

2014 Annual Oncology Meeting in Chicago

*prIME Downloadable Slides in
Non-Small Cell Lung Cancer*

May 30 – June 3, 2014



Ceritinib in Advanced Anaplastic Lymphoma Kinase Rearranged (ALK+) Non-Small Cell Lung Cancer (NSCLC)—Results of the ASCEND-1 Trial

Abstract 8003

**Kim D-W, Mehra R, Tan D, Felip E, Chow L, Camidge DR,
Vansteenkiste J, Sharma S, De Pas T, Riely G, Solomon B, Wolf J,
Thomas M, Schuler MH, Liu G, Santoro A, Geraldes M, Boral A,
Yovine AJ, and Shaw AT**

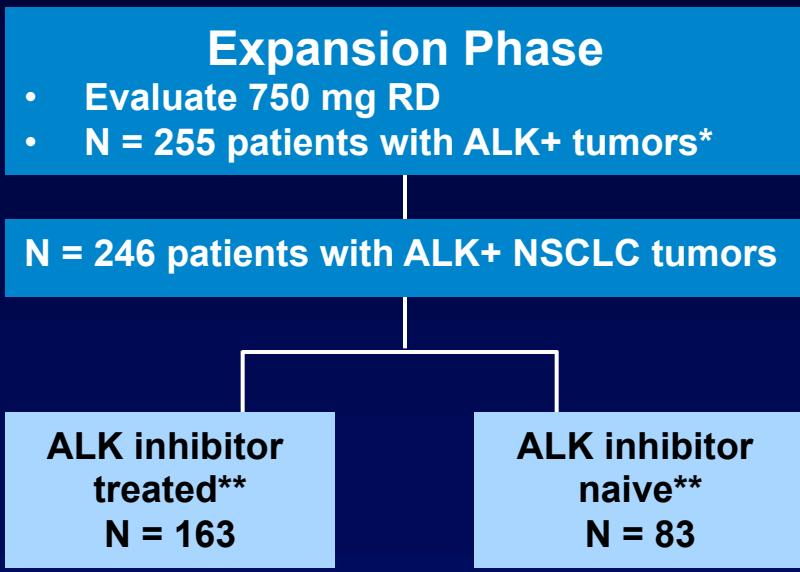
Introduction

- **Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase activated in 3%-7% non-small cell lung cancer (NSCLC) by chromosomal rearrangement¹**
- **Crizotinib is an ALK inhibitor with high efficacy in ALK+ NSCLC patients²**
- **However, acquired resistance is common³**
- **Ceritinib (LDK378) is a potent and selective FDA approved oral ALK inhibitor^{4,5}**
- **Ceritinib has shown anti-tumor activity against ALK inhibitor-naive tumors as well as tumors that have progressed on crizotinib⁴**

1. Kwak EL, et al. *NEJM*. 2010;363(18):1693-1703. 2. Camidge DR, et al. *Lancet Oncol*. 2012;13:1011-1019. 3. Katayama R, et al. *Sci Transl Med*. 2012;4:120ra17. 4. Shaw A, et al. *NEJM*. 2014;370(13):1189-1197. 5. US Food and Drug Administration News Release. Accessed 1 May 2014.

Study Design

Global pivotal phase 1 trial, including 20 centers across 11 countries¹



Recruitment closed July 2013

- 31 October 2013 data cut-off used for current analysis
- Study ongoing

*9 ALK+ patients had cancers other than NSCLC

**All received crizotinib and 5 also received alectinib

Key Objectives: to determine anti-tumor efficacy and safety of ceritinib

Dose escalation phase (n = 59) closed May 2012 with RD of 750 mg/day

1. Shaw A, et al. *NEJM*. 2014;370(13):1189-1197.

ALKi, ALK inhibitor; RD, recommended dose

Patient Demographics (NSCLC)

Characteristics	ALK inhibitor treated (N = 163)	ALK inhibitor naive (N = 83)	ALL (N = 246)
Age (median), years (range)	52 (24-80)	55 (22-80)	53 (22-80)
Sex (female/male; n [%])	88/75 (54.0/46.0%)	44/39 (53.0/47.0%)	132/114 (53.7/46.3%)
ECOG performance status			
0	33 (23.3%)	25 (30.1%)	63 (25.6%)
1	104 (63.8%)	51 (61.4%)	155 (63.0%)
2	20 (12.3%)	7 (8.4%)	27 (11.0%)
3	1 (0.6%)	0	1 (0.4%)
Smoking history	109/49	44/38	153/87
Never/Former or current	(66.9/33.1%)	(53.0/47.0%)	(62.2/37.8%)

Disease Characteristics (NSCLC)

Characteristics	ALK inhibitor treated (N = 163)	ALK inhibitor naive (N = 83)	ALL (N = 246)
Tumor histology/cytology, n (%)			
Adenocarcinoma	152 (93.3)	76 (91.6)	228 (92.7)
Squamous cell carcinoma	3 (1.8)	0	3 (1.2)
Other/Missing	8 (4.9)	7 (8.4)	15 (6.1)
No. of prior treatment regimens, n (%)			
0	0	16 (19.3)	16 (6.5)
1	26 (16.0)	38 (45.8)	64 (26.0)
2	45 (27.6)	16 (19.3)	61 (24.8)
≥3	92 (56.4)	13 (15.6)	105 (42.7)
Median time from initial diagnosis to first dose, months (range)	21.2 (2.4-174.2)	18.1 (1.0-109.3)	18.0 (1.0-174.2)

Of patients who had received prior ALK inhibitor therapy, 91% had progressive disease during prior ALKi therapy (≤2weeks from last dose) and 77% had received ALKi as last prior therapy

Patient Disposition (NSCLC)

Characteristics	ALK inhibitor treated (N = 163)	ALK inhibitor naive (N = 83)	ALL (N = 246)
Median duration of follow-up months (range)	6.9 (0.1-19.1)	7.6 (0.4-17.6)	7.0 (0.1-19.1)
Patients ongoing at cut off, n (%)	74 (45.4%)	54 (65.1%)	128 (52%)
Primary reason for end of treatment, n (%)	17 (10.4%)	7 (8.4%)	24 (9.8%)
Adverse event	59 (36.2%)	18 (21.7%)	77 (31.3%)
Disease progression	3 (1.8%)	3 (3.6%)	6 (2.4%)
Death	10 (6.1%)	1 (1.2%)	11 (4.5%)
Consent withdrawal			

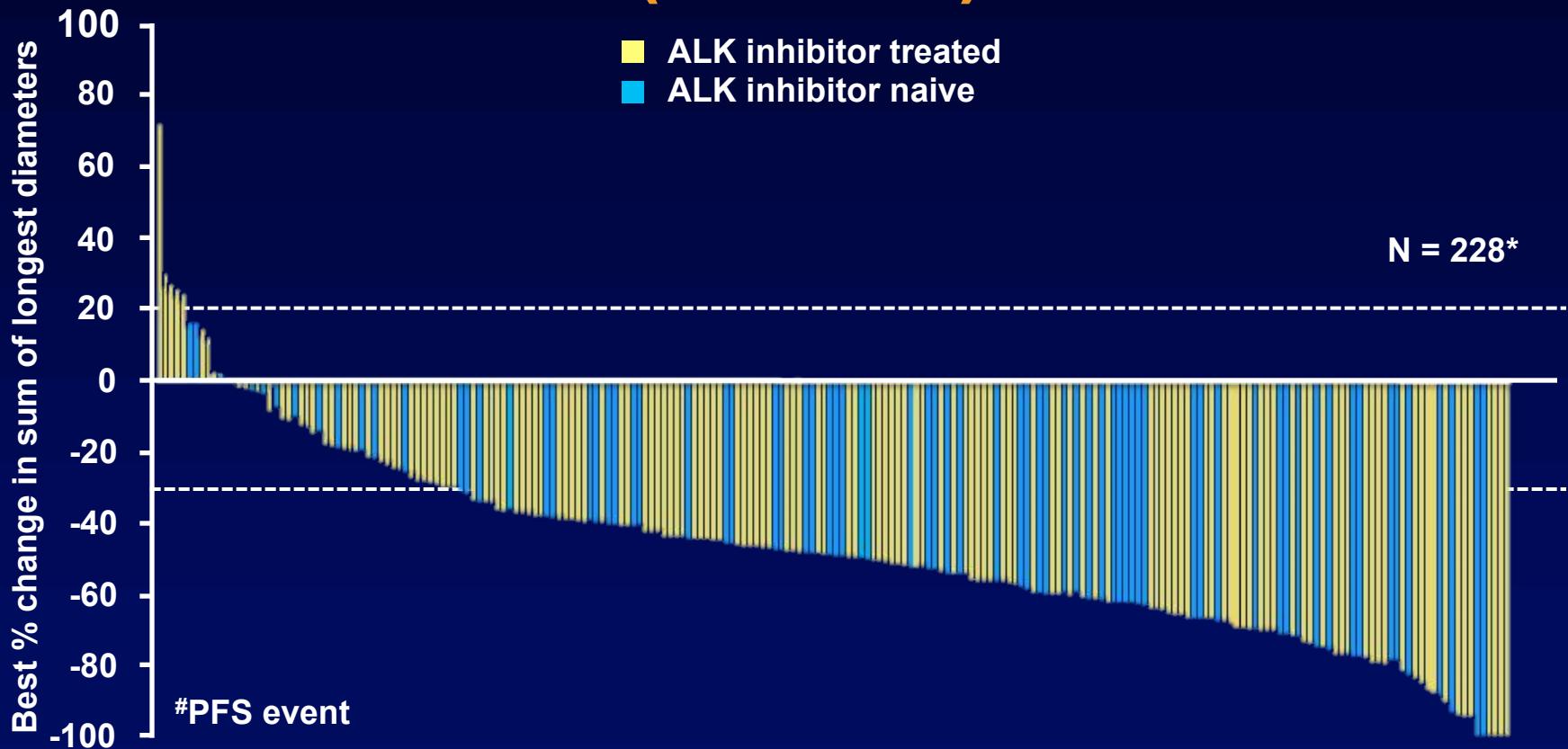
Overall Response Rate in ALK+ NSCLC Patients Treated With Ceritinib (750 mg Daily)

Efficacy Parameter (RECIST 1.0)	ALK inhibitor treated (N = 163)	ALK inhibitor naive (N = 83)	ALL (N = 246)
Complete response (CR), n (%)	2 (1.2)	1 (1.2)	3 (1.2)
Partial response (PR), n (%)	87 (53.4)	54 (65.1)	141 (57.3)
Stable disease (SD), n (%)	32 (19.6)	19 (22.9)	51 (20.7)
Progressive disease (PD), n (%)	16 (9.8)	0	16 (6.5)
Unknown*, n (%)	26 (16.0)	9 (10.8)	35 (14.2)
Overall response rate (ORR), n (%) [95% CI]	89 (54.6) [46.6, 62.4]	55 (66.3) [55.1, 76.3]	144 (58.5) [52.1, 64.8]

*No post-baseline assessment done, or the post-baseline assessment had overall response that was not CR, PR, SD, or PD

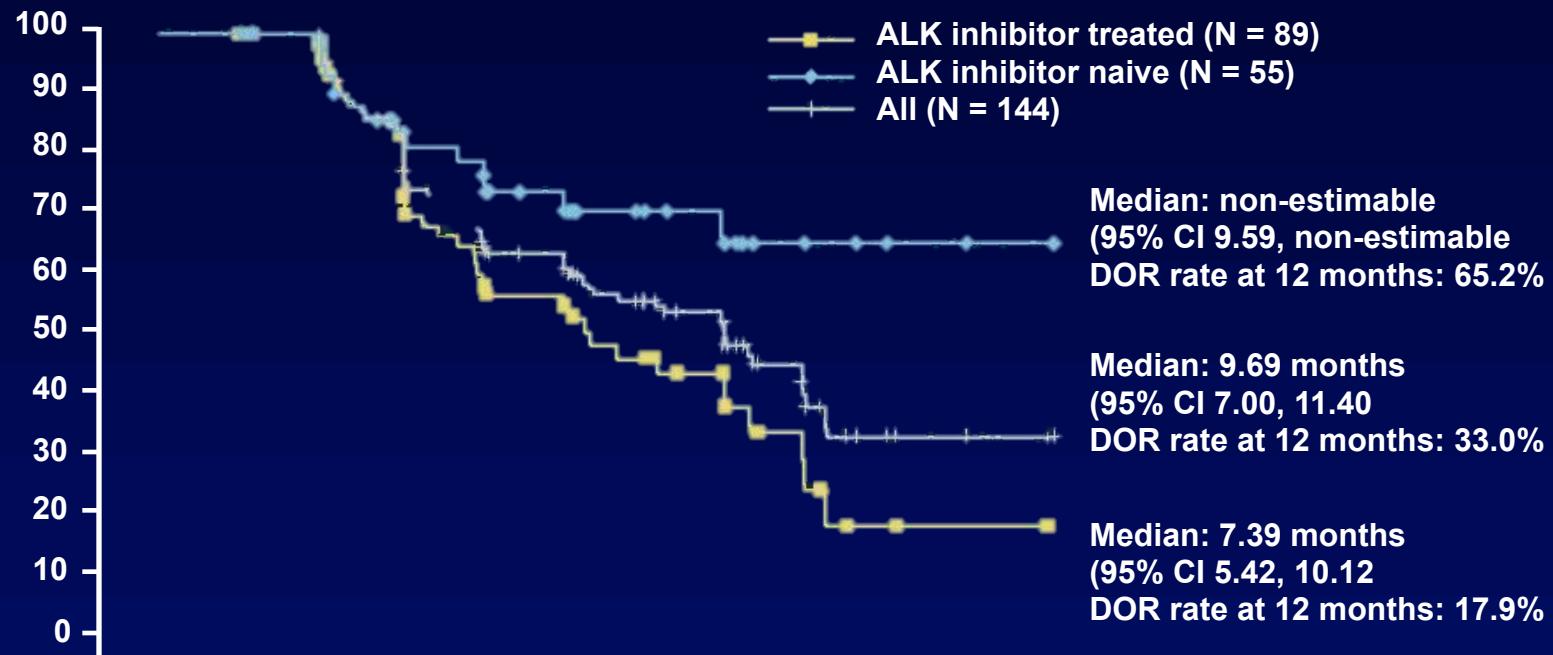
Kim D-W, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8003.

Best Percentage Change From Baseline (NSCLC)



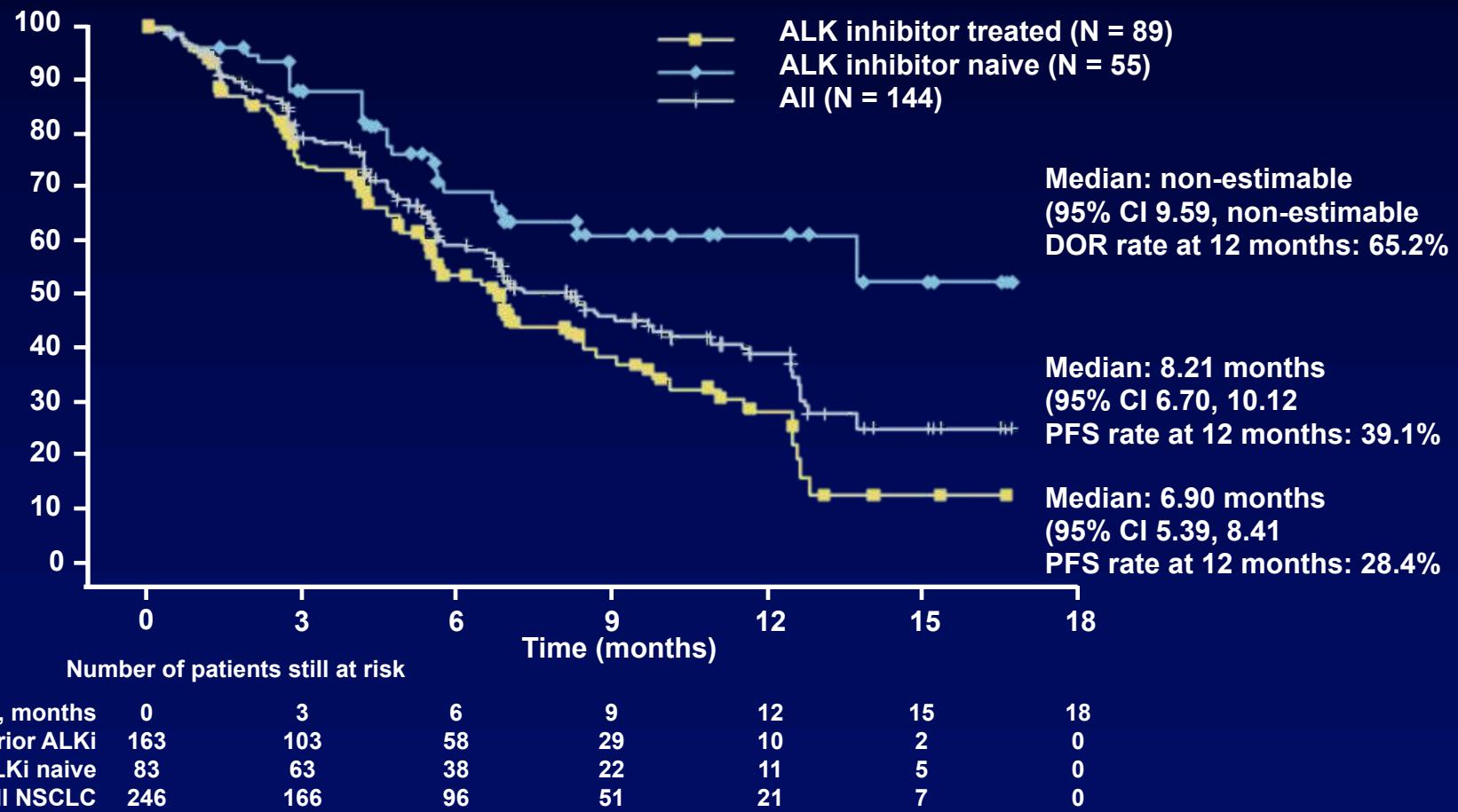
*Patients with measurable disease at baseline and at least 1 post baseline assessment without unknown response for target lesion or overall response

Duration of Response in ALK+ NSCLC Patients With Confirmed CR or PR



Time, months	0	3	6	9	12	15	18
NSCLC with prior ALKi	89	69	29	16	2	1	0
NSCLC ALKi naive	55	44	24	13	3	1	0
All NSCLC	144	113	53	29	5	2	0

Progression-Free Survival in Patients With ALK+ NSCLC



Adverse Events & Laboratory Abnormalities Regardless of Study Drug Relationship

All patients treated with 750 mg (N=255; includes 9 non-NSCLC patients)		
Most common adverse events (AE)	All grades* (%)	Grade 3/4* (%)
Diarrhea	86	6
Nausea	80	4
Vomiting	60	4
Abdominal pain	54	2
Constipation	29	0
Fatigue	52	5
Decreased appetite	34	1
Interstitial lung disease (ILD)/pneumonitis	4	3
Key Laboratory abnormalities	All grades* (%)	Grade 3/4* (%)
Hemoglobin decreased	84	5
Alanine transaminase (ALT) increased	80	27
Aspartate transaminase (AST) increased	75	13
Creatinine increased	58	2
Glucose increased	49	13
Phosphate decreased	36	7
Lipase increased	28	10

*All grades (>20%); Grade 3/4 ($\geq 2\%$)

QTc prolongation $>60\text{ms}$ occurred in 3% of pts. 1 pt at 700mg had QTc $>500\text{ms}$

Kim D-W, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8003.

