#IASLCUPDATES

Iniciativa científica de:

GECP lung cancer research

LUNG CANCER UPDATES

IASLC HIGHLIGHTS

7-10 DE SEPTIEMBRE 2019

Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

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Targeted Therapies
Let´s talk about and old friend… EGFR mut

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Con la colaboración de:
Bristol-Myers Squibb
illumina
Lilly

Despite the success of EGFR TKIs…

- Variability of the response…
- Variability of the response duration…
- Some patients do not respond…
- We are not curing anyboy…
- All patients progress…

CAN WE DO IT BETTER?

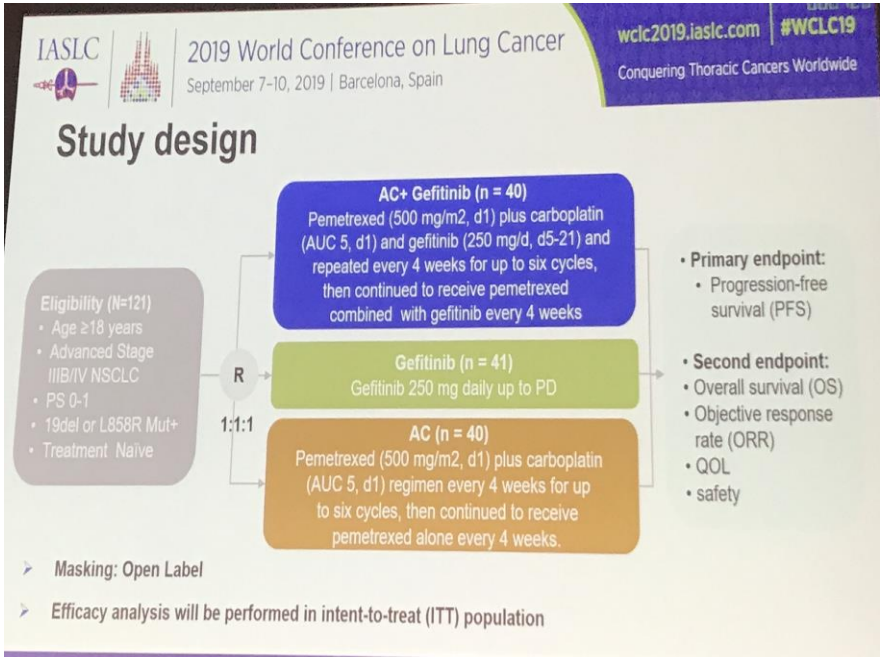
Options for 1st Line Treatment of EGFR M+ NSCLC

