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Immunotherapy for Advanced NSCLC

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Research Support:

BMS

Genentech/Roche

Pfizer

Biodesix

MSD

Merck Serono

Lilly Oncology

Boheringer Ingelheim

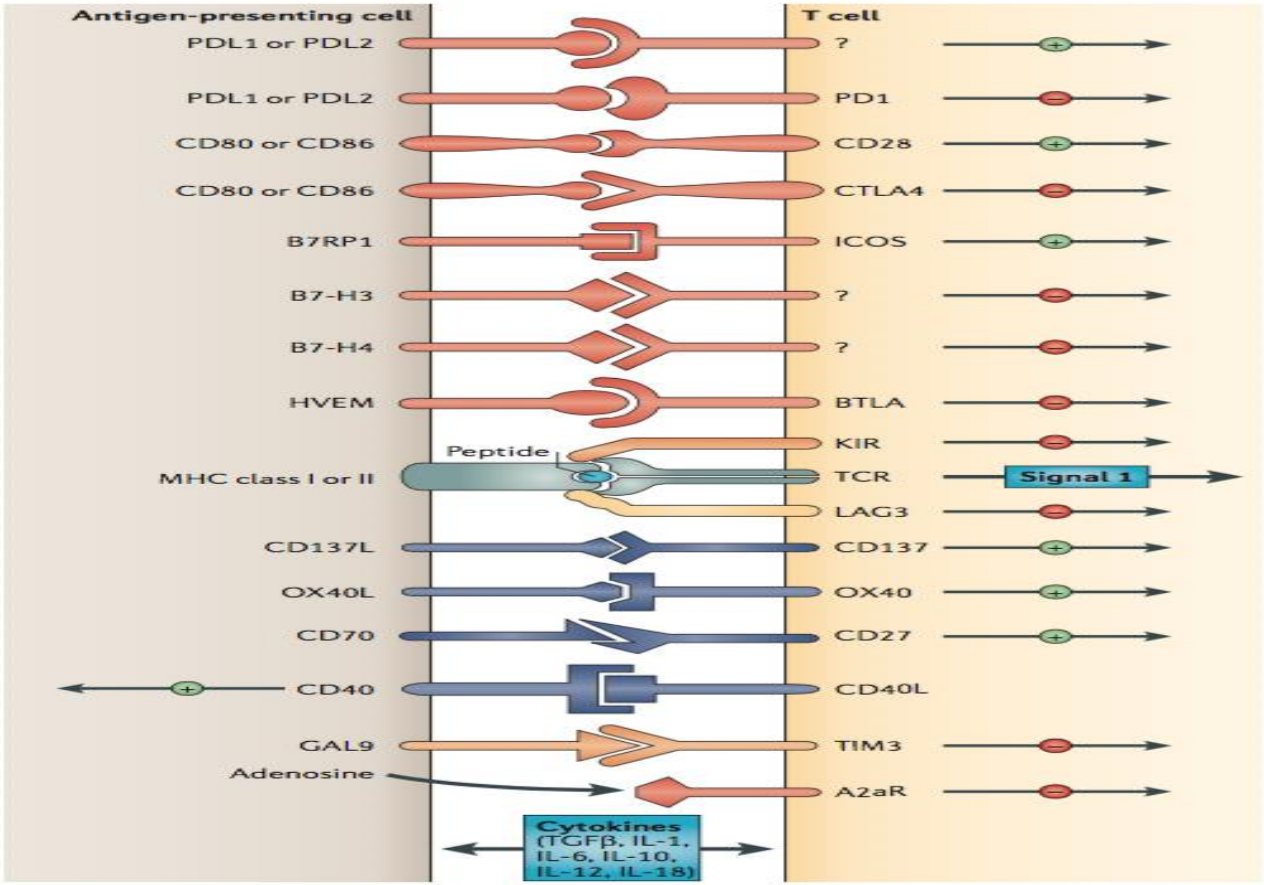
Novartis

Astra-Zeneca

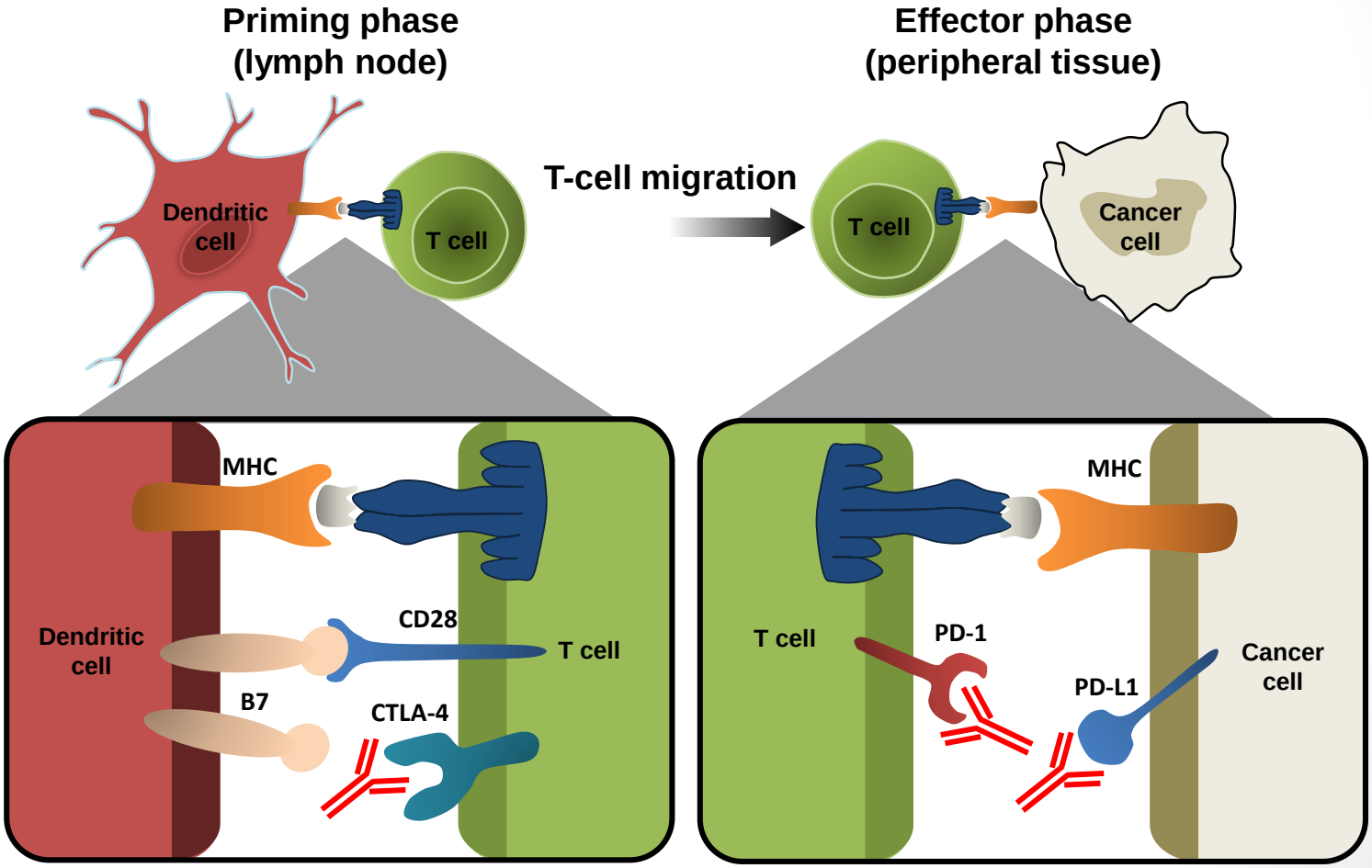
Liquid Genomics

Speakers Bureau/Stocks: *None*

Inhibition of one Immune Checkpoint...



Immunotherapy: Checkpoint blockade



Ribas A. N Engl J Med. 2012;366:2517-2519.

Checkpoint Blockade

Anti-CTLA-4	Anti-PD-L1	Anti-PD-1
Ipilimumab (Fully human IgG1) FDA approved 2011	**MDX-1105** (Fully human IgG4) Phase I	**MDX-1106, Nivolumab** (Fully human IgG4) FDA approved for melanoma, NSCLC, urothelial carcinoma, RCC, HL, SCCHN
Tremelimumab (Fully human IgG2) Phase III	**MPDL3280A, RG7446, Atezolizumab** Phase II-III FDA approved 2016 NSCLC	**CT-011 Pidilizumab** (Humanized IgG1) Phase II
	MEDI4736, Durvalumab; Phase III	**MK3475 Pembrolizumab** (formerly Lambrolizumab) (Humanized IgG4) FDA approved for melanoma, NSCLC, SCCHN
	MSB0010718C, Avelumab Phase I-II	**AMP-224** (B7-DC/IgG1fusion protein) Phase I-II
		MEDI0680, AMP514 Phase I

Second line Immunotherapy

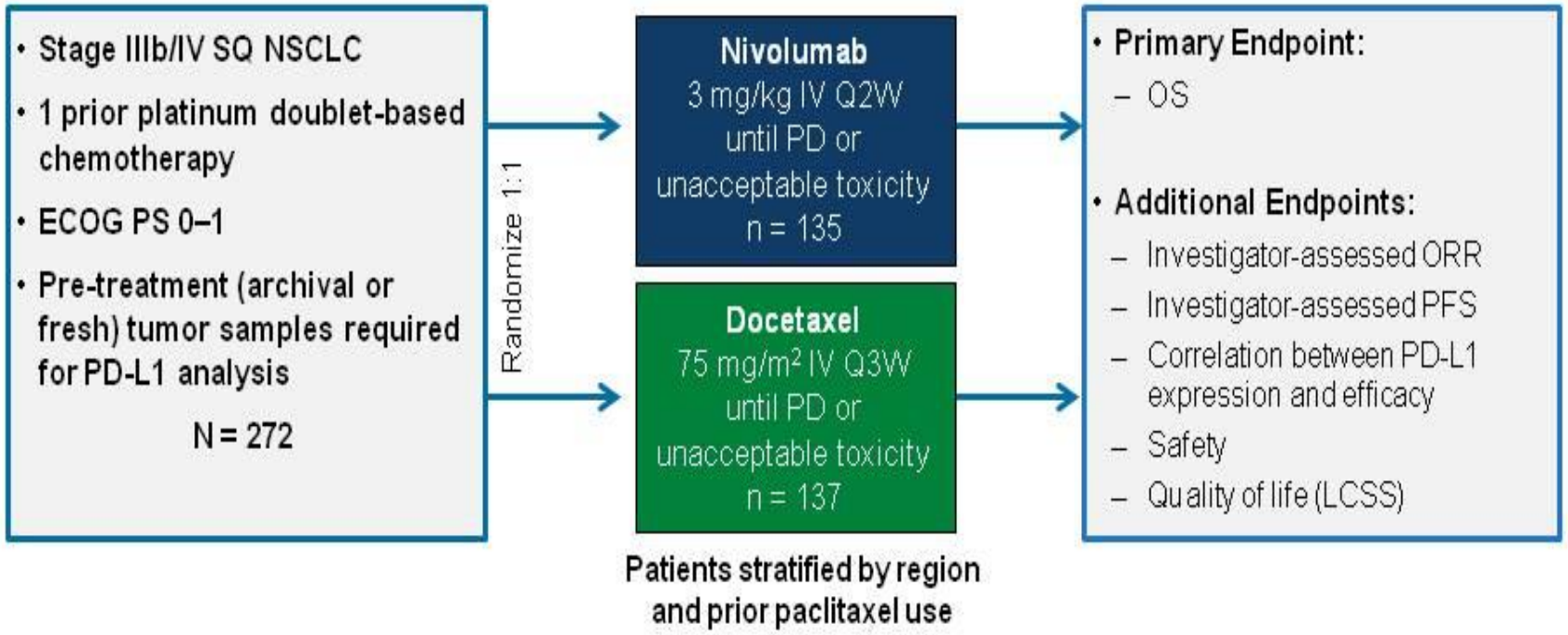
Nivolumab

Pembrolizumab [Pdl-1 +]

