Yeni Tedaviler ve Enfeksiyon Yönetimi

Dr. Bircan Kayaaslan

Ankara Yıldırım Beyazıt Üniversitesi

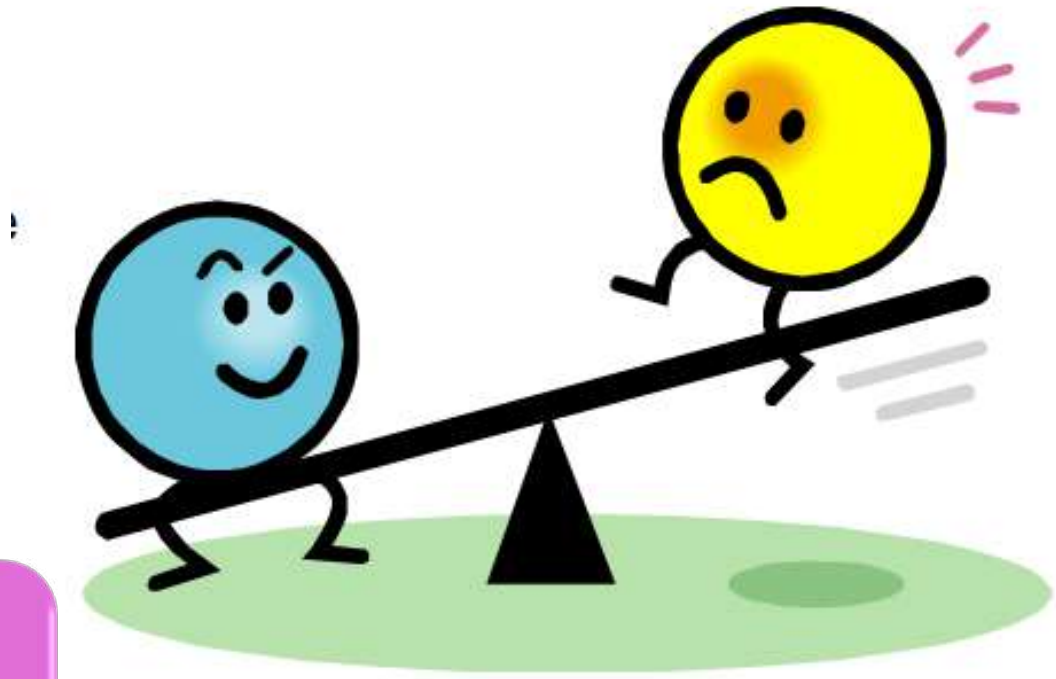
Ankara Şehir Hastanesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

Kullanım alanları

- Romatolojik hastalıklar
- Maligniteler
- İnflamatuar barsak / göz hastalıkları
- Psöriazis
- Organ transplantasyonu
- Multiple skleroz
- Şiddetli astım
- ……

Enfeksiyon (akut, latent)



Hastalık aktivitesini etkin şekilde baskılama

İmmünsüpresif Tedaviler

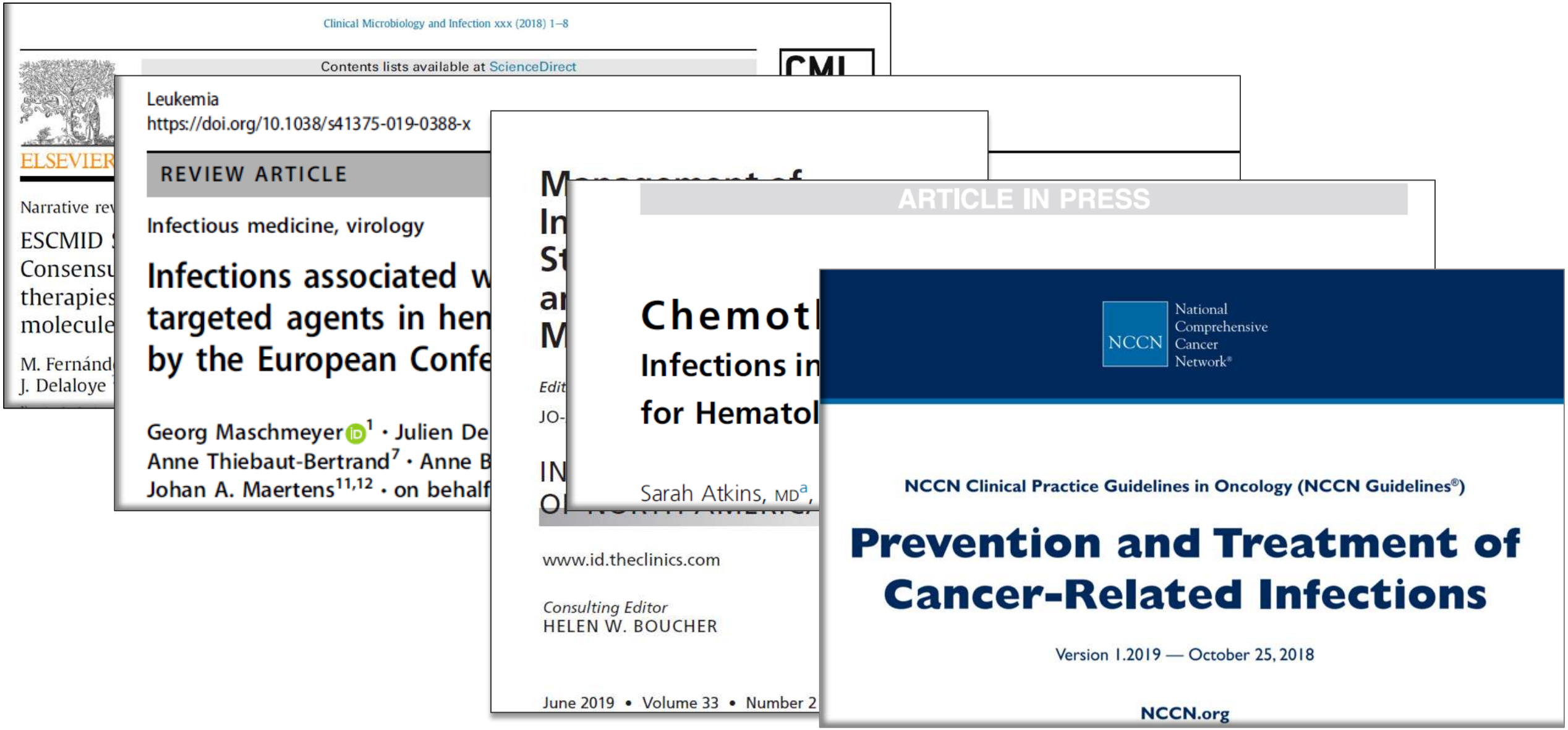
Klasik İmmünsüpresif ajanlar → **Total İmmünsüpresyon**

Biyolojik Ajanlar →

- **Total immünsüpresyon yapmaz**
- **Bağışıklık sistemi üzerinde konak savunmasını tehlikeye sokabilecek ciddi enfeksiyonlar g.b**

- **Akut enfeksiyon yanıtını**
- **Kronik, latent enfeksiyonun kontrolünü bozabilir**

Kaynak


Clinical Microbiology and Infection xxx (2018) 1–8
Contents lists available at ScienceDirect
ELSEVIER
Narrative rev
ESCMID
Consensu
therapies
molecule
M. Fernánd
J. Delaloye
Leukemia
https://doi.org/10.1038/s41375-019-0388-x
REVIEW ARTICLE
Infectious medicine, virology
Infections associated w
targeted agents in hem
by the European Confe
Georg Maschmeyer[1] · Julien De
Anne Thiebaut-Bertrand[7] · Anne B
Johan A. Maertens[11,12] · on behalf
Management of
In
St
ar
M
Edit
JO-
IN
OF NORTH AMERICA
www.id.theclinics.com
Consulting Editor
HELEN W. BOUCHER
June 2019 • Volume 33 • Number 2
ARTICLE IN PRESS
Chemotl
Infections in
for Hematol
Sarah Atkins, MD[a],
NCCN
National
Comprehensive
Cancer
Network®
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Prevention and Treatment of
Cancer-Related Infections
Version 1.2019 — October 25, 2018
NCCN.org

Hematoloji ve Onkolojide Klinik Pratikte Kullanılan Yeni İlaçlar

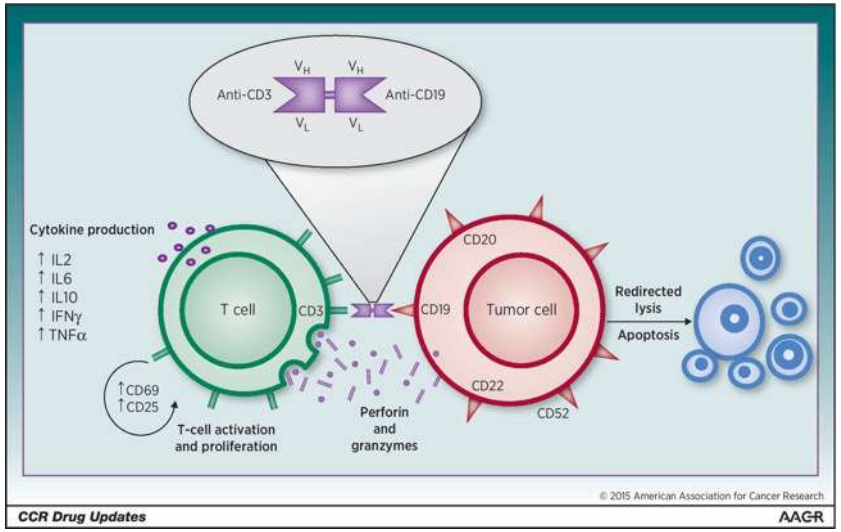
Monoklonal Antikorlar	Anti-CD20 inhibitörleri: Rituksimab Anti-CD30 inhibitörleri: Brentuximab Anti-CD52 inhibitörleri: Alemtuzumab	**Bispesifik T-hücre engager (CD19 directed Cd3)**	Blinatumomab
BCR-ABL Tirozin Kinaz İnhibitörleri	İmatinib (ilk çıkan) Dasatinib Nilotinib Bosutinib Ponatinib	**BCL-2 İnhibitörleri**	Venotoclax
Bruton Tirozin Kinaz İnhibitörleri	Ibrutinib Acalabrutinib	**İmmün check point inhibitörleri (PD-1 inh)**	İpilimumab Pembrolizumab Nivolumab
Proteozom inhibitörleri	Bortezomib, carfilzomid, ixazomid	**PK-3 inhibitörleri**	İdelalisib
CD19 CAR-T	CD19 'u hedefleyen Chimeric Antijen Receptor (CAR) T hücreleri		

