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

Ramaswamy Govindan, MD
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

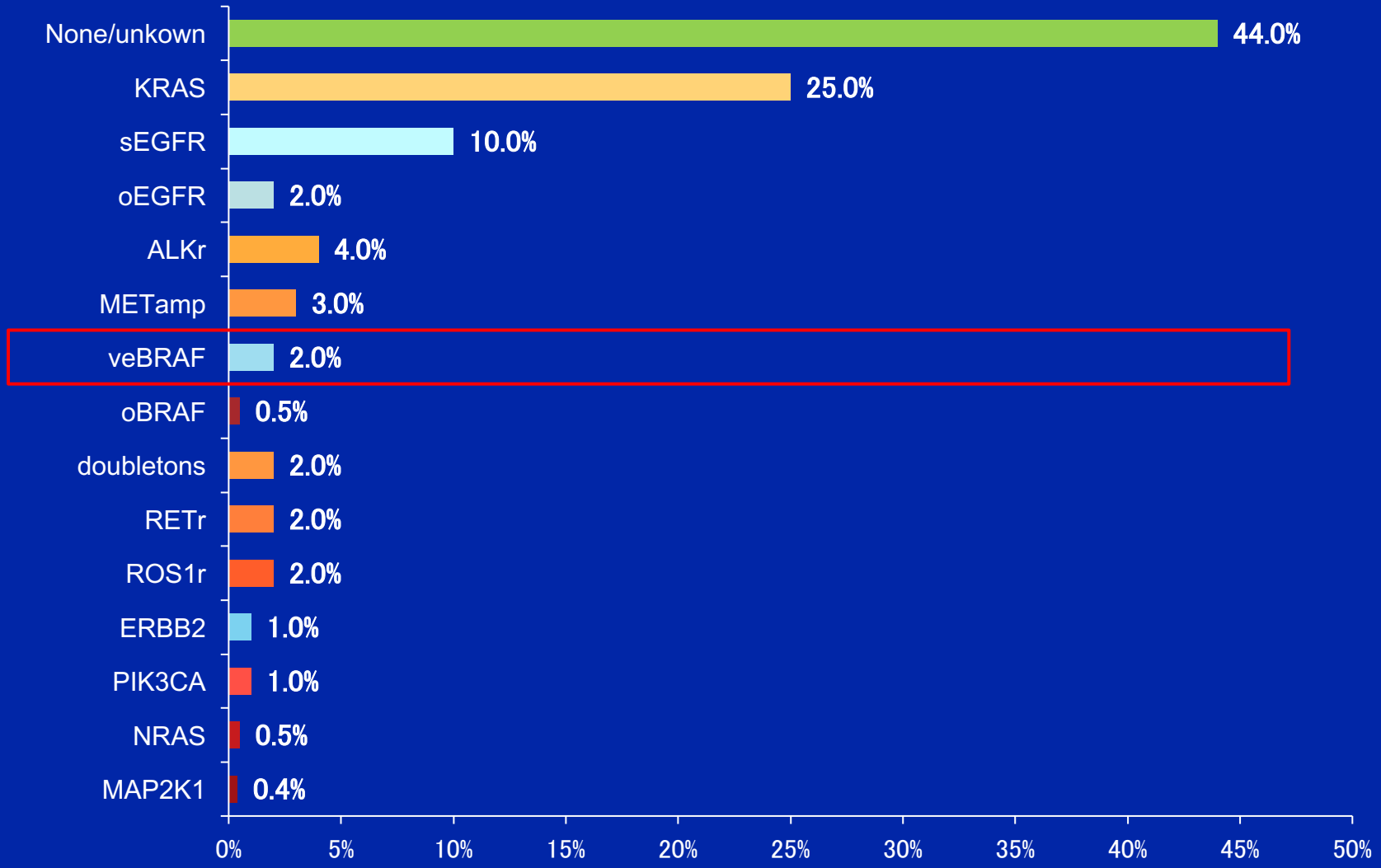
Consulting Agreement	Genentech BioOncology
Contracted Research	Ariad Pharmaceuticals Inc, Astellas Pharma Global Development Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc

Disclosures for Moderator Neil Love, MD

Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma, Agendia Inc, Amgen Inc, Ariad Pharmaceuticals Inc, Array BioPharma Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Baxalta Inc, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, CTI BioPharma Corp, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Halozyme Inc, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lexicon Pharmaceuticals Inc, Lilly, Medivation Inc, a Pfizer Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, NanoString Technologies, Natera Inc, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seattle Genetics, Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro Inc, Teva Oncology, Tokai Pharmaceuticals Inc and VisionGate Inc.

Module 3: Treatment of Patients with Other Potentially Targetable Tumor Mutations (BRAF V600E, MET, RET, et cetera)

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



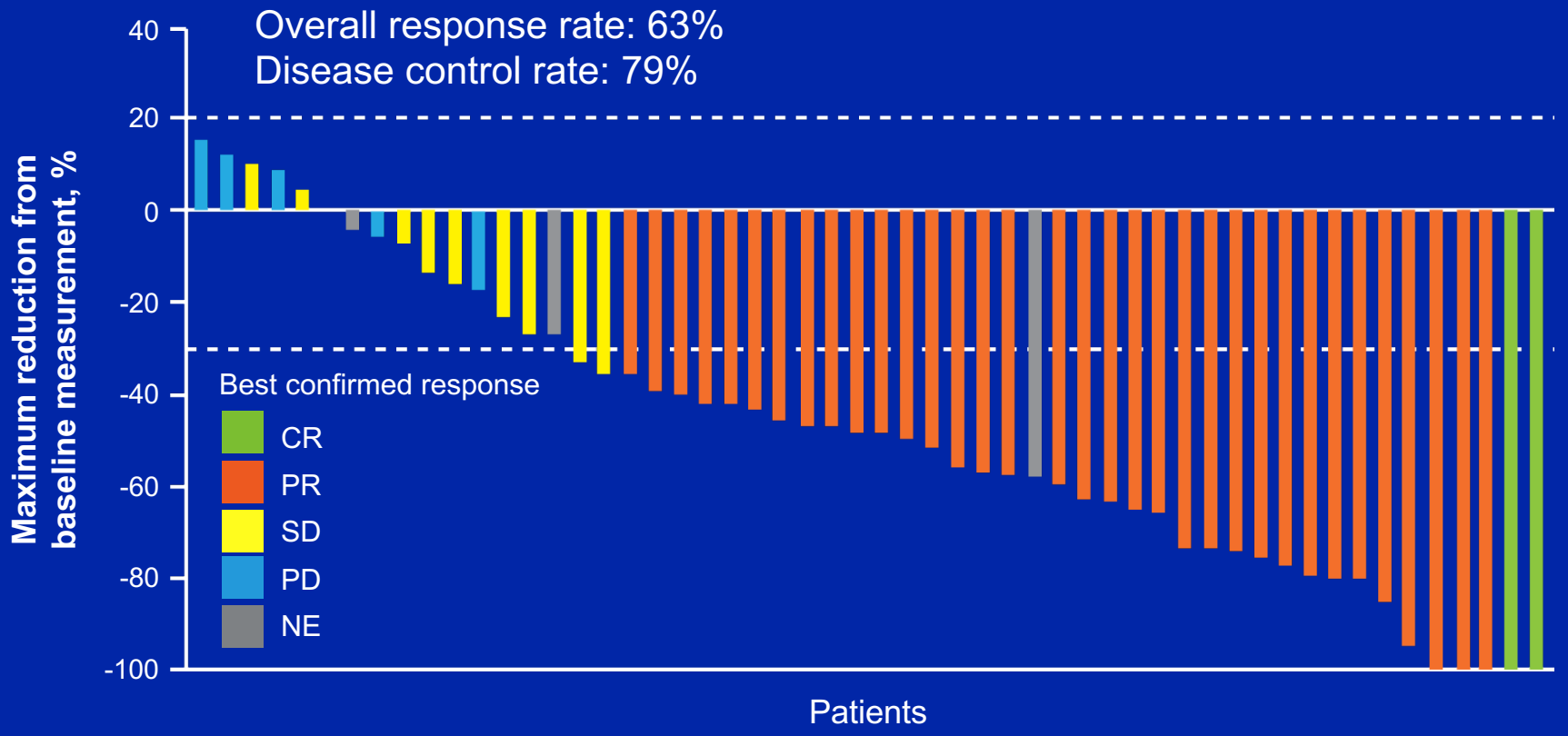
s = sensitizing; r = rearrangement; o = other; veBRAF = BRAF V600E

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

Cost and reimbursement issues aside, what targeted therapy, if any, would you most likely recommend for a patient with metastatic NSCLC and a BRAF V600E tumor mutation? In which line of therapy, if any, would you most likely administer a BRAF inhibitor (with or without a MEK inhibitor)?

	TARGETED THERAPY	LINE OF TREATMENT
 RAMASWAMY GOVINDAN, MD	Dabrafenib with trametinib	First line
 JOEL W NEAL, MD, PHD	Dabrafenib and trametinib	First line
 GREGORY J RIELY, MD, PHD	Dabrafenib with trametinib	First line
 JULIE R BRAHMER, MD	Dabrafenib with trametinib	Second line
 COREY J LANGER, MD	Dabrafenib with trametinib	First line
 HEATHER WAKELEE, MD	Dabrafenib with trametinib	Second line

Dabrafenib and Trametinib in BRAF V600E-Mutant Metastatic NSCLC



NE patients did not have a follow-up scan required for confirmation.

Planchard D et al. *Lancet Oncol* 2016;17:984-93.

Dabrafenib and Trametinib Combination Receives FDA Breakthrough Therapy Designation in NSCLC

The FDA breakthrough therapy designation in BRAF V600 mutation-positive NSCLC is based on interim analysis results from an ongoing single-arm, 2-stage Phase II trial investigating the combination in patients with metastatic NSCLC who had the BRAF V600E mutation and failed at least 1 line of chemotherapy. The data showed an ORR of 63% based on investigator assessment. The most common adverse events (incidence ≥20%) among patients included in this analysis were pyrexia, diarrhea, nausea, vomiting, decreased appetite, asthenia, cough, peripheral edema and rash.

https://www.novartis.com/news/media-releases/novartis-combination-therapy-tafinlar%C2%AE-and-mekinist%C2%AE-achieves-important-eu-and

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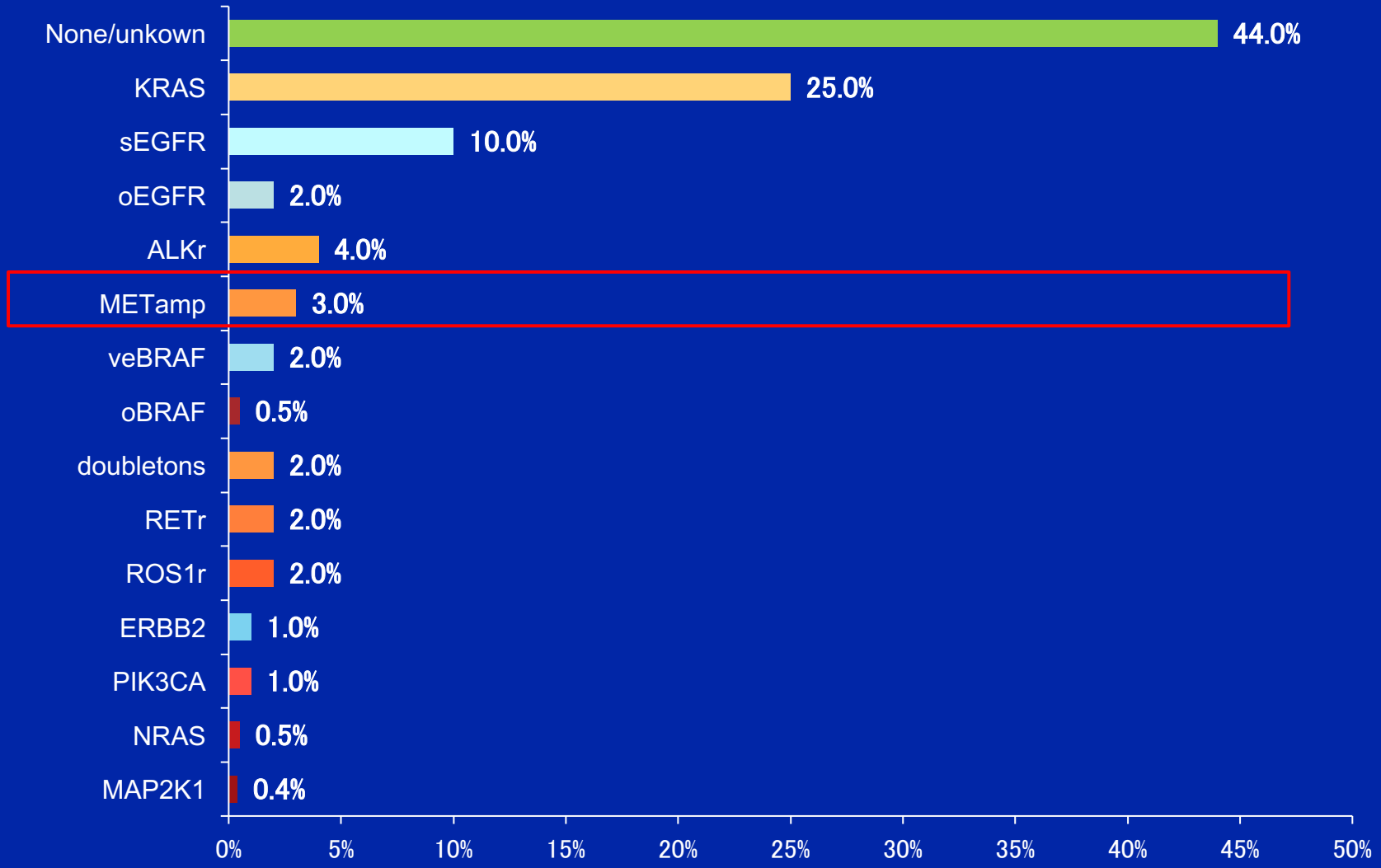

s = sensitizing; r = rearrangement; o = other; veBRAF = BRAF V600E

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

Outside of a protocol setting, do you generally use targeted therapy for patients with NSCLC and a MET exon 14 alteration?

 RAMASWAMY GOVINDAN, MD	Yes, first line
 JOEL W NEAL, MD, PHD	Yes, crizotinib (and cabozantinib once) in second line, before checkpoint inhibitor
 GREGORY J RIELY, MD, PHD	Yes, crizotinib during any line
 JULIE R BRAHMER, MD	Yes, second line with crizotinib
 COREY J LANGER, MD	Yes, crizotinib in first line
 HEATHER WAKELEE, MD	Yes, crizotinib after first-line chemotherapy

