Immunotherapy for the Treatment of Non-Small Cell Lung Cancer (NSCLC)

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Consultant

- Boehringer Ingelheim
- Pinnacle Biologics
- AbbVie

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NSCLC, the Impact

- The number one cause of Cancer Related Death
- 1.6 million people die each year and 1/10 or 160,000 die each year in the US
- 85% are NSCLC, subdivided into Adenocarcinoma, squamous and large cell

Chances of long term survival (5 year)

- Early stage (stage I-II), 50-60%
- Locally advanced stage (III) 15-30%
- Metastatic (IV), 5%

- Metastatic lung cancer usually non-curable, median survival 11 months

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Immunotherapy as a Treatment option for NSCLC

Precision Medicine:

Molecularly targeted therapy e. g TKIs;

Immunotherapy

- Immune checkpoint targeted therapies, PD-1, PD-L1, CTLA-1,
- Others, such as imprime PGG?
- Future, Treg, MDSC, IDO, A2aR targeting agents

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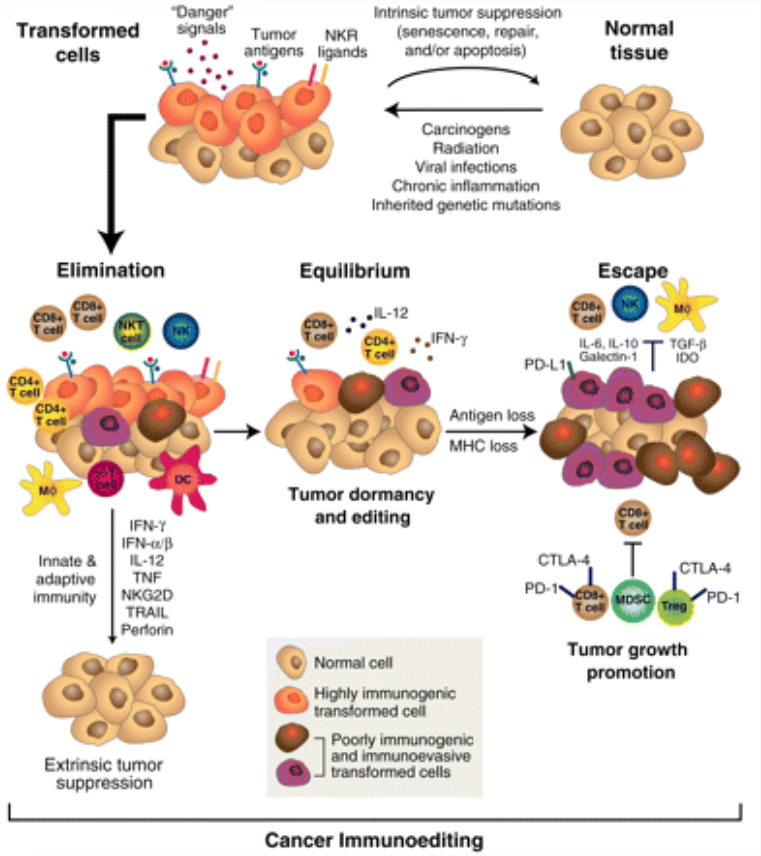
Immunoediting and Cancer Immune Escape



Elimination phase

Equilibrium phase

Escape phase

Immune checkpoint mechanisms are hijacked to promote tumor Growth in cancer patients

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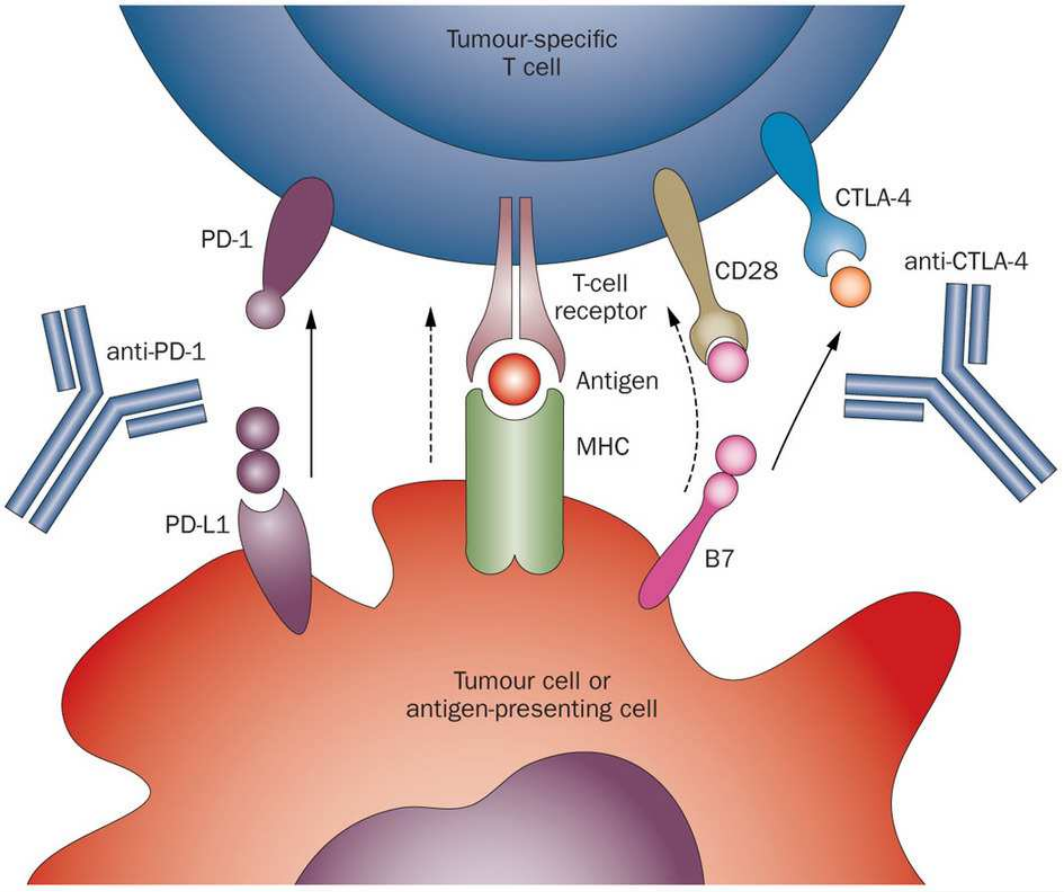
Schreiber RD et al Science 2011 331:1565

Immune Checkpoint Inhibitors



Ipilumumab
Tremellimumab
Nivolumab
Pembrolizumab
Durvalumab (Medi4736)

Humanized Monoclonal Antibodies directed Against CTLA-4
PD1, PD-L1

Charles G. Drake et al: *Nature Reviews Clinical Oncology* **11**, 24–37 (2014)

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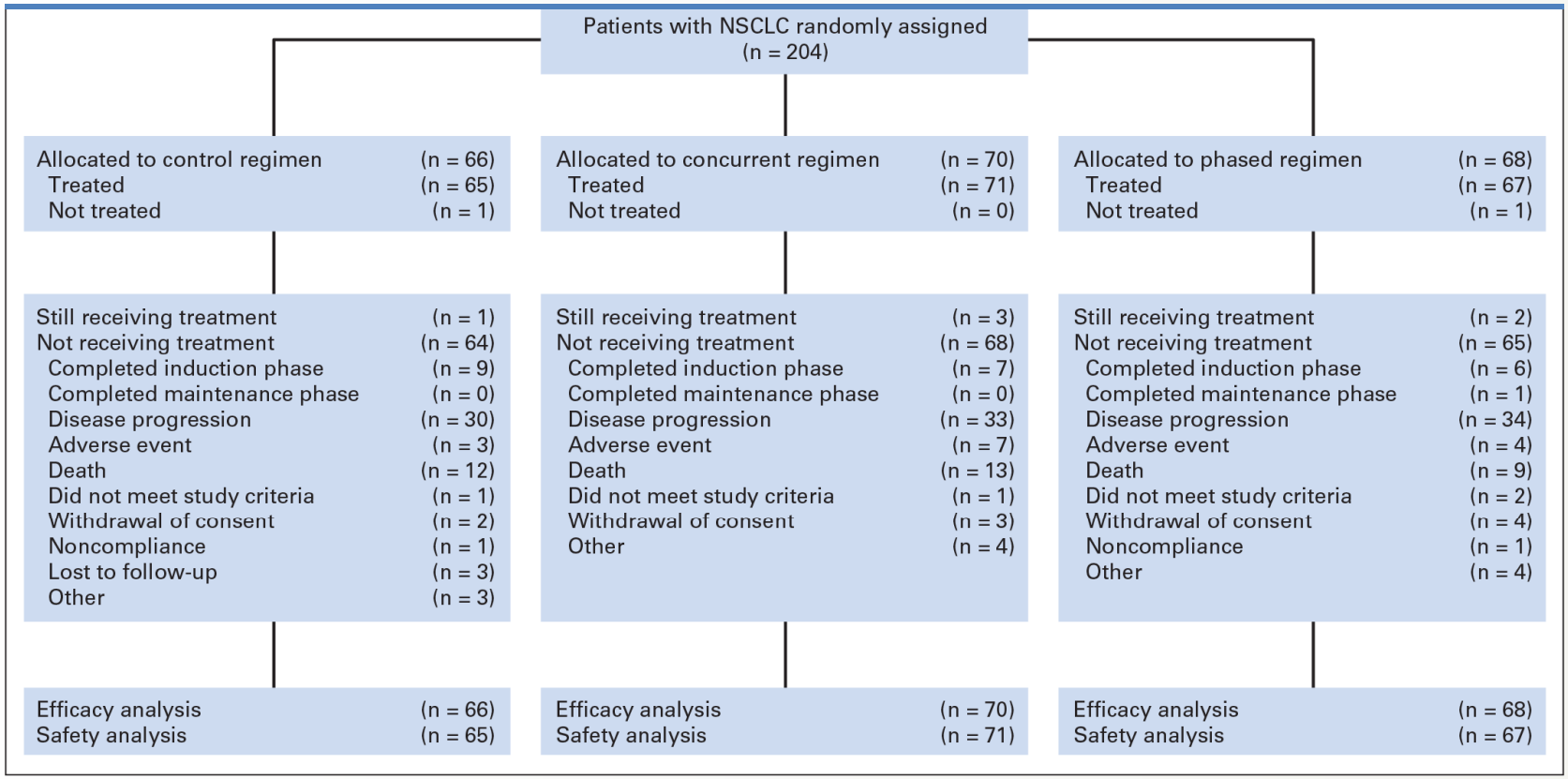
Ipilimumab improve chemo for NSCLC?



