Belgian Association of Dermato-Oncology

BADO

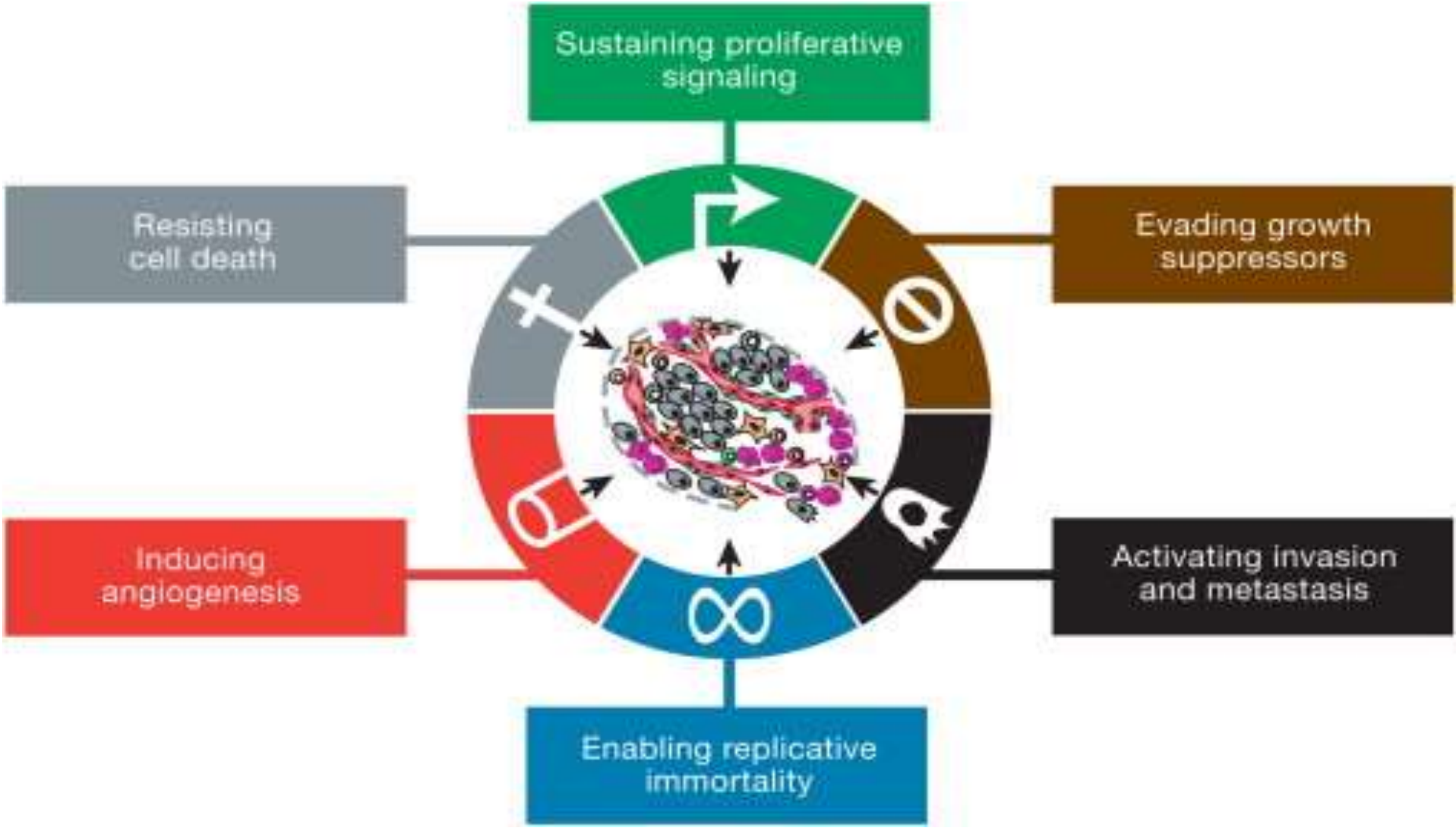
Specific side effects of the new immunotherapies: case illustrations

3rd Meeting of the
Belgian Association of Dermato-Oncology
Saturday January 16th 2016

Dr. Pascal Wolter, CHR Verviers East Belgium, Centre d'Oncologie et d'Hématologie, Belgium

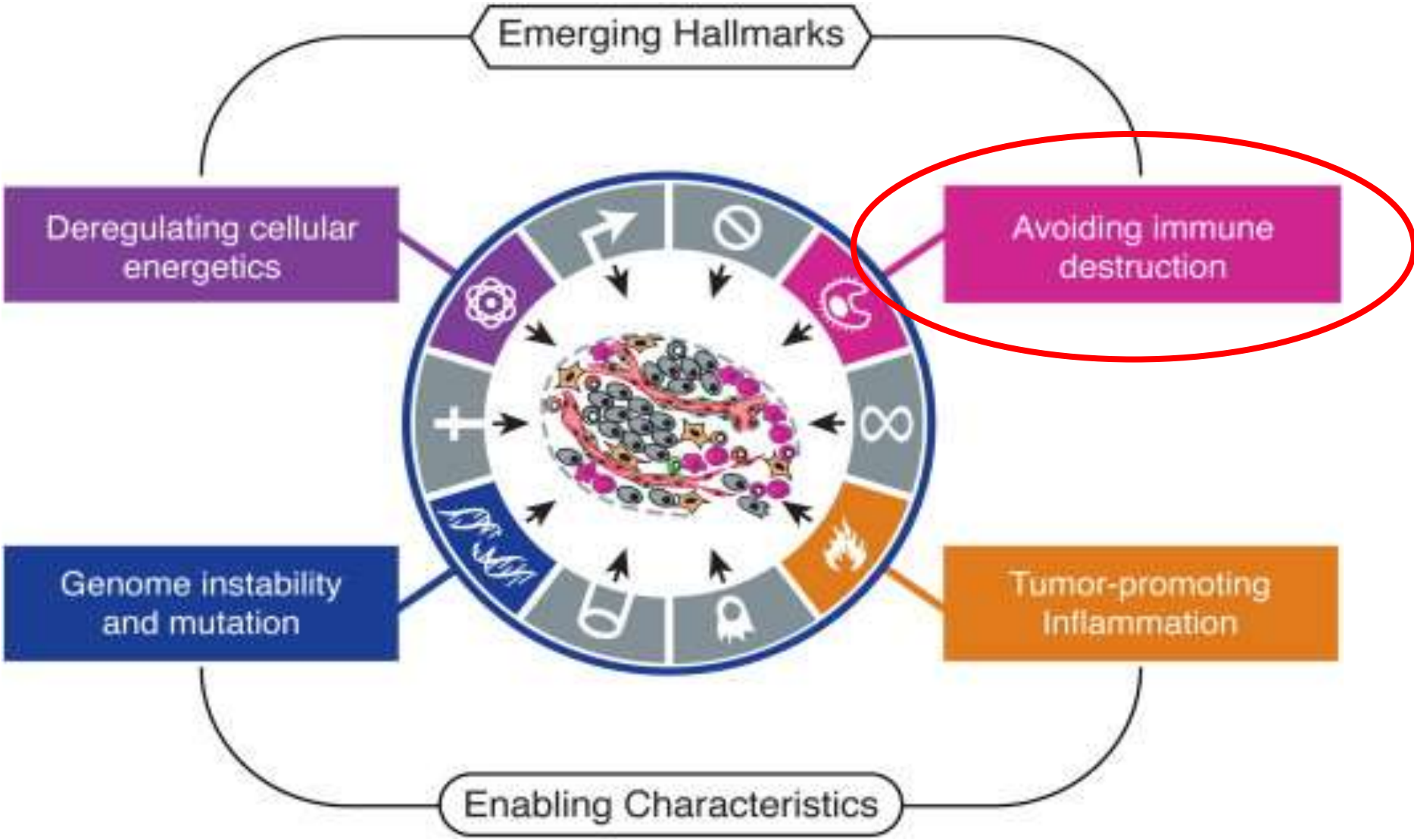
http://www.sciencemagazinedigital.org/sciencemagazine/20_december_2013?pg=7#pg1

The hallmarks of cancer – 2000:



Hanahan D, Weinberg RA, Cell, Volume 144, Issue 5, 2011, 646 - 674

The hallmarks of cancer – 2011:



Douglas Hanahan , Robert A. Weinberg, Cell, Volume 144, Issue 5, 2011, 646 - 674

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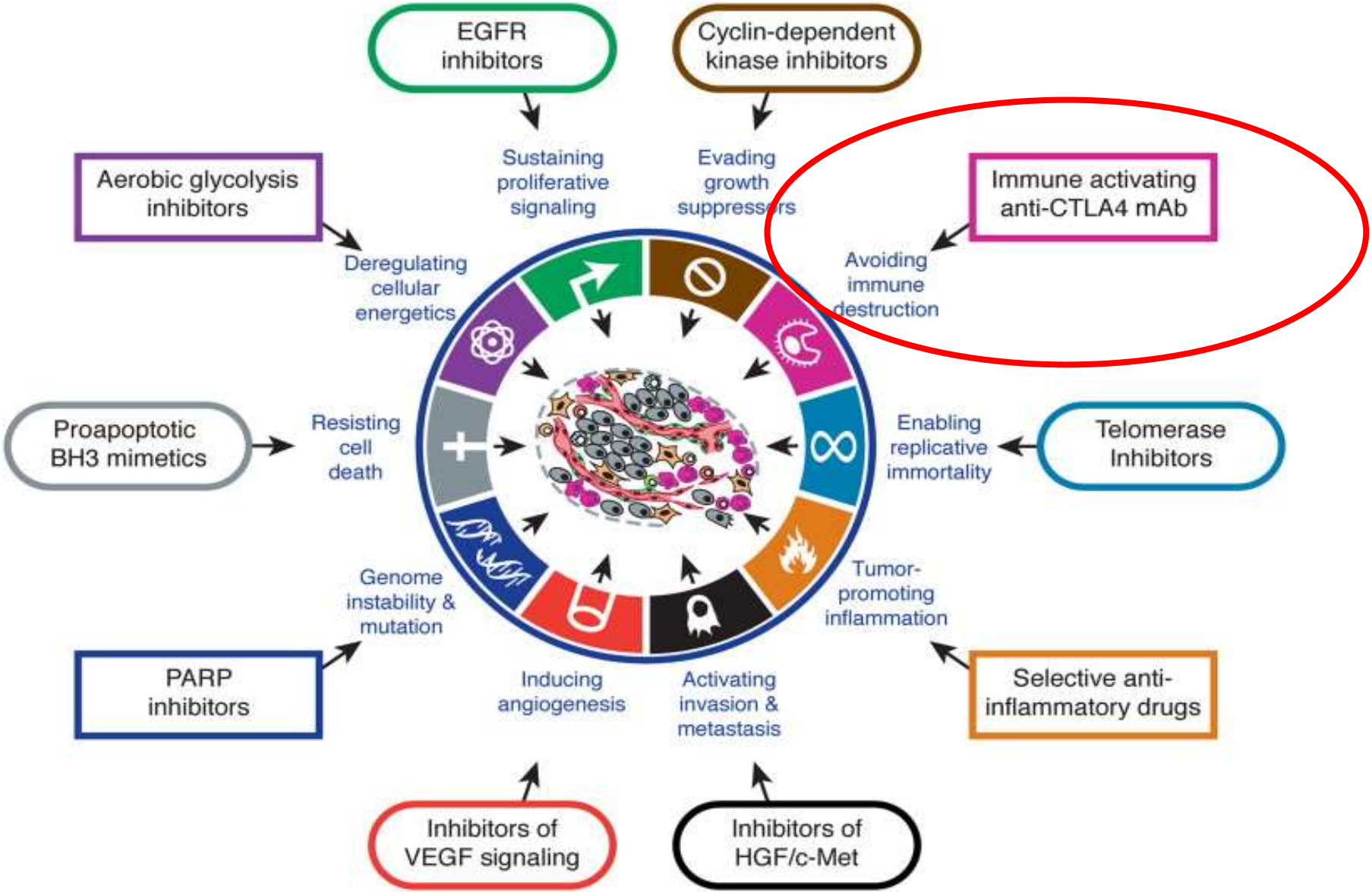


Douglas Hanahan , Robert A. Weinberg, Cell, Volume 144, Issue 5, 2011, 646 - 674

Historical overview of immunology and cancer:

Paul Ehrlich suggests that the immune system can control cancers

(1909)

Search for tumor-associated antigens (TAA) begins
First human TAA recognised in 1991 (MAGE-A1)
(Van der Bruggen et al)

Interleukin-2 approved by FDA 1998 for treatment of advanced metastatic melanoma

Ipilimumab approved by FDA/EMEA (03-2011 / 07-2011)

1890s Coley's toxin

1960s tumor 'immunosurveillance' hypothesis by Burnet

Interferon-α approved by FDA (1995) for adjuvant treatment of stage IIB/III melanoma

1995: dendritic cells can present TAA to the adaptive immune system

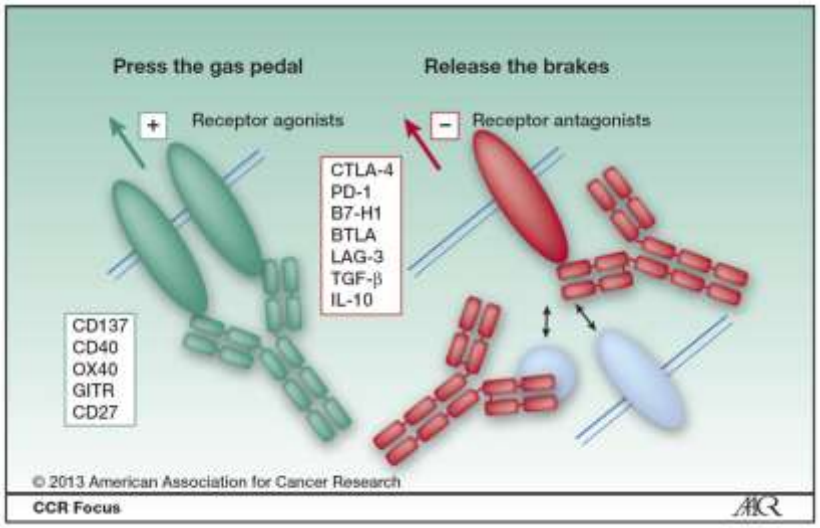
Anti-PD1 and several other immunomodulatory drugs in pipeline

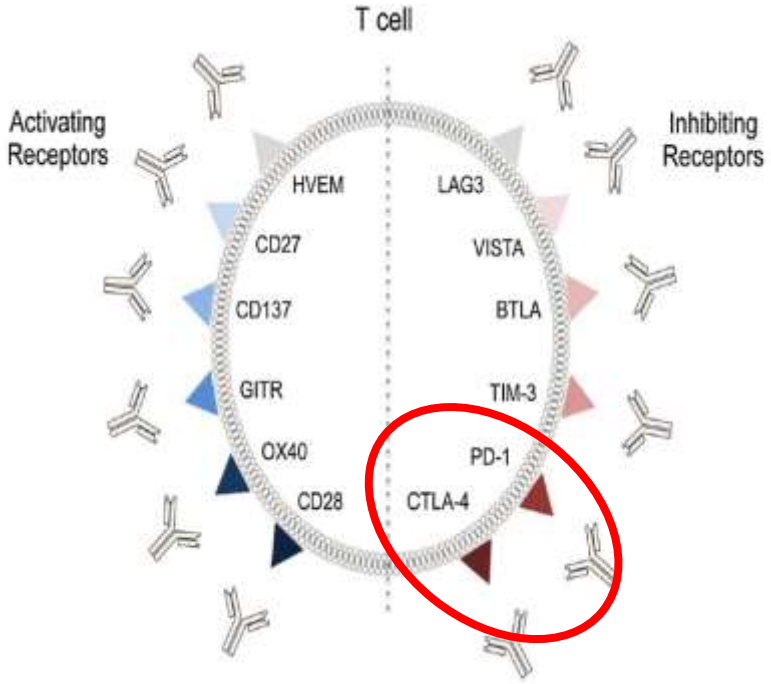
Can the immune system recognize and eliminate malignant tumors?

