Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Coupling and decoupling of tumor immunity from autoimmunity induced by checkpoint inhibitors

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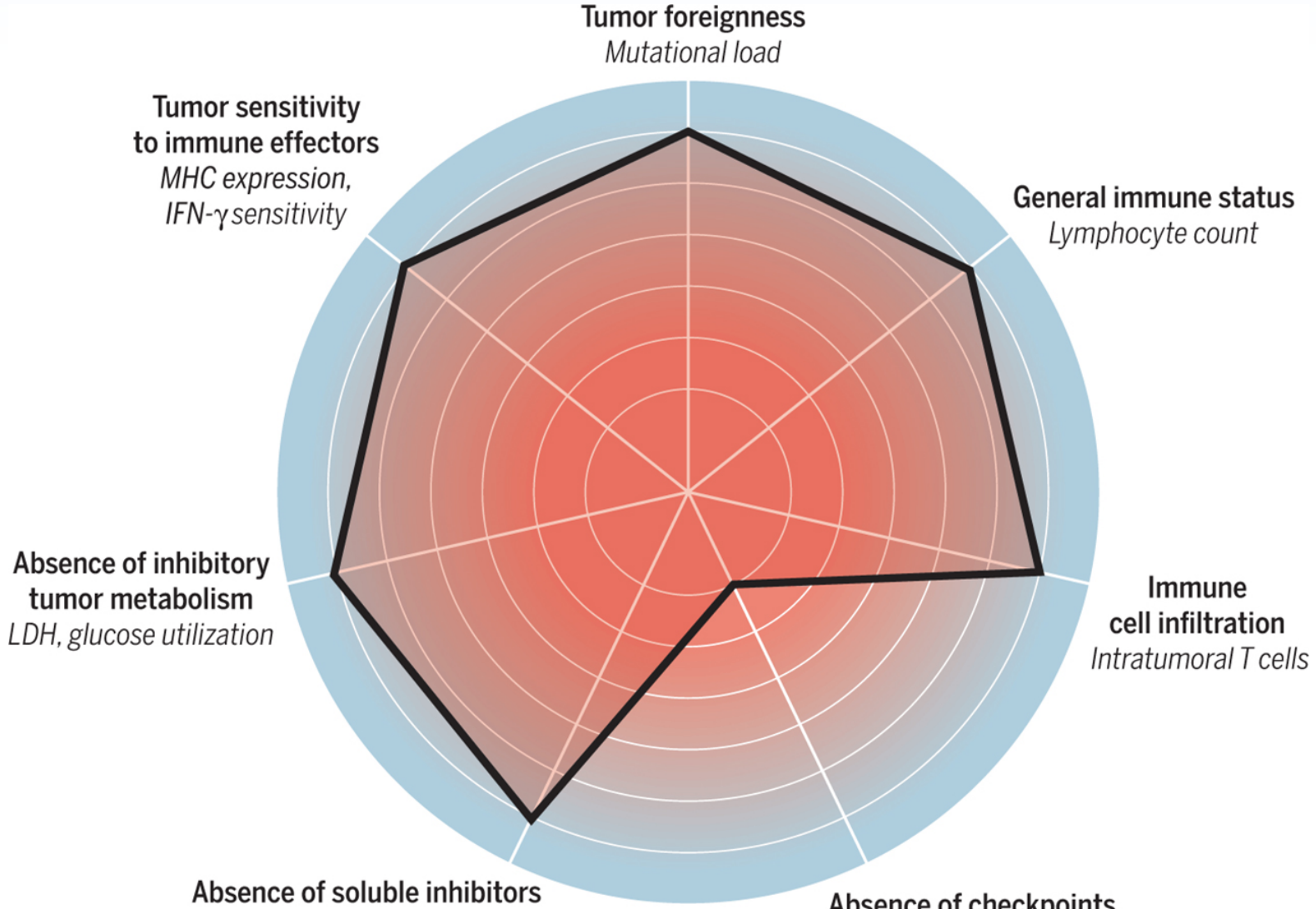
Disclosures

- Consulting or advisory role: Apexigen, Array, BMS, Celgene, CureVac, Dragonfly, Iovance, Nektar, Memgen
- Research funding (institution): Idera, Nektar, Pfizer, BMS , Apexigen
- I will be discussing non-FDA approved indications during my presentation.

Multiple Mechanisms of Immune Resistance/Escape



Blank C et al Science 2016

- Toxicity of the combined ICI therapy remains a major challenge
- Immune-related adverse events (irAEs) require treatment with immunosuppressants, and can sometimes be fatal
- Identification of strategies to mitigate toxicity without hindering antitumor immune response remain **a critical unmet need**

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

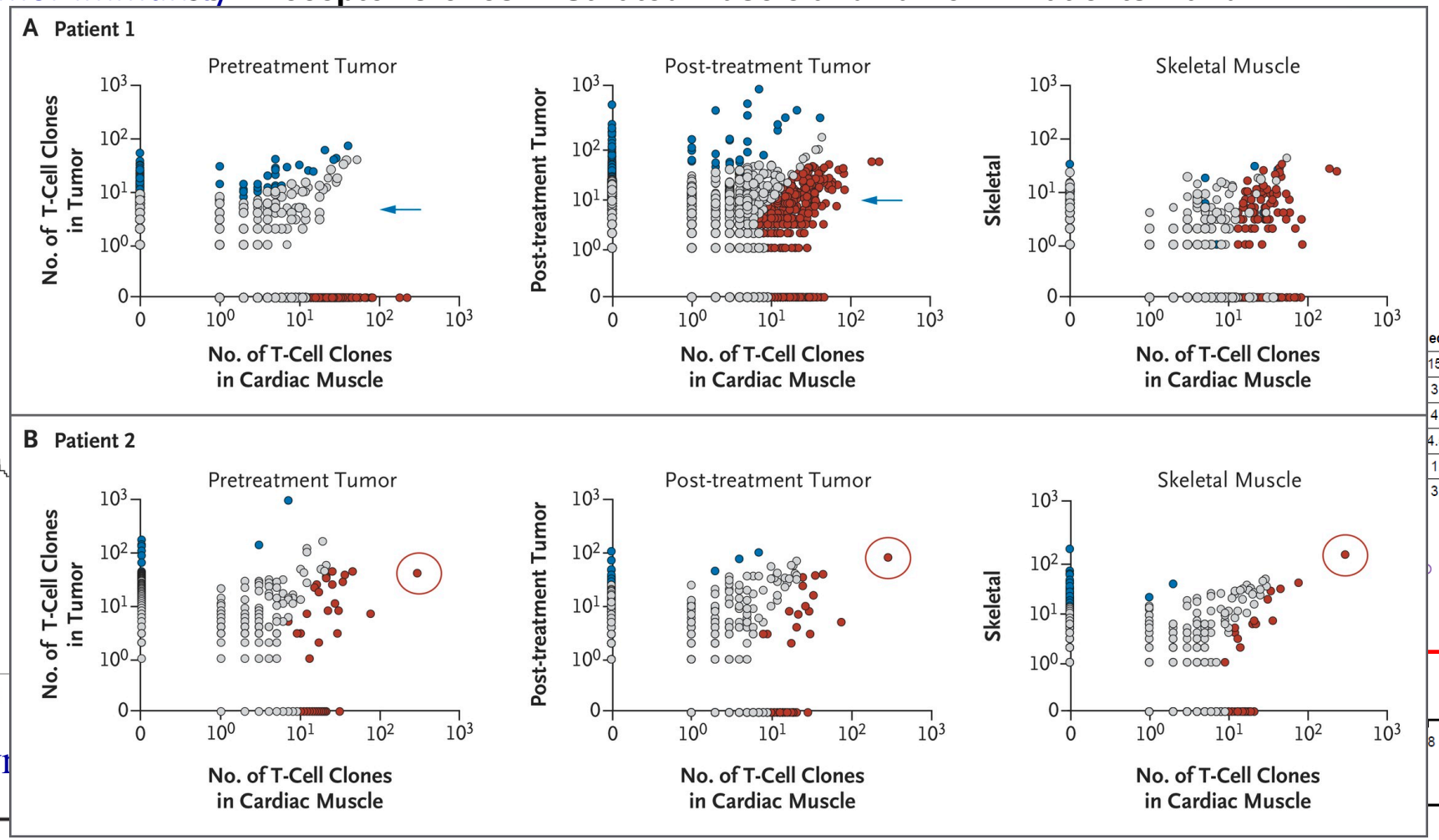
Larkin et al. NEJM. 2015

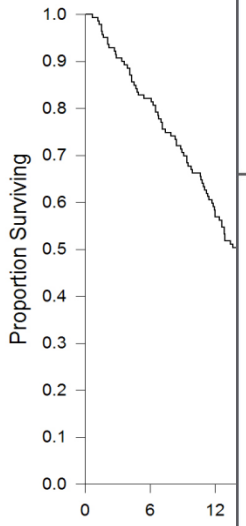
Tumor immunity and autoimmunity
Share many common features

Tumor Immunity

Auto-Immunity /irAE

T-Cell–Receptor Clones in Striated Muscle and Tumor in Patients 1 and 2.

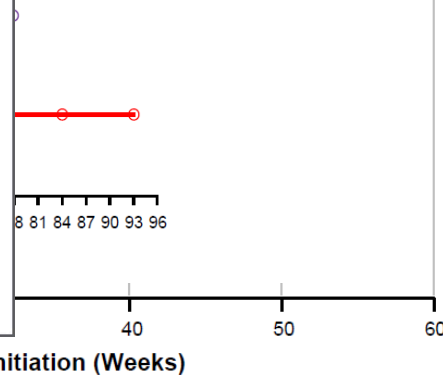




10 yr

-100

	Resolved, n/N (%)	
edian (95% CI)	Overall	Treated with IMM
15.1 (4.6, NA)	13/21 (61.9)	9/16 (56.3)
3.6 (2.0, 4.3)	69/73 (94.5)	62/65 (95.4)
4.3 (3.1, 5.6)	74/76 (97.4)	52/52 (100)
4.5 (0.3, 10.1)	6/6 (100)	5/5 (100)
1.9 (0.4, 3.6)	7/7 (100)	4/4 (100)
3.9 (2.1, 6.1)	27/33 (81.8)	23/29 (79.3)



Hodi et al. ESMO 2013

Association between toxicity and immune response

Table 2. Impact of Treatment-Related Select AEs and IM Use on Response to Nivolumab Therapy

		Any-Grade Treatment-Related Select AEs*				Grade 3 to 4 Treatment-Related Select AEs		Patients Receiving Systemic IM	
	All Patients (N = 576)	Any (n = 255)	None (n = 321)	1-2 (n = 242)	≥ 3 (n = 13)	Yes (n = 18)	No (n = 558)	Yes (n = 114)	No (n = 462)
ORR, No. of patients (%)	181 (31.4)	124 (48.6)	57 (17.8)	113 (46.7)	11 (84.6)	5 (27.8)	176 (31.5)	34 (29.8)	147 (31.8)
95% CI	27.6 to 35.4	42.3 to 54.9	13.7 to 22.4	40.3 to 53.2	54.6 to 98.1	9.7 to 53.5	27.7 to 35.6	21.6 to 39.1	27.6 to 36.3
P		< .001		< .0001†	< .001†	1.00		.736	

Abbreviations: AE, adverse event; IM, immune-modulating agent; ORR, objective response rate.
*Data in these columns are for patients with the indicated numbers of any-grade treatment-related select AEs: any AE, no AEs, 1-2 AEs, and ≥ 3 AEs.
†Versus no treatment-related select AEs.

Webber et al JCO 2017

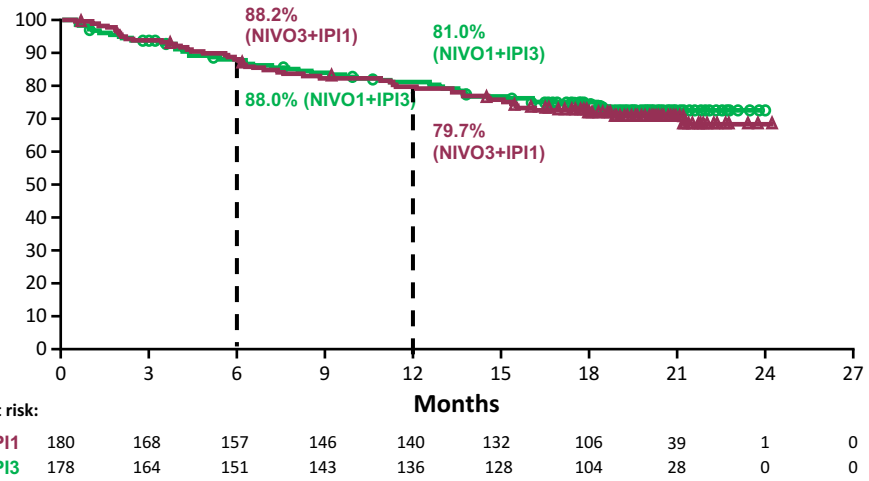
CheckMate 511

	NIVO3+IPI1 (N=180)	NIVO1+IPI3 (N=178)
Rate of treatment-related grade 3-5 AEs, % (n/N) (95% CI)	**33.9%** (61/180) (27.0, 41.3)	**48.3%** (86/178) (40.8, 55.9)
P value	**0.0059**	
Treatment-related AEs, %	85.6	93.8
Grade 3-4	33.3	48.3
Grade 5	0.6	0
All cause serious AEs, %	47.8	63.5
Grade 3-4	33.9	47.8
Grade 5	3.3	1.7
Treatment-related AEs leading to discontinuation, %	23.9	33.1

	NIVO3+IPI1 (N=180)	NIVO1+IPI3 (N=178)
Investigator-assessed ORR, % (95% CI)	45.6 (38.1–53.1)	50.6 (43.0–58.1)
P value	0.3451	

Overall survival

HR (95% CI)=1.09 (0.73, 1.62)



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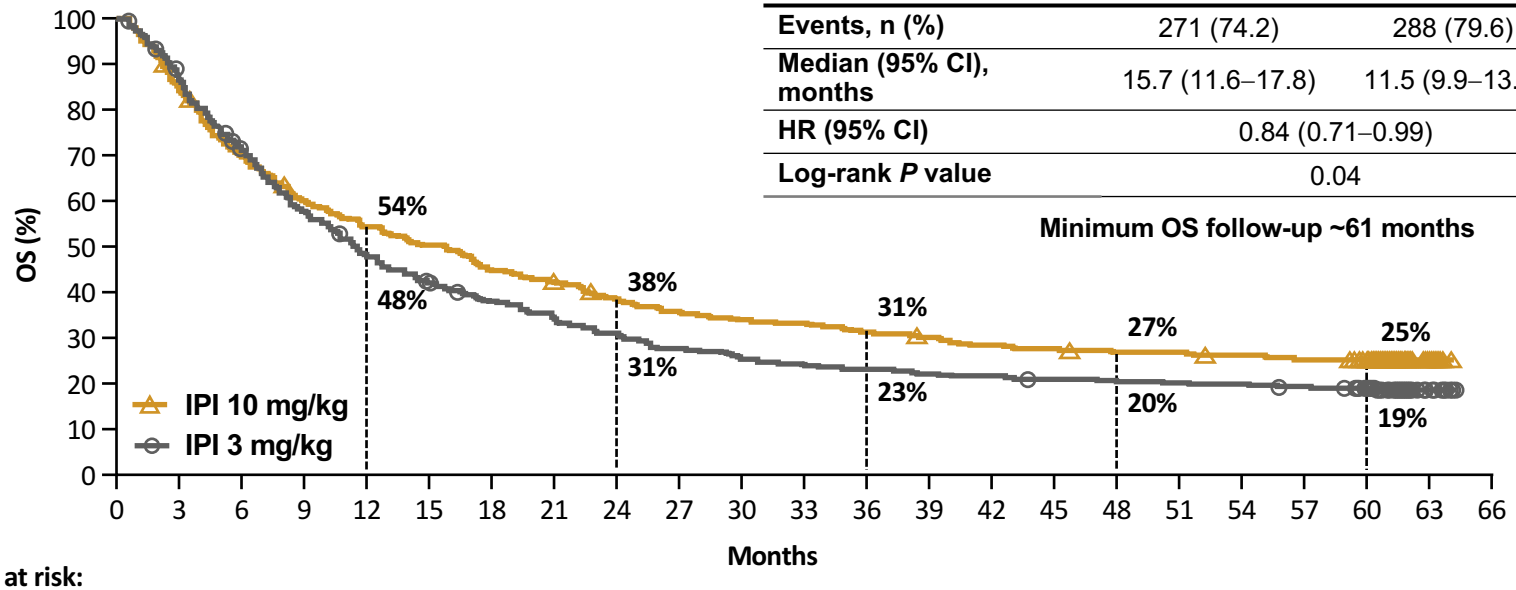
Lebbe et al. JCO. 2019

CA184-169

OS: All Randomized Patients

	IPI 10 mg/kg n = 365	IPI 3 mg/kg n = 362
Events, n (%)	271 (74.2)	288 (79.6)
Median (95% CI), months	15.7 (11.6–17.8)	11.5 (9.9–13.3)
HR (95% CI)	0.84 (0.71–0.99)	
Log-rank *P* value	0.04	



Patients at risk:

IPI 10 mg/kg	365	306	253	217	196	181	161	151	137	126	120	118	111	106	100	97	93	93	90	87	78	13	0
IPI 3 mg/kg	362	310	253	205	168	146	131	118	107	95	87	83	80	76	74	71	69	68	67	64	58	7	0

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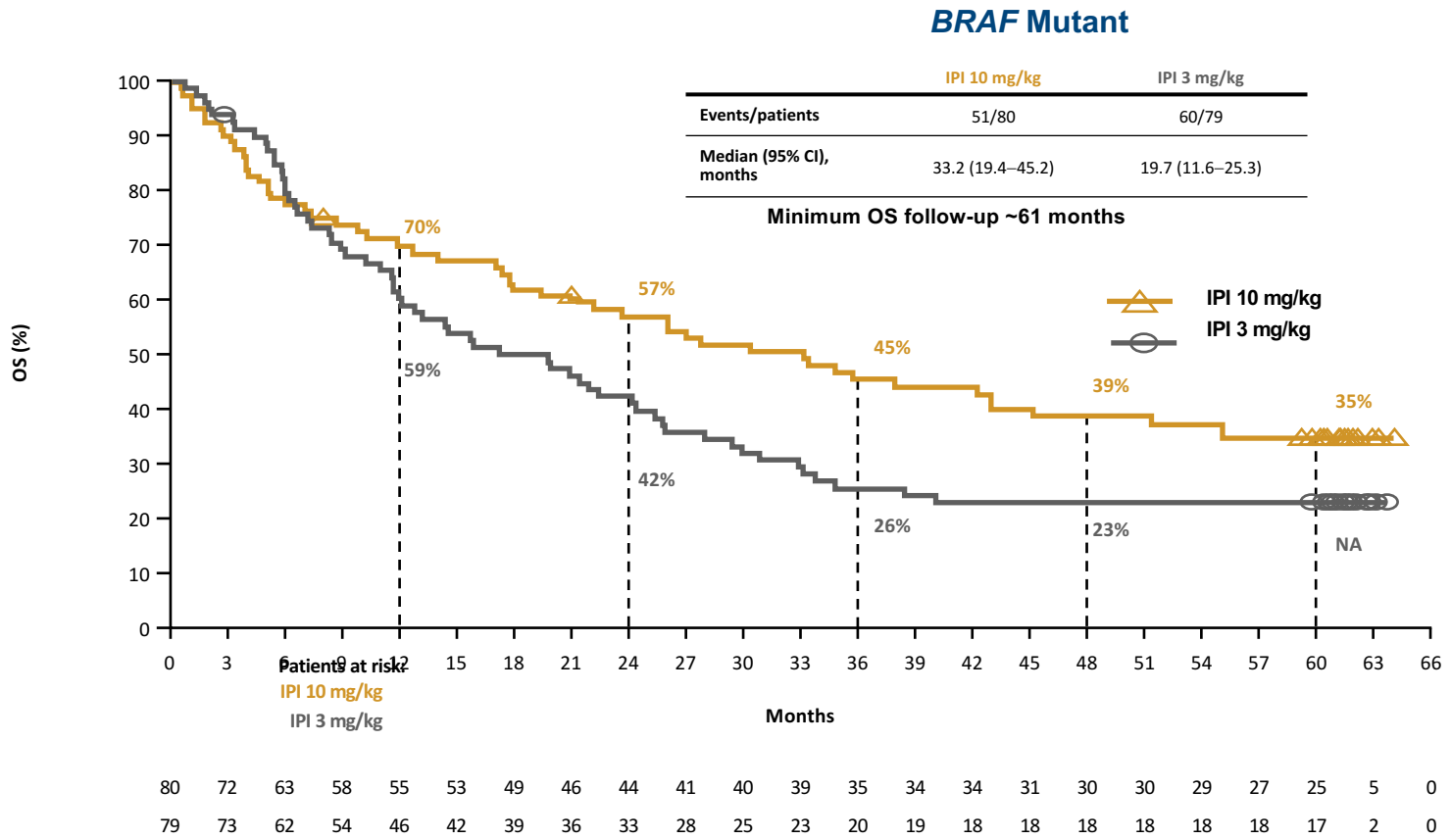
CA184-169

