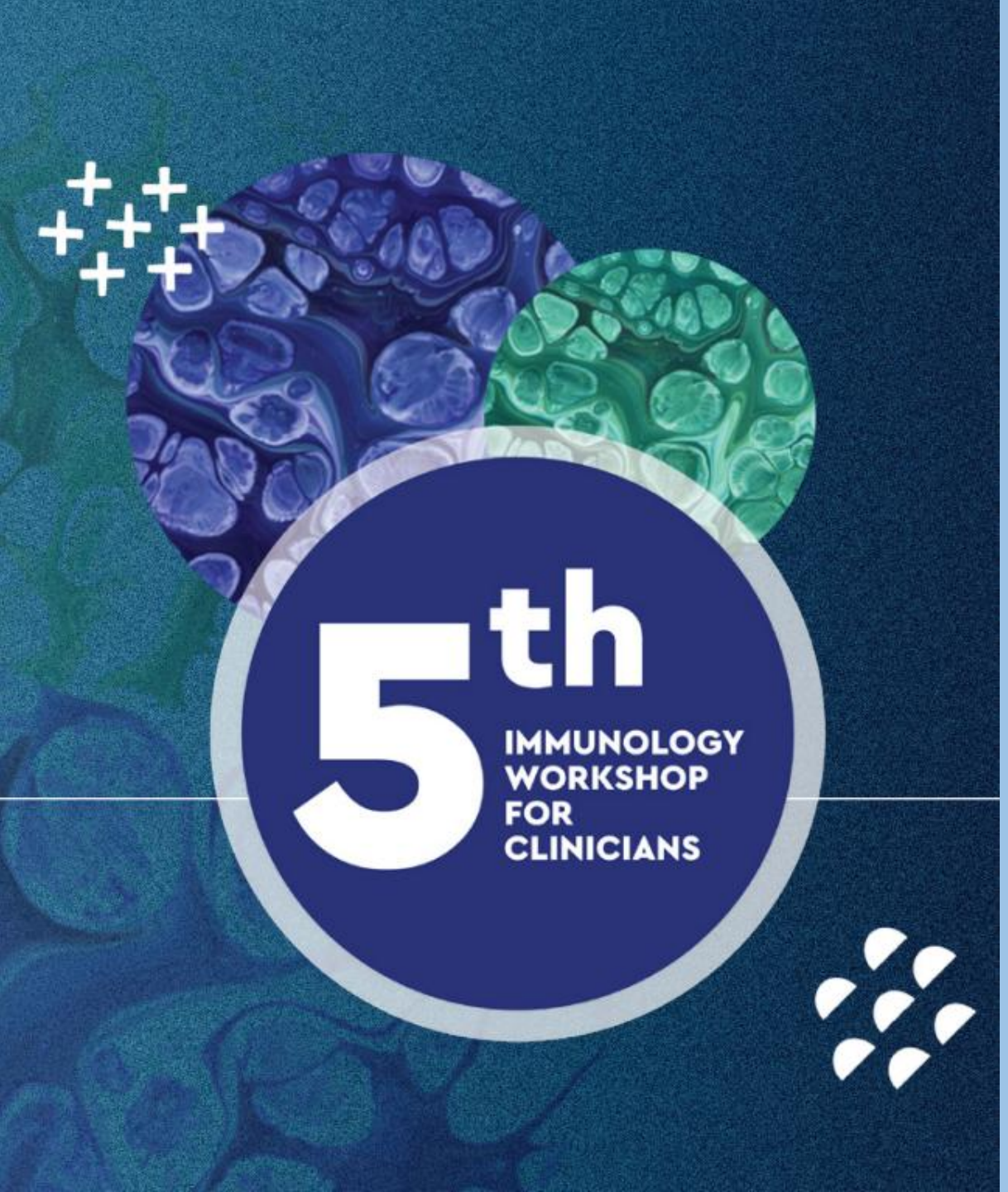


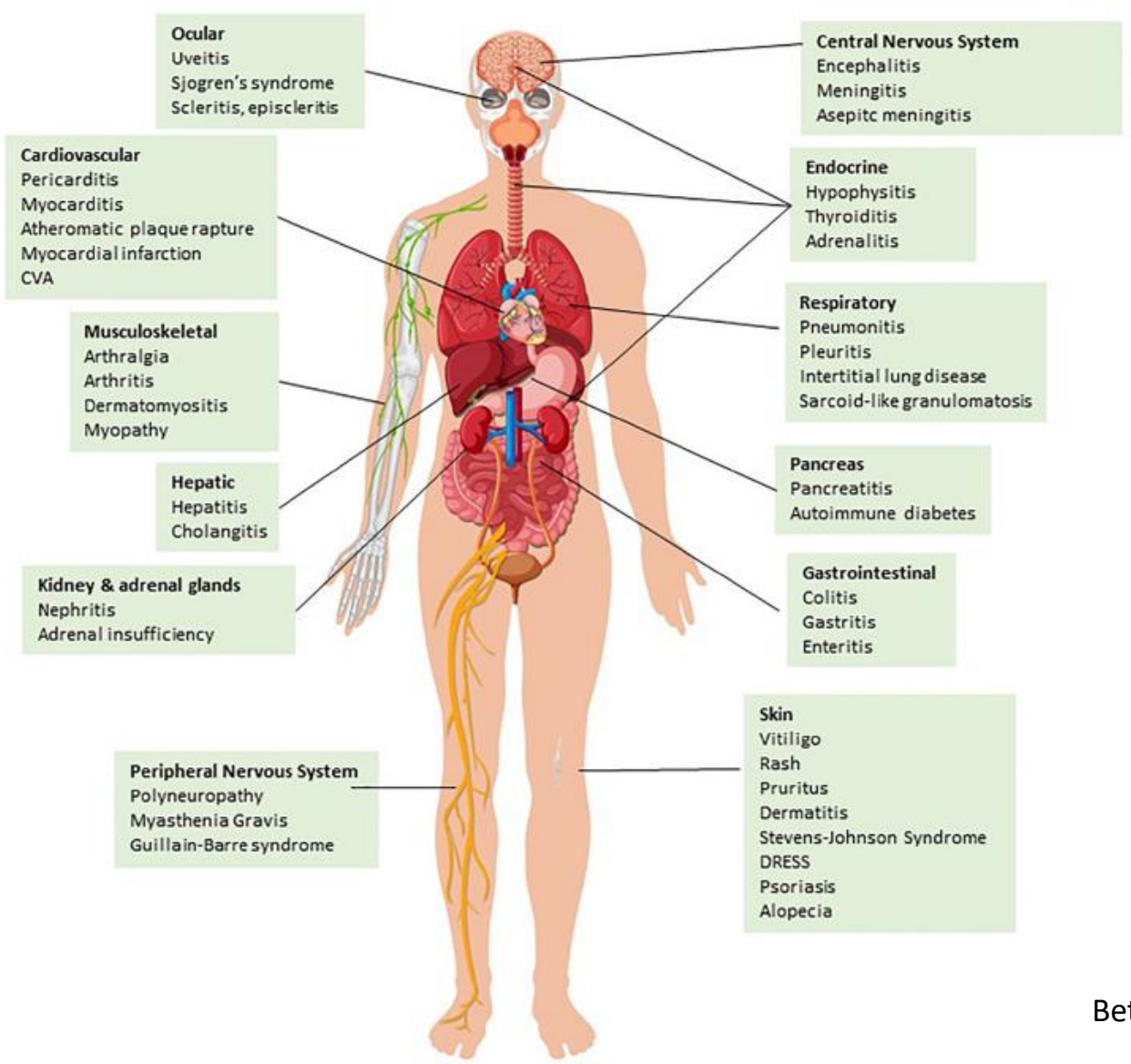
Therapeutic guidelines for immune related side effects of CPI

Sofia Pitsigavdaki

Rheumatologist

31/5/2025

ICI treatment and irAEs by organ system



Betul Ibis et al, Front Immunol, 2023 Jun 5:14:1197364

irAEs occurrence

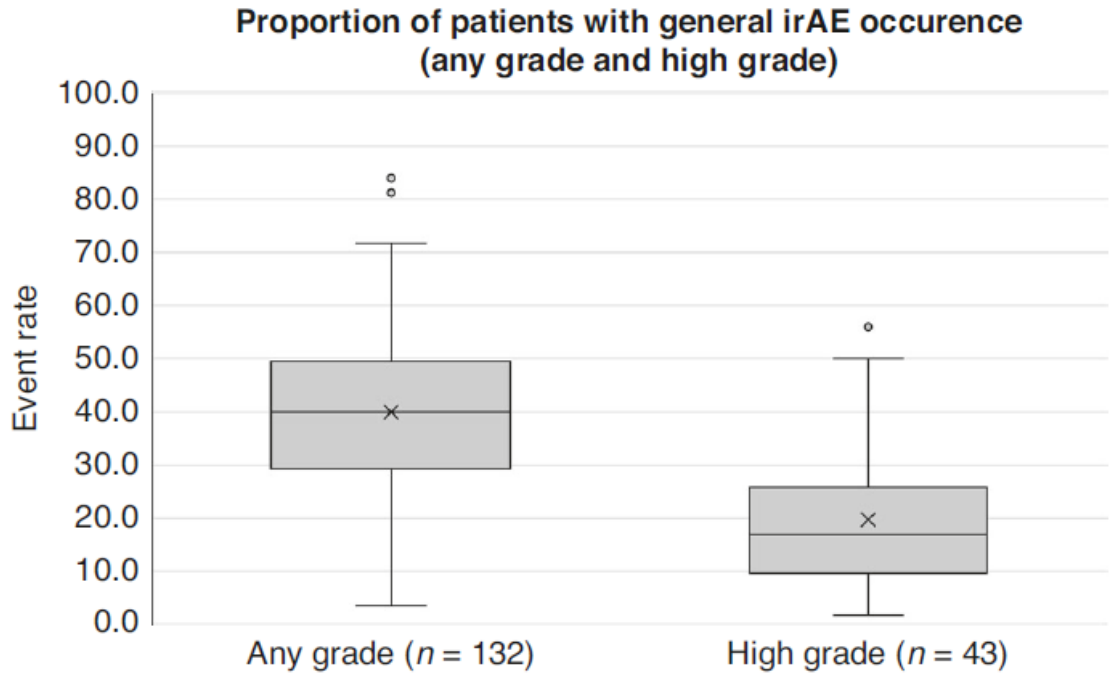


Fig. 2 Box and whisker distribution of general irAE occurrence for any grade and high grade among included studies. *n = 175 studies*. Any grade: minimum 3.5%; first quartile 29.3%; median 40.0%; third quartile 49.4%; maximum 84.0%; mean 40.0%; interquartile range 20.1%. High grade: minimum 1.7%; first quartile 9.6%; median 16.9%; third quartile 25.8%; maximum 56.0%; mean 19.7%; interquartile range 16.2%.

