GÜNCEL ONKOLOJİK TEDAVİLERİN YAN ETKİLERİ

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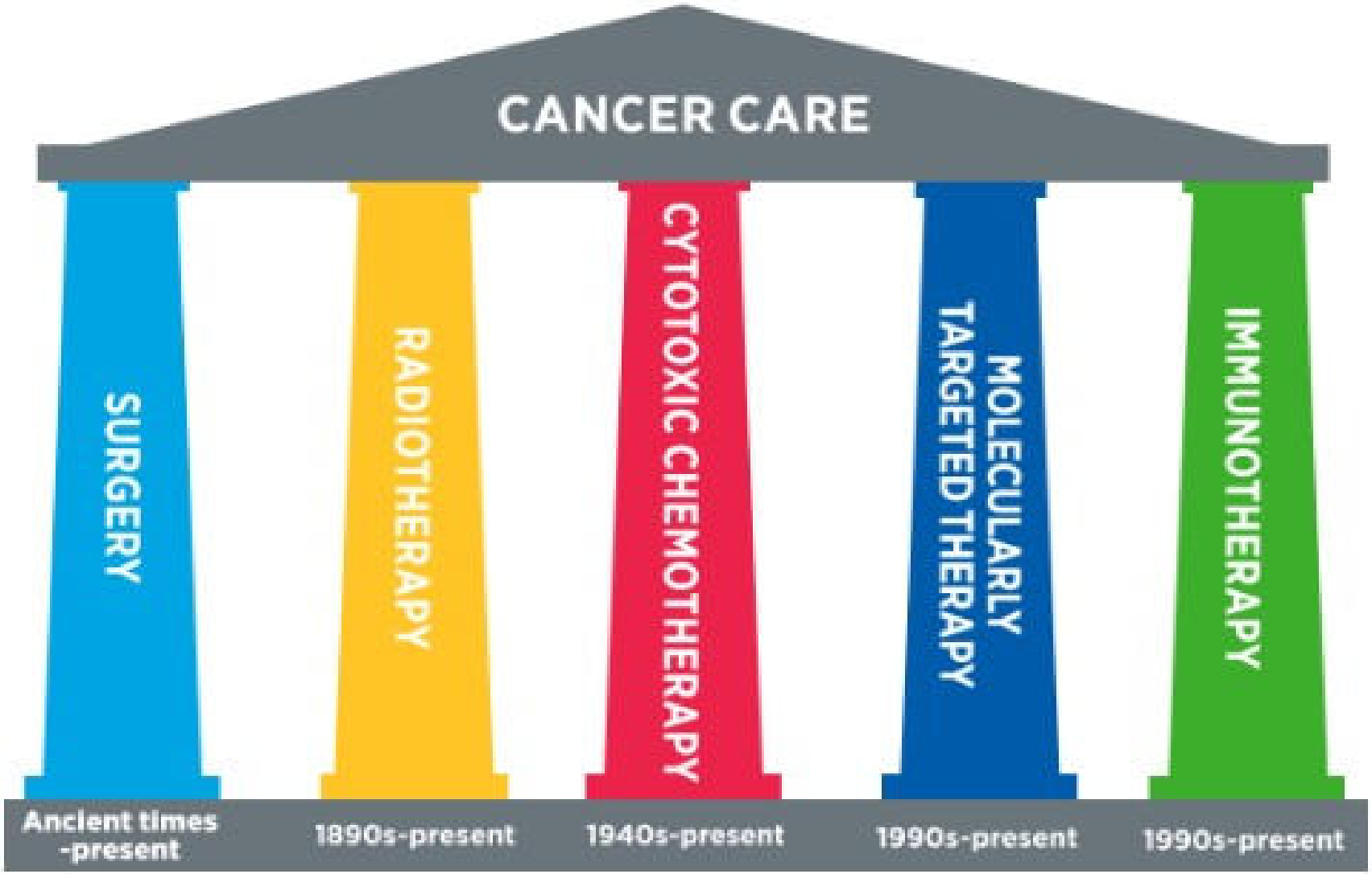
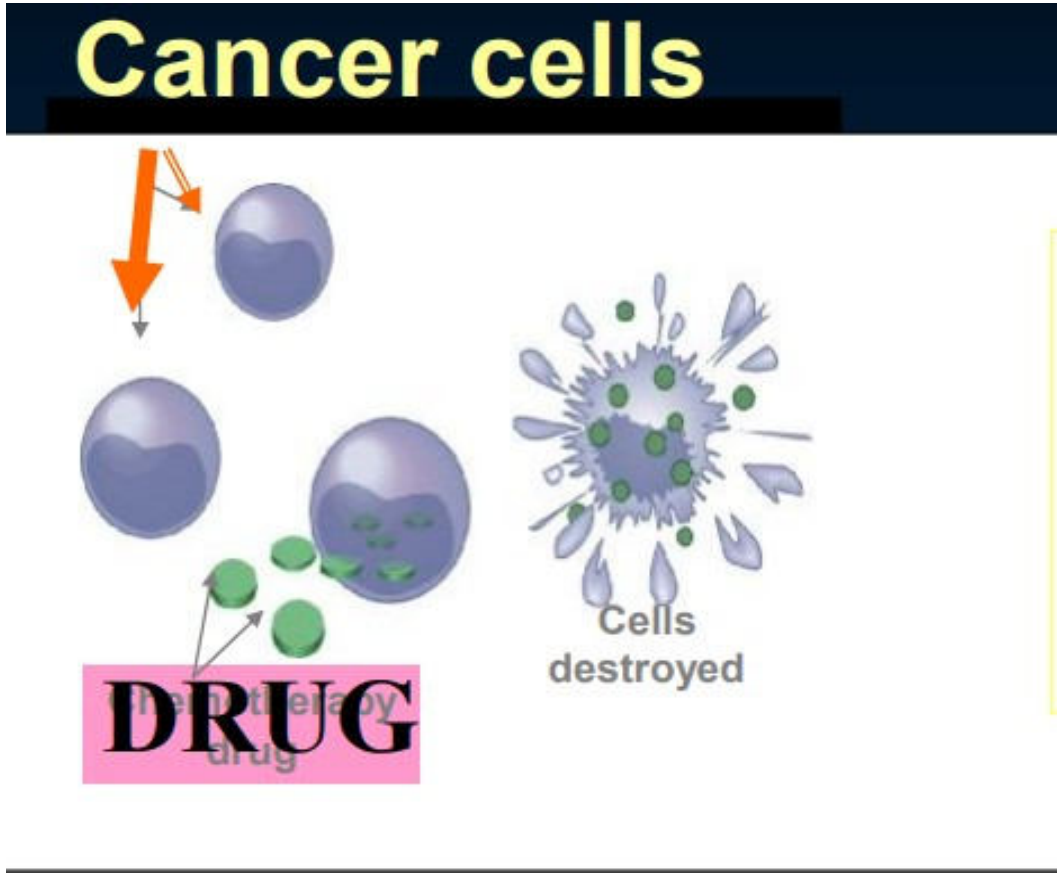
Tıbbi Onkoloji


CANCER CARE
SURGERY
RADIOTHERAPY
CYTOTOXIC CHEMOTHERAPY
MOLECULARLY TARGETED THERAPY
IMMUNOTHERAPY
Ancient times -present
1890s-present
1940s-present
1990s-present
1990s-present

Kemoterapi

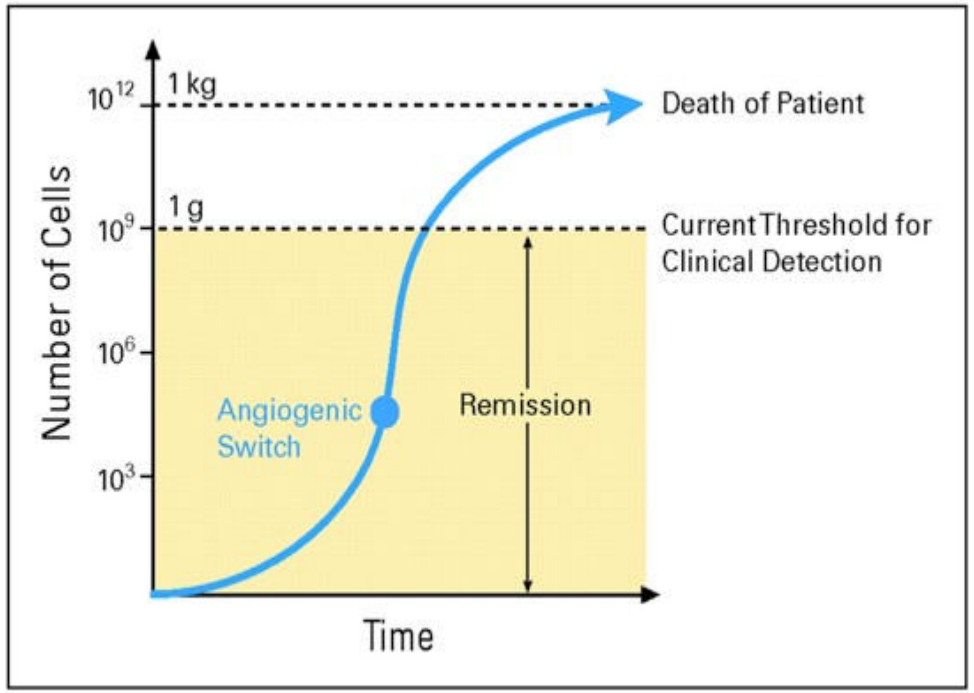


Kemoterapötikler:

- DNA-interaktif ajanlar
- Mitoz inhibitörleri
- Antimetabolitler

Kemoterapi

Gompertzian growth curve of a solid tumor and its relationship to cancer detection and imaging.



Frangioni J V JCO 2008;26:4012-4021

JOURNAL OF CLINICAL ONCOLOGY

- En hızlı bölünen hücreler en fazla etkilenir
- Kemoterapinin hücre öldürmesi, tm büyüme hızı ile orantılıdır
- Myelosüpresyon, alopesi, diare, mukozit….

Hedefe Yönelik Tedaviler

- Kanser hücresinin yüzeyindeki veya içindeki anormal çalışan proteinleri hedef alırlar.

- Bir hücreye hangi proteini yapacağını anlatan DNA dır. DNA hasarlanırsa, anormal davranış sergileyen hasarlı proteinler olur.

- Bir hücrenin hangi DNA hasarını taşıdığını bilirsek hangi anormal proteini ürettiğini de biliriz. Hangi anormal proteini ürettiğini bulduğumuz zaman, hedefe yönelik tedaviyi kullanabiliriz.

Hedefe Yönelik Tedaviler

- Kanser hücresinin yüzeyindeki veya içindeki anormal çalışan proteinleri hedef alırlar.

- Bir hücrey arlanırsa, anormal davranı

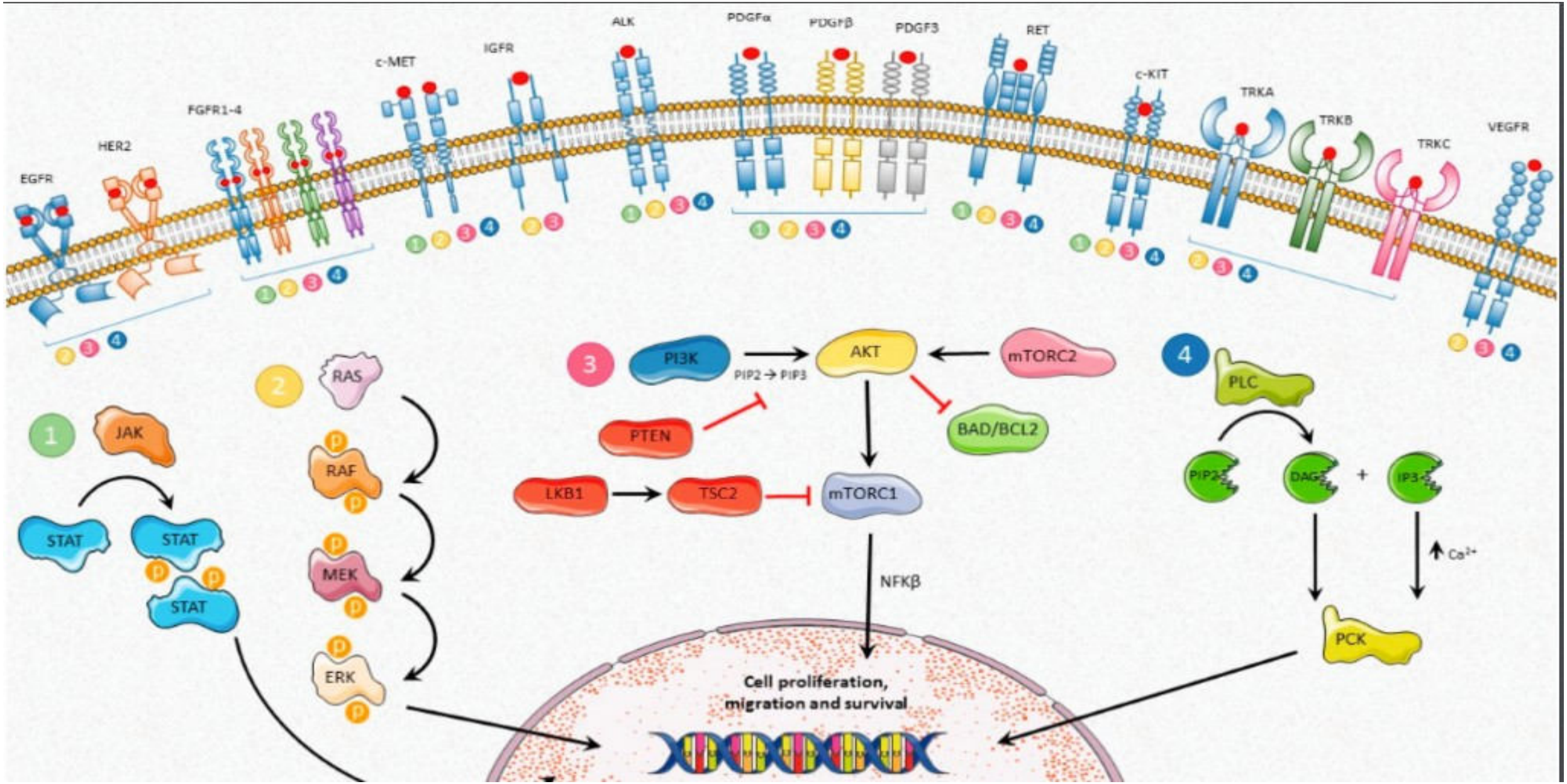
- Bir hücrenin proteini ürettiğini de biliriz. Hangi hata edefli tedaviyi kullanacağımızı biliriz.

HEDEF= DNA hasarı

Onkojenik mutasyonlar

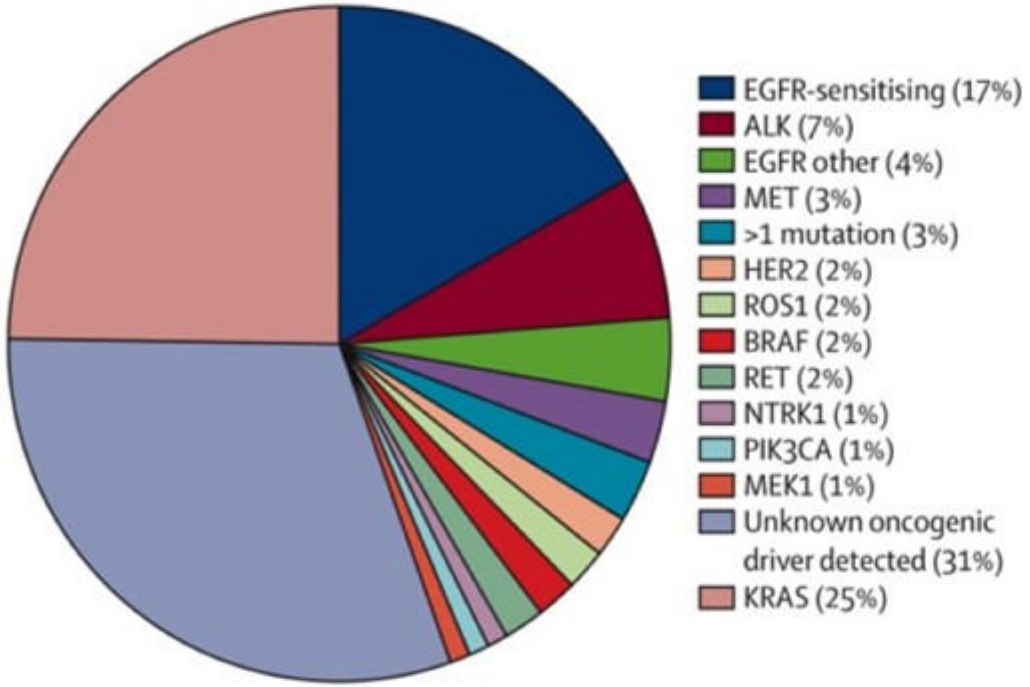
Target	Testing Methodologies
EGFR mutations*	PCR, NGS
BRAF mutations	PCR, NGS, IHC (extensive validation)
KRAS mutations	PCR, NGS
ALK rearrangements†	FISH,‡ NGS, IHC (screening)
ROS1 rearrangements†	FISH,‡ NGS, IHC (screening)
RET rearrangements†	FISH,‡ NGS
*MET*ex14 skipping mutations	NGS
NTRK rearrangements†	FISH,‡ NGS, IHC
MET amplifications	FISH, NGS
HER mutations	PCR, NGS
Tumor mutational burden	NGS

*Majority are L858R or ex19del; ~ 10% are uncommon variants, including exon 20 insertions.
†Real-time qPCR will miss novel fusion partners.
‡Using break-apart probes designed to detect rearrangements.


EGFR
HER2
FGFR1-4
c-MET
IGFR
ALK
PDGFα
PDGFβ
PDGF3
RET
c-KIT
TRKA
TRKB
TRKC
VEGFR
1
JAK
STAT
STAT
STAT
2
RAS
RAF
MEK
ERK
3
PI3K
PIP2 → PIP3
AKT
mTORC2
PTEN
BAD/BCL2
LKB1
TSC2
mTORC1
NFKβ
4
PLC
PIP2
DAG
+
IP3
Ca2+
PCK
Cell proliferation,
migration and survival

Non-skuamoz akciğer kanseri

Frequency of Molecular Aberrations in Driver Oncogenes in Lung Adenocarcinomas[a]



ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.
*FDA breakthrough designation.