OS by BRAF Mutation



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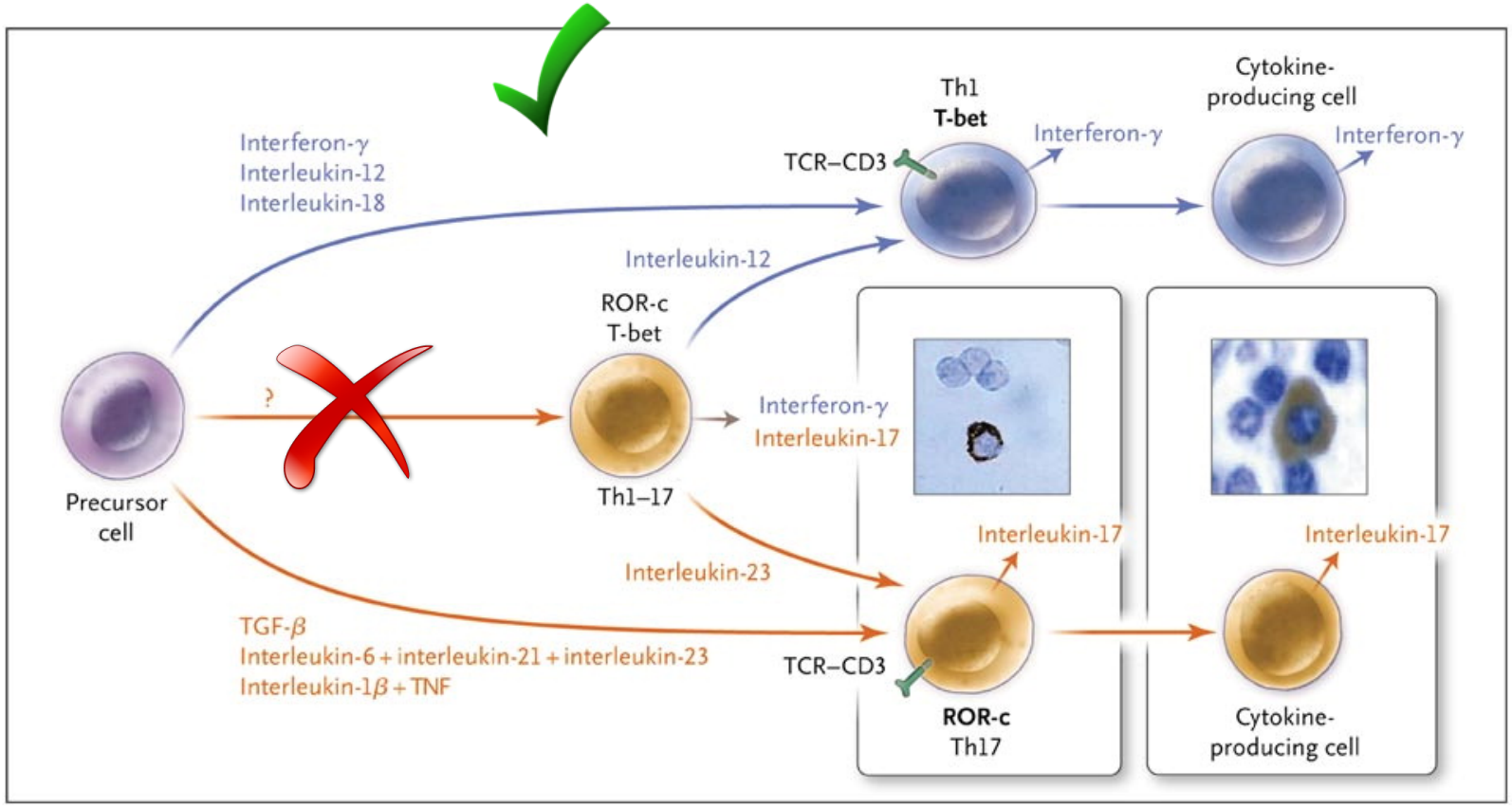
Can We Achieve Decoupling

Blocking IL-6(R) preventing induction of TH-17



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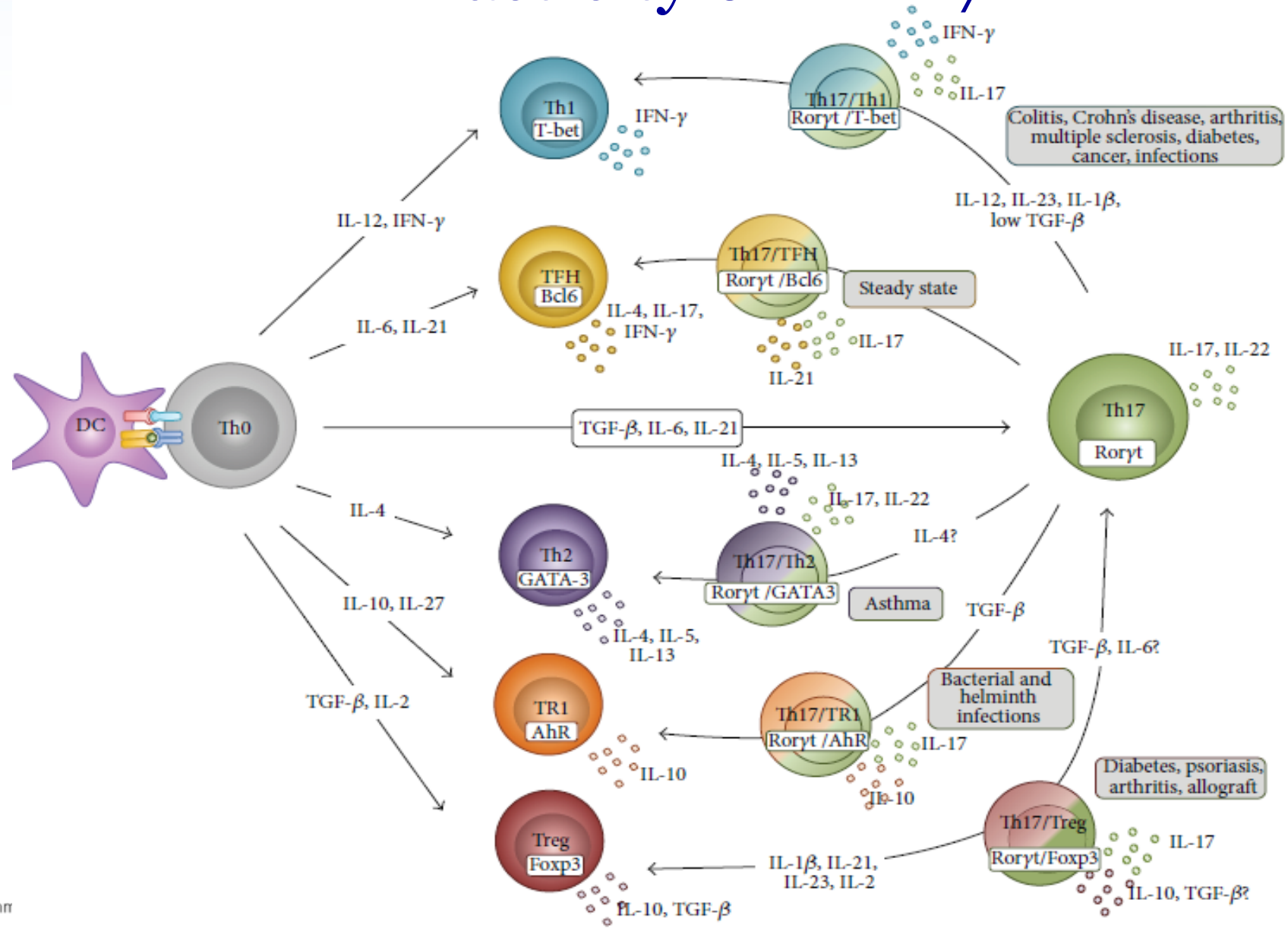
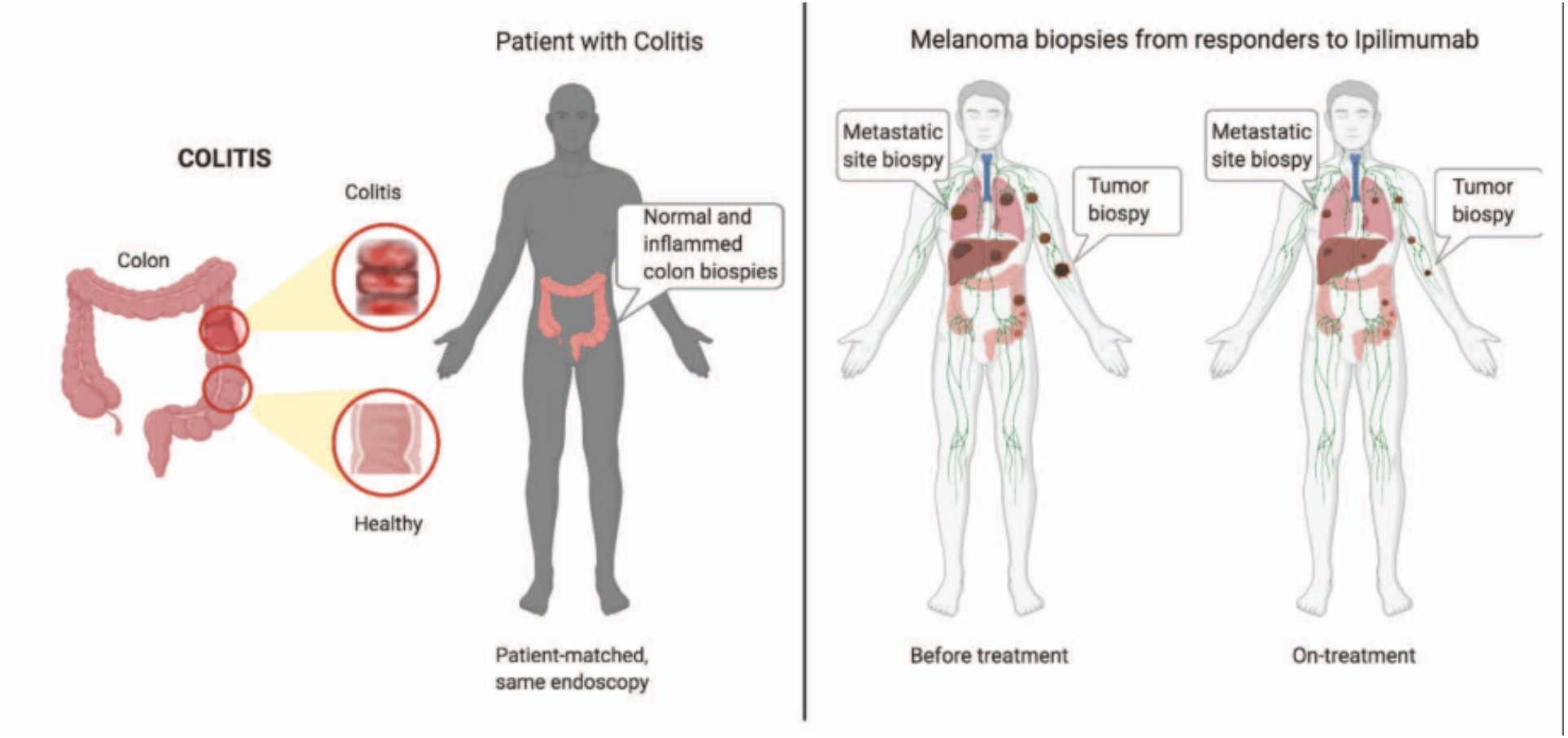
Miossec P et al. N Engl J Med 2009;361:888-898

