Emerging Therapeutic Landscape in Advanced Non-small Cell Lung Cancer (NSCLC): A New Immunotherapy Paradigm

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Langer Disclosures: Past 12 months

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  - Genentech, OSI (Astellas), Merck, GlaxoSmithKline, Nektar, Advantagene, Clovix; Ariad; Inovio, Threshold, AZ, Celgene, MGA
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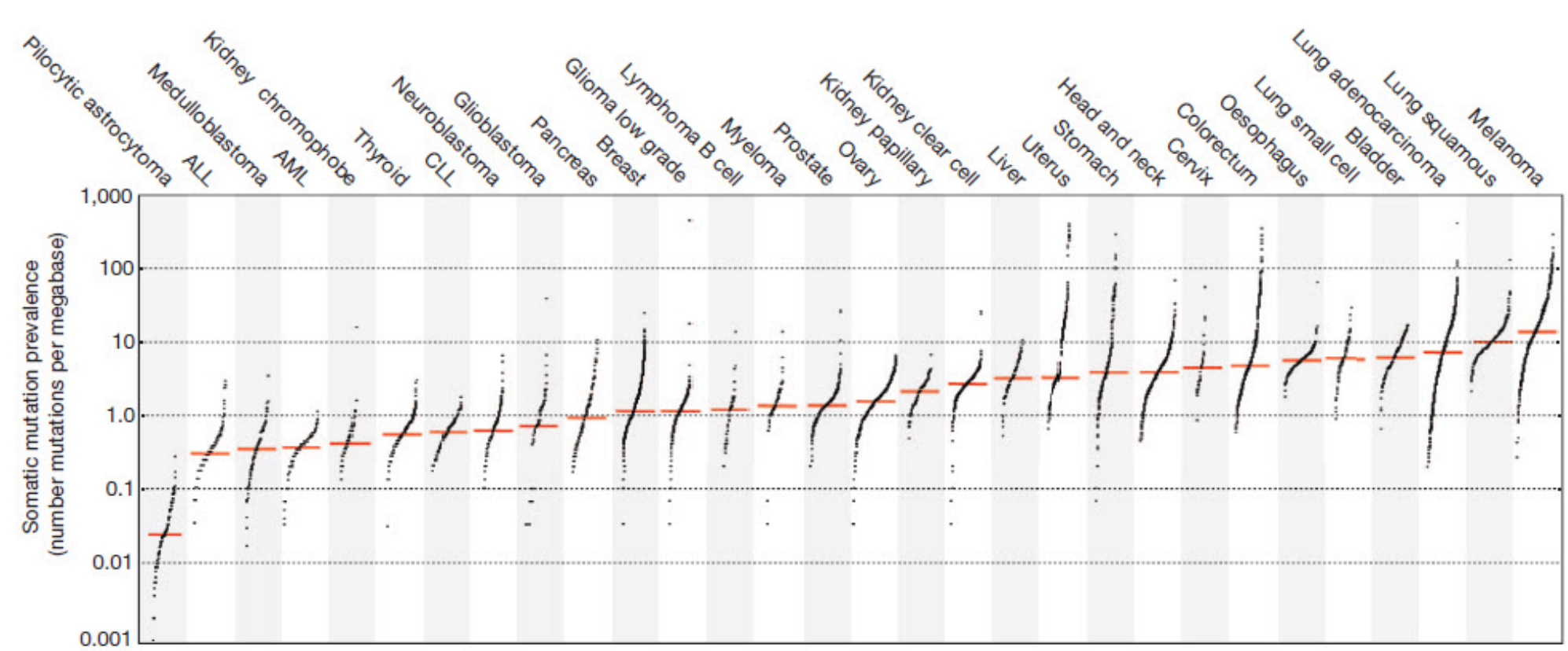
- Scientific Advisor:
  - Bristol Myers Squibb, Pfizer, Lilly, Astra Zeneca, Novartis, Genentech, Abbott, Celgene, Boehringer-Ingelheim, Hospira, Clovis, Merck

Mutational Burden



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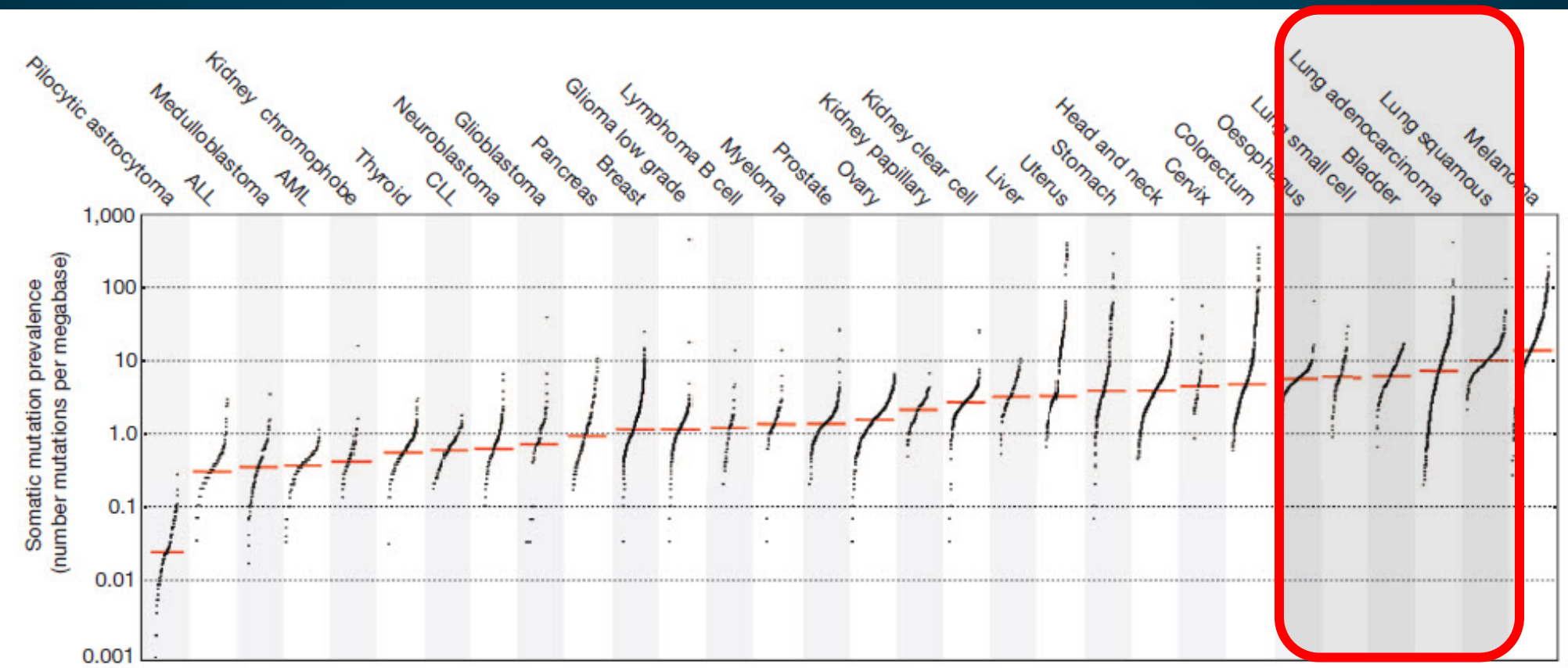
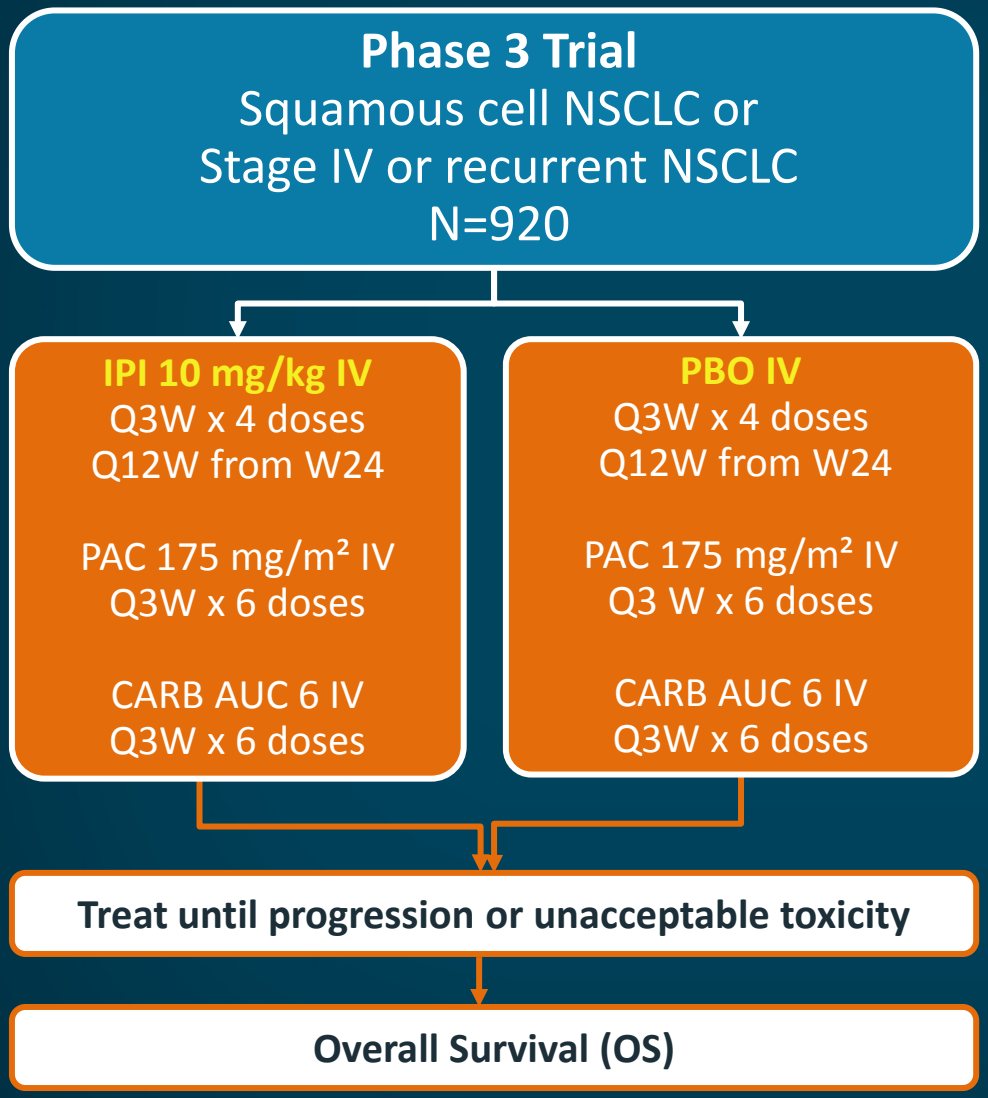


Phase 3 Trial Comparing Ipilimumab Plus Paclitaxel and Carboplatin vs. Placebo Plus Paclitaxel and Carboplatin in Squamous NSCLC (CA184-104/NCT01285609)



Primary endpoint

- OS in pts receiving 1 dose of blinded therapy

Secondary endpoints

- OS in all randomized pts
- PFS

Key eligibility criteria

- ≥18 years of age
- Squamous-cell NSCLC
- Stage IV or recurrent NSCLC
- ECOG PS ≤1
- No brain metastases or autoimmune disease

CARB = carboplatin; ECOG PS = Eastern Cooperative Oncology Group performance status; IPI = ipilimumab; OS = overall survival; PAC = paclitaxel; PFS = progression-free survival; PBO = placebo; W = week

https://clinicaltrials.gov/ct2/show/NCT01285609?term=NCT01285609&rank=1

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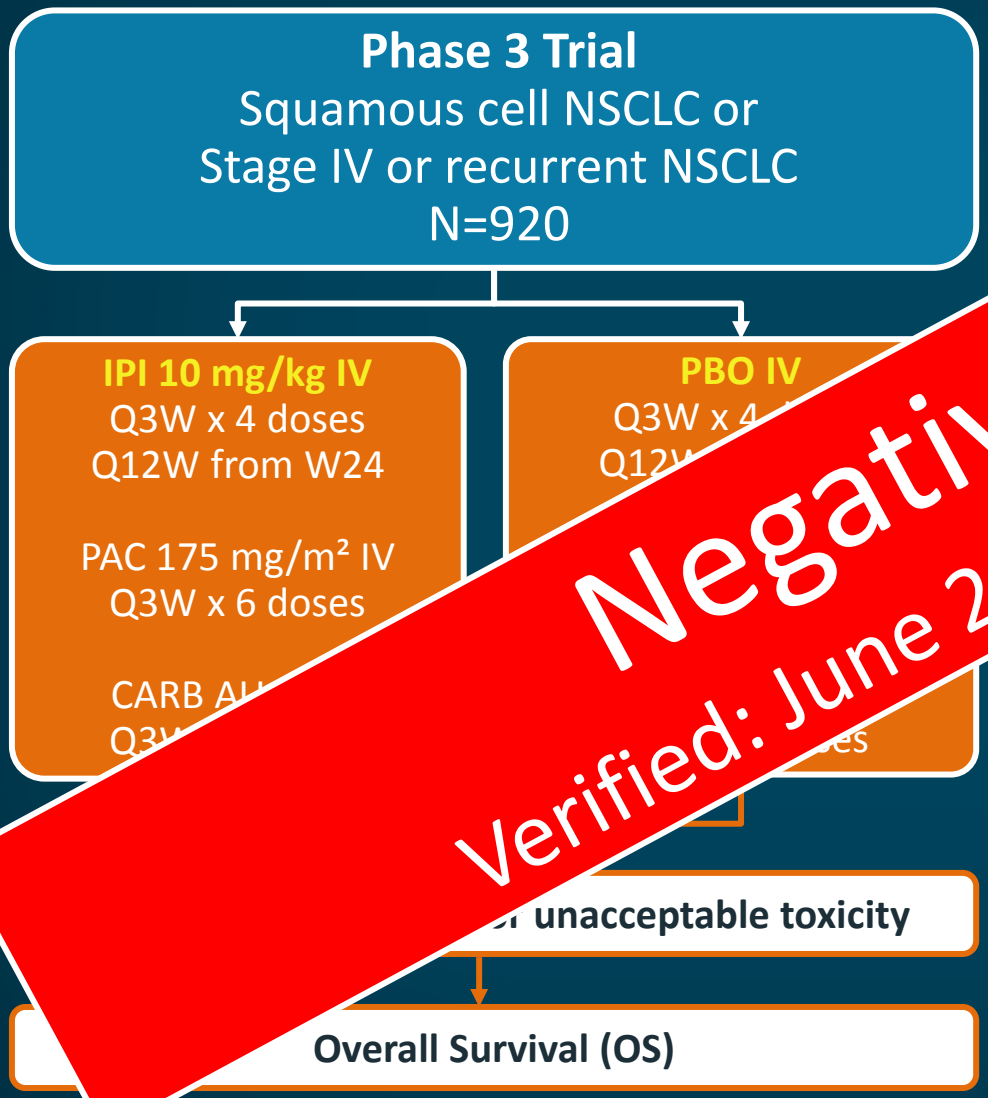

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- OS in pts
- the

- teria
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https://clinicaltrials.gov/ct2/show/NCT01285609?term=NCT01285609&rank=1

OS and PFS: Phase 3 Pac/Carbo +/- Ipilimumab
Squamous NSCLC (CA184-104/NCT01285609)

	Ipilimumab With Paclitaxel/Carboplatin	Placebo With Paclitaxel/Carboplatin
Participants Analyzed [Units: Participants]	479	477
Median Overall Survival All Randomized Participants Median (95% Confidence Interval)	10.94 (9.56 to 12.02)	10.74 (9.66 to 11.73)
Median PFS (95% Confidence Interval)	5.55 (5.36 to 5.85)	5.59 (5.52 to 5.72)

Groups [	All groups
Statistical Method	Log Rank
P Value	0.2517
Hazard Ratio (HR)	0.907
95% Confidence Interval	0.767 to 1.072

Results First Received: May 16, 2016. CT.GOV

Reasons for Tx D/C: Phase 3 Pac/Carbo +/- Ipilimumab
Squamous NSCLC (CA184-104/NCT01285609)

	Ipilimumab With Paclitaxel/Carboplatin	Placebo With Paclitaxel/Carboplatin
STARTED	388	361
COMPLETED	9 [1]	8 [1]
NOT COMPLETED	379	353
Progressive Disease	220	305
Study Drug Toxicity	**87**	**14**
Adverse Event Unrelated to Study Drug	**36**	**14**
Withdrawal by Subject	**18**	**7**
Death	**11**	**3**
Maximum Clinical Benefit	2	4
Not Reported	4	4
Poor/Non-Compliance	0	2
Subject No Longer Met Study Criteria	1	0

Results First Received: May 16, 2016. CT.GOV

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Subject No Longer Met Study Criteria	1	0

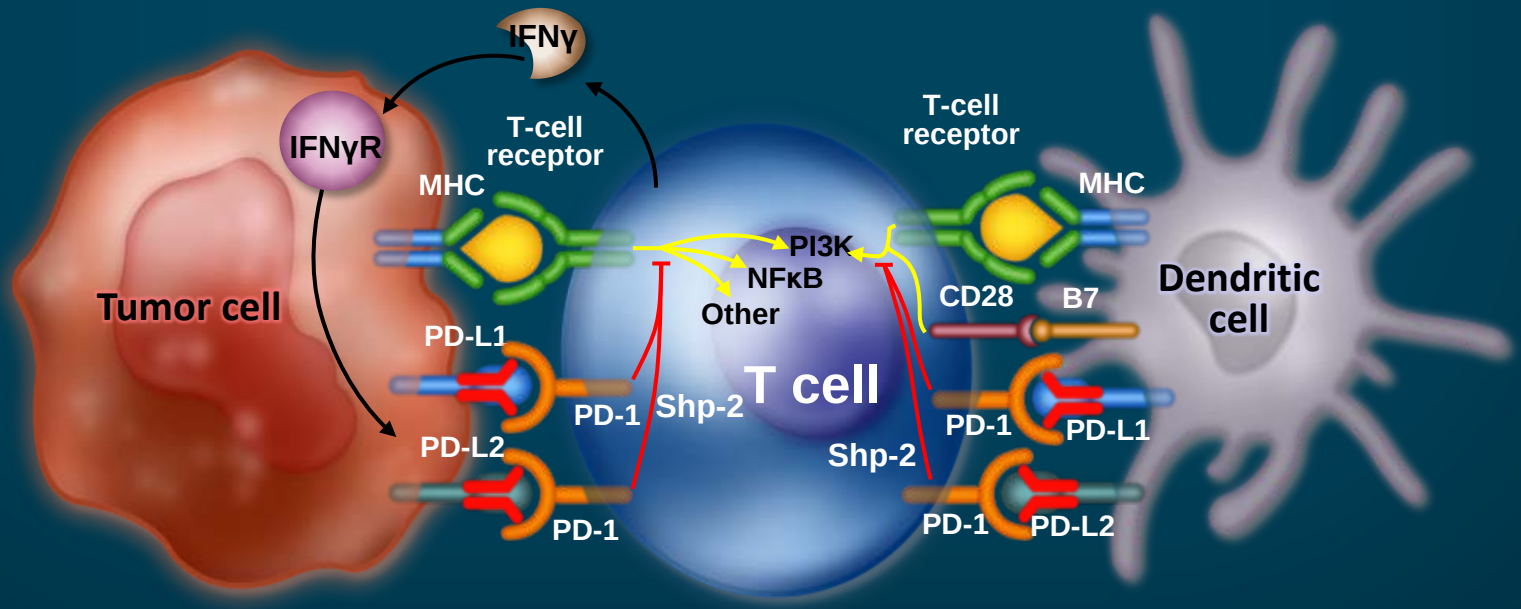
152

38

Results First Received: May 16, 2016. CT.GOV

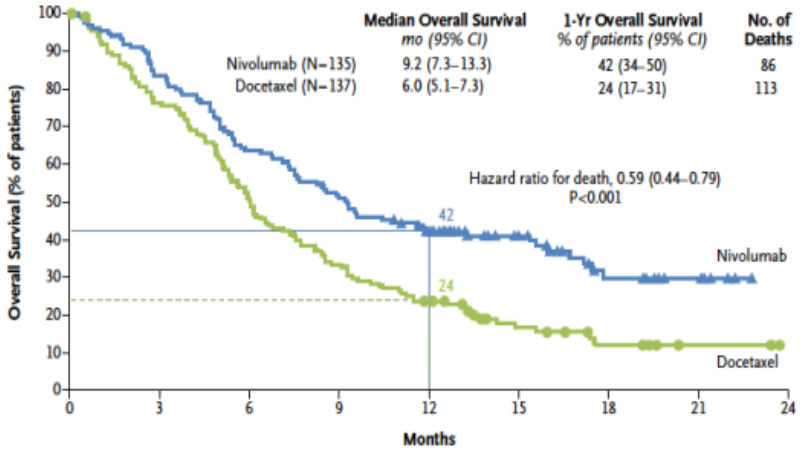
Anti-PD-1/PD-L1 Antibodies:
Mechanism of Action

- PD-1 expression on tumor-infiltrating lymphocytes (TILs) associated with decreased cytokine production and effector function; binding with PDL1 and PDL2 on tumor cells disables T cell function
- 3 Approved Drugs target PD1 and PDL1 in NSCLC:
  - **Nivolumab/pembrolizumab** bind PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function
  - **Atezolizumab** binds PD-L1 receptors

