IMMUNE-RELATED ADVERSE EVENTS

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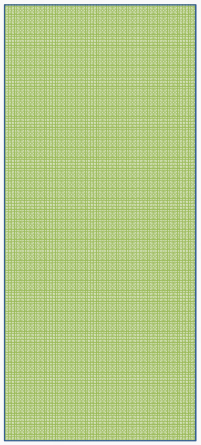
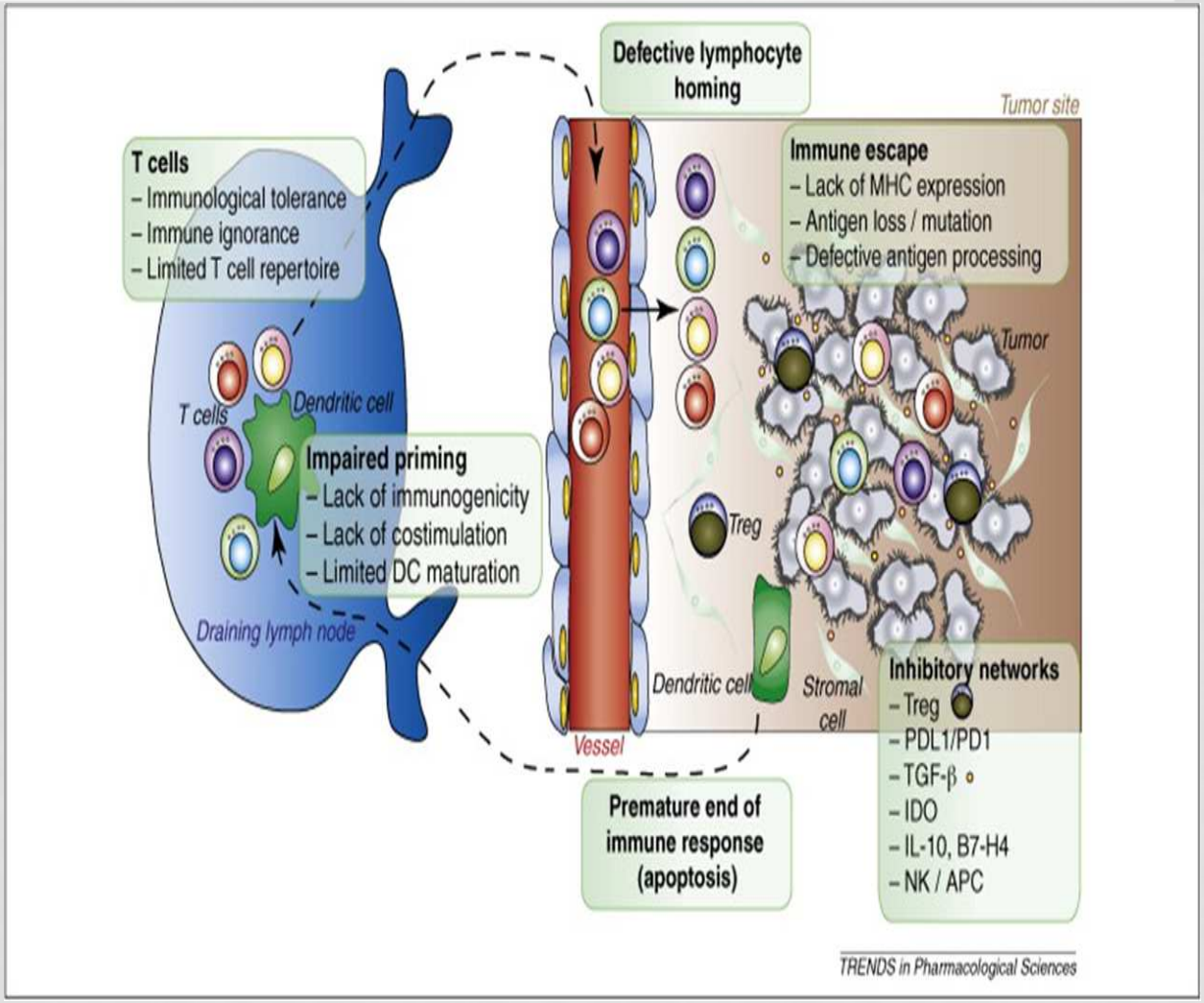


DISCLOSURE

- No relevant financial relationships to disclose

OBJECTIVES

- Interferon
- IL-2
- Anti-CTLA-4
- Anti-PD-1
- Anti-PDL-1



TOXICITY SCALE

Grade	
I	mild
2	moderate
3	severe
4	Life threatening
5	death

INTERFERON

INTERFERON

- IFN alpha is a Type I interferon, binding to it's receptor activates numerous signaling pathways:
  - JAK-STAT
  - Crk
  - Insulin Receptor substrate (IRS)
  - MAPK
  - Increases MHC class I Ag expression which is associated with activation of cytotoxic T-cells

INDICATIONS

- AIDS-related Kaposi sarcoma
- Chronic hepatitis B
- Chronic hepatitis C
- Follicular lymphoma
- Hairy cell leukemia
- Malignant melanoma

INTERFERON

- **CONTRAINDICATIONS**
  - Hypersensitivity to interferon alpha or any component of the product
  - Autoimmune hepatitis
  - Decompensated liver disease