Plasticity of TH-17

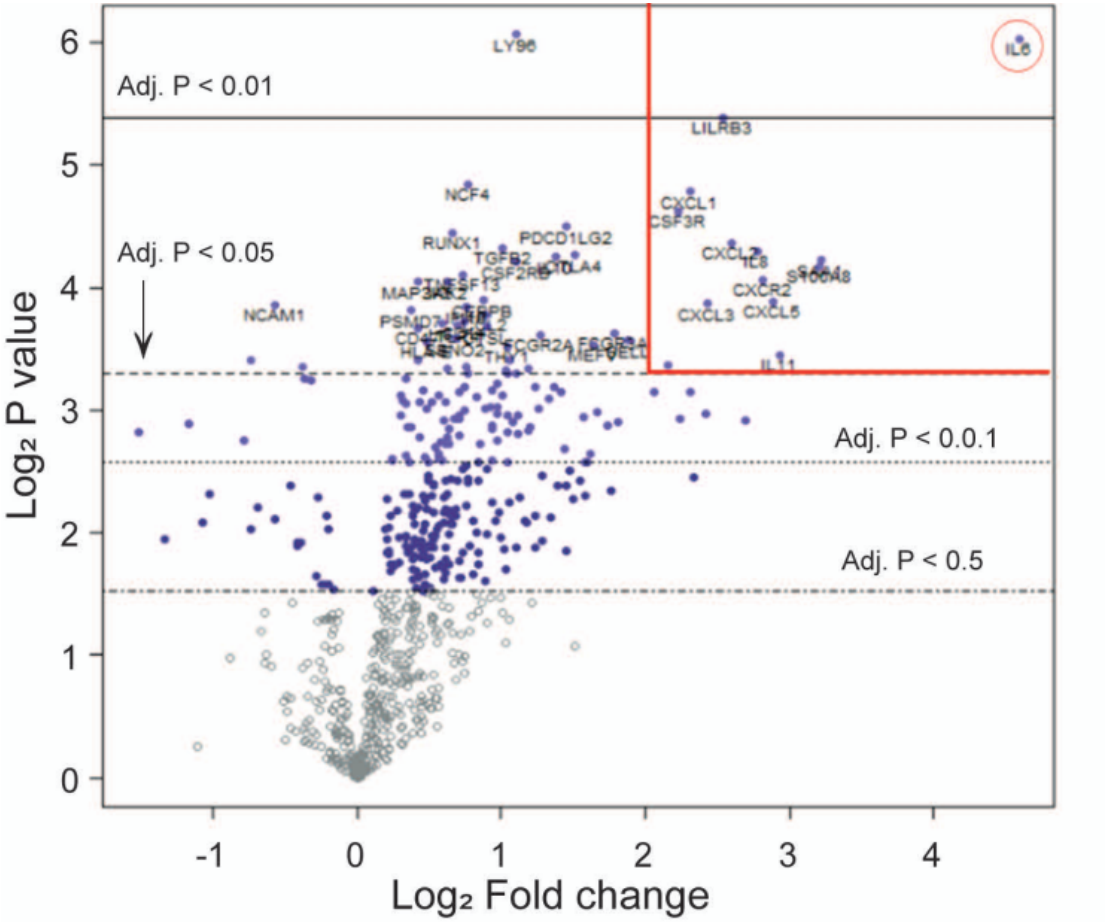


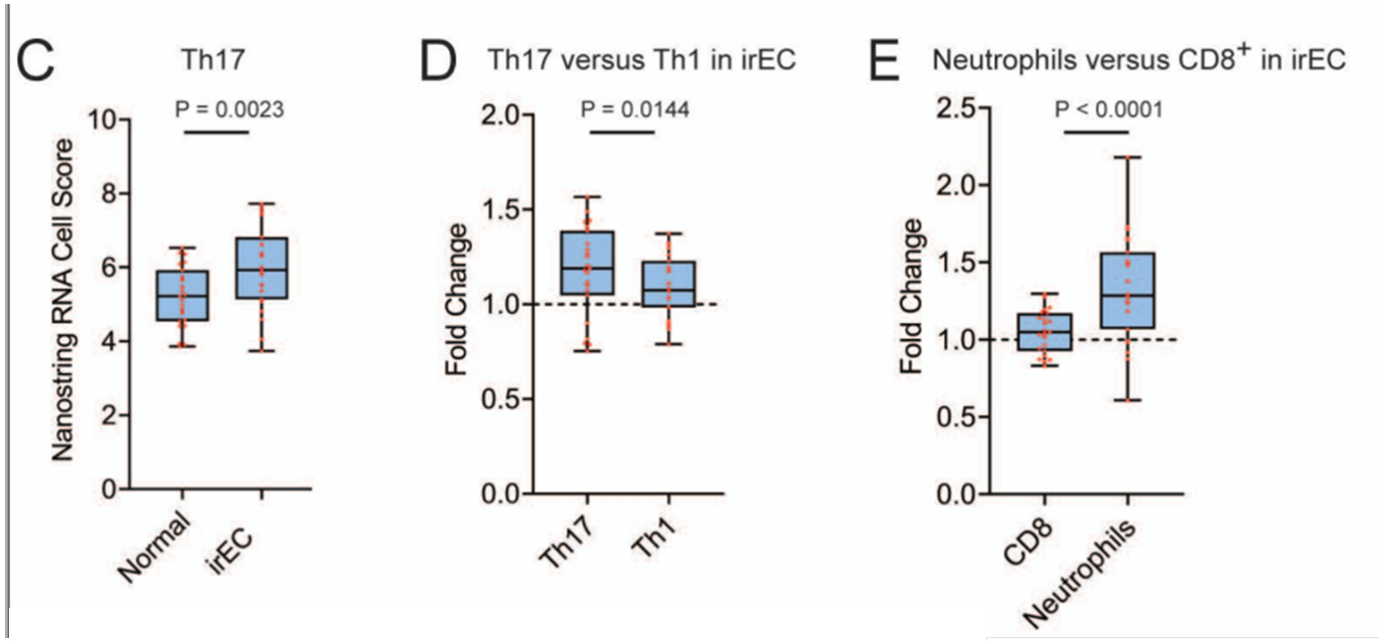
Guery L et al BioMed Res. Int. 2015

Colitis vs. Responding Tumor



Nanostring Gene Expression Profiling and Multiplex IHC of inflamed irEC





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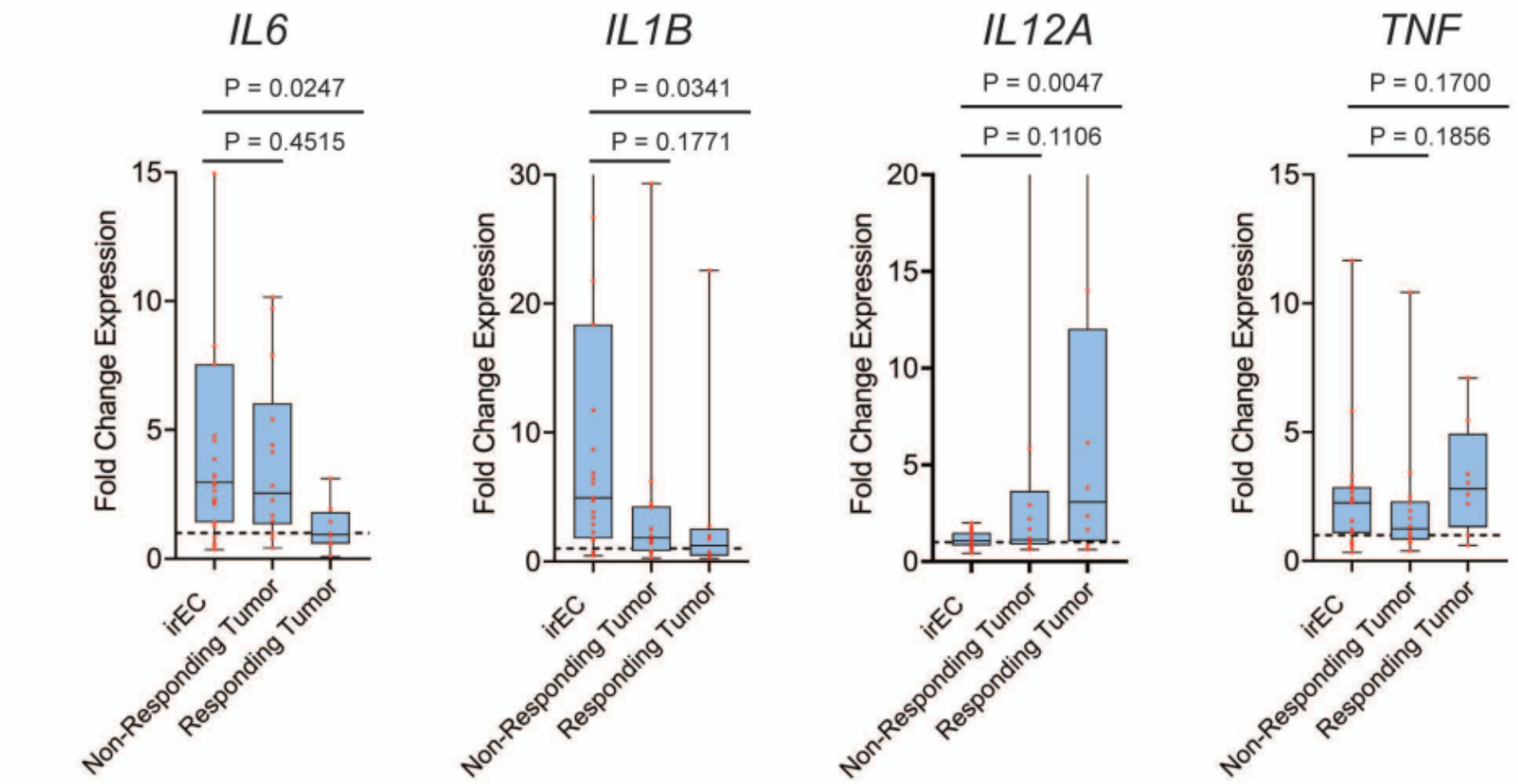
