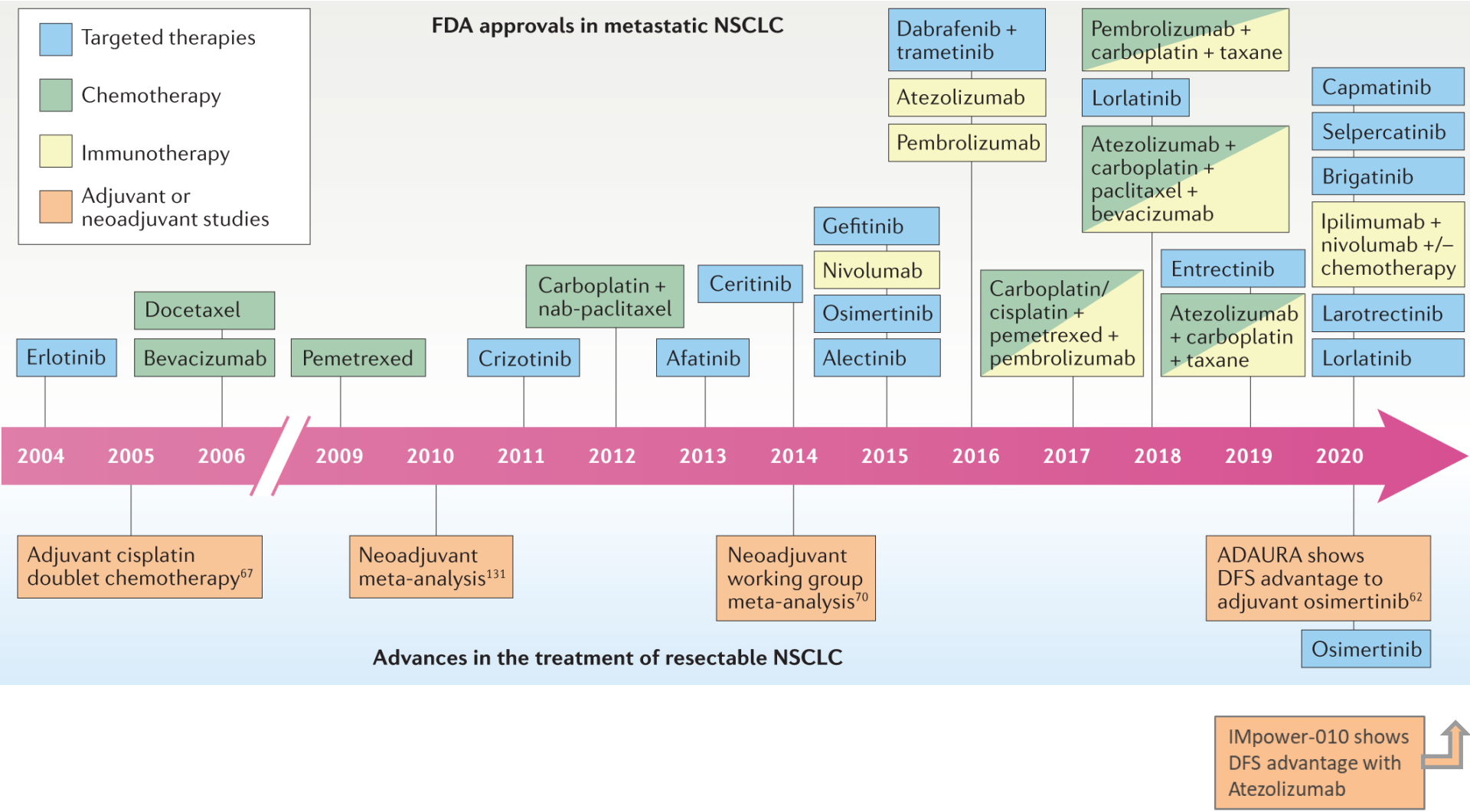
Adapted from Gandara et al: Clin Lung Cancer, 2017

Paradox in Application of Predictive Biomarkers in Therapeutic Decision-Making for NSCLC



Adapted from Redman, Gandara et al: Clin Cancer Research 2013

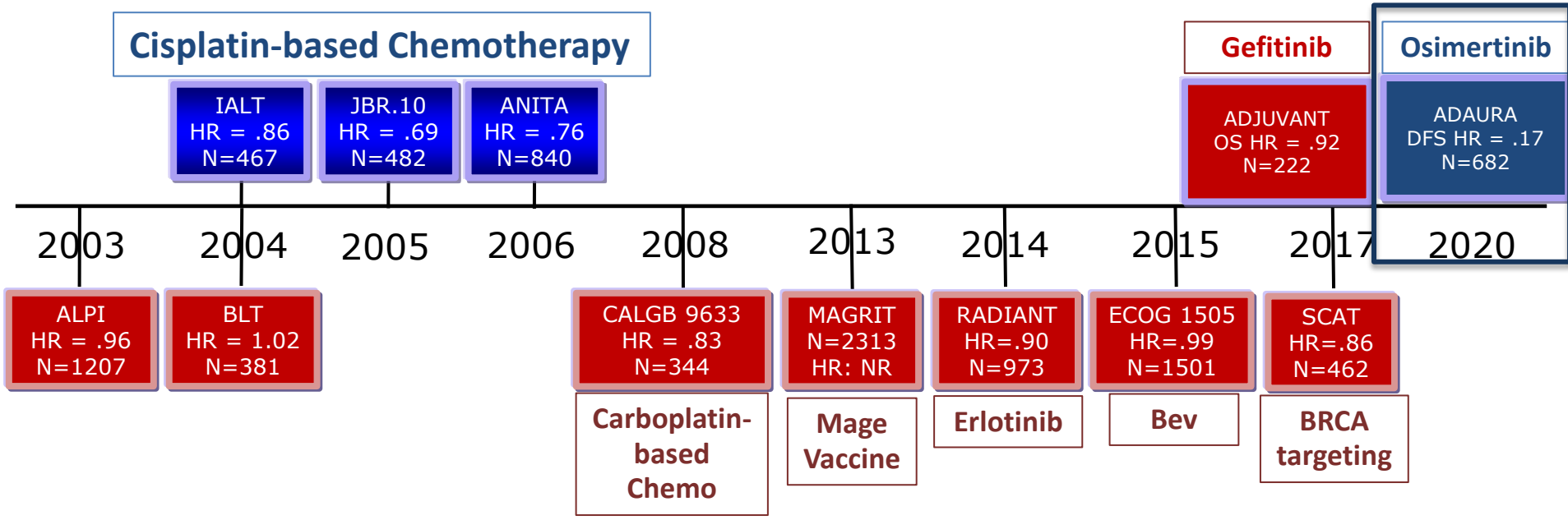
Timeline of FDA Approvals in NSCLC: Stage IV vs Early Stage



Chaft et al. Nat Rev Clin Oncol, 2021

Timeline of Adjuvant Therapy in NSCLC

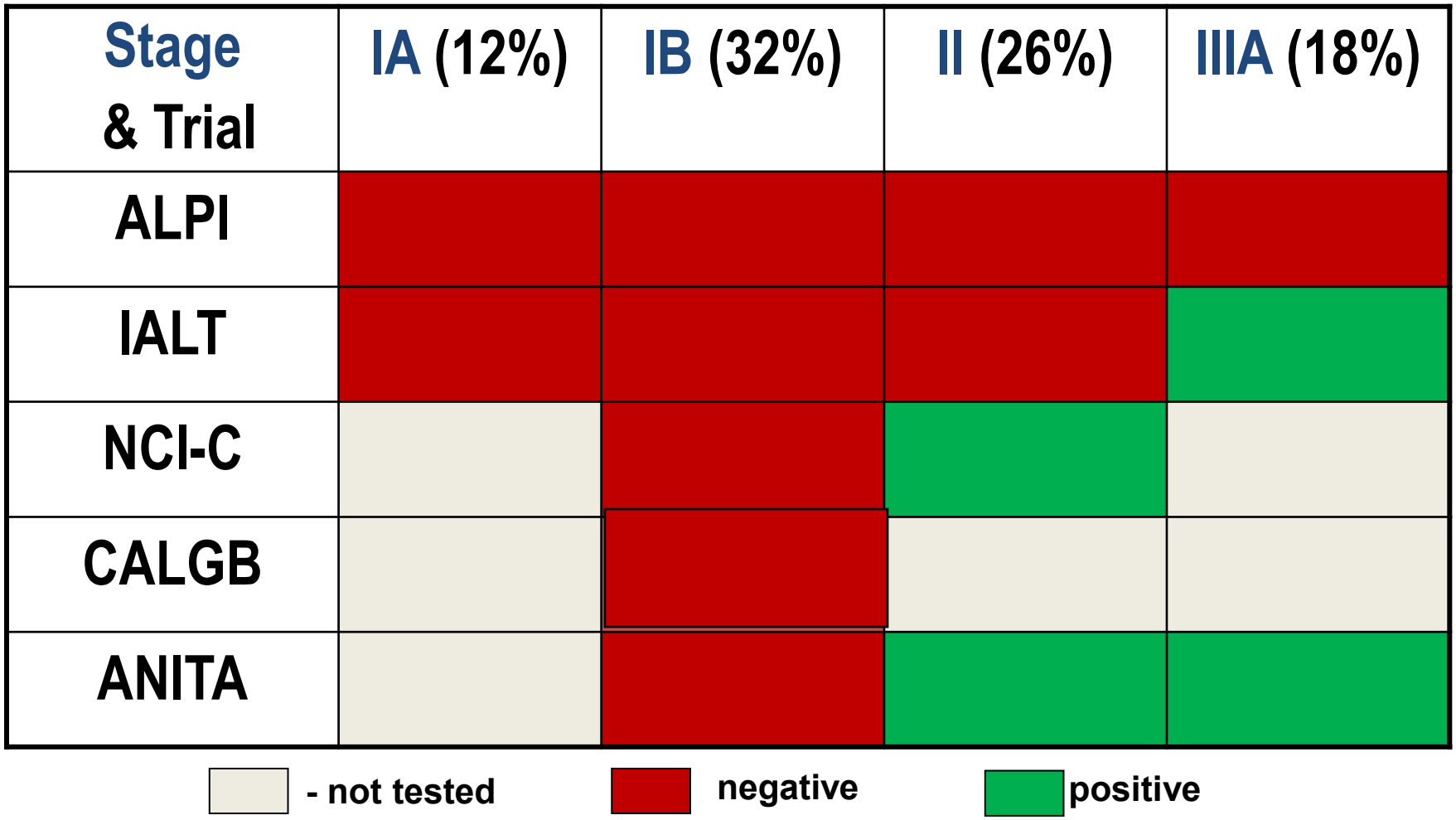
Overall Survival (OS) as a consistent Primary Endpoint



- Adjuvant chemotherapy produces a ~5% absolute survival benefit at 5 years
- This benefit is greatest in patients with Stage II and IIIA disease
- **Patients with stage IB may be considered for adjuvant chemotherapy *(NCCN Guidelines 2020) if "high-risk"***
- Prior novel systemic regimens (EGFR TKIs, Bev, IO) have not produced additional survival advantage (ADAURA osimertinib trial in EGFR-mutated NSCLC has shown improved DFS)