Parish C Immunol Cell Biol; 81:106-113, 2003
Kirkwood, J. M. et al. J Clin Oncol; 26:3445-3455 2008

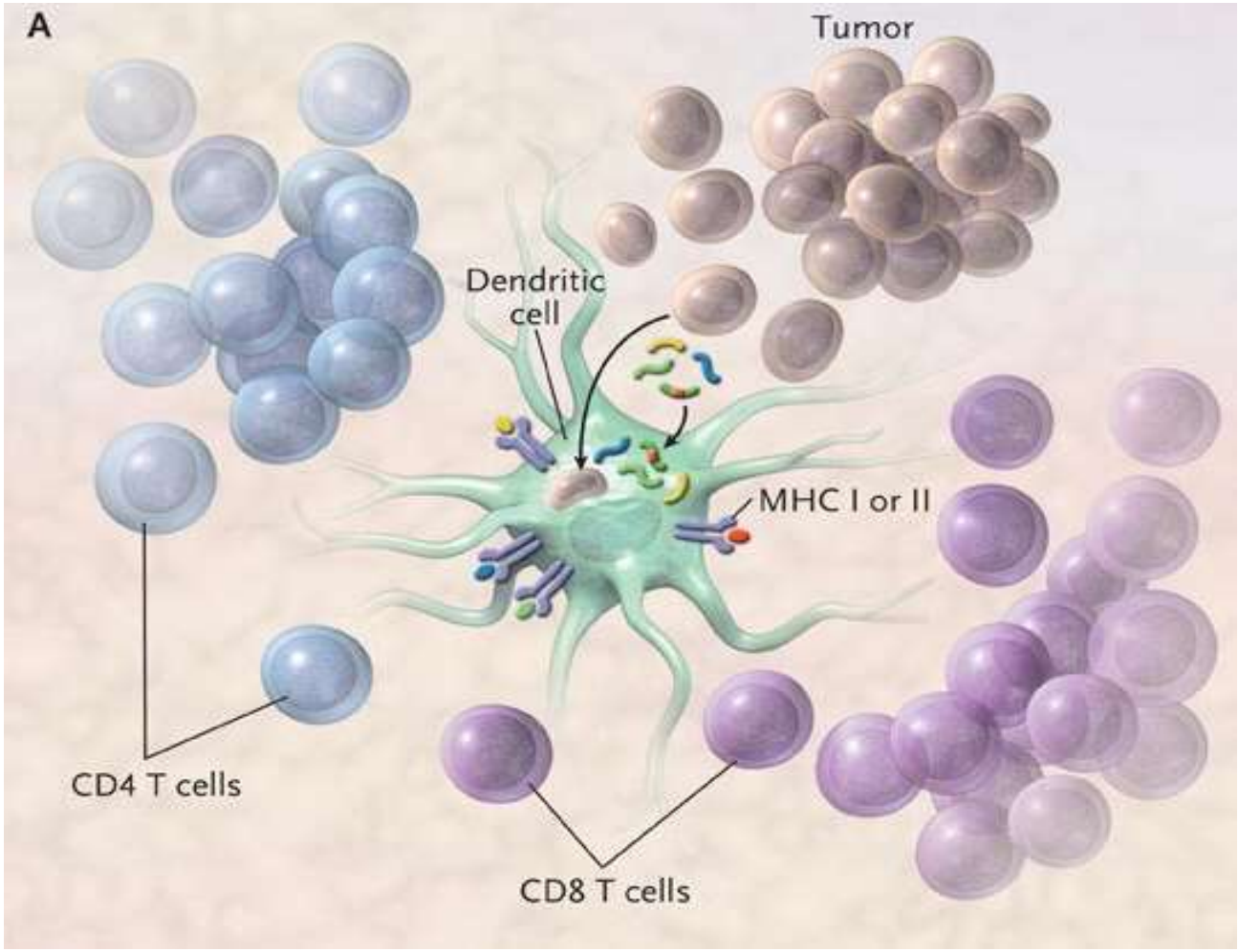
Immunology and cancer

- Regulation of the immune system depends on fine control system in which a key role is played by cellular receptors that ensure activation of inhibition of cells involved in the control of infections or tumors and the development of autoimmunity
- Some of these mechanisms are activating and dictate whether a response arises, others play the role of powerful repressors
- Antagonist antibodies acting on repressors result in enhanced immune responses, similar to agonist antibodies acting on the activating antibodies



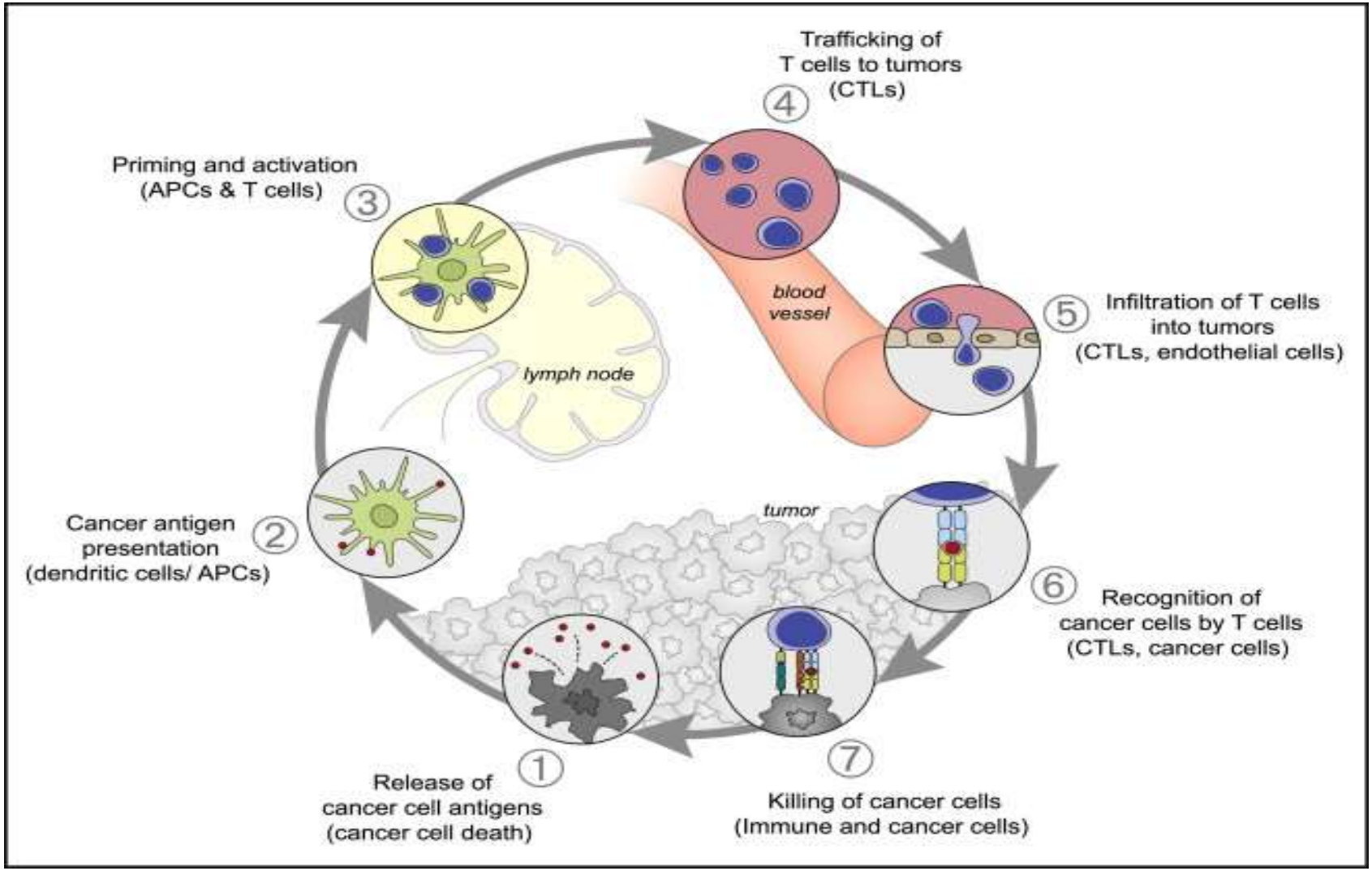


Melero I et al Clin Canc Resl; 19(5):997-1008, 2013
Merelli B et al Crit Rev Oncol Hematol 89:140-165, 2014



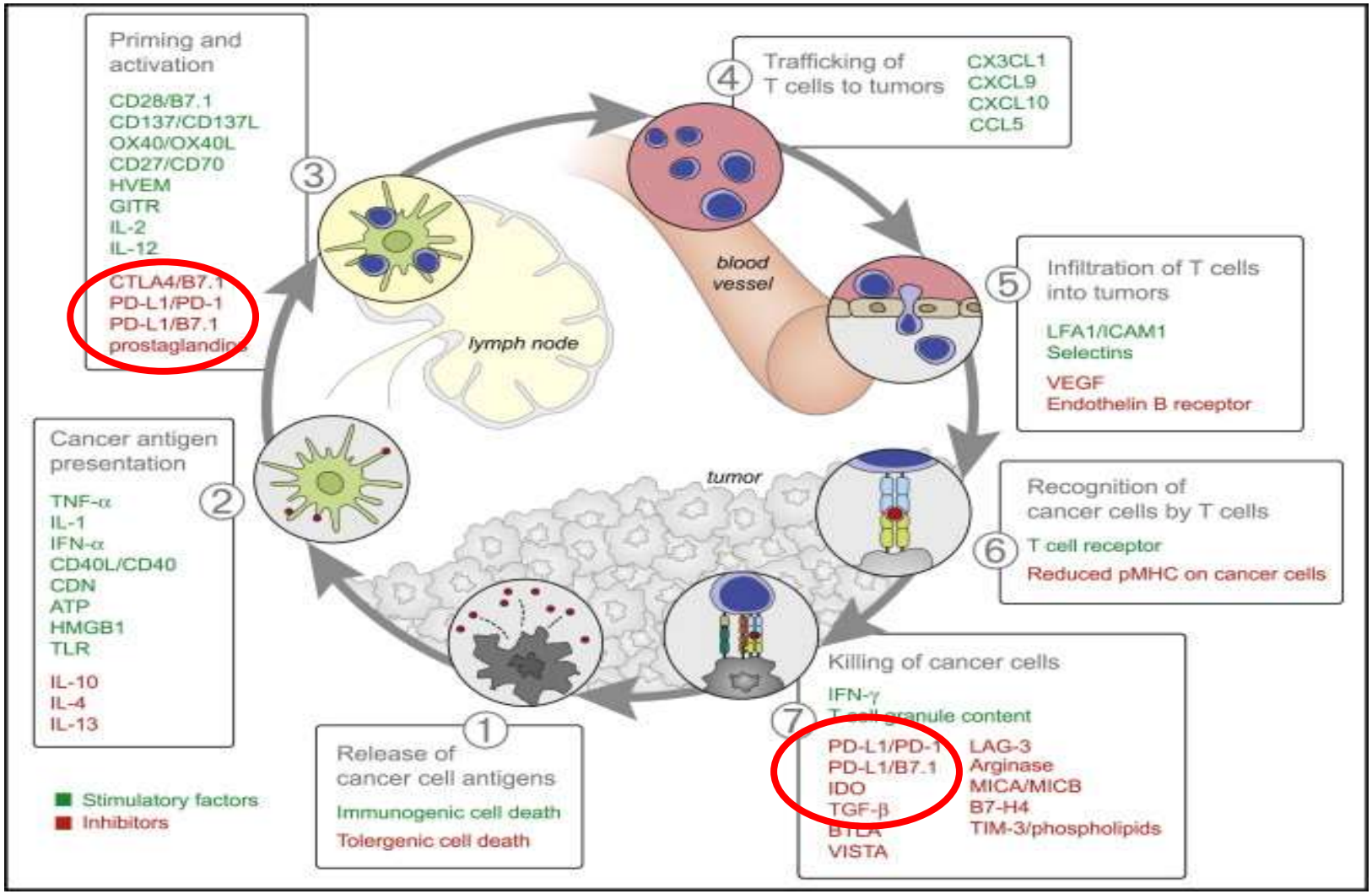
Tumor Antigens Eliciting T-Cell Immunity When Presented to Naive T Cells by Antigen-Presenting Dendritic Cells. Dendritic cells in the tumor or the tumor-draining lymph node take up dying tumor cells, tumor proteins, and tumor peptides and process and display them in their major-histocompatibility-complex (MHC) class I and class II molecules. If properly activated by immunostimulatory tumor products or other factors in the tumor microenvironment, the dendritic cells induce effective tumor-specific CD4 and CD8 T cells.

Finn OJ NEJM 2008;358:2704-2715



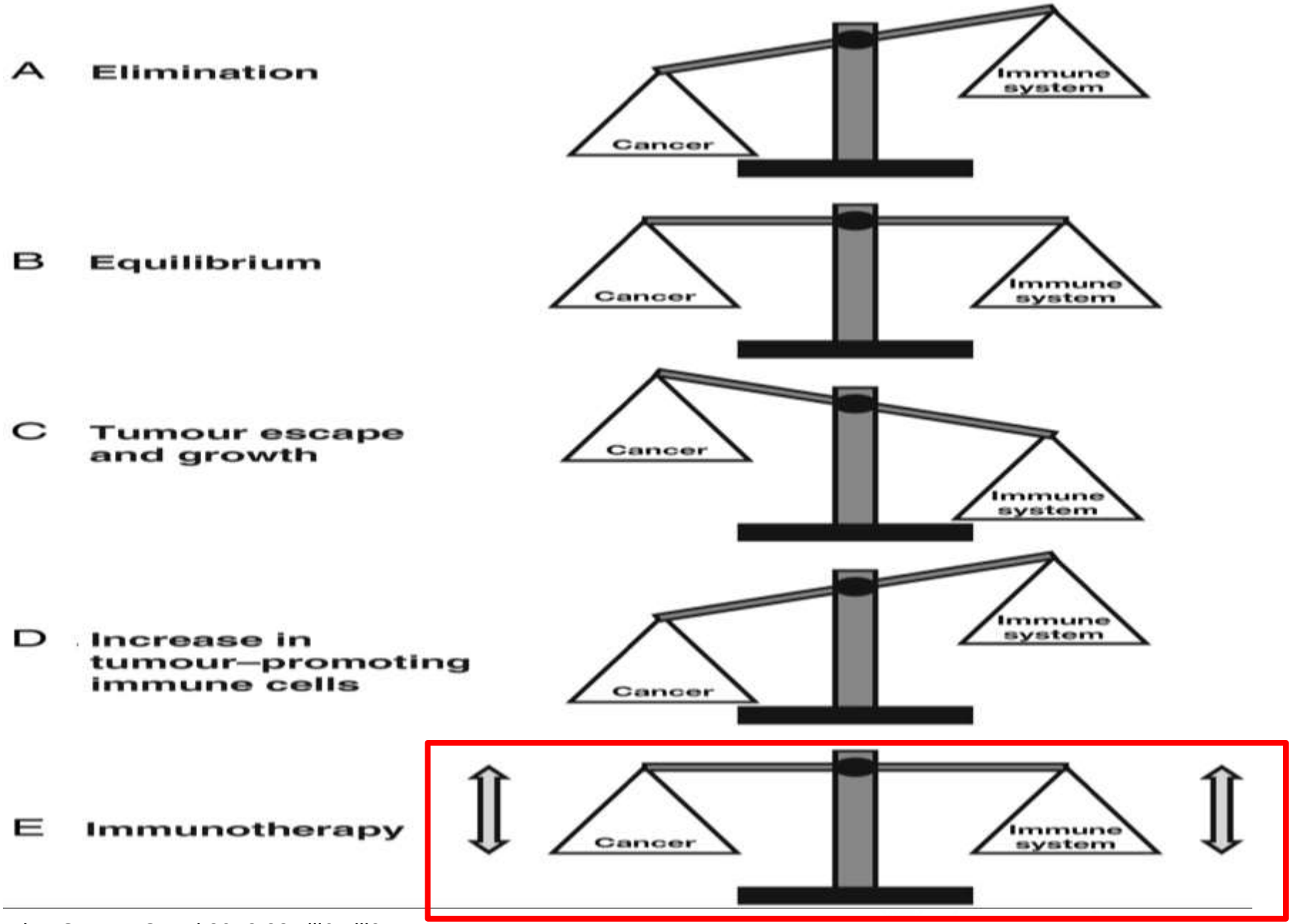
Cancer-Immunity Cycle: The generation of immunity to cancer is a cyclic process that can be self propagating, leading to an accumulation of immune-stimulatory factors that in principle should amplify and broaden T cell responses. The cycle is also characterized by inhibitory factors that lead to immune regulatory feedback mechanisms, which can halt the development or limit the immunity. This cycle can be divided into seven major steps, starting with the release of antigens from the cancer cell and ending with the killing of cancer cells.

Chen DS, Mellman; Immunity, 39(1): 1- 10 (2013)



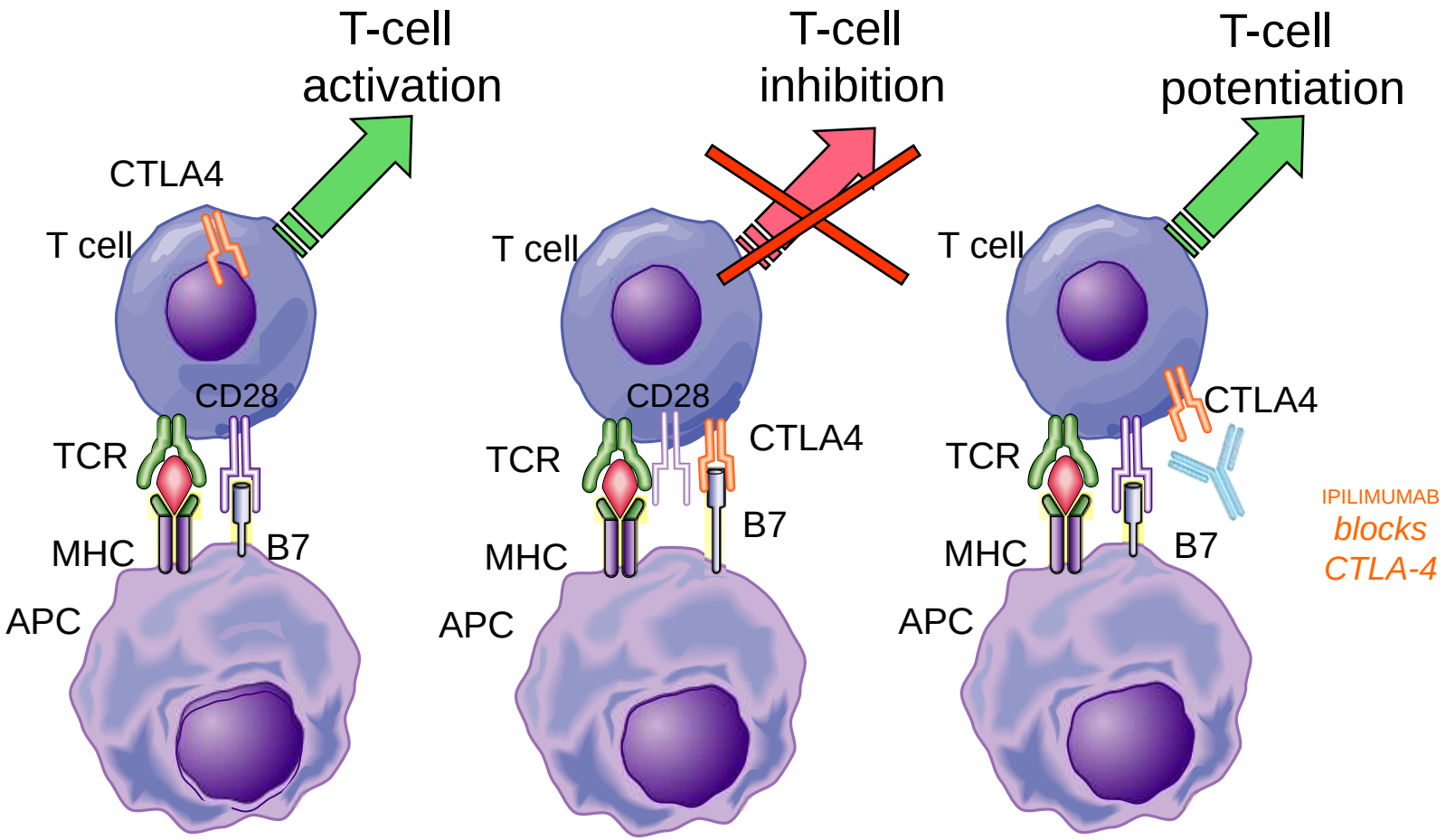
Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle: Each step of the Cancer-Immunity Cycle requires the coordination of numerous factors, both stimulatory and inhibitory in nature. Stimulatory factors shown in green promote immunity, whereas inhibitors shown in red help keep the process in check and reduce immune activity and/or prevent autoimmunity. Immune checkpoint proteins, such as CTLA4, can inhibit the development of an active immune response by acting primarily at the level of T cell development and proliferation (step 3). We distinguish these from immune rheostat ("immunostat") factors, such as PD-L1, can have an inhibitory function that primarily acts to modulate active immune responses in the tumor bed (step 7).

