Lung Cancer UPDATES
IASLC HIGHLIGTHS
28-31 ENERO 2021

VIRTUAL

Iniciativa científica de:
GECP
lung cancer research

Estadios Iniciales

Manuel Dómine

Hospital Universitario Fundación Jiménez Díaz
Universidad Autónoma de Madrid

BIOMARCADORES

P07.02

Detection of Molecular Residual Disease (MRD) using ctDNA in NSCLC: A Systematic Review and Meta-Analysis

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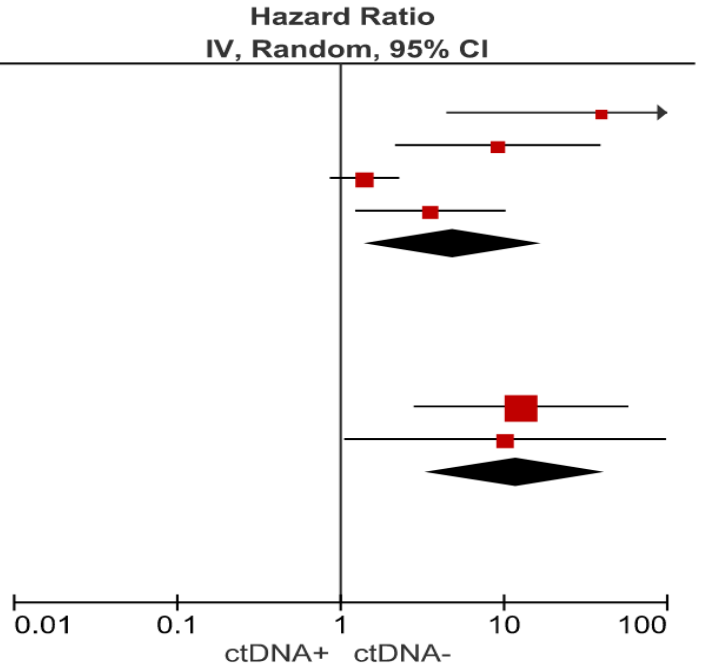
Role of ctDNA detected in biofluids (plasma and urine) and MRD associated to clinical outcomes in surgically resected NSCLC,stage I-IIIA

RESULTS

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 1-month DFS/RFS				
Chauduri et al	3.6774	1.116	16.7%	39.54 [4.44, 352.38]
Chen et al	2.215	0.739	23.4%	9.16 [2.15, 38.99]
Hu et al	0.336	0.25	32.5%	1.40 [0.86, 2.28]
Wang et al	1.264	0.542	27.4%	3.54 [1.22, 10.24]
Subtotal (95% CI)			**100.0%**	**4.89 [1.41, 16.98]**
Heterogeneity: Tau² = 1.18; Chi² = 14.45, df = 3 (P = 0.002); I² = 79%				
Test for overall effect: Z = 2.50 (P = 0.01)				
1.1.2 OS				
Chauduri et al	2.542	0.773	69.1%	12.71 [2.79, 57.80]
Chen et al	2.318	1.157	30.9%	10.16 [1.05, 98.07]
Subtotal (95% CI)			**100.0%**	**11.86 [3.36, 41.79]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%				
Test for overall effect: Z = 3.85 (P = 0.0001)				

Test for subgroup differences: Chi² = 0.96, df = 1 (P = 0.33), I² = 0%



The pooled analysis showed a ctDNA detection rate of 34.6%.
One-month post surgery ctDNA positivity in radically resected NSCL was associated with a higher risk of recurrence or death.

NEOADYUVANCIA

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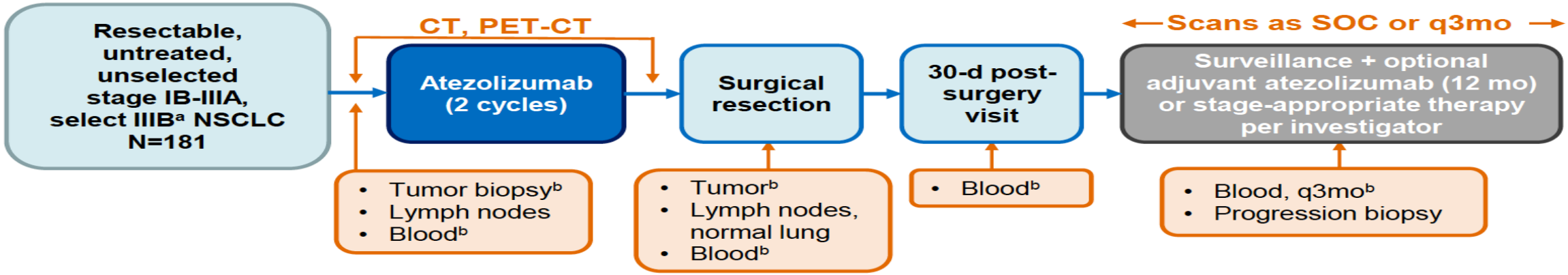
CONQUERING THORACIC CANCERS WORLDWIDE

Surgical and Clinical Outcomes With Neoadjuvant Atezolizumab in Resectable Stage IB-IIIB NSCLC: LCMC3 Trial Primary Analysis

Jay M. Lee,[1] Jamie Chaft,[2] Alan Nicholas,[3] G. Alexander Patterson,[4] Saiama N. Waqar,[4] Eric M. Toloza,[5] Eric Haura,[5] Dan J. Raz,[6] Karen L. Reckamp,[7] Robert E. Merritt,[8] Dwight Owen,[8] David J. Finley,[9] Ciaran J. McNamee,[10] Justin D. Blasberg,[11] Edward B. Garon,[1] John D. Mitchell,[12] Robert C. Doebele,[12] Frank Baciewicz,[13] Misako Nagasaka,[14] Harvey I. Pass,[15] Katja Schulze,[3] See Phan,[3] Ann Johnson,[3] Paul A. Bunn,[12] Bruce E. Johnson,[16] Mark G. Kris,[2] David J. Kwiatkowski,[10] Ignacio I. Wistuba,[17] David P. Carbone,[8] Valerie W. Rusch[2]

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

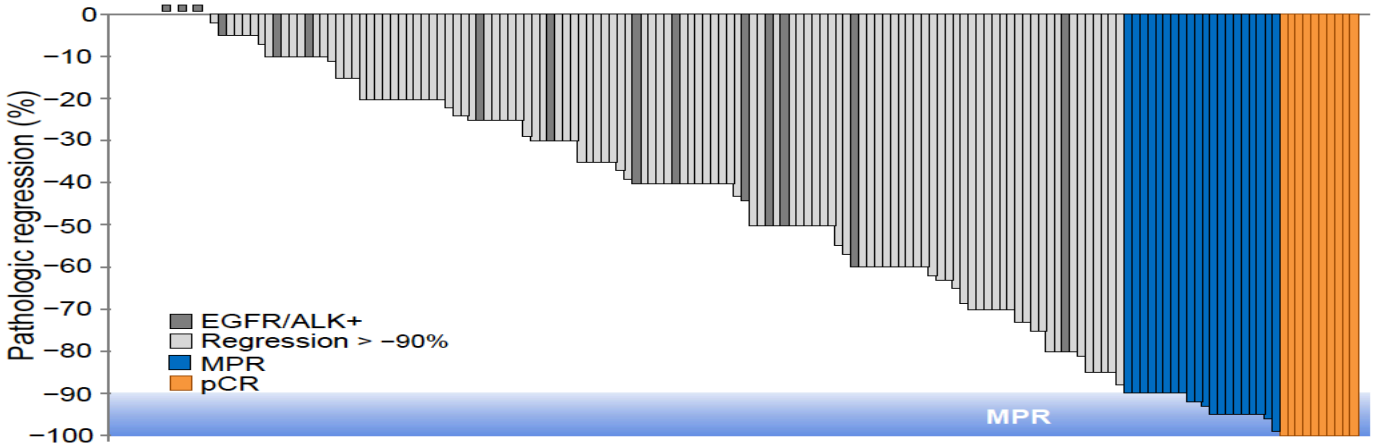
Exploratory endpoints:
- DFS, OS
- Biomarkers
  - ctDNA, TCRseq, flow cytometry, IF, IHC, NGS

Safety:
- Adverse events

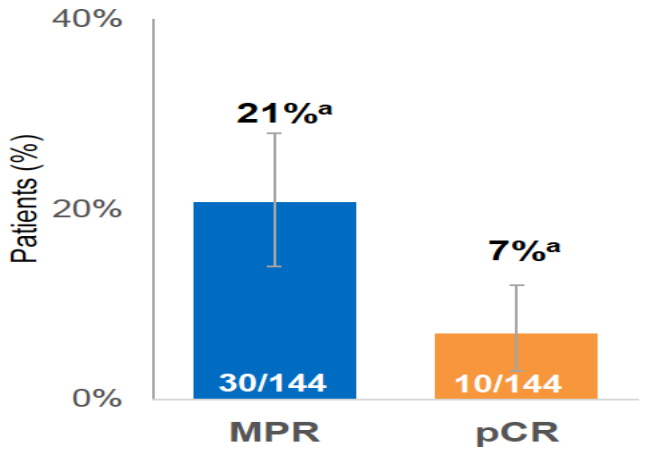
NCT02927301
ctDNA, circulating tumor DNA; DFS, disease-free survival; IF, immunofluorescence; NGS, next-generation sequencing; PET-CT, positron emission tomography–computed tomography; q3mo, every 3 months. SOC, standard of care; TCRseq, T-cell receptor sequencing; TMB, tumor mutational burden.
[a] T4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

Primary endpoint: major pathologic response in surgery population

Pathologic response in surgery population (n=159)



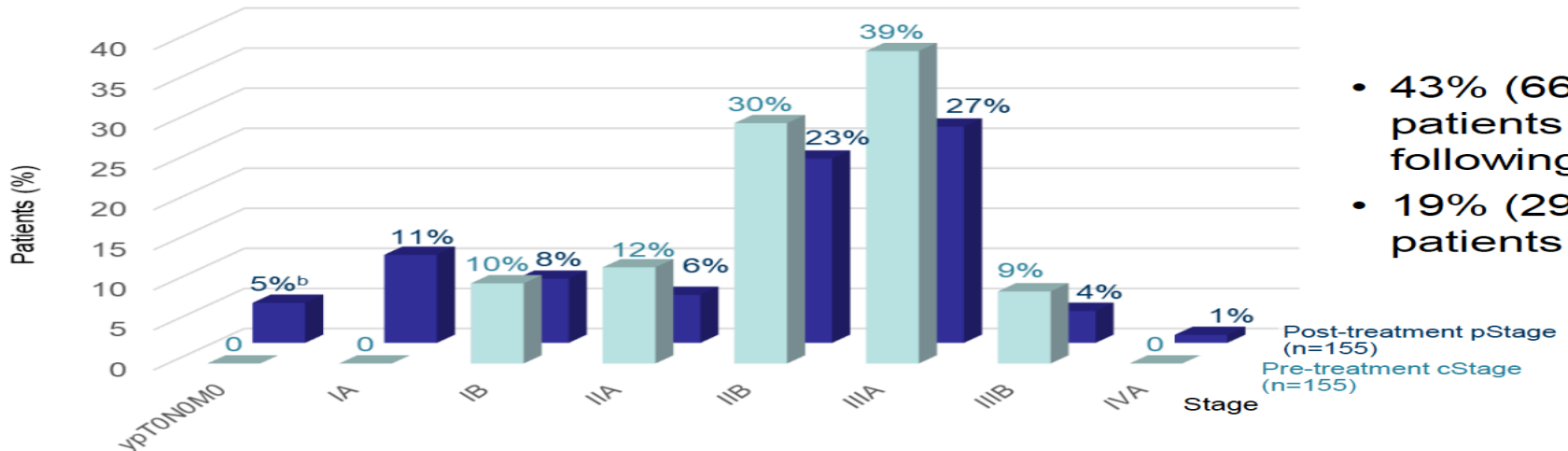
Major pathologic response in primary efficacy population (n=144)



Pathologic regression defined as % viable tumor cells – 100%.
MPR, major pathologic response; pCR, pathologic complete response.

Downstaging

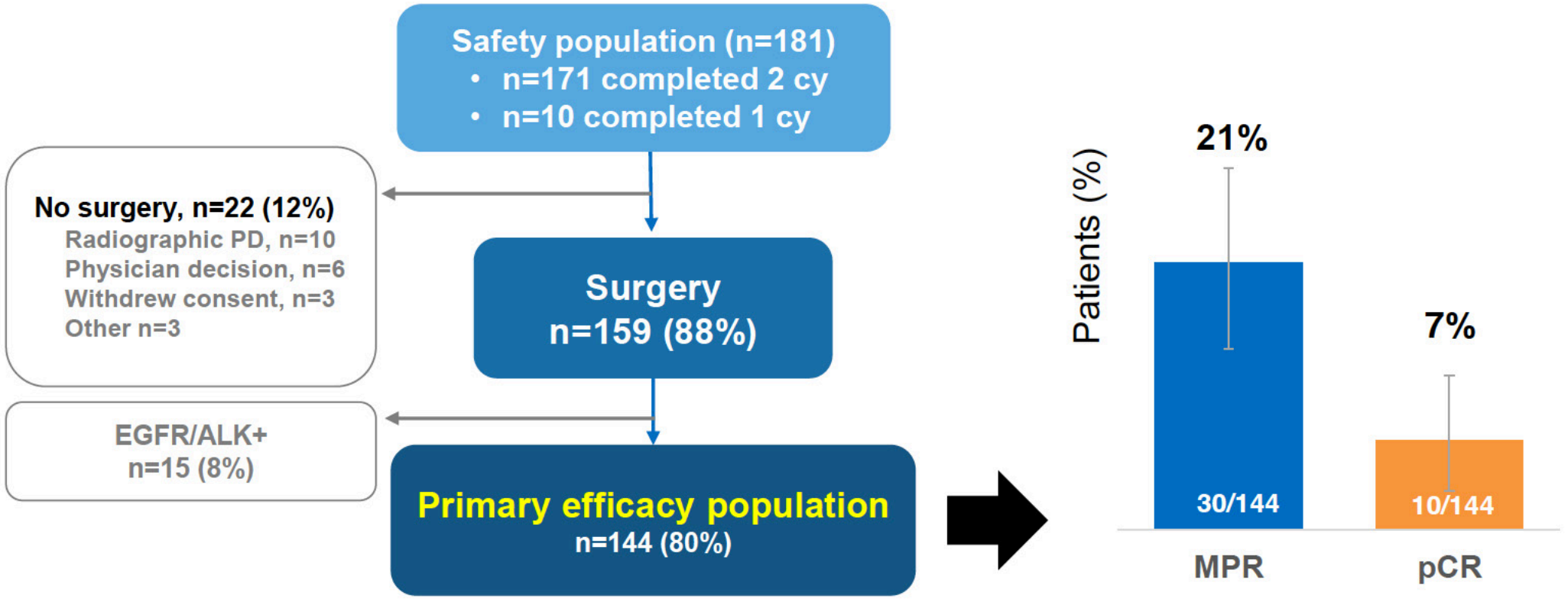
Pre- and post-treatment stage[a]



