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Antitumor Activity of Pembrolizumab (Pembro; MK-3475) and Correlation With Programmed Death Ligand 1 (PD-L1) Expression in a Pooled Analysis of Patients With Advanced NSCLC

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Pembrolizumab: Initial Experience

- Pembrolizumab is a humanized monoclonal antibody against PD-1 in clinical development for the treatment of advanced solid tumors
  - Promising antitumor activity and a manageable safety profile have been observed in patients with advanced melanoma, NSCLC, head and neck cancer, gastric cancer, and urothelial cancer
  - Pembrolizumab was recently approved in the United States for the treatment of patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if *BRAF* V600 mutation-positive, a BRAF inhibitor
- In the initial cohort of 38 patients with previously treated NSCLC who received pembrolizumab dosed at 10 mg/kg Q3W in the phase 1 KEYNOTE-001 study, the best overall response rate was 21% by RECIST v1.1, and the median PFS of responders was not reached at 62 weeks[1]
  - Correlation between tumor PD-L1 expression and improved antitumor activity with pembrolizumab has been observed[2]

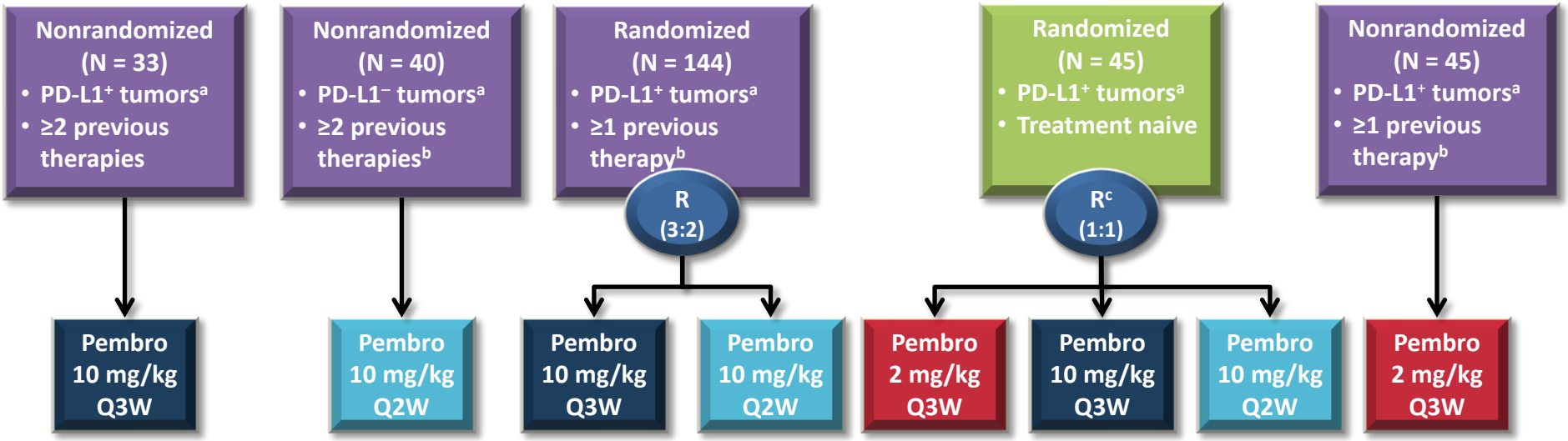
1. Garon E et al. Abstract 2416. Presented at: 15th World Conference on Lung Cancer; October 27-30, 2013; Sydney, Australia.
2. Gandhi L et al. Abstract CT105. Presented at: AACR 2014; April 5-9, 2014; San Diego, CA, USA.

Phase 1b KEYNOTE-001 Study: NSCLC Key Eligibility Criteria

- Measurable disease
- Age ≥18 years
- ECOG PS 0-1
- Known PD-L1 status[a]
  - Positive defined as ≥1% tumor PD-L1 expression
- *EGFR* mutation or *ALK* gene rearrangement:
  - Not permitted for treatment-naive patients[b]
  - Permitted in previously-treated patients, with progression of disease on the relevant tyrosine kinase inhibitor
- Progression of disease on most recent prior systemic therapy[c]
- No systemic steroid therapy
- No active autoimmune disease
- No active brain metastases

[a]PD-L1 expression determined centrally from a new tumor biopsy performed in the 60 days before treatment initiation or an archival tumor specimen using a prototype immunohistochemistry assay and the 22C3 antibody.
[b]Patients enrolled under an earlier protocol amendment could be *EGFR* or *ALK* wild type.
[c]In previously treated patients, excluding the first 33 patients who enrolled under an earlier protocol amendment.

