CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Immuntherapie-assoziierte Toxizität

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Zwei Hauptthemen

- Therapie mit Immuncheckpoint-Inhibitoren (anti-PD1/PD-L1, anti-CTLA4, Kombinationen)

- CAR T-Zelltherapie

Leitlinien

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

CLINICAL PRACTICE GUIDELINES
An ESMO Product

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 toxicities from immunotherapy

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. Haanen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan, on behalf of the ESMO Guidelines Committee

onkopedia

onkopedia leitlinien

CAR-T Zellen: Management von Nebenwirkungen

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Version 1.2022 — February 28, 2022

NCCN.org

esmo.org; onkopedia.com; nccn.org

Immuncheckpoint-Inhibitoren (ICI)

Anti-PD1

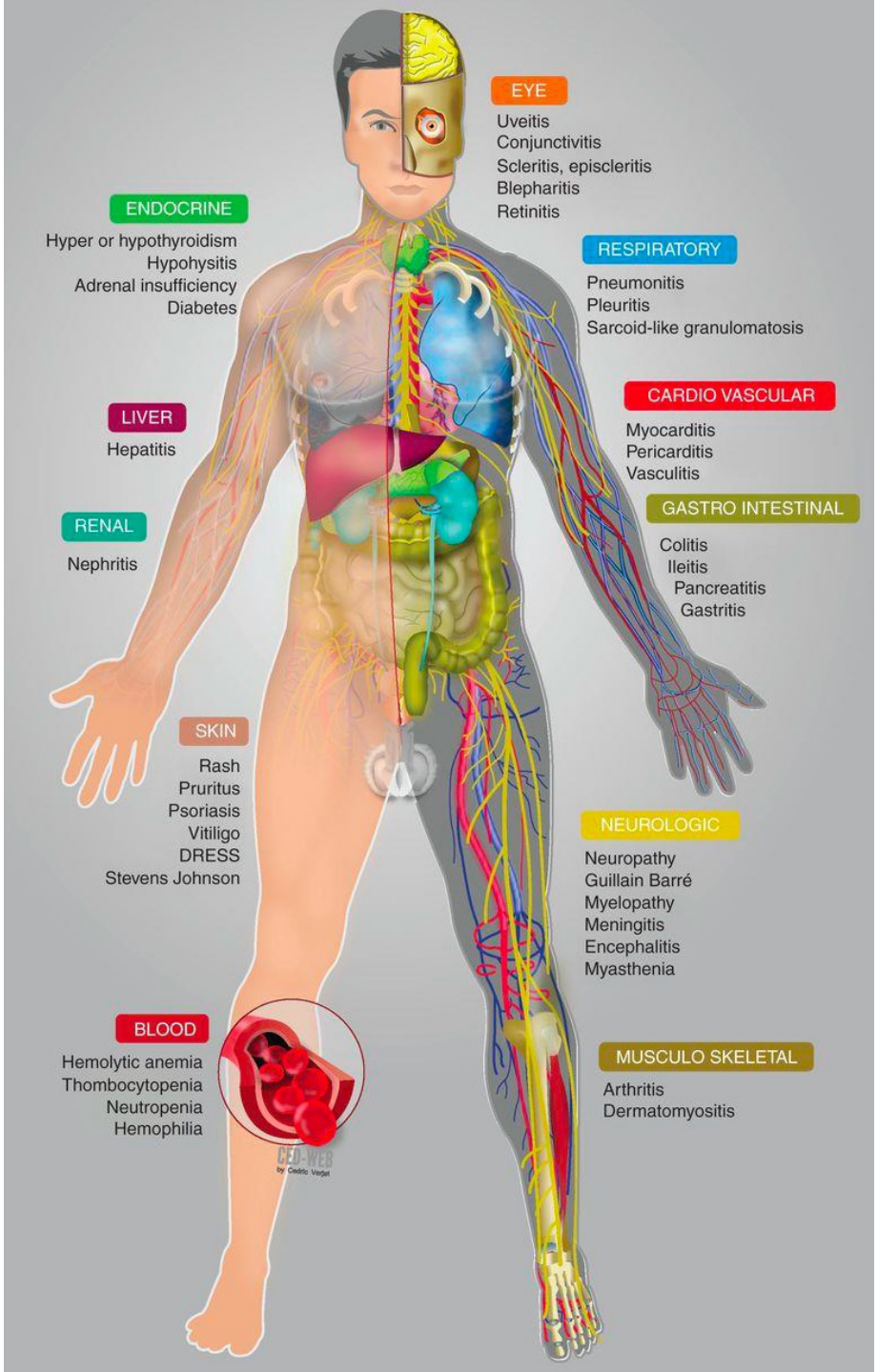
- Pembolizumab
- Nivolumab
- Dostarlimab
- Cemiplimab

Anti-PD-L1

- Atezolizumab
- Durvalumab
- Avelumab

Anti-CTLA4

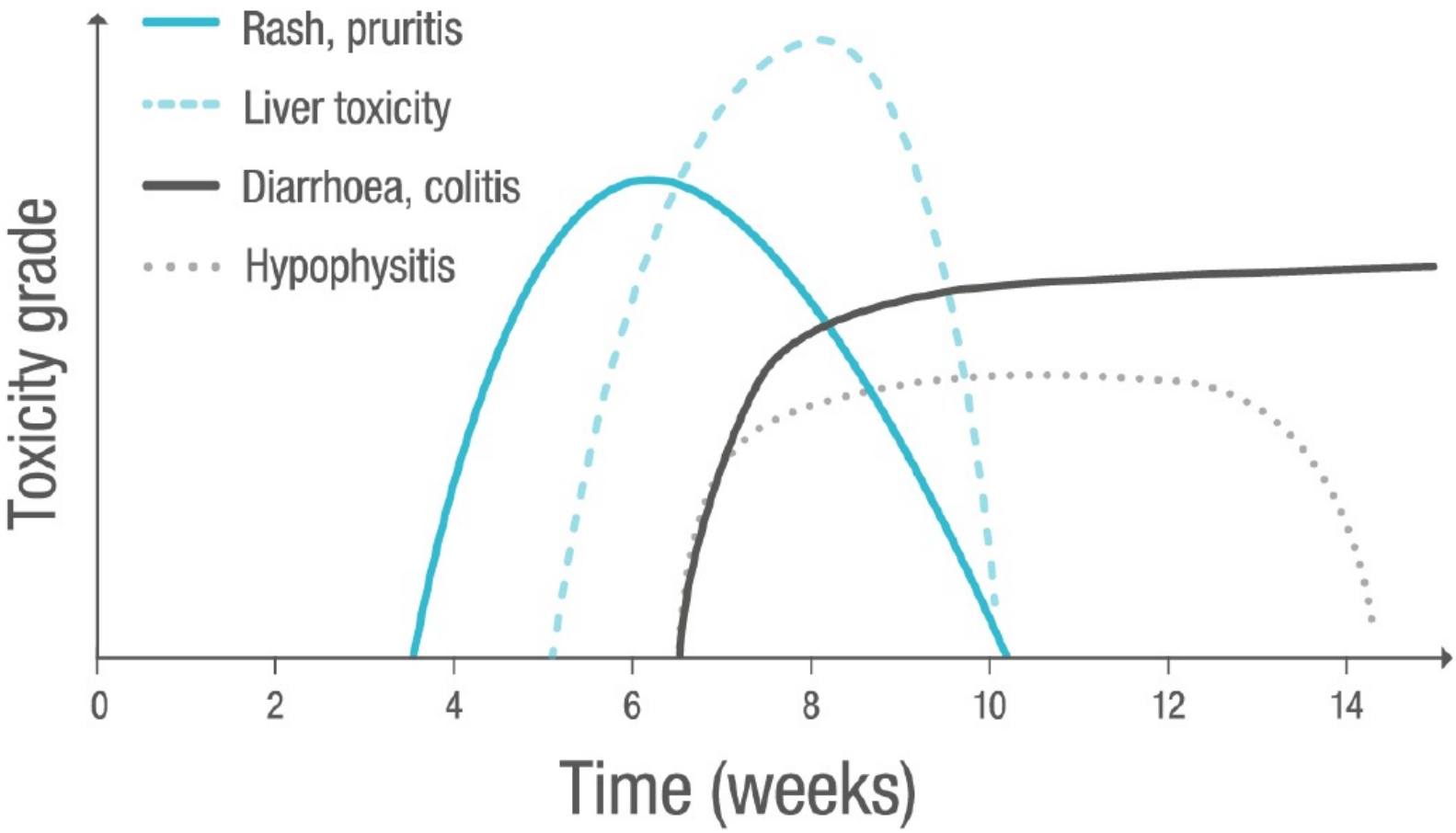
- Ipilimumab
- Tremelimumab



Spektrum ICI-assoziierter Toxizitäten

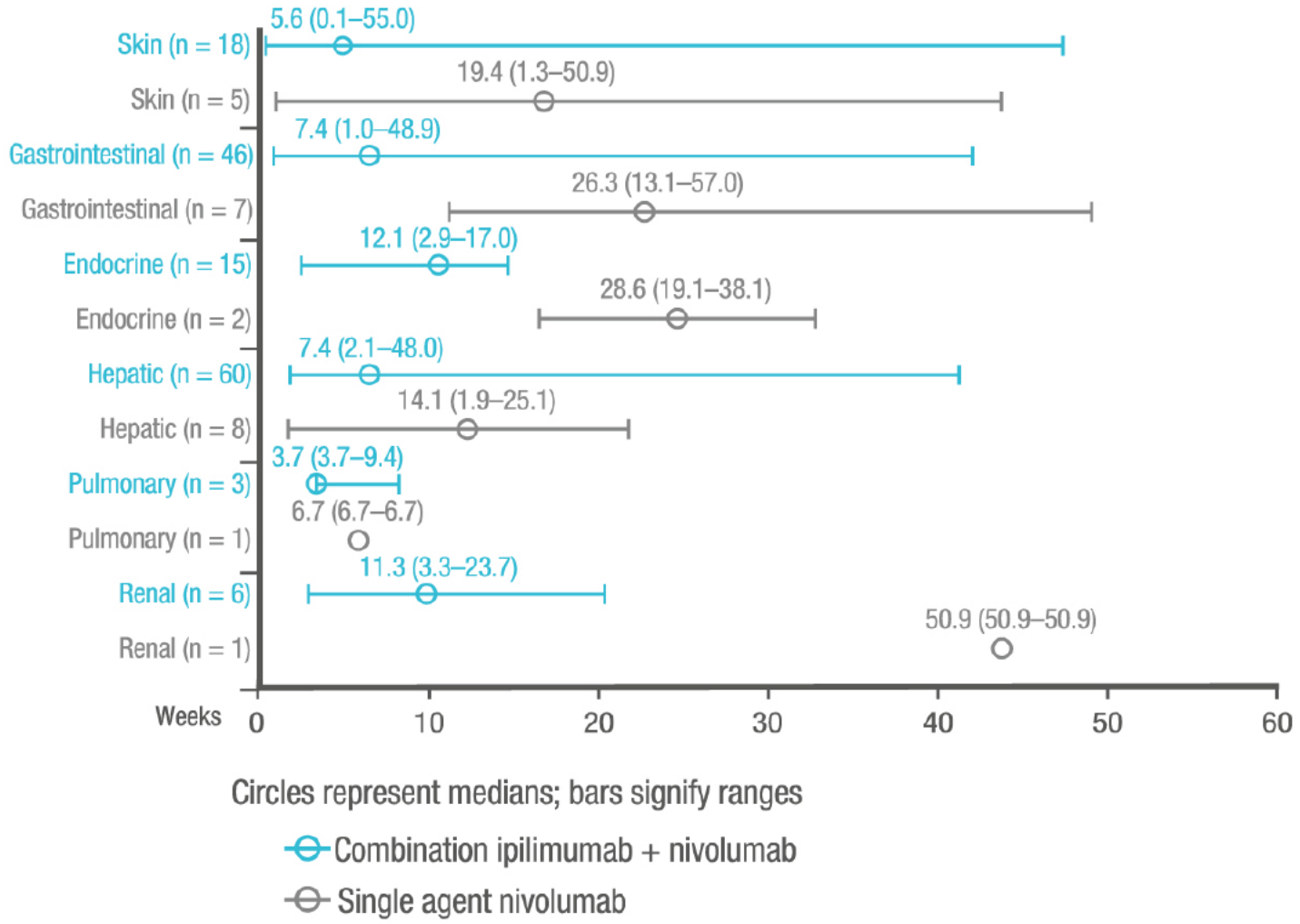
Champiat S et al, Ann Oncol 2016;27:559-574

