Challenges for the approval of anti-cancer immunotherapeutic drugs

NSCLC, academic perspective: lessons learnt

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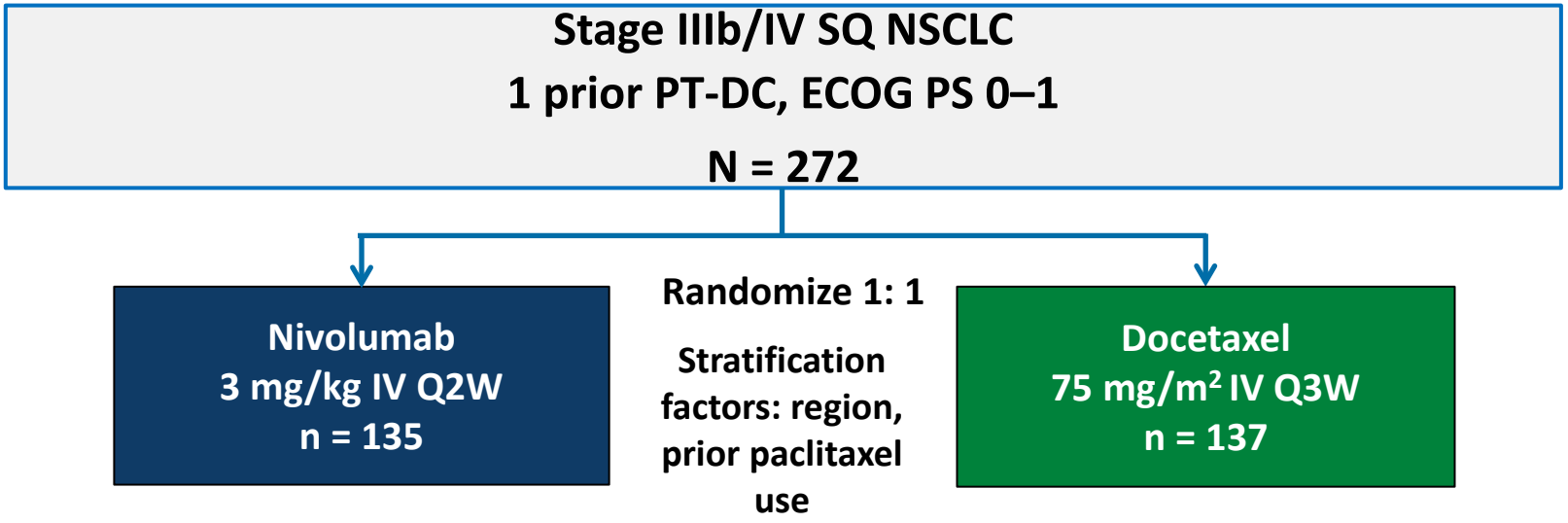
Anti-cancer immunotherapeutic drugs
NSCLC, academic perspective
Outline

- Anti-PD1/-PDL1 agents as monotherapy
- Anti-PD1/-PDL1 agents in combination
- Biomarkers
- Lessons learnt, future perspectives

Anti-PD1/-PDL1 agents as monotherapy

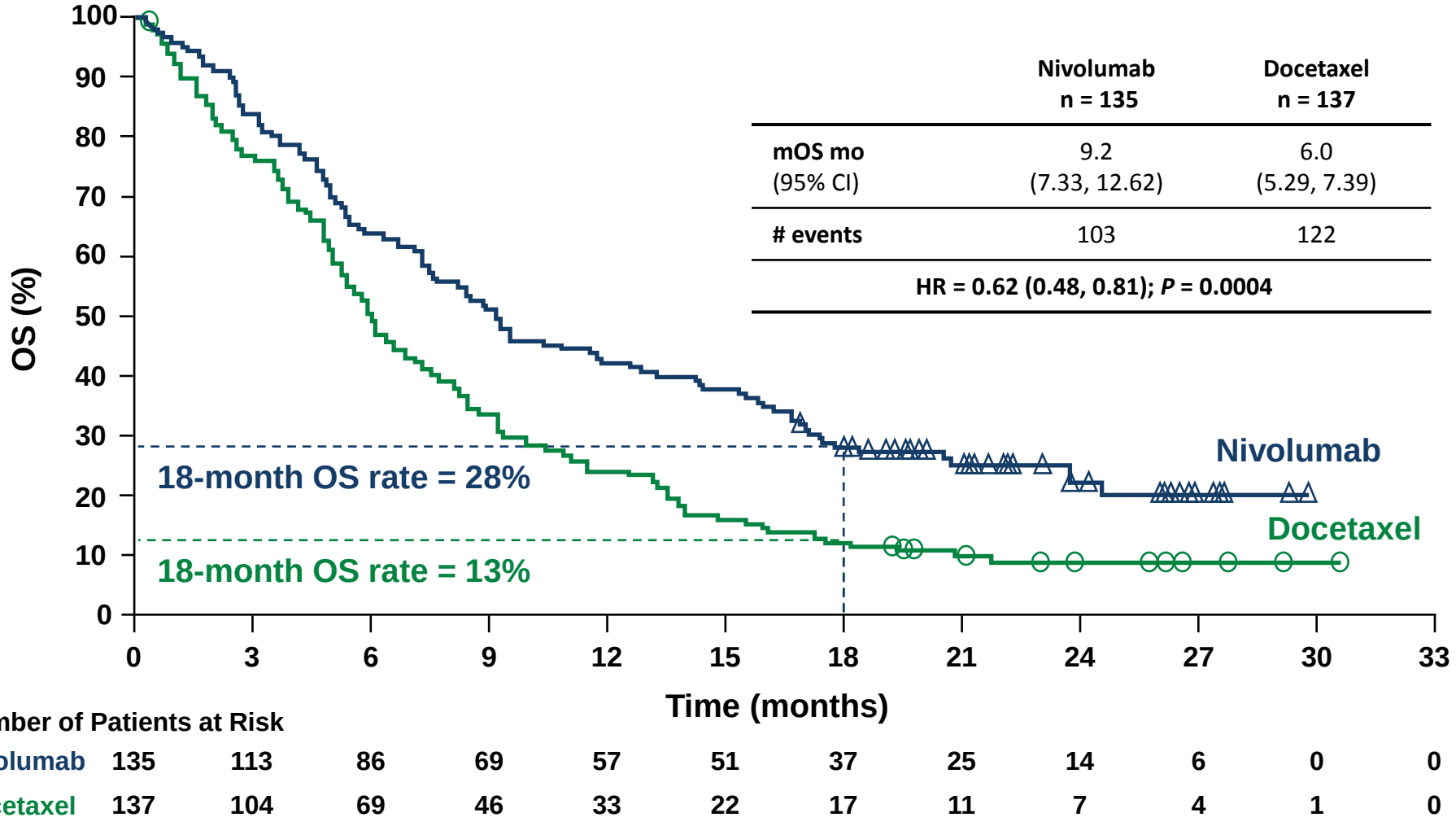
CheckMate 017: study design



Primary Endpoint: OS

- Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis
- DMC recommended early termination of study based on pre-specified interim analysis showing superior OS of nivolumab over docetaxel

CheckMate 017: updated overall survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR = 0.62 (0.48, 0.81); *P* = 0.0004		

Number of Patients at Risk

Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	17	11	7	4	1	0

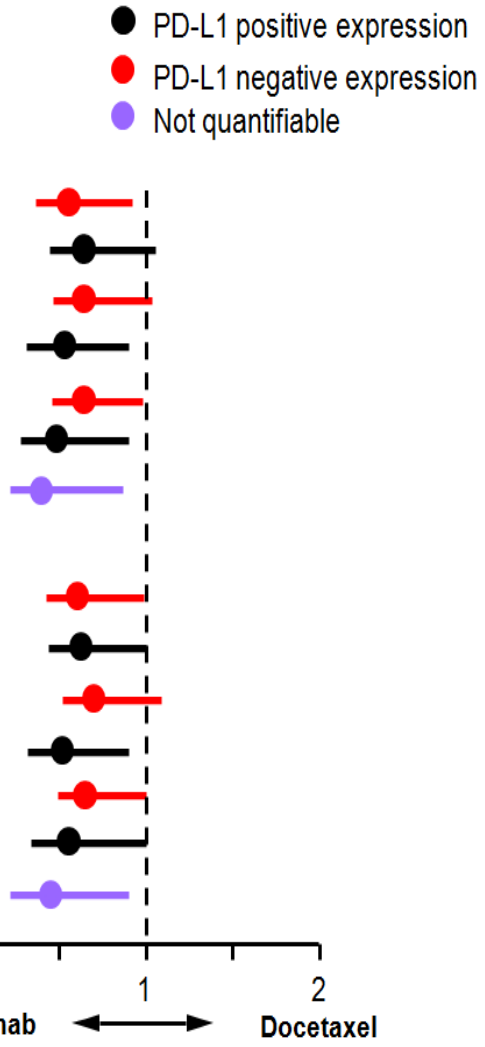
Based on August 2015 DBL.
Symbols refer to censored observations.