Phased vs concurrent vs placebo with carbo/paclitaxel
A phase 2 study.
Lynch TJ et al; J Clin Oncol 2012, 30:2046-54

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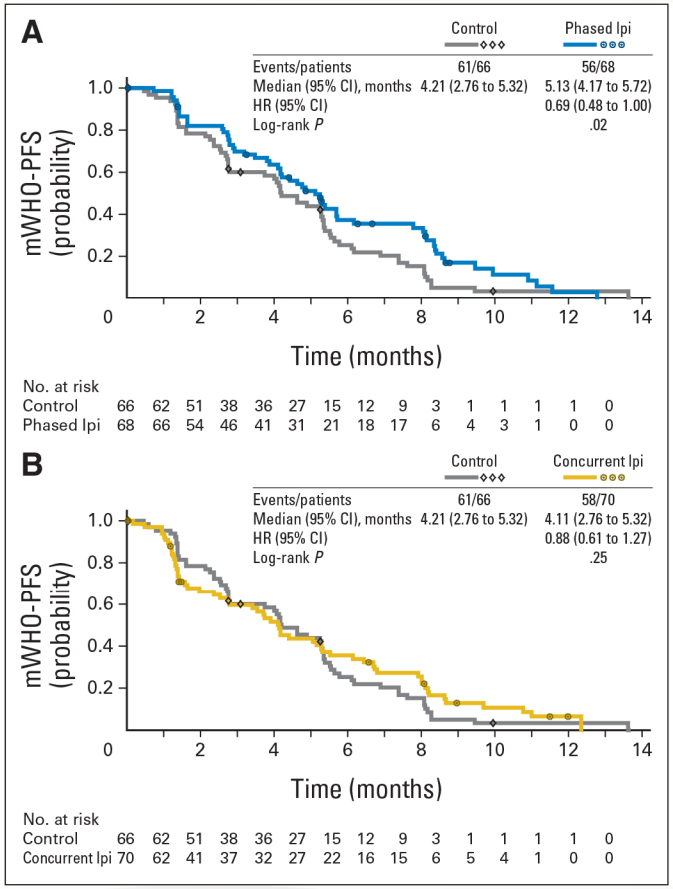
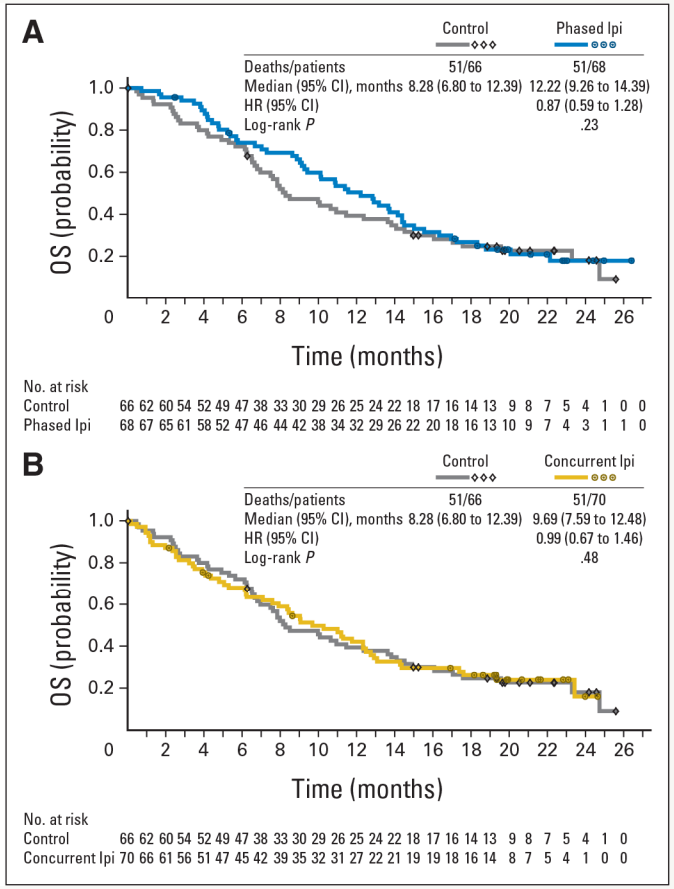
Ipilimumab and chemo for NSCLC





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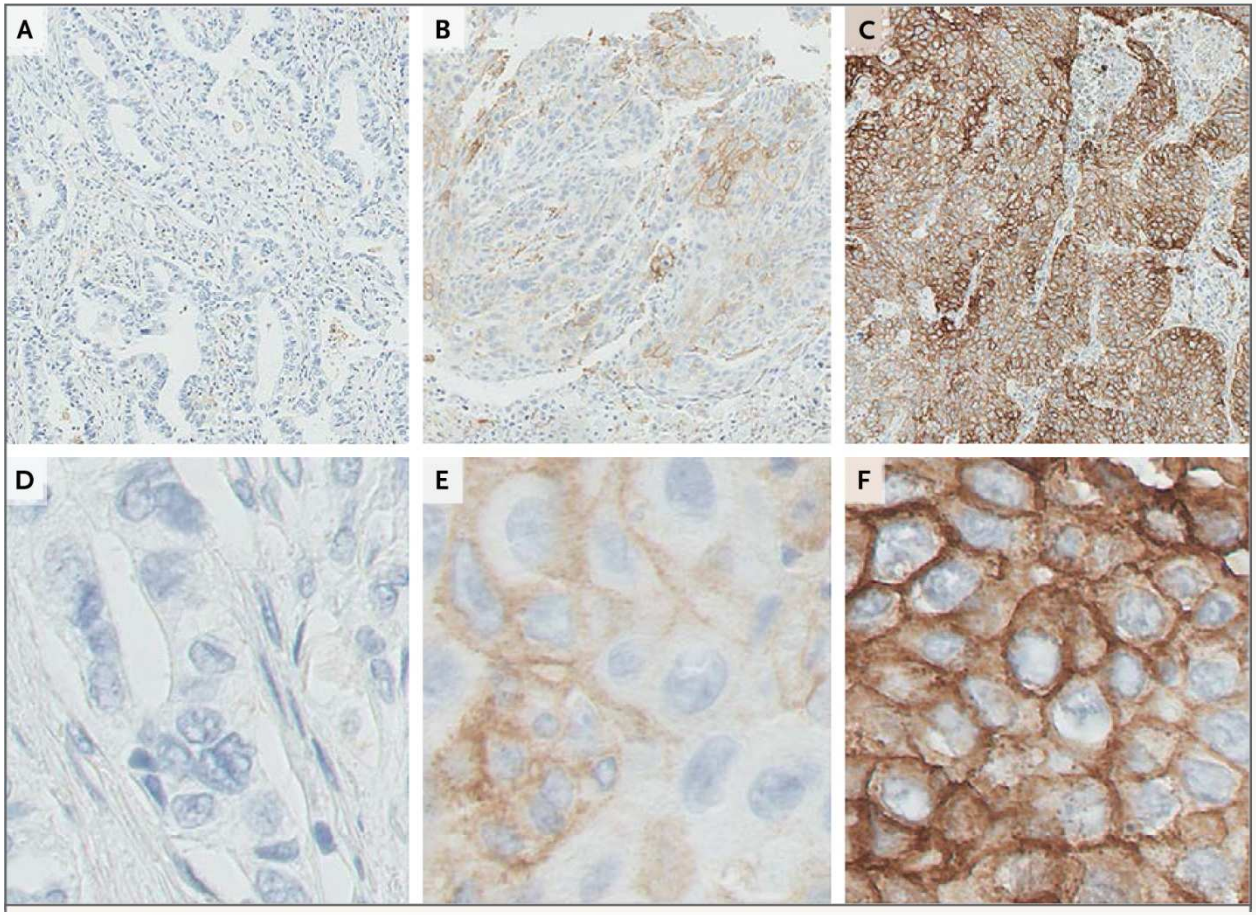
PD-L1 IHC in Tumor Specimen



Enrollment 22 m
1143 screened
495 got >1 dose
Median F/U 10.9m
115 continued to

ORR: 19.4%
(16-23.2%)

Treated: 18% 394
Not Tr: 24.8% 101
?better as first line

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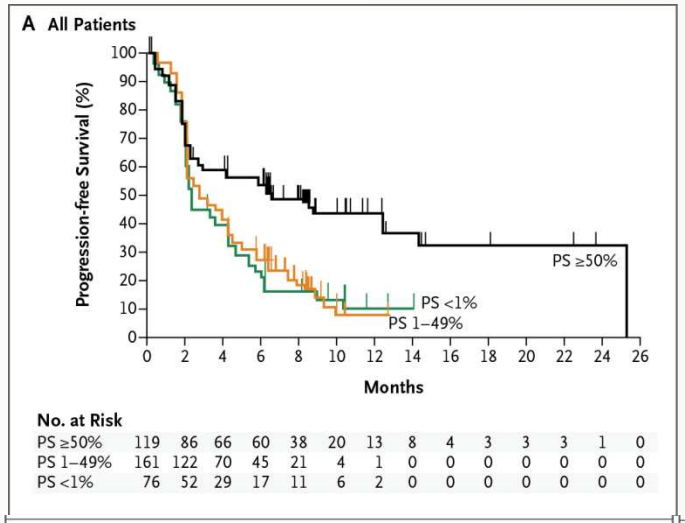
Edward B Garon et al N Engl J Med 372 (21)2018 May 21 2015

