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NEW ORLEANS SUMMER CANCER MEETING

June 24-26, 2022
The Roosevelt Hotel
New Orleans, LA

17TH ANNUAL
New Orleans Summer Cancer Meeting

Adjuvant and NeoAdjuvant Novel Concepts and Strategies in NSCLC

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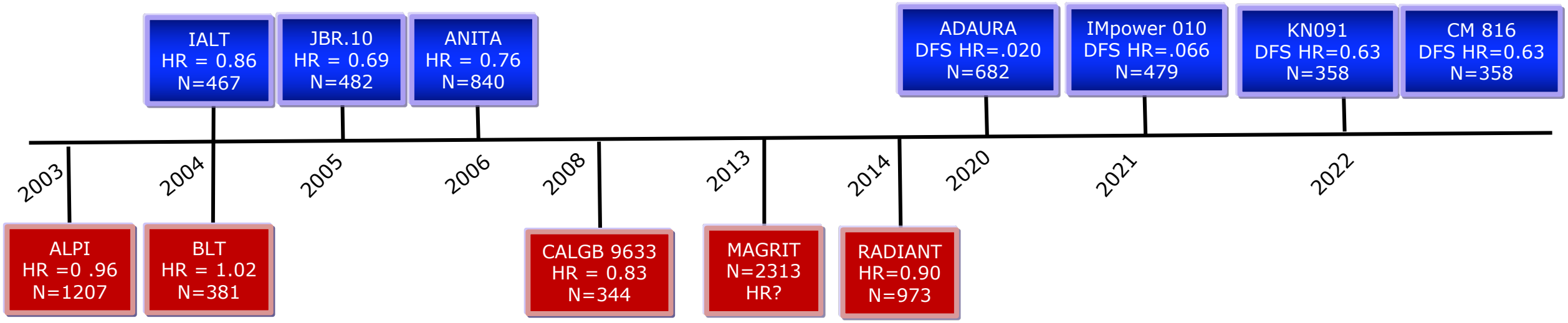
Outline

- Review the current data for the role of adjuvant and neoadjuvant systemic therapies in early-stage non-small cell lung cancer.
- Highlight relevant pending clinical trials.
- Discuss future neoadjuvant and adjuvant strategies.

Major Systemic Treatment Advances in Early-Stage NSCLC

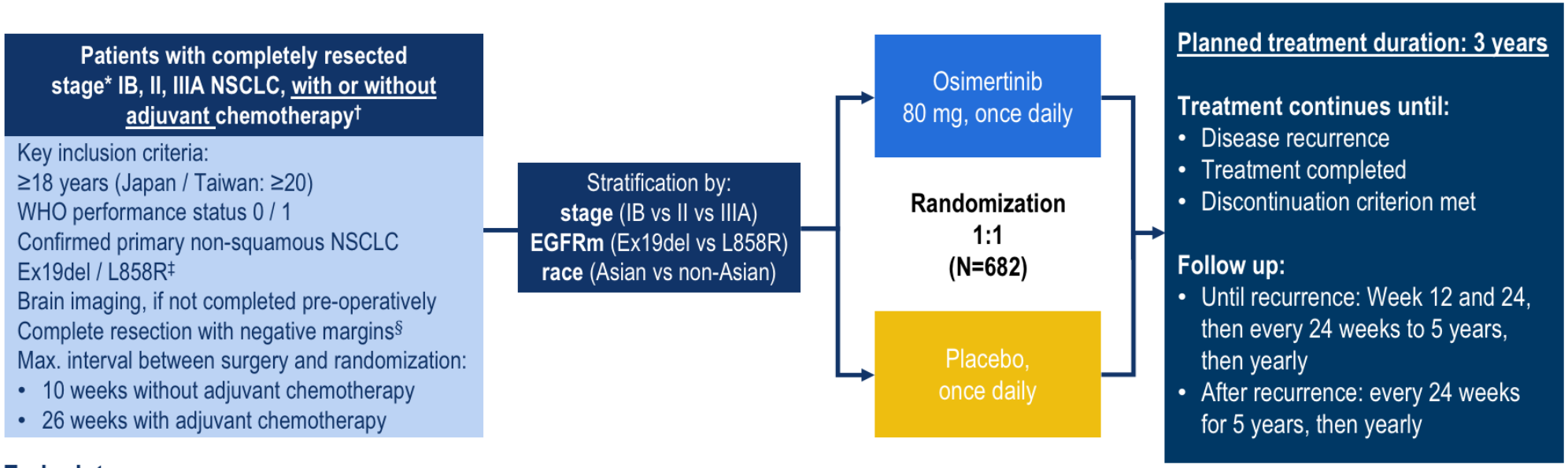
Phase III Trials



ALPI–Scagliotti GV et al. J Natl Cancer Inst 2003
BLT- Waller D et al. Eur J Cardiothorac Surg 2004
IALT–Arriagada R et al. N Engl J Med 2004
JBR.10–Winton T et al. N Engl J Med 2005
ANITA–Douilland JY et al. Lancet Oncol 2006
CALGB 9633–Strauss GM et al. J Clin Oncol 2008
MAGRIT-Vansteenkiste J et al. Lancet Oncol 2016
RADIANT – Kelly K et al. J Clin Oncol 2014
ADAURA-Herbst R et al. N Engl J Med 2021
IMpower 010 -Felip E et al. Lancet Oncol 2021
PEARLS- Paz-Ares L et al. ESMO 2022
CheckMate 816- Forde P et al. N Engl J Med 2022

Leading the way:
The FIRST adjuvant agent approved in the modern era

ADAURA Phase III double-blind study design



Endpoints

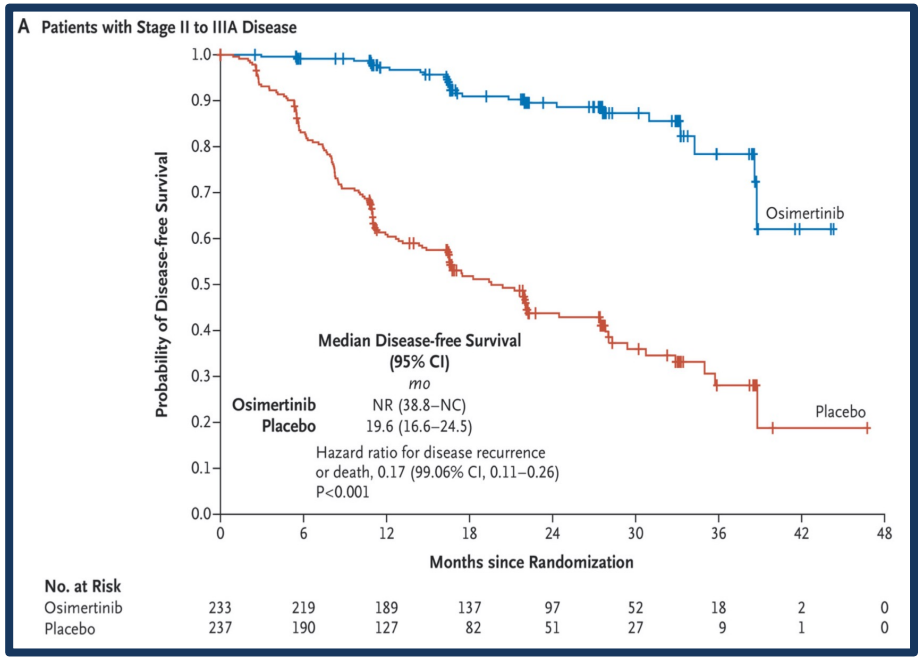
- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue; §Patients received a CT scan after resection and within 28 days prior to treatment; ¶Stage IB / II / IIIA.
CT, computed tomography; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; WHO, World Health Organization.