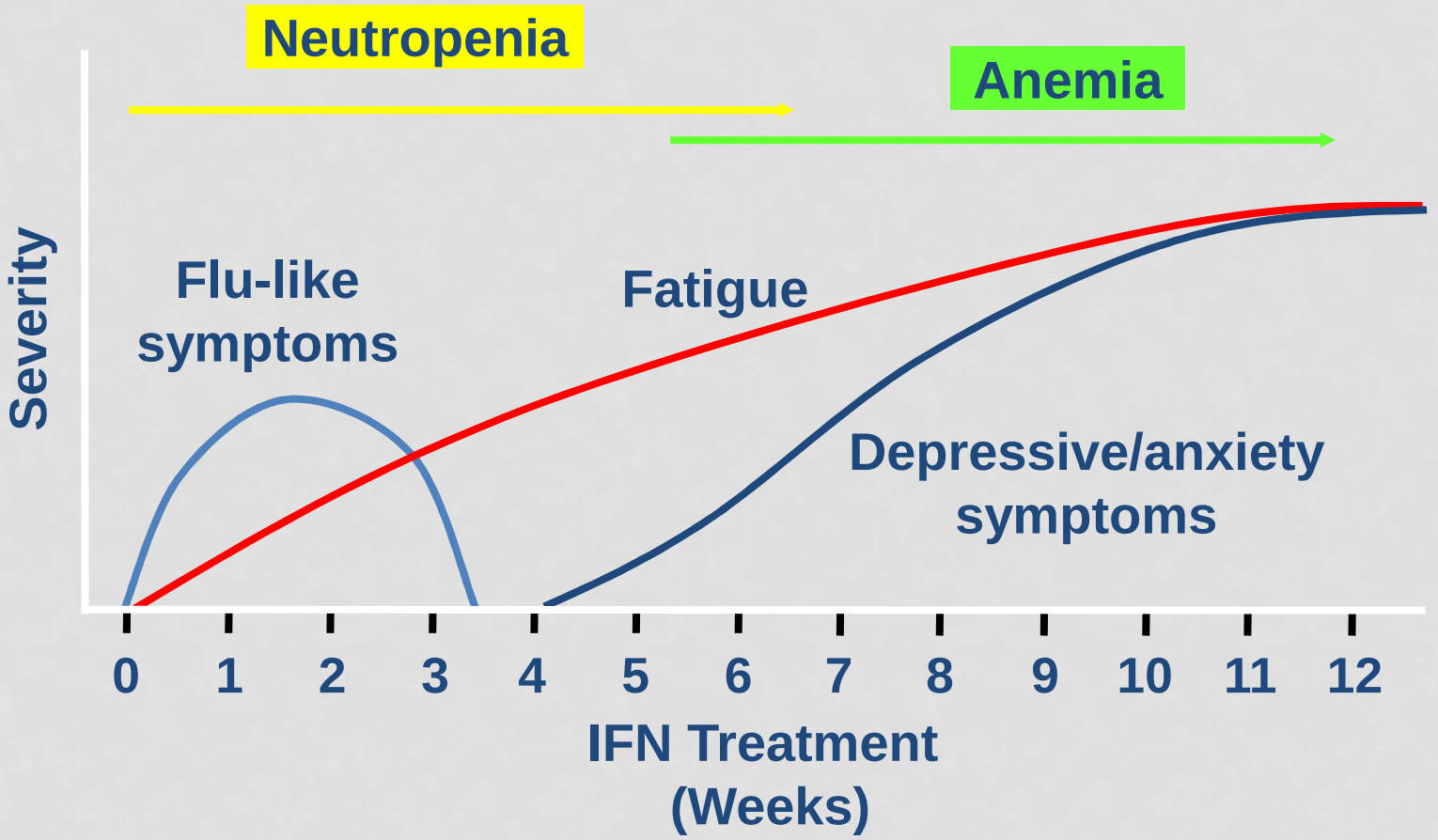
IFN TOXICITY

- **Cardiovascular**: Chest pain
- **Central nervous system**: **Fatigue**, headache, **chills, rigors**, **depression** (3% to 40%; grades 3/4: 2%), drowsiness, dizziness, irritability, paresthesia, pain, amnesia, lack of concentration, malaise, confusion, insomnia
- **Dermatologic**: Alopecia, **skin rash**, diaphoresis, **pruritus**
- **Endocrine & metabolic**: Weight loss ,amenorrhea, thyroid
- **Gastrointestinal**: **Anorexia**, **nausea**, **diarrhea, vomiting,** xerostomia ,dysgeusia ,abdominal pain ,constipation ,gingivitis

IFN TOXICITY

- **Hematologic**: **Neutropenia** (≤92%; grade 4: 1% to 4%), leukopenia, anemia, thrombocytopenia
- **Hepatic: Increased serum AST (≤63%; grades 3/4: 14%),** increased serum ALT, increased serum alkaline phosphatase
- **Infection:** Candidiasis
- **Local:** Injection site reaction
- **Neuromuscular & skeletal: Myalgia**, weakness, **arthralgia**
- **Renal:** Increased blood urea nitrogen (≤12%)
- **Respiratory:** Flu-like symptoms, **dyspnea**, cough, pharyngitis, sinusitis
- Miscellaneous: **Fever**

TIME COURSE OF IFN SIDE EFFECTS



IFN TOXICITY

- Autoimmune disease: **[US Boxed Warning]: May cause or aggravate fatal or life-threatening autoimmune disorders; monitor closely with clinical and laboratory evaluations (periodic); discontinue treatment for severe persistent or worsening symptoms; some cases may resolve with discontinuation.** Autoimmune disorders (thrombocytopenia, vasculitis, Raynaud disease, rheumatoid arthritis, lupus erythematosus and rhabdomyolysis) have been associated with alfa interferons. Worsening of psoriasis and sarcoidosis (and the development of new sarcoidosis) have been reported; use caution in patients with these conditions.