ECIL 2019. Leukemia
https://doi.org/10.1038/s41375-019-0388-x

Table 2
Targeted and biological agents reviewed ESGICH Consensus Document

Section of document (study)	Targeted molecule	Agents reviewed
2 [1]	TNF-α	Infliximab, adalimumab, golimumab, certolizumab pegol, etanercept
3 [2]	IL-1	Canakinumab, anakinra, rilonacept, gevokizumab
	IL-5	Mepolizumab, reslizumab
	IL-6	Tocilizumab, siltuximab
	IL-12/23 common p40 subunit	Ustekinumab
	IL-17	Secukinumab, ixekizumab, brodalumab
	IgE	Omalizumab
	Complement factor C5	Eculizumab
4 [3]	VEGF	Bevacizumab, aflibercept
	VEFGR	Sorafenib, sunitinib, axitinib, pazopanib, regorafenib, vandetanib, cabozantinib, ramucirumab
	EGFR	Cetuximab, panitumumab
	ErbB2/HER2	Trastuzumab, pertuzumab
	ErbB receptor tyrosine kinases	Erlotinib, gefitinib, afatinib, osimertinib, lapatinib, neratinib
5 [4]	BCR-ABL tyrosine kinase	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib
	BRAF/MEK kinases	Vemurafenib, dabrafenib, trametinib, cobimetinib, selumetinib, encorafenib
	Bruton tyrosine kinase	Ibrutinib, acalabrutinib
	PI3K	Idelalisib, buparlisib, rigosertib, duvelisib
	Bcl-2	venetoclax
	Janus kinases	Ruxolitinib, tofacitinib, baricitinib
	mTOR	Everolimus, temsirolimus
6 [5]	CD19	Blinatumomab, inebilizumab, combotox
	CD20	Rituximab, ^{90}Y-ibritumomab tiuxetan, ofatumumab, ocrelizumab, veltuzumab, ^{131}I-tositumomab, obinutuzumab, ocaratuzumab, ublituximab
	CD52	Alemtuzumab
7 [6]	CD22	Epratuzumab, inotuzumab ozogamicin, moxetumomab pasedotox, combotox
	CD30	Brentuximab vedotin
	CD33	Gemtuzumab ozogamicin
	CD38	Daratumumab, isatuxumab
	CD40	Dacetuzumab, lucatumumab
	CD319 (SLAMF7)	Elotuzumab
	CCR4	Mogamulizumab
8 [7]	CTLA-4	Ipilimumab, tremelimumab
	PD-1 and PD1L	Nivolumab, pembrolizumab, atezolizumab
	LFA-3	Alefacept
	α4-Integrins, LFA-1	Natalizumab, vedolizumab, efalizumab
	Sphingosine 1−phosphate receptor	Fingolimod
	Proteosome	Bortezomib, carfilzomib, ixazomib

CD 19 antikoru: Blinatumomab



- Bispecific T-hücre angaje edici antikor
- Birbirine bağlanmış tek zincirli anti-CD19 antikoru ve tek zincirli anti-CD3 antikoru
- Philadelphia kr (-) nüks veya refrakter B-hücreli (R / R) ALL'de FDA onayı var
- İmmün sistem üzerindeki etkileri;
  - B hücresi aplazisi
  - Hipogamaglobulinemi
  - Nötropeni y.b

CD 19 antikoru: Blinatumomab

- Belirgin bir enfeksiyon artışına yol açmaz

4 haftalık iv sürekli infüzyona → Kİ-KDE ???

- **HİPOGAMAGLOBULİNEMİ**: Ciddi olgularda **IG replasman tedavisi** verilebilir
- Nötropeni

- **Kuzey Amerika Rehberi: IFI profilaksisi öneriyor**

- PCP profilaksisi ÖNERİLMİYOR

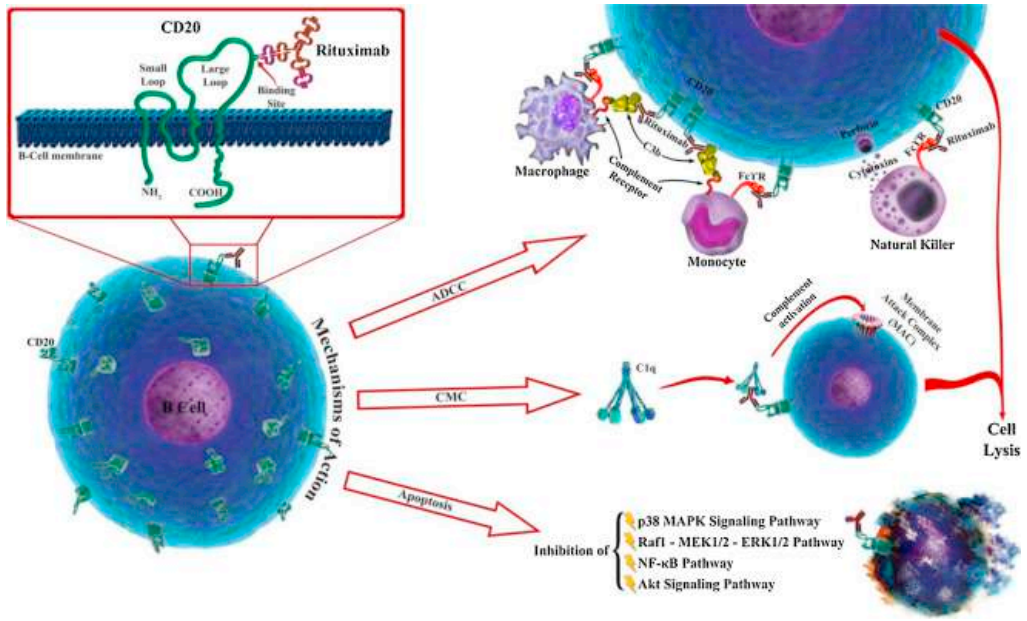
PCP profilaksi
- **ECIL 2019 ve Kuzey Amerika rehberinde yok**
- **ESGICH Rehberinde önerisi yok (tabloda VAR)**

ESCMID ument on the safety of targeted and biological therapies: an Infectious Diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52).10.1016/j.cmi.2018.02.003
Atkins S et al. Chemotherapy and Beyond. Infections in the Era of Old and New Treatments for Hematologic Malignancies.Infect Dis Clin N Am - (2019) -–- https://doi.org/10.1016/j.idc.2019.01.001

CD 20 antikorları: Rituximab, Ofatumumab, Obinutuzumab, Ocrelizumab

- **Anti-CD20 monoklonal IgG**

- **Endikasyonları:**
  - ✓ B hücre maligniteleri
  - ✓ Otoimmün bozuklukları (RA, otoimmün cilt hast, otoimmün sitopeni, Sjögren ve bazı vaskülit formlarında)
  - ✓ Allo HSCT yapılanlarda preemptif EBV reakt önlemek için



- **Periferik kan B hücre sayısını azaltır**, normale gelmesi 6-9 ay
- **Hipogamaglobulinemi:** Tüm hastalarda değil, RF olanlarda

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52).10.1016/j.cmi.2018.02.003
Kuzey Amer

CD20 - Hipogamaglobulinemi

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for HBsAg+ / HBsAg- anti-HBc+)	Risk of CMV infection (monitoring warranted)	Other infections to be considered
CD19-	Blinatumomab	No	Yes	Yes	Yes / yes	ND	Immunoglobulin replacement therapy if severe HGG
						ND	Immunoglobulin replacement therapy if severe HGG
						ND, symptom-based approach in hematological malignancies	
						ND, symptom-based approach in hematological malignancies	Enteroviral infections

Accepted Manuscript

Re: 'ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies' by Mikulska et al.

Sonali Wijetilleka, David Jayne, Chetan Mukhtyar, Mohammed Karim

PII: S1198-743X(18)30815-2

DOI: https://doi.org/10.1016/j.cmi.2018.12.025

Reference: CMI 1530

To appear in: *Clinical Microbiology and Infection*

Received Date: 25 November 2018

Revised Date: 17 December 2018

Accepted Date: 17 December 2018

CD20: Çözülmemiş konu idi

ESGICH→ Daha önce anti-CD19 için belirttiğimiz hipogamaglobulinemi ve enfeksiyon riskine yönelik kaygılar anti-CD20 için de geçerlidir

ESGICH Conser
10.1016/j.cmi.2018.02.003

CD20 - Hipogamaglobulinemi

Geç gelişene DİKKAT

HİPOGAMAGLOBULİNEMi:
- Çoğu asemptomatik
- Rekürren ciddi enfeksiyon g.b

- SİNOPULMONER ENFEKSİYONLAR (Kapsüllü m.o ilişkili)
- Nadiren enteroviral menenjit (rituksimab)

- Başlangıçta ve 6-12 ayda bir taranması
- İmmünglobulin replasman tedavisi v.b

CD 20 antikorları : Rituximab, Ofatumumab, Obinutuzumab, Ocrelizumab

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for HBsAg+ / HBsAg- anti-HBc+)	Risk of CMV infection (monitoring warranted)	Other infections to be considered
CD20-targeted agents	Rituximab	Yes	ND (consider in hematological malignancies depending and concomitant therapy)	Possible (consider if concomitant corticosteroid therapy)	Yes / yes	ND, symptom-based approach in hematological malignancies	PML, HCV, enteroviral infections
	Obinutuzumab	Potentially yes	ND (consider depending on underlying disease and concomitant therapy)	ND, consider depending on underlying disease and concomitant therapy	ND, probably yes / yes	ND, symptom-based approach in hematological malignancies	Enteroviral infections
	Ofatumumab	Yes	ND (consider depending on underlying disease and concomitant therapy)	ND, consider depending on underlying disease and concomitant therapy	Yes / yes	ND, symptom-based approach in hematological malignancies	
	Veltuzumab	Potentially yes	ND (consider if hematological malignancies depending and concomitant therapy)	ND, possibly as rituximab	ND, probably yes / yes	ND, symptom	

x6

Nötropeni → Hepsi ile gelişebilir
HBV → Hepsi ile gelişebilir
PCP → Rituksimab için KS,KT ile komb.
CMV → Hiçbiri için kesin öneri yok

ESCMID Study Group for Infe
an Infectious Diseases perspe

Risk derecesi	HBsAg +/anti-HBc+	HBsAg -/anti-HBc+*	Öneri
Yüksek risk (HBVr >%10)	**B hücre deplesyonu yapan ajanlar** (rituximab, ofatumumab) **Antrasiklin deriveleri** (doxorubicin, epirubicin) **Orta** (10–20 mg/gün**)** veya **yüksek doz prednizon** (>20 mg/gün) **4 hafta**	**B hücre deplesyonu yapan ajanlar** (rituximab, ofatumumab)	**Profilaksi**
Orta risk (HBVr % 1-10)	**TNF-alfa tedavisi** (etanercept, adalimumab, certolizumab, infliximab) **Sitokin veya integrin inhibitörleri** (abatacept, ustekinumab, natalizumab, vedolizumab) **Tirozin kinaz inhibitörleri** (imatinib, nilotinib) **Düşük doz steroid** (<10 mg/gün prednisone)**, 4 haftalık tedavi**	**TNF-alfa tedavisi** (etanercept, adalimumab, certolizumab, infliximab) **Sitokin veya integrin inhibitörleri** (abatacept, ustekinumab, natalizumab, vedolizumab) **Tirozin kinaz inhibitörleri** (imatinib, nilotinib) **Orta doz** (10–20 mg/gün) veya **yüksek doz prednizon** (>20 mg/gün) 4 hafta **Antrasiklin deriveleri** (doxorubicin, epirubicin)	**Profilaksi Preemptif**
Düşük risk (HBVr < %1)	**İmmunsupresif ajanlar** (azathioprine, 6-mercaptopurine, methotrexate) **İntra-artiküler kortikosteroidler** 1 hafta süreli herhangi bir dozda oral steroid tedavisi	**İmmunsupresif ajanlar** (azathioprine, 6-mercaptopurine, methotrexate) **İntra-artiküler kortikosteroidler** 1 hafta süreli herhangi bir dozda oral steroid tedavisi Düşük doz 4 haftalık steroid (<10 mg prednison)	**Profilaksiye gerek yok**

AGA Guideline, Gastroenterology 2015

CD 20 Antikorları vs HBV

Tedavi öncesi serolojik tarama

Seronegatif

Aşılama
- ✓ Yüksek doz veya güçlendirilmiş aşı gerekebilir

HBsAg +
HBsAg - / Anti-HBc +

- ✓ **ETV, TDF, TAF**
- ✓ Tedavi bitiminden sonra en az 12 ay (rituksimab için 18 ay) antiviral
- ✓ Antiviral kesildikten sonra 3-6 ayda bir takip (en az 1 yıl)

EASL, 2017

Monoklonal Antikorlar (MAB) ve PML

Review

Cancer Control
2017, Vol. 24(4) 1–9
© The Author(s) 2017
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1073274817729901
journals.sagepub.com/home/ccx
SAGE

Progressive Multifocal Leukoencephalopathy and Monoclonal Antibodies: A Review

Chandrashekar Bohra, MD[1,2,3], Lubomir Sokol, MD, PhD[1,2,3], and Samir Dalia, MD[1,2,3]

Table 2. Incidence of PML in Different Populations.