Typischer Zeitverlauf Immuntherapie-assoziierter Toxizitäten und Schweregrade



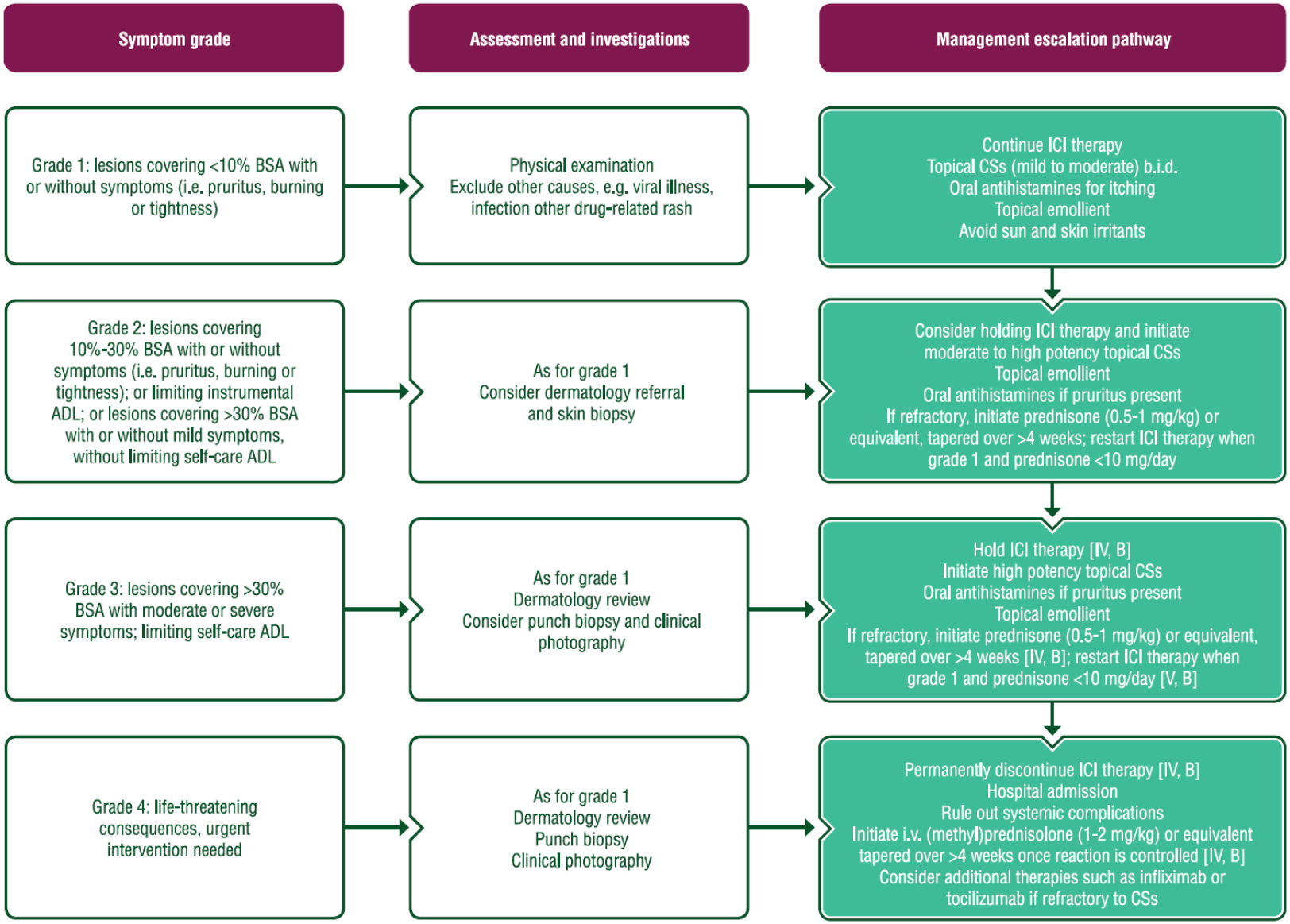
Haanen JBAG, ESMO 2018

Grad 3-4 Immuntherapie-assoziierter Toxizitäten unter Nivo bzw. Nivo/Ipi

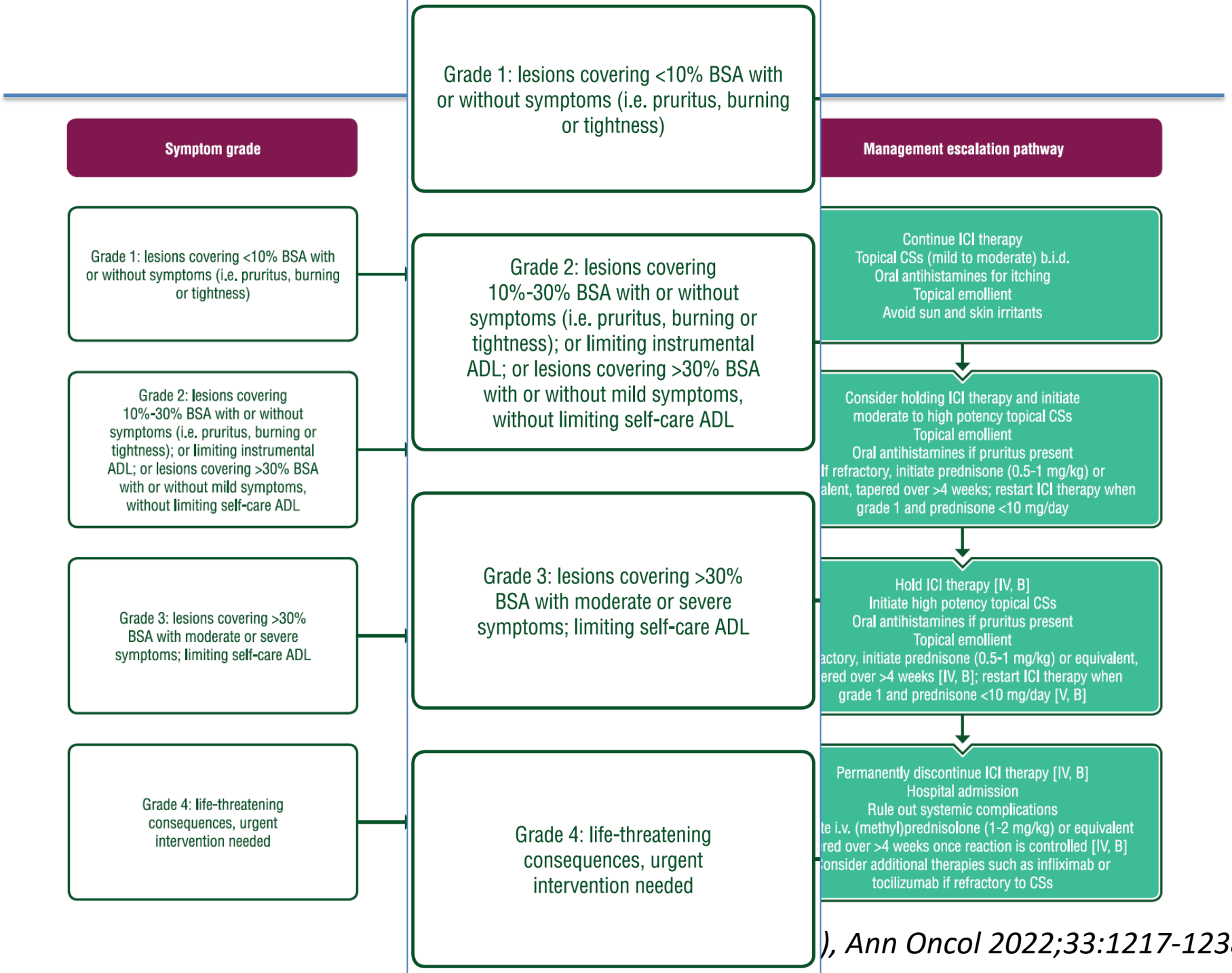


Haanen JBAG, ESMO 2018

Hauttoxizität



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



), Ann Oncol 2022;33:1217-1238

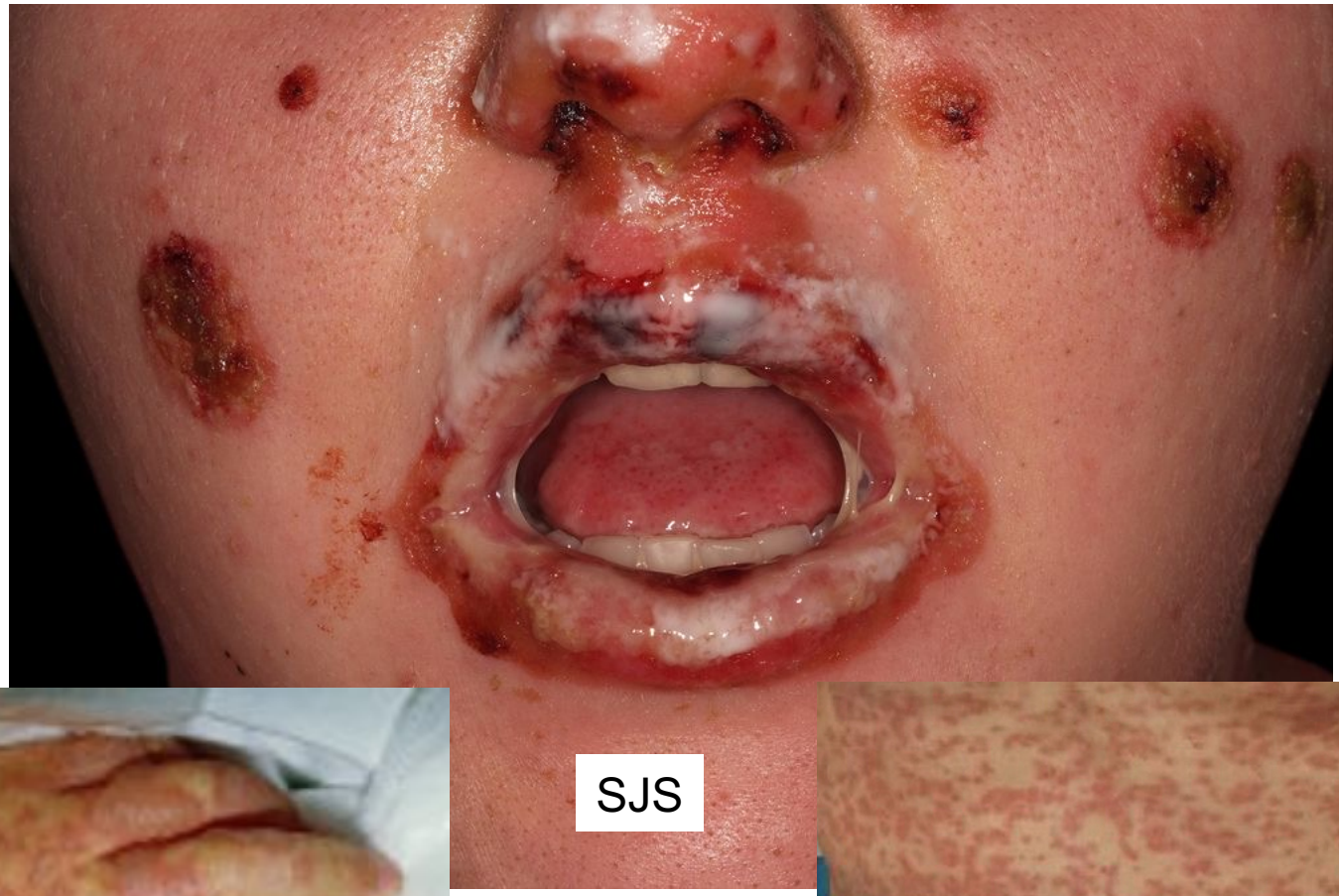
Hauttoxizität

Recommendations

- The relationship between ICI therapy and the skin AE (since the patient is usually on several medications) should be evaluated and confirmed, if possible [IV, A].
- The severity of the skin AE should be evaluated and the need for specialist advice or a referral should be assessed. Physicians should be capable of diagnosing early signs of DRESS, Lyell disease and Stevens–Johnson syndrome [IV, A].
- The entire skin and mucosae of the patient should be examined before initiation of ICI therapy [IV, A].
- The history of skin disorders such as psoriasis or ADs with a skin manifestation should be queried [IV, A].

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

Hauttoxizität



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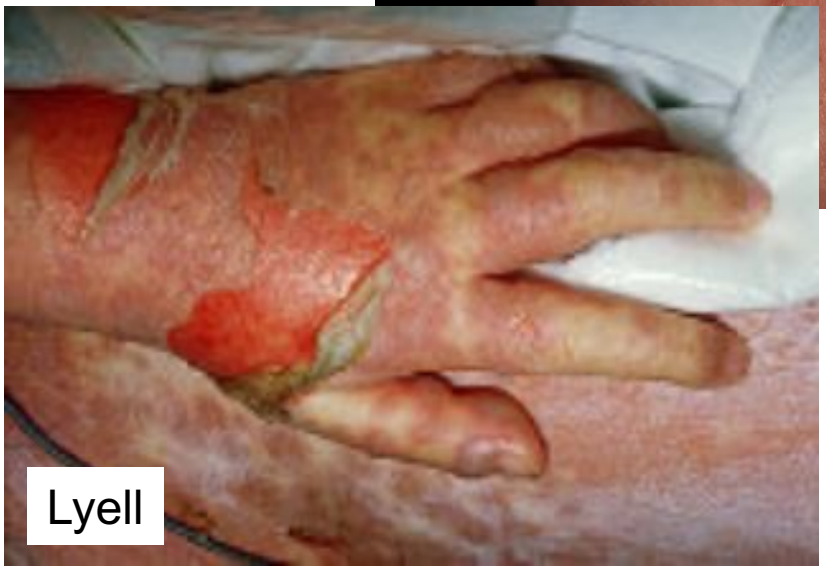
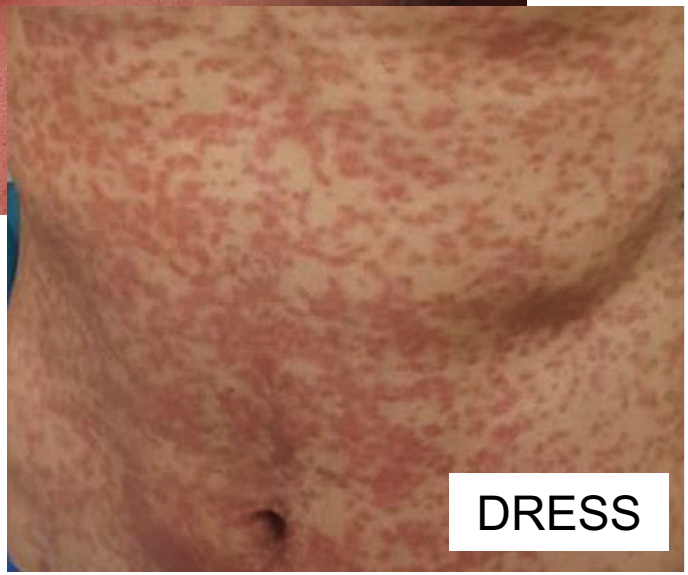
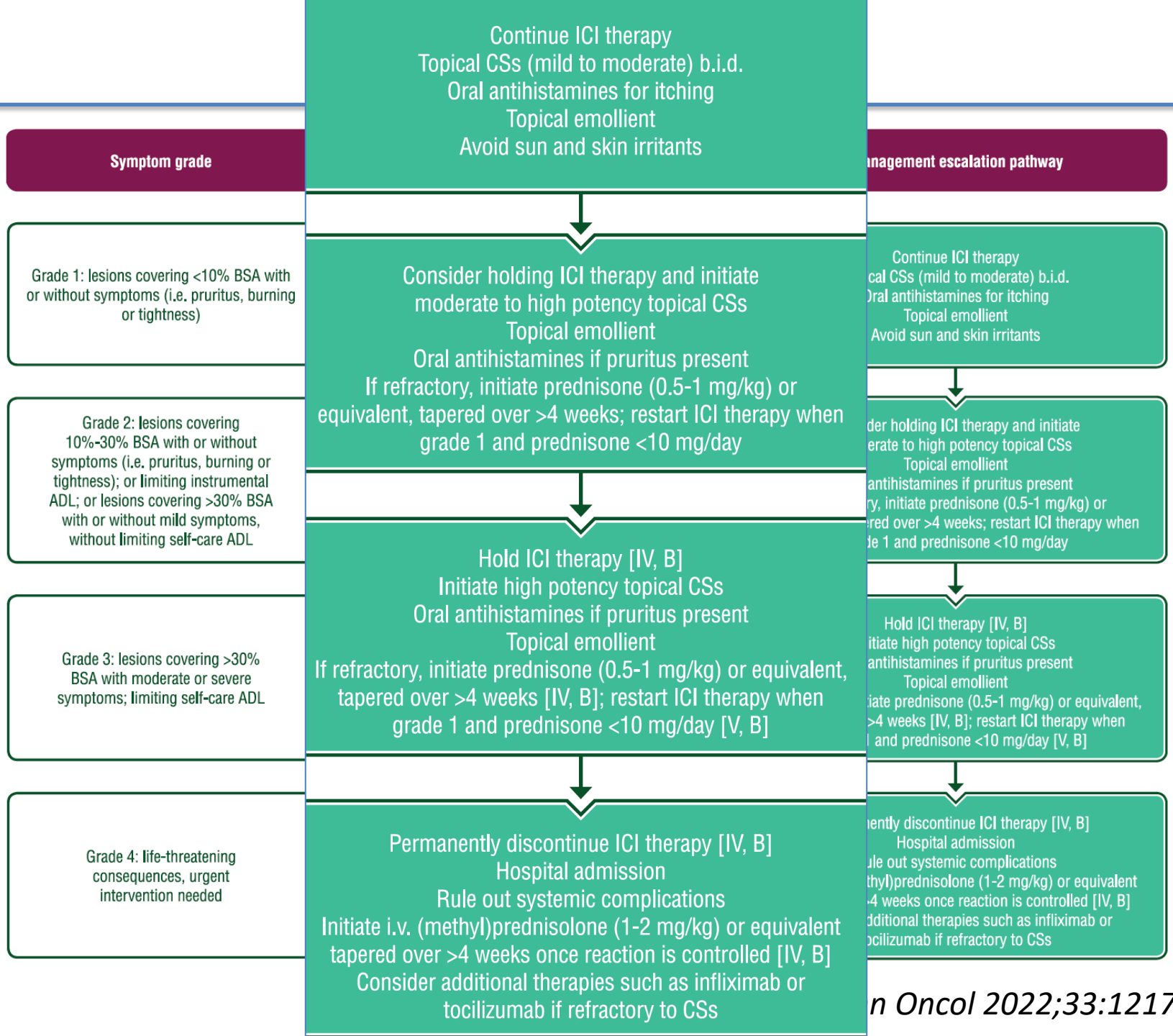