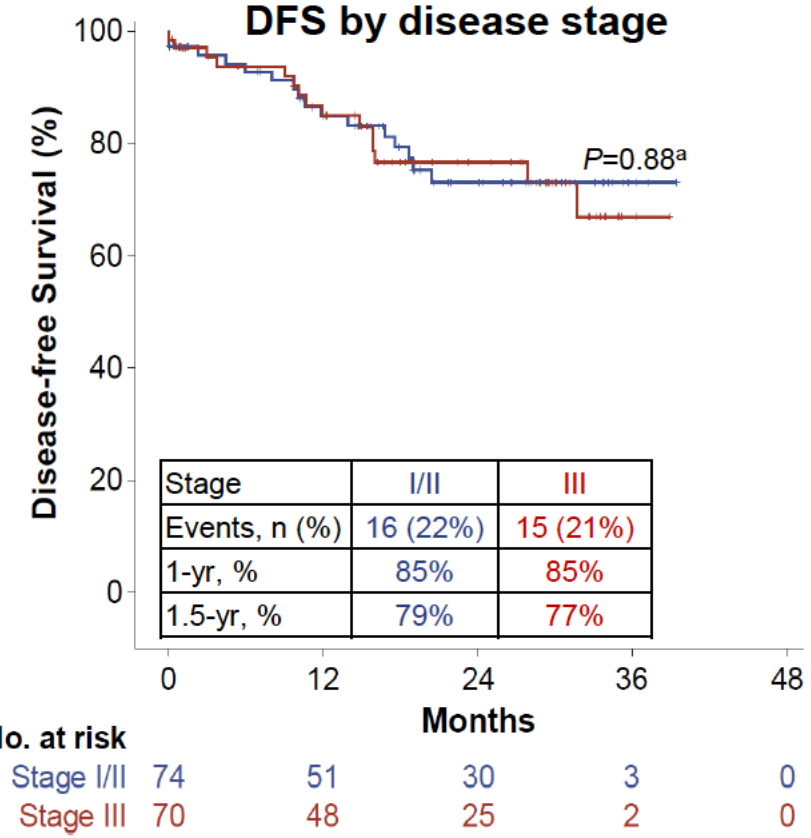
- 43% (66/155[c]) of patients downstaged following atezolizumab
- 19% (29/155[c]) of patients up-staged

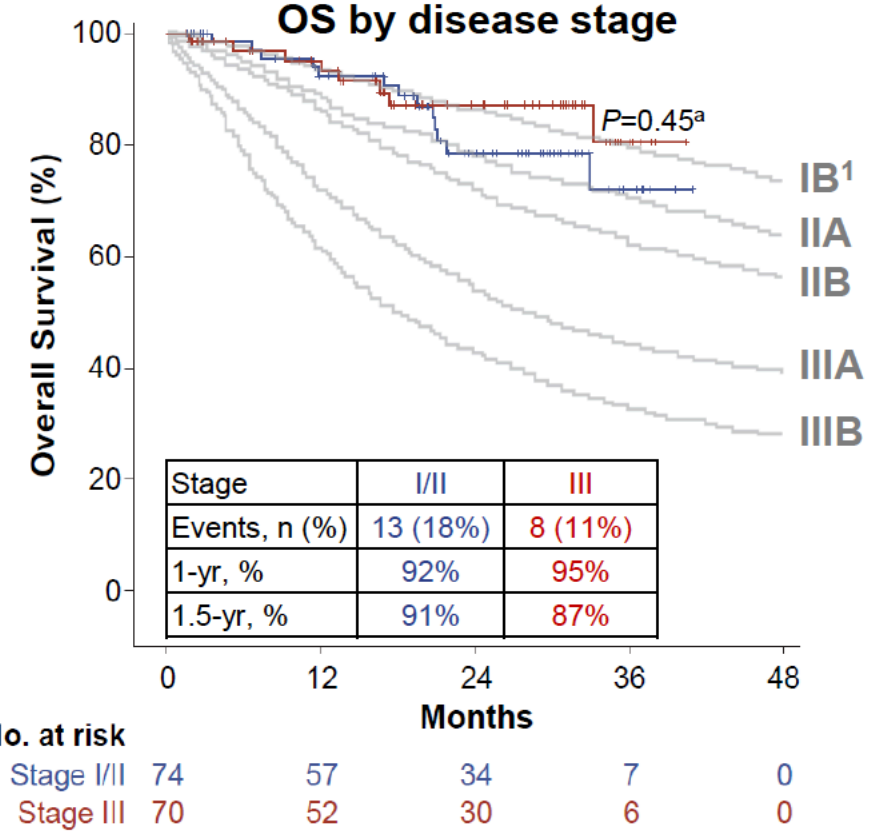
[a] Patients with both clinical stage (cStage) and pathologic stage (pStage) per AJCC 8th edition staging system.
[b] pCR and pStage data are slightly discrepant: 10 patients had a pCR vs 8 who had ypT0N0M0. [c] 4 patients did not have a pathologic stage evaluation.

Patients population and Primary Endpoint (PR)



Exploratory endpoints: efficacy outcomes in the primary efficacy population





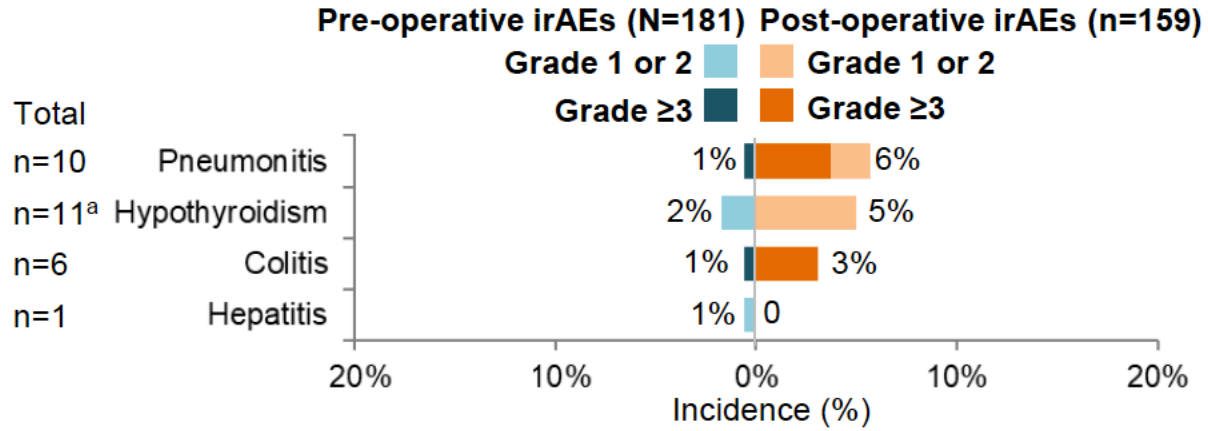
[a]*P*-values are based on a log-rank test between the survival curves and are descriptive only.

1. Chansky K, et al. J Thorac Oncol 2017;12:1109-21.

Median follow-up for OS: 2.1 years.

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.

NEOADJUVANT IO MONOTHERAPY

Trial	Nº patients	Stage	Drug (Nº doses)	Primary Endpoint	Pathological Response	
Forde et al (2018)	22	I-IIIA	Nivolumab(2)	Safety-Feasibility	MPR: 45%	pCR:13%
Reuss J et al (2020)	9	IB-IIIA	Nivo+Ipi (3-1)	Safety-Feasibility		pCR:33%
Cascone T et al. NEOSTAR (2019)	44	I-IIIA	Nivo/+/-Ipi (3-1)	MPR	MPR:19% MPR:44%	pCR:10% pCR:38%
Gao S et al. (2020)	40	I-IIIB	Sintilimab (2)	Safety	MPR:40.5%	pCR:16%
Kwiatkowski et al LCMC3 (2019)	101	IB-IIIA	Atezolizumab (2)	MPR	MPR:19%	pCR:5%
Bar J et al (2019) MK3475-223	14	I-II	Pembrolizumab (1-2)	Safety	MPR:40%	.
IoNESCO (2020)	50	IB-IIIA	Durvalumab (3)	% of R0	MPR:18.6%	.
Besse B et al Princeps (2020)	30	I-IIIA	Atezolizumab (1)	Tolerance	MPR:14%	.
IO Monotherapy		**33% IIIA**		**6.5% Progression**	**62/265 MPR 23.4%**	**22/265 pCR 7.5%**
LCMC3	**144**	**IB-IIIB**	**Atezolizumab**	**MPR**	**21%**	**7%**

Courtesy by M Provencio. ES06.01

NEOADJUVANT CHEMOTHERAPY- IO

Trial	Stage	Nº patients	Pathologic Response MPR	Pathologic Response pCR	Radiographic Response	Downstaging
Shu C et al (2020)	IIA-IIIA	30 23(77% IIIA)	17/30 (57%)	10/30(33%)	63%(19PR,2PD)	11/19 (68%)
Provencio M et al (2020)	IIIA	46	34/41(83%)	26/41(63%)	76%(33PR,2 CR)	37/41 (90%)
Rothschild S et al (2020)	IIIA	65	33/55 (60%)	10/55(18.2%)	58%(32PR,4CR)	37/55 (67%)
Zinner R et al (2020)	IB-IIIA	13 (54% IIIA)	6/13 MPR(46%)	5/13 (38%)	46%(5PR,1CR)	ND
TOTAL		**154 (141, 91% IIIA)**	**64.7%MPR**	**36.7% pCR**	**4.5% CR 58% PR 2% PD**	**74%**

Courtesy by M Provencio. ES06.01

LUNG CANCER EARLY STAGES

BIOMARKERS IO / IO+CT

Tumor cells

PDL- 1 expression

TMB

Specific mutated gene pathways

- INF-γ
- KRAS
- STK11

Tumor microenvironment

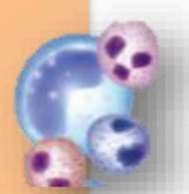
PDL- 1 expression

- Immune cells with specific phenotypes

- CD8+, CD4+ T-cells, FOXP3 T-cells
- TAMs, myeloid cells

Diversity of TCR repertoires:

- TILs, TCR clonality



Circulating factors

ct-DNA

Cytokines

Inflammatory factors

Soluble proteins

Pheripheral blood cells:

- CD8+, CD 4+ T-cells, FOXP3 T-cells

Host-related markers

Gender

Age

Intestinal microbiota

Specific mutations

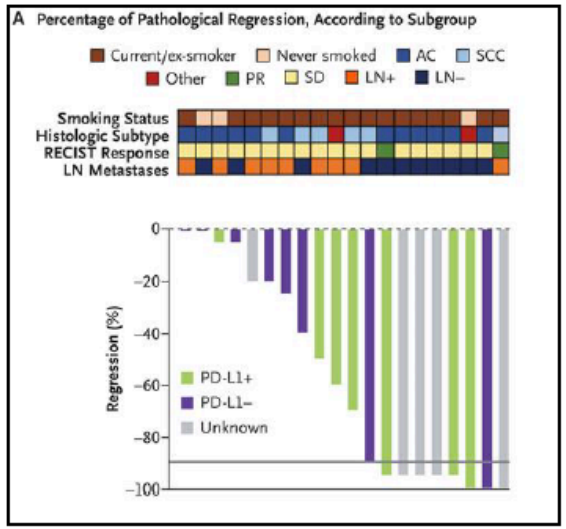
Microbiome

Epigenetics

BIOMARKERS IO monotherapy

Nivolumab

- No associated to PD-L1 IHC expression
- WES-based on 11 cases, MPR associated to tumor mutational burden



PD-L1 IHC Expression

LCMC3

Atezolizumab two doses
MPR were observed irrespective of pretherapy PD-L1 expression
TMB was no found to correlate with MPR

Pembrolizumab, phase I trial

Two doses, no correlation PD-L1

NEOSTAR

Some relation elevated pretreatment PDL1

Sintilimab

MPR occurred in both PD-L1 positive or negative tumors
PD-L1 expression in stromal cells correlated with pathologic response

TMB and selected mutations in resectable stage IIIA NSCLC patients receiving neo-adjuvant chemo-immunotherapy from NADIM trial.

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Servicio de Oncología Médica, Instituto de Investigación Sanitaria Puerta de Hierro-Segovia de Arana (IDIPHISA). SPAIN

TMB AND SELECTED MUTATIONS PFS NADIM

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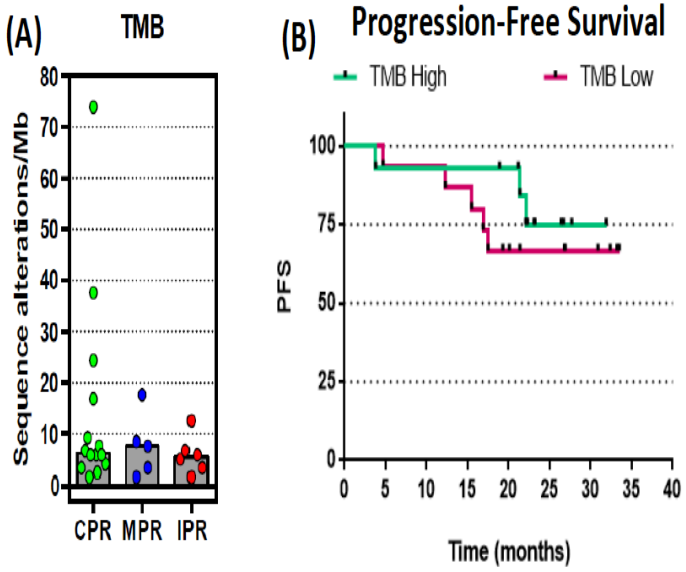
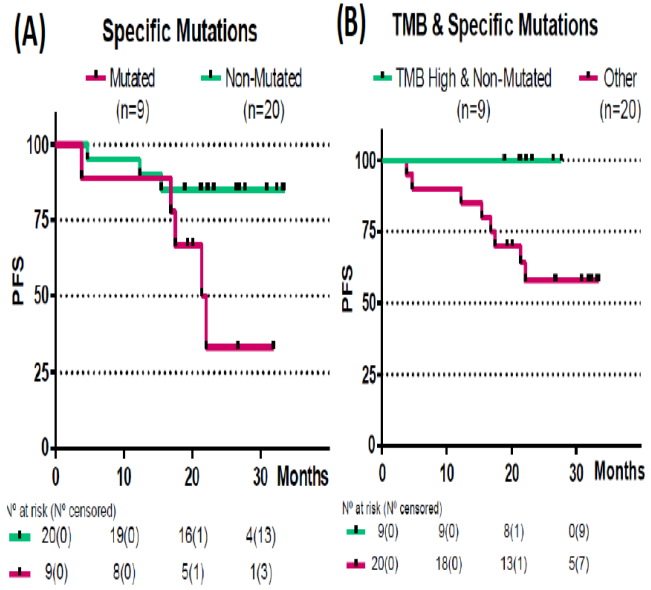
Results TMB



Median TMB was 5.89 (range 1.68 – 73.95). No differences in TMB value between histologies (adenocarcinoma vs squamous cell), smoking status (former vs current), age or sex were observed.

(A) No differences in the number of somatic alterations were observed between patients with IPR and MPR including CPR (p=0.412) or CPR alone (p=0.32).