Clinical Entity	Incidence (Post 1996)
General population	1 per 200 000
HIV	1.3 per 1000
Natalizumab (HIV negative)	1 per 1000
Rituximab (HIV negative)	1 per 32 000

Brentuximab vedotin: PML riski ⬆

- **MAB tedavisi PML riskini artırır**
- **Tarama ÖNERİLMEZ** (Natalizumab hariç)
- **Nörolojik semptomu olan hastalarda PML ayırıcı tanıda düşünülmelidir**

CD52 antikorları: Alemtuzumab

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for HBsAg+ / HBsAg- anti-HBc+)	Risk of CMV infection (monitoring warranted)	Other infections to be considered
CD52-targeted agents	Alemtuzumab (MabCampath®)	Yes ✓	Yes ✓	Yes ✓	Yes / prophylaxis or monitoring ✓	Yes ✓	IFI, BK and JC polyomaviruses reactivation ✓
	Alemtuzumab (Lemtrada®)	No	Yes	No (lower dose, no need of additional immunosuppression)	Probably yes / prophylaxis or monitoring	No	HPV, TB, listeriosis, candidiasis

Ciddi enfeksiyon riski (HIV benzeri)

- NÖTROPENİ
- HSV / VZV
- PCP
- HBV
- CMV
- IFI
- BK, Poliyoma reak.
- HPV
- TB
- LİSTERYOZ

PCP Önleme Rehberi, ECIL 2017

Table 1. ECIL guidelines in haematology patients at risk of *Pneumocystis* pneumonia: indication and duration of prophylaxis

	Adults		Children	
Indication for prophylaxis	disease/condition	duration of prophylaxis	disease/condition	duration of prophylaxis
Main (A)	ALL	from induction to end of maintenance	ALL	from induction to end of maintenance
	allogeneic HSCT	from engraftment to ≥6 months and as long as immunosuppression is ongoing	allogeneic HSCT	from engraftment to ≥6 months and as long as immunosuppression is ongoing
	alemtuzumab	>6 months after completion of treatment	alemtuzumab	
	fludarabine/cyclophosphamide/ rituximab	≥6 months after completion of treatment	SCID, WAS, X-linked agammaglobulinaemia, HLA II combined immunodeficiency	life-long or until restoration of underlying defect
	steroids (>20 mg/day prednisone for 4 weeks)		steroids (>0.4 mg/kg or 16 mg/day for ≥1 mo	
Optional (B)	Lymphoma treated with R-CHOP14 or escalated BEACOPP		AML	
	nucleoside analogues (fludarabine, cladribine, mycophenolate mofetil)		solid tum	
	radiotherapy for brain tumours/ metastasis + high-dose steroids			

HLA, human leucocyte antigen; SCID, severe combined immunodeficiency; WAS, Wiskott–Aldrich syndrome.

ESGICH-2018 ve NCCN-2019

- **PCP profilaksisi süresi: Tedavi kesildikten sonra 2-6 ay veya CD4 sayısı > 200 hc/ml olana kadar**

PCP - Profilaksi

- **İlk seçenek:**
  - TMP-SMZ (% 91 etkili**)**
- **Alternatif:**
  - Pentamidin, 300 mg/ay, inhale
  - Dapson, 100 mg/gün, oral
  - Atovaquon, 1500 mg/gün, oral süsp.

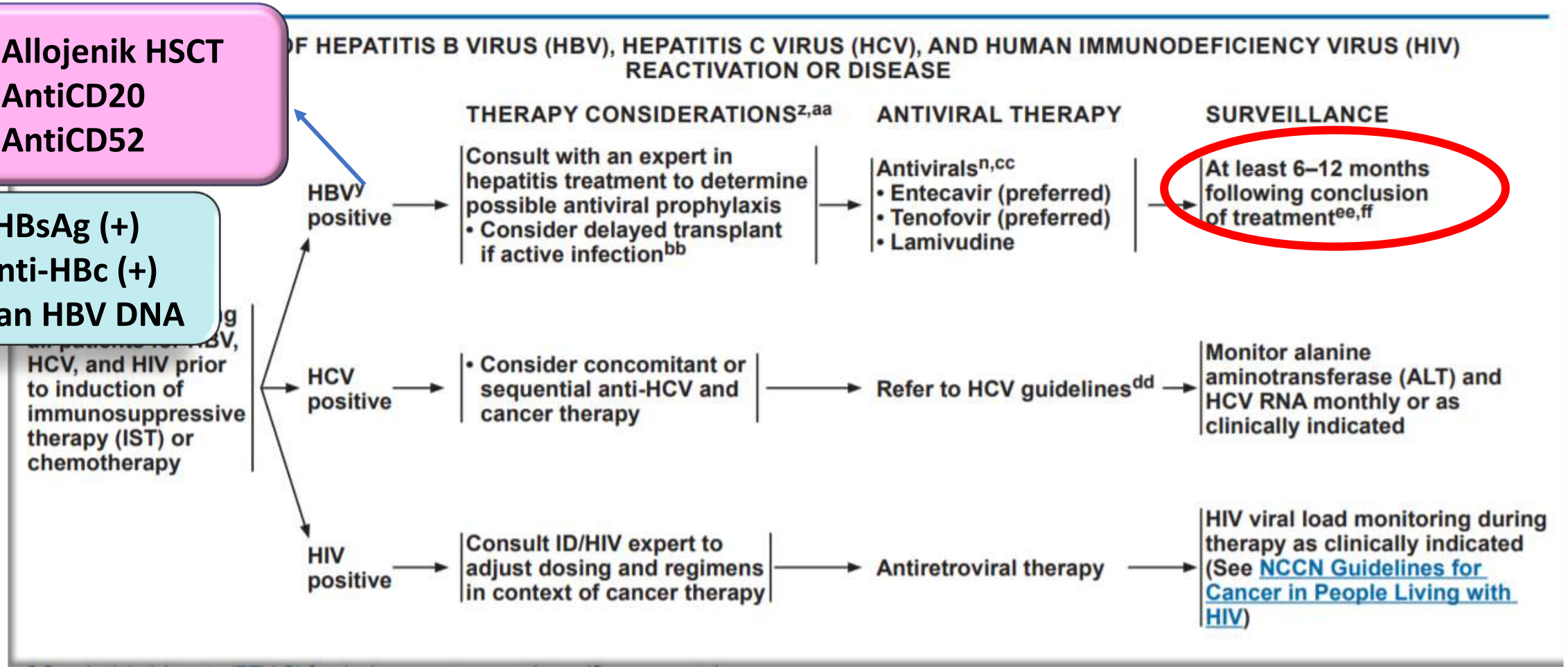
- **PCP** ✓
- **Bakteriyel etkenler** ✓
- **Toksoplazma** ✓
- **Listeryoz** ✓
- **Nokardiyoz** ✓

- Hematolojik malignite: **Overall mortaliteyi düşürmez**

HBV Profilaksisi

- Allojenik HSCT
- AntiCD20
- AntiCD52

HBsAg (+)
Anti-HBc (+)
Artan HBV DNA



NCCN, 2019

HSV ve VZV Profilaksisi

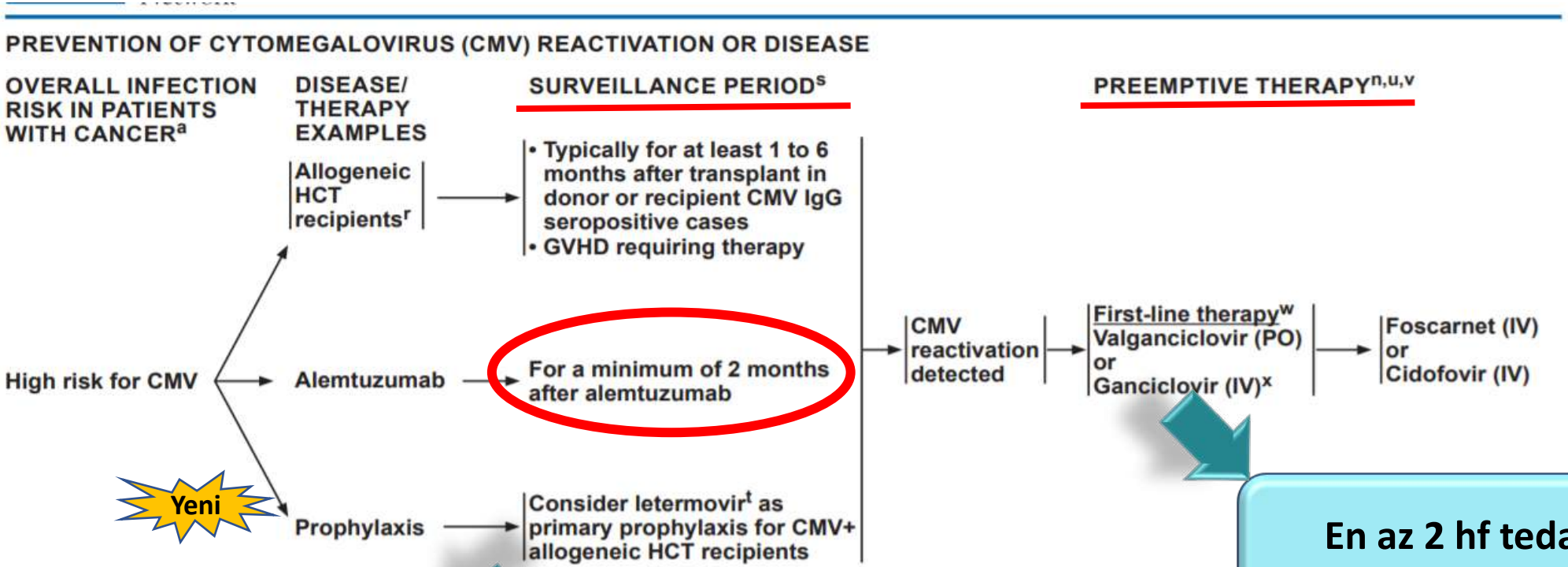
PREVENTION OF HERPES SIMPLEX VIRUS (HSV) AND VARICELLA ZOSTER VIRUS (VZV) REACTIVATION OR DISEASE[o]

OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	VIRAL INFECTION or REACTIVATION	ANTIVIRAL PROPHYLAXIS	MINIMUM DURATION[g]
Low	• Standard chemotherapy regimens for solid tumors	HSV	None unless prior HSV episode	During active therapy including periods of neutropenia
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple Myeloma[c] • CLL[c] • Purine analog therapy (eg, fludarabine)	HSV VZV	Acyclovir Famciclovir Valacyclovir	HSV prophylaxis • Consider during active therapy and possibly longer depending on degree of immunosuppression VZV prophylaxis • Consider for at least 6–12 months after autologous HCT
High	• Acute leukemia ▸ Induction ▸ Consolidation	HSV	Acyclovir Famciclovir Valacyclovir	HSV prophylaxis during active therapy including periods of neutropenia
	• Proteasome inhibitors	VZV	Acyclovir Famciclovir Valacyclovir	VZV prophylaxis during active therapy including periods of neutropenia
	• Alemtuzumab therapy • Allogeneic HCT • GVHD requiring steroid treatment	HSV VZV	Acyclovir Famciclovir Valacyclovir	HSV prophylaxis • Minimum of 2 mo after alemtuzumab and until CD4 ≥200 cells/mcL VZV prophylaxis • Prophylaxis should be considered for at least 1 y after allogeneic HCT

KEY: CLL = chronic lymphocytic leukemia, CMV = cytomegalovirus, GVHD = graft-versus-host disease, HBV = hepatitis B virus, HCT = hematopoietic cell transplant

NCCN, 2019

CMV Profilaksisi



LETERMOVİR
- **240 mg/gün, oral/IV**
- **Allo-HSCT 0-28 gün başlanır**
- **100 gün verilir**

ESGICH, 2018:
Preemtif (Profilaksi o.b)

En az 2 hf tedavi ve CMV saptanamaz olana kadar tedavi

Infect Dis Clin N Am - (2019) -–-
https://doi.org/10.1016/j.idc.2019.01.001

NCCN, 2019

CD52 antikoru: Alemtuzumab

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Fever & Neutropenia Risk (See FEV-2)	Antimicrobial Prophylaxis[d]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 d	Incidence low	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7–10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia and for anticipated mucositis (See INF-2); consider PCP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia ▸ Induction ▸ Consolidation/maintenance • Alemtuzumab therapy • GVHD treated with high-dose steroids (>20 mg daily) • Anticipated neutropenia greater than 10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia (See INF-2); consider PCP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)

KEY: CLL = chronic lymphocytic leukemia, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant, HSV = herpes simplex virus, PCP = pneumocystis pneumonia

NCCN, 2019

CD52 antikoru: Alemtuzumab

- PCP profilaksisi
- HSV / VZV profilaksisi
- CMV preemptif tedavi
- HBV reaktivasyonu açısından DİKKAT
- HCV reaktivasyonu açısından DİKKAT !!
- Nötropeni sırasında bakteriyel, viral ve fungal profilaksi
- HPV açısından yıllık tarama
- Hijyenik ve güvenli gıda (listeriozis, toxoplazmozis vs)
- TB açısından taranmalı

ESGICH Consensus Document (Agents targeting lymphoid cells surface antigens : CD19, CD20 and CD52), 10.1016/j.cmi.2018.02.003

CD30 antikoru: Brentuximab vedotin (BV)

Antikor-ilaç konjugatı (ADC)

PML açısından dikkat!!!!!!

Table 1 Summary of drug characteristics, reported infectious complications and ECIL recommendations for clinical practice

Class of agents	Agent	Impact on immune system	Infectious events	ECIL recommendations
[illegible]	Blinatumomab	B-cell aplasia; hypogammaglobulinemia; neutropenia	No clear evidence of increased infection rate	•Consideration of IgG substitution [illegible] case of serious infection
Anti-CD30 antibody	Brentuximab vedotin	Poorly defined, impairment of memory cell generation and surv[illegible]l; transient neutropenia	Pneumocystis pneumonia; CMV and HBV reactivation; JC virus-associated PML	•CMV monitoring; •No routine systemic antimicrobial prophylaxis; •High alertness to PML
Immune checkpoint inhibitors	Ipilimumab (anti-CTLA4); Nivolumab, pembrolizumab, atezolizumab and others (anti-PD-1/anti-PD-L1)	No direct immunosuppression	Frequent immune-related auto-inflammatory complications; infections [illegible] to anti-inflam[illegible]	•High alertness to infections if anti-inflammatory/immunosuppressive [illegible]
Bruton Tyrosine Kinase Inhibitor	Ibrutinib	Toll-like receptor-mediated recognition of infectious agents; Maturation, recruitment and function of innate immune cells, including neutrophils, monocytes and macrophages; Regulation of $NLRP_3$ inflammasome activation	Slight increas[illegible] viral infection pretreated pati[illegible] Cerebral asper[illegible] for lymphoma	[illegible] prophylaxis
Phosphatidylinositol- 3-kinase inhibitor	Idelalisib	Decrease in number and function of regulatory T cells; Inhibition of NK cell and neutrophil inflammatory response; Neutropenia	Slight increase in Pneumocystis pneumonia	•Anti-Pneumocystis prophylaxis (see label); •Check CMV serostatus and consider CMV monitoring; •At signs of infection, consider immune-related adverse reaction
Histone deacetylase inhibitors	Vorinostat, panobinostat, romidepsin	Inhibition of toll-like receptor-mediated dendritic cell and macrophage function (sensing, phagocytosis, cytokine production, adhesion)	No clear evidence of increased infection rate	•HBV screening, consideration of antiviral prophylaxis in HBsAg- or anti-HBc-positive patients
mTOR inhibitors	Sirolimus, temsirolimus, everolimus	Inhibition of T-cell proliferation, antigen-presenting cells, B cells, neutrophil granulocytes	No clear evidence of increased infection rate	•High alertness of infections; •No routine antimicrobial prophylaxis; •At signs of pulmonary infection,

- **Çok iyi tanımlanmamış**
- **Hafıza hücrelerini etkiliyor?**
- **TB - Listeria açısından belirgin ilişki gösterilememiş**
- **CMV izlemi**

ECIL 2019. Leukemia
https://doi.org/10.1038/s41375-019-0388-x

CD30 antikoru: Brentuximab vedotin (BV)

- HSV / VZV olguları var, ancak açık bir ilişki ?
- Tek başına kullanımda rutin PCP profilaksisi GEREKMEZ (PCP nadir). BV + eş zamanlı diğer kemoterapötikler ile gerekebilir
- **ECIL:** CMV monitorizasyonu
- **Kuzey Amerika Rehberi:** CMV ile uyumlu semptomların varlığında CMV akla gelmelidir, ancak pr[illegible]ilmez
- PML ile uyumlu yeni baş[illegible]JC virüs akla gelmelidir

Antimikrobiyal profilaksi ile ilgili spesifik öneri YOK

İmmün Checkpoint İnhibitörleri

Anti-CD30 antibody	Brentuximab vedotin	Poorly defined; impairment of memory cell generation and survival; transient neutropenia	Pneumocystis pneumonia; CMV and HBV reactivation; JC virus-associated PML	•CMV monitoring; •No routine systemic antimicrobial prophylaxis; •High alertness to PML
Immune checkpoint inhibitors	Ipilimumab (anti-CTLA4); Nivolumab, pembrolizumab, atezolizumab and others (anti-PD-1/anti-PD-L1)	No direct immunosuppression	Frequent immune-related auto-inflammatory complications; infections due to anti-inflammatory/ immunosuppressive agents	•High alertness to infections if anti-inflammatory/immunosuppressive agents are required; •Pneumocystis prophylaxis if glucocorticosteroid medication exceeds 3–4 weeks
Bruton Tyrosine Kinase Inhibitor	Ibrutinib		e in bacterial, fungal and s, particularly in heavily ients; rgillosis in patients treated a with brain involvement	•Update protective vaccinations before ibrutinib treatment;
Phosphatidylinositol- 3-kinase inhibitor	Idelalisib	Decrease in number and function of regulatory T cells; Inhibition of NK cell and neutrophil inflammatory response; Neutropenia	Slight increase in Pneumocystis pneumonia	•Check CMV serostatus and consider CMV monitoring; •At signs of infection, consider immune-related adverse reaction
Histone deacetylase inhibitors	Vorinostat, panobinostat, romidepsin	Inhibition of toll-like receptor-mediated dendritic cell and macrophage function (sensing, phagocytosis, cytokine production, adhesion)	No clear evidence of increased infection rate	•HBV screening, consideration of antiviral prophylaxis in HBsAg- or anti-HBc-positive patients
mTOR inhibitors	Sirolimus, temsirolimus, everolimus	Inhibition of T-cell proliferation, antigen-presenting cells, B cells, neutrophil granulocytes	No clear evidence of increased infection rate	•High alertness of infections; •No routine antimicrobial prophylaxis; •At signs of pulmonary infection, consider immune-related adverse reaction
Janus kinase inhibitor	Ruxolitinib	Inhibition of dendritic cell and $CD4^+$ T-cell function; Reduction of regulatory T cells; NK cell inhibition	Marginally increased risk of opportunistic infections; Occasional HBV reactivation	•Careful monitoring for infections; •HBV screening, prophylactic entecavir in HBsAg- or anti-HBc-positive patients; •MTB screening in patients-at-risk

- **Yeni bir terapötik kavram**
- **Onaylı iki tane çekpoint var**
  - Anti-CTLA4
  - Anti-PD-1/Anti-PD-L1

- **İmmün ilişkili olaylar nedeniyle antiinflamatuar/ immünsüpresif kullanımı**
- **PCP prof. > 3-4 hf steroid**

ECIL 2019. Leukemia
https://doi.org/10.1038/s41375-019-0388-x

Agents	Pathway affected	Current indications	Increased risk of infection	Observations
Ipilimumab, tremelimumab	CTLA-4	Melanoma	Variable	• No intrinsic increase in the risk of infection • Increased risk of infection in patients developing irAEs and treated with additional immunosuppressive (i.e., corticosteroids and/or TNF-α-targeted agents)
Nivolumab, pembrolizumab, atezolizumab	PD-1 or PD-L1	Melanoma, NSCLC, HNSCC, Hodgkin lymphoma, urothelial carcinoma, bladder carcinoma, metastatic RCC, tumor with microsatellite instability	Variable	• No intrinsic increase in the risk of infection • Increased risk of infection in patients developing irAEs and treated with additional immunosuppressive (i.e., corticosteroids and/or TNF-α-targeted agents)
Alefacept	LFA-3/CD2 interaction	Plaque psoriasis (currently withdrawn)	Minor	• No apparent increase in the risk of infection (currently halted for economic reasons, not safety issues) • Transient peripheral blood CD4+ T-cell lymphopenia
Natalizumab, vedolizumab, efalizumab	α4β1, α4β7 and αLβ2 (CD11a subunit) integrins	MS, Crohn's disease, plaque psoriasis (currently withdrawn)	Major	• Increased risk of PML associated with the use of natalizumab and efalizumab (no cases described so far with vedolizumab) • Risk factors for natalizumab-induced PML include pre-treatment JCV serostatus, anti-JCV IgG antibody index, prior immunosuppression, and duration of treatment
Fingolimod	Sphingosine-1-phosphate receptor	Relapsing-remitting MS	Mild	• Increase in the risk of opportunistic infections, mainly due to herpesviruses (VZV) • Sustained, albeit reversible, peripheral blood lymphopenia (mostly affecting *naïve* and central memory CD4+ and CD8+ T-cell subsets)
Bortezomib, carfilzomib, ixazomib	Ubiquitin proteasome pathway	MM, relapsed or refractory mantle cell lymphoma	Major	• Increased risk of HZ and respiratory tract infections (including pneumonia) • Likely increased risk of influenza-related complications

!!!