- **175 studies**
- **irAE occurrence is very common in the real-world setting**
- Mean event rate for general irAE occurrence **across any grade was 40.0%** and **high grade was 19.7%**

Bishma Jayathilaka et al, Br J Cancer 2025 Jan;132(1):51-57

Higher occurrence of irAEs for ICI combination therapy

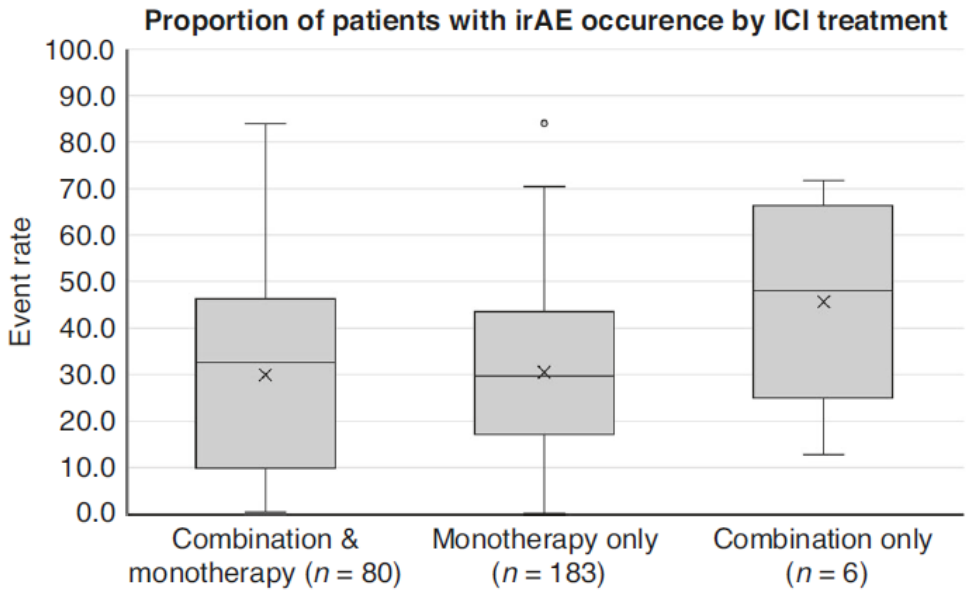


Fig. 4 Box and whisker distribution of specific irAE occurrence for different ICI treatment types. *n = 269 studies.* Monotherapy: minimum 0.1%; first quartile 17.1%; median 29.7%; third quartile 43.5%; maximum 84.0%; mean 30.5%; interquartile range 26.4%. Combination: minimum 12.8%; first quartile 24.9%; median 48.0%; third quartile 66.3%; maximum 71.7%; mean 45.7%; interquartile range 41.4%. Combination & monotherapy: minimum 0.4%; first quartile 9.8%; median 32.6%; third quartile 46.3%; maximum 84.0%; mean 30.0%; interquartile range 36.5%.

- Mean **event rate** for ICI **monotherapy 30.5%**
- **45.7%** for ICI **combination therapy**

Bishma Jayathilaka et al, Br J Cancer 2025 Jan;132(1):51-57

Potential mechanisms of irAEs of ICIs

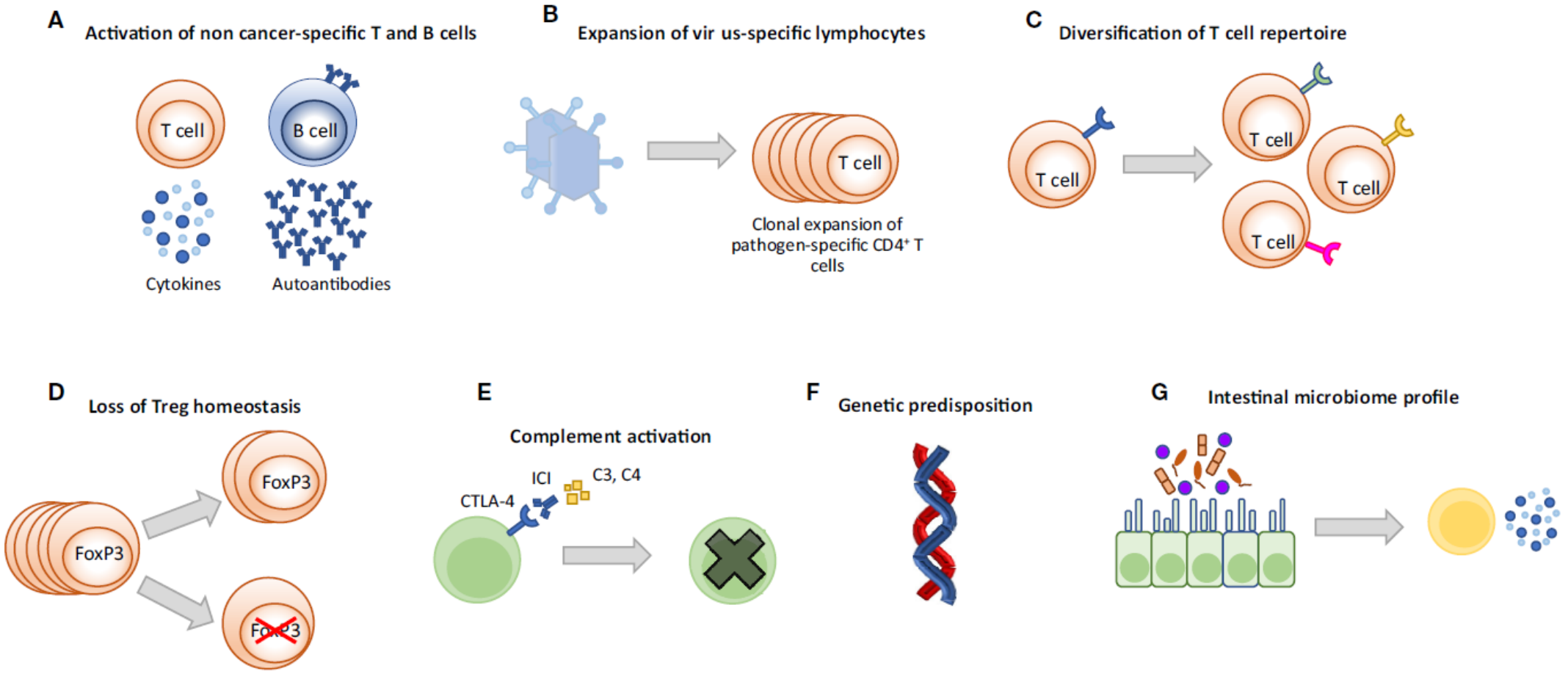


FIGURE 2
Potential mechanisms driving irAEs. **(A)** Activation of cytotoxic self-reactive T cells causes damage in off-target healthy tissues by extensive production of