(B) No association was found between TMB levels and PFS using any TMB cutoff. (p=0.42 using median TMB as threshold)



The presence of these selected mutations was not associated with pathologic response (Chi-square p=0.89) but was associated with shorter PFS.

(A) The median PFS in patients with mutant STK11, KEAP1, RB1 or EGFR was 21.4 months (95% CI, 18 to 25), whereas median PFS was not reached in non-mutated patients (p=0.026).

(B) The 3 patients with TMB-High (TMB>5,.89) that had disease progression harbored somatic mutations in STK11, KEAP1 or RB1. Thus, PFS at 24 months was 100% (95% CI not estimable) for TMB-High (TMB>5.89) and non-mutated in STK11, KEAP1, RB1 or EGFR patients (n=9) vs 58% (95% CI, 35 to 76) for the remainder of patients (n=20) (p-value=0.038).

TMB was not associated to pathologic response or PFS/OS

Presence of *EGFR/STK11/KEAP1/RB1* mutations alone, or in combination with TMB predicted PFS

Provencio et al. Lancet Oncology 2020, in press

ADYUVANCIA

PS01-04

International Tailored Chemotherapy Adjuvant (ITACA) Phase III study of Pharmacogenomic-Driven versus Standard Adjuvant Chemotherapy in completely Resected Stage II-IIIA Non-Small Cell Lung Cancer

Silvia Novello

(**on behalf of the ITACA investigators**)

University of Turin,

Department of Oncology

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IASLC 2020 World Conference on Lung Cancer Singapore

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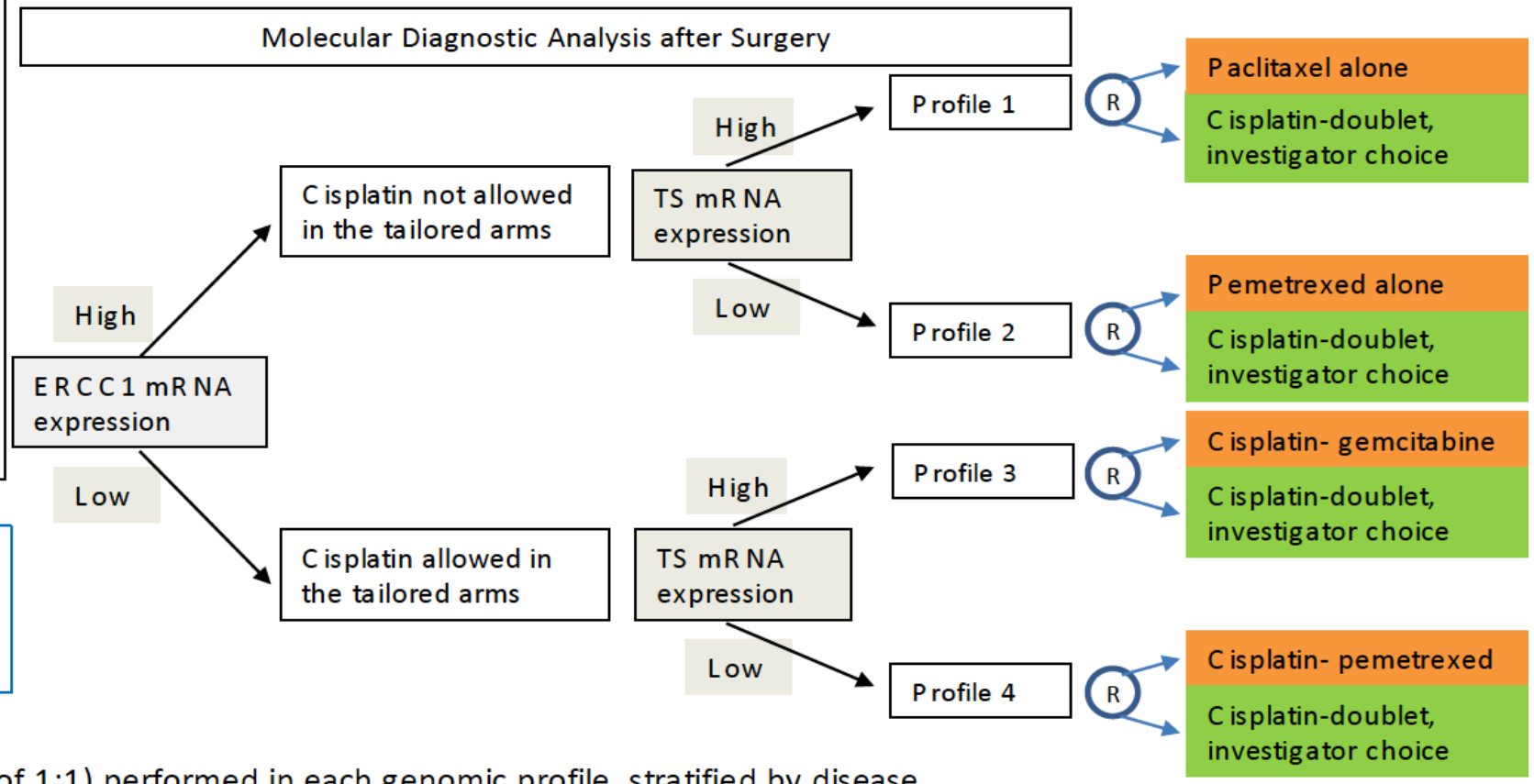
Design of the study

- 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)

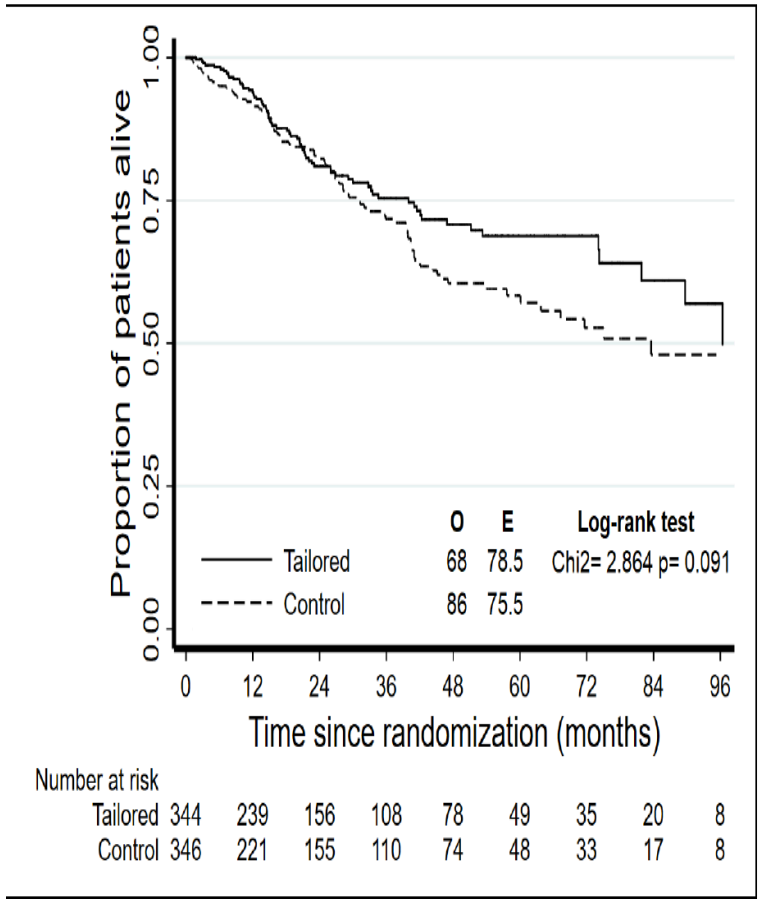
Novello S. et al. WCLC 2015

Primary endpoint: OS

Secondary: Recurrence free survival, toxicity, Therapeutic compliance

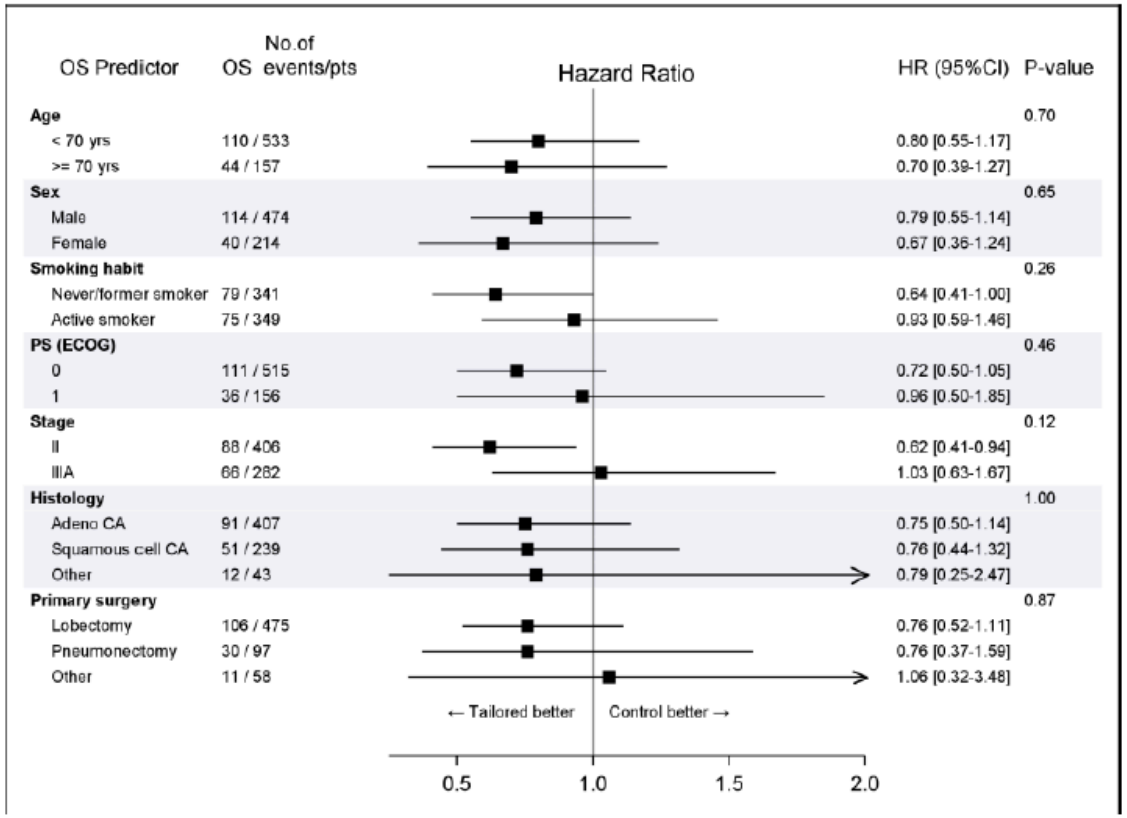
Overall survival

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)

Overall survival

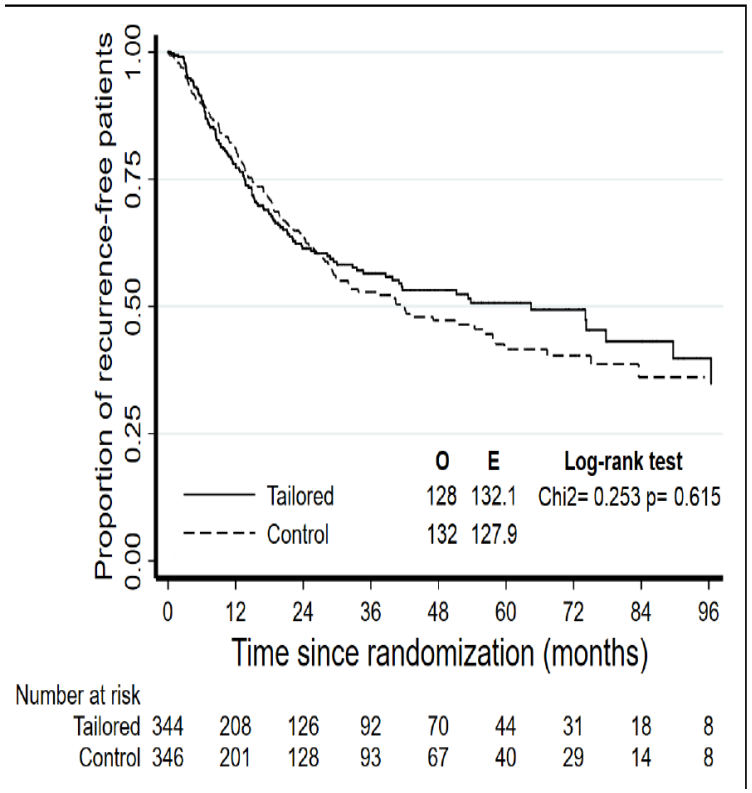


Adjuvant chemotherapy customization based on the primary tumor tissue mRNA expression of ERCC 1 and TS did not significantly improve OS

There was a non statistically significant trend for OS favoring the customized arm. When the final analysis was performed the study was underpowered

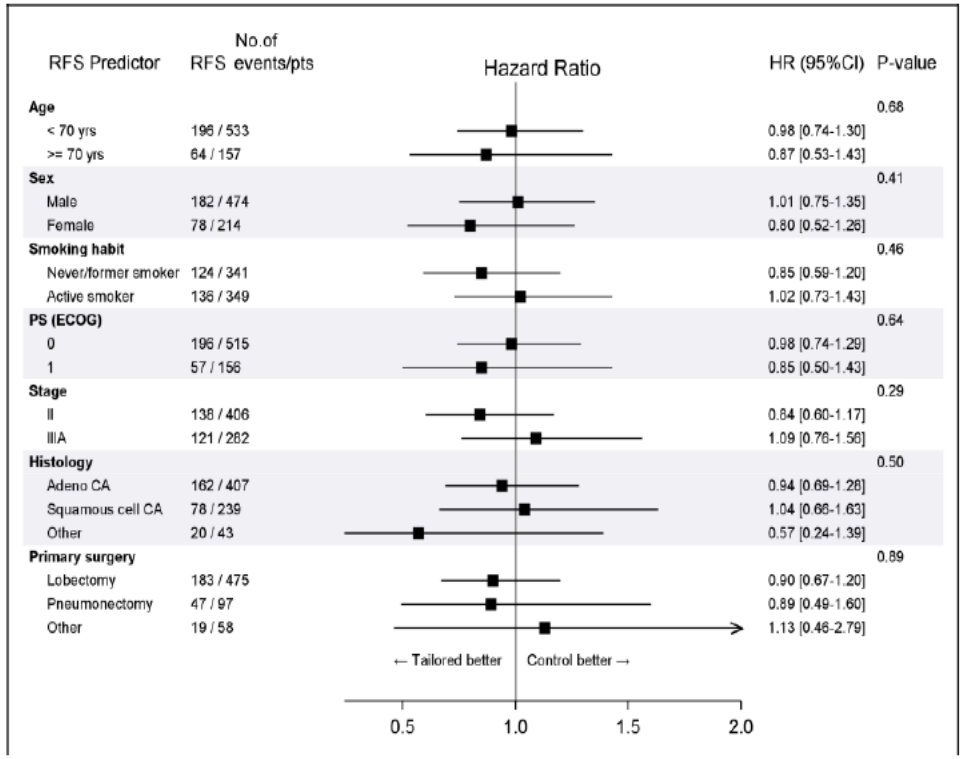
Recurrence-free Survival

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)

