KEYNOTE-010: Phase 2/3 Study of Pembrolizumab (MK-3475) vs Docetaxel for PD-L1–Positive NSCLC After Platinum-Based Therapy

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Disclosures

- Roy S. Herbst
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- Study supported by MSD (Merck & Co., Inc., Kenilworth, NJ, USA)

THE LANCET

Articles

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

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Summary

Background Despite recent advances in the treatment of advanced non-small-cell lung cancer, there remains a need for effective treatments for progressive disease. We assessed the efficacy of pembrolizumab for patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.

Methods We did this randomised, open-label, phase 2/3 study at 202 academic medical centres in 24 countries. Patients with previously treated non-small-cell lung cancer with PD-L1 expression on at least 1% of tumour cells were randomly assigned (1:1:1) in blocks of six per stratum with an interactive voice-response system to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m² every 3 weeks. The primary endpoints were overall survival and progression-free survival both in the total population, and in patients with PD-L1 expression on at least 50% of tumour cells. We used a threshold for significance of $p<0\cdot00825$ (one-sided). This trial is registered at ClinicalTrials.gov, number NCT01905657.

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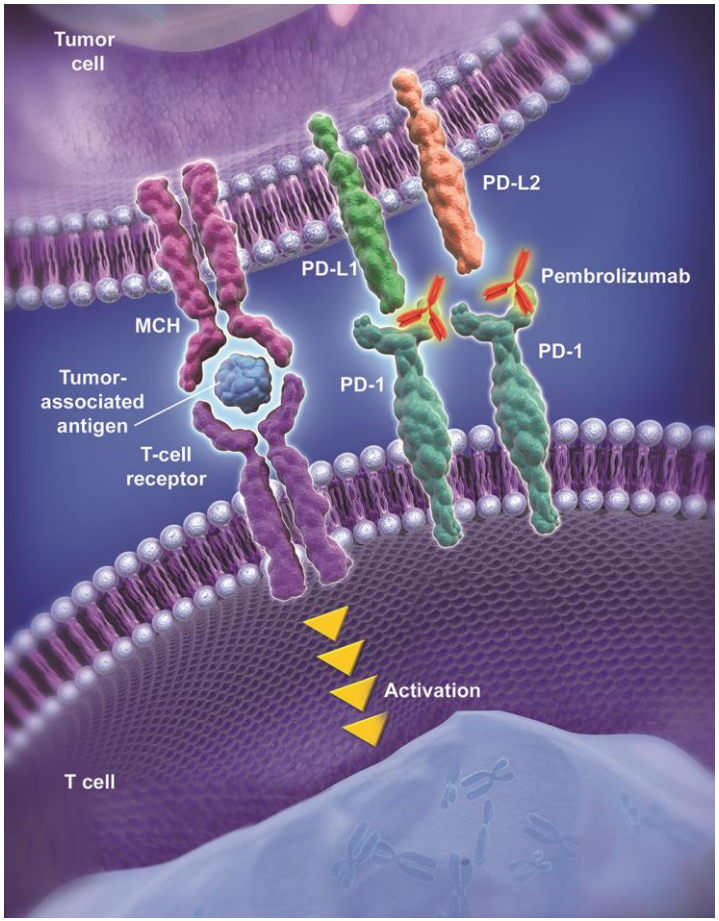
Yale School of Medicine, Yale Cancer Center, and Smilow Cancer Hospital, New Haven, CT, USA (Prof R S Herbst MD); **The Netherlands Cancer Institute and The Academic Medical Hospital Amsterdam,**

Pembrolizumab (MK-3475)

- High-affinity, humanized monoclonal IgG4κ antibody against PD-1 that prevents interaction with PD-L1 and PD-L2
- KEYNOTE-001: antitumor activity and manageable safety in advanced NSCLC with improved outcomes in patients with PD-L1 TPS ≥50%[1]
- Currently approved in the US for treating advanced NSCLC that expresses PD-L1 and has progressed after platinum-containing chemotherapy, as well as an appropriate TKI for patients with *EGFR* or *ALK* genomic aberrations

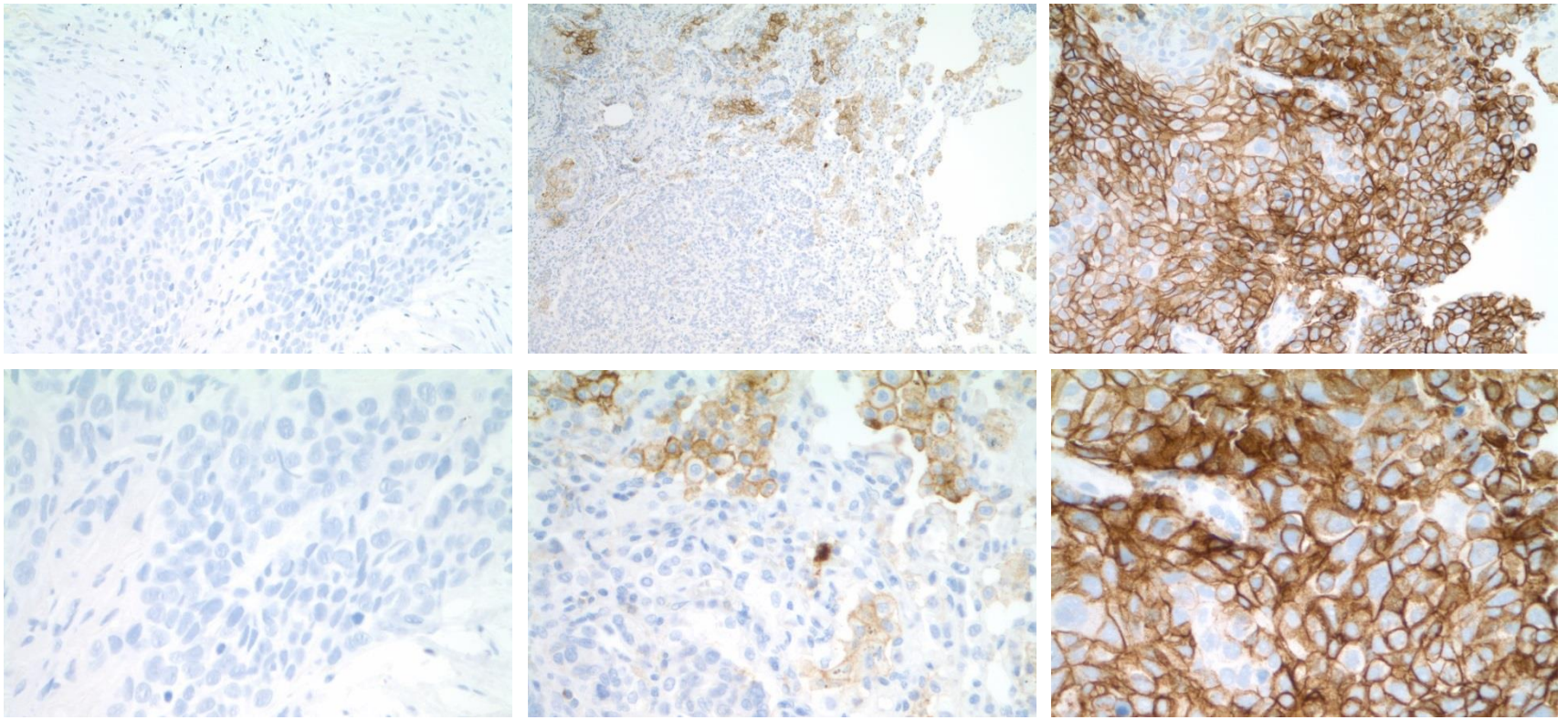


TPS = tumor proportion score (ie, percentage of tumor cells with membranous PD-L1 expression).

