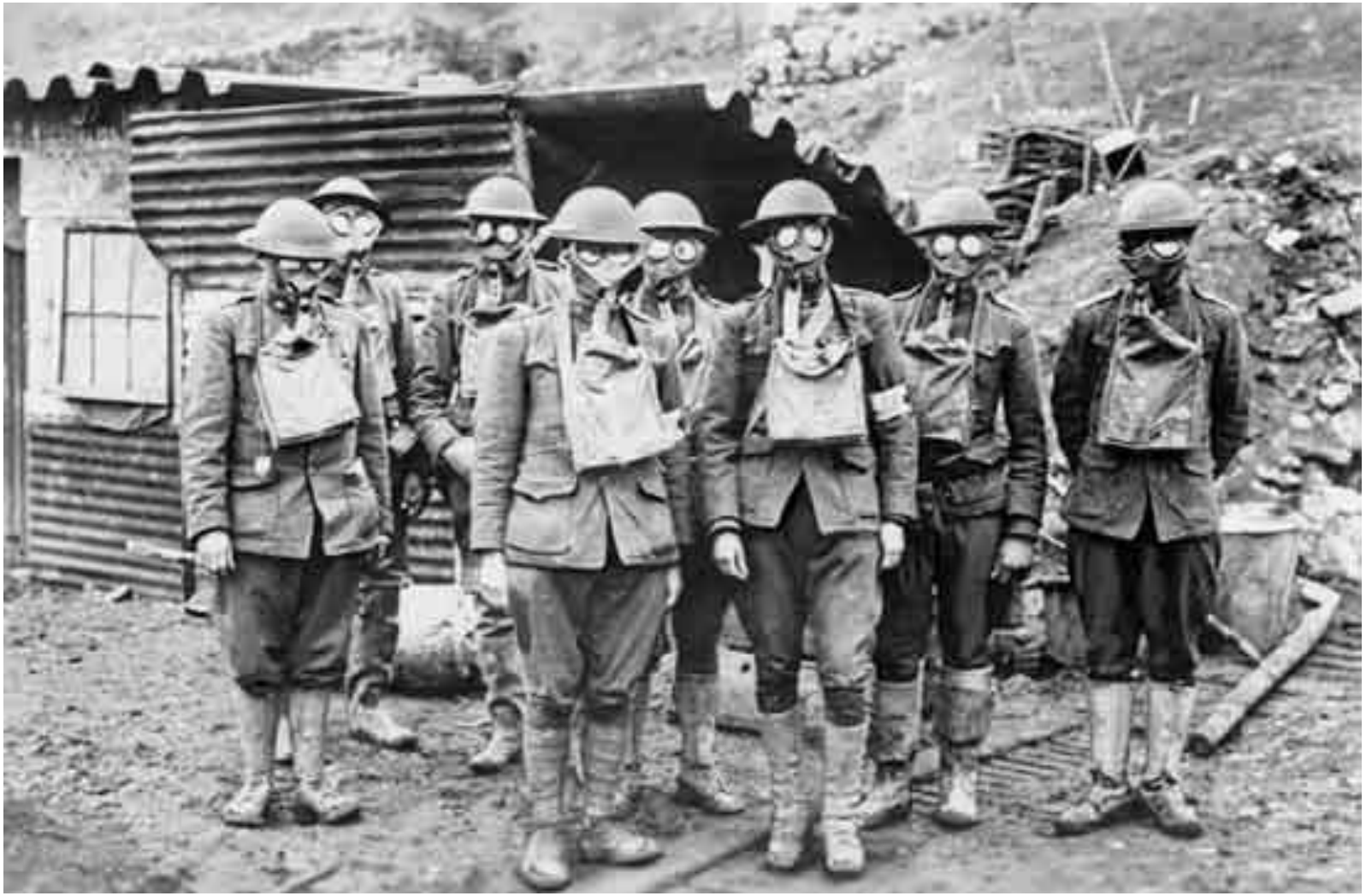
YENİ AJANLAR, YENİ RİSK GRUPLARI

Prof Dr Mustafa ÇETİNER
Koç Üniversitesi Tıp Fakültesi
Amerikan Hastanesi

KLİMİK 2016 - 30. YIL KURULTAYI
09 – 12 Mart 2016
Cornelia Diamond Golf Resort & Spa – Belek / Antalya

HARDAL GAZINDAN …



NITROJEN MUSTARD'a...

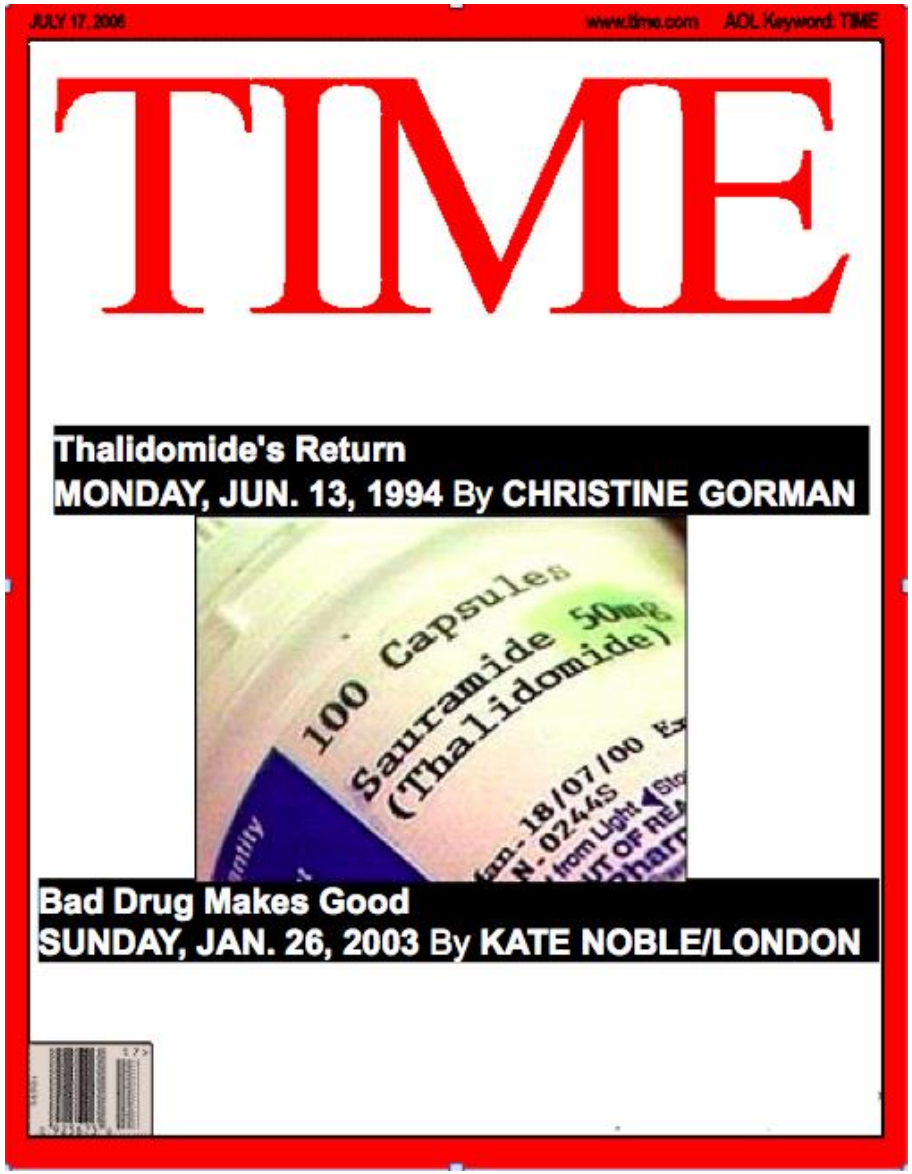
NITROGEN MUSTARD THERAPY

Use of Methyl-Bis(Beta-Chloroethyl)amine Hydrochloride and Tris(Beta-Chloroethyl)amine Hydrochloride for Hodgkin's Disease, Lymphosarcoma, Leukemia and Certain Allied and Miscellaneous Disorders

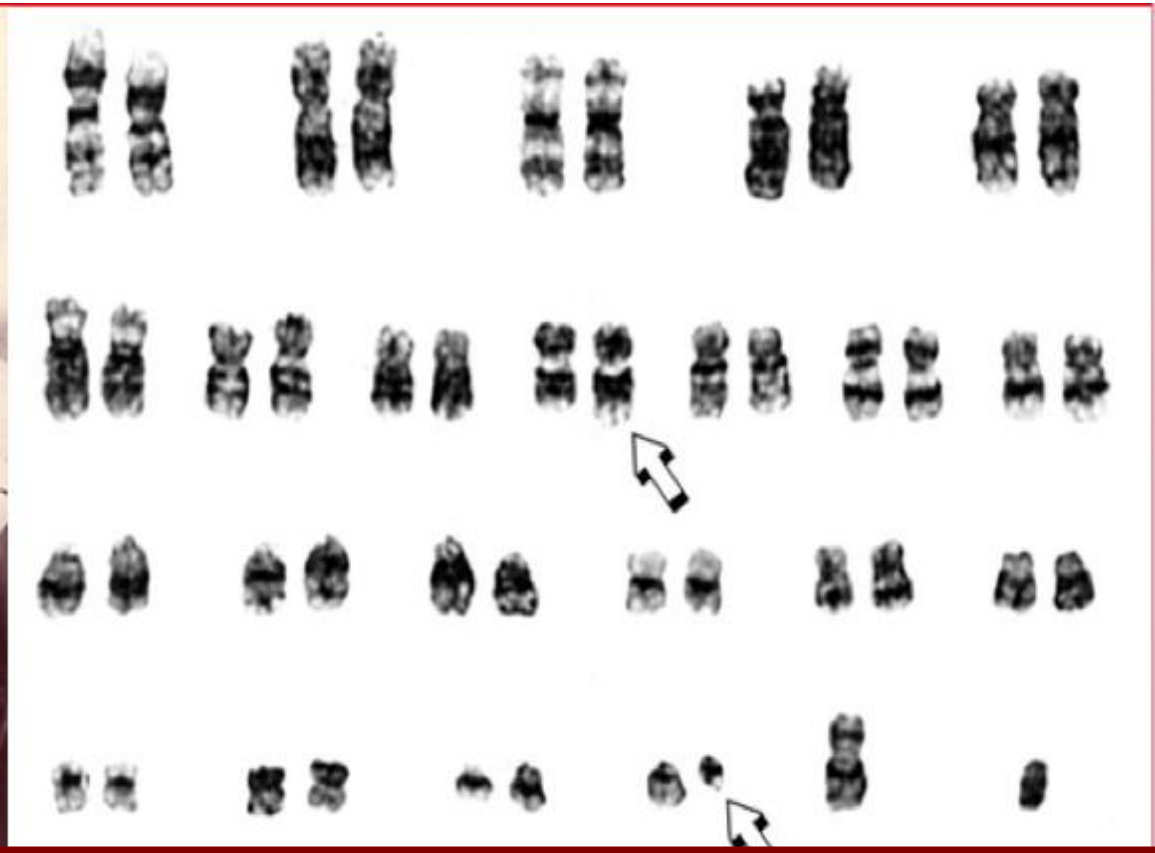
LOUIS S. GOODMAN, M.D., Salt Lake City
MAXWELL M. WINTROBE, M.D., Salt Lake City
WILLIAM DAMESHEK, M.D., Boston
MORTON J. GOODMAN, M.D., Portland, Ore.
MAJOR ALFRED GILMAN
Medical Corps, Army of the United States
and
MARGARET T. McLENNAN, M.D., Salt Lake City

In a recent report the historical aspects of the use of β-chloroethyl amines (halogenated alkyl amines, nitrogen mustards) in the treatment of certain diseases of the blood-forming organs were presented and the chemical, pharmacologic, toxicologic and animal experimental aspects of these compounds reviewed.[1] The interested reader is referred to that report for orientation.

TALİDOMİD'e…

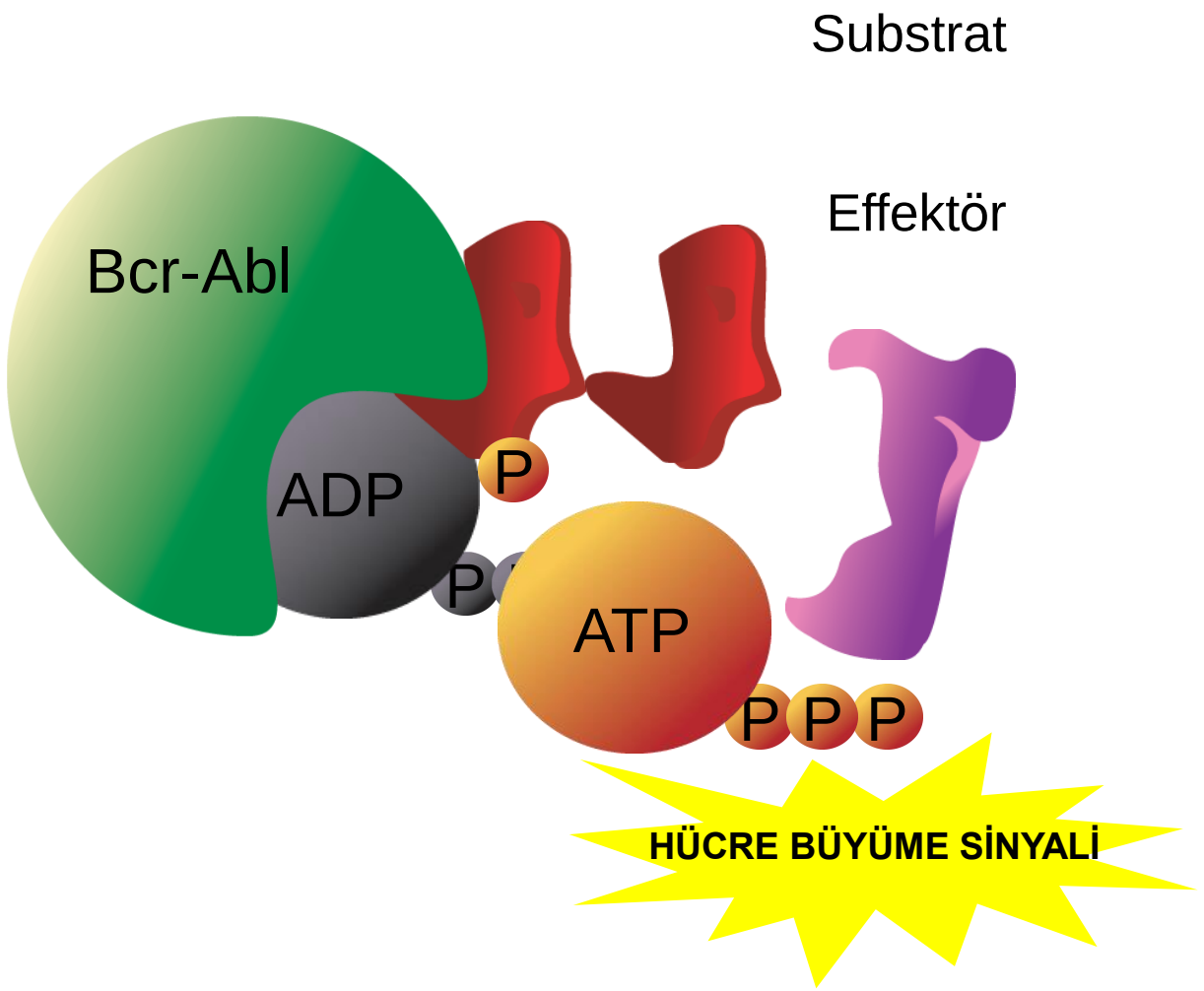

JULY 17, 2006
www.time.com
AOL Keyword: TIME
TIME
Thalidomide's Return
MONDAY, JUN. 13, 1994 By CHRISTINE GORMAN
100 Capsules
Sauramide
(Thalidomide)
Bad Drug Makes Good
SUNDAY, JAN. 26, 2003 By KATE NOBLE/LONDON

GENETİK ANORMALLİKLERİN ÖNEMİNDEN…

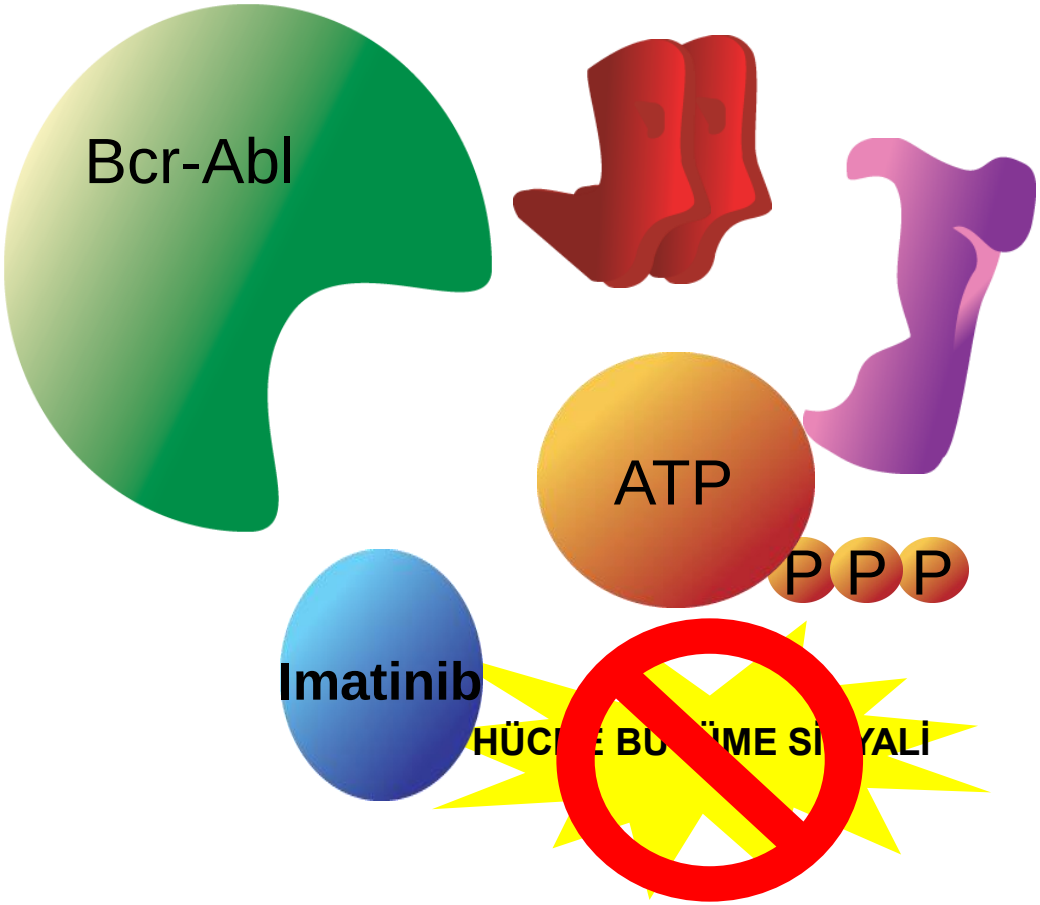


Nowell and Hungerford, 1960 yılında Philadelphia'da çalışırken kronik granülositik lösemi olarak bilinen bir grup hastada anormal bir kromozomun farkına vardılar.

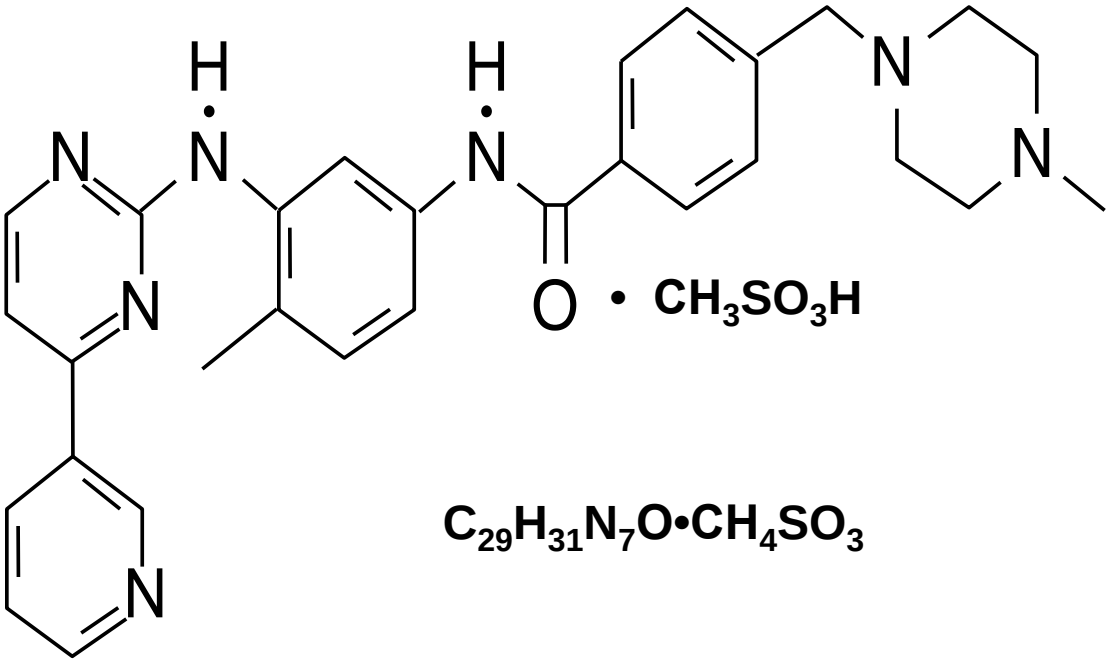
TİROZİN KİNAZ'LARIN ÖNEMİNE...



TİROZİN KİNAZ İNHİBİTÖRLERİ'ne



IMATINIB MESİLAT'a…



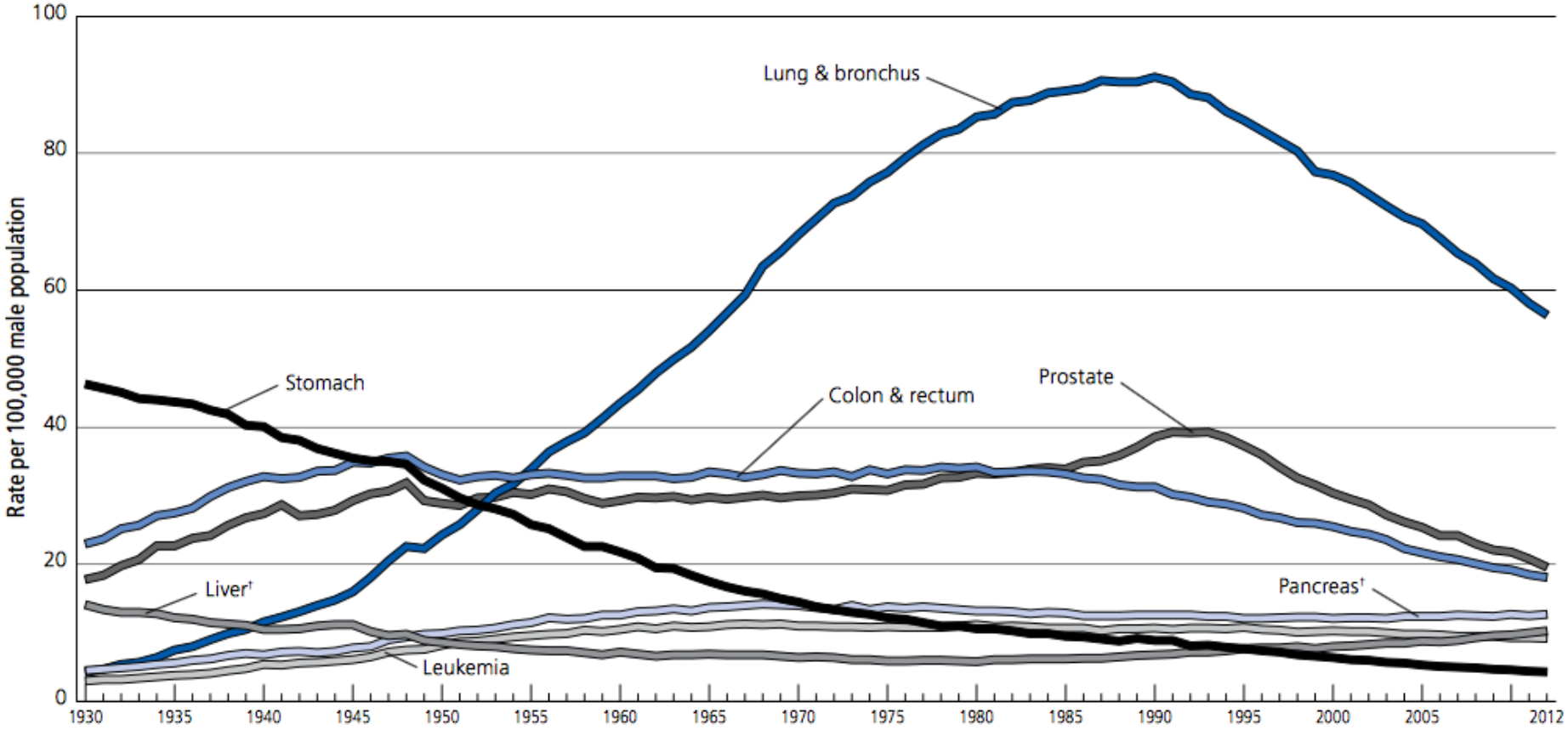
$C_{29}H_{31}N_7O \cdot CH_4SO_3$

SINIF: Phenylaminopyrimidines, 589.7 mw

KANSERDE NEREDEYİZ?

KANSER SIKLIĞI

Figure 1. Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2012



KANSERİN ETYOLOJİSİ

- **DOĞAL**
  - Ailevi Kanser Sendromları
    - p53, BRCA1 ve 2, MMR
  - İmmün Yetmezlik Sendromları
    - Genetik / Doğumsal veya kazanılmış
- **KAZANILMIŞ**
  - Radyasyon
  - Kimyasal Tedavilere ikincil (MDS)
  - Virus ve bakteriler
    - EBV, HTLV-I/II, *H. pylori*
  - Yineleyen doku hasarı(Asit reflü, hepatit)

KANSER OLUŞUMUNUN YOLU

- Klonal Proliferasyon
- Tek bir hücrenin klonal evaluasyonu
- Klonal hücrenin ekspansiyonu
- Kanser öncesi durumlar (pre-malignant condition)
  - Poliposis, MDS, MGUS
- Eklenen yeni mutasyonlar
  - Klonal evolusyon
  - Direnç

KANSERİN “PÜF” NOKTALARI

- Kendi başına “büyüme sinyali” oluşturma yeteneği
- “Anti-growth” sinyallere direnç
- Apoptosis’den kaçış
- Sınırsız çoğalma potansiyeli
- “Angiogenesis” indüksiyonu
- Doku invazyonu ve uzak metastaz
- Genomik instabilite

KANSER KÖK HÜCRESİ

- Küçük bir fraksiyon ama hep var…!
- Tanımak için bilinen bir “marker” yok…!
- Klasik tedavilere “genellikle” dirençli…!

“Hedefe yönelik tedaviler” için ANA HEDEF…!

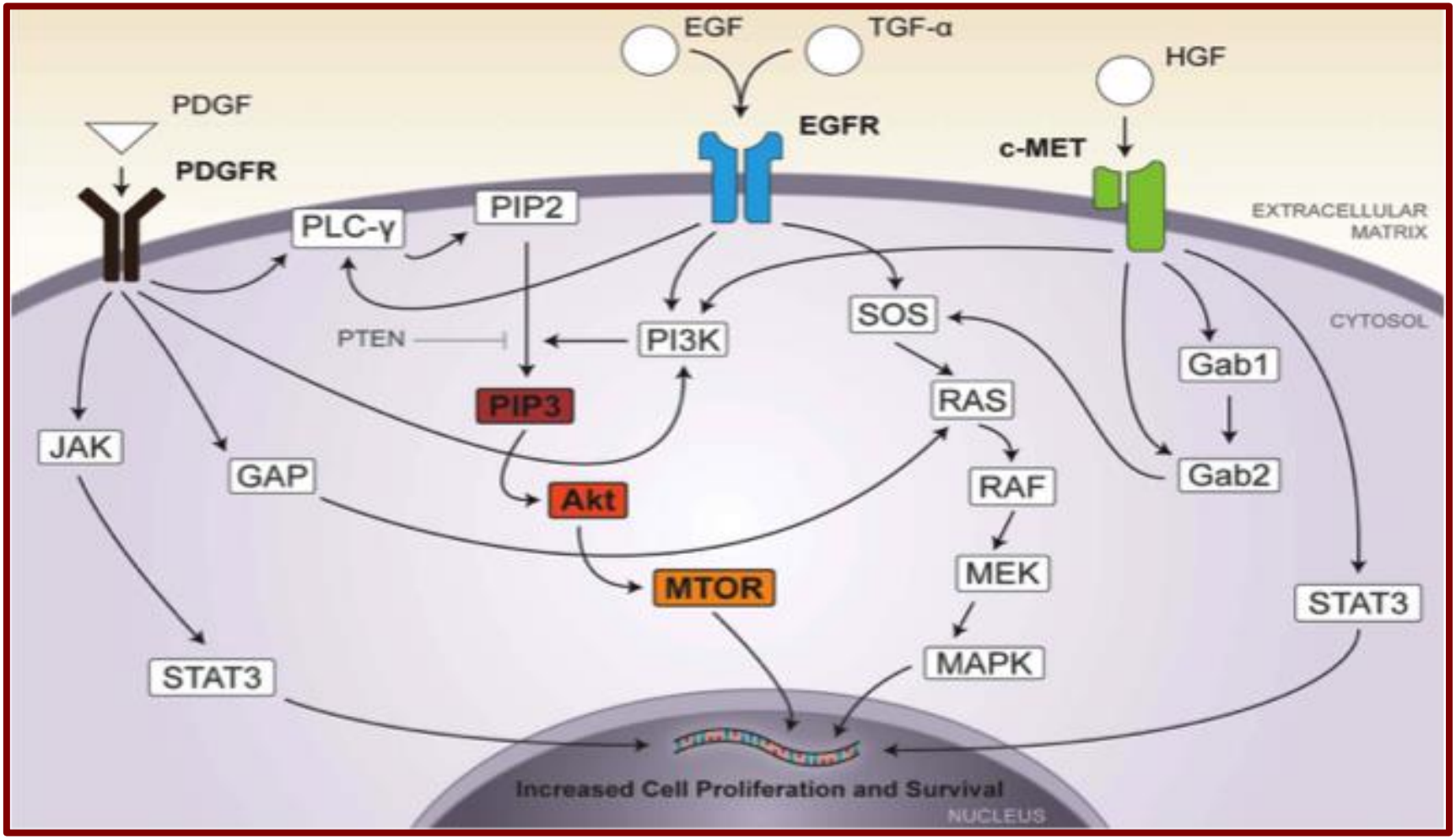
KANSERDE MOLEKÜLER TSUNAMİ…?

HEDEFE YÖNELİK TEDAVİ ?

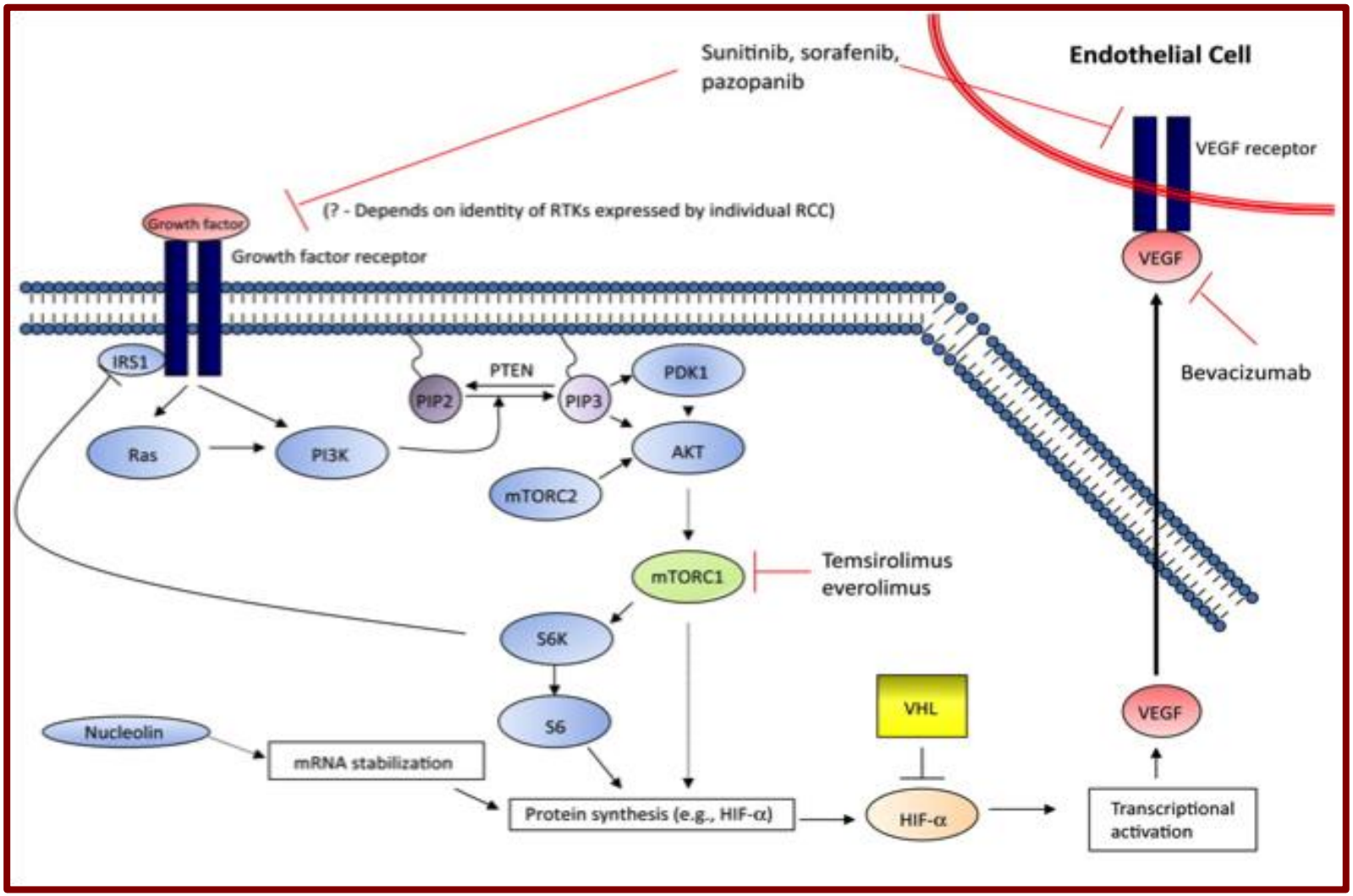
- **Kanser gelişimine neden olan moleküler anormalliğe veya hedefe karşı doğrudan geliştirilen tedavi…**

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

HEDEFE YÖNELİK TEDAVİ ?



HEDEFE YÖNELİK TEDAVİ ?



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 →

-mab	monoclonal antibody
-ib	small molecule with inhibitory properties

variable

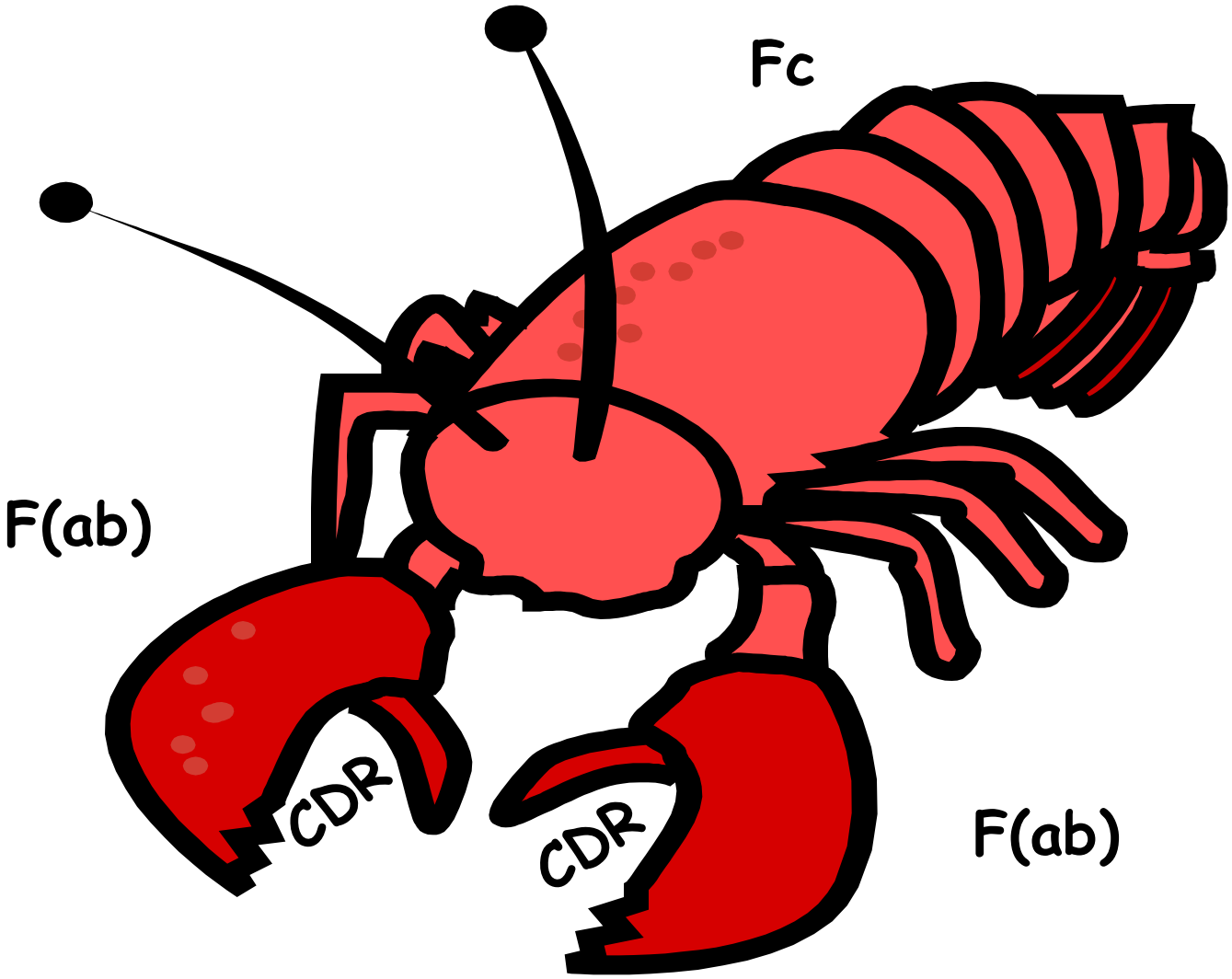
Monoclonal antibodies

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

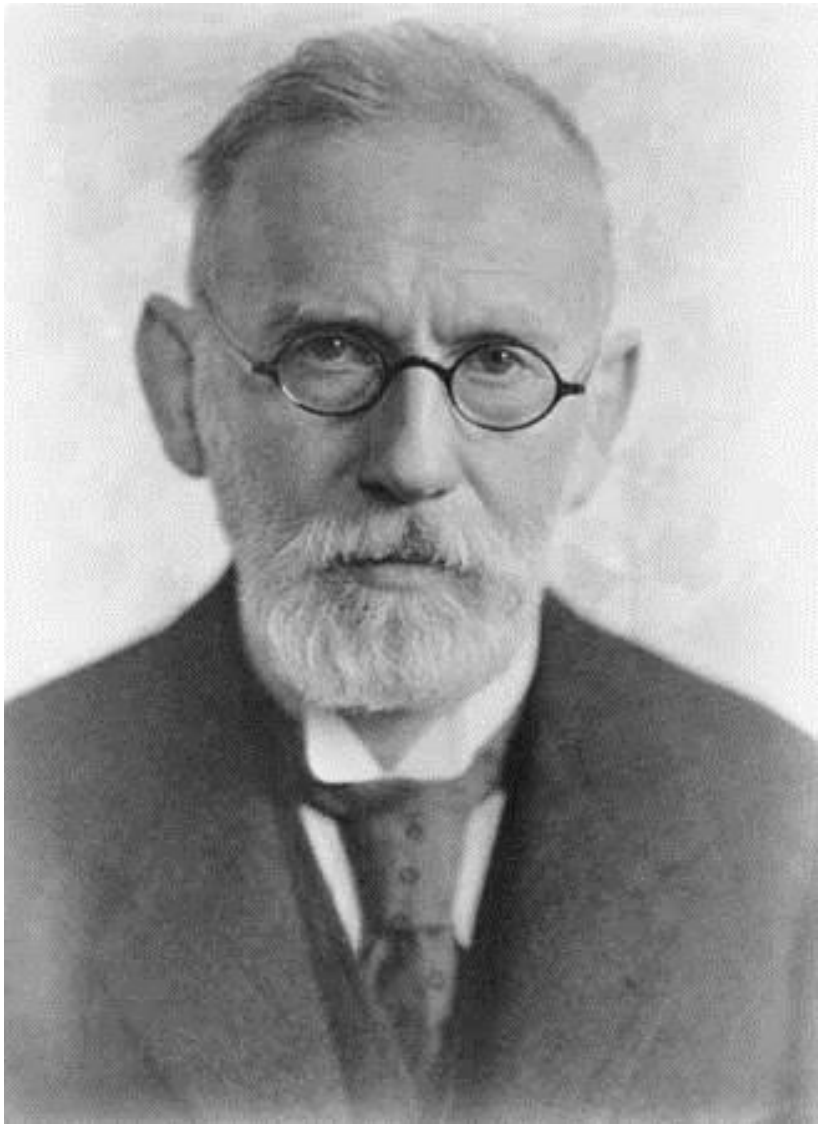
Small molecules

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

ANTİKOR TEDAVİLERİ (Mab's)



Paul Ehrlich (1854-1915)



“Antikorlar, onlar BÜYÜLÜ KURŞUNLARDIR, hedeflerini kendi başlarına bulurlar

1904

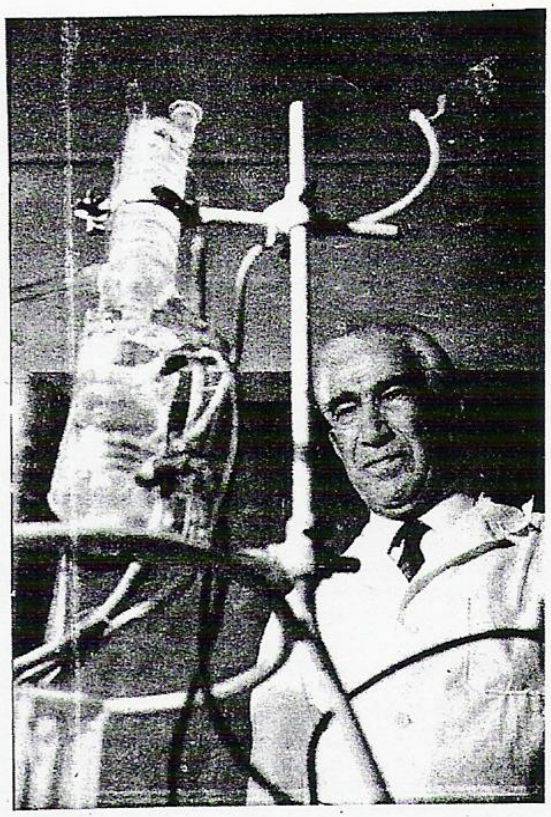
Kanser'e karşı bir Türk

Yetmiş yaşındaki «genç» bilim adamı, kanser araştırmaları yapıyor! Ord. Prof. Dr. Süreyya Aygün, Veteriner Fakültesinden -yaş nedeni ile- emekli olmuştu. Ama, bir kenara çekilip oturmayı düşünmemişti. Yıllarca emek verdiği «hücre ve doku kültürleri» üzerindeki çalışmalarını aralıksız sürdürdü.

Emekliliğinden sonra Almanya'ya gitti. Almanlar bile, 2,5 milyon marklık bir fon ayırarak, çalışmaları ile ilgilendiler. Araştırmalarını orada yürütmesini istediler. Bir süre Almanya'da kaldı. «Düşük» yapması beklenen «cenin»lerden, yani ana rahmindeki çocuklardan sağladığı «kültür»le, kanser, siroz, geri zekâlılık ve erken bunama gibi hastