Immune-checkpoint blockade for the treatment of advanced NSCLC

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Disclosure

Scientific advice and clinical trials

- **MSD**
- **BMS**
- **Roche**
- **Astra Zeneca**

Background

1.- Introduction

2.- PD-1/PD-L1 blockade

- 2.1.- Efficacy overview
- 2.2.- Toxicity profile

3.- Patient selection

4.- Conclusions

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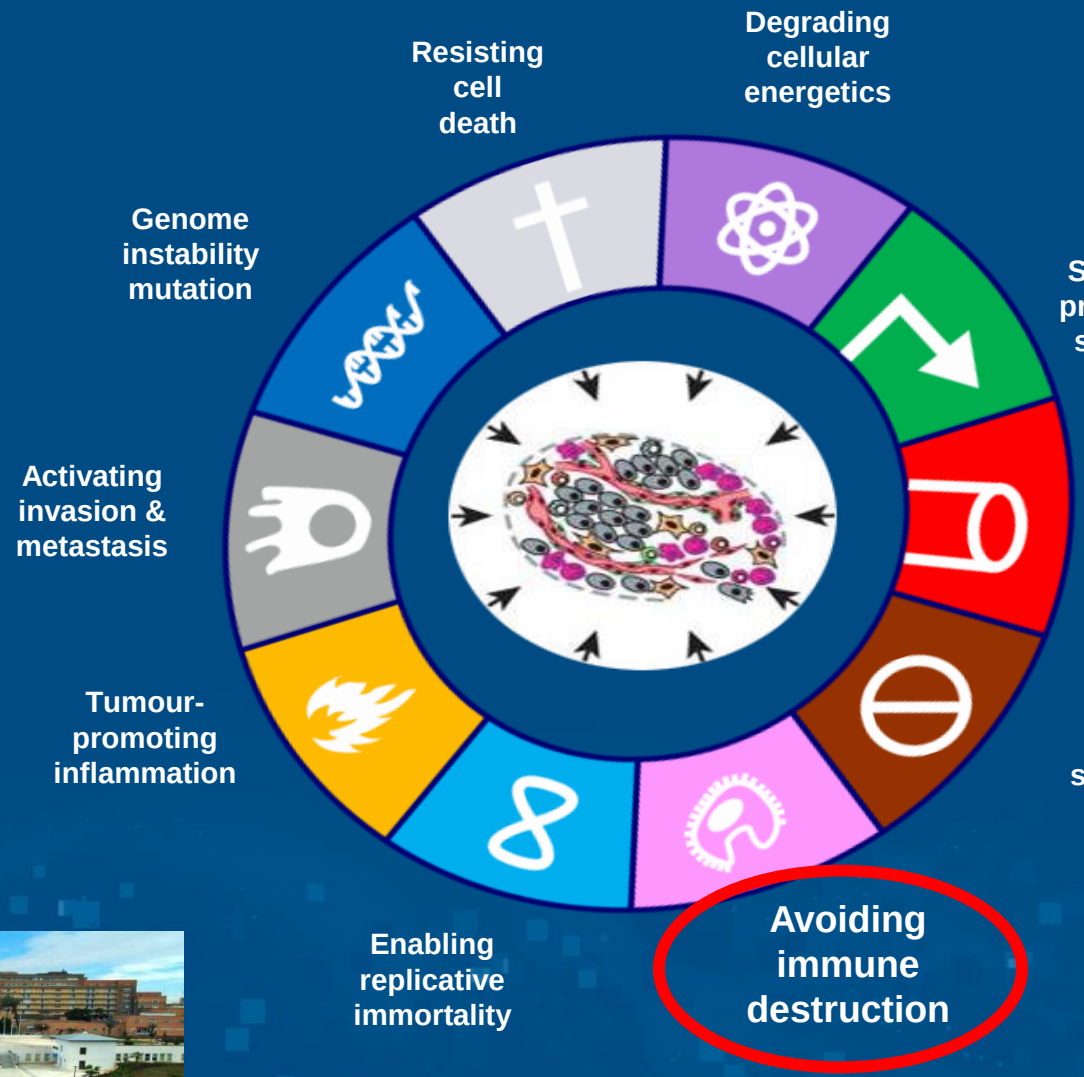
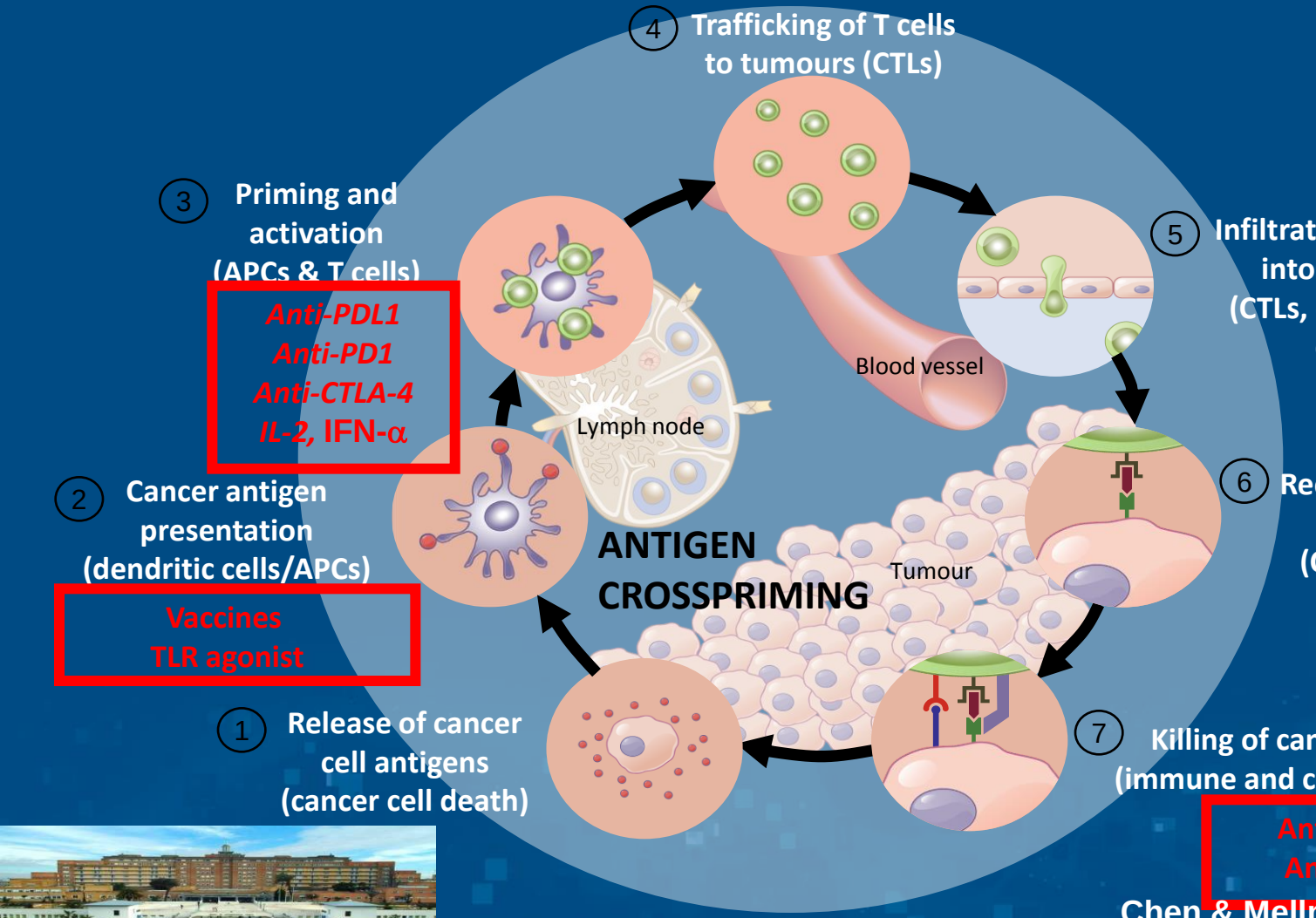
Therapeutic Intervention at Cancer Hallmarks



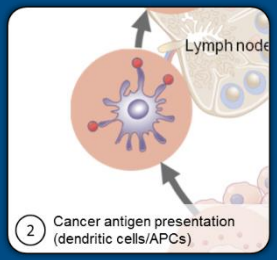
Hanahan & Weinberg. Cell 2011

Cancer-immunity cycle and Immunotherapy



Chen & Mellman. Immunity 2013

Vaccines have shown limited efficacy in NSCLC



Tecemotide[1]
(L-BLP25; MUC1 vaccine)

Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial

*Charles Butts, Mark A Socinski, Paul L Mitchell, Nick Thatcher, Libor Havel, Maciej Krzakowski, Sergiusz Nawrocki, Tudor-Eliade Ciuleanu, Lionel Bosquée, José Manuel Trigo, Alexander Spira, Lise Tremblay, Jan Nyman, Rodryg Ramlau, Gun Wickart-Johansson, Peter Ellis, Oleg Gladkov, José Rodrigues Pereira, Wilfried Ernst Erich Eberhardt, Christoph Helwig, Andreas Schröder, Frances A Shepherd, on behalf of the START trial team**

GSK1572932A[2]
(MAGE-A3 vaccine)

ABSTRACT

1173O - MAGRIT, a double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC)

Belagenpumatucel-L[3]
(NSCLC cellular vaccine)

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Phase II Study of Belagenpumatucel-L, a Transforming Growth Factor Beta-2 Antisense Gene-Modified Allogeneic Tumor Cell Vaccine in Non–Small-Cell Lung Cancer

John Nemunaitis, Robert O. Dillman, Paul O. Schwarzenberger, Neil Senzer, Casey Cunningham, Jodi Cutler, Alex Tong, Padmasini Kumar, Beena Pappen, Cody Hamilton, Edward DeVol, Phillip B. Maples, Lily Liu, Terry Chamberlin, Daniel L. Shawler, and Habib Fakhrai

CIMAvax[4]
(EGF vaccine)

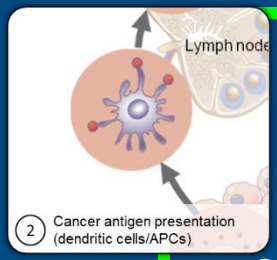
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Phase II Randomized Controlled Trial of an Epidermal Growth Factor Vaccine in Advanced Non–Small-Cell Lung Cancer

Elia Neninger Vinageras, Ana de la Torre, Marta Osorio Rodríguez, Mauricio Catalá Ferrer, Idania Bravo, Mario Mendoza del Pino, Daniel Abreu Abreu, Soraida Acosta Brooks, Rolando Rives, Concepción del Castillo Carrillo, Marta González Dueñas, Carmen Viada, Beatriz García Verdecia, Tania Crombet Ramos, Gisela González Marinello, and Agustín Lage Dávila

1. Butts, et al. Lancet Oncol 2014; 2. Vansteenkiste, et al. ESMO 2014
3. Nemunaitis, et al. J Clin Oncol 2006; 4. Neninger Vinageras, et al. J Clin Oncol 2008

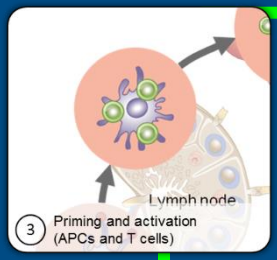
Other NSCLC immunotherapy approaches



Toll-like receptors[1,2]

Toll-like receptors (TLRs) are membrane proteins that recognise foreign pathogens[1]

Stimulation of TLR9 by receptor agonists can enhance tumour vaccination and can promote antigen-specific anti-tumour immunity without a vaccine



IL-2[3–5]

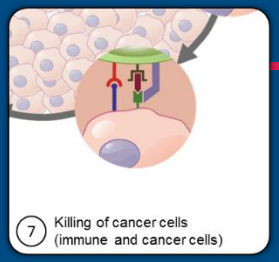
A regulatory cytokine produced mainly by T cells and NK cells and promotes activation and proliferation of immune cells but also regulates immune tolerance

IFN-α[5]

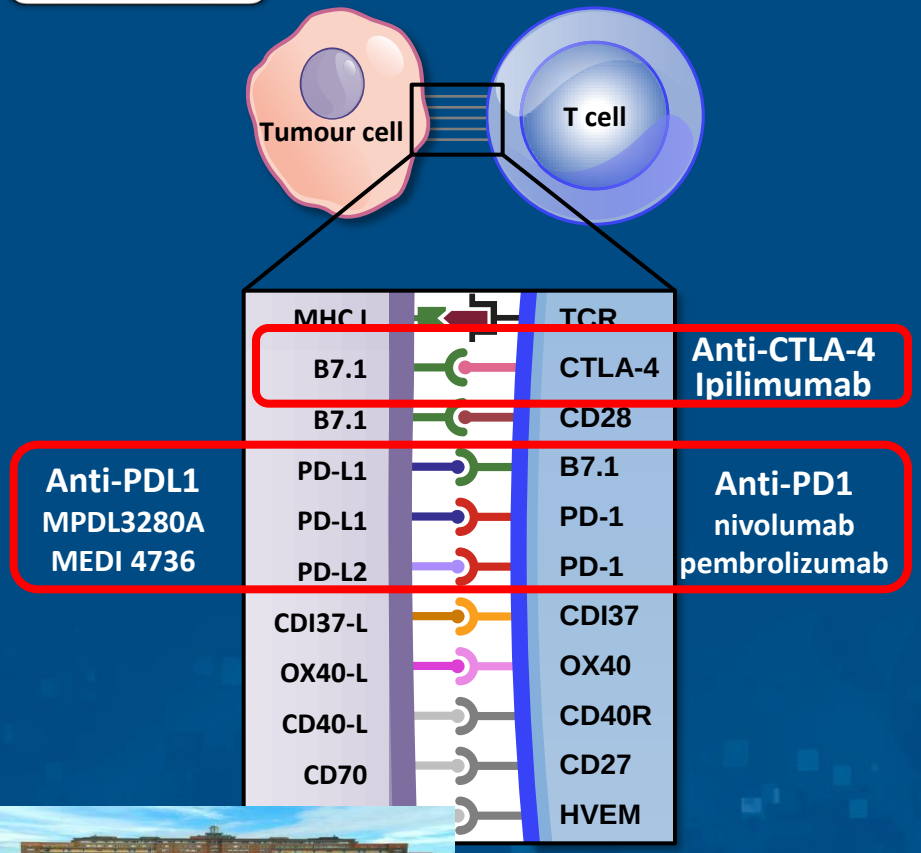
IFN-α is a type-I interferon which induces tumour MHC class I expression, activate several immune cell types can cause direct tumour cells apoptosis

1. Krieg. J Clin Invest 2007; 2. Droemann, et al. Resp Res 2005
3. Ridolfi, et al. Int J Oncol 2011; 4. Lissoni, et al. Br J Cancer 1992;
5. Jansen, et al. J Immunother 1992

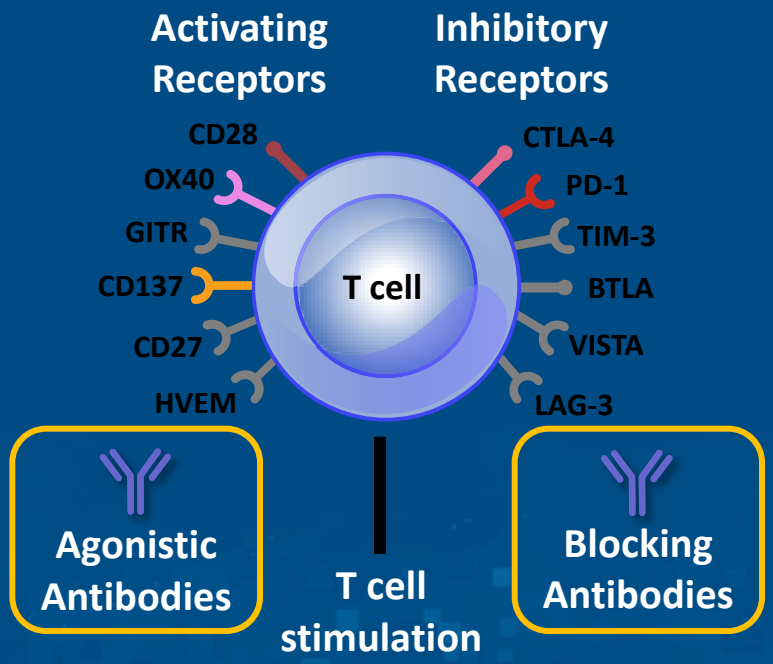
Checkpoint inhibition



Checkpoint inhibitors can potentially restore immune responses against tumour cells

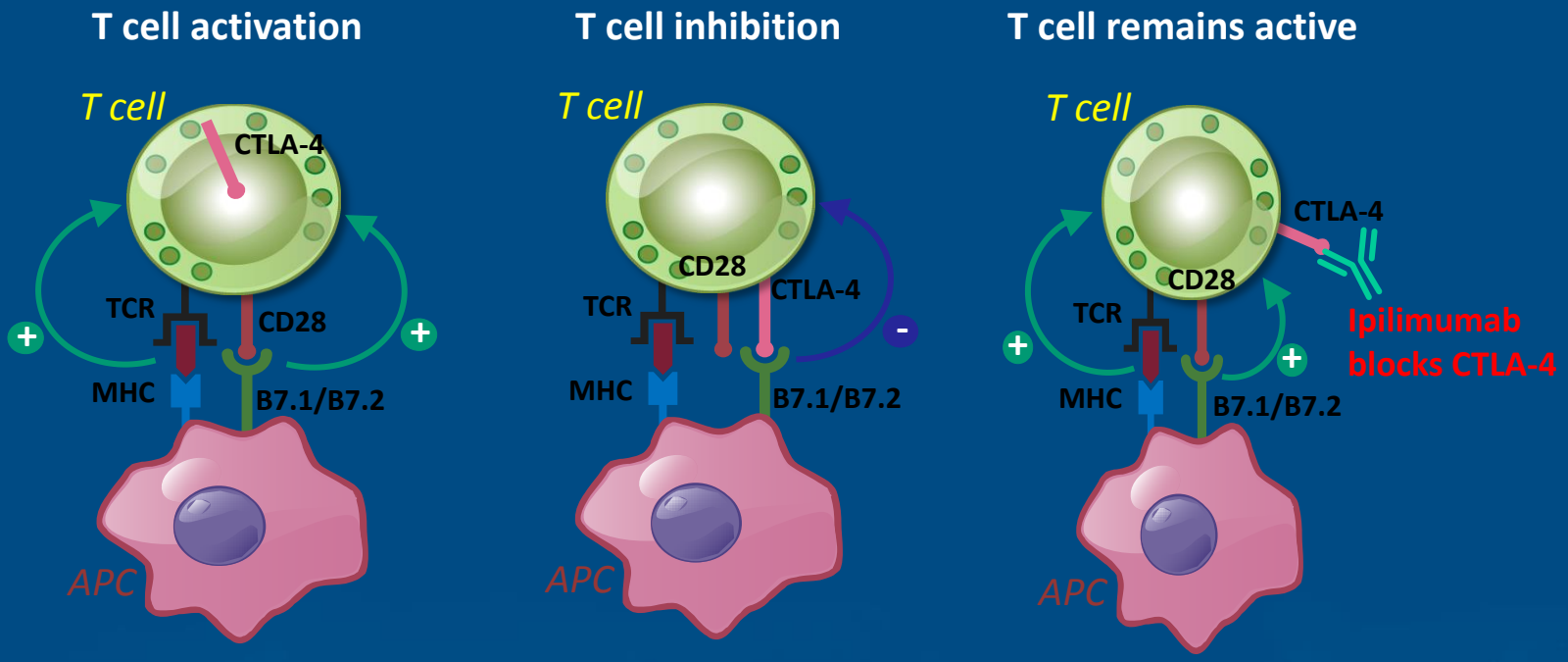


T cell targets for modulating activity



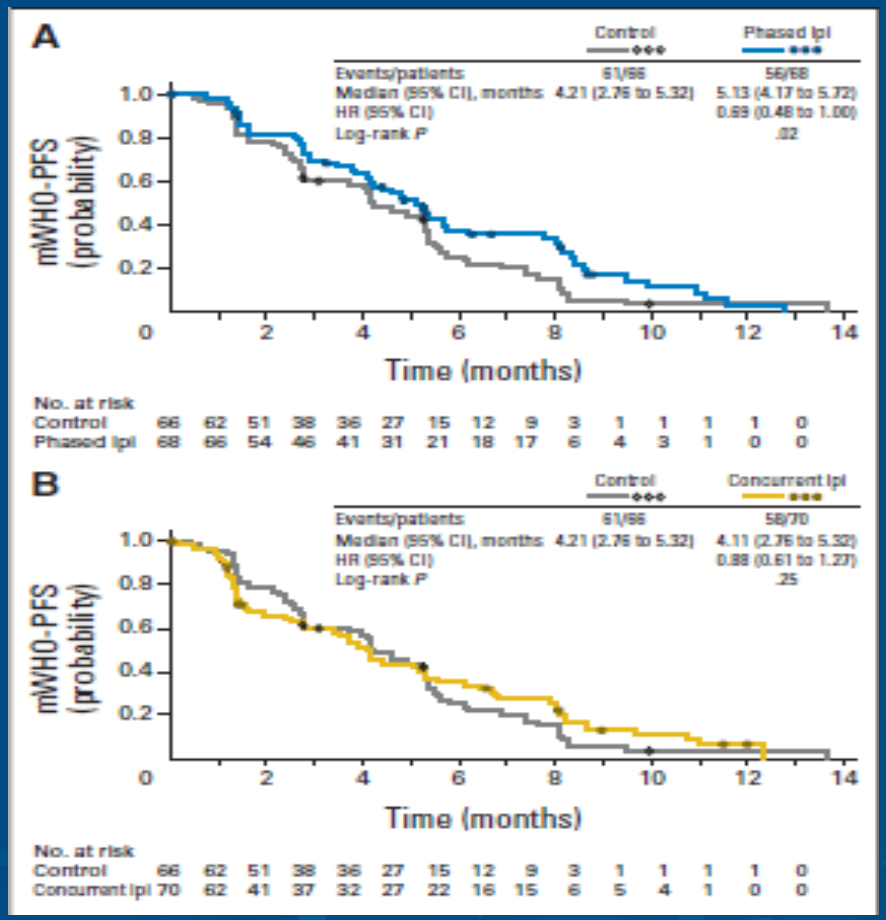
Abbas, et al. Basic Immunology, 4th Ed 2012
Mellman, et al. Nature 2011

