İSTANBUL MEDENİYET ÜNİVERSİTESİ

OLGULARLA İMMUN CHECK POINT TEDAVİSİ KOMPLİKASYONLARI

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Tıbbı Onkoloji

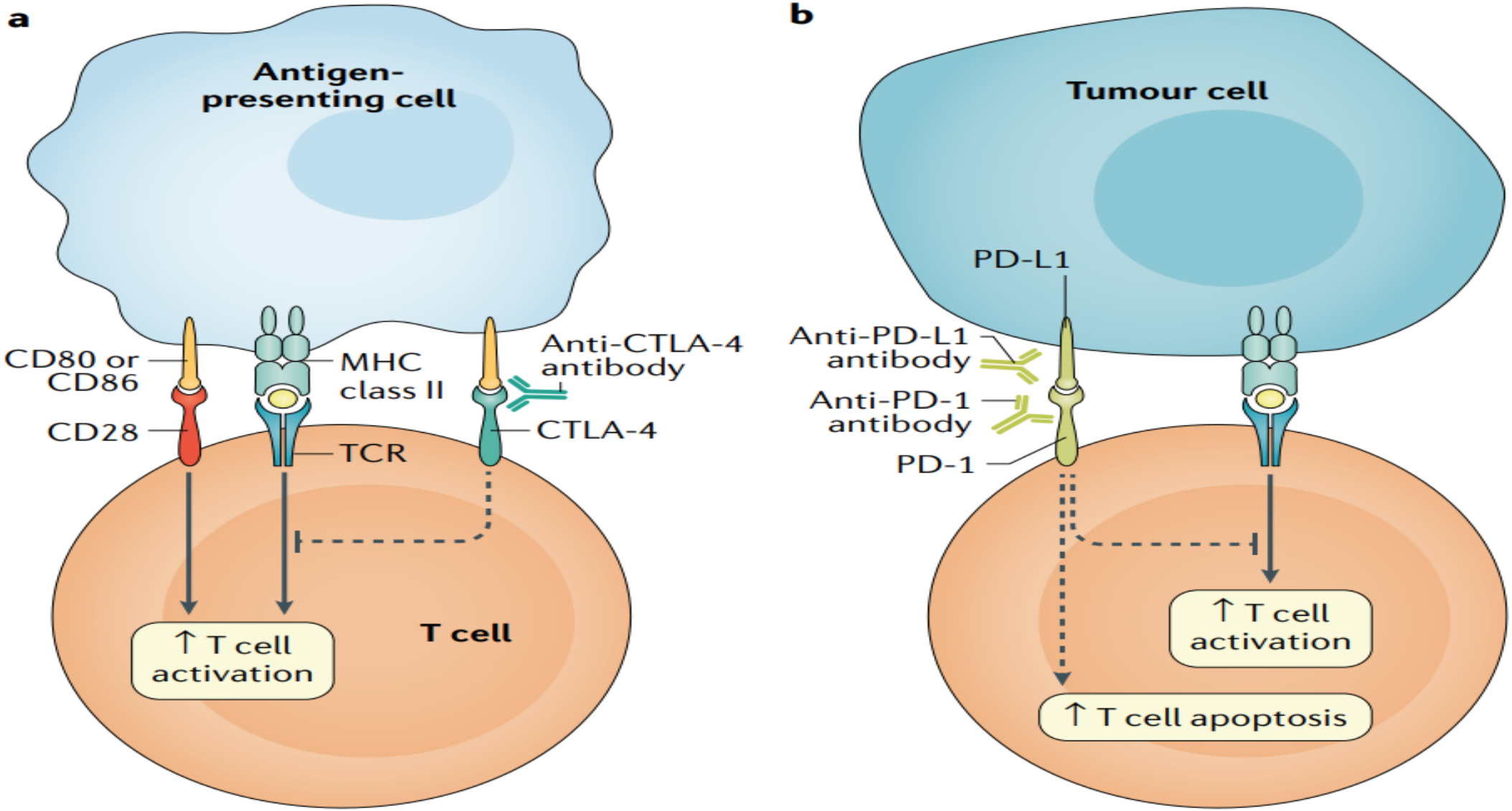
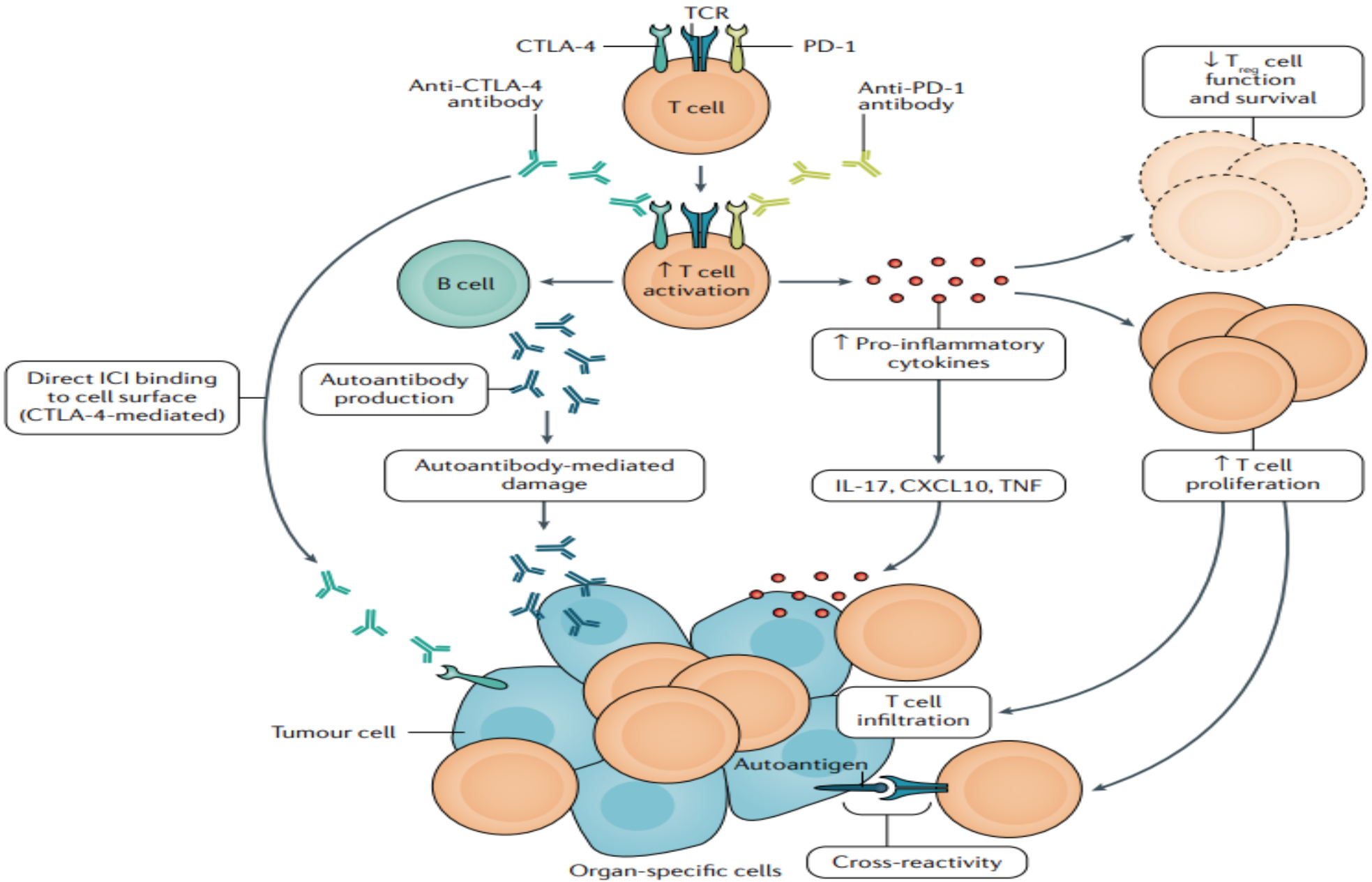


Fig. 1 | **Mechanism of immune checkpoints and immune checkpoint inhibitors.**

Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. Nature Reviews Disease Primers 2020 6:1 [Internet]..



Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. Nature Reviews Disease Primers 2020 6:1 [Internet]..

