Immunotherapy For Lung Cancer

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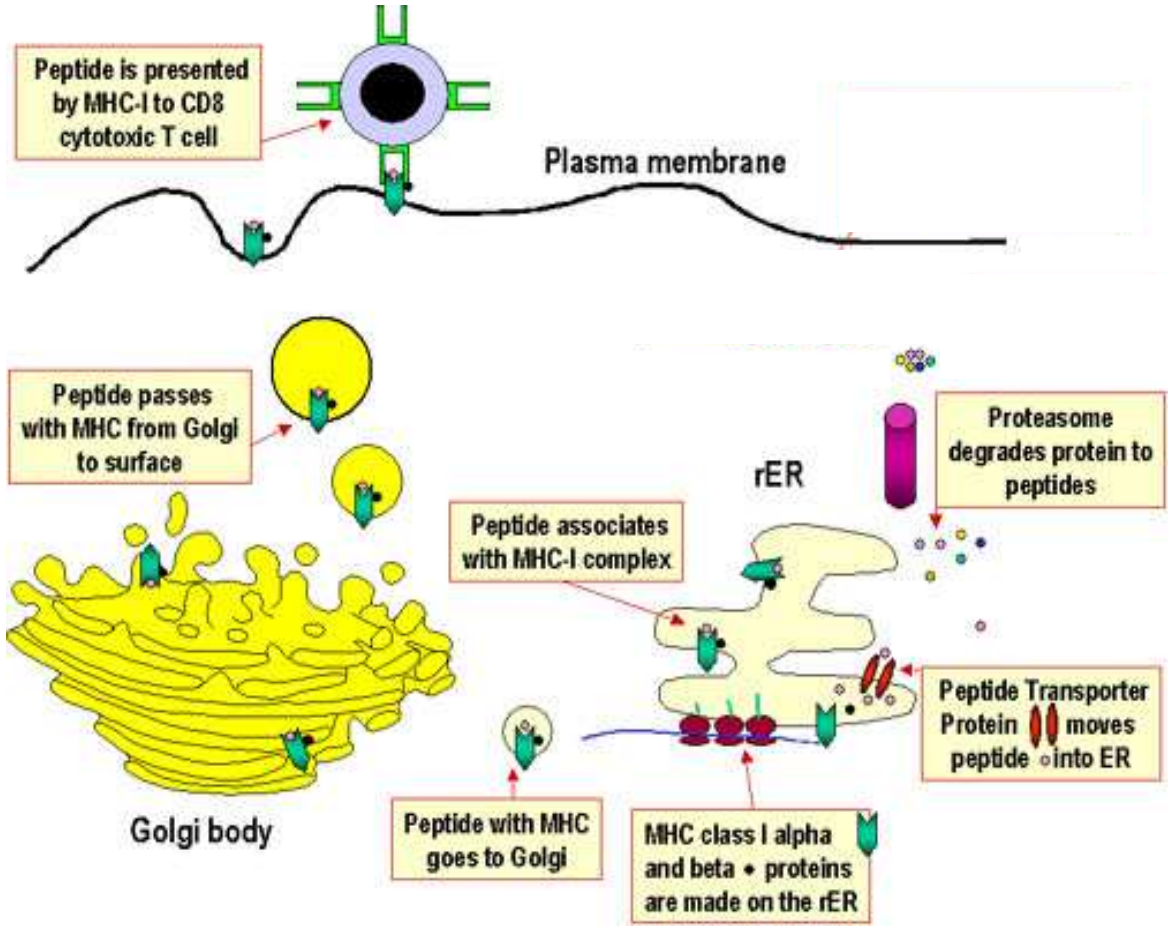
Disclosures

Advisory Boards/ Consulting:

