Toxicity induced by immunotherapy: management by the medical oncologist

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The development of therapeutic agents that modulate the immune system to induce or potentiate its anti-tumor activity has revolutionized cancer treatment in recent years. Focusing on the immune system of the host rather than the tumor has proven to be an effective strategy in a large number of malignancies. In recent years, the development of antibodies able to inhibit key immune checkpoints has meant a breakthrough in cancer therapy. For decades, efforts were done in directly stimulate the immune system. This approach achieved modest results but when a different strategy was used (the inhibition of inhibitors of the immune system), results have been dramatic. The first checkpoint inhibitor to be granted approval by the Food and Drug Administration (FDA) was the anti-Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) antibody ipilimumab for the treatment of advanced melanoma in 2011. Since then, a number of checkpoint inhibitors and other immunotherapeutic strategies have been assessed in clinical trials with very successful results, mostly inhibitors of the programmed death (PD1) / PD ligand 1 (PD-L1) axis such as pembrolizumab, nivolumab, atezolizumab, durvalumab or avelumab.

But these treatments are not exempt from toxicity. Differently from classic chemotherapy and targeted therapies, with which we are directly attacking tumor cells, with the immunotherapeutic agents we are indirectly attacking the tumor by stimulating the immune system. Therefore, the potential side effects are very different from the ones caused by chemotherapy or targeted therapies since they are derived from an excessive stimulation of the immune system. Thus, a unique profile of toxicities termed immune-related adverse events has been described with immunotherapeutic agents.

The immune system controls infections at any part of the human body so the alteration of its function by the immunotherapy can potentially cause side effects in any organ. The most common immune-related adverse events described with anti-CTLA-4 and anti-PD1/PDL-1 are autoimmune skin phenomena, hepatitis, pneumonitis, colitis and endocrine alterations (hypothyroidism, adrenal insufficiency, autoimmune diabetes…). Fortunately, the incidence of these side effects in severe grades with single agents is low (around 5% of patients). However, when these drugs are combined with other agents, either other immunotherapeutic drug or other antineoplastic compounds, the incidence of immune-related adverse events is usually higher. In recent years, there has been a

large number of immunotherapy drugs approved as single agents in many different tumor types, but it is expected that there will be more new approvals of combinatory regimes in a forthcoming future. Indeed, combinations of immunotherapies with other agents have already been approved in melanoma, renal cell carcinoma or non-small cell lung cancer. Therefore, it is crucial that any healthcare professional involved in the care of cancer patients treated with immunotherapy is aware of these side effects and have enough knowledge to treat them or to refer the patient where appropriate.

The usual first treatment of severe immune-related adverse events is the administration of steroids, initially orally or intravenously in case that the toxicity is not improved or resolved after 48-72 hours of oral treatment. If toxicity persists in spite of several days of intravenous treatment, more potent immunosuppression drugs such as infliximab, mycophenolate or tocilizumab should be considered. Given the complexity of the management of some of these side effects and the potential life-threatening consequences of some of them, the involvement of a wide array of different medical specialities other than medical oncologists is essential in order to provide an optimal care to our cancer patients treated with immunotherapy.

Toxicity induced by immunotherapy: management by the medical oncologist

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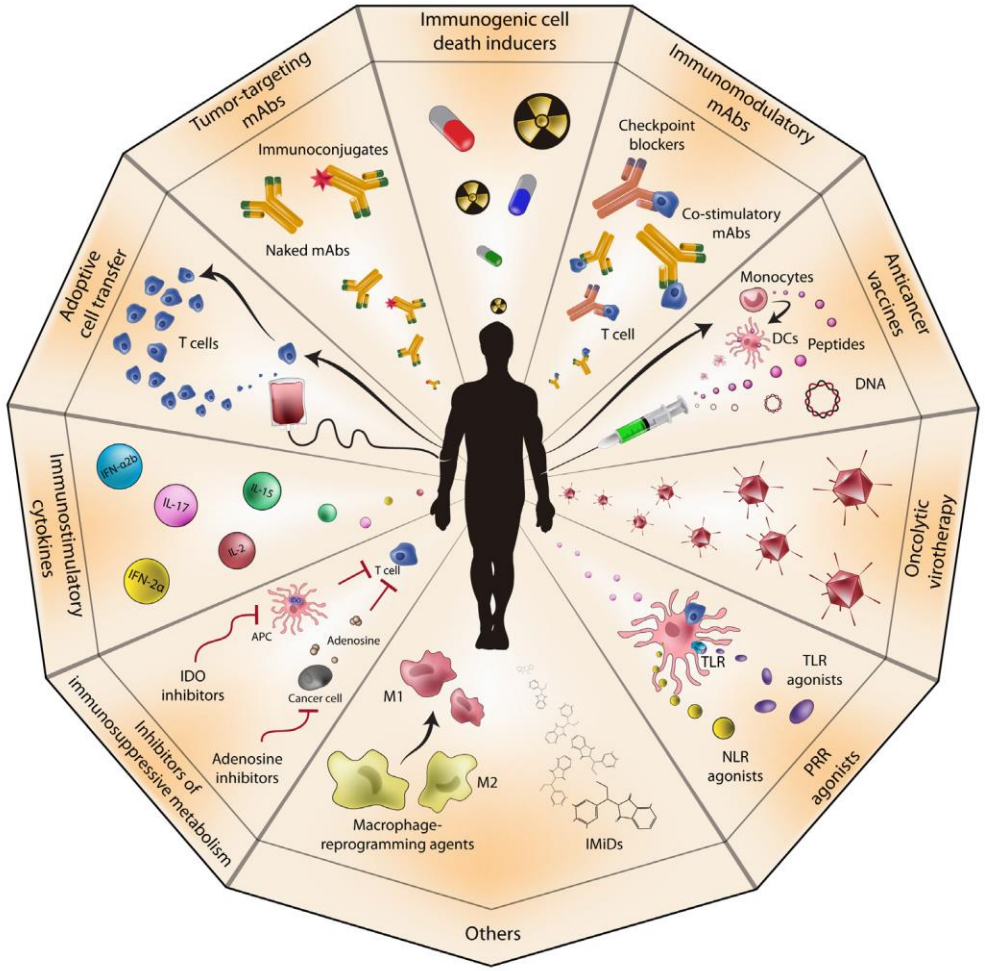
Immunotherapy definition

Immunotherapy

Therapeutic agents able to modulate the immune system to induce/potentiate its anti-tumor activity

Steve Gschmeissner. Science Photo Library.

Immunotherapy agents



Galluzzi L et al. Oncotarget 2014.

Box 1 | **Immunotherapies that are approved or in development**

Vaccines

- Dendritic cell-based vaccines
- Autologous granulocyte–macrophage colony-stimulating factor (GM-CSF)-transfected vaccines
- Viral vector vaccines
- mRNA-based vaccines
- Multipeptide-based vaccines
- Locally released virotherapy

Targets of modulatory monoclonal antibodies

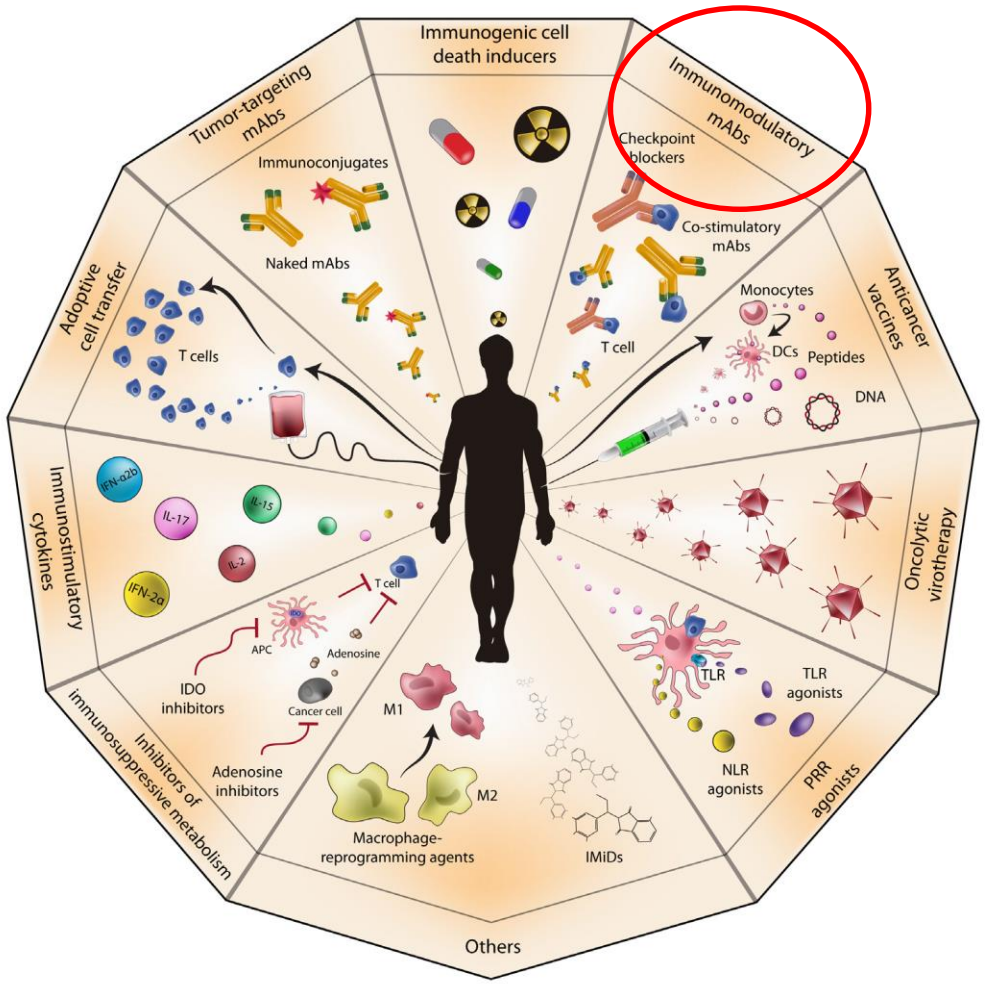
- Cytotoxic T lymphocyte-associated antigen 4 (CTLA4)
- Programmed cell death protein 1 (PD1)
- PD1 ligand 1 (PDL1)
- CD137
- OX40
- Lymphocyte activation gene 3 protein (LAG3)
- T cell immunoglobulin and mucin-domain containing 3 (TIM3)
- Glucocorticoid-induced tumour necrosis factor receptor family-related protein (GITR)
- CD27

Adoptive T cell therapy

- Tumour-infiltrating lymphocytes
- Chimeric antigen receptors (CARs)
- CAR-transduced T lymphocytes

Melero I et al. Nat Rev Cancer 2015.

