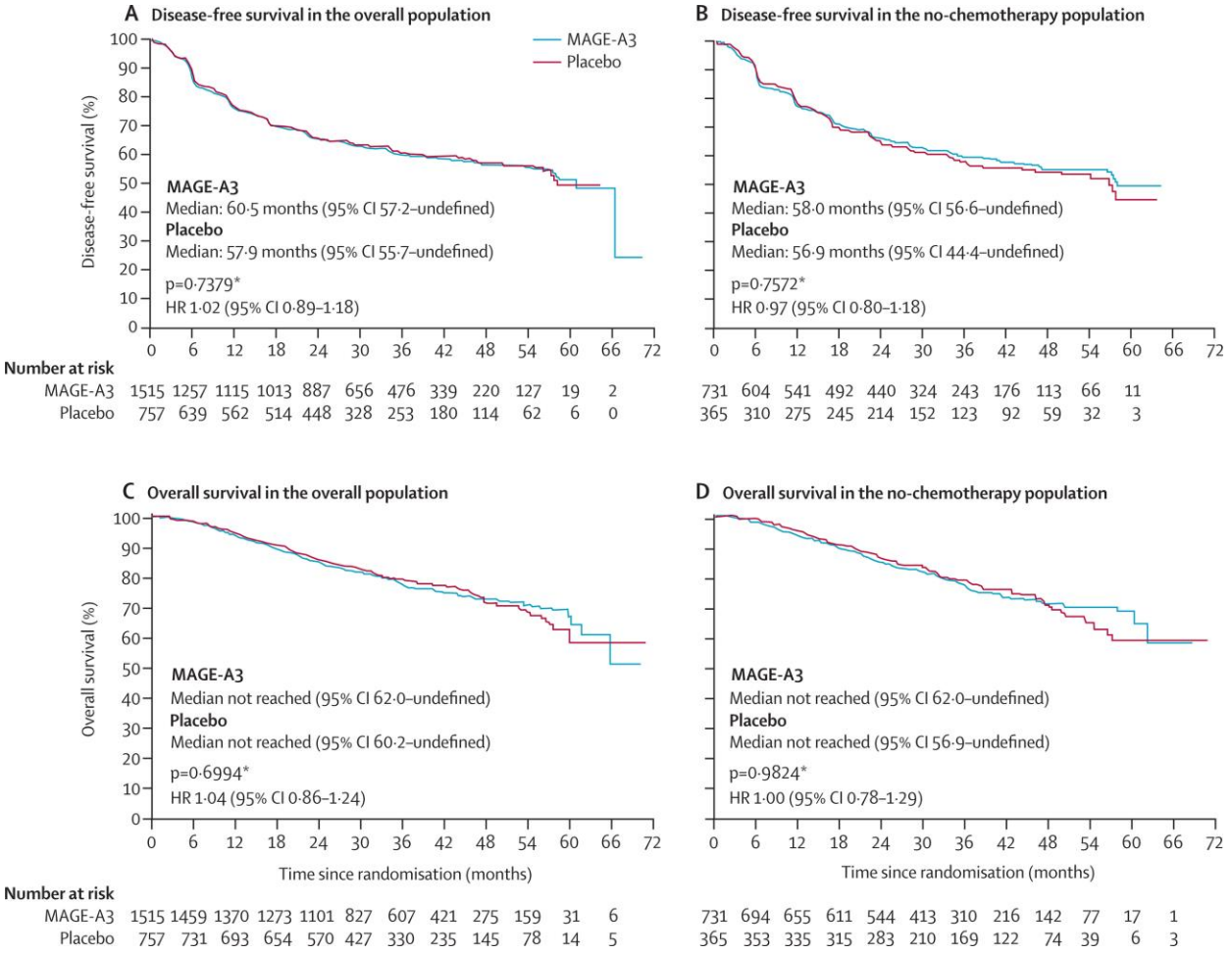
Harnessing the immune system to combat cancer

Gary Middleton,

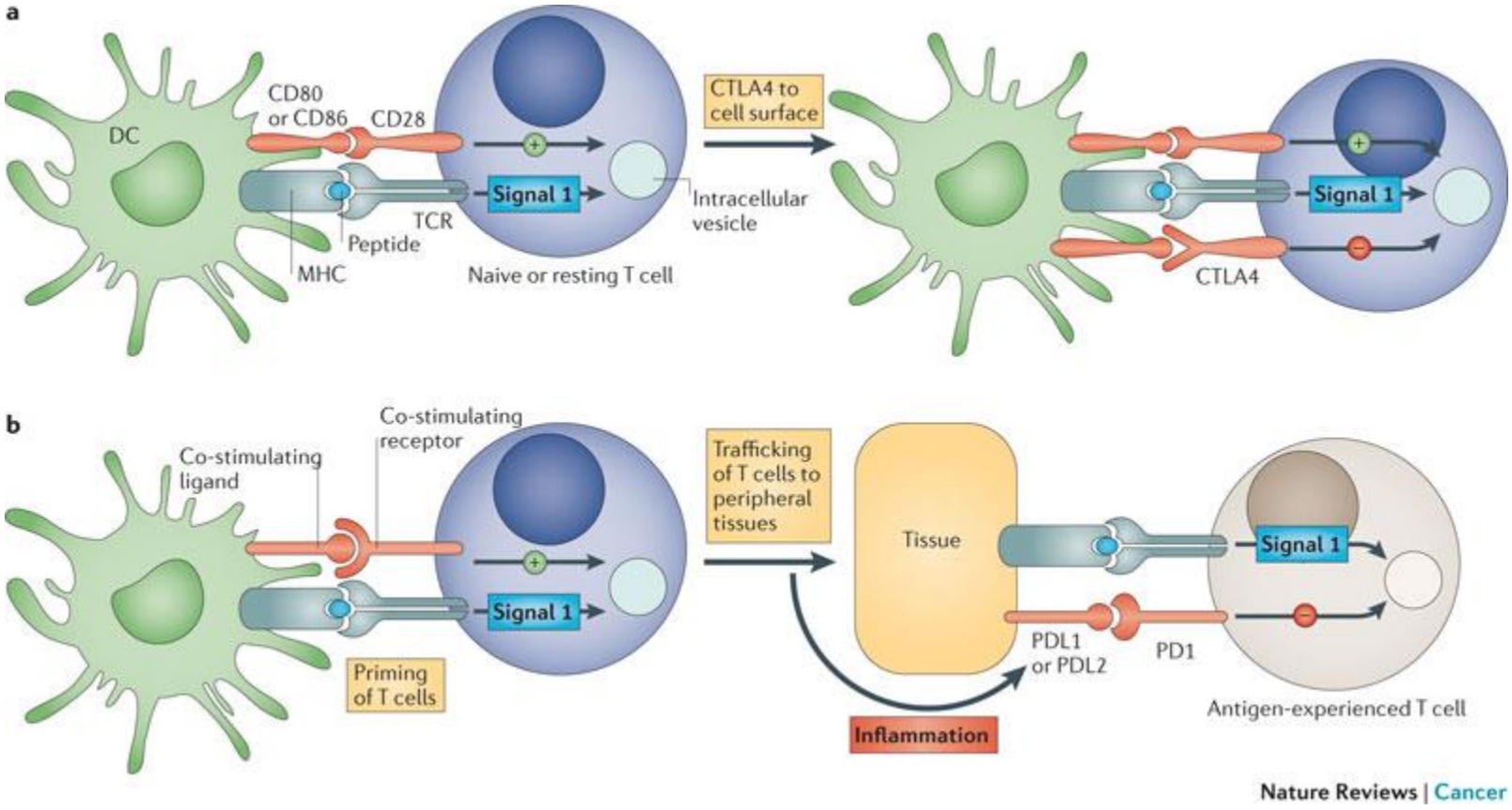
University of Birmingham

Going nowhere fast



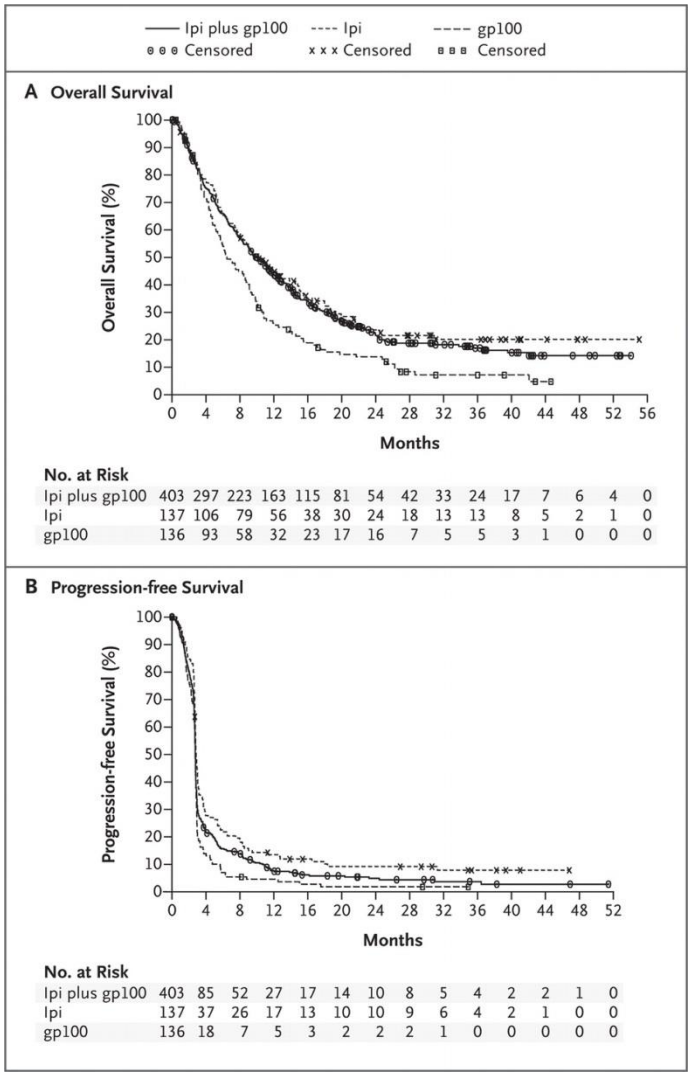
Vansteenkiste J et al. Lancet Oncol. 2016 Apr 27. pii: S1470-2045(16)00099-1.

Immune checkpoints regulate different components in the evolution of an immune response



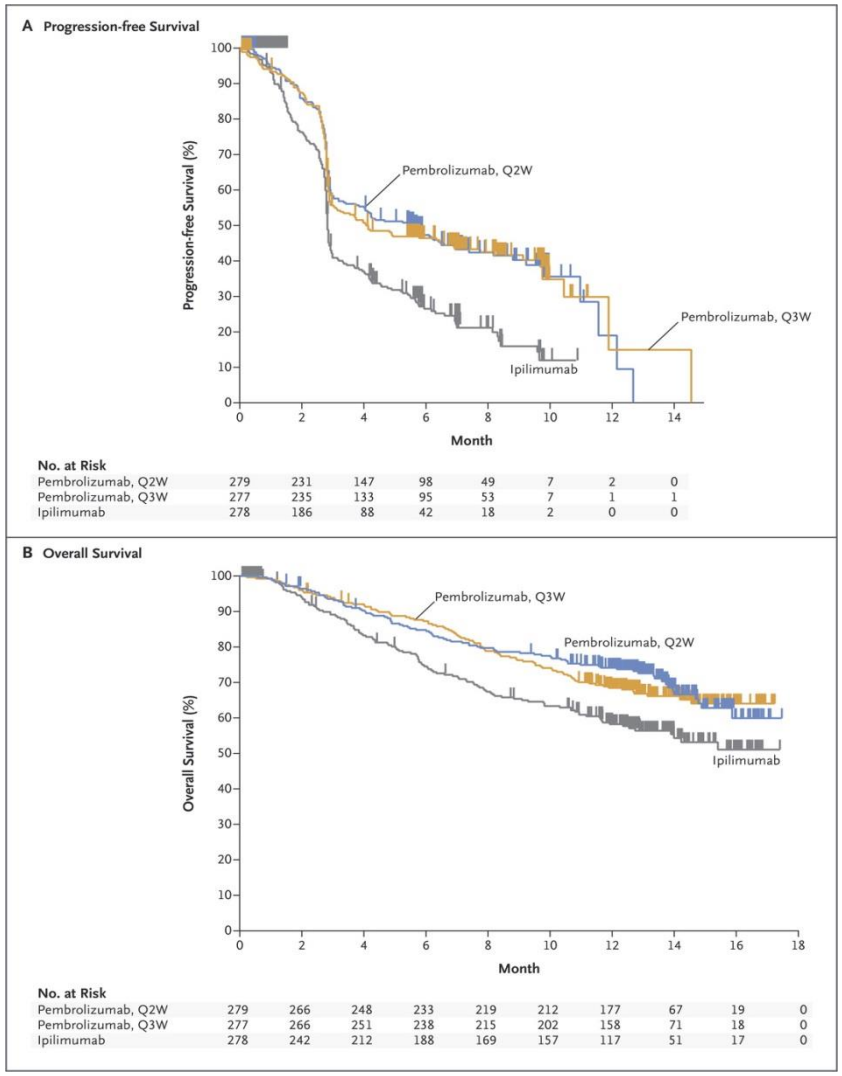
Pardoll DM. Nat Rev Cancer 2012 12:252-64