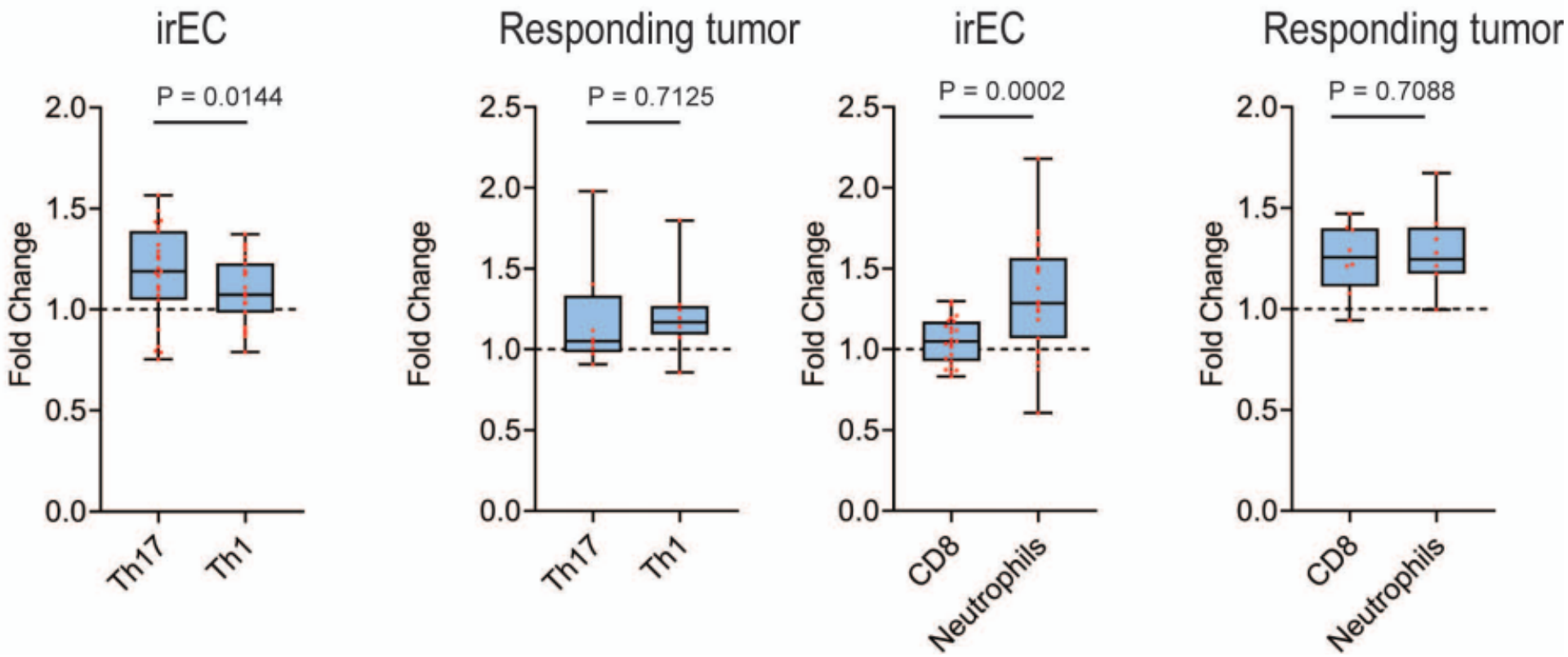
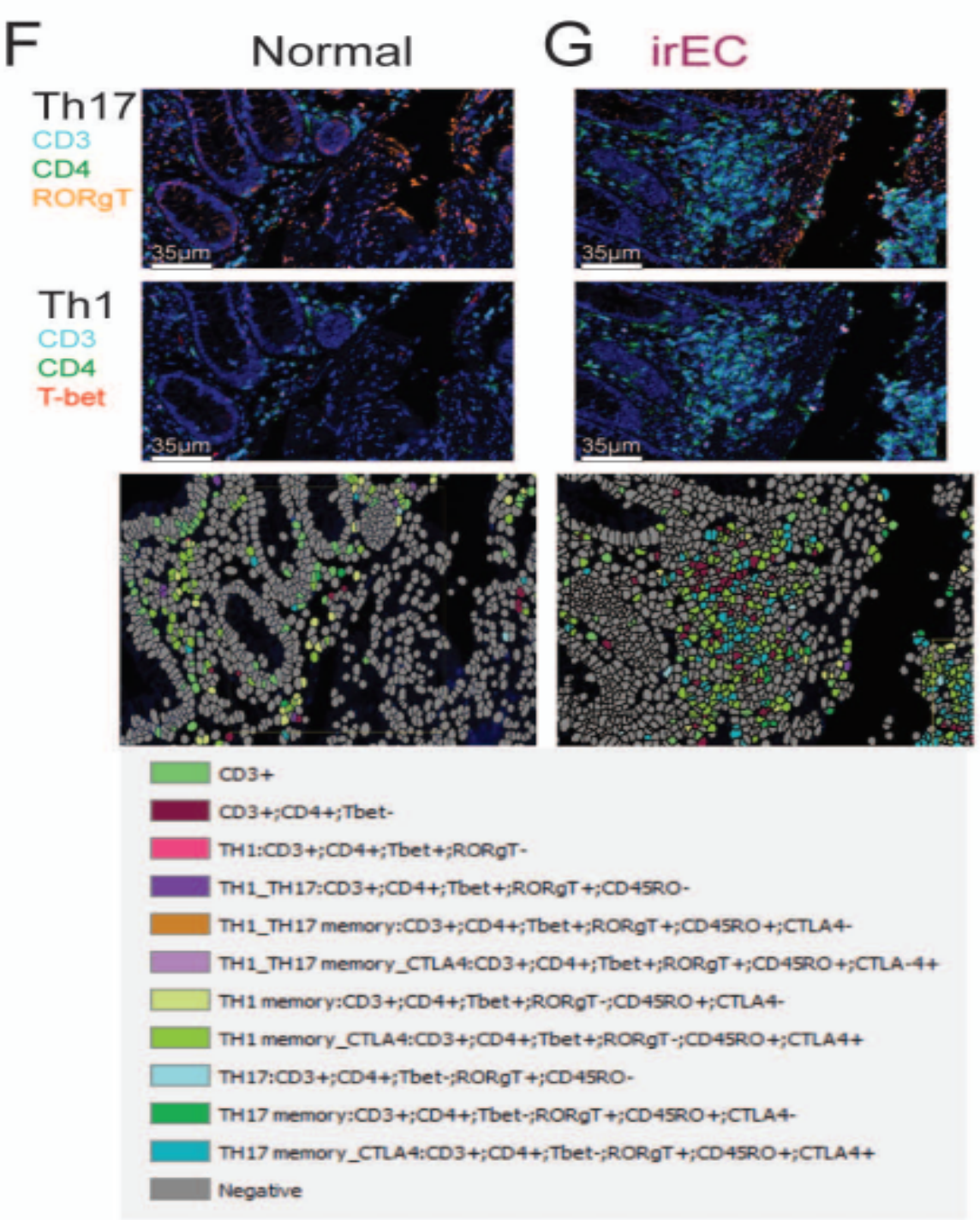
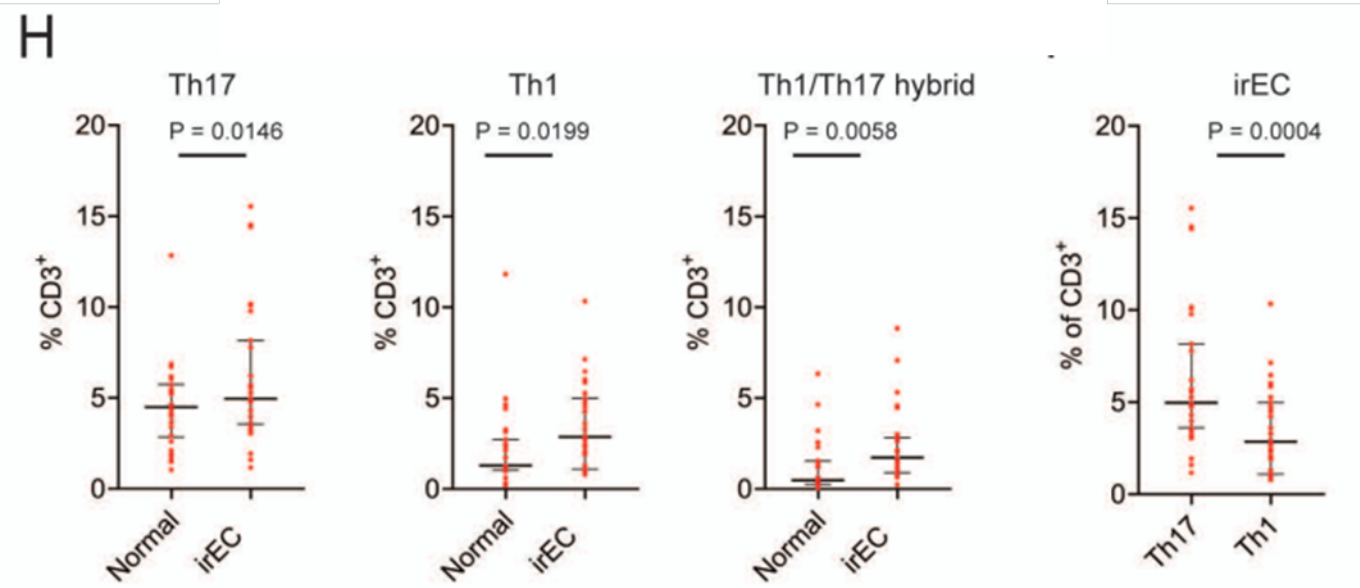
Nanostring Gene Expression Analysis Tumor versus irEC



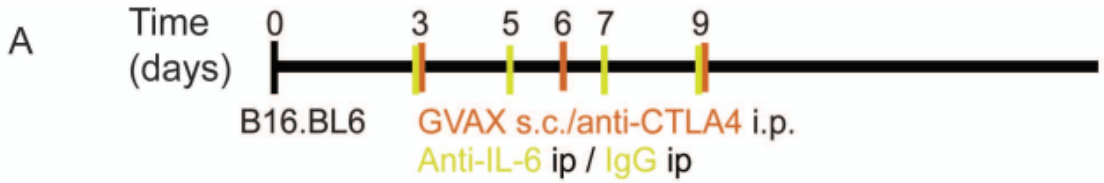
Nanostring Gene Expression Analysis Tumor versus irEC

