Immunotherapy in Lung Carcinoma

Dr Kenneth O'Byrne
Princess Alexandra Hospital and Queensland University of Technology, Brisbane, Australia
& Trinity College, Dublin, Ireland

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- Honoraria for advisory boards, speaker bureau work, travel, accommodation, and/or registration expenses for meetings/congresses from Boehringer Ingelheim, Merck Sharp Dohme, Lilly Oncology, AstraZeneca, Roche, Pfizer, BMS, Novartis and Teva
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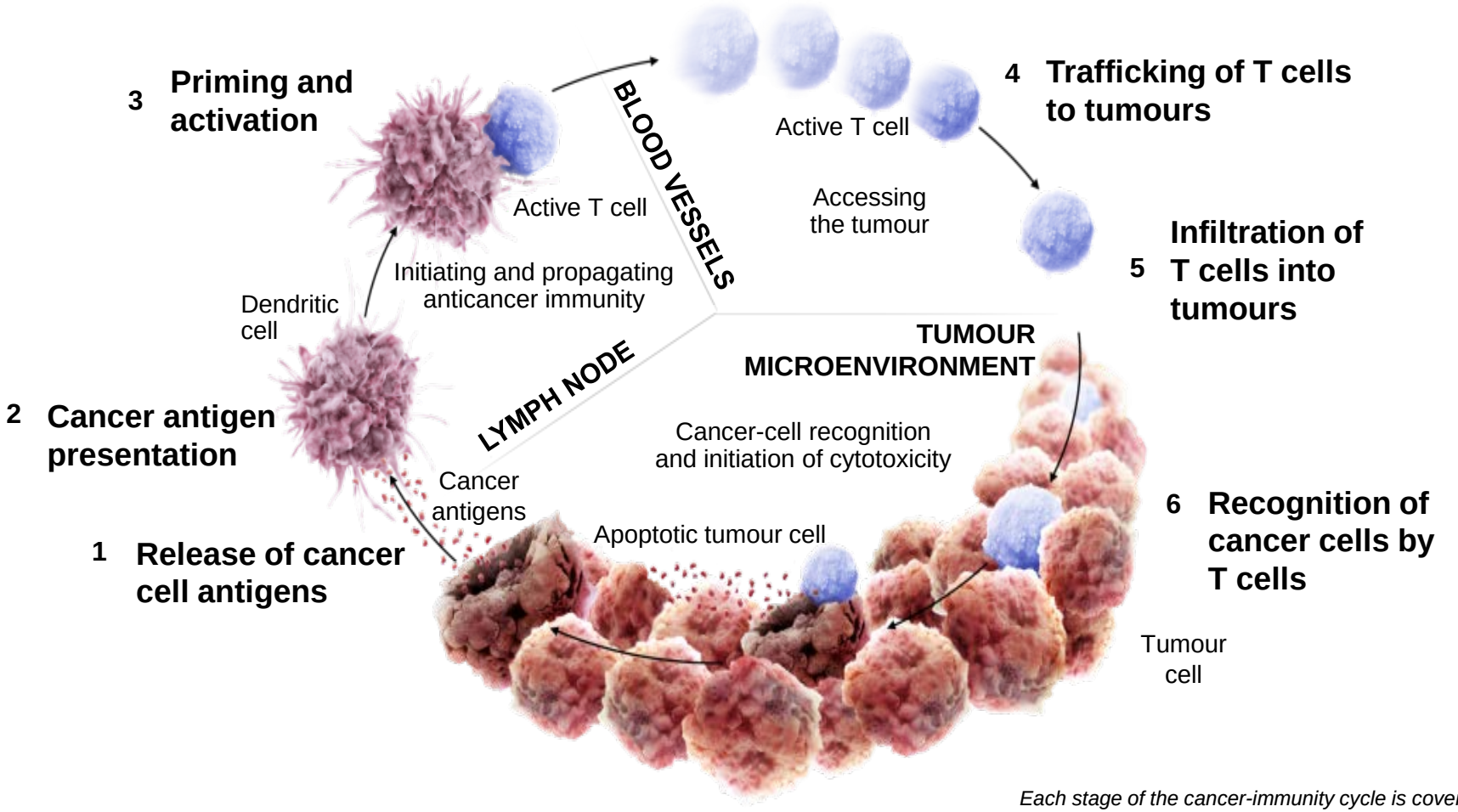
- Share holder in CARP pharmaceuticals

For an anticancer immune response to lead to effective killing of cancer cells, a series of stepwise events must be initiated and allowed to proceed and expand iteratively

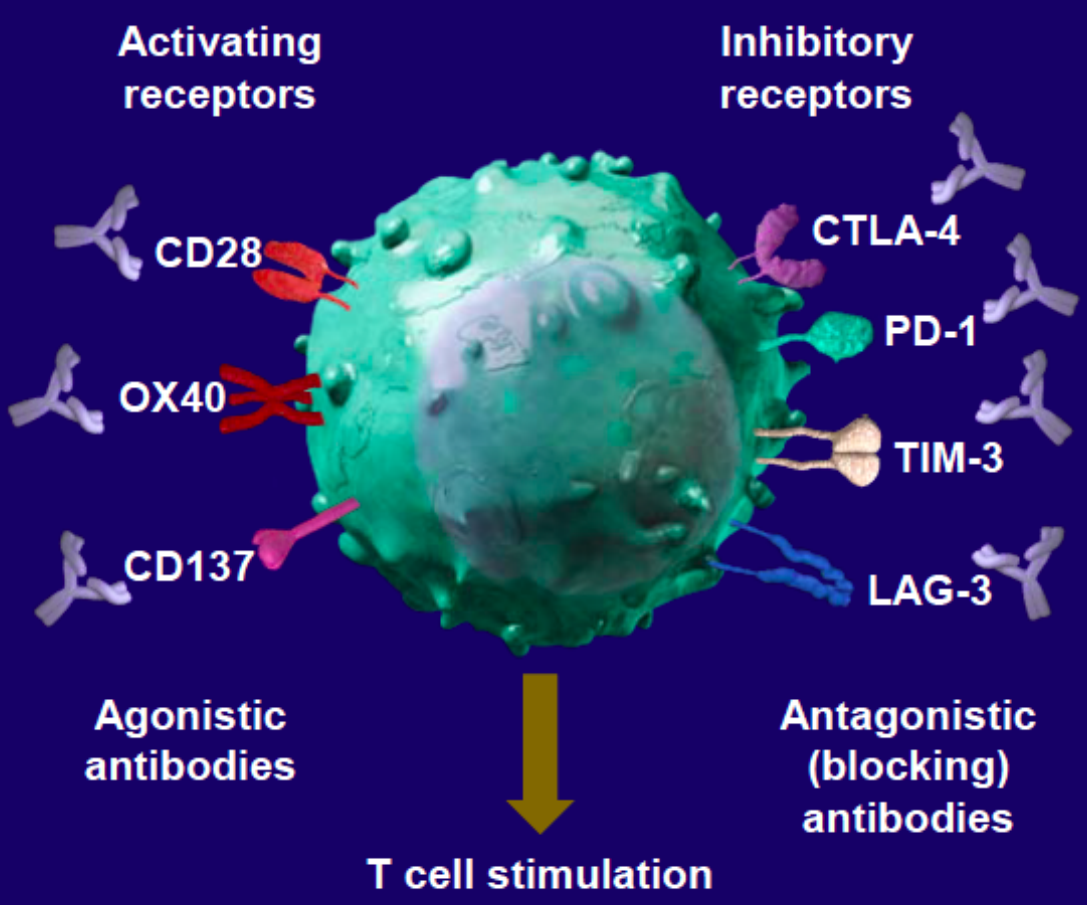
The cancer-immunity cycle



Chen DS, et al. Immunity 2013

*Each stage of the cancer-immunity cycle is covered in further detail in **'Basic immunology and the cancer-immunity cycle'***

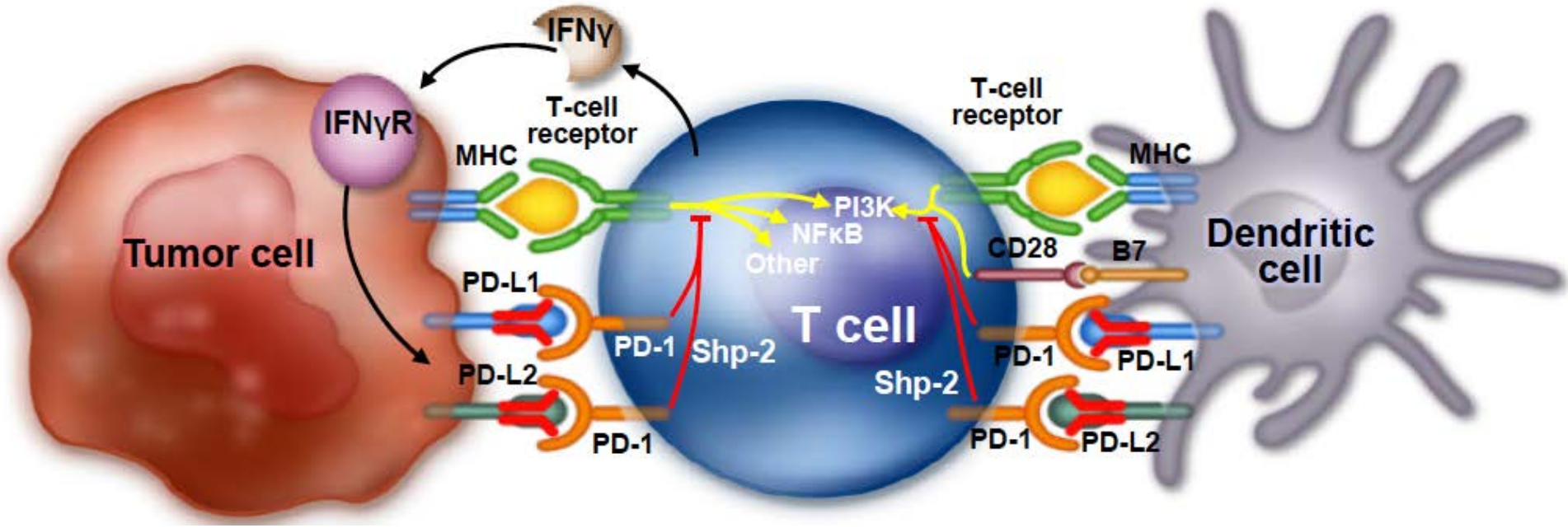
Regulating the T cell immune response



- T cell responses are regulated through a complex balance of inhibitory ('checkpoint') and activating signals
- Tumours can dysregulate checkpoint and activating pathways, and consequently the immune response
- Targeting checkpoint and activating pathways is an evolving approach to cancer therapy, designed to promote an immune response

Adapted from Mellman I, et al. *Nature*. 2011:480;481–489; Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

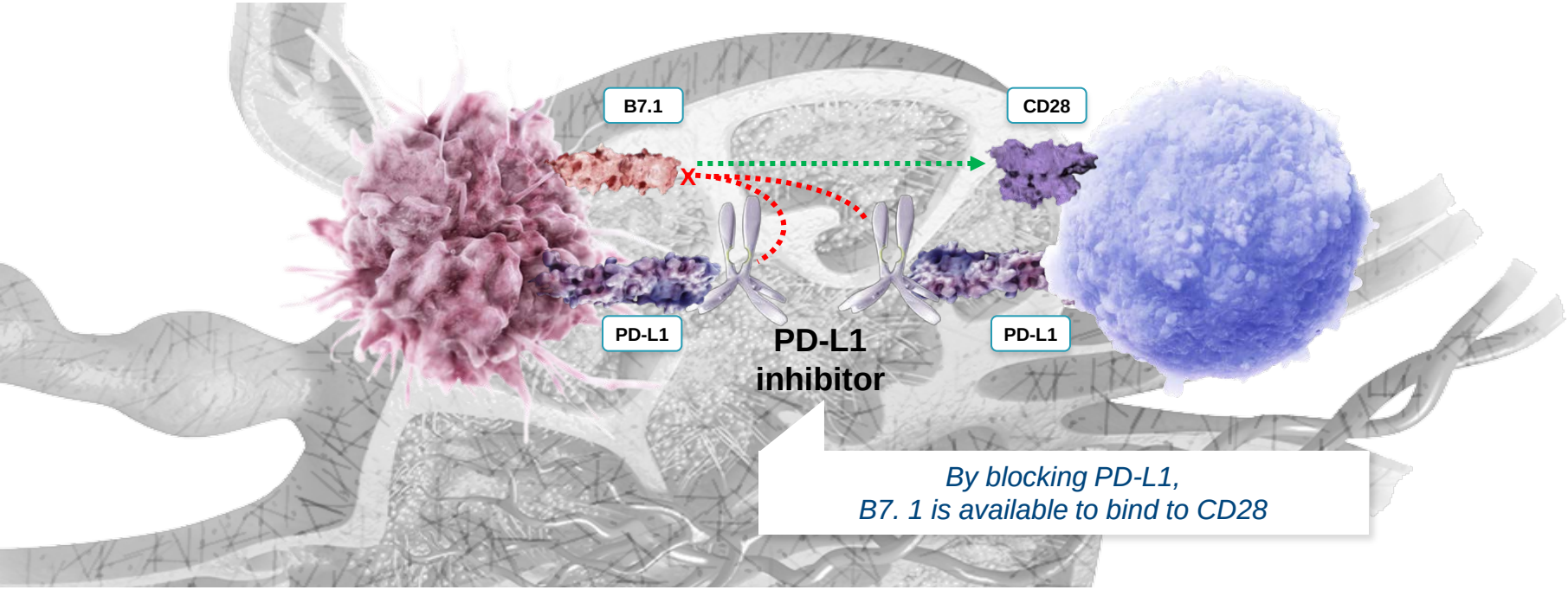
Anti-PD1-Monoclonal Antibody Mechanism of Actio



In the lymph node

PD-L1 inhibitor (e.g. atezolizumab) can enhance T-cell priming and activation in the lymph node

B7.1 binding to CD28 provides a co-stimulatory signal to T cells for priming and activation



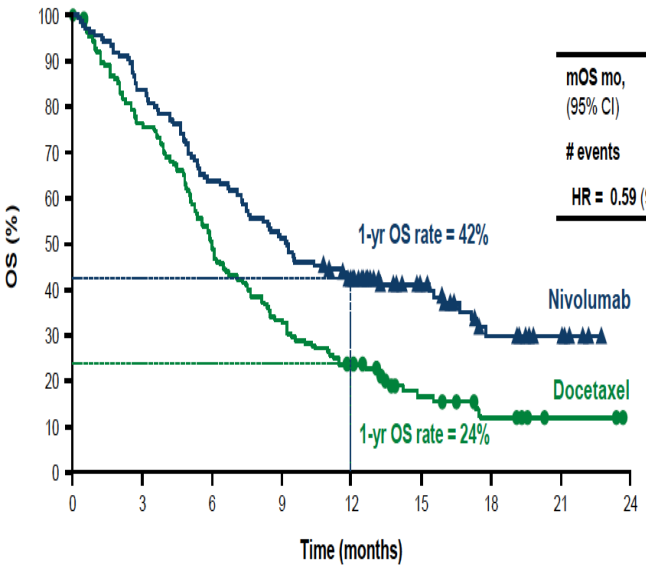
By blocking PD-L1, B7. 1 is available to bind to CD28

PD-L1 inhibitor can enhance T-cell priming and activation through blocking the interaction of PD-L1 with B7.1

Park JJ, et al. Blood 2010; Paterson AM, et al. J Immunol 2011; Yang J, et al. J Immunol 2011; Chen DS, et al. Clin Cancer Res 2012. Genentech data, submitted

Checkmate 017: Squamous cell cancer

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), *P* = 0.00025

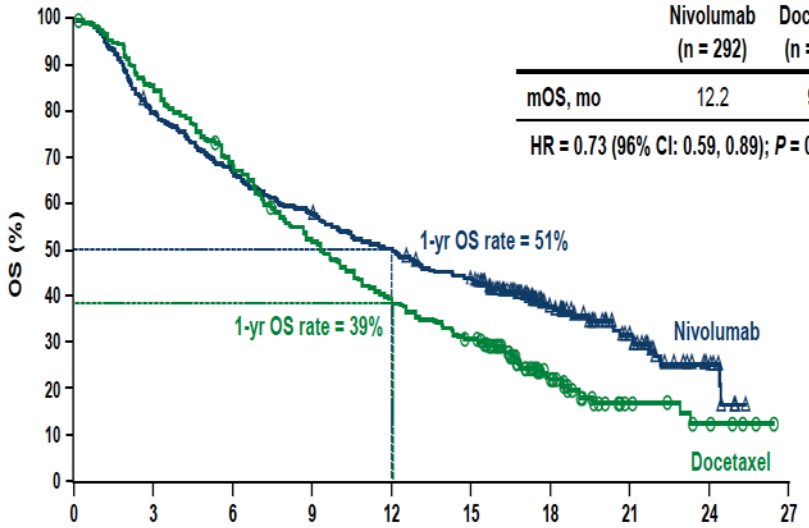
Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Symbols represent censored observations

Checkmate 057: Non-Squamous NSCLC

Overall Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

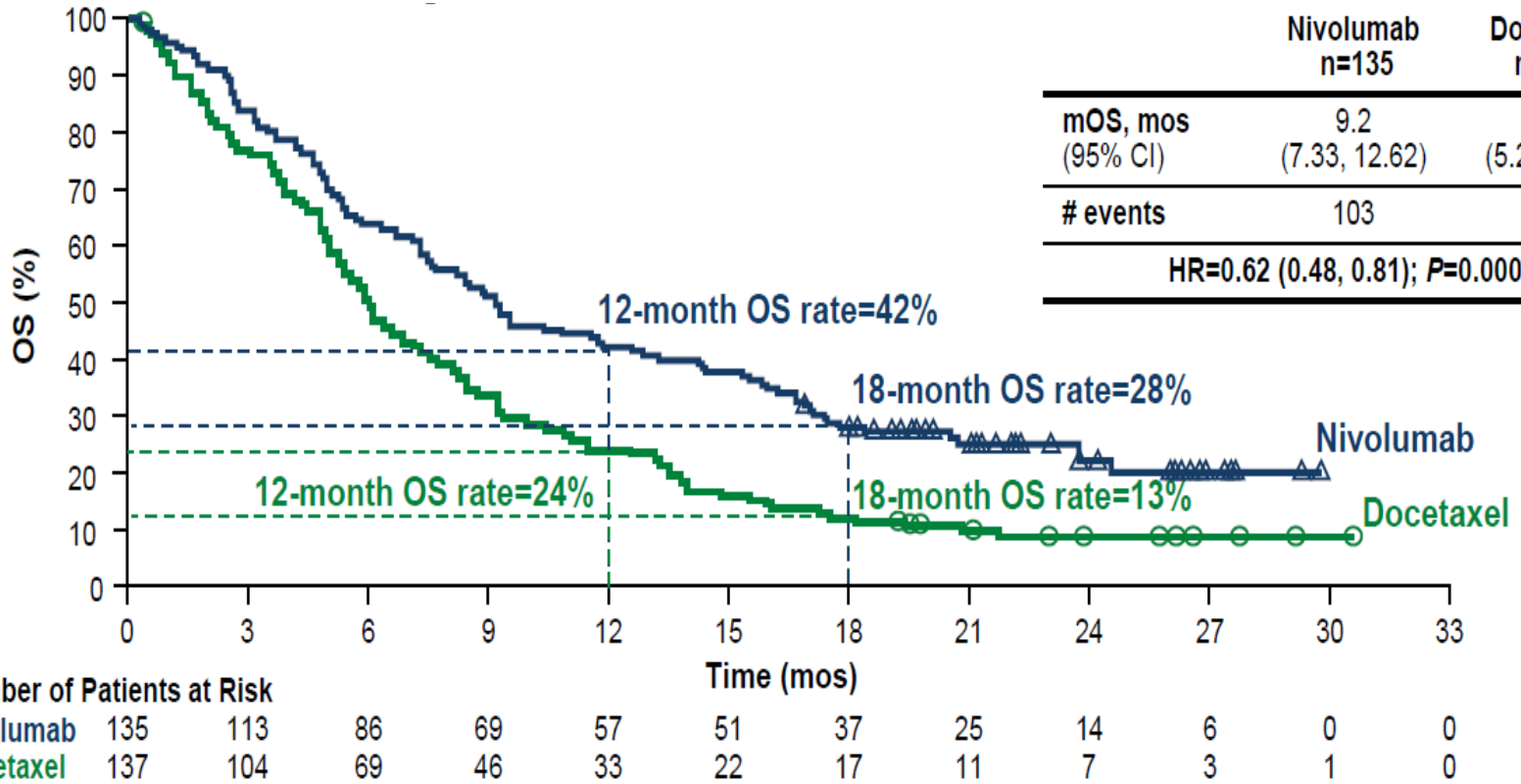
HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015

Number of Patients at Risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

CheckMate 017: updated OS

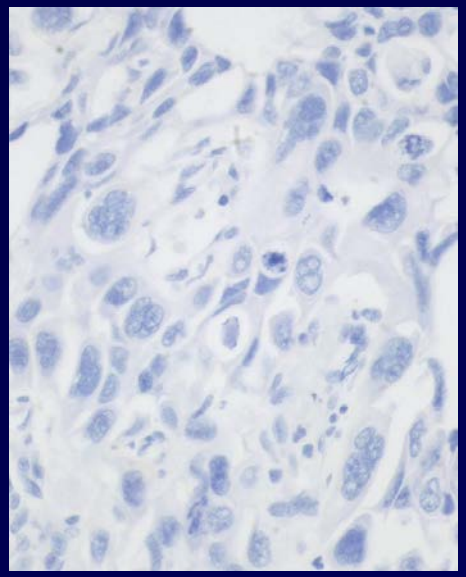


	Nivolumab n=135	Docetaxel n=137
mOS, mos (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR=0.62 (0.48, 0.81); *P*=0.0004		

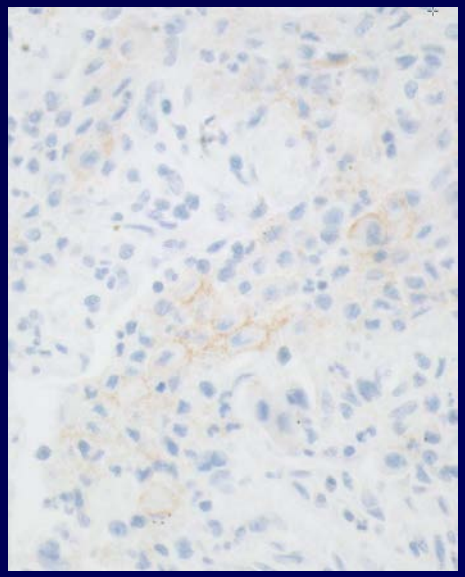
Minimum follow-up for survival: 18 months

Reckamp, et al. WCLC 2015

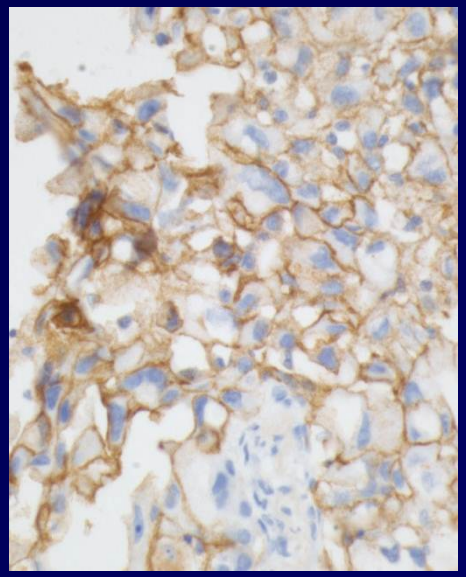
PD-L1 NSCLC Sample Immunohistochemical Staining using the 22C3 antibody



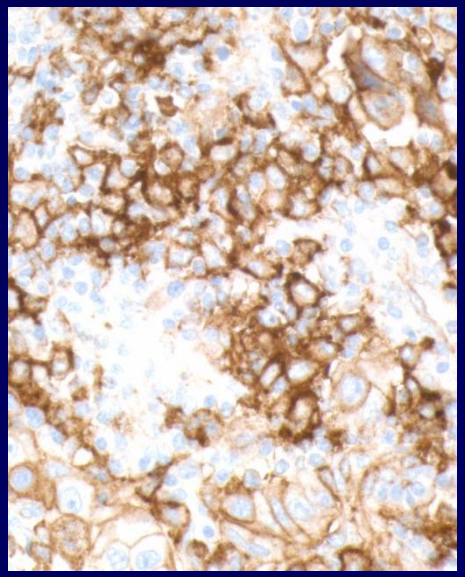
Staining intensity: 0+
PD-L1 = 0% positive



Staining intensity: 1+
PD-L1 = 2% positive



Staining intensity: 2+
PD-L1 = 100% positive



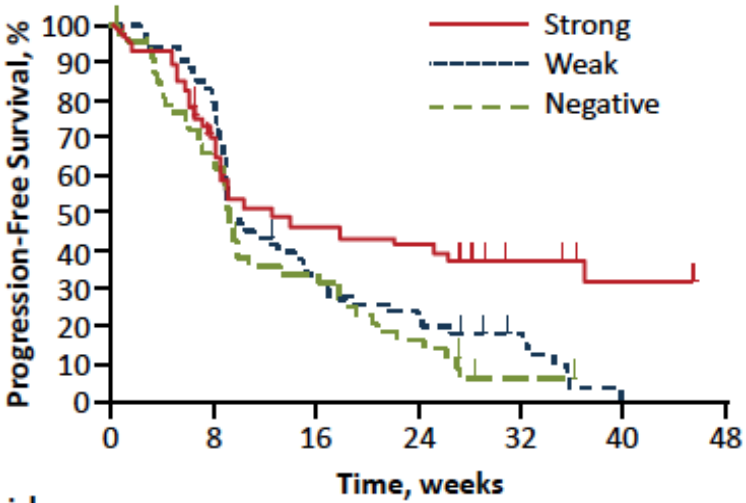
Staining intensity: 3+
PD-L1 = 100% positive

PD-L1-Negative **PD-L1-Positive**

Gandhi L et al, AACR 2014

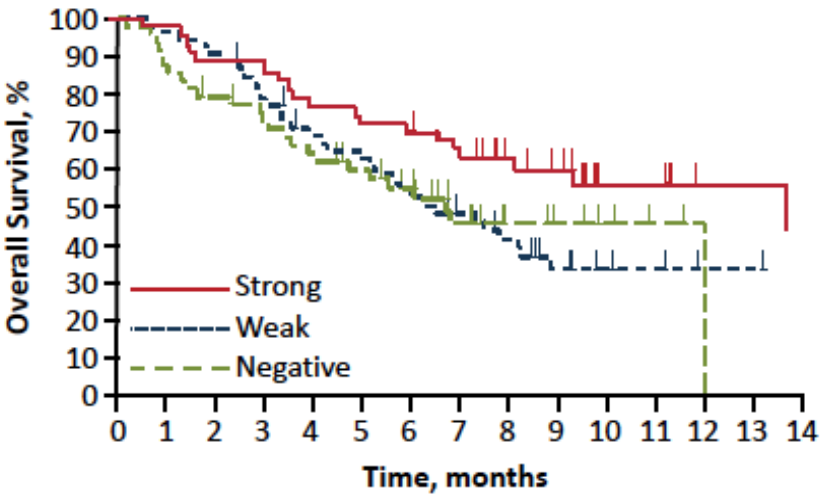
Kaplan-Meier Estimates of Survival

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

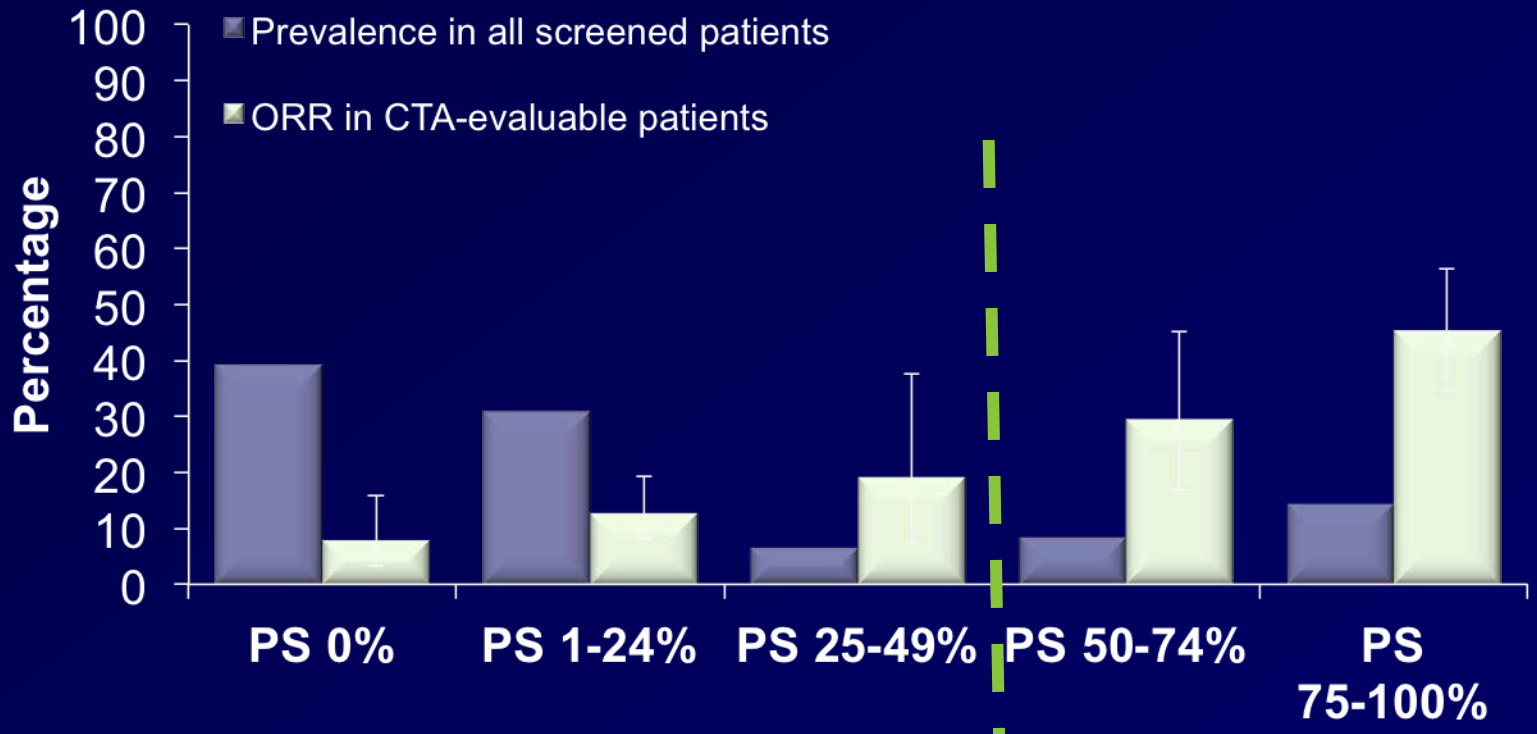


Strong	44	43	38	38	34	32	30	27	21	18	9	8	5	5	4
Weak	53	51	48	40	34	31	26	22	18	11	8	7	5	5	4
Negative	49	42	38	34	29	26	21	14	8	6	4	2	0	0	0

- 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)

Garon EB et al, ESMO, 2014

Prevalence of PD-L1 Positivity and ORR by PD-L1 Proportion Score:

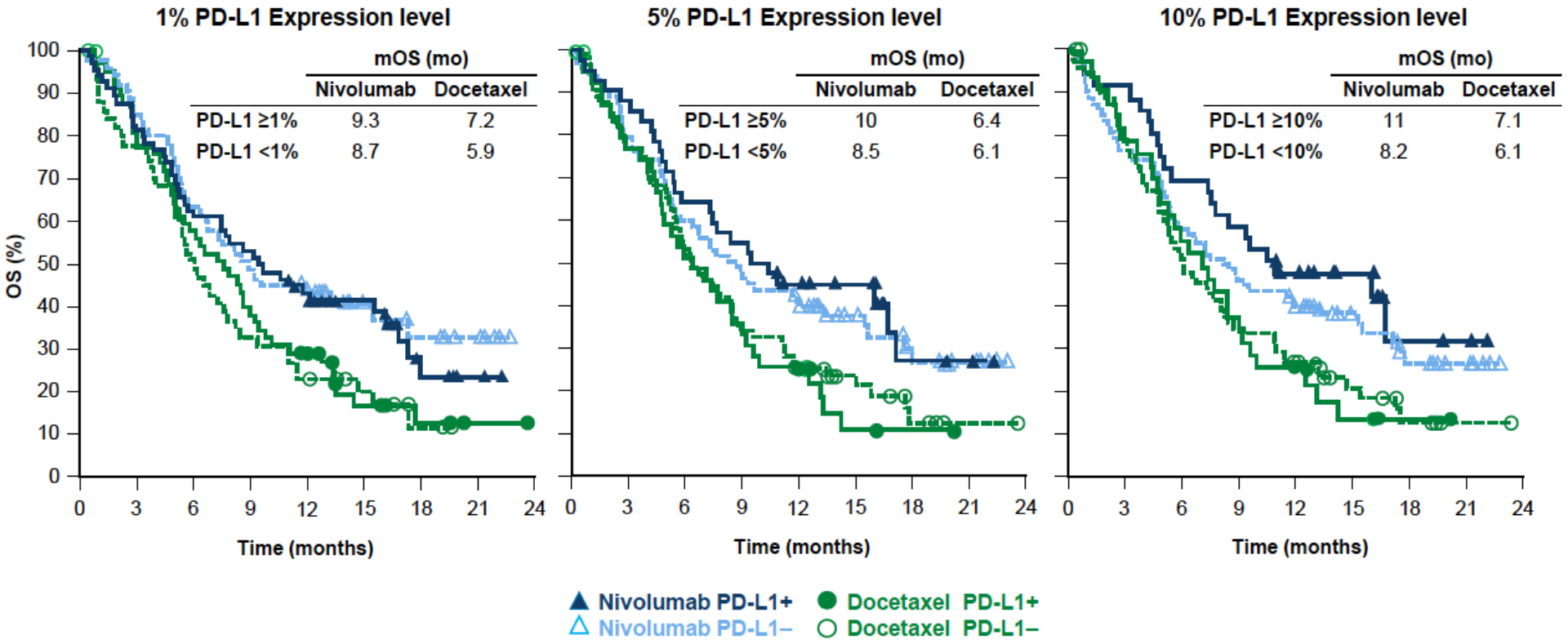


	PS 0%	PS 1-24%	PS 25-49%	PS 50-74%	PS 75-100%
Prevalence, all screened patients, n (%)	323 (39.2)	255 (31.0)	55 (6.7)	71 (8.6)	120 (14.6)
ORR in CTA-evaluable patients, n (%) [95% CI]	7 (8.1) [3.3-15.9]	19 (12.9) [8.0-19.4]	6 (19.4) [7.5-37.5]	13 (29.6) [16.8-45.2]	39 (45.4) [34.6-56.5]

Garon et al, AACR 2015

Checkmate 017: Squamous cell cancer

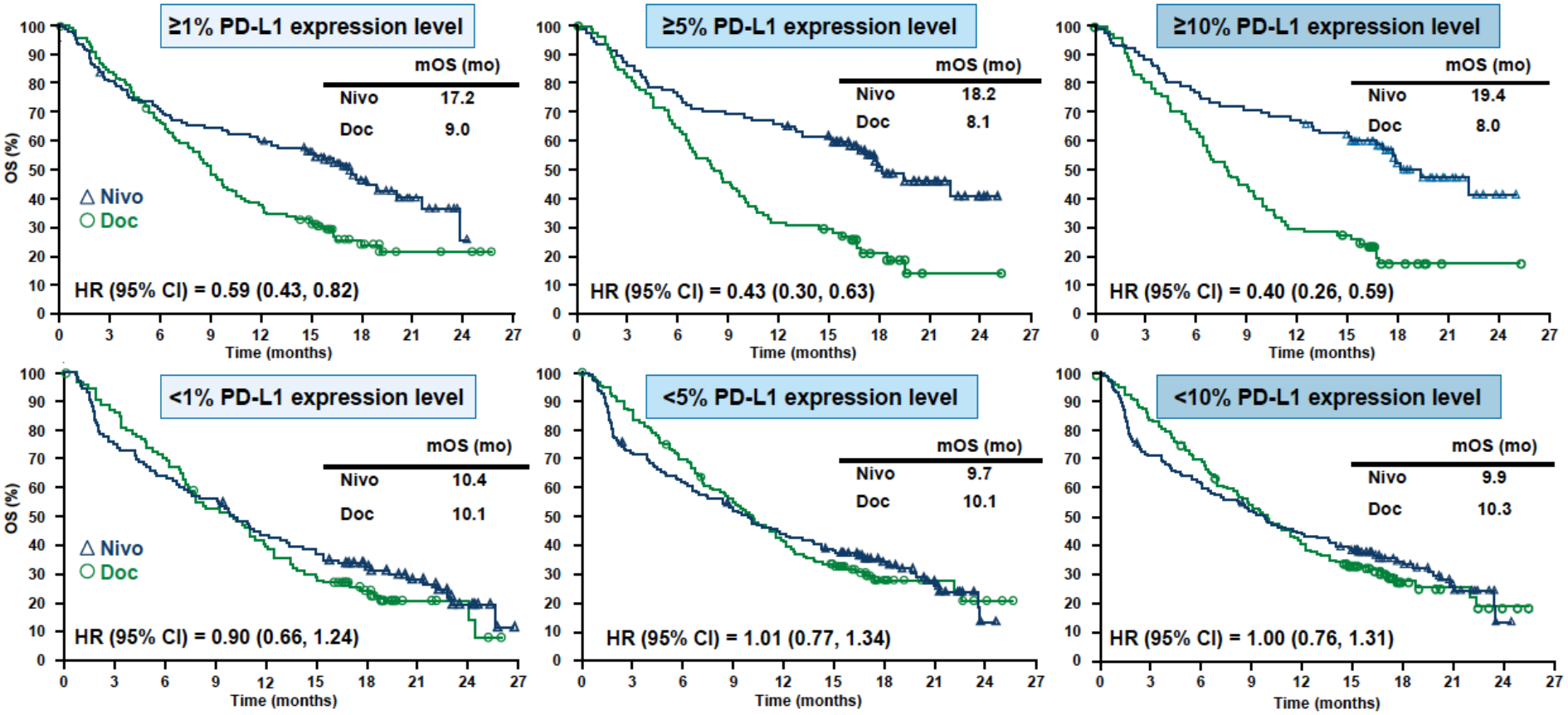
OS by PD-L1 Expression



PRESENTED AT: ASCO Annual '15 Meeting

Checkmate 057: Non-Squamous NSCLC

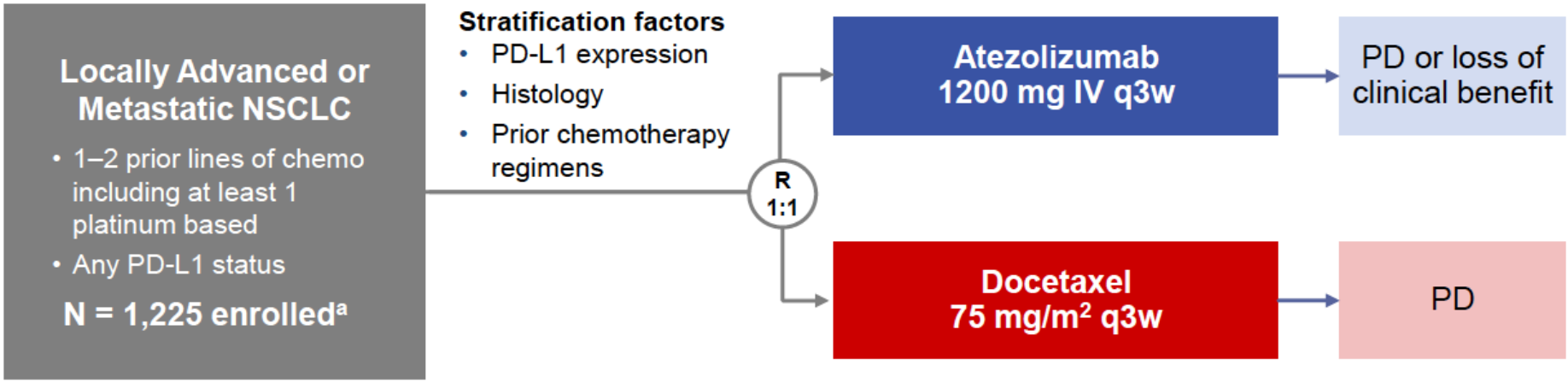
OS by PD-L1 Expression



Symbols represent censored observations.

PRESENTED AT: ASCO Annual '15 Meeting

PHASE III OAK STUDY DESIGN



Primary Endpoints (first 850 enrolled patients):

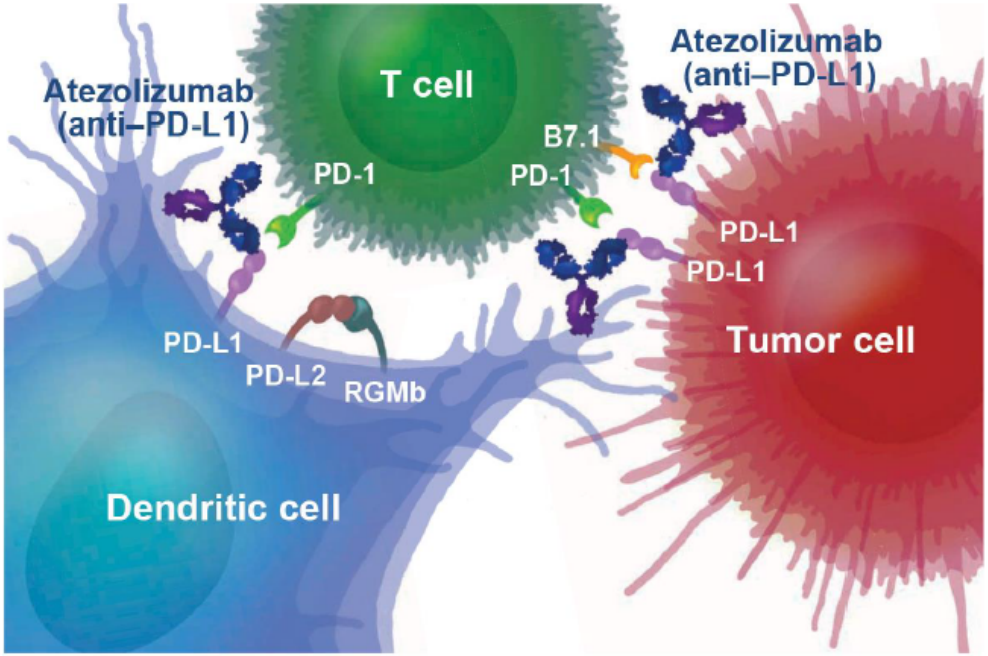
- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

Secondary Endpoints: ORR, PFS, DoR, Safety

[a]A prespecified analysis of the first 850 patients provided sufficient power to test the co-primary endpoints of OS in the ITT and TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression).
TC, tumor cells; IC, tumor-infiltrating immune cells.

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

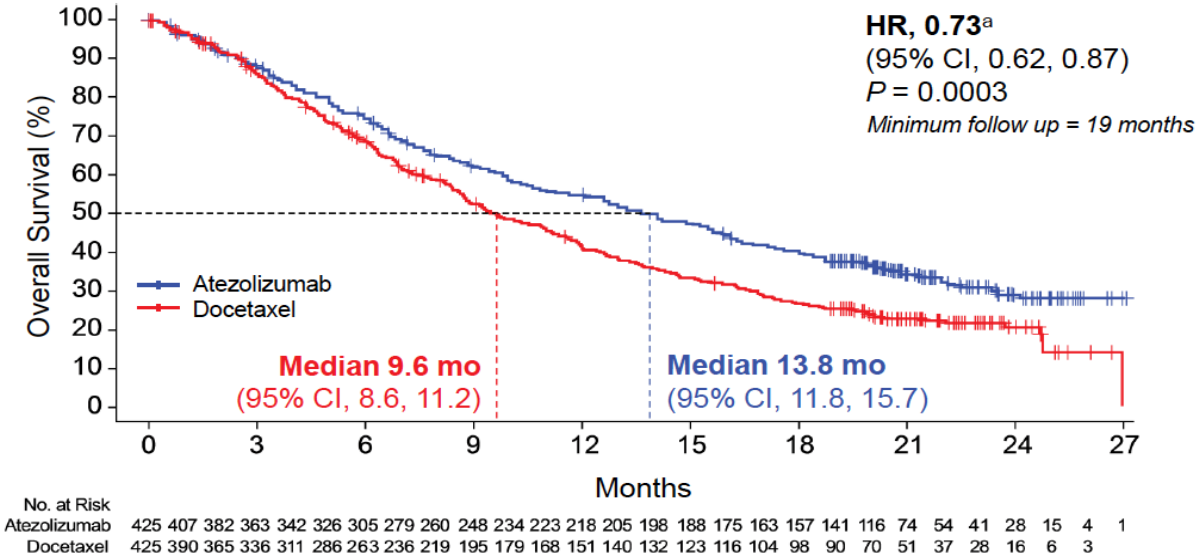
BACKGROUND



- Atezolizumab (anti–PD-L1) is an engineered mAb that inhibits the PD-L1/PD-1 and PD-L1/B7.1 interactions to restore anti-tumor T-cell activity and enhance T-cell priming[1,2]
- In previously treated NSCLC, atezolizumab improved OS vs docetaxel in the randomized Phase II POPLAR study (median OS 12.6 vs 9.7 mo; HR = 0.69)[3,4]
- The data from OAK are the first Phase III results for a PD-L1-directed antibody

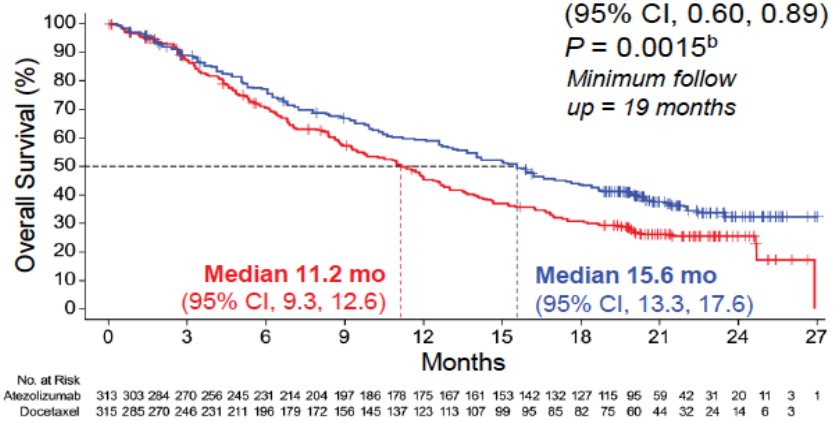
1. Herbst *Nature* 2014. 2 Chen *Immunity* 2013.
3. Fehrenbacher *Lancet* 2016; 4. Smith *J Clin Oncol* 2016.

OVERALL SURVIVAL, ITT (N = 850)

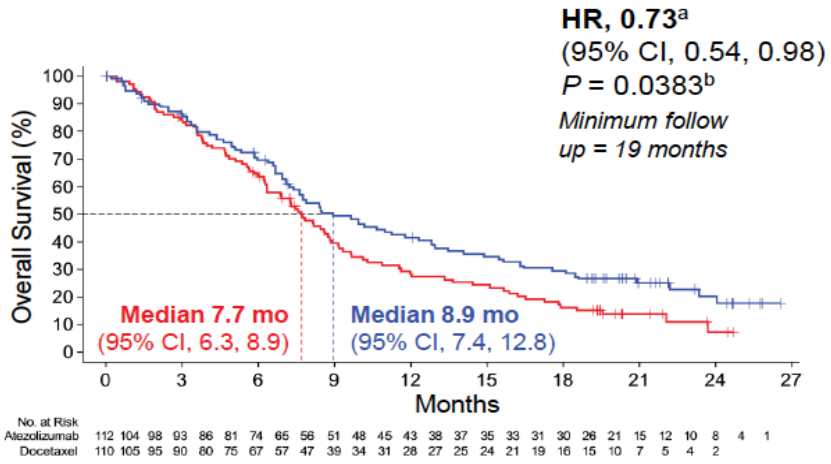


OS BY HISTOLOGY

Non-squamous

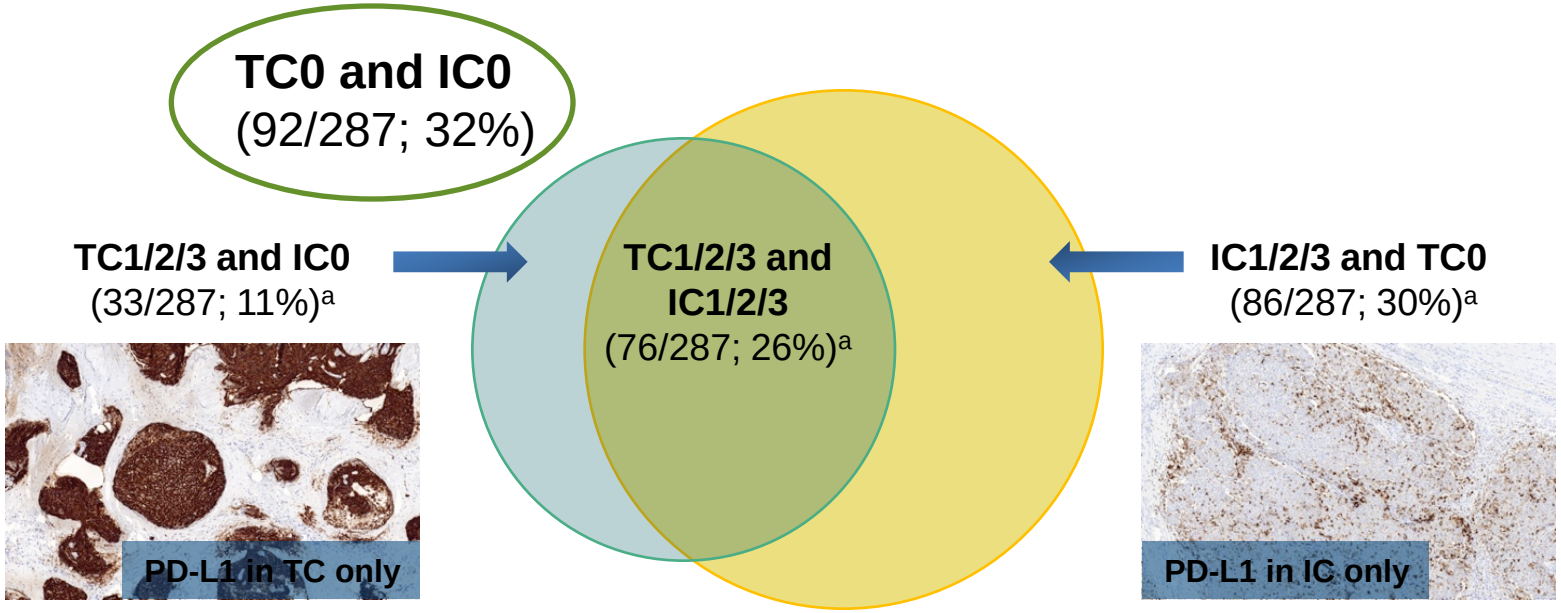


Squamous



Atezolizumab
Docetaxel

POPLAR: Both TC and IC are independent predictors of survival improvement



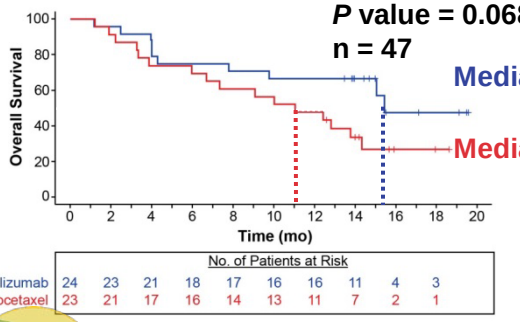
PD-L1 status	OS HR[b] (95% CI)
TC1/2/3 and IC0	0.37 (0.12,1.13)
IC1/2/3 and TC0	0.63 (0.36,1.12)
TC1/2/3 and IC1/2/3	0.60 (0.34, 1.08)
TC1/2/3 or IC1/2/3	0.59 (0.40, 0.85)

[a]Number of patients within subgroup/total study population; Percentage of total study population. [b]Unstratified HR.

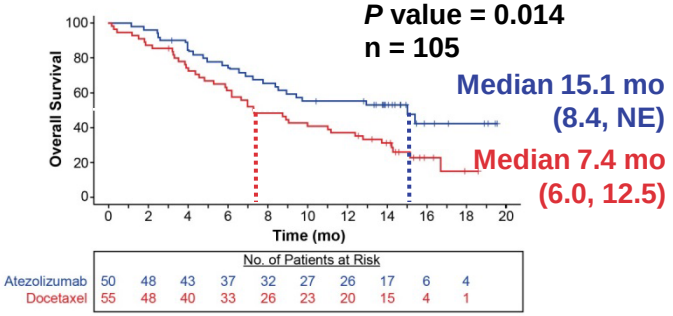
Data cut-off May 8, 2015.

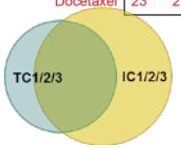
POPLAR: OS by PD-L1 expression

HR[a] = 0.49 (0.22, 1.07)
P value = 0.068
n = 47

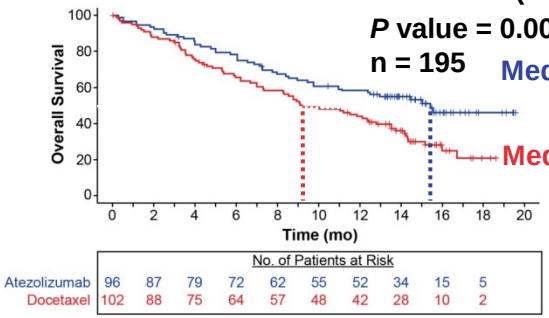


HR[a] = 0.54 (0.33, 0.89)
P value = 0.014
n = 105

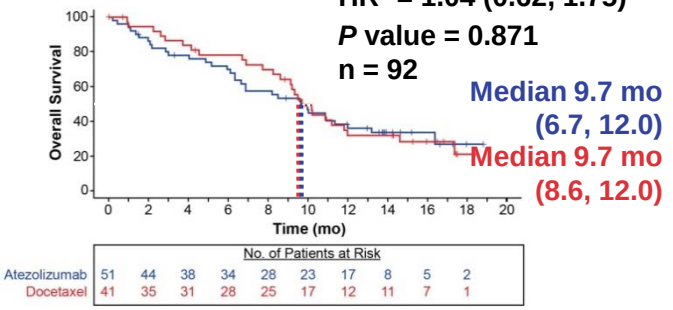




HR[a] = 0.59 (0.40, 0.85)
P value = 0.005
n = 195



HR[a] = 1.04 (0.62, 1.75)
P value = 0.871
n = 92



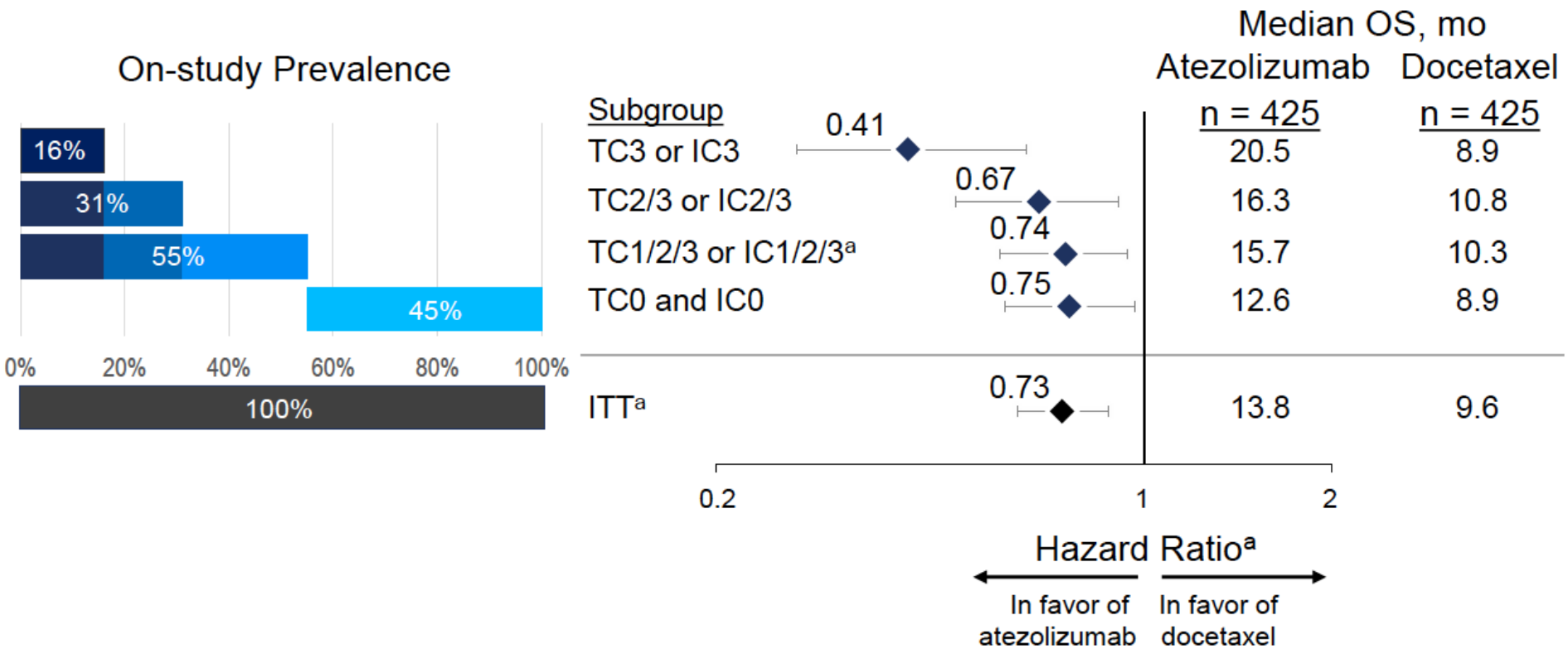
Atezolizumab Docetaxel + Censored

[a]Unstratified HR for subgroups and stratified HR for ITT.

Data cut-off May 8, 2015.

