How to handle the side effects of targeted therapeutics: Immunotherapy

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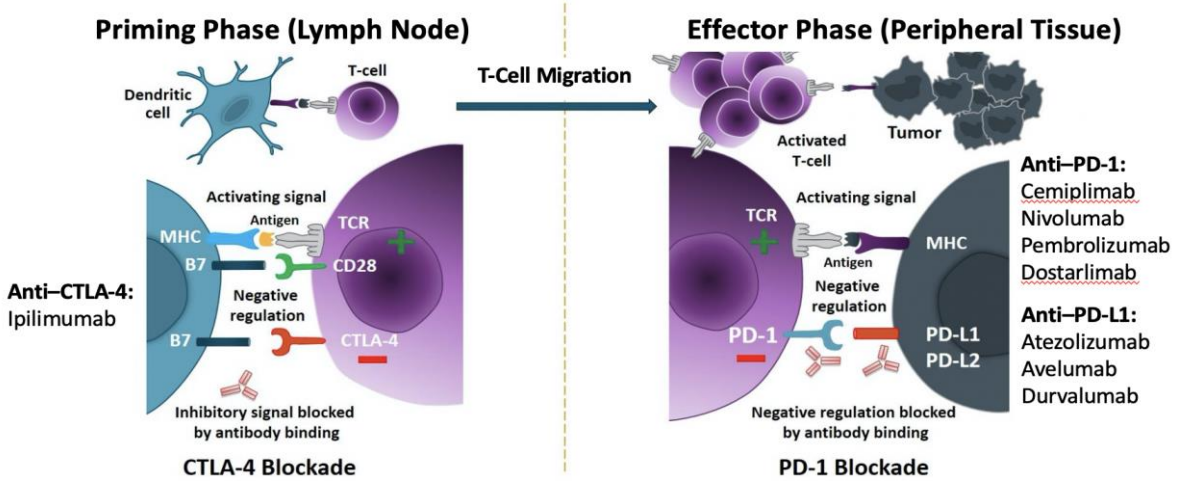
Introduction

- Immunotherapy has revolutionized the treatment of many different types of cancers, including Gynecological malignancies.
- Immune checkpoint inhibitors (ICIs) targeting CTLA-4, PD-1, and PD-L1 work by preventing the receptors and ligands from binding to each other, thereby disrupting signalling so T cells can recognize and attack cancer cells.



- In 2017, the FDA granted accelerated approval for pembrolizumab for the treatment of MSI-H or dMMR recurrent cancers in a landmark disease site–agnostic manner.
- Since then, in the EU there have been three additional approvals for pembrolizumab, one for dostarlimab and one for Cemiplimab for the treatment of gynecologic cancers.

Schneider BJ et al; J Clin Oncol. 2021 Dec 20;39(36):4073-4126; R.E. O'Cearbhaill et al; Gynecologic Oncology 166 (2022) 25–35; Ribas. NEJM. 2012;366:2517.

Pivotal clinical trials resulting in FDA and/or EMA approval of ICIs in gynaecologic cancer (and disease site–agnostic approvals).

	Study	Disease Site	Treatment Arms	N	Primary Endpoint	Efficacy Outcome(s)	
	Keynote studies[a] (Keynote 016, 164, 012, 028, and 158) [21–25]	Site agnostic, dMMR[b]	Pembrolizumab 10 mg/kg IV every 2 weeks or 200 mg IV every 3 weeks	$N = 149$ (MSI-H or dMMR) 59 CRC	ORR and DOR	ORR, 39.6% (95% CI: 31.7–47.9) ORR in non-CRC arm, 46%	CR, 7% PR, 32% Median DOR, not reached
EMA APPROVED	Keynote 775 (NCT03517449) [26]	Endometrial cancer	Pembrolizumab + lenvatinib vs. Physicians' choice of chemotherapy: (doxorubicin or paclitaxel)	$N = 827$ (697 not dMMR)	BICR-assessed PFS and OS (co-primary endpoints)	Median OS, 17.4 vs 12 mo HR, 0.68 (95% CI: 0.56–0.84) $P = 0.0001$	Median PFS, 6.6 vs 3.8 mo HR, 0.60 (95% CI: 0.50–0.72) $P < 0.0001$
EMA APPROVED	Keynote 158 (NCT02628067) [27]	Site agnostic, dMMR[b]	Pembrolizumab 200 mg IV every 3 weeks	$N = 102$ (all dMMR) (Approval based on 13 patients with high tumor mutational burden (≥10 mutations/ megabase)	ORR and DOR	ORR, 29% (95% CI: 21–39)	CR, 4% PR, 25% Median DOR, not reached
	Keynote 158 (NCT02628067) [28]	Cervical cancer cohort	Pembrolizumab 200 mg IV every 3 weeks	$N = 98$ (Approval based on 77 patients with PD-L1 CPS ≥1)	ORR and DOR	ORR, 14.3% (95% CI: 7.4–24.1)	CR, 2.6% PR, 11.7% Median DOR, not reached
EMA APPROVED	GARNET Trial (NCT02715284) Cohort A1 [29]	Endometrial cancer	Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks	$N = 71$ (all dMMR)	ORR and DOR	ORR, 42.3% (95% CI: 30.6–54.6)	CR, 12.7% PR, 29.6% Median DOR: Not reached
	GARNET Trial (NCT02715284) [30]	Site agnostic, dMMR	Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks	$N = 209$ (all dMMR)	ORR and DOR	ORR, 41.6% (95% CI: 34.9–48.6)	CR, 9.1% PR, 32.5% Median DOR, 34.7 months
EMA APPROVED	Keynote 826 (NCT03635567) [31]	Cervical cancer, PD-L1+	Pembrolizumab 200 mg IV every 3 weeks with platinum/paclitaxel +/−bevacizumab vs platinum/paclitaxel +/−bevacizumab	$N = 617$	BICR-assessed PFS and OS	Median PFS, 10.4 vs 8.4 mo HR, 0.62 (95% CI: 0.5–0.77) $P = 0.001$	Median OS, Not reached vs 16.3 mo HR, 0.64 (95% CI: 0.5–0.81) P = 0.001

R.E. O'Cearbhaill et al; Gynecologic Oncology 166 (2022) 25–35

irAEs in patients treated with ICIs

Basics of principles

ICIs are associated with a unique spectrum of side effects.[1]

irAEs are related to the mechanism of action of ICIs:[2]

- Activation of immune cells in non-tumour compartments
- irAEs are inflammatory in nature and can mimic autoimmune conditions

ICI, immune checkpoint inhibitor; irAE, immune related adverse event.

