Immunoterapia

Evidenze dalla Letteratura

Dr. Rita Chiari

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In order of appearance..

1. Checkmate 017: finally something for Squamous and Smokers
2. The landscape of PD-1/PD-L1 inhibitors :
    A) Efficacy and safety data as monotherapy in 2nd line
    B) Preliminary data in 1st line → ongoing trials
4. Activity in some soubgroups:
    A)Brain metastases
    B)Oncogene-addicted
5. The future appears to be in “combinations”..

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1. Checkmate 017: finally something for Squamous and Smokers

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

N=272

Primary endpoint: OS

NEJM, July 2015

Checkmate 017: OS

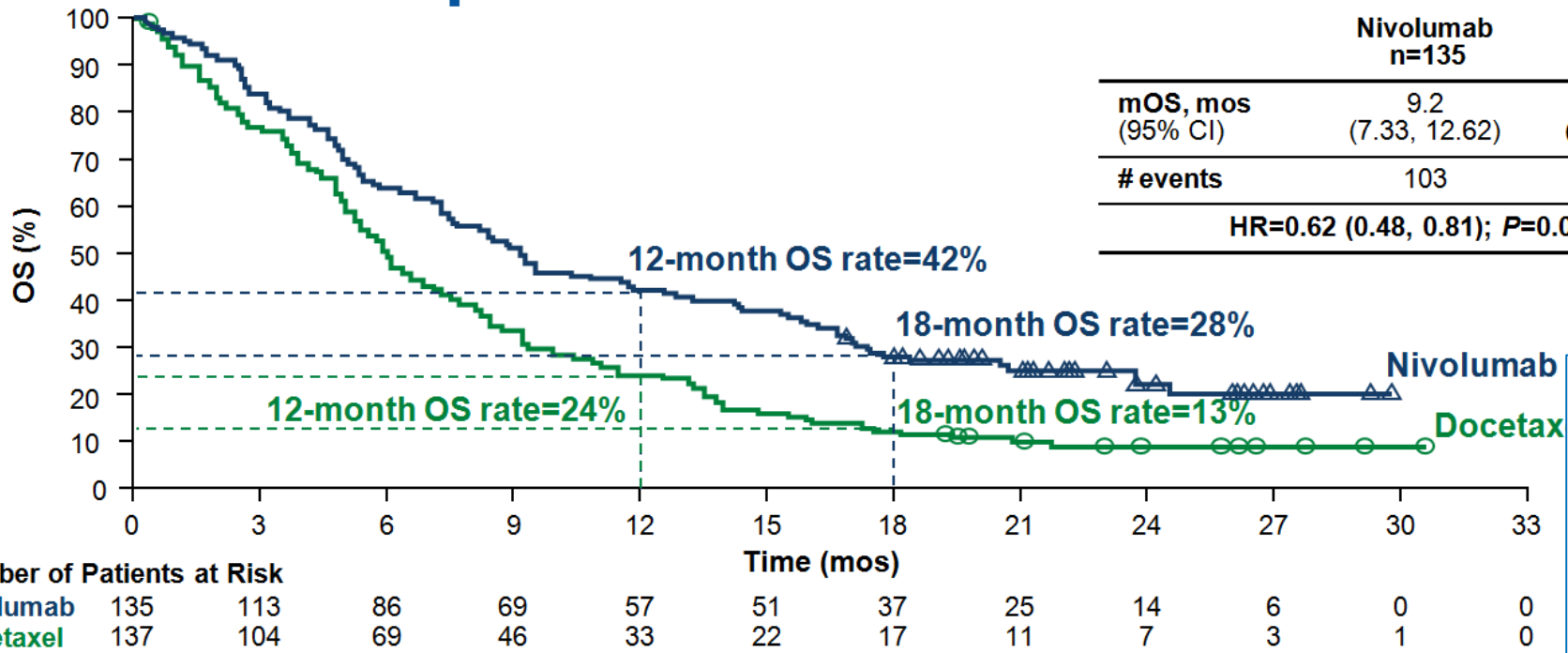
Reckamp K et al. , WCLC 2015 ORAL 02.01

Increase in OS of 3,2 months for nivolumab vs docetaxel (HR 0.62 = 38 % decrease of the risk of death)

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 → DENVER, COLORADO, USA

Updated Overall Survival



	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		

Number of Patients at Risk

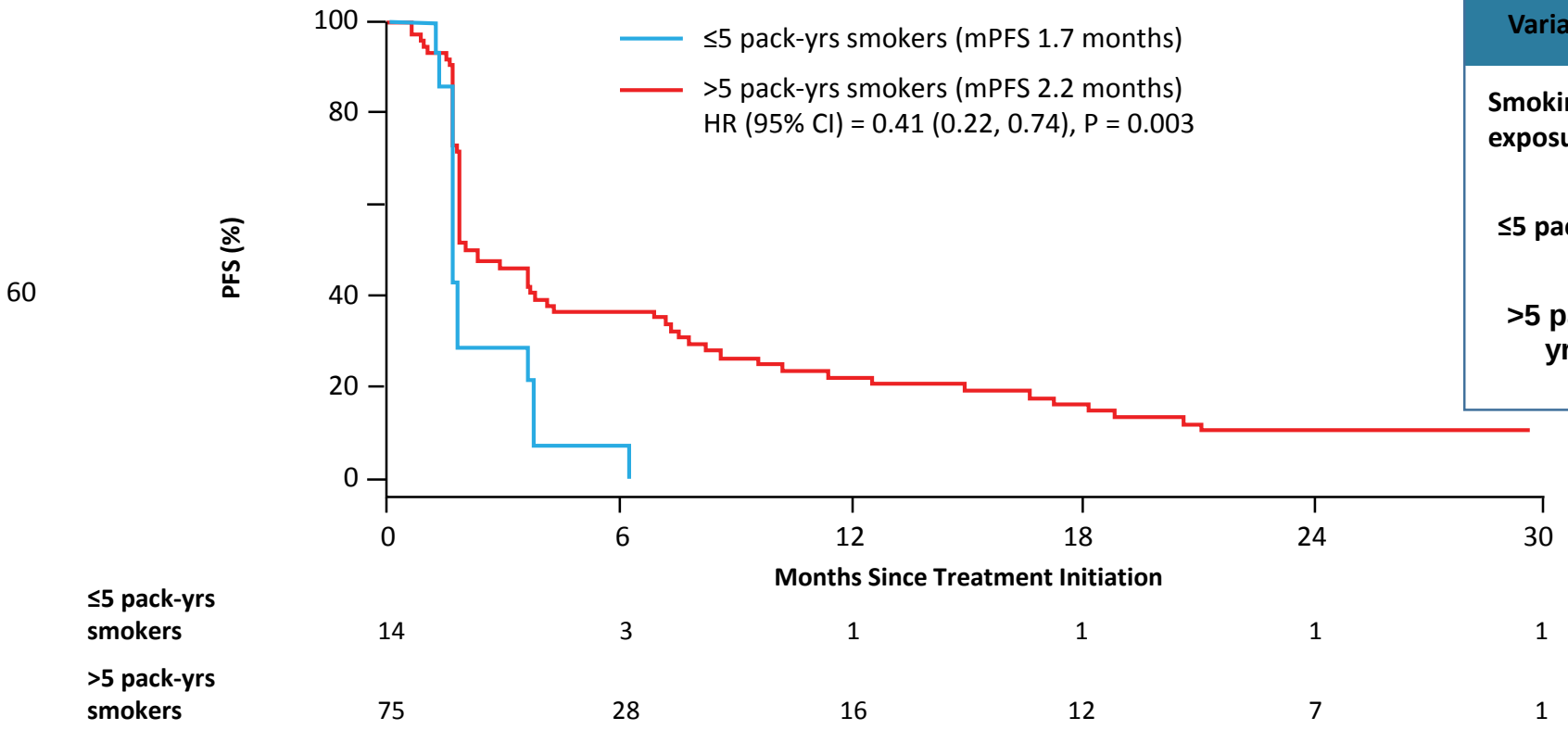
Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	17	11	7	3	1	0

Minimum follow-up for survival: 18 months

- Updated safety and longer-term survival (18 months) are reported here
- At the time of analysis, 13% of patients in the nivolumab arm were continuing treatment vs no patients in the docetaxel arm

Smoking status and response to immunotherapy in NSCLC

PFS by smoking exposure



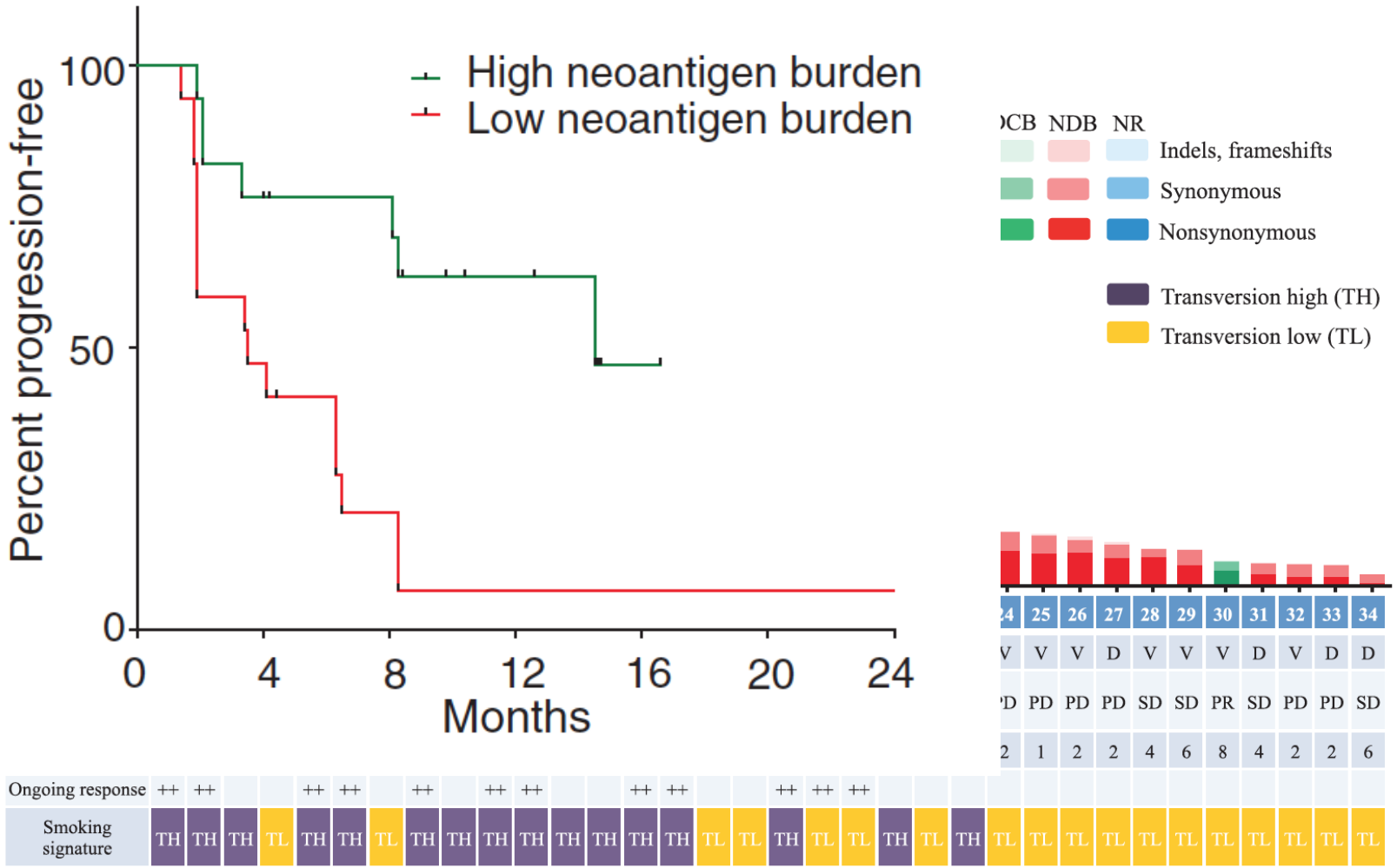
≤5 pack-yrs smokers	14	3	1	1	1	1
>5 pack-yrs smokers	75	28	16	12	7	1

Variable	ORR, % (n/N) [95% CI]	*P*-value
Smoking exposure		
≤5 pack-yrs	**0 (0/14) [0, 23]**	**0.018**
>5 pack-yrs	**30 (20/66) [20, 43]**	

HR = hazard ratio; mPFS = median progression-free survival; ORR = objective response rate; PFS = progression-free survival.