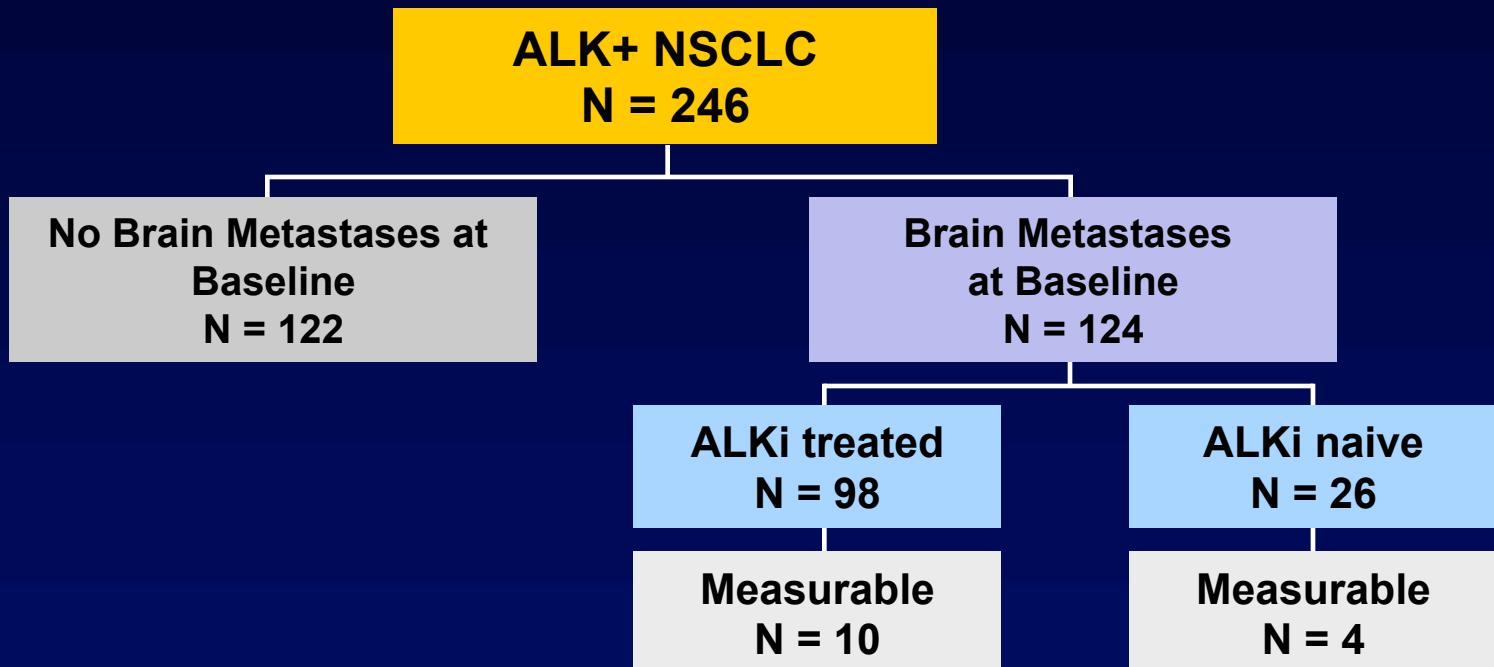
Disposition and Dose Reductions Related to Adverse Events (750 mg/day)

- **59% (150/255) of patients had at least 1 dose reduction**
- **9.4% (24/255) of patients discontinued due to AEs**
- **3.9% (10/255) patients developed ILD/pneumonitis***
 - **3 patients discontinued study drug treatment, including 1 fatal case**
 - **Remaining ILD/pneumonitis events were managed by dose adjustments and /or interruptions**

*1 patient at 700mg also had pneumonitis
ILD, interstitial lung disease

Efficacy of Ceritinib in Patients With Brain Metastases

Subset analysis of patients with clinically and neurologically stable brain metastases at baseline



Measurable brain metastases:

- Investigator identified, measured using RECIST 1.0; longest diameter 10mm or more
- Either not previously radiated, or if previously radiated lesion has grown after irradiation

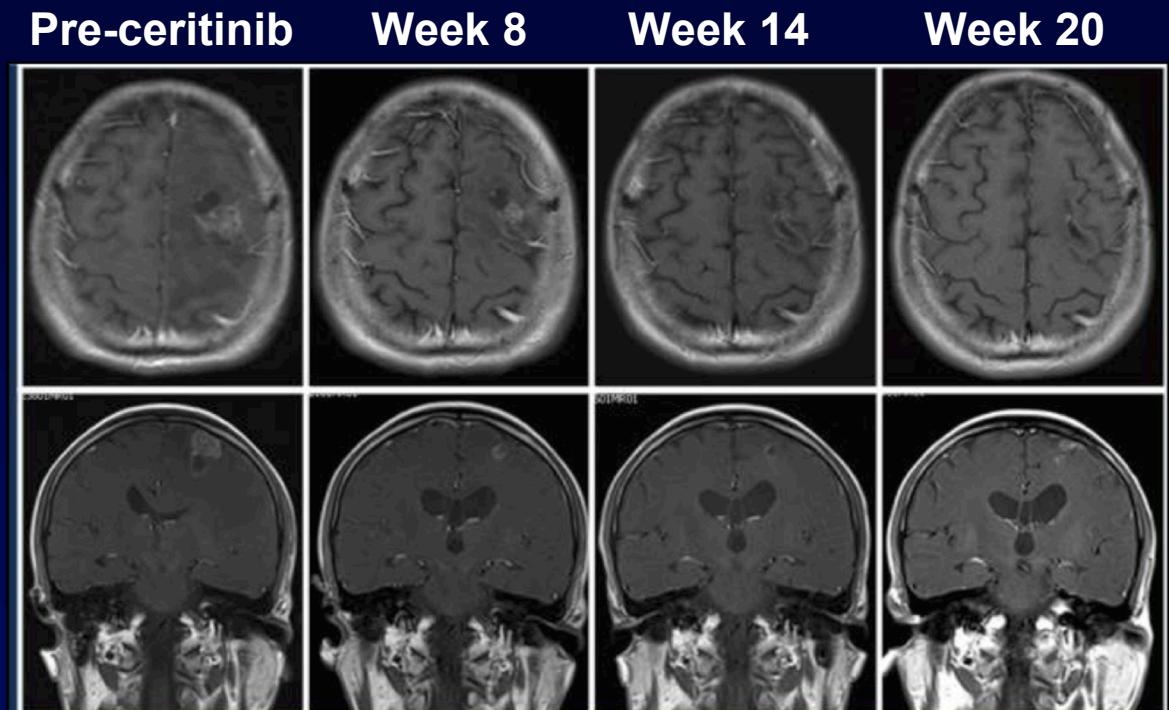
Overall Response to Ceritinib in Patients With Brain Metastases at Baseline

Efficacy parameter	ALK inhibitor treated	ALK inhibitor naive	All patients
Patients with brain metastases	N = 98	N = 26	N = 124
ORR, n (%) (95% CI)	49 (50.0%) [39.7, 60.3]	18 (69.2%) [48.2, 85.7]	67 (54.0%) [44.9, 63.0]
DOR, median (months) (95% CI)	6.93 [4.80, 8.54]	NE [5.52, NE]	7.0 [5.45, 9.69]
6 month DOR (%) (95% CI)	53.1% [36.5, 67.1]	65.9% [35.4, 84.5]	56.3% [41.9, 68.4]
PFS, median (months) (95% CI)	6.70 [4.86, 8.38]	8.31 [4.63, NE]	6.90 [5.39, 8.38]
6 month PFS (%) (95% CI)	52.3% [40.9, 62.5]	65.6% [42.7, 81.2]	55.1% [45.0, 64.1]

CI, confidence interval; ORR, overall response rate; DOR, duration of response; PFS, progression-free survival; NE, non-estimable

Ceritinib Treatment Showed Anti-Tumor Activity in the Brain

- 36 year-old male patient with lymph node, brain, adrenal, and liver metastases
- Previously treated with radiation therapy, chemotherapy, and progressed on crizotinib



Patient remains on ceritinib 750 mg after 17 months

Figure courtesy of Dr Daniel Tan

Kim D-W, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8003.

Overall Intracranial Response Rate for Patients With Measurable Brain Metastases at Baseline

Best Overall Response n (%)	ALK inhibitor treated N = 10	ALK inhibitor naive N = 4	All patients N = 14
Complete response	0	1	1
Partial response	4	2	6
Stable disease	3	0	3
Progressive disease	0	0	0
Unknown	3	1	4
OIRR [95% CI]	4 (40.0) [12.2, 73.8]	3 (75.0) [19.4, 99.4]	7 (50.0) [23.0, 77.0]

Conclusions

- A high rate of durable responses and prolonged PFS were seen in both ALKi treated and ALKi naive patients
 - In ALKi naive patients, the median DOR and PFS have not been reached
- In all patients, the most common AEs were nausea, vomiting, and diarrhea and most were grade 1 or 2
- In the subset of patients with baseline brain metastases, ceritinib also demonstrated a high rate of durable responses and prolonged PFS in both ALKi treated and ALKi naive patients
- Ceritinib treatment showed activity in brain metastases

Ceritinib Trials in Progress

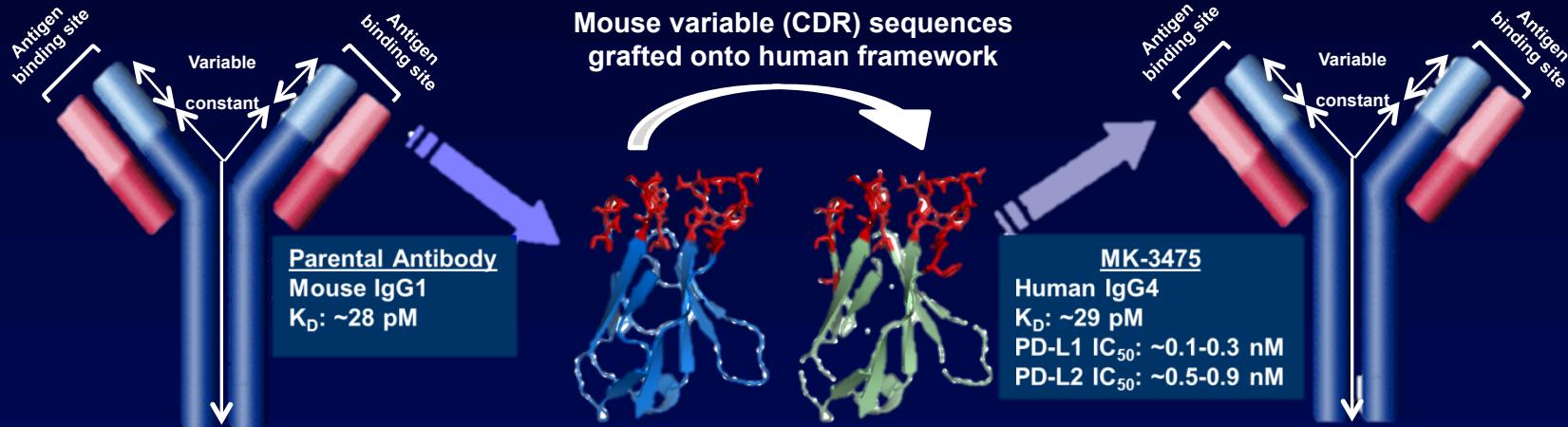
- Ongoing phase III trials
 - Ceritinib (LDK378) versus chemotherapy in patients who have received prior chemotherapy and crizotinib (NCT01828112)
 - Ceritinib (LDK378) versus chemotherapy in patients who are both chemotherapy-naive and crizotinib-naive (NCT01828099)
- Two phase II trials have completed enrollment
 - Ceritinib (LDK378) in adult patients previously treated with chemotherapy and crizotinib (NCT01685060)
 - Ceritinib (LDK378) in crizotinib-naive adult patients (NCT01685138)

Safety and Clinical Activity of Pembrolizumab (MK-3475) as Initial Therapy in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC)

Abstract 8007

Rizvi NA, Garon EB, Patnaik A, Gandhi L, Eder JP, Johnson E, Blumenschein GR Jr, Gubens MA, Papadopoulos KP, Lubiniecki GM, Zhang J, Niewood M, Emancipator K, Dolled-Filhart M, Hui R

Pembrolizumab Is a High-Affinity, Humanized IgG4 PD-1 Blocking Antibody

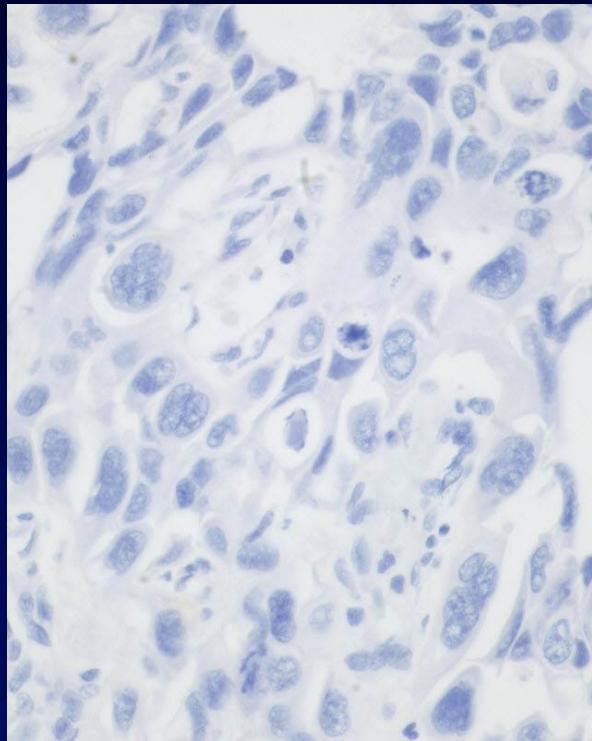


- Exerts dual ligand blockade of the PD-1 pathway
- Similar reactivity to human and other primate PD-1, no reactivity to mouse or rat PD-1
- Humanized IgG4 – no cytotoxic (ADCC/CDC) activity
- Contains stabilizing S228P sequence alteration

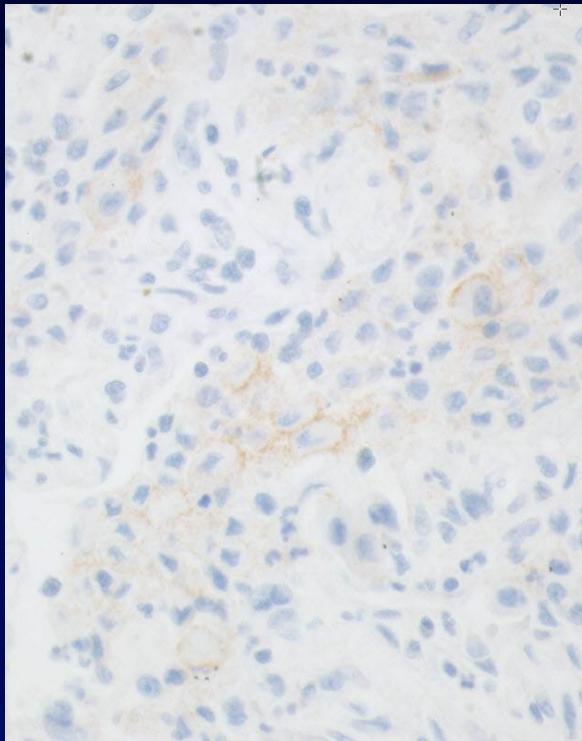
Biomarker Training Set Assessments

- Tumor biopsies obtained within 60 days prior to treatment were stained for PD-L1 using the 22C3 antibody with a prototype assay used to determine study eligibility
 - Sponsor remained blinded to quantitative PD-L1 staining result
 - ≥1% Tumor PD-L1 expression was considered positive
- Additionally, the same tissue samples were analyzed for percent tumor cells with membranous staining for PD-L1 with a clinical trial assay (CTA, also using 22C3)
 - Results scored independently from the prototype assay
 - Variety of scoring methods were assessed; proportion score chosen (percentage of tumor cells with PD-L1 staining)
 - Sponsor remained blinded to CTA results
- Once all patients in the training set had at least 19 weeks of follow-up, clinical outcome data were merged with quantitative CTA results

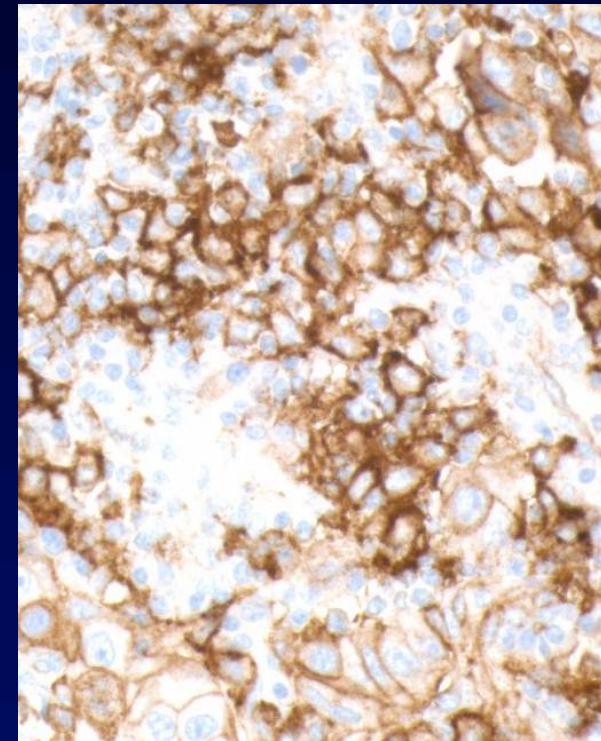
Examples of PD-L1 NSCLC Sample Immunohistochemical Staining^a



