Adjuvant/Neo-adjuvant SystemicTherapy

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DISCLOSURES

Commercial Interest	Relationship(s)
Merck, Genentech/Roche	Unpaid Consultant
AstraZeneca, Xcovery, Janssen, Mirati, Daiichi Sankyo, Helsinn, Blueprint	Consultant
ACEA Biosciences, Arrys Therapeutics, AstraZeneca/Medimmune, BMS, Celgene, Clovis Oncology, Exelixis, Genentech/Roche, Gilead, Merck, Novartis, Pharmacyclics, SeaGen, Xcovery	Contracted research (funds to University)

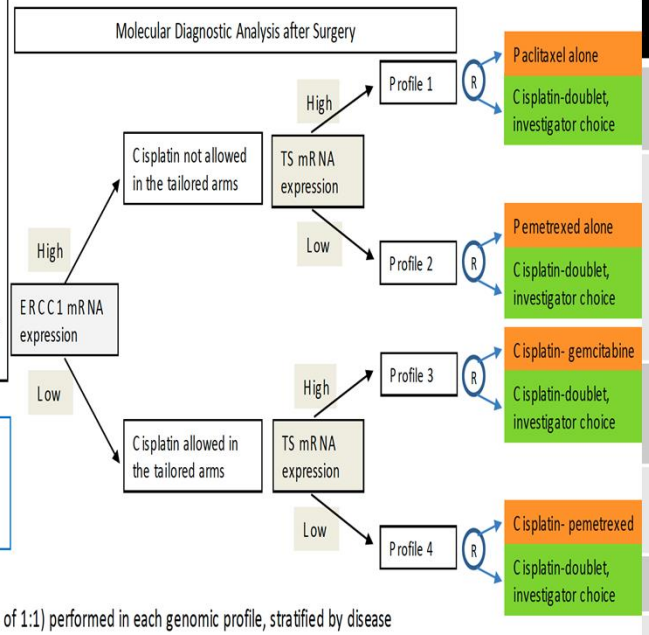
Adjuvant/Neo-adjuvant systemic therapy

Chemotherapy - ITACA
Targeted Therapy - ADAURA updates
IO - LCMC3

Chemotherapy

ITACA study design

- Completely resected NSCLC R0 stage II-IIIA, Complete mediastinal LN resection or sampling
- ECOG PS 0-1
- Interval of 45-60 days between surgery and start of chemotherapy
- Adequate organ functions
- No prior malignancies except for treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancers from which the patient has been disease-free for at least five years prior to enrolment



- 8Aug 2008: first pt randomized; 29Aug 2014 last pt randomized
- Dec 2010: Study Amendment for Staging (21% pts randomized)

- Randomization (allocation ratio of 1:1) performed in each genomic profile, stratified by disease stage (stage II v IIIA) and smoking status (never/former versus current)
- For the primary statistical analysis all control arms were grouped together (standard arm) as well as all tailored arms (tailored arm)

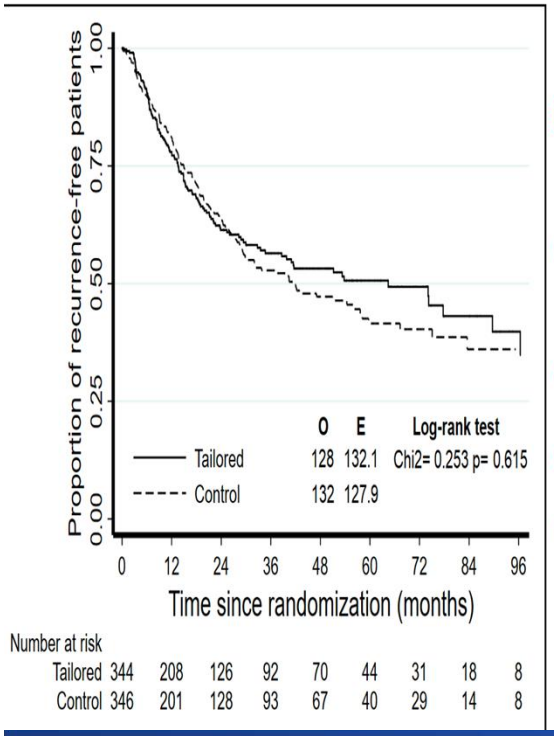
Treatment received per arm and genetic profile

Treatment	General		Profile 1		Profile 2		Profile 3		Profile 4	
	Control	Tailored	Control	Tailored	Control	Tailored	Control	Tailored	Control	Tailored
DDP- Vino	36%		35%		32%		39%		34%	
DDP- Gem	46%	24%	46%		34%		49%	98%	49%	
DDP- Doc	7%		7%		15%		5%		4%	
DDP-Pem	2%	26%	0%			3%	1%		5%	100%
DDP- NS*	8%		6%		17%		6%		8%	
Single agent Paclitaxel		39%	5%	98%		3%				
Single Agent Pemetrexed		10%	0%	1%	2%	94%		1%		
Never treated		1%	0%					1%		
Other agents			1%	1%						

Novello S. et al. WCLC 2015 **In the control arm and in the tailored arm, the median N of cycles was 4 (range: 1-4)**

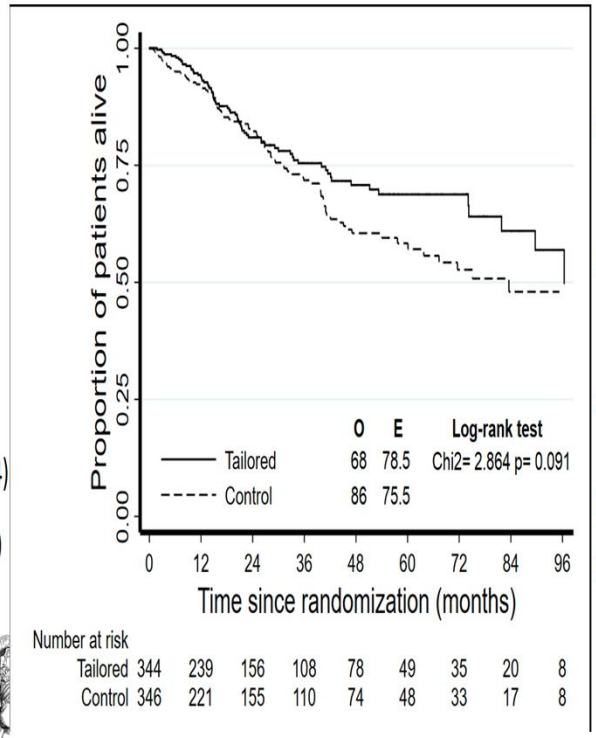
ITACA

Recurrence-free survival, ITT population



- **Median follow up** of 28.2 months (IQR: 9.9-55.8 months)
- **N° of events:** 260 (38% of ITT population)
- **HR (95%CI):** 0.94 (0.74-1.20)
- **Median RFS, Tailored:** 64.4 (34.7-96.4)
- **Median RFS, Control:** 41.5 (29.2-58.1)