Recurrence-free survival



Toxicity

Toxicities grade 3-4, PP population

	Overall			
	Tailored		Control	
	N	%	N	%
Anemia	3	0.9	9	2.7
Neutropenia	45	13.4	64	18.9
Leucopenia	13	3.9	45	13.3
Thrombocytopenia	11	3.3	26	7.7
Fatigue	9	2.7	5	1.5
Nausea	13	3.9	15	4.4
Vomiting	7	2.1	6	1.8
Diarrhea	5	1.5	1	0.3
Constipation	1	0.3	0	0
Abdominal pain	0	0	0	0
Stomatitis	1	0.3	0	0
Tinnitus/vertigo	0	0	1	0.3

	Overall			
	Tailored		Control	
	N	%	N	%
Asthenia	1	0.3	5	1.5
Mucositis	2	0.6	0	0
Pyrexia	0	0	0	0
Decreased appetite	2	0.6	1	0.3
Hyperglycaemia	3	0.9	1	0.3
Myalgia	3	0.9	2	0.6
Paraesthesia	0	0	0	0
Dyspnea	2	0.6	1	0.3
Alopecia	7	2.1	0	0
Rash	0	0	0	0
Worst degree 3-4	**110**	**32.6**	**155**	**45.9**

Odds Ratio of at least one toxicity grade 3-4 (tailored arm vs control arm):
0.57; (95%CI: 0.42-0.78); p<0.001

Treatment customization significantly improved toxicity profile without compromising the activity

P03.03: MERMAID-1: A Phase III study of adjuvant durvalumab plus chemotherapy in resected NSCLC patients with MRD+ post-surgery

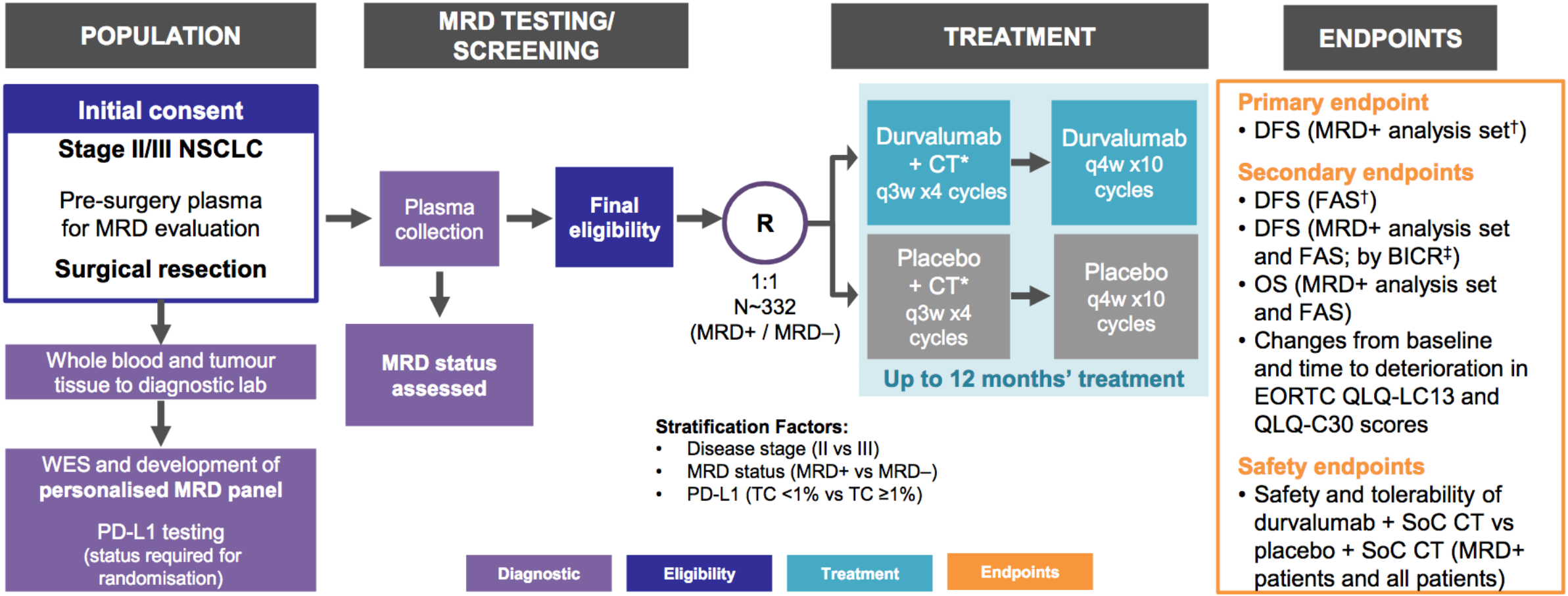
Solange Peters[1], David Spigel[2], Myung-Ju Ahn[3], Masahiro Tsuboi[4], Jamie Chaft[5], David Harpole[6], Glenwood Goss[7], Fabrice Barlesi[8], Chris Abbosh[9], Lynne Poole[10], Rena May[10], Phillip Dennis[10], Charles Swanton[9,11]

[1]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [2]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [3]Sungkyunkwan University School of Medicine, Seoul, Korea; [4]Division of Thoracic Surgery and Oncology National Cancer Center Hospital East, Kashiwa, Japan; [5]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [6]Duke University Medical Center, Durham, NC, USA; [7]The Ottawa Hospital Cancer Centre, Division of Medical Oncology, Ottawa, ON, Canada; [8]Université de la Méditerranée–Assistance Publique Hôpitaux de Marseille, France; [9]The Francis Crick Institute, London, UK; [10]AstraZeneca, Gaithersburg, MD, USA; [11]UCL Hospitals NHS Trust, London, UK

MRD: Minimal residual disease

Study design

MERMAID-1: a phase III, randomised, double-blind, placebo-controlled, parallel-arm, multicentre study



*SoC CT: carboplatin + paclitaxel or cisplatin/carboplatin + pemetrexed, dependent on tumour histology and at investigator's discretion;
†Investigator-assessed by RECIST v1.1; ‡per BICR by RECIST v1.1.

BICR, Blinded Independent Central Review; EORTC, European Organization for Research and Treatment of Cancer; FAS, full analysis set; q3w, once every three weeks; QLQ-C30, Quality of Life Questionnaire - Core 30; QLQ-LC13, Quality of Life Questionnaire – Lung Cancer Module 13; RECIST, Response Evaluation Criteria in Solid Tumors; WES, whole exome sequencing

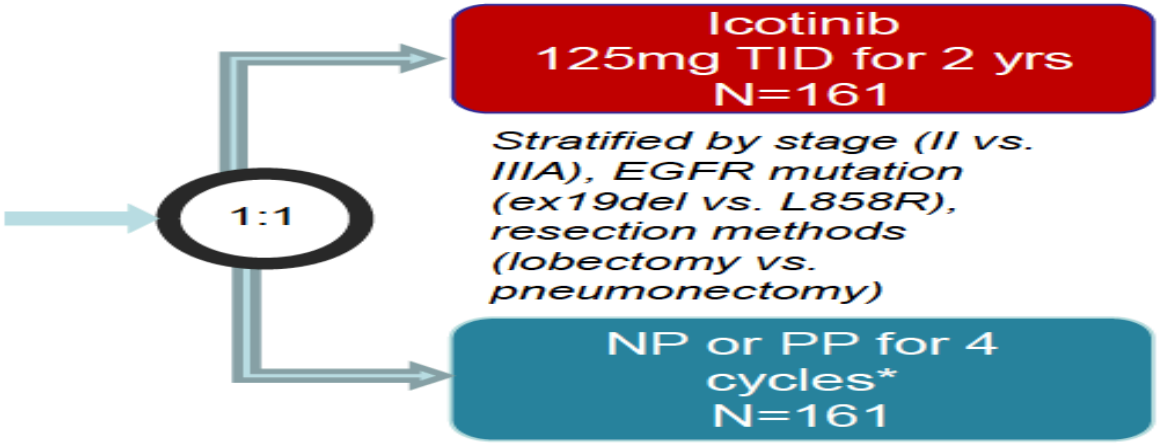
TARGETED THERAPY

Icotinib versus chemotherapy as adjuvant treatment for stage II–IIIA EGFR-mutant NSCLC (EVIDENCE): a randomized, open-label, phase 3 study

Dr. Caicun Zhou

Shanghai Pulmonary Hospital & Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China

- Patients with completely resected stage II-IIIA NSCLC
- Primary NSCLC with *EGFR* ex19del or L858R
- Aged ≥ 18 yrs and < 70 yrs
- ECOG PS 0-1
- N=322

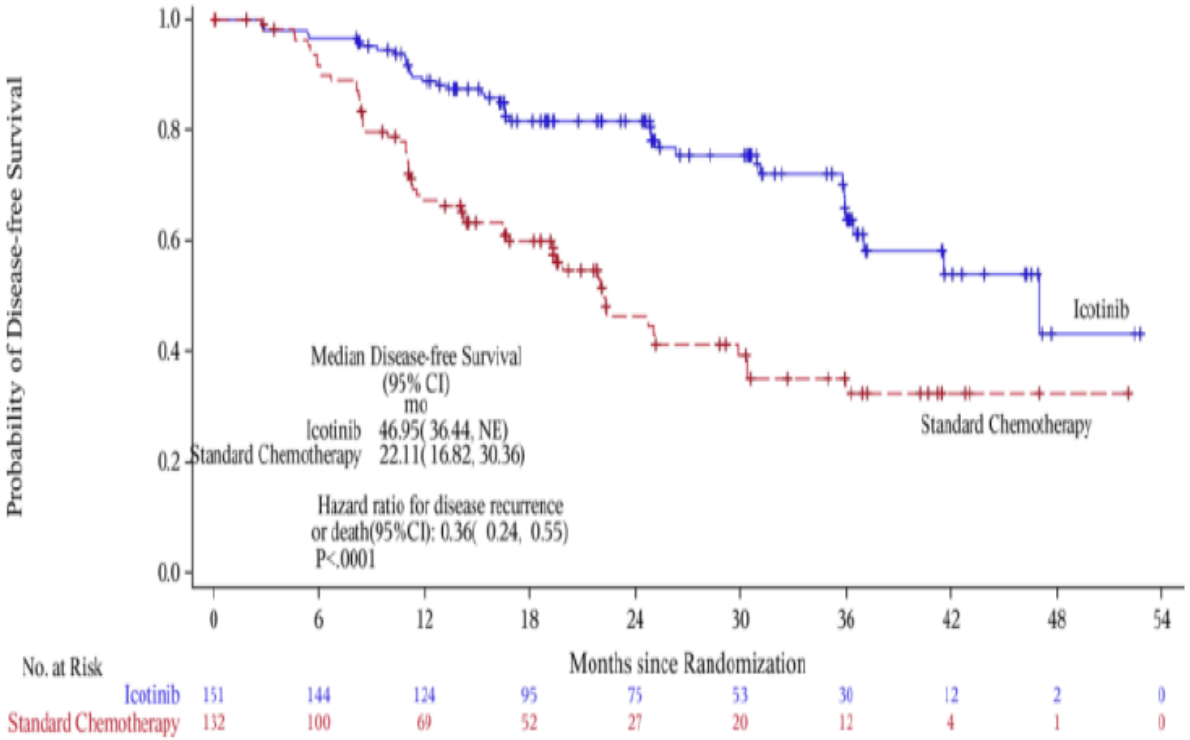


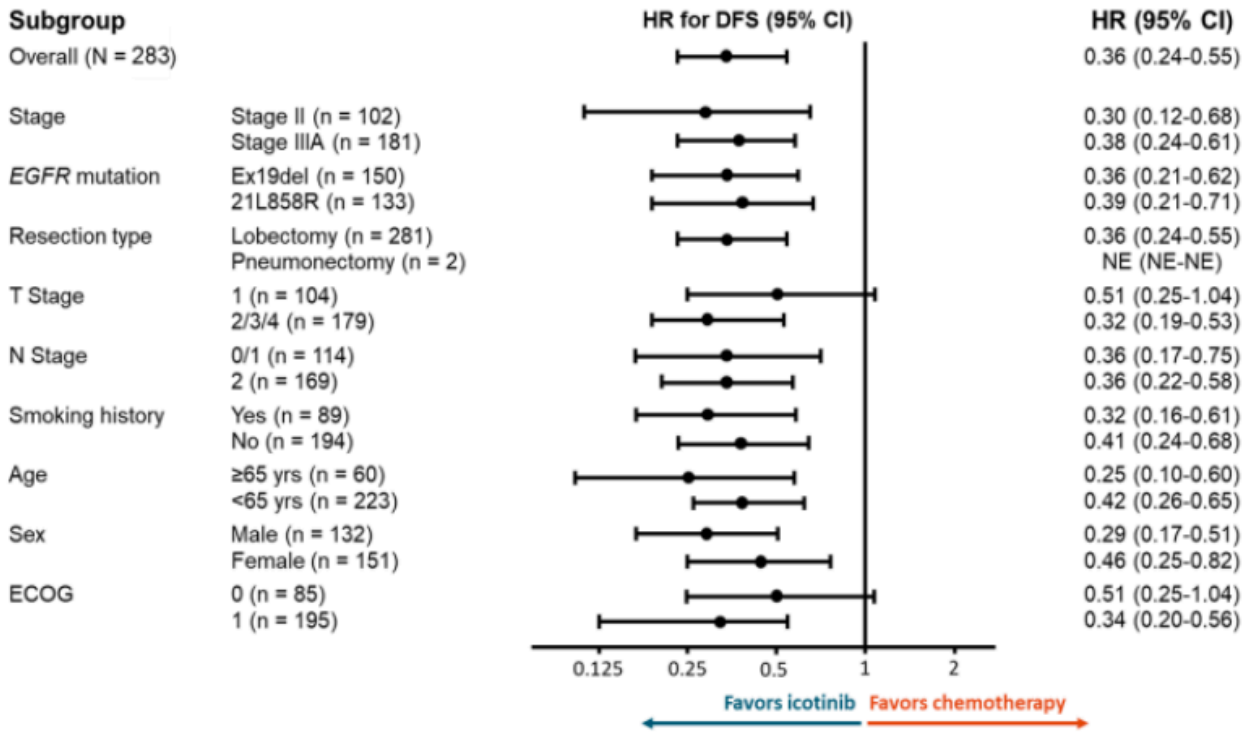
*cisplatin plus vinorelbine for adenocarcinoma or squamous carcinoma, cisplatin plus pemetrexed for non-squamous carcinoma

- Primary endpoint: DFS
- Secondary endpoints: DFS rates at Yrs 3, and 5; OS; safety
- Data cutoff: 31st Mar, 2020