Lyell

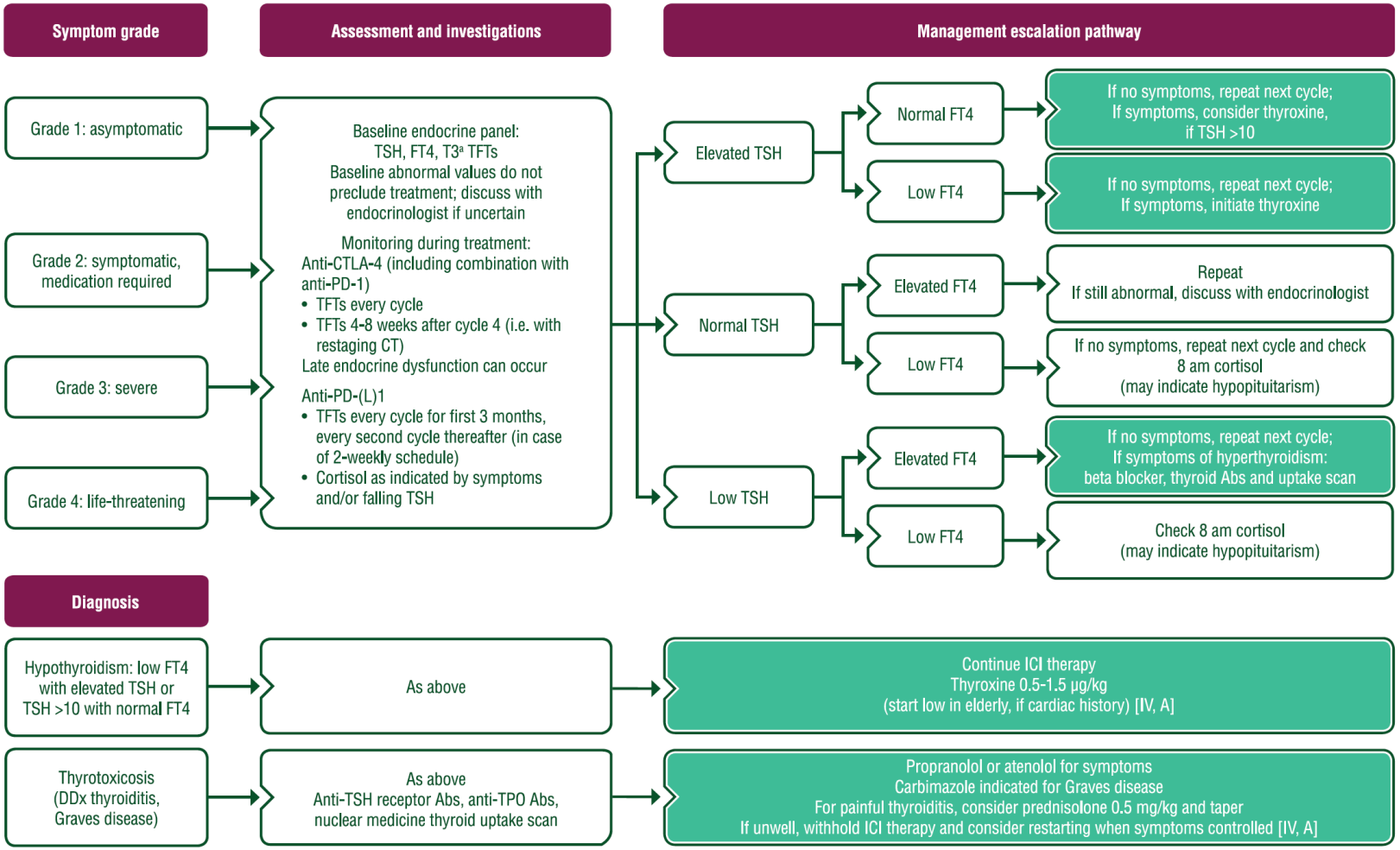


DRESS



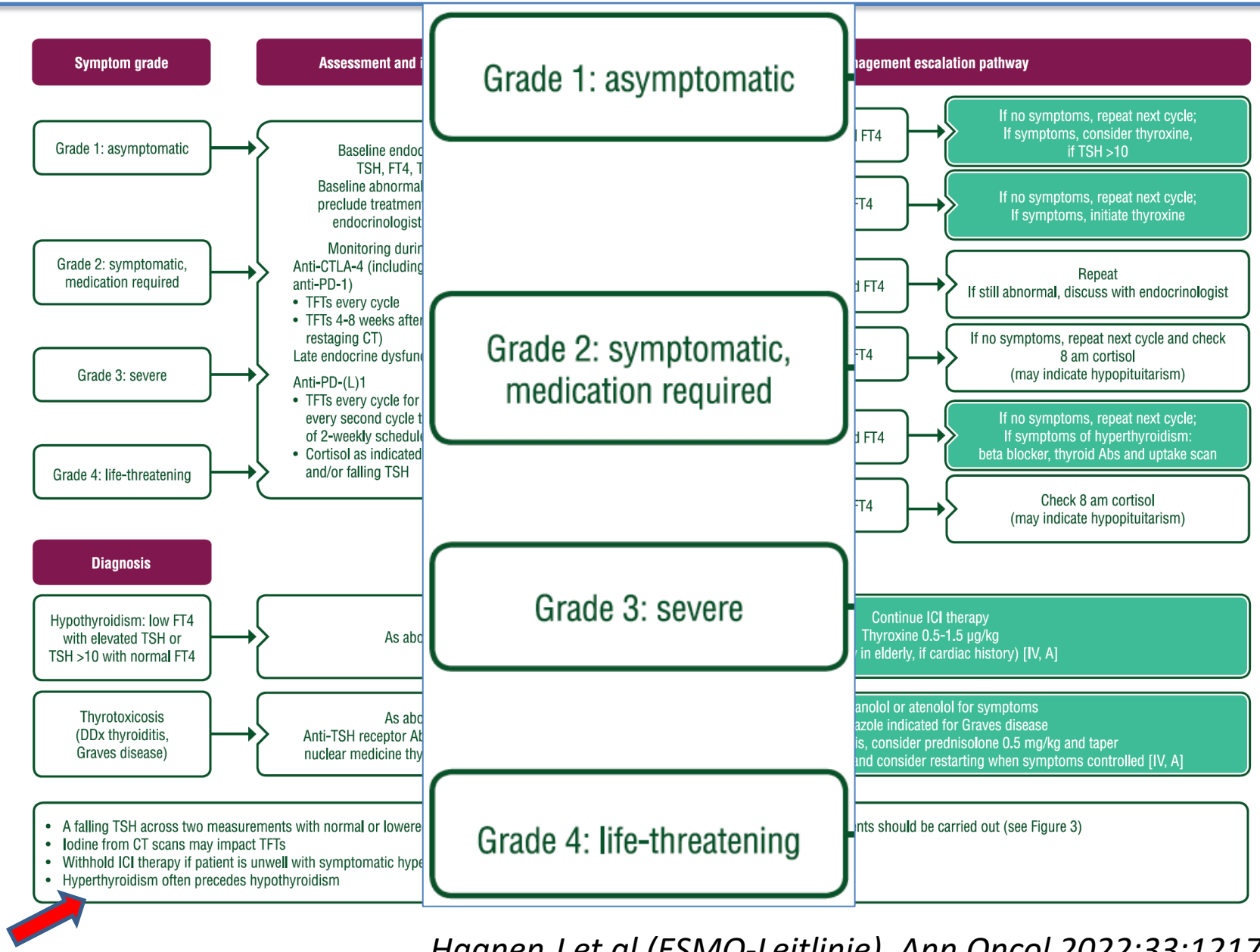
n Oncol 2022;33:1217-1238

Thyreotoxizität



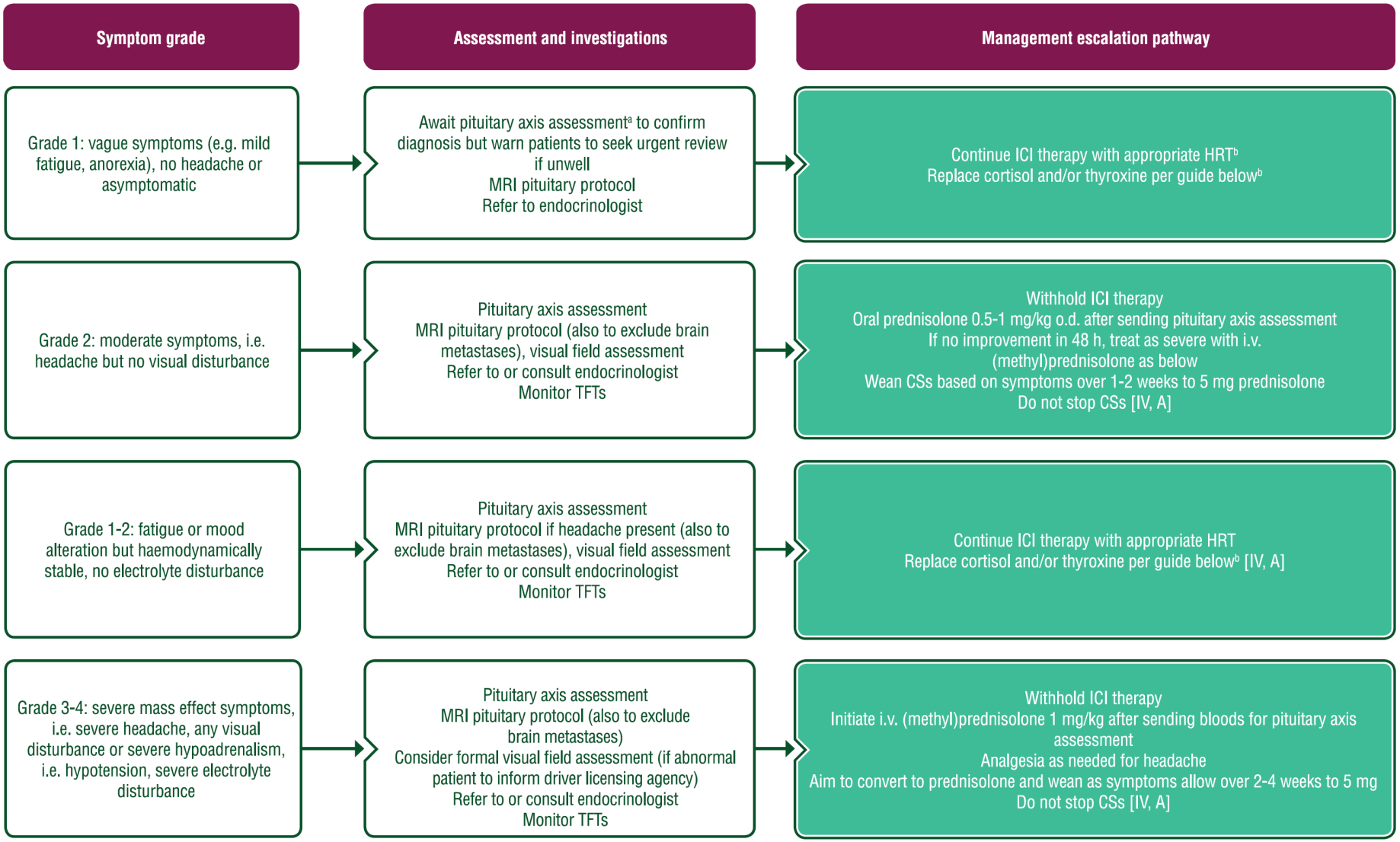
Haanen J et al (ESMO-Leitlinie), Ann Oncol 2022;33:1217-1238

Thyreotoxizität

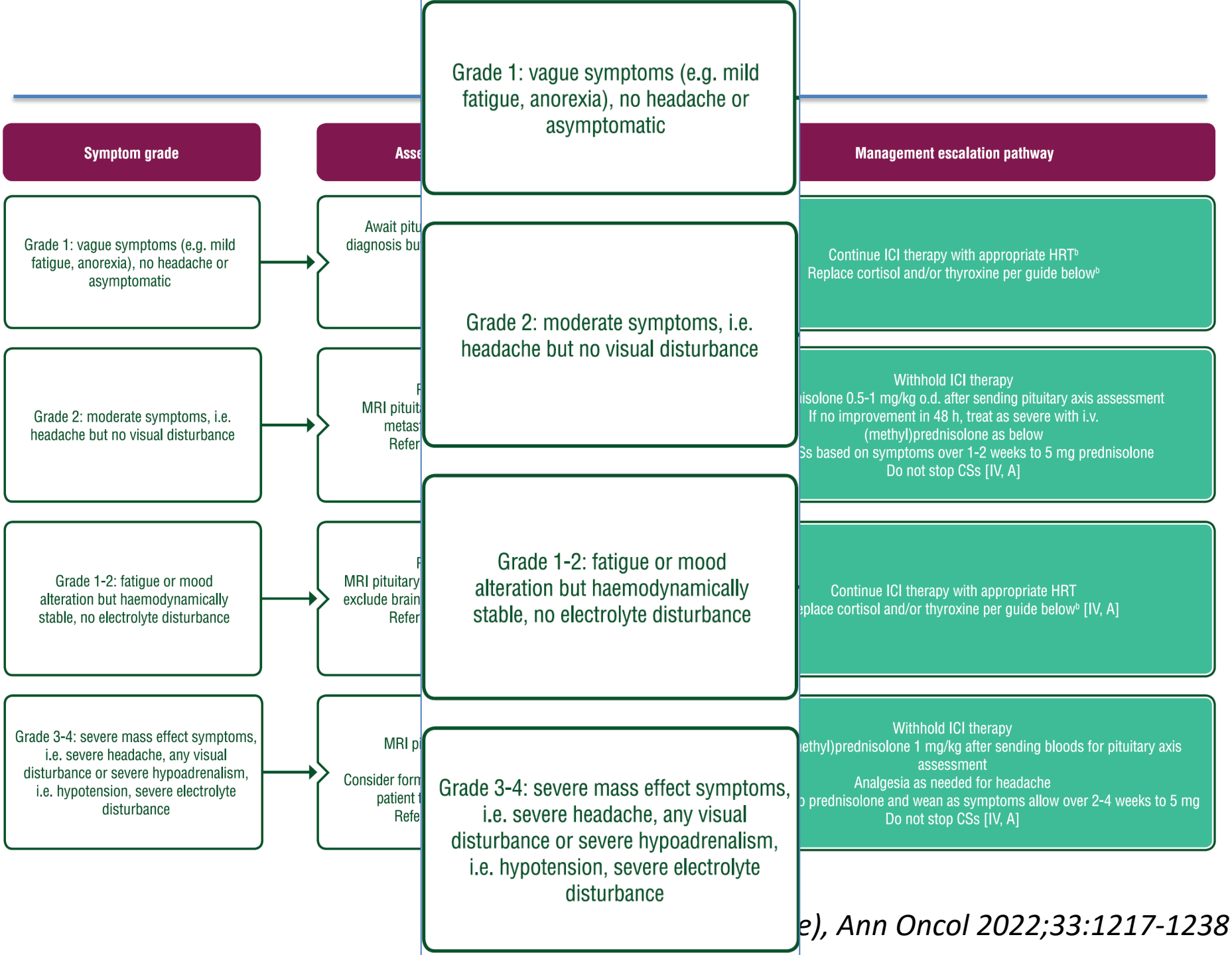


Haanen J et al (ESMO-Leitlinie), Ann Oncol 2022;33:1217-1238

Hypophysitis



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



e), Ann Oncol 2022;33:1217-1238

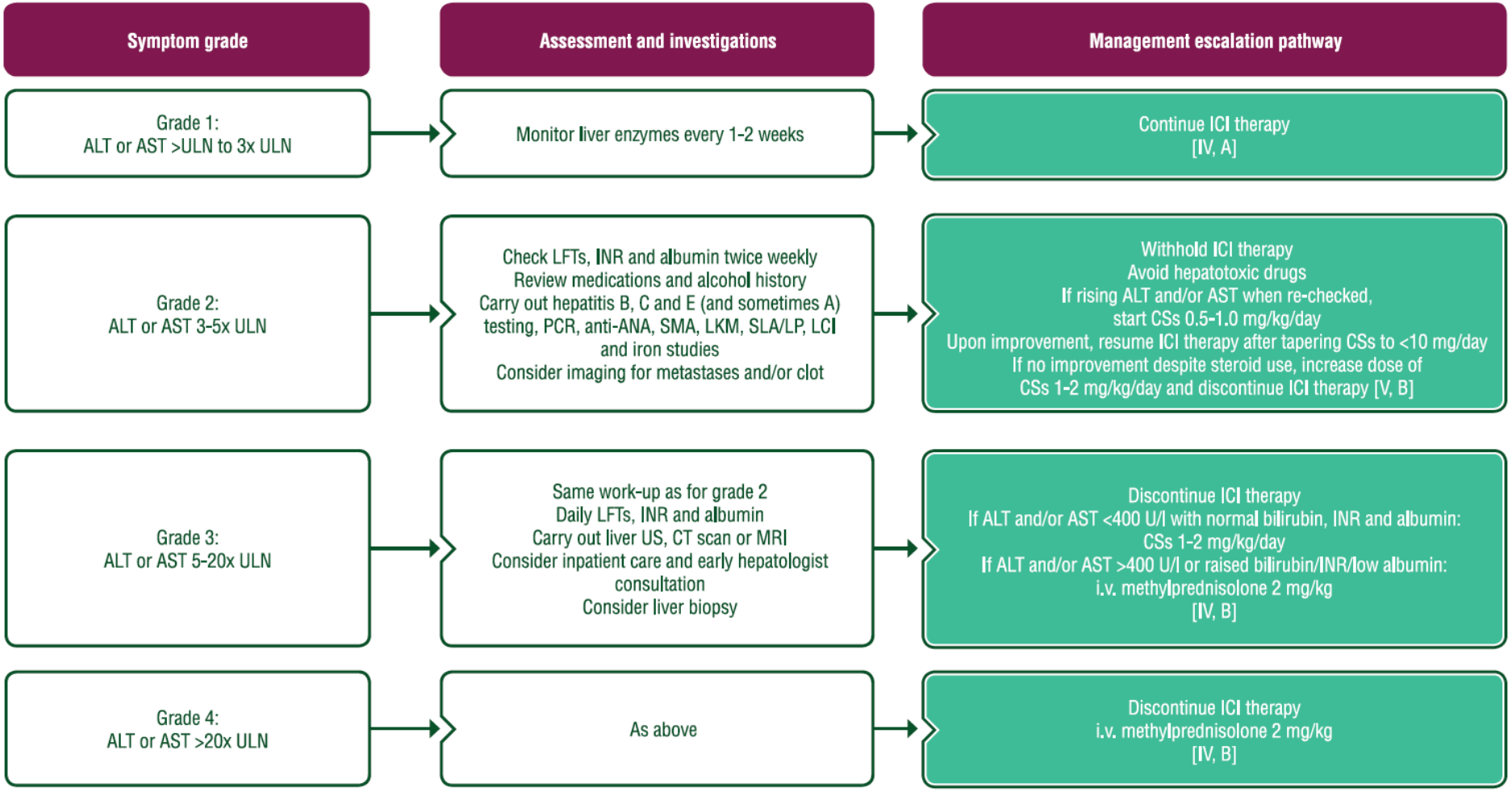
Endokrine Toxizität

Recommendations

- In grade >2 IR-hypothyroidism, hormone replacement therapy (levothyroxine 50-100 µg/day) should be started in symptomatic cases, and the dose should be increased over several weeks until thyroid-stimulating hormone levels normalise. ICI therapy should be interrupted only if symptoms are severe (grade ≥3) [IV, A].
- In symptomatic IR-hyperthyroidism (grade ≥2), ICI therapy should be interrupted and beta blocker therapy should be started. Oral prednisolone 0.5-1 mg/kg may be required short-term for gland inflammation or if symptoms are severe. ICI therapy should be restarted in asymptomatic cases [IV, A].
- For IR-hypophysitis, if severe headache, diplopia or other neurological symptoms are present (grade 3), (methyl) prednisolone 1 mg/kg is indicated. Secondary adrenal crisis (grade 3 insufficiency) should be managed with stress-dose CS replacement. In asymptomatic and symptomatic cases without severe features (grade 1-2), replacement doses of deficient hormones (adrenal, thyroid and gonadal axes) should be initiated [IV, A].
- For IR-primary adrenal insufficiency, in asymptomatic or minimally symptomatic cases (grade 1-2), replacement CSs are indicated. In severe cases (grade ≥3), stress replacement doses are required [IV, A].
- For new-onset IR-DM, prompt insulin initiation is warranted. Patients presenting with ketoacidosis should be admitted to the hospital. Diabetic ketoacidosis should be managed according to the institutional guidelines, including intravenous (i.v.) insulin, correction of fluid loss and close monitoring of serum potassium, hourly glucose and anion gap. High-dose CSs are not indicated [IV, E].

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

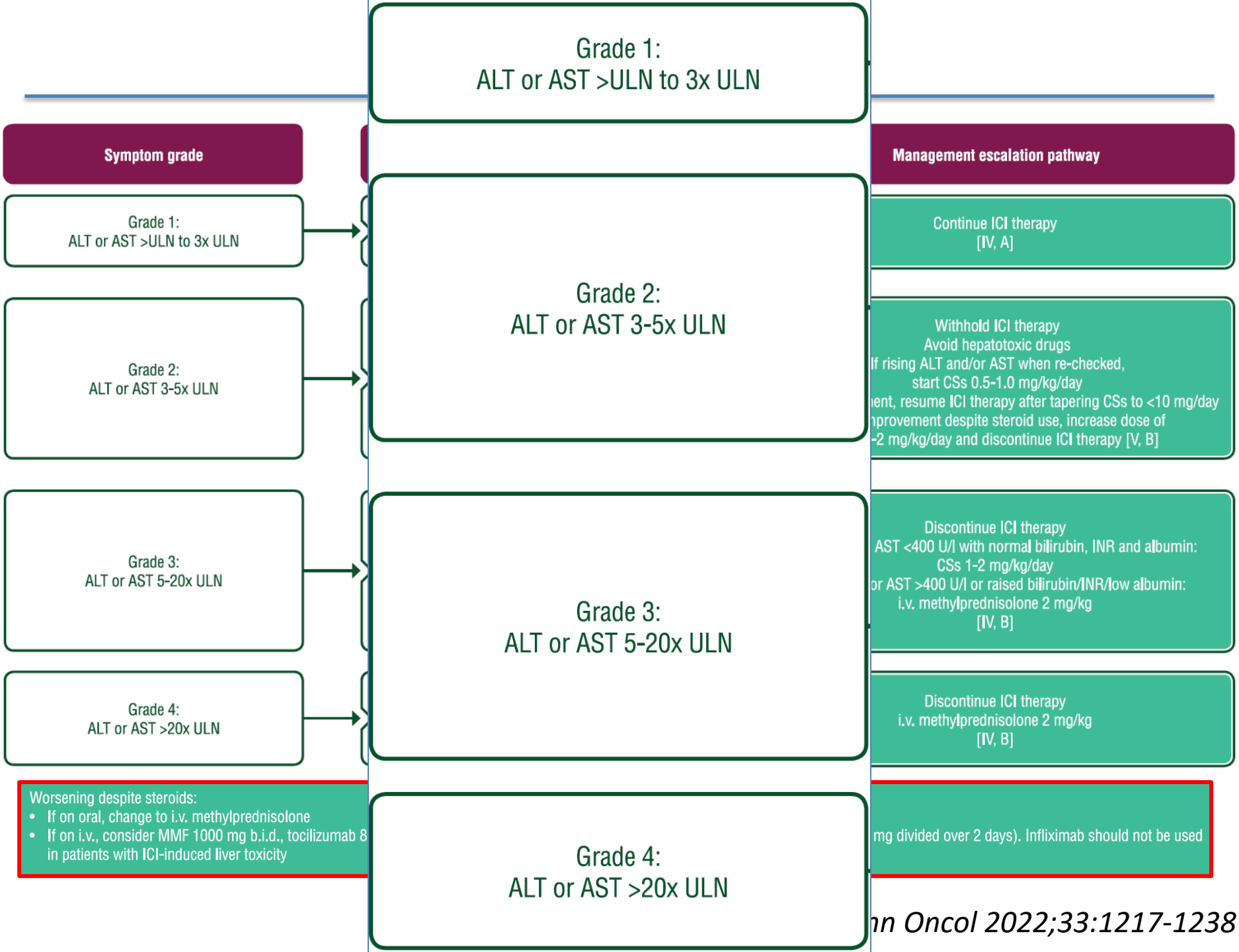
Hepatotoxizität



Worsening despite steroids:

- If on oral, change to i.v. methylprednisolone
- If on i.v., consider MMF 1000 mg b.i.d., tocilizumab 8 mg/kg, tacrolimus, azathioprine, cyclosporine or anti-thymocyte globulin (ATG, 100 mg divided over 2 days). Infliximab should not be used in patients with ICI-induced liver toxicity