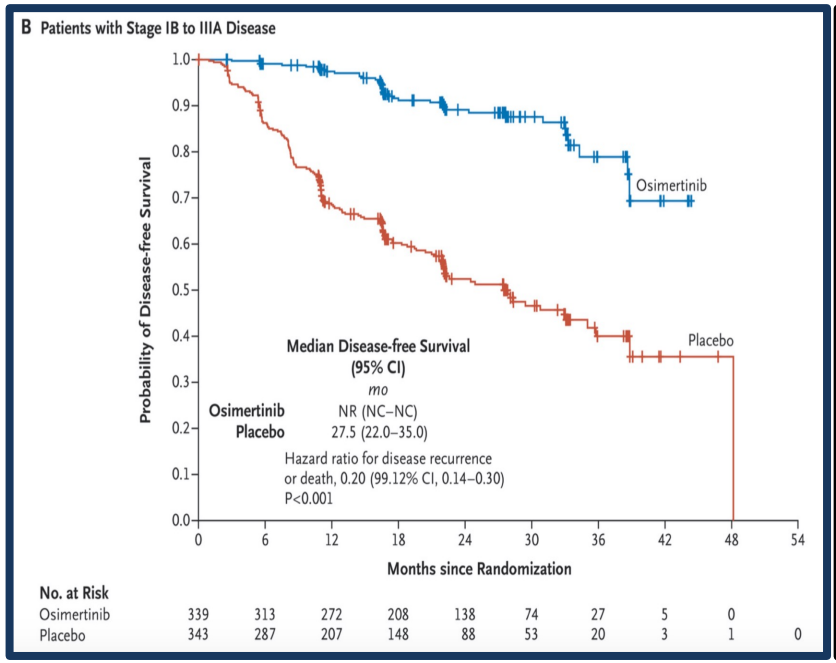
ADAURA: Efficacy Results

Primary Endpoint
DFS

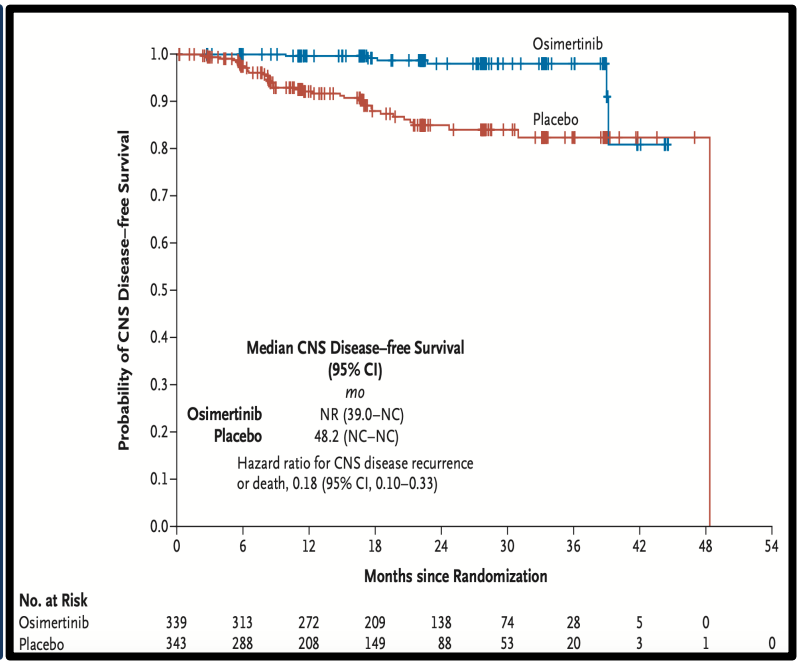


Secondary Endpoints

Stage IB-IIIA DFS



CNS DFS



Wu Yi-Long, et al. NEJM 2020

Adjuvant Chemotherapy *VS* Gefitinib

Name, Author Year	Design	*EGFR* Status (*n*)	Stages	HR DFS (*p*)	HR OS (*p*)
ADJUVANT, Zhong 2018	Phase III Gefitinib vs. chemo (V + P)	*EGFR*m (222)	II–IIIA (N1-2)	0.51 (0.001)	0.92 (0.674)
IMPACT, Tada 2021	Phase III Gefitinib vs. chemo (V + P)	*EGFR*m (234)	II–IIIA	0.92 (0.63)	1.03 (0.89)
EVIDENCE, He 2021	Phase III Icotinib vs. chemo (V + P)	*EGFR*m (322)	II–IIIA (7th TNM)	0.36 (<0.0001)	0.75 (>0.05)

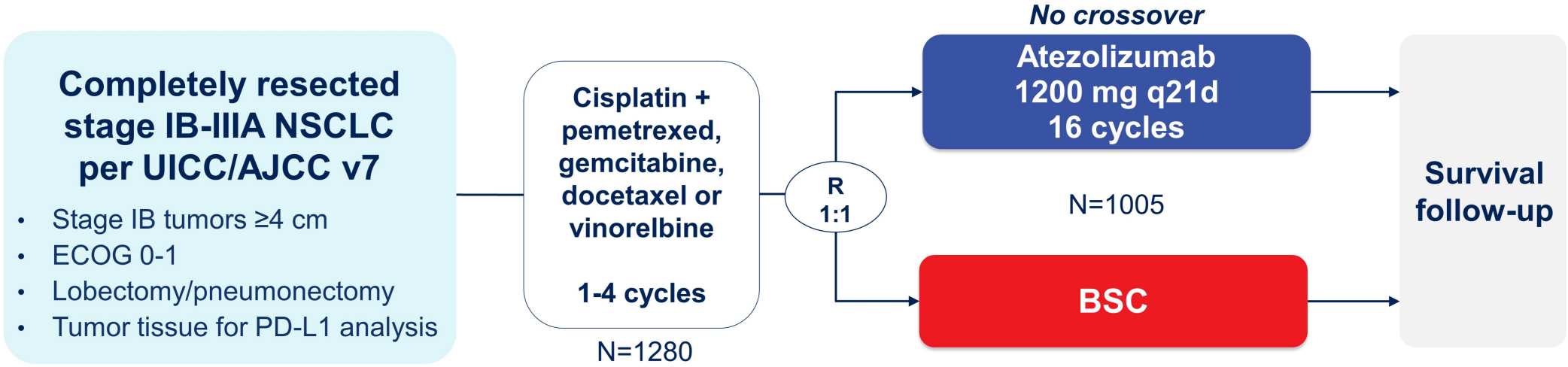
ADJUVANT AND EVIDENCE- primary endpoint DFS
IMPACT – primary endpoint was DFS at 5 years

Ongoing Adjuvant TKI Trials

EGFR M+	N	Design	Primary Endpoint
ALCHEMIST	410 pts Stage IB-IIIA	Erlotinib versus placebo x 2 yrs (after chemotherapy)	Overall survival
ADUARA 2	380 Stage IA2 and IA3	Phase III, randomized, controlled, multi-center, international, 2-arm trial of Osimertinib versus placebo	DFS
APEX	606 Stage II-IIIA	Phase III, randomized, open label multi-center, 3-arm trial of Almonertinib vs Almonertinib + Chemotherapy vs Chemotherapy	DFS
ALK +	**N**	**Design**	**Primary Endpoint**
ALCHEMIST	168 pts Stage IB-IIIA	Crizotinib versus observation x 2 yrs (after chemotherapy)	Overall Survival
ALINA	255 pts Stage IB–IIIA.	Alectinib versus chemotherapy	Disease free survival

The FIRST adjuvant immunotherapy agent in the modern era

IMpower010: study design

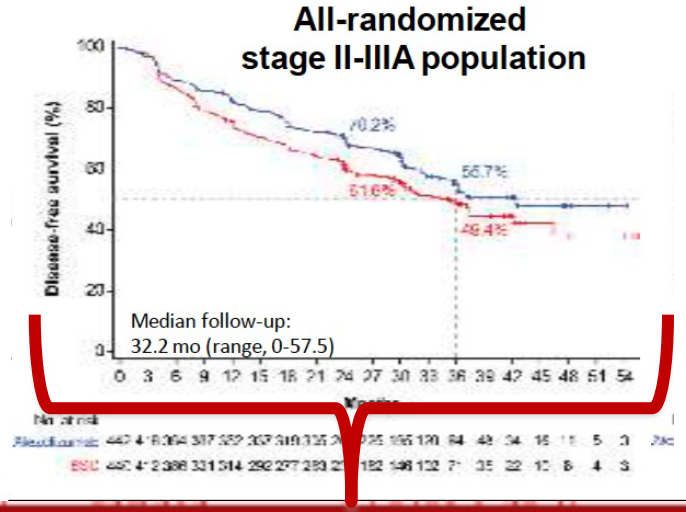


Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

IMPOWER010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA, all-randomized stage II-IIIA and ITT populations (primary endpoint)

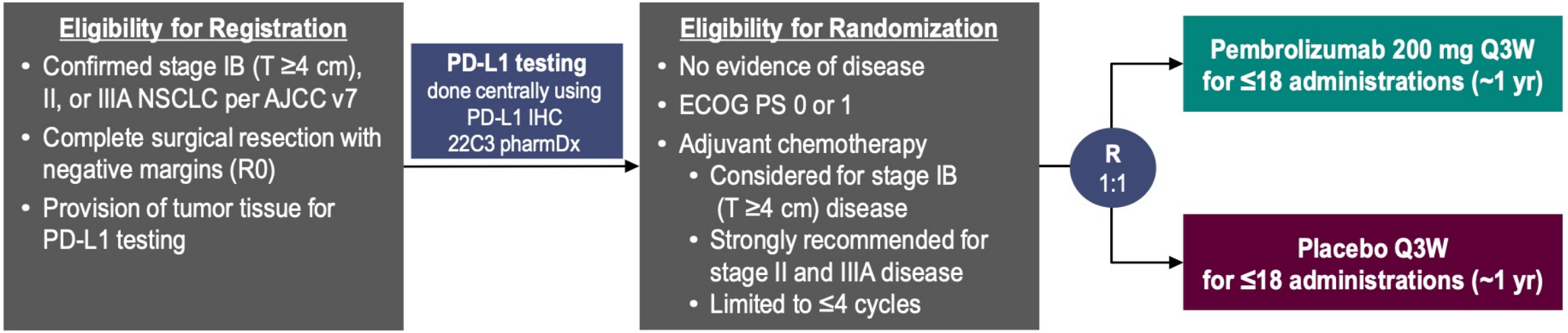


PD-L1 status by SP263					
TC <1%	181/383	36·1 (30·2-NE)	202/383	37·0 (28·6-NE)	0·97 (0·72-1·31)
TC ≥1%	248/476	NE (36·1-NE)	228/476	35·3 (29·0-NE)	0·66 (0·49-0·87)
TC 1-49%	133/247	32·8 (29·4-NE)	114/247	31·4 (24·0-NE)	0·87 (0·60-1·26)
TC ≥50%	115/229	NE (42·3-NE)	114/229	35·7 (29·7-NE)	0·43 (0·27-0·68)