PD-L1 = 0% positive
Negative



PD-L1 = 2% positive
Weak Positive
(1% to 49%)

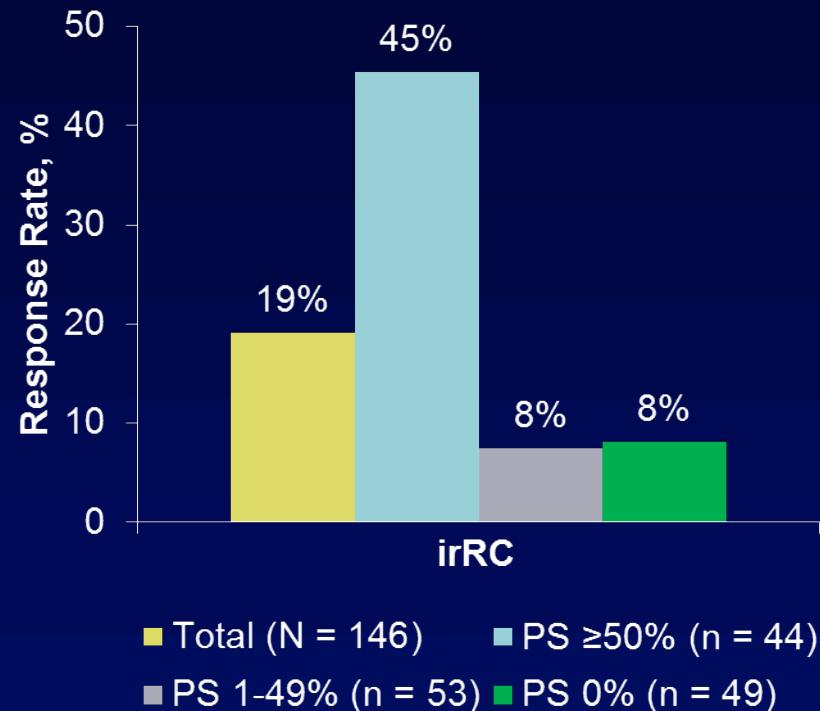
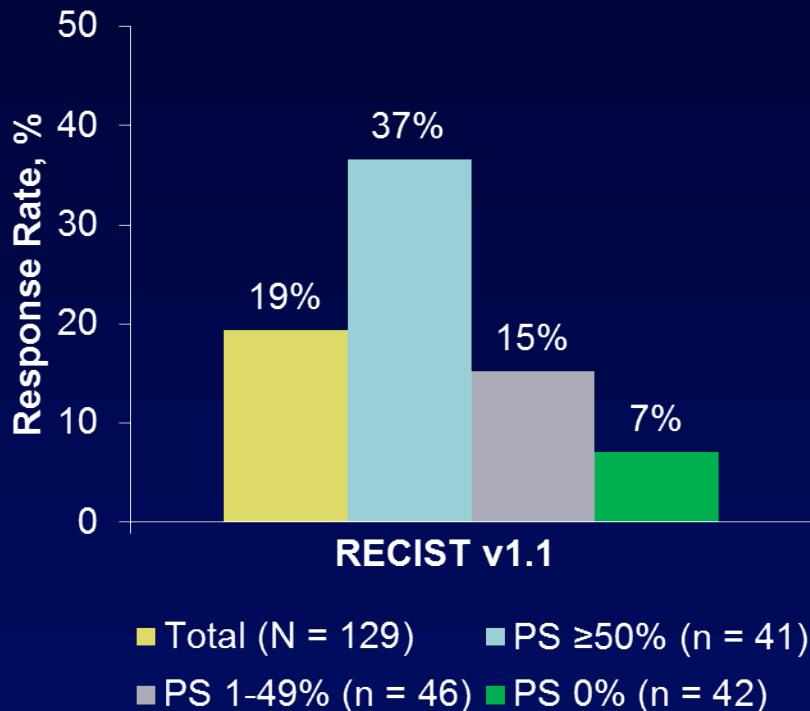


PD-L1 = 100% positive
Strong Positive
(50% to 100%)

^aClinical trial assay

Courtesy of Gandhi L. Presented at: 2014 Annual AACR Meeting; April 5-9, 2014; San Diego, CA; Abstract CT105.
Rizvi NA, et al. *J Clin Oncol*. 2014;32(5s): Abstract 8007.

Response Rate by RECIST v1.1 (Central Review) and by Immune-Related Response Criteria (irRC; Investigator-Assessed) with PD-L1 Clinical Trial Assay^a



RR, response rate (confirmed and unconfirmed complete and partial response).

PS, Proportion score. Strong PD-L1 positive staining was considered ≥50% of tumor cells, and weak was defined as staining between 1% to 49% of positively staining tumor cells.

Negative had no tumor staining for PD-L1.

Data cut-off: December 31, 2013.

^aEvaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per imaging assessment criteria.

Courtesy of Gandhi L. Presented at: 2014 Annual AACR Meeting; April 5-9, 2014; San Diego, CA; Abstract CT105.

Rizvi NA, et al. *J Clin Oncol*. 2014;32(5s): Abstract 8007.

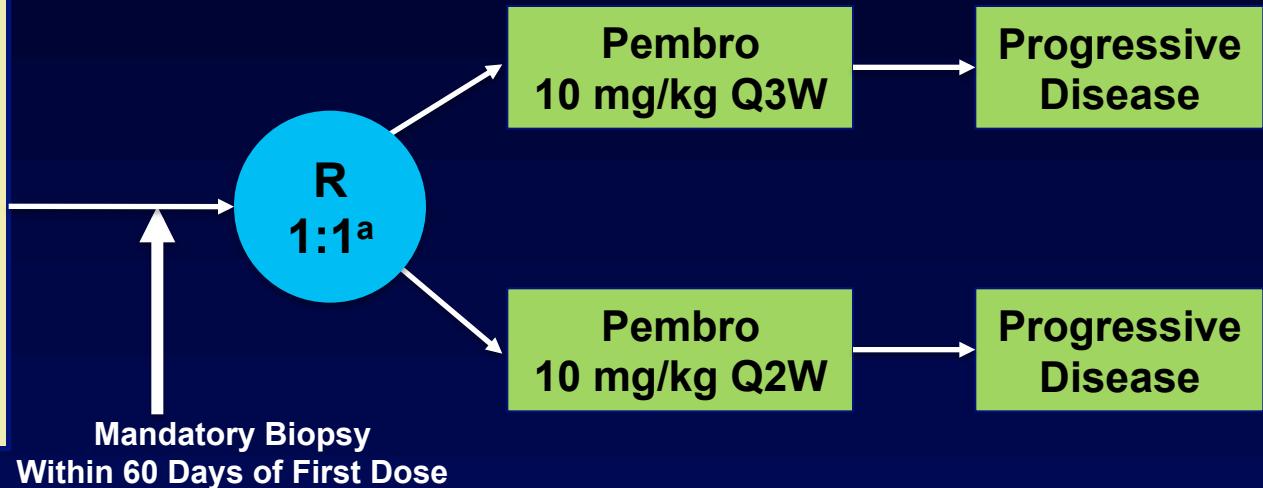
Analysis Objectives: Patients With Advanced NSCLC Enrolled in KEYNOTE-001

- Evaluate safety and tolerability of pembrolizumab (pembro)
- Evaluate clinical activity of pembro
- Evaluate correlation between clinical activity of pembro and PD-L1 expression

Other KEYNOTE-001 NSCLC Presentation:
E. Garon, Abstract 8020
Tues, June 3; 8.00-11.00 am

Study Design

- Treatment-naïve, stage IV NSCLC
- ECOG PS 0-1
- *EGFR* negative
- *ALK* negative
- PD-L1 positive ≥1%
- No systemic steroid
- No autoimmune disease
- No or stable brain mets



Response assessment

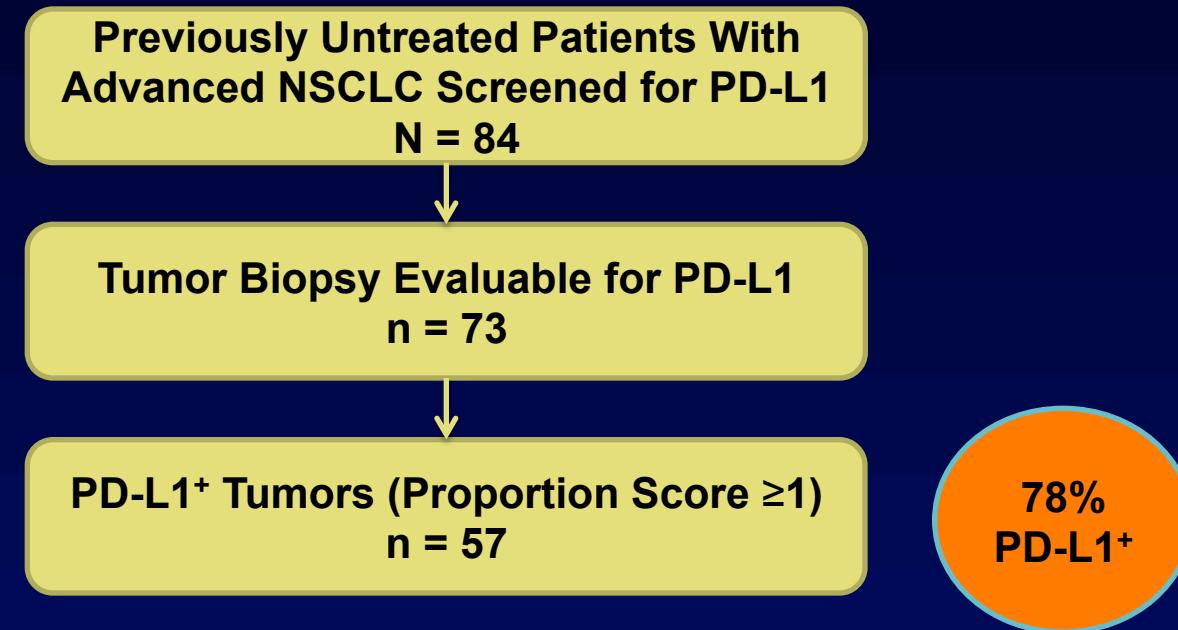
- Performed every 9 weeks
- Primary measure: RECIST v1.1 per independent central review
- Secondary measure: irRC¹ per investigator assessment

^aFirst 11 patients randomized to 2 mg/kg Q3W and 10 mg/kg Q3W (until Amendment 07).

1. Wolchok JD, et al. *Clin Cancer Res*. 2009;15(23):7412-20.

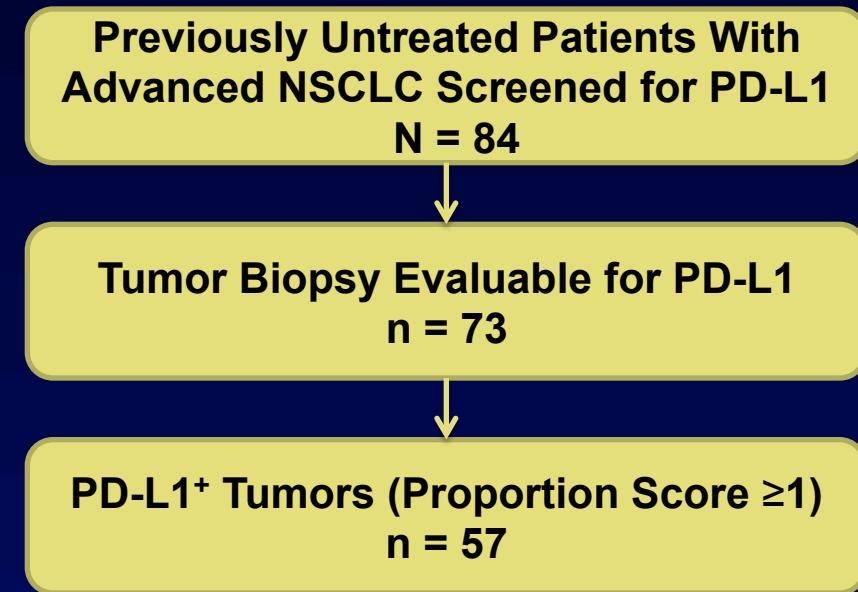
Rizvi NA, et al. *J Clin Oncol*. 2014;32(5s): Abstract 8007.

KEYNOTE-001: PD-L1 Expression in Previously Untreated NSCLC



Analysis cut-off date: March 3, 2014.

KEYNOTE-001: PD-L1 Expression in Previously Untreated NSCLC

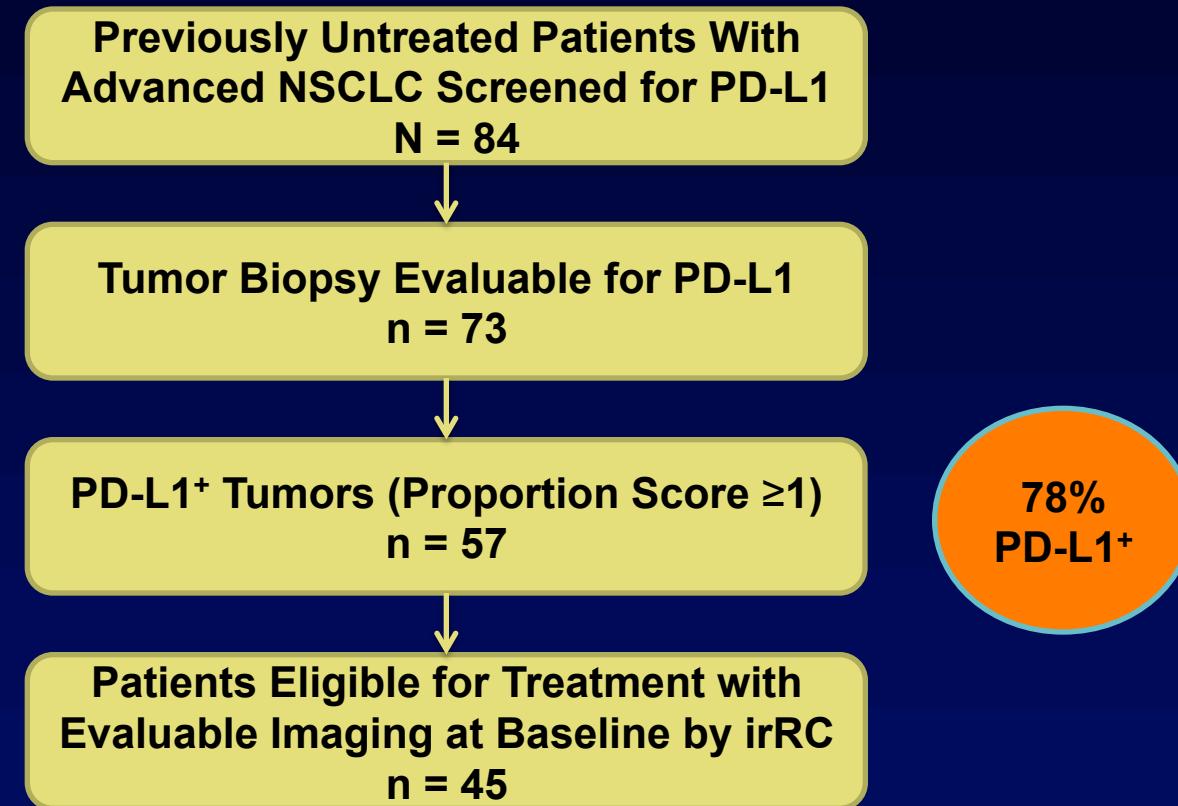


78%
PD-L1⁺

62%
PD-L1⁺
in 2L⁺

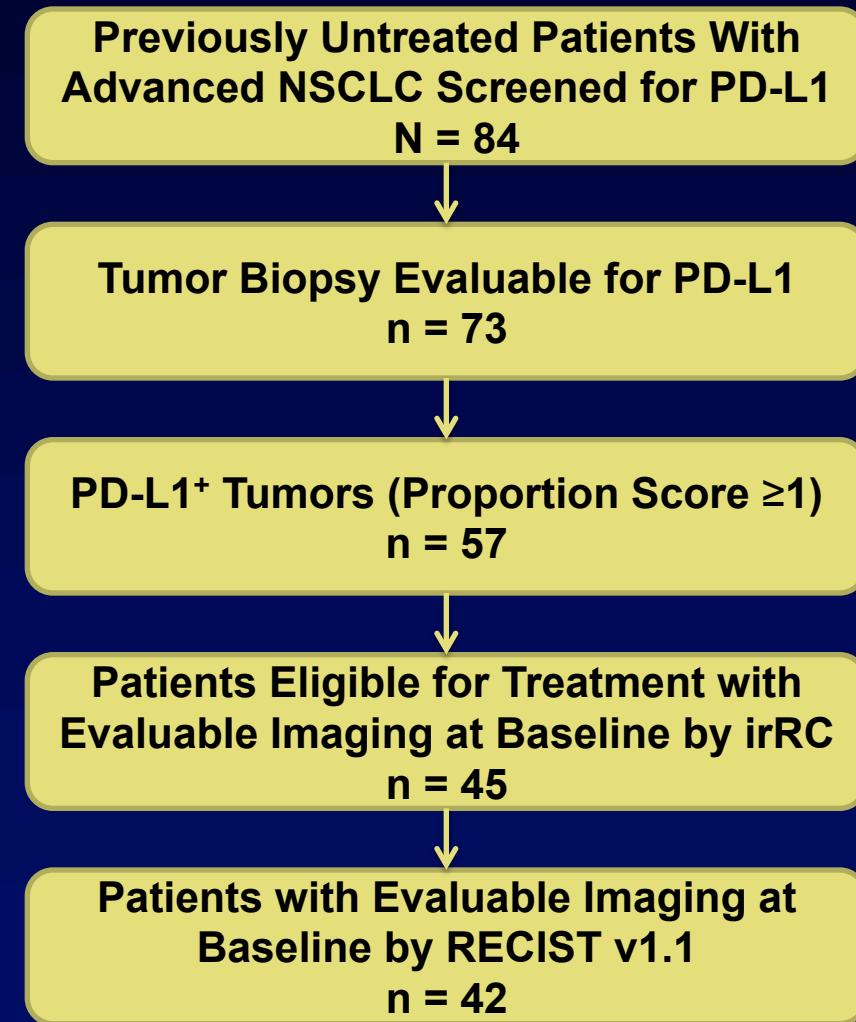
Analysis cut-off date: March 3, 2014.

