CONSENSUS OR CONTROVERSY?

Clinical Investigators Provide Perspectives on Targeted Treatment of Metastatic Non-Small Cell Lung Cancer

March 16, 2017
6:30 PM – 8:00 PM

Faculty

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Joel W Neal, MD, PhD
Gregory J Riely, MD, PhD

Moderator

Neil Love, MD

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Disclosures for Dr Govindan

Advisory Committee	AbbVie Inc, Ariad Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Baxalta Inc, INC Research, Roche Laboratories Inc
Consulting Agreements	AbbVie Inc, Ariad Pharmaceuticals Inc, Astellas Pharma Global Development Inc, Baxalta Inc, Bristol-Myers Squibb Company, Genentech BioOncology, INC Research
Contracted Research and Speakers Bureau	AbbVie Inc, Ariad Pharmaceuticals Inc, Baxalta Inc, INC Research

Disclosures for Dr Neal

Consulting Agreements	Ariad Pharmaceuticals Inc, ARMO BioSciences, Boehringer Ingelheim Pharmaceuticals Inc, CARET/Physicians Resource Management, Clovis Oncology, Nektar
Contracted Research	Ariad Pharmaceuticals Inc, ArQule Inc, Boehringer Ingelheim Pharmaceuticals Inc, Exelixis Inc, Genentech BioOncology, Merck, Nektar, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc

Disclosures for Dr Riely

Consulting Agreement	Genentech BioOncology
Contracted Research	Ariad Pharmaceuticals Inc, Astellas Pharma Global Development Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc

Disclosures for Moderator Neil Love, MD

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Module 1: Optimal Testing Algorithms; Treatment of Patients with EGFR Tumor Mutations

What type of mutation testing, if any, should be ordered for a patient who is a current smoker presenting with metastatic adenocarcinoma?

 RAMASWAMY GOVINDAN, MD	EGFR, ALK and ROS1; if negative, initiate systemic therapy and order multiplex/NGS
 JOEL W NEAL, MD, PHD	EGFR, ALK and ROS1; if negative, initiate systemic therapy and order multiplex/NGS
 GREGORY J RIELY, MD, PHD	Multiplex/NGS
 JULIE R BRAHMER, MD	EGFR, ALK and ROS1; if negative, initiate systemic therapy and order multiplex/NGS
 COREY J LANGER, MD	EGFR, ALK and ROS1; if negative, initiate systemic therapy and order multiplex/NGS
 HEATHER WAKELEE, MD	Multiplex/NGS

NGS = next-generation sequencing

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What type of mutation testing, if any, should be ordered for a patient who is a current smoker presenting with metastatic squamous cell carcinoma?

 RAMASWAMY GOVINDAN, MD	Multiplex/NGS panel
 JOEL W NEAL, MD, PHD	None
 GREGORY J RIELY, MD, PHD	Multiplex/NGS unless diagnosis is based on resection specimen
 JULIE R BRAHMER, MD	None
 COREY J LANGER, MD	Order NGS, but proceed with chemo or pembro if PD-L1(+) > 50%
 HEATHER WAKELEE, MD	Multiplex/NGS, but low likelihood to change therapy so just PD-L1 would be reasonable

NGS = next-generation sequencing

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A plasma mutational assay ordered for a patient with newly diagnosed metastatic NSCLC demonstrates an EGFR exon 19 deletion. Is that result adequate to initiate treatment with an EGFR tyrosine kinase inhibitor (TKI)? Is a plasma mutational assay demonstrating no actionable mutation adequate to initiate treatment with chemotherapy?

	INITIATE EGFR TKI?	INITIATE CHEMOTHERAPY?
 RAMASWAMY GOVINDAN, MD	Yes	No, I would send tissue for an assay
 JOEL W NEAL, MD, PHD	Yes	No, I would send tissue for an assay
 GREGORY J RIELY, MD, PHD	Yes	No, I would send tissue for an assay
 JULIE R BRAHMER, MD	Yes	No, I would send tissue for an assay
 COREY J LANGER, MD	Yes	No, I would send tissue for an assay
 HEATHER WAKELEE, MD	Yes	No, I would send tissue for an assay

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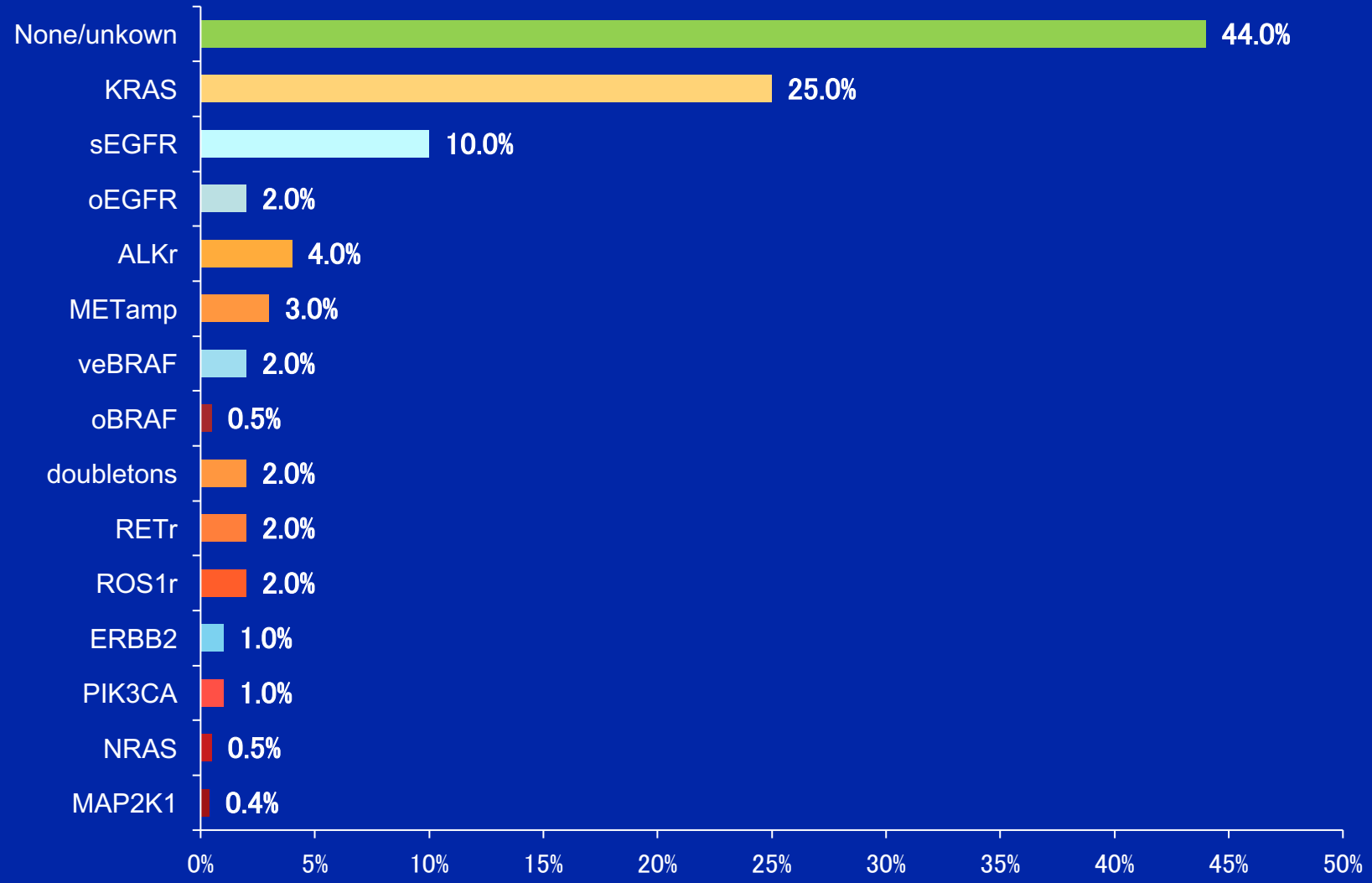
Frequency of Oncogenic Drivers in Lung Adenocarcinoma (n = 875)



s = sensitizing; r = rearrangement; o = other; veBRAF = BRAF V600E

Aisner DL et al. *Proc ASCO* 2016;Abstract 11510.