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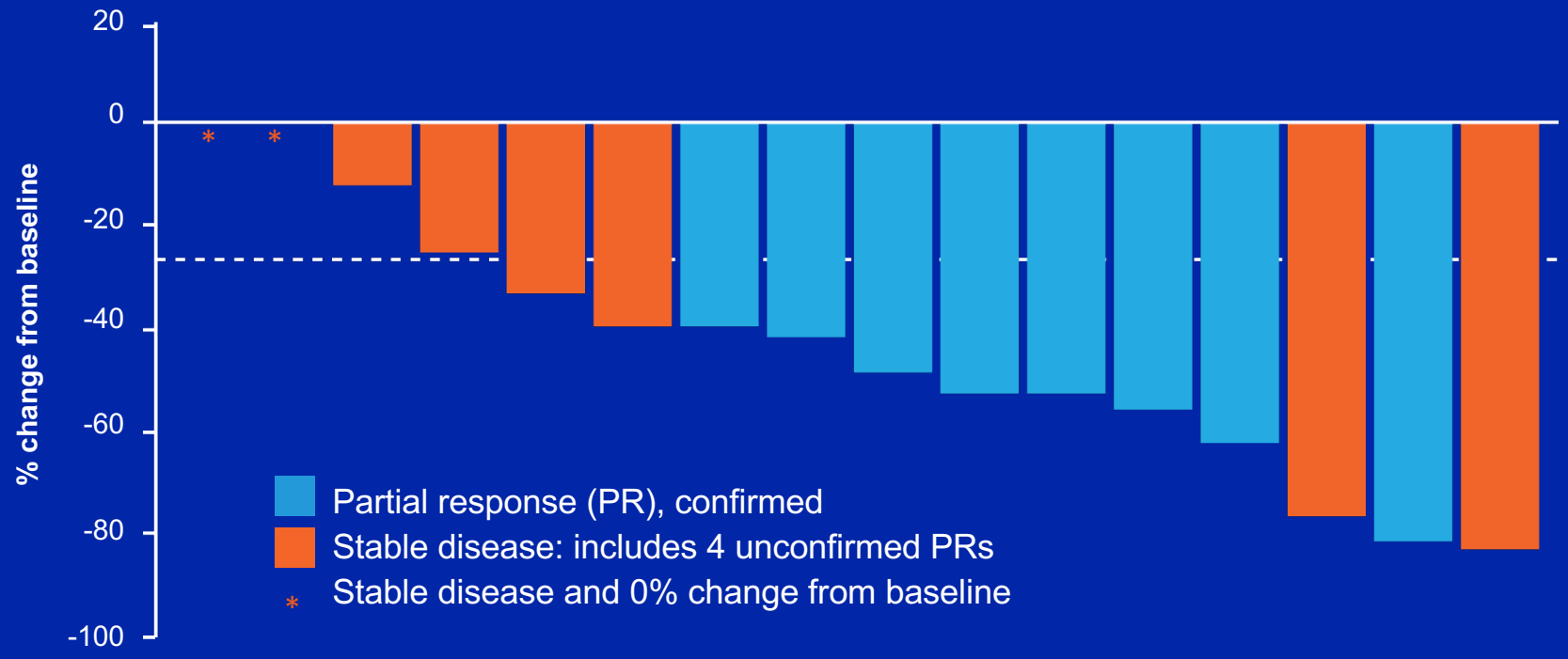
MET Exon 14 Alterations

- MET exon 14 encodes the ubiquitin ligase binding site which is used in receptor degradation
- MET exon 14 alterations are heterogeneous and encompass deletions, insertions and base substitutions.
- Many of these mutations disrupt splice sites resulting in MET exon 14 skipping and produce a MET receptor that lacks ubiquitin binding site → reduced degradation of MET protein → sustained MET activation
- Next-generation sequencing is the preferred testing method
- MET exon 14 alterations occur in approximately 3% of lung adenocarcinoma, 2% of squamous cell carcinoma, and 20% of pulmonary sarcomatoid carcinoma

Drilon A et al. *Proc ASCO* 2016;Abstract 108; Reungwetwattana T et al. *Lung Cancer* 2017;103:27-37.

Antitumor Activity of Crizotinib in Advanced MET Exon 14-Altered NSCLC

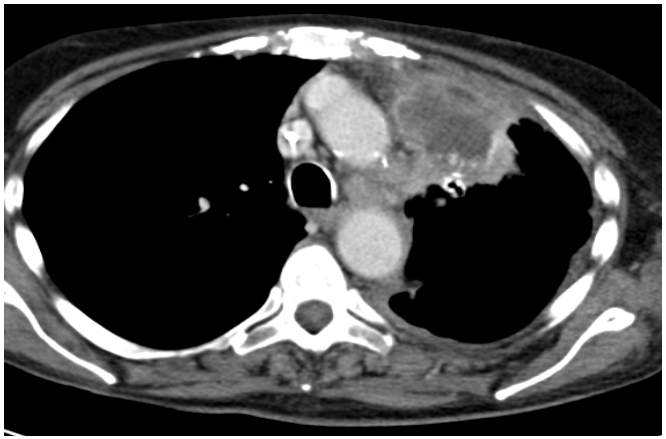
Maximum Response to Crizotinib in Patients with MET Exon 14-Altered Lung Cancers
(n = 16 with measurable disease at baseline and ≥1 response assessment scan)