Reckamp K, et al. WCLC. 2015. Abstract 736

Efficacy by PDL1 expression

- Survival benefit with nivolumab was independent of PD-L1expression level

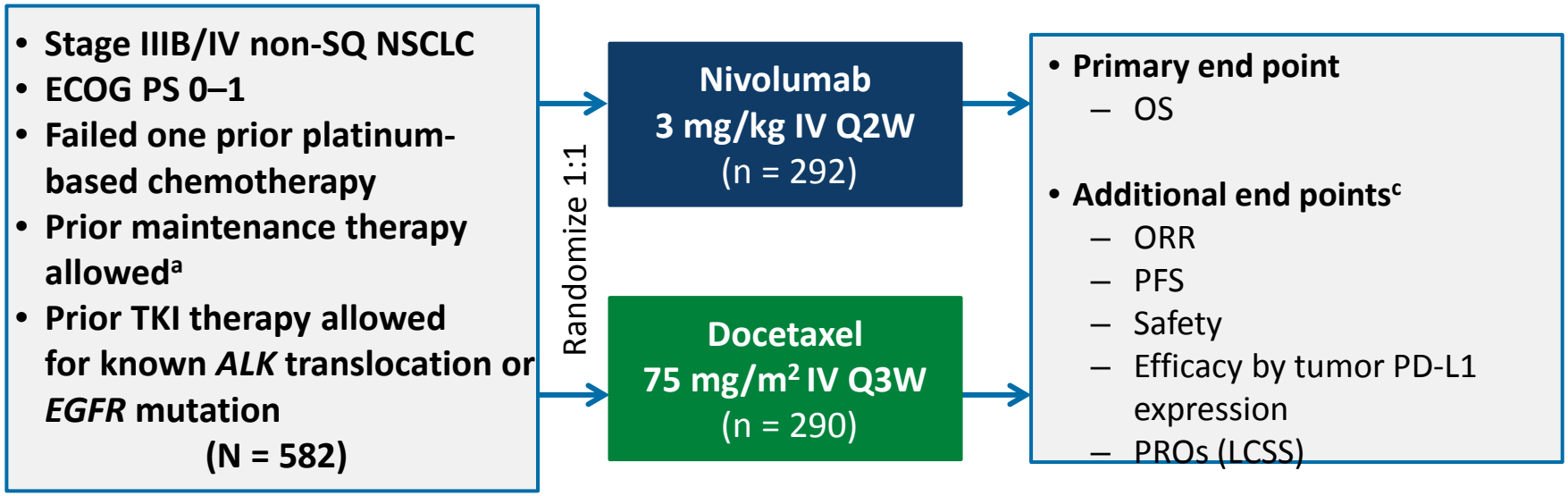
PD-L1 Expression	Patients, n Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P*-value
OS				
<1%	54	52	0.58 (0.37, 0.92)	**0.56**
≥1%	63	56	0.69 (0.45, 1.05)	
<5%	75	69	0.70 (0.47, 1.02)	**0.47**
≥5%	42	39	0.53 (0.31, 0.89)	
<10%	81	75	0.70 (0.48, 1.01)	**0.41**
≥10%	36	33	0.50 (0.28, 0.89)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	
PFS				
<1%	54	52	0.66 (0.43, 1.00)	**0.70**
≥1%	63	56	0.67 (0.44, 1.01)	
<5%	75	69	0.75 (0.52, 1.08)	**0.16**
≥5%	42	39	0.54 (0.32, 0.90)	
<10%	81	75	0.70 (0.49, 0.99)	**0.35**
≥10%	36	33	0.58 (0.33, 1.02)	
Not quantifiable	18	29	0.45 (0.23, 0.89)	



- 83% patients (225/272) had quantifiable PD-L1 expression

Based on December 2014 DBL

CheckMate 057: study design



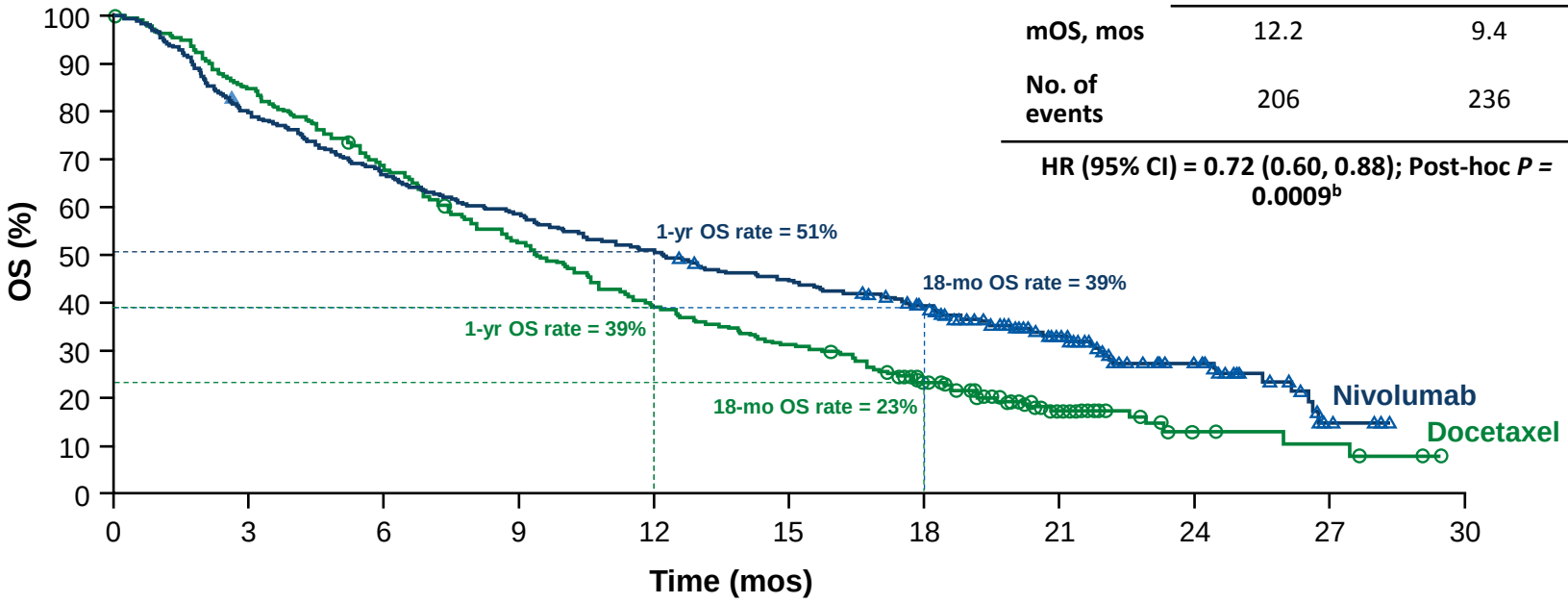
Patients stratified by prior maintenance therapy and line of therapy (second-line vs third-line)

- Pretreatment (archival or recent) tumor samples required for PDL1 expression analysis

CheckMate 057: updated overall survival

	Nivo (n = 292)	Doc (n = 290)
mOS, mos	12.2	9.4
No. of events	206	236

HR (95% CI) = 0.72 (0.60, 0.88); Post-hoc *P* = 0.0009[b]



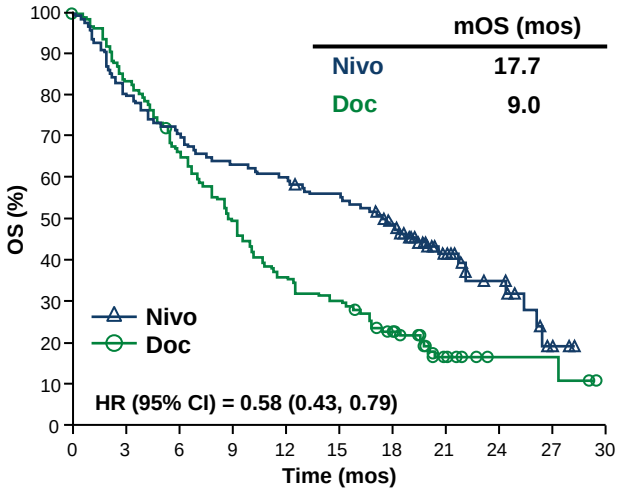
No. of patients at risk (18-mo OS)[b]

Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

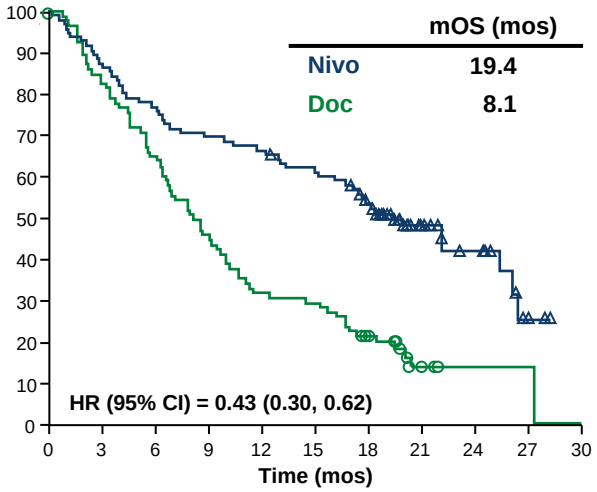
[a]Based on a July 2, 2015, DBL; [b]The formal primary end point testing was based on the interim analysis (March 18, 2015).
HR for 1-yr OS rate: 0.73 (96% CI: 0.59, 0.89), P = 0.0015

