Current role of anti-PD-1/PD-L1 antibodies in patients with EGFR- or ALK-positive disease

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EGFR mutation case

- 60 year old male never smoker with newly diagnosed lung adenocarcinoma. He presented with escalating cough
- PET scan 12/24/16 showed left neck and left paratracheal nodal enlargement; RUL mass and RLL infiltrate, para-aortic, pretracheal, subcarinal and right hilar nodes were noted.
- He underwent left supraclavicular excisional biopsy and open biopsy of the RLL area confirming adenocarcinoma.
- His molecular results returned positive for EGFR mutation (exon 19 deletion) and PD-L1 (50% positive with SP142 clone)

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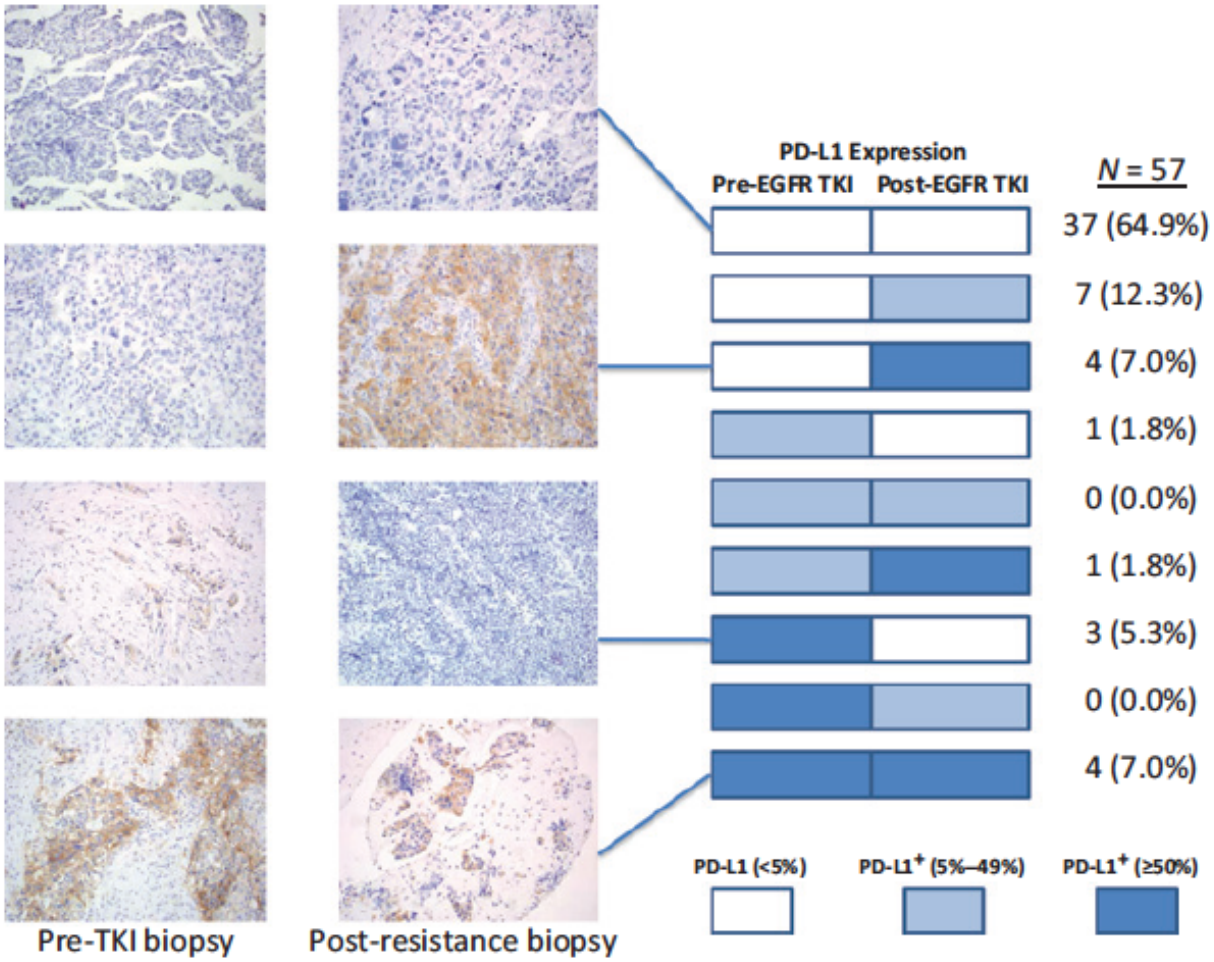
Disclosures