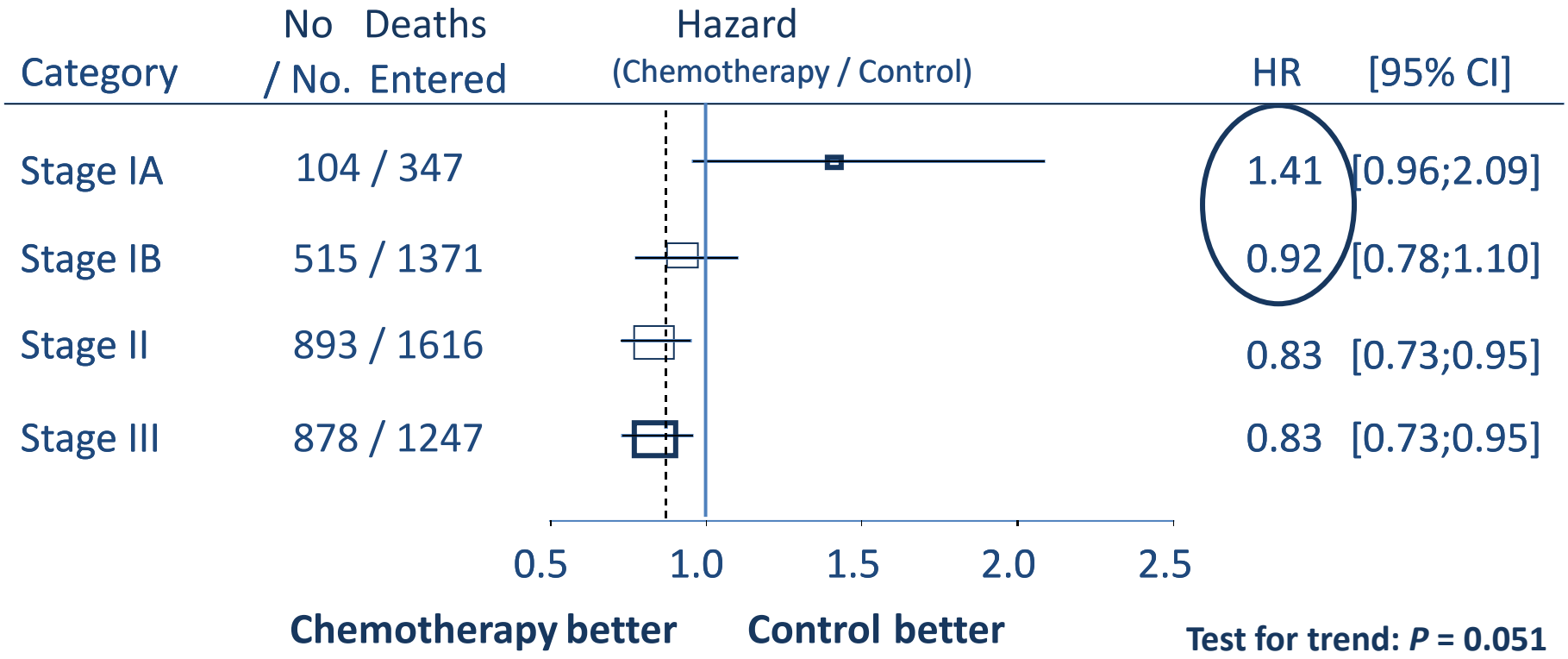
ALPI Scagliotti et al. J Natl Cancer Inst 95: 1453-61, 2003; BLT Waller et al. Eur J Cardiothorac Surg 26:173-182, 2004; IALT Arriagada et al. N Engl J Med 350: 350-61, 2004; JBR.10 Winton et al. N Engl J Med 352:2589-97, 2005; ANITA Douilland et al. Lancet Oncol 7: 719-27, 2006; CALGB 9633 Strauss et al. J Clin Oncol 26: 5043-51, 2008; MAGRIT GSK press release Mar 2014; RADIANT Kelly et al. J Clin Oncol 32 (abstr 7501), 2014; ECOG 1505 Wakelee et al. WCLC 2015 PLEN04.03; SCAT Massuti et al J Clin Oncol 33 (abstr 7507); Y-L Wu et al, ASCO 2017 Abstract #8500

Adjuvant Chemotherapy has not improved Overall Survival (OS) in Stage IA & IB NSCLC (6^{th}-7^{th} Staging Edition)



Adjuvant Chemotherapy for NSCLC

LACE Analysis by Stage



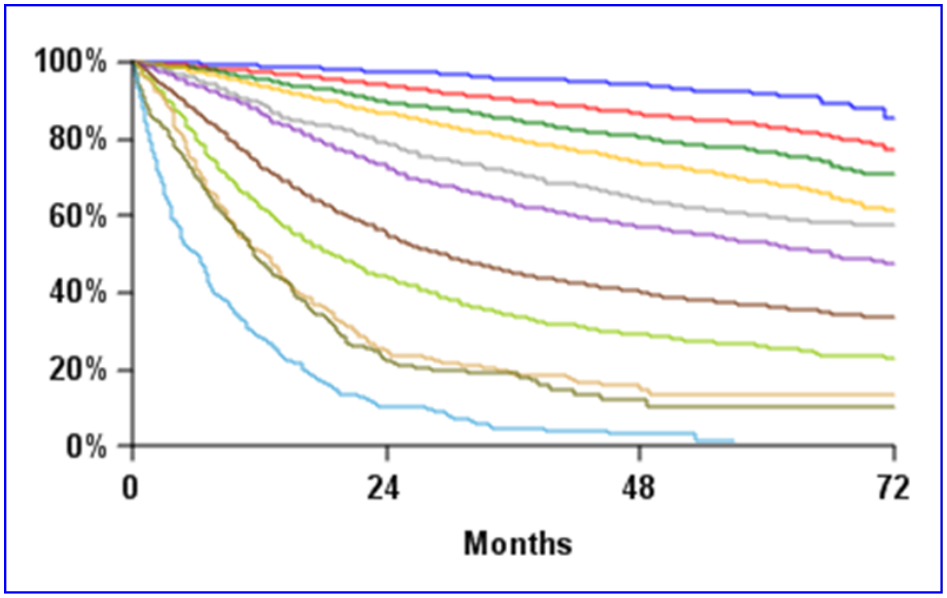
Adjuvant chemotherapy has greatest benefit for stage II and III and may be detrimental for stage IA

Pignon JP, et al. *J Clin Oncol*. 2008;26:3552-3559.

8th Staging Edition of Non-Small Cell Lung Cancer

Descriptor	Category
</= 1 cm	T1a
>1-2 cm	T1b
>2-3 cm	T1c
>3-4 cm	T2a
>4-5 cm	T2b
>5-7 cm	T3
>7 cm	T4
Bronchus < 2 cm	T2
Total atelectasis	T2
Diaphragm	T4

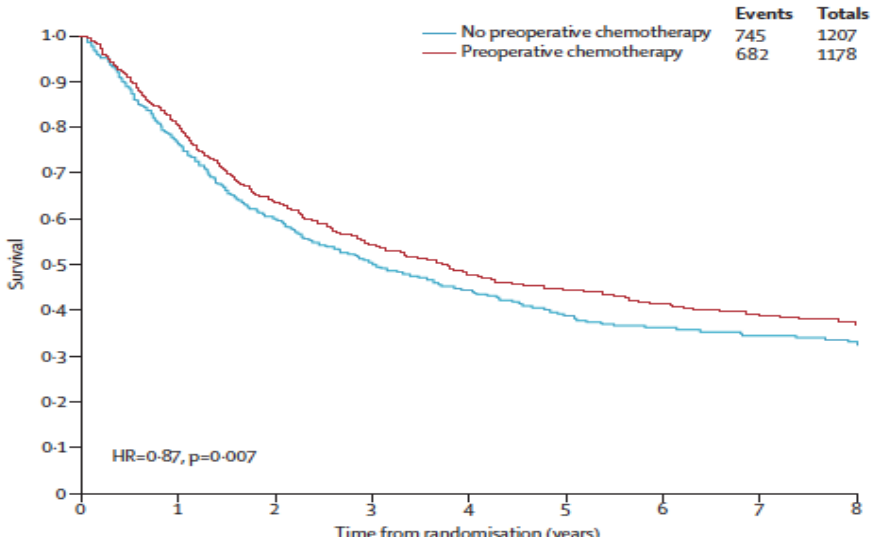
	N0	N1	N2	N3	M1a any N	M1b any N	M1c any N
T1a	IA1	IIB	IIIA	IIIB	IVA	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVA	IVB



	Events/N	MST	24 months	60 months
IA1	68/781	NR	97%	92%
IA2	505/3105	NR	94%	83%
IA3	546/2417	NR	90%	77%
IB	560/1928	NR	87%	68%
IIA	215/585	NR	79%	60%
IIB	605/1453	66.0	72%	53%
IIIA	2052/3200	29.3	55%	36%
IIIB	1551/2140	19.0	44%	26%
IIIC	831/986	12.6	24%	13%
IVA	336/484	11.5	23%	10%
IVB	328/398	6.0	10%	0%

Rami-Porta: IASLC World Congress Lung Cancer 2017

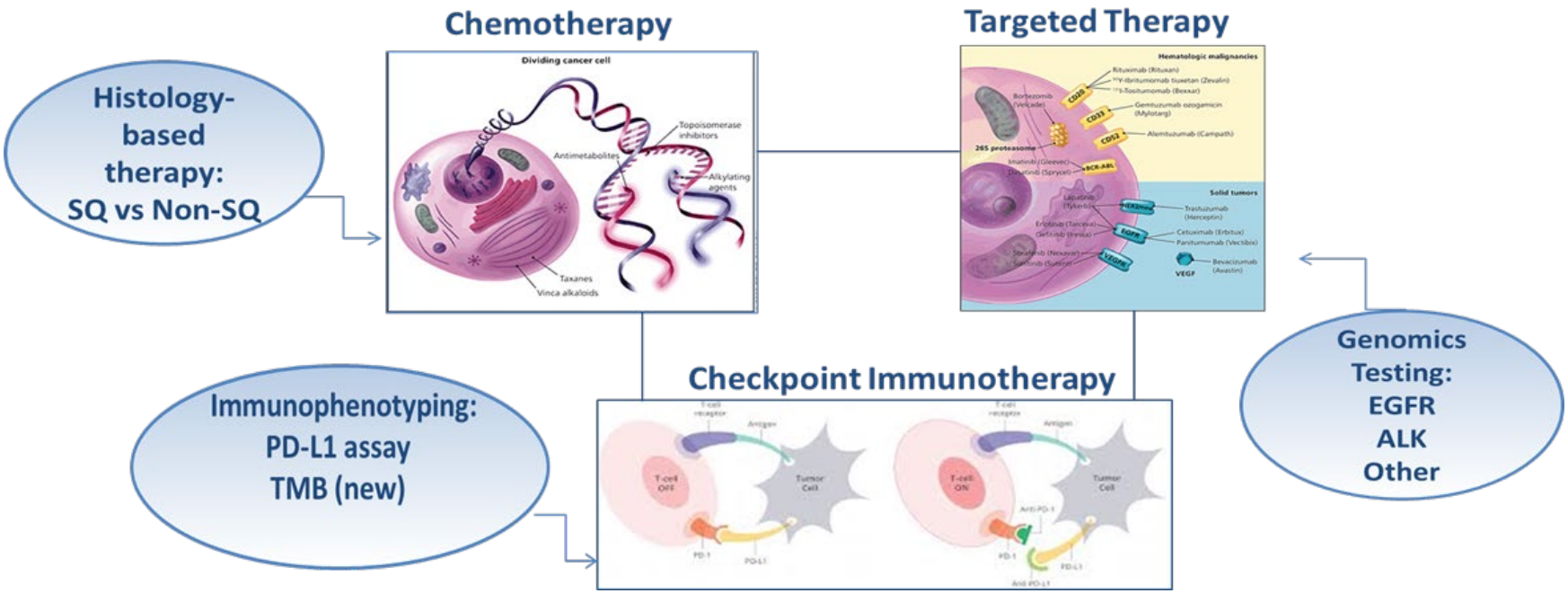
Neoadjuvant vs Adjuvant Chemotherapy in Early Stage NSCLC: Meta-Analysis



	N	HR	P value
Neoadjuvant Trials	2385	0.87 (95% CI 0.78-0.96)	.007
Adjuvant Trials	8447	0.86 (95% CI 0.81-0.92)	<.0001

NSCLC Meta-analysis collaborative Group Lancet 2014
NSCLC Meta-analysis Collaborative Group Lancet 2010

Optimizing use of Available Therapeutic Modalities in Early Stage NSCLC before or after Surgical Resection (Chemotherapy; Targeted Agents; Immunotherapy)