KEYNOTE-001 Study: NSCLC Expansion Cohorts (N = 307)



- Response assessment
  - Primary measure: ORR by RECIST v1.1[1] per independent central review
  - Secondary measure: immune-related response criteria (irRC)[2] per investigator assessment
- Pembrolizumab was given until disease progression, unacceptable toxicity, or death
- Analysis cut-off date: March 3, 2014[d]

[a]Tumor PD-L1 expression was determined by a prototype assay to inform enrollment. Samples were independently reanalyzed using a clinical trial IHC assay. [b]Including ≥1 therapy platinum-containing doublet. [c]First 11 patients randomized to 2 mg/kg Q3W and 10 mg/kg Q3W. The remaining 34 patients were randomized to 10 mg/kg Q2W and 10 mg/kg Q3W. [d]Analysis cut-off date is September 11, 2014 for the nonrandomized cohort of 45 patients treated at 2 mg/kg Q3W.

1. Eisenhauer EA et al. *Eur J Cancer*. 2009;45:228-247. 2. Wolchok JD et al. *Clin Cancer Res*. 2009;15:7412-20.

Baseline Characteristics

Characteristic, %	N = 262
Age, median (range), years	65 (28-86)
Male	50
ECOG PS	
0	31
1	68
Missing	1
Race	
White	83
Black or African American	4
Asian	11
Other	2
Squamous histology	17
No. prior therapies	
0	17
≥1	83

Characteristic, %	N = 262
Stage	
M0	13
M1a	28
M1b	49
Unknown	11
History of brain metastases	5
EGFR mutation (N = 250)	16
KRAS mutation (N = 156)	26
ALK translocation (N = 231)	3
Smoking history	
Current	5
Former	64
Never	28
Unknown	2

Analysis cut-off date: March 3, 2014.

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Summary of Exposure and Treatment-Related AEs

	N = 262
Exposure	
Median (range) time on therapy, days	85.5 (1-400)
Median (range) doses, n	5.5 (1-23)
Treatment-related AE summary, n (%)	
Any grade	175 (67)
Grade 3-4	23 (9)
Death	1 (0.4)
Discontinued	8 (3)

- Infusion-related reactions occurred in 4 patients (1.5%)

AE, %	N = 262	
	Any Grade	Grade 3-5
Treatment-related with incidence ≥5%		
Fatigue	20	<1
Pruritus	9	0
Arthralgia	8	<1
Decreased appetite	8	0
Diarrhea	7	0
Hypothyroidism	6	0
Pyrexia	6	0
Rash	6	0
Nausea	5	<1
Other of clinical interest ≥1%		
Pneumonitis	4	2
Hyperthyroidism	2	<1

- Other potentially immune-mediated AEs that occurred in <1% of patients were colitis and hyponatremia

Analysis cut-off date: March 3, 2014.

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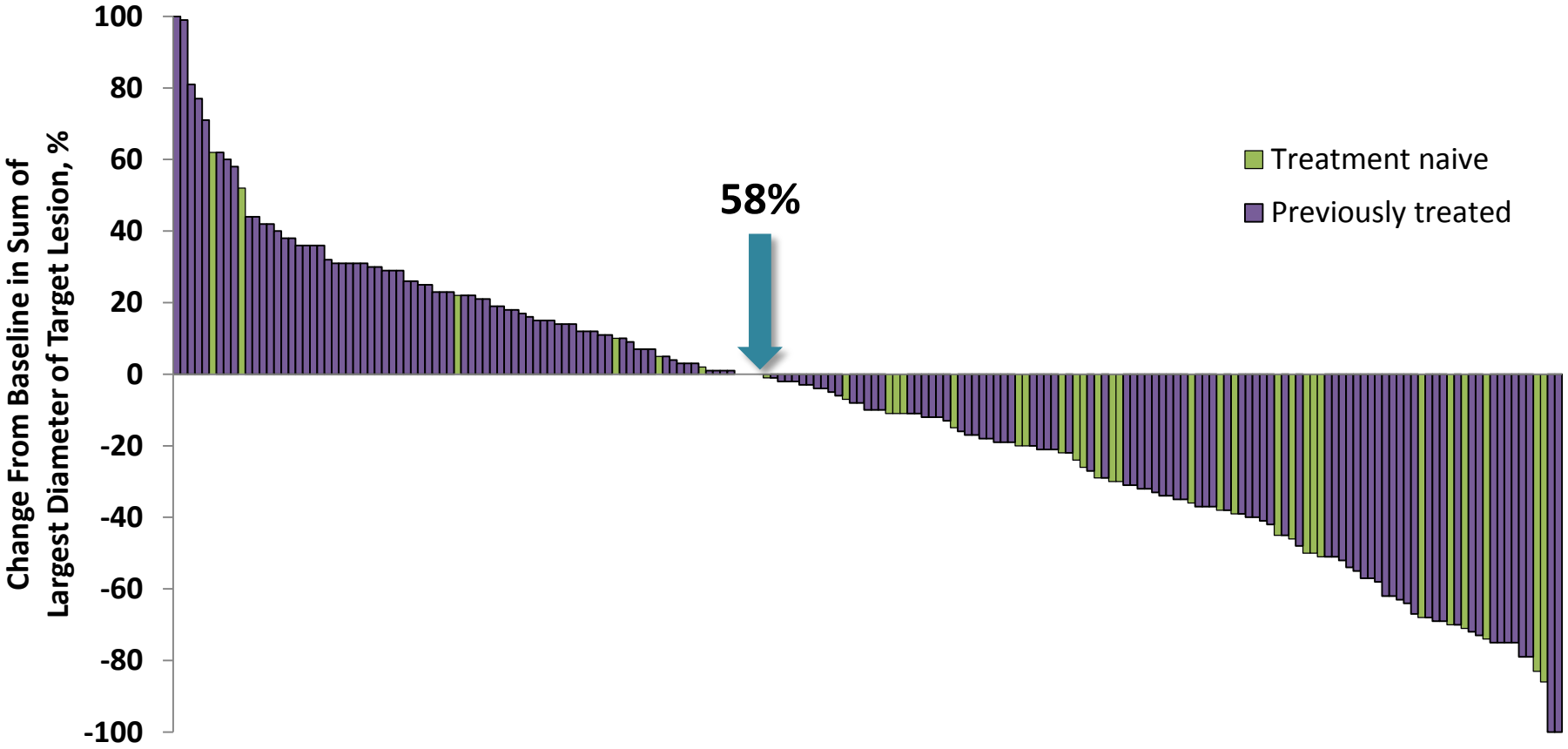
Maximum Percent Change From Baseline in Tumor Size[a] (RECIST v1.1, Central Review)



