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UNINTENDED CONSEQUENCES OF THE THERAPEUTIC PROMOTION OF INFLAMMATION

Neurologic Complications of Immune Checkpoint Inhibitors

Michelle L. Mauermann, MD

Disclosures

- None

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Overview

New Therapies for the Treatment of Cancers that involve targeting the Immune System

Immune Checkpoint Inhibitors (ICIs)

Immune Related Adverse Events

Neurological Toxicities

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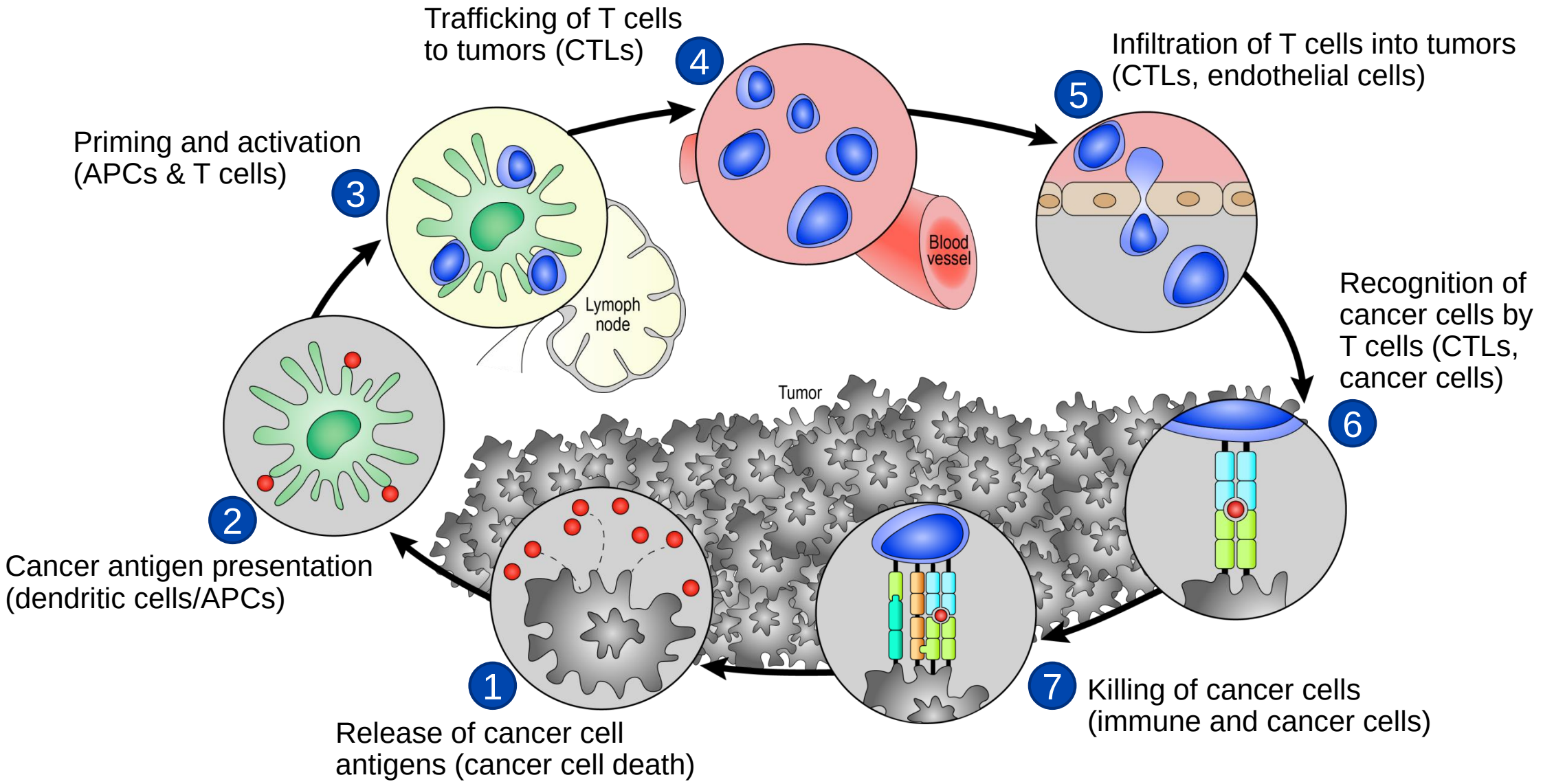
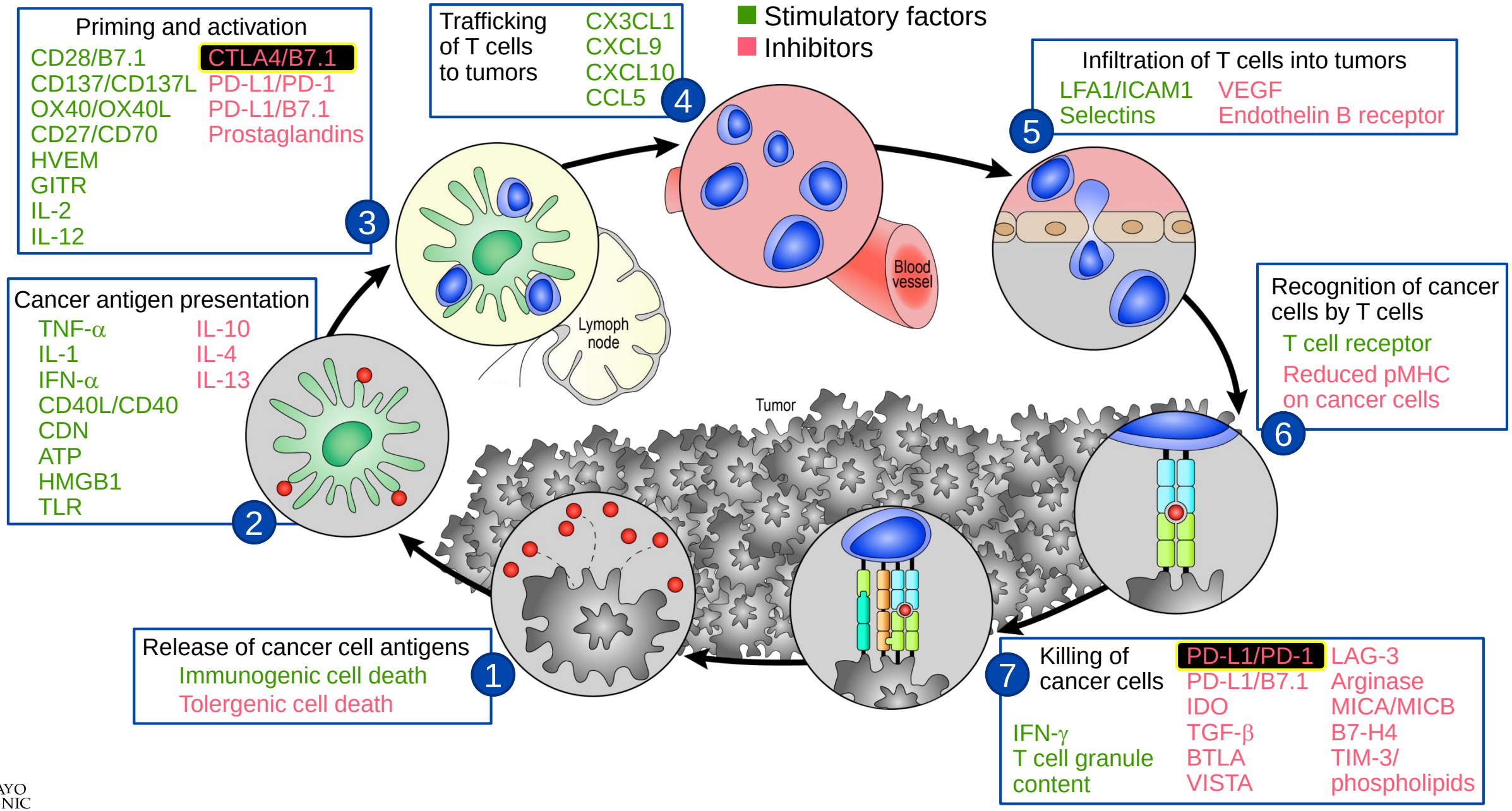
Cancer-Immunity Cycle



Chen DS and Mellman I: Immunity 39:1, 2013



Chen DS and Mellman I: Immunity 39:1, 2013

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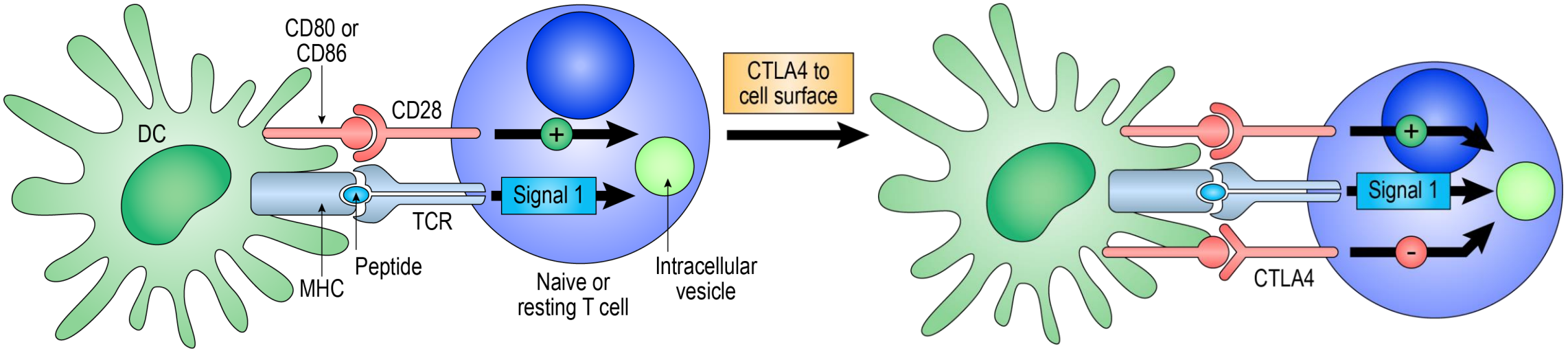
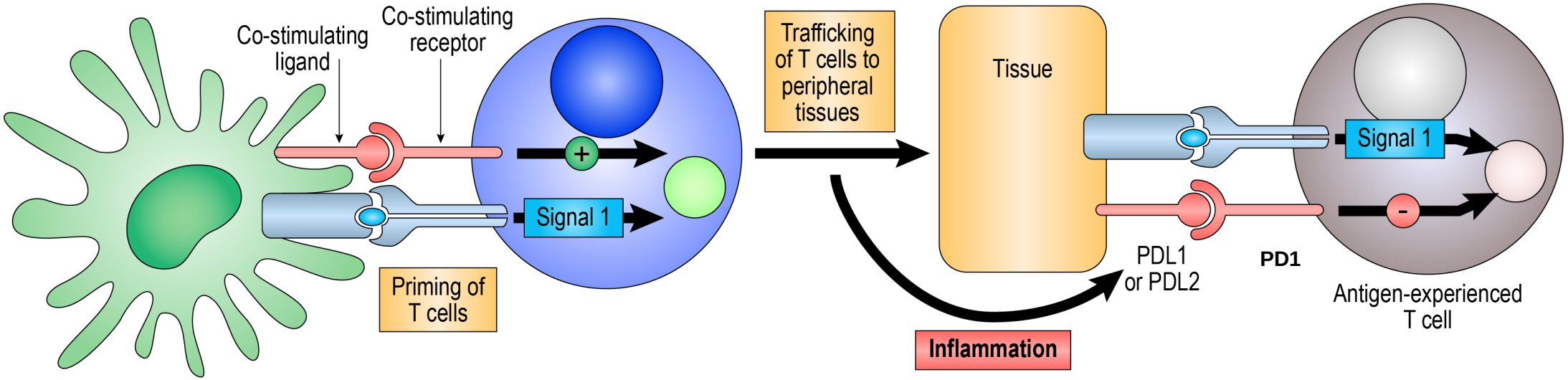
Role of CTLA-4