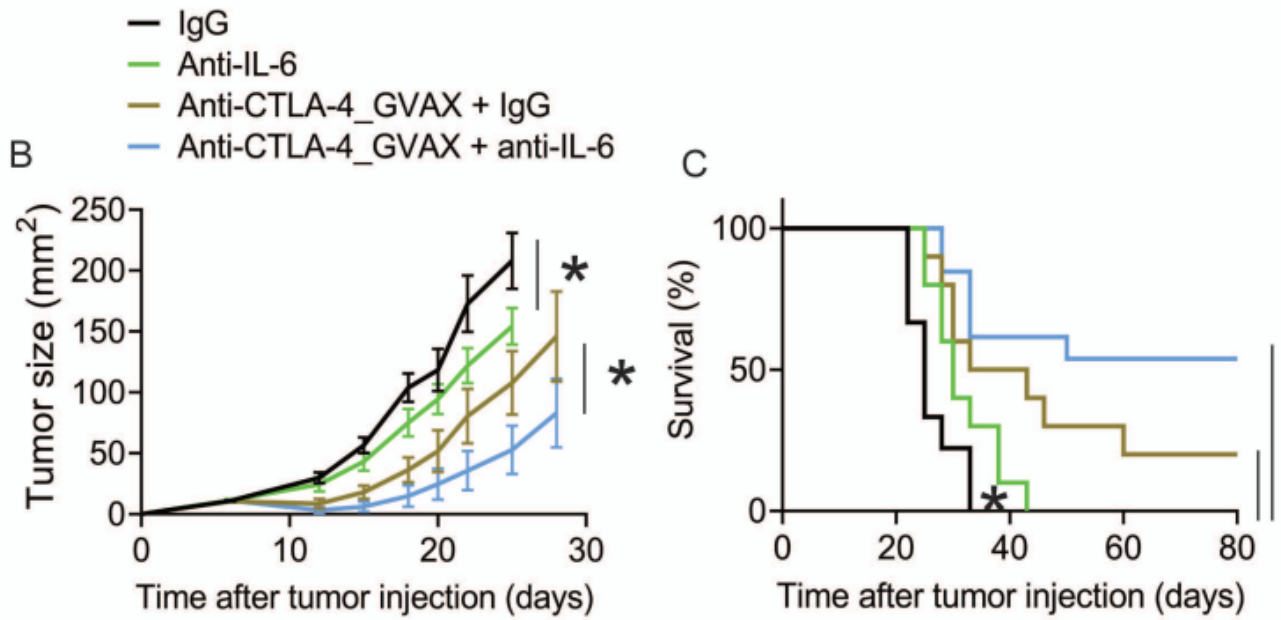


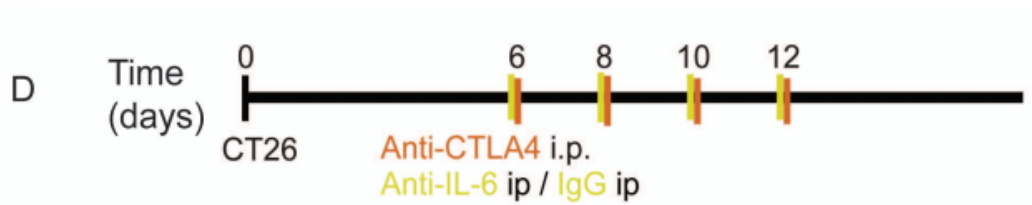

F
Normal
G
irEC
Th17
CD3
CD4
RORgT
35μm
Th1
CD3
CD4
T-bet
CD3+
CD3+;CD4+;Tbet-
TH1:CD3+;CD4+;Tbet+;RORgT-
TH1_TH17:CD3+;CD4+;Tbet+;RORgT+;CD45RO-
TH1_TH17 memory:CD3+;CD4+;Tbet+;RORgT+;CD45RO+;CTLA4-
TH1_TH17 memory_CTLA4:CD3+;CD4+;Tbet+;RORgT+;CD45RO+;CTLA-4+
TH1 memory:CD3+;CD4+;Tbet+;RORgT-;CD45RO+;CTLA4-
TH1 memory_CTLA4:CD3+;CD4+;Tbet+;RORgT-;CD45RO+;CTLA4+
TH17:CD3+;CD4+;Tbet-;RORgT+;CD45RO-
TH17 memory:CD3+;CD4+;Tbet-;RORgT+;CD45RO+;CTLA4-
TH17 memory_CTLA4:CD3+;CD4+;Tbet-;RORgT+;CD45RO+;CTLA4+
Negative

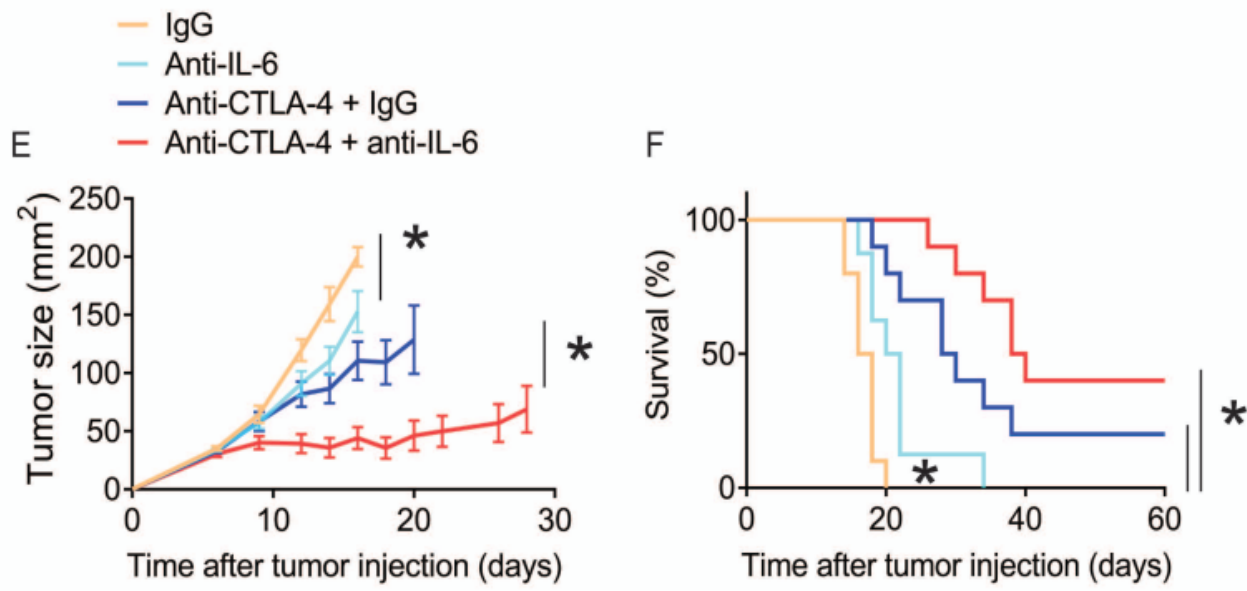

H
Th17
P = 0.0146
% CD3+
Normal
irEC
Th1
P = 0.0199
% CD3+
Normal
irEC
Th1/Th17 hybrid
P = 0.0058
% CD3+
Normal
irEC
irEC
P = 0.0004
% of CD3+
Th17
Th1

IL-6 blockade increases anti-CTLA-4 therapeutic efficacy in murine models









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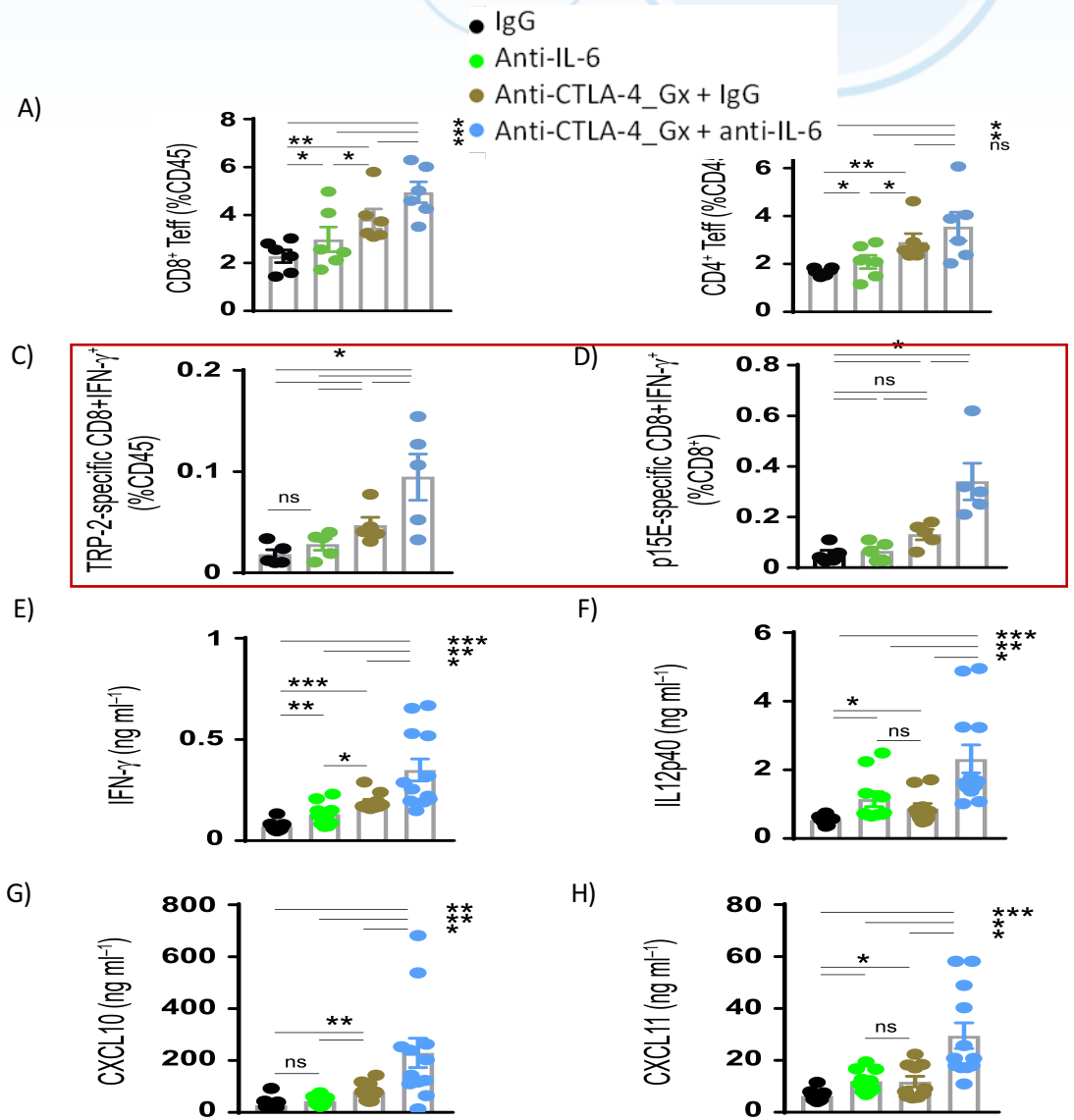
IL-6 blockade increases anti-CTLA-4 therapy-induced Teff localization in murine models