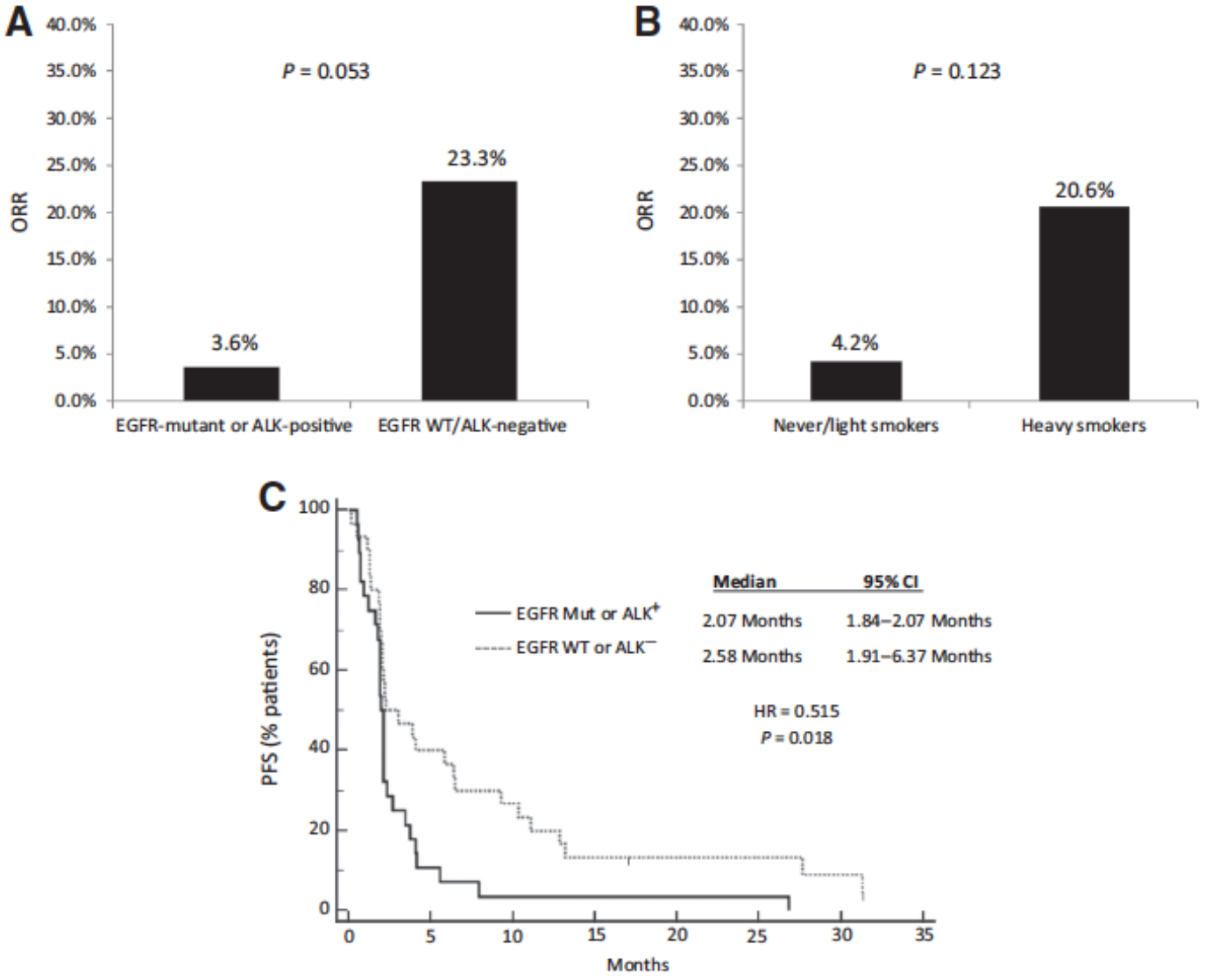
Advisory Committee and Consulting Agreements	AstraZeneca Pharmaceuticals LP, Merck, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc
Ownership Interest	Gritstone Oncology