Pardoll DM: Nat Rev 12:252, 2012

Role of PD-1 & PD-L1/L2



Pardoll DM: Nat Rev 12:252, 2012

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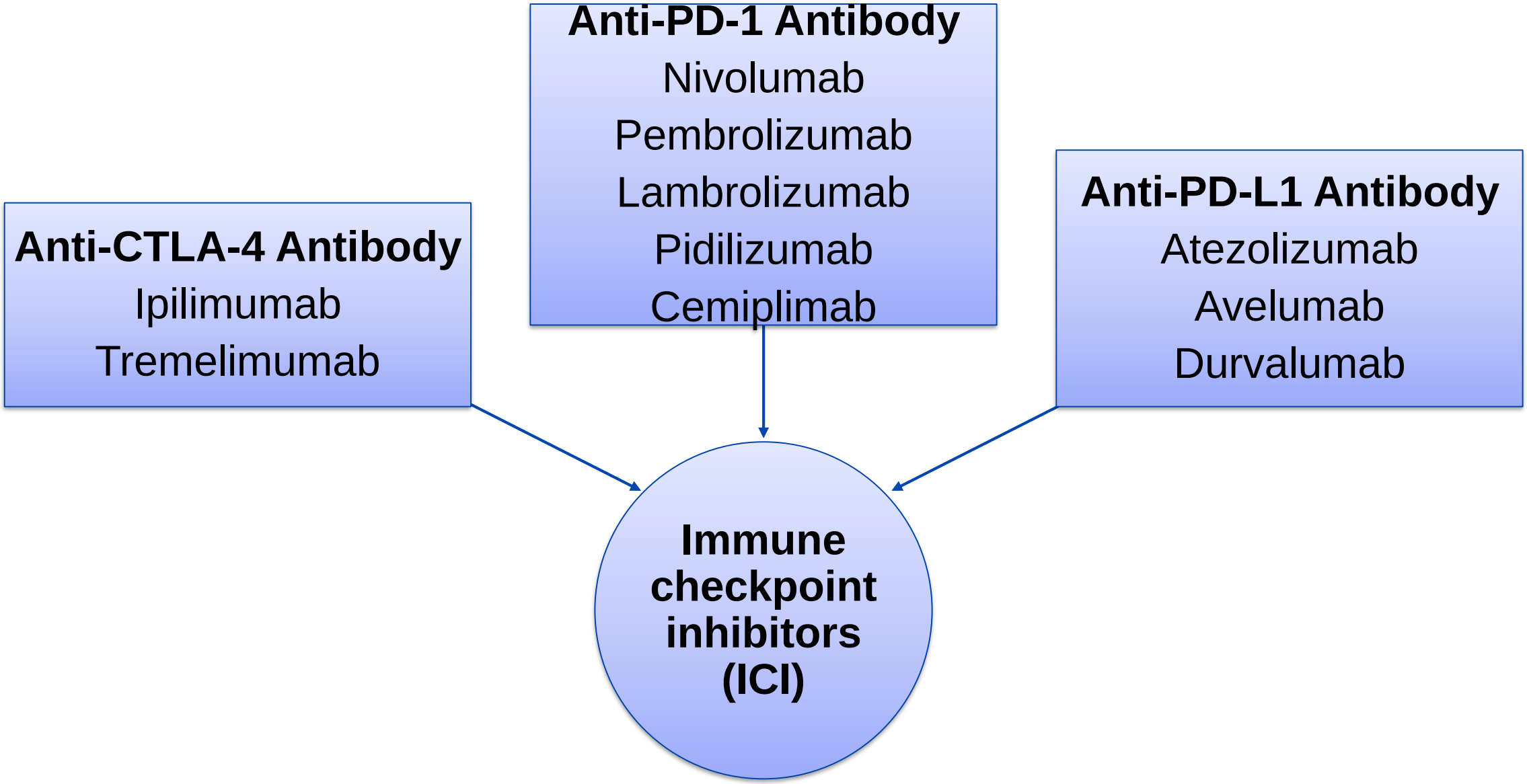

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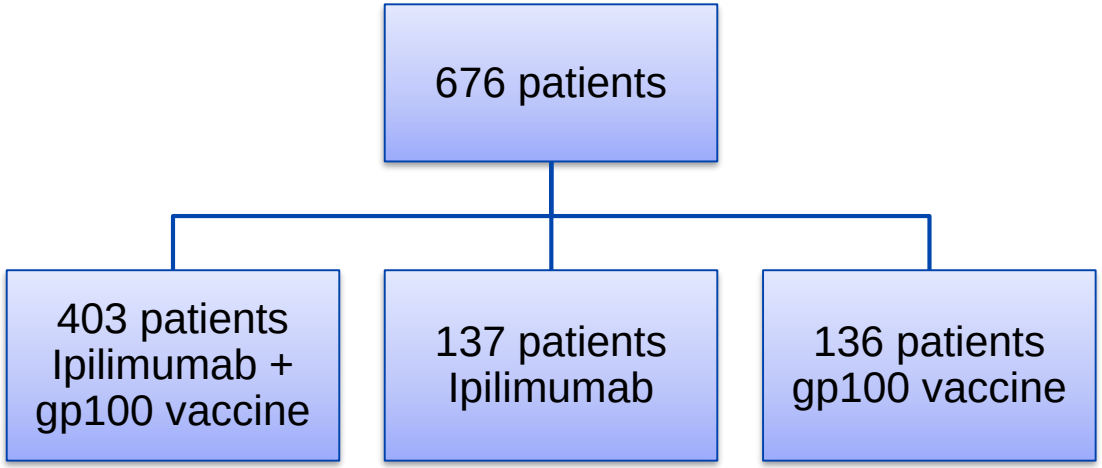
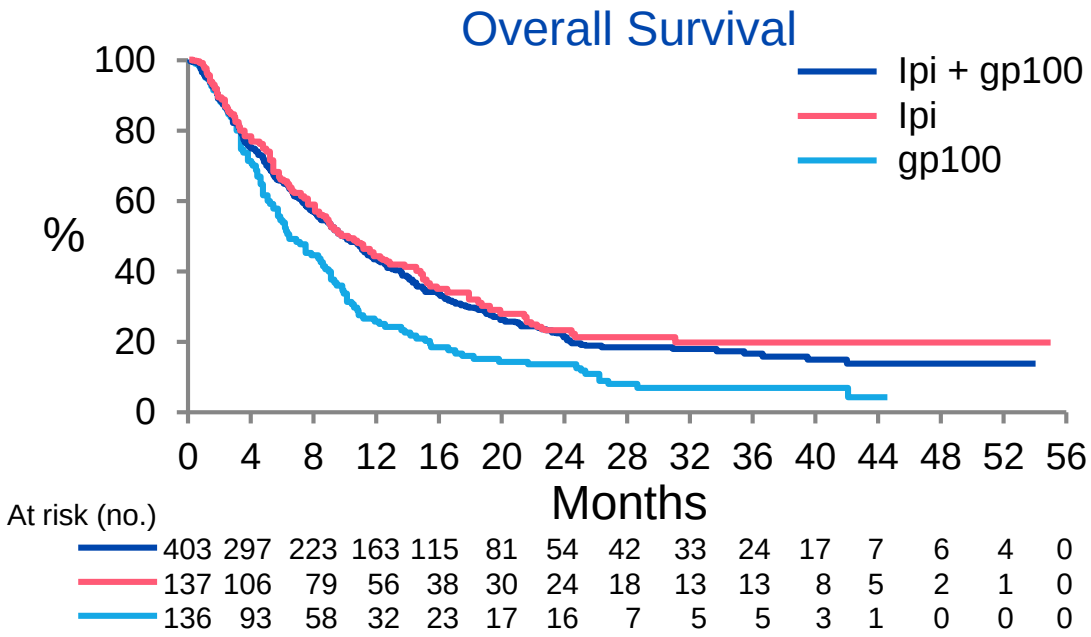
The NEW ENGLAND JOURNAL of MEDICINE

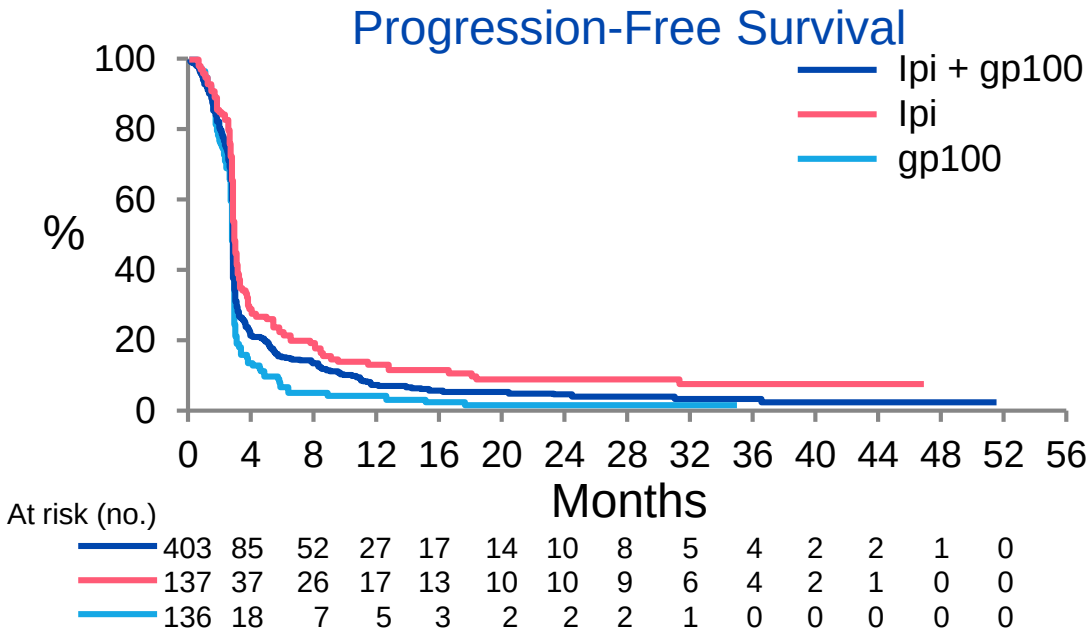
ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.







Hodi et al: NEJM 363(8):711, 2010

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates

Julie R. Brahmer, Charles G. Drake, Ira Wollner, John D. Powderly, Joel Picus, William H. Sharfman, Elizabeth Stankevich, Alice Pons, Theresa M. Salay, Tracee L. McMiller, Maria M. Gilson, Changyu Wang, Mark Selby, Janis M. Taube, Robert Anders, Lieping Chen, Alan J. Korman, Drew M. Pardoll, Israel Lowy, and Suzanne L. Topalian

Phase I Study o
(MDX-1106) i
Activity, Pharm

Julie R. Brahmer, Charles
Elizabeth Stankevich, Alice
Mark Selby, Janis M. Taub
and Suzanne L. Topalian

From the Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Henry Ford Health Systems, Detroit, MI; Carolina BioOncology Institute, Huntersville, NC; Washington University School of Medicine Siteman Cancer Center, St Louis, MO; and Medarex, Bloomsbury, NJ, and Milpitas, CA.

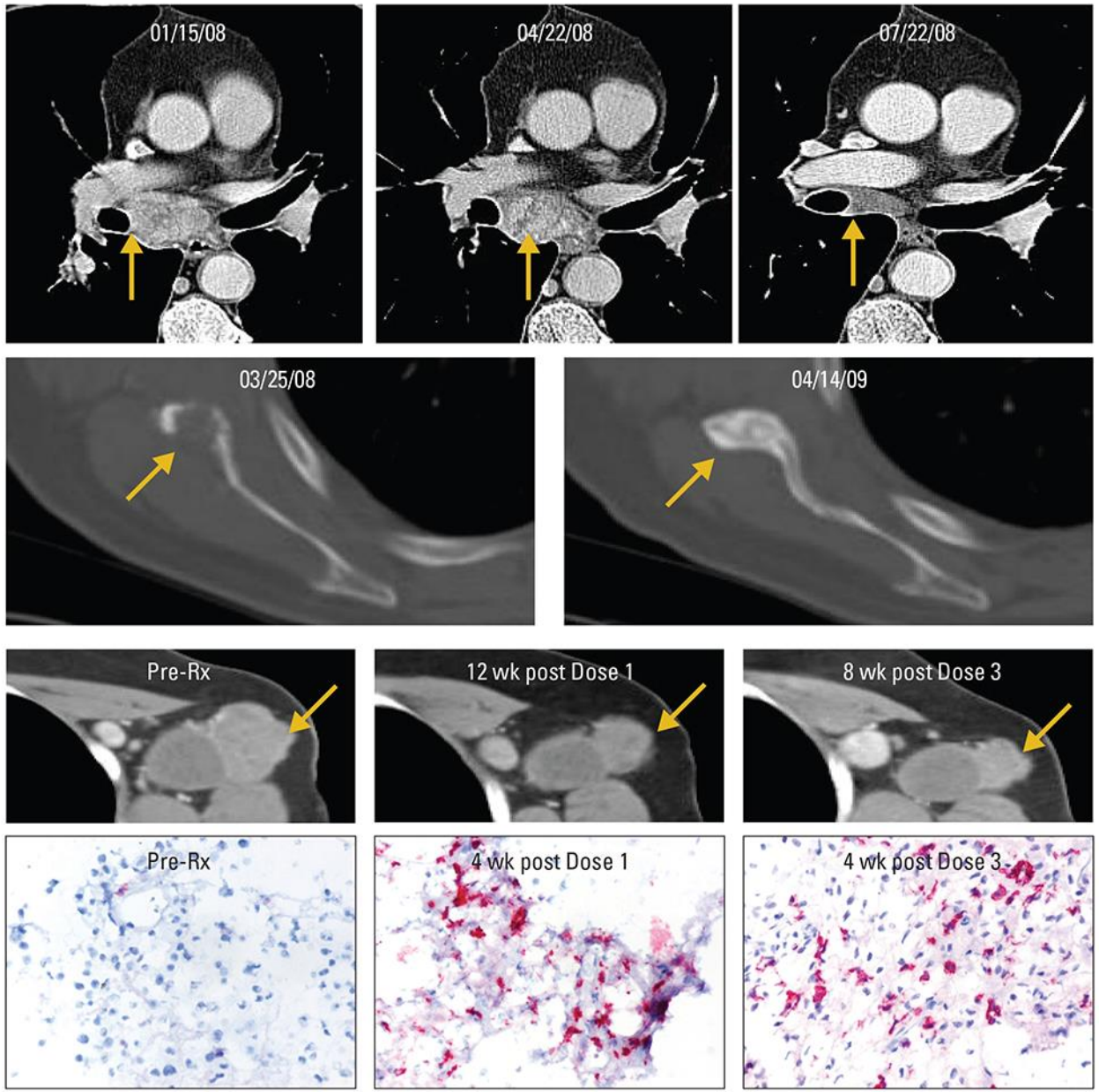
Submitted November 21, 2009;

Purpose

Programmed death-1 (
antitumor immunity. Th
blockade in patients wi
activity, pharmacodyna

Patients and Methods

Thirty-nine patients w
resistant prostate can



Brahmer et al: J Clin Oncol 28:3167, 2010

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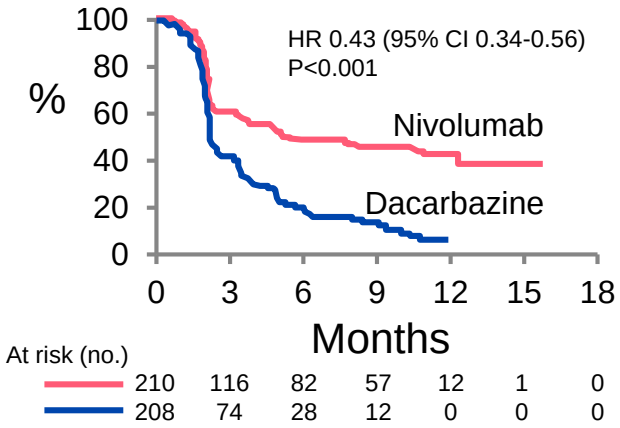
ORIGINAL ARTICLE

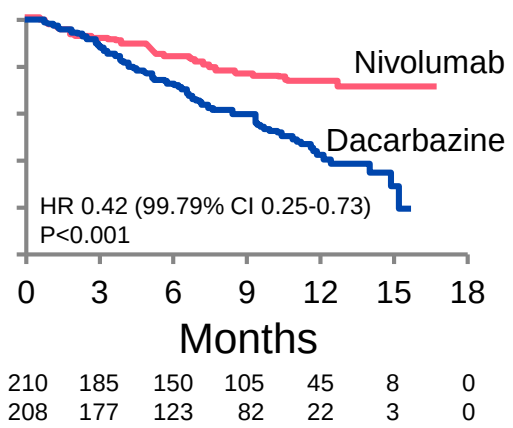
Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalcioiu, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.

Progression-Free Survival



Overall Survival



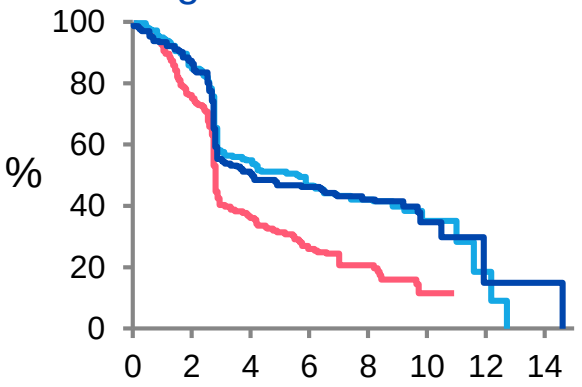
Robert et al: NEJM 372:320, 2015

ORIGINAL ARTICLE

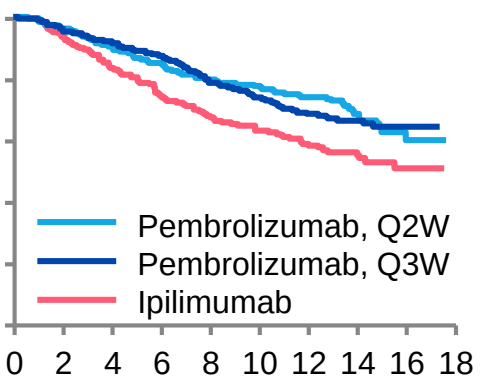
Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*

Progression-Free Survival



Overall Survival



Robert et al: NEJM 372:2521, 2015

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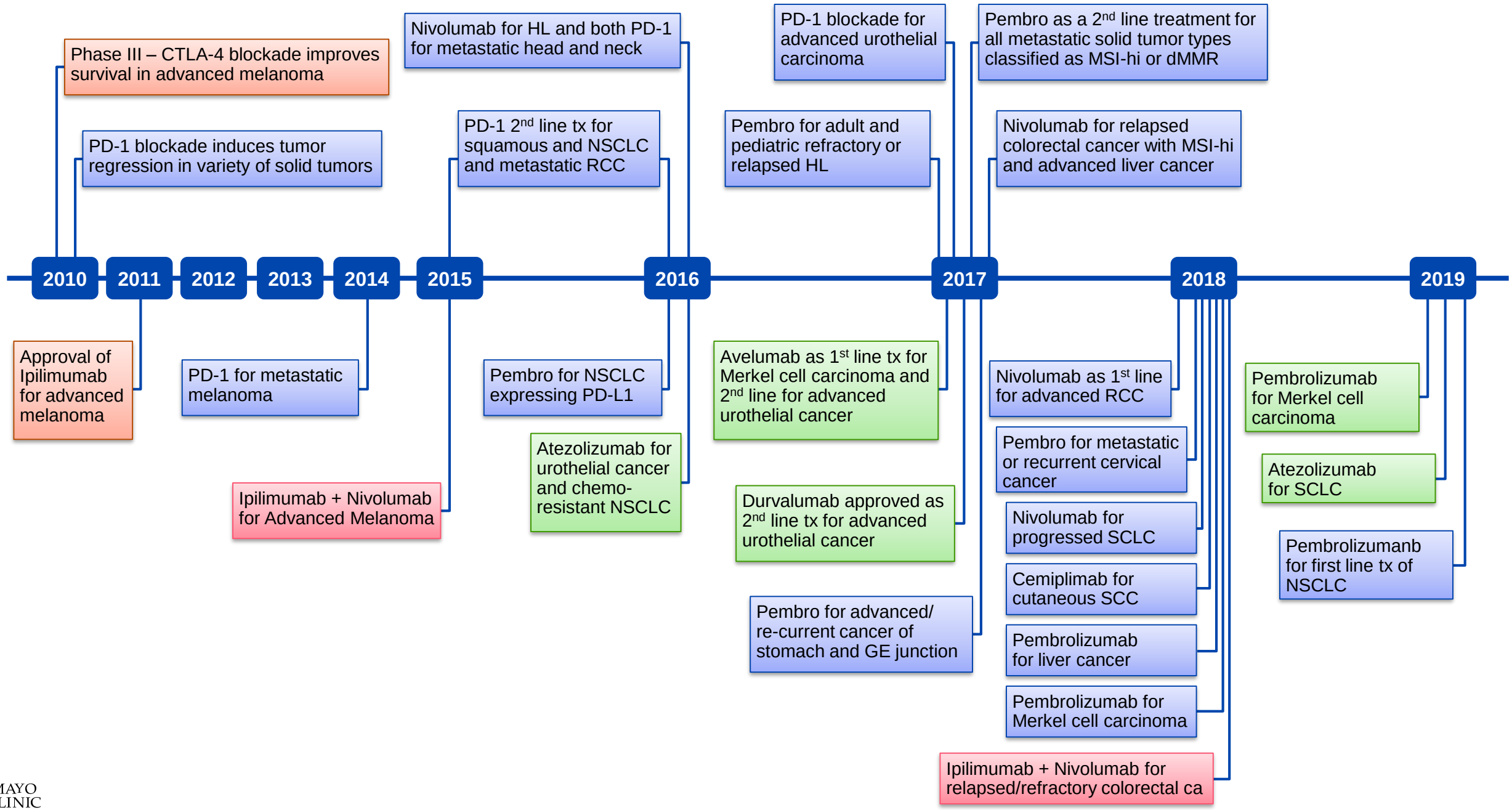

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Neuro

Endocrine

Hyperthyroidism
Hypothyroidism
Adrenalitis
Hypophysitis

Liver

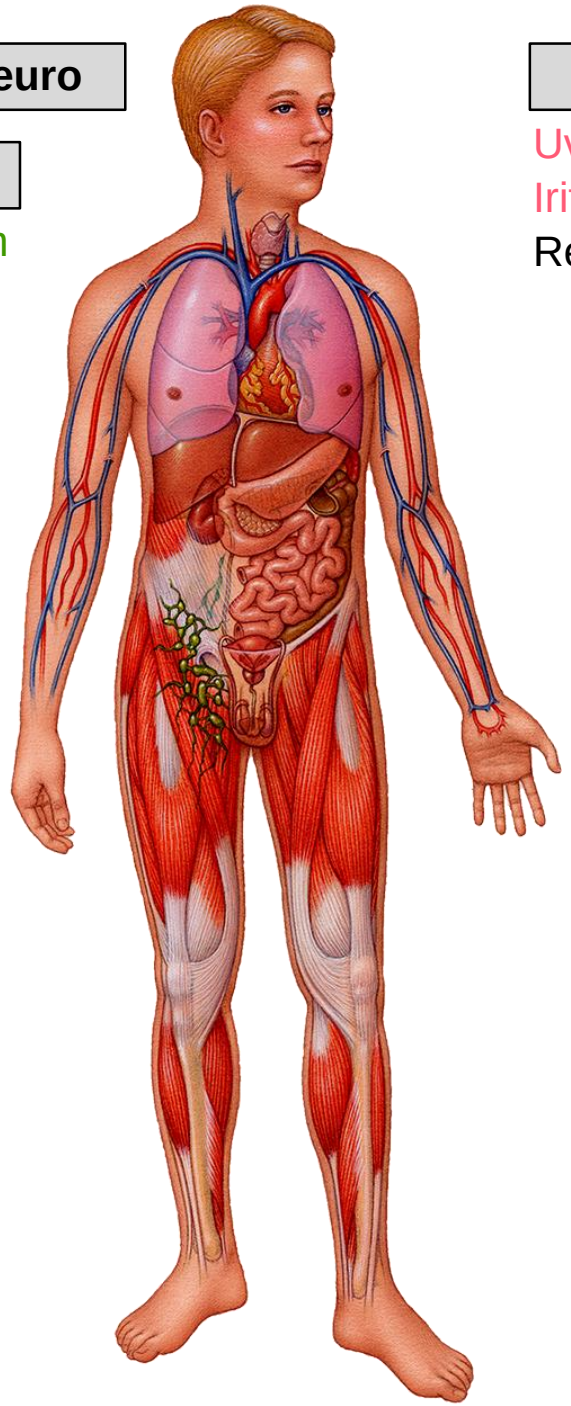
Hepatitis

Renal

Nephritis

Skin

Pruritis
Rash
Vitiligo
Mucositis



Ocular

Uveitis
Iritis
Retinopathy

Respiratory

Pneumonitis

Cardiovascular

Myocarditis
Pericarditis
Vasculitis

GI

Diarrhea
Colitis
Enteritis

Blood

Hemolytic anemia
Thrombocytopenia
Neutropenia
Hemophilia

■ CTLA-4
■ PD-1/PD-L1

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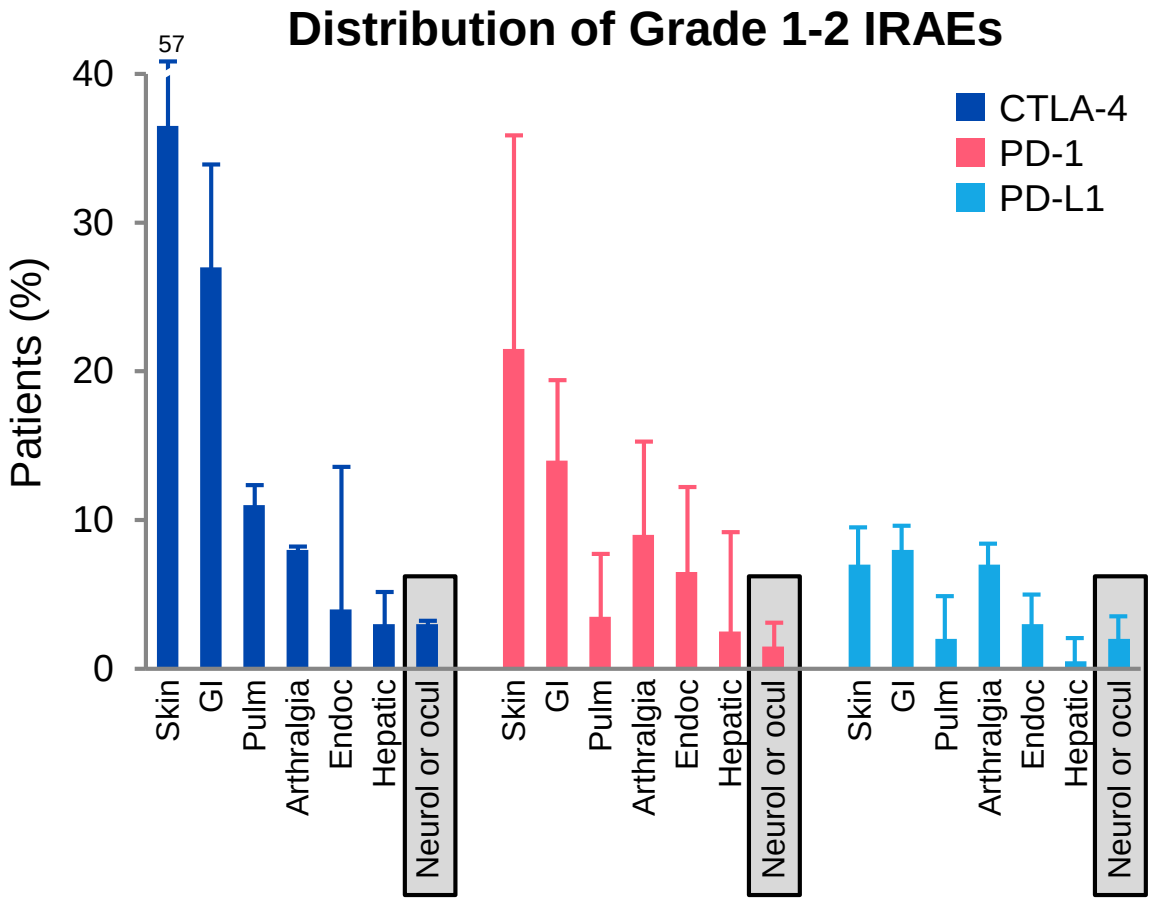
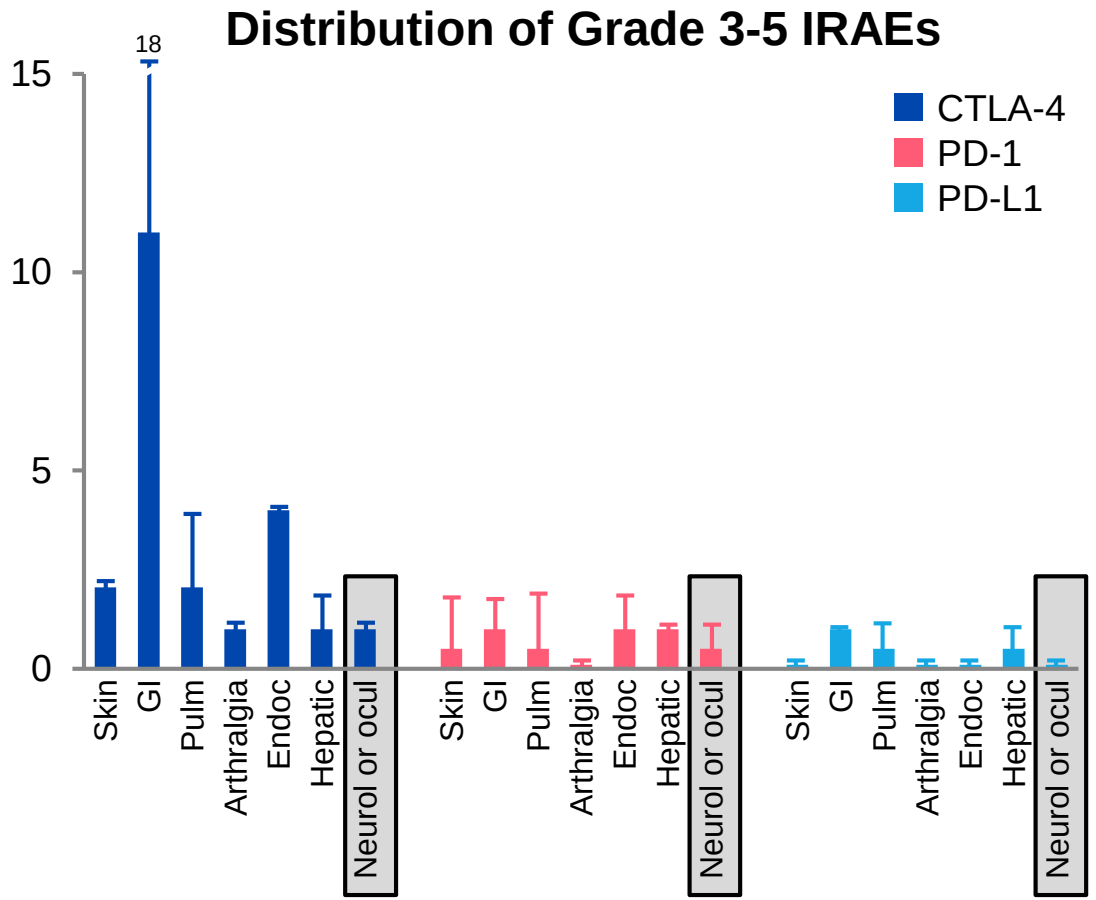
Distribution of Immune-Related Adverse Events (IRAEs) for All Tumor Types