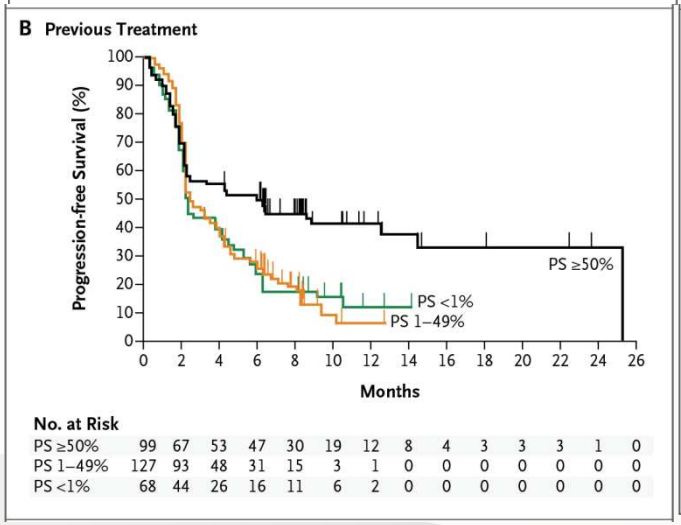
Kaplan-Myer Survival Analysis (PFS)

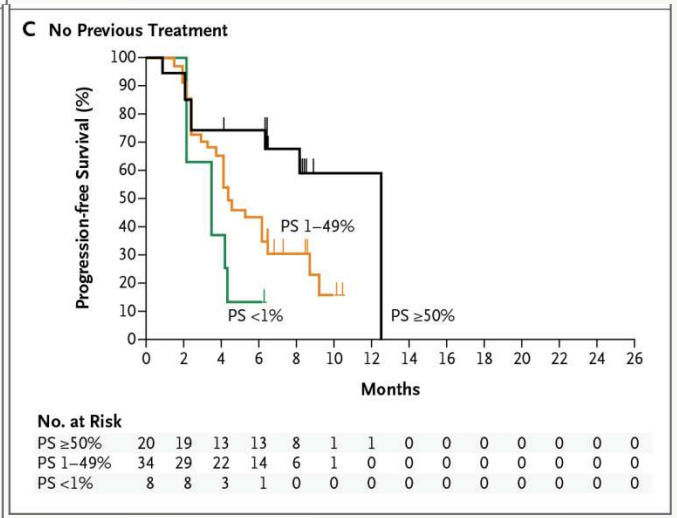
mDOR 12.5
Range: 1.0-23.3m

Treated:
10.4m,
95%CI 1.0-10.4m

Not treated:
23.3m,
95% range
1.0-23.3m







PFS for all: 3.7m (2.9-4.1 m)

Treat Before: 3.0m (2.2-4.0m)
Not Treated: 6.0m (4.1-8.6m)

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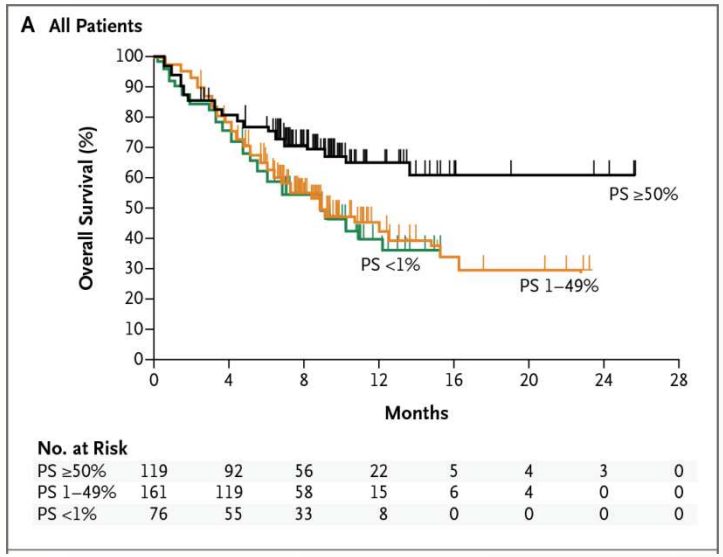
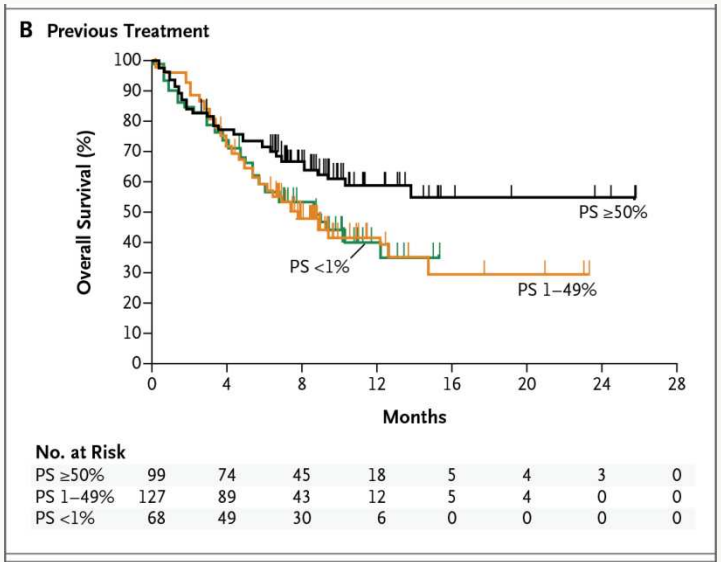
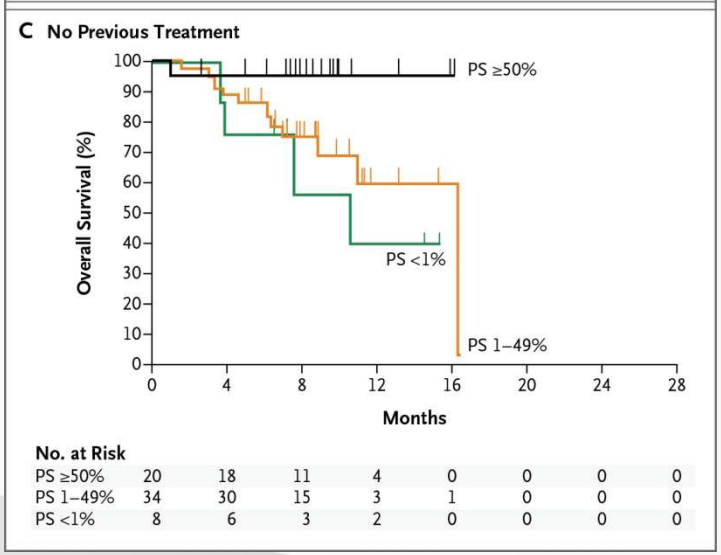
Pembrolizumab Survival data (OS)







OS for all: 12 m (9.3-14.7 m)
Treated: 9.3m (8.4-12.4 m)
Not Treated 16.2m (16.2-NR)

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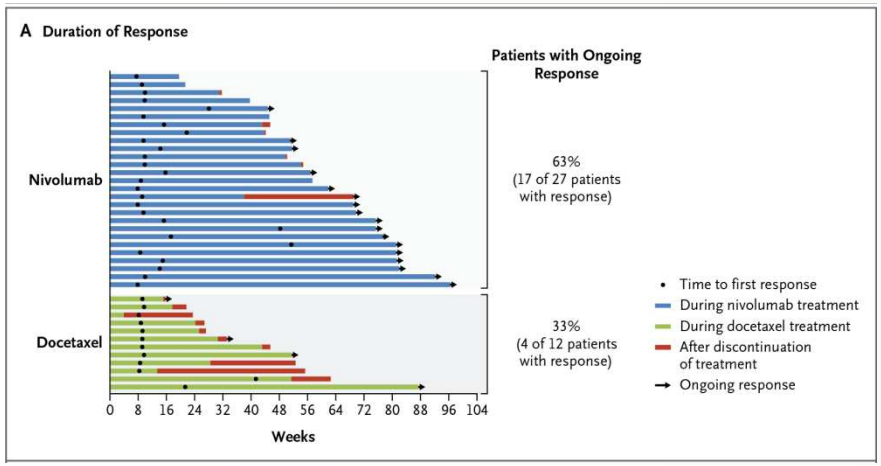
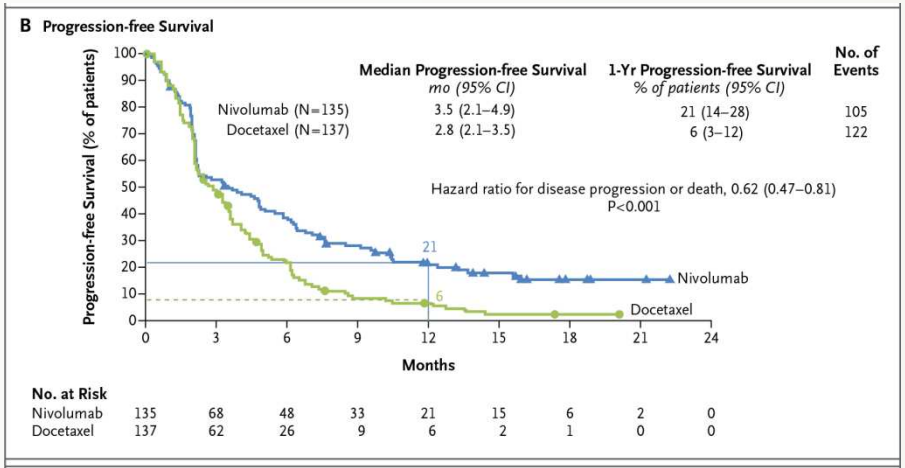
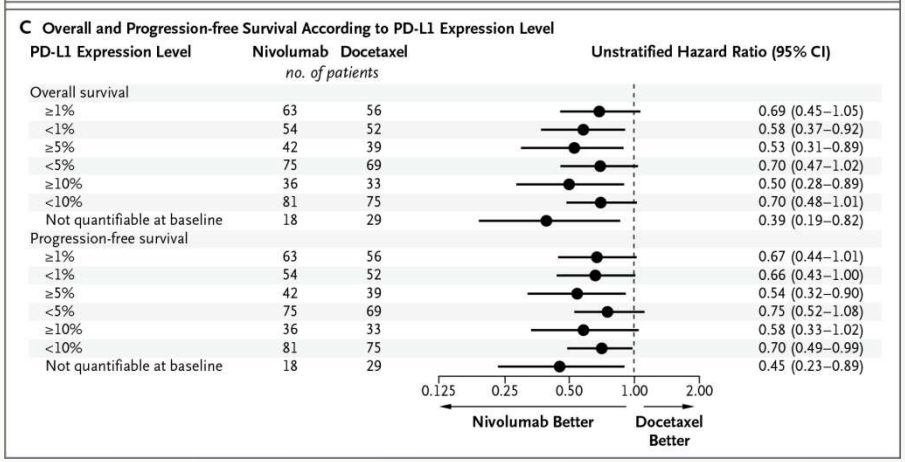
Nivolumab vs Docetaxel, Phase III (Checkmate 017)







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Brahmer J et al: New Engl J Med May 31, 2015

Nivo vs Doc: OS data

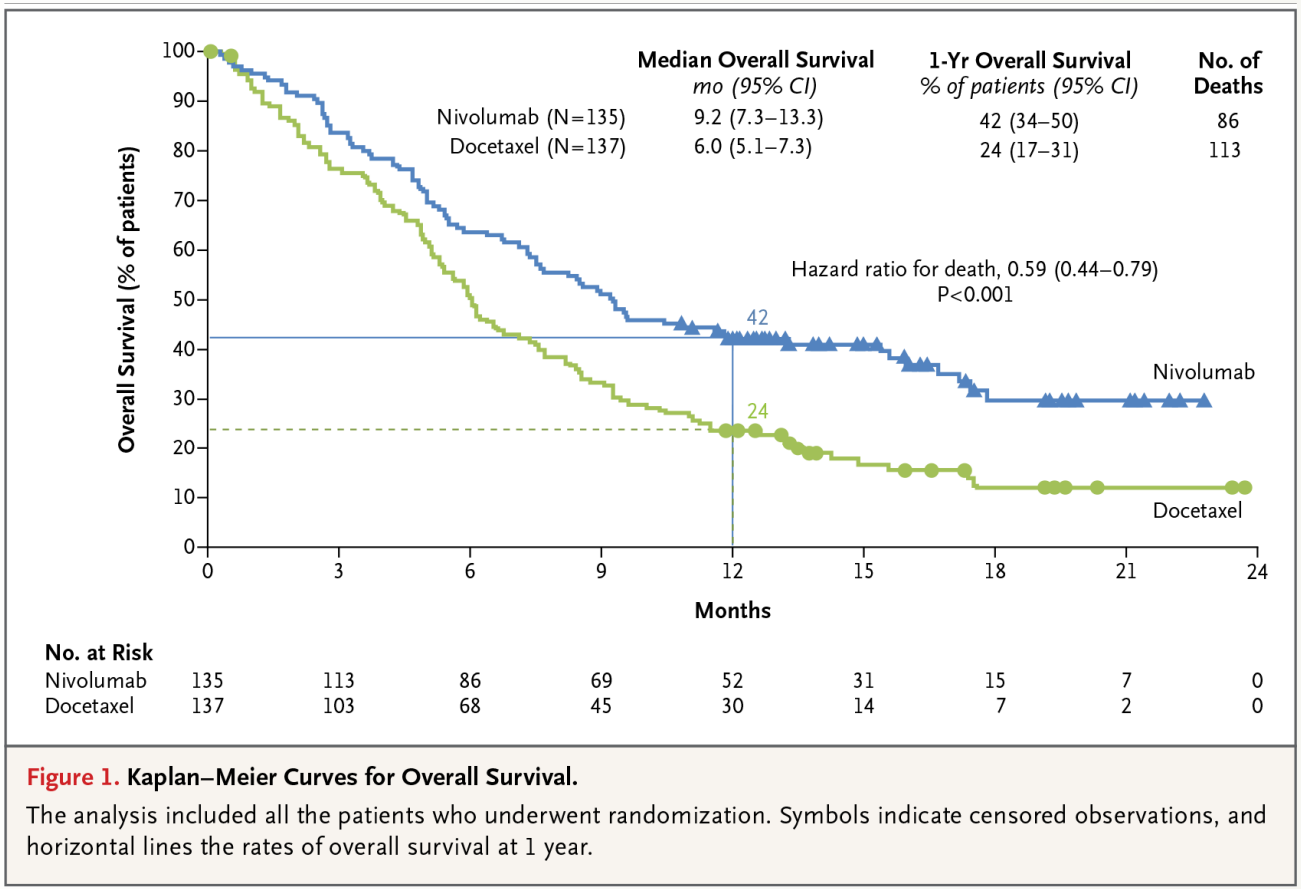

Figure 1. Kaplan–Meier Curves for Overall Survival.

The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

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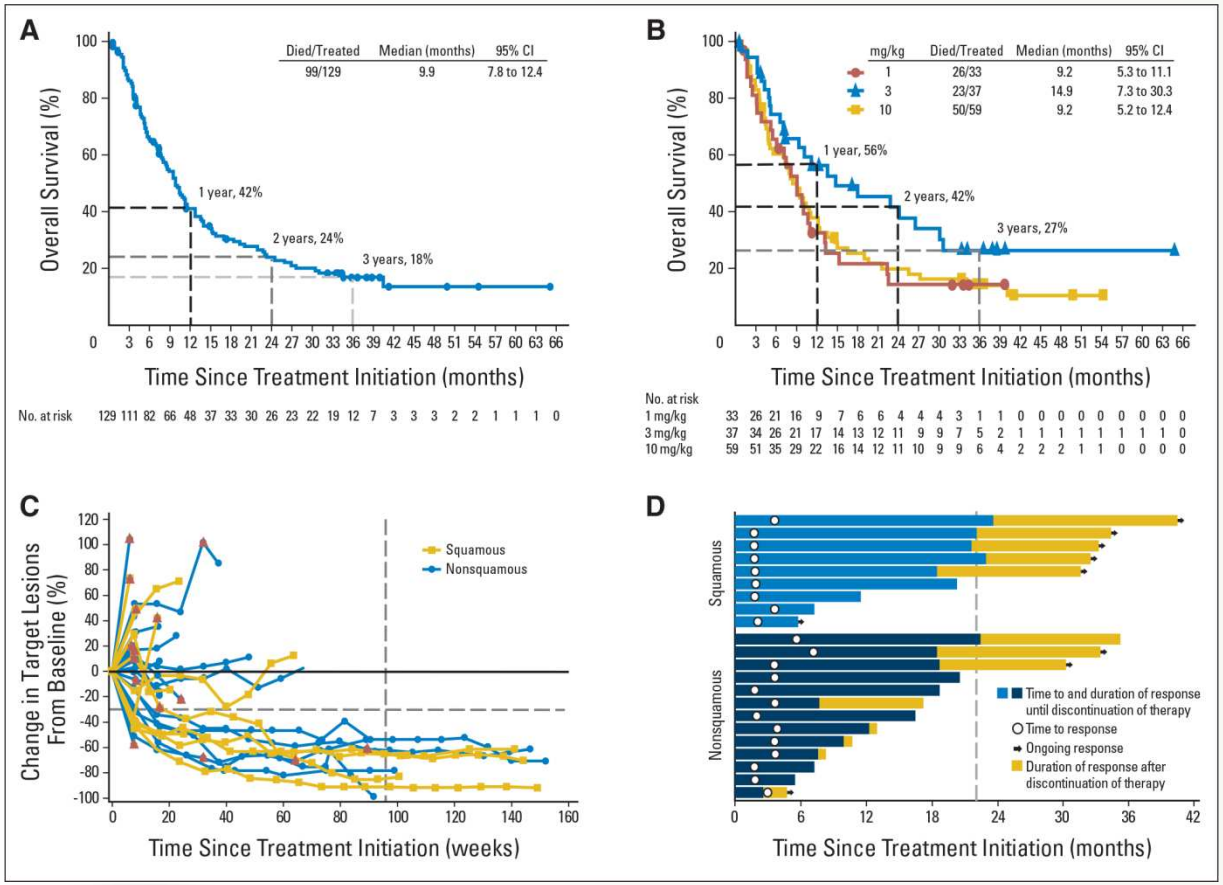
Response to Nivolumab



