CONSENSUS OR CONTROVERSY?

Clinical Investigators Provide Perspectives on the Treatment of Metastatic Non-Small Cell Lung Cancer in Patients Without Targetable Tumor Mutations

March 17, 2017
7:30 PM – 9:00 PM

Faculty

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Moderator

Neil Love, MD

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Disclosures for Dr Brahmer

Advisory Committee	Bristol-Myers Squibb Company, Merck
Consulting Agreements	Bristol-Myers Squibb Company, Celgene Corporation, Lilly, Merck
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Merck

Disclosures for Dr Langer

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Contracted Research	Advantagene Inc, Celgene Corporation, GlaxoSmithKline, Merck, Inovio Pharmaceuticals
Data and Safety Monitoring Board	Abbott Laboratories, Amgen Inc, Lilly, Peregrine Pharmaceuticals Inc, Synta Pharmaceuticals Corp

Disclosures for Dr Rizvi

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

Disclosures for Dr Wakelee

Consulting Agreements	ACEA Biosciences Inc, Genentech BioOncology, Helsinn Group, Peregrine Pharmaceuticals Inc, Pfizer Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Exelixis Inc, Genentech BioOncology, Gilead Sciences Inc, Lilly, Novartis Pharmaceuticals Corporation, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Roche Laboratories Inc, Xcovery
Grants	Clovis Oncology, Exelixis Inc, Gilead Sciences Inc, Pharmacyclics LLC, an AbbVie Company, Xcovery

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 2: Second- and Later-Line Therapy

A 60-year-old current smoker with asymptomatic squamous cell cancer of the lung with limited pulmonary metastases and a TPS of 70% receives pembrolizumab but on first evaluation is found to have disease progression on imaging with new lesions and is still asymptomatic. What would be your most likely treatment recommendation? What if the patient were moderately symptomatic?

	ASYMPTOMATIC	SYMPTOMATIC
 JULIE R BRAHMER, MD	Continue pembrolizumab	Carbo/*nab* paclitaxel
 COREY J LANGER, MD	Continue pembrolizumab	Carbo/*nab* paclitaxel +/- ramucirumab
 HEATHER WAKELEE, MD	Carbo/gem +/- ramucirumab	Carbo/gem +/- ramucirumab
 RAMASWAMY GOVINDAN, MD	Carbo/*nab* paclitaxel +/- ramucirumab	Continue pembrolizumab and add carbo/*nab* paclitaxel
 JOEL W NEAL, MD, PHD	Carbo/paclitaxel	Carbo/paclitaxel
 GREGORY J RIELY, MD, PHD	Cis/gem	Cis/gem

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A patient with metastatic squamous cell lung cancer and a PD-L1 TPS of <1% receives first-line chemotherapy and experiences asymptomatic disease progression. What would you most likely recommend for this patient? What if the patient were symptomatic?

	ASYMPTOMATIC	SYMPTOMATIC
 JULIE R BRAHMER, MD	Nivolumab	Nivolumab
 COREY J LANGER, MD	Atezolizumab	Atezolizumab
 HEATHER WAKELEE, MD	Atezolizumab	Atezolizumab
 RAMASWAMY GOVINDAN, MD	Atezolizumab	Atezolizumab
 JOEL W NEAL, MD, PHD	Atezolizumab	Atezolizumab
 GREGORY J RIELY, MD, PHD	Atezolizumab	Atezolizumab

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A patient with metastatic nonsquamous lung cancer and a PD-L1 TPS of <1% receives first-line chemotherapy and experiences asymptomatic disease progression. What would you most likely recommend for this patient? What if the patient were symptomatic?

	ASYMPTOMATIC	SYMPTOMATIC
 JULIE R BRAHMER, MD	Nivolumab	Nivolumab
 COREY J LANGER, MD	Atezolizumab	Atezolizumab
 HEATHER WAKELEE, MD	Atezolizumab	Atezolizumab
 RAMASWAMY GOVINDAN, MD	Atezolizumab	Atezolizumab
 JOEL W NEAL, MD, PHD	Atezolizumab	Atezolizumab
 GREGORY J RIELY, MD, PHD	Atezolizumab	Atezolizumab