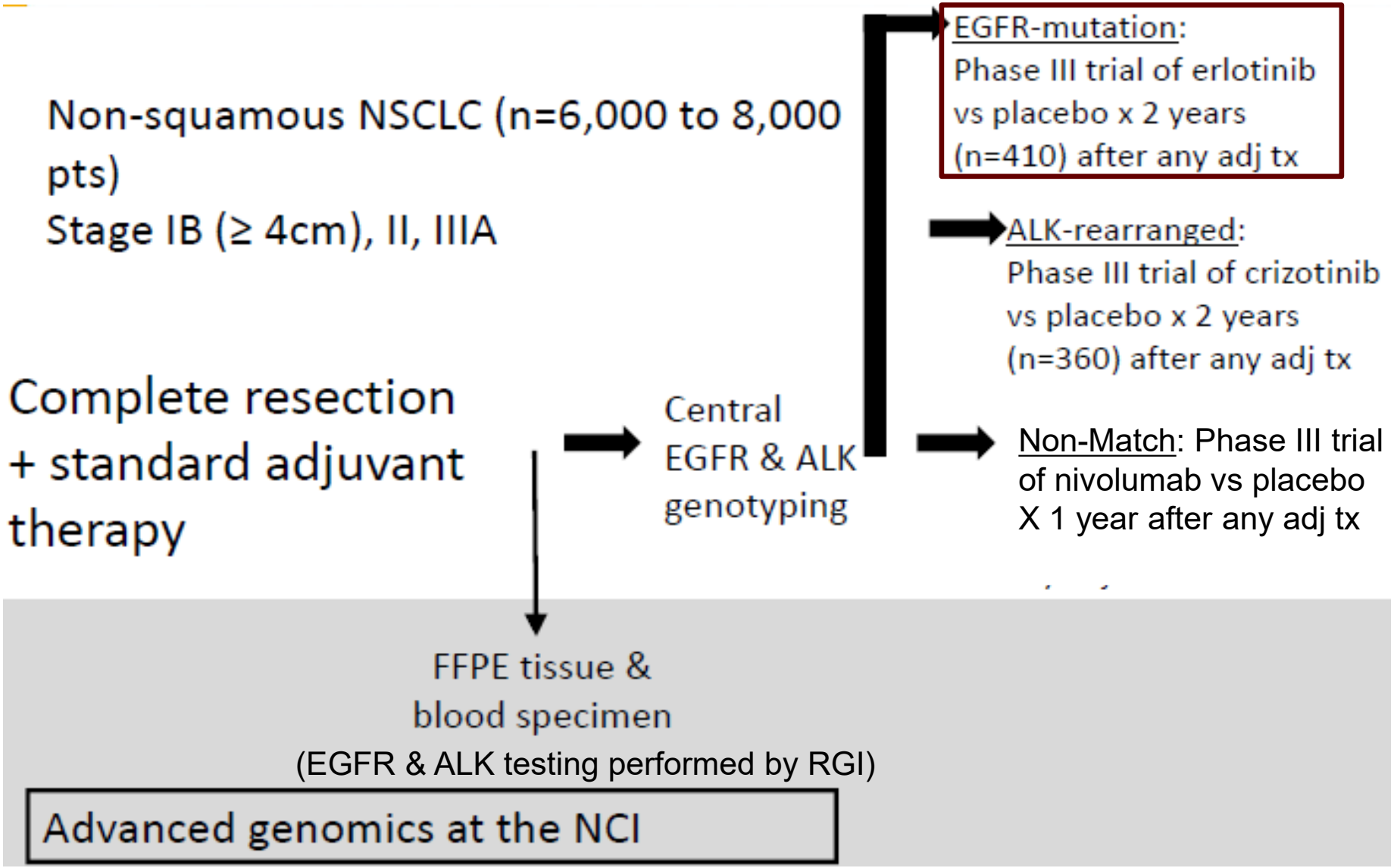


- **Targeted Therapies:** How to best move Targeted Therapies into the adjuvant & neo-adjuvant settings? ADAURA: Osimertinib in EGFR-mutated NSCLC (approved)

- **Immunotherapy:** How to best move Checkpoint Immunotherapy into the adjuvant & neo-adjuvant settings? ImPower010: Adjuvant Atezolizumab (approved)

Adapted from Gandara: Master Lecture Series

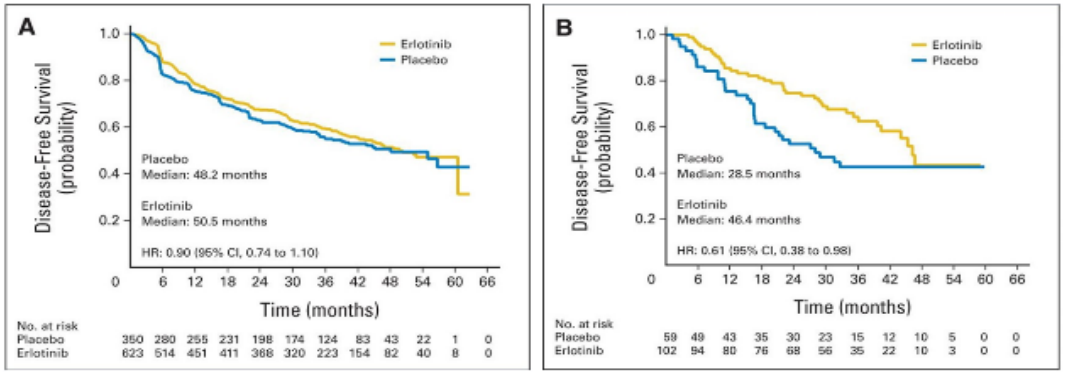
ALCHEMIST Master Protocol Trials for Adjuvant Therapy of NSCLC (NCI)



Prior Studies of Post-Operative Adjuvant EGFR-Targeted Therapy

RADIANT: Adjuvant Erlotinib v Placebo Stage IB-IIIA NSCLC (EGFRwt and EGFRm)

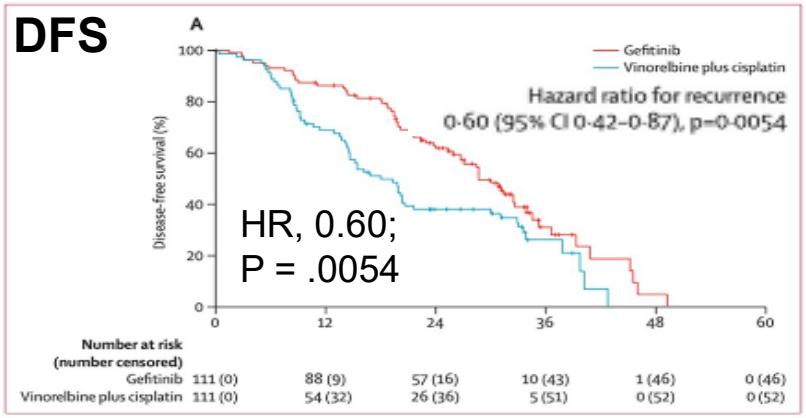
DFS



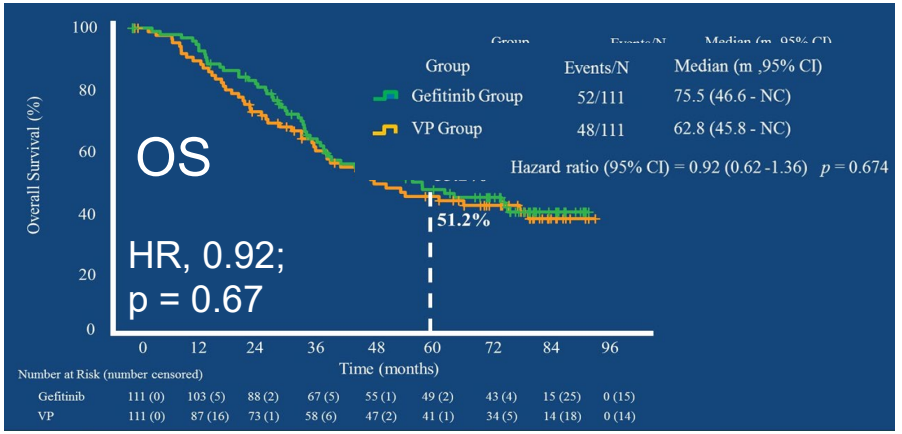
Kelly, JCO 2015

ADJUVANT: Gefitinib v Vinorelbine/Cisplatin as Adjuvant Treatment for Stage II-IIIA (N1-N2) EGFRm NSCLC

DFS



Zhong, Lancet Onc 2017

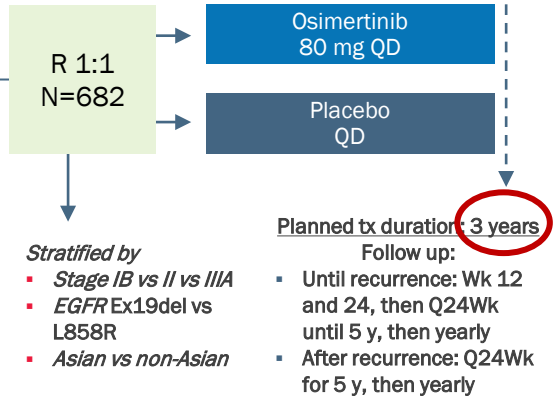


Wu, ASCO 2020

ADAURA: Osimertinib as adjuvant therapy in patients with stage IB–IIIA *EGFR*-mutated NSCLC after surgical resection

Completely resected stage[a] IB, II, IIIA NSCLC with or without adjuvant CT[b]

- Key inclusion criteria:
- ≥18 years (Japan/Taiwan: ≥20)
- WHO PS 0/1
- Confirmed primary nonsquamous NSCLC
- *EGFR* Exon 19 del/L858R[c]
- Brain imaging, if not completed preoperatively
- Complete resection with negative margins[d]
- Max interval between surgery and randomization:
  - 10 wks w/o adjuvant CT
  - 26 wks w/ adjuvant CT



Primary endpoint: INV-assessed DFS in stage II/IIIA patients (designed for superiority under assumed DFS HR of 0.70)
Secondary endpoints: DFS (overall population[e]), DFS (2, 3, 4, 5 years), OS, safety, HRQoL

- **Following data monitoring committee recommendation, the study was unblinded early due to efficacy**
- At time of unblinding, the study had completed enrollment and all patients were followed up for ≥1 year

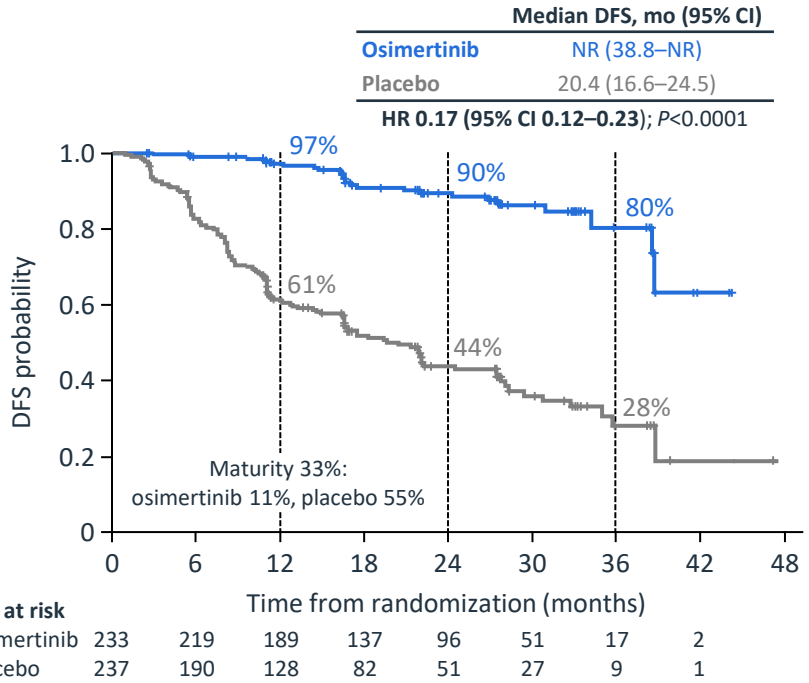
Baseline Characteristic, %	Osimertinib (n=339)	Placebo (n=343)
Sex: male/female	32/68	28/72
Median age (range), years	64 (30-86)	62 (31-82)
Race:[f] Asian/non-Asian	64/36	64/36
Smoking history: no/yes	68/32	75/25
WHO PS: 0/1	64/36	64/36
AJCC staging at diagnosis (7th edition)[g] IB II IIIA	 32 34 35	 32 34 34
Histology: adenocarcinoma/other	96/4	97/3
EGFR mutation: Ex19del/L858R	55/45	55/45
Prior adjuvant therapy: yes/no	60/40	60/40

[a]AJCC 7th edition; [b]Prior, post, or planned radiation was not allowed; [c]Centrally confirmed in tissue; [d]Patients received a computed tomography scan after resection and within 28 days prior to treatment; [e]Stage IB, II, IIIA
[f]Race was missing for 1 patient in the placebo arm; [g]If not performed prior to surgery, brain MRI or CT scans were performed prior to randomization. Imaging methods used at baseline (MRI or CT) were required to be used at each subsequent follow-up assessment.