The impact of Ipilimumab in pre-treated melanoma
The first breakthrough (of many)



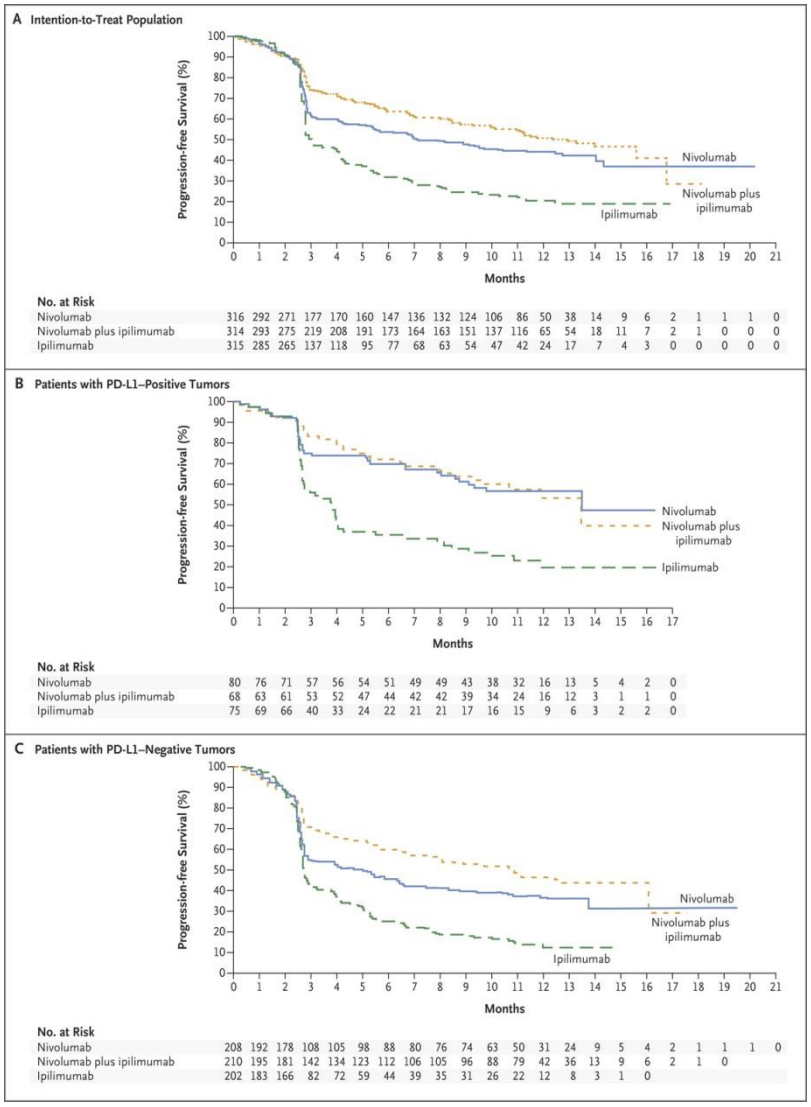
Hodi FS et al. N Engl J Med 2010;363:711-723.

Even if you can increase your T cells they still need to be able to effectively attack
PD-1 blockade versus CTLA4 blockade in melanoma



Robert C et al. N Engl J Med 2015;372:2521-2532.

So if both work why not try dual blockade PD-1 *plus* CTLA4 in melanoma



Larkin J et al. N Engl J Med 2015;373:23-34.

Response to Treatment

Table 2. Response to Treatment.

Variable	Nivolumab (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab (N=315)
Best overall response — no. (%)*			
Complete response	28 (8.9)	36 (11.5)	7 (2.2)
Partial response	110 (34.8)	145 (46.2)	53 (16.8)
Stable disease	34 (10.8)	41 (13.1)	69 (21.9)
Progressive disease	119 (37.7)	71 (22.6)	154 (48.9)
Could not be determined	25 (7.9)	21 (6.7)	32 (10.2)
Objective response†			
No. of patients with response	138	181	60
% of patients (95% CI)	43.7 (38.1–49.3)	57.6 (52.0–63.2)	19.0 (14.9–23.8)
Estimated odds ratio (95% CI)‡	3.40 (2.02–5.72)	6.11 (3.59–10.38)	—
Two-sided P value	<0.001	<0.001	—
Time to objective response — mo			
Median	2.78	2.76	2.79
Range	2.3–12.5	1.1–11.6	2.5–12.4

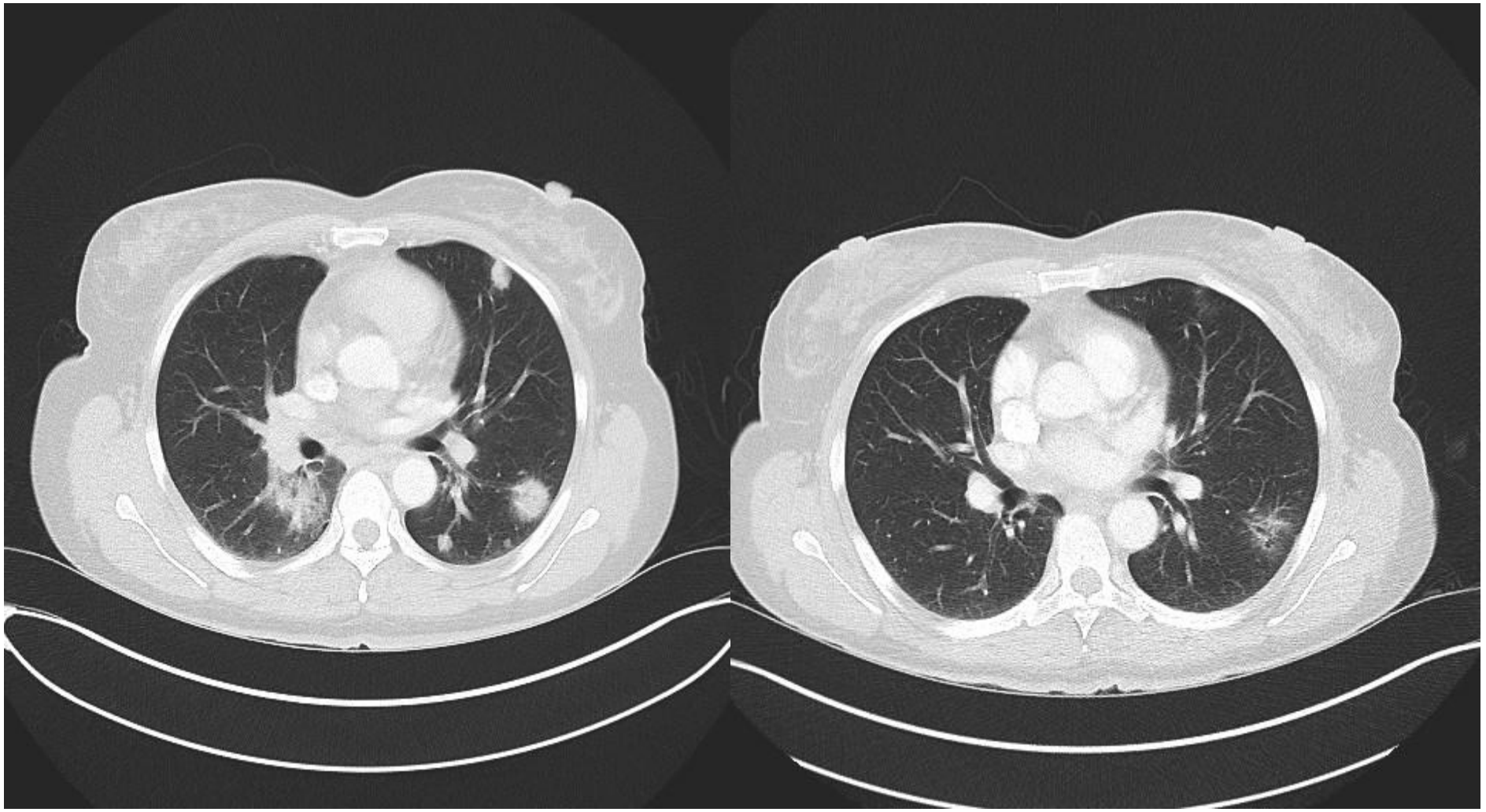
* The best overall response was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
† Data included patients with a complete response and those with a partial response. The calculation of the confidence interval was based on the Clopper–Pearson method. These analyses were conducted with the use of a two-sided Cochran–Mantel–Haenszel test stratified according to PD-L1 status, *BRAF* mutation status, and metastasis stage.
‡ The comparison is with the ipilimumab group.

Larkin J et al. N Engl J Med 2015;373:23-34.

But melanoma is an immunogenic cancer

What about a cancer where you don't expect much immune response

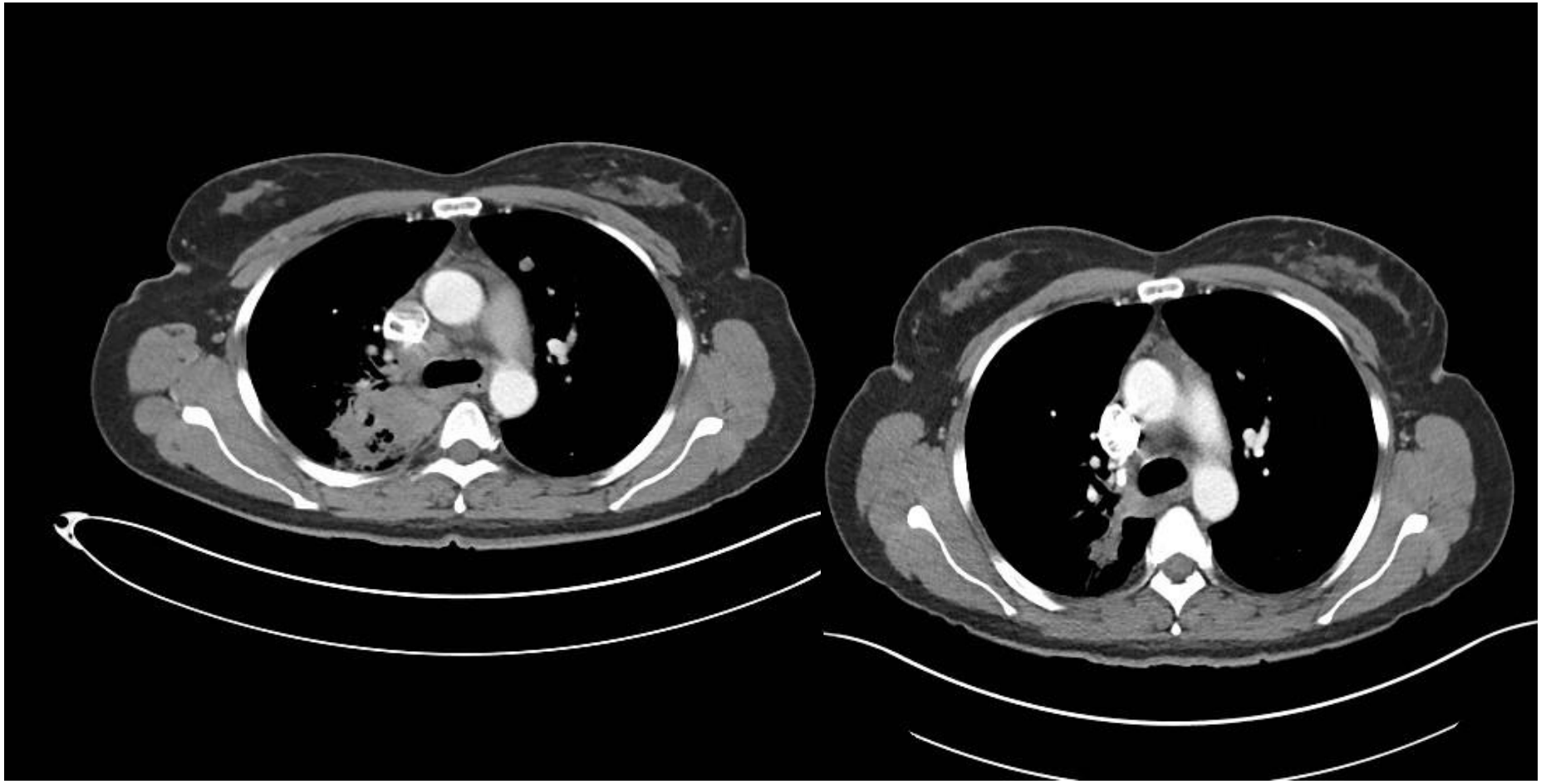
51, female, adenocarcinoma progressing on Pem/Cis