Second Trial of Adjuvant ICI

PEARLS/KEYNOTE-091 Study Design

Randomized, Triple-Blind, Phase 3 Trial



Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points

- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

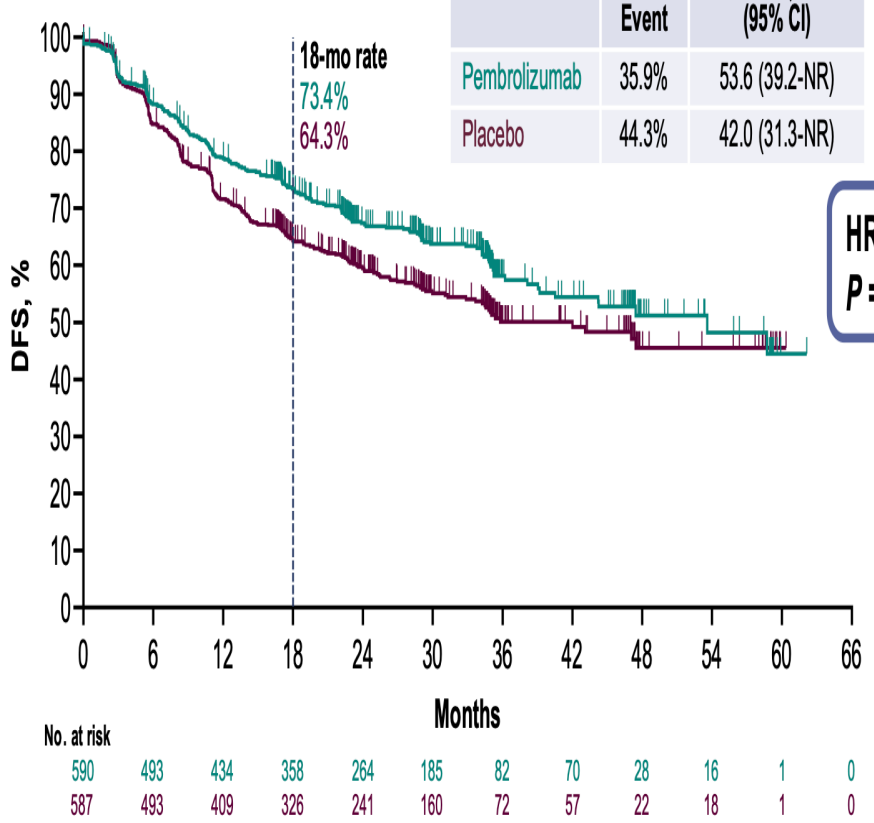
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

ClinicalTrials.gov number, NCT02504372.

PEARLS/KEYNOTE 191: Efficacy Results

DFS, Overall Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)



HR 0.76 (95% CI, 0.63-0.91)
P = 0.0014

No. at risk

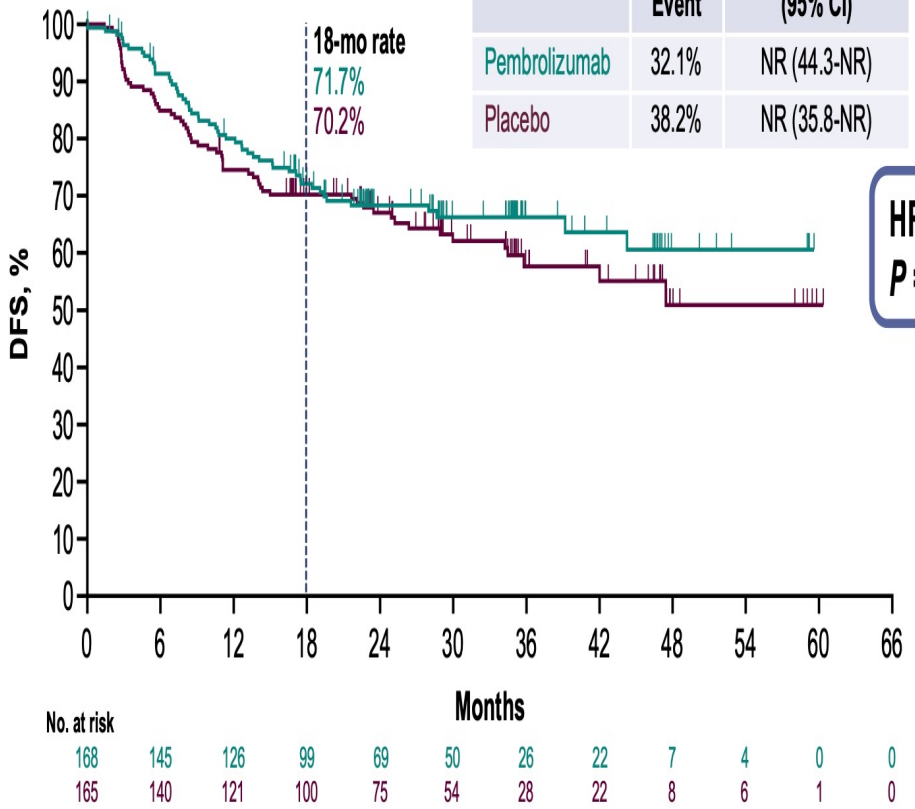
590	493	434	358	264	185	82	70	28	16	1	0
587	493	409	326	241	160	72	57	22	18	1	0

ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

DFS, PD-L1 TPS ≥50% Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	32.1%	NR (44.3-NR)
Placebo	38.2%	NR (35.8-NR)



HR 0.82 (95% CI, 0.57-1.18)
P = 0.14

No. at risk

168	145	126	99	69	50	26	22	7	4	0	0
165	140	121	100	75	54	28	22	8	6	1	0

ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

IMpower010 and PEARLS/KEYNOTE 191

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Dual Primary endpoints
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Stratification factors: Gender/Stage/Histology/PD-L1 expression

Stratification factors: Stage/PD-L1 expression/Geographic region

Baseline Characteristics	IMpower 010 N=1280	KEYNOTE-091 N=1177
Median Age	62	65
Male	66.9%	68%
PS 1	44.4%	38.6%
Current/former smoker	77.9%	87%
Stage IB/II/IIIA	11.8%/46.7%/41.1%	14.3%/56.7%/28.8%
NonSquamous histology	65.6%	64.7%
PD-L1 expression	45.4% <1%/54.6% ≥ 1% (SP263)	39.5% < 1%/ 32.3% 1-49%/28.3% ≥ 50% (Dako 22C3)
EGFR mutation positive/unknown	11.6%/35.9%	6.2%/56.9%
Adjuvant chemotherapy	99% (required)	85.6%

Phase III Adjuvant Trials with Immune Checkpoint Inhibitors

Drug/Trial	Description	Stages	Selection	Primary Endpoint	N	UPDATE
Nivolumab ALCHEMIST/ANVIL	US NCI, observation control arm	IB (4 cm) – IIIA After adjuvant chemotherapy and/or radiation	Unselected	OS/DFS	903	Accrual completed
MEDI4736 Durvalumab	Global, placebo controlled	IB (4 cm) – IIIA After adjuvant chemotherapy	Unselected	DFS	1360	Accrual completed
Canakinumab CANOPY-A	Global, placebo controlled	II-IIIA IIIB (T>5cmN2) After adjuvant chemotherapy and/or radiation	Unselected	DFS	1500	Recruiting
Pembrolizumab ALCHEMIST Chemo-IO (revised)	US NCI	IB (4 cm)-IIIA Concurrent chemotherapy with or without Pembrolizumab followed by pembrolizumab	Unselected	DFS	1210	Recruiting

Why are Neoadjuvant Trials Attractive?

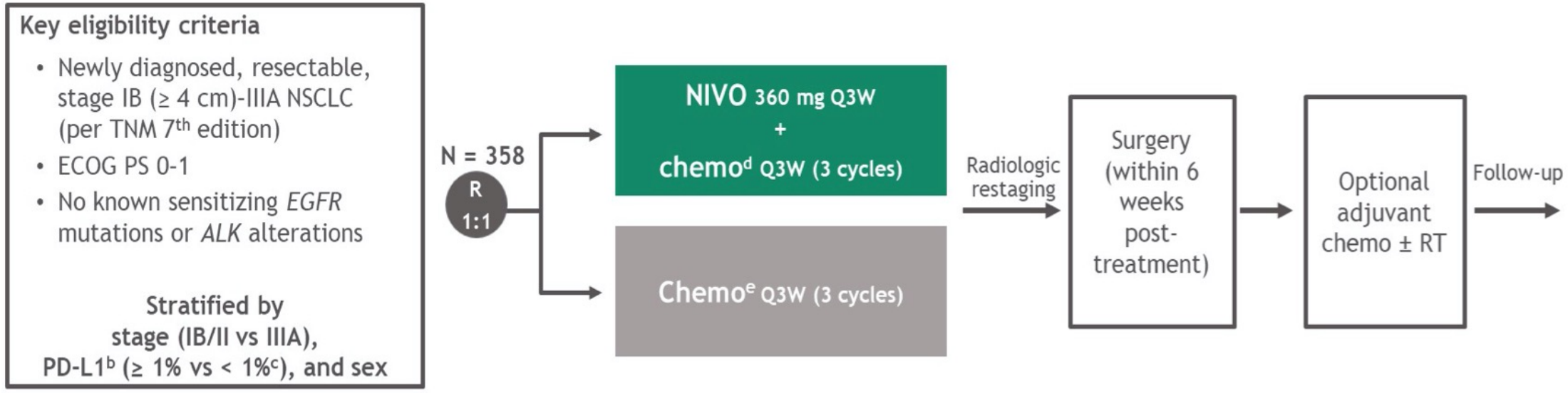
Pro
Earliest opportunity to eradicate micrometastatic disease
Achievement of a major pathological response is indicative of antitumor activity and may be an early surrogate for prolonged survival /cure.
Resected tumor and normal lung provides an opportunity to understand a drug/regimen mechanism(s) of action, and tumor PK/PD
Better priming of the immune system
Increased resectability and R0 resections