PD-L1 expression in EGFRm NSCLC



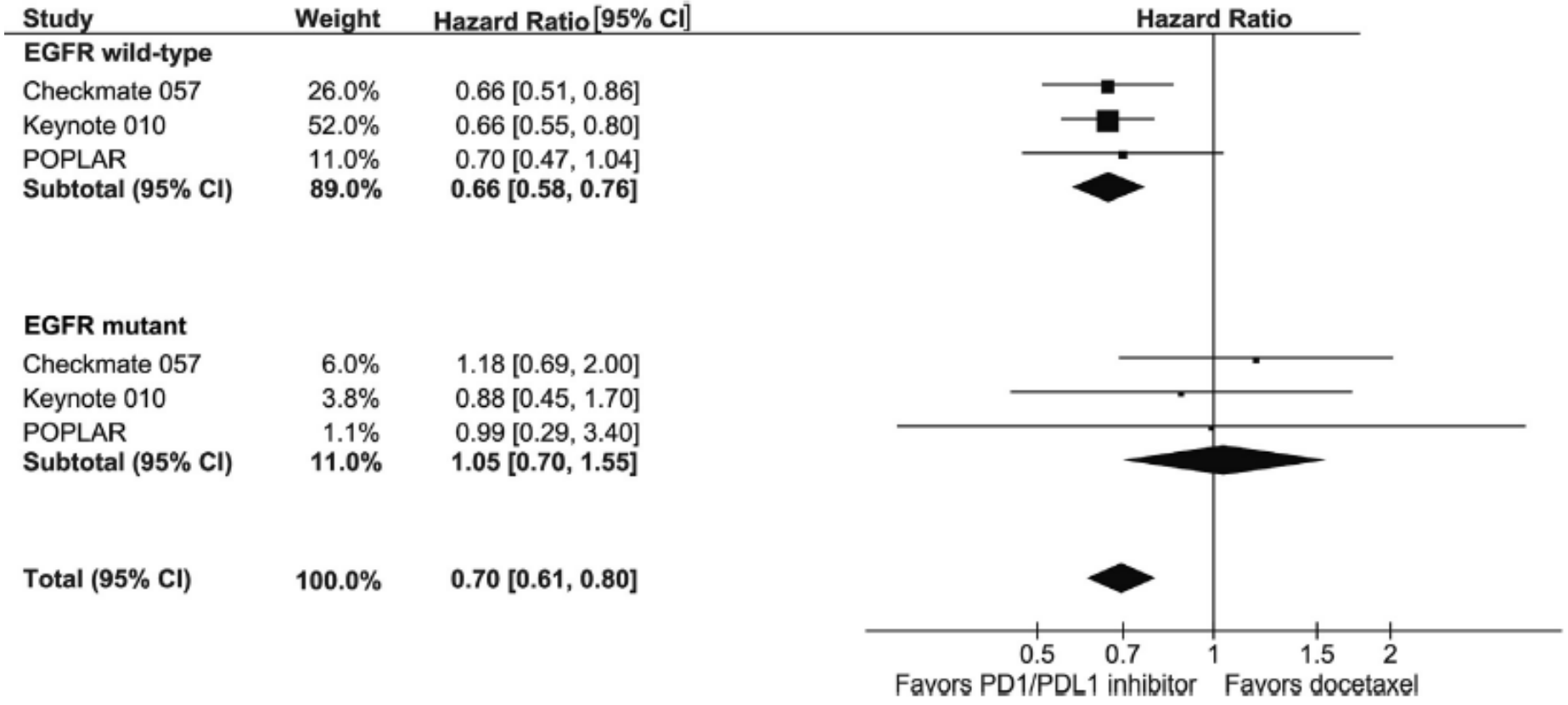
Gainor et al, CCR 2016

ORR and PFS in EGFR/ALK positive vs. WT



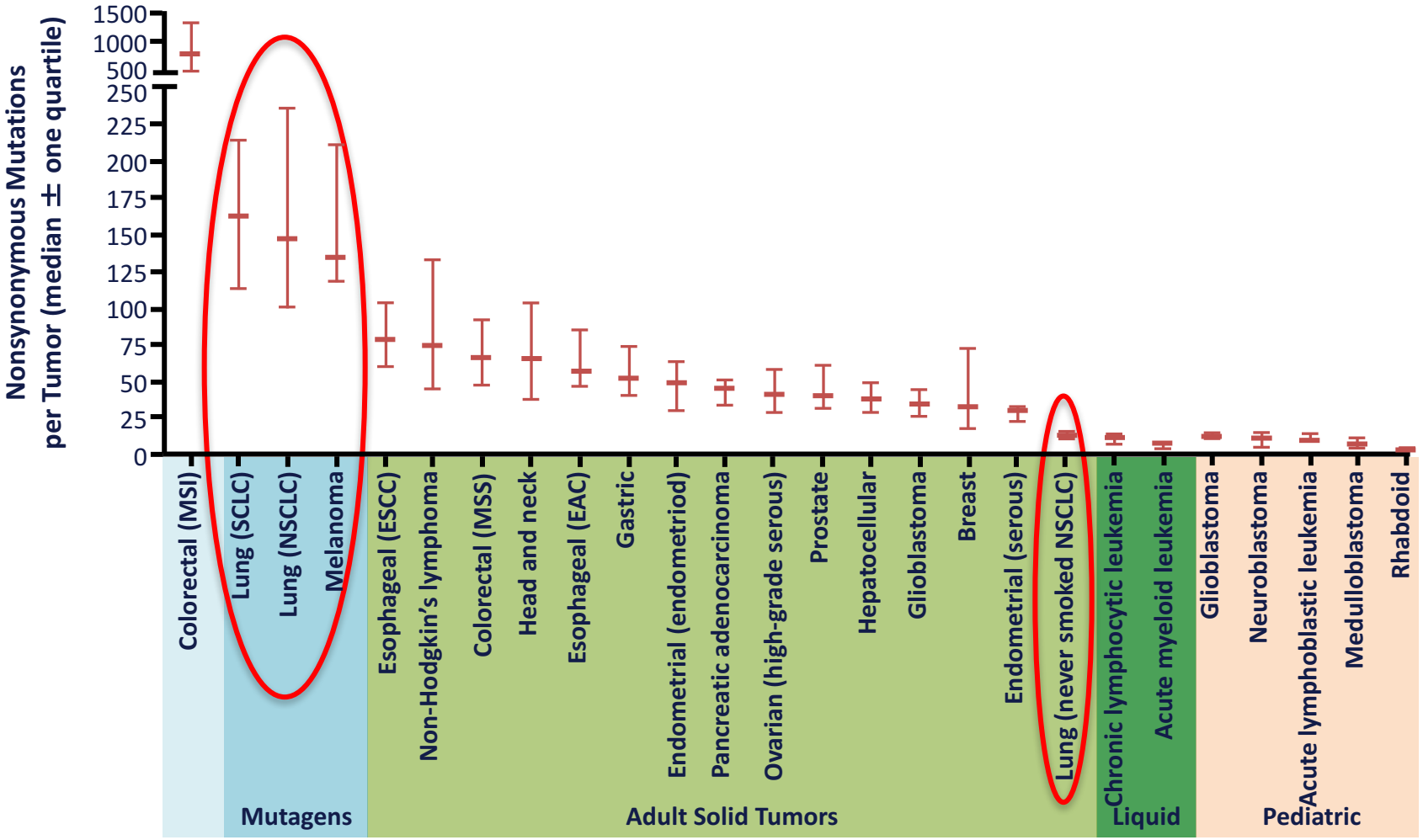
Gainor et al, CCR 2016

EGFRm PD-(L)-1 meta-analysis



Chee Khoon Lee et al, JTO 2016

Nonsynonymous Somatic Mutations by Tumor Type



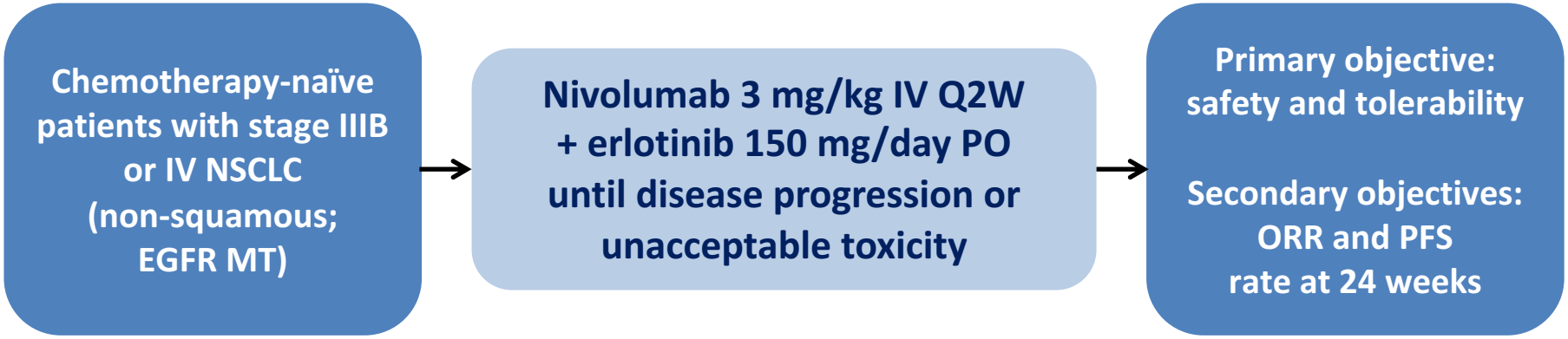
Vogelstein B, et al. Science. 2013;339:1546-1558.

KEYNOTE-001 trial of pembrolizumab: OS in key subgroups

Subgroup	TPS ≥50%		TPS ≥1%		TPS <1%	
	n/N[a]	Median, months (95% CI)	n/N[a]	Median, months (95% CI)	n/N[a]	Median, months (95% CI)
Histology						
Squamous	16/28	14.0 (8.0-NR)	33/54	14.0 (8.3-17.9)	12/15	14.7 (1.2-18.4)
Nonsquamous	65/108	15.4 (9.9-18.8)	164/248	10.5 (7.1-13.7)	50/73	8.6 (5.5-10.6)
Smoking history						
Current or former	59/108	15.7 (11.1-NR)	136/221	13.2 (9.4-15.6)	47/66	8.6 (4.9-13.3)
Never	23/30	8.2 (4.9-17.3)	63/85	7.3 (5.1-13.7)	17/24	9.1 (4.2-21.3)
EGFR mutation status						
Wild type	60/109	15.7 (11.1-NR)	152/245	13.2 (9.2-15.4)	51/71	9.1 (5.8-13.6)
Mutant	17/19	6.5 (2.0-13.7)	37/45	6.5 (4.4-12.6)	11/17	5.7 (2.2-NR)

