Immunotherapy in Non-Small Cell Lung Cancer

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Philadelphia, Pa.

Financial Disclosures

- I do not currently have any relevant financial relationships to disclose

Off-Label Use Disclosures

- I plan to discuss the following off-label uses of products during this activity:
  - pembrolizumab for treatment of NSCLC
  - nivolumab for treatment of non-squamous cell carcinoma

NSCLC in 2015

- Five groups of patient have a much better prognosis of advanced NSCLC:

1. Activating EGFR mutation
2. ALK translocation
3. ROS-1 translocation
4. Prolonged disease control on maintenance pemetrexed (almost ¼ patients who start maintenance pemetrexed will get more than 10 cycles)
5. Prolonged response to immunotherapy

Case

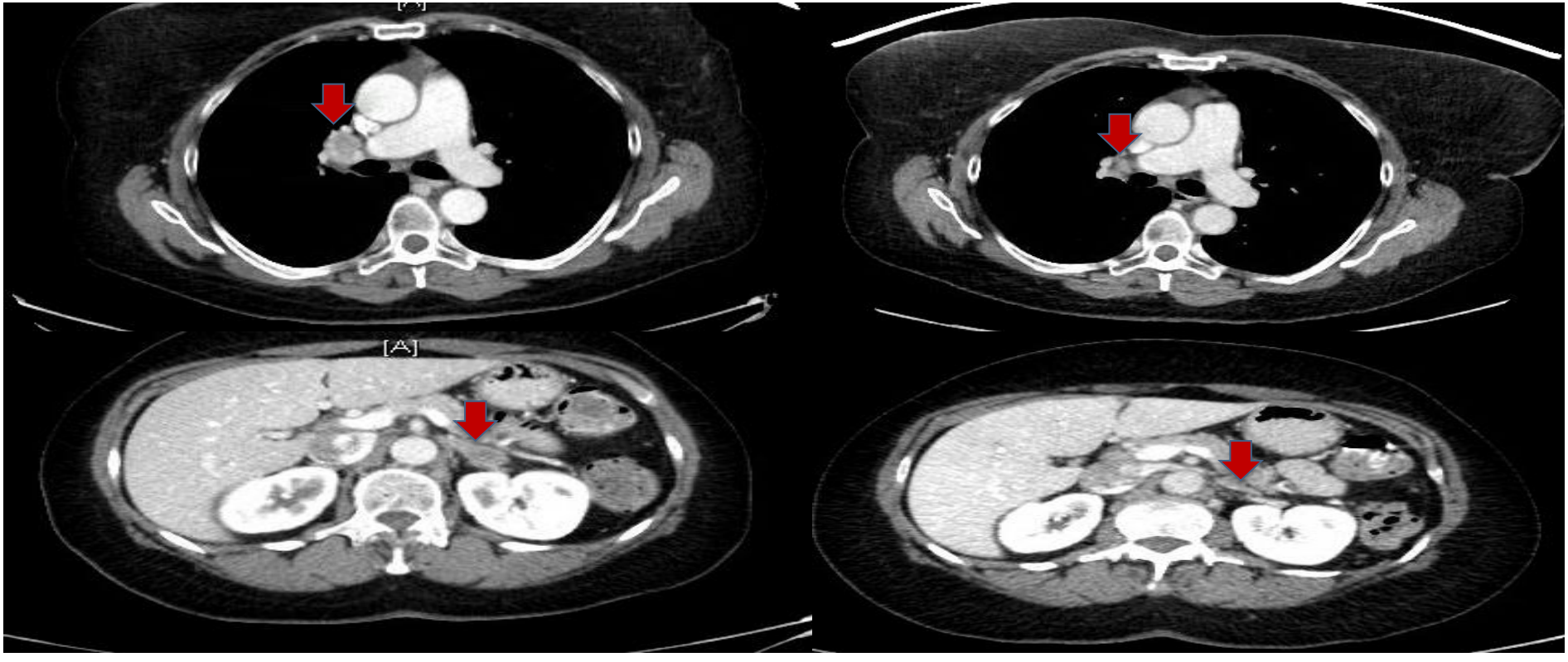
- 55yo presented outside of our system with stage IV (cervical LN)
- Smoker up to her diagnosis of 20pack/year
- Pathology: Poorly differentiated NSCLC CK7 and p63 (+) TTF-1 (-) (3-25-2011)
- Treated with combination of docetaxel+cisplatin+XRT (70Gy)

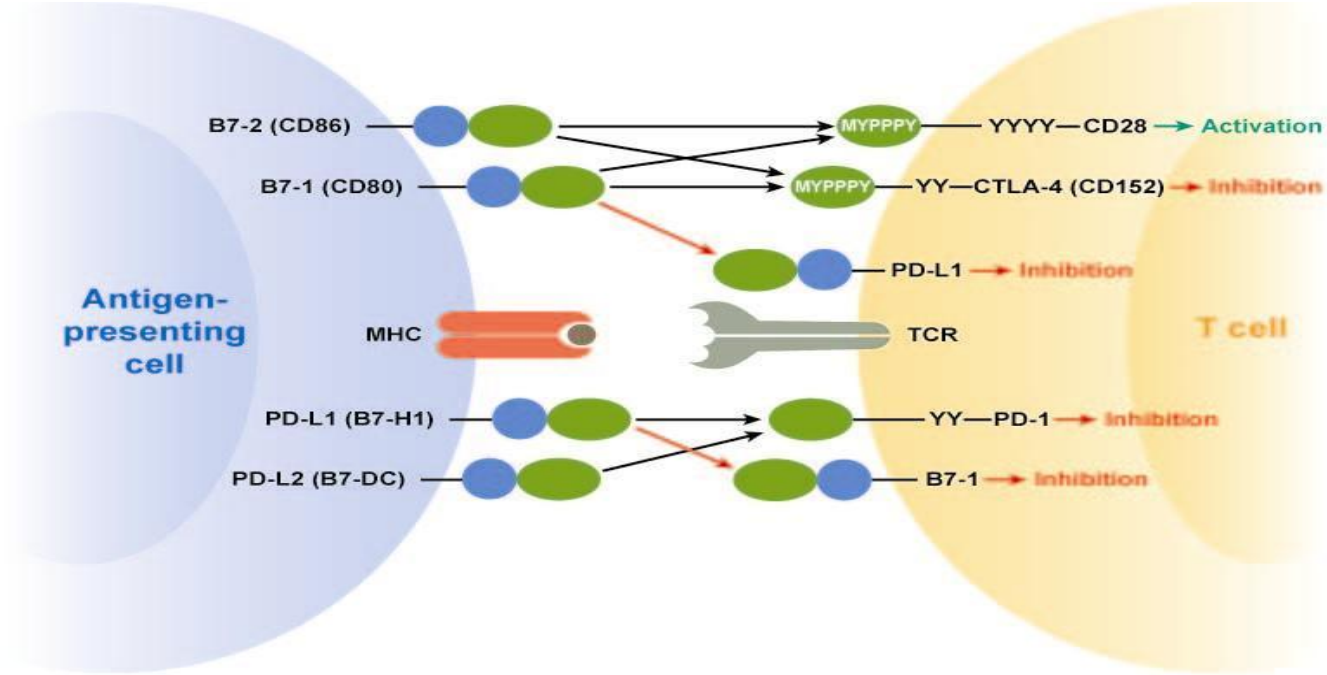
Case

- Trial of a vaccine for 6 months until she had evidence progression
- Performance status 1
- Enrolled on a phase I clinical trial of an anti-PD-L1 antibody
- First dose 3-20-2012