AUTOIMMUNITY AND PROGNOSIS

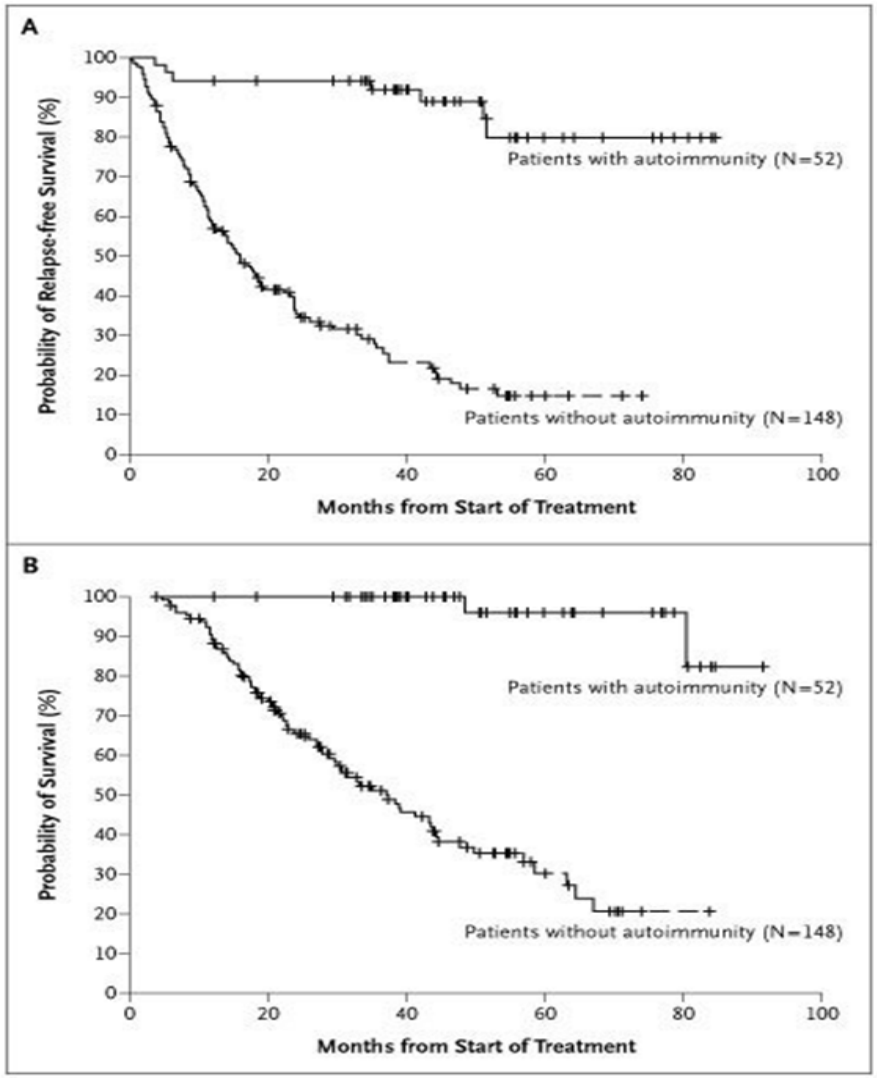
Table 2. Autoantibodies or Manifestations of Autoimmunity in Patients Treated with Interferon Alfa-2b.*

Autoantibodies or Manifestations of Autoimmunity	All Patients (N=200)	Induction-Therapy Group (N=96)	Extended-Therapy Group (N=104)
		no. of patients (%)	
Autoantibodies or autoimmune disorders	52 (26)	23 (24)	29 (28)
Antithyroid antibodies	43 (22)	16 (17)	27 (26)
Antinuclear antibodies	12 (6)	2 (2)	10 (10)
Anticardiolipin antibodies	10 (5)	2 (2)	8 (8)
Vitiligo	11 (6)	5 (5)	6 (6)
Clinical manifestations	19 (10)	2 (2)	17 (16)
With autoantibodies	16 (8)	2 (2)	14 (13)
Without autoantibodies (vitiligo)	3 (2)	1 (1)	2 (2)
Multiple manifestations of autoimmunity	16 (8)	1 (1)	15 (14)

* Patients in the induction-therapy group received interferon alfa-2b (15 million IU per square meter of body-surface area per day, intravenously, five days per week for four weeks) followed by observation. Patients in the extended-therapy group received the same induction dose for 4 weeks, followed by subcutaneous therapy (10 million IU per day thrice weekly) for an additional 48 weeks.

Gogas et al, N Engl J Med 2006;354:709-18

AUTOIMMUNITY AND PROGNOSIS



Gogas et al, N Engl J Med 2006;354:709-18

AUTOIMMUNITY AND PROGNOSIS

Table 4. Landmark Analyses of Relapse-free and Overall Survival According to Autoimmunity Status.*

Time Point and Autoimmunity Status	Relapse-free Survival				Overall Survival			
	Rate	Median Duration (95% CI)	Hazard Ratio (95% CI)	P Value†	Rate	Median Duration (95% CI)	Hazard Ratio (95% CI)	P Value†
	no. of events/ no. of patients	*mo*			*no. of events/ no. of patients*	*mo*		
At 3 mo				<0.001				<0.001
No autoimmunity	96/152	20.8 (13.5–28.1)	0.15 (0.06–0.37)		80/166	40.8 (32.5–49.1)	0.07 (0.02–0.28)	
Autoimmunity	5/34	NR (NE)			2/34	NR (NE)		
At 12 mo				<0.001				<0.001
No autoimmunity	46/83	21.6 (14.4–28.8)	0.08 (0.03–0.22)		64/127	29.4 (23.1–35.7)	0.02 (<0.01–0.15)	
Autoimmunity	4/48	NR (NE)			2/52	NR (NE)		

* CI denotes confidence interval, NR not reached, and NE not evaluable.
† P values were calculated with the use of the Wald test.

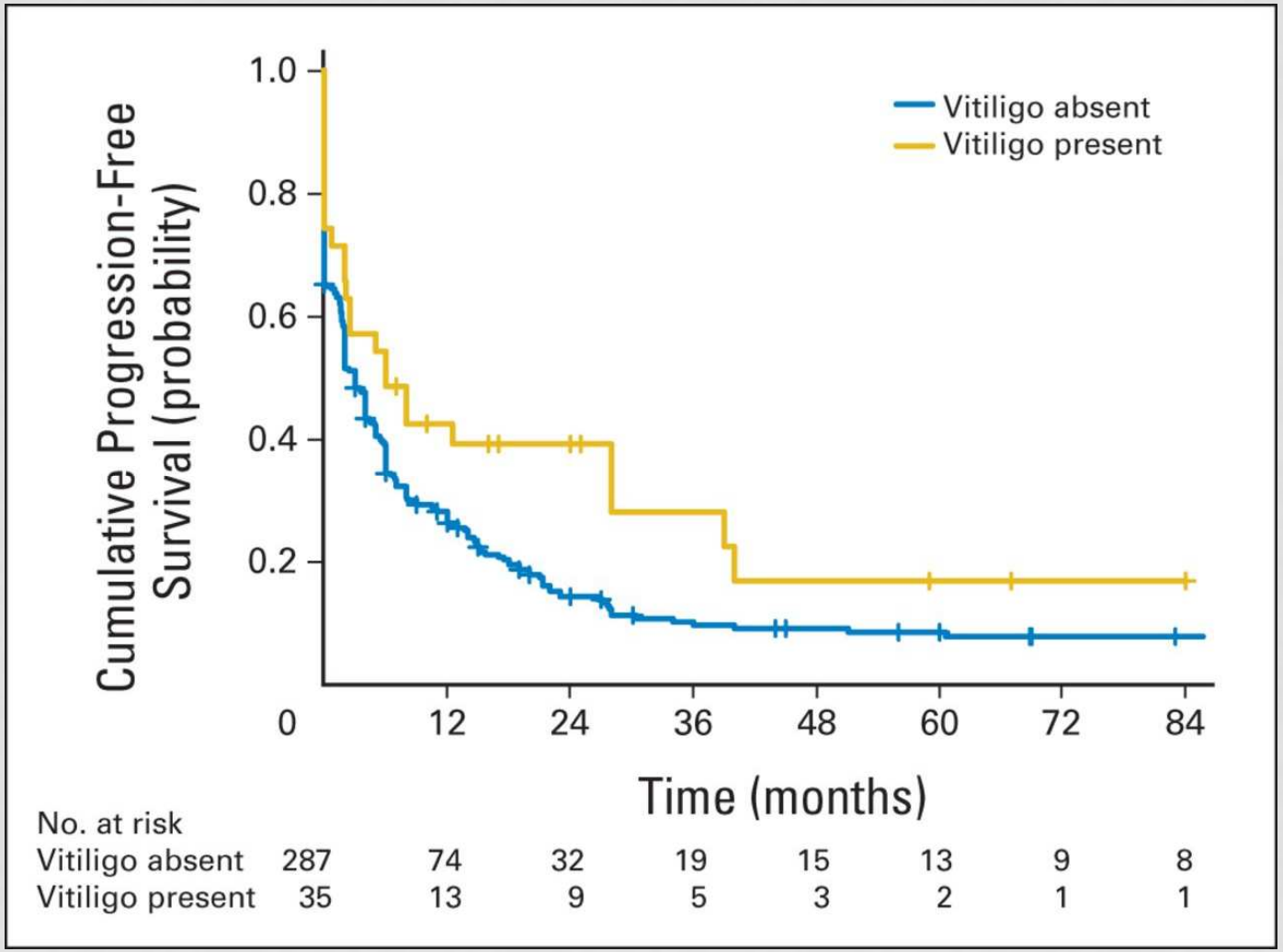
Gogas et al, N Engl J Med 2006;354:709-18