Frequency of Mutations in LCMC I Compared to LCMC II

Gene	LCMC I	LCMC II	*p*-value
EGFR	23%	16%	0.001
ALK	9%	4%	<0.001
KRAS	25%	27%	0.434
ERBB2	3%	2%	0.653
BRAF V600E	2%	3%	0.074

Smoking status	LCMC I	LCMC II	*p*-value
Current	7%	12%	<0.001
Former	59%	62%	
Never	34%	25%	

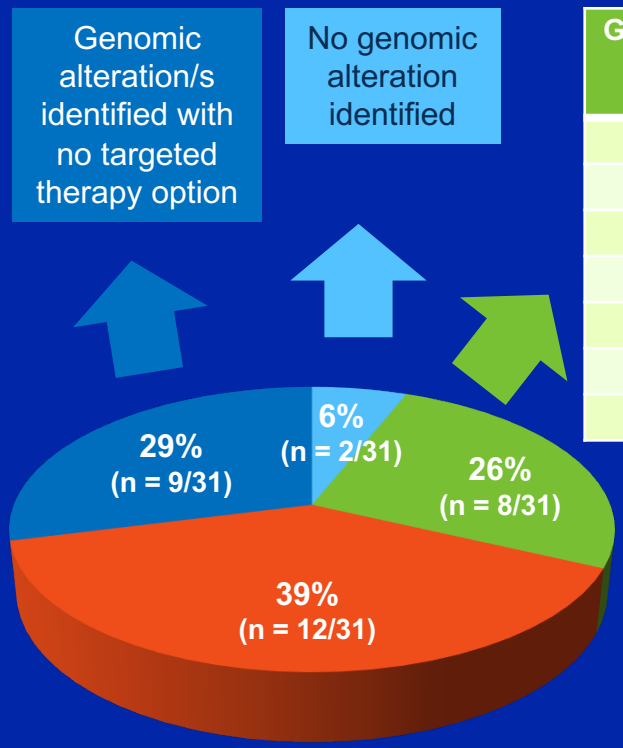
Aisner DL et al. *Proc ASCO* 2016;Abstract 11510.

Florida Cancer Specialists Case Survey: Patients with Metastatic Nonsquamous Lung Cancer (N = 91)

	Mutated (n = 43)	Wild type* (n = 54)
Current heavy smoker	1 (2%)	18 (33%)
Current light smoker	2 (5%)	0 (0%)
Former heavy smoker	14 (33%)	26 (54%)
Former light smoker	9 (21%)	7 (13%)
Never smoker	17 (39%)	3 (6%)

*WT – 12 of 54 patients (22%) with wild-type (WT) tumors had multiplex testing

Next-Generation Sequencing (NGS) to Identify Actionable Genomic Alterations in "Pan-Negative" Lung Adenocarcinomas from Patients with No Smoking or a Light Smoking History



Genomic alteration with targeted therapy in NCCN guidelines
EGFR G719A
BRAF V600E
SOCS5-ALK
CLIP4-ALK
CD74-ROS1
KIF5B-RET
CCDC6-RET

Genomic alteration with targeted agent available on or off a clinical trial
CDKN2A loss
EGFR L747P
EGFR exon 18 del (n = 2)
EGFR exon 20 ins
ERBB2 L755F
FGFR1 T141R
KRAS G12C
KRAS Q61H
MDM2 amp (n = 3)

Drilon A et al. *Clin Cancer Res* 2015;21(16):3631-9.

What type of assay is generally used to test ALK status in patients in your practice?

 RAMASWAMY GOVINDAN, MD	FISH
 JOEL W NEAL, MD, PHD	FISH, NGS
 GREGORY J RIELY, MD, PHD	IHC
 JULIE R BRAHMER, MD	FISH
 COREY J LANGER, MD	FISH
 HEATHER WAKELEE, MD	FISH

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In general, what would be your likely initial treatment recommendation for a younger patient with metastatic adenocarcinoma of the lung, a PD-L1 tumor proportion score (TPS) of 10% and an EGFR…

	EXON 19 DELETION MUTATION	EXON 21 L858R MUTATION
 RAMASWAMY GOVINDAN, MD	Erlotinib	Erlotinib
 JOEL W NEAL, MD, PHD	Erlotinib	Erlotinib
 GREGORY J RIELY, MD, PHD	Erlotinib	Erlotinib
 JULIE R BRAHMER, MD	Afatinib	Erlotinib
 COREY J LANGER, MD	Afatinib	Erlotinib
 HEATHER WAKELEE, MD	Erlotinib	Erlotinib

In general, what would be your likely initial treatment recommendation for a younger patient with metastatic adenocarcinoma of the lung with an EGFR exon 19 deletion mutation and a TPS of 60%?

 RAMASWAMY GOVINDAN, MD	Erlotinib
 JOEL W NEAL, MD, PHD	Erlotinib
 GREGORY J RIELY, MD, PHD	Erlotinib
 JULIE R BRAHMER, MD	Afatinib
 COREY J LANGER, MD	Afatinib
 HEATHER WAKELEE, MD	Erlotinib

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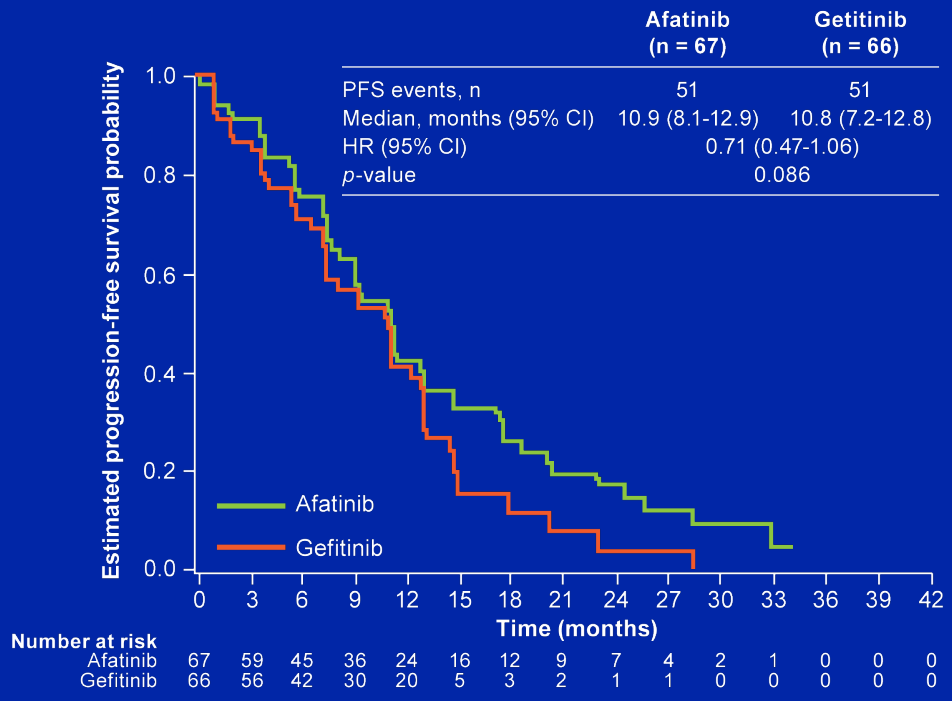
Meta-Analysis of PFS Benefit Observed with EGFR TKIs: Exon 19 Deletion and Exon 21 L858R Substitution