Con
Delay in surgical resection by 9-12 weeks
Risk of disease progression prior to resection (NATCH 5%)
May not identify a complete adverse effect profile
Concern about postoperative morbidity and mortality (NATCH postop mortality: 5.0% (neoadjuvant) 7.5% (adjuvant)

Felip et al. *J Clin Oncol* 2010

The FIRST neoadjuvant immunotherapy combination approved in the modern era

CheckMate 816 study design

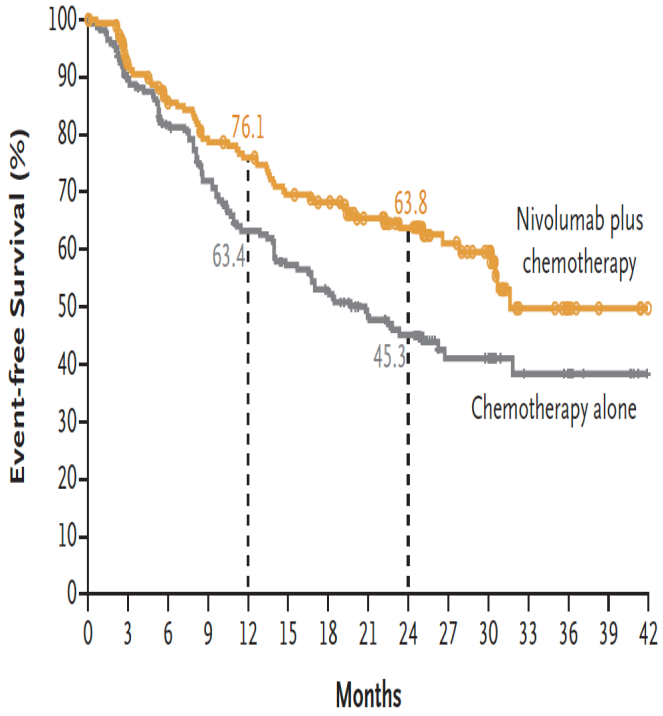


Primary endpoints
- pCR by BIPR
- EFS by BICR

Key secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory endpoints included
- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

CheckMate 816: Efficacy Results



	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

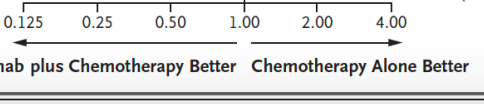
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

No. at Risk

Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

B

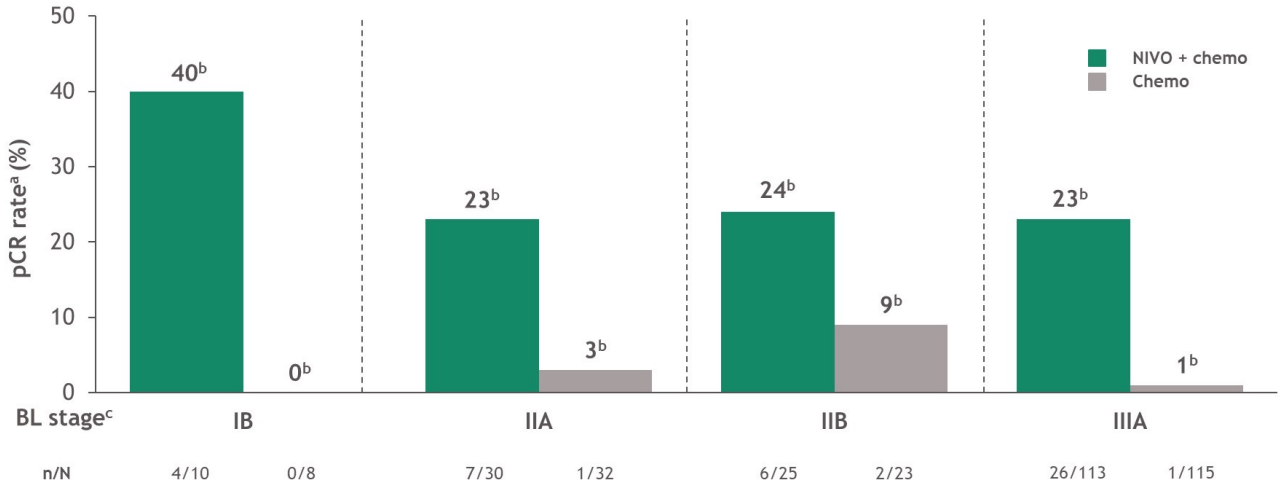
Subgroup	No. of Patients	Median Event-free Survival (95% CI) Nivolumab plus chemotherapy (N=179) *mo*	Median Event-free Survival (95% CI) Chemotherapy alone (N=179) *mo*	Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)	0.63 (0.45–0.87)
Age				
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)	0.57 (0.35–0.93)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)	0.70 (0.45–1.08)
Sex				
Male	255	30.6 (20.0–NR)	16.9 (13.8–24.9)	0.68 (0.47–0.98)
Female	103	NR (30.5–NR)	31.8 (13.9–NR)	0.46 (0.22–0.96)
Geographic region				
North America	91	NR (25.1–NR)	NR (12.8–NR)	0.78 (0.38–1.62)
Europe	66	31.6 (13.4–NR)	21.1 (10.2–NR)	0.80 (0.36–1.77)
Asia	177	NR (30.2–NR)	16.5 (10.8–22.7)	0.45 (0.29–0.71)
ECOG performance-status score				
0	241	NR (30.2–NR)	22.7 (16.6–NR)	0.61 (0.41–0.91)
1	117	30.5 (14.6–NR)	14.0 (9.8–26.2)	0.71 (0.41–1.21)
Disease stage at baseline				
IB or II	127	NR (27.8–NR)	NR (16.8–NR)	0.87 (0.48–1.56)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)	0.54 (0.37–0.80)
Histologic type of tumor				
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)	0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)	0.50 (0.32–0.79)
Smoking status				
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)	0.68 (0.48–0.96)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)	0.33 (0.13–0.87)
PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)
TMB				
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)	0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)	0.69 (0.33–1.46)
Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)	0.31 (0.14–0.67)



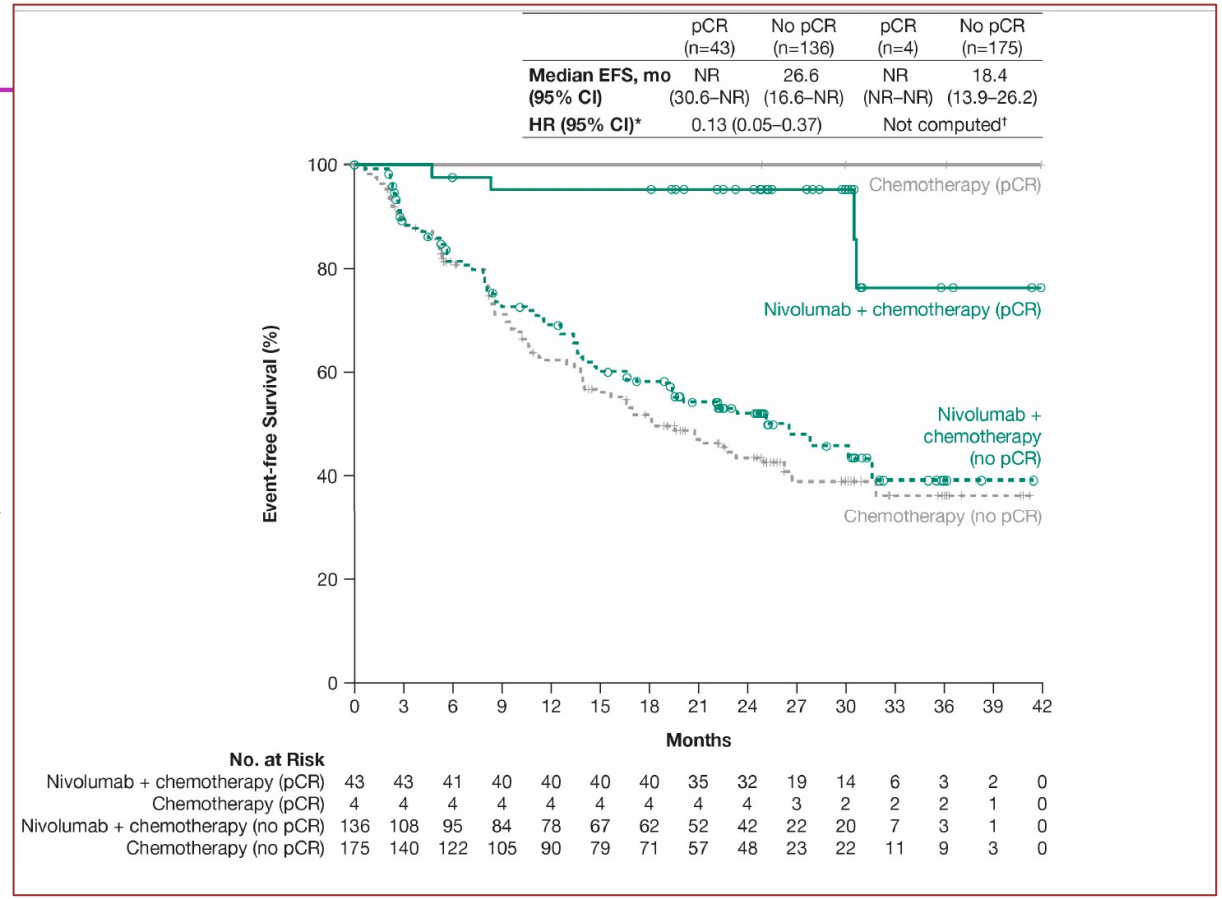
Spicer J, et al. NEJM 2022

CheckMate 816: Efficacy Results

pCR by baseline stage of disease



- pCR improvement with NIVO + chemo vs chemo was observed regardless of radiologic down-staging[d]
- Numerically, a greater percentage of patients treated with neoadjuvant NIVO + chemo vs chemo had definitive surgery and complete resection while fewer patients underwent pneumonectomy



