KANSER TEDAVİSİNDE YENİ MOLEKÜLLER VE İNFEKSİYON

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HEDEFE YÖNELİK TEDAVİ NE DEMEK?

- Kanser gelişimine neden olan moleküler anormalliğe veya hedefe karşı doğrudan geliştirilen tedavi…

- **ÖRNEK:**
  - Tirozin Kinaz yolağı (bcr-abl, PDGF)
  - Proteozomal yolaklar
  - Sağ kalım sinyalleri (MCL1, BCL2)
  - “heat shock” proteinler
  - İmmünolojik aktivasyon/tolerans

HEDEFE YÖNELİK TEDAVİ (?)

- Hücre büyüme sinyalini bloke ederek
- Yeni damar oluşumunu inhibe ederek
- Apoptosis indükleyerek
- İmmün sistemi uyararak
- Kanser hücresine toksisite gösterecek molelekülü kanser hücresine ulaştırarak

YENİ MOLEKÜLLER NASIL OKUMALI ?

Generic naming formula:

Name = prefix + substem(s) + stem →

variable

-mab	monoclonal antibody
-ib	small molecule with inhibitory properties

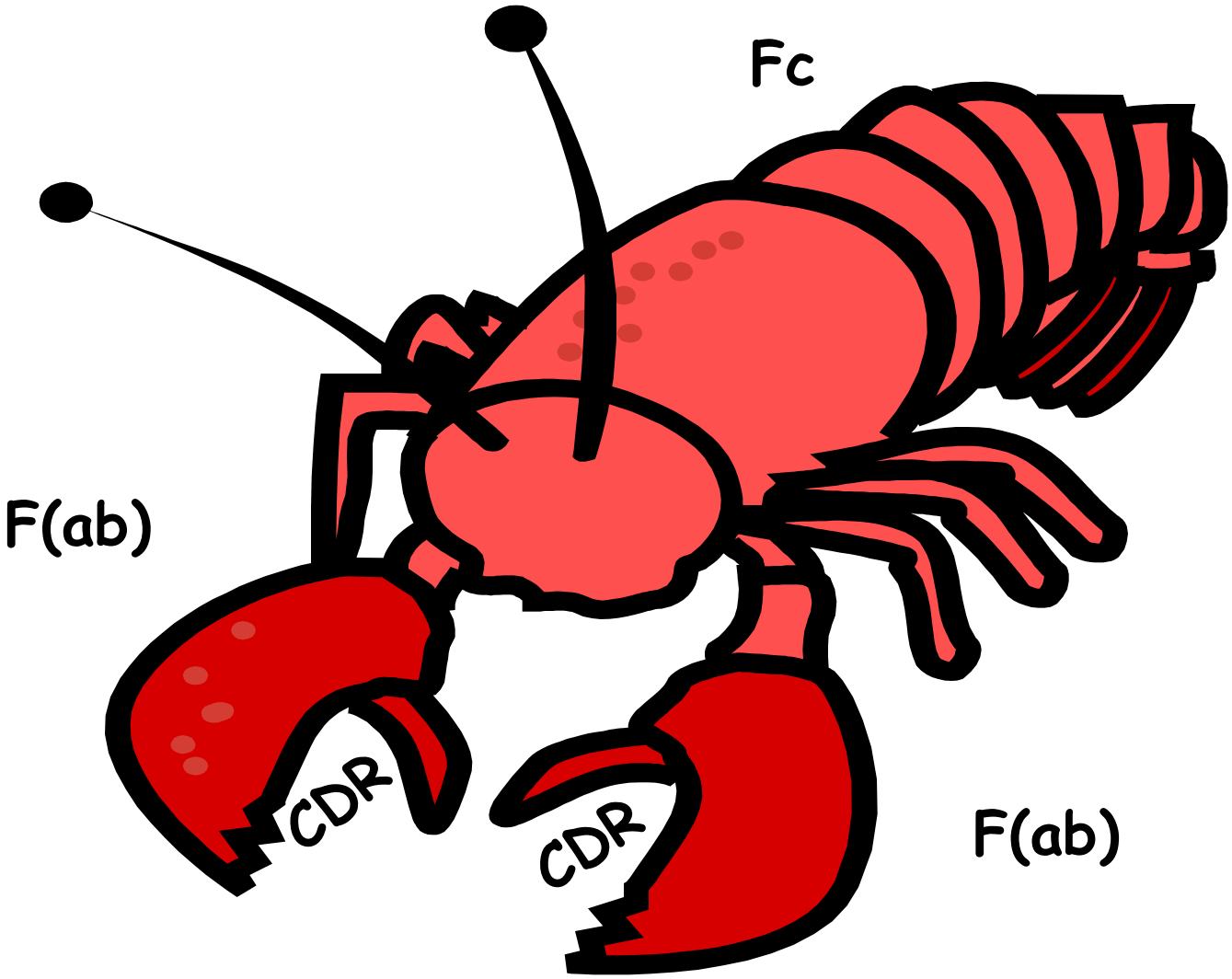
Monoclonal antibodies

Target		*Source*	
-ci(r)-	circulatory system	-ximab	chimeric human-mouse
-li(m)-	immune system	-zumab	humanized mouse
-t(u)-	tumor	-mumab	fully human

Small molecules

-tinib	tyrosine kinase inhibitor
-zomib	proteasome inhibitor
-ciclib	cyclin-dependent kinase inhibitor
-parib	poly ADP-ribose polymerase inhibitor

MONOKLONAL ANTİKORLAR



MONOKLONAL ANTİKORLAR

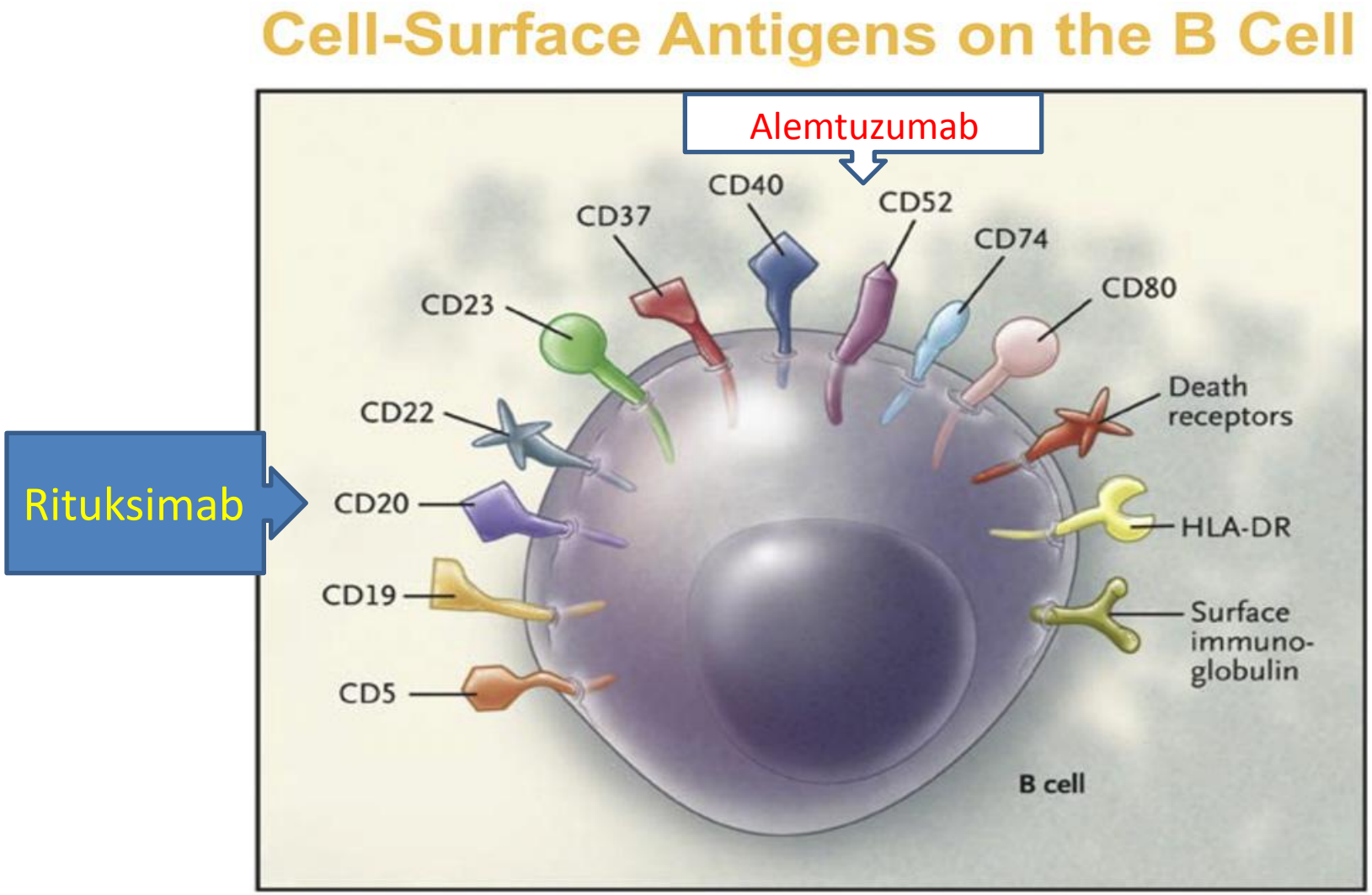
- Büyük moleküller
- Genetik mühendisliğin ürünleri
- Genellikle IV yol ile uygulanıyorlar
- Yan etkiler genellikle non-human proteinler ile ilişkili
- Genellikle bir çok farklı yolla etkililer
- Genellikle hücre yüzey reseptörleri üzerinden etkililer