Atezolizumab

Nivolumab

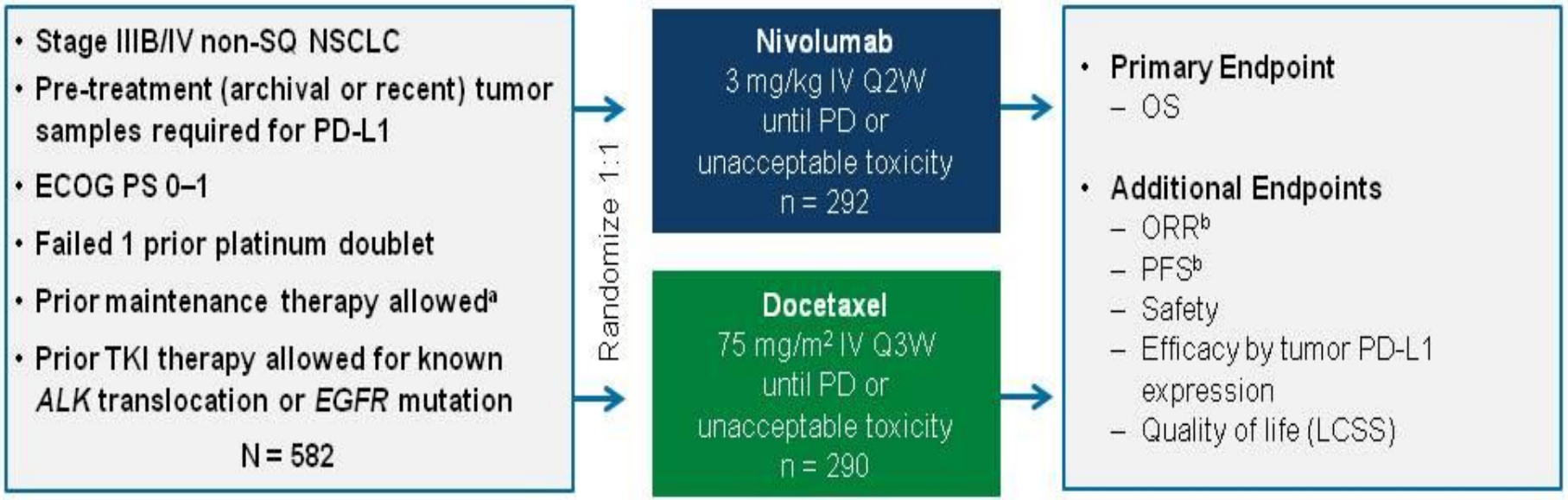
CheckMate 017 (NCT01642004) - Study Design



- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was $P < 0.03$

LCSS = Lung cancer symptom scale

CheckMate 057 (NCT01673867) Study Design



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

- PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

[a]Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b]Per RECIST v1.1 criteria as determined by the investigator.

Presented By Luis Paz-Ares at 2015 ASCO Annual Meeting

Kaplan–Meier Estimates of OS (2 Years Minimum Follow-up)

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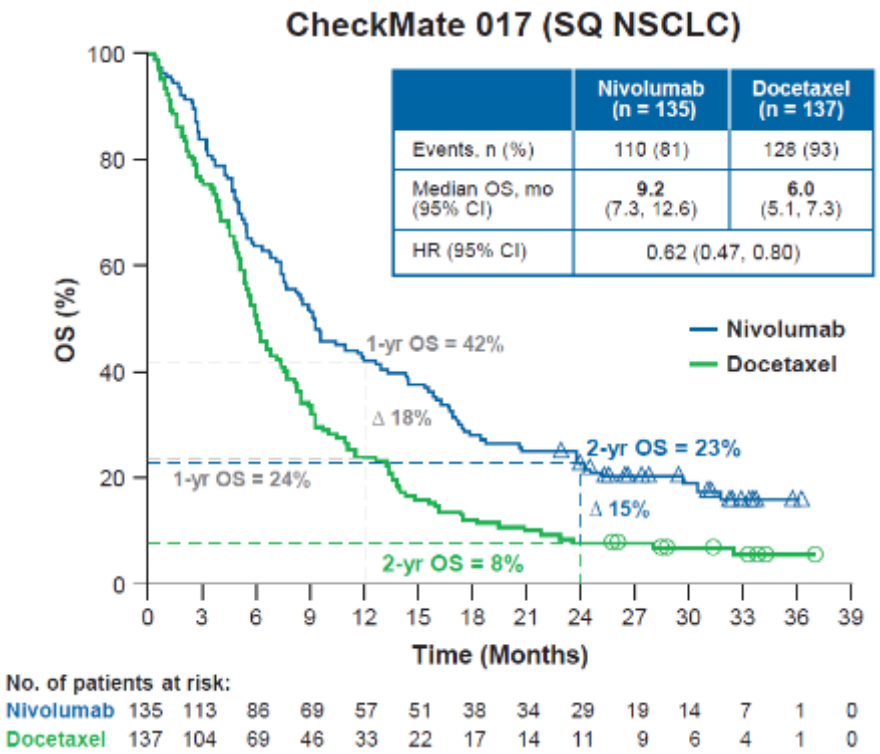
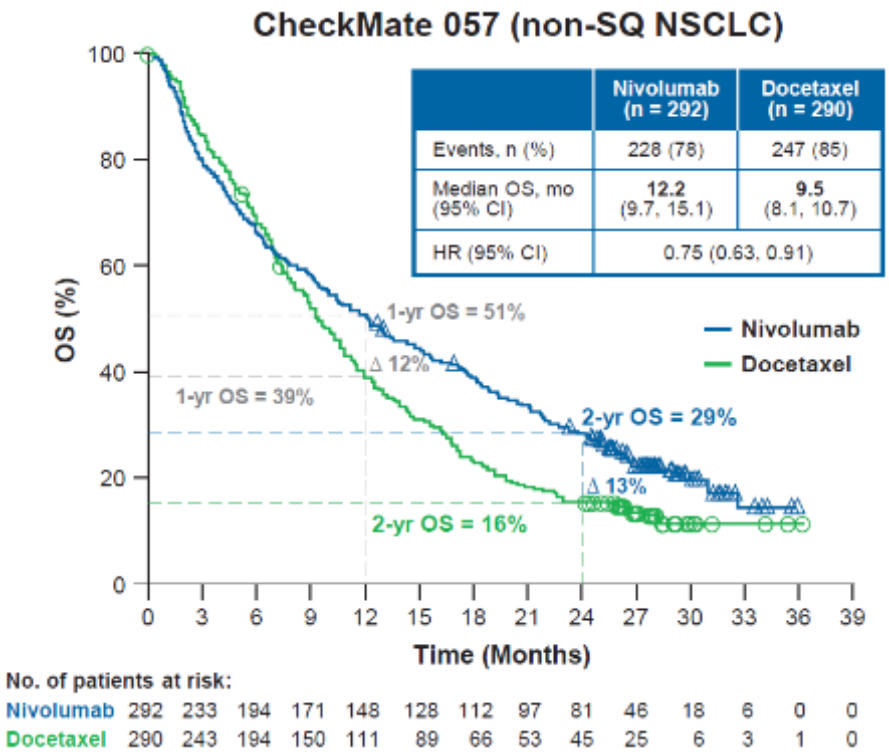
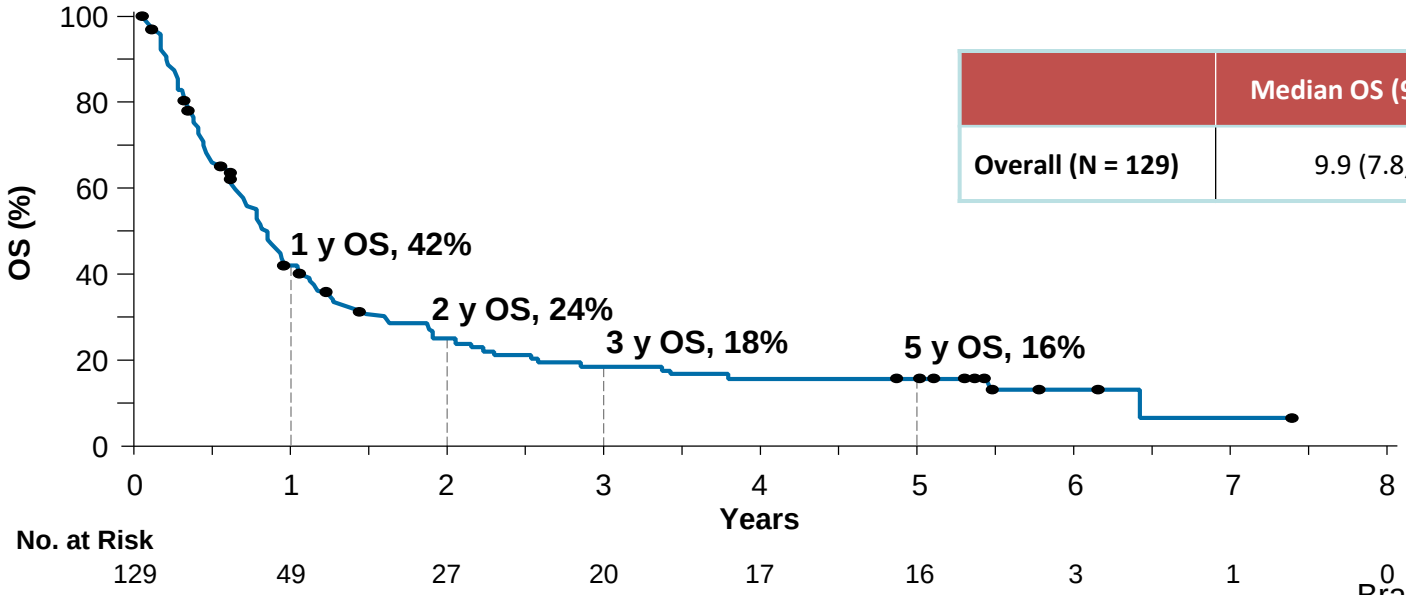