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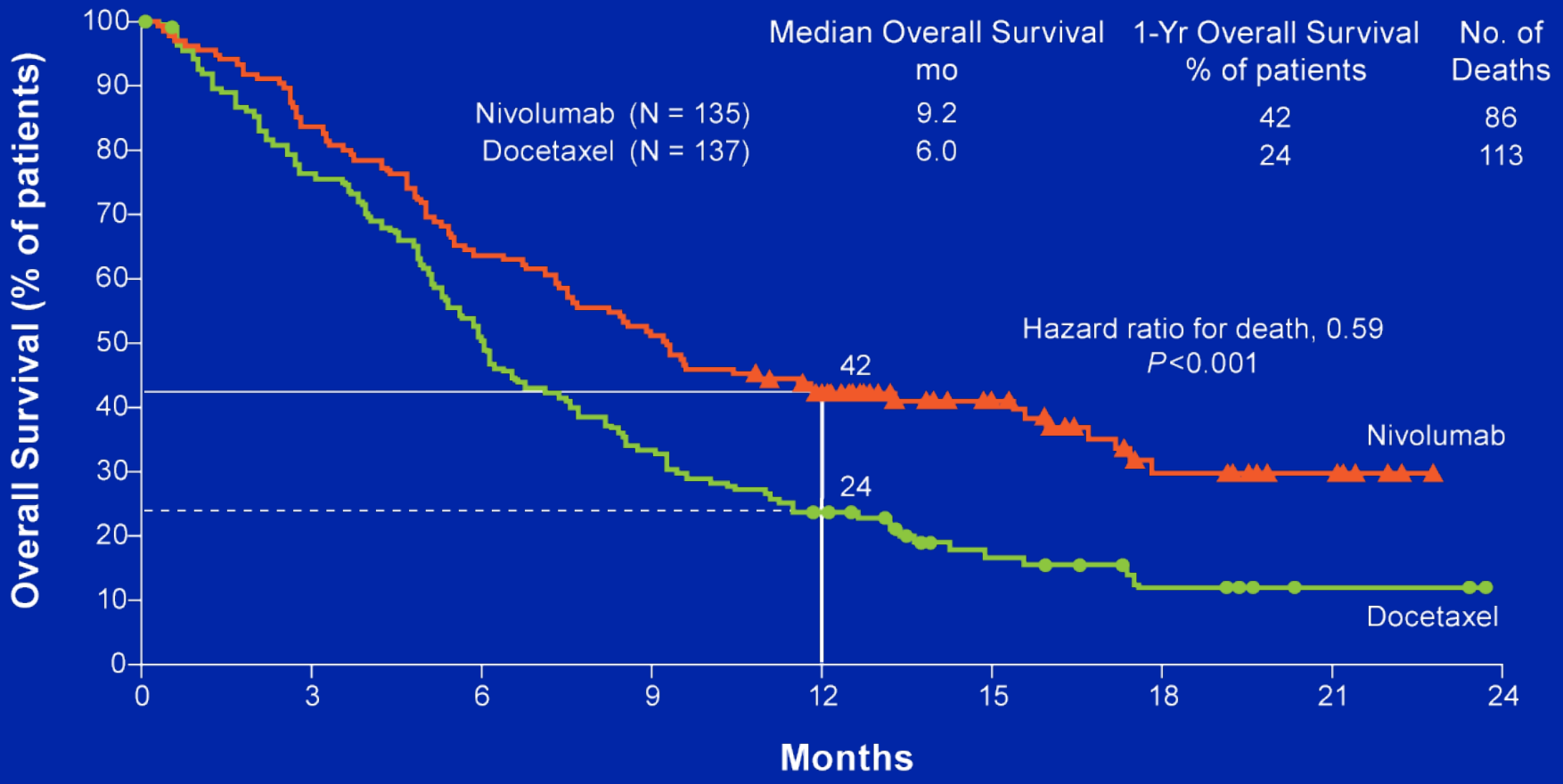
CheckMate 017: Nivolumab versus Docetaxel in Squamous NSCLC