Table 1. Grading system (Common Terminology Criteria for Adverse Events version 5.0, European Society for Medical Oncology guideline, American Society of Clinical Oncology guideline)

The organ(s)	Grade 1	Grade 2	Grade 3	Grade 4
Acute kidney injury (Cr increased)	1.0–1.5 × ULN <1.5 × baseline	1.5–3.0 × ULN 1.5–3.0 × baseline	3.0–6.0 × ULN >3.0 × baseline	>6.0 × ULN Dialysis indicated
Inflammatory arthritis	- Mild pain with inflammation, erythema, or joint swelling	- Moderate pain with inflammation, erythema, or joint swelling - Limiting instrumental ADL	- Severe pain with inflammation, erythema, or joint swelling - Irreversible joint damage - Limiting self-care ADL	
Colitis	- Asymptomatic - Increase of fewer than 4 stools per day	- Abdominal pain - Mucus or blood in stool - Increase of four to 6 stools per day	- Severe abdominal pain peritoneal signs - Change in bowel habit - Increase of seven or more stools per day	- Life-threatening consequences
Hepatitis (AST, ALT increased)	<3.0 × ULN - Asymptomatic	3.0–5.0 × ULN - Asymptomatic	5.0–20.0 × ULN - Symptomatic liver dysfunction - Compensated cirrhosis - Reactivation of chronic hepatitis	>20.0 × ULN - Decompensated liver function (ascites, coagulopathy, encephalopathy, coma)
Hypophysitis	- Asymptomatic or mild symptoms	- Moderate symptoms limiting age-appropriate instrumental ADL	- Severe or medically significant limiting self-care ADL	- Life-threatening consequences (visual field impairment)
Skin rash	- Target lesions covering <10% BSA and not associated with skin tenderness	- Target lesions covering 10%–30% BSA and associated with skin tenderness	- Target lesions covering >30% BSA - Severe/life-threatening symptoms - Generalized exfoliative/ulcerated/bullous rash	
Fatal adverse effects				
Myasthenia gravis	- Asymptomatic or mild symptoms	- Moderate symptoms - Limiting age-appropriate instrumental ADL	- Severe or medically significant - Limiting self-care ADL	- Life-threatening consequences (respiratory muscle involved)
Myocarditis	- Asymptomatic - Cardiac enzyme elevation or abnormal EKG	- Symptoms with moderate activity or exertion	- Severe with symptoms at rest or with minimal activity or exertion	- Life-threatening consequences (hemodynamic impairment)
Pneumonitis	- Asymptomatic - Confined to one lobe of the lung or <25% of lung parenchyma	- Symptomatic (dyspnea, cough or chest pain) - More than one lobe of the lung or 25%–50% of lung parenchyma	- Severe symptoms (new or worsening hypoxia) - All lung lobes or >50% of lung parenchyma - Need oxygen therapy	- Life-threatening respiratory compromise (need intubation and ventilator care)

Cr, creatinine; ULN, upper limit normal; ADL, activity of daily living; BSA, body surface area; EKG, electrocardiogram.

Choi J, Lee SY. Clinical characteristics and treatment of immune-related adverse events of immune checkpoint inhibitors. Vol. 20, Immune Network. Korean Association of Immunologists; 2020.

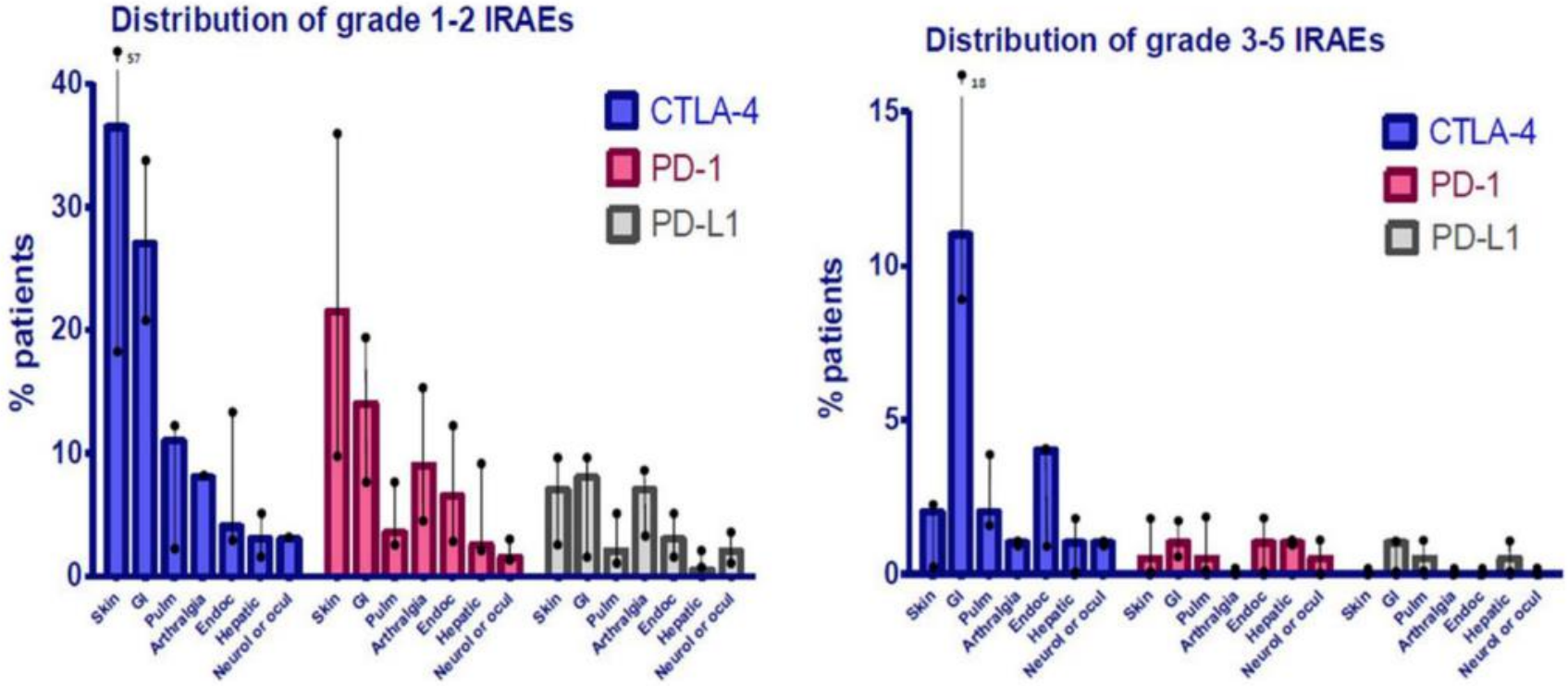
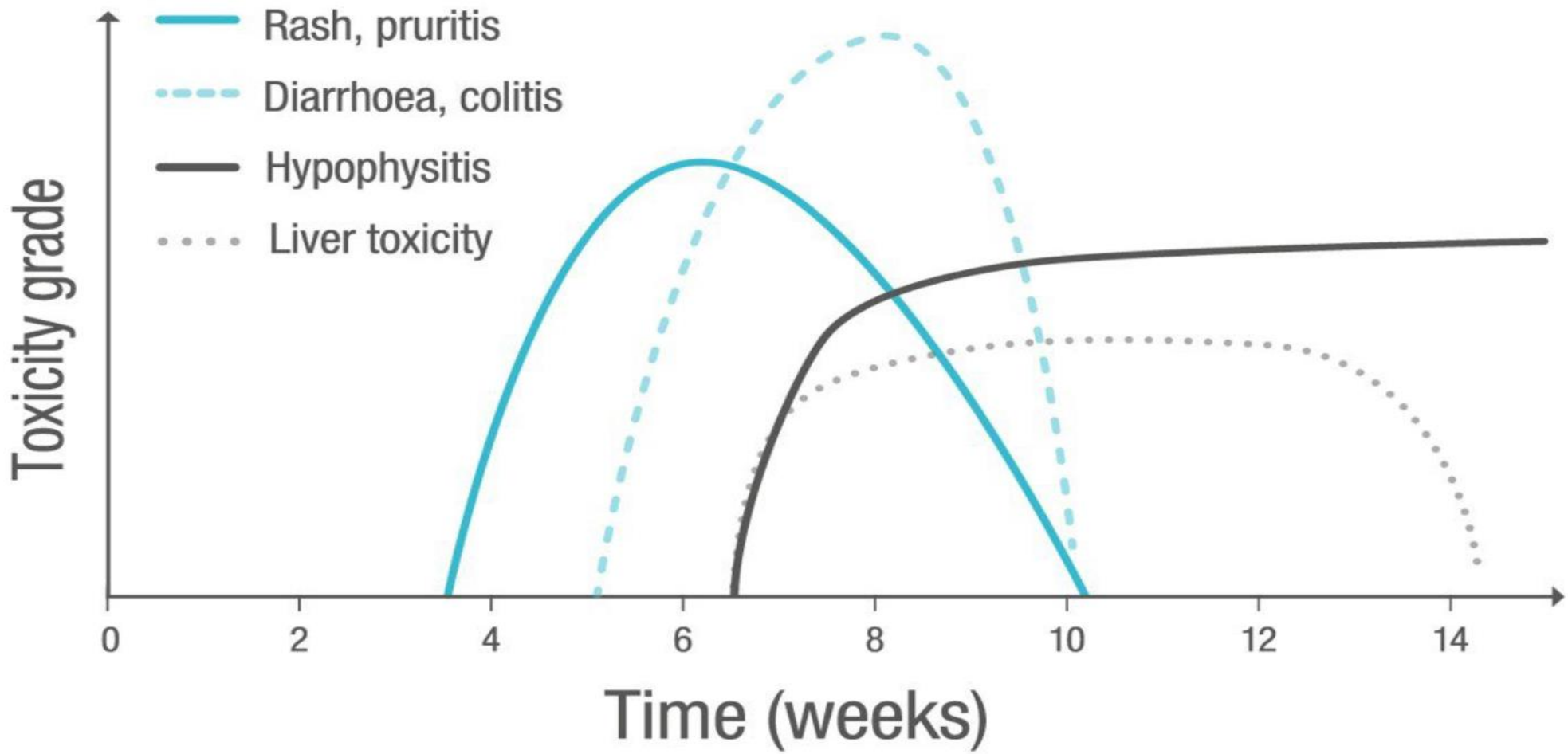


Fig. 1 Distribution of mild and severe immune-related adverse events (irAEs) associated with immune checkpoint inhibitor therapy. [Adapted from [88]]

Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017 Nov 21;5(1).



Haanen J, Carbonnel F, Robert C, Kerr K, Peters S, Larkin J, et al. Management of toxicities from immunotherapy ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018.

Olgu 1

- N.Y. 68 yaşında Erkek
- Mesane ca nedeniyle 07/2021 tarihinde Sistoprostatektomi op. olmuş. Adjuvan Sisplatin + Gemsitabin tedavisi sonrası takibe alınmış.
- Özgeçmiş : Koroner arter hastalığı (9yıl), KOAH (4yıl)
- Soygeçmiş: Özellik yok
- Sigara : 40 paket/yıl
- Alkol kullanım öyküsü yok.
- Kullandığı ilaçlar : ASA 100mg/gün , aralıklı inhaler
- Fizik muayene doğal, sistem muayenelerinde patolojik özellik yok.

- 01/2022 tarihinde kontrol görüntülemesinde
  - Karaciğer segment 6 da 22x12mm, segment 3,4B,5,6,7,8 de metastatik lezyonlar
  - Batın içi multipl LAP

- Adjuvan kemoterapi tamamlanmasından 12 ay içinde nüks gelişen hastaya 2. seri Pembrolizumab 200mg 21 günde bir tedavisi başlandı.
- Kontrol görüntülemelerinde tam yanıt elde edildi.

lesion no	t/n	organ	description	modality procedure	contrast	procedure code	body part	location	diagnosis	date	dimensions	response
1	target	Liver	4A segment	CT	yes	CT with contrast	abdomen	code	metastasis	Apr 28, 2022	22*20 mm	screening
2	target	Liver	6th segment	CT	yes	CT with contrast	abdomen	code	metastasis	Apr 28, 2022	16*15 mm	screening
3	non-target	Liver	other	CT	yes	CT with contrast	abdomen	code	metastasis	Apr 28, 2022	non target	screening
4	target	soft tissue	pelvic mesenteric implant	CT	yes	CT with contrast	pelvis	code	metastasis	Apr 28, 2022	18*15 mm	screening
5	non-target	soft tissue	pelvic mesenteric implant	CT	yes	CT with contrast	pelvis	code	metastasis	Apr 28, 2022	non target	screening
											sum:56 mm	

Radiological Evaluations are performed according to RECIST 1.1 criteria

Perigastric lymph node is not considered pathologic as it is not fdg avid at PET CT and show central fat density
L aparaaortic lymph nodes are not large enough to be considered pathologic they are not dg avid at PET CT

Apr 28, 2022 Cranial MR No sign of metastasis

Apr 30, 2022 Bone Scan No sign of metastasis

1	target	Liver	4A segment	CT	yes	CT with contrast	abdomen	code	metastasis	Jul 04, 2022	0*0 mm	
2	target	Liver	6th segment	CT	yes	CT with contrast	abdomen	code	metastasis	Jul 04, 2022	0*0 mm	
3	non-target	Liver	other	CT	yes	CT with contrast	abdomen	code	metastasis	Jul 04, 2022	non target	absent
4	target	soft tissue	pelvic mesenteric implant	CT	yes	CT with contrast	pelvis	code	metastasis	Jul 04, 2022	7*6 mm	
5	non-target	soft tissue	pelvic mesenteric implant	CT	yes	CT with contrast	pelvis	code	metastasis	Jul 04, 2022	non target	absent
											sum:7 mm	

Radiological Evaluations are performed according to RECIST 1.1 criteria

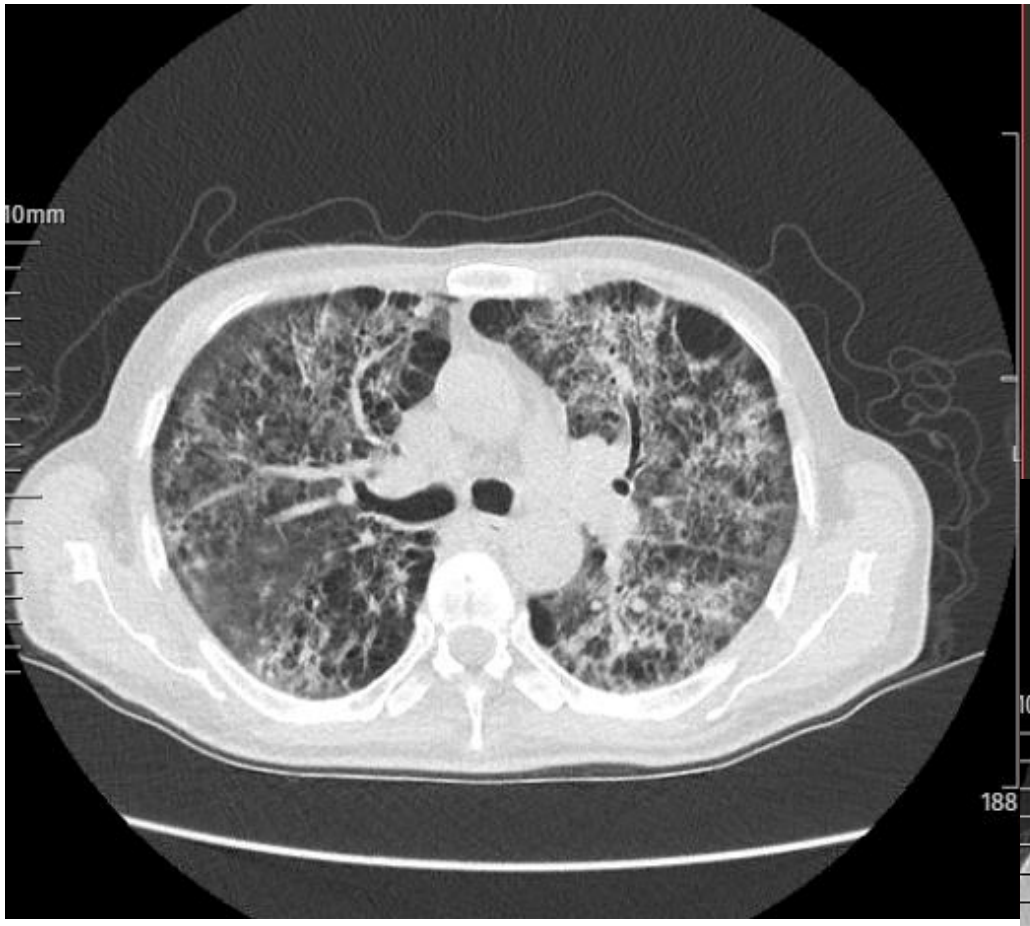
Perigastric lymph node which was not considered pathologic as it was not fdg avid at PET CT and which show central fat density sho
L aparaaortic lymph nodes which were not large enough to be considered pathologic as they were not dg avid at PET CT are stable
NEW Liver density heterogenity suggesting inflamation

Jul 08, 2022 Abdomen MR No sign of metastasis
Liver intensity heterogenity suggesting inflamation

non-target lesion response	CR
target lesion respone	PR
New lesions	No
Overall RECIST response	PR

1	target	Liver	4A segment	CT	yes	CT with contrast	abdomen	code	metastasis	Sep 15, 2022	0*0 mm	
2	target	Liver	6th segment	CT	yes	CT with contrast	abdomen	code	metastasis	Sep 15, 2022	0*0 mm	
3	non-target	Liver	other	CT	yes	CT with contrast	abdomen	code	metastasis	Sep 15, 2022	non target	absent
4	target	soft tissue	pelvic mesenteric implant	CT	yes	CT with contrast	pelvis	code	metastasis	Sep 15, 2022	0*0 mm	
5	non-target	soft tissue	pelvic mesenteric implant	CT	yes	CT with contrast	pelvis	code	metastasis	Sep 15, 2022	non target	absent
											sum:0 mm	

- Pembrolizumab tedavisinin 7. ayında hasta Nefes darlığı nedeniyle başvurdu.
- Fizik muayenesinde solunum sesleri alınamadı.
- SaO2: %75 oda havasında
- Hasta YBÜ’ne alındı.
- Toraks BT çekildi.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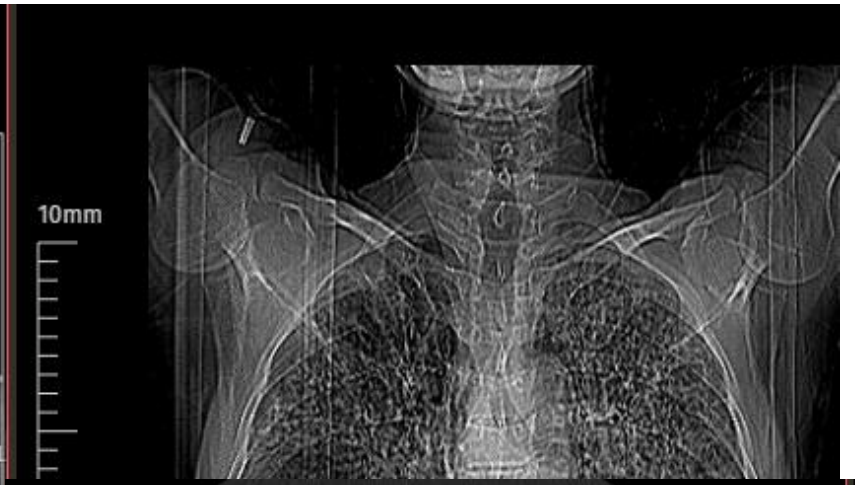
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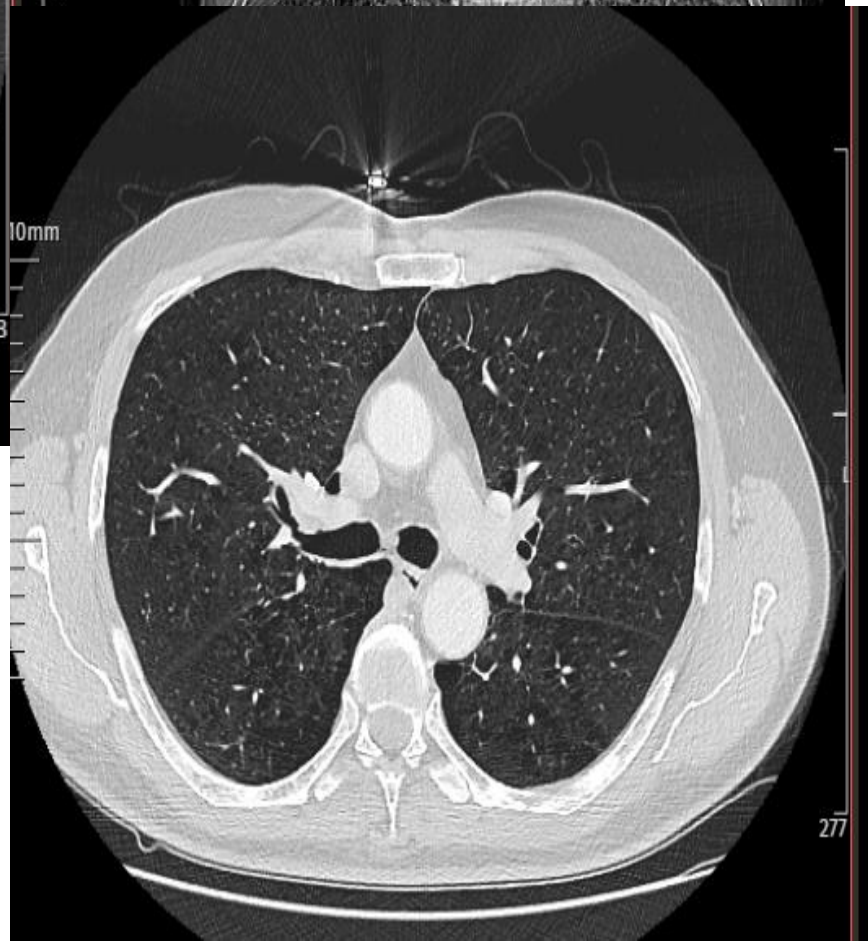
10mm
188
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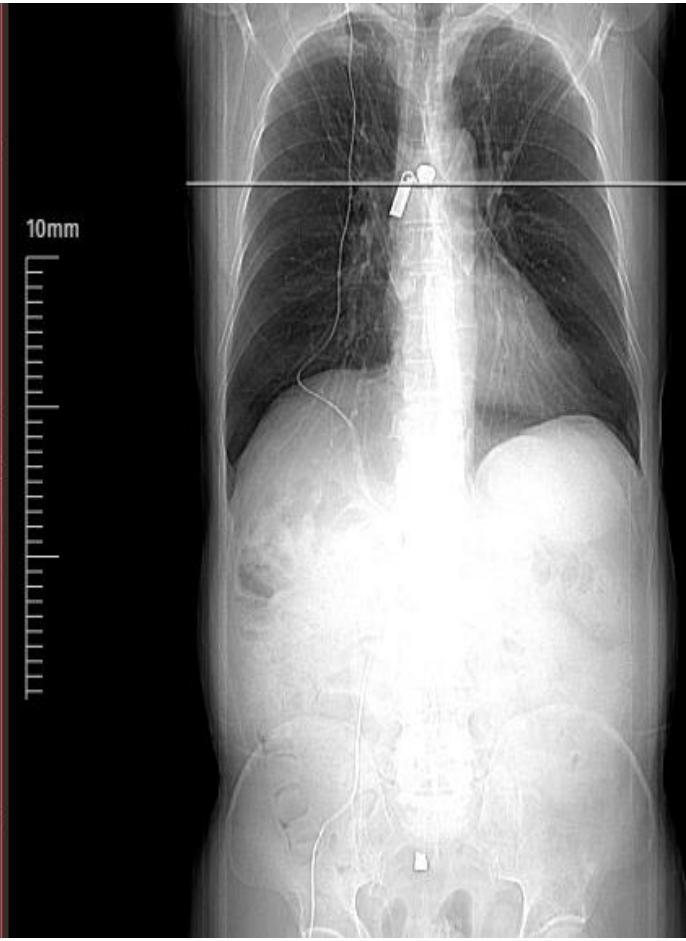
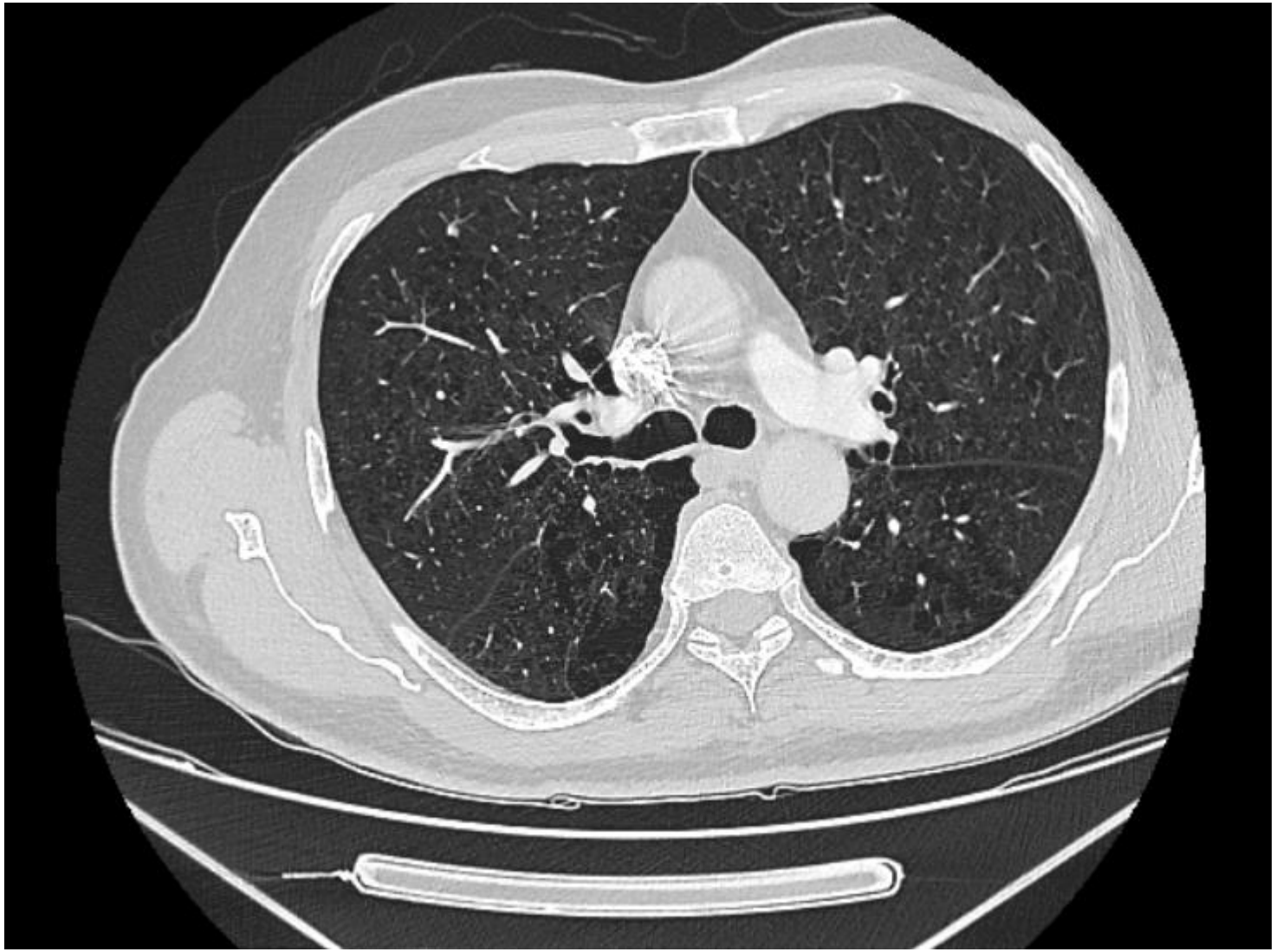

10mm

- Enfeksiyon ekarte edildi.
- Grad IV, immun Pnömonit saptandı.
- 1mg/kg metil prednisolon başlandı.
- Ampirik antibiyotik başlandı.
- Steroid tedavisinin 2.gününde SaO2 değerlerinde yükselme görüldü.
- Steroid tedavisinin 10. gününde oksijen gereksinimi kalmadı.
- Steroid tedavisine 6 hafta devam edildi, daha sonra doz azaltılarak kesildi.

- Hastanın klinik şikayetleri geriledi.
- Fizik muayene bulguları düzeldi.
- 8. haftada kontrol Toraks BT çekildi
- İmmunoterapi kalıcı olarak kesildi.



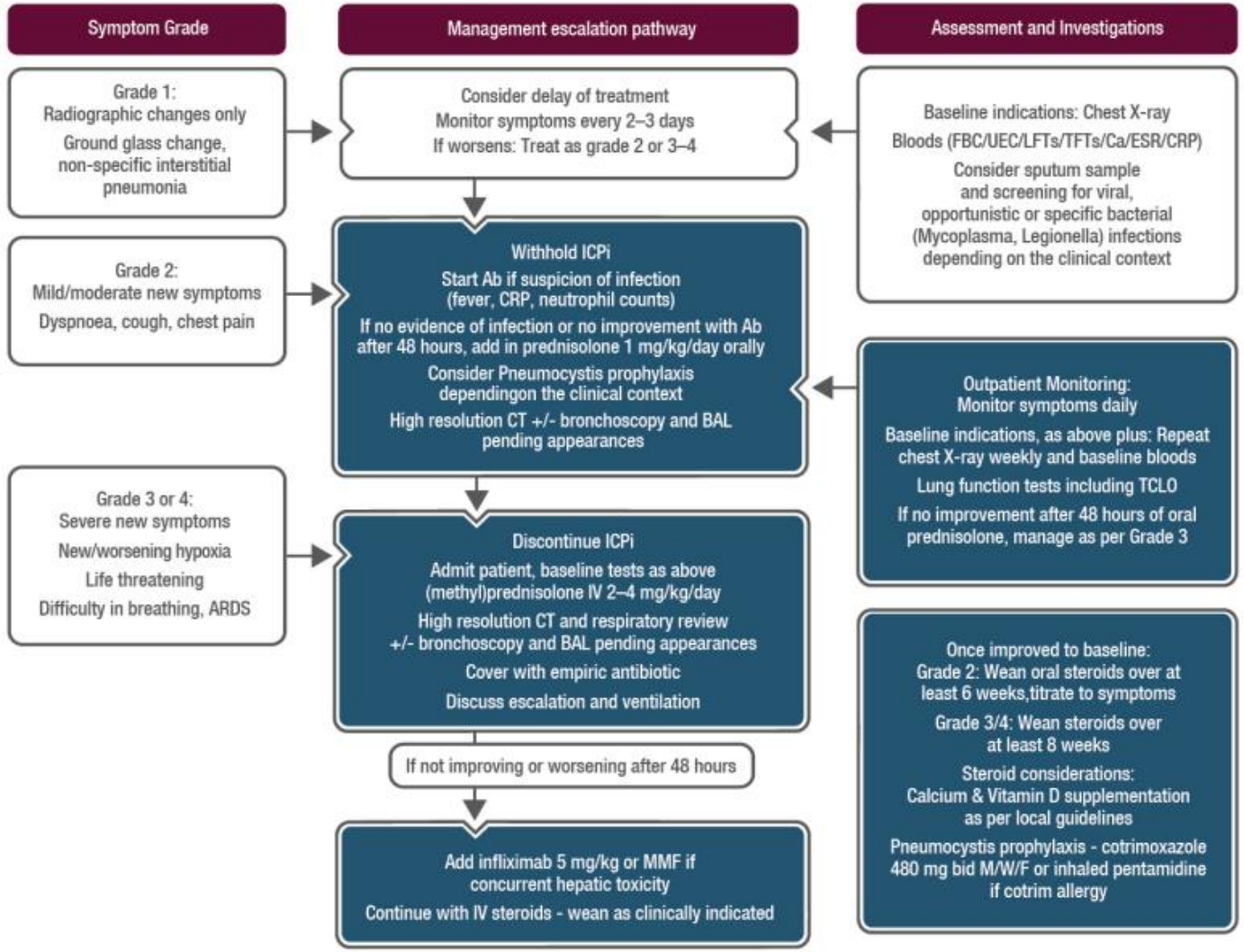
CLINICAL PRACTICE GUIDELINES

Immune related pneumonitis toxicities

ICPi-related toxicity: Management of pneumonitis

History:
Pulmonary hypertension/respiratory; disease/connective tissue disease; Influenza/Mycobacterium; tuberculosis exposure; Smoking history; Travel history; Allergy history including exposure to home/occupational aeroallergens

Differential Diagnosis:
Pneumonia (including atypical, pneumocystis, tuberculosis); Lymphangitis; Usual interstitial pneumonias; Pulmonary oedema; Pulmonary emboli; Sarcoidosis

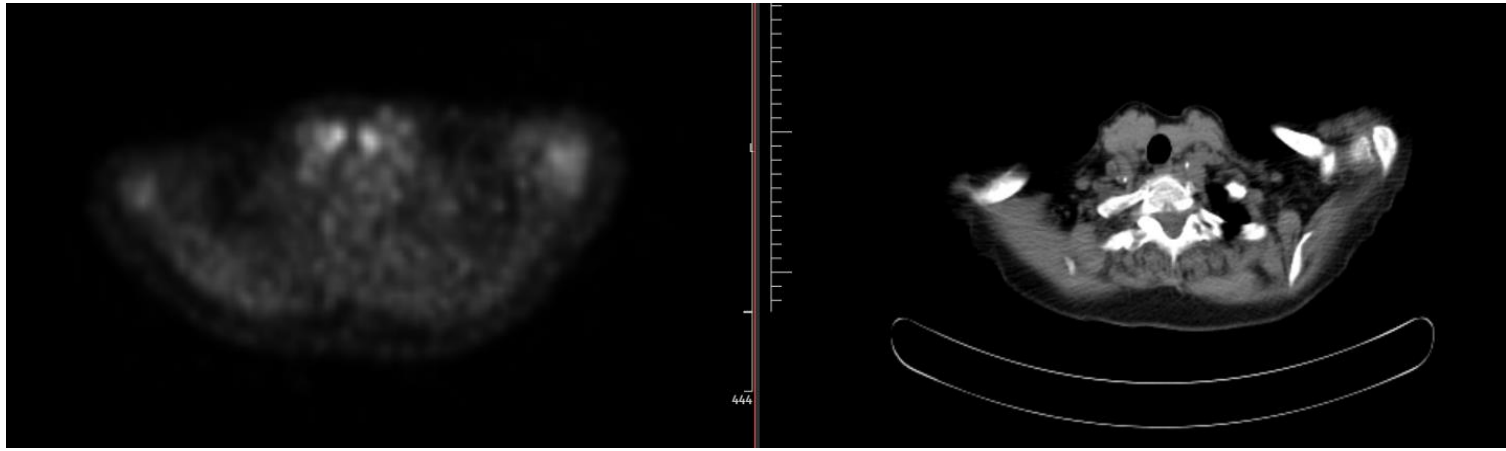


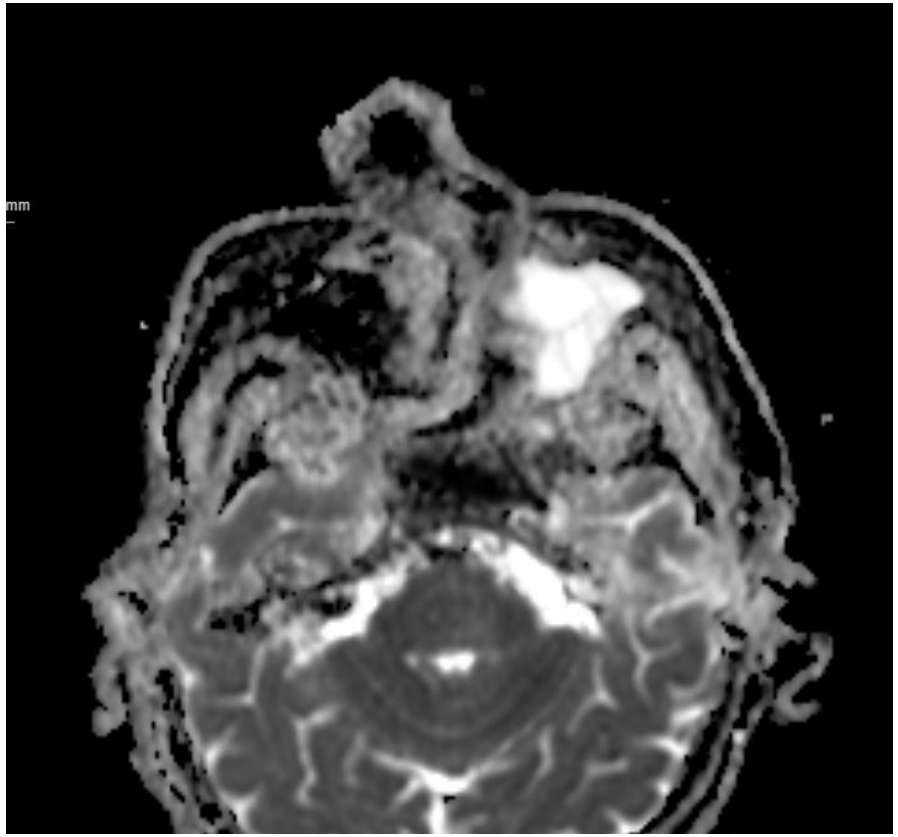
ESMO

Olgu 2

- N.D. 68 yaşında Kadın
- Göz kuruluğu nedeniyle yapılan tetkiklerinde sol orbita nazal kısım, maksiller sinüste polip saptanmış,
- Polip Punch Biyopsi Malign Melanom (12/2021)
- Özgeçmiş : Hipertansiyon, Hipotiroidi
- Soygeçmiş: Özellik yok
- Sigara, Alkol kullanım öyküsü yok.
- Kullandığı ilaçlar : Amlodipin 5mg/gün, Levotiroksin 50mcg/gün
- Fizik muayene doğal, sistem muayenelerinde patolojik özellik yok.

- Evreleme PET-BT :
  - Nazal kavite sol lateralinde hipermetabolik tümöral lezyon,
  - Bilateral servikal ve sol supraklaviküler alanda multipl metastatik lezyon.
- KBB ile operabilite açısından görüşüldü. Unrezektable olarak değerlendirildi.
- Hedefe yönelik tedaviler açısından BRAF mutasyonu istendi. BRAF mutasyonu saptanmadı.





- Rezeke edilemeyen Malign Melanom tanısıyla
- Nivolumab 3mg/kg dozundan 14 günde bir başlanmıştır.
- Tedavi öncesi hemogram ve biokimya değerlerinde patolojik bulgu saptanmadı.
  - Üre : 24 mg/dl, Kre : 0,79 mg/dl , Elektrolit imbalansı yok.
  - ALT : 7 U/L , AST : 14U/L
  - TSH : 2,7
- 3. ayda kontrol görüntülemesinde yanıt saptanması üzerine Nivolumab tedavisine devam edildi.

- Nivolumab tedavisinin 8. ayında (toplam 14 doz tedavi sonrası)
- Tetkiklerinde Üre: 117mg/dl Kreatinin : 3,04 mg/dL saptanması üzerine
- Post-renal patolojilerin ekartasyonu açısından üriner usg çekildi. Post renal patoloji saptanmadı.
- Hastanın öyküsünde ve fizik muayenesinde pre-renal patolojiye neden olacak patolojik bulgu saptanmadı.
- Nefrotoksik ilaç kullanım öyküsü yok.

- Böbrek Biyopsi yapıldı.
- İmmunoterapi almakta olan hastada bazal değerine göre 3 kattan fazla kreatinin artışı saptandı. (Grade III)
- İnterstisyel nefrit ön tanısıyla 1mg/kg Metilprednizolon başlandı. Hidrasyon sağlandı. İmmunoterapi kesildi.
- Biyopsi sonucunda Tubulointerstisyel nefrit saptandı.
- Steroid tedavisi sonrası kreatinin değerlerinde gerileme saptandı.

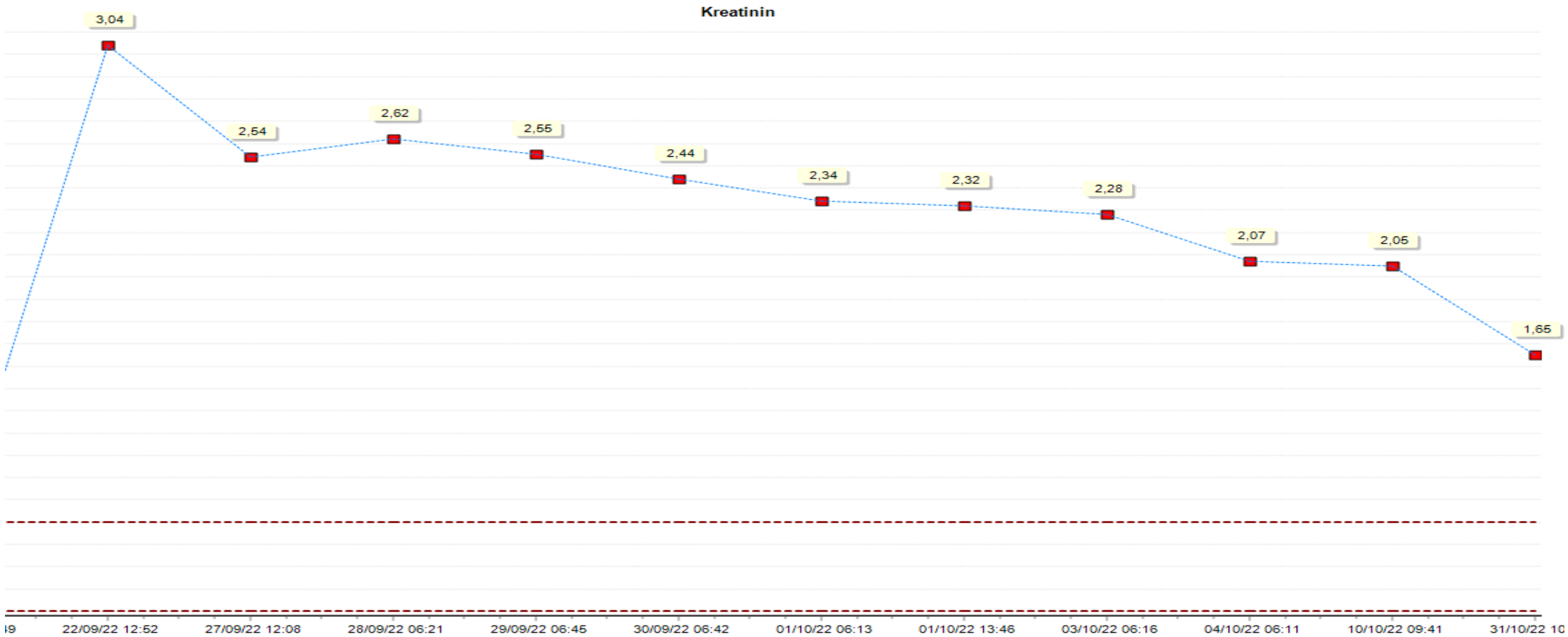

Kreatinin
3,04
2,54
2,62
2,55
2,44
2,34
2,32
2,28
2,07
2,05
1,65
22/09/22 12:52
27/09/22 12:08
28/09/22 06:21
29/09/22 06:45
30/09/22 06:42
01/10/22 06:13
01/10/22 13:46
03/10/22 06:16
04/10/22 06:11
10/10/22 09:41
31/10/22 10

Table 2. Management of irAEs (European Society for Medical Oncology guideline, American Society of Clinical Oncology guideline)

The organ(s)	Grade 1	Grade 2	Grade 3	Grade 4
Acute kidney injury	- Consider 'Hold immunotherapy' - Hydration - Check and stop nephrotoxic drug (PPI or NSAIDs)	- Hold immunotherapy - Oral prednisone 0.5–1 mg/kg/day - A nephrology consultation	- Permanently discontinue immunotherapy - Oral prednisone 1–2 mg/kg/day	- IV methylprednisone 1–2 mg/kg/day - Start dialysis

CLINICAL PRACTICE GUIDELINES

Rare immune-related toxicities

ICPi-related toxicity: Management of nephritis: **grade 3-4**

Renal injury occurs in around 1–4% of patients treated with ICPis, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate

Attention needs to be paid to the patient's baseline creatinine, not just abnormal results per biochemistry ULN

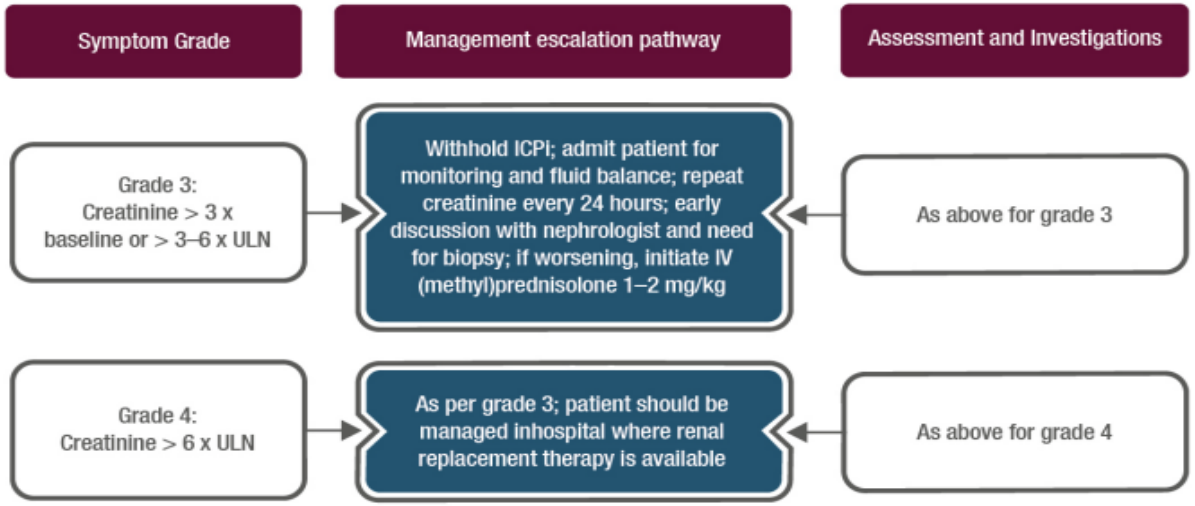
Confounding diagnoses include dehydration, recent IV contrast, urinary tract infection, medications, hypotension or hypertension

Early consideration for renal biopsy is helpful which may negate the need for steroids and determine if renal deterioration related to ICPis or other pathology

Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy

Steroid wean: Begin to wean once creatinine grade 1; grade 2 severity episode: wean steroids over 2–4 weeks; grade 3–4 episode: wean over ≥ 4 weeks

If on steroids for > 4 weeks–PJP prophylaxis, calcium/vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycaemia



ESMO

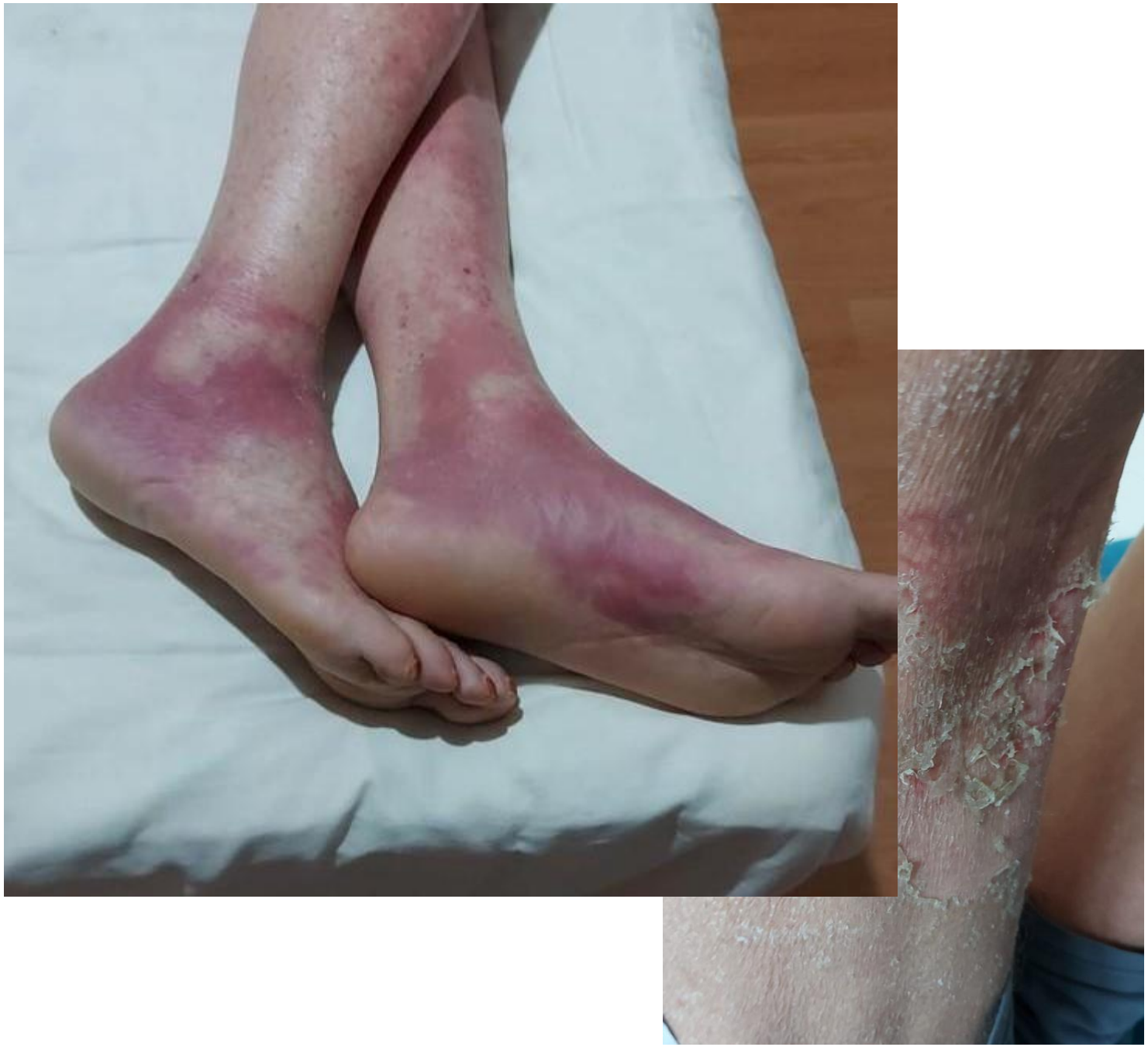
Olgu 3

- S.B. 58 yaşında Erkek
- Sağ böbrekte kitle nedeniyle Sağ nefrektomi operasyonu yapıldı
- Patoloji : pT3N0 Berrak hücreli Renal Hücreli Karsinom post-op takip
- Özgeçmiş : özellik yok
- Soygeçmiş: Özellik yok
- Sigara : 20 paket/yıl
- Alkol kullanım öyküsü yok.
- Düzenli ilaç kullanımı yok
- Fizik muayene doğal, sistem muayenelerinde patolojik özellik yok.

- Post-op 3. ay kontrollerinde nüks saptanması üzerine
- Yeniden evreleme PET-BT:
- Her iki Akciğerde metastatik Nodüller
- Batın içi multipl metastatik LAP

- IMDC Risk skoru : 2 orta Risk grubu

- Metastatik RCC nedeniyle Nivolumab 3mg/kg, İpilimumab 1mg/kg dozunda kombinasyon tedavisibaşlandı.
- İmmunoterapi başlanmasının 3. haftasın VYA’nın 30%sinden fazlasını kapsayan Makülopapüller Raş saptandı.