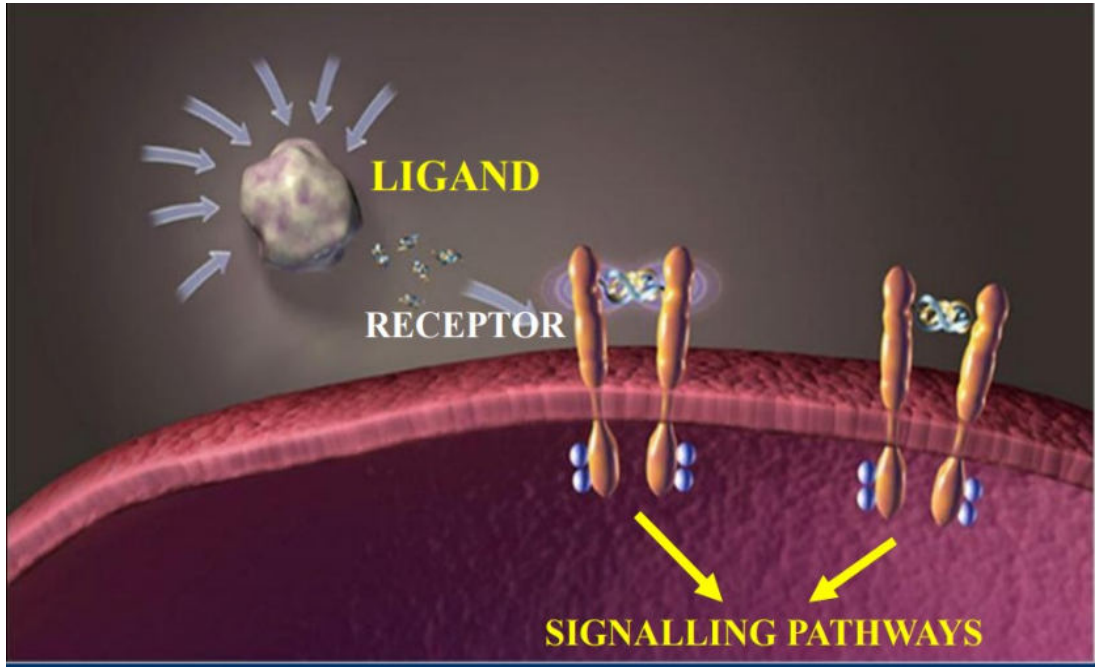
Approved Targeted Agents[b-d]

Target	Approved Drug(s)
EGFR	Gefitinib, erlotinib, afatinib, dacomitinib, osimertinib, erlotinib/ramucirumab patritumab deruxtecan*
EGFR exon 20	Amivantamab, mobocertinib, sunvozertinib*, CLN-081*
ERBB2 (*HER2*) exon 20	Trastuzumab deruxtecan
ALK	Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib
ROS1	Crizotinib, entrectinib, repotrectinib*, taletrectinib*
NTRK 1/2/3	Larotrectinib, entrectinib, repotrectinib*
RET	Pralsetinib, selpercatinib
MET exon 14	Capmatinib, tepotinib
MET high	Telisotuzumab vedotin*
BRAF V600E	Dabrafenib-trametinib
KRAS G12C	Sotorasib, adagrasib*

Hedefe Yönelik Tedaviler

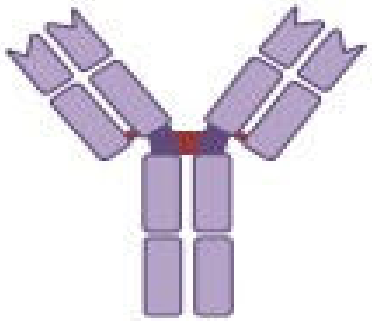
1. Monoklonal Antibodiler (Mab)

2. Kinaz İnhibitörleri (TKİ)



Monoklonal Antibodiler

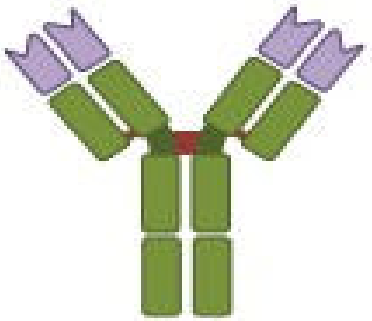
-mab



mouse

tositumomab

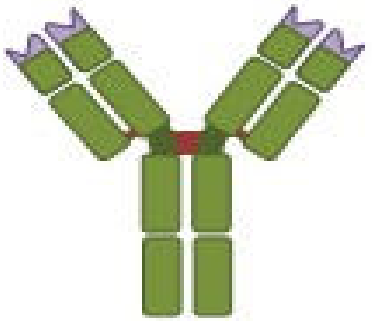
ibritumomab



chimeric

cetuximab

rituximab



humanized

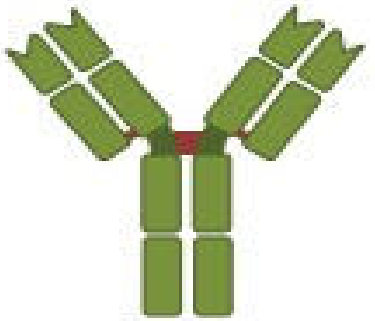
trastuzumab

bevacizumab

pertuzumab

pembrolizumab

atezolizumab



fully human

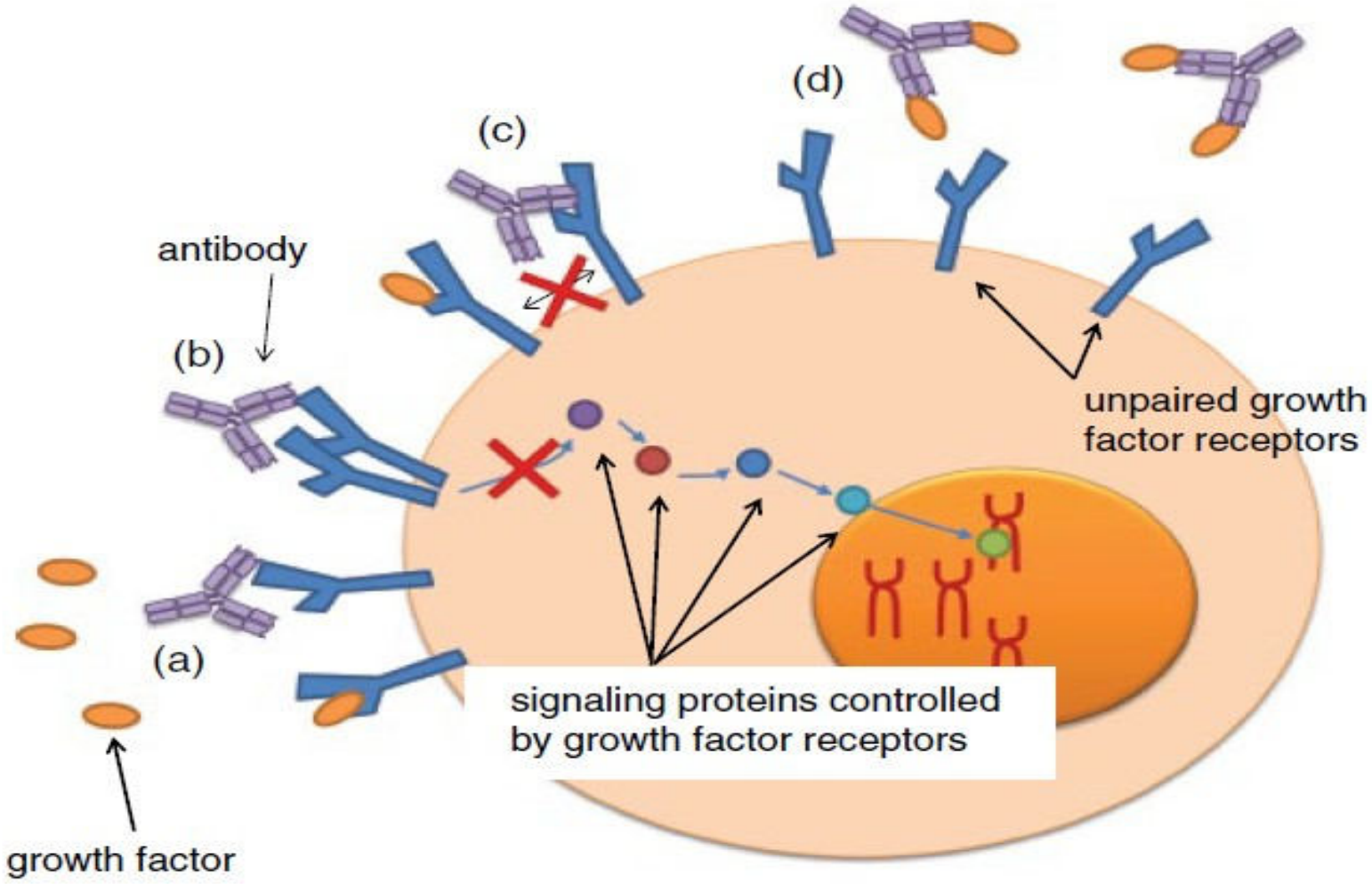
panitumumab

ofatumumab

nivolumab

durvalumab

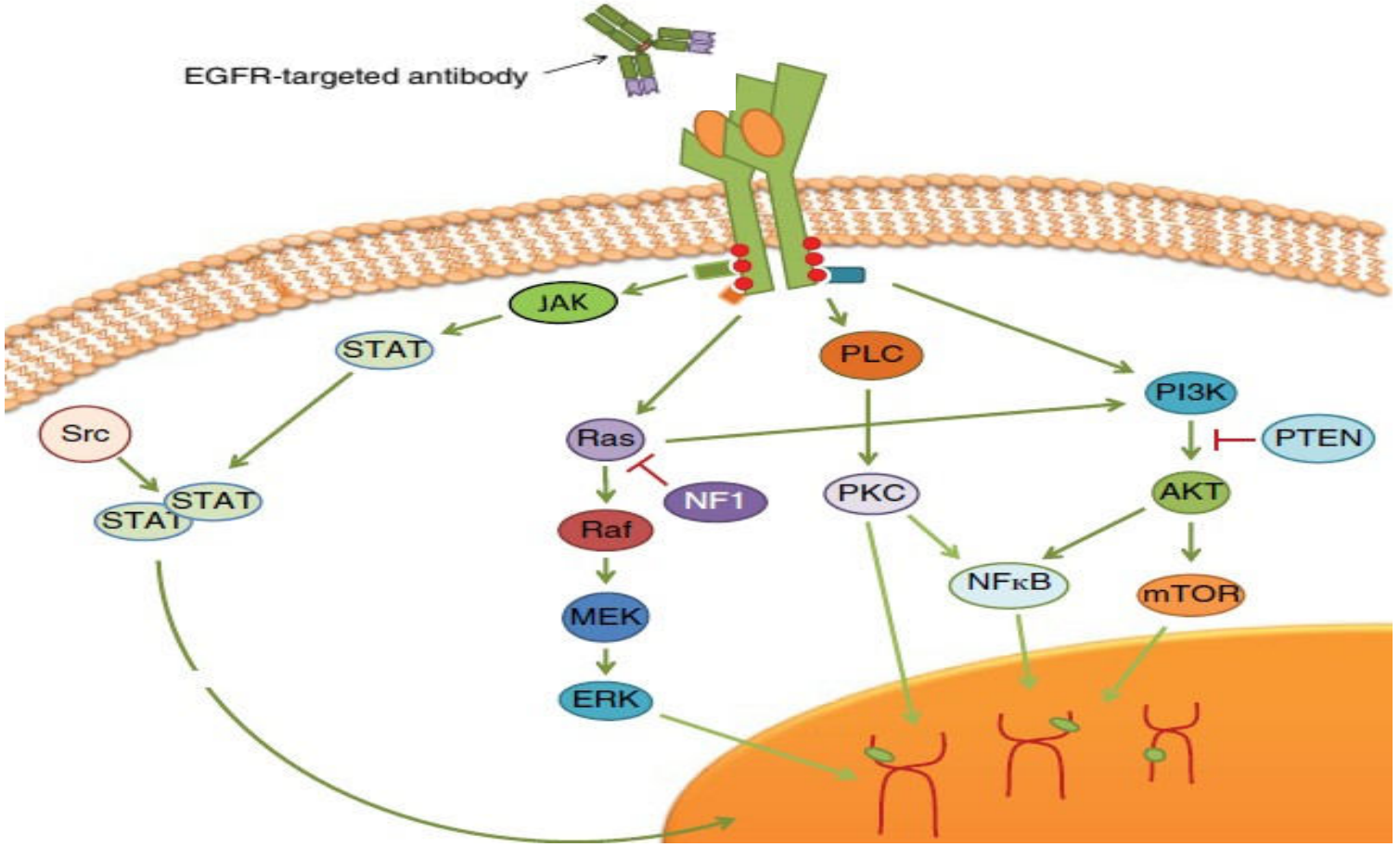
Monoklonal Antibodiler



Anti-EGFR Mab

-Cetuximab

-Panitumumab

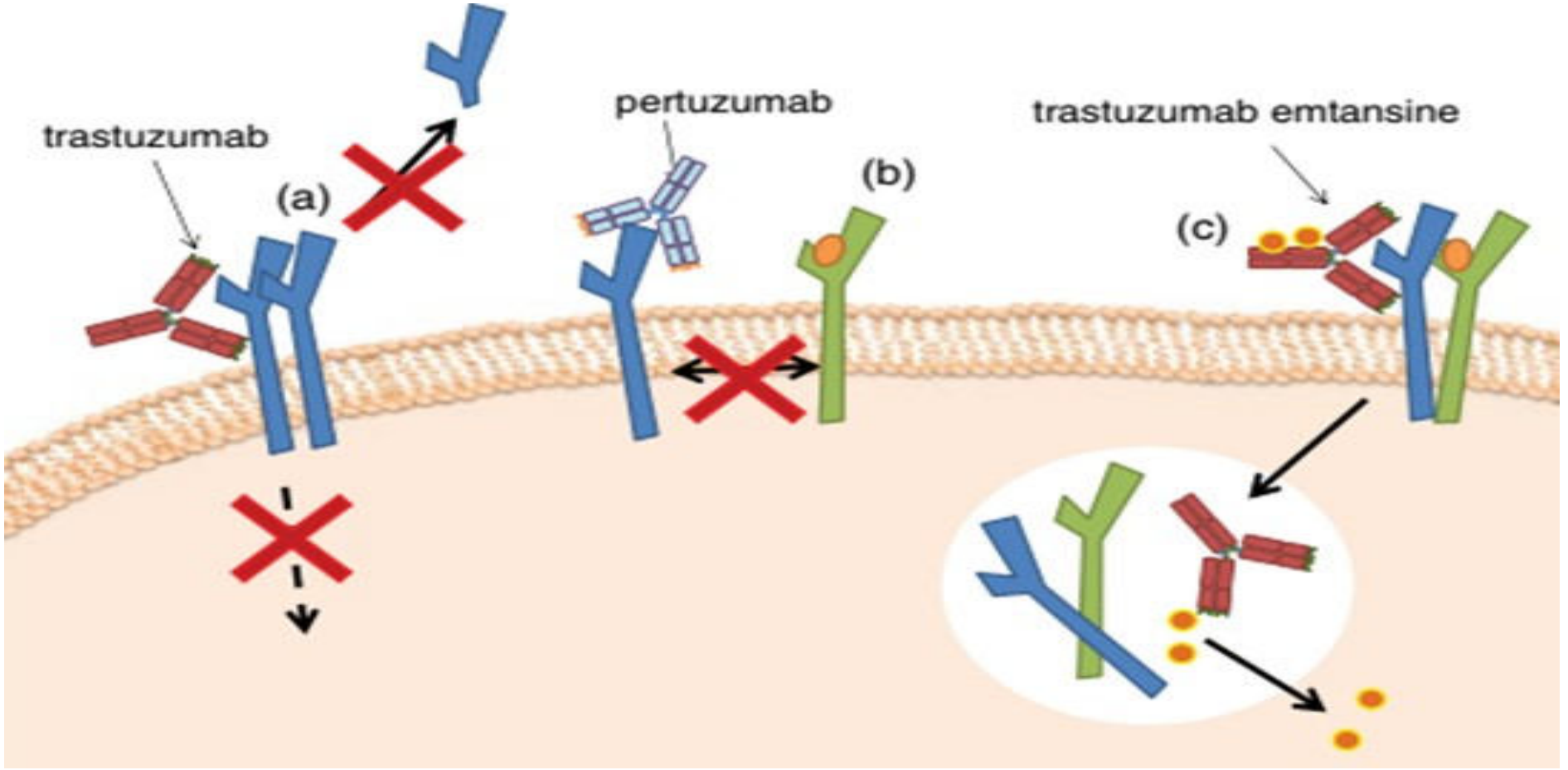


Anti Her-2 Mab

-Trastuzumab

-Pertuzumab

-Trastuzumab-emtansine (TDM-1)