Spicer J, et al. NEJM 2022

Perioperative Immunotherapy Phase III Clinical Trials

Drug	N	Stages	Description	Primary Endpoint
Atezolizumab + platinum based chemotherapy Impower030	374	Stage II-IIIB (T3N2), resectable NSCLC	Neo-adjuvant chemo+ICI or placebo then surgery followed by adjuvant ICI or observation	mPR/RFS
Pembrolizumab + platinum based chemotherapy KN671	786	Stage II, IIIA, and Resectable IIIB (T3-4N2) NSCLC	Neo-adjuvant chemo+ICI or placebo followed by surgery then adjuvant ICI or placebo	RFS/OS
Durvalumab + platinum based chemotherapy AEGEAN	300	Stage II-IIIA, resectable NSCLC	Neo-adjuvant chemo+ICI or placebo then surgery followed by adjuvant ICI or placebo	mPR
Nivolumab + platinum based chemotherapy CheckMate 77T	452	Stage II-IIIA, resectable	Neo-adjuvant chemo-ICI/ surgery/adjuvant ICI or chemo-placebo/surgery/adjuvant placebo	EFS
Tislelizumab + platinum based chemotherapy BGB A317-315	450	Stage II-IIIA, resectable	Neo-adjuvant chemo+ICI or placebo then surgery followed by adjvuant ICI or placebo	mPR/EFS
Adebrelimab + platinum based chemotherapy SHR-1316-111-303	537	Stage II – IIIA/B, resectable	Neo-adjuvant chemo+ICI or placebo then surgery followed by adjvuant ICI or placebo	mPR/EFS
Sintilimab + platinum based chemotherapy CIBI308G301	800	Stage II(>4cm), IIIA/B resectable	Neo-adjuvant chemo+ICI or placebo then surgery followed by adjvuant ICI or placebo	EFS/pCR

Neoadjuvant TKI

EMERGING-CTONG 1103 Study Design

- Treatment naïve IIIA-N2 NSCLC
- N2 confirmed by mediastinoscopy /EBUS /PET-CT
- EGFR activating mutation
- ECOG 0-1
- Age ≥18y

Randomization 1:1

N=72

Erlotinib 150mg/d for 42 days

G 1250mg/m^2 d1.8 + C 75mg/m^2 d1, q3w for 2 cycles

Surgery (Non-PD)

Erlotinib 150mg/d for 12 months

GC q3w for 2 cycles

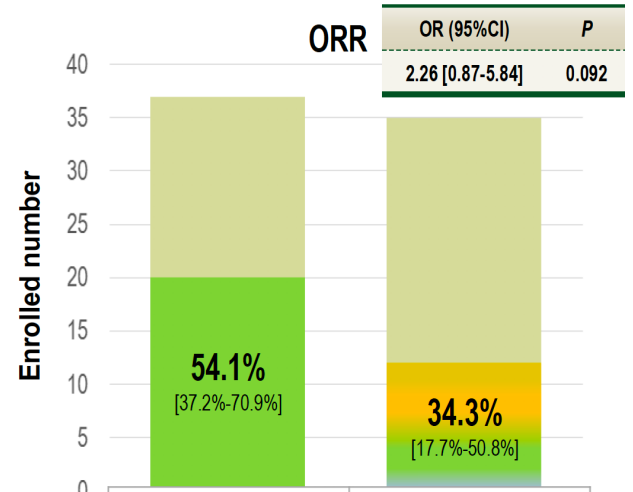
Primary endpoint

- ORR

Secondary endpoint

- Downstaging rates of pathological lymph node
- pCR
- PFS
- 3y and 5y OS rate
- Safety & Tolerability

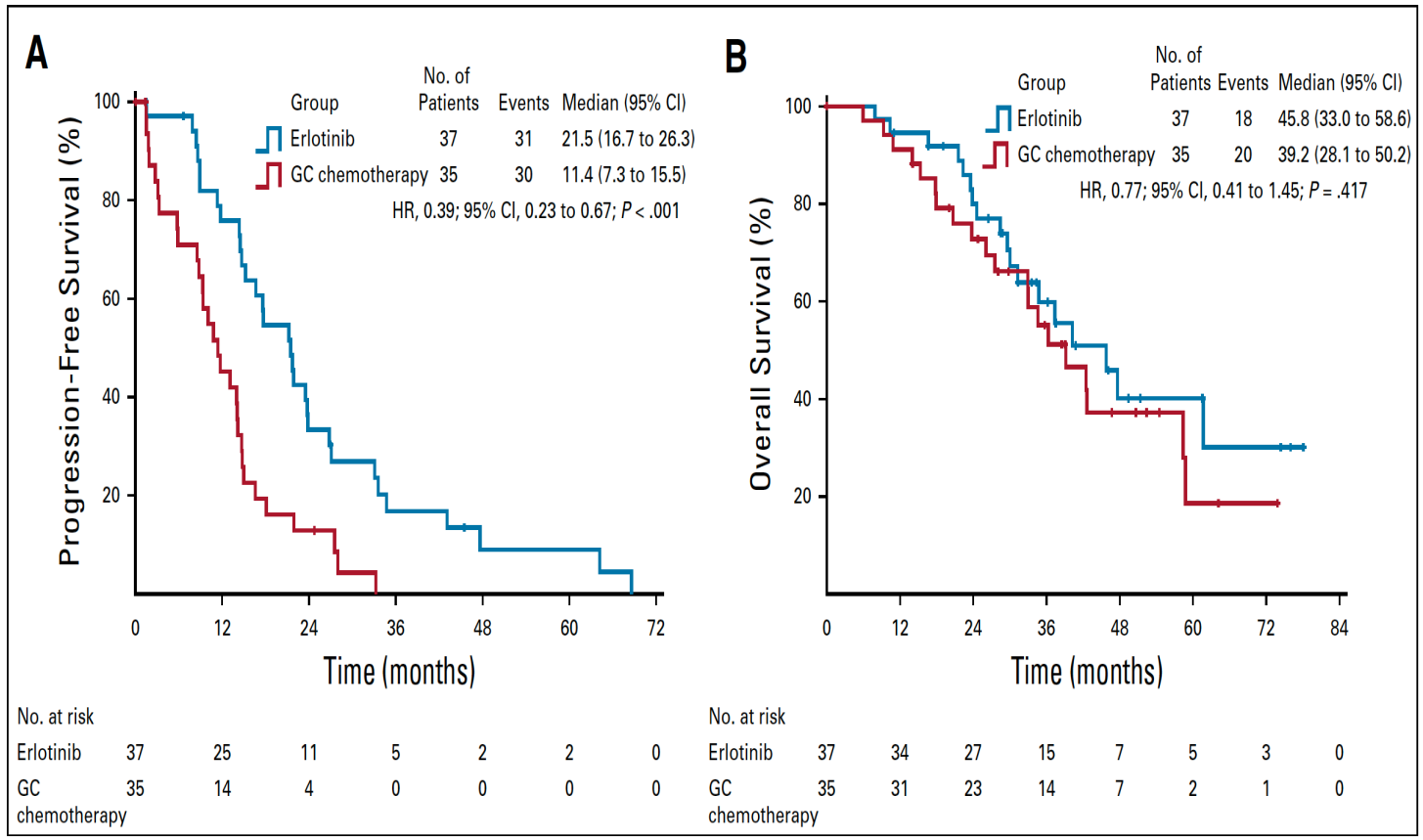
- Stratification by lymph node status, histology, smoking status and sex.

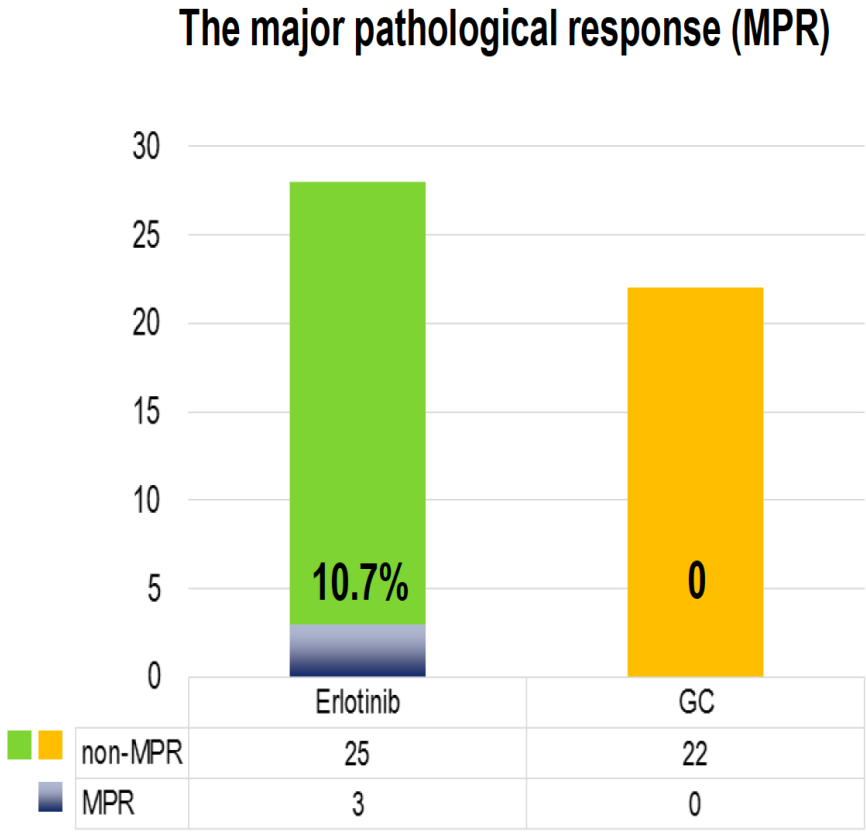


	Erlotinib	GC
PD	3 (8.1%)	4 (11.4%)
SD	13 (35.1%)	15 (42.9%)
PR	20 (54.1%)	12 (34.3%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; G, gemcitabine ; C, cisplatin;
ORR, objective response rate; pCR, pathological complete response; PFS, progression free survival; OS, overall survival.