10/01/14

25/03/14

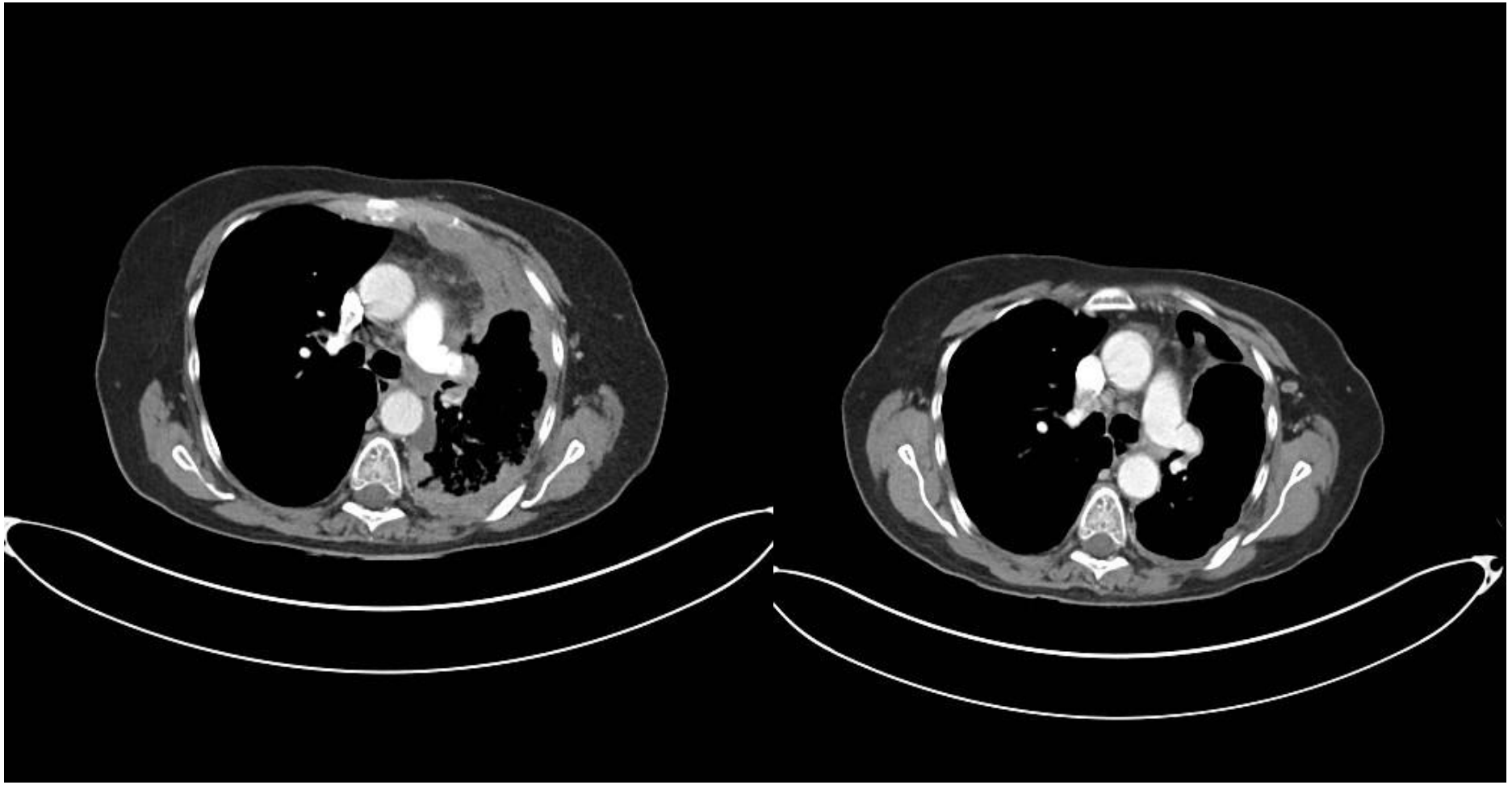
51, female, adenocarcinoma progressing on Pem/Cis



10/01/14

25/03/14

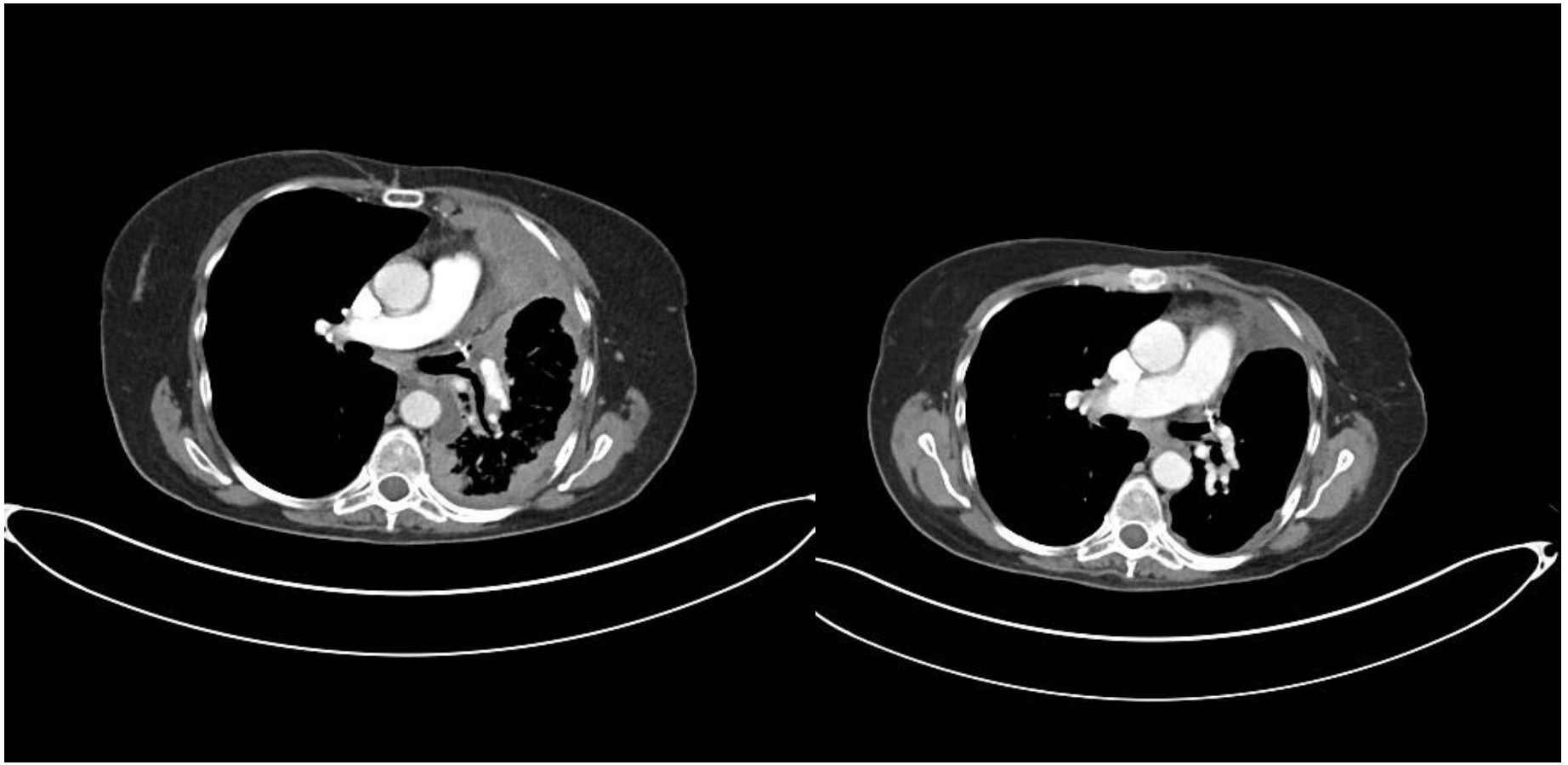
59, female, adenocarcinoma LUL lobectomy 11/12 9pT2a, N2 (station 5 node), then adjuvant chemotherapy till 4/13, then pleural effusion 9/13



4/12/13

12/2/14

59, female, adenocarcinoma LUL lobectomy 11/12 9pT2a, N2 (station 5 node), then adjuvant chemotherapy till 4/13, then pleural effusion 9/13