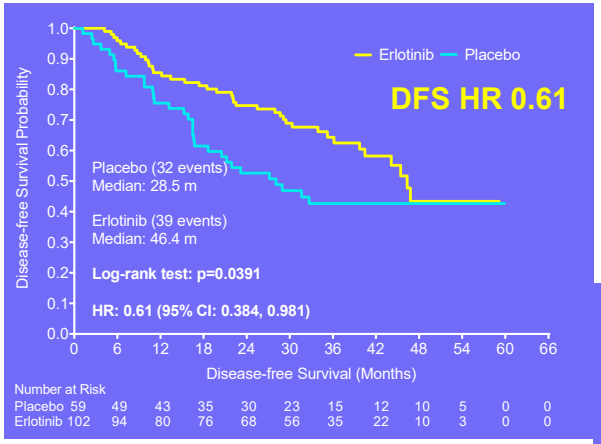
Overall survival, ITT population



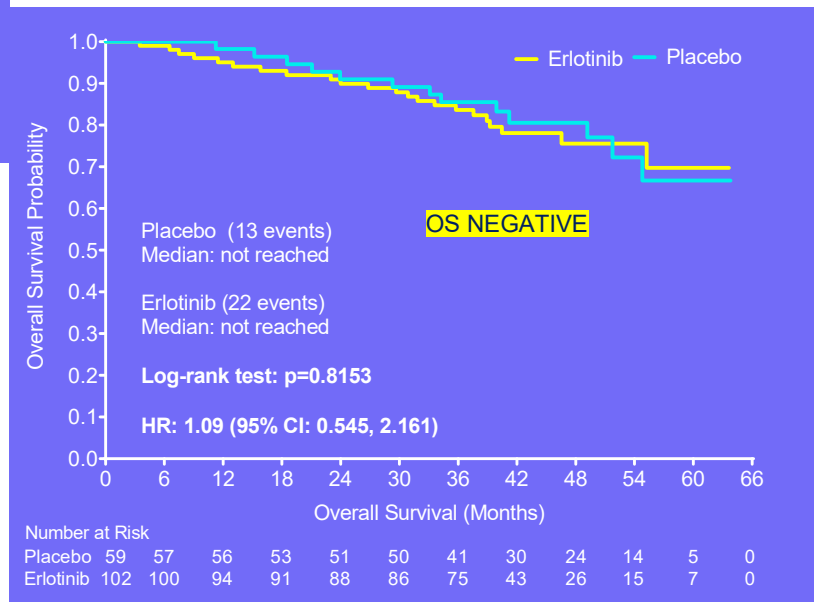
- **Median follow up** of 28.2 months (IQR: 9.9-55.8 months)
- **N. of deaths:** 154 (46% of expected events; 22% of ITT population)
- **HR (95%CI):** 0.76 (0.55-1.04)
- **Median OS, Tailored:** 96.4 (81.8- NR)
- **Median OS, Control:** 83.5 (60.1- NR)

TKI Therapy

RADIANT DFS/OS – *EGFR* M+ (Erlotinib)

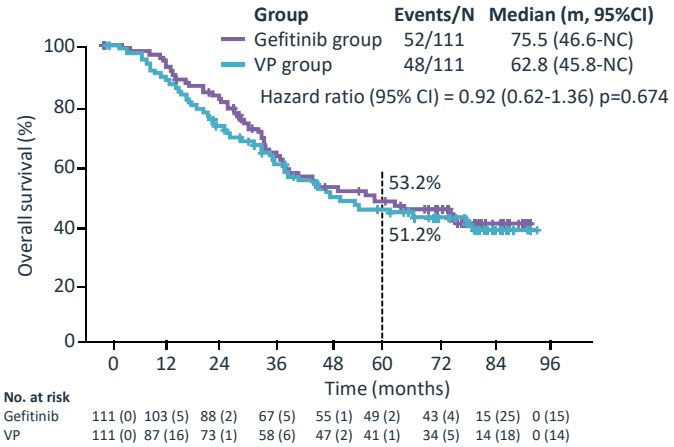


IN ALL PATIENTS
DFS HR 0.90, p.0.32
OS HR 1.13, p.34

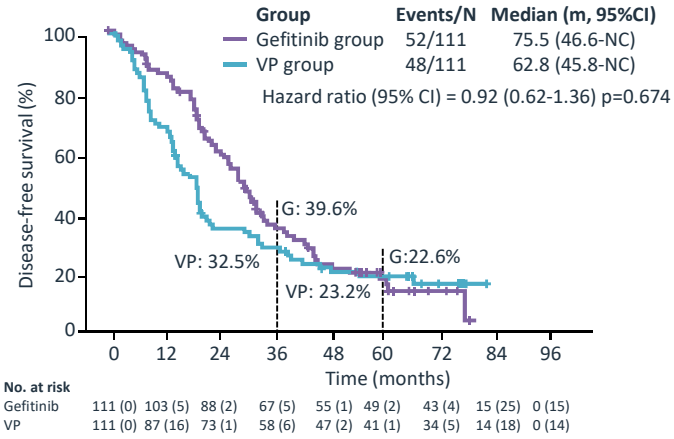


CTONG1104/ADJUVANT: OS and DFS - Gefitinib

Overall survival (ITT population)



Disease-free survival (ITT population)



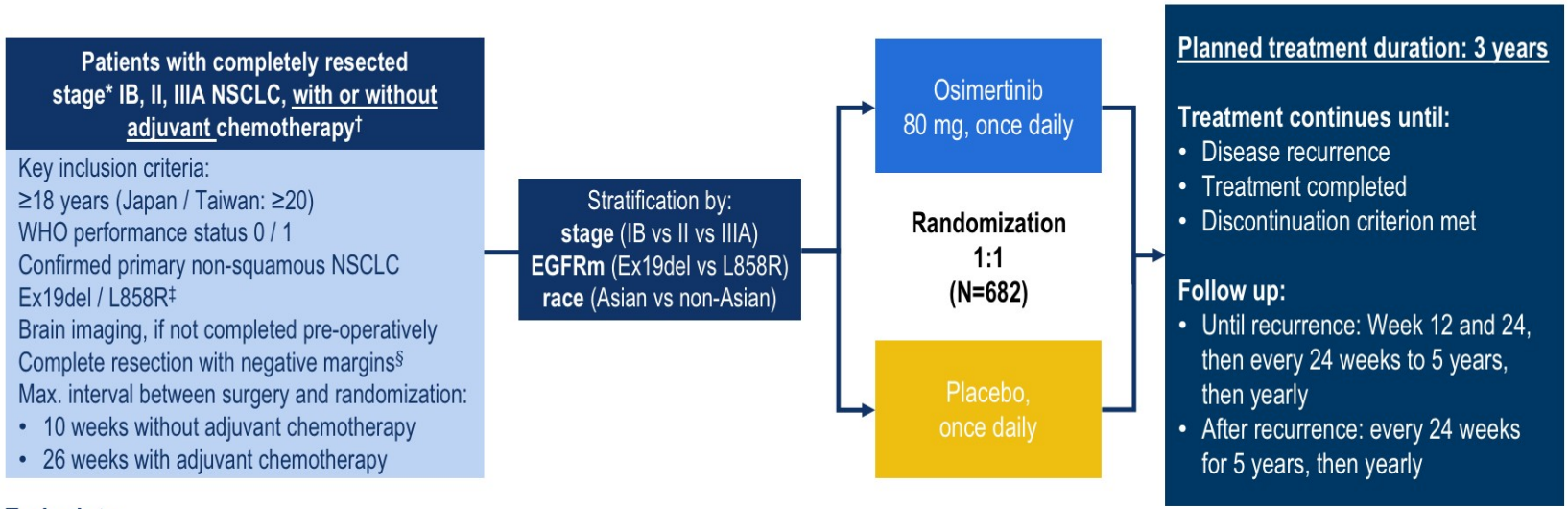
Loss of benefit at about 1 year after stopping the two years adjuvant therapy

Duration may matter
Or may reflect why came off early

	<18 months duration	≥18 months duration
Events, n/N	22/34	30/72
Median, mo (95% CI)	35.7 (25.7–NR)	NR (64.0–NR)
	HR 0.38 (95% CI 0.22–0.66)	