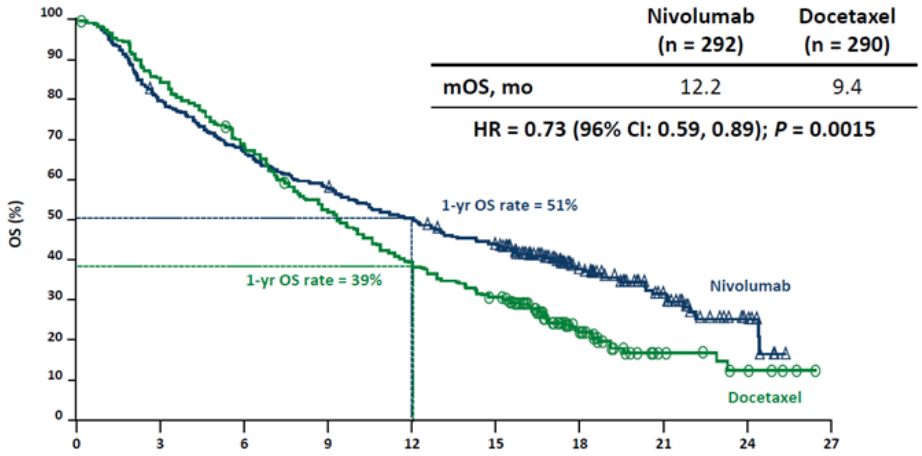


PD1/PD-L1 Inhibitors increased Overall Survival

CHECKMATE 017



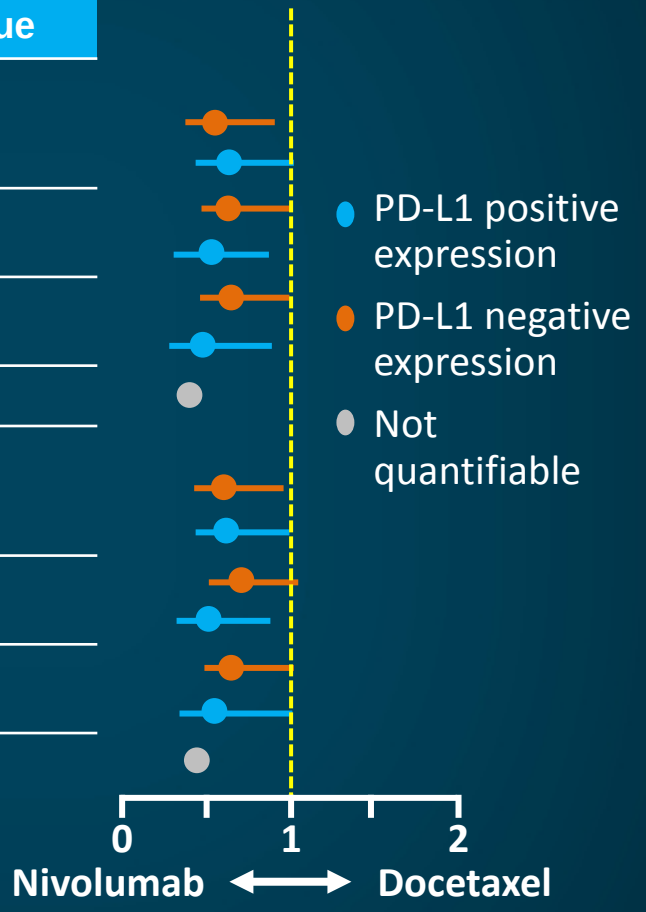
CHECKMATE 057



Brahmer NEJM 2015 Borghaei, NEJM 2015
Herbst Lancet 2016. Rittmeyer Lancet 2017

CheckMate 017: Survival Benefit by PD-L1 Expression

PD-L1 Expression	Patients, n		Unstratified HR (95% CI)	Interaction *P*-value
	Nivolumab	Docetaxel		
OS				
<1%	54	52	0.58 (0.37–0.92)	**0.56**
≥1%	63	56	0.69 (0.45–1.06)	
<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)	

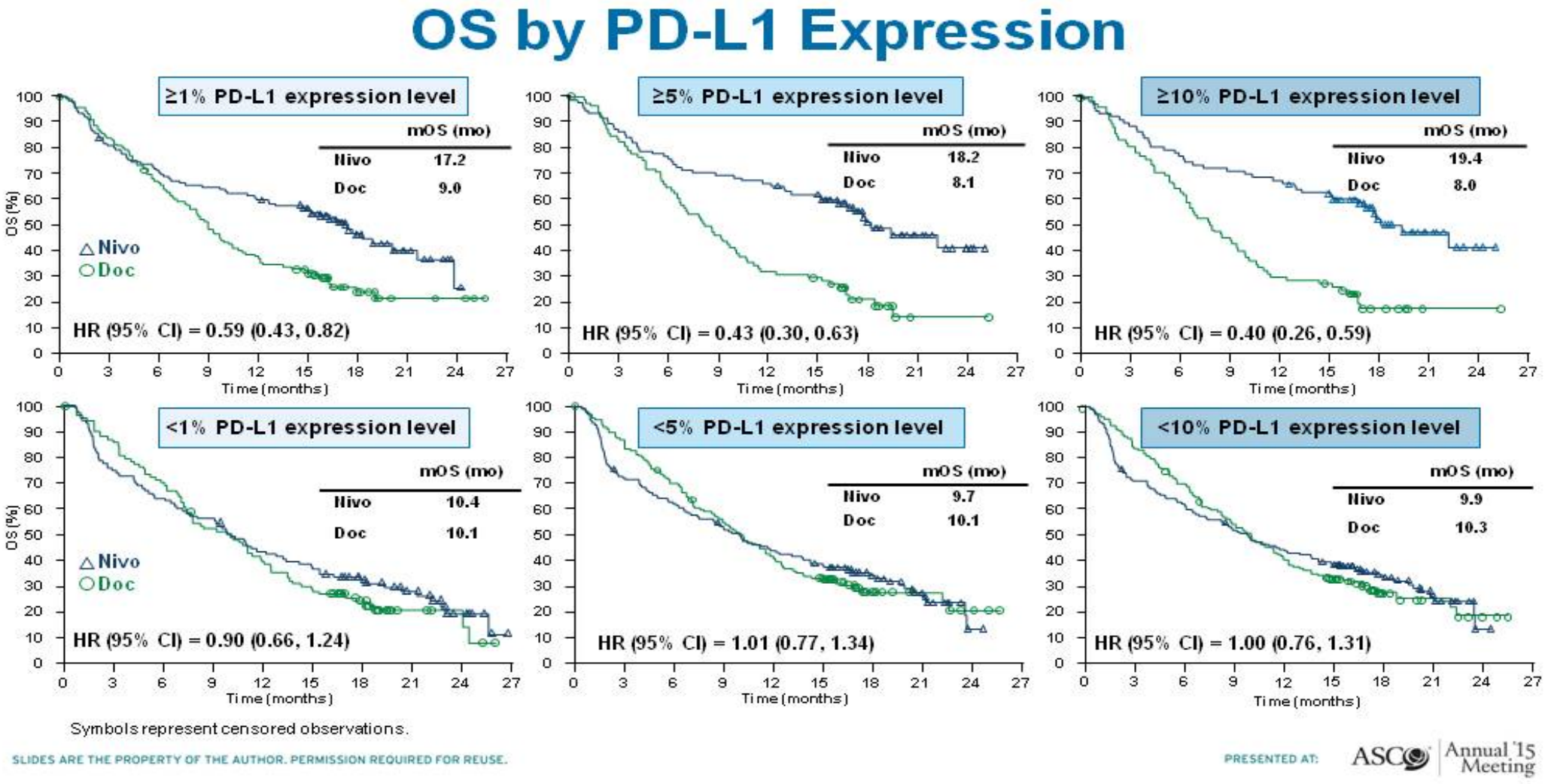


Nivolumab benefit was independent of PD-L1 expression.

83% of patients (225/272) had quantifiable PD-L1 expression. Based on December 2014 DBL

Reckamp K et al. WCLC meeting. 2015:abstract 02.01.

CheckMate 057: Survival Benefit by PD-L1 Expression



Presented By Luis Paz-Ares at 2015 ASCO Annual Meeting

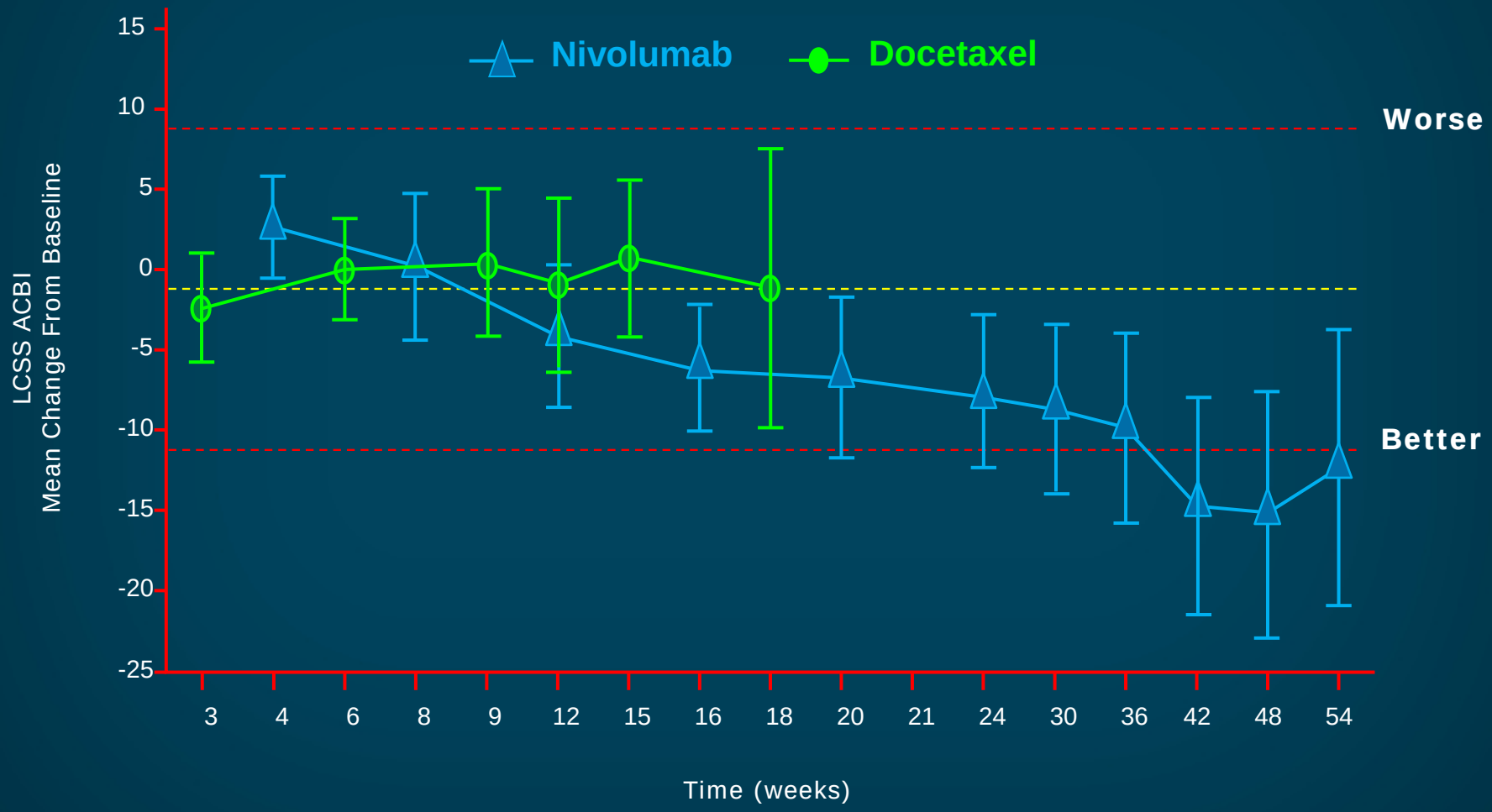
CheckMate 017: Objective Response Rate

	Nivolumab (n = 135)	Docetaxel (n = 137)
ORR, % (95% CI)	20 (14–28)	9 (5–15)
P value[a]	0.0083	
Best overall response, %		
Complete response	1[b]	0
Partial response	19	9
Stable disease	29	34
Progressive disease	41	35
Unable to determine	10	22
Median DOR[c], mos. (range)	NR (2.9–21+)	8.4 (1.4+–15+)
Median time to response[c], mos. (range)	2.2 (1.6–12)	2.1 (1.8–9.5)
Ongoing response, % (no. ongoing/total responders)	63 (17/27)	33 (4/12)

[a]Based on two-sided stratified Cochran-Mantel-Haenszel test on estimated odds ratio of 2.6 (95% CI: 1.3–5.5). [b]One pt experienced complete response. [c]Values are for all confirmed responders per RECIST v1.1 (nivolumab, n = 27; docetaxel, n = 12).
Symbol "+" indicates a censored value.

Reckamp K et al. WCLC meeting. 2015:abstract 02.01.

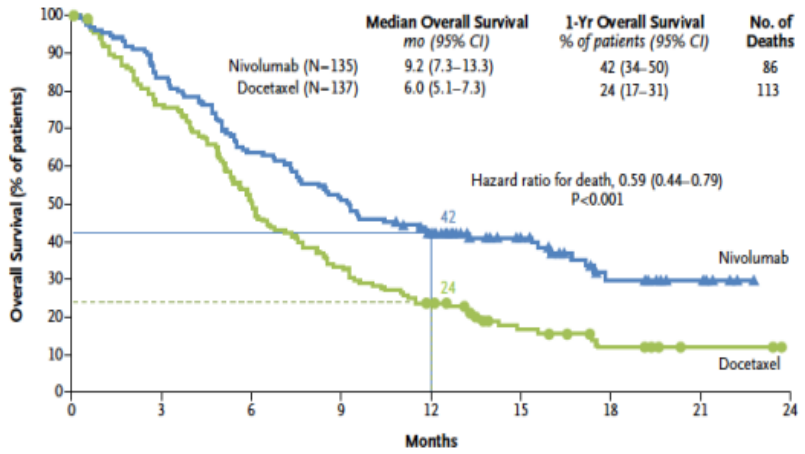
LCSS Average Symptom Burden Index: Mean Change From Baseline While on Treatment



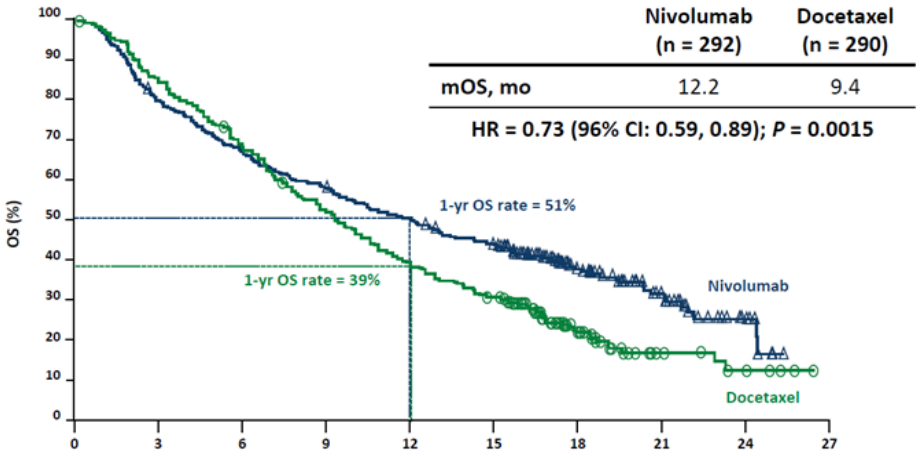
Only time points where data are available for >10 patients are plotted on the graph. MID (minimally important difference) consists of a change of ≥10 points (indicated by dotted lines). Bars represent 95% confidence intervals (based on parametric t-test). Bars that do not cross 0 indicate means that are significantly different from 0.
ASBI = Average Symptom Burden Index

PD1/PD-L1 Inhibitors increased Overall Survival

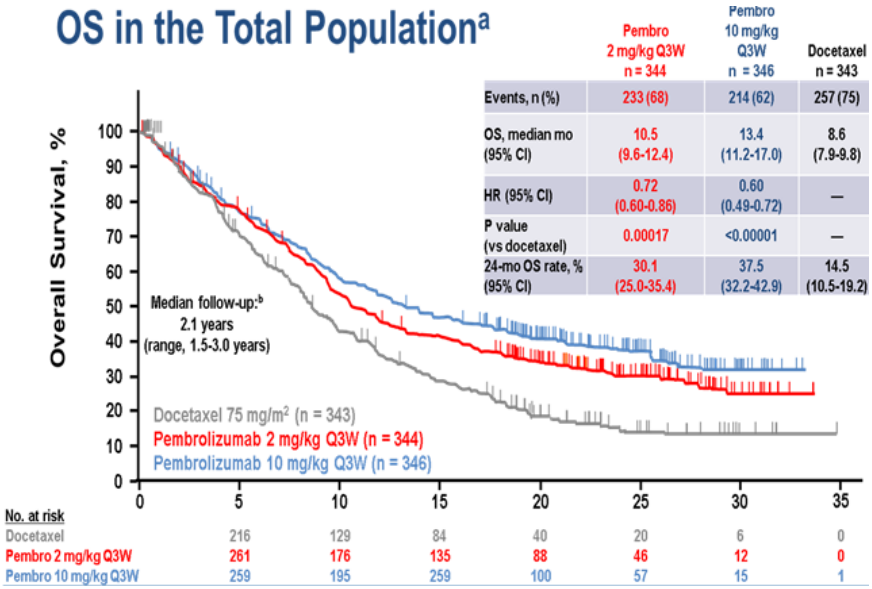
CHECKMATE 017



CHECKMATE 057

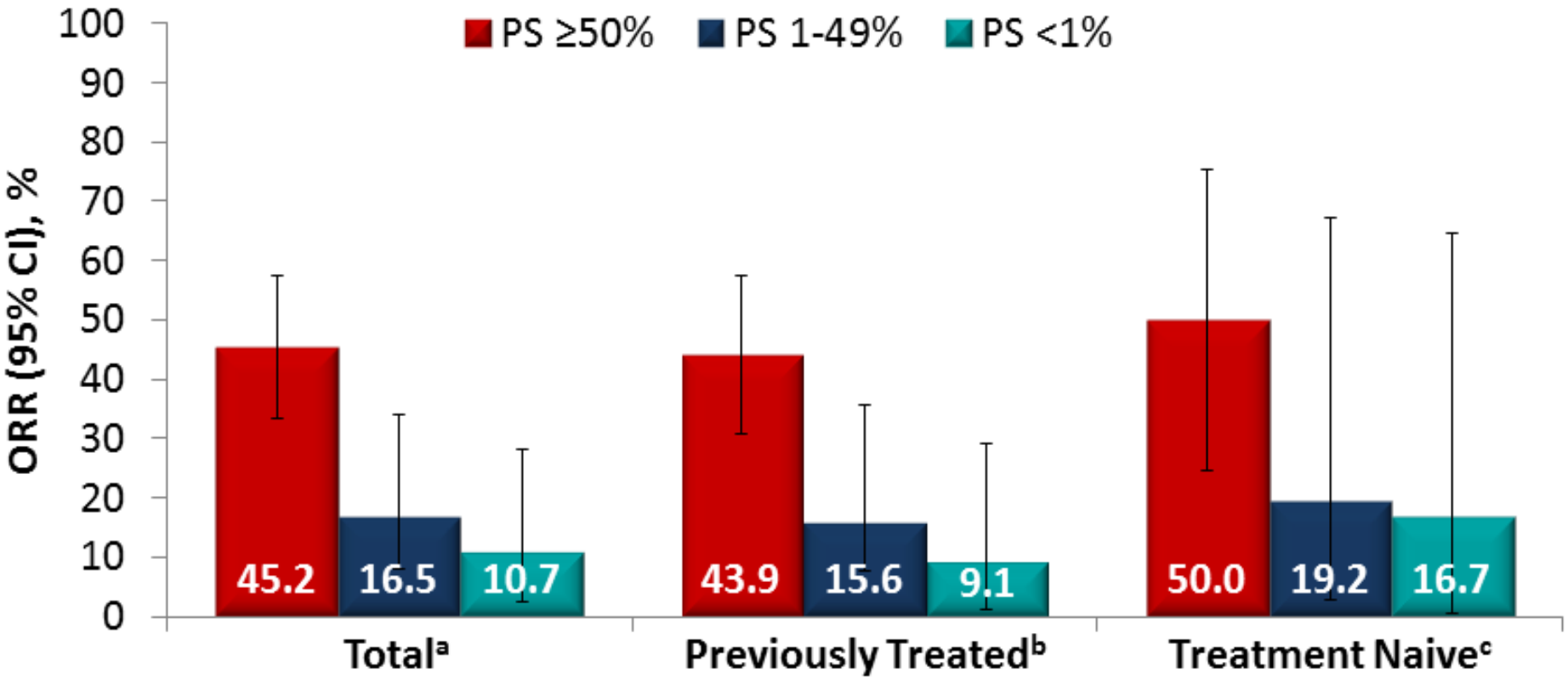


KEYNOTE 010 (TPS ≥ 1%)



Brahmer NEJM 2015 Borghaei, NEJM 2015
Herbst Lancet 2016. Rittmeyer Lancet 2017

ORR by PD-L1 Proportion Score: CTA-Evaluable Validation Set Patients With Measurable Disease

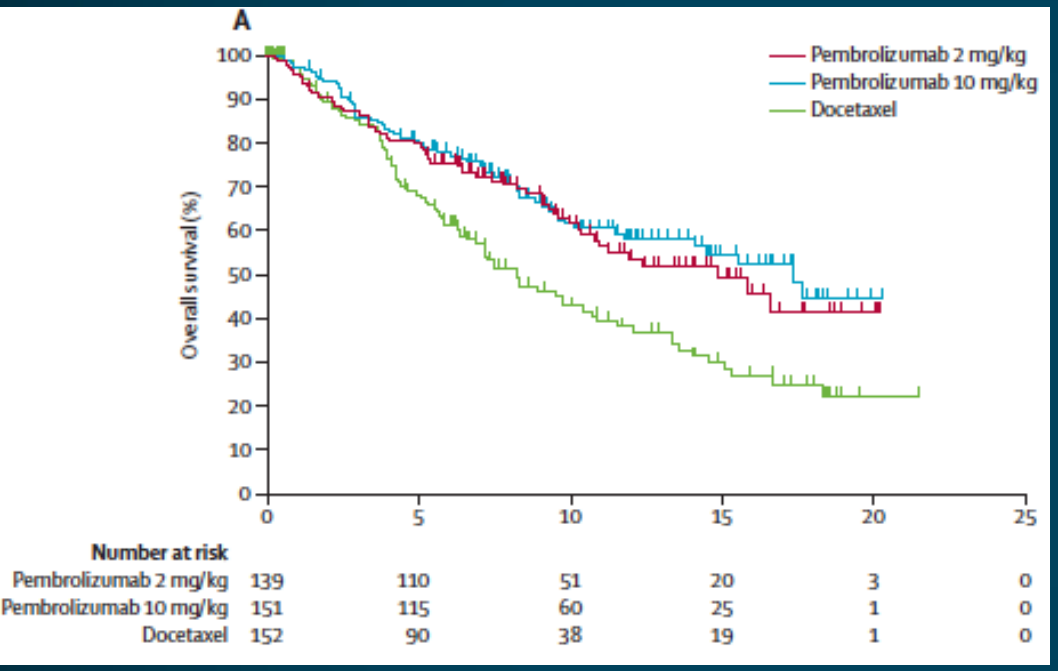


When measurable disease is NOT required, the ORR (95% CI) in the PS ≥50% subgroups are: **42.3%, 41.0%, and 47.1%** in the total, previously treated, and treatment-naive populations[d]

[a]n = 73, 103, and 28, respectively. [b]n = 57, 77, and 22, respectively. [c]n = 16, 26, and 6, respectively. [d]n = 78, 61, and 17, respectively.
ORR was assessed per RECIST v1.1 by central review in the biomarker-evaluable population (ie, patients with measurable disease per RECIST v1.1 by central review at baseline whose slides were cut within 6 months of staining and for which a proportion score could be assigned).
Analysis cut-off date: August 29, 2014.