1. Garon EB et al. *N Engl J Med* 2015;372:2018-28.

PD-L1 Expression Associated with Favorable Outcome With Pembrolizumab

- TPS ≥50% cutpoint rigorously determined using independent training and validation sets derived from KEYNOTE-001[1]
- PD-L1 IHC 22C3 pharmDx (Dako) approved in the US as a companion diagnostic for pembrolizumab



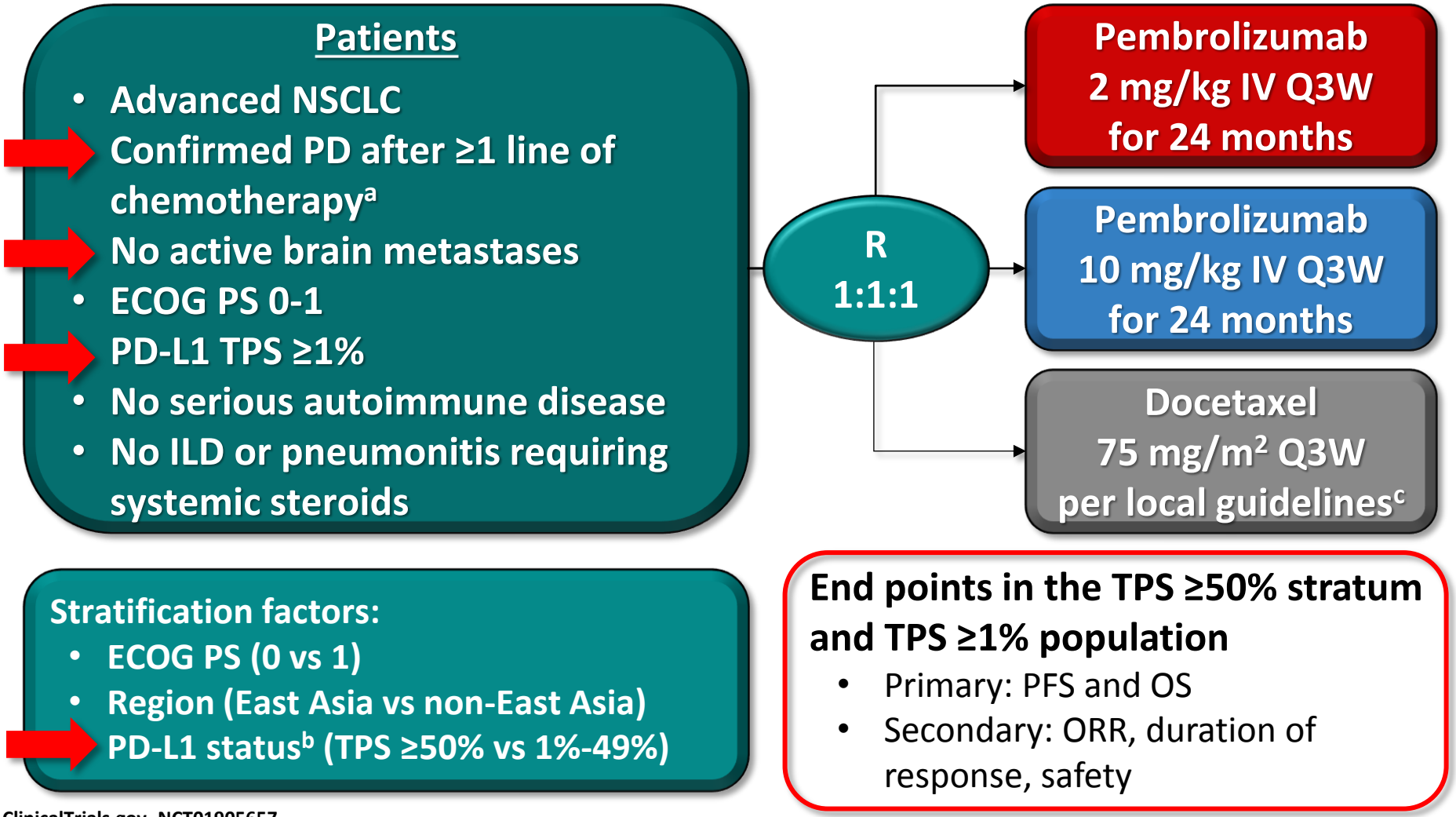
20x

40x

Negative **TPS 1%–49%** **TPS ≥50%**

1. Garon EB et al. *N Engl J Med* 2015;372:2018-28.

KEYNOTE-010 Study Design



ClinicalTrials.gov, NCT01905657.

[a]Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an *EGFR* sensitizing mutation or an *ALK* translocation.

[b]Added after 441 patients enrolled based on results from KEYNOTE-001 (Garon EB et al. *N Engl J Med*. 2015;372:2018-28).

[c]Patients received the maximum number of cycles permitted by the local regulatory authority.