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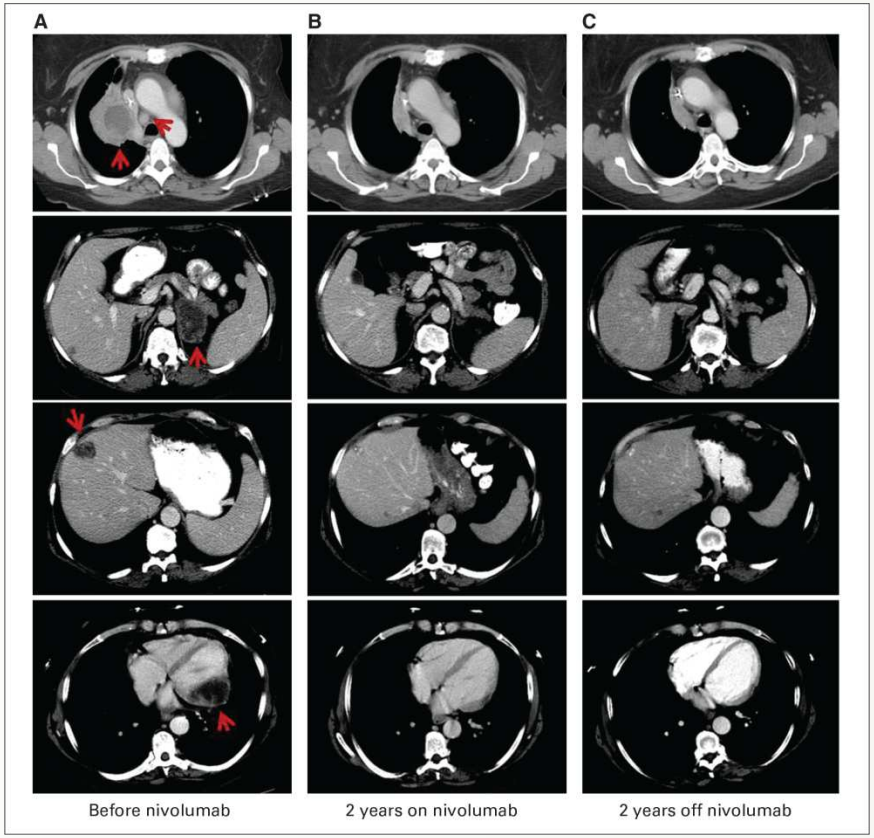
Gettinger SN et al: JCO 2015, 33:2004-2012

Response and basic characteristics

Table 3. ORRs by Baseline Characteristic Subgroups*

Subgroup	ORR†		
	No. of Patients	%	95% CI
Age, years			
< 70	15 of 90	16.7	9.6 to 26.0
≥ 70	7 of 39	17.9	7.5 to 33.5
Sex			
Male	13 of 79	16.5	9.1 to 26.5
Female	9 of 50	18.0	8.6 to 31.4
ECOG performance status[17]			
0	3 of 27	11.1	2.4 to 29.2
1-2‡	19 of 102	18.6	11.6 to 27.6
Tumor cell histology			
Squamous	9 of 54	16.7	7.9 to 29.3
Nonsquamous	13 of 74	17.6	9.7 to 28.2
No. of prior therapies			
1-2	7 of 59	11.9	4.9 to 22.9
≥ 3	15 of 70	21.4	12.5 to 32.9
Prior TKI therapy			
Yes	4 of 36	11.1	3.1 to 26.1
No	18 of 93	19.4	11.9 to 28.9
EGFR tumor status			
Mutant	2 of 12	16.7	2.1 to 48.4
Wild type	11 of 56	19.6	10.2 to 32.4
Unknown	9 of 61	14.8	7.0 to 26.2
KRAS tumor status			
Mutant	3 of 21	14.3	3.0 to 36.3
Wild type	9 of 36	25.0	12.1 to 42.2
Unknown	10 of 72	13.9	6.9 to 24.1



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Gettinger SN et al: JCO 2015, 33:2004-2012

Anti-PD1 Treatment Toxicities

Table 1. Adverse Events in 495 Patients in the Treated Population.*

Adverse Event	Any Grade	Grade 3–5
	no. of patients (%)	
Fatigue	96 (19.4)	4 (0.8)
Pruritus	53 (10.7)	0
Decreased appetite	52 (10.5)	5 (1.0)
Rash	48 (9.7)	1 (0.2)
Arthralgia	45 (9.1)	2 (0.4)
Diarrhea	40 (8.1)	3 (0.6)
Nausea	37 (7.5)	4 (0.8)
Hypothyroidism	34 (6.9)	1 (0.2)
Asthenia	24 (4.8)	5 (1.0)
Anemia	21 (4.2)	0
Dyspnea	21 (4.2)	19 (3.8)
Pyrexia	21 (4.2)	3 (0.6)
Decreased weight	19 (3.8)	2 (0.4)
Dry skin	18 (3.6)	0
Pneumonitis†	18 (3.6)	9 (1.8)
Elevation in aspartate aminotransferase	15 (3.0)	3 (0.6)
Vomiting	14 (2.8)	3 (0.6)
Dermatitis acneiform	13 (2.6)	0
Myalgia	13 (2.6)	0
Cough	12 (2.4)	0
Elevation in alanine aminotransferase	11 (2.2)	2 (0.4)
Chills	10 (2.0)	0
Constipation	10 (2.0)	2 (0.4)
Infusion-related reaction	15 (3.0)	1 (0.2)

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)

Edward B Garon et al N Engl J Med 372 (21)2018 May 21 2015

Brahmer J et al: New Engl J Med May 31, 2015

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Nivo vs Doc in Non-squamous cell (Checkmate 057)

http://bcove.me/jouyocph

Efficacy mo, (95% CI)	Nivo	Doc
mOS	12.2 (9.7, 15)	9.4 (8.0, 10.7)
1-yr OS	50.5 (44.6, 56.1)	3.9 (33.3, 44.6)
mDOR	17.1 (8.4-NR)	5.6 (4.4, 7.0)
mPFS	2.3 (2.2, 3.3)	4.2 (3.4, 4.9)
1-yr PFS	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)

PD-L1 Expression	Nivo (N=231)	Doc (N=224)	OS HR (95% CI)
<1	108	101	0.9 (0.66, 1.24)
>1	123	123	0.59 (0.43, 0.81)
<5	136	138	1.01 (0.76, 1.33)
>=5	95	86	0.43 (0.3, 0.63)
<10	145	145	1.00 (0.76, 1.33)
>=10	86	79	0.4 (0.27, 0.59)

Luis Paz-Ares et al: J Clin Oncol 33, 2015 Abstract LBA109

PD-L1 expression and response

	ORR (%) n/N (%)	mDOR (wks, Range	mOS (wks, range)
All	11/52 (21)	NR (7.6-, 85.6)	98.3 (1.0, 104.4)
Non-SQ	9/39 (23)	NR (7.6, 85.6)	NR(1.0-, 104.4)
SQ	2/13 (15)	NR(46.9, 77.3)	73.1(13.3, 87.3-)
PD-L1+	8/26 (31)	NR(7.6-, 85.6)	NR(1, 103.3-)
PD-L1-	2/21 (10)	NR(13-, 24.1)	98.3((8, 104.4)

Scott N Gettinger et al: J Clin Oncol, 33 2015 Suppl; Abstract 8025

PD-L1 >5% as cut off

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ORR: Overall Response Rare
mDOR: median Duration of Response
mOS: Median Overall Survival
SQ: Squamous Cell Lung Cancer
N: number
NR: Not reached

PD-L1 Expression as a marker for Response

PD-L1 (tumor)	N	ORR % (95% CI)	DCR % (95% CI)	Median	[mo (95% CI)]
				PFS	OS
>50%	17	47(23-72)	77(50-93)	NR(2.4-NR)	NR(NR-NR)
1-49%	31	19(8-38)	71(52-86)	4.4(3.6-6.4)	NR(8.6-NR)
<1%	7	14(0.4-58)	57(18-90)	3.4(2.1-4.2)	7.3(3.4-NR)
Total	90	24(16-35)	68(57-77)	6.0(4.1-8.6)	NR(10.6-NR)

Nauyer A Razvi et al: J Clin Oncol 33, 2015 Suppl, abstract 8026

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ORR: Overall Response Rate
DCR: Disease Control Rate
PFS: Progression Free Survival
OS: Overall Survival
NR: Not reached

PD-L1 Assays Used in NSCLC Clinical Trials

	Nivolumab (Opdivo)	Pembrolizumab (Keytruda)	Atezolizumab (MPDL3280A)	Durvalumab (MEDI4736)
mAb clone used in assay	28-8	22C3	SP142	SP263
Cells scored	Tumor cell membrane	Tumor cell and stroma	Infiltrating immune cells	Tumor cell membrane
Tissue	Archival	Recent	Archival/recent	Archival/recent
Positive cutoff used in trials	1%-5%	1%-50%	1%-10%	n/a
ORR in PD-L1–positive patients	13%-31%	19%-47%	31%-83%	26%
ORR in PD-L1–negative patients	10%-17%	9%-13%	18%-20%	10%
Drug developer	Bristol-Myers Squibb	Merck	Genentech	AstraZeneca

mAB indicates monoclonal antibody; NSCLC, non–small cell lung cancer; ORR, objective response rate; PD-L1, programmed death ligand-1.

See more at: http://www.onclive.com/publications/oncology-live/2015/august-2015/effort-to-harmonize-pd-l1-assays-launched-in-nsclc/2#sthash.lUoDD3vM.dpuf