KEYNOTE-010: Pembrolizumab vs docetaxel

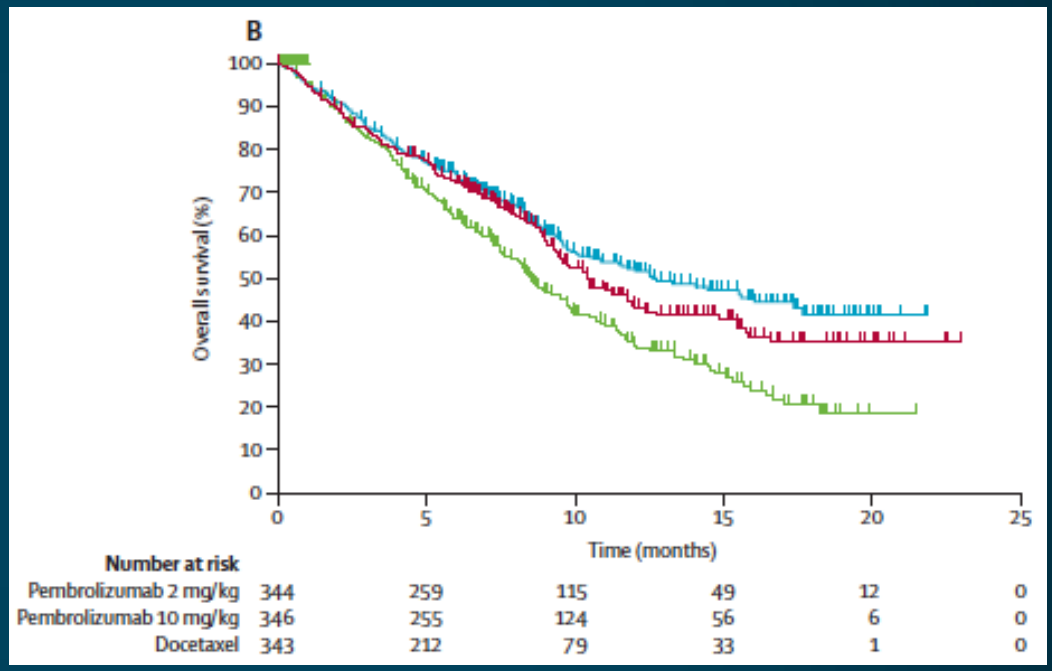
22C3 PS ≥50%



Pembro 2 mg/kg vs. docetaxel HR 0.54 (14.9 mo vs. 8.2 mo; 95% CI 0.38–0.77; *p* = 0.0002)

Pembro 10 mg/kg vs. docetaxel HR 0.50 (17.3 mo vs. 8.2 mo; 0.36–0.70; *p*<0.0001).

22C3 PS ≥1%

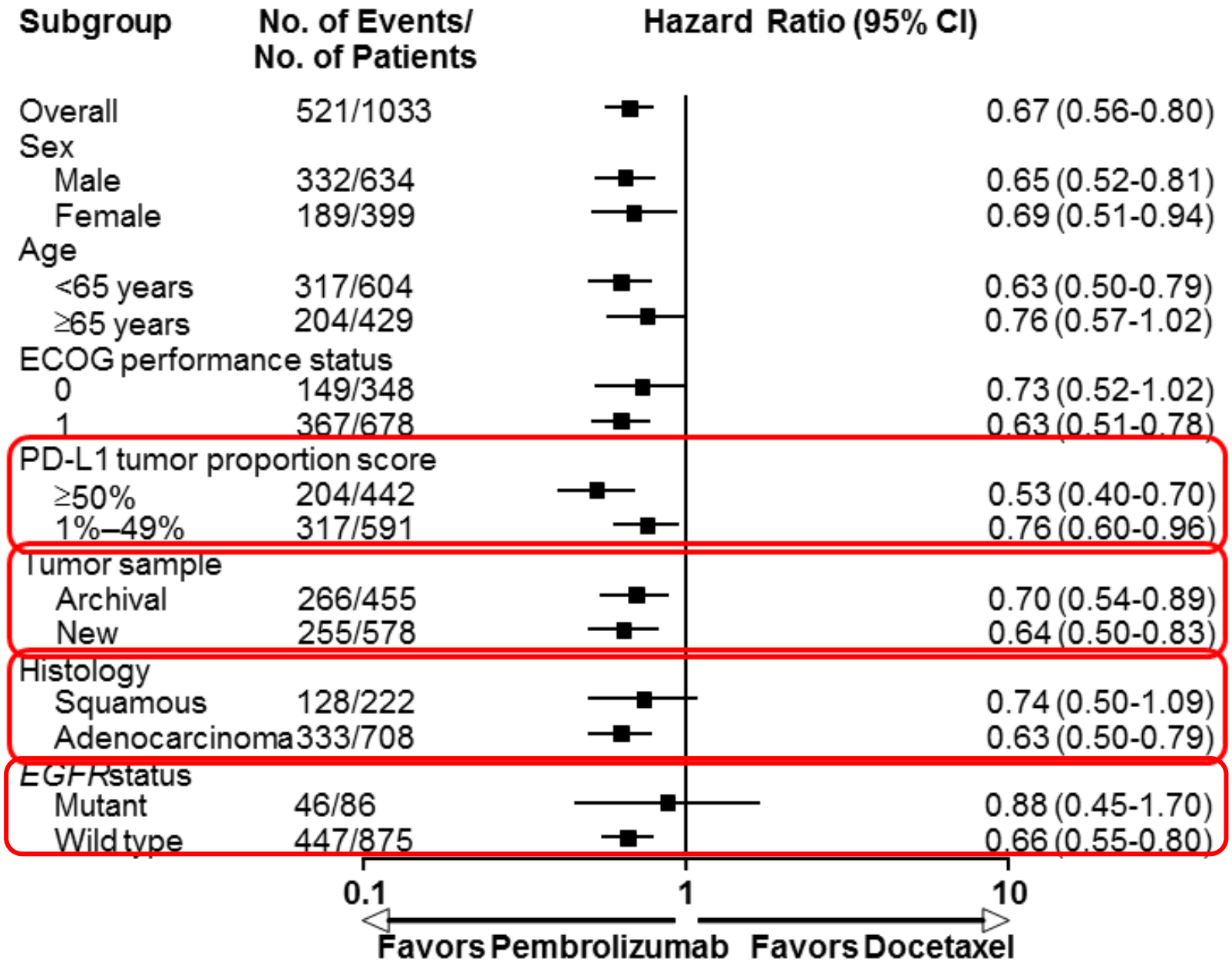


Pembro 2 mg/kg vs. docetaxel HR 0.71 (10.4 mo vs. 8.5 mo; 95% CI 0.58–0.88; *p* = 0.0008)

Pembro 10 mg/kg vs. docetaxel HR 0.61 (12.7 mo vs.8.5 mo; 0.49–0.75; *p*<0.0001)

Herbst et al. *Lancet* 2015.

OS in Key Subgroups, PD-L1 TPS ≥1%[a]

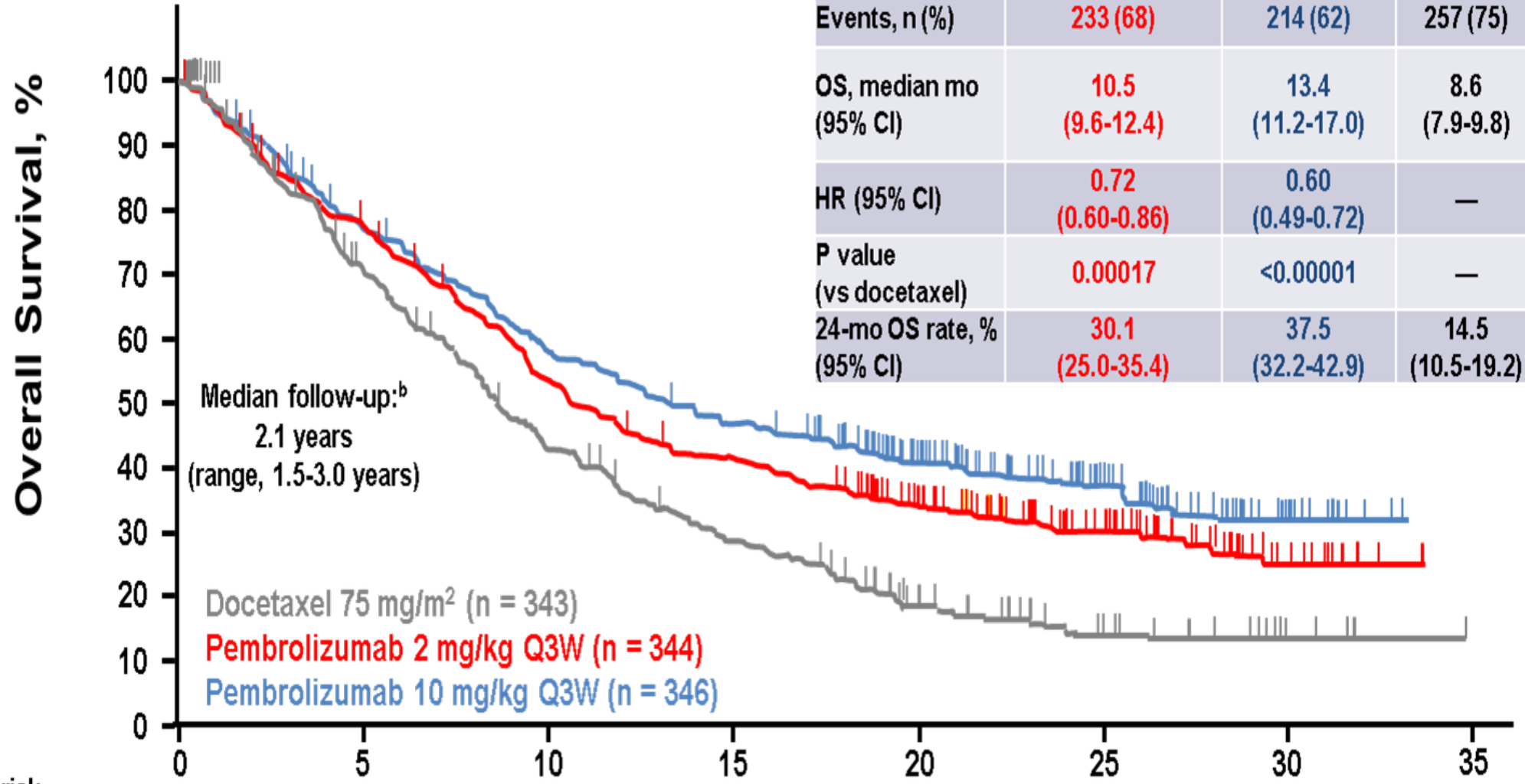


Analysis cut-off date: September 30, 2015.

[a]Data for the pembrolizumab doses were pooled.

OS in the Total Population[a]

	Pembro 2 mg/kg Q3W n = 344	Pembro 10 mg/kg Q3W n = 346	Docetaxel n = 343
Events, n (%)	233 (68)	214 (62)	257 (75)
OS, median mo (95% CI)	10.5 (9.6-12.4)	13.4 (11.2-17.0)	8.6 (7.9-9.8)
HR (95% CI)	0.72 (0.60-0.86)	0.60 (0.49-0.72)	—
P value (vs docetaxel)	0.00017	<0.00001	—
24-mo OS rate, % (95% CI)	30.1 (25.0-35.4)	37.5 (32.2-42.9)	14.5 (10.5-19.2)



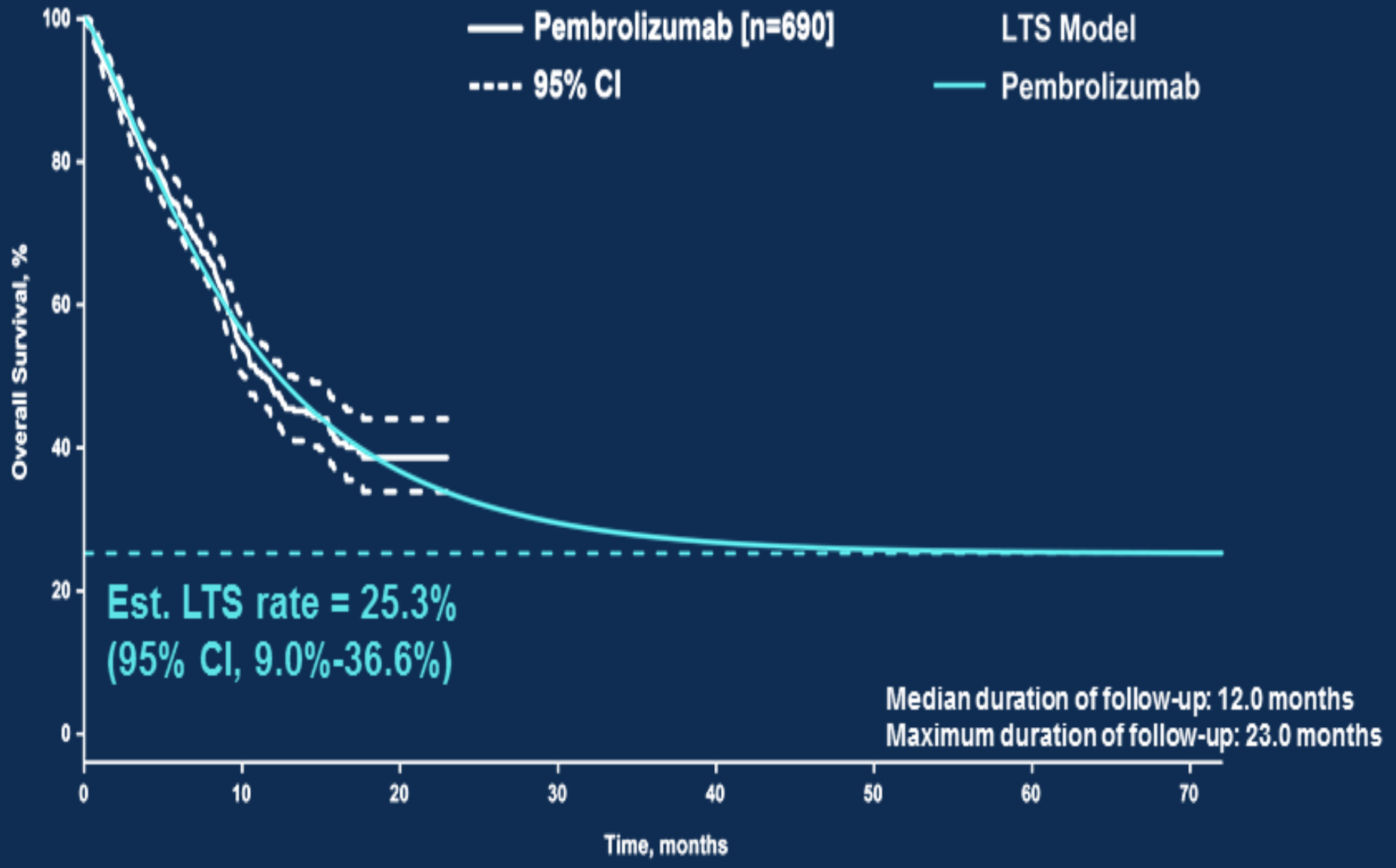
No. at risk

Docetaxel	216	129	84	40	20	6	0
Pembro 2 mg/kg Q3W	261	176	135	88	46	12	0
Pembro 10 mg/kg Q3W	259	195	259	100	57	15	1

[a]Comparison of pembrolizumab vs docetaxel. Data are an additional 12 months of follow-up from the final analysis, [b]Median time from first randomization to current DBL. Data cutoff date: September 30, 2016.

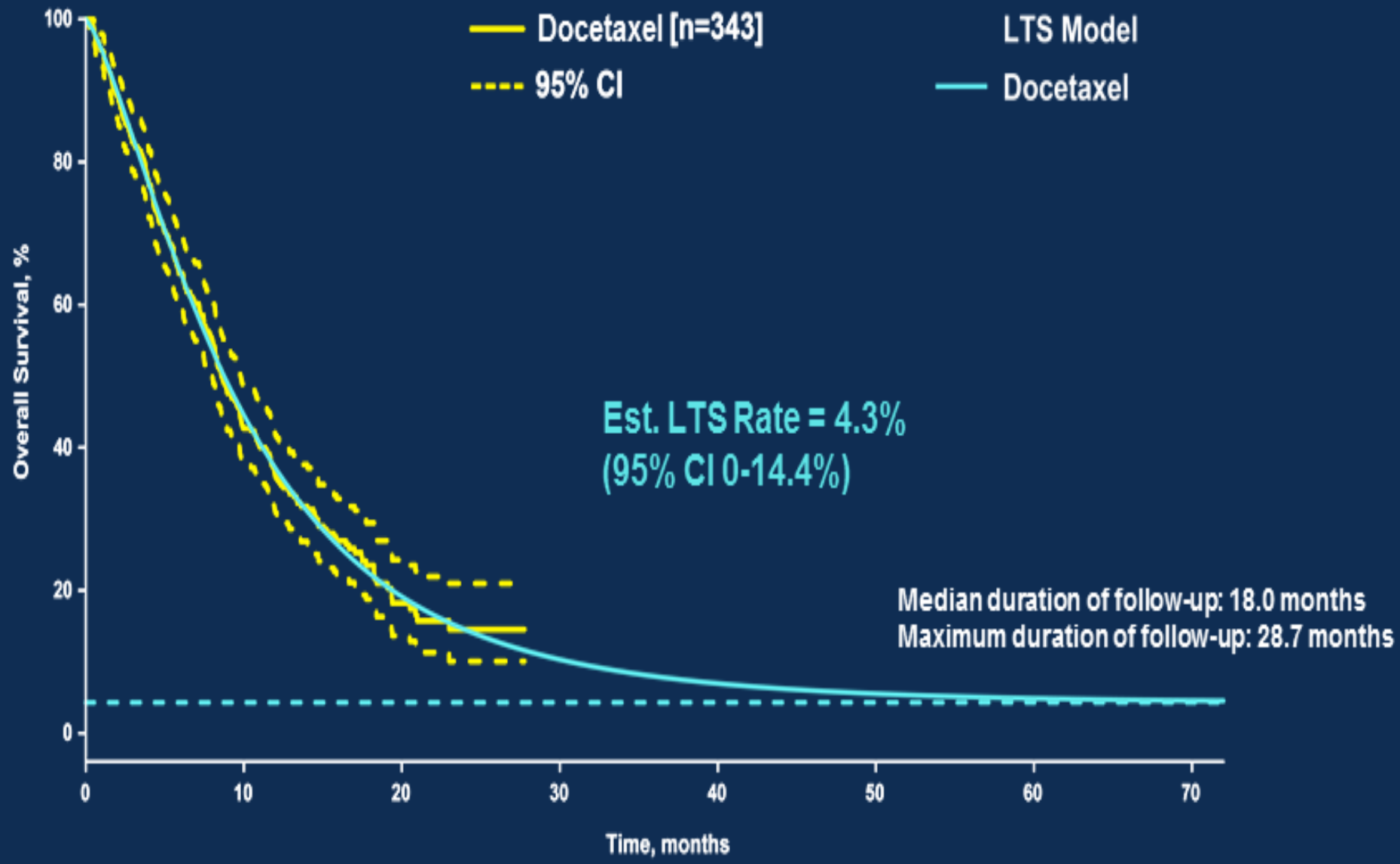
Independent Validation of LTS Estimate Using KEYNOTE-010: Sept 30, 2015 cutoff

Hellmann, ASCO-SITC, Feb 2017



Comparison of LTS Estimate Using KEYNOTE-010: Docetaxel (Data cutoff date: March 31, 2016)