EVIDENCE: DFS

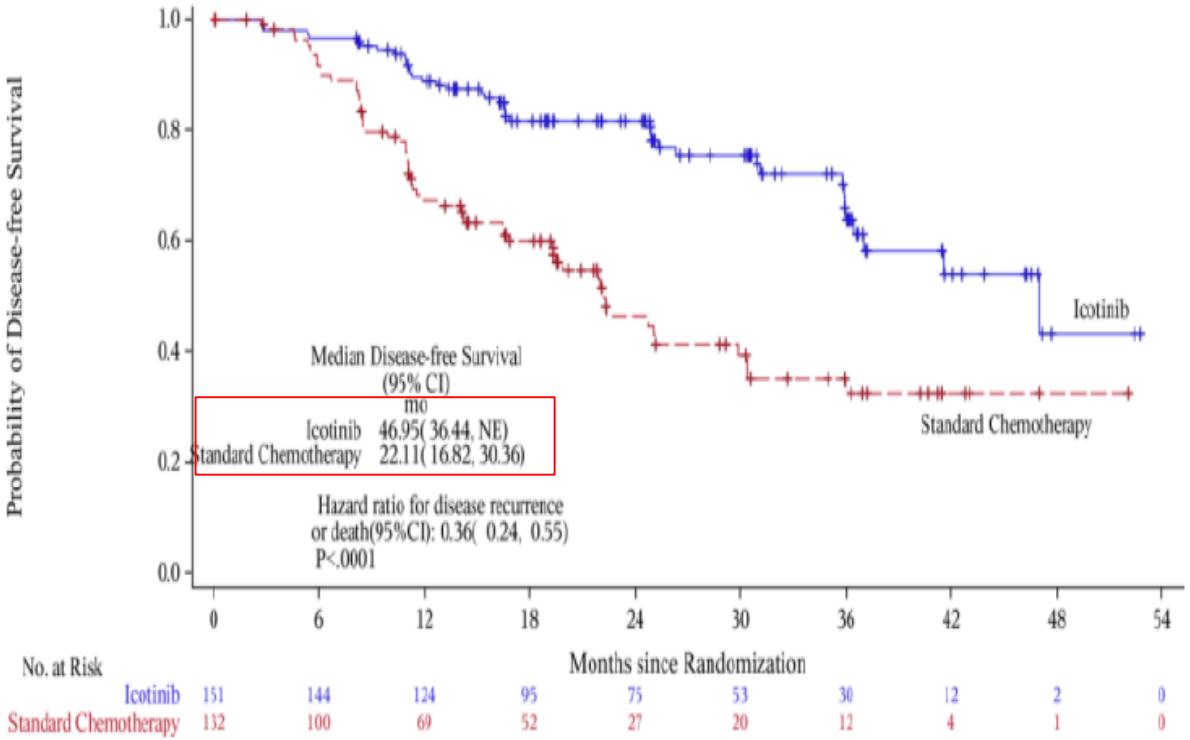
- Adjuvant icotinib significantly prolonged DFS vs chemo in stage II-IIIA disease (*P* < .0001)

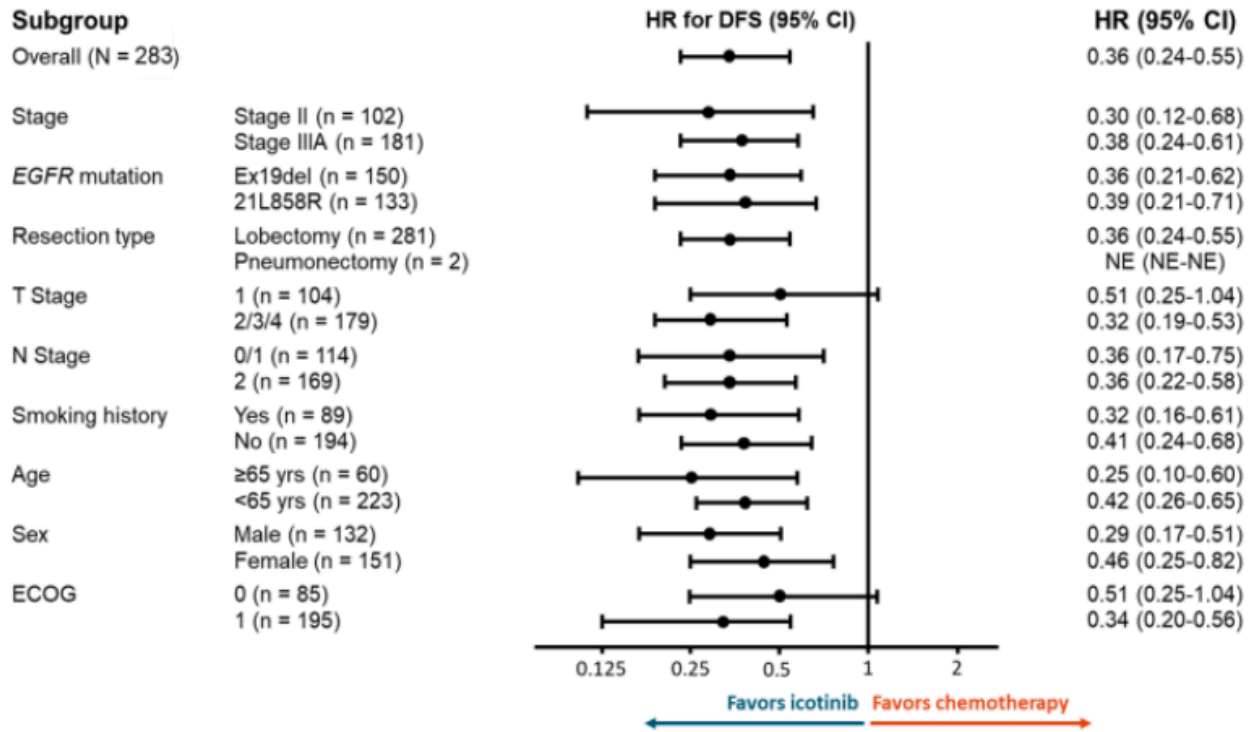




EVIDENCE: DFS

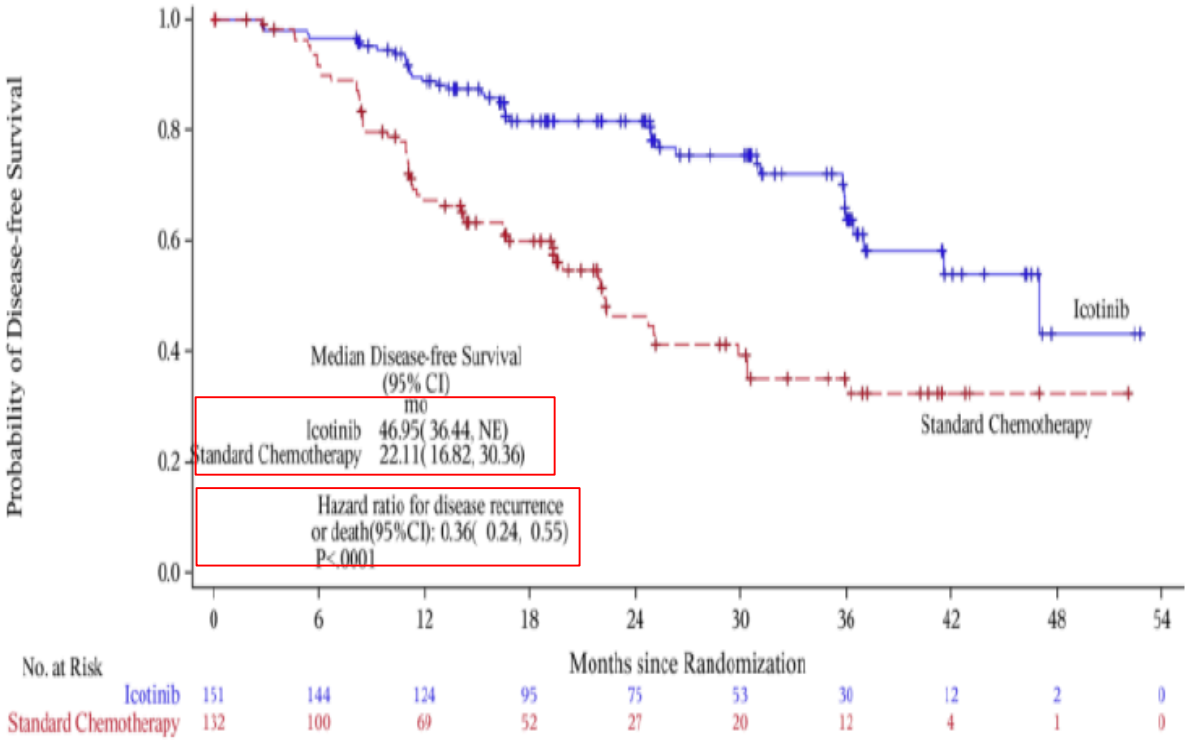
- Adjuvant icotinib significantly prolonged DFS vs chemo in stage II-IIIA disease (*P* < .0001)

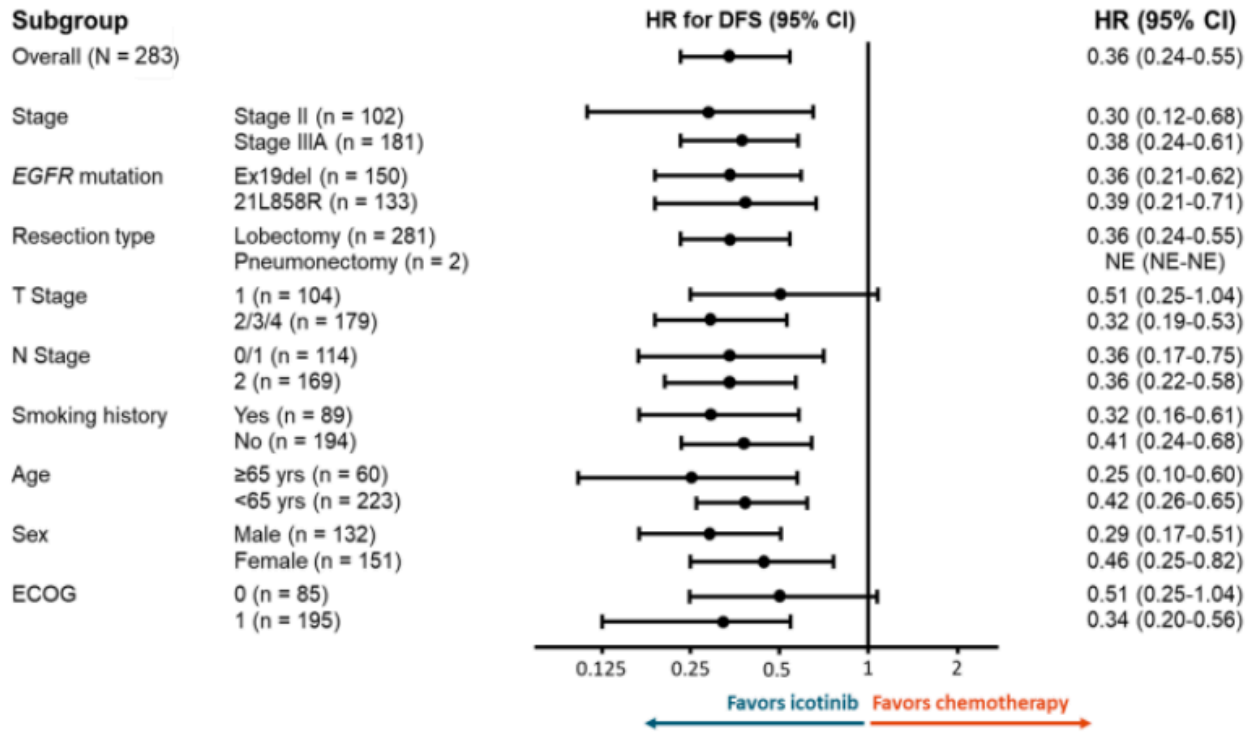




EVIDENCE: DFS

- Adjuvant icotinib significantly prolonged DFS vs chemo in stage II-IIIA disease (*P* < .0001)





Event	Icotinib (N=156)		Chemotherapy (N=139)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	Number of patients (percent)			
Any adverse event	139 (89.1)	17 (11.0)	136 (97.8)	85 (61.2)
Treatment-related adverse event	119 (76.3)	7 (4.5)	135 (97.1)	83 (59.7)
Rash	60 (38.5)	3 (1.9)	2 (1.4)	0
Diarrhea	31 (19.9)	1 (0.6)	7 (5.0)	0
Elevated alanine aminotransferase level	29 (18.6)	0	21 (15.1)	1 (0.7)
Dry skin	12 (7.7)	1 (0.6)	0	0
γ-glutamyltransferase increased	7 (4.4)	0	11 (7.9)	1 (0.7)
Cough	5 (3.2)	0	7 (5.0)	1 (0.7)
Thrombocytopenia	3 (1.9)	0	29 (20.9)	4 (2.9)
Neutropenia	3 (1.9)	0	96 (69.1)	57 (41.0)
Leukopenia	2 (1.3)	0	84 (60.4)	27 (19.4)
Nausea	2 (1.3)	0	82 (59.0)	10 (7.2)
Abdominal distention	2 (1.3)	0	9 (6.5)	3 (2.2)
Chest discomfort	1 (0.6)	0	7 (5.0)	1 (0.7)
Decreased appetite	1 (0.6)	0	23 (16.5)	2 (1.4)
Hypokalemia	1 (0.6)	0	11 (7.9)	4 (2.9)
Vomiting	1 (0.6)	0	71 (51.1)	18 (12.9)
Constipation	0	0	21 (15.1)	1 (0.7)
Hyponatremia	0	0	10 (7.2)	4 (2.9)
Feed intake reduction	0	0	9 (6.5)	1 (0.7)
Fatigue	0	0	29 (20.9)	3 (2.2)
Bone marrow failure	0	0	10 (7.2)	5 (3.6)
Anemia	0	0	55 (39.6)	9 (6.5)
Lymphocyte decrease	0	0	7 (5.0)	1 (0.7)

- Median duration of treatment:

  Icotinib: 22.2 mos (range: 1.1-27.8)

  Chemo: 2.8 mos (range: 0.7-3.6)

- The most common grade 3/4 treatment-related AEs in icotinib group are rash (1.9%), which is not observed in chemotherapy group. While in the chemotherapy group, the most common grade 3/4 treatment-related AEs are neutropenia (41.0%), leucopenia (19.4%), vomiting (12.9%) and nausea (7.2%), which are not observed in icotinib group

- No ILD occurred in each group

Adjuvant Icotinibmay provides a new treatment option for patients EGFRmut early stage NSCLC after complete resection

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CONQUERING THORACIC CANCERS WORLDWIDE

Postoperative chemotherapy use and outcomes from ADAURA: Osimertinib as adjuvant therapy for resected EGFR mutated NSCLC

Yi-Long Wu[1], Thomas John[2], Christian Grohe[3], Margarita Majem[4], Jonathan W Goldman[5], Sang-We Kim[6], Terufumi Kato[7], Konstantin Laktionov[8], Huu Vinh Vu[9], Zhijie Wang[10], Shun Lu[11], Kye Young Lee[12], Charuwan Akewanlop[13], Chong-Jen Yu[14], Filippo de Marinis[15], Laura Bonanno[16], Manuel Domine[17], Frances A Shepherd[18], Lingmin Zeng[19], Ajlan Atasoy[20], Roy S Herbst[21], Masahiro Tsuboi[22]

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ADAURA Phase III double-blind study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO PS 0 / 1
Confirmed primary non-squamous NSCLC
Ex19del / L858R‡
MRI or CT scan of the brain prior to surgery or randomization
Complete resection with negative margins¶
Maximum interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Adjuvant chemotherapy use was per physician and patient choice, and should have consisted of a platinum-based doublet for ≤4 cycles