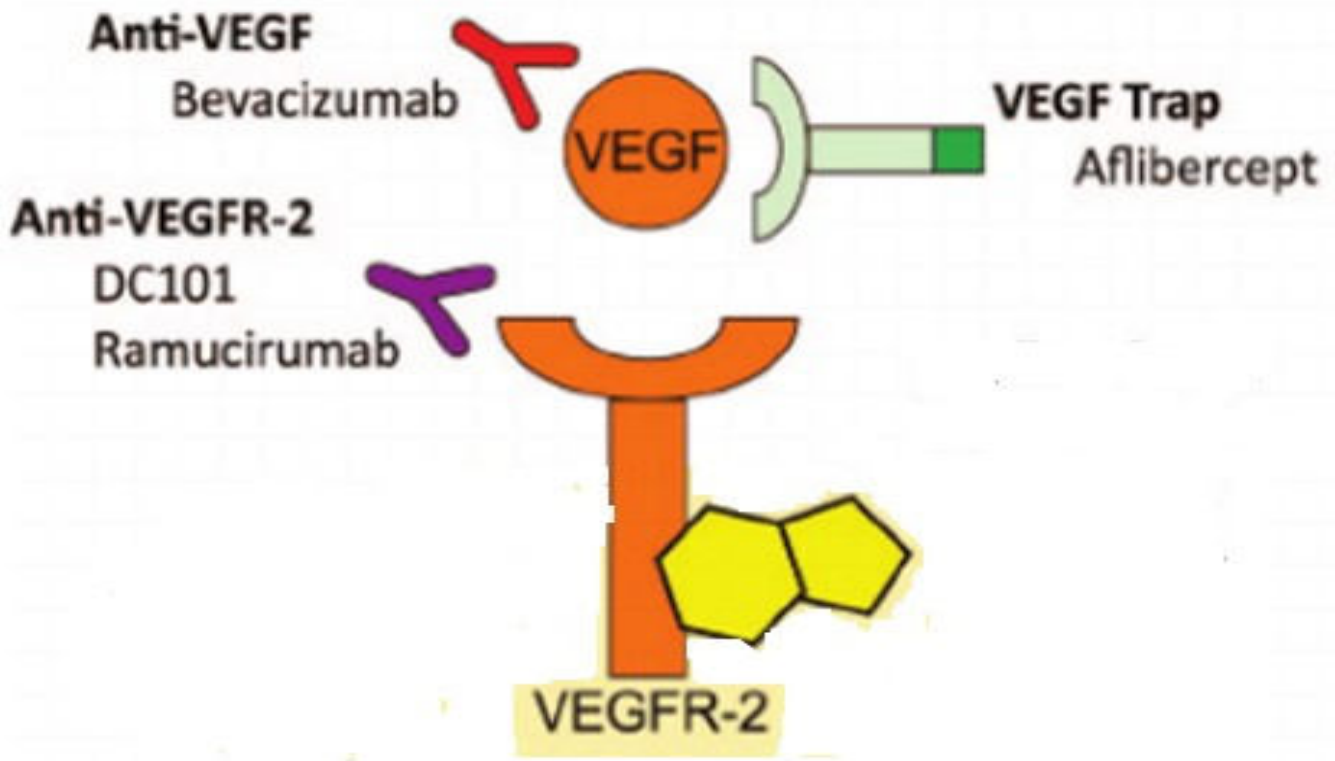


Anti-VEGF(R) Mab

Bevacizumab

Ramucirumab

Aflibercept



Kinaz İnhibitörleri

-nib

Sunitinib

Sorafenib

Pazopanib

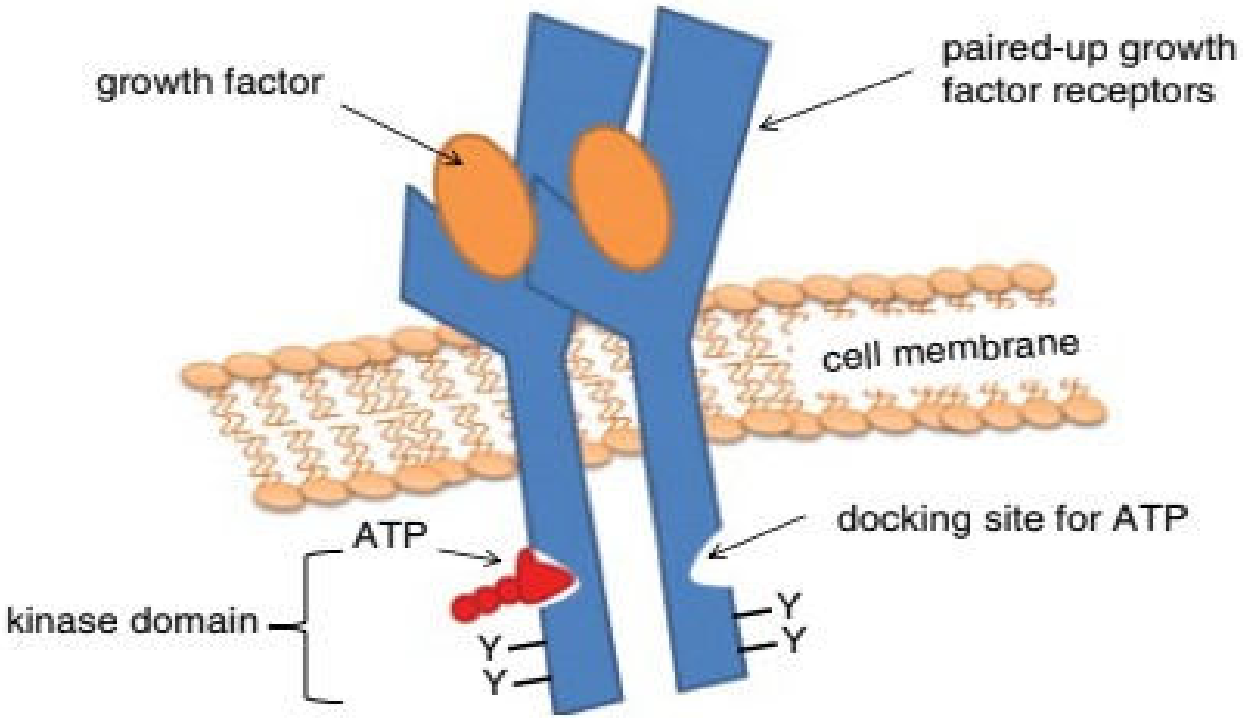
Erlotinib

Afatinib

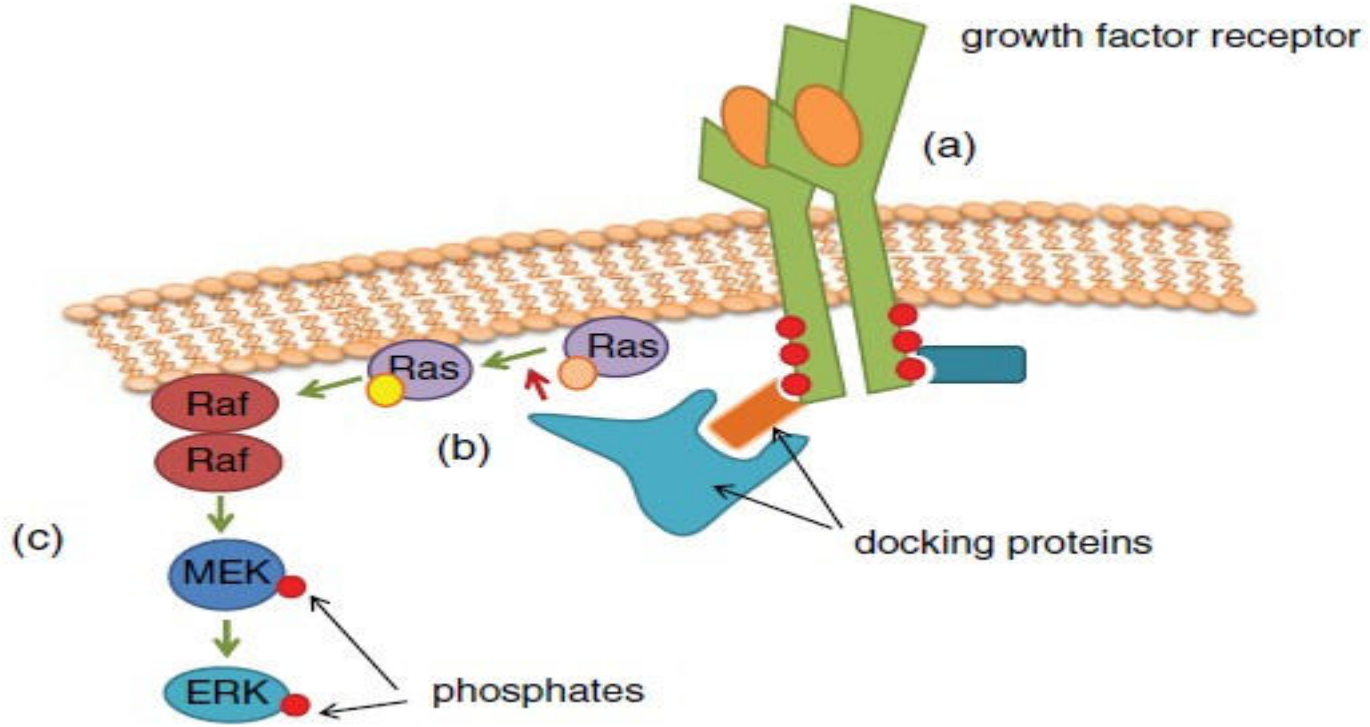
Gefitinib

Lapatinib

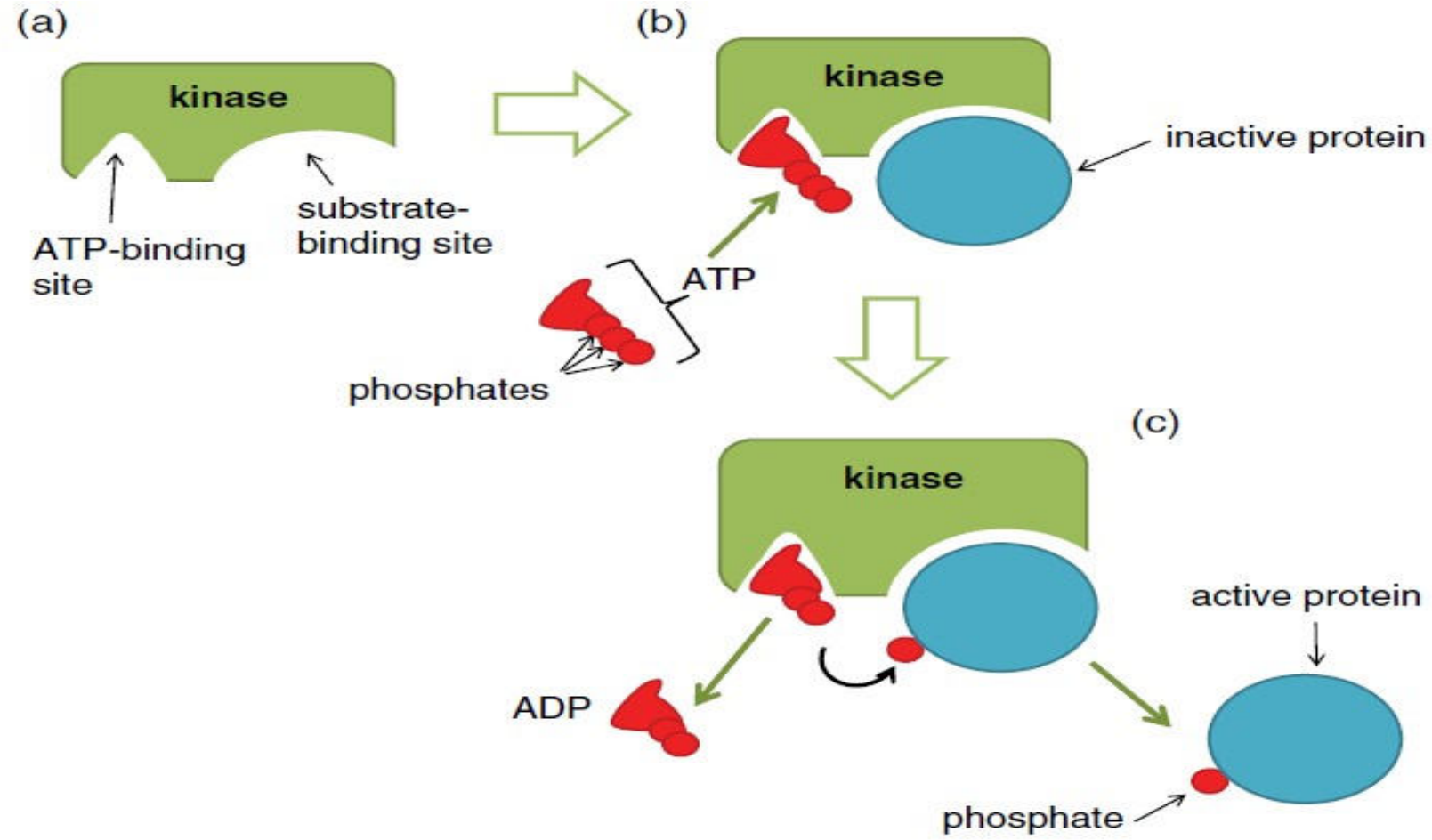
Vandetanib



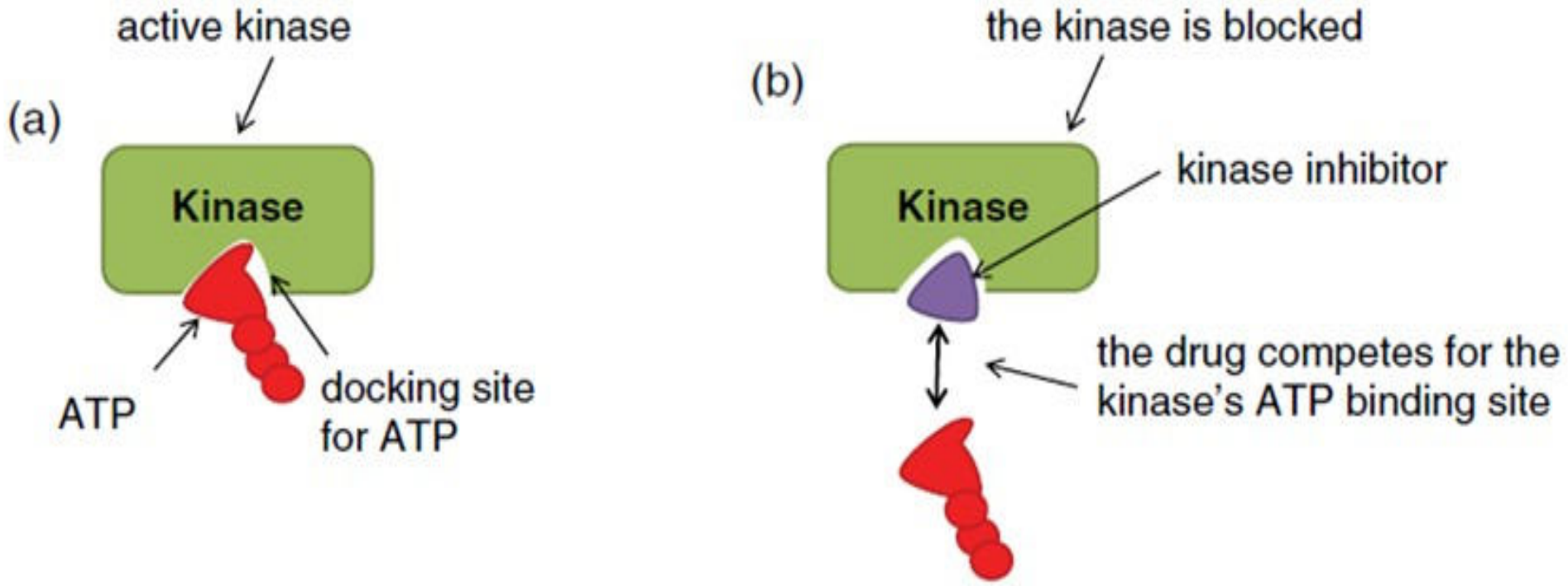
Kinazlar


growth factor receptor
(a)
Ras
Ras
Raf
Raf
(b)
(c)
MEK
ERK
phosphates
docking proteins

Kinazlar


(a)
kinase
ATP-binding site
substrate-binding site
(b)
kinase
inactive protein
ATP
phosphates
(c)
kinase
active protein
ADP
phosphate

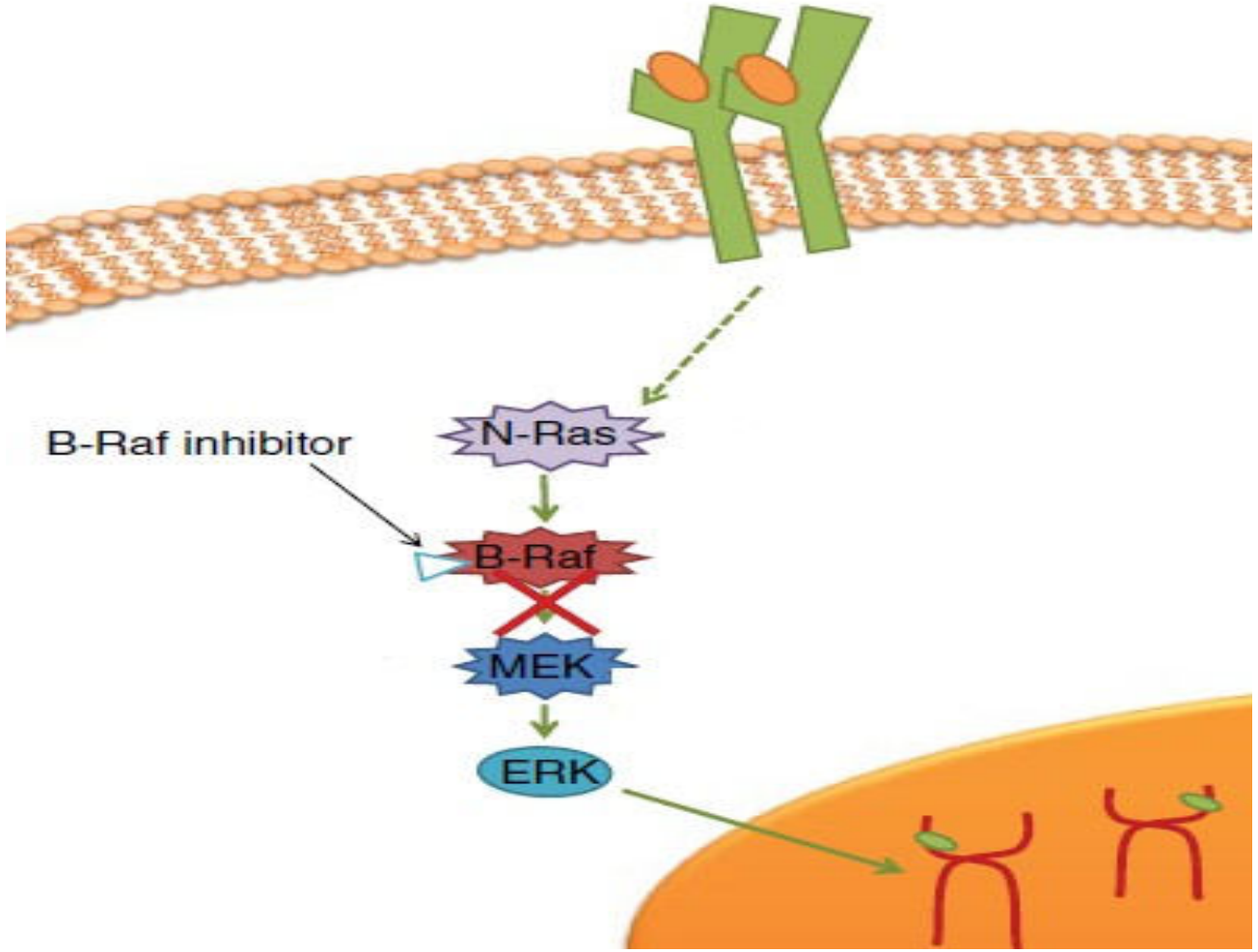
Kinaz İnhibitörleri



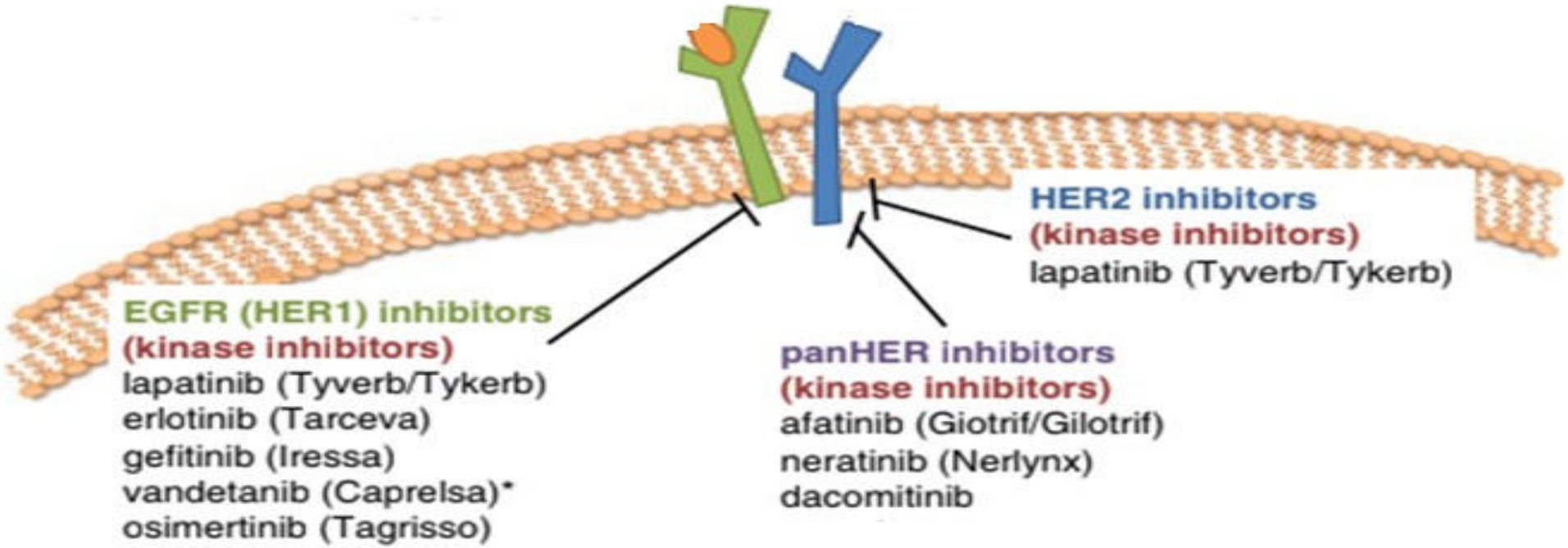
Anti-BRAF TKİ

-Vemurafenib

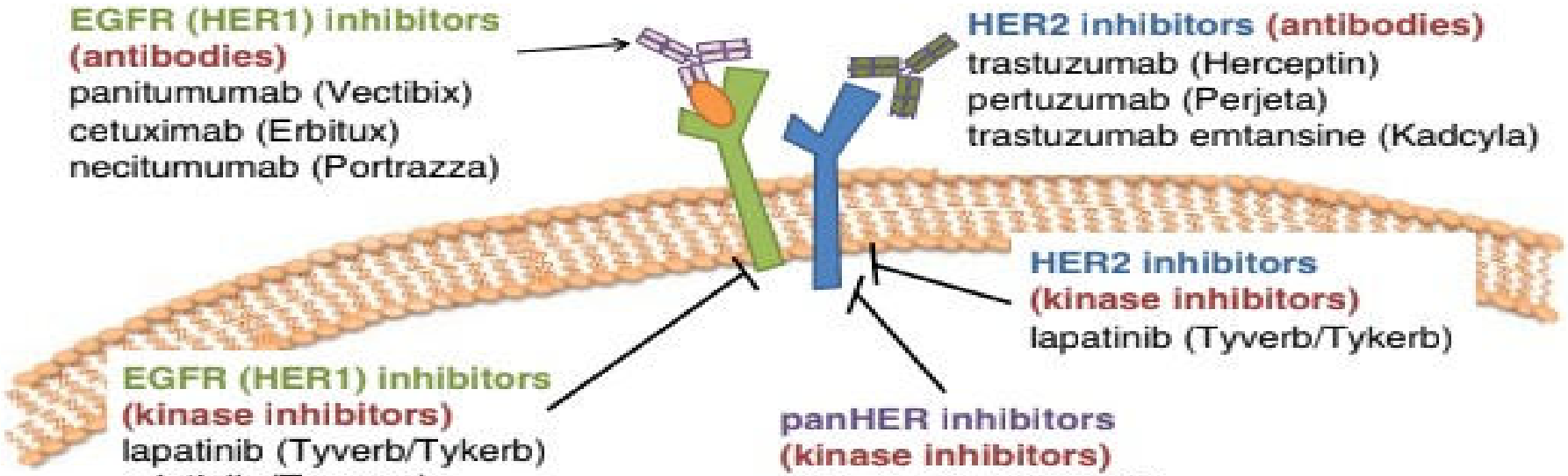
-Dabrafenib



Anti-EGFR TKİ

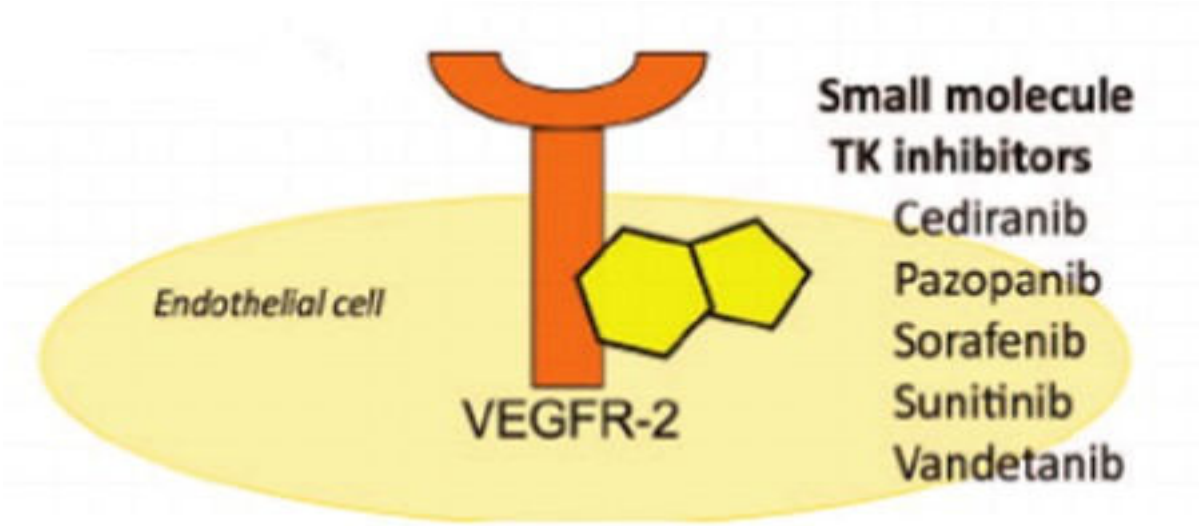


EGFR inhibitörleri (TKİ ve Mab)