Hui et al ASCO 2016

CheckMate 012: nivolumab + erlotinib

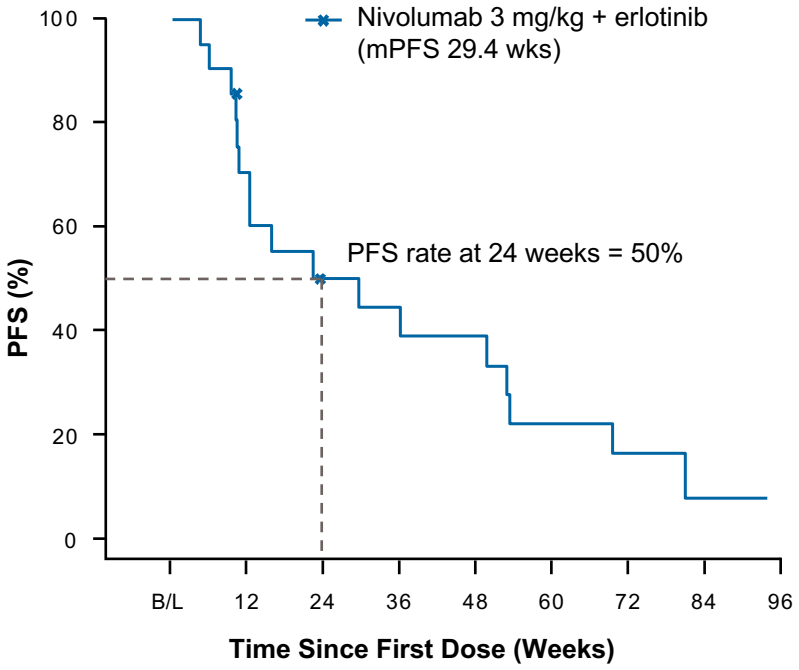


Rizvi et al. ASCO 2014;Abstract 8022.

Tumor response in NSCLC pts treated with nivolumab plus erlotinib

Confirmed ORR, n (%) [95% CI]	4/21 (19) including 1 TKI naïve patient

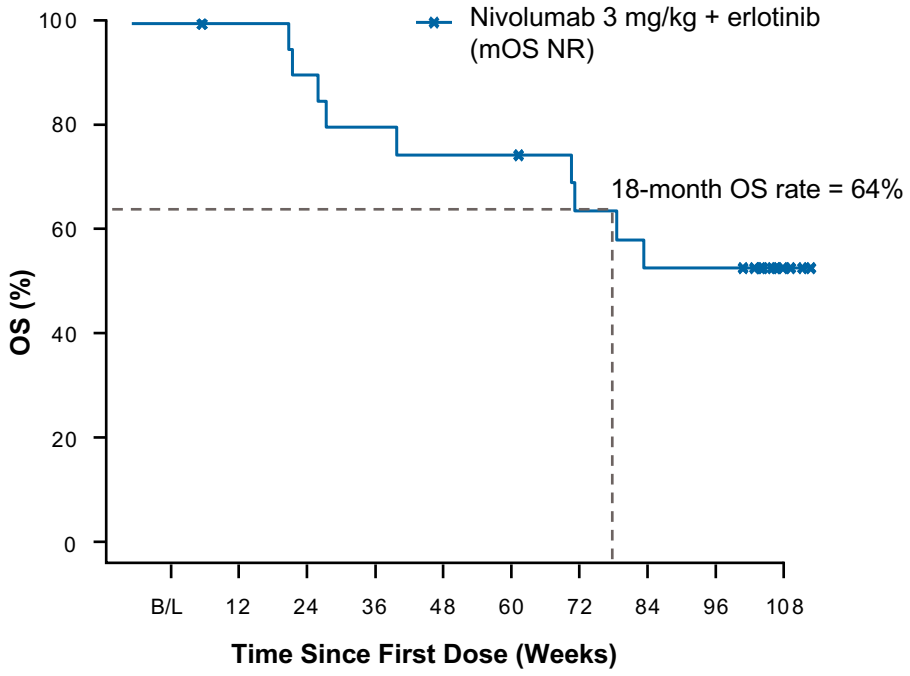
PFS



Number of Pts at Risk

Nivolumab + erlotinib	21	14	9	7	7	4	3	1	0

OS



Number of Pts at Risk

Nivolumab + erlotinib	21	20	20	16	15	15	13	10	10	2

Rizvi et al, *ASCO* 2014

Tumor response in NSCLC pts treated with nivolumab plus erlotinib

Most treatment-related adverse events (AEs) were low grade

- No grade 4 or 5 AEs were reported
- One pt (5%) had grade 1 pneumonitis
- Treatment-related diarrhea (n = 2, both grade 3), increased aspartate aminotransferase (AST) (n = 1, grade 3), increased alanine aminotransferase (ALT), flushing, and tubulointerstitial nephritis (n = 1 each, grade 2) led to discontinuation of study medication in 4 pts (19%)
  - One pt had both grade 3 diarrhea and grade 2 flushing
- At the time of analysis, 9 pts had died, including 8 due to disease progression and 1 due to an unknown cause

Phase Ib trial of anti-PD-L1 (atezolizumab; MPDL3280A) + erlotinib

EGFR TKI Treatment-Naïve Advanced NSCLC

Stage 1: Safety Evaluation Stage
TKI treatment-naïve,
Optional biopsies
(n=6-12)

150mg oral erlotinib qd
1200mg IV atezolizumab q3w

Combination
MTD/MAD
Established

Stage 2: Expansion Stage
Previously untreated,
EGFR mutation-positive NSCLC,
Mandatory biopsies
(n=20)