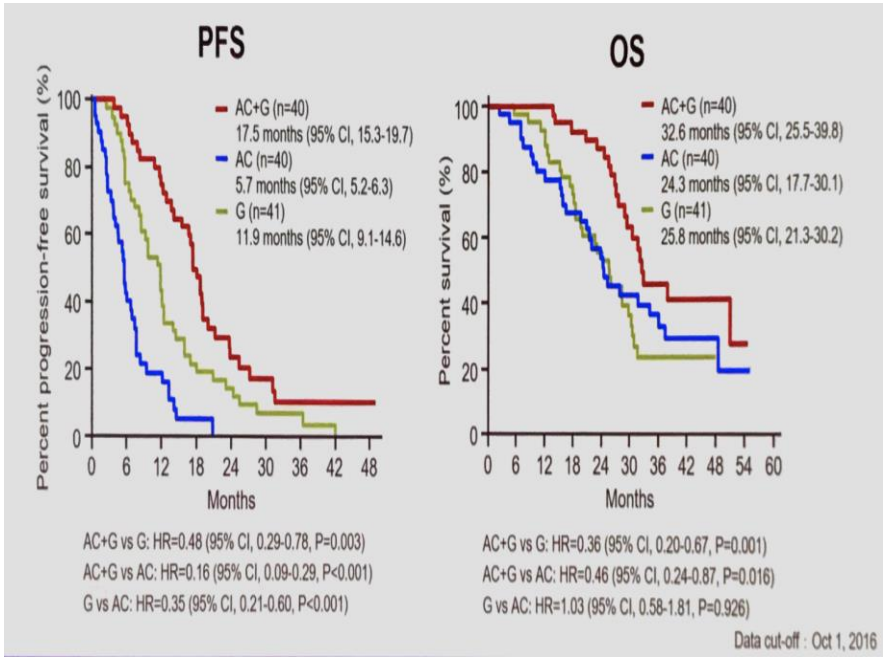
Strategy	Trial	Treatment	Median PFS, months	PFS HR (95%CI)	Median OS, months	OS HR (95%CI)
2nd *or* 1st generation EGFR TKI	CTONG 091	Erlotinib *vs.* gefitinib	**13.0 *vs.*** 10.4	0.81 (0.62-1.05)	-	-
	LUX-Lung 7	Afatinib *vs.* gefitinib	**11.0 *vs.*** 10.9	**0.73 (0.57-0.95)**	27.9 *vs.* 24.5	0.86 (0.66-1.12)
	Archer 1050	Dacomitinib *vs.* gefitinib	**14.7 *vs.*** 9.2	**0.59 (0.47-0.74)**	**34.1** *vs.* 26.8	**0.76 (0.58-0.99)**
1st generation EGFR TKI + Antiangiogenic agents	JO25567	Erlotinib + bevacizumab *vs.* erlotinib	**16.0** *vs.* 9.7	**0.54 (0.36-0.79)**	47.0 vs. 47.4	0.81 (0.53-1.23)
	NEJ026	Erlotinib + bevacizumab *vs.* erlotinib	**16.9** *vs.* 13.3	**0.61 (0.42-0.88)**	-	-
	RELAY	Erlotinib + ramucirumab *vs.* erlotinib + placebo	**19.4** *vs.* 12.4	**0.59 (0.46-0.76)**	NR *vs.* NR	0.83 (0.53-1.30) Not mature
EGFR TKI + EGFR MAb	IFCT 1503	Afatinib + cetuximab *vs.* afatinib	Stopped for futility (ASCO 2019 #9079)			
1st generation EGFR TKI + chemotherapy	NEJ009	Gefinib + carbo-pemetrexed *vs.* gefitinib	**20.9** *vs.* 11.2	**0.49 (0.39-0.63)**	**52.2** *vs.* 38.8	**0.60 (0.52-0.93)**
	Noronha	Gefinib + carbo-pemetrexed *vs.* gefitinib	**16** *vs.* 8	**0.51 (0.39, 0.66)**	**NR** *vs.* 17	**0.45 (0.31-0.65)**
3rd generation EGFR TKI	FLAURA	Osimertinib *vs.* gefitinib or erlotinib	**18.9 *vs.*** 10.2	**0.46 (0.37-0.57)**	NR *vs.* NR	0.63 (0.45-0.88) Not mature (ESMO)

Yang JC et al., BJC 2017; Paz-Ares et al., Ann Oncol 2017; Mok et al., JCO 2018; Seto et al., ASCO 2018; Saito et al., Lancet Oncol 2019; Nakagawa et al., ASCO 2019; Nakamura et al., ASCO 2018; Noronha et al., ASCO 2019; Soria et al., NEJM 2018; Cortot, ASCO 2019

Is time for chemotherapy resurrection?