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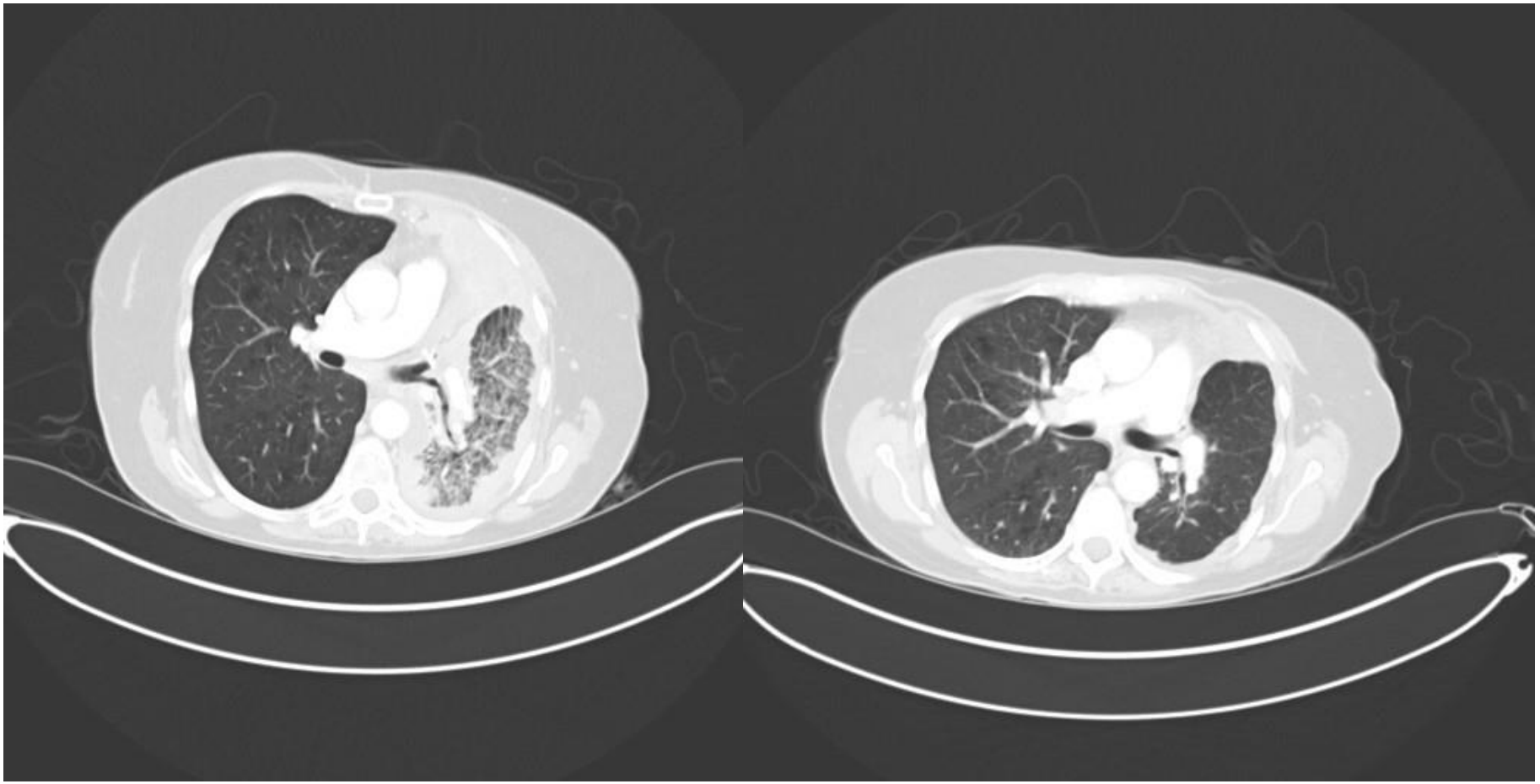
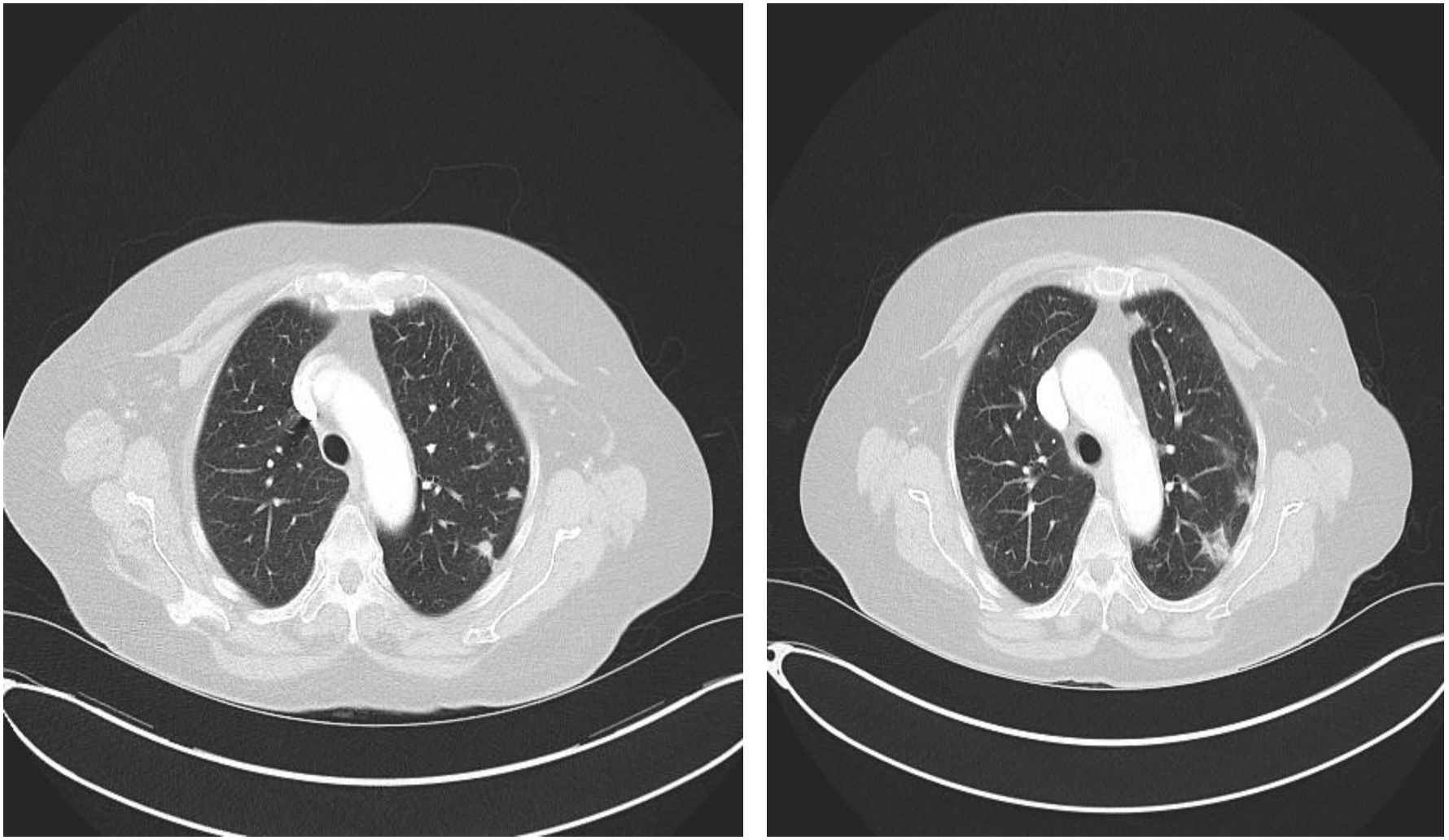