150mg oral erlotinib qd
1200mg IV atezolizumab q3w

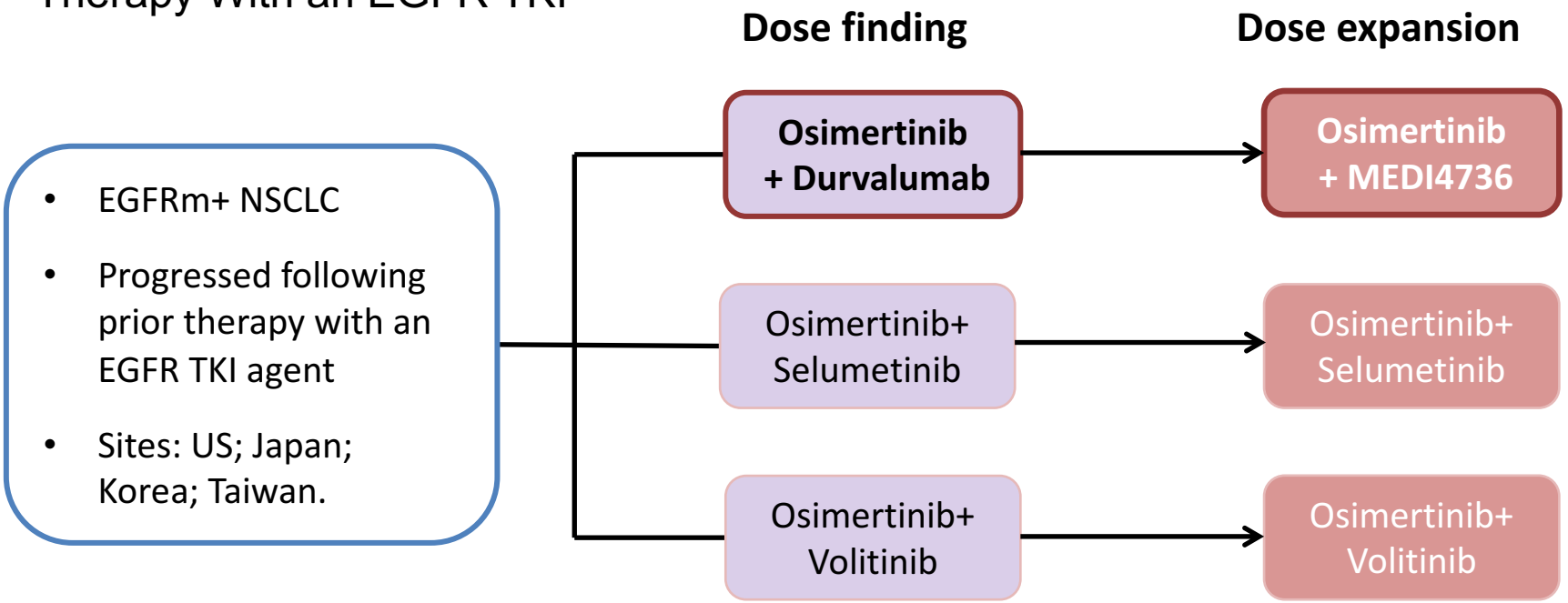
Completed

Enrolling

TATTON: Osimertinib (AZD9291) with Durvalumab (MEDI4736), Selumetinib* & Volitinib (AZD6094)

Principal Investigator: Geoff Oxnard (Dana Farber Cancer Institute)

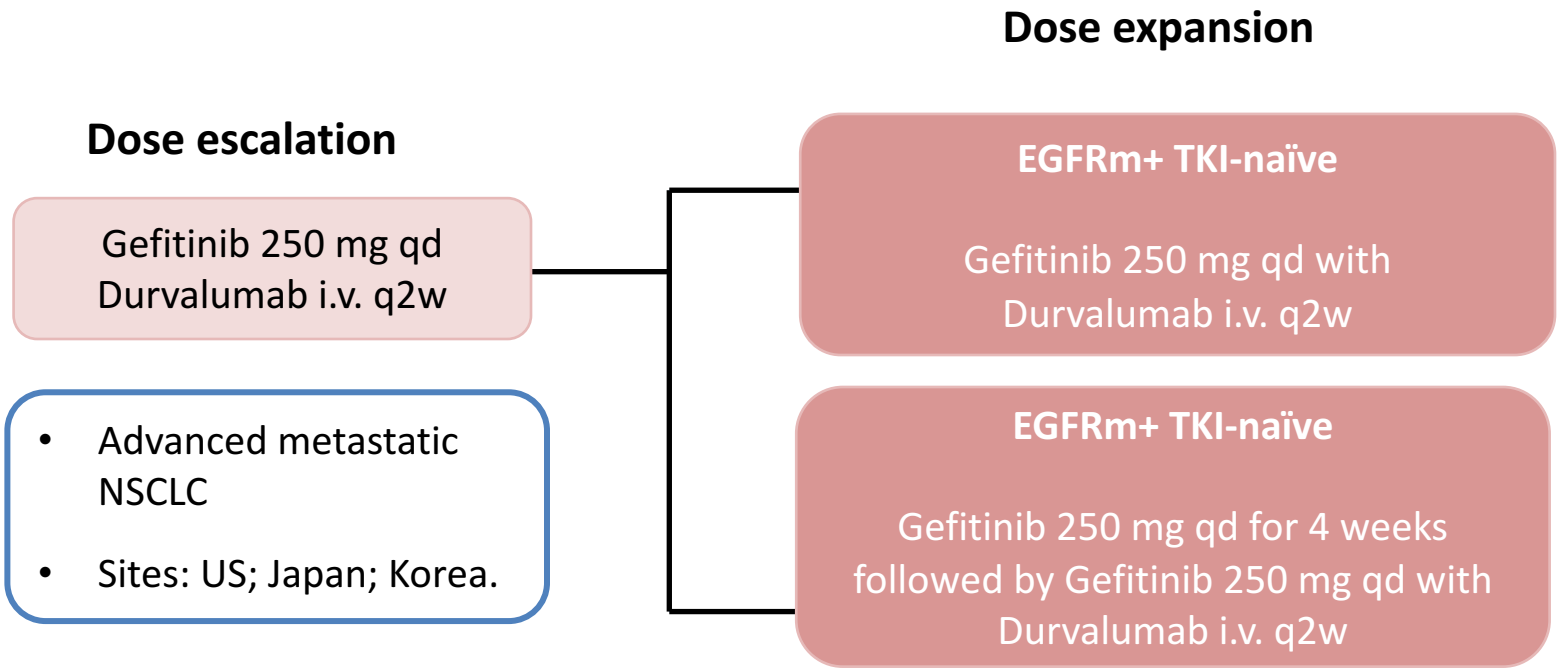
NCT02143466: A Multi-arm, Phase Ib, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD9291 in Combination With Ascending Doses of Novel Therapeutics in Patients With EGFRm+ Advanced NSCLC Who Have Progressed Following Therapy With an EGFR TKI