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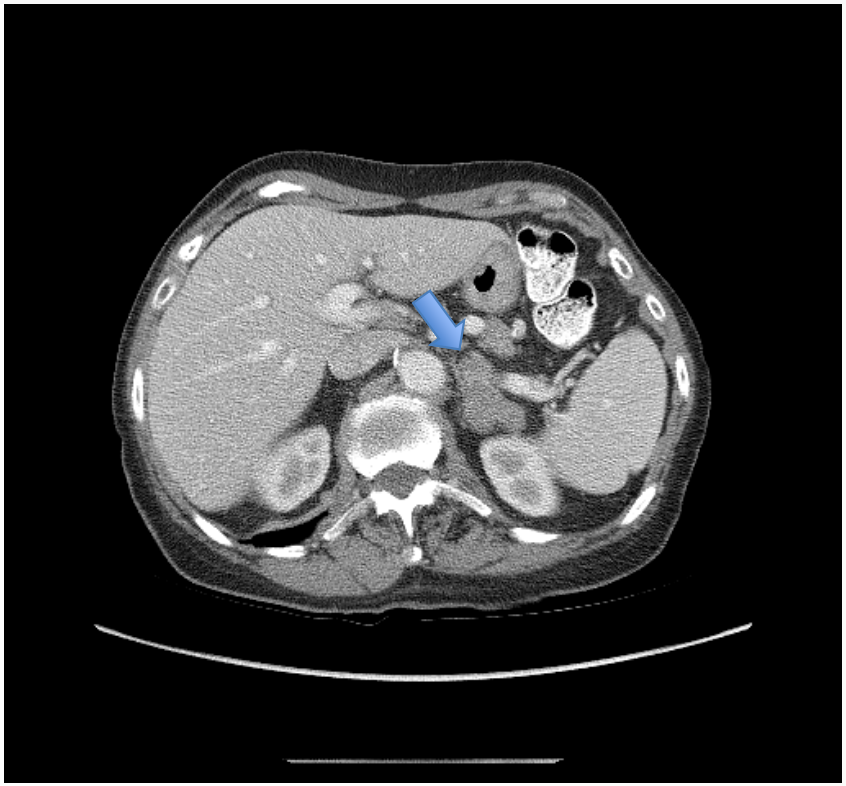
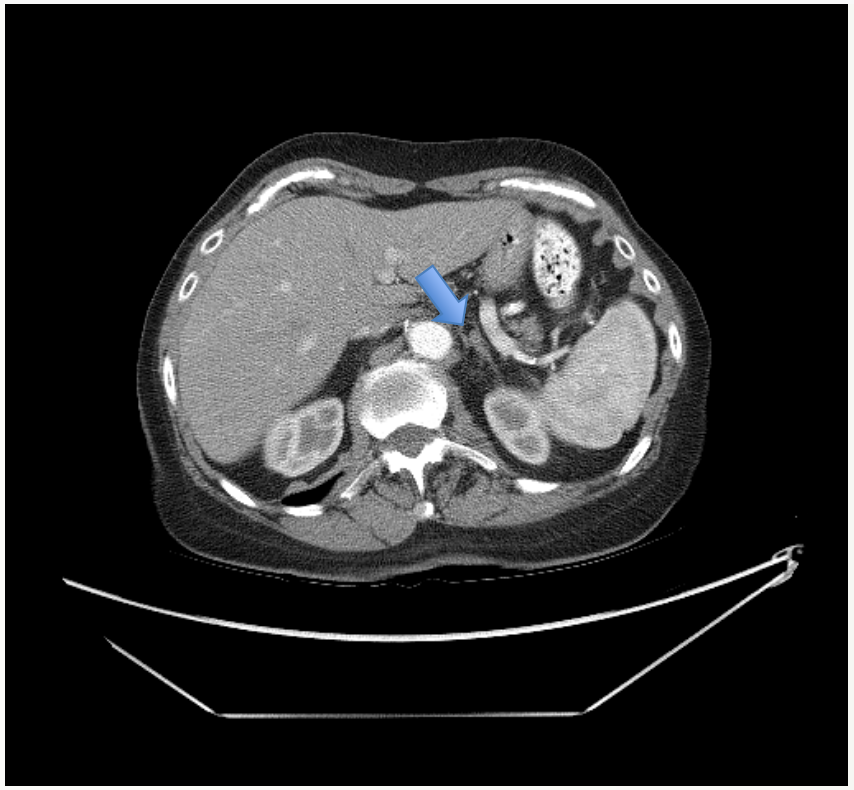
NSNSCLC with Adrenal Metastasis, Treated by Medi4736 on Protocol, Q2W



(3/4/13)



(5/15/14, 14 months later)

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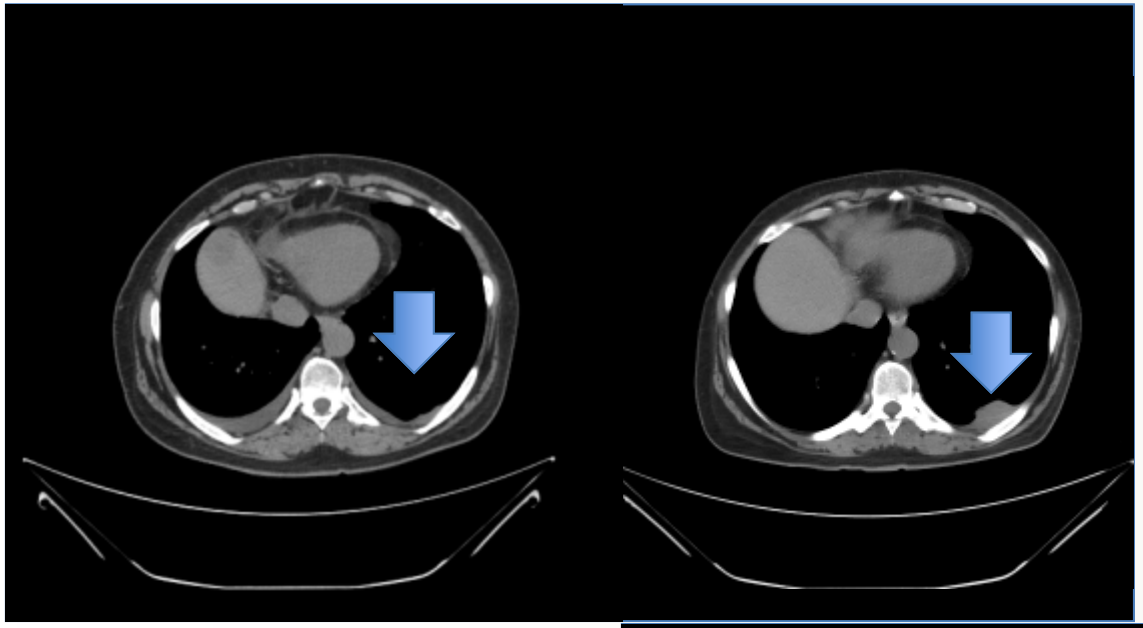
The Power of Immunotherapy



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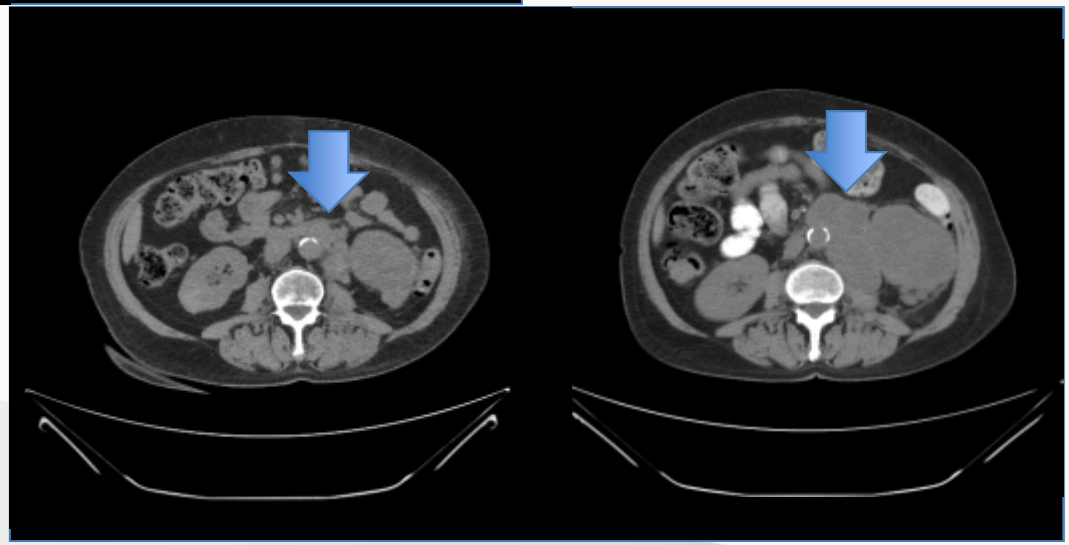

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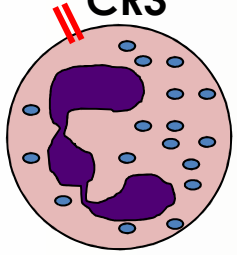
Biothera's PGG Glucan MOA: Targeting the Innate Immune System

PGG

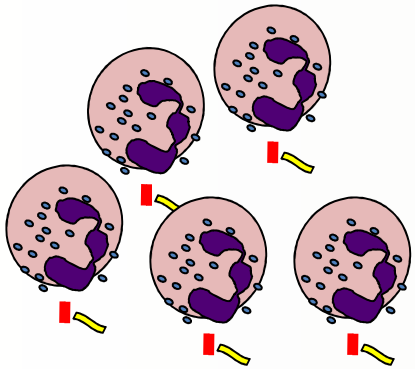
CR3



PGG Glucan + Anti-Tumor MAb

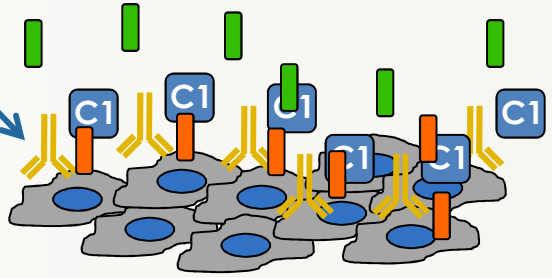
Antibody

2. PGG Glucan binds to neutrophils via CR3.

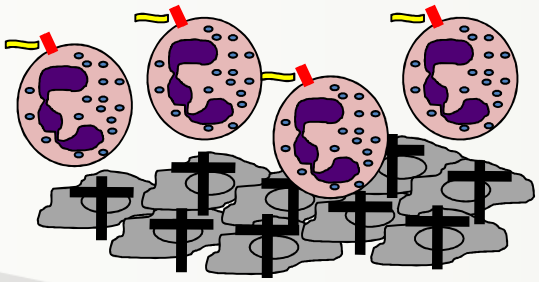


3. 'Primed' PGG Glucan bound neutrophils are recruited to the tumor microenvironment (C5a).

Tumor Cells



1. Anti-tumor MAb binds to tumor cells, recruits complement (C1), activates complement deposition (iC3b), and induces inflammation (C5a) at the tumor site.