Overall survival by PDL1 expression

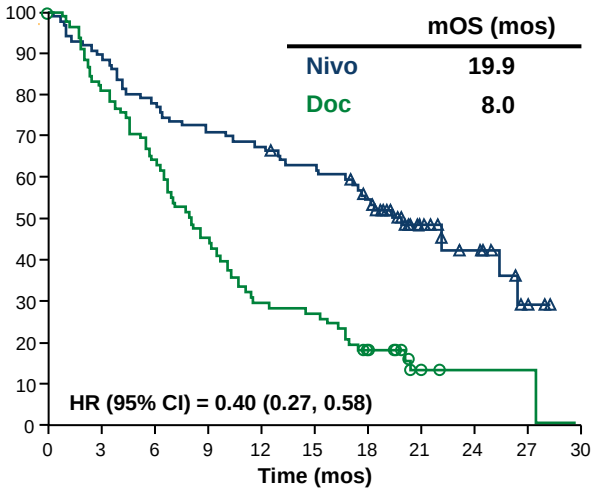
≥1% PD-L1 expression level



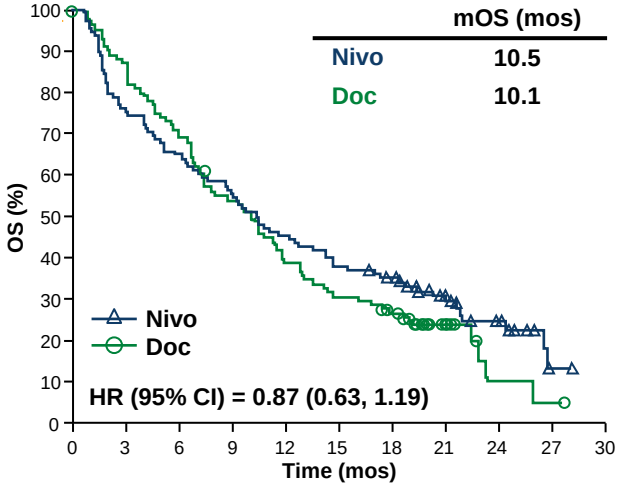
≥5% PD-L1 expression level



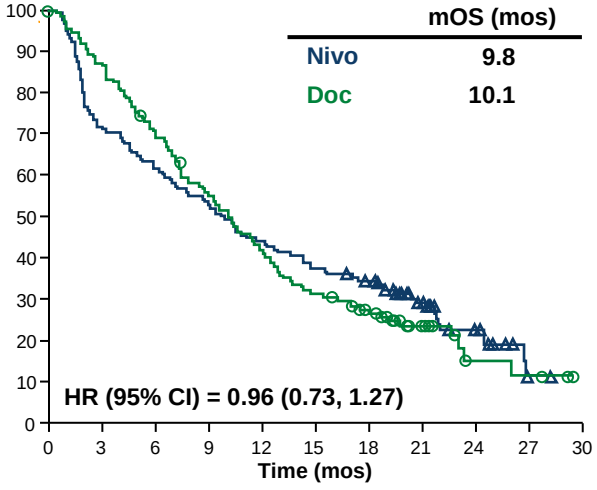
≥10% PD-L1 expression level



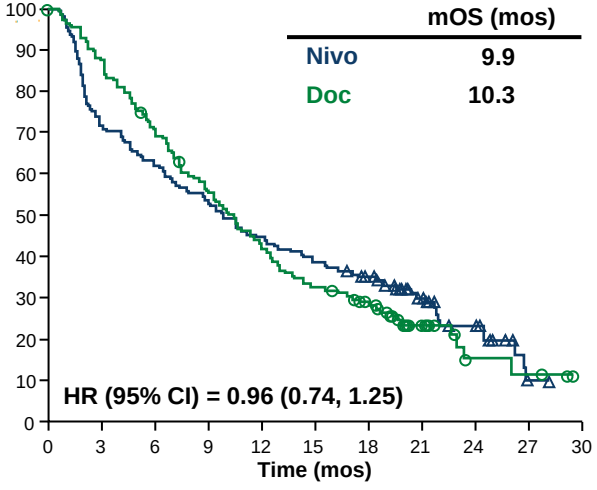
<1% PD-L1 expression level



<5% PD-L1 expression level



<10% PD-L1 expression level



Based on a July 2, 2015 DBL. Symbols represent censored observations.

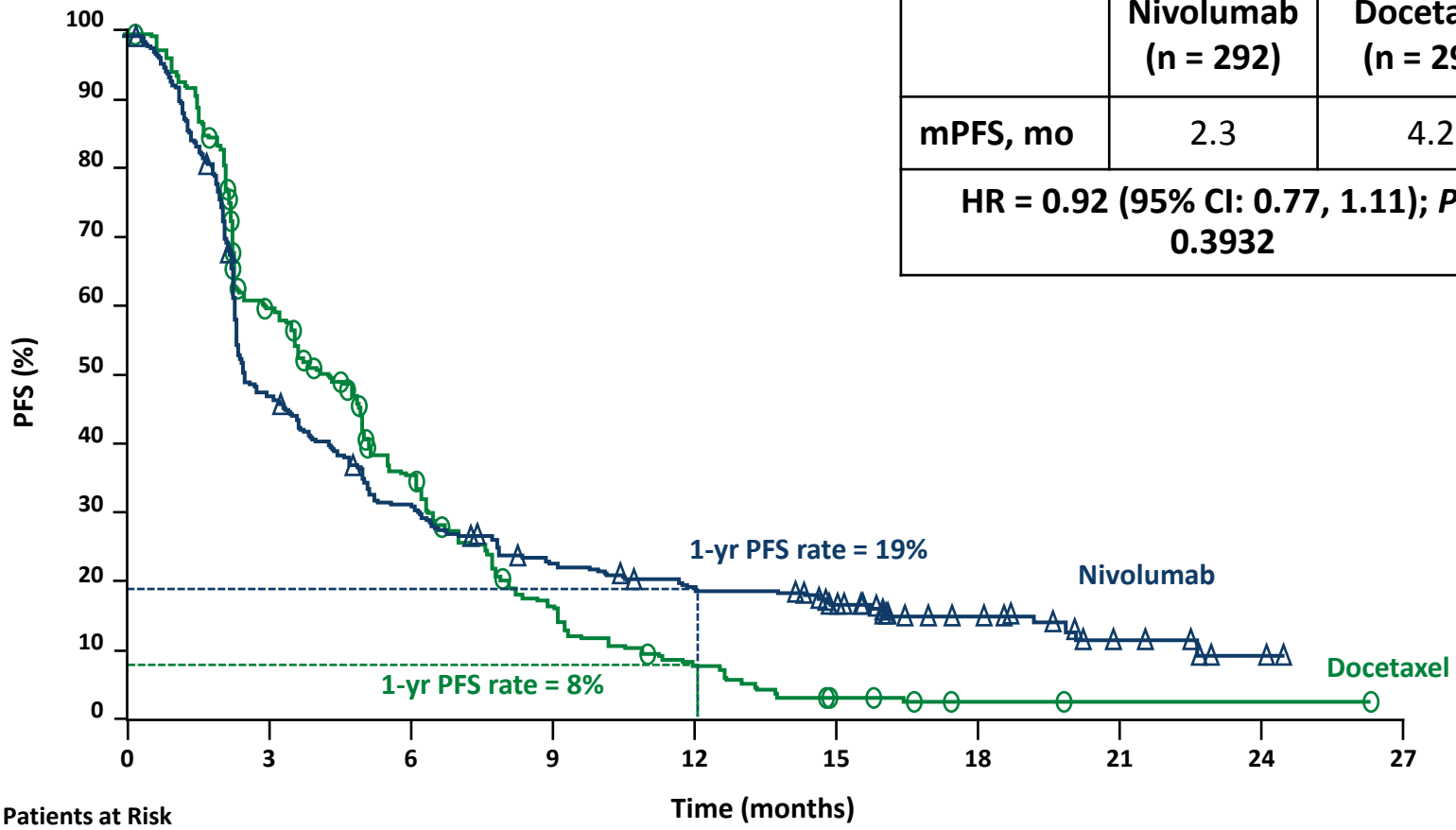
Response by tumor PD-L1 expression

PD-L1 expression level	ORR,[a] %		Median DOR, mos	
	Nivolumab	Docetaxel	Nivolumab	Docetaxel
≥1%	31	12	16.0	5.6
≥5%	36	13	16.0	5.6
≥10%	37	13	16.0	5.6
<1%	9	15	18.3	5.6
<5%	10	14	18.3	5.6
<10%	11	14	18.3	5.6
Not quantifiable	13	9	7.3	6.6

[a]Confirmed CR+PR (investigator assessment) as per RECIST v1.1 criteria. Interaction *P*-values for 1% (*P* = 0.0019), 5% (*P* = 0.0020), and 10% (*P* = 0.0021) PD-L1 expression are based on a logistic regression model with treatment, PD-L1 expression level, and treatment by PD-L1 interaction
Based on a March 18, 2015, DBL

CheckMate 057: progression-free survival

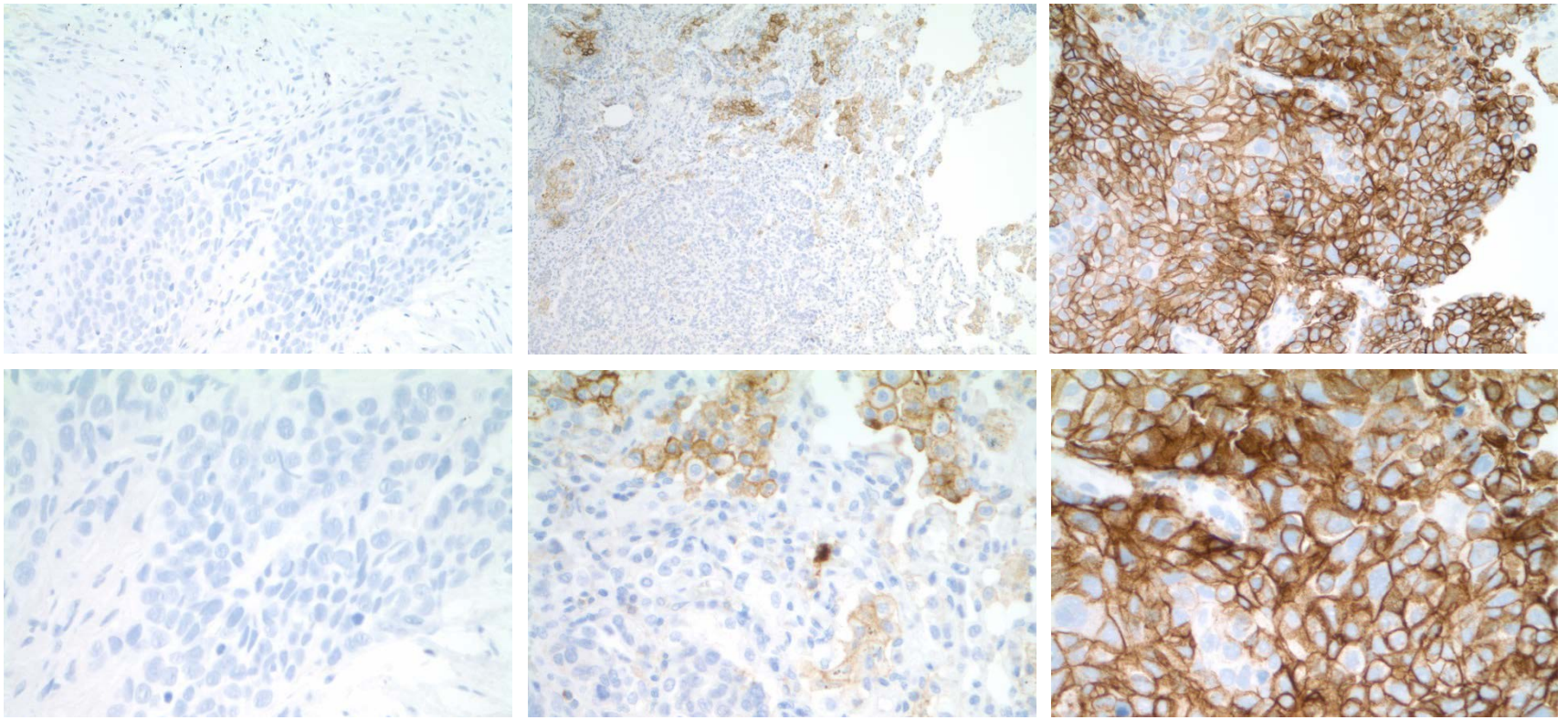
	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2
HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932		



Number of Patients at Risk										
Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