Immunotherapy agents



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Melero I et al. Nat Rev Cancer 2015.

Toxicity

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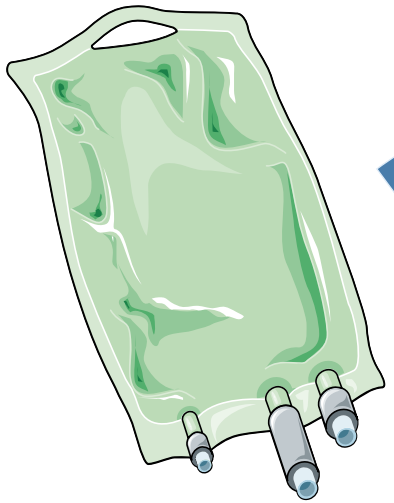
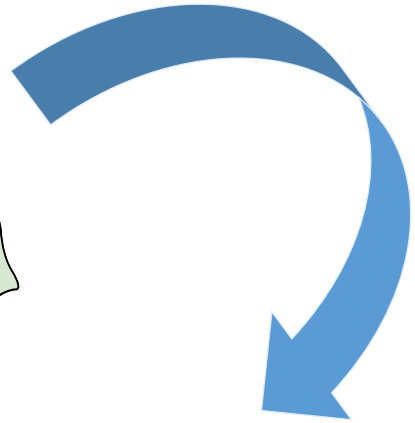
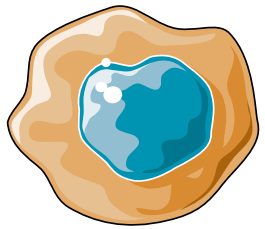
Target Tumor Cells

Cytotoxic/targeted therapy



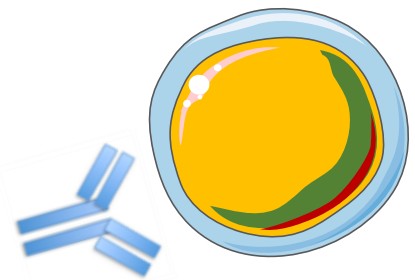


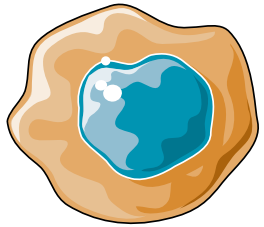


Tumor cell

Activate Immune Cells

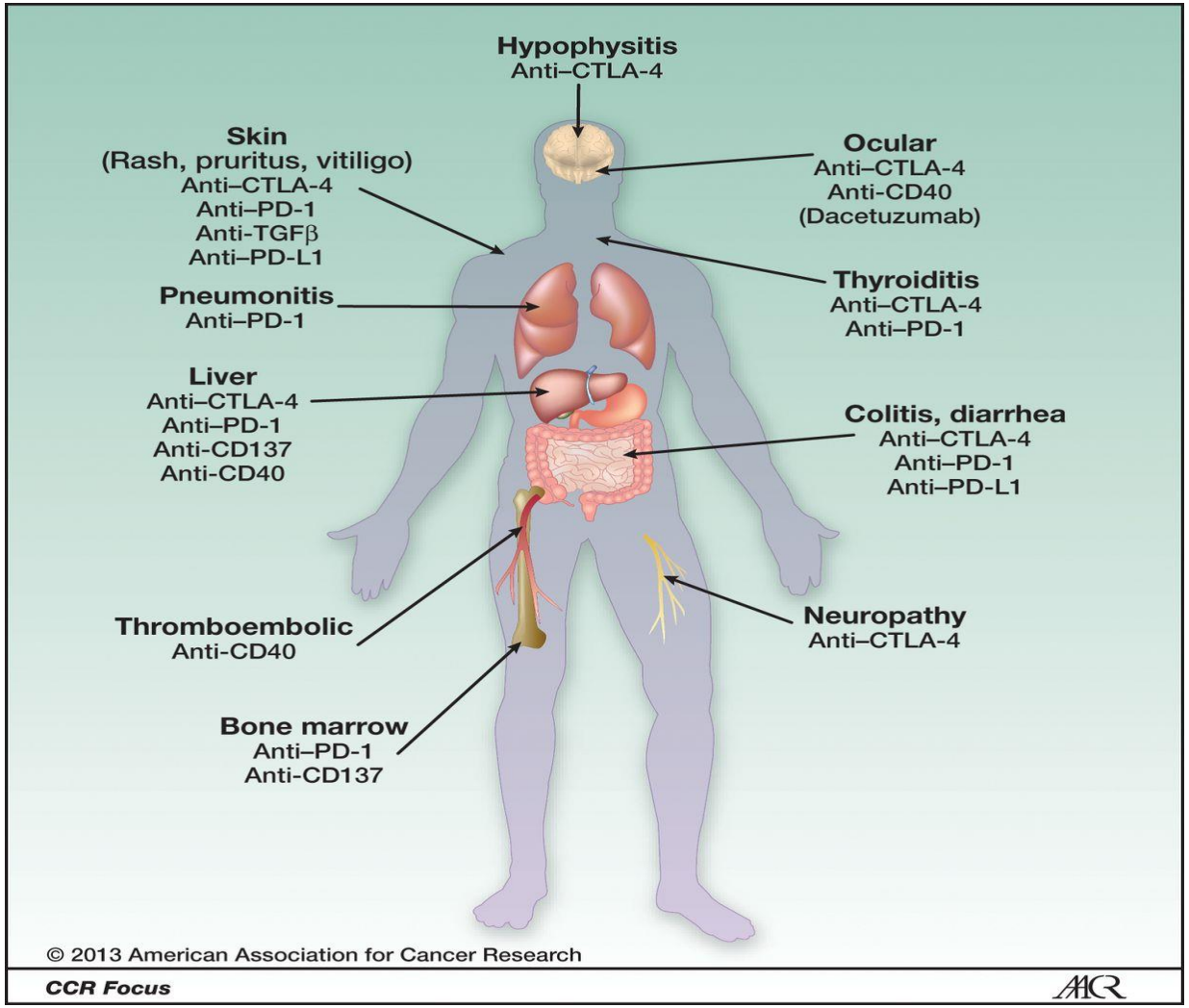
Immune cells





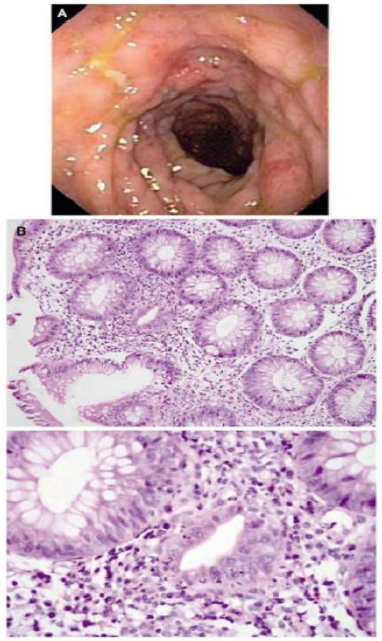
Tumor cell

Toxicity



Melero I et al. Clin Cancer Res 2013.

Toxicity



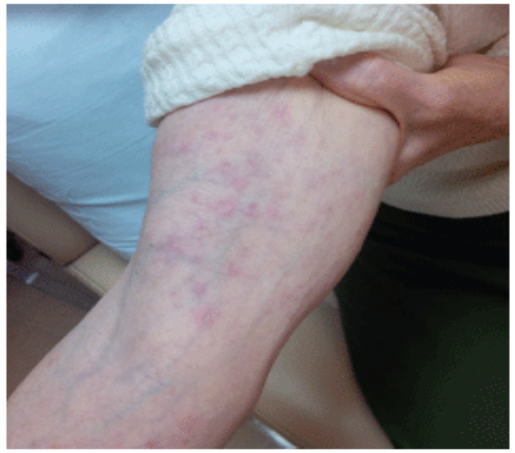


Figure 2: Ipilimumab-Related Autoimmune Dermatitis Manifesting as a Maculopapular Rash on the Arm of a Patient With Metastatic Melanoma. (Photo courtesy of Dr. Michael Postow.)