Trial	HR	95% CI	HR	95% CI
	Exon 19 deletions		Exon 21 L858R substitution	
ENSURE	0.20	0.12 to 0.33	0.54	0.32 to 0.91
EURTAC	0.27	0.17 to 0.43	0.53	0.29 to 0.97
LUX-Lung 3	0.28	0.18 to 0.44	0.73	0.46 to 1.16
LUX-Lung 6	0.20	0.13 to 0.32	0.32	0.19 to 0.54
NEJ002	0.24	0.15 to 0.38	0.33	0.20 to 0.54
OPTIMAL	0.13	0.07 to 0.24	0.26	0.14 to 0.48
WJTOG 3405	0.42	0.26 to 0.66	0.69	0.44 to 1.07
All	0.24	0.20 to 0.29	0.48	0.39 to 0.58

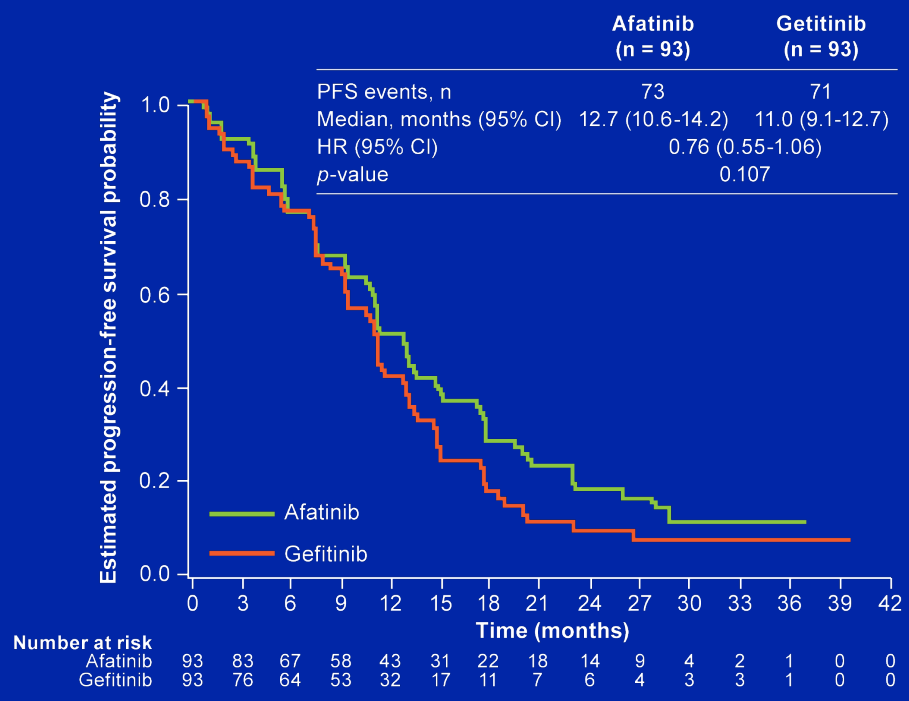
Lee CK et al. *J Clin Oncol* 2015;33(17):1958-65.

LUX-Lung 7: PFS with Afatinib and Gefitinib by EGFR Mutation

L858R



Ex19del



Final analysis for overall survival (the study's **co-primary endpoint**) showed no statistically significant difference in OS between afatinib (27.9 mos) and gefitinib (24.5 mos) [HR 0.86, $p = 0.258$], including in ex19del subgroup

Park K et al. *Lancet Oncol* 2016;17(5):577-89.

For a patient with EGFR-mutant NSCLC who initially responds to an EGFR TKI and is now experiencing disease progression, how do you approach the issue of T790M mutation testing? Have you or would you use a urine mutation assay to evaluate for a T790M mutation?

	SERUM AND/OR TISSUE	URINE
 RAMASWAMY GOVINDAN, MD	Plasma first; if negative, tissue	I haven't but would for the right patient
 JOEL W NEAL, MD, PHD	Plasma first; if negative, tissue	I have
 GREGORY J RIELY, MD, PHD	Plasma first; if negative, tissue	I haven't but it is reasonable
 JULIE R BRAHMER, MD	Plasma and tissue concurrently	I haven't but would for the right patient
 COREY J LANGER, MD	Plasma and tissue concurrently	I have
 HEATHER WAKELEE, MD	Plasma first; if negative, tissue	I have

Association between Plasma Genotyping and Outcomes with Osimertinib

- Sensitivity of plasma genotyping for detection of EGFR mutations:
  - T790M: 70%
  - Exon 19 del: 82%
  - Exon 21 L858R: 86%
- Plasma positive for T790M in 31% of cases negative for T790M in tumor

Outcome	Tumor T790M+	Tumor T790M-	Plasma T790M+	Plasma T790M-
ORR (n = 173, 58, 164, 102)	62%	26%	63%	46%
Median PFS (n = 179, 58, 169, 104)	9.7 mo	3.4 mo	9.7 mo	8.2 mo

Oxnard GR et al. *J Clin Oncol* 2016;34(28):3375-82.

Plasma and Urine Detection Is Sensitive and Complements Tissue T790M Testing

- Tissue as reference, plasma sensitivity = 80.9% (313/387)

Plasma vs tissue					
T790M		Tissue			Total
		Positive	Negative	Inadequate	
Plasma (BEAMing)	Positive	313	23	38	374
	Negative	74	17	17	108
Total		387	40	55	482

- Tissue as reference, urine sensitivity = 81.1% (142/175)

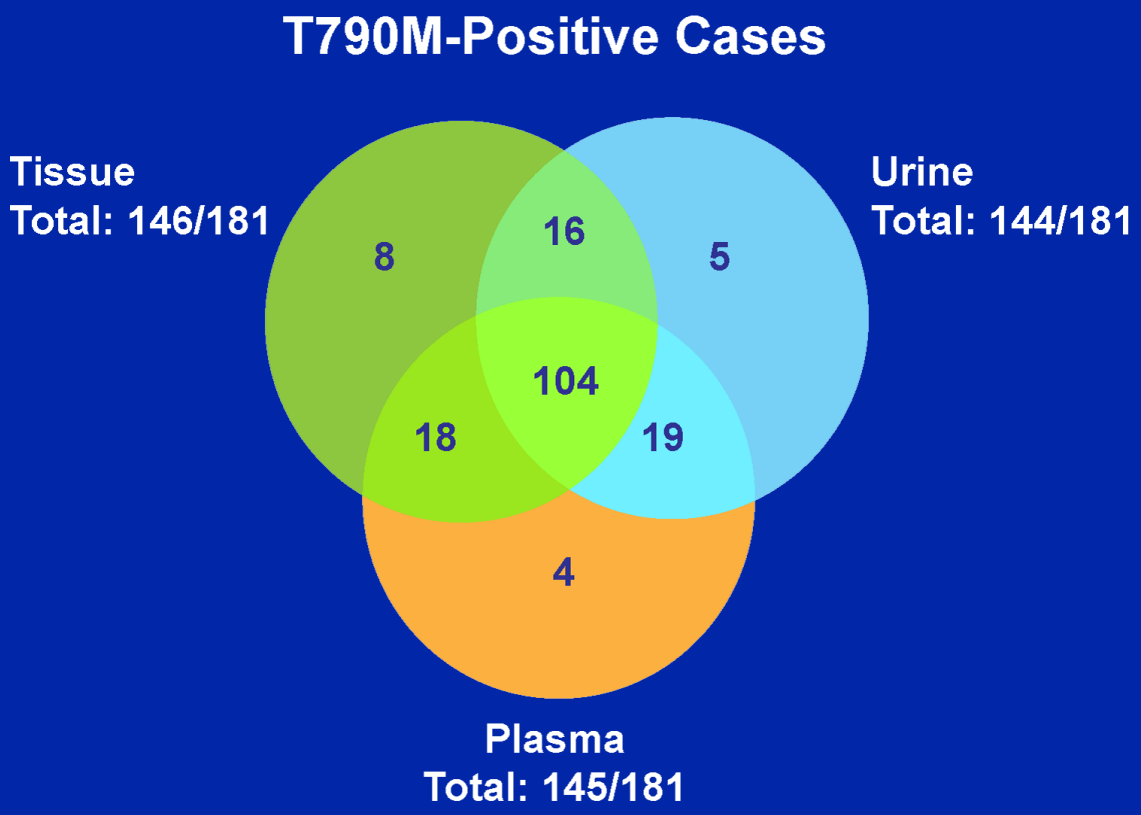
Urine vs tissue					
T790M		Tissue			Total
		Positive	Negative	Inadequate	
Urine	Positive	142	11	16	169
	Negative	31	5	6	42
	Inadequate	2	0	0	2
Total		175	16	22	213

In T790M-positive patients, response was similar whether status was identified by plasma, tissue or urine.