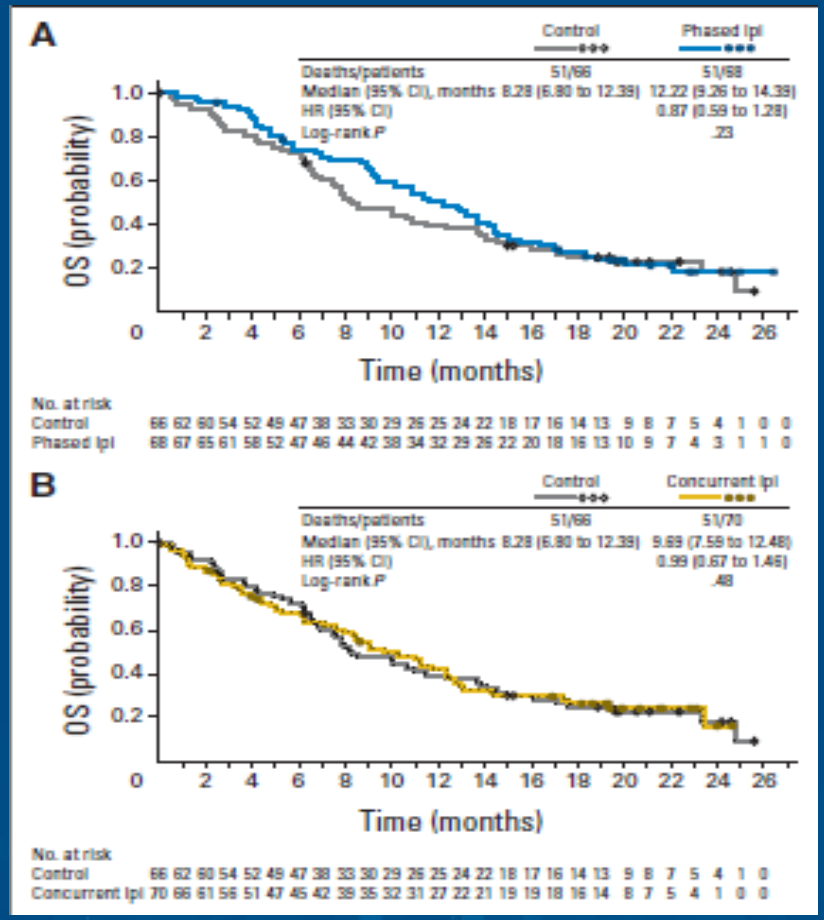
Targeting the CTLA-4 pathway



Lynch T, et al. J Clin Oncol 2012

Ipilimumab has shown modest efficacy in NSCLC





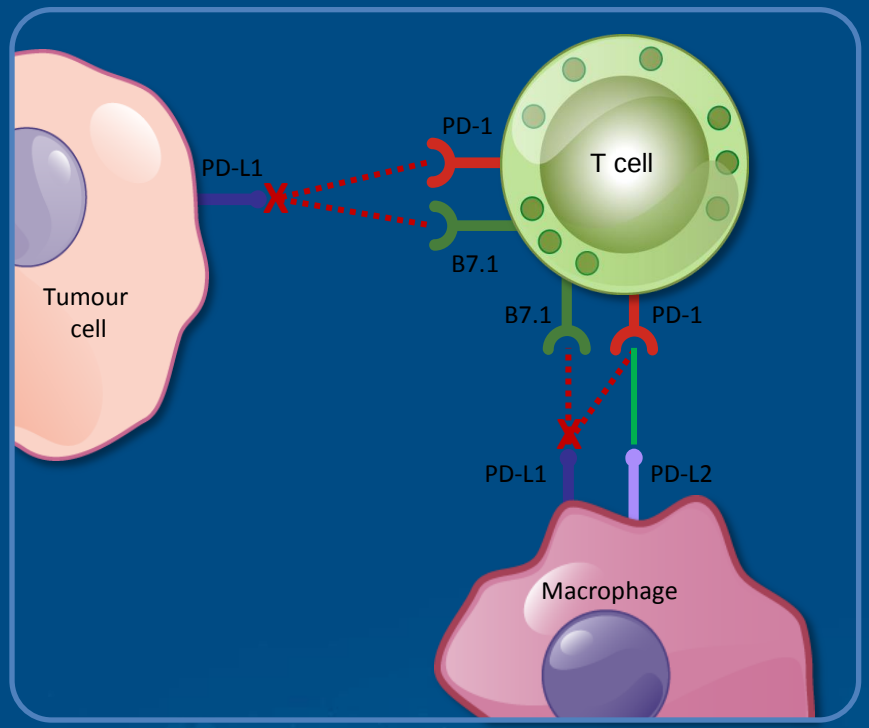
Lynch T, et al. J Clin Oncol 2012

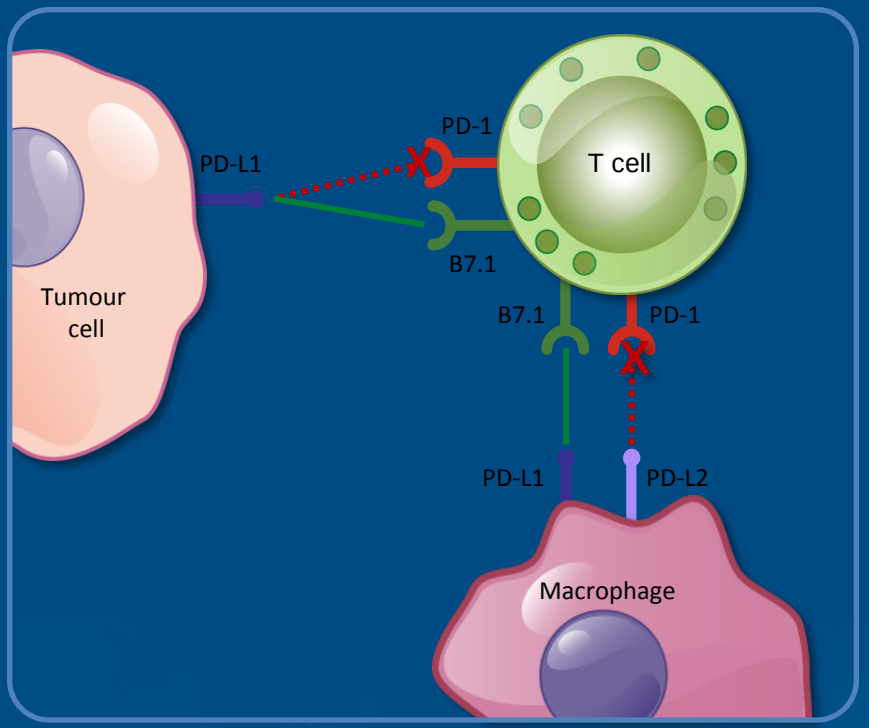
Ipilimumab ongoing trials in patients with NSCLC

Status	Study
Recruiting	Study of combined Ionizing Radiation and Ipilimumab in metastatic NSCLC
Recruiting	Phase 3 in Squamous NSCLC subjects comparing Ipilimumab plus Paclitaxel and Carboplatin versus Placebo plus Paclitaxel and Carboplatin
Recruiting	Phase Ib trial with Ipilimumab plus Erlotinib or Crizotinib for EGFR or ALK mutated stage IV NSCLC

www.ClinicalTrials.gov

Targeting the PD-L1/ PD-1 pathway





Chen, et al. Clin Cancer Res 2012; Paterson, et al. J Immunol 2011
Yang, et al. J Immunol 2011; Brahmer, et al. N Engl J Med 2012

Overview of PD-L1 and PD-1 inhibitors
Clinical data in Lung Cancer

Therapeutic	Lead company	Antibody type	Affinity/K_2	Reference
Anti-PDL1				
MPDL3280A	Roche	Engineered IgG1 (no ADCC)	0.4nM	Herbst et al. ASCO 2013
MEDI-4736	AstraZeneca	Modified IgG1 (no ADCC)	Not available	Stewart et al. Cancer Res 2011
Anti-PD1				
Nivolumab	Bristol-Myers Squibb	IgG4	2.6nM	Brahmer et al. J Clin Oncol 2010
MK3475	Merck & Co	IgG4 (humanised)	29pM	Patnaik et al. ASCO 2012

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1) Monotherapy pretreated ≥2 lines NSCLC patients

2) Monotherapy 1st and 2nd line

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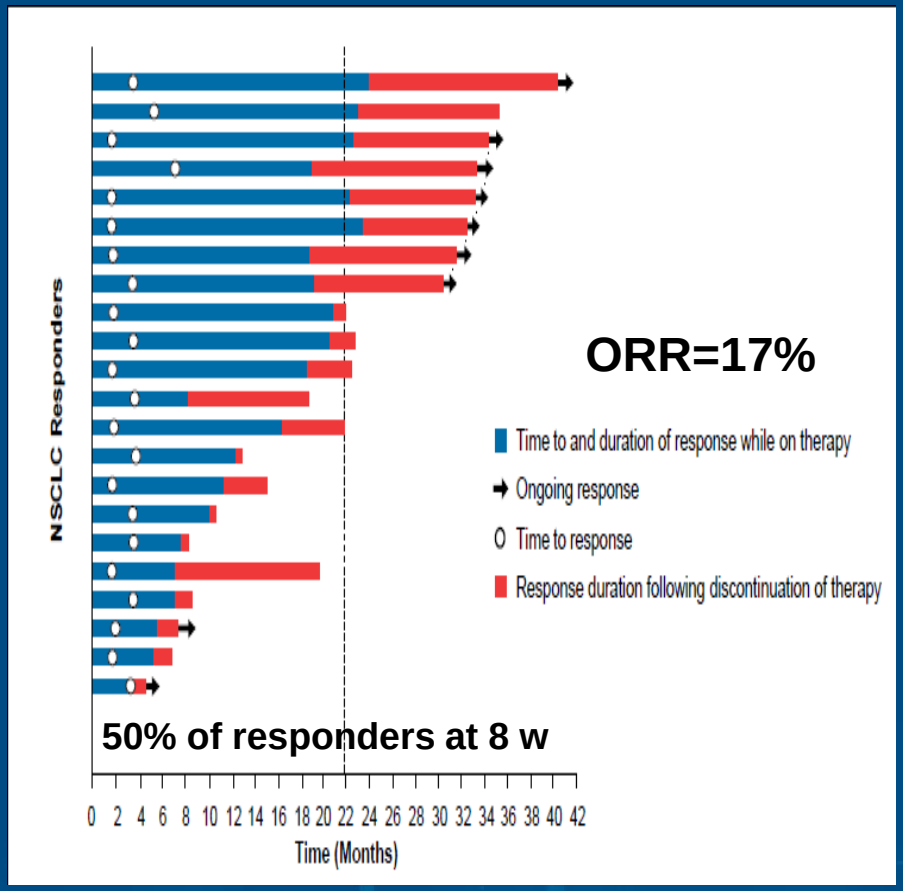
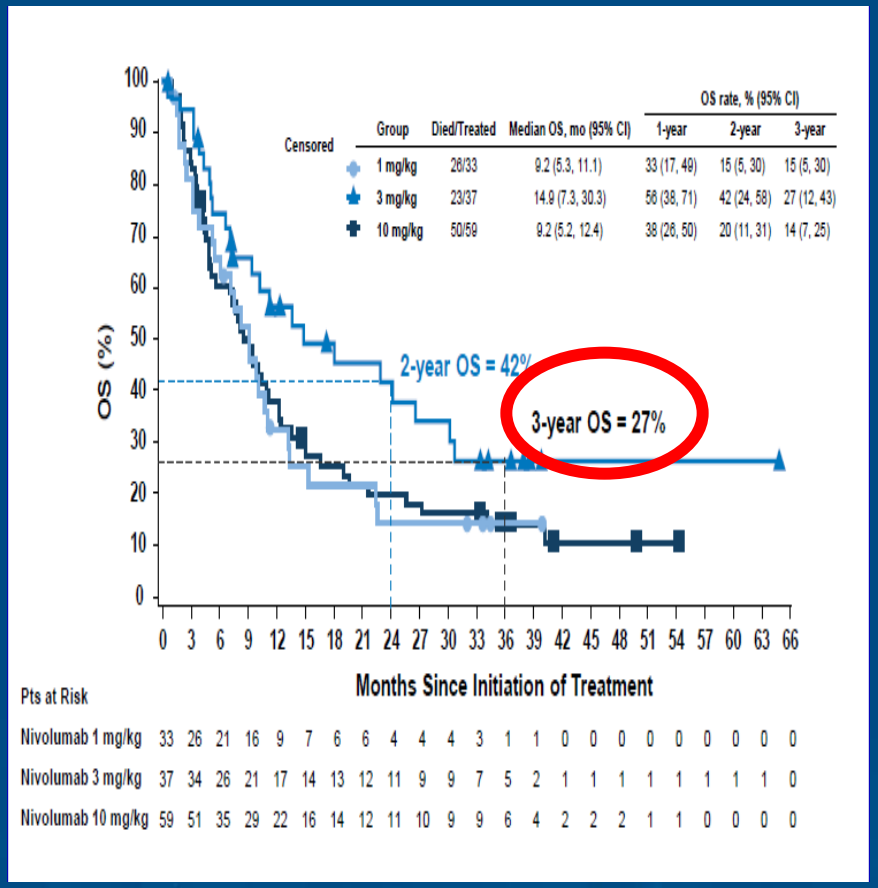
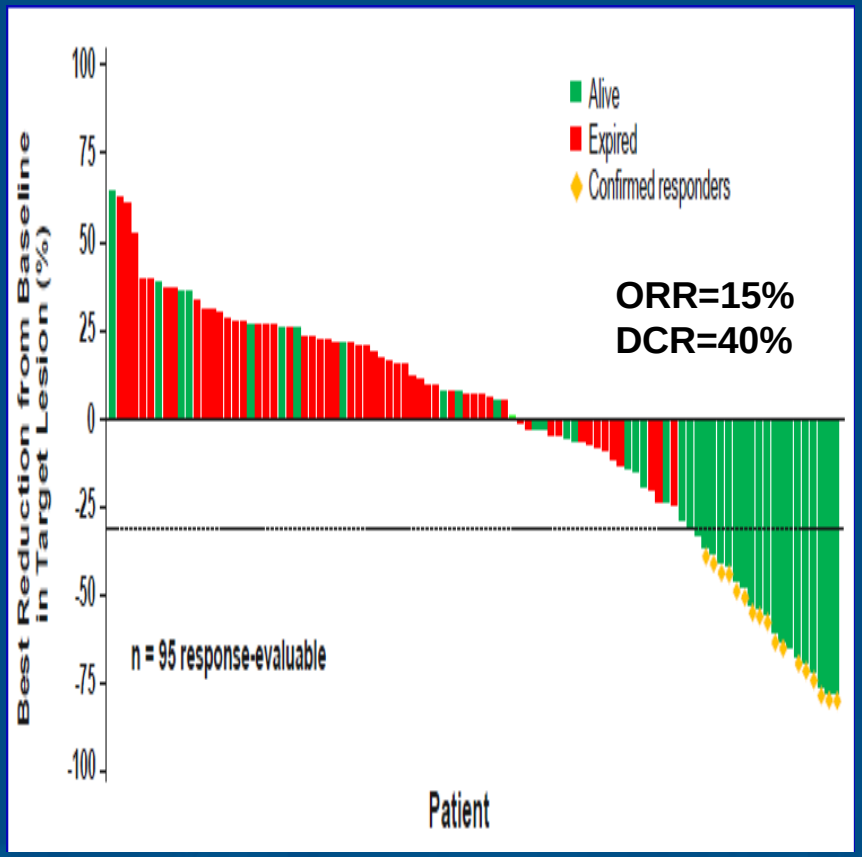
PD-1 blockade: Nivolumab