KEYNOTE-001: PD-L1 Expression in Previously Untreated NSCLC



Analysis cut-off date: March 3, 2014.

KEYNOTE-001: PD-L1 Expression in Previously Untreated NSCLC



78%
PD-L1⁺

Analysis cut-off date: March 3, 2014.

Baseline Demographics and Disease Characteristics

Characteristic	N = 45	Characteristic	N = 45
Median age, year (range)	70 (48 - 86)	Race	
Sex		Asian	1 (2%)
Male	25 (56%)	Black or African American	1 (2%)
Female	20 (44%)	White	42 (93%)
Mutation		Native Hawaiian/Pacific Islander	1 (2%)
<i>EGFR</i>	1/41 (2%)	Smoking status	
<i>KRAS</i>	4/15 (27%)	Current	8 (18%)
<i>ALK</i> rearrangement	1/38 (3%)	Former	31 (69%)
Histology		Never	5 (11%)
Nonsquamous	34 (76%)	Unknown	1 (2%)
Squamous	10 (22%)		
Unknown	1 (2%)		
ECOG performance status			
0	22 (49%)		
1	23 (51%)		

Analysis cut-off date: March 3, 2014.

Rizvi NA, et al. J Clin Oncol. 2014;32(5s): Abstract 8007.

Treatment-Related Adverse Event Profile

**AEs of Any Grade,
Incidence >5%**

Treatment-Related Adverse Event, n (%)	Total N = 45
Any	36 (80%)
Fatigue	10 (22%)
Pruritus	6 (13%)
Hypothyroidism	4 (9%)
Dermatitis acneiform	3 (7%)
Diarrhea	3 (7%)
Dyspnea	3 (7%)
Rash	3 (7%)

**Grade 3-4 AEs or
AEs Leading to Discontinuation**

Treatment-Related Adverse Event, n (%)	Total N = 45	Resulted in Discontinuation
Blood creatine phosphokinase increased (Gr 4)	1 (2%)	No
Pericardial effusion (Gr 3)	1 (2%)	No
Pneumonitis (Gr 3)	1 (2%)	Yes
Acute kidney injury (Gr 2)	1 (2%)	Yes

- Specific AE terms listed are grade 1-2 only

Analysis cut-off date: March 3, 2014.

AE, adverse event; Gr, grade

Rizvi NA, et al. J Clin Oncol. 2014;32(5s): Abstract 8007.

KEYNOTE-001: Patient Disposition

Patients With Initial Treatment from
March 4, 2013 to November 7, 2013
N = 45

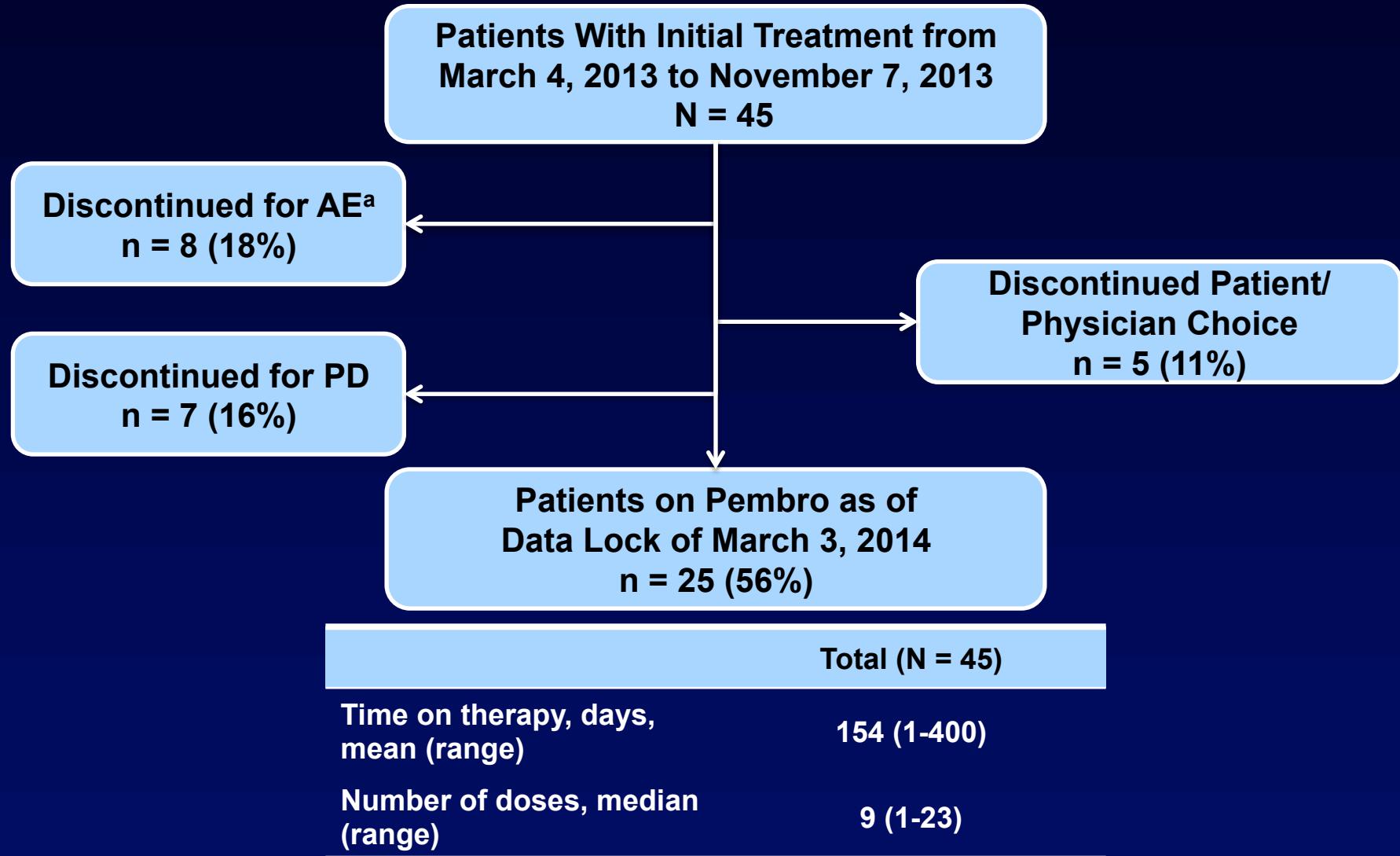
Total (N = 45)

Time on therapy, days, mean (range)	154 (1-400)
Number of doses, median (range)	9 (1-23)

^aOnly 2 patients discontinued for treatment-related AEs.

Analysis cut-off date: March 3, 2014.

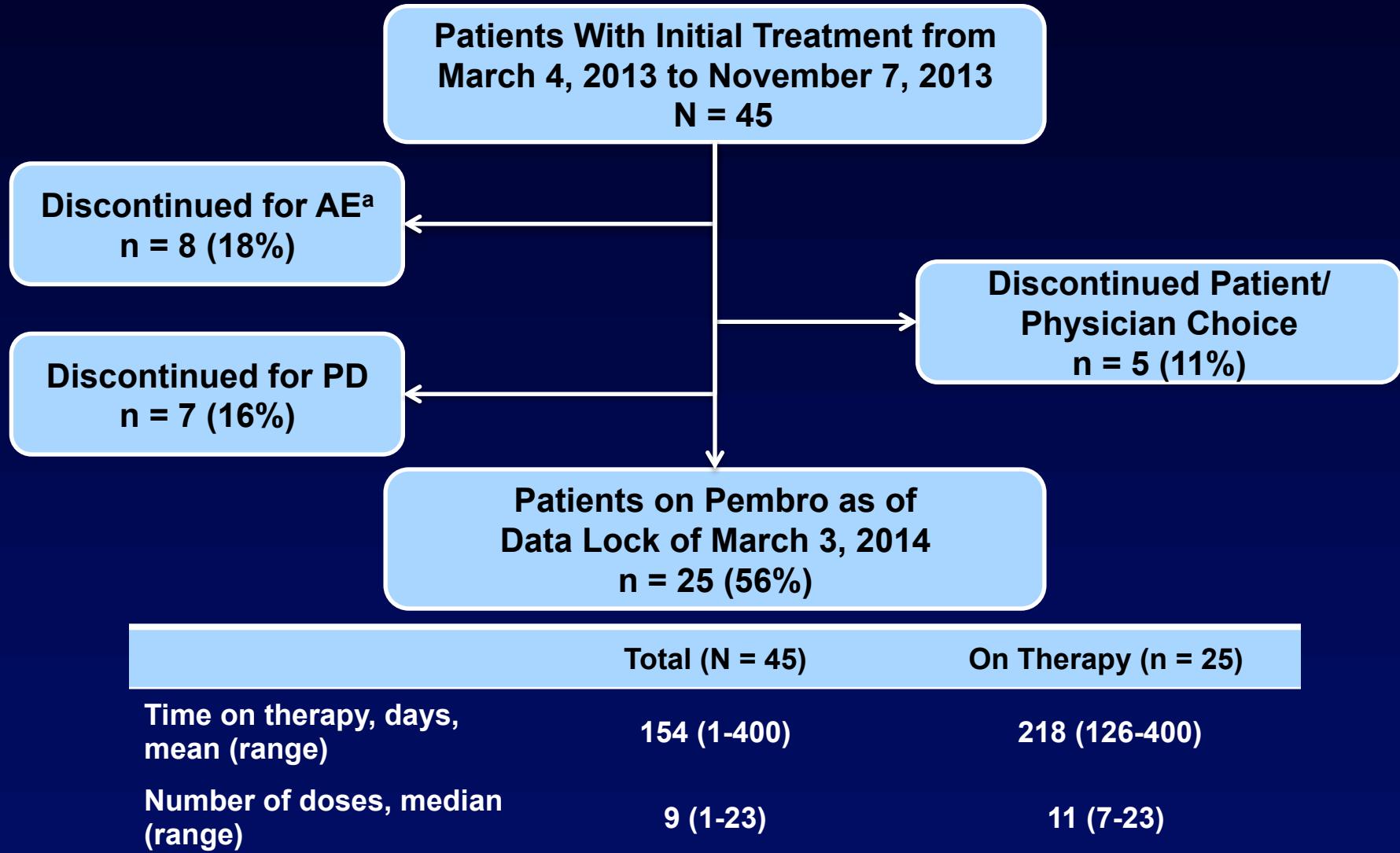
KEYNOTE-001: Patient Disposition



^aOnly 2 patients discontinued for treatment-related AEs.

Analysis cut-off date: March 3, 2014.

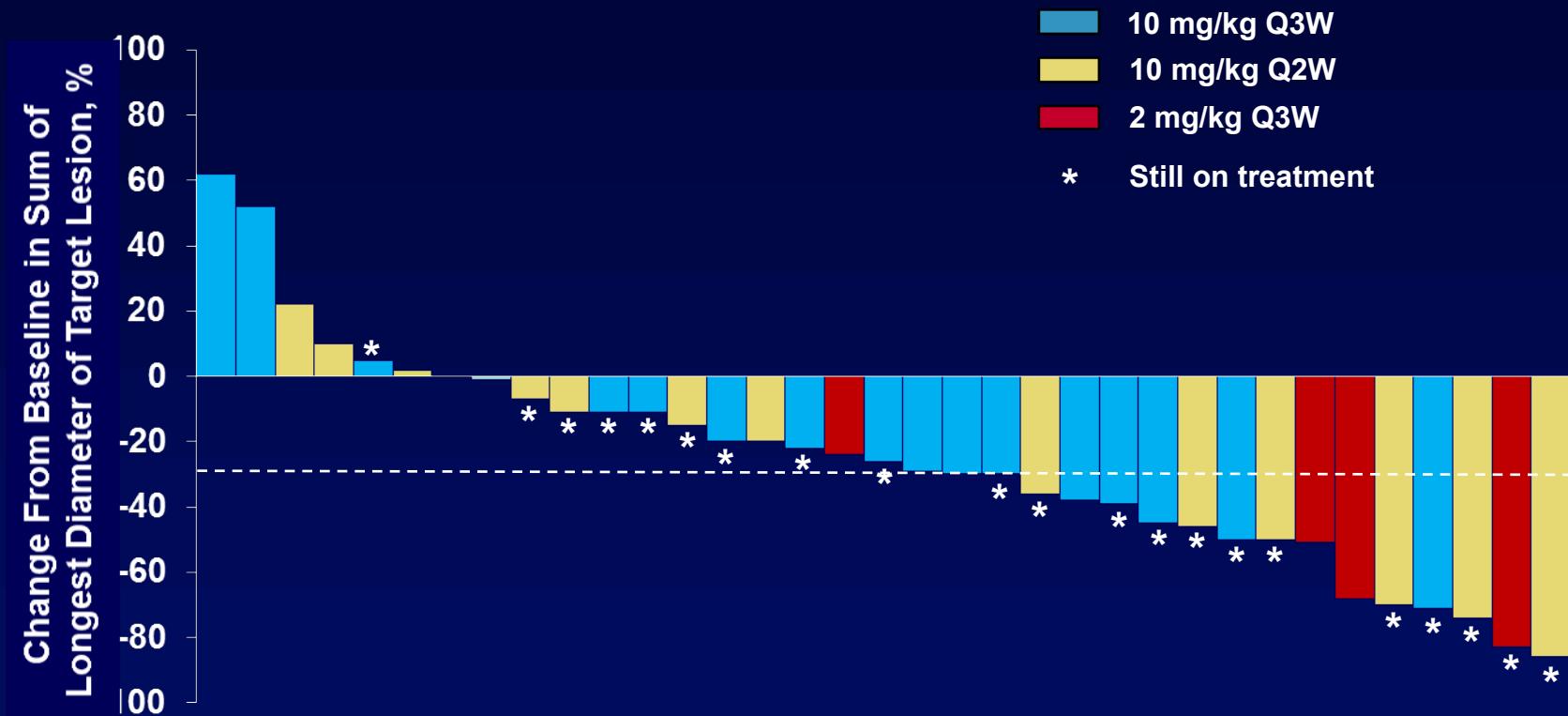
KEYNOTE-001: Patient Disposition



^aOnly 2 patients discontinued for treatment-related AEs.

Analysis cut-off date: March 3, 2014.

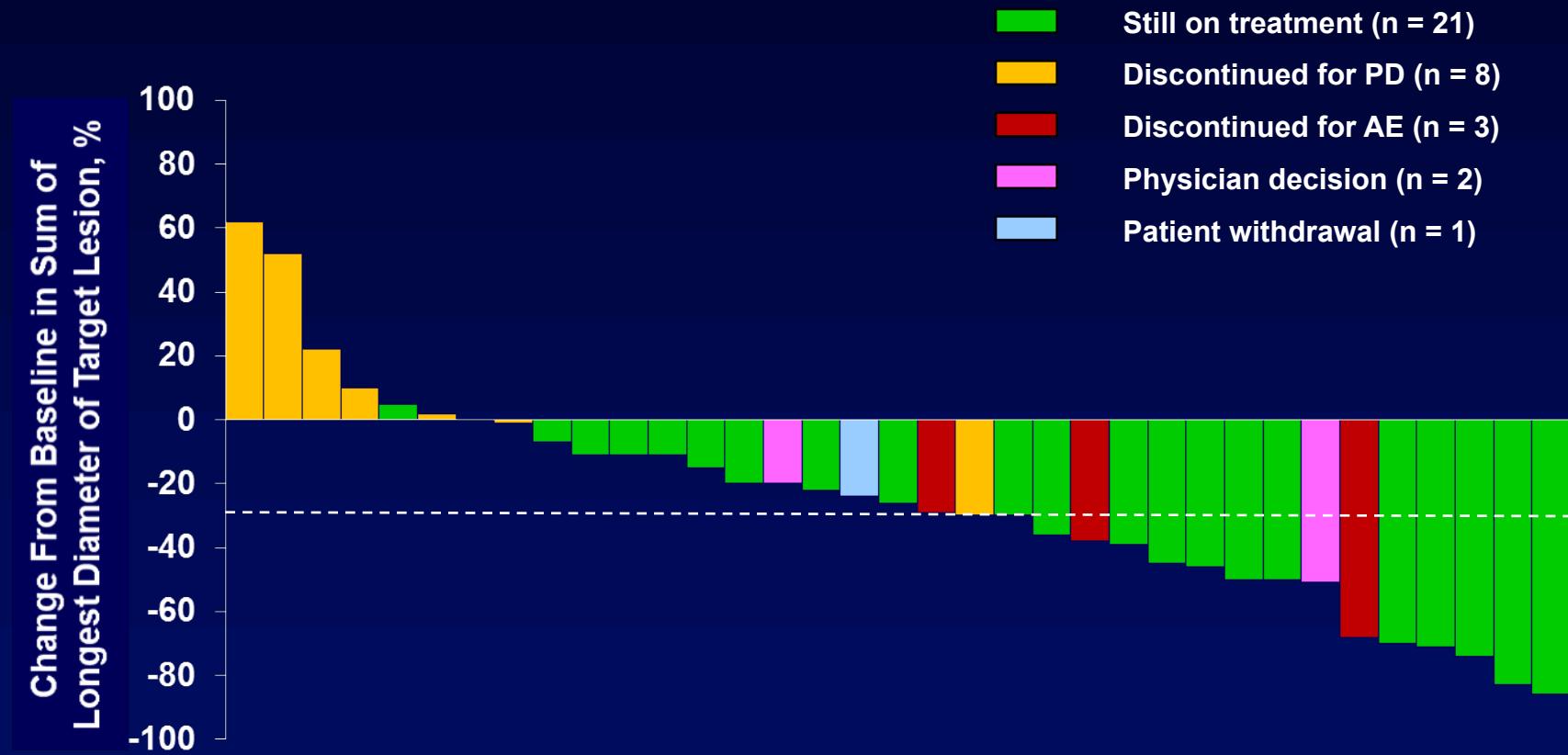
Maximum Percent Change from Baseline in Tumor Size in Evaluable Patients^a (Central Review, RECIST v1.1)



Analysis cut-off date: March 3, 2014.