Stronger Together

has improved long term OS in patients with heavily pretreated metastatic NSCLC

CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC



	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

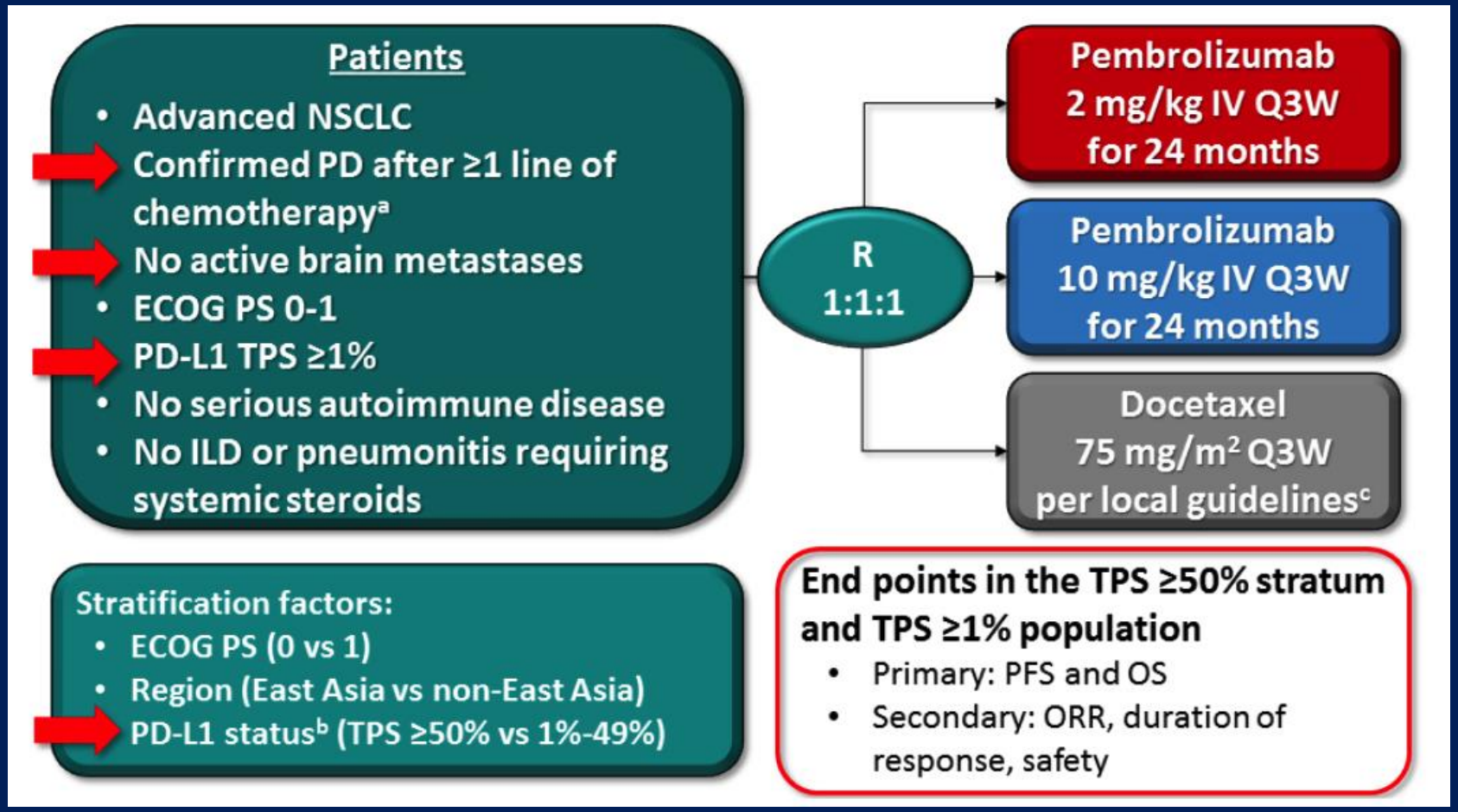
Brahmer J, AACR 2017

[a]There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

Pembrolizumab

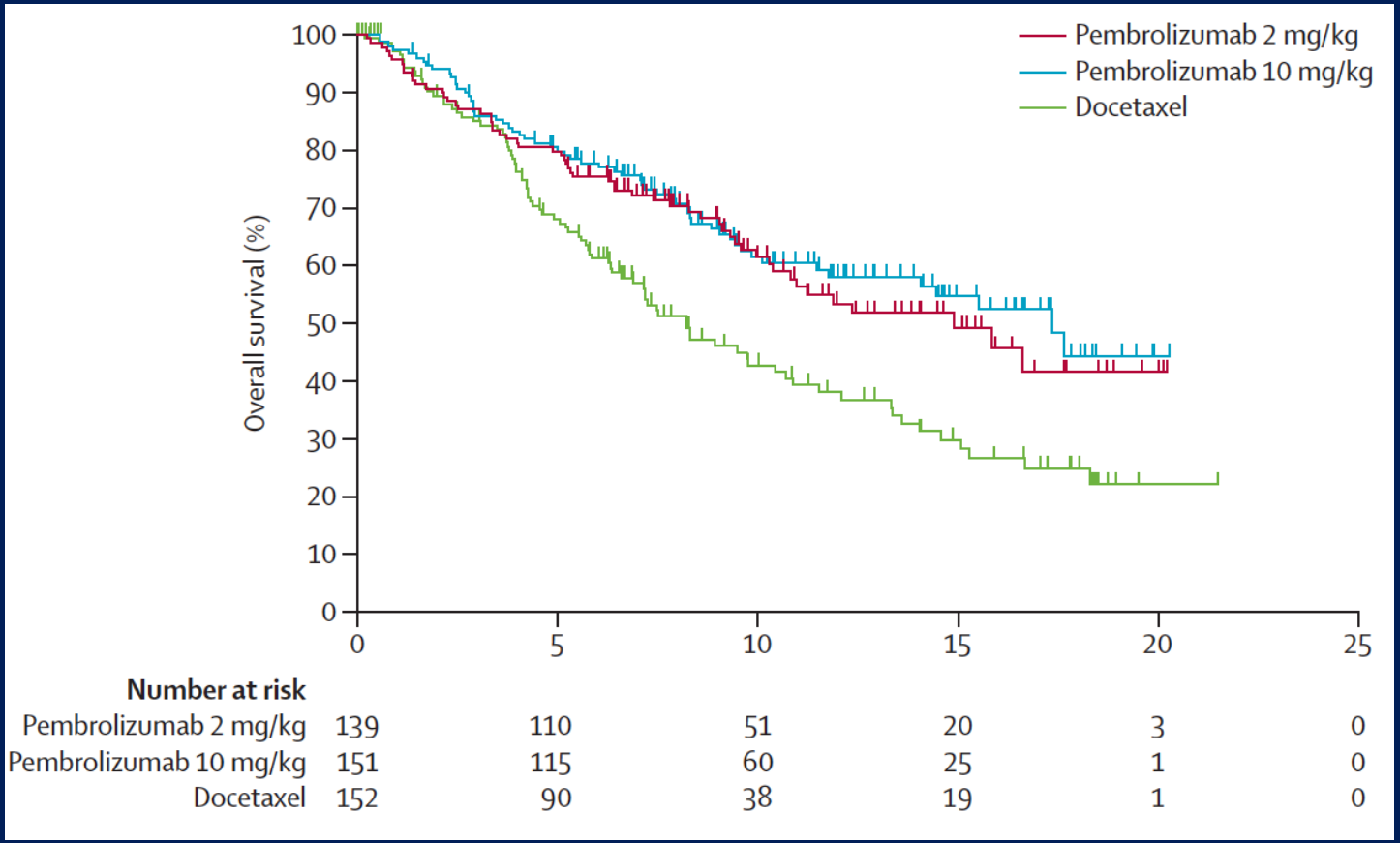
KEYNOTE-010 Trial

Pembrolizumab vs Docetaxel



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

KEYNOTE-010: *Pembrolizumab vs Docetaxel*
Overall Survival in Patients with PD-L1 Positive Disease



- Pembro demonstrated a longer OS than Doce in all PD-L1 tumor proportion score (TPS) categories with the longest OS, PFS, and highest ORR seen in pts with TPS ≥75%.

Herbst RS et al. *Lancet.* 2016;387:1540-1550; Baas P et al. *J Clin Oncol.* 2016;34(suppl). Abstract 9015.

Atezolizumab

IASLC
International Association for the Study of Lung Cancer
IASLC 17TH WORLD CONFERENCE ON LUNG CANCER
WWW.IASLC.ORG
DECEMBER 4–7, 2016 VIENNA, AUSTRIA

OAK, a randomized Ph III study of atezolizumab vs docetaxel in patients with advanced NSCLC: results from subgroup analyses

Shirish M. Gadgeel,[1] Fortunato Ciardiello,[2] Achim Rittmeyer,[3] Fabrice Barlesi,[4] Diego Cortinovis,[5] Carlos Barrios,[6] Toyoaki Hida,[7] Keunchil Park,[8] Dariusz Kowalski,[9] Manuel Cobo Dols,[10] Joseph Leach,[11] Christina Matheny,[12] Pei He,[12] Marcin Kowanetz,[12] Daniel S. Chen,[12] Daniel Waterkamp,[12] Marcus Ballinger,[12] Alan Sandler,[12] David R. Gandara,[13] Joachim von Pawel[14]

[1] Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; [2] Seconda Università degli Studi di Napoli, Napoli, Italy; [3] Lungenfachklinik Immenhausen, Immenhausen, Germany; [4] Aix Marseille University; Assistance Publique Hôpitaux de Marseille, Marseille, France; [5] Medical Oncology Unit, AOU San Gerardo, Monza, Italy; [6] PUCRS School of Medicine, Porto Alegre, Brazil; [7] Aichi Cancer Center Hospital, Nagoya, Japan; [8] Sungkyunkwan University School of Medicine, Seoul, South Korea; [9] Oncology Centre, Institute M. Sklodowska - Curie, Warsaw, Polandomg; [10] Medical Oncology Section, Hospital Regional Universitario Carlos Haya, Málaga, Spain; [11] PRA Health Sciences, Raleigh, NC, USA; [12] Genentech, Inc., South San Francisco, CA, USA; [13] UC Davis Comprehensive Cancer Center, Sacramento, CA, USA; [14] Asklepios-Fachkliniken München-Gauting, Gauting, Germany

Gadgeel et al., WCLC 2016

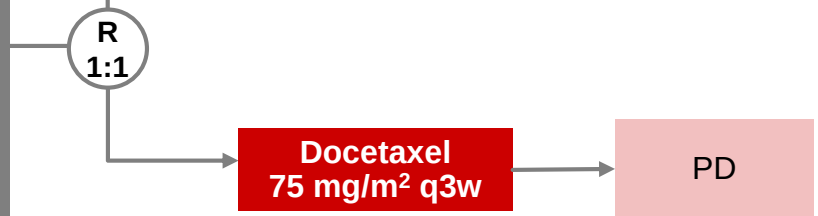
Phase III OAK study design

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]

OAK study design

Locally Advanced or Metastatic NSCLC[3]

- N = 1225 enrolled[a]
- 1–2 prior lines of chemo including ≥ 1 platinum-based
- Any PD-L1 status[b]
- Stratification factors: PD-L1 expression, histology, prior chemotherapy regimens



Primary Endpoints (first 850 enrolled patients)

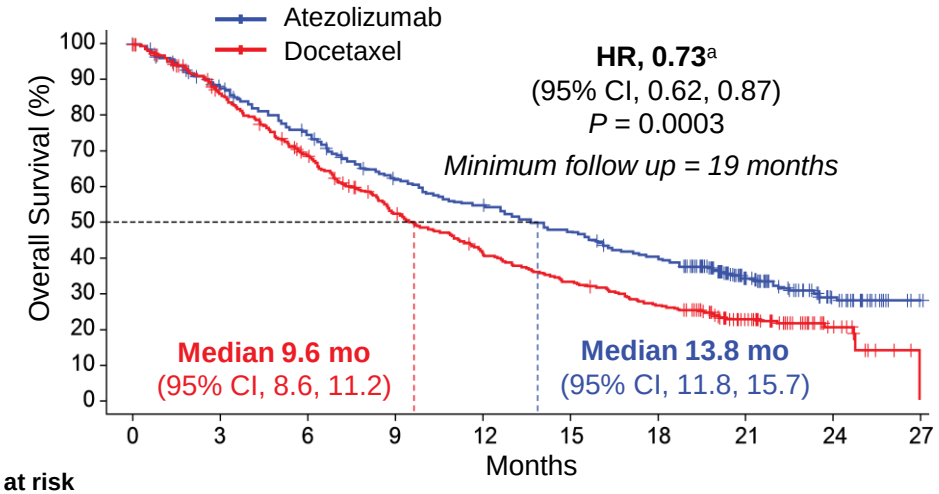
- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

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).
[b]PD-L1 expression assessed with VENTANA SP142 IHC assay
1. Herbst *Nature* 2014. 2. Chen *Immunity* 2013. 3. Barlesi et al. ESMO 2016 LBA44