Autoantibody	Results	Reference range
Anti-GAD	70.1 U/mL	0–5
Pancreatic islet cell	Negative	
IgG insulin	2.2 mg/L	0–5

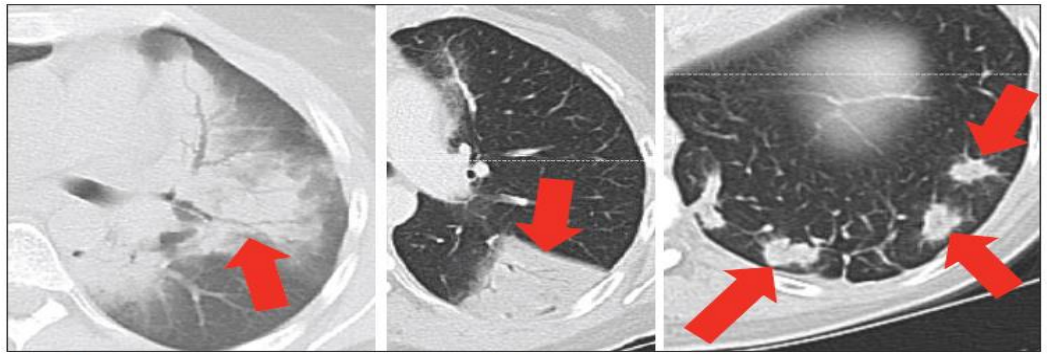


Figure 3: Different Radiographic Patterns of Checkpoint Blockade–Associated Pneumonitis Seen on CT Scanning in a Single Patient Treated With Ipilimumab and Nivolumab—Pneumonitis secondary to ipilimumab is shown in the left-hand panel, and pneumonitis secondary to nivolumab is shown in the center and right-hand panels. Red arrows indicate areas of radiologic abnormality.

Maker AV et al. Ann Surg Oncol 2005.
Teply BA et al. Oncology 2014.
Martin-Liberal J et al. Cancer Immunol Immunother 2015.

Toxicity

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Adverse effect	Hamid O *et al.* 2013 [8]		Robert C *et al.* 2014 [9]			Hodi FS *et al.* 2010 [2]		Robert C *et al.* 2011 [3]		Topalian S *et al.* 2014 [32]		Wolchok *et al.* 2013 [34]		Brahmer *et al.* 2012 [40]	
	Pembrolizumab n = 135 Phase I and II		Pembrolizumab n = 173 Phase I			Ipilimumab n = 137 Phase III		Ipilimumab + DTIC* n = 250 Phase III		Nivolumab n = 107 Phase I		Ipilimumab + nivolumab n = 53 Phase I		BMS-936559 n = 55	
	All AEs	Grade 3/4	All AEs – 10 mg/kg	All AEs – 2 mg/kg	Grade 3/4	All AEs	Grade 3/4	All AEs	Grade 3/4	All AEs	Grade 3/4	All AEs	Grade 3/4	All AEs	Grade 3/4
Any	107 (79%)	17 (13%)	73 (82%)	69 (82%)	20 (12%)	127 (97%)	60 (44%)	244 (99%)	139 (56%)	90 (84%)	24 (22%)	98%	72%	81 (39%)	10 (5%)
Generalized symptoms															
Fatigue	41 (30%)	2 (1%)	33%	37%	5 (3%)	55 (42%)	9 (7%)	-	-	34 (32%)	2 (2%)	38%	-	-	-
Myalgia/arthralgia	16 (12%)	-	-	-	1 (< 1%)	-	-	-	-	11 (10%)	-	-	-	-	-
Pyrexia/chills	19 (14%)	-	-	-	-	16 (12%)	0	91 (37%)	0	5 (5%)	-	-	-	-	-
Gastrointestinal															
Nausea/ vomiting	13 (10%)	-	-	-	-	46 (35%)	3 (2%)	-	-	14 (13%)	2 (2%)			-	-
Diarrhea	27 (20%)	1 (1%)	-	-	1 (< 1%)	36 (28%)	6 (5%)	81 (33%)	10 (4%)	19 (18%)	2 (2%)	18 (34%)	3 (6%)	19 (9%)	0
Colitis	-	-	-	-	-	10 (8%)	7 (5%)	11 (4.5%)	4 (1.6%)	-	-	5 (9%)	2 (4%)	-	-
Autoimmune hepatitis		2 (1%)	-	-	1 (< 1%)	1 (1%)	0	4 (2%)	3 (1%)	-	-			-	-
Raised aminotransferases	24 (18%)	2 (1%)	-	-	-	2 (2%)	0	72 (29%)	51 (21%)	9 (8%)	-	11 (21%)	7 (13%)	2 (1%)	0
Endocrine															
Hypothyroidism	11 (8%)	1 (1%)	-	-	-	2 (2%)	0	-	-	6 (6%)	1 (1%)	2 (4%)	0	6 (3%)	0
Hypophysitis	-	-	-	-	1 (< 1%)	2 (2%)	2 (2%)	-	-			2 (4%)	1 (2%)	-	-
Adrenal insufficiency	1 (1%)	-	-	-	-	2 (2%)	0	-	-	-	-	2 (4%)	0	2 (1%)	1 (< 1%)
Skin															
Rash	28 (21%)	1 (1%)	16 (18%)	16 (18%)	2 (1%)	25 (19%)	1 (1%)	55 (22%)	3 (1%)	31 (29%)	-	29 (55%)	2 (4%)	14 (7%)	0
Pruritis	28 (21%)	1 (1%)	23 (26%)	16 (19%)	-	32 (24%)	0	66 (27%)	5 (2%)	14 (13%)	-	25 (47%)	0	12 (6%)	0
Vitiligo	12 (9%)	-	-	-	-	3 (2%)	0	-	-	10 (9%)				5 (2%)	0
Respiratory															
Cough	11 (8%)	-	-	-	-	21 (16%)	0	-	-	4 (4%)	-				
Breathlessness	6 (4%)	-	-	-	-	19 (15%)	5 (4%)	-	-						
Pneumonitis	6 (4%)	-	-	-	1 (1%)			-	-			3 (6%)	1 (2%)		
Other															
Renal failure	3 (2%)	2 (1%)	-	-	-	-	-	-	-	-	-	1 (2%)	1 (2%)		

Martin-Liberal J et al. Expert Opin Drug Saf 2015.

Immunotherapy combinations

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Table 3. Adverse Events.*

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	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	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)

* The safety population included all the patients who received at least one dose of study drug. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
† The treatment-related adverse events listed here were those reported in at least 10% of the patients in any of the three study groups.

Larkin J et al. N Engl J Med 2015.

Immunotherapy combinations

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ASCO 2014

Grade 3-4 treatment-related AEs in ≥ 10% of patients

	S + N (n=33)		P + N2 (n=20)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Total patients with an event, n (%)	33 (100)	27 (81.8)	20 (100)	14 (70.0)
Hypertension	16 (48.5)	6 (18.2)	5 (25.0)	2 (10.0)
Increased ALT	13 (39.4)	6 (18.2)	5 (25.0)	4 (20.0)
Hyponatremia	6 (18.2)	5 (15.2)	0	0
Increased lymphocyte count	6 (18.2)	5 (15.2)	1 (5.0)	1 (5.0)
Diarrhea	20 (60.6)	3 (9.1)	12 (60.0)	4 (20.0)
Increased AST	12 (36.4)	3 (9.1)	6 (30.0)	4 (20.0)
Fatigue	27 (81.8)	3 (9.1)	12 (60.0)	3 (15.0)

- Patients with any event (any grade): 53 (100%)
- No grade 5 treatment-related AEs were observed
- Most toxicities were consistent with the known profile of TKIs

8

Amin A et al. ASCO 2014.