Stratification by:
stage
(IB vs II vs IIIA)
EGFRm
(Ex19del vs L858R)
race
(Asian vs non-Asian)

Osimertinib 80 mg, once daily

Placebo, once daily

Planned treatment duration: three years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

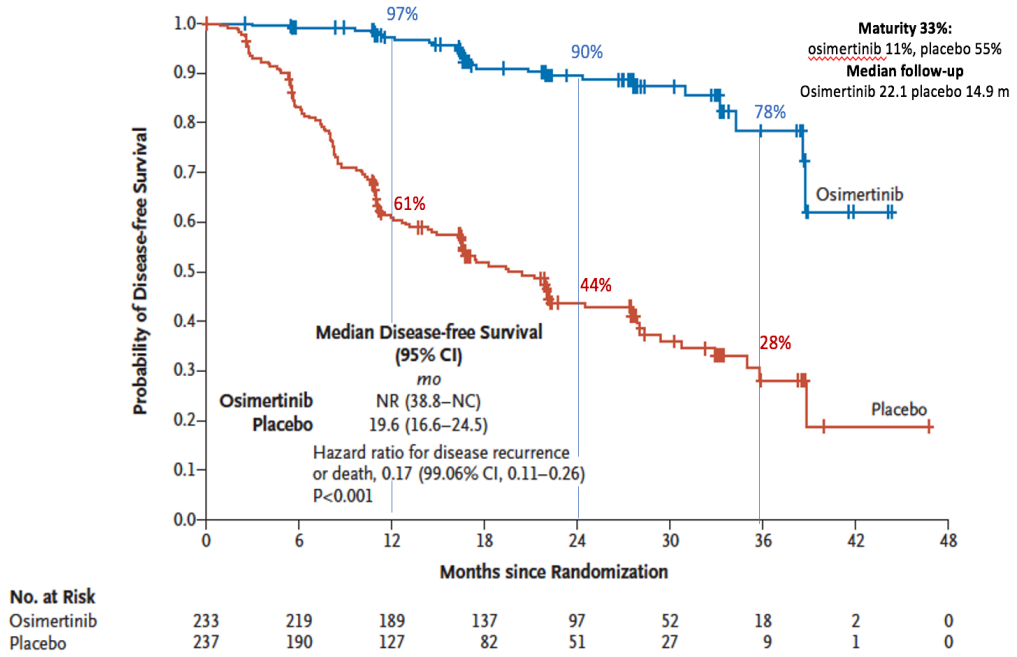
Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

- The primary and key secondary endpoints of DFS§ in stage II / IIIA patients and the overall population, respectively, have been reported previously[1]
- **Here we report an exploratory analysis of adjuvant chemotherapy use and outcomes in ADAURA**

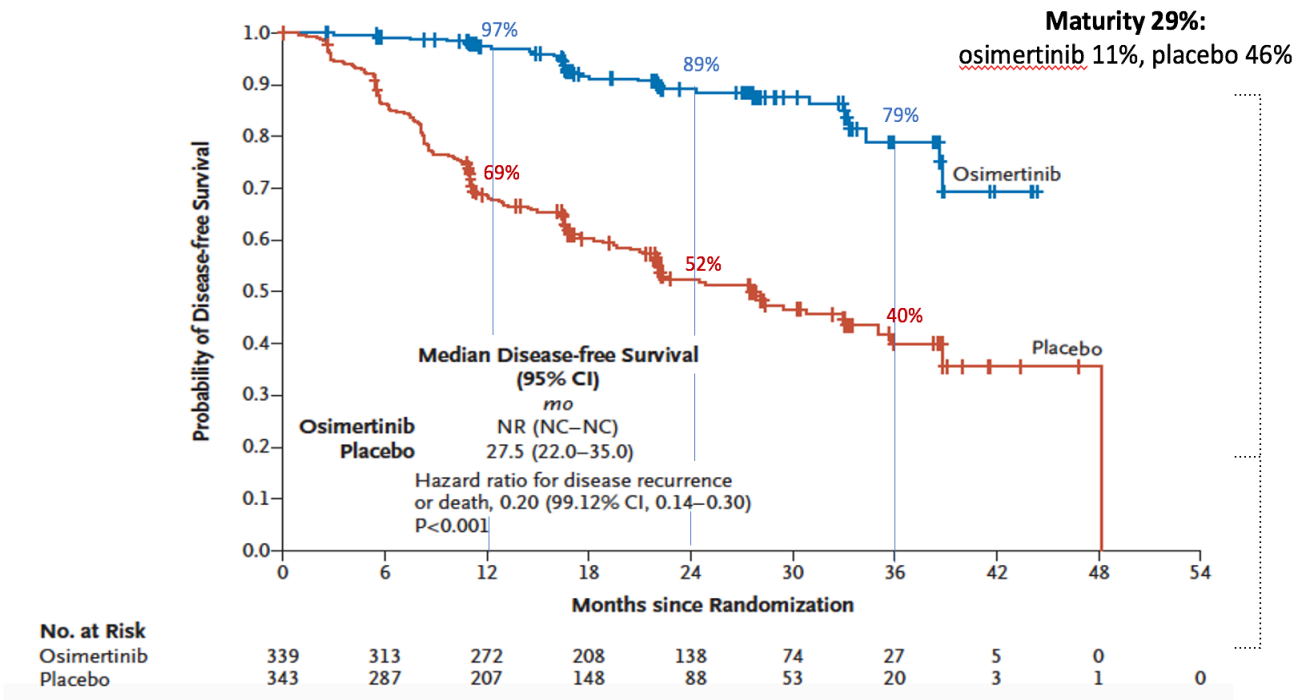
1. Wu et al. N Engl J Med 2020;383:1711–23. NCT02511106; ADAURA data cut-off: January 17, 2020.
*AJCC 7th edition; disease staging based on electronic case report forms for baseline characteristics data, and interactive voice response system for efficacy data (per statistical analysis plan);
†Prior, 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; §By investigator assessment.
AJCC, American Joint Committee on Cancer; CT, computed tomography; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; MRI, magnetic resonance imaging; PS, performance status; WHO, World Health Organization.

ADAURA DFS

Primary endpoint: DFS in patients with stage II/IIIA



Secondary endpoint: DFS in the overall population stage (IB/II/IIIA)



Adjuvant chemotherapy use

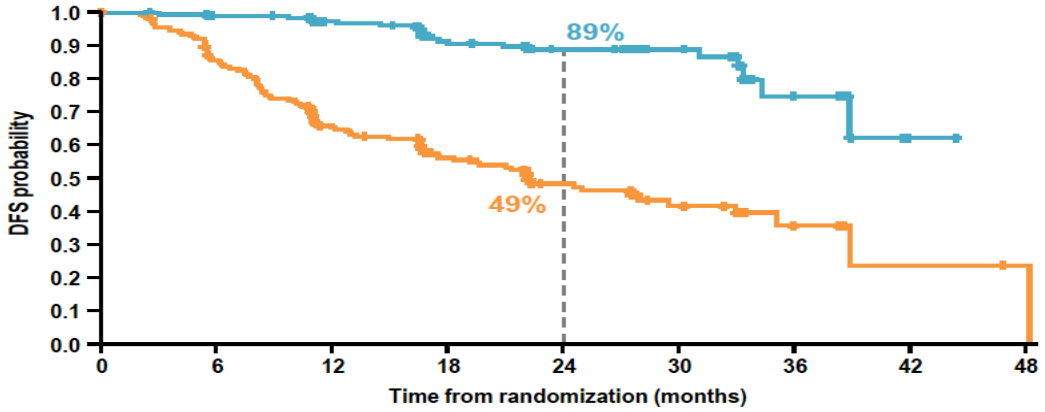
- Overall, 410 / 682 (60%) patients received adjuvant chemotherapy, for a median duration of 4.0 (Q1: 4.0, Q3: 4.0) cycles, consistent across treatment arms
- The majority of patients (409 / 410)* received platinum-based† chemotherapy, most with stage II / IIIA disease (76%), and fewer with stage IB 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.

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

With adjuvant chemotherapy



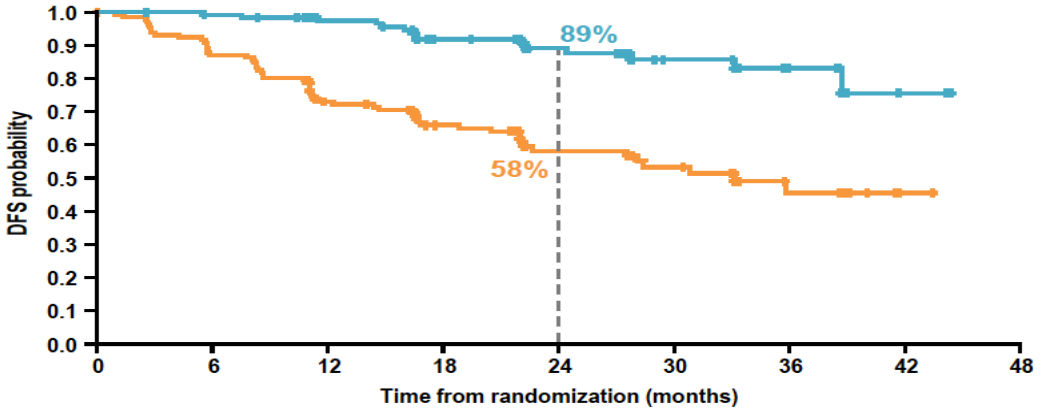
No. at risk

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 (0.10, 0.26)**
Placebo (n=207)	103 (50)	22.1 (17.4, 32.9)	

Maturity 30%: osimertinib 11%, placebo 50%

Without adjuvant chemotherapy

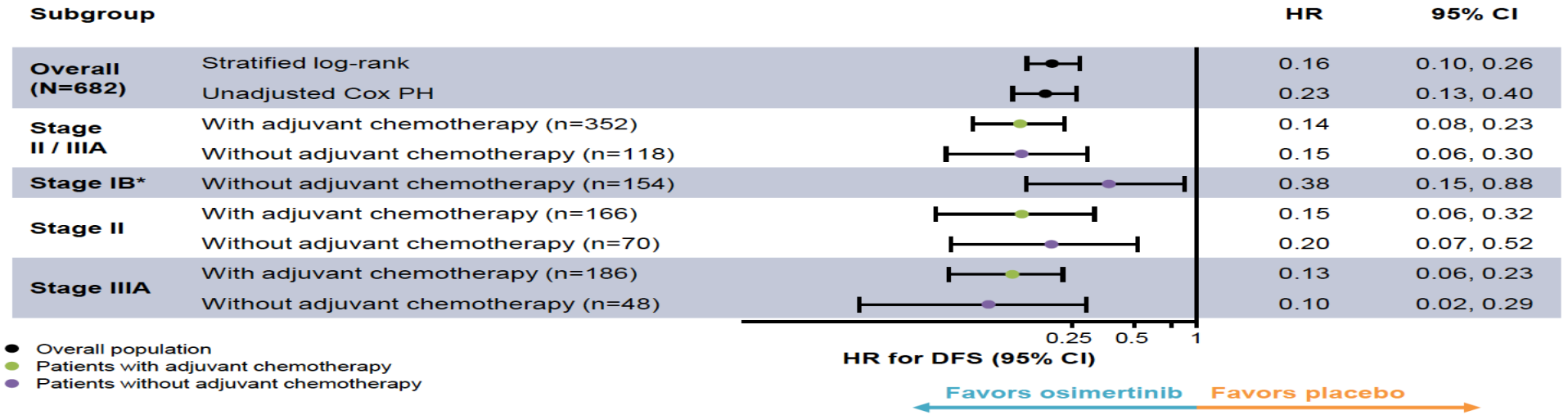


Osimertinib	136	123	106	87	58	34	13	4	0
Placebo	136	115	88	68	42	29	13	1	0

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

Maturity 26%: osimertinib 11%, placebo 41%

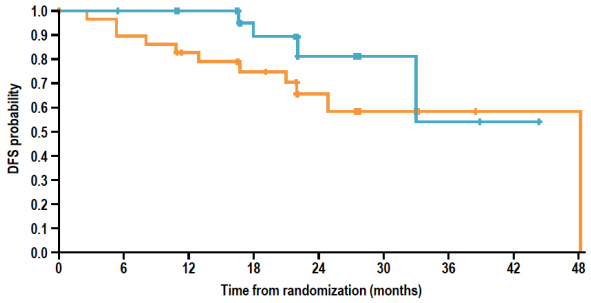
Wu, Tsuboi et al. N Engl J Med 2020;383:1711–23. ADAURA data cut-off: January 17, 2020.
Tick marks indicate censored data. NC, not calculable, NR, not reached.



ADAURA data cut-off: January 17, 2020.
Performed using a Cox proportional hazards model including treatment, subgroup and a treatment-by-subgroup interaction term.
*Subgroup categories with less than 20 events, such as patients with stage IB disease with adjuvant chemotherapy, were excluded from the analysis. A HR of less than 1 favors osimertinib.