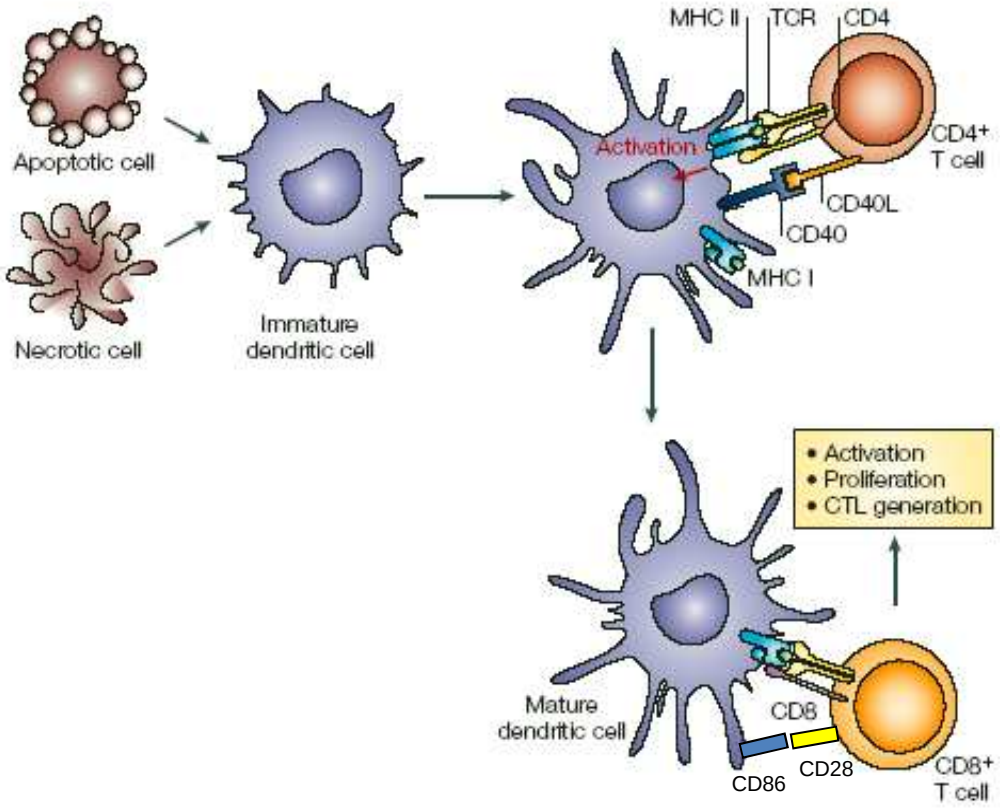
- BMS
- MedImmune/AZ
- Merck

MHC Class I Antigen Processing Pathway

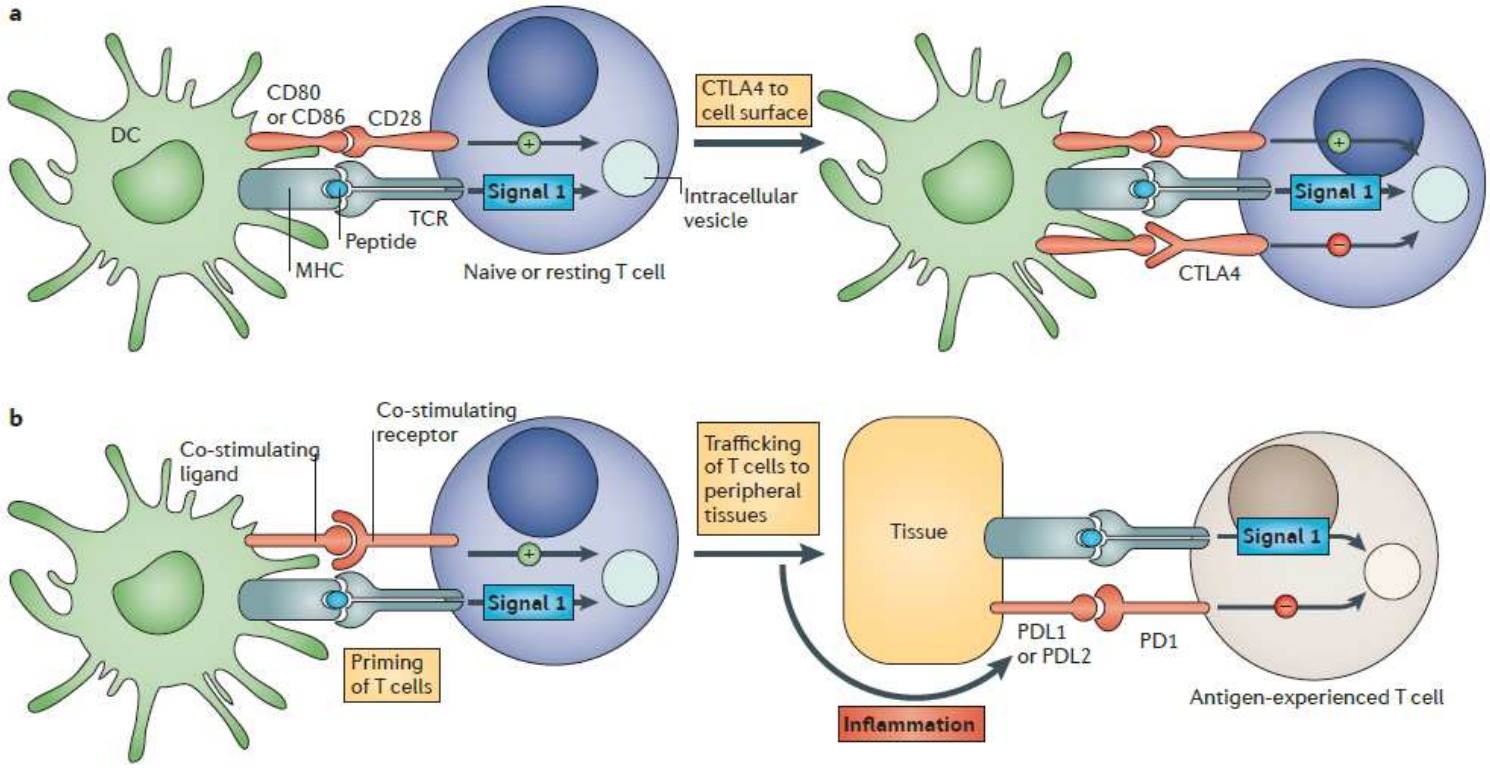
Tumor Cells



Productive Anti-TAA Specific Cytolytic T Lymphocyte (CTL) Response



Immune Checkpoints

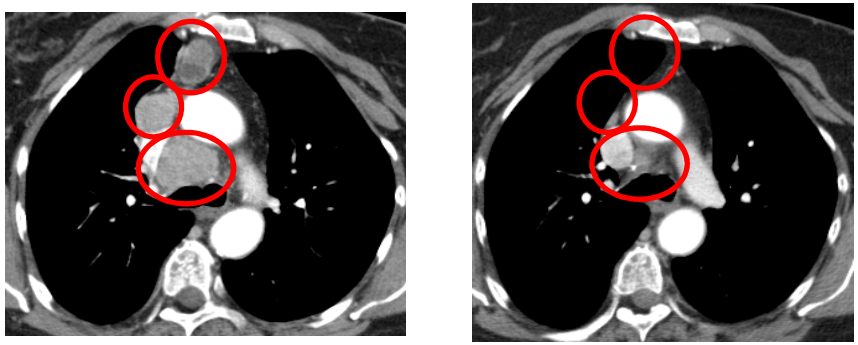


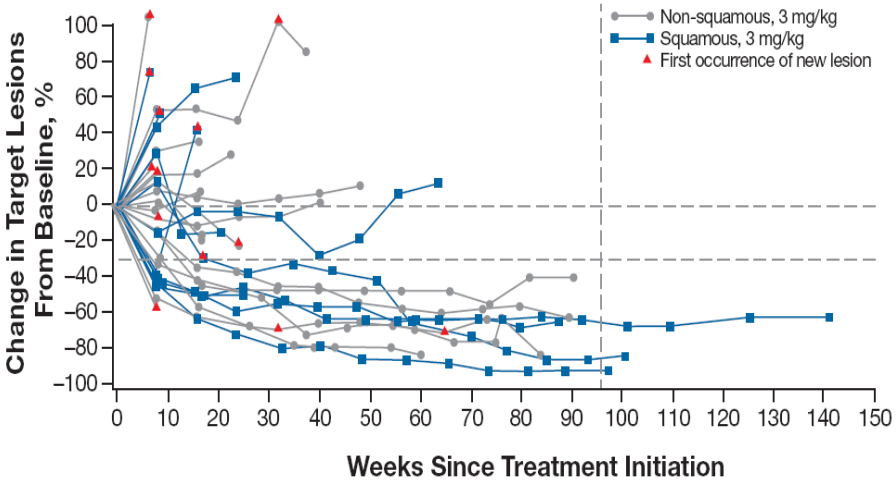
Pardoll. Nat Rev Cancer 2012.

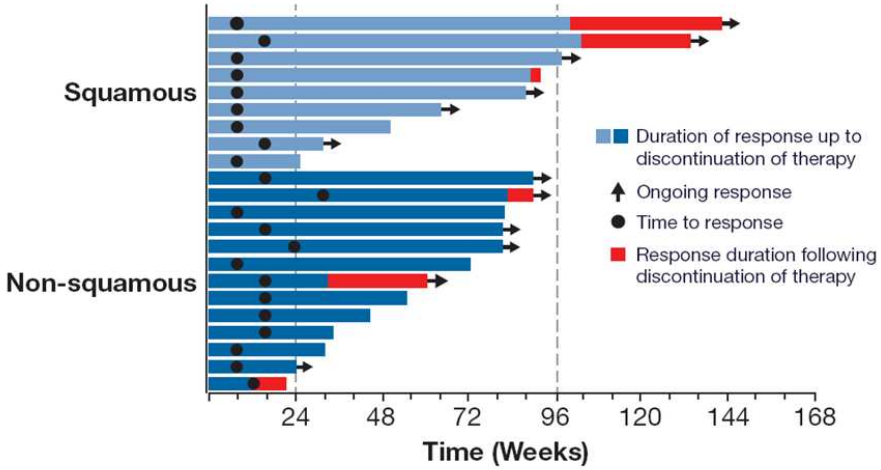
Nivolumab Responses in NSCLC

Rapid, durable, and persist after stopping

BEFORE **AFTER**







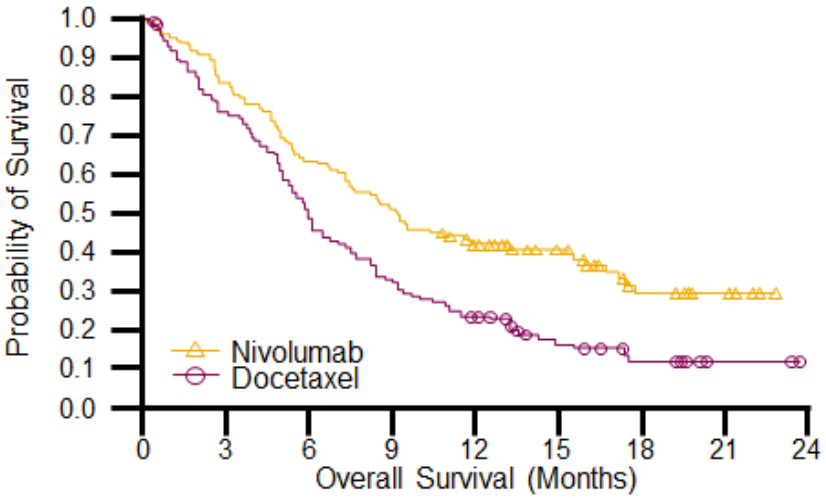
Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