Hellmann, ASCO-SITC, Feb 2017



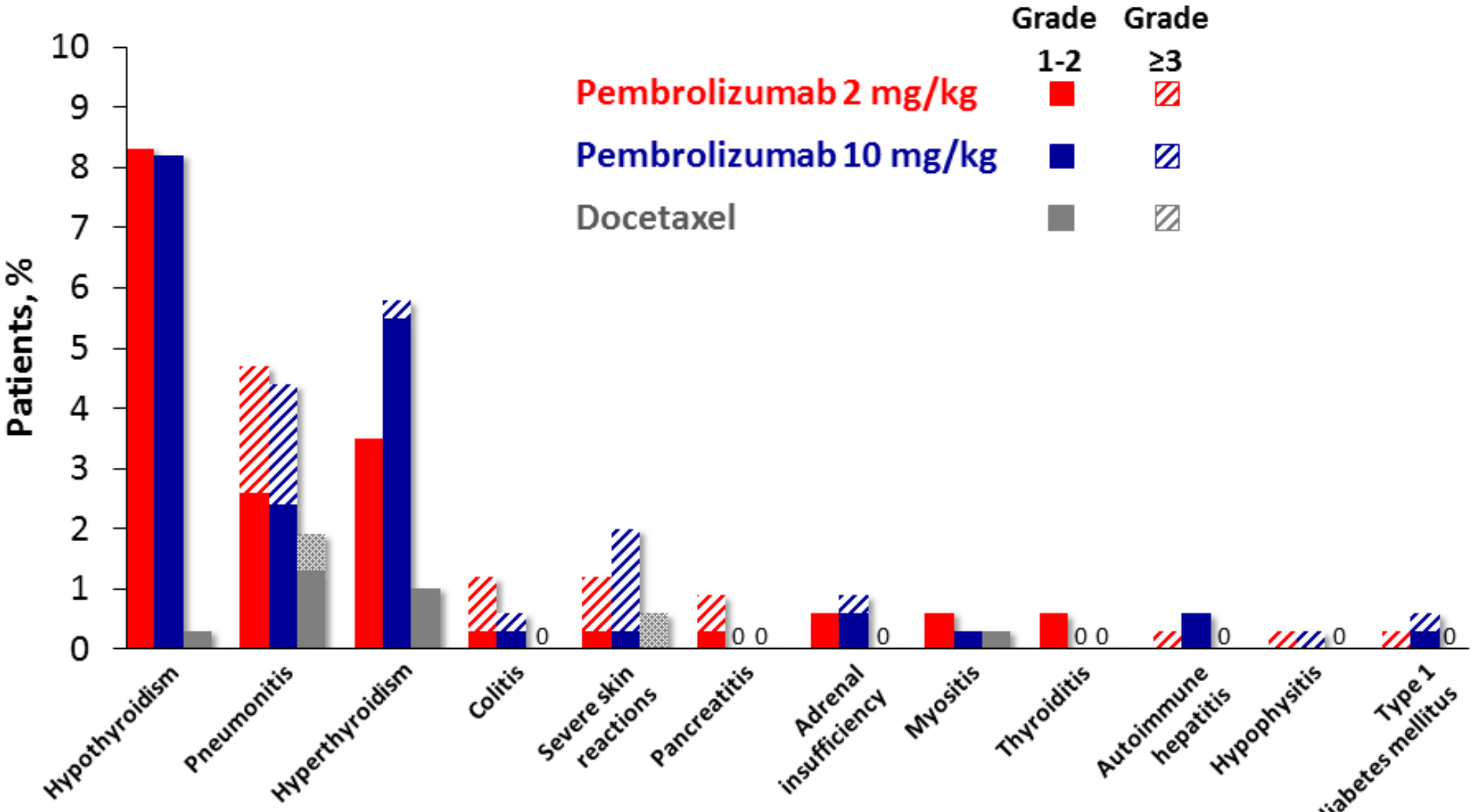
KEYNOTE 010: Safety

Related to treatment*	Pembrolizumab 2 mg/kg (n = 339)		Pembrolizumab 10 mg/kg (n = 343)		Docetaxel (n = 309)	
	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
Any	**215 (63%)**	**43 (13%)**	**226 (66%)**	**55 (16%)**	**251 (81%)**	**109 (35%)**
Occurring in ≥10% of patients in any group						
Decreased appetite	46 (14%)	3 (1%)	33 (10%)	1 (<1%)	49 (16%)	3 (1%)
Fatigue	46 (14%)	4 (1%)	49 (14%)	6 (2%)	76 (25%)	11 (4%)
Nausea	37 (11%)	1 (<1%)	31 (9%)	2 (1%)	45 (15%)	1 (<1%)
Rash	29 (9%)	1 (<1%)	44 (13%)	1 (<1%)	14 (5%)	0 (0%)
Diarrhea	24 (7%)	2 (1%)	22 (6%)	0 (0%)	56 (18%)	7 (2%)
Asthenia	20 (6%)	1 (<1%)	19 (6%)	2 (1%)	35 (11%)	6 (2%)
Stomatitis	13 (4%)	0 (0%)	7 (2%)	1 (<1%)	43 (14%)	3 (1%)
Anemia	10 (3%)	3 (1%)	14 (4%)	1 (<1%)	40 (13%)	5 (2%)
Alopecia	3 (1%)	0 (0%)	2 (1%)	0 (0%)	101 (33%)	2 (1%)
Neutropenia	1 (<1%)	0 (0%)	1 (<1%)	(0%)	44 (14%)	38 (12%)

***Decided by the investigator. Events are listed in descending frequency in the pembrolizumab 2 mg/kg group. †Irrespective of attribution to study drug. Events are listed in descending order of frequency in the pembrolizumab 2 mg/kg group. ‡Includes patients with interstitial lung disease (one in the pembrolizumab 2 mg/kg group, two in the pembrolizumab 10 mg/kg group, and two in the docetaxel group). §Includes one patient with acute pancreatitis.**

Herbst RS et al. *Lancet*. 2016;387:1540-1550.

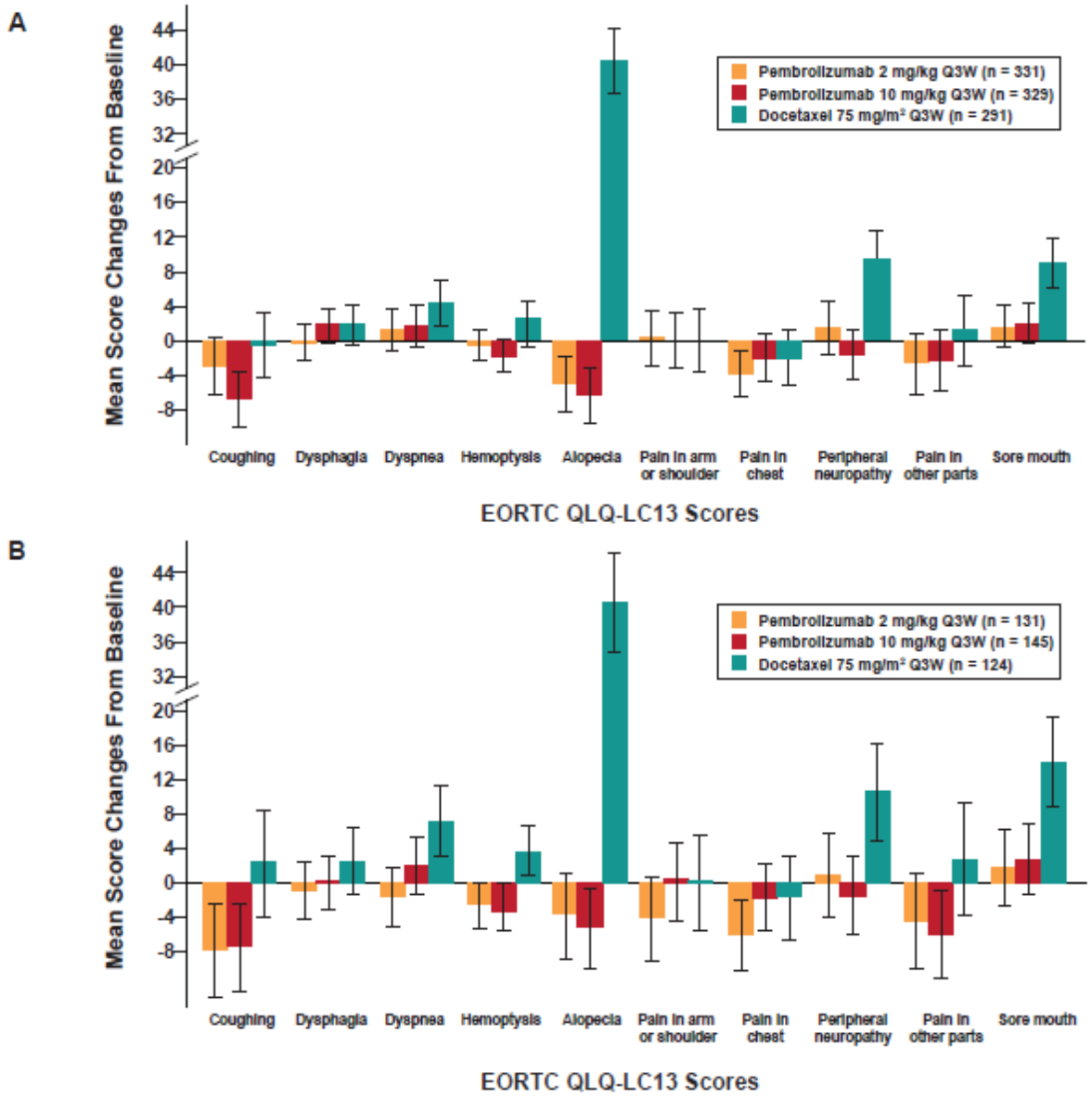
Immune-Mediated AEs Occurring in ≥2 Patients in the Pembrolizumab Arms



Analysis cut-off date: September 30, 2015.

EORTC QLQ-LC13 SYMPTOMS

Change from baseline to week 12 in EORTC QLQ-LC13 symptoms by PD-L1 TPS (FAS population).† (A) PD-L1 TPS ≥1%. (B) PD-L1 TPS ≥50%.

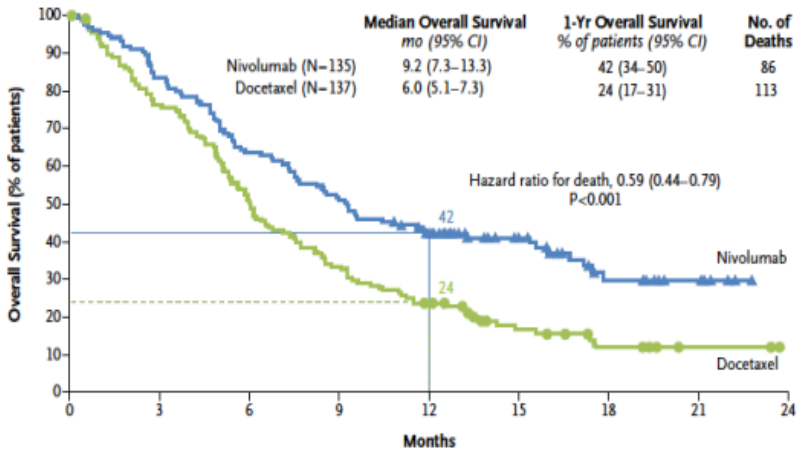


- Patients who received pembrolizumab had significant improvements from baseline in several symptoms across doses and PD-L1 TPS expression, including alopecia, chest pain, coughing, hemoptysis, and pain in other parts. In contrast, patients in the docetaxel arm experienced significant worsening from baseline in many symptoms, including hemoptysis, alopecia, peripheral neuropathy, sore mouth, and dyspnea
- Compared with docetaxel, significant improvements were observed for hemoptysis, alopecia, peripheral neuropathy, sore mouth, and dyspnea among patients receiving pembrolizumab across dose and PD-L1 TPS expression categories

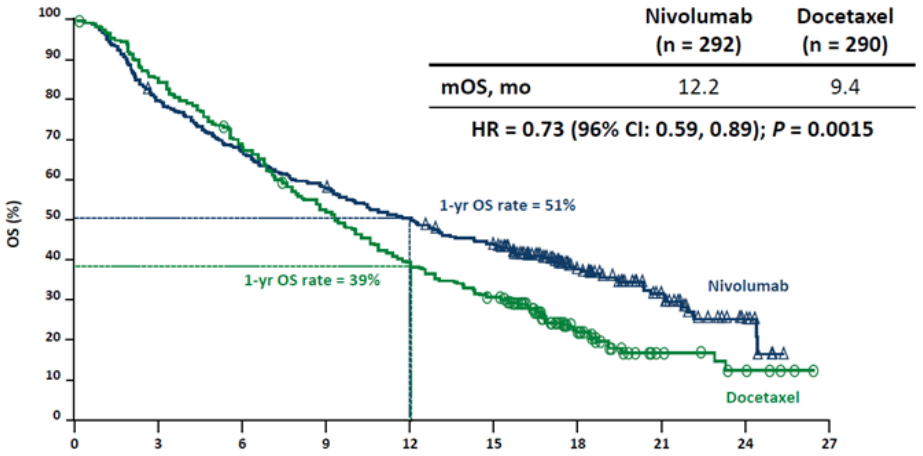
EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13; FAS = full analysis set.
†Error bars are 95% CI. For symptom scores, a negative change from baseline indicates improvement, and a positive change from baseline indicates worsening.

PD1/PD-L1 Inhibitors increased Overall Survival

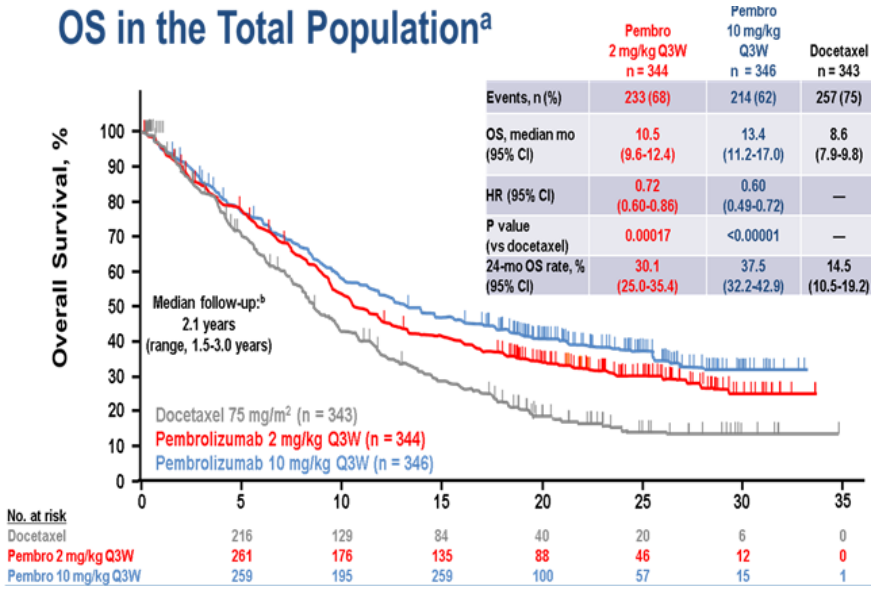
CHECKMATE 017



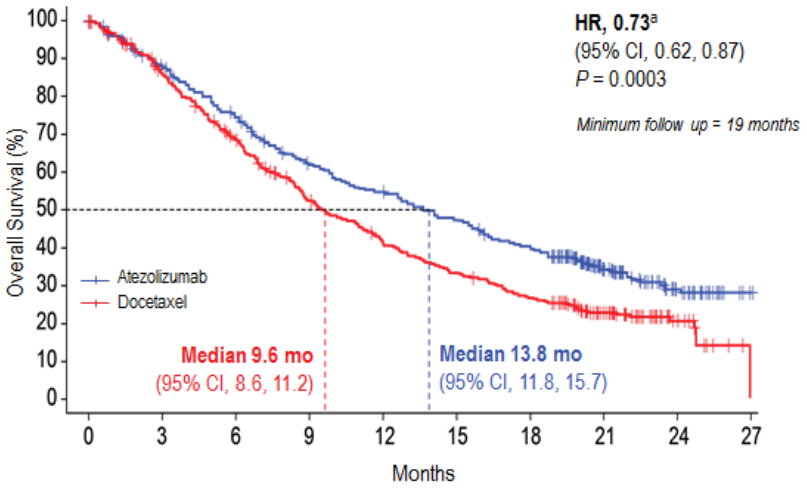
CHECKMATE 057



KEYNOTE 010 (TPS ≥ 50%)

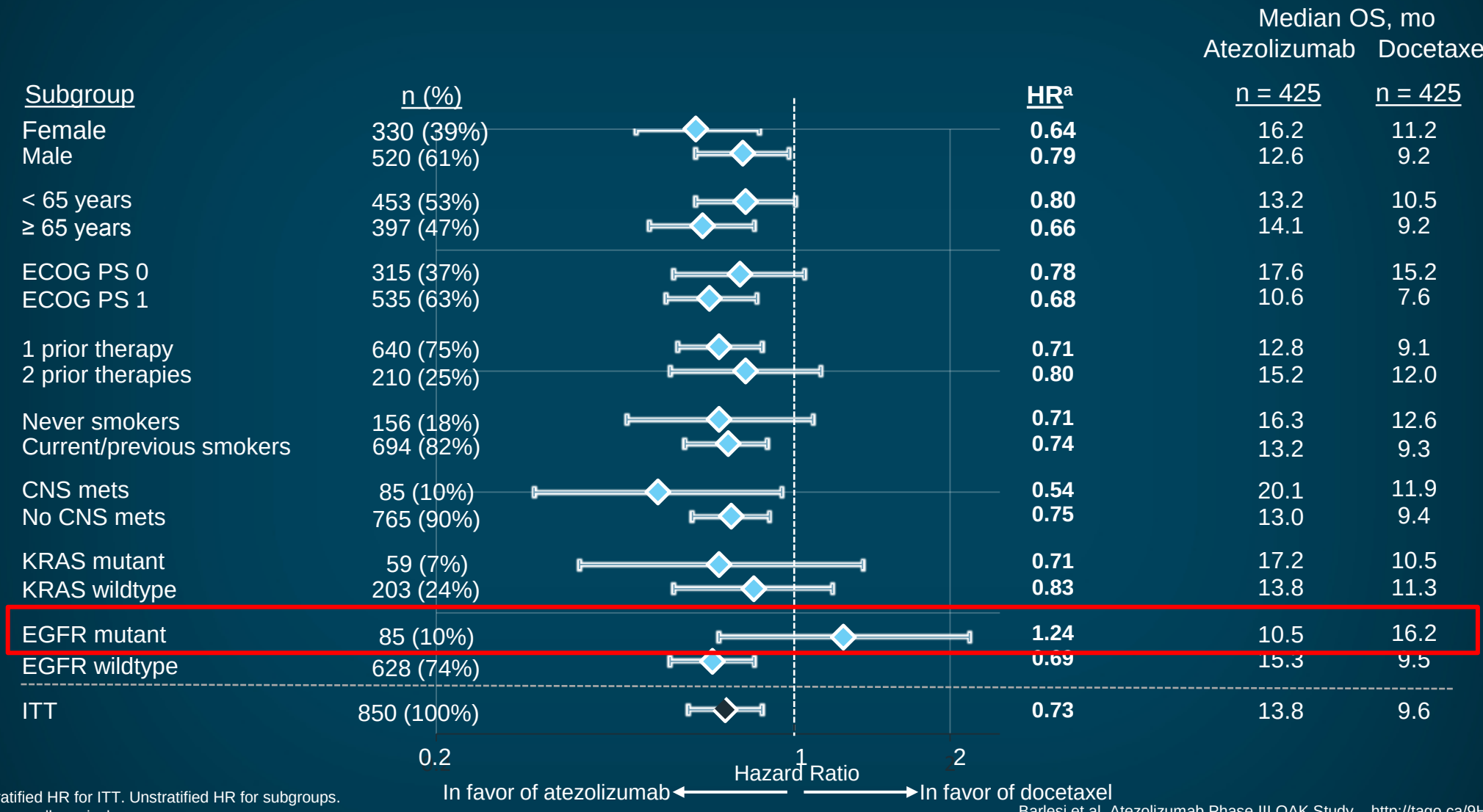


OAK



Brahmer NEJM 2015 Borghaei, NEJM 2015
Herbst Lancet 2016. Rittmeyer Lancet 2017

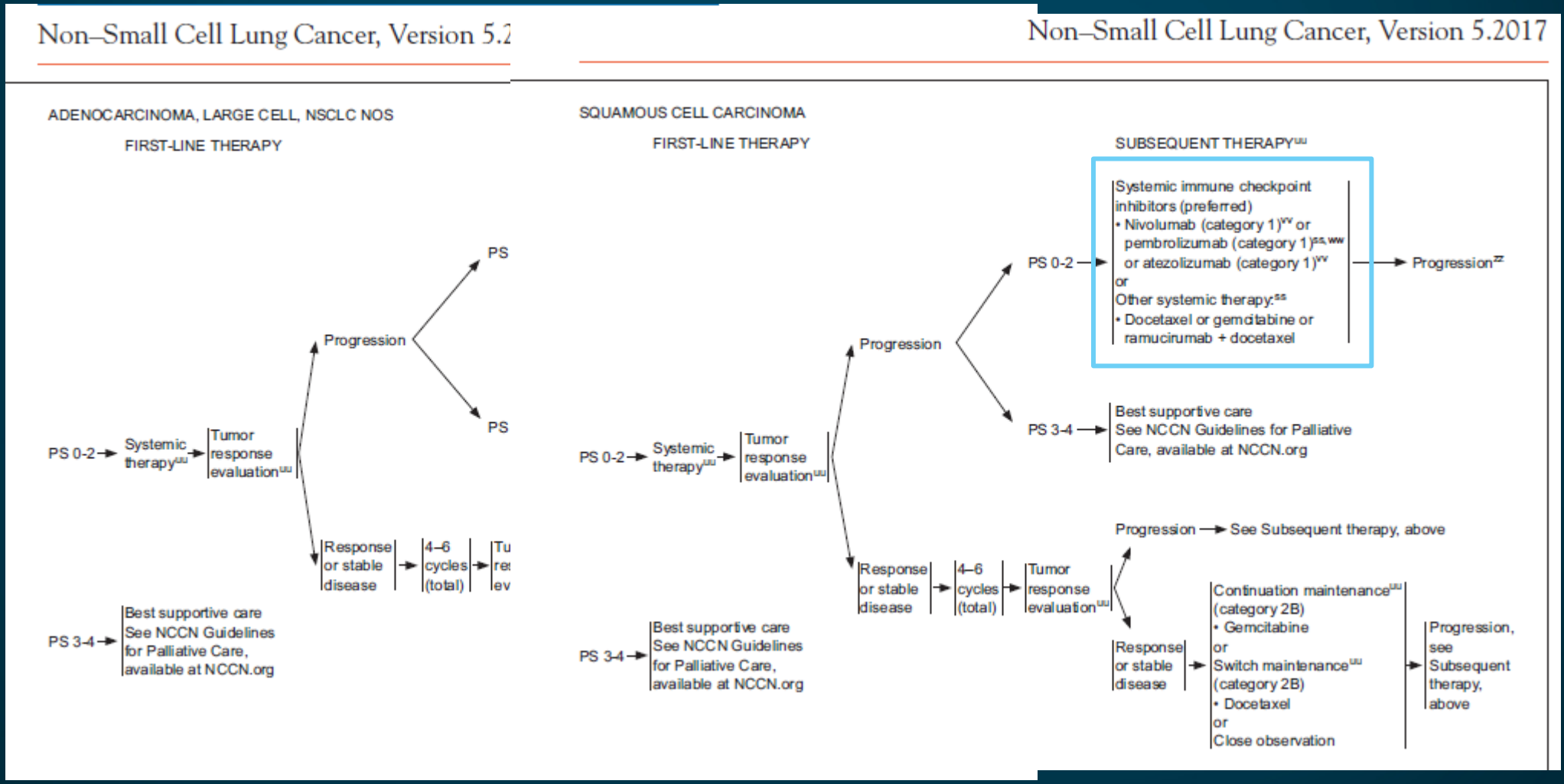
OS IN SELECTED SUBGROUPS



[a]Stratified HR for ITT. Unstratified HR for subgroups.
OS, overall survival.

Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

Latest Version NCCN Guideline (2017 Version 5)



What about front-line Tx?

Keynote 24

Keynote 21 – Cohort G

Merck's KEYTRUDA® (pembrolizumab) Demonstrates Superior Progression-Free and Overall Survival Compared to Chemotherapy as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer

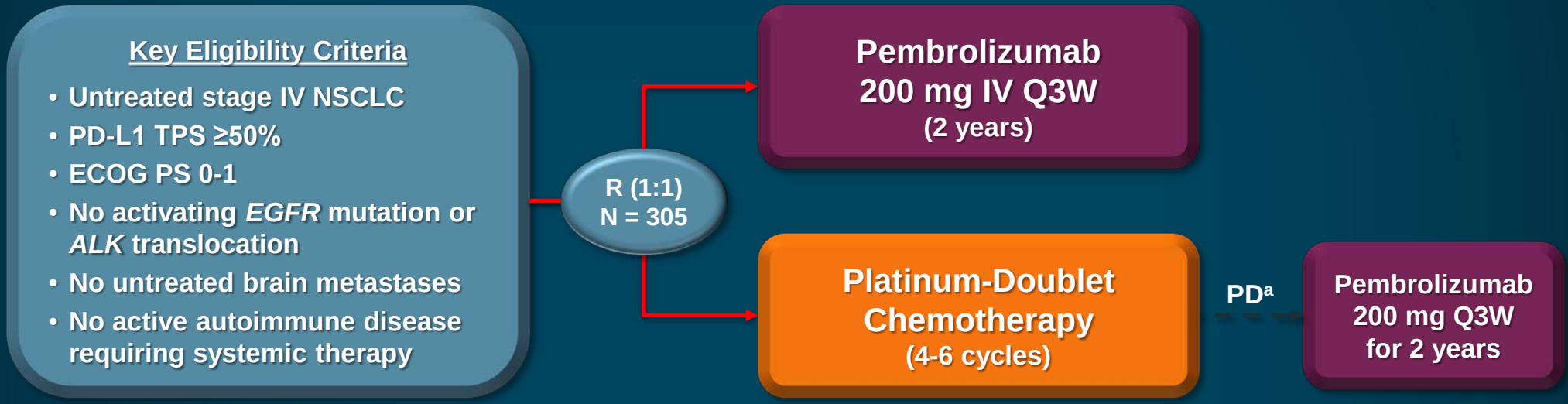
KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1

June 16, 2016 06:45 AM Eastern Daylight Time

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the KEYNOTE-024 trial investigating the use of KEYTRUDA® (pembrolizumab), in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1 (tumor proportion score of 50 percent or more), met its primary endpoint. In this trial, KEYTRUDA was superior compared to chemotherapy for both the primary endpoint of progression-free survival (PFS), and the secondary endpoint of overall survival (OS). Based on these results, an independent Data Monitoring Committee (DMC) has recommended that the trial be stopped, and that patients receiving chemotherapy in KEYNOTE-024 be offered the opportunity to receive KEYTRUDA.

"We believe that the KEYNOTE-024 results have the potential to change the therapeutic paradigm in first-line treatment of non-small-cell lung cancer."

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

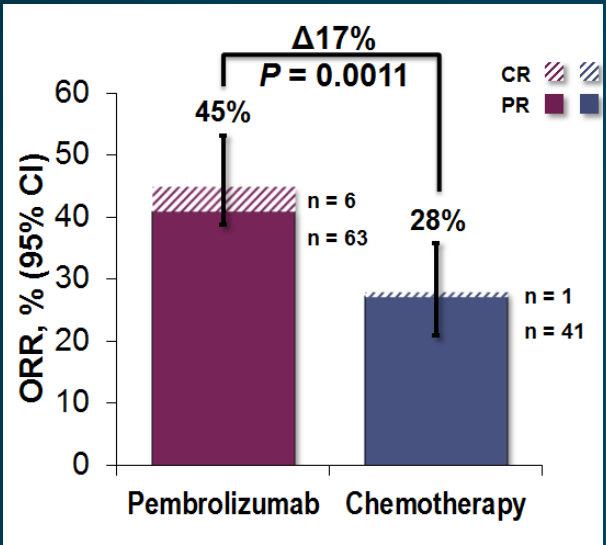
Primary: PFS (RECIST v1.1 per blinded, independent central review)

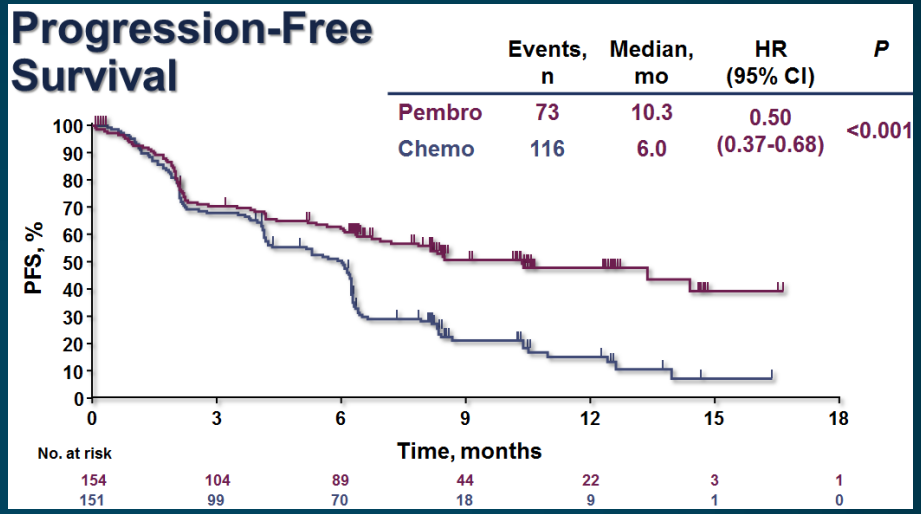
Secondary: OS, ORR, safety

Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Efficacy data: KEYNOTE- 24

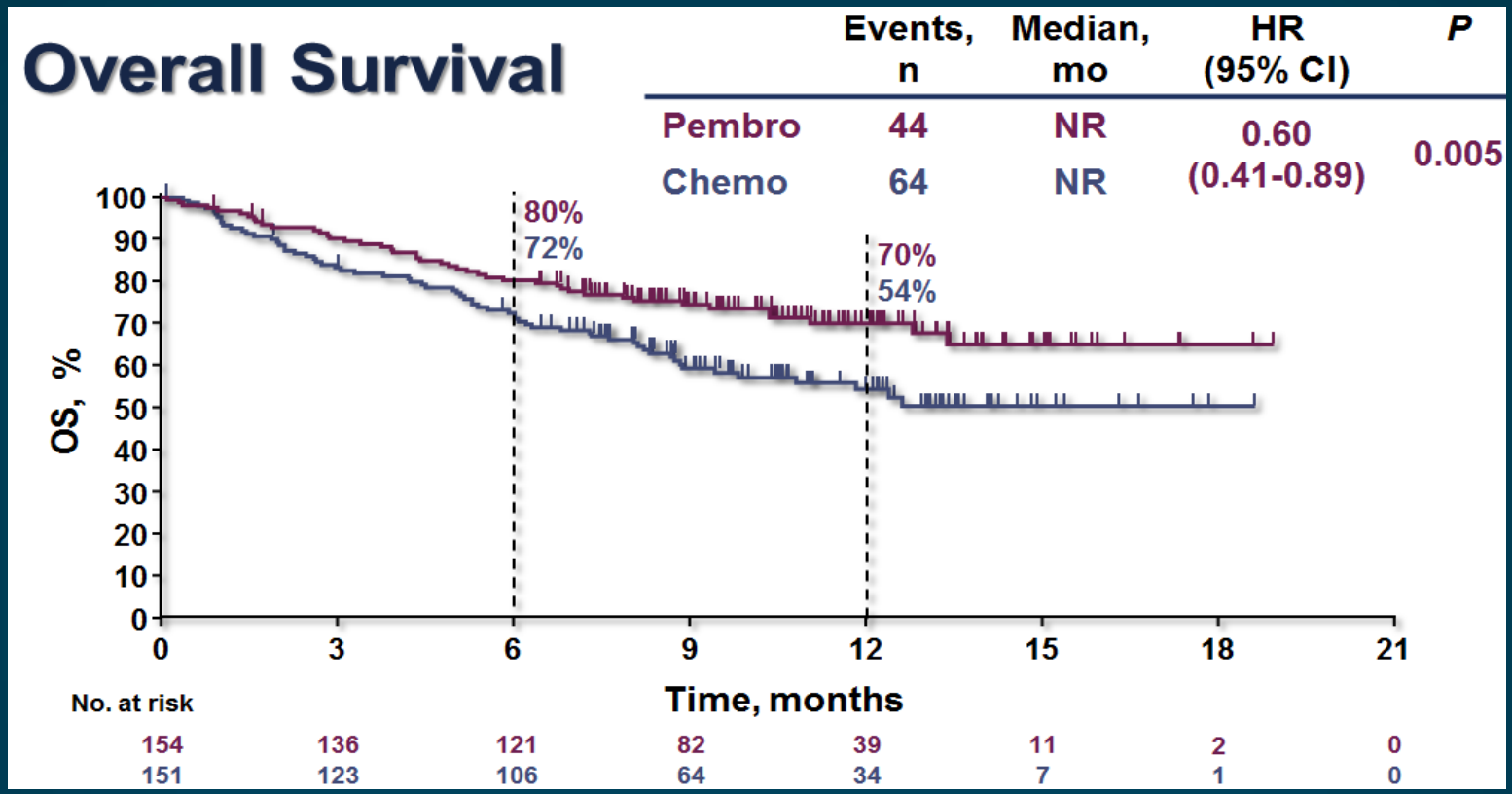




imaging was every 9 weeks

- **Clear and strong signal of activity**
  - → ORR is improved, with a control arm that performs as expected (based on other phase III trials)
  - → 45% ORR is the one of best RRs ever reported in 1st line setting (and with monotherapy !)
  - → Time to Response is identical between Pembro and Chemo
  - → PFS is improved by 4.3 months (HR of 0.50)
  - → Improvement of PFS in all subgroups (except female/never smokers => lower mutational load ?)
  - → Strongest signal of PFS benefit observed in SqCC (HR of 0.35)

KEYNOTE 24: Survival data



- **Clearcut survival benefit for NSCLC pts with PDL1 ≥ 50%**
  - Estimated rate of OS @ 12 months: 70% (Pembro) vs 54% (CT)
  - HR for death: 0.60
  - Despite cross-over in 50% of patients on the control arm

KEYNOTE-024: Change From Baseline in HRQoL at Week 15

EORTC QLQ-C30 Global Health Status			
	Units	**Pembrolizumab n=150**	**Chemotherapy n=147**
Baseline	Mean (SD) n	62.2 (22.3) 145	59.8 (22.3) 137
Week 15	Mean (SD) n	71.0 (21.2) 109	63.7 (20.5) 92
CFB	LS Mean (95% CI) n*	+6.9 (3.3-10.6) 150	-0.9 (-4.8 to 3.0) 147
Difference in LS mean (95% CI); *P* value		7.8 (2.8-12.8); *P* = .002	

*Based on constrained longitudinal data analysis model. For baseline and week 15, n is the number of patients with nonmissing assessments at the specific time point; for change from baseline, n is the number of patients in the analysis population in each treatment group.
CFB, change from baseline; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HRQoL, health-related quality of life.
Brahmer JR, et al. WCLC 2016. Presented at: WCLC 2016. Vienna, Austria. Abstract #PL04a.01.

Pembrolizumab Plus Chemotherapy as Front-Line Therapy for Advanced NSCLC: KEYNOTE-021 Cohorts A-C

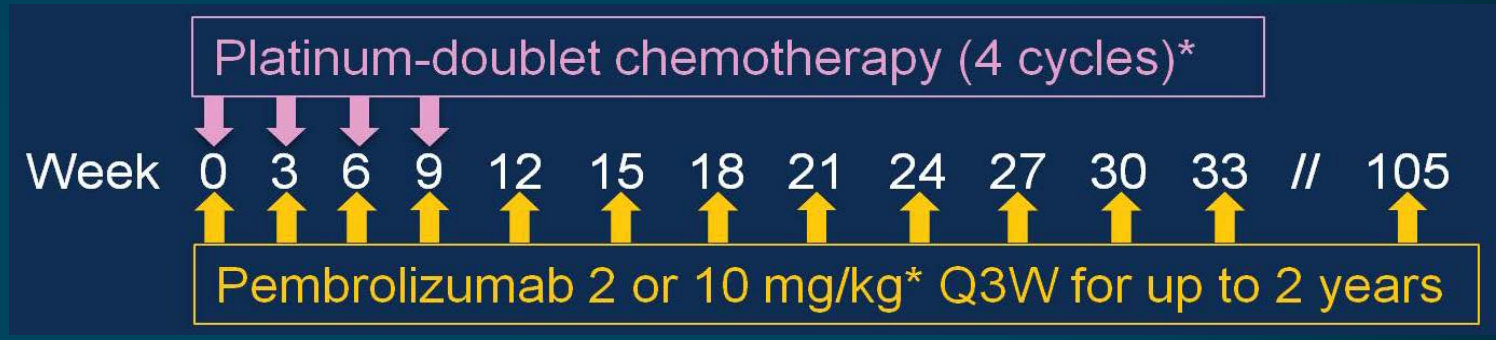
Gadgeel S[1]; Stevenson J[2]; Langer C[3]; Gandhi L[4]; Borghaei H[5]; Patnaik A[6]; Villaruz LC[7]; Gubens M[8]; Hauke R[9]; Yang JC-H[10]; Van Dam Sequist L[11]; Bachman R[12]; Ge J[12]; Raftopoulos H[12]; Papadimitrakopoulou V[13]

Chemotherapy + Pembrolizumab (2mg/kg or 10 mg/kg q3 week)

Cohort A: Carbo/ Pac q3 wk

Cohort B: Carbo/ Pac/ Bev q3 wk

Cohort C: Carbo/ Pem q3 wk

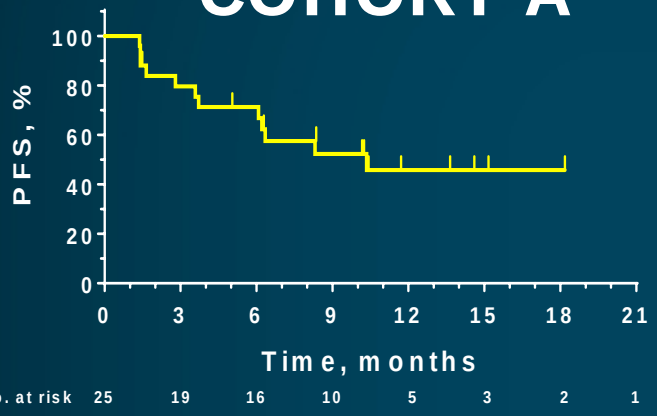


Response	A (N=25)	B (N=25)	C (N=24)	ALL (N=74)
ORR n (%)	13 (52%)	12 (48%)	17 (71%)	42 (57%)
Results based on PDL-1 staining				
TPS ≥ 50%	56%	50%	75%	60%
TPS ≥1%	53%	50%	69%	57%
TPS < 1%	44%	40%	75%	54%

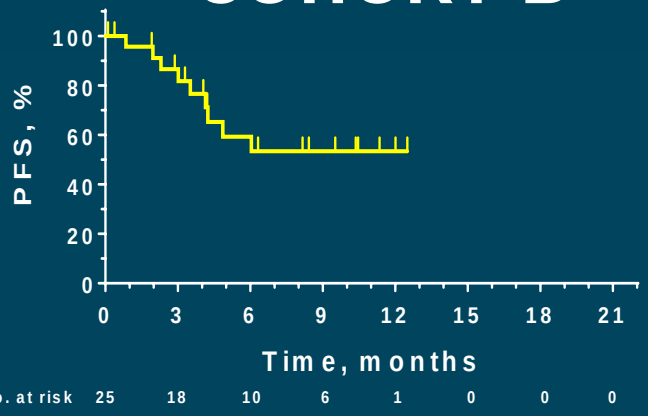
Presented By Shirish Gadgeel at 2016 ASCO Annual Meeting

RESULTS: PFS

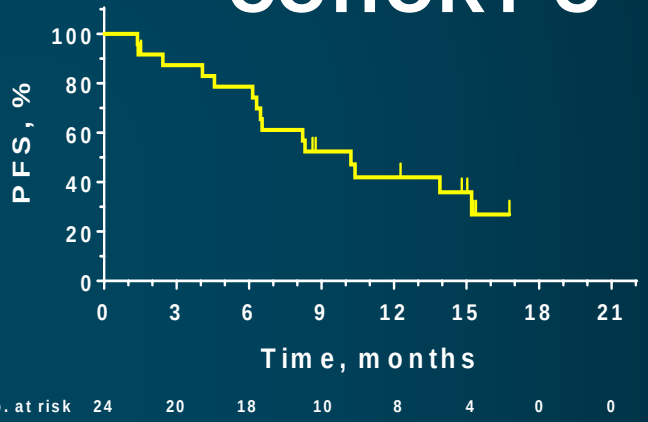
COHORT A



COHORT B



COHORT C

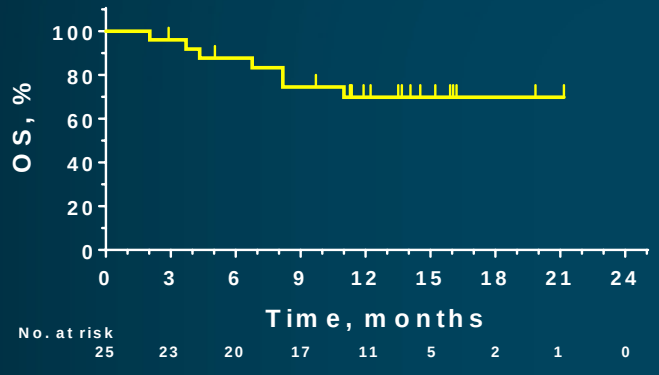


Population	Cohort A: Carbo/Pac			Cohort B: Carbo/Pac/Bev			Cohort C: Carbo/Pem		
	n	No. of events, n (%)	PFS, months, median (95% CI)	n	No. of events, n (%)	PFS, months, median (95% CI)	n	No. of events, n (%)	PFS, months, median (95% CI)
Total	25	12 (48)	10.3 (3.7-NR)	25	9 (36)	NR (4.1-NR)	24	15 (63)	10.2 (6.3-15.2)

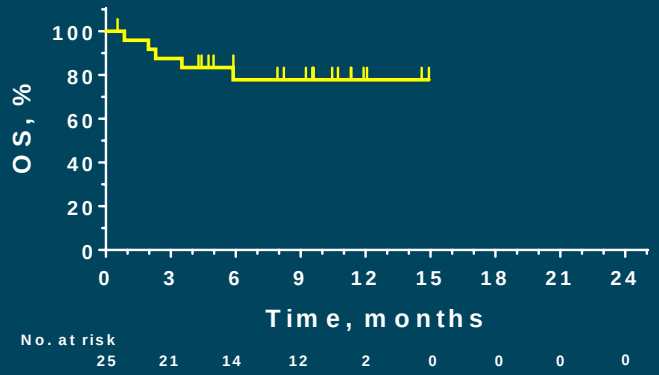
NR = not reached; PFS = progression-free survival.

RESULTS: OS

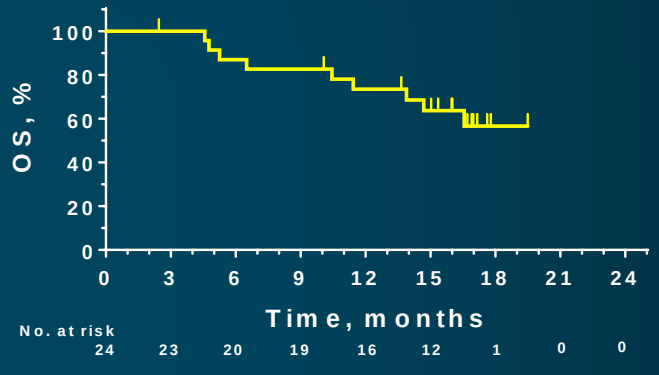
COHORT A



COHORT B



COHORT C



	Cohort A: Carbo/Pac			Cohort B: Carbo/Pac/Bev			Cohort C: Carbo/Pem		
Population	n	No. of events, n (%)	OS, months, median (95% CI)	n	No. of events, n (%)	OS, months, median (95% CI)	n	No. of events, n (%)	OS, months, median (95% CI)
Total	25	7 (28)	NR (11.0-NR)	25	5 (20)	NR (NR-NR)	24	9 (38)	NR (13.9-NR)

NR = not reached; OS = overall survival.