MONOKLONAL ANTİKORLAR

MONOKLONAL ANTİKORLAR

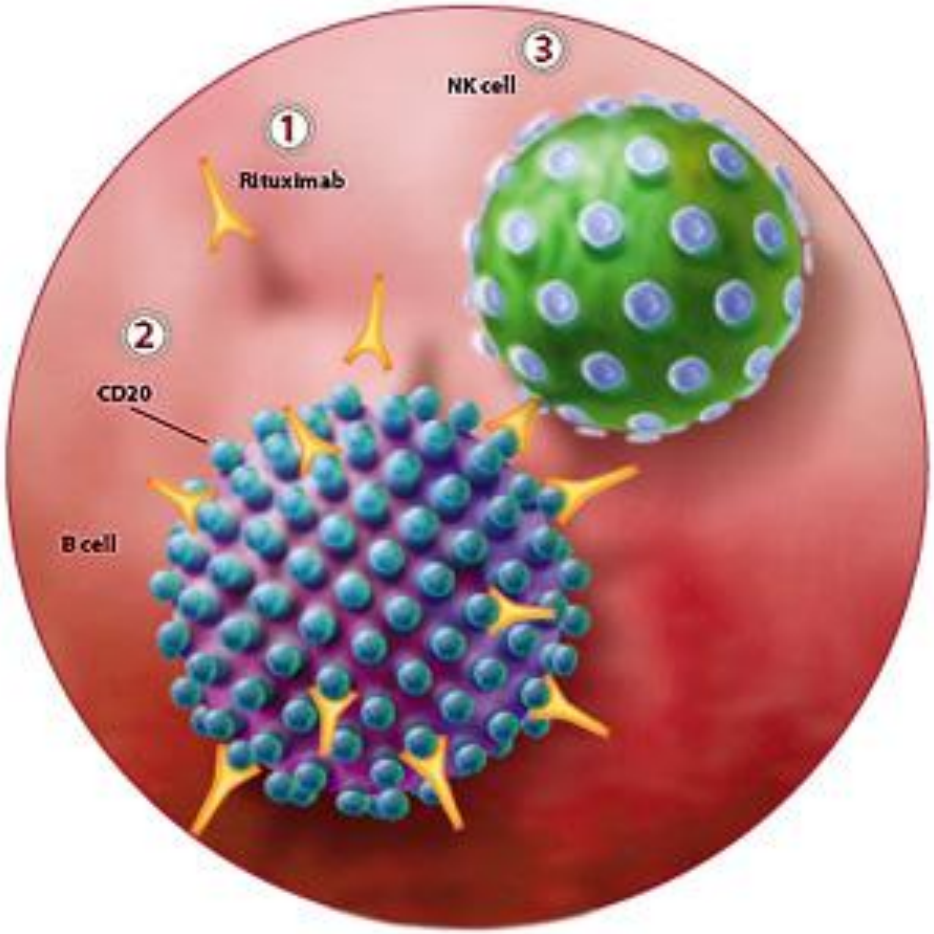
JENERİK İSİM	FİRMA İSMİ	HEDEF	KANSER
ALEMTUZUMAB	Campath	CD52	KLL, Lenfoma
Bevacizumab	Avastin	VEGF	Çok sayıda kanser
Cetuximab	Erbitux	EGFR1	Kolon, Baş-boyun
Panitumumab	Vectibix	EGFR1	Kolon
RITUXIMAB	Rituxan	CD20	Lenfoma
Trastuzumab	Herceptin	HER-2	Meme
BRENTUXIMAB	Adcetris	CD30	Hodgkin Hastalığı
GEMTUZUMAB	Myelotarg	CD33	AML

RITUXIMAB & ALEMTUZUMAB



Bruce D. Cheson, Best Practice & Research Clinical Haematology ,2010

RİTUKSİMAB



RİTUKSİMAB... Öykünün Başlangıcı

- Preliminary analysis revealed **no major difference** between the two arms in hematological toxicity, or in **grade 3 or 4 infection**, mucositis, vomiting, liver, cardiac, neurological, renal or lung toxicity.

- **R-CHOP : grade II-IV infeksiyon: %41**
- **CHOP : grade II-IV infeksiyon: %45**

Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235 – 242.

RİTUKSİMAB... etki mekanizması

- **Rituksimab etkinliği:**
  - **Kompleman bağımlı sitotoksisite (CDC)**
  - **Antikor bağımlı hücresel sitotoksisite (ADCC)**
  - **Apoptosis indüksiyonu**
  - **Kemoterapiye artmış duyarlılık**

RİTUKSİMAB… B hücre sayıları

- **Rituksimab etkinlik süresi:**
  - **Periferik B hücre deplesyonu ilk dozu izleyen 24-48 h**
  - **Tedavi sonrası 6-9. aylarda düzelmeye başlar**
  - **Normal düzeyler 9-12. aylarda sağlanır**
  - **Otolog KIT hazırlama normal düzeyler 24. ayda sağlanır…**

RİTUKSİMAB… B hücreleri

Swiss Group for Clinical Cancer Research Study

Objektif: uzun süreli vs kısa süreli RİTUKSİMAB

Kısa süreli kullanım : B hücreleri 12 ayda normal

4 ek infüzyon : 12. ay sonunda B hücreleri düşük…

Uzamış kullanımda : IgM depresyonu

İNFEKSİYON SIKLIĞINDA FARK YOK…

Ghielmini M, Schmitz SF, Cogliatti S, Bertoni F, Waltzer U, Fey MF, et al. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). J Clin Oncol 2005;23:705 – 711.

RİTUKSİMAB... Ig düzeyleri...

- **Ig düzeyleri düşüyor...**
  - **Ig G : 12 ay**
  - **Ig M: 6 ay**
  - **Ig A : 9 ay sırasında en düşük düzeye iniyor.**
- **Klinik anlamı var mı?...**

Rao A, Kelly M, Musselman M, et al. Safety, efficacy, and immune reconstitution after rituximab therapy in pediatric patients with chronic or refractory hematologic autoimmune cytopenias. Pediatr Blood Cancer 2008;50:822–825.

RİTUKSİMAB... Ig düzeyleri...

- **AYKIRI SONUÇ:**
- **Lenfoma hastalarında hazırlama rejimlerinde Rituksimab varlığı serum immunoglobulin düzeylerini etkilemiyor.**

Copelan E, Pohlman B, Rybicki L, et al. A randomized trial of etoposide and G-CSF with or without rituximab for PBSC mobilization in B-cell non-Hodgkin's lymphoma. Bone Marrow Transplant 2009;43:101–105.

RİTUKSİMAB... Ig düzeyleri...

- **Hipogammaglobulinemi**
- **6 doz Rituksimab ve fazla alanlarda daha belirgin**

Filanovsky K, Shvidel L, Shtalrid M, Haran M, Duek A, Berrebi A. Predictive factors to hypogammaglobulinemia and non-neutropenic infection complications after rituximab/chemotherapy treatment. Blood 2007;110:Abstract 1288.

RİTUKSİMAB... immünolojik etki...

- **Rituksimab kullanımından aylar sonra...**
  - **Akut romatoid artirit**
  - **Lökositoklastik vaskülit**
  - **Psoriatik deri değişiklikleri**
- **Rituksimab kullanımından 1-13 gün sonra**
  - **Serum hastalığı**
- **B HÜCRE DEPLESYONU SONUCU...**

RİTUKSİMAB... İnfeksiyon ne kadar sık ?

356 olgu:

İnfeksiyon oranı	**:**	**%30**
Bakteriyal infeksiyonlar	**:**	**%19**
Viral infeksiyonlar	**:**	**%10**
Fungal infeksiyon	**:**	**%1**
Sepsis: (rituksimab tedavisi sırasında)	**:**	**%1**
Sepsis: (takip sırasında)	**:**	**%2**

Kimby E. Tolerability and safety of rituximab (MabThera). Cancer Treat Rev 2005;31:456 – 473.

RİTUKSİMAB… neden artmış infeksiyon ?

- **Rituksimab'ın infeksiyon gelişim riski:**
  - **Nötropeni süresi ile ilişkisiz**
  - **B cell depletion ***
  - **T hücreleri (CD3, CD4 ve CD8) sabit**
  - **NK hücre sayıları sabit**
  - **Ig M, G düzey düşüklüğü ***

McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R,Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825 – 2833

RİTUKSİMAB… Sitopeni…

- **Grade 3/4 nötropeni : %4.2**
- **Trombositopeni : %1.7**
- **Anemi: % : %1.1**

- **LATE ONSET TROMBOSİTOPENİ**
- **LATE ONSET ANEMİ:**

McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R,Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825 – 2833

RİTUKSİMAB... agranülositozis

- **Agranülositoz:**
- **Genellikle 4 kür R-kemoterapi sonrası**
- **Ortalama 11. gün**

Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med 2007;146:657–665.

RİTUKSİMAB… Late Onset Neutropenia

- **130 hasta, retrospektif analiz:**
- **12 ay takip (12–132)**

- **Late Onset Neutropenia: insidans: %8 vs %0**

Dunleavy K, Hakim F, Kim HK. B-cell recovery following rituximab-based therapy is associated with perturbations in stromal derived factor-1 and granulocyte homeostasis. Blood 2005;106:795–802.

RİTUKSİMAB… Late Onset Neutropenia

- Tedavinin bitiminden **4 hafta sonra**
- Mutlak nötrofil sayısı **≤1.5 × 10^9/L**
- **6-12. aylara** dek sürebilir.

- **Riskler:**
- Önceden tedavi (kümülatif rituksimab)
- Yüksek doz metotreksat
- HSCT (otolog ve allogeneik)

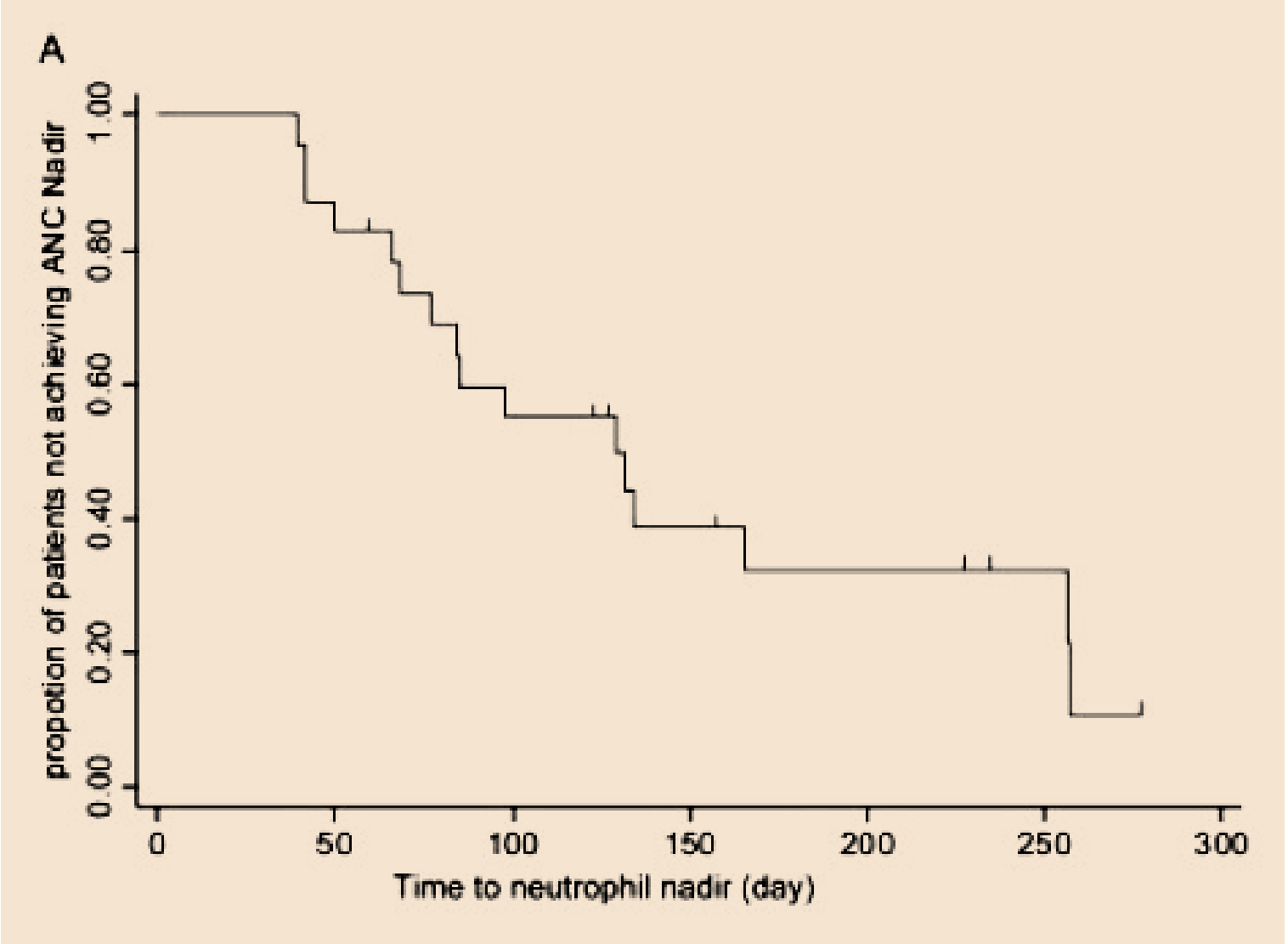
RİTUKSİMAB… Late Onset Neutropenia

- **Rituksimab içeren rejimlerde**
  - **Grade 3-4 LON sıklığı : 25%… (?)**
  - **Ortaya çıkma süresi : 46–384 gün…**
  - **İyi tolere edilen ve "self limited"…**
  - **GCSF etkili…**