Brahmer et al: J Clin Oncol 36:1714, 2018

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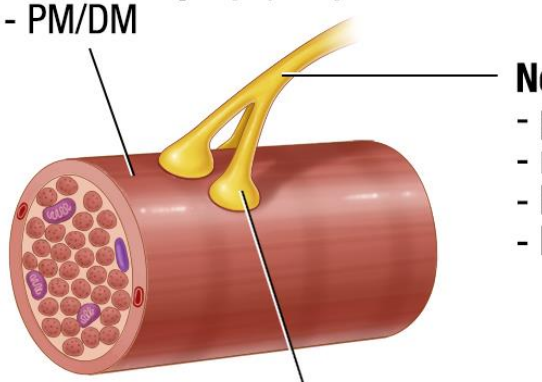
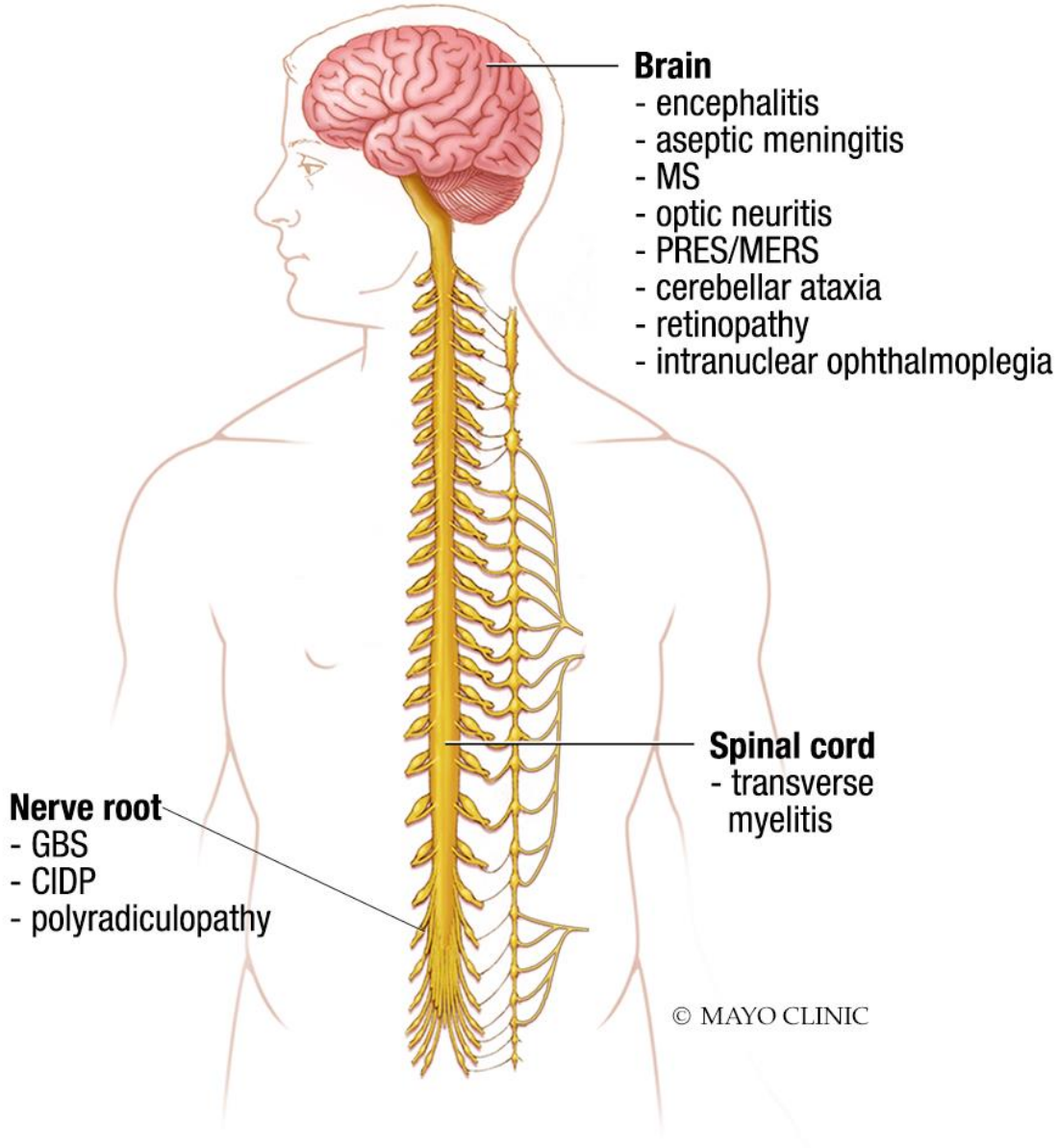
Nervous System Targets

Muscle
- necrotizing myopathy
- PM/DM



Nerve
- peripheral neuropathy
- mononeuropathy
- brachial plexopathy
- lumbosacral plexopathy

Neuromuscular junction
- MG



Frequency of Neurologic Immune Related Adverse Events (NirAEs)

Incidence of neurological AEs in patients included in clinical trials

Class antibody	Drugs	Pt (no.)	Incidence of any grade nAEs, % (range of reported incidence)	Incidence of grade 3-4 nAEs, % (range of reported incidence)
Anti-CTLA4	**All**	**3672**	**3.8 (0-27.3)**	**0.7 (0-7.1)**
	Ipilimumab	2734	3.0 (0-22.2)	0.8 (0-7.1)
	Tremelimanab	938	6.3 (0-27.3)	0.3 (0-3.5)
Anti-PD1	**All**	**5076**	**6.1 (0-26.8)**	**0.4 (0-5.0)**
	Nivolumab	2536	5.2 (0-23.5)	0.4 (0-5.0)
	Pembrolizumab	2333	6.3 (0-26.8)	0.2 (0-1.7)
	Lambrolizumab	135	21.5	0
	Pidilizumab	72	5.6	5.6
Anti-CTLA4 CTLA4 + anti-PD1	**All**	**460**	**12.0 (10.2-18.9)**	**0.7 (0-2.1)**

Series	Frequency (%)	Onset within 4 mo (%)
Germany (Zimmer et al: Eur J Ca 60, 2016)	3.2 PD-1	75
Mayo Clinic (Kao et al: JAMA Neurol 74, 2017)	2.9 PD-1	60
London (Spain et al: Annals of Oncol 28, 2017)	2.4 PD-1 & CTLA-4	80
Germany (Voskens et al: PLoSone 8, 2013)	1.4 CTLA-4	73

Cuzzubbo et al: Eur J Ca 73:1, 2017

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Myasthenia Gravis

Frequency 0.12-0.2%

Occurs following 1-4 treatments (median 2)

Clinical presentation

- De novo 2/3, pre-existing or AchR Ab +
- Only 18% pure ocular

	nivoMG n=12	iMG n=105	P	Literature
Age, y, mean +/- SD	73.5 ± 6.3	47.8 ± 16.7	<0.001	
MGFA classification class 5, no. (%)	6 (50)	7 (7)	0.004 overall	
Facial muscle weakness, no. (%)	5 (42)	12 (11)	0.02	
Dysphagia, no. (%)	7 (58)	23 (22)	0.02	
Dysarthria , no. (%)	6 (50)	18 (17)	0.02	
Dyspnea, no. (%)	8 (67)	12 (11)	<0.001	
Respiratory support, no. (%)	5 (42)	7 (7)	0.001	12/24 (50%)
AchR Ab + (%)	10 (83)	82 (78)	1.0	

Suzuki S et al: Neurology 89:1127, 2017

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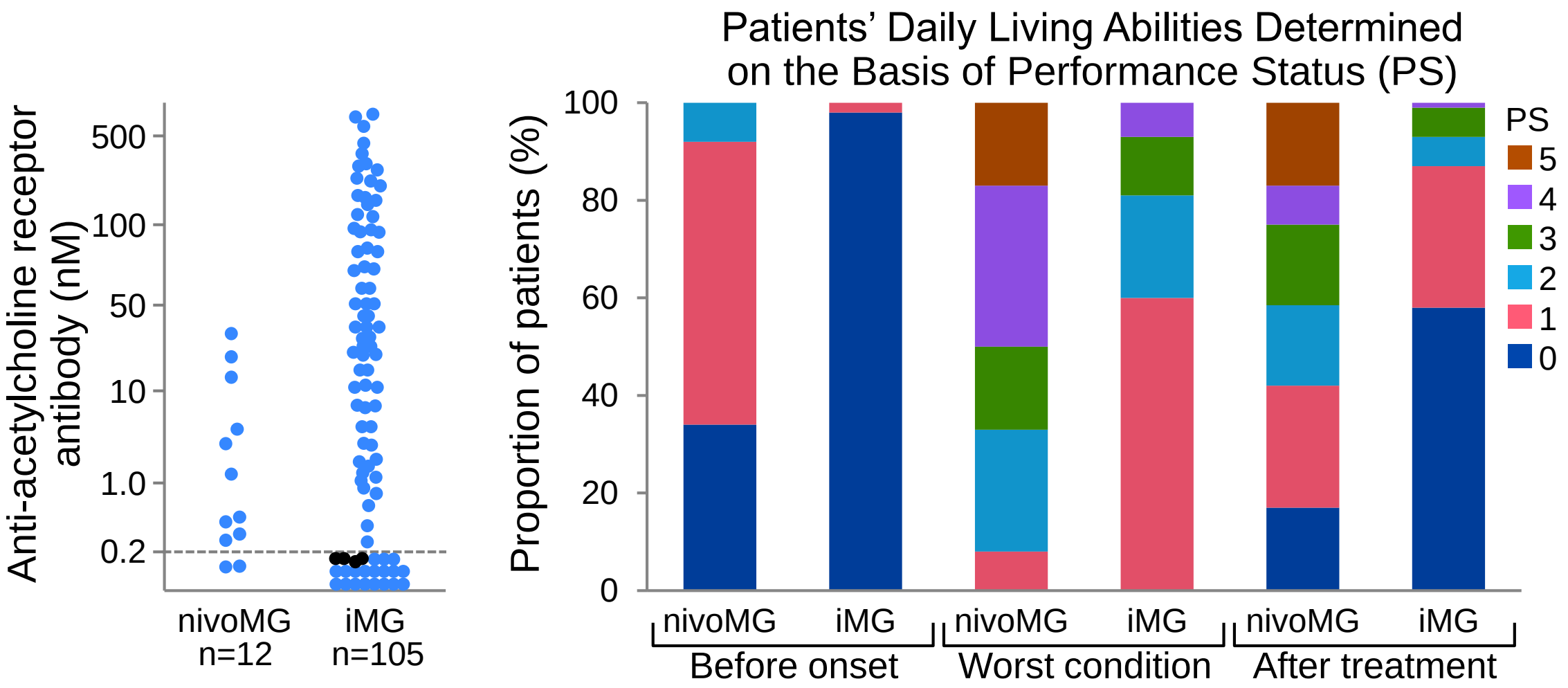
Myasthenia Gravis