OA11.07 – Chemotherapy Plus EGFR-TKI as First-Line Treatment Provides Better Survival for EGFR Mutation NSCLC Patients: Update Data for NCT02148380





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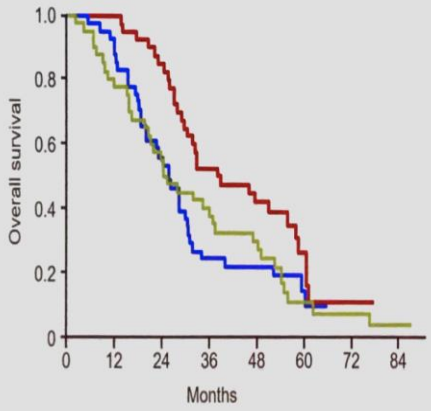
OS

AC + gefitinib vs gefitinib: HR = 0.56, 95%CI: 0.34-0.91, P = 0.02



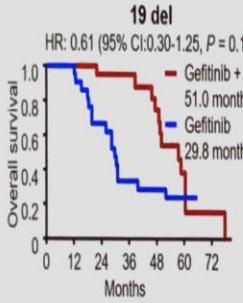
Gefitinib + chemotherapy
37.9 months, 95% CI: 17.3-58.6
Gefitinib
25.8 months, 95% CI: 19.2-32.3
Chemotherapy
24.4 months, 95% CI: 18.3-30.5

	AC+Gefitinib	Gefitinib	P
2Y OS rate	85.0% (34/40)	56.1% (23/41)	0.004
3Y OS rate	52.5% (21/40)	24.4% (10/41)	0.009

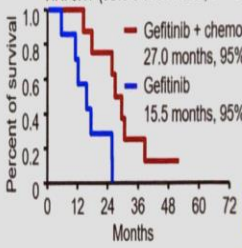
Data cut-off : Sep 28, 2018

OS

19 del
HR: 0.61 (95% CI:0.30-1.25, *P* = 0.18)
Gefitinib + chemotherapy
51.0 months, 95% CI: 36.6-65.5
Gefitinib
29.8 months, 95% CI: 26.7-32.9

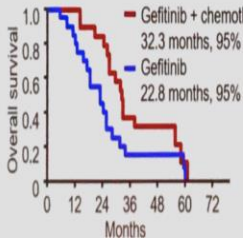


CNS metastases
HR: 0.17 (95% CI: 0.04-0.68, *P* = 0.013)
Gefitinib + chemotherapy
27.0 months, 95% CI: 21.8-32.3
Gefitinib
15.5 months, 95% CI: 6.8-24.3

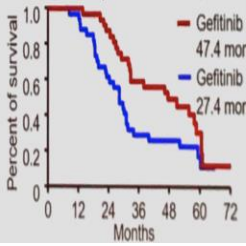


	CNS	No CNS	P
OS	25.6m	31.7m	0.001

21 I858r
HR: 0.50 (95% CI:0.25-1.00, *P* = 0.05)
Gefitinib + chemotherapy
32.3 months, 95% CI: 27.8-36.7
Gefitinib
22.8 months, 95% CI: 13.1-32.5

