MADRID 2017 ESMO congress

ESMO Clinical Practice Guidelines

Immunotherapy in Melanoma… and others
Pseudo-progression, Management of Toxicities

Clinical Case Discussion

Ulrich Keilholz, MD

Charité Comprehensive Cancer Center

Berlin, Germany

DISCLOSURES

Consultancy/Advisory Board:

Astra Zeneca, Bristol-Myers Squibb, Glycotope, MSD, Merck, Novartis, Pfizer

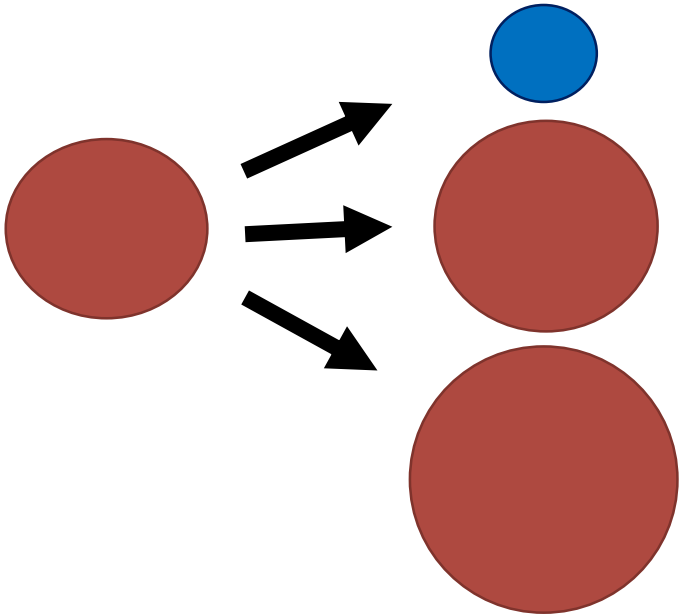
Research Grants:

AstraZeneca, Merck, Pfizer

Educational presentation/Speaker/ Travel Accommodation

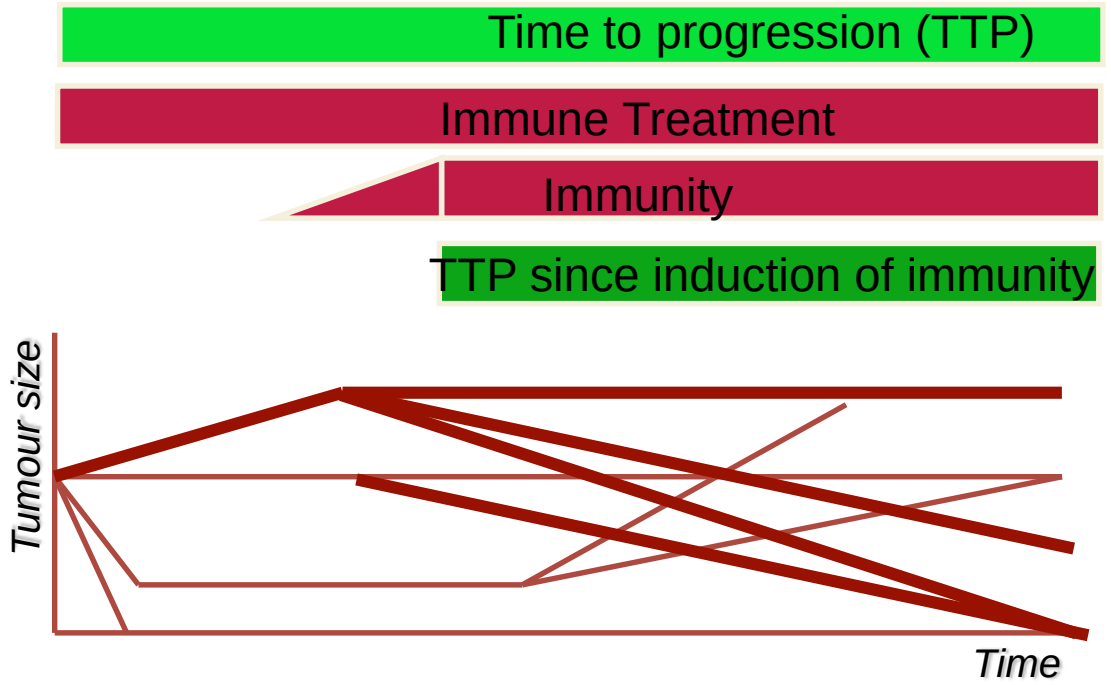
Amgen, Astra Zeneca, Bristol-Myers Squibb, Glycotope, MSD, Merck, Novartis, Pfizer, Roche

Immune checkpoint inhibitors typical tumour evolution week 6-8



Induction of immunity may need time
Efficacy occurs only with immunity

Workshop and Annual Meeting
Arlington VA Nov 10-13 2005



Induction of immunity may need time Efficacy occurs only with immunity

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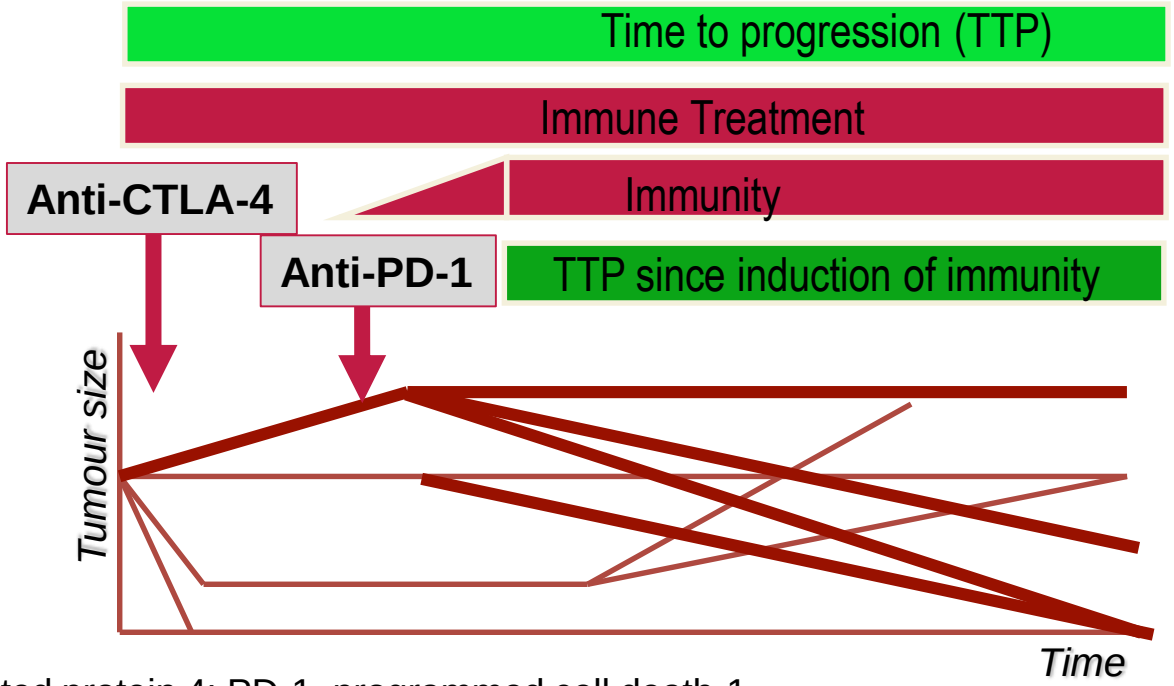
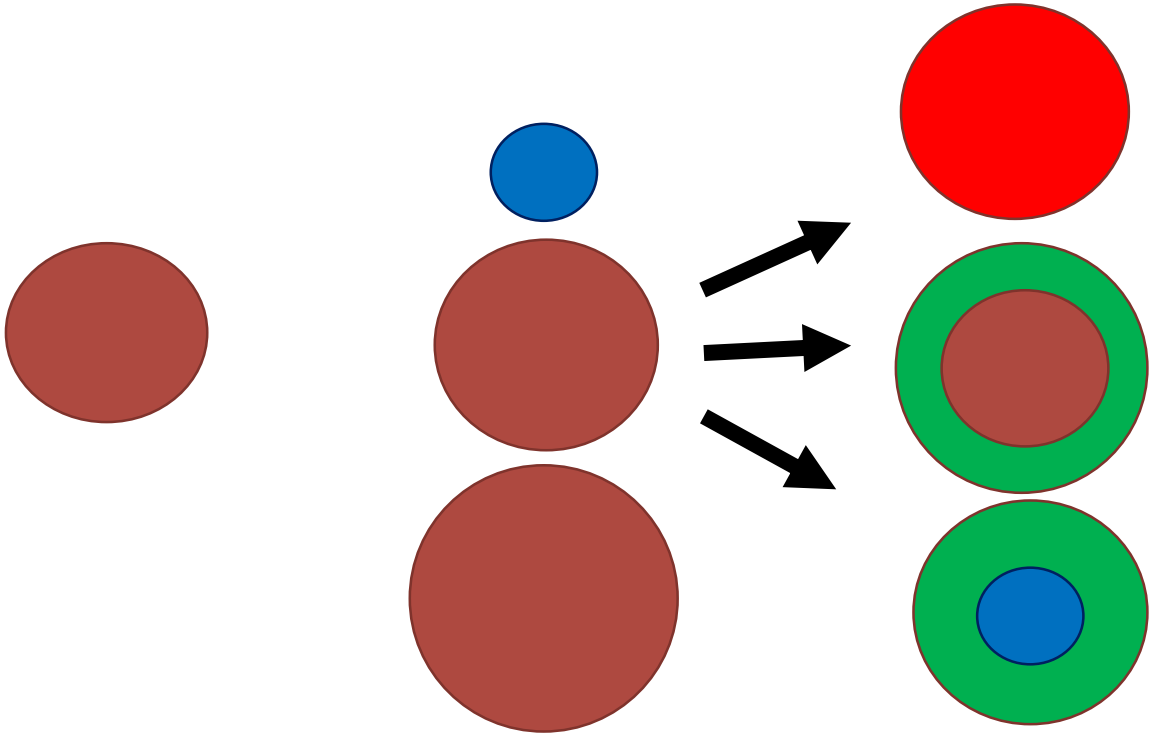
SBT