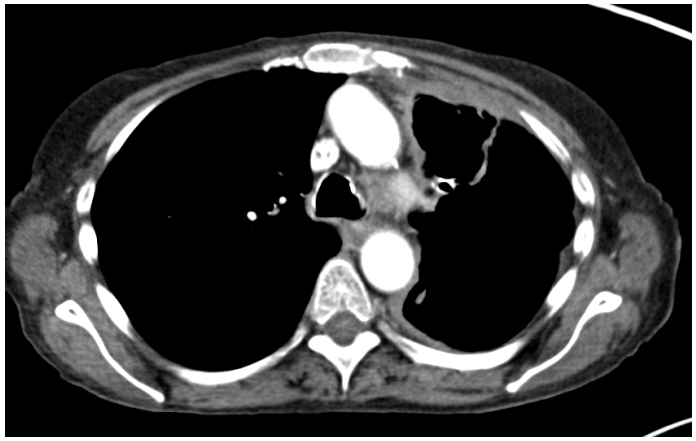


Drilon AE et al. *Proc ASCO* 2016;Abstract 108.

Cabozantinib in MET e14 splice alterations

- Stanford series of 14 identified patients with MET e14 alterations, of which 6 were treated with a MET inhibitor (mostly crizotinib)
- 76F with MET e14 adenocarcinoma identified following carbo/pem and nivolumab failure.
- Crizotinib was started – rash, angioedema, pruritis after 1 week. Failed re-challenge. Took drug holiday.
- Cabozantinib started, scans showed great response with necrosis





S Wang, Chicago Multidisciplinary Symposium 2016

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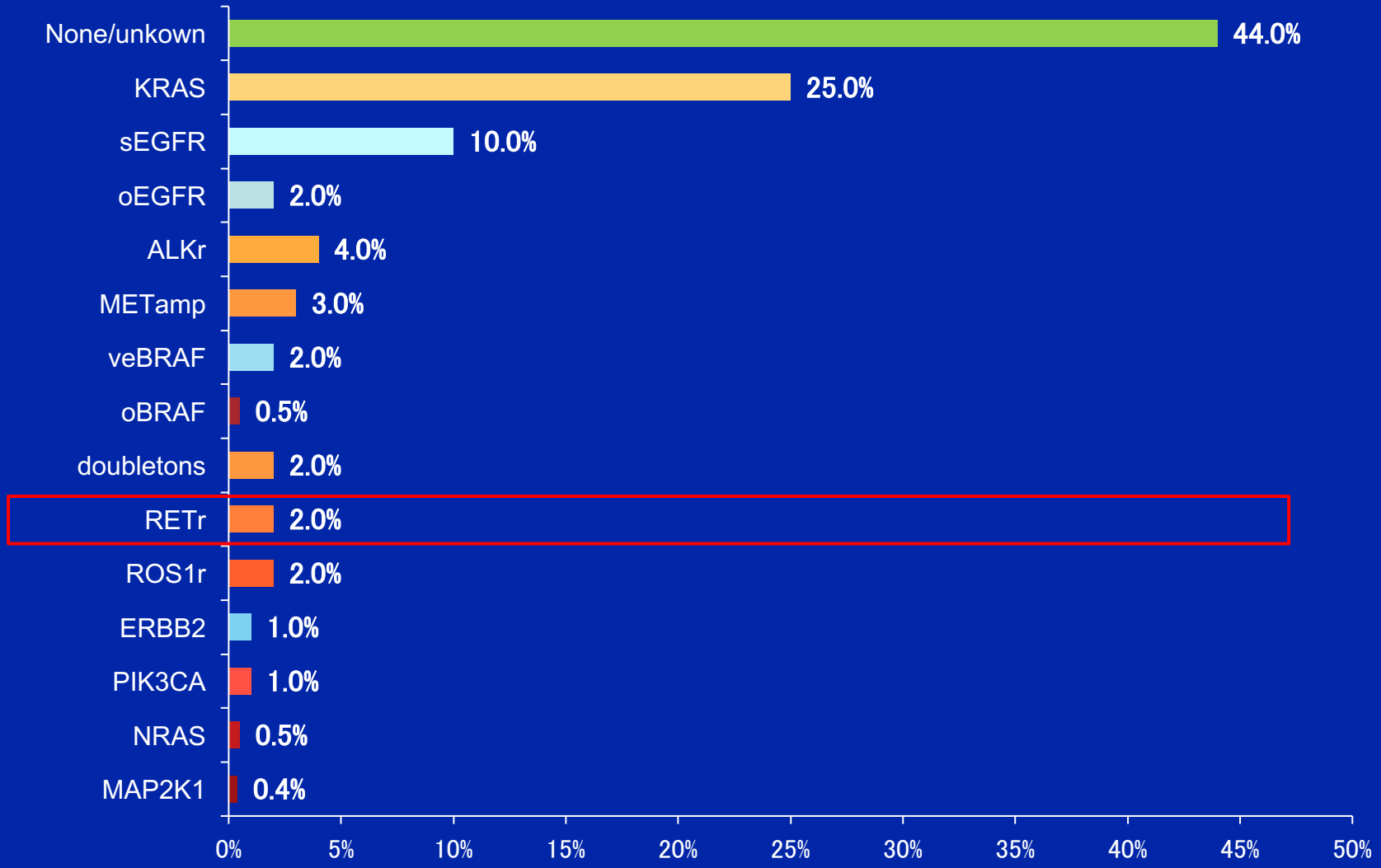