1. **Wu YL, et al. *N Engl J Med*. 2020. 2. Herbst RS, et al. Presented at ASCO 2020. Abstract LBA5. 3. Wu YL, et al. Presented at WCLC 2020. Abstract OA6.04.**

ADAURA: Disease-free survival (DFS)

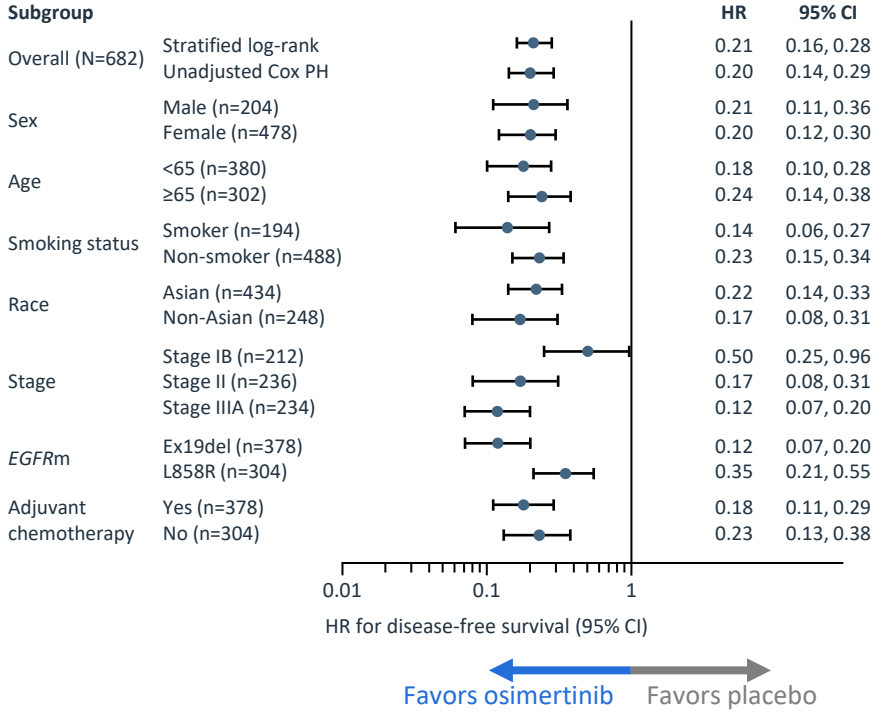
Primary endpoint: DFS in patients with Stage II/IIIA disease



No. at risk

Osimertinib	233	219	189	137	96	51	17	2
Placebo	237	190	128	82	51	27	9	1

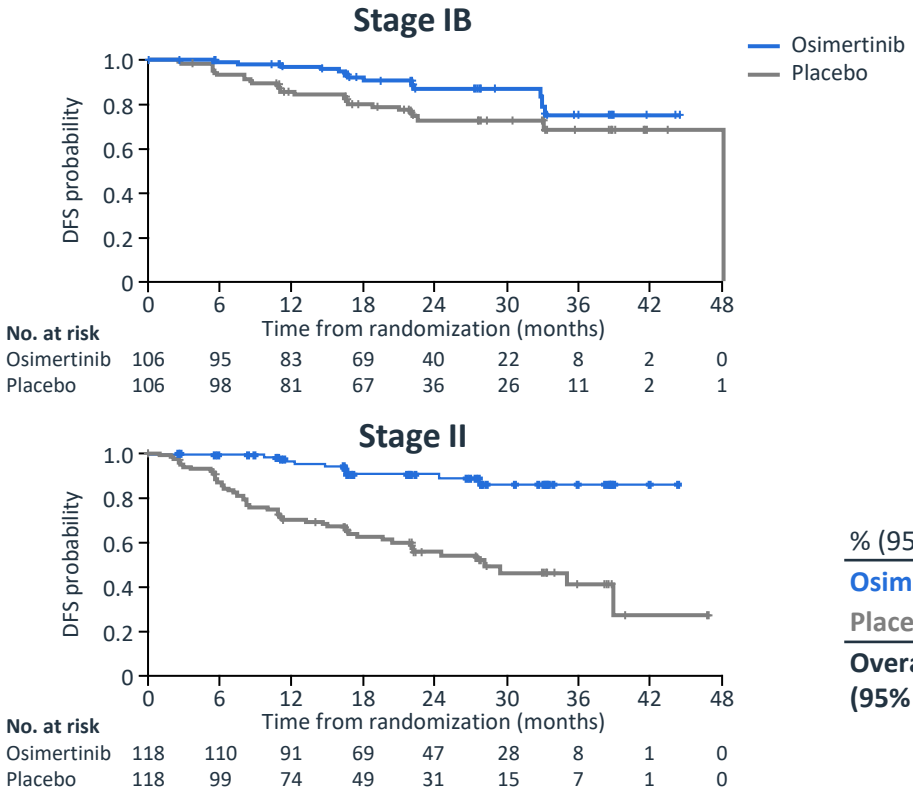
DFS across subgroups in the overall population

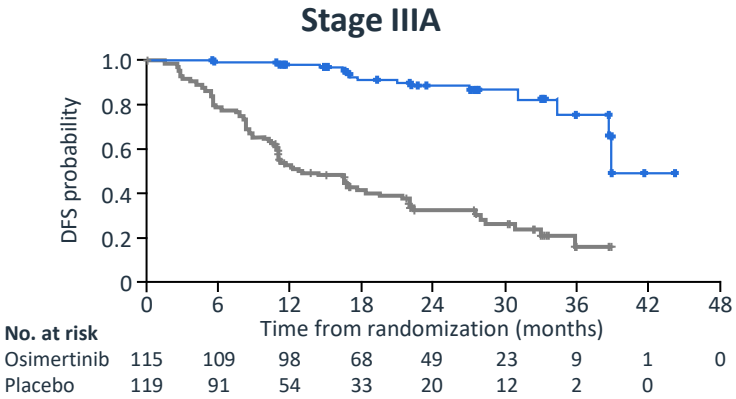


Data cutoff: January 17, 2020. NR, not reached

Herbst RS, et al. ASCO 2020. Abstract LBA5; Wu et al NEJM 2020.

ADAURA: Disease-free survival by stage





2 Year DFS rate

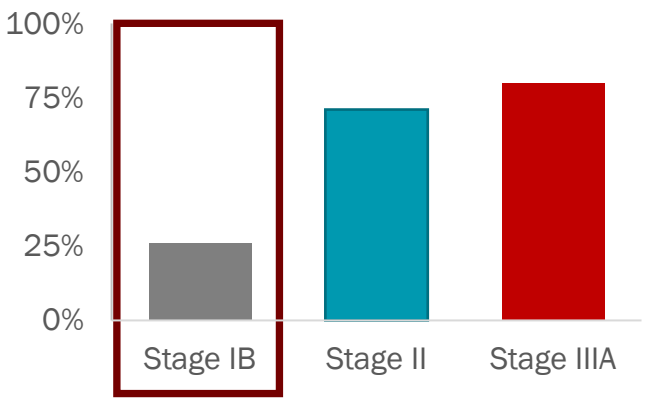
% (95% CI)	Stage IB	Stage II	Stage IIIA
Osimertinib	87 (77–93)	91 (82–95)	88 (79–94)
Placebo	73 (62–81)	56 (45–65)	32 (23–42)
Overall HR (95% CI)	**0.50 (0.25–0.96)**	**0.17 (0.08–0.31)**	**0.12 (0.07–0.20)**

Data cutoff: January 17, 2020.

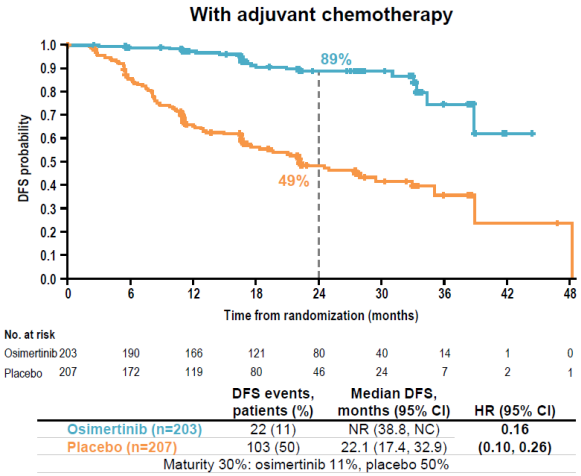
Herbst RS, et al. ASCO 2020. Abstract LBA5; Wu et al. NEJM 2020.

ADAURA: Osimertinib as Adjuvant Therapy in Patients With Resected *EGFR*m NSCLC: Adjuvant Chemotherapy Use and DFS (IIT)

Adjuvant Chemotherapy Use by Stage[a]

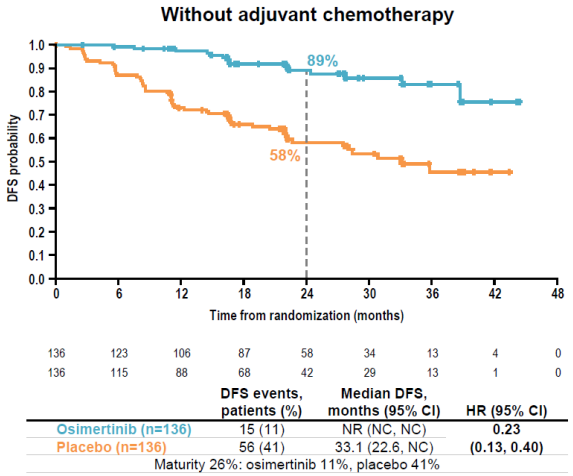


DFS IN OVERALL POPULATION



	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n=203)	22 (11)	NR (38.8, NC)	**0.16**
Placebo (n=207)	103 (50)	22.1 (17.4, 32.9)	**(0.10, 0.26)**

Maturity 30%: osimertinib 11%, placebo 50%



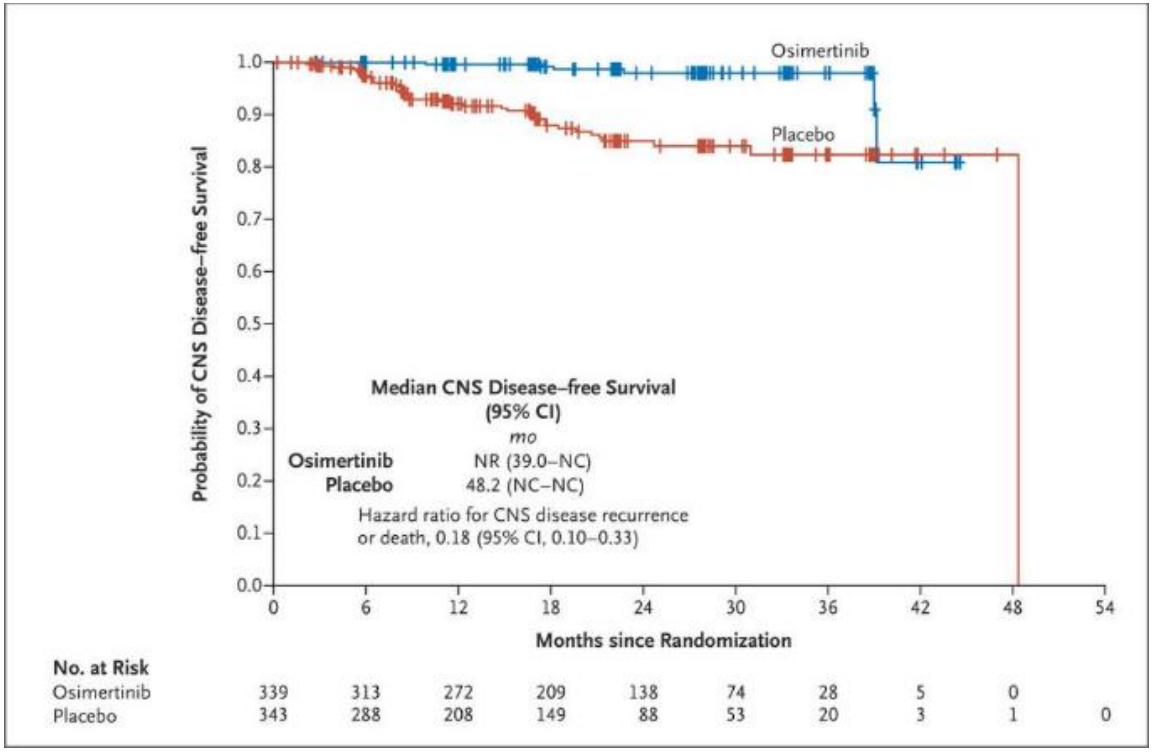
	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n=136)	15 (11)	NR (NC, NC)	**0.23**
Placebo (n=136)	56 (41)	33.1 (22.6, NC)	**(0.13, 0.40)**

Maturity 26%: osimertinib 11%, placebo 41%

[a]Includes only patients who received platinum-based chemotherapy (n=409).[b]No patients with stage Ib from Japan. [c]Japan n=71, China n=106, Asia non-Japan/non-China n=91.[d]Enrolled in Europe, Australia, United States, Canada, or Brazil.

Wu YL, et al. Abstract 006.04. IASLC 2020.