Suzuki S et al: Neurology 89:1127, 2017

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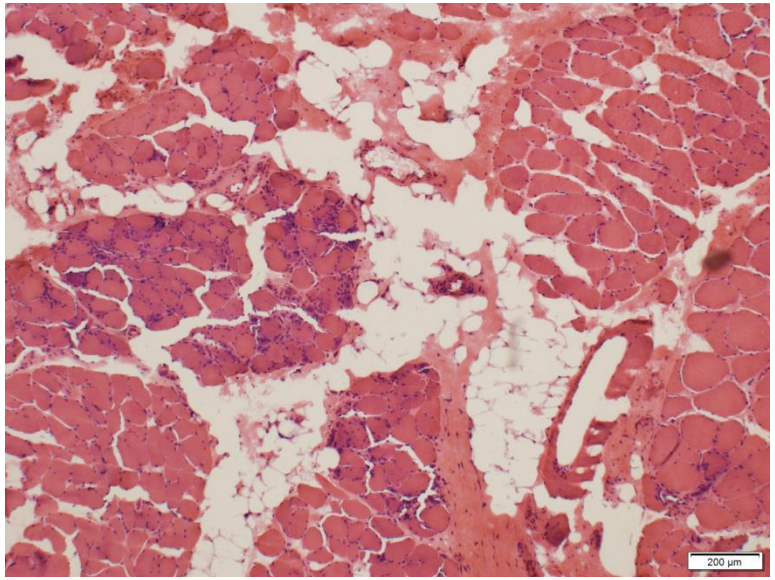
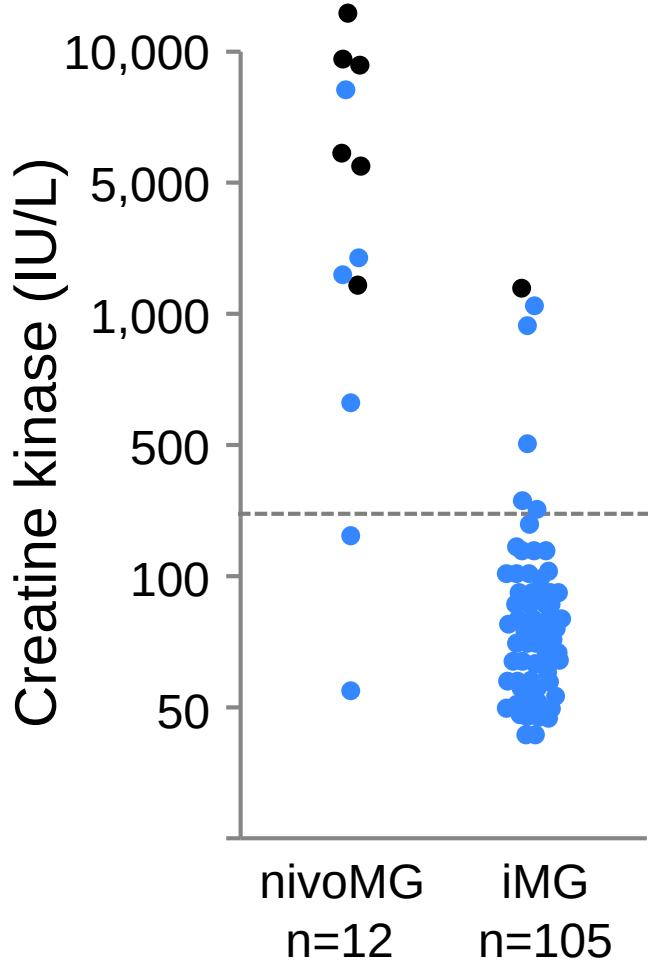
Myasthenia Gravis

Myositis Overlap Syndrome

	nivoMG n=12	iMG n=105	P	Literature
Creatine kinase IU/L	4799 ± 4415	119 ± 193	0.003	↑ 20/23 (87)
Myositis, no. (%)	4 (33)	1 (1)	<0.001	6/20 biopsy proven
Myocarditis, no. (%)	3 (25)	0 (0)	<0.001	
Thymoma, no. (%)	0 (0)	24 (23)	0.1	





Suzuki S et al: Neurology 89:1127, 2017

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Myopathy

	Liewluck et al 2018, PD-1 (n=5)	Touat et al 2018, CTLA-4, PD-1, PD-L1 (n=10)
Frequency, no. (%)	5/654 (0.76)	
Age, median (range)	76 (55-86)	73 (56-87)
Gender (M:F)	5:0	7:3
Days to onset	30 (17-72)	25 (5-87)
Time to max severity (d)	9 (6-30)	1 - >21
Ocular	3	7
Bulbar	3	2
Neck flexor	4	7
Proximal	4	7
Myalgias		8
CK (U/L)	333 (72-7307)	2,668 (1,059-16,620)
RNS	0	0
Myopathic EMG	5/5	9/9
Achr ab +	1	0
Striational ab +	3 range (1:3840-1:61,440)	
Myositis associated ab	1 (PM/Scl)	0

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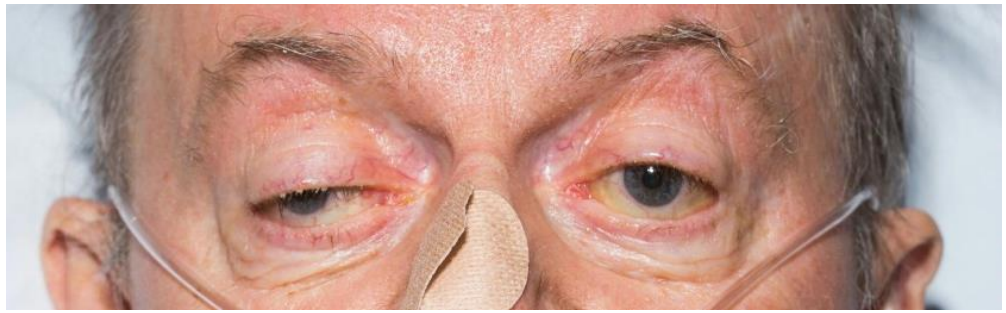

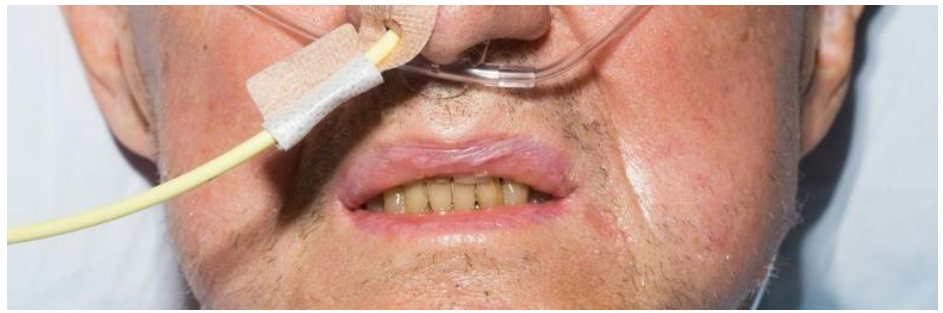

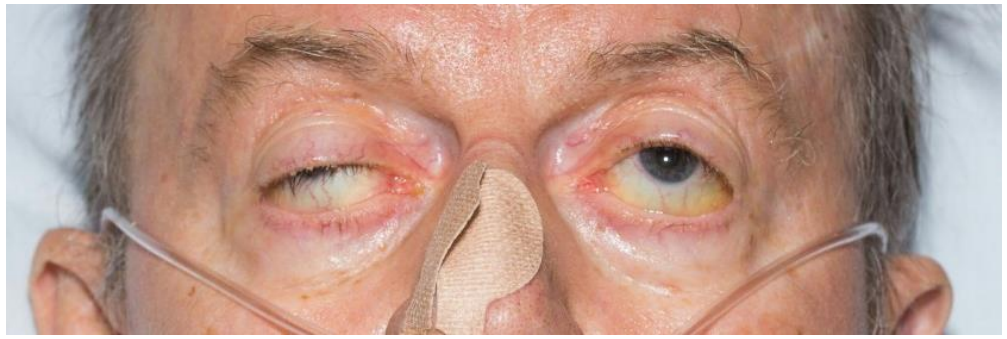

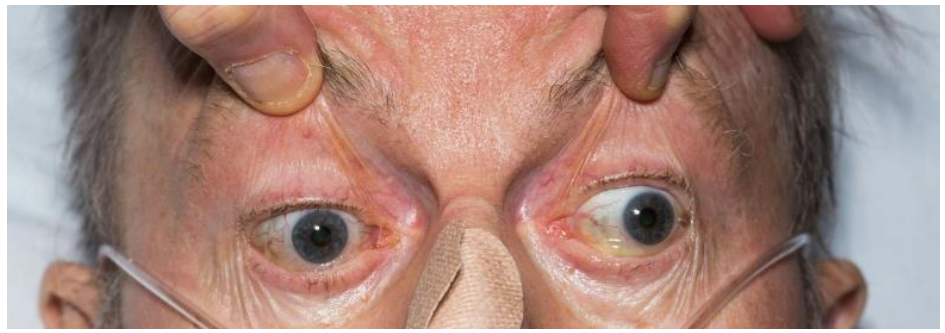

Haddoz et al: Ann Oncol 28:673, 2017

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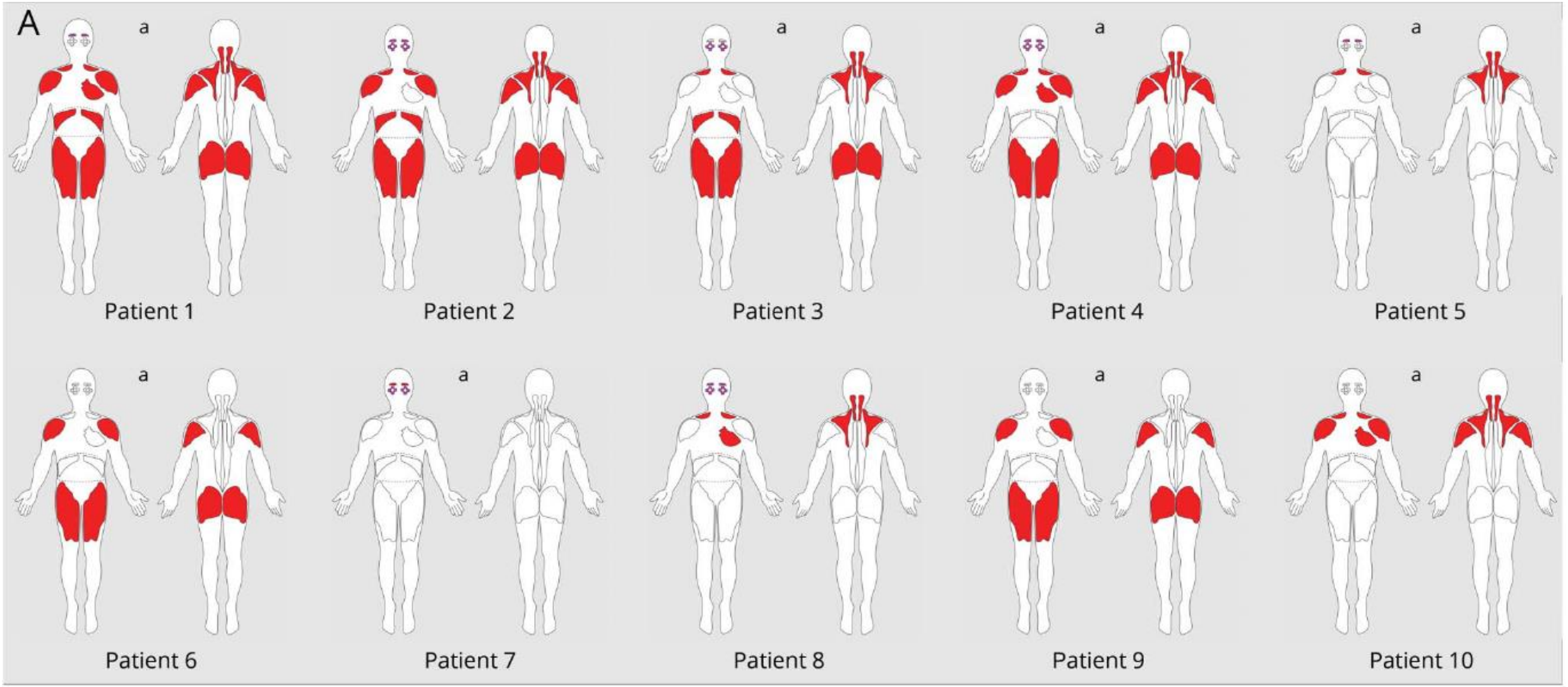

Touat et al: Neurology 2018; epub.