Chen DS, Mellman; Immunity, 39(1): 1- 10 (2013)

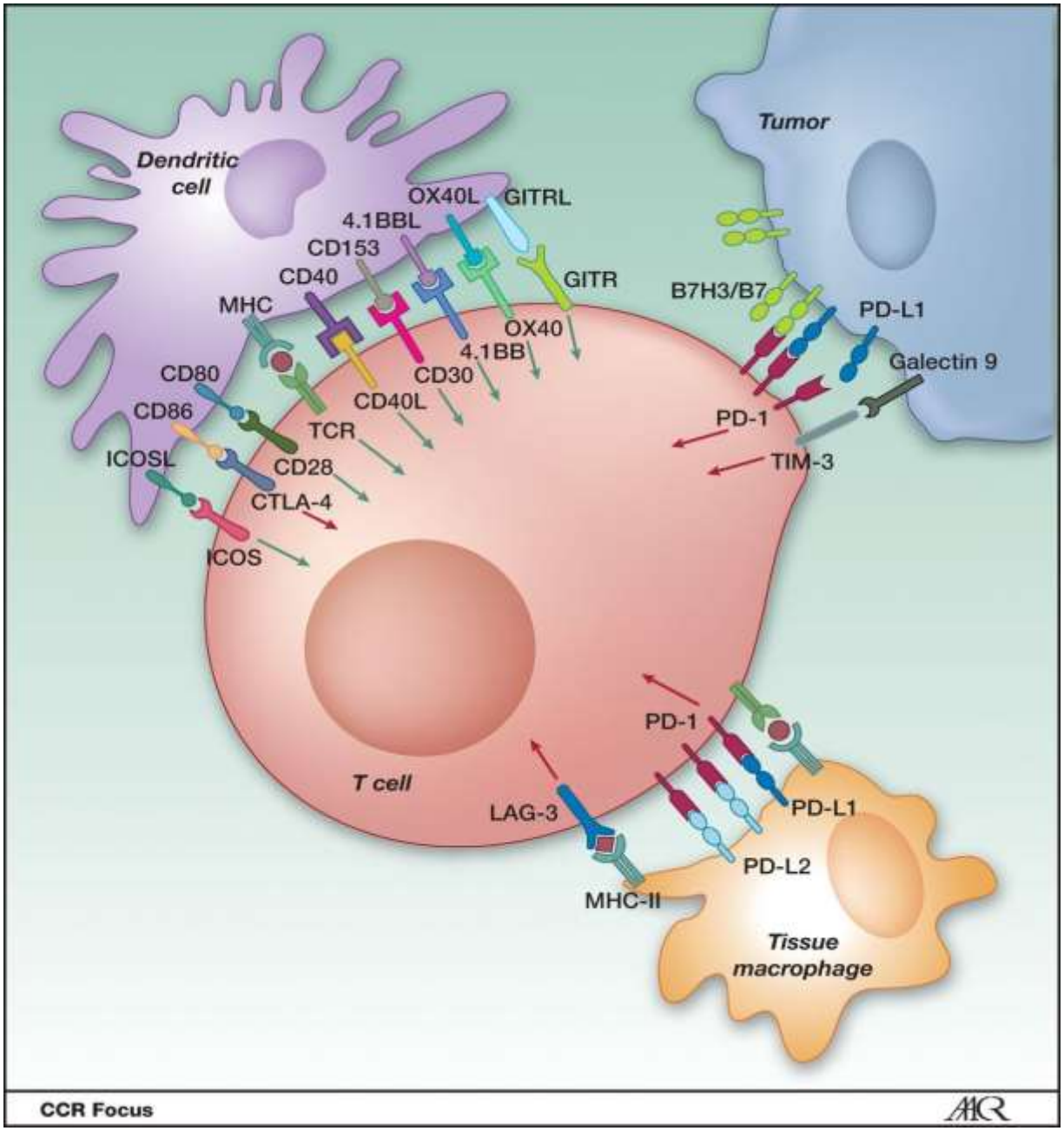


Finn OJ Ann Oncol 2012;23:viii6-viii9

Ipilimumab: Mechanism of Action



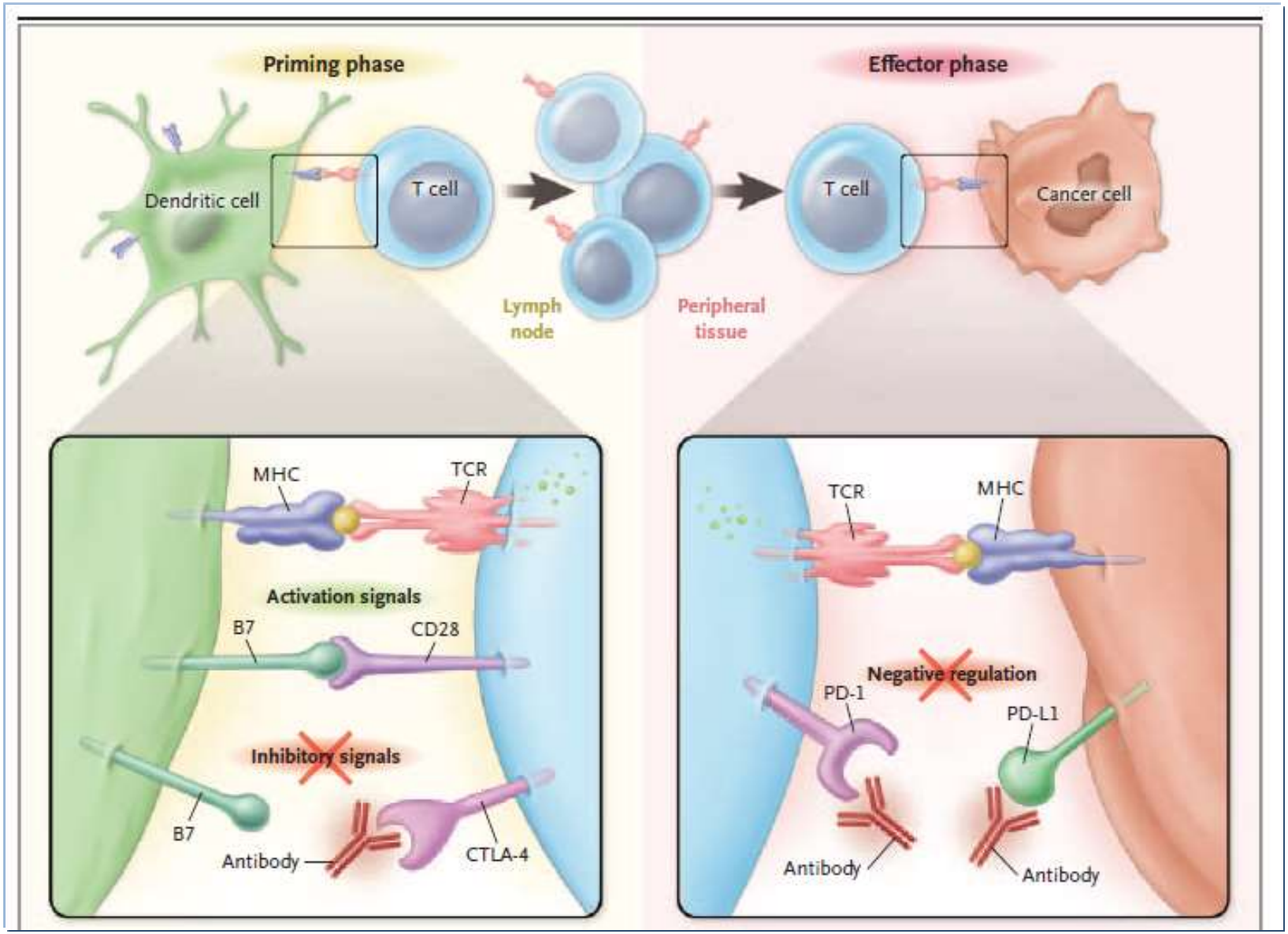
O'Day S et al. ASCO 2010 plenary session (#4)



Schematic representation of immune synapses formed by a tumor-reactive T lymphocyte with a dendritic cell, a tumor cell, and a macrophage in the tumor microenvironment. Costimulatory and coinhibitory receptors modulate the function of both the antigen-presenting and the antigen-sensing lymphocytes. Tampering with these interactions underlies the mechanism of action of immunostimulatory mAb conceivably acting mainly in the malignant tissue and in its draining lymph nodes

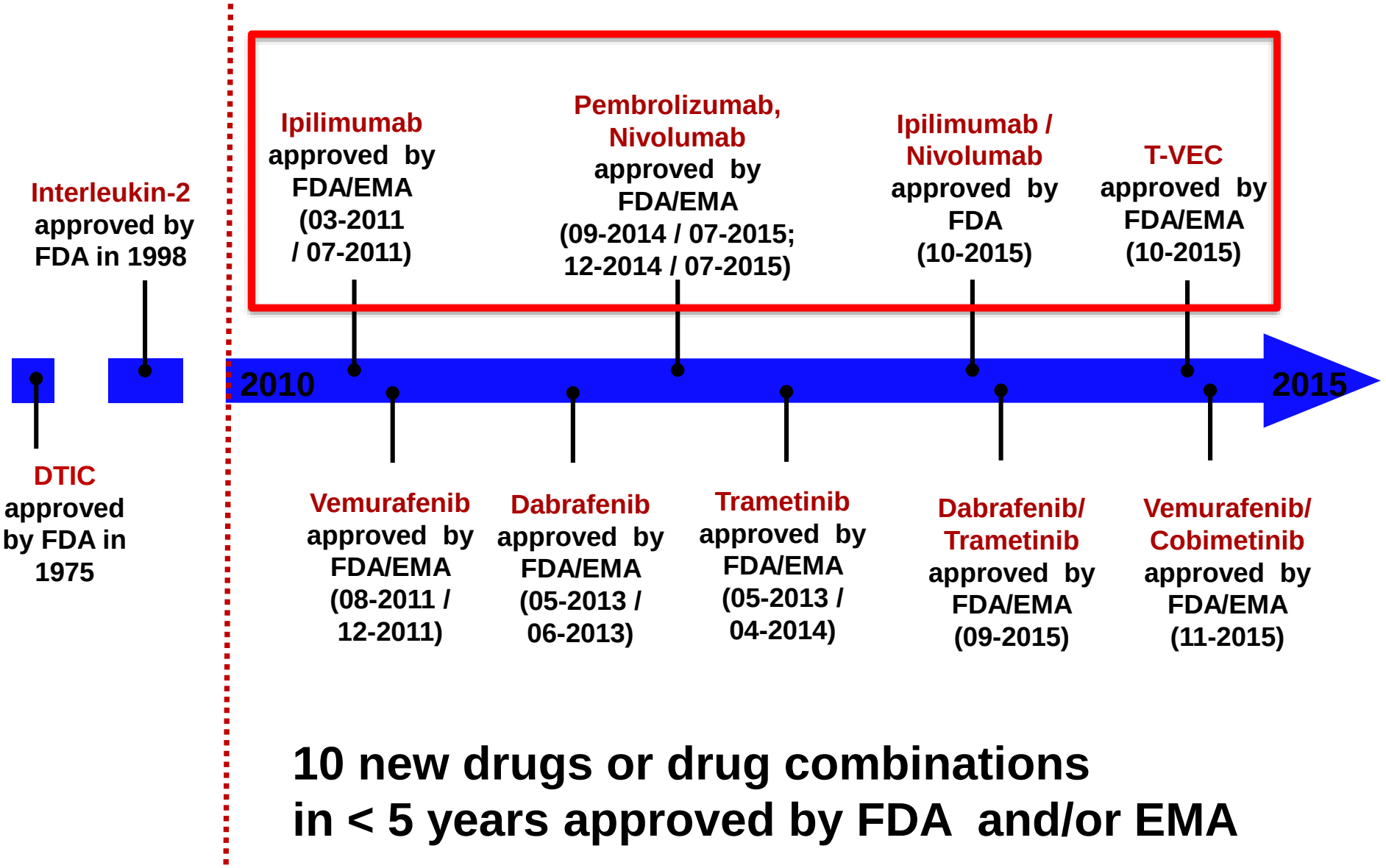
Melero I et al. Clin Cancer Res 2013;19:997-1008

Mechanism of action of anti-PD-1/-PD-L1:



Ribas A NEJM 2012; 366:2517-2519

Historical overview of treatments for metastatic melanoma:



10 new drugs or drug combinations in < 5 years approved by FDA and/or EMA

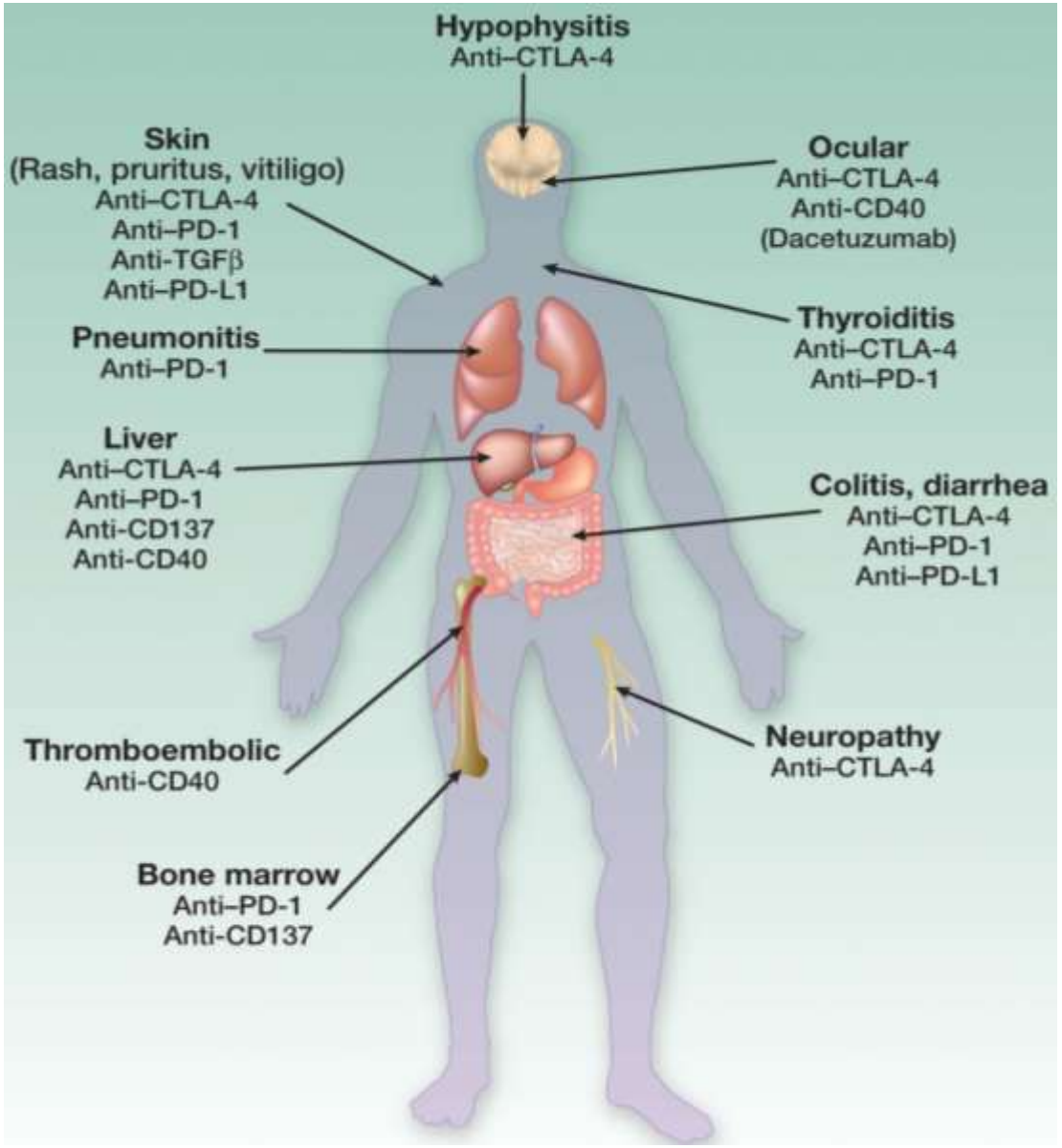
Recent phase 3 studies with anti CTLA-4/ PD1 and combi in melanoma:

Ref.	Nr. of pts.	Study endpoint	Responses	Median PFS/OS	Safety	PD-L1 / BRAF status
Larkin J NEJM 2015 (CA209-067) Phase 3, Placebo	945 pts 1st line, 1:1:1 Nivo 3 mg/kg (316 pts) Nivo/Ipi 1/3 mg/kg -> 3mg/kg (314) Ipi 3 mg/kg (315)	Coprimary: PFS/OS (invest.) Secondary: ORR, PD-L1 expression, safety	N vs N/I vs I CR: 9/11/2% PR: 35/46/17% SD: 11/13/23% PD: 38/23/49% ORR: 44/58/19% Time to response: 2,78/2,76/2,79 mo	mPFS: Nivo: 6.9 months (95%CI 4,3-9,5) N/I: 11,5 months (8,9-16,7) Ipi: 2,9 (2,8-3,4) median OS: not reported	any gr 3/4 Nivo: 82% 16% N/I: 95% 55% Ipi: 86% 27% Discont. due to AE: 13/66/28%	PD-L1 pos = ≥ 5% tumor cells positive on cell surface PD-L1 pos.: 23,6% ORR: 57/72/21% PD-L1 neg.: 65,6% ORR: 41/55/18% BRAF pos.: 23% BRAF neg.: 67% No diff in ORR
Robert C NEJM 2015 (Keynote-006) Phase 3, open label, Ipi-naïve 1st + 2nd line (BRAFi)	834 pts, 1:1:1 Pembro 10 mg/kg,2wk 279 pts) Pembro 10mg/kg, 3wk (277) Ipi 3 mg/kg (278) max. 24 months tx	Coprimary: PFS/OS (invest.) Secondary: ORR, DOR, safety	P2 vs P3 vs Ipi CR: 5/6,1/1,4% PR: 29/27/10% SD: 13/14/16% PD: 38/41/49% ORR: 34/33/12% Time to response: 86/85/87 days	mPFS: Pembro2: 5,5 months Pembro3: 4,1 months Ipi: 2,8 months 1yr survival: Pembro2: 74,1% Pembro3: 68,4% Ipi: 58,2% median OS: not reached	any gr 3/4/5 P2: 79% 13% P3: 73% 10% Ipi: 73% 20% Discont.due to AE: 4/7/9%	PD-L1 pos = ≥ 1% membranous staining on tumor cells PD-L1 pos.: 80,4% PD-L1 neg.: 19,6% BRAF pos.:36% BRAF neg.: 64%
Robert C NEJM 2015 (CA209-066) Phase 3, placebo	418 pts 1st line, 1:1, BRAF wt Nivo 3 mg/kg (210 pts) DTIC 1000 mg/m² (208)	Primary: OS Secondary: PFS (invest.) , ORR, PD-L1 expression	Nivo vs DTIC CR: 7,6/1% PR: 32,4/13% SD: 16,7/22,1% PD: 32,9/15,4% ORR: 40/14% Time to response: median 2,1 mo	mOS: Nivo: not reached DTIC: 10,8 months OS 1-yr: 73 vs 42% mPFS: Nivo: 5,1 months DTIC: 2,2 months	any gr 3/4 Nivo: 74,3 11,7% DTIC: 75,6% 17,6% Discont. due to AE: 13/21%	PD-L1 pos = ≥ 5% tumor cells positive on cell surface PD-L1 pos.: 35,4% ORR N/DTIC: 52/11% PD-L1 neg.: 64,6% ORR N/DTIC: 33/16% BRAF pos.:0% BRAF neg.: 97%

The challenge: finding the right balance …

The other side of the coin … immune related adverse events.

Occurrence of adverse events with Ipilimumab (10 mg/kg)		
Adverse event	Any gr (%)	gr. 3 or 4 (%)
Skin (rash, pruritus)	**47-68**	**0-4**
GI (diarrhea, colitis)	**31-46**	**8-23**
Hepatitis	**3-9**	**3-7**
Hypophysitis	**4-6**	**1-5**



Melero I et al. Clin Cancer Res 2013;19:997-1008

Occurrence of ir-adverse events with Ipi and anti-PD1

Type of study	MDX010-20 (ph 3, 676 pts.)		CA184-024 (ph 3, 502 pts.)		Tremelimumab (ph 3, 655 pts.)		Nivolumab (CA209-066) (ph 3, 418 pts.)		MK-3475-006 (ph 3, 834 pts.)		Ipi + Nivo (CA209-067 (ph 3, 945 pts., I/N 313)	
	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)
Any (ir) event	61.1	14.5	77.7	41.7	96	52	74.3	11.7	79/73	13/10	**95**	**55**
Skin (rash, pruritis)	43.5	1.5	26.7	2.0	33	2	15	0.5	15/13	0/0	40	5
GI (diarrhea, colitis	29	7.6	32.8	4.0	51	18	16	1.0	2/4	1/3	44	9
Hepatitis	3.8	0	**29.1**	**20.7**	1	1	n.r.	n.r.	1/2	1/2	17	8
Endocrine	7.6	3.8	2.8	0.0	5	1	n.r.	n.r.	7/3	0.4/0	15	0.5
Pneumon.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.4/2	0/0.4	n.r.	n.r.
Renal	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0	0	2	1	n.r.	n.r.

Hodi FS et al N Engl J Med. 2010 Aug 19;363(8):711-23; Robert C et al NEJM 364(26):2517-2526 June 30, 2011; Ribas A et al JCO 2013; 31(5):616-622; Topalian SL et al JCO 2014; 32(10):1020-1030; Wolchok JD et al NEJM 2013; 369:122-33; Hamid O et al NEJM 2013; 369:134-44

Occurrence of ir-adverse events with Ipi and anti-PD1

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	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)
Any (ir) event	61.1	14.5	77.7	41.7	86	52	74.3	11.7	79/73	13/10	**95**	**55**
Skin (rash, pruritis)	43.5	1.5	26.7	2.0	33	2	15	0.5	15/13	0/0	40	5
GI (diarrhea, colitis	29	7.6	32.8	4.0	51	18	16	1.0	2/4	1/3	44	9
Hepatitis	3.8	0	**29.1**	**20.7**	1	1	n.r.	n.r.	1/2	1/2	17	8
Endocrine	3.8	3.8	2.8	0.0	5	1	n.r.	n.r.	7/3	0.4/0	15	0.5
Pneumon.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.4/2	0/0.4	n.r.	n.r.
Renal	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0	0	2	1	n.r.	n.r.

"reporting of irAEs is suboptimal"

Problem:

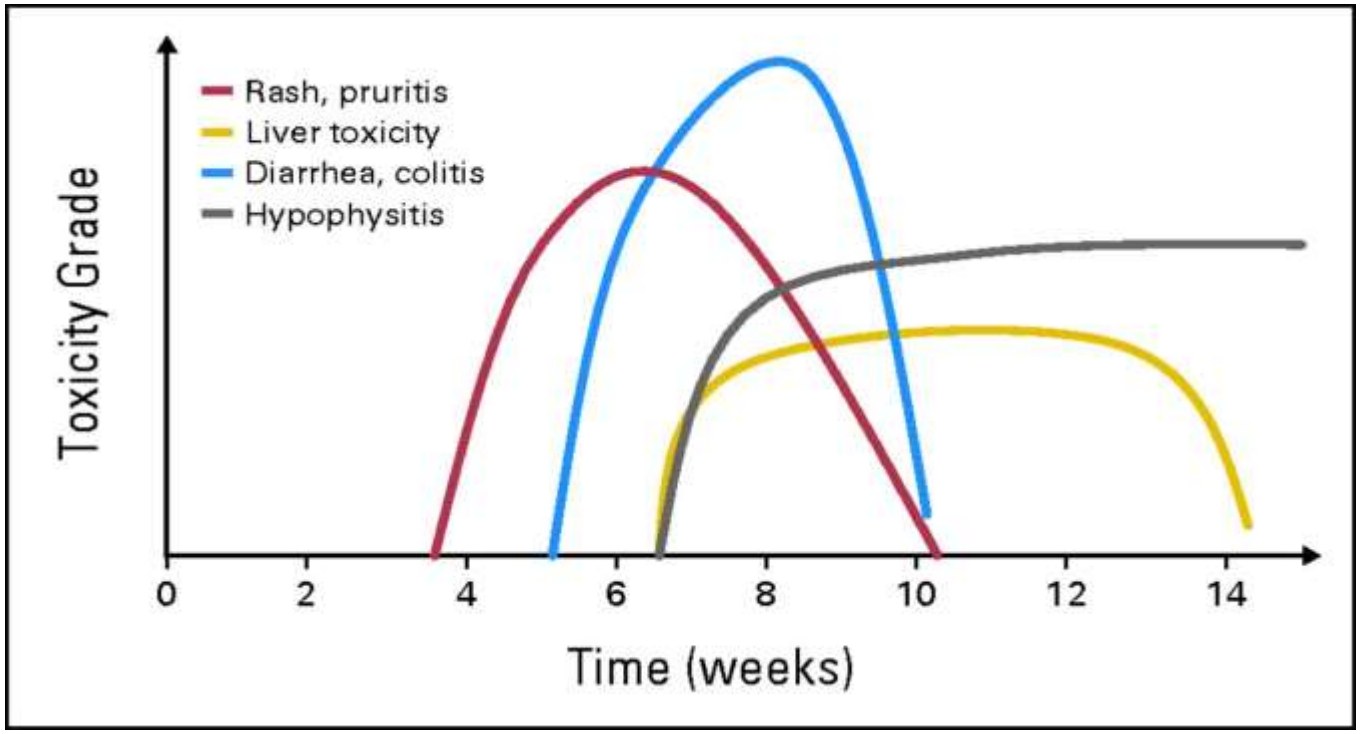
Chen TW et al. Ann Oncol 2015

Hodi FS et al N Engl J Med. 2010 Aug 19;363(8):711-23; Robert C et al NEJM 364(26):2517-2526 June 30, 2011; Ribas A et al JCO 2013; 31(5):616-622; Topalian SL et al JCO 2014; 32(10):1020-1030; Wolchok JD et al NEJM 2013; 369:122-33; Hamid O et al NEJM 2013; 369:134-44

Kinetics of appearance of immune-related adverse event under Ipilimumab:

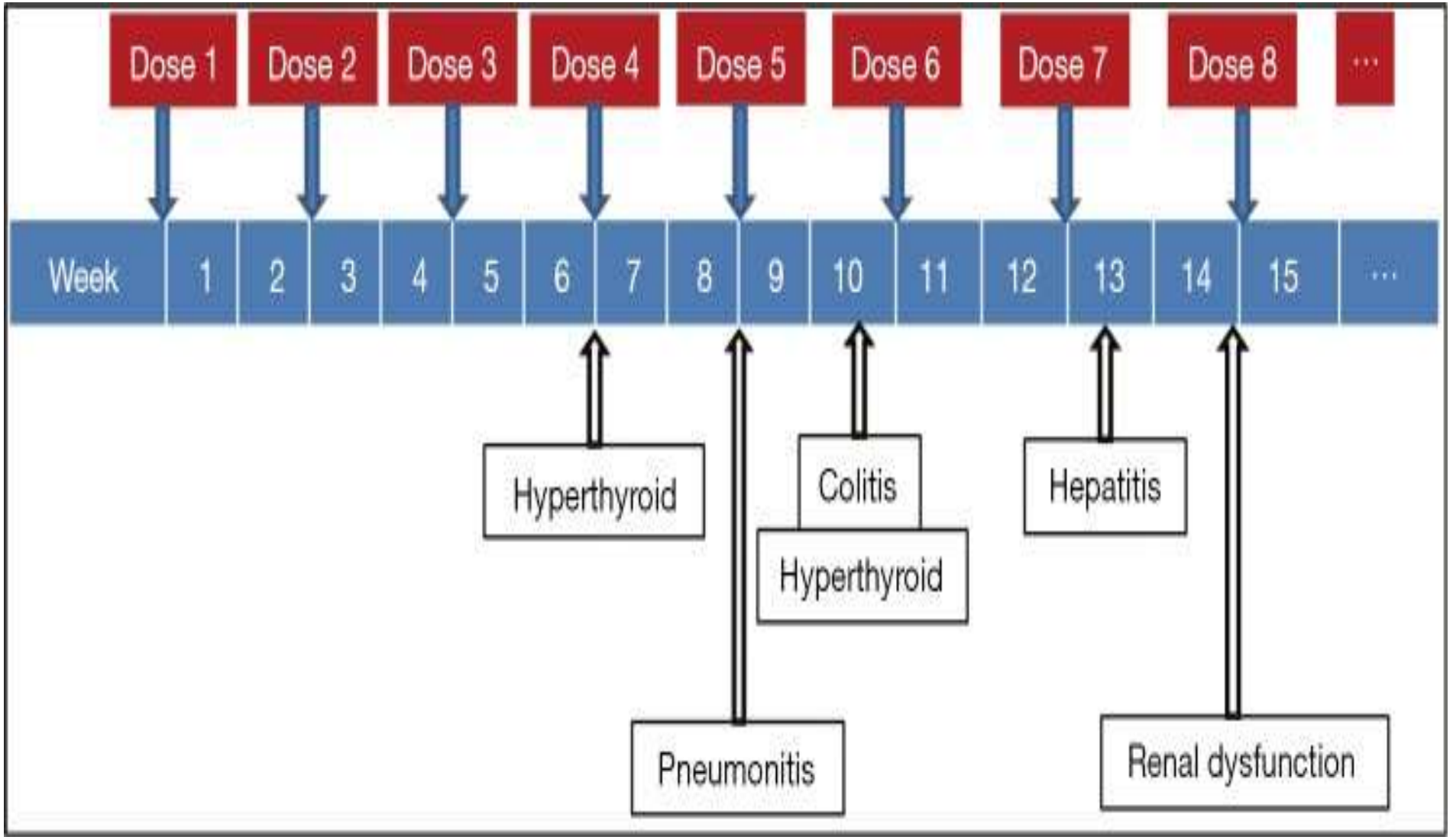
Type of Immune-Related Adverse Event	Median Time to Onset, wk	Median Time From Onset to Resolution, wk
Skin	3	5
Hepatic	3-9	0.7-2.0
Gastrointestinal reactions	8	4
Endocrine	7-20	NR

Abbreviations: NR, not reported.



Weber JS et al. JCO 2012;30:2691-2697; Weber JS et al. Cancer 2013; 119:1675-82

Kinetics of appearance of immune-related adverse event under Nivolumab (in CA209-037):



Villadolid j et al Trans Lung Cancer Res 2015 4 (5):560-75
Weber JS et al. Lancet Oncol 2015;16:375-84

Immune-related adverse event under anti-PD1 and anti-PDL1 antibodies:

- Recent Review by Naidoo et al.:
  - in general, toxicities with anti-PD1/PDL1 mAbs less common and less severe in comparison with anti-CTLA-4 mAbs
  - grade 3-4 ranging from 7-12% with single agent anti-PD1/PDL1 vs 10-18% with single agent anti-CTLA-4

Table 1. Adverse events in selected single-agent studies with anti-PD-1/PD-L1 antibodies

Agent	First author (year)	Phase	Tumor type	No. of patients receiving anti-PD-1/PD-L1 agent (*N*)	Therapy schedule	Treatment-related toxicities (grade 1–5)	Treatment-related grade 3–4 toxicities
Anti-PD-1 agent							
Nivolumab	Topalian (2012) [22]	I	NSCLC; RCC; CRC; CRPC; melanoma	296	0.1–10 mg/kg every 2 weeks for up to 2 years	Total: 70% ($n = 207$) Fatigue (24%, $n = 72$) Rash (12%, $n = 36$) Pruritus (10%, $n = 28$) Pneumonitis (9%, $n = 3$) Infusion reaction (9%, $n = 3$) Hypothyroidism (2%, $n = 7$)	Total: 7% ($n = 22$) Hypothyroidism (<1%, $n = 1$) Pneumonitis (1%, $n = 3$) Diarrhea (1%, $n = 3$) AST elevation (1%, $n = 2$) ALT elevation (1%, $n = 2$) Rash (1%, $n = 2$) Infusion reaction (<1%, $n = 1$)
	Ansell (2015) [7]	I	Hodgkin's lymphoma	23	3 mg/kg every 2 weeks	Total: 78% ($n = 18$) Rash (22%, $n = 5$) Thrombocytopenia (17%, $n = 4$) Fatigue (13%, $n = 3$) Pyrexia (13%, $n = 3$)	Total: 22% ($n = 5$) Lipase elevation (4%, $n = 1$) Lymphopenia (4%, $n = 1$) MDS[a] (4%, $n = 1$) Pancreatitis (4%, $n = 1$)
	Motzer (2014) [5]	II	RCC	168	0.3, 2, or 10 mg/kg every 2 weeks	Total: 73% ($n = 122$) Fatigue (27%, $n = 45$) Rash (10%, $n = 17$) Pruritus (10%, $n = 16$) Hypothyroidism (12%, $n = 10$) AST elevation (5%, $n = 8$) ALT elevation (4%, $n = 7$) Pneumonitis (3%, $n = 5$)	Total: 11% ($n = 19$) AST elevation (2%, $n = 3$) ALT elevation (2%, $n = 3$) Nausea (1%, $n = 2$) Hypothyroidism (<1%, $n = 1$) Pruritus (<1%, $n = 1$) Arthralgia (<1%, $n = 1$)
	Sampson (2014) [23]	I	GBM	20 ($n = 10$ single-agent arm)	Single-agent arm: 3 mg/kg every 2 weeks	Total: 60% ($n = 6$) Fatigue (30%, $n = 3$) Nausea (30%, $n = 3$)	Total: 0%
	El-Khoueiry (2015) [8]	I/II	HCC	47	0.1–10 mg/kg every 2 weeks	Total = 68% ($n = 32$) AST elevation (19%, $n = 9$) Lipase elevation (17%, $n = 8$) Rash (17%, $n = 8$) Amylase elevation (15%, $n = 7$) ALT elevation (15%, $n = 7$)	Total = 19% ($n = 9$) AST elevation (11%, $n = 5$) ALT elevation (9%, $n = 4$) Lipase elevation (9%, $n = 4$) Fatigue (2%, $n = 1$) Anemia (2%, $n = 1$)
	Gettinger (2015) [24]	I	NSCLC	129	1, 3, or 10 mg/kg every 2 weeks	Total = 71% ($n = 91$) Fatigue (24%, $n = 31$) Decreased appetite (12%, $n = 16$) Diarrhea (10%, $n = 13$) Pyrexia (6%, $n = 8$) Pruritus (9%, $n = 11$) Pneumonitis (6%, $n = 8$)	Total = 14% ($n = 18$) Fatigue (3%, $n = 4$) Pneumonitis (2%, $n = 3$) Low CD-4 cells (2%, $n = 3$) Diarrhea (<1%, $n = 1$)

Continued

Naidoo J et al. Ann Oncol 2015; 26(12):2375-91
Weber JS et al JCO 2015: 33:2092-2099

Common Terminology Criteria for Adverse Events (CTCAE)

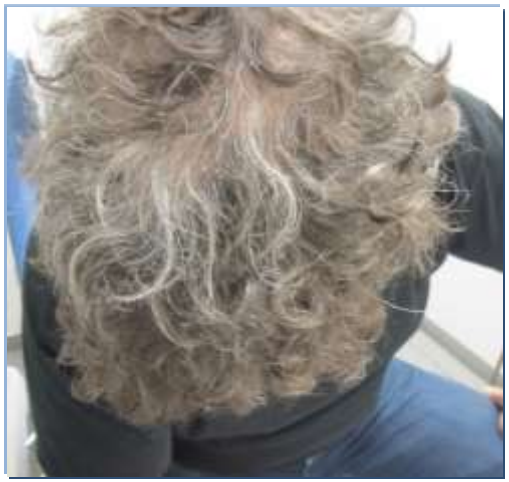
Version 4.0

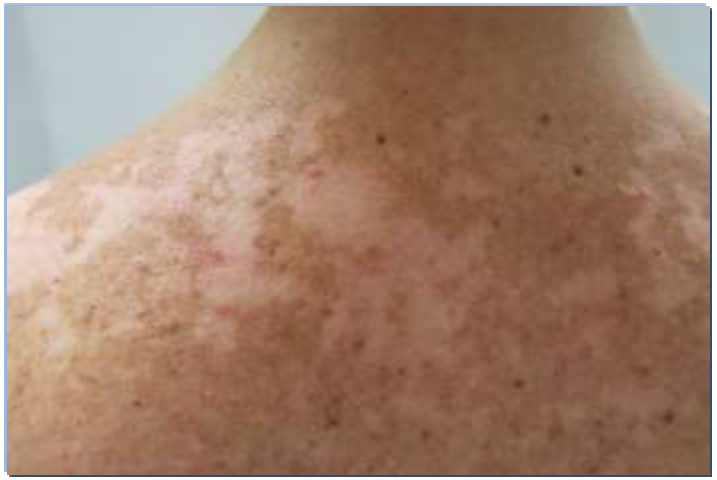
Published: May 28, 2009 (v4.03: June 14, 2010)

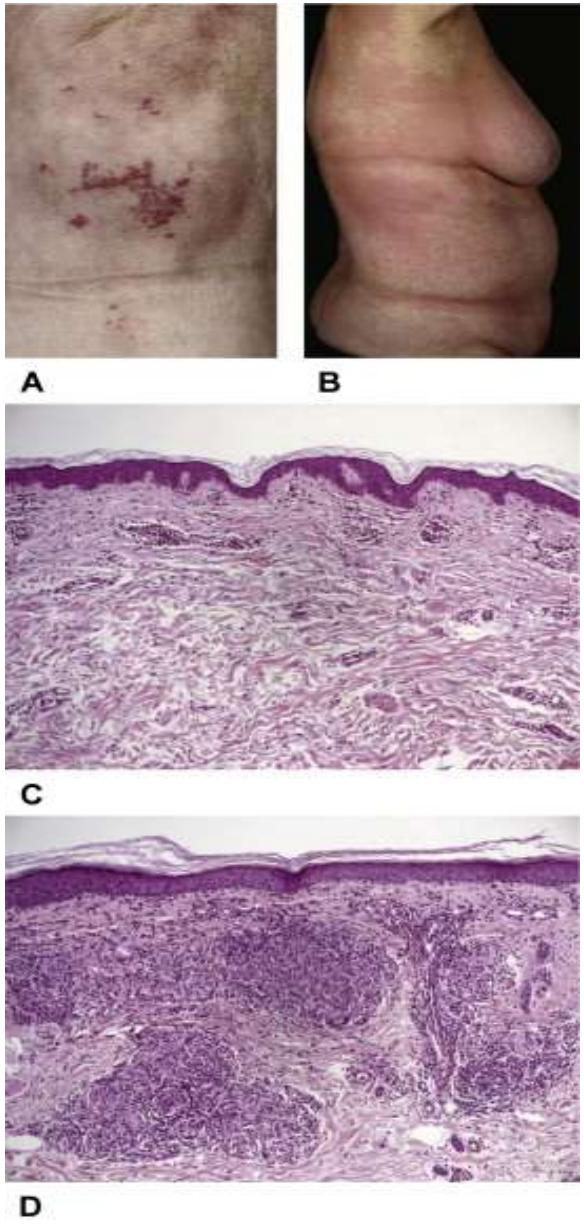
U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Skin toxicity

- In 47-68% of pts receiving ipilimumab, observed after an average of 3.6 weeks, in 34% with nivolumab and 39% with pembrolizumab, typically after 2nd course
- Diffuse, maculopapular rash, with pruritus
- Histopathology: perivascular lymphocytic infiltrate extending deep into the dermis and up to epidermis
- CD4+ and CD8+ T cells in close proximity to apoptotic melanocytes → ~**10% vitiligo with Pembrolizumab**
- Managed symptomatically (topical or oral steroids), rarely require skipping a dose or discontinuation
- BUT: rare cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported with Ipi, eventually resulting in death

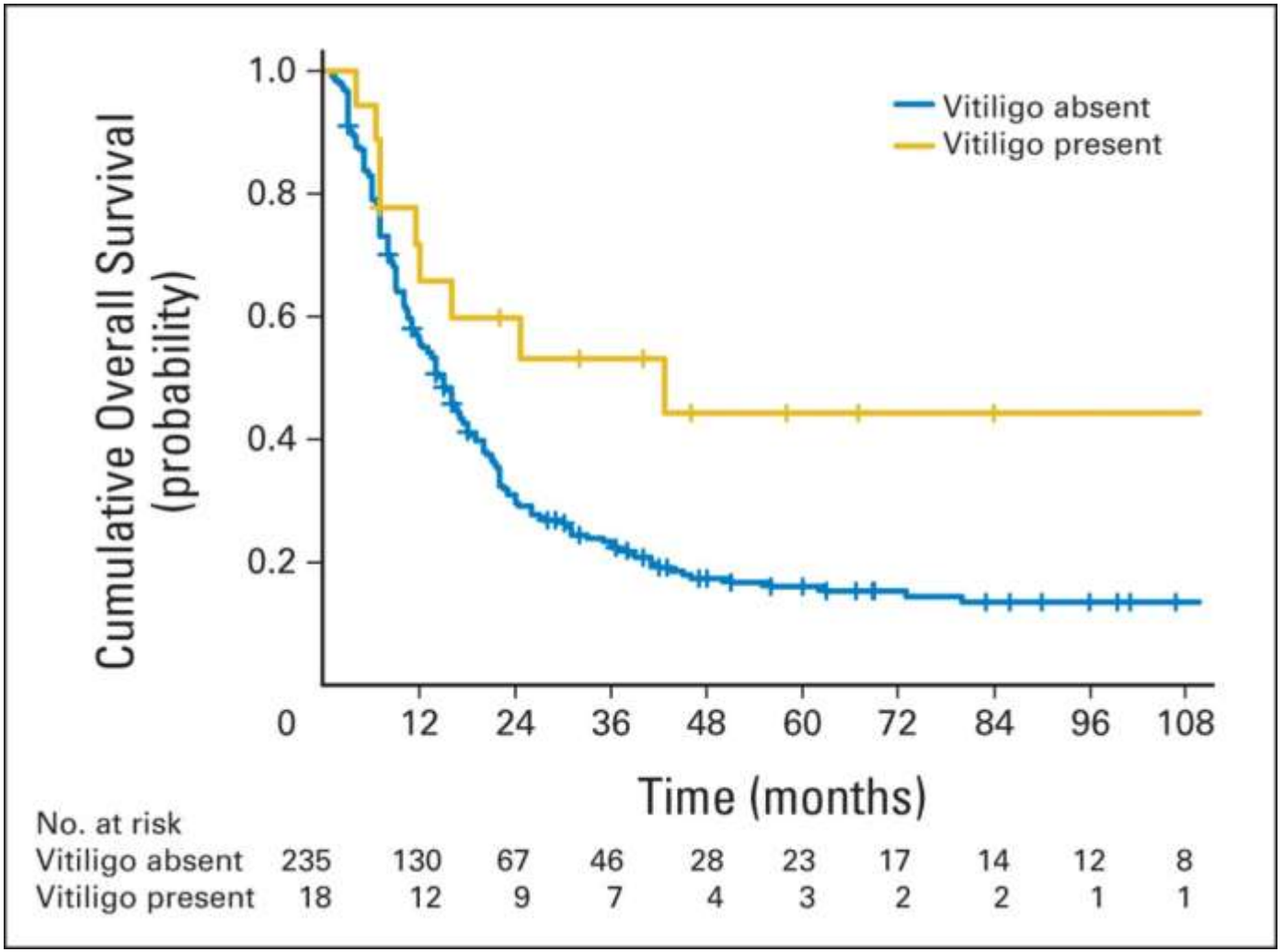






Weber J S et al. JCO 2012;30:2691-2697
Minkis K et al JAAD 2013; 69:e121-8
Lacouture M et al JAAD 2014, epub
Naidoo J et al. Ann Oncol 2015; 26(12):2375-91

Overall survival in 253 patients receiving immunotherapy from 15 studies.



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

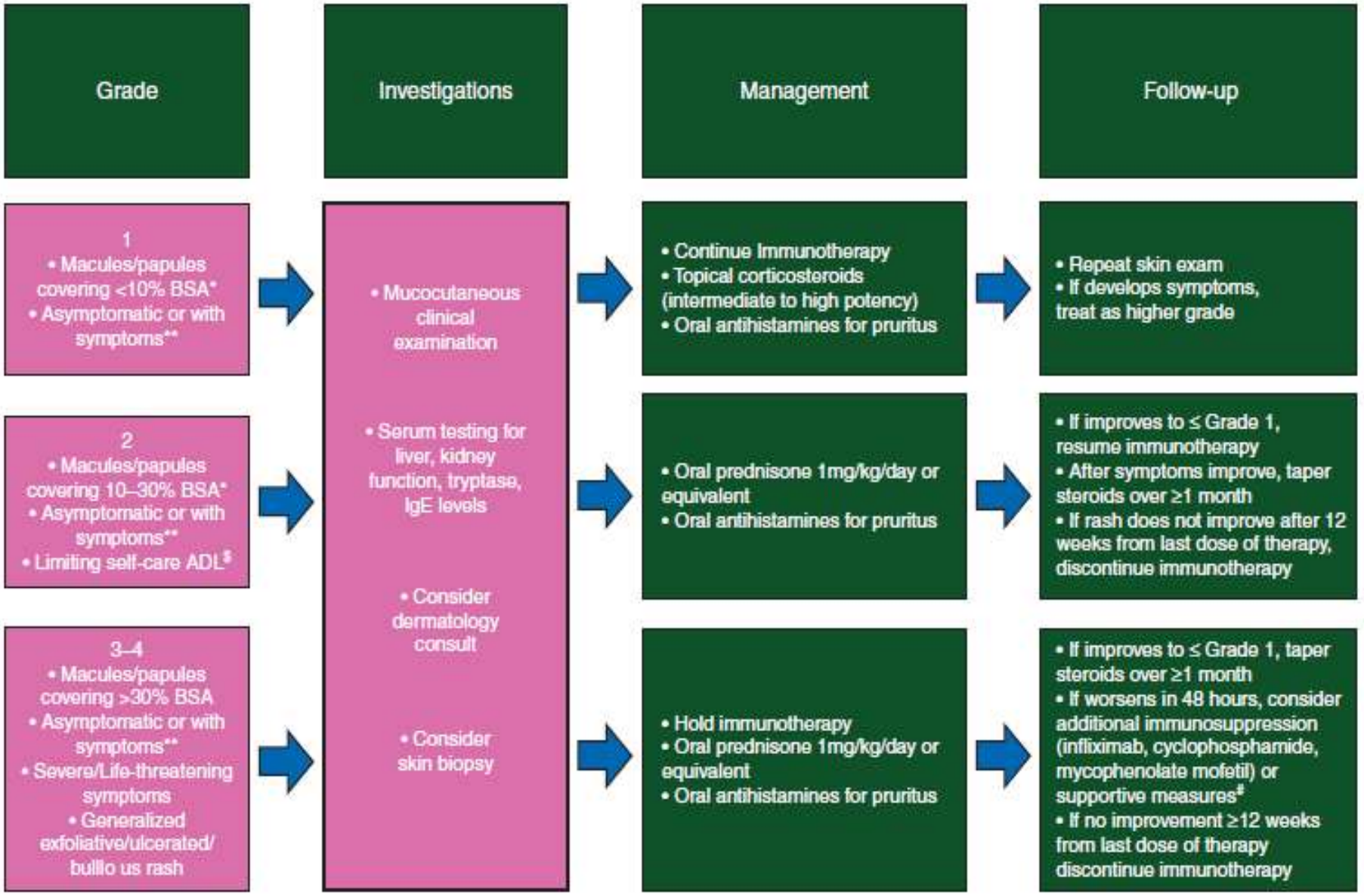


Figure 1. Adapted management algorithm for skin rash with immune checkpoint blockade. *BSA, body surface area, **Symptoms as per CTCAE version 4.0. For example: pruritus, burning and skin tightness. $Additional supportive measures: this denotes the use of, for example, prophylatic antibiotics and management in the burns unit.

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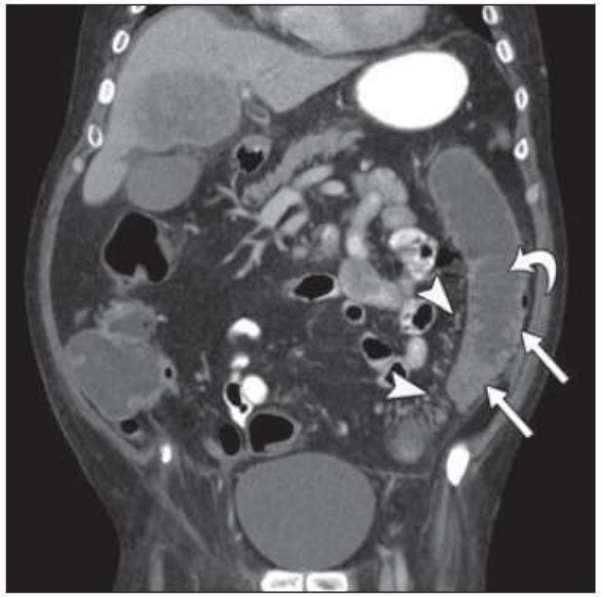
Gastrointestinal side-effects:

- Diarrhea in up to 44% of pts receiving ipilimumab, grade 3/4 in 18% with 10 mg/kg; 6-8 weeks after start, only 1-3% with anti-PD1/PDL1
- Can be associated with colitis, leading to obstruction and bowel perforation
- Predominantly descending colon
- Histopathology: neutrophilic infiltrates in 46%, lymphocytic infiltrates in 15%, mixed in 38%
- Managed symptomatically according algorithm (methylprednisolone 1-2 mg/kg, eventually infliximab 5mg/kg)
- BUT: rare cases of perforation resulting in death have been reported with Ipi → early intervention key!



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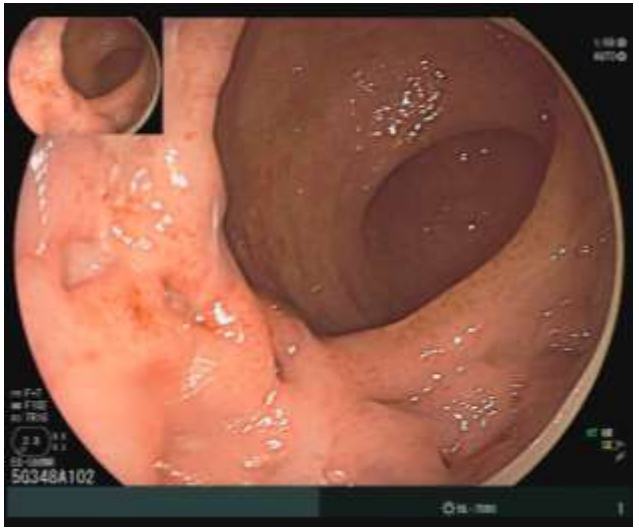


Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by frequent and watery bowel movements.

Weber J S et al. JCO 2012;30:2691-2697
Kim KW et al AJR 2013
Naidoo J et al. Ann Oncol 2015; 26(12):2375-91

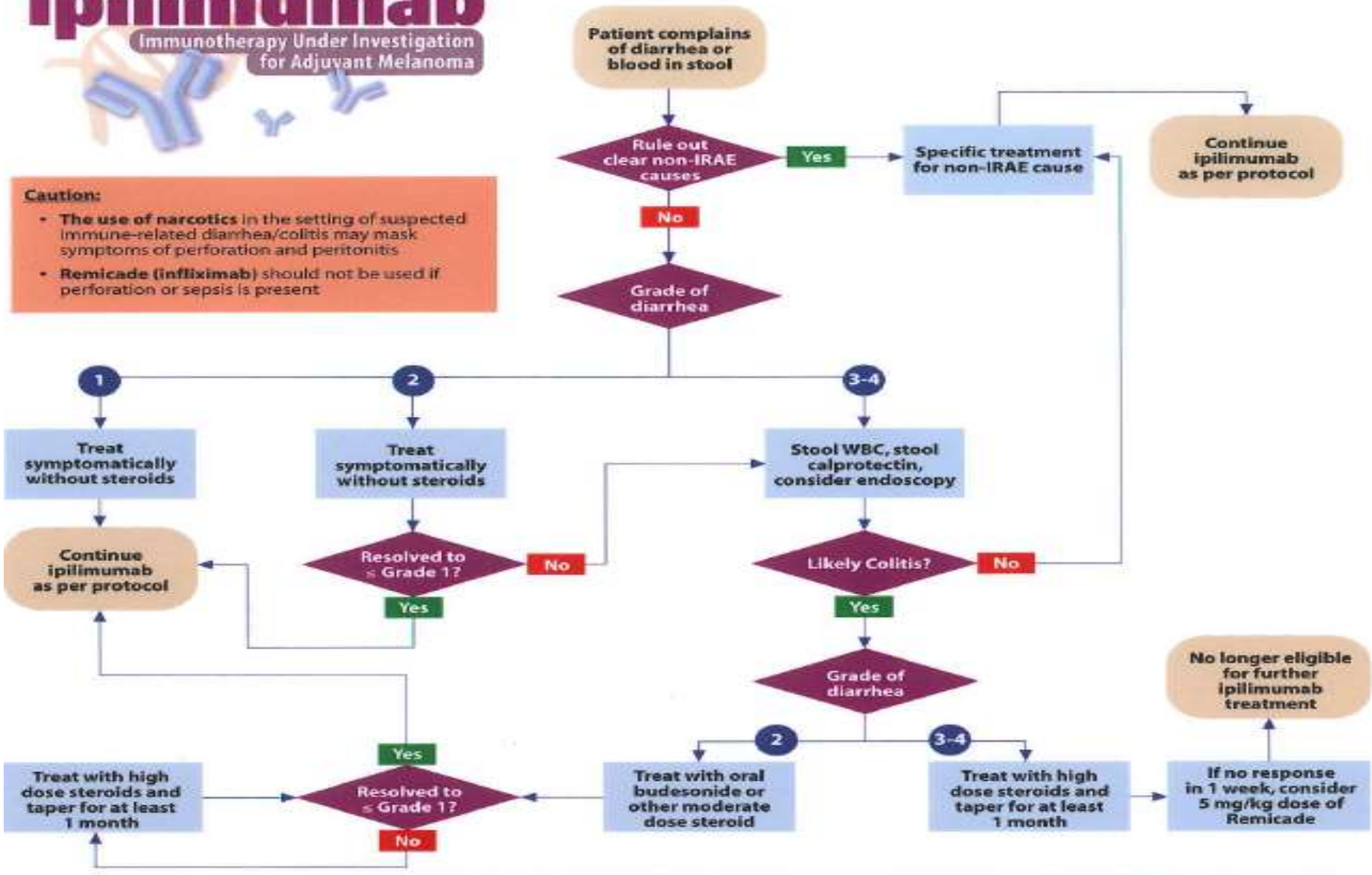
ipilimumab

Immunotherapy Under Investigation for Adjuvant Melanoma

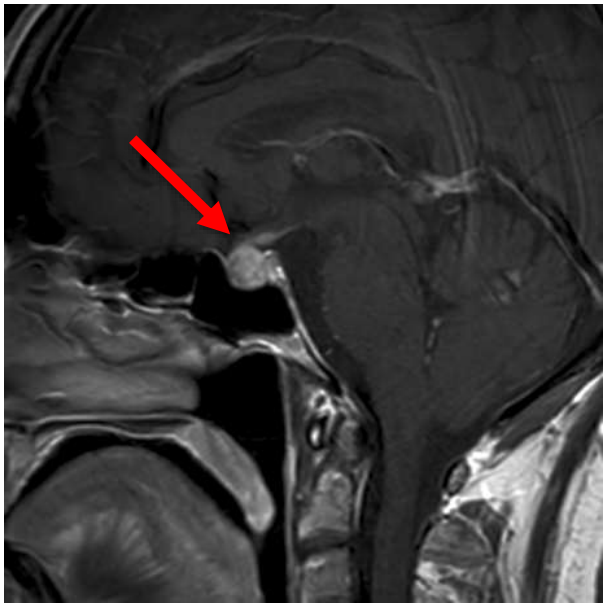
Diarrhea Management Algorithm

Caution:

- **The use of narcotics** in the setting of suspected immune-related diarrhea/colitis may mask symptoms of perforation and peritonitis
- **Remicade (infliximab)** should not be used if perforation or sepsis is present



Endocrine side-effects:

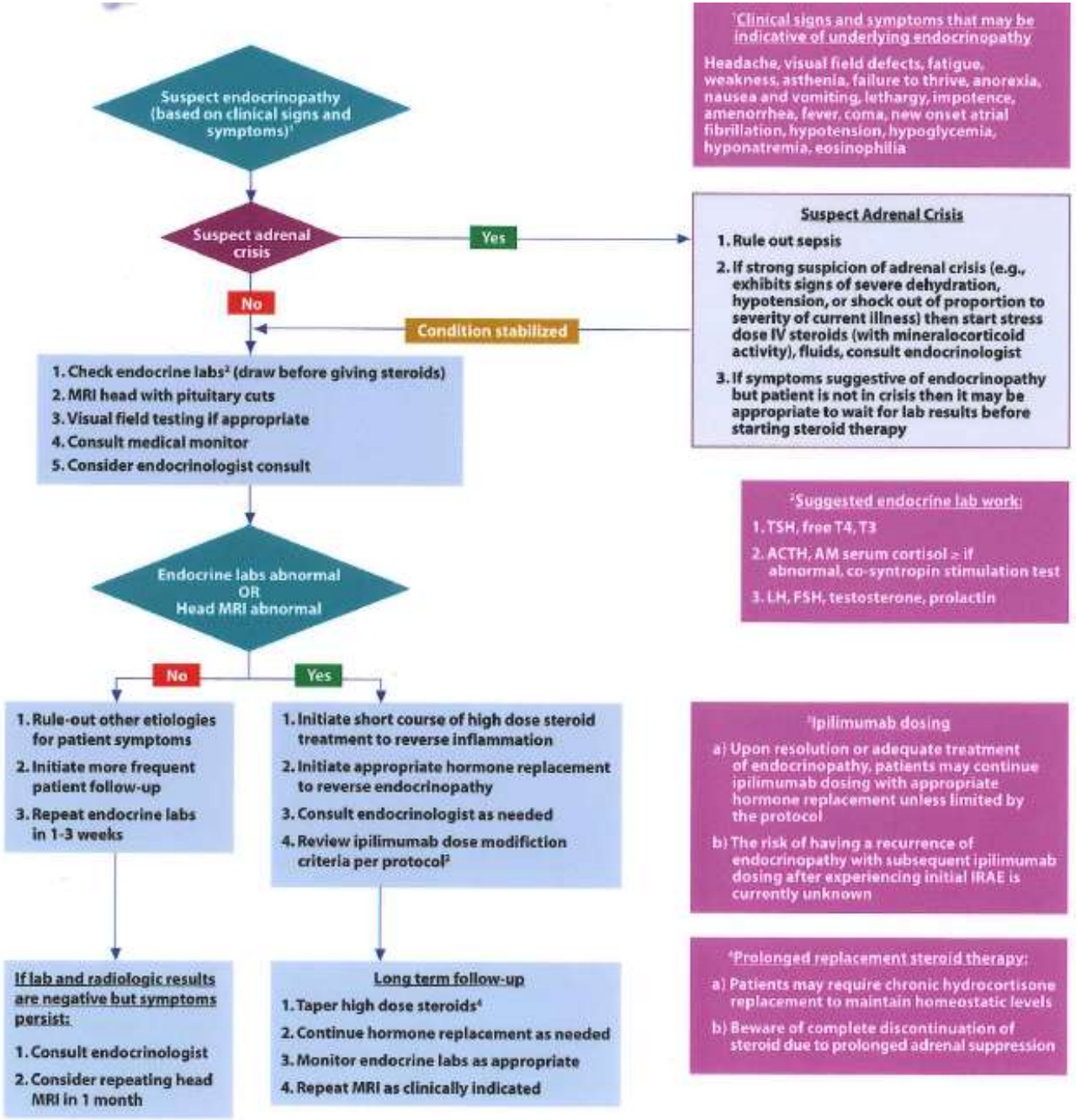


- Immune-related hypophysitis in 1-6% of patients treated with 3 or 10 mg/kg ipilimumab, 1-6% with anti-PD1/PDL1, recovery in 37-50%
- Problem: nonspecific symptoms such as headache, nausea, vertigo, behavior change, visual disturbances and weakness occur at an average of 6 weeks after initiation of therapy with Ipi
- MRI can show enlargement or heterogeneity of the pituitary
- Before treatment: determine pituitary, thyroid, adrenal and gonadal status
- Before each dose: thyroid function tests and biochemistry profile, including mineral electrolyte, and hepatic functions
- Median time to resolution of symptoms and the substitution of physiologic doses of hydrocortisone can be longer than 20 weeks with Ipi
- Also possible: isolated thyroid dysfunction (hypothyroidism and/ or thyreotoxicosis) or adrenal insufficiency
- As most endocrinopathies can be treated with hormone replacement, discontinuation usually not needed

Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

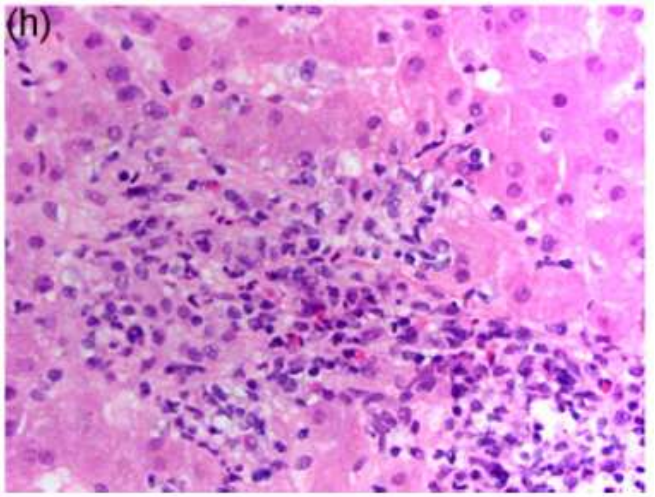
Definition: A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland.

Weber J S et al. JCO 2012;30:2691-2697 Corsello SM et al JCEM 2013; 98(4):1361-1375 Torino F et al 2013 Eur J Endocrinol 169 R153-164; Naidoo J et al. Ann Oncol 2015; 26(12):2375-91


Suspect endocrinopathy (based on clinical signs and symptoms)[1]
Suspect adrenal crisis
Yes
No
Condition stabilized
1. Check endocrine labs[2] (draw before giving steroids)
2. MRI head with pituitary cuts
3. Visual field testing if appropriate
4. Consult medical monitor
5. Consider endocrinologist consult
Endocrine labs abnormal OR Head MRI abnormal
No
Yes
1. Rule-out other etiologies for patient symptoms
2. Initiate more frequent patient follow-up
3. Repeat endocrine labs in 1-3 weeks
If lab and radiologic results are negative but symptoms persist:
1. Consult endocrinologist
2. Consider repeating head MRI in 1 month
1. Initiate short course of high dose steroid treatment to reverse inflammation
2. Initiate appropriate hormone replacement to reverse endocrinopathy
3. Consult endocrinologist as needed
4. Review ipilimumab dose modifiction criteria per protocol[3]
Long term follow-up
1. Taper high dose steroids[4]
2. Continue hormone replacement as needed
3. Monitor endocrine labs as appropriate
4. Repeat MRI as clinically indicated
[1]Clinical signs and symptoms that may be indicative of underlying endocrinopathy
Headache, visual field defects, fatigue, weakness, asthenia, failure to thrive, anorexia, nausea and vomiting, lethargy, impotence, amenorrhea, fever, coma, new onset atrial fibrillation, hypotension, hypoglycemia, hyponatremia, eosinophilia
Suspect Adrenal Crisis
1. Rule out sepsis
2. If strong suspicion of adrenal crisis (e.g., exhibits signs of severe dehydration, hypotension, or shock out of proportion to severity of current illness) then start stress dose IV steroids (with mineralocorticoid activity), fluids, consult endocrinologist
3. If symptoms suggestive of endocrinopathy but patient is not in crisis then it may be appropriate to wait for lab results before starting steroid therapy
[2]Suggested endocrine lab work:
1. TSH, free T4, T3
2. ACTH, AM serum cortisol ± if abnormal, co-syntropin stimulation test
3. LH, FSH, testosterone, prolactin
[3]Ipilimumab dosing
a) Upon resolution or adequate treatment of endocrinopathy, patients may continue ipilimumab dosing with appropriate hormone replacement unless limited by the protocol
b) The risk of having a recurrence of endocrinopathy with subsequent ipilimumab dosing after experiencing initial IRAE is currently unknown
[4]Prolonged replacement steroid therapy:
a) Patients may require chronic hydrocortisone replacement to maintain homeostatic levels
b) Beware of complete discontinuation of steroid due to prolonged adrenal suppression
CL-BDS017A 04/08

Hepatotoxicity:

- Has been observed in 3-9% patients treated with ipilimumab, <5% with anti-PD1/PDL1, higher in HCC pts.; in combi with Ipi and other targeted agents or chemotherapy → significant rate of hepatotoxicity with Ipi/DTIC and Ipi/vemurafenib
- With Ipi ~8-12 weeks after starting therapy
- Usually asymptomatic increase of transaminases and bilirubin
- Rule out viral hepatitis, disease progression or other drug-related causes
- Liver function tests before treatment and before each dose, every three months thereafter
- Median time to resolution 0.7-2 weeks with Ipi



Histopathology: diffuse T-cell infiltrate consistent with immune-related hepatitis

Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.				
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.				
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.				
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.				

Weber J S et al. JCO 2012;30:2691-2697

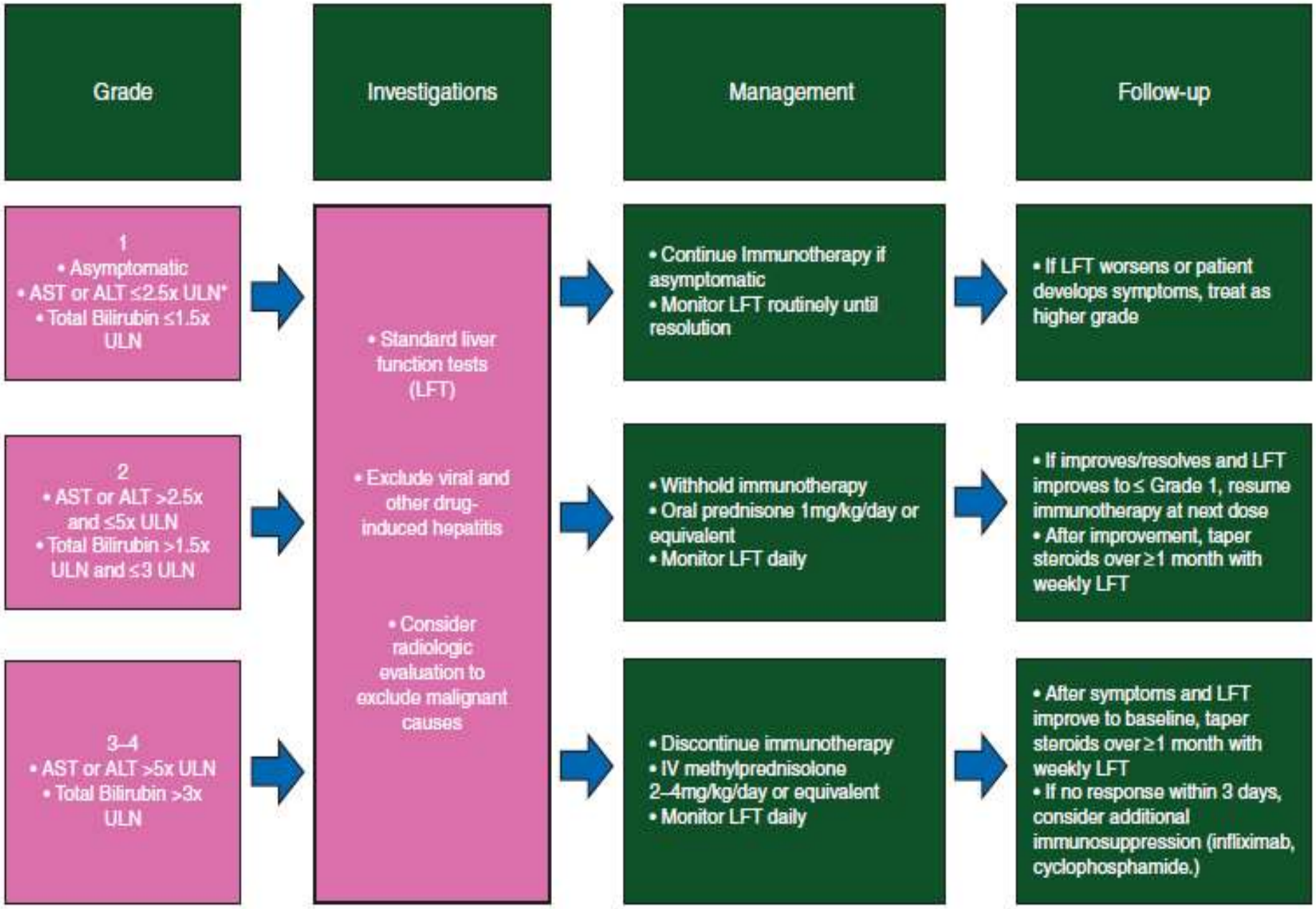


Figure 2. Adapted management algorithm for hepatitis with immune checkpoint blockade. *ULN, upper limit of normal.

Naidoo J et al. Ann Oncol 2015; 26(12):2375-91

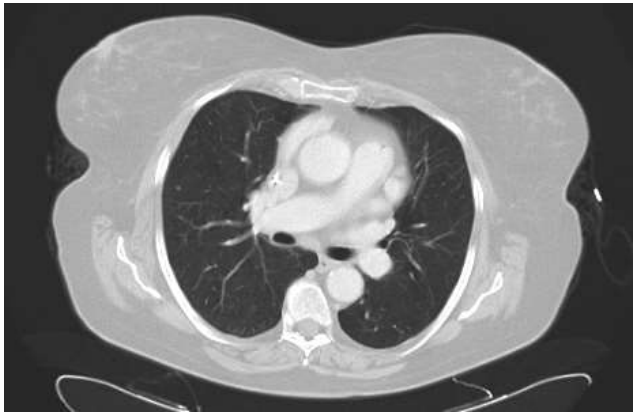
Pneumonitis:

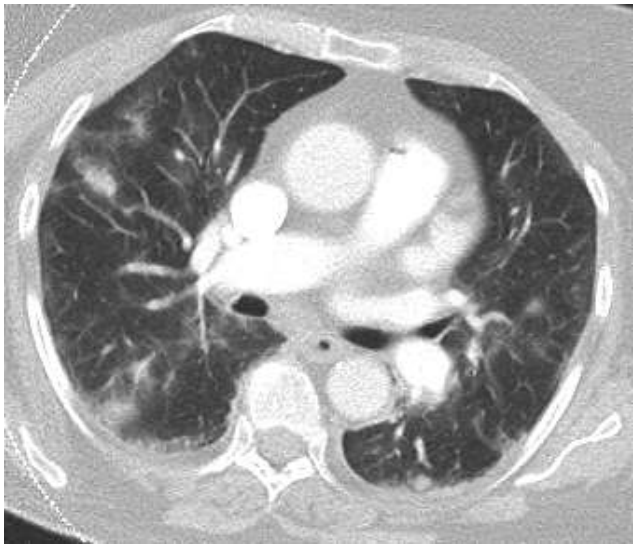
- In <10% with anti-PD1/PDL1, higher in NSCLC pts.; 3 treatment related deaths in ph. 1 nivolumab studies, most likely less with Ipi alone
- With Ipi more sarcoid-like granulomatous reactions → CAVE: enlarged LN under Ipi → if possible take a biopsy!
- Timing of development wide range (between 7,4 and 24,3 months after start therapy)
- Usually shortness of breath, cough, fever or chest pain, can also be asymptomatic
- Rule out infectious diseases, disease progression or other drug-related causes
- High resolution CT and bronchoscopy indicated, eventually lung function testing
- Severe cases require hospitalization and intravenous corticosteroids, sometimes infiliximab or mycophenolate mofetil

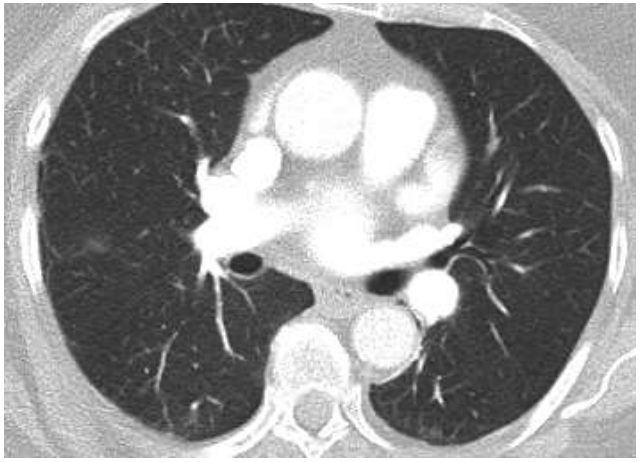
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death

Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.

Weber J S et al. JCO 2012;30:2691-2697
Naidoo J et al. Ann Oncol 2015; 26(12):2375-91

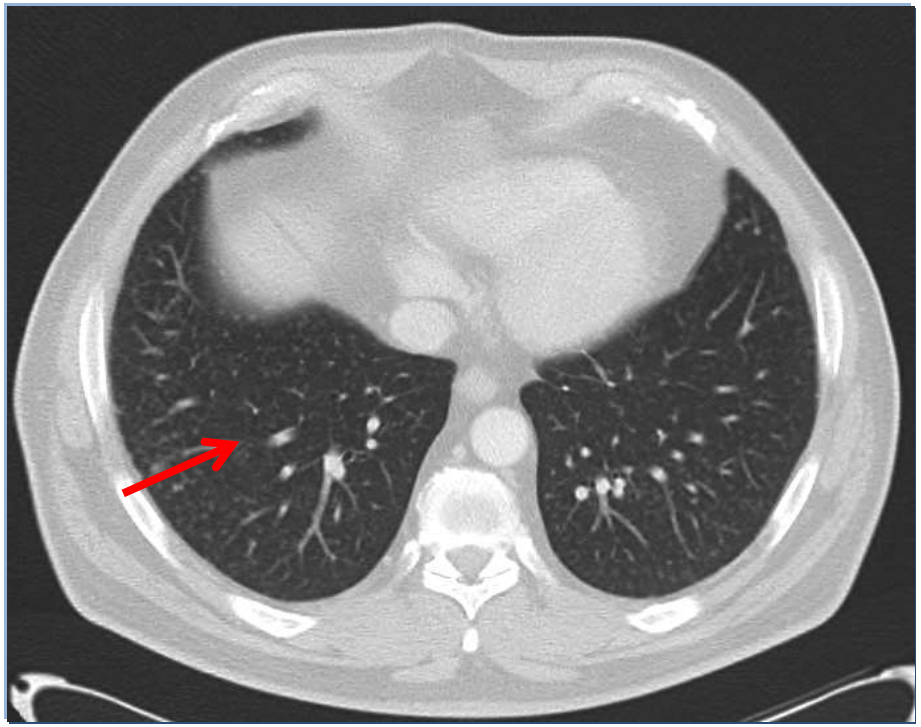


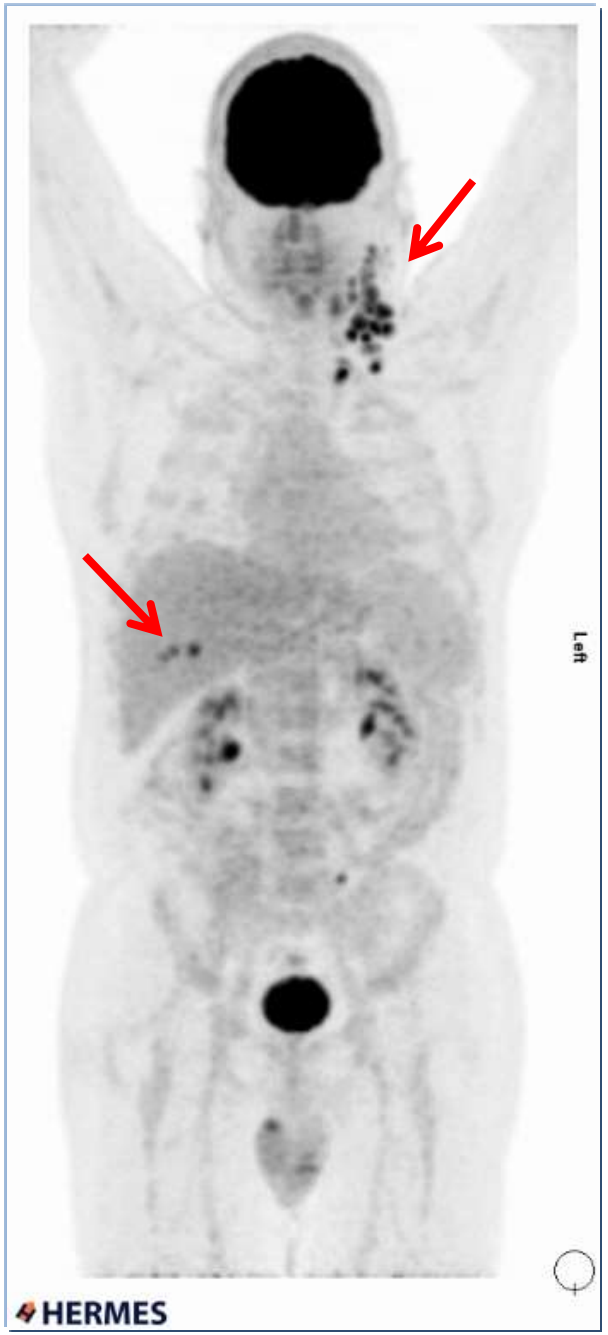




Case 1:

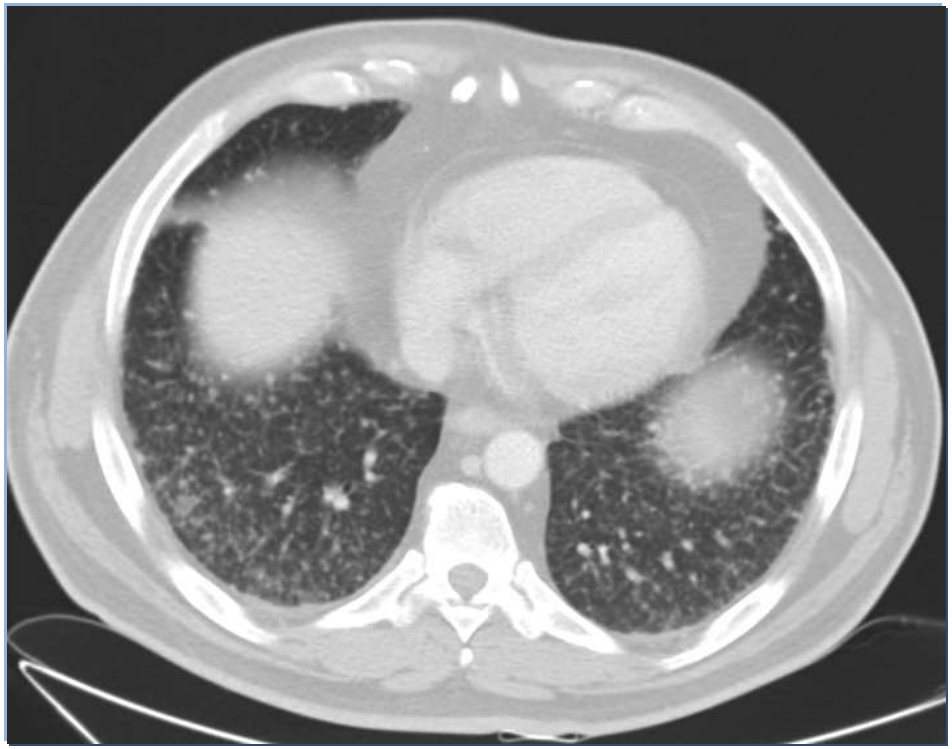
- 07-2006 (♂, * 1971): excision of nodular melanoma of the left ear, Clark level IV, Breslow 1.56 mm without ulceration
- 09-2013: diagnosis of metastasis to lymph nodes and galbladder, suspicion of lung metasasis
- 18-10-2013: inclusion CHECKMATE 067 study (comparison of Ipilimumab/placebo vs Nivolumab/placebo vs Ipilimumab/Nivolumab.



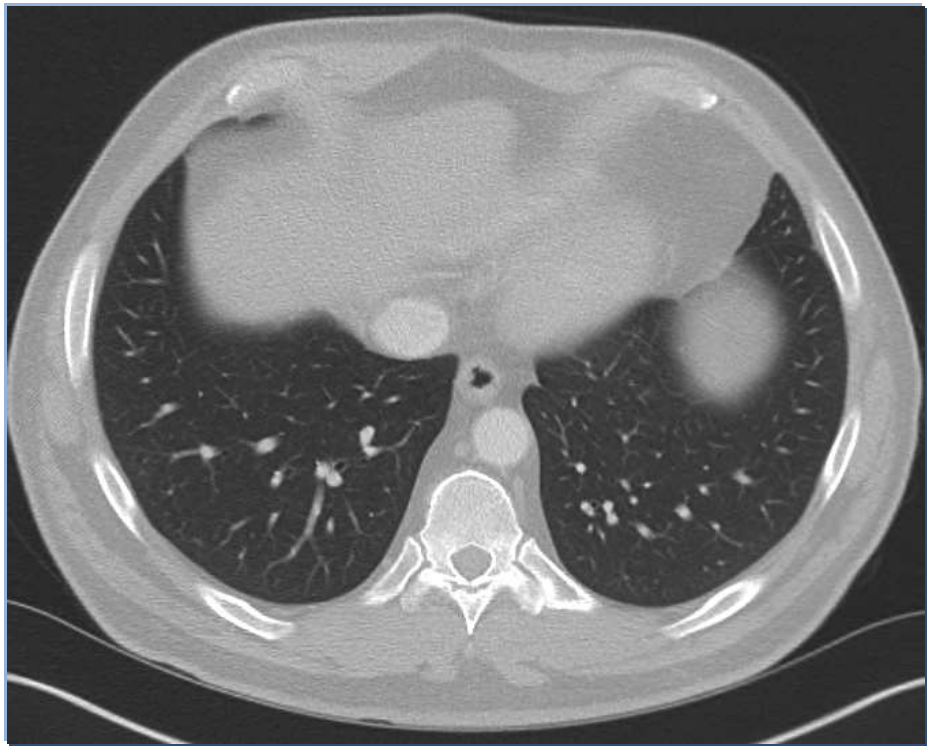


Case 1:

- 31-10-2013: shortly after first infusion development of dry cough, skin rash and subfebrilitas, on high resolution CT of the chest massive disease progression with new miliary lung metastasis (dd: pseudoprogression, dd: pneumonitis)



31-10-2013



10-01-2014

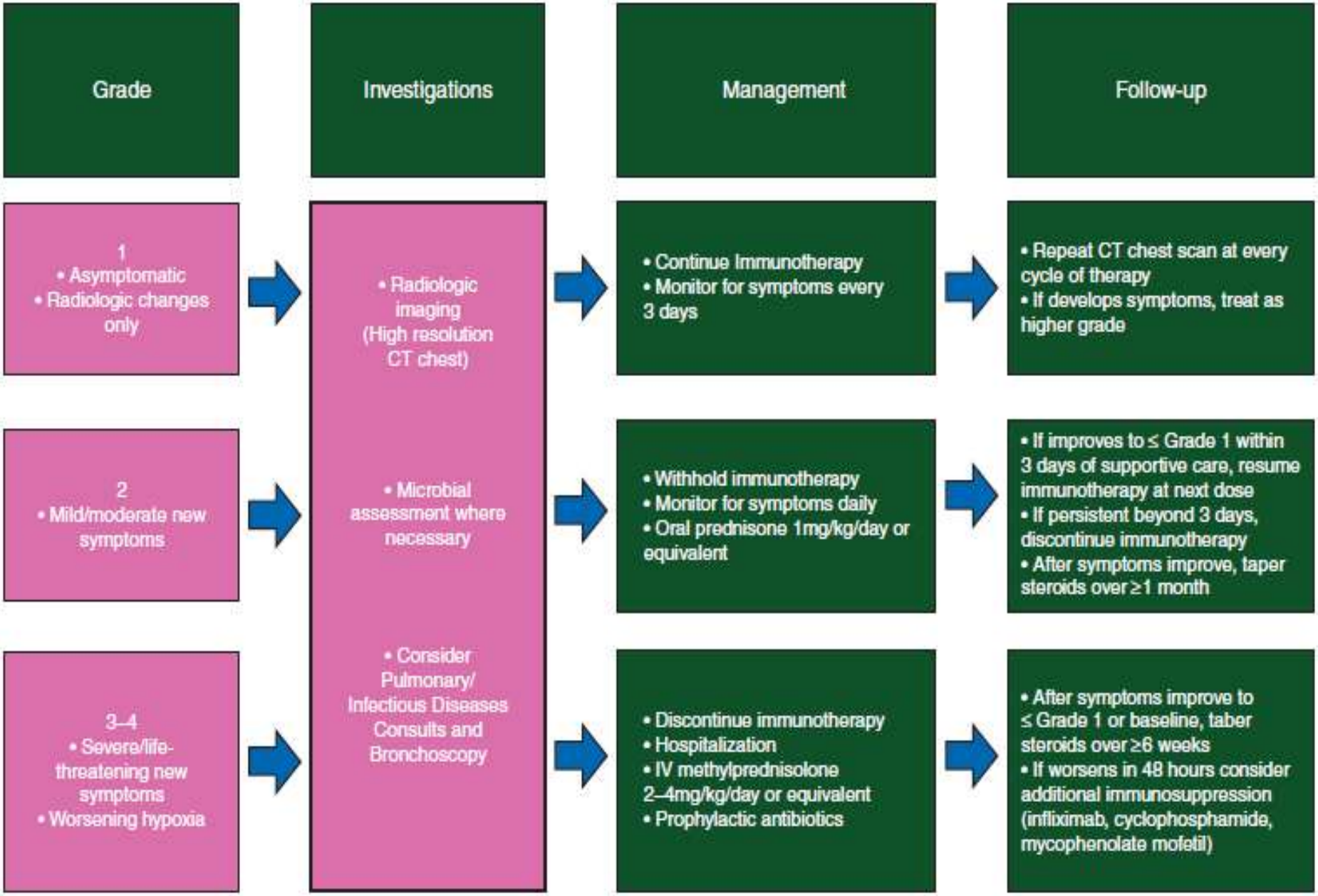


Figure 3. Adapted management algorithm for pneumonitis with immune checkpoint blockade.

Naidoo J et al. Ann Oncol 2015; 26(12):2375-91

Other immune related adverse effects:

- Renal toxicity (tubolointerstitial nephritis)
- Pancreatitis (can be monitored without immunosuppressive therapy → asymptomatic elevated lipase do not discontinuation!)
- Neuropathy (Guillain-Barré syndrome, Myasthenia gravis-like syndrome, enteric neuropathy, aseptic meningitis)
- Sarcoid-like syndrome
- Episcleritis /Uveitis
- Others: hemophilia A, DRESS (drug rash with eosinophilia and systemic symptoms),

Neurological Toxicity Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.
Discontinue ipilimumab for any grade 3-4 motor neuropathy, regardless of relationship.

Severity of neurological toxicity	Management	Follow-up
Grade 1	• Continue ipilimumab	Continue monitoring the patient. If symptoms worsen, treat as below.
Grade 2	• Hold/delay ipilimumab • Treat symptoms per local guidelines	Resume ipilimumab when resolved / grade 1 If symptoms worsen, treat as below.
Grade 3-4 sensory	• Discontinue ipilmumab if considered related • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g., 1-2 mg/kg/ day methylprednisolone)	**Symptoms resolve / return to grade 2:** • Taper steroids over at least 1 month
Grade 3-4 motor	• Discontinue ipilimumab **regardless of relationship** • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g., 1-2 mg/kg/ day methylprednisolone)	**Symptoms resolve / return to grade 2:** • Taper steroids over at least 1 month **Symptoms do not resolve or progress; atypical presention:** • Consider IVIg or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose 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 PO corticosteroids.

Ask patients if they are experiencing any of the following symptoms:

Consider potential toxicity and contact provider:

- diarrhea
- abdominal pain/cramping
- nausea/vomiting
- changes in bowel movements
- blood in stool

→ GI

- rash
- itch
- changes to color of skin

→ Dermatologic

- weakness in hands and feet
- difficulty standing or walking
- tingling or numbness

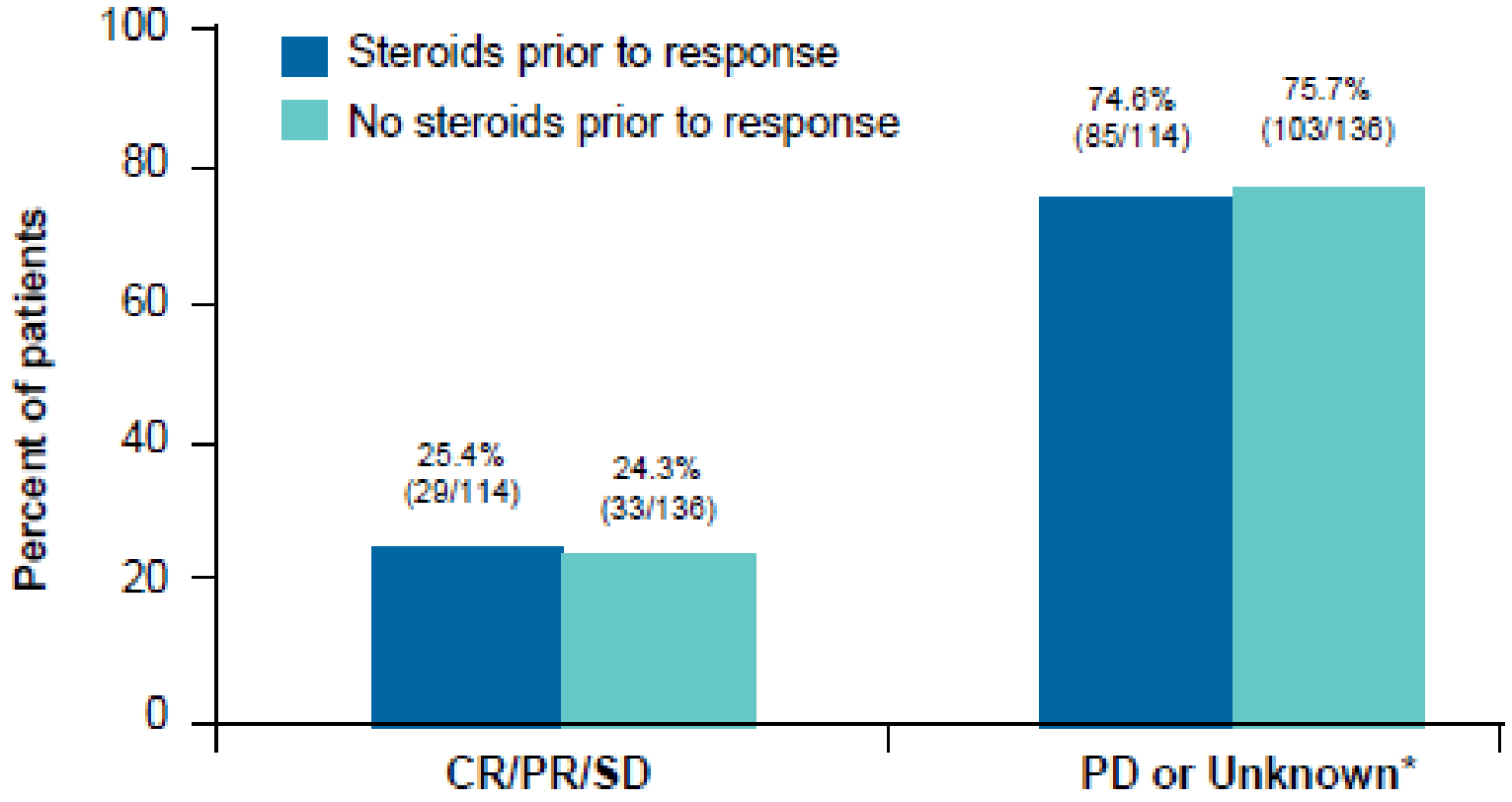
→ Neurologic

- fatigue
- headache
- unusual bowel habits
- cognitive problems

→ Endocrine

General symptoms that may require follow-up:
fever, vision changes, difficulty sleeping, changes in appetite, difficulty performing daily activities, respiratory distress, pain, coughing

Figure 2. Analyses of the impact of steroid use on ipilimumab responses

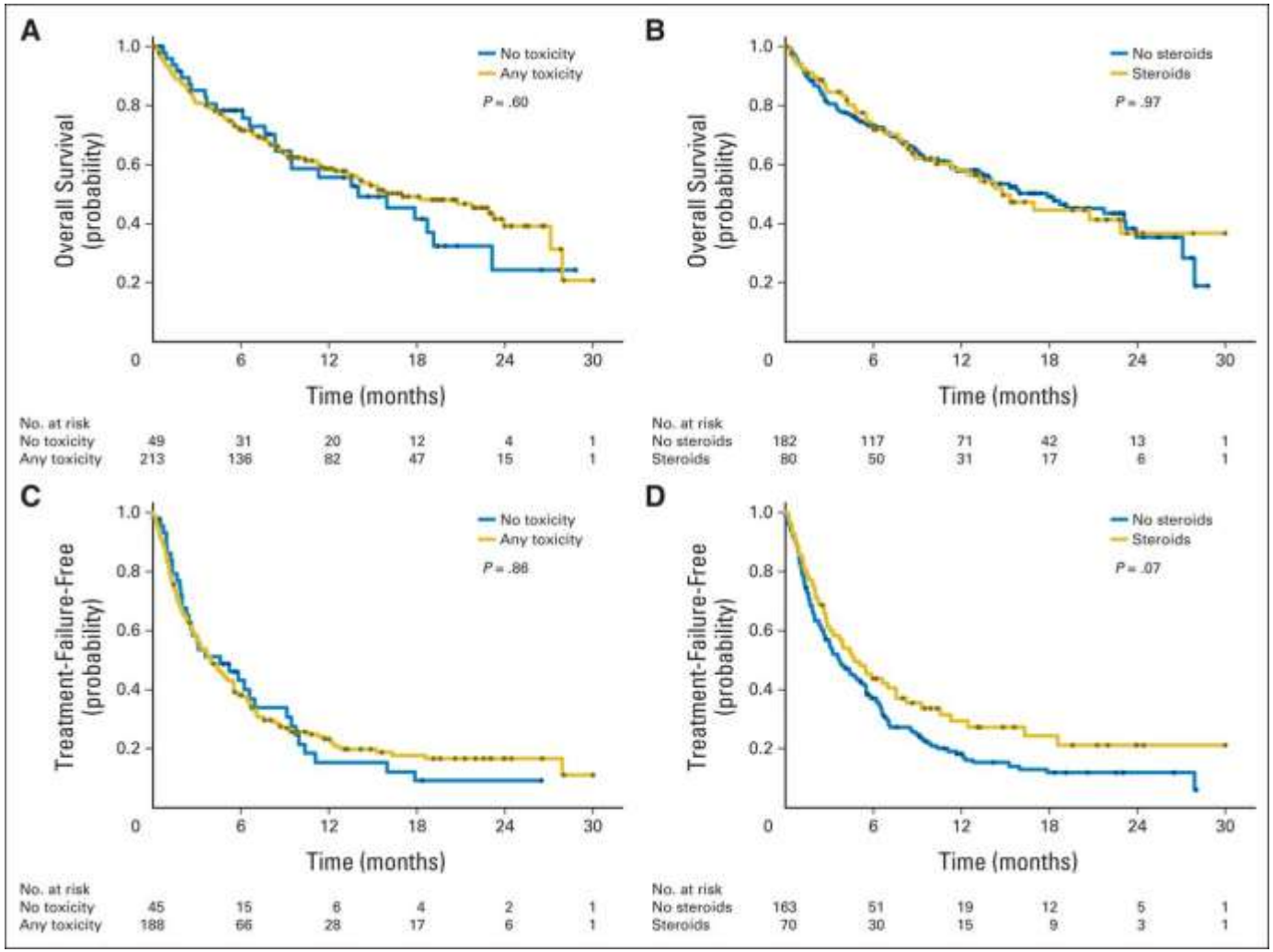


*Including patients who had SD followed by PD

CR= complete response; PR= partial response; SD= stable disease; PD= progressive disease

Baurain JF abstract 8539, ASCO 2012

Landmark of correlates of overall survival (OS) and time to treatment failure (TTF) in patients treated with ipilimumab.



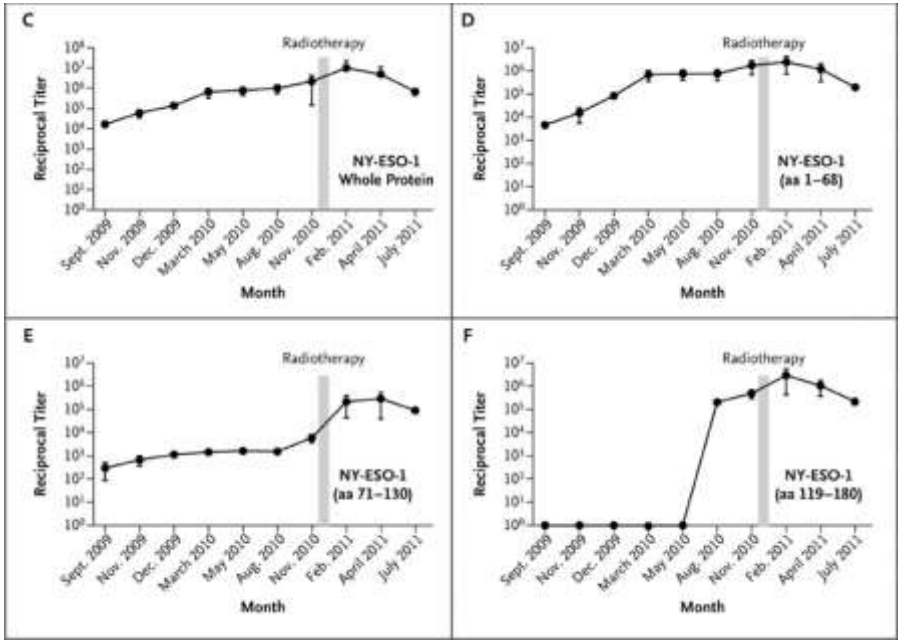
Troy Z. Horvat et al. JCO 2015;33:3193-3198

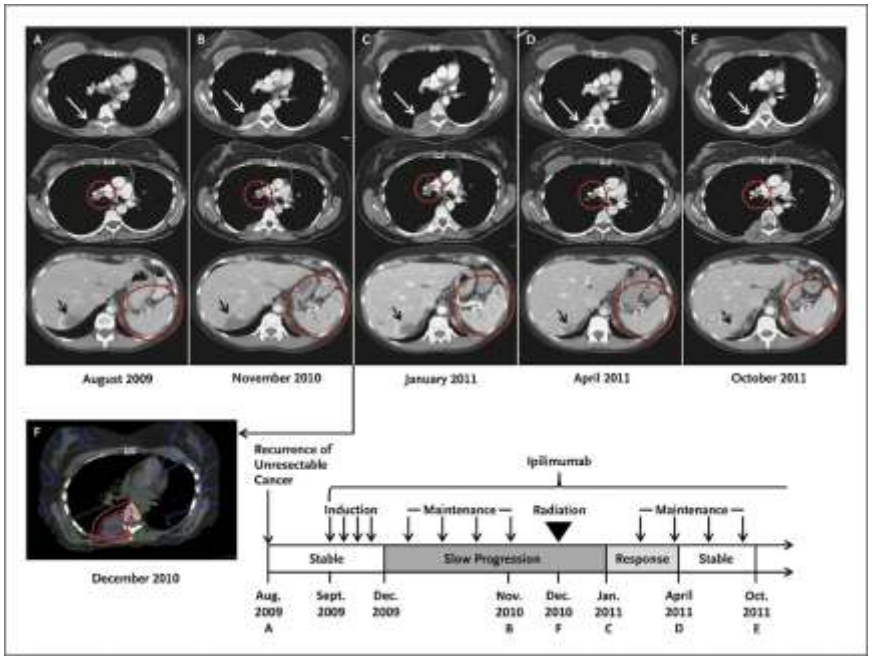
Specific situations:

- **Safety of pembrolizumab in pts who stopped Ipi due to irAEs, abstract e22023, ASCO 2015:** 10 pts with MM: “pts who stop ipi due to irAEs may have different irAEs emerge when receiving pembro; experiencing a severe irAE from ipi does not preclude a pt from subsequently receving pembro.
- **Toxicity of Ipi in pts progressing under anti-PD1, abstract 9059 at ASCO 2015:** 10 pts with MM, 1/10 of pts achieved a PR, 3/10 pts experienced grade3/4 immune related adverse events (irAE), CAVE: cases of severe and unusual irAEs (eg pneumonitis) observed!
- **Ipilimumab in MM pts with pre-existing auto-immune disorders, abstract 9019 at ASCO 2015:** Of 12 pts, 5 had baseline rheumatoid arthritis, 3 had psoriasis/psoriatic arthritis, 1 had systemic lupus erythematosus, 1 had Crohn’s disease, 1 had transverse myelitis, and 1 had sarcoidosis. Ten (83%) had previously received corticosteroids or other systemic therapy for their AD, including 5 ongoing at the time of Ipi initiation (low-dose prednisone in 2 pts and hydroxychloroquine in 3). Following Ipi, 6 pts (50%) had symptomatic worsening or flares of their AD; all resolved with short courses of corticosteroids and none required additional immune suppression. Grade 3-5 irAEs were observed in 5 pts (42%) including colitis (n = 2), hypophysitis (n = 2), and acute angle glaucoma (n = 1). One treatment-related death occurred, presumably from colitis and possibly hypophysitis (no laboratory confirmation) following dose 3 of Ipi. ORR was 17% (2/12 pts)

Ipilimumab and surgery / radiotherapy:

- **Abstract 8583: Surgery for patients receiving ipilimumab: Safety profile and immunological insights (Gyorki DE et al):**
  - Surgery is safe in patients receiving ipi. Immune modulation caused by CTLA-4 blockade does not appear to impact wound healing, even in the bowel. In carefully selected patients metastectomy may be appropriate for breakthrough metastases. The high percentage of T regulatory cells and low T effector cells in the progressive tumors suggests a mechanism of immune escape.
- **See also: Immunologic correlates of the abscopal effect in a patient with melanoma (Postow MA et al. N Engl J Med 2012;366:925-931).**
  - Case report of the abscopal effect (= clearance of nonirradiated tumors after localized radiation therapy) in a patient with melanoma treated with ipilimumab and radiotherapy. Temporal associations were noted: tumor shrinkage with antibody responses to the cancer-testis antigen NY-ESO-1, changes in peripheral-blood immune cells, and increases in antibody responses to other antigens after radiotherapy.





Belgian Association of Dermato-Oncology

BADO

Disclosures of Potential Conflict of Interest:

Employment or leadership positions	Consultant or Advisory Role	Stock ownership	Honoraria	Research funding	Other remunenra-tion
no	No personal renumeration	no	no	Pfizer GSK Bayer Novartis	No travel grants

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Questions?