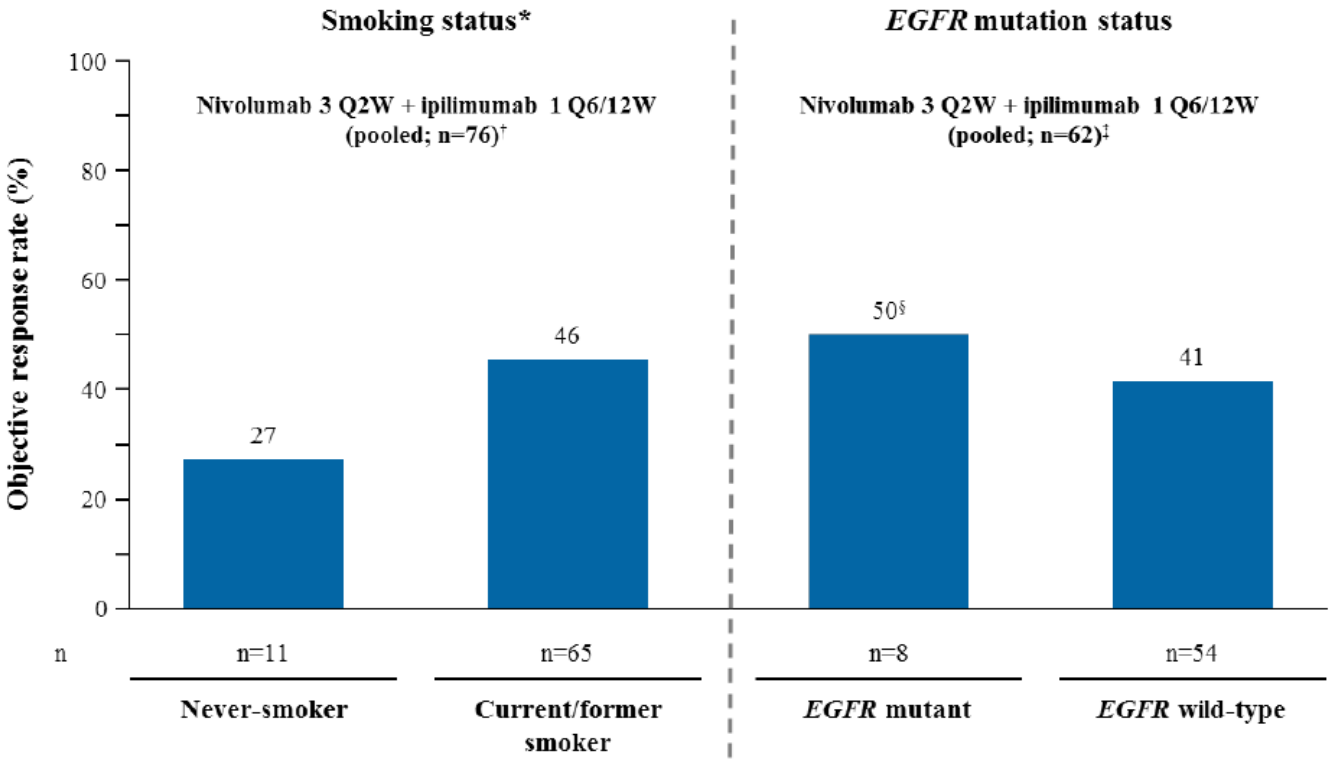
*selumetinib (AZD6244, ARRY-142886)