PD-L1 expression linked to favorable outcome with pembrolizumab

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



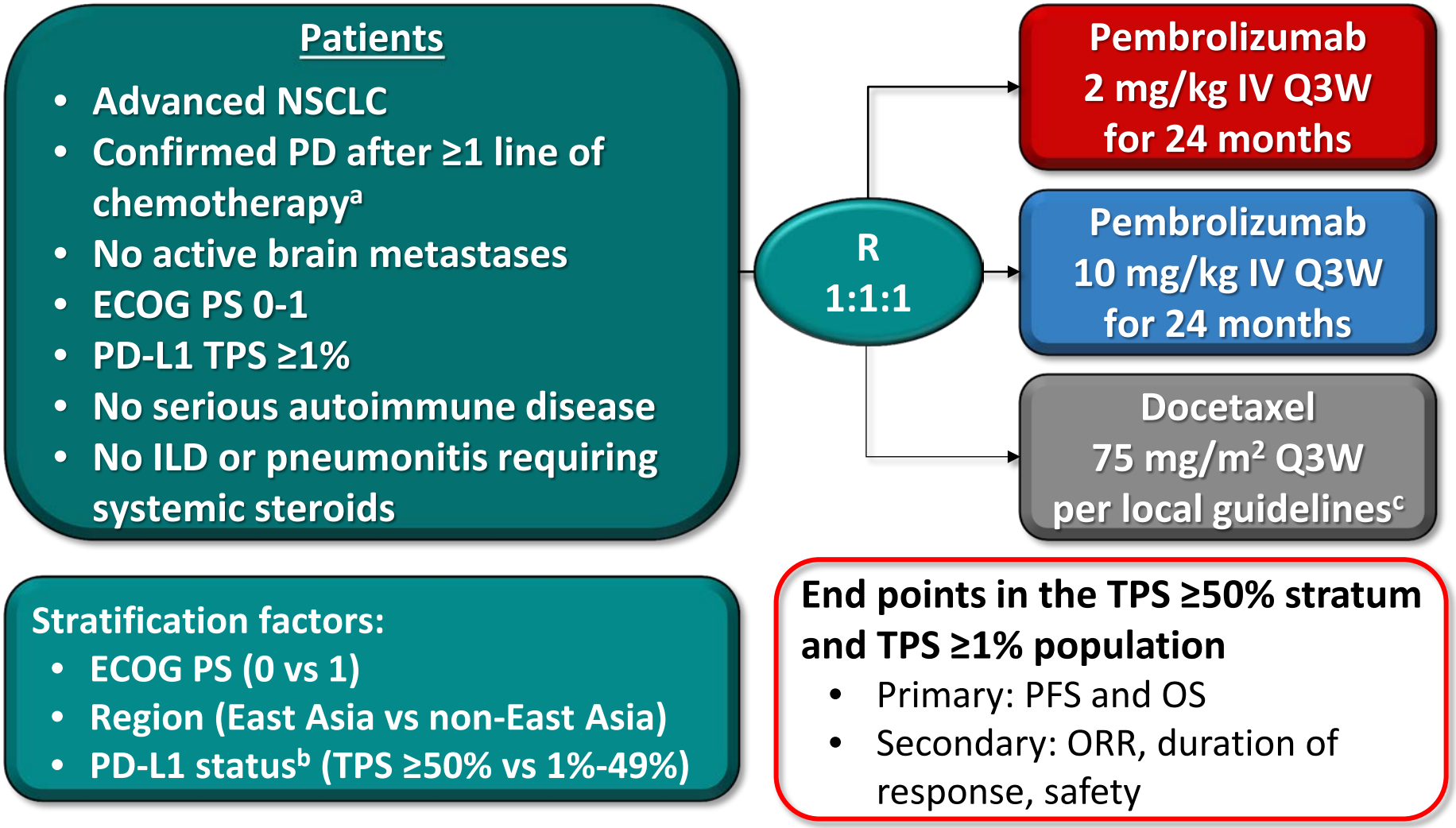
20x

40x

Negative **TPS 1%–49%** **TPS ≥50%**

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

KEYNOTE-010 study design

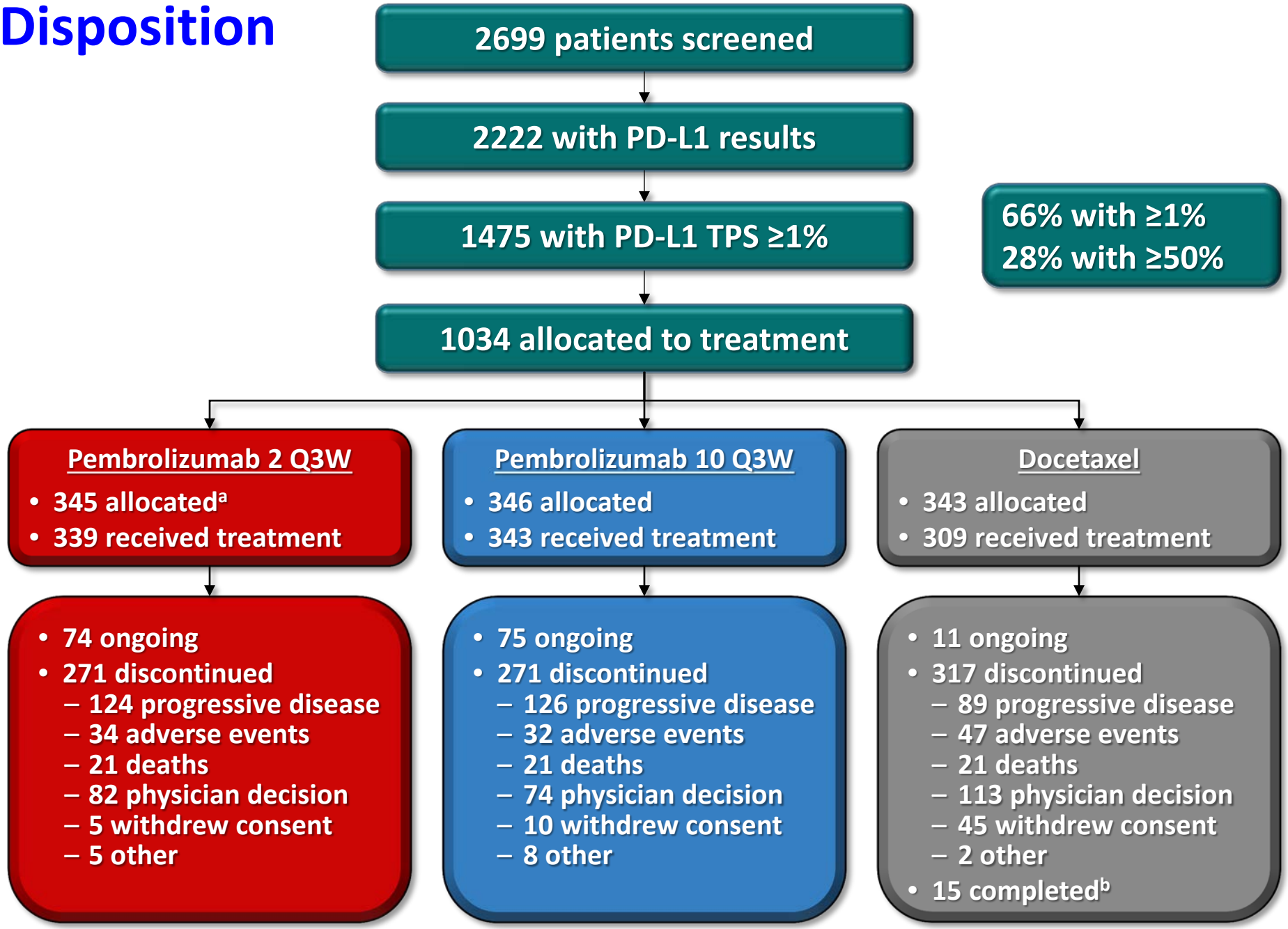


[a]Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an *EGFR* sensitizing mutation or an *ALK* translocation.

[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.

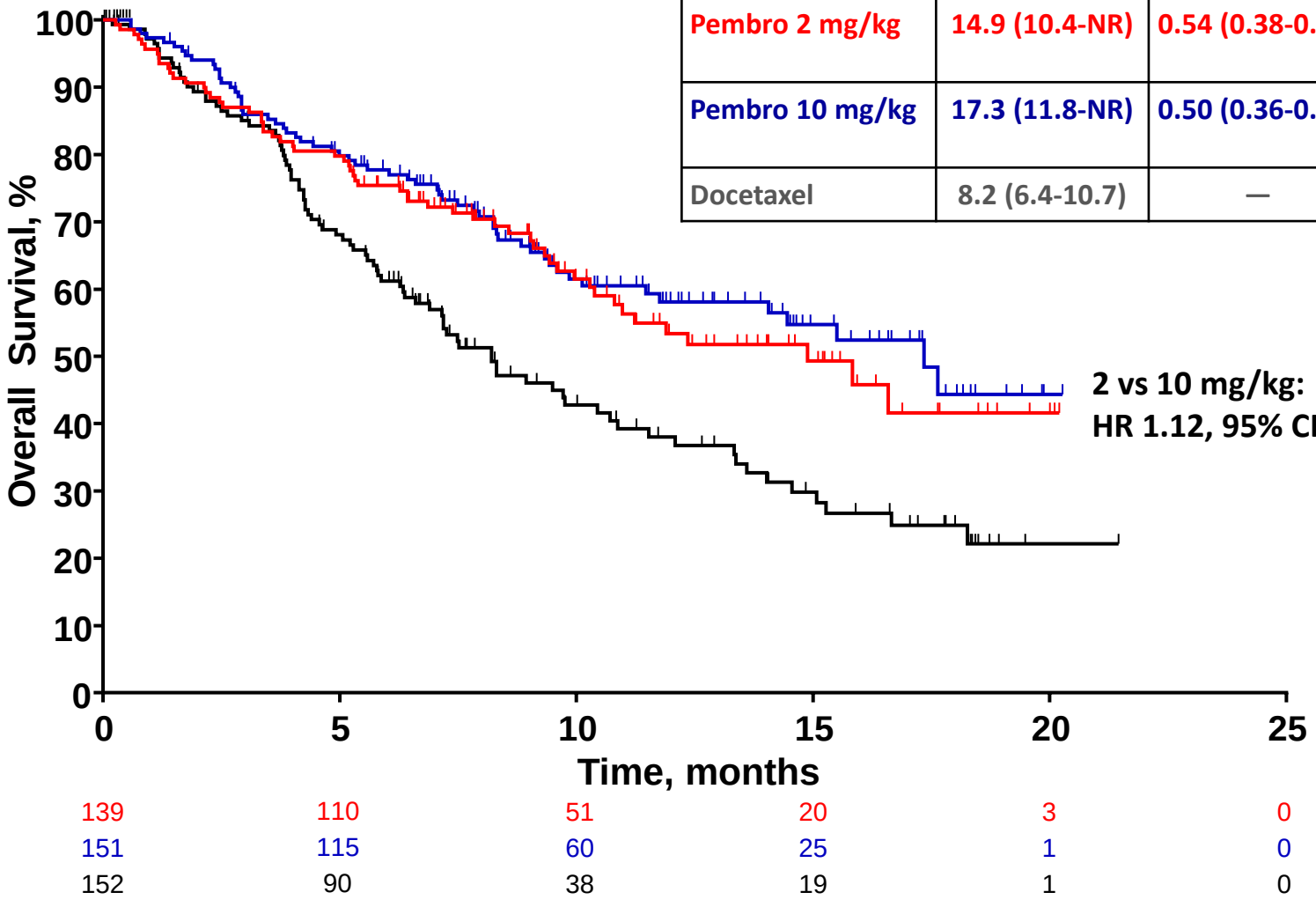
Disposition



[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.