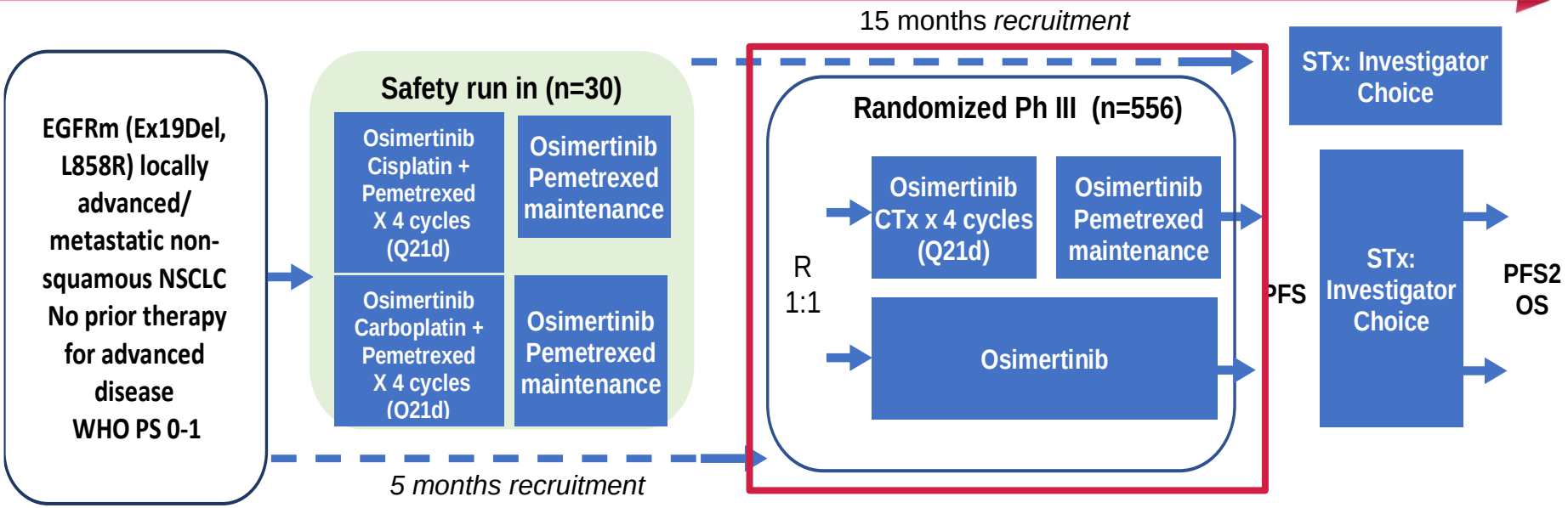


No CNS metastases
HR: 0.57 (95%CI:0.32-0.99, P=0.044)
Gefitinib + chemotherapy
47.4 months, 95% CI: 27.2-67.7
Gefitinib
27.4 months, 95% CI: 23.0-33.7



Zhang W, et al. OA 11.07

Osimertinib Plus Platinum/ Pemetrexed in Newly-Diagnosed Advanced EGFRm-Positive NSCLC; The Phase 3 FLAURA2 Study



Stratification factors:

1) Central or local method for tissue testing for potential differences in EGFR mutation detection
2) Race Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian
3) Baseline performance status based on the WHO PS.

Primary Objective

Progression-free survival (PFS) according to RECIST v1.1 by Investigator assessment

Secondary Objectives

Overall survival, Objective response rate, Duration of response
Depth of response, Disease control rate, PFS2, QoL

Janne P, et al. OA 07.01

PC02 - Combining with Chemo: Old School Is New Again (ID 84)

Type: **Pro-Con Session** | Track: **Advanced NSCLC** | Presentations: **0**

Moderators: Julien Mazieres, Javier De Castro Carpeno

Coordinates: 9/09/2019, 14:00 - 15:30, Vienna (2016)

PC02.01 - TKIs Should Be Given as Single Agent

14:00 - 14:20 | Presenting Author(s): Tony Mok

PC02.02 - TKIs Should Be Given with Chemo

14:20 - 14:40 | Presenting Author(s): Rafael Rosell

OA11.01 – Complex EGFR Mutations in Lung Adenocarcinoma

MATERIAL AND METHOD

- Collect specimens of lung adenocarcinoma from patients treated with EGFR TKIs were collected for *EGFR* sequencing from **June 2005 to July 2018** .
- *EGFR* mutation analysis by Sanger sequencing.
- Patients' clinical characteristics, *EGFR* mutation status, treatment response, progression-free survival (PFS) and overall survival (OS) were analyzed.
- Patients harboring tumor with de novo T790M were excluded.
- **Definition:**
  - **Complex *EGFR* mutations :** two or more concomitant sites of *EGFR* mutations
  - **Complex mutation with "classical mutation pattern" :** contain del-19 or L858R
  - **Complex mutation with "non-classical mutation pattern":** contain neither del-19 nor L858R