1. Zhou X, *et al. BMC Med.* 2020;18(1):1–4.; **2.** Choi J, *et al. Immune Netw.* 2020;20(1):e9.

irAEs in patients treated with ICI therapy

Basics of principles

The side effects may involve any organ or system of the body; however, gastrointestinal, dermatologic, hepatic, endocrine and pulmonary toxicities predominate.[1]

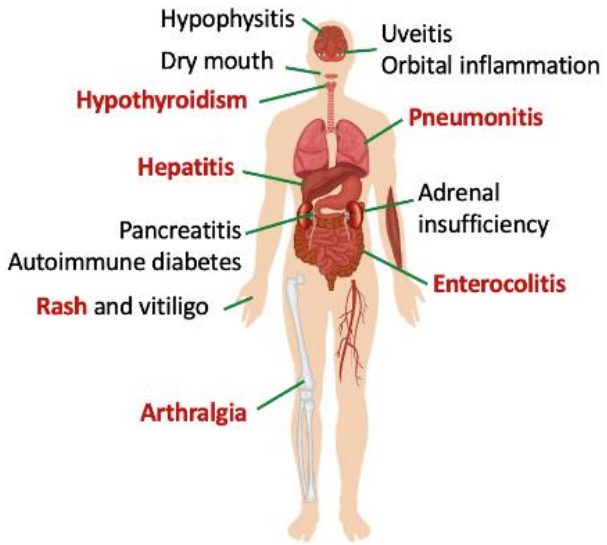
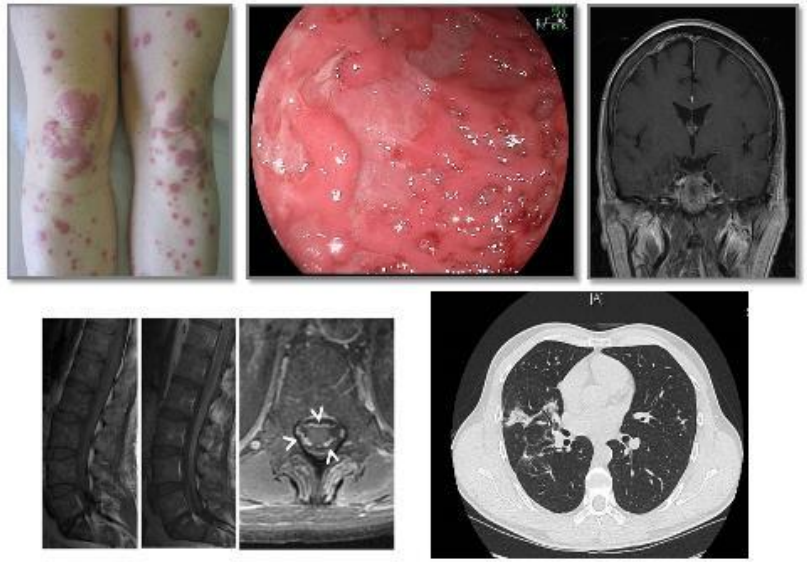


Figure adapted from Michot, *et al* 2016.[1]



Patient images courtesy of Prof. Dr Juhasz-Böss

ICI, immune checkpoint inhibitor; irAE, immune related adverse event.

1. Michot J, *et al. Eur J Cancer.* 2016;54:139.

How should clinicians manage irAEs in patients treated with ICIs?[1]

The five pillars of immunotherapy toxicity management

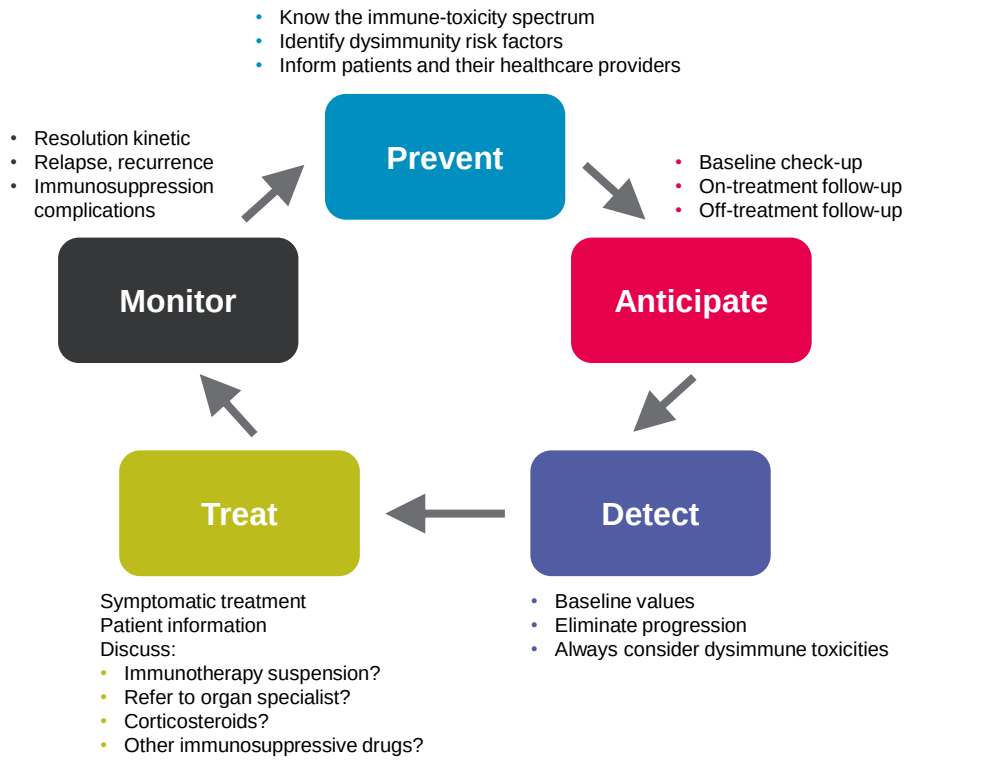


Figure adapted from Champiat S, *et al.* 2016.[1]