4. Tumors are killed by the Neutrophils

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Biothera BT-CL-PGG-LCA0822 PGG Glucan + Cetuximab+Carboplatin/Paclitaxel - Clinical Trial Update [a]

80 subjects enrolled to date:

	Cetuximab + C/P	PGG Glucan + Cetuximab + C/P
Number of Subjects Enrolled	26	54
Number of Subjects Still Under Active Treatment	2 (1%)	8 (15%)
Number of Evaluable Subjects to Date	19	34
Partial Responders	**2 (11%)** **(1 confirmed/ 1 waiting confirmation)**	**9 (26%)** **(7 confirmed / 2 waiting confirmation)**
Confirmed (per RECIST) Partial Responders	**1 (5%)**	**7 (21%)**

BLINDED INDEPENDENT READ data available to Biothera as of 082611 based on independent reads of evaluable N with at least one post-treatment CT scan.

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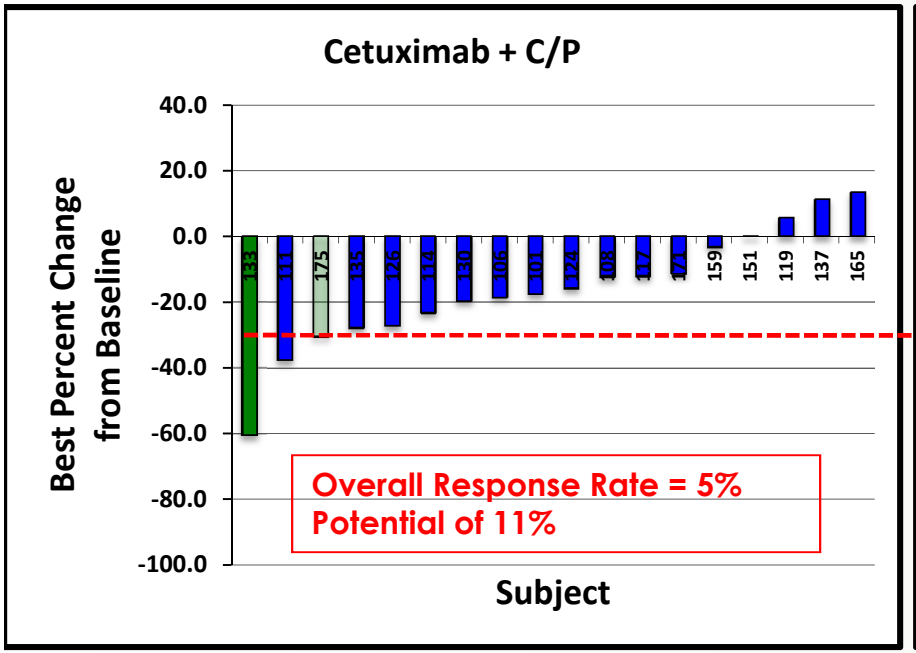
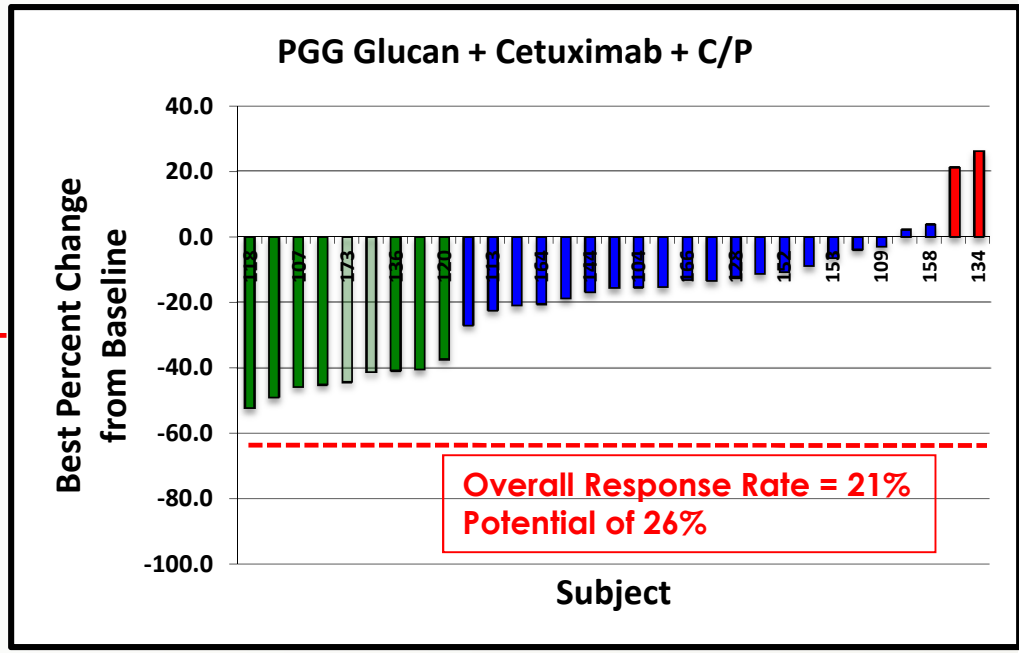
Biothera BT-CL-PGG-LCA0822 PGG Glucan + Cetuximab + Carboplatin/Paclitaxel - Preliminary Efficacy [a]

Best percent change from baseline in sum of target tumor burden to date

- Confirmed partial response
- Partial response waiting confirmation
- Stable disease (includes partial responses that could never be confirmed or failed confirmation)
- Progressive disease





[a] BLINDED INDEPENDENT READ data available to Biothera as of 082611 based on independent reads of evaluable N with at least one post-treatment CT scan.

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Genomic Profile of Responders

Disc. N=16 Valid. N=18	Disc. Set (MBH)	Disc. Set (MBL)	P (HR, 95% CI)	Valid. Set (MBH)	Valid. Set (MBL)	P (HR, 95% CI)
Score	302	148	0.02	244	125	0.04
DCB (%)	73	13	0.04	83	22	0.04
ORR(%)	63	0	0.03	N/A	N/A	N/A
PFS(m)	14.5	3.7	0.01 (0.19, 0.05-0.70)	NR	3.4	0.006 (0.15, 0.04-0.59)

MBH: Mutation Burden High, somatic non-synonymous
MBL: Mutation Burden Low, somatic non-synonymous
DCB: Durable Clinical Benefit
N/A: Not available
Naiyer A Rizvi et al: Sciencexpress Report 12 M 2014

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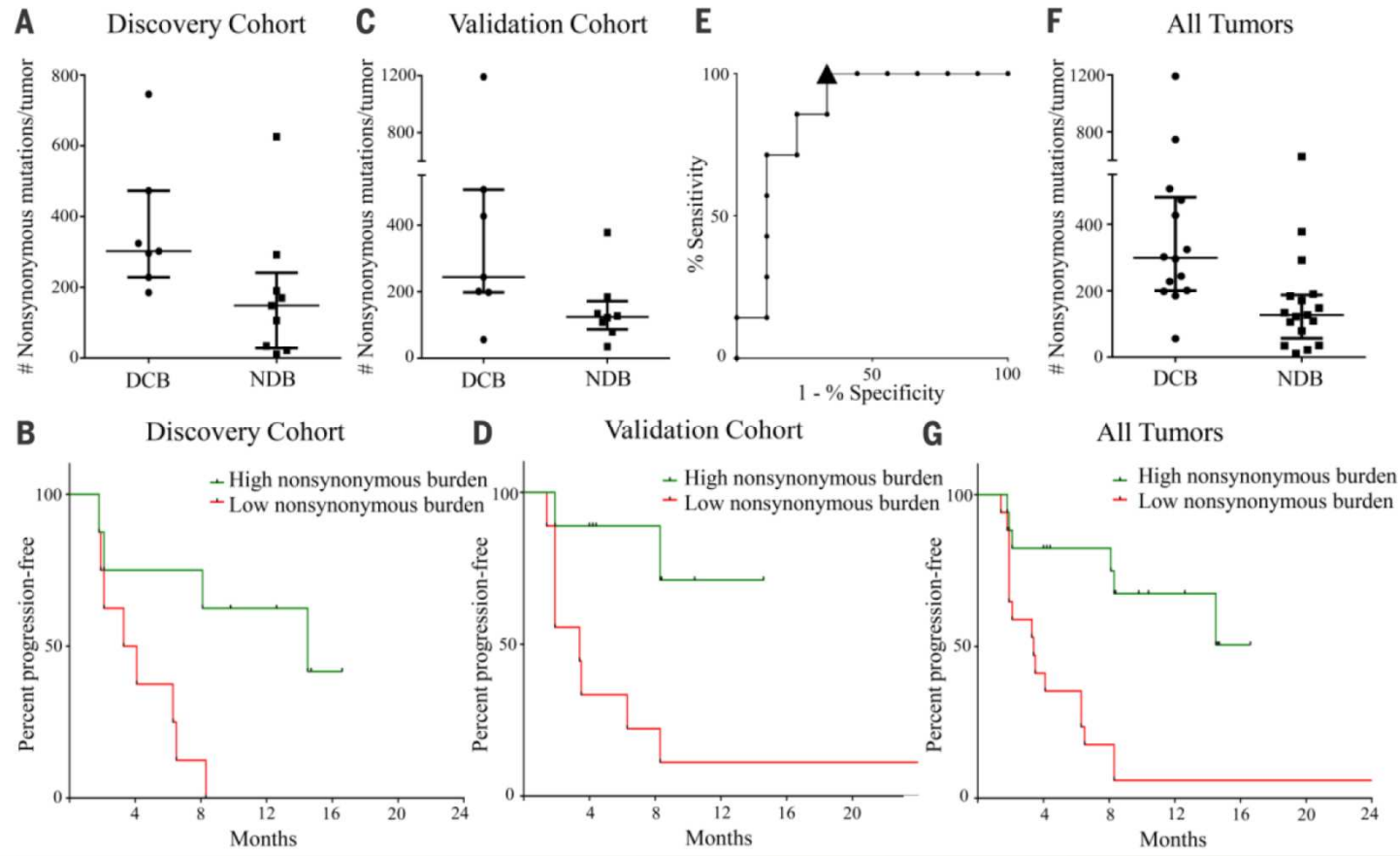
Genomic Profile of Responders