Betul Ibis et al, Front Immunol, 2023 Jun 5:14:1197364

Key recommendations

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

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

J. Haanen[1†], M. Obeid[2,3,4†], L. Spain[5,6,7], F. Carbonnel[8,9], Y. Wang[10], C. Robert[11,12], A. R. Lyon[13,14], W. Wick[15,16], M. Kostine[17], S. Peters[4], K. Jordan[18,19] & J. Larkin[20], on behalf of the ESMO Guidelines Committee*

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

ASCO® American Society of Clinical Oncology

Bryan J. Schneider, MD[1]; Jarushka Naidoo, MD[2,3]; Bianca D. Santomasso, MD, PhD[4]; Christina Lacchetti, MHSc[5]; Sherry Adkins, MS[6]; Milan Anadkat, MD[7]; Michael B. Atkins, MD[8]; Kelly J. Brassil, PhD[6]; Jeffrey M. Caterino, MD, MPH[9]; Ian Chau, MD[10]; Marianne J. Davies, DNP[11]; Marc S. Ernstoff, MD[12]; Leslie Fecher, MD[1]; Monalisa Ghosh, MD[13]; Ishmael Jaiyesimi, DO, MS[14]; Jennifer S. Mammen, MD, PhD[15]; Aung Naing, MD[6]; Loretta J. Nastoupil, MD[6]; Tanyanika Phillips, MD[16]; Laura D. Porter, MD[17]; Cristina A. Reichner, MD[18]; Carole Seigel, MBA[19]; Jung-Min Song, MSN, RN, CNS[20]; Alexander Spira, MD, PhD[21]; Maria Suarez-Almazor, MD[6]; Umang Swami, MD[22]; John A. Thompson, MD[23]; Praveen Vikas, MD[24]; Yinghong Wang, MD[6];

General principles in management irAEs of ICI

- Early Recognition and Monitoring
- Organ-Specific Management
- Multidisciplinary Approach
- Patient Education
- Rechallenge Considerations

General principles in management irAEs of ICI

Diagnosis and grading of irAEs

Ruling out differential diagnoses and pre-immunosuppression work-up

Selecting the appropriate immunosuppression strategy for grade ≥2 events

Active evaluation to adapt treatment

Grading the irAEs

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

General guidance for immunosuppression

- **GCs are the mainstay of treatment for high-grade irAEs, with the dose increasing according to irAE grade**
- **ICI therapy should be continued** with close active monitoring for **grade 1 irAEs**
- For grade **≥2-3 irAEs**, **dc ICI therapy and starting PDN 0.5-1 mg**/kg/day therapy
- **Grade 4 toxicities** require **high-dose** CSs, **definite ICI dc & initiation of immunosuppressants**

General guidance for GCs

- The **lowest effective CS dose** should be prescribed for the **shortest possible duration**
- **Tapering of CSs should be considered after 48h** of consistent symptom improvement
- In **grade≥3 taper slowly through 4-6 weeks** & **discontinue carefully**

Optimizing the choice of immunosuppressive agents

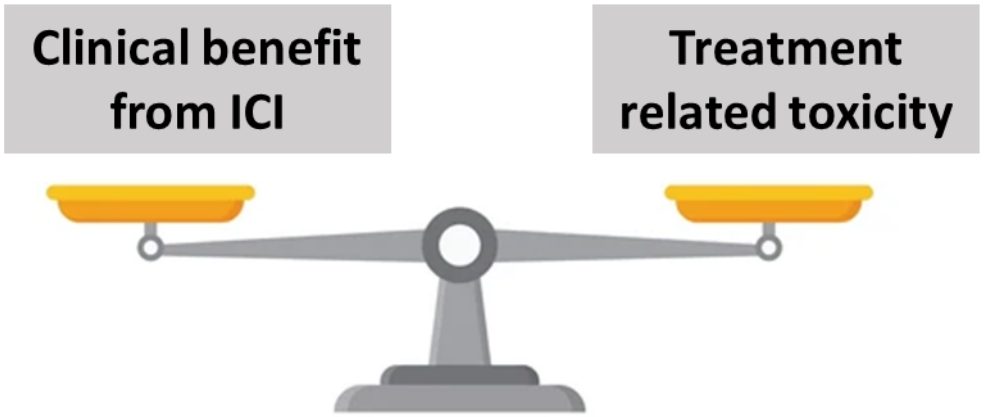
Retrospective observational data for several CS-sparing immune-modulating agents:

- **TNFis**
- Gut-specific immunosuppressants (**vedolizumab**)
- Anti-CD20 monoclonal antibodies
- **Anti-IL6R**
- Anti-IL-4Ra therapy (dupilumab)
- Anti-IL-17A therapies
- Anti-IL-23a antibody
- Anti-IL-12 and IL-23 therapy (ustekinumab)
- csDMARDs, MMF, calcineurin inhibitors, CYC, MTX, AZA, HQ
- tDMARDs, including Janus kinase inhibitors
- IVIG

Is rechallenging possible after irAEs?