1. Prevent

- Before starting an ICI therapy, oncologists need to be aware of their spectrum of toxicity
- Patients and their health care providers should be informed of the specific risks of ICI toxicities

2. Anticipate

- **Before immunotherapy initiation:** 'Immunotherapy baseline checklist'
  - physical examination,
  - laboratory tests (including LFT, TSH, T4)
  - imaging performed
- **During treatment:** New symptoms or increase of pre-existing symptoms should be checked and appropriately investigated
- **After treatment termination:** Patients should be clinically and biologically evaluated on a 3-month basis for the first year and then every 6 months

ICI, immune checkpoint inhibitor; irAE, immune related adverse event; LFT, liver functioning test; T4, thyroxine; TSH, thyroid stimulating hormone.

1. Champiat S, *et al. Ann Oncol.* 2016:27; 559–574.

How should clinicians manage irAEs in patients treated with ICIs?[1]

The five pillars of immunotherapy toxicity management

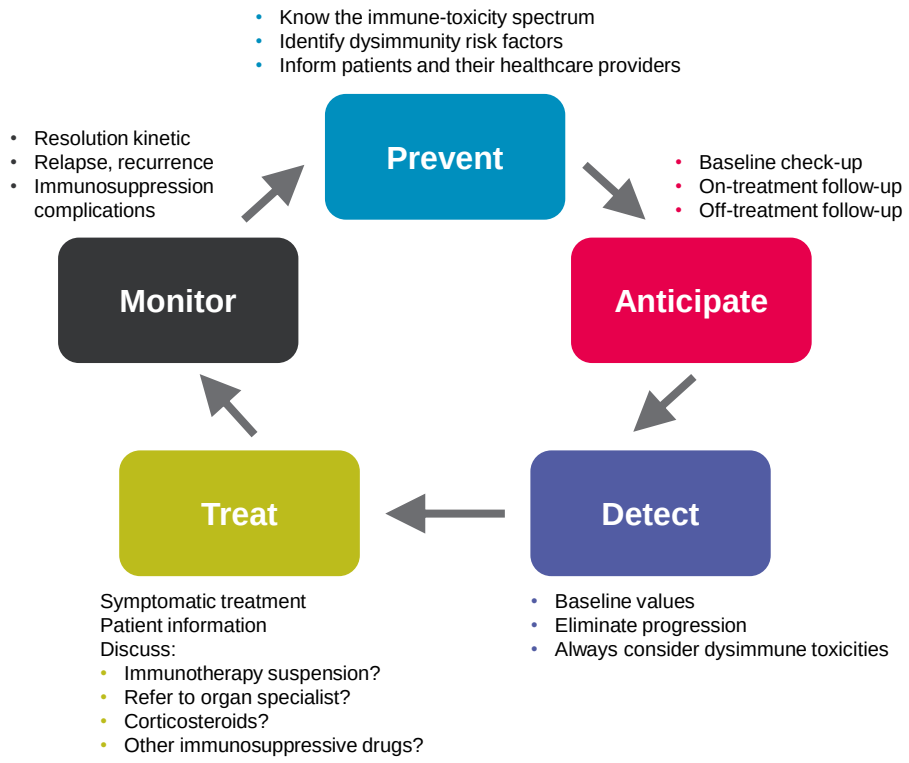


Figure adapted from Champiat S, *et al.* 2016.[1]

3. Detect

- When an adverse event occurs during ICIs therapy, consider:
  - a disease progression: (first, rule-out progression!)
  - a chance event (e.g., infection and thrombosis)
  - a treatment-related immune toxicity
- Always considered an irAEs when work-up suggests an underlying Disease Stability (clinical presentation is often non-specific!)
- Neglecting immune-related toxicities could be potentially fatal; it also seems that delaying adequate care of immune disease could lead to a worse prognosis

ICI, immune checkpoint inhibitor; irAE, immune related adverse event.

1. Champiat S, *et al. Ann Oncol.* 2016:27; 559–574.

How to manage irAEs in patients treated with ICIs?

The five pillars of immunotherapy toxicity management

3. Detect: Common irAEs, typical presentations

irAE	Common Presentation
Dermatologic[1,2]	Maculopapular rash with pruritus, predominantly on the trunk and, to a lesser extent, the upper limbs, spreading to extremities; eczematous, lichenoid, psoriasiform manifestations; blistering skin reactions
Diarrhoea/colitis[3]	Diarrhoea, abdominal pain, hematochezia, weight loss, fever, vomiting
Hepatic[3]	Often asymptomatic and diagnosed via routine blood tests
Pancreatic[1]	Asymptomatic elevation in amylase/lipase; CT, clinical findings of pancreatitis
Endocrine[3]	Headaches, visual disturbances, fatigue, altered consciousness, abnormal electrolytes (particularly hyponatremia), anorexia, mood changes

Table adapted from Thompson A, *et al.* 2019, Sibaud V, *et al.* 2018 and Pickwell-Smith A, *et al*. 2018.[1-3]

CT, computerised tomograph; ICI, immune checkpoint inhibitor; irAE, immune related adverse event.