2-29-2012

4-29-2015





Keir ME, et al. 2008.
Annu. Rev. Immunol. 26:677–704

Original Article

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

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Table 2. Clinical Activity of Anti–PD-L1 Antibody in the Efficacy Population.*

Tumor Type and Dose	No. of Patients	Objective Response†		Duration of Response‡	Stable Disease ≥24 Weeks		Rate of Progression-free Survival at 24 Weeks§
		no. of patients	*% (95% CI)*	*mo*	*no. of patients*	*% (95% CI)*	*% (95% CI)*
Melanoma							
0.3 mg/kg	1	0	0 (0–98)	NA	0	0 (0–98)	NA
1 mg/kg	18	1	6 (0–27)	6.9	6	33 (13–59)	39 (16–61)
3 mg/kg	17	5¶	29 (10–56)	23.5+, 22.9+, 16.2+, 4.1+, 3.5	3	18 (4–43)	47 (21–72)
10 mg/kg	16	3‖	19 (4–46)	20.8+, 16.6, 2.8	5	31 (11–59)	44 (19–68)
All doses	52	9	17 (8–30)		14	27 (16–41)	42 (28–56)
Non–small-cell lung cancer							
All patients, 1 mg/kg	11	0	0 (0–29)	NA	0	0 (0–29)	NA
All patients, 3 mg/kg	13	1	8 (0–36)	2.3+	1	8 (0–36)	34 (7–60)
Squamous subtype	4	0	0 (0–60)	NA	1	25 (0–81)	50 (1–99)
Nonsquamous subtype	9	1	11 (0–48)	ND	0	0 (0–34)	25 (0–55)
All patients, 10 mg/kg	25	4	16 (5–36)	16.6+, 12.6+, 9.8, 3.5	5	20 (7–41)	46 (25–67)
Squamous subtype	8	1	13 (0–53)	ND	2	25 (3–65)	47 (10–83)
Nonsquamous subtype	17	3	18 (4–43)	ND	3	18 (4–43)	46 (20–72)
All patients, all doses	49	5	10 (3–22)		6	12 (5–25)	31 (17–45)
Squamous subtype	13	1	8 (0–36)	ND	3	23 (5–54)	43 (15–71)
Nonsquamous subtype	36	4	11 (3–26)	ND	3	8 (2–23)	26 (10–42)
Ovarian cancer	1	0	0 (0–98)	NA	0	0 (0–98)	NA
3 mg/kg	1	0	0 (0–98)	NA	0	0 (0–98)	NA
10 mg/kg	16	1	6 (0–30)	1.3+	3	19 (4–46)	25 (4–46)
All doses	17	1	6 (0–29)		3	18 (4–43)	22 (2–43)
Renal-cell cancer, 10 mg/kg	17	2	12 (2–36)	17, 4	7	41 (18–67)	53 (29–77)

* The efficacy population included 160 patients in whom a response could be evaluated and who initiated treatment by August 1, 2011. These patients had measurable disease at a baseline tumor assessment and at least one of the following: an assessment of tumor burden during the study, clinical progression, or death. NA denotes not applicable, and ND not determined.
† Objective response rates (including both complete response and partial response) are based on confirmed responses only, with 95% confidence intervals calculated with the use of the Clopper–Pearson method.
‡ The duration of response is the time from the first response to the time of documented disease progression, death, censoring of data (denoted by a plus sign), or last tumor assessment.
§ The rate of progression-free survival was the proportion of patients who did not have disease progression and were alive at 24 weeks, as calculated by the Kaplan–Meier method. The Greenwood method was used to calculate confidence intervals.
¶ Two of these patients had a complete response.
‖ One of these patients had a complete response.

Brahmer JR et al. N Engl J Med 2012;366:2455-2465

Table 1. Adverse Events of Special Interest in 207 Patients Receiving Anti–PD-L1 Antibody.*

Event	Anti–PD-L1, 0.3 mg/kg (N=3)		Anti–PD-L1, 1 mg/kg (N=37)		Anti–PD-L1, 3 mg/kg (N=42)		Anti–PD-L1, 10 mg/kg (N=125)		Anti–PD-L1, Total (N=207)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	number of patients (percent)									
Any adverse event of special interest†	1 (33)	0	18 (49)	2 (5)	14 (33)	2 (5)	48 (38)	6 (5)	81 (39)	10 (5)
Skin or subcutaneous disorder										
Any rash	0	0	5 (14)	0	1 (2)	0	8 (6)	0	14 (7)	0
Pruritus	0	0	6 (16)	0	3 (7)	0	3 (2)	0	12 (6)	0
Vitiligo	0	0	3 (8)	0	1 (2)	0	1 (1)	0	5 (2)	0
Pruritic rash	0	0	1 (3)	0	1 (2)	0	2 (2)	0	4 (2)	0
Macular rash	0	0	2 (5)	0	1 (2)	0	0	0	3 (1)	0
Erythema	0	0	2 (5)	0	0	0	0	0	2 (1)	0
Erythematous rash	0	0	0	0	1 (2)	0	1 (1)	0	2 (1)	0
Gastrointestinal disorder										
Diarrhea	1 (33)	0	4 (11)	0	6 (14)	0	8 (6)	0	19 (9)	0
Procedural complication										
Infusion-related reaction	0	0	0	0	2 (5)	0	19 (15)	1 (1)	21 (10)	1 (<1)
Endocrine disorder										
Hypothyroidism	0	0	0	0	1 (2)	0	5 (4)	0	6 (3)	0
Adrenal insufficiency	0	0	0	0	1 (2)	1 (2)	1 (1)	0	2 (1)	1 (<1)
Autoimmune thyroiditis	0	0	2 (5)	0	0	0	0	0	2 (1)	0
Eye disorder										
Dry eye	0	0	0	0	2 (5)	0	0	0	2 (1)	0
Immune-system disorder										
Hypersensitivity	0	0	1 (3)	0	0	0	2 (2)	0	3 (1)	0
Laboratory investigation										
Increased alanine aminotransferase	0	0	1 (3)	0	0	0	1 (1)	0	2 (1)	0

* Listed events were reported in at least 1% of the patients. The following events that were categorized as adverse events of special interest occurred in one patient each: sarcoidosis, diabetes mellitus, and myasthenia gravis (in patients receiving the 10-mg dose) and endophthalmitis (in patients receiving the 3-mg dose).

† The numbers reported within a column may not add up to the total number reported because patients who had more than one adverse event were counted for each event but were counted only once for "any adverse events of special interest."