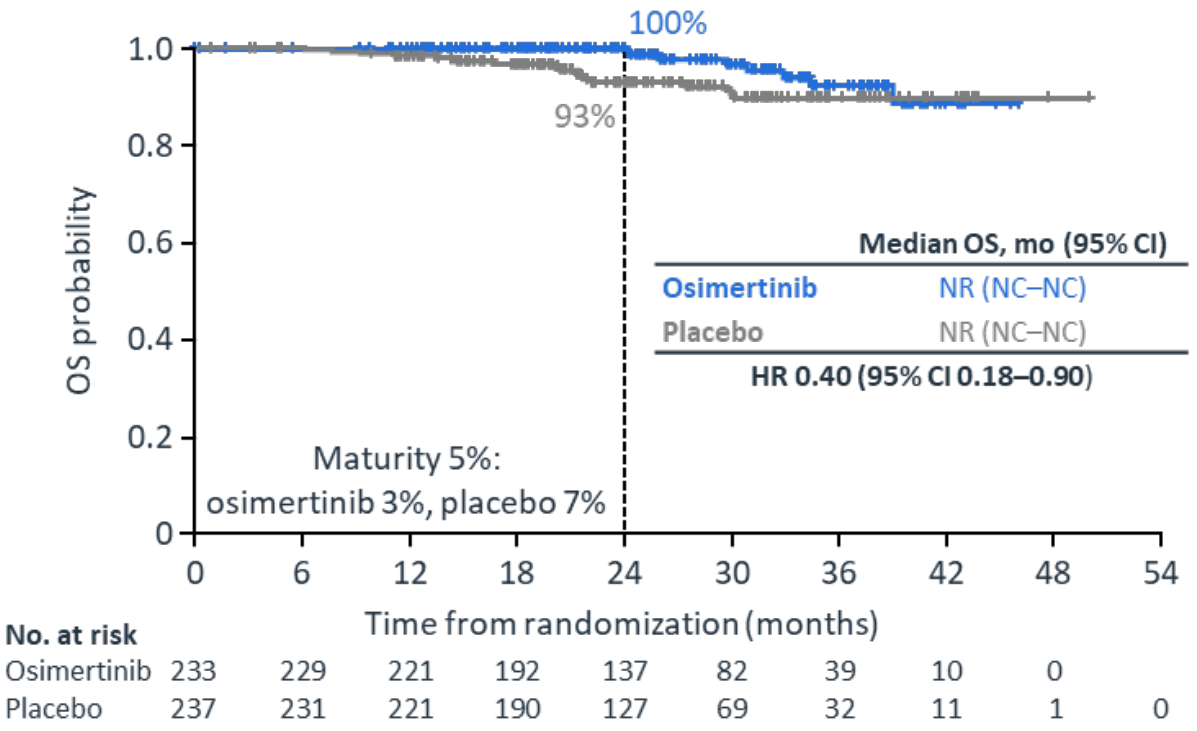
ADAURA: CNS DFS —Overall Population



82% reduction in the risk of CNS disease recurrence or death

Wu Y-L, R, et al. *N Engl J Med*. 2020;383(18):1711-1723..

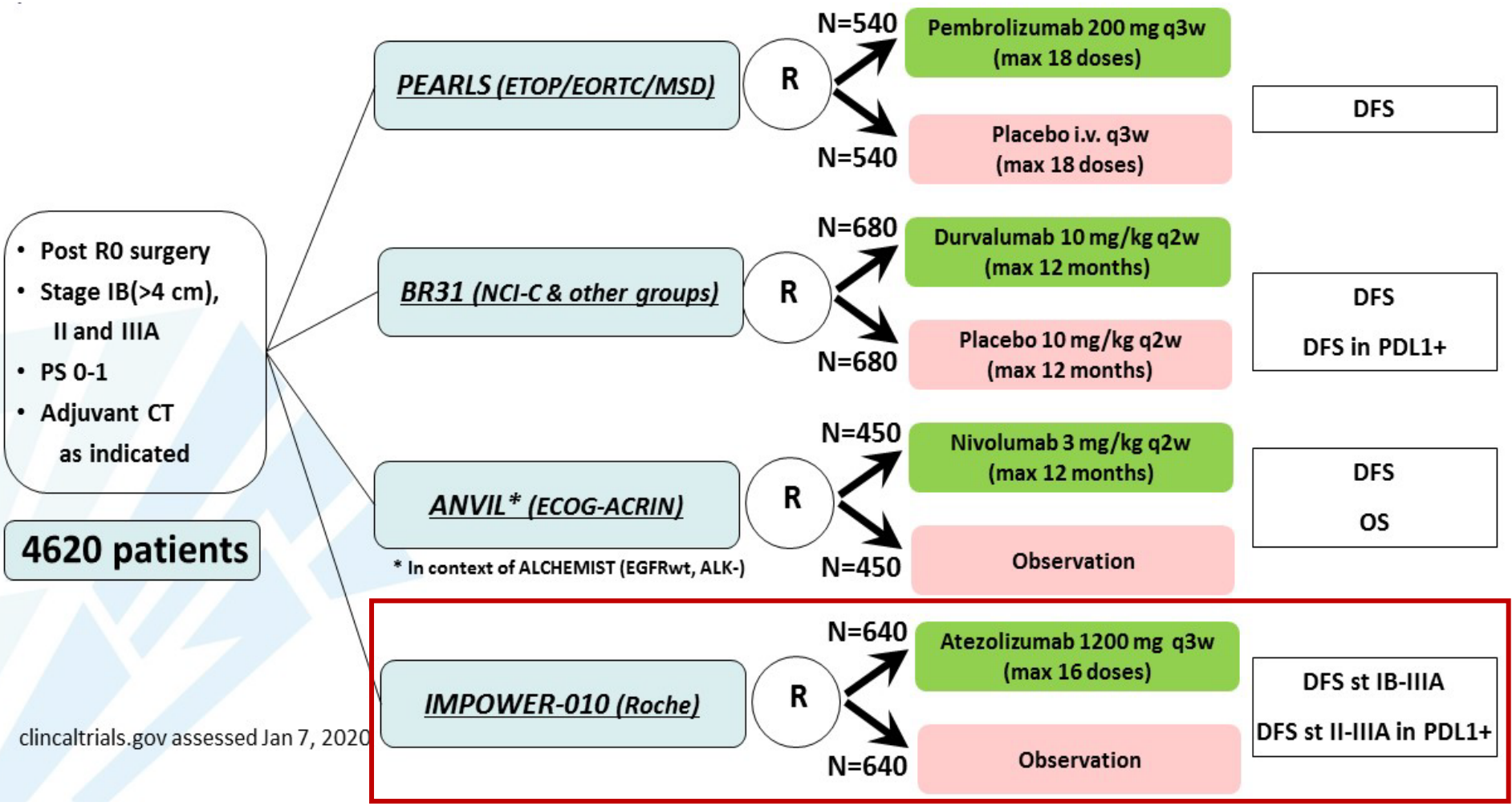
ADAURA: Overall survival in patients with Stage II/IIIA disease



Data cutoff: January 17, 2020.

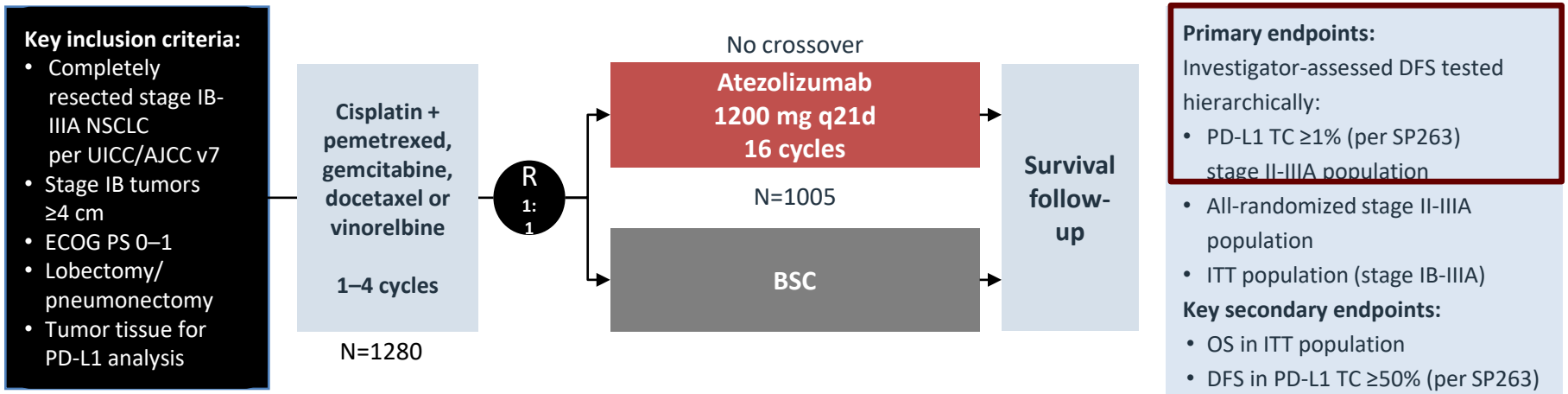
Herbst RS, et al. ASCO 2020. Abstract LBA5; Wu et al. NEJM 2020.

Ongoing Adjuvant Checkpoint Immunotherapy (CPI) Phase III Trials



clincaltrials.gov assessed Jan 7, 2020

IMpower010 (primary results): Atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA NSCLC



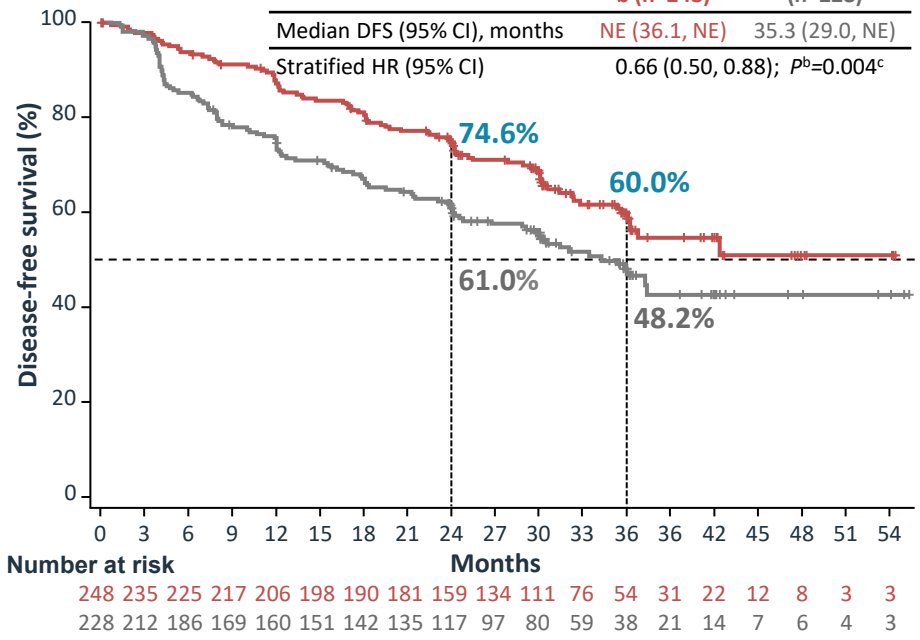
[a]Per SP142 assay. Both arms included observation and regular scans for disease recurrence on the same schedule.

AJCC, American Joint Committee on Cancer; BSC, best supportive care; DFS, disease free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, tumor-infiltrating immune cells; ITT, intent to treat; OS, overall survival; TC, tumor cells; UICC, International Union Against Cancer.

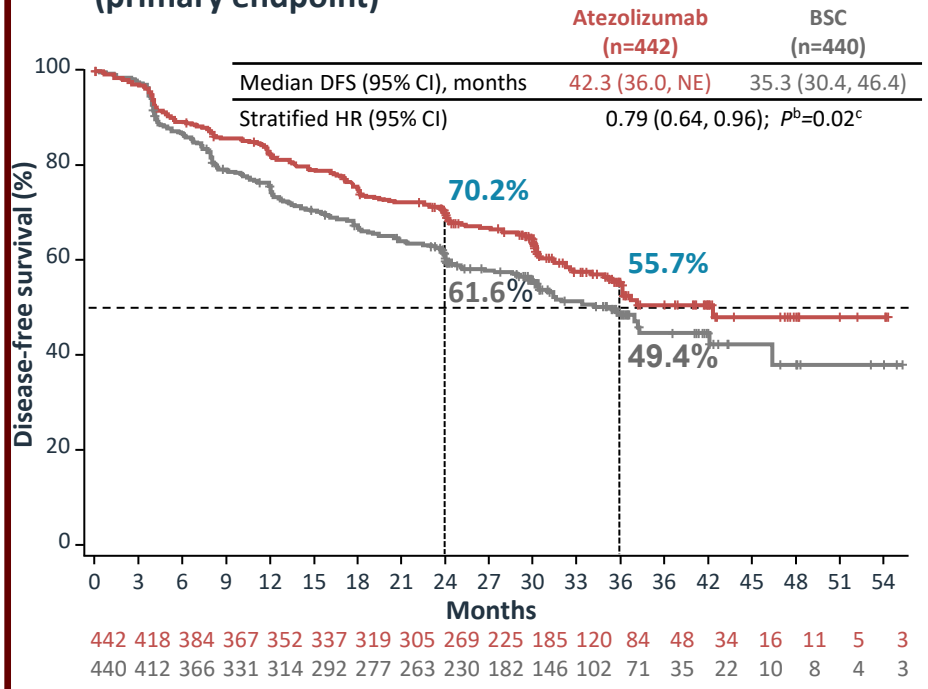
Wakelee H, et al. ASCO 2021. Abstract 8500.

IMpower010: Primary efficacy results

DFS in PD-L1 TC ≥1%[a] stage II-IIIA NSCLC (primary endpoint)

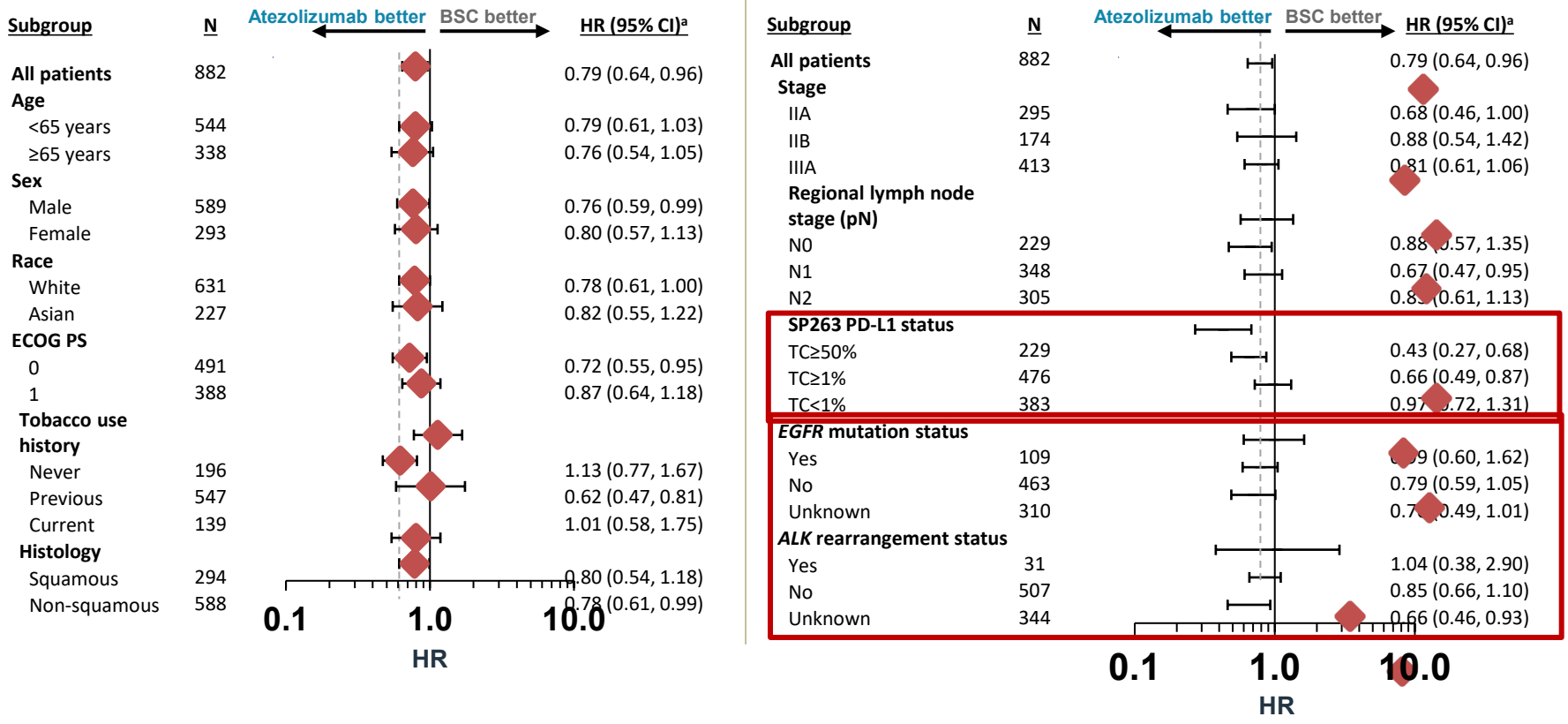


DFS in all-randomized stage II-IIIA NSCLC (primary endpoint)



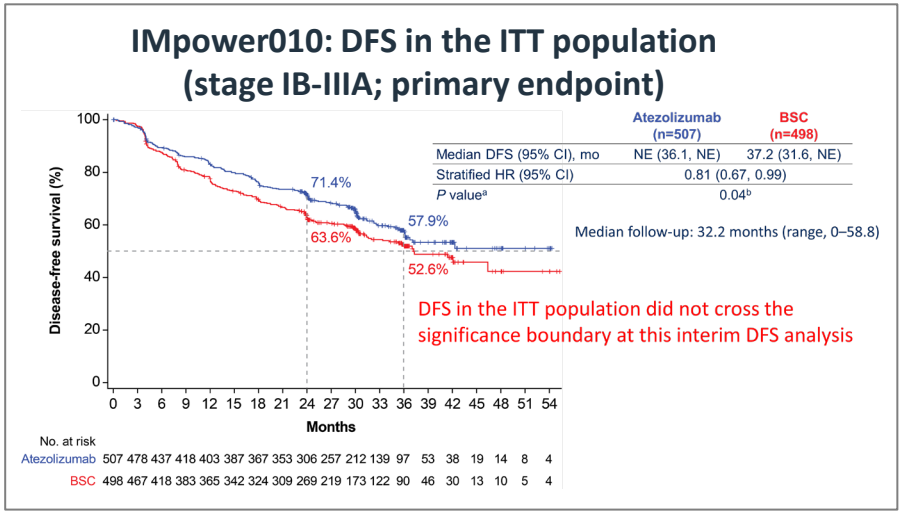
Median follow-up: 32.8 months (range: 0.1–57.5). [a]Per SP263 assay. [b]Stratified log-rank. [c]Crossed the significance boundary for DFS.
BSC, best supportive care; DFS, disease free survival; NE, not evaluable.
Wakelee H, et al. ASCO 2021. Abstract 8500.

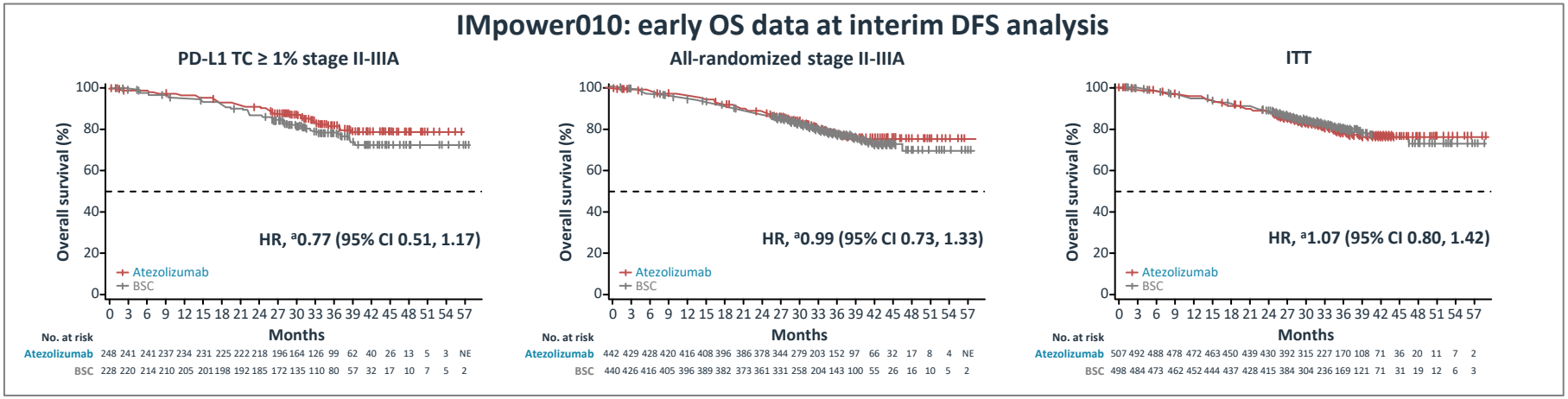
IMpower010: DFS in key subgroups of the all-randomized Stage II-IIIA population



Clinical cutoff: January 21, 2021. [a]Stratified for all patients; unstratified for all other subgroups.
BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; TC, tumor cell.
Wakelee H, et al. ASCO 2021. Abstract 8500.

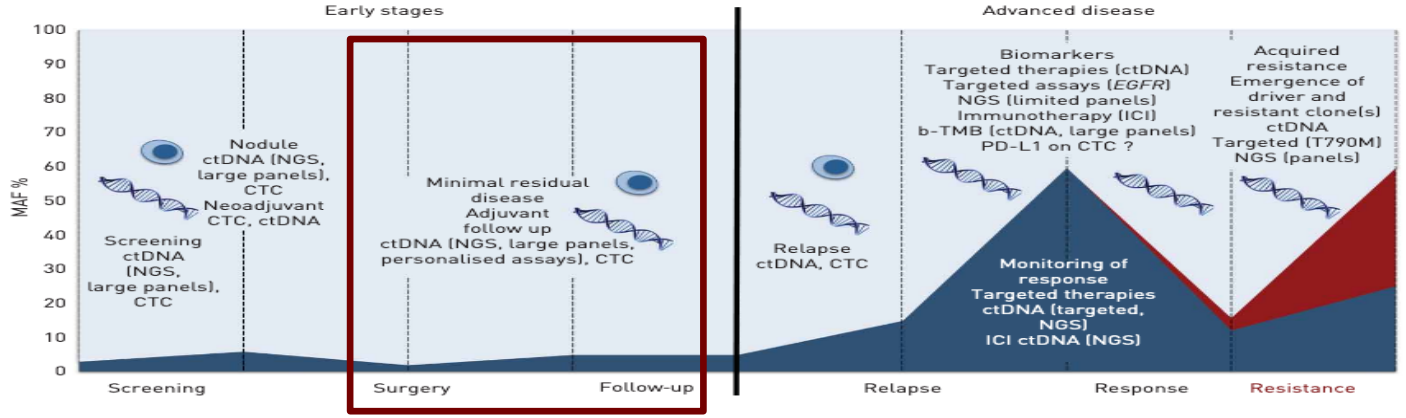
IMpower010: DFS in ITT population & OS





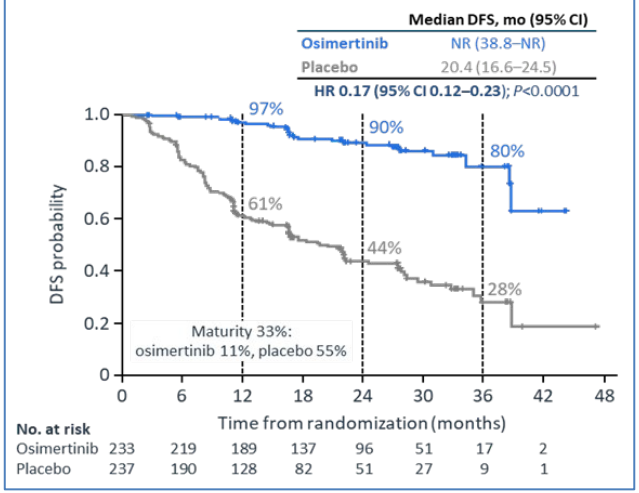
[a]Stratified log-rank. [b]The statistical significance boundary for DFS was not crossed. BSC, best supportive care; DFS, disease free survival; HR, hazard ratio; ITT, intention to treat; NE, not evaluable; OS, overall survival; TC, tumor cell. Wakelee H, et al. ASCO 2021. Abstract 8500.

Two landmark trials in the adjuvant NSCLC space ADAURA & IMpower010: Can plasma ctDNA analysis for MRD define who benefits and who does not?