PML

Zona

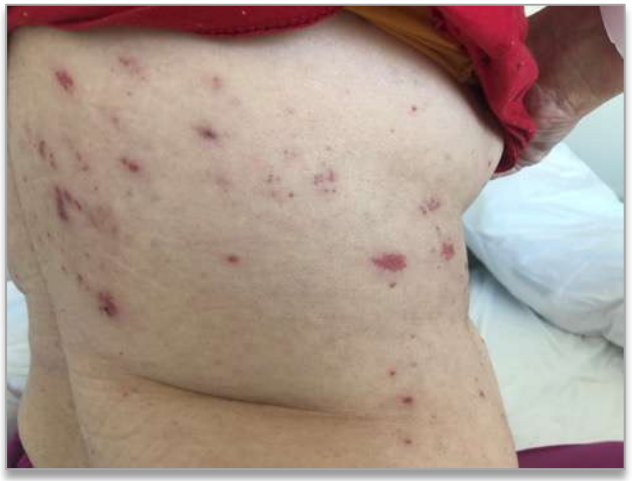
ACCEPTED MANUSCRIPT

Proteozom inhibitörleri : Bortezomib, carfilzomib, ixazomib

	observed (theoretical risk if persistent decrease of CD4+ T-cell counts)	observed (theoretical risk if persistent decrease of CD4+ T-cell counts)		vaccination for VZV-seronegative patients without history of varicella (at least 1 month before starting therapy) • HZ/su may be considered for VZV-seropositive patients aged ≥50 years	with (val)acyclovir may be considered for selected patients with additional risk factors (i.e., prolonged high-dose corticosteroid therapy)
Bortezomib, carfilzomib, ixazomib	No	May be considered for selected MM patients with additional risk factors (i.e., prolonged high-dose corticosteroid therapy)	Yes	• Live attenuated varicella vaccination for VZV-seronegative patients without history of varicella (at least 1 month before starting therapy) • HZ/su may be considered for VZV-seropositive patients aged ≥50 years • Seasonal TIV (at least 2 weeks before starting therapy and annually thereafter) • Completed pneumococcal vaccination series (PCN7 or PCN13 followed by PPV23) (at least 2 weeks before starting therapy) with revaccination 5 years latter with PPV23	Antiviral prophylaxis with (val)acyclovir for VZV-seropositive patients during induction therapy and for at least 4 weeks after its discontinuation

İnfluenza ilişkili komplikas yüksek

- **VZV seronegatif: 4 hf önce VZV aşısı**
- **VZV seropozitif: > 50 y, HZ aşısı**
- **Sezonal influenza aşısı**
- **Pnömokok aşıları**



Bruton tirozin kinaz (BTK) inhibitörü: İbritunib

- **B-hücre malignitelerinin tedavisinde** kritik öneme sahip

- **Kronik GVHD'de** bir veya daha fazla sistemik tedavi sonrasında kullanım için onaylanmış ilk ilaç

Bakteriyel, viral ve fungal enfeksiyonlarda HAFİF bir artış !!!!!

Bruton tirozin kinaz (BTK) inhibitörü: İbritunib

- En sık solunum yolu enfeksiyonları
  - ✓Ciddi pnömoni g.b
  - ✓PCP g.b

- Sporadik fırsatçı enfeksiyonlar bildirimleri var
  - Kriptokok enfeksiyonu (menenjit/dissemine enfeksiyon)
  - Tüberküloz (miliyer)
  - Endemik mikozlar
  - PML (öncesinde ritüksimab ile tedavi edilenler)
  - EBV'nin tetiklediği hemofagositik sendrom

Table 1 Summary of drug characteristics, reported infectious complications and ECIL recommendations for clinical practice

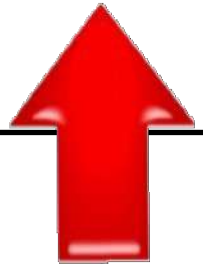
Class of agents	Agent	Impact on immune system	Infectious events	ECIL recommendations
CD19-directed CD3 bispecific T-cell engager	Blinatumomab	B-cell aplasia; hypogammaglobulinemia; neutropenia	No clear evidence of increased infection rate	•Consideration of IgG substitution in case of serious infection
Anti-CD30 antibody	Brentuximab vedotin	Poorly defined; impairment of memory cell generation and survival; transient neutropenia	Pneumocystis pneumonia; CMV and HBV reactivation; JC virus-associated PML	•CMV monitoring; •No routine systemic antimicrobial prophylaxis; •High alertness to PML
Immune checkpoint inhibitors	Ipilimumab (anti-CTLA4); Nivolumab, pembrolizumab, atezolizumab and others (anti-PD-1/anti-PD-L1)	No direct immunosuppression	Frequent immune-related auto-inflammatory complications; infections due to anti-inflammatory/ immunosuppressive agents	•High alertness to infections if anti-inflammatory/immunosuppressive agents are required; •Pneumocystis prophylaxis if glucocorticosteroid medication exceeds 3–4 weeks
Bruton Tyrosine Kinase Inhibitor	Ibrutinib	Toll-like receptor-mediated recognition of infectious agents; Maturation, recruitment and function of innate immune cells, including neutrophils, monocytes and macrophages; Regulation of $NLRP_3$ inflammasome activation	Slight increase in bacterial, fungal and viral infections, particularly in heavily pretreated patients; Cerebral aspergillosis in patients treated for lymphoma with brain involvement	•Update protective vaccinations before ibrutinib treatment; •Increased alertness to infections; •At signs of infection, diagnostics including bacterial, viral and fungal pathogens; •No routine systemic antimicrobial prophylaxis
Phosphatidylinositol- 3-kinase inhibitor	Idelalisib	Decrease in number and function of regulatory T cells; Inhibition of NK cell and neutrophil inflammatory response; Neutropenia	Slight increase in Pneumocy… pneumonia	…nti-Pneumocystis prophylaxis (see
Histone deacetylase inhibitors	Vorinostat, panobinostat, romidepsin	Inhibition of toll-like receptor-mediated dendritic cell and macrophage function (sensing, phagocytosis, cytokine production, adhesion)	No clear evidence… rate	
mTOR inhibitors	Sirolimus, temsirolimus, everolimus	Inhibition of T-cell proliferation, antigen-presenting cells, B cells, neutrophil granulocytes	No clear evidence of increased infection rate	•High alertness of infections; •No routine antimicrobial prophylaxis; •At signs of pulmonary infection, consider immune-related adverse reaction
Janus kinase inhibitor	Ruxolitinib	Inhibition of dendritic cell and $CD4^+$ T-cell function; Reduction of regulatory T cells; NK cell inhibition	Marginally increased risk of opportunistic infections; Occasional HBV reactivation	•Careful monitoring for infections; •HBV screening, prophylactic entecavir in HBsAg- or anti-HBc-positive patients; •MTB screening in patients-at-risk

Beyin tutulumu ile giden lenfomada→ serebral aspergilloz riski

ECIL 2019. Leukemia
https://doi.org/10.1038/s41375-019-0388-x

Bruton Tirozin Kinaz İnhibitorü: İbrutinib

AJAN	İMMÜN SİSTEMDEKİ ETKİSİ	ENFEKSİYONLAR	ECIL ÖNERİSİ
İbrutinib	• Düzenleyici T hücre sayı ve fonksiyonunda azalma • NK hücresi ve nötrofil enflamatuar yanıtının inhibis. • Nötropeni	• PCP'te hafif artış • Pnömoni • Beyin tutulumu ile seyreden lenfoma tedavisi gören hastalarda serebral aspergilloz	• İbrutinib tedavisi öncesi aşıları güncellenmeli • Enfeksiyonlara karşı alert olunmalı; Enfeksiyon bulgusu varsa bakteri, viral ve mantar patojenleri dahil • **Rutin sistemik antimikrobiyal profilaksi ÖNERİLMİYOR**



Enfeksiyöz komplikasyonlar ilk 6 ay sık, sıklıkla da ilk 2-3 ay

ECIL 2019. Leukemia
https://doi.org/10.1038/s41375-019-0388-x

Hücre içi sinyal yolları üzerine etkili ajanlar: Tirozin kinaz inhibitörleri, mTOR inhibitörleri

Agents	Increased risk of overall infection	Risk of OI	Risk of PCP	Risk of HBV reactivation	Observations and recommendations
Imatinib, dasatinib, nilotinib, bosutinib, ponatinib **BCR-ABL tirozin kinaz inhibtörleri**	Modest	IFI, HZ, tuberculosis, CMV (particularly with dasatinib)	No	Yes	• Higher risk of infection with dasatinib (particularly after HSCT) • Screening for chronic HBV infection before starting therapy • Antiviral prophylaxis while on therapy in HBsAg-positive patients • Monitoring for HBV viral load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection • No expected benefit from the universal use of antibacterial, antiviral or anti-*Pneumocystis* prophylaxis
Vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib selumetinib,	None	No	No	No	• No apparent increase in the risk of infection • Some of the most common drug-related adverse effects (pyrexia, fatigue, arthralgia and skin rash) may mimicry an ongoing infection
Ibrutinib, acalabrutinib **Bruton's tirozin kinaz inhibitörleri**	Modest	PCP, IFI, PML	Yes (particularly in presence of additional risk factors)	No	• Modest increase in the risk of infection (contributing role of prior or concurrent therapies or inherent immune defects) • No expected benefit from the universal use of antibacterial or antifungal prophylaxis • Anti-*Pneumocystis* prophylaxis for CLL patients with additional risk factors (e.g., purine analogues or high-dose corticosteroids) • PML occasionally associated with the use of ibrutinib

ACCEPTED MANUSCRIPT

Reinwald M et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors), *Clinical Microbiology and Infection* (2018)