Balancing clinical benefit and treatment-related toxicities for each patient is challenging

Patients with **grade 3 or 4 irAEs** are **at risk of redeveloping severe toxicities on ICI rechallenge**



J Haanen et al, Ann Oncol, 2022 Dec;33(12):1217-1238

Rik J Verheijden et al, Nature Portfolio J Precis Oncol, 2023 May 12;7(1):41

Resuming ICI or rechallenge strategy

3 scenarios of ICI resumption possible

Class switch from anti-PD-(L)1 to anti-CTLA-4 therapy, or vice versa.

Rechallenge scenario with the reintroduction of the same class agent or the same molecule

ICI therapy is resumed concomitantly with immunosuppressive therapy (very limited reports)

J Haanen et al, Ann Oncol, 2022 Dec;33(12):1217-1238

Are there data for combined treatment of ICI and immunosuppressants?

- Few **retrospective observational** data for **immunosuppression in combination to ICIs after irAEs**. **No proven loss of ICI effect after treatment.**

- Re-initiation of ICI with concurrent SIT **is most probable safe**, **may reduce severe irEC recurrence** after restarting ICI therapy. **No negative impact on survival outcomes.**

- **Randomised controlled trials comparing different irAE management** regimens would provide clear answers for **effectiveness, safety and survival**.

J Haanen et al, Ann Oncol, 2022 Dec;33(12):1217-1238

Rik J Verheijden et al, Nature Portfolio J Precis Oncol, 2023 May 12;7(1):41

Open access Original research

Journal for ImmunoTherapy of Cancer

Concurrent immune checkpoint inhibition and selective immunosuppressive therapy in patients with immune-related enterocolitis

Yousef R Badran,[1,2] Fangwen Zou,[3,4] Sienna M Durbin,[2,5] Barbara E Dutra,[6] Hamzah Abu-Sbeih,[7] Anusha S Thomas,[3] Mehmet Altan ,[8] John A Thompson,[9] Wei Qiao,[10] Donna E Leet,[2,11] Po-Ying Lai,[12] Nora K Horick,[12] Michael A Postow ,[13,14] David M Faleck ,[13,14] Yinghong Wang ,[3] Michael Dougan [1,2]

- **138 patients, retrospective data**
- After irAEs by ICI patients restarted treatment **with or without combination with immunosuppression** (infliximab or vedolizumab)
- Recurrence of severe colitis or diarrhea after ICI resumption was seen in 34.4% of controls compared with **20.8% of patients receiving concurrent SIT**
- Concurrent SIT was associated with reduced risk of severe irEC recurrence after ICI resumption (**OR 0.34, p=0.034**).
- There was **no difference in survival outcomes** between patients

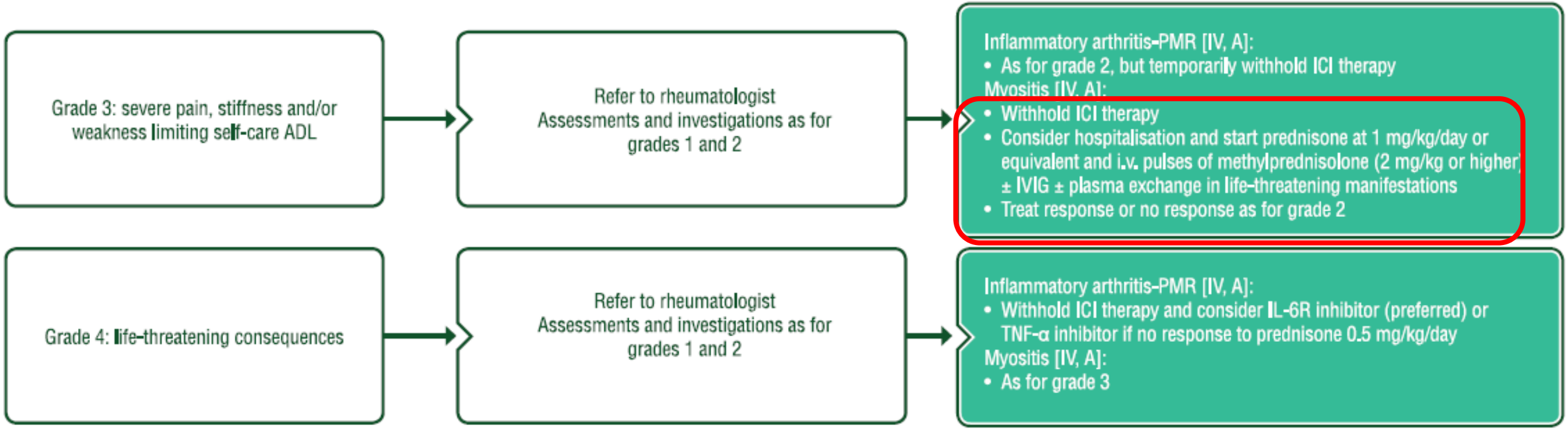
Y R Badran et al, J Immunother Cancer, 2023 Jun;11(6):e007195