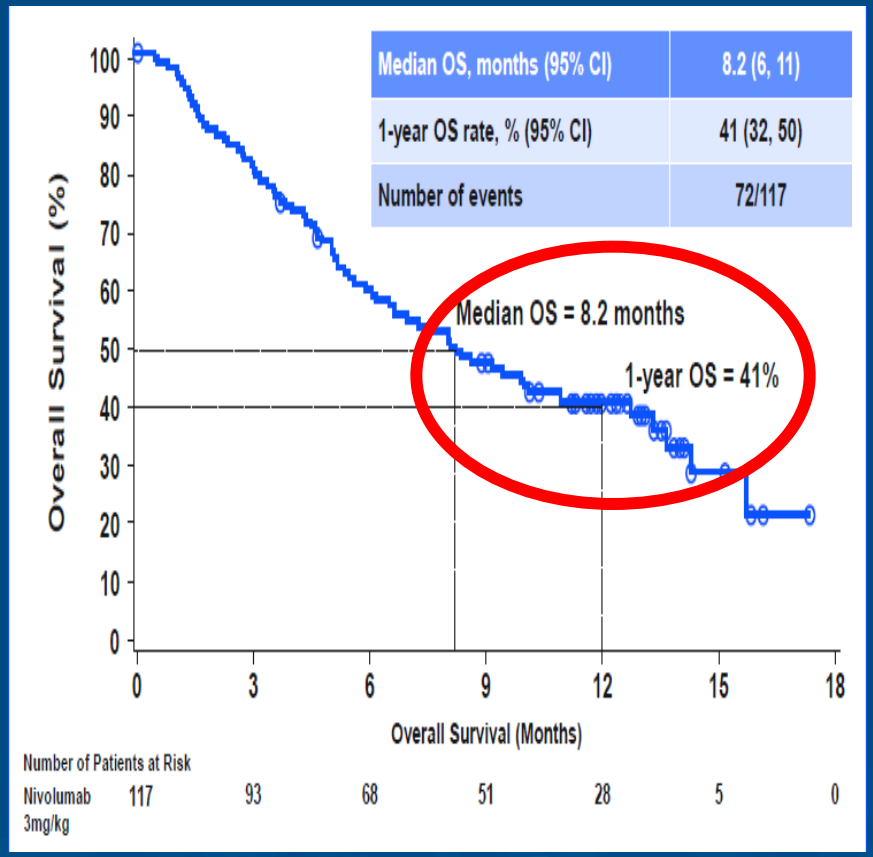




Gettinger SN, et al. CMSTO 2014

PD-1 blockade: Nivolumab (squamous)

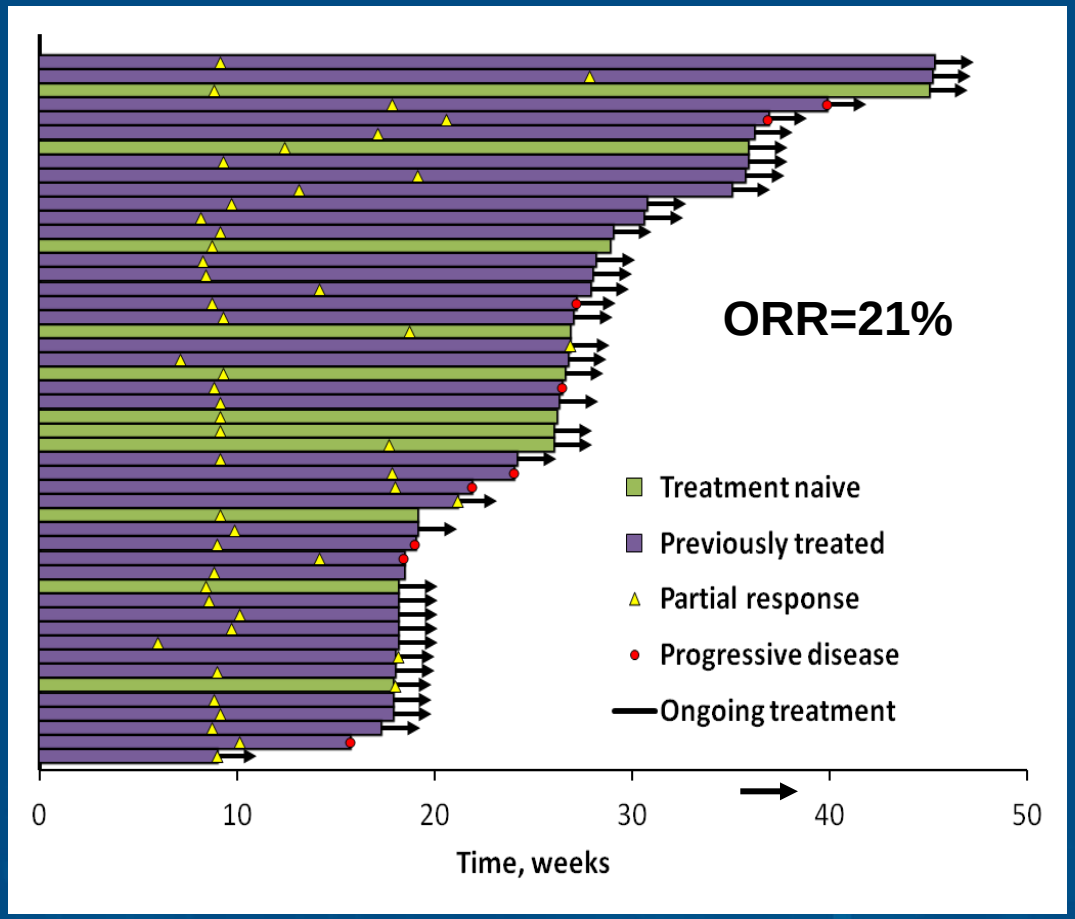


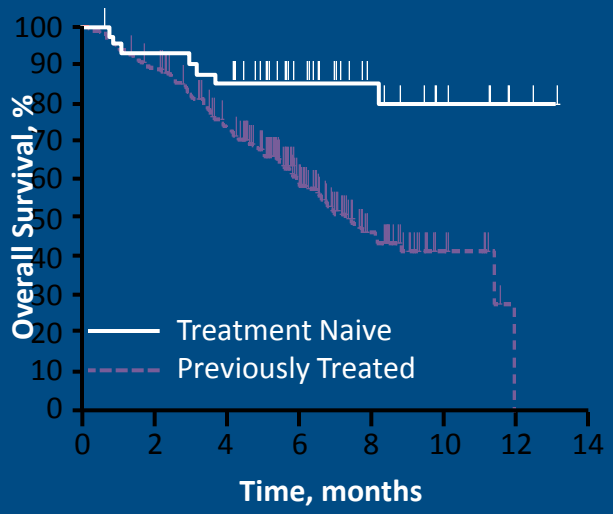


65% > 3 prior chemo lines AND 76% < 3 months from completion last regimen

Ramalingam SS, et al. CMSTO 2014

PD-1 blockade: Pembrolizumab





- Treatment naive
  - Median OS: NR (95% CI, NE-NE)
  - 6-month OS: 86%
- Previously treated
  - Median OS: 8.2 months (7.3-NR)
  - 6-month OS: 59%

EB Garon. ESMO 2014

PD-L1 Blockade: MPDL3280A

	Single Agent RECIST 1.1 Response Rate (ORR[a])	SD of 24 Weeks or Longer	24-Week PFS Rate
Overall population (N = 175)	21%	19%	42%
NSCLC (n = 53)	23%	17%	45%
Nonsquamous (n = 42)	21%	17%	44%
Squamous (n = 11)	27%	18%	46%

[a] ORR includes investigator-assessed unconfirmed and confirmed PR.
Six patients who did not have a post-baseline scan were included as non-responders.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.

Soria JC. ESMO 2013

PD-L1 Blockade: MEDI4736

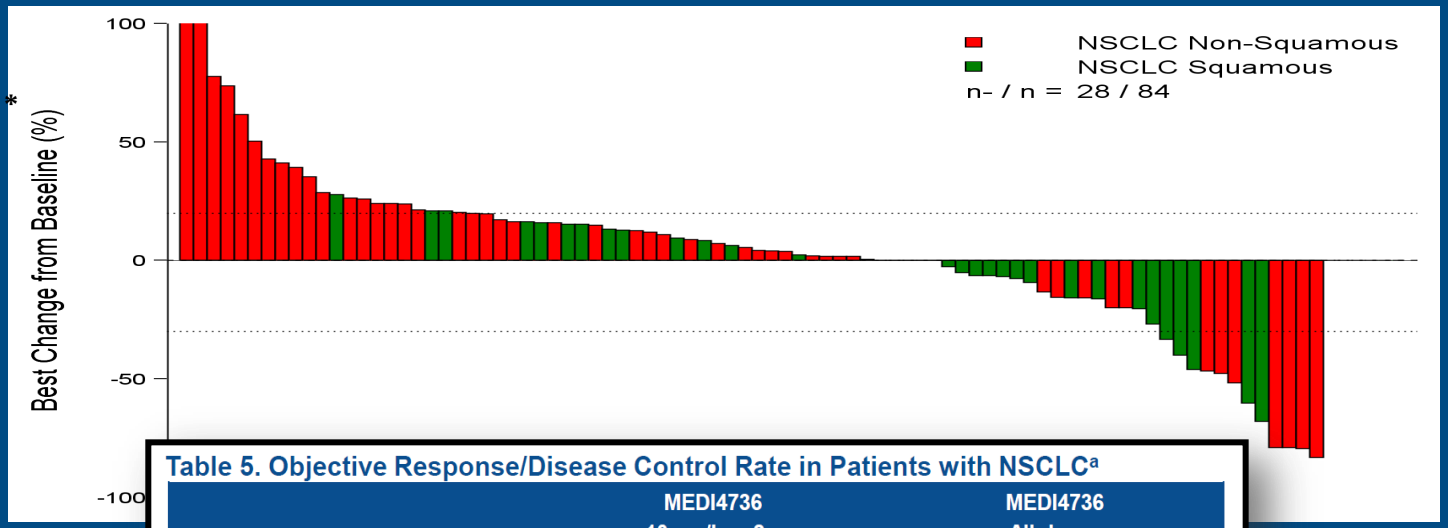


Table 5. Objective Response/Disease Control Rate in Patients with NSCLC[a]

	MEDI4736 10 mg/kg q2w	MEDI4736 All doses
RECIST Response[b]		
Response evaluable[c]	13% (6/47)	16% (9/58)
PD-L1+	39% (5/13)	25% (5/20)
PD-L1-	5% (1/19)	3% (1/29)
Disease Control Rate[d]		
Response evaluable[c]	30% (14/47)	35% (20/58)
PD-L1+	54% (7/13)	45% (9/20)
PD-L1-	32% (6/19)	24% (7/29)

[a]All patients were enrolled ≥12 Weeks prior to data cut-off date, not all patients were assessed for PD-L1 expression; [b]RECIST Response = confirmed/unconfirmed complete response (CR) or partial response (PR) based on conventional RECIST criteria; [c]Patients with baseline assessment + ≥1 follow-up scan (includes those that discontinued due to PD or death prior to first follow-up scan); [d]Disease Control = RECIST Response + stable disease ≥12 Weeks

J Brahmer. ASCO 2014

Monotherapy pretreated ≥2 lines: Summary efficacy overview

	Anti PD1		Anti PD-L 1	
	MK-3475	Nivolumab	MEDI4736	MPDL3280A
All, N	236	129	58	53
ORR	21%	17%	16%	23%
Pretreated, N	194	129	58	53
ORR	20%	17%	16%	23%
PFS	2,5 m	2,3 m	NR	45% at 6m
OS	8,2 m	9,9 m	NR	NR

Garon E, ESMO 2014; Brahmer J, ASCO 2014; Gettinger ASCO 2014; Soria JC, ESMO 2014

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Monotherapy 1st line: Summary efficacy overview

	Anti PD1	
	MK-3475	Nivolumab
N	42	20+52
ORR	26%	30-21%
PFS	6,5 m; 51% at 6 m	9 m; 15,6 w
OS	NR; 86% at 6 m	42% at 1 y; 98,3 w