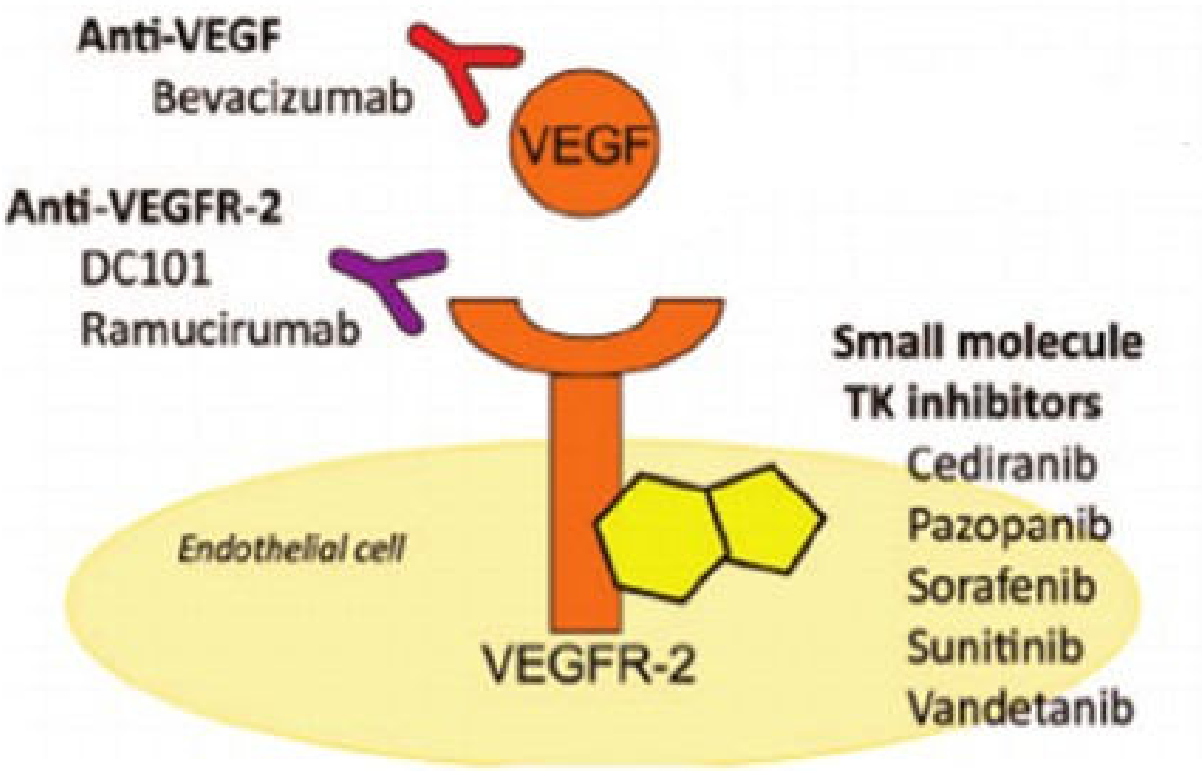


* As well as blocking EGFR, vandetanib also blocks VEGF receptors and RET

Anti-VEGFR TKİ



VEGF inhibitörleri (TKİ ve Mab)



HEDEFE YÖNELİK TEDAVİLER

Mab (monoklonal antikorlar)

- ✓Büyük olduklarından hücre membranını geçememe
- ✓Tek antijen inhibisyonu
- ✓Sınırlı etki ve yan etki
- ✓Intravenöz/subkutan
- ✓Uzun yarılanma ömrü, haftada/ayda bir

TKİ (tirozin kinaz inhbitörleri)

- ✓Daha fazla penetrasyon, kan-beyin bariyeri ulaşımı
- ✓Multipl kinaz inhibisyonu
- ✓Fazla yan etki, daha potent
- ✓Tablet
- ✓Kısa yarılanma ömrü, günde 1 veya 2 kez

Yan Etkiler

Substance-spesifik, sınıf yan etkileri

- Anti-VEGF
- Anti-EGFR
- Anti-Her2

Yan Etkiler

Anti-VEGF:

- hipertansiyon (%42)
- proteinüri (%5)
- Kanama (%9-30)
- intestinal perforasyon
- yara iyileşmesinde gecikme(%10)
- hafif myelosupresyon (%4-6)
- Diare (%52)
- Hepatotox (%53)
- Stomatit(%25-40)
- el-ayak reaksiyonu (%11)
- tiroid disfonksiyonu (18-90%)
- PRES (<%1)

Yan Etkiler

Anti-EGFR:

- döküntü (%90)
- diare (%30-40)
- pulmoner toksisite (<%1)

Yan Etkiler

Anti-Her2:

- kardiyak toksisite (%2.5)
- diare (%15-30)
- pulmoner toksisite (<%1)

Vaka

- 50 yaş, kadın
- Sol nefrektomi: RCC, stage II
- 20 yıl sonra pankreas metastazı ile prezente .
- Tedavi: Pazopanib (VEGFR, PDGFR, KIT reseptör TKİ), 800 mg/gün başlandı.
- 2 hafta sonra günde 10 kez olan diare başladı.

Yan Etkiler

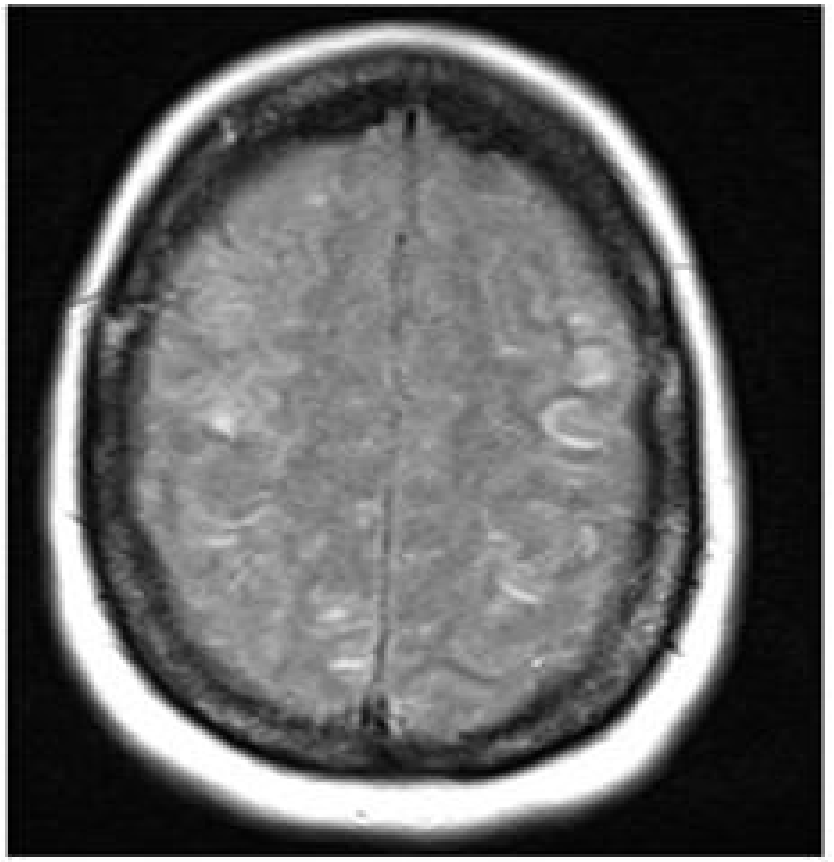
- Doz bağımlıdır.
- Prognostiktir.
- Tedavi: ilacın durdurulması ve şikayete göre destek tedavi
- Şikayet gerilediğinde düşük doz ile ilaca başlanır (fatal olabilecek yan etki gelişti ise kalıcı olarak ilaç kesilir.)

Vaka

- Pazopanib durduruldu
- Loperamide ile ishal kontrol altına alındı
- Pazopanib yarı dozda tekrar başlandı(400mg/gün)
- 3 ay sonra görüntülemelerde metastazlarda gerileme saptanmışken,
- Hastane otoparkında nöbet

Vaka

- Kranial MRI: bilateral parietal/oksipital loblarda subkortikal beyaz madde T2 de sinyal artışı

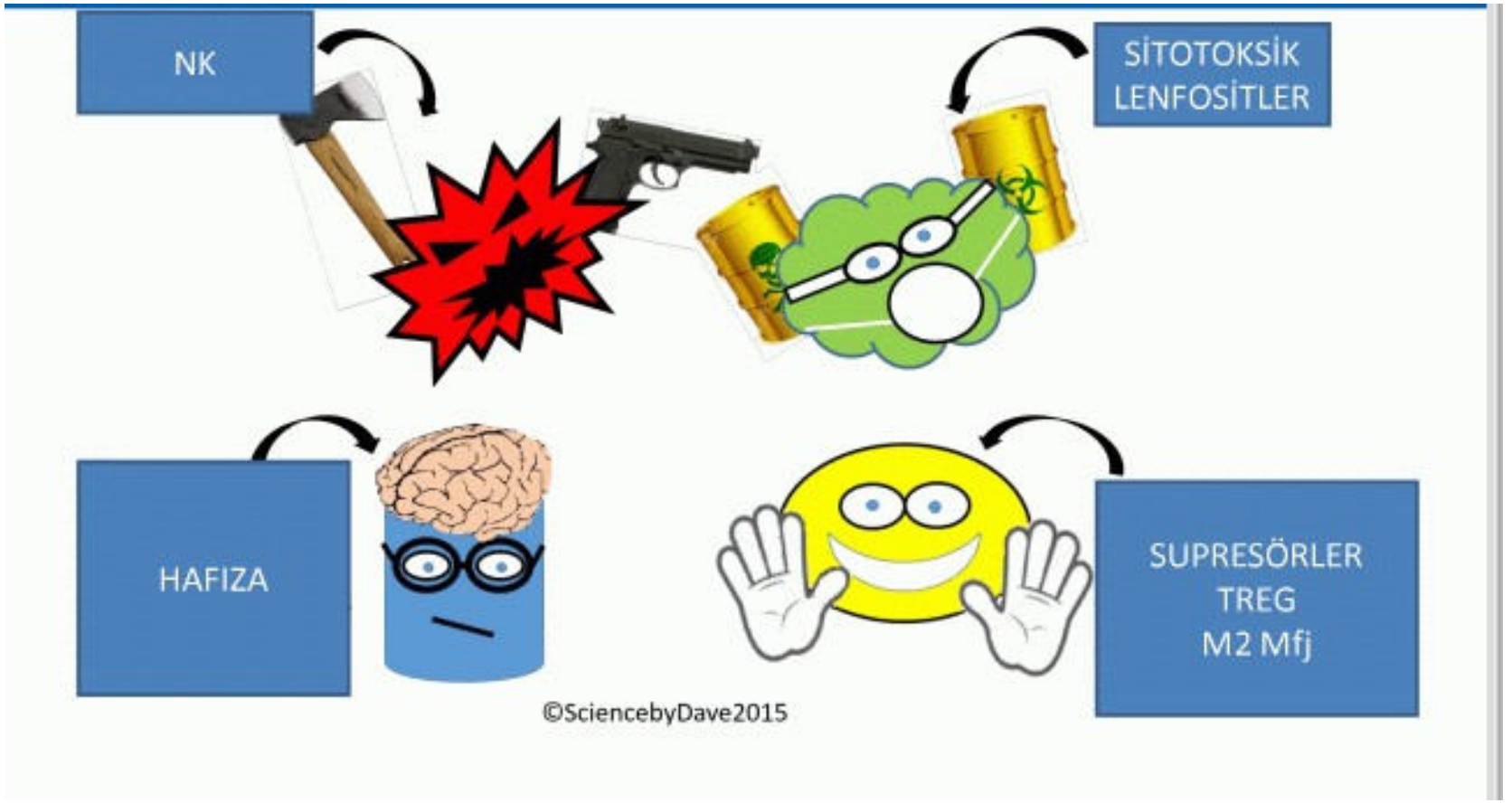


- Metastaz/kanama/enfeksiyon lehine değil
- İlaç ilişkili?
- PRES? (posterior reversible ensefalopati sendr)

Vaka

- Nöbet ve hipertansiyon için tedavi uygulandı.
- 3 hafta sonra kranial radyolojik bulgularda tama yakın gerileme saptandı
- Pazopanib kalıcı olarak kesildi.

İmmunoterapi



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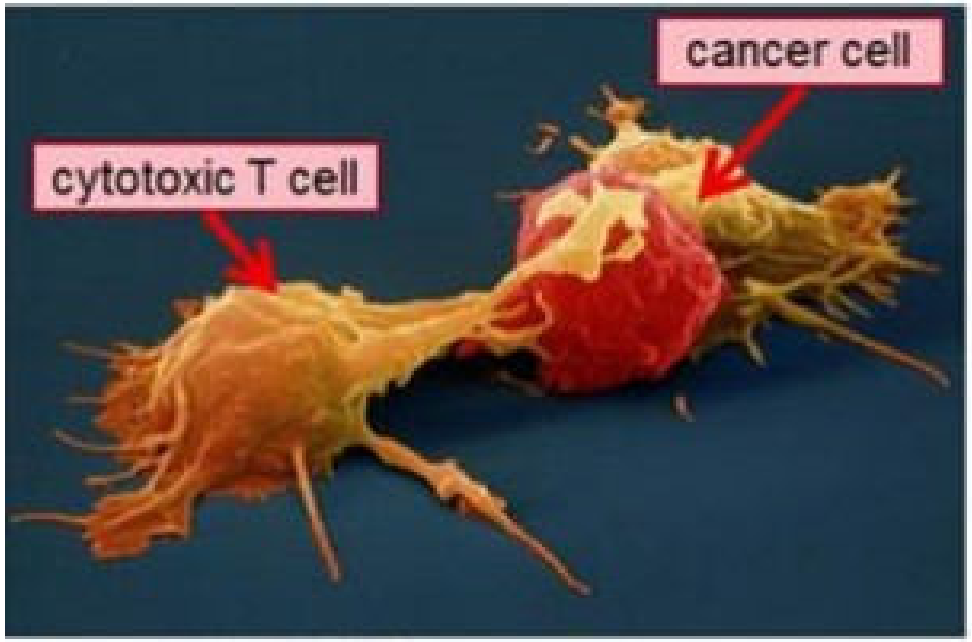


Image courtesy of MSKCC. Link

İmmunoterapi

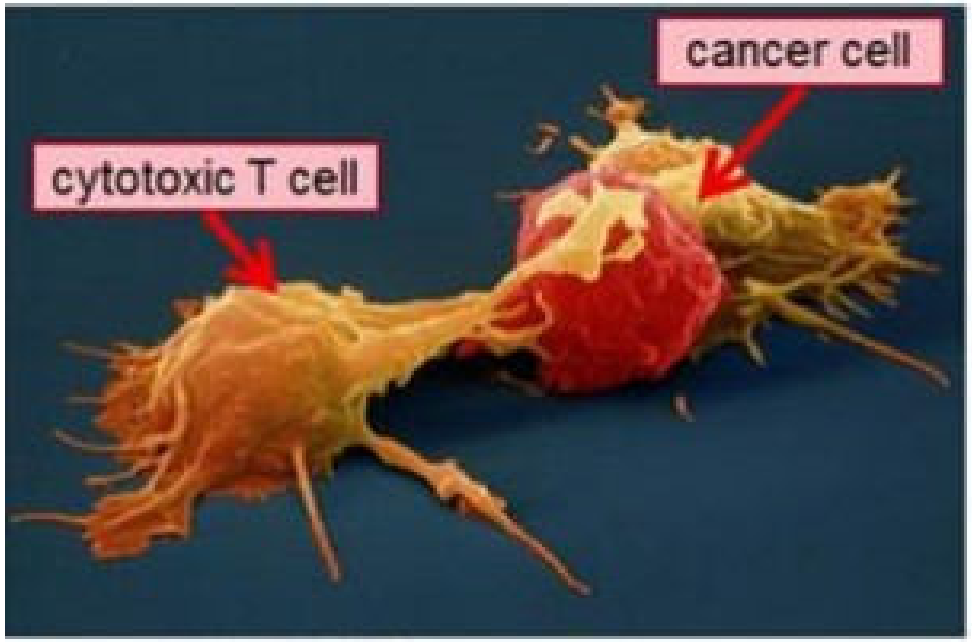
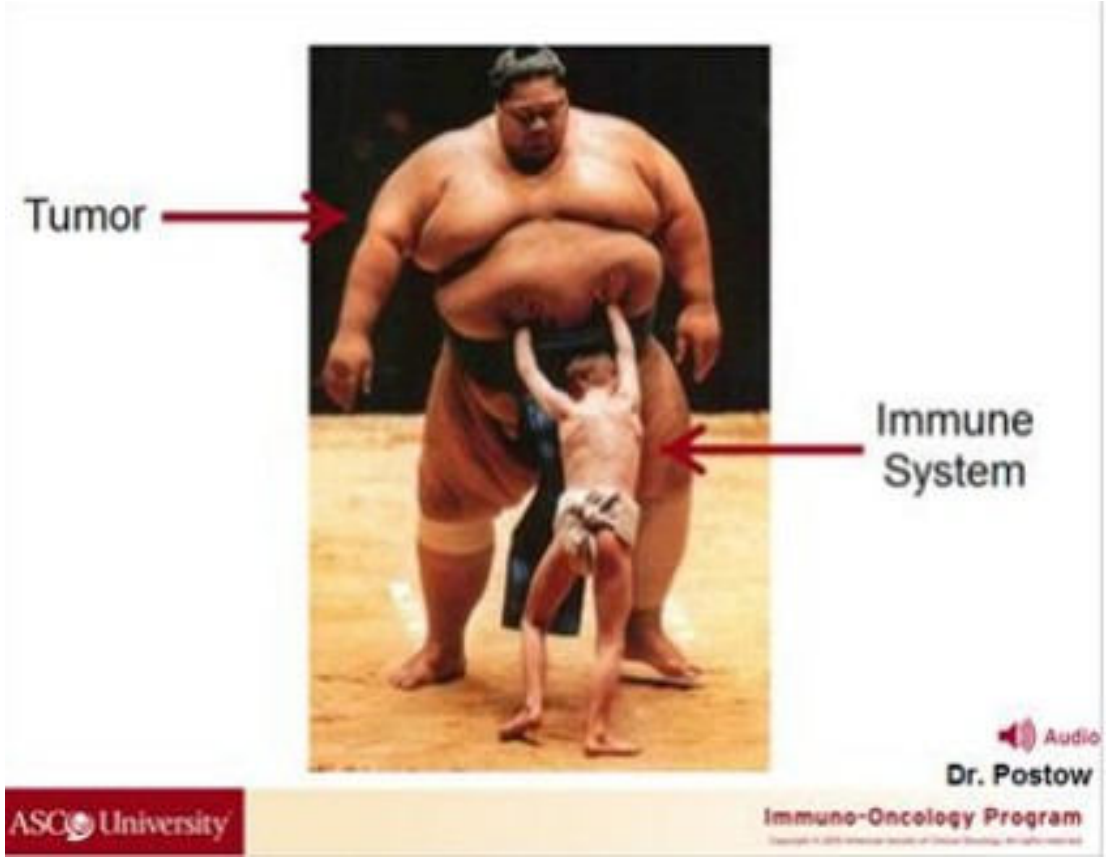