Vansteenkiste, et al. ECC 2015

OS BY PD-L1 EXPRESSION



KEYNOTE-010 (NCT01905657): International, Phase 2/3 Study

Patients

- Advanced NSCLC
- Confirmed PD after ≥2 cycles of platinum-doublet chemotherapy[a]
- PD-L1 TPS ≥1%
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease
- No ILD or pneumonitis requiring systemic steroids

R
1:1:1

- Pembrolizumab 2 mg/kg IV Q3W for 24 months
- Pembrolizumab 10 mg/kg IV Q3W for 24 months
- Docetaxel 75 mg/m^2 Q3W per local guidelines[c]

Stratification factors:

- ECOG PS (0 vs 1)
- Region (East Asia vs non-East Asia)
- PD-L1 status[b] (TPS ≥50% vs 1%-49%)

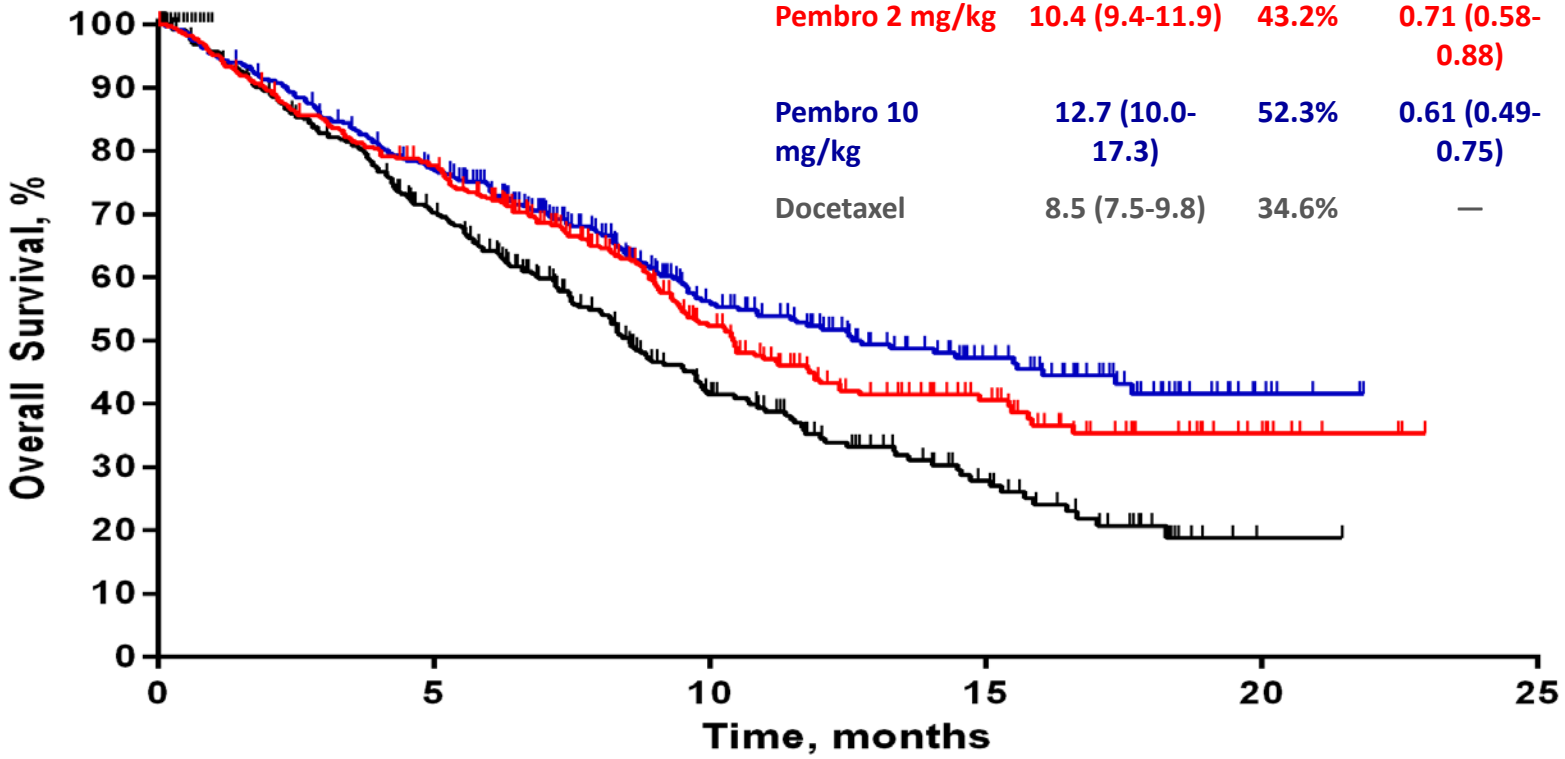
End points in the total population and TPS ≥50% stratum

- Primary: PFS and OS
- Secondary: ORR, duration of response, safety

[a]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.

OS, 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)	0.00076
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.00001
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—

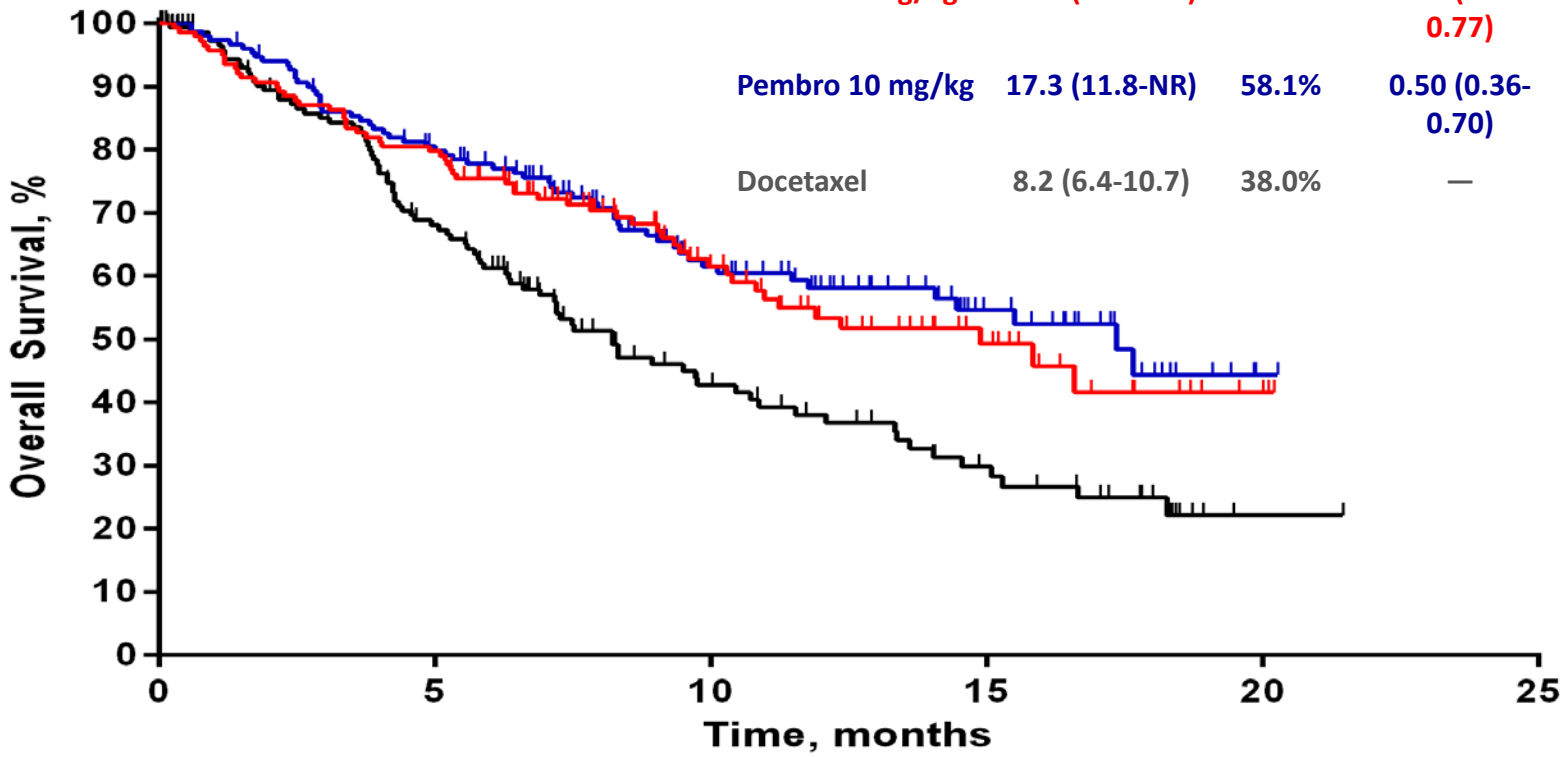


Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

OS, PD-L1 TPS ≥50% Stratum

Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	14.9 (10.4-NR)	53.4%	0.54 (0.38-0.77)	0.00024
Pembro 10 mg/kg	17.3 (11.8-NR)	58.1%	0.50 (0.36-0.70)	0.00002
Docetaxel	8.2 (6.4-10.7)	38.0%	—	—



Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

COPENHAGEN 2016 ESMO congress

KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy as First-Line Therapy for Advanced NSCLC With a PD-L1 TPS ≥50%

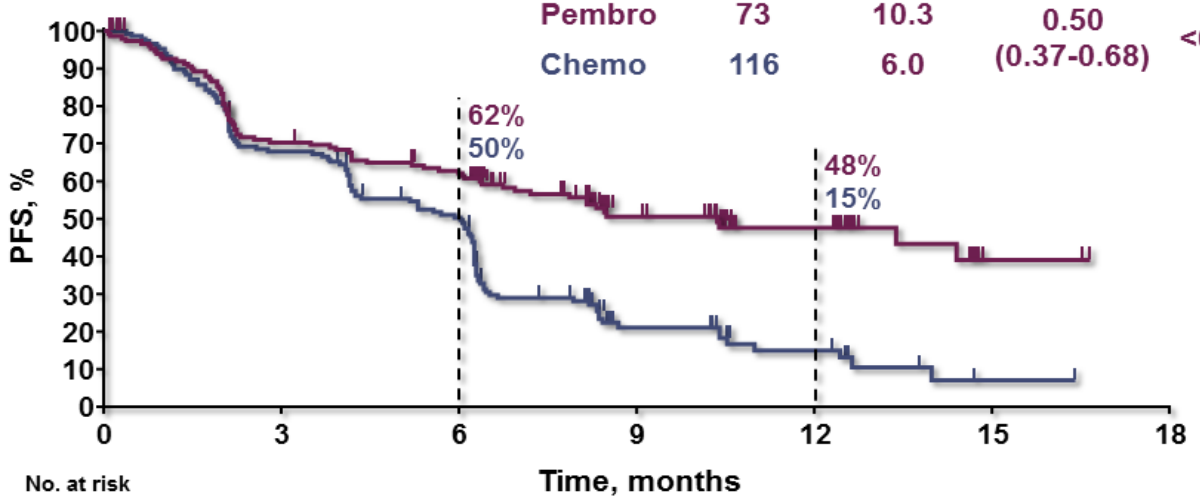
Martin Reck,[1] Delvys Rodríguez-Abreu,[2] Andrew G. Robinson,[3] Rina Hui,[4] Tibor Csőszi,[5] Andrea Fülöp,[6] Maya Gottfried,[7] Nir Peled,[8] Ali Tafreshi,[9] Sinead Cuffe,[10] Mary O'Brien,[11] Suman Rao,[12] Katsuyuki Hotta,[13] Melanie A. Leiby,[14] Gregory M. Lubiniecki,[14] Yue Shentu,[14] Reshma Rangwala,[14] and Julie R. Brahmer[15] on behalf of the KEYNOTE-024 investigators

[1]Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), member of the German Center for Lung Research (DZL), Grosshansdorf, Germany; [2]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [3]Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; [4]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [5]Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; [6]Országos Korányi TBC és Pulmonológiai Intézet, Budapest, Hungary; [7]Meir Medical Center, Kfar-Saba, Israel; [8]Davidoff Cancer Center, Tel Aviv University, Petah Tikva, Israel; [9]Southern Medical Day Care Centre, Wollongong, NSW, Australia; [10]St. James's Hospital and Cancer Trials Ireland (formerly ICORG – All Ireland Cooperative Oncology Research Group), Dublin, Ireland; [11]The Royal Marsden Hospital, London, UK; [12]MedStar Franklin Square Hospital, Baltimore, MD, USA; [13]Okayama University Hospital, Okayama, Japan; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

M Reck. ESMO 2016.

Progression-Free Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



No. at risk

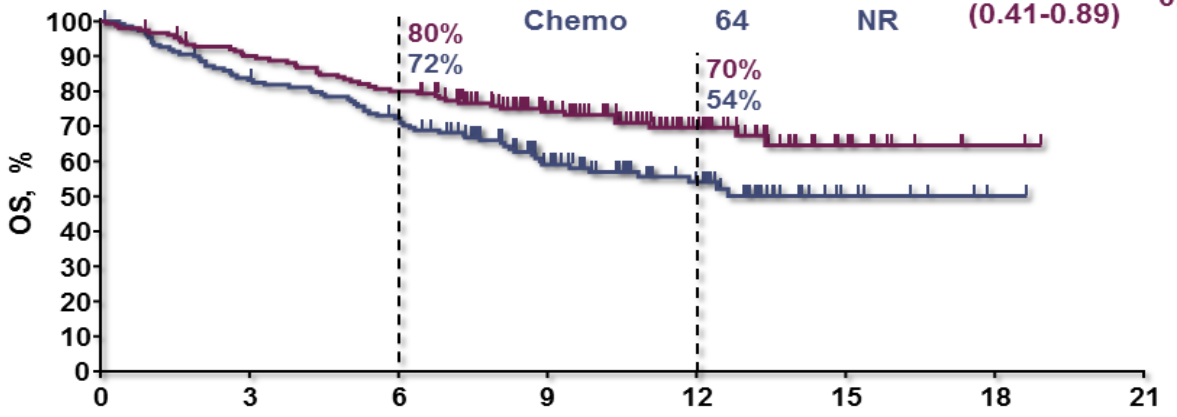
154	104	89	44	22	3	1
151	99	70	18	9	1	0

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

M Reck. ESMO 2016.

Overall Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		

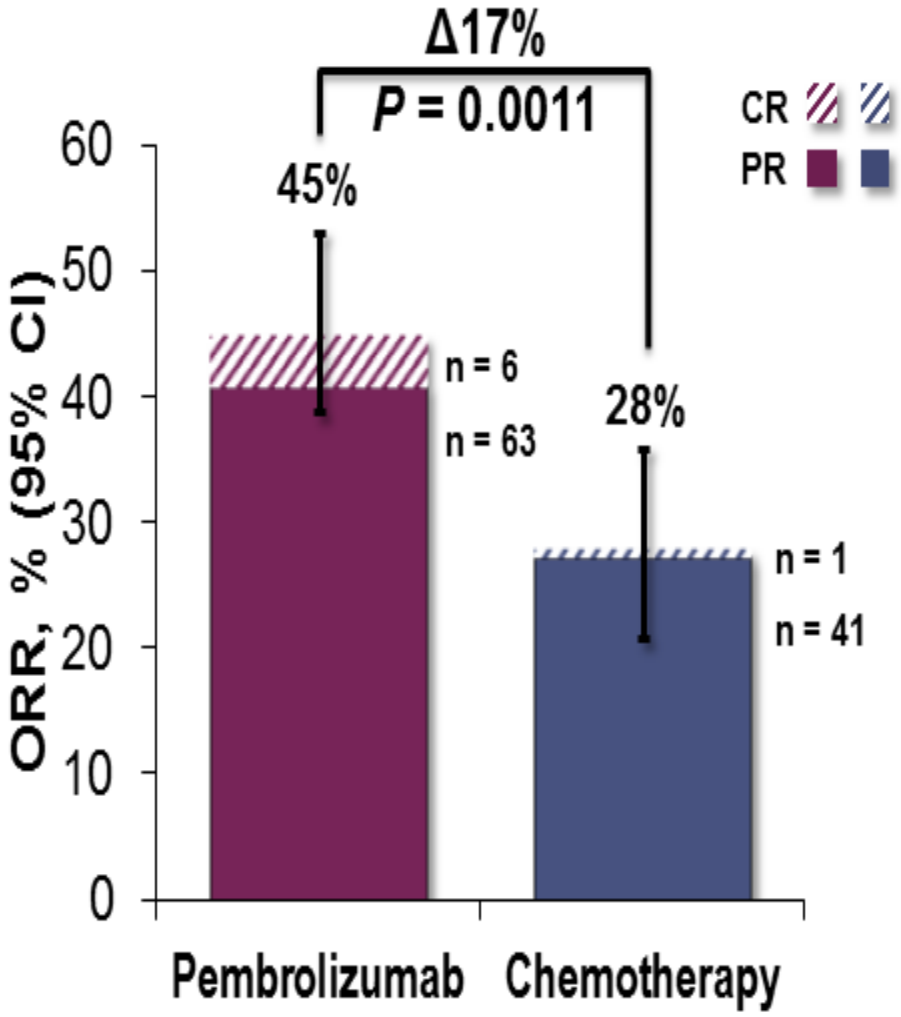


No. at risk

154	136	121	82	39	11	2	0
151	123	106	64	34	7	1	0

Data cut-off: May 9, 2016.

Confirmed Objective Response Rate



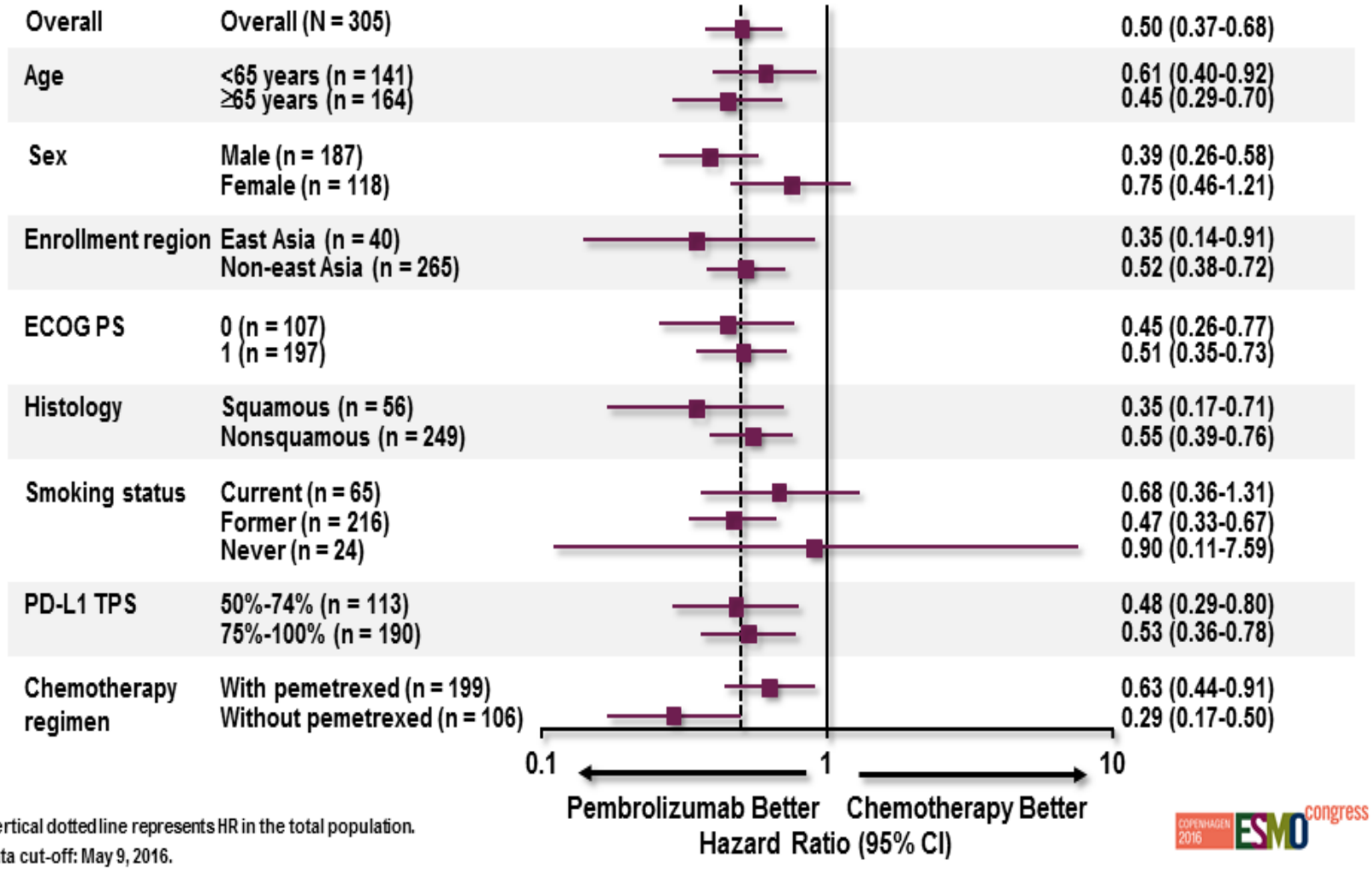
	Pembro Responders n = 69	Chemo Responders n = 42
TTR, mo median (range)	2.2 (1.4-8.2)	2.2 (1.8-12.2)
DOR, mo median (range)	NR (1.9+ to 14.5+)	6.3 (2.1+ to 12.6+)

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

Keynote -024

M Reck. ESMO 2016.

Progression-Free Survival in Subgroups



Vertical dotted line represents HR in the total population.
Data cut-off: May 9, 2016.

COPENHAGEN 2016 ESMO congress

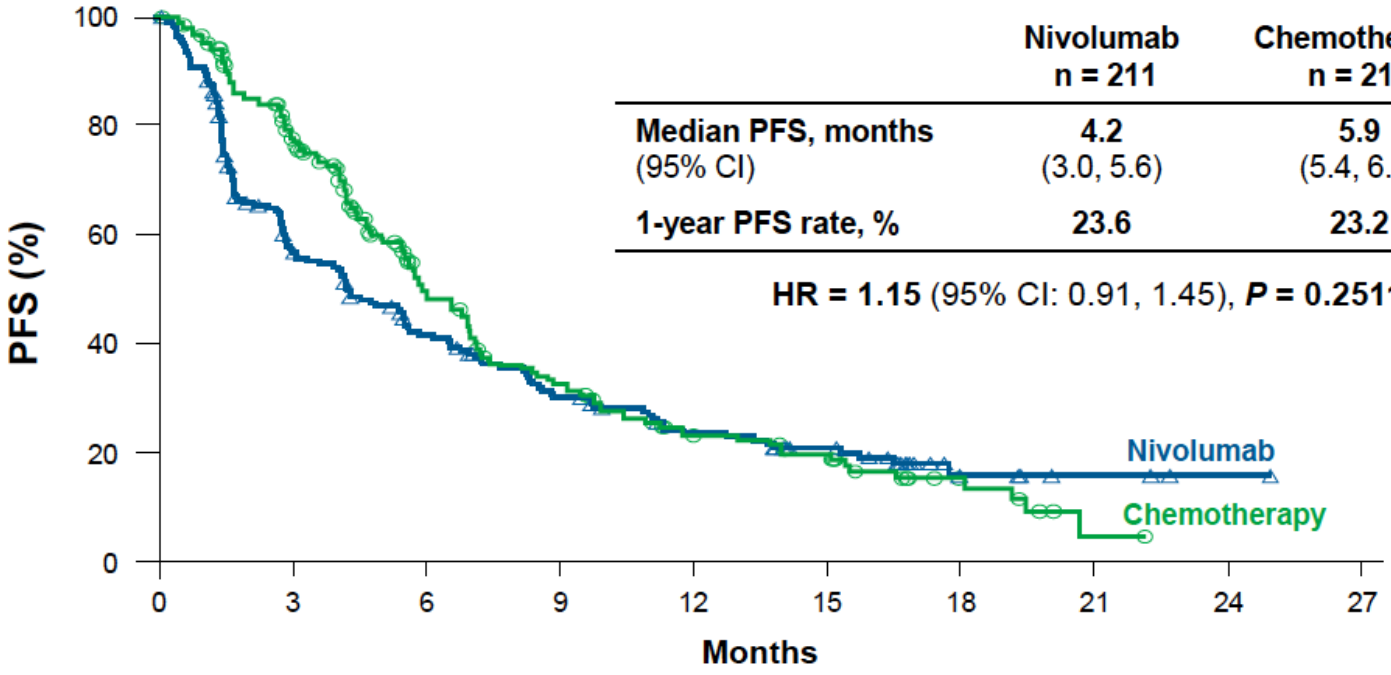
CheckMate 026: A Phase 3 Trial of Nivolumab vs Investigator's Choice of Platinum-Based Doublet Chemotherapy as First-line Therapy for Stage IV/ Recurrent Programmed Death Ligand 1–Positive NSCLC

Mark A. Socinski,[1] Benjamin Creelan,[2] Leora Horn,[3] Martin Reck,[4] Luis Paz-Ares,[5] Martin Steins,[6] Enriqueta Felip,[7] Michel van den Heuvel,[8] Tudor Eliade Ciuleanu,[9] Firas Badin,[10] Neal Ready,[11] T. Jeroen N. Hiltermann,[12] Suresh Nair,[13] Rosalyn Juergens,[14] Solange Peters,[15] Elisa Minenza,[16] William J. Geese,[17] Prabhu Bhagavatheeswaran,[17] Allen C. Chen,[17] David P. Carbone[18]

[1]UPMC Cancer Center, Pittsburgh, PA, USA; [2]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [3]Vanderbilt University Medical Center, Nashville, TN, USA; [4]LungenClinic Grosshansdorf, Airway Research Center North (ARCN), Grosshansdorf, Germany; [5]Hospital Universitario Doce de Octubre & CNIO, Madrid, Spain; [6]Thoraxklinik-Heidelberg GmbH, Heidelberg, Germany; [7]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [8]Antoni Van Leeuwenhoek Ziekenhuis, Amsterdam, Netherlands; [9]Prof. Dr. Ion Chiricuta Institute of Oncology and UMF Iuliu Hatieganu, Cluj-Napoca, Romania; [10]Baptist Health Lexington, Lexington, KY, USA; [11]Duke University Medical Center, Durham, NC, USA; [12]University of Groningen and University Medical Center Groningen, Groningen, Netherlands; [13]Lehigh Valley Health Network, Allentown, PA, USA; [14]Juravinski Cancer Centre, Ontario, Canada; [15]University of Lausanne, Lausanne, Switzerland; [16]Ospedale S. Maria Nuova, Terni, Italy; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months (95% CI)	**4.2** (3.0, 5.6)	**5.9** (5.4, 6.9)
1-year PFS rate, %	**23.6**	**23.2**

HR = 1.15 (95% CI: 0.91, 1.45), ***P* = 0.2511**

No. of patients at risk:										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

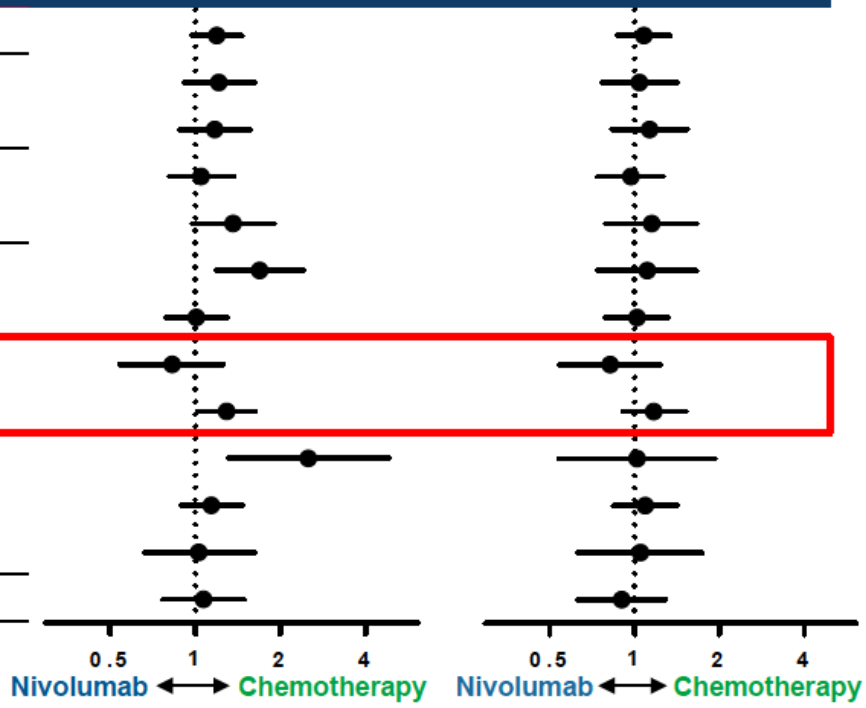
All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)

Checkmate-026

PFS and OS Subgroup Analyses (All Randomized Patients)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