Hellmann MD, et al. ESMO 2014 (asbtr. 1229PD).

Mutational landscape determines sensitivity to PD-1 blockade NSCLC



"…we show that in NSCLCs treated with pembrolizumab, elevated nonsynonymous mutation burden strongly associates with clinical efficacy. …clinical efficacy correlates with a molecular signature characteristic of tobacco carcinogen–related mutagenesis, certain DNA repair mutations, and the burden of neoantigens."

Rizvi NA et al, Science April 2015

Science

REPORTS

Cite as: N. McGranahan *et al.*, *Science*
10.1126/science.aaf490 (2016).

Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade

Nicholas McGranahan,[1,2,3*] Andrew J. S. Furness,[3,4*] Rachel Rosenthal,[3*] Sofie Ramskov,[5] Rikke Lyngaa,[5] Sunil Kumar Saini,[5] Mariam Jamal-Hanjani,[3] Gareth A. Wilson,[1,3] Nicolai J. Birkbak,[1,3] Crispin T. Hiley,[1,3] Thomas B. K. Watkins,[1,3] Seema Shafi,[3] Nirupa Murugaesu,[3] Richard Mitter,[1] Ayse U. Akarca,[4,6] Joseph Linares,[4,6] Teresa Marafioti,[4,6] Jake Y. Henry,[3,4] Eliezer M. Van Allen,[7,8,9] Diana Miao,[7,8] Bastian Schilling,[10,11] Dirk Schadendorf,[10,11] Levi A. Garraway,[7,8,9] Vladimir Makarov,[12] Naiyer A. Rizvi,[13] Alexandra Snyder,[14,15] Matthew D. Hellmann,[14,15] Taha Merghoub,[14,16] Jedd D. Wolchok,[14,15,16] Sachet A. Shukla,[7,8] Catherine J. Wu,[7,8,17,18] Karl S. Peggs,[3,4] Timothy A. Chan,[13] Sine R. Hadrup,[5] Sergio A. Quezada,[3,4†] Charles Swanton[1,3†]

«We demonstrate a relationship between clonal neoantigen burden and overall survival in primary lung adenocarcinomas (n = 139).
Cytotoxic chemotherapy-induced subclonal neoantigens, contributing to an increased mutational load, were enriched in certain poor responders.»

March 2016

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    A)Brain metastases
    B)Oncogene addicted
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Clinical development of checkpoint inhibitors

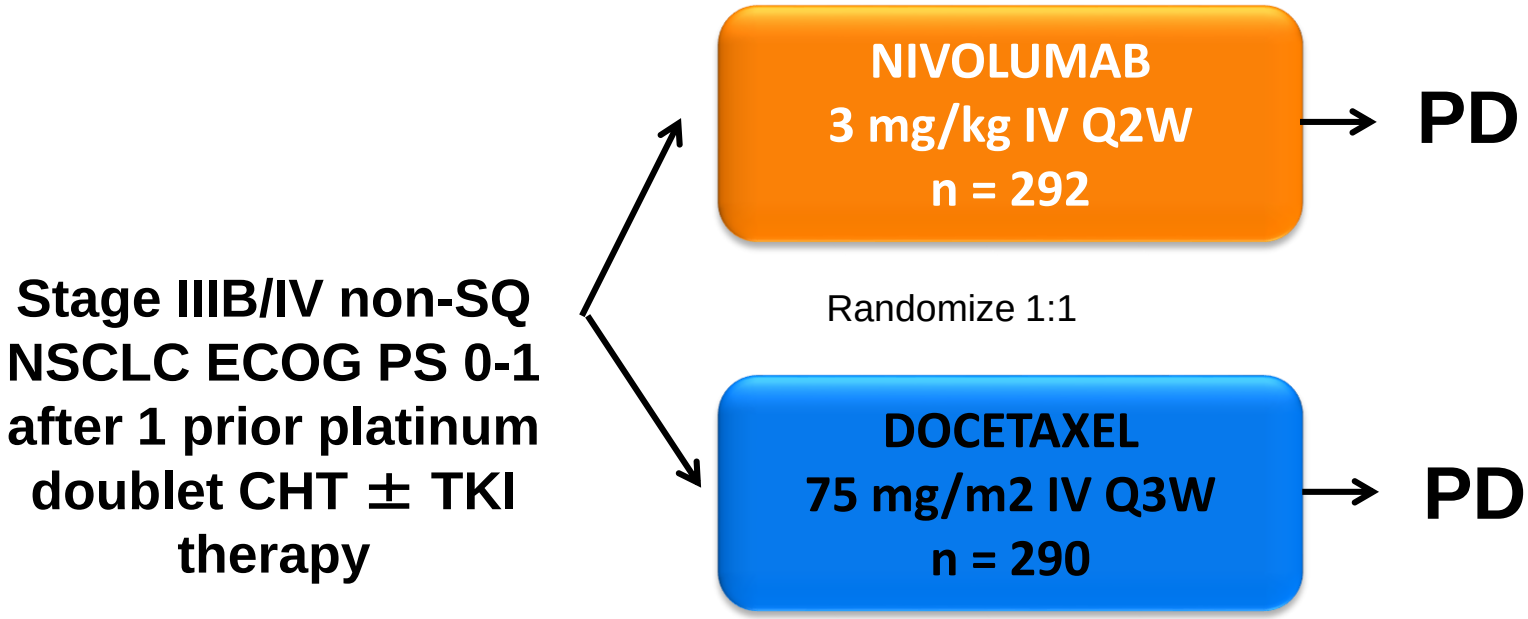
PD-1	**Nivolumab**	Fully human IgG4 mAb	BMS	**FDA, EMA approved**
	Pidilizumab	Humanized IgG1 mAb	Cure Tech	ph II (NOT in Lung)
	Pembrolizumab	Humanized IgG4 mAb	MSD	**FDA, EMA approved**
	AMP-224	Recombinant PD-L2 Fc fusion protein	GSK	ph I: NCT01352884 in advanced cancers

- FDA approved **Nivolumab** (Opvido) for metastatic **NSCLC Squamous** (March 4, 2015) and **Non-Squamous** (October 9, 2015) progressing during or after platinum-based CHT.
- FDA accelerated approval for **Pembrolizumab** Keytruda for metastatic **NSCLC** (October 2, 2015) progressing during or after platinum-based CHT. with tumors that express PD-L1 (companion diagnostic, the PD-L1 IHC 22C3 pharmDx test).

CTLA-4	Ipilimumab	fully human IgG1 mAb	BMS	5 ph III combo trials
	Tremelimumab	Fully human IgG2 mAb	AZ	3 ph III combo with durvalumab (NCT02352948, NCT02453282, NCT02542293)