Garon E, ESMO 2014; Brahmer J, ASCO 2014)
Rizvi NA, CMSTO 2014

Overview of anti-PD-L1/PD-1 therapies currently under investigation in NSCLC

Target	Therapy	Phase	Trial Design	Trial ID
Anti-PD-L1	MPDL3280A (Engineered IgG1, no ADCC)	II	≥1L PD-L1+ NSCLC (FIR)	NCT01846416
		II	≥1L PD-L1+ NSCLC (BIRCH)	NCT02031458
		II	2/3L NSCLC vs docetaxel (POPLAR)	NCT01903993
		III	2/3L NSCLC vs docetaxel (OAK)	NCT02008227
	MEDI4736 (Modified IgG1, no ADCC)	I	Solid tumours	NCT01693562
		III	≥2L NSCLC after chemoradiation vs placebo (PACIFIC)	NCT02125461
		II/III	2L squamous NSCLC biomarker-targeted vs docetaxel	NCT02154490
		II	≥3L NSCLC (ATLANTIC)	NCT02087423
Anti-PD-1	Nivolumab (IgG4)	I	≥2L NSCLC	NCT00730639
		III	≥2L squamous NSCLC vs docetaxel	NCT01642004
		III	2/3L non-squamous NSCLC vs docetaxel	NCT01673867
		II	≥3L squamous NSCLC	NCT01721759
		III	1L non-squamous PD-L1+ NSCLC vs Chemo	NCT02041533
	Pembrolizumab (IgG4, humanised)	I	NSCLC	NCT01295827
		III	1L PD-L1+ NSCLC vs platinum-chemo	NCT02142738
		II/III	≥2L PD-L1+ NSCLC vs docetaxel	NCT01905657

Phase III Nivolumab vs Docetaxel 2nd line squamous NSCLC

Disease Progression after platinum-based doublet chemotherapy

1:1 Randomization

A — Nivolumab 3mg/kg IV Q2wks until disease progression

B — docetaxel 75mg/M^2 IV Q3wks until disease progression

- Primary Endpoint:
  - ORR* and OS
- Addl. Endpoints:
  - PFS*
  - Benefit in PD-L1+/- subgroups
  - Duration and time to OR
  - Safety and Tolerability
  - PRO

* ORR (using RECIST 1.1 criteria) and PFS as determined by an independent review committee (IRC)

FDA Nivolumab approval press note

FDA Approves Opdivo (nivolumab) for the Treatment of Patients with Previously Treated Metastatic Squamous Non-Small Cell Lung Cancer
Opdivo is the first and only immuno-oncology therapy proven to extend survival in patients treated with one prior therapy
CheckMate -017 achieved the benchmark goal of improving overall survival in previously treated squamous non-small cell lung cancer (NSCLC)
Wednesday, March 4, 2015 4:13 pm EST

U.S. Food and Drug Administration (FDA) has approved *Opdivo* (nivolumab) injection, for intravenous use, for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. *Opdivo* is the first and only PD-1 (programmed death receptor-1) therapy to demonstrate overall survival in previously treated metastatic squamous NSCLC. *Opdivo* demonstrated significantly superior overall survival (OS) vs. docetaxel, with a 41% reduction in the risk of death (hazard ratio: 0.59 [95% CI: 0.44, 0.79; p=0.00025]), in a prespecified interim analysis of a Phase III clinical trial. The median OS was 9.2 months in the *Opdivo* arm (95% CI: 7.3, 13.3) and 6 months in the docetaxel arm (95% CI: 5.1, 7.3).

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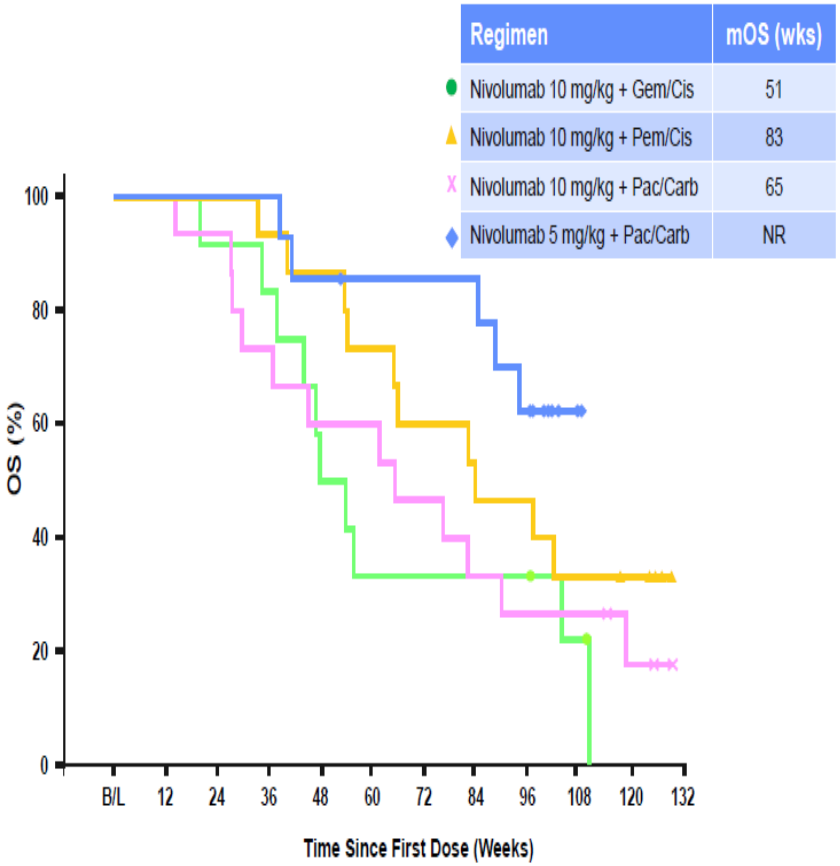
Nivolumab in combination with chemo

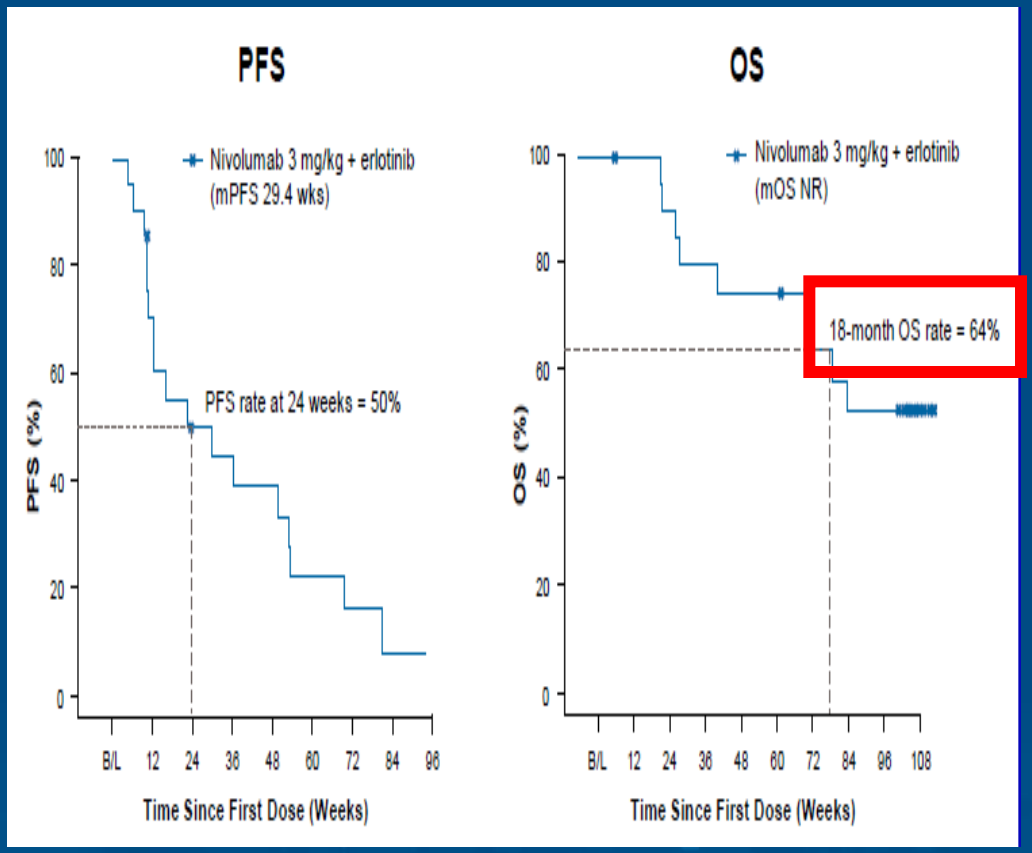
	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg
	Gem/Cis (n = 12)	Pem/Cis (n = 15)	Pac/Carb (n = 15)	Pac/Carb (n = 14)
ORR, %	33	47	47	43
SD, %	58	47	27	43
18-month OS rate, %	33	60	40	86
Median OS, weeks	51	83	65	NR