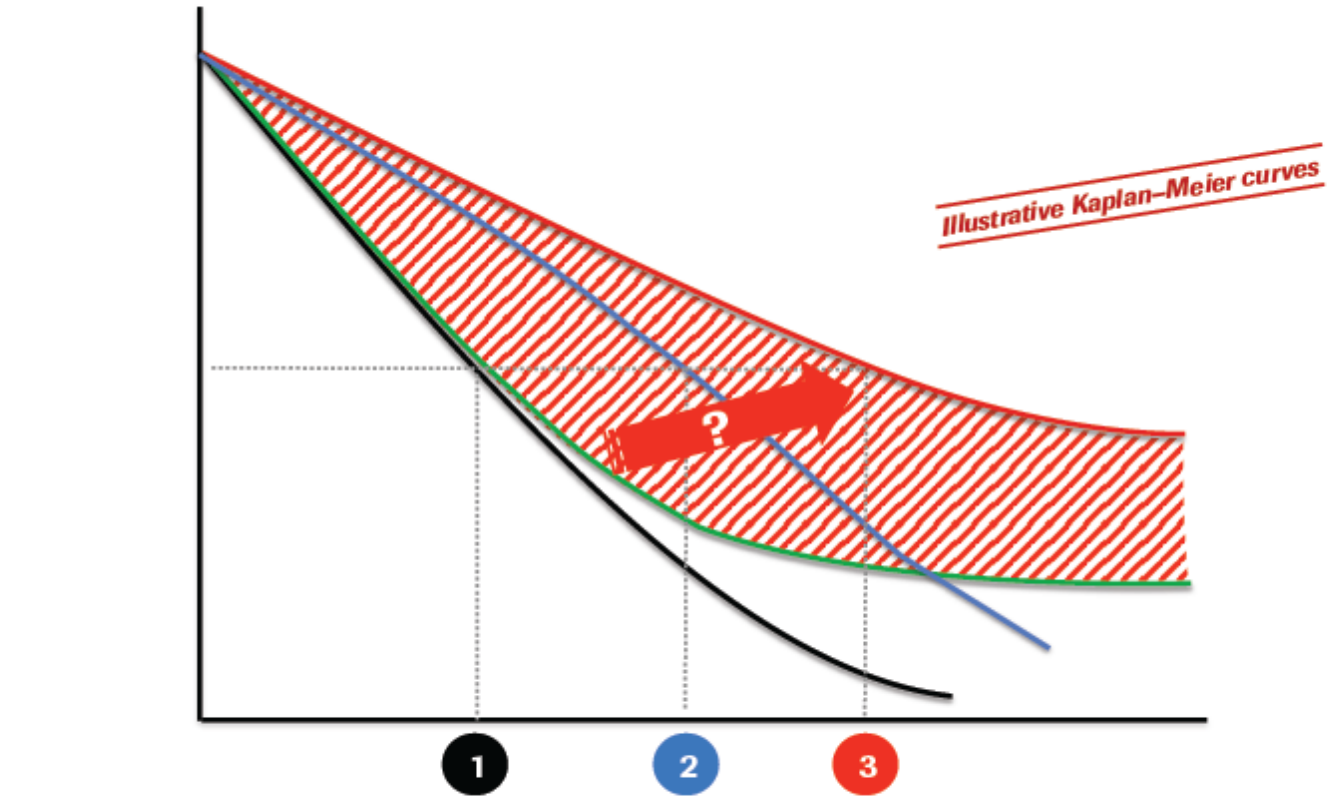
Subgroup	Patients, n		Unstratified HR	
	Nivolumab	Chemotherapy	PFS	OS
Overall	271	270	1.19	1.08
≥65 years	123	137	1.21	1.04
<65 years	148	133	1.17	1.13
Male	184	148	1.05	0.97
Female	87	122	1.36	1.15
ECOG PS = 0	85	93	1.69	1.11
ECOG PS ≥1	185	177	1.01	1.02
Squamous	65	64	0.83	0.82
Non-squamous	206	206	1.29	1.17
Never smoker	30	29	2.51	1.02
Former smoker	186	182	1.14	1.09
Current smoker	52	55	1.03	1.05
≥50% PD-L1+	88	126	1.07	0.90



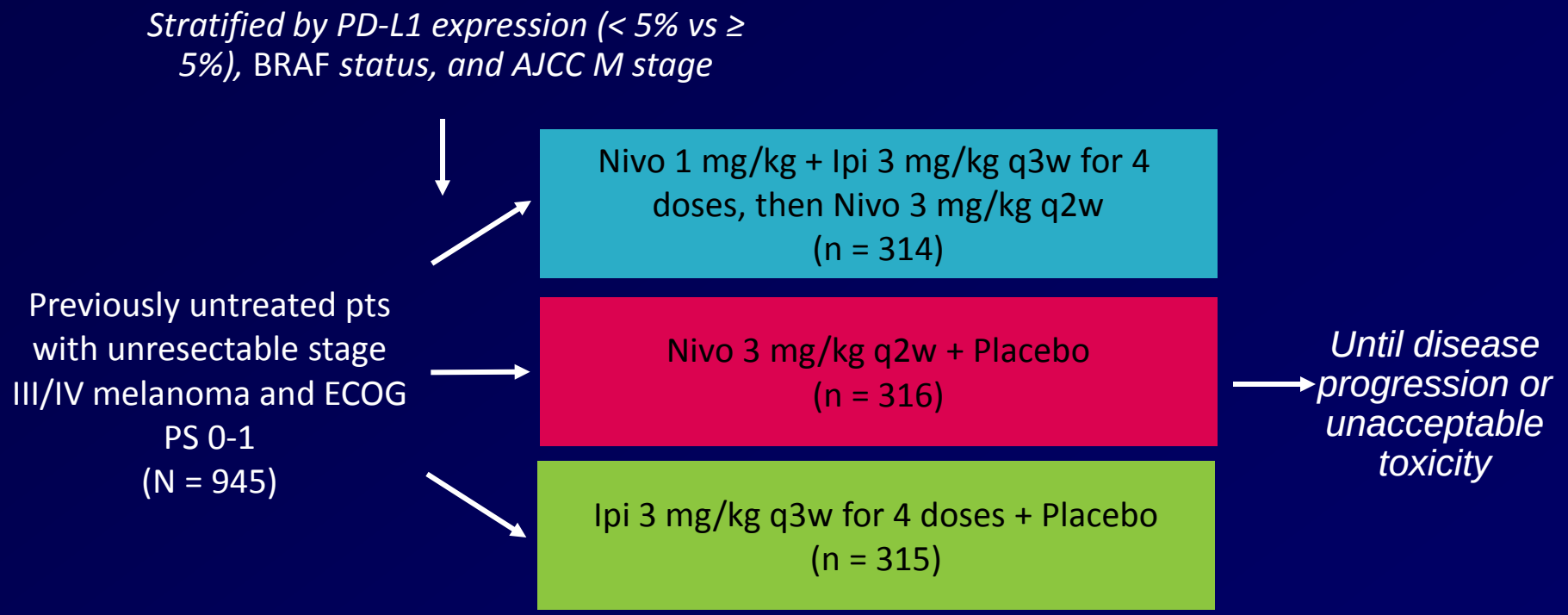
Is Combination Immune Checkpoint Therapy Better?

Cancer immunotherapy in the future

Better patient selection, combinations, broader use?



CheckMate 067: Phase III Trial of Nivo + Ipi vs Nivo vs Ipi for 1st line Treatment of Melanoma

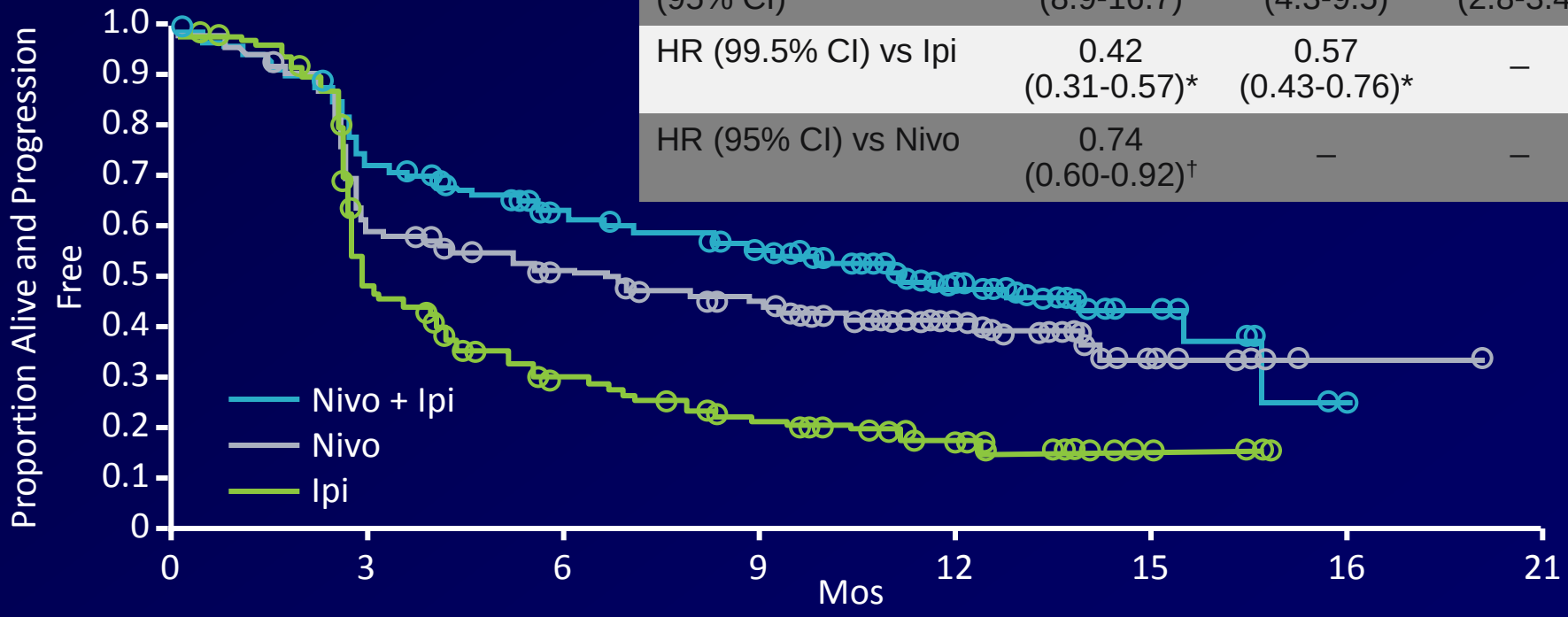


- **Coprimary endpoints: PFS, OS (OS data still blinded)**
- **Secondary endpoints: ORR, tumor PD-L1 expression and efficacy, safety**

Wolchok JD, et al. ASCO 2015. Abstract LBA1.

CheckMate 067: Improved PFS with Nivo + Ipi or Nivo Alone vs Ipi Alone

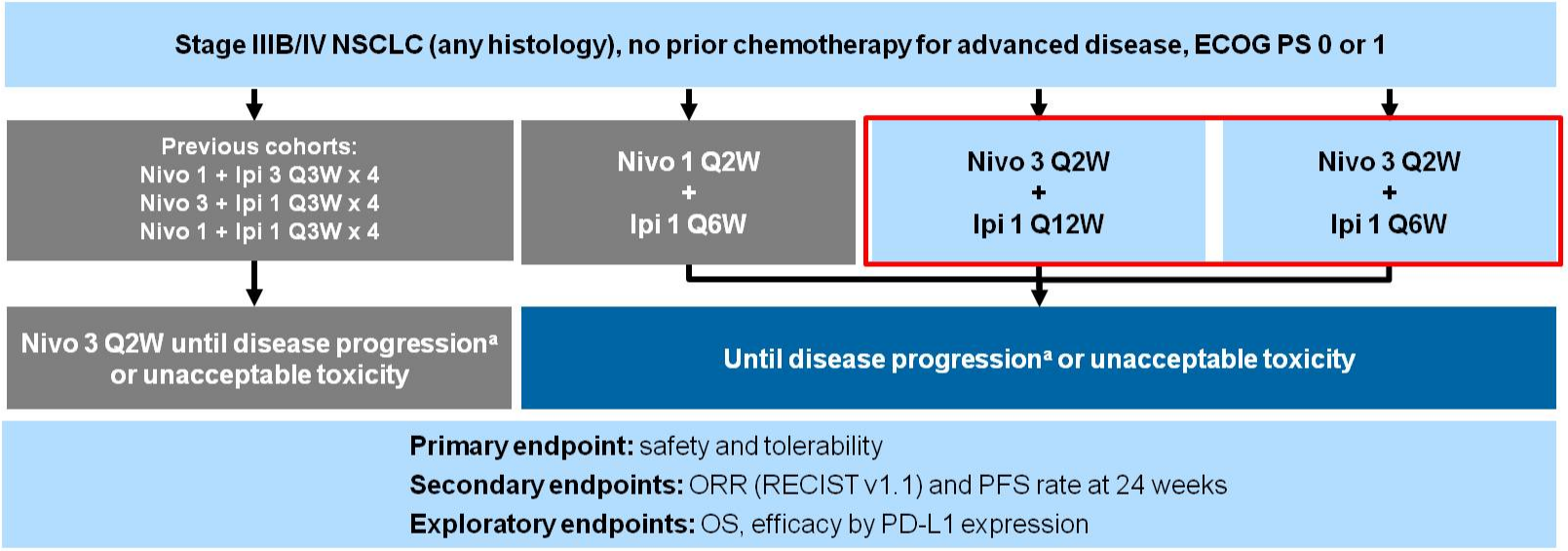
	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median PFS, mos (95% CI)	11.5 (8.9-16.7)	6.9 (4.3-9.5)	2.9 (2.8-3.4)
HR (99.5% CI) vs Ipi	0.42 (0.31-0.57)*	0.57 (0.43-0.76)*	–
HR (95% CI) vs Nivo	0.74 (0.60-0.92)†	–	–



*Stratified log-rank $P < .00001$ vs Ipi.

†Exploratory endpoint. Study not powered to detect a statistical difference between Nivo + Ipi and Nivo.

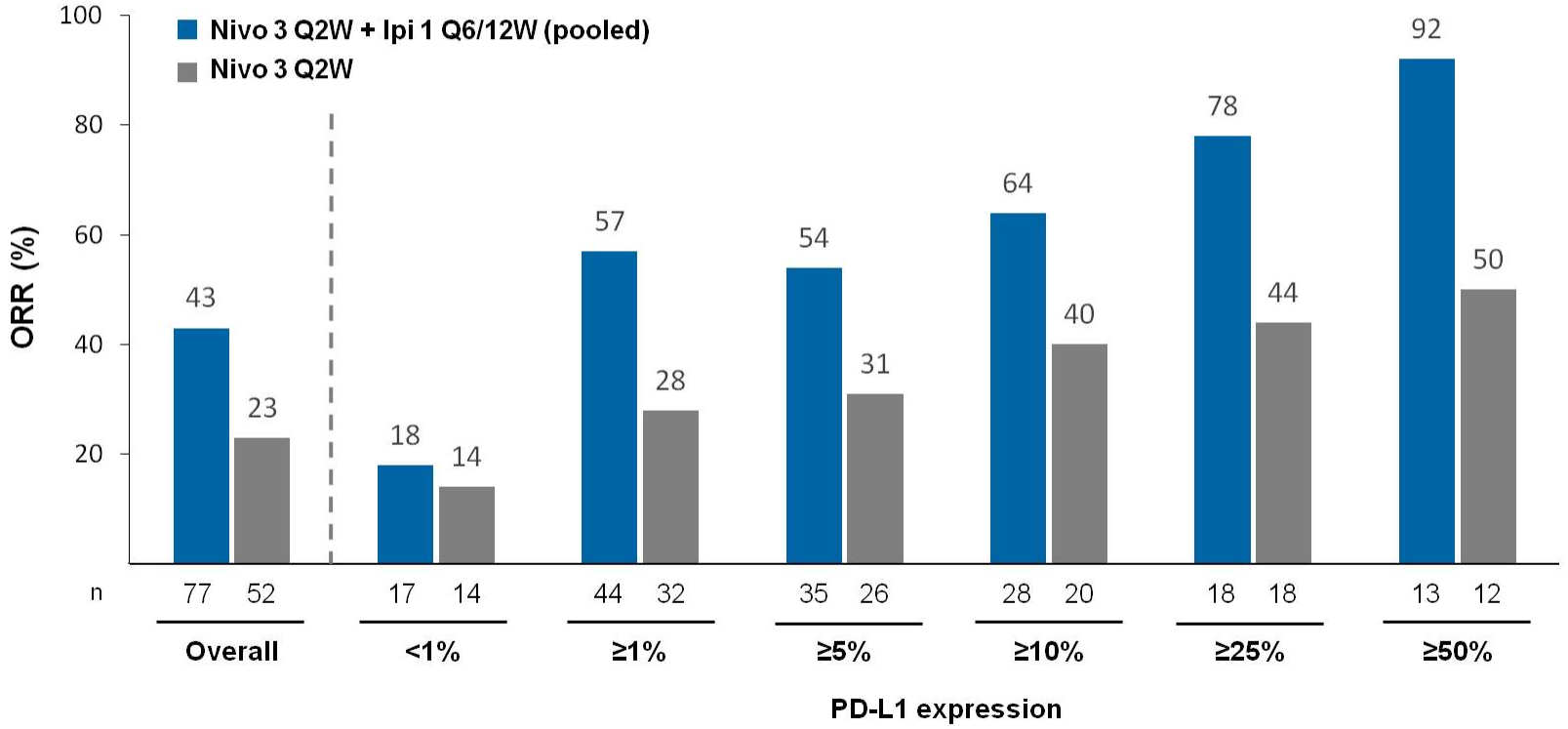
Phase 1 CheckMate 012 Study Design: Nivolumab Plus Ipilimumab in First-line NSCLC



- The safety and tolerability of the nivolumab–ipilimumab combination was improved with less frequent ipilimumab dosing[5]
- Schedules with nivolumab 3 mg/kg also showed increased clinical efficacy in a previous analysis[5]
- Here, we report longer follow-up on nivolumab 3 mg/kg plus ipilimumab schedules[b]

[a]Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit
[b]February 2016 database lock
Ipilimumab and nivolumab dosing are shown in mg/kg IV (eg, nivo 1 = nivolumab 1 mg/kg IV)

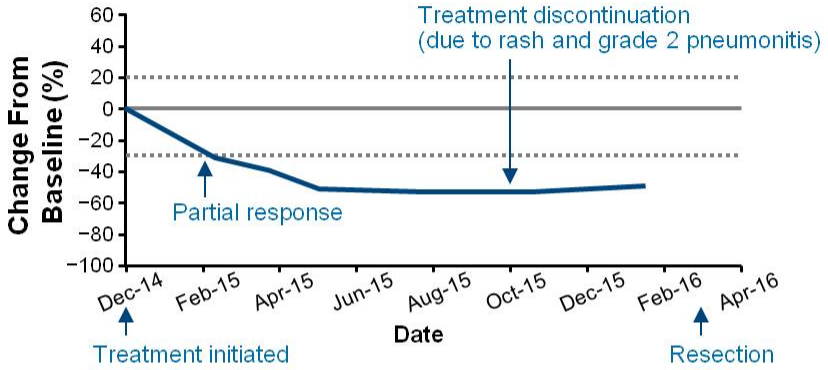
Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy Across All Tumor PD-L1 Expression Levels



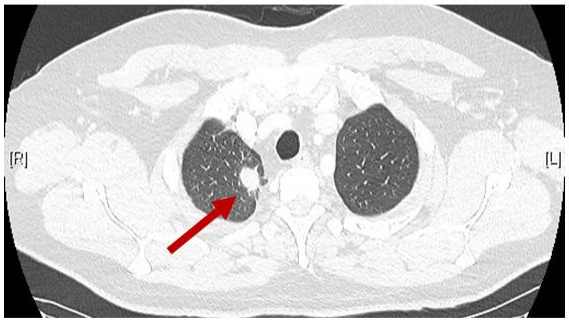
Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock

Case of Pathological CR in One Patient Treated With Nivo 3 Q2W + Ipi 1 Q6W

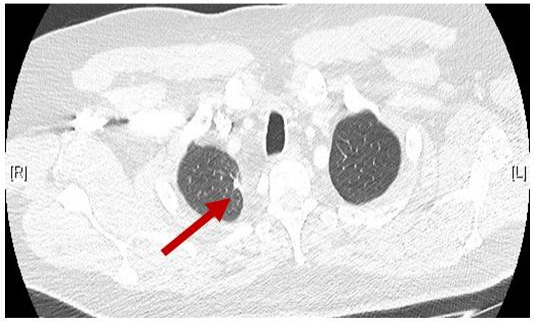
- 54-yr-old male (former smoker, 52 pack-yr) with metastatic large-cell lung cancer (PD-L1 <1%[a])
  - 53% total tumor size reduction by RECIST
  - Radiographic residual lesions in the lung and mediastinal lymph nodes, without distant disease



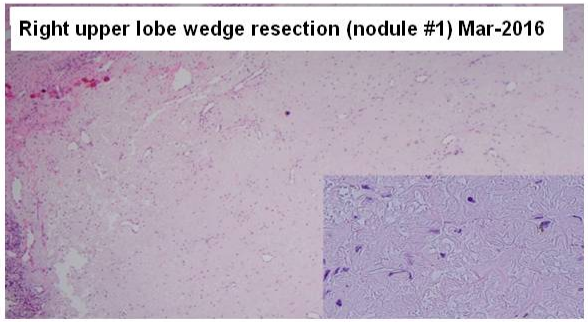
Before nivo + ipi therapy



Following nivo + ipi therapy



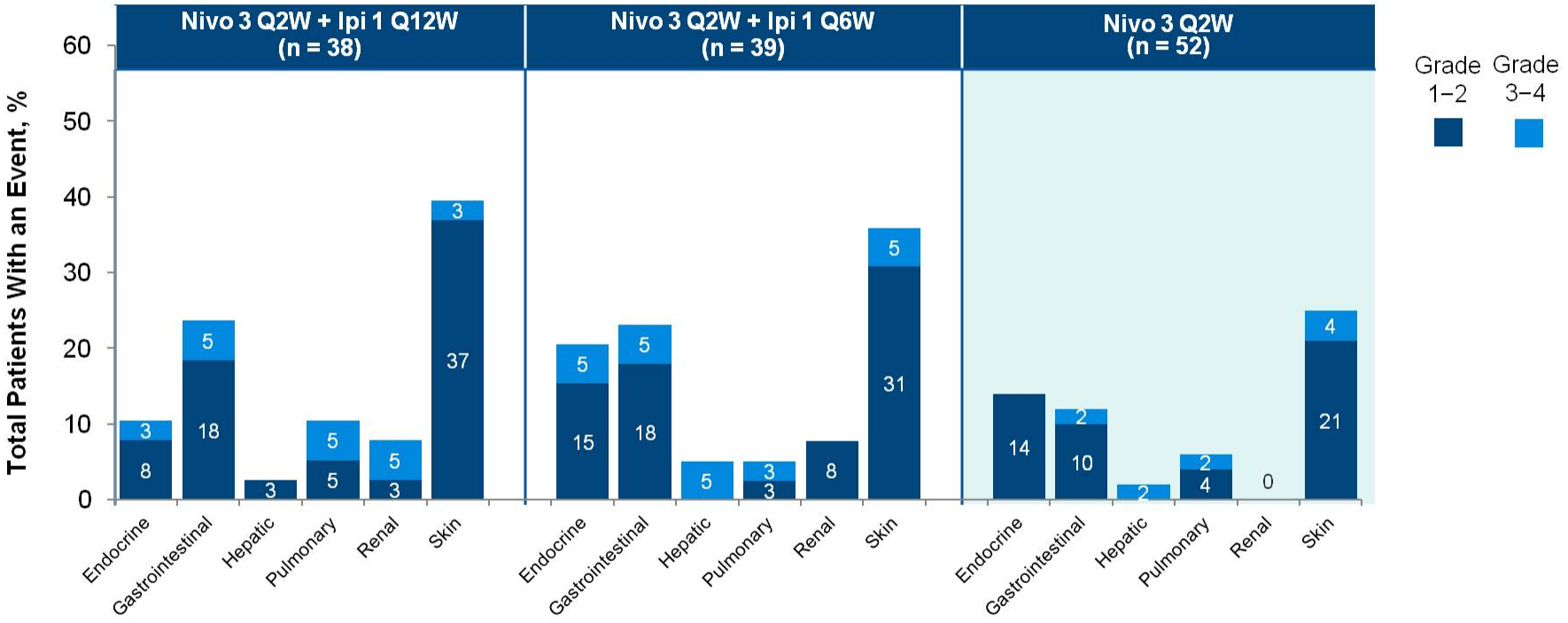
No viable tumor in resected residual lesion



Courtesy of Dr. William Travis, MSKCC

[a]Patient was included as having partial response and PD-L1 expression unknown in analysis at time of database lock

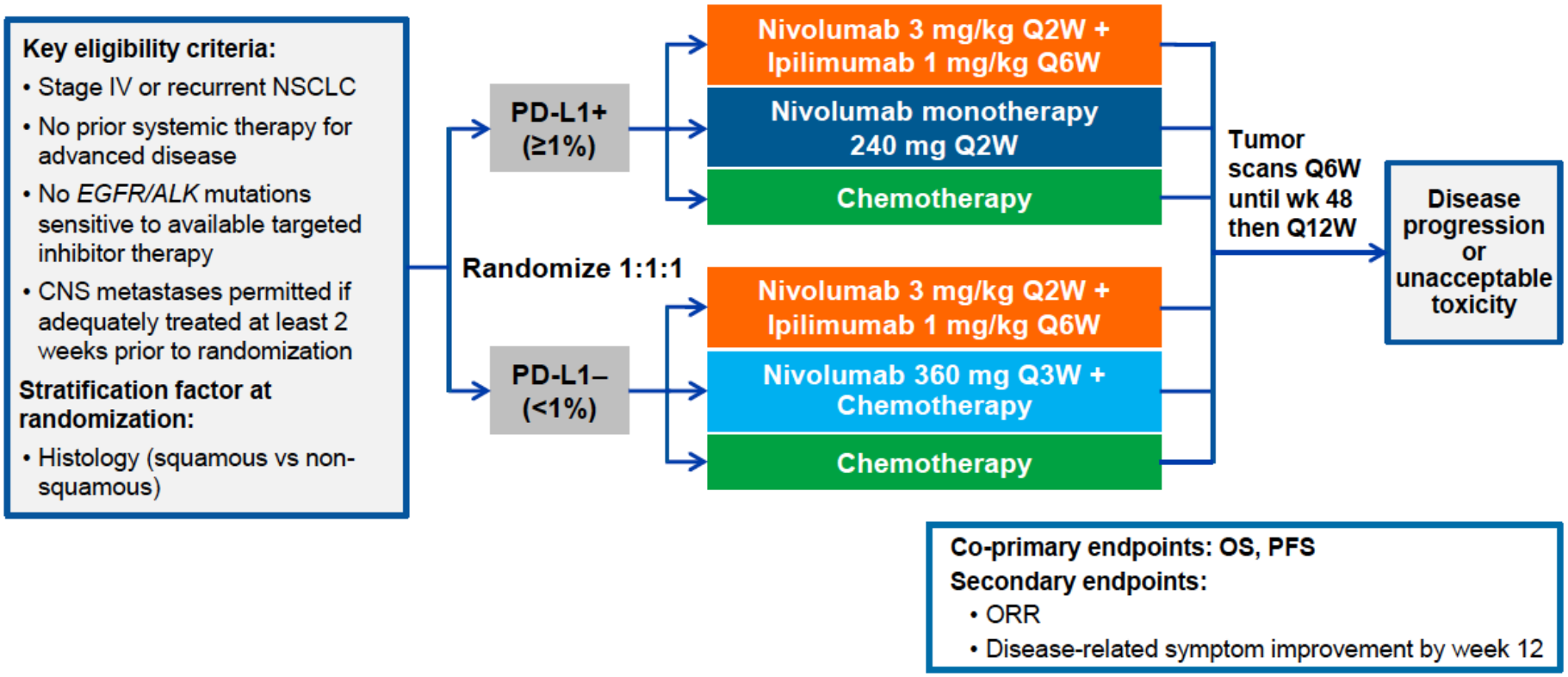
Nivolumab Plus Ipilimumab in First-line NSCLC: Treatment-related Select AEs



- All treatment-related pulmonary events were pneumonitis
- Grade 1–2 hypersensitivity/infusion reaction occurred in 5% and 6% of patients in the nivo 3 Q2W + ipi 1 Q12W and monotherapy groups, respectively

Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock
Select AEs are those with potential immunologic etiology that require frequent monitoring/intervention

Phase 3 CheckMate 227 (NCT02477826): Study Design



Immunotherapy + Chemotherapy

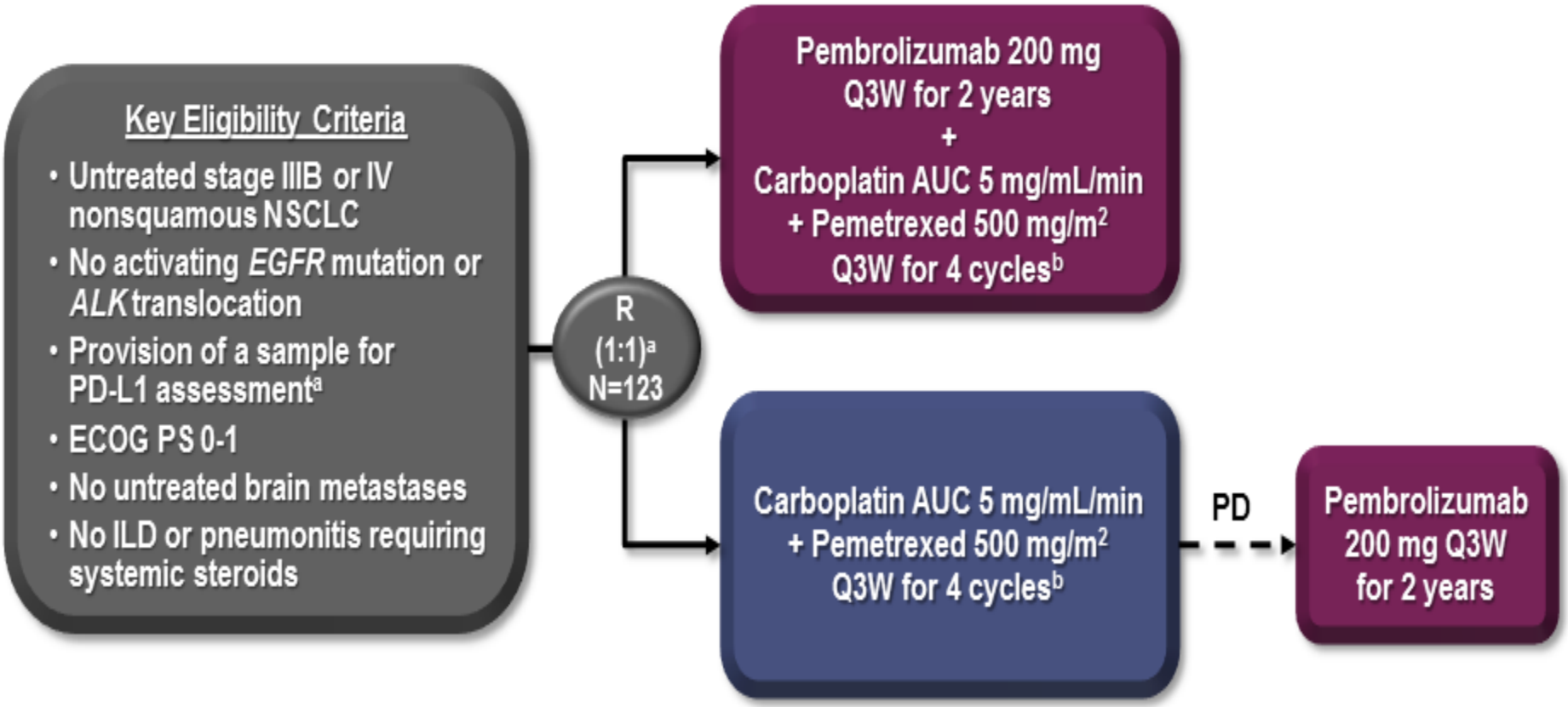
COPENHAGEN 2016 ESMO congress

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

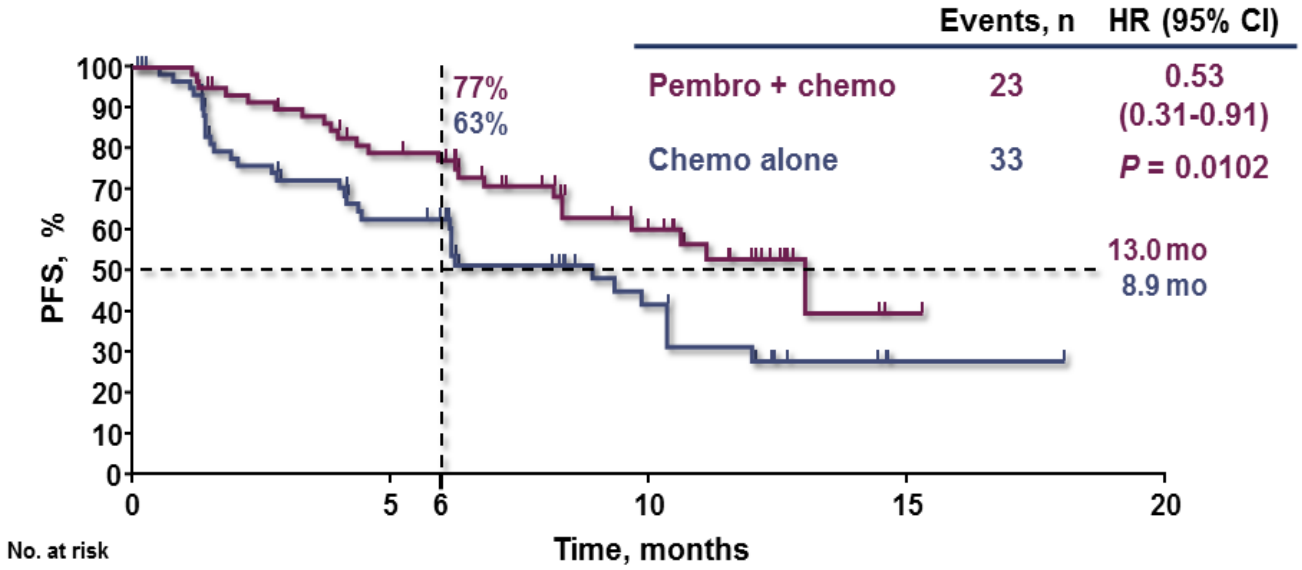
PD=progressive disease.