PD-L1 Expression Level				
	SqCCa		Non-SqCCa	
	≥1%	<1%	≥1%	<1%
ORR, %	18	17	31	9

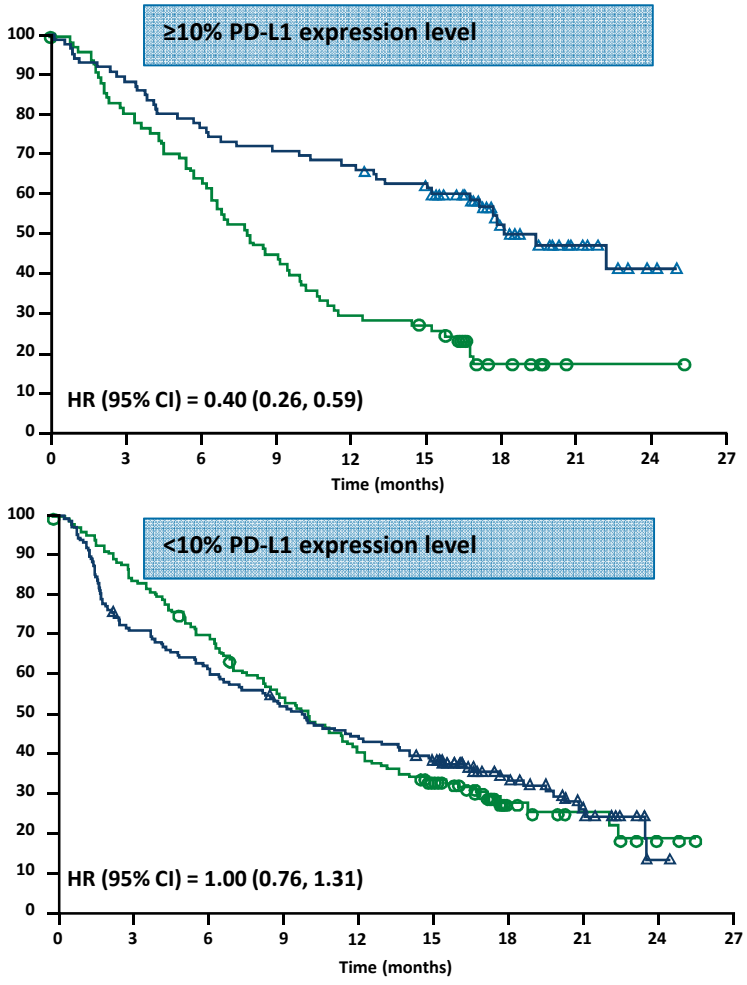
Nivolumab Randomized Trials

Versus docetaxel in second line

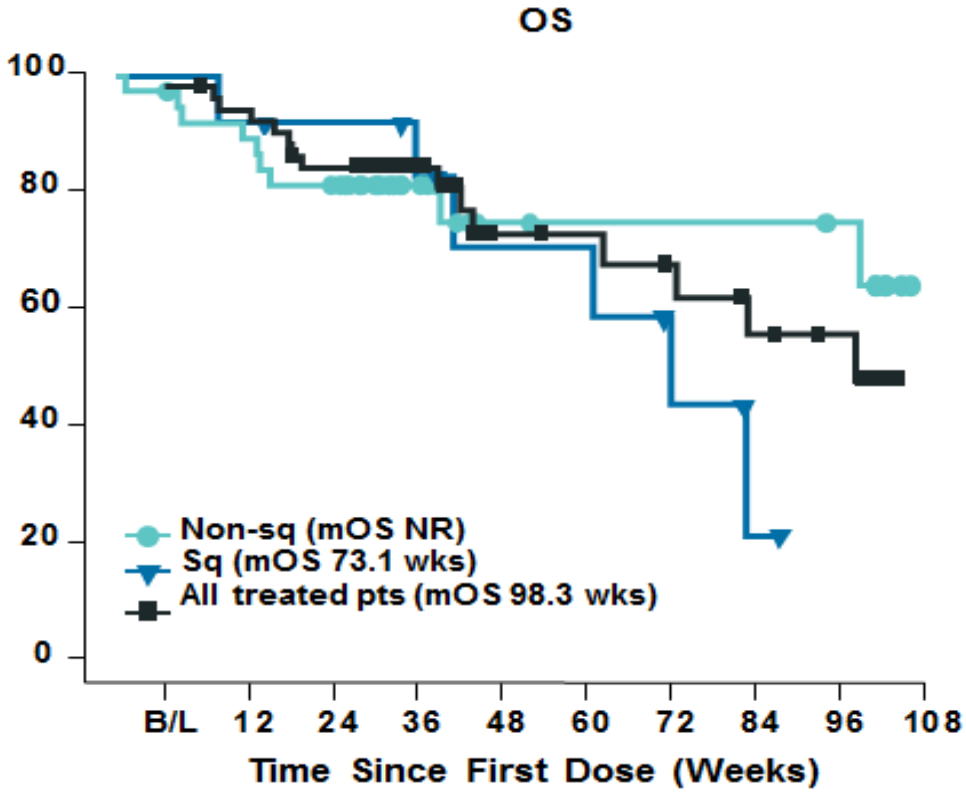
Squamous



Non-Squamous



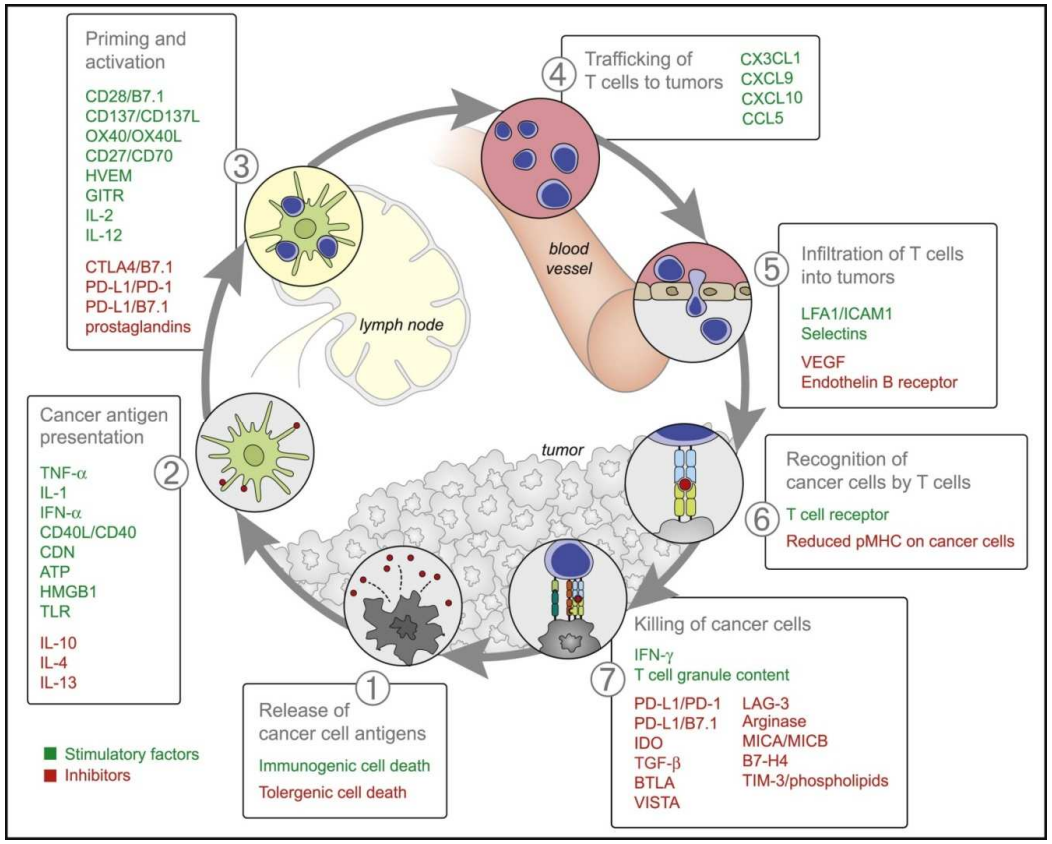
Nivolumab Monotherapy in First Line Setting



Number of Pts at Risk

All treated pts	52	48	42	30	15	14	12	9	7	0
Sq	13	13	11	11	6	6	4	1	0	0
Non-sq	39	35	31	19	9	8	8	8	7	0

Anti-Tumor Immune Response
Inhibition by Tumors



Chen DS, et al. Immunity. 2013;39:1-10.

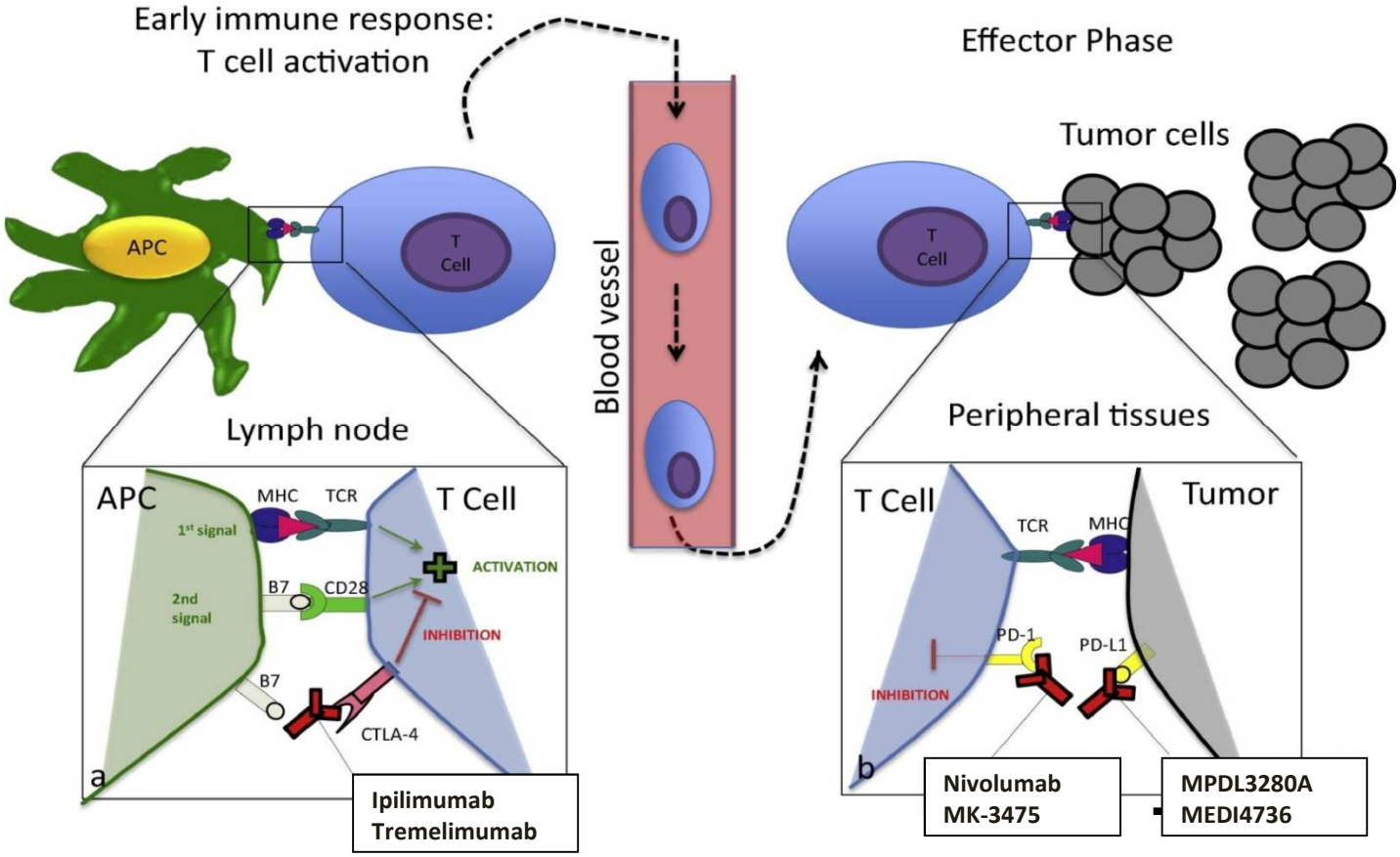
1. Insufficient number of T cells are generated within the lymphoid compartment.
2. Insufficient number of T cells extravasate into the tumor.
3. T cells are inhibited in the tumor microenvironment.