Antonia SJ, et al. CMSTO 2014

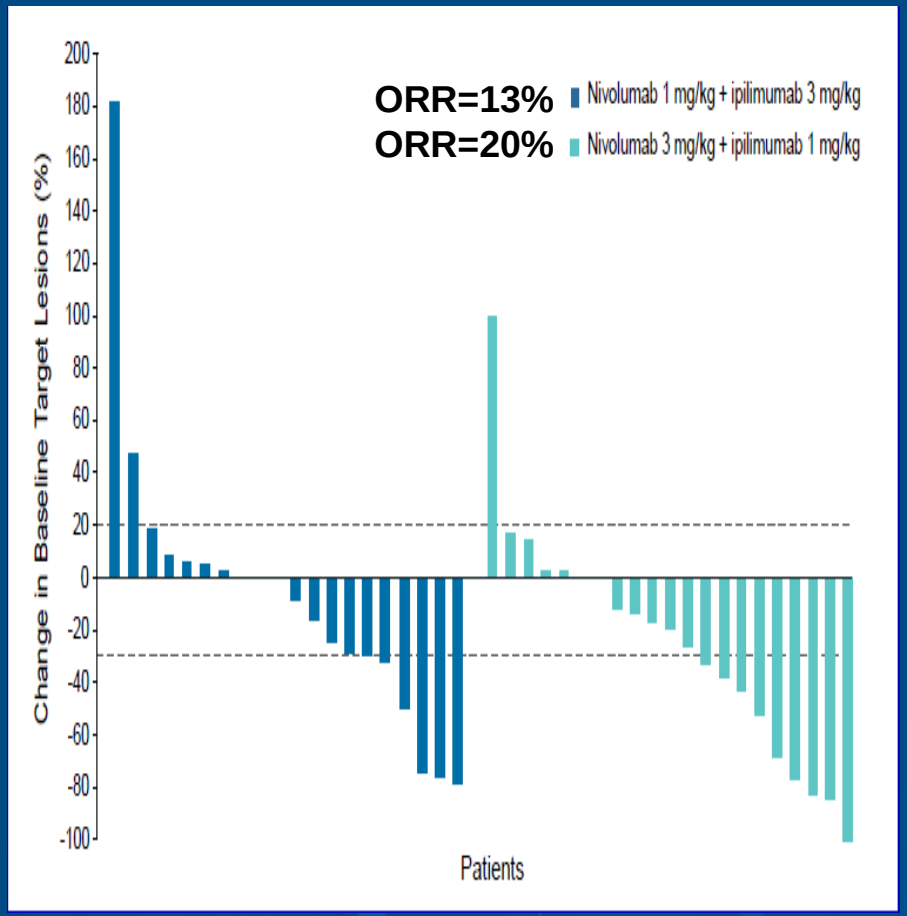
Nivolumab in combination with erlotinib

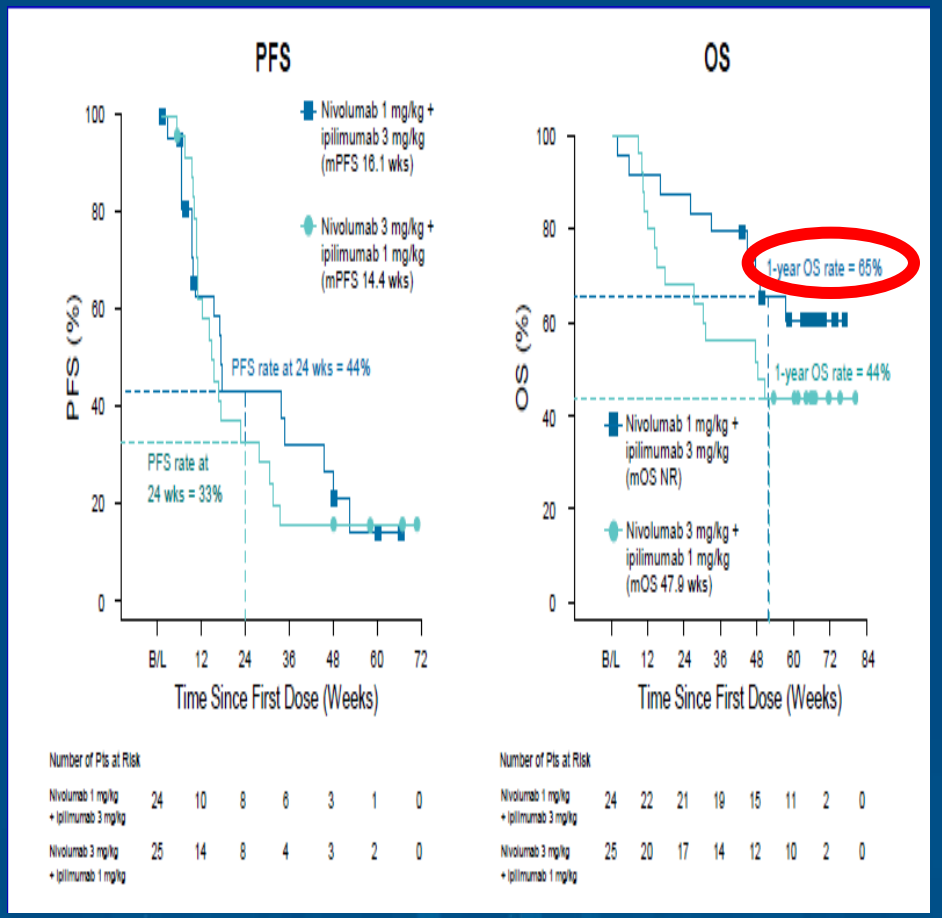
	Prior treatment with erlotinib (n = 20)	No prior treatment with erlotinib (n = 1)
Confirmed ORR, n (%) [95% CI]	4 (19) [5, 42]	
Ongoing responders, n (%)	2 (67)	1 (100)
Best overall response, n (%) PR[a] SD PD	3 (15) 9 (45) 8 (40)[b]	1 (100) 0 0



Gettinger SN, et al. CMSTO 2014

Nivolumab in combination with Ipilimumab





Antonia SJ, et al. CMSTO 2014

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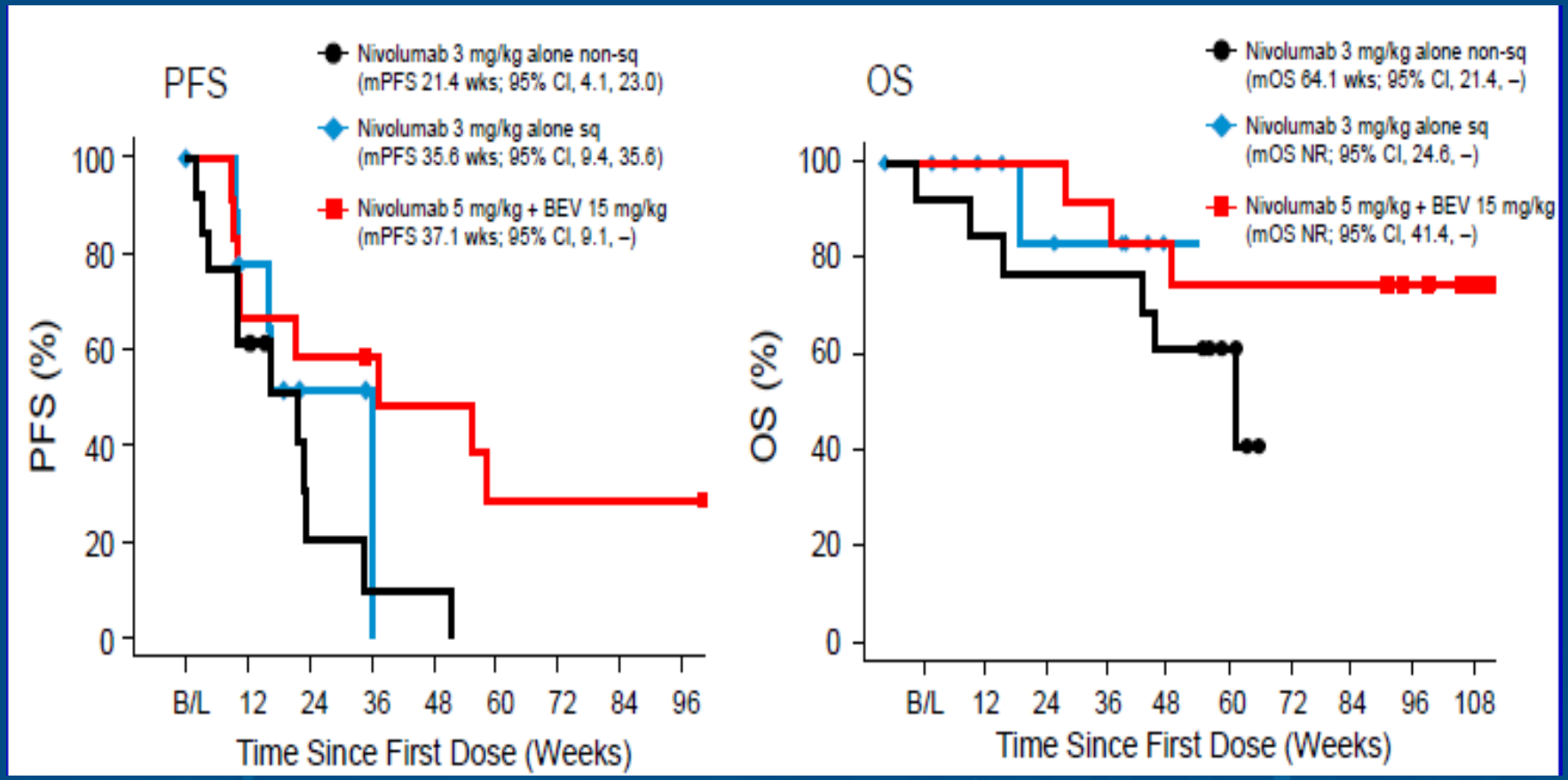
Nivolumab maintenance therapy



Rizvi NA, et al. CMSTO 2014

Overall Study Design

Stratification of Randomization

- Age at randomisation (<65 versus ≥65 years of age)
- Sex (male versus female)
- Smoking status (smoker versus non-smoker).

Patients with unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation
N = 702

2 : 1

Arm 1
MEDI4376
10mg/kg Q2W for up to 12 months

Arm 2
Placebo (matching placebo for infusion Q2W iv for up to 12 months)

OS
PFS using PI assessments according to RECIST 1.1*

Follow-up Period

MEDI4736 will commence treatment on Day 1 and continue on a Q2W schedule for a maximum of 12 months or until PD– IV administration

EORTC Lung Cancer Group-ETOP

(Coordinators: M. O,Brien and L. Paz Ares)

International, blind, randomized phase III trial to compare Pembrolizumab versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (PEARLS)

Primary endpoint:
- DFS (overall and strong PDL-1+ population)

Secondary endpoints:
- OS (overall and strong PDL-1+ population)
- Toxicity profile, QoL

Stratification of randomization

- Stage (IB vs II vs IIIA)
- Adjuvant chemotherapy (no vs yes)
- Institution
- Histology (non-squamous versus squamous)
- PD-L1 (3 groups: 0 (negative) versus 1-49% (weak positive) versus > 50% (strong positive)
- Smoking status (smoker versus non-smoker)

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PD-1 Blockade Toxicity

Treatment-related select AE category	All Grades,[b] % (n)	Grade 3–4, % (n)
Pts with any treatment-related select AE	**41 (53)**	**5 (6)**
Skin	16 (20)	0
Gastrointestinal	12 (15)	1 (1)
Pulmonary	7 (9)[c]	2 (3)
Endocrinopathies	6 (8)	0
Hepatic	5 (6)	1 (1)
Infusion reaction	4 (5)	1 (1)
Renal	3 (4)	0

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Toxicity profile by PD-L1 expression

Treatment-related select AE category	Baseline PD-L1 Expression[a]			
	PD-L1+ (n = 26)		PD-L1− (n = 21)	
	All grades, n (%)	Grade 3–4, n (%)	All grades, n (%)	Grade 3–4, n (%)
Skin	6 (23)	1 (4)	6 (29)	1 (5)
Endocrinopathies	4 (15)	0	1 (5)	0
Gastrointestinal	3 (12)	0	2 (10)	0
Infusion reaction	2 (8)	0	1 (5)	0
Pulmonary	2 (8)	1 (4)	1 (5)	0
Hepatic	1 (4)	1 (4)	0	0
Renal	0	0	0	0

Rizvi NA, et al. CMSTO 2014

Toxicity profile by line of treatment

Treatment-related select AE category	All Grades,[b] % (n)	Grade 3–4, % (n)
Pts with any treatment-related select AE	**41 (53)**	**5 (6)**
Skin	16 (20)	0
Gastrointestinal	12 (15)	1 (1)
Pulmonary	7 (9)[c]	2 (3)
Endocrinopathies	6 (8)	0
Hepatic	5 (6)	1 (1)
Infusion reaction	4 (5)	1 (1)
Renal	3 (4)	0

Pretreated patients

Treatment-related AEs	Nivolumab monotherapy (N = 52)	
	All grades,[a] n (%)	Grade 3–4,[b] n (%)
Pts with any treatment-related AE	33 (64)	8 (15)
Fatigue	13 (25)	0
Rash	10 (19)	2 (4)
Diarrhea	5 (10)	0
Nausea	5 (10)	0
Pruritus	5 (10)	0
Hypothyroidism	3 (6)	0
Pneumonitis	3 (6)	1 (2)

1st line patients

Gettinger SN, et al. CMSTO 2014

Toxicity profile by PD-1 vs PD-L1 blockade

Treatment-related select AE category	All Grades,[b] % (n)	Grade 3–4, % (n)
Pts with any treatment-related select AE	41 (53)	5 (6)
Skin	16 (20)	0
Gastrointestinal	12 (15)	1 (1)
Pulmonary	7 (9)[c]	2 (3)
Endocrinopathies	6 (8)	0
Hepatic	5 (6)	1 (1)
Infusion reaction	4 (5)	1 (1)
Renal	3 (4)	0

Adverse Event	Treatment-Related, n (%) N = 85	
	Any Grade[a]	Grade 3-4
Any AE	56 (66%)	9 (11%)
Fatigue	17 (20%)	2 (2%)
Nausea	12 (14%)	1 (1%)
Decreased appetite	10 (12%)	0
Dyspnea	8 (9%)	1 (1%)
Diarrhea	7 (8%)	0
Asthenia	6 (7%)	0
Headache	6 (7%)	0
Rash	6 (7%)	0
Pyrexia	5 (6%)	0
Vomiting	5 (6%)	1 (1%)
Upper respiratory tract infection	4 (5%)	0

Gettinger SN, et al. CMSTO 2014
Soria JC. ESMO 2013

AEs related with Nivolumab in combination

13% pneumonitis
7% grade 3-4

	Total (N = 56)		
	All Grades	Grade 3	Grade 4
Patients with any treatment-related AE, % (n)	**95 (53)**	**41 (23)**	**4 (2)**
Treatment-related AE, % (n)			
Fatigue	71 (40)	5 (3)	0
Nausea	46 (26)	2 (1)	0
Decreased appetite	36 (20)	2 (1)	0
Alopecia	30 (17)	0	0
Anemia	27 (15)	4 (2)	0
Rash	27 (15)	2 (1)	0
Arthralgia	21 (12)	0	0
Diarrhea	21 (12)	2 (1)	0
Constipation	20 (11)	0	0
Peripheral neuropathy	20 (11)	0	0

Chemotherapy

Treatment-related AE	Nivolumab + erlotinib (N = 21)	
	All Grades, n (%)	Grade 3,[a] n (%)
Pts with any treatment-related AE	21 (100)	5 (24)
Rash	10 (48)	0
Fatigue	6 (29)	0
Paronychia	6 (29)	0
Skin fissures	5 (24)	0
Diarrhea	4 (19)	2 (10)
Dry skin	4 (19)	0
Nausea	4 (19)	0
ALT increased	3 (14)	1 (5)
Alopecia	3 (14)	0
AST increased	3 (14)	2 (10)
Dry mouth	3 (14)	0
Hypothyroidism	3 (14)	0
Nail disorder	3 (14)	0
Pruritus	3 (14)	0
Vomiting	3 (14)	0