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



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Hepatotoxizität

Bei Glukokortikoid-Refraktärität:

- Orales Präparat auf IV umstellen

IV-Glukokortikoid umstellen auf:

- MMF oder
- Tocilizumab oder
- Tacrolimus oder
- Azathioprin oder
- Ciclosporin oder
- ATG

- KEIN Infliximab bei Hepatotoxizität

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

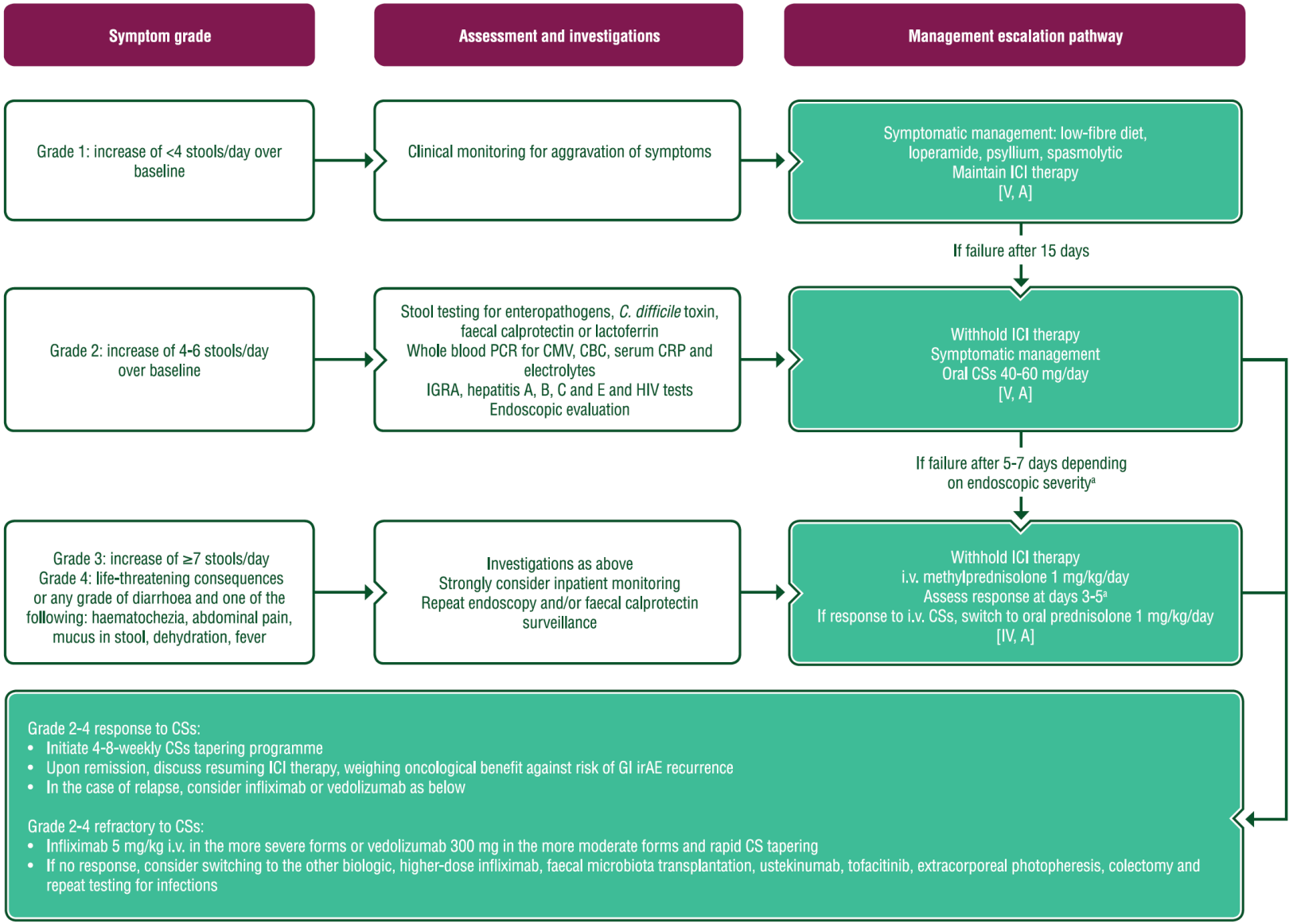
Hepatotoxizität

Recommendations

- Assessment of serum transaminases, ALP and bilirubin before every cycle of ICI therapy is recommended [IV, A].
- For grade 1 IR-liver injury, monitoring of liver enzymes every 1-2 weeks is recommended, with no need to hold ICI therapy [IV, A].
- For grade 2 IR-liver injury, temporarily withholding ICI therapy is suggested, with monitoring of transaminases and bilirubin twice weekly. CS 0.5-1 mg/kg/day should be considered [V, B].
- For patients with grade 3 or 4 IR-liver injury, hospitalisation and initiation of CS 1-2 mg/kg/day should be considered. If there is no response to CS within 2-3 days, alternative immunosuppressive therapy should be considered, such as MMF (1000 mg twice daily), tocilizumab (8 mg/kg), tacrolimus, azathioprine, cyclosporine or anti-thymocyte globulin [IV, B].

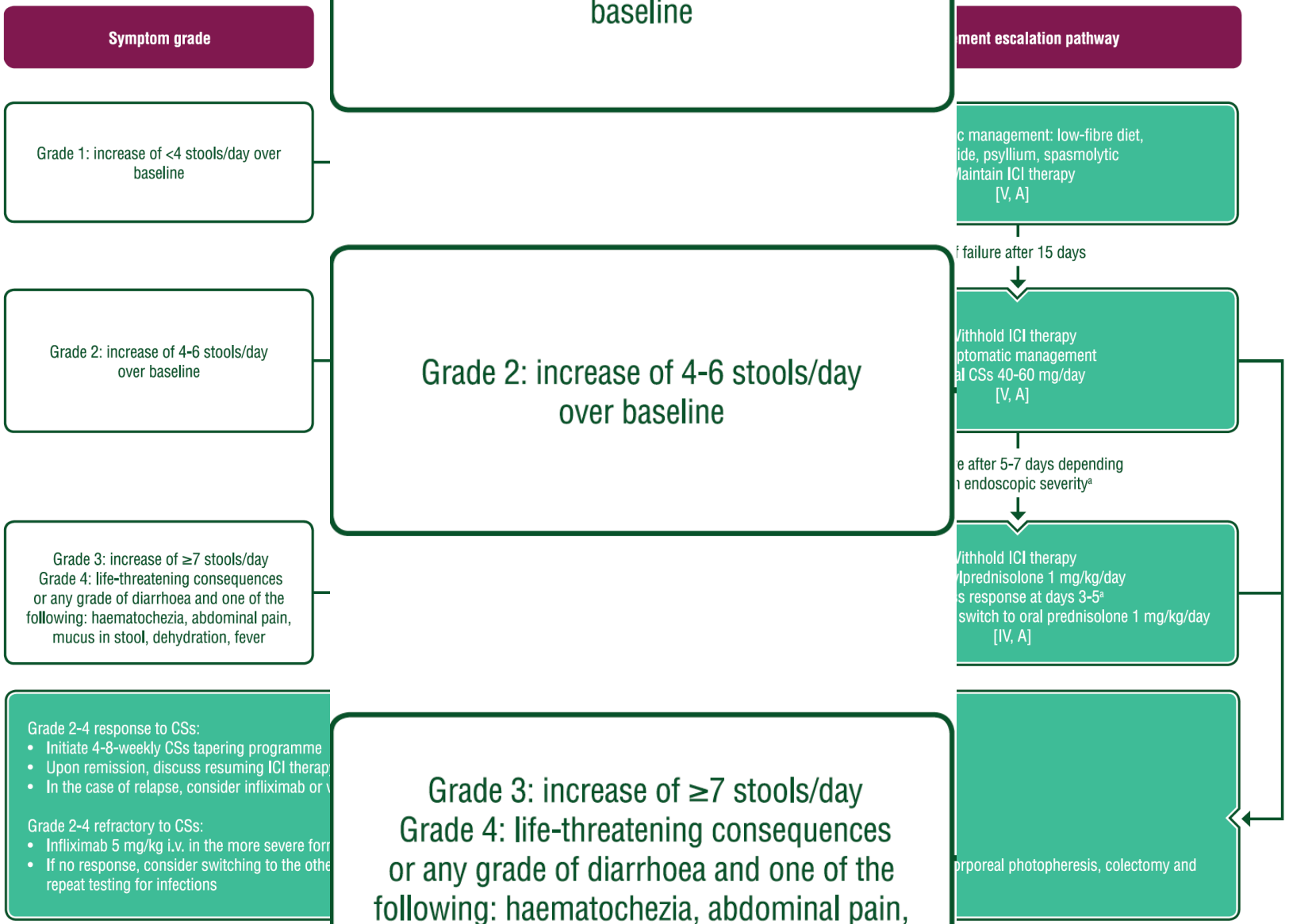
Haanen J et al (ESMO-Leitlinie), Ann Oncol 2022;33:1217-1238

Diarrhoe und Enterocolitis



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

Dia itis



n Oncol 2022;33:1217-1238

Diarrhoe und Enterocolitis

Recommendations

- Flexible sigmoidoscopy or colonoscopy and biopsies in patients treated with ICIs experiencing grade >1 diarrhoea should be carried out [IV, A].
- A CT scan to diagnose IR-enterocolitis is not recommended because of insufficient sensitivity [IV, E].
- Grade 1 diarrhoea or colitis should be treated with a low-fibre diet and loperamide; ICI therapy can be continued under close medical supervision [V, A].
- Grade 2 colitis should be treated with oral CSs, with vedolizumab or infliximab used for non-responders [V, A].
- Grade 3-4 colitis should be treated by hospitalisation, with i.v. CSs [IV, A]. Infliximab is the drug of choice for non-responders with acute, severe colitis [IV, A]. Vedolizumab is an option but is associated with a slightly delayed response [IV, B].
- Resuming ICI therapy in patients who have experienced GI irAEs should be discussed on a case-by-case and multidisciplinary basis [IV, A].

Anti-Integrin a4b7

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Diarrhoe und Enterocolitis

Bei Grad 2-4 Tox und Glukokortikoid-Refraktärität:

- Infliximab 5 mg/kg IV (oder Vedolizumab 300 mg bei moderater Ausprägung)

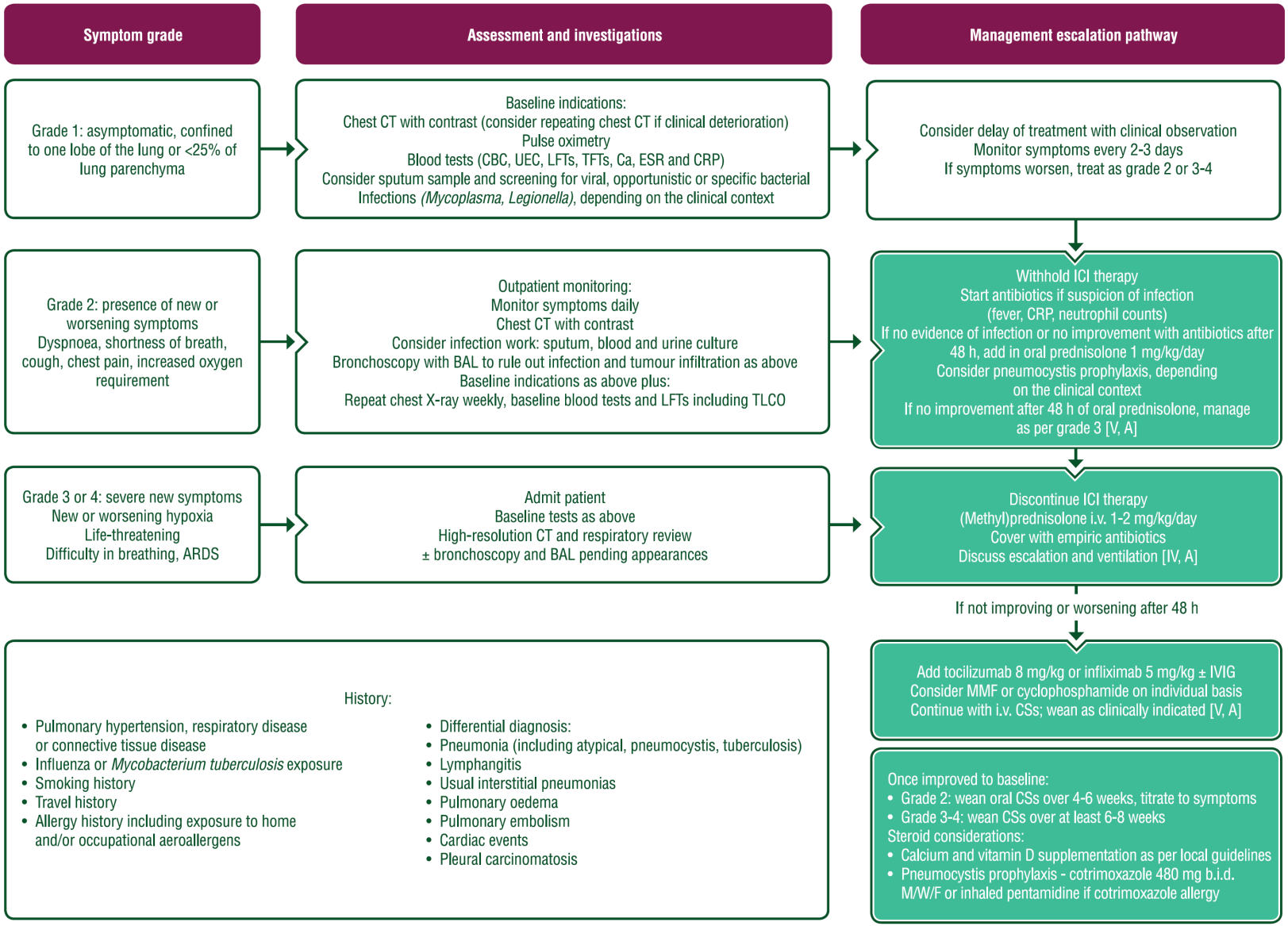
Bei anhaltender Refraktärität:

- Wechsel auf den jeweils anderen Antikörper
- Höhere Infliximab-Dosis
- Fecal microbiota transfer
- Ustekinumab
- Tofacitinib
- Extrakorporale Photopherese
- Kolektomie

- Wiederholte Suche nach GI-Infektionen!

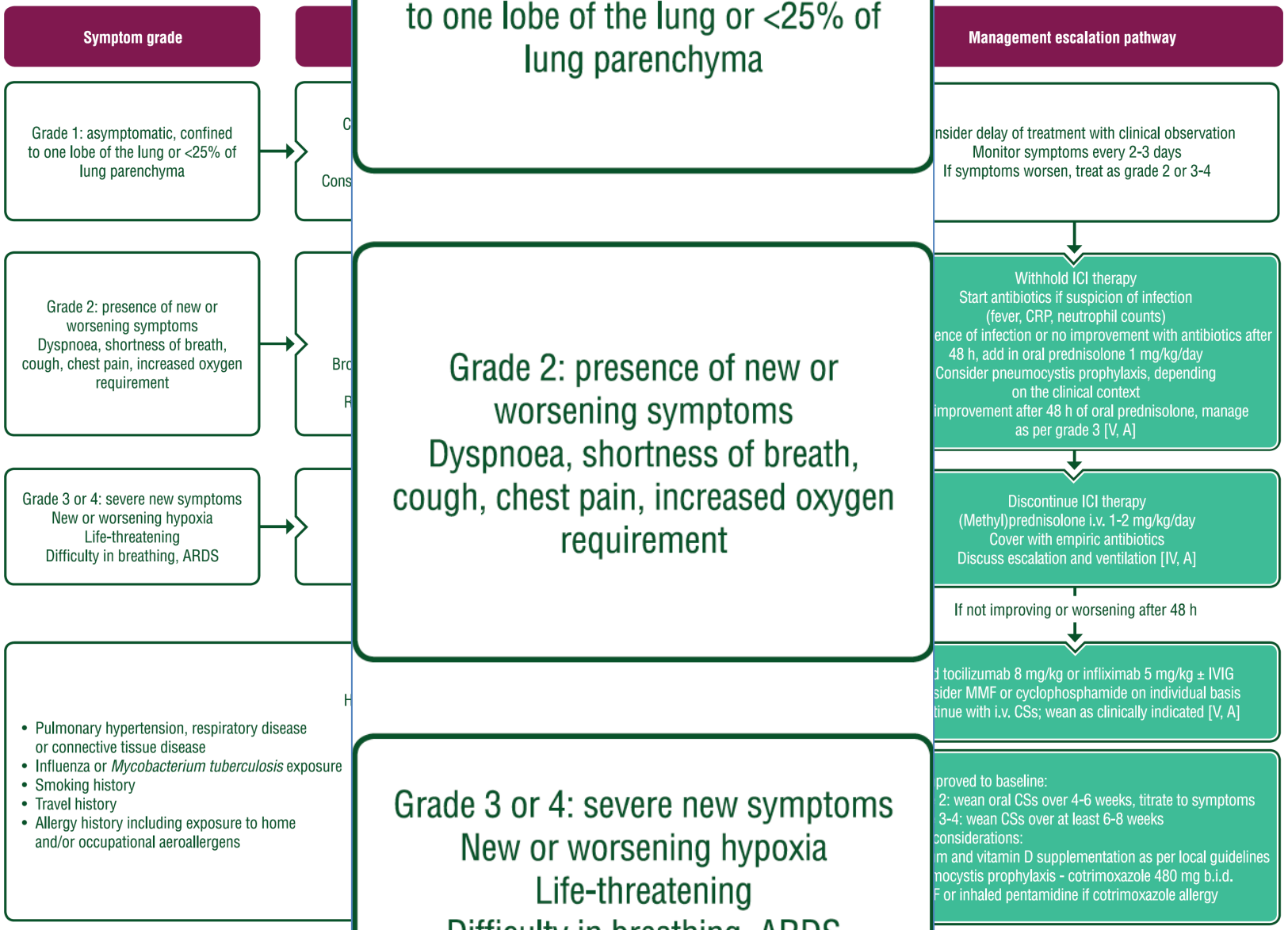
Haanen J et al (ESMO-Leitlinie), Ann Oncol 2022;33:1217-1238

Pulmonale Toxizität (ILD)



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

Pul LD)