1. Insufficient number of T cells generated within the lymphoid compartment.

Clinical Trials

1. Anti-CTLA.4.
2. Vaccines.
3. Radiation.
4. ACT with TILs
5. ACT with CAR or TCR transgenic T cells.

Anti-PD1/PDL1 plus Anti-CTLA.4 to Influence the Lymphoid Compartment



Kyi C, et al. FEBS Lett. 2014;588:368-376

Nivolumab (Anti-PD1) Plus Ipilimumab (Anti-CTLA.4)

Safety

	Nivo 1 + Ipi 1 Q3W (n = 31)		Nivo 1 Q2W + Ipi 1 Q6W (n = 40)		Nivo 3 Q2W + Ipi 1 Q12W (n = 38)		Nivo 3 Q2W + Ipi 1 Q6W (n = 39)		Nivo 3 Q2W[a] (n = 52)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related AEs, %	77	29	73	35	74	29	69	28	71	19
Treatment-related AEs leading to discontinuation, %	13	10[b]	8	8[c]	5	3[d]	10	10[e]	10	10[f]

- There were no treatment-related deaths

Nivolumab (Anti-PD1) Plus Ipilimumab (Anti-CTLA.4)

Efficacy

	Nivo 1 + Ipi 1 Q3W (n = 31)	Nivo 1 Q2W + Ipi 1 Q6W (n = 40)	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)	Nivo 3 Q2W[a] (n = 52)
Confirmed ORR, % (95% CI)	**13** (4, 30)	**25** (13, 41)	**39** (24, 57)	**31** (17, 48)	**23** (13, 37)
Best overall response, %					
Complete response	0	0	0	0	8
Partial response	13	25	39	31	15
Unconfirmed partial response	3	3	5	8	0

Durvalumab (Anti-PD-L1) Plus Tremelimumab (Anti-CTLA.4)

Efficacy

	M10–20 q4/2w T1 mg/kg (n=27)	M10–20 q4/2w T3 mg/kg (n=24)	M15 q4w T10 mg/kg (n=9)	All Cohorts (Including M3/T1) (N=63)
All evaluable patients				
ORR, n (%)	9 (33)	6 (25)	2 (22)	17 (27)
PD-L1^{+}	N=9	N=5	N=4	N=18
ORR, n (%)	3 (33)	2 (40)	1 (25)	6 (33)
PD-L1^{-}	N=13	N=14	N=4	N=33
ORR, n (%)	5 (38)	3 (21)	1 (25)	9 (27)
PD-L1 Unknown	N=5	N=5	N=1	N=12
ORR, n (%)	1 (20)	1 (20)	0 (0)	2 (17)

Includes all patients in the as-treated population who were dosed ≥16 weeks prior to the cut-off date, with measurable disease at baseline, ≥1 follow-up scan (includes those that discontinued due to PD or death without any follow-up scan). ORR includes confirmed and unconfirmed CR or PR.

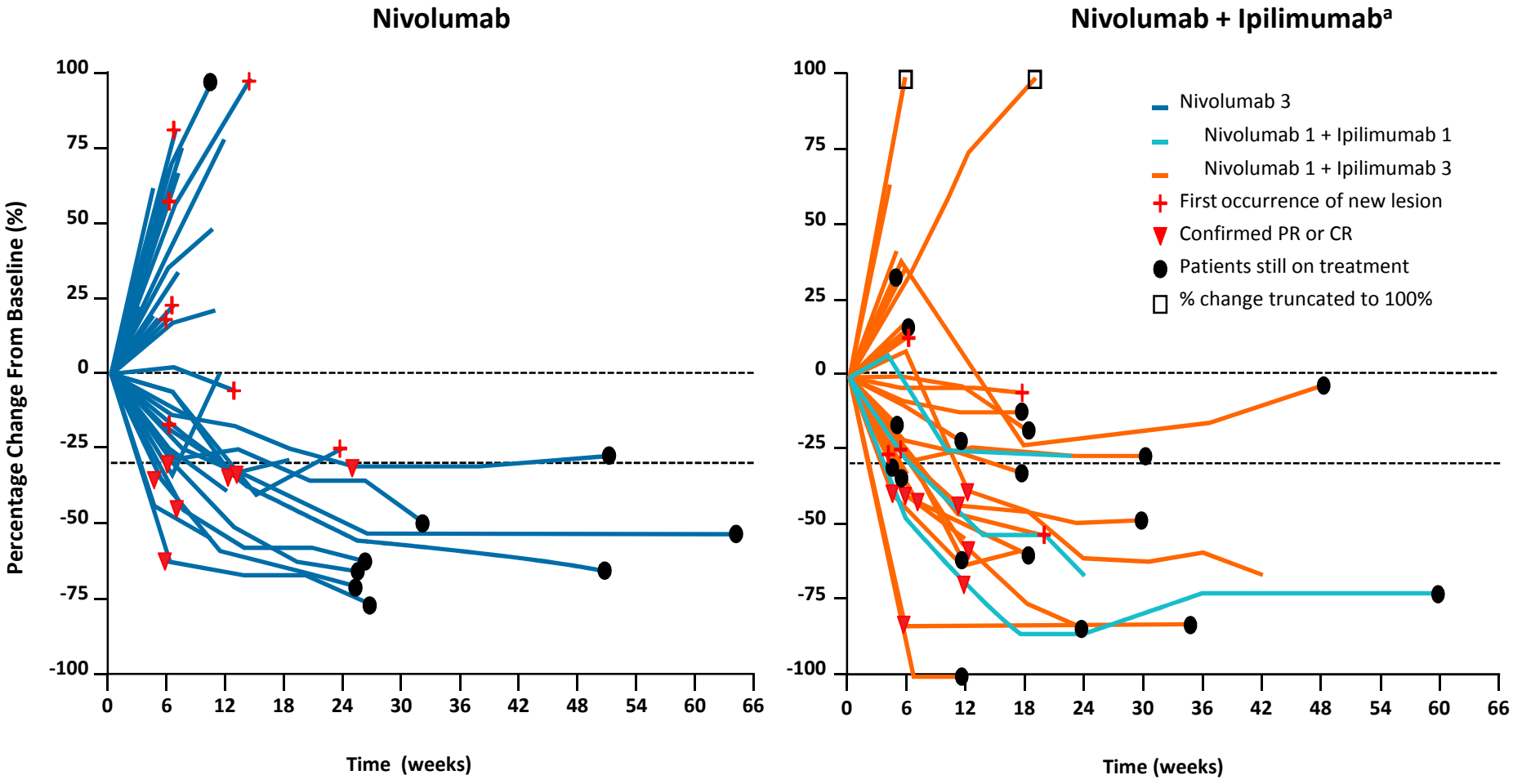
CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; SD, stable disease

Clinical Activity

	Platinum-sensitive[a]		Platinum-resistant[b]	
	Nivolumab 3 (n = 44)	Nivolumab 1+ Ipilimumab 3 (n = 21)	Nivolumab 3 (n = 22)	Nivolumab 1 + Ipilimumab 3 (n = 16)
ORR, %	11.4	33.3	9.1	25.0
Complete response, %	0	0	0	6.3
Partial response, %	11.4	33.3	9.1	18.8
Stable disease, %	11.4	28.6	9.1	12.5
Disease control rate, %	22.7	61.9	18.2	37.5
Progressive disease, %	45.5	23.8	50.0	50.0
Death prior to first response assessment, %	2.3	9.5	13.6	0
Other, %	29.5	4.8	13.6	12.5
Not reported, %	0	0	4.5	0

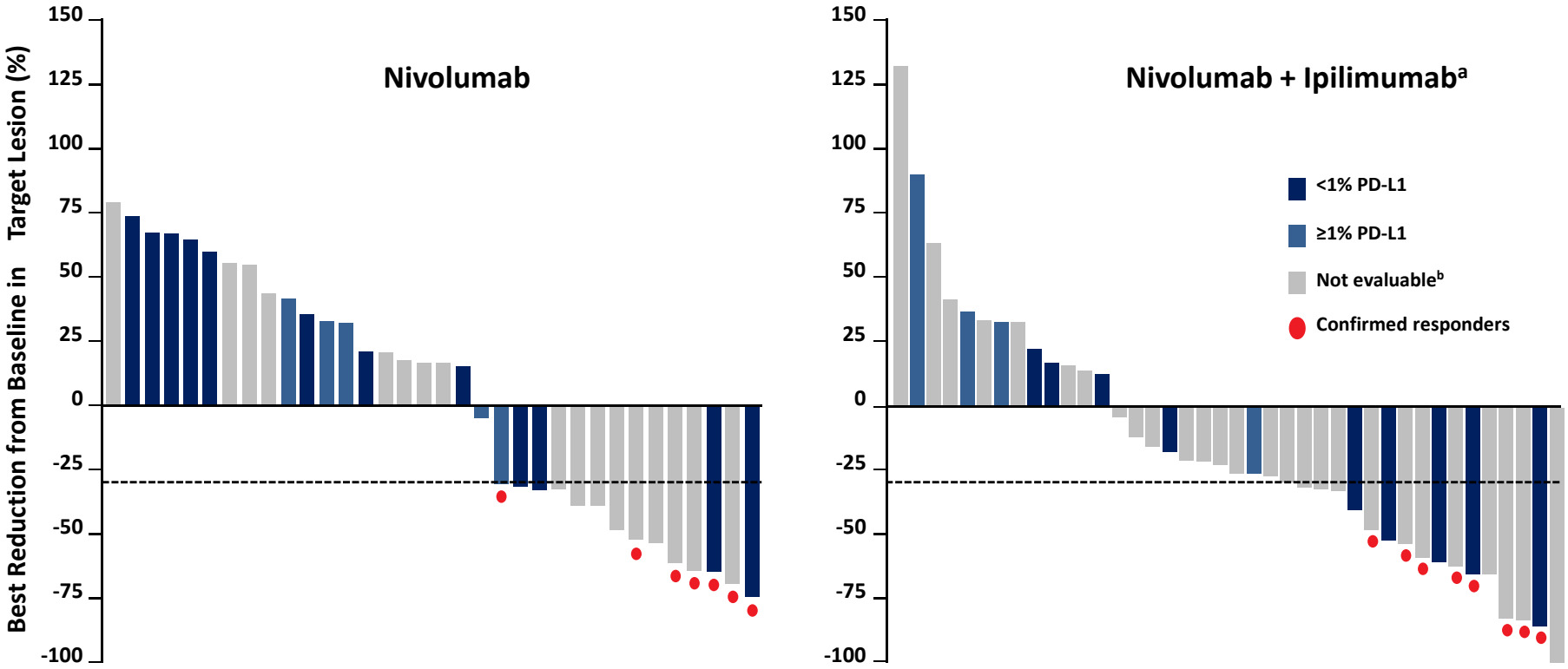
[a]Patient relapsed ≥90 days following platinum-based chemotherapy
[b]Patient relapsed <90 days following platinum-based chemotherapy

Changes in Tumor Burden



[a]Combined data for nivolumab 1 + ipilimumab 1 and nivolumab 1 + ipilimumab 3 cohorts. Only pts with target lesion at baseline and ≥1 on-treatment tumor assessment are included (nivolumab, n = 34, nivolumab + ipilimumab, n = 40).