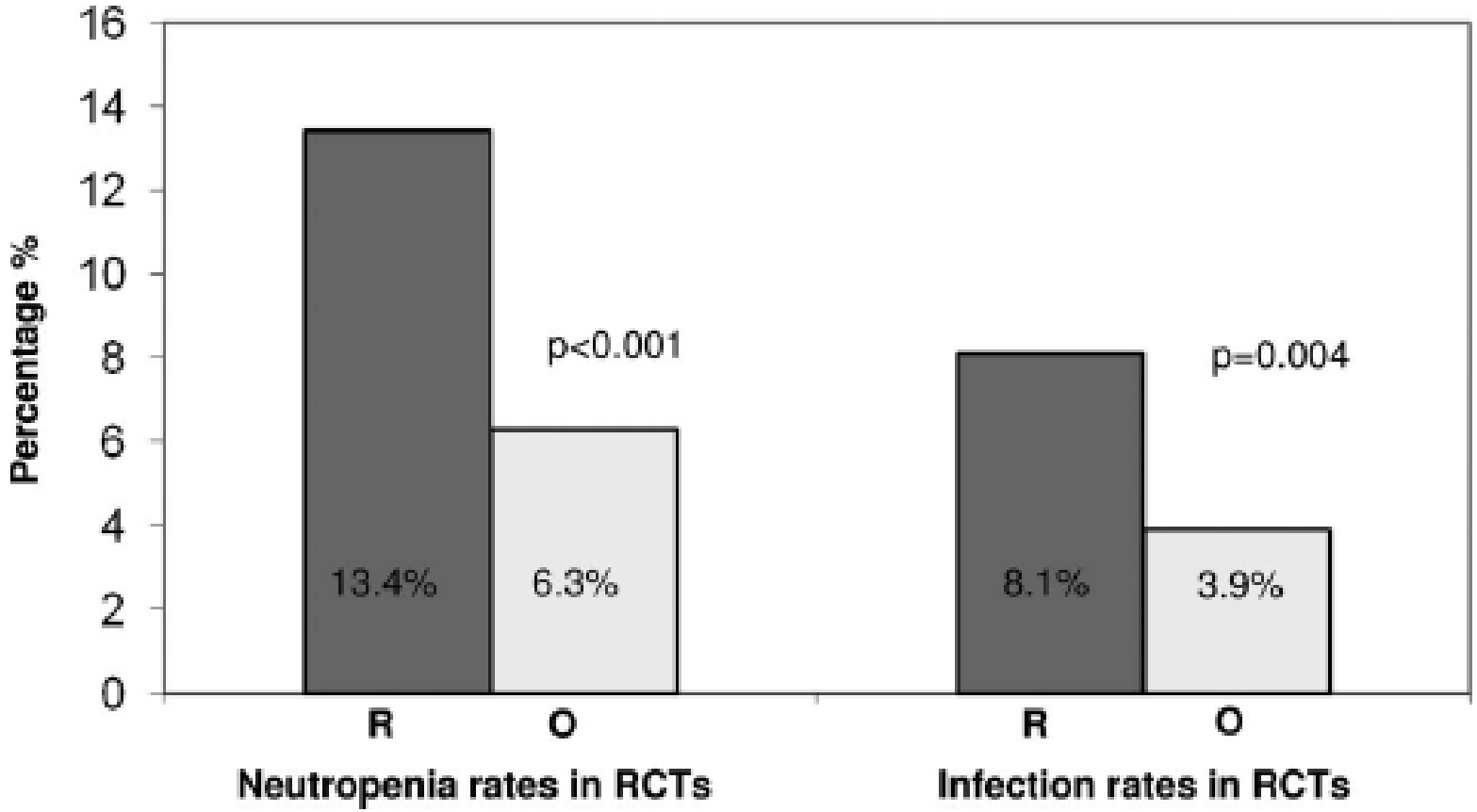
Nitta E, Izutsu K, Sato T, et al. A high incidence of late-onset neutropenia following rituximab-containing chemotherapy as a primary treatment of CD20-positive B cell lymphoma: a single- institution study. Ann Oncol 2007;18:364–369

Lemieux B, Tartas S, Traulle C, et al. Rituximab-related late-onset neutropenia after autologous stem cell transplantation for aggressive non-Hodgkin's lymphoma. Bone Marrow Transplant 2004;33:921–923.

RİTUKSİMAB... Late Onset Neutropenia



RİTUKSİMAB... Ne kadar sık ?



Aksoy S, Dizdar Ö, Hayran M, Harputluoğlu H. İnfectious complications of rituximab in patients with lymphomaduring maintenance therapy: a systematic review and meta-analysis.Leukemia&Lymphoma: 2009; 50:357-365

RİTUKSİMAB... Viral infeksiyonlar

- Hepatit B
- CMV
- Varisella Zoster
- Nadir olanlar
  - West Nile" virus
  - İnfluenza, parainfluenza
  - RSV

RİTUKSİMAB... İnfeksiyon ne kadar sık ?

META-ANALİZ:

Oportunistik İnfeksiyon sıklığı:

		299 hasta	(%31)
Nedeni gösterilemeyen	:	109 hasta	(%36.5)
Viral re-aktivasyon	:	100 hasta	(%33.4)
Bakteriyel infeksiyon	:	44 hasta	(%14.7)
Fungal infeksiyon	:	26 hasta	(%8.7)
Protozoal infeksiyon	:	11 hasta	(%3.7)
Viral infeksiyon	:	9 hasta	(%3.0)

Cornely OA, Ullmann AJ, Heidecke CN, Karthaus M. Opportunistic infections (OI) following monoclonal antibody treatment. J Clin Oncol ASCO Ann Meeting Proc 2005;23(16S, Part I of II (June 1, Suppl.)):2562.

RİTUKSİMAB... İnfeksiyon ne kadar sık ?

META-ANALİZ:

Viral reaktivasyon

Sitomegalovirus:	**58 hasta (%19.4)**
Herpes Simpleks:	**30 hasta (%10)**
Varicella Zoster:	**11 hasta (%3.7)**
Epstein Barr virus:	**1 hasta (%0.3)**
P.Carinii:	**11 hasta (%3.7)**

Cornely OA, Ullmann AJ, Heidecke CN, Karthaus M. Opportunistic infections (OI) following monoclonal antibody treatment. J Clin Oncol ASCO Ann Meeting Proc 2005;23(16S, Part I of II (June 1, Suppl.)):2562.

RİTUKSİMAB... İnfeksiyon ne kadar sık ?

META-ANALİZ:

OPORTUNİSTİK İNFEKSİYONLARA BAĞLI ÖLÜM ORANI

20 HASTA (%2)

Cornely OA, Ullmann AJ, Heidecke CN, Karthaus M. Opportunistic infections (OI) following monoclonal antibody treatment. J Clin Oncol ASCO Ann Meeting Proc 2005;23(16S, Part I of II (June 1, Suppl.)):2562.

RİTUKSİMAB... İnfeksiyon ne kadar sık ?

Viral İnfeksiyon sıklığı:

HBV (39.1%)

CMV (23.4%)

VZV (9.4%)

Diğer (28.1%)

HBV infeksiyonu olan %52 hasta karaciğer yetmezliği nedeniyle kaybedildi.

Aksoy S, Harputluoglu H, Kılıckap S, Dede DS, Dizdar O, Altundag K, Barista I. Rituximab-related viral infection Leukemia&Lymphoma 2007; 48(7): 1307-12

RİTUKSİMAB... İnfeksiyon ne kadar sık ?

- **<u>İnfeksiyonun görülme zamanı: (tanı-infeksiyon)</u>**
- **5.0 ay (1 – 20 ay)**

- **<u>HBV görülme zamanı: (tanı-infeksiyon)</u>**
- **6.0 ay (3 – 27 ay)**

Aksoy S, Harputluoglu H, Kılıckap S, Dede DS, Dizdar O, Altundag K, Barista I. Rituximab-related viral infection Leukemia&Lymphoma 2007; 48(7): 1307-12

RİTUKSİMAB... İnfeksiyon ne kadar sık ?

FLUDARABİN eklenmesi ölüm oranlarını etkilemiyor.

Aksoy S, Harputluoglu H, Kılıckap S, Dede DS, Dizdar O, Altundag K, Barista I. Rituximab-related viral infection Leukemia&Lymphoma 2007; 48(7): 1307-12

RİTUKSİMAB... İnfeksiyon ne kadar sık ?

HCV (+) veya HBV taşıyıcılarda re-aktivasyon riski:

Lenfoma	**:**	**(%84)**
Diğer hematolojik maligniteler	**:**	**(%11)**
Solid tümörler	**:**	**(%5)**

Reaktivasyona bağlı ölüm oranı: %44

Coiffier B. Hepatitis B virus reactivation in patients receiving chemotherapy for cancer treatment: role of Lamivudine prophylaxis. Cancer Invest 2006;24:548 – 552.

RİTUKSİMAB… Risk grupları.. HBV

Toplam 128 hasta (HBV pozitif)

Re-aktivasyon oranı: 36 hasta (%26)

Lenfomaların % 56'sı

Solid tümörlerin %25'i

Yeo W, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, et al. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. Br J Cancer 2004;90: 1306 – 1311

RİTUKSİMAB… ne yapalım? HBV

IVIg kullanımı:

Sınırlı deneyim…

Viral İnfeksiyon görüldükten sonra etkisiz…

RİTUKSİMAB… ne yapalım? HBV

LAMUVİDİNE

En etkili gibi…

Buna rağmen yanıtsızlık sık…

Aksoy S, Harputluoglu H, Kılıckap S, Dede DS, Dizdar O, Altundag K, Barista I. Rituximab-related viral infection Leukemia&Lymphoma 2007; 48(7): 1307-12

RİTUKSİMAB... ne yapalım? HBV

LAMUVİDİNE

HBV taşıyıcılarında Rituksimab içeren rejim ile başlamalı ve son kemoterapiyi izleyen ilk 6 ay kullanılmalıdır.

Rossi G, Pelizzari A, Motta M, Puoti M. Primary prophylaxis with lamivudine of hepatitis B virus reactivation in chronic HbsAg carriers with lymphoid malignancies treated with chemotherapy. Br J Haematol 2001;115:58 – 62.

Yeo W, Chan PK, Ho WM, Zee B, Lam KC, Lei KI, et al. Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. J Clin Oncol 2004;22:927 –934.

Stroffolini T, Andriani A, Bibas M, Barlattani A. Successful treatment with lamivudine for reactivated hepatitis B infectionfollowing chemotherapy for non-Hodgkin's lymphoma. Ann Hematol 2002;81:48 – 49.