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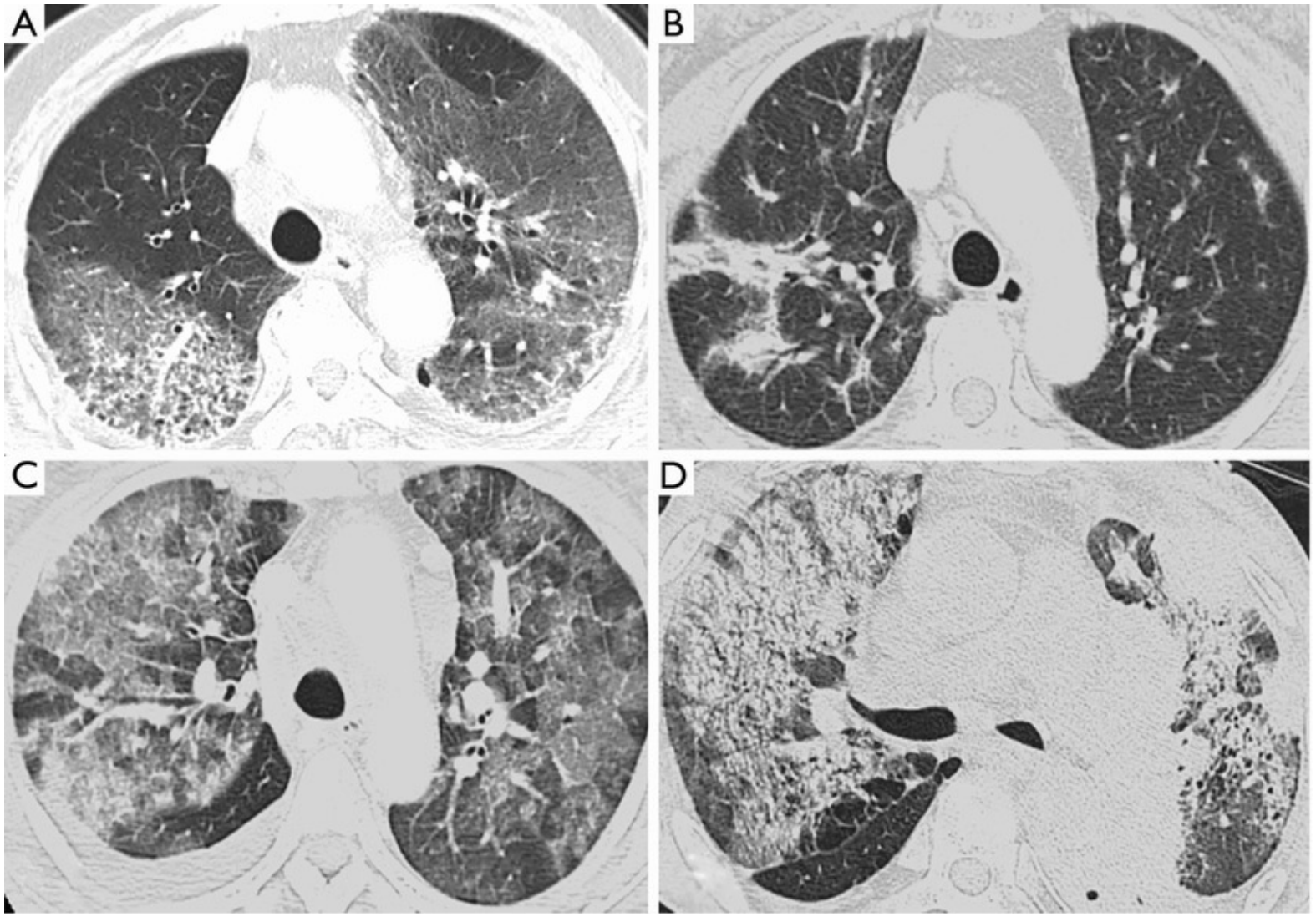
Drug-Induced Interstitial Lung Disease („DILD“)



Kim S et al (Korea), J Thorac Dis 2014;6:1209-17

Pulmonale Toxizität (ILD)

Recommendations

- Dyspnoea should trigger a full clinical work-up, including the exclusion of infectious pneumonia, tumour progression, pulmonary embolism, cardiac events (including heart failure, myocarditis, acute myocardial infarction and arrhythmias) and pleural carcinomatosis or effusion [IV, A].
- Patient cases with pre-existing ILD should be discussed with a specialist before initiation of ICI [IV, A].
- If IR-ILD is suspected, a high-resolution chest CT with contrast should be considered to rule out other aetiologies. If the CT scan is negative, pulmonary function tests should be considered to identify a potential functional deficit [IV, A].
- Bronchoalveolar lavage to rule out infection or tumour infiltration and investigations for infection with sputum, blood and urine culture if clinically indicated should be considered [IV, A].
- In cases of grade 2 IR-pneumonitis, rechallenge with ICI therapy upon complete resolution of symptoms can be considered on an individual basis with close monitoring [V, B].
- In cases of grade 2 IR-ILD, 1 mg/kg/day prednisolone (or equivalent) should be considered. For grade $\geq$3 IR-ILD, 1-2 mg/kg/day methylprednisolone i.v. or equivalent should be considered. CS tapering should be initiated after improvement to grade $<$1, over 4-6 weeks for grade 2 and over $\geq$6-8 weeks for grade $\geq$3 [V, A].
- If there is no improvement within 72 h of CS use, consultation with or referral to an expert should be arranged and therapeutic escalation should occur. Additional options include tocilizumab (8 mg/kg, one dose and every 2 weeks if needed),[62] infliximab (5 mg/kg, one dose and every 2 weeks if needed)[51,63-65] and IVIG (2 g/kg over 2-5 days).[66] Other options, such as MMF (1 g twice daily)[67] or cyclophosphamide,[51] are possible [V, A].

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

Pulmonale Toxizität (ILD)

Therapieoptionen

- Glukokortikoid
- Tocilizumab
- Infliximab
- IV-Ig
- MMF
- *(Cyclophosphamid?)*

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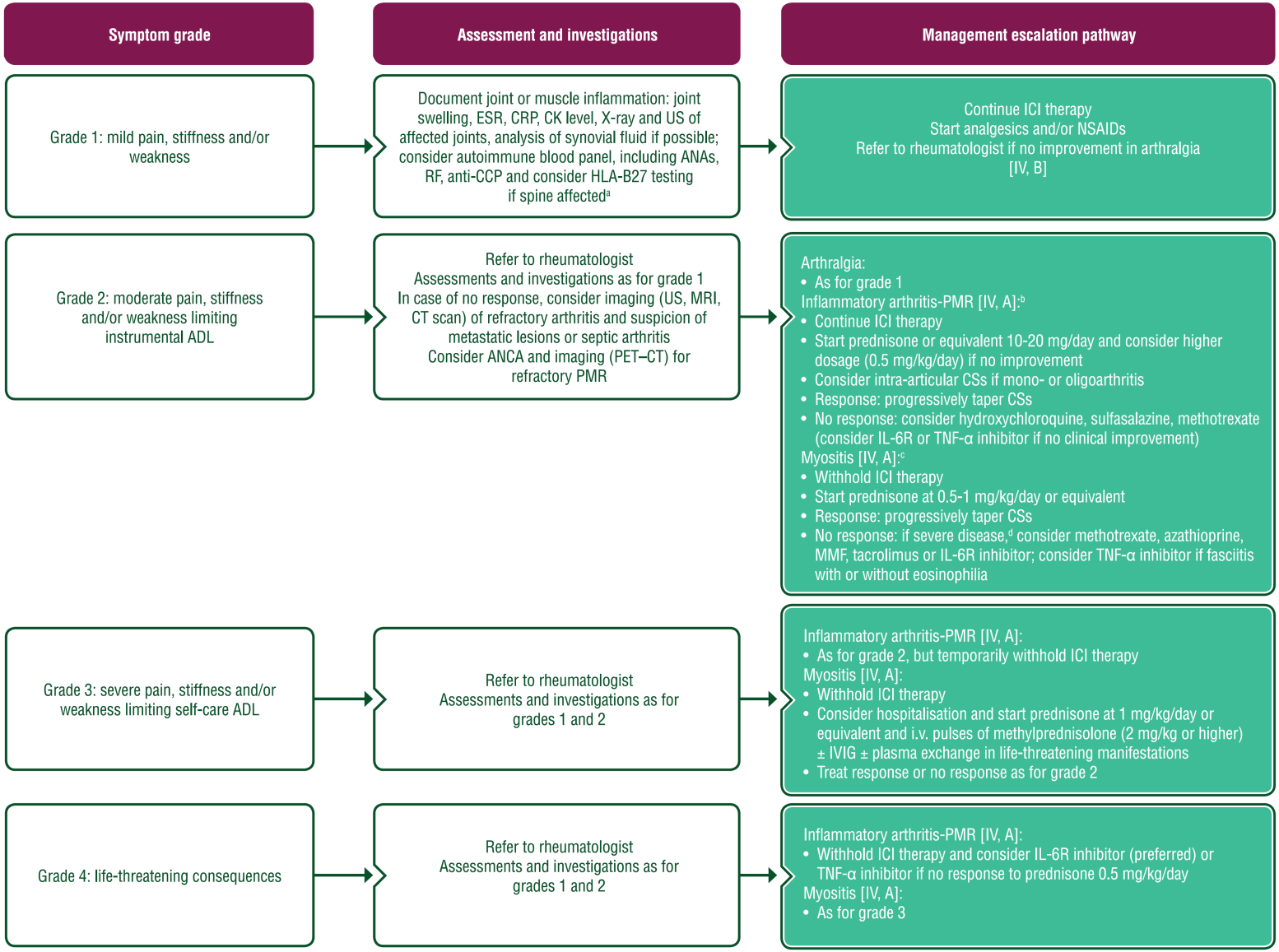
Rheumatologische Toxizität



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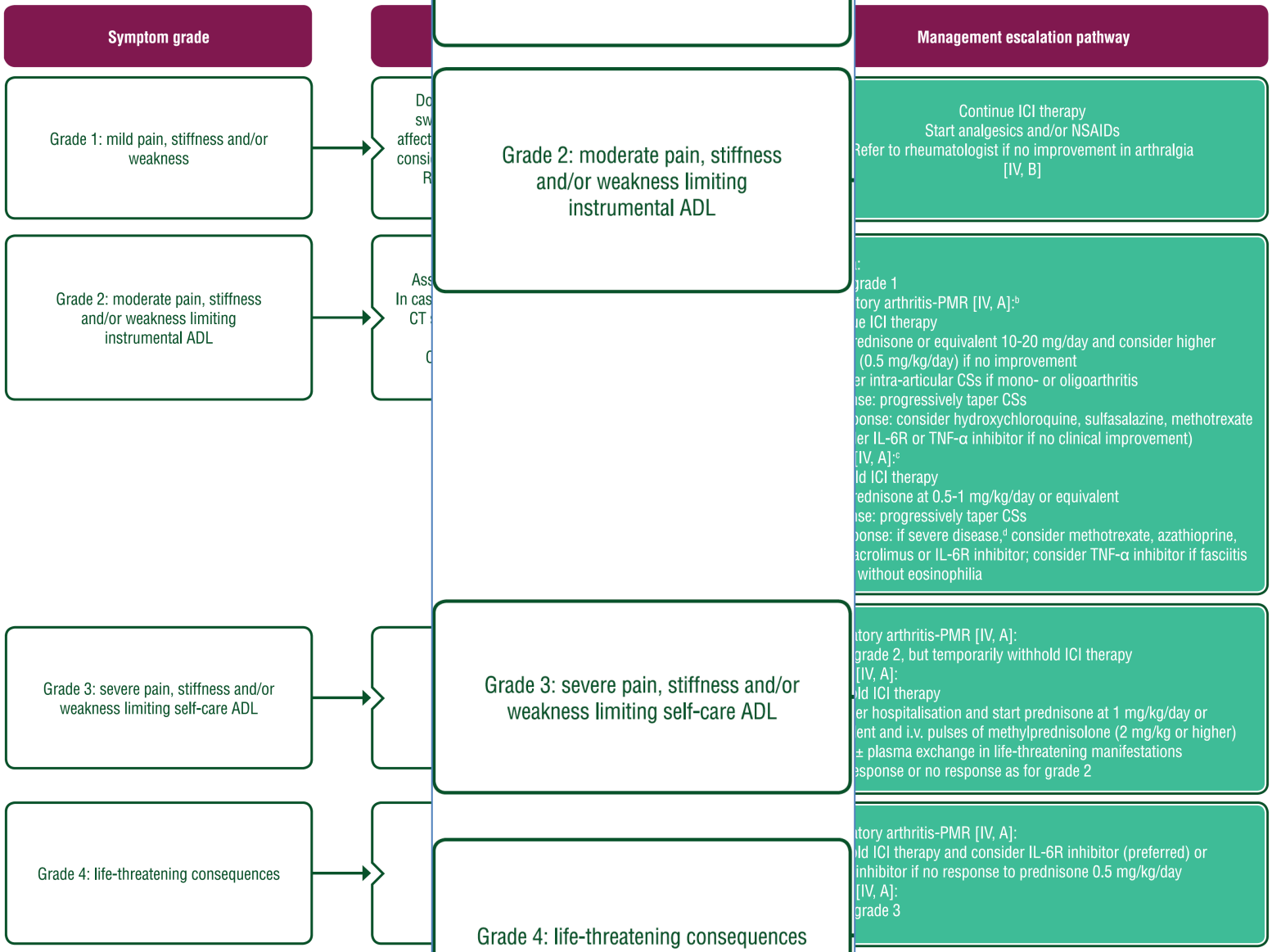
Rheum oxizität



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Rheumatologische Toxizität

Recommendations

- Early referral to a rheumatologist should be considered (grade $\geq$2 symptoms) before starting CSs, in cases of insufficient response to acceptable doses of CSs and in cases requiring CS-sparing regimens [V, B].
- Initial evaluation of possible IR-inflammatory arthritis or IR-PMR should include joint count, analysis of synovial fluid whenever possible, ESR, CRP, RF, CCP, ANAs (for inflammatory arthritis), X-rays and US of affected joints [IV, A].
- CK level must be assessed in patients experiencing myalgia or PMR to rule out myositis. If elevated, myositis-associated autoantibodies, MRI and EMG $\pm$ biopsy should be considered [IV, A].
- Following a definitive diagnosis, symptomatic treatment (analgesics $\pm$ NSAIDs) should be initiated for arthralgia and myalgia [IV, B].
- In patients with mild forms of arthritis or with mono- or oligoarthritis, NSAIDs and/or intra-articular CSs should be considered [IV, B].
- Prednisone 10-20 mg/day should be initiated in grade $\geq$2 IR-inflammatory arthritis and IR-PMR, and then progressively tapered following improvement. A higher dosage (0.5 mg/kg) may be considered if no improvement, as well as csDMARDs (methotrexate, hydroxychloroquine or sulfasalazine) or bDMARDs [anti-IL-6R (preferred), TNF-α inhibitor] for severe or persistent symptoms. ICI treatment continuation should be evaluated on an individual basis [IV, A].
- Prednisone 0.5-1 mg/kg should be initiated in grade $\geq$2 IR-myositis. In the presence of life-threatening manifestations, high-dose CSs, IVIG and/or plasma exchange/selective separation should be considered; ICI withdrawal is always necessary [IV, A].
- Symptomatic treatment, pilocarpine and hydroxychloroquine may be considered for any grade of IR-sicca syndrome, after testing for specific autoantibodies and, if possible, minor salivary gland biopsy. Systemic CSs are advocated only in cases of extra-glandular manifestations or grade $\geq$3 symptoms [IV, B].

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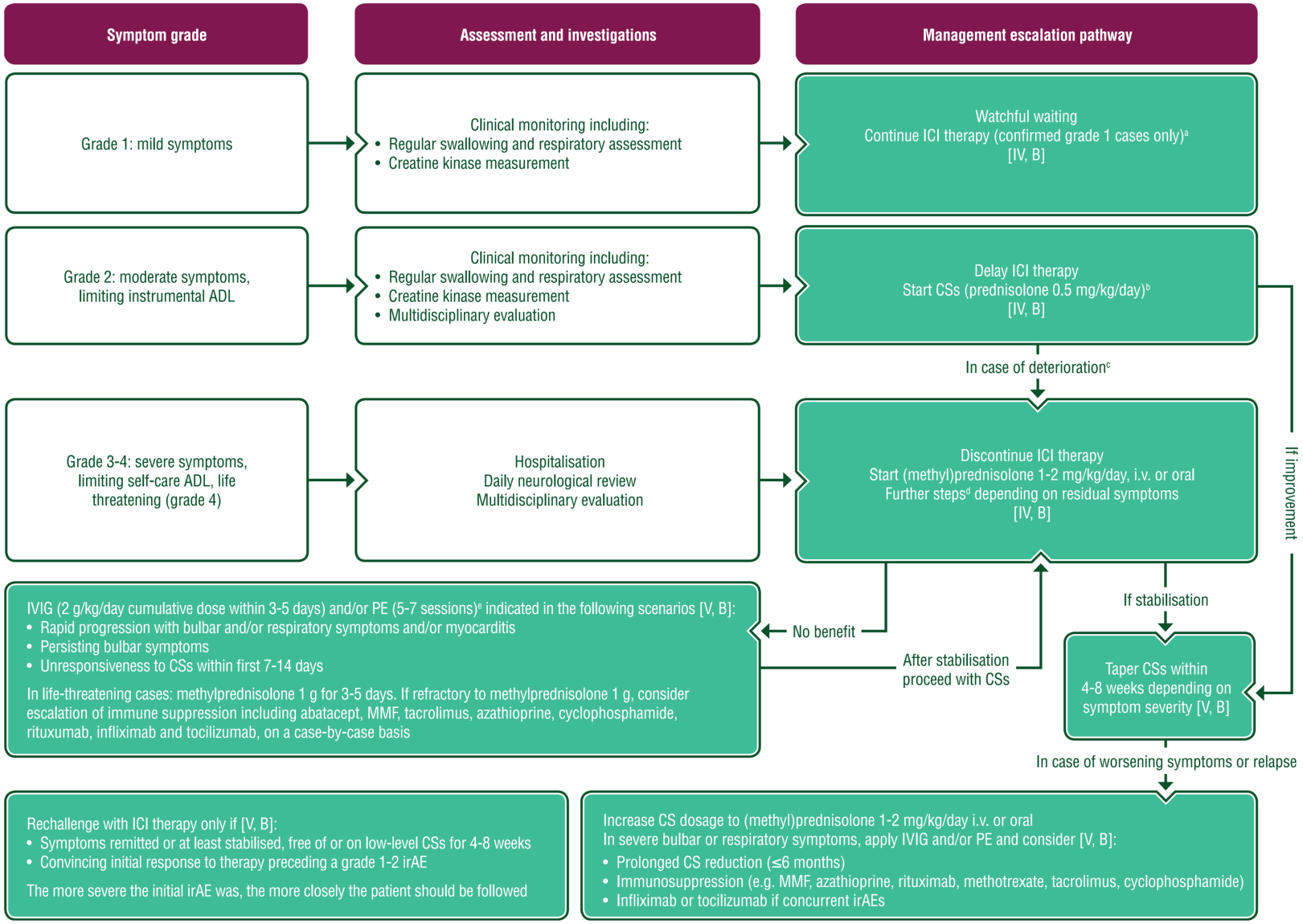
Neuro(-muskuläre) Toxizität