Assessments

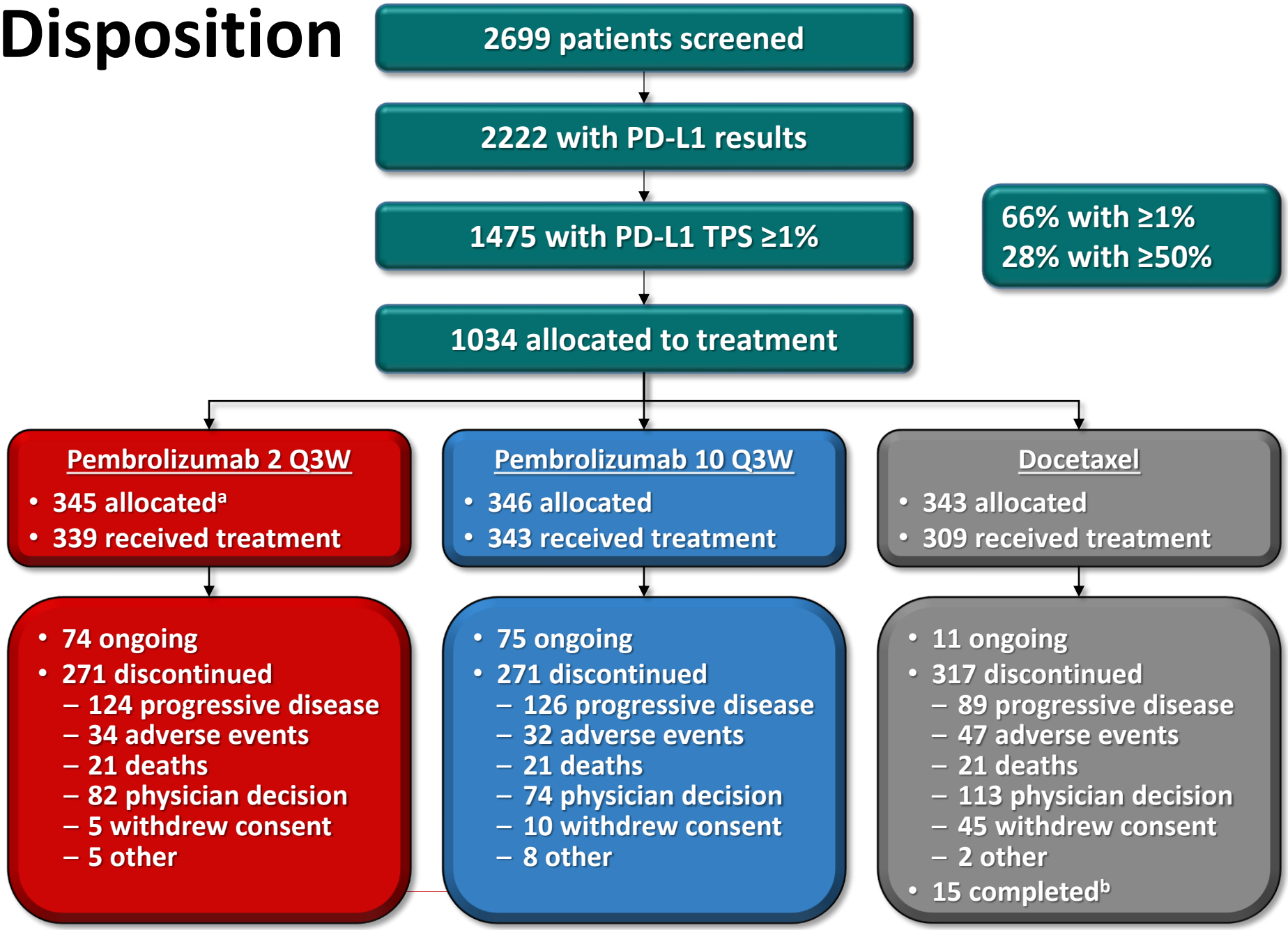
- PD-L1 assessed during screening using clinical-trial IHC assay with 22C3 antibody[1]
  - Initial protocol: archival or new tissue sample
  - Amendment: new sample only unless a biopsy associated with too much risk
  - 456 patients enrolled based on archival samples
- Response assessed every 9 weeks
  - Primary for efficacy: RECIST v1.1 by independent central review
  - Primary for treatment management: immune-related response criteria (irRC)
- Survival assessed every 2 months after study treatment discontinuation

1. Garon EB et al. *N Engl J Med* 2015;372:2018-28.

Statistical Considerations

- Final analysis planned to occur after ~200 deaths observed across all treatment groups in the TPS ≥50% stratum
  - ≥81% power to detect a 0.55 HR for OS, with a one-sided alpha=0.00825 using the Hochberg procedure
  - ~550 deaths expected in the total population, giving ≥80% power to detect a 0.70 HR for OS in the total (ie, TPS ≥1%) population
- Analysis cutoff date: September 30, 2015
  - Median follow-up duration: 13.1 months (range, 5.7-23.7)

Disposition



[a]1 patient excluded from efficacy analyses because of noncompliance with imaging guidelines for prebaseline scans.
[b]Patients who received the maximum number of docetaxel doses permitted per local guidelines.

Baseline Characteristics

	Pembro 2 Q3W n = 344	Pembro 10 Q3W n = 346	Docetaxel n = 343
Age, median (range), years	63 (29-82)	63 (20-88)	62 (33-82)
Male, %	62	62	61
Race, %			
White	72	72	73
Asian	21	21	21
Other or unknown	7	7	6
ECOG PS,[a] %			
0	33	35	34
1	67	65	65
Smoking status, %			
Former/current	81	82	78
Never	18	17	20
Unknown	1	<1	2
PD-L1 TPS, %			
≥50%	40	44	44
1-49%	60	56	56

Analysis cut-off date: September 30, 2015.

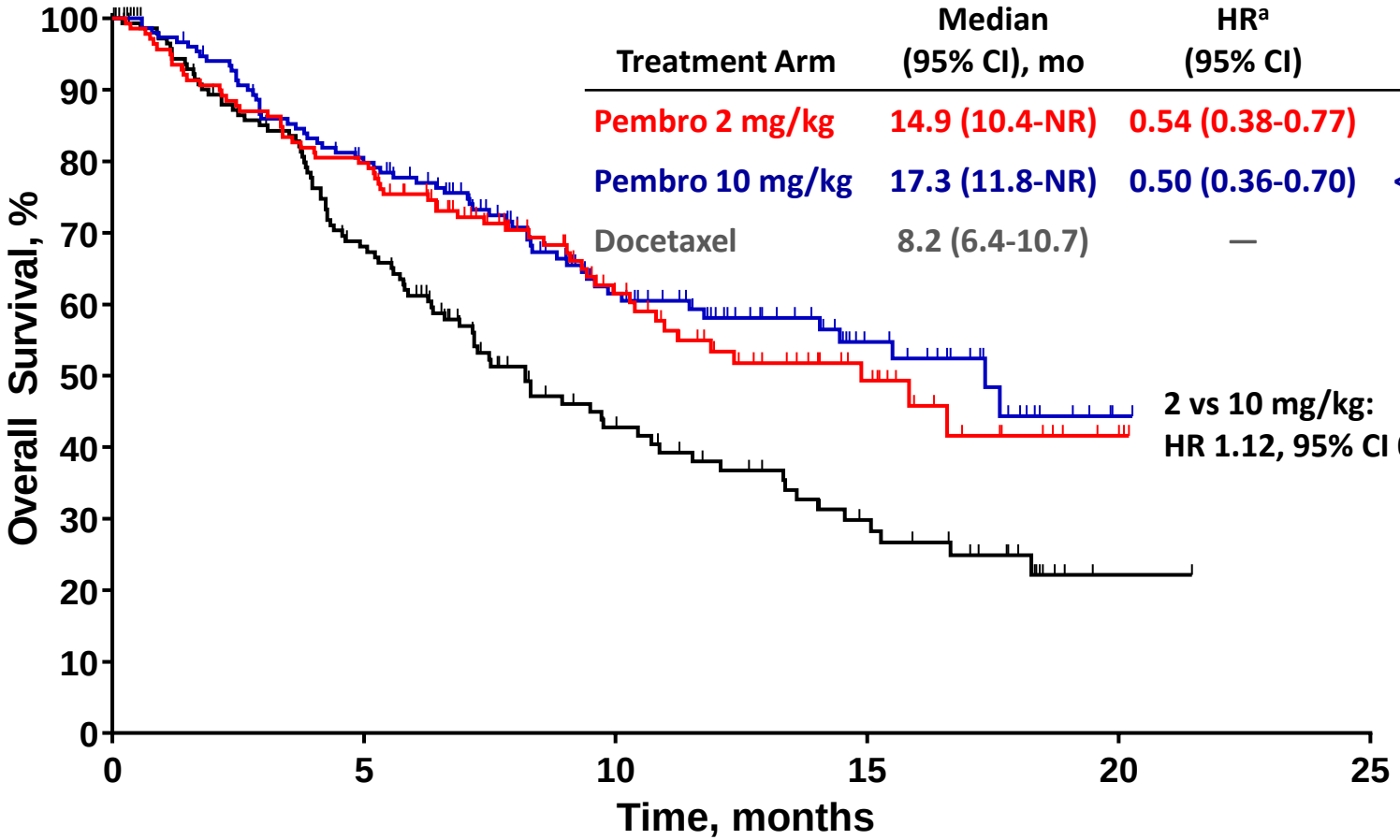
[a]1 patient had unknown ECOG PS. 5/6 patients with ECOG PS ≥2 during screening resolved to ≤1 by treatment assignment.