Adapted from Pennel NA Seminars in Oncology 2015

CHECKMATE 057
Nivolumab (anti PD-1) in NON-SQUAMOUS



N = 582

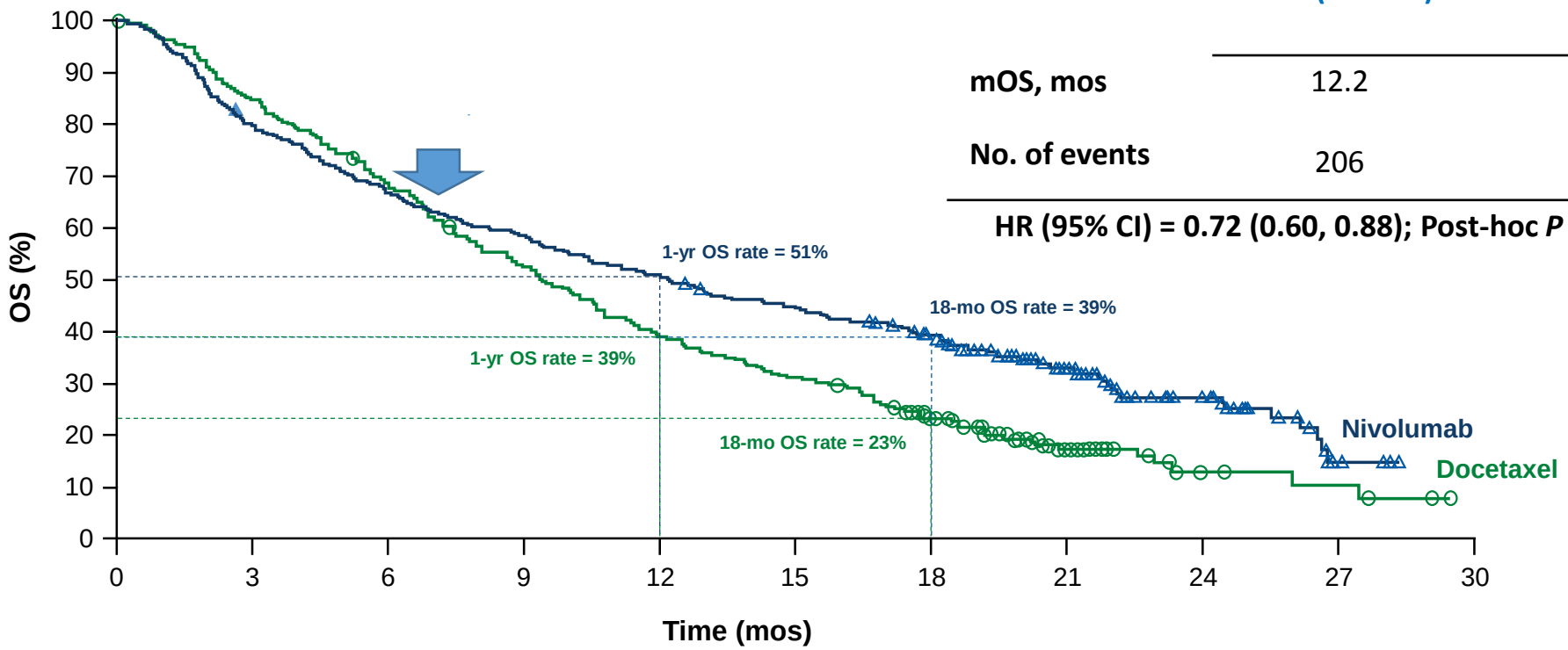
PRIMARY ENDPOINT OS

Borghaei, H NEJM October 2015

CheckMate 057: OS

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

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



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

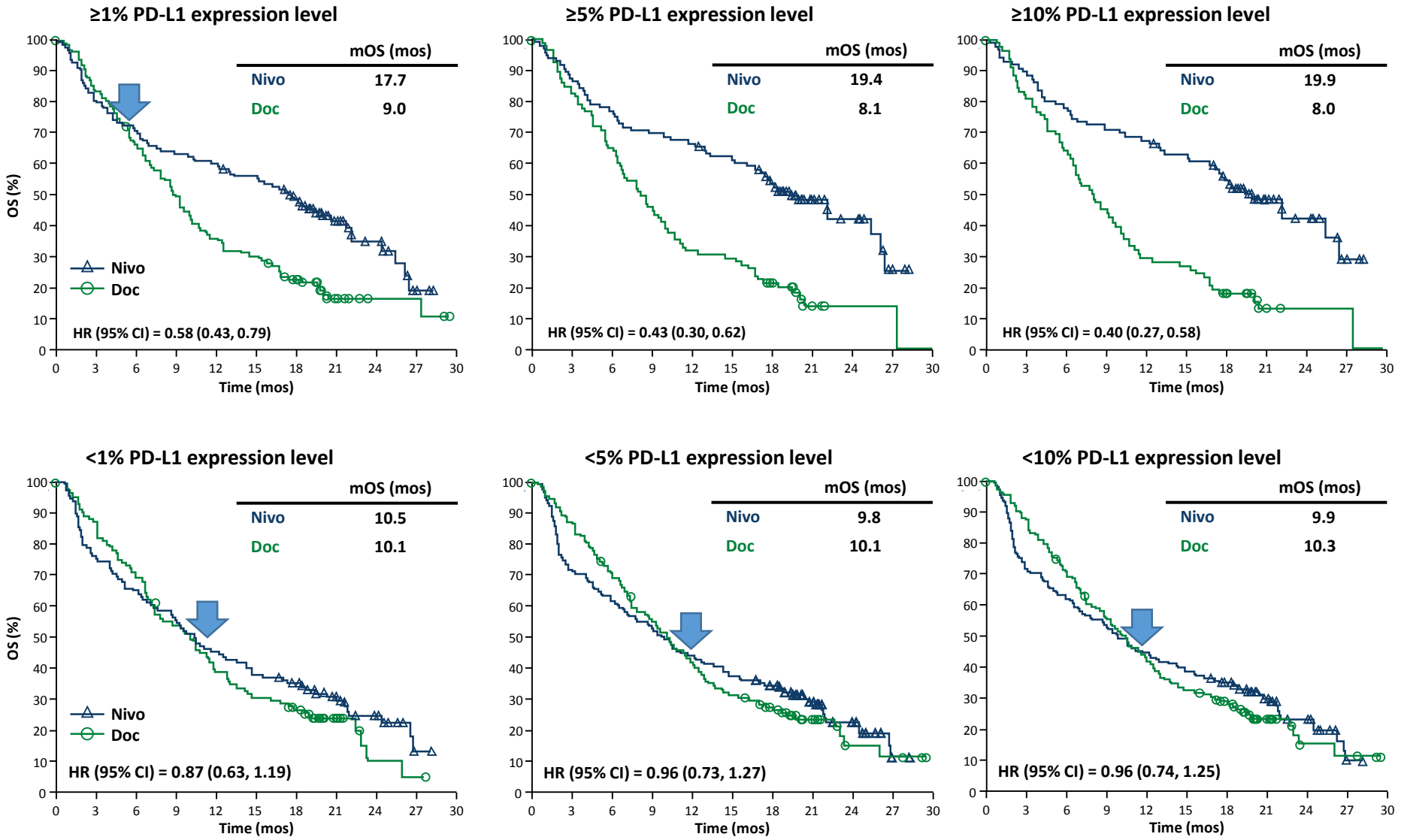
Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

- Minimum follow-up for 12-mo OS rate, 13.2 mos; for 18-mo OS rate, 17.1 mos

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

Horn L. et al ESMO Asia

CheckMate 057 – OS by PD-L1 Expression



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

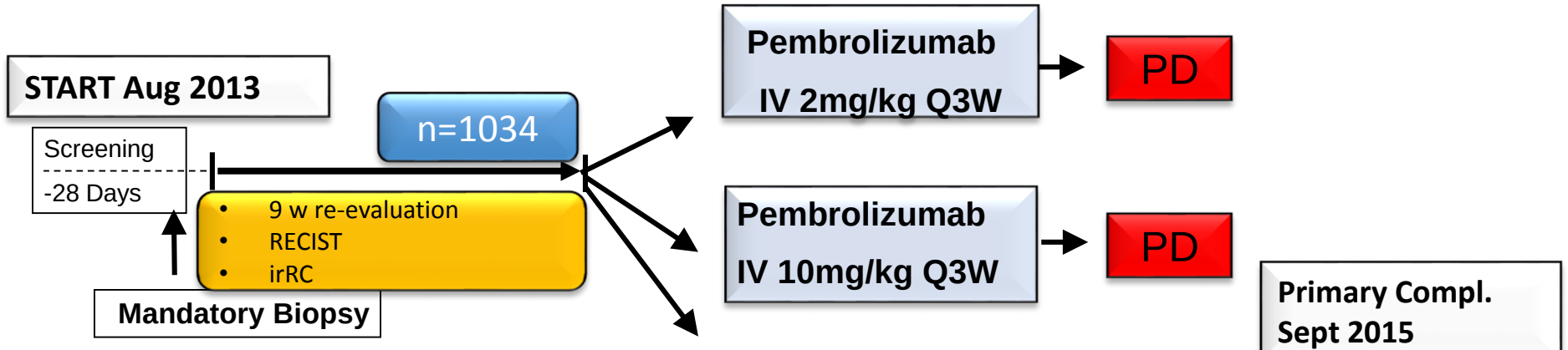
Horn L. et al ESMO Asia

Pembrolizumab: Summary of KEYNOTE-001 & 010

	KEYNOTE-001	KEYNOTE-010
phase	I	II/III
line	Any, Naive (19%)	≥2
Sample size	495	1034 (691 with Pembro)
PD-L1 Expression **<1%** **1-49%** **≥50%**	 68 146 111	 0 442 592
Dose, schedule	2 mg/kg Q3w OR 10 mg/kg Q3w OR 10 mg/kg Q2w	2 mg/kg Q3w OR 10 mg/kg Q3w
ORR (%)	19.4%	18% (vs 9.3% for docetaxel)
Median duration of response	12.5	NR
OS (months) **2 mg/kg Q3w** **10mg/kg Q3w**	**12.0**	 **10.4** **12.7** (vs 8.5 for docetaxel)
PFS (months) **2 mg/kg Q3w** **10mg/kg Q3w**	3.7	 3.9 4.0 (vs 4.0 for docetaxel)
Treatment releted Aes (%) **≥Grade 3** **Pneumonitis**	70.9 9.5 3.6	64.6 14.4 4.5

Adapted from Lim SH et al Expert Opinion on Biological Therapy, Feb 2016

KEYNOTE-010: (Phase II-III) Study Design
[PD-L1+, pre-treated NSCLC]



Inclusion

- **Advanced or recurrent NSCLC**
- **≥ 2nd line**
- **PD-L1 + at least 1%**
- Adequate organ function
- ECOG performance status of 0 or 1

Objectives

Primary Outcome Measures:

- **Overall Survival (OS)**
- **Progression free survival (PFS)** by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Number of participants experiencing adverse events
- Number of participants discontinuing study drug due to adverse events

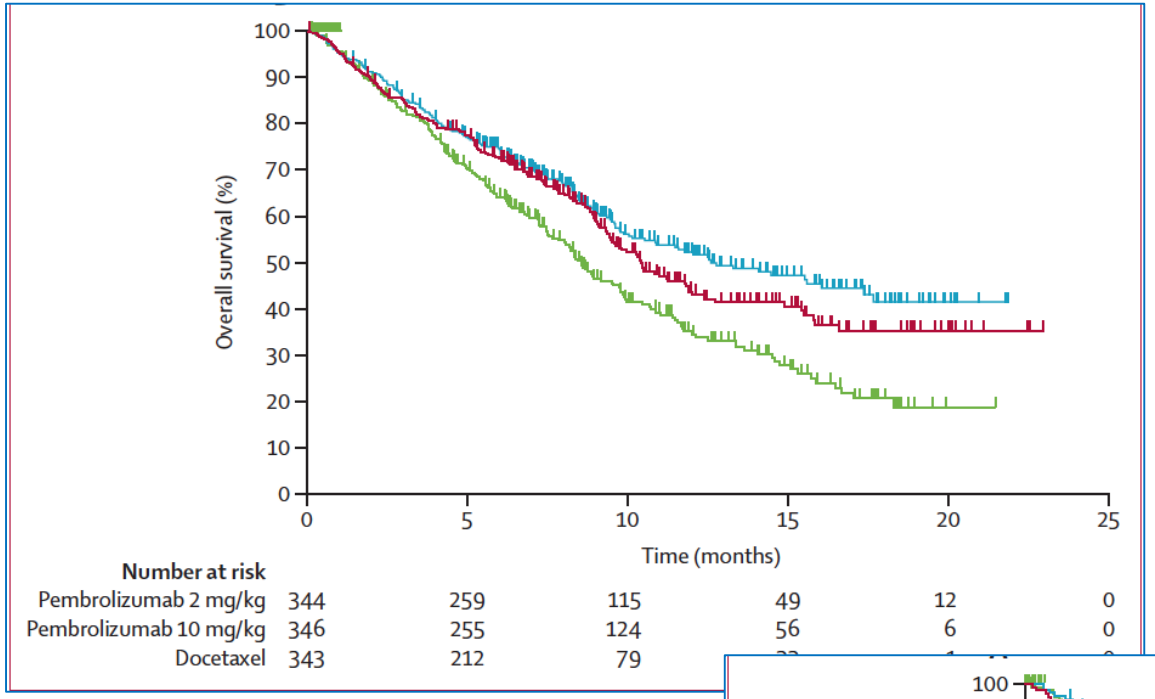
Secondary Outcome Measures:

- Overall response rate (ORR) by RECIST 1.1
- Response duration by RECIST 1.1

Herbst RS, The Lancet Dec 2015

KEYNOTE-010: (Phase II-III) Overall Survival

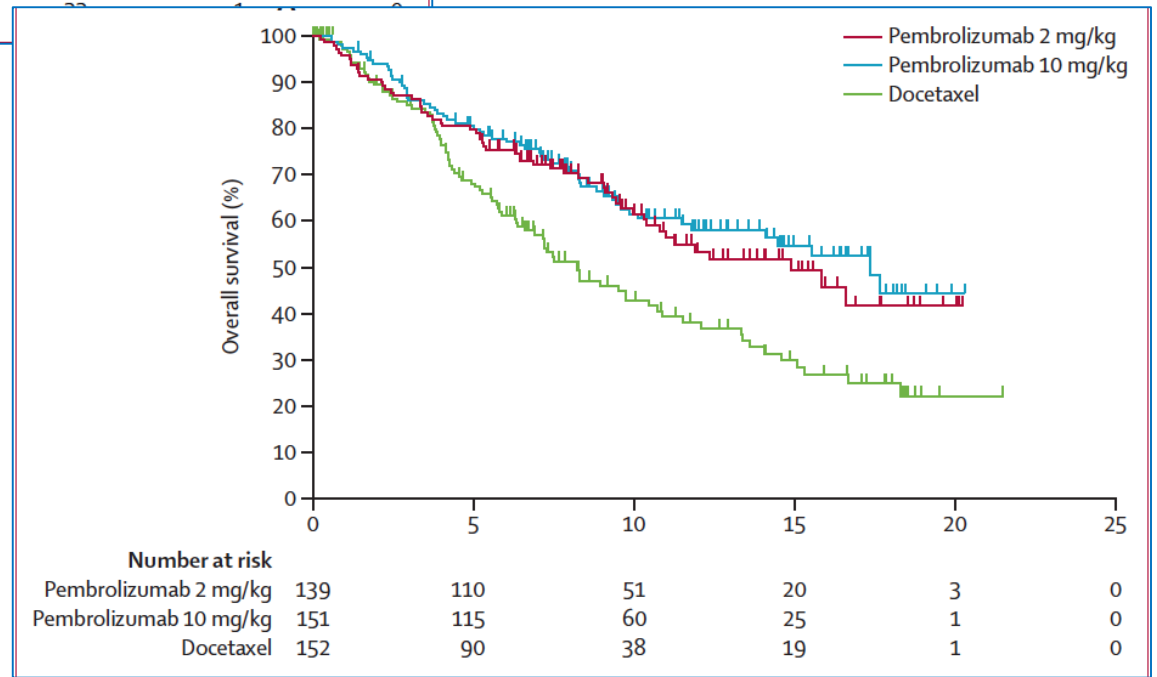
Overall Population



10.4 mo
12.7 mo
8.5 mo

Pembro 2mg/kg vs Doc
HR 0.71 (p=0·0008)
Pembro 10mg/kg vs Doc
HR 0.61 (p<0·0001)