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

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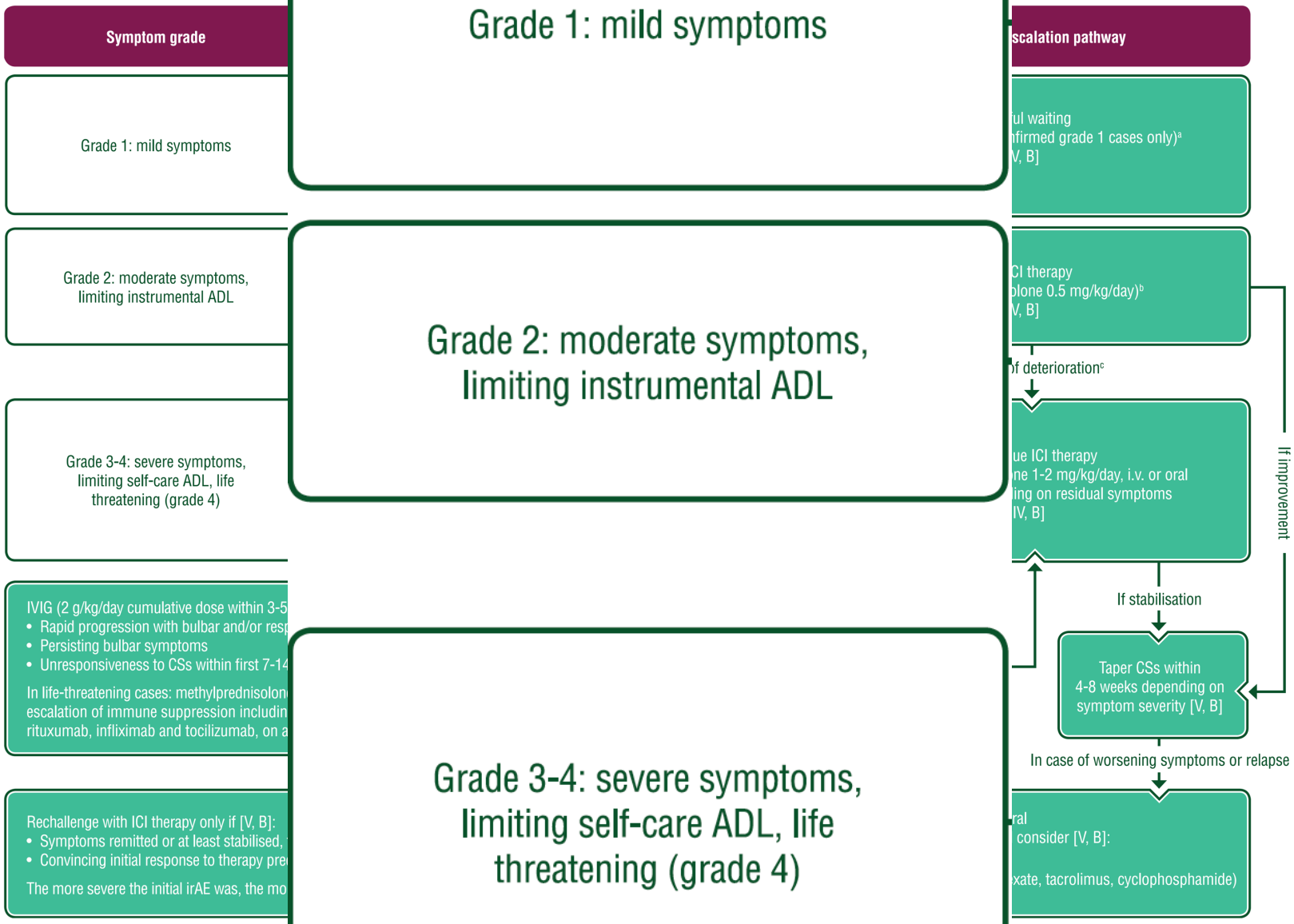

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Neuro(-muskuläre) Toxizität

Recommendations

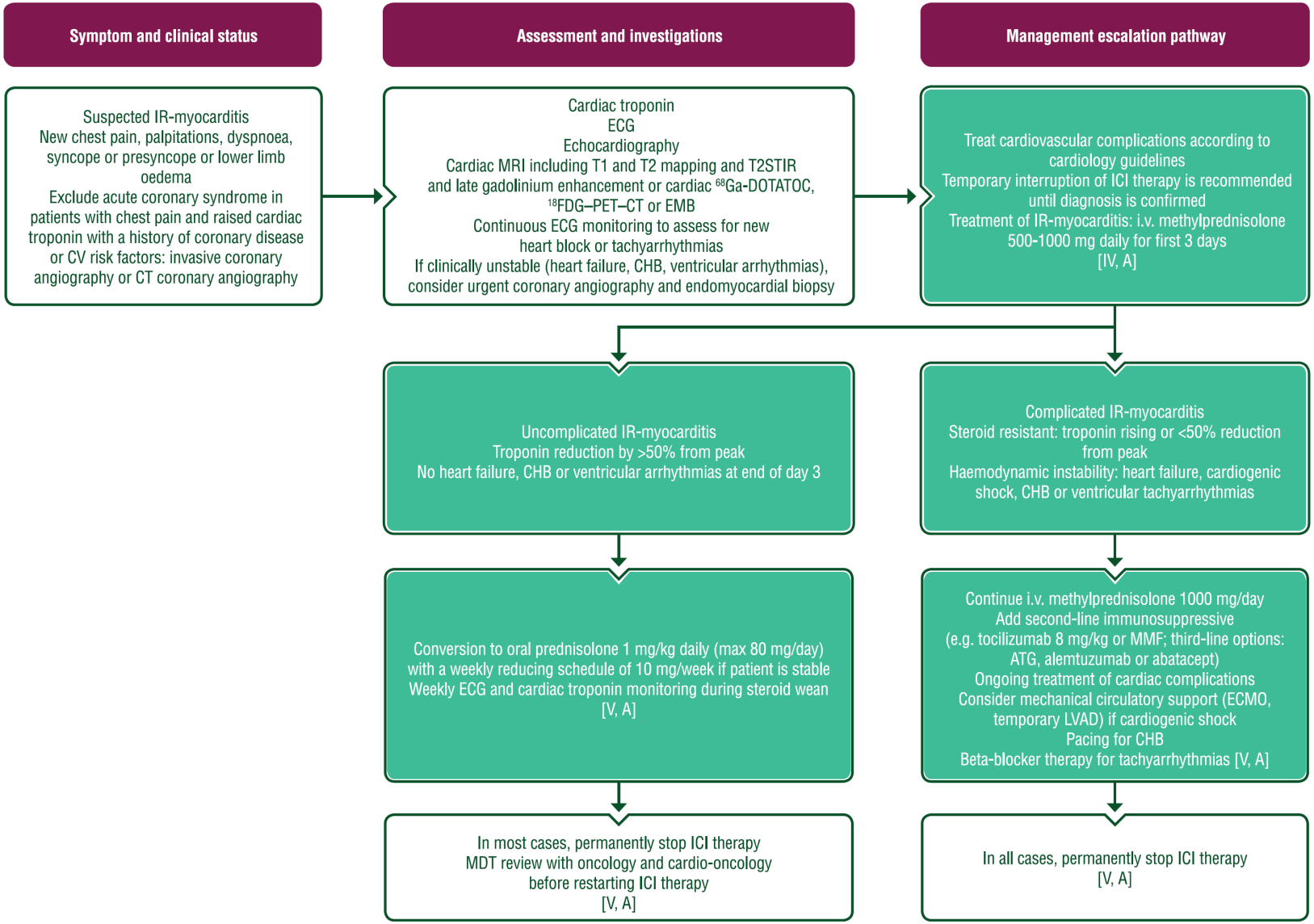
- Referral to a neurologist should be considered for mild (or more severe) symptoms of GBS, leukoencephalopathy, MG, myopathy and peripheral neuropathy. The type and frequency of assessments vary according to the grade of symptoms [IV, B].
- Patients presenting with any neurological symptoms should be referred to a neurologist and ICI should be held until the grade of symptoms is confirmed [IV, B].
- For grade 1 symptoms, ICI treatment can be continued and the patient monitored for deterioration [IV, B].
- For grade 2 symptoms, ICI treatment should be interrupted and oral or i.v. (methyl)prednisolone initiated [IV, B].
- For grade 3 or 4 symptoms, more intensive immune modulation may be required in addition to CSs or by exchanging CSs for IVIG (or plasma exchange or selective separation in cases of GBS, leukoencephalopathy, MG or IR-myopathy) [V, B].

Bei Steroidrefraktärität:

- Infliximab oder Tocilizumab

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

Autoimmun-Myokarditis



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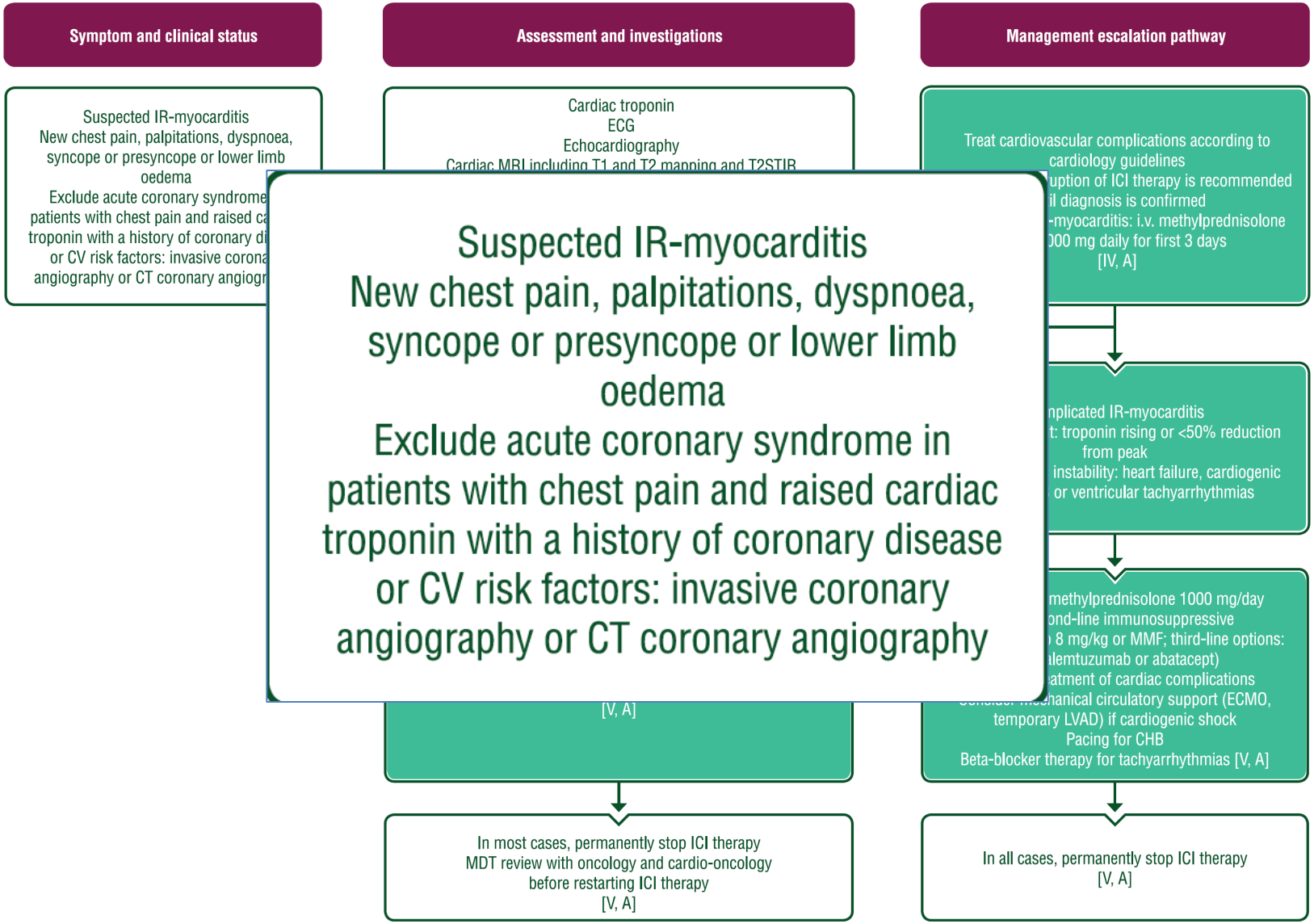
Autoimmun-Myokarditis



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

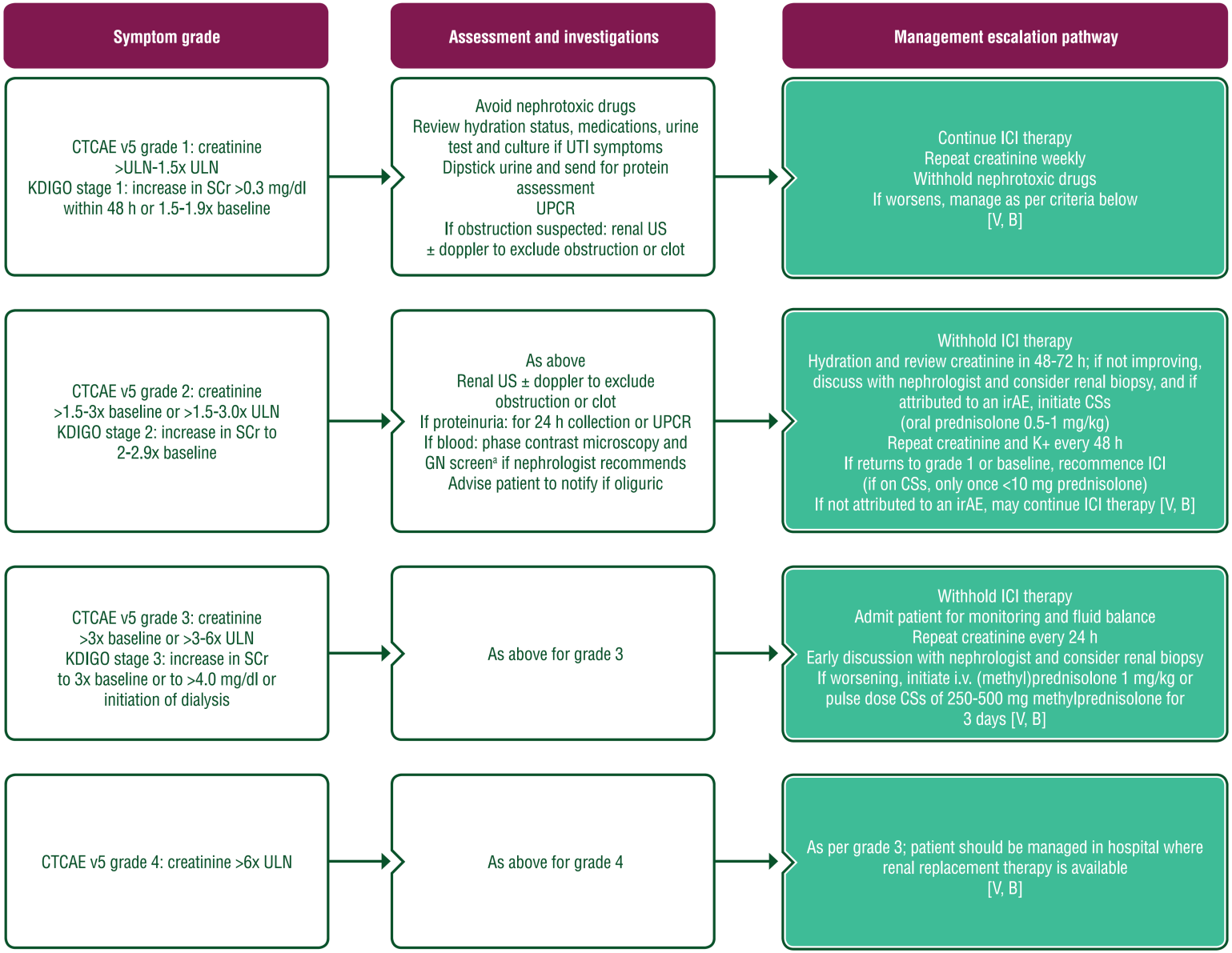
Autoimmun-Myokarditis

Recommendations

- Suspected cases of IR-myocarditis should be admitted to level 2 or 3 care with electrocardiogram monitoring and resuscitation facilities [V, A].
- Other causes of troponin elevation should be ruled out, including ACS if appropriate (patients with CV risk factors or established coronary artery disease) [V, A].
- ICI therapy should be interrupted and, in most cases, if IR-myocarditis is confirmed, permanently discontinued [V, A].
- A diagnostic CMR with inflammatory sequences (T2STIR, T1, LGE) and cardiac troponin are recommended in cases of suspected IR-myocarditis or pericarditis [IV, A].
- If ^{68}Ga-DOTATOC—PET—CT is not available, endomyocardial biopsy should be considered to confirm or refute the diagnosis in suspected cases where CMR and troponin are not diagnostic before restarting ICI [V, A].
- i.v. methylprednisone 500-1000 mg should be initiated daily for 3 days and then reviewed in confirmed cases of IR-myocarditis [V, A].
- If troponin has fallen to <50% of peak level or to normal after 3 days of i.v. methylprednisolone and the patient is clinically stable (no heart failure, ventricular arrhythmias, complete heart block) then conversion to oral prednisolone 1 mg/kg/day (up to a maximum of 80 mg/day) is recommended, reducing by 10 mg/week with troponin monitoring providing CV stability continues [V, A].
- Heart failure or cardiogenic shock should be treated according to the European Society of Cardiology heart failure guidelines [III, A].[90]
- An MDT discussion is recommended before restarting ICI treatment in patients with mild, clinically uncomplicated IR-myocarditis [V, A].
- Treatment of uncomplicated IR-pericarditis with oral prednisolone and colchicine (500 µg twice daily) is recommended [IV, A].
- Treatment of IR-pericarditis complicated by moderate or large pericardial effusion with i.v. methylprednisone 500-1000 mg and colchicine (500 µg twice daily) and temporary interruption of ICI are recommended. Large pericardial effusions with or without tamponade physiology require urgent percutaneous pericardiocentesis [V, A].