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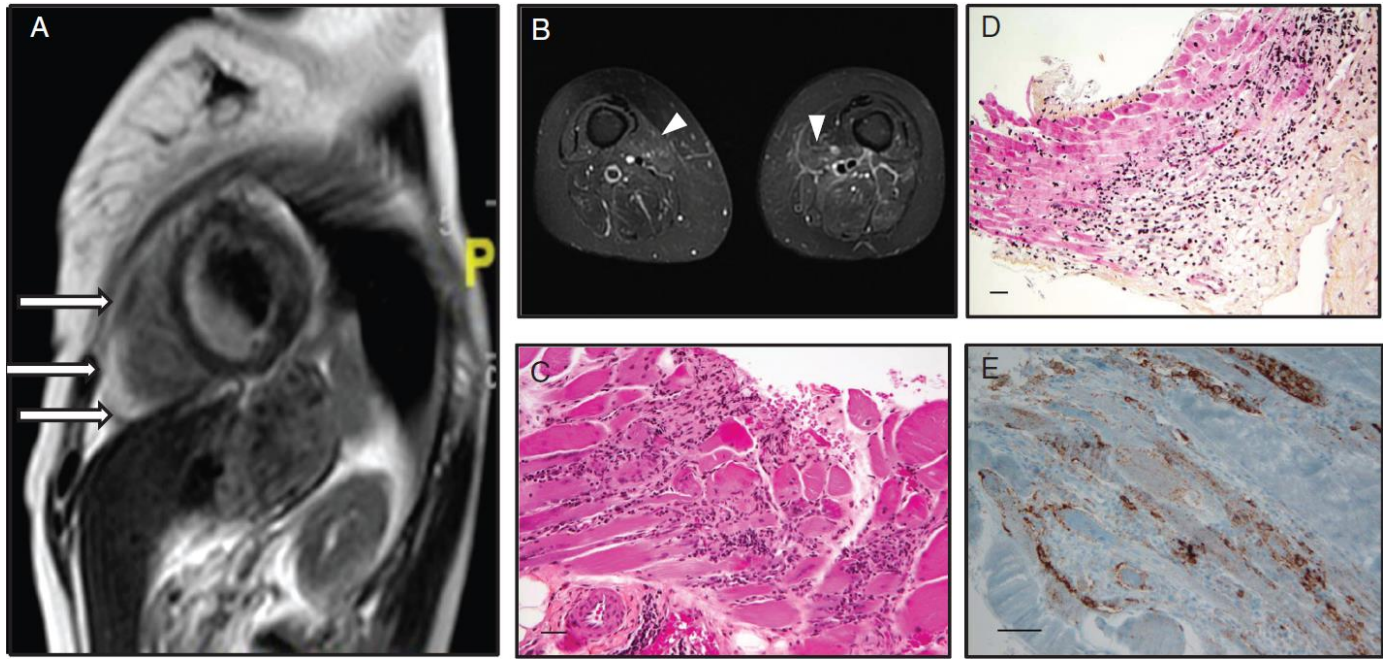
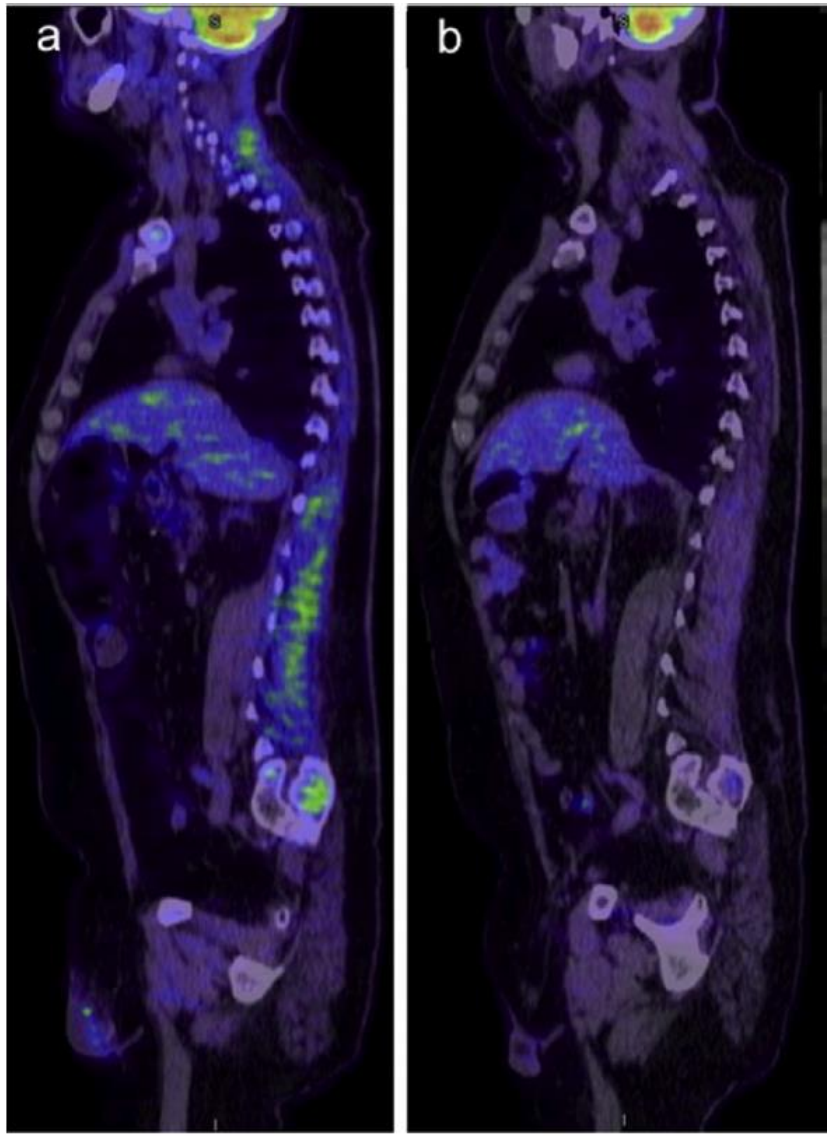
Imaging Findings in Myopathy





Gallay et al: Neuro Oncol 20:861, 2018
Mitchell et al: Eur J of Cancer 105:88, 2018

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WHO Myopathy cohort

	n=180
Median age	71 (29-90)
ICI monotherapy	153 (85%)
Time to onset (days)	26/61 (18-39)
Myocarditis	29 (16.1%)
Myasthenia gravis like sxs	28 (15.6%)
Death	36/170 (21.2%)
Severe complications	49.4%

- Prior to 2016: 0.5 cases/mo
- 2016: 3.6 cases/mo
- 2017: 7.3 cases/mo
- 2018: approx 11cases/mo

Anquetil et al. Circulation 138;743, 2018

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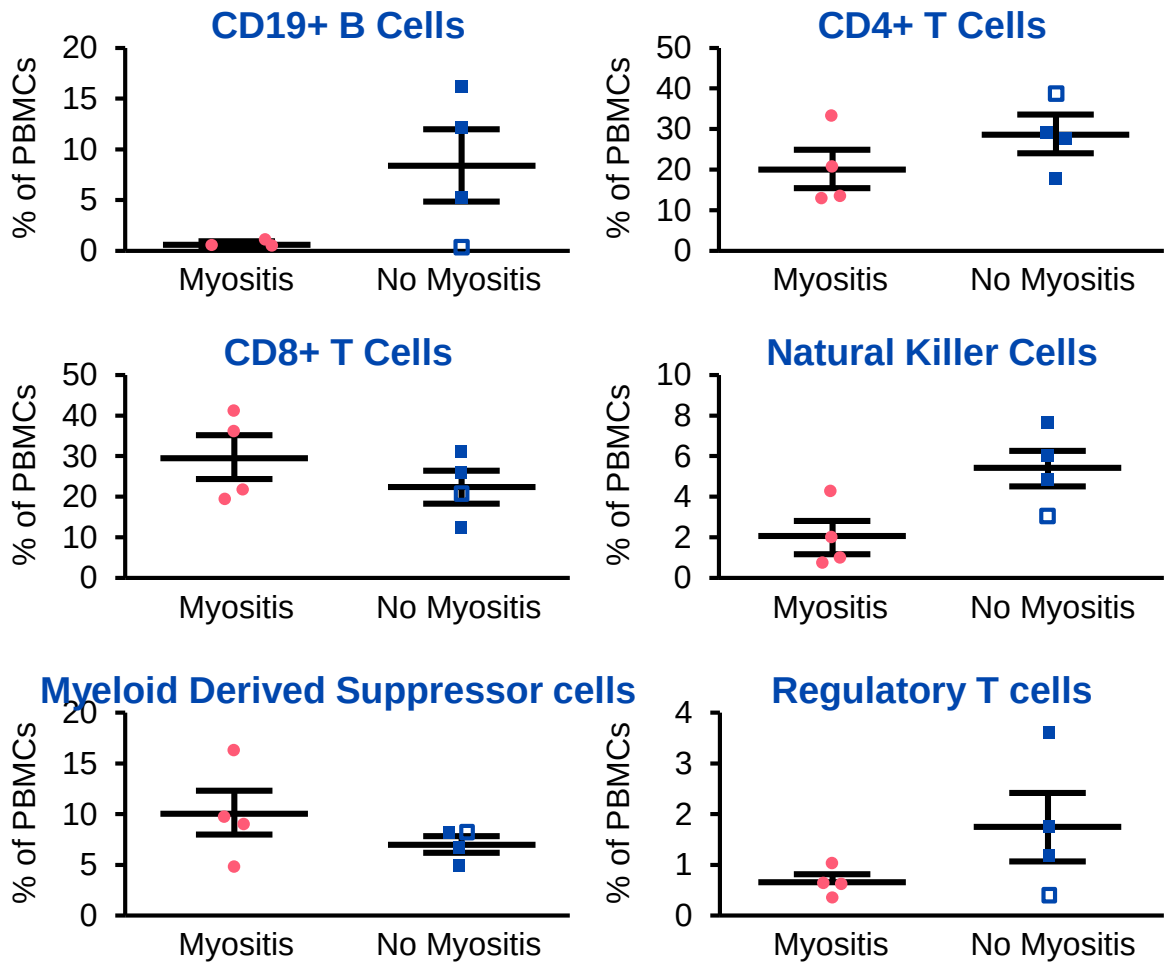
Overlap Syndrome – Role of AchAb and B Cells

Mean pre-treatment CK	128 (45-435)
15-day post-treatment CK	1021 (28-3939)
# of pts with elevated CK	4/8 (762-16037 within 5 wks)
# with weakness	4/8*
# with elevated pre-tx AchR Ab	4/8 (titer: 0.24-2.59)
# with elevated pre-tx striational Ab	3/8 (titer: 3840- 30,720)
# with MSA Ab +	0/8
NMJ defect by NCS	1/4
# with myocarditis	1/4

- Thymoma – MG 30%, Myositis 5%
- Phase I trial of avelumab
  - 7 with recurrent thymoma
  - 1 with recurrent thymic carcinoma



Mamman et al: Ann Rheum Dis 78:150, 2019

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Role of Pre-Existing Autoimmune Disease

- Pre-existing autoimmune disease:
  - Higher incidence of any grade irAE higher 65.9% vs 39.9%
- Inactive and active pre-existing AID, ♀, ECOG performance status <2 → higher incidence of any grade irAEs
- No significant differences were observed regarding grade ¾ irAEs
- Not associated with PFS or OS

Table 3. Immune-related adverse events of any grade and G3/G4 immune-related adverse events by subgroups

Category	Patients with irAEs, n (%)	Flare of AIDS (%)
Overall (751 patients)		
NCI-CTC AE		
Any grade	322 (42.9, 95% CI: 38.3-47.8)	
G3/G4	67 (8.9, 95% CI): 6.9-11.3)	
No pre-existing AIDs (666 patients)		
NCI-CTC AE)		
Any grade	266 (39.9, 95% CI: 35.2-45.0)	
G3/G4	59 (8.8, 95% CI): 6.7-11.4)	
Pre-existing AIDs (85 patients)		
NCI-CTC AE		
Any grade	56 (65.9, 95% CI: 49.7-85.5)	
G3/G4	8 (9.4, 95% CI: 4.1-18.5)	
Inactive AIDs (70 patients)		
NCI-CTC AE		
Any grade	45 (64.3, 95% CI: 46.8-86.0)	33 (47.1, 95% CI: 32.4-66.2)
G3/G4	6 (8.6, 95% CI: 3.1-18.6)	6 (8.6, 95% CI: 3.1-18.6)
Active AIDs (15 patients)		
NCI-CTC AE		
Any grade	11 (73.3, 95% CI: 44.9-92.2)[a]	7 (46.7, 95% CI: 18.7-96.1)
G3/G4	2 (13.3, 95% CI: 1.6-48.1)	2 (13.3, 95% CI: 1.6-48.1)