Image courtesy of MSKCC. Link



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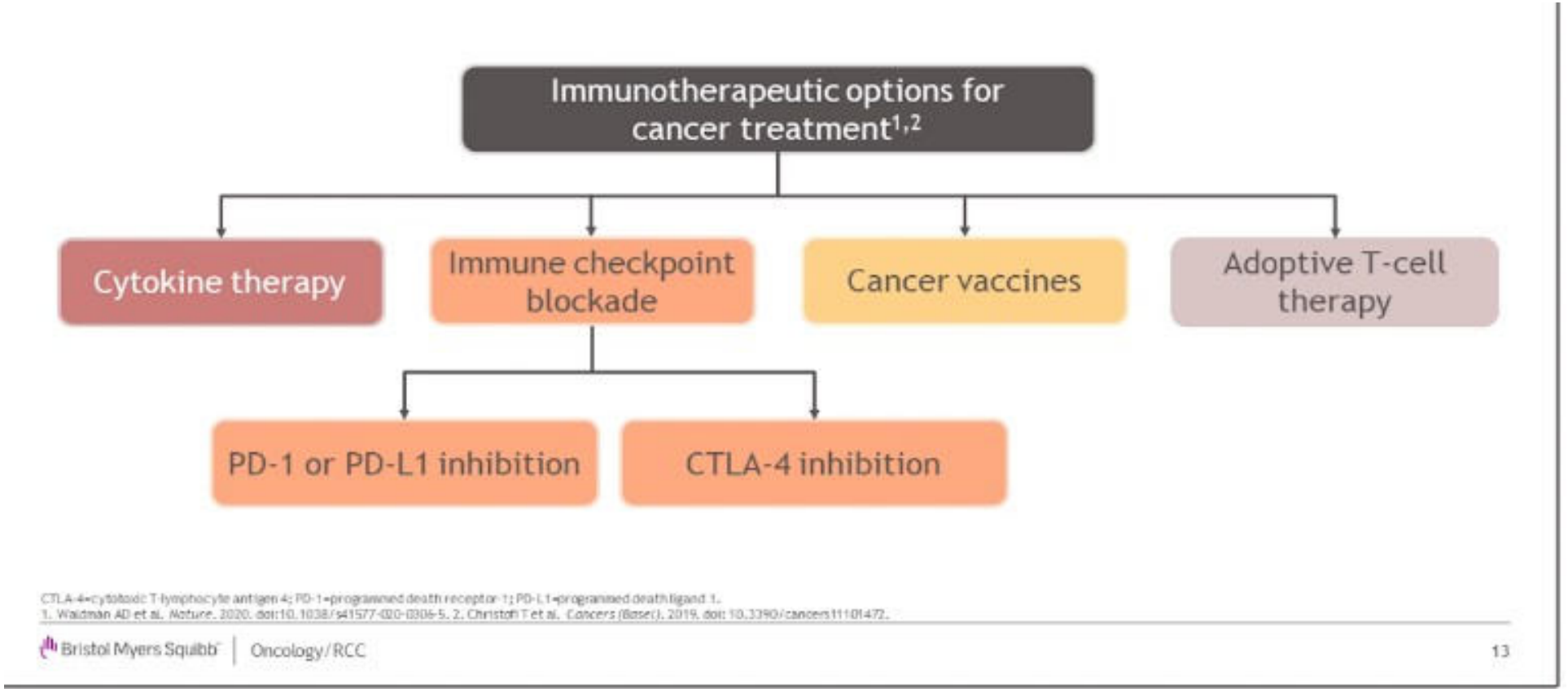

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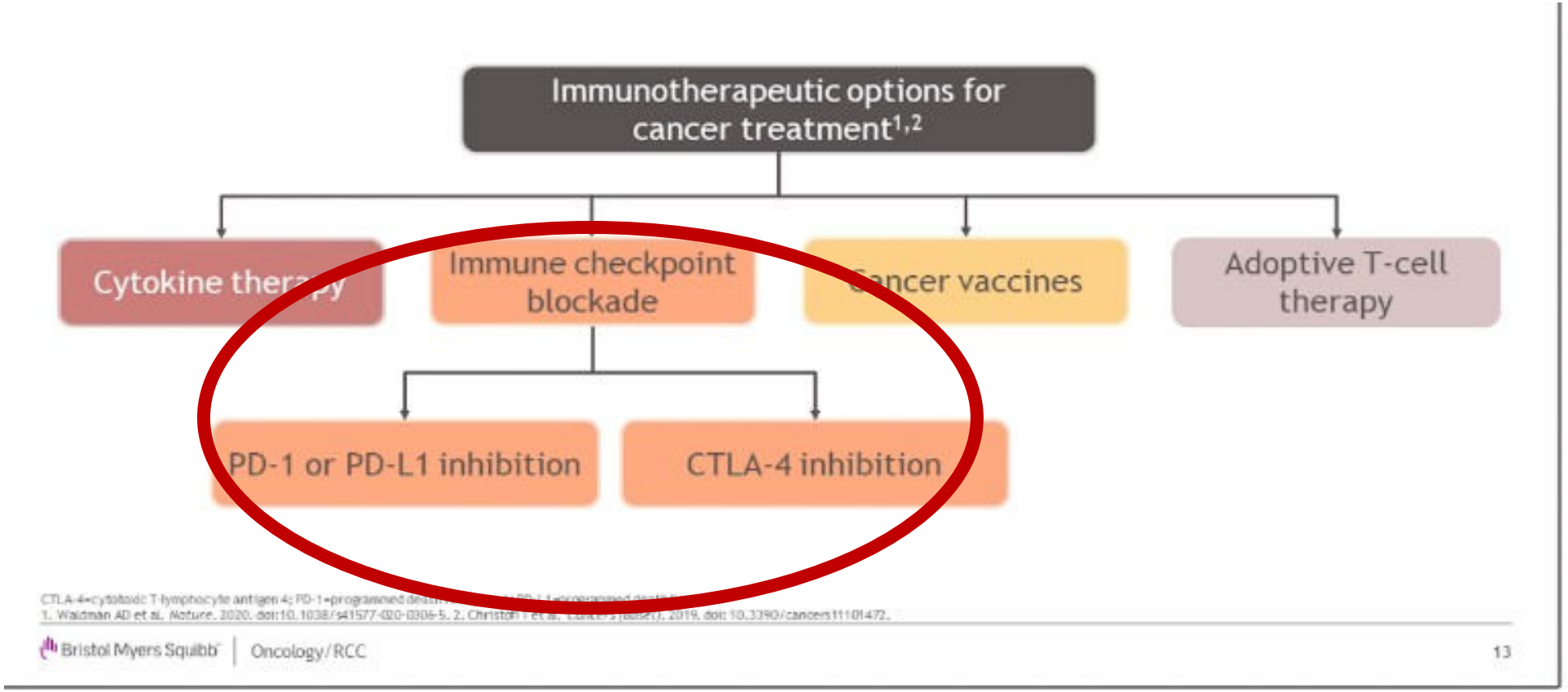
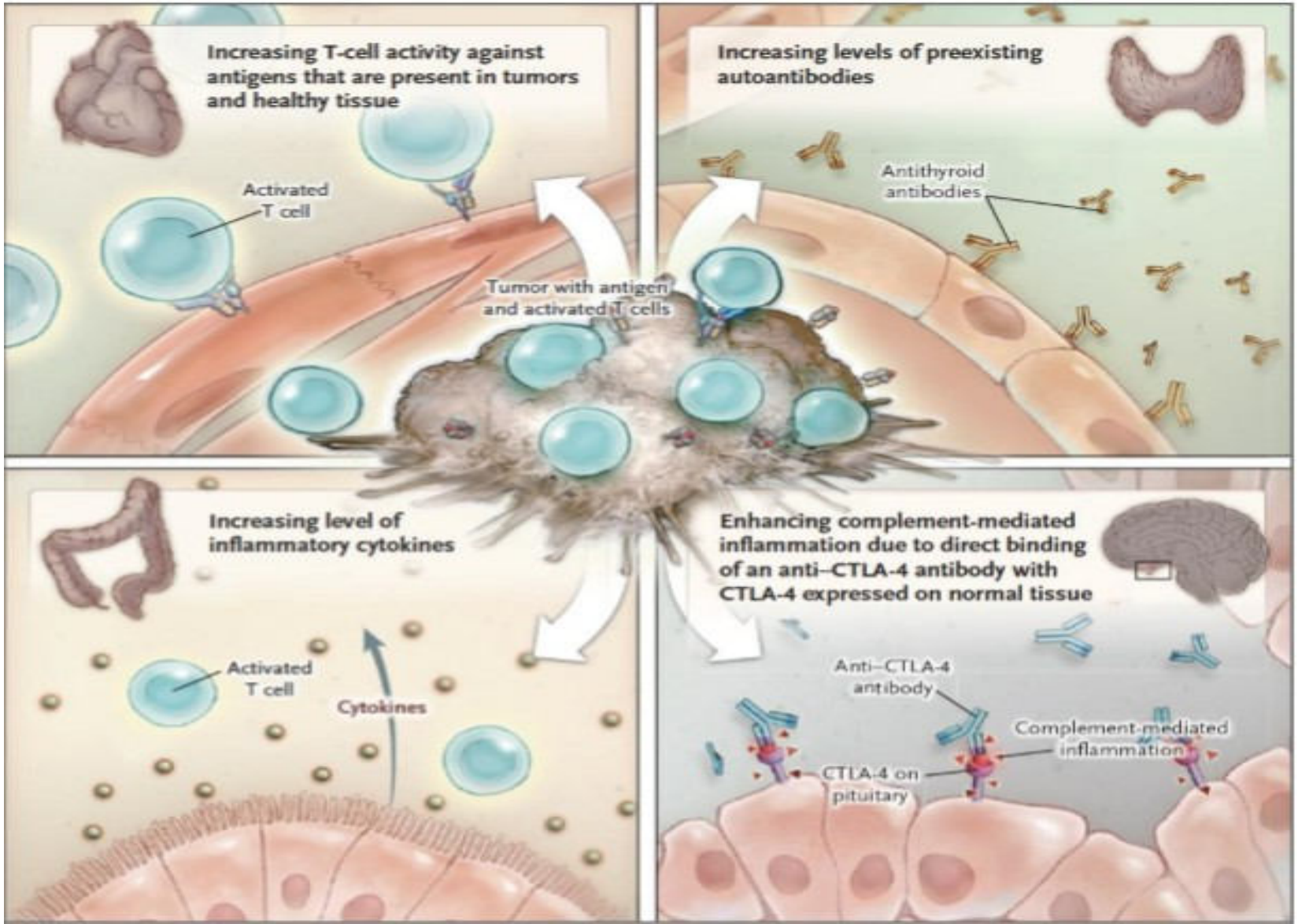


İmmun checkpoint inhibitörleri

- İpilimumab
- Nivolumab
- Pembrolizumab
- Atezolizumab
- Avelumab
- Durvalumab
- Dostarlimab

İmmun checkpoint inhibitörleri

İmmunoterapi yan etkiler



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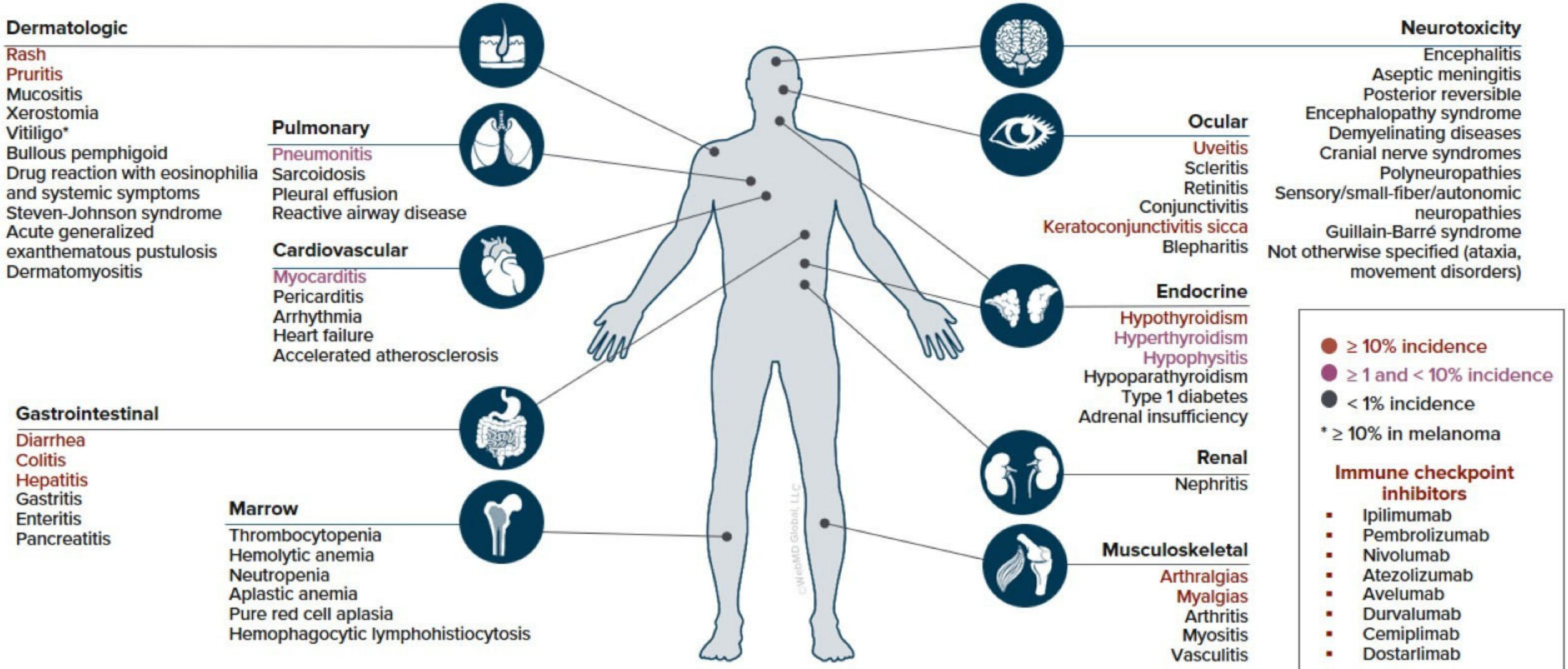
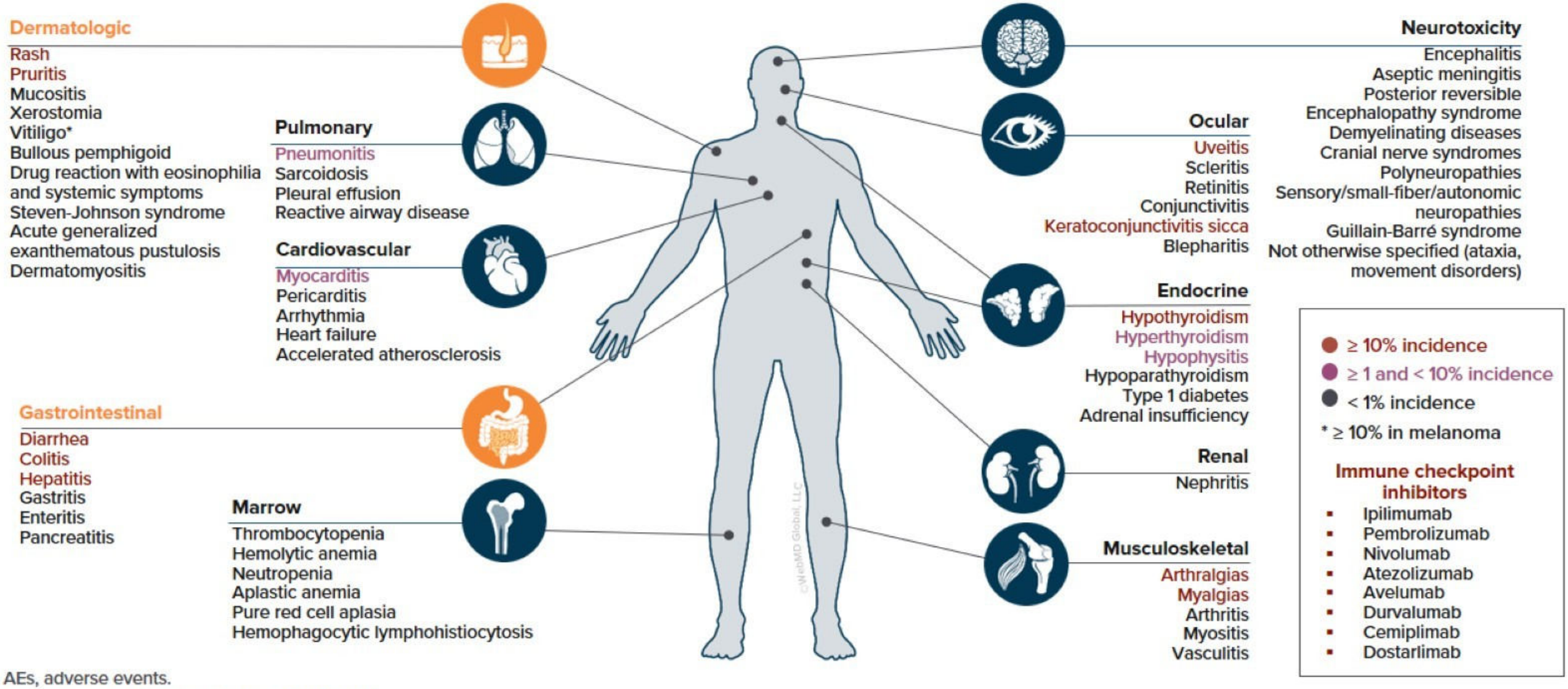


AEs, adverse events.

Darnell EP, et al. Curr Oncol Rep. 2020;22:39.