Kinetics

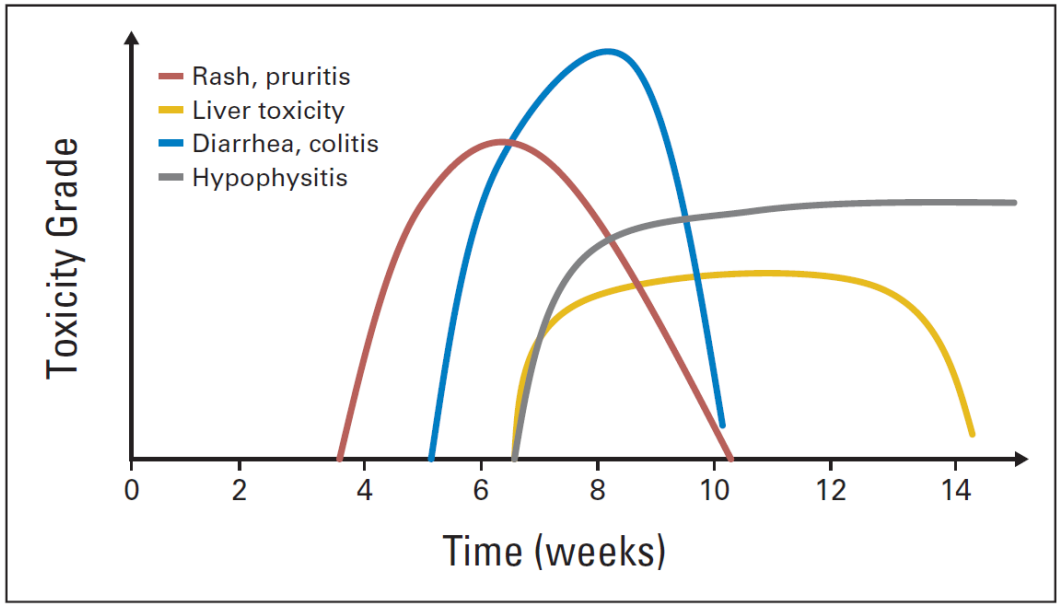
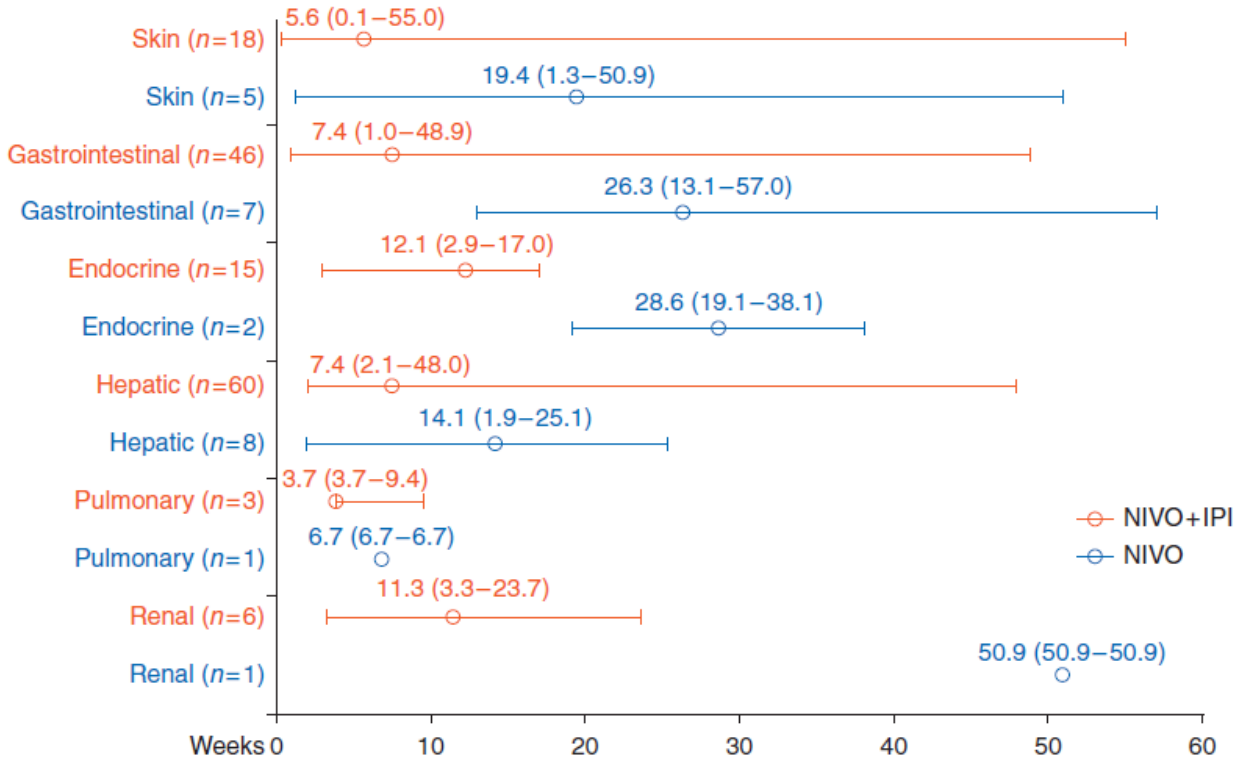


Fig 2. Kinetics of appearance of immune-related adverse event.

Weber JS et al. J Clin Oncol 2012.



Larkin J et al. Eur J Cancer 2015.

Differential diagnosis

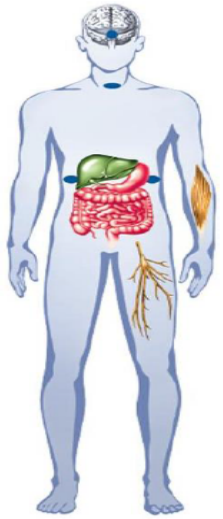
- **Infectious diseases**
  Pneumocystis jirovecii,
  Clostridium difficile, salmonella,
  viral hepatitis…

- **Tumor progression**
  Linfangitis, liver metastases…

- **Other drugs**

- **Others**
  Crohn's disease, radiation pneumonitis…

General principles



Mild	• Treat symptomatically
Persistent mild or moderate	• Treat with oral corticosteroids (prednisone 1mg/kg daily or equivalent) • Omit next dose of ipilimumab until symptoms resolve or return to baseline
Symptoms worsen, are severe, or life threatening	• Treat with high-dose IV corticosteroids (methylprednisolone 2mg/kg daily or equivalent) • If symptoms improve then consider a gradual steroid taper over at least 4 weeks • If symptoms do not respond within 5–7 days, consider alternative immunosuppressive therapies • Permanently discontinue ipilimumab

Robert C. ESMO Meeting 2014.

Special situations

- **Colitis:**
  Infliximab (anti-TNF-α) 5mg/kg iv (maximum 2-3 doses)
  Octeotride 100-200µg tds if high volume liquid diarrhea
  Colectomy

- **Hepatitis:**
  Mycophenolate mofetil 1g BD po

- **Endocrine:**
  Propranolol, levothyroxine, steroids as replacement therapy, insuline…

- **Uveitis:**
  1% Prednisolone acetate (1 drop/1-2h)

- **Neurologic:**
  IV Ig 0.4g/kg x 5 days (Guillain-Barré syndrome)

- **Cytokine release syndrome:**
  Tocilizumab 4-8mg/kg iv

Guidelines

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

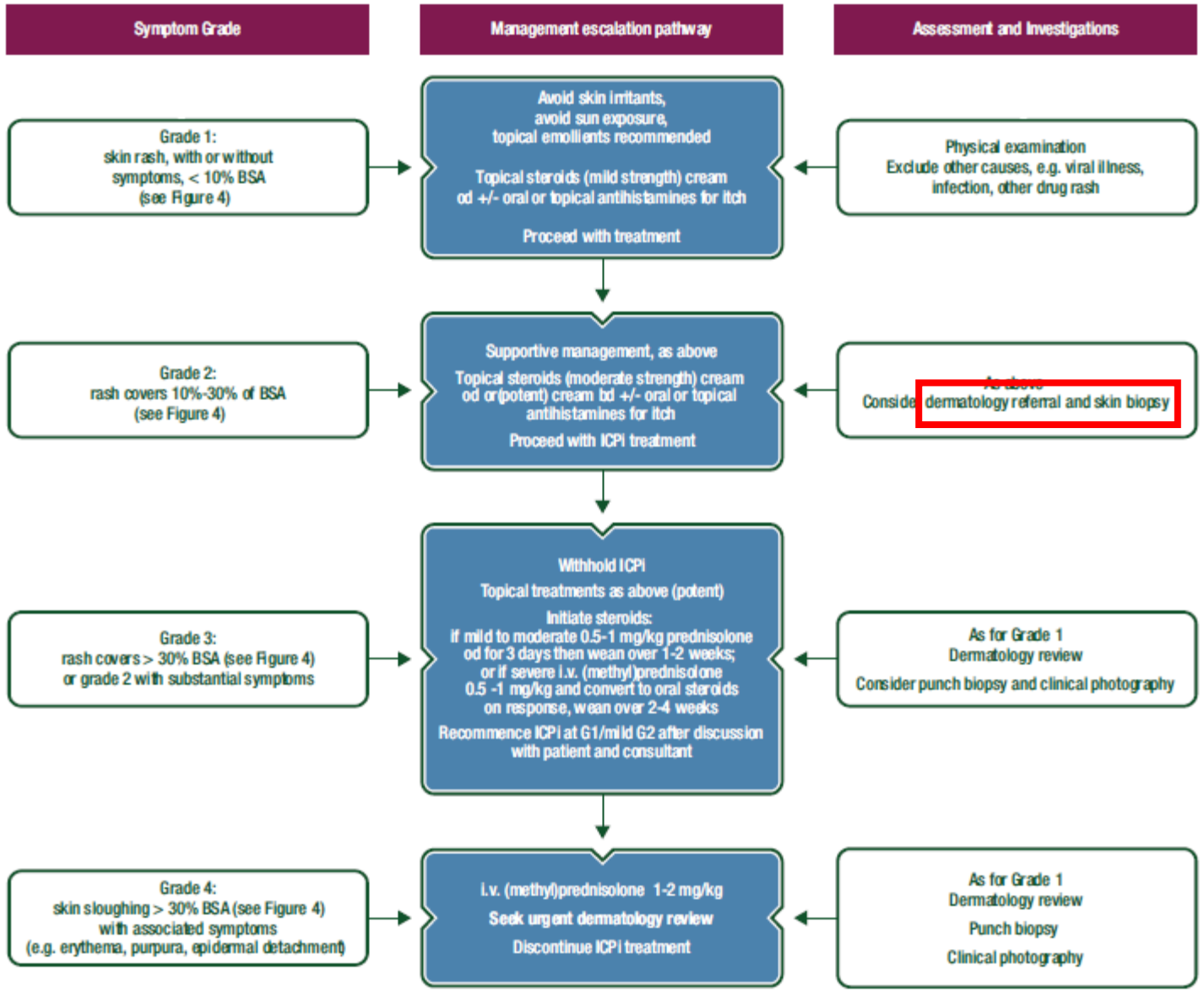
Annals of Oncology 28 (Supplement 4): i119–i142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