[a]Evaluable patients were those with measurable disease at baseline per central review who had ≥1 post baseline tumor assessment.
Analysis cut-off date: March 3, 2014.

Antitumor Activity (RECIST v1.1, Central Review)

	N	ORR[a] % (95% CI)
Total	**236**	**21 (16-27)**
Previous treatment	236	
Treatment naive	42	26 (14-42)
Previously treated	194	20 (15-26)
Histology	230	
Nonsquamous	191	23 (17-29)
Squamous	39	18 (8-34)
Smoking history	230	
Current/Former	165	27 (20-34)
Never	65	9 (4-19)

	N	ORR[a] % (95% CI)
Dose/schedule	236	
2 Q3W	6	33 (4-78)
10 Q3W	126	21 (14-29)
10 Q2W	104	21 (14-30)
PD-L1 expression[b]	236	
Positive	201	23 (18-30)
Negative	35	9 (2-23)
EGRFR mutation	36	14 (5-30)
KRAS mutation	39	28 (15-45)
ALK rearrangement	6	17 (0-64)

[a]Includes confirmed and unconfirmed responses.
[b]As assessed using a prototype assay. Positive was defined as staining in ≥1% of tumor cells.
Analysis cutoff date: March 3, 2014.

Antitumor Activity (irRC, Investigator Review)

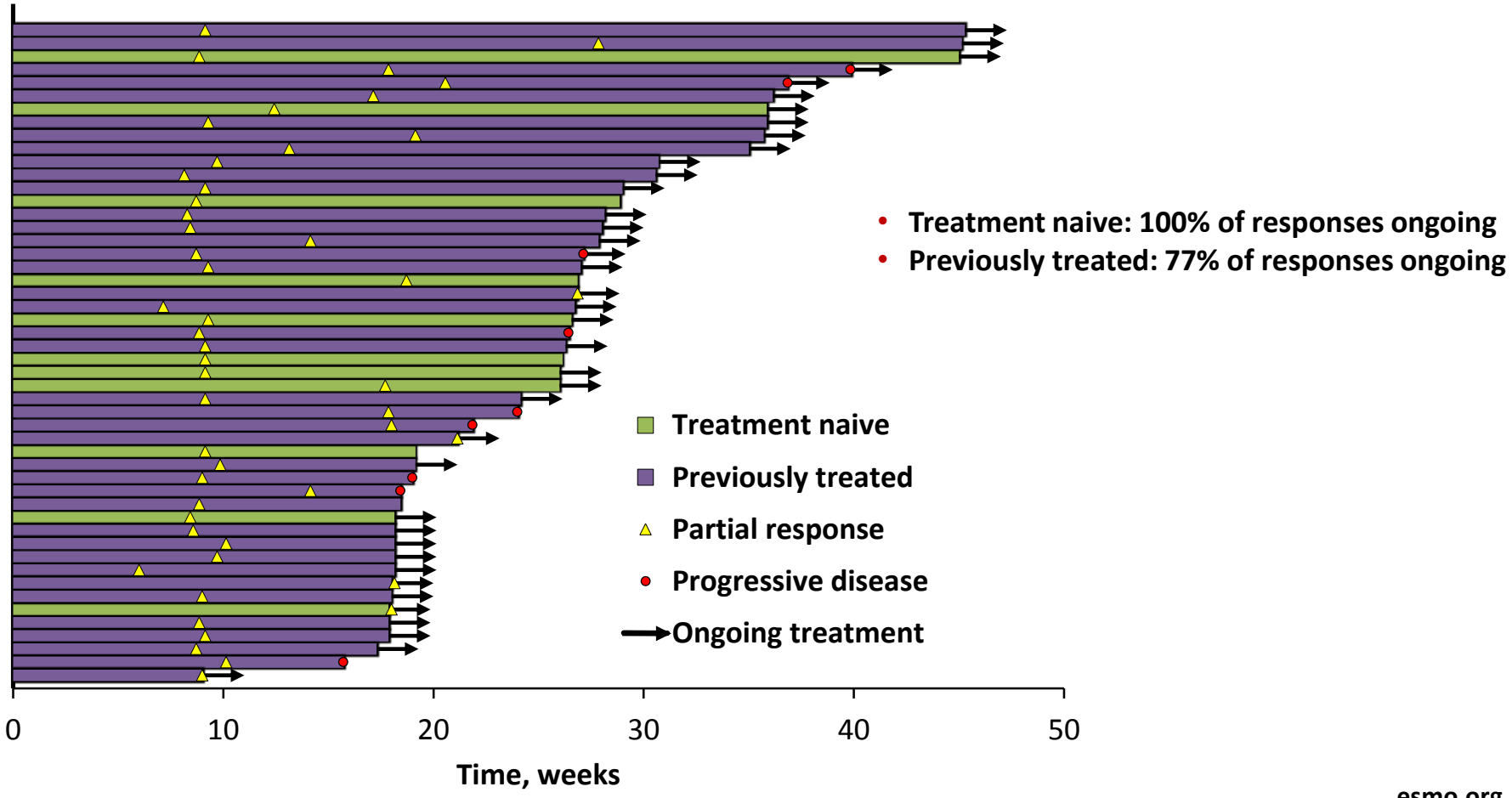
	N	ORR[a,b] % (95% CI)
Total	**262**	**23 (18-29)**
Previous treatment	262	
Treatment naive	45	47 (32-62)
Previously treated	217	18 (13-24)
Histology	258	
Nonsquamous	212	23 (17-29)
Squamous	44	25 (13-40)
Smoking history	256	
Current/Former	182	27 (21-34)
Never	74	14 (7-24)

	N	ORR[a,b] % (95% CI)
Dose/schedule	262	
2 Q3W	6	67 (22-96)
10 Q3W	141	22 (16-30)
10 Q2W	115	22 (15-30)
PD-L1 expression[c]	262	
Positive	222	25 (19-31)
Negative	40	13 (4-27)
EGFR mutation	41	12 (4-26)
KRAS mutation	41	32 (18-48)
ALK rearrangement	6	33 (4-78)

- In 45 additional patients treated at 2 mg/kg Q3W, ORR[a] was 20% (95% CI, 10%-35%)[d]

[a]Includes confirmed and unconfirmed responses.
[b]Analysis cutoff date: March 3, 2014.
[c]As assessed using a prototype assay. Positive was defined as staining in ≥1% of tumor cells.
[d]Analysis cutoff date: September 11, 2014.

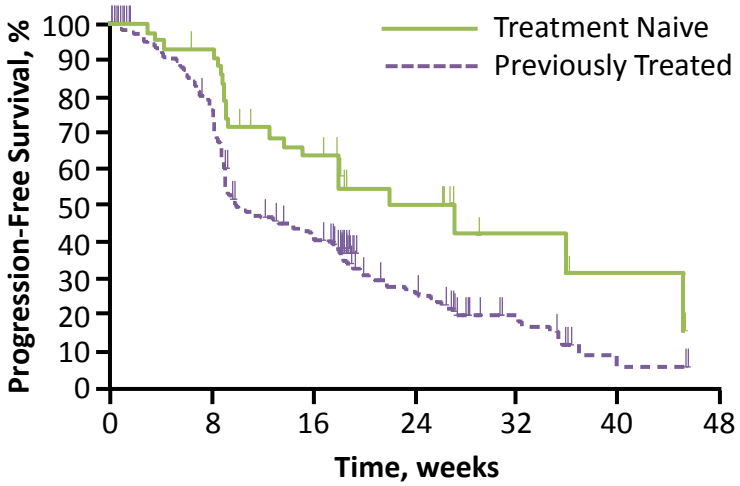
Time to and Durability of Response
(RECIST v1.1, Central Review)[a]



[a]Includes confirmed and unconfirmed responses.
Analysis cutoff date: March 3, 2014.