Gefitinib with Durvalumab

NCT02088112: A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Gefitinib in Combination With MEDI4736 (Anti PD-L1) in Subjects With Non-Small Cell Lung Cancer (NSCLC)



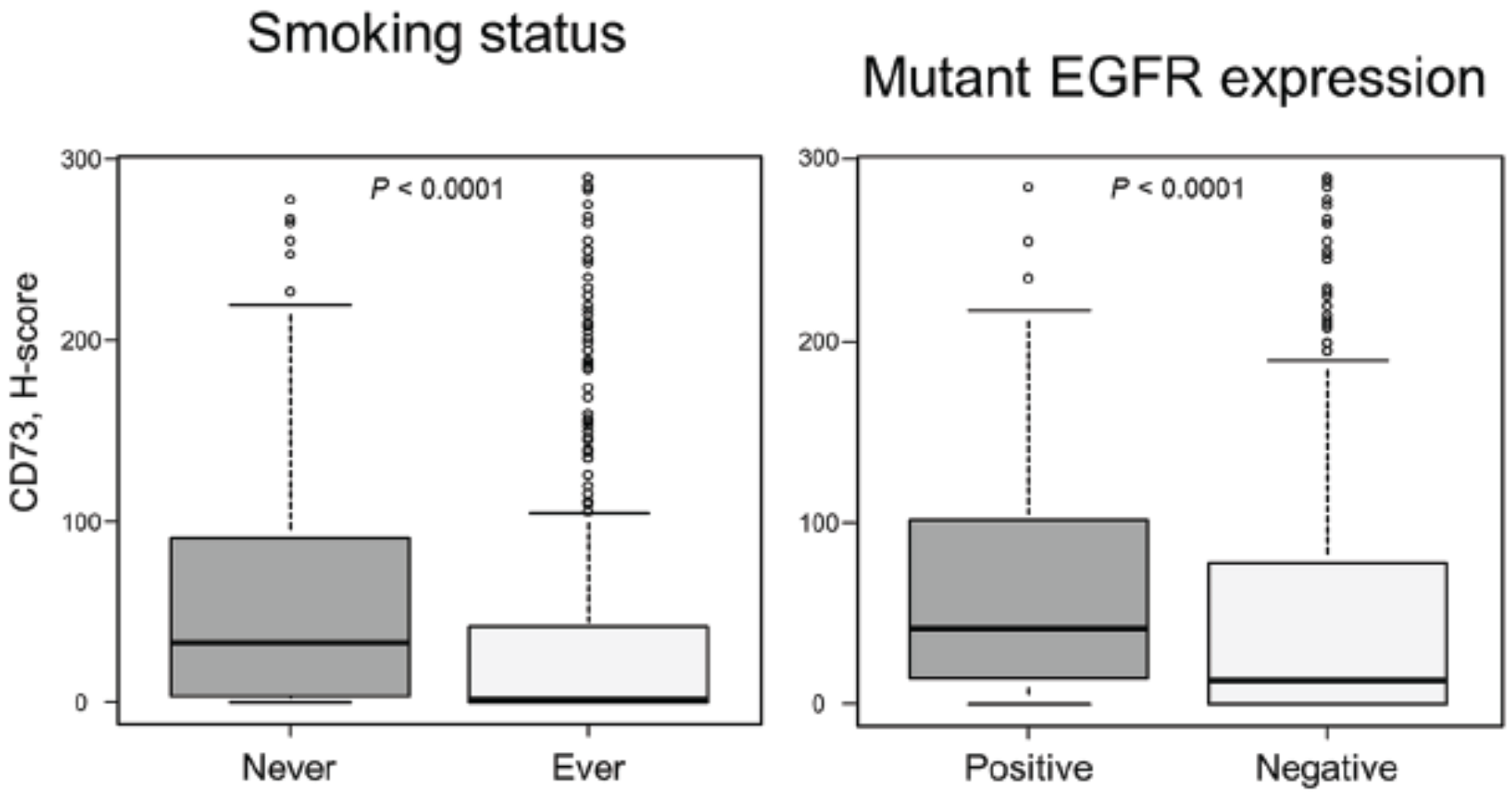
CheckMate 012



	Nivolumab 3 Q2W + Ipilimumab 1 Q6/12W *EGFR* mutation-positive (n=8)
Confirmed ORR – % (n/N)*	
≥1% PD-L1	57 (4/7)
≥50% PD-L1	100 (3/3)
Median PFS, months (range)	
≥1% PD-L1	13.6 (0+ – 16.2+)
≥50% PD-L1	13.6 (5.5+ – 13.6)

Hellmann et al, Lancet Oncology 2016

CD73 expression in NSCLC



Inoue et al, Oncotarget 2017)

Summary

- Single agent anti-PD-1 in EGFRm NSCLC: response rate and durability low
- Need for better biomarker to identify candidates: smoking history, mutation load…
- Combination EGFR TKI + IO studies ongoing
- Need for better combination strategies
  - A Study of Nivolumab + Chemotherapy or Nivolumab + Ipilimumab Versus Chemotherapy in Patients With EGFR Mutation, T790M Negative NSCLC Who Have Failed 1L EGFR TKI Therapy (CheckMate 722)

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