RİTUKSİMAB… ne yapalım? HCV

HCV'nin viral yükü Rituksimab ile artıyor

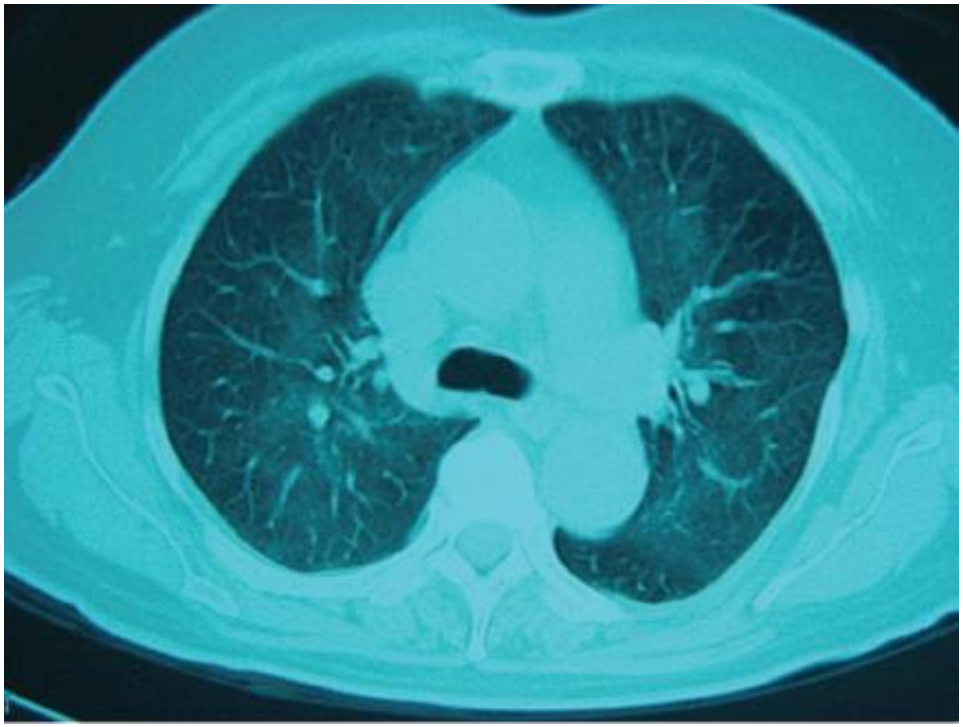
Rituksimab HCV'ye bağlı kriyoglobulinemi olgularında etkili…

Aksoy S, Abali H, Kilickap S, Erman M, Kars A. Accelerated hepatitis C virus replication with rituximab treatment in a non-Hodgkin's lymphoma patient. Clin Lab Haematol 2006;28: 211 – 214.

Roccatello D, Baldovino S, Rossi D, Mansouri M, Naretto C, Gennaro M, et al. Long-term effects of anti-CD20 monoclonal antibody treatment of cryoglobulinaemic glomerulonephritis. Nephrol Dial Transplant 2004;19: 3054 – 3061.

RİTUKSİMAB… interstisyel pnömoni

İntersisyel pnömoni: % 0.03… ACABA ?



Burton C, Kaczmarski R, Jan-Mohamed R. Interstitial pneumonitis related to rituximab therapy. New Engl J Med 2003;348:2690–2691.

RİTUKSİMAB... interstisyel pnömoni

107 pts : (Rituksimab + kemoterapi)

9/107 pts : intersisyel pnömoni (%8.4)

Ortaya çıkma zamanı: 2. kür

8/9 hasta: glukokortikoid + antibiyotik

1/9 hasta: exitus (sekonder infeksiyon)

Xin-Liu, Xiao-Naan Hong, Ya-Jia Gu, Bi-Yun Wang, Zhi-Guo Luo Junning Cao: Interstitial pneumonitis during rituximab-containing chemotherapy for non-Hodgkin lymphomaLeukemia & Lymphoma: September 2008; 49(9): 1778–1783

RİTUKSİMAB… interstisyel pnömoni

- **Ani başlangıçlı, yüksek ateş…**
- **Radyolojik olarak pulmoner infiltratlar**
- **Steroid tedavisine dramatik yanıt**

Xin-Liu, Xiao-Naan Hong, Ya-Jia Gu, Bi-Yun Wang, Zhi-Guo Luo Junning Cao: Interstitial pneumonitis during rituximab-containing chemotherapy for non-Hodgkin lymphomaLeukemia & Lymphoma: September 2008; 49(9): 1778–1783

RİTUKSİMAB… diğer viral infeksiyonlar

- **Enterovirus ansefaliti**
- **Kaposi Sarkom agrevasyonu**
  - **HIV + kaposi sarkomlu hastaların %75'i**
  - **Olasılıkla B hücre deplesyonu sonucu**

Quartier P, Tournilhac O, Archimbaud C, et al. Enteroviral meningoencephalitis after anti-CD20 (rituximab) treatment. Clin Infect Dis 2003;36:e47–e49.

Archimbaud C, Bailly JL, Chambon M, Tournilhac O, Travade P, Peigue-Lafeuille H. Molecular evidence of persistent echovirus 13 meningoencephalitis in a patient with relapsed lymphoma after an outbreak of meningitis in 2000. J Clin Microbiol 2003;41:4605–4610.

Ge´rard L, Be´rezne´ A, Galicier L, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. J Clin Oncol 2007;25:3350–3356.

Stebbing J, Gazzard B, Newsom-Davis T, et al. Nadir B cell counts are significantly correlated with the risk of Kaposi's sarcoma. Int J Cancer 2004;108:473–474.

RİTUKSİMAB… bakteriyal infeksiyonlar

- **Risk artmaz ?**
- **İlişki IgM düzeyinde azalma ile ilişkili ?**
- **Tbc ile ilişkili bir risk yok… ?**
- **Olgu bildirimi (Tbc ile ilişkili)**

Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235–242.

Iguchi T, Yokoyama K, Mitsuishi M, Chen CK, Ikeda Y,Okamoto S. Pulmonary tuberculosis and adenovirus-hemorrhagic cystitis after autologous peripheral blood stem cell transplantation for follicular lymphoma. Rinsho Ketsueki 2005;46:1049–1054.

RİTUKSİMAB... fungal infeksiyonlar

- **Özellikle ileri yaşlarda Candida riski artmış**
- **P.carinii (P.jiroveci) riski artmış ?**
  - **Son gözlemler ilişkili olduğunu gösteriyor**
  - **Özellikle HIV + hastalarda**

Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235–242.

Lin PC, Hsiao LT, Poh SB, et al. Higher fungal infection rate in elderly patients (more than 80 years old) suffering from diffuse large B cell lymphoma and treated with rituximab plus CHOP. Ann Hematol 2007; 86:95–100.

Pfreundschuh M, Tru¨mper L, Osterborg A, et al. CHOPlike chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379–391.

RİTUKSİMAB... P. Carinii

- **PCP için riskler:**
  - **Düşük IgG düzeyi**
  - **Düşük CD4 düzeyi**
  - **Doz dense rejimler (CHOP-14 vb)**

Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235–242.

Lin PC, Hsiao LT, Poh SB, et al. Higher fungal infection rate in elderly patients (more than 80 years old) suffering from diffuse large B cell lymphoma and treated with rituximab plus CHOP. Ann Hematol 2007; 86:95–100.

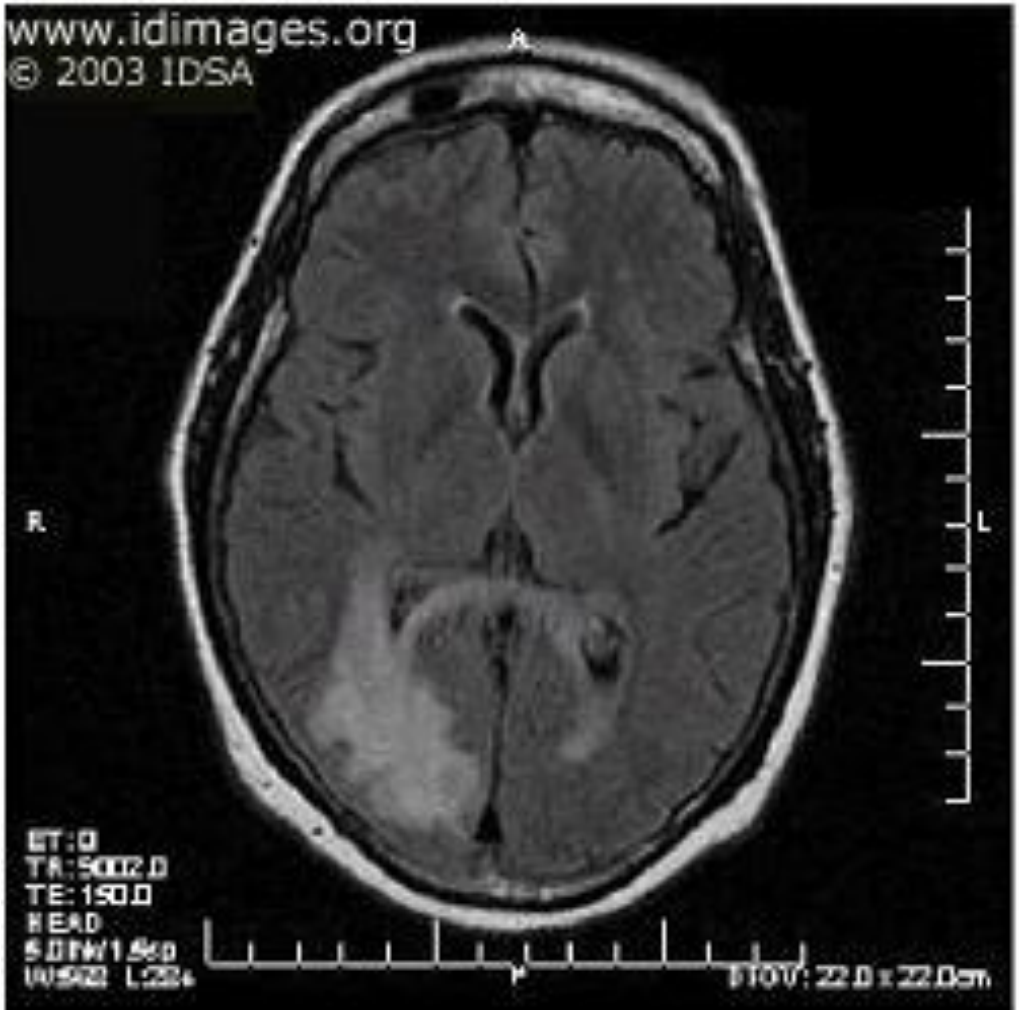
Pfreundschuh M, Tru¨mper L, Osterborg A, et al. CHOPlike chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379–391.

RİTUKSİMAB… parazitik infeksiyonlar

- **Babesiosis riski yüksek?**
  - **14 babesiosis olgusu**
  - **8 olgunun geçmişinde rituksimab kullanımı**
  - **Çok nadir ancak ölümcül…**

Krause PJ, Gewurz BE, Hill D, et al. Persistent and relapsing babesiosis in immunocompromised patients. Clin Infect Dis 2008;46:370–376..

