St. Nikolaus-Hospital
Eupen

CHR
VERVIERS
EAST BELGIUM

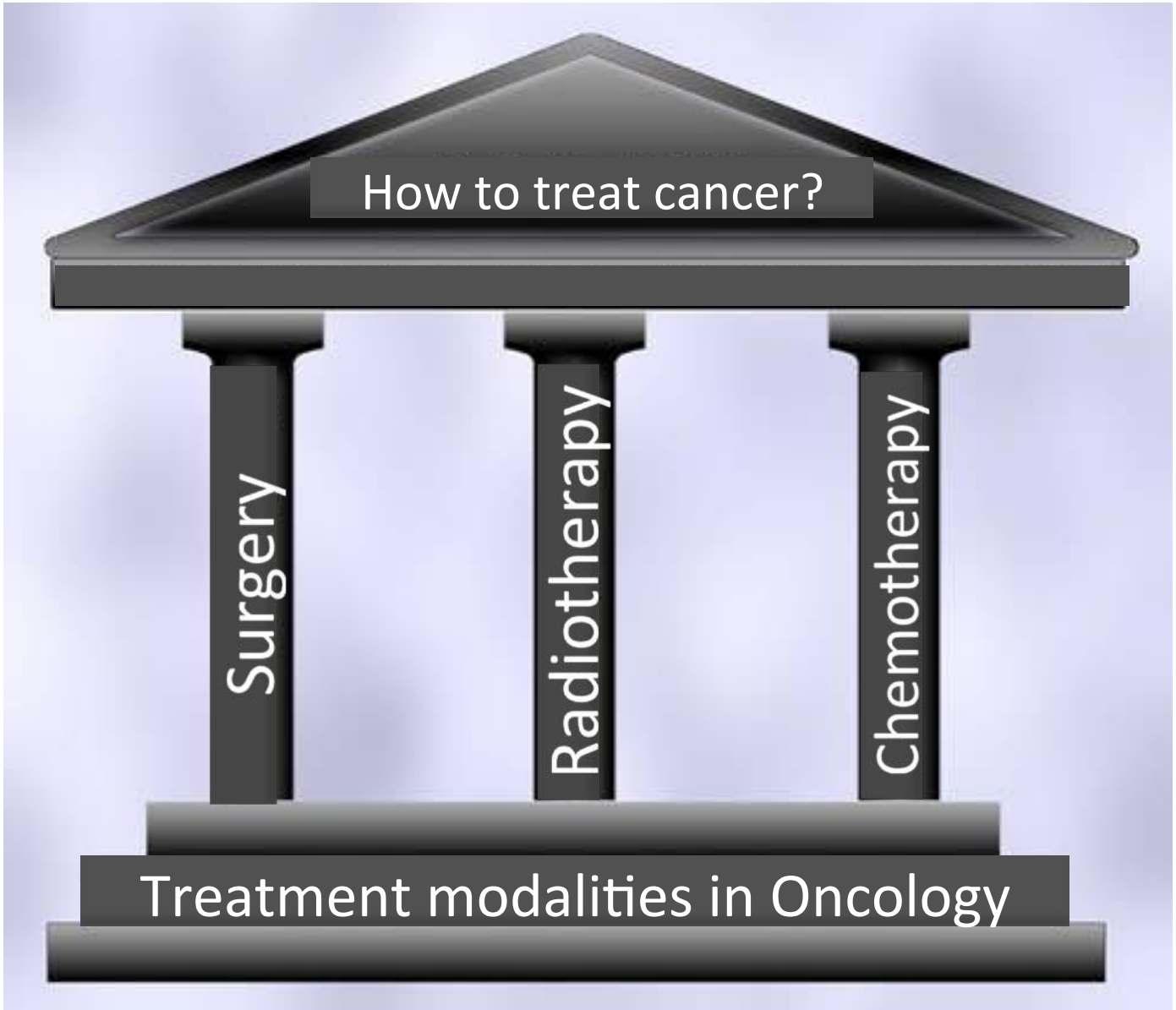
KLINIK ST.JOSEF
ST.VITH

Immunotherapie: hoe omgaan met de bijwerkingen, een praktische gids

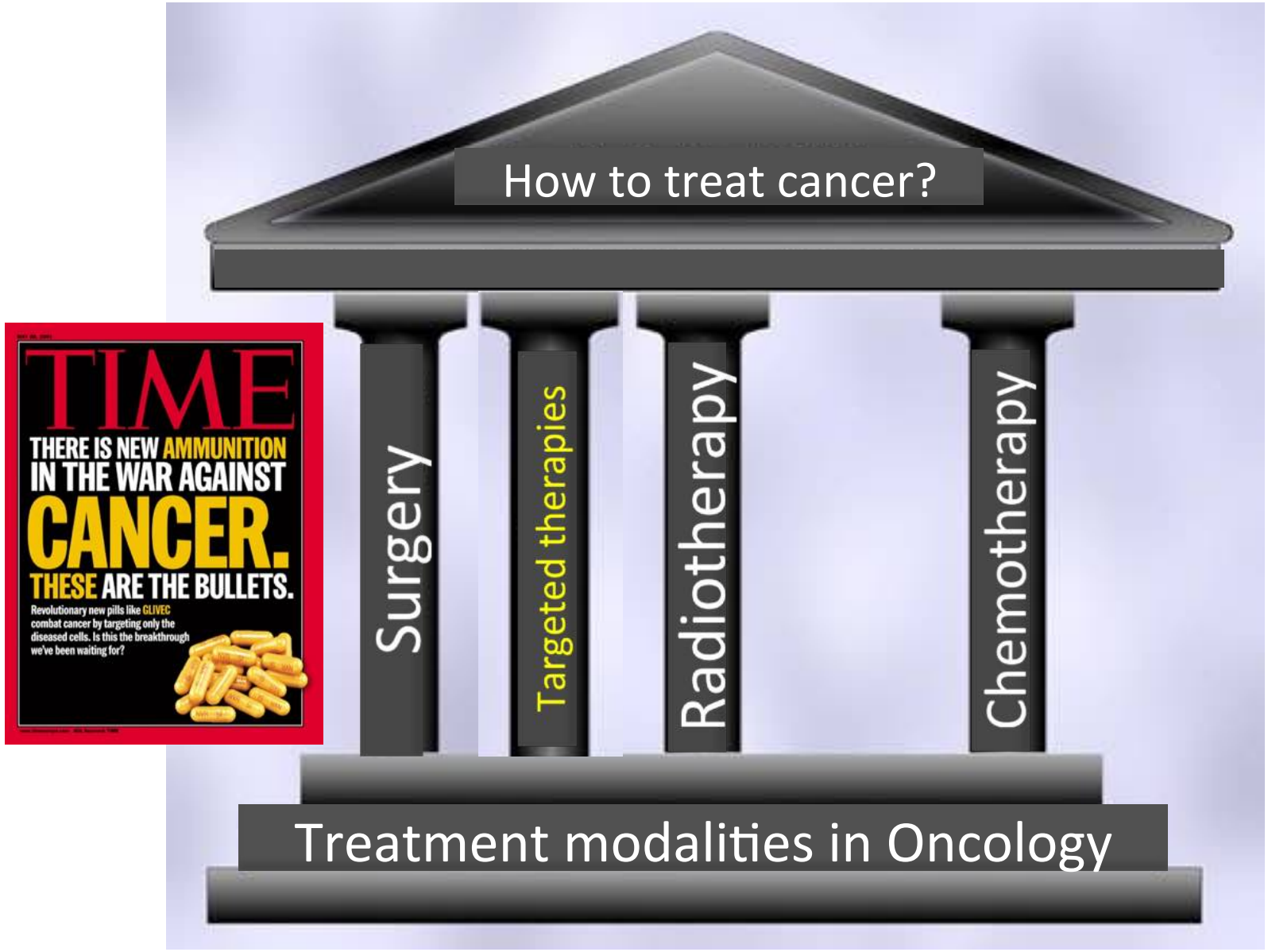
14de TOGA meeting, Antwerpen
14-10-2016

Dr. Pascal Wolter, M.D.
CHR Verviers

Treatment of cancer in the past:



Treatment of cancer in 2000:



Treatment of cancer in 2016:

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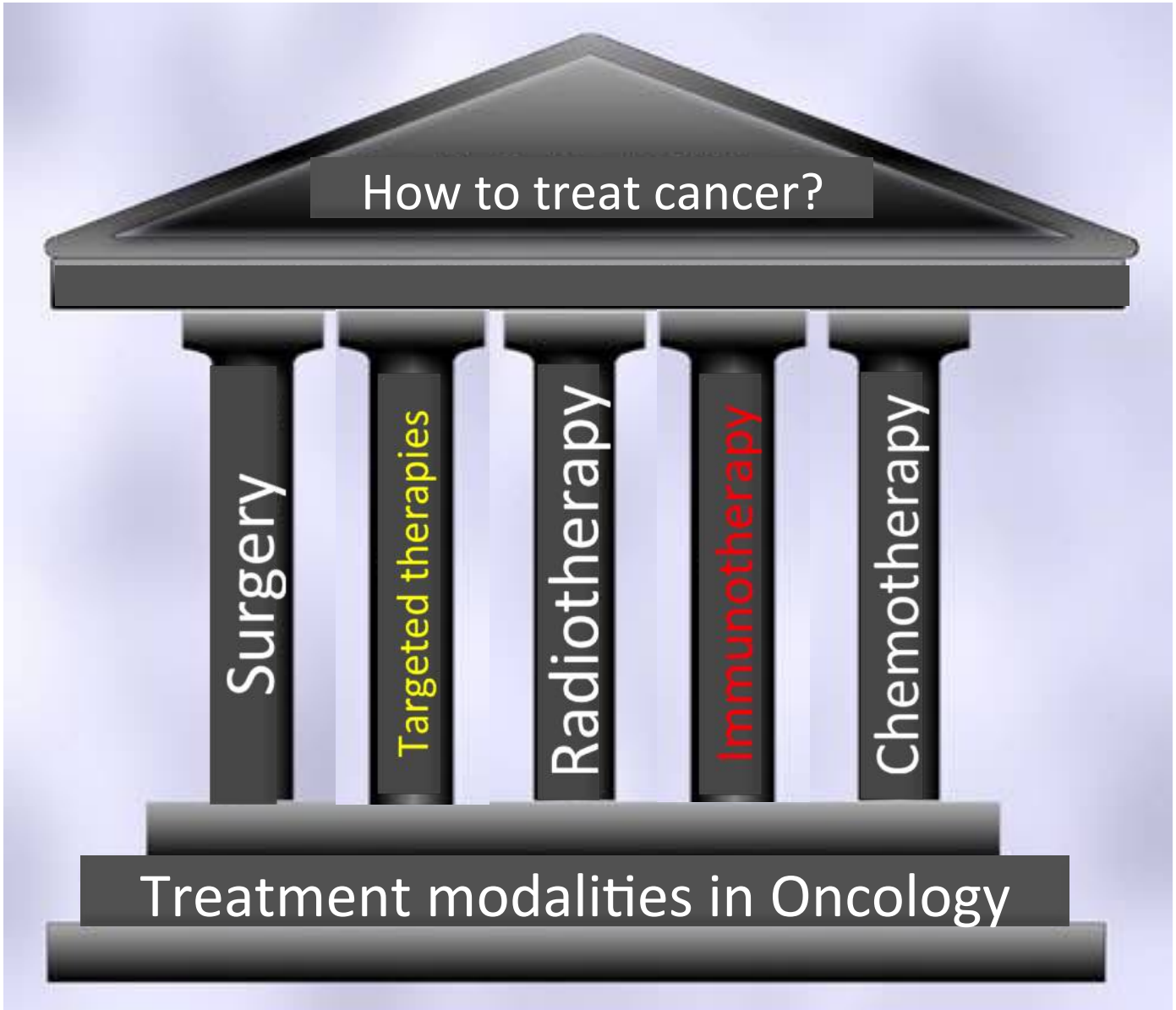

Historical overview of immunology and cancer:

Paul Ehrlich suggests that the immune system can control cancers

(1909)

1890s Coley's toxin

1960s tumor 'immunosurveillance' hypothesis by MF Burnet

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

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

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

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

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

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

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Can the immune system recognize and eliminate malignant tumors? **YES!**

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

Overview of approved immunotherapies in oncology – the past:

Drug	FDA approval		EMA approval	
	Indication	Date of approval	Indication	Date of approval
Interferon α-2b	Melanoma adjuvant	12-1995	CML, FL, CTCL, Melanoma	09-03-2000
Interleukin-2	Advanced melanoma	1998	RCC	27-10-2006
Intravesical BCG	Bladder cancer adjuvant (Tis, Ta, T1)	04-08-1998	Bladder cancer adjuvant (Tis, Ta, T1)	28-04-1998
Peginterferon alfa-2b (Sylatron®)	Melanoma adjuvant	29-03-2011	-	-
Sipuleucel-T (Provenge®)	CRPC	29-04-2010	-	-

Drugs (2011-2016)	FDA approval		EMA approval	
	Indication	Date of approval	Indication	Date of approval
Ipilimumab (Yervoy®)	advanced melanoma	25-03-2011	advanced melanoma	13-07-2011 (2nd) 05-2013 (1st)
	melanoma adjuvant	28-10-2015	-	-
Nivolumab° (Opdivo®)	Advanced melanoma after ipilimumab	22-12-2015	advanced melanoma	19-06-2015
	Squamous NSCLC (after platinum chemotherapy)	04-03-2015	squamous NSCLC (previously pretreated)	20-06-2015
	Advanced RCC (previously pretreated)	23-11-2015	Advanced RCC (previously pretreated)	26-02-2016*
	Advanced classical HL after auto-TX and Adcetris	17-05-2016	-	-
	Non-squamous NSCLC (previously pretreated)	09-10-2015	Non-squamous NSCLC (previously pretreated)	26-02-2016*

*CHMP positive opinion ° first approval in Japan in 07/2015

Drugs (2011-2016)	FDA approval		EMA approval	
	Indication	Date of approval	Indication	Date of approval
Pembrolizumab (Keytruda®)	advanced melanoma	04-09-2014 (after ipi) 18-12-2015 (1st)	advanced melanoma	17-07-2015
	Advanced NSCLC	02-10-2015	-	-
	HNSCC after platinum	05-08-2016	-	-
T-VEC (Imlygic®)	melanoma lesions in the skin and lymph nodes	27-10-2015	irresectable melanoma (st. III, M1a)	16-12-2015
Combination of Ipi/Nivo	(BRAF V600 wild-type) unresectable or metastatic melanoma	30-09-2015	"Opdivo as monotherapy **or in combination with ipilimumab** is indicated for the treatment of advanced melanoma in adults. **Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression.**	01-04-2016*
Atezolizumab (Tecentriq®)	Recurrent bladder cancer	18-05-2016	-	-

*CHMP positive opinion

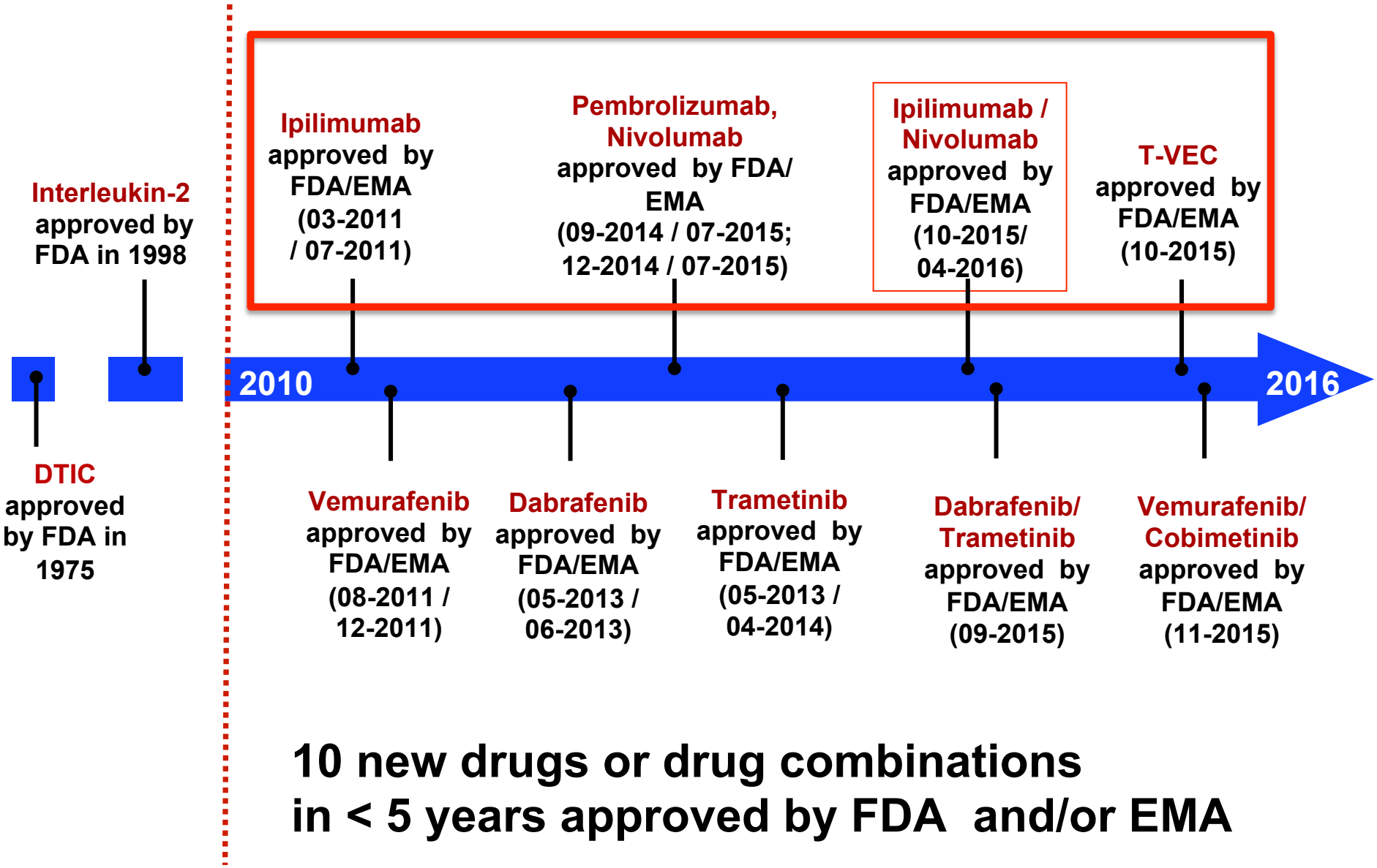
Overview of anti-PD1/L1 agents in clinical development:

Drug	Market name	Prior names	Manufacturer	IgG type
Nivolumab	Opdivo®	MDX1106, BMS936558	BMS - ONO	IgG4 fully human AB
Pembrolizumab	Keytruda®	MK-3745	MSD	IgG4 engineered humanized AB
Pidilizumab	-	CT-011	Cure Tech	IgG1k fully human AB
BMS936559	-		BMS - ONO	IgG4 fully human AB
Atezolizumab	Tecentriq®	MPDL3280A, RG7446	Genentech/ Roche	IgG1 engineered fully human AB
Durvalumab	-	MEDI4736	Medimmune	IgG1 engineered fully human AB
Avelumab	-	MSB0010718C	Merck Serono	IgG1 fully human AB

Clinicaltrials.gov: 353 recruiting studies with anti-PD1/PD-L1 (02-10-16)