Baseline Characteristics cont.

	Pembro 2 Q3W n = 344	Pembro 10 Q3W n = 346	Docetaxel n = 343
Histology, %			
Squamous	22	23	19
Nonsquamous	70	71	70
Other/unknown	8	6	11
EGFR mutant, %	8	9	8
ALK translocated, %	1	1	1
Prior therapy, %			
Adjuvant	2	2	1
Neoadjuvant	<1	<1	0
Prior lines, advanced disease			
1	71	68	69
≥2	27	20	22

Analysis cut-off date: September 30, 2015.

OS, PD-L1 TPS ≥50% Stratum



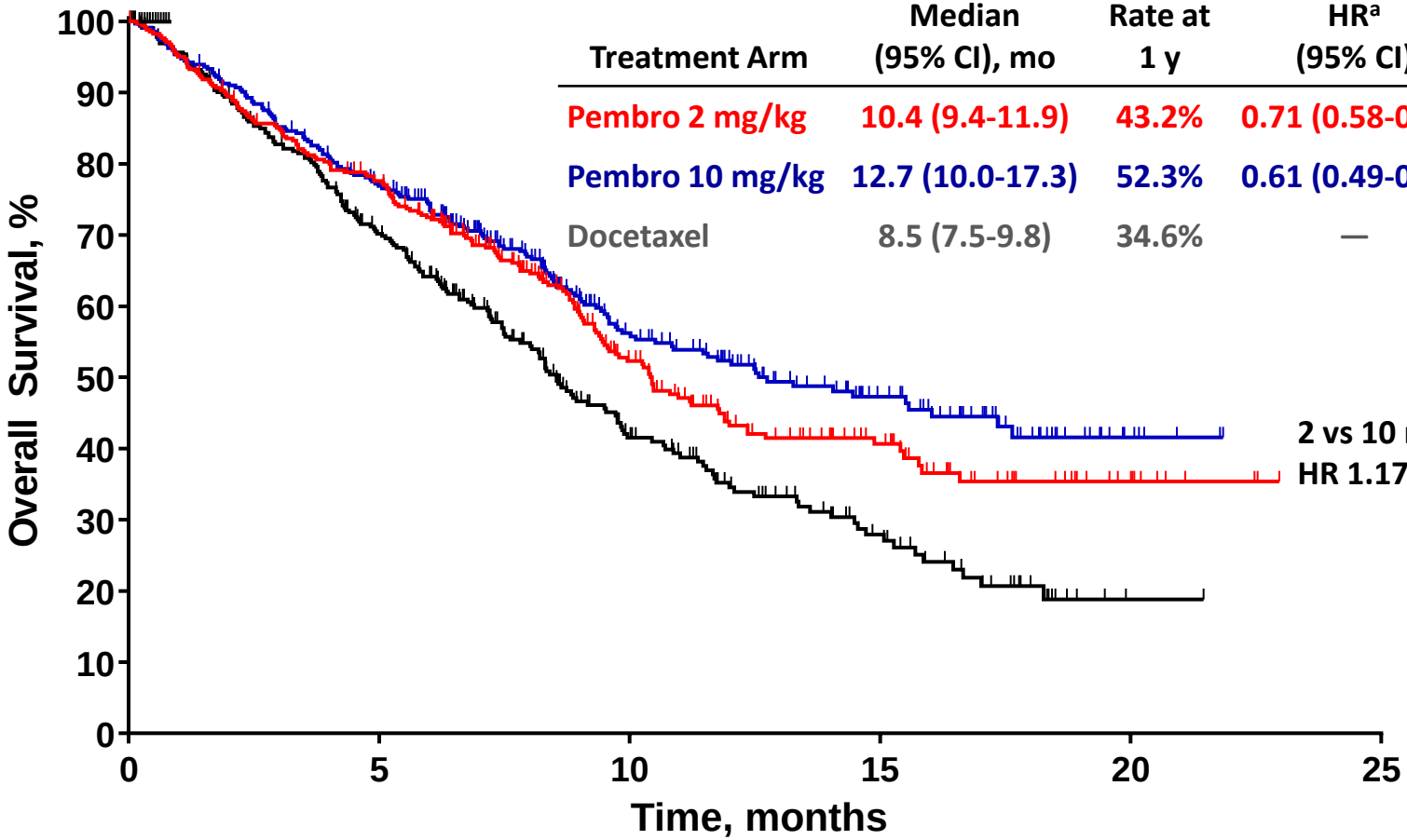
Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	14.9 (10.4-NR)	0.54 (0.38-0.77)	0.0002
Pembro 10 mg/kg	17.3 (11.8-NR)	0.50 (0.36-0.70)	<0.0001
Docetaxel	8.2 (6.4-10.7)	—	—

2 vs 10 mg/kg:
HR 1.12, 95% CI 0.77-1.62

Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

OS, PD-L1 TPS ≥1% (Total Population)