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

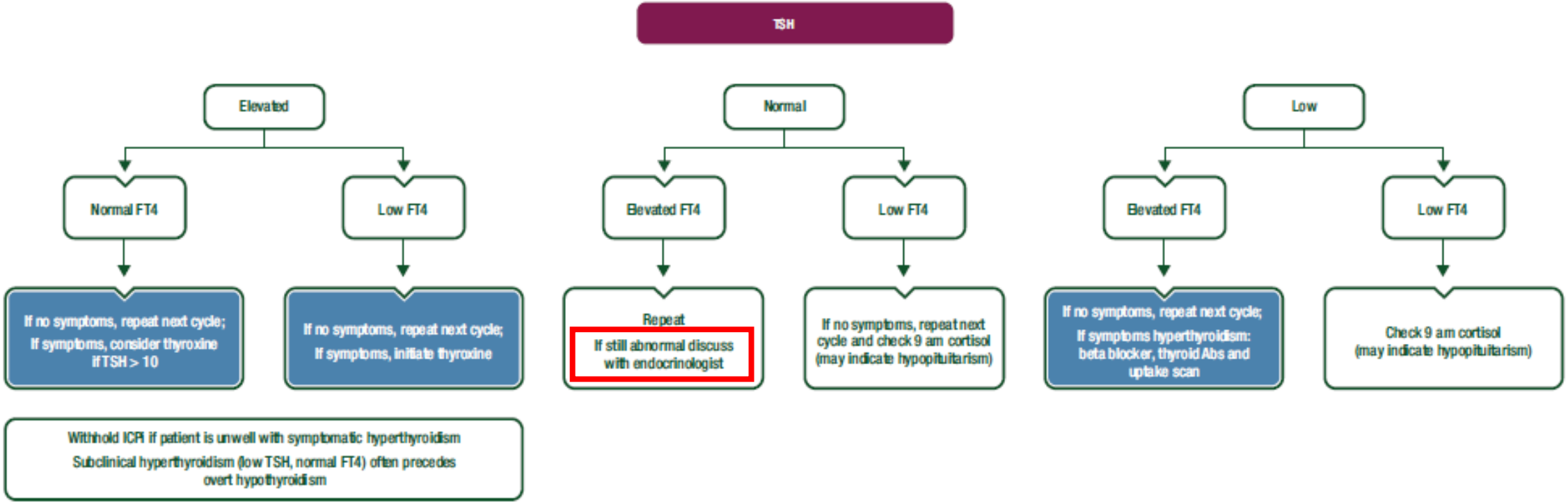
J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

Multidisciplinary Team: dermatologist



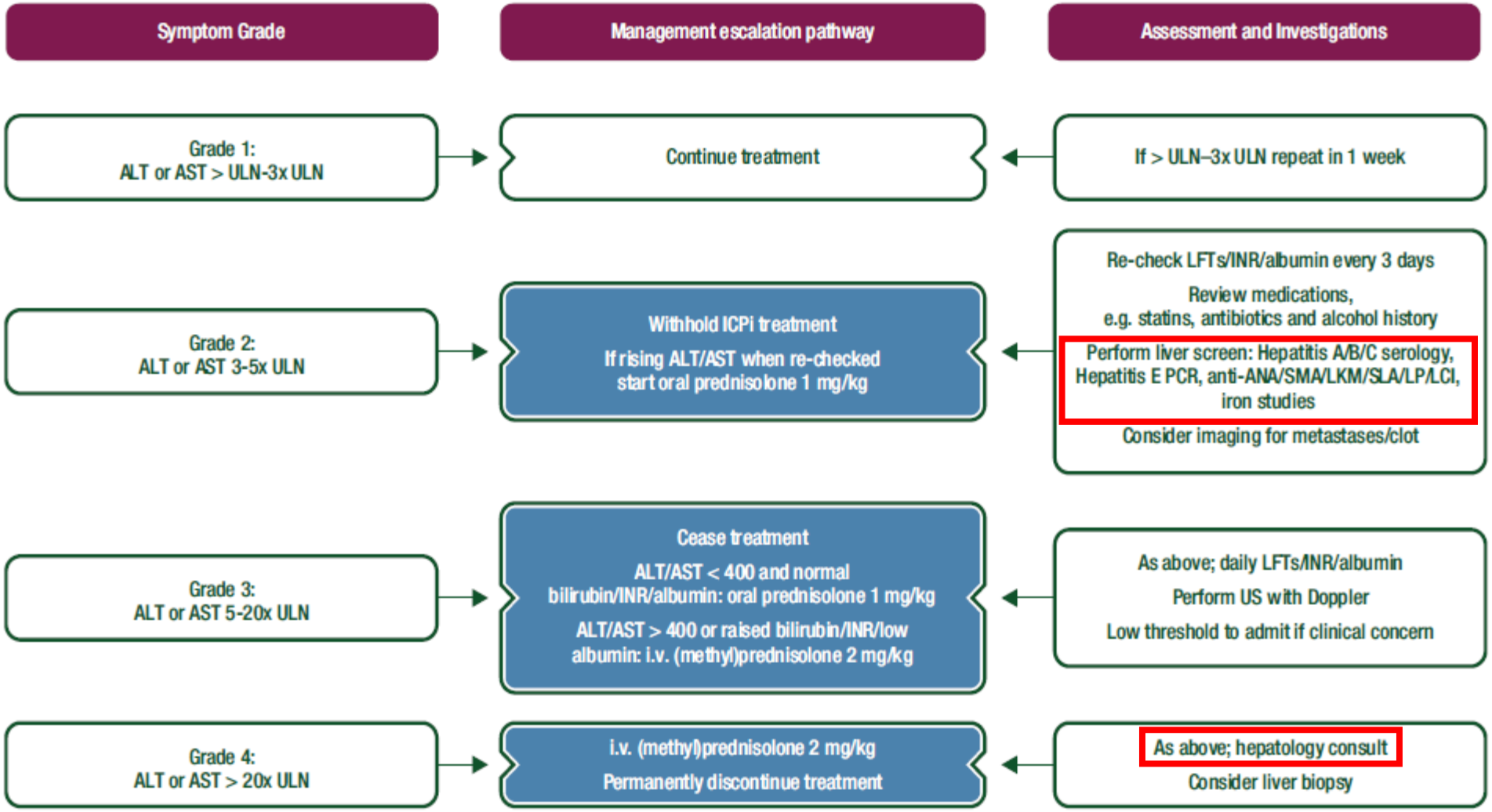
Haanen J et al. Ann Oncol 2017.

Multidisciplinary Team: endocrinologist



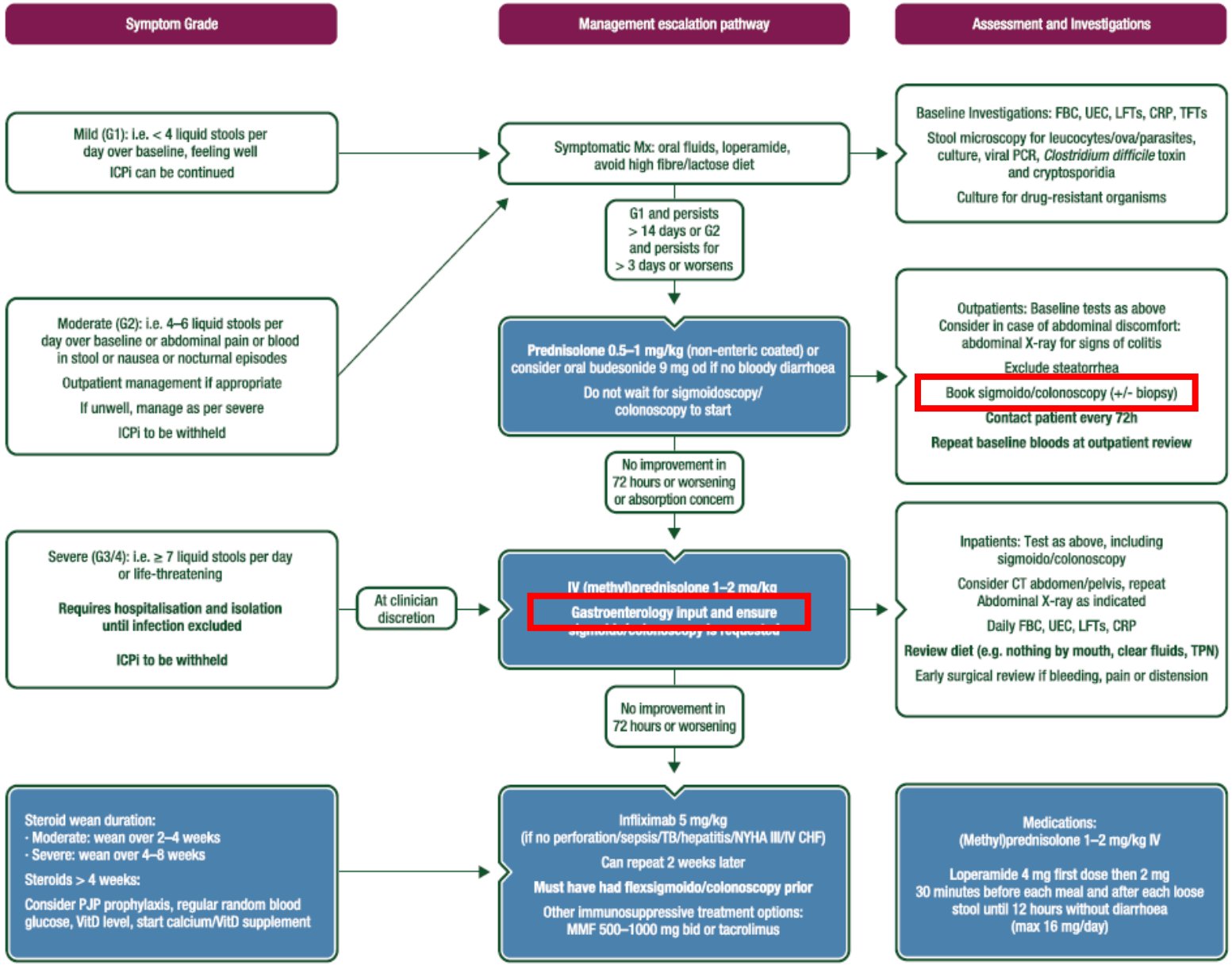
Haanen J et al. Ann Oncol 2017.