AUTOIMMUNITY AND PROGNOSIS

- 137 trials identified (N=5,737)
  - 11 general immune stimulation
  - 84 vaccine
  - 28 antibody-based
  - 16 adoptive transfer
- In 27 studies reporting individual patient data, vitiligo development was significantly associated with both PFS and OS

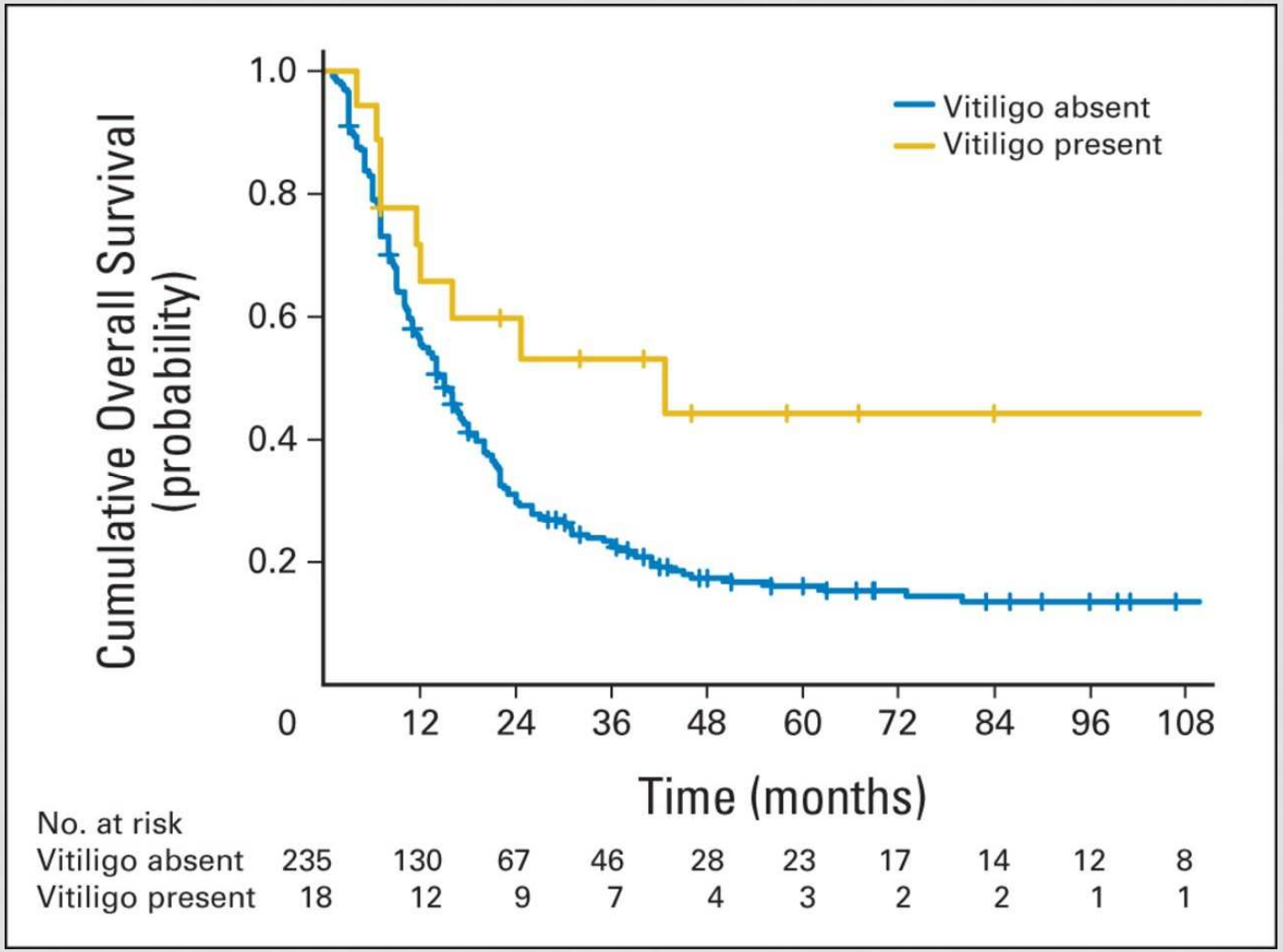
Hansje-Eva Teulings et al. JCO 2015;33:773-781

Progression-free survival in 322 patients receiving immunotherapy from 22 studies.