Secondary endpoints



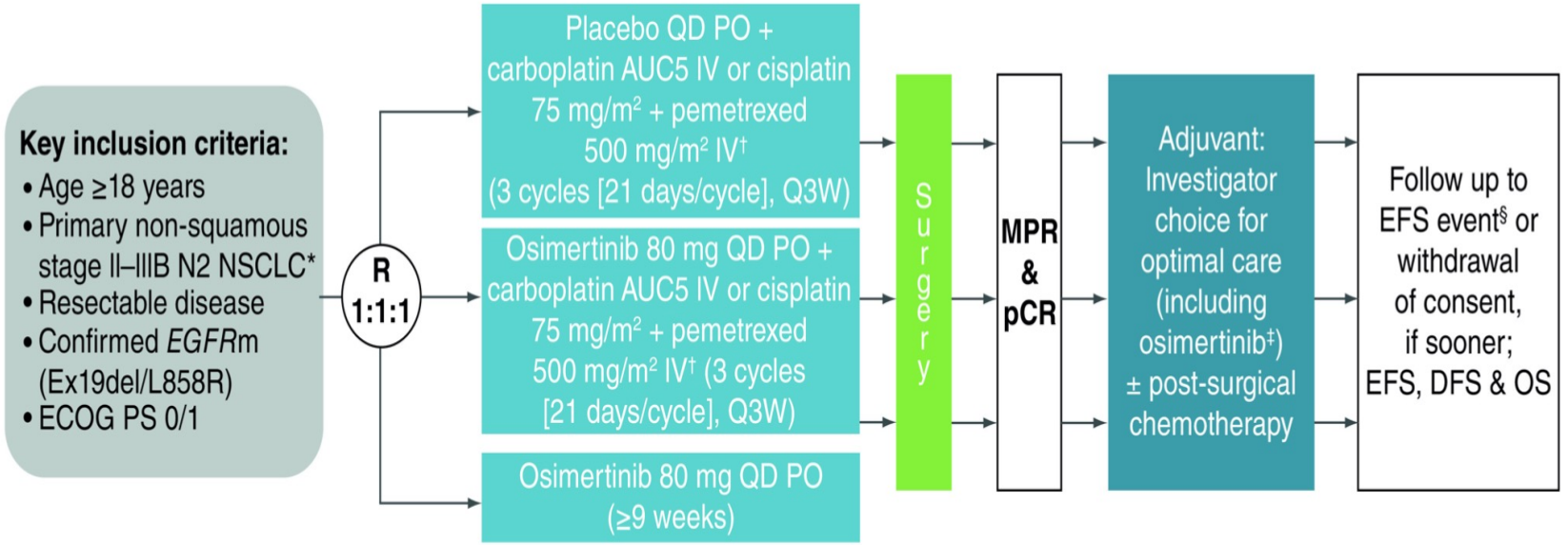


Neoadjuvant Targeted Therapy Phase III Clinical Trials

Pilot trial neoadjuvant osimertinib
-13 patients with early-stage
  6 stage IA/B
  2 Stage IIA/B
  5 Stage IIIA
-Treated with osimertinib for an average of 59 days prior to surgical resection.
-The mPR rate was 15% (2 of 13).
-No pCR's were observed

Blakely C et al JTO 2021 abst P26.02

NeoADAURA



N = 351 patients
Primary endpoint is MPR

TKIs and Early-Stage Disease

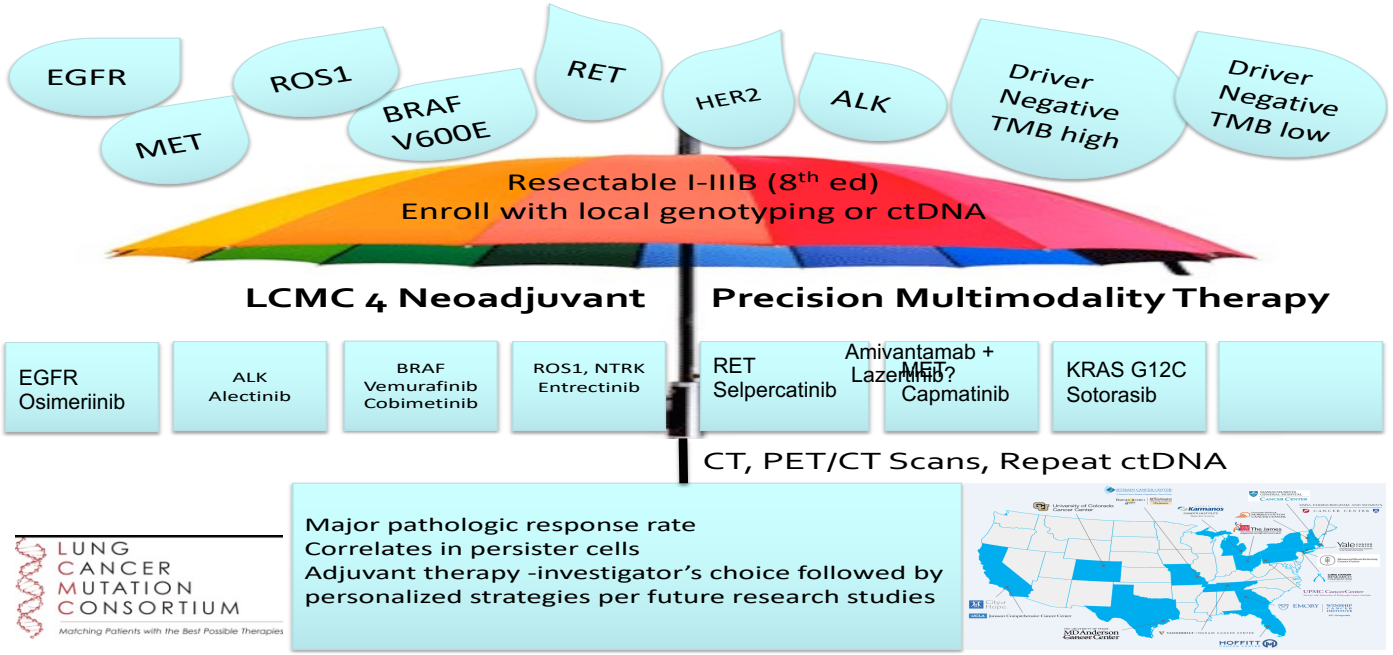
- Will TKIs cure patients or do they just delay progression?
- What is the optimal duration of TKI therapy?
- How do we build upon the current data?

  Combining TKI with Chemotherapy

  NEOADAURA

  Sequencing: Adjuvant chemotherapy + TKI ⟶ TKI *vs* chemotherapy ⟶ TKI

  Window of opportunity trials – Neoadjuvant



Immune Checkpoint Inhibitors and Early-Stage Disease

- Will patients be cured?
- Optimal sequencing? Neoadjuvant VS Adjuvant?
- Who needs adjuvant therapy after neoadjuvant?
- Patients with squamous cell histology, stage IB and PD-L0 are not benefiting.
- Novel regimens are needed.

NEOCOAST Phase II

	Durvalumab (D) N = 24	D + O N = 18	D + M N =18	D + D N = 16
MPR	11.1%	19%	30%	31.3%
CPR	3.7%	9.5%	10%	12.5%
ORR	7.4%	4.8%	15%	6.3%

untreated, resectable (> 2 cm), stage I to IIIA NSCLC

Oleclumab (MEDI9447) is a human IgG1λ mAb that inhibits the function of cluster of differentiation 73 (CD73). Invovled in immunosuppression.

Monalizumab (IPH2201) is a first-in-class, humanized, IgG4 mAb that specifically binds to and blocks the inhibitory receptor NKG2A from binding to the major histocompatibility complex E (HLA-E), reducing inhibition of natural killer and CD8+ T cells.