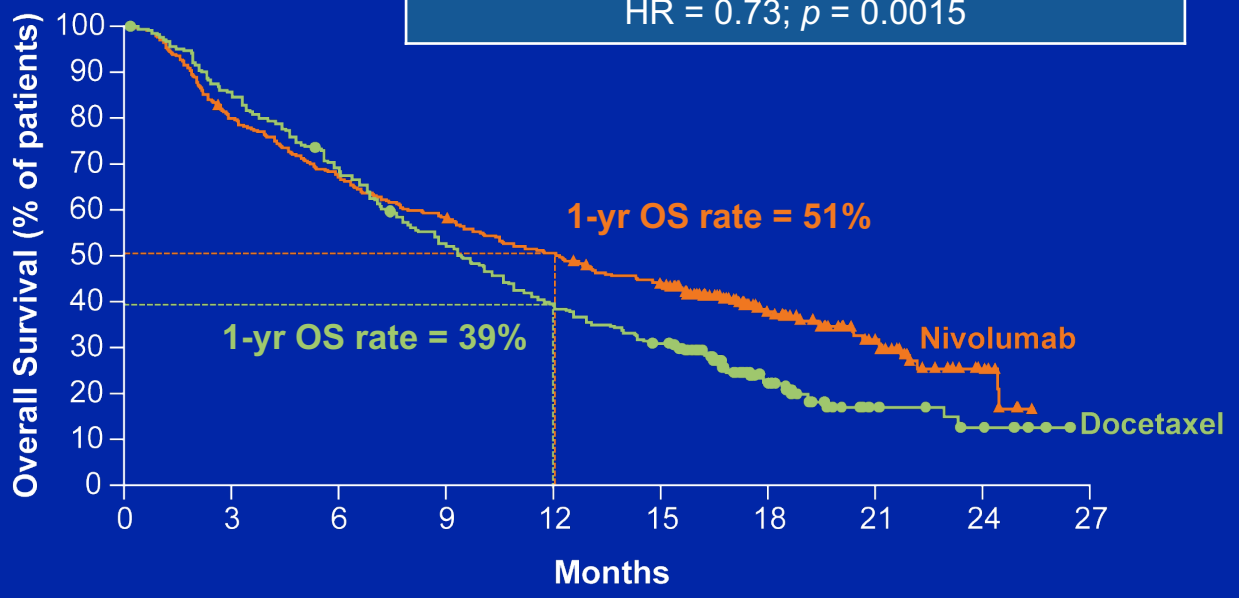


Brahmer J et al. *N Engl J Med* 2015;373(2):123-35.

CheckMate 057: Nivolumab vs Docetaxel in Nonsquamous NSCLC

- Phase III, 582 patients randomized
- Nivolumab 3 mg/kg q2wk vs docetaxel 75 mg/m^2 Q3
- Primary endpoint OS
- Trial stopped early by DSMC, met its primary endpoints at interim analysis

	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4
HR = 0.73; *p* = 0.0015		



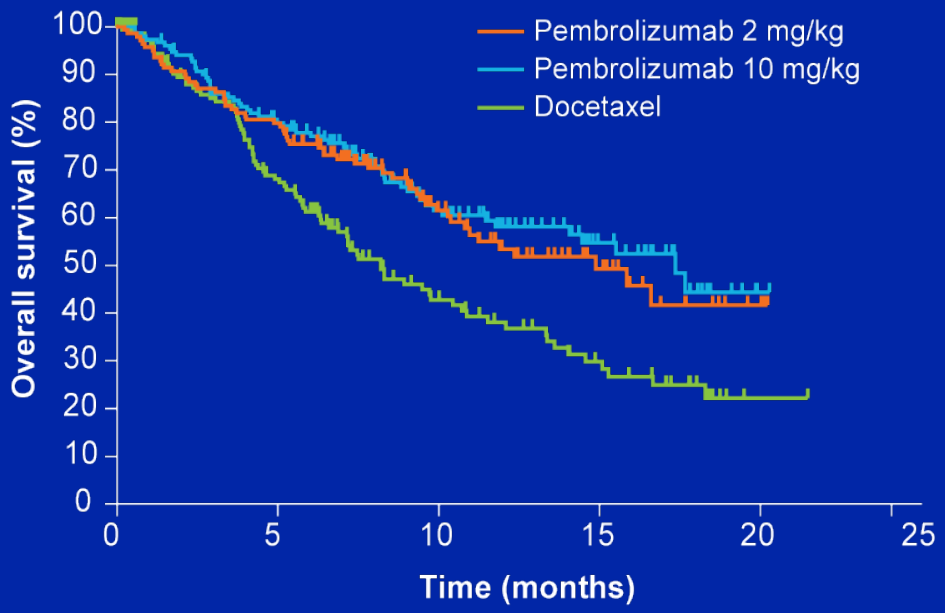
	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR	19%	12%
P-value	0.02	
Median DOR, mos	17.2	5.6

- 71 (24%) patients on nivolumab were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 16 patients (not included in best overall response)

Borghaei H et al. *N Engl J Med* 2015;373(17):1627-39.

KEYNOTE-010: Pembrolizumab versus Docetaxel

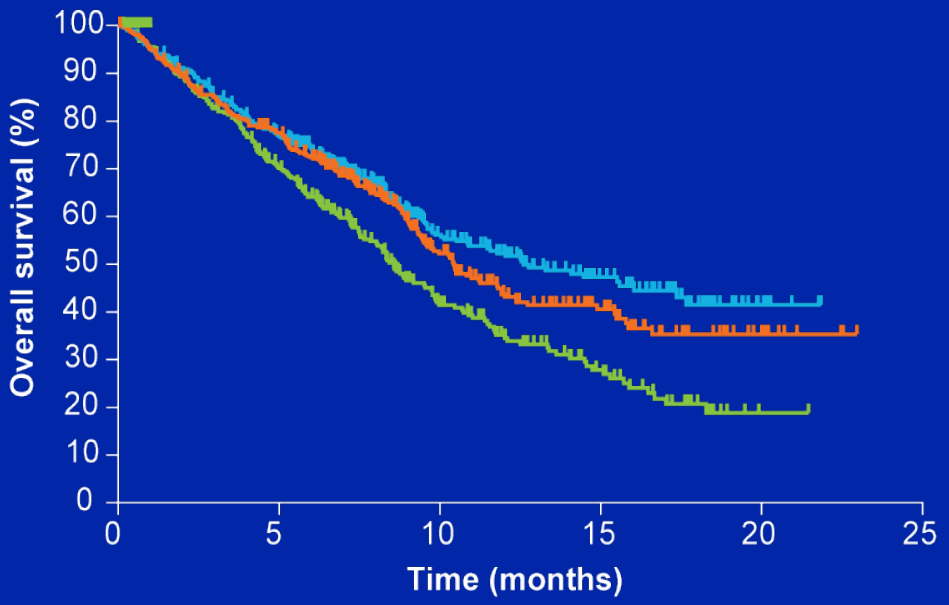
TPS ≥50%



Pembro 2 mg/kg vs docetaxel HR 0.54
(14.9 mo vs 8.2 mo; $p = 0.0002$)

Pembro 10 mg/kg vs docetaxel HR 0.50
(17.3 mo vs 8.2 mo; $p < 0.0001$).