Workshop and Annual Meeting
Arlington VA Nov 10-13 2005



CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death-1

Immune checkpoint inhibitors typical tumour evolution week 6-8



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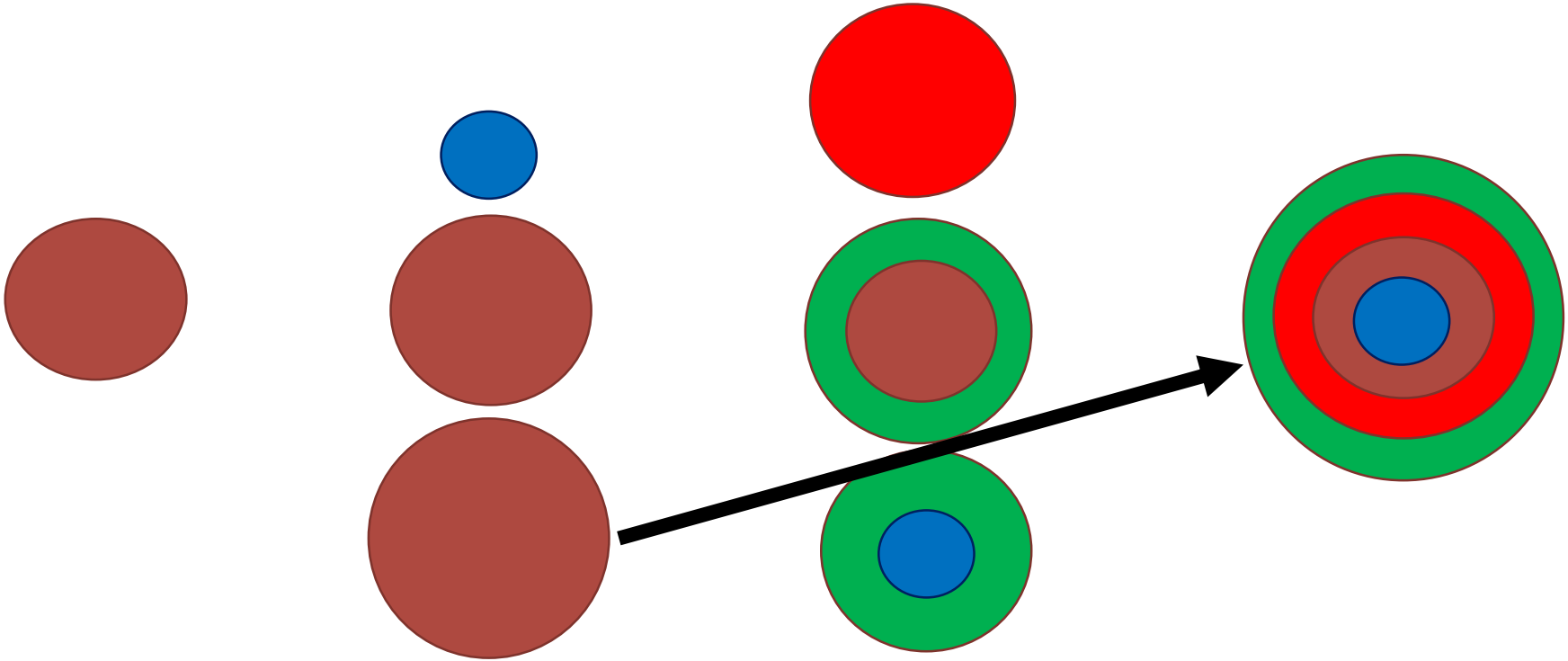
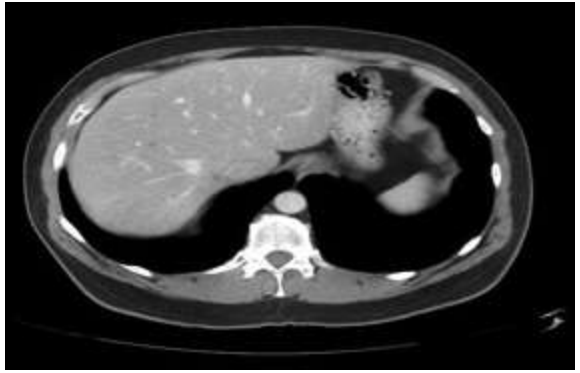


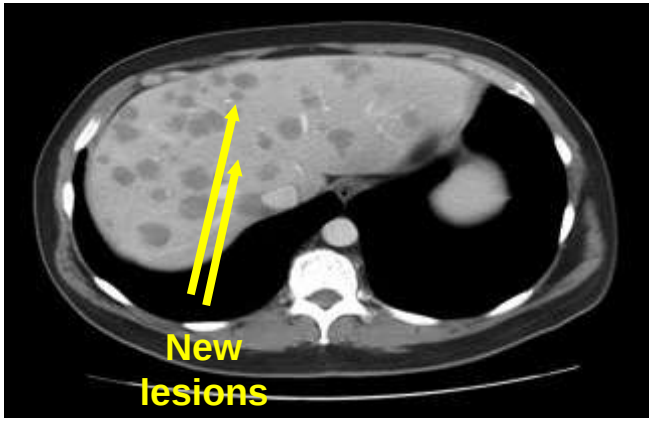
Immune-Related Patterns of Response with anti-CTLA-4: Melanoma Response After the Appearance and Subsequent Disappearance of New Lesions