İmmunoterapi yan etkiler



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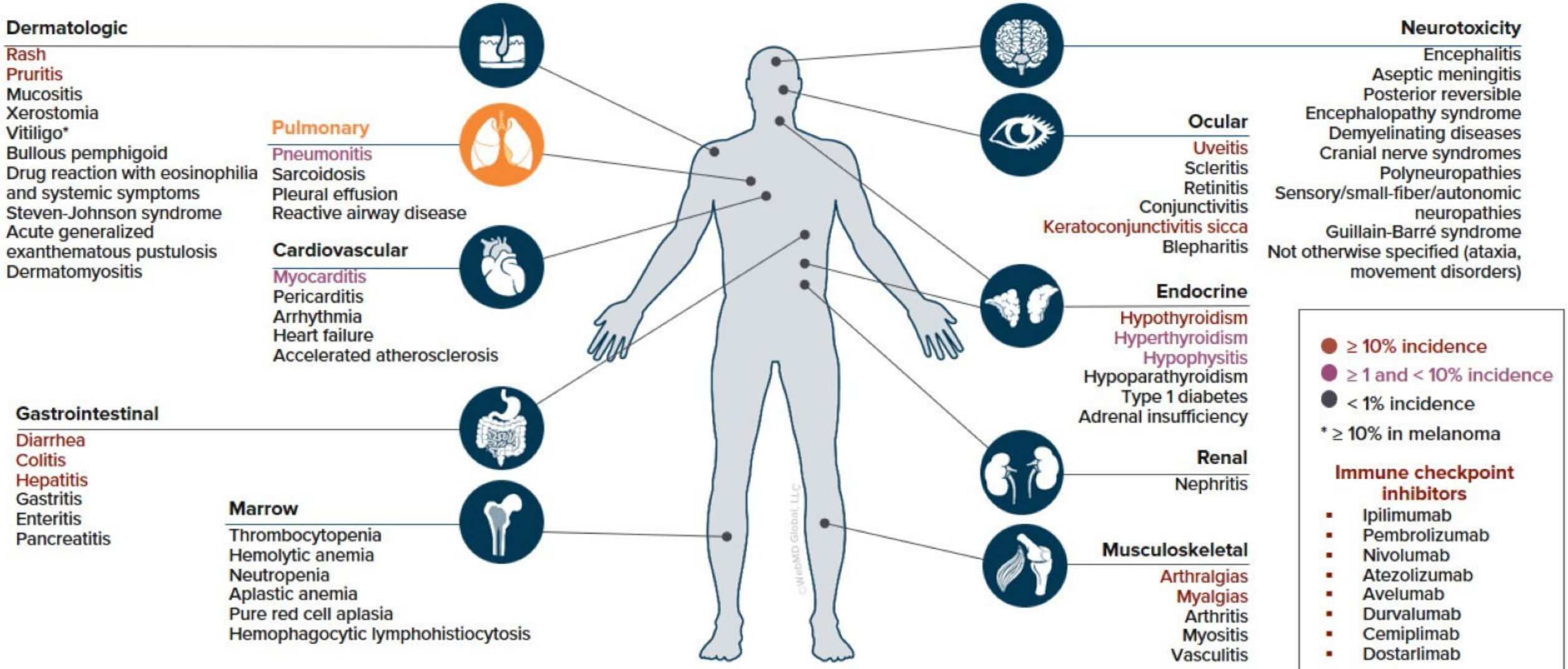

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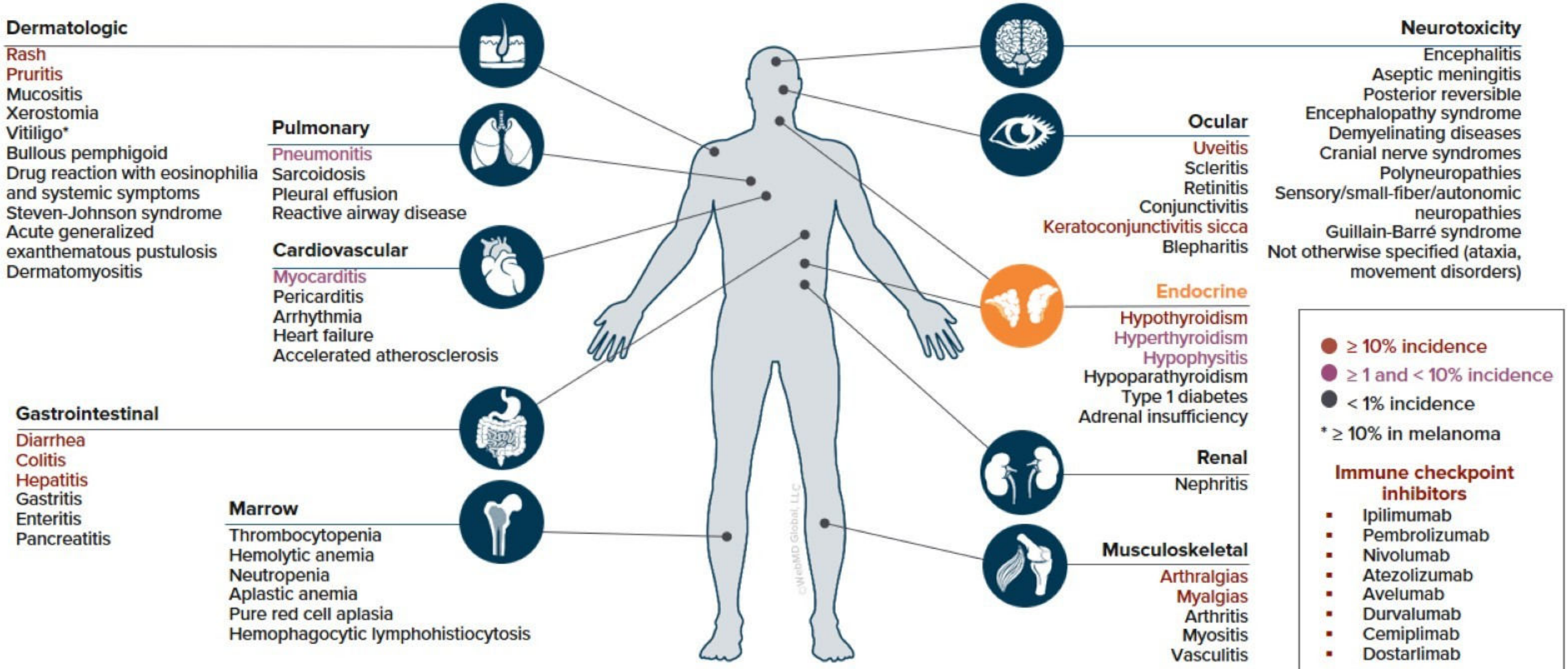


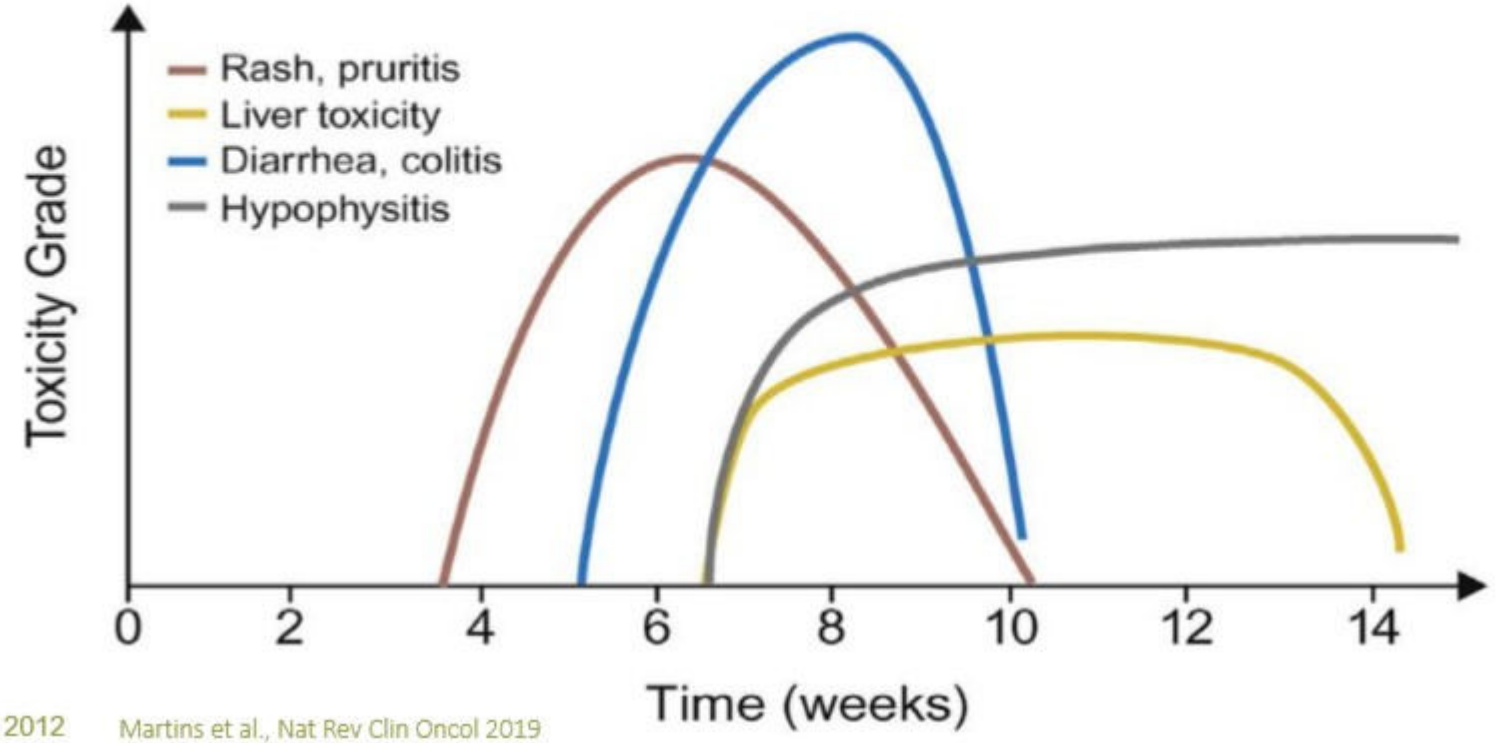
AEs, adverse events.

Darnell EP, et al. Curr Oncol Rep. 2020;22:39.

İmmunoterapi yan etkiler

İmmunoterapi yan etkiler

Study details		Any-grade adverse events (grade ≥3 adverse events)							
Study	Dose (n)	Diarrhoea	Colitis	Pulmonary	Rash	Neurological	Endocrinopathy	Hepatic	Renal
Ipilimumab									
EORTC 18071 (REF.[17])	10 mg/kg, 3-weekly (471)	41.2% (9.8%)	15.5% (8.2%)	–	34.2% (1.1%)	4.5% (1.9%)	37.8% (7.8%)	24.4% (10.9%)	–
Hodi et al.[108]	3 mg/kg, 3-weekly (131)	27.5% (4.6%)	7.6% (5.3%)	–	19.1% (0.8%)	–	7.6% (3.8%)	3.8% (0%)	–



Weber et al J Clin Oncol 2012

Martins et al., Nat Rev Clin Oncol 2019

İmmunoterapi yan etki yönetimi

ASCO special articles

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

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]; Jeffrey S. Weber, MD, PhD[25]; Pauline Funchain, MD[20]; and Kathryn Bollin, MD[26]

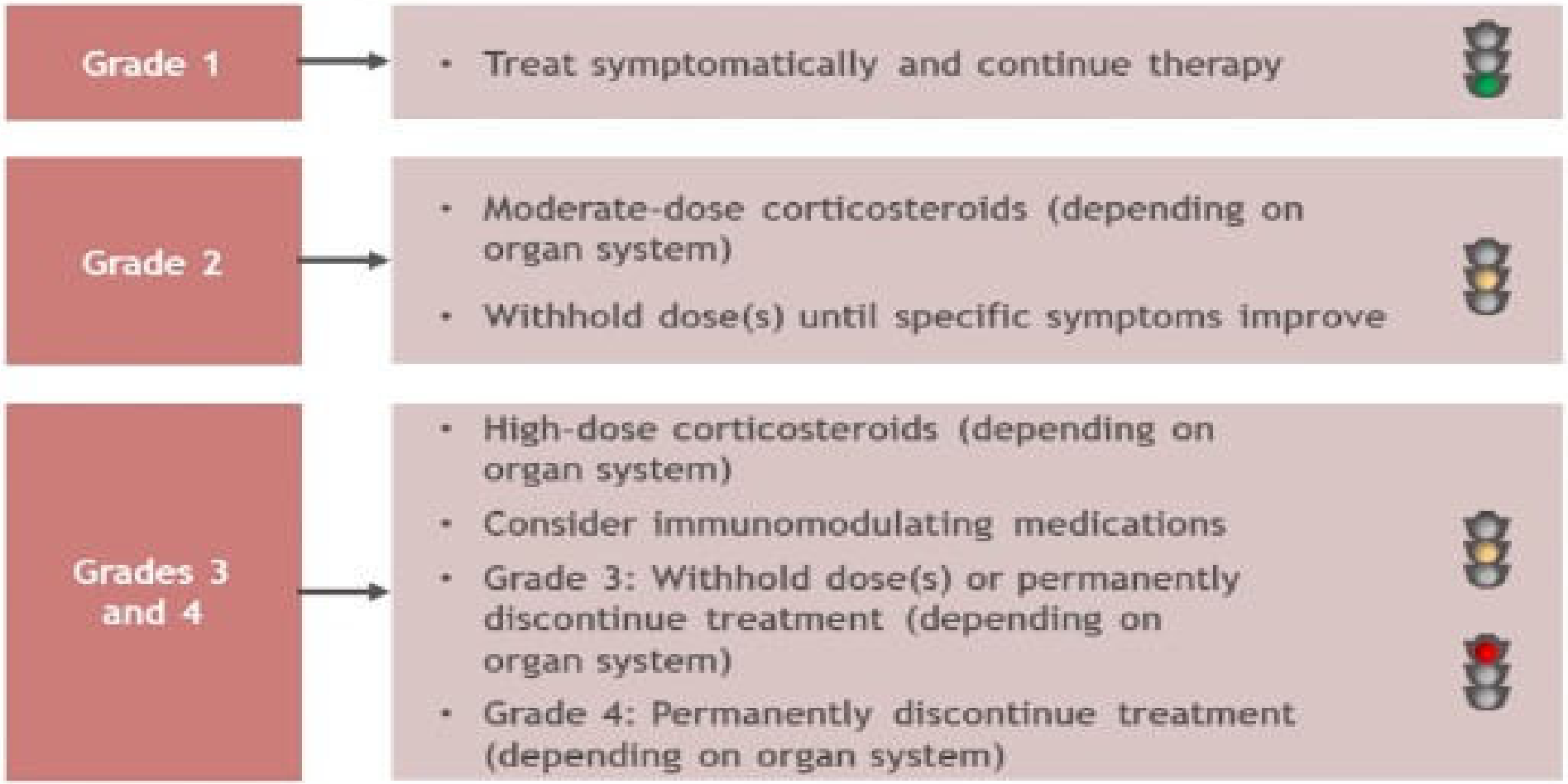
NCCN Guidelines Version 1.2022
Management of Immunotherapy-Related Toxicities

Management of Immunotherapy-Related Toxicities. Version 1.2022. Fort Washington (PA): National Comprehensive Cancer Network; February 2022 Brahmer JR, Lacchetti C, Schneider BJ, et al. J Clin Oncol. 2018 Jun 10;36(17):1714-1768.
Schneider BJ, Naidoo J, Santomasso BD, et al. J Clin Oncol. 2021 Dec 20;39(36):4073-4126.

CTCAE- (Common toxicity criteria for adverse events)

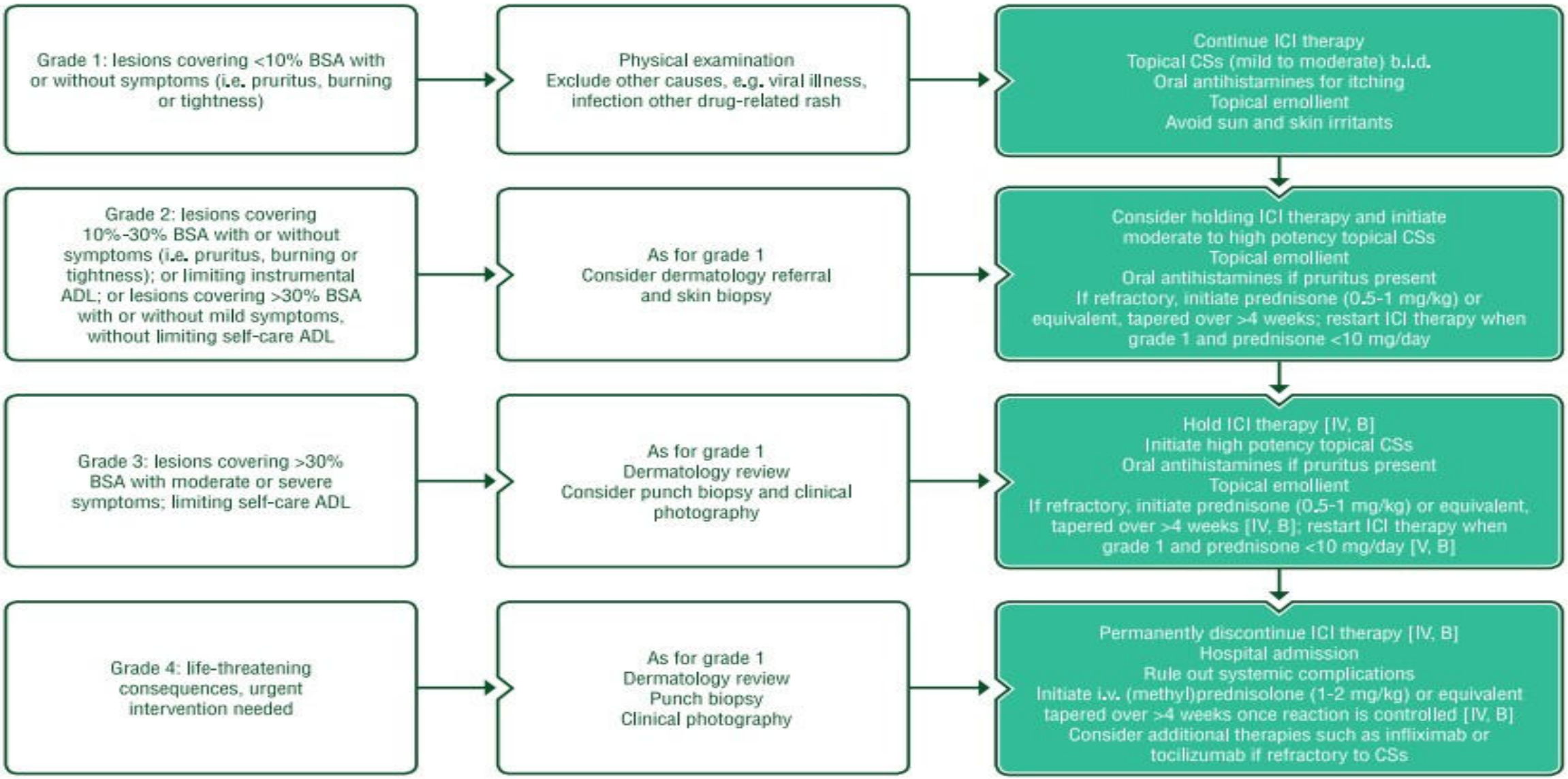
- *Grade-1*: Hafif
- *Grade-2*: Orta
- *Grade-3*: Ciddi
- *Grade 4*: Hayatı tehdit edici

İmmunoterapi yan etkiler

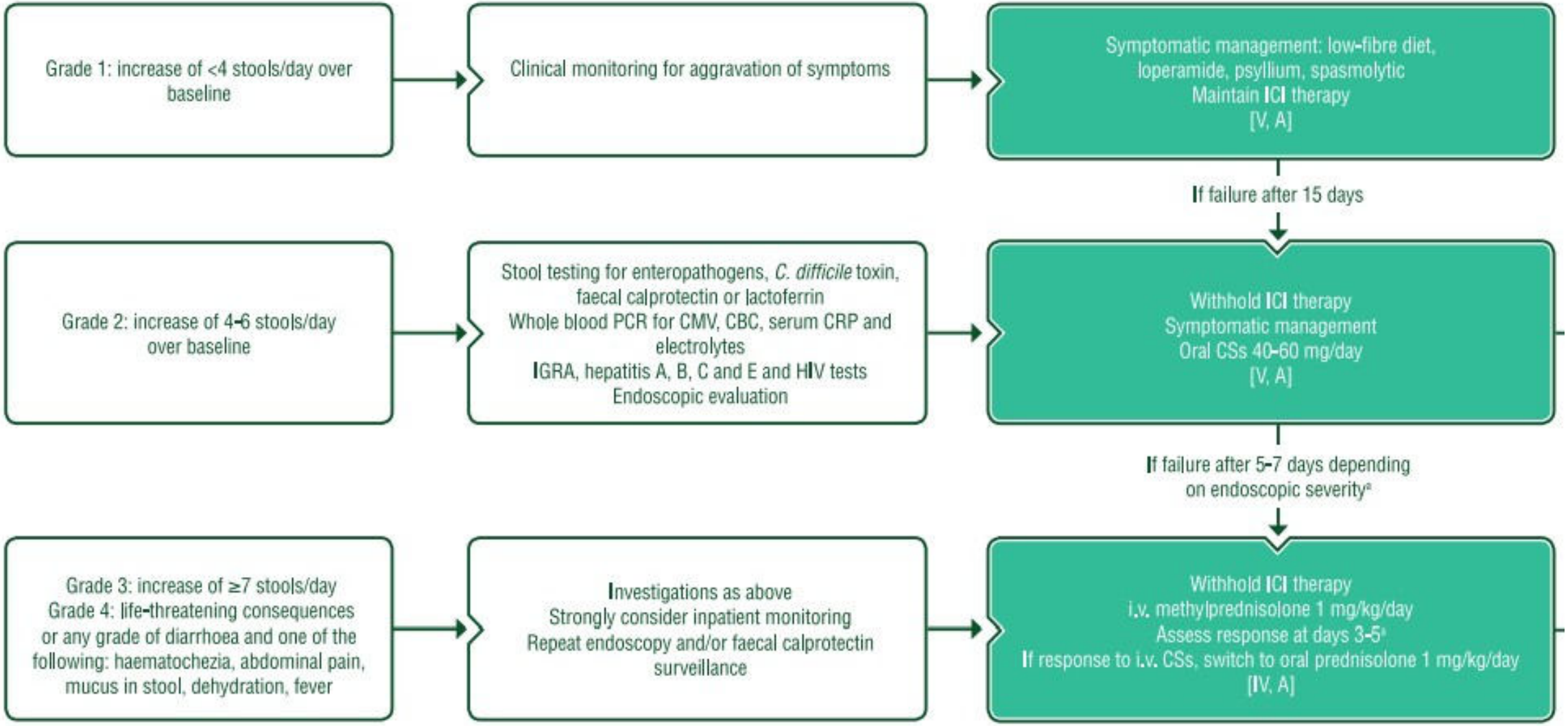


For details and specific information, please see the PI/SmPC for the respective checkpoint inhibitor.
I-O=immuno-oncology.
1. OPDIVO (SmPC). Bristol-Myers Squibb Pharma EEIG; 2020. 2. Ledezma B, Hong A. *Cancer Manage Res*. 2013;6:5-14. 3. Haanen JBAG et al. *Ann Oncol*. 2017;28(suppl_4):iv119-iv142.