Management of Rheumatological toxicity

Symptom grade	Assessment and investigations	Management escalation pathway
Grade 1: mild pain, stiffness and/or weakness	Document joint or muscle inflammation: joint swelling, ESR, CRP, CK level, X-ray and US of affected joints, analysis of synovial fluid if possible; consider autoimmune blood panel, including ANAs, RF, anti-CCP and consider HLA-B27 testing if spine affected[a]	Continue ICI therapy Start analgesics and/or NSAIDs Refer to rheumatologist if no improvement in arthralgia [IV, B]
Grade 2: moderate pain, stiffness and/or weakness limiting instrumental ADL	Refer to rheumatologist Assessments and investigations as for grade 1 In case of no response, consider imaging (US, MRI, CT scan) of refractory arthritis and suspicion of metastatic lesions or septic arthritis Consider ANCA and imaging (PET–CT) for refractory PMR	Arthralgia: • As for grade 1 Inflammatory arthritis-PMR [IV, A]:[b] • Continue ICI therapy • Start prednisone or equivalent 10–20 mg/day and consider higher dosage (0.5 mg/kg/day) if no improvement • Consider intra-articular CSs if mono- or oligoarthritis • Response: progressively taper CSs • No response: consider hydroxychloroquine, sulfasalazine, methotrexate (consider IL-6R or TNF-α inhibitor if no clinical improvement) Myositis [IV, A]:[c] • Withhold ICI therapy • Start prednisone at 0.5-1 mg/kg/day or equivalent • Response: progressively taper CSs • No response: if severe disease,[d] consider methotrexate, azathioprine, MMF, tacrolimus or IL-6R inhibitor; consider TNF-α inhibitor if fasciitis with or without eosinophilia

J Haanen et al, Ann Oncol, 2022 Dec;33(12):1217-1238

Management of Rheumatological toxicity



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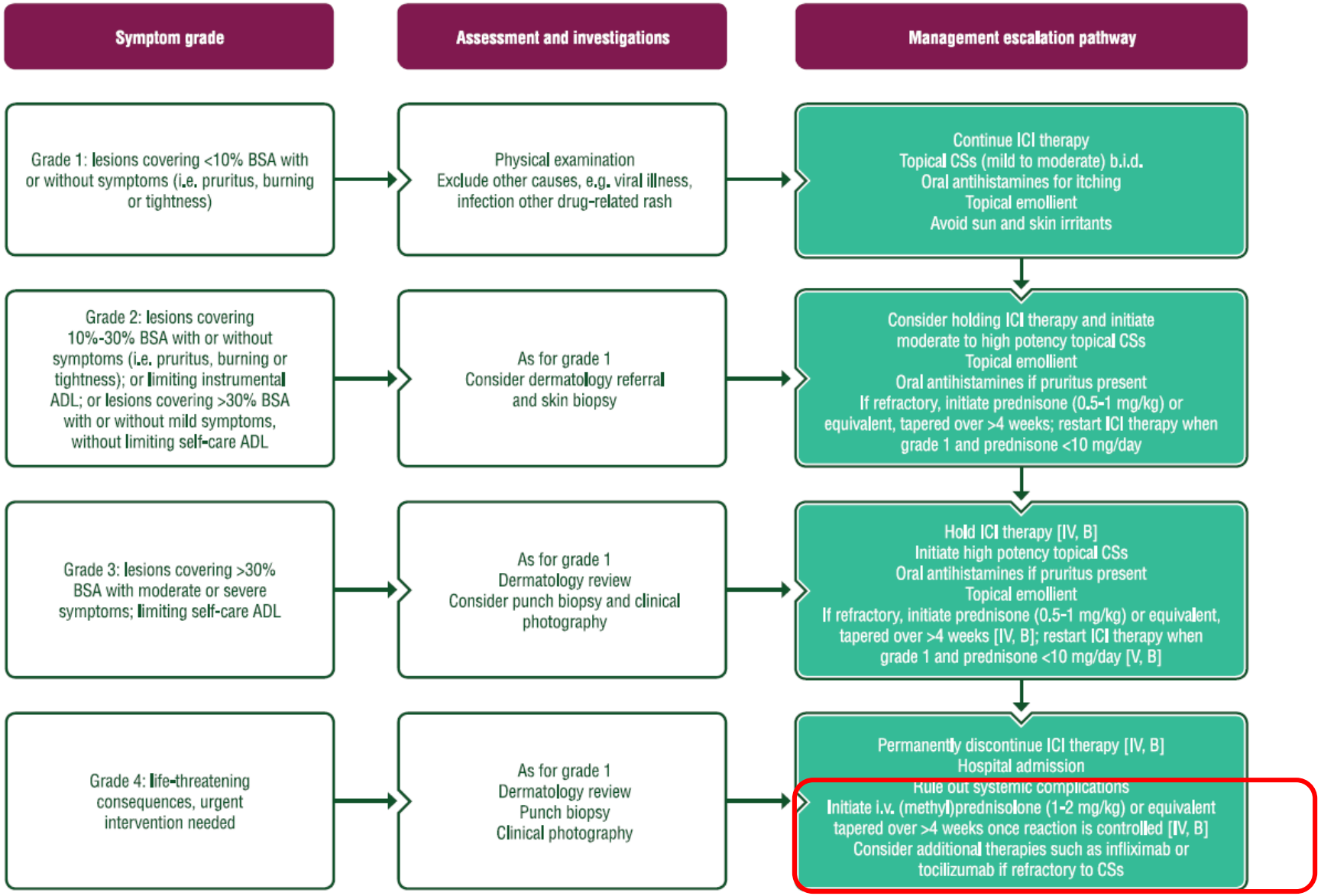
Management of skin toxicity (very common)