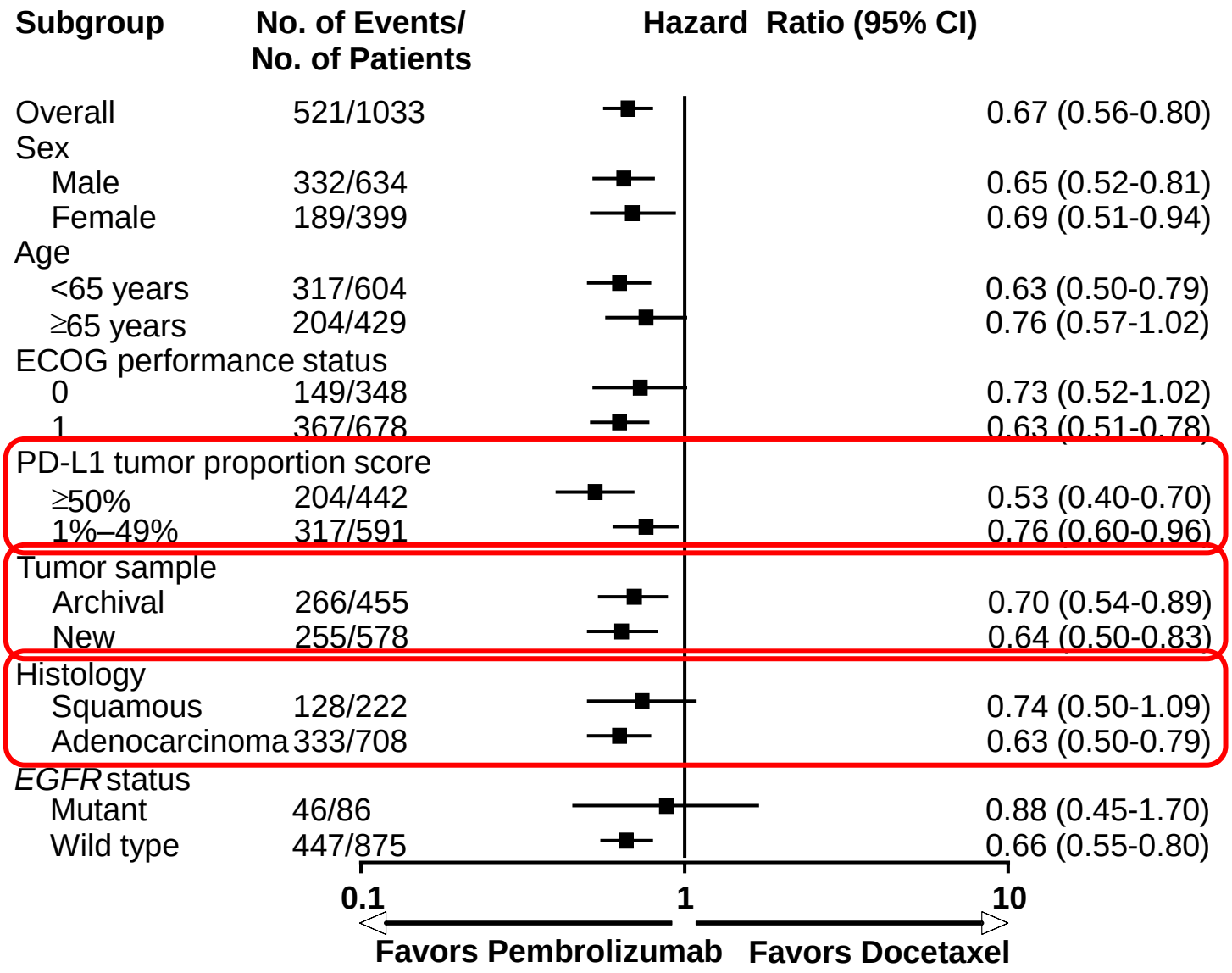
Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2%	0.71 (0.58-0.88)	0.0008
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.0001
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—

2 vs 10 mg/kg:
HR 1.17, 95% CI 0.94-1.45

Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

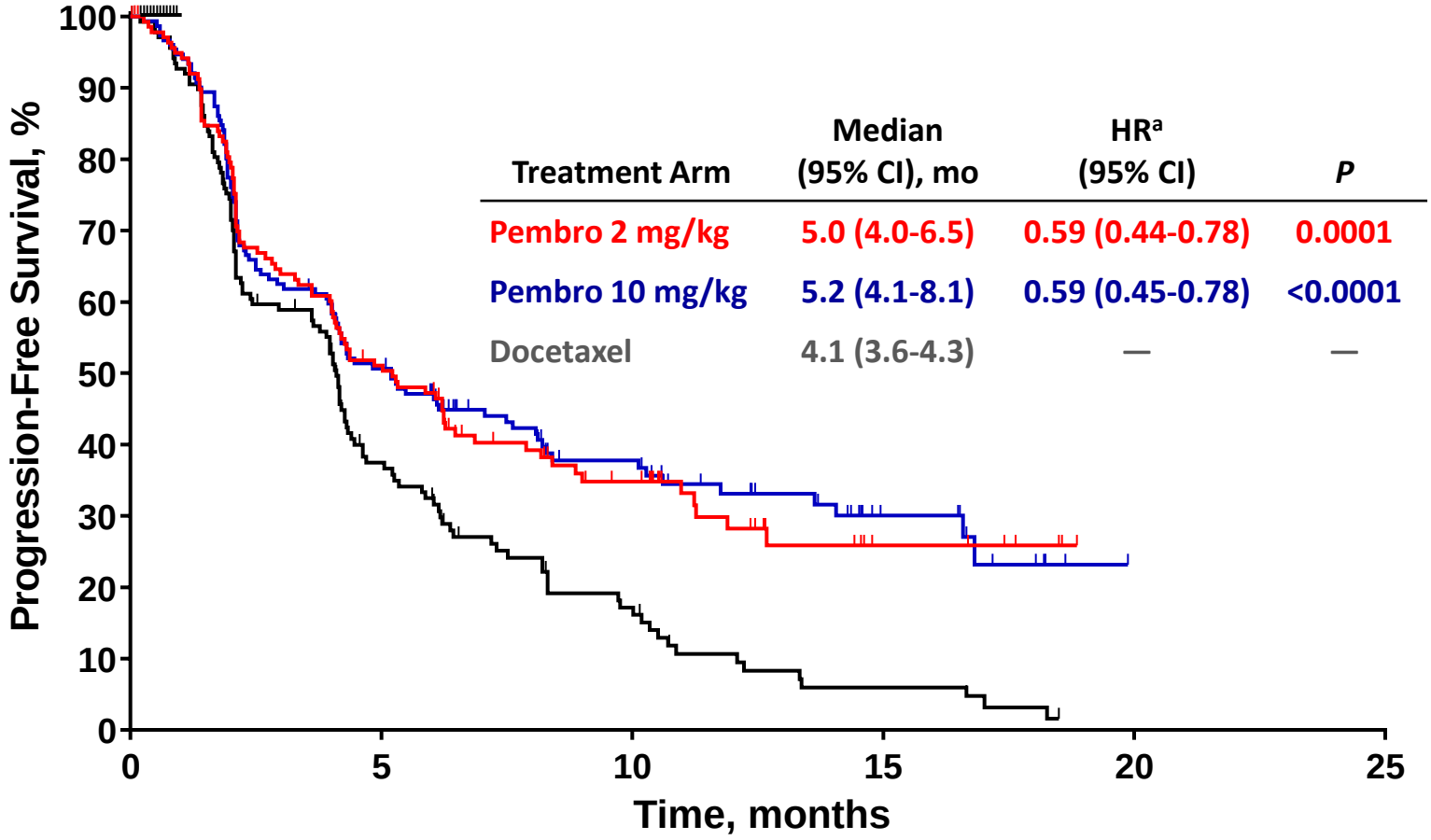
OS in Key Subgroups, PD-L1 TPS ≥1%[a]