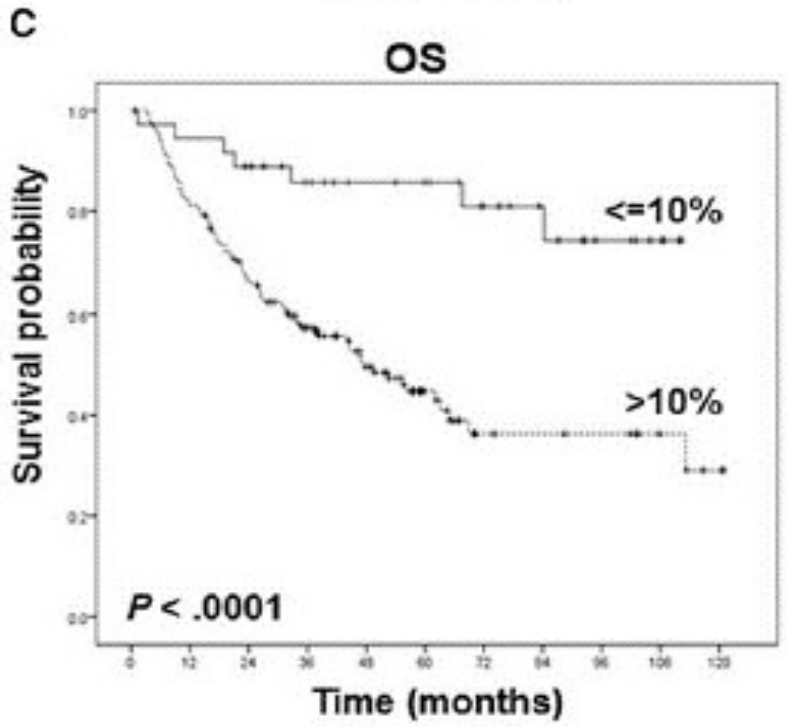
Danvatirsen (AXD1950) is a16-nucleotide antisense oligonucleotide targeting STAT3

NEOCOAST 2 Randomize Phase II in Stage II –IIIA
N = 140 (3 arms)

Cascone T, et al. AACR 2022

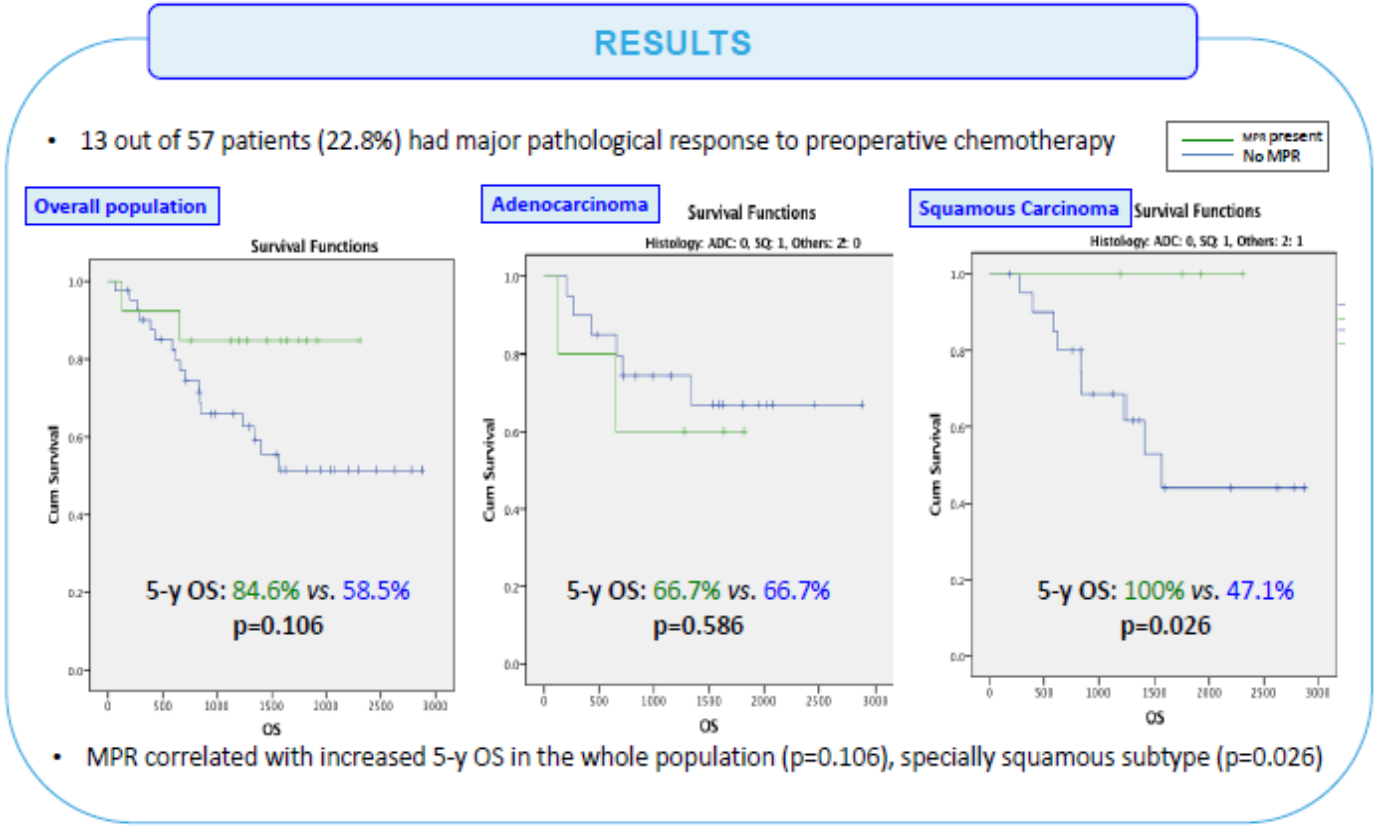
Early Efficacy Endpoints
Major Pathological Response

Single institution study
36/192 patients (19%) with a major pathological response



Prataer, A JTO 2012

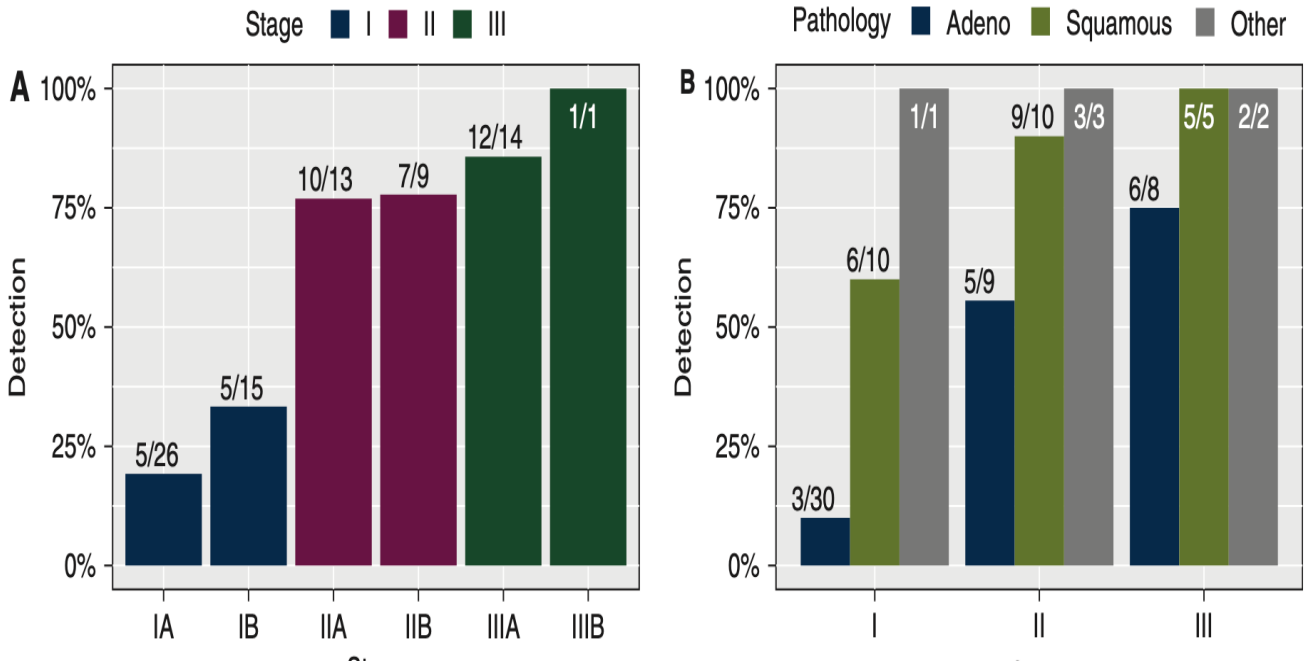
In neoadjuvant arm of NATCH 19 patients with a major pathological response (10.5%) had a 5 year DFS benefit (59% vs 38%)