DFS in patients with and without adjuvant chemotherapy (stage IB)

With adjuvant chemotherapy



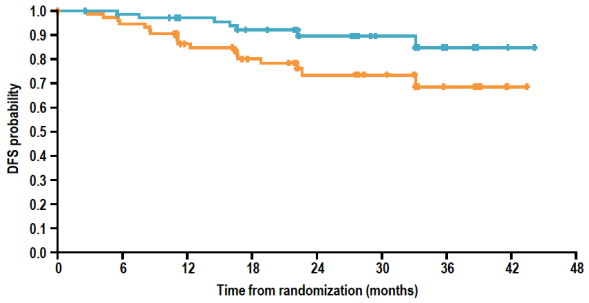
No. at risk

Osimertinib	28	26	24	17	8	3	2	1	0
Placebo	30	26	22	18	9	5	2	1	1

	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n=28)	4 (14)	NR (33.0, NC)	**NC**
Placebo (n=30)	11 (37)	48.2 (21.0, 48.2)	**(NC, NC)**

Maturity 26%: osimertinib 14%, placebo 37%

Without adjuvant chemotherapy



No. at risk

Osimertinib	78	68	59	54	33	19	7	2	0
Placebo	76	71	58	48	28	21	9	1	0

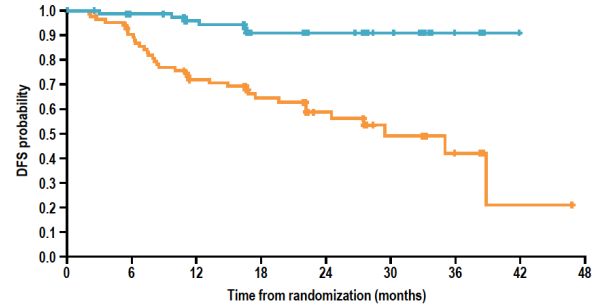
	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n=78)	7 (9)	NR (NC, NC)	**0.38**
Placebo (n=76)	18 (24)	NR (NC, NC)	**(0.15, 0.88)**

Maturity 16%: osimertinib 9%, placebo 24%

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

DFS in patients with and without adjuvant chemotherapy (stage II)

With adjuvant chemotherapy



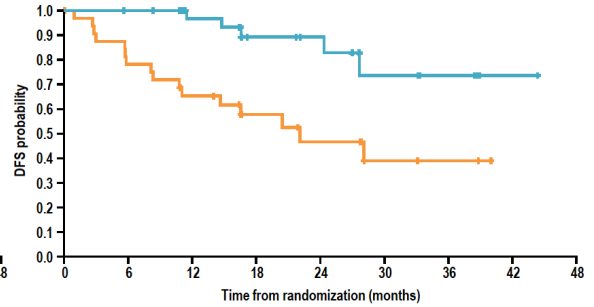
No. at risk

Osimertinib	81	74	62	50	33	20	5	0	
Placebo	85	74	55	38	23	11	5	1	0

	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n=81)	6 (7)	NR (NC, NC)	**0.15**
Placebo (n=85)	36 (42)	29.4 (22.1, NC)	**(0.06, 0.32)**

Maturity 25%: osimertinib 7%, placebo 42%

Without adjuvant chemotherapy



No. at risk

Osimertinib	37	36	29	19	14	8	4	1	0
Placebo	33	25	19	11	8	4	2	0	

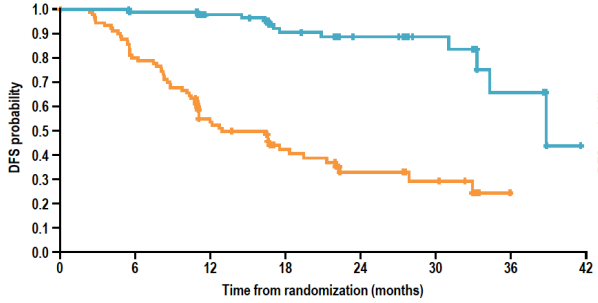
	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n=37)	5 (14)	NR (27.7, NC)	**0.20**
Placebo (n=33)	16 (48)	22.1 (10.8, NC)	**(0.07, 0.52)**

Maturity 30%: osimertinib 14%, placebo 48%

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

DFS in patients with and without adjuvant chemotherapy (stage IIIA)

With adjuvant chemotherapy



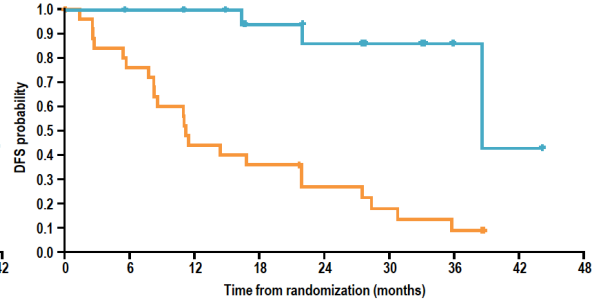
No. at risk

Osimertinib	94	90	80	54	39	17	7	0
Placebo	92	72	42	24	14	8	0	

	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n=94)	12 (13)	38.8 (34.3, NC)	**0.13**
Placebo (n=92)	56 (61)	12.9 (10.9, 19.4)	**(0.06, 0.23)**

Maturity 37%: osimertinib 13%, placebo 61%

Without adjuvant chemotherapy



No. at risk

Osimertinib	21	19	18	14	11	7	2	1	0
Placebo	27	19	11	9	6	4	2	0	

	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n=21)	3 (14)	38.6 (38.6, NC)	**0.10**
Placebo (n=27)	22 (81)	11.2 (8.2, 21.9)	**(0.02, 0.29)**

Maturity 52%: osimertinib 14%, placebo 81%

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

DFS benefit with osimertinib versus placebo was observed irrespective of whether patients received prior chemotherapy or not, supporting that adjuvant osimertinib will provide a highly effective treatment for patients with stage IB / II / IIIA EGFRm NSCLC after resection, with or without adjuvant chemotherapy as indicated

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CONQUERING THORACIC CANCERS WORLDWIDE

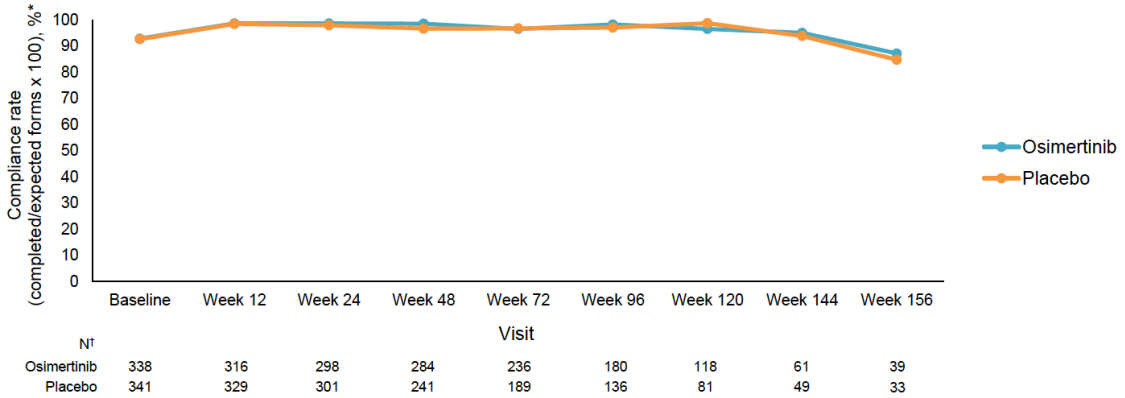
Patient-reported outcomes from ADAURA: Osimertinib as adjuvant therapy in patients with resected EGFR mutated (EGFRm) NSCLC

Margarita Majem[1], Jonathan W Goldman[2], Thomas John[3], Christian Grohe[4], Konstantin Laktionov[5], Sang-We Kim[6],Terufumi Kato[7], Huu Vinh Vu[8], Shun Lu[9], Kye Young Lee[10], Charuwan Akewanlop[11] , Chong-Jen Yu[12], Filippo de Marinis[13], Laura Bonanno[14], Manuel Domine[15], Frances A Shepherd[16] , Lingmin Zeng[17], Dakshayini Kulkarni[18], Nenad Medic[19], Masahiro Tsuboi[20], Roy S Herbst[21], Yi-Long Wu[22]

[1]Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [2]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA; [3]Department of Medical Oncology, Austin Health, Melbourne, Australia; [4]Klinik für Pneumologie - Evangelische Lungenklinik Berlin Buch, Berlin, Germany; [5]Federal State Budgetary Institution "N.N.Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia; [6]Department of Oncology, Asan Medical Center, Seoul, South Korea; [7]Department of Thoracic Oncology, Kanagawa Cancer Center, Asahi Ward, Yokohama, Japan; [8]Department Thoracic Surgery, Choray Hospital, Ho Chi Minh City, Vietnam; [9]Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [10]Precision Medicine Lung Cancer Center, Konkuk University Medical Center, Seoul, Republic of Korea; [11]Division of Medical Oncology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand; [12]Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [13]Thoracic Oncology Division, European Institute of Oncology (IEO), IRCCS, Milan, Italy; [14]Medical Oncology 2, Istituto Oncologico Veneto IOV IRCCS, Padova, Italy; [15]Department of Oncology, Hospital Universitario Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain; [16]Department of Medical Oncology and Hematology, University Health Network, Princess Margaret Cancer Centre and the University of Toronto, Toronto, Ontario, Canada; [17]Late Oncology Statistics, AstraZeneca, Gaithersburg, MD, USA; [18]Late oncology R&D, AstraZeneca, Cambridge, UK; [19]AstraZeneca Oncology Business Unit, Academy House, Cambridge, UK; [20]Department of Thoracic Surgery and Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [21]Medical Oncology, Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA; [22]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China.

Compliance with the SF-36 health survey over time

- Over time, compliance rates with the SF-36 health survey were high (≥85%) in both the osimertinib arm and the placebo arm



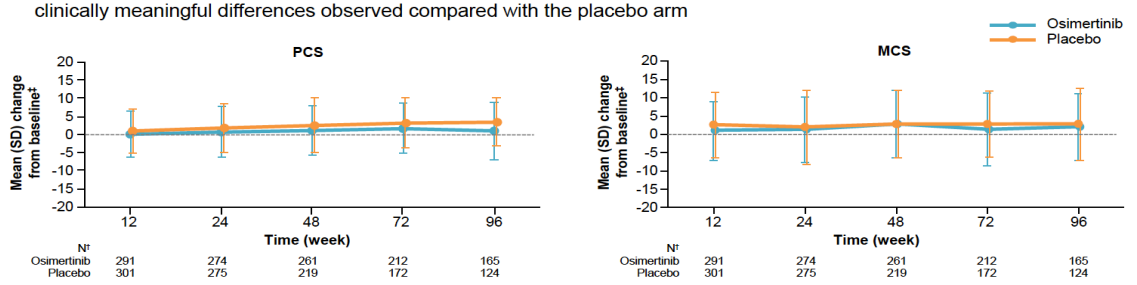
N†								
Osimertinib	338	316	298	284	236	180	118	61	39
Placebo	341	329	301	241	189	136	81	49	33

- At data cutoff, median duration of total treatment exposure was 22.5 months with osimertinib and 18.7 months with placebo[1]
- 12% vs 10% of patients receiving osimertinib vs placebo had completed study treatment (3 years) at data cutoff[1]

*Number of evaluable forms (n) divided by the number of expected forms (N), multiplied by 100. †Number of expected forms. 1. Wu, Tsuboi et al. N Engl J Med 2020;383:1711–1723. Data cutoff: 17 Jan 2020

Adjusted mean change in SF-36 physical (PCS) and mental (MCS) component summary T-scores

- In disease-free patients receiving osimertinib, SF-36 PCS and MCS were maintained from baseline to week 96,* with no clinically meaningful differences observed compared with the placebo arm



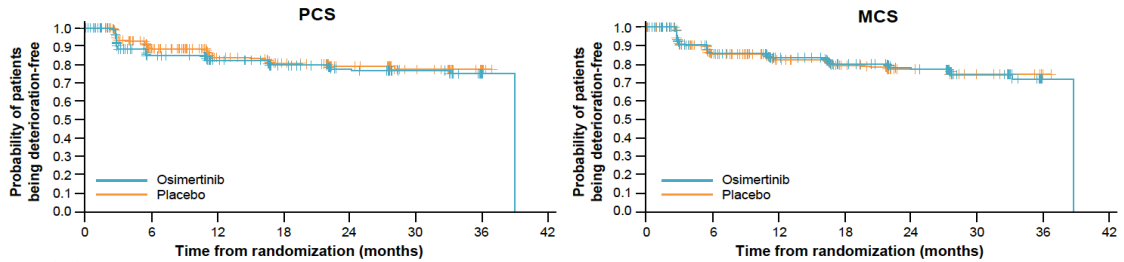
N†					
Osimertinib	291	274	261	212	165
Placebo	301	275	219	172	124

	Mixed model of repeated measures – adjusted mean change from baseline (95% CI)			Definition of clinically meaningful change based on the 3rd edition of the SF-36 scoring manual
SF-36 component	Osimertinib	Placebo	Osimertinib - placebo	
PCS	1.13 (0.54, 1.72)	2.31 (1.70, 2.91)	-1.18 (-2.02, -0.34)	±2
MCS	1.34 (0.60, 2.08)	2.68 (1.92, 3.44)	-1.34 (-2.40, -0.28)	±3

*Change from baseline was examined until Week 96, to ensure balanced comparison between arms, given the earlier discontinuation in completing the SF-36 health survey in the placebo arm, due to earlier events of disease recurrence. †Number of patients with data available at each visit. ‡Error bars represent SD. CI, confidence interval. Data cutoff: 17 Jan 2020

Time to deterioration of physical (PCS) and mental (MCS) component summary

- During the disease-free period, the majority of patients (>80% of patients across both arms) did not experience a clinically meaningful deterioration in PCS or MCS
- For those patients who had deterioration, there were no differences in TTD of PCS (HR 1.17 [95% CI 0.82, 1.67])* or MCS (HR 0.98 [95% CI 0.70, 1.39]) between osimertinib and placebo†



No. of patients at risk								
Osimertinib	339	245	201	145	93	50	8	0
Placebo	343	249	167	117	67	40	8	0
Osimertinib	339	245	200	143	89	43	8	0
Placebo	343	239	164	116	66	37	7	0

*HR <1 favors osimertinib. †Comparable results were obtained using pre-specified values for clinically important differences defined per the 2nd edition of the SF-36 scoring manual (2002) in the overall patient population (TTD PCS HR 1.25 [95% CI 0.90, 1.73]; TTD MCS HR 0.95 [95% CI 0.69, 1.30]) and in stage II / IIIA patients (per-protocol analysis: TTD PCS HR 1.43 [95% CI 0.96, 2.13]; TTD MCS HR 0.9 [95% CI 0.61, 1.33]). HR, hazard ratio. Data cutoff: 17 Jan 2020

- **Overall, HRQoL was maintained during adjuvant osimertinib treatment with no clinically meaningful differences vs placebo, despite prolonged treatment**
- **Adjuvant osimertinib, with or without prior adjuvant chemotherapy, provided a significant DFS benefit without affecting HRQoL**

Estudios Fase II/III de tratamiento adyuvante con EGFR TKIs

Study	Phase	Population	n	Arm(s)	Patients Receiving Adjuvant Chemotherapy (%)	Median DFS (mos)	2-Year DFS	3-Year DFS	Median OS (mos)
RADIANT [9]	III	IB-IIIA NSCLCs, EGFR-positive by IHC and/or FISH	623 vs. 250	Erlotinib for 2 years vs. placebo	50.6% vs. 57.1%	50.5 vs. 48.2 (HR 0.90)	75% vs. 54%	N.R.	Not reached vs. Not reached (HR 1.09)
BR19 [10]	III	IB-IIIA NSCLCs	251 vs. 252	Gefitinib for 2 years vs. placebo	17% vs. 17%	4.2 years vs. Not reached (HR 1.22)	N.R.	N.R.	5.1 years vs. Not reached (HR 1.24)
SELECT [11]	II	IA-IIIA EGFR-mutated NSCLC	100	Erlotinib for 2 years	N.R.	Not reached	88%	N.R.	Not reached
CTONG1104 ADJUVANT [12]	III	II-IIIA EGFR-mutated NSCLC	111 vs. 111	Gefitinib for 2 years vs. vinorelbine/cisplatin	0% vs. 100%	30.8 vs. 19.8 (HR 0.56)	N.R.	39.6% vs. 32.5%	75.5 vs. 62.8 (HR 0.92)
EVAN [20]	II	IIIA EGFR-mutated NSCLC	51 vs. 51	Erlotinib for 2 years vs. vinorelbine/cisplatin	0% vs. 100%	42.4 vs. 21.0 (HR 0.268)	81.4% vs. 44.6%	54.2% vs. 19.8%	Not reached vs. Not reached (HR 0.165)
ADAURA [21]	III	IB-IIIA EGFR-mutated NSCLC	339 vs. 343	Osimertinib for 3 years vs. placebo	55% vs. 56%	Not reached vs. 20.4 (HR 0.17) *	90% * vs. 44% *	80% * vs. 28% *	Not reached vs. Not reached (HR 0.40) *
EVIDENCE. Zhou C IASLC20	III	II-IIIA EGFR mutated. NSCLC	161 161	Icotinib for 2 y Pl –VNR or PL-PEM.	NR NR	46.95 22.11 (HR 0.36)	NR NR	NR NR	Not reached Not reached

Ongoing phase II–III neoadjuvant and adjuvant trials with tyrosine kinase inhibitors (TKIs).