Pre-treatment

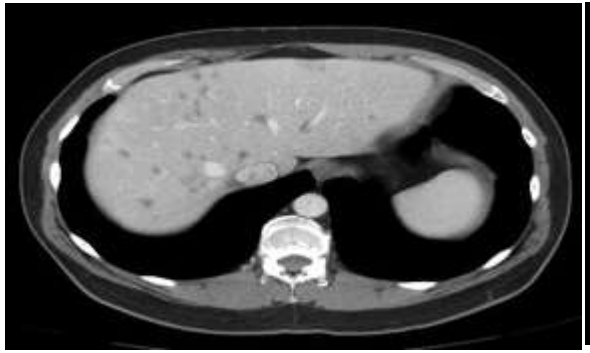


3 mg/kg
Ipilimumab
Q3W X 4

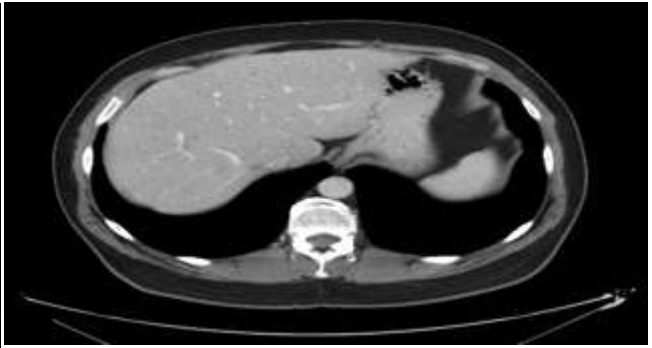
Week 12: Progression



Week 20: Regression



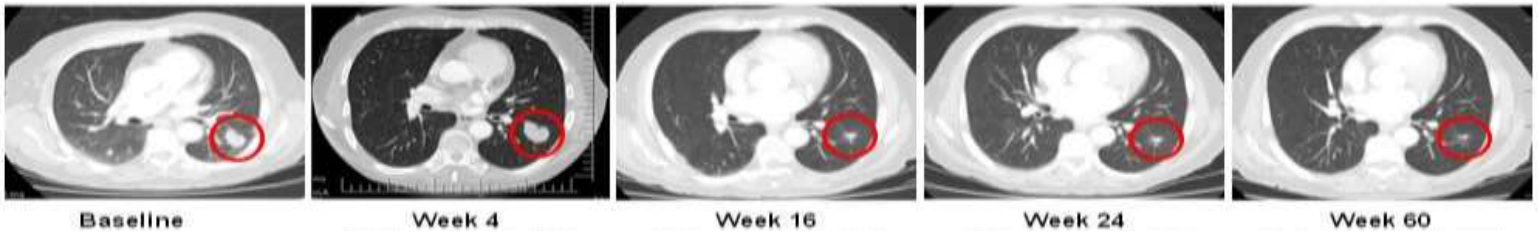
Week 36: Still Regressing



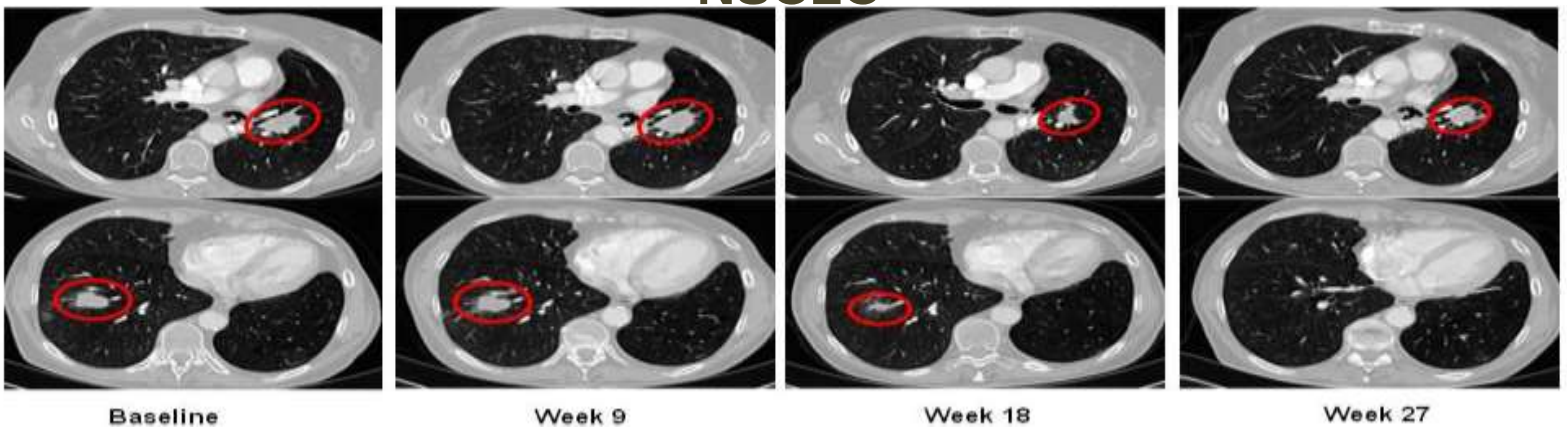
Wolchok et al. ASCO 2008, Abstract #3020

PD-1 Blockade Kinetics of Response
(Pembrolizumab, Keynote 001)

Metastatic Melanoma



NSCLC



NSCLC, Non-Small Cell Lung Cancer

Wolchok et al. ASCO 2015

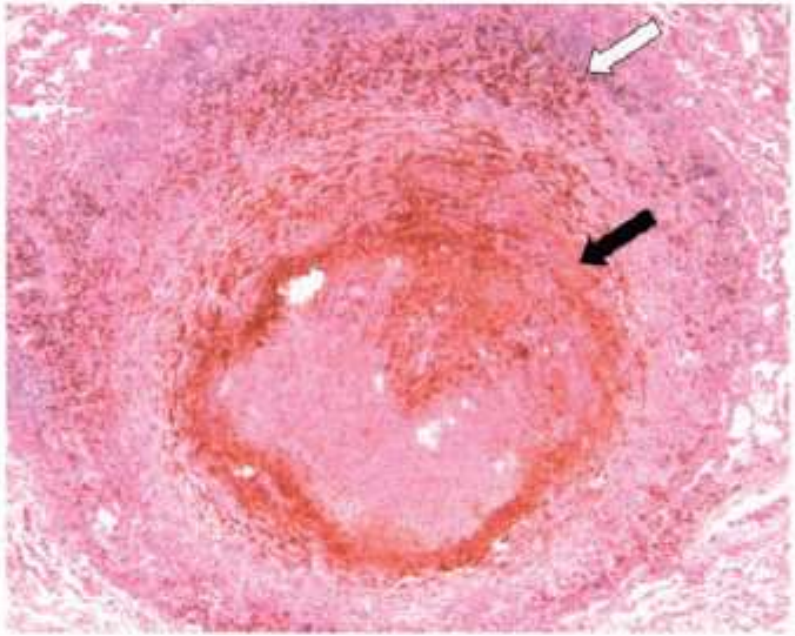
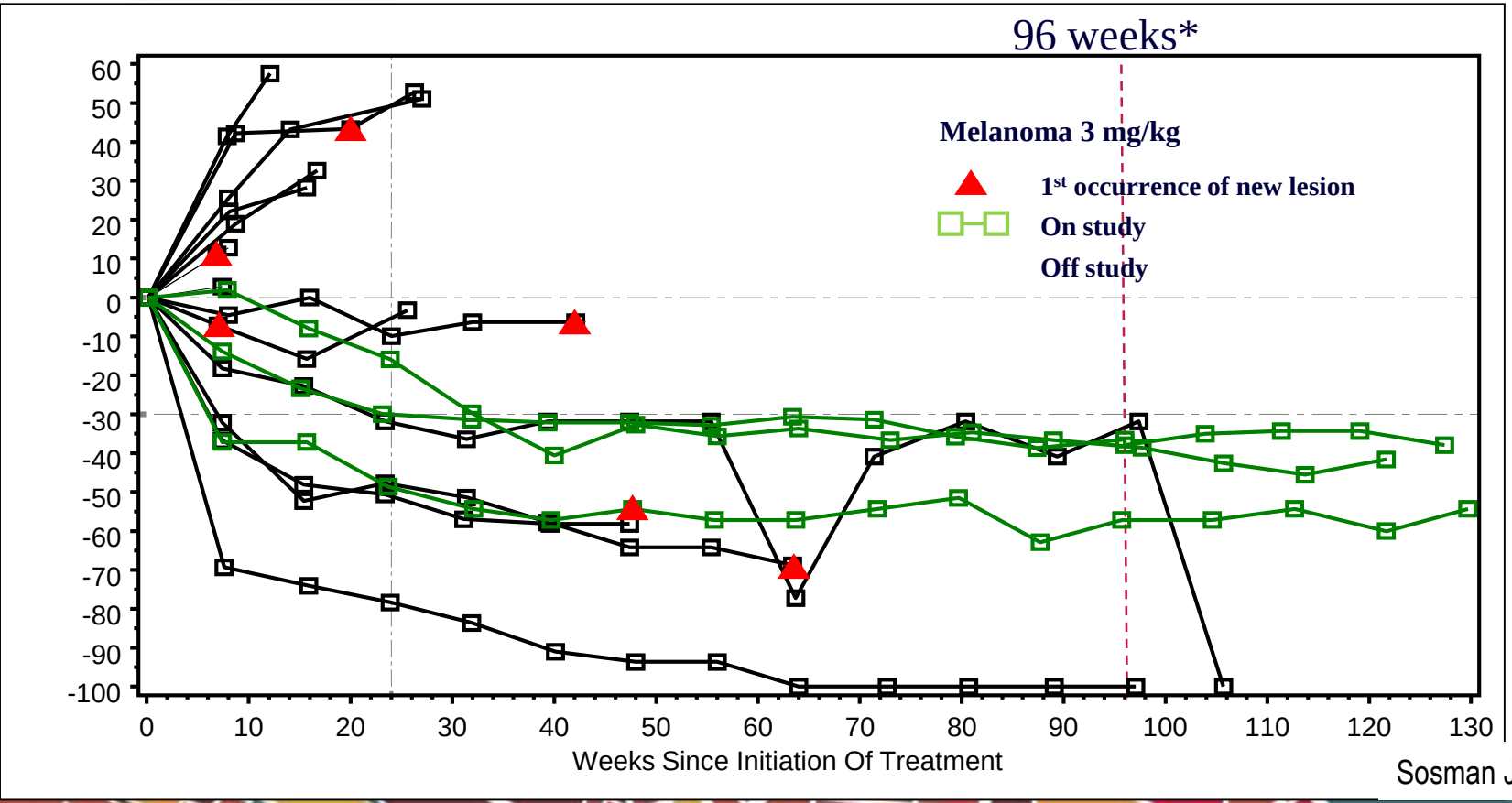


Fig. 4. Resected metastatic melanoma tumor nodule of the lung. This case is a 53-y-old male, diagnosed with melanoma of the scalp, who underwent resection and adjuvant biochemotherapy. After two cycles, imaging confirmed multiple new lung nodules consistent with recurrent disease (stage M1b). Eight months after starting ipilimumab, the dominant lung lesion was resected along with two small nodules (3 mm each). From a biopsy of one of the small nodules, note the T-cell infiltrate (*white arrow*) and extensive necrosis (*black arrow*) with no residual tumor cells. Section was stained with H&E.

Wolchok et al. Clin Cancer Res 2009;15(23)



Sosman J et al. ESMO 2009

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok,[1] Axel Hoos,[2] Steven O'Day,[3] Jeffrey S. Weber,[4] Omid Hamid,[3] Celeste Lebbé,[5] Michele Maio,[6] Michael Binder,[7] Oliver Bohnsack,[8] Geoffrey Nichol,[9] Rachel Humphrey,[2] and F. Stephen Hodi[10]

Abstract

Purpose: Immunotherapeutic agents produce antitumor effects by inducing cancer-specific immune responses or by modifying native immune processes. Resulting clinical response patterns extend beyond those of cytotoxic agents and can manifest after an initial increase in tumor burden or the appearance of new lesions (progressive disease). Response Evaluation Criteria in Solid Tumors or WHO criteria, designed to detect early effects of cytotoxic agents, may not provide a complete assessment of immunotherapeutic agents. Novel criteria for the evaluation of antitumor responses with immunotherapeutic agents are required.

Experimental Design: The phase II clinical trial program with ipilimumab, an antibody that blocks CTL antigen-4, represents the most comprehensive data set available to date for an immunotherapeutic agent. Novel immune therapy response criteria proposed, based on the shared experience from community workshops and several investigators, were evaluated using data from ipilimumab phase II clinical trials in patients with advanced melanoma.

Results: Ipilimumab monotherapy resulted in four distinct response patterns: (*a*) shrinkage in baseline lesions, without new lesions; (*b*) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (*c*) response after an increase in total tumor burden; and (*d*) response in the presence of new lesions. All patterns were associated with favorable survival.