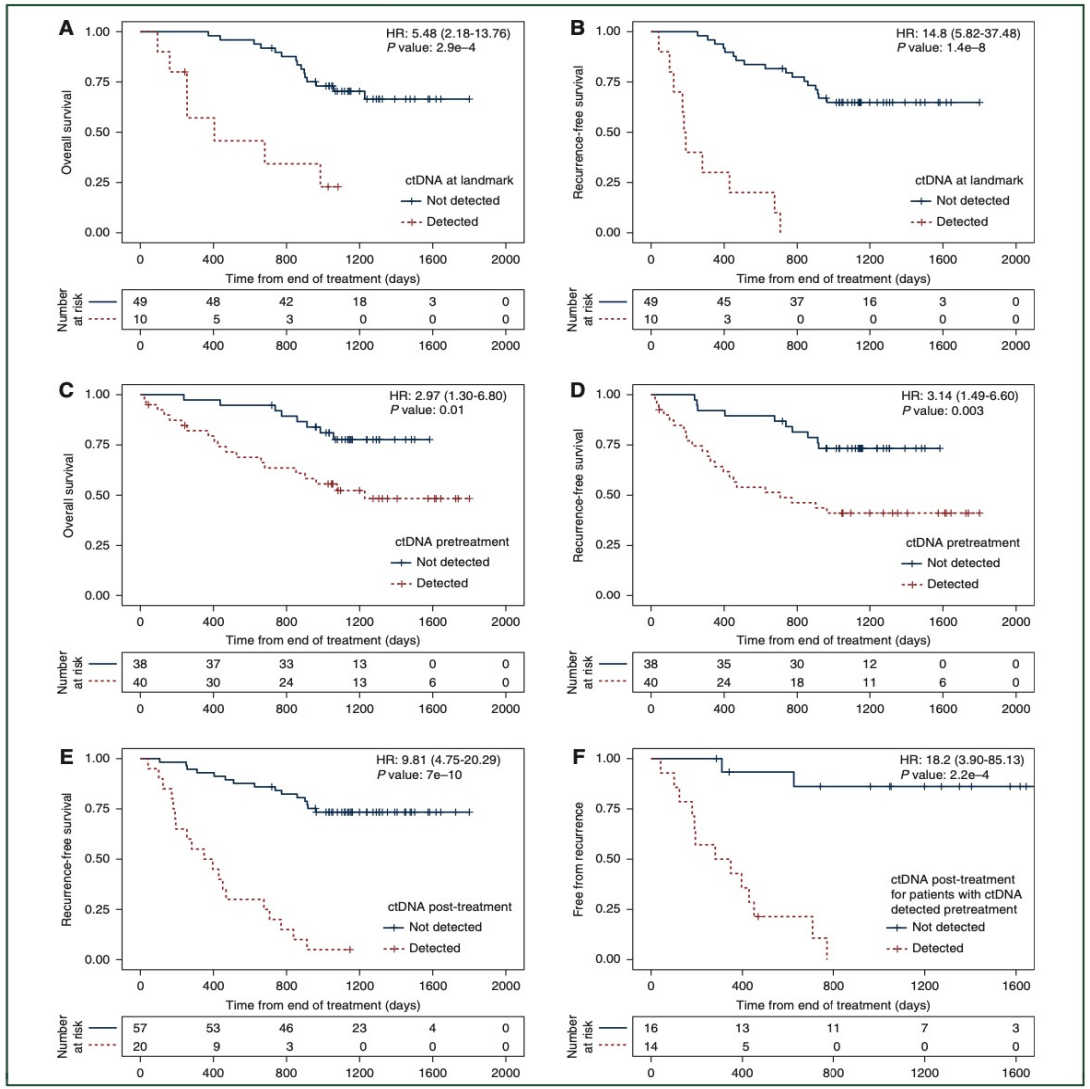
Remon J, et al: ESMO 2017

Early Efficacy Endpoints
Circulating Tumor DNA

- Can we detect minimal residual disease?



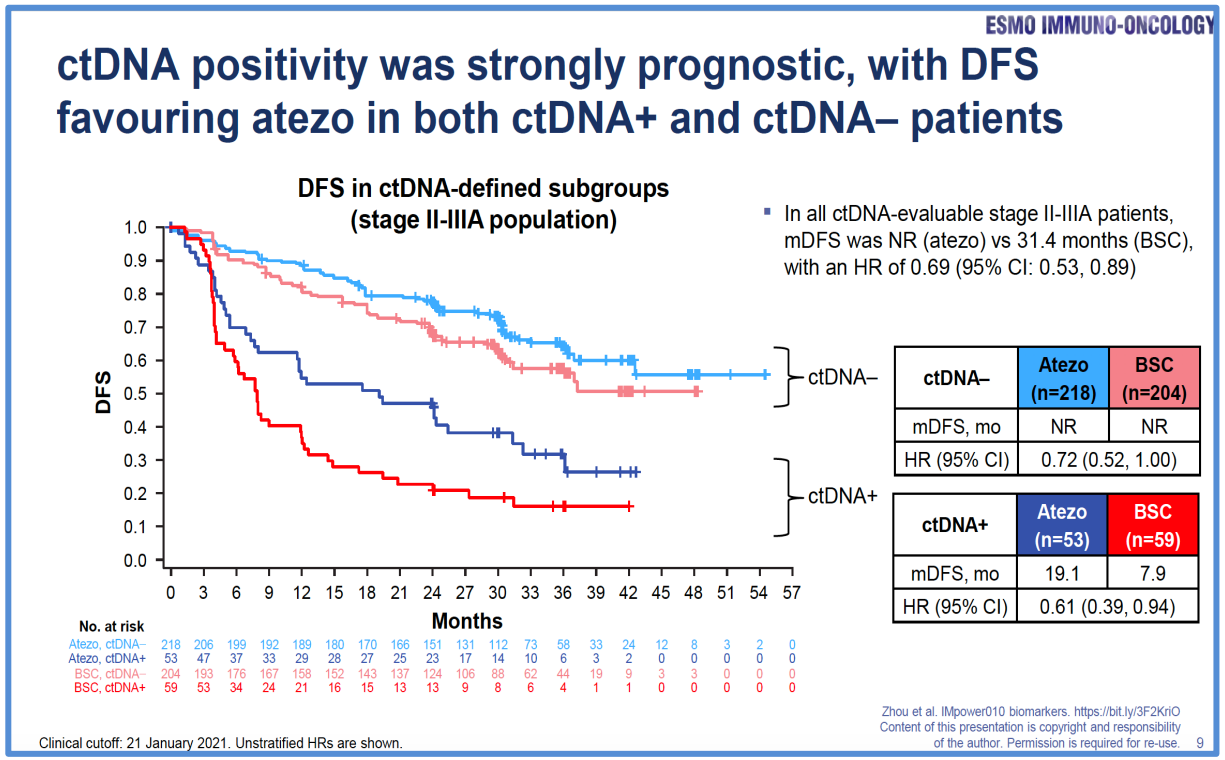
88 patients who underwent treatment with curative intent, by surgery (69 patients or chemoradiotherapy (19 patients). Never smokers 9%.

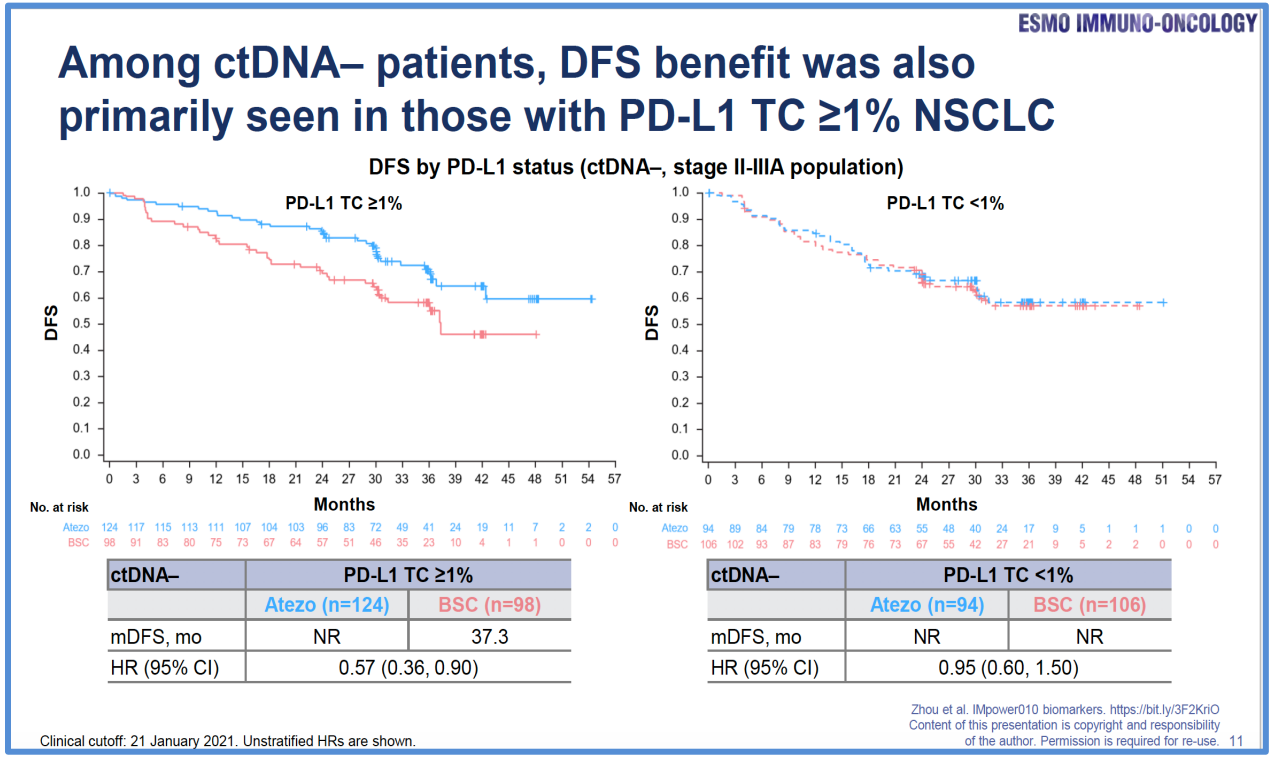


Gale D, et al. Ann Oncol 2022

Early Efficacy Endpoints
Circulating Tumor DNA

IMpower 010





- ctDNA after surgery before systemic treatment

Is it time for randomized biomarker selected trials?

Zhou C, et al. ESMO IMMUNO-ONCOLOGY 2021

Take home messages

- Advances in the systemic treatment of early-stage resectable disease have recently been made utilizing both the adjuvant and neoadjuvant approach in selected patients.

- Looking forward to:
  - the overall survival analysis from the reported trials
  - initial analysis of numerous trials for confirmation

- Building upon both approaches (adjuvant and neoadjuvant) is needed.

- Biomarker selection of patients is the key to optimizing individual therapy.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