Erlotinib

Antonia SJ, et al. CMSTO 2014
Gettinger SN, et al. CMSTO 2014

AEs related with Nivolumab plus Ipilimumab

	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 24)		Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n = 25)		Total (N = 49)	
Treatment related AE, n (%)	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4
Pts with any treatment-related AE	22 (92)	14 (58)	21 (84)	11 (44)	43 (88)	25 (51)
Diarrhea	11 (46)	3 (13)	6 (24)	2 (8)	17 (35)	5 (10)
Colitis	1 (4)	1 (4)	4 (16)	3 (12)	5 (10)	4 (8)
Lipase increased	4 (17)	2 (8)	4 (16)	2 (8)	8 (16)	4 (8)
AST increased	4 (17)	3 (13)	1 (4)	1 (4)	5 (10)	4 (8)
ALT increased	4 (17)	3 (13)	1 (4)	1 (4)	5 (10)	4 (8)
Pneumonitis	4 (17)	2 (8)	2 (8)	1 (4)	6 (12)	3 (6)
Fatigue	13 (54)	2 (8)	11 (44)	1 (4)	24 (49)	3 (6)
Rash	5 (21)	1 (4)	7 (28)	1 (4)	12 (25)	2 (4)
Amylase increased	3 (13)	1 (4)	3 (12)	1 (4)	6 (12)	2 (4)
Adrenal insufficiency	2 (8)	1 (4)	2 (8)	1 (4)	4 (8)	2 (4)
Lymphopenia	1 (4)	1 (4)	1 (4)	1 (4)	2 (4)	2 (4)

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AEs related with Nivolumab plus Ipilimumab

	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 24)		Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n = 25)		Total (N = 49)	
Treatment related AE, n (%)	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4
Pts with any treatment-related AE	22 (92)	14 (58)	21 (84)	11 (44)	43 (88)	25 (51)
Diarrhea					(35)	5 (10)
Colitis					10)	4 (8)
Lipase increased					16)	4 (8)
AST increased					10)	4 (8)
ALT increased					10)	4 (8)
Pneumonitis					12)	3 (6)
Fatigue	13 (54)	2 (8)	11 (44)	1 (4)	24 (49)	3 (6)
Rash	5 (21)	1 (4)	7 (28)	1 (4)	12 (25)	2 (4)
Amylase increased	3 (13)	1 (4)	3 (12)	1 (4)	6 (12)	2 (4)
Adrenal insufficiency	2 (8)	1 (4)	2 (8)	1 (4)	4 (8)	2 (4)
Lymphopenia	1 (4)	1 (4)	1 (4)	1 (4)	2 (4)	2 (4)

32-50% Grade 3-4
37% discontinuation rate
Tolerable??

Antonia SJ, et al. CMSTO 2014

Background

1.- Introduction

2.- PD-1/PD-L1 blockade

- 2.1.- Efficacy overview
- 2.2.- Toxicity profile

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4.- Conclusions

Histology is not Predictive for Response

	Squamous Carcinoma	Non SCC
Nivolumab (PD-1)	**16.7%** (9/54)	**17.6%** (13/74)
Nivolumab + platinum doublet chemotherapy	**~33%** (4/12)	**~47%** (7/15)
BMS-936559 (PD-L1)	**8%** (1/13)	**11%** (4/36)
MPDL3280A (PD-L1)	**33%** (3/9)	**19%** (6/31)
Pembrolizumab	**18%** (2/6)	**23%** (4/26)

Garon E, ESMO 2014; Brahmer J, ASCO 2014; Gettinger ASCO 2014; Soria JC, ESMO 2014

Anti PD1/PD-L1 Inhibitors: ORR by PD-L1 Status

	Anti PD1		Anti PD-L 1	
	MK-3475	Nivolumab	MEDI4736	MPDL3280A
All, N	236	129	58	53
RR	21%	17%	16%	23%
PD-L1 +	201 23%	33 15%	20 25%	26 31%
PD-L1 -	35 9%	35 14%	29 3%	20 20%

Garon E, ESMO 2014; Brahmer J, ASCO 2014;
Gettinger ASCO 2014; Soria JC, ESMO 2014

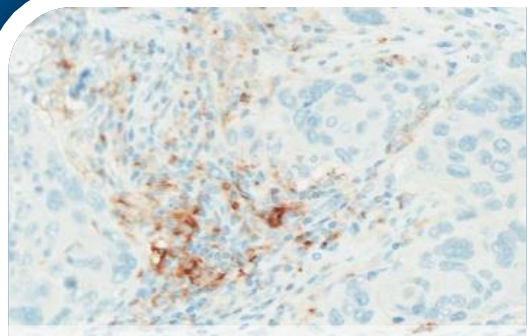
PD-L1 expression: analysis challenges

Agent	Assay	Analysis	Definition of positivity	PD-L1 expression
Nivolumab (anti-PD-1) [1–4]	Dako automated IHC assay (28-8 rabbit Ab) Analytically validated	• Archival FFPE	• 1% and 5% cut-off among >100 evaluable tumour cells	• 56%: 1% cut-off • 49%: 5% cut-off
Pembrolizumab (anti-PD-1)[5,6]	Dako automated IHC assay (22C3 mouse Ab)	• Archival FFPE	• Tumour dependent: - Melanoma > 1% - NSCLC PD-L1 (+): Strong (≥50%) and weak staining (1–49%) PD-L1 (–): no staining	• ~25%: ≥50% staining • ~45–70%: ≥1% staining
MPDL3280A (anti-PD-L1)[7,8]	Ventana automated clinical research IHC assay	• Archival FFPE	• PD-L1 (+): IHC 3 (≥10%), IHC 2,3 (≥5%), IHC 1,2,3 (≥1%) • PD-L1 (–): IHC 1, 0 or unknown	• 11%: IHC 3 • 75%: IHC 1, 0
MEDI-4736 (anti-PD-L1)[9]	First-generation or Ventana IHC Automated Assay lopment)	• Archival FFPE	• Not reported	• Not reported

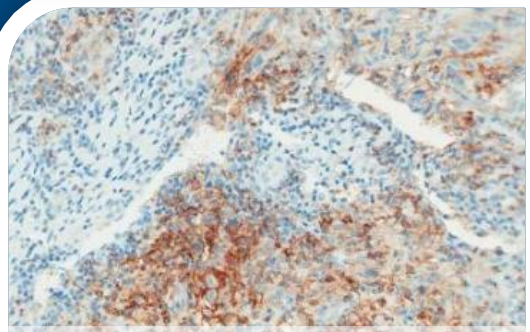
PD-L1 is broadly expressed tumour cells and tumour-infiltrating immune cells

PD-L1 prevalence[1–3]

Tumour type	Phase I study	
	Immune cell*	Tumour cell‡
NSCLC	26%	24%
RCC	25%	10%
Melanoma	36%	5%
Bladder	27%	11%
HNSCC	28%	19%
Gastric cancer	18%	5%
CRC	35%	1%
Pancreatic cancer	12%	4%



PD-L1+ immune cells (NSCLC)[1]

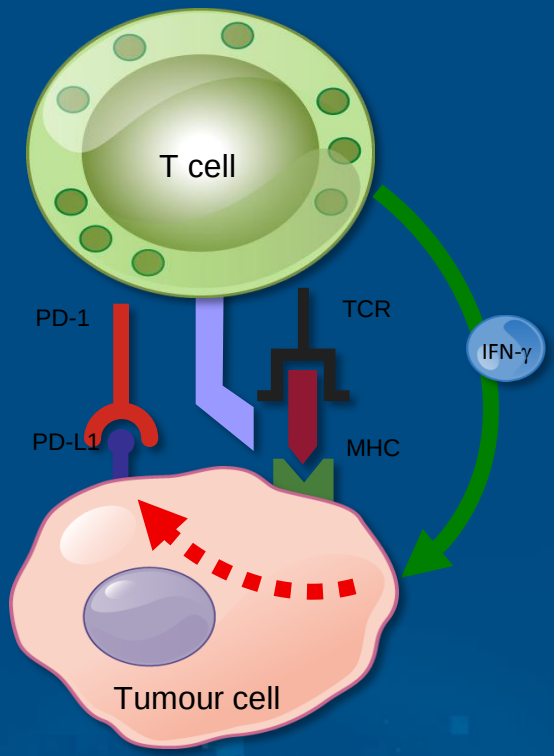


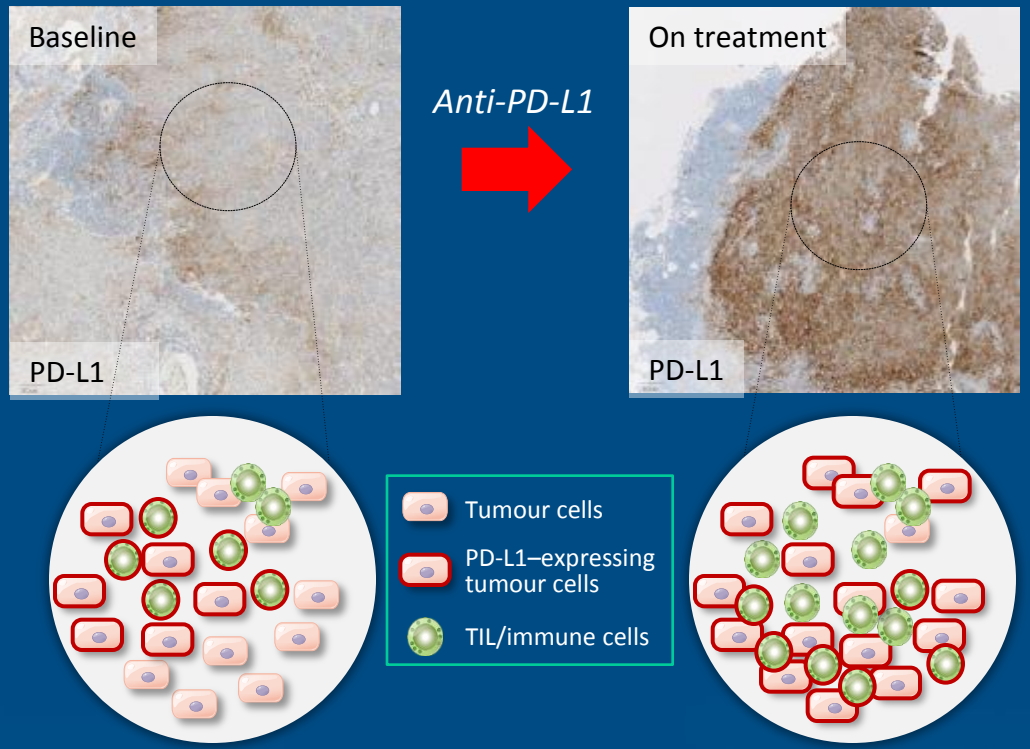
PD-L1+ tumour cells (melanoma)[1]

1. Kohrt, et al. SITC 2013; 2. Herbst, et al. ASCO 2014; 3. Powles, et al. ASCO 2014

Adaptive immune resistance: increased tumour PD-L1 expression

Adaptive immune resistance

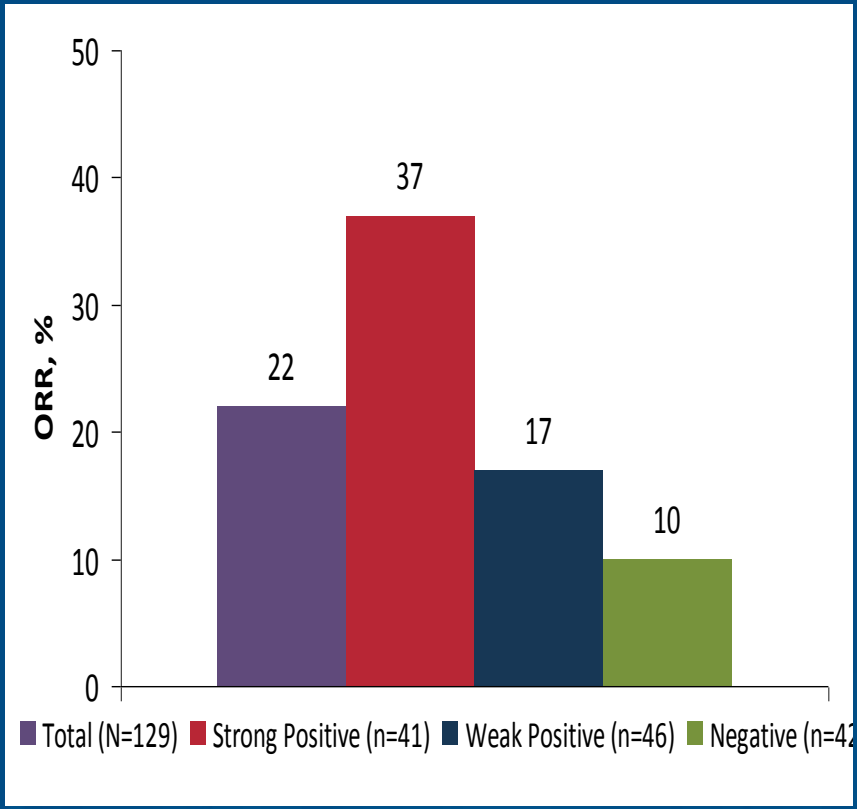




Adaptive increase of PD-L1 expression in tumour cells may actually be an indicator of local tumour-infiltrating lymphocytes attacking the tumour