Moreno BH and Ribas T BJC 2015, 112:1421-27

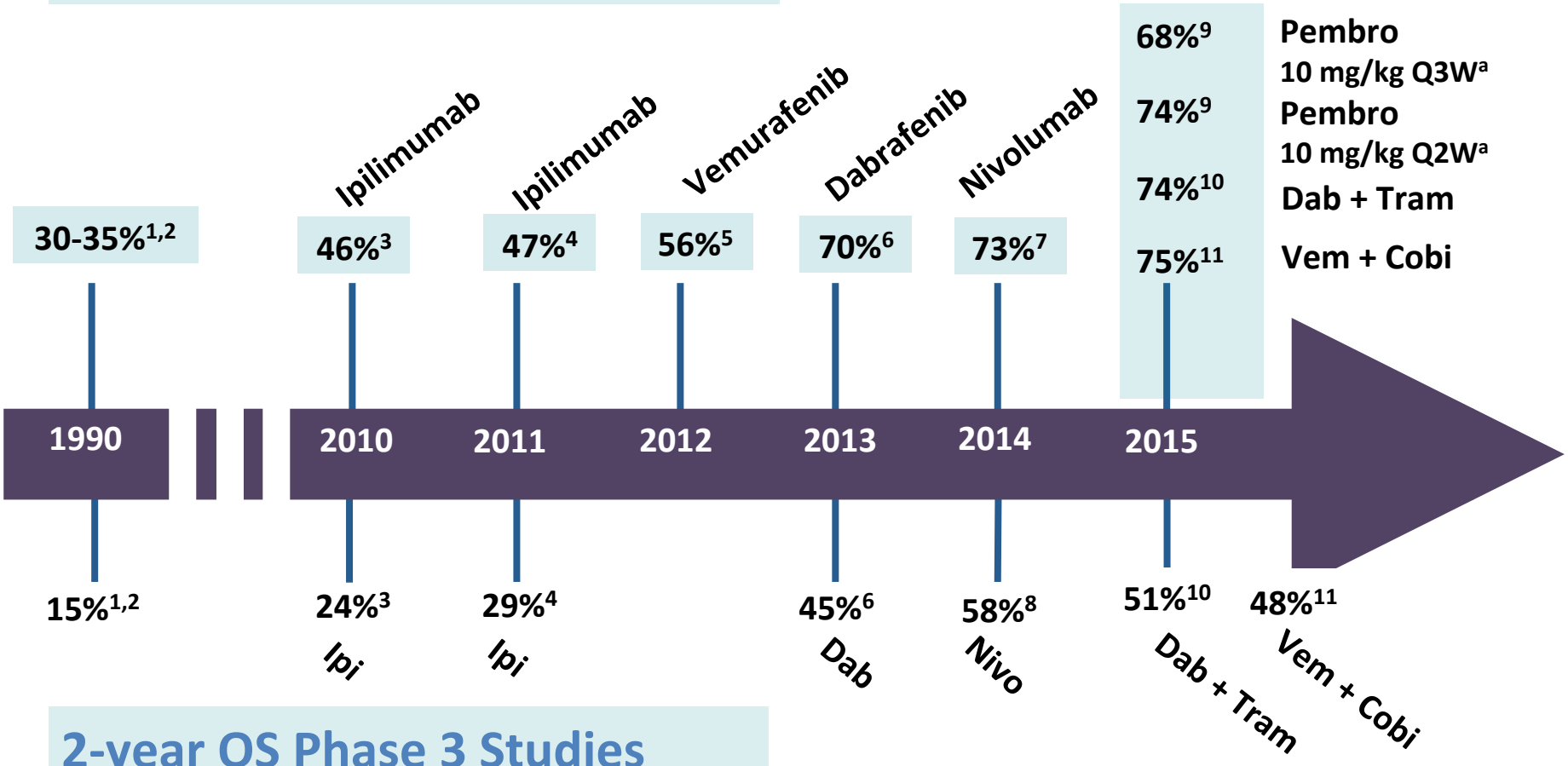
Historical overview of treatments for metastatic melanoma:



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

Overall Survival Metastatic Melanoma

1-year OS Phase 3 Studies



2-year OS Phase 3 Studies

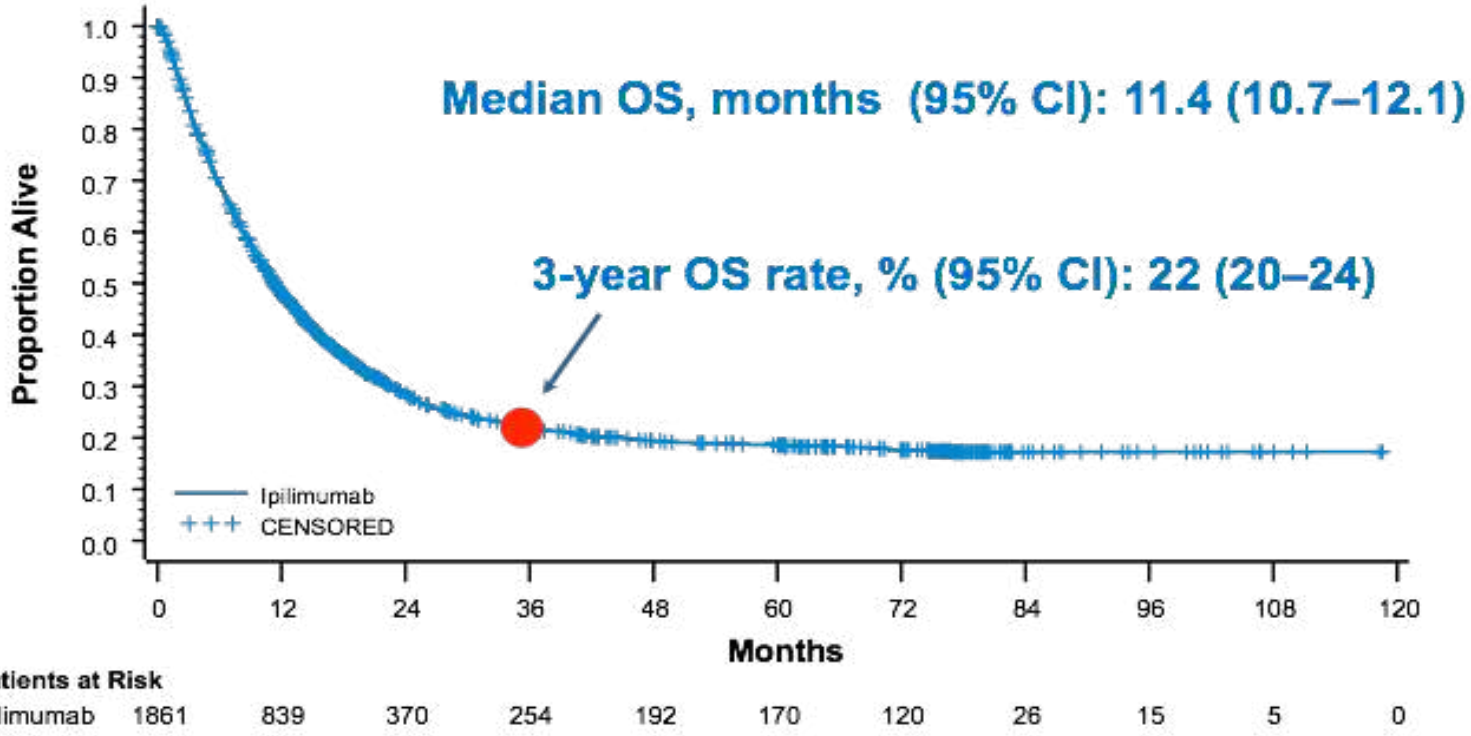
[a]2 mg/kg Q3W is the approved dosing for pembrolizumab in advanced melanoma

Cobi=cobimetinib; Dab=dabrafenib; Ipi=ipilimumab; Nivo=nivolumab; Pembro=pembrolizumab; Q2W=every 2 weeks; Q3W=every 3 weeks; Tram=trametinib; Vem=vemurafenib.

Adapted from ©Georgina V. Long 2015

1. Middleton M, et al. *Ann Oncol*. 2007;18:1691-1697. 2. Balch CM, et al. *J Clin Oncol.* 2001;19:3635-3648. 3. Hodi FS, et al. *N Engl J Med*. 2010;363:711-723. 4. Robert C, et al. *N Engl J Med*. 2011;64:2517-2526. 5. McArthur GA, et al. *Lancet Oncol*. 2014;15:323-332. 6. Grob JJ, et al. Presented at SMR 2014. 7. Robert C, et al. *N Engl J Med.* 2015;372:320-323. 8. Atkinson V et al. Presented at SMR 2015. 9. Robert C, et al. *N Engl J Med.* 2015;372:2521-2532. 10. Long G, et al. *Lancet*. 386:444-451. 11. Atkinson et al. Oral presentation at SMR 2015

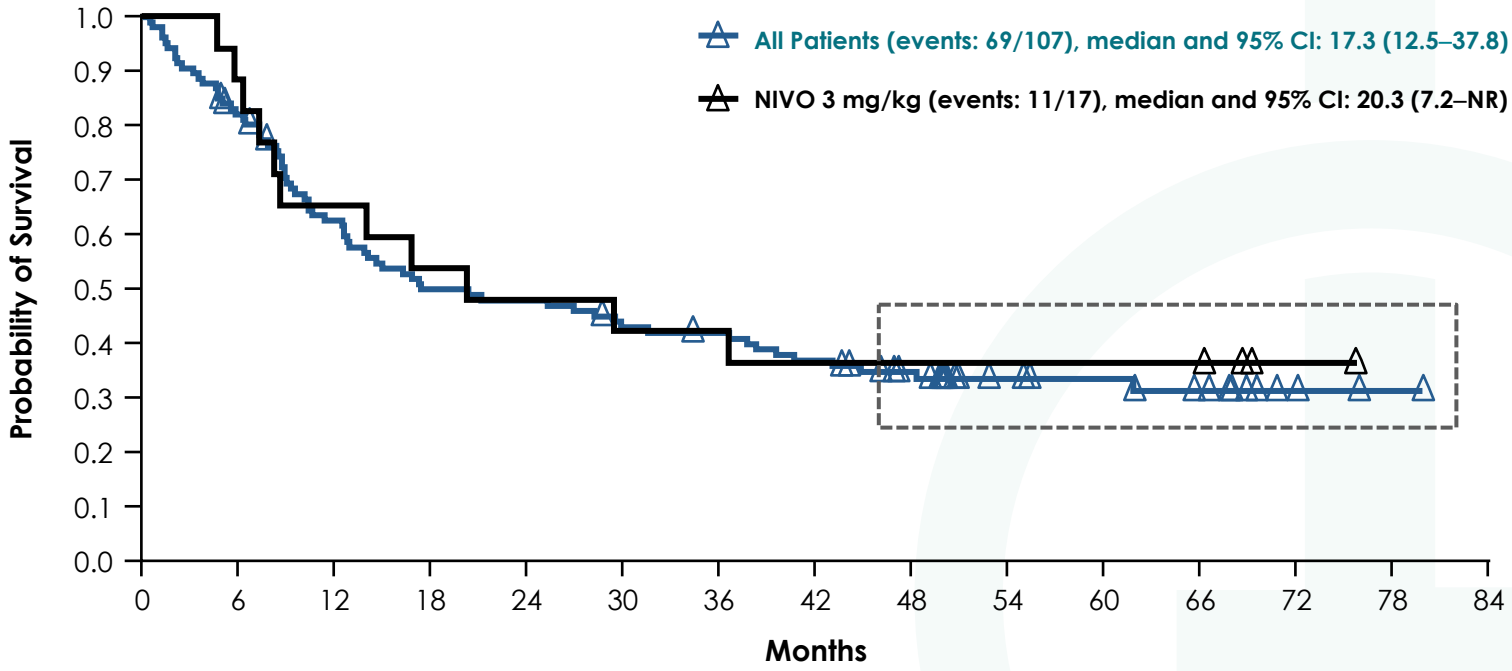
Primary Analysis of Pooled OS Data: 1861 Patients



About 20% are still alive with Ipilimumab

Schadendorf D et JCO 2015, 33(17): 1889-94

Study CA209-003: Overall Survival at 5 Years



Number of Patients at Risk															
All Patients	107	86	64	51	49	43	41	36	29	17	15	12	3	1	0
NIVO 3 mg/kg	17	15	11	9	8	7	7	6	6	6	6	6	1	0	

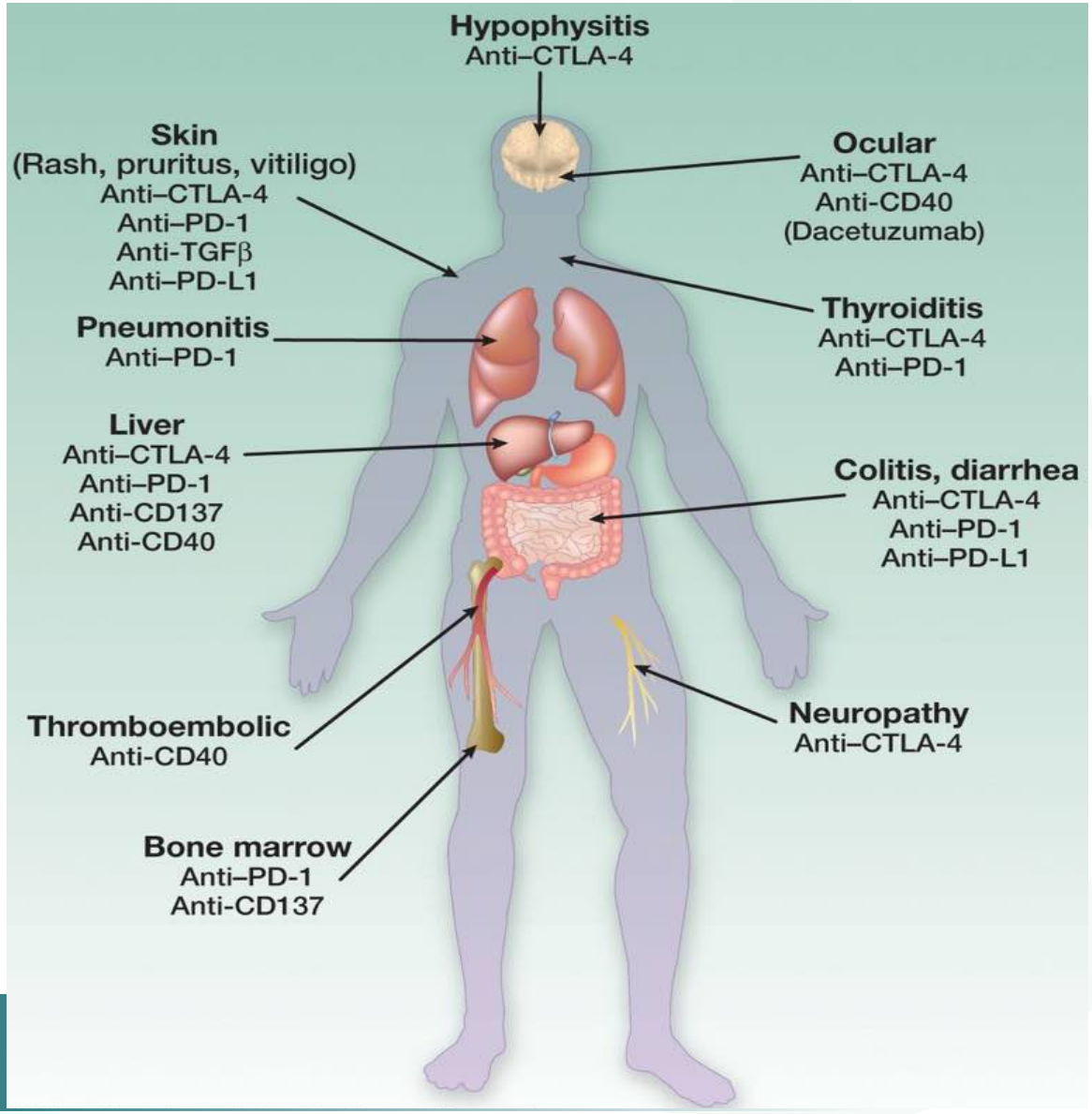
Database lock Oct 2015

Hodi S et al AACR 2016 Annual Meeting (Abstract CT001)

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**

Toxicities with anti-PD1/PDL1 mAbs less common and less severe in comparison with anti-CTLA-4 mAbs → gr. 3-4 ranging from 7-12% with single agent anti-PD1/PDL1 vs 10-18% with single agent anti-CTLA-4



Melero I et al. Clin Cancer Res 2013;19:997-1008
Naidoo J et al. Ann Oncol 2015; 26(12):2375-91
Champiat S et al Ann Oncol 2015 Dec 28. pii: mdv623. [Epub ahead of print]
Michot JM et al Eur J Cancer 2016 Feb;54:139-48

Systemic Oncology Therapies

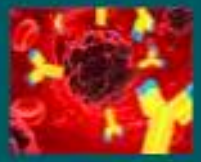
CHEMOTHERAPY

Target: rapidly dividing tumour and normal cells

Adverse events: diverse due to non-specific nature of therapy

TARGETED THERAPIES

Target: specific molecules involved in tumour growth and progression



Adverse events: reflect targeted nature

IMMUNO-ONCOLOGY (I/O) THERAPIES

Target: immune system

Adverse events: unique events can occur as a result of immune-system activity

Different spectrum of adverse events with each type of therapy

Although adverse events may have different etiologies, some adverse events with I-O may present like those with other therapies

Require different management strategies

American Cancer Society. *Treatment types* http://www.cancer.org/; Bristol-Myers Squibb. YERVOY™ (ipilimumab) prescribing informati
2454 and oral presentation at ASCO 2013: *J Clin Oncol* 2013;31(15 suppl):abstract 3002; 3. Hamid O, et al. *N Eng J Med* 2013;369(2):134-
updated June 2011; Bristol-Myers Squibb. YERVOY (ipilimumab) Immune-related Adverse Reactions (IrAR) Management Guide and Onl
(ipilimumab) SmPC updated July 2013, available at http://www.ema.europa.eu.