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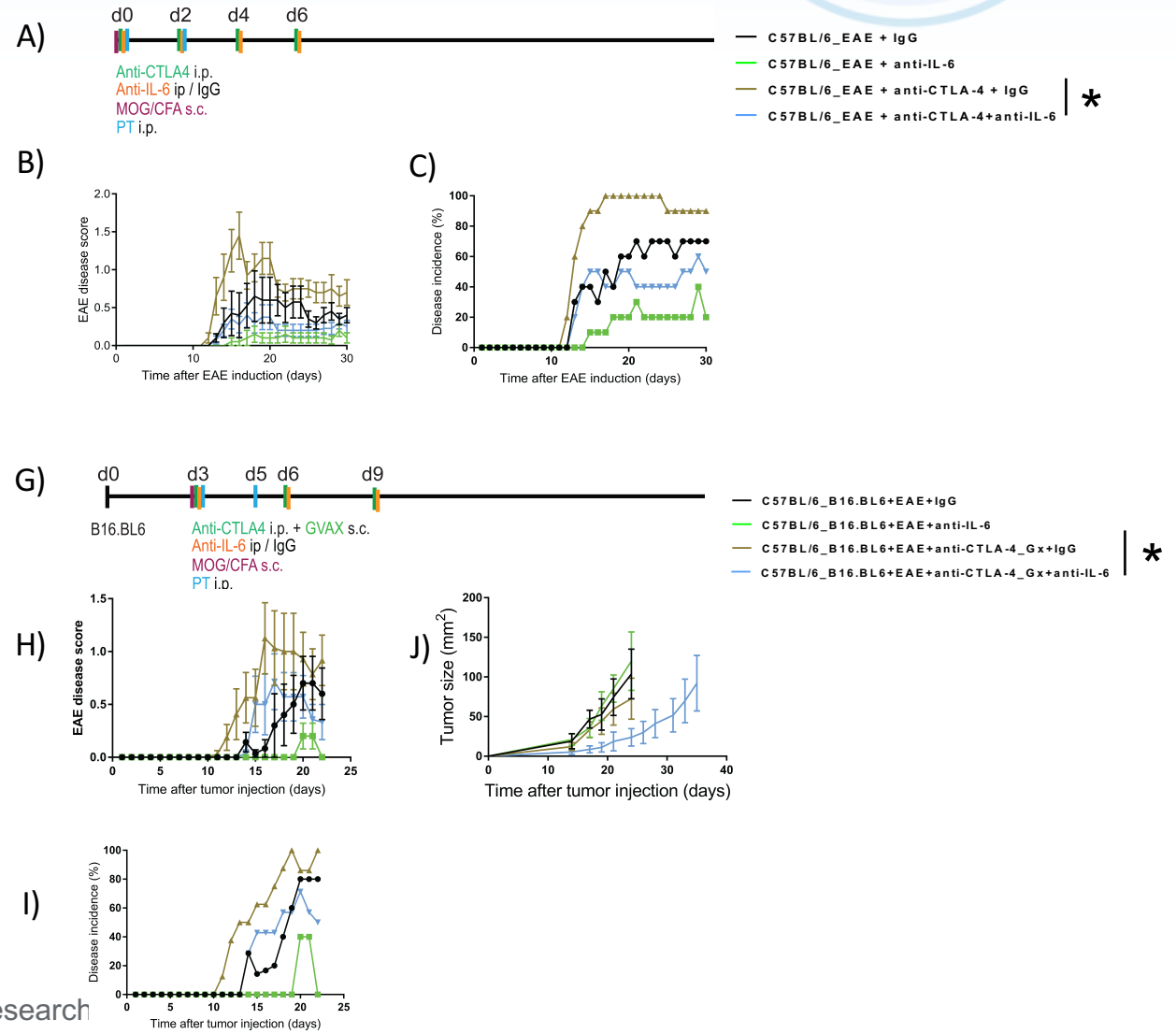
IL-6 blockade improves anti-CTLA-4 therapeutic activity while not exacerbating autoimmunity in EAE model



IOTOX Research

A Multicenter Retrospective Study - Clinical Cohort treated with IL-6R Blockade

- Cancer types were primarily melanoma **(46%)**, genitourinary cancer (34%), and lung cancer (8%)
- **74%** received single-agent anti-PD-1 and 24% received nivolumab plus ipilimumab
- **86** % of patients received glucocorticoids as first-line therapy, and **34%** received disease-modifying antirheumatic drugs, without improvement

Demographics

- Inflammatory arthritis **(69%)**
- Polymyalgia rheumatica-like syndrome (6%)
- Myositis/MG/myocarditis (6%)
- Hepatitis/Cholangitis (6%)
- Encephalitis (5%)
- Other irAEs (1% each): Pneumonitis, colitis, nephritis, CNS vasculitis, scleroderma, oral mucositis, and pre-existing CD

Indications

- **73%** had irAEs improvement after a median of 2 months
  - ❖ Of 42 evaluable patients with arthritis-irAE, the median **CDAI score was 24 and dropped to 6**
- The median **CRP level was 57.6 mg/L and dropped to 1.2 mg/L** within 10 weeks
- **9.5%** stopped IL-6R blockade due to side effects

Primary Outcome

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A Multicenter Retrospective Study - Clinical Cohort treated with IL-6R Blockade

- Seventy-four patients had documented tumor response; the ORR was **59% prior** to IL-6R blockade and **61% after** treatment
  - ❖ Of 33 evaluable melanoma patients by RECIST 1.1, the ORR was **45.5% versus 51.5%**
- **33%** continued ICI therapy
- **5%** died primarily because of irAEs

Secondary Outcome

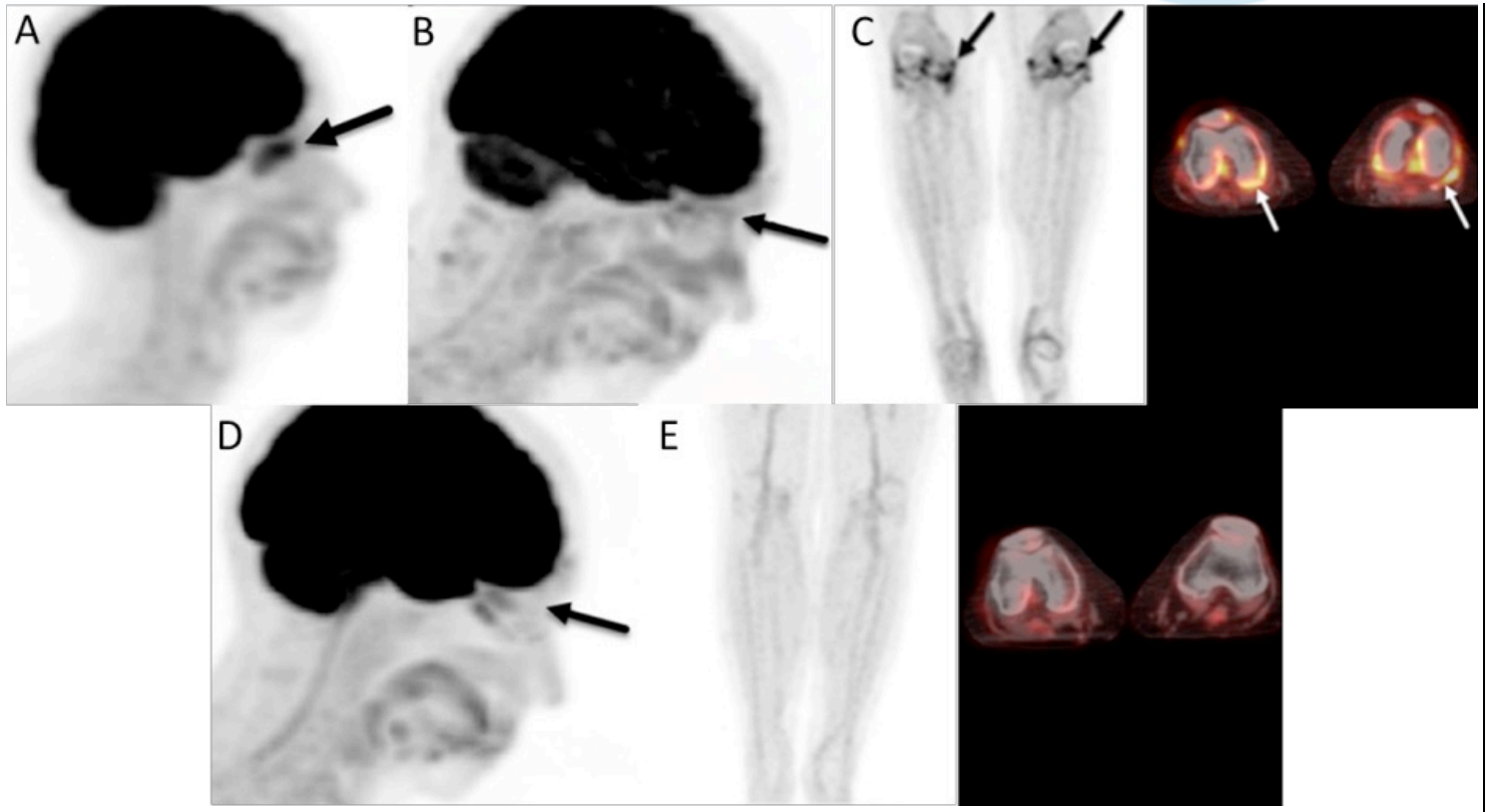
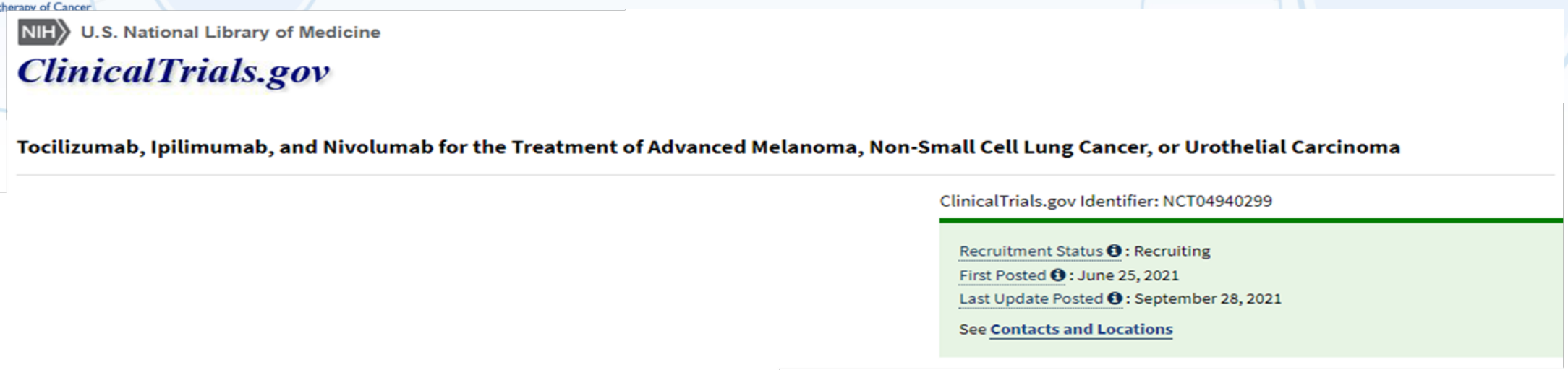