All patients

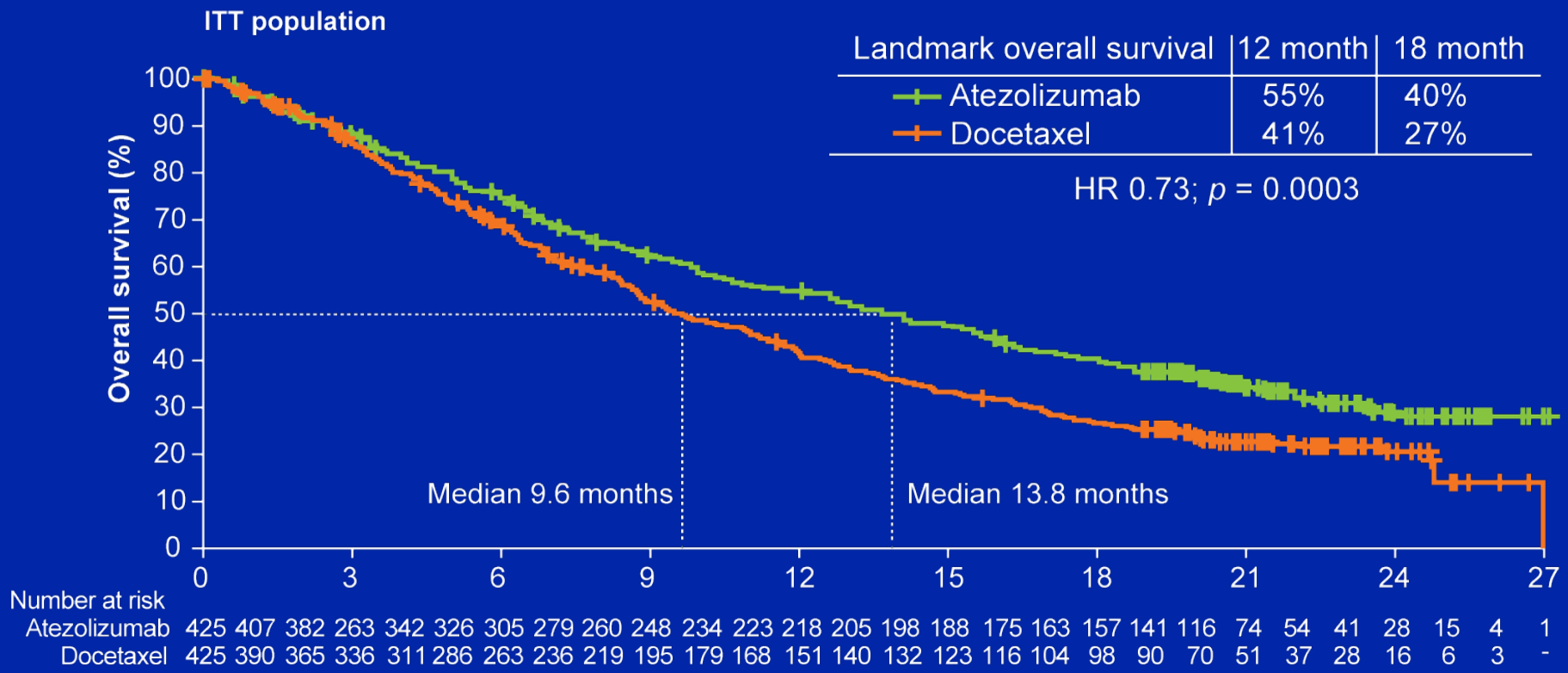


Pembro 2 mg/kg vs docetaxel HR 0.71
(10.4 mo vs 8.5 mo; $p = 0.0008$)

Pembro 10 mg/kg vs docetaxel HR 0.61
(12.7 mo vs 8.5 mo; $p < 0.0001$)

Herbst RS et al. *Lancet* 2016;387(10027):1540-50.

OAK: Atezolizumab versus Docetaxel in NSCLC



Rittmeyer A et al. *Lancet* 2017;389(10066):255-65.