Hansje-Eva Teulings et al. JCO 2015;33:773-781

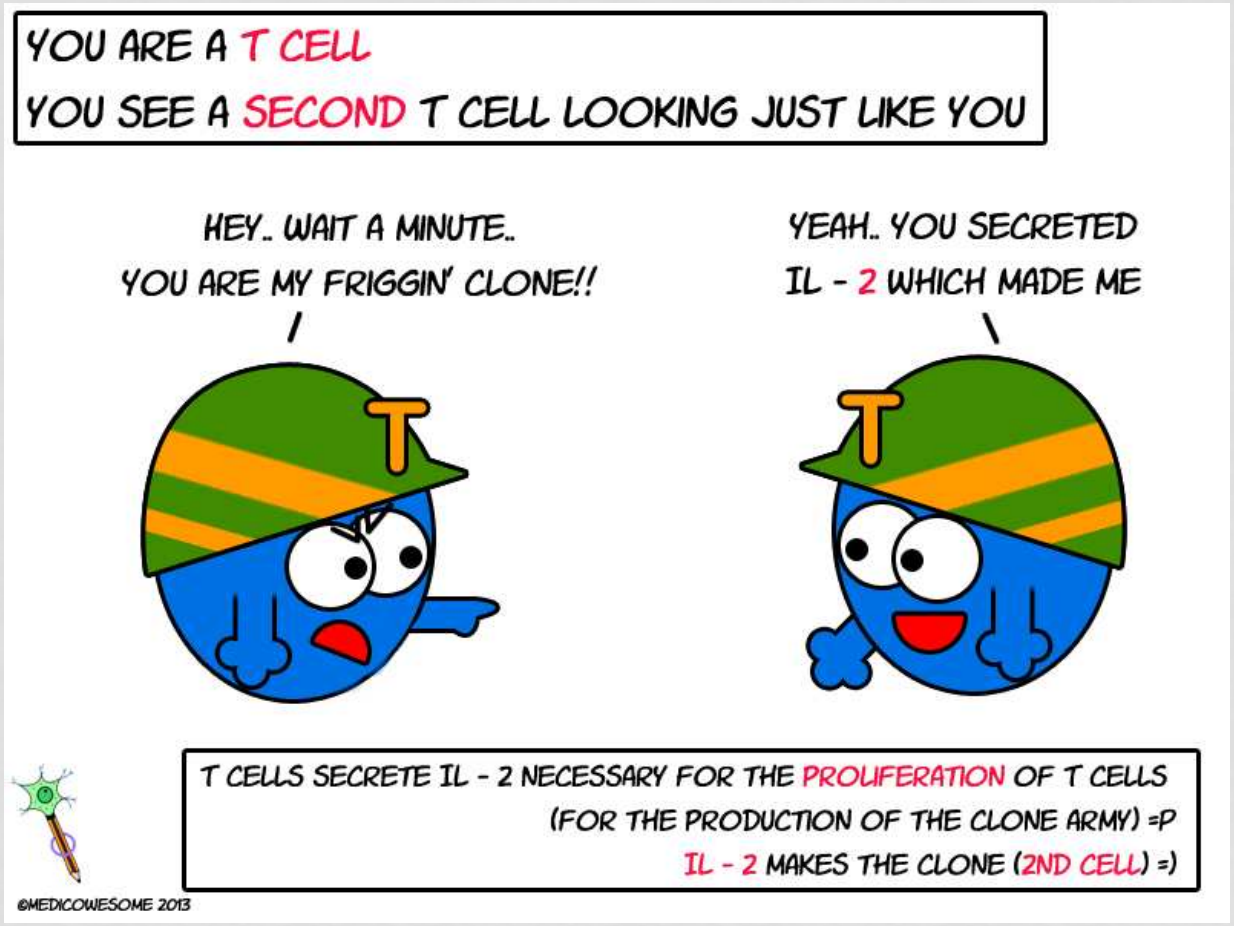
Overall survival in 253 patients receiving immunotherapy from 15 studies.



Hansje-Eva Teulings et al. JCO 2015;33:773-781

IL-2

INTERLEUKIN 2



IL-2 TOXICITY

- **ALERT: US Boxed Warning** Cardiopulmonary disease: Restrict therapy with aldesleukin to patients with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing. Use extreme caution in patients with a normal thallium stress test and a normal pulmonary function test who have a history of cardiac or pulmonary disease.
- **Experienced physician**: Administer aldesleukin in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.

IL-2 TOXICITY

- **CNS toxicity**: Withhold administration in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.
- **Capillary leak syndrome**: administration has been associated with capillary leak syndrome (CLS) which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.
- **Infections**: treatment is associated with impaired neutrophil function and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of therapy. Patients with indwelling central lines are particularly at risk for infection with gram-positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections.

IL-2 TOXICITY

- **Cardiovascular**: Hypotension (71%; grade 4: 3%), peripheral edema, tachycardia , vasodilation, supraventricular tachycardia
- **Central nervous system**: Chills , confusion, fever, malaise, somnolence, anxiety, pain, dizziness
- **Dermatologic**: Rash, pruritus, exfoliative dermatitis
- **Endocrine & metabolic**: Acidosis, hypomagnesemia , hypocalcemia
- **Gastrointestinal**: Diarrhea, vomiting, nausea, stomatitis, anorexia, weight gain, abdominal pain

IL-2 TOXICITY

- **Hematologic**: Thrombocytopenia (37%; grade 4: 1%), anemia (29%), leukopenia (16%)
- **Hepatic**: Hyperbilirubinemia (40%; grade 4: 2%), AST increased (23%; grade 4: 1%)
- **Neuromuscular & skeletal**: Weakness
- **Renal**: Oliguria , creatinine increased
- **Respiratory**: Dyspnea, pulmonary congestion, rales, and rhonchi, cough, acute respiratory distress syndrome, infiltrates and pulmonary changes
- **Miscellaneous**: Antibody formation, infection

IL-2 TOXICITY MANAGEMENT

- Holding doses
- IVF
- Demerol
- Dopamine
- Cipro
- Supportive measures

- Transient

ANTI-CTLA-4

IPILIMUMAB TOXICITY

Table 1
Safety Profile of Ipilimumab Across Phase II Trials in Melanoma

irAEs	Study 008		Study 022						Study 007	
	10 mg/kg		0.3 mg/kg		3 mg/kg		10 mg/kg		10 mg/kg + Placebo	
	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
Skin %	49	3	13	0	45	1	47	4	68	0
GI %	31	8	17	0	32	3	39	16	46	23
Hepatitis %	9	8	0	0	0	0	3	3	9	7
Hypo-physitis %	6	1	0	0	6	3	4	1	5	5