The challenge: finding the right balance …

Occurrence of ir-adverse events with Ipi and anti-PD1 in melanoma:

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 in NSCLC:

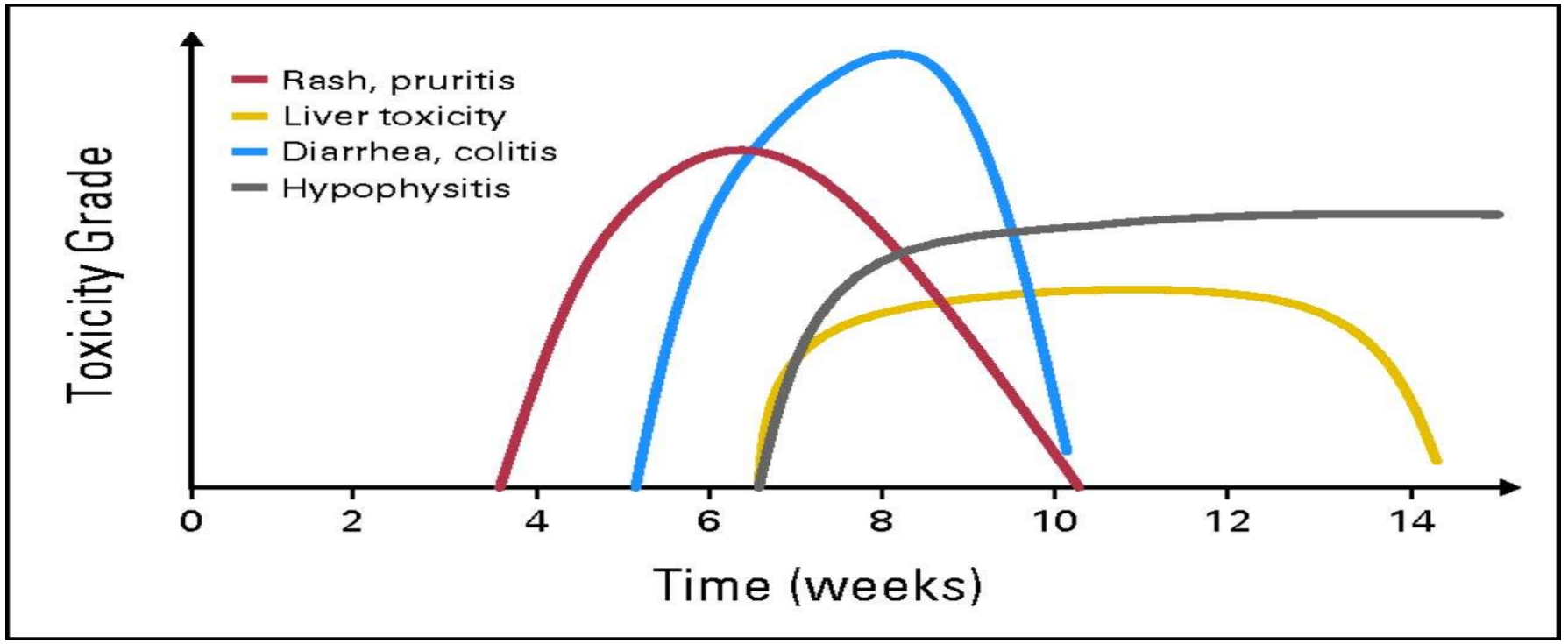
Type of study	CA209-017 (ph 3, 272 sqNSCLC pts.)		CA209-057 (ph 3, 582 non-sq NSCLC pts.)		CA209-012 (ph 1, 52 pts.)		Keynote-001 (ph 1, 495 NSCLC pts.)		Keynote--010 (ph 3, 991 NSCLC pts.)		POPLAR (ph 3, 287 NSCLC pts.)	
	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)	all gr (%)	gr3/4 (%)
Any (ir) event	58	7	69	10	71	19	70,9	9,5	63/66	13/16	**67**	**11**
Skin (rash, pruritis)	4	0	n.r.	n.r.	19	4	9,7	0.2	9/13	<1/1	n.r.	n.r.
GI (diarrhea, colitis	8	0	8	1	12	2	8,1	0,6	7/6	1/0	1	<1
Hepatitis	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	3,0	0,6	1/1	1/0	4	<1
Endocrine	n.r.	n.r.	n.r.	n.r.	6	0	6,9	0,2	8/8	0/0	7	1
Pneumon.	5	0	n.r.	n.r.	6	2	3,6	1,8	5/4	2/2	3	<1
Renal	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

Brahmer J et al N Engl J Med. 2015;373(2):123-135; Borghaei H et al NEJM 2015;373(17):1627-39; Gettinger S et al JCO 2016;34:2980-2987; Garon EB et al NEJM 2015; 372:2018-28; Herbst RS et al Lancet 2016; 387:1540-50; Fehrenbacher L et al Lancet 2016; 387:1837-46

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

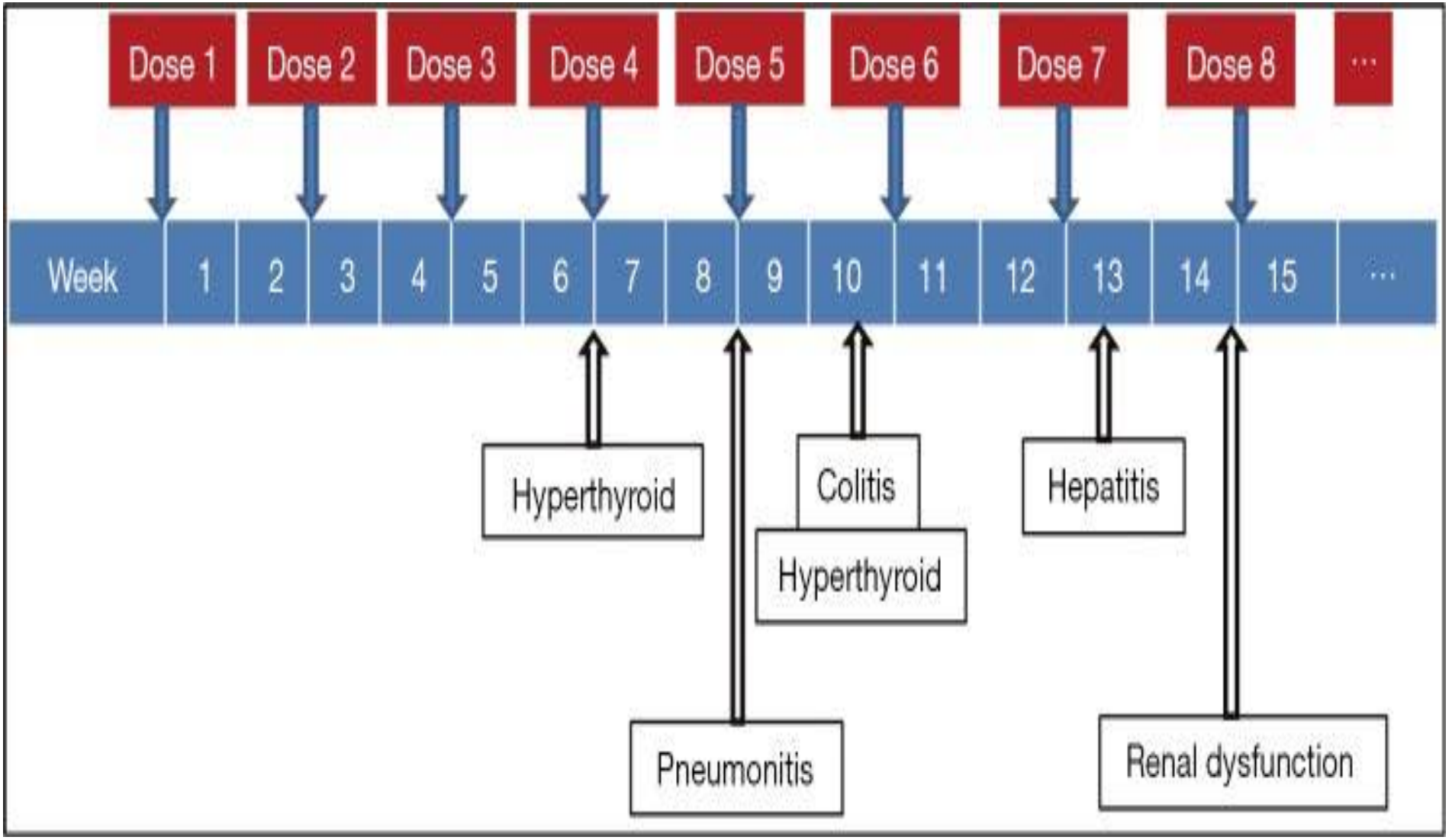
Type of Immune-Related Adverse Event	Median Time to Onset, wk	Median Time From Onset to Resolution, wk
Skin	3	5
Hepatic	3-9	0.7-2.0
Gastrointestinal reactions	8	4
Endocrine	7-20	NR

Abbreviations: NR, not reported.



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

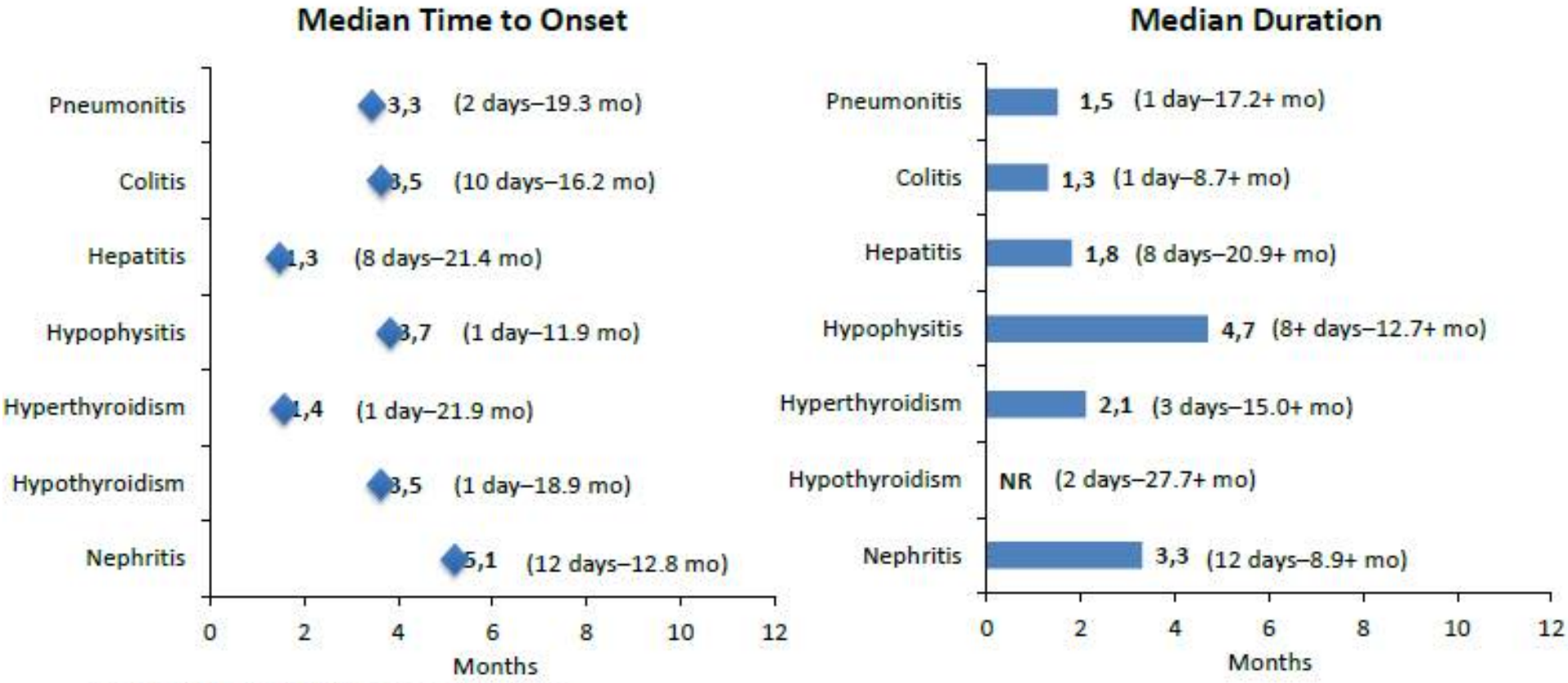
Kinetics of appearance of IR-AEs under Nivolumab (in CA209-037):



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

Pembrolizumab: Immune-mediated Adverse Reactions Median Time to Onset and Median Duration[1]

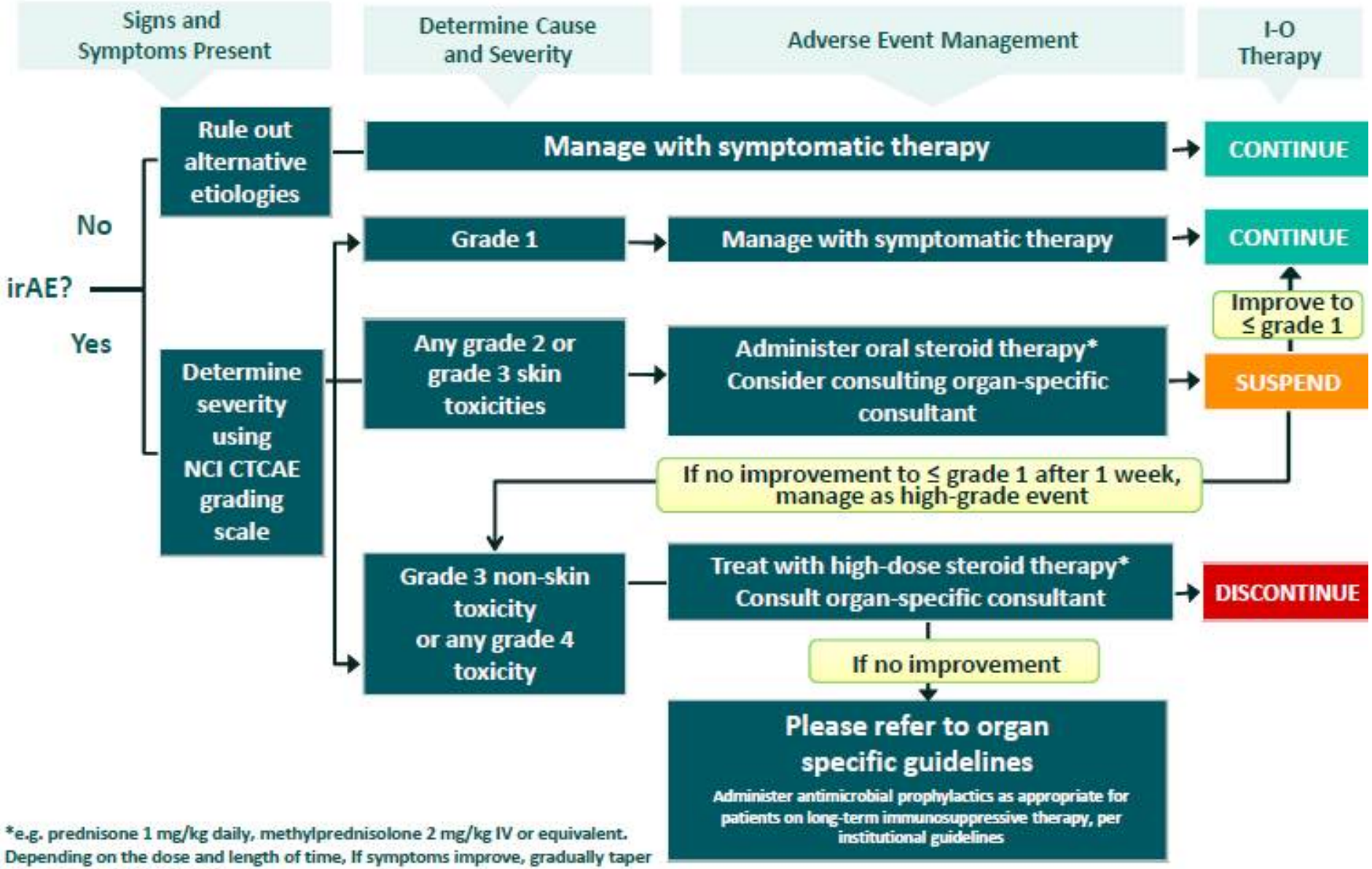
- Median time to onset and median duration of immune-mediated adverse reactions are presented based on 2799 patients with NSCLC and melanoma treated with Pembrolizumab



mo = months; NR = not reached; NSCLC = non–small cell lung cancer.

1) Please Refer to the SmPC (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf)

General Management Guidelines for irAEs



*e.g. prednisone 1 mg/kg daily, methylprednisolone 2 mg/kg IV or equivalent. Depending on the dose and length of time, If symptoms improve, gradually taper over a minimum of 4 weeks

Common Terminology Criteria for Adverse Events (CTCAE)

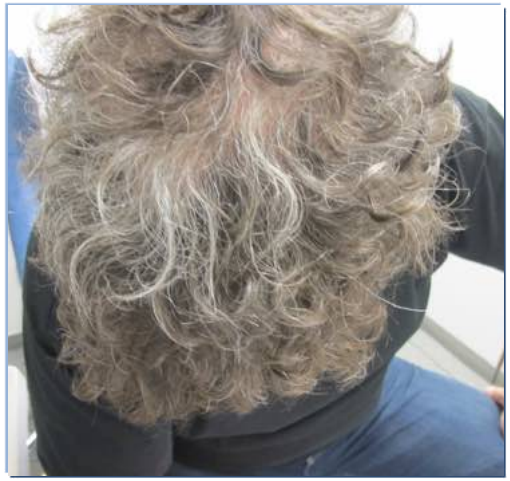
Version 4.0

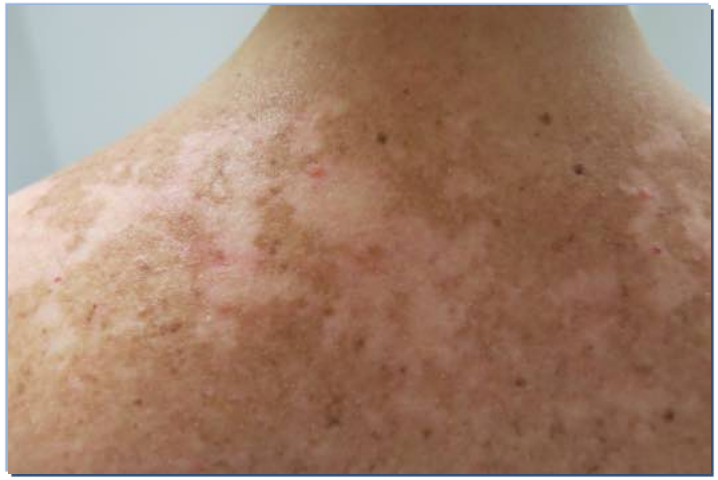
Published: May 28, 2009 (v4.03: June 14, 2010)

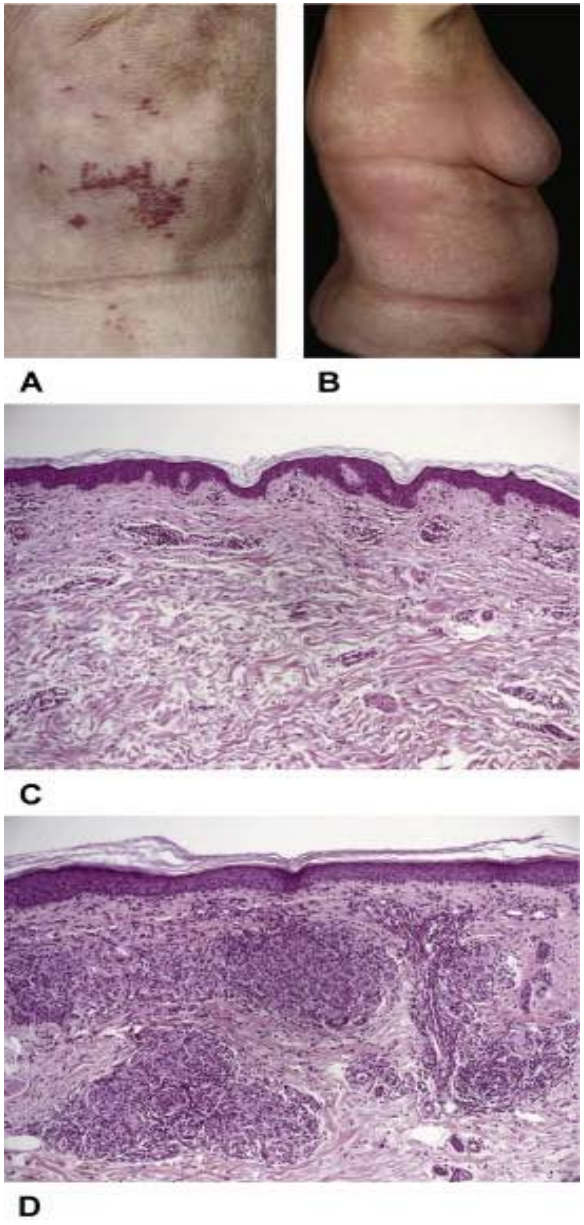
U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