OAK: Overall Survival According to PD-L1 Levels

Population	Atezolizumab	Docetaxel	Hazard ratio	*p*-value
ITT (N = 850)	**13.8 mo**	**9.6 mo**	**0.73**	**0.0003**
TC3 or IC3 (N = 137)	20.5 mo	8.9 mo	0.41	<0.0001
TC2/3 or IC2/3 (N = 265)	16.3 mo	10.8 mo	0.67	0.0080
TC1/2/3 or IC1/2/3 (N = 463)	15.7 mo	10.3 mo	0.74	0.0102
TC0 and IC0 (N = 379)	12.6 mo	8.9 mo	0.75	0.0215

Rittmeyer A et al. *Lancet* 2017;389(10066):255-65 ; Barlesi F et al. *Proc ESMO* 2016;Abstract LBA44_PR

Issues in Second-Line or Later Treatment of Patients with TPS < 50%

- Role of ramucirumab
- EGFR TKIs in patients with non-EGFR mutated disease
- Lung-MAP trial

A 60-year-old patient with metastatic squamous cell lung cancer and no targetable mutations with a TPS of 10% receives carboplatin/paclitaxel, followed by nivolumab, which results in disease progression. What would be your most likely treatment recommendation?

 JULIE R BRAHMER, MD	Docetaxel + ramucirumab
 COREY J LANGER, MD	Gemcitabine
 HEATHER WAKELEE, MD	Gemcitabine
 RAMASWAMY GOVINDAN, MD	Docetaxel + ramucirumab
 JOEL W NEAL, MD, PHD	Gemcitabine
 GREGORY J RIELY, MD, PHD	Gemcitabine

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A 60-year-old patient with metastatic nonsquamous lung cancer and no targetable mutations with a TPS of 10% receives carboplatin/pemetrexed followed by pemetrexed maintenance, experiences progressive disease, is started on pembrolizumab and experiences progression again. What would be your most likely treatment recommendation?

 JULIE R BRAHMER, MD	Docetaxel + ramucirumab
 COREY J LANGER, MD	Resume carbo, add taxane and consider bev
 HEATHER WAKELEE, MD	Docetaxel + ramucirumab
 RAMASWAMY GOVINDAN, MD	Docetaxel + ramucirumab
 JOEL W NEAL, MD, PHD	Gemcitabine
 GREGORY J RIELY, MD, PHD	Docetaxel + ramucirumab

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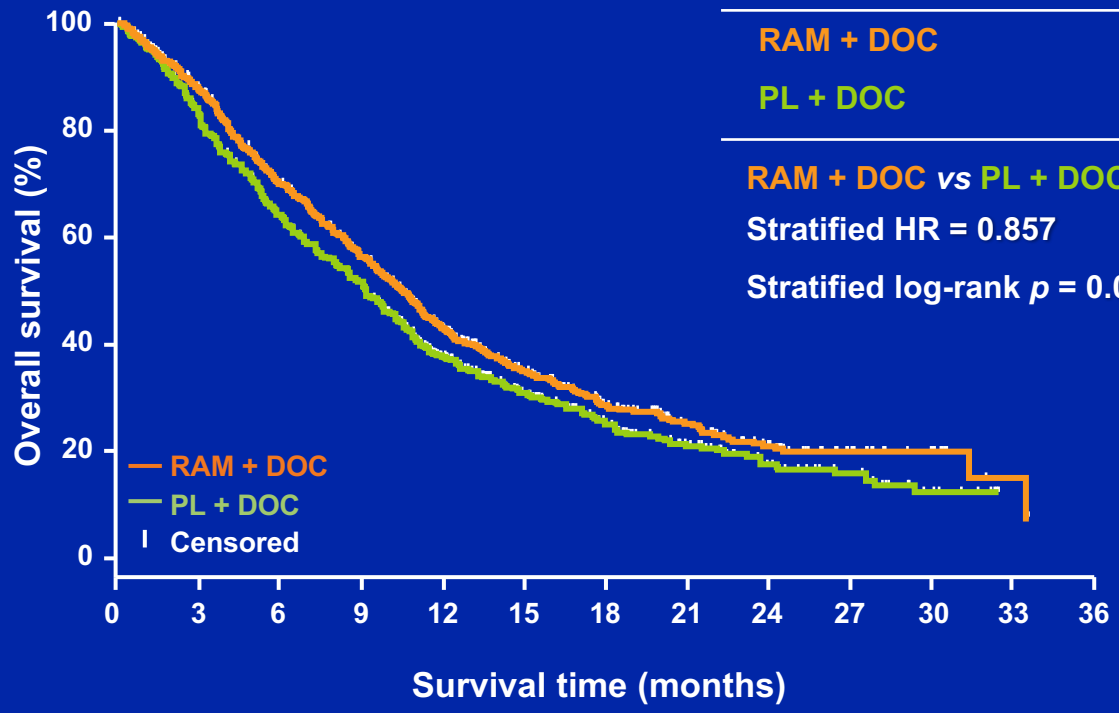
REVEL: Docetaxel ± Ramucirumab in the Second-Line Setting

328 of 1,240 (26%) patients had squamous histology



	Median (95% CI)	Censoring rate
RAM + DOC	10.5	31.8%
PL + DOC	9.1	27.0%

RAM + DOC *vs* PL + DOC:

Stratified HR = 0.857

Stratified log-rank *p* = 0.0235

OS HR squamous subset = 0.88 (*p* = NS)

Toxicities (Gr ≥3): Fatigue/nausea 14 vs 10%, stomatitis 4 vs 2%

No increase in Gr 3-4 hemorrhage but Gr 1-2 hemorrhage = 26.5 vs 12.9% (largely epistaxis)

Garon EB et al. *Lancet* 2014;384(9944):665-73.