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

Nephrotoxizität



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

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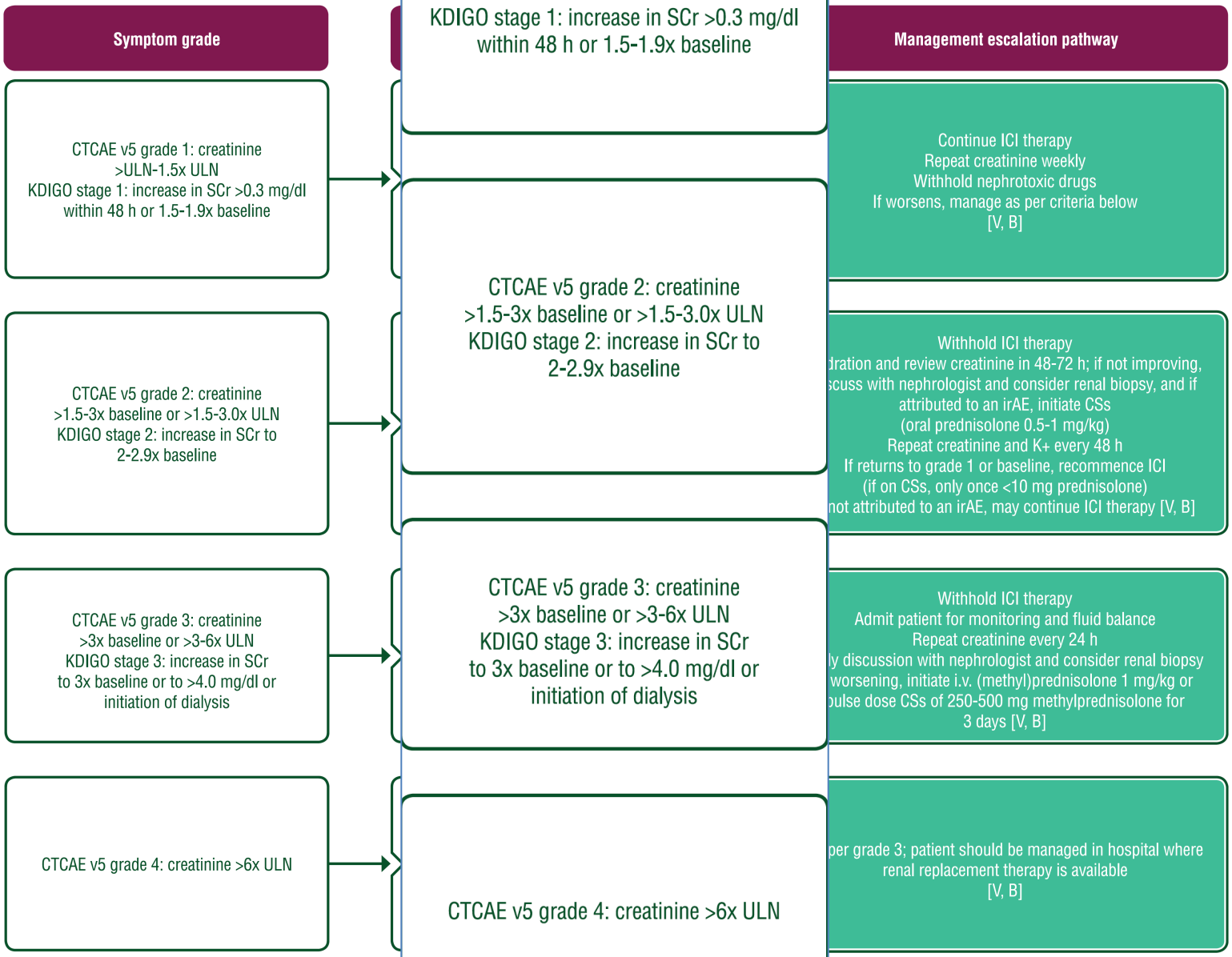

ie), Ann Oncol 2022;33:1217-1238

Nephrotoxizität

Recommendations

- In cases of suspected IR-nephritis [V, B]:
  - Other causes of renal failure should be ruled out.
  - ICI therapy should be interrupted or permanently discontinued depending on the severity of the renal insufficiency.
  - Other nephrotoxic drugs should be stopped.
  - (Methyl)prednisone 1 mg/kg should be started, or pulse methylprednisolone should be considered in stage 3 AKI.
  - Renal biopsy should be considered on a case-by-case basis to confirm the diagnosis.

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

CART-Zelltherapie-assoz. Toxizität

- **CRS (Cytokine Release Syndrome; „Zytokinsturm“)**
- **ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome)**

CART-Zelltherapie-assoz. CRS und ICANS

	Tisagenlecleucel (Kymriah®)		Axicabtagen-Ciloleucel (Yescarta®)
	BCP-ALL	**DLBCL§**	**DLBCL / PMBCL§**
Inzidenz CRS [%]	90,5 ± 9,7†	57,5 ± 0,7‡	93
CRS ≥ Grad 3 [%]	29,25 ± 11,4†	20 ± 2,8‡	13
Anzahl CRS-assoziierter Todesfälle	1 (0,5%)†	0 (0%)‡	2 (1,9%)
Zeit bis CRS-Symptombeginn im Median (min - max)	3 Tage (1-22) [3, 9] ≥ Grad 3: 1 Tag (n.a.), < Grad 3: 4 Tage (n.a.) [10]	3 Tage (n.a.) [2] ≥ Grad 3: 4 Tage (2-8) [2]	2 Tage (1-12)
Mediane Dauer des CRS (min – max)	8 Tage (1-36) [5]	7 Tage (2-30) [2]	8 Tage (n.a.)
Inzidenz ICANS [%]	36,8 ± 16,3†	30,2 ± 12,9	64
ICANS ≥ Grad 3 [%]	17,0 ± 5,7 [3, 11]	11,4 ± 0,9	28
Anzahl ICANS-assoziierter Todesfälle	1/199 (0,5%)†	1 (0,8%)	0 (0%)
Zeit bis ICANS-Symptombeginn im Median (min - max)	6 Tage [10]	6 Tage (1-17) [2]	5 Tage (1-17)
Mediane Dauer des ICANS (min – max)	4 Tage (3-9,5) [10]	≤ 7 Tage in 10/11 Patienten [12]	17 Tage
		14 Tage [2]	

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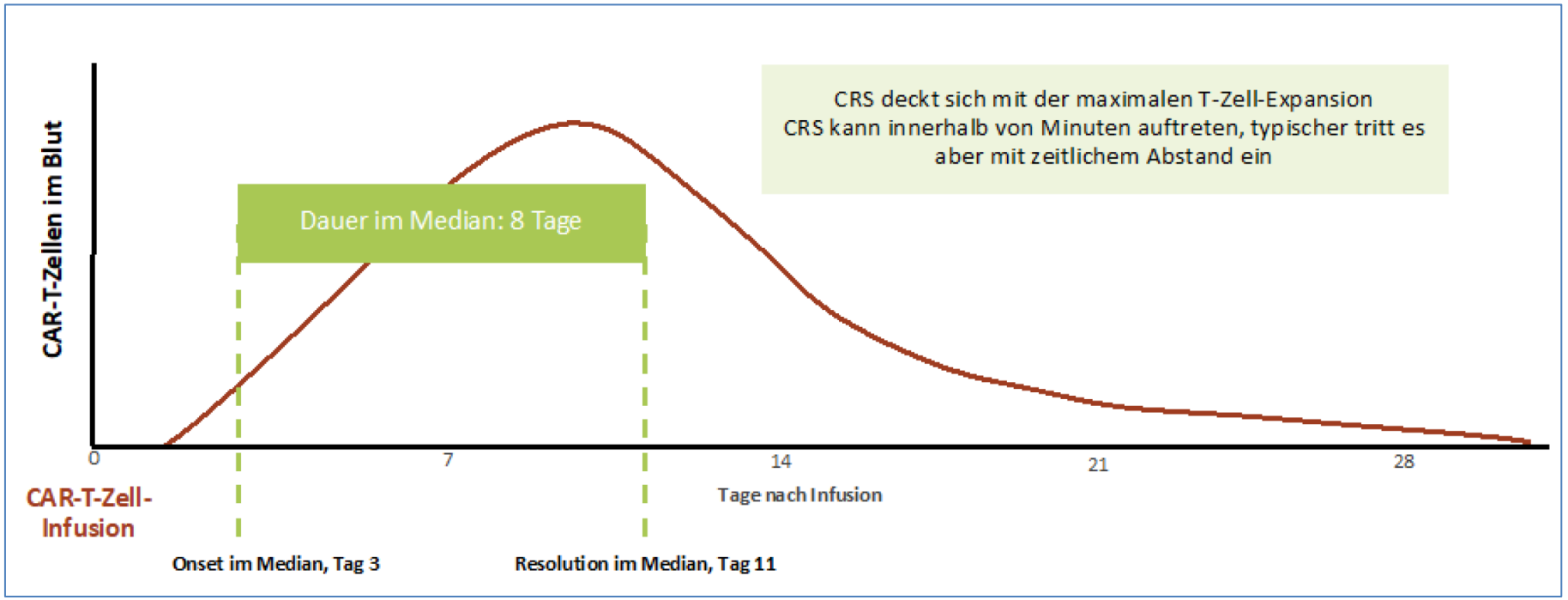
CART-Zelltherapie-assoz. CRS: zeitlicher Verlauf



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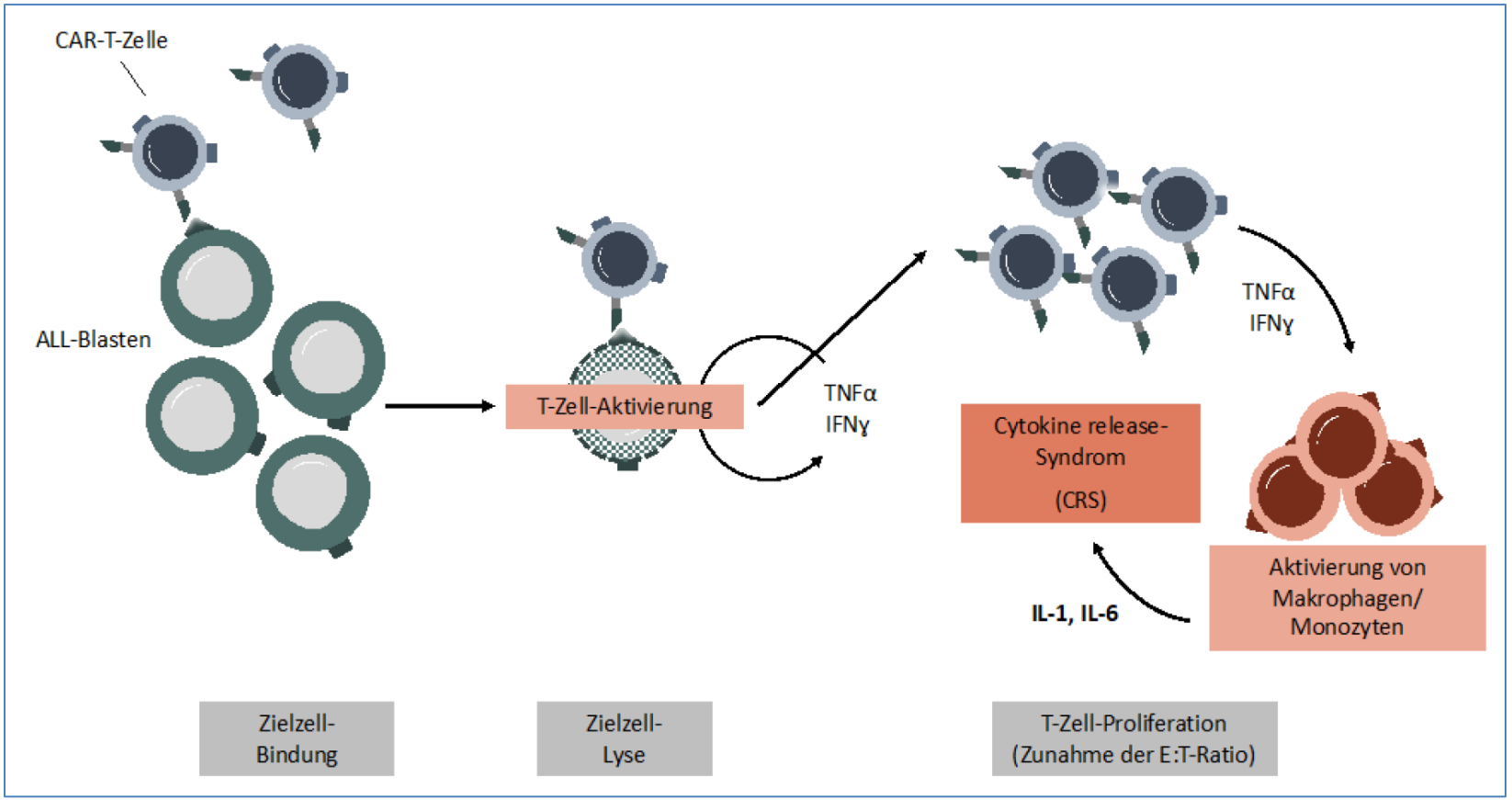
CART-Zelltherapie-assoz. CRS: Pathogenese



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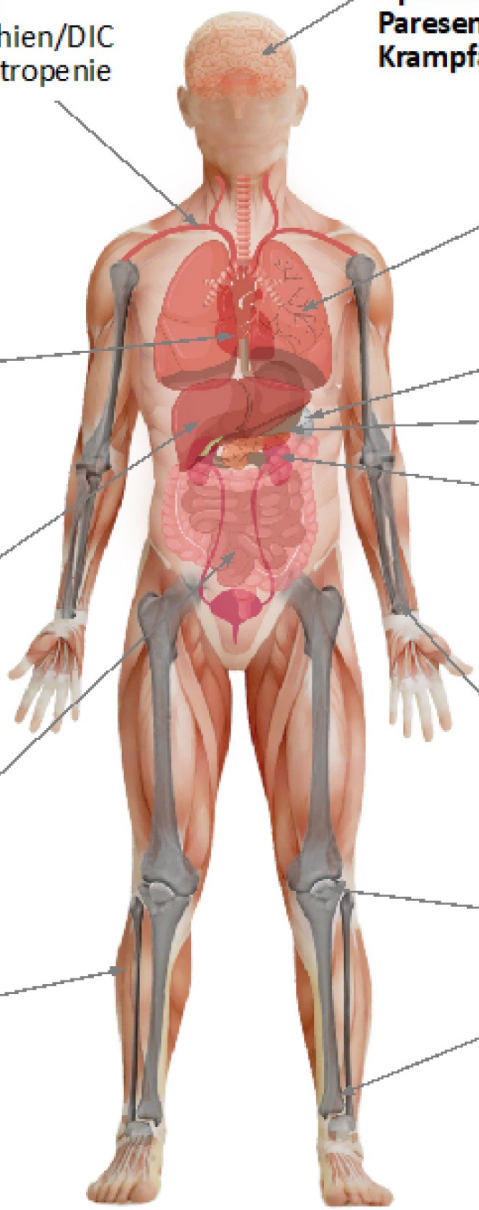
CART-Zelltherapie-assoz. CRS: Symptomatik



Kopfschmerzen
Verwirrtheit
Halluzinationen
Delir
Aphasie
Paresen
Krampfanfälle

Unspezifische Symptome
Fieber
Fatigue
Anorexie

Zytopenien
Koagulopathien/DIC
Febrile Neutropenie

Tachypnoe
Hypoxie
Lungenödem

Tachykardie
Hypotonie
Arrhythmien
QT-Verlängerung
Stress-Kardiomyopathie/ Myokarditis
Akute Herzinsuffizienz

Splenomegalie

Übelkeit
Erbrechen

Akutes und/oder chronisches **Nierenversagen**

Hepatomegalie
Leberwerterhöhung
Hypofibrinogenämie
Leberversagen

Diarrhoen

Myalgien
Arthralgien
Rigor

Ausschläge
Ödeme

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CART-Zelltherapie-assoz. CRS: Schweregrade

Vitalzeichen	**CRS Grad 1**	**CRS Grad 2**	**CRS Grad 3**	**CRS Grad 4**
Körpertemperatur (°C)	>38°C**	>38°C**	>38°C**	>38°C**
Hypotonie	Keine	**Ohne** Vasopressor-Bedarf	Mit Bedarf an **einem** Vasopressor ± Vaso-pressin	Mit Bedarf an **mehreren** Vasopressoren (außer Vasopressin)
Hypoxie	Keine	Moderater O_2-Bedarf **(≤6 L/min** über NB)	Hoher O_2-Bedarf **(>6 L/min** über NB, RHM, **ohne PAP**)	Mit **PAP**-Bedarf/ Intubati-ons-notwendigkeit

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CART-Zelltherapie-assoz. CRS: **Basis**therapie

Innerhalb von 5 h vor und bis 10 Tage nach CAR-T-Zell-Therapie (bei Symptomfreiheit) oder bis 5 Tage nach Abklingen CRS-spezifischer Symptome

- Auf ausreichende Volumentherapie (in Abhängigkeit von der kardialen Funktion) achten, ggf. diuretische Maßnahmen
- Regelmäßige Kontrolle der Vitalzeichen (alle 8 Stunden) vom Tag des Therapiestarts bis zum Abklingen einer evtl. CRS-Symptomatik bzw. bis zur Entlassung:
  - Temperaturkontrolle (ggf. alle 4 Stunden)
  - Herzfrequenz, RR und sO2-Messung
- Bestimmung des ICE-Scores alle 12 Stunden (siehe Kapitel 3.2.4.2)
- Hochrisikopatienten (z.B. mit signifikant erhöhtem CRP/Ferritin vor CAR-T-Zell-Transfusion oder hoher Tumorlast) sollten ggf. ab CAR-T-Zell-Transfusion noch engmaschiger überwacht werden, z.B. analog der Empfehlungen für Patienten mit CRS Grad 2 inkl. kontinuierlicher zentraler Monitorüberwachung