^aEvaluable patients were those with measurable disease at baseline per central review who had ≥ 1 post baseline tumor assessment.

Maximum Percent Change from Baseline in Tumor Size in Evaluable Patients^a (Central Review, RECIST v1.1)



Analysis cut-off date: March 3, 2014.

^aEvaluable patients were those with measurable disease at baseline per central review who had ≥ 1 post baseline tumor assessment.

Rizvi NA, et al. J Clin Oncol. 2014;32(5s): Abstract 8007.

Antitumor Activity by Pembrolizumab Dose

Pembro Dose	n	RECIST v1.1, Central Review ^a		irRC, Investigator Review		
		ORR ^b n (%) [95% CI]	DCR ^b n (%) [95% CI]	n	ORR ^b n (%) [95% CI]	DCR ^b n (%) [95% CI]
2 mg/kg Q3W	6	2 (33%) [4%-78%]	3 (50%) [12%-88%]	6	4 (67%) [22%-96%]	5 (83%) [36%-100%]
10 mg/kg Q3W	20	4 (20%) [6%-44%]	14 (70%) [46%-88%]	22	10 (46%) [24%-68%]	18 (82%) [60%-95%]
10 mg/kg Q2W	16	5 (31%) [11%-59%]	10 (63%) [35%-85%]	17	7 (41%) [18%-67%]	12 (71%) [44%-90%]
Total	42	11 (26%) [14%-42%]	27 (64%) [48%-78%]	45	21 (47%) [32%-62%]	35 (78%) [63%-89%]

- Interim median PFS^c:
 - 27.0 weeks (95% CI, 13.6-45.0) by RECIST v1.1 per central review
 - 37.0 weeks (95% CI, 27.0-NR) by irRC per investigator review

Analysis cut-off date: March 3, 2014. DCR = Disease control rate (complete response + partial response + stable disease)

^a3 patients did not have measurable disease by RECIST v1.1 per independent central review at baseline and were not evaluated for response by RECIST v1.1.

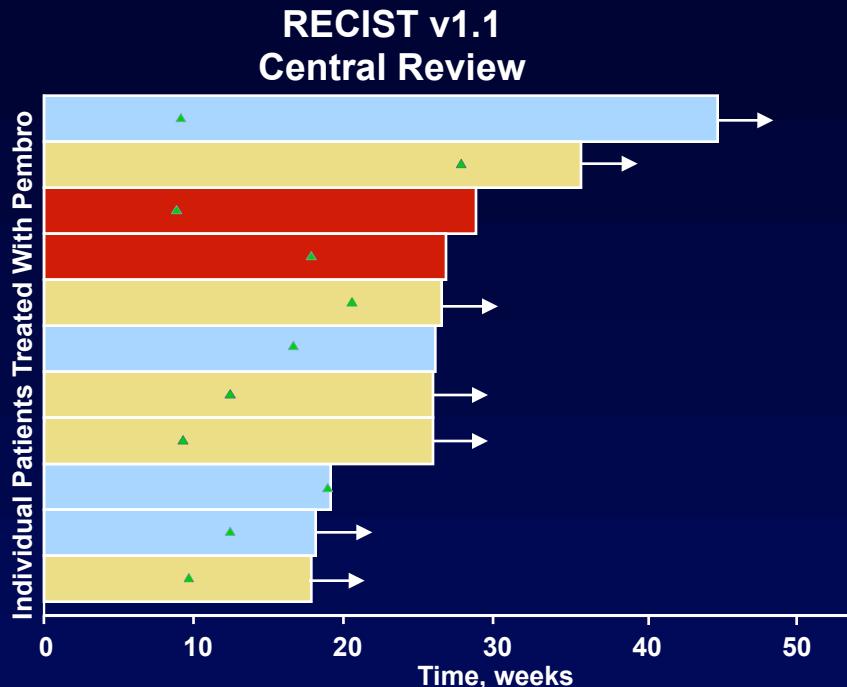
^bIncludes confirmed and unconfirmed responses.

^cFrom product-limit (Kaplan-Meier) method for censored data.

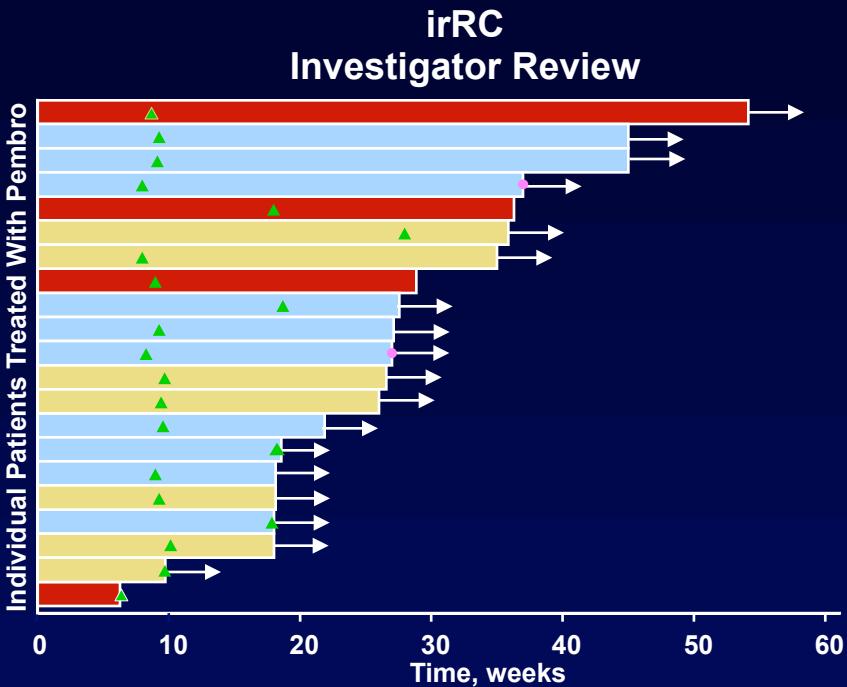
Rizvi NA, et al. J Clin Oncol. 2014;32(5s): Abstract 8007.

Time to and Durability of Response^a

■ Pembro 2 mg/kg Q3W
■ Pembro 10 mg/kg Q3W
■ Pembro 10 mg/kg Q2W

- 11 of 11 (100%) responses are ongoing
 - Median duration of response not reached (median follow-up, 36 weeks)
- 7 of 11 (64%) responders remain on treatment
 - Median duration of treatment: 27.1 weeks (range, 15.0+ – 48.3+)

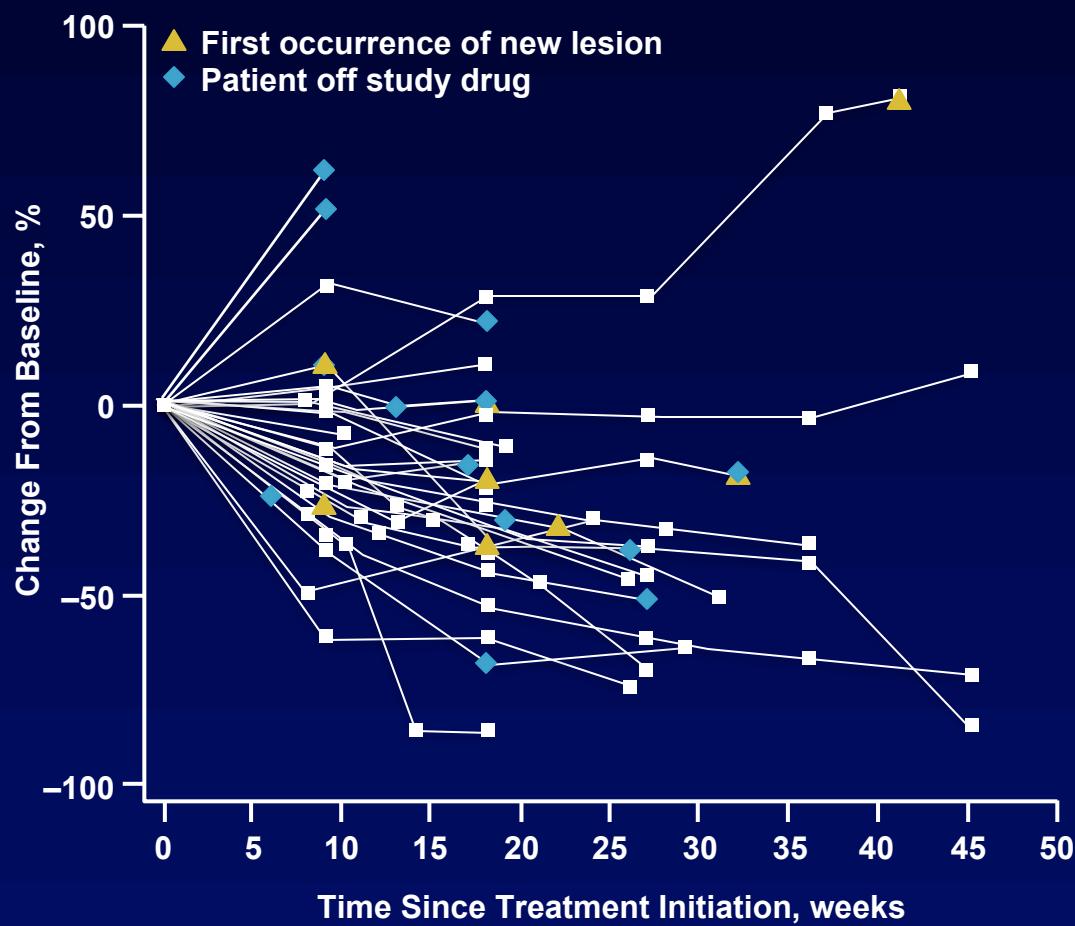


- 19 of 21 (90%) responses are ongoing
 - Median duration of response not reached (median follow-up, 36 weeks)
- 18 of 21 (86%) responders remain on treatment^b
 - Median duration of treatment: 27.1 weeks (range, 6.1 – 57.1+)

^aIncludes confirmed and unconfirmed responses. ^bIncludes 2 responders who showed progressive disease at the most recent tumor assessment but remain on therapy pending confirmation of disease progression.

Bars represent the relative number of weeks from first pembro dose to progressive disease (PD) or last non-PD assessment.
Analysis cut-off date: March 3, 2014.

Change From Baseline in Tumor Size in All Evaluable Patients^a (RECIST v1.1 by Central Review)

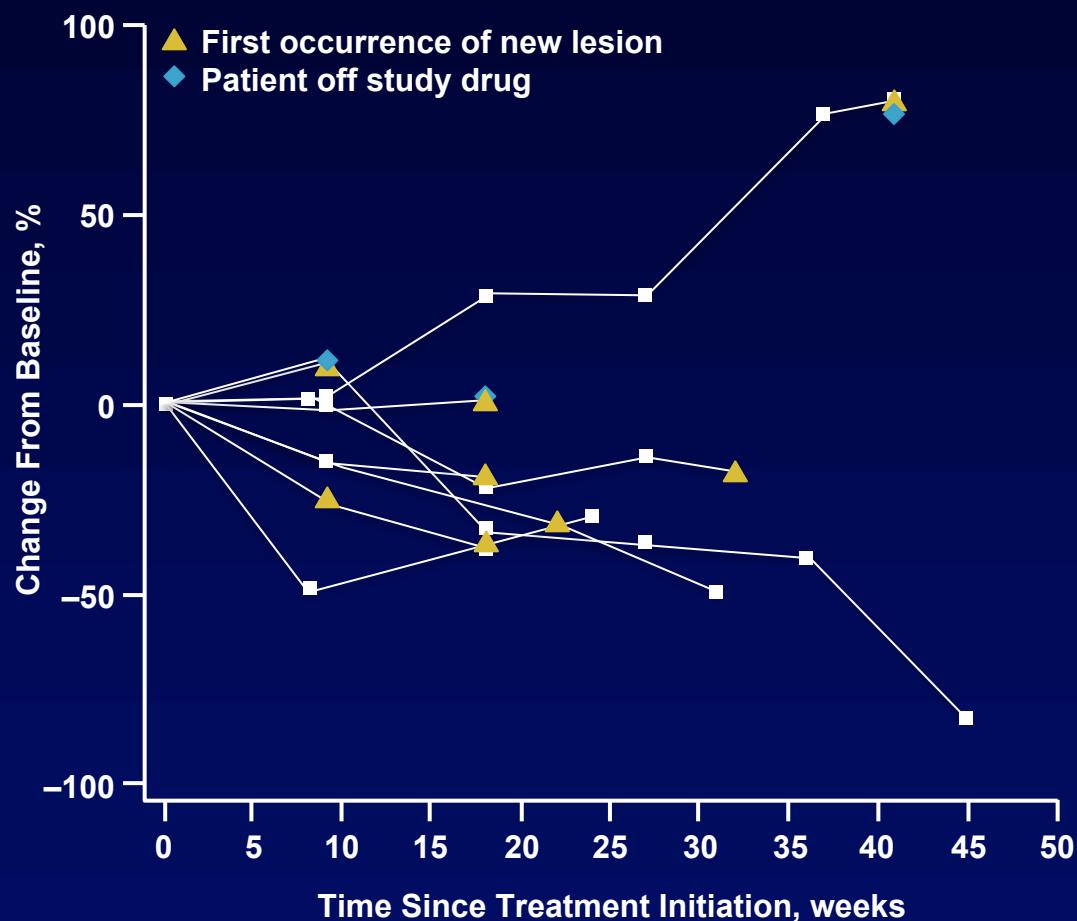


Analysis cut-off date: March, 3 2014.

^aEvaluable patients were those with measurable disease at baseline per central review who had ≥ 1 post baseline tumor assessment.

Rizvi NA, et al. J Clin Oncol. 2014;32(5s): Abstract 8007.

Change From Baseline in Tumor Size in Patients With New Lesions (RECIST v1.1 by Central Review)



Analysis cut-off date: March 3, 2014.

Rizvi NA, et al. *J Clin Oncol*. 2014;32(5s): Abstract 8007.

Conclusions

- Pembrolizumab has an acceptable and manageable toxicity profile
- Pembrolizumab provides robust antitumor activity as first-line therapy for PD-L1⁺ NSCLC^a
 - 26% ORR by RECIST, 47% by irRC
 - 100% of responders by RECIST and 90% of responders by irRC remain in response (median duration of response not reached)
 - 64% of responders by RECIST and 86% of responders by irRC remain on treatment
 - 27-week median PFS by RECIST, 37 weeks by irRC
- An additional 50 PD-L1⁺, treatment-naïve patients are enrolled in KEYNOTE-001 as part of the biomarker validation set
 - At final analysis, total population will be analyzed using the 50% cutpoint with the clinical trial assay
- KEYNOTE-024
 - Phase III study that will compare pembrolizumab monotherapy to platinum-based doublet chemotherapy in treatment-naïve patients with PD-L1⁺ metastatic NSCLC
 - Recruitment to begin in September 2014
 - KEYNOTE-010 (abstract TPS8124 presented on May 31 by RS Herbst)
 - Phase 2/3 study that will compare two doses of pembrolizumab to docetaxel in previously-treated patients with NSCLC

^aProportion score ≥1% by prototype assay.

Rizvi NA, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8007.

Safety and Clinical Activity of Pembrolizumab (MK-3475) in Previously Treated Patients With Non-Small Cell Lung Cancer

Abstract 8020

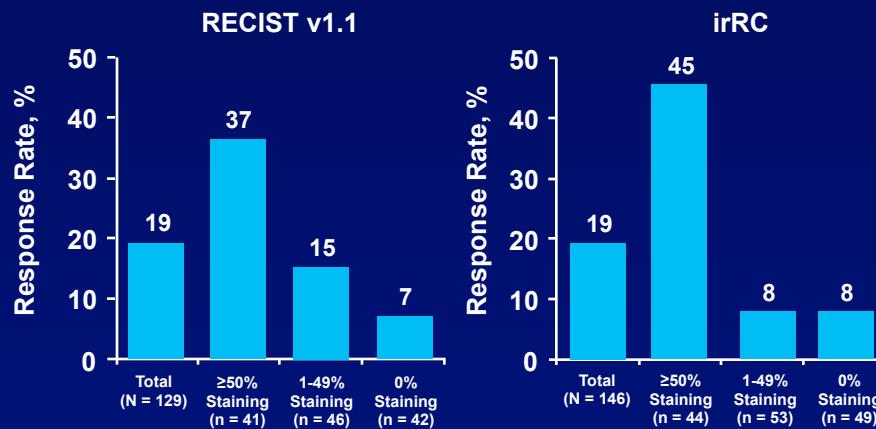
Garon EB, Leighl NB, Rizvi NA, Blumenschein Jr GR, Balmanoukian AS, Eder JP, Goldman JW, Hui R, Soria JC, Gangadhar TC, Sun JM, Patnaik A, Gubens MA, Lubiniecki GM, Zhang J, Niewood M, Emancipator K, Dolled-Filhart M, Gandhi L

Background

- Although treatment with approved second-line chemotherapies is associated with a median overall survival (OS) of 6 to 9 months, objective responses are observed in <10% of patients and the median duration of response is approximately 5 to 9 months
- Programmed death-1 (PD-1) is an inhibitory T-cell co-receptor that can lead to suppression of antitumor immunity upon interaction with its ligands, PD-L1 and PD-L2
- Pembrolizumab (MK-3475) is a humanized monoclonal IgG4 antibody against PD-1 that has high affinity for the PD-1 receptor and blocks PD-L1/2 binding
- This is a presentation of KEYNOTE-001 study, an ongoing phase 1 trial of MK-3475 that includes patients with NSCLC

PD-L1 Expression as a Biomarker

- Higher levels of PD-L1 expression in tumor specimens are associated with greater antitumor activity in patients with advanced NSCLC
- In a biomarker training study of pembrolizumab, 14 patients with strongly positive PD-L1 expression derived greater clinical benefit than patients with weak or negative PD-L1 expression¹



1. Gandhi L, et al. Presented at: 2014 AACR Annual Meeting; April 5-9, 2014; San Diego, CA. Abstract CT105.

Garon EB, et al. *J Clin Oncol*. 2014;32(5s): Abstract 8020.