PDL-1≥50%



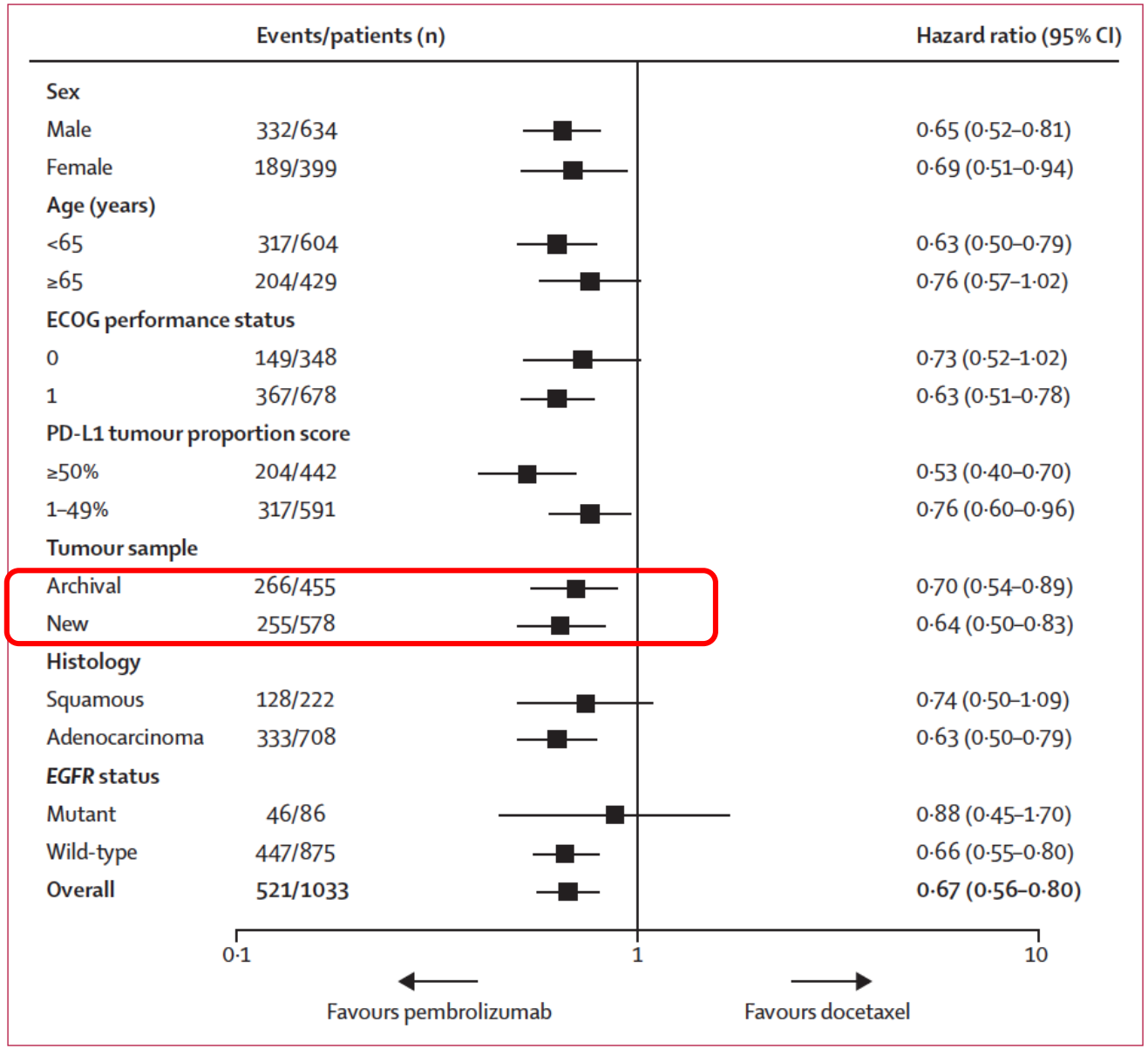
14.9 mo
17.3 mo
8.2 mo

Pembro 2mg/Kg vs Doc
HR 0.54 (p=0.0002)

Pembrol 10mg/Kg vs Doc
HR 0.50 (p<0.0001)

Herbst RS, The Lancet Dec 2015

KEYNOTE-010: Overall Survival-Subgroups



Herbst RS, The Lancet Dec 2015

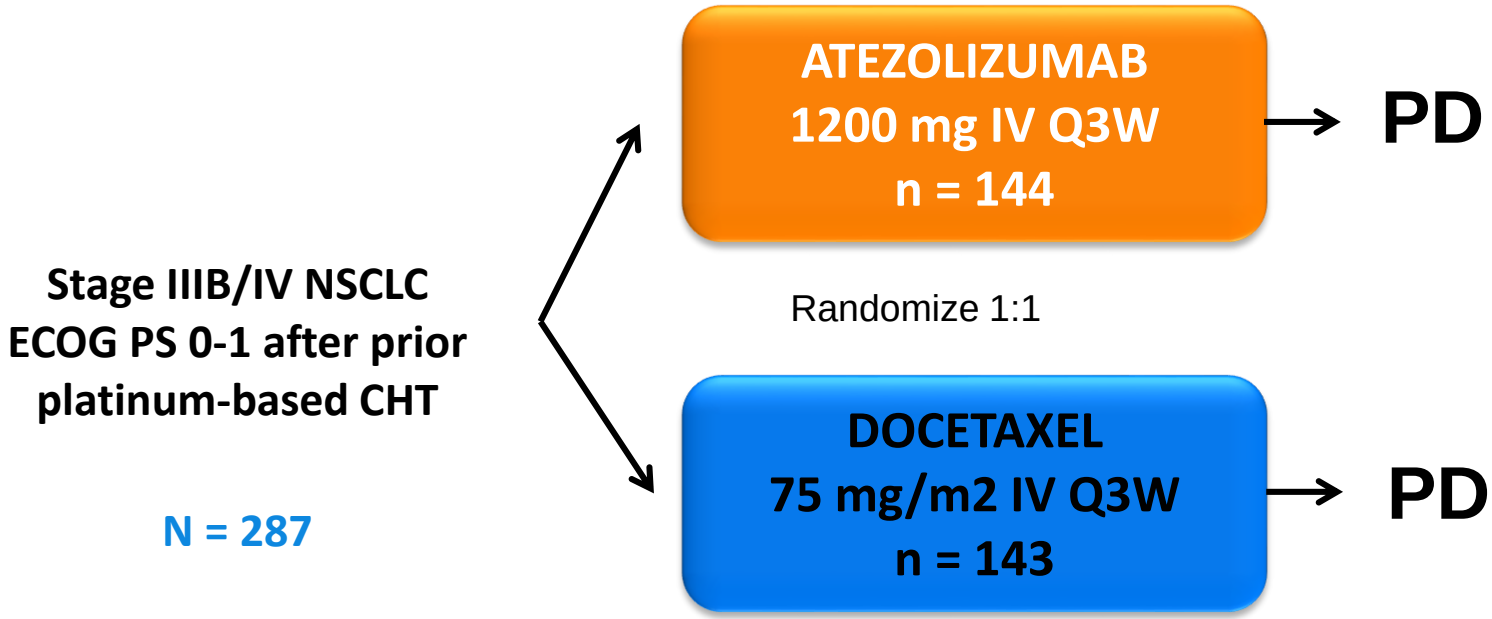
Clinical development of checkpoint inhibitors

PD-1	**Nivolumab**	**Fully human IgG4 mAb**	**BMS**	**FDA, EMA approved**
	Pidilizumab	Humanized IgG1 mAb	Cure Tech	ph II (NOT in Lung)
	Pembrolizumab	Humanized IgG4 mAb	MSD	**FDA, EMA approved**
	AMP-224	Recombinant PD-L2 Fc fusion protein	GSK	ph I: NCT01352884 in advanced cancers
PD-L1	BMS-936559	Fully human IgG4 mAb	BMS	ph I: (NCT00729664) recurrent/advanced solid tumors
	MEDI4736 (Durvalumab)	Engineered human IgG1 mAb	MedImmune, AZ	**ph III**: (NCT02125461) PACIFIC in stage III NSCLC; (NCT02273375) in completely resected NSCLC
	MPDL3280A (Atezolizumab)	Engineered human IgG1 mAb	Genentech	**ph III:** (NCT02008227) OAK Advanced NSCLC who Have Failed Platinum Therapy vs TXT; (NCT02486718) in completely resected NSCLC
	MSB0010718C (Avelumab)	Engineered human IgG1 mAb	EMD Serono Pfizer	**ph III** (NCT02395172): recurrent advanced NSCLC
CTLA-4	Ipilimumab	fully human IgG1 mAb	BMS	5 ph III combo trials
	Tremelimumab	Fully human IgG2 mAb	AZ	3 ph III combo with durvalumab (NCT02352948, NCT02453282, NCT02542293)

Adapted from Pennel NA Seminars in Oncology 2015

Phase II POPLAR Trial
Atezolizumab (MPDL3280A)

Stratified by PD-L1 immune cell expression (0 vs 1 vs 2 vs 3), histology (squamous vs nonsquamous), and line of therapy (second vs third line)



PRIMARY ENDPOINT OS BY: a) PD-L1 EXPRESSION on TC;

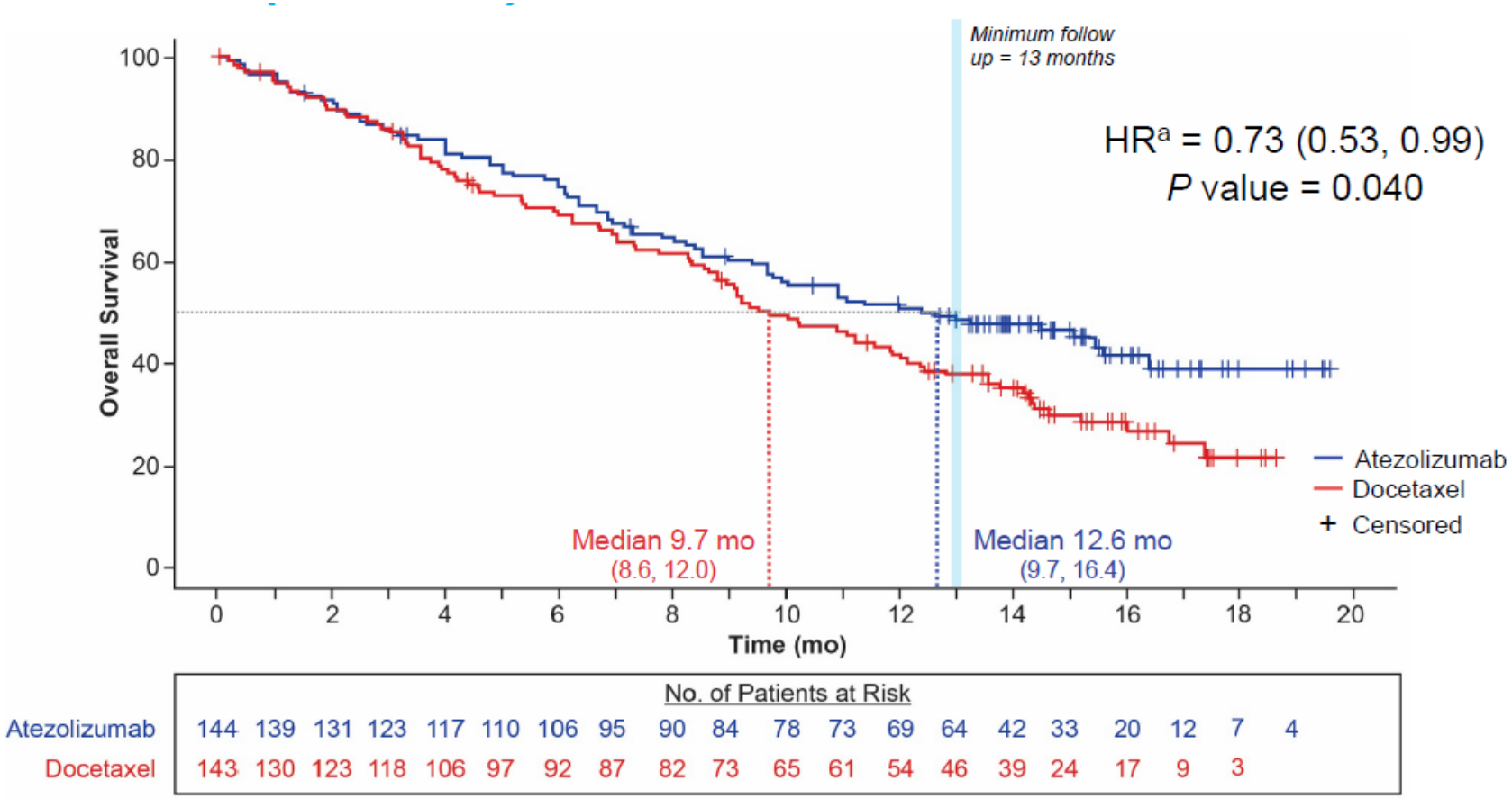
b) IC= lymphocyte infiltrate as percentage of tumour area

TC= percentage of PD-L1-expressing tumour cells: TC3≥50%, TC2≥5% and <50%, TC1≥1% and <5%, and TC0<1%)

IC = percentage of tumour area: IC3≥10%, IC2≥5% and <10%, IC1≥1% and <5%, and IC0<1%).