OS, PDL1 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)	—	—



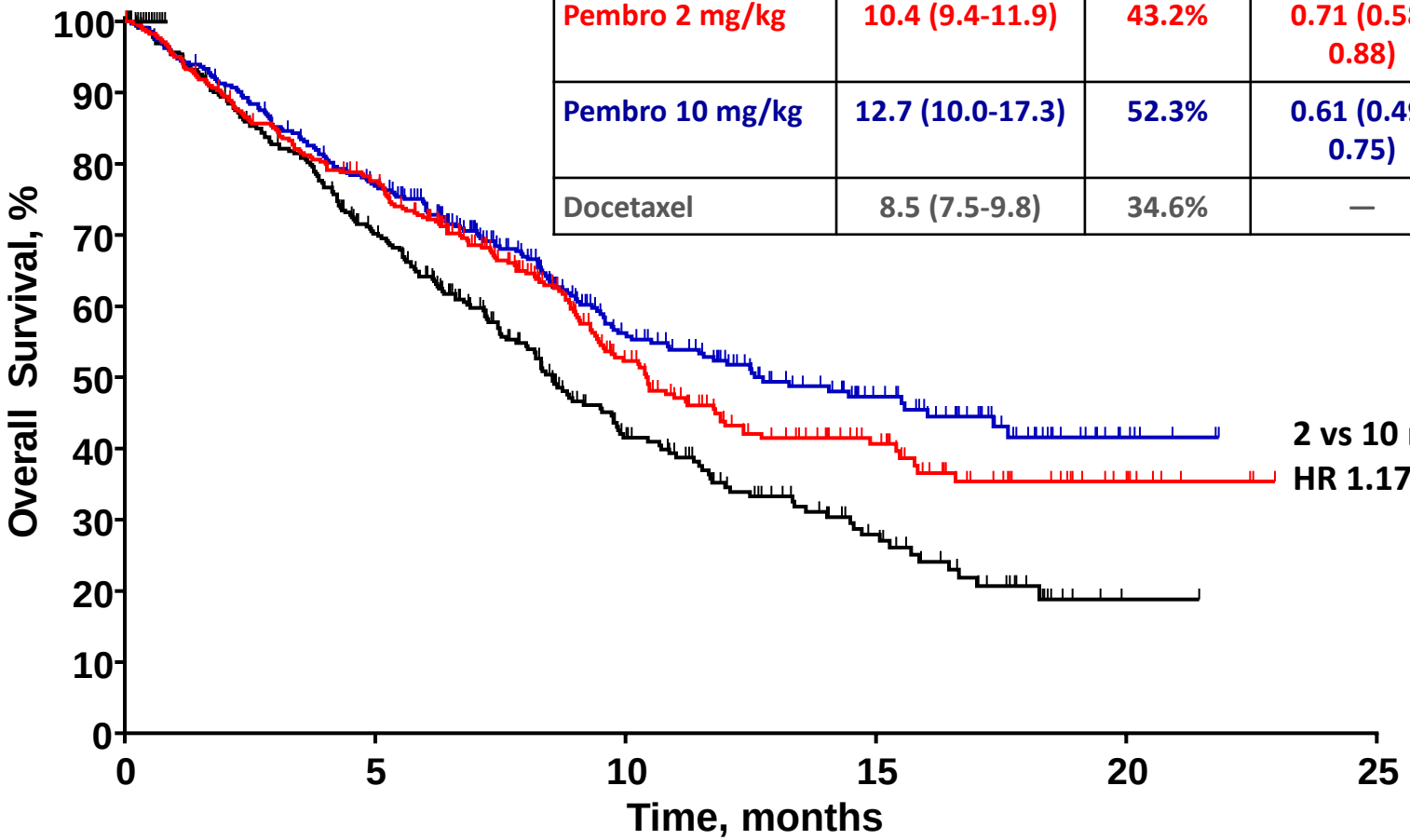
2 vs 10 mg/kg:
HR 1.12, 95% CI 0.77-1.62

Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

OS, PD-L1 TPS ≥1% (total population)

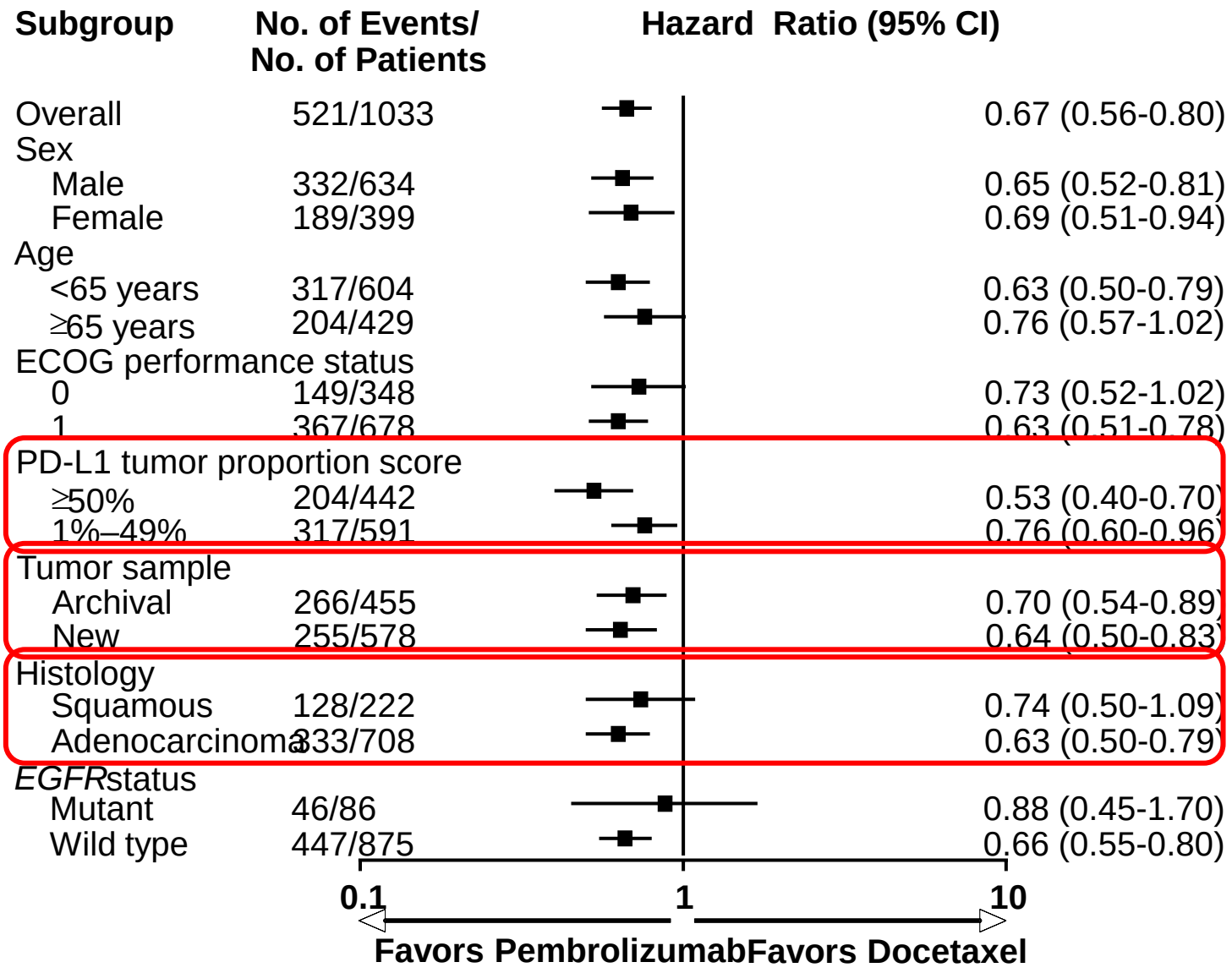
Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2%	0.71 (0.58-0.88)	0.0008
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.0001
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—



Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

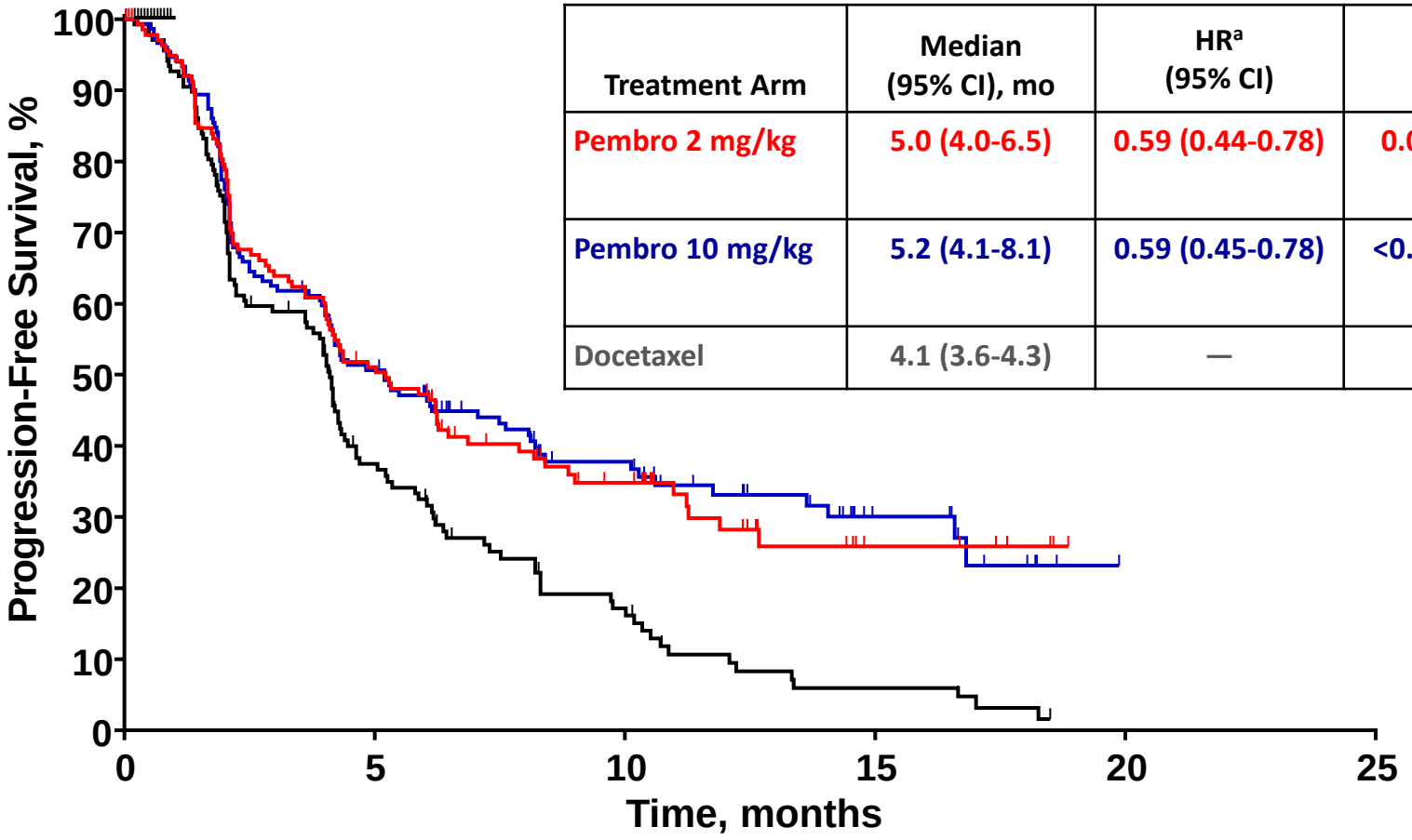
OS in key subgroups, PD-L1 TPS ≥1%[a]



Analysis cut-off date: September 30, 201

[a]Data for the pembrolizumab doses were pooled.

PFS (RECIST v1.1, central review), PD-L1 TPS ≥50%

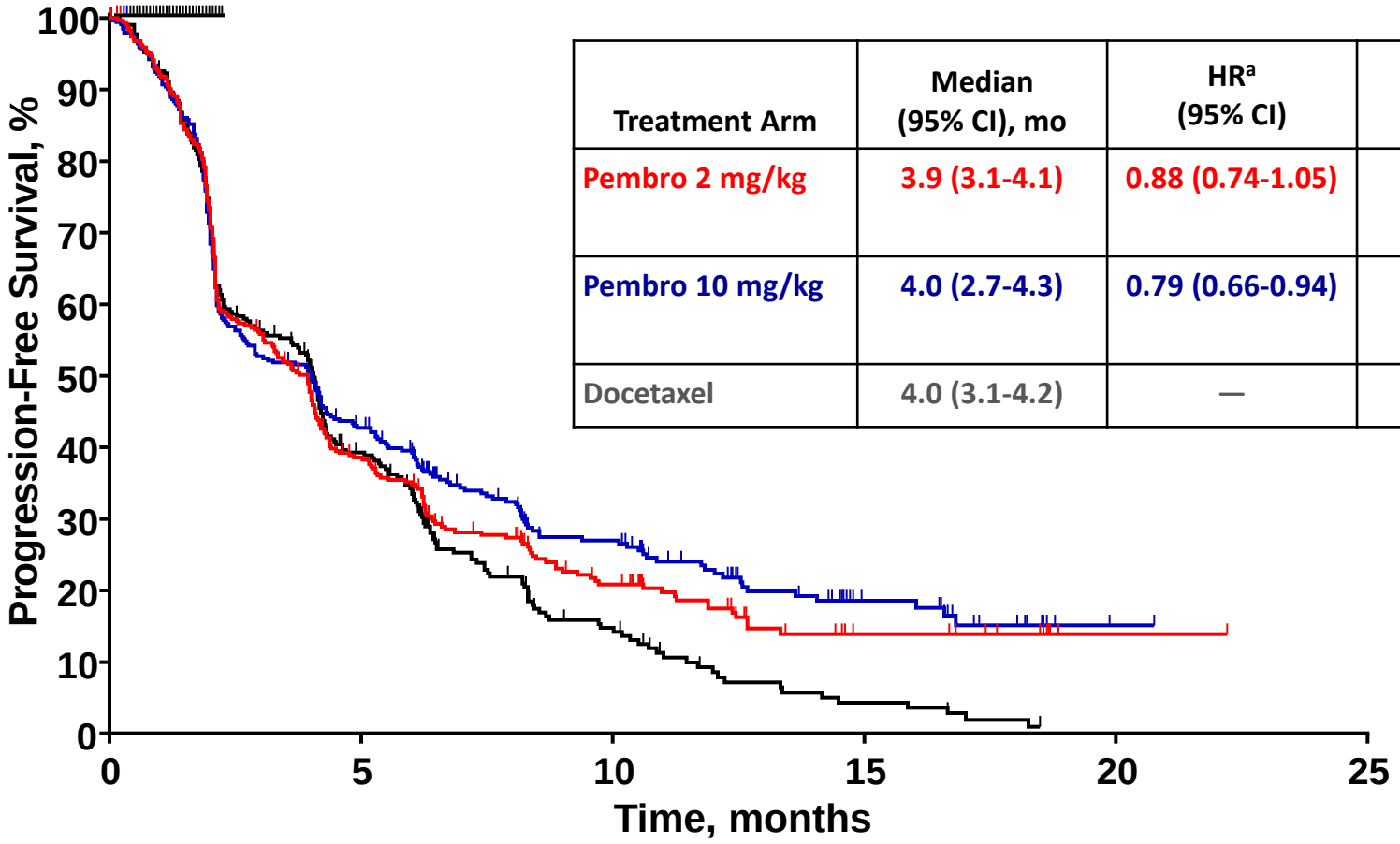


Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	5.0 (4.0-6.5)	0.59 (0.44-0.78)	0.0001
Pembro 10 mg/kg	5.2 (4.1-8.1)	0.59 (0.45-0.78)	<0.0001
Docetaxel	4.1 (3.6-4.3)	—	—

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)

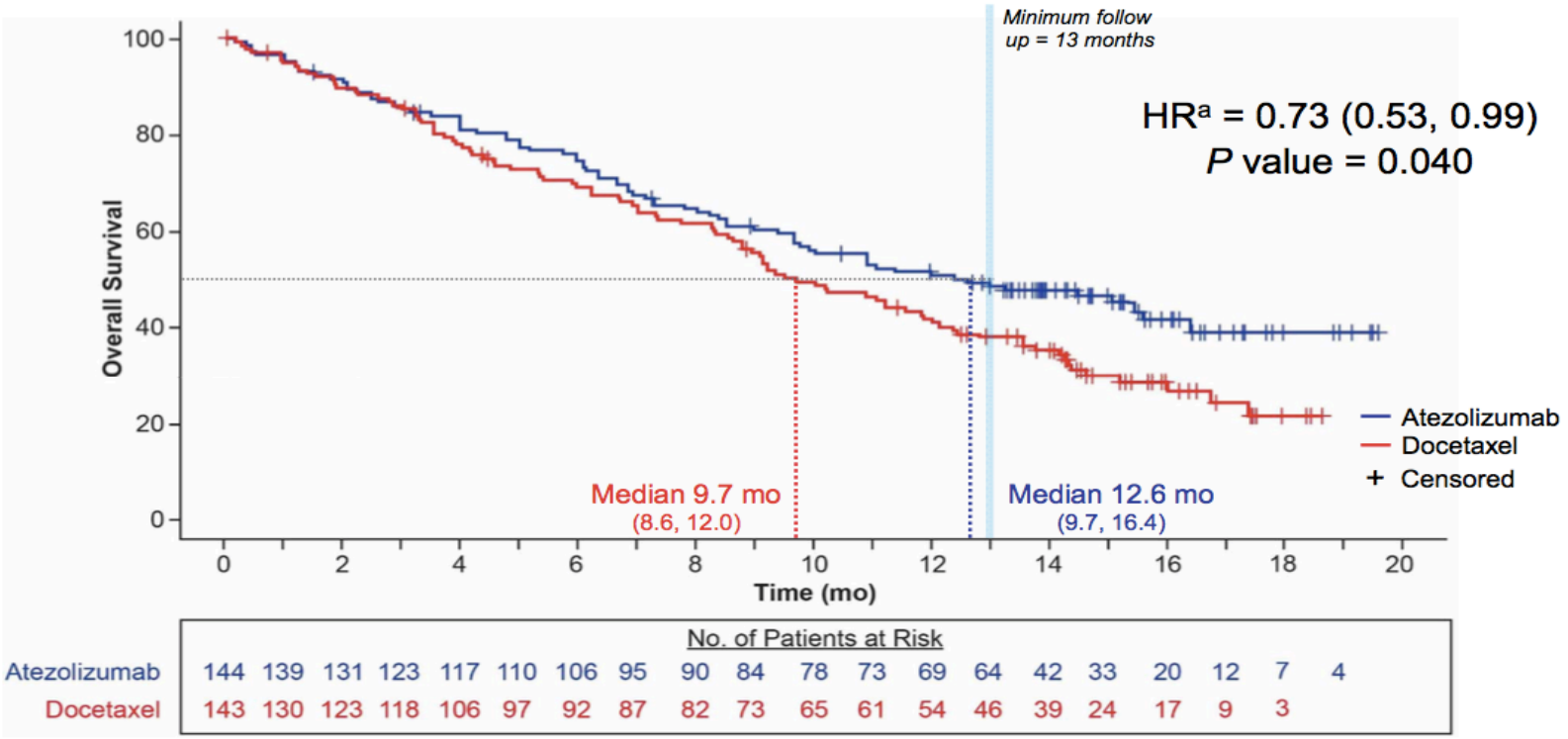
Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