Trial Design

- Patients with previously treated advanced NSCLC enrolled in the following cohorts who had ≥18 weeks of follow-up

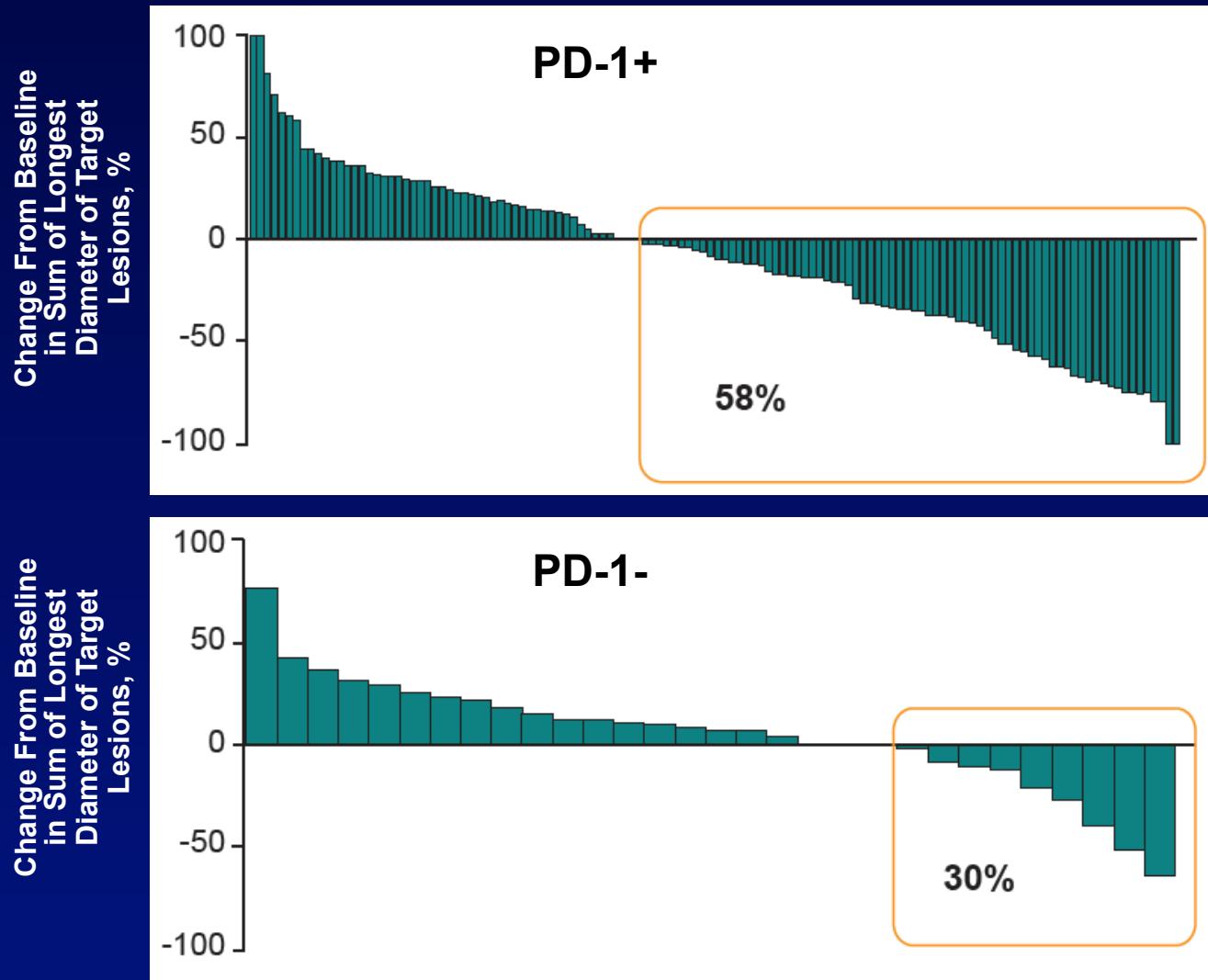
	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Randomization	Randomized	Randomized	Non-randomized	Non-randomized
Biomarker	PD-L1+	PD-L1+	PD-L1+	PD-L1-
Prior therapy	≥1 prior line of therapy	≥1 prior line of therapy	≥2 previous therapies	≥2 previous therapies
MK-3475 administration	10 mg/kg IV Q2W or 10 mg/kg IV Q3W	10 mg/kg IV Q2W or 10 mg/kg IV Q3W	10 mg/kg IV Q3W	10 mg/kg IV Q2W

- Pembrolizumab (MK-3475) was continued until disease progression, intolerable toxicity, or investigator decision
- Primary Endpoint: Overall response rate (ORR)

Baseline Demographics

Characteristic	PD-L1+	PD-L1-
Age, y, median (range)	64 (28-80)	62 (50-82)
Male, %	48	50
ECOG PS 0/1 / missing, %	28/71/1	25/72/3
EGFR mutant / wild type / unknown, %	17/79/4	25/75/0
KRAS mutant / wild type / unknown, %	17/47/36	18/52/30
ALK gene rearrangement / wild type / unknown, %	3/85/12	0/95/5
History of brain metastases, %	6	8
Stage M0 / M1a / M1b / missing, %	12/27/50/11	5/22/58/15
Squamous / nonsquamous / missing histology, %	16/81/3	15/85/0
Never / former / current / unknown smoking history	32/63/3/2	32/65/3/0

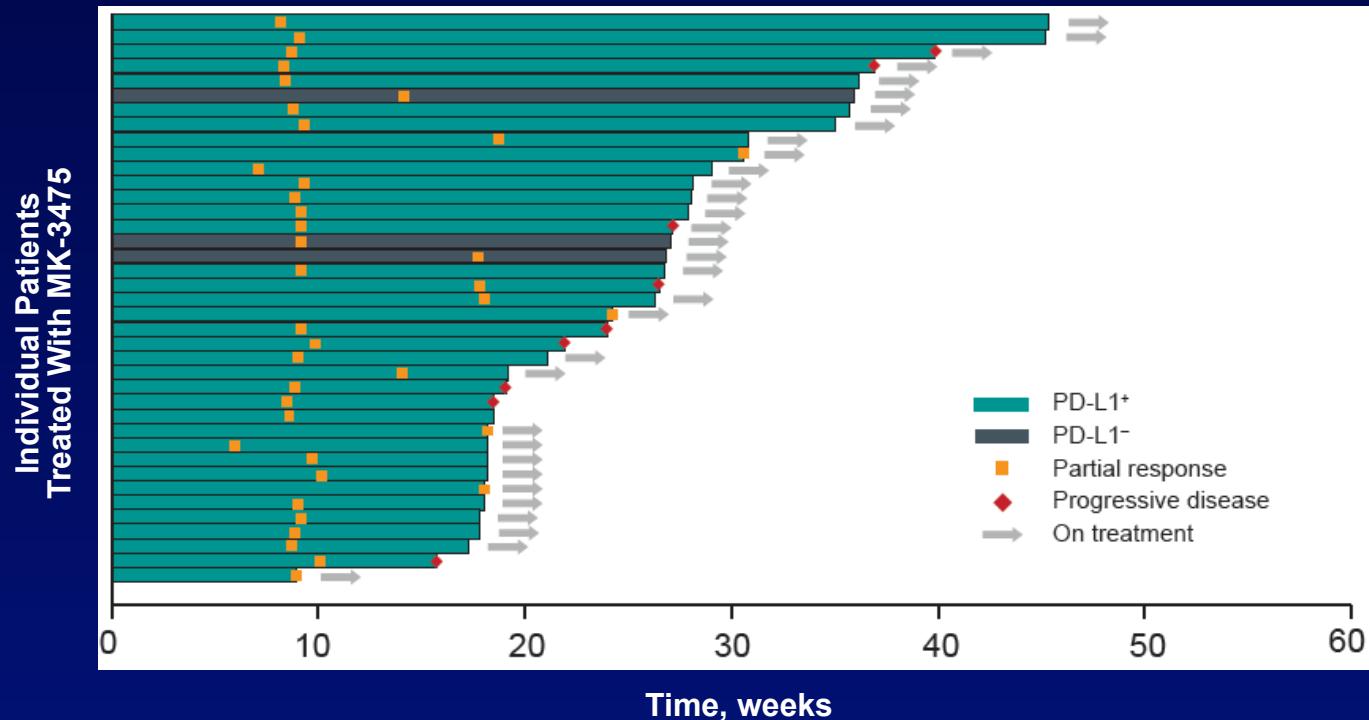
Change in Baseline Lesion



Response to Treatment

	RECIST v1.1, independent central review		irRC, investigator review	
	PD-L1+	PD-L1-	PD-L1+	PD-L1-
Best overall response	N = 159	N = 35	N = 177	N = 40
ORR, % (95% CI)	23 (16-30)	9 (2-23)	19 (14-26)	13 (4-27)
DCR, % (95% CI)	42 (34-50)	31 (17-49)	51 (44-59)	53 (36-69)
Time to response, week, median (range)	9 (6-31)	14 (9-18)	9 (6-22)	13 (9-18)
Response duration, week, median (range)	31 (0+ to 37+)	NR (9+ to 22+)	NR (0+ to 37+)	NR (0+ to 30+)
PFS	N = 177	N = 40	N = 177	N = 40
Median, week (95% CI)	11 (9-16)	10 (9-16)	16 (10-18)	16 (9-28)

Time to and Duration of Response



82% of patients with PD-L1+ tumors who experienced response by RECIST v1.1 remain on treatment

Drug-Related Adverse Events With Incidence $\geq 5\%$ in the Total Population

Adverse event, %	10 mg/kg Q2W		10 mg/kg Q3W		Total	
	Any grade	Grade 3-5	Any grade	Grade 3-5	Any grade	Grade 3-5
Any	71	9	58	10	64	10
Fatigue	24	1	16	<1	20	<1
Arthralgia	9	1	8	<1	9	<1
Decreased appetite	10	0	8	0	9	0
Pruritus	7	0	8	0	8	0
Diarrhea	8	0	7	0	7	0
Nausea	7	1	4	0	6	<1
Pyrexia	7	0	6	0	6	0
Rash	6	0	5	0	6	0
Hypothyroidism	8	0	3	0	5	0

Conclusion

- In 194 evaluable patients with previously treated NSCLC, MK-3475 provided an ORR of 20% with durable responses
 - ORR was 23% in patients with PD-L1+ NSCLC and 9% in patients with PD-L1- NSCLC
 - MK-3475 had an acceptable and manageable toxicity profile
- Several trials are ongoing to evaluate MK-3475 in lung cancer and other malignancies
 - KEYNOTE-001: Evaluating MK-3475 in 150 previously treated PD-L1+ patients with NSCLC
 - KEYNOTE-010: Phase II/III trial comparing 2 dose levels of MK-3475 with docetaxel in patients with NSCLC who have received ≥1 prior treatment regimen
 - KEYNOTE-021: Phase I/II trial evaluating MK-3475 in combination with chemotherapy or ipilimumab
 - Clinical development of MK-3475, both as monotherapy and as part of combination strategies, is ongoing in multiple solid tumors and hematologic malignancies

Nivolumab in Combination With Platinum-Based Doublet Chemotherapy in Advanced Non-Small Cell Lung Cancer

Abstract 8113

Antonia SJ, Brahmer JR, Gettinger SN, Chow LQM, Juergens RA, Shepherd FA, Laurie SA, Gerber DE, Goldman JW, Shen Y, Harbinson C, Alparthy S, Chen AC, Borghaei H, Rizvi NA

Immunotherapy in NSCLC

- The immune system plays an important role in many cancers, including lung cancer
- Programmed death 1 (PD-1) is an immune checkpoint receptor expressed by activated T cells that downregulates T cell activation upon interaction with its ligand PD-L1 and PD-L2
- PD-L1 expression on the surface of NSCLC tumor cells is associated with poor prognosis

Nivolumab

- Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody
- Monotherapy with nivolumab has shown durable objective response, prolonged stable disease, and encouraging survival outcomes in a phase I study of heavily pretreated patients with advanced melanoma, renal cell cancer, or NSCLC
- The phase I multicohort CA209-012 study is evaluating the safety, tolerability, and clinical activity of nivolumab as monotherapy, or combined with chemotherapy, targeted therapy, or ipilimumab in patients with advanced NSCLC
- Here we present interim results of nivolumab in combination with three standard platinum-based doublet chemotherapy regimens in four arms of this study

Study Design

- Chemotherapy-naïve patients with stage IIIB or IV NSCLC and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 were assigned based on histology to one of four treatment arms
- The study used a dose de-escalation design based on the modified toxicity probability interval method with nivolumab-related dose-limiting toxicities evaluated for the first 2 cycles of therapy
- Primary objective: Safety and tolerability
- Secondary objectives: ORR and PFS at 24 weeks

Patient Cohorts

Chemotherapy-naïve patients with stage IIIB or IV NSCLC

Group	Histology	Induction (4 x 21 day cycles)	Maintenance*
Group 1	Squamous	Nivolumab 10 mg/kg IV q3w + Gem 1250 mg/m ² + Cis 75 mg/m ²	Nivolumab 10 mg/kg q3w
Group 2	Nonsquamous	Nivolumab 10 mg/kg IV q3w + Pem 500 mg/m ² + Cis 75 mg/m ²	Nivolumab 10 mg/kg q3w
Group 3	Any histology	Nivolumab 10 mg/kg IV q3w + Pac 200 mg/m ² + Carb AUC 6	Nivolumab 10 mg/kg q3w
Group 4	Any histology	Nivolumab 5 mg/kg IV q3w + Pac 200 mg/m ² + Carb AUC 6	Nivolumab 5 mg/kg q3w

*Maintenance continued until progression or unacceptable toxicity

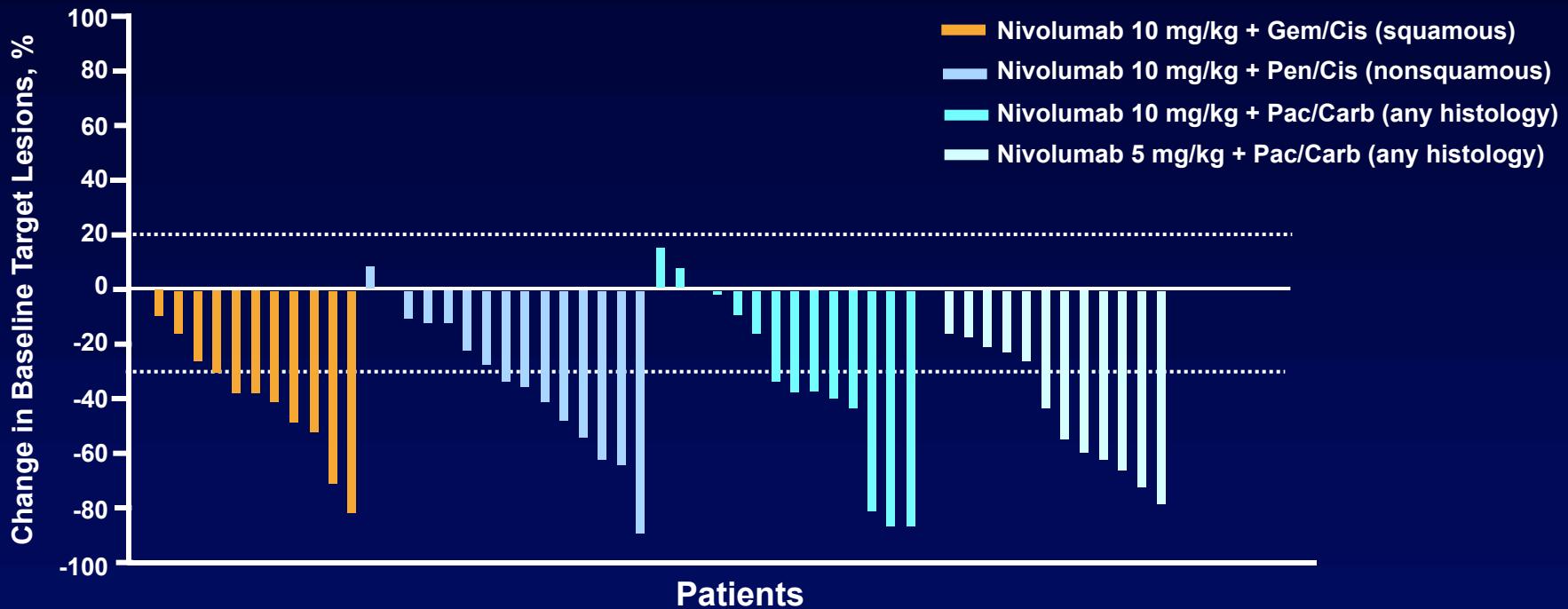
Baseline Patient Characteristics

	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg	Total N = 56
	Gem/Cis n = 12	Pem/Cis n = 15	Pac/Carb n = 15	Pac/Carb n = 14	
Median age, years (range)	67 (49-76)	60 (34-78)	58 (34-69)	64 (47-83)	63.5 (34-83)
Male, n (%)	7 (58)	6 (40)	7 (47)	6 (43)	26 (46)
Disease stage, n (%)					
Stage IIIB	1 (8)	0	0	1 (7)	2 (4)
Stage IV	11 (92)	15 (100)	15 (100)	13 (93)	54 (96)
Histology, n (%)					
Adenocarcinoma	0	15 (100)	10 (67)	12 (86)	37 (66)
Squamous cell	12 (100)	0	3 (20)	1 (7)	16 (29)
Large cell	0	0	0	1 (7)	1 (2)
Other	0	0	2 (13)	0	2 (4)
EGFR mutation, n (%)					
Positive	0	4 (27)	1 (7)	1 (7)	6 (11)
Negative	2 (17)	10 (67)	10 (67)	12 (86)	34 (61)
Unknown	10 (83)	1 (7)	4 (27)	1 (7)	16 (29)
Prior erlotinib, n (%)	0	2 (13)	1 (7)	0	3 (5)

Response to Treatment

	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg
	Gem/Cis n = 12	Pem/Cis n = 15	Pac/Carb n = 15	Pac/Carb n = 14
ORR, n (%)	4 (33)	7 (47)	7 (47)	6 (43)
Ongoing responders, n %	1 (25)	2 (29)	3 (43)	5 (83)
Best overall response, n (%)				
Complete response (CR)	1 (8)	0	0	0
Partial response (PR)	3 (25)	7 (47)	7 (47)	6 (43)
Stable disease (SD)	7 (58)	7 (47)	4 (27)	6 (43)
Progressive disease (PD)	0	0	3 (20)	1 (7)
Unable to determine	1 (8)	1 (7)	1 (7)	1 (7)
Estimated median duration of response (DOR), weeks	45	25.4	23.9	NR
Response duration by patient, weeks	6+, 18, 45, 57	13, 14+, 18, 21, 25, 38, 77+	11+, 12, 14, 18+, 24, 27, 92+	11+, 17+, 22, 60+, 65+, 73+