Brahmer JR et al. N Engl J Med 2012;366:2455-2465

Toxicity: Case

- 70 yo male with adenocarcinoma of lung with L858R diagnosed 8/210. No history of diabetes
- Prior therapies : dacomitinib; carboplatin+pemetrexed→pem maintenance; weekly paclitaxel
- Started on PD-L1 antibody on 10/2013
- 15 weeks latter presented with glucose of 512mg/dl
- Started on metformin and 10 days latter presented with diabetic ketoacidosis

Diabetes Care 2015 Sep;38(9):e137-8. doi: 10.2337/dc15-0889. Epub 2015 Jun 26

Table 1—Patients' characteristics at the time of presentation with DKA

	Patient 1	Patient 2
BMI, kg/m^2	23.2	15.1
Plasma glucose, mmol/L	22.83	41.77
Anion gap (3–11)	18	22
Bicarbonate (22–32 mEq/L)	15	7
Arterial pH	Unavailable	7.09
A1C [4–6% (20–42 mmol/mol)]	9.8 (84)	9.4 (79)
Thyroid-stimulating hormone (0.4–5.0 μIU/mL)	0.944	34.19
Total triiodothyronine (73–178 ng/dL)	126	26
Free triiodothyronine (2.3–3.9 pg/mL)	—	1.7
Total thyroxine (4.8–10.8 μg/dL)	13.2	—
Free thyroxine (0.6–1.2 ng/dL)	—	0.3
Thyroid peroxidase antibody (0.0–8.9 IU/mL)	—	83.3
C-peptide (1.0–7.1 ng/mL)	0.3	<0.1
GAD65 antibody	0 (≤0.02 nmol/L)*	465 (<142 WHO units)
Insulin autoantibody	0 (0.0–0.02 nmol/L)*	0.02 (<0.05 index)
IA2 autoantibody	—	11 (<21 WHO units)
ZnT8 autoantibody	—	0.00 (<0.033 index)
IA2β/phogrin	—	0.001 (<0.0015 index)
HLA+	—	DR3-DQ2/DR4-DQ8
Islet-specific T cell^	—	7 positive protein bands

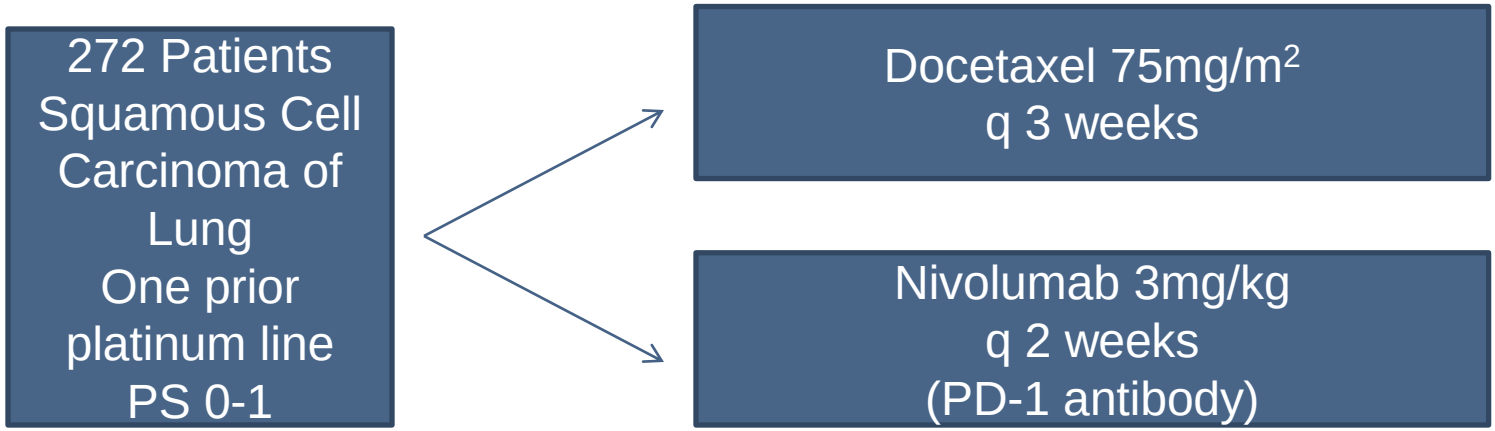
Normal ranges given in parentheses where appropriate. WHO, World Health Organization. *Measured only at the clinical laboratory. +Genotyping at the HLA class II locus (IDDM1) was performed using the direct sequencing of separately amplified exons 2 of DRB1, DQA1, and DQB1. ^Cellular immunoblotting was performed on blood mononuclear cells to test for the presence of islet-specific T cells, as described previously (5). Control subjects without diabetes respond to 0–3 blots, whereas patients with autoimmune diabetes respond to 4–18 blots (5).

Diabetes Care 2015 Sep;38(9):e137-8. doi: 10.2337/dc15-0889. Epub 2015 Jun 26

Safety
CheckMate-063

- Phase II single arm trial
- At least 2 lines of prior therapy including platinum based
- 117 patients included
- RR:15% with 59% of those lasting for 6 months or longer
- Serious adverse events: 59%
- Most common SAEs: dyspnea; pneumonia; COPD exacerbation; pneumonitis; hypercalcemia; pleural effusion; hemoptysis; and pain
- Treatment was discontinued in 27% of patient because of adverse events

CheckMate-017



PD-L1 status not used for inclusion
Primary endpoint: Overall Survival

Brahmer J et al Published on line on May 31, 2015

Results

- Former/current smoker: 92%
- No CNS metastases: 94%
- ORR: 20% (N) and 9% (D)
- Median follow-up: 11 months
- Median duration of response of nivolumab: not reached
- PFS at 1 year: 21% (N) and 6% (D)