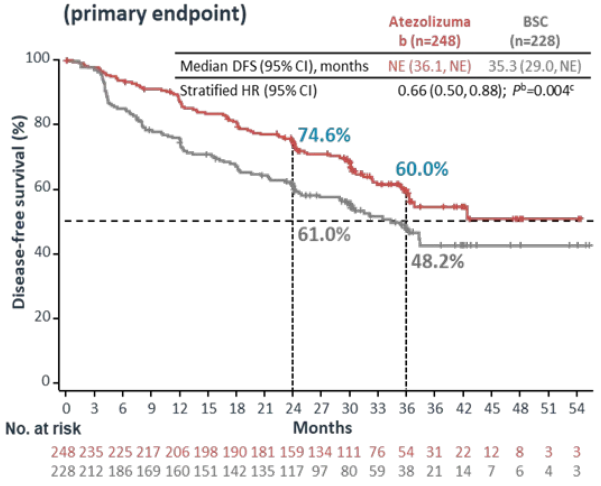
ADAURA: Adjuvant Osimertinib in *EGFR*m NSCLC

Primary endpoint: DFS in Stage II/IIIA disease



IMpower 010: Adjuvant Atezolizumab

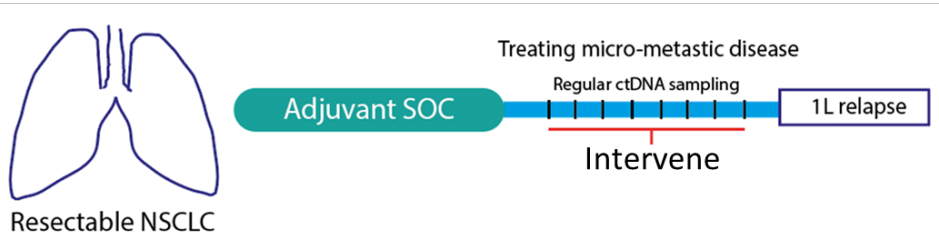
DFS in PD-L1 TC ≥1%a stage II-IIIA NSCLC (primary endpoint)



- Is MRD detection by plasma ctDNA only prognostic in these trials? (poor outcome regardless of therapeutic intervention)
- Is MRD detection by plasma ctDNA predictive for outcome with therapeutic intervention?
  - Do only patients with positive MRD after surgery benefit from these therapies?

Yi-Long Wu et al. N Engl J Med 2020; 383:1711-1723 Wakelee H, et al. ASCO 2021. Abstract 8500.

ctDNA as an MRD biomarker

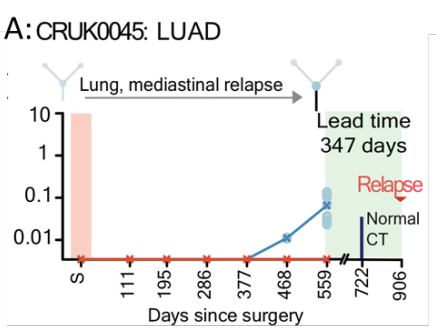


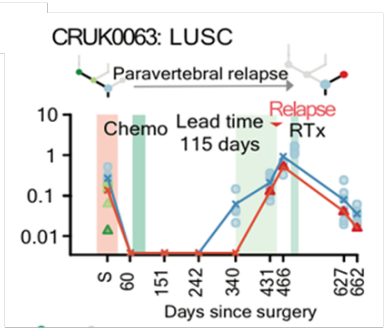
Advantages:

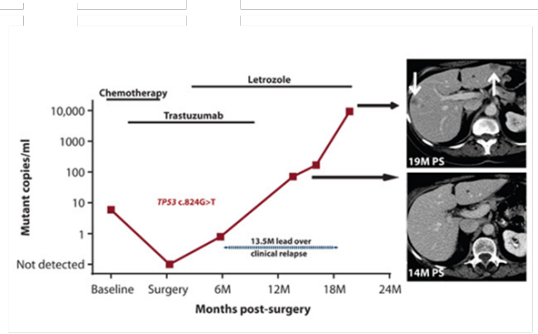
- larger proportion of DFS events across a population identified.
- ctDNA monitoring feasible at frequencies exceeding imaging [facilitates intervention at small disease volumes].
- Decreases screen failure rate

Disadvantages:

- Translatable into routine practice, relationship with surveillance imaging?

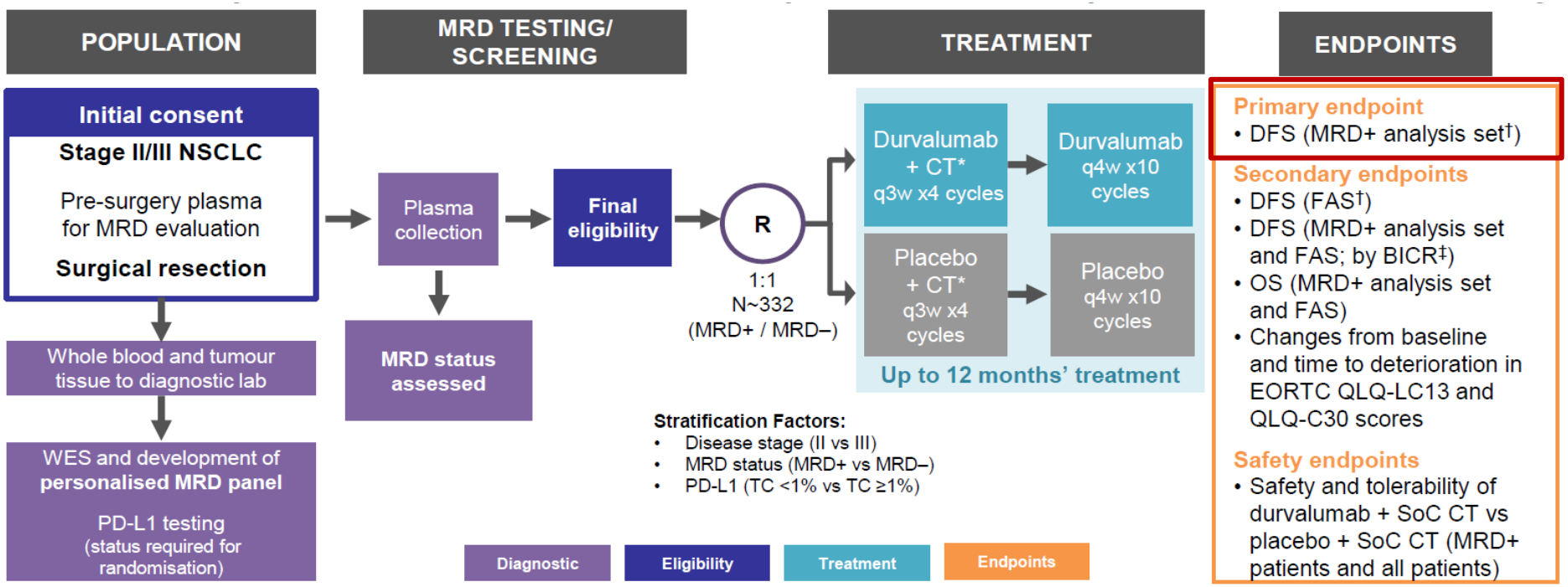






A: Abbosh et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution, Nature 545, 2017
B: Garcia-Murillas I, Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer, Sci Transl Med. 2015 Aug 26;7(302)

MERMAID-1: MRD Adjuvant Trial in surgically resected Stage II-III NSCLC: Chemotherapy + Durvalumab or Placebo

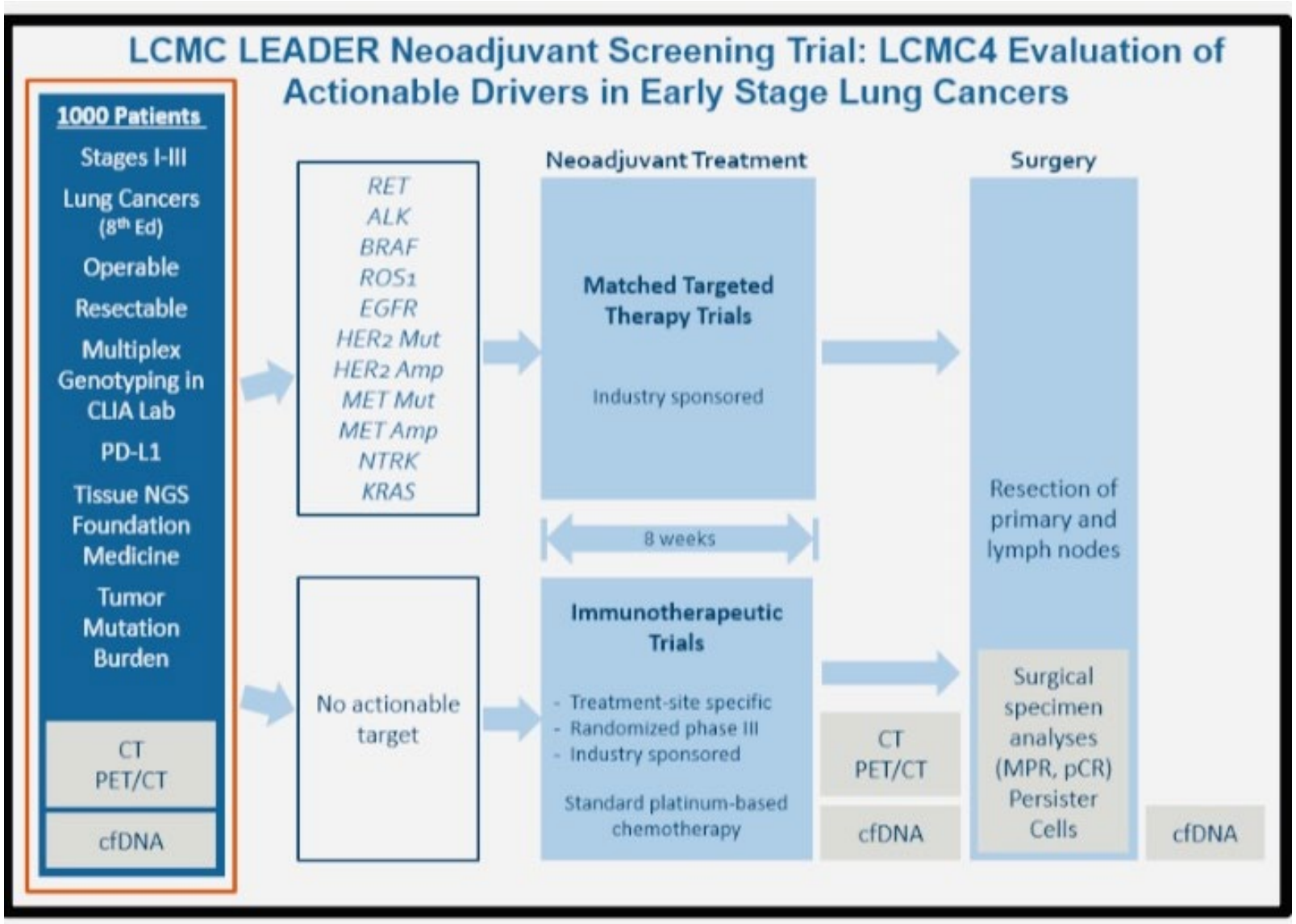


Peters et al: IASLC WCLC 2020

Neoadjuvant Phase III Trials in Early Stage NSCLC

Study*	CheckMate 816[1] CT + nivolumab	KEYNOTE-617[2] CT+ pembrolizumab	IMpower030[3] CT + Atezolizumab	AEGEAN[4] CT + Durvalumab	NeoADAURA[5] CT + Osimertinib
Stage	IB–IIIA	II–IIIB (T3-4N2)	II–IIIB (cT3N2)	IIA–IIIB	II-IIIB
Patients, No.	350	786	374	300	328
Study arms	CT + nivolumab (360 mg) × 3 cycles → S vs. CT × 3 cycles → S	CT + pembrolizumab (200 mg)/placebo × 4 cycles → S →pem/placebo × 13 cycles	CT + atezolizumab (1200 mg)/placebo × 4 cycles → S → atezo/placebo × 16 cycles	CT + durvalumab (1500 mg)/placebo × 3 cycles → S → durvalumab/placebo Q4W × 12 cycles	CT + osimertimib (80 mg) x 3 cycles → S
Key inclusion criteria	▪ Early stage IB-IIIA, operable NSCLC, confirmed in tissue ▪ Lung function capacity tolerating the surgery ▪ Available tissue of primary tumor	▪ Confirmed resectable Stage II, IIIA, or IIB (N2) NSCLC ▪ Eligible for protocol therapy, including surgery ▪ Tissue sample available	▪ Confirmed resectable Stage II, IIIA, IIIB (T3N2) NSCLC ▪ Eligible for R0 resection ▪ Measurable disease by RECIST v1.1 ▪ Negative HIV, HBV, HCV	▪ Confirmed resectable Stage II, IIIA, IIIB (N2) NSCLC ▪ ≥1 lesion, no prior irradiation, qualifying as a RECIST 1.1 target lesion ▪ No prior IO	▪ ≥ 18 years old ▪ Resectable Stage II-IIIB N2 NSCLC ▪ Complete surgical resection achievable ▪ ≥1 *EGFR* mutation associated with *EGFR*-TKI sensitivity
Primary Endpoints	▪ EFS, pCR, MPR	▪ EFS, OS	▪ EFS	▪ MPR	▪ MPR
ORR, %	▪ N/A	▪ N/A	▪ N/A	▪ N/A	▪ N/A
Median PFS, mo	▪ N/A	▪ N/A	▪ N/A	▪ N/A	▪ N/A
Median OS, mo	▪ N/A	▪ N/A	▪ N/A	▪ N/A	▪ N/A

1. ClinicalTrials.gov. NCT02998528. Accessed April 8th, 2021. 2. ClinicalTrials.gov. NCT03425643. Accessed April 8th, 2021. 3. ClinicalTrials.gov. NCT03456063. Accessed April 8th, 2021. 4. ClinicalTrials.gov. NCT03800134. Accessed April 8th, 2021. 5. ClinicalTrials.gov. NCT04351555. Accessed April 8th, 2021.