Kaplan-Meier Estimates of Survival

PFS (RECIST v1.1, Central Review)

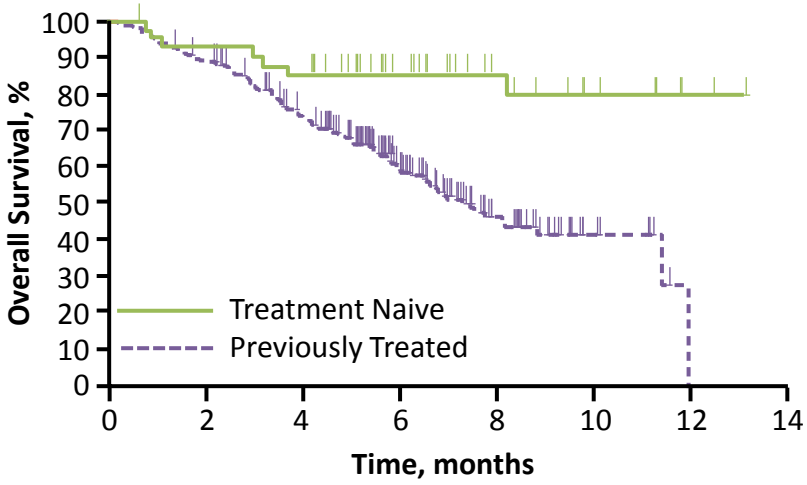


n at risk

Treatment Naive	45	39	25	11	4	2	0
Previously Treated	217	159	81	33	13	2	0

- Treatment naive
  - Median PFS: 27 weeks (95% CI, 14-45)
  - 24-week PFS: 51%
- Previously treated
  - Median PFS: 10 weeks (9.1-15.3)
  - 24-week PFS: 26%

OS



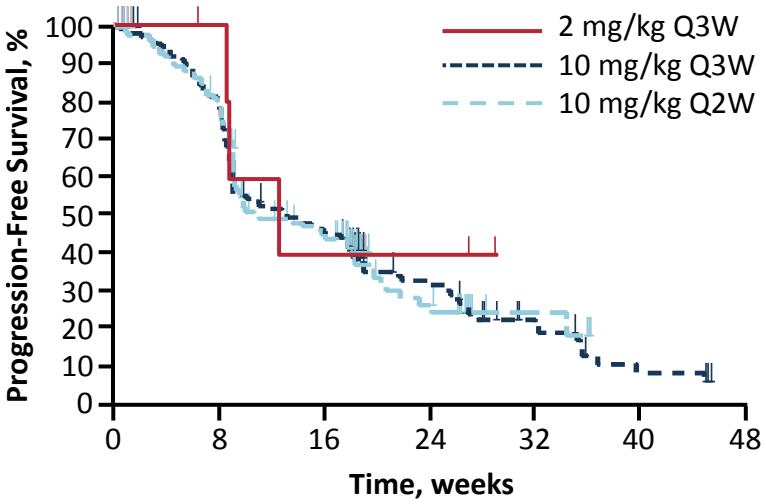
	45	41	38	24	13	7	2	0
	217	192	146	77	33	8	0	0

- Treatment naive
  - Median OS: NR (95% CI, NE-NE)
  - 6-month OS: 86%
- Previously treated
  - Median OS: 8.2 months (7.3-NR)
  - 6-month OS: 59%

Analysis cutoff date: March 3, 2014.

Kaplan-Meier Estimates of Survival

PFS (RECIST v1.1, Central Review)