Fehrenbacher L et al.,The lancet March 2016

POPLAR: All patient efficacy



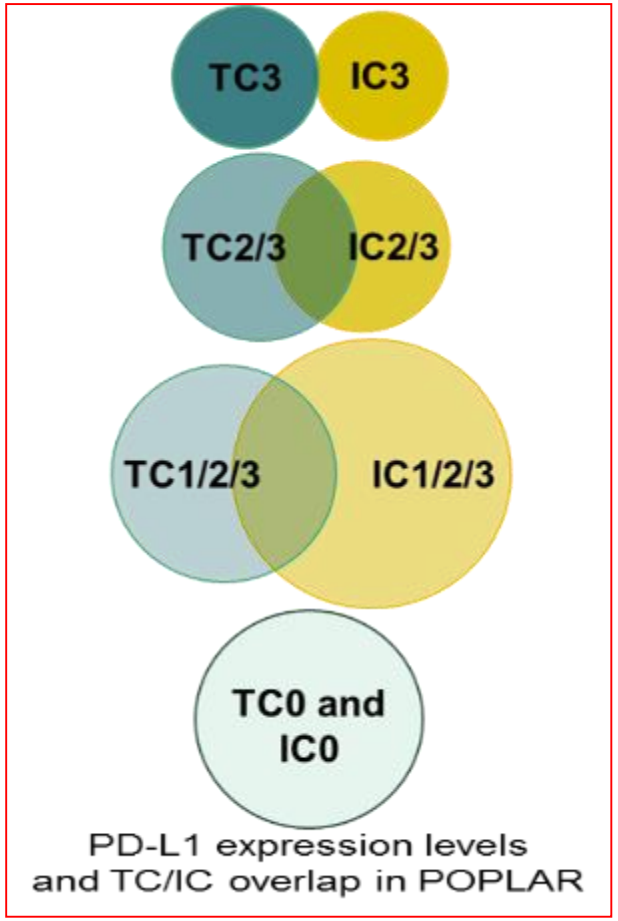
- **Event/patient ratio: 60%** (54% for atezolizumab, 66% for docetaxel)

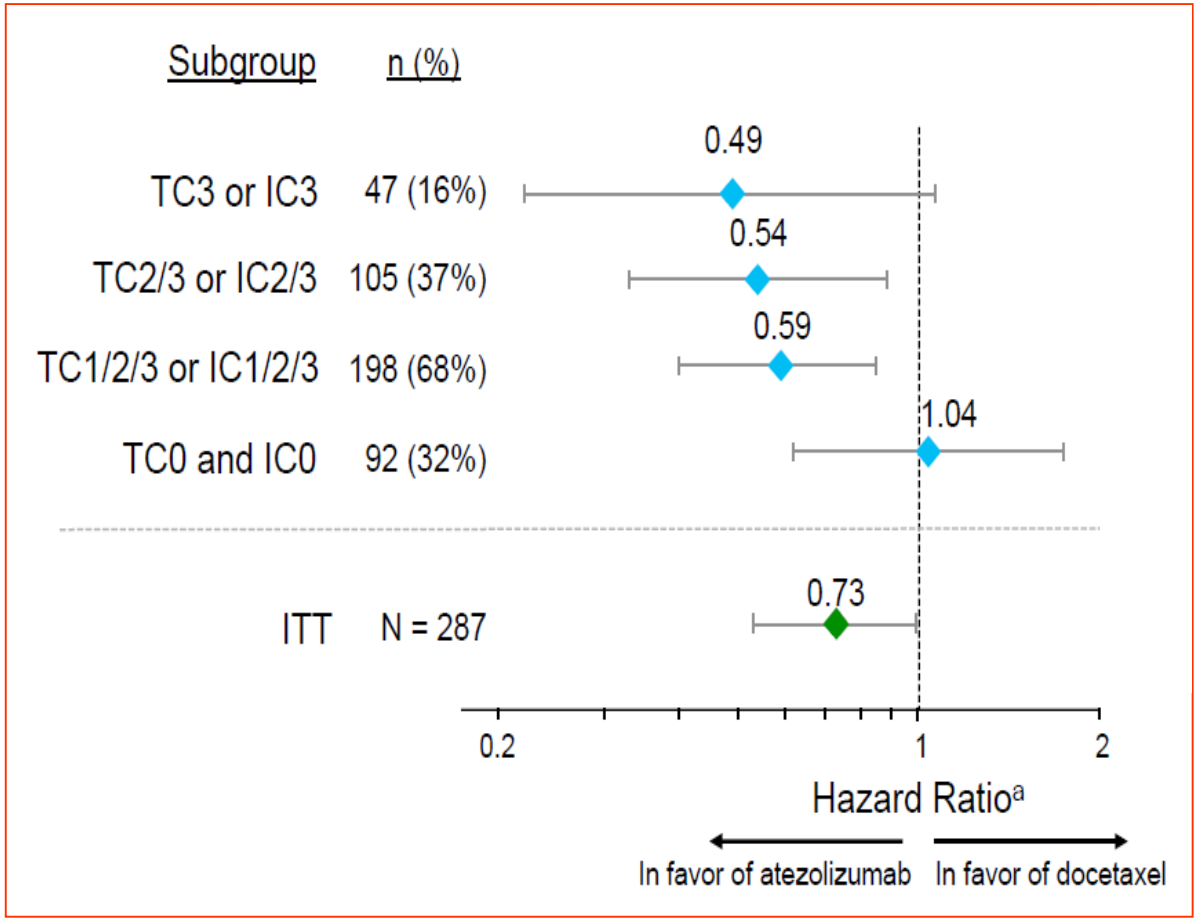
[a]Stratified HR; data cut-off 8 May 2015

Fehrenbacher L et al., The Lancet March 2016

Survival benefit by PD-L1 expression

POPLAR: Atezolizumab vs docetaxel all comers ≥2nd-line



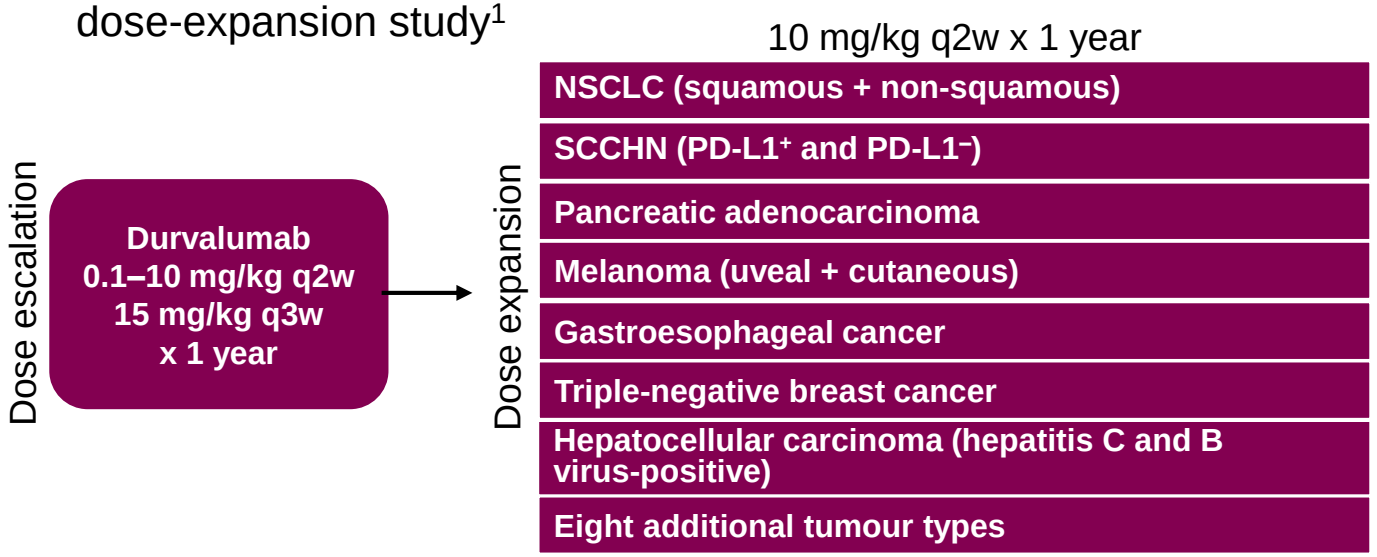


[a]Unstratified HR for subgroups and stratified HR for ITT; data cut-off 8 May 2015

Fehrenbacher L et al., The Lancet March 2016

Phase 1 Study 1108: Durvalumab (MEDI4736) monotherapy in advanced solid tumours

- Multicentre, open-label, first-in-human Phase 1 dose-escalation (3+3 design) and dose-expansion study[1]



- After one year of treatment, patients enter follow-up[1]
- Upon evidence of progressive disease, patients were offered retreatment with durvalumab[1]

Primary endpoints

- MTD or OBD (escalation only)[2]
- Safety and tolerability of durvalumab[2]

Secondary endpoints

- Anti-tumour activity of durvalumab (tumour response assessed by RECIST v1.1)[2]
- PK of durvalumab[2]
- Immunogenicity of durvalumab[3]

1. Segal NH, et al. Poster presented at ESMO 2014. Poster 1058PD;
2. Lutzky J, et al. Oral presentation at ASCO 2014. Abstract 3001
3. ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT01693562

Study 1108: NSCLC cohort

Safety and Clinical Activity of Durvalumab, an Anti-programmed Cell Death-ligand 1 (PD-L1) Antibody, in Patients with Non-small Cell Lung Cancer (NSCLC)