LCMC LEADER Neoadjuvant Screening Trial: LCMC4 Evaluation of Actionable Drivers in Early Stage Lung Cancers
1000 Patients
Stages I-III
Lung Cancers (8th Ed)
Operable
Resectable
Multiplex Genotyping in CLIA Lab
PD-L1
Tissue NGS Foundation Medicine
Tumor Mutation Burden
CT PET/CT
cfDNA
RET
ALK
BRAF
ROS1
EGFR
HER2 Mut
HER2 Amp
MET Mut
MET Amp
NTRK
KRAS
No actionable target
Neoadjuvant Treatment
Matched Targeted Therapy Trials
Industry sponsored
8 weeks
Immunotherapeutic Trials
- Treatment-site specific
- Randomized phase III
- Industry sponsored
Standard platinum-based chemotherapy
CT PET/CT
cfDNA
Surgery
Resection of primary and lymph nodes
Surgical specimen analyses (MPR, pCR) Persister Cells
cfDNA

Neoadjuvant CPI in Resectable NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neodjuvant PD-1 Blockade in Resectable Lung Cancer

Methods: 21 patients planned for surgical resection

2 doses of neoadjuvant Nivolumab followed by surgical resection at 4 weeks

Results:

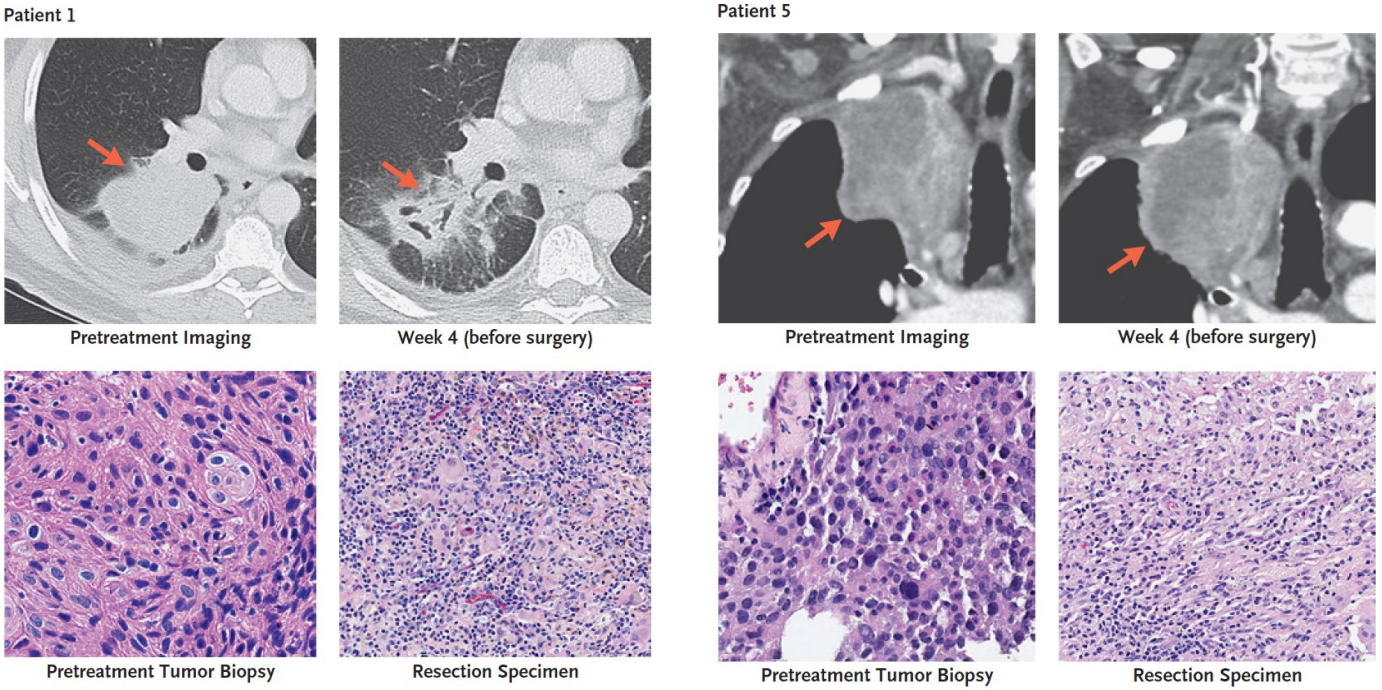
Poor correlation of Radiographic ORR & Major Path Response

Major Path RR in 9/20(45%)

Only 2 patients (10%) with radiographic ORR

Conclusion:

Even brief exposure to CPI can induce major biologic effects



Forde et al: NEJM 2018

Subsequent Neo-Adjuvant Trials of Checkpoint Inhibitors

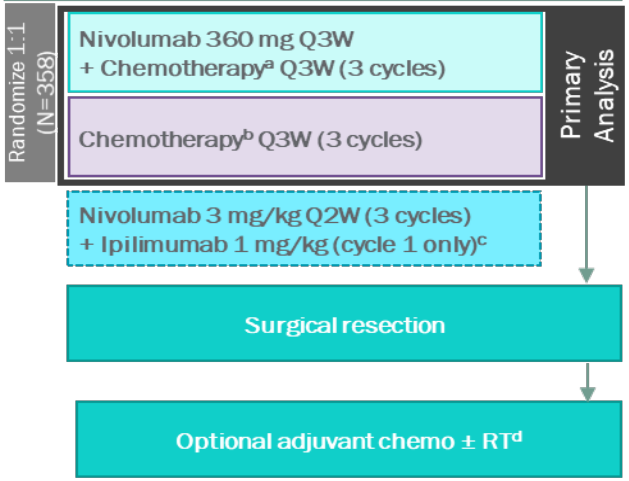
Trial	Regimen	Stage & IIT Patient Sample Size	MPR – IIT population	RECIST Response	Lost to Surgery (N)
LCMC3	Atezo	Stage I-IIIA (101)	(15 of 77*) 19%	(6) 7%	(11) 11%
NEOSTAR (Arm A)	Nivo	Stage I-IIIA (23)	(4) 17%	(9) 21%	(2) 9%
NEOSTAR (Arm B)	Nivo-Ipi	Stage I-IIIA (21)	(7) 33%		(5) 24%

Kwiatkowski DJ, et al. ASCO 2019; Cascone et al. ASCO 2019

Neoadjuvant Nivolumab +CT in Resectable Stage IB-IIIA (CheckMate 816): Study Design and Patients

Key eligibility criteria

- Newly diagnosed, resectable, untreated, unselected, stage IB-IIIA, patients with NSCLC
- No known sensitizing *EGFR* mutations or *ALK* alterations

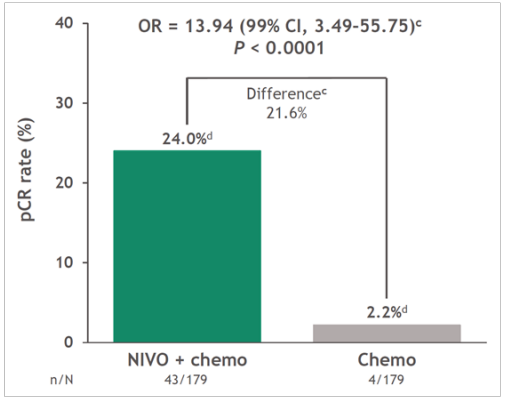


Patient Characteristics, %		Nivo + chemo (n=179)	Chemo (n=179)
Median age (range), years		64 (41-82)	65 (34-84)
Female, %		28	29
Region[e], n (%)	North America	23	28
	Europe	23	14
	Asia	48	51
Clinical stage[f], n (%)	IB-II[g]	36	35
	IIIA	63	64
Histology, %	Squamous	49	53
	Non-squamous	51	47
Smoking status[h], %	Current / former	89	88
	Never	11	11
Tumor PD-L1 expression, %[i]	Not evaluable	7	7
	<1%	44	43
	≥1%	50	50
	1-49%	28	16
	≥50%	21	24
TMB, %[j]	Not evaluable / not reported	51	50
	<12.3 mut/Mb	27	30
	≥12.3 mut/Mb	22	21

Primary endpoints: pCR by BIPR, EFS by BICR
Secondary endpoints: MPR by BIPR, OS, time to death or distant metastases
Exploratory endpoints: ORR by BICR, predictive biomarkers (PD-L1, TMB, ctDNA[k])

Baseline characteristics in the Nivolumab + Ipilimumab (exploratory) arm were generally similar to the NIVO + chemo and chemo arms

PRIMARY ENDPOINT: ITT (ypT0N0)[b]

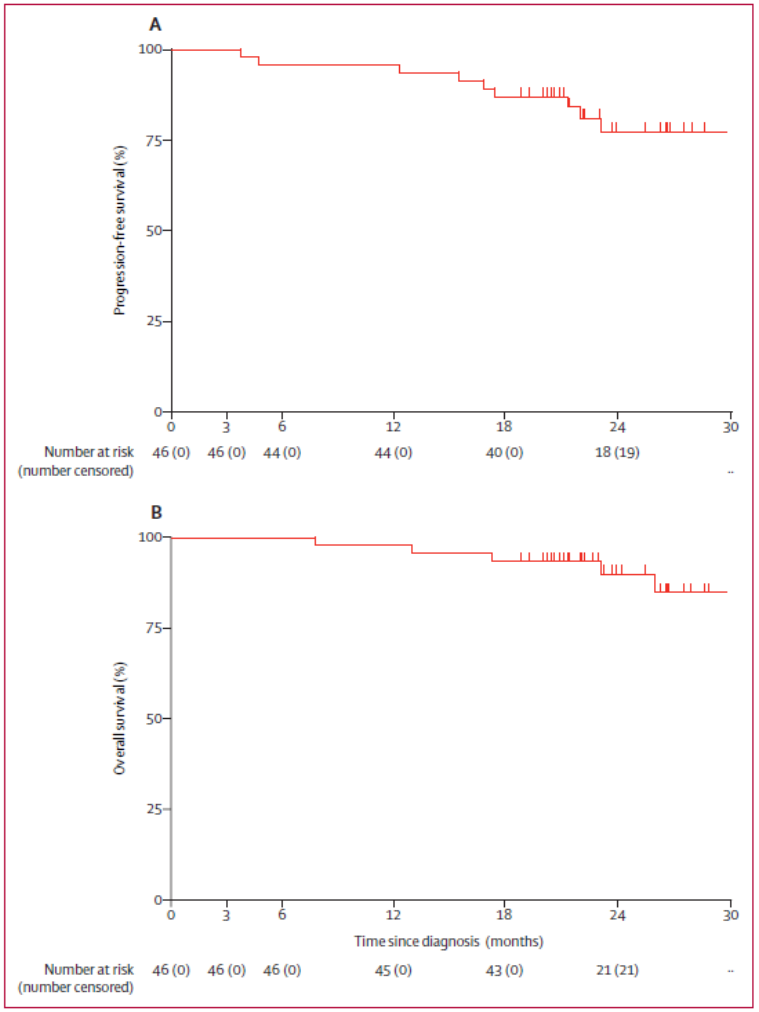


pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4 29.0)

Forde P, et al. AACR 2021.

Pilot Study of Neoadjuvant CPI + Chemotherapy in Resectable Stage III NSCLC

- 46 patients with resectable stage III NSCLC
- Neoadjuvant therapy**: paclitaxel-carboplatin + nivolumab X 3 cycles** prior to surgery
- Median follow up: 24 months
- Of 43 patients undergoing surgery, PFS at 24 months is 77%
- 14 patients (30%) had ≥grade 3 side effects
- No treatment-related deaths



Provencio et al: Lancet Onc 2020

Summary

1. Adjuvant cisplatin-based chemotherapy is the standard of care (SOC) for treatment of stage II- IIIA NSCLC due to improved OS (gold standard)

2. Adjuvant chemotherapy for Stage I disease is controversial (6^{th}-7^{th} staging edition)

3. Prior adjuvant trials in EGFR-mutated NSCLC of 1^{st}-2^{nd} generation TKIs have shown variable results. Recently, ADAURA showed improved DFS with Osimertinib & is now FDA-approved in Stage IB-IIIA surgically resected NSCLC

4. Clinical trials of neo-adjuvant & adjuvant TKIs in several other Oncogene-driven NSCLC subtypes are ongoing but are not yet SOC

5. Phase III trials of immunotherapy given in the neo-adjuvant & adjuvant setting are also ongoing: adjuvant Atezolizumab can now be considered SOC based on improved DFS in the Impower-010 trial