[a]Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

[b]Indefinite maintenance therapy with pemetrexed 500 mg/m² Q3W permitted.

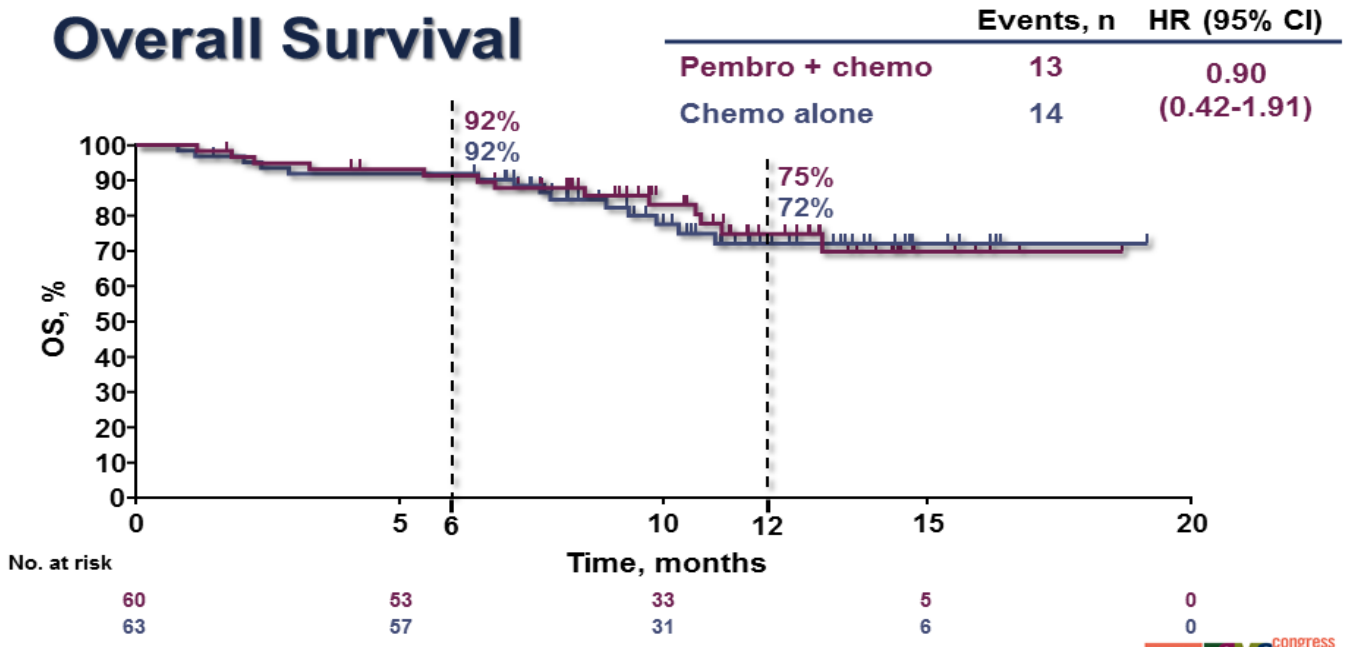
Progression-Free Survival
(RECIST v1.1 by Blinded, Independent Central Review)

CJ Langer. ESMO 2016.



CJ Langer. ESMO 2016.

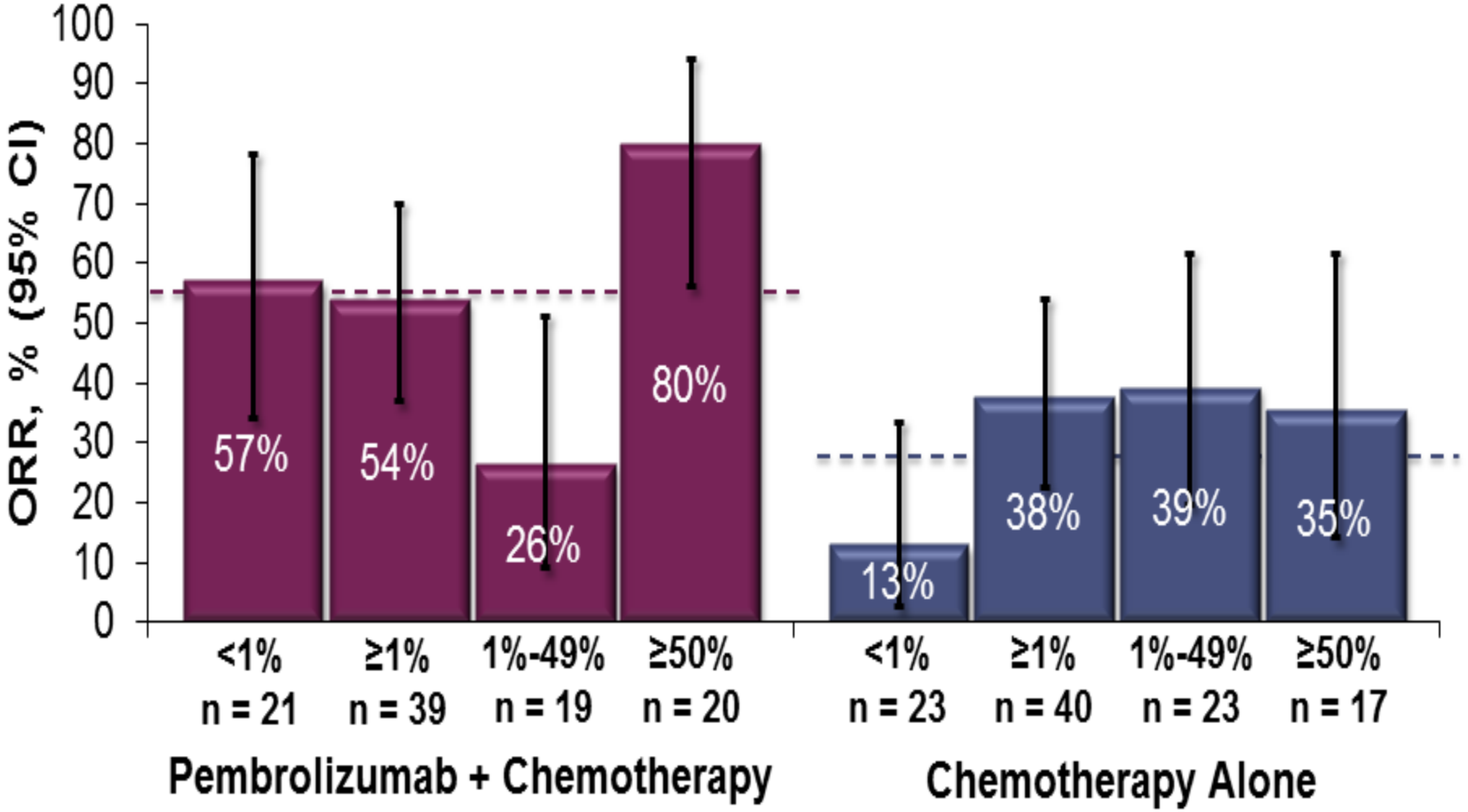
Overall Survival



Data cut-off: August 8, 2016.

Objective Response Rate by PD-L1 Status

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



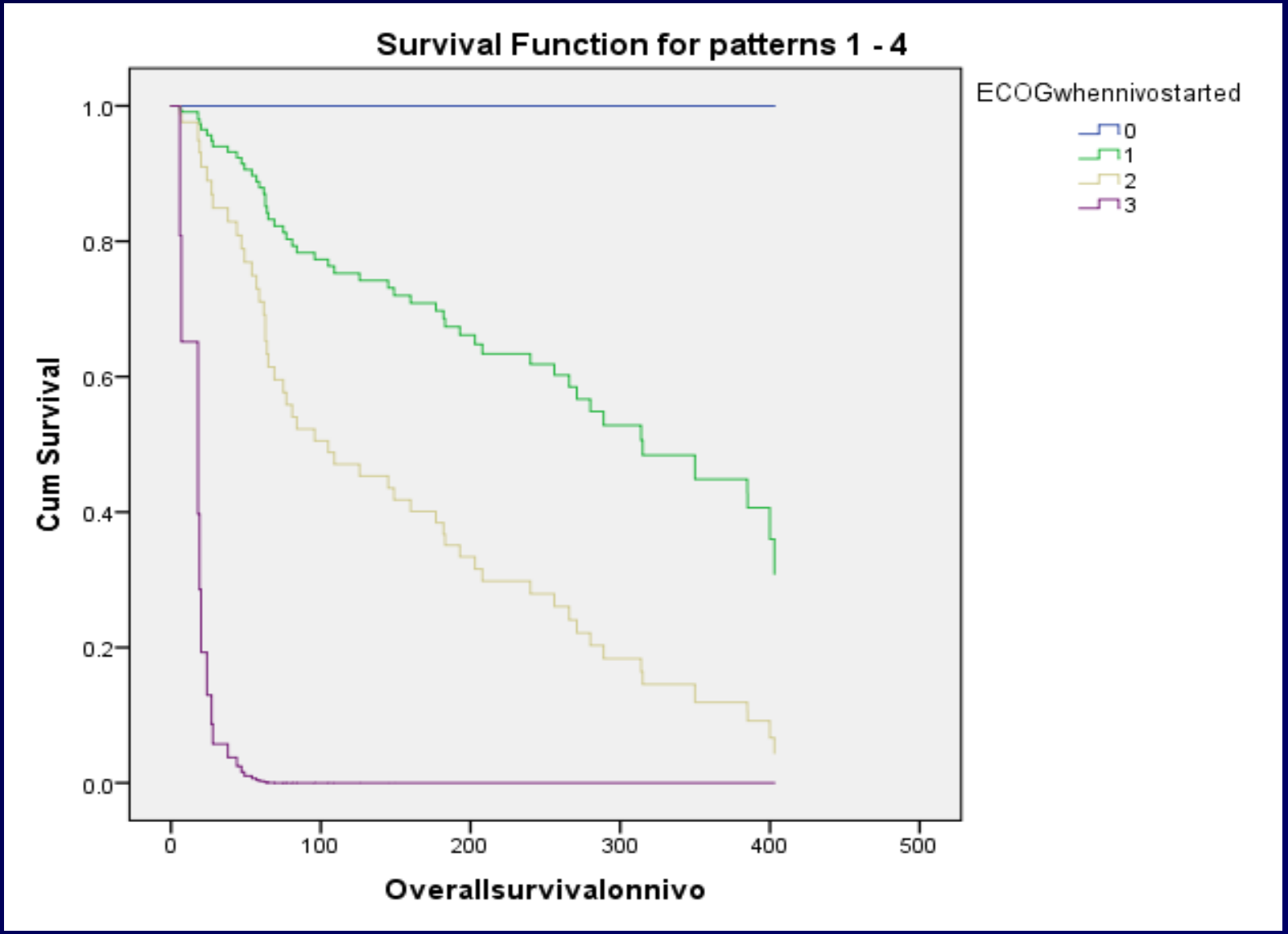
Horizontal dotted lines represent the ORR in the total population.

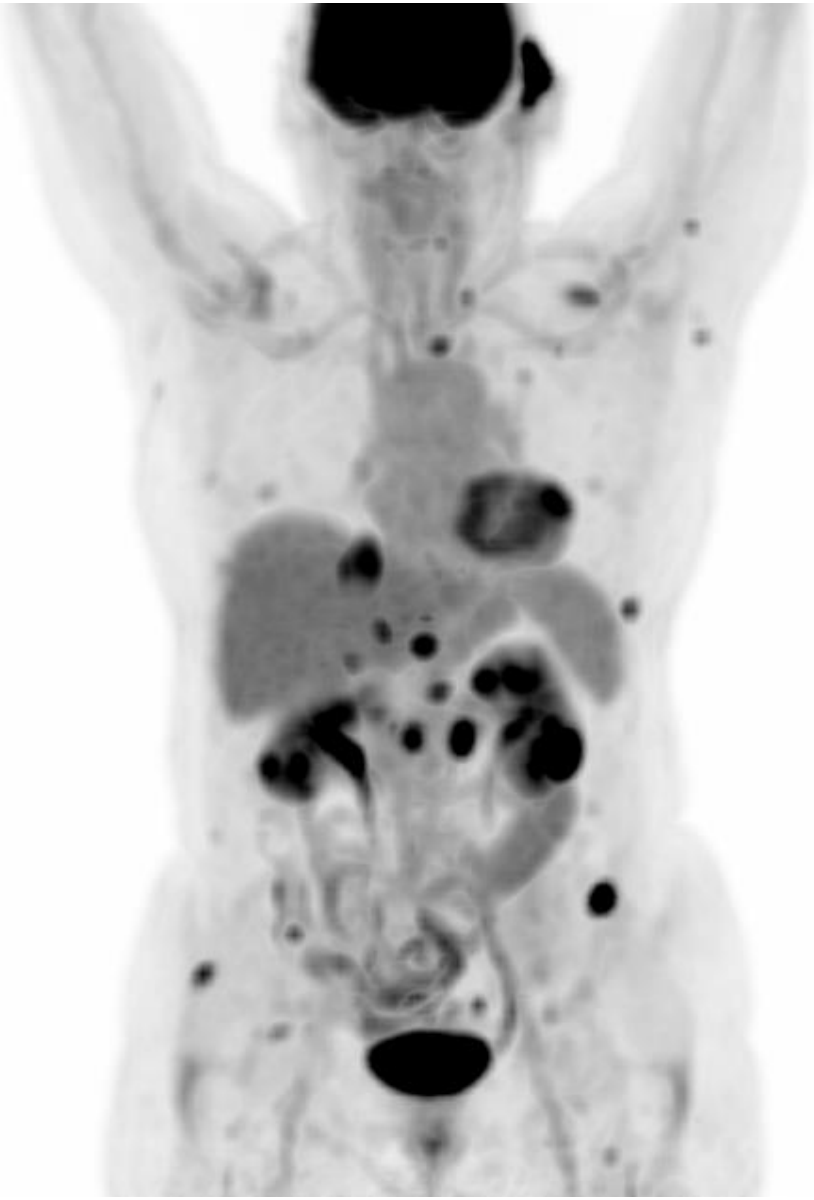
Data cut-off: August 8, 2016.

Issues

- Should we treat everyone?

Audit of Patient Treated with Nivolumab for Relapsed Disease in Brisbane





January 2016
(Post-chemotherapy)

68yo female patient

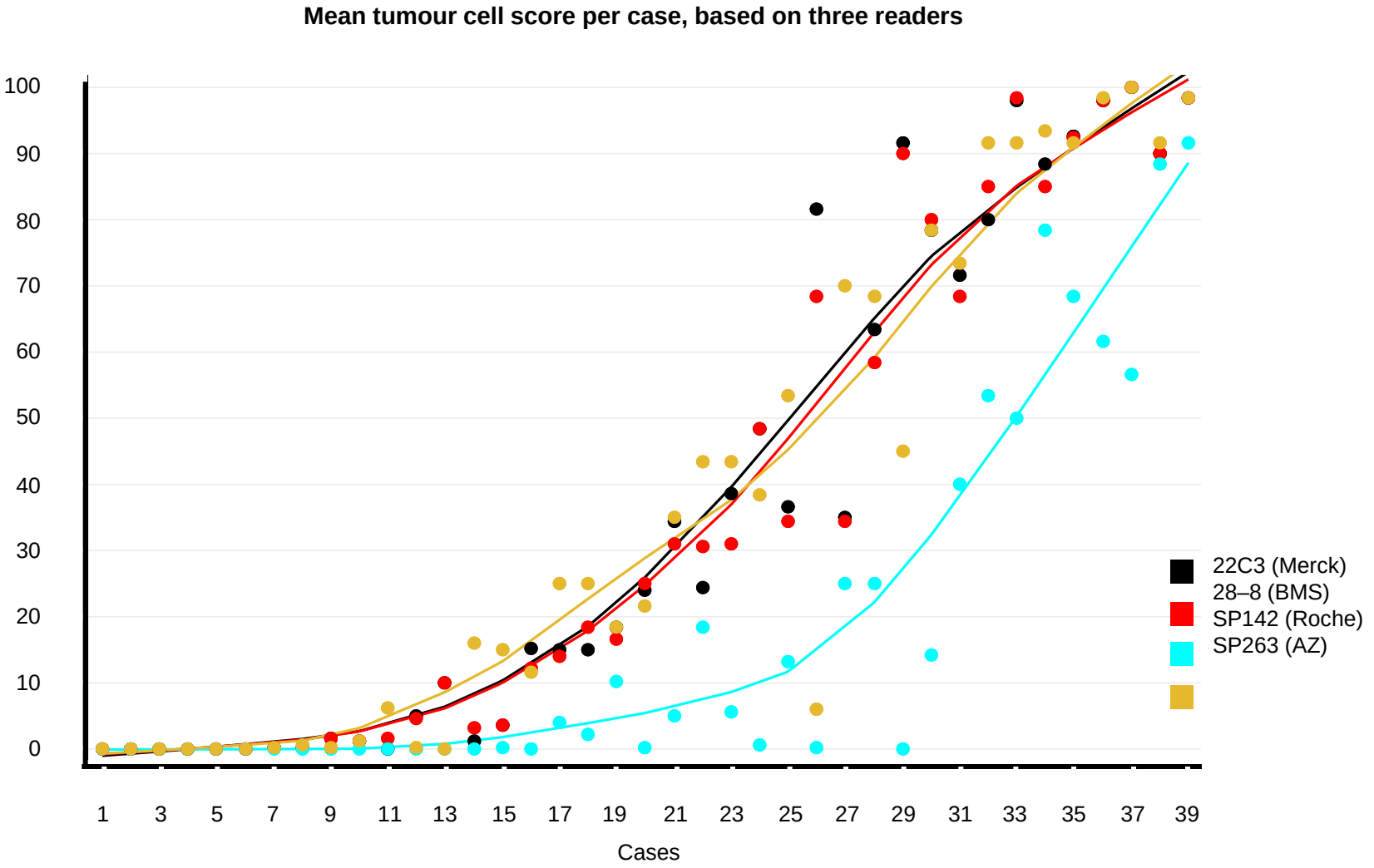
- **Diagnosed with metastatic sarcomatoid lung cancer August 2015 following resection of a scalp lesion**
- **Resection L distal femur metastasis Sept 2015**
- **Received 4 cycles of carboplatin and gemcitabine Oct – Dec 2015 showed progressive disease**
- **Radiotherapy to a skin lesion – no effect**
- **PS=3 but alert and well and symptoms related to disease only**
- **Received Nivolumab**
- **Complete remission**
- **Feels NORMAL today!**

Biomarkers: The Target

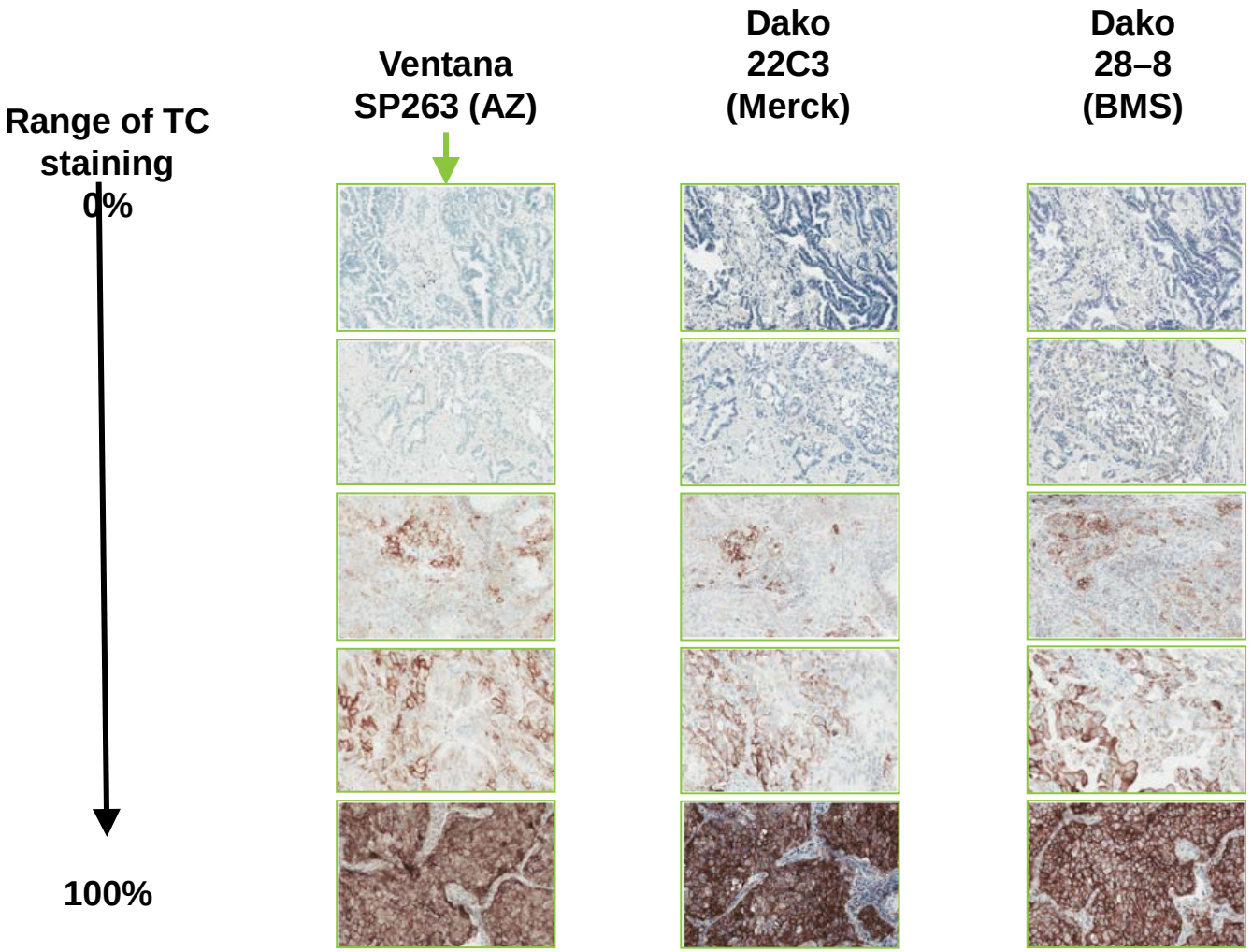
Known PD-L1 diagnostic assays differ in many key aspects

	MERCK	Bristol-Myers Squibb	MedImmune / AstraZeneca	Roche
Diagnostic	**Dako**	**Dako**	**Ventana**	**Ventana**
PD-L1 antibody clone	**22C3**	**28–8**	**SP263**	**SP142**
Machines utilised	**Link 48**	**Link 48**	**BenchMark ULTRA**	**BenchMark ULTRA**
Compartment	**TM**	**TM**	**TM**	**TC/IC**
Variables	**% of cells**	**% of cells**	**% of cells**	**% of cells**
Cut-off used for patient subgroups	**Strong(+): ≥50%**	**>1%, 5%, 10% TC**	**PD-L1(high): ≥25%[4]**	**≥1%, 5% or 10% for IC ≥1%, 5% or 50% for TC**
Diagnostic type	**Companion diagnostic in NSCLC**	**Complementary diagnostic in NSCLC**	**Companion diagnostic in NSCLC, SCCHN and UC**	**Complementary diagnostic in UC[1]**

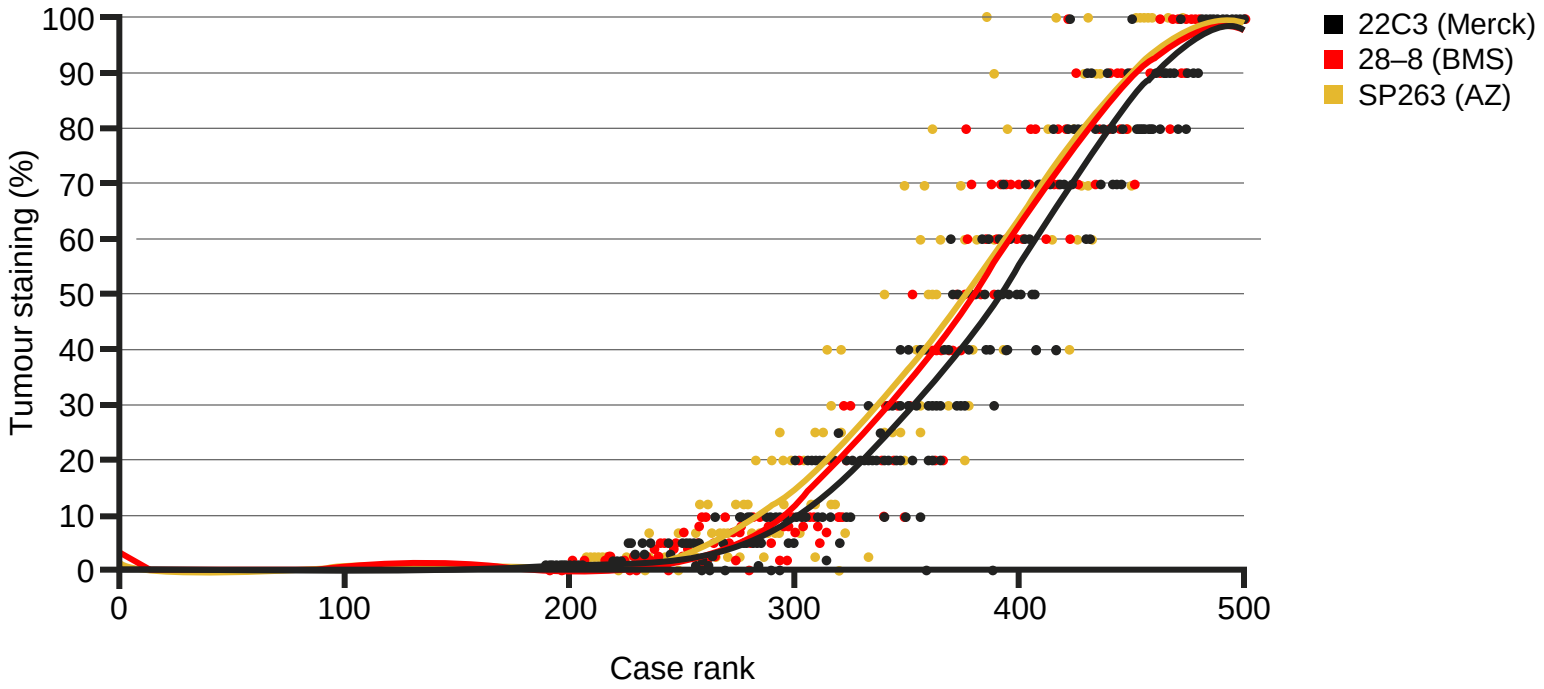
Results from Blueprint demonstrate concordance between three assays with respect to TC staining