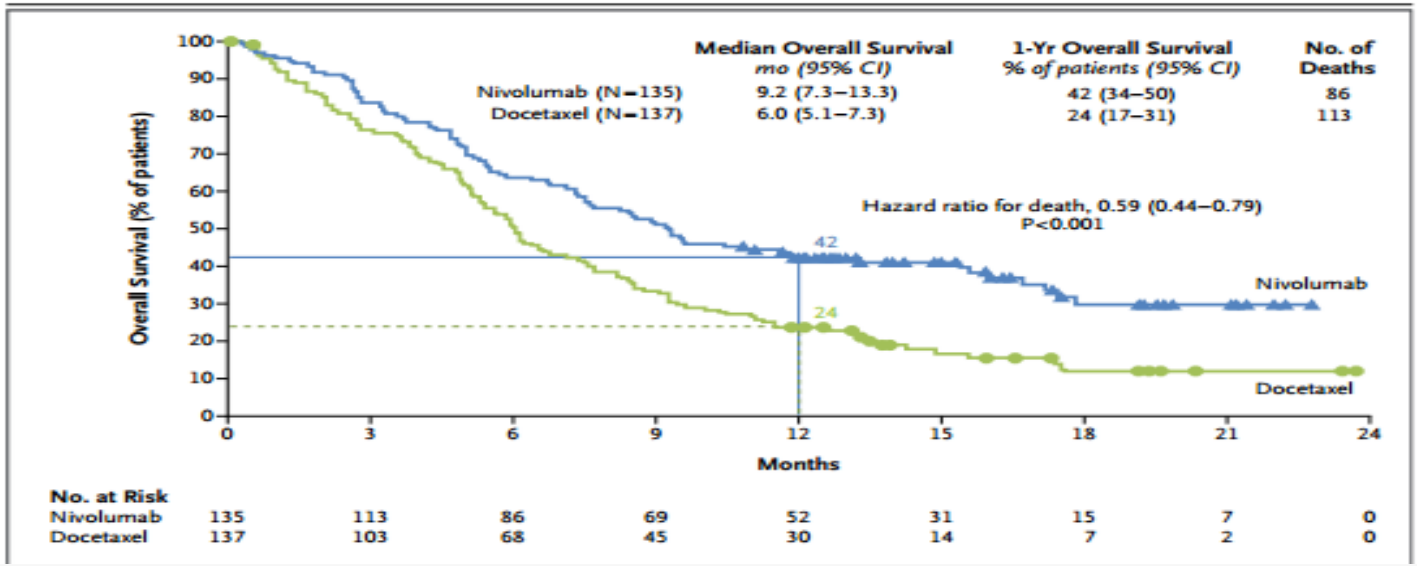
Safety

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

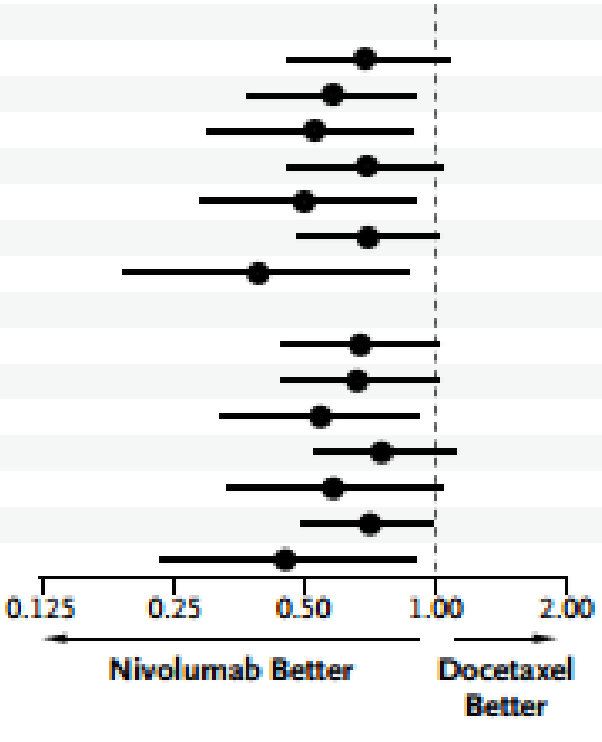
Results

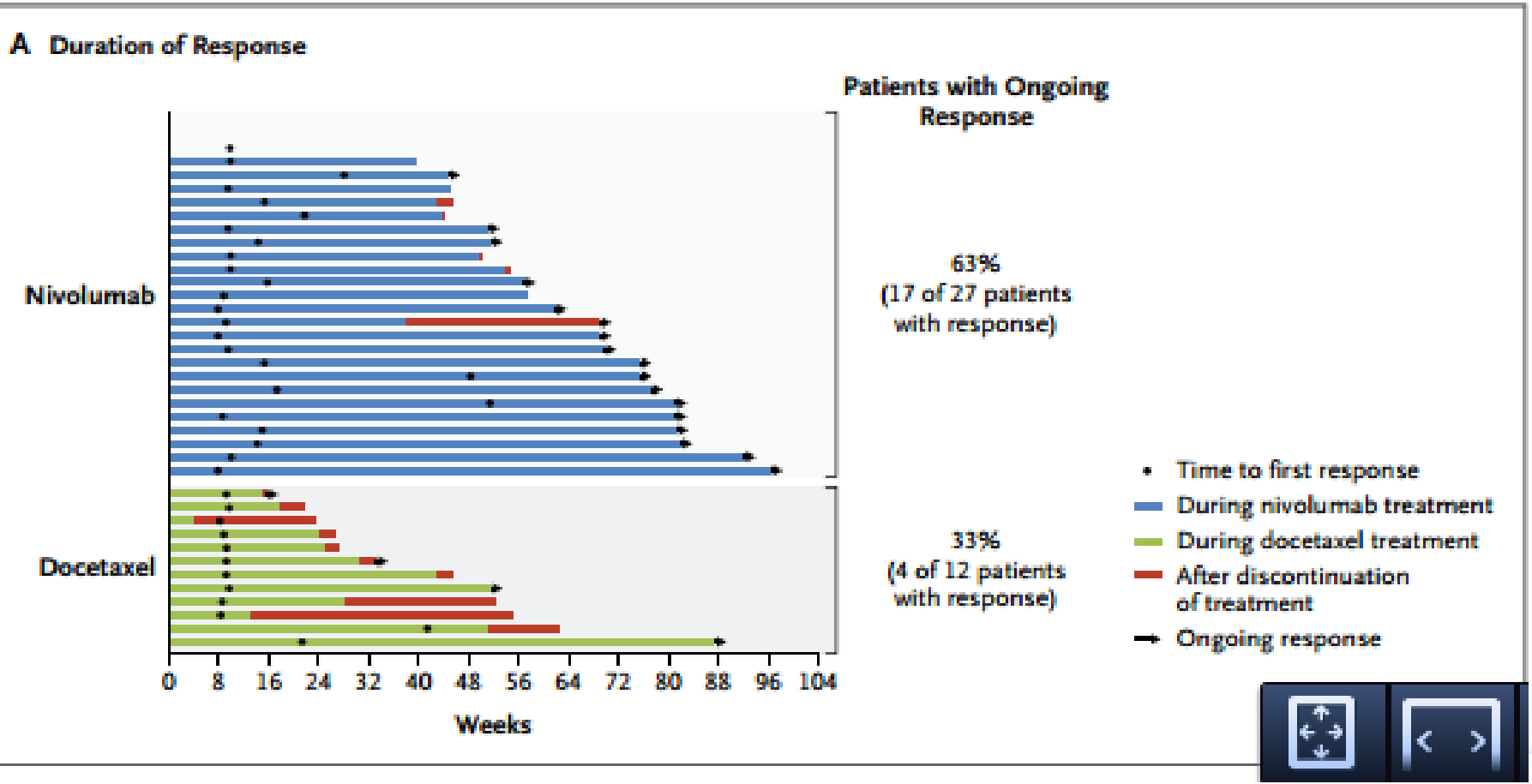
- Median survival improvement: 3.2 months (9.2 months vs 6 months)



C Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)
Progression-free survival			
≥1%	63	56	0.67 (0.44–1.01)
<1%	54	52	0.66 (0.43–1.00)
≥5%	42	39	0.54 (0.32–0.90)
<5%	75	69	0.75 (0.52–1.08)
≥10%	36	33	0.58 (0.33–1.02)
<10%	81	75	0.70 (0.49–0.99)
Not quantifiable at baseline	18	29	0.45 (0.23–0.89)




A Duration of Response
Patients with Ongoing Response
Nivolumab
Docetaxel
63%
(17 of 27 patients with response)
33%
(4 of 12 patients with response)
0 8 16 24 32 40 48 56 64 72 80 88 96 104
Weeks
Time to first response
During nivolumab treatment
During docetaxel treatment
After discontinuation of treatment
Ongoing response

CheckMate 057

- Randomized phase III of nivolumab vs docetaxel in previously treated advanced “non-squamous” NSCLC
- One prior platinum doublet (maintenance allowed)
- No PD-L1 expression required but tissue submission was a requirement
- Nivolumab 3mg/kg Q2weeks vs docetaxel 75mg/m^2 Q3weeks
- Primary endpoint: Overall survival

Results

- Interim analysis with 93% of the events of the final analysis declared the superiority of nivolumab
- PD-L1 expression:

	Nivolumab	Docetaxel
≥1%	53%	55%
≥5%	41%	38%
≥10%	37%	35%

- 22% did not have enough tissue for evaluation

Results

- Median survival:

12.2 months Nivolumab

9.4 months Docetaxel p=0.0015; HR 0.73

- 1 year survival:

51% Nivolumab

39% Docetaxel

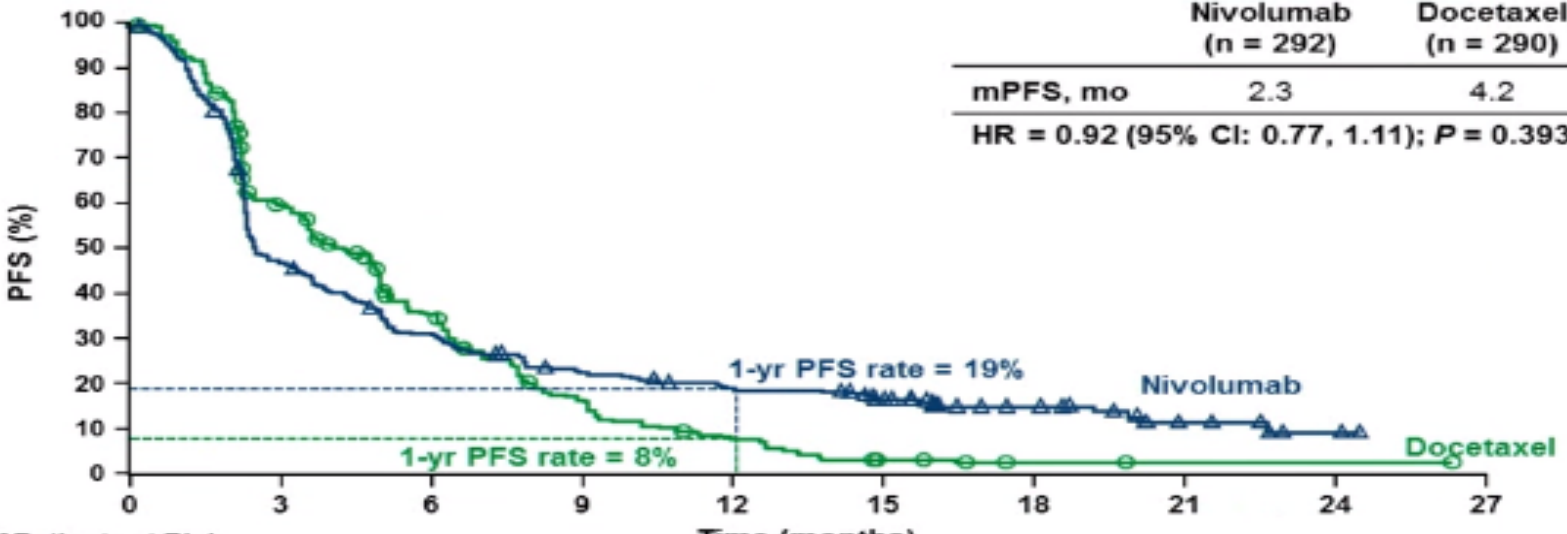
- Two subsets did not benefit in the subgroup analysis: EGFR mut (+) and never smokers
- ORR: 19% (N) and 12% (D) p=0.02
- Median duration of response:

17.2 months (N) and 5.6 months (D)

Progression-free Survival

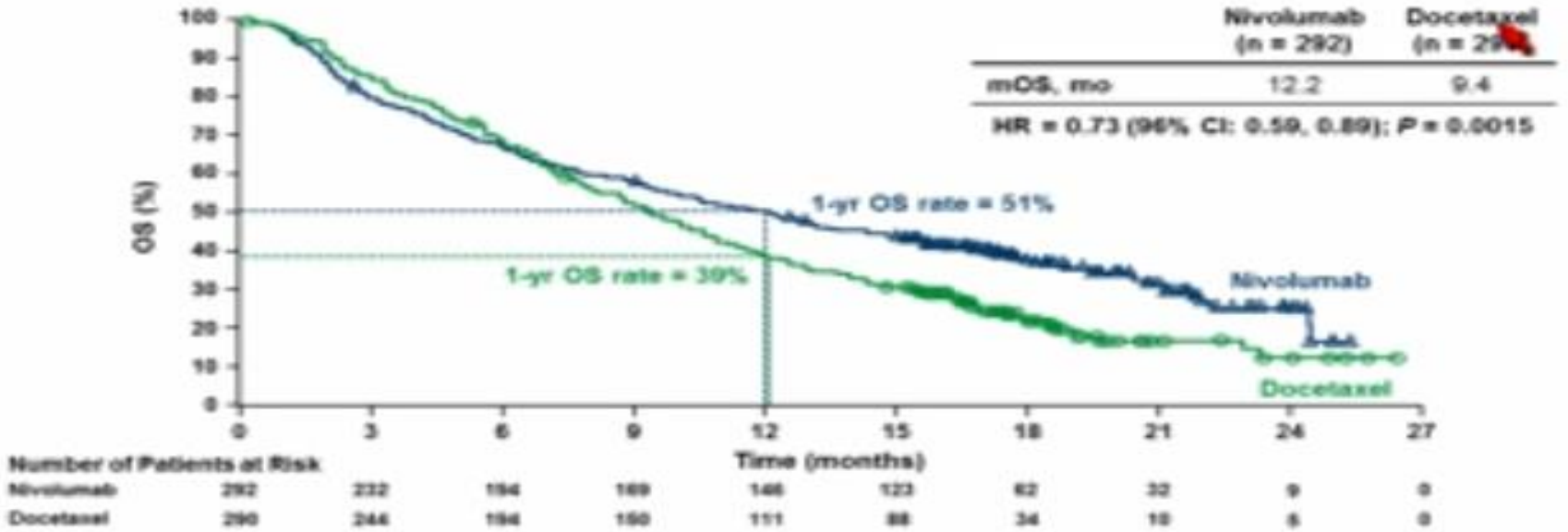
	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2

HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932

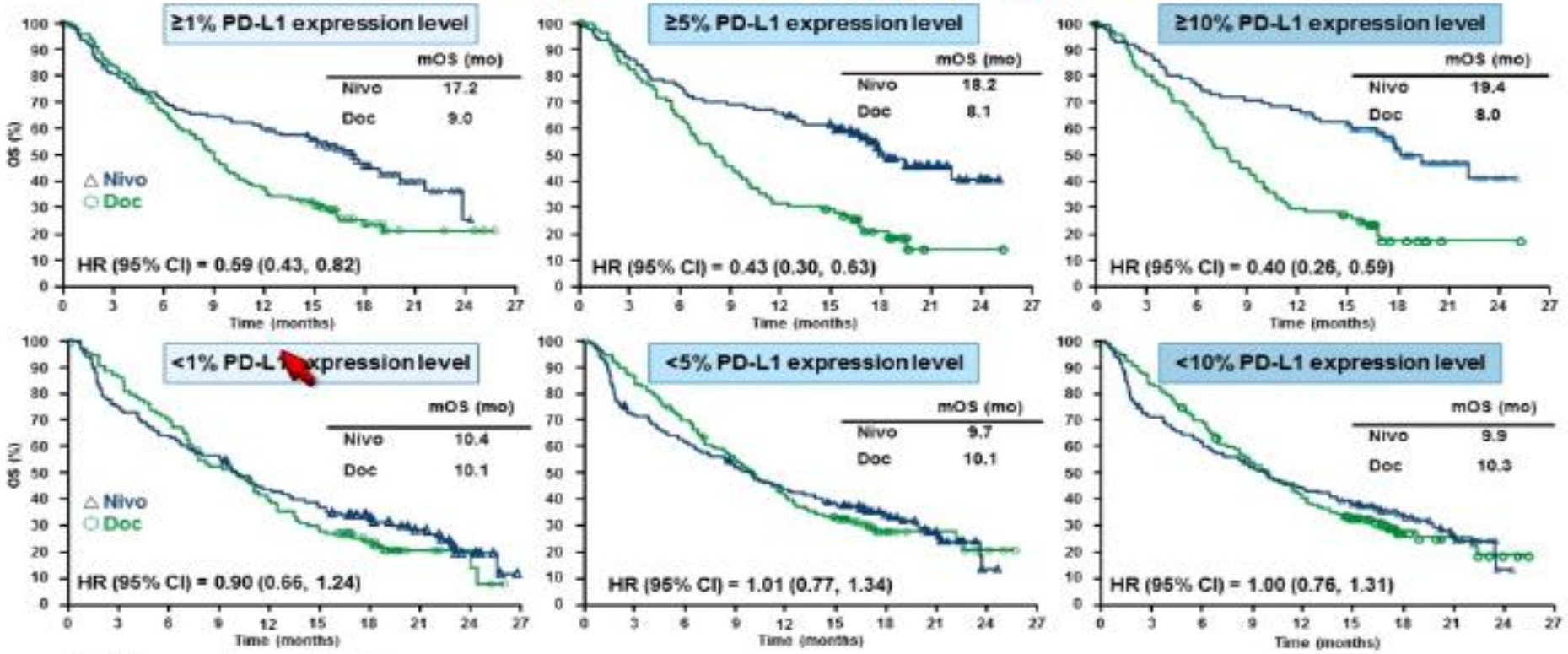


Number of Patients at Risk										
Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

Overall Survival



OS by PD-L1 Expression



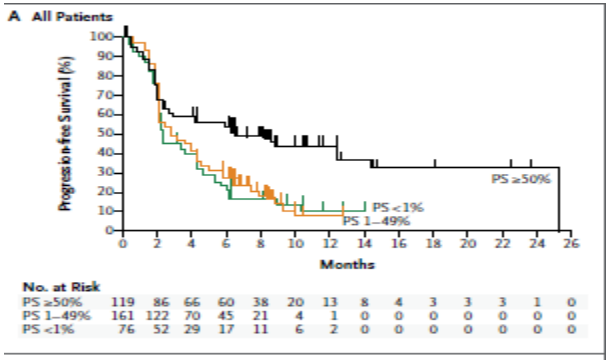
Toxicity

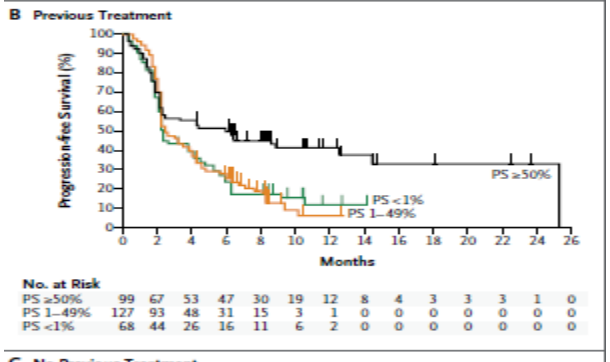
- Treatment related SAEs: 7% (N) and 20% (D)
- Treatment AEs leading to discontinuation: 5% (N) and 15% (D)
- Immune toxicity of nivolumab (%G3-4): hypothyroidism 7%(0); diarrhea 8 %(1); AST 3% (0); ALT 3% (<1); pulmonary 3% (1); rash 9% (<1)

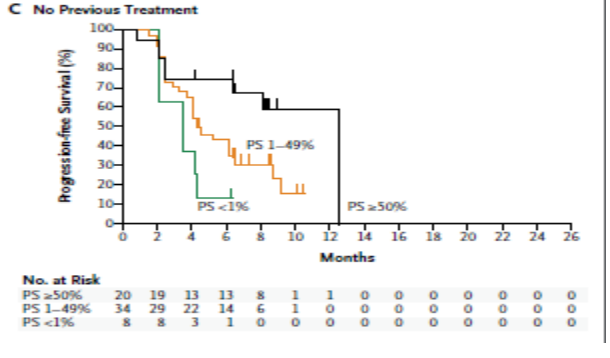
Pembrolizumab in NSCLC

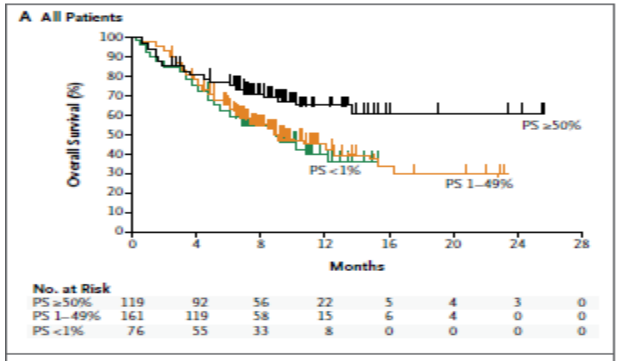
- 495 patients with advanced NSCLC
- 182 patients in the training group and 313 in the validation group
- ORR 19.4% and median duration of response was 12.5 months
- Tumors were divided into those with more or less of the cells positive for PD-L1 expression (in cancer cells)

Garon et al. N Engl J Med 2015;372:2018-2028


A All Patients
Progression-free Survival (%)
PS ≥50%
PS <1%
PS 1–49%
Months
No. at Risk
PS ≥50% 119 86 66 60 38 20 13 8 4 3 3 3 1 0
PS 1–49% 161 122 70 45 21 4 1 0 0 0 0 0 0 0
PS <1% 76 52 29 17 11 6 2 0 0 0 0 0 0 0


B Previous Treatment
Progression-free Survival (%)
PS ≥50%
PS <1%
PS 1–49%
Months
No. at Risk
PS ≥50% 99 67 53 47 30 19 12 8 4 3 3 3 1 0
PS 1–49% 127 93 48 31 15 3 1 0 0 0 0 0 0 0
PS <1% 68 44 26 16 11 6 2 0 0 0 0 0 0 0


C No Previous Treatment
Progression-free Survival (%)
PS 1–49%
PS <1%
PS ≥50%
Months
No. at Risk
PS ≥50% 20 19 13 13 8 1 1 0 0 0 0 0 0 0
PS 1–49% 34 29 22 14 6 1 0 0 0 0 0 0 0 0
PS <1% 8 8 3 1 0 0 0 0 0 0 0 0 0 0


A All Patients
Overall Survival (%)
PS ≥50%
PS <1%
PS 1–49%
Months
No. at Risk
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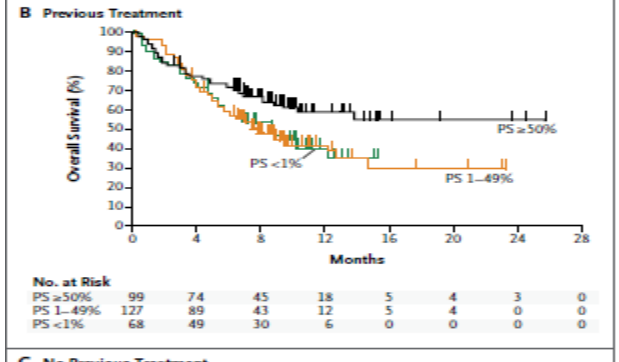
PS 1–49% 161 119 58 15 6 4 0 0
PS <1% 76 55 33 8 0 0 0 0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Months
No. at Risk
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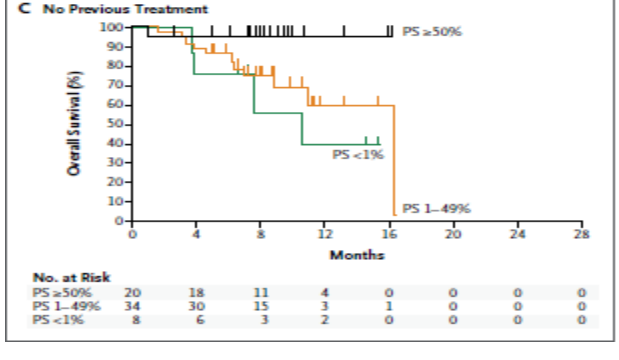
PS 1–49% 127 89 43 12 5 4 0 0
PS <1% 68 49 30 6 0 0 0 0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PS <1%
PS 1–49%
Months
No. at Risk
PS ≥50% 20 18 11 4 0 0 0 0
PS 1–49% 34 30 15 3 1 0 0 0
PS <1% 8 6 3 2 0 0 0 0

Who Benefits?
Is there a Biomarker?

- Patients with tumor with (-) expression of PD-L1 have lower response. However a few do respond and there is no established method to define PD-L1 status
- Smokers may have higher response rate
- Patients with SCCa have higher benefit or lager gain vs current available therapies

PD-L1 expression as a predictor of response

- CheckMate 057[1]: 108/287 (37%) treated with nivolumab had <1% tumor cells expressing PD-L1
- Keynote-001[2]: 12/91 (13%) patients had tumor or stroma with <1% PD-L1 expression
- POPLAR[3]: 51/144 (35%) patients had tumor or infiltrating immune cells graded as 0

1. J Clin Oncol 33,2015(suppl; abstr LBA 109)
2. J Clin Oncol 33;2015 (suppl;abstr 8026)
3. J Clin Oncol 33,2015 (suppl;abstr 8010)

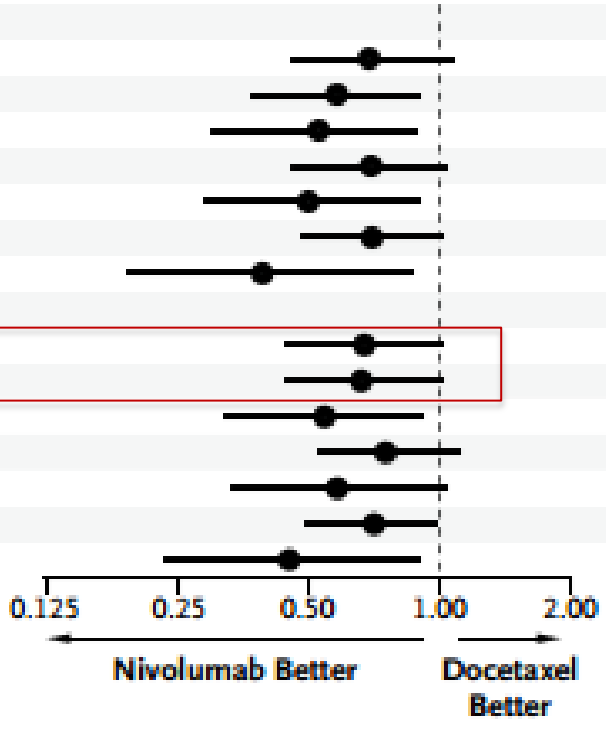
PD-L1 expression as a predictor of response

	# Negative tumors	# Responded among (-) tumors	RR (%)
CheckMate 057[1]	108	10	9%
Keynote-001[2]	12	1	8%
POPLAR[3]	51	4	8%
Combined	171	15	8.7% (95% CI 5-14%)

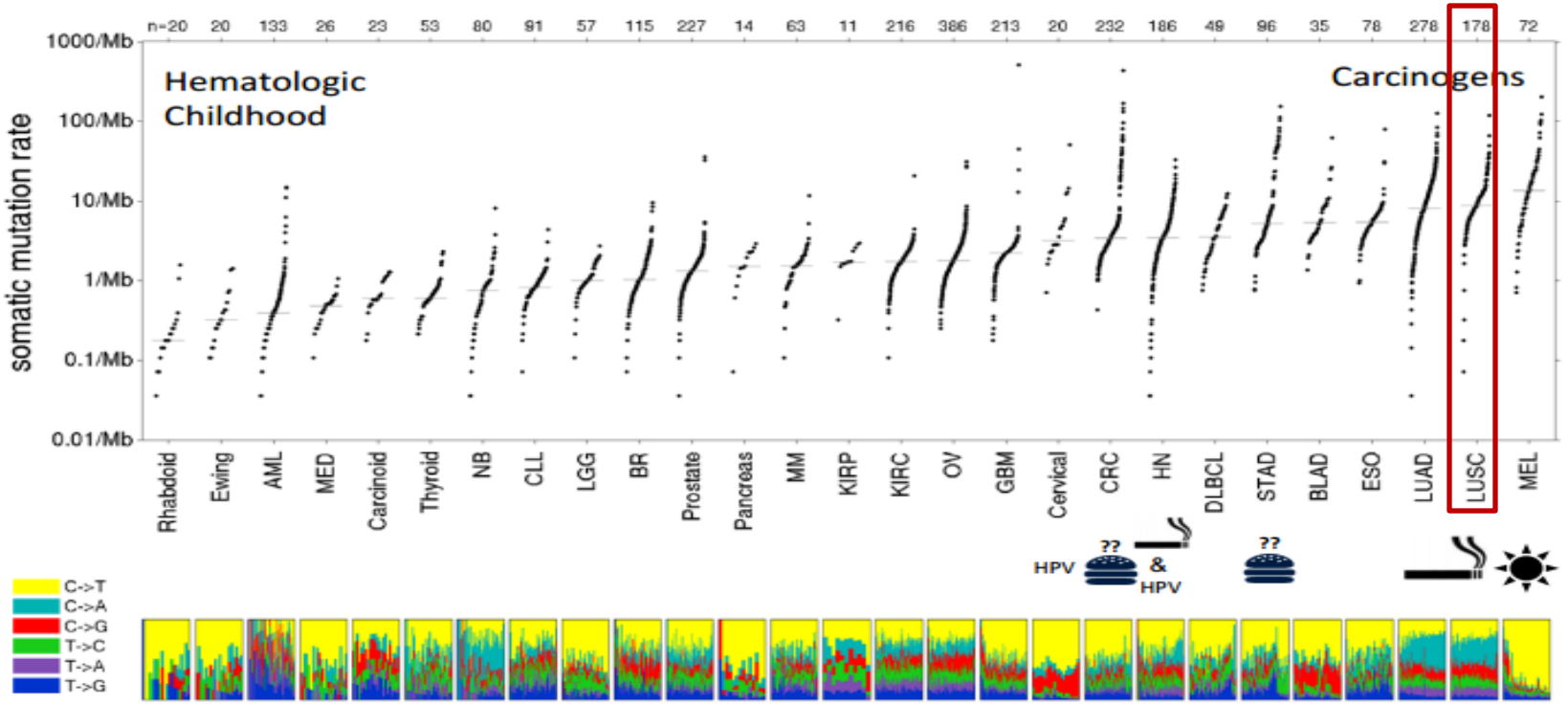
1. J Clin Oncol 33,2015(suppl;abstr LBA 109)
2. J Clin Oncol 33;2015 (suppl;abstr 8026)
3. J Clin Oncol 33,2015 (suppl;abstr 8010)

C Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)
Progression-free survival			
≥1%	63	56	0.67 (0.44–1.01)
<1%	54	52	0.66 (0.43–1.00)
≥5%	42	39	0.54 (0.32–0.90)
<5%	75	69	0.75 (0.52–1.08)
≥10%	36	33	0.58 (0.33–1.02)
<10%	81	75	0.70 (0.49–0.99)
Not quantifiable at baseline	18	29	0.45 (0.23–0.89)



mutation rates across cancer



https://www.genome.gov/Multimedia/Slides/TCGA1/TCGA1_Lawrence.pdf

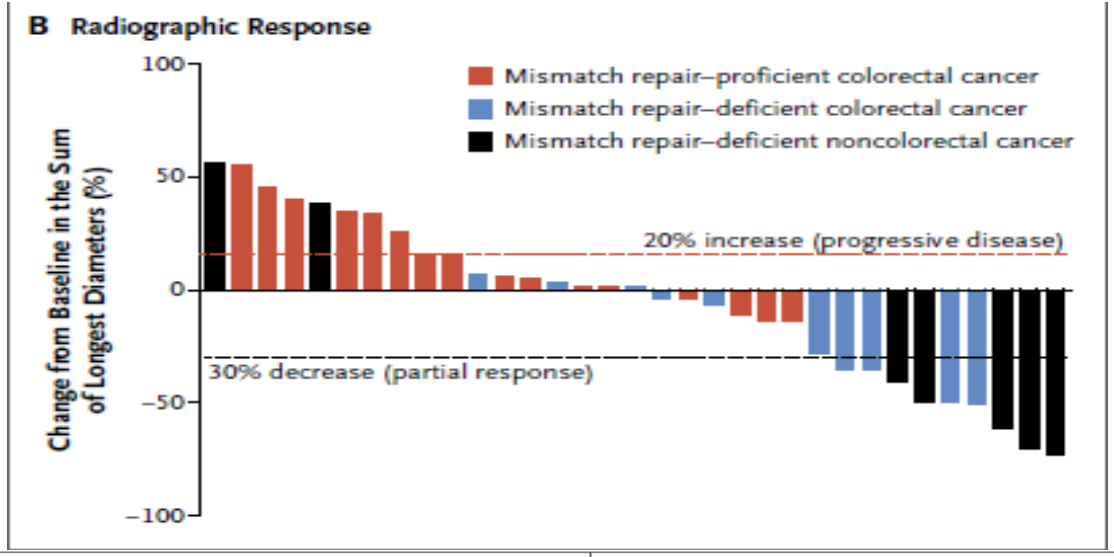
Tumors With High Somatic Mutation Rate Respond Better to a PD-1 Antibody

- In the initial reports of phase I of PD-1/PD-L1 antibodies only 1 of 33 patients with metastatic colorectal cancer responded. Investigators from Johns Hopkins hypostasized and proved that this patient had a mismatched repair-deficient tumor
- Nonpolyposis colorectal cancer: inherited germline defect in 1 of 4 mismatch-repair genes
- Patients with metastatic, treatment refractory tumors in 3 cohorts:

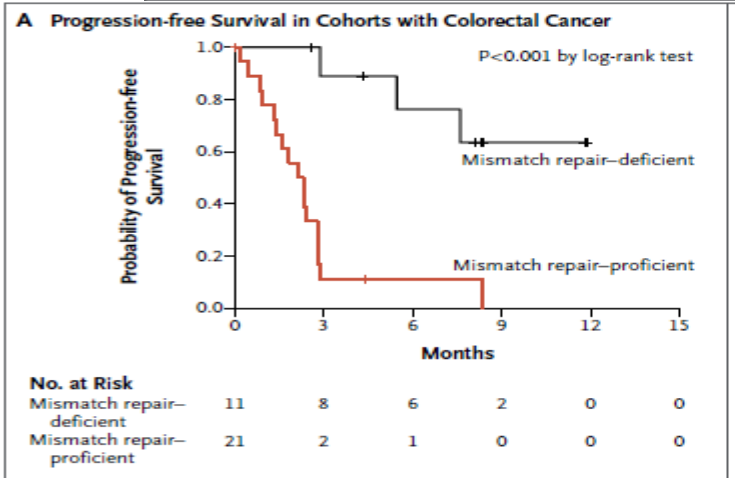
A. Mismatch repair deficient colorectal cancer
B. Mismatch repair proficient colorectal cancer
C. Mismatch repair deficient other than colorectal cancer (ampullary or cholangiocarcinoma 4;endometrial 2; small bowel 2; gastric 1)

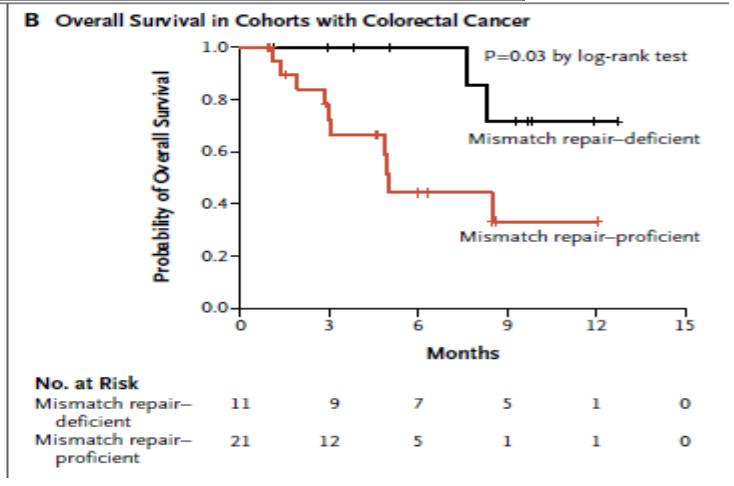
Le Dt et al Published on line at NEJM.org om May 30, 2015

Mismatch-deficient tumors: Mean of 1782 somatic mutations



Mismatch-proficient tumors: Mean of 73 somatic mutations





So What Do We Know?

- Response seems to be irrespective of number of prior therapies
- Tumors with multiple somatic mutations appear to be more immunogenic
- Serious immune toxicities may appear months into treatment

Future Directions

- Biomarker
- Combination therapies
- Management of toxicities particularly those developing late in patients with a good response

Thank you!

Audience Questions

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