RİTUKSİMAB... Progresif Multifokal Lökoensefalopati



RİTUKSİMAB… Progresif Multifokal Lökoensefalopati

- JC virus, papovavirus (DNA)
- Beynin demiyelizan hastalığı
- Bilateral ve asimetrik
- hemiparezi, entellektüel yıkım, afazi, dizartri, hemianopsi, sensoryal bozukluklar
- **ÖLÜMCÜL…**

RİTUKSİMAB... ÖZET

Table 1. Rituximab Infectious Complications

	Evidence	Comments
Established increased infectious complications		
Overall infections	Meta-analyses in hematologic malignancies[11,12] Randomized trials in RA[1]	Increased severe infections (grade 3 or 4) when used as maintenance therapy in follicular lymphoma Mild infections in RA
Hepatitis B reactivation	Case series[13–15] Case reports[16–18]	Reports only in hematologic malignancies
PML	Case series,[19] case reports[20–22]	Most cases in hematologic malignancies, but a few in RA, SLE, and immune cytopenia

Rituximab-Associated Infections

Juan C. Gea-Banacloche

Seminars in Hematology, Vol 47, No 2, April 2010, pp 187–198

RİTUKSİMAB... ÖZET

Possibly increased infectious complications		
Pneumocystis jirovecii pneumonia	Retrospective series compared to historical controls[23,24] Case series[25–27] Case reports[28–31]	Cases in hematological malignancies, RA, autoimmune diseases, solid organ transplant
Enterovirus encephalitis	Case reports[32–35]	Known complication of other B-cell immunodeficiencies
Parvovirus B19	Case reports[36–39]	Good response to IVIG
Cytomegalovirus	Case reports[20,28,40]	CMV disease is very uncommon except in HIV or following allogeneic transplant; there are several reports in hematologic malignancies treated with combination chemotherapy
West Nile virus	Case reports[41,42]	Increased severity and negative serology may be anticipated because of effect of rituximab on B cells
Babesiosis	Case-control study[43]	Most patients with persistent babesiosis had received rituximab
Mycobacterial disease	Case reports[44]	Severe *Mycobacterium avium* and *M kansasii*, no other reports

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RİTUKSİMAB... ÖZET

Table 2. Prevention and Management of Hepatitis B Reactivation in Patients Receiving Rituximab-Containing Regimens for Hematologic Malignancies

	Interpretation	Action
HBsAg$^-$ plus anti-HBs$^-$ plus anti-HBc$^-$	Hepatitis B–naive	HBV immunization if feasible

Seminars in Hematology, Vol 47, No 2, April 2010, pp 187–198

RİTUKSİMAB... ÖZET

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HbSAg$^+$	Active HBV replication; probably carrier, but it could be acute hepatitis B	Obtain baseline HBV DNA level Obtain HBeAg and anti-HBe Start anti-HBV treatment with lamivudine* Monitor with HBV DNA levels and ALT

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RİTUKSİMAB... ÖZET

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HBsAg$^-$ plus anti-HBs$^+$ plus anti-HBc$^+$	Past hepatitis B	Monitor ALT Measure HBV DNA level with sensitive assay if ALT is or becomes abnormal

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RİTUKSİMAB... ÖZET

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HBsAg$^-$ plus anti-HBs$^+$ plus anti-HBc$^+$	Past hepatitis B	Monitor ALT Measure HBV DNA level with sensitive assay if ALT is or becomes abnormal
HBsAg$^-$ plus Anti-HBs$^-$ plus anti-HBc$^+$	Possible occult HBV infection *or* False positive anti-HBc	Measure HBV DNA level with sensitive assay HBV immunization if feasible†
HbsAg$^-$ plus HBsAb$^+$ plus HbcAb$^-$	Vaccination to hepatitis B *or* Occult hepatitis B infection	Measure HBV DNA level with sensitive assay‡ Start anti-HBV treatment with lamivudine

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RİTUKSİMAB... ÖZET

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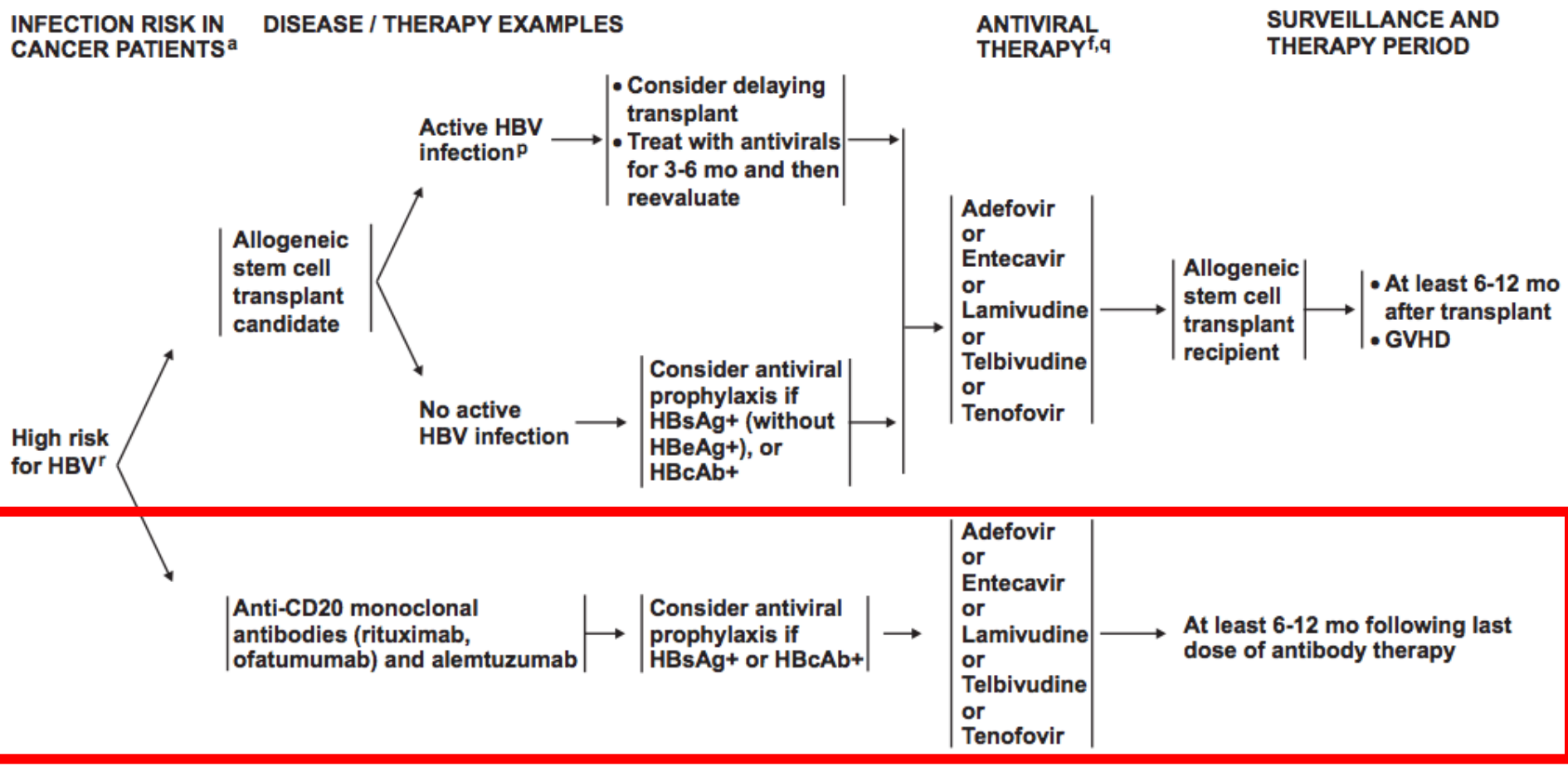
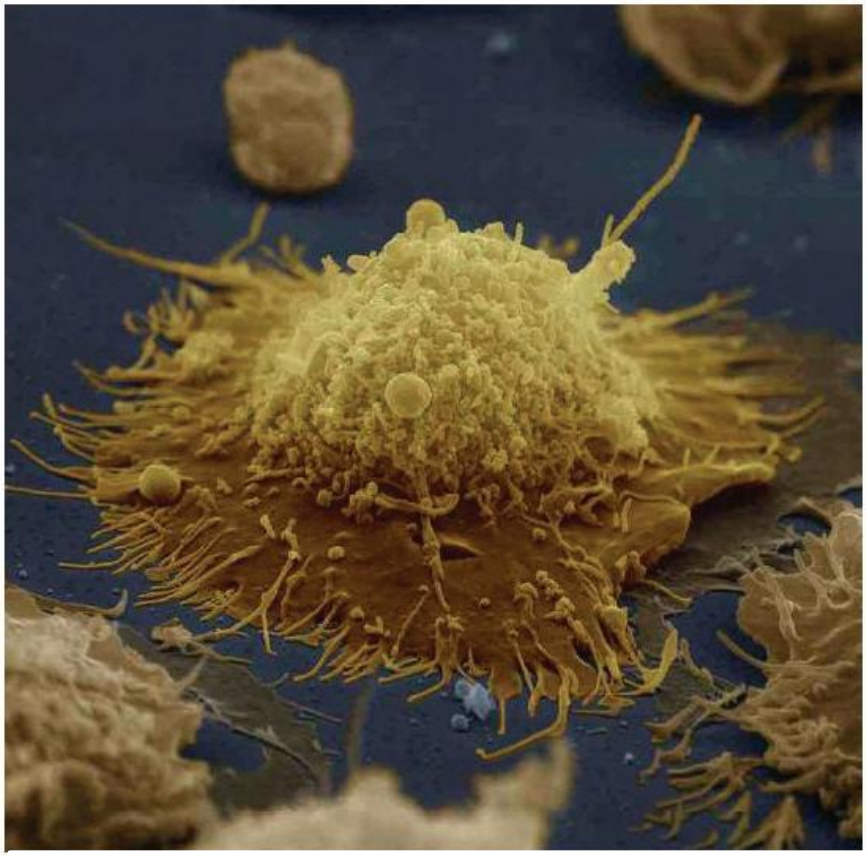
PREVENTION OF HEPATITIS B VIRUS (HBV) REACTIVATION OR DISEASE

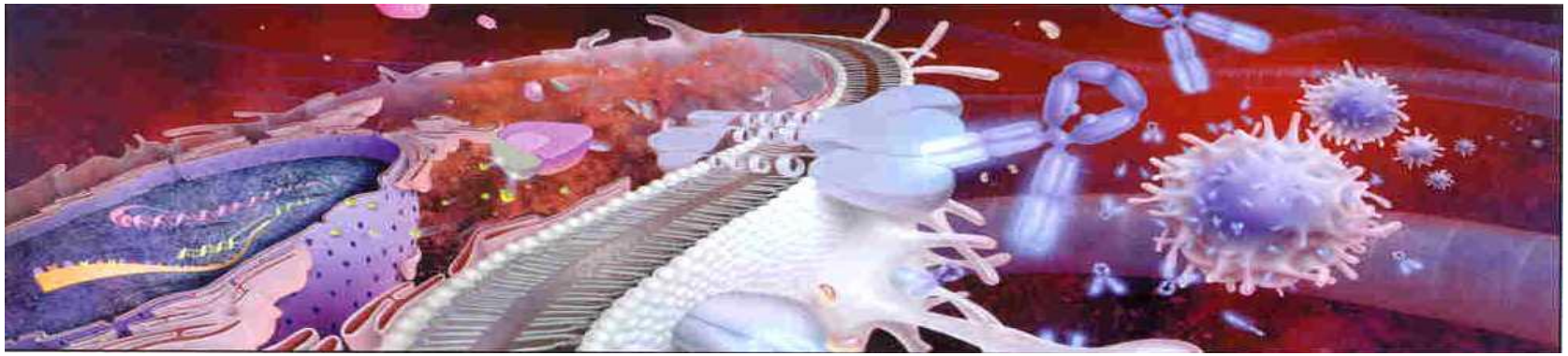


ALEMTUZUMAB



Alemtuzumab (Mabcampath®)

- Anti CD-52
- CD52 yüzey antijeni pozitif hücreler
  - T&B lenfositler, monositler, makrofajlar



Alemtuzumab (Mabcampath®)

- Nötropeni (%70)
- Lenfopeni
- T ve B hücre sayılarında düşüş
  - 4. hafta sonunda ortalama CD4: 0/mcL
  - 6. ayın sonunda ortalama CD4: 238/mcL
  - 9. Ayda lenfosit sayıları normalin %25 veya altında

Alemtuzumab (Mabcampath®)

CD4 ve CD8 düzeyleri ilk bir yıl içine asla başlangıç düzeylerine dönmez.