Conclusion: Systematic criteria, designated immune-related response criteria, were defined in an attempt to capture additional response patterns observed with immune therapy in advanced melanoma beyond those described by Response Evaluation Criteria in Solid Tumors or WHO criteria. Further prospective evaluations of the immune-related response criteria, particularly their association with overall survival, are warranted. (Clin Cancer Res 2009;15(23):7412–20)

Best Overall Response by irRC

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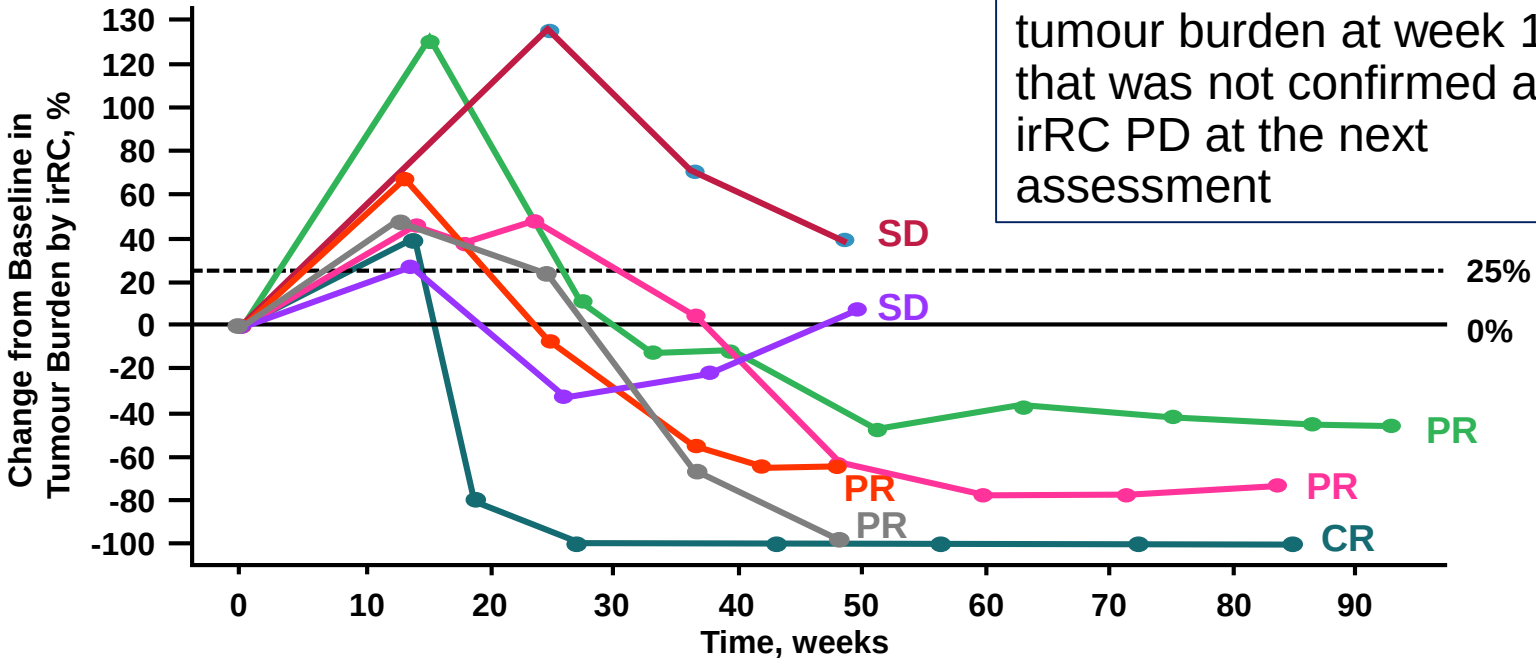
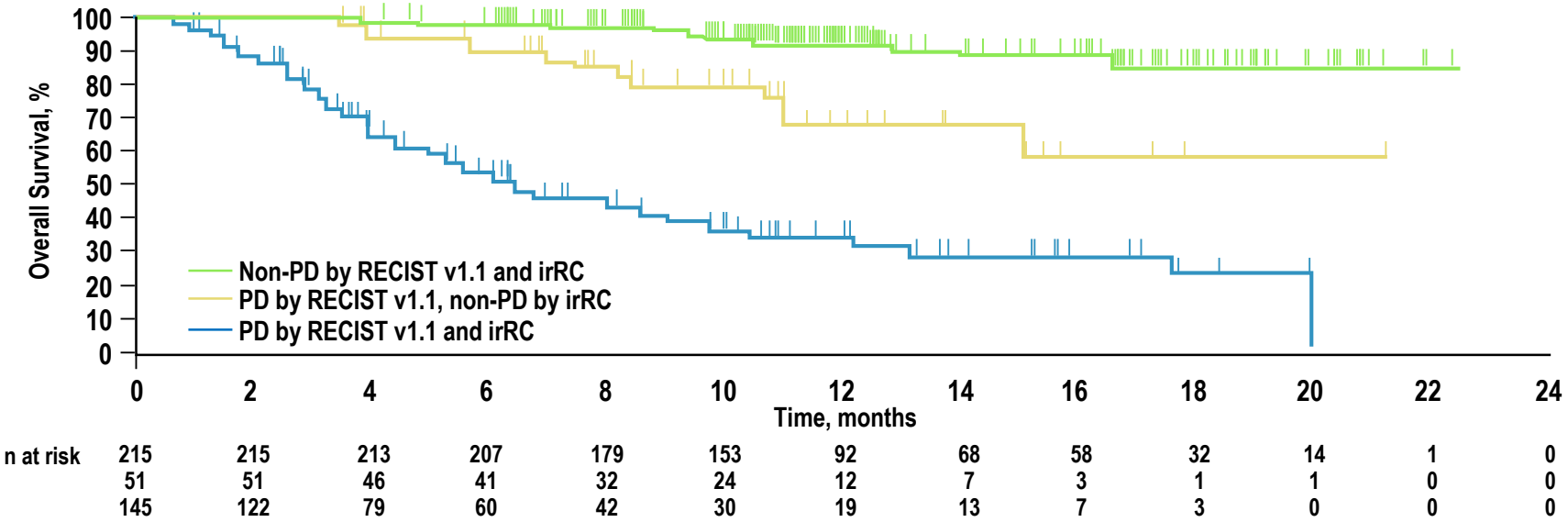
7 of 192 patients (3.6%) showed ≥ 25% increase of tumour burden at week 12 that was not confirmed as irRC PD at the next assessment



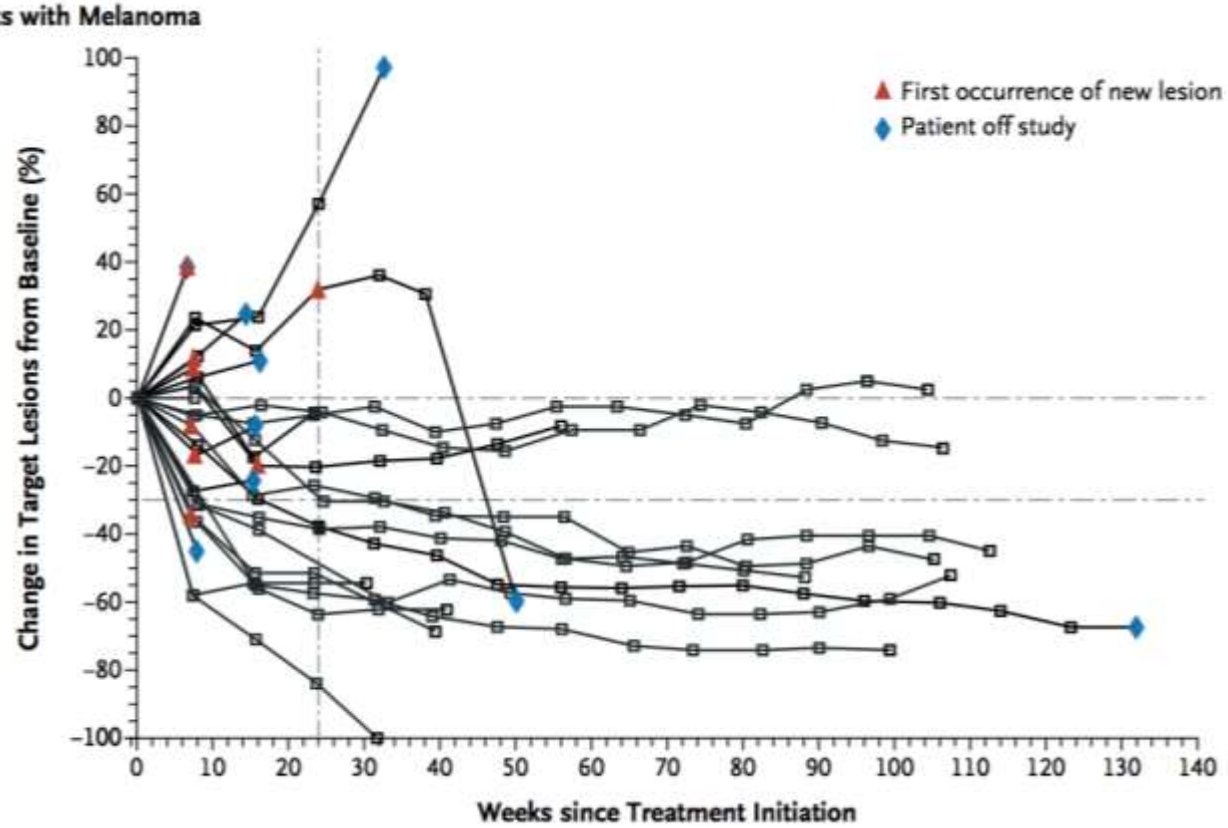
irRC, Immune-Related Response Criteria; PD, Progressive Disease

Of the 196 patients with PD by RECIST v1.1, the 51 patients (26%) with non-PD by irRC had favorable OS compared with the 145 patients with PD by both criteria
A landmark analysis showed similar results



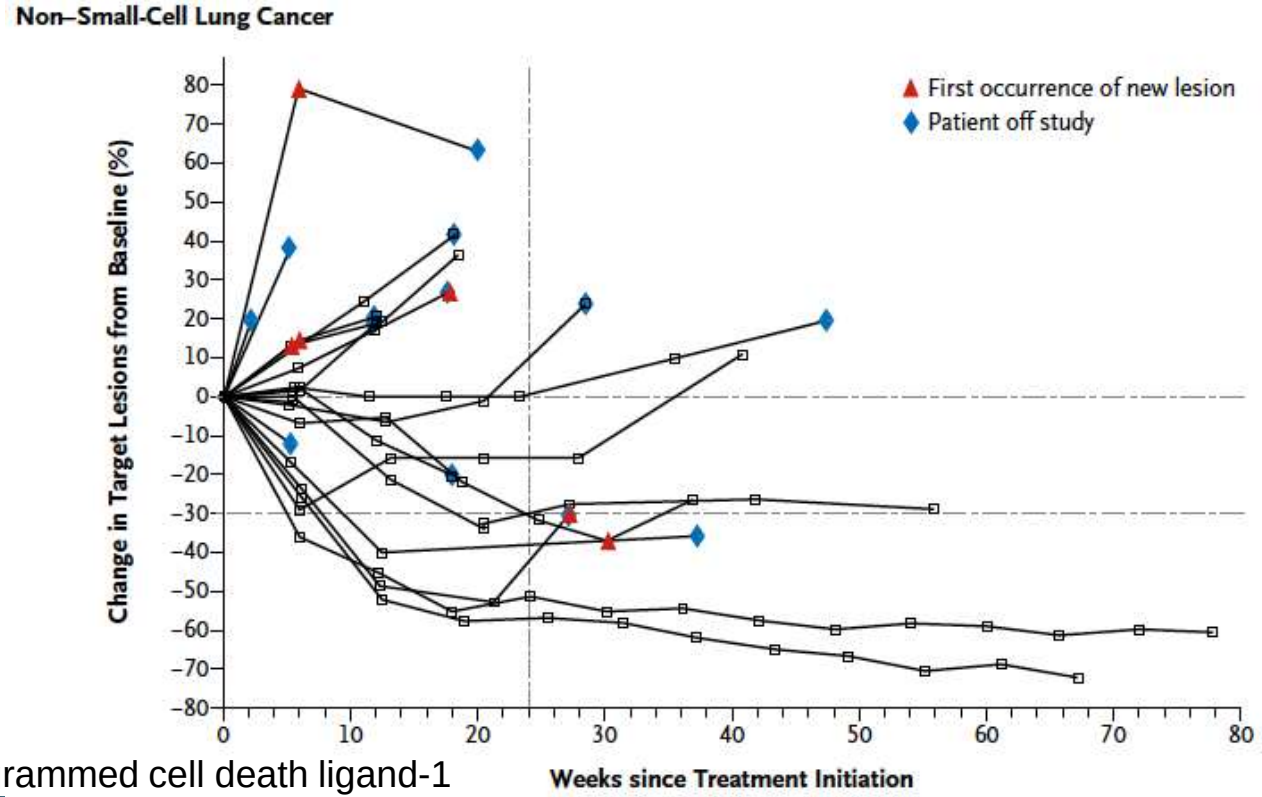
Analysis cut-off date: October 18, 2013
Hodi et al. ESMO 2014

irRC, Immune-Related Response Criteria; OS, overall survival; PD, Progressive Disease; RECIST, Response Evaluation Criteria In Solid Tumours



Topalian et al. NEJM 2012
Nivolumab in melanoma

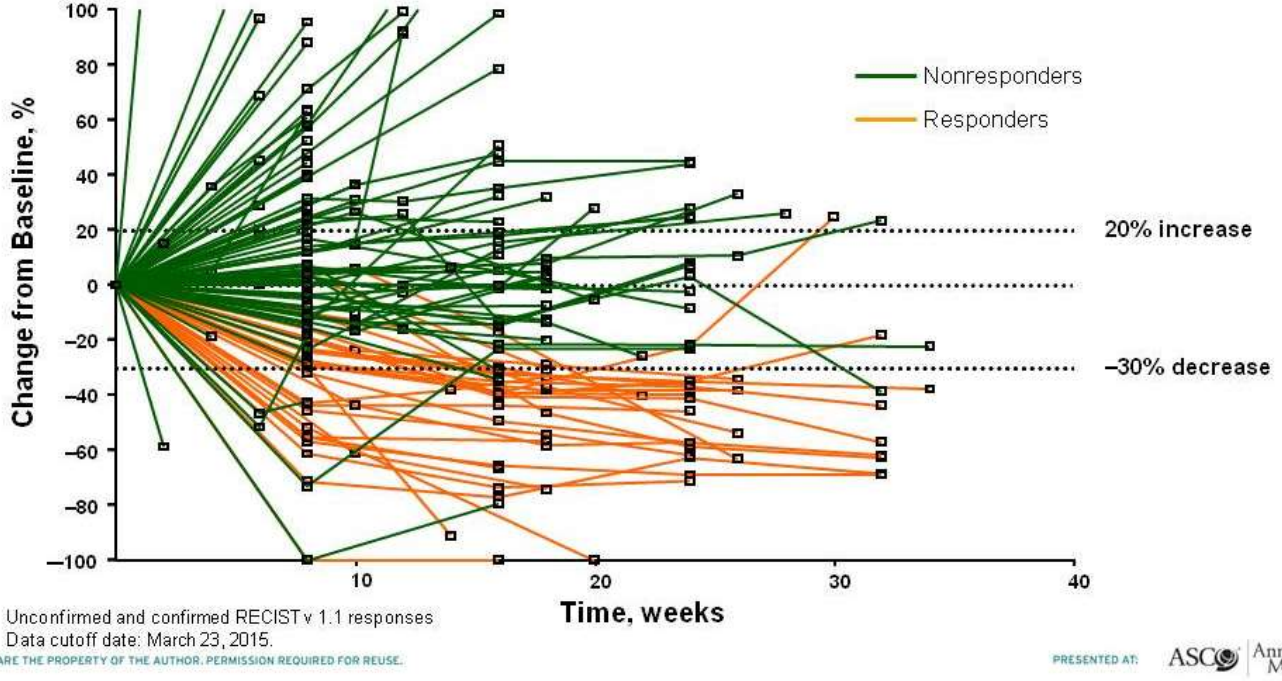
Blocking of PD-L1 in Lung Cancer
Nivolumab



PD-L1, programmed cell death ligand-1

Sznol ASCO 2013

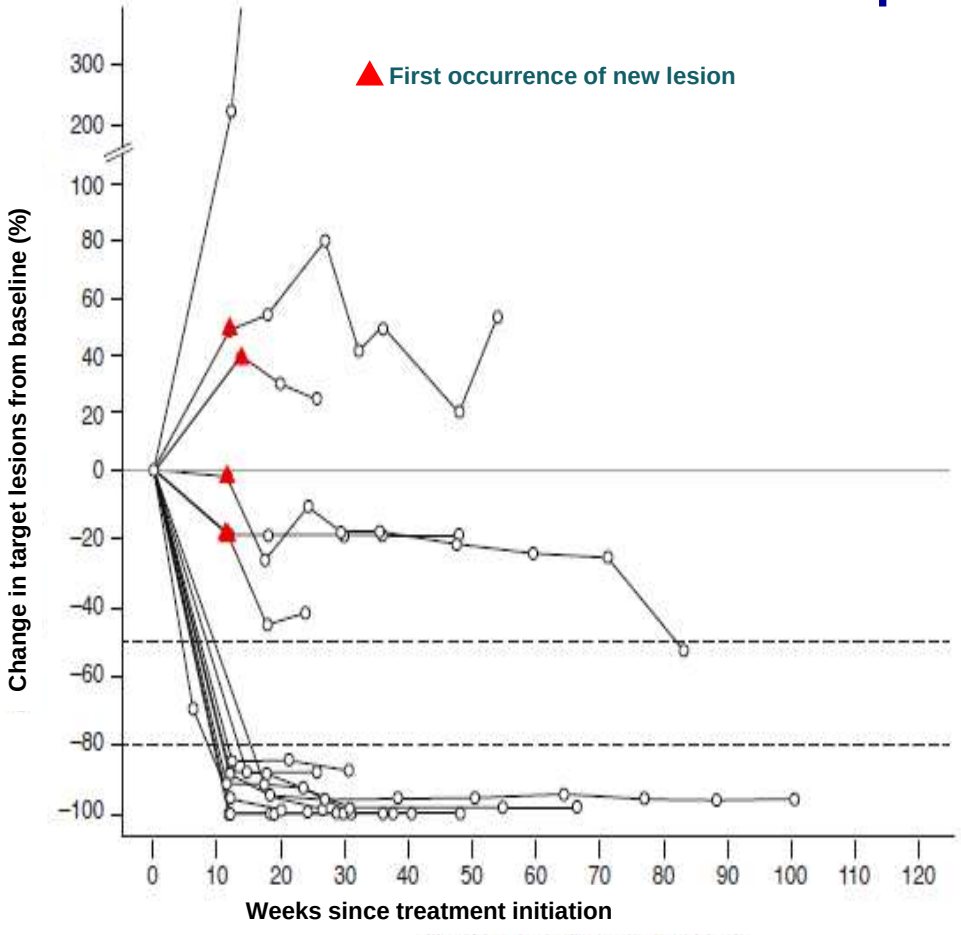
Tumour shrinkage over time in SCCHN
Pembrolizumab



SCCHN, Squamous Cell Carcinoma of the Head and Neck

Seiwert et al. 2015 ASCO Annual Meeting, Abstract 8006

CA209-004: response patterns with nivolumab + ipilimumab



Wolchok et al. ASCO 2013-2014

Transient progression

- occurs in a subset of patients
- often in some lesions without increase in overall tumour burden
- no need for change in treatment if PS and tumour markers ok

PS, performance status

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Immunotherapy in Melanoma… and others

Management of Toxicities

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

[1]Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; [2]Department of Gastroenterology, Kremlin Bicêtre Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; [3]Department of Medicine, Dermatology Unit, Gustave Roussy Cancer Campus, Villejuif, France; [4]Department of Pathology, Aberdeen University Medical School & Aberdeen Royal Infirmary, Aberdeen, UK; [5]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [6]Royal Marsden Hospital NHS Foundation Trust, London, UK; [7]Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital of Heidelberg, Heidelberg, Germany

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: May 2017.