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

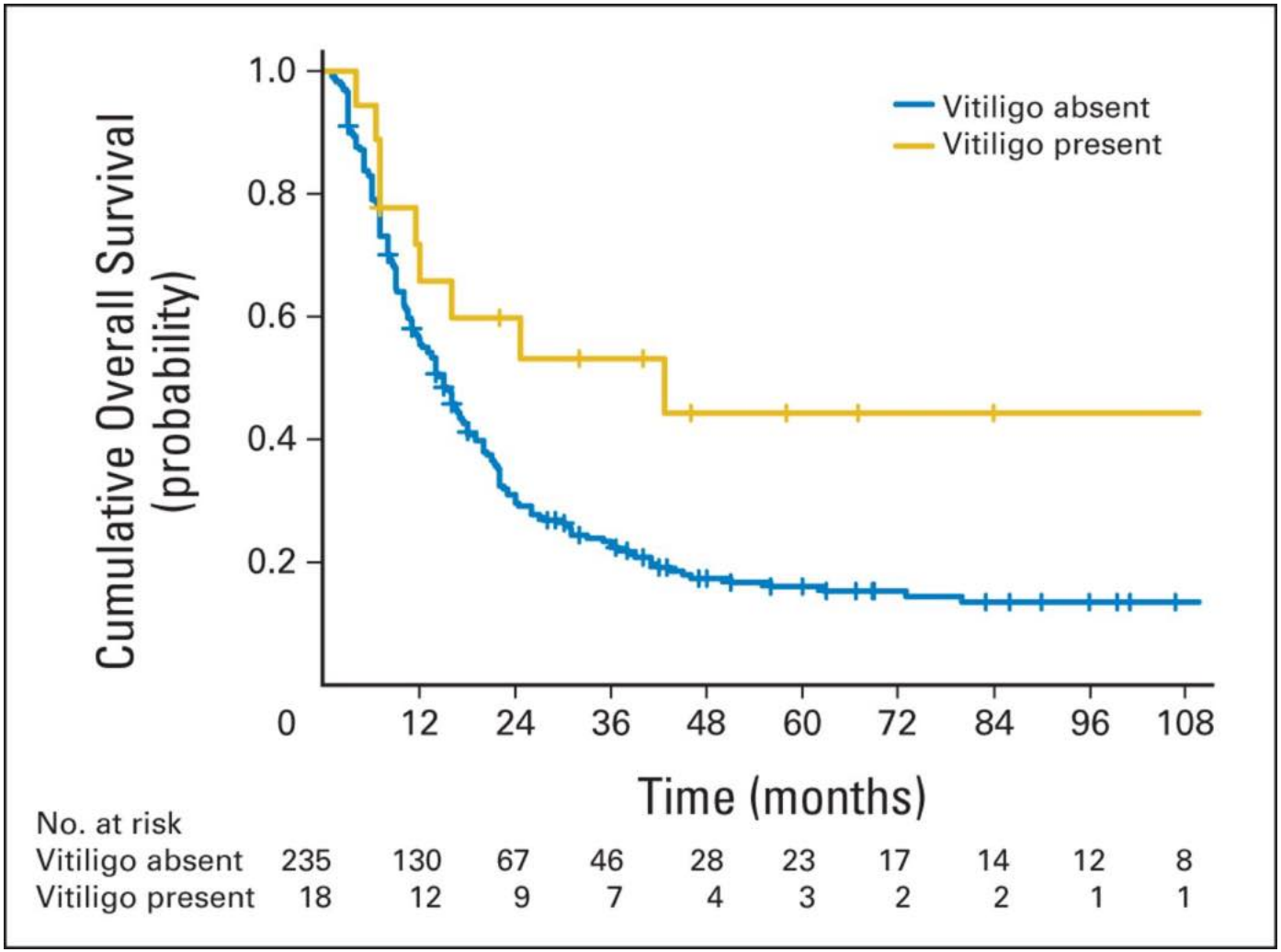




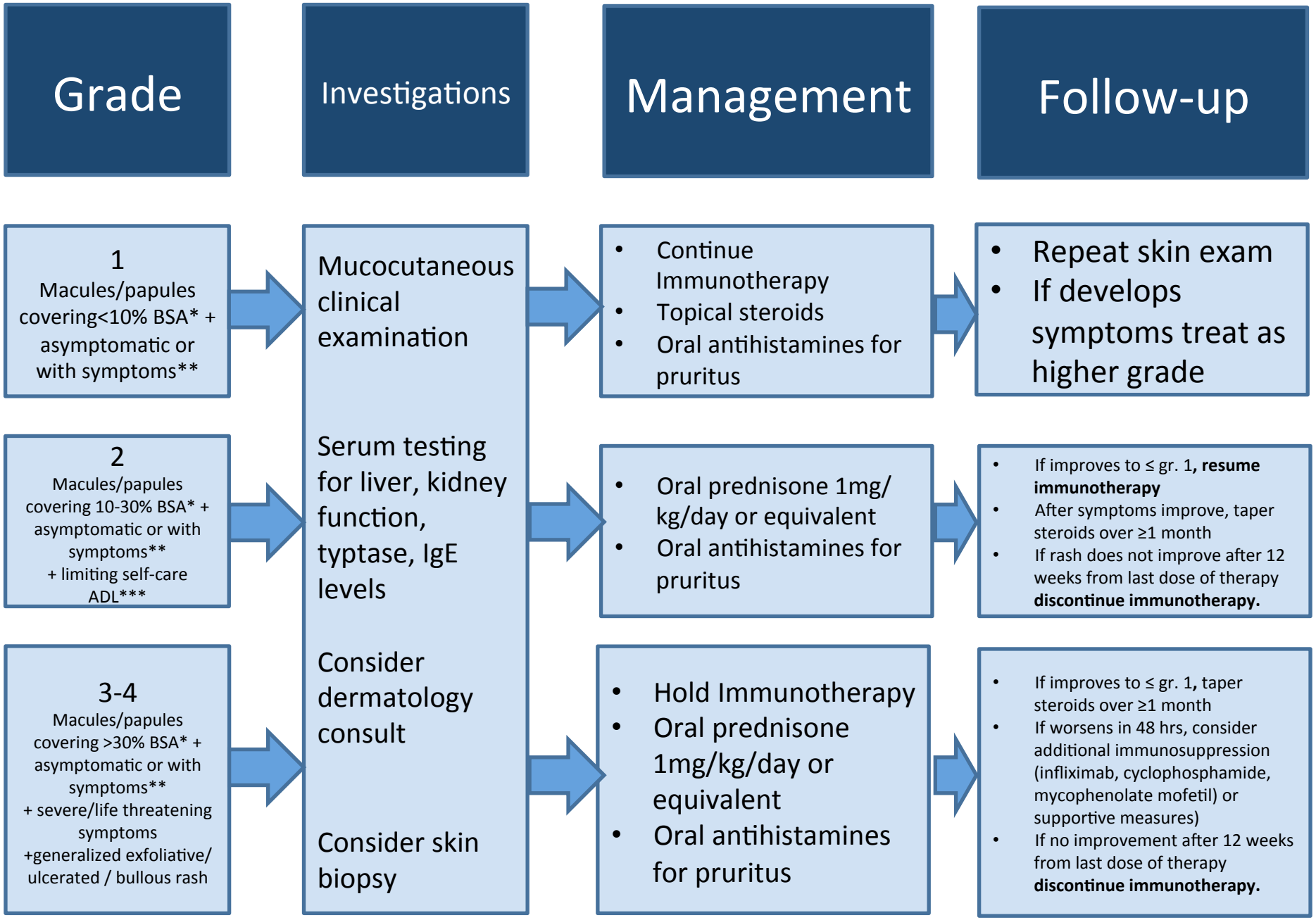


Weber J S et al. JCO 2012;30:2691-2697
Minkis K et al JAAD 2013; 69:e121-8
Lacouture M et al JAAD 2014, epub
Naidoo J et al. Ann Oncol 2015; 26(12):2375-91

Overall survival in 253 patients receiving immunotherapy from 15 studies.



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

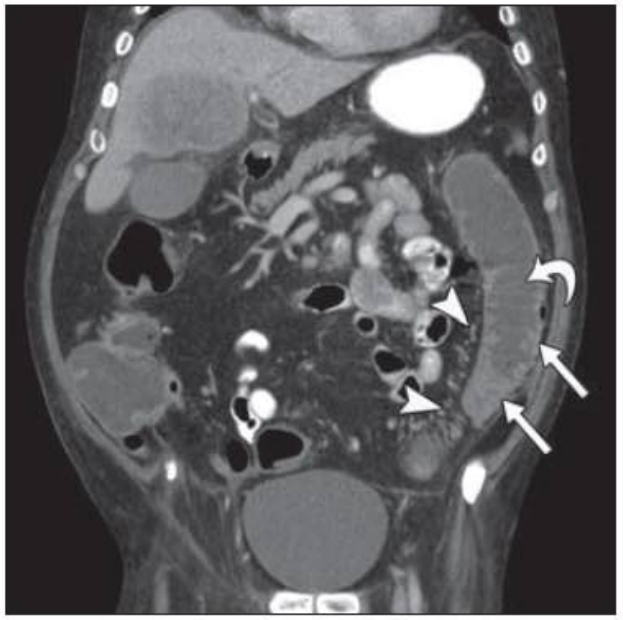


BSA = Body surface area, ** symptoms as per CTCAE 4.0, i.e. pruritus, burning, tightness, ***ADL = activity of daily living, ° additional supportive measures = prophylactic antibiotics, management in the burns unit

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

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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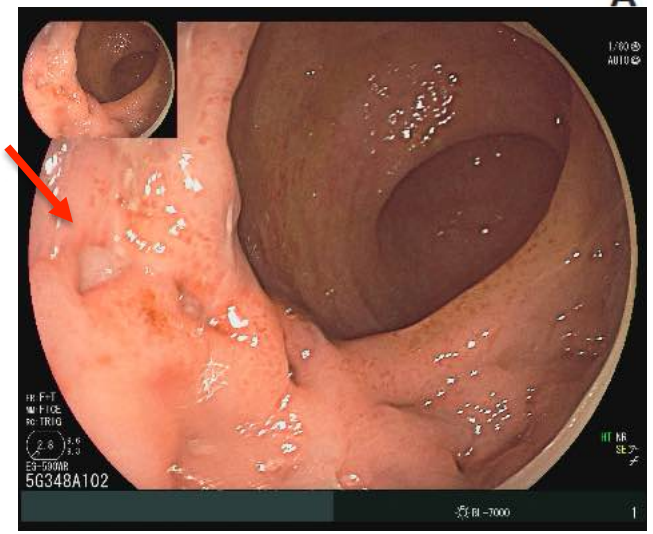
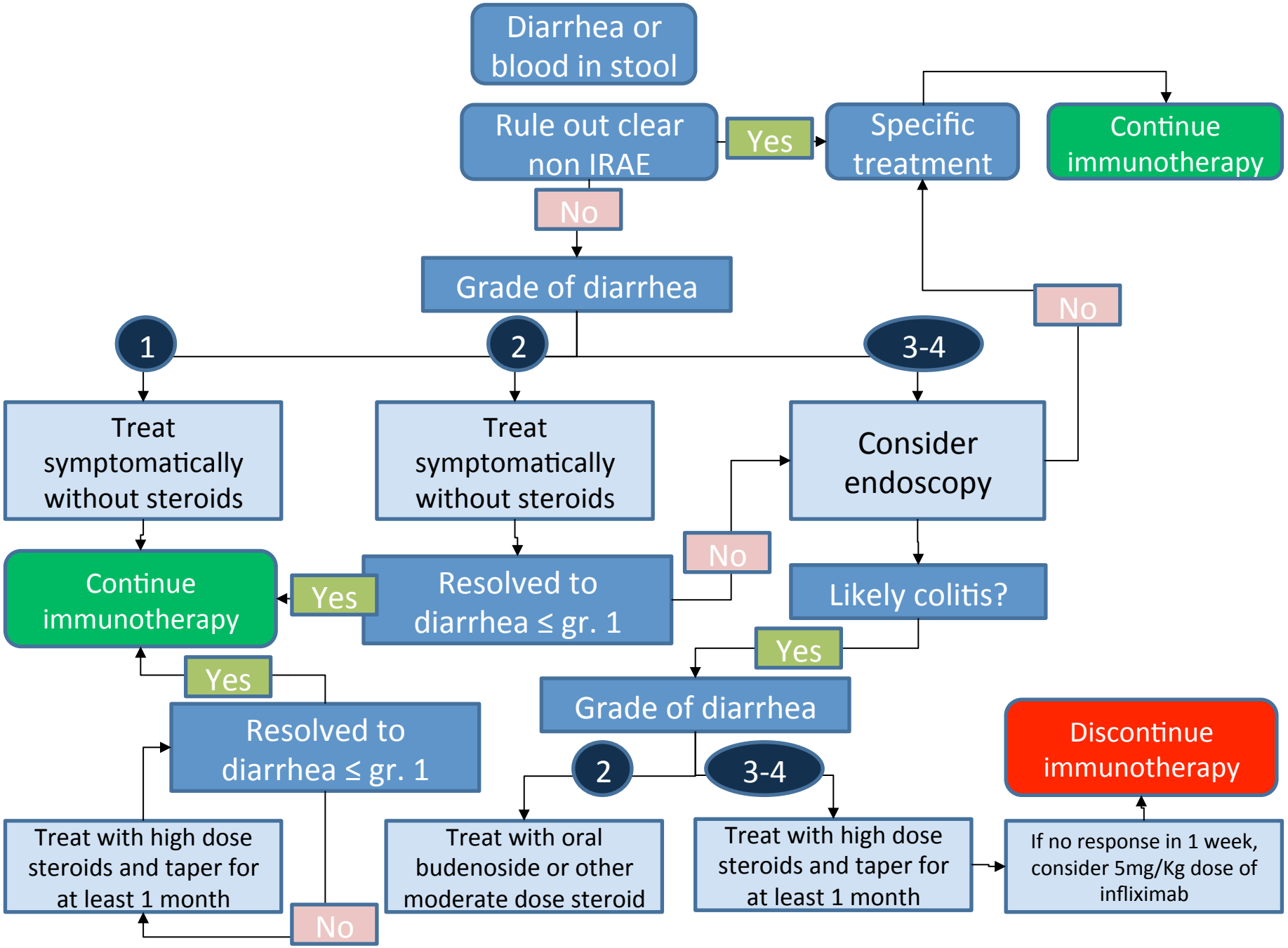


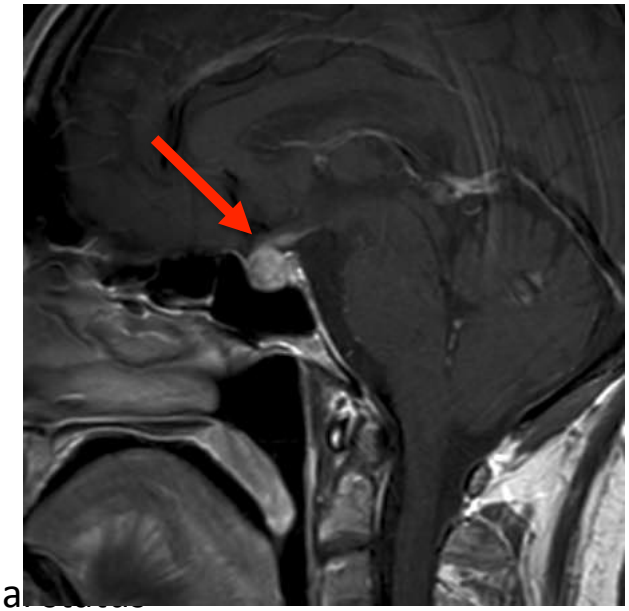
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea (= frequent and watery bowel movements	Increase of < 4 stools per day over baseline; mild increase in ostomu output compared to baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomu output compared to baseline	Increase of > 7 stools per day over baseline; incontinence, hospi indicated; severe increase in ostomu output compared to baseline, limiting self care ADL	Life-threatening consequences, urgent intervention indicated	death

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

Diarrhea Management Algorithm:



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, behaviour change, visual disturbances and weakness occur at an average of 6 weeks after initiation of therapy with Ipilimumab
- 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

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypothyroidism (= decreased production of thyroid hormone by the thyroid gland)	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid repcalemnet indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospi indicated	Life-threatening consequences, urgent intervention indicated	death

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

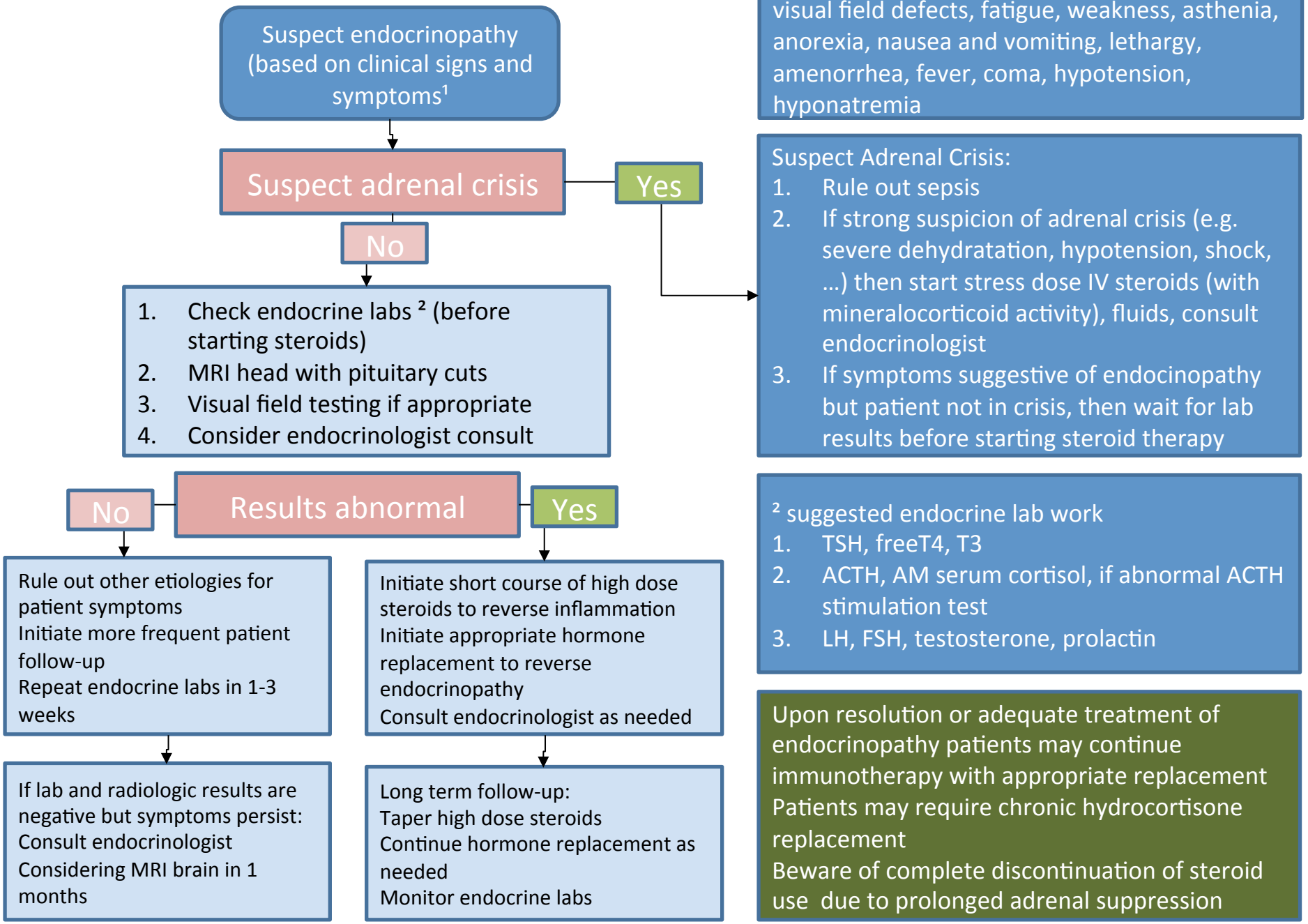
Presentation of Immune-related Endocrinopathies

Endocrinopathy	Presentation	Notes
Hypophysitis	Clinical symptoms: headache and fatigue Radiographic findings: pituitary enhancement and enlargement Biochemical findings: low ACTH and TSH due to pituitary dysfunction	Biochemical tests distinguish between primary adrenal insufficiency (low cortisol or inappropriate cortisol stimulation test; high ACTH) and primary hypothyroidism (low free T4; high TSH)
Hyperthyroidism / hypothyroidism	Revealed through routine monitoring of thyroid function (TSH) during immune checkpoint inhibitor therapy	Distinguish primary hypothyroidism (low free T4 and high TSH) from hypophysitis, which can cause secondary hypothyroidism (low free T4 and low TSH)
Adrenal insufficiency	Low cortisol or inappropriate cortisol stimulation test; high ACTH	Potentially serious consequences of adrenal crisis associated with dehydration, hypotension, and electrolyte imbalances (eg, hyperkalemia and hyponatremia)

ACTH = adrenocorticotropic hormone; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Postow MA. *ASCO Educational Book*. 2015;75-83.