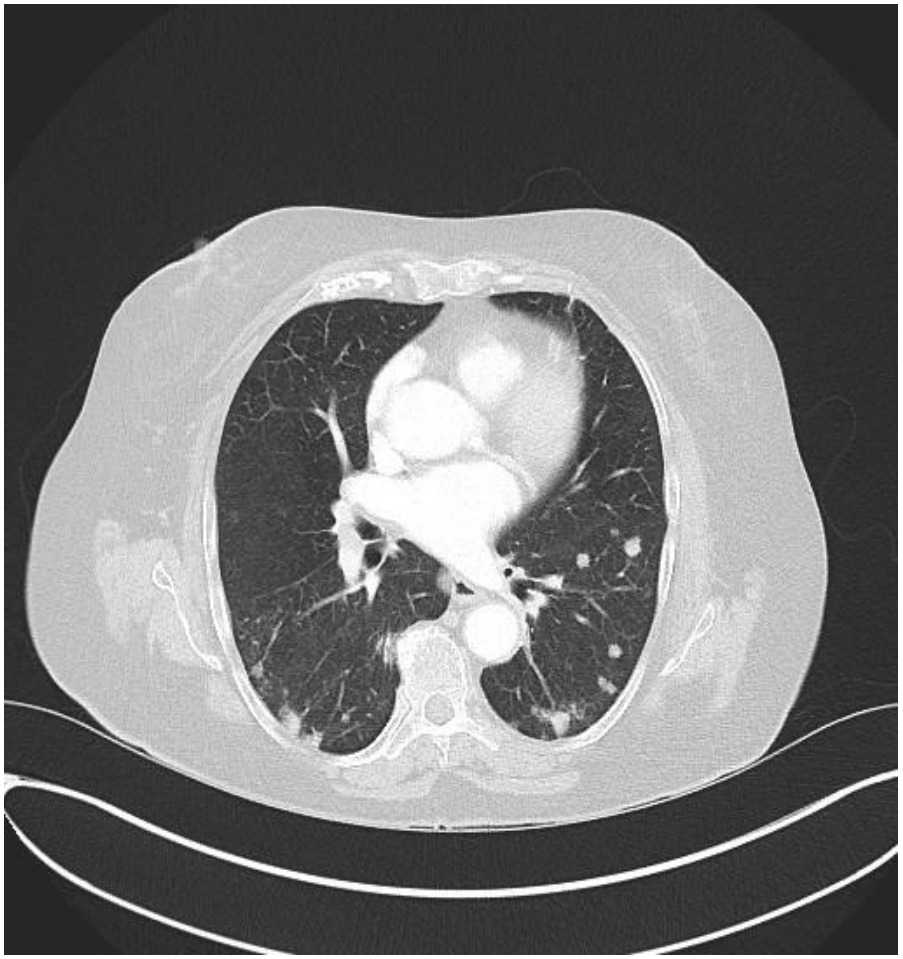
4/12/13

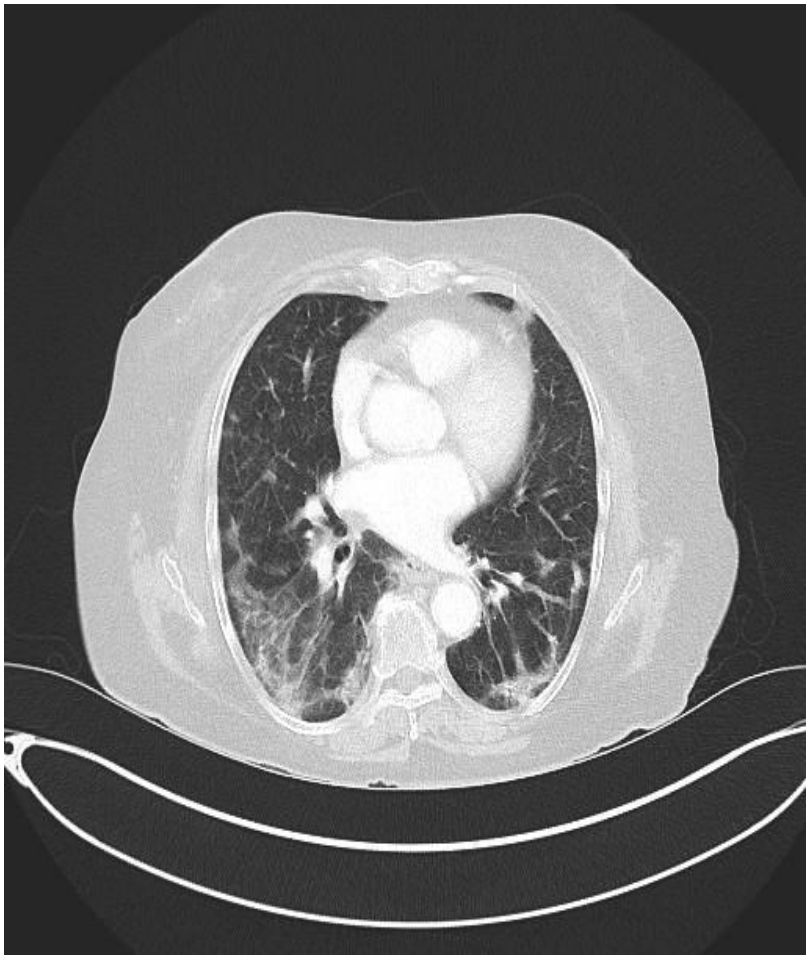
12/2/14

78, female, no previous therapy: Baseline and first on treatment scans

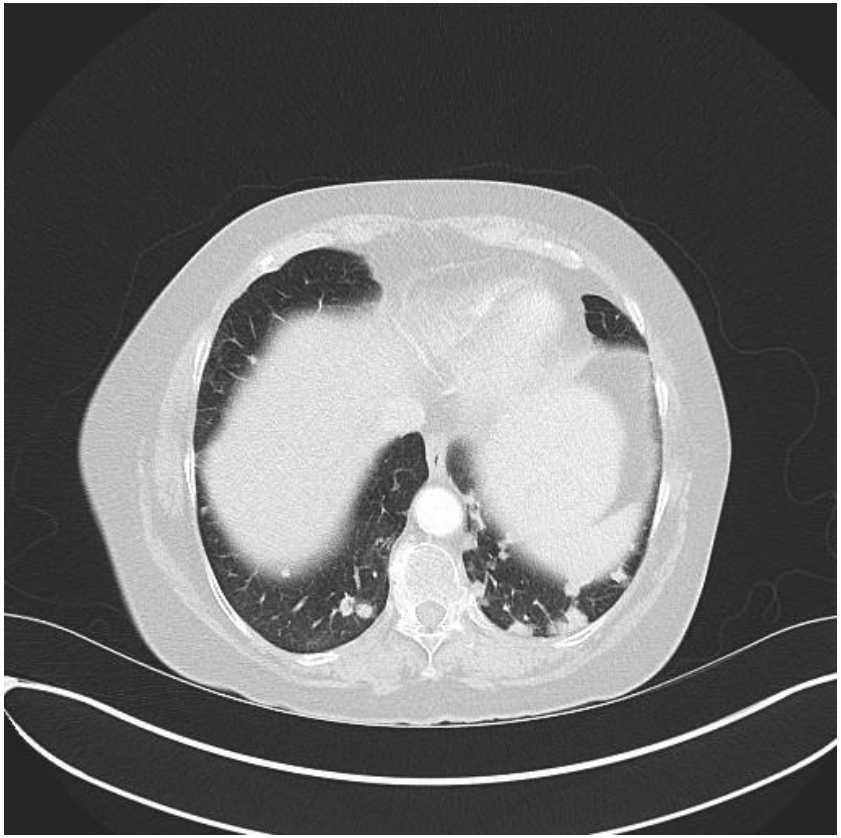


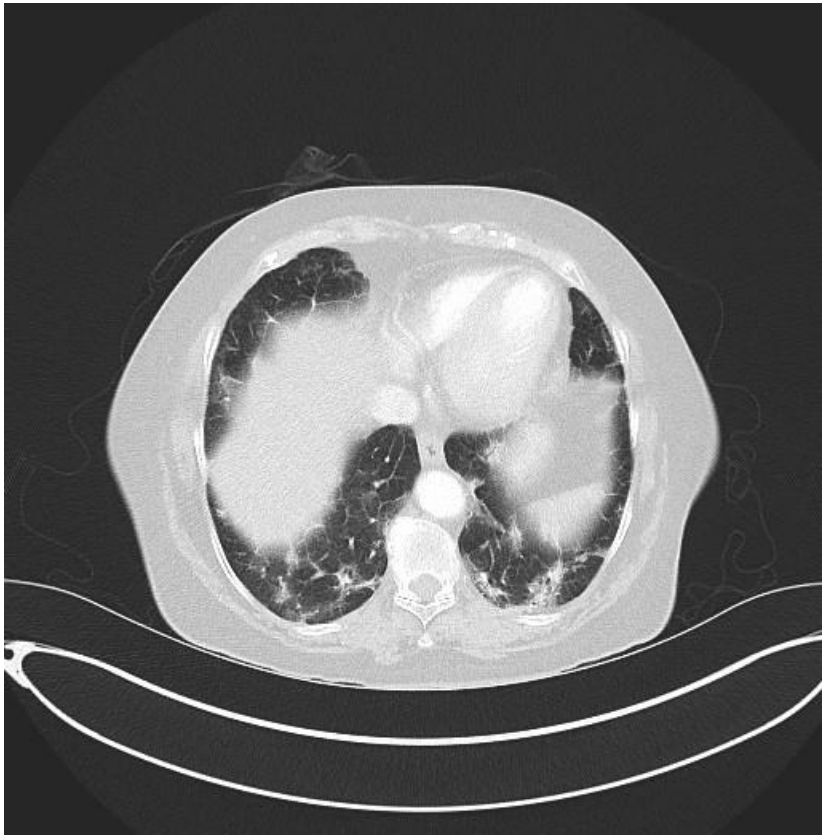
78, female, no previous therapy: Baseline and first on treatment scans



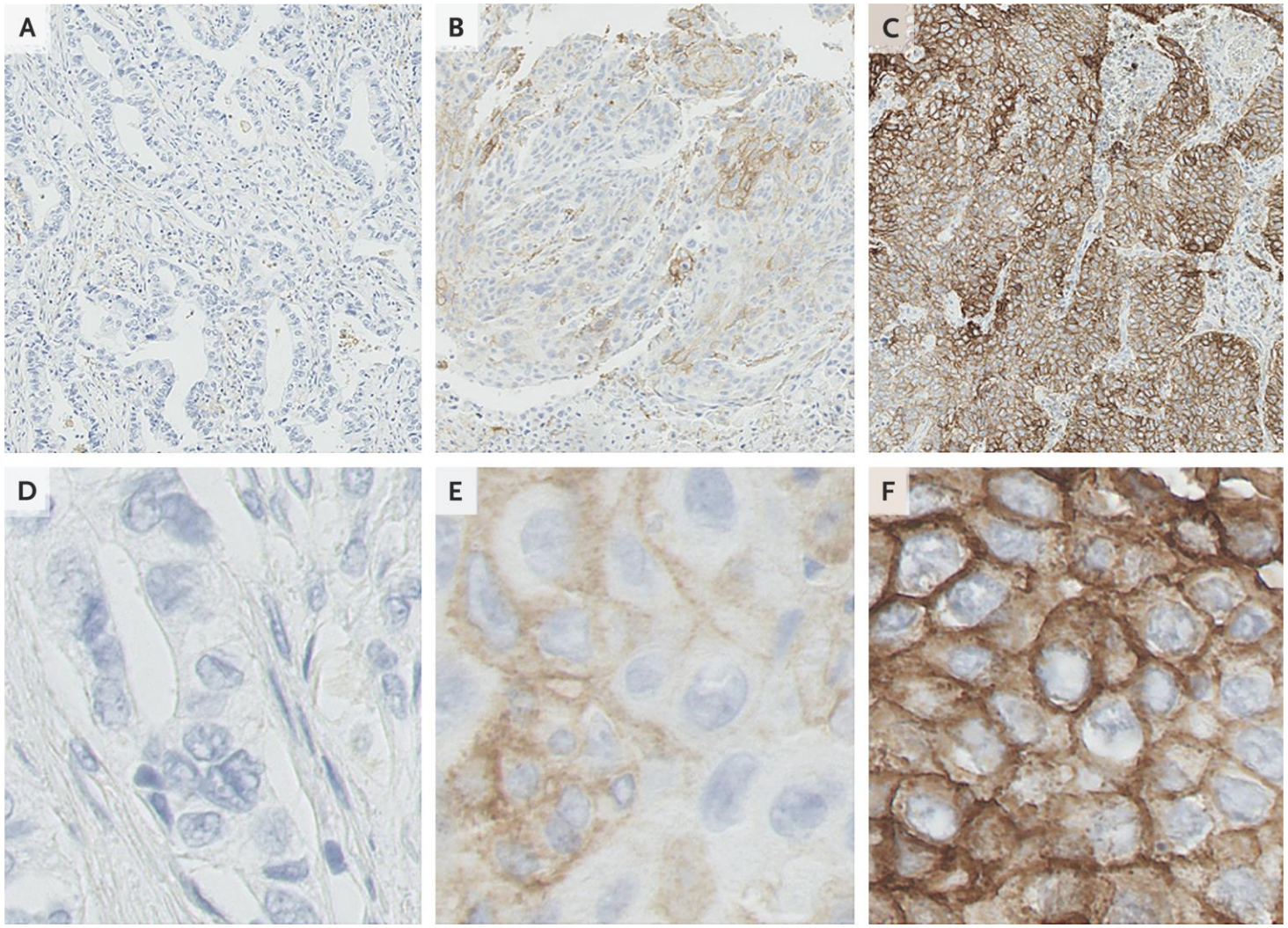


78, female, no previous therapy: Baseline and first on treatment scans





PD-L1 Expression in Non–Small-Cell Lung



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

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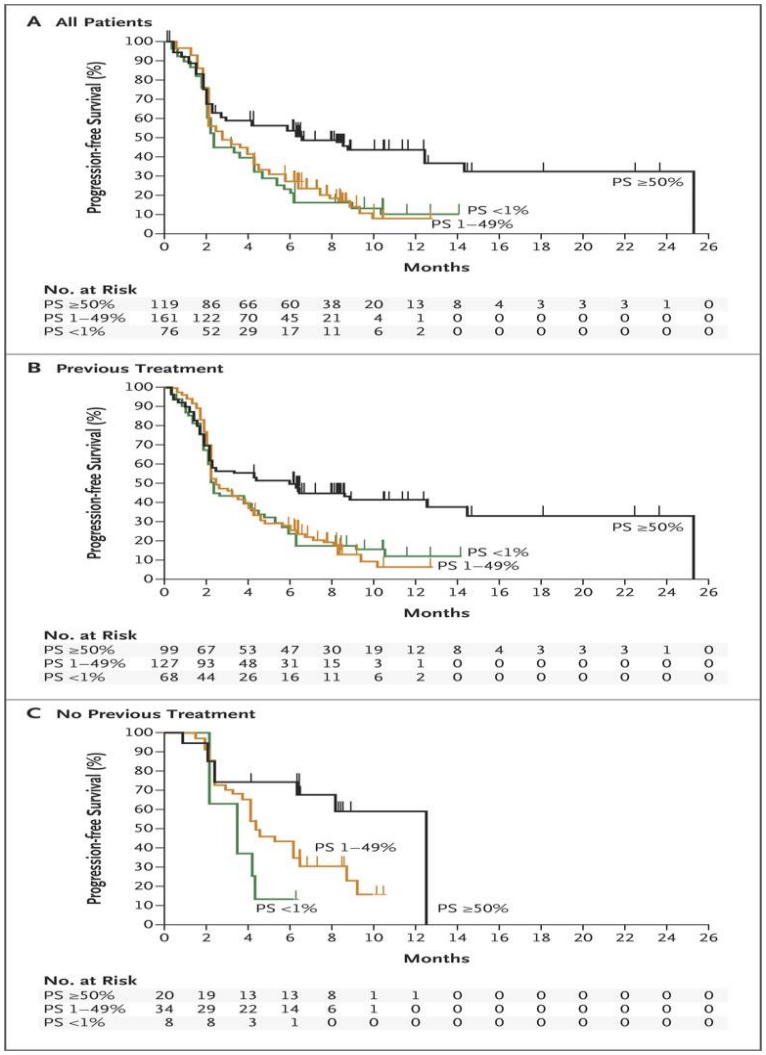
Progression-free Survival – KEYNOTE-001