Alemtuzumab (Mabcampath®)

Alemtuzumab doz ve uygulanım süresi ile arasında bir korelasyon YOKTUR...

Alemtuzumab (Mabcampath®)

- **Önceden başka kemoterapi alanlarda CMV riski başta olmak üzere infeksiyon DAHA YÜKSEKTİR**

- **FLUDARABİN sonrası alemtuzumab: risk %55**
- **İLK BASAMAK alemtuzumab: risk %21**

Alemtuzumab (Mabcampath®)

1- Sitomegalovirus

2- Pnomosistitis Carinii

3- Herpes Simpleks

4- Herpes Zooster

Alemtuzumab (Mabcampath®)

EN SIK CMV REAKTİVASYONU…

ORAN: %10-30

Tedavi sonrası 3.-6. haftalar

CMV Patogenezi

- **Hastalığın spektrumu**
  - Asemptomatik taşıyıcılar
  - HIV hastalarında hastalık
  - Transplant hastaları
  - Bağışıklığı yetersiz olan hastalar
- **T hücreleri latent virüsü kontrol eder**
  - T hücre sayımı <50-100/mm3: aktivasyon

ALEMTUZUMAB... CMV reaktivasyonu

Çalışma	N	CMV (%)	PCR	Ölüm
Rai	24	4	Yok	0
Keating	93	8	Yok	0
Nguyen	18	28	Yok	0
Ferrajoli	42	29	Yok	0
Moreton	91	9	Var	1
Lundin*	41	10	Yok	0
Hillmen*	147	11	Var	0

*Birinci basamak tedavi

O'Brien SM, ve ark. *Clin Lymphoma Myeloma*. 2006; 7:125-130

ALEMTUZUMAB... CMV reaktivasyonu

- **Başlangıç**
  - **Alemtuzumab tedavisi sonrası 4-6 haftalar**
  - **Lenfopeni ve nötropeni ile eş zamanlı**
  - **Tedavi sonrası takipte reaktivasyon riski düşük**
- **İzleme ve antiviral tedavilerle mortalite azalır**

ALEMTUZUMAB... CMV reaktivasyonu

- **Sıklık : (%4-29)**
- **Değişken bir sıklık.**
- **Çünkü…**
    - **Seçilen hasta popülasyonları (önceden tedavi edilen ve edilmeyen)**
    - **İzlem biçimi ve sıklığı**
    - **Virus tespit yöntemleri**
    - **Proflaksi ??**

ALEMTUZUMAB... CMV proflaksi

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PREVENTION OF CYTOMEGALOVIRUS (CMV) REACTIVATION OR DISEASE

INFECTION RISK IN CANCER PATIENTS[a]	DISEASE / THERAPY EXAMPLES	SURVEILLANCE PERIOD[n]	PRE-EMPTIVE THERAPY[f,o]
High risk for CMV	Allogeneic stem cell transplant recipients	• 1 to 6 months after transplant • GVHD	Ganciclovir (IV) or Valganciclovir (PO) or Foscarnet (IV) or Cidofovir (IV)
	Alemtuzumab	For a minimum of 2 mo after alemtuzumab	

ALEMTUZUMAB... CMV proflaksi

Profilaksi:

- Tedavi: Günde 900 mg oral Valgansiklovir
- Süre: Alemtuzumab ile tedavi sırasında ve tedavi sona erdikten sonra 2 ay
- CMV Testleri: her 2 haftada bir

ALEMTUZUMAB... proflaksi

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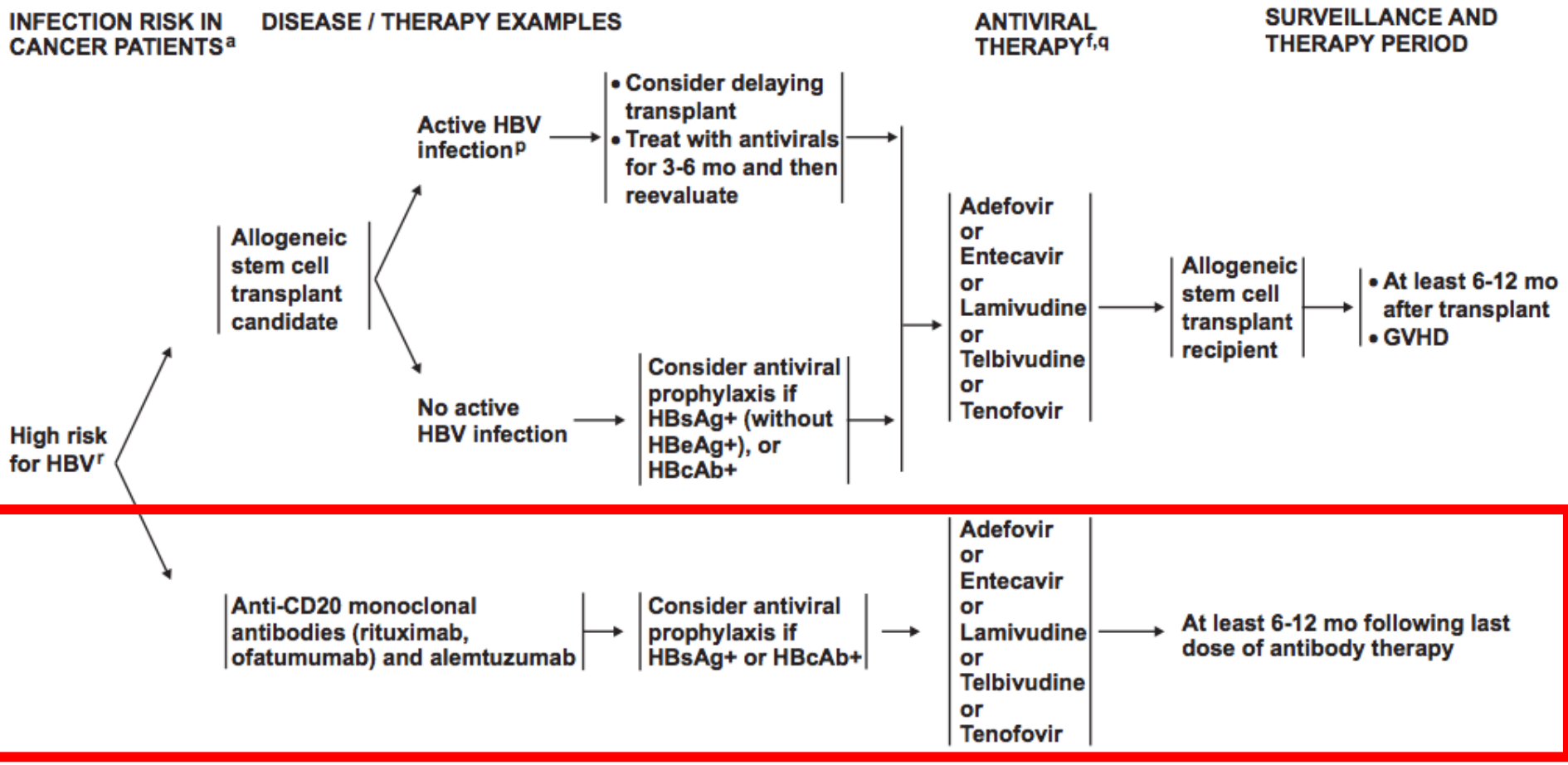
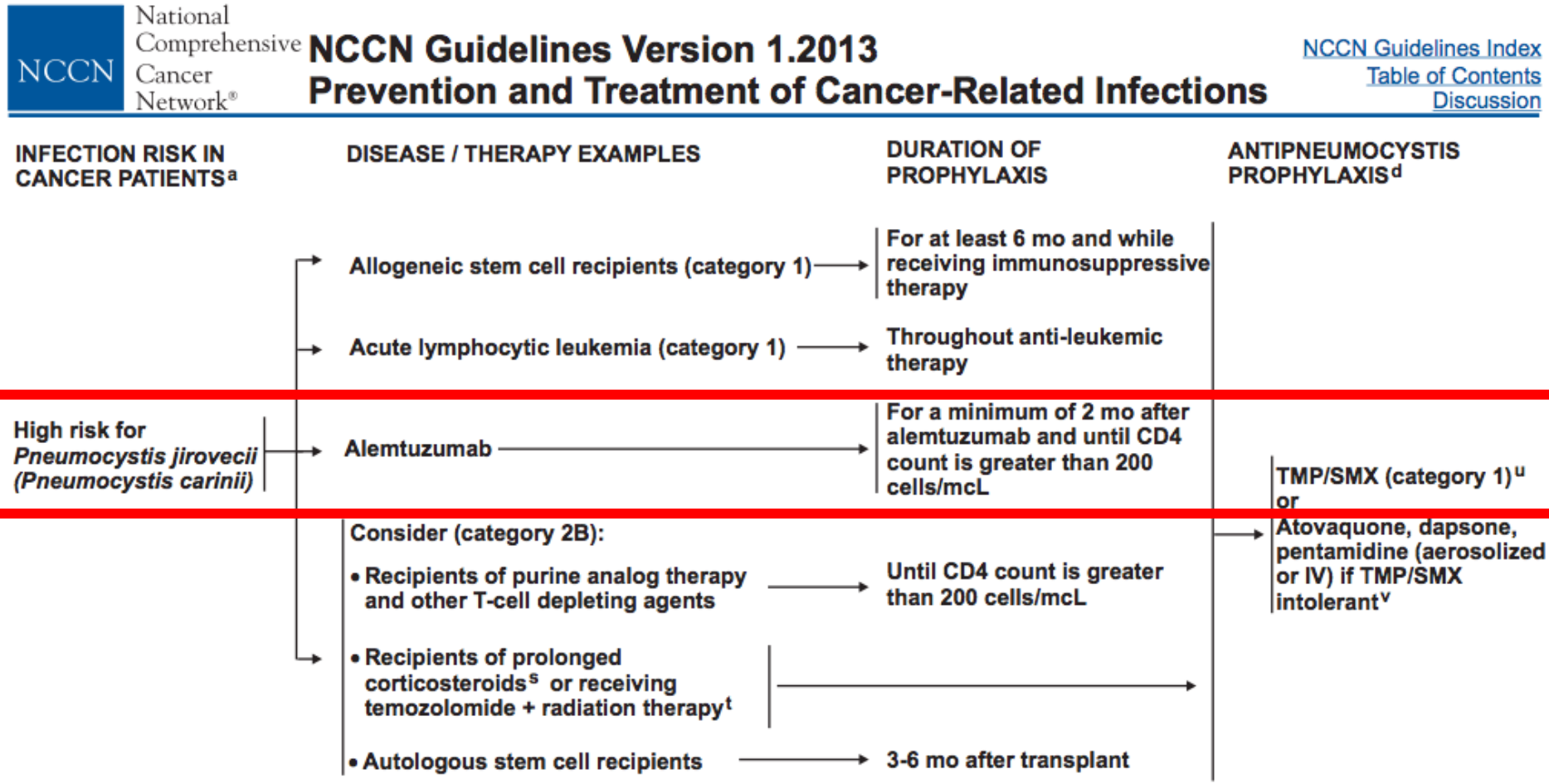
PREVENTION OF HEPATITIS B VIRUS (HBV) REACTIVATION OR DISEASE