200 patients were evaluable for response with ≥12 weeks of follow-up

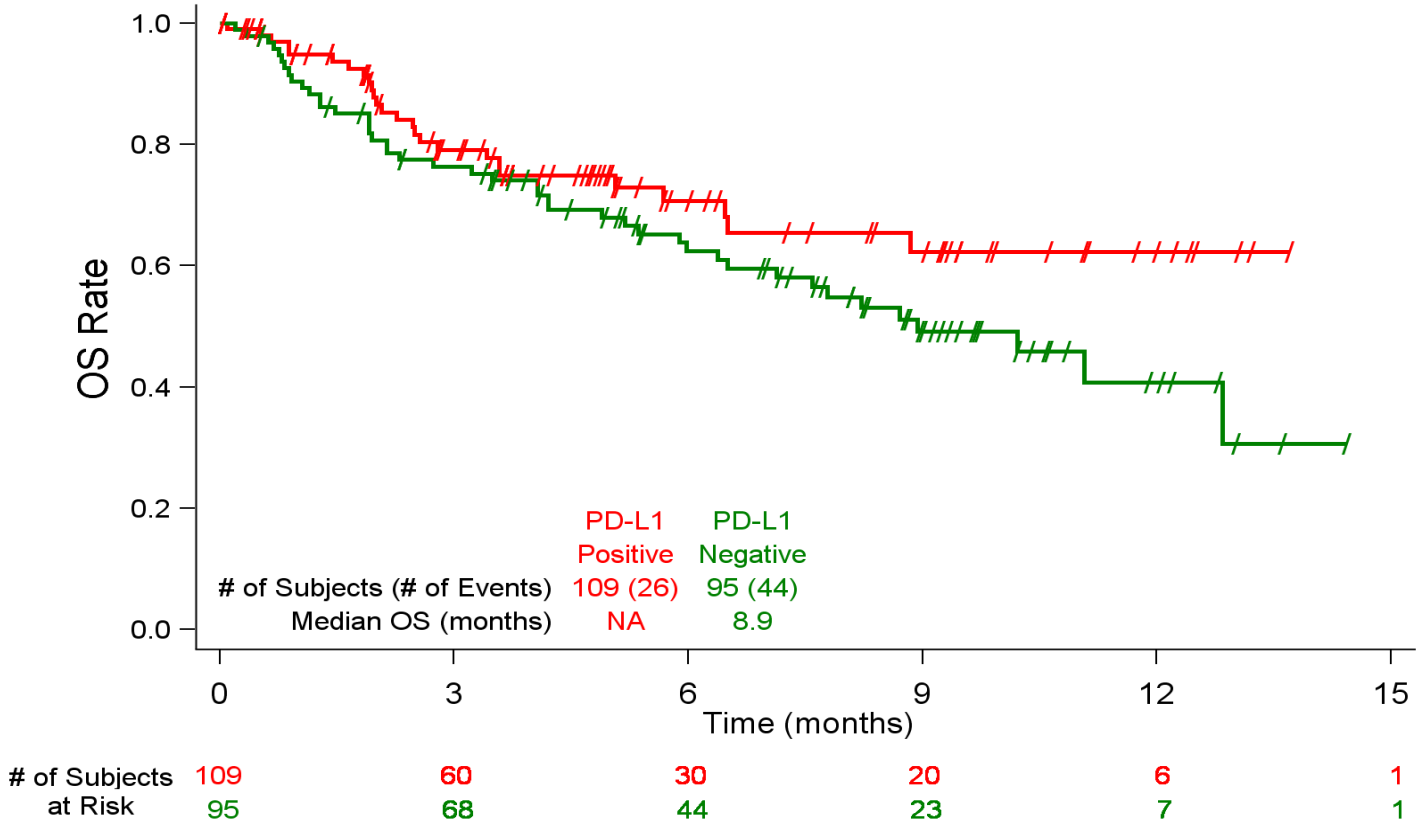
N. Rizvi[1], J. Brahmer[2], S-H. Ou[3], N.H. Segal[4], S.N. Khleif[5], W.J. Hwu[6], M. Gutierrez[7], P. Schöffski[8], O. Hamid[9], J. Weiss[10], J. Lutzky[11], M. Maio[12], J. Nemunaitis[13], D. Jaeger[14], A. Balmanoukian[9], M.C. Rebelatto[15], K.E. Steele[15], X. Li[15], J.A. Blake-Haskins[15], S. Antonia[16]

[1]Columbia University Medical Center, New York, NY, USA; [2]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [3]University of California Irvine School of Medicine, Orange, CA, USA; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]GRU Cancer Center, Georgia Regent University, Augusta, GA, USA; [6]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]Hackensack University Medical Center, Hackensack, NJ, USA; [8]University Hospitals Leuven, Leuven, Belgium; [9]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [10]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA; [11]Mount Sinai Medical Center, New York, NY, USA; [12]University Hospital of Siena, Siena, Italy; [13]Mary Crowley Cancer Research Centers, Dallas, TX, USA; [14]National Center for Tumor Diseases, University Hospitals Heidelberg, Heidelberg, Germany; [15]MedImmune, Gaithersburg, MD, USA; [16]Moffitt Cancer Center, Tampa, FL, USA

Rizvi N, et al. Poster presented at ASCO 2015. Poster 8032

Durvalumab (anti PD-L1): OS by PD-L1 status

Preliminary OS data suggest that patients with PD-L1 positive tumours have improved OS compared with those with PD-L1 negative tumours



Rizvi et al. J Clin Oncol 2015;33 (suppl; abstr 8032)

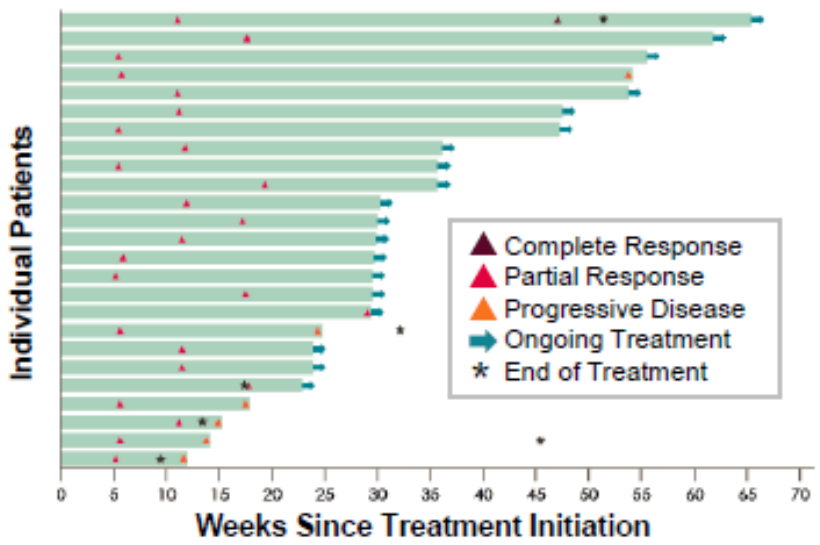
Avelumab (MSB0010718C) in NSCLC

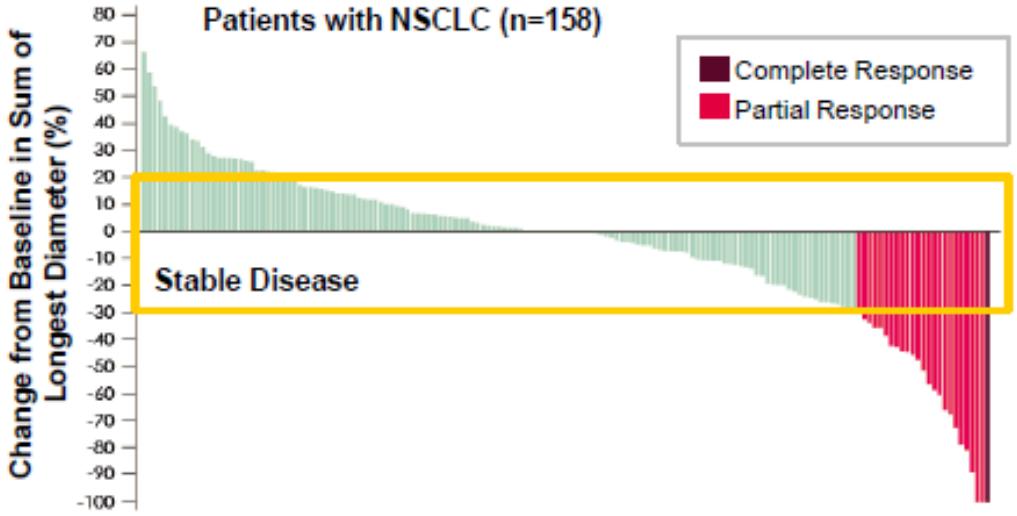
- Treatment with avelumab was associated with a manageable safety profile
- We believe data support registration study starts in 2015 in 1L and 2L NSCLC
- Combination studies with 4-1BB and with PF-3922 (ALK+) also expected to start in 2015

Best Overall Response* n=184	n (%)
Objective Response Rate (ORR)	25 (13.6)
Disease Control Rate* (DCR)§	93 (50.5)

Survival Data

- Median OS was 8.4 months
- Proportion of patients alive at 12 months was 37.0% (95% CI: 27.1, 46.9)





Avelumab (MSB0010718C), an anti-PD-L1 antibody, in advanced NSCLC patients: A phase 1b, open-label expansion trial in patients progressing after platinum-based chemotherapy; Gulley et al

* Includes confirmed and unconfirmed responses as assessed by RECIST 1.1 in patients with measurable disease at baseline
§ DCR is defined by CR + PR + SD

Gulley JL. J Clin Oncol 33, 2015 (ASCO: abstr 8034)

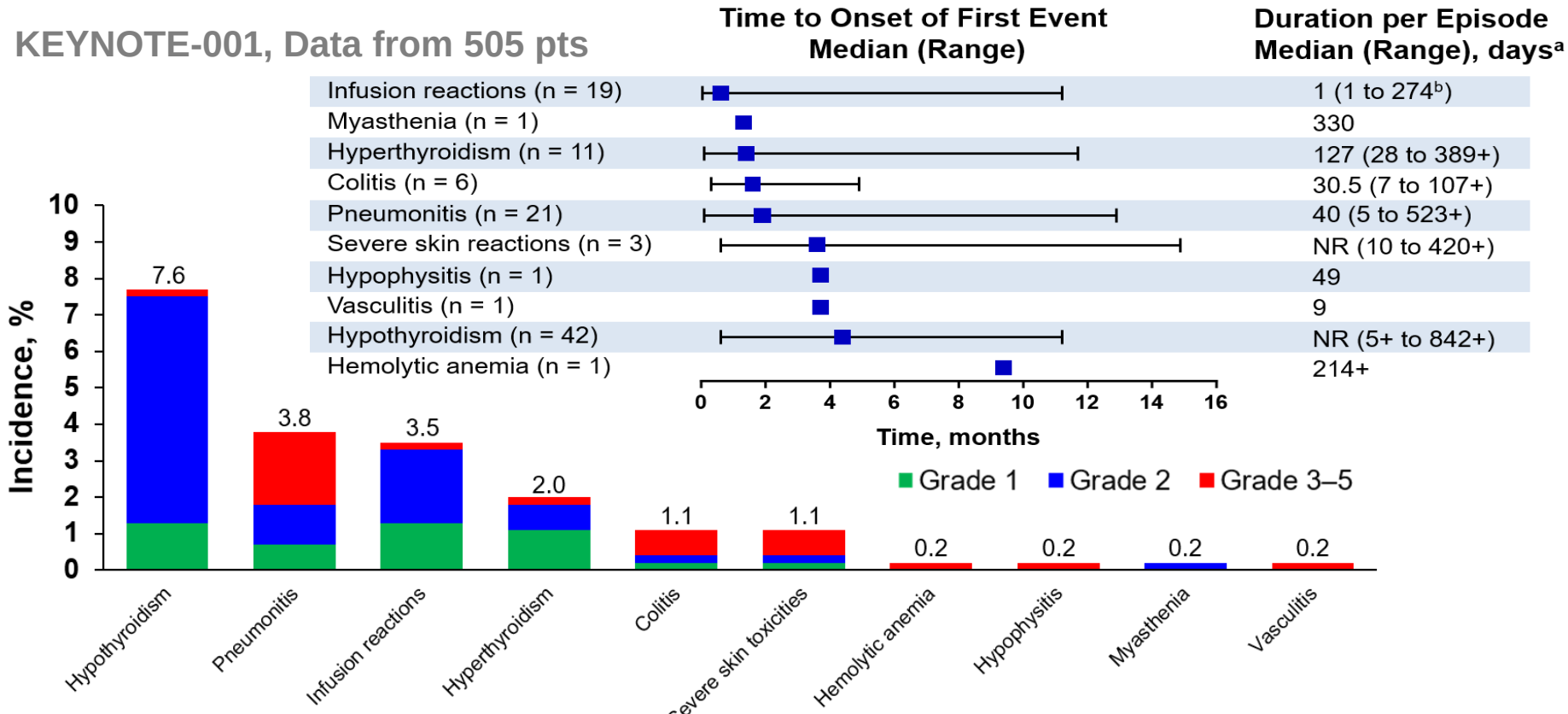
Toxicity Profile for Pembrolizumab & Nivolumab

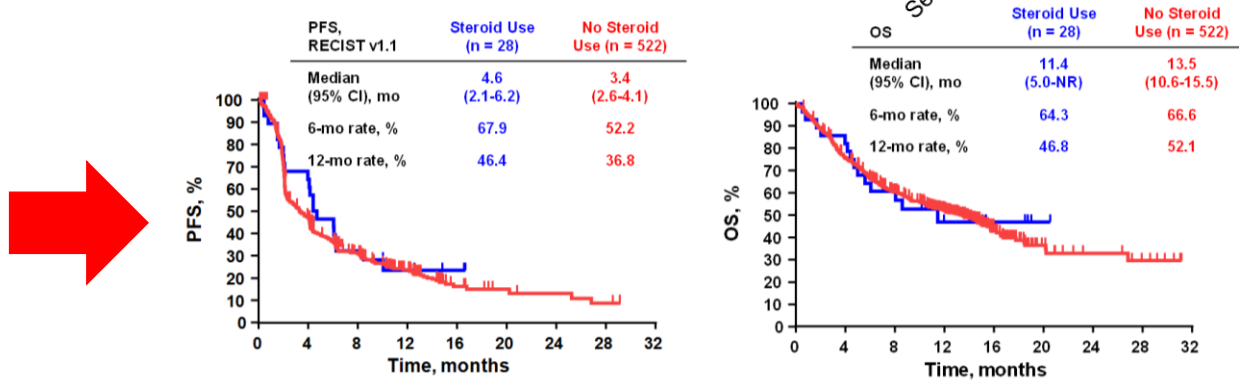
	Pembrolizumab		Nivolumab	
	All grade	Grade3/4	All grade	Grade 3/4
diarrhoea	8	1	8-10	0-3
colitis	1	1	1	<1
hepatitis	1-3	<1	1-3	<1
pruritus	11	0	6-8	0-1
rash	10	0.2	4-11	0-1
pneumonitis	5	2	3-5	1-3
hypothyroidism	8	<1	4-7	0
hyperthyroidism	2-4	0	1-2	0
hypophysitis	<1	<1	NR	NR
Renal injury	<1	0	0-4	1
Reumatological myalgia arthralgia	 3 9	 0 <1	 2.5 5	 0-1 NR
Fatigue	14	1	16	1-4
Anemia	3	1	2	1

Adapted from Spain L et al, Cancer Treatment Reviews Feb 2016

Pembrolizumab: Immune-Related Events & Steroids

KEYNOTE-001, Data from 505 pts





- **PFS and OS and Steroids Use to Manage Immune-Mediated AEs**

WLCC Leighl N ORAL31.02

PD-L1 as a predictive biomarker: a different companion diagnostic for each drug!