Poplar: atezolizumab *vs* docetaxel, OS data

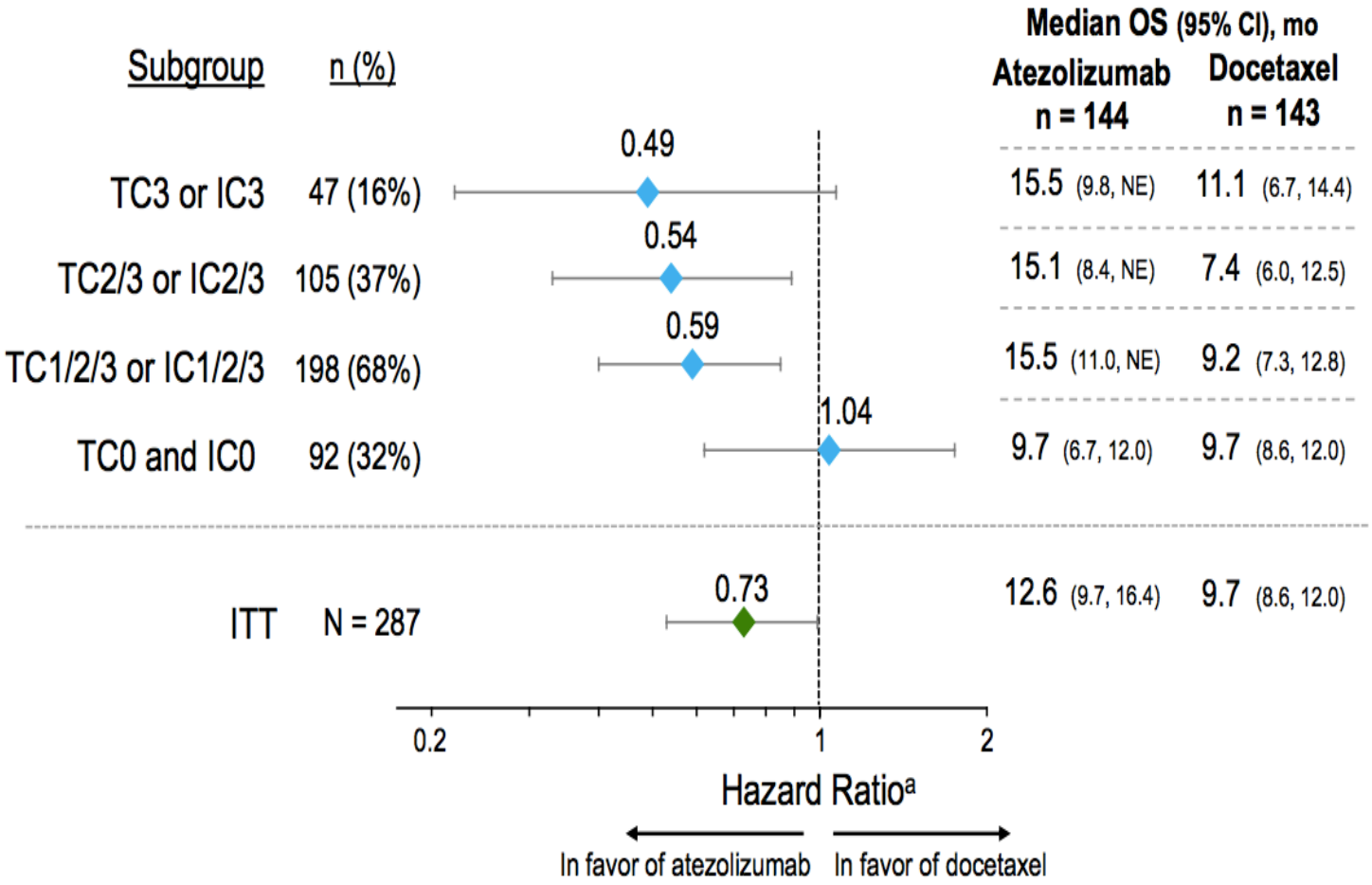
ecco

POPLAR: All Patient Efficacy
ITT OS (N = 287)



Vansteenkiste, ESMO 2015

Poplar: atezolizumab *vs* docetaxel
OS data according to PDL1 level

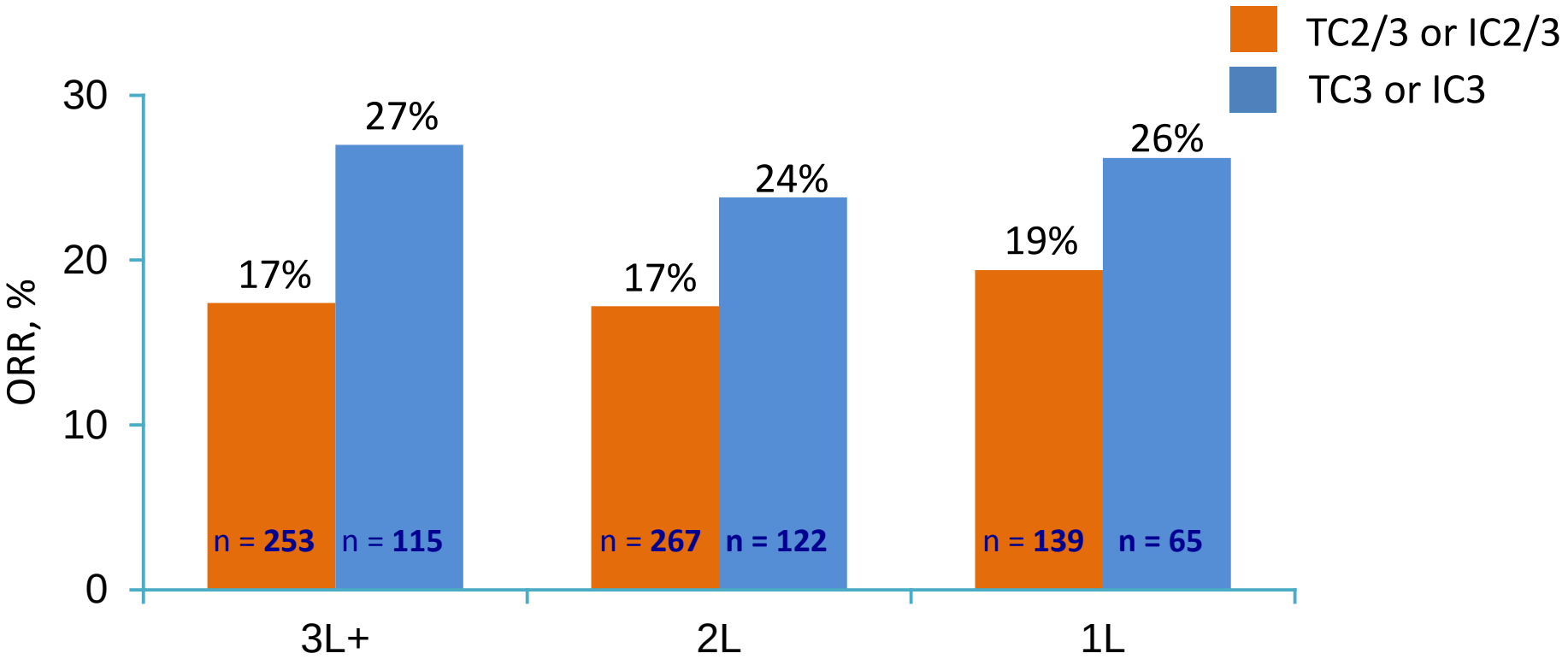


Vansteenkiste, ESMO 2015, Schmid ECCO 2015

Anti-PD1/-PDL1 toxicity

- Treatment-related AEs less common with anti-PD1/-PDL1 than with docetaxel
- Common side effects are fatigue, pruritus, decreased appetite
- AEs uncommon (<5% of pts) but with special clinical relevance: pulmonary, GI, endocrinophaties

Checkpoints in 1st line
BIRCH: TC3 or IC3 and TC2/3 or IC2/3 subgroups



- BIRCH enrolled patients with tumors that were PDL1 TC2/3 or IC2/3
- 34% of screened pts

Besse, ESMO 2015

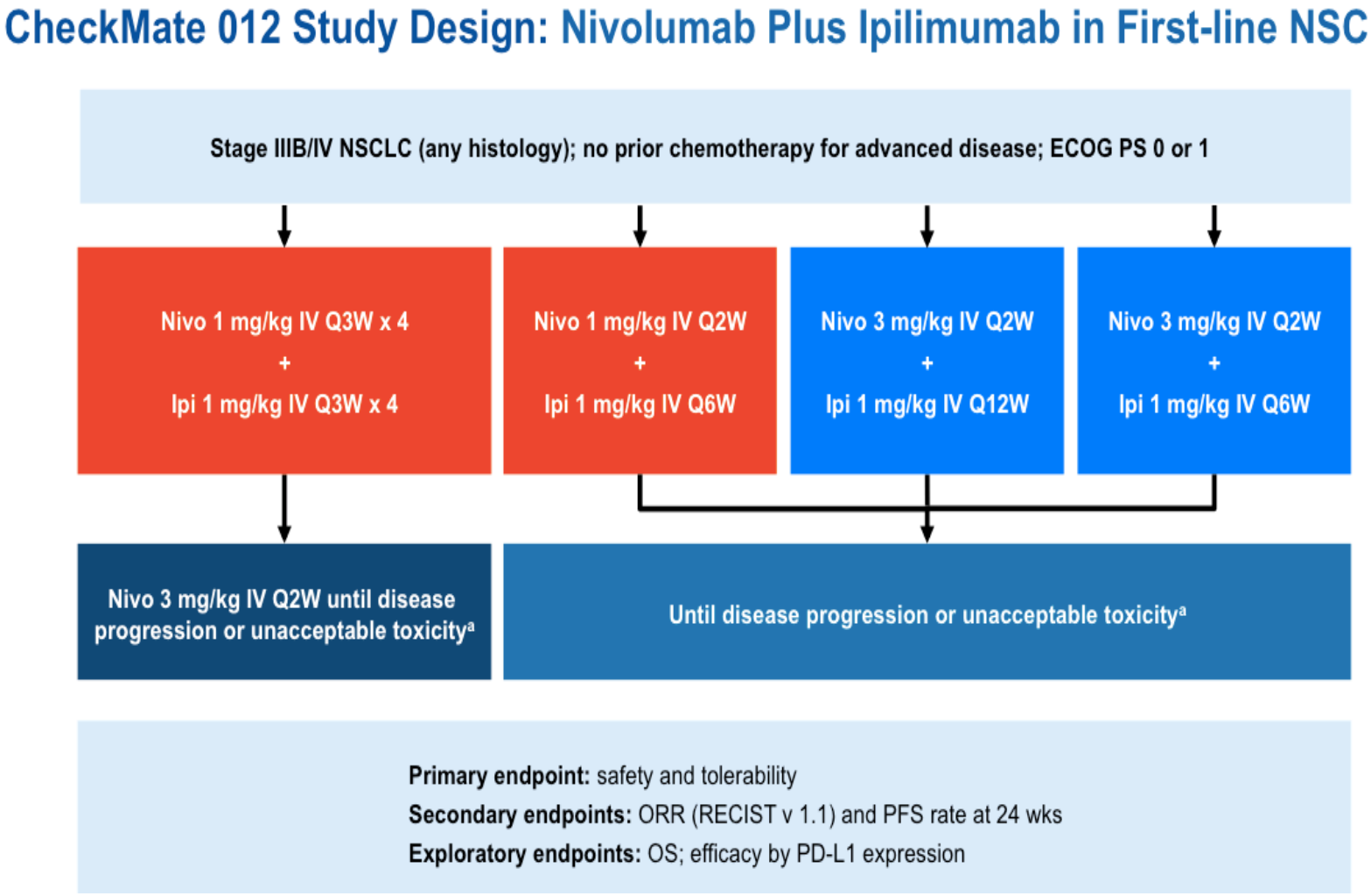
Checkpoints in monotherapy *vs* CT in 1st line