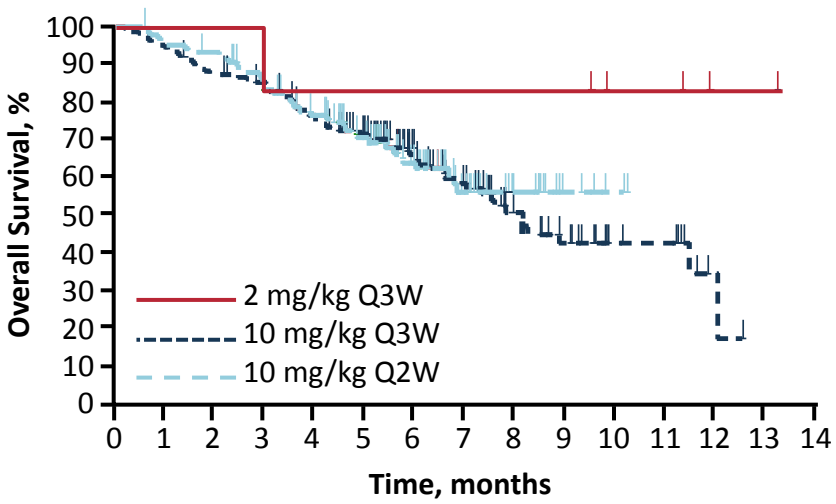


n at risk

Q3W 2 mg/kg	6	5	2	2	0	0	0
Q3W10 mg/kg	141	106	60	27	13	4	0
Q2W10 mg/kg	115	87	44	15	4	0	0

- Pooled population
  - Median PFS: 13.0 weeks (95% CI, 9.4-17.6)
  - 24-week PFS: 30%

OS



	6	6	6	5	5	5	5	5	5	5	3	3	1	1	0
	141	131	122	114	99	84	56	41	27	19	10	9	1	0	0
	115	108	105	91	80	63	40	21	14	5	2	0	0	0	0

- Pooled population
  - Median OS: 8.2 months (95% CI, 7.3-NR)
  - 6-month OS: 64%

Analysis cutoff date: March 3, 2014.