1. Thompson A, *et al. J Natl Compr Canc Netw.* 2019;17(3):255–289; **2.** Sibaud V. *Am J Clin Dermatol.* 2018;19:345; **3.** Pickwell-Smith A, *et al*. *Br J Hosp Med.* 2018:2;79(7):372–7.

How to manage irAEs in patients treated with ICIs?[1]

The five pillars of immunotherapy toxicity management

3. Detect: Onset of common irAEs

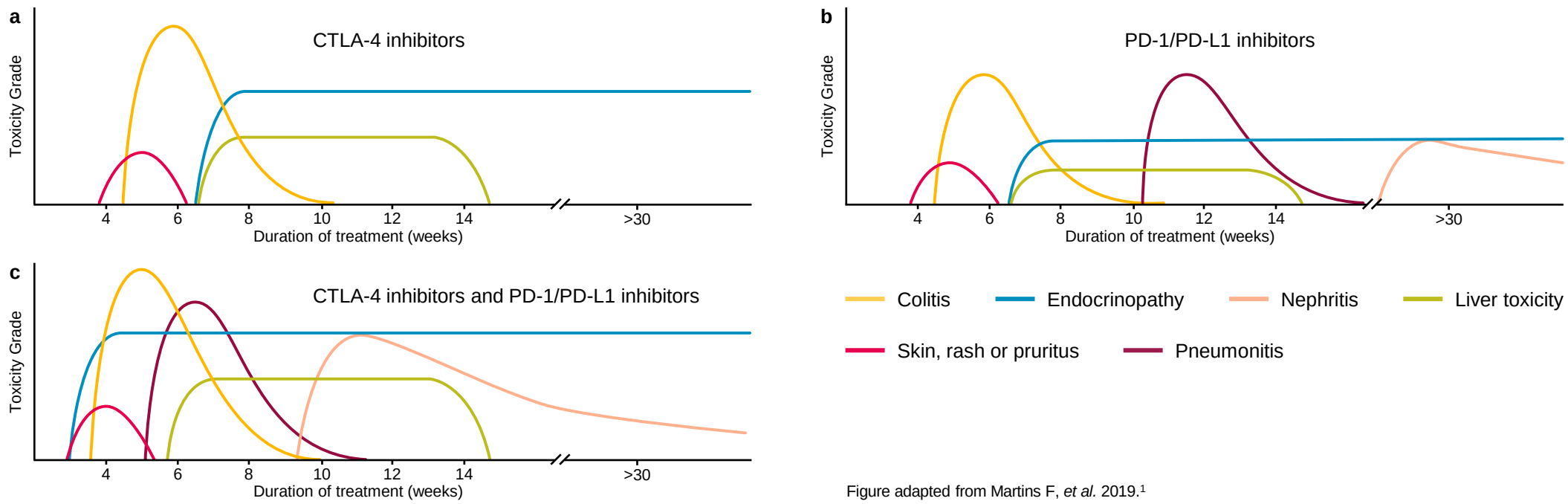


Figure adapted from Martins F, *et al.* 2019.[1]

CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; ICI, immune checkpoint inhibitor; irAE, immune related adverse event; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

1. Martins F, *et al. Nat Rev Clin Oncol*. 2019;16(9):563–80.

How should clinicians manage irAEs in patients treated with ICIs?

4. Treatment/monitor: Key recommendations[1]

For Grade 1 toxicities: In general, ICI therapy should be continued with close monitoring, except for some neurologic, hematologic and cardiac toxicities for which ICI must be permanently discontinued

For most Grade 2 toxicities: Consider withholding ICIs and resume when symptoms and/or laboratory values revert ≤Grade 1

- Corticosteroids (CS) (initial dose of 0.5–1 mg/kg/d of prednisone or equivalent) may be administered

For Grade 3 toxicities: Discontinue ICIs and initiate high-dose CS (prednisone 1–2 mg/kg/d or equivalent):

- If symptoms do not improve within 48–72 hours of high-dose CS, infliximab may be offered for some toxicities. (Never in case of Liver toxicity!!)
- CS should be tapered over the course of at least 4–6 weeks

For Grade 4 toxicities: In general, warrant permanent discontinuation of ICIs, except for endocrinopathies that have been controlled by hormone replacement

When symptoms and/or laboratory values revert ≤ Grade 1, **rechallenging with ICIs may be offered**; however, caution is advised, especially in those patients with early-onset irAEs

- Dose adjustments are not recommended

CS, corticosteroids; ICI, immune checkpoint inhibitor; irAE, immune related adverse event.

1. Schneider J, *et al. J Clin Oncol.* 2021:20;39(36):4073–4126.

Treatment guidelines for immune checkpoint inhibitors (ICIs)[1-4]

NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY: Management of Immunotherapy - Related Toxicities, Version 1.2019

John A. Thompson, MD; Bryan J. Schneider, MD; Julie Brahmer, MD, MSc; Stephanie Andrews, MS, RN, ANP-BC; Philippe Armand, MD, PhD; Shailender Bhatia, MD; Lihua E. Budde, MD, PhD; Luciano Costa, MD, PhD; Marianne Davies, MSN, DNP; David Dunnington, MA; Marc S. Ernstoff, MD; Matthew Frigault, MD; Brianna Hoffner, MSN; Christopher J. Hoimes, MD; Mario Lacouture, MD; Frederick Locke, MD; Matthew Lunning, DO; Nisha A. Mohindra, MD; Jarushka Naidoo, MD; Anthony J. Olszanski, MD, RPh; Olalekan Oluwole, MD; Sandip P. Patel, MD; Sunil Reddy, MD; Mabel Ryder, MD; Bianca Santomasso, MD, PhD; Scott Shofer, MD, PhD; Jeffrey A. Sosman, MD; Momen Wahidi, MD; Yinghong Wang, MD, PhD; Alyse Johnson-Chilla, MS; and Jillian L. Scavone, PhD.