- İmmunoterapi ara verildi.
- Dermatoloji konsültasyonu istendi.
- 0,5mg/kg/gün metilprednisolon tedavisi başlandı.
- 2 hafta steroid kullanımı sonrası döküntüleri geriledi.
- Steroid dozu azaltılarak kesildi.
- 2 haftalık interval sonrası Nivolumab / İpilimumab tekrar başlandı.

	afternoon, levothyroxine by weight)			
Skin rash	- Continue immunotherapy - Topical emollients - Topical corticosteroids - Oral antihistamines for pruritus	- Consider 'Hold immunotherapy' - Oral prednisone 1 mg/kg/day	- Hold immunotherapy - A dermatology consultation - Oral prednisone 1–2 mg/kg/day	- IV prednisone 1–2 mg/kg/day - Consider immunomodulatory therapy in steroid non-responders

CLINICAL PRACTICE GUIDELINES

Immune-related skin toxicity

ICPi-related toxicity:
Management of skin rash/toxicity

Recognised skin AEs include:

Most common: Erythema, maculopapular and pustulopapular rash

Rare: TEN, Steven-Johnson syndrome and DRESS

Vasculitis may also be present with purpuric rash

ESMO

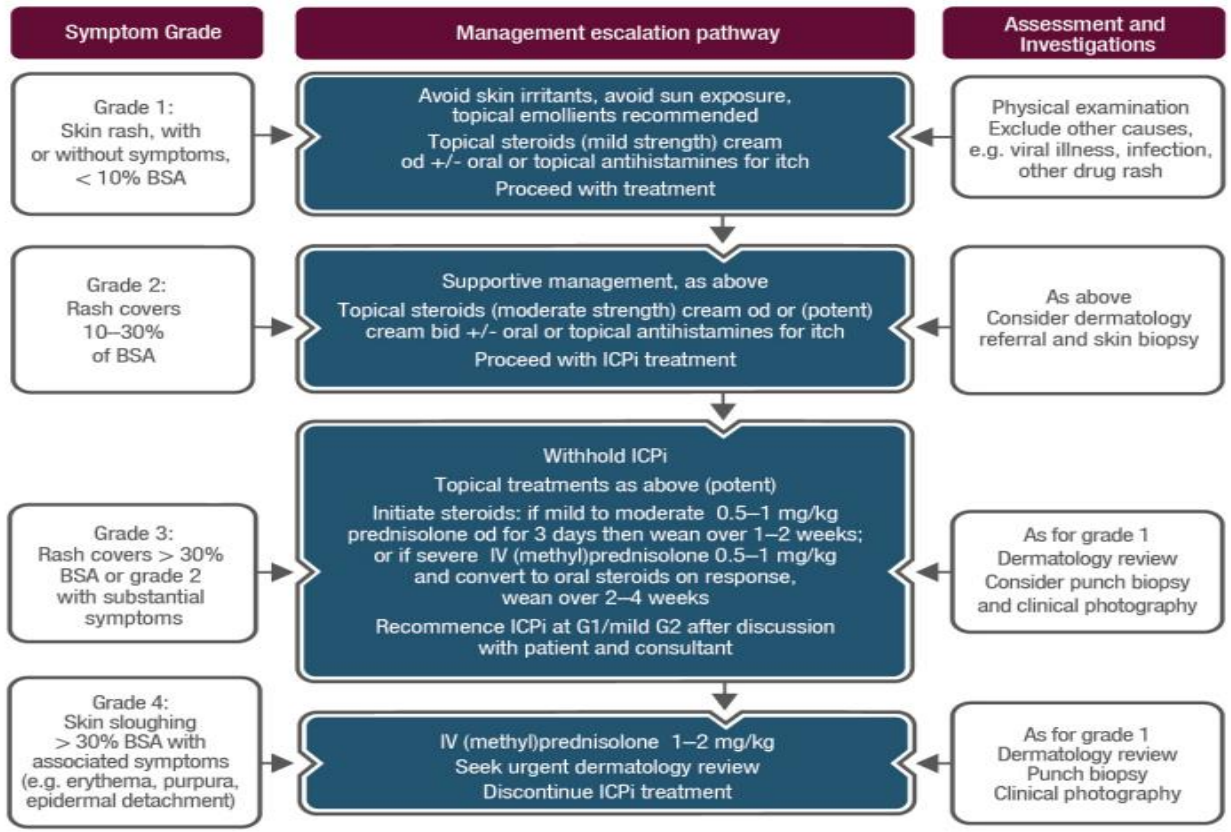


Table 2. Management of irAEs (European Society for Medical Oncology guideline, American Society of Clinical Oncology guideline)

The organ(s)	Grade 1	Grade 2	Grade 3	Grade 4
Acute kidney injury	- Consider 'Hold immunotherapy' - Hydration - Check and stop nephrotoxic drug (PPI or NSAIDs)	- Hold immunotherapy - Oral prednisone 0.5–1 mg/kg/day - A nephrology consultation	- Permanently discontinue immunotherapy - Oral prednisone 1–2 mg/kg/day	- IV methylprednisone 1–2 mg/kg/day - Start dialysis
Inflammatory arthritis	- Continue immunotherapy - NSAIDs (eg, ibuprofen) or acetaminophen	- Consider 'Hold immunotherapy' - Oral prednisone 10–20 mg/day - Intra-articular steroid injection - A rheumatology consultation	- Hold immunotherapy - Oral prednisone 0.5–1 mg/kg/day - Consider immunomodulatory therapy (DMARDs) in steroid non-responders	
Colitis	- Continue immunotherapy - Oral fluids - Antidiarrheal agents (eg, loperamide) - Avoid high fibre/lactose diet	- Consider 'Hold immunotherapy' - Oral prednisone 0.5–1 mg/kg/day - Consider sigmoidoscopy/ colonoscopy - A gastroenterology consultation	- Hold immunotherapy - Oral prednisone 1–2 mg/kg/day	- Permanently discontinue immunotherapy - IV methylprednisone 1–2 mg/kg/day - Consider immunomodulatory therapy (infliximab 5–10mg/kg, mycophenolate mofetil or tacrolimus) in steroid non-responders
Hepatitis	- Continue immunotherapy - Check hepatotoxic drug	- Hold immunotherapy - Oral prednisone 0.5–1 mg/kg/day	- Permanently discontinue immunotherapy - IV methylprednisone 1–2 mg/kg/day - Consider immunomodulatory therapy (mycophenolate mofetil, azathioprine or tacrolimus) in steroid non-responders - Do not offer infliximab - A hepatology consultation	
Hypophysitis	- Consider 'Hold immunotherapy' - Start glucocorticoid replacement with stress day rules (e.g., hydrocortisone 10–20 mg orally in the morning, 5–10 mg orally in early afternoon, levothyroxine by weight)	- Consider 'Hold immunotherapy' - Oral prednisone 0.5–1 mg/kg/day - An endocrinology consultation	- Hold immunotherapy - Oral prednisone 1–2 mg/kg/day	
Skin rash	- Continue immunotherapy - Topical emollients - Topical corticosteroids - Oral antihistamines for pruritus	- Consider 'Hold immunotherapy' - Oral prednisone 1 mg/kg/day	- Hold immunotherapy - A dermatology consultation - Oral prednisone 1–2 mg/kg/day	- IV prednisone 1–2 mg/kg/day - Consider immunomodulatory therapy in steroid non-responders

	- Oral antihistamines for pruritus		
Fatal adverse effects			
Myasthenia gravis	- Continue immunotherapy - Monitor symptoms for progression	- Hold immunotherapy - Oral prednisone 1–1.5 mg/kg/day - Pyridostigmine starting at 30 mg orally three times a day	- Permanently discontinue immunotherapy - IV methylprednisone 1–2 mg/kg/day - Consider IVIG or plasmapheresis in steroid non-responders - Consider immunomodulatory therapy (azathioprine, cyclosporine, mycophenolate) in steroid non-responders - A neurology consultation
Myocarditis	- Hold or permanently discontinue immunotherapy at any sign of cardiotoxicity - Systemic steroid (oral prednisone 1–2 mg/kg/day – methylprednisolone 1 g every day) - Consider additional immunomodulatory therapy (mycophenolate, infliximab, tacrolimus, or antithymocyte globulin) - Consider IVIG or plasmapheresis for unstable patients		
Pneumonitis	- Hold immunotherapy	- Hold immunotherapy - Oral prednisone 1–2 mg/kg/day - Consider empirical antibiotics - Consider bronchoscopy and/or BAL	- Permanently discontinue immunotherapy - IV methylprednisone 1–2 mg/kg/day - Empirical antibiotics - Consider additional immunomodulatory therapy (infliximab 5 mg/kg, mycophenolate mofetil IV 1 g twice a day or cyclophosphamide) - Consider IVIG if there is no improvement - A pulmonology consultation

Choi J, Lee SY. Clinical characteristics and treatment of immune-related adverse events of immune checkpoint inhibitors. Vol. 20, Immune Network. Korean Association of Immunologists; 2020.

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