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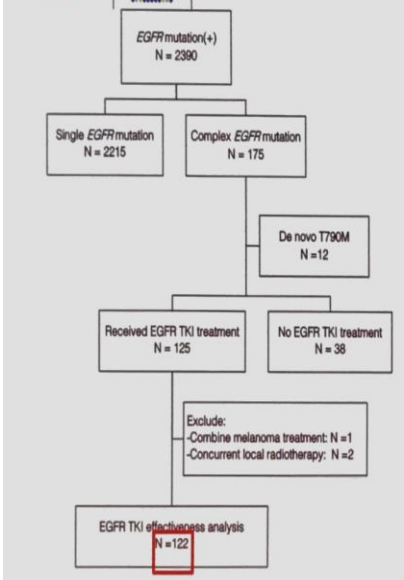


	All patients	Classical mutation pattern	Non-classical mutation pattern	P
Total	122	84 (68.9%)	38 (31.1%)	
Age, median, years (range)	64.8 (27.5–87.4)	63.0 (27.5–87.4)	65.9 (28.1–82.3)	0.398[§]
Sex				0.973
Female	80	55 (65.5%)	25 (65.8%)	
Male	42	29 (34.5%)	13 (34.2%)	
Smoking status				0.138[*]
Never-smokers	99	65 (77.4%)	34 (89.5%)	
Smokers	23	19 (22.6%)	4 (10.5%)	
ECOG PS				0.156
0-1	99	71 (84.5%)	28 (73.7%)	
2-4	23	13 (15.5%)	10 (26.3%)	
Stage				0.655
Relapse[†]	26	16 (19.0%)	10 (26.3%)	
IV(M1a)	25	18 (21.4%)	7 (18.4%)	
IV(M1b)	71	50 (59.5%)	21 (55.3%)	
Mutation subtype distribution				
Exon 18	45	21 (25.0%)	24 (63.2%)	<0.001
Exon 19	33	28 (33.3%)	5 (13.2%)	0.020
Exon 20	37	24 (28.6%)	13 (34.2%)	0.530
Exon 21	86	70 (83.3%)	16 (42.1%)	<0.001
EGFR TKI				0.454
gefitinib	65	46 (54.8%)	19 (50.0%)	
erlotinib	33	24 (28.6%)	9 (23.7%)	
afatinib	24	14 (16.7%)	10 (26.3%)	
Line of EGFR TKI				0.402
1st-line	97	64 (76.2%)	33 (86.8%)	
2nd-line	15	12 (14.3%)	3 (7.9%)	
≧3rd-line	10	8 (9.5%)	2 (5.3%)	

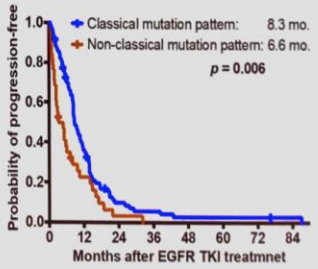
Discussion OA11.01-03: Joel W. Neal, MD, PhD; Stanford University, USA

OA11.01 – Complex EGFR Mutations in Lung Adenocarcinoma

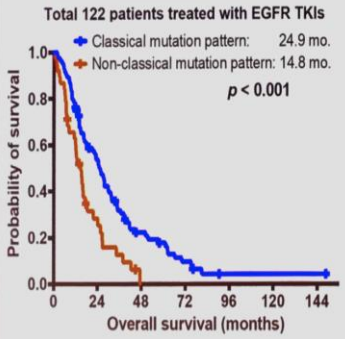
Classical mutation pattern was associated higher treatment response rate and longer PFS of EGFR TKI

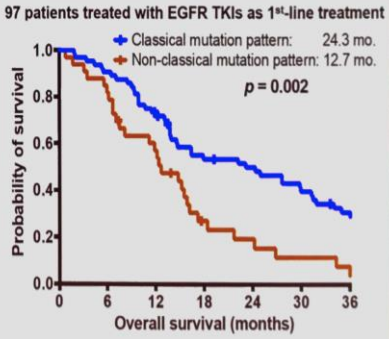
EGFR mutations \ Response	PR	SD	PD	Total
Classical mutation pattern	66 (**78.6%**)	4 (4.8%)	14 (16.7%)	84
Non-classical mutation pattern	18 (**47.4%**)	1 (2.6%)	19 (50.0%)	38
Total	84 (68.9%)	5 (4.1%)	33 (27.0%)	122

p = 0.001 for complex *EGFR*-mutant patients with classical mutation patterns versus non-classical mutation patterns.

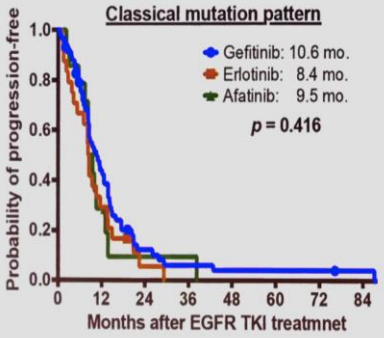


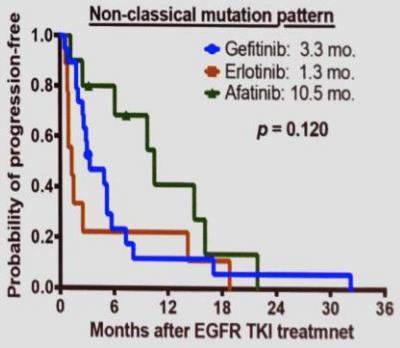
Classical mutation pattern was associated longer OS





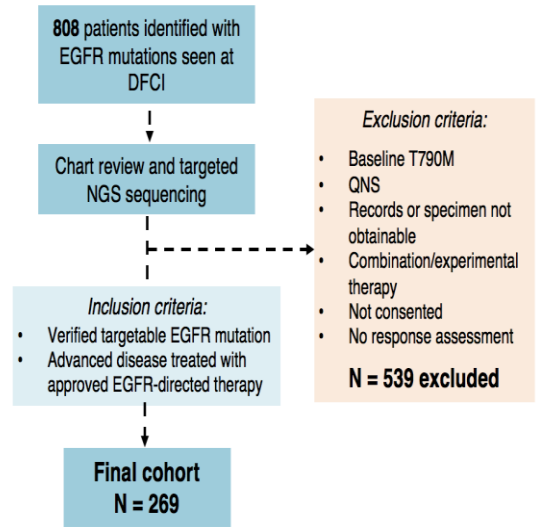
The PFS of different EGFR TKIs in patients with complex *EGFR* mutation with and without classical mutation pattern





Genomic correlates of differential response to EGFR-directed tyrosine kinase inhibitors

Cohort Diagram

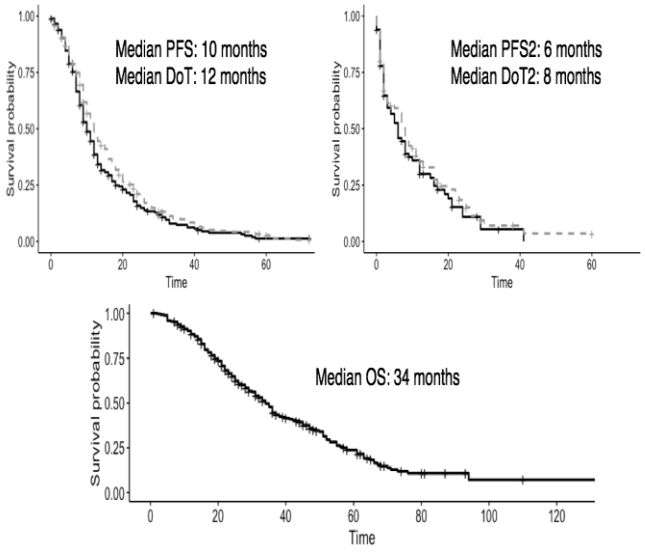


Pre-TKI-1 specimen: *N = 189* → 1st line TKI → TKI-1 resistance specimen: *N = 86*

26 patients with paired pre/post specimens

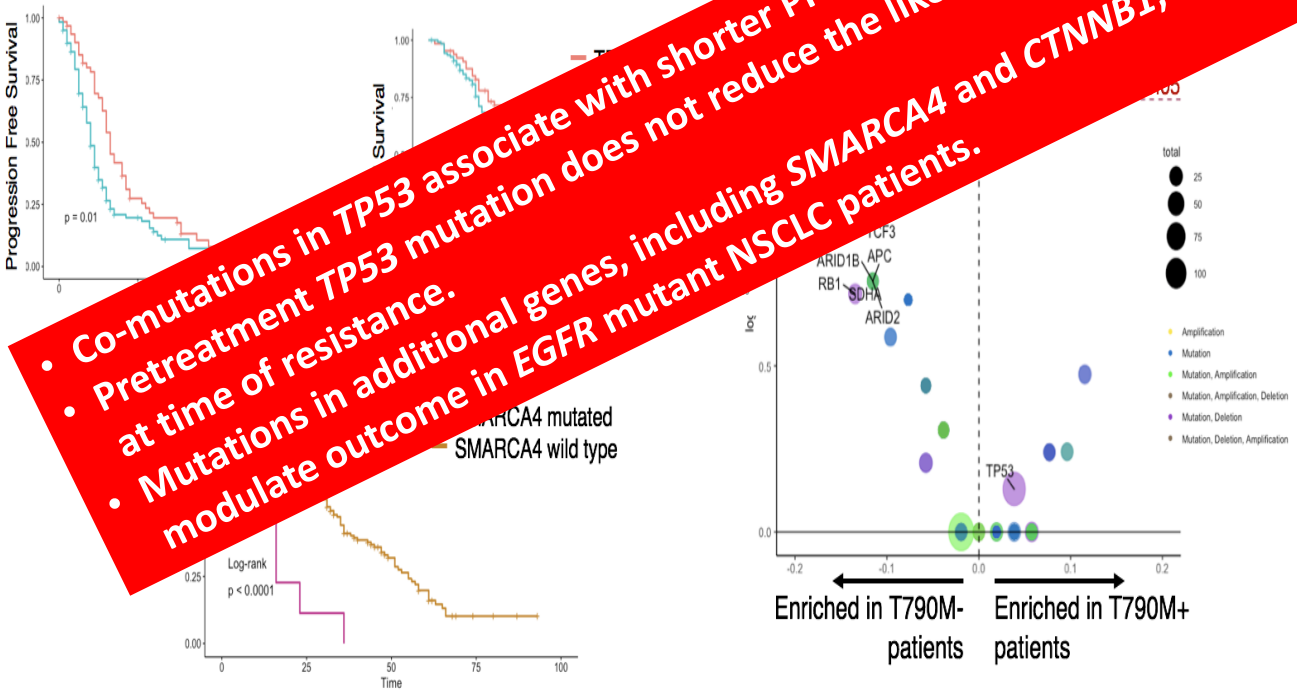
Cohort characteristics

Cohort Characteristics	
Characteristic	No. (%)
No of patients	269
Med age at diagnosis	62 (29-93)
Sex	
Male	80 (30)
Female	190 (70)
Smoking status	
Ever	107 (40)
Never	163 (60)
EGFR mutation	
Exon 19 deletion	137 (51)
L858R	103 (38)
Other	29 (11)
Stage at diagnosis	
I, II	37 (14)
III	22 (8)
IVa	69 (26)
IVb	141 (52)
Line of therapy, first TKI	
First	226 (84)
Second	39 (14)
Third or higher	4 (1)
1st line TKI	
Erlotinib	255 (94)
Afatinib	9 (3)
Gefitinib, Icotinib	3 (1)
Osimertinib	2 (1)
Received 2nd/3rd line Osimertinib	94 (35)