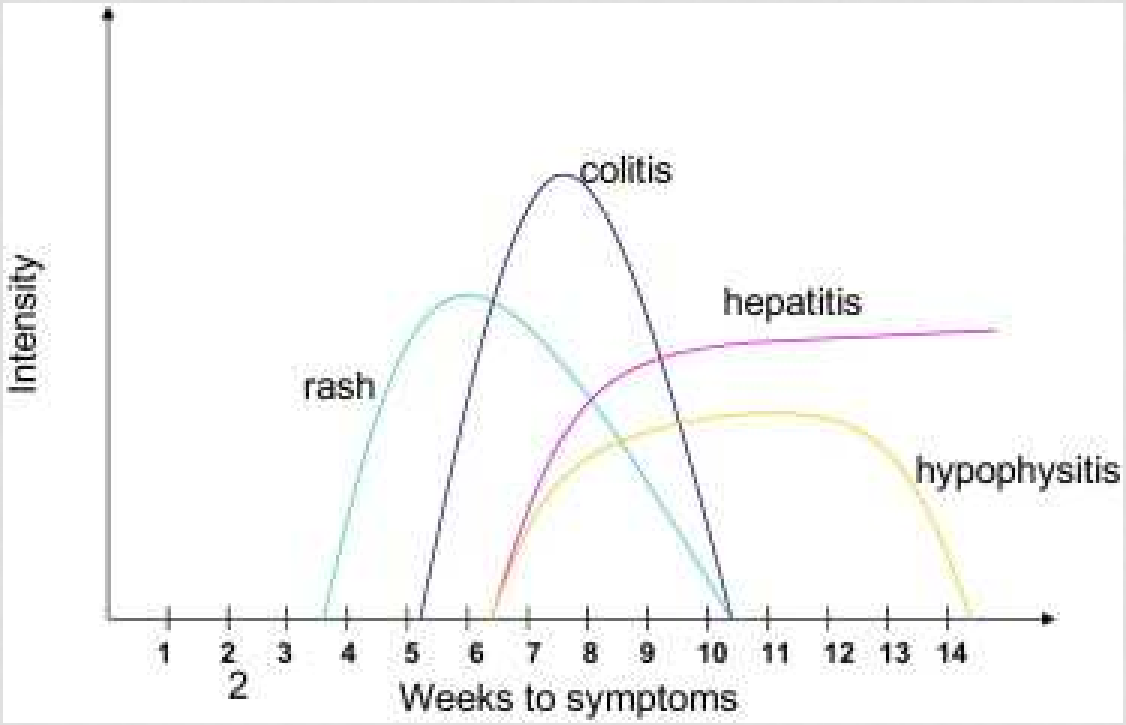
Table 2

Adverse Reactions to Ipilimumab

Gastrointestinal	Colitis with diarrhea/bleeding/bowel perforation Autoimmune hepatitis: elevated liver enzymes to fatal liver failure Autoimmune pancreatitis Inflammatory enteric neuropathy with severe constipation [52]
Endocrine	Hypophysitis with panhypopitutarism Adrenalitis with hypoadrenalism (elevated ACTH) Thyroiditis/hypothyroidism (elevated TSH)
Dermatological	Pruritus Rash Vitiligo
Hematological	Neutropenia Thrombocytopenia Anemia Immune-mediated red cell aplasia [54] Pancytopenia [29]
Ocular	Conjunctivitis Uveitis/scleritis
Neurological	Autoimmune inflammatory myopathy [55] Guillain-Barré syndrome [14] Aseptic meningitis [18] Temporal arteritis [35]
Renal	Lupus-type nephritis [53]
Musculoskeletal	Arthritis
Systemic Vasculitis/ Autoimmune Syndromes	Sarcoidosis Vasculitis with multiple organ involvement
General/Constitutional	Nausea/vomiting Constipation Headache Cough Fatigue Decreased appetite Fever Infusion associated reactions
Death	Bowel perforation Multiorgan failure Liver failure Gullain Barré syndrome

ACTH = adrenocorticotrophic hormone; TSH = thyroid-stimulating hormone

TIMING OF IPI TOXICITY



IPILIMUMAB

- **ALERT: US Boxed Warning**
- Immune-mediated adverse reactions:
- Ipilimumab can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most **common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab.**

- Permanently discontinue ipilimumab and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

- Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy, and evaluate clinical chemistries, including liver function tests and thyroid function tests, at baseline and before each dose.

AUTOIMMUNE COLITIS

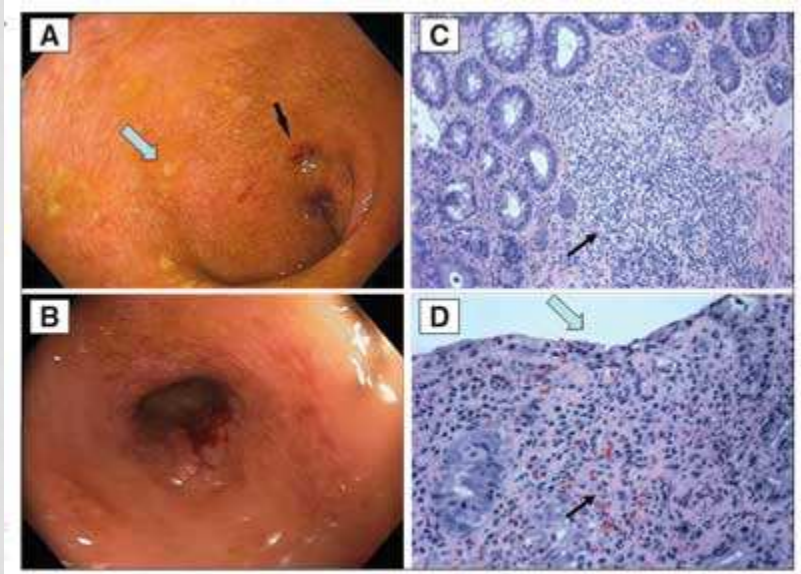


Figure 1: Colonoscopy and Histopathological Findings in an Ipilimumab-Treated Patient With Colitis — The endoscopic appearance of ulcerated **(gray arrow)** and bleeding **(black arrow)** colonic mucosa is shown in **A** and **B**; **C** and **D** show the histological features of ulceration (**gray arrow**) and inflammatory infiltration **(black arrow)** associated with ipilimumab-induced autoimmune colitis.