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

J. Haanen, M. Obeid, L. Spain, F. Carbonnel , Y. Wang, C. Robert, A. R. Lyon, W. Wick, M. Kostine, S. Peters, K. Jordan & J. Larkin, on behalf of the ESMO Guidelines Committee

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

Bryan J. Schneider, MD; Jarushka Naidoo, MD; Bianca D. Santomasso, MD, PhD; Christina Lacchetti, MHSc; Sherry Adkins, MS; Milan Anadkat, MD; Michael B. Atkins, MD; Kelly J. Brassil, PhD; Jeffrey M. Caterino, MD, MPH; Ian Chau, MD; Marianne J. Davies, DNP; Marc S. Ernstoff, MD; Leslie Fecher, MD; Monalisa Ghosh, MD; Ishmael Jaiyesimi, DO, MS; Jennifer S. Mammen, MD, PhD; Aung Naing, MD, Loretta J. Nastoupil, MD; Tanyanika Phillips, MD; Laura D. Porter, MD; Cristina A. Reichner, MD; Carole Seigel, MBA, Jung-Min Song, MSN, RN, CNS; Alexander Spira, MD, PhD; Maria Suarez-Almazor, MD; Umang Swami, MD; John A. Thompson, MD; Praveen Vikas, MD; Yinghong Wang, MD; Jeffrey S. Weber, MD, PhD; Pauline Funchain, MD; and Kathryn Bollin, MD.

Immunotherapy Toxicities: An SGO Clinical Practice Statement

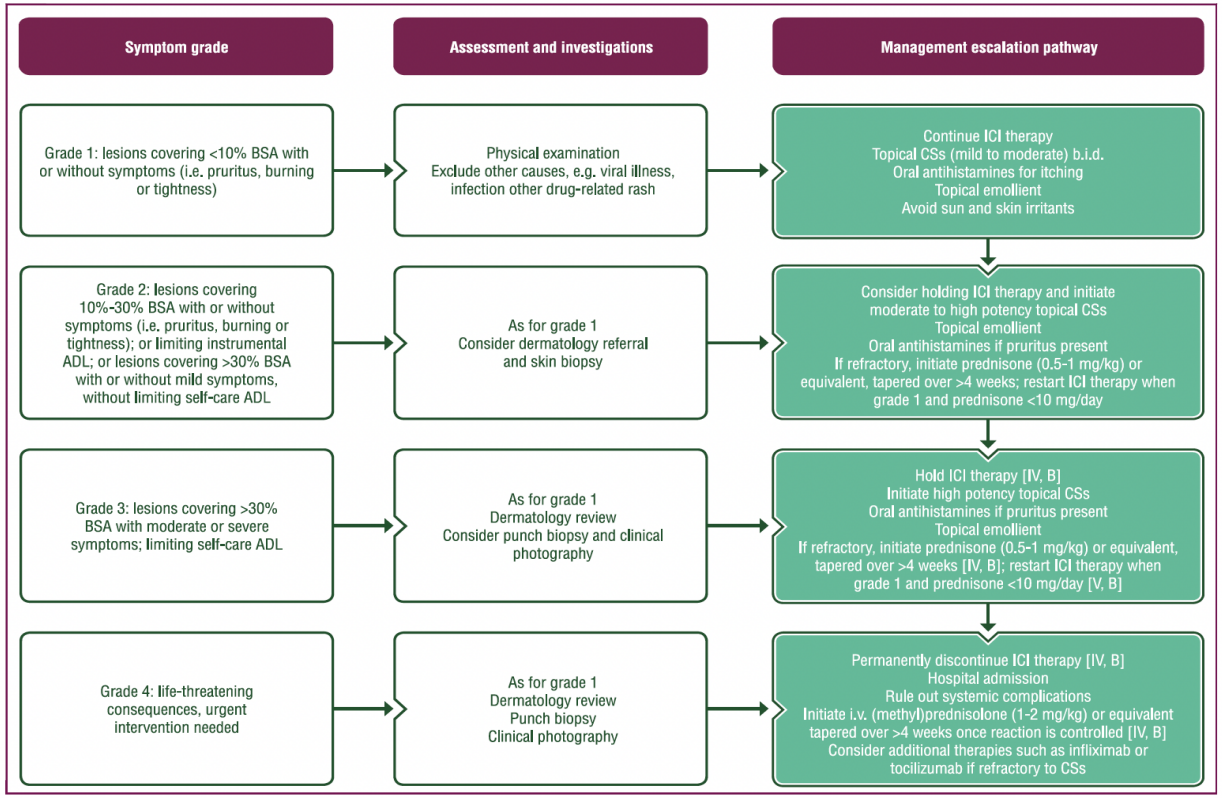
R.E. O'Cearbhaill, L. Clark, R.N. Eskander, S. Gaillard, J. Moroney, E. Pereira, B. Pothuri.

ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; ICI, immune checkpoint inhibitor; NCCN, National Comprehensive Cancer Network; SGO, Society of Gynaecologic Oncology.

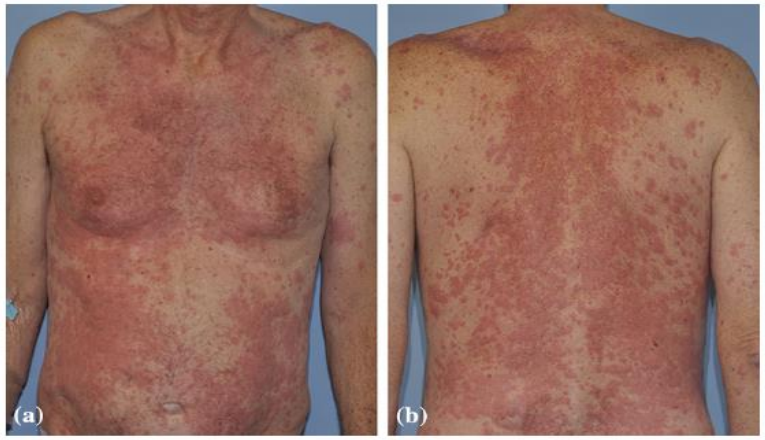
1. Thompson A, *et al. J Natl Compr Canc Netw.* 2019;17(3):255–289; **2.** Haanen B, *et al. Ann Oncol.* 2022;33(12):1217-1238; **3.** Schneider J, *et al. J Clin Oncol.* 2021;39(36):4073–126; **4.** O'Cearbhaill E, *et al. Gynecol Oncol*. 2022;166(1):25–35.