Vokes N et al. MA09.05

TP53 mutations associate with shorter PFS and *SMARC* with shorter OS



- Co-mutations in *TP53* associate with shorter PFS but not with shorter OS.
- Pretreatment *TP53* mutation does not reduce the likelihood of T790M mutation at time of resistance.
- Mutations in additional genes, including *SMARCA4* and *CTNNB1*, may also modulate outcome in *EGFR* mutant NSCLC patients.

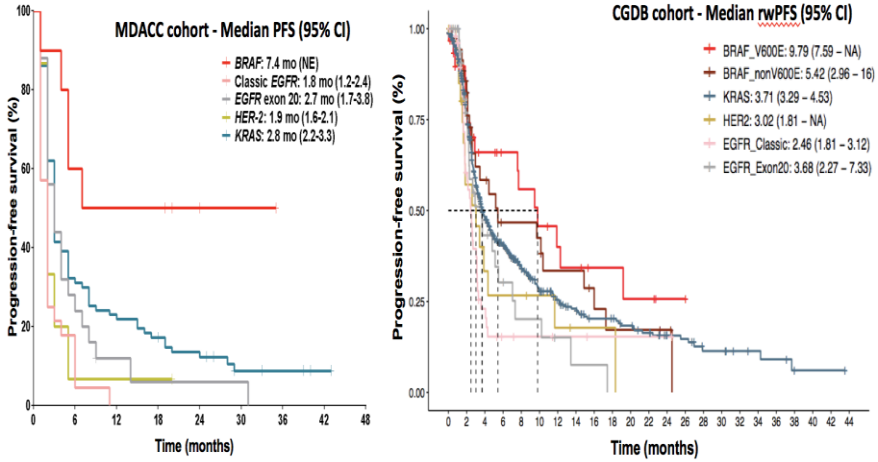
- to alterations in *MET*, post- nt tumors are enriched for terations in cell cycle genes *CDKN2A* and *BUB1B*, with a trend toward enrichment in cell cycle genes on pathway analysis.
- Co-mutations in *TP53* associate with shorter PFS but not with shorter OS.
- Pretreatment *TP53* mutation does not reduce the likelihood of T790M mutation at time of resistance.
- Mutations in additional genes, including *SMARCA4* and *CTNNB1*, may also modulate outcome in *EGFR* mutant NSCLC patients

Vokes N et al. MA09.05

IO IN SPECIFIC ONCOGENIC DRIVEN NSCLC

BRAF mutations are associated with increased benefit from PD-1/PD-L1 blockade compared with other oncogenic drivers in non-small cell lung cancer

Marcelo V. Negrao[1], Ferdinandos Skoulidis[1], Meagan Montesion[2], Katja Schulze[3], Ilze Bara[3], Vincent Shen[3],



Dramatic responses to Immune Checkpoint Inhibitors in MET exon 14 skipping mutation (METex14mut) Non Small Cell Lung Cancers

	MET mutation	PDL1 expression	Time between diagnosis and ICI	Time under ICI	Tumor response
A	C.3082+1 G>A	70%	5,5 months 12 months when rechallenging	28 months (ongoing)	Complete
B	C.3082+1 G>C	20%	10,5 months	23 months	Partial
C	C.3082 G>A Kras c.34G>A (minority)	40%	4,5 months	25 months	Complete
D	C.2942-51_2961del	40%	34 months	42 months (ongoing)	Partial
E	C.3082+1 G>C	90%	5 months	15 months (ongoing)	Partial
F	NA	NA	24 months	23 months (ongoing)	Partial

Negrao M, et al. MA 03.05
Mayenga M, et al. MA 03.09