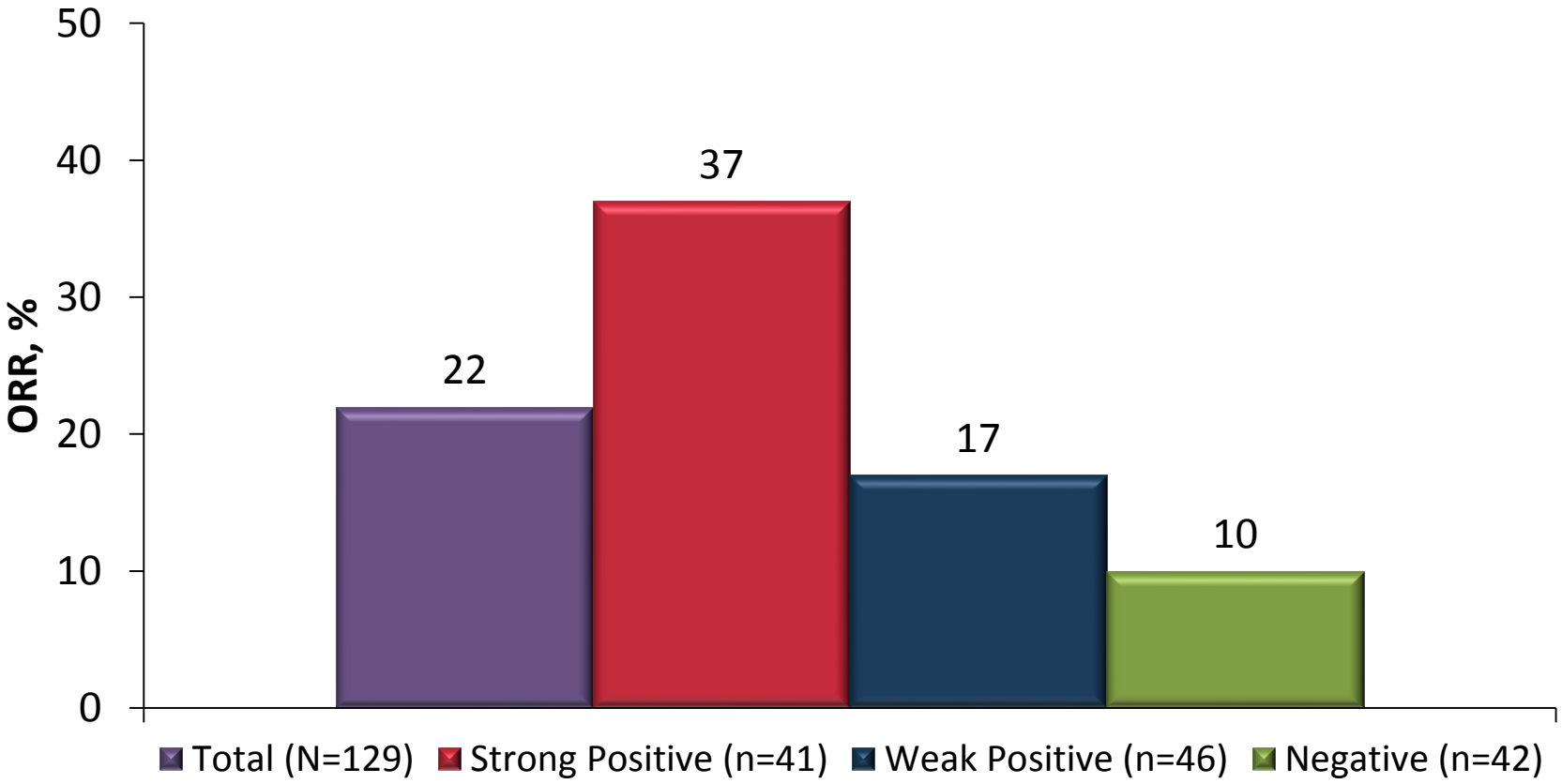
Analysis of PD-L1 Expression

- As assessed by IHC using the 22C3 antibody, PD-L1 tumor expression in patients with advanced NSCLC is not associated with a favorable prognosis[1]
- In a subset of the patients analyzed here, with the addition of an initial 38-patient cohort,[2] tumor samples were analyzed for PD-L1 expression independently of the eligibility assessment using a different PD-L1 IHC assay by a different vendor but the same 22C3 antibody
- Clinical trial assay
  - Strong PD-L1 expression: defined as ≥50% membranous staining in tumor cells
  - Weak PD-L1 expression: defined as 1-49% membranous staining in tumor cells

1. Sun J-M et al. Abstract 8066. Presented at: 2014 Annual Meeting of ASCO; May 30-June 30, 2014; Chicago, IL, USA.
2. Garon E et al. Abstract 2416. Presented at: 15th World Conference on Lung Cancer; October 27-30, 2013; Sydney, Australia.

Response Rate by Level of PD-L1 Expression

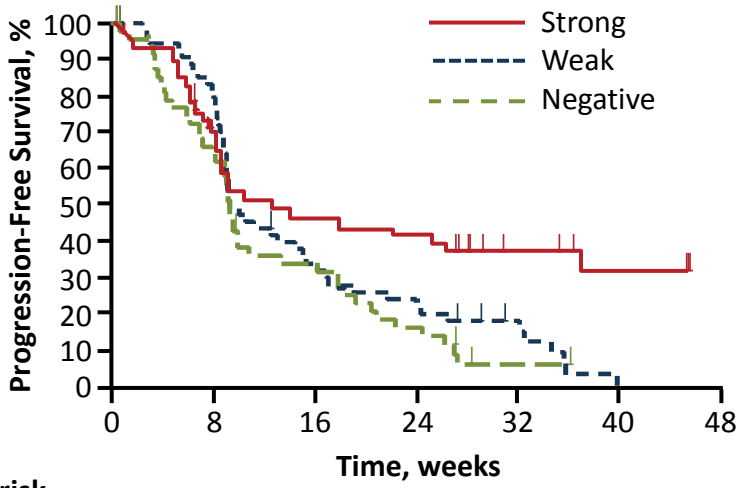
(RECIST 1.1, Central Review)



[a]Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per imaging assessment criteria. Analysis cut-off date: March 3, 2014.

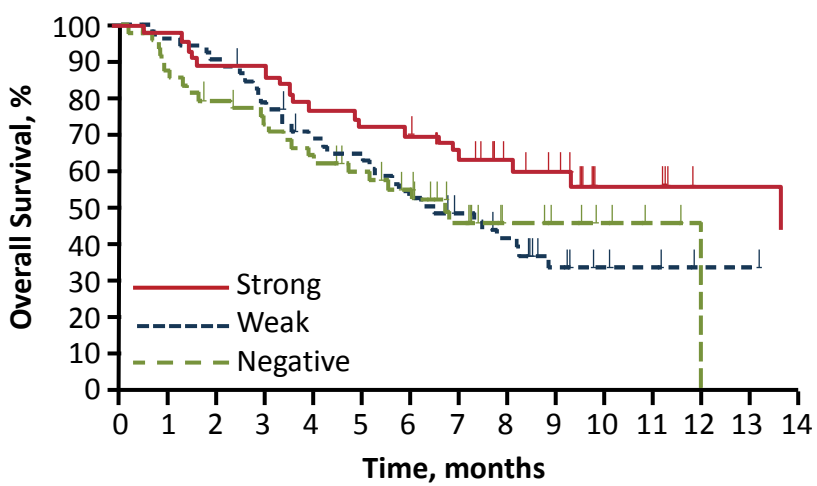
Kaplan-Meier Estimates of Survival

PFS (RECIST v1.1, Central Review)



n at risk							
Strong	44	28	18	17	9	6	3
Weak	53	43	17	12	6	0	0
Negative	49	30	15	7	1	0	0

OS



Strong	44	43	38	38	34	32	30	27	21	18	9	8	5	5	4
Weak	53	51	48	40	34	31	26	22	18	11	8	7	5	5	4
Negative	49	42	38	34	29	26	21	14	8	6	4	2	0	0	0