Oral fosfotidil kinaz-3 (PK) inhibitörü: İdelalisib

PK3 inhibitörleri

JAK/STAT inhibitörleri

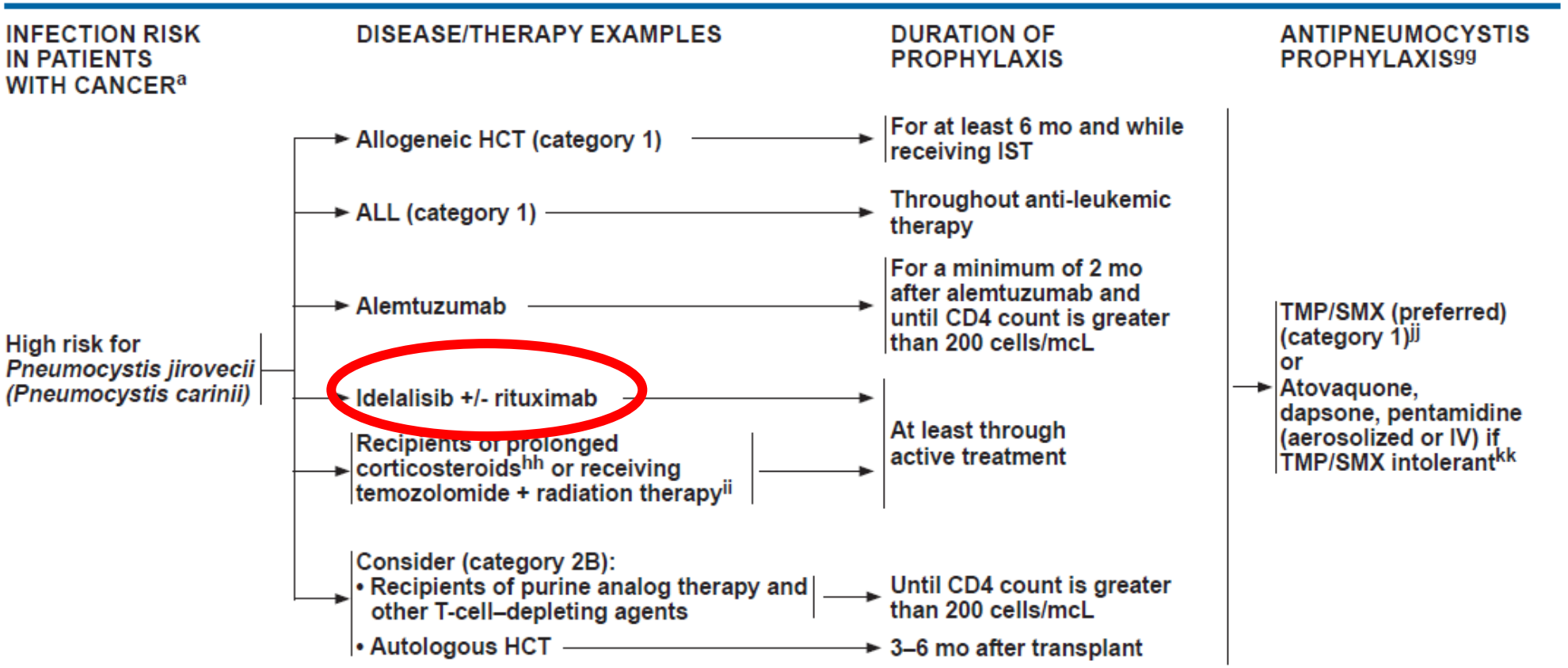
mTOR inhibitörleri

	Increased risk of overall infection	Risk of OI	Risk of PCP	Risk of HBV reactivation	Observations and recommendations
Idelalisib, buparlisib rigosertib, duvelisib	Major	IFI, PCP, CMV	Yes	No	• Increased risk of OIs and life-threatening adverse events (hepatotoxicity, colitis and pneumonitis). • Anti-*Pneumocystis* prophylaxis during the course of therapy and for 2-6 month after its discontinuation • Monitoring for CMV infection during the course of therapy in CMV-seropositive patients or in presence of suspected CMV disease • Discontinuation of therapy in presence of suspected pneumonitis or grade 3-4 aminotransferase elevation or diarrhoea/colitis
Ruxolitinib, tofacitinib, baricitinib	Major	PCP, HZ, tuberculosis, CMV, EBV, PML	Yes (particularly in presence of additional risk factors)	Yes	• Increased risk of overall infection and OIs • Screening for chronic HBV infection before starting therapy • Antiviral prophylaxis while on therapy in HBsAg-positive patients • Monitoring for HBV viral load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection • Screening for LTBI before starting treatment (followed by appropriate therapy if needed) • Anti-*Pneumocystis* prophylaxis in patients with additional risk factors (e.g., high-dose corticosteroids)
Sirolimus, everolimus temsirolimus,	Major	HZ, tuberculosis	No	Yes	• Increased risk of infection in cancer patients, especially in those with additional risk factors (i.e., RCC, prior or concomitant cancer therapies, delay in wound healing or aphthous stomatitis). • Screening for chronic HBV infection and LTBI before starting therapy (followed by appropriate therapy if needed)

ACCEPTED MANUSCRIPT

Reinwald M et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors), *Clinical Microbiology and Infection* (2018)

Oral fosfotidil kinaz-3 (PK) inhibitörü: İdelalisib



NCCN, 2019

Oral fosfotidil kinaz-3 (PK) inhibitörü: İdelalisib

- Antimikrobiyal profilaksi önerisi YOK

- PCP profilaksisi VAR → **Tedavisi sırasında ve kesilmesinden sonra 2-6 ay TMP-SMZ profilaksisi**

- CMV monitorizasyonu → **CMV serolojisi bakılmalı**
  CMV PCR takibi: En azından 4 hf da
  Artış: Gansiklovir/valgansiklovir

mTOR inhibitors:
Sirolimus, temsirolimus, everolimus

ECIL: enfeksiyon risk artışı için kesin kanıt yok diyor

- **Enfeksiyon riskinde artış:** kanser zemininde diğer RF olanlarda var
- Antibakteriyel, antiviral, anti-PCP profilaksi önerisi YOK
- HBV risk artışı VAR → **HBV taranmalı, gerekiyorsa tedavi edilmeli**
- LTBI'ye DİKKAT → **Tedavi başlanmadan taranmalı**

Reinwald M et al. (ESGICH) Consensus Document *Clinical Microbiology and Infection* (2018)

Ruxolitinib

- JAKs inhibitörü
- **Ruxolitinib:** IL-1b, IL-6 ve TNF-alfa down regülasyonu
  miyelofibrozun konstitüsyonel semptomlarını ha
- **İleri miyelofibroz** ve **polistemia vera** anılmaktadır
- İmmünmodülatör etki ve etkisi

Genel olarak bakteriyel, viral, mantar ve parazitik enfeksiyonlarda ARTIŞ !!!!!

JAK/STAT İnhibitörleri: Ruxolitinib, tofacitinib, baricitinib

Agents	Increased risk of overall infection	Risk of OI	Risk of PCP	Risk of HBV reactivation	Observations and recommendations
Idelalisib, buparlisib, rigosertib, duvelisib **Ras/PI3K/Akt/ mTOR inhibitörleri**	Major	IFI, PCP, CMV	Yes	No	• Increased risk of OIs and life-threatening adverse events (hepatotoxicity, colitis and pneumonitis). • Anti-*Pneumocystis* prophylaxis during the course of therapy and for 2-6 month after its discontinuation • Monitoring for CMV infection during the course of therapy in CMV-seropositive patients or in presence of suspected CMV disease • Discontinuation of therapy in presence of suspected pneumonitis or grade 3-4 aminotransferase elevation or diarrhoea/colitis.
Ruxolitinib, tofacitinib, baricitinib **JAK/STAT inhibitörleri**	Major	PCP, HZ, tuberculosis, CMV, EBV, PML	Yes (particularly in presence of additional risk factors)	Yes	• Increased risk of overall infection and OIs • Screening for chronic HBV infection before starting therapy • Antiviral prophylaxis while on therapy in HBsAg-positive patients • Monitoring for HBV viral load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection • Screening for LTBI before starting treatment (followed by appropriate therapy if needed) • Anti-*Pneumocystis* prophylaxis in patients with additional risk factors (e.g., high-dose corticosteroids)
Sirolimus, everolimus temsirolimus, **mTOR inhibitörleri**	Major	HZ, tuberculosis	No	Yes	• Increased risk of infection in cancer patients, especially in those with additional risk factors (i.e., RCC, prior or concomitant cancer therapies, delay in wound healing or aphthous stomatitis). • Screening for chronic HBV infection and LTBI before starting therapy (followed by appropriate therapy if needed) • No expected benefit from the universal use of antibacterial, antiviral or anti-*Pneumocystis* prophylaxis

Reinwald M et al. (ESGICH) Consensus Document *Clinical Microbiology and Infection* (2018)

Ruxolitinib

- **HBV reaktivasyon riski**
  - HBV-seropozitiflerde antiviral (entekavir, tenofovir)
  - HBV seronegatif → CDC aşılama sonrası anti-HBs kontrolü, immünsüpreselerde ve yüksek riskli gruplarda yıllık aşılama

- **TB riskini:**
  - TB açısından öykü alınmalı
  - Epidemiyolojik RF mevcutsa (öyküsü, endemik alanlar, endemik bölgelerde geziler) latent TB taraması
  - PPD veya (tercihen) IGRA (yani Quanti-FERON testi) taranmalı
  - Özellikle ilk 6 ay

Table 1 Summary of drug characteristics, reported infectious complications and ECIL recommendations for clinical practice

Class of agents	Agent	Impact on immune system	Infectious events	ECIL recommendations
CD19-directed CD3 bispecific T-cell engager	Blinatumomab	B-cell aplasia; hypogammaglobulinemia; neutropenia	No clear evidence of increased infection rate	•Consideration of IgG substitution in case of serious infection
Anti-CD30 antibody	Brentuximab vedotin	Poorly defined; impairment of memory cell generation and survival; transient neutropenia	Pneumocystis pneumonia; CMV and HBV reactivation; JC virus-associated PML	•CMV monitoring; •No routine systemic antimicrobial prophylaxis; •High alertness to PML
Immune checkpoint inhibitors	Ipilimumab (anti-CTLA4); Nivolumab, pembrolizumab, atezolizumab and others (anti-PD-1/anti-PD-L1)	No direct immunosuppression	Frequent immune-related auto-inflammatory complications; infections due to anti-inflammatory/ immunosuppressive agents	•High alertness to infections if anti-inflammatory/immunosuppressive agents are required; •Pneumocystis prophylaxis if glucocorticosteroid medication exceeds 3–4 weeks
Bruton Tyrosine Kinase Inhibitor	Ibrutinib	Toll-like receptor-mediated recognition of infectious agents; Maturation, recruitment and function of innate immune cells, including neutrophils, monocytes and macrophages; Regulation of $NLRP_3$ inflammasome activation	Slight increase in bacterial, fungal and viral infections, particularly in heavily pretreated patients; Cerebral aspergillosis in patients treated for lymphoma with brain involvement	•Update protective vaccinations before ibrutinib treatment; •Increased alertness to infections; •At signs of infection, diagnostics including bacterial, viral and fungal pathogens; •No routine systemic antimicrobial prophylaxis
Phosphatidylinositol- 3-kinase inhibitor	Idelalisib	Decrease in number and function of regulatory T cells; Inhibition of NK cell and neutrophil inflammatory response; Neutropenia	Slight increase in Pneumocystis pneumonia	•Anti-Pneumocystis prophylaxis (see label); •Check CMV serostatus and consider CMV monitoring; •At signs of [illegible] consider [illegible]mune-related adverse reaction
Histone deacetylase inhibitors	Vorinostat, panobinostat, romidepsin	Inhibition of toll-like receptor-mediated dendritic cell and macrophage function (sensing, phagocytosis, cytokine production, adhesion)	No clear evidence of increased infectio[illegible] rate	•HBV screening, consideration of antiviral prophylaxis in HBsAg- or anti-HBc-positive patients
mTOR inhibitors	Sirolimus, temsirolimus, everolimus	Inhibition of T-cell proliferation, antigen-presenting cells, B cells, neutrophil granulocytes	No clear evidence of increased infection rate	•High alertness of infections; •No routine antimicrobia[illegible] prophylaxis; •At signs of pulmonary infe[illegible] consider immune-related adverse reaction
Janus kinase inhibitor	Ruxolitinib	Inhibition of dendritic cell and $CD4^+$ T-cell function; Reduction of regulatory T cells; NK cell inhibition	Marginally increased risk of opportunistic infections; Occasional HBV reactivation	•Careful monitoring for infections; •HBV screening, prophylactic entecavir in HBsAg- or anti-HBc-positive patients; •MTB screening in patients-at-risk

HBV !!!