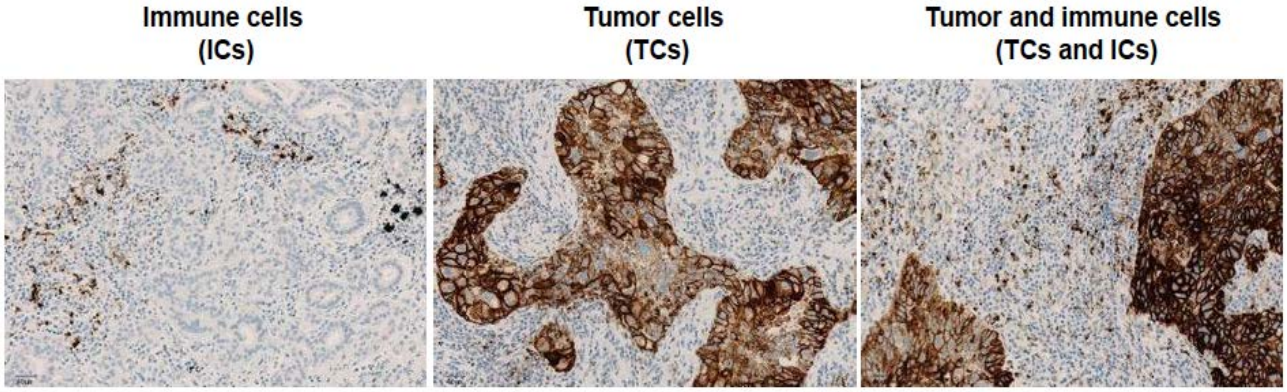
AstraZeneca is generating proprietary data sets: NSCLC concordance study



The NSCLC concordance study showed correlation between the three assays examined

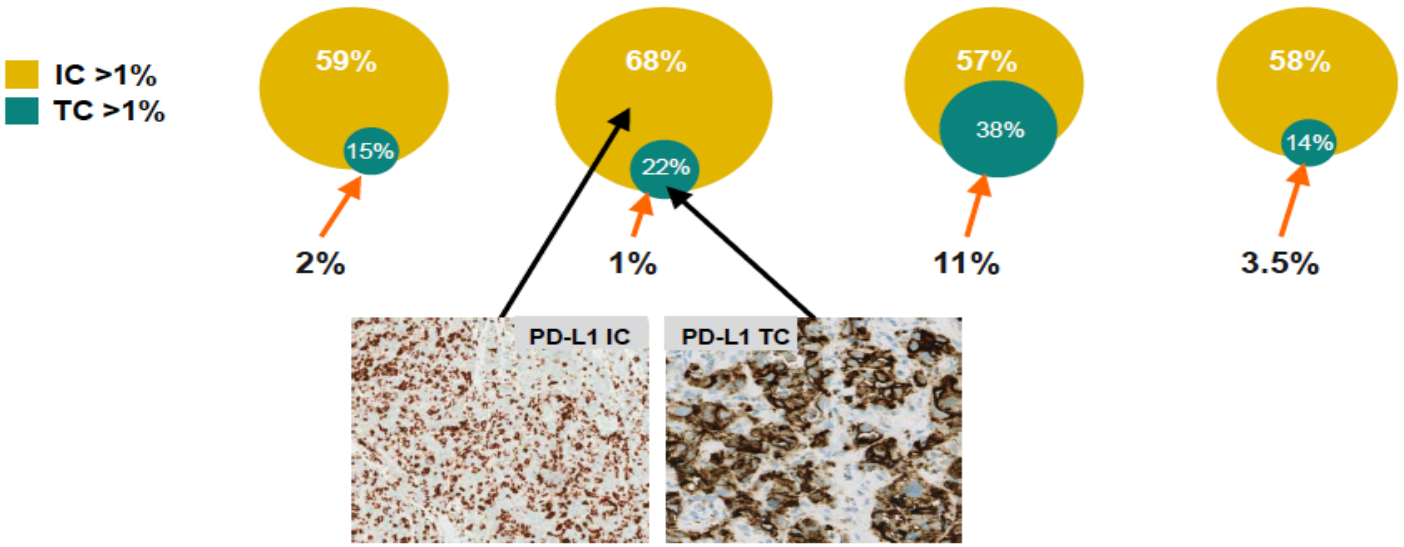


PD1/PDL1 Targeted Therapies work best in Inflammed Tumors



Immune cell expression of PD-L1 is more prevalent across indications

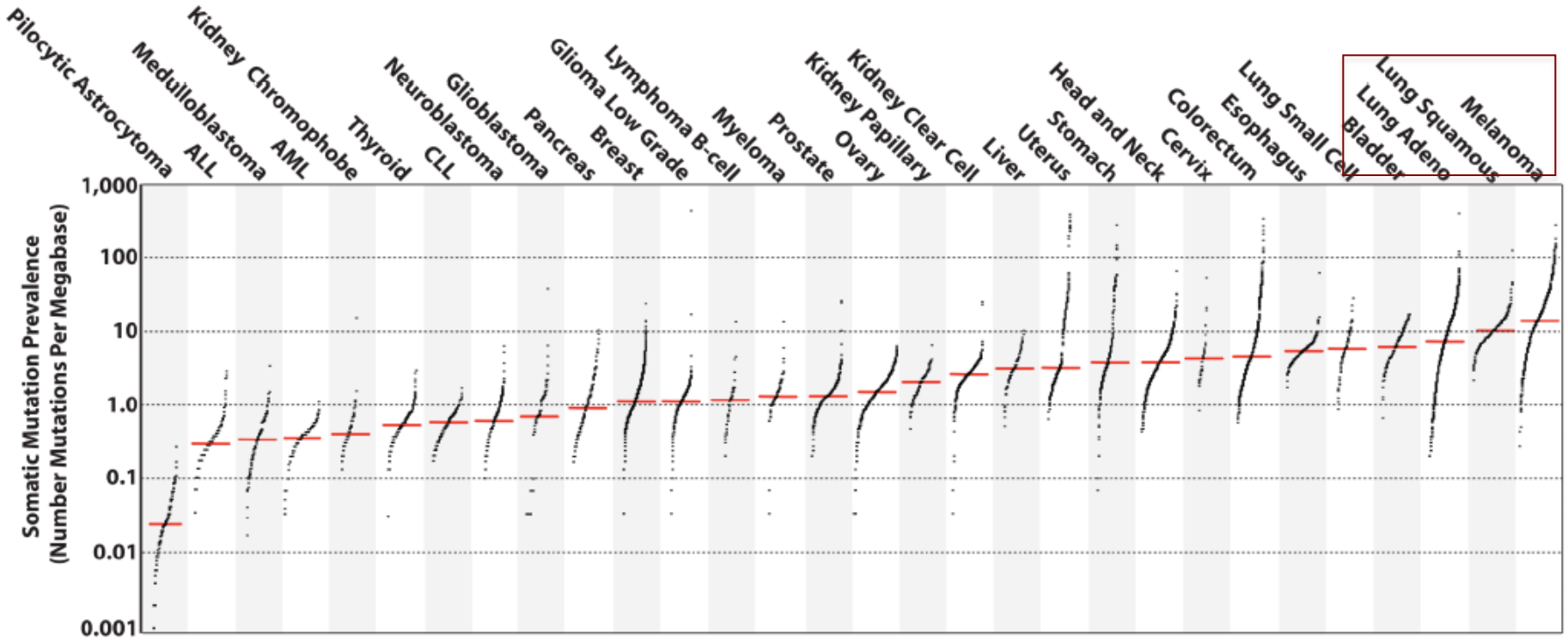
	RCC	UBC	NSCLC	TNBC
Study (N)	WO29074 (253) Phase II	GO29023 (592) Phase II	POPLAR (287) Phase II	PCD4989g (413) Phase I



TNBC = triple negative breast cancer
Data from ongoing clinical trials

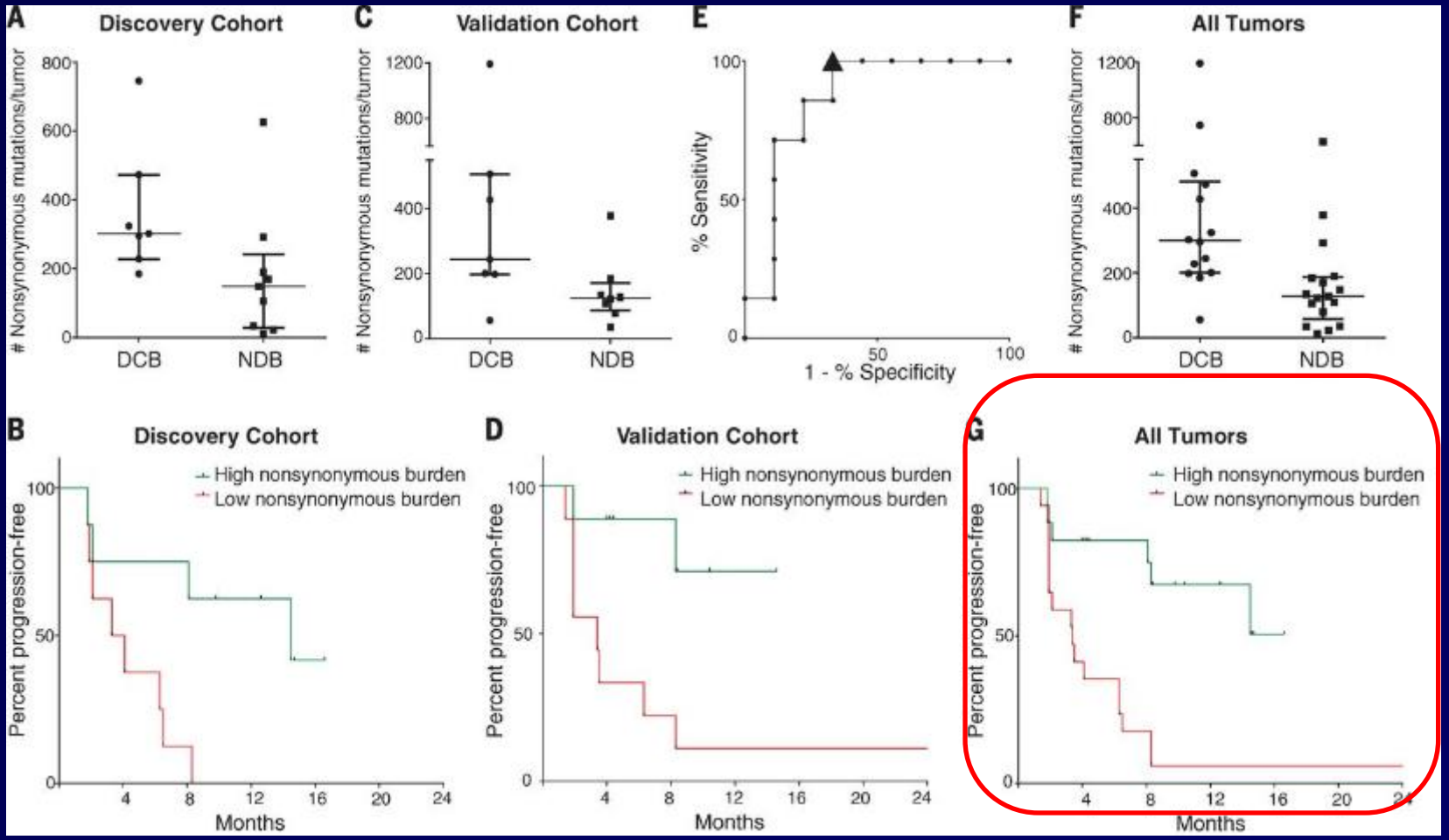
Mutations and Response to Therapy

Lung Cancer and Melanoma are Immunogenic Tumor:
Gene Mutations Result in Neoantigens



Alexandrov LB. Nature. 2013;500(7463):415-21.

Nonsynonymous mutation burden (whole exome sequencing) associated with PFS benefit of anti–PD-1 therapy (pembro).



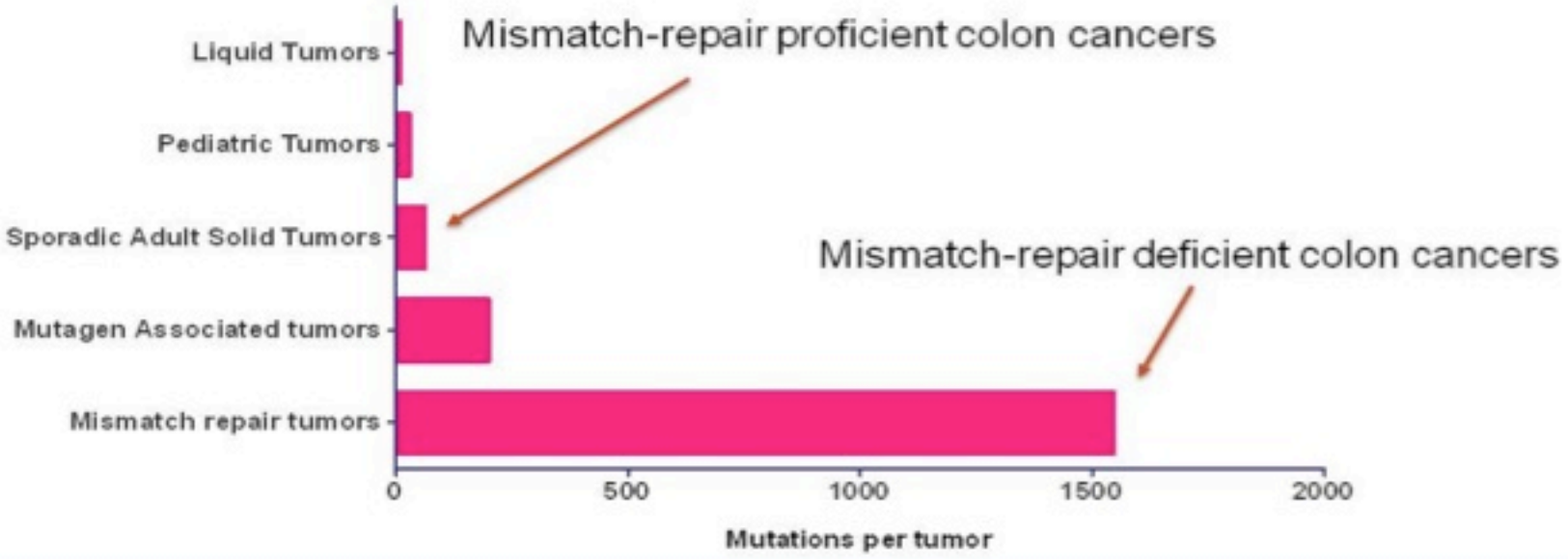
Naiyer A. Rizvi et al. Science 2015;348:124-128

Mismatch Repair Deficiency

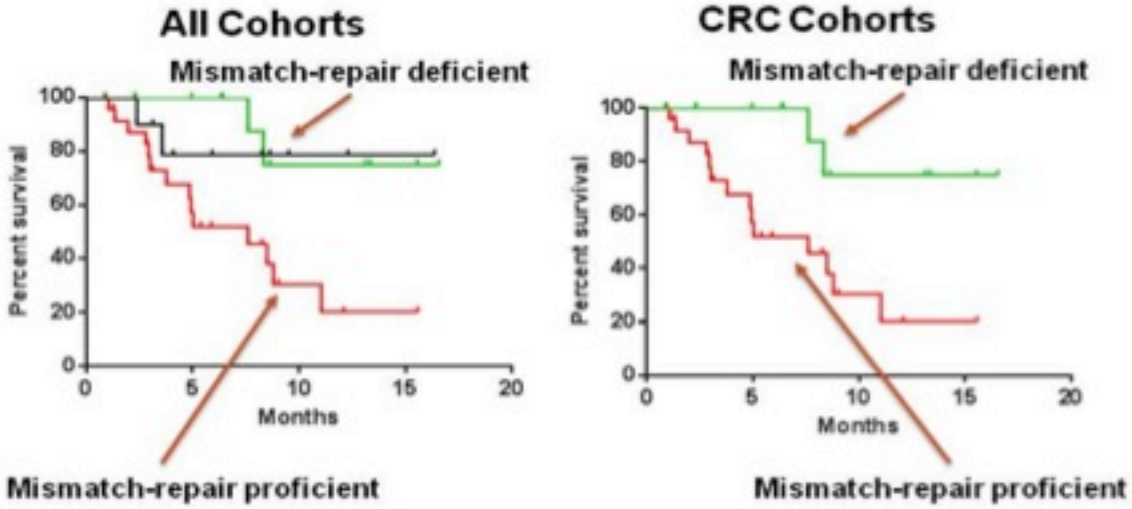
Microsatellite instability in tumor cells is due to deficient DNA mismatch repair:

- **germline** (Lynch syndrome) and/or **sporadic** mutations (MLH1, MSH2, MSH6, PMS2, EpCAM)
- **epigenetic silencing** (MLH1 hyper-methylation)

Mutations per tumor



Overall Survival



Objective Responses

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC
N	13	25	10
Objective Response Rate	62%	0%	60%
Disease Control Rate	92%	16%	70%

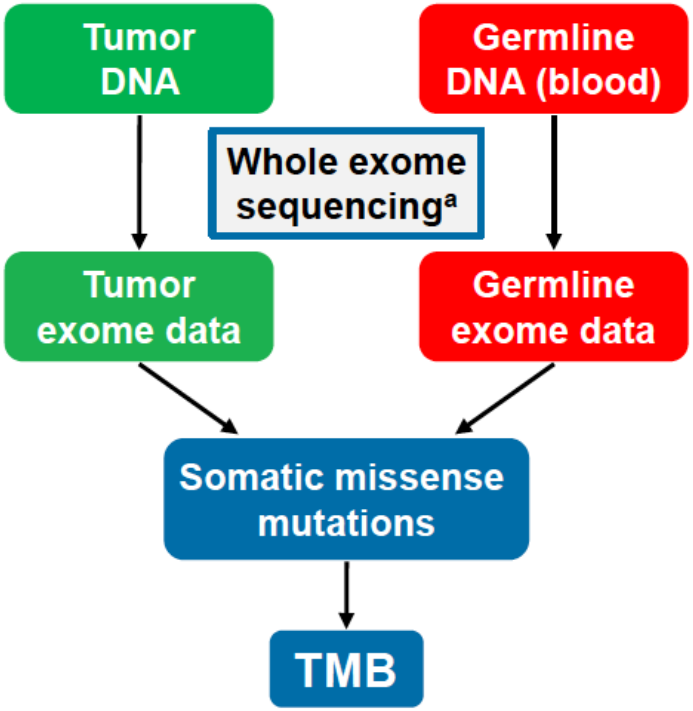
Impact of Tumor Mutation Burden on the Efficacy of First-Line Nivolumab in Stage IV or Recurrent Non-Small Cell Lung Cancer: An Exploratory Analysis of CheckMate 026

Solange Peters,[1] Benjamin Creelan,[2] Matthew D. Hellmann,[3] Mark A. Socinski,[4] Martin Reck,[5] Prabhu Bhagavatheeswaran,[6] Han Chang,[6] William J. Geese,[6] Luis Paz-Ares,[7] David P. Carbone[8]

[1]Oncology Department, Lausanne University Hospital, Lausanne, Switzerland; [2]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Florida Hospital Cancer Institute, Orlando, FL, USA; [5]LungenClinic Grosshansdorf, Airway Research Center North (ARCN), German Center for Lung Research (DZL), Grosshansdorf, Germany; [6]Bristol-Myers Squibb, Princeton, NJ, USA; [7]Hospital Universitario Doce de Octubre, CNIO and Universidad Complutense, Madrid, Spain; [8]Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

Exploratory TMB Methods

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



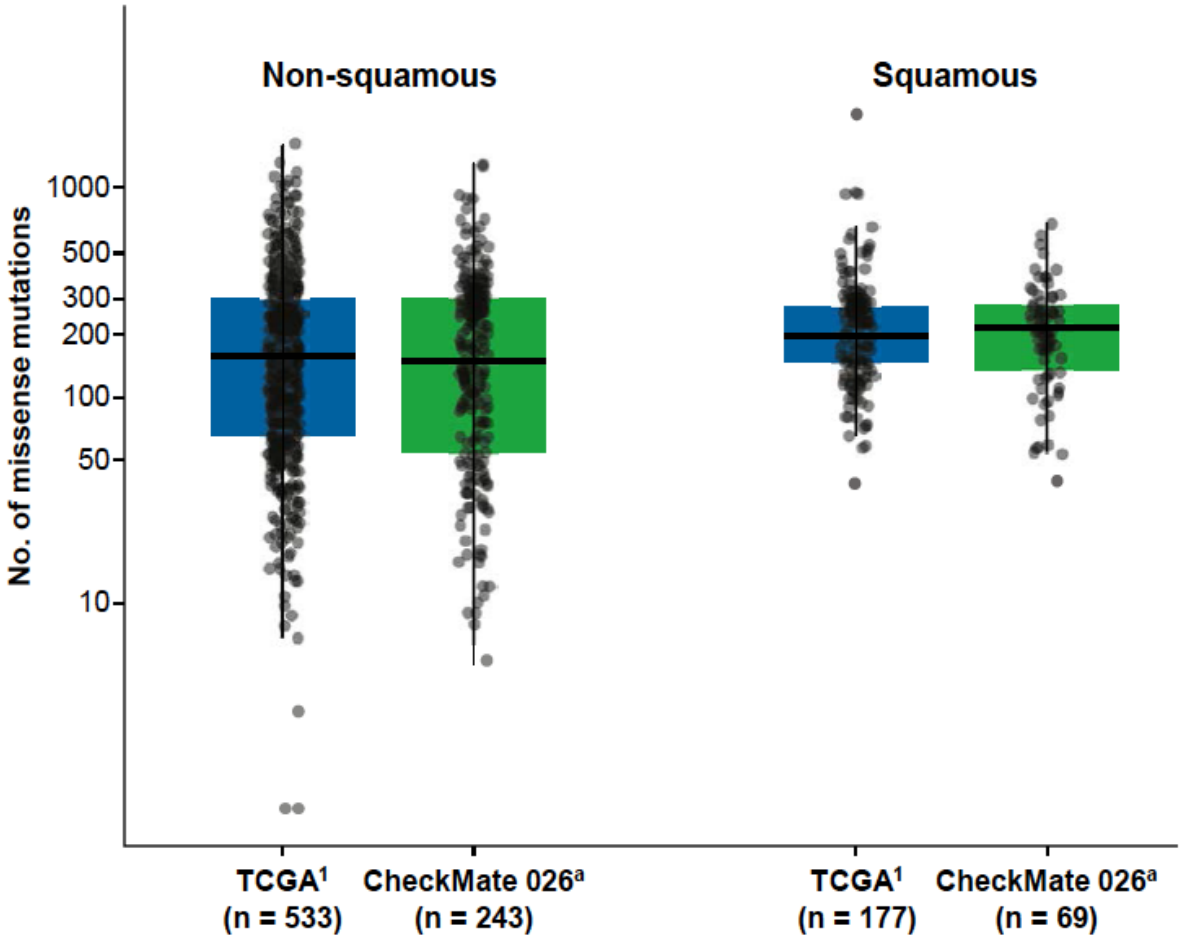
[a]DNA was sequenced on the Illumina HiSeq 2500 using 2 × 100-bp paired-end reads; an average of 84 and 89 million reads were sequenced per tumor and germline sample, respectively (average 84.6 × and 93 × the mean target coverage, respectively)

Sample size throughout TMB determination		
Patients, n (%)	**Tumor DNA**	**Germline DNA**
Randomized	541 (100)	541 (100)
Samples available for DNA extraction[a]	485 (90)	452 (84)
DNA available for sequencing	408 (75)	452 (84)
Successful preparation of next-generation sequencing library	402 (74)	452 (84)
Passed internal quality control[b]	320 (59)	432 (80)
Matched tumor-germline exome sequences for TMB analysis[c]	312 (58)	

[a]Samples were not available for various reasons, including but not limited to lack of patient pharmacogenetic consent, samples exhausted for PD-L1 testing, or poor tissue sampling
[b]Internal quality control failure included factors such as discordance between tumor and germline DNA, too few sequence reads, and low or uneven target region coverage
[c]8 patients with available tumor DNA sequences did not have matched germline DNA sequences

TMB in The Cancer Genome Atlas[1] and CheckMate 026 Samples

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



[a]Samples were from whole exome sequencing

1. Broad Institute TCGA Genome Data Analysis Center (2015): Firehose stddata__2015_02_04 run. Broad Institute of MIT and Harvard. doi:10.7908/C19P30S6

Exploratory Analysis by TMB Tertile
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

- For initial exploratory analyses, patients were divided into 3 subgroups based on TMB tertile distribution

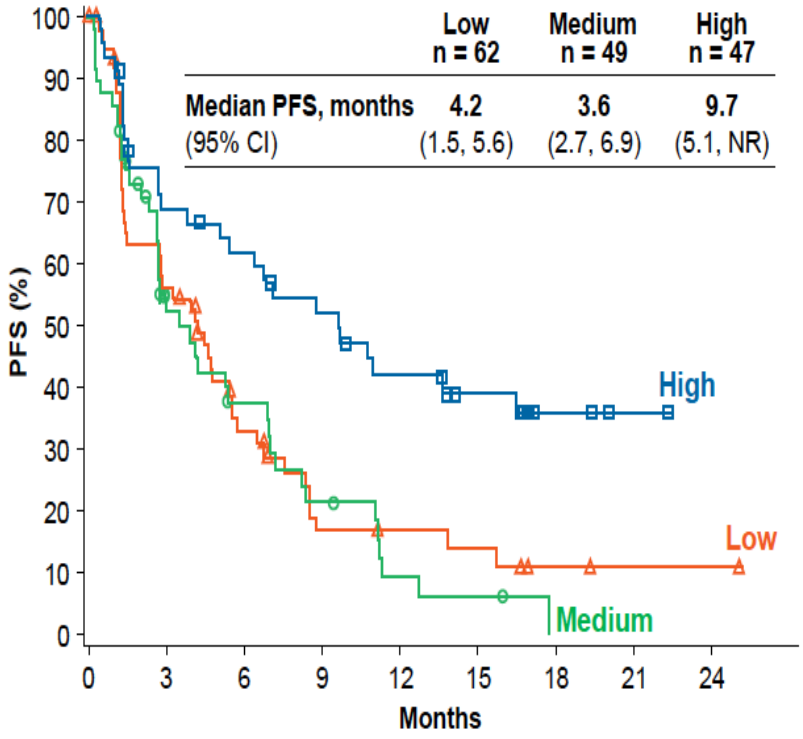
TMB tertile	Total missense mutations, no.
Low	0 to <100
Medium	100 to 242
High	≥243

- ROC curves were generated and suggested TMB has predictive power
  - Additional analyses to help further refine potential optimal cutpoints are ongoing