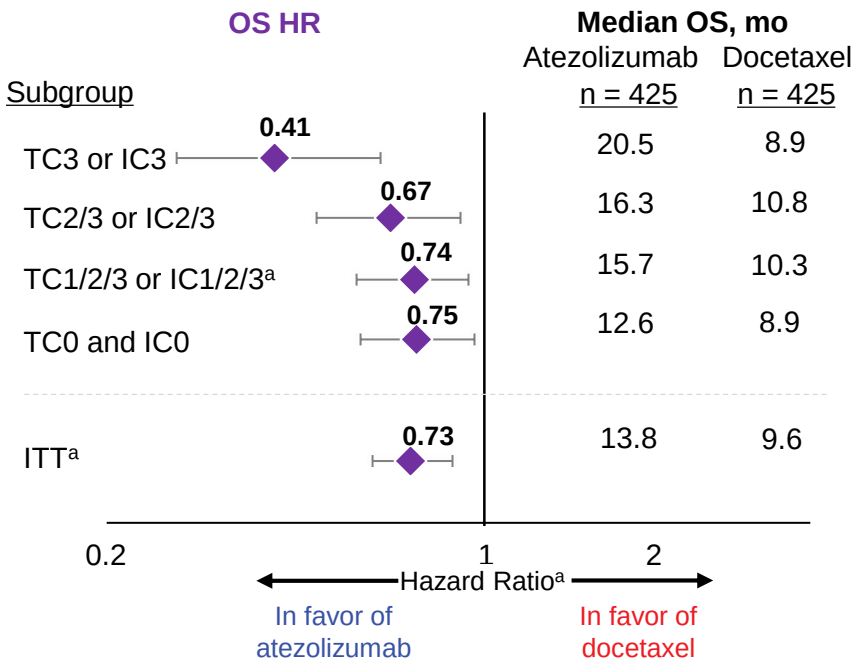
Gadgeel et al., WCLC 2016

Overall survival, ITT (n = 850) and PD-L1 subgroups



No. at risk

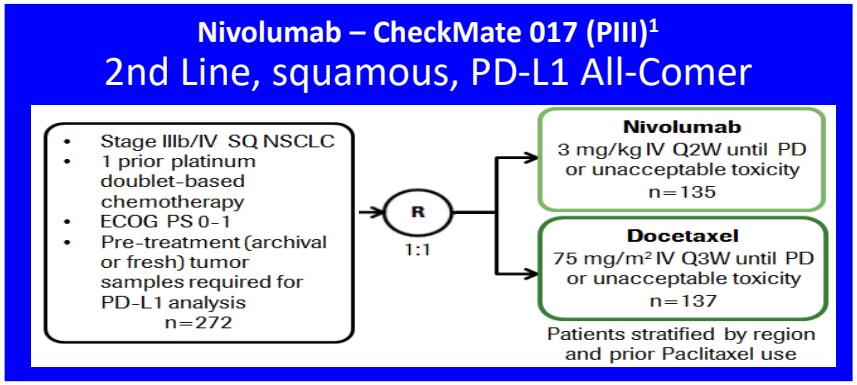
Atezolizumab	425	363	305	248	218	188	157	74	28	1
Docetaxel	425	336	263	195	151	123	98	51	16	0

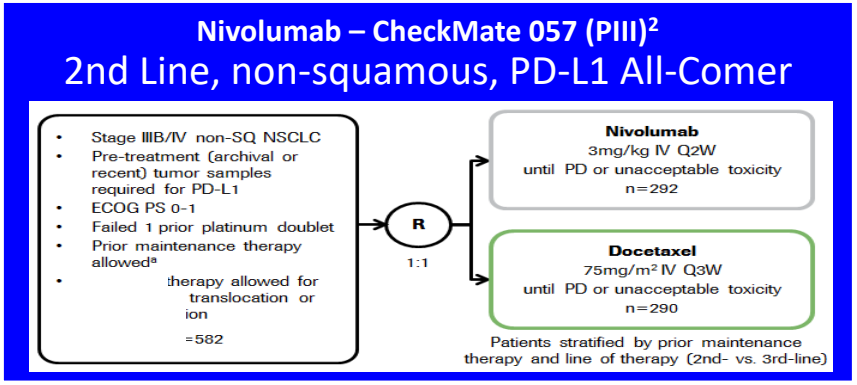


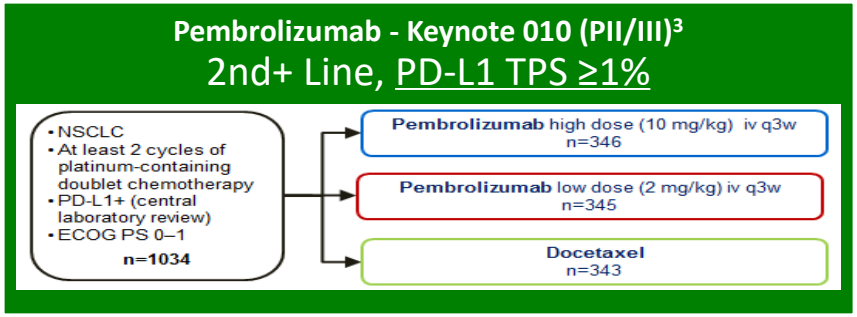
[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for other subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.
Barlesi et al. ESMO 2016 LBA44

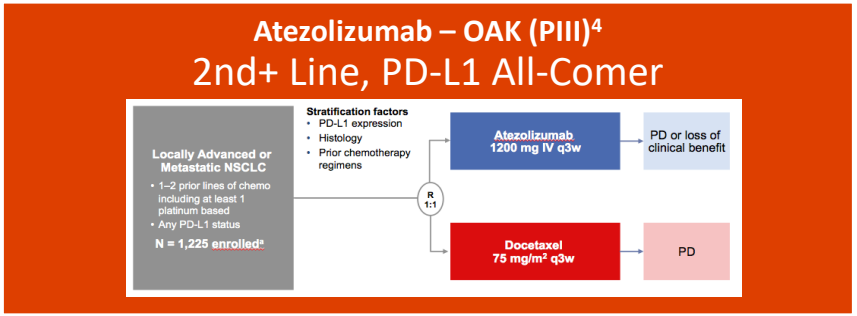
Gadgeel et al., WCLC 2016

The Past (2015 – 2016) - Immunotherapy in pretreated patients





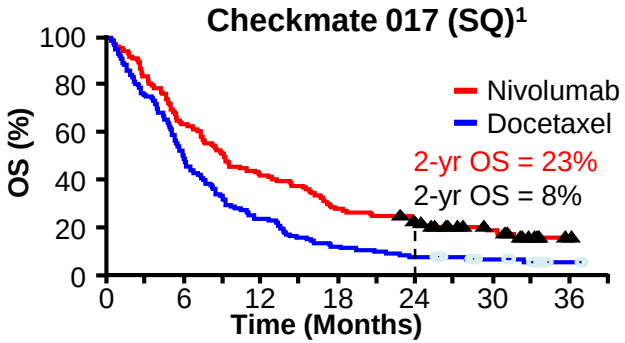


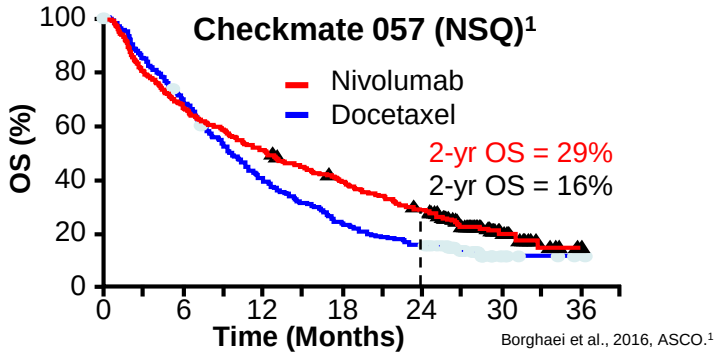


9025. 2. Brahmer JR et al. Oral presentation at AACR 2017. CT077. 3. Herbst RS et al. Poster presentation at ASCO 2017. 9090. 4. Rittmeyer A et al. *Lancet.* 2017;389(10066):255-265. Ma

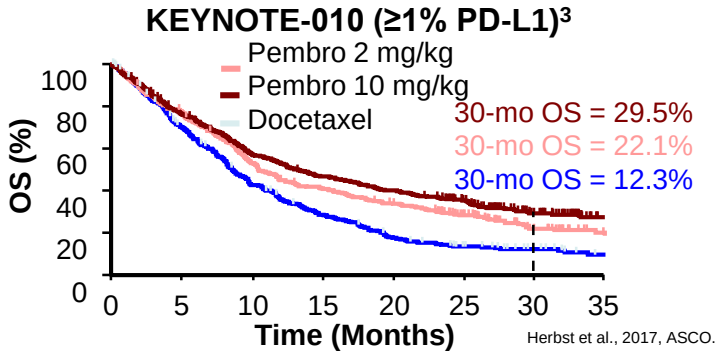
Martin Reck WLCC 2017

Consistent Benefit in OS

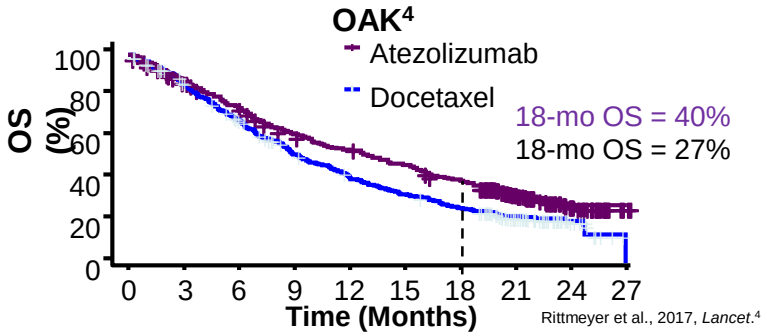




Borghaei et al., 2016, ASCO.[1]



Herbst et al., 2017, ASCO.[3]

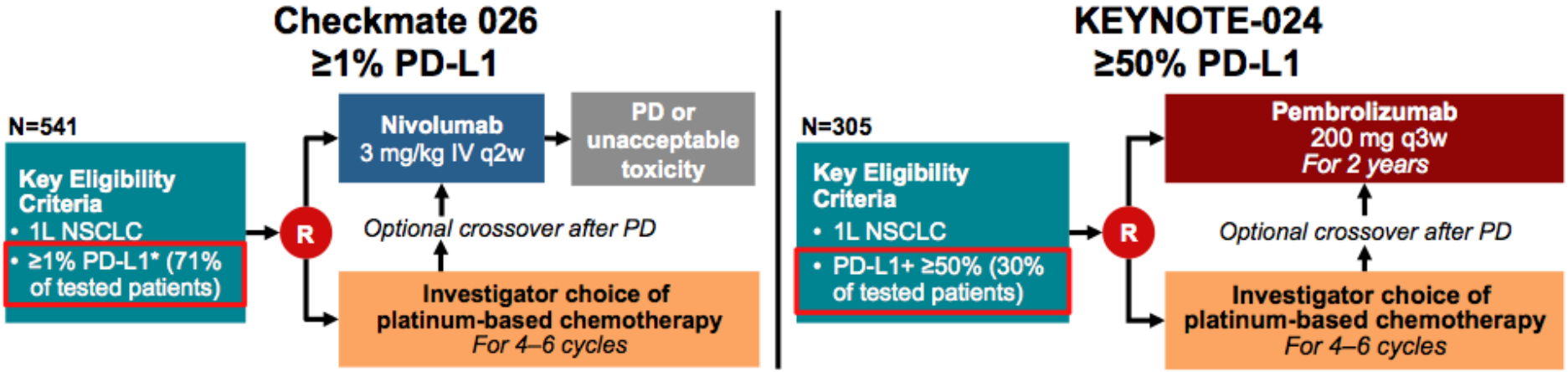


Rittmeyer et al., 2017, *Lancet*.[4]

First line Immunotherapy

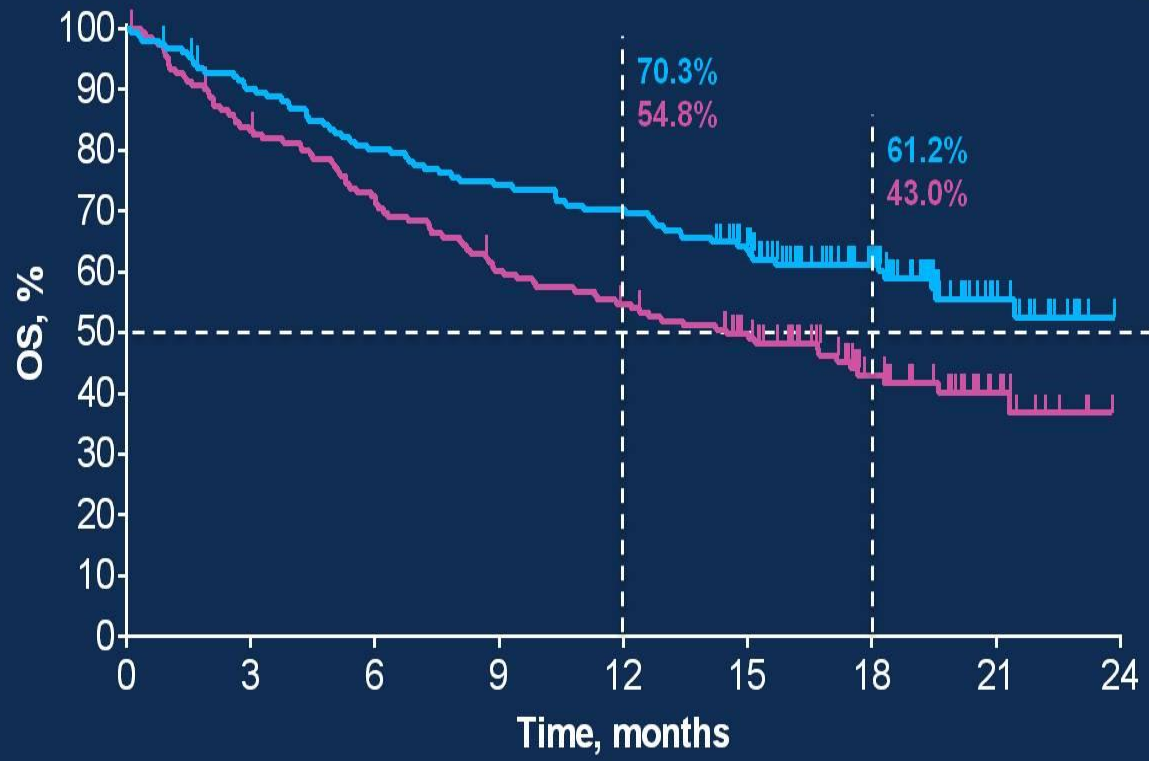
Pembrolizumab

Two „similar“ trials..