Ipilimumab: A Promising Immunotherapy for Melanoma
Review Article | December 15, 2010 | Melanoma, Oncology Journal
By Jaykumar R. Thumar, MD and Harriet M. Kluger, MD

MANAGEMENT OF COLITIS

- Grade I diarrhea initiate Lomotil and Imodium on first day of symptoms
- Grade II add budesonide and consider sigmoidoscopy
- Grade III oral or IV steroids followed by prednisone 60mg/day taper over 30 to 60 days
  - If symptoms persist despite IV steroids, give Infliximab 5mg/kg x1 (may repeat in 2 weeks)

MANAGEMENT OF IPI COLITIS

Table 3
Management of Diarrhea/Colitis in Patients Treated With Ipilimumab

Severity of Diarrhea	Management
Grade I (2 or fewer episodes in 24 hrs)	Antidiarrheals with close follow up Urgent sigmoidoscopy
Grade II (3 to 6 episodes in 24 hrs)	Oral budesonide (9 mg/d) along with antidiarrheals [34] Urgent sigmoidoscopy
Grade III (7 or more episodes) without other complications	Oral corticosteroids: Prednisone, 1-2 mg/kg *or* Methylprednisolone, 1-2 mg/kg *or* Dexamethasone, 4 mg q6hr [45] Consider inpatient treatment if no response
Dehydration or bleeding Evidence of severe colitis on sigmoidoscopy	Inpatient admission Intravenous corticosteroids: Methylprednisolone, 1-2 mg/kg *or* Dexamethasone, 4 mg q6hr Addition of hydrocortisone enema can be considered [42] For corticosteroid-refractory cases: Infliximab, 5 mg/kg; may be repeated in 2 wks [41-45] Bowel rest and TPN for prolonged diarrhea
Prolonged diarrhea not responding to the treatment	For infliximab-resistant disease, tacrolimus or rapamycin can be added [43] Diverting ileostomy or partial/total colectomy can be considered

TPN = total parenteral nutrition.

Ipilimumab: A Promising Immunotherapy for Melanoma
Review Article | December 15, 2010 | Melanoma, Oncology Journal
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IPILIMUMAB DOSE ADJUSTMENT

- Renal Impairment -No dosage adjustment necessary.

- Hepatic Impairment at baseline:
  - Mild impairment (total bilirubin >1 to 1.5 x ULN or AST >ULN): No dosage adjustment necessary.
  - Moderate or severe impairment (total bilirubin >1.5 x ULN and any AST): No dosage adjustment provided in manufacturer's labeling (has not been studied).

- Hepatic Impairment during treatment:
  - AST or ALT >2.5 to ≤5 x ULN or bilirubin >1.5 to ≤3 x ULN: **Temporarily** withhold treatment.
  - ALT or AST >5 times ULN, or total bilirubin >3 times ULN: **Permanently** discontinue.

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/2934459?hl=433670

IPILIMUMAB PERMANENTLY DISCONTINUED

- Failure to complete treatment course within 16 weeks of initial dose
- Persistent moderate adverse reactions or unable to reduce corticosteroid dose to prednisone 7.5 mg daily (or equivalent)
- Severe or life-threatening adverse reactions
- Central nervous system or neuromuscular toxicity: Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis

IPILIMUMAB PERMANENTLY DISCONTINUED

- **Dermatologic toxicities**: Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
- **Gastrointestinal toxicities**: Colitis with abdominal pain, fever, ileus, or peritoneal symptoms, increase in stool frequency (≥7 over baseline), stool incontinence, require IV hydration for >24 hours, or GI hemorrhage or perforation; grades 3/4 amylase or lipase increases (Weber, 2012)
- **Hepatotoxicities**: ALT or AST >5 times ULN, or total bilirubin >3 times ULN
- **Ophthalmic toxicities**: Immune-mediated ocular disease unresponsive to topical immunosuppressive treatment
- Severe immune-mediated reactions involving any organ system (eg, myocarditis [noninfectious], nephritis, pancreatitis, pneumonitis

ANTI-PD-1/PDL-1

NIVOLUMAB

- **Cardiovascular**: Edema, chest pain
-
- **Central nervous system**: Fatigue (50%; grade 3/4: 7%)
- **Dermatologic**: Skin rash (16%; grade 3/4: <1%), pruritus (11%; grade 3/4: <1%)
- **Neuromuscular & Skeletal**: Musculoskeletal pain weakness, arthralgia
- **Respiratory**: Dyspnea (38%; grade 3/4: 9%), cough, pneumonia

http://www.uptodate.com/contents/nivolumab-drug-information?source=search_result&search=nivolumab&selectedTitle=1~28

NIVOLUMAB

- **Endocrine & metabolic**: Hyponatremia, hypokalemia, hypomagnesemia, hypercalcemia hyperkalemia, hypocalcemia, weight loss

- **Hematologic**: Lymphocytopenia (47%; grade 3/4: 16%), anemia, thrombocytopenia

http://www.uptodate.com/contents/nivolumab-drug-information?source=search_result&search=nivolumab&selectedTitle=1~28

NIVOLUMAB

- **Gastrointestinal**: Decreased appetite, nausea, constipation, colitis (≤21%, grades 3/4: 2%), diarrhea, vomiting, abdominal pain
- **Hepatic**: Increased serum AST (16%), increased serum alkaline phosphatase (14%), increased serum ALT (12%)
- **Renal**: Increased serum creatinine (22%)

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NIVOLUMAB

- Endocrine:
  - Hypothyroidism (4%),
  - hyperthyroidism (2%),
  - adrenocortical insufficiency (<2%),
  - diabetic ketoacidosis,
  - hypophysitis,
  - pituitary insufficiency

http://www.uptodate.com/contents/nivolumab-drug-information?source=search_result&search=nivolumab&selectedTitle=1~28

PEMBROLIZUMAB

AEs of Interest Based on Immune Etiology

Adverse Event, n (%)	Any Grade	Grade 3-4
Hypothyroidism	49 (7.5)	1 (0.2)
Hyperthyroidism	15 (2.3)	2 (0.3)
Pneumonitis[a]	18 (2.7)	2 (0.3)
Colitis[b]	11 (1.7)	7 (1.1)
Hepatitis[c]	4 (0.6)	2 (0.3)
Nephritis[d]	3 (0.5)	2 (0.3)
Uveitis[e]	6 (0.9)	0 (0.0)

- Some reported skin rashes may have been immune-mediated
- Other immune-mediated events observed in >2 patients: thyroiditis (n = 6); hypophysitis, hypopituitarism, pruritus, and rash (n = 3 each); autoimmune thyroiditis, myositis, and rash generalized (n = 2 each)

[a]Includes interstitial lung disease of grade 1-2. [b]Includes colitis microscopic and enterocolitis. [c]Includes autoimmune hepatitis. [d]Includes renal failure. [e]Includes iridocyclitis and iritis.
Analysis cut-off date: April 18, 2014.