Best Change in Baseline Lesion



Only includes patients with baseline target lesion and at least one post-baseline target lesion assessment with non-missing value

Survival

	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg
	Gem/Cis n = 12	Pem/Cis n = 15	Pac/Carb n = 15	Pac/Carb n = 14
PFS				
PFS rate at 24 weeks, % (95% CI)	51 (19, 76)	71 (39, 88)	38 (14, 61)	51 (21, 75)
Median PFS, weeks (range)	24.7 (0.1+, 61.4)	29.7 (4.0+, 91.9+)	21.0 (3.1, 97.9+)	31.0 (0.1+, 82.4+)
OS				
1-year OS rate, % (95% CI)	50 (21, 74)	87 (56, 96)	60 (32, 80)	85 (51, 96)
Median OS, weeks (range)	50.5 (19.7, 99.3+)	83.4 (33.0, 105.1+)	64.9 (13.9, 105.0+)	NR (33.7+, 87.1+)

Safety

- No dose-limiting toxicity occurred during the first 6 weeks of treatment
- Treatment-related AEs of any grade occurred in 93% of patients
- Treatment-related grade 3/4 AEs were reported in 45% of patients
- Across treatment arms, treatment-related pneumonitis of any grade was reported in 7 patients (13%) with grade 3/4 in 4 patients (7%)

Treatment-Related AEs in >15% of Patients

	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg	Total N = 56	
	Gem/Cis n = 12	Pem/Cis n = 15	Pac/Carb n = 15	Pac/Carb n = 14		
AE, n (%)	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	All Grades	Grade 3/4
Patients with any AE	3 (25)	7 (47)	11 (73)	4 (29)	52 (93)	25 (45)
Fatigue	0	1 (7)	2 (13)	0	40 (71)	3 (5)
Nausea	0	1 (7)	0	0	26 (46)	1 (2)
Decreased appetite	0	0	1 (7)	0	20 (36)	1 (2)
Alopecia	0	0	0	0	17 (30)	0
Anemia	1 (8)	0	1 (7)	0	15 (27)	2 (4)
Rash	0	0	1 (7)	1 (7)	14 (25)	2 (4)
Diarrhea	0	0	1 (7)	0	12 (21)	1 (2)
Arthralgia	0	0	0	0	11 (20)	0
Constipation	0	0	0	0	11 (20)	0
Peripheral neuropathy	0	0	0	0	10 (18)	0

Conclusion

- The study met its primary endpoint of safety and tolerability of nivolumab in combination with platinum-based chemotherapy
 - No dose-limiting toxicities were seen in the first 6 weeks
 - Grade 3/4 adverse events occurred in 45% of patients
- Nivolumab in combination with chemotherapy demonstrated activity in first-line NSCLC
 - 1-year OS ranged from 50% to 85%
 - Approximately 40% of patients responded to treatment, depending on chemotherapy regimen
- Nivolumab is also being studied as a monotherapy for NSCLC

REVEL: A Randomized, Double-Blind, Phase III Trial of Ramucirumab, a VEGFR-2 Monoclonal Antibody, plus Docetaxel versus Placebo plus Docetaxel for Second-Line Treatment of Non-Small Cell Lung Cancer

Abstract LBA8006

Pérol M*, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, Park K, Kowalszyn RD, Pikel J, Czyzewicz G, Orlov S, Lewanski CR, Alexandris E, Zimmermann A, Chouaki N, John WJ, Yurasov S, and Garon EB

***On behalf of the REVEL Investigators**



Limited Advancement in Second-Line Therapy

- Despite advancements in genomics, chemotherapy remains the treatment of choice for the majority of patients
- Only three agents, docetaxel, pemetrexed, and erlotinib, are approved by the FDA for second-line therapy, with median OS from approximately 7 months to 8 months



- Outside of subgroup analyses, no other trials evaluating addition of a new agent to standard second-line chemotherapy demonstrated an improvement of OS in NSCLC patients

BSC, best supportive care; Doc, docetaxel; HR, hazard ratio; m, months; OS, overall survival

Some HRs not reported.

1. Shepherd FA, et al. *J Clin Oncol*. 2000;18(10):2095-2103. 2. Shepherd FA, et al. *N Engl J Med*. 2005;353(2):123-132. 3. Scagliotti G, et al. *Oncologist*. 2009;14(3):253-263.

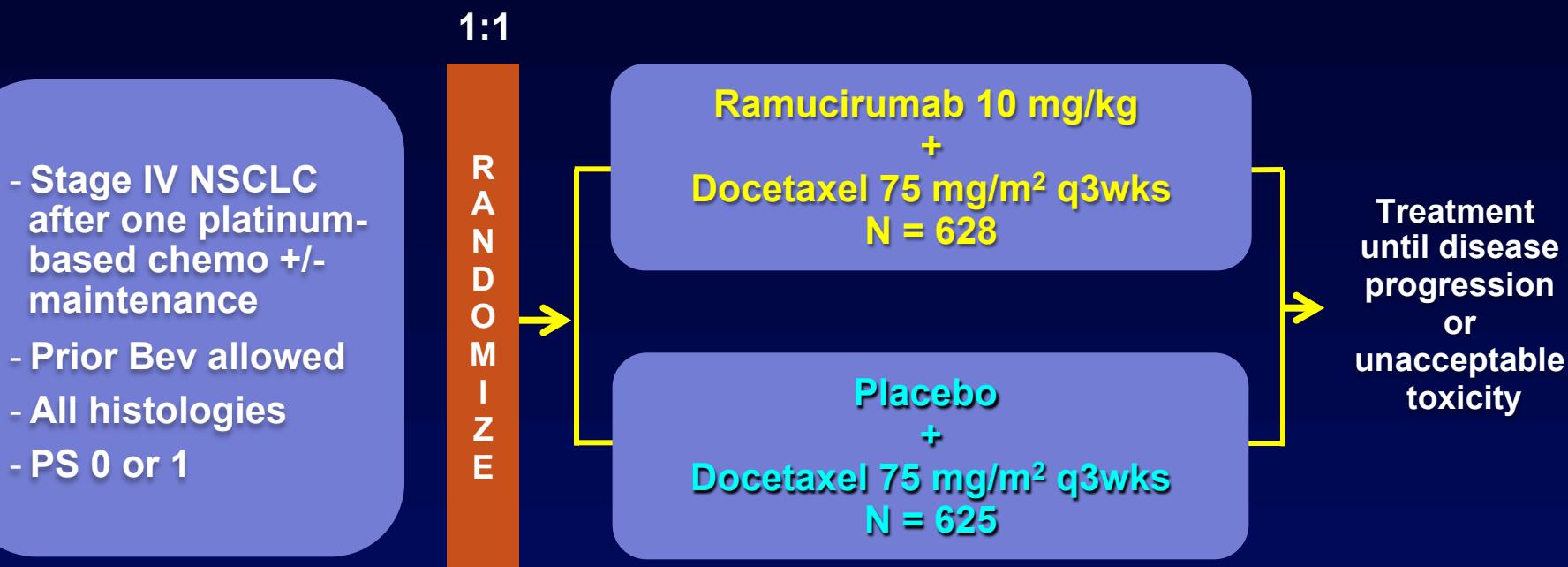
Pérol M, et al. *J Clin Oncol*. 2014;32(5s): Abstract LBA8006.

Ramucirumab and Angiogenesis

- Angiogenesis is a critical target in advanced NSCLC, with VEGF-A/VEGFR-2 axis as main angiogenic driver
- Ramucirumab (RAM) is a human IgG1 monoclonal antibody, specifically binding to the extracellular domain of VEGFR-2
- RAM inhibits VEGFR-2 signaling in preclinical studies and has shown antitumor activity in phase I/II studies
- Two phase III studies in second-line gastric cancer demonstrated that RAM monotherapy or in combination with chemotherapy prolongs OS
 - Ramucirumab monotherapy is approved by the FDA as second-line treatment of advanced gastric cancer (April 2014)¹

IgG1, immunoglobulin subgroup 1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor
1. Fuchs CS, et al. *Lancet.* 2014;383(9911):31-39.

REVEL: Study Design



Stratification factors:

- ECOG PS 0 vs 1
- Gender
- Prior maintenance
- East-Asia vs ROW

Primary endpoint: Overall Survival

Secondary endpoints: PFS, ORR, safety, patient-reported outcomes

Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; PFS, progression-free survival; ROW, rest of the world; q3wks, every 3 weeks

Patient Eligibility

Key Inclusion Criteria

- Stage IV
- NSCLC - All histologies (squamous and nonsquamous)
- Disease progression during or after one prior first-line platinum-based therapy with or without maintenance therapy for advanced/metastatic disease
- Prior bevacizumab allowed
- ECOG PS ≤1 and adequate organ function

Key Exclusion Criteria

- Prior docetaxel treatment or monotherapy with EGFR TKI
- Untreated CNS metastases (treated asymptomatic brain metastases were eligible)
- Major blood vessel invasion, or significant intratumor cavitation
- Significant bleeding disorders, vasculitis, grade 3-4 GI bleeding within 3 months, or arterial thromboembolic events, GI perforation and/or fistula within 6 months
- Gross hemoptysis within 2 months
- Poorly controlled hypertension

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; GI, gastrointestinal

Pérol M, et al. *J Clin Oncol.* 2014;32(5s): Abstract LBA8006.

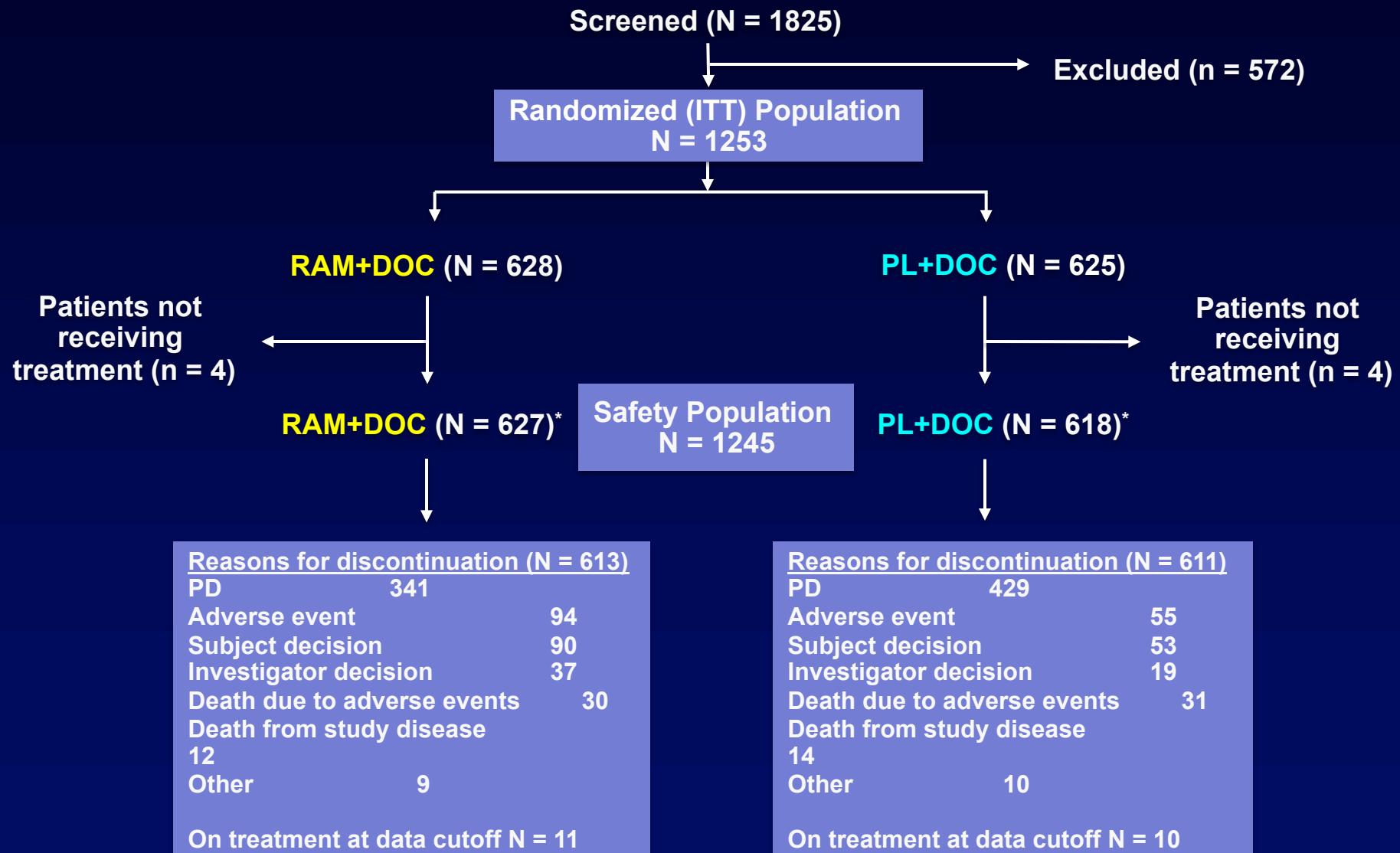
Statistical Considerations for OS

- Stratified log-rank comparison of OS in the ITT population
- Planned enrollment of 1242 patients for 869 OS events (30% censoring) with 85% power to detect $HR = 0.816$ with a two-sided α -level of <0.05
- Projected median OS of 7.5 months in PL+DOC and 9.2 months in RAM+DOC
- HR was estimated with stratified Cox proportional hazards model

DOC, docetaxel; HR, hazard ratio; ITT, intention-to-treat; PL, placebo; RAM, ramucirumab

Pérol M, et al. *J Clin Oncol.* 2014;32(5s): Abstract LBA8006.

Patient Disposition



*Three PL+DOC arm patients were inadvertently treated with RAM and are therefore considered part of the RAM+DOC arm for the safety analyses, but the PL+DOC arm for the ITT efficacy analysis.

Baseline Demographics and Patient Characteristics

Parameter		RAM+DOC N = 628	PL+DOC N = 625
Gender, n (%)	Male	419 (66.7)	415 (66.4)
Age, years	Median (range)	62.0 (21.0-85.0)	61.0 (25.0-86.0)
Race, n (%)	Caucasian	526 (83.8)	503 (80.5)
	Asian	74 (11.8)	86 (13.8)
Geographic region, n (%)	East Asia	43 (6.8)	46 (7.4)
Histology, n (%)	Nonsquamous	465 (74.0)	447 (71.5)
	Squamous	157 (25.0)	171 (27.4)
ECOG PS, n (%)	1	420 (66.9)	425 (68.0)
EGFR status, n (%)	Wildtype	207 (33.0)	197 (31.5)
	Mutant	15 (2.4)	18 (2.9)
	Unknown	402 (64.0)	406 (65.0)
	Missing	4 (0.6)	4 (0.6)
Prior taxane, n (%)	Yes	153 (24.4)	149 (23.8)
Prior bevacizumab, n (%)	Yes	88 (14.0)	92 (14.7)
Best response to platinum, n (%)	CR/PR/SD	420 (66.9)	417 (66.7)
	PD	178 (28.3)	182 (29.1)

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PR, partial response; SD, stable disease

Tumor Response by RECIST v1.1

ITT Population, Investigator Assessment

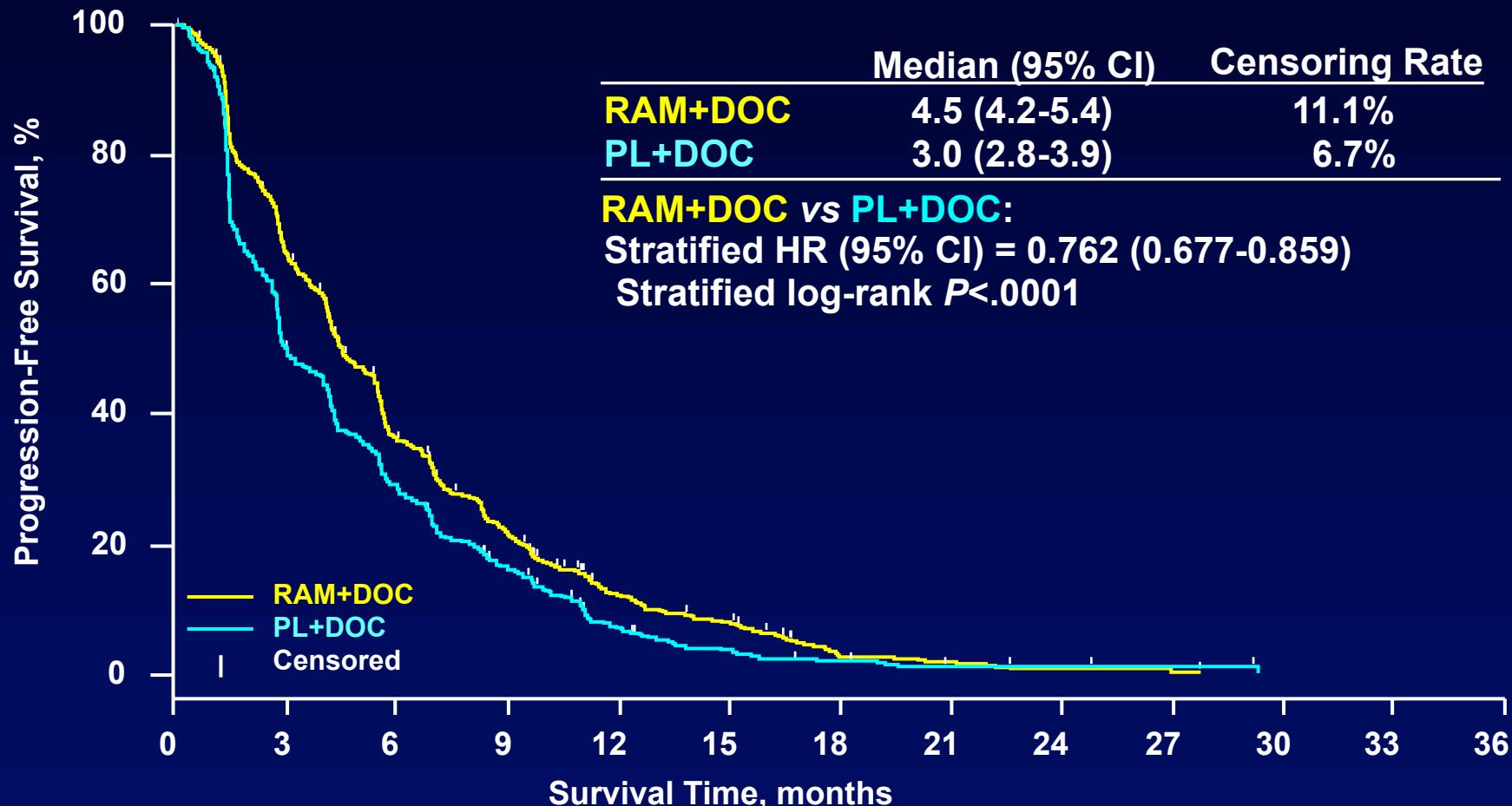
	RAM+DOC N = 628	PL+DOC N = 625	P Value
Response, n (%)			
CR	3 (0.5)	2 (0.3)	
PR	141 (22.5)	83 (13.3)	
SD	258 (41.1)	244 (39.0)	
PD	128 (20.4)	206 (33.0)	
Unknown/not assessed	98 (15.6)	90 (14.4)	
ORR (CR+PR), % (95% CI)	22.9 (19.7-26.4)	13.6 (11.0-16.5)	<.001
DCR (CR+PR+SD), % (95% CI)	64.0 (60.1-67.8)	52.6 (48.6-56.6)	<.001

CI, confidence interval; DCR, disease control rate; ITT, intention-to-treat; PD=progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Pérol M, et al. *J Clin Oncol.* 2014;32(5s): Abstract LBA8006.