Trial	Phase	Design	Population	Arm(s)	Primary Outcome	Clinical Trial Identification
ALCHEMIST	III	adjuvant	IB-IIIA NSCLCs, EGFR-mutated NSCLC	erlotinib for 2 years vs. placebo	OS	NCT02194738
ALCHEMIST	III	adjuvant	IB-IIIA NSCLCs, ALK-rearranged NSCLC	crizotinib for 2 years vs. placebo	OS	NCT02194738
ALINA	III	adjuvant	IB-IIIA NSCLCs, ALK-rearranged NSCLC	alectinib for 2 years vs. chemotherapy	DFS	NCT03456076
EMERGING	II	Neoadjuvant + adjuvant	IIIA EGFR-mutated NSCLCs	erlotinib for 6 weeks then 1 year post-op vs. cisplatin-gemcitabine	ORR	NCT01407822
NCT03203590	III	neoadjuvant	II-IIIA EGFR-mutated NSCLC	gefinitib for 8 weeks vs. carboplatin-vinorelbine	2 year DFS	NCT03203590
NeoADAURA	III	neoadjuvant	II-IIIA EGFR-mutated NSCLC	osimertinib +/− platinum-pemetrexed vs. platinum-pemetrexed	MPR	NCT04351555
NCT04302025	II	Neoadjuvant +/− adjuvant	IB-IIIB NSCLC with altered ALK, ROS1, NTRK or BRAF	8 weeks neoadjuvant +/− adjuvant with alectinib, entrectinib or vemurafenib+cobimetinib	MPR	NCT04302025
NCT03088930	II	neoadjuvant	IA-IIIA NSCLC with altered MET, ROS1 or ALK	crizotinib for 6 weeks	ORR	NCT03088930

Abbreviations: DFS, disease-free survival; OS, overall survival; MPR, major pathological response; ORR, objective response rate.

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P03.02

Neoadjuvant osimertinib with/without chemotherapy vs chemotherapy for EGFR mutated resectable NSCLC: NeoADAURA

Masahiro Tsuboi[1], Walter Weder[2], Carles Escriu[3], Collin Blakely[4], Jianxing He[5], Sanja Dacic[6], Yasushi Yatabe[7], Lingmin Zeng[8], Andrew Walding[9], Jamie Chaft[10]

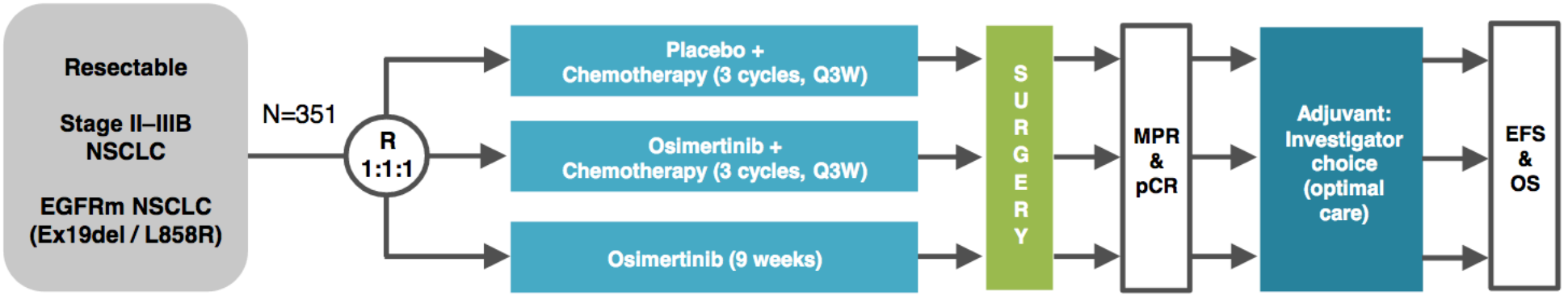
[1]National Cancer Center Hospital East, Kashiwa, Japan; [2]Klinik Bethanien, Zürich, Switzerland; [3]The Clatterbridge Cancer Centre, Liverpool, UK; [4]University of California, San Francisco, CA, USA; [5]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [6]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [7]National Cancer Center, Tokyo, Japan; [8]AstraZeneca, Gaithersburg, MD, USA; [9]AstraZeneca, Alderley Park, UK; [10]Memorial Sloan Kettering Cancer Center, New York, USA

https://bit.ly/3nzebvL

Scan the QR code or visit the link for: a copy of these slides, a mobile-friendly version or a plain language summary

Study design

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

AUC, area under plasma concentration-time curve; Ex19del, Exon 19 deletion; EFS, event-free survival; EGFRm, epidermal growth factor receptor mutation-positive; NSCLC, non-small cell lung cancer; R, randomization, Q3W, every three weeks; QD, once per day; MPR, major pathological response; pCR, complete pathological response; OS, overall survival

Primary endpoint: Major pathological response

Secondary: EFS, pCR, downstaging, DFS, OS, QoL, safety

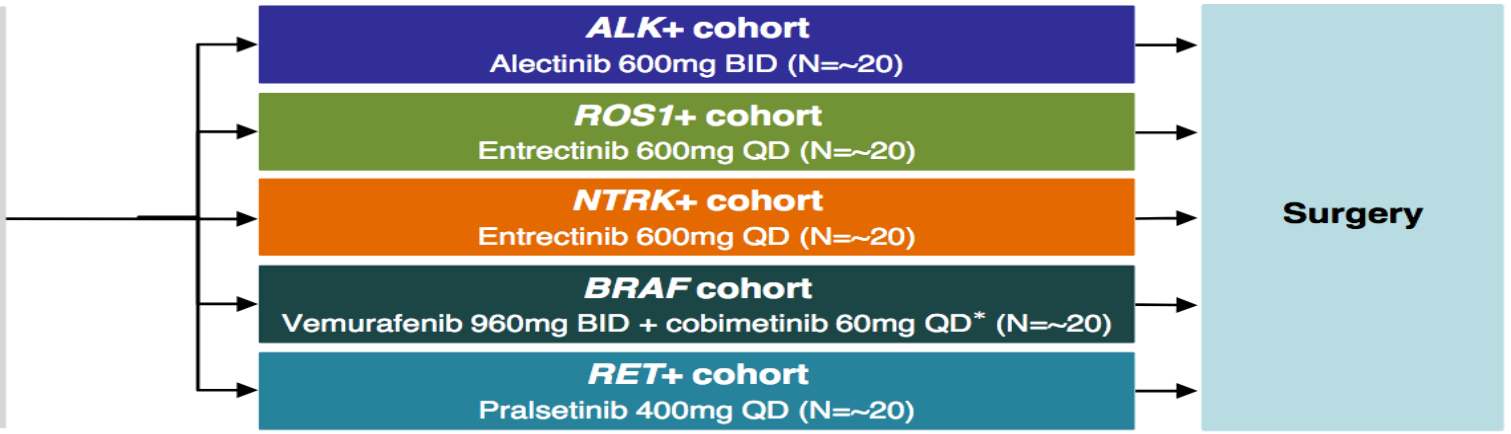
Phase II Study of TKIs as Neo(adjuvant) Therapy in Stage II–III Resectable NSCLC with *ALK*, *ROS1*, *NTRK* or *BRAF V600* Alterations

Jay M. Lee, Ignacio I. Wistuba, Celina Ngiam, Wei Yu, Katja Schulze, Marilia Rocha, Ilze Bara, David P. Carbone, Bruce E. Johnson, David J. Kwiatkowski, Valerie Rusch, Jamie Chaft

NAUTIKA1: study design overview (neoadjuvant treatment)

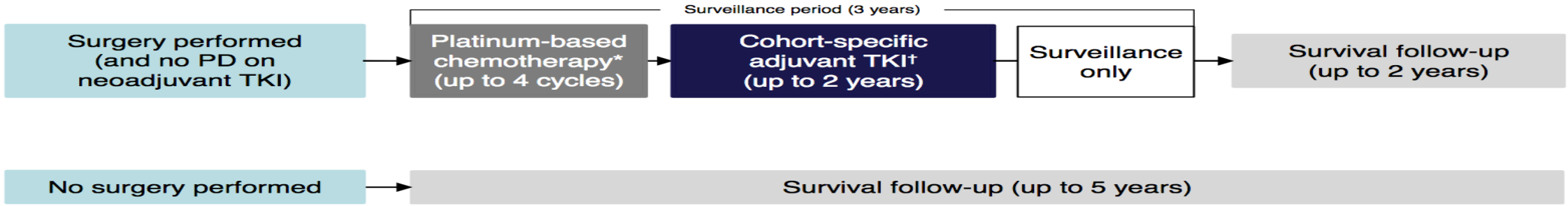
Key eligibility criteria

- Resectable Stage IIA, IIB, IIIA or select IIIB (T3N2) NSCLC
- *ALK+, ROS1+, NTRK+, RET+* or *BRAF V600* mut+
- ECOG PS 0–1
- No prior therapy for lung cancer within 2 years



Neoadjuvant treatment and response assessment

- Patients will be assigned a neoadjuvant therapy based on their driver mutation
  - Patients will receive 8 weeks (2 cycles) of neoadjuvant therapy
- PET/CT scans will be performed at screening and pre-surgery to determine tumour response



Primary endpoint: Major pathological response

Secondary: Pathological regression, ORR, pCR, downstaging, DFS, EFS, OS, Pre-surgery ctDNA clearance rate, S afety

P03.03: MERMAID-1: A Phase III study of adjuvant durvalumab plus chemotherapy in resected NSCLC patients with MRD+ post-surgery

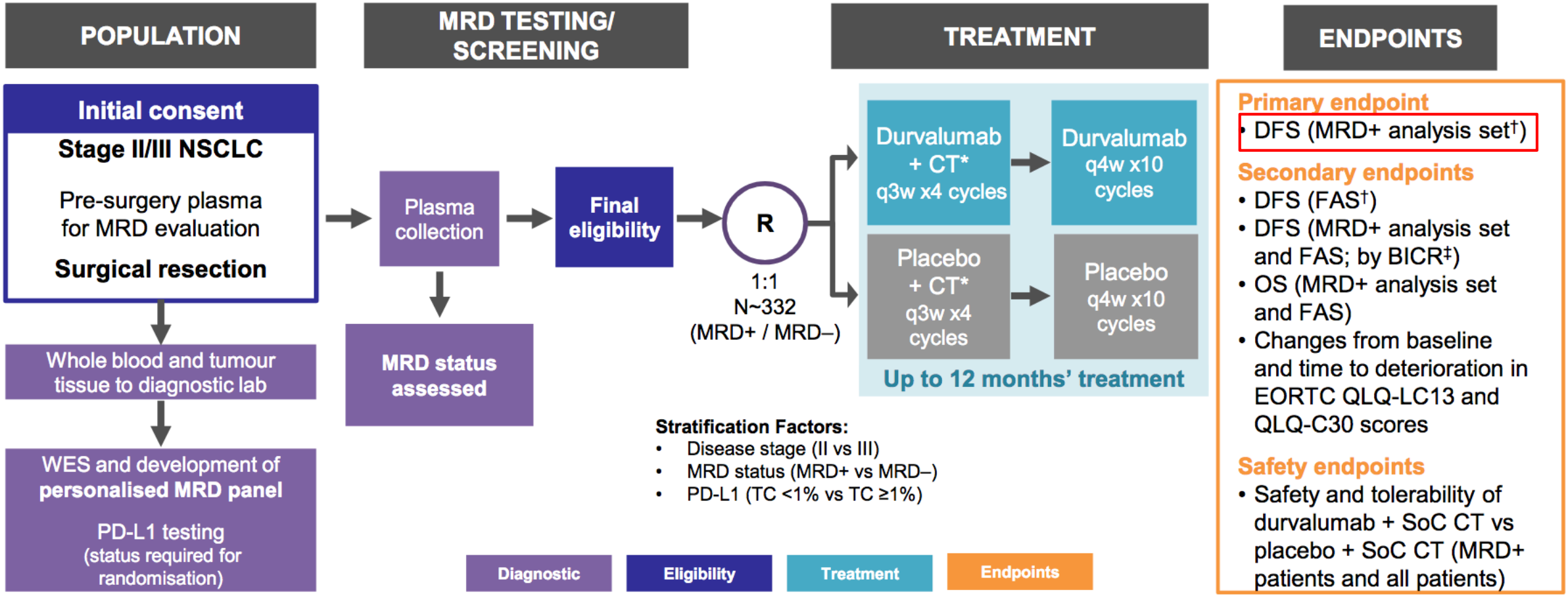
Solange Peters[1], David Spigel[2], Myung-Ju Ahn[3], Masahiro Tsuboi[4], Jamie Chaft[5], David Harpole[6], Glenwood Goss[7], Fabrice Barlesi[8], Chris Abbosh[9], Lynne Poole[10], Rena May[10], Phillip Dennis[10], Charles Swanton[9,11]

[1]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [2]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [3]Sungkyunkwan University School of Medicine, Seoul, Korea; [4]Division of Thoracic Surgery and Oncology National Cancer Center Hospital East, Kashiwa, Japan; [5]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [6]Duke University Medical Center, Durham, NC, USA; [7]The Ottawa Hospital Cancer Centre, Division of Medical Oncology, Ottawa, ON, Canada; [8]Université de la Méditerranée–Assistance Publique Hôpitaux de Marseille, France; [9]The Francis Crick Institute, London, UK; [10]AstraZeneca, Gaithersburg, MD, USA; [11]UCL Hospitals NHS Trust, London, UK

MRD: Minimal residual disease

Study design

MERMAID-1: a phase III, randomised, double-blind, placebo-controlled, parallel-arm, multicentre study



*SoC CT: carboplatin + paclitaxel or cisplatin/carboplatin + pemetrexed, dependent on tumour histology and at investigator's discretion;
†Investigator-assessed by RECIST v1.1; ‡per BICR by RECIST v1.1.

BICR, Blinded Independent Central Review; EORTC, European Organization for Research and Treatment of Cancer; FAS, full analysis set; q3w, once every three weeks; QLQ-C30, Quality of Life Questionnaire - Core 30; QLQ-LC13, Quality of Life Questionnaire – Lung Cancer Module 13; RECIST, Response Evaluation Criteria in Solid Tumors; WES, whole exome sequencing

Conclusiones

- **La positividad de ctDNA en NSCLC completamente resecados se asocia a un mayor riesgo de recurrencia o muerte.**
- **El estudio de biomarcadores nos ayudará a diseñar de manera más eficiente los tratamientos de los pacientes en estadios inicales**
- **Neoadyuvancia con inmunoterapia y sobre todo quimio-inmunoterapia mejora de manera muy significativa las MPR, pCR, downstaging and PFS comparado con controles históricos**
- **La quimioterapia diseñada según niveles de ERCC1 y TS no mejora OS con respecto a tratamiento estándar**
- **Los tratamientos con terapias dirigidas contra EGFR han mostrado en la mayoría de los estudios un aumento significativo en SLP con un mejor perfil de toxicidad**
- **Pendientes de nuevos estudios de neoadyuvancia, adyuvancia con combinaciones de quimioterapia-inmunoterapia y terapias dirigidas**