REVEL: Select Treatment-Emergent Adverse Events

	Ramucirumab + docetaxel (n = 627)		Placebo + docetaxel (n = 618)	
AEs	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	55%	14%	49%	10%
Hypertension	11%	6%	5%	2%
Neutropenia	55%	49%	45%	39%
Febrile neutropenia	16%	16%	10%	10%
Leucopenia	21%	14%	19%	12%

Garon EB et al. Lancet 2014; 384(9944):665-73.

Do you generally use EGFR TKIs in patients with metastatic NSCLC without targetable mutations who have exhausted other options?

 JULIE R BRAHMER, MD	No
 COREY J LANGER, MD	No
 HEATHER WAKELEE, MD	No
 RAMASWAMY GOVINDAN, MD	No
 JOEL W NEAL, MD, PHD	No
 GREGORY J RIELY, MD, PHD	No

FDA Modifies the Indication for Erlotinib in NSCLC

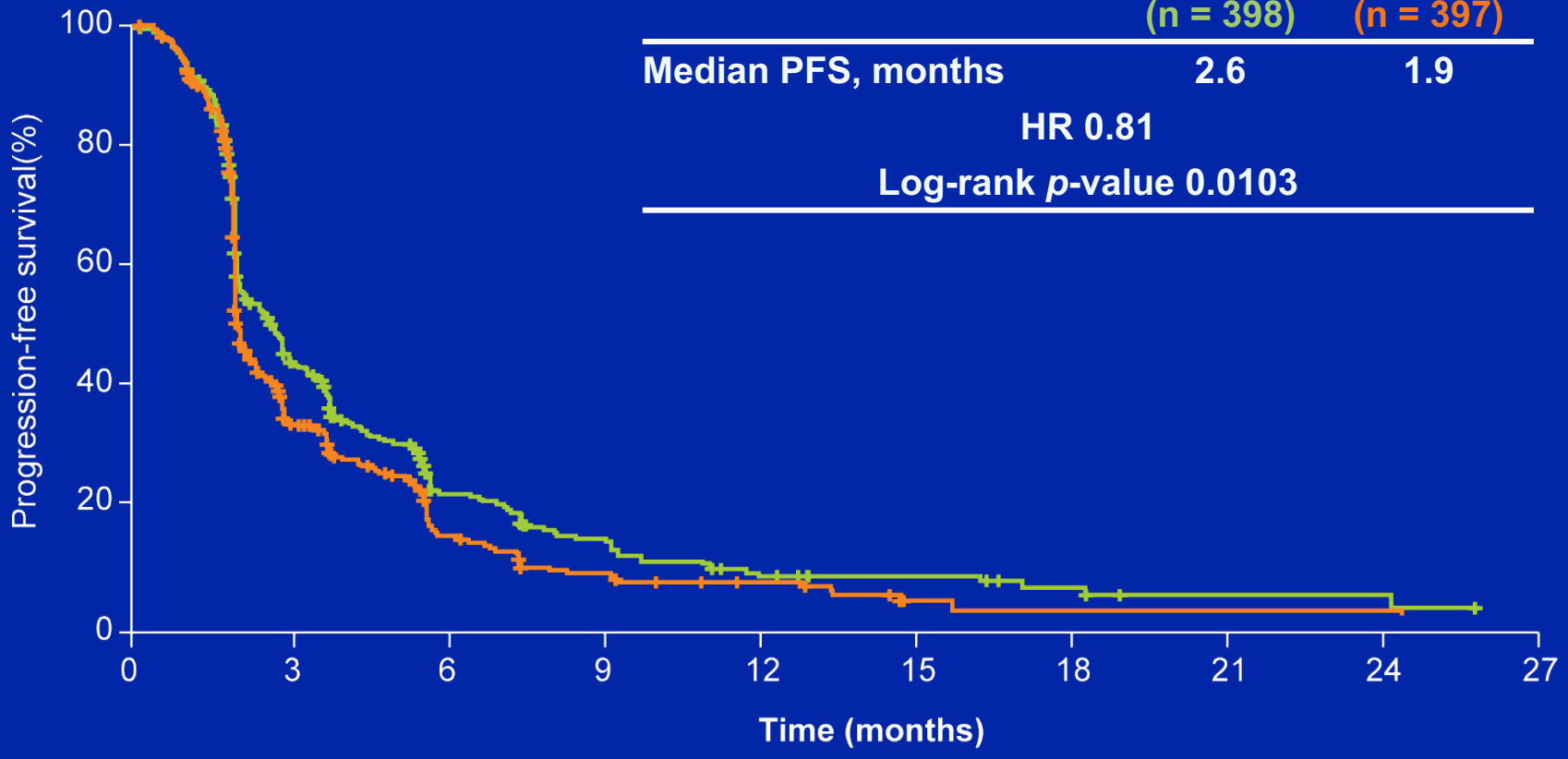
"On October 18, 2016, the US Food and Drug Administration modified the indication for erlotinib in the treatment of non–small cell lung cancer (NSCLC) to limit its use to patients whose tumors have specific epidermal growth factor receptor (*EGFR)* mutations.