Cortellini et al: The Oncologist 24:1, 2019

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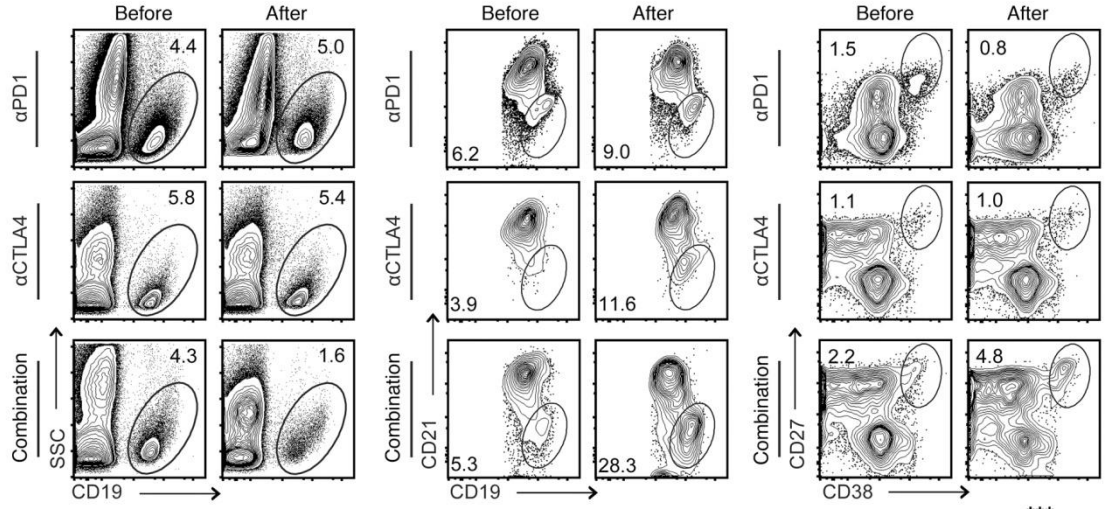
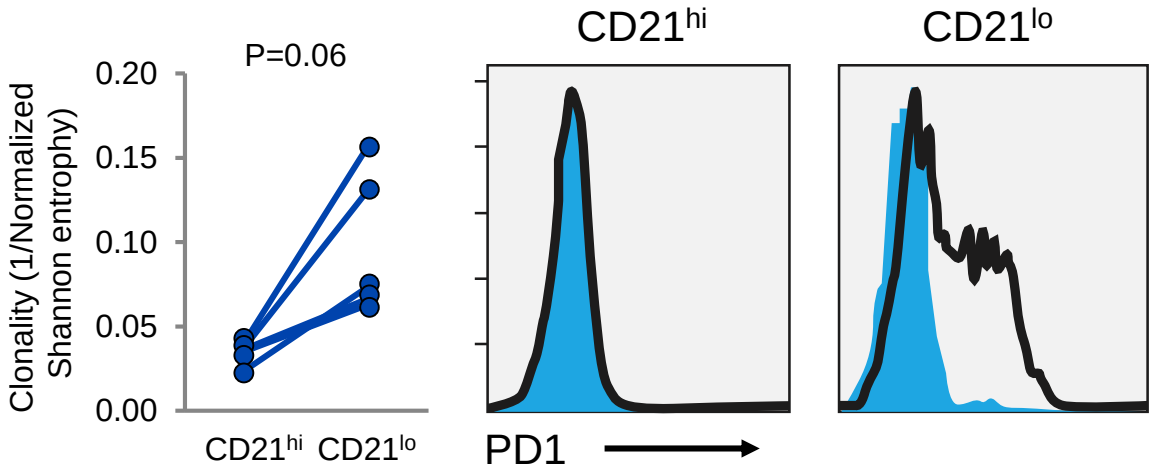
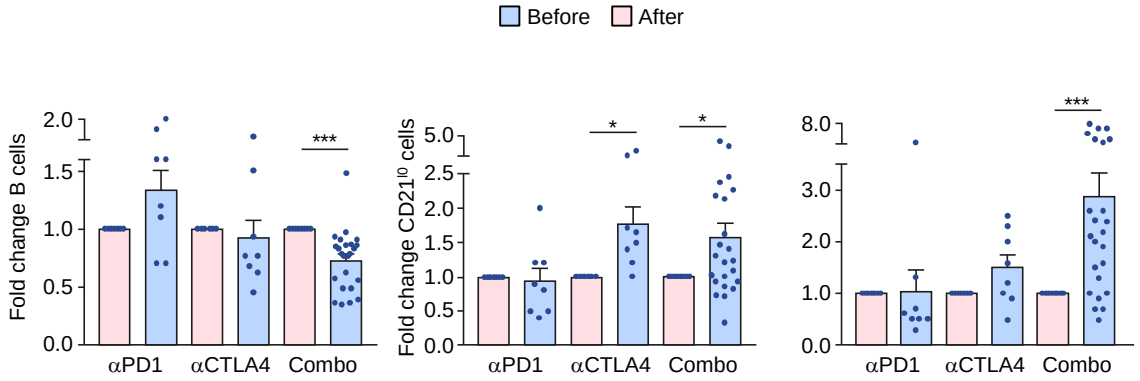
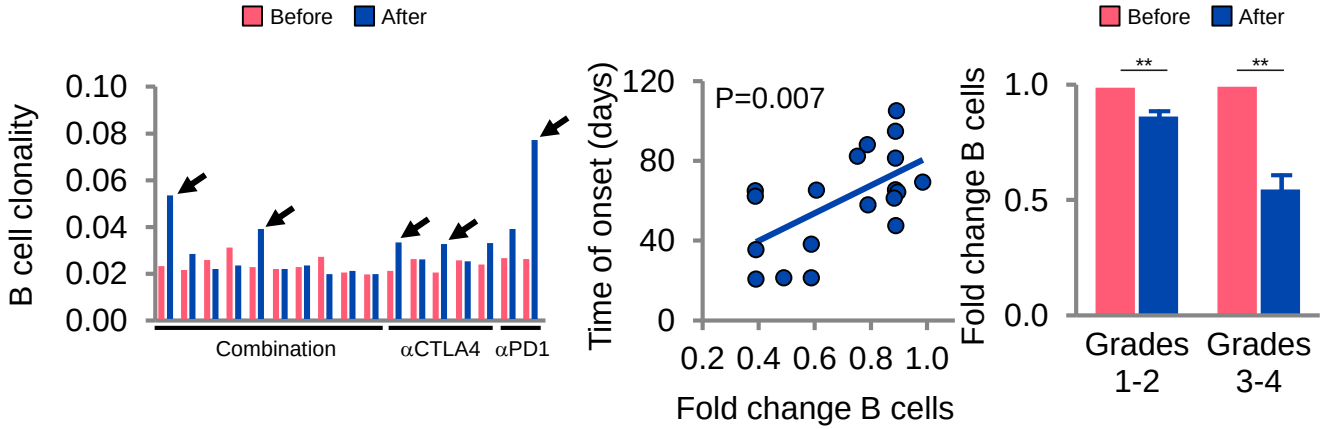
Changes in Circulating B Cells Prior to irAEs









Das et al: JCI 128:715, 2018

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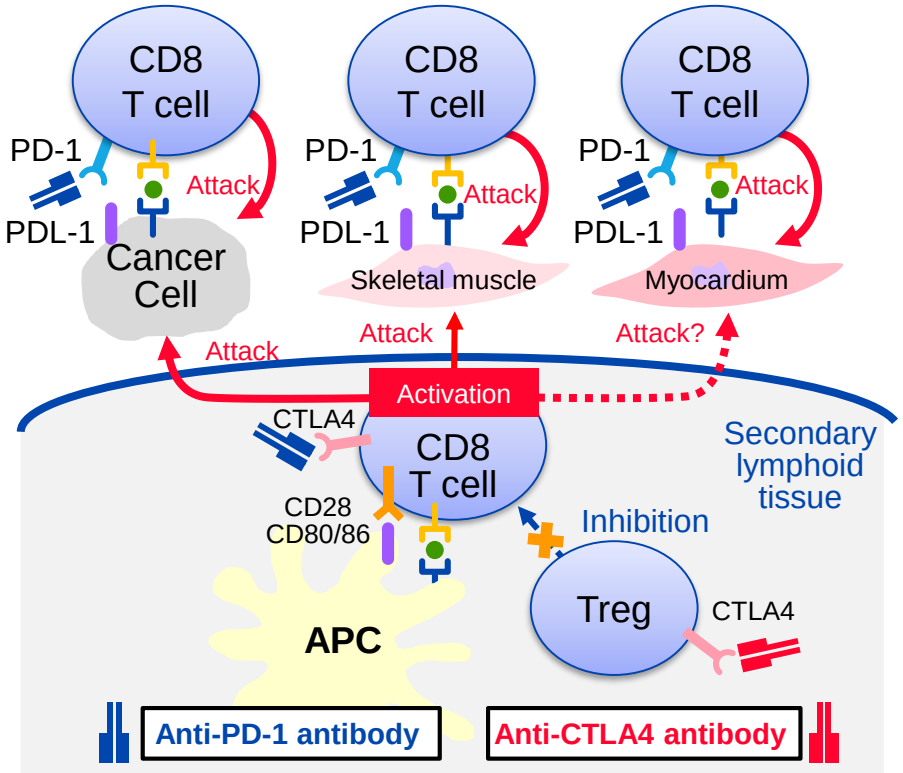
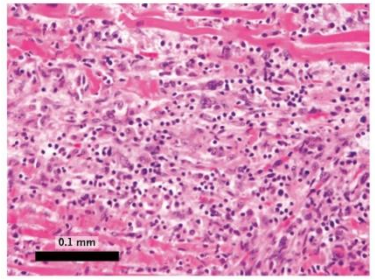
Skeletal Muscle Disorders With or Without Myocarditis as irAEs or ICIs

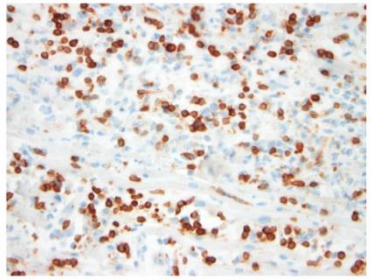


According to Bristol Myers Squibb corporate safety databases until Apr 2016

- 15/20,594 (0.09%) with myocarditis after PD-1, CTLA-4 or both
- Combo – more frequent and severe compared to Pd-1 0.27% vs 0.06%
- Median 17 days after first treatment

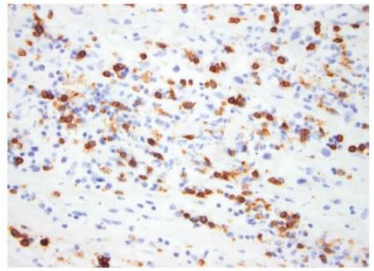
Lymphocytic Infiltration of the Myocardium