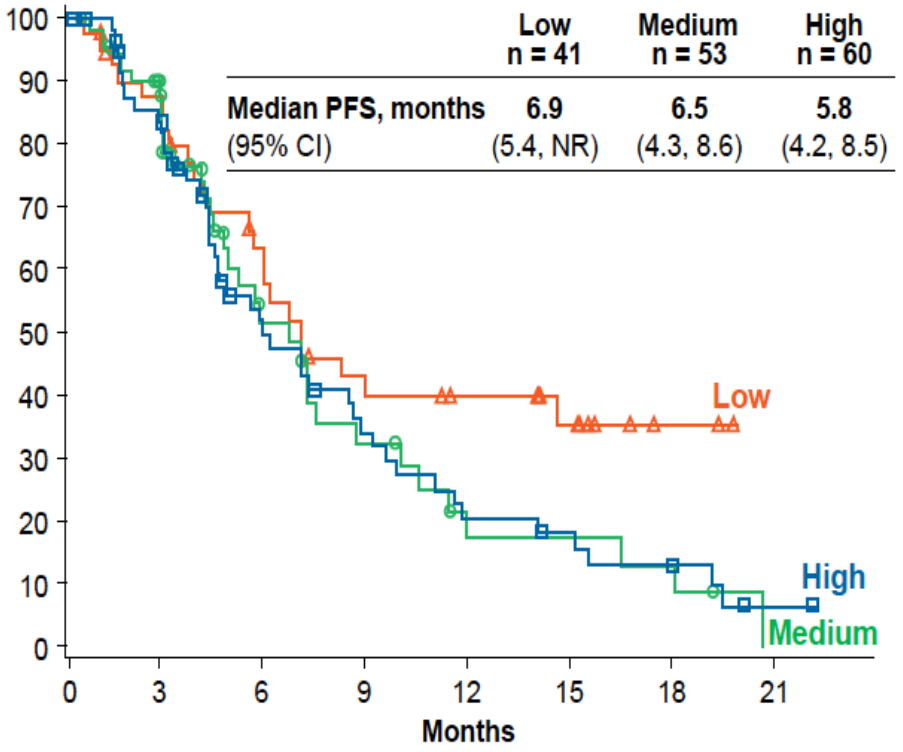
PFS by Tumor Mutation Burden Tertile

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

Nivolumab Arm



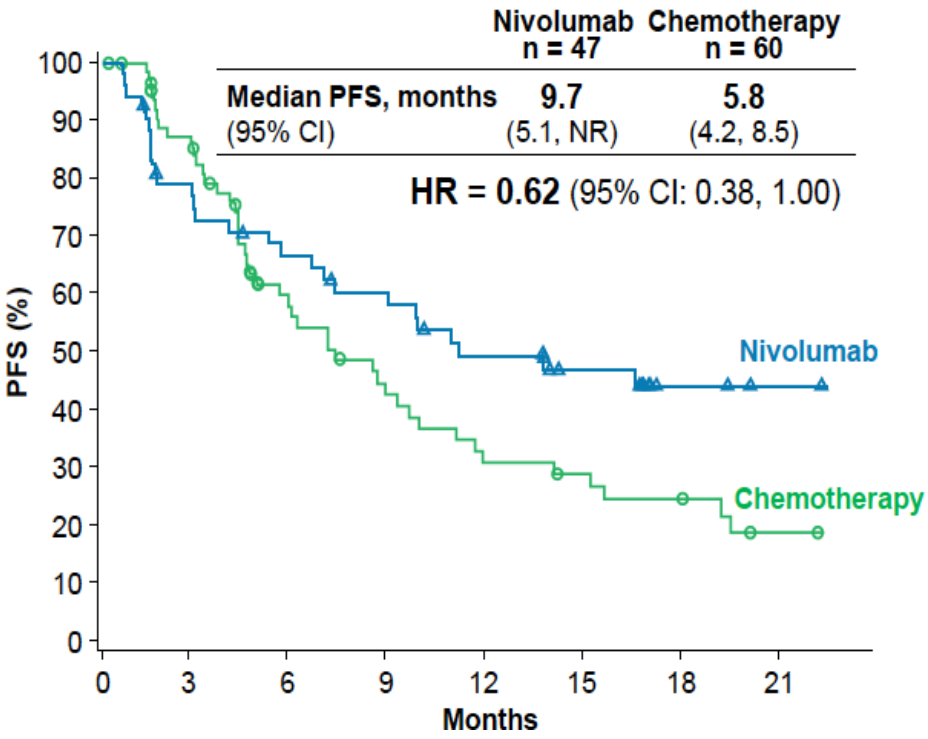
Chemotherapy Arm



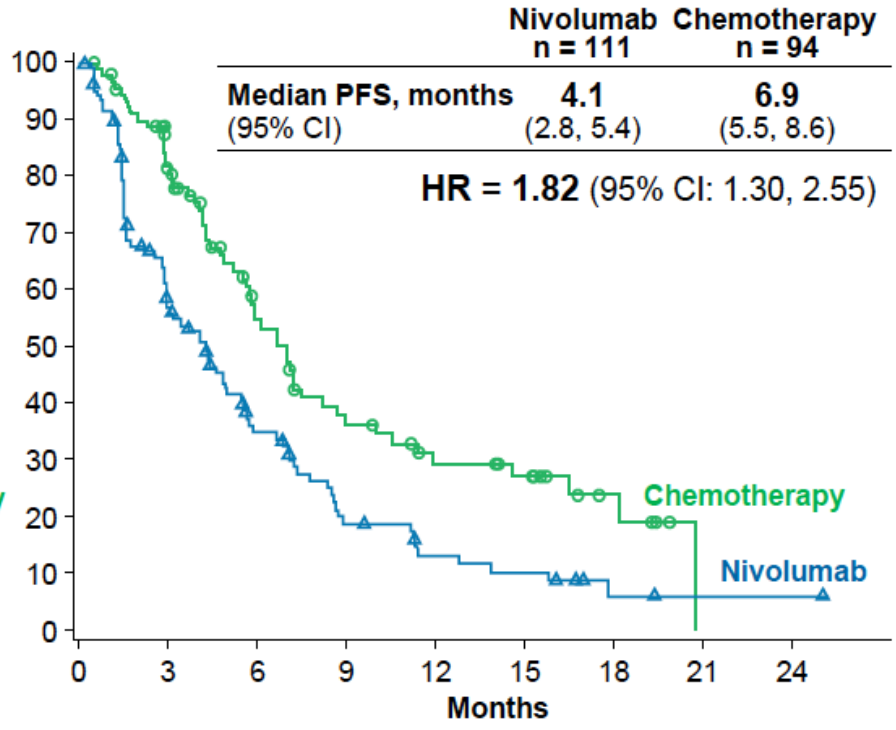
PFS by Tumor Mutation Burden Subgroup

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

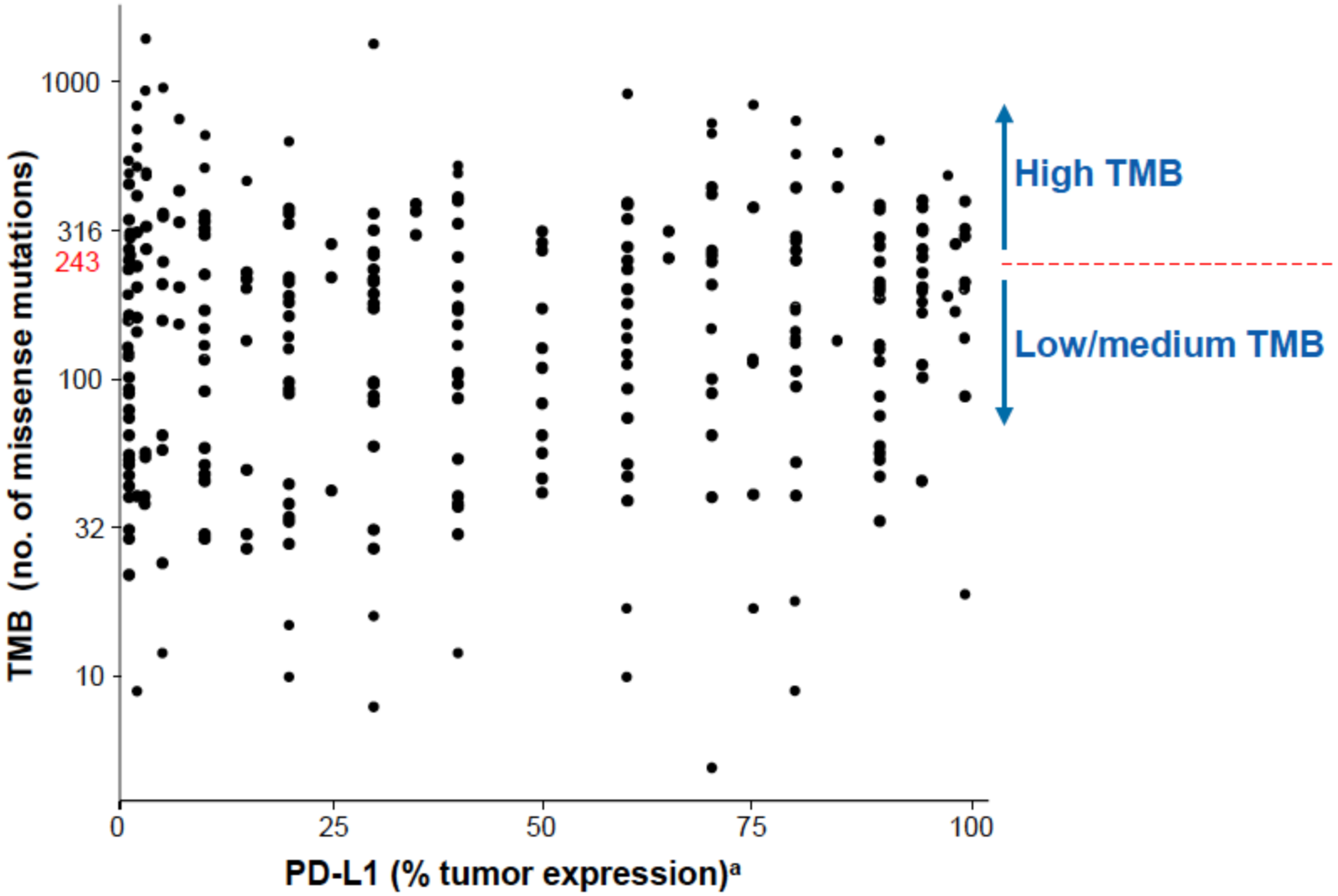
High TMB



Low/medium TMB

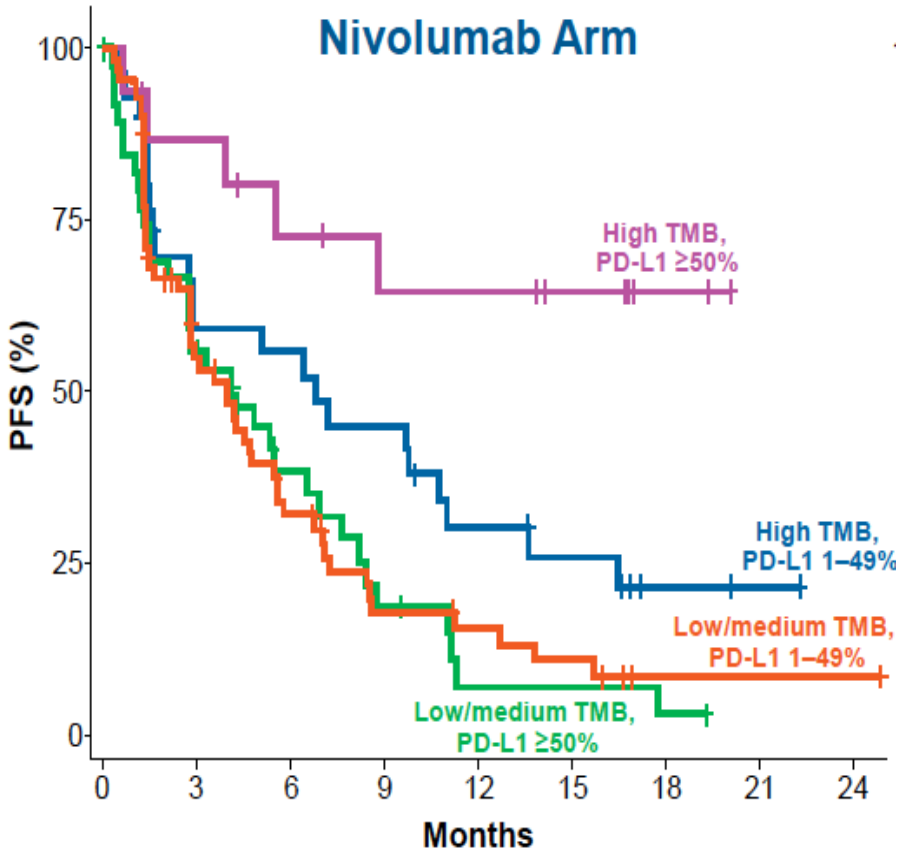


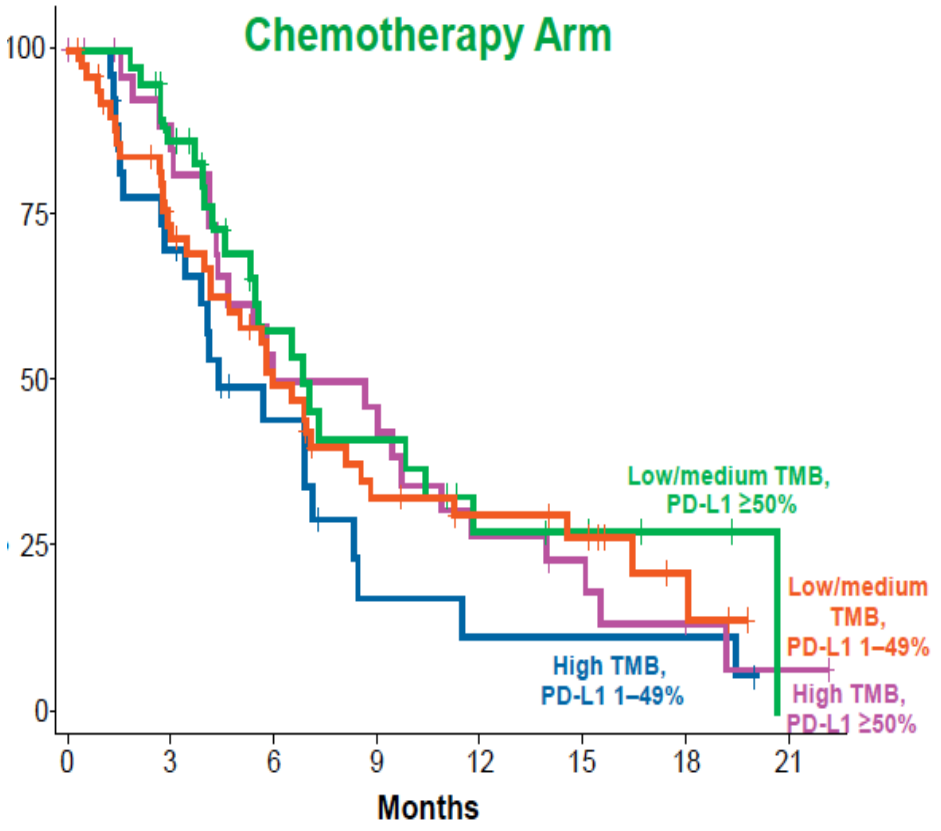
No Association Found Between PDL1 Expression and Mutational Burden



PFS by TMB Subgroup and PD-L1 Expression

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC





Oncogene Drivers and Efficacy of Therapy

Nivolumab (CA209-153 study)

	CR, n(%)	PR, n(%)	SD, n(%)
Total patients N=531	0	63 (12)	233 (44)
EGFR Mut+ (n=55)	0	9 (16)	26 (47)
EGFR WT (n=300)	0	34 (11)	123 (41)
ALK+ (n=12)	0	1 (8)	7 (58)
ALK neg (n=299)	0	35 (12)	123 (41)

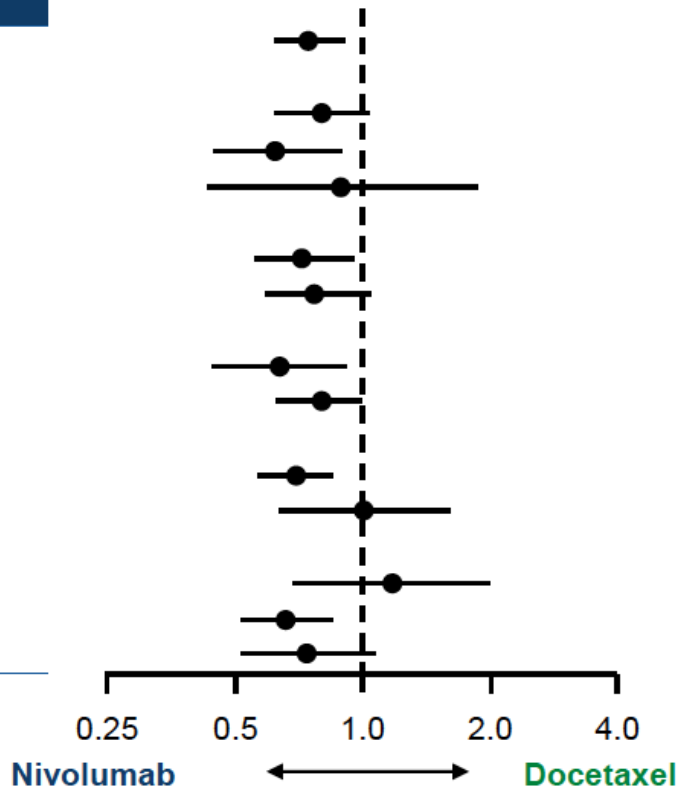
Pembrolizumab (KEYNOTE-001)

	TPS ≥50%		TPS 1-49%		TPS <1%		Total[a]	
	n	ORR, % (95% CI)	n	ORR, % (95% CI)	n	ORR, % (95% CI)	N	ORR, % (95% CI)
Overall	144	38.2 (30.2-46.7)	185	11.9 (7.6-17.4)	80	10.0 (4.4-18.8)	550	20.2 (16.9-23.8)
EGFR wild type	113	39.8 (30.7-49.5)	156	12.2 (7.5-18.4)	63	12.7 (5.6-23.5)	450	21.6 (17.8-25.6)
EGFR mutant	20	20.0 (5.7-43.7)	23	8.7 (1.1-28.0)	14	0.0 (0.0-23.2)	77	7.8 (2.9-16.2)

Hussein, et al. WCLC 2015

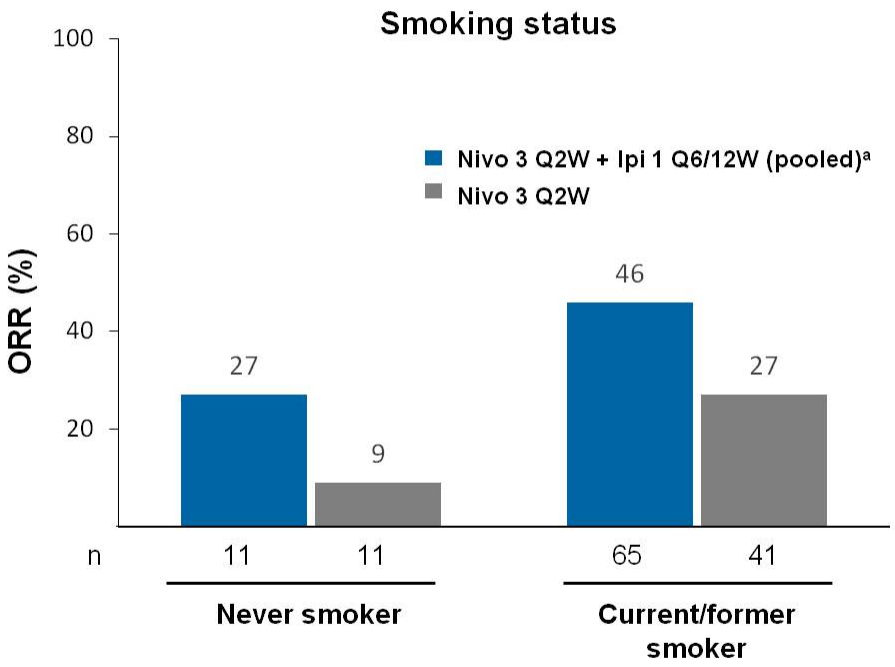
Treatment Effect on OS in Predefined Subgroups

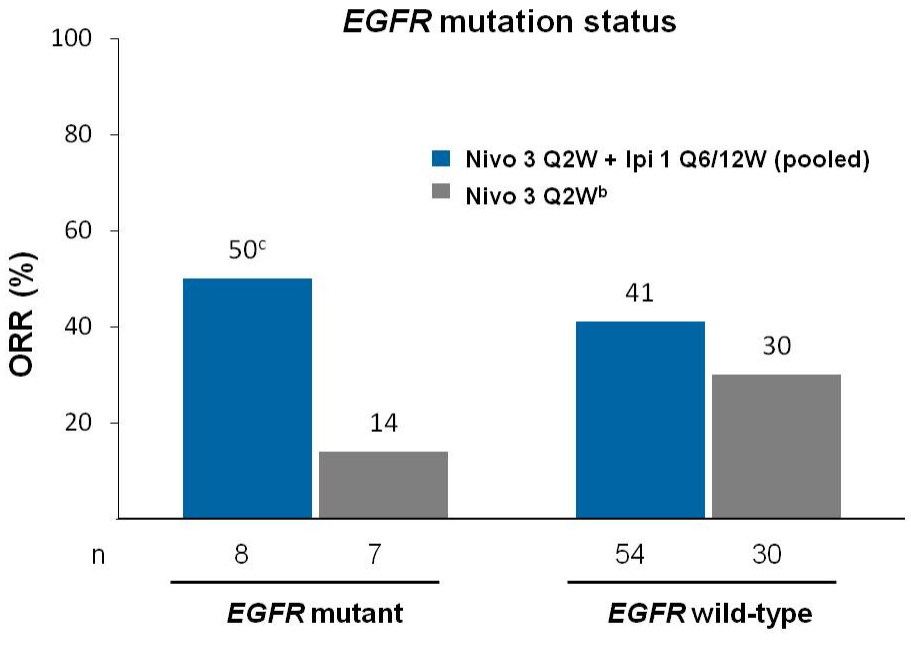
	N	Unstratified HR (95% CI)
Overall	582	0.75 (0.62, 0.91)
Age Categorization (years)		
<65	339	0.81 (0.62, 1.04)
≥65 and <75	200	0.63 (0.45, 0.89)
≥75	43	0.90 (0.43, 1.87)
Gender		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
≥1	402	0.80 (0.63, 1.00)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)
***EGFR* Mutation Status**		
Positive	82	1.18 (0.69, 2.00)
Not Detected	340	0.66 (0.51, 0.86)
Not Reported	160	0.74 (0.51, 1.06)



All randomized patients (nivolumab, n = 292; docetaxel, n = 290).

Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy by Smoking and *EGFR* Mutation Status





Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock

[a]Excludes 1 patient with unknown smoking status (nivo 3 Q2W + ipi 1 Q6W)

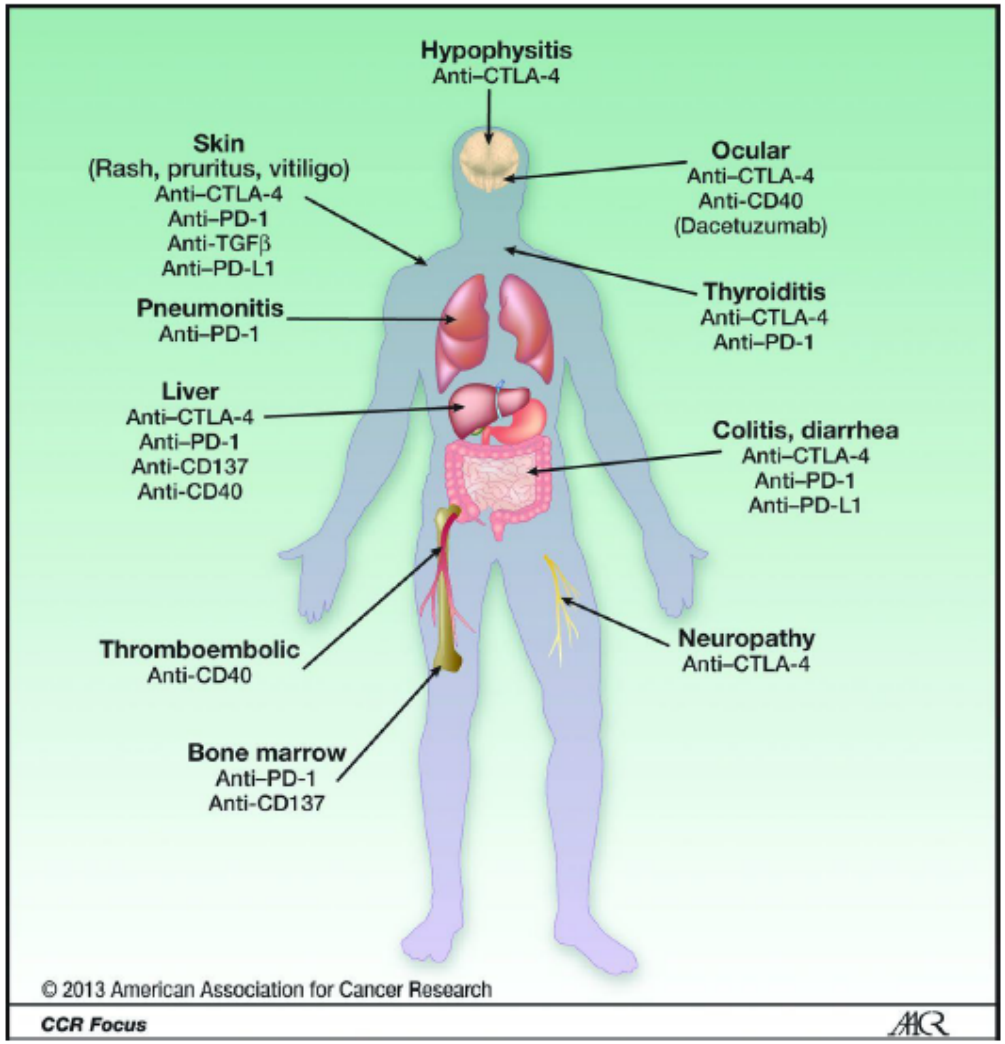
[b]In patients with non-squamous histology only

[c]Must be interpreted with caution: of these 4 responders, 1 did not have a classical exon 19 deletion or L858R *EGFR* activating mutations, 3 were former/current smokers, and 3 had high PD-L1 expression levels

Issues

- What's the optimal duration of therapy?
  - Long term toxicities

Tissue distribution of the most frequent irAEs observed with immunostimulatory mAbs.

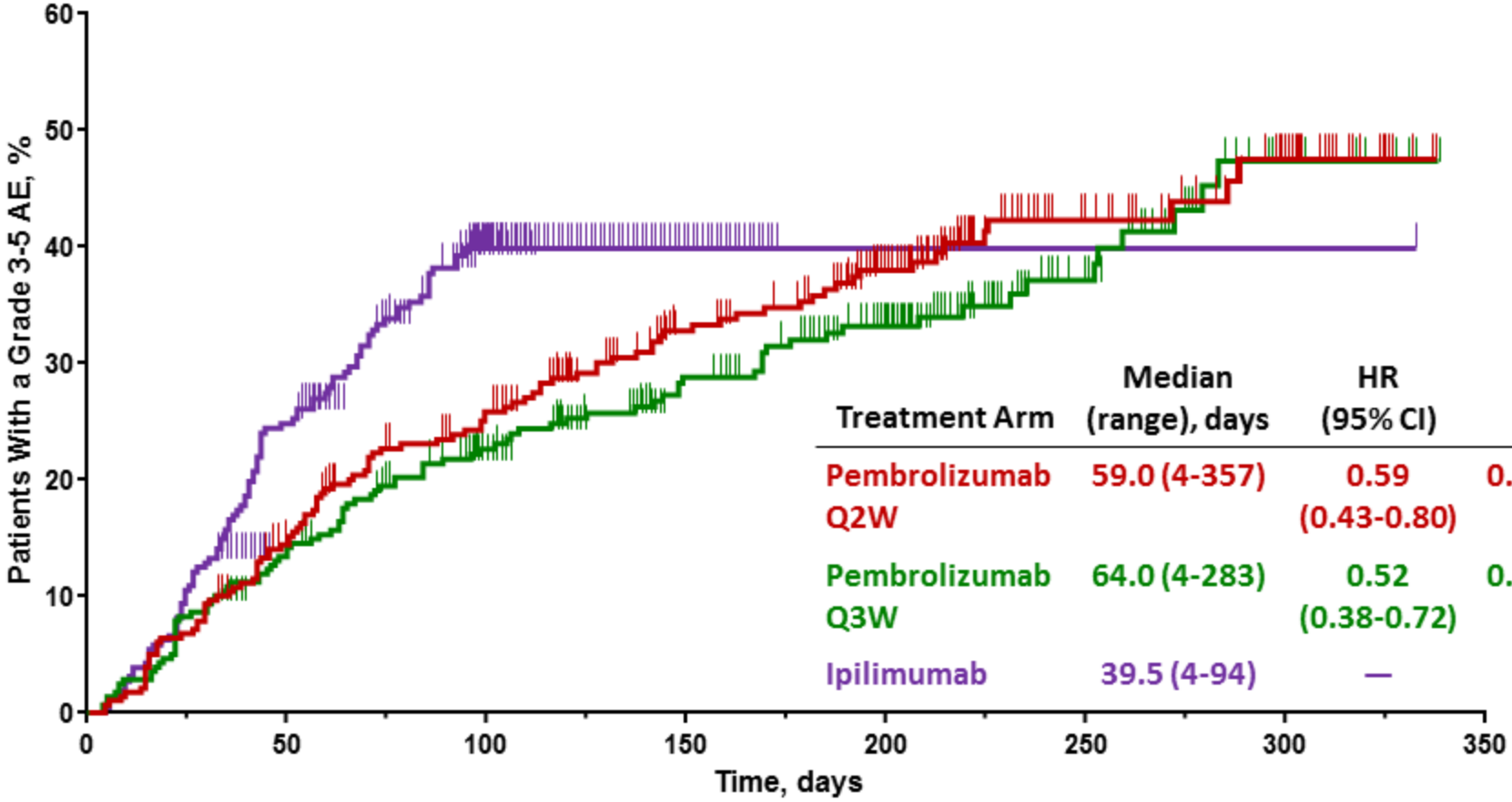


Melero I et al. Clin Cancer Res 2013;19:997-1008

Immune Adverse Events

- Onset:
  - Average is 6-12 weeks after initiation of therapy
  - Can occur within days of the first dose, after several months of treatment, and after discontinuation of therapy
- Pt complaints are autoimmune and drug related until proven otherwise
  - Rule out infections, metabolic causes, tumor effects, etc
- Early recognition, evaluation, and treatment are critical

Time to First Grade 3-5 Adverse Event[a] at IA1



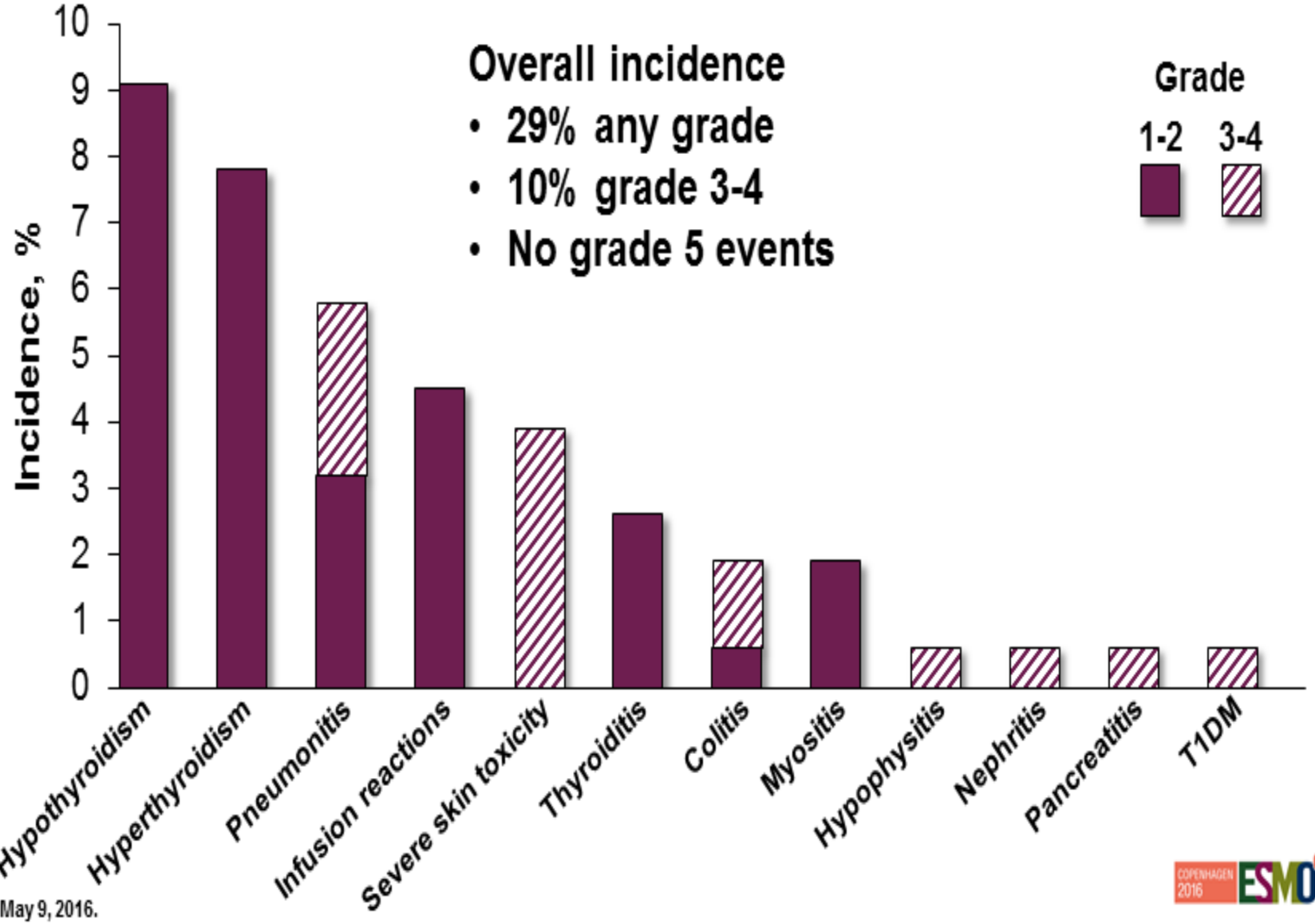
Treatment Arm	Median (range), days	HR (95% CI)	*P*
Pembrolizumab Q2W	59.0 (4-357)	0.59 (0.43-0.80)	0.00037
Pembrolizumab Q3W	64.0 (4-283)	0.52 (0.38-0.72)	0.00003
Ipilimumab	39.5 (4-94)	—	—

No. at risk

278	230	188	139	98	45	22	1
277	233	179	140	97	47	17	0
256	182	6	1	1	1	1	0

[a]Adverse events are presented regardless of causality.
Analysis cut-off date: September 3, 2014.