Tumor Responses (PD-L1 expression)



Evaluable samples (40 of 90)	PD-L1 expression level, n (%)	
	<1%	≥1%
Nivolumab (n = 22)	15 (68)	7 (32)
Nivolumab + Ipilimumab (n = 18)	12 (67)	6 (33)

[a]Combined data for nivolumab 1 + ipilimumab 1 and nivolumab 1 + ipilimumab 3 cohorts. [b]Not evaluable due to specimens that are not quantifiable, indeterminate, or not yet obtained; 10 nonevaluable samples and 8 not yet obtained in the nivolumab arm, 6 nonevaluable samples and 26 not yet obtained in the nivolumab 1 + ipilimumab 3 arm. Only pts with target lesion at baseline and ≥1 on-treatment tumor assessment are included (nivolumab, n = 34, nivolumab + ipilimumab, n = 40).

Vaccines

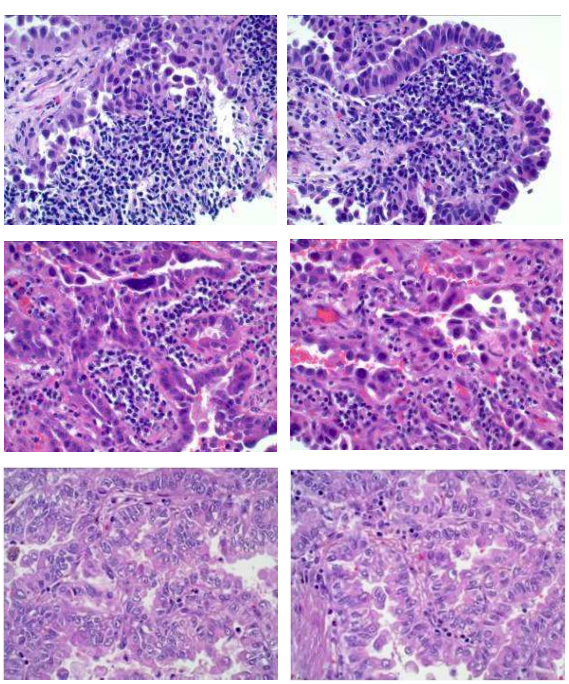
- CD40LGVAX
  - Adenocarcinoma.
  - Nivolumab +/- CD40LGVAX
- Ad.p53-DC
  - SCLC
  - Pembrolizumab +/- Ad.p53-DC

Adoptive T cell Therapy with TIL or CAR/TCR TG T cells

- Previous experience with TIL ACT in NSCLC produced no clinical responses.
- In melanoma 50% RR, only after discovery that lymphopenia must be induced prior to ACT.

- ACT with CAR or TCR transgenic T cells.
  - Redirect peripheral T cells of any specificity.

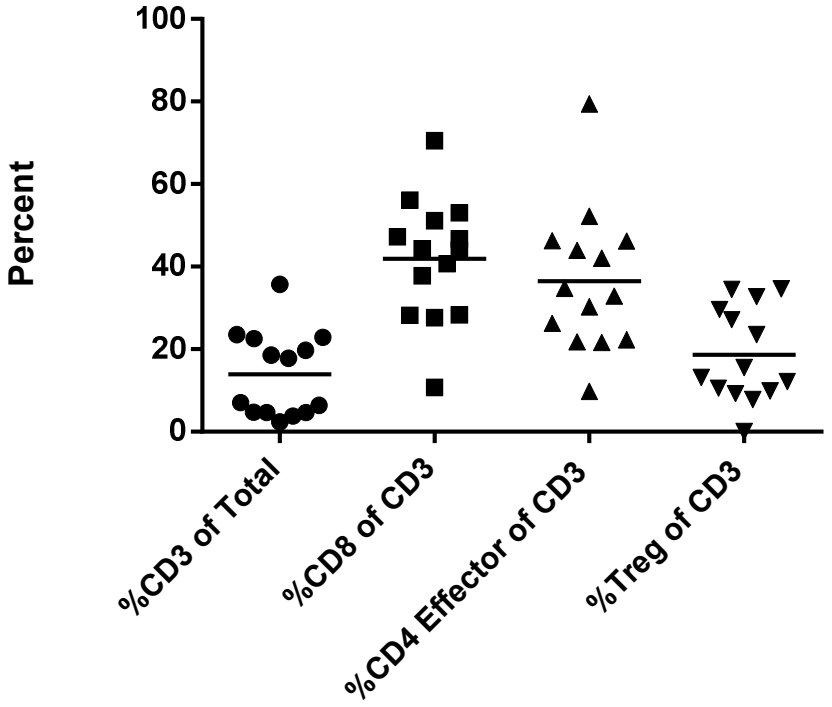
2. Insufficient number of T cells extravasate into some tumors.