Endocrinopathy Management Algorithm:



[1] Possible clinical signs & symptoms: headache, visual field defects, fatigue, weakness, asthenia, anorexia, nausea and vomiting, lethargy, amenorrhea, fever, coma, hypotension, hyponatremia

Suspect Adrenal Crisis:

1. Rule out sepsis
2. If strong suspicion of adrenal crisis (e.g. severe dehydratation, hypotension, shock, …) then start stress dose IV steroids (with mineralocorticoid activity), fluids, consult endocrinologist
3. If symptoms suggestive of endocinopathy but patient not in crisis, then wait for lab results before starting steroid therapy

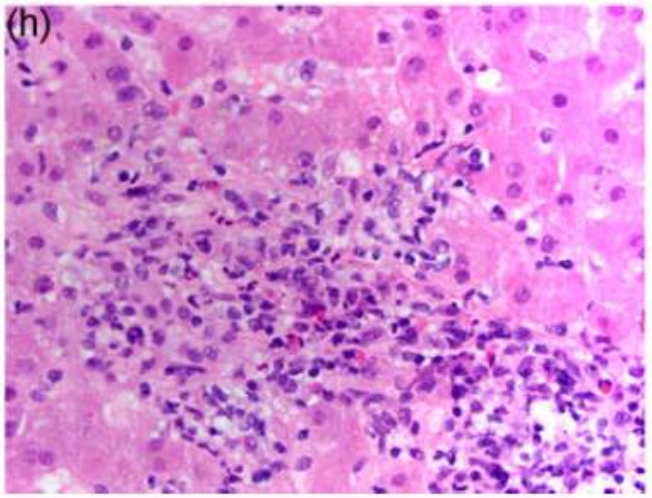
[2] suggested endocrine lab work

1. TSH, freeT4, T3
2. ACTH, AM serum cortisol, if abnormal ACTH stimulation test
3. LH, FSH, testosterone, prolactin

Upon resolution or adequate treatment of endocrinopathy patients may continue immunotherapy with appropriate replacement
Patients may require chronic hydrocortisone replacement
Beware of complete discontinuation of steroid use due to prolonged adrenal suppression

Hepatotoxicity:

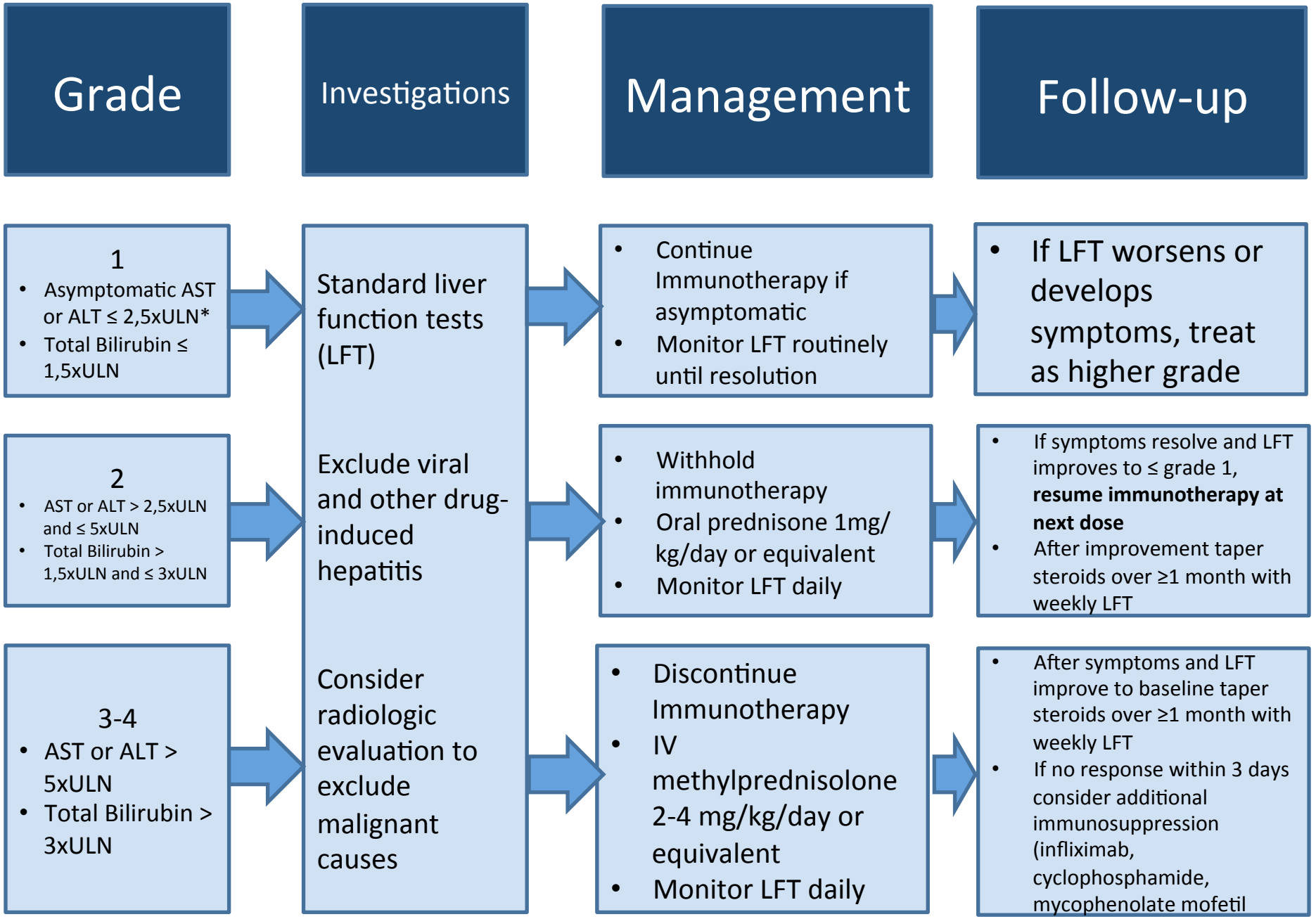
- Has been observed in 3-9% patients treated with ipilimumab, <5% with anti-PD1/PDL1, higher in HCC pts.; in combi with Ipi and other targeted agents or chemotherapy → significant rate of hepatotoxicity with Ipi/DTIC and Ipi/vemurafenib
- With Ipi ~8-12 weeks after starting therapy
- Usually asymptomatic 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



* ULN = upper limit of normal

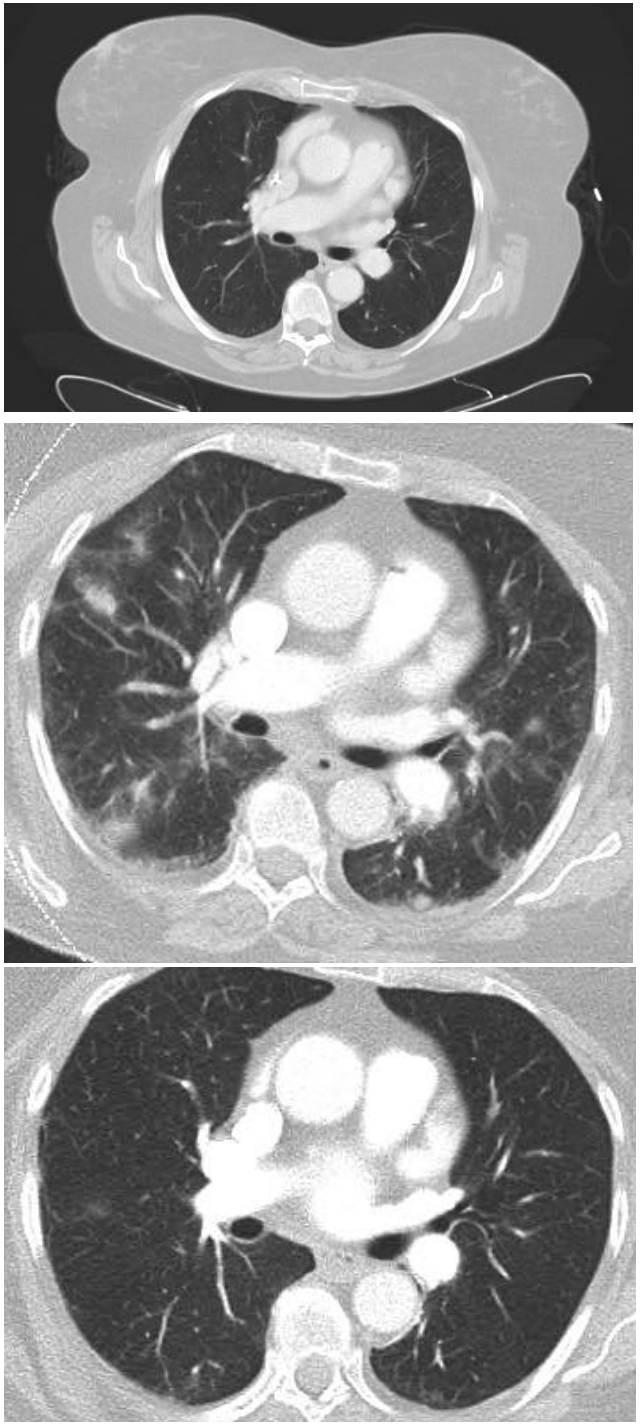
Naidoo J et al. Ann Oncol 2015; 26(12):2375-91

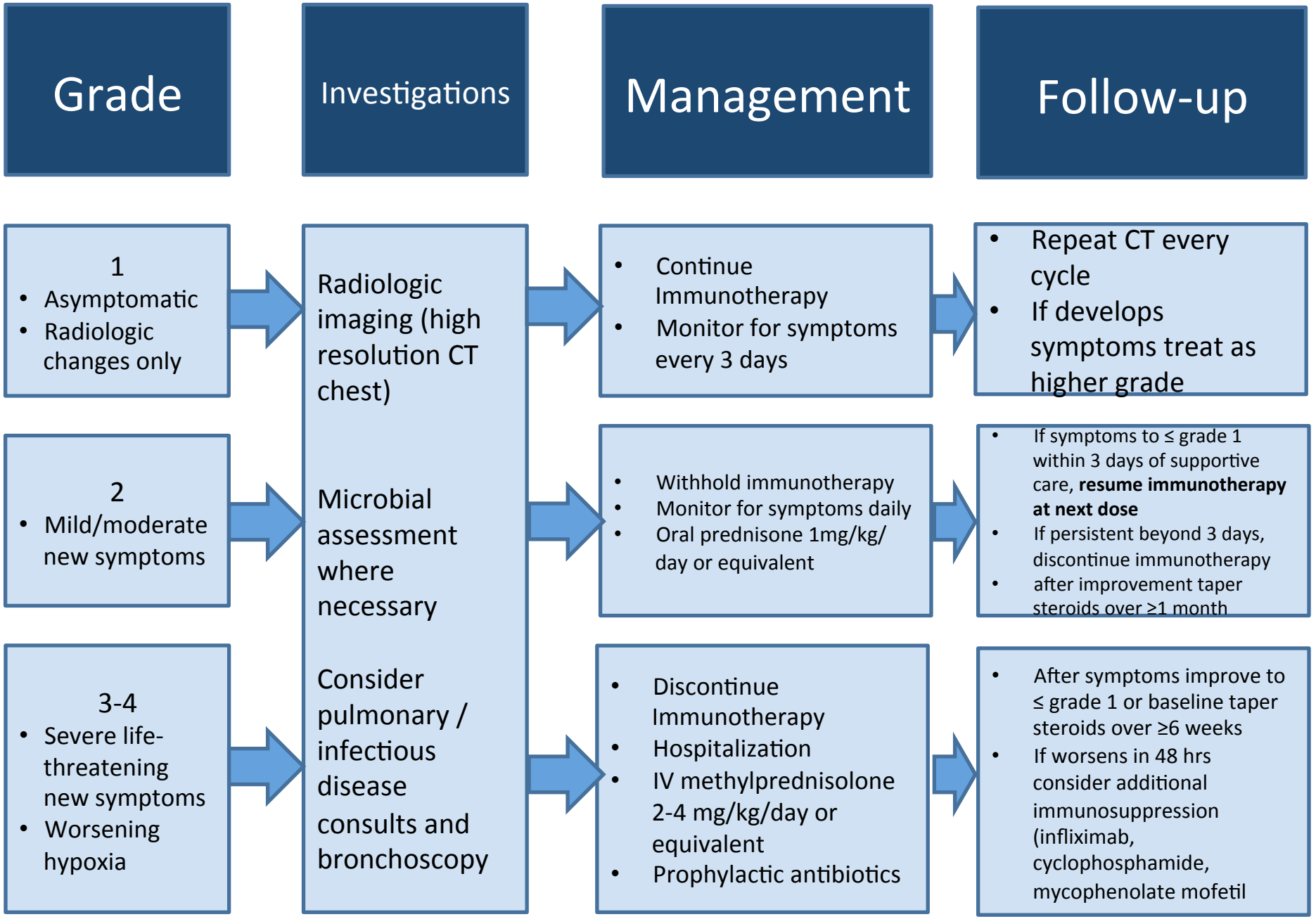
Pneumonitis:

- 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 MMT

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonitis (= inflammation focally or diffusely affecting lung parenchyma)	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	death

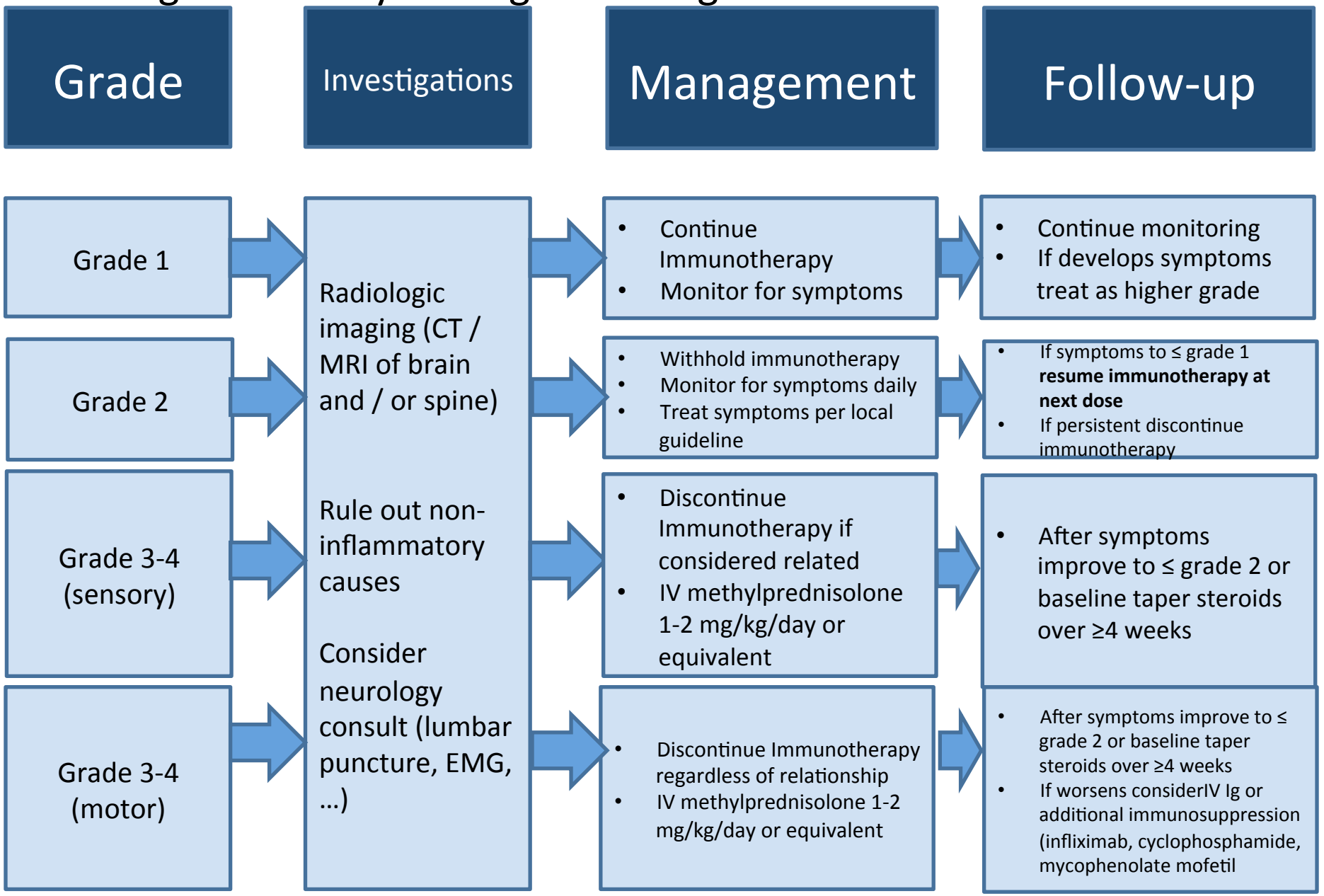
Naidoo J et al. Ann Oncol 2015; 26(12):2375-91





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

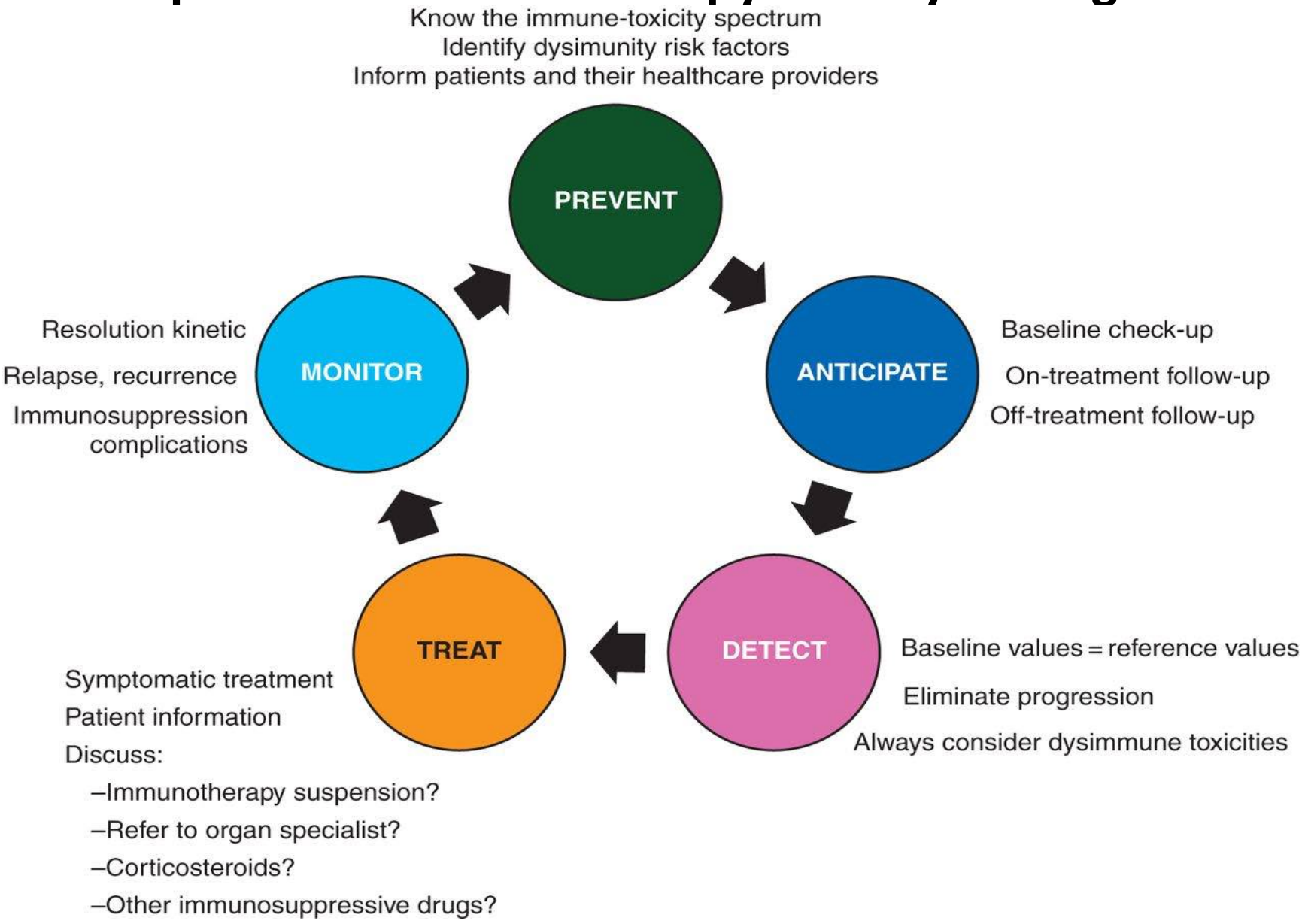
Neurological Toxicity Management Algorithm:



Other immune related adverse effects:

- Renal toxicity (tubolointerstitial nephritis)
- Pancreatitis (can be monitored without immunosuppressive therapy → asymptomatic elevated grade 3 lipase do not need 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),

The five pillars of immunotherapy toxicity management:



S. Champiat et al. Ann Oncol 2016;annonc.mdv623

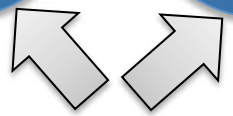
Recommendations for Patient/Caregiver Education

General Educational Points

- Vigilance[1]
- Prompt symptom reporting[1]
- Advise emergency HCPs about anticancer medication[2]
  - *Show patient wallet card*
- Do not take over the counter dietary supplements[1]
  - *Unless approved by HCP*

Educational Points for Follow-up Visits[1]

- Reinforce importance of early detection and prompt reporting
- Confirm patient's ability to verbalize important symptoms
- Procedure for AE reporting or seeking medical attention when office is closed
- Symptoms may occur weeks to months after infusion



Use patient monitoring checklist[3]

1. Yervoy Risk Evaluation and Mitigation Strategy. http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_IMMUNE%20MEDIATED%20ADVERSE%20REACTION%20MANAGEMENT%20GUIDE.pdf. Accessed January 2016. 2. Opdivo patient wallet card. http://www.opdivo.bmscustomerconnect.com/servlet/servlet.FileDownload?file=00Pi000000FuuLYEAZ. Accessed February 2016. 3. Opdivo patient monitoring checklist. http://www.opdivohcp.bmscustomerconnect.com/servlet/servlet.FileDownload?file=00Pi000000Hj19qEAB. Accessed February 2016.

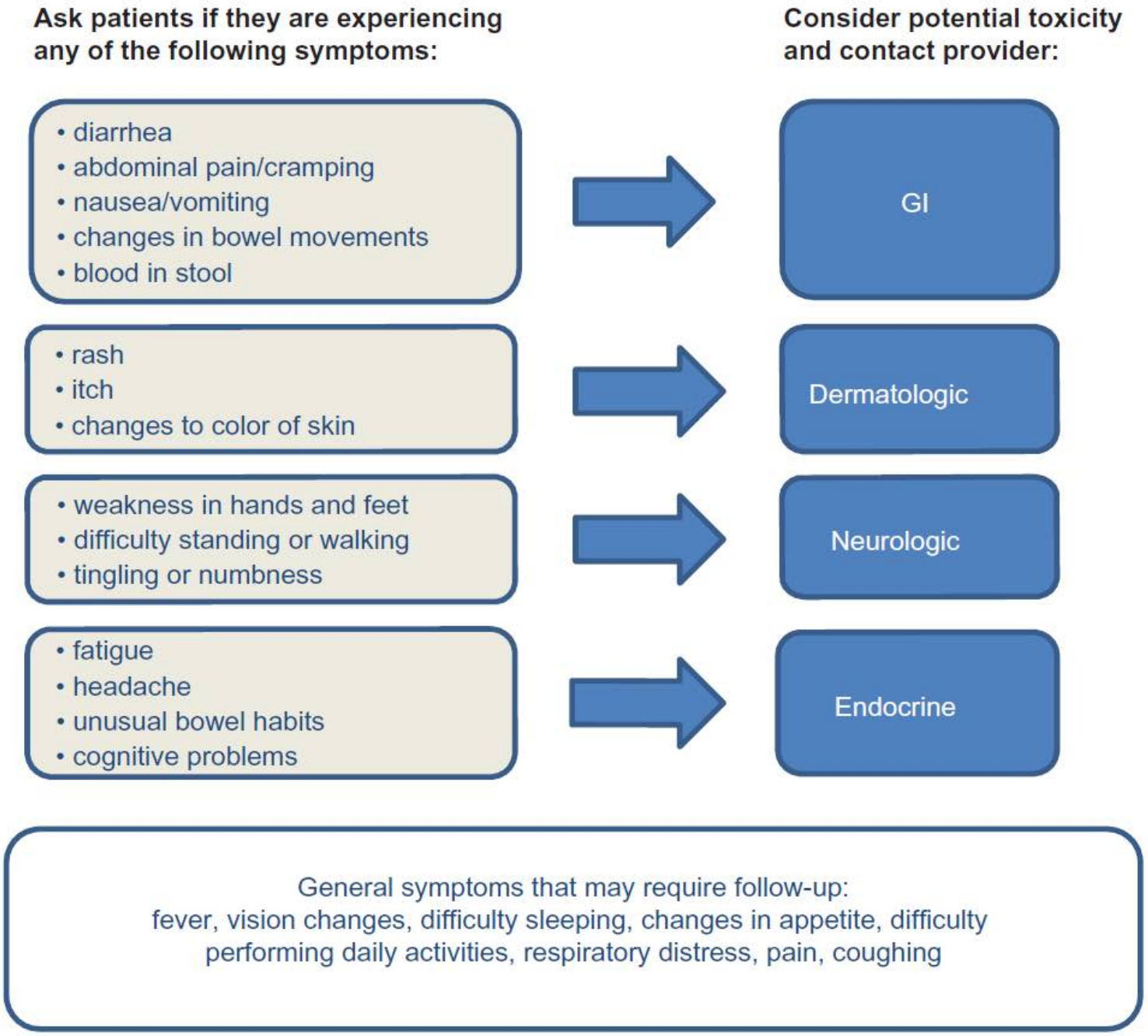
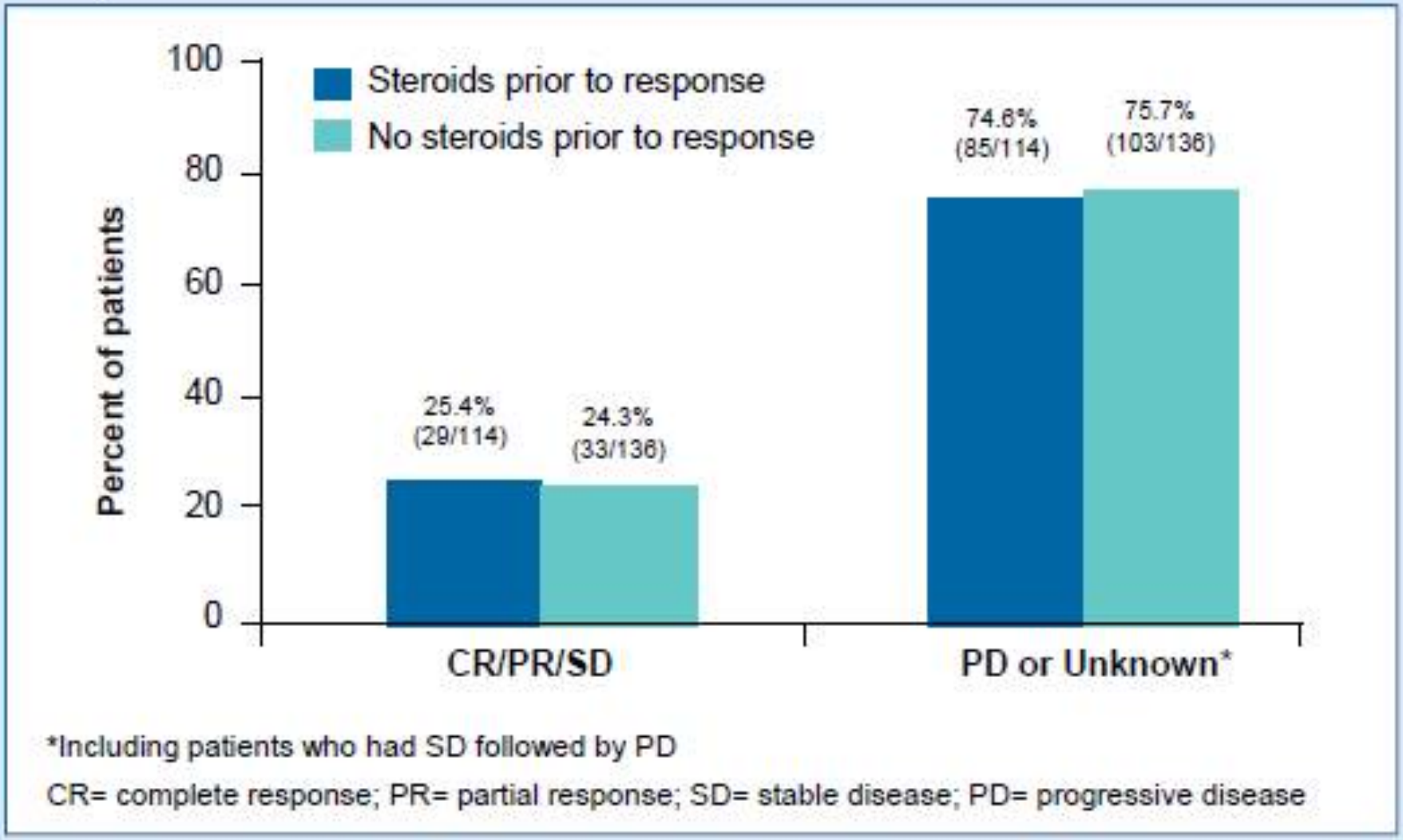

Ask patients if they are experiencing any of the following symptoms:
Consider potential toxicity and contact provider:
• diarrhea
• abdominal pain/cramping
• nausea/vomiting
• changes in bowel movements
• blood in stool
GI
• rash
• itch
• changes to color of skin
Dermatologic
• weakness in hands and 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

Overview of Resolution of Grade 3/4 Regimen-associated imARs in Patients Managed Using Established Guidelines (CheckMate 067)[1]

- Most grade 3/4 imARs were effectively managed using established guidelines[1]

imAR organ category[a]	NIVO + IPI (n = 313)		NIVO (n = 313)	
	Patients with resolution of imARs, n (%)	Median time to resolution, weeks (range)	Patients with resolution of imARs, n (%)	Median time to resolution, weeks (range)
Skin	12 (86)	3.4 (0.7–53.0+)	3 (75)	2.1 (0.9–24.3+)
Gastrointestinal	41 (98)	3.0 (0.3–33.1+)	3 (50)	NE (0.9–31.4+)
Endocrine	5 (46)	NE (1.6–46.6+)	0 (0)	NE (14.4+–39.6+)
Hepatic	38 (100)	4.1 (0.3–26.0)	6 (100)	7.0 (2.0–27.1)
Pulmonary	2 (100)	4.2 (1.1–7.3)	1 (100)	2.3 (2.3–2.3)
Renal	3 (100)	1.7 (0.4–3.6)	-	-

- Similar data were reported from the CheckMate 069 phase 2 trial[2]

NA = not available.

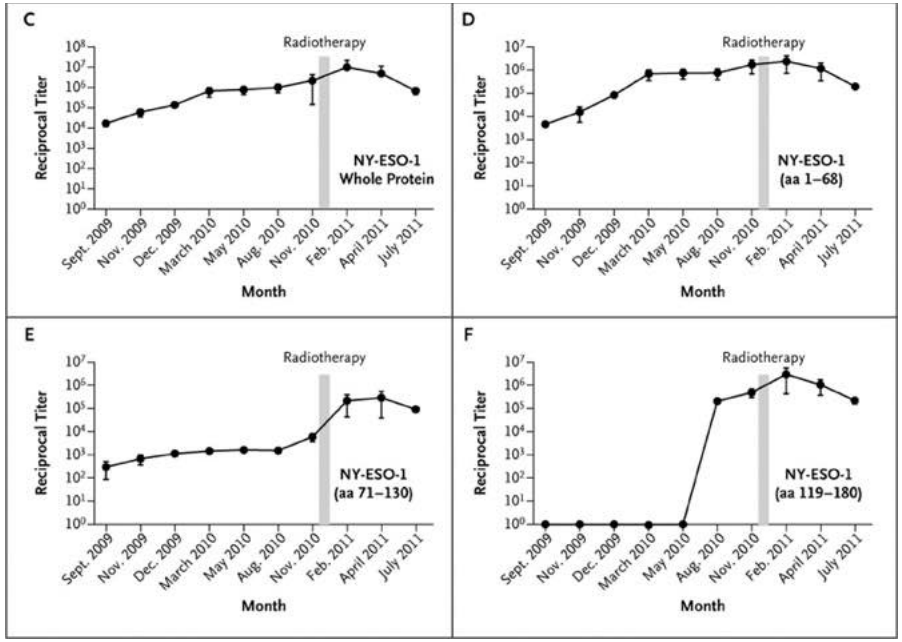
1. Larkin J, et al. Presented at ECC 2015; abstract 3303. 2. Hodi FS, et al. Presented at ASCO 2015; abstract 9004.

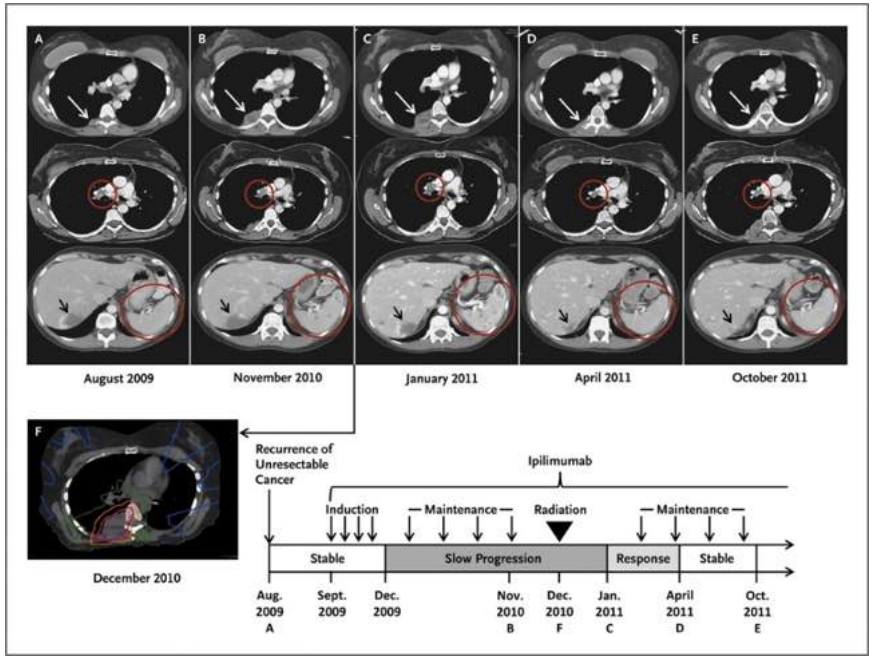
Specific situations:

- **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:

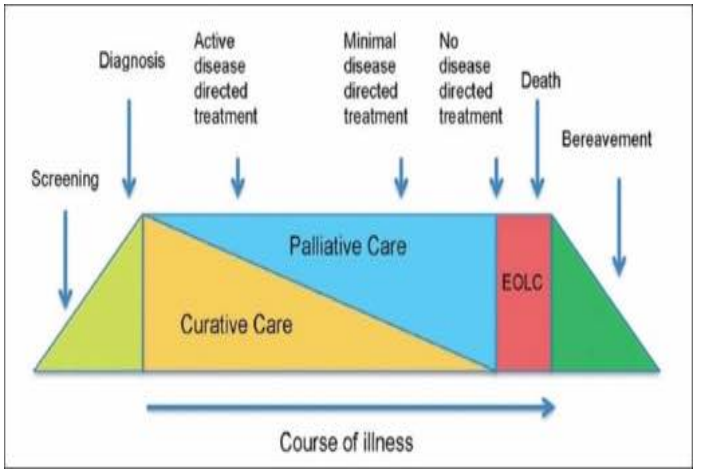
- **Abstract 8583: Surgery for patients receiving ipilimumab: Safety profile and immunological insights (Gyorki DE et al):**
  - Surgery is safe in patients receiving ipi. Immune modulation caused by CTLA-4 blockade does not appear to impact wound healing, even in the bowel. In carefully selected patients 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.





Integration of Immuno-Oncology and palliative care:

- **Overwhelming enthusiasm for immunotherapeutics in several tumor types, but:**
  - **Not all patients will have benefit, responses can be heterogeneous, lack of predictive biomarkers of response and/or toxicity**
  - **Only a small of patients with enlarging or new lesions will subsequently experience an immune-related response, but: these can be associated with durable benefit measured in years**



  - **On the other hand: treatment beyond progression can also mean continuation of futile treatment, slowing the transition to "end of life care (EOLC)" and contributing to patient suffering, for example restriction to use supportive medications such as steroids because of concerns about reducing the efficacy of immunotherapy.**
  - **Challenge of maintaining hope while establishing of realistic expectations**
  - **Even more difficult in resource-constrained environment**
  - **More research needed on QoL, palliative care and survivor ship research in the era of immuno-oncology**

Wong A et al, J Clin Oncol 2016; 34:1561-1562

Changing the face of melanoma … the modern melanoma patient:

Disclosure of potential conflict of interests:

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

St. Nikolaus-Hospital Eupen

KLINIK ST.JOSEF ST.VITH

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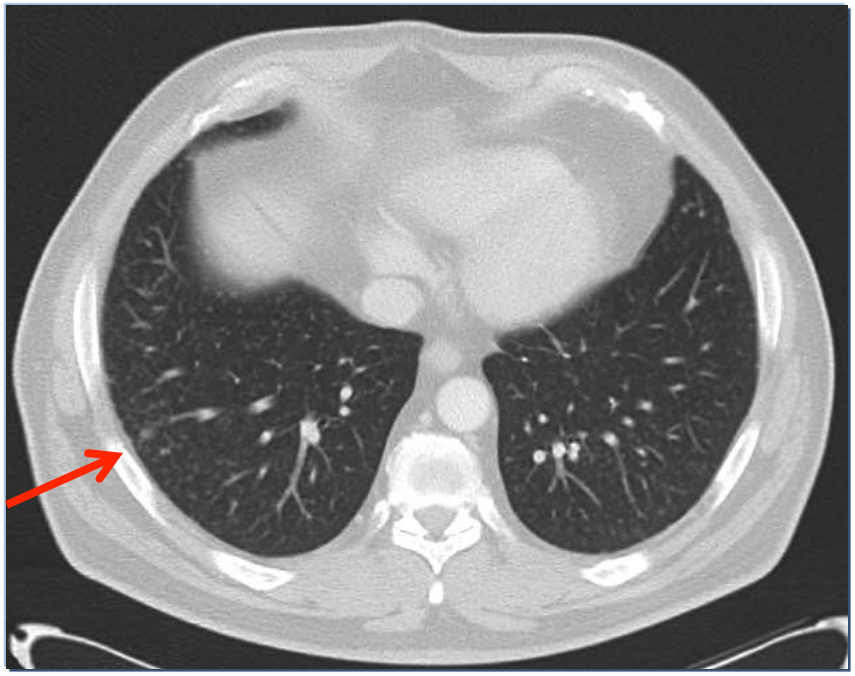
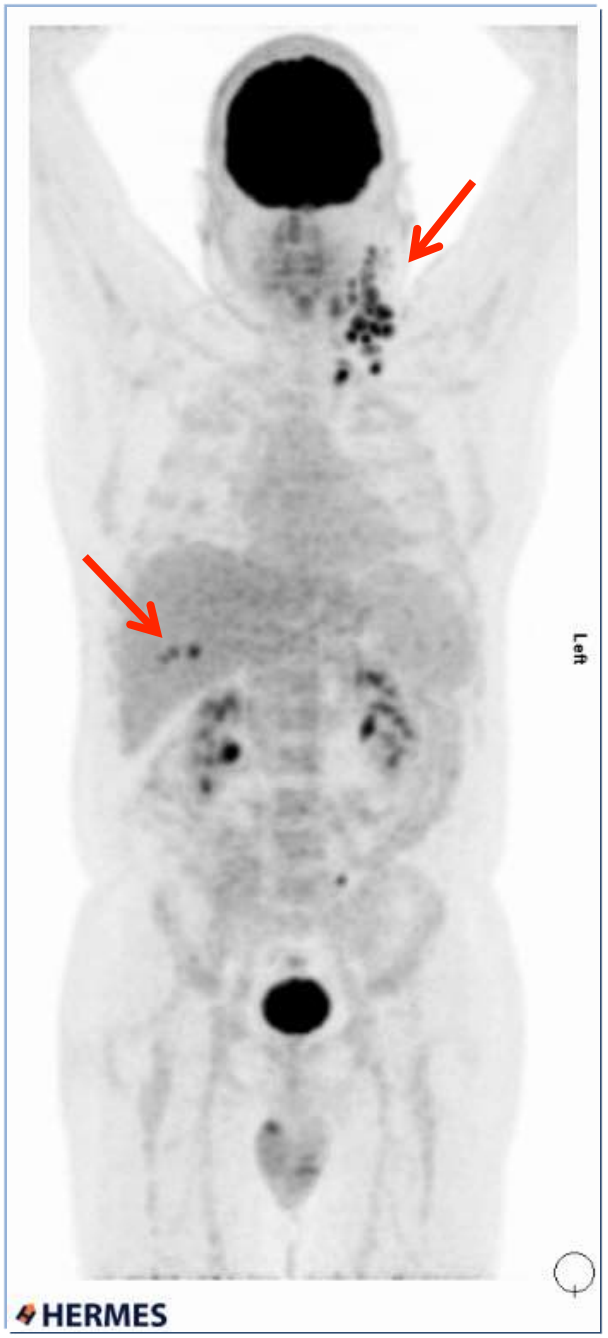
pascalwolter@hotmail.com, +32 87 21-1111 or -2987

Casus 1:

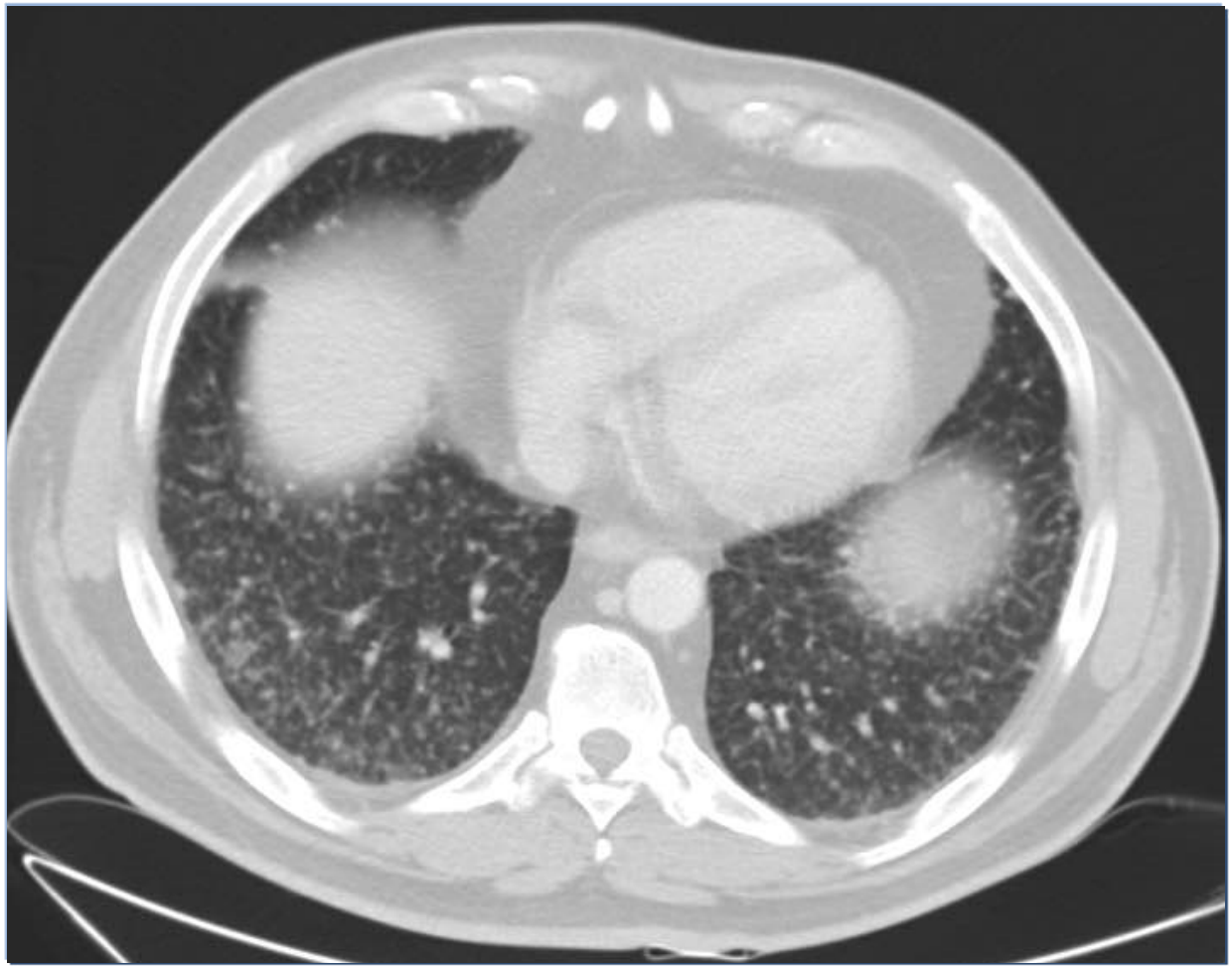
- 07-2006 (♂, * 1971): excisie nodulair melanoma posterieur linker oor, Clark level IV, dikte meting volgens Breslow 1.56 mm.
- 09-2013: klier- en galblaasmetastasen, vermoeden longmetastasen
- 18-10-2013: inclusie CHECKMATE studie vergelijking van de immunotherapie Ipilimumab/placebo vs Nivolumab/placebo vs Ipilimumab/Nivolumab.





Casus 1:

- 31-10-2013: na eerste toediening ontwikkelen van droge hoest, urticariële rash en subfebrilitas, op CT massieve progressie thv miliaire longmetastasen (dd: pseudoprogressie, dd: pneumonitis)

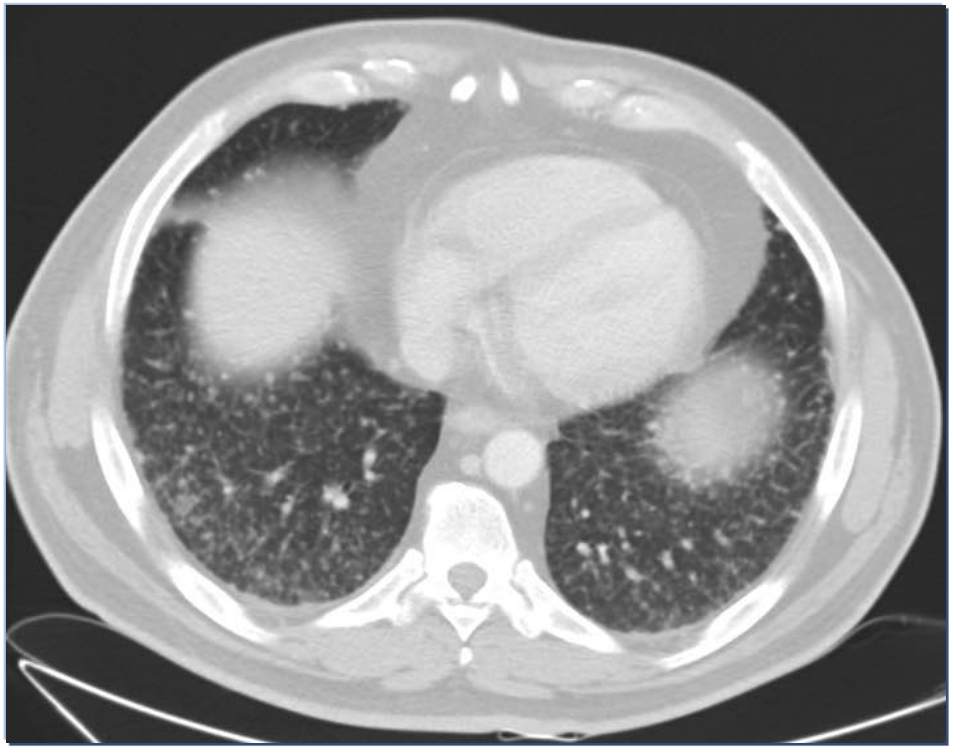


Questions – What do you do?

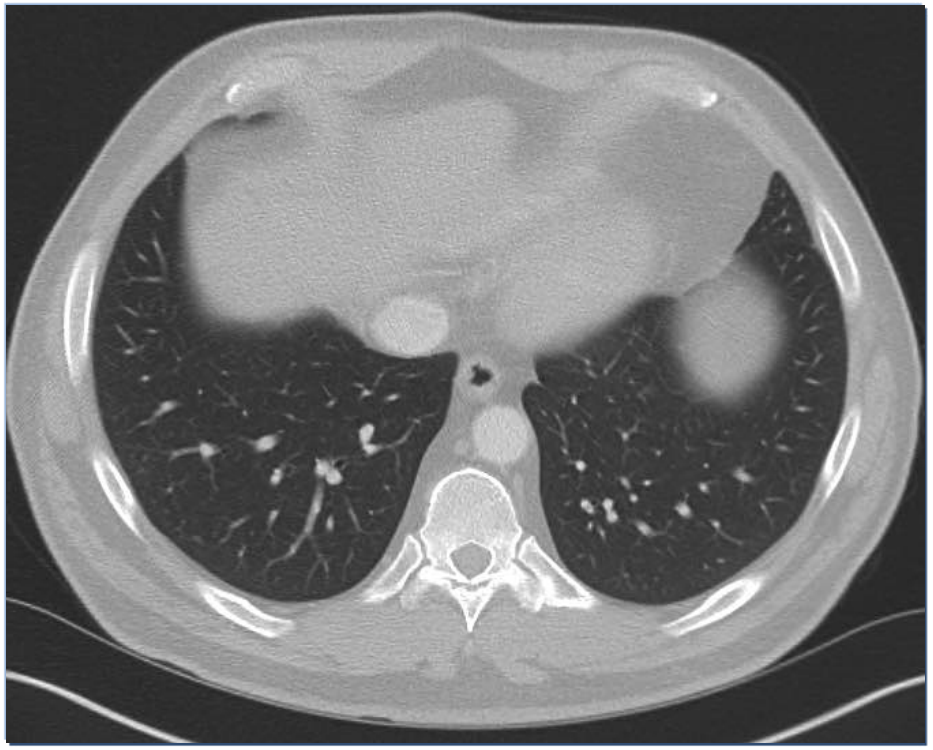
1. I stop the immunotherapy immediately
2. I go on with the immunotherapy
3. I go on with immunotherapy but I start corticosteroids
4. I don’t know

Casus 1:

- 31-10-2013: na eerste toediening ontwikkelen van droge hoest, urticariële rash en subfebrilitas, op CT massieve progressie thv miliaire longmetastasen (dd: pseudoprogressie, dd: pneumonitis)

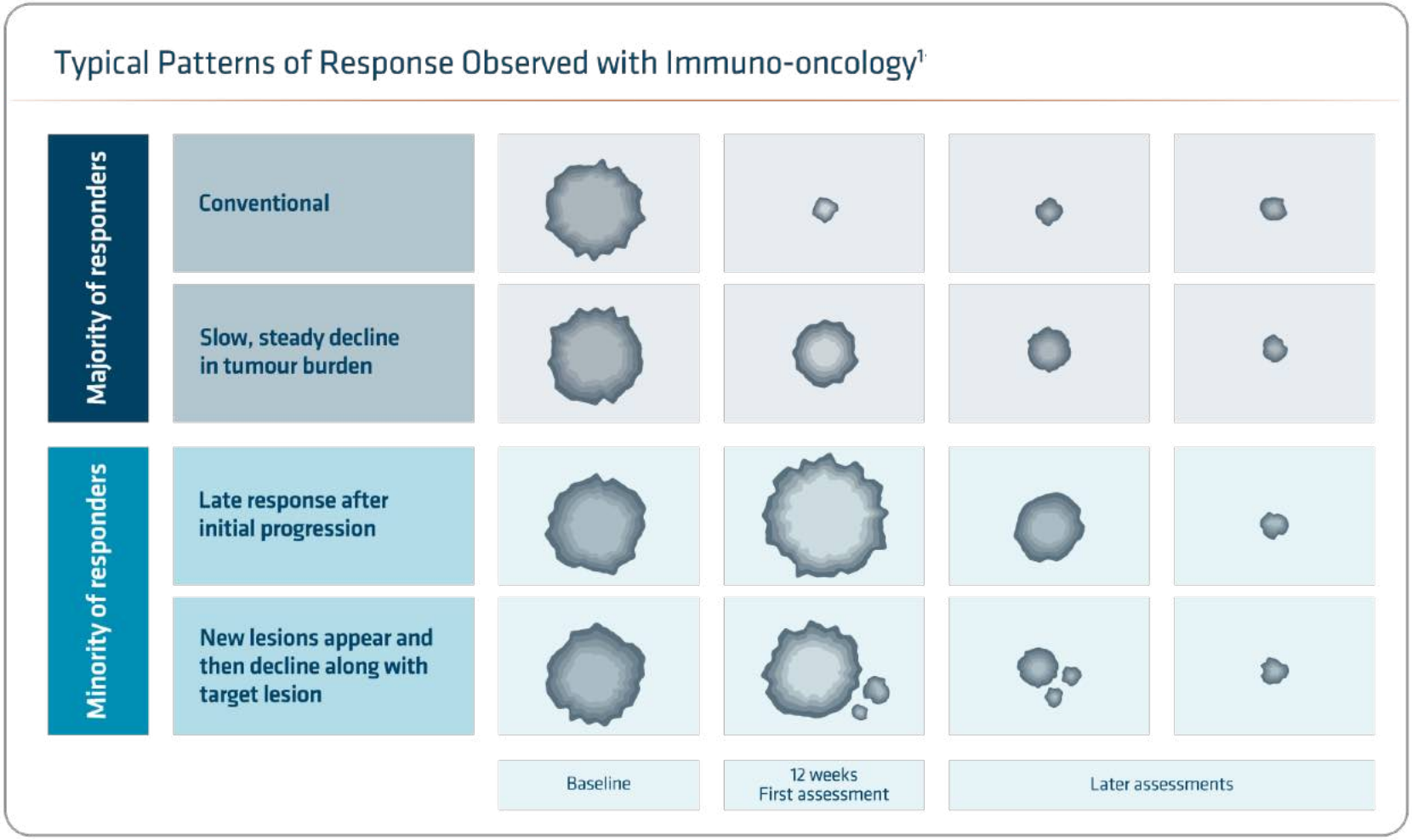


31-10-2013



10-01-2014

Immuno-oncology – Patterns of Response in Melanoma



1. Wolchok JD et al. Clin Cancer Res 2009;15:7412−20.

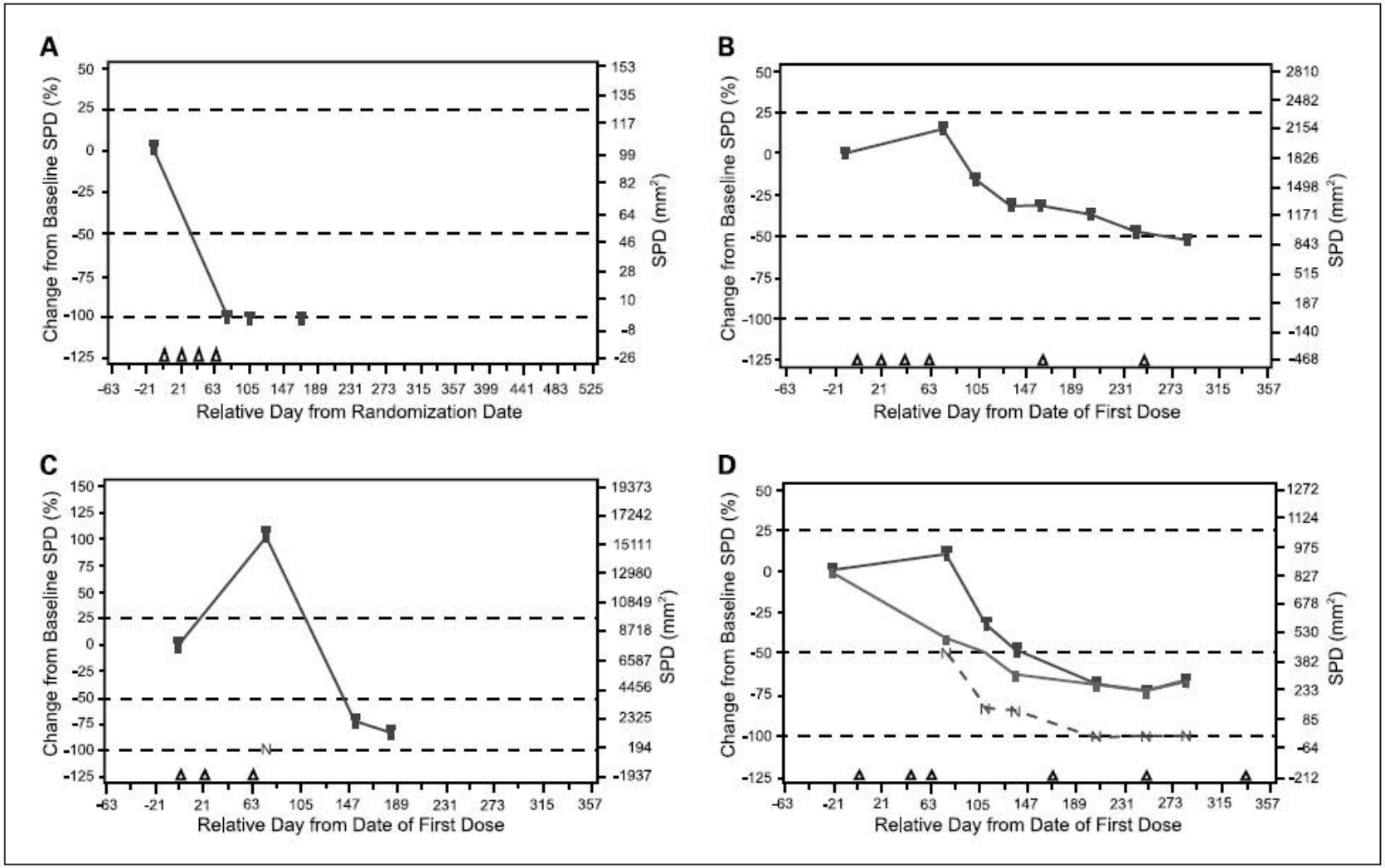


Fig. 1. Patterns of response to ipilimumab observed in advanced melanoma. Shown are the four response patterns observed in advanced melanoma patients treated with ipilimumab at 10 mg/kg in the CA184-008 and CA184-022 studies. *A,* response in baseline lesions; *B,* "stable disease" with slow, steady decline in total tumor volume; *C,* response after initial increase in total tumor volume; *D,* reduction in total tumor burden after the appearance of new lesions. SPD, sum of the product of perpendicular diameters. N, tumor burden of new lesions (*C* and *D*). *D,* top line, total tumor burden; middle line, tumor burden of baseline lesions; bottom line, tumor burden of new lesions. Triangles, ipilimumab dosing time points; dashed lines, thresholds for response or PD/irPD.

Wolchok JD et al. Clin Cancer Res 2009

Table 1. Comparison between WHO criteria and the irRC

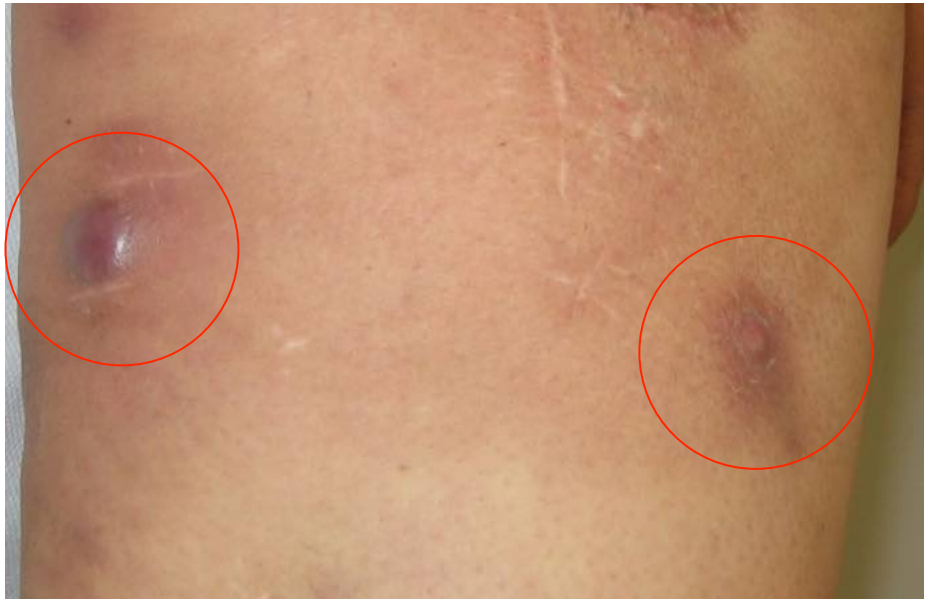
	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

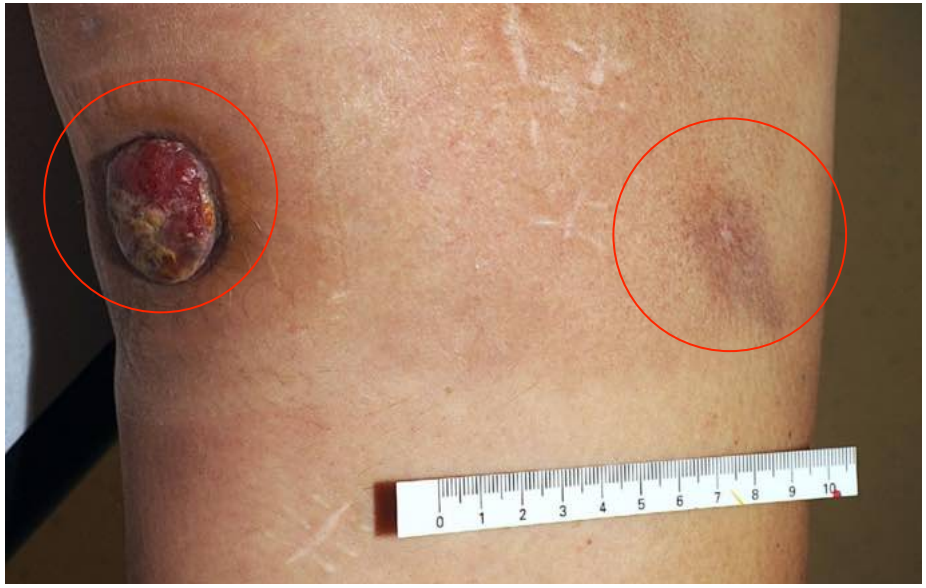
Wolchok JD et al. Clin Cancer Res 2009

Casus 2:

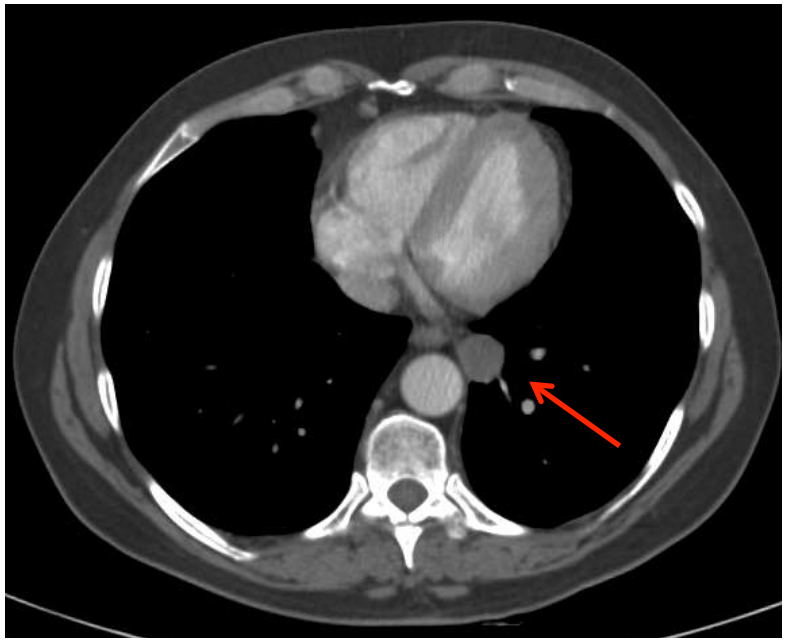
- 04-2008: diagnose acraal lentigineus maligne melanoma thv de linker hiel, Breslow 2,7 mm, Clark level III, pT3a,
- 05-2008: brede resectie (2cm marge), correctie huiddefect dmv full thickness graft genomen uit rechter lies, sentinelklierbiospie positief, gevolgd door een iliacofemoraal links (2/6 klieren positief)
  07-2009: opstarten adjuvant Intron A tot half juli 2009 buiten studieverband
- 09-2009: diagnose van in transit metastasen thv de linker dij en lies.
- 10-2009: huidexcisie met subcutis in linker lies, bij APO: verspreide metastasen
- 11-2009: aanvullend radiotherapie tot 60 Gy in 30 fracties
- 01-2010: gunstige respons van de intransit metastasen in bestraal gebied, maar nieuwe metastasen mediaal van net bestralingsveld.
- 02-2010: resectie van in transit metastasen thv de linker dij en lies
- 03-2010: opnieuw resectie van in transit metastasen thv de linker dij
- 04-2010: start systemische chemotherapie ovv DTIC in monotherapie owv van verdere lokale en niet resecabele ziekteprogressie, onder de chemotherapie regressie van de meeste noduli
- 08-2010: toename van 2 letsels aan de rand van het vroegere bestraalde gebied, bestraling met rechtstreeks elektronenveld (25 Gy in 5 zittingen)
- 10-2010: multipele recidieven in transit letsels melanoom
- 7-11-2010: geïsoleerde lidmaat perfusie linkerbeen, op iliacaal niveau, met profylactische klierevidement, zonder tumor.
- 19-05-2011: ziekteprogressie met ontstaan van multipele klier- en subcutane metastasen, tevens levermetastasen, start Ipilimumab ikv expanded access program

Case 2:

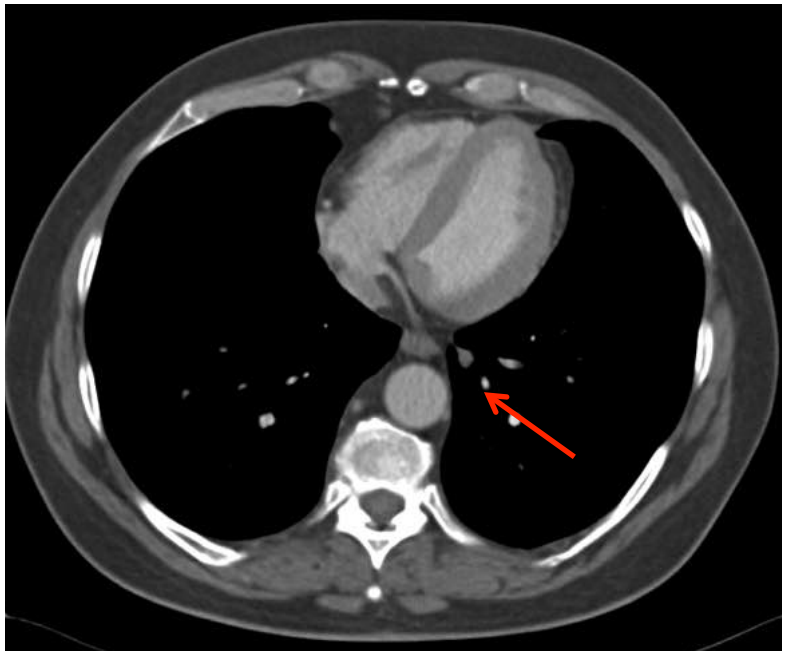




Skin (left) and longmetastasis (right) before (upper) and after 12 weeks (lower) of Ipilimumab.



CT scan of the lung at baseline



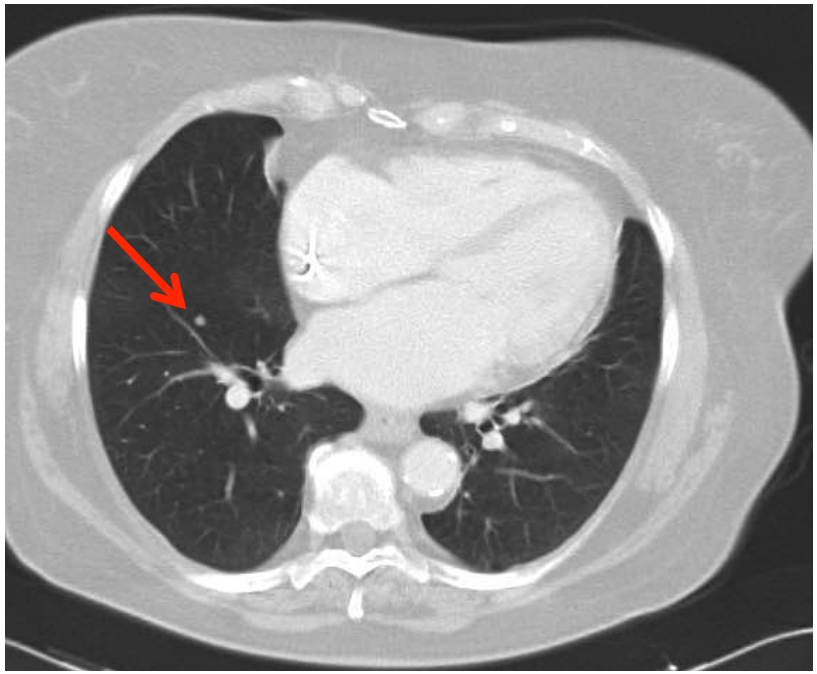
CT scan of the lung at week 12

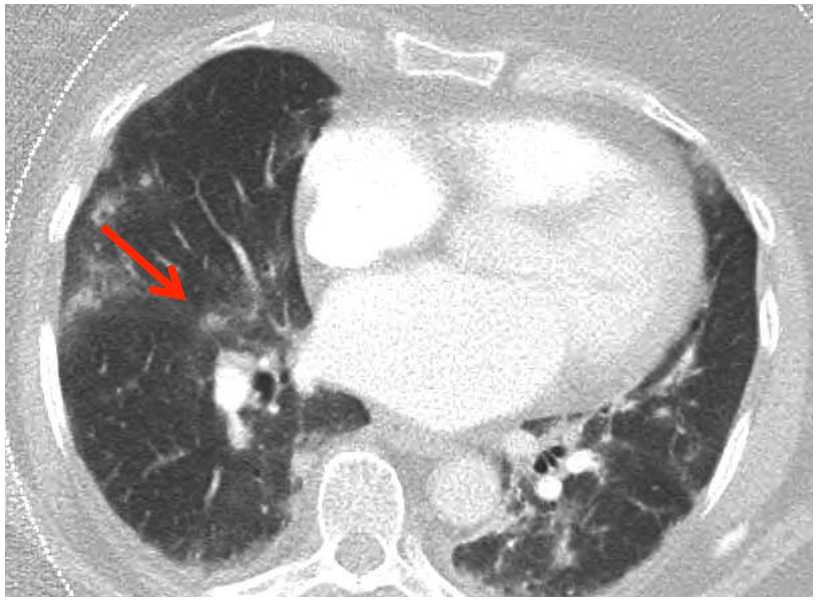
Questions – What do you do?

1. I stop the immunotherapy immediately and give another treatment
2. I go on with the immunotherapy
3. I go on with immunotherapy but I resect the progressing lesions
4. I don’t know

Casus 3:

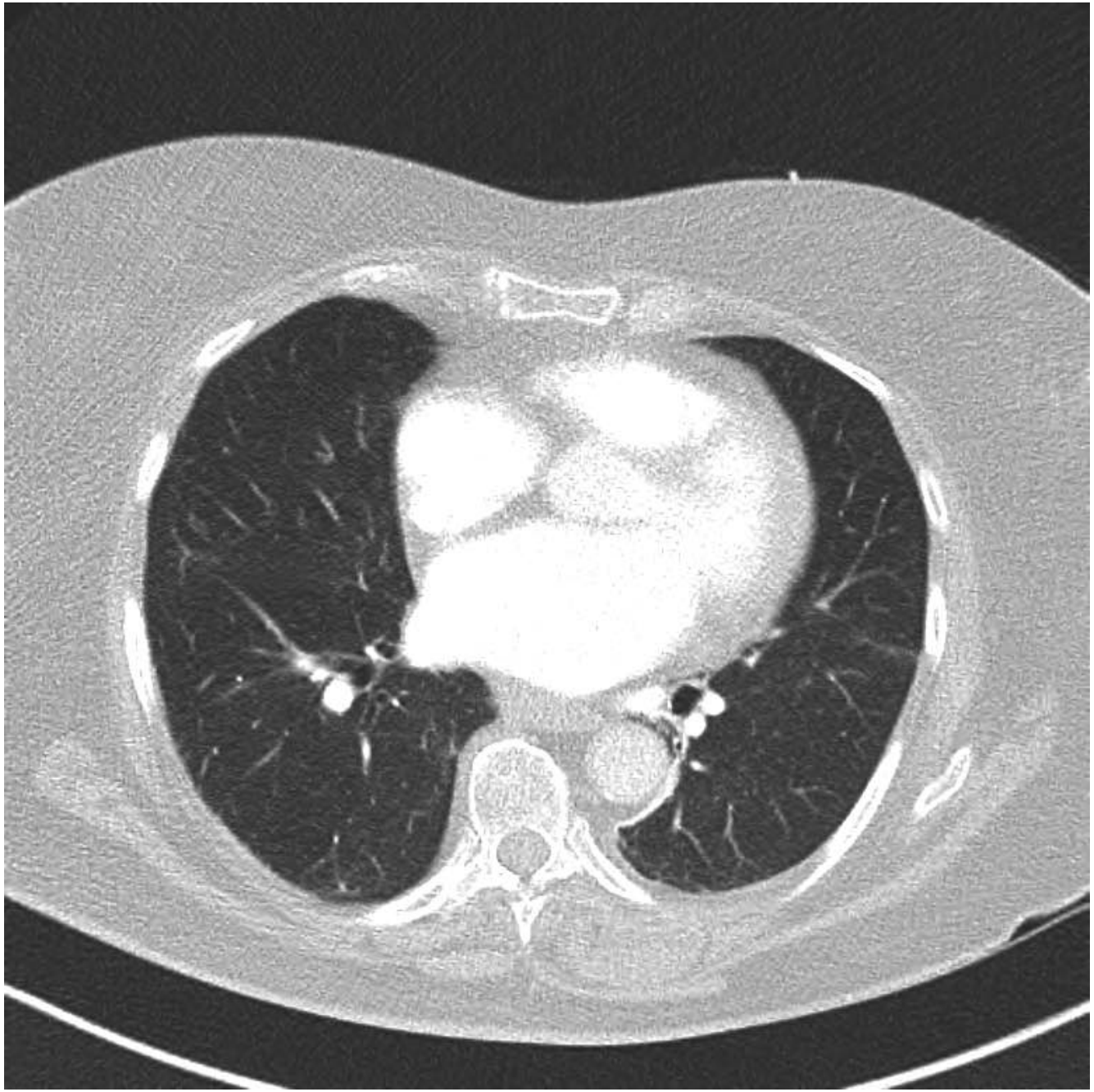
- 08-1994 (♀, * 1931): excisie superficieel spreidend melanoma dorsaal aan de enkel, Clark level IV, dikte meting volgens Breslow 2,9 mm.
- tussen 2010 en 2011: recidiverende intransit metastasen waarvoor resectie en geïsoleerde lidmaatperfusie met Melphalan
- 09-2013: intransit-, klier- en longmetasasen
- 04-10-2013: inclusie CHECKMATE studie vergelijking van de immunotherapie Ipilimumab/placebo vs Nivolumab/ placebo vs Ipilimumab/Nivolumab.
- 20-11-2013: opname op spoedgevallen voor kortademigheid en lage saturaties





Questions – What is your diagnosis / treatment?

1. Early progression under immunotherapy, I stop the immunotherapy
2. Must be pseudoprogression, I go on with the immunotherapy
3. Most likely pneumonitis, I stop immunotherapy and start immediately corticosteroids
4. I don’t know



Questions?