Wu, Y-L ASCO 2020, Abstr 9005

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**

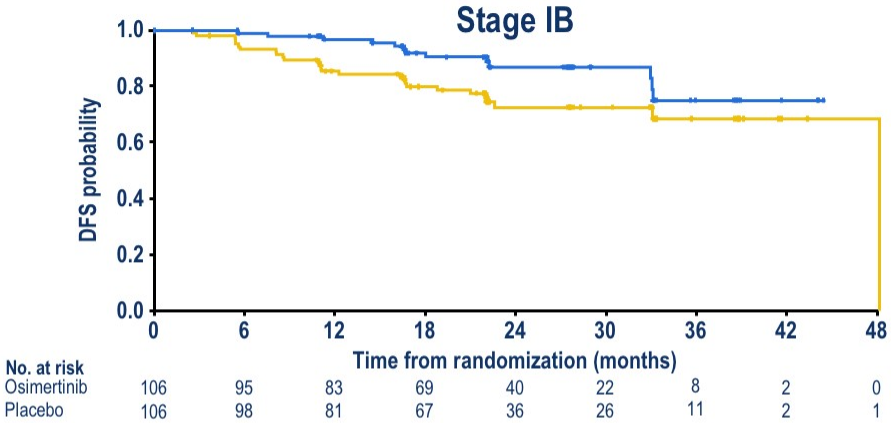
NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue; §Patients received a CT scan after resection and within 28 days prior to treatment; ¶Stage IB / II / IIIA.
CT, computed tomography; Ex19del, exon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

Baseline characteristics in the overall population (stage IB/II/IIIA)

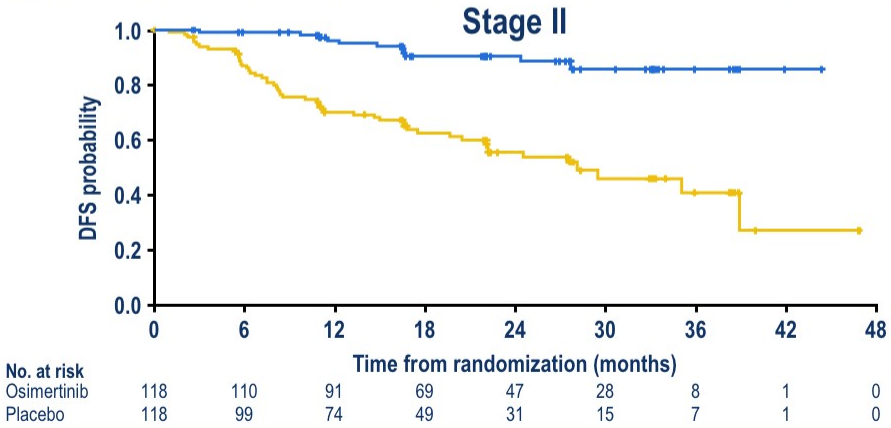
Characteristic, %	Osimertinib (n=339)	Placebo (n=343)
Sex: male / female	32 / 68	28 / 72
Age, median (range), years	64 (30–86)	62 (31–82)
Smoking status: smoker* / non-smoker	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
WHO performance status: 0 / 1	64 / 36	64 / 36
AJCC staging at diagnosis (7th edition): IB / II / IIIA	31 / 35 / 34	31 / 34 / 35
Histology: adenocarcinoma / other†	95 / 5	96 / 4
EGFR mutation at randomization‡: Ex19del / L858R	55 / 45	56 / 44
Adjuvant chemotherapy: yes / no	55 / 45	56 / 44

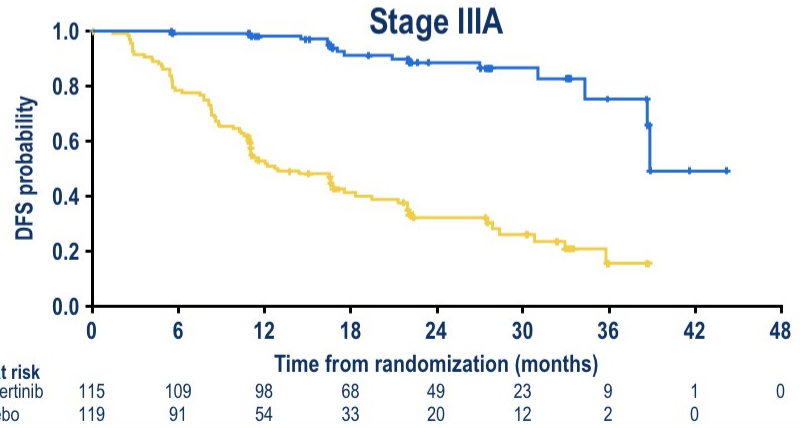
ADAURA data cut-off: January 17, 2020. *Former: osimertinib n=104, placebo n=83; current: osimertinib n=4, placebo n=3; never: osimertinib n=231, placebo n=257; †Includes bronchial gland carcinoma (NOS): osimertinib n=1; placebo n=2; malignant adenosquamous carcinoma: osimertinib n=4; placebo n=5; other: osimertinib n=11; placebo n=7; ‡Central test.

DFS by stage



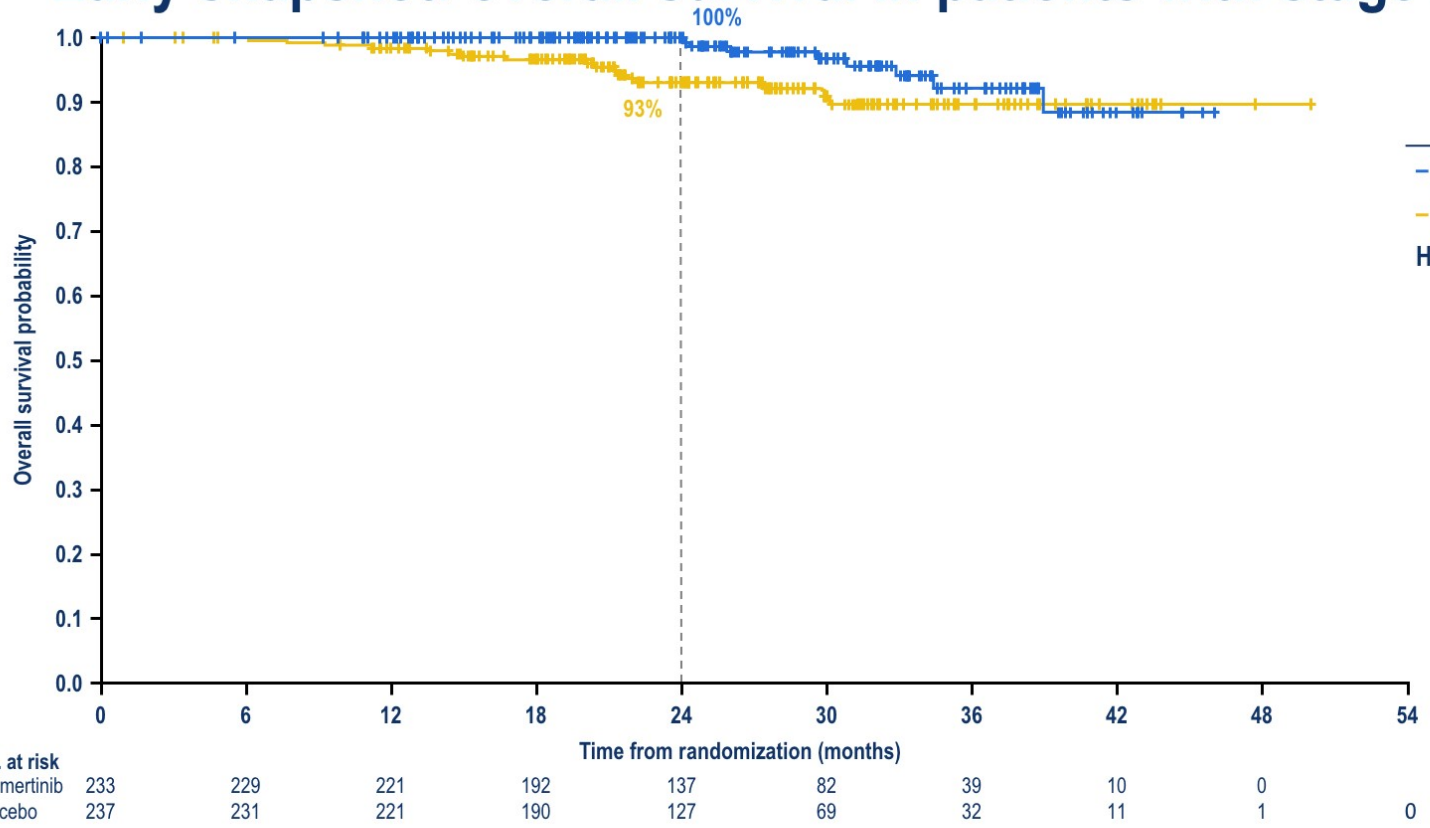
	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	0.50 (0.25, 0.96)	0.17 (0.08, 0.31)	0.12 (0.07, 0.20)





ADAURA data cut-off: January 17, 2020.
Tick marks indicate censored data.

Early snapshot: overall survival in patients with stage II/IIIA disease



No. at risk										
Osimertinib	233	229	221	192	137	82	39	10	0	
Placebo	237	231	221	190	127	69	32	11	1	0

Median OS, months (95% CI)	
– Osimertinib	NR (NC, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.40 (0.18, 0.90)**

Maturity 5%:
osimertinib 3%, placebo 7%

ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 26.1, placebo 24.7 months.
Tick marks indicate censored data.

ADAURA- Wu OA06.04

Adjuvant chemotherapy use

- Overall, 410 / 682 (60%) patients received adjuvant chemotherapy, for a median duration of 4.0 (Q1: 4.0, Q3: 4.0) cycles, consistent across treatment arms
- The majority of patients (409 / 410)* received platinum-based† chemotherapy, most with stage II / IIIA disease (76%), and fewer with stage IB disease (26%)
- Adjuvant chemotherapy use was more frequent in patients aged <70 years and in patients enrolled in Asia, and was not influenced by WHO PS (0 or 1)

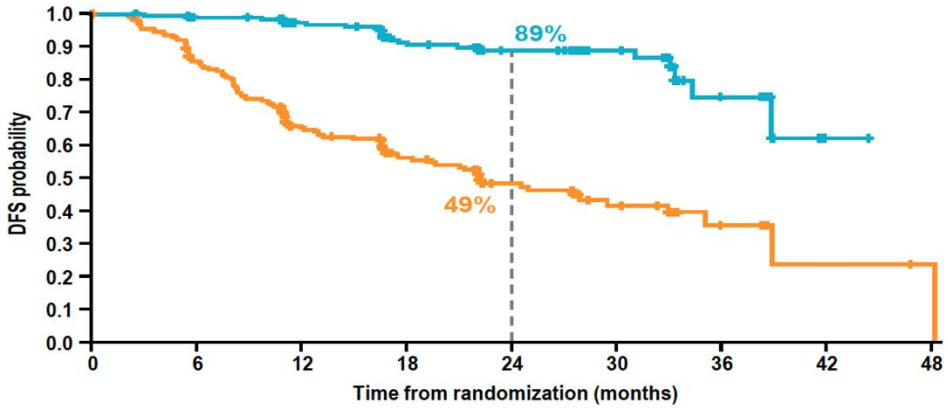
Characteristic	Patients, n	Received adjuvant chemotherapy
Stage IB	216	26%‡
Stage II	231	71%‡
Stage IIIA	235	80%‡
Aged <70 years	509	66%
Aged ≥70 years	173	42%
WHO PS 0	434	60%
WHO PS 1	248	60%
Enrolled in Asia¶	414	65%§
Enrolled outside of Asia#	268	53%

ADAURA data cut-off: January 17, 2020.
*One patient received only single-agent non-platinum chemotherapy (pemetrexed) as adjuvant treatment with an adjunct traditional Chinese medicine (protocol deviation); †Predominantly cisplatin- or carboplatin-based (cisplatin: n=275; carboplatin: n=139); ‡Includes only patients who received platinum-based chemotherapy (n=409); ¶No Japan patients with stage IB disease; §Japan: n=71; China: n=106; Asia non-Japan, non-China: n=91); #Enrolled in Europe, Australia, United States, Canada or Brazil.

ADAURA- Wu OA06.04

DFS in patients with and without adjuvant chemotherapy (overall population)

With adjuvant chemotherapy



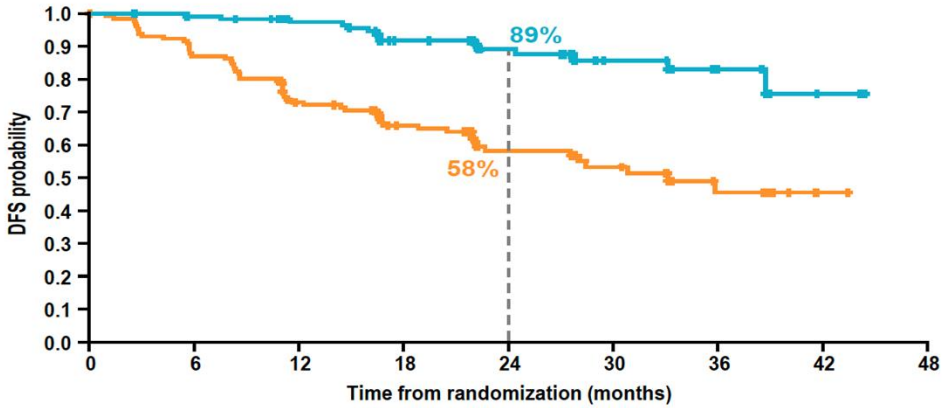
No. at risk

Osimertinib	203	190	166	121	80	40	14	1	0
Placebo	207	172	119	80	46	24	7	2	1

	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%

Without adjuvant chemotherapy



	136	123	106	87	58	34	13	4	0
	136	115	88	68	42	29	13	1	0

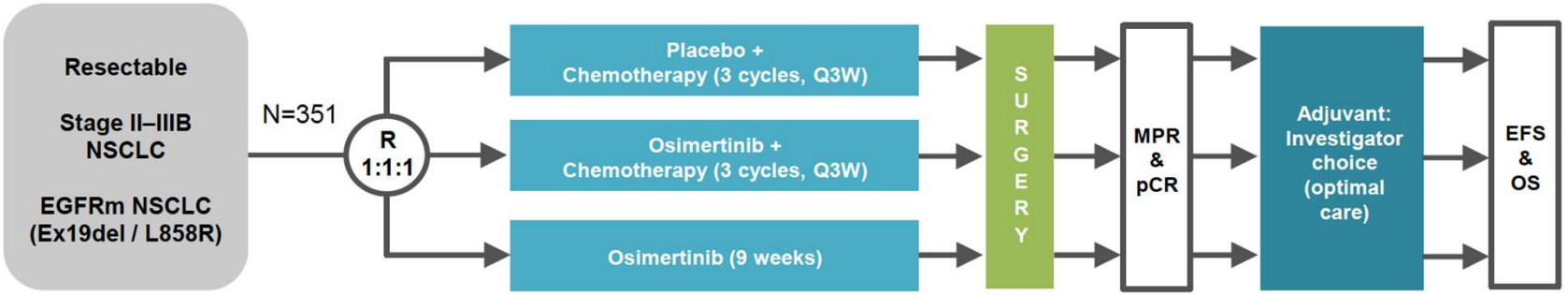
	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n=136)	15 (11)	NR (NC, NC)	**0.23**
Placebo (n=136)	56 (41)	33.1 (22.6, NC)	**(0.13, 0.40)**

Maturity 26%: osimertinib 11%, placebo 41%

Wu, Tsuboi et al. N Engl J Med 2020;383:1711–23. ADAURA data cut-off: January 17, 2020.
Tick marks indicate censored data. NC, not calculable, NR, not reached.