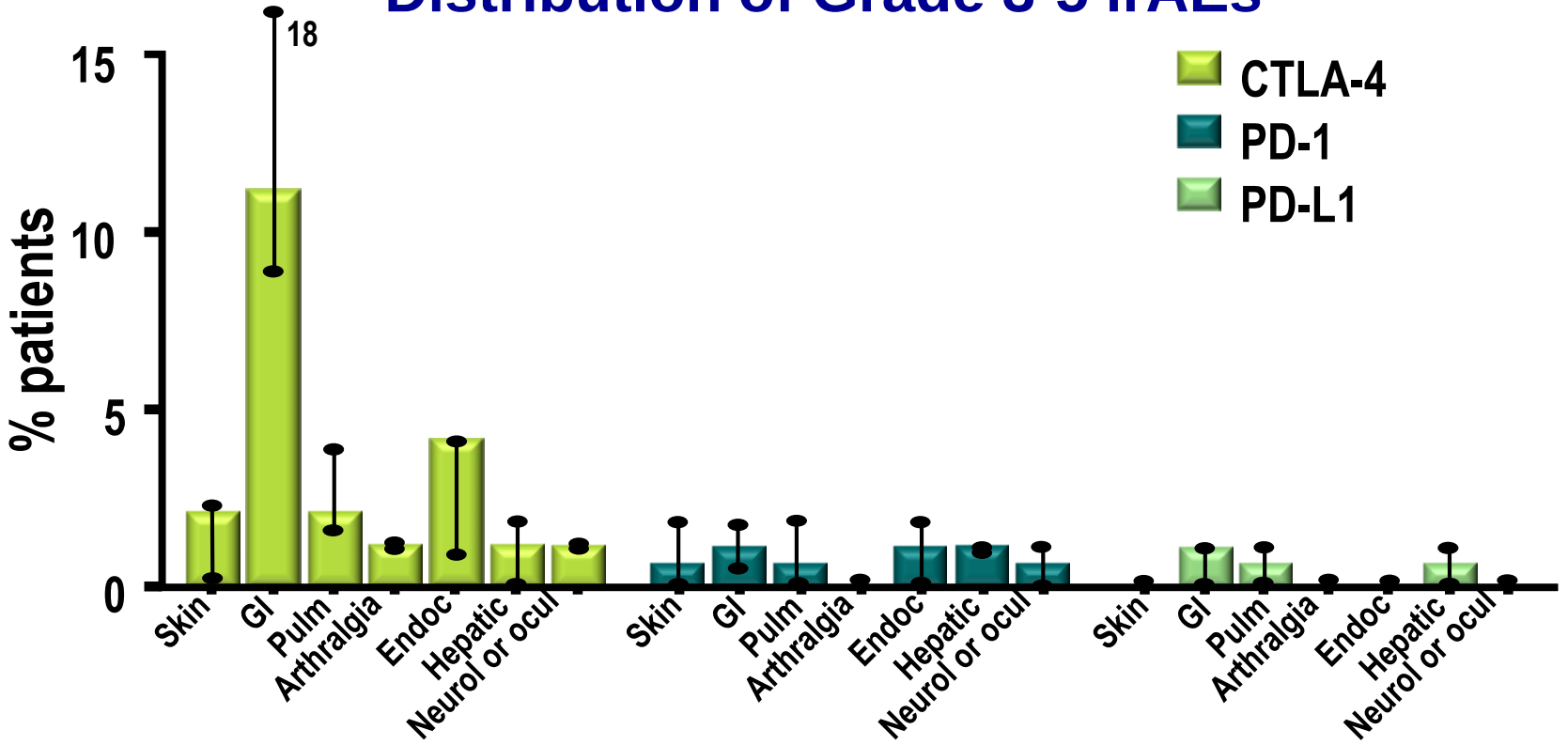
Management of Toxicities

- Early recognition
- Early treatment
- Corticosteroids often necessary
- Immunosuppressive agents as reserve
- No impairment of tumour control

- Knowledge of spectrum and kinetics essential

CTLA-4 and PD-1/PD-L1 Blockade

Distribution of Grade 3-5 irAEs

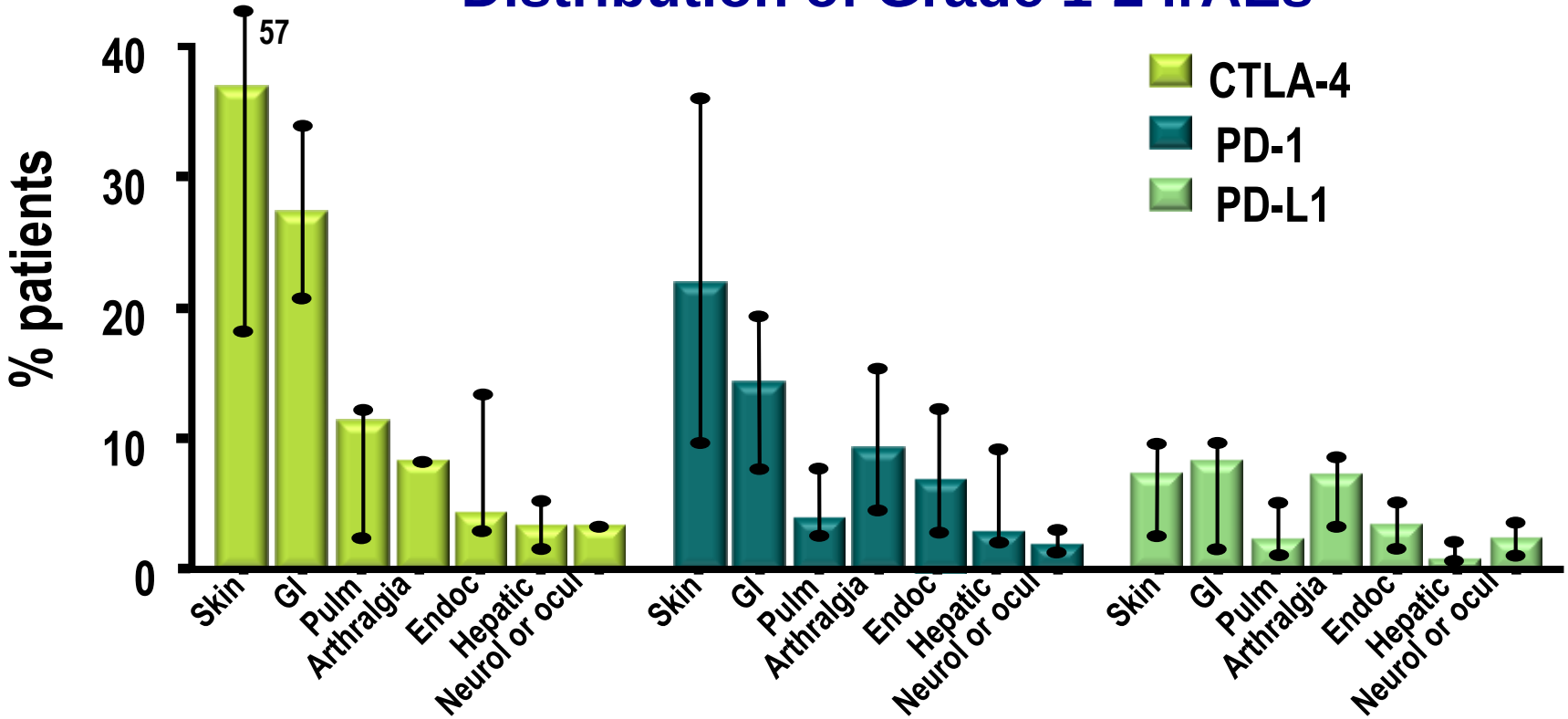


CTLA-4, cytotoxic T-lymphocyte-associated protein 4; irAEs, immune-related adverse events; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1

Michot, et. al. Eur J Cancer 2016

CTLA-4 and PD-1/PD-L1 Blockade

Distribution of Grade 1-2 irAEs



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Michot, et. al. Eur J Cancer 2016

Larkin NEJM 2015

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Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	11 (99.4)	136 (43.5)	12 (99.7)	215 (68.7)	08 (99.0)	173 (55.6)
Treatment-related adverse event†	57 (82.1)	51 (16.3)	99 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	[illegible]	7 (2.2)	[illegible]	29 (9.3)	[illegible]	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