...but completely different outcomes!

Kaplan-Meier Estimate of OS: Updated Analysis



	Events, n	HR (95% CI)
Pembrolizumab	63	0.63 (0.46-0.88)
Chemotherapy	84	$P = 0.003$[a]

Median (95% CI)
NR (19.4 mo-NE)
14.5 mo (9.8-19.6)

No. at risk

154	136	121	112	106	88	57	20	4
151	123	107	88	79	64	35	15	4

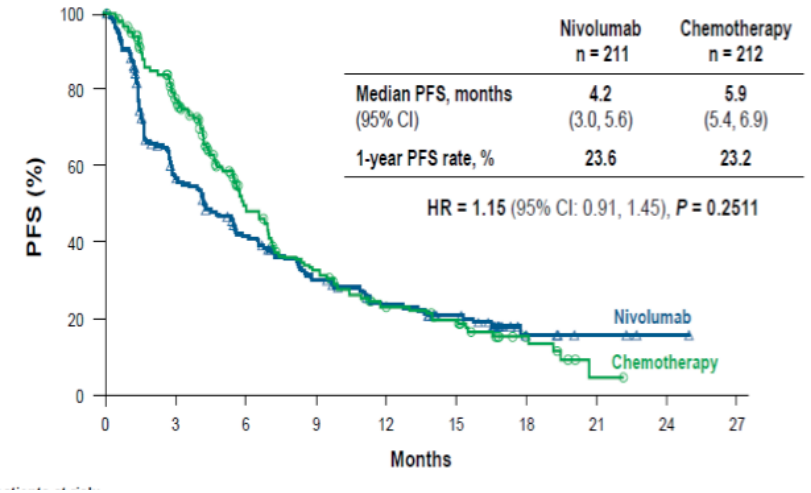
[a]Nominal *P* value.
Data cutoff: Jan 5, 2017.

Summary and Conclusions

- Pembrolizumab continued to show OS benefit over chemotherapy as first-line therapy for advanced NSCLC with PD-L1 TPS ≥50%
  - Median OS for pembrolizumab was not reached with a median follow-up of 19 months
  - Despite an effective crossover rate of 60%, there remained a high degree of separation of the OS curves
- PFS2 was substantially improved for patients in the pembrolizumab arm vs the chemotherapy arm
- Patients whose tumors have PD-L1 TPS ≥50% have better survival if beginning treatment with pembrolizumab rather than platinum-doublet chemotherapy
- Along with a favorable safety profile, these data support pembrolizumab as a standard of care for first-line treatment of NSCLC with PD-L1 TPS ≥50%

CheckMate - 026

- PFS: 4.2 vs 5.9 m (chemo) (HR 1.15, p=0.25)
- RR: 26% vs 33% (chemo)
- OS: 13.2 vs 14.4 m (chemo) (HR1.02)
- No difference in patients with PDL-expression =/> 50%
- TRAE 3/4: 18% vs 51% (chemo)
- Exploration of novel biomarker (TMB)
- Inhomogenities in patient populations



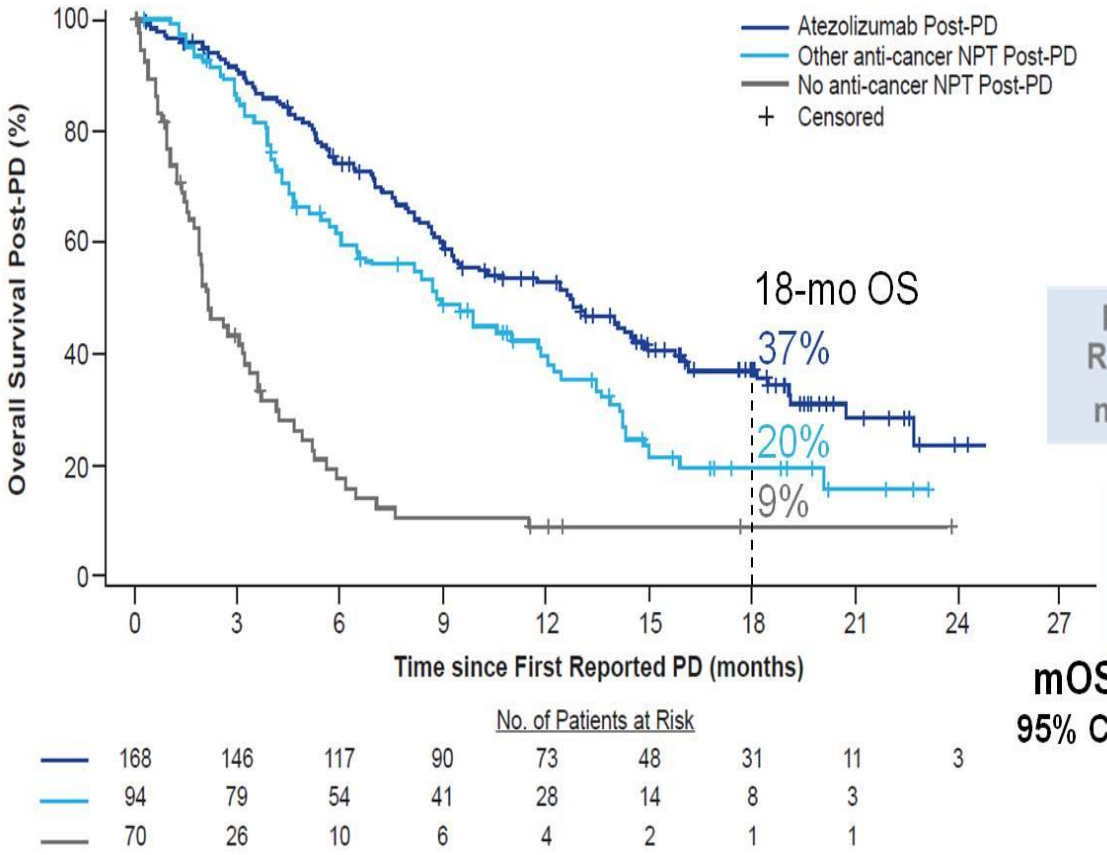
Randomised Trials of Anti PD-1 / anti-PD-L1 Agents

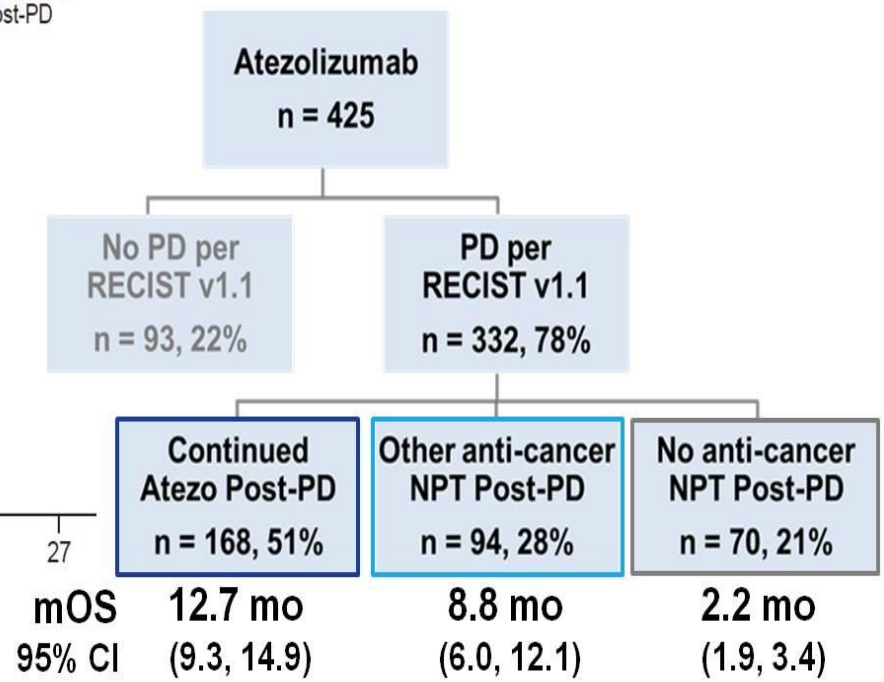
Study	Line	Agents	PD-L1	Result	HR
CheckMate 017	2nd	Nivo vs Docetaxel	Unselected	Improved OS	0.59
CheckMate 057	2nd*	Nivol vs Docetaxel	Unselected	Improved OS	0.73
KEYNOTE-010	2nd*	Pembro vs Docetaxel	>1%	Improved OS (2, 10 mg/kg)	0.61, 0.71
POPLAR	2nd or 3rd	Atezo vs Docetaxel	Unselected	Improved OS	0.73
OAK	2nd or 3rd	Atezo vs Docetaxel	Unselected	Improved OS	0.73
CheckMate 026	1st	Nivo vs Chemo	≥1%	No difference in PFS, OS	1.15, 1.02
KEYNOTE-024	1st	Pembro vs Chemo	>50%	Improved OS	0.60

Borghaei et al. N Engl J Med 2015; 373: 1627-39. Brahmer et al. N Engl J Med 2015; 373: 123 – 35.
Herbst et al. Lancet 2016; 387: 1540 – 50. Fehrenbacher et al. Lancet 2016; 387: 1837 – 46.
Barlesi et al. ESMO 2016 LBA44. Socinski et al. ESMO 2016
Reck et al. N Engl J Med 2016; 375: 1823 - 33

Use of Anti-PDL1 Post Progression (PD) ?

OS Post-PD in Atezolizumab Arm: By Post-PD Treatment





Data cutoff: 7 July, 2016.