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

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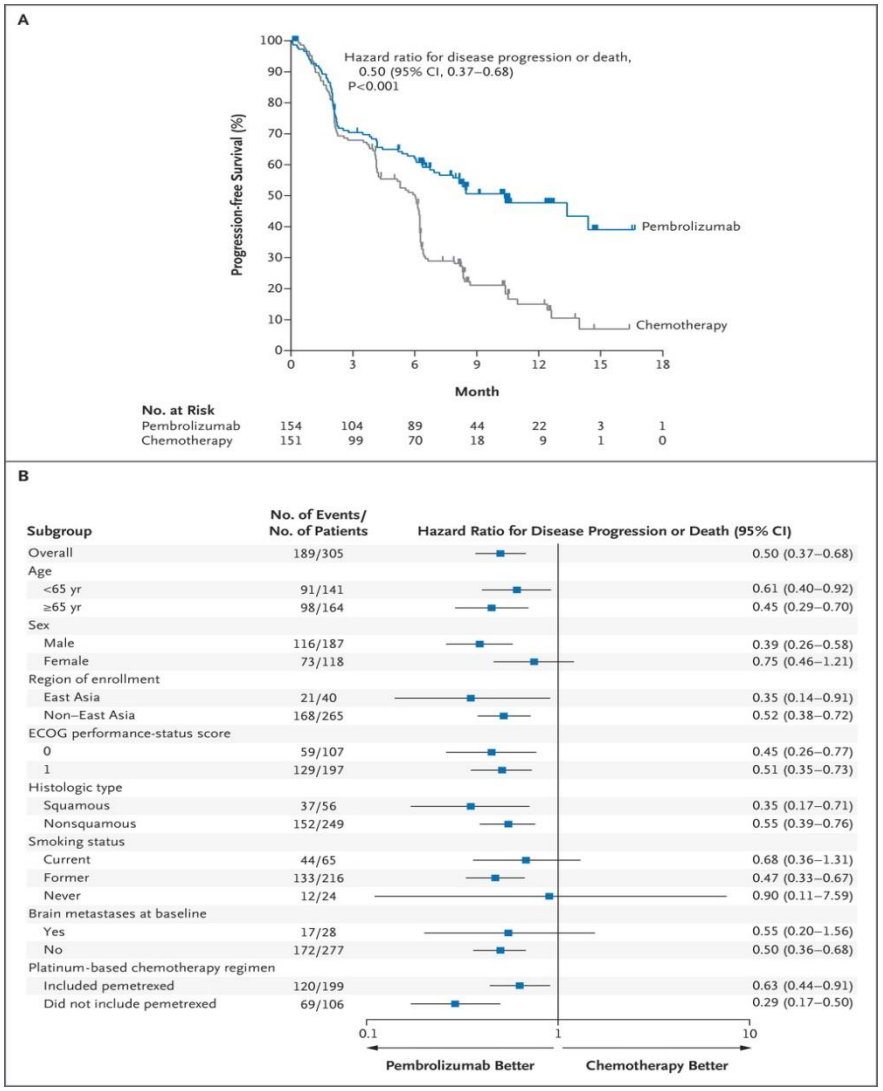
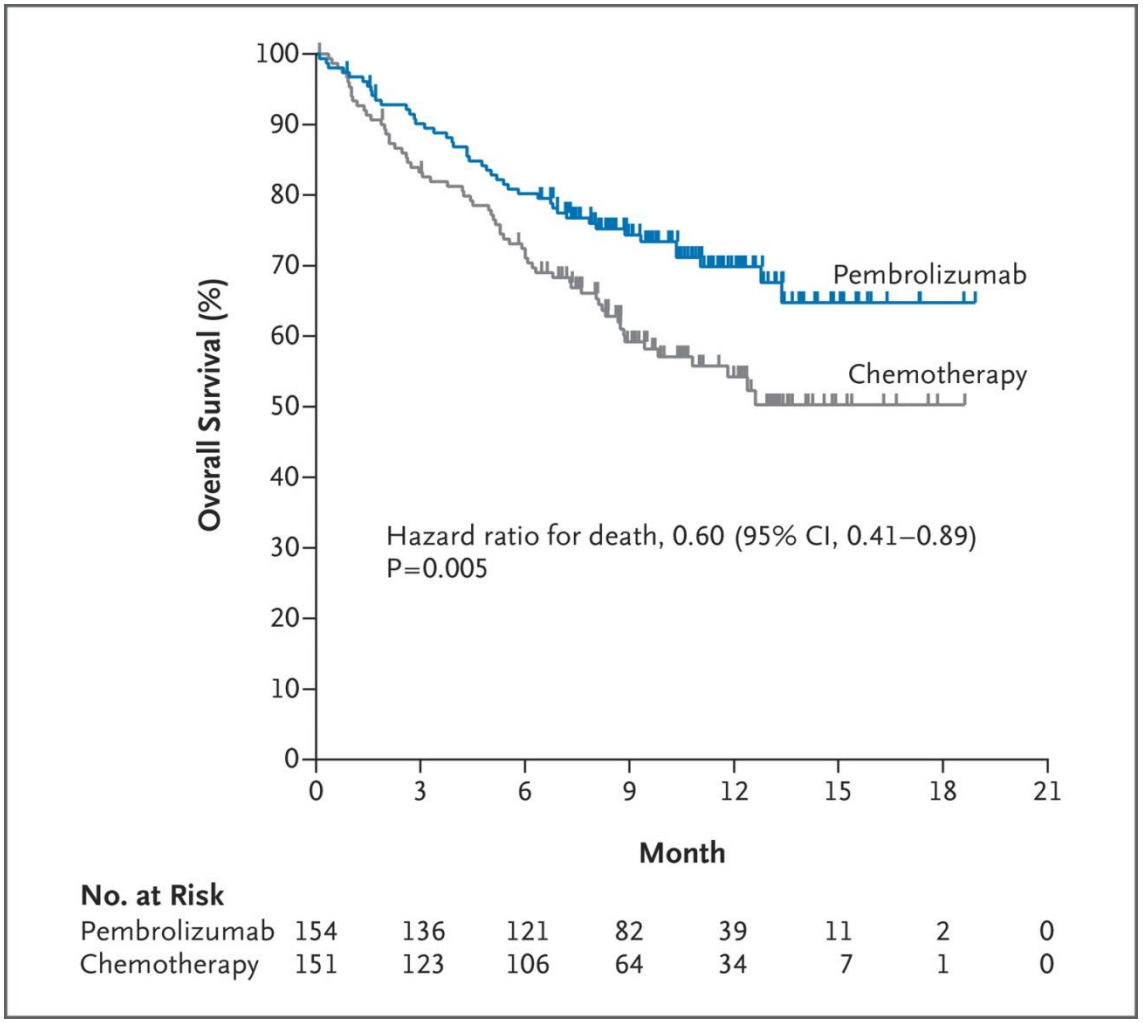
Head to head first-line with chemotherapy in the >50% PD-L1 expressing patient



Reck M et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1606774

Overall Survival in the Intention-to-Treat Population



Reck M et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1606774

Summary of Response in the Intention-to-Treat Population.

Table 2. Summary of Response in the Intention-to-Treat Population.*

Variable	Pembrolizumab Group (N=154)	Chemotherapy Group (N=151)
Objective response†		
No. of patients	69	42
% (95% CI)	44.8 (36.8 to 53.0)	27.8 (20.8 to 35.7)
Time to response — mo‡		
Median	2.2	2.2
Range	1.4 to 8.2	1.8 to 12.2
Duration of response — mo‡§		
Median	NR	6.3
Range	1.9+ to 14.5+	2.1+ to 12.6+

* The intention-to-treat population included all patients who underwent randomization. NR denotes not reached.

† Objective response was considered to be a confirmed complete or partial response, as assessed by means of blinded, independent, central radiologic review according to Response Evaluation Criteria in Solid Tumors, version 1.1. The estimated difference between the pembrolizumab group and the chemotherapy group, which was assessed with the use of the stratified method of Miettinen and Nurminen, was 16.6 percentage points (95% CI, 6.0 to 27.0).

‡ Time to response and duration of response were evaluated in the patients who had an objective response (69 patients in the pembrolizumab group and 42 in the chemotherapy group).

§ Duration of response was calculated with the use of the Kaplan–Meier method for censored data. Plus signs in the ranges indicate the response was ongoing at cutoff.

Reck M et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1606774

Adverse Events in the As-Treated Population.

Table 3. Adverse Events in the As-Treated Population.*

Adverse Event	Pembrolizumab Group (N=154)		Chemotherapy Group (N=150)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Treatment-related†				
Any	113 (73.4)	41 (26.6)	135 (90.0)	80 (53.3)
Serious	33 (21.4)	29 (18.8)	31 (20.7)	29 (19.3)
Led to discontinuation	11 (7.1)	8 (5.2)	16 (10.7)	9 (6.0)
Led to death	1 (0.6)	1 (0.6)	3 (2.0)	3 (2.0)
Occurred in ≥10% of patients in either group‡				
Nausea	15 (9.7)	0	65 (43.3)	3 (2.0)
Anemia	8 (5.2)	3 (1.9)	66 (44.0)	29 (19.3)
Fatigue	16 (10.4)	2 (1.3)	43 (28.7)	5 (3.3)
Decreased appetite	14 (9.1)	0	39 (26.0)	4 (2.7)
Diarrhea	22 (14.3)	6 (3.9)	20 (13.3)	2 (1.3)
Neutropenia	1 (0.6)	0	34 (22.7)	20 (13.3)
Vomiting	4 (2.6)	1 (0.6)	30 (20.0)	1 (0.7)
Pyrexia	16 (10.4)	0	8 (5.3)	0
Constipation	6 (3.9)	0	17 (11.3)	0
Stomatitis	4 (2.6)	0	18 (12.0)	2 (1.3)
Decreased neutrophil count	0	0	20 (13.3)	6 (4.0)
Increased blood creatinine level	3 (1.9)	0	15 (10.0)	1 (0.7)
Decreased platelet count	0	0	18 (12.0)	9 (6.0)
Thrombocytopenia	0	0	17 (11.3)	8 (5.3)
Decreased white-cell count	1 (0.6)	0	16 (10.7)	3 (2.0)
Dysgeusia	1 (0.6)	0	15 (10.0)	0
Immune-mediated§				
Any	45 (29.2)	15 (9.7)	7 (4.7)	1 (0.7)
Hypothyroidism	14 (9.1)	0	2 (1.3)	0
Hyperthyroidism	12 (7.8)	0	2 (1.3)	0
Pneumonitis	9 (5.8)	4 (2.6)	1 (0.7)	1 (0.7)
Infusion reaction	7 (4.5)	0	2 (1.3)	0
Severe skin reaction	6 (3.9)	6 (3.9)	0	0
Thyroiditis	4 (2.6)	0	0	0
Colitis	3 (1.9)	2 (1.3)	0	0
Myositis	3 (1.9)	0	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Nephritis	1 (0.6)	1 (0.6)	0	0
Pancreatitis	1 (0.6)	1 (0.6)	0	0
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)	0	0

* The as-treated population included all patients who received at least one dose of a trial treatment. For the patients in the chemotherapy group who crossed over to the pembrolizumab group after disease progression, only events that occurred during treatment with the assigned chemotherapy regimen are included.
† Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case-report form. Although decreased neutrophil count and neutropenia may reflect the same condition, they were listed by the investigators as two distinct events; this is also the case for decreased platelet count and thrombocytopenia.
‡ Events are listed in descending order of frequency in the total population.
§ The immune-mediated events, both those that were and those that were not attributed to study treatment by the investigator, are listed in descending order of frequency in the pembrolizumab group. In addition to specific preferred terms, related terms are also included.

Reck M et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1606774

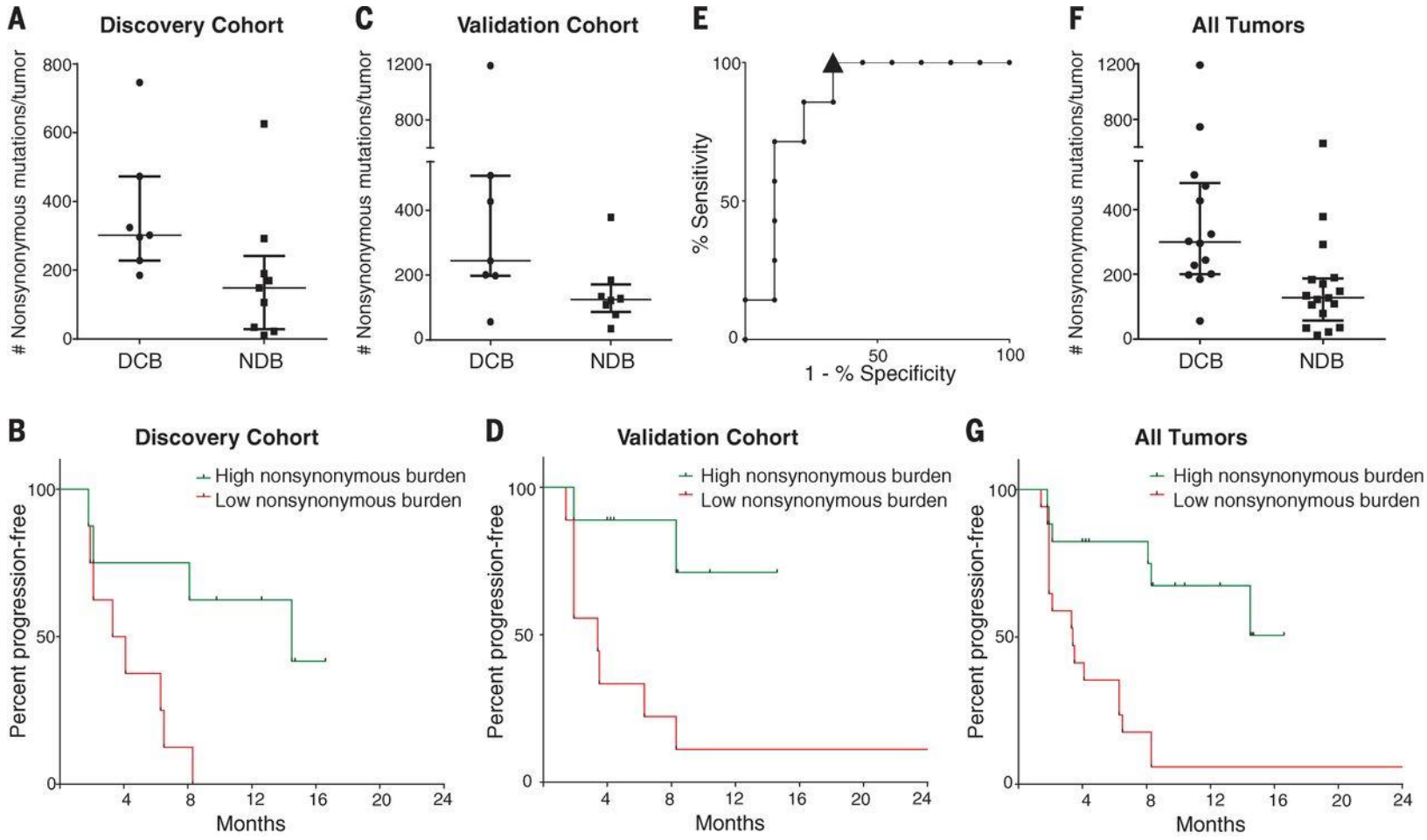
CheckMate 012: Safety and efficacy of first-line (1L) nivolumab (nivo; N) and ipilimumab (ipi; I) in advanced (adv) NSCLC. Hellmann M et al. ASCO #3001