The labeling change applies to patients with NSCLC receiving maintenance, second-line, or later treatment. These indications will be limited to patients whose tumors have *EGFR* exon 19 deletions or exon 21 L858R substitution mutations as detected by an FDA-approved test. The first-line indication previously was limited to patients with *EGFR* exon 19 deletions or exon 21 substitution mutations."

http://www.ascopost.com/News/44048

LUX-Lung 8: Progression-Free Survival with Second-Line Afatinib versus Erlotinib in Squamous Cell Carcinoma of the Lung

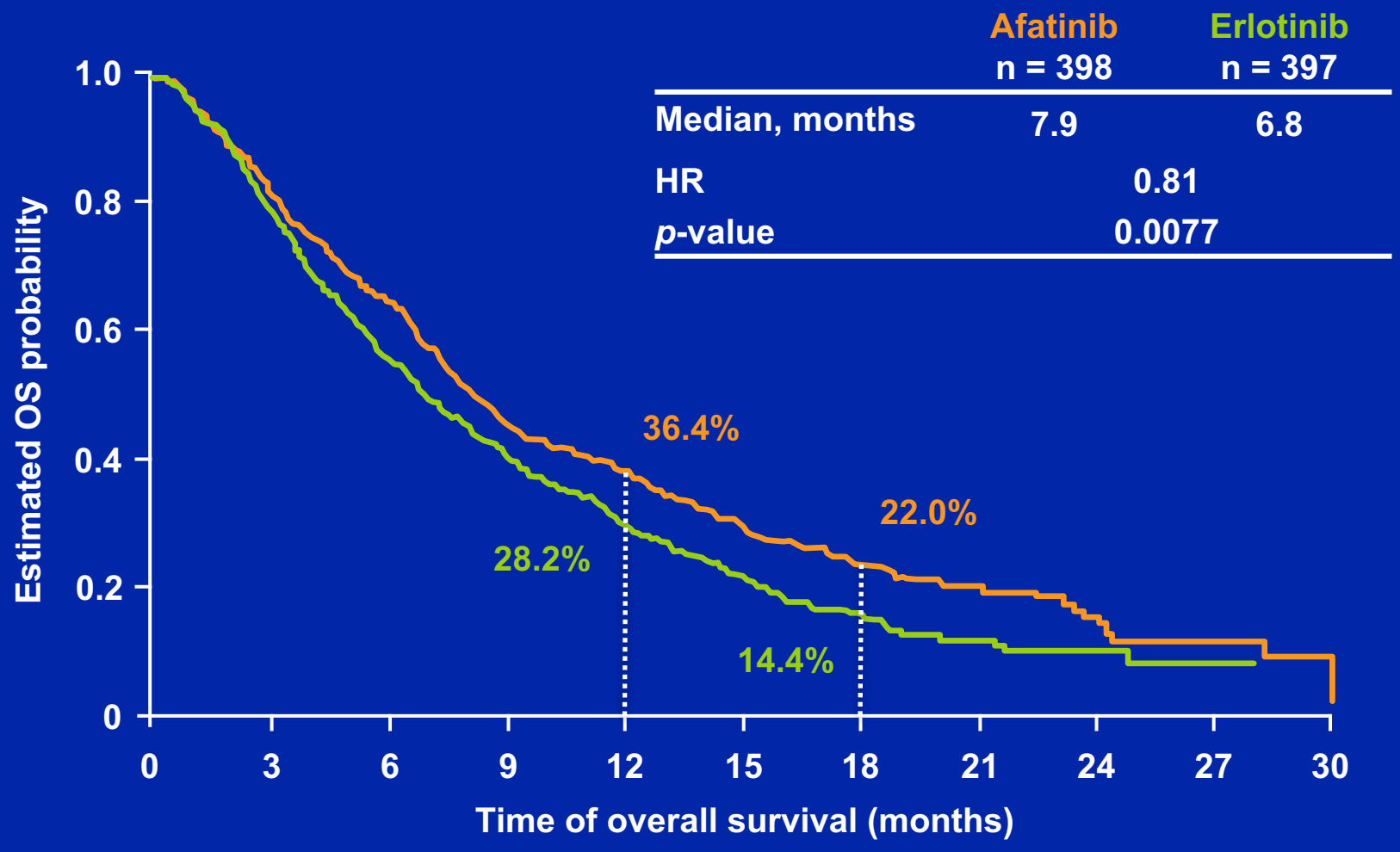
	Afatinib (n = 398)	Erlotinib (n = 397)
Median PFS, months	2.6	1.9
HR 0.81		
Log-rank *p*-value 0.0103		



Median follow-up time: 18.4 months

Soria JC et al. *Lancet Oncol* 2015;16(8):897-907.