IASLC:PDL-1 PROJECT

	Pembrolizumab Merck	Nivolumab Bristol-Myers Squibb	MPDL3280A Roche/Genentech	
PD-L1	• Prototype or clinical trial IHC assay (22C3 Ab)[1]	• Dako automated IHC assay (28-8 Ab)[3,4]	• Ventana a… assa…	
Sample Source and Collection	• Surface expression of PD-L1 on tumor specimen*	• Sur…		…pression of PD-…on TILs
	• Ph I: Fre… • Bi…		…or fresh tissue	• PhI: Fresh tissue
Definition of Positivity†	…quired …nrollment[2] …e that one arm of KEYNOTE 001 trial requires PD-L1⁻ tumors[1] **Tumor PD-L1 expression:**[1] • ≥50% PD-L1⁺ cut-off: 32% (41/129) • 1-49% PD-L1⁺ cut-off: 36% (46/129)	…g vs weak expression[3,4] • Patients not restricted in PD-L1 status in 2nd- & 3rd-line[4] • Ph III 1st-line trial in PD-L1+[3] **Tumor PD-L1 expression:**[4] • 5% PD-L1⁺ cut-off: 49% (33/68)[4]	**IHC Staining intensity (0, 1, 2, 3):** • IHC 3 (≥10% PD-L1⁺): Ph III trial[5] • IHC 2,3 (≥5% PD-L1⁺)[5] • IHC 1,2,3 (≥1% PD-L1⁺)[5] • IHC 1, 0, or unknown • PD-L1 expression required for NSCLC for enrollment **TIL PD-L1 expression:**[5,6] • IHC 3 (≥10% PD-L1⁺): 11% (6/53) • PD-L1 low (IHC 1, 0): 75% (40/53)	**IHC Staining intensity:** • Not presented to date[7,8,9] **TIL PD-L1 expression:** • Not presented to date[7,8,9]

In order of appearance..

1. Checkmate 017: finally something for Squamous and Smokers
2. The landscape of PD-1/PD-L1 inhibitors :
    A) Efficacy and safety data as monotherapy in 2nd line
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4. Activity in some subgroups :
    A)Brain metastases
    B)Oncogene addicted
5. The future appears to be in “combinations”…

- **KEYNOTE-001: 101/495 pts received pembrolizumab as a first-line therapy.**

  ORR 24.8% (95% CI, 16.7%-34.3%) in the 1° line group:, vs 19.4% (95% CI, 16%-23.2%)in the second line setting.

  PD-L1+ > 50%: RR 50%

  PD-L1+ 1% to 49%: RR 19%

  PD-L1+less than 1%: RR 17%

- **Checkmate-052 patients were treated with nivolumab as a first-line therapy.**

  ORR was 21%

  n°46 had tissue available for PDL1 analysis

  PD-L1+ > 50% n°12 : RR 50%

  PD-L1+ 5% to 49%: RR 14%

  PD-L1+less than 5%: RR 115%

Available data from first-line nivolumab and pembrolizumab suggest that the RR is approximately 50% in pts with high PD-L1 expression, which is comparable to, if not superior to the RR seen with first-line CHT and responses may last longer.

Phase 3 Trials Comparing T-cell Checkpoint Blockade With First-Line Chemotherapy

Trial ID	Intervention	Status
NCT02041533 (Checkmate-026)	Nivolumab vs CHT in pts with with PD-L1 pos (>5%) tumors	Accrued
NCT02142738 (Keynote-024)	Pembrolizumab vs CHT in pts with PD-L1 pos (>50%) tumors	Accrued
NCT02409342 and NCT02409355 (IMpower 110 and IMpower 111, respectively)	Atezolizumab vs CHT in pts with PD-L1 pos tumors	Recruiting
NCT02453282 and NCT02542293 (MYSTIC and NEPTUNE, respectively)	Durvalumab + tremelimumab vs durvalumab vs CHT	Recruiting
NCT02477826 (CheckMate-227)	Nivolumab vs nivolumab + ipilimumab vs nivolumab + platinum-doublet CHT vs platinum-doublet CHT	Recruiting

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Phase II Trial of Pembrolizumab for Untreated Brain Metastases

Key Eligibility:
- **Advanced NSCLC or melanoma**
- **At least 1 untreated or progressive brain metastasis 5-20mm**
- **No neurologic symptoms or steroid requirement**
- **PS 0-1**
- **PD-L1 expression after the most recent systemic therapy**

→ **Pembrolizumab 10mg/kg q2 weeks**

- → **Brain metastasis PD** → **Consider radiation or surgery to progressing lesions**
- → **Brain metastasis CR, PR, or SD** → **Continue pembrolizumab if systemic control achieved**

Safety evaluation at 4 weeks:
- **Brain MRI**

Response evaluation every 8 weeks:
- **Brain MRI**
- **CT chest/abdomen/pelvis**

Primary Endpoint:
Brain Metastasis Response Rate

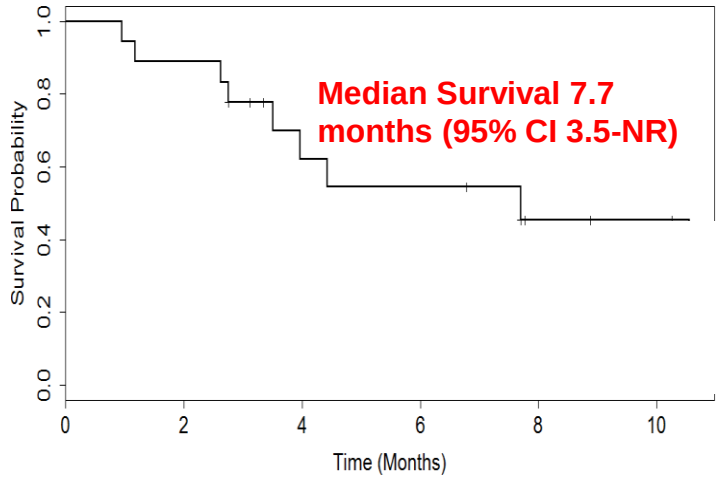
Secondary Endpoints:
Overall response rate, safety, PFS, OS

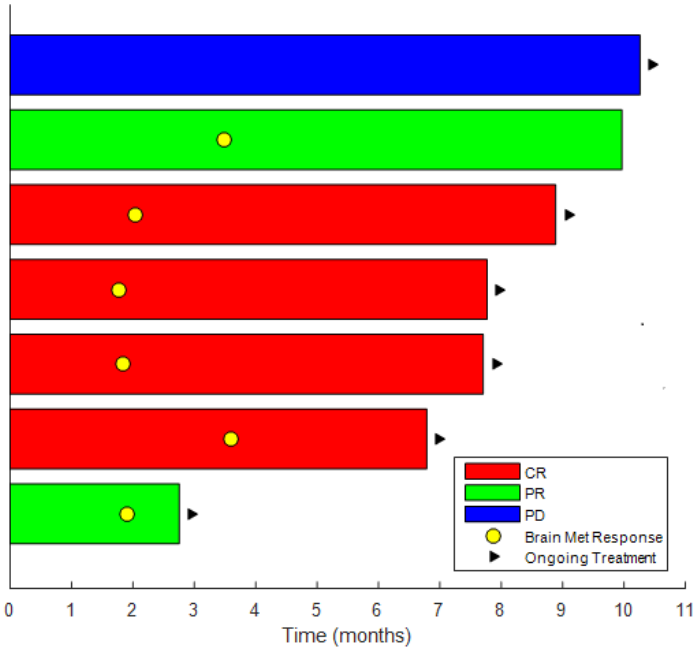
- Brain metastasis response by modified RECIST allows up to 5 target lesions with diameter ≥5mm
- Data presented from an interim analysis with cut-off date June 30, 2015

Sarah B. Goldberg, et al; WCLC 2015, ORAL 31

Phase II Trial of Pembrolizumab for Untreated Brain Metastases

Total evaluable patients	Brain Metastasis Responses (CR + PR)			Duration of BrM Response	Systemic Responses (CR + PR)		
N	No. of patients	%	95% CI	Individual duration (months)	No. of patients	%	95% CI
18	6*	33	0.14-0.59	3.2+, 6.0+, 6.1+, 6.6, 7.0+	6	33	0.14-0.59





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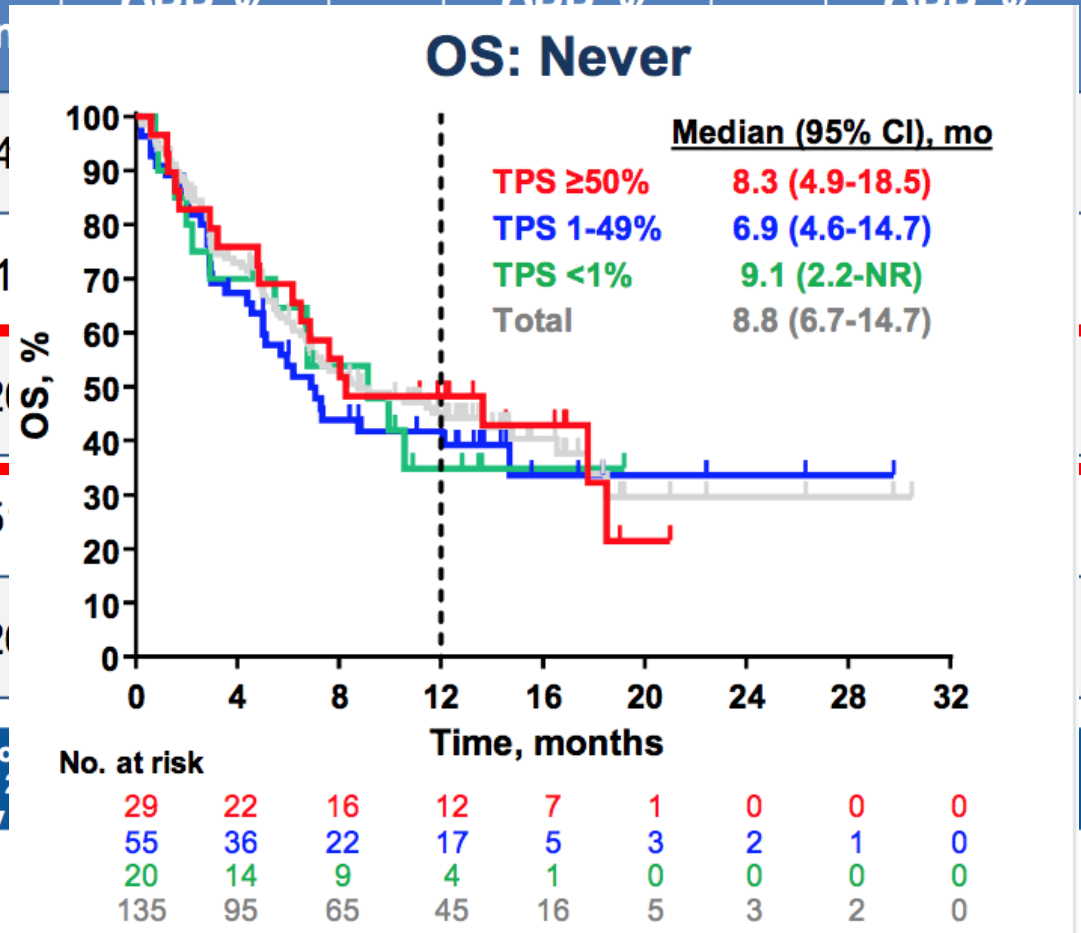
Keynote 001– Subgroups analyses