IMMUNE RELATED SKIN TOXICITY

- IR cutaneous AEs (ircAEs) are the most common side-effects of ICI therapy (>50% for all grades) but are rarely severe and usually do not impair treatment continuation.
- Clinical presentation:
  - Non-specific maculopapular rashes being the most common
  - Usually **occur within the first 6 weeks** of therapy
  - Can be preceded by or associated with **pruritus(** it can also be the sole manifestation of a ircAE)
  - **Usually involve <30% of body surface** area**(Grade 1-2)** and are considered severe **(>30%=grade 3) in <5% of cases**



Grade 3 Maculopapular Rash



Haanen J et al. on behalf of the ESMO Guidelines Committee, Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and followup; Annals of Oncology (2022), doi: https://doi.org/10.1016/j.annonc.2022.10.001.

IMMUNE RELATED(IR) ENDOCRINOPATHIES

Their management differs from other irAEs in three key ways:

- ICI therapy can be continued in most cases
- High-dose CSs are rarely required
- Endocrine deficiency usually persists, necessitating lifelong replacement.

1. IR-primary hypothyroidism.

- Primary hypothyroidism is the most common IR endocrinopathy, occurs in ~6%-9% of patients treated with anti-PD-1/PD-L1 monotherapy
- It may be preceded by a hyperthyroid state, which may be subclinical.
- While the majority of cases occur within 3 months of therapy initiation, onset may occur at any time during treatment

2. IR-hyperthyroidism.

- IR-hyperthyroidism occurs less frequently≤2%- 5% of patients treated with with anti-PD-1/PD-L1 monotherapy
- Transient thyroiditis is the most common cause, with ~40% presenting as symptomatic thyrotoxicosis and 60% as subclinical followed by hypothyroidism

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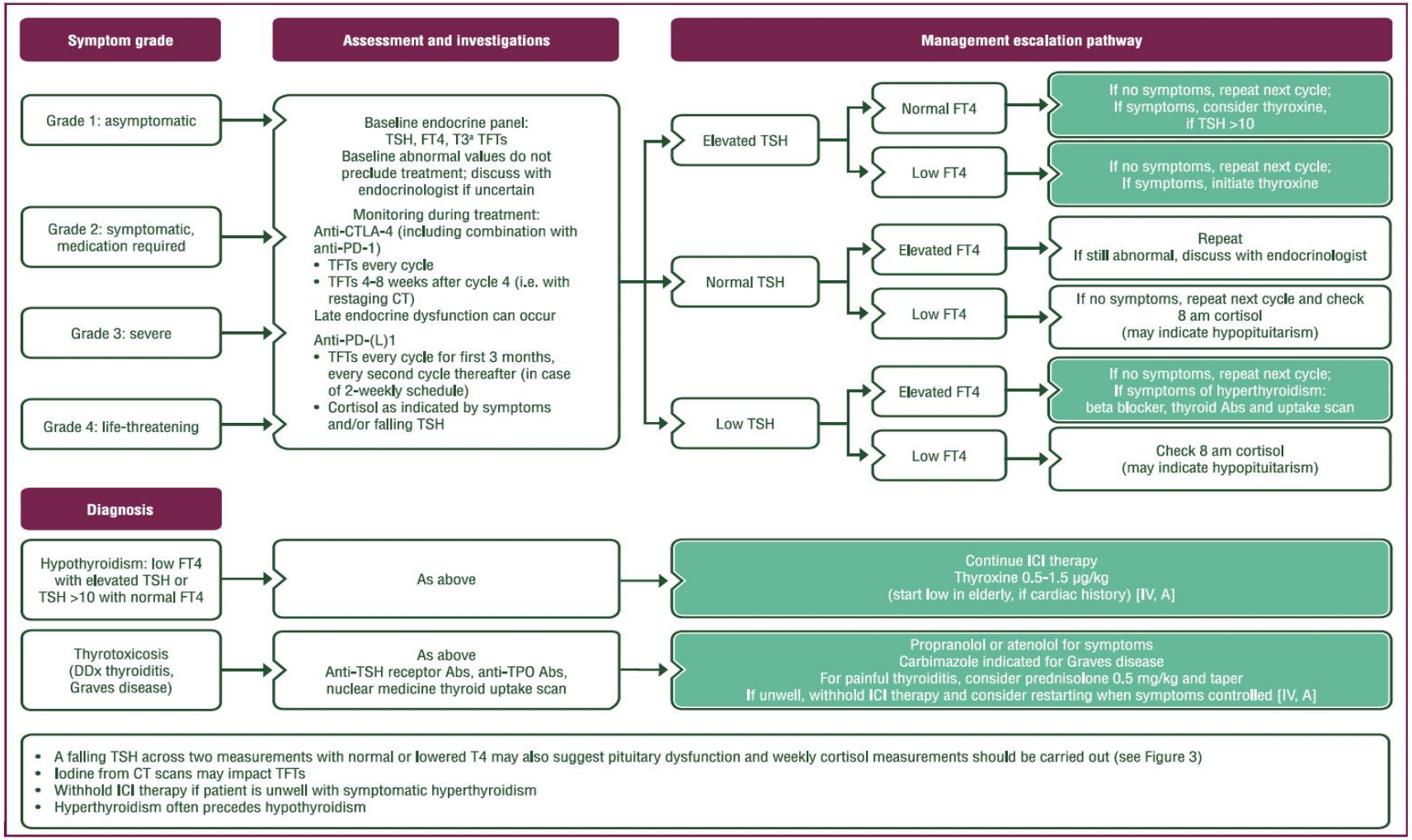
IMMUNE RELATED(IR) ENDOCRINOPATHIES

Management



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TFT: Thyroid Function Test

IMMUNE RELATED(IR) HEPATOTOXICITY

- Hepatitis occurs in 5%-10% (1%-2% grade 3) of patients treated with anti-PD-1/PD-L1 monotherapy
- All patients undergoing ICI therapy should be routinely assessed with **LFT**(e.g. serum transaminases, alkaline phosphatase (ALP) and **bilirubin before every treatment cycle**.
- Alternative causes of liver injury should be excluded (e.g. medication, alcohol, viruses, metabolic disorders, ADs if suspected, vascular disease, tumoural involvement).
- **Liver biopsy** may assist in the differential diagnosis and guide management

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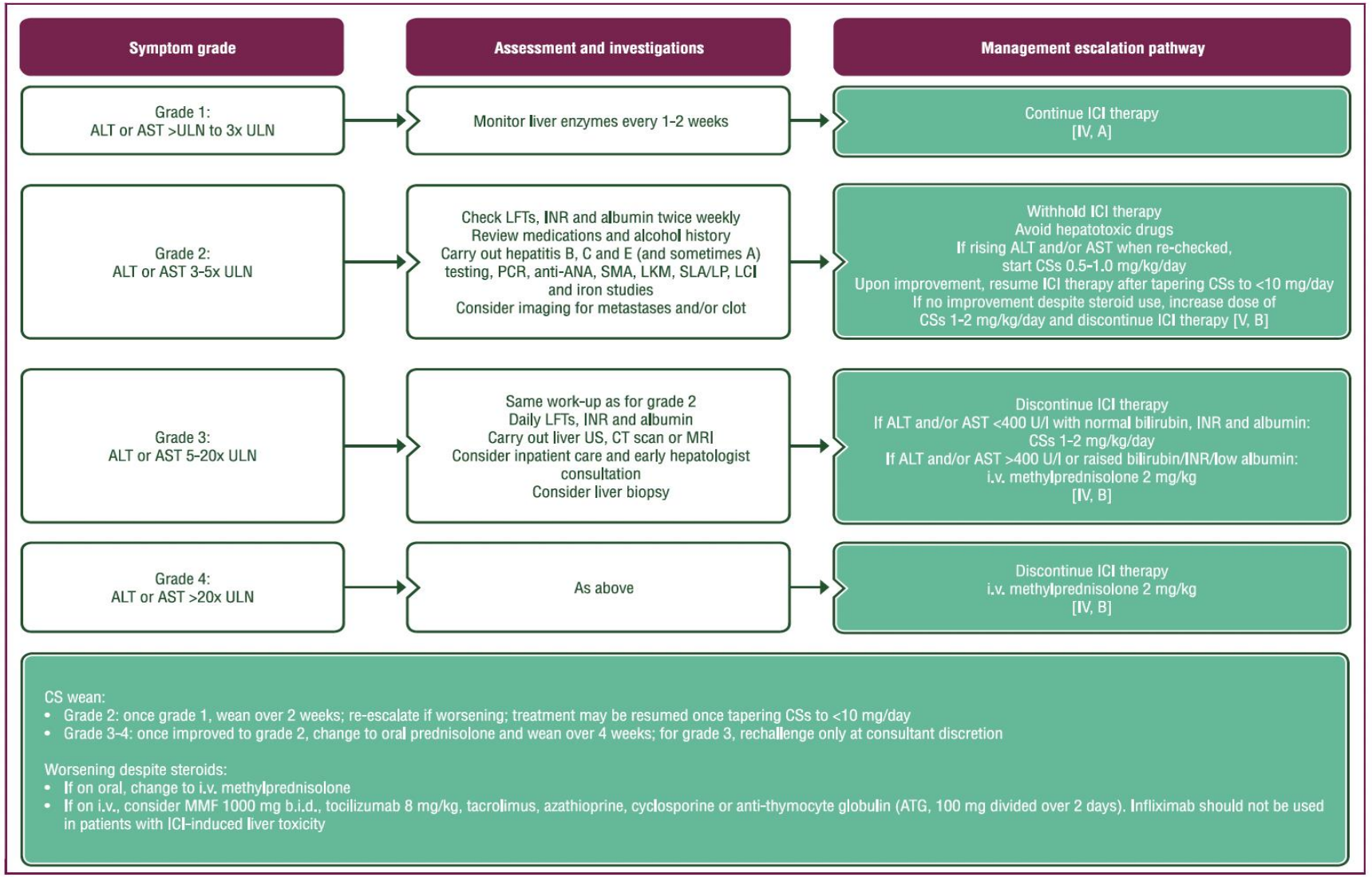
IMMUNE RELATED(IR) HEPATOTOXICITY

Management



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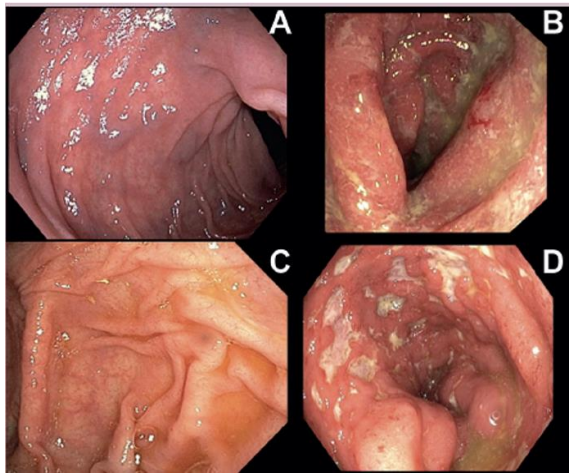
IMMUNE RELATED(IR) ENTEROCOLITIS