No Rx-related deaths >70% PD-L1 + (>1%)

	Nivo3/Ipi1 q12w	***N3/I1q6w***	***Nivo mono***
n=	38	39	
Gd 3/4 AE	37%	33%	19%
ORR	47%	39%	23%
DOR	NR	NR	NR
>1% PD-L1 +	**57%**	**57%**	**28%**
>50%	**100%**	**87%**	

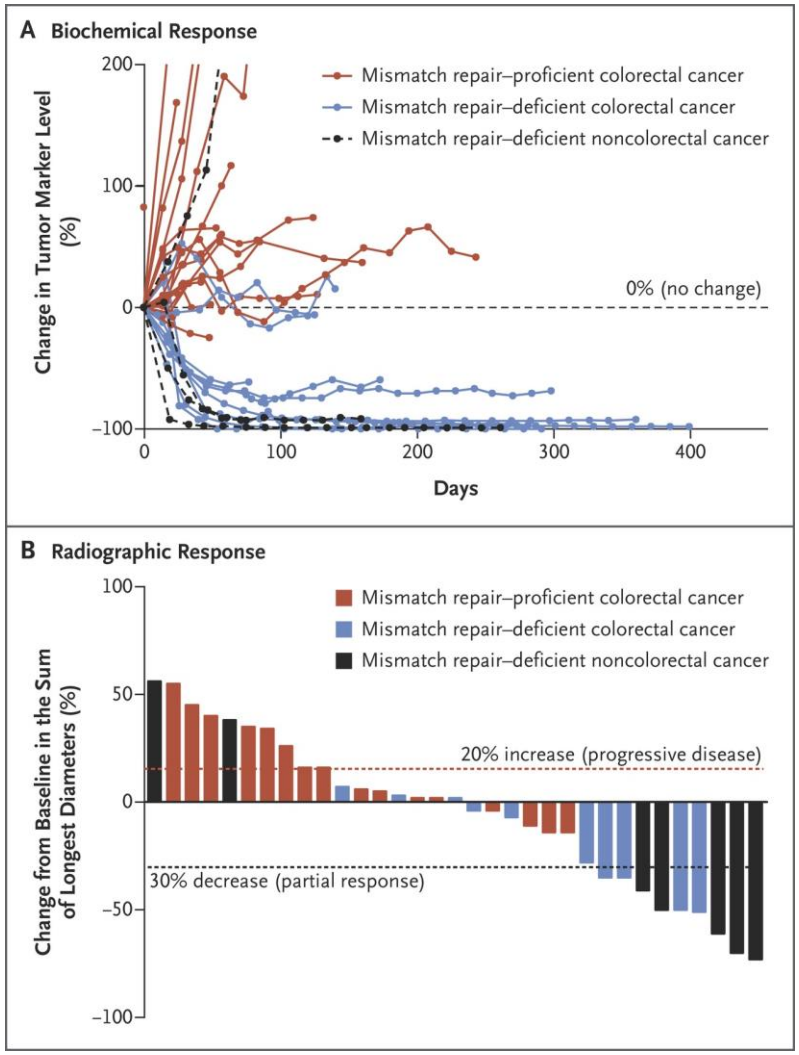
Never smokers	27%	9%
EGFR mut	56%	14%

Nonsynonymous mutation burden associated with clinical benefit of anti–PD-1 therapy.



Naiyer A. Rizvi et al. Science 2015;348:124-128

Clinical Responses to Pembrolizumab Treatment.



Le DT et al. N Engl J Med 2015;372:2509-2520

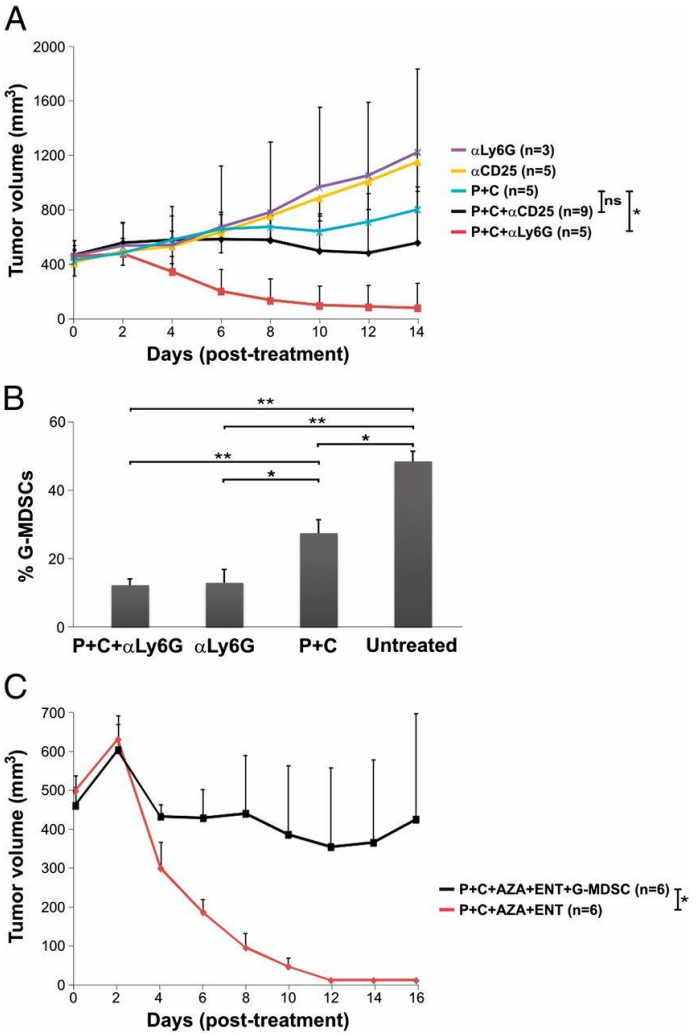
The NEW ENGLAND JOURNAL of MEDICINE

What else might limit checkpoint inhibitor efficacy beyond low mutation rate?

The myeloid derived suppressor cell

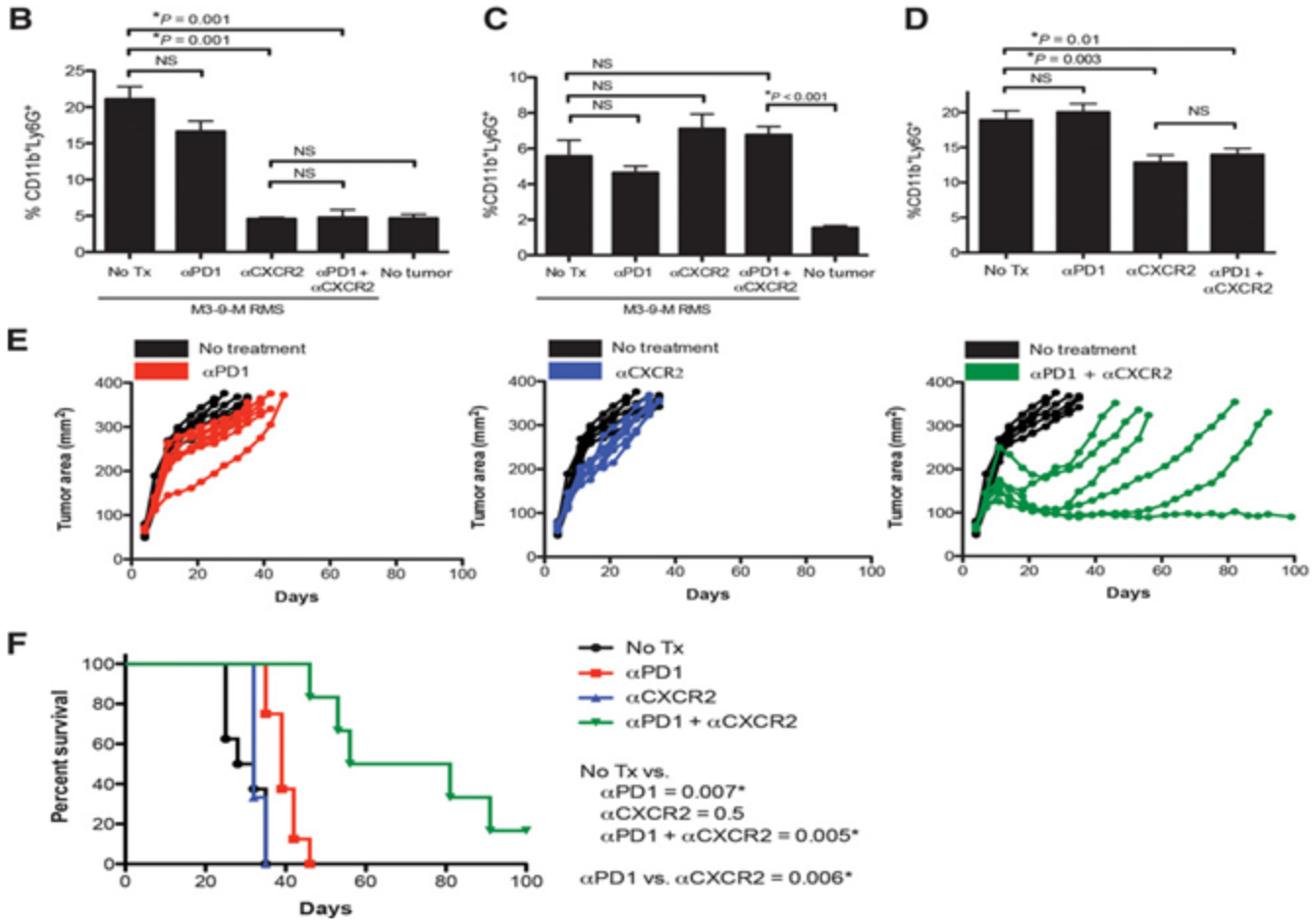
Multiple immune suppressive mechanisms in one cell

Myeloid-derived Ly6G+ cells are responsible for resistance to immune checkpoint blockade.



KiBem Kim et al. PNAS 2014;111:11774-11779

The effectiveness of PD1 checkpoint blockade on established tumors is enhanced by anti-CXCR2 mAb therapy.