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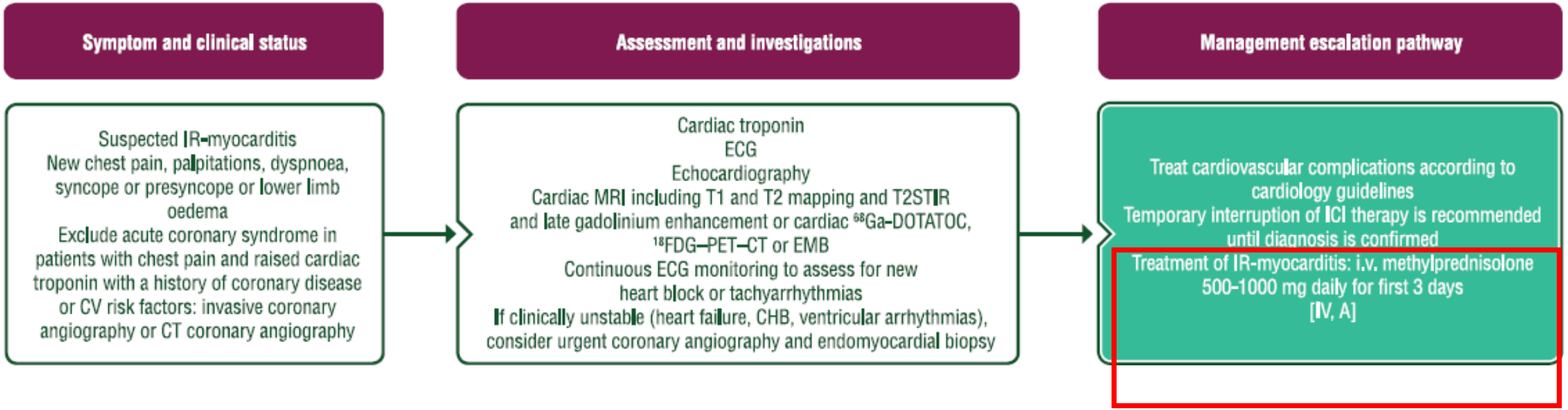
Management of myocarditis (severe is rare)

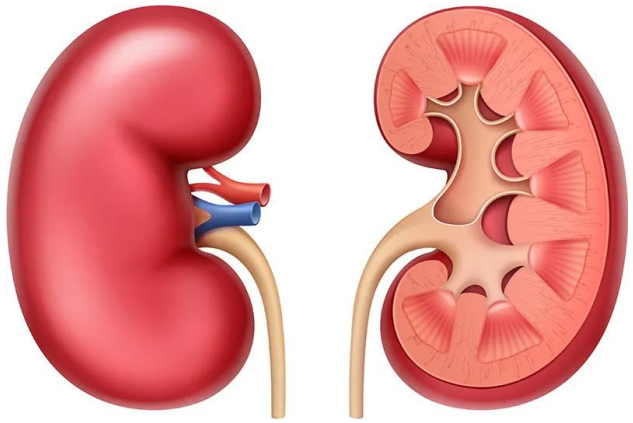


- **Dc of ICI therapy** in most cases
- If **severe involvement** add a **2nd line** treatment: **TCZ, MMF, ATG, alemtuzumab or abatacept**

J Haanen et al, Ann Oncol, 2022 Dec;33(12):1217-1238

Management of acute interstitial nephritis (5-7%)

- Other causes of renal failure should be ruled out
- **ICI therapy discontinued depending on the severity of the renal insufficiency**
- Other nephrotoxic drugs should be stopped
- **MP 1 mg/kg or pulse MP should be considered in stage 3 AKI**
- **Renal biopsy** should be considered on a case-by-case basis



J Haanen et al, Ann Oncol, 2022 Dec;33(12):1217-1238

Management of hematological toxicity (~5%)

- Anaemia (including aplastic and AIHAs)
- Leukopenia, lymphopenia, neutropenia, thrombocytopenia, pancytopenia
- TTP, HUS
- HLH
- Clotting disorders, including acquired haemophilia

- Bone marrow aspiration
- **Blood product** and **growth factor support** in addition to **IV MP 1mg/kg** as 1st line treatment
- **Anti-IL-6R therapy for IR-HLH**
- **oral TPO-RAs** in refractory thrombopenia

Management of endocrinopathies

Hypothyroidism 10%

- Hormone replacement therapy (levothyroxine 50-100 mg/day
- Continue ICI treatment

Hyperthyroidism 5%

- B-blocker therapy
- **Oral prednisolone 0.5-1 mg/kg if thyroiditis**
- ICI therapy should be restarted in asymptomatic cases

Management of endocrinopathies

Hypophysitis (<2-5%)

- Pituitary MRI, visual field assessment
- **Grade 1-2: do not dc ICI**
- **If severe headache, diplopia or other neurological symptoms: MP 1mg/kg**
- **Grade 3-4: dc ICI therapy**

Primary adrenal insufficiency (1-2%)

- Replacement CSs are indicated
- Can lead to life-threatening adrenal crisis

Management of diarrhea and enterocolitis (10-30%)