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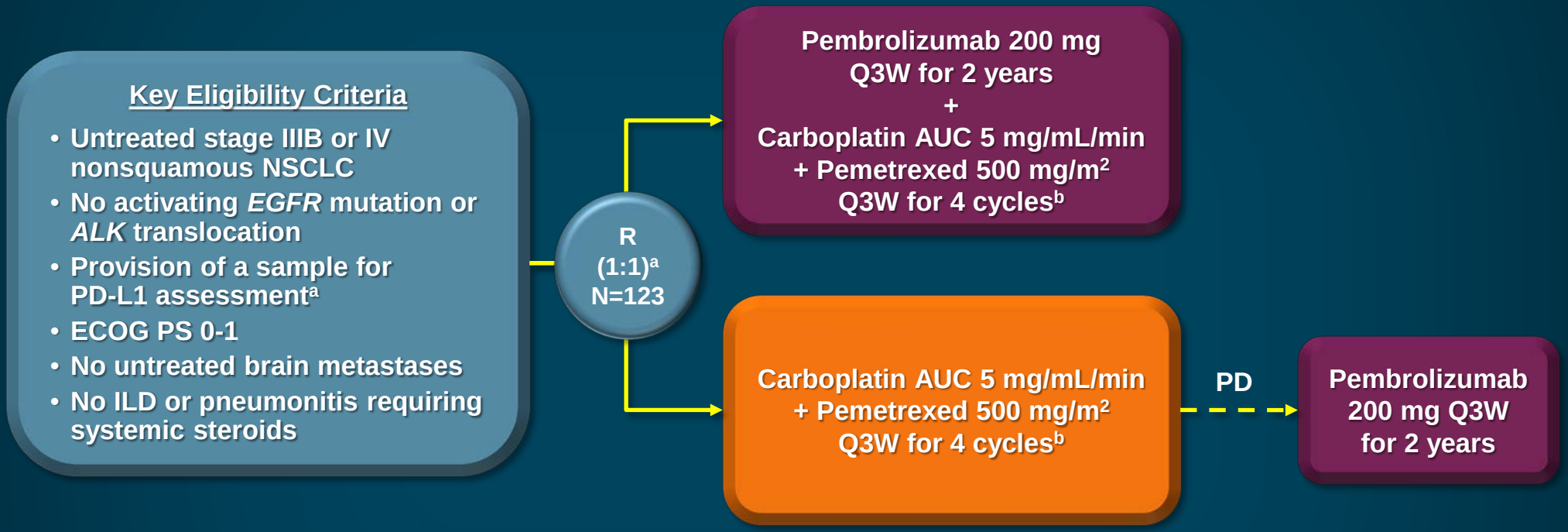
Randomized Phase 2 Study of Carboplatin and Pemetrexed ± Pembrolizumab as First-Line Therapy for Advanced NSCLC: KEYNOTE-021 Cohort G

Corey J. Langer,[1] Shirish M. Gadgeel,[2] Hossein Borghaei,[3] Vassiliki A. Papadimitrakopoulou,[4] Amita Patnaik,[5] Steven F. Powell,[6] Ryan D. Gentzler,[7] Renato G. Martins,[8] James P. Stevenson,[9] Shadia I. Jalal,[10] Amit Panwalkar,[11] James Chih-Hsin Yang,[12] Matthew Gubens,[13] Lecia V. Sequist,[14] Mark M. Awad,[15] Joseph Fiore,[16] Yang Joy Ge,[16] Harry Raftopoulos,[16] Leena Gandhi[15,17]

[1]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; [2]Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; [3]Fox Chase Cancer Center, Philadelphia, PA, USA; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]South Texas Accelerated Research Therapeutics, San Antonio, TX, USA; [6]Sanford Cancer Center, University of South Dakota Sanford School of Medicine, Sioux Falls, SD, USA; [7]Emily Couric Clinical Cancer Center, University of Virginia School of Medicine, Charlottesville, VA, USA; [8]Seattle Cancer Care Alliance, Seattle, WA, USA; [9]Cleveland Clinic, Cleveland, OH, USA; [10]Indiana University School of Medicine, Indianapolis, IN, USA; [11]Sanford Roger Maris Cancer Center, Fargo, ND, USA; [12]National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan, Republic of China; [13]University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [14]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [15]Dana-Farber Cancer Institute, Boston, MA, USA; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Current affiliation: Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, New York, USA

KEYNOTE-021 Cohort G



End Points

Primary: ORR (RECIST v1.1 per blinded, independent central review)

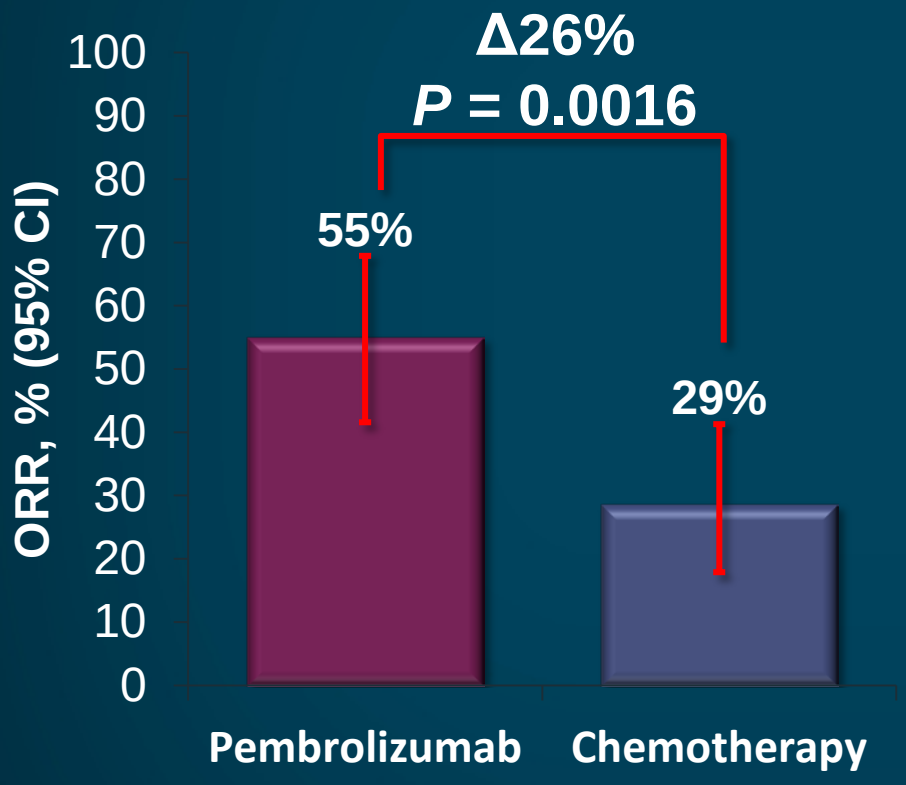
Key secondary: PFS

Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

Langer et al, Lancet Oncology, 2016

Confirmed Objective Response Rate

(RECIST v1.1 by Blinded, Independent Central Review)



	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response, [a] n (%)	29 (88)	14 (78)

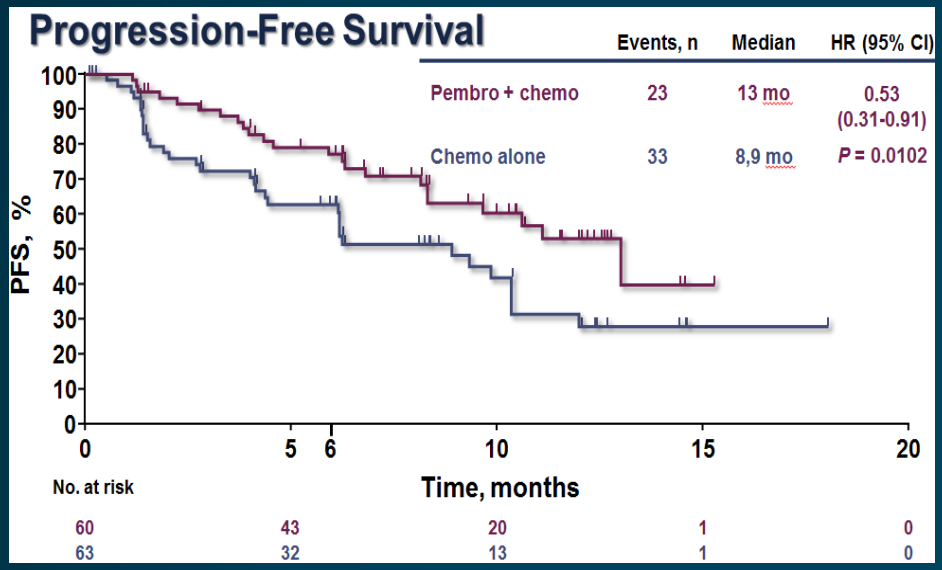
DOR = duration of response; TTR = time to response.

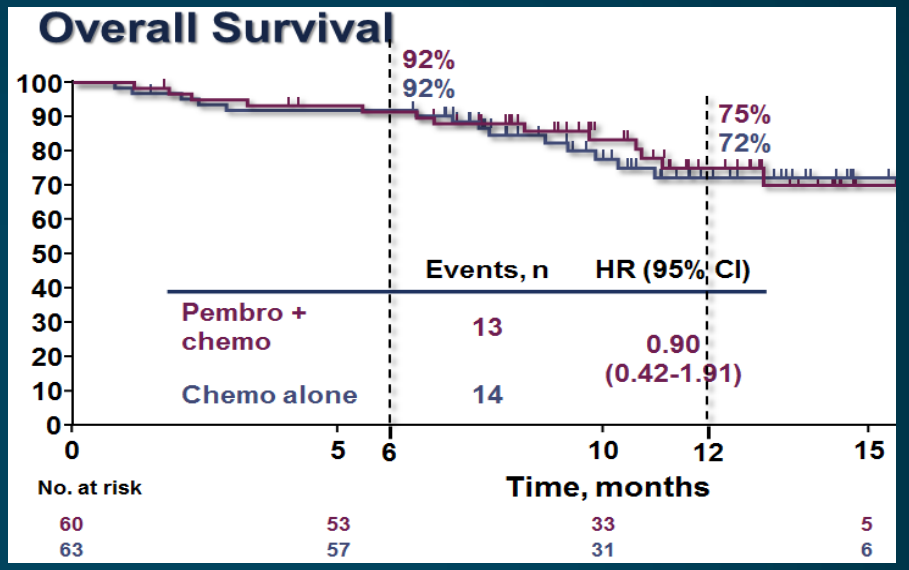
[a]Alive without subsequent disease progression.

Data cut-off: August 8, 2016.

Langer et al, Lancet Oncology, 2016

PFS and OS Survival data



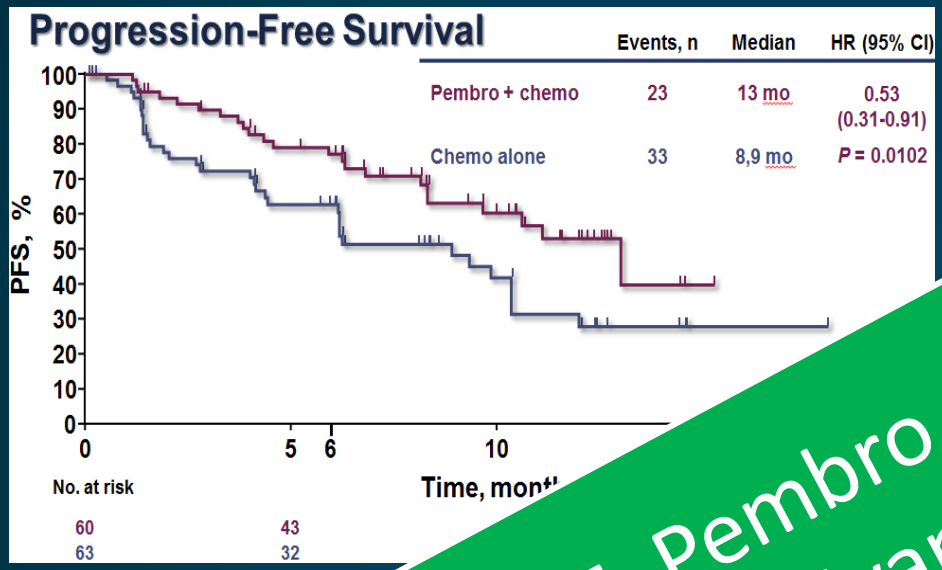


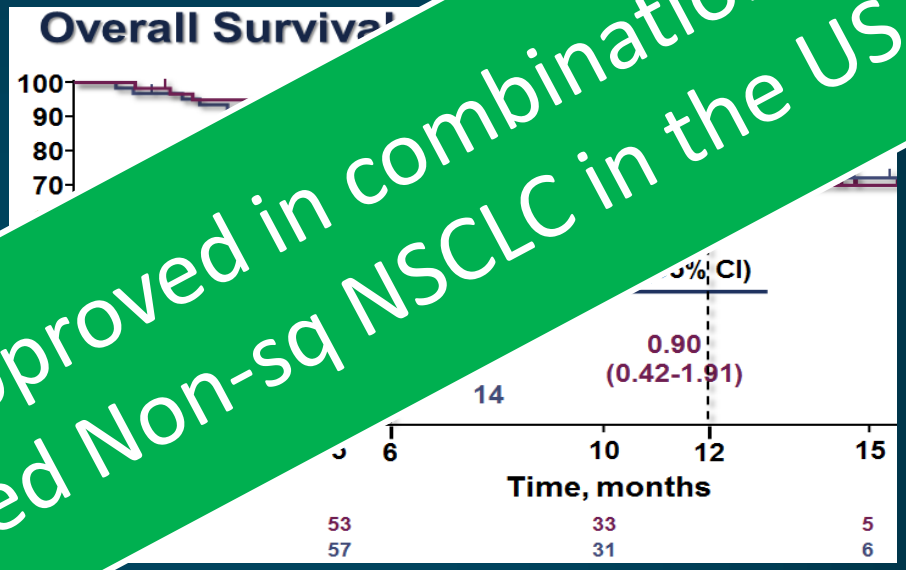
- Clear PFS benefit and no OS advantage
  - Median PFS improved by 4.1 months
  - PFS HR is 0.53
  - No difference for OS
  - Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
  - In CT arm cross-over is 51% to PD-(L)1 therapies (pembro & others), but > 70% in those eligible

COPENHAGEN 2016 ESMO congress

Langer et al, Lancet Oncology, 2016

PFS and OS Survival data





As of 05/09/17 , Pembro approved in combination with Pem/Carbo in Advanced Non-sq NSCLC in the US

- Clear PFS be
  - A
  - @ 12 months: 75% (Combo) vs 72% (CT)
  - ss-over is 51% to PD-(L)1 therapies (pembro & others), but > 70% in those

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Langer et al, Lancet Oncology, 2016

Study Design

Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

Stratify:
- PDL1 prop score: ≥1%, <1%
- Smoking status
- cisplatin vs carboplatin

RANDOMIZATION

2:1

N=570

Carboplatin / Cisplatin
Pemetrexed
Pembrolizumab
200 mg Q3W
X4 cycles

Pemetrexed
Pembrolizumab

PD → *Follow*

Carboplatin/Cisplatin
Pemetrexed
+Saline
X4 cycles

Pemetrexed
+Saline

PD

Pembrolizumab

Primary Endpoint: PFS – target HR 0.7
Secondary Endpoints: OS, ORR, AE
Exploratory Endpoints: QoL

Study Design

Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

Stratify:
- PDL1 prop score: ≥1%, <1%
- Smoking status
- cisplatin vs carboplatin

RANDOMIZAT

N=570

Carboplatin / Cis
Pemetre
Pembro
200

Pemetrexed
Pembrolizumab

PD → Follow

in/Cisplatin
emetrexed
+Saline
X4 cycles

Pemetrexed
+Saline

PD

Pembrolizumab

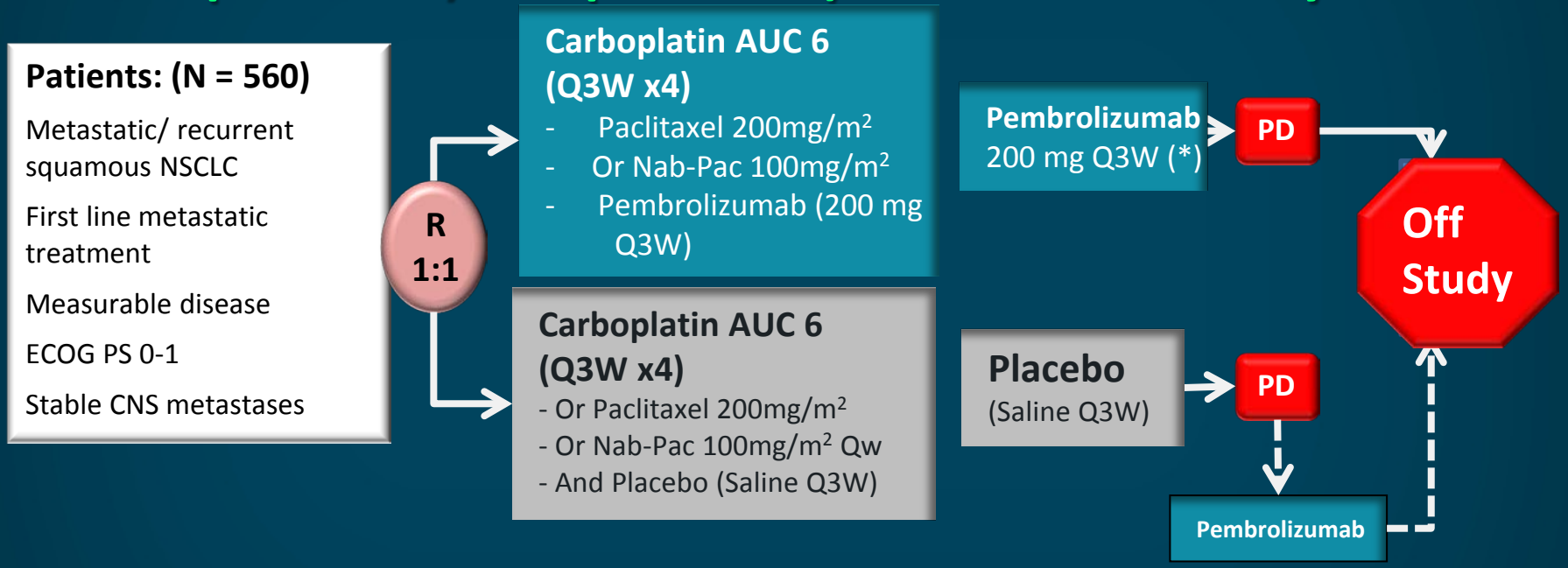
Completed Accrual 02/17

Keynote 189
A Clinical Trial for Non-Small Cell Lung Cancer

Primary Endpoint: PFS – target HR 0.7
Secondary Endpoints: OS, ORR, AE
Exploratory Endpoints: QoL

KEYNOTE 407 (Squamous NSCLC)

First line pembrolizumab + chemotherapy (carboplatin + paclitaxel/nab-paclitaxel) combination study



- **Primary Endpoint:** Overall and Progression Free Survival
- **Secondary Endpoints:** ORR, AE
- **Exploratory Endpoints:** QoL

Stratify:

PDL1 TPS score: ≥1% vs <1%

Paclitaxel vs nab-paclitaxel

* Up to 2 years

NSCLC Phase 3 Durvalumab trials

Adjuvant	Unresectable Stage III	1st line	≥3rd line
CCTG ADJUVANT Durvalumab vs. placebo	PACIFIC Durvalumab vs. placebo	MYSTIC Durvalumab + tremelimumab vs. durvalumab vs. SoC	ARCTIC *PD-L1*$^{+}$: Durvalumab vs. SoC *PD-L1*$^{-}$: Durvalumab + tremelimumab vs. durvalumab/ tremelimumab mono vs. SoC
		NEPTUNE Durvalumab + tremelimumab vs. SoC	

NSCLC Phase 3 Durvalu…s

Adjuvant	Unresectable Stage III…		
CCTG ADJUVANT Durvalumab vs. placebo		…umab vs. SoC	…IC *PD-L1*+: Durvalumab vs. SoC *PD-L1*–: Durvalumab + tremelimumab vs. durvalumab/ tremelimumab mono vs. SoC
		NEPTUNE Durvalumab + tremelimumab vs. SoC	

PACIFIC
Durvalumab vs. placebo after CT/RT for LA-NSCLC met its PFS endpoint

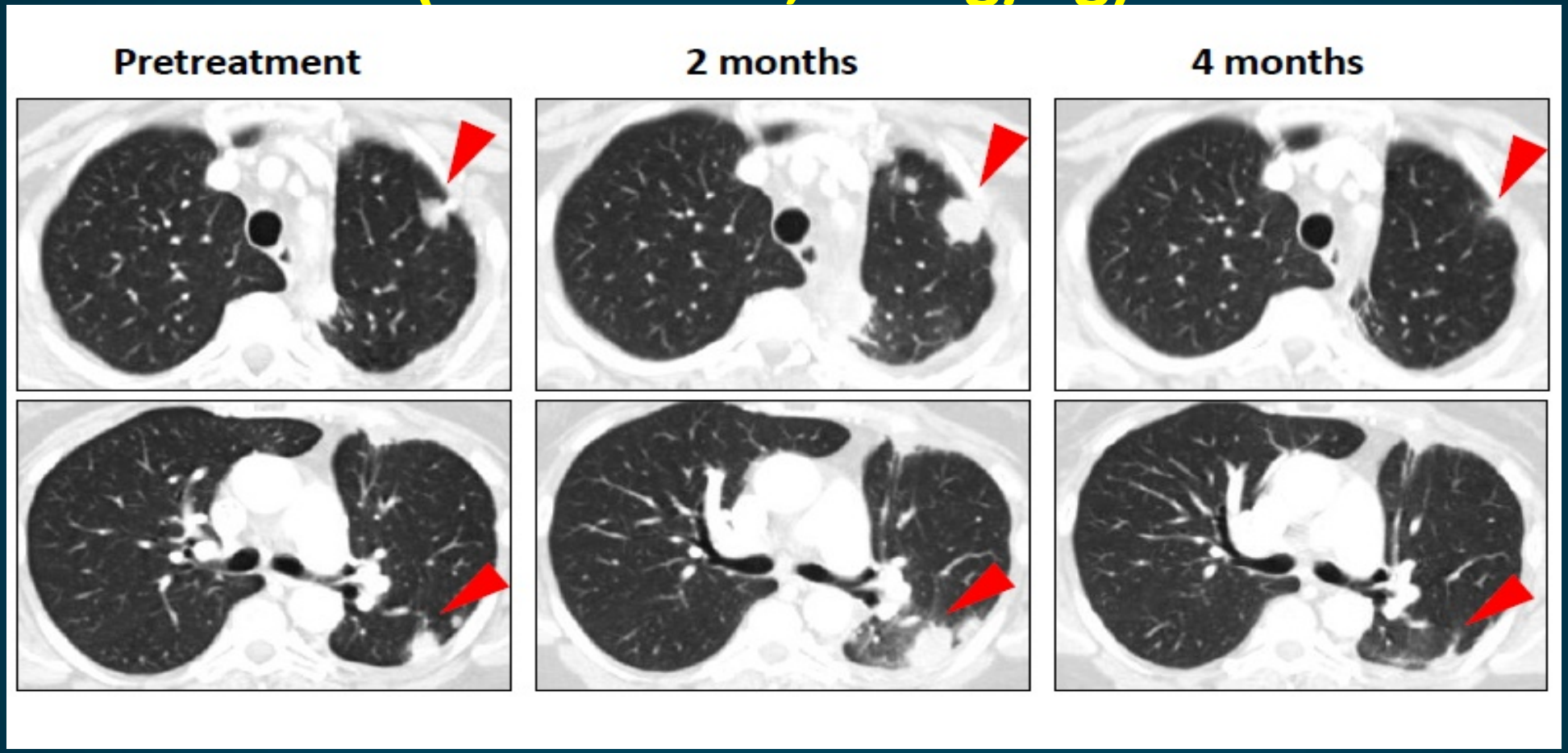
Ongoing Questions

- Does pseudo-progression occur in lung cancer?
- How reliable a marker is PDL1 by IHC? Are there other markers of interest?
- What is the rationale for flat dosing? Is it safe?
- Are there unique toxicity concerns in the front-line setting?