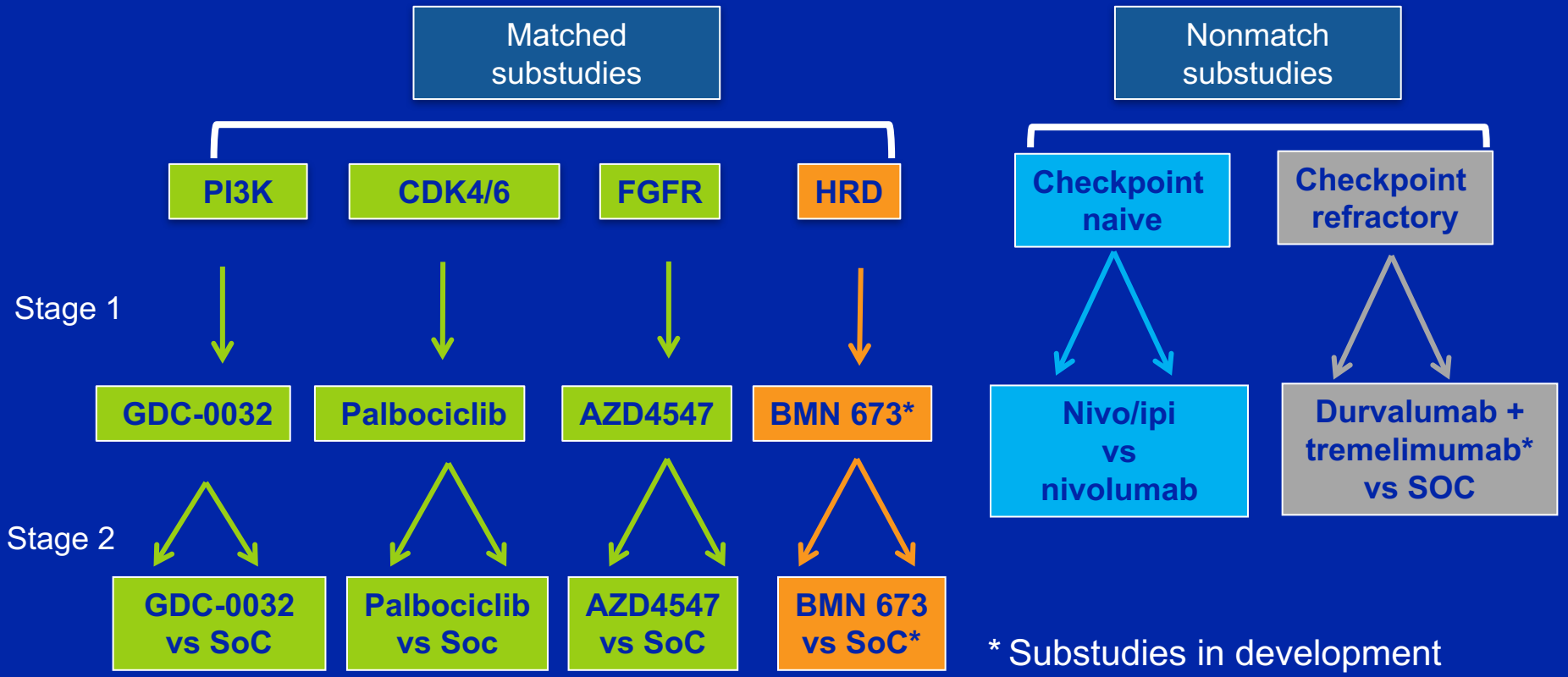
LUX-Lung 8 Primary Analysis: Overall Survival



Median follow-up time: 18.4 months

Soria JC et al. *Lancet Oncol* 2015;16(8):897-907.

Second-Line Squamous NSCLC: Updated Lung-MAP Trial Schema



* Substudies in development

- Lung-MAP amended to 2nd line therapy & beyond to accommodate nivolumab approval
- Prescreening added back
- Eligibility criteria broadened

http://www.lung-map.org/healthcare-providers. Accessed March 2017

In general, when do you believe checkpoint inhibitors should be introduced into the treatment of patients with EGFR-mutant NSCLC? 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?
 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
 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	Yes
 GREGORY J RIELY, MD, PHD	After EGFR TKIs and platinum doublet with bevacizumab	Yes

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