ALEMTUZUMAB... proflaksi



ALEMTUZUMAB... proflaksi

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OVERALL INFECTION RISK IN CANCER PATIENTS[a]	DISEASE / THERAPY EXAMPLES	FEVER & NEUTROPENIA RISK CATEGORY (See FEV-2)	ANTIMICROBIAL PROPHYLAXIS[c,d,e,f,g,h]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 d	Low	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HSCT • Lymphoma • Multiple myeloma • CLL • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7 to 10 d	Usually HIGH, but some experts suggest modifications depending on patient status. Purine analogs, intermediate risk when used as single agents; when combined with intensive chemotherapy regimens, the risk converts to high.	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - Consider fluconazole during neutropenia and for anticipated mucositis • Viral - During neutropenia and at least 30 d after HSCT
High[b]	• Allogeneic HSCT including cord blood • Acute leukemia ➤ Induction ➤ Consolidation • Alemtuzumab therapy • GVHD treated with high dose steroids • Anticipated neutropenia greater than 10 d	Usually HIGH, but significant variability exists related to duration of neutropenia, immunosuppressive agents, and status of underlying malignancy	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - See INF-2 • Viral - during neutropenia and at least 30 d after HSCT

ALEMTUZUMAB... proflaksi

OVERALL INFECTION RISK IN CANCER PATIENTS[a]	DISEASE / THERAPY EXAMPLES	VIRAL INFECTION or REACTIVATION	ANTIVIRAL PROPHYLAXIS	DURATION[f]
Low	• Standard chemotherapy regimens for solid tumors	HSV	None unless prior HSV episode	During neutropenia
Intermediate	• Autologous HSCT • Lymphoma • Multiple Myeloma • CLL • Purine analog therapy (ie, fludarabine)	HSV VZV	Acyclovir Famciclovir Valacyclovir	During neutropenia and at least 30 d after HSCT (Consider VZV prophylaxis given for at least 1 year after HSCT)
High	• Acute leukemia ▸ Induction ▸ Consolidation	HSV	Acyclovir Famciclovir Valacyclovir	During neutropenia
	• Proteasome inhibitors	VZV	Acyclovir Famciclovir Valacyclovir	During active therapy
	• Alemtuzumab therapy • Allogeneic HSCT	HSV VZV	Acyclovir Famciclovir or Valacyclovir as HSV prophylaxis	VZV prophylaxis • In allogeneic transplant recipients, acyclovir prophylaxis should be considered for at least 1 y after HSCT HSV prophylaxis • Minimum of 2 mo after alemtuzumab and until CD4 ≥ 200 cells/mcL • During neutropenia and at least 30 d after HSCT
		CMV	(See INF-4) for CMV	Pre-emptive therapy for CMV (See INF-4)
		HBV	(See INF-5) for HBV	Antiviral therapy for HBV (See INF-5)

KÜÇÜK MOLEKÜLLER (Nib'ler)

- Tirozin Kinaz İnhibitörü
- Onkogene spesifik
  - Bcr-Abl, PML-RARA,
- Sinyal yollarını inhibe ederek etki
- Daha iyi bir güvenlik profili
- Özel yan etki profili
- Genellikle oral

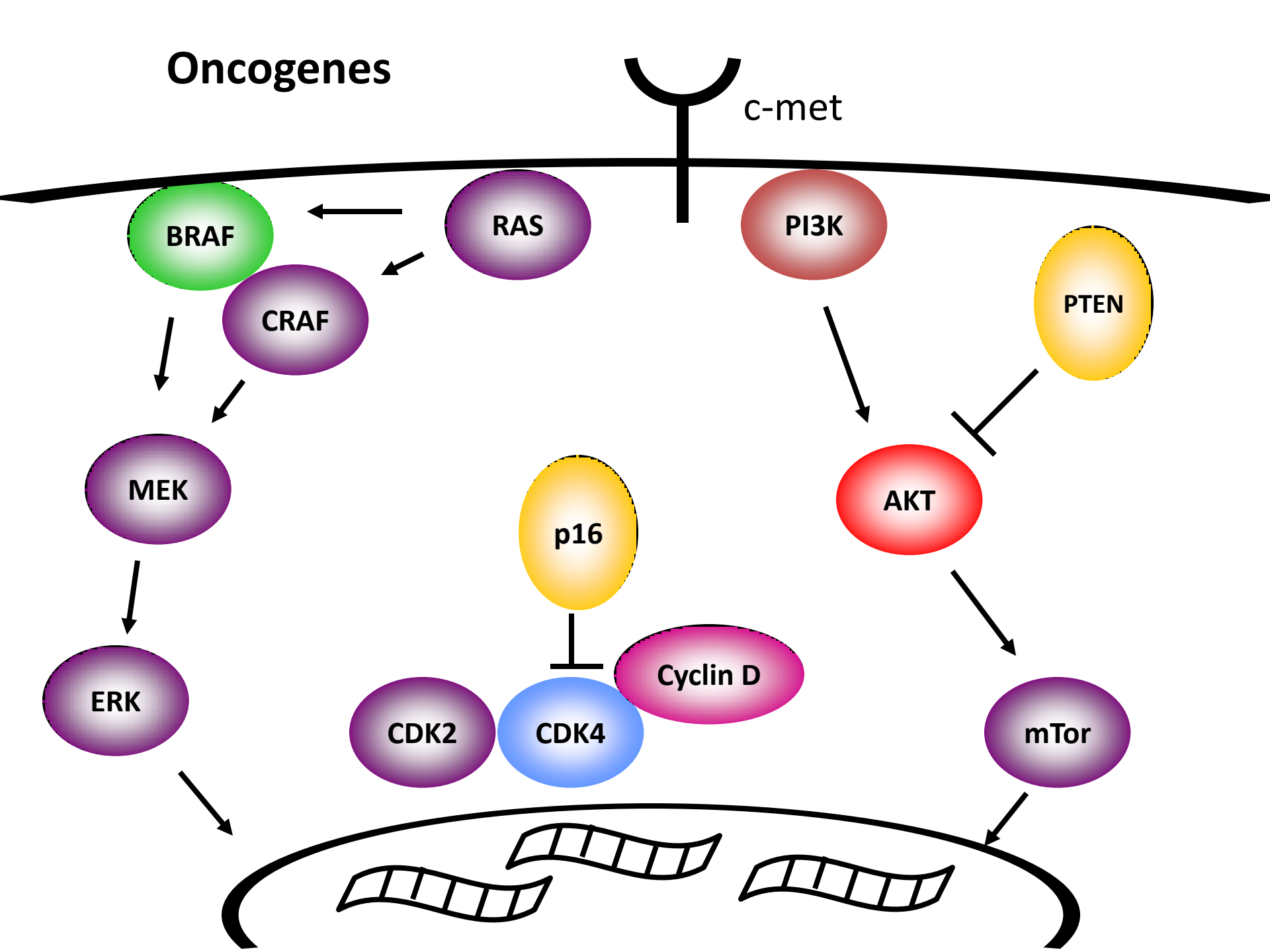
KÜÇÜK MOLEKÜLLER (Nib'ler)

KÜÇÜK MOLEKÜLLER (Nib'ler)

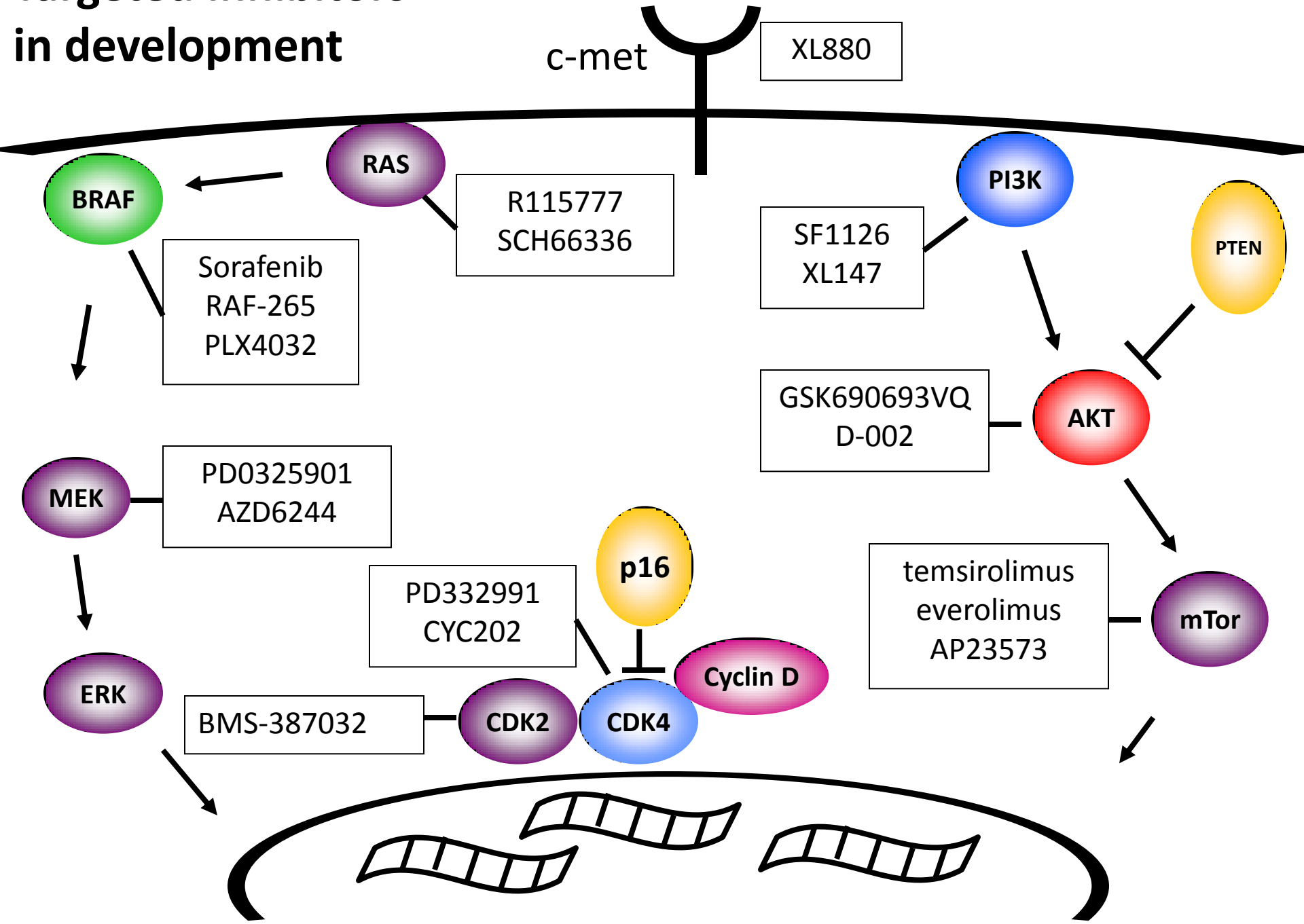
JENERİK İSİM	FİRMA İSMİ	KANSER
IMATINIB	Gleevec	KML, GIST, ALL
DASATINIB	Sprycel	KML, ALL
NILOTINIB	Tasigna	KML
Gefitinib	Iressa	Akciğer
Erlotinib	Tarceva	Akciğer & Pankreas
Lapatinib	Tykerb	Meme
Sorafenib	Nexavar	Böbrek, Karaciğer
Sunitinib	Sutent	Böbrek
RUXOLITINIB	Jakafi	MPD