Progression-Free Survival

ITT Population, Investigator Assessment

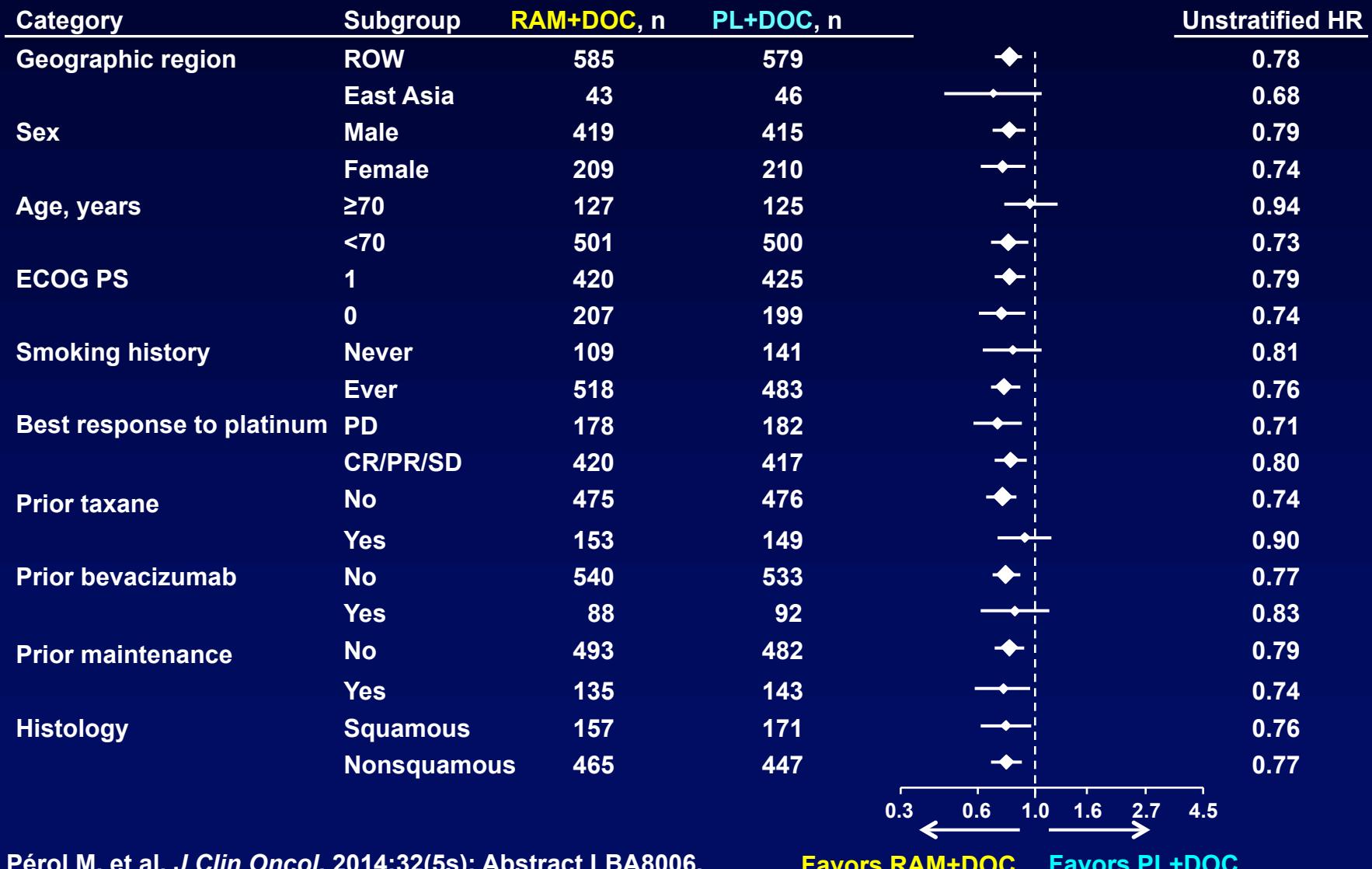


Number at risk

RAM+DOC	628	383	204	120	59	38	11	7	3	3	0	0	0
PL+DOC	625	301	172	95	37	17	9	4	3	2	0	0	0

Forest Plot of PFS by Subgroups

Unstratified Analysis

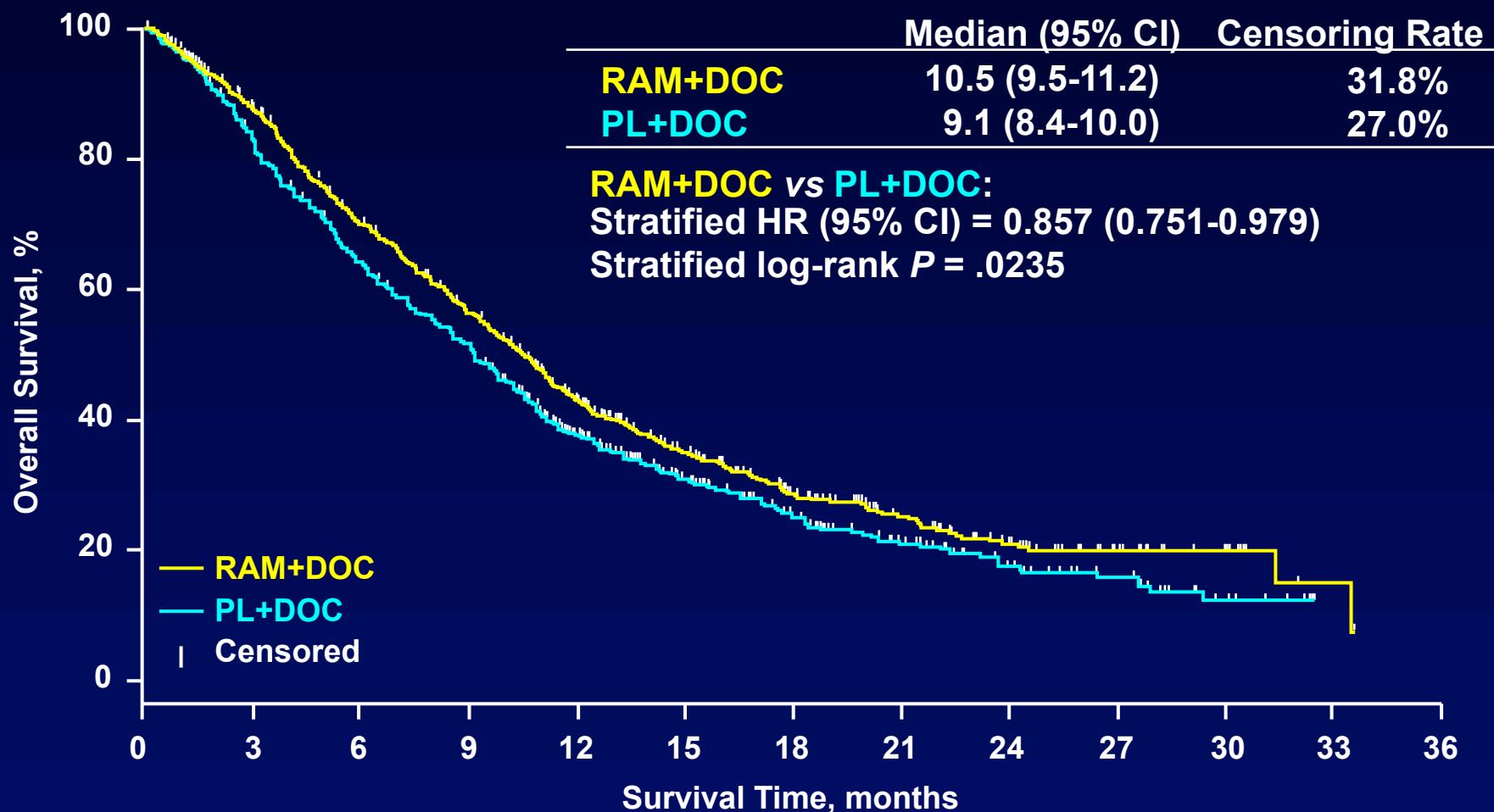


Postdiscontinuation Therapy

	RAM+DOC N = 628 n (%)	PL+DOC N = 625 n (%)
Systemic therapy	285 (45.4)	302 (48.3)
Selected therapies		
EGFR TKI	118 (18.8)	133 (21.3)
Gemcitabine	76 (12.1)	72 (11.5)
Vinorelbine	59 (9.4)	64 (10.2)
Pemetrexed	66 (10.5)	47 (7.5)

Overall Survival

ITT Population

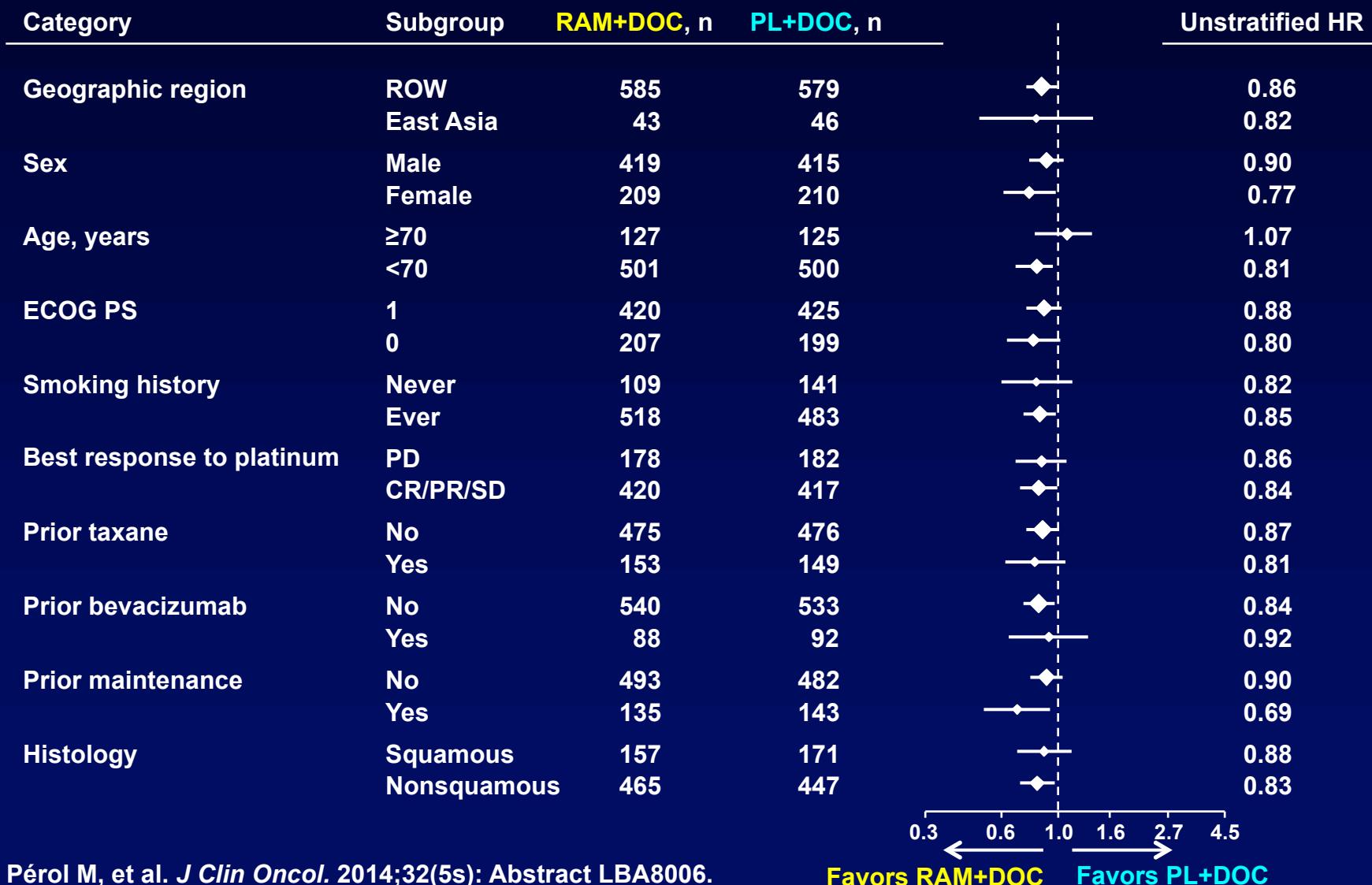


Number at risk

RAM+DOC	628	527	415	329	231	156	103	70	45	23	11	2	0
PL+DOC	625	501	386	306	197	129	86	56	36	23	9	0	0

Forest Plot of OS by Subgroups

Unstratified Analysis



Safety Overview

	RAM+DOC N = 627 n (%)	PL+DOC N = 618 n (%)
Any TEAE	613 (97.8)	594 (96.1)
Grade ≥3 TEAE	495 (78.9)	444 (71.8)
Serious TEAE	269 (42.9)	262 (42.4)
Related to any study drug	196 (31.3)	147 (23.8)
TEAE leading to disc. of any study drug	58 (9.3)	32 (5.2)
Ramucirumab disc.	9 (1.4)	6 (1.0)
Chemotherapy disc.	49 (7.8)	26 (4.2)
TEAE with outcome of death	34 (5.4)	35 (5.7)
Related to any study drug	15 (2.4)	9 (1.5)

Difference between arms was ≥5% higher in the RAM+DOC arm.

Disc, discontinuation; TEAE, treatment-emergent adverse events.

Pérol M, et al. *J Clin Oncol*. 2014;32(5s): Abstract LBA8006.

Selected Treatment-Emergent Adverse Events Occurring in $\geq 20\%$ of Patients or $\geq 5\%$ Higher in the RAM+DOC Arm

Preferred and Consolidated [†] Term	RAM+DOC (N = 627)		PL+DOC (N = 618)	
	Grade 1-2 %	Grade 3-4 %	Grade 1-2 %	Grade 3-4 %
Neutropenia[†]	6.2	48.8	6.1	39.8
Febrile neutropenia	0	15.9	0	10.0
Thrombocytopenia[†]	10.5	2.9	4.5	0.6
Fatigue[†]	40.7	14.0	39.5	10.5
Decreased appetite	26.8	2.2	23.6	1.3
Nausea	25.8	1.1	26.1	1.5
Stomatitis	19.0	4.3	11.3	1.6
Mucosal inflammation	13.2	2.9	6.5	0.5
Diarrhea	27.1	4.6	24.6	3.1
Neuropathy[†]	20.4	2.7	18.8	1.6
Edema peripheral	16.3	0	8.3	0.3
Lacrimation increased	13.2	0.2	4.5	0

Difference between arms for term was $\geq 5\%$ higher in the RAM+DOC arm.

- No grade 5 toxicity was observed for the events presented on this slide.

Select AEs of Special Interest

Adverse Events of Special Interest	RAM+DOC (N = 627)			PL+DOC (N = 618)		
	Grade 1-2 %	Grade 3-4 %	Grade 5 %	Grade 1-2 %	Grade 3-4 %	Grade 5 %
Bleeding/hemorrhage [†]	26.5	1.1	1.3	12.9	1.0	1.3
Epistaxis	18.2	0.3	0	6.3	0.2	0
GI hemorrhage	0	0	0.2	0	0	0
Hemoptysis	5.1	0.3	0.3	4.5	0.3	0.3
Pulmonary hemorrhage	1.4	0	0.6	1.1	0	0.5
Hypertension [†]	5.3	5.6	0	2.8	2.1	0
Infusion-related reaction [†]	2.9	0.8	0	3.9	0.6	0
Proteinuria	3.2	0.2	0	0.8	0	0
Venous thromboembolic [†]	0.8	1.4	0.3	2.9	2.9	0
Arterial thromboembolic [†]	0.6	0.3	0.6	0.8	0.8	0.5
Renal failure [†]	1.8	0.3	0.2	1.9	0.3	0
Congestive heart failure [†]	0.2	0.8	0	0.5	0.2	0
Gastrointestinal perforation [†]	0.2	0.8	0	0	0.3	0

Difference between arms for term was $\geq 5\%$ higher in the RAM+DOC arm.

[†]Combined AE category comprising MedDRA preferred terms.

Perol M, et al. *J Clin Oncol*. 2014;32(5s); Abstract LBA8006.

REVEL: Conclusions

- REVEL met its primary endpoint of OS improvement
- RAM+DOC showed statistically significant improvement in PFS and ORR compared to PL+DOC
- OS and PFS improvement were consistent in most major subgroups, including squamous and nonsquamous histology
- The addition of RAM to DOC did not result in an increase of SAEs and AEs leading to death. Safety profile was as expected for an anti-VEGFR agent in combination with DOC
- REVEL is the first study showing that addition of a novel agent to standard chemotherapy improves survival in stage IV NSCLC patients with progression after platinum-based chemotherapy