Figure 1. A patient with sinonasal malignant melanoma involving the ethmoid air cells. (A) Baseline maximum intensity projection (MIP) PET image at 1 month before initiation of ICI (ipilimumab and nivolumab) shows avid FDG uptake of the tumor at the ethmoid air cells (arrow). (B) MIP PET image at 7 months after ICI initiation shows resolution of the FDG uptake at the site of the tumor, consistent with complete response. (C) Concurrent MIP PET and corresponding fused PET-CT images 7 months after initiation of ICI show avid radiotracer uptake at the knee joints, suggestive of arthritis. (D) MIP PET image at 10 months after concomitant therapy with IL6R antagonist and nivolumab shows persistent absence of hypermetabolic radiotracer activity at the paranasal sinuses, consistent with complete response. (E) Concurrent MIP PET and corresponding fused PET-CT images show physiologic radiotracer uptake at the knee joints, consistent with resolving arthritis.


NIH U.S. National Library of Medicine

ClinicalTrials.gov

Tocilizumab, Ipilimumab, and Nivolumab for the Treatment of Advanced Melanoma, Non-Small Cell Lung Cancer, or Urothelial Carcinoma

ClinicalTrials.gov Identifier: NCT04940299

Recruitment Status : Recruiting
First Posted : June 25, 2021
Last Update Posted : September 28, 2021

See Contacts and Locations

- Characterize the safety and tolerability of this novel combination
- Determine grade 3 or higher toxicity rate for patients with advanced cutaneous melanoma

Primary Objectives

- Characterize the efficacy of this novel combination
- Estimate the ORR, and DRR, as determined by RECIST 1.1/irRECIST
- Estimate PFS and OS

Secondary Objectives

- Identify potential biomarkers for risk stratification
- Identify predictive biomarkers of response

Exploratory Objective

This trial is supported by the Immunotherapy Platform at MD Anderson

Study Design

Figure 5. Imaging and Biopsy Schedule for Melanoma, and Urothelial cancer (cohort 1)

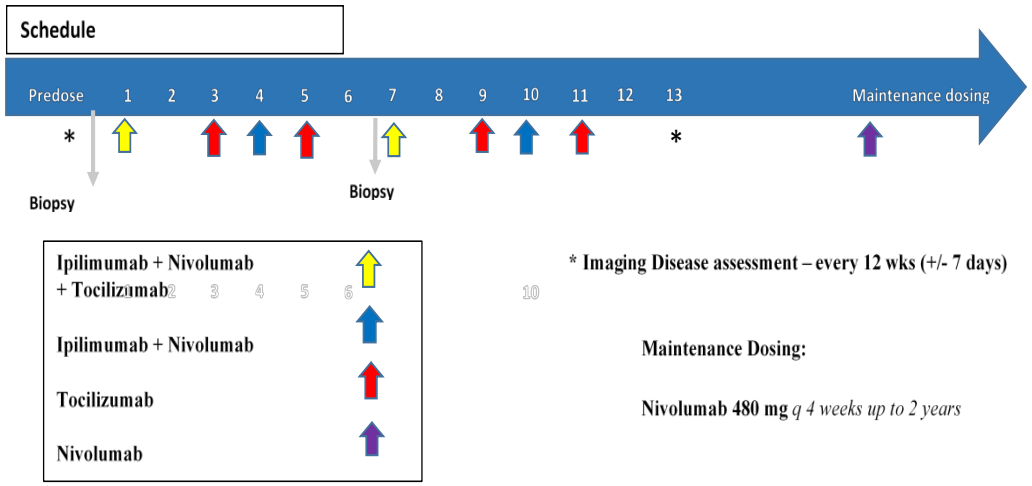
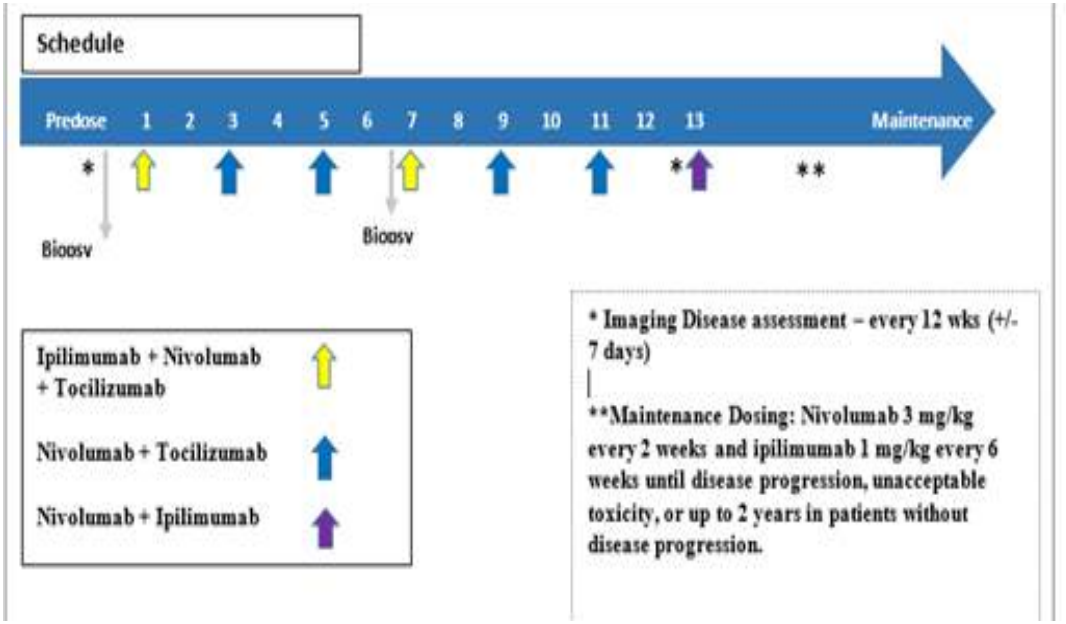


Figure 6. Imaging and Biopsy Schedule for NSCLC cancer (cohort 2)



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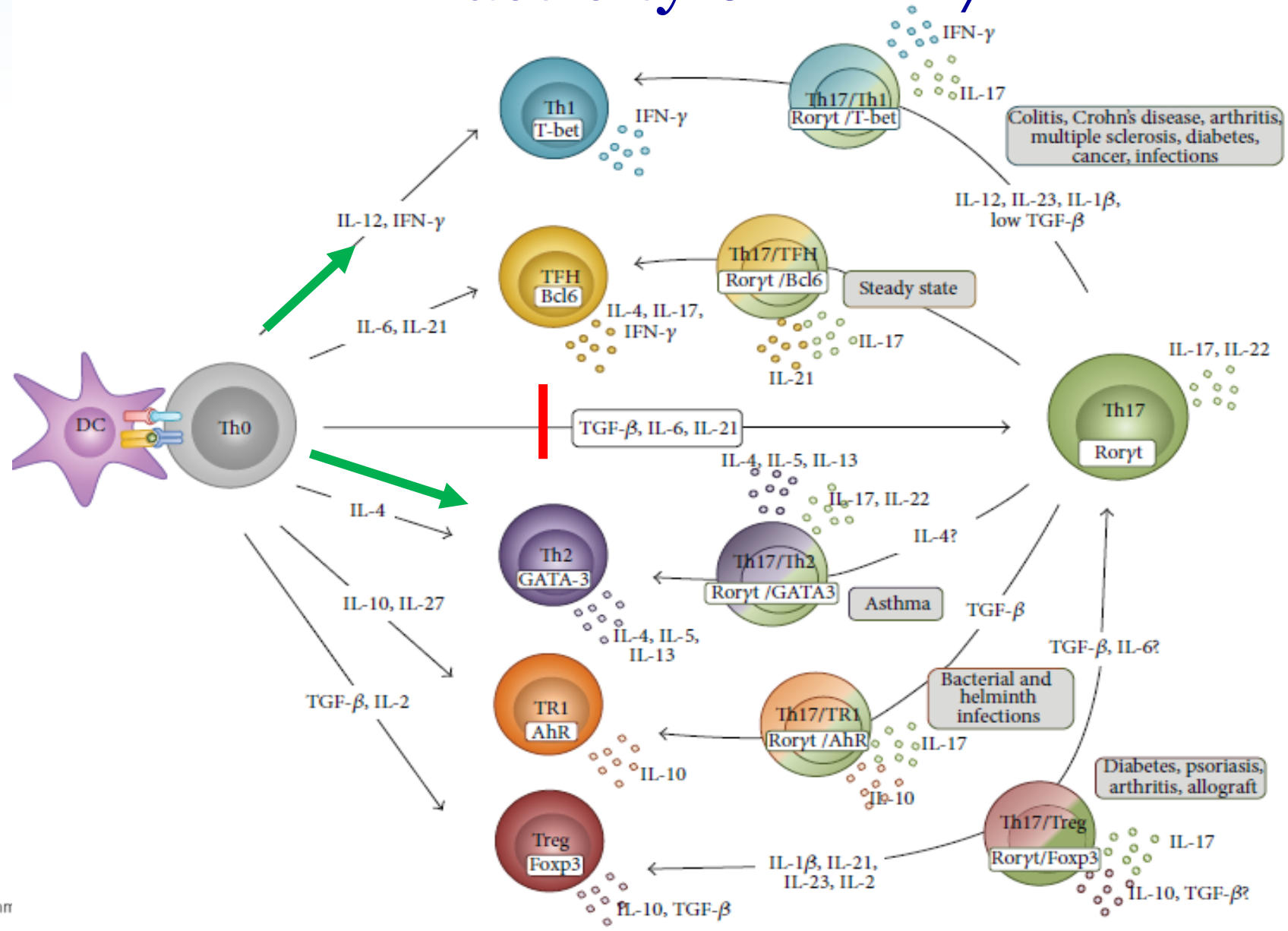
Plasticity of TH-17



Guery L et al BioMed Res. Int. 2015

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Gastroenterology

Yinghong (Mimi) Wang

Immune Platform (MDACC)

James Allison

Padmanee Sharma

Pathology

Tim Foo