- **Phase II trial of nivolumab *vs* investigator's choice CT as 1st-line for stage IV or recurrent PD-L1+ NSCLC (CheckMate 026)**
  - Primary outcome measures: PFS in subjects with strongly PD-L1+ tumor expression

- **Phase III trial of MK-3475 *vs* platinum-based CT in 1L subjects with PD-L1 strong metastatic NSCLC**
  - Primary outcome measures: PFS

Anti-PD1/-PDL1 agents in combination

Should we favor 1st-line combinations?



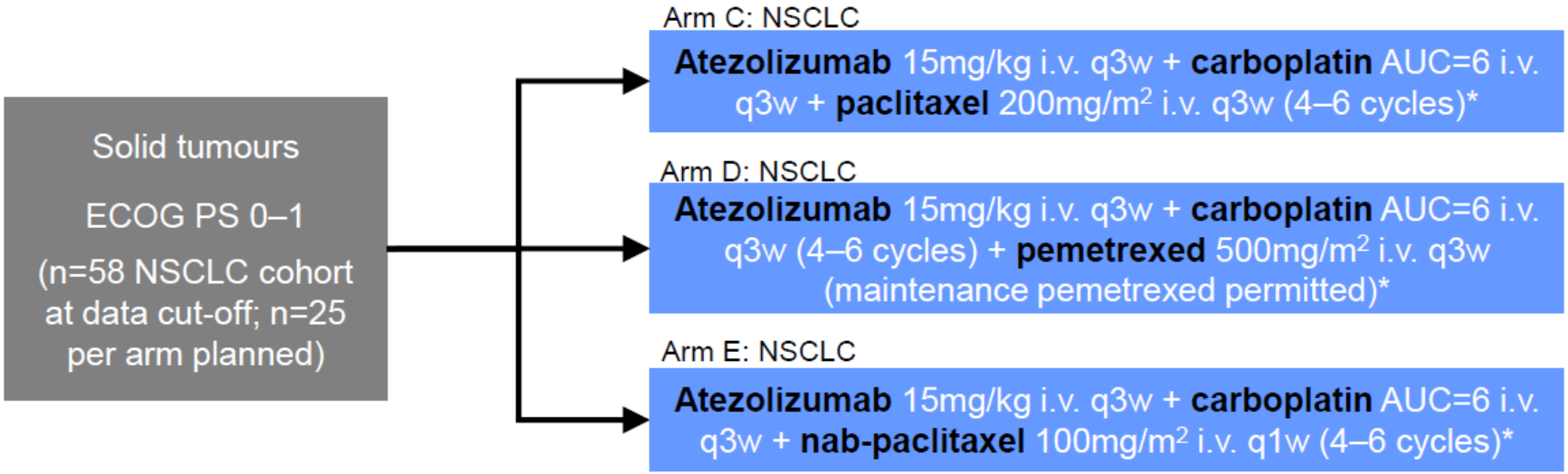
Rizvi, WCLC 2015

Summary of efficacy

	Nivo 1 + Ipi 1 Q3W (n = 31)	Nivo 1 Q2W + Ipi 1 Q6W (n = 40)	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)
Confirmed ORR, % (95% CI)	**13** (4, 30)	**25** (13, 41)	**39** (24, 57)	**31** (17, 48)
Confirmed DCR, % (95% CI)	55 (36, 73)	58 (41, 73)	74 (57, 87)	51 (35, 68)
Best overall response, %				
Complete response Partial response Unconfirmed partial response	0 13 3	0 25 3	0 39 5	0 31 8
Stable disease Progressive disease Unable to determine	42 35 6	33 30 10	34 13 8	21 26 15
PFS rate at 24 wks, % (95% CI)	55 (36, 71)	NC	63 (44, 76)	NC
Median PFS, mos (95% CI)	10.6 (2.1, 16.3)	4.9 (2.8,)	8.0 (4.2,)	8.3 (2.6,)
Median OS, mos (95% CI)	NR (11.5,)	NR (8.9,)	NR	NR (8.7,)
Median length of follow-up, mos (range)	16.6 (1.8–24.5)	6.2 (0.4–13.1)	8.4 (0.9–12.3)	7.7 (1.1–12.2)

- Median DOR was not reached in any arm
- Unconventional immune-related responses were observed in arms Nivo 3 Q2W + Ipi 1 Q12W (n = 2), Nivo 3 Q2W + Ipi 1 Q6W (n = 1) and Nivo 3 Q2W (n = 3)

Phase Ib GP28328 (NCT01633970) study design and endpoints: NSCLC cohort



- Primary endpoint: safety (including dose-limiting toxicities)
- Secondary endpoints: pharmacokinetics; best overall response; objective response rate (ORR); duration of response (DOR); progression-free survival (PFS)
- Date of cut-off: 10 Feb 2015; median safety follow-up: 128.5 days (4.2 months)

*supportive care (including steroids if necessary) was permitted, at the investigators' discretion; atezolizumab was given until loss of clinical benefit

Summary of response by RECIST v1.1 (response-evaluable patients*)

- Data are preliminary; ~25 patients will be included in each arm for final analysis

	Arm C – cb/pac (n=8)	Arm D – cb/pem (n=17)	Arm E – cb/nab (n=16)	All NSCLC patients (n=41)
Overall response, n (ORR %)	4 (50.0)	13 (76.5)	9 (56.3)	26 (63.4)
[95% CI for ORR]	[15.7–84.3]	[50.1–93.2]	[29.9–80.3]	[46.9–77.9]
Complete response, n (%)	0 (0)	0 (0)	4 (25.0)	4 (9.8)
Partial response, n (%)	4 (50.0)	13 (76.5)	5 (31.3)	22 (53.7)
Stable disease, n (%)	4 (50.0)	1 (5.9)	4 (25.0)	9 (22.0)
Progressive disease, n (%)	0 (0)	2 (11.8)	2 (12.5)	4 (9.8)
Missing or not evaluable, n (%)	–	1 (5.9)	1 (6.3)	2 (4.9)

*Includes all patients dosed by 10 Nov 2014; data cut-off: 10 Feb 2015

Biomarkers

PD-1/PD-L1 CDx in development, companions tests

pembrolizumab	nivolumab	Atezolizumab	Durvalumab
22C3	28-8	SP142	SP263
1% or 50% • Tumor only • Only validated cut-off in a prospective clinical study	• Retrospective analysis of 1, 5 and 10%	IHC 3: ≥ 10% tumor immune cells positive for PD-L1 (IC+); IHC 2 and 3: ≥ 5% tumor immune cells positive for PD-L1 (IC+); IHC 1/2/3: ≥ 1% tumor immune cells positive for PD-L1 (IC+); IHC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status	• Cut-off 25% tumor cells in NSCLC
• Developing PD-L1+ IHC CDx with Dako	• Developing PD-L1+ IHC CDx with Dako • No need for PD-L1+ testing in 2L +	• CDx platform (Ventana) for development and to validate commercial PD-L1+ CDx	• Developing CDx for PD-L1+ with Ventana

Biomarkers for immunotherapy: tumor mutational load

- Whole-exome sequencing of NSCLC patients treated with pembrolizumab
- In two independent cohorts, higher nonsynonymous mutation burden in tumors associated with improved ORR and PFS
- Efficacy also correlated with molecular smoking signature, higher neoantigen burden, and DNA repair pathway mutations

Rizvi N, Science 2014

Lessons learnt, future perspectives

Anti-PD1/-PDL1 in NSCLC, lessons learnt

- Large number of similar drugs compete in same treatment area
- RR around 20% consistent across studies
- 2^{nd}-line, improves OS, less toxicity when compared with docetaxel (optimal control arm)
- Higher RR in pts with PDL1+ tumors, greater benefit in pts with more PDL1 staining (except in checkmate 017)

Anti-PD1/-PDL1 in NSCLC, lessons learnt

- Should we choose the drug according to the antibody used for PDL1?
- PDL1 analyzed in pivotal trials; involvement by scientific societies needed to optimize markers before starting trials with compounds from different companies
- Less relevance of predictive markers when used in combination

Anti-PD1/-PDL1 in NSCLC, future perspectives

- Define their role in 1st-line; trials comparing nivolumab/pembrolizumab with CT in PDL1+ tumors ongoing (recruitment closed)

- Additional information from clinical trials would be of interest
  - What percentage of long-term-survival (18-mo or 24 mo) pts have PDL1 negative tumors?

- Blueprint project; pathology committee of the IASLC with 6 of the commercial stakeholders to compare the tests for PDL1

Thanks!!!

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