Larkin NEJM 2015

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Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
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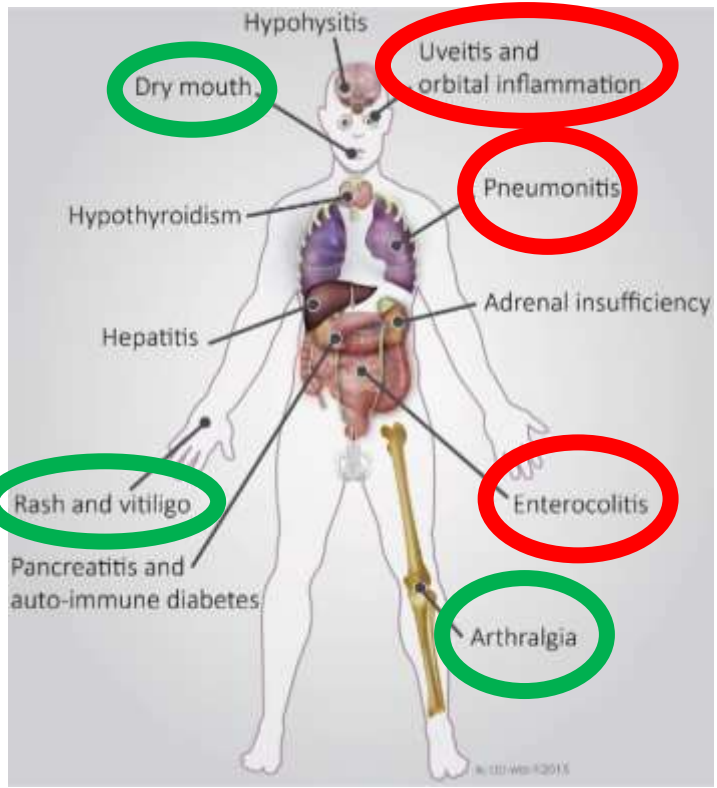
irAEs: Clinical Spectrum discovered by history and exam



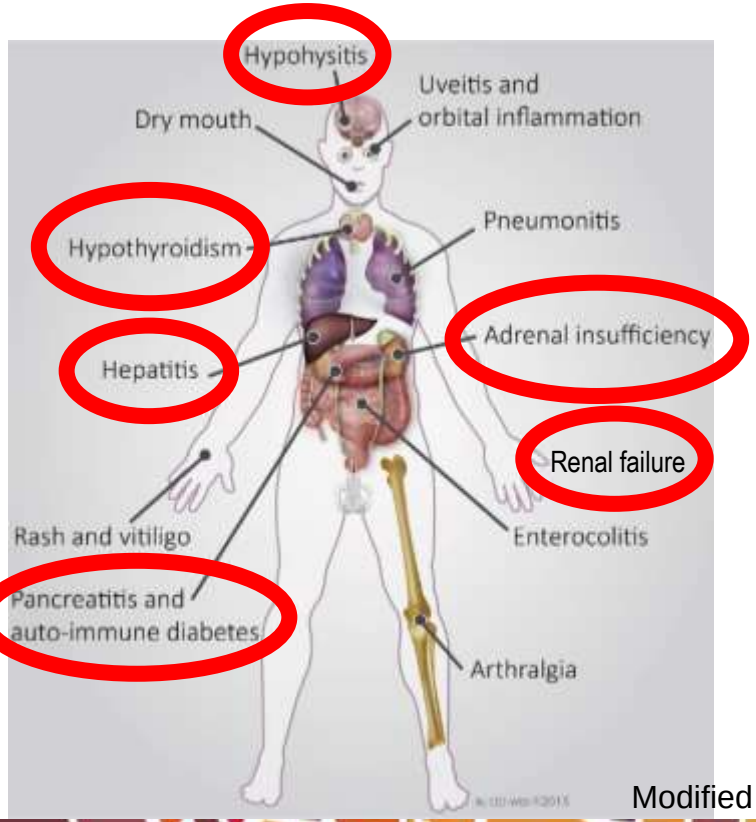
Green: patient will tell you

Red: you have to ask for early signs

irAEs, immune-related adverse events

Modified from Michot, et. al. Eur J Cancer 2016

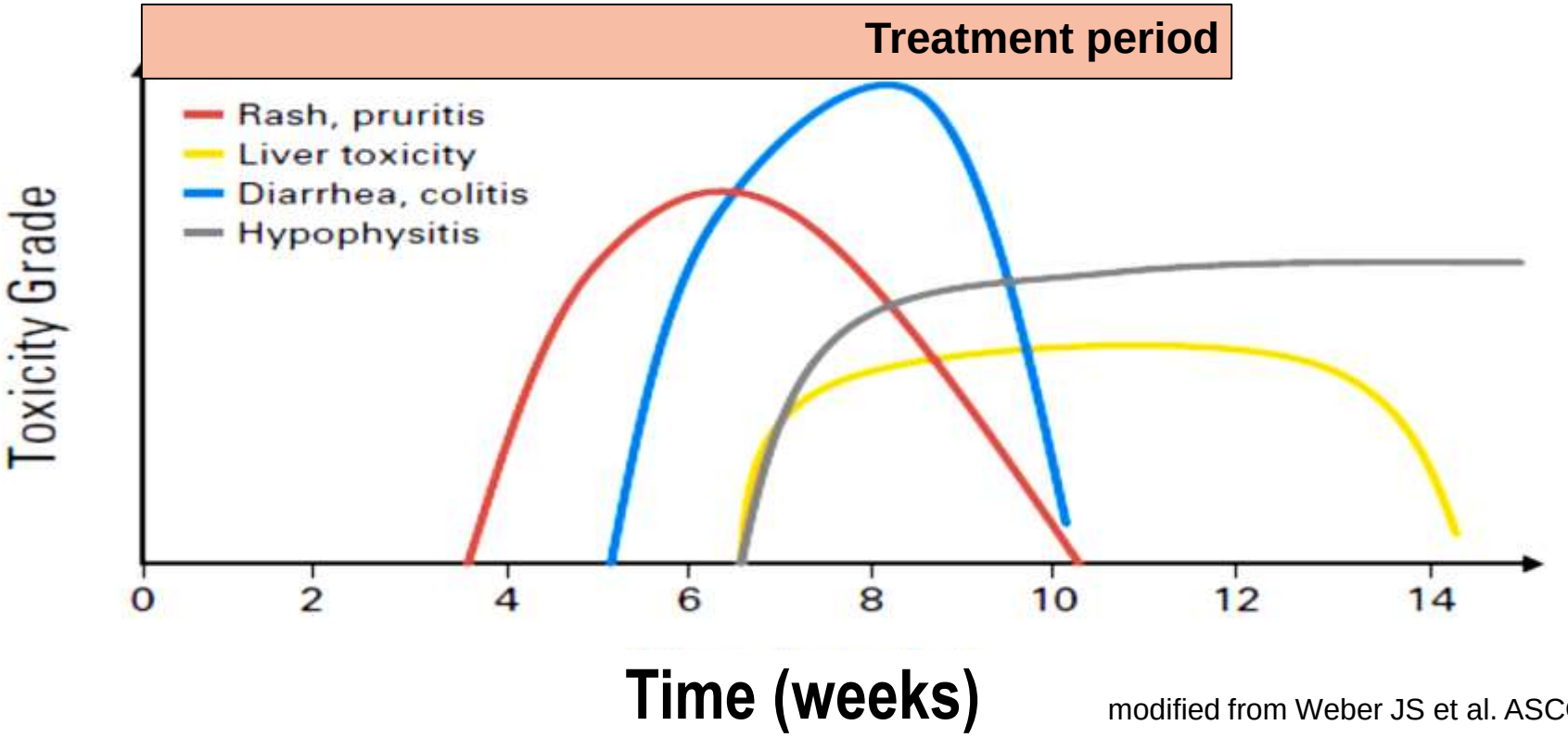
irAEs: Clinical Spectrum discovered by history and exam