Tsuboi, P03.02

NeoADAURA (NCT04351555): Phase III, Randomized, Controlled, Multicenter Study of Neoadjuvant Osimertinib in EGFRm Resectable NSCLC



Stratification:

- Stage II/III
- Non-Asian/Chinese/ other Asian
- Ex19del/L858R

Double-blind treatment arms:

1. Placebo QD + investigator's choice of pemetrexed 500 mg/m^2 plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m^2
2. Osimertinib 80 mg QD + investigator's choice of pemetrexed 500 mg/m^2 plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m^2

Open-label (sponsor-blind) treatment arm:

3. Osimertinib 80 mg QD

Adjuvant therapy and follow-up:

- Patients will be followed up for OS until 5 years from surgery, with evaluation at 12 and 24 weeks post-surgery, then every 24 weeks, until disease recurrence or withdrawal of consent
- Osimertinib will be offered to all patients who complete surgery (+/- post-surgical chemotherapy) for up to 3 years or until disease recurrence

IO Therapy

Neo-adjuvant Nivolumab :

Feasibility N=21: Nivo 3 mg/kg Days -28 and -14, resect day 0

➢Nivolumab did not interfere with surgery

Safety: No unexpected findings

PR	**2 (10%)**
SD	18 (85%)
PD	1 (5%)

•Major Pathologic Response (MPR) in 9/21 pts = 43%

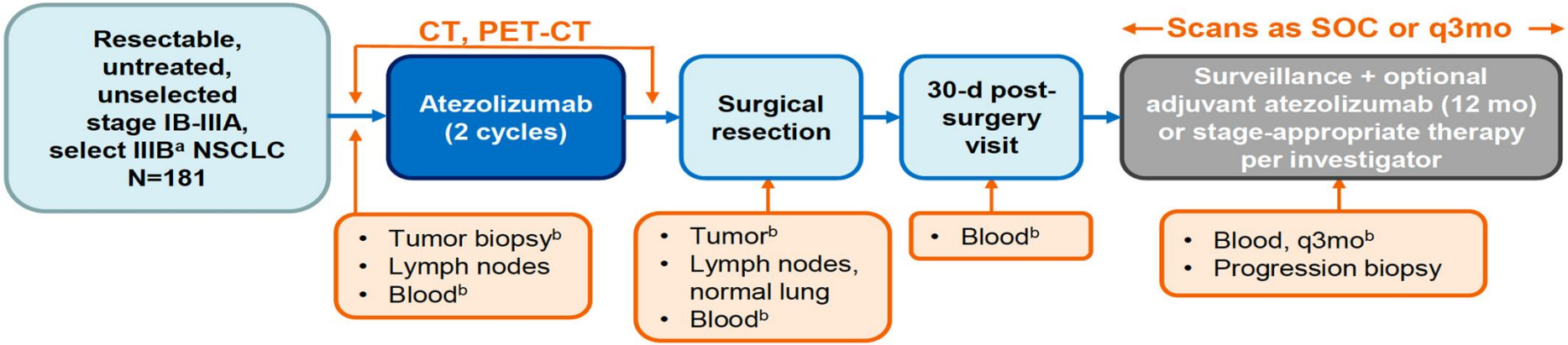
•Pre-treatment PD-L1 positivity did not correlate with MPR

•TMB seemed to correlate more with MPR

Drug-related Adverse Events N=22 (All treated)	Any Grade N(%)
Fever	1* (5)
Thyroid dysfunction	1 (5)
GI Anorexia/dysgeusia Vomiting/diarrhea LFT abnormality	 2 (9) 1 (5) 1 (5)
Pneumonia	0
Infusion reaction	1 (5)
CNS (delirium)	1 (5)

Chaft & Forde, et al.; NEJM 2018

LCMC3 study design



Primary endpoint:
- Major pathologic response (≤10% viable tumor cells)

Secondary endpoints:
- Pathologic response by PD-L1
- Radiographic response by
  - PD-L1, TMB, neoantigen, gene expression profiling

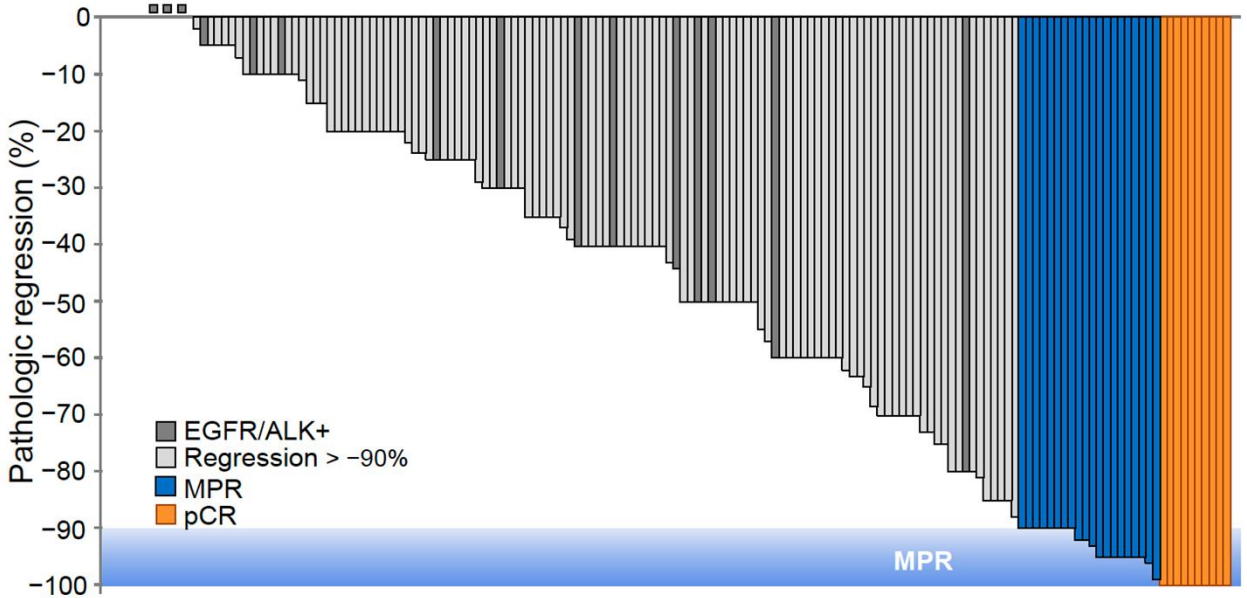
Exploratory endpoints:
- DFS, OS
- Biomarkers
  - ctDNA, TCRseq, flow cytometry, IF, IHC, NGS

Safety:
- Adverse events

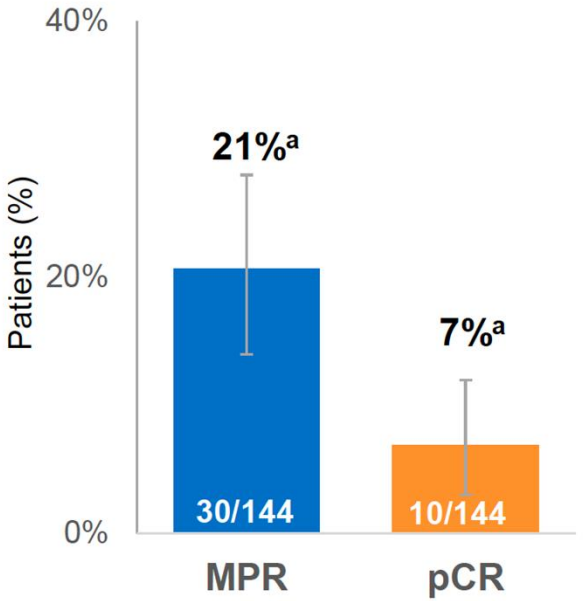
NCT02927301
ctDNA, circulating tumor DNA; DFS, disease-free survival; IF, immunofluorescence; NGS, next-generation sequencing; PET-CT, positron emission tomography–computed tomography; q3mo, every 3 months. SOC, standard of care; TCRseq, T-cell receptor sequencing; TMB, tumor mutational burden.
[a] T4 due to mediastinal organ invasion were excluded. [b] Mandatory

Primary endpoint: major pathologic response in surgery population LCMC3

Pathologic response in surgery population (n=159)