Ongoing Questions

- Does pseudo-progression occur in lung cancer?
- How reliable a marker is PDL1 by IHC? Are there other markers of interest?
- What is the rationale for flat dosing? Is it safe?
- Are there unique toxicity concerns in the front-line setting?

Response of Metastatic NSCLC (Nivolumab, 10mg/kg)

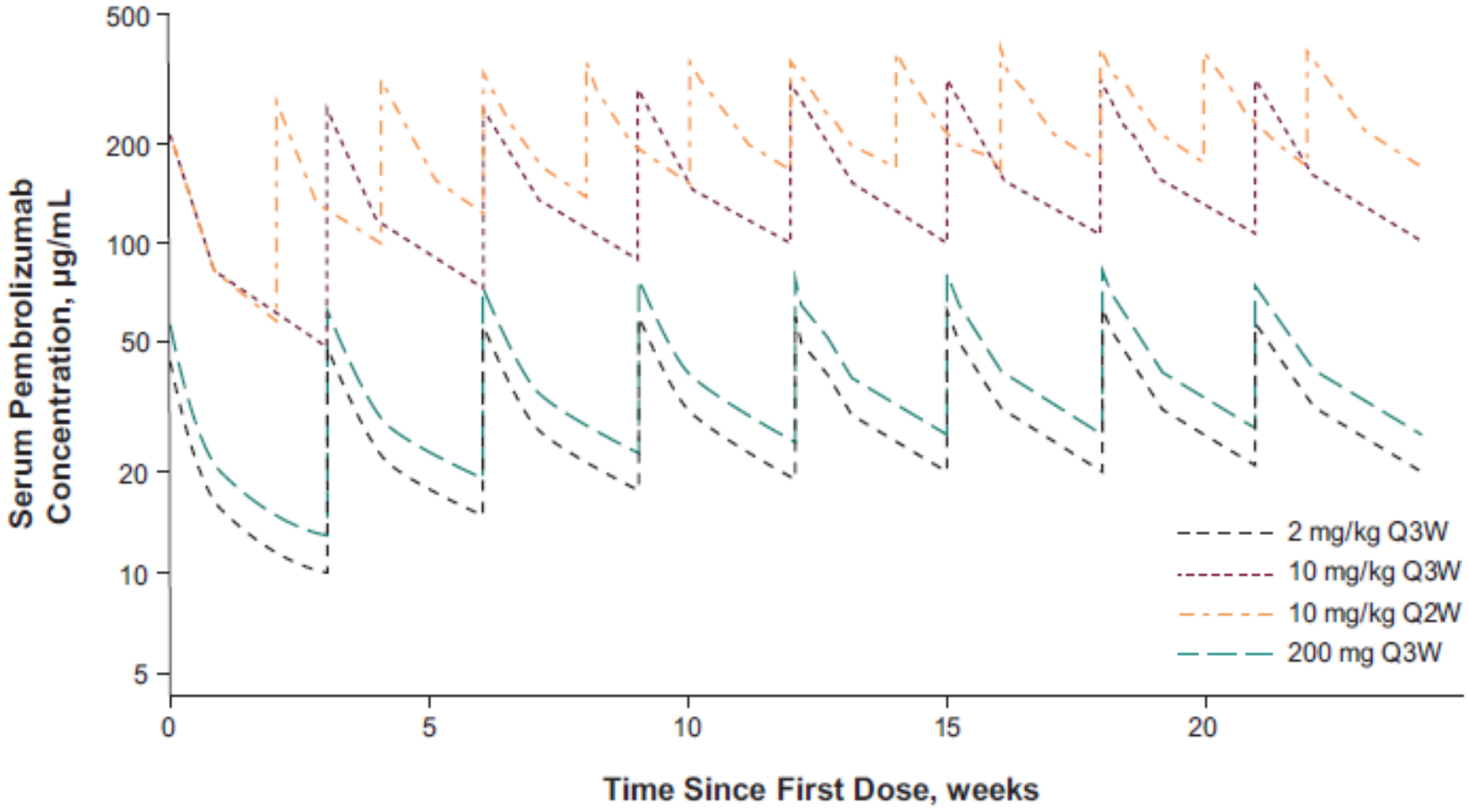


- Initial progression of pulmonary lesions in a patient with EGFR mutant (del19, T790M) NSCLC, followed by regression
- Prior treatment with gemcitabine/ carboplatin, erlotinib, erlotinib + LBH589 (trial for T790 mutation), and pemetrexed

Pharmacokinetics from KN 001, 002, and 006

200-mg Q3W regimen exhibits a similar accumulation pattern to 2 mg/kg Q3W and maintained between clinical bounds of 2 and 10 mg/kg

Figure 1. Predicted pembrolizumab concentration-time profiles.

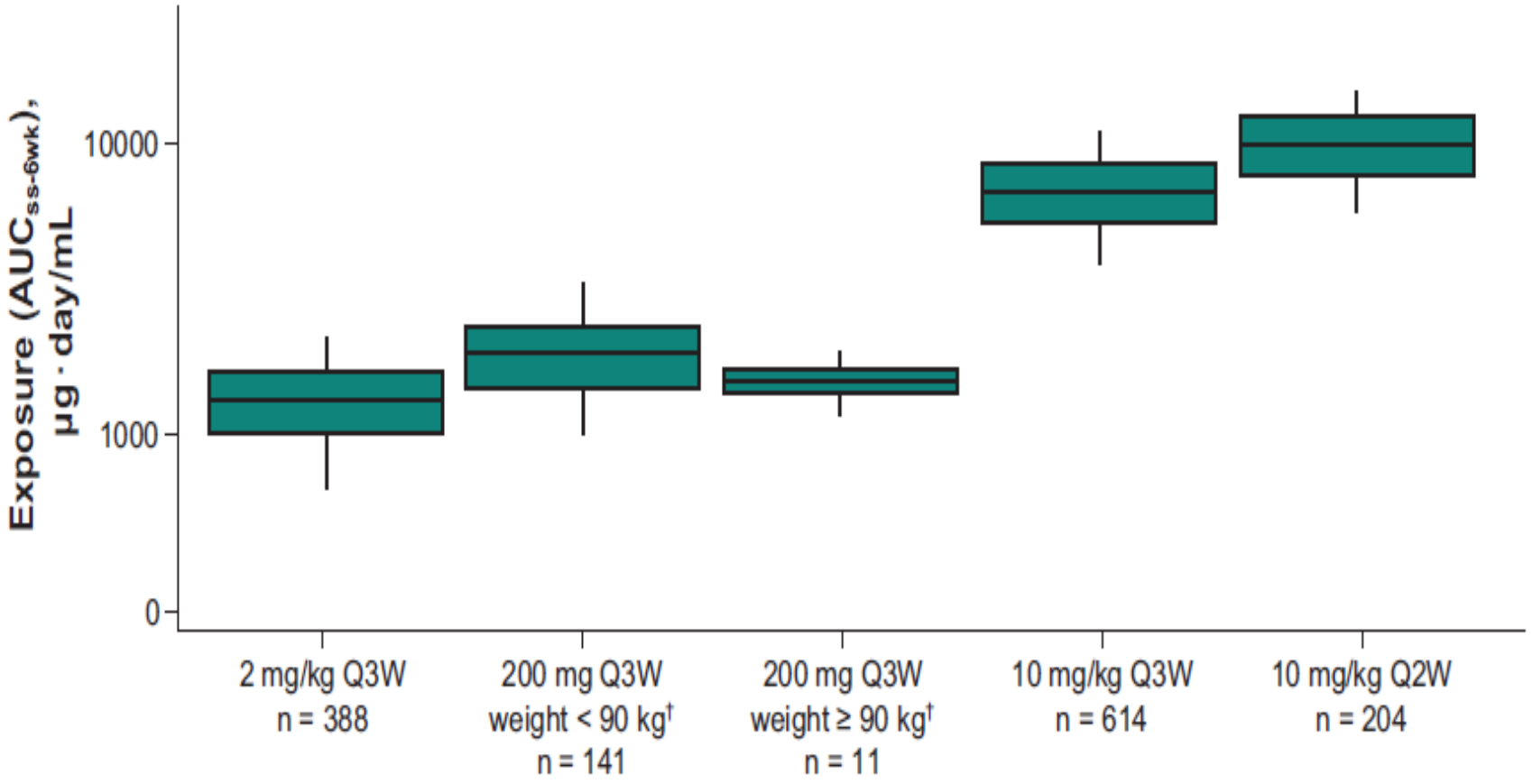


Q2W = every 2 weeks; Q3W = every 3 weeks.

Garon et al WCLC '16

Pharmacokinetics from KN 001, 002, and 006

Figure 3. Observed exposure for patients with first-line NSCLC at clinically tested dose regimens.



AUC_{ss-6wk} = area under the concentration curve, steady state to 6 weeks; NSCLC = non–small cell lung cancer; Q2W = every 2 weeks; Q3W = every 3 weeks.
Data are plotted on the log scale. For each dose, straight line = median; upper and lower edges of the box = 25th and 75th percentages; and whiskers = 5th and 95th percentiles.
†90 kg was chosen as the cutpoint because there were only 5 patients with weight >100 kg.

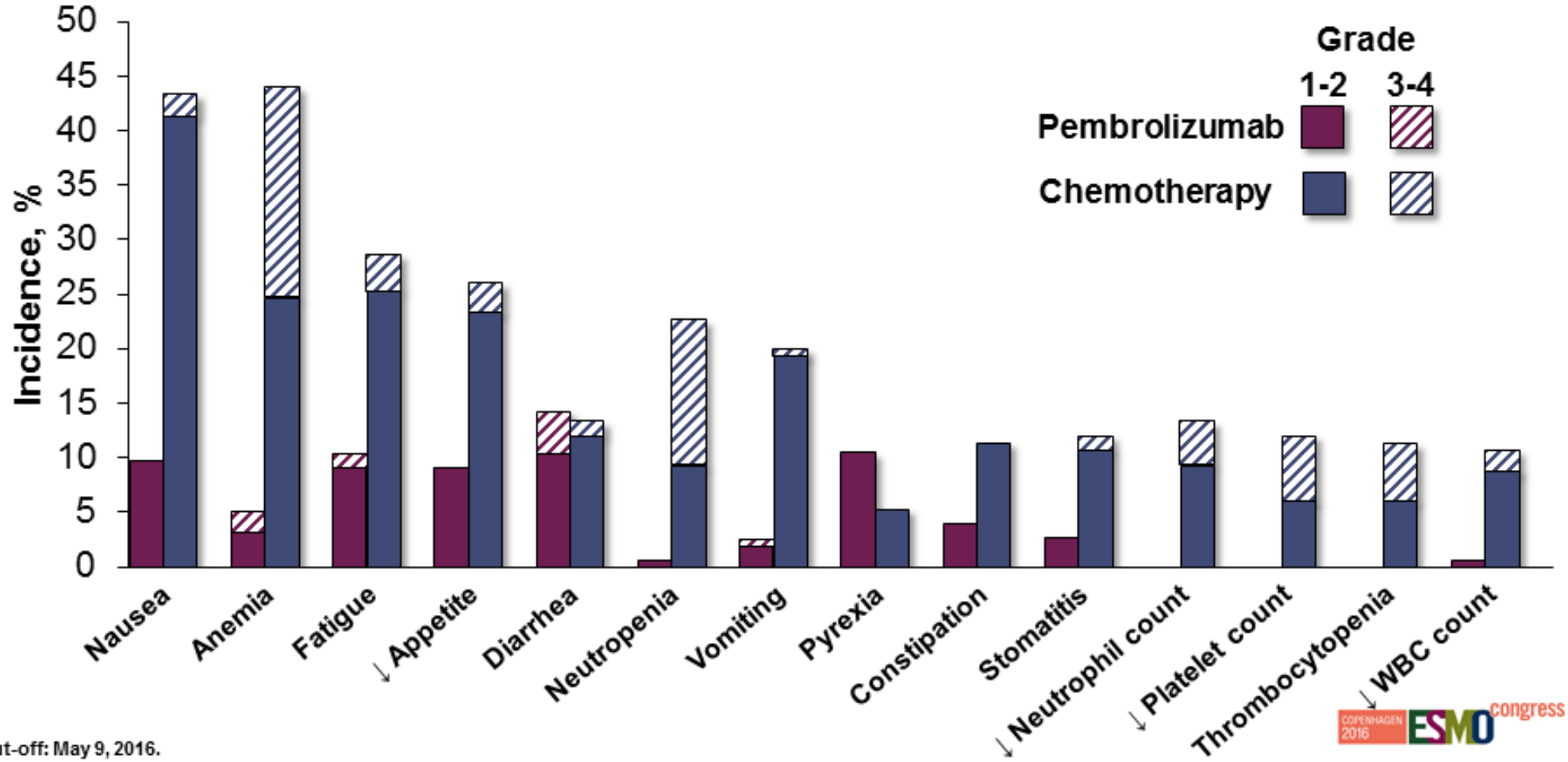
200-mg Q3W fixed-dose regimen--No clinically meaningful difference in PK variability compared with 2-mg/kg Q3W weight-based dosing, regardless of whether patient weight was greater or less than 90 kg

Garon et al WCLC ‘16

Keytnote 024: Pembro vs Platinum-based Doublets

M Reck. ESMO 2016.

Treatment-Related AEs With Incidence >10%

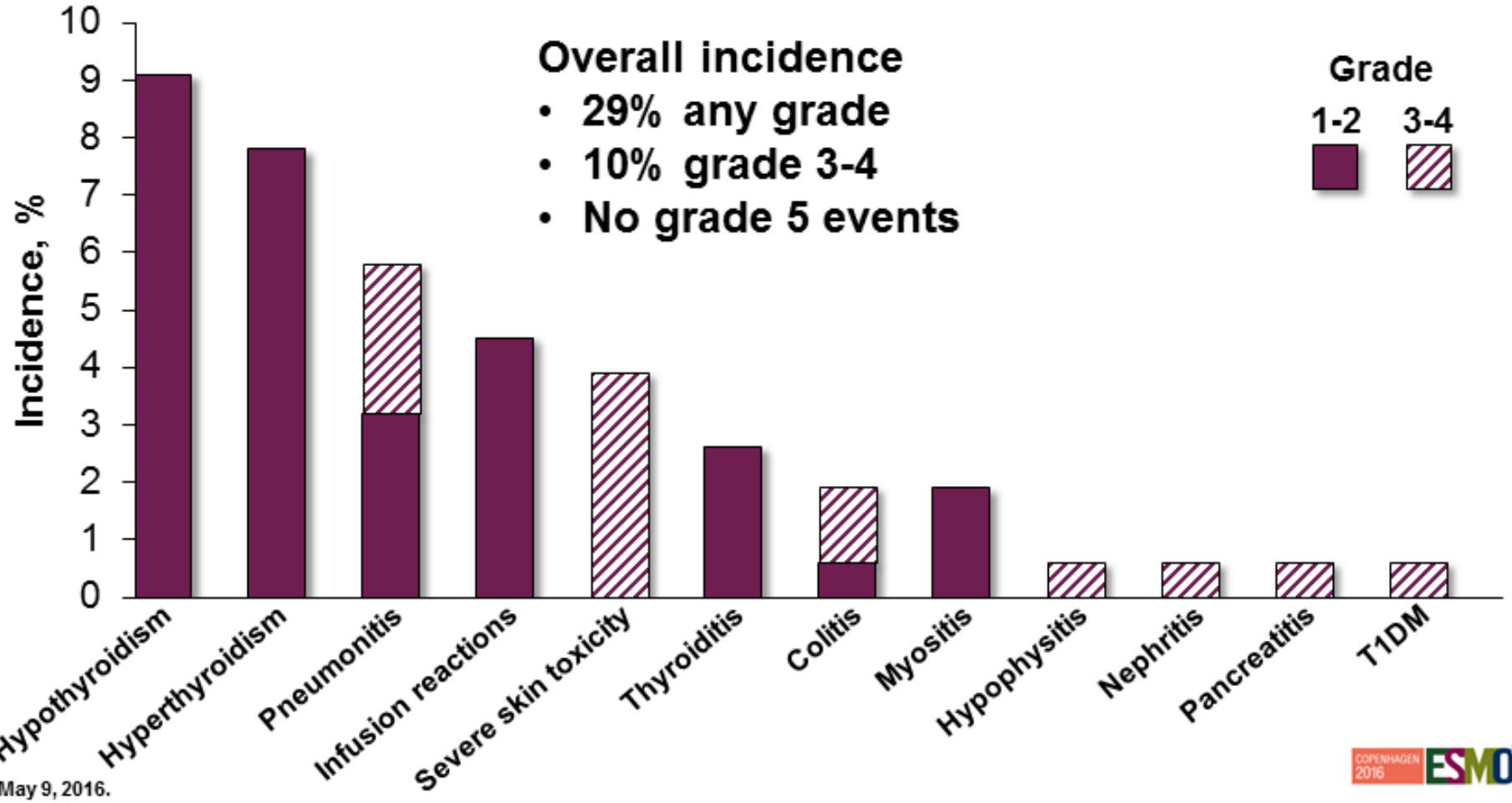


Data cut-off: May 9, 2016.

Keytnote 024: Pembro vs Platinum-based Doublets

M Reck. ESMO 2016.

Immune-Mediated AEs With Pembrolizumab



Data cut-off: May 9, 2016.