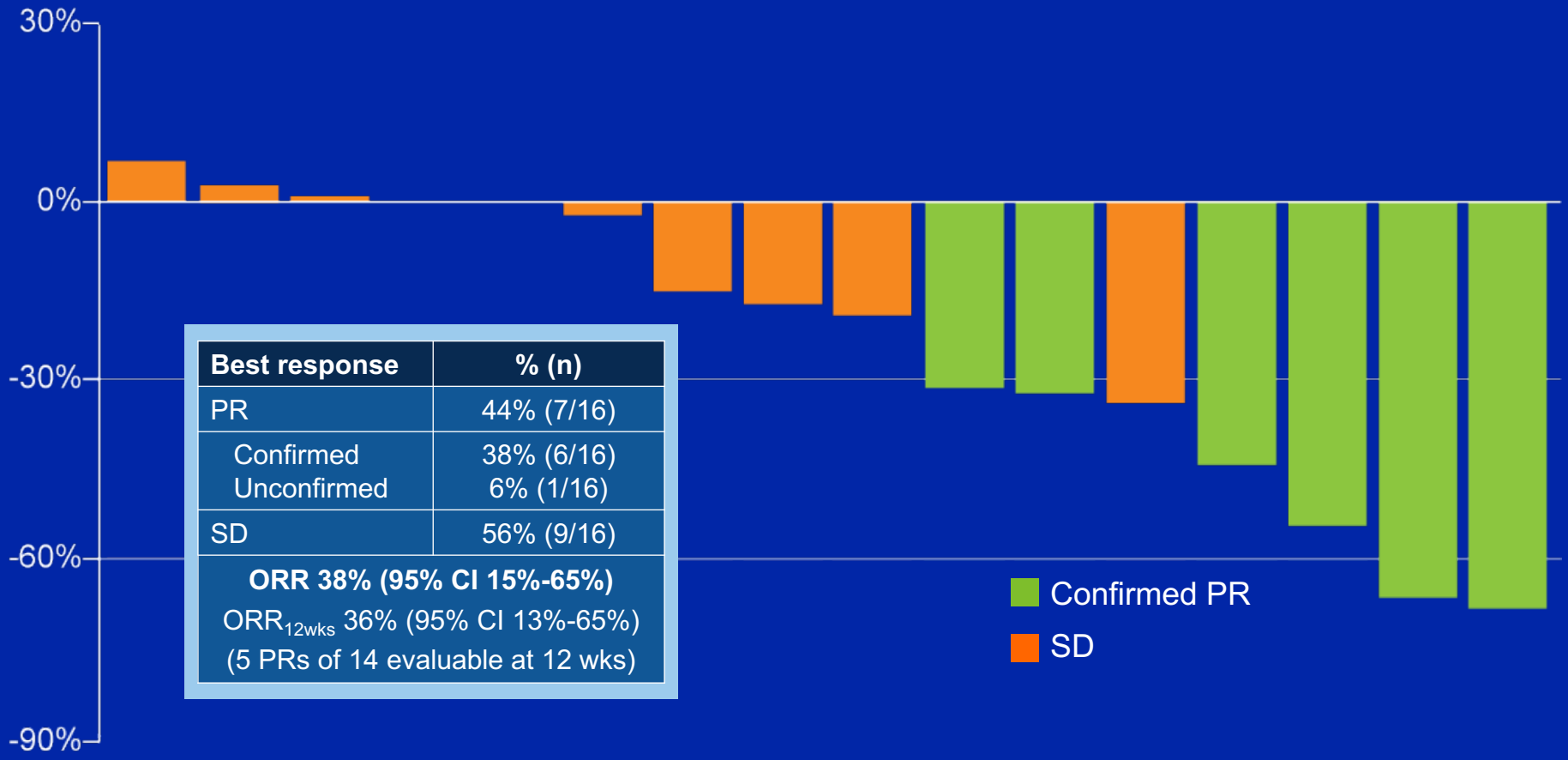
s = sensitizing; r = rearrangement; o = other; veBRAF = BRAF V600E