Wakelee HA et al. *Proc ASCO* 2016;Abstract 9001.

Plasma, Tissue and Urine Identify Unique and Overlapping Subsets of T790M-Positive Patients

181 samples with matched pretreatment T790M results in plasma, tissue and urine



- 57% were positive by all 3 sample types

Wakelee HA et al. *Proc ASCO* 2016;Abstract 9001.

In general, what would be your most likely systemic therapy recommendation for a patient with EGFR mutation-positive nonsquamous NSCLC who responded to erlotinib, is now experiencing disease progression and has a biopsy-proven T790M mutation and a PD-L1 TPS of 60%?

 RAMASWAMY GOVINDAN, MD	Osimertinib
 JOEL W NEAL, MD, PHD	Osimertinib
 GREGORY J RIELY, MD, PHD	Osimertinib
 JULIE R BRAHMER, MD	Osimertinib
 COREY J LANGER, MD	Osimertinib
 HEATHER WAKELEE, MD	Osimertinib

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What is your usual treatment approach for a patient with EGFR mutation-positive lung adenocarcinoma and a PD-L1 TPS of 60% whose disease progresses 9 months after starting erlotinib for whom a biopsy is T790M-negative?

 RAMASWAMY GOVINDAN, MD	Discontinue erlotinib and start carbo/pem +/- bev
 JOEL W NEAL, MD, PHD	Discontinue erlotinib and start carbo/pem/bev
 GREGORY J RIELY, MD, PHD	Continue erlotinib and add platinum/pem/bev
 JULIE R BRAHMER, MD	Discontinue erlotinib and start carbo/pem +/- bev or carbo/paclitaxel +/- bev
 COREY J LANGER, MD	Discontinue erlotinib and start carbo/pem/bev if rapid or symptomatic PD
 HEATHER WAKELEE, MD	Discontinue erlotinib and add carbo/pem +/- bev

Carbo = carboplatin; pem = pemetrexed; bev = bevacizumab

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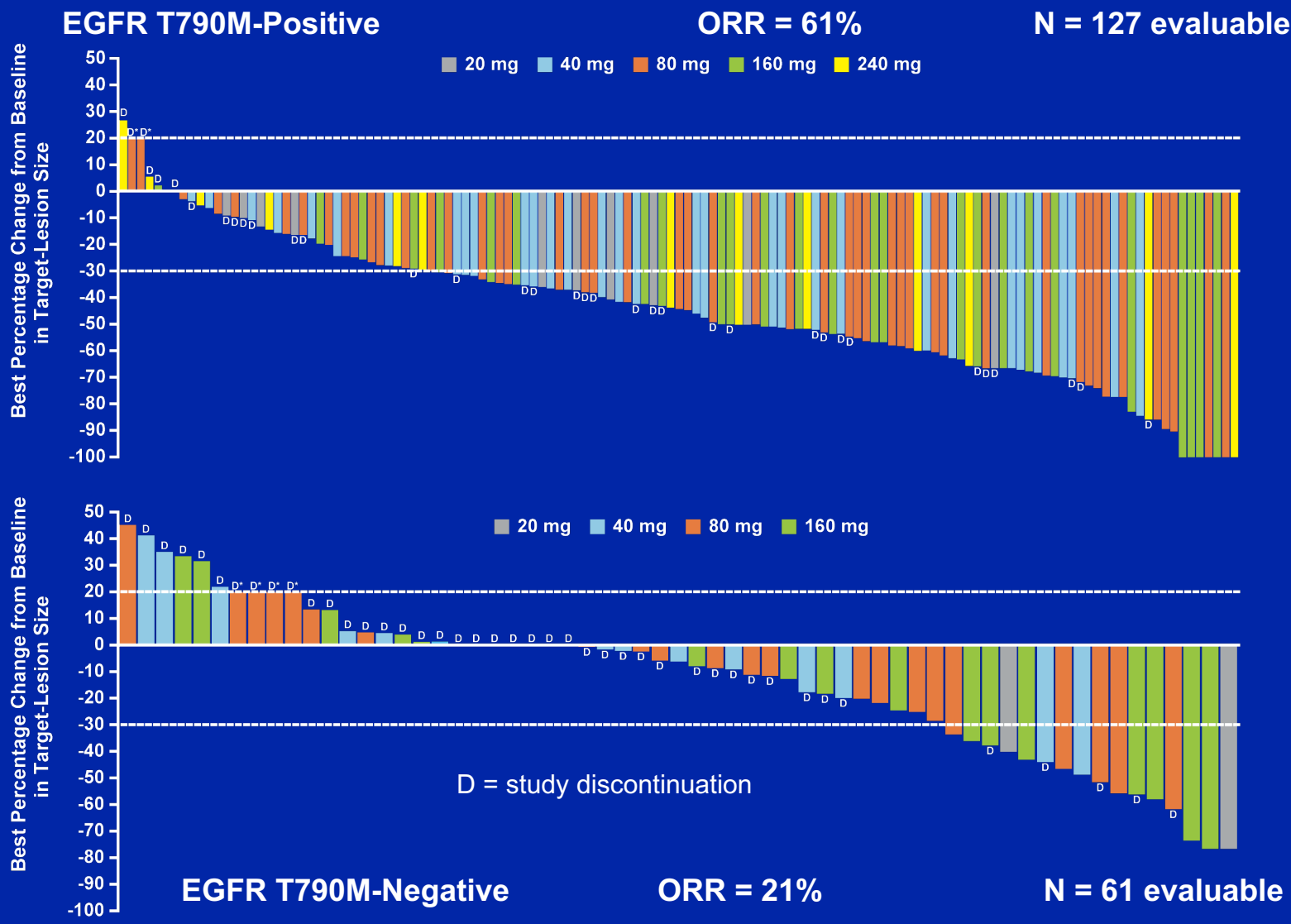
Change in Tumor Size with Osimertinib in EGFR TKI-Resistant T790M Mutation-Positive and -Negative NSCLC



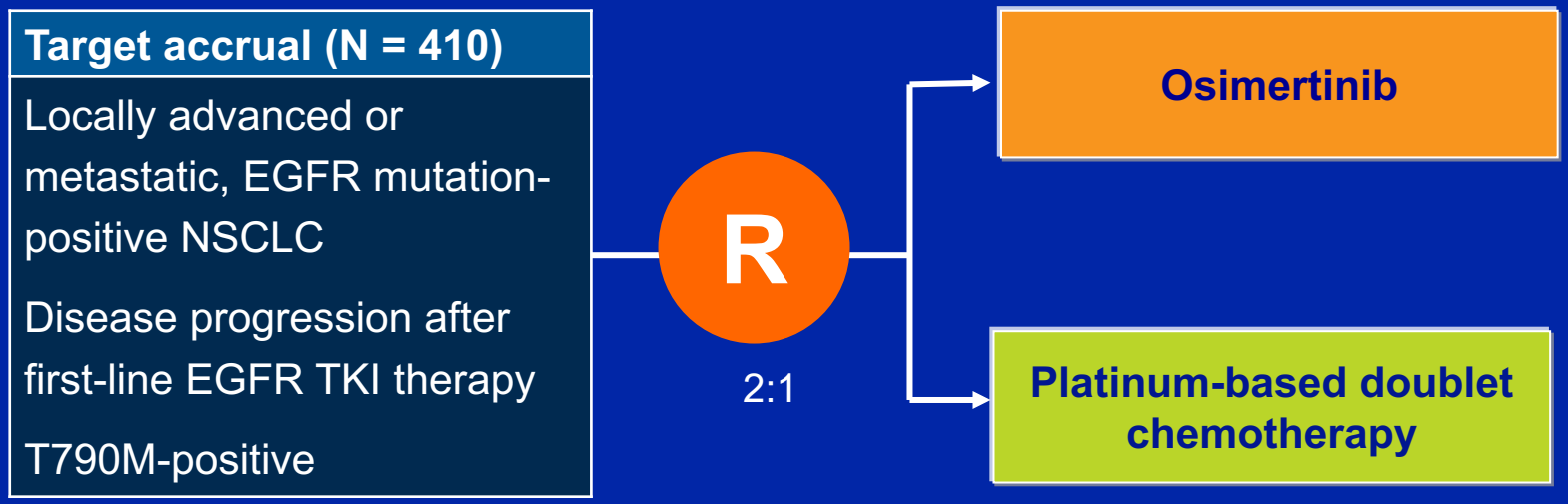
Jänne PA et al. *N Engl J Med* 2015;372(18):1689-99.