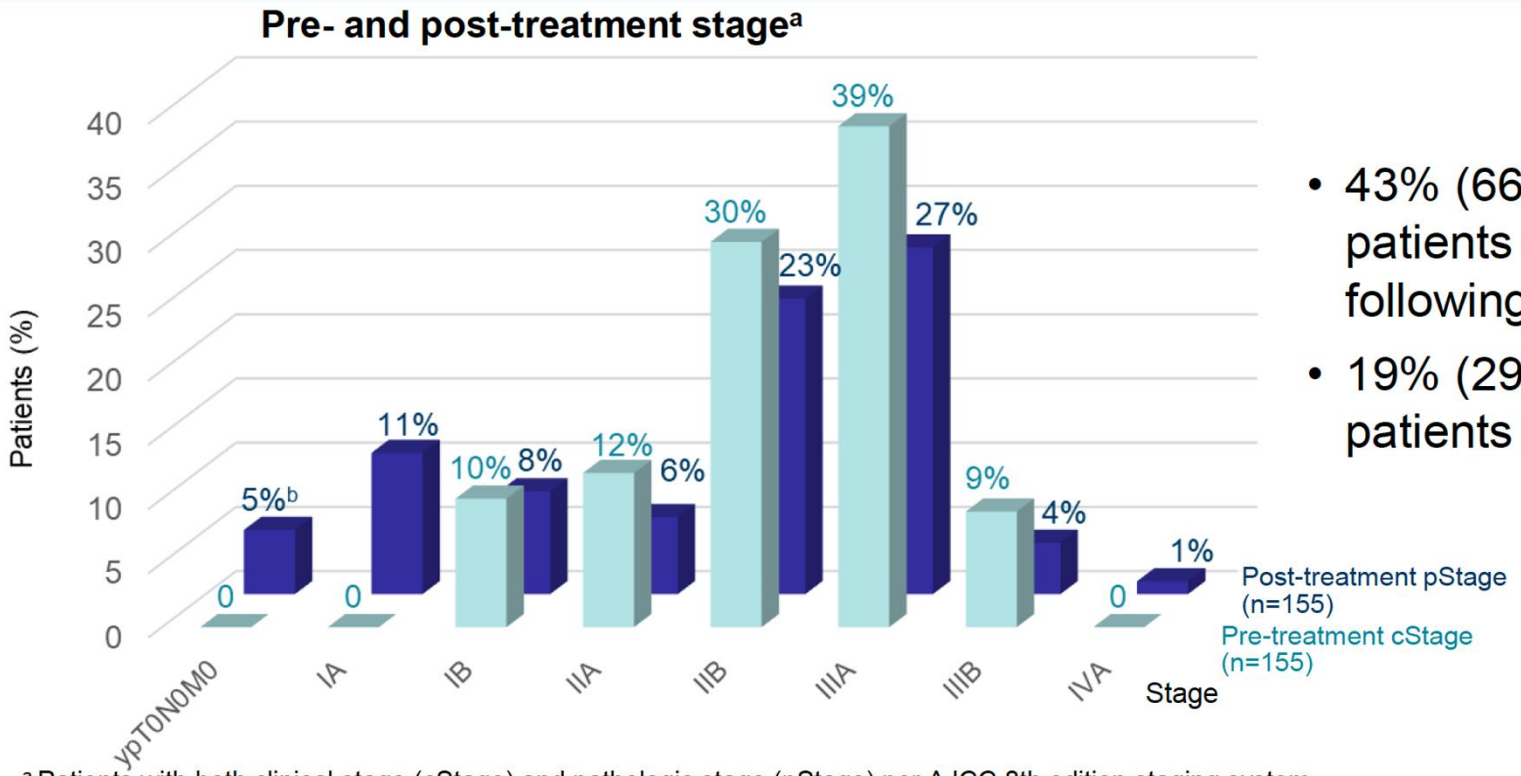
Major pathologic response in primary efficacy population (n=144)



Pathologic regression defined as % viable tumor cells – 100%.
MPR, major pathologic response; pCR, pathologic complete response.
[a] Error bars indicate 95% CI.

LCMC3: 2 doses atezolizumab, stage IB-IIIA
No surgery, n=22 (12%) of 181 total enrolled

Downstaging

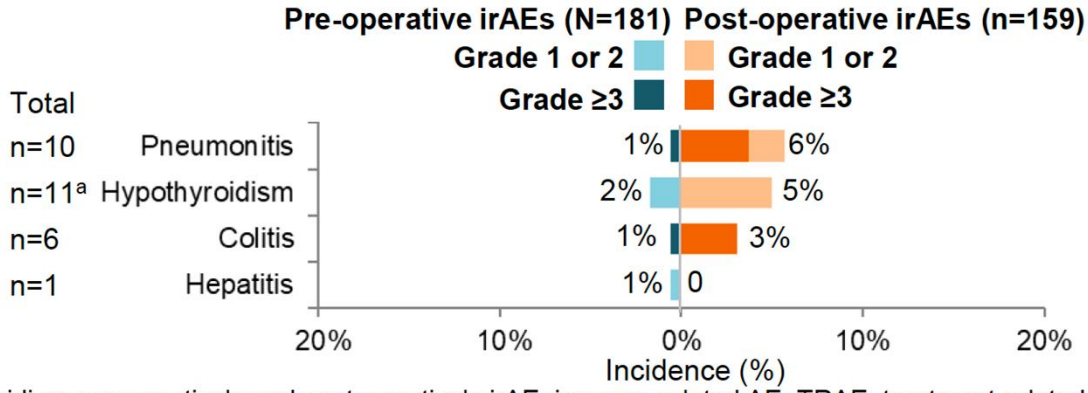


- 43% (66/155[c]) of patients downstaged following atezolizumab
- 19% (29/155[c]) of patients up-staged

[a] Patients with both clinical stage (cStage) and pathologic stage (pStage) per AJCC 8th edition staging system.
[b] pCR and pStage data are slightly discrepant: 10 patients had a pCR vs 8 who had ypT0N0M0. [c] 4 patients did not have a pathologic stage evaluation.

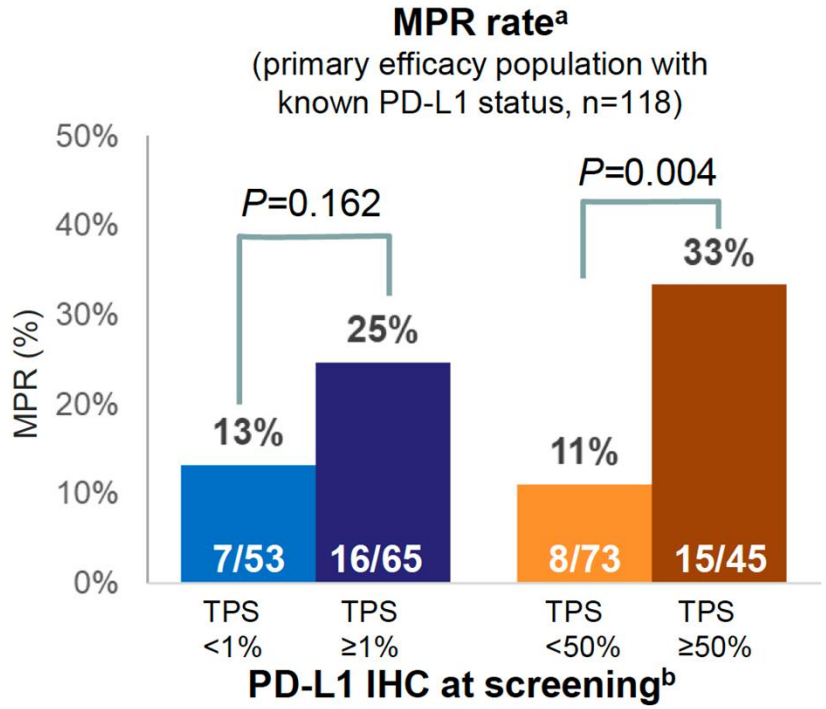
Pre- and post-operative treatment-related AEs and immune-related AEs