DİĞER YENİ İLAÇLAR

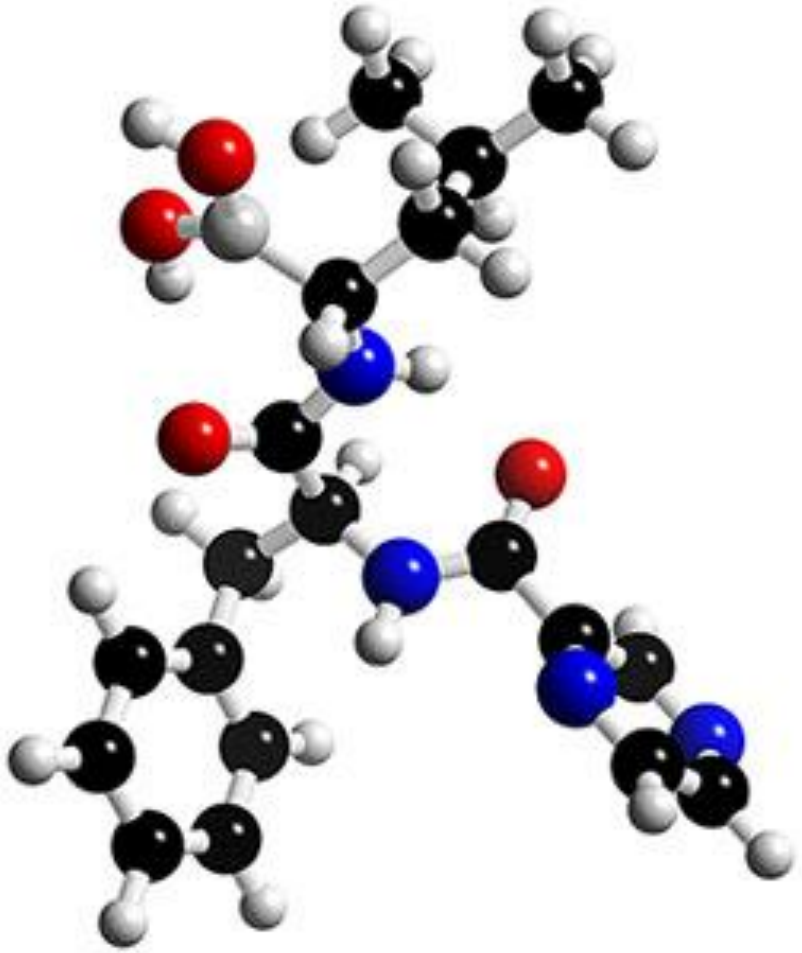
- **Proteasome inhibitörleri** (Bortezomib)
- **mTOR inhibitörleri** (Temsirolimus, Everolimus)
- **DNA demetile edici ajanlar agents** (Azacytidine, Decitabine)
- **Histone deacetylase inhibitörleri** (Vorinostat)
- **Translocation targeters** (retinoic acid)
- **Antianjiogenik ilaçlar** (Thalidomide, Lenalidomide)


Oncogenes
c-met
BRAF
RAS
PI3K
CRAF
PTEN
MEK
p16
AKT
ERK
Cyclin D
CDK2
CDK4
mTor

Targeted inhibitors in development



BORTEZOMİB



BORTEZOMİB

Adverse event	Creatinine clearance (ml/min)		
	>80	51–80	≤50
Thrombocytopenia	30%	27%	33%
Fatigue	12%	10%	10%
Diarrhea	7%	6%	10%
Anemia	10%	6%	10%
Neutropenia	12%	15%	17%
Peripheral neuropathy	11%	9%	13%
Dyspnea	1%[a]	4%	12%[a]
Weakness	6%	5%	10%
Pyrexia	2%	5%	6%
Constipation	2%	1%	4%

[a] $p = .01$
From [21].

BORTEZOMİB

- Hafif nötropeni
- T hücre proliferasyonunda ve sayısında azalma
- NK hücre sayısında azalma
- CD8 T hücre sayısında azalma
- Dendiritik hücre canlılık ve sayısında azalma

- **HSV ve VZV infeksiyon riskinde artış**
- **Diğer infeksiyon riski deksametazon ile aynı**

BORTEZOMİB

663 hasta (nüks MM; faz III APEX trial)

VZV reaktivasyonu

Bortezomib kolu	:	%13
Deksametazon kolu	:	%5

Lenfosit sayıları aynı… NEDEN?

J Clin Oncol. 2008 Oct 10;26(29):4784-90. Epub 2008 Aug 18.

BORTEZOMİB

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		HBV	(See INF-5) for HBV	Antiviral therapy for HBV (See INF-5)

MOLEKÜLER TSUNAMİ…?

ENDİŞELER HEP AYNI…!

Voltaire (1694–1778)

“Doktorlar; hakkında hiç bir şey bilmedikleri insanların pek az şey bildikleri hastalıklarını hakkında az şey bildikleri ilaçlar ile iyileştirmeye çalışırlar...

İBRUTİNİB… İMBRUVİCA©

- Ibrutinib is a first-in-class oral inhibitor of Bruton tyrosine kinase (BTK), a kinase in the BCR pathway.

- Toxicity profile modest (loose stools, arthralgia, fatigue
- dyspepsia, rash) with minimal myelosuppression

- PCYC 1109: Ibrutinib + Ofatumumab in relapsed CLL/SLL (completed, OSU)
- ▪▪ PCYC 1108: Ibrutinib + BR or FCR in relapsed CLL/SLL (completed, multicenter)
- ▪▪ IIT: Ibrutinib + Rituximab in high-risk CLL (completed, MDA)
- ▪▪ CTEP: Ibrutinib + Lenalidomide (U Col and OSU)
- **Summation of Results: Higher response rate and no obvious added toxicity**
- ▪▪ **Planned Intergroup Phase III studies**
  ▪▪ FCR vs Ibrutinib + Rituximab (< 70 yrs)
  ▪▪ BR vs Ibrutinib + Rituximab vs Ibrutinib (> 65 yrs)

MOLEKÜLER TSUNAMİ…?

Kolon Kanserinde sağ kalım süresinin iki katına çıkması tedavi maliyetini 340 kat arttırmıştır.

New England Journal of Medicine (2004)

MOLEKÜLER TSUNAMİ…?

2000-2010:

Onaylanan toplam 25 ilaç

Bir yıllık sağ kalım artışı

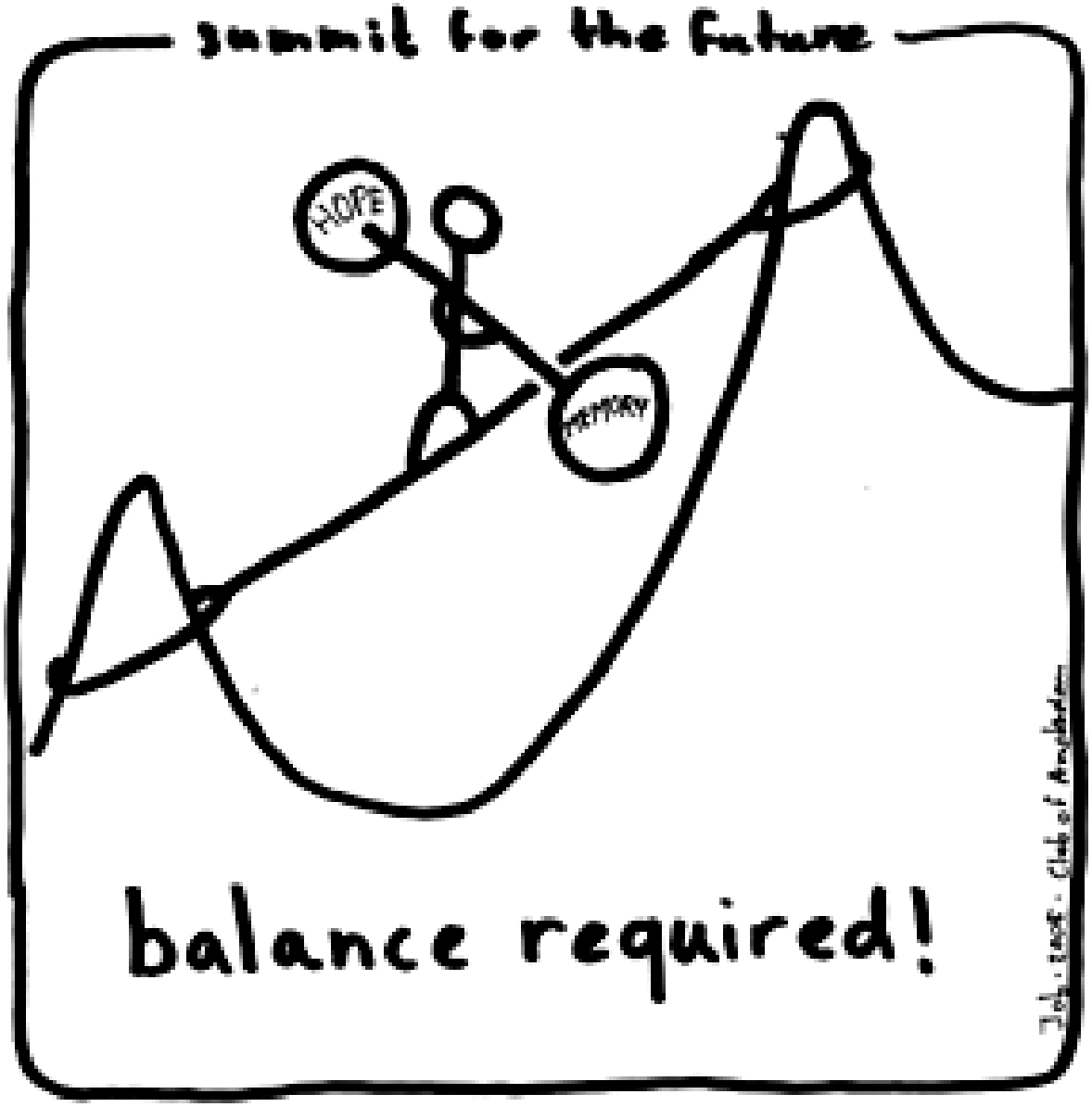
Kişi başına 100.000 dolar ek maliyet

MOLEKÜLER TSUNAMİ…?

Onkoloji uzmanı Prof. Dr. Ian Tannock (Toronto Üniversitesi)

“Eğer Ford marka bir araba aldıysak kimse bizden bunun karşılığı Ferrari ücreti ödememezi bekleyemez. Kanser ilaçlarında durum tam da budur”

UMUT ve TALEPLER BİTMİYOR…!


summit for the future
HOPE
MEMORY
balance required!