Select Adverse Events with Osimertinib

	Osimertinib (N = 253)	
	Any grade	Grade 3-5
Diarrhea	47%	2%
Nausea	22%	<0.5%
Rash	40%	1%
Pruritus	19%	0%
Decreased appetite	21%	1%
Constipation	16%	0%
Hyperglycemia	6 (2.4%)	
QT interval prolongation	11 (4.3%)	
Pneumonitis-like event	6 (2.4%)	

Jänne PA et al. *N Engl J Med* 2015;372(18):1689-99.

AURA3: A Phase III Study of Osimertinib versus Platinum-Based Doublet Chemotherapy for Locally Advanced or Metastatic NSCLC

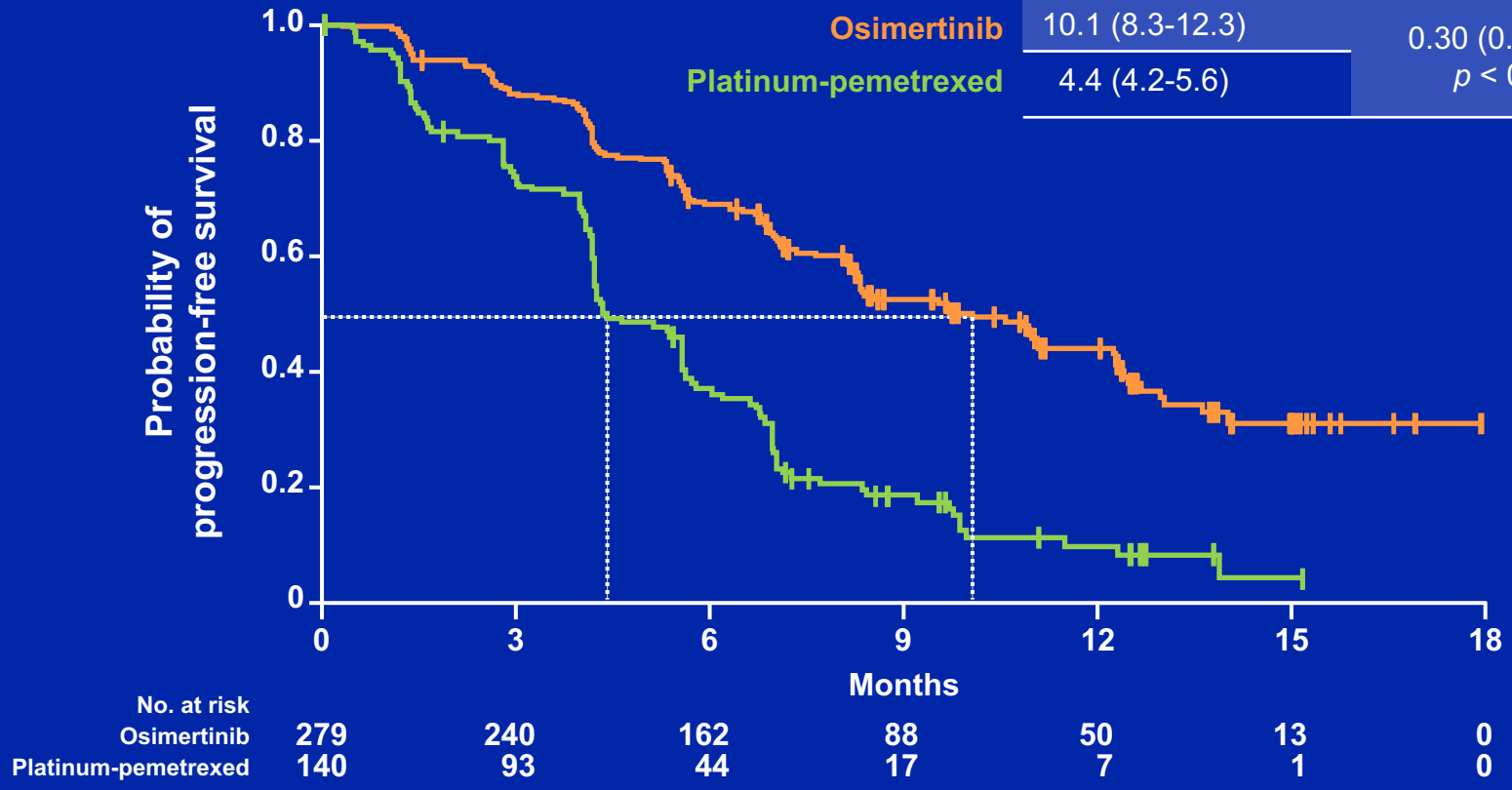


Primary Endpoint: Progression-free survival by investigator assessment
Key Secondary Endpoints: Objective response rate, overall survival and safety

Mok TS et al. *N Engl J Med* 2017;376(7):629-40.

AURA3 Primary Endpoint: PFS by Investigator Assessment

	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	10.1 (8.3-12.3)	0.30 (0.23-0.41) $p < 0.001$
Platinum-pemetrexed	4.4 (4.2-5.6)	



- Analysis of PFS by blinded independent central review was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20-0.38), $p < 0.001$; median PFS 11.0 vs 4.2 months.

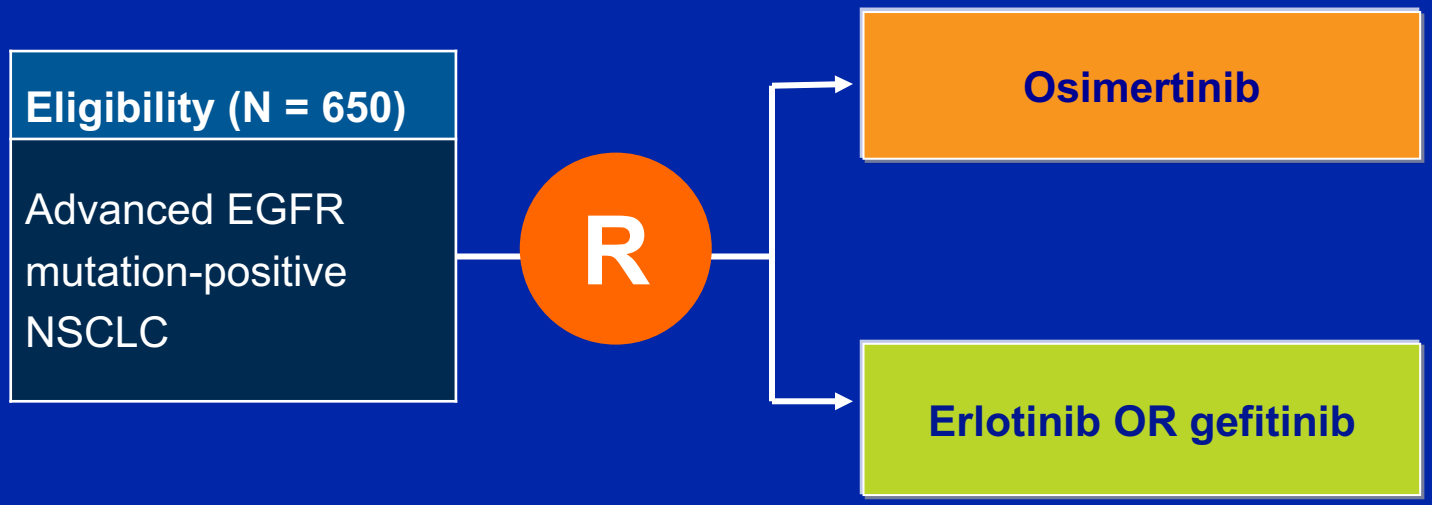
Mok TS et al. *N Engl J Med* 2017;376(7):629-40.