Analysis cut-off date: September 30, 2015.

[a]Data for the pembrolizumab doses were pooled.

PFS (RECIST v1.1, Central Review), PD-L1 TPS ≥50%



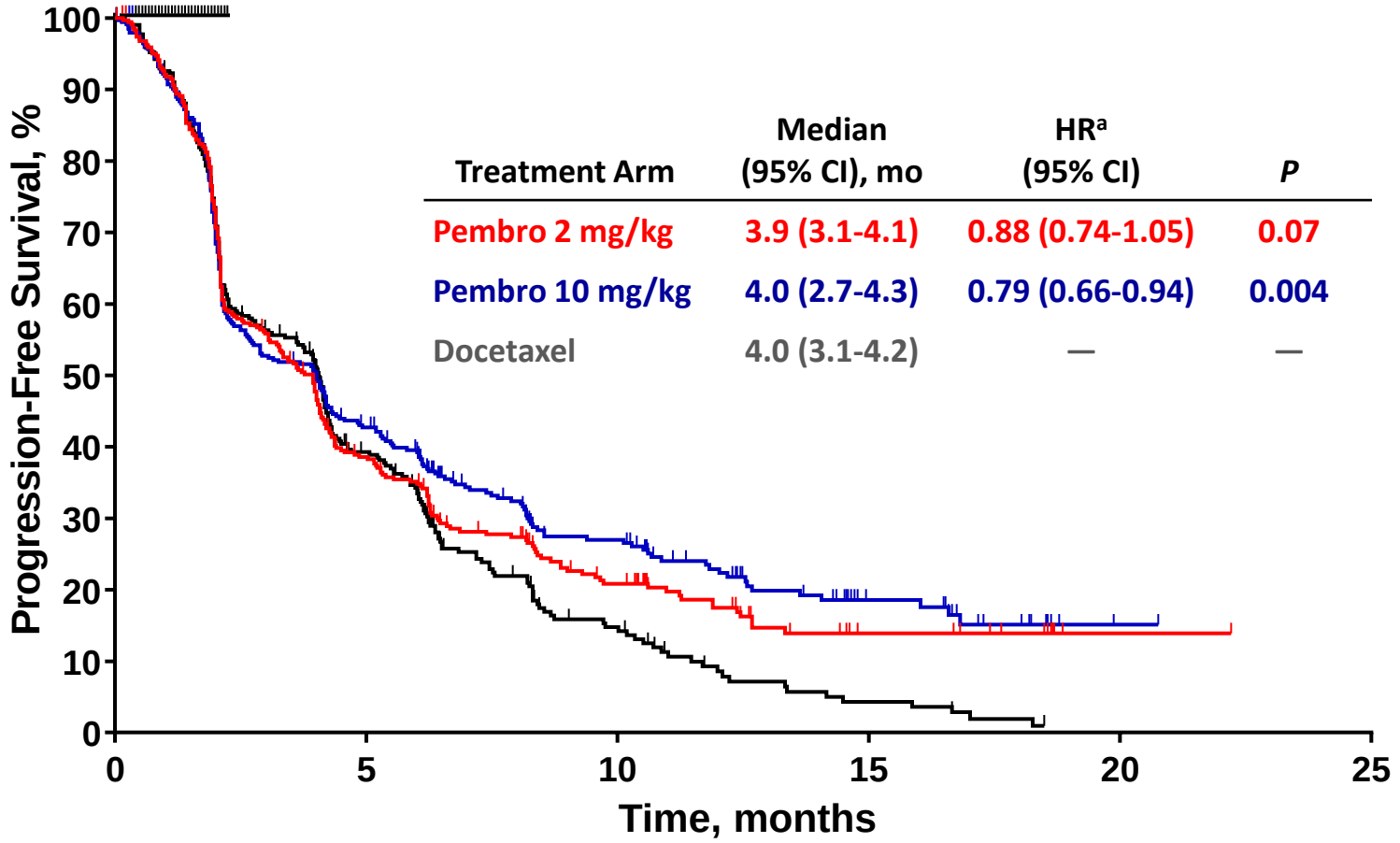
Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	5.0 (4.0-6.5)	0.59 (0.44-0.78)	0.0001
Pembro 10 mg/kg	5.2 (4.1-8.1)	0.59 (0.45-0.78)	<0.0001
Docetaxel	4.1 (3.6-4.3)	—	—

139	66	29	6	0	0
151	72	36	12	0	0
152	45	17	5	0	0

Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

PFS (RECIST v1.1, Central Review), PD-L1 TPS ≥1%



Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	3.9 (3.1-4.1)	0.88 (0.74-1.05)	0.07
Pembro 10 mg/kg	4.0 (2.7-4.3)	0.79 (0.66-0.94)	0.004
Docetaxel	4.0 (3.1-4.2)	—	—

Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

ORR (RECIST v1.1, Central Review)

PD-L1 TPS ≥50%	Pembro 2 mg/kg n = 139	Pembro 10 mg/kg n = 151	Docetaxel n = 152
ORR, % (95% CI)	30 (23-39) *P* < 0.0001[a]	29 (22-37) *P* < 0.0001[a]	8 (4-13)