PEMBROLIZUMAB

Exposure and AE Summary

Adverse Event, n (%)	IPI-T (n = 342)	IPI-N (n = 313)	Total (N = 655)
Duration of therapy, mean (range), weeks	31.9 (0.1-116.3)	35.1 (0.1-123.1)	33.4 (0.1-123.1)
No. of doses, median (range)	8 (1-59)	11 (1-58)	10 (1-59)
Any grade treatment related	82%	85%	83%
Grade 3-4 treatment related	14%	14%	14%
Treatment-related death	0%	0%	0%
Discontinuation due to treatment-related AE	4%	4%	4%

- Median duration of follow-up was 15 months (range, 8-29)
- As of data cutoff date, 244 patients (37%) were still receiving pembrolizumab
  - As of May 2015, ~180 patients (~27%) remain on treatment

Analysis cut-off date: April 18, 2014.

Anti-PD1 Rx: AE and SAE

	DTIC	Gp100	IPI-3	Nivo-3	Pembro-2 Q3
Author	Robert	Hodi	Hodi	Robert	Daud*
AE (3+4)	38.0%	47.0%	45.8%	34.0%	--
Rx-AE (3+4)	17.6%	15.0%	30.0%	11.7%	14%
Rx-AE (5)	0%	1.5%	1.5%	0%	0%
Rx-SAE (3+4)	5.9%	--	--	5.8%	--

Anti-PD1+ : AE

	IPI-3	Pembro-10 Q2W	Pembro-10 Q3W	IPI + Nivo Phase 1	IPI + Nivo Phase 2*	IPI + Nivo Phase 3
	Robert	Robert	Robert		Hodi	
Rx-AE 3+4 (5)	19.9% (1)	13.3% (0)	10.1% (0)		54% (3%)	
GI-colitis	7%	1.4%	2.5%		17%	
Liver	0.4%	1.1%	1.8%		15%	
Skin rash	0.8%	0%	0%		5%	
Endocrine	0.8%	1.2%	0.8%		5%	
Lung	0.4%	0%	0.4%		2%	

3+3 phase 1

ASCO2015

Anti-PD1+: toxicity management

- Acute toxicity management:
  - Systemic corticosteroids or anti-TNF
- Biomarkers of early toxicity (early intervention):
  - Exhaled NO, stool calprotectin…
- Organ specific tox treatment/prevention:
  - Colitis: lessons from IBD
    - Enteric corticosteroids*, antibiotics (microbiome), anti-integrins (natalizumab, vedolizumab), CCR9 inhibitors
  - Hepatitis: ursodeoxycholate, budesonide, microbiome
  - Pneumonitis: inhaled corticosteroids

*Weber, J., et al., Clin Cancer Res 15:5591, 2009

Table 2 Selected Adverse Events

Agent, Patients (N), and Study [Reference]	Nivolumab N = 296[7]		Pembrolizumab N = 135[65]		MPDL3280A N = 171[a][49]		BMS-936559 N = 207[17]		MEDI4736 10 mg/kg q2wk N = 346[19]		MSB-0010718C N = 28[67]	Ipilimumab N = 131[68]	
Adverse Event	**Any Gr**	**Gr 3/4**	**Any Gr**	**Gr 3/4**	**Any Gr**	**Gr 3/4**	**Any Gr**	**Gr 3/4**	**Any Gr**	**Gr 3/4**	**Any Gr**	**Any Gr**	**Gr 3/4**
Pneumonitis	3%	1%	4%	0%	NR	0%	NR	NR	1%	0%	NR	NR	NR
Diarrhea	11%	1%	20%	1%	26%	1%	9%	0%	5%	0%	10.7%	32.8%	5.3%
Colitis	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7.6%	5.3%
Rash	12%	0%	21%	2%	18%	1%	7%	0%	0%	< 1%	NR	19.1%	0.8%
Pruritus	9%	< 1%	21%	1%	NR	NR	6%	0%	0%	< 1%	NR	24.4%	0%
Vitiligo	3%	0%	9%	0%	NR	NR	2%	0%	NR	NR	NR	2.3%	0%
ALT elevation	4%	1%	8%	0%	NR	3%	1%	0%	4%	1%	NR	1.5%	0%
AST elevation	3%	1%	10%	1%	NR	NR	NR	NR	4%	1%	10.7%	0.8%	0%
Infusion reaction/hypersensitivity	3%	< 1%	NR	NR	NR	NR	11%	< 1%	NR	NR	NR	NR	NR
Fatigue	NR	NR	30%	1%	43%	4%	NR	NR	13%	1%	35.7%	42%	6.9%
Hyperthyroidism/hypothyroidism	3%	< 1%	8%	1%	NR	NR	3%	0%	3%	< 1%	NR	1.5%	0%

[a]Regardless of attribution.

ALT = alanine transaminase; AST = aspartate transaminase; Gr = grade; NR = not reported.

CONCLUSIONS

- Immunotherapy has unique adverse events
- Autoimmunity has been associated with a favorable prognosis
- The majority of toxicity is mild to moderate and managed with routine supportive measures
  - Anti-emetics
  - Anti-pyretics
  - Anti-histamines
  - Anti-diarrheal
  - Temporary break

CONCLUSIONS

- Moderate to severe toxicity requires prompt attention and consideration of systemic steroids
- Permanently discontinue:
  - Severe immune-mediated reactions involving any organ system
  - Colitis with abdominal pain, fever, ileus, or peritoneal symptoms
  - ALT or AST >5 times ULN, or total bilirubin >3 times ULN

THANK YOU