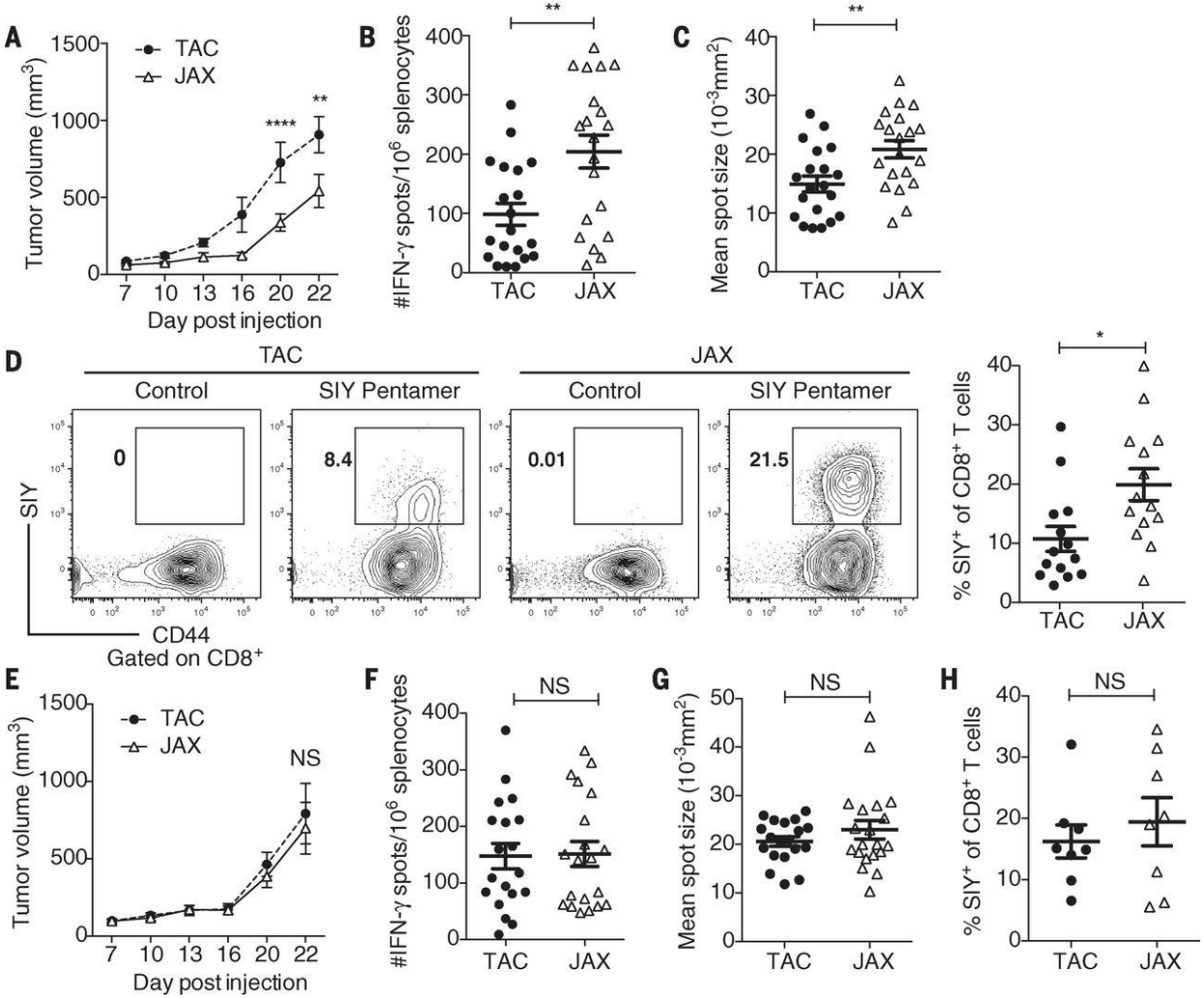


Steven L. Highfill et al., Sci Transl Med 2014;6:237ra67

The microbiome

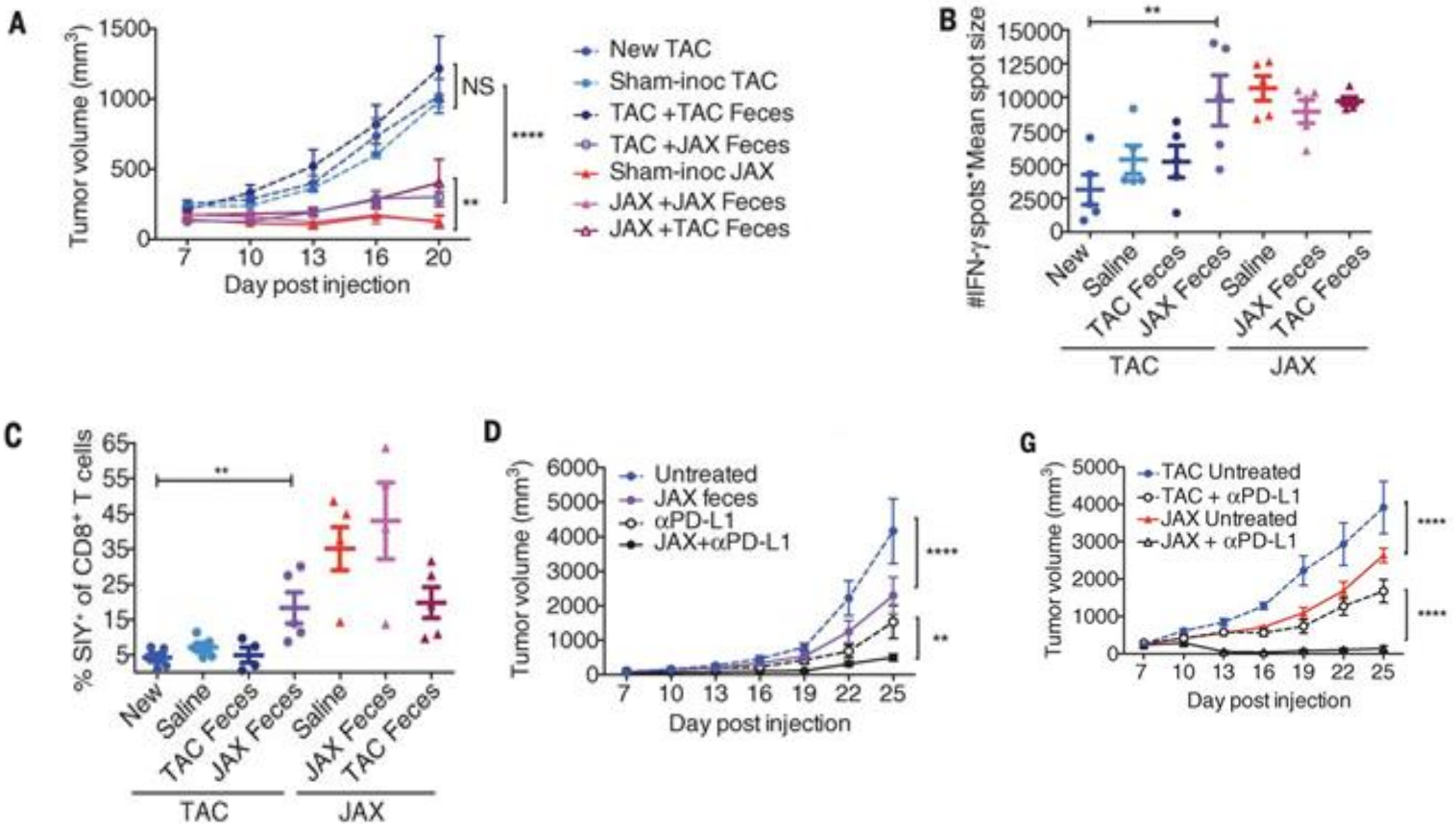
What effect on the immune system does what you have in your gut have?

Differences in melanoma outgrowth and tumor-specific immune responses between C57BL/6 JAX and TAC mice are eliminated when mice are cohoused.



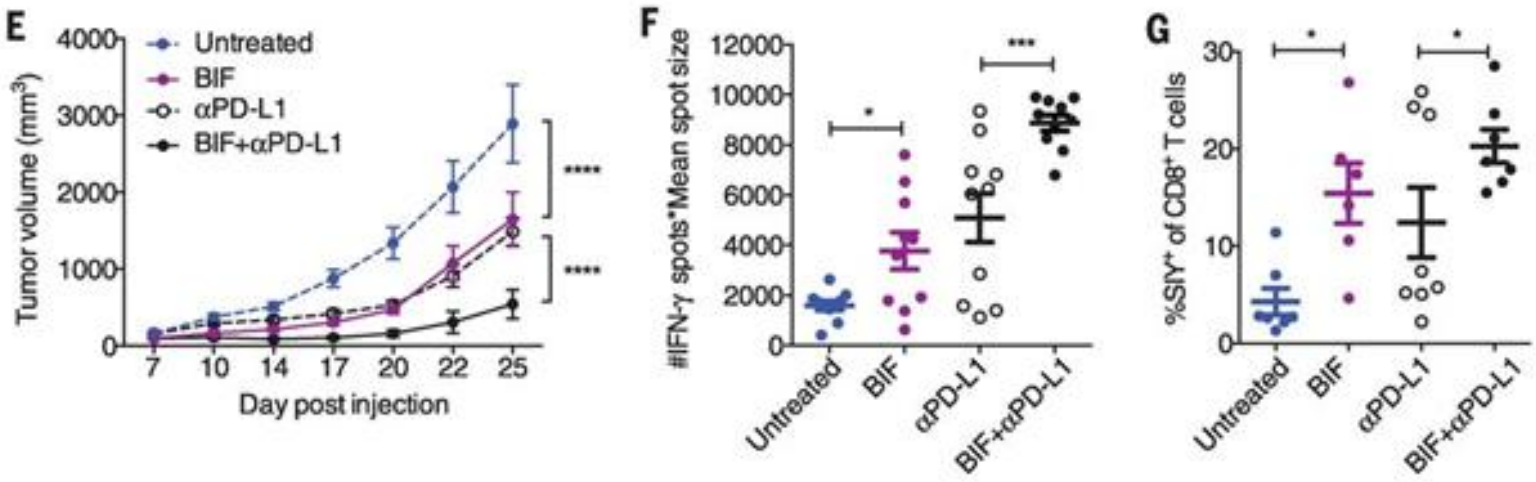
Ayelet Sivan et al. Science 2015;350:1084-1089

Oral administration of JAX fecal material to TAC mice enhances spontaneous antitumor immunity and response to αPD-L1 mAb therapy.



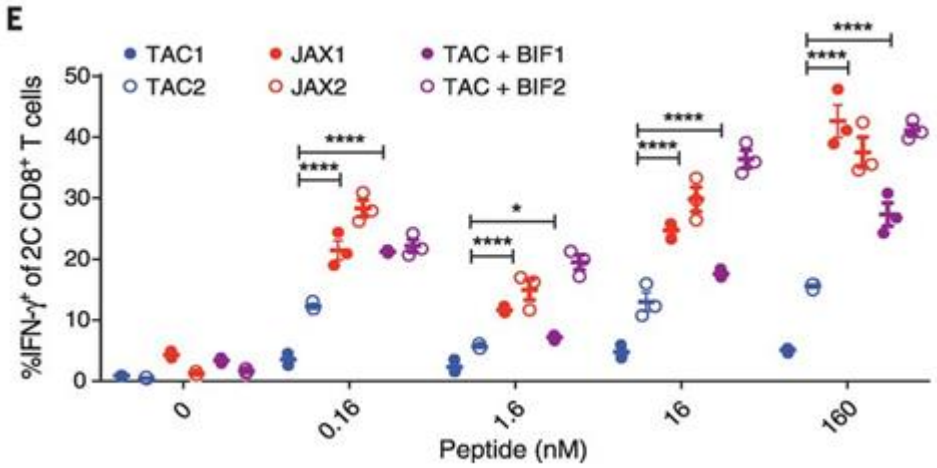
Ayelet Sivan et al. Science 2015;350:1084-1089

Direct administration of Bifidobacterium to TAC recipients with established tumors improves tumor-specific immunity and response to αPD-L1 mAb therapy.



Ayelet Sivan et al. Science 2015;350:1084-1089

Dendritic cells isolated from JAX and Bifidobacterium-fed TAC mice show increased expression of genes associated with antitumor immunity and heightened capability for T cell activation.



Ayelet Sivan et al. Science 2015;350:1084-1089

Published by AAAS

Pulling it all together
PePS2

Expanding the population

ctDNA as surrogate for mutational load

Longitudinal MDSC analysis

Gut bacterial metagenomics

Back to the future

A vaccine to prevent cancer??!!