Antitumor Activity by *EGFR* and *KRAS* Status

	TPS ≥50%		TPS 1-49%		TPS <1%		Total[a]	
	n	ORR, %					N	ORR, % (95% CI)
Overall	14						550	20.2 (16.9-23.8)
EGFR wild type	11						450	21.6 (17.8-25.6)
EGFR mutant	2(						77	7.8 (2.9-16.2)
KRAS wild type	5						238	16.4 (11.9-21.7)
KRAS mutant	2(						87	17.2 (10.0-26.8)



[a]Includes patients for whc
with unknown *EGFR* (n =
Data cutoff date: January

3057 – Matthew D. Hellmann

Checkmate 057 – Subgroups ORR

		Nivolumab		Docetaxel	
		n	ORR,[a] %	n	ORR,[a] %
Overall		292	19	290	12
Age categorization (yrs)	<65	184	17	155	13
	≥65	108	22	135	12
Gender	Male	151	21	168	12
	Female	141	17	122	13
Baseline ECOG PS[b]	0	84	24	95	15
	1	208	17	194	11
CNS metastases	Yes	34	18	34	6
	No	258	19	256	13
Prior use of maintenance therapy	Yes	122	17	111	14
	No	170	21	179	11
Time from completion of most recent regimen to randomization	<3 mos	181	18	183	11
	≥3 mos	111	21	107	15
Smoking status	Current/Former smoker	231	22	227	11
	Never smoked	58	9	60	15
***EGFR* mutation status**	Positive	44	11	38	16
	Not detected	168	18	172	9
	Not reported	80	25	80	18

[a]Confirmed CR+PR (investigator assessment) as per RECIST v1.1 criteria
[b]Includes one patient in the docetaxel arm who had ECOG PS = 3
Based on a March 18, 2015, DBL

Horn L. et al

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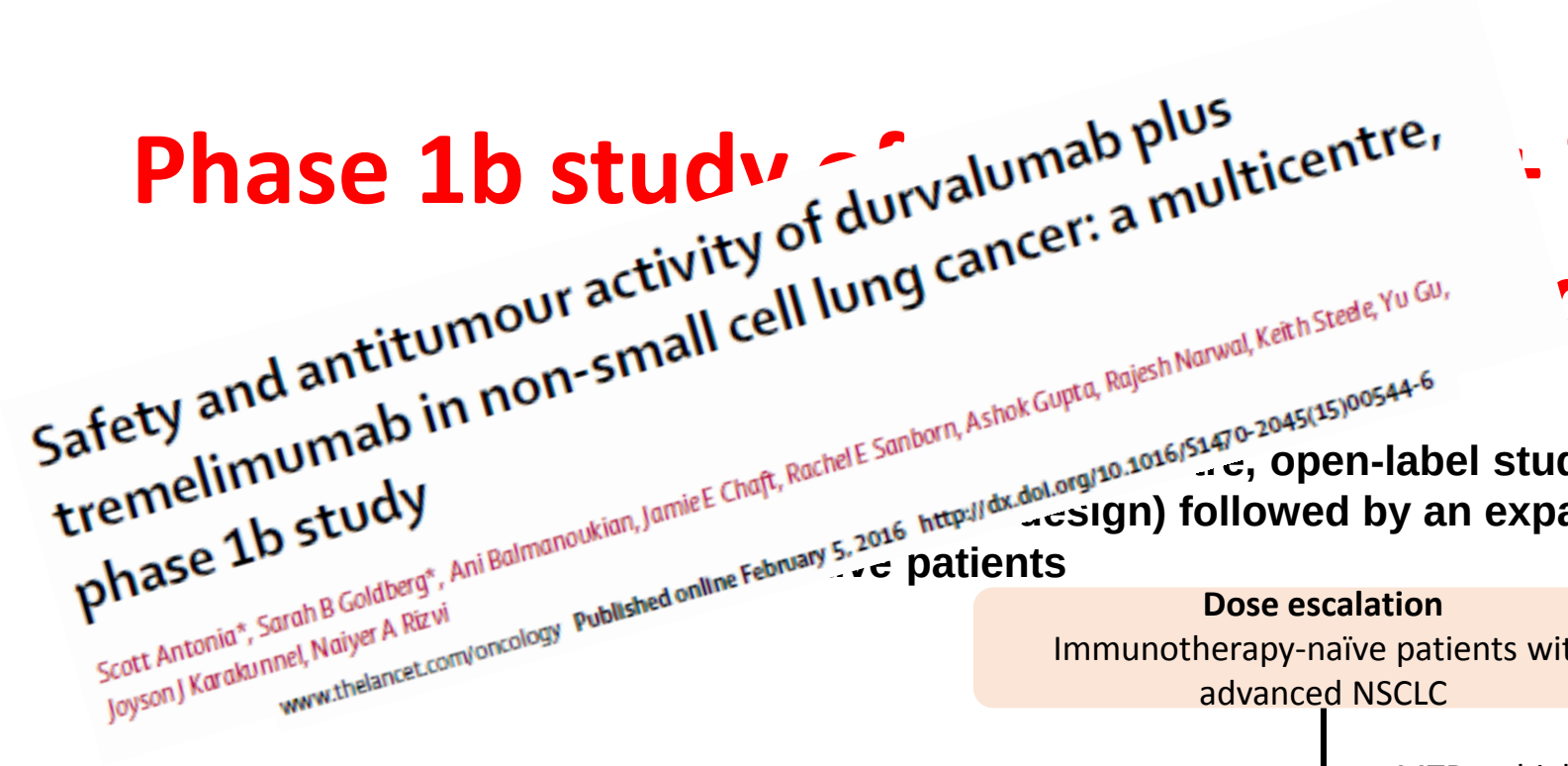
Phase 1b study of [illegible] - Tremelimumab in [illegible] NSCLC



Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study

Scott Antonia*, Sarah B Goldberg*, Ani Balmanoukian, Jamie E Chaft, Rachel E Sanborn, Ashok Gupta, Rajesh Narwal, Keith Steele, Yu Gu, Joyson J Karakunnel, Nairyer A Rizvi

www.thelancet.com/oncology Published online February 5, 2016 http://dx.doi.org/10.1016/S1470-2045(15)00544-6

[illegible], open-label study with a standard [illegible]design) followed by an expansion phase in [illegible]ve patients

Dose escalation
Immunotherapy-naïve patients with advanced NSCLC

MTD or highest protocol-defined dose

Dose expansion
Treatment-naïve patients

Dose expansion
One or two prior lines of therapy

Primary objectives:
- MTD
- Safety and tolerability

ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02000947.
Antonia S, et al. Poster presented at ASCO 2015. Poster 3014
Antonia S, et al. Poster presented at ESMO 2014. Poster 1327P

April 15, 2015 data cut-off

Lancet Oncology 2016;17:299-308

Study 006

Steroid use was limited

n (%)	M3 q4w T1 n=3	M10 q4w T1 n=3	M15 q4w T1 n=18	M20 q4w T1 n=18	M10 q2w T1 n=17	M10 q4w T3 n=3	M15 q4w T3 n=14	M20 q4w T3 n=6	M10 q2w T3 n=11	M15 q4w T10 n=9	All Cohorts N=102
Corticosteroids	1 (33)	3 (100)	5 (28)	3 (17)	2 (12)	3 (100)	4 (29)	3 (50)	3 (27)	5 (56)	32 (31)
Infliximab	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	1 (9)	1 (11)	3 (3)

- Red box=selected Phase 3 dose

- Grade 3/4 drug-related AEs were manageable and generally reversible using standard treatment guidelines

- In the Q4W cohorts, M20/T1 had the lowest frequency of steroid use and no patients required infliximab or mycophenylate mofetil

Data presented at ASCO 2015 Poster #3014; April 15, 2015 data cut-off

Study 006

Durvalumab + Tremelimumab show activity regardless of PD-L1 status

	M10–20 q4/2w T1 mg/kg n=27	M10–20 q4/2w T3 mg/kg n=24	M15 q4w T10 mg/kg n=9	All Cohorts (Including M3/T1) N=63
All evaluable patients				
ORR, n (%) 95% CI	9 (33) 17–54	6 (25) 10–47	2 (22) 3–60	17 (27) 17–40
DCR (CR, PR, SD ≥16 weeks), n (%) 95% CI	14 (52) 32–71	10 (42) 22–63	2 (22) 3–60	26 (41) 29–54
PD-L1^{+}	N=9	N=5	N=4	N=18
ORR, n (%) 95% CI	3 (33) 7–70	2 (40) 5–85	1 (25) 1–81	6 (33) 13–59
DCR (CR, PR, SD ≥16 weeks), n (%) 95% CI	4 (44) 14–79	2 (40) 5–85	1 (25) 1–81	7 (39) 17–64
PD-L1^{-}	N=13	N=14	N=4	N=33
ORR, n (%) 95% CI	5 (38) 14–68	3 (21) 5–51	1 (25) 1–81	9 (27) 13–46
DCR (CR, PR, SD ≥16 weeks), n (%) 95% CI	8 (62) 32–86	7 (50) 23–77	1 (25) 1–81	16 (48) 31–66
PD-L1 Unknown	N=5	N=5	N=1	N=12
ORR, n (%) 95% CI	1 (20) 1–72	1 (20) 1–72	0 (0) 0–98	2 (17) 2–48
DCR (CR, PR, SD ≥16 weeks), n (%) 95% CI	2(40) 5–85	1 (20) 1–72	0 (0) 0–98	3 (25) 5–57

Includes all patients in the as-treated population who were dosed ≥16 weeks prior to the cut-off date, with measurable disease at baseline, ≥1 follow-up scan (includes those that discontinued due to PD or death without any follow-up scan). ORR includes confirmed and unconfirmed CR or PR.

CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; SD, stable disease

Red Box = Dose Selected for Phase 3 Studies

Data presented at ASCO 2015 Poster #3014;

April 15, 2015 data cut-off

And the Garon's point of view….The race for combined checkpoint inhibition in NSCLC

- The data presented by Antonia and have a median follow-up of 18,8 weeks (IQR 11–33) thus PFS, OS cannot be assessed.
- Both RR and AEs these could be underestimated, because events occurring more than a few months after initiation of treatment are not captured.
- Although this accelerated approach has the potential to validate a novel combination more quickly, the potential for negative consequences is real.
  - overtreatmnt of subgroups that would benefit similarly froma a single drug
  -the dosing regimen might not yet have been optimised.

However, at this point, the race is on, and the oncology community will hope that combined inhibition of the CTLA-4 and PD-1 checkpoints is a winner.

The Lancet Oncol February 5, 2016

Take home messages

- Level 1 evidence supports the use of nivolumab/pembrolizumab as 2nd-line NSCLC therapy both in squamous and in non-squamous disease.
- The benefit of this class of drugs in patients with targetable driver mutations remains uncertain.
- The use of PD-L1 expression to guide therapy in NSCLC is controversial (nivolumab approval regardless of PD-L1 status and pembrolizumab approval of in PD-L1–pos pts).
- Although PD-L1 expression is the best available biomarker for these pts further validation and standardization are needed.
- Research into other checkpoint inhibitors new combinations, biomarkers, and use in earlier settings is ongoing.

IS CHEMOTHERAPY GOING TO DIE?

Thank you for your attention!

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