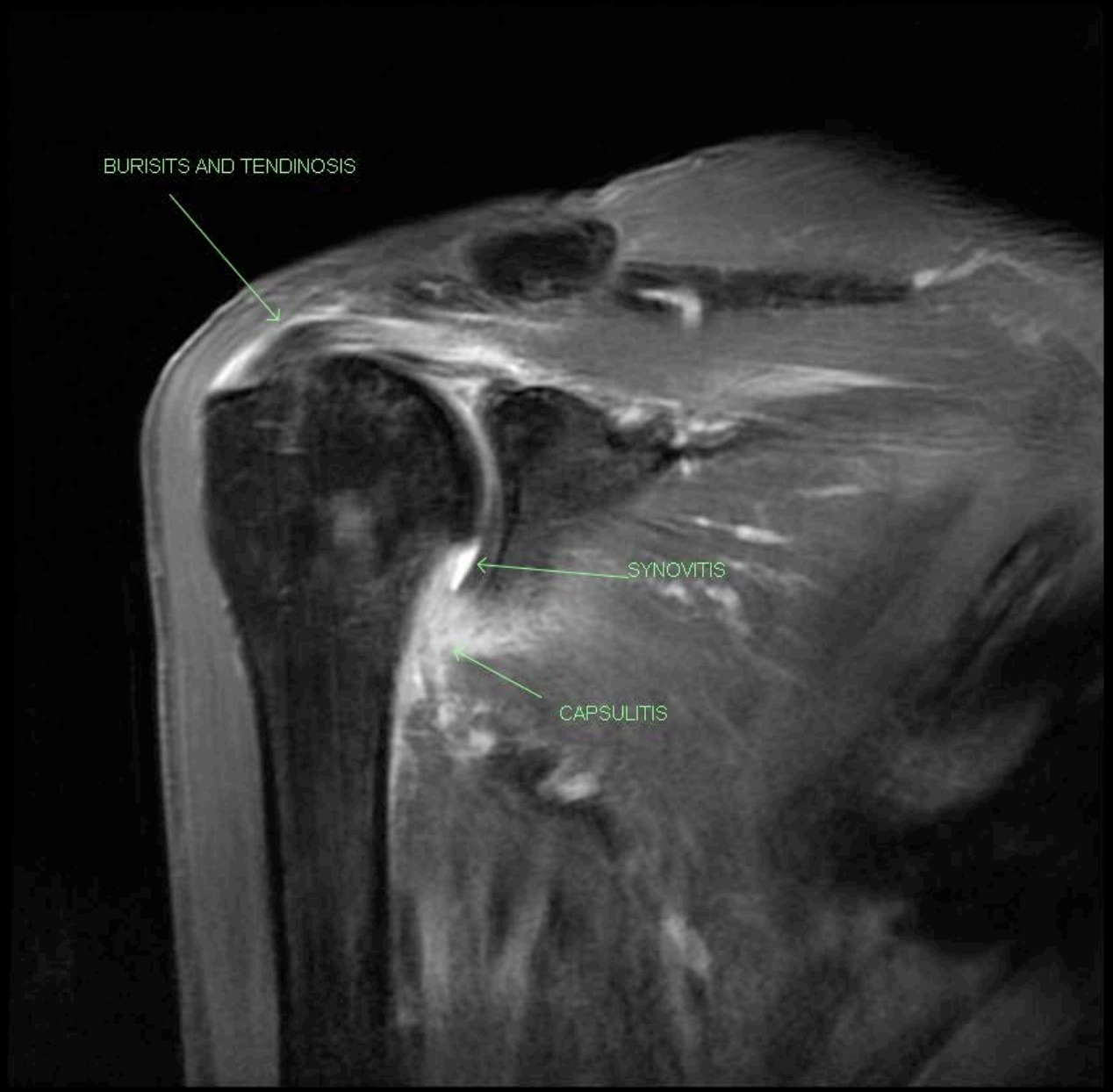
Immune-Mediated AEs With Pembrolizumab



Data cut-off: May 9, 2016.

Event	Nivolumab (N=131)	
	Any Grade	Grade 3 or 4
	number of patients	
Any event	76 (58)	9 (7)
Fatigue	21 (16)	1 (1)
Decreased appetite	14 (11)	1 (1)
Asthenia	13 (10)	0
Nausea	12 (9)	0
Diarrhea	10 (8)	0
Arthralgia	7 (5)	0
Pyrexia	6 (5)	0
Pneumonitis	6 (5)	0
Rash	5 (4)	0
Mucosal inflammation	3 (2)	0
Myalgia	2 (2)	0
Anemia	2 (2)	0
Peripheral neuropathy	1 (1)	0
Leukopenia	1 (1)	1 (1)
Neutropenia	1 (1)	0
Febrile neutropenia	0	0
Alopecia	0	0

Treatment Related Adverse Events Reported in at Least 5% Patients


BURISITS AND TENDINOSIS
SYNOVITIS
CAPSULITIS

Progress

- Symptoms improved with NSAIDs

Other significant issue

- A CT scan after 2 cycles demonstrated ground glass changes consistent with pneumonitis

Toxicity

- Received cycle 2 anti-PD1 therapy on the 28/1/2016
- 1/2/2016 contacted by wife
  - Symptoms of somnolence, memory loss, expressive dysphasia and ataxia
- Admitted to hospital
  - Investigations including CT brain and MRI scan unremarkable apart from post-surgical and radiotherapy changes
  - CSF – completely normal (including subsequent JC virus PCR)

Progress

- Auto-antibody and vasculitic screen normal
- EEG demonstrated a generalised encephalopathy
- Condition deteriorated further over 3 days in hospital
  - Decision to commence high dose methyl-prednisone (1G daily for 3 days and subsequent weaning)
- Patients condition improved signficantly and symptoms on follow-up have now virtually resolved
    - Anti-PDL1 therapy discontinued

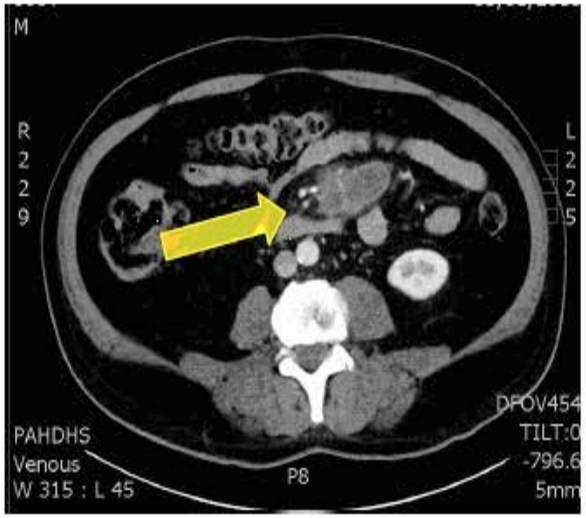
Neurological side-effects

- Neurological adverse events were considered rare with checkpoint inhibitors
- Recent review of melanoma in Royal Marsden – 2.8%
- Ipililumab associated with Guillain-Barre Syndrome, Transverse myelitis, Myasthenia Gravis, meningitis, and Posterior Reversible Encephalopathy Syndrome
- Limbic encephalitis secondary to pembrolizumab reported
  - MRI and CSF findings abnormal but EEG no epileptiform discharges
  - cognitive decline was not reversed with high dose corticosteroids
- The majority resolve high dose steroids, however fatalities have been reported
- Significant toxicities probably under-called

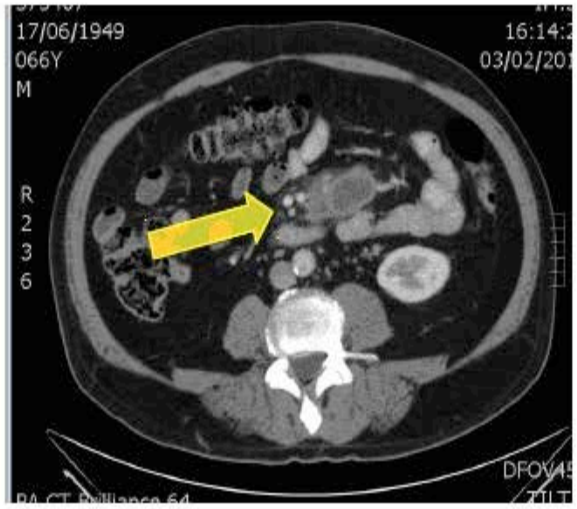
Issues

- …..and the optimal duration of therapy?

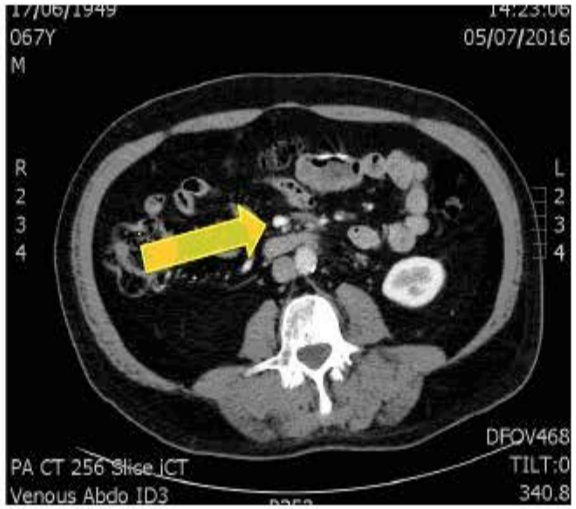
Deep Partial Response to Pembrolizumab



5th Janurary 2016- prior to pembrolizumab



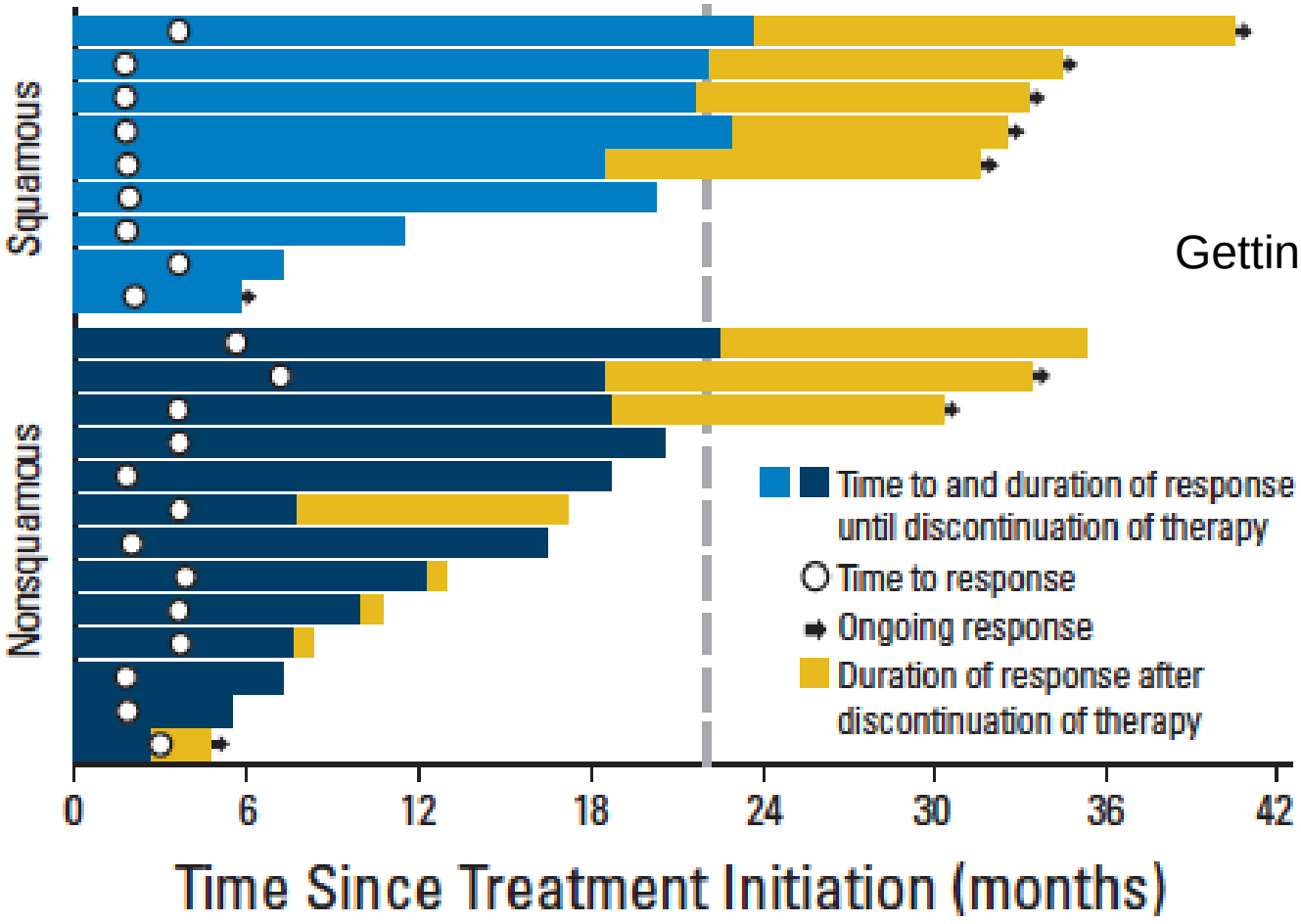
3rd February 2016- First scan after discontinuation of pembrolizumab



5th July 2016- 5 months after discontinuation of pembrolizumab

Response ongoing 16 months after stopping Pembrolizumab

Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer



Gettinger SN et al

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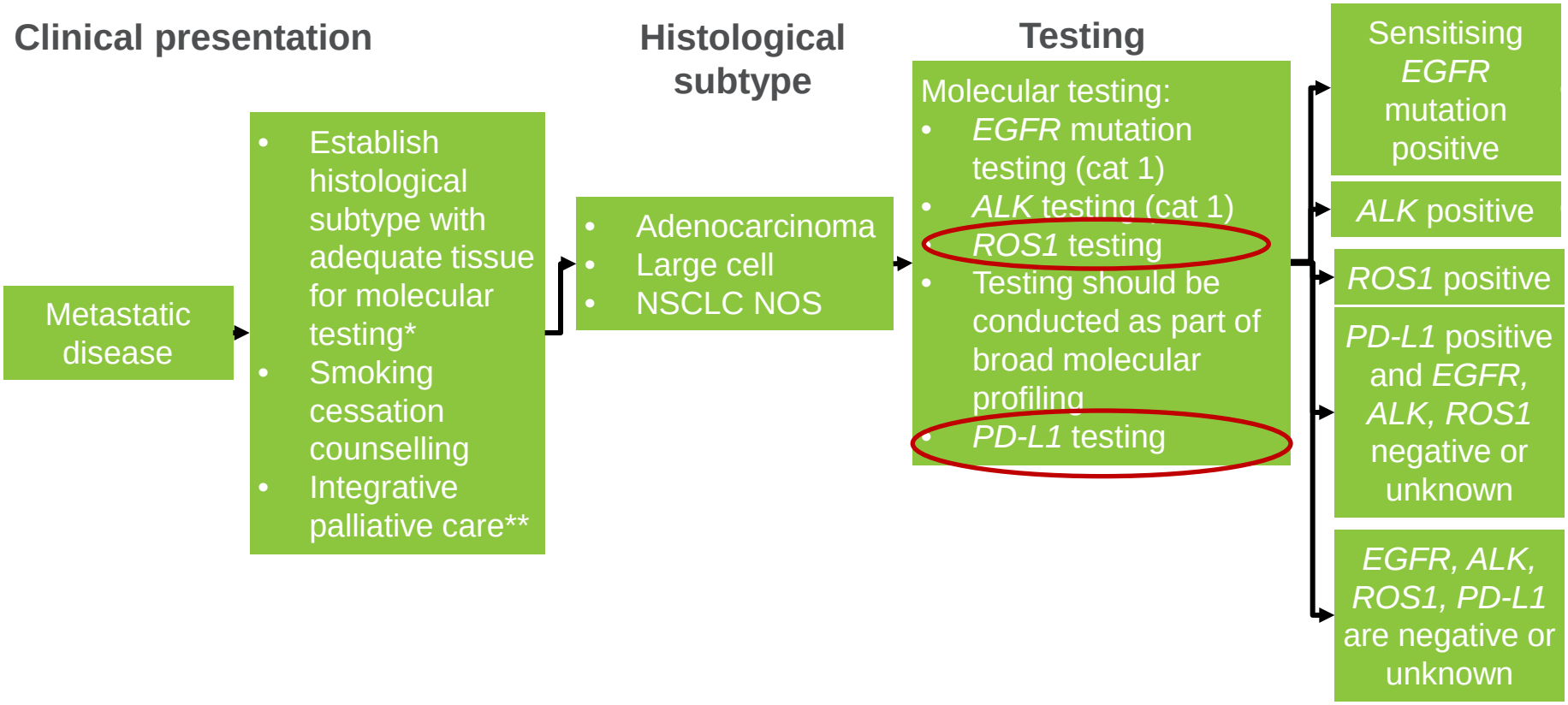
ORIGINAL REPORT

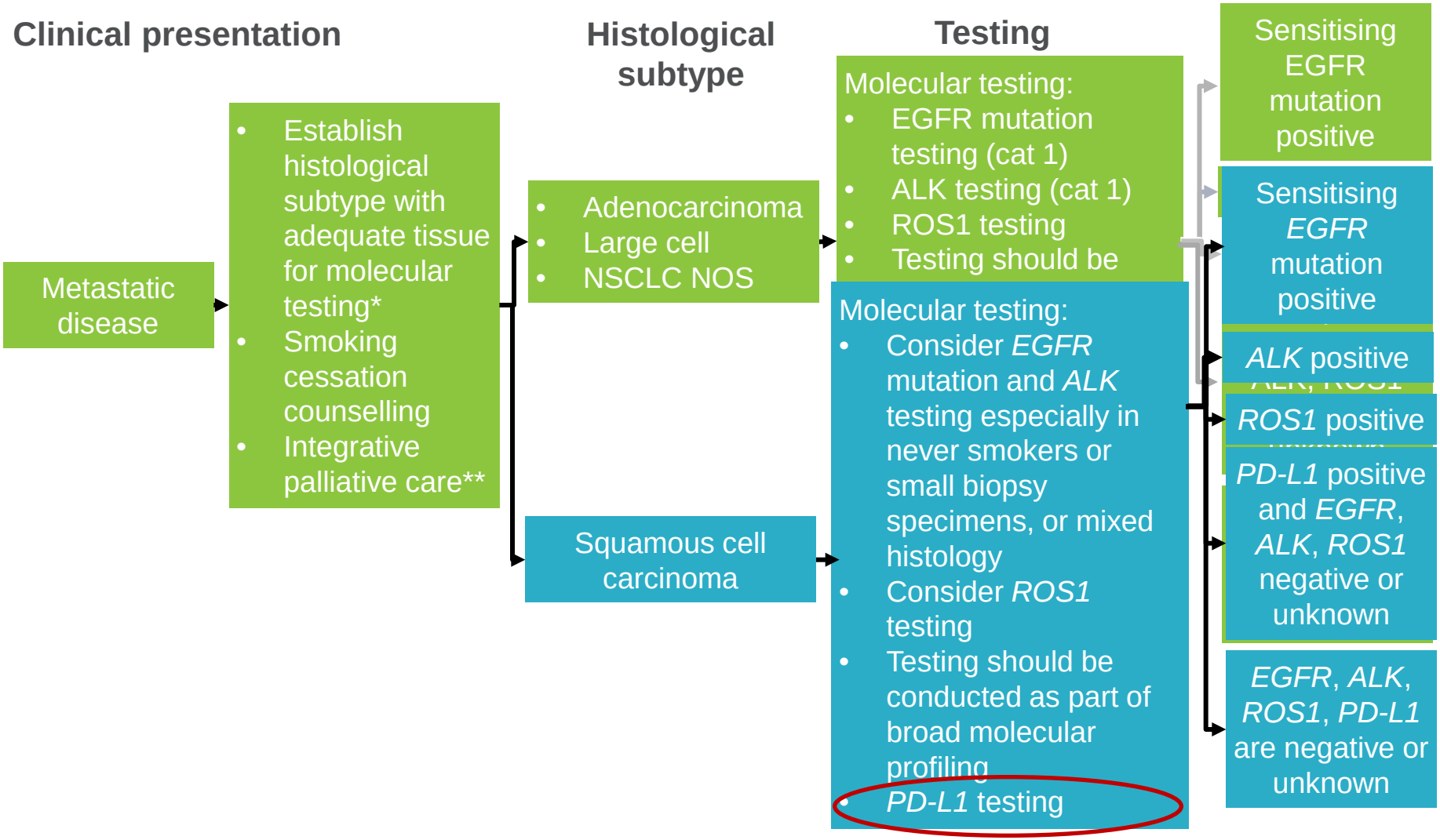
NCCN guidelines for NSCLC V5, 2017



* Consider rebiopsy, if appropriate; ** See NCCN Guidelines for Palliative Care.
NGS, next generation sequencing; NOS, not otherwise specified.

1. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 5. 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed April 2017)

NCCN guidelines for NSCLC V5, 2017



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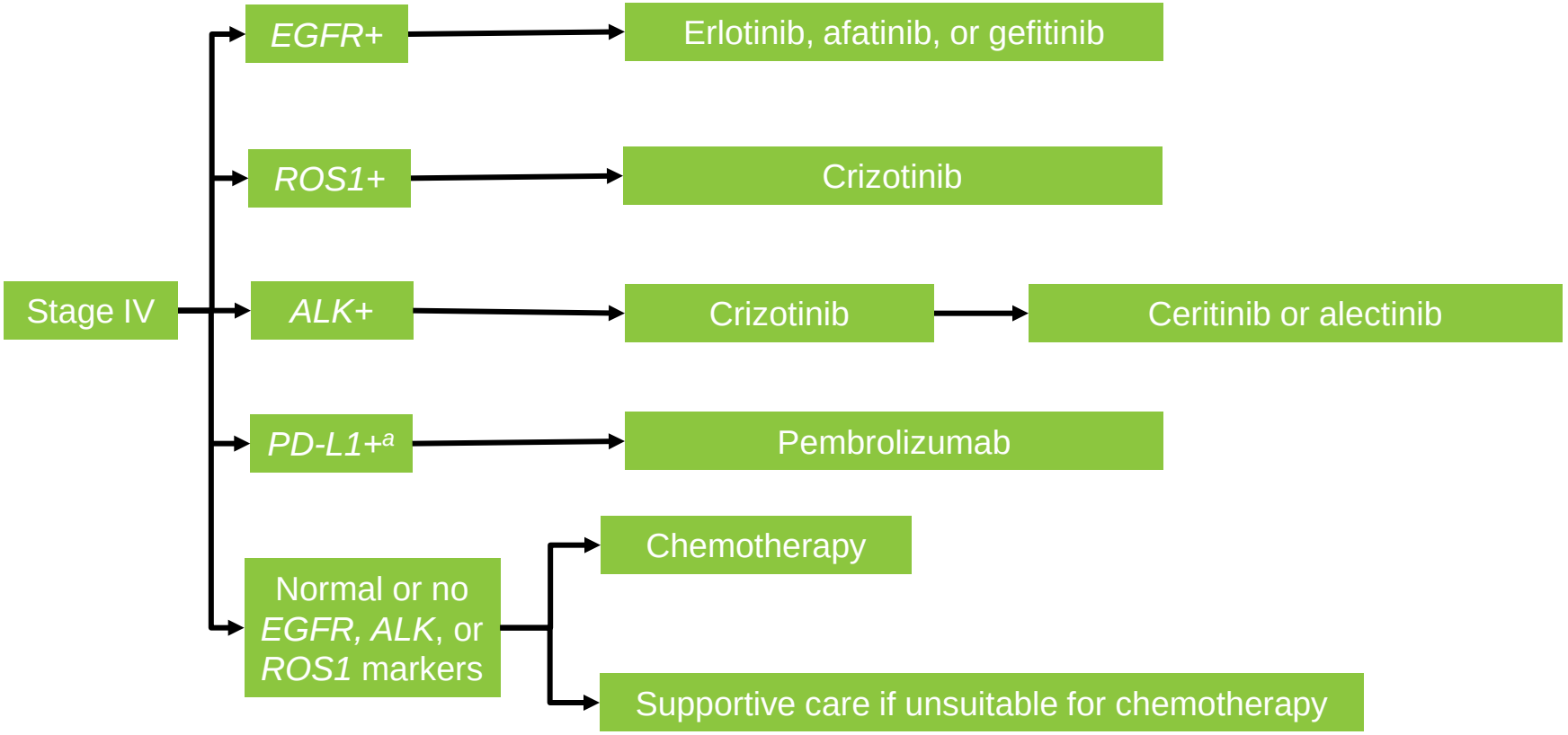
1. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 5. 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed April 2017)

Current NCCN guidelines for 1L treatment of stage IV NSCLC[1,2]



1. https://www.nccn.org/patients/guidelines/quick_guides/lung-nsclc/treatment_options/ 2. NCCN guidelines. Non-Small Cell Lung Cancer Version 5. 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed April 2017)

[a] *EGFR, ALK* and *ROS1* negative or unknown

Conclusions

- Immune checkpoint inhibitors targeting the PD1/PDL1 pathway are a new standard of care in the treatment of NSCLC
- In the first line setting selection of patients using PDL1 IHC is required
- Combination therapies with either anti-CTLA4 antibodies or chemotherapy in the first line setting, and in patients with oncogene driver mutations, are promising
- Better biomarkers to select patients, particularly with poor prognostic features, are required