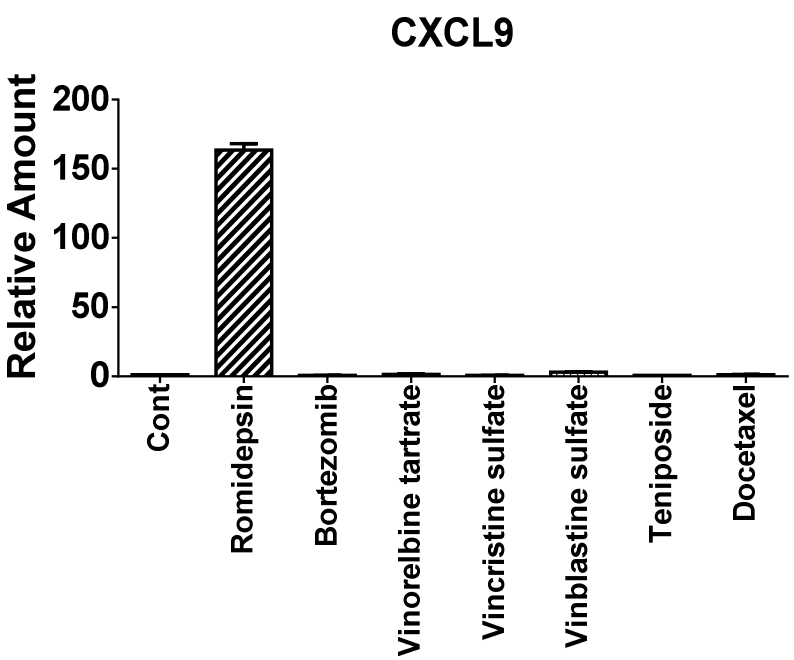
High

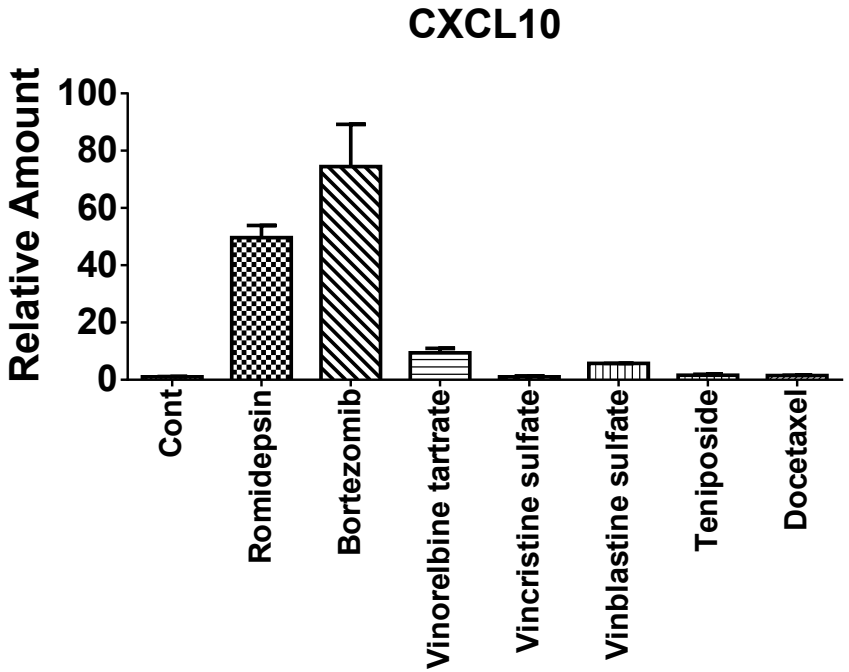
Moderate

Low



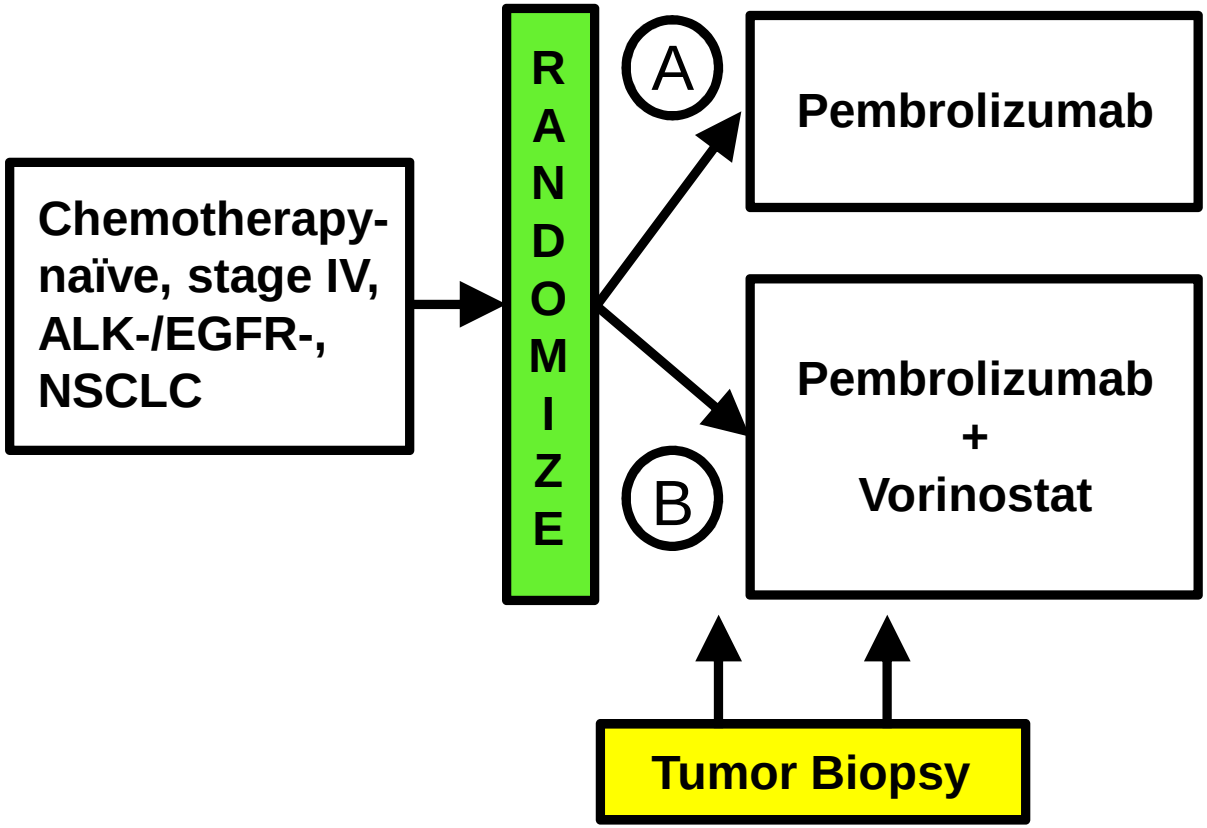
HDACi Induce the Secretion of T cell Chemokines





2. Insufficient number of T cells extravasate into the tumor.

Clinical Trial

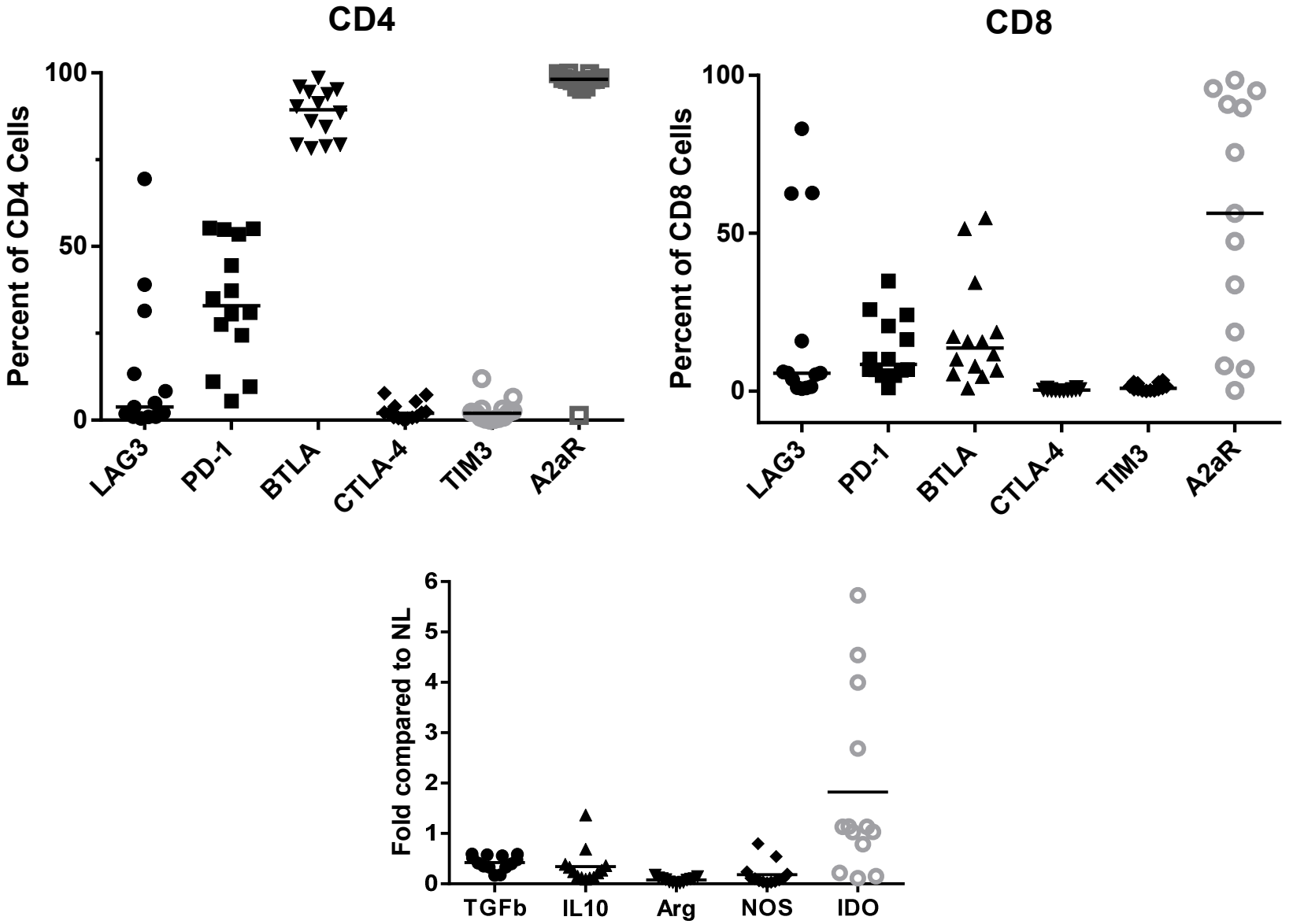


3. T cells are inhibited in the tumor microenvironment

Relevant Targets for NSCLC

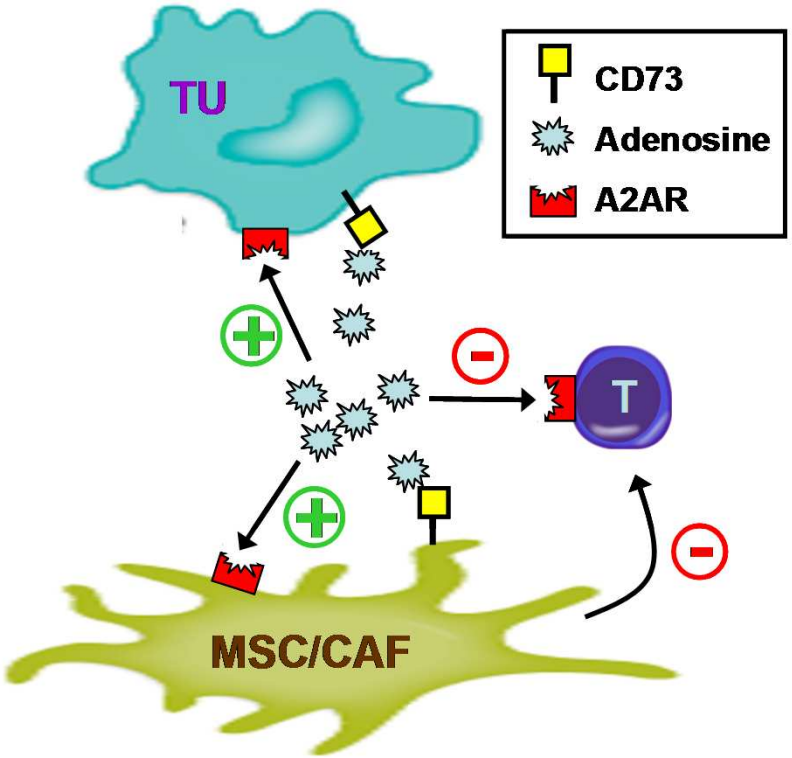
- **Surface membrane proteins- checkpoints**
  - **PD1**, CTLA4, **LAG3**, TIM3, **BTLA**, **Adenosine A2AR**
- **Soluble factors and metabolic alterations**
  - IL10, TGFβ, **Adenosine**, **IDO**, Arginase
- **Inhibitory cells**
  - **Cancer Associated Fibroblasts, Regulatory T cells, Myeloid Cells**