- IR-enterocolitis is the most common form of IR-gastrointestinal (GI) toxicity:
- The median onset time is 2-4 months after first Anti-PD-1/PD-L1 infusion, however it may develop after weeks or months of ICI treatment:
- Incidence rates of all-grade diarrhoea and colitis are ~10% and ~1% with Anti-PD-1/PD-L1monotherapy respectively.
- The hallmark symptoms of IR-enterocolitis are diarrhoea and abdominal pain;
  - Haematochezia and fever are less frequent.
  - Severe acute colitis can lead to dehydration, toxic megacolon, colonic perforation (seen in 1%-6.6% of patients) and death, especially in cases of diagnostic delay.
- Early flexible rectosigmoidoscopy or ileocolonoscopy with biopsies in patients with suspected IR-enterocolitis of grade >1 is strongly recommended



Grade 2 diarrhea with swollen, erosive, and friable mucosa

Grade 3 diarrhea with deeply red colon where vascular pattern partially absent, mucosa severely friable, multiple ulcers

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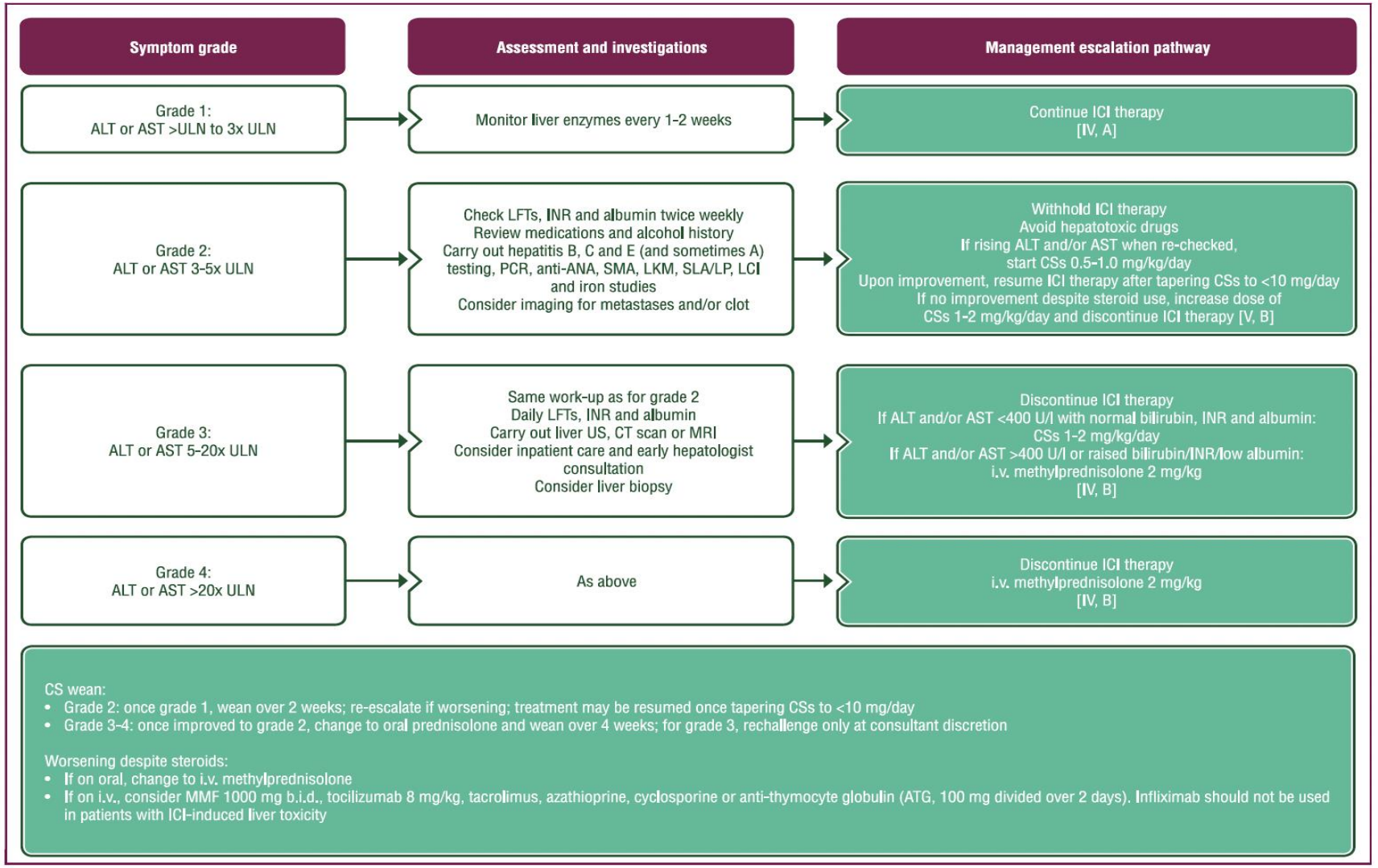
IMMUNE RELATED(IR) ENTEROCOLITIS: Management



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Conclusions

- The number of Patients with Gyn Malignancies treated with ICIs are dramatically increasing due to recent ICIs approvals.
- ICIs can cause irAEs by activating immune cells in non-tumor tissues
  - irAEs can occur after discontinuing ICI
- The most common irAEs are rash, endocrinopathies ,diarrhea, colitis and hepatitis.
- IrAE should be managed based on severity of symptoms :
  - supportive care, holding/discontinuing immunotherapy, and administering corticosteroids, as appropriate
- Health providers must learn how to detect and manage irAE before starting therapy:
  - Make use of resources on identification and management of irAEs, including ESMO Guidelines, SGO Guidelines , NCCN Guidelines and ASCO Guidelines