Multidisciplinary Team: hepatologist



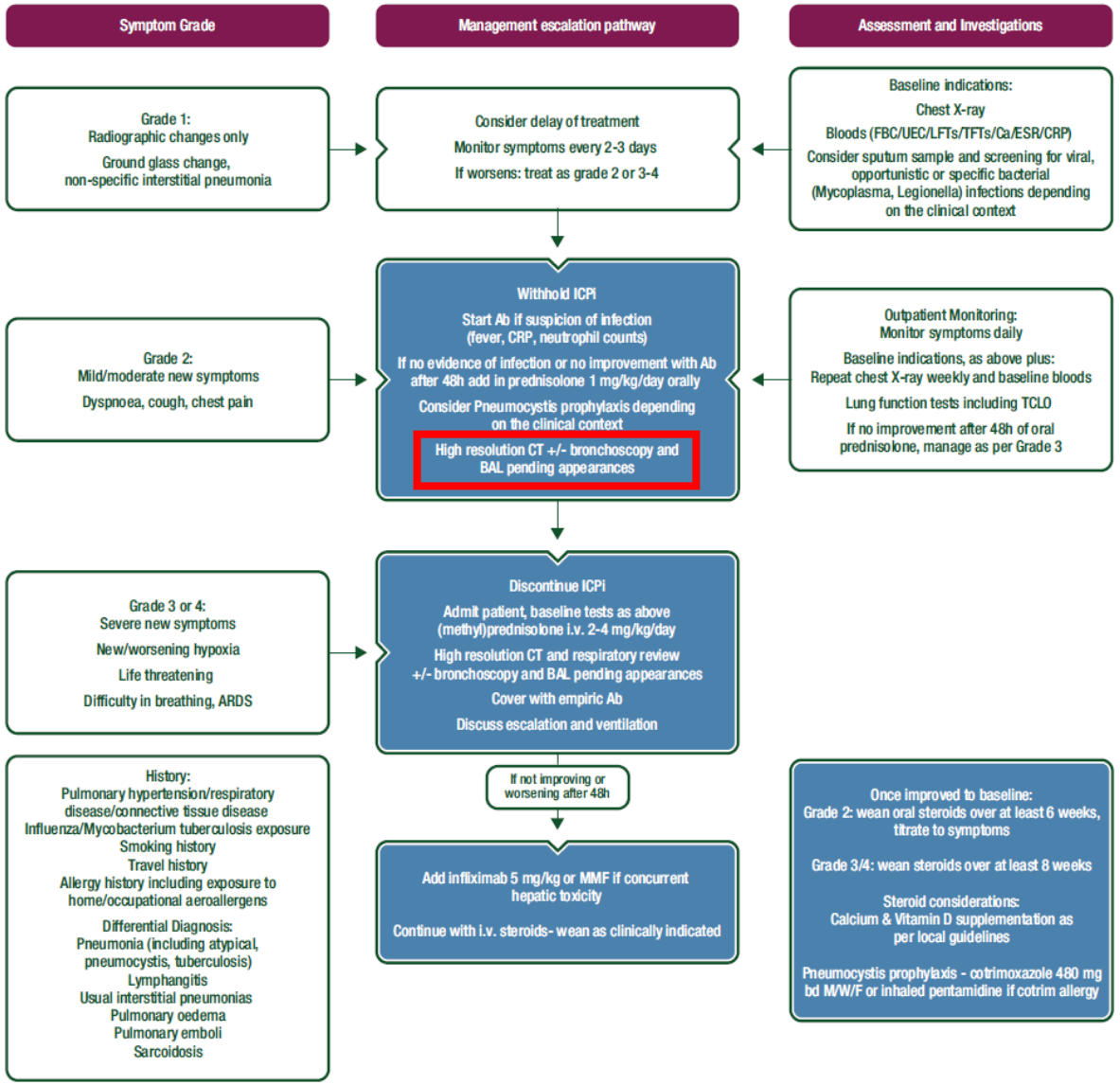
Haanen J et al. Ann Oncol 2017.

Multidisciplinary Team: gastroenterologist



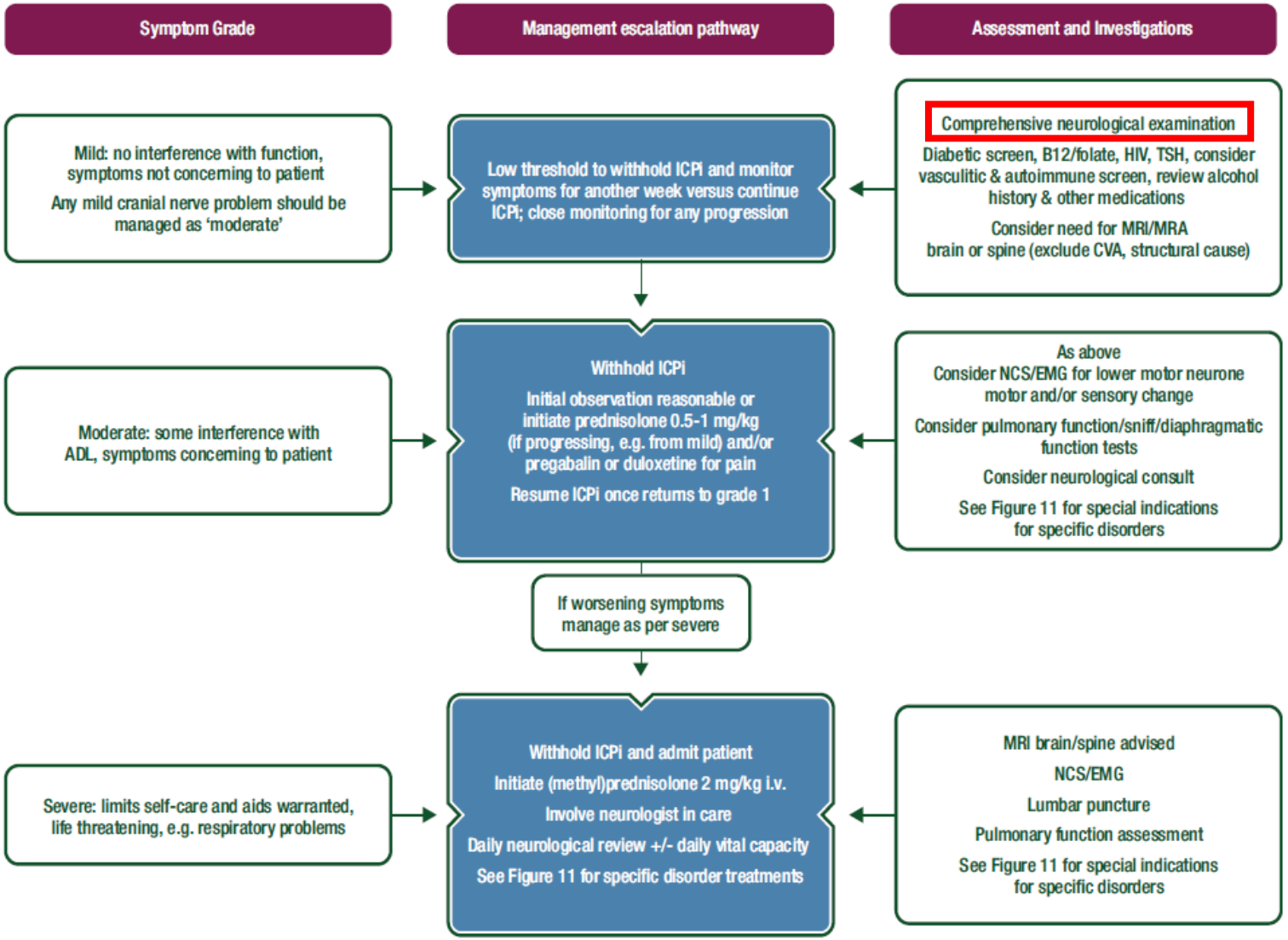
Haanen J et al. Ann Oncol 2017.