Osimertinib as First-Line Treatment for EGFR Mutation-Positive NSCLC

Outcome	Osimertinib 80 mg (n = 30)	Osimertinib 160 mg (n = 30)	All patients (n = 60)
Objective response rate	67%	87%	77%
Median PFS	Not reached	19.3 mo	19.3 mo

Ramalingam S et al. *Proc ELCC* 2016;Abstract LBA1_PR.

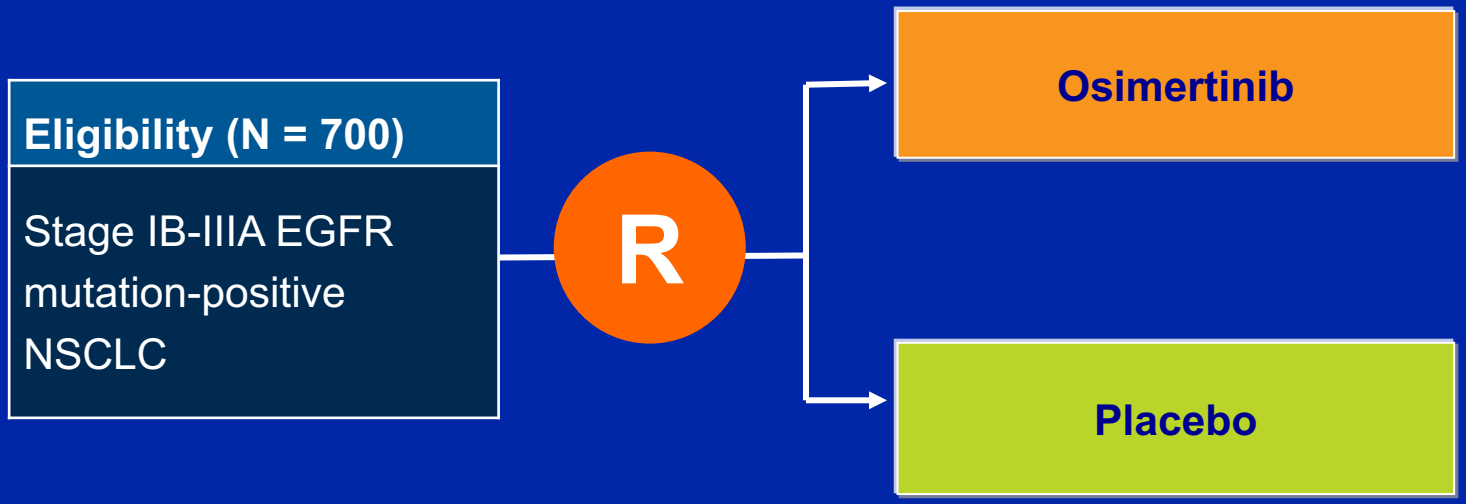
FLAURA: A Phase III Study of Osimertinib versus a Standard-of-Care EGFR TKI as First-Line Treatment for EGFR Mutation-Positive Locally Advanced or Metastatic NSCLC



Primary Endpoint: Progression-free survival
Key Secondary Endpoints: Overall response rate, overall survival and quality of life

www.clinicaltrials.gov. NCT02296125

ADAURA: A Phase III Study of Osimertinib versus Placebo for EGFR Mutation-Positive Stage IB-IIIA NSCLC After Complete Tumor Resection with or without Adjuvant Chemotherapy



Primary Endpoint: Disease-free survival
Key Secondary Endpoints: Overall survival and quality of life

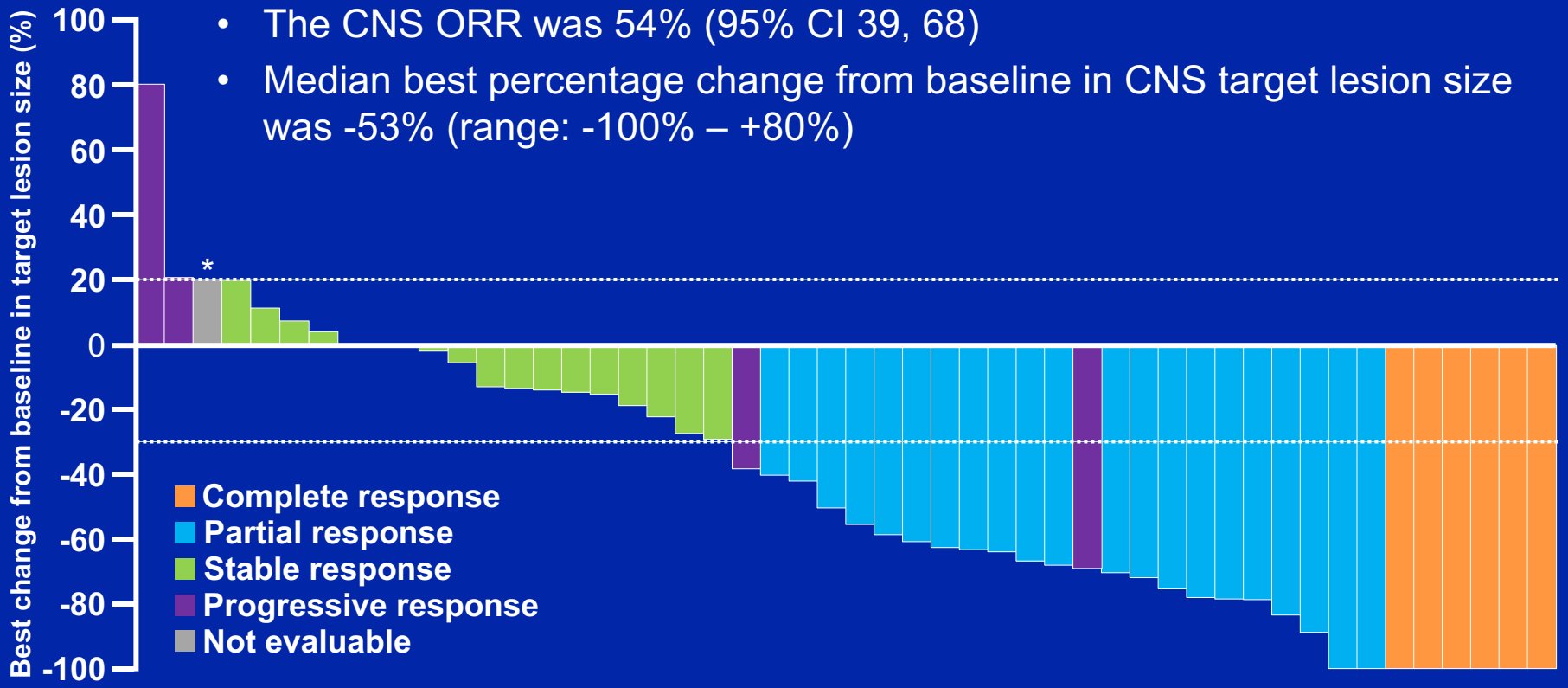
www.clinicaltrials.gov. NCT02511106

Cost and reimbursement issues aside, for a patient with untreated EGFR-mutant, widely metastatic nonsquamous cancer with multiple bilateral asymptomatic brain metastases that would require whole brain radiation therapy, do you generally start with a TKI and hold radiation therapy?