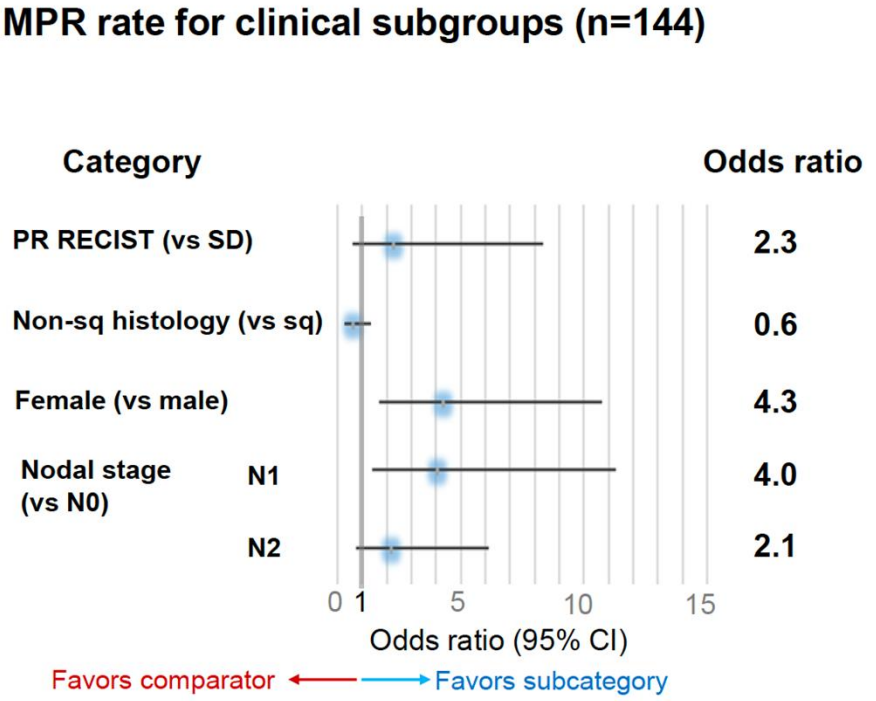
	Pre-operative (N=181) and post-operative AEs (n=159)			
Patients with ≥1 AE, n (%)	**Pre-operative TRAE N=181**	**Post-operative TRAE n=159**	**Pre-operative irAEs N=181**	**Post-operative irAEs n=159**
Grade 1	55 (30%)	13 (8%)	22 (12%)	18 (11%)
Grade 2	36 (20%)	18 (11%)	16 (9%)	12 (8%)
Grade 3	**11 (6%)**	**17 (11%)**	**3 (2%)**	**11 (7%)**
Grade 4	**0**	**3 (2%)**	**0**	**1 (1%)**
Grade 5	**0**	**1 (1%)**	**0**	**1 (1%)**



[a] One patient had hypothyroidism preoperatively and postoperatively irAE, immune-related AE; TRAE, treatment-related AE.

MPR by PD-L1 status at screening and selected patient categories



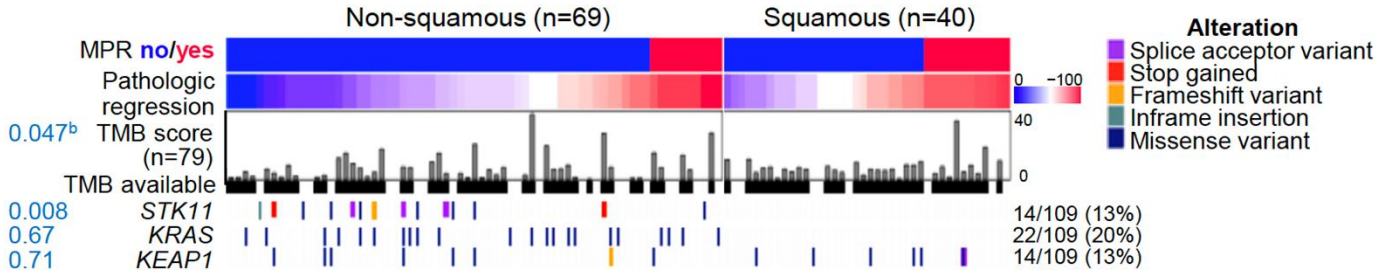


sq, squamous.

[a] Analysis population excluded of EGFR and ALK positive patients. [b] Local TPS score used if central score was not available.

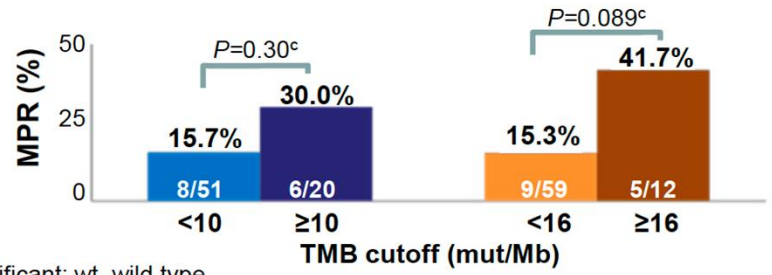
Pathologic regression weakly correlated with TMB and trended toward less regression in STK11-mutated tumors

Pathologic regression by mutation status (n=109)[a]

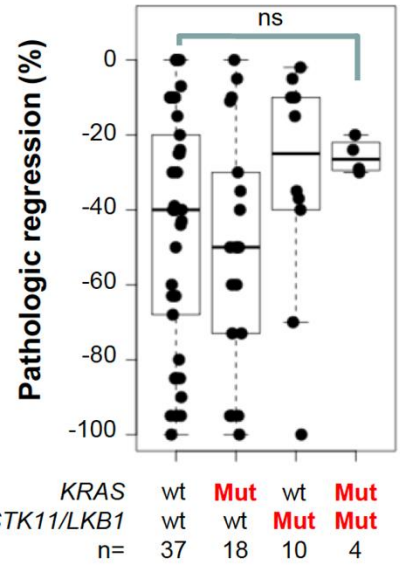


P value for correlation with pathologic regression

MPR rate by TMB cutoff for all histologies (n=71)[c]



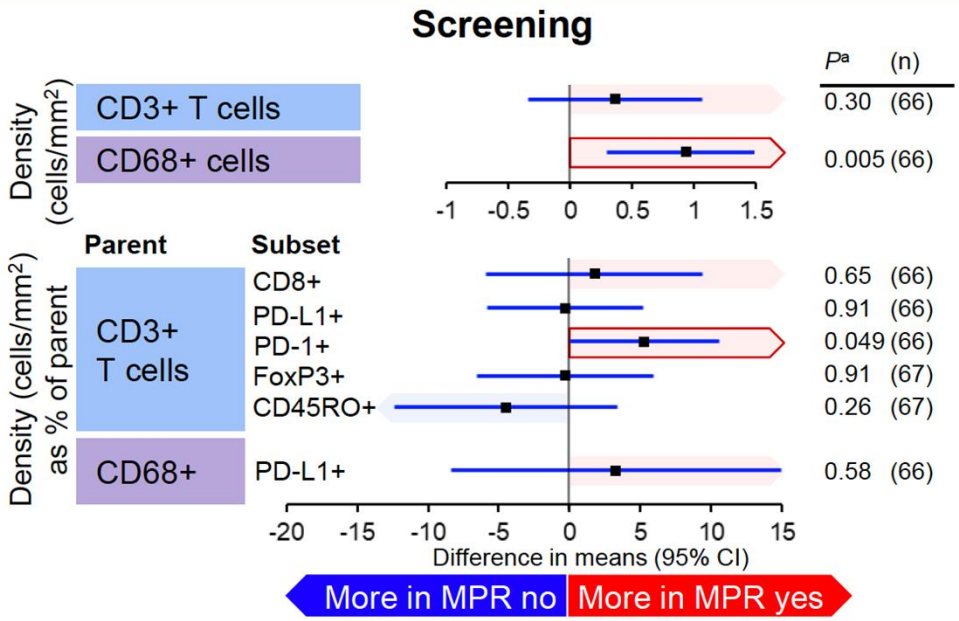
Pathologic regression by *KRAS* and *STK11/LKB1*, non-squamous (n=69)[a]

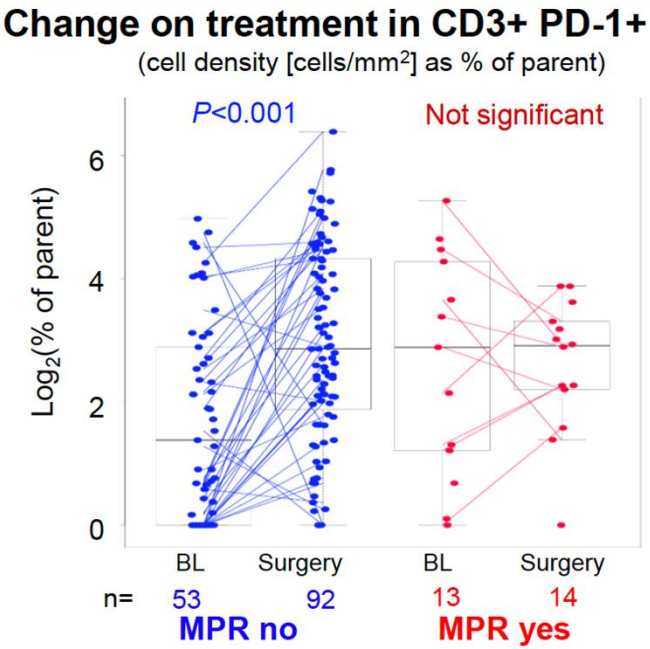


Mut, mutated; ns, not significant; wt, wild type.

[a] Includes patients with pathologic regression assessment and with baseline and/or surgery whole exome sequencing, Wilcoxon. [b] Includes patients with pathologic regression assessment and TMB, Pearson. [c] MPR rate was calculated in the primary efficacy population with TMB results, χ^2; unadjusted *P* values.

Multiplex IF shows that pre-existing activated tumor microenvironment enriches for MPR





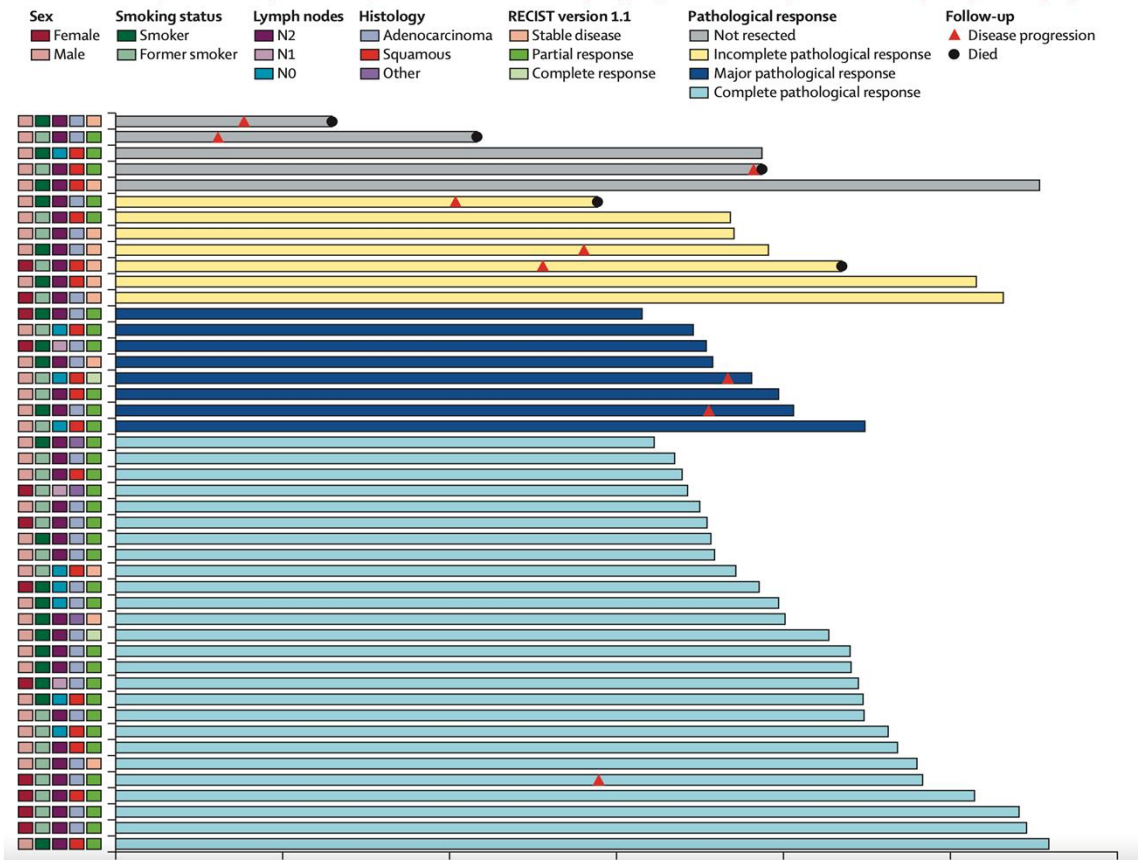
- Enrichment of CD68+ cells and CD3+/PD-1+ T cells, in "MPR yes" patients

- Activation of tumor microenvironment after therapy, in "MPR no" patients

BL, baseline; IF, immunofluorescence analysis.
PD-L1 antibody, clone E1L3N (Cell Signaling)
Preliminary data. Includes enrolled patients with NSCLC and multiplex IF passing QC. [a] *t* test.

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

Mariano Provencio, Ernest Nadal, Amelia Insa, María Rosario García-Campelo, Joaquín Casal-Rubio, Manuel Dómine, Margarita Majem,



NADIM

Lancet Oncol 2020; 21: 1413–22

Screened 51 pts, enrolled 46pts
PFS 77% at 24 mo,
5 no surgery
7 minor response
8 MPR
26 pCR

The Future of IO

Ongoing Ph 3 NEO-Adj PD-(L)1 NSCLC IO

Drug	N	Stages	Description	Primary Endpoint
Nivo + platinum Chemo (ipi/nivo closed) CM816	350	Stage IB–IIIA, resectable NSCLC	Neo-adjuvant, no adjuvant	MPR / RFS
Atezo + platinum Chemo Impower030	374	Stage II–IIIB (T3N2), resectable NSCLC	Neo-adjuvant chemo-ICI, then adjuvant IO	MPR / RFS
Pembro + platinum-doublet Chemo KN671	786	Stage IIB–IIIA, resectable NSCLC	Neo-adjuvant chemo-ICI then adjuvant IO	RFS / OS
Durva + platinum-doublet Chemo	300	Stage II–IIIA, resectable NSCLC	Neo-adjuvant chemo-ICI then adjuvant IO	MPR

Ongoing Adjuvant PD-1/PD-L1 IO trials

Drug/Trial	Description	Stages entered	Description	Primary endpoint
Nivolumab	US, NCI (ECOG), Observational control	IB (4cm)-IIIA After Adj Chemo +/- radiation	Phase 3 Allows PD-L1 +/-	OS/DFS
Atezolizumab	Global, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS
Durvalumab	Global, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS
Pembrolizumab	ETOP/EORTC, Placebo Controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS

CONCLUSIONS:

Adjuvant/Neo-adjuvant systemic therapy

Chemotherapy – ITACA

- ERCC1/TS tailoring not practice changing

Targeted Therapy - ADAURA updates

- Osimertinib DFS benefit regardless of Chemotherapy Use

IO - LCMC3

- Single Agent Atezolizumab shows promise
- Await results of ongoing phase III IO trials