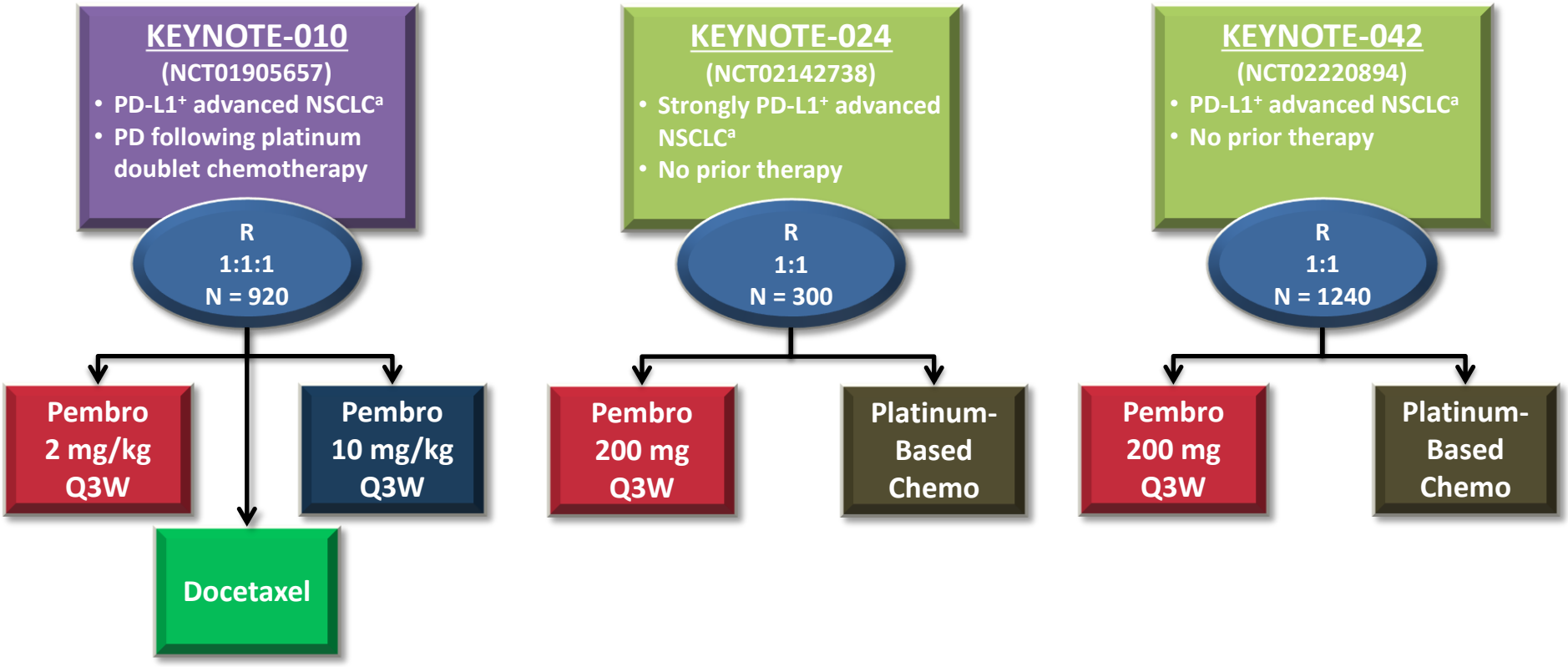
- PFS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (HR, 0.52; 95% CI, 0.33-0.80)
- OS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (HR, 0.59; 95% CI, 0.35-0.99)

[a]Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression.
Strong PD-L1 positivity defined as staining in ≥50% of tumor cells, and weak PD-L1 positivity as staining in 1-49% of tumor cells. Negative staining is no PD-L1 staining in tumor cells.
Data cut-off: March 3, 2014.

Summary and Conclusions

- Robust antitumor activity in both treatment-naive (ORR, 26%) and previously treated (20%) advanced NSCLC observed for all doses and schedules assessed
- At 2 mg/kg Q3W, ORR was 20% (irRC)
- Responses are durable
- Manageable safety and toxicity profile
- Strong PD-L1 tumor expression correlated with improved response (37%), PFS (HR = 0.52), and OS (HR = 0.59)
- Validation of the prospective PD-L1 cutpoint will be performed in an additional 300 patients enrolled in KEYNOTE-001

Ongoing Studies of Pembrolizumab in NSCLC



- **Primary end points: OS, PFS**
- **Primary end point: PFS**
- **Primary end point: OS**

[a]As assessed using the clinical trial assay and the 22C3 antibody.

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