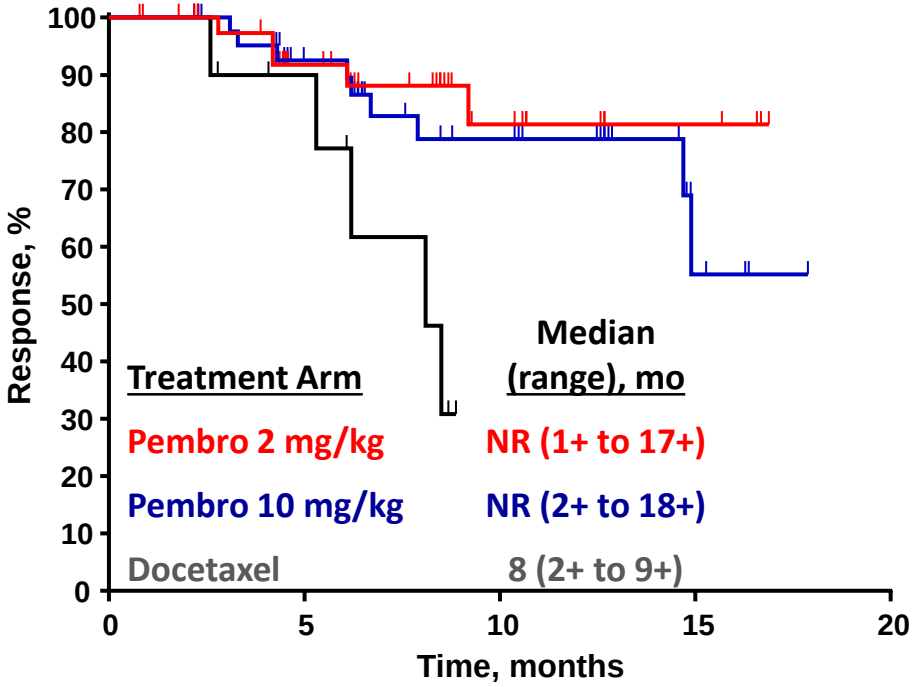
PD-L1 TPS ≥1%	Pembro 2 mg/kg n = 344	Pembro 10 mg/kg n = 346	Docetaxel n = 343
ORR, % (95% CI)	18 (14-22) *P* = 0.0005[a]	18 (14-23) *P* = 0.0002[a]	9 (6-13)

Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

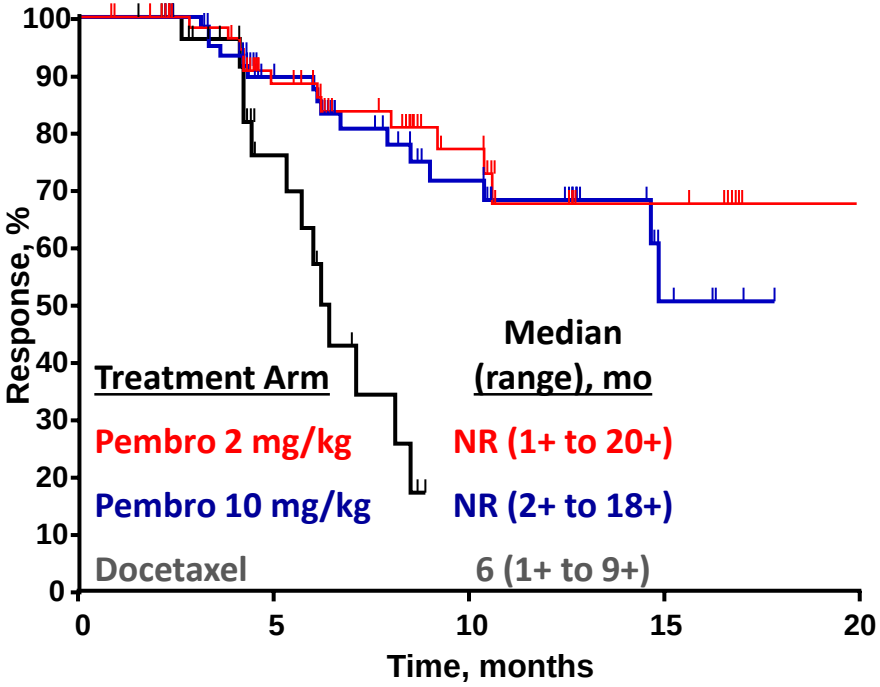
Duration of Response
(RECIST v1.1, Central Review)

PD-L1 TPS ≥50%



42	27	11	4	0
44	31	18	4	0
12	7	0	0	0

PD-L1 TPS ≥1%



62	40	19	8	1
64	42	22	5	0
32	12	0	0	0

Analysis cut-off date: September 30, 2015.

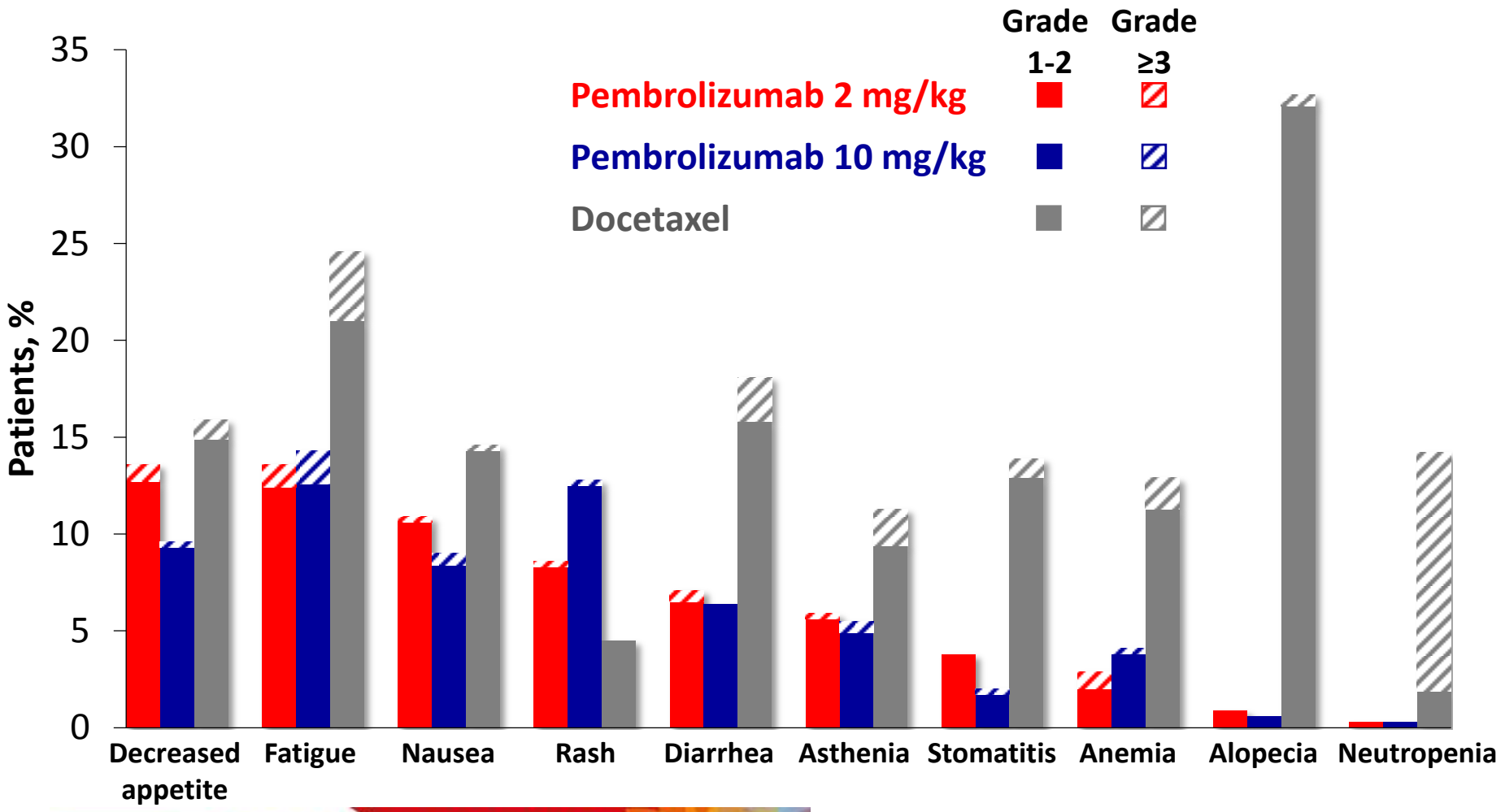
Treatment Exposure and Adverse Event Summary