Presented By David Gandara at 2017 ASCO Annual Meeting

Immunotherapy for Locally Advanced Disease:

Durvalumab

PACIFIC: Study Design

Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Study (NCT02125461)

- Patients with Stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1-42 days post-cCRT

2:1 randomization, stratified by age, sex and smoking history
N = 713

Durvalumab
10 mg/kg q2wk for up to 12 months
N = 476

Placebo
10 mg/kg q2wk for up to 12 months
N = 237

Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

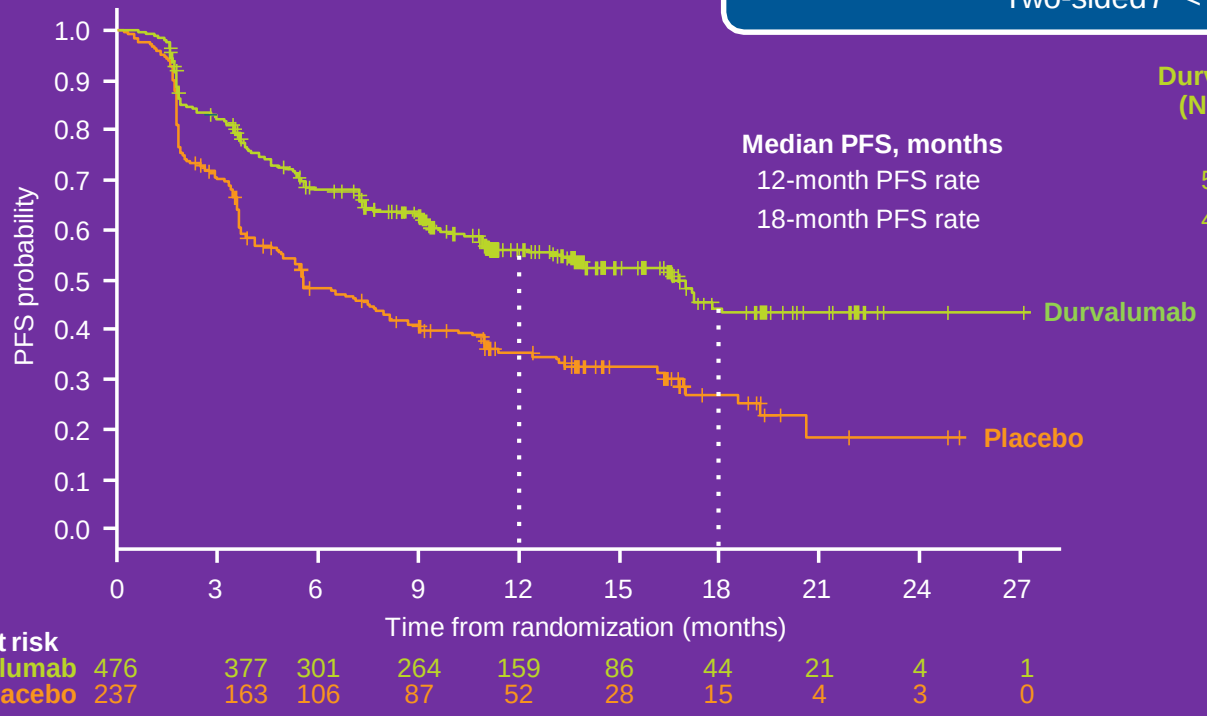
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- Patient-reported outcomes

* Defined as the time from randomization (which occurred up to 6 weeks post-cCRT) to the first documented event of tumor progression or death in the absence of progression. cCRT = concurrent chemoradiation therapy; WHO = World Health Organization; PS = performance status; BICR = blinded independent central review; RECIST = Response Evaluation Criteria In Solid Tumors; OS = overall survival; ORR = objective response rate; DoR = duration of response

PFS by BICR (Primary Endpoint; ITT)

Stratified hazard ratio, 0.52
Two-sided *P* < 0.0001

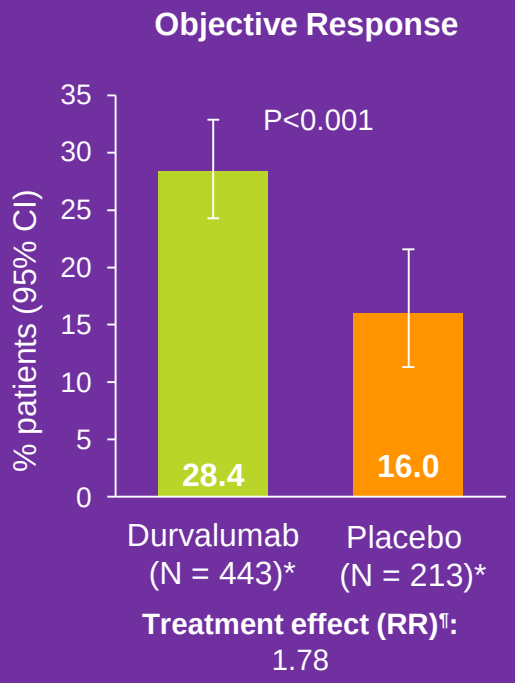
	Durvalumab (N = 476)	Placebo (N = 237)
Median PFS, months	**16.8**	**5.6**
12-month PFS rate	55.9%	35.3%
18-month PFS rate	44.2%	27.0%



No. at risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

BICR = blinded independent central review; ITT = intention to treat

Antitumor Activity by BICR (ITT)



	Durvalumab (N = 443)*	Placebo (N = 213)*	Treatment effect (HR)¶
Best overall response, n (%)†			
Complete response	6 (1.4)	1 (0.5)	
Partial response	120 (27.1)	33 (15.5)	
Stable disease	233 (52.6)	119 (55.9)	
Progressive disease	73 (16.5)	59 (27.7)	
Nonevaluable	10 (2.3)	1 (0.5)	
Duration of response, months Median	NR	13.8	0.43
Ongoing response at data cutoff, %‡			
At 12 months	72.8	56.1	
At 18 months	72.8	46.8	

* Patients with measurable disease at baseline, as determined by either of the 2 independent reviewers; † One patient could not be grouped into any of the best overall response categories due to inconsistency in the baseline assessment for measurable disease between the 2 independent central reviewers. ‡ Percentages calculated by Kaplan-Meier method; ¶ Placebo was the reference group when RR and HR were calculated; therefore, an RR value greater than 1 is in favor of durvalumab and an HR value less than 1 is in favor of durvalumab

BICR = blinded independent central review; NR = not reached; RR = relative risk

Pneumonitis or Radiation Pneumonitis

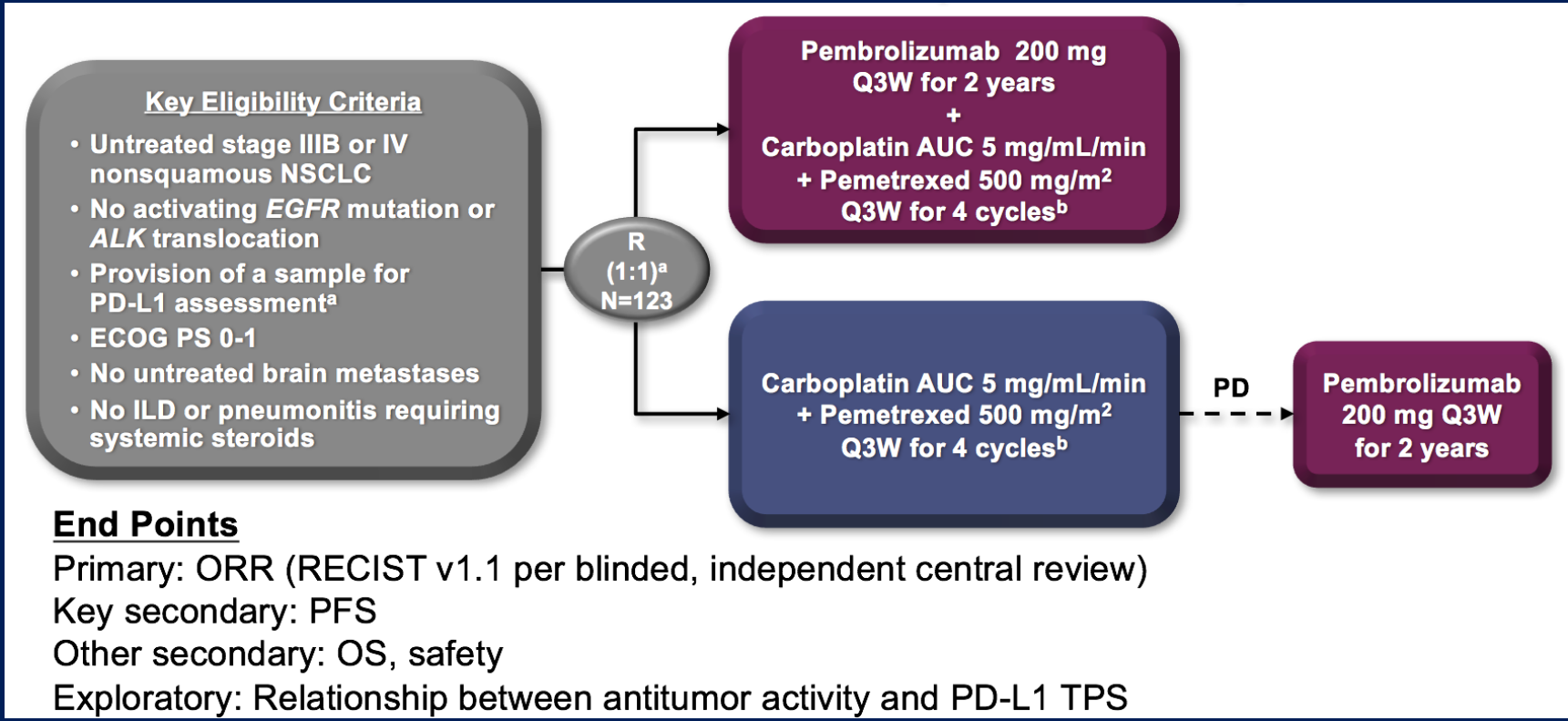
Pneumonitis (grouped terms) or radiation pneumonitis, n (%)*	Durvalumab (N = 475)	Placebo (N = 234)
Any grade	161 (33.9)	58 (24.8)
Grade 3/4	16 (3.4)	6 (2.6)
Grade 5	5 (1.1)	4 (1.7)
Leading to discontinuation	30 (6.3)	10 (4.3)

Safety analysis set (all-causality). * Pneumonitis/radiation pneumonitis was assessed by investigators with subsequent review and adjudication by the study sponsor. In addition, pneumonitis, as reported in the table, is a grouped term, which includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis and pulmonary fibrosis. Two patients randomized to placebo received at least 1 dose of durvalumab and were considered part of the durvalumab arm for safety reporting.

Combining Immunotherapy (Anti PD1/PDL-1):

1) Chemotherapy
2) Immunotherapy agents
3) Targeted therapy

KEYNOTE 021: Cohort G Study Design

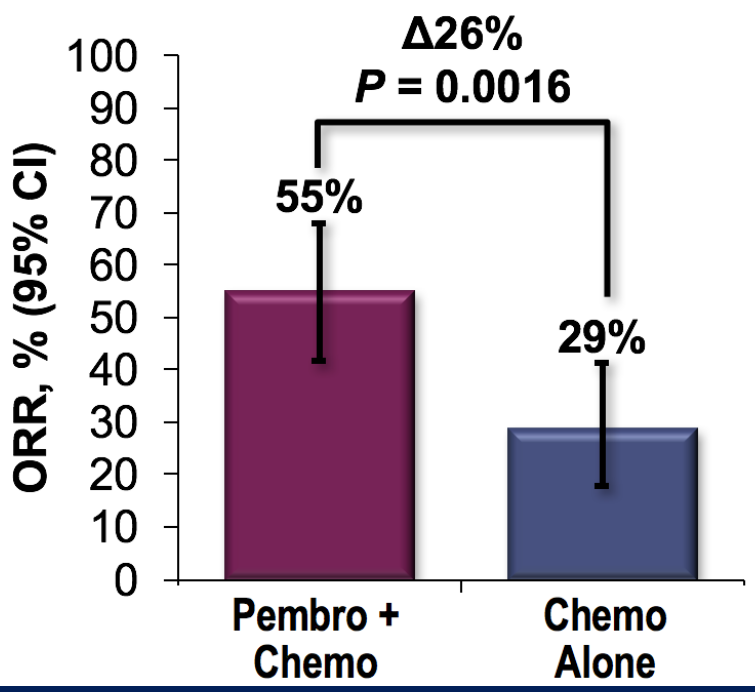


End Points

Primary: ORR (RECIST v1.1 per blinded, independent central review)
Key secondary: PFS
Other secondary: OS, safety
Exploratory: Relationship between antitumor activity and PD-L1 TPS

Langer et al. *Lancet Oncol.* 2017.