Checkpoint Protein Expression of Fresh Lung TILs

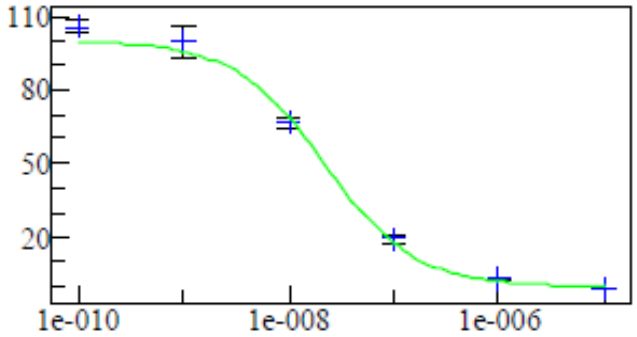


PBF-509: Adenosine A2AR Antagonist

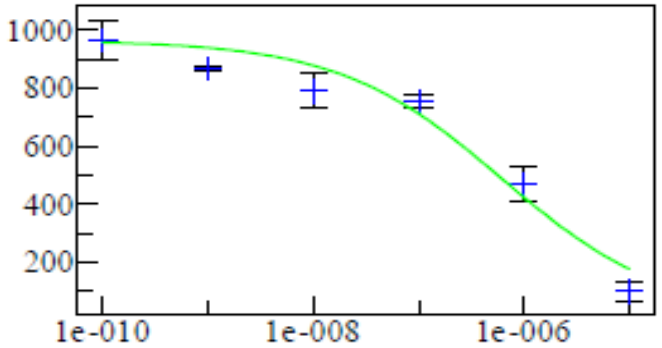
Target Cells



Specific Binding
Ki 12nM

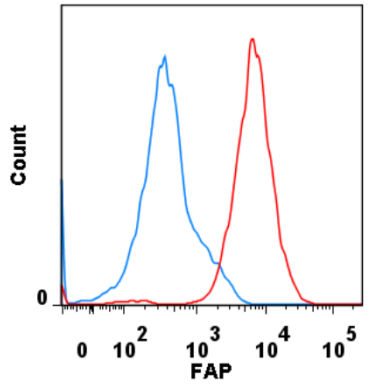


cAMP Accumulation
IC_{50} 26nM

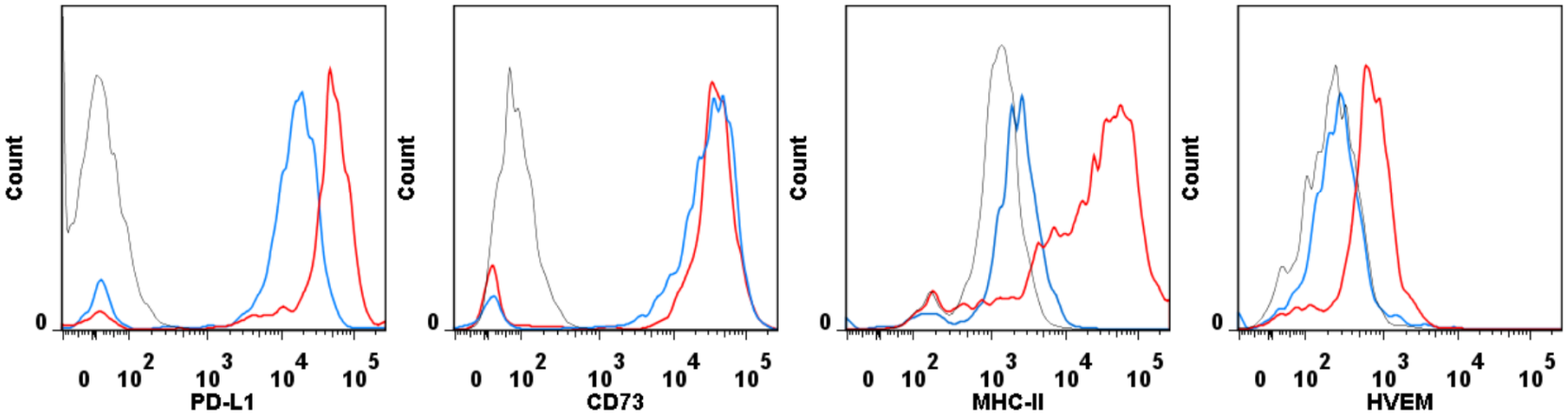


Cancer Associated Fibroblasts

Immunosuppressive in the TME



α-SMA



Unstained Untreated IFN-γ

Cancer Associated Fibroblasts

Repurpose IPF Drugs

- Pirfenidone plus atezolizumab.
- Nintedanib plus durvalumab and tremelimumab.

Triterprenoid

Myeloid Cells

- Tumor infiltrating myeloid cells produce peroxynitrite.
  - Nitrosylates MHC/peptide complex, TCR, etc.
- RTA408 induces Nrf1.
  - Activates genetic program that reduces peroxynitrite.
- RTA408 phase I complete.
- RTA408 plus nivolumab phase I initiated.

Conclusions

- Immunotherapy can be very efficacious in lung cancer.
- There are a myriad of ways tumors evade rejection.
- There is considerable heterogeneity across patients.
- Relevant biomarkers need to be discovered to deliver proper immunotherapeutic combinations to individual patients.

Immune-Related Adverse Events

Frequently rapidly responsive to steroids

- Diarrhea/ colitis
- Mucositis
- Dermatitis
- Pneumonitis
- Hepatitis
- Nephritis
- Lipase elevation
- Neurologic: GBS, achalsia, myasthenia gravis
- Polymyositis
- Arthritis
- Myalgias

Diarrhea/ Colitis

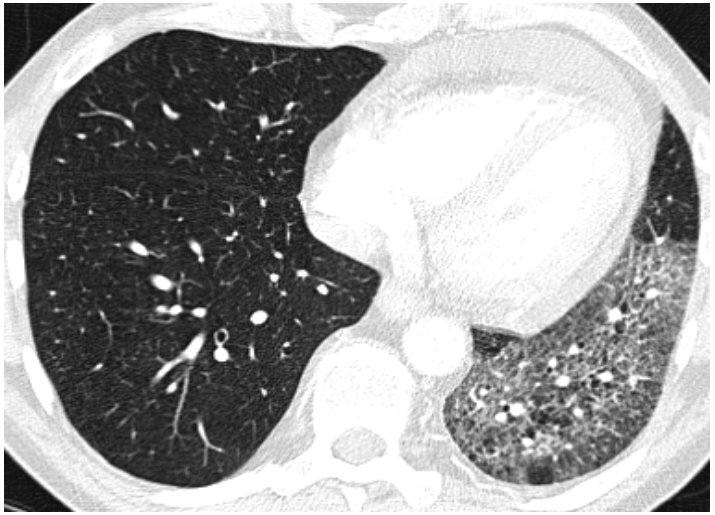
GI Adverse Event Management Algorithm

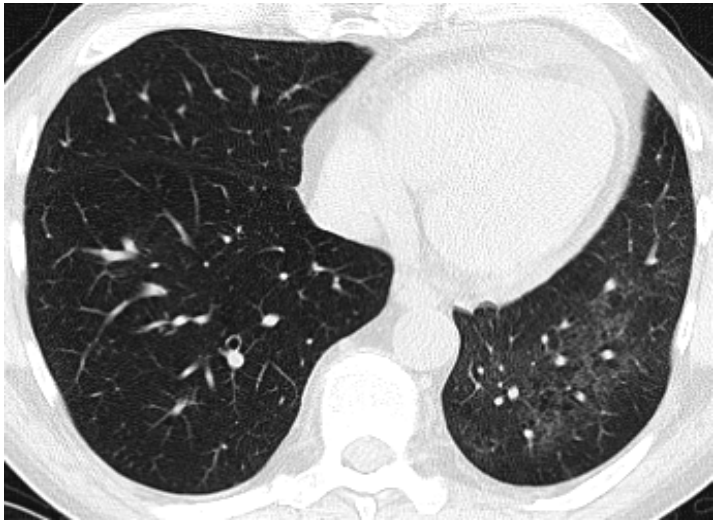
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

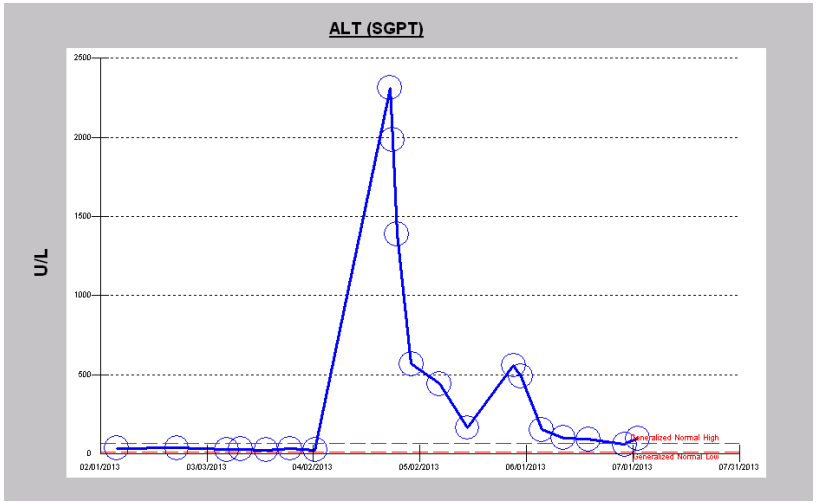
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pneumonitis