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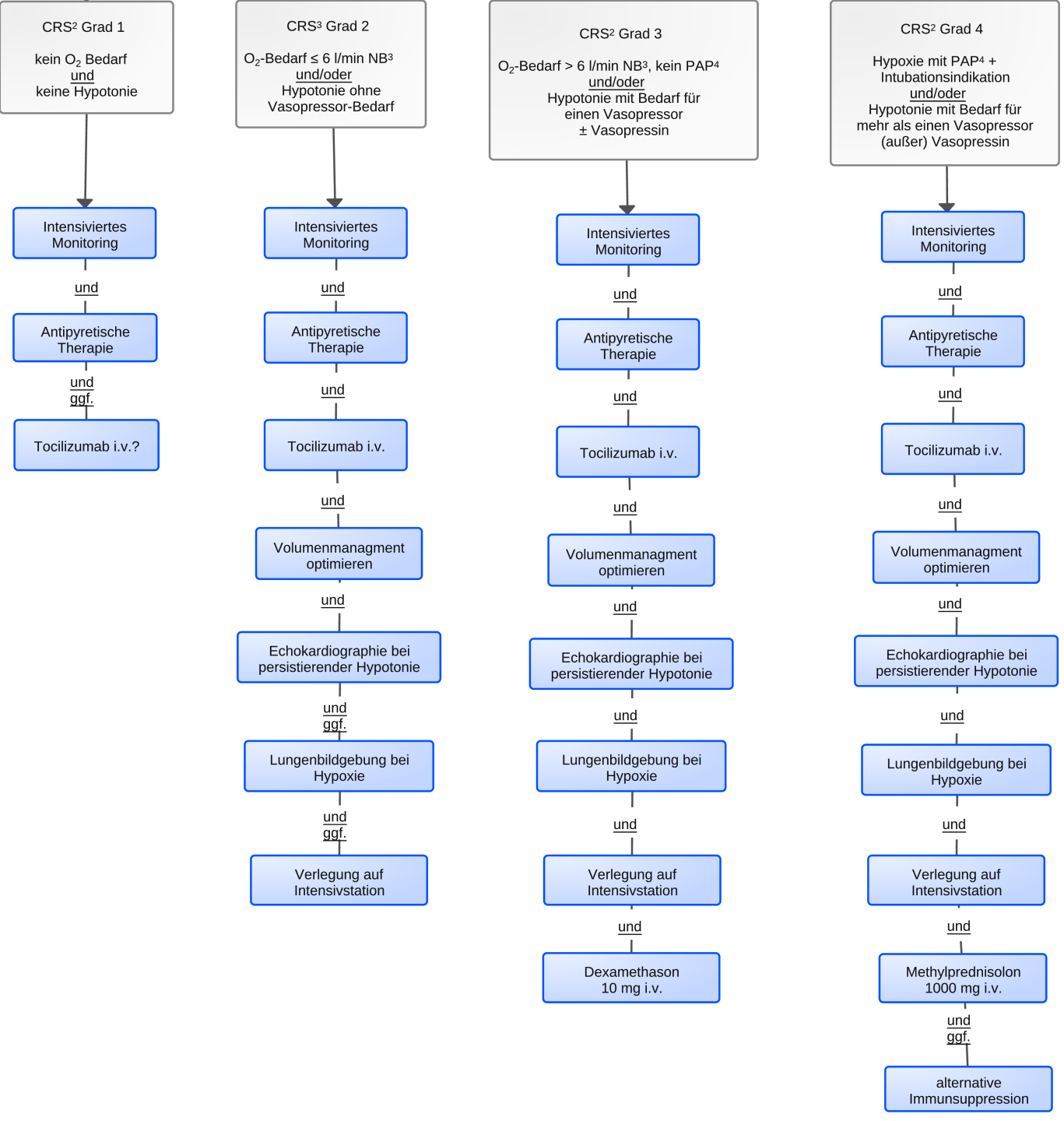
CART-Zelltherapie-assoz. CRS: Therapiealgorithmus



Ab Grad 1:
empirische antimikrobielle Therapie wie bei FUO in der Neutropenie

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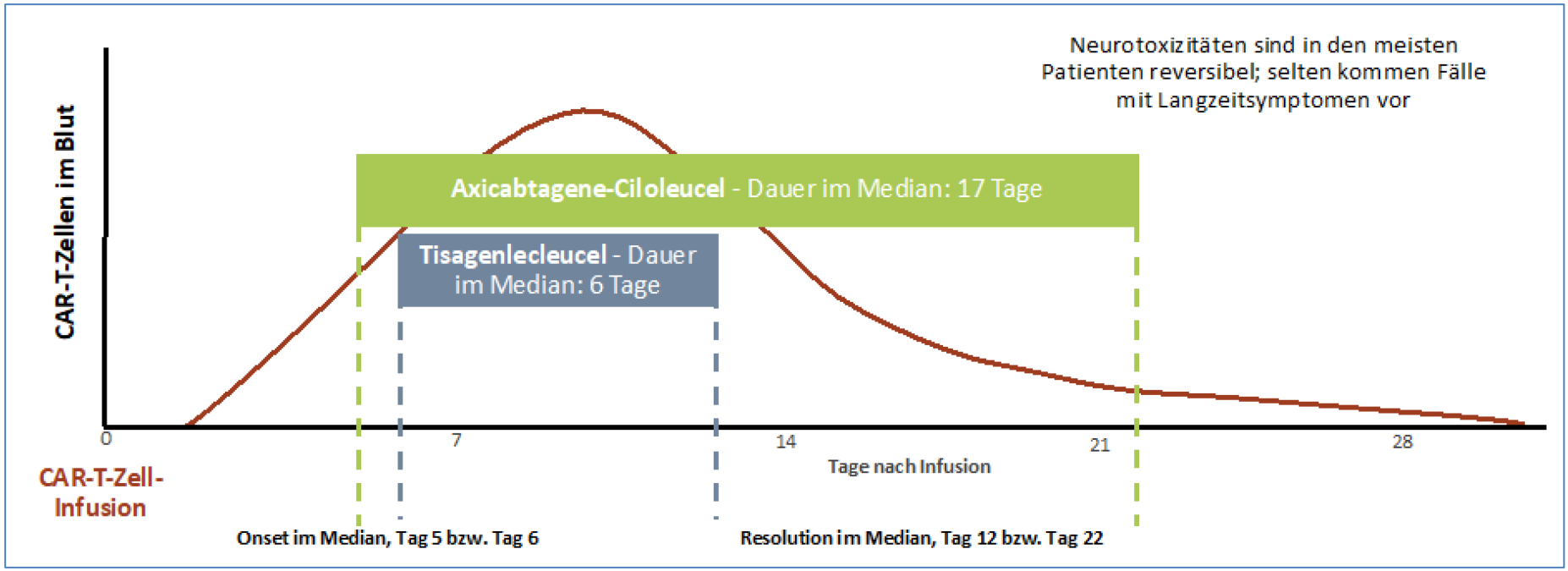
CART-Zelltherapie-assoz. ICANS: zeitlicher Verlauf



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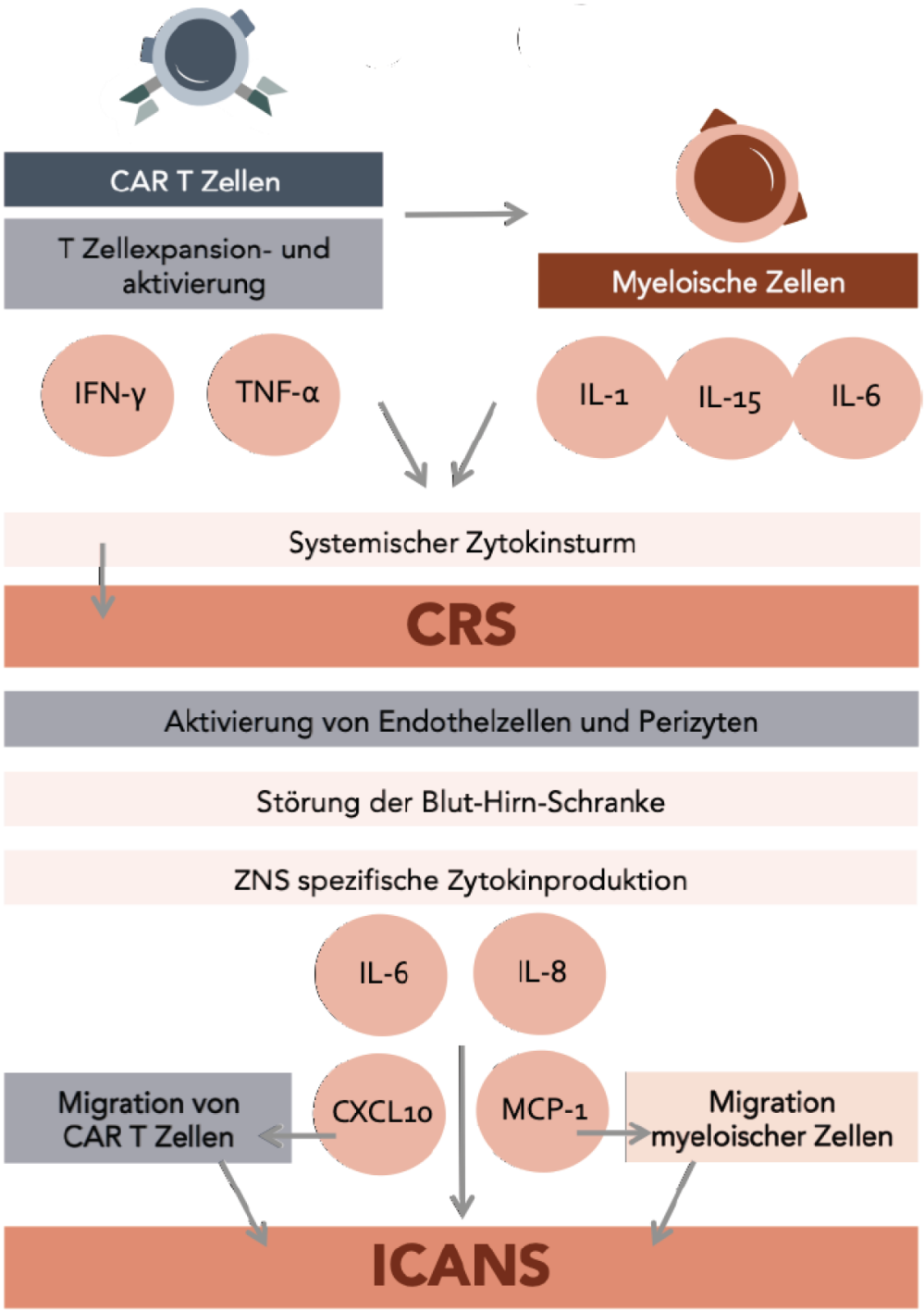
CART-Zelltherapie-assoz. ICANS: Pathogenese



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CART-Zelltherapie-assoz. ICANS: Schweregrade

	ICANS Grad 1	ICANS Grad 2	ICANS Grad 3	ICANS Grad 4
ICE-Score*	7-9	3-6	0-2	0 (Patient nicht erweckbar; keine Fähigkeit zur Testdurchführung)
Bewusstseins-störung	Spontan erweckbar	Durch Ansprache erweckbar	Durch taktilen Reiz erweckbar	Patient ist nicht erweckbar oder nur durch repetitive taktile Reize. Stupor oder Koma
Epileptischer Anfall	N/A	N/A	Jeder Anfall mit rascher, vollständiger Rückbildung, oder nicht konvulsive Anfälle im EEG die auf Intervention ansprechen	Lebensbedrohlicher Anfall (Dauer >5 min), oder repetitive Anfälle ohne Rückkehr zur Baseline
Motorik	N/A	N/A	N/A	Höhergradiges motorisches Defizit (Hemi- oder Paraparese)
Erhöhter ICP oder zerebrales Ödem	N/A	N/A	Fokales zerebrales Ödem in der zerebralen Bildgebung	Diffuses zerebrales Ödem in der zerebralen Bildgebung; Dekortikations- oder Dezerebrationsstarre, oder Abducensparese oder Papillenödem oder Cushing-Reflex (ICP↑ RR↑, HF↓)

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CART-Zelltherapie-assoz. ICANS: ICE Score

Kategorie	Aufgabe	Punkte
Orientieren	Jahr	1
	Monat	1
	Stadt	1
	Krankenhaus	1
Benennen	Gegenstand 1	1
	Gegenstand 2	1
	Gegenstand 3	1
Schreiben	Schreiben eines Standardsatzes	1
Konzentrieren	Rückwärtszählen von 100 auf 10 in 10er-Schritten	1
Befolgen	Durchführen einer Geste (z.B. zwei Finger zeigen, Augen schließen, Zunge herausstrecken)	1
ICE SCORE GESAMT		**10**

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CART-Zelltherapie-assoz. ICANS: **Basis**therapie

Innerhalb von 5 h vor und bis 10 Tage nach CAR-T-Zell-Therapie (bei Symptomfreiheit) oder bis 5 Tage nach Abklingen ICANS-spezifischer Symptome

- Bestimmung des ICE-Scores alle 12 Stunden (siehe Kapitel 3.2.4.2)
- Hochrisikopatienten (z.B. mit signifikant erhöhtem CRP/Ferritin vor CAR-T-Zell-Transfusion oder hoher Tumorlast) sollten ggf. bereits ab CAR-T-Zell-Transfusion engmaschig überwacht werden, z.B. mittels kontinuierlicher zentraler Monitorüberwachung und 8-stündlicher Bestimmung des ICE-Scores
- Zentralnervös wirksame Medikamente, die sedierend oder die Krampfschwelle senkend wirken können (z.B. Benzodiazepine, Neuroleptika), sollten während des stationären Aufenthalts und in den ersten vier Wochen nach CAR-T-Zell-Gabe nur mit Vorsicht angewendet werden.

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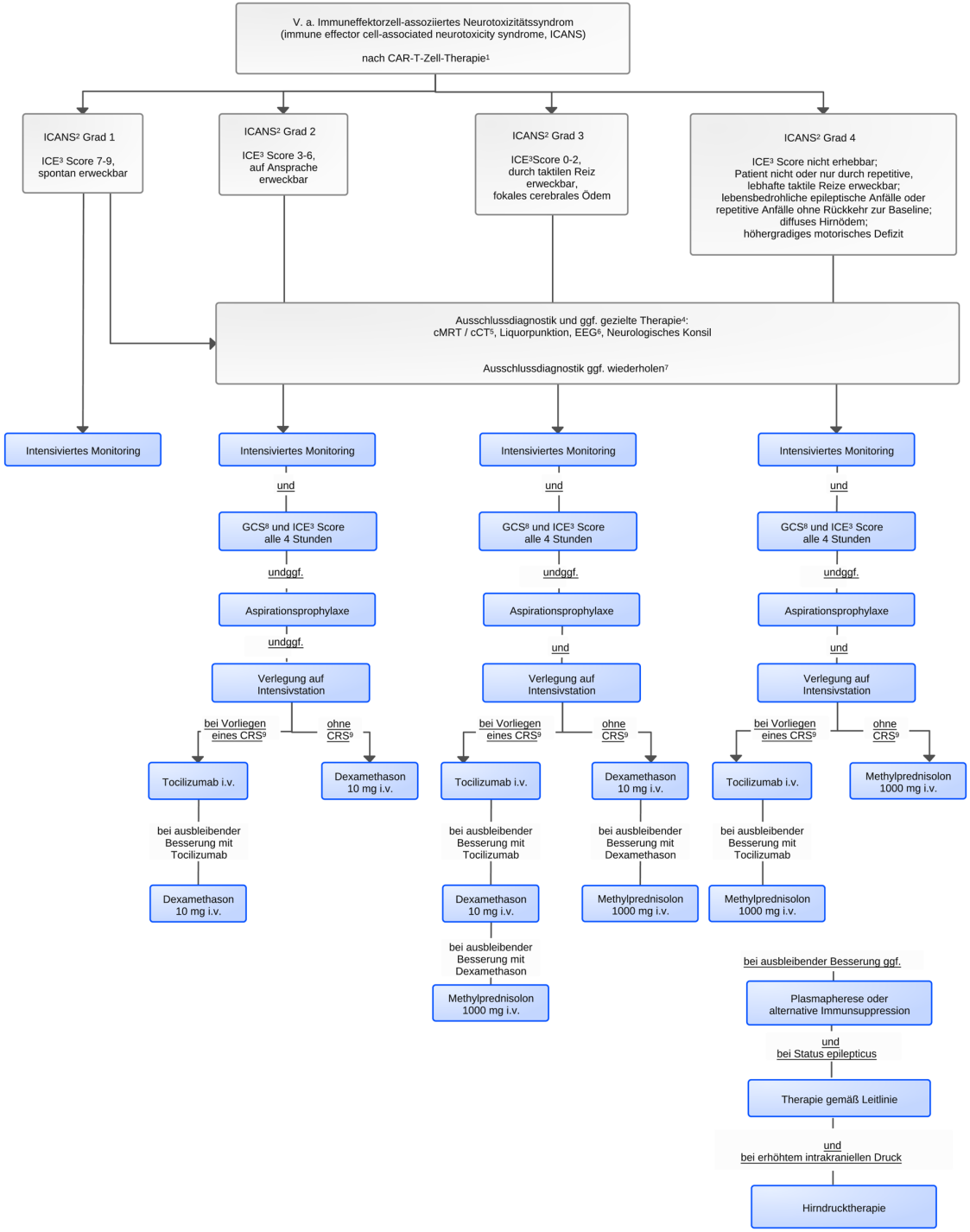
CART-Zelltherapie-assoz. ICANS: Therapiealgorithmus



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CART-Zelltherapie-assoz. ICANS: Glukokortikoid-Tapering

Tag	Methylprednisolon-Dosis
1-3	1 g i.v. 1x tgl.
4-5 (bei Regredienz zu ICANS °1)	250 mg 2x tgl.
6-7	125 mg 2x tgl.
8-9	60 mg 2x tgl.

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CART-Zelltherapie-assoz. ICANS: Aufklärung und Screening

Aufklärung des Patienten und der Angehörigen

- Aufenthalt des Patienten in räumlicher Nähe zum Zentrum (maximal 2 Stunden Fahrzeit) für vier Wochen nach CAR-T-Zell-Therapie
- Keine aktive Teilnahme am Straßenverkehr, keine Bedienung von Maschinen, kein Umgang mit gefährlichen Substanzen o.ä. für acht Wochen nach CAR-T-Zell-Transfusion
- Schulung über die Bedeutung der Symptome mit sofortiger notfallmäßiger Vorstellung in der Klinik
- Aushändigung des produktspezifischen CAR-T-Zell-Notfallpasses

Aufklärung des Patienten über Warnsymptome

- Fieber, Schüttelfrost
- Atembeschwerden
- Schneller oder unregelmäßiger Herzschlag
- Starke Übelkeit oder Erbrechen
- Durchfall
- Verwirrtheit
- Schwindelgefühl oder Benommenheit
- Starke Müdigkeit oder Schwäche
- Zittern oder unkontrollierte Bewegungen
- Kopfschmerzen
- Getrübter Bewusstseinszustand
- Krampfanfälle

Checkliste zur Anamnese möglicher neurologischer Symptome

- Haben Sie Kopfschmerzen?
- Ist Ihnen übel oder müssen Sie erbrechen?
- Sehen oder hören Sie merkwürdige ungewohnte Dinge (z.B. Stimmen, Geräusche, Lichtblitze, Figuren), die Personen in Ihrer Umgebung nicht wahrnehmen können?
- Haben Sie Probleme beim Sprechen?
- Verspüren Sie ein Zittern oder ungewöhnliche Zuckungen (z.B. in den Händen)?
- Haben Sie Probleme beim Schreiben?
- Haben Sie Taubheitsgefühle (z.B. an den Händen und Füßen) bemerkt?
- Haben Sie Schwierigkeiten, wach zu bleiben?

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