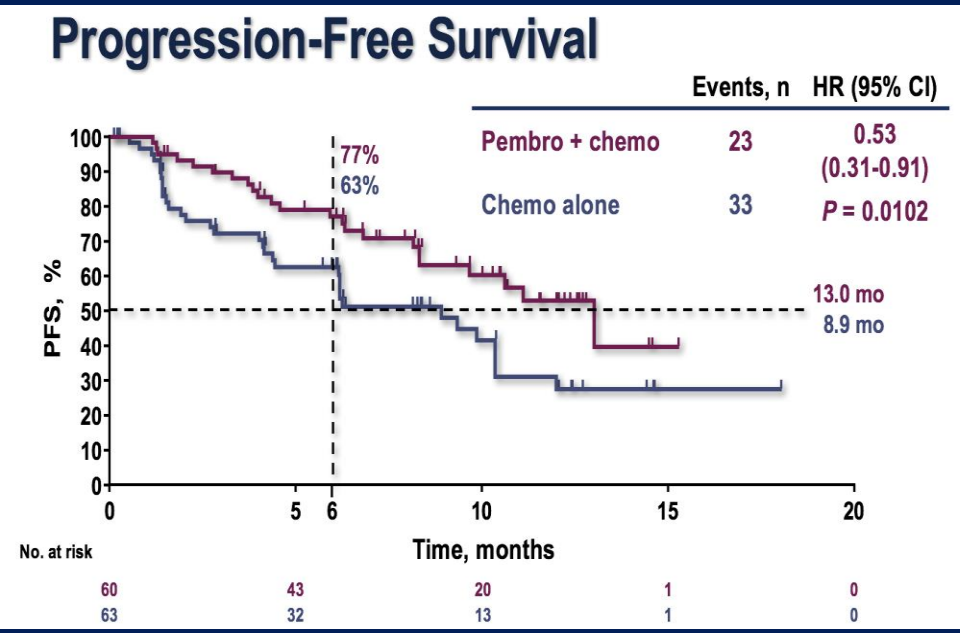
KEYNOTE 021: ORR

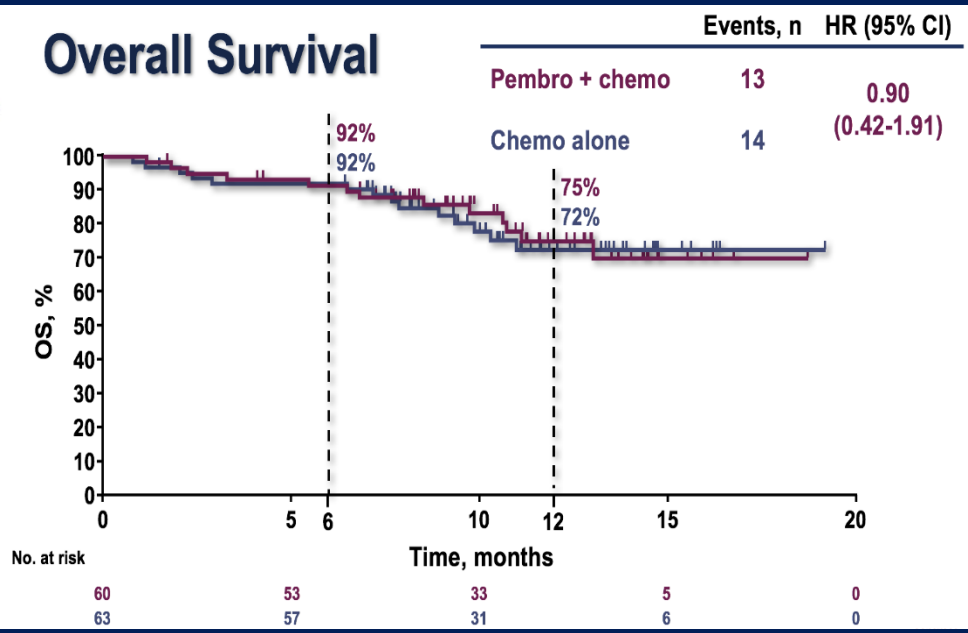


	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response,[a] n (%)	29 (88)	14 (78)

Langer et al. *Lancet Oncol.* 2017.

KEYNOTE 021: PFS & OS





Langer et al. *Lancet Oncol.* 2017.

KEYNOTE-189

Pembrolizumab Significantly Improved Overall Survival and Progression-Free Survival as First-Line Treatment in Combination with Pemetrexed and Platinum Chemotherapy for Patients with Metastatic Nonsquamous Non-Small Cell Lung Cancer

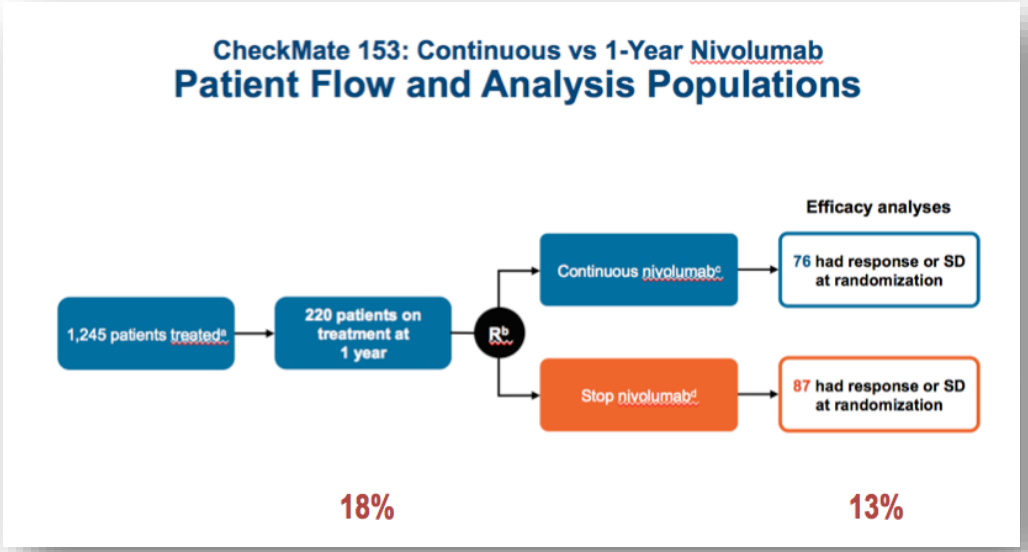
Jan 16, 2018.

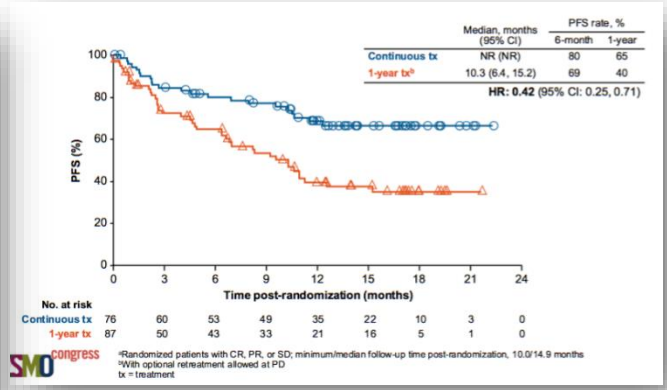
CheckMate-227

The combination of nivolumab (Opdivo) and ipilimumab (Yervoy) improved progression-free survival (PFS) compared with chemotherapy in treatment-naïve patients with high tumor mutation burden (TMB) non–small cell lung cancer (NSCLC). Bristol-Myers Squibb (BMS), the manufacturer of both immunotherapies, announced the preliminary findings from part 1a of the phase III CheckMate-227 trial in a press release.

February 5th 2018

A Signal – CheckMate 153





Exploratory Analysis

- Improvement in PFS (HR 0.42), 1 year PFS: 65% vs 40%
- Improvement in PFS independent from RR
- Trend in OS (HR 0.63)
- Some stabilizations by reexposure

Selection of patients based on biomarkers other than PDL-1 and Tumor Mutation Burden (TMB)

Patients with actionable genetic aberrations (EGFR, ALK, ROS-1, MET) and responses to checkpoint inhibitors

PD-L1 Expression and Response to Immunotherapy in Patients with *MET* Exon 14 Altered Non-Small Cell Lung Cancer

Joshua K. Sabari,[1] Joseph Montecalvo,[1] Ruqin Chen,[1] Jordan Dienstag,[1] Chebli Mrad,[1] Isabella Bergagnini,[1] W. Victoria Lai,[1] Kathryn C. Arbour,[1] Catherine A. Shu,[2] Matthew Hellmann,[1] Paul K. Paik,[1] Gregory J. Riely,[1] Mark G. Kris,[1] Charles M. Rudin,[1] Natasha Rekhtman,[1] Alexander Drilon[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY;
[2]Columbia University Medical Center, New York, NY.

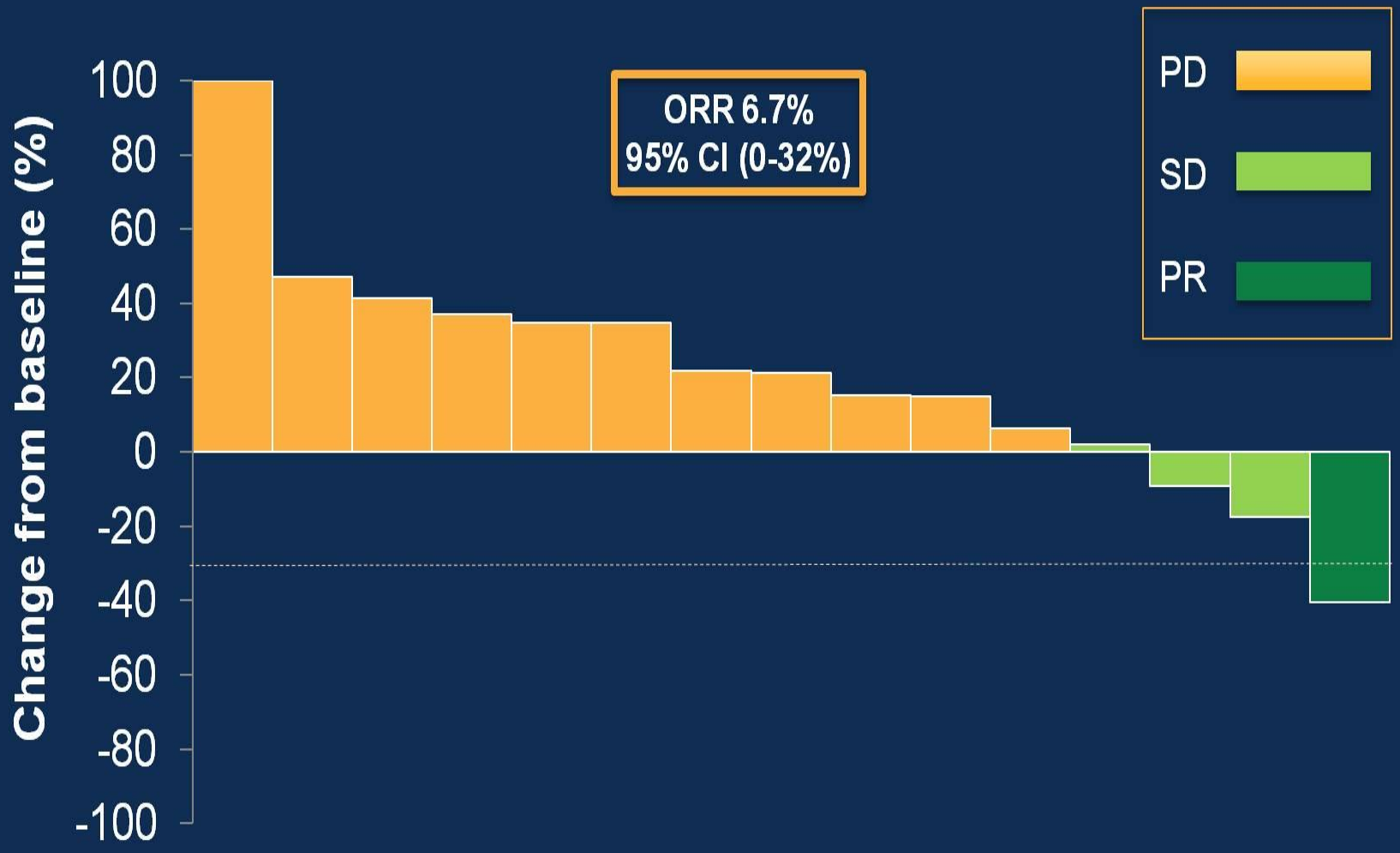
Clinical Science Symposium: Old Targets, New Drugs: *HER2* and *MET*; Sun, Jun 04 8:48 AM; Abstract 8512

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented by: Joshua K. Sabari MD

Presented By Joshua Sabari at 2017 ASCO Annual Meeting

Response to immunotherapy by irRECIST criteria



Conclusions: Which mutations may be best for PD-(L)1 monotherapy?