 RAMASWAMY GOVINDAN, MD	Yes, erlotinib
 JOEL W NEAL, MD, PHD	Yes, erlotinib
 GREGORY J RIELY, MD, PHD	Yes, erlotinib
 JULIE R BRAHMER, MD	Yes, afatinib
 COREY J LANGER, MD	Yes, erlotinib if exon 21
 HEATHER WAKELEE, MD	Yes, erlotinib

CNS Response to Osimertinib in Patients with T790M-Positive Advanced NSCLC: Pooled Data from Two Phase II Trials

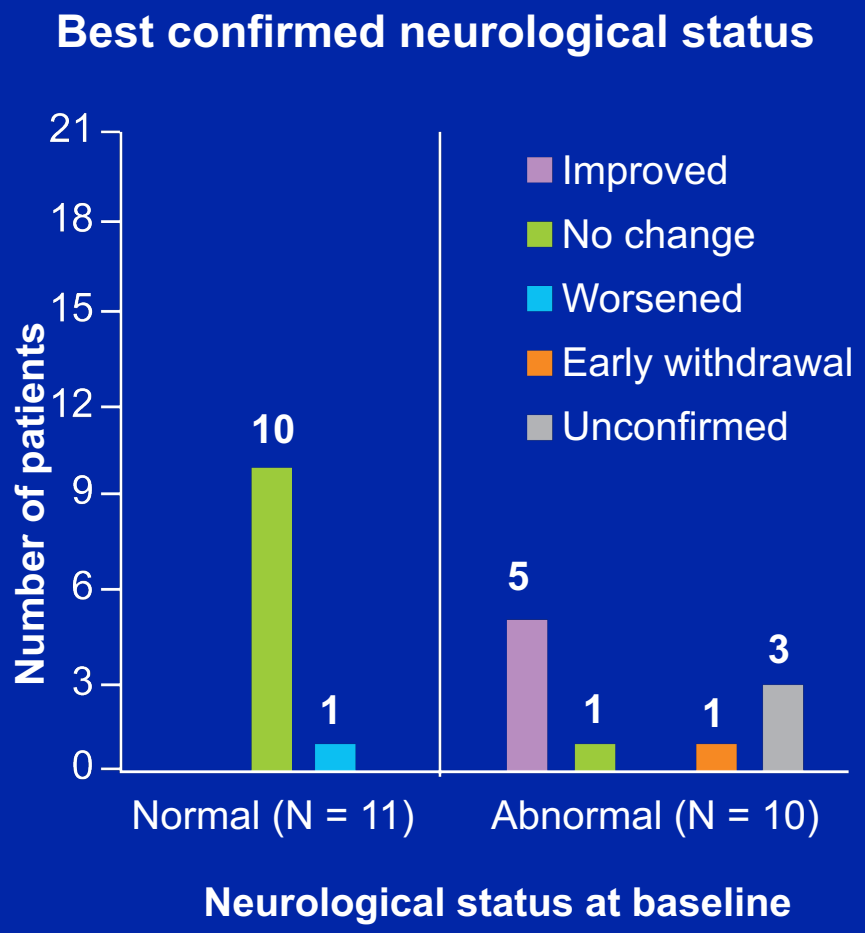
- The CNS ORR was 54% (95% CI 39, 68)
- Median best percentage change from baseline in CNS target lesion size was -53% (range: -100% – +80%)



Goss G et al. *Proc WCLC* 2016;Abstract MA16.11.

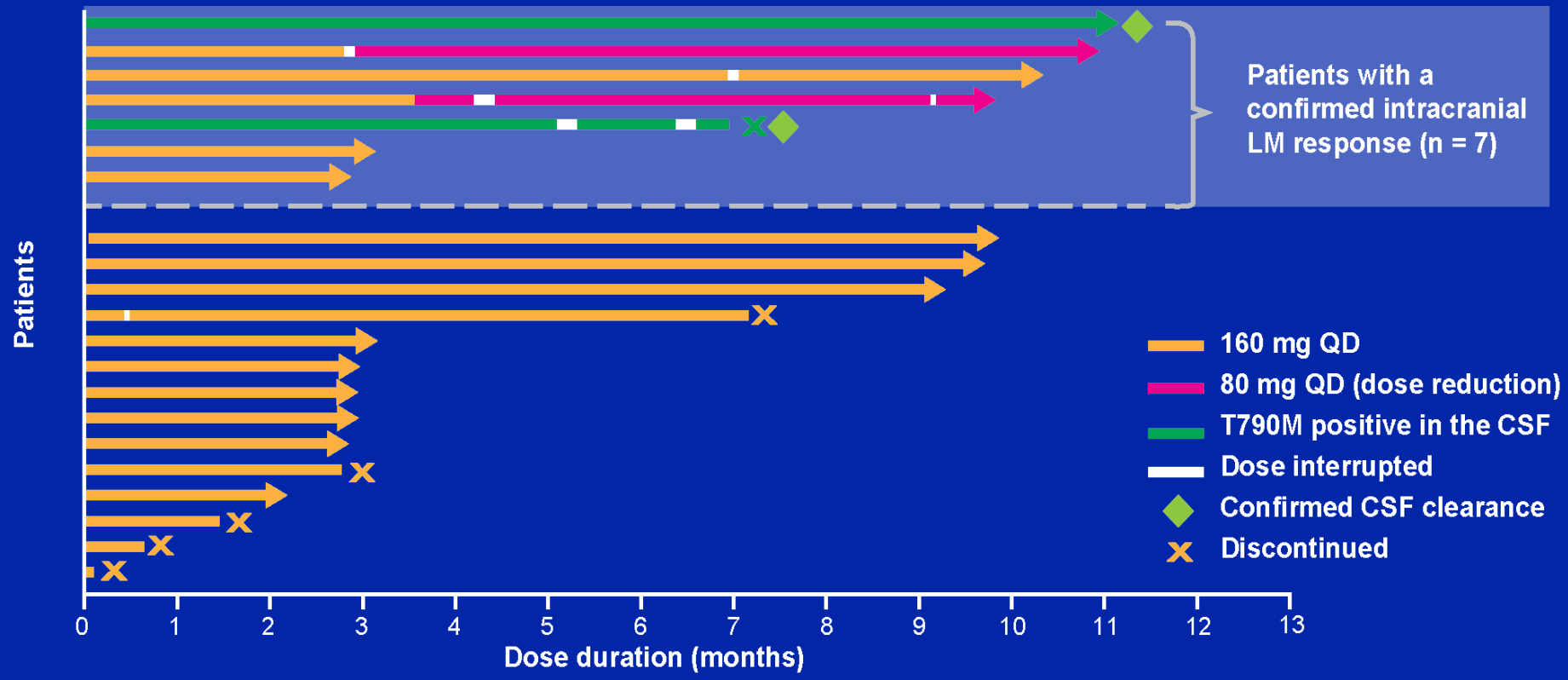
BLOOM: Activity of Osimertinib Across Leptomeningeal Assessments

Best MRI intracranial response, n (%)	N = 21	
	Confirmed	Unconfirmed
Responding	7 (33)	1 (5)
Stable disease	9 (43)	2 (10)
Early withdrawal	2 (10)	



Yang JC et al. *Proc ASCO* 2016;Abstract 9002.

BLOOM: Time on Treatment with Osimertinib for Patients with Leptomeningeal Carcinomatosis



Yang JC et al. *Proc ASCO* 2016;Abstract 9002.

In general, when do you believe checkpoint inhibitors should be introduced into the treatment of patients with EGFR-mutant NSCLC and a TPS of <50%? Have you observed any meaningful clinical responses to anti-PD-1/PD-L1 antibodies in a patient with an EGFR or other tumor driver mutation?