ECIL 2019. Leukemia
https://doi.org/10.1038/s41375-019-0388-x

Venotoclax

- **Venetoclax→** Potent ve spesifik anti-apoptotic BCL-2 protein inhib.
- BCL-2 proteini apopitozise dirençli KLL hücrelerine yol açar
- **B-KLL tek başına ve AML'de** yoğun KT tolere edemeyen yaşlılarda düşük doz sitarabin veya azasitidin ile
- Tek immünsüpresif etkisi **sitopeni**dir
- Tedavinin **ilk 3 ayında nötropeni**
- Gerçek enfeksiyon riski bilinmiyor

ECIL 2019. Leukemia
https://doi.org/10.1038/s41375-019-0388-x

BCL2 inhibitör - Venetoclax

Table 2
Suggested prophylaxis by treatment regimen

Disease	Treatment Regimen	Prophylaxis Recommended?				
		Bacterial	CMV	HSV/VZV	IFI	PCP
AML	AML induction and consolidation	■		■	■	▒
	Azacitidine, Decitabine	▒		▒	■	▒
	Venetoclax + Azacitidine	■		▒	■	▒
ALL	ALL induction and consolidation	■		■	■	■
	ALL induction and consolidation + TKI	■		■	■	■
	Imatinib + steroids	▒		▒	■	■
	Dasatinib + steroids	▒		▒	■	■
	Blinatumomab	▒		▒	■	
	CD19 CAR-T	■		■	■	
MDS	Azacitidine, Decitabine	▒		▒	▒	
CLL	Purine analogues (FCR)	▒		■		■
	Chlorambucil + Rituximab					
	Bendamustine + Rituximab					
	Ibrutinib			■		■
	Venetoclax			▒	▒	▒
	Idelalisib	▒	[b]			■
	Alemtuzumab	■	[b]	■		■
CML	Imatinib			▒		

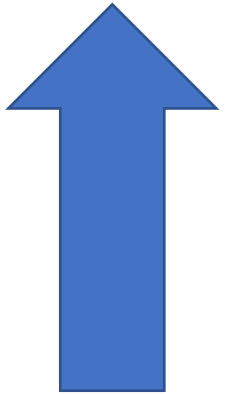
- **KLL** → Tek başına
  IFI profilaksisi yok
- **AML**→ Azasitidin ile kombine
  IFI profilaksisi var
  Bakteriyel profilaksi var
- Posakonazol ile kombine kullanımında venetoclax dozu % 75 azaltılmalı

Atkins S et al. Chemotherapy and Beyond. Infections in the Era of Old and New Treatments for Hematologic Malignancies.Infect Dis Clin N Am - (2019) -–-https://doi.org/10.1016/j.idc.2019.01.001

ECIL 2019. Leukemia
https://doi.org/10.1038/s41375-019-0388-x

TNF İnhibitörleri:
Infliximab, Adalimumab,Certolizumab, Golimumab, Etanercept

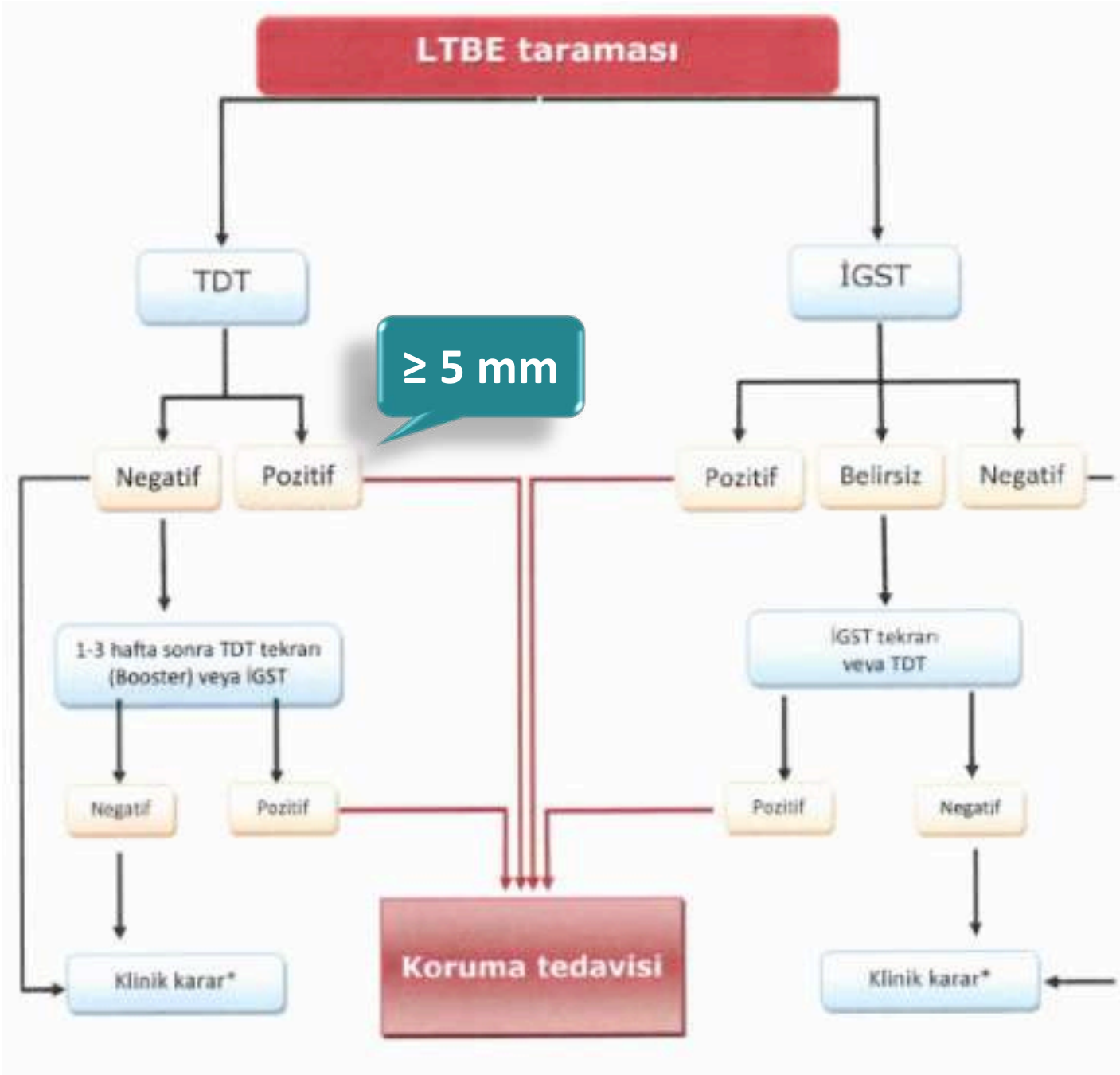
- **Tüberküloz** ve diğer granülomatöz enfeksiyonlar: **2-4 kat** artış
- Hücre içi bakteri enf (*L. monocytogenes* veya *Salmonella spp*)
- Viral enfeksiyonlar (HBV, VZV, JCV)
- İnvaziv fungal enfeksiyonlar (nötropeni)



TB açısından takip ?

Anti-TNF Kullanan Hastalarda Tüberküloz Rehberi, THSK 2016

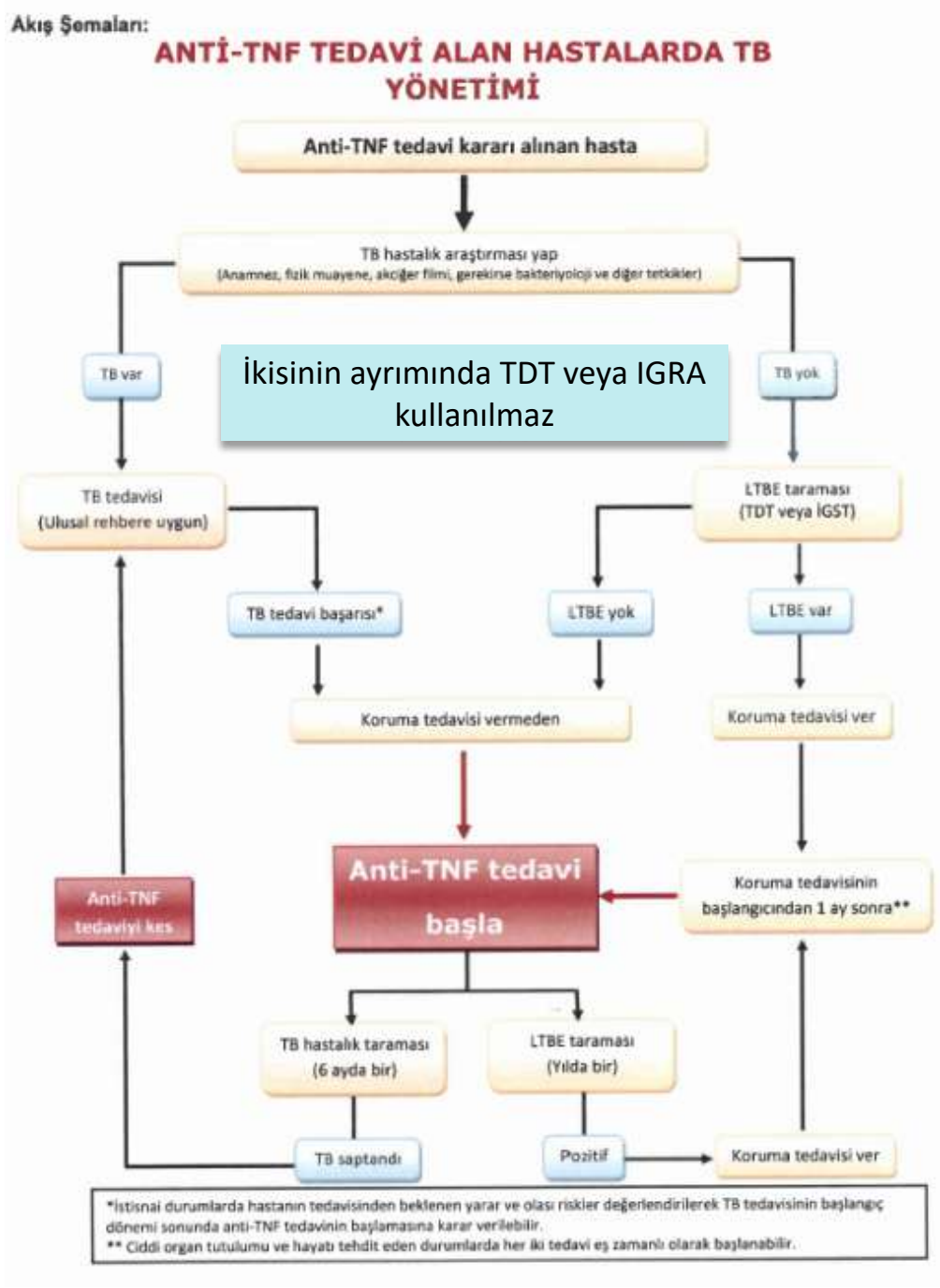
Koruma tedavisi:
9 ay INH
4 ay RİF



TB açısından takip ?