- *EGFR* activating mutation 
- STK11 deficiency 
- KRAS activation without co-mutation 
- MET ex14 short variants 
- High TMB / p53 

CORRELATION OF PD-L1 FROM PLASMA WITH CLINICAL RESPONSE IN PATIENTS WITH LUNG CANCER

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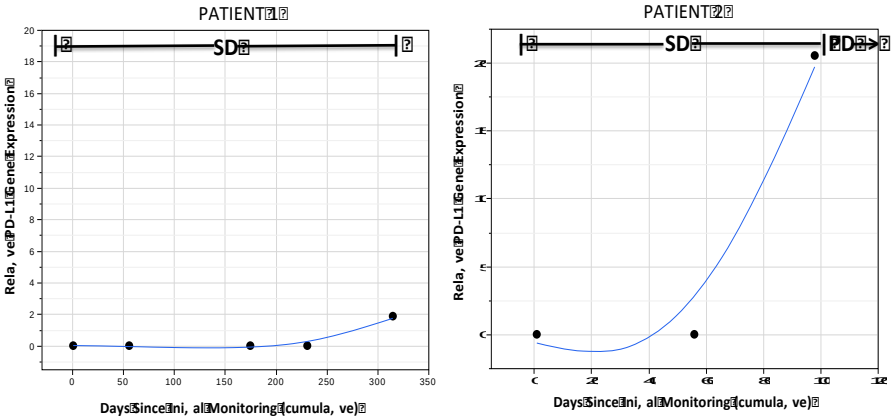
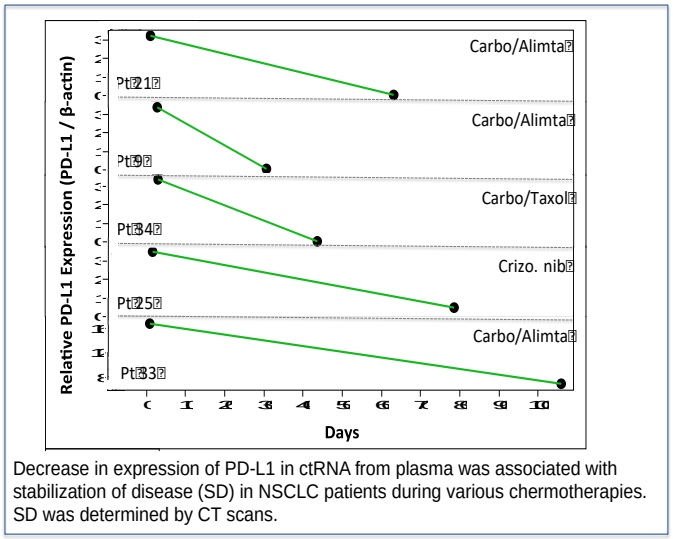
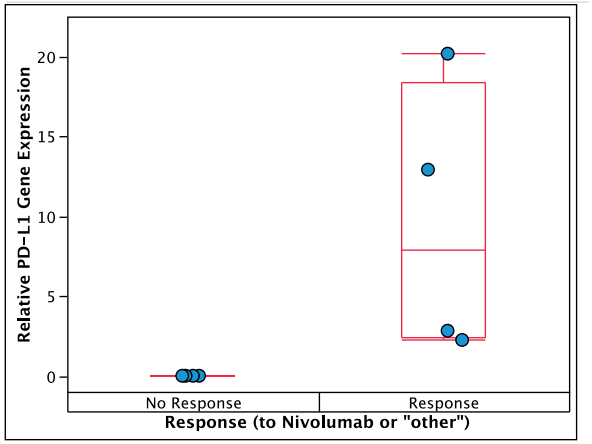


In two patients with stabilized disease (SD) treated with Nivolumab, PD-L1 became undetectable upon treatment. An increase in PD-L1 ctRNA was predictive of resistance to therapy approx. 1.5 months before progression was seen on CT scans.



Decrease in expression of PD-L1 in ctRNA from plasma was associated with stabilization of disease (SD) in NSCLC patients during various chermotherapies. SD was determined by CT scans.



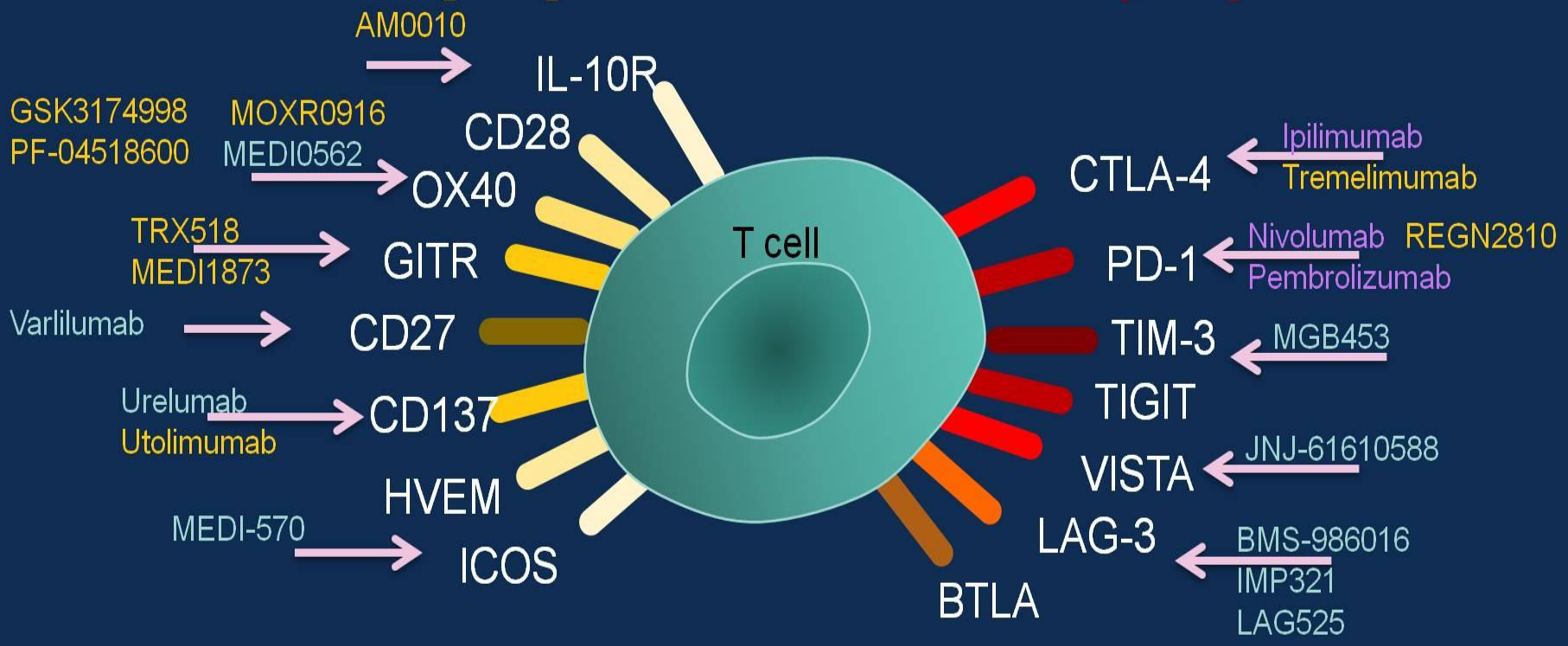
No overlap in relative PD-L1 expression between patients showing response to Nivolumab in (p = 0.0073, Wilcoxon Rank Sums)

Raez L. et al. J Clin Oncol 35, 2017 (suppl; a11550)

Stronger Together

More Immunotherapy is coming!!!

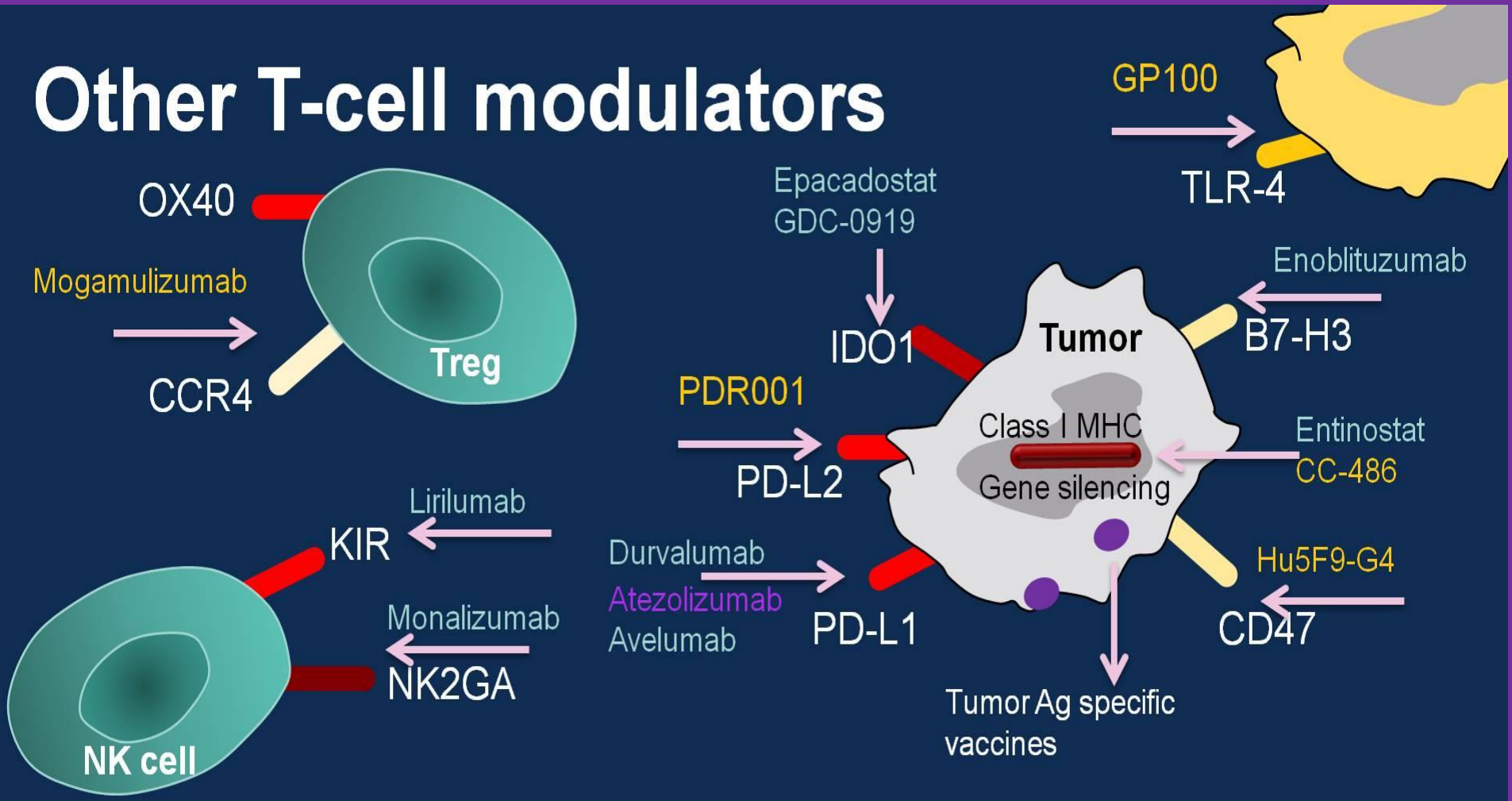
T-cell complexities = more drug targets



Drug Color Key:

Approved | In development | Presented at ASCO 2016

Other T-cell modulators



Drug Color Key:
Approved | In development | Presented at ASCO 2016

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