	Pembro 2 Q3W n = 339	Pembro 10 Q3W n = 343	Docetaxel n = 309
Months on therapy, median (range)	3.5 (0.03-22.4)	3.5 (0.03-20.8)	2.0 (0.03-13.7)
≥1 Treatment-related AE, %			
Any grade	63	66	81
Grade 3-5	13	16	35
Led to discontinuation	4	5	10
Led to death	1[a]	1[b]	2[c]

Analysis cut-off date: September 30, 2015.

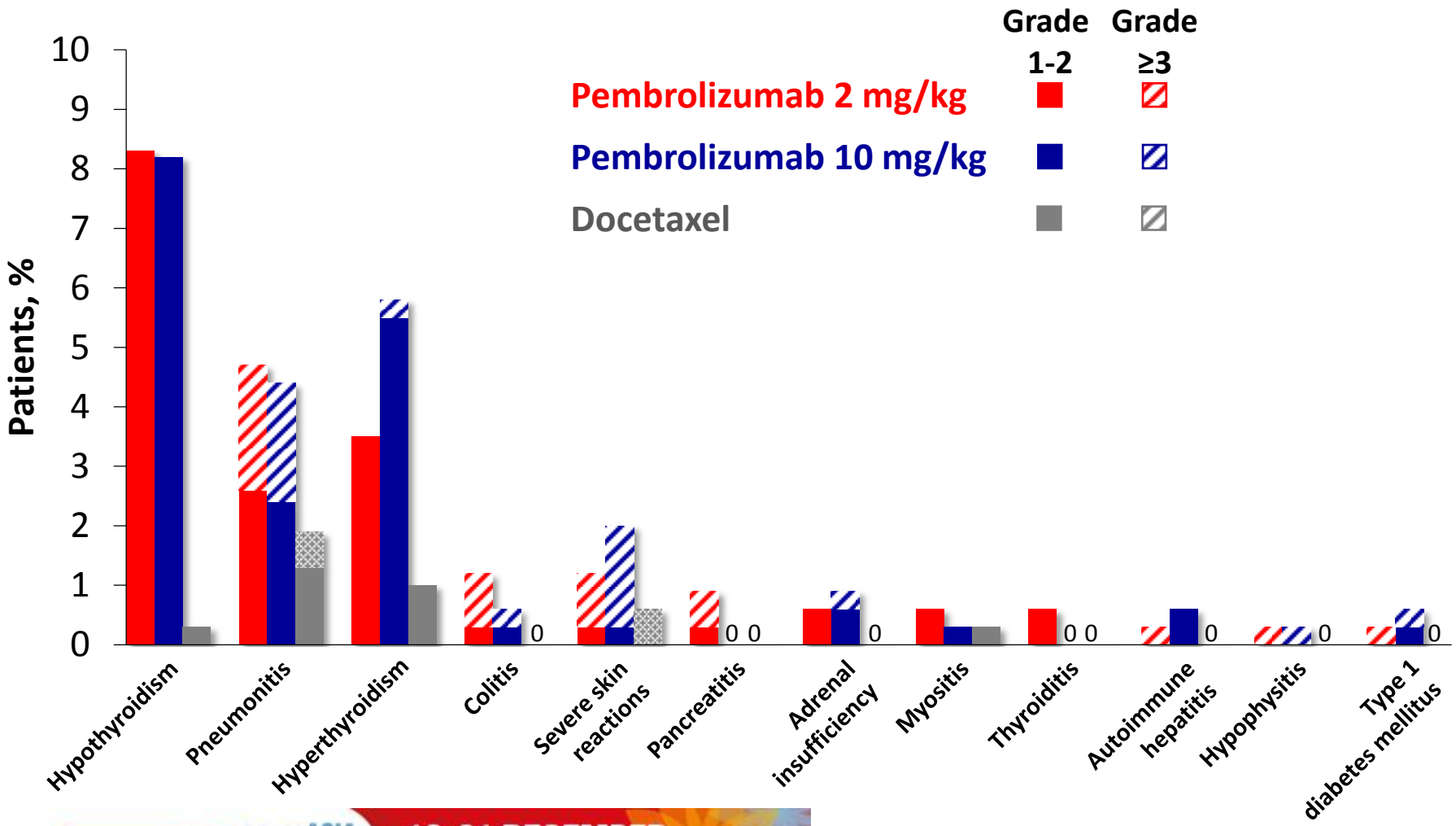
[a]n = 2 pneumonitis, n = 1 pneumonia.
[b]n = 1 each myocardial infarction, pneumonia, and pneumonitis.
[c]n = 1 each acute cardiac failure, dehydration, febrile neutropenia, interstitial lung disease, and respiratory tract infection.

Treatment-Related AEs With Incidence ≥10% in Any Arm, TPS ≥1%



Analysis cut-off date: September 30, 2015.

Immune-Mediated AEs Occurring in ≥2 Patients in the Pembrolizumab Arms



Analysis cut-off date: September 30, 2015.

Conclusions

- Superior OS for pembrolizumab over docetaxel for previously treated, PD-L1–positive advanced NSCLC
- Pembrolizumab improved OS for both TPS 1%-49% and ≥50%
- Comparable efficacy for pembrolizumab 2 and 10 mg/kg Q3W
- Pembrolizumab well tolerated with less high-grade toxicity than docetaxel
- These data
  - Validate the use of PD-L1 selection in advanced NSCLC
  - Support the 2-mg/kg–Q3W dose currently approved in the US for the treatment of advanced NSCLC
  - Support pembrolizumab as a new standard-of-care for advanced NSCLC that progressed on platinum-containing chemotherapy

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