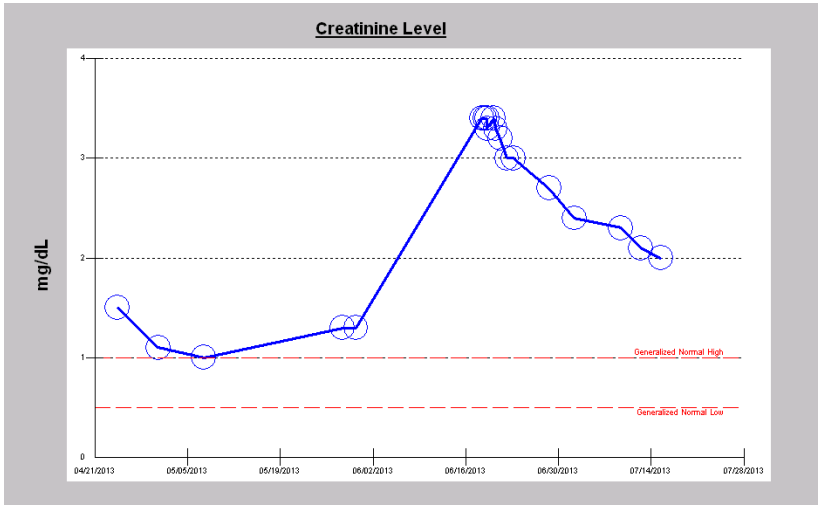




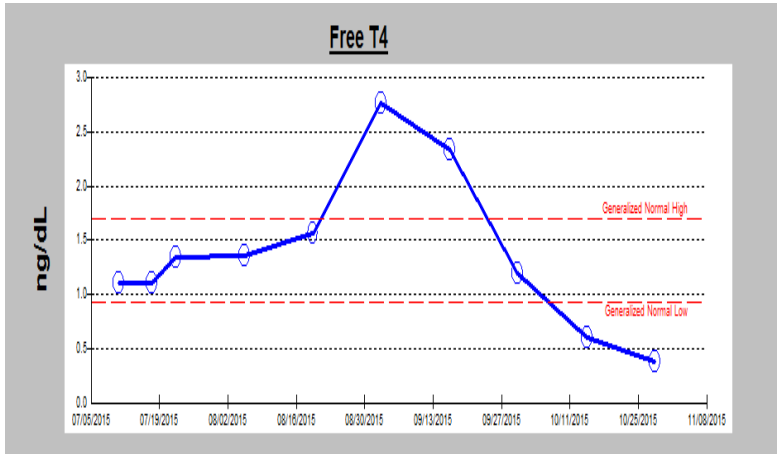
Hepatitis

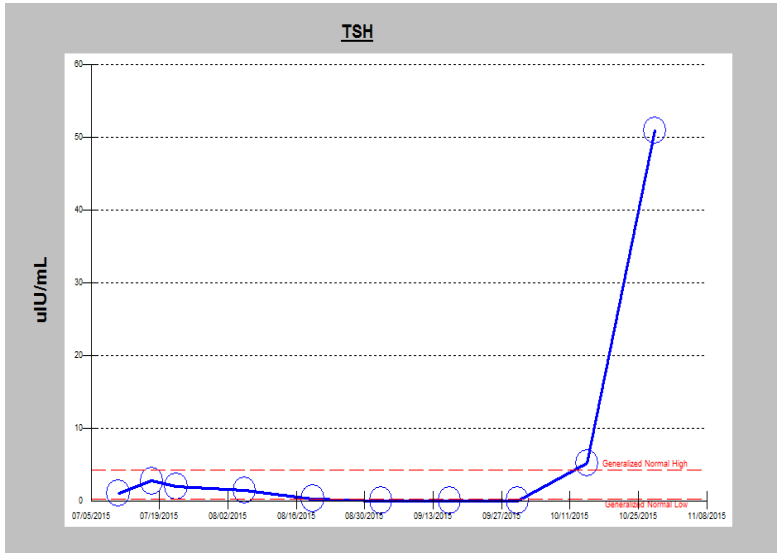


Nephritis

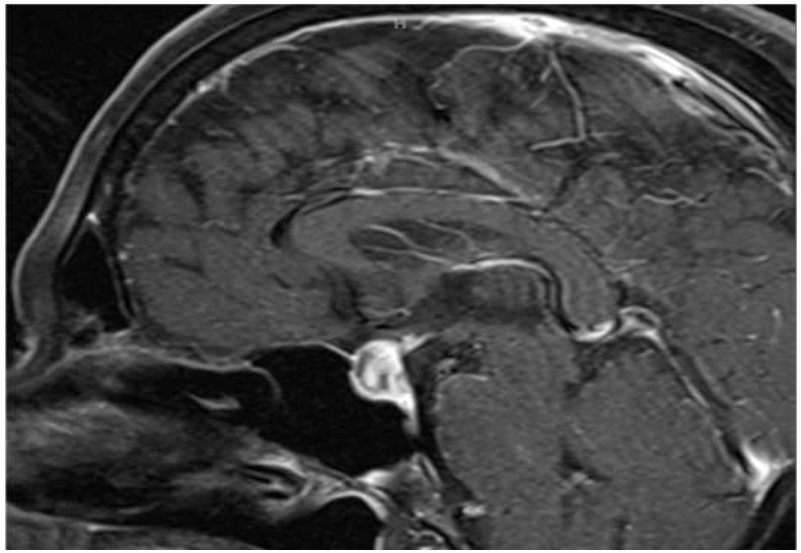


Thyroiditis





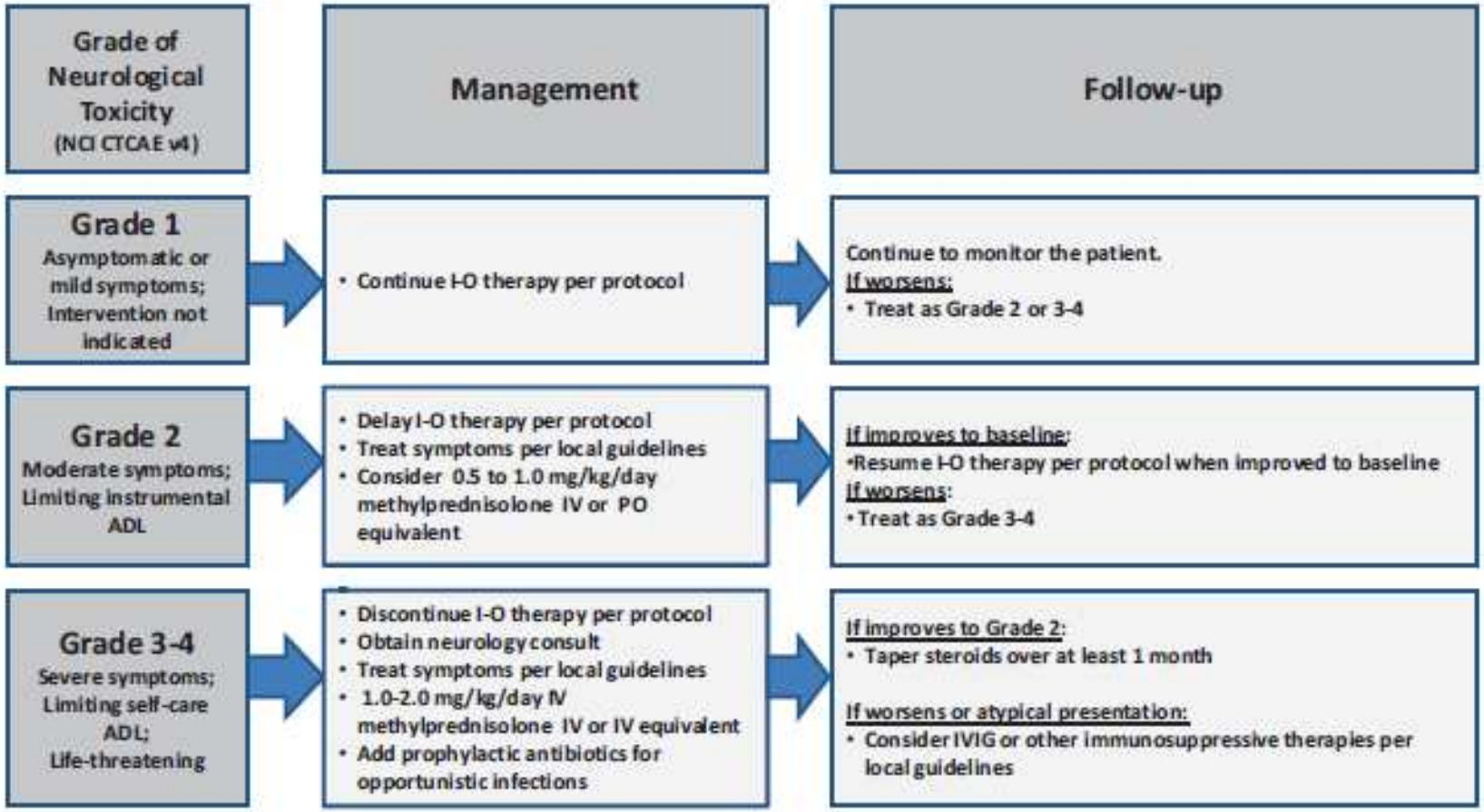
Hypophysitis



Neurologic Toxicity

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Conclusions

- Predictable set of immune related AEs.
- Early detection is important.
- Often rapidly responsive to steroids.
  - High dose.
  - Slow taper (4-6 weeks).
  - PCP prophylaxis.
- Occasionally need to use infliximab.
- IVIG for neurotoxicity.
- Don’t retreat if severe.