	CHECKPOINT INHIBITORS FOR EGFR+, TPS <50%	MEANINGFUL CLINICAL RESPONSES?
 RAMASWAMY GOVINDAN, MD	After appropriate targeted treatment and 2 lines of chemotherapy	No
 JOEL W NEAL, MD, PHD	After appropriate targeted treatment and 1 line of chemotherapy	No
 GREGORY J RIELY, MD, PHD	After EGFR TKIs and platinum doublet with bevacizumab	Yes
 JULIE R BRAHMER, MD	After appropriate targeted treatment and 1 line of chemotherapy	Yes
 COREY J LANGER, MD	After appropriate targeted treatment and 1 line of chemotherapy	No
 HEATHER WAKELEE, MD	After appropriate targeted treatment and 1 line of chemotherapy	Yes

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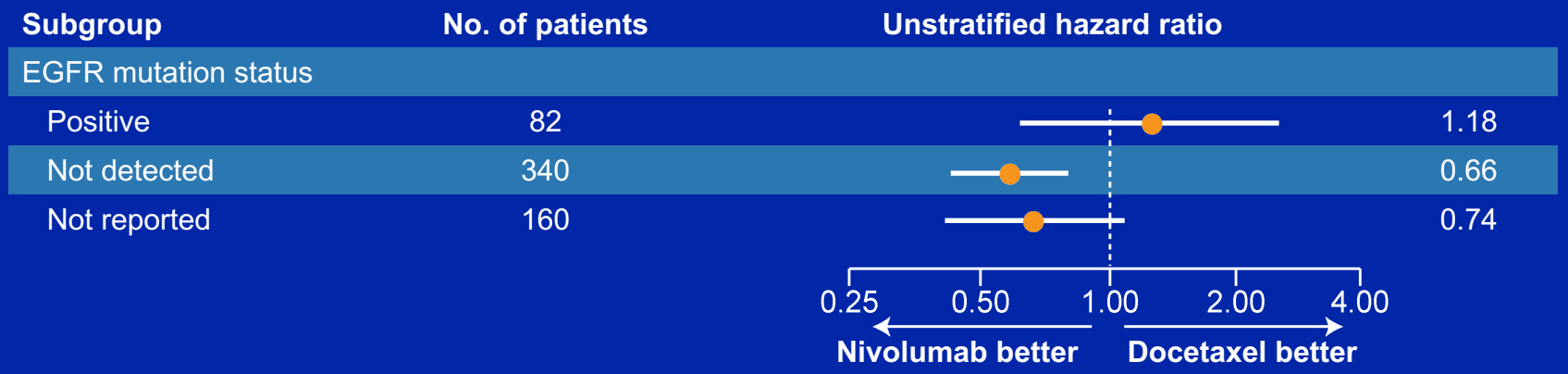
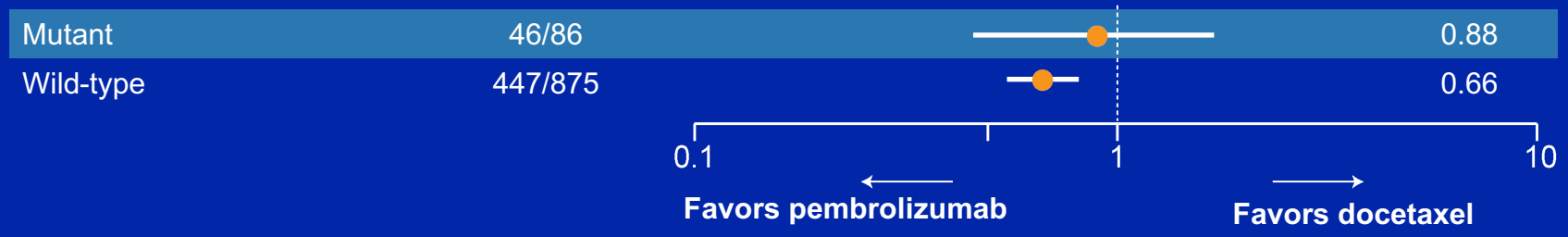
Association between Overall Survival and EGFR Mutation Status in Response to PD-1 Pathway Blockade

CheckMate 057[1]: Nivolumab vs docetaxel

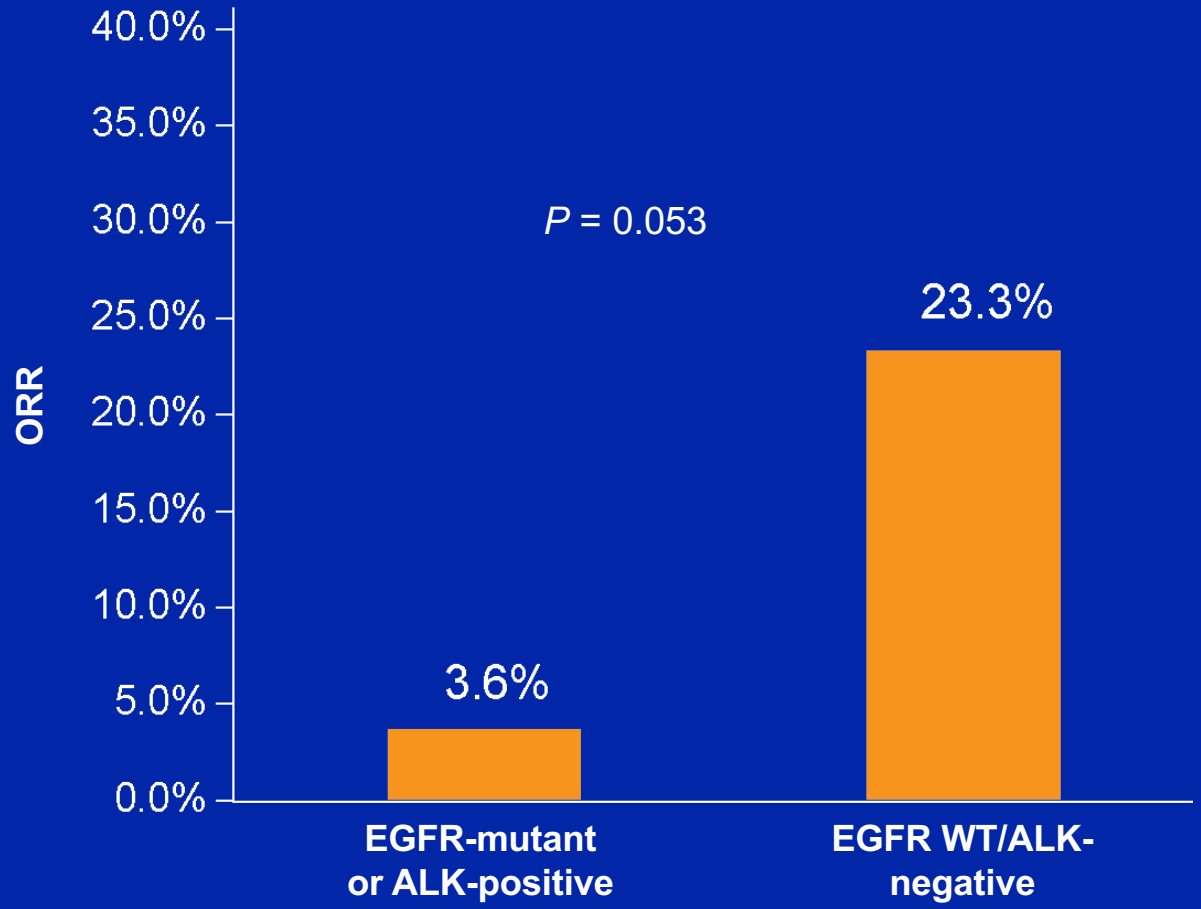


KEYNOTE-010[2]: Pembrolizumab vs docetaxel



[1] Borghaei H et al. *N Engl J Med* 2015;373(17):1627-39; [2] Herbst RS et al. *Lancet* 2016; 387(10027):1540-50.

Association between Response Rates to PD-1 Pathway Blockade and EGFR and ALK Status in NSCLC



Gainor JF et al. *Clin Cancer Res* 2016;22(18):4585-93.