irAEs, immune-related adverse events

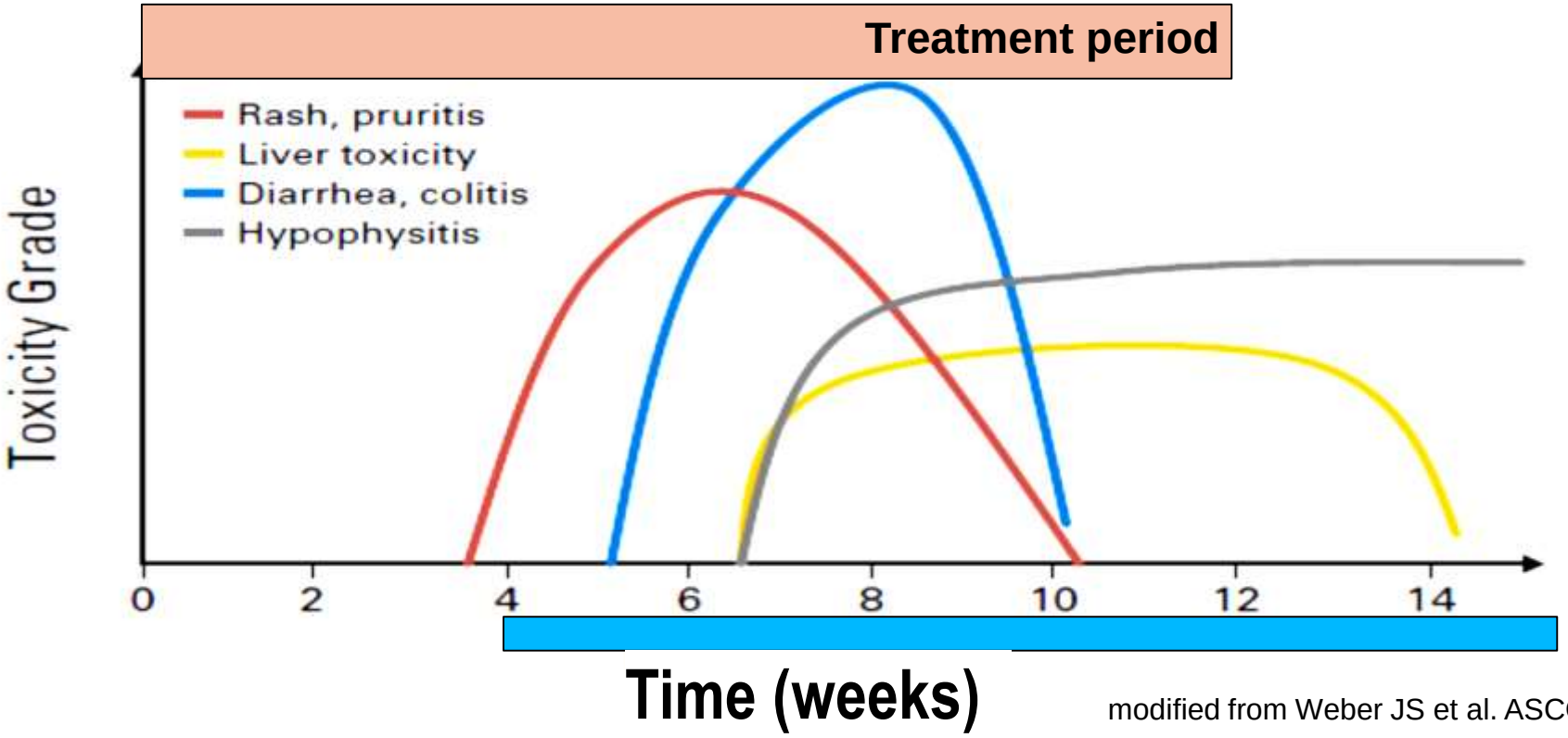
Modified from Michot, et. al. Eur J Cancer 2016

CTLA-4 BLOCKADE



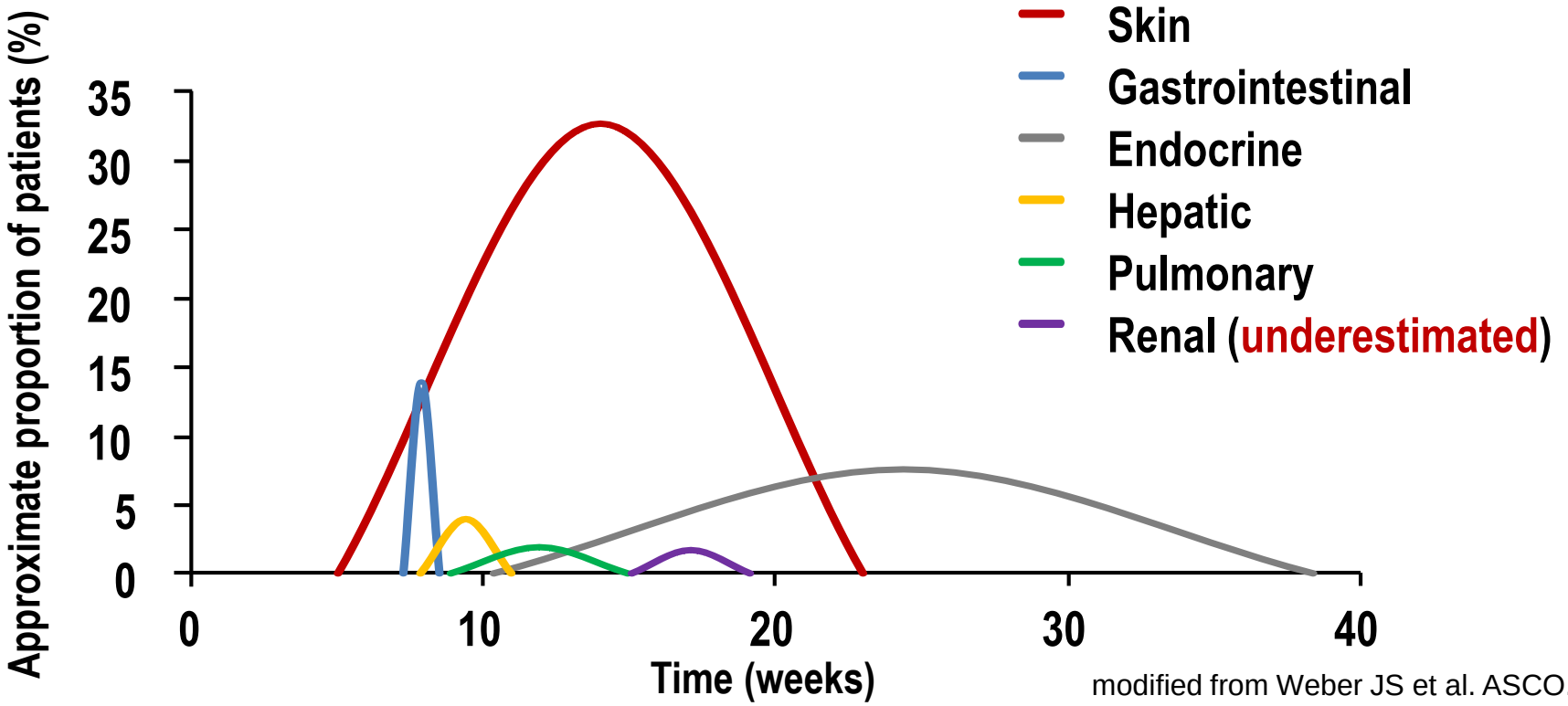
modified from Weber JS et al. ASCO. 2015

CTLA-4 BLOCKADE



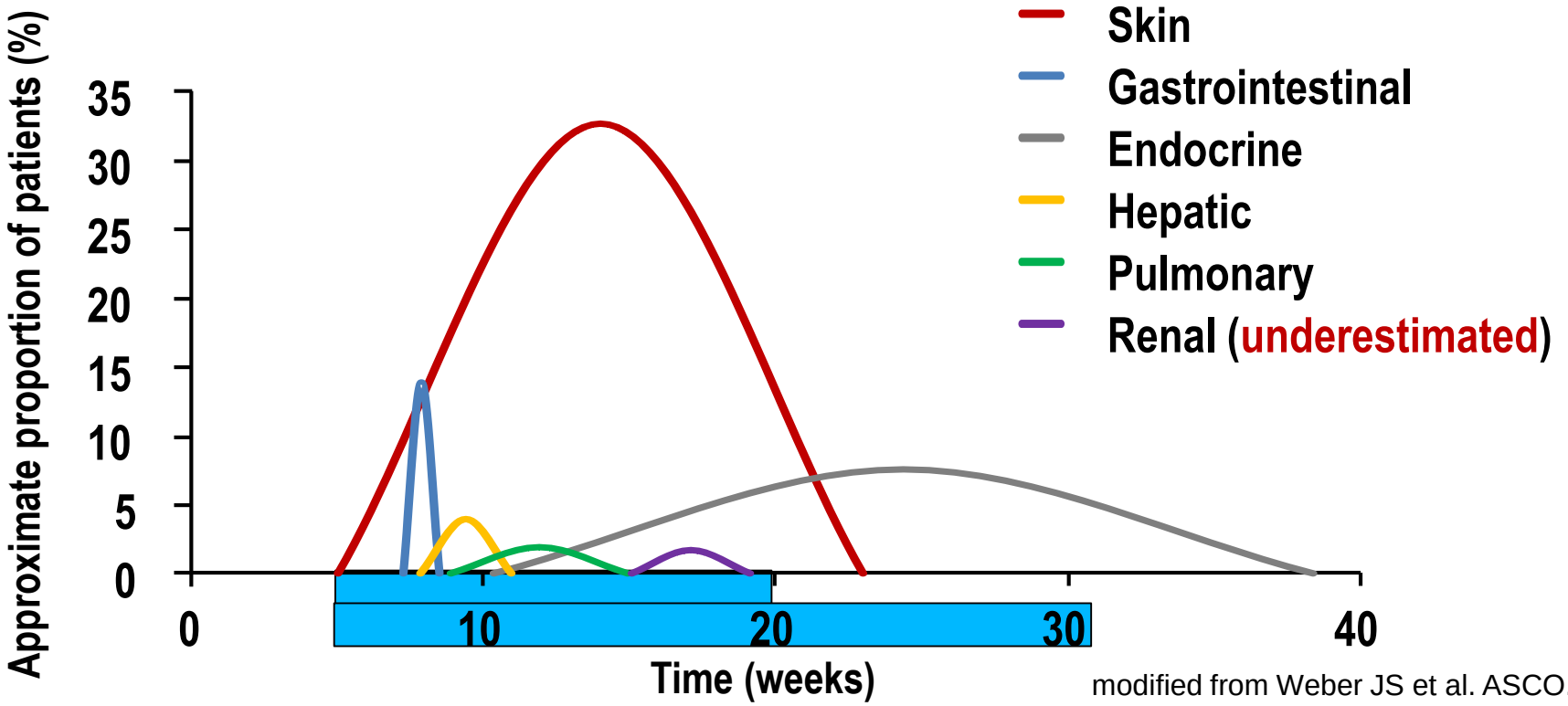
modified from Weber JS et al. ASCO. 2015

PD1 ODER PD-L1 BLOCKADE



modified from Weber JS et al. ASCO. 2015

PD1 ODER PD-L1 BLOCKADE



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? Questions ?

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