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

Outside of a protocol setting, do you generally use targeted therapy for patients with metastatic NSCLC and a tumor RET rearrangement?

 RAMASWAMY GOVINDAN, MD	Yes, cabozantinib in second line
 JOEL W NEAL, MD, PHD	Yes, cabozantinib in second or third line
 GREGORY J RIELY, MD, PHD	Yes, any line
 JULIE R BRAHMER, MD	Yes, vandetanib and everolimus in patient with leptomeningeal disease in second line and beyond
 COREY J LANGER, MD	Yes, cabozantinib in second or third line
 HEATHER WAKELEE, MD	Yes, cabozantinib in second or third line

Response to Cabozantinib in Advanced RET-Rearranged Lung Cancer



Best response	% (n)
PR	44% (7/16)
Confirmed	38% (6/16)
Unconfirmed	6% (1/16)
SD	56% (9/16)
ORR 38% (95% CI 15%-65%)	
ORR_{12wks} 36% (95% CI 13%-65%) (5 PRs of 14 evaluable at 12 wks)	

PR = partial response; SD = stable disease; ORR = overall response rate

Drilon AE et al. *Proc ASCO* 2015;Abstract 8007.

Cost and reimbursement issues aside, what targeted therapy (alone or with chemotherapy), if any, would you most likely recommend for a patient with metastatic NSCLC and a HER2 tumor mutation?

 RAMASWAMY GOVINDAN, MD	Neratinib
 JOEL W NEAL, MD, PHD	Trastuzumab + either taxane or vinorelbine
 GREGORY J RIELY, MD, PHD	T-DM1
 JULIE R BRAHMER, MD	Trastuzumab, lapatinib, trastuzumab/lapatinib, afatinib, T-DM1, pertuzumab
 COREY J LANGER, MD	Trastuzumab with carboplatin/paclitaxel
 HEATHER WAKELEE, MD	Trastuzumab + docetaxel, afatinib or T-DM1

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Do you believe there are currently any other actionable tumor mutations beyond those mentioned previously?

 RAMASWAMY GOVINDAN, MD	Yes, TSC1/TSC2 and DDR2
 JOEL W NEAL, MD, PHD	High MET amplification, NTRK alterations but only in clinical trials
 GREGORY J RIELY, MD, PHD	No
 JULIE R BRAHMER, MD	Yes, NTRK alterations
 COREY J LANGER, MD	Yes, NTRK and others
 HEATHER WAKELEE, MD	Yes, but only with clinical trial implications

Ongoing Phase II Trials Evaluating NTRK1-Targeted Agents in NSCLC

Therapeutic agent	Trial identifier	Phase	Study population
Entrectinib	STARTRK-2: NCT02568267 (Open)	II	• Locally advanced or metastatic NSCLC with NTRK rearrangement
Cabozantinib	NCT01639508 (Open)	II	• Group B: Metastatic or unresectable NSCLC with NTRK rearrangement
Larotrectinib (LOXO-101)	NAVIGATE: NCT02576431 (Open)	II	• Locally advanced or metastatic NSCLC with NTRK rearrangement

www.clinicaltrials.gov. Accessed March 2017.