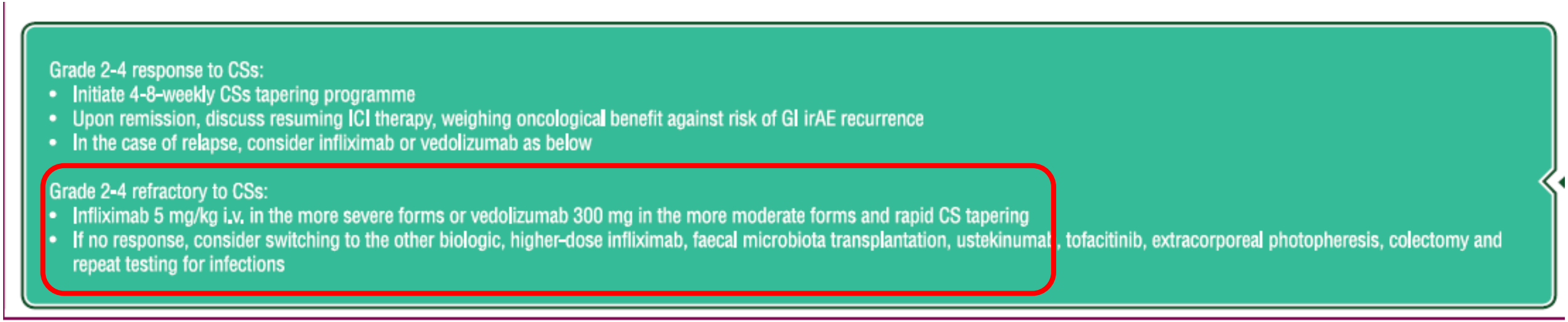
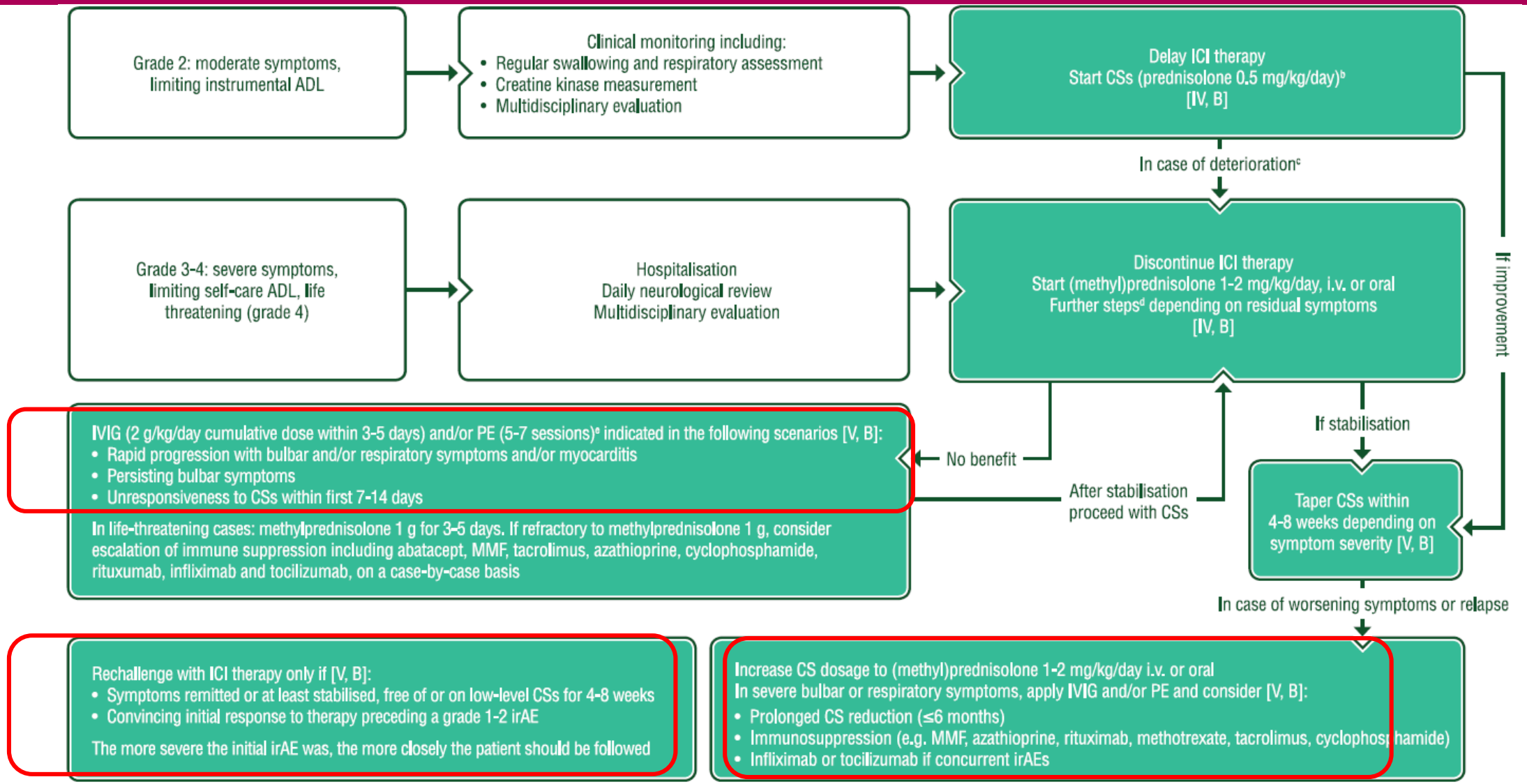


Figure 5. Management of IR-diarrhoea and enterocolitis.

- Exclude other causes (endoscopy and stool testing)
- If responsive to GCs, discuss resuming ICI therapy
- **In severe disease Infliximab or Vedolizumab**

Management of neurological toxicity (1-5%)



Management of hepatitis, pneumonitis

hepatitis (5-10%)

- **Dc ICI**
- Pulse **MP**
- **Grade 3-4 non-responsive to GCs:** add MMF, tacrolimus or TCZ
- **Do not use INFL**

Pneumonitis (<4%)

Grade 3-4

- **Dc ICI**
- Pulse **MP**
- Add **TCZ or INFL ± IVIG,** consider **MMF or CYC**

Take home messages

- Grade the irAE and **treat with steroids**
- **In moderate to severe manifestations use immunosuppression as steroid sparing**
- **Preliminary data of immunosuppressants in combination to ICI do not humper their action and have no adverse impact on the survival**
- **Rechallenging is feasible in most cases with grade 1-3**
- Rechallenging is not recommended in severe myocarditis, neurological manifestation such as Guillain-Barre & encephalitis, severe hepatitis, severe hematological irAEs or Steven-Johnson/TEN

Ευχαριστώ πολύ!