Merelli, et al. Crit Rev Oncol Hematol 2014; Gerlinger, et al. N Engl J Med 2012

Maximum benefit by high PD-L1 IHC expression

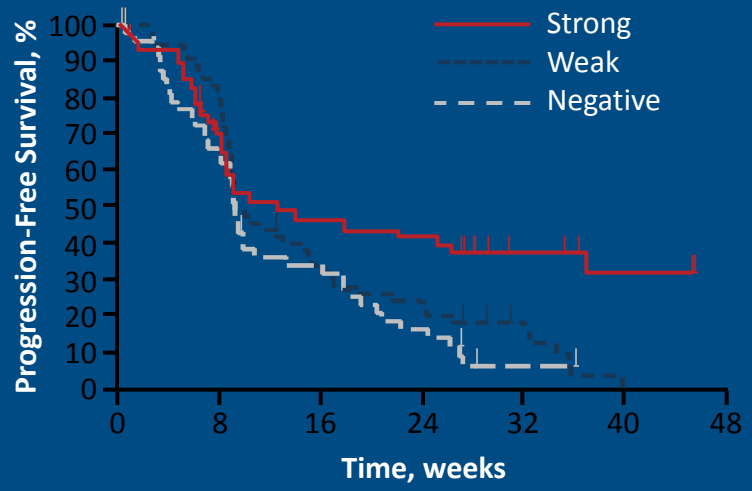


Diagnostic Population[a] (n = 53)	ORR[b] % (n/n)	PD Rate % (n/n)
IHC 3	83% (5/6)	17% (1/6)
IHC 2 and 3	46% (6/13)	23% (3/13)
IHC 1/2/3	31% (8/26)	38% (10/26)
All Patients[c]	23% (12/53)	40% (21/53)

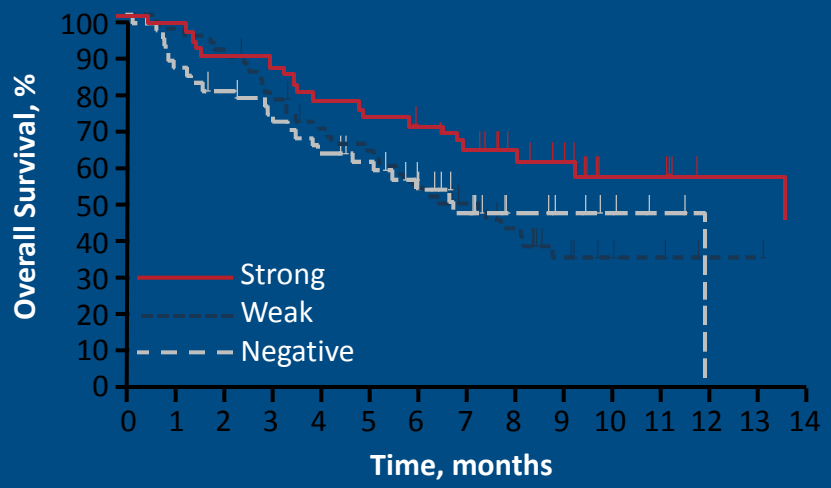
Garon EB, et al. ESMO 2014
Soria JC. ECCO 2013

Maximum benefit by high PD-L1 IHC expression

PFS (RECIST v1.1, Central Review)



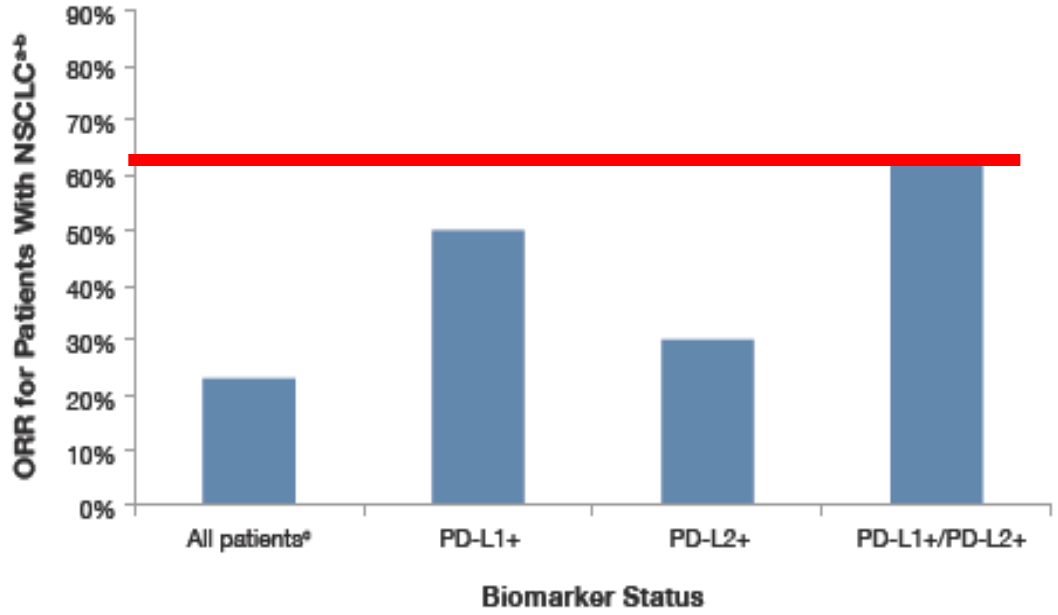
OS



- **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

MPDL3280A Activity According to PDL-2 Expression



[a] MPDL3280A was administered to patients by October 1, 2012, at ≥ 1 mg/kg; data cutoff was April 30, 2013.
[b] Includes investigator-assessed responses per RECIST v1.1, including 1 unconfirmed response.
[c] All patients include PD-L2–positive patients, PD-L2–negative patients and patients with unknown tumor PD-L2 status (n = 46).

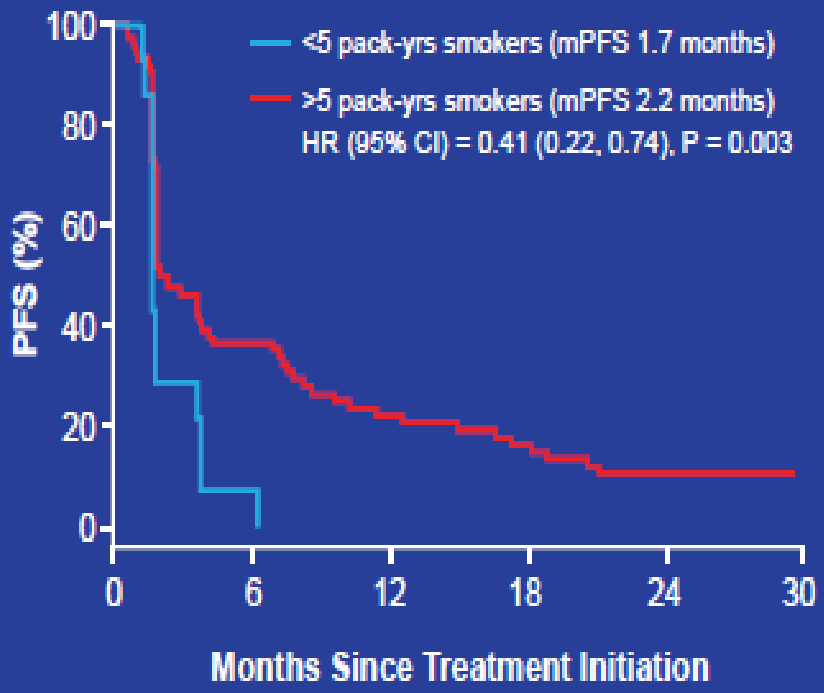
Soria JC, et al. ESMO 2014

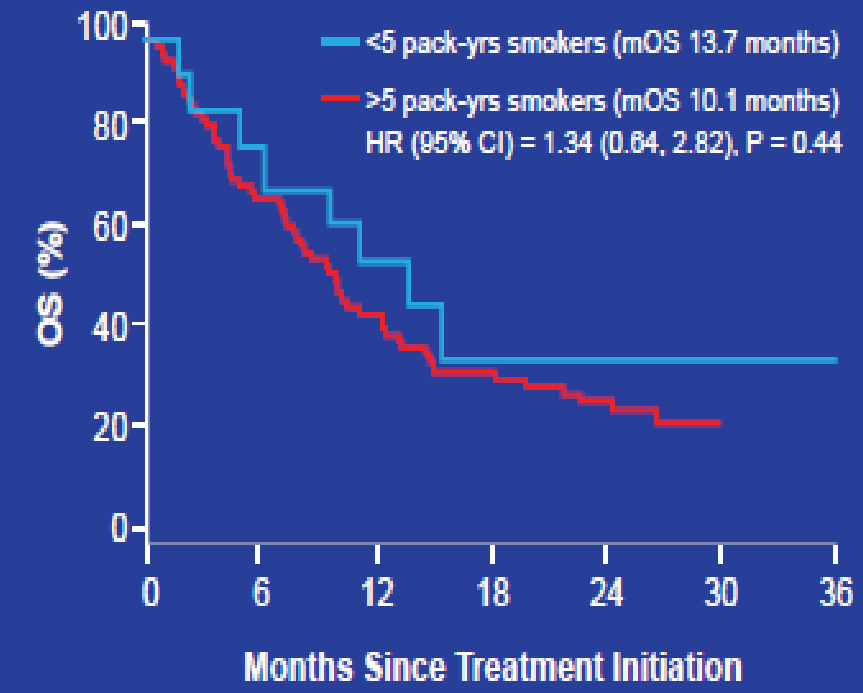
Anti PD1/PD-L1 Inhibitors: ORR by Smoking Status

	Anti PD1		Anti PD-L 1	
	MK-3475	Nivolumab	MEDI4736	MPDL3280A
All, N	236	129	58	53
RR	21%	17%	16%	23%
Smokers	165 27%	75 20%	?	43 26%
Never/min smokers	65 9%	13 0%	?	10 10%

Garon E, ESMO 2014; Hellman M ESMO 2014; Soria JC, ESMO

Nivolumab: PFS/OS by smoking status





Hellman MD, et al. ESMO 2014

Smoking influence by time exposure and therapy

Variable	ORR, % (n/N) [95% CI][a]
Smoking exposure	
>5 pack-years	30 (20/66) [20, 43]
≤5 pack-years[b]	0 (0/14) [0, 23]
Time since quitting	
>15 yrs prior	26 (6/23) [10, 48]
6–15 yrs prior	17 (2/12) [2, 48]
1–5 yrs prior	46 (6/13) [19, 75]
Current smoker	27 (6/22) [11, 50]
0/never smoker	0 (0/10) [0, 31]

	Total (N = 52)				
	N	ORR, n (%)	SD, n (%)	DCR,[b] n (%)	SD ≥21 wks, n (%)
Smoking status					
Current	3	1 (33)	1 (33)	2 (67)	1 (33)
Former	38	9 (24)	10 (26)	19 (50)	6 (16)
Never	11	1 (9)	3 (27)	4 (36)	3 (27)
Smoking exposure,[c] pack-yrs					
>5	27	5 (19)	8 (30)	13 (48)	5 (19)
≤5	14	1 (7)	4 (29)	5 (36)	3 (21)
Time since quitting,[d] yrs					
>15	27	4 (15)	9 (33)	13 (48)	8 (30)
≤15	24	6 (25)	5 (21)	11 (46)	2 (8)

Gettinger SN, et al. CMSTO 2014
Rizvi NA, et al. CMSTO 2014

Anti PD1/PD-L1 Inhibitors: ORR by mutation profile

EGFR status	
Mutant	17 (2/12) [2, 48]
Wild-type	20 (11/56) [10, 32]
KRAS status	
Mutant	14 (3/21) [3, 36]
Wild-type	25 (9/36) [12, 42]

Gettinger SN, et al. CMSTO 2014

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Conclusions

1) The aim of cancer immunotherapy is to benefit patients exploiting cancer antigenicity and overcoming immune tolerance mechanisms

2) Cancer immunotherapy with anti-PD-L1/PD-1 therapies represent a highly promising approach in NSCLC

* durable responses and preliminary survival benefit are observed
* these therapies are generally well tolerated

3) Biomarkers allow for tailored therapy, however, identifying clinically relevant biomarkers for cancer immunotherapy is challenging

4) Understanding the molecular evolution and heterogeneity of tumours may lead to more effective use of new and existing therapies

* combination strategies p.e. anti-PD-L1/PD-1 therapies