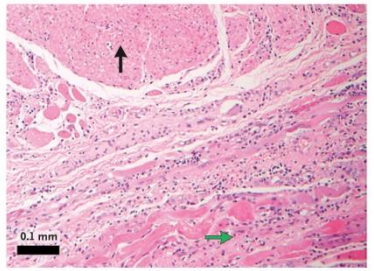




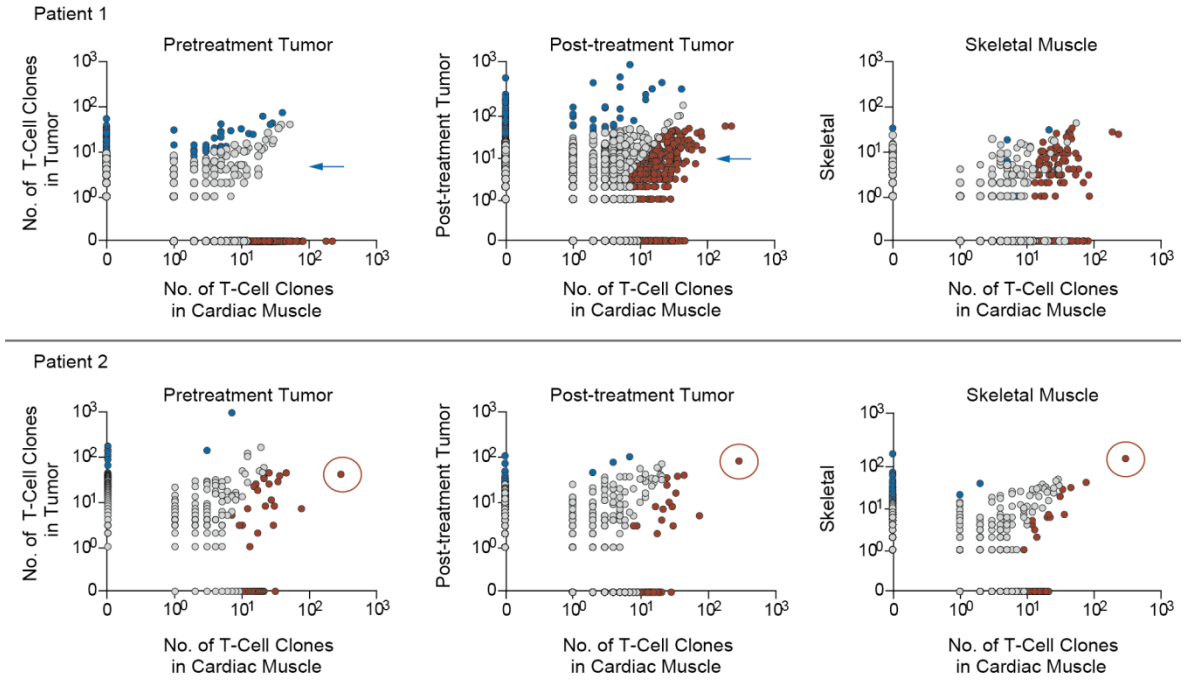
Infiltrate with CD3+ T cells

Infiltrate with CD8+ T Cells





Skeletal and Smooth Muscle



Kadota et al. Curr Rheum Reports 21;1, 2019
Johnson et al: NEJM 375:1749, 2016

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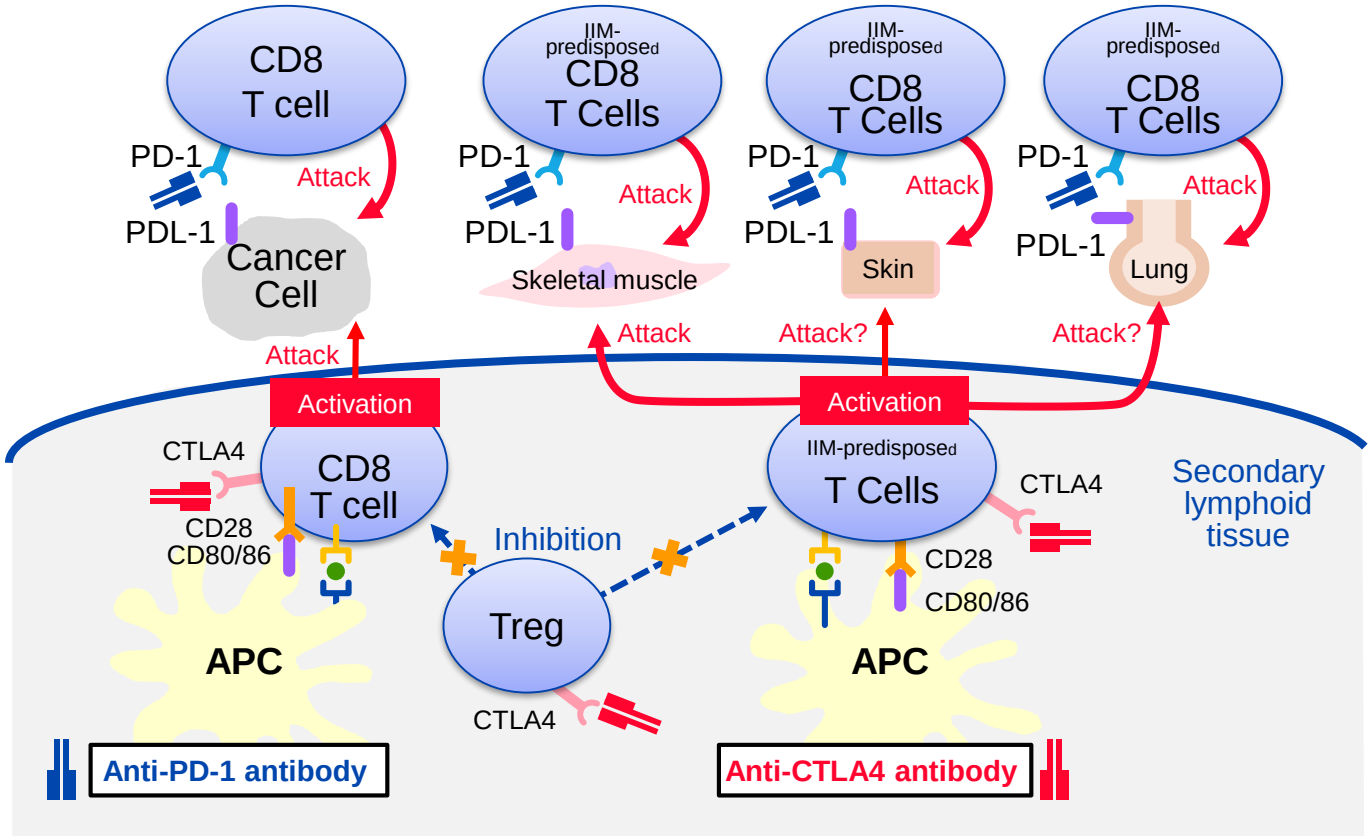
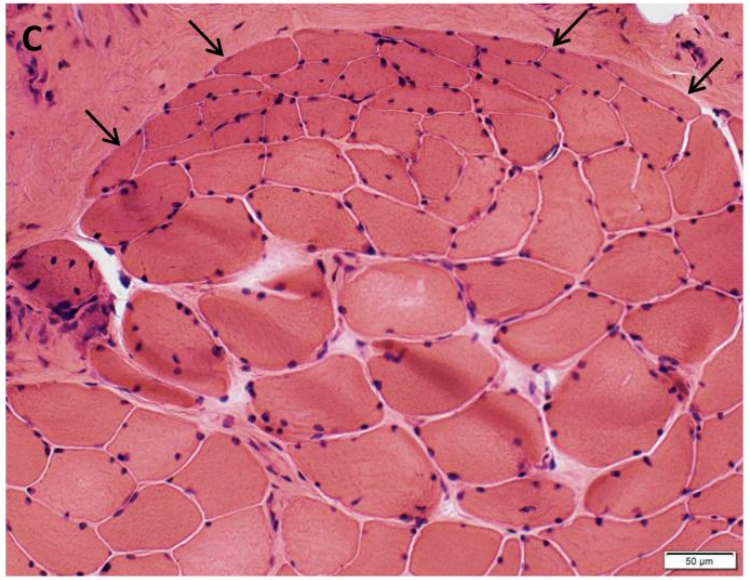
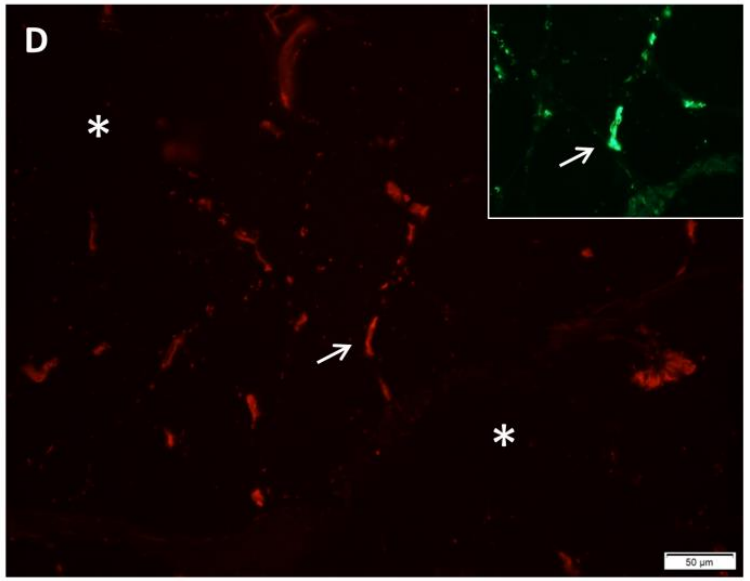
Full-Brown IIMs Progressed from the Prodromal Phase IIMs







Kadota et al. Curr Rheum Reports 21;1, 2019
Liewluck et al. J Immunother 41;208, 2018

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Peripheral Nerve

Guillain Barré Syndrome

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Axonal polyradiculopathy

Brachial plexopathy

Mononeuropathy

Peripheral Neuropathy

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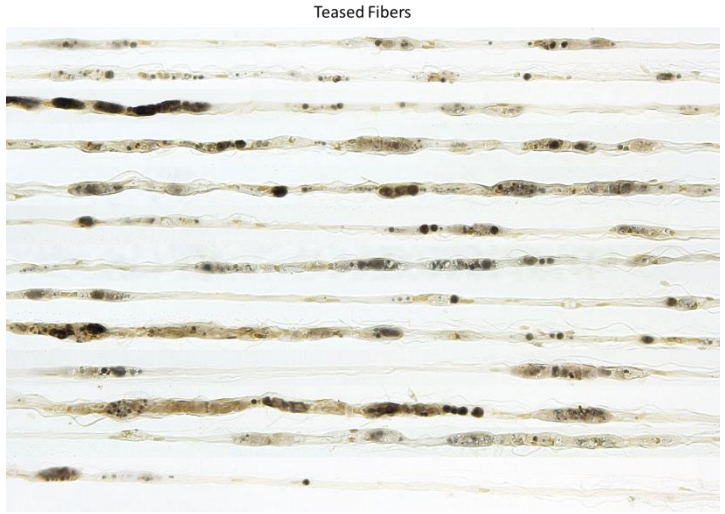
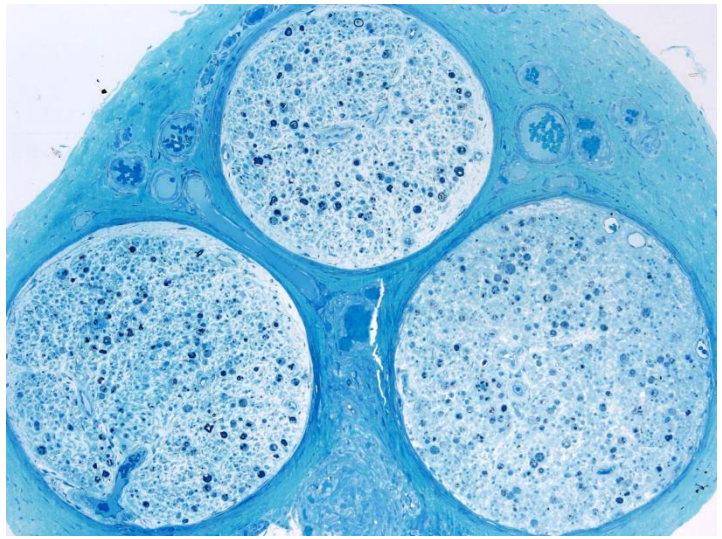
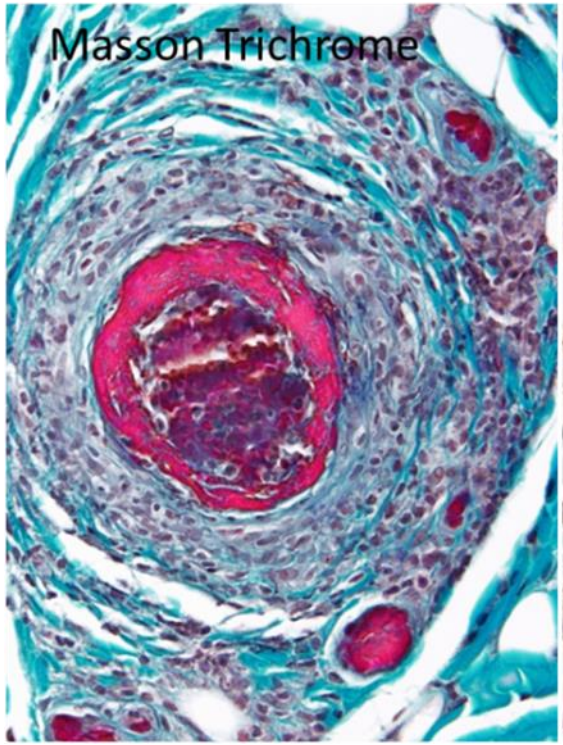
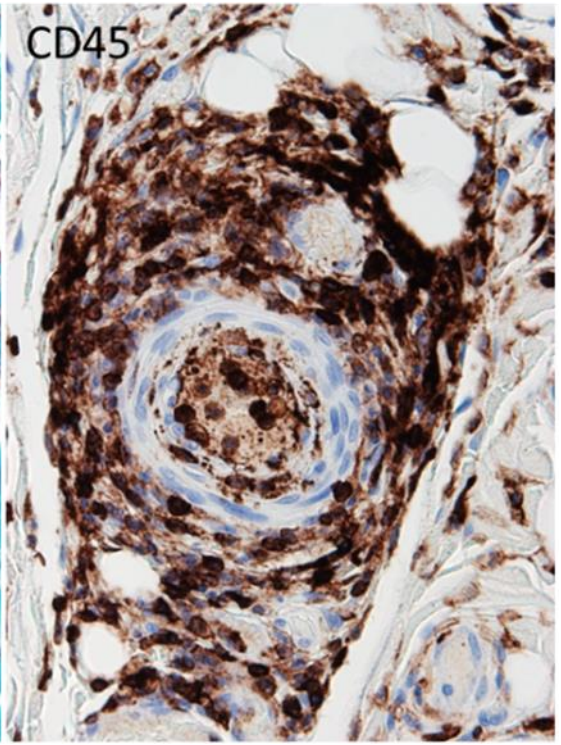
Vasculitic Neuropathy









Kao JC et al: JAMA Neurol 2017

Treatment Recommendations for Neurological irAE

Grade CTCAE	Recommendation
1	Continue ICPi therapy with close monitoring
≥2	Hold ICPi until determine nature and progression of the irAE and initiate corticosteroids equivalent of methylprednisolone 1-4 mg/kg
3 or 4	Discontinue ICPi and may need to escalate to pulse dose methylprednisolone 1 gm daily for 5 days with taper over 4-6 weeks, may need IVIG/PLEX

Brahmer et al: J of Clin Oncol 36(17), 2018

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Special Considerations

Neurologic irAE	Special Considerations
Myositis/Myopathy	Consider addition of IVIG/PLEX at Grade 2
Myasthenia Gravis	Pyridostigmine PLEX for crisis
Guillain Barré Syndrome	IVIG or PLEX (consider corticosteroids)
Peripheral Neuropathy	Grade 3-4 any weakness or gait instability
Aseptic Meningitis/Encephalitis	Tx with acyclovir (+/- bacterial) Add IVIG to severe or progressing encephalitis or positive OC bands

Brahmer et al: J of Clin Oncol 36(17), 2018

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Final Thoughts

- Can you rechallenge?
  - Guidelines currently do not suggest rechallenging with Grade 3-4 toxicities (most of NirAE's)
    - Ocular myasthenia gravis, meningoencephalitis
    - 2 cases of myositis rechallenged successfully (PD-L1, CTLA-4/PD-1; 1 with prednisone 20 mg/d)
- Increasing frequency of NirAE's
  - Will be seen with expanding use as 1st line therapy
    - Will not have had other therapies suppressing immune system prior to treatment

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Brahmer et al: J of Clin Oncol 36(17), 2018
Deylon J et al: Ann Rheum Dis . Epub Sept 2018

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Questions & Discussion

Peripheral Nerve

Guillain Barré Syndrome

3rd most common NirAE
Variable onset
Similar to GBS (CSF, EMG, MRI)
IVIG/PLEX, ? steroid

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Peripheral Nerve

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Rare NirAE

Similar to CIDP (CSF, EMG, MRI)

IVIG/PLEX/steroids

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Peripheral Nerve

Axonal polyradiculopathy

Motor predominant
Asymmetric over weeks to months
Elev CSF protein, MRI enhancing roots

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Peripheral Nerve

Brachial plexopathy

Rare NirAE
PD-1
Lower trunk plexopathies
Acute onset
Improvement with treatment

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Peripheral Nerve

Mononeuropathy

Cranial nerve – VI, VII
Enteric
Phrenic

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Peripheral Nerve

Peripheral Neuropathy

Variable types

- Sensory
- Sensorimotor
- Mononeuritis multiplex

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