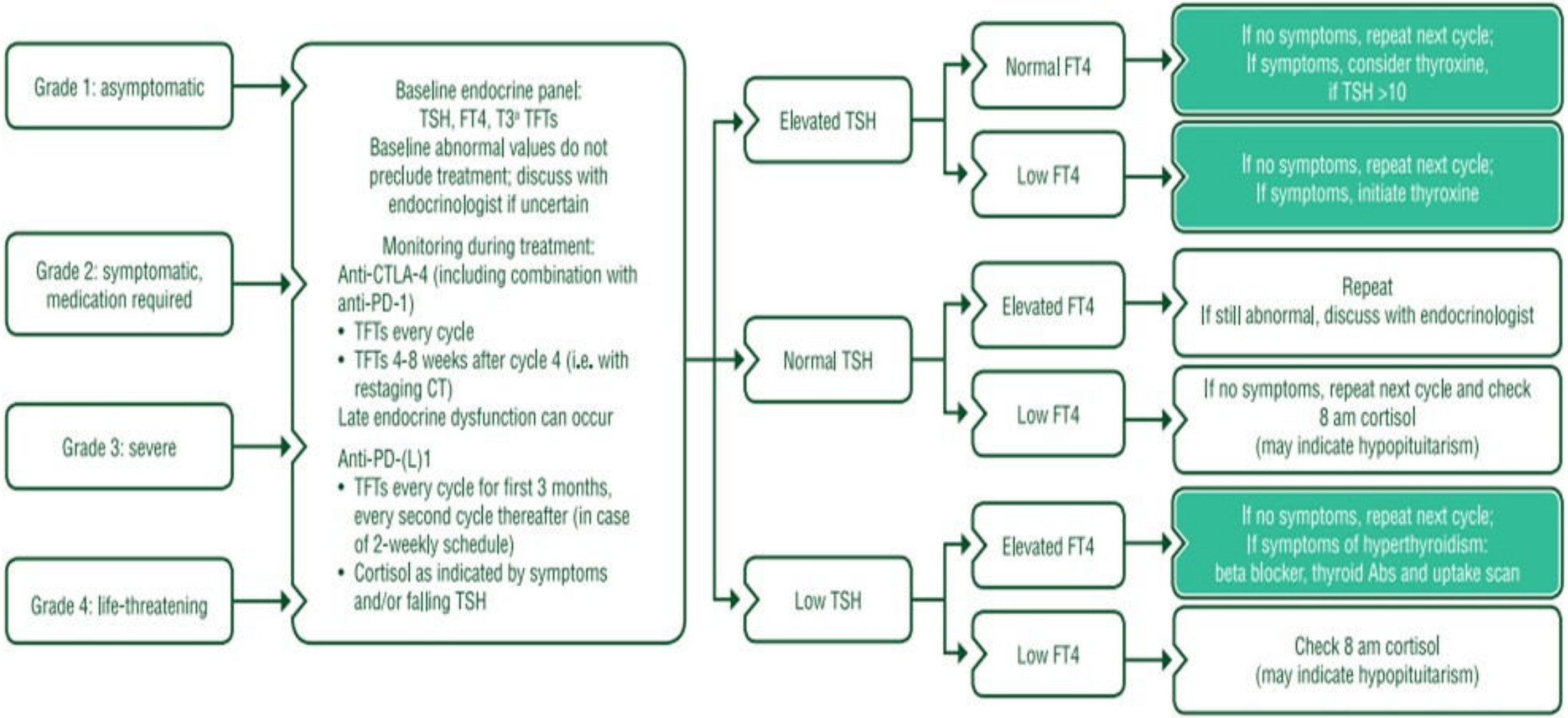
Döküntü


Grade 1: lesions covering <10% BSA with or without symptoms (i.e. pruritus, burning or tightness)
Physical examination
Exclude other causes, e.g. viral illness, infection other drug-related rash
Continue ICI therapy
Topical CSs (mild to moderate) b.i.d.
Oral antihistamines for itching
Topical emollient
Avoid sun and skin irritants
Grade 2: lesions covering 10%-30% BSA with or without symptoms (i.e. pruritus, burning or tightness); or limiting instrumental ADL; or lesions covering >30% BSA with or without mild symptoms, without limiting self-care ADL
As for grade 1
Consider dermatology referral and skin biopsy
Consider holding ICI therapy and initiate moderate to high potency topical CSs
Topical emollient
Oral antihistamines if pruritus present
If refractory, initiate prednisone (0.5-1 mg/kg) or equivalent, tapered over >4 weeks; restart ICI therapy when grade 1 and prednisone <10 mg/day
Grade 3: lesions covering >30% BSA with moderate or severe symptoms; limiting self-care ADL
As for grade 1
Dermatology review
Consider punch biopsy and clinical photography
Hold ICI therapy [IV, B]
Initiate high potency topical CSs
Oral antihistamines if pruritus present
Topical emollient
If refractory, initiate prednisone (0.5-1 mg/kg) or equivalent, tapered over >4 weeks [IV, B]; restart ICI therapy when grade 1 and prednisone <10 mg/day [V, B]
Grade 4: life-threatening consequences, urgent intervention needed
As for grade 1
Dermatology review
Punch biopsy
Clinical photography
Permanently discontinue ICI therapy [IV, B]
Hospital admission
Rule out systemic complications
Initiate i.v. (methyl)prednisolone (1-2 mg/kg) or equivalent tapered over >4 weeks once reaction is controlled [IV, B]
Consider additional therapies such as infliximab or tocilizumab if refractory to CSs

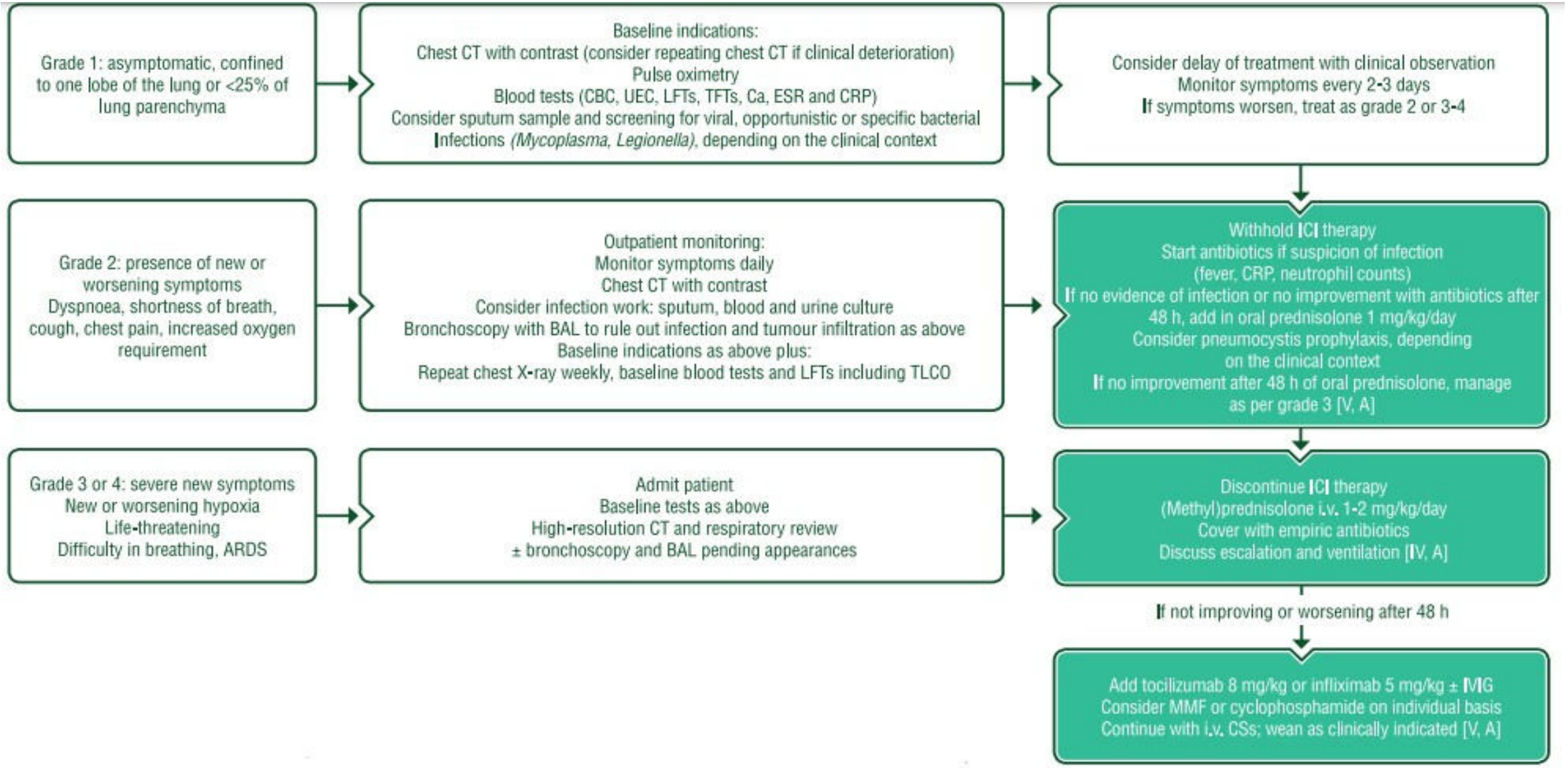
Kolit/Diare


Grade 1: increase of <4 stools/day over baseline
Clinical monitoring for aggravation of symptoms
Symptomatic management: low-fibre diet, loperamide, psyllium, spasmolytic
Maintain ICI therapy
[V, A]
If failure after 15 days
Grade 2: increase of 4-6 stools/day over baseline
Stool testing for enteropathogens, C. difficile toxin, faecal calprotectin or lactoferrin
Whole blood PCR for CMV, CBC, serum CRP and electrolytes
IGRA, hepatitis A, B, C and E and HIV tests
Endoscopic evaluation
Withhold ICI therapy
Symptomatic management
Oral CSs 40-60 mg/day
[V, A]
If failure after 5-7 days depending on endoscopic severity[a]
Grade 3: increase of ≥7 stools/day
Grade 4: life-threatening consequences or any grade of diarrhoea and one of the following: haematochezia, abdominal pain, mucus in stool, dehydration, fever
Investigations as above
Strongly consider inpatient monitoring
Repeat endoscopy and/or faecal calprotectin surveillance
Withhold ICI therapy
i.v. methylprednisolone 1 mg/kg/day
Assess response at days 3-5[a]
If response to i.v. CSs, switch to oral prednisolone 1 mg/kg/day
[IV, A]

Tiroid bozuklukları



Pnömonit


Grade 1: asymptomatic, confined to one lobe of the lung or <25% of lung parenchyma
Baseline indications:
Chest CT with contrast (consider repeating chest CT if clinical deterioration)
Pulse oximetry
Blood tests (CBC, UEC, LFTs, TFTs, Ca, ESR and CRP)
Consider sputum sample and screening for viral, opportunistic or specific bacterial infections (Mycoplasma, Legionella), depending on the clinical context
Consider delay of treatment with clinical observation
Monitor symptoms every 2-3 days
If symptoms worsen, treat as grade 2 or 3-4
Grade 2: presence of new or worsening symptoms
Dyspnoea, shortness of breath, cough, chest pain, increased oxygen requirement
Outpatient monitoring:
Monitor symptoms daily
Chest CT with contrast
Consider infection work: sputum, blood and urine culture
Bronchoscopy with BAL to rule out infection and tumour infiltration as above
Baseline indications as above plus:
Repeat chest X-ray weekly, baseline blood tests and LFTs including TLCO
Withhold ICI therapy
Start antibiotics if suspicion of infection (fever, CRP, neutrophil counts)
If no evidence of infection or no improvement with antibiotics after 48 h, add in oral prednisolone 1 mg/kg/day
Consider pneumocystis prophylaxis, depending on the clinical context
If no improvement after 48 h of oral prednisolone, manage as per grade 3 [V, A]
Grade 3 or 4: severe new symptoms
New or worsening hypoxia
Life-threatening
Difficulty in breathing, ARDS
Admit patient
Baseline tests as above
High-resolution CT and respiratory review
± bronchoscopy and BAL pending appearances
Discontinue ICI therapy
(Methyl)prednisolone i.v. 1-2 mg/kg/day
Cover with empiric antibiotics
Discuss escalation and ventilation [IV, A]
If not improving or worsening after 48 h
Add tocilizumab 8 mg/kg or infliximab 5 mg/kg ± MG
Consider MMF or cyclophosphamide on individual basis
Continue with i.v. CSs; wean as clinically indicated [V, A]

Steroid-refrakter durumlar

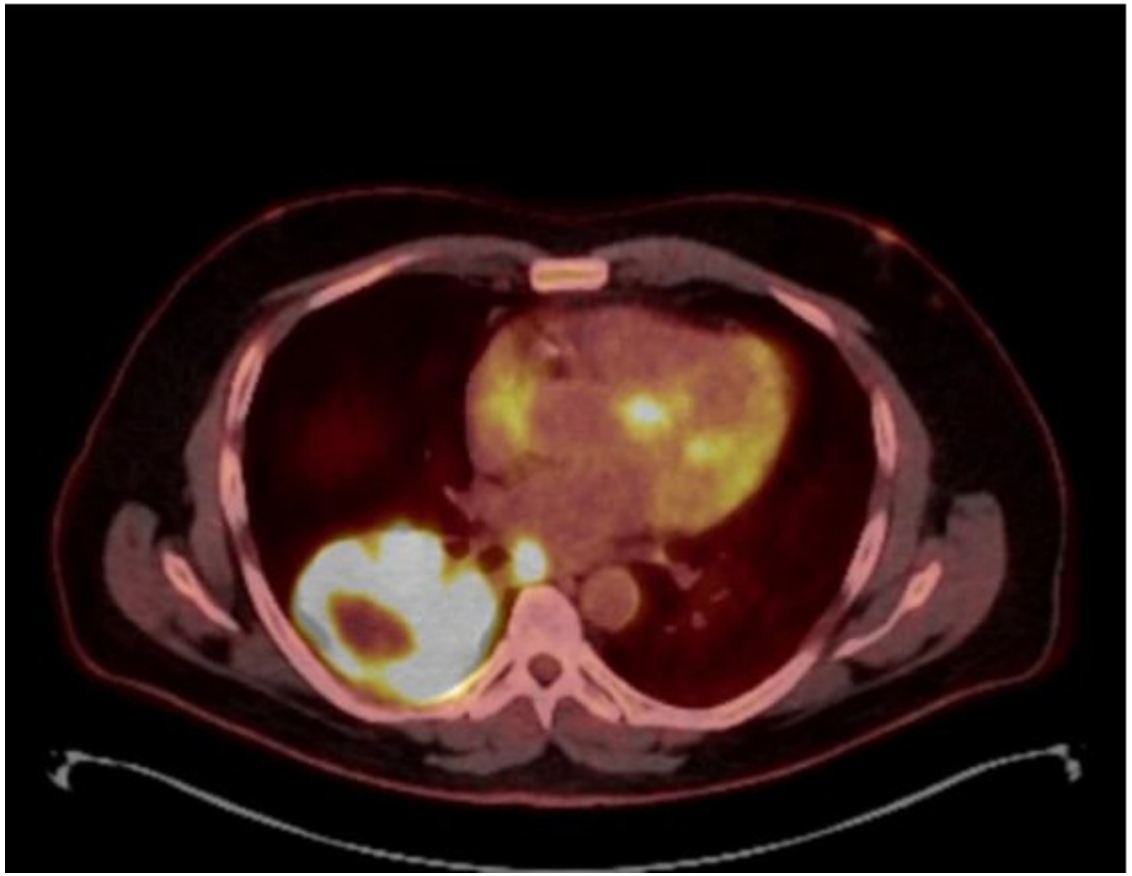
- TNF-a inhibitors (infliximab, adalimumab, etanercept, certolizumab, golimumab)
- Gut-specific immunosuppressants (vedolizumab)
- Anti-B-cell CD 20 monoclonal antibodies (rituximab, obinutuzumab, ocrelizumab)
- Anti-IL 6 receptor (tocilizumab, sarilumab)
- Anti-IL-4Ra (dupilumab)
- Anti-IL-17A (secukinumab, ixekizumab, brodalumab)
- Anti-IL-12 and IL-23 (ustekinumab)
- Anti-CTLA-4 (abatacept)
- Anti-CD52 (alemtuzumab)
- Anti-thymocyte globulin therapy
- Mycophenolate mofetil (MMF), calcineurin inhibitors, cyclophosphamide, methotrexate, azathioprine, sulfasalazine and hydroxychloroquine
- IVIG

İmmunoterapi yan etki yönetimi

- Yan etki kontrolü için CS gerekli (endokrin yan etkiler hariç).
- CS başlangıç dozu: 0.5-1 mg/kg/gün veya 1-2 mg/kg/gün
- CS'e 48-72 sa yanıt yoksa diğer immunsüpresanlara geçilmeli.
- CS kesilmesi 4-6 haftayı bulmalı
- CS<10 mg/gün olduğunda immunoterapi tekrar başlanabilir
- İmmunoterapilerde doz redüksiyonu yoktur.

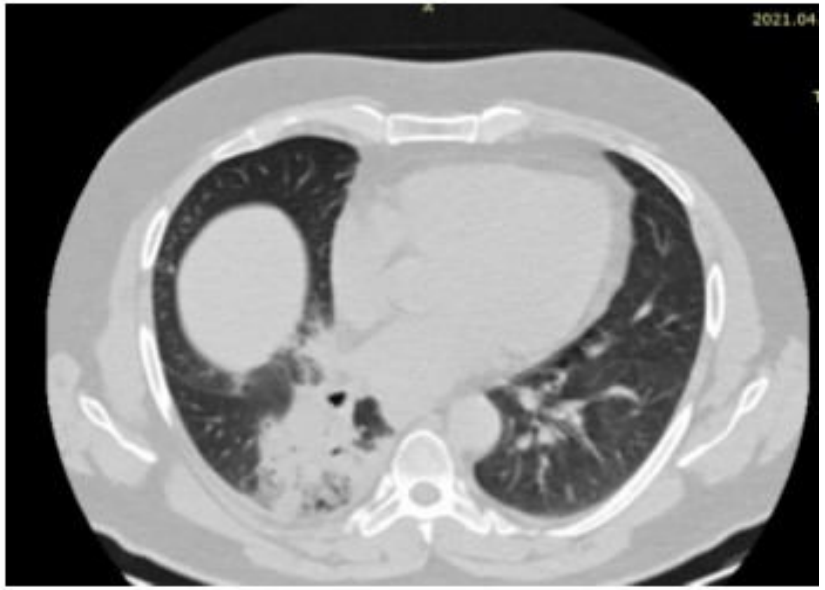
Vaka

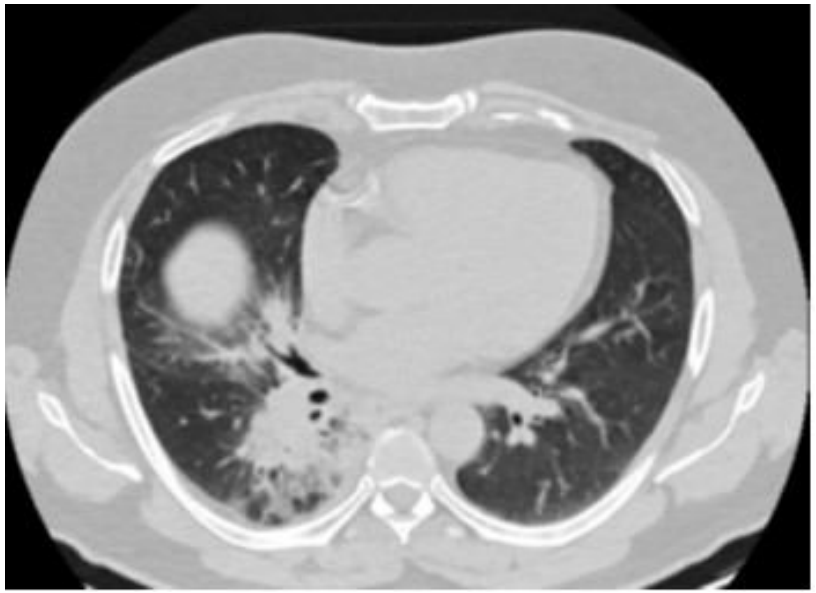
- 55 yaş, erkek
- Bronkoskopik biyopsi: adeno ca
- Pdl-1: %100
- Pembrolizumab başlandı



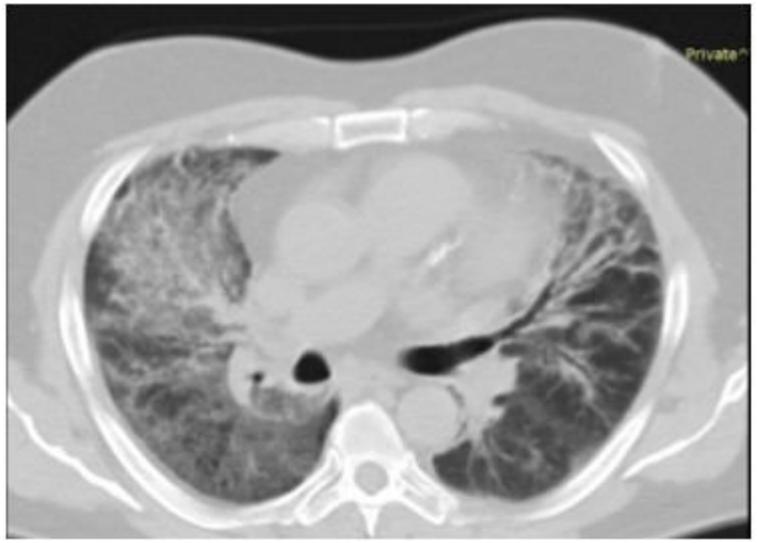
Vaka

6 siklus sonra regresyon





Vaka



24 siklus sonra:

- Klinik kötü, Dispne, SpO2: %70
- BT: Non-spesifik intersitisyel tutulum

✓*Kanser progresyonu?*

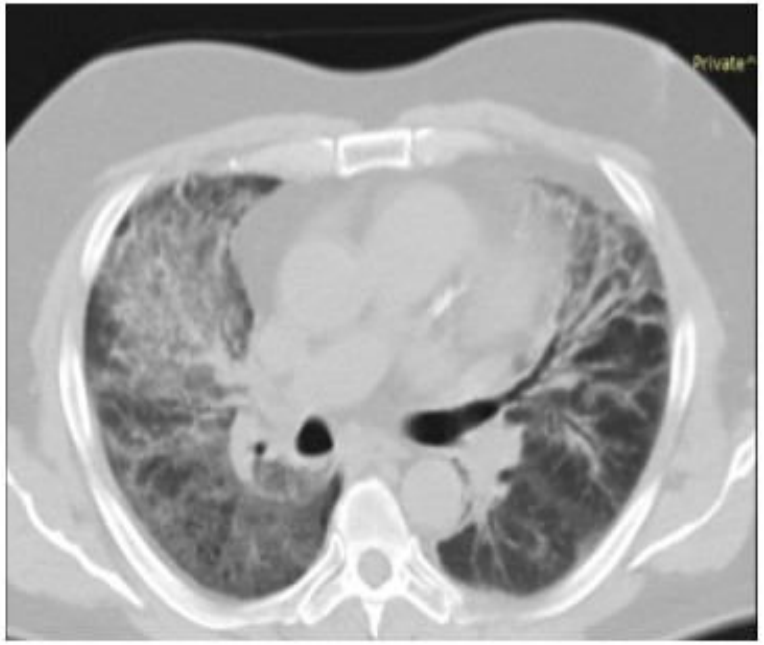
✓*Enfeksiyöz Pnömoni?*

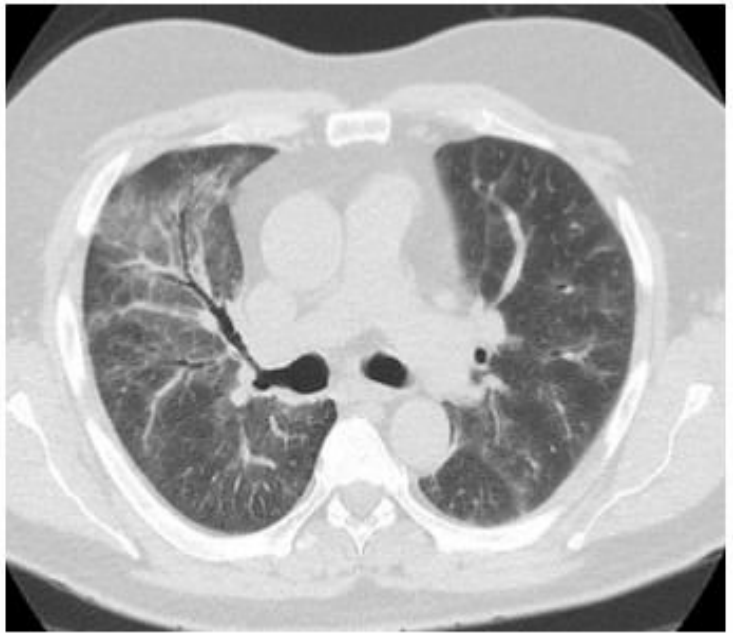
✓*Pembrolizumab pnömonit?*

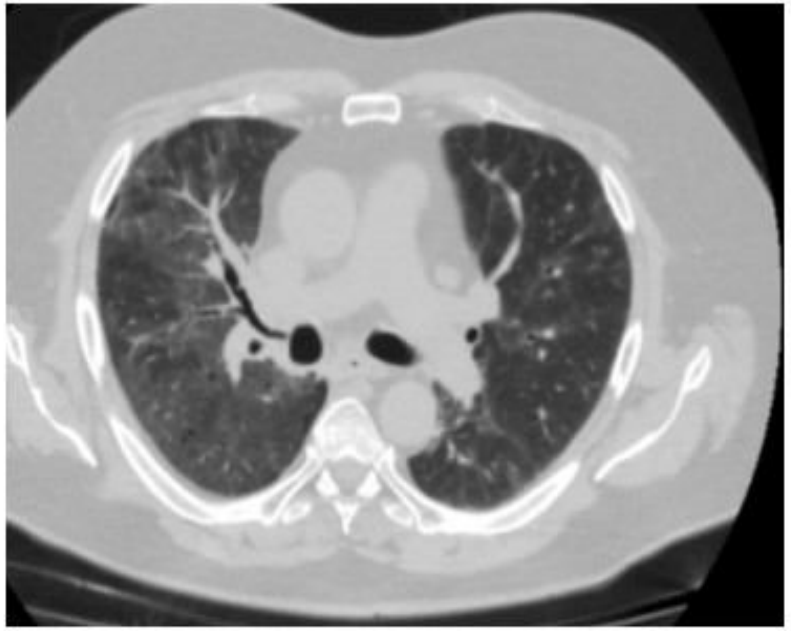
Vaka

- Hasta yatırıldı.
- Ampirik antibiyoterapi başlandı.
- 2 mg/kg/gün prednizolone başlandı.

Vaka

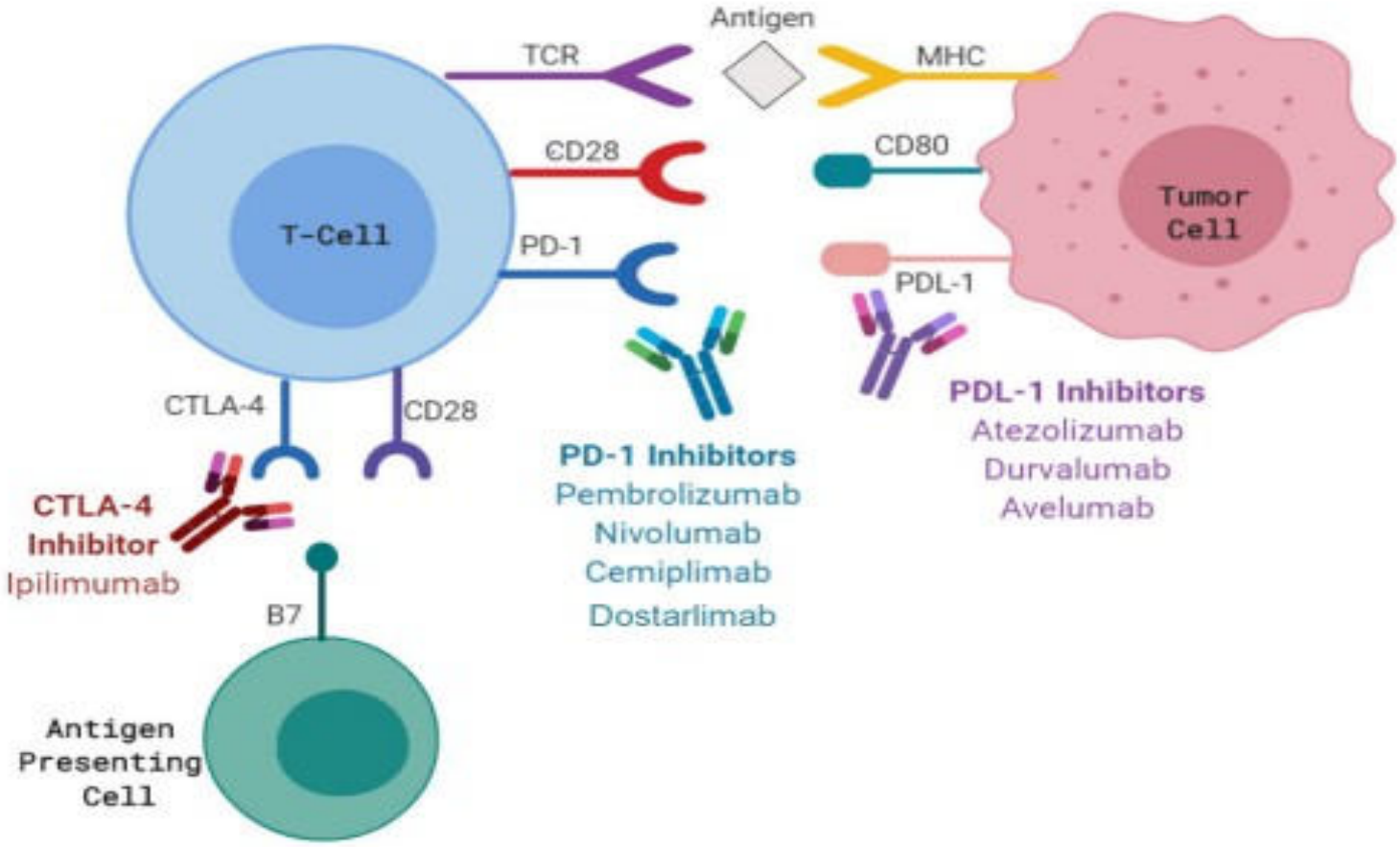






TEŞEKKÜRLER

İmmunoterapi



Management of ILD/Pneumonitis With Pralsetinib

Required monitoring

- Withhold drug
- Promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms, which may be indicative of ILD
  - (eg, dyspnea, cough, and fever)

Dose modification

- Grade 1 or 2: Withhold until resolution
  - Resume by reducing dose
  - Permanently discontinue for recurrent ILD/pneumonitis
- Grade 3 or 4: Permanently discontinue for confirmed ILD/pneumonitis

Pralsetinib [PI]. EMA. Authorized November 18, 2021. Updated June 10, 2022.

Multidisciplinary Guidance on T-DXd–Related ILD/Pneumonitis
Focus on Proactive Monitoring, Diagnosis, and Management

Use a Multidisciplinary Team in Evaluating Patients for ILD/Pneumonitis

Workup

- Radiographic changes consistent with ILD/pneumonitis
- Acute onset of new or worsening pulmonary or other symptoms (dyspnea, cough, fever)

Evaluations Should Include:

- High-resolution CT
- Pulmonologist consultation
- Infectious disease consultation, if indicated
- Blood culture and CBC
- Consider bronchoscopy, bronchoalveolar lavage
- Pulmonary function tests and SpO_2
- Arterial blood gases if indicated
- PK analysis when ILD/pneumonitis is suspected
- Other tests, as needed

Other etiology, follow routine clinical practice

If ILD/pneumonitis is confirmed, follow the ILD/pneumonitis management guidelines according to severity

CBC, complete blood cell count; SpO^2, saturation of peripheral oxygen.

Swain SM, et al. Cancer Treat Rev. 2022;106:102378.

Multidisciplinary Guidance on T-DXd–Related ILD/Pneumonitis
Focus on Proactive Monitoring, Diagnosis, and Management

	Grade 1	Grade 2	Grade 3/4
T-DXd Dosing Modification	▪ **Interrupt T-DXd** ▪ Resume if ILD/pneumonitis is fully resolved to grade 0 • If resolved in ≤ 28 days, maintain dose • If resolved in > 28 days, reduce dose • Occurrence > day 22 and not resolved ≤ 49 days, discontinue	**Permanently discontinue T-DXd**	**Permanently discontinue T-DXd**
ILD/Pneumonitis Management	▪ Monitor and closely follow up in 2 to 7 days ▪ Consider imaging ▪ Consider systemic steroids until improvement **If worsening despite steroids, follow grade 2 guidelines**	▪ Start systemic steroids ▪ Monitor symptoms closely ▪ Reimage as indicated **If worsening or no improvement in 5 days, consider increasing steroid dose; escalate as indicated**	▪ Hospitalization required ▪ Start high-dose steroids ▪ Reimage as indicated **No improvement within 3 to 5 days, reconsider additional work-up or immuno-suppressants**

Regardless of severity, patients with ILD/pneumonitis should be followed up until **complete resolution of clinical/chest CT findings**

Swain SM, et al. Cancer Treat Rev. 2022;106:102378.

General Principles

- Low Grade
  - Monitor closely (grade 1 and 2)
  - Delay therapy (grade 2)

Moderate Grade ?

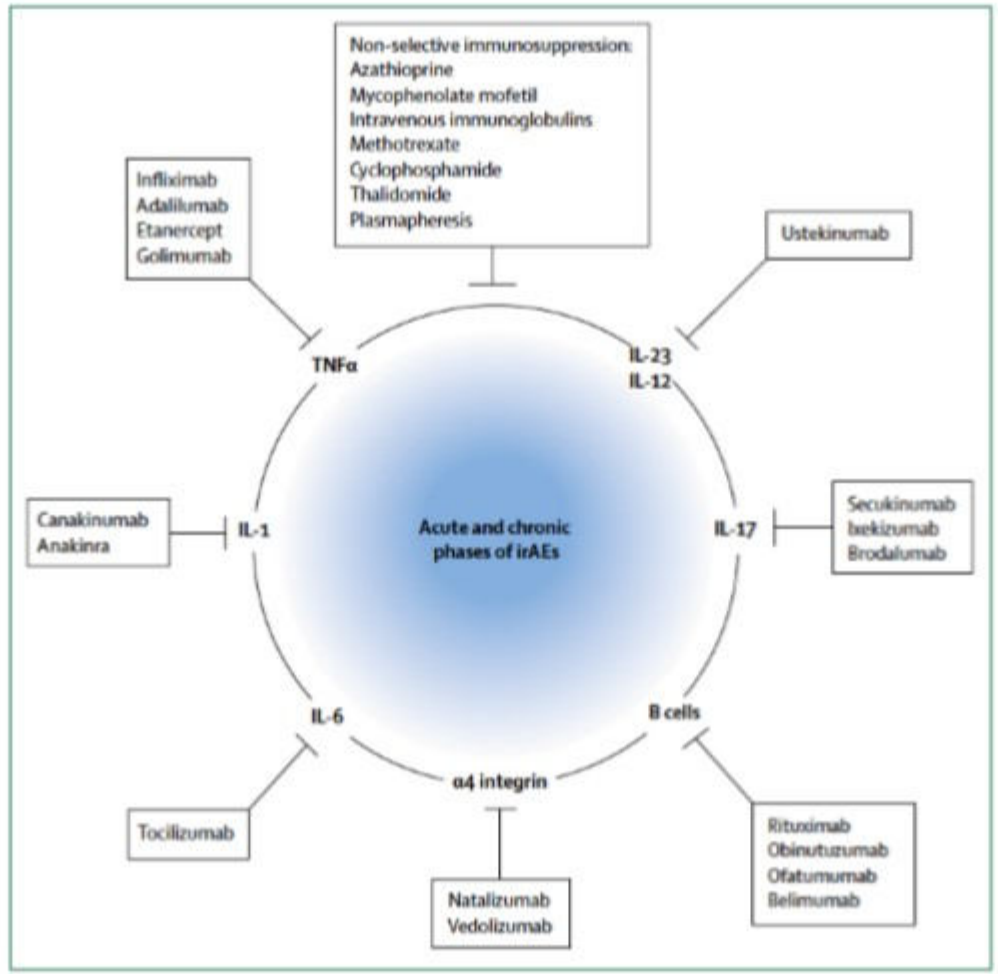
- High Grade → Immunosuppression
  - **Cease checkpoint inhibitor, consult sub-specialty and consider hospitalisation**
  - Systemic corticosteroids
  - Infliximab (anti-TNFa)
  - Mycophenolate mofetil
  - Tacrolimus
  - Other → plasmapheresis, anti-thymocyte globulin, IVIG

ESMO

Take home messages

Risk assessment (AID, organ transpant etc)
Every organ can be involved
Severity can vary from grade 1 – 5
Requires immediate action
Hold further treatment (depending on severity)
Consult organ specialist if necessary
Start immunosuppression (depending on severity)
Careful follow-up warranted
Taper immunosuppression

As a (medical) oncologist: be in the lead!



tins et al., Lancet Oncol 2019

Immunotherapy AEs	VEGF TKI AEs
May never occur	Almost guaranteed
Dose independent	Dose dependent
Can emerge anytime	Usually emerge by 3-4 weeks
Need treatment to resolve	Resolve with holding drug

Unpredictable Variety at Patient Level

Reasons for Permanent Discontinuation

Immunotherapy

- Neurotoxicity
- Hypoxic Pneumonitis
- Refractory colitis/diarrhea
- Myocarditis

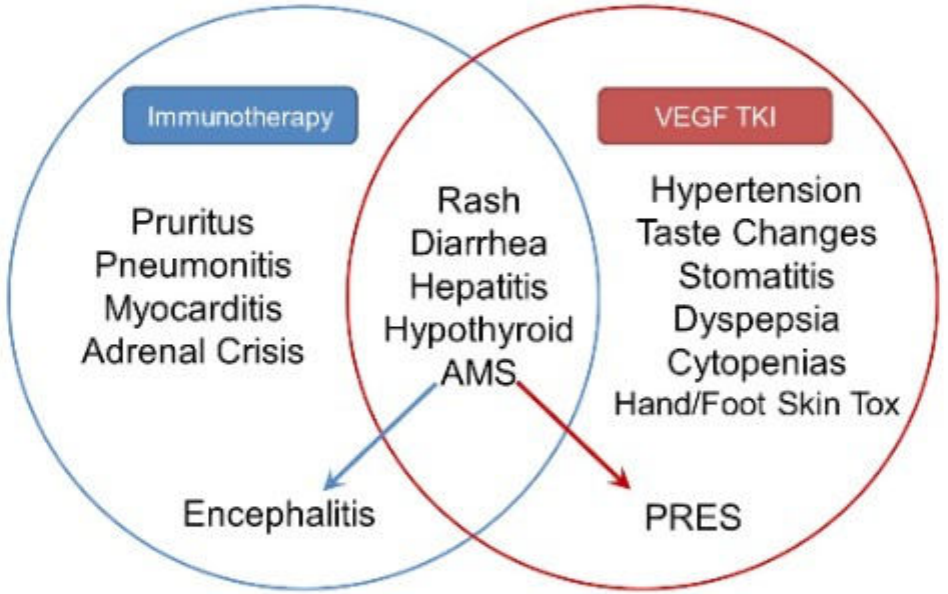
VEGF TKI Therapy

- Nephrotic Syndrome
- PRES
- Persistent LFT elevation
- Non-healing wounds

Disease Progression

Presented By Elizabeth Plimack at 2020 Genitourinary Cancers Symposium

Combination Therapy → Overlapping Toxicity



Presented By Elizabeth Plimack at 2020 Genitourinary Cancers Symposium