Multidisciplinary Team: pneumologist



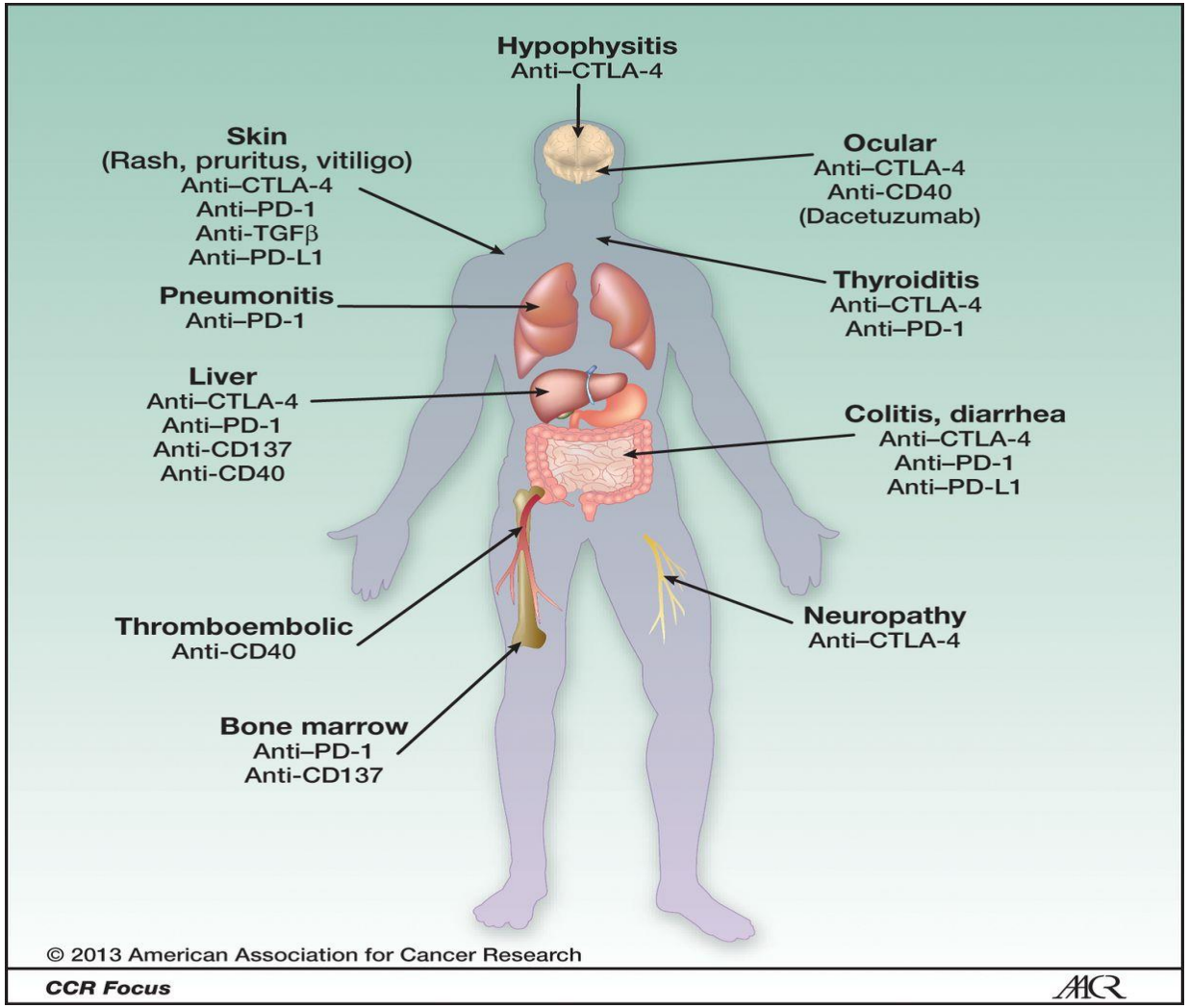
Haanen J et al. Ann Oncol 2017.

Multidisciplinary Team: neurologist



Haanen J et al. Ann Oncol 2017.

Multidisciplinary Team



Melero I et al. Clin Cancer Res 2013.

Multidisciplinary Team

ICO Institut Català d'Oncologia

Agenda de la Jornada

08:45-09:05
Bienvenida Institucional
Presentación de la jornada
Dr. Ernest Nadal / Dr. Juan Martín-Liberal – Servicio de Oncología Médica, ICO Hospitalet

09:05-09:25
La revolución de la inmunoterapia en cáncer
Dr. Ernest Nadal – Servicio de Oncología Médica, ICO Hospitalet

09:25-09:45
Manejo del oncólogo médico de la toxicidad inducida por inmunoterapia
Dr. Juan Martín-Liberal – Servicio de Oncología Médica, ICO Hospitalet

9:45-10:30
Manejo del paciente en tratamiento con inmunoterapia en urgencias y en situación crítica o de gravedad
Moderadora: Eva Coma – Unidad de Atención Continuada Oncológica, ICO Hospitalet
- Dra. Xesca Mitjavila – Servicio de Medicina Interna, Hospital Universitario de Bellvitge
- Dra. Irene Cabello – Servicio de Urgencias, Hospital Universitario de Bellvitge
- Dr. Gabriel Moreno – Servicio de Medicina Intensiva, Hospital Universitario de Bellvitge

10:30-11:30
Toxicidad cutánea, endocrinológica y pulmonar
Moderador: Dr. Ernest Nadal – Servicio de Oncología Médica, ICO Hospitalet
Ponentes:
- Dra. Samanta Aso – Servicio de Neumología, Hospital Universitario de Bellvitge
- Dra. Inma Peiró – Unidad Funcional de Nutrición, ICO Hospitalet
- Dra. Anna Jucglà – Servicio de Dermatología, Hospital Universitario de Bellvitge

11.30- 12:00 Pausa – Café

12:00-13:00
Toxicidad Digestiva y Renal
Moderador: Dr. Juan Martin-Liberal – Servicio de Oncología Médica, ICO Hospitalet
Ponentes:

- Dra. Silvia Salord – Servicio de Gastroenterología, Hospital Universitario de Bellvitge
- Dra. Juliana Bordignon – Servicio de Nefrología, Hospital Universitario de Bellvitge

13:00-14:00
Toxicidad neurológica, cardiológica y osteomuscular
Moderadora: Dra. Eva Domingo – Servicio de Hematología, ICO Hospitalet
Ponentes:
- Dra. Roser Velasco – Servicio de Neurología, Hospital Universitario de Bellvitge
- Dra. Elena García Romero – Servicio de Cardiología, Hospital Universitario de Bellvitge
- Dr. Francisco Javier Narváez –Servicio de Reumatología, Hospital Universitario de Bellvitge

14:00-14:15
Conclusiones y cierre
Dr. Ernest Nadal / Dr. Juan Martín-Liberal – Servicio de Oncología Médica, ICO Hospitalet

Para más información

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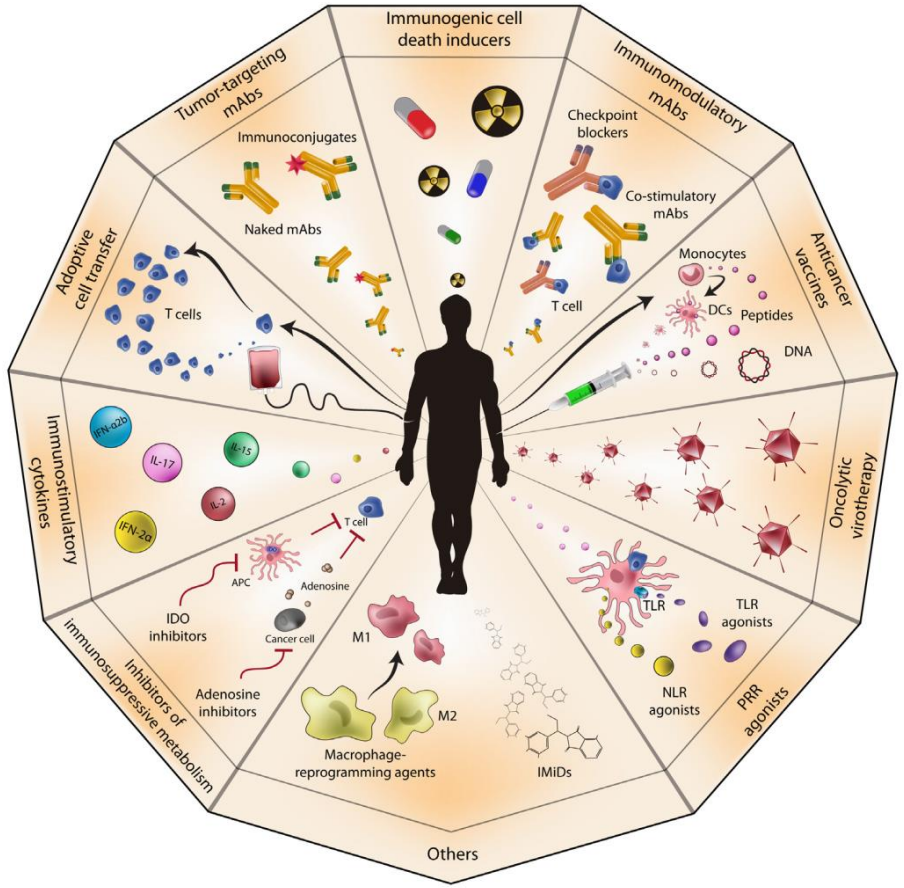
Other immunotherapeutic agents



Galluzzi L et al. Oncotarget 2014.

Box 1 | **Immunotherapies that are approved or in development**

Vaccines

- Dendritic cell-based vaccines
- Autologous granulocyte–macrophage colony-stimulating factor (GM-CSF)-transfected vaccines
- Viral vector vaccines
- mRNA-based vaccines
- Multipeptide-based vaccines
- Locally released virotherapy

Targets of modulatory monoclonal antibodies

- Cytotoxic T lymphocyte-associated antigen 4 (CTLA4)
- Programmed cell death protein 1 (PD1)
- PD1 ligand 1 (PDL1)
- CD137
- OX40
- Lymphocyte activation gene 3 protein (LAG3)
- T cell immunoglobulin and mucin-domain containing 3 (TIM3)
- Glucocorticoid-induced tumour necrosis factor receptor family-related protein (GITR)
- CD27

Adoptive T cell therapy

- Tumour-infiltrating lymphocytes
- Chimeric antigen receptors (CARs)
- CAR-transduced T lymphocytes

Melero I et al. Nat Rev Cancer 2015.