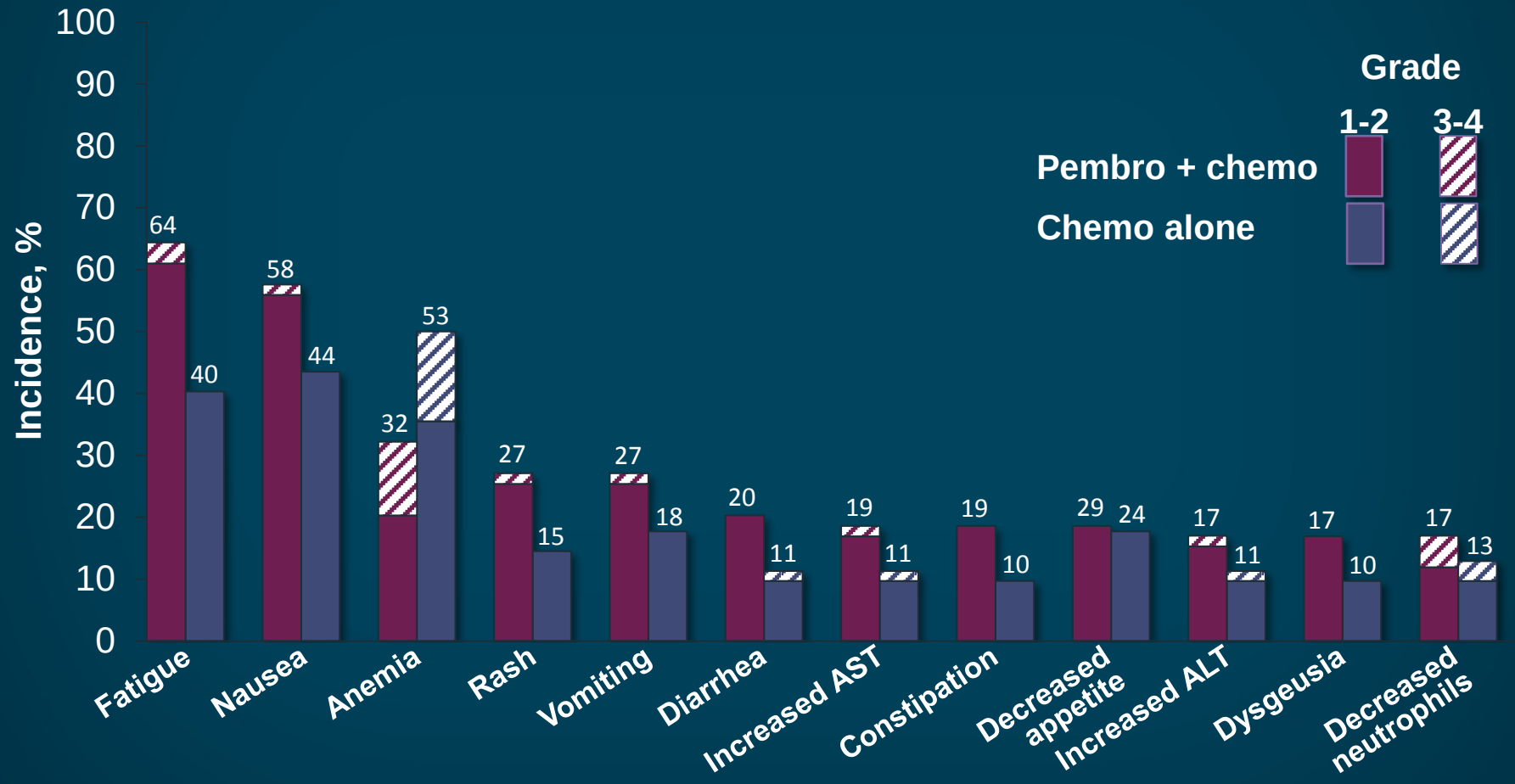
COPENHAGEN 2016 ESMO congress

KN021G--Exposure and AE Summary

	Pembro + Chemo n = 59	Chemo Alone n = 62
Exposure, median (range)	8.0 mo (1 d - 16.1 mo)	4.9 mo (1 d - 15.3 mo)
Treatment-related AEs, n (%)	55 (93)	56 (90)
Grade 3-4	23 (39)	16 (26)
Led to discontinuation	6 (10)	8 (13)
Led to death	1 (2)	2 (3)

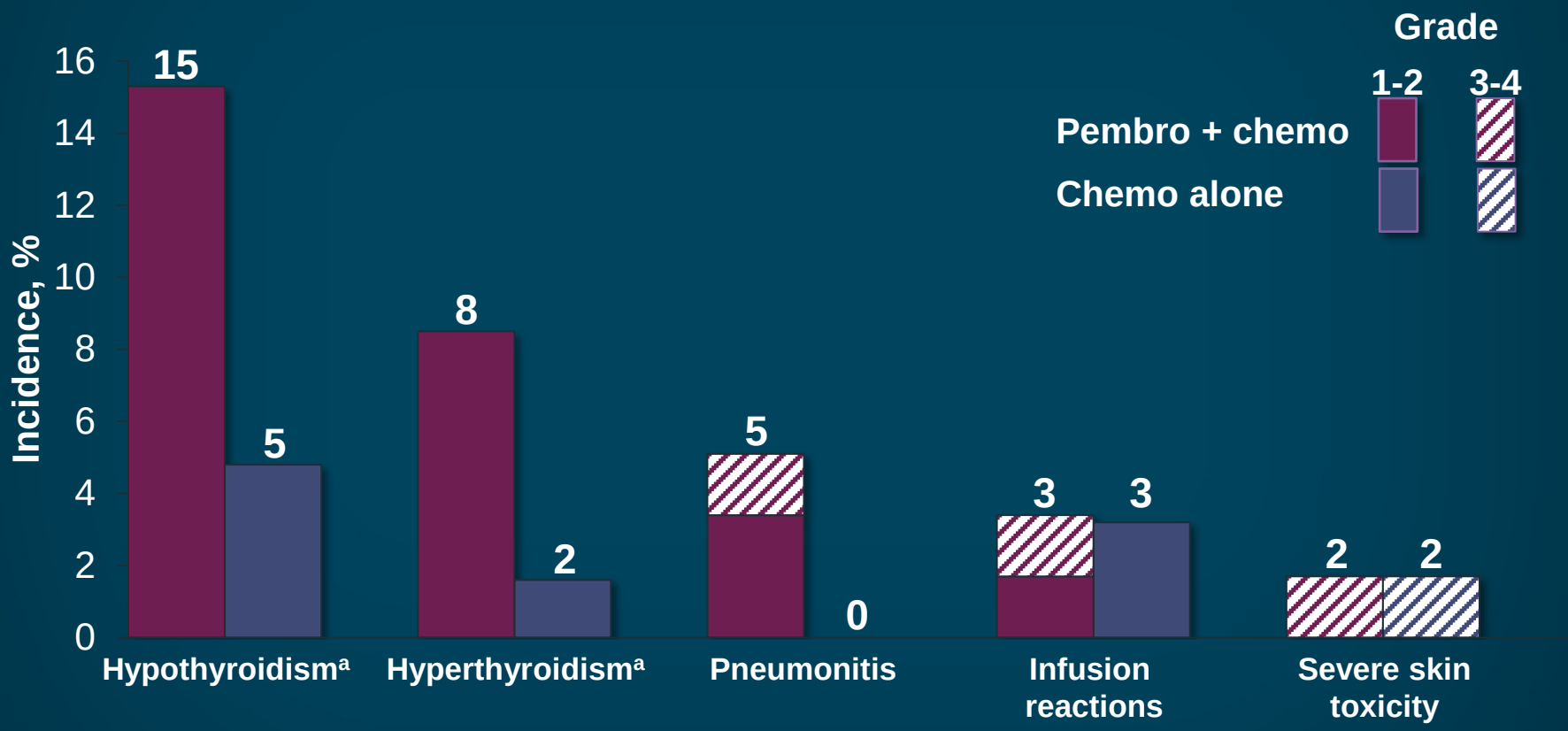
Data cut-off: August 8, 2016.

KN021G--Treatment-Related Adverse Events With Incidence ≥15%



Data cut-off: August 8, 2016.

KN021G-- AEs With Possible Immune Etiology



[a]3 patients in the pembrolizumab + chemotherapy arm had both hyperthyroidism and hypothyroidism. No patients in the chemotherapy alone arm had both events.

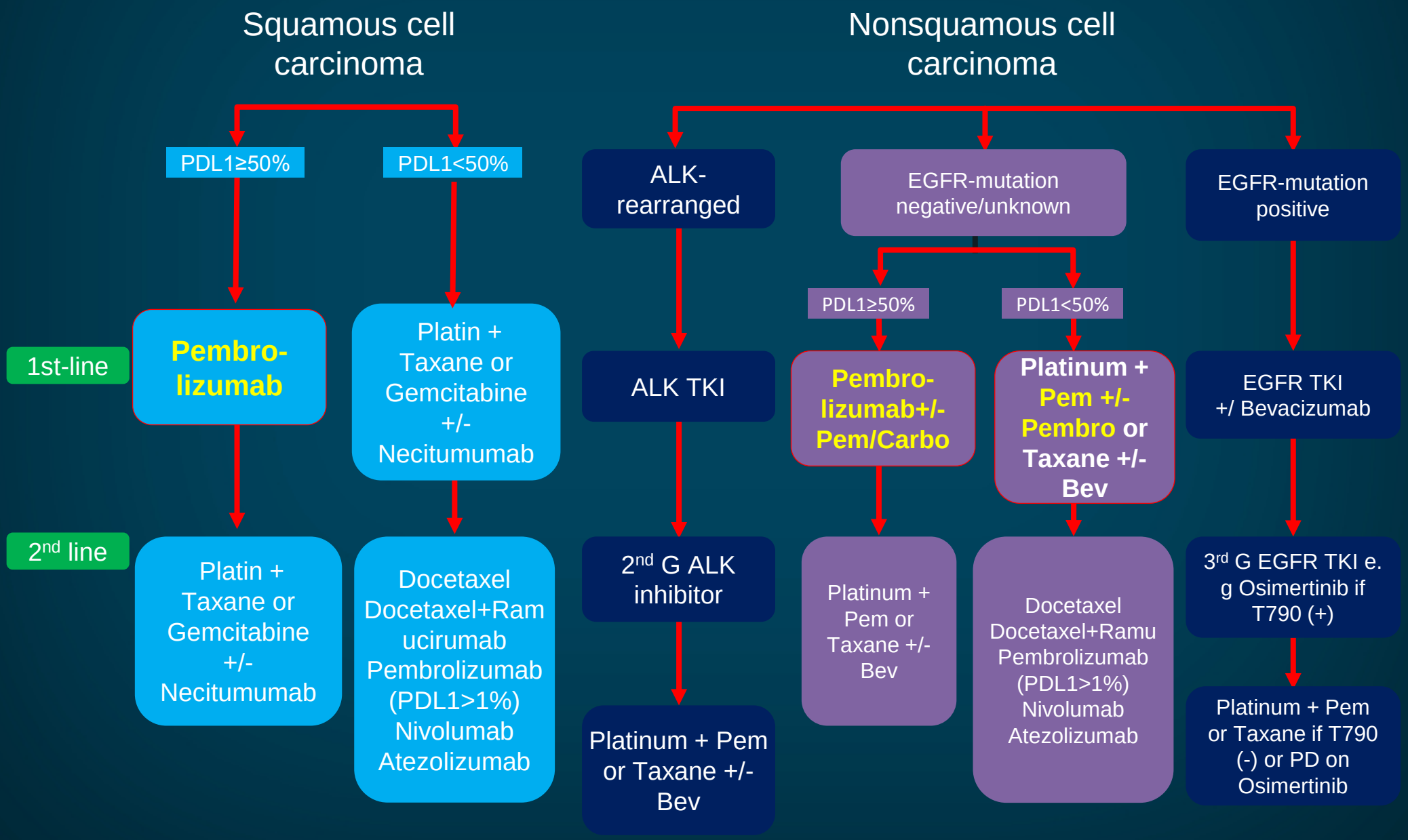
Data cut-off: August 8, 2016.

Conclusions: Checkpoint Inhibitors

Lung Cancer

- Checkpoints inhibitors are active, with often durable responses in platinum-refractory setting in NSCLC
  - Higher responses seen in settings with increased "mutation burden," eg. KRAS mt, former/heavy smokers, etc
  - RR ~ 20% independent of line of Tx
  - Based on RP3 data, Nivolumumab is approved in 2nd line Squamous and Non-Sq NSCLC, independent of PDL1 status
  - Pembrolizumab approved in PDL1 (+) NSCLC (initially $\geq$ 50%, now > 1%)
- PD-L1 IHC is the best available biomarker currently in 2017
- Pseudo-progression can be observed, but is rare (<3-5%)
- Unique side effects consistent with the immune mechanism of action
  - Toxicities of CTLA4 inhibitors >> PD1/PD-L1 inhibitors
- Pembro has shown OS/PFS/RR advantage c/w platinum-based combination chemo in Tx-naïve NSCLC with > 50% PDL1 (+)
- Combination Pembro and Pem/Carbo in Tx-naive Non-Sq NSCLC has yielded significant improvement in RR (>55%) and PFS (> 13 mos) and is now approved in the US as of 05/17

First- and Second-Line Treatment of Metastatic NSCLC (After KEYNOTE 24)



Case Study

Case # 1

- 76-year-old white male has multifocal squamous cell cancer of the lung.
- S/P: Carboplatin + gemcitabine X 6 followed by Carbo/paclitaxel concurrently with XRT to lungs (6000 cGy in 240cGy fractions) 2/20/2012–3/23/2012, then at PD, XRT (SRS and Tomo) to RUL RLL and right hilar lesions with concurrent chemotherapy (Carbo and paclitaxel x 2 doses on 9/20/2012 and 9/27/2012).
- Received weekly nab-paclitaxel, monthly Carbo beginning 3/2013
- CT after 2 cycles showed stability in the RLL on repeat imaging and diminution in other lesions, most of which had been irradiated; received 5 cycles with clear PR,
- But then dev'd clear-cut PD in RLL and R SCN in 7/2013
- He undergoes bx of the R SCN, which proves PDL1 at 60%

Case #1 Hx (cont'd)

- Which of the following Checkpoint inhibitors has shown a survival benefit vs Docetaxel in this setting?
  A. Nivolumab
  B. Pembrolizumab
  C. Atezolizumab
  D. All of the above
  E. A+B only

Case # 1 Hx (cont'd)

- Which of the following Checkpoint inhibitors has shown a survival benefit vs Docetaxel in this setting?
  - A. Nivolumab
  - B. Pembrolizumab
  - C. Atezolizumab
  - **D. All of the above**
  - E. None of the above

Case #1 Hx (cont'd)

- Which of the following Checkpoint inhibitors has been approved for use specifically in pts with PDL1 expression $\geq$ 1%?
  A. Nivolumab
  B. Pembrolizumab
  C. Atezolizumab
  D. All of the above
  E. None of the above

Case #1 Hx (cont'd)

- Which of the following Checkpoint inhibitors has been approved for use specifically in pts with PDL1 expression $\geq$ 1%?
  - A. Nivolumab
  - **B. Pembrolizumab**
  - C. Atezolizumab
  - D. All of the above
  - E. None of the above

Case Study 2

- RM is a 65-year-old man current smoker with *KRAS* mutation-positive advanced adenocarcinoma of the lung, involving liver and bone.
- He received treatment with combination pemetrexed and carboplatin with partial response after 4 cycles; he was then put on maintenance treatment with pemetrexed alone.
- However, after 4 cycles of maintenance treatment, his tumor started to progress, with enlarging lung lesions and a new supraclavicular node.

Case 2—Question 1

What is the next step?

A. Biopsy the node for PD-L1 expression

B. Empiric therapy with docetaxel +/- ramucirumab

C. Treat with Nivolumab

C. Empiric therapy with erlotinib

D. Resumption of carboplatin with a taxane

Case 2—Question 2

- A supraclavicular node biopsy shows progressive adenocarcinoma, *KRAS* mutant-positive and positive for PD-L1 expression on IHC (70%).
- What is the next step?

A. Docetaxel alone

B. Erlotinib alone

C. Empiric therapy with nivolumab

D. Empiric therapy with pembrolizumab

D. Enrollment on a clinical trial comparing chemotherapy with either pembrolizumab to combination pembrolizumab + epacadostat, an IDO inhibitor

Case 2—Question 3

- He is randomized on clinical trial to single agent Pembro and sustains a striking partial response, with resolution of supraclavicular node, liver metastases, and 80% reduction of lung lesions.
- However, after 6 months, updated CT scans show new ground-glass changes around the tumor in the left lung; the patient starts to complain of dyspnea on exertion and cough, with pulse ox desaturating to 86% on exertion.
- What is the next step?

A. Withhold the PD1 inhibitor, at least temporarily

B. Empiric steroids

C. A + B

D. None of the above

Case 2—Question 4

- Within 4 weeks, after withholding treatment and institution of steroids, CT changes have resolved, and the patient's PS has improved to "0" from "2." There is no overt progression off treatment.
- What do you do next?

A. Resume treatment

B. Resume treatment at 50% dose

C. Resume treatment, but continue low-dose steroids

D. Observe off treatment

Pneumonitis on IO Tx

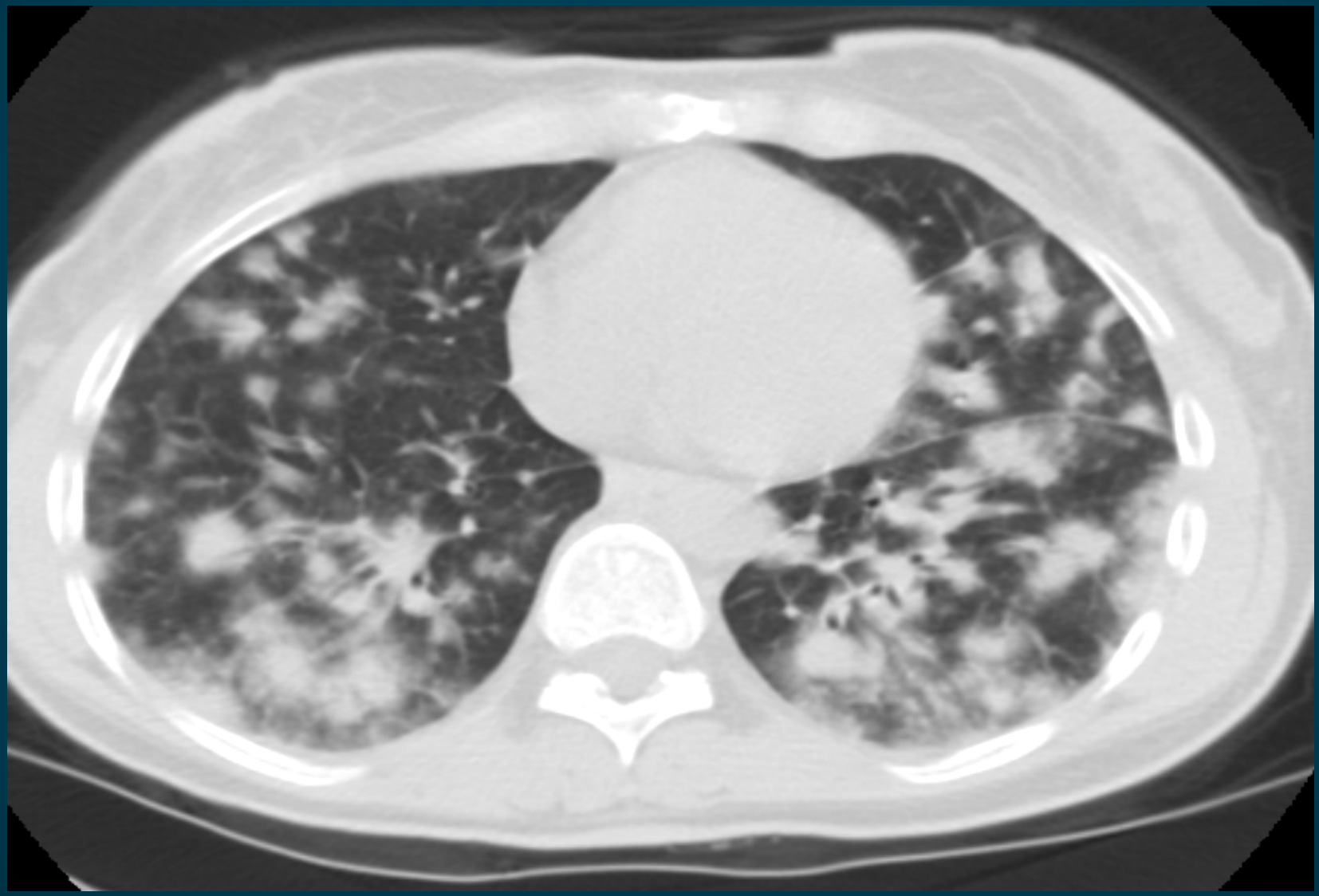
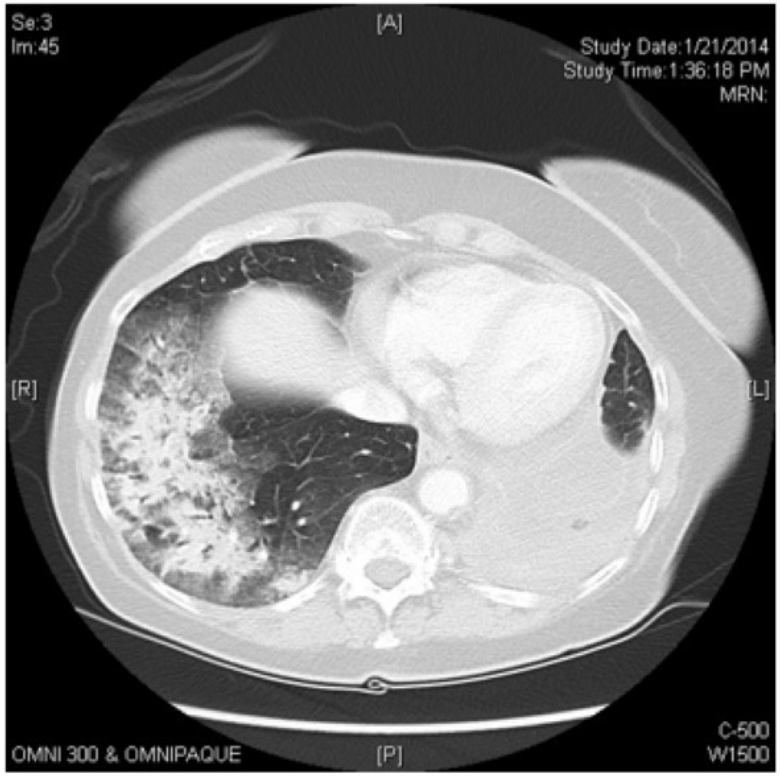


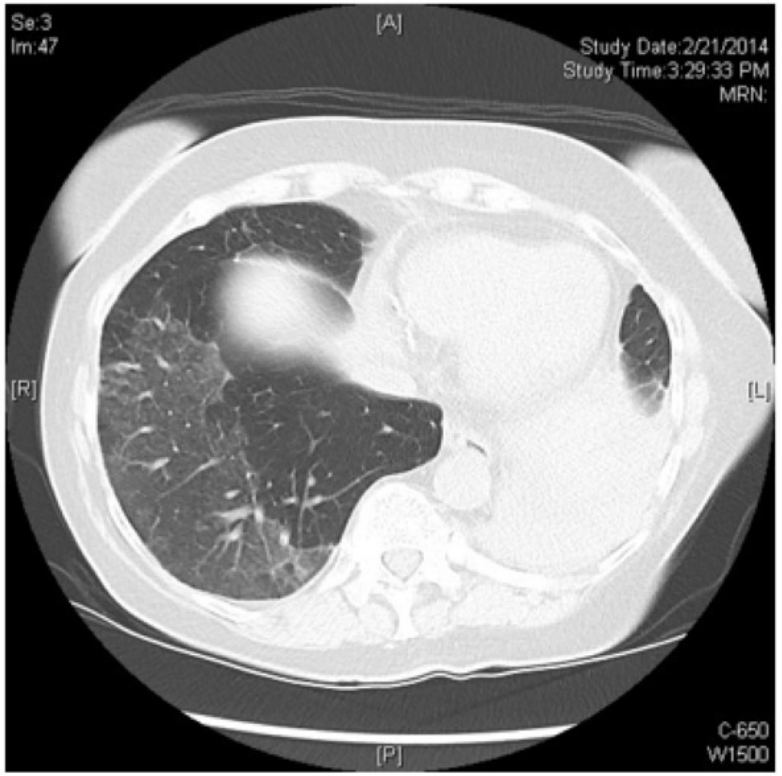
Image from Mike Postow

Pneumonitis

New SOB, cough, hypoxia (90% RA, 85% with exertion)

- CT: new RLL consolidation/GGO concerning for pneumonitis. Admitted -- methylprednisolone 60 mg twice daily
- Improved with steroids; tapered over 6 weeks





Images courtesy of Naiyer Rizvi, MD.

Pneumonitis Management

1. Radiographic changes: monitor

2. Mild to moderate symptoms: high dose prednisone, consider hospitalization/pulmonary eval

3. Severe symptoms or hypoxia: high dose steroid, hospitalize, pulmonary eval, bronchoscopy

Taper steroids slowly over at least several weeks and consider opportunistic infectious prophylaxis

Questions & Answers