Anti-TNF Kullanan Hastalarda Tüberküloz Rehberi, THSK 2016

- ✓ Aktif TB dışlanmalı
- ✓ Aktif TB→ Tedavi tamamlanmadan anti-TNF tedavi başlanmamalı
- ✓ Anti-TNF kesildikten sonra en az 6 ay takip
- ✓ Anti-TNF başlanan hastalar asemptomatik olsalar bile TB açısından
  - ✓ 6 ayda: Anamnez, FM, radyoloji
  - ✓ Yılda: LTBI kontrolü



TNF İnhibitörleri

- **Kronik hepatit B açısından tarama:**
  - HBsAg pozitif → Antiviral tedavi
  - HBsAg- / antiHBc + → Viral yük takibi, gerekirse tedavi

- Bakteriyel profilaksi, antifungal profilaksi ve PCP profilaksi GEREKMEZ

- Pnömokok ve influenza aşısı

Kompleman komponent C5 antagonisti: Eculizumab

Membran atak kompleks oluşumunun inhibisyonu

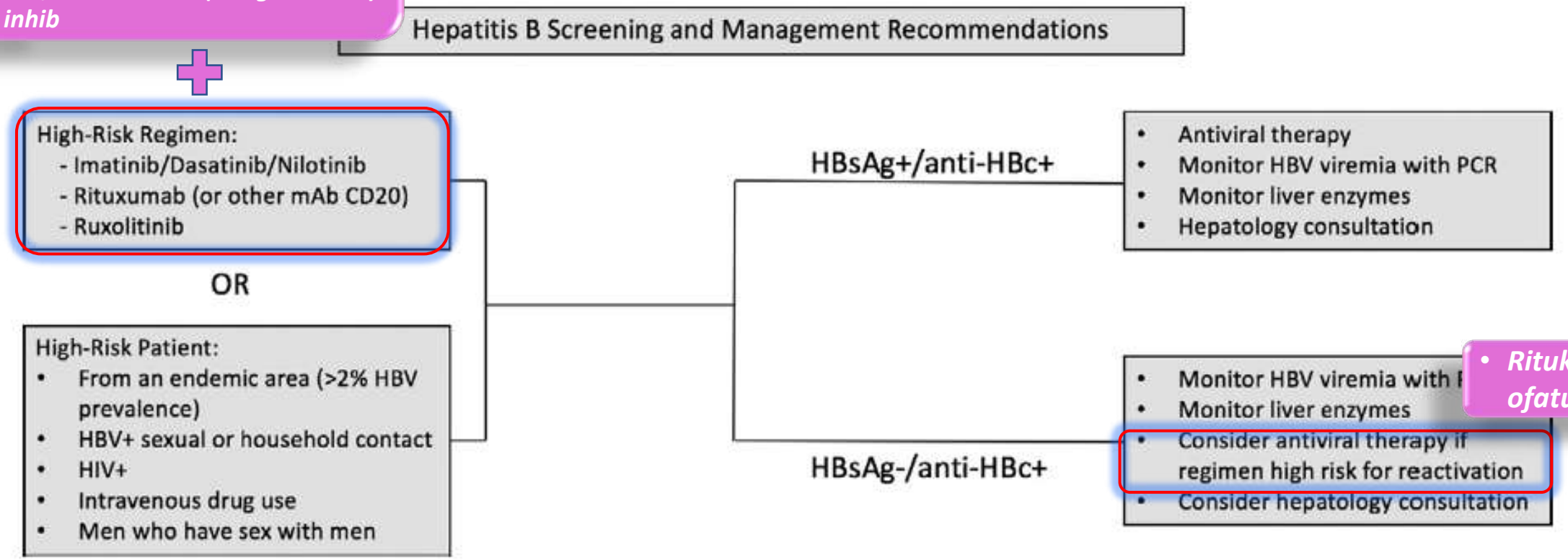
- *Neisseria* spp
- *S. pneumoniae*
- *H. influenzae*

İnvaziv meningokok 10.000 kat fazla

İnvaziv meningokokal hastalık
Dissemine gonokok enfeksiyonu

HBV Tarama ve Yönetimi

- *Alemtuzumab (anti-CD52)*
- *HDAC inhibitörleri*
- *Sirolimus, everolimus (mTOR inhib.)*
- *Natalizumab, vedolizumab (integrin inhib.)*
- *Anti-TNF inhib*



- *Rituksimab, ofatumumab*

Fig. 1. Screening and management recommendations for

- **1-3 ayda HBV DNA ve HBsAg bakılmalı**
- **HBV DNA pozitifleşirse, HBsAg seroreversiyonu olursa hemen tedavi**

Atkins S et al. Chemotherapy and Beyond. Infections in the Era of Old and New Treatments for Hematologic Malignancies.Infect Dis Clin N Am - (2019) -–-https://doi.org/10.1016/j.idc.2019.01.001

HBV Profilaksisi

- **PROFİLAKSİ :** 1-3 hf önce başlanmalı, en geç immünsüpresif tedavi ile birlikte

- **İLAÇ:** ETV / TDF / TAF

- **SÜRESİ:** İmmünsüpresyon kesildikten sonra 1 yıl daha (Ritux 18 ay)
- İmmünsüpresyon kesilmeyenlerde profilaksiye devam edilmelidir

Aygen B et al. Turk J Gastroenterol. 2018 May; 29(3): 259–269.

Table 2
Suggested prophylaxis by treatment regimen

CMV 'de profilasi YOK

Disease	Treatment Regimen	Prophylaxis Recom[12]				
		Bacterial	CMV	HSV/VZV	IFI	PCP
AML	AML induction and consolidation	■		■	■	▒
	Azacitidine, Decitabine	▒		▒	■	▒
	Venetoclax + Azacitidine	■		▒	■	▒
ALL	ALL induction and consolidation	■		■	■	■
	ALL induction and consolidation + TKI	■		■	■	■
	Imatinib + steroids	▒		▒	■	■
	Dasatinib + steroids	▒		▒	■	■
	Blinatumomab	▒		▒	■	
	CD19 CAR-T	■		■	■	
MDS	Azacitidine, Decitabine	▒		▒	▒	
CLL	Purine analogues (FCR)	▒		■		■
	Chlorambucil + Rituximab					
	Bendamustine + Rituximab					
	Ibrutinib			■		■
	Venetoclax			▒	▒	▒
	Idelalisib	▒	[b]			■
	Alemtuzumab	■	[b]	■		■
CML	Imatinib			▒		
	Dasatinib			▒		
High Grade Non- Hodgkin Lymphomas	R-CHOP/CHOP	▒				
	R-DHAP, R-ICE	▒				
	DA-R-EPOCH	▒				
	R-HyperCVAD	▒				
	CD19 CAR-T	■		■		
	Ibrutinib			■		■
Hodgkin	ABVD	▒				
	A-AVD (Brentuximab + AVD)	▒				■
	Escalated BEACOPP	▒				
	Brentuximab	▒	[a]			[a]
	Nivolumab/Pembrolizumab	▒				
Low Grade Non- Hodgkin Lymphomas	Rituximab monotherapy					
	R-CVP	▒				
	BR	▒				
Myeloma	RD	▒				▒
	RVD/KRD	▒		■		▒
	Lenalidomide maintenance	▒	[a]			[a]
	Bortezomib maintenance	▒	[a]	■		[a]
	Daratumumab	▒				▒
	VDT-PACE	▒				▒
MPN	Ruxolitinib			■		

■	▒	
Recommended	Consider for multiply relapsed disease or susceptible host[c] during periods of neutropenia	Not recommended

Atkins S et al. Chemotherapy and Beyond. Infections in the Era of Old and New Treatments for Hematologic Malignancies.Infect Dis Clin N Am - (2019) -–-https://doi.org/10.1016/j.idc.2019.01.001

Table 2 Recommended Adult Immunization Schedule by Medical Condition and Other Indications United States, 2019

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 count <200	HIV infection CD4 count ≥200	Asplenia, complement deficiencies	End-stage renal disease, on hemodialysis	Heart or lung disease, alcoholism[1]	Chronic liver disease	Diabetes	Health care personnel[2]	Men who have sex with men
IIV or RIV	1 dose annually										
or										or	
LAIV	CONTRAINDICATED						PRECAUTION			1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td booster every 10 yrs									
MMR	CONTRAINDICATED				1 or 2 doses depending on indication						
VAR	CONTRAINDICATED				2 doses						
RZV (*preferred*)	DELAY	2 doses at age ≥50 yrs									
or											
ZVL	CONTRAINDICATED	1 dose at age ≥60 yrs									
HPV Female	DELAY	3 doses through age 26 yrs			2 or 3 doses through age 26 yrs						
HPV Male		3 doses through age 26 yrs			2 or 3 doses through age 21 yrs						2 or 3 doses through age 26 yrs
PCV13		1 dose									
PPSV23		1, 2, or 3 doses depending on age and indication									
HepA		2 or 3 doses depending on vaccine									
HepB		2 or 3 doses depending on vaccine									
MenACWY	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains										
MenB	PRECAUTION	2 or 3 doses depending on vaccine and indication									
Hib		3 doses HSCT[3] recipients only			1 dose						

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction

Delay vaccination until after pregnancy if vaccine is indicated

Contraindicated—vaccine should not be administered because of risk for serious adverse reaction

No recommendation

1. Precaution for LAIV does not apply to alcoholism. 2. See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. 3. Hematopoietic stem cell transplant.

Profilaksi

CMV	HSV/VZV	HBV	PCP	LTBI	PML
Alemtuzumab	Alemtuzumab	Rituksimab	Alemtuzumab	TNF inhibitörleri	Rituksimab
Brentuximab	Bortezomib/ Carfilzomib	Diğer CD20 antikorlar	İbritunib	Ruxolitinib	Natalizumab/ efalizumab
İdelalisib		Alemtuzumab	İdelalisib	mTOR inh (everolimus/sirolimus)	Brentuximab vedotin
Bortezomib		İmatinib/dasatinib	Pürin analogları		
			Ruxolutinib		
			Rituksimab + KS veya KT		
			İmatinib + steroid		
			Dasatinib + steroid		

Ne kalsın aklımızda…..

- **Alemtuzumab :** Ciddi immünsüpresyon
- **CD20 ve CD19:** Hipogamaglobulinemide IG replasmanı, HBV reaktivasyonu
- **Brentuximab vedotin:** PML riski
- **Natalizumab, vedolizumab:** PML dikkat, JCV IgG takibi
- **Venotoclax:** AML için kombine kullanımda IFI profilaksisi
- **TNF-alfa inb:** TB riski, tedavi öncesi tarama, HBV tarama

Teşekkürler….