Other immunotherapeutic agents

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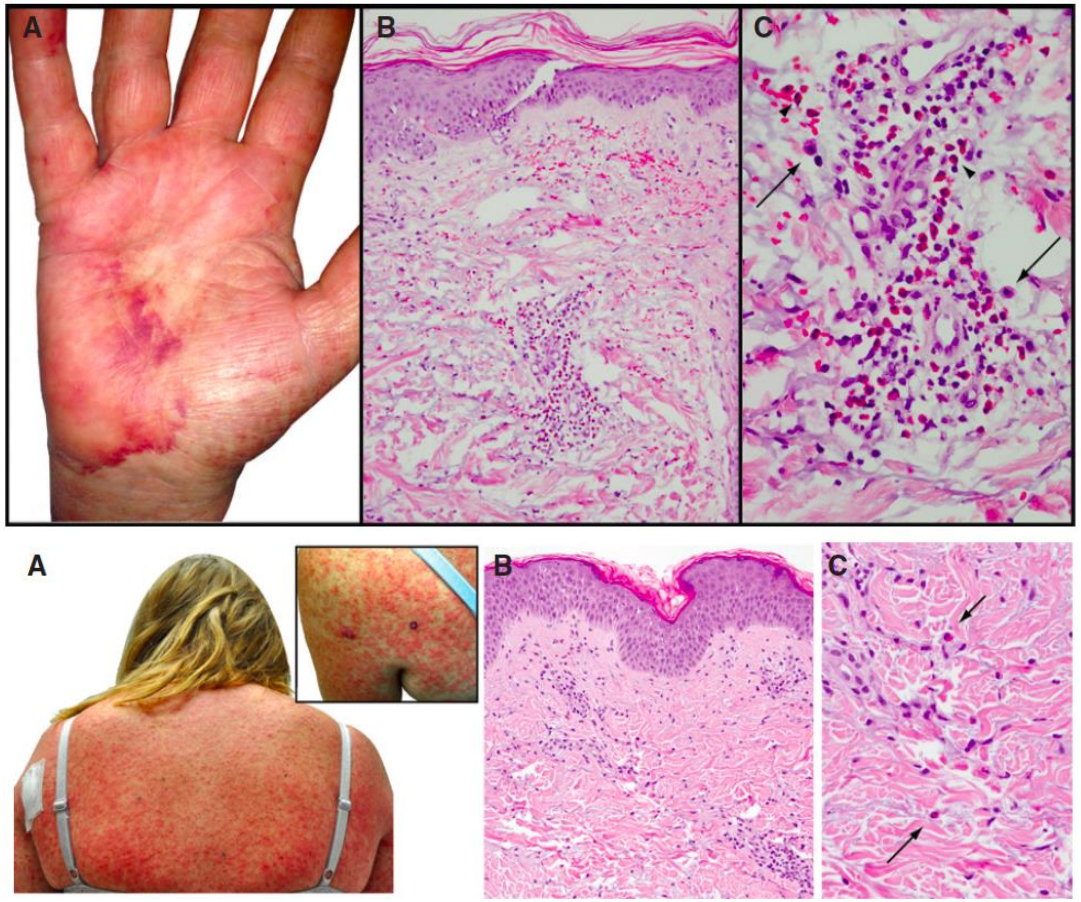
Table 1. Immunotherapy Toxicity

Type of Immunotherapy	General Symptoms	Skin Toxicity	GI Toxicity	Hepatotoxicity	Endocrinopathy	Other Toxicities
Vaccines	Fevers, chills, lethargy	Maculopapular, vitiligo[1]	Rare diarrhea[5]	Rare[5]	None	Local reactions, back pain,[8] rare hypotension[5]
Cytokines: IFN	Fevers, chills, and flu-like symptoms[19]	Maculopapular[19]	Nausea, diarrhea, and rare vomiting[22]	Elevated LFTs common[23]	Thyroiditis; often associated with benefit[24]	Congestive heart failure,[19] anemia,[26] thrombocytopenia,[26] leukopenia,[26] depression[21]
Cytokines: IL-2	Fevers, chills, and lethargy[31]	Petechial and macular[31]	Transient nausea, vomiting, and diarrhea[31]	Elevated LFTs and bilirubin common[31]	Thyroiditis; often associated with benefit[36]	Pulmonary edema,[32] hypotension,[32] azotemia,[32] myocarditis,[32] altered mental status[31]
Cell therapy: TILs	Fevers, chills, and fatigue[43-45]	Maculopapular[43]	Rare diarrhea[43-45]	Elevated LFTs rare[43-45]	Thyroiditis; often associated with benefit[43-45]	Prolonged lymphopenia, CMV infections[43-45]
Cell therapy: CAR	Fevers, chills, and lethargy	Maculopapular	Rare diarrhea	Elevated LFTs with CA-IX CAR[56]	None	Cytokine release with tachycardia, hypotension, oliguria; B-cell aplasia[54]; pulmonary edema[55]
Cell therapy: TCR	Fevers, chills, and lethargy[47]	Maculopapular,[47] vitiligo [52]	Colitis with CEA TCR[53]	Elevated LFTs rare[47]	None	Encephalopathy[59] and carditis[60] with MAGE-3 TCR

Weber JS et al. J Clin Oncol 2015.

Other considerations



Cancer Immunology Miniatures

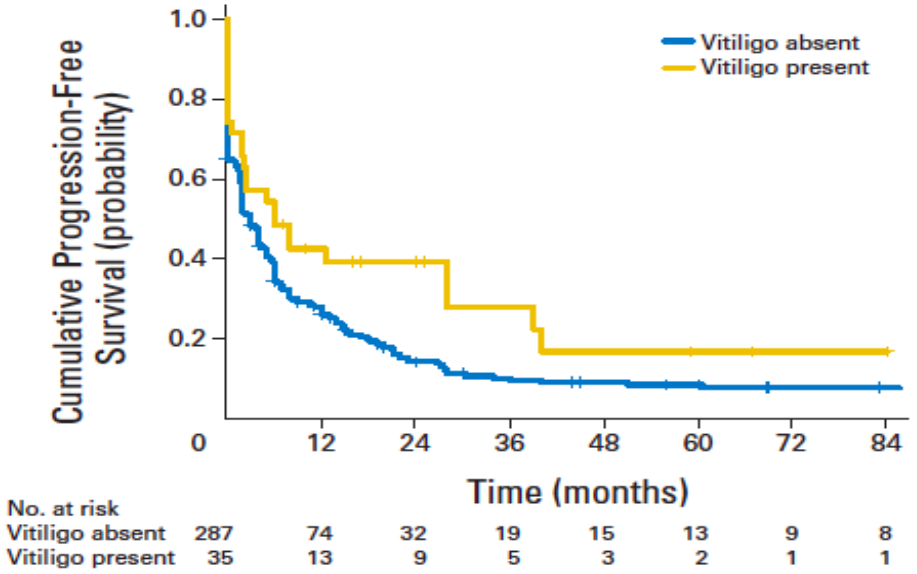
Cancer Immunology Research

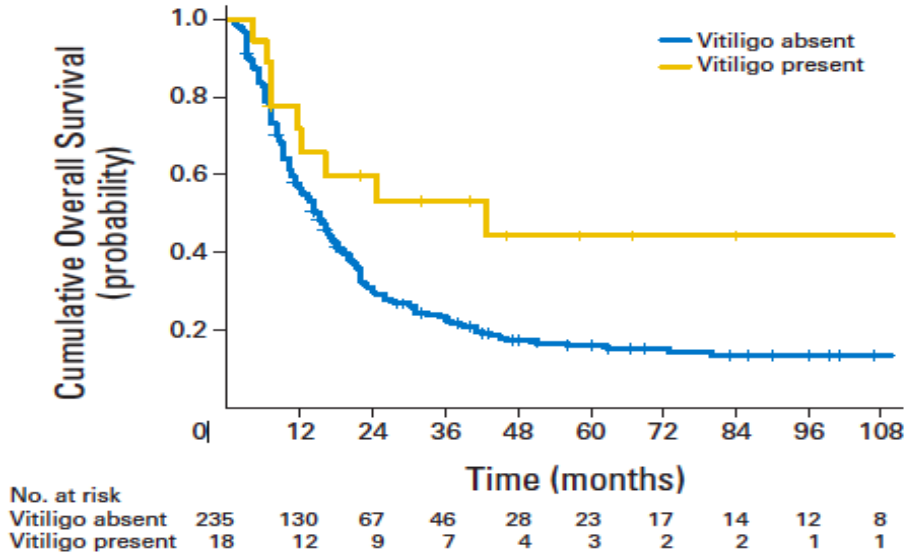
Severe Cutaneous and Neurologic Toxicity in Melanoma Patients during Vemurafenib Administration Following Anti-PD-1 Therapy

- 2 pts with BRAF V600E-mutant melanoma
- Previously treated with anti-PD-1 agents
- Both developed severe hypersensitivity drug eruptions with multiorgan injury early in their BRAF inhibitor

Johnson DB et al. Cancer Immunol Res 2013.

Other considerations





Teulings HE et al. J Clin Oncol 2015.

Other considerations

- Most select AEs were managed and resolved within 3-4 weeks (85–100% across organ categories)
- **ORR** was **70.7%** for pts who discontinued NIVO+IPI due to AEs, with median OS not reached

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death, n (%)	2 (0.6)		1 (0.3)		1 (0.3)	

Larkin J et al. AACR 2017.

Conclusions

- New mechanism of action → new toxicities

- Different toxicity profiles and severity depending on the type of drug, monotherapy/combination...

- Critically important to correctly identify and early treat irAEs

- Some situations require special treatments: infliximab, mycophenolate, tocilizumab...

- **<u>Importance of a Multidisciplinary Team</u>**

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Gracias

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