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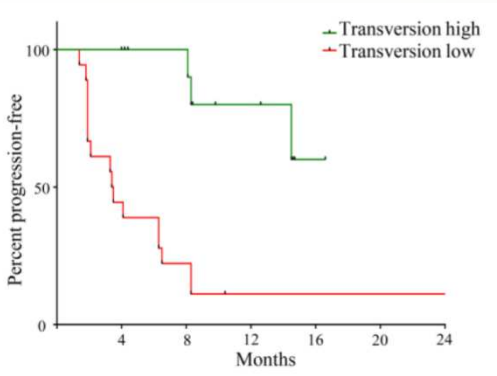
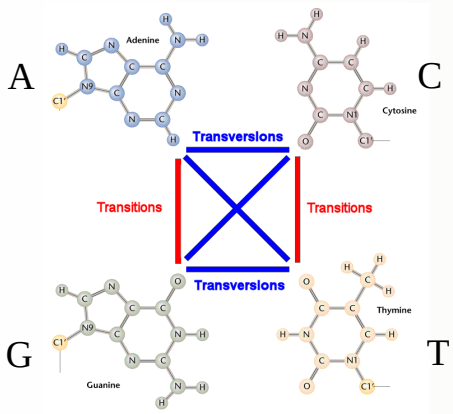
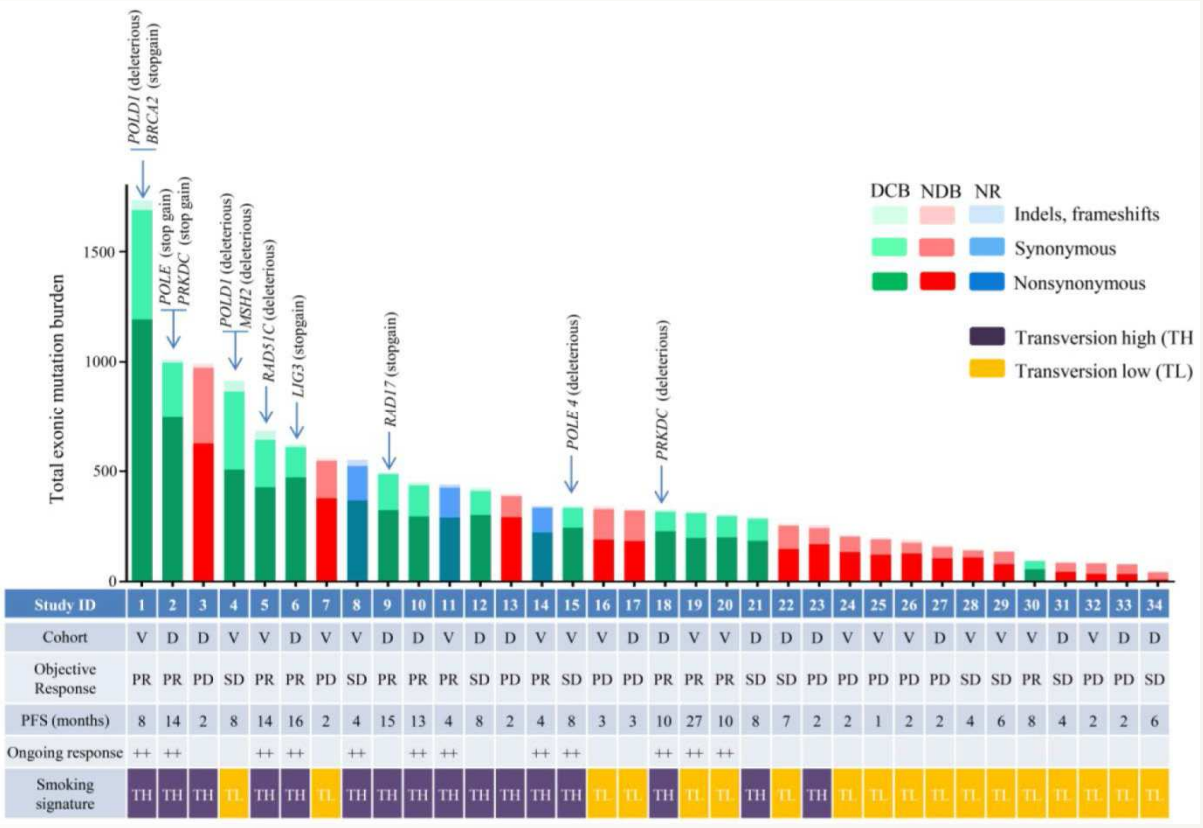
Rizvi NA et al: Science. 2015 348(6230):124-8

Smoking Signature in Patients







Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective Response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL

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Rizvi NA et al: Science. 2015 348(6230):124-8

Ras Mutation and Response

Ras Status	Number	Percent ORR	95% CI
Mutation	3/21	14.3%	3-36.3
Wild type	9/36	25%	12.1-42.2
Unknown	10/72	13.9%	6.9-24.1

Gettinger SN et al: JCO 2015, 33:2004-2012

Benefit	DCB	NDB
Number	7/14	1/17

Rizvi NA et al: Science. 2015 348(6230):124-8

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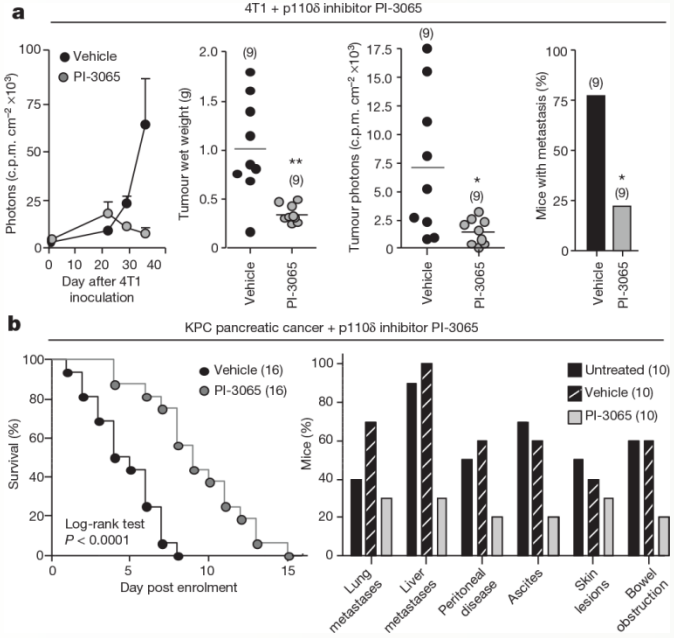
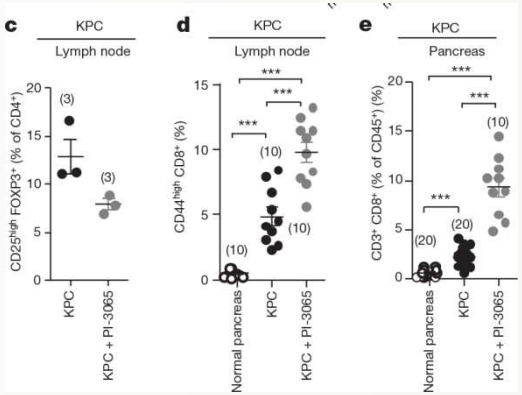
Treg and immunity?

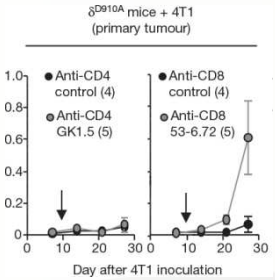


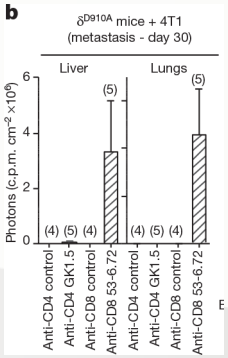


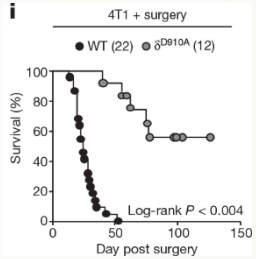
Effective tumor immunity is limited by Treg.

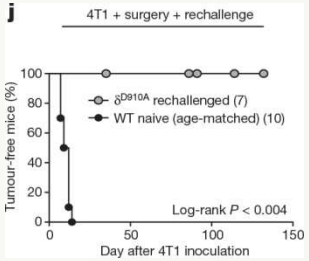
PI3K delta inactivation in Treg unleashes CD8+ T

Inactivation of Treg is sufficient to confer tumor Resistance and can be achieved Pharmacologically.









Ali K et al: Nature 2014, 510:407,

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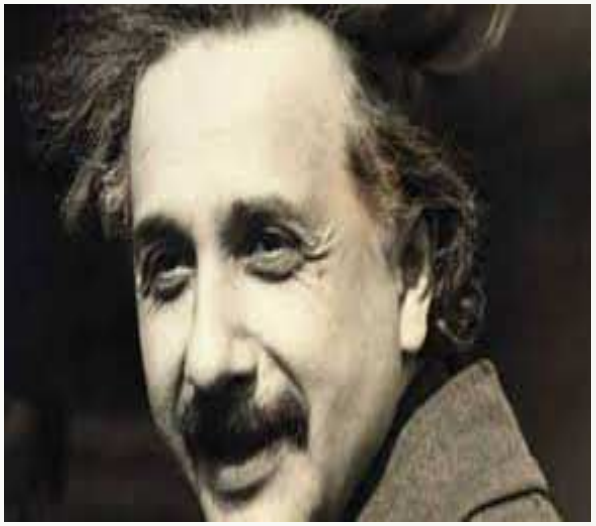
Other Targets?

- IDO
- MDSC
- A2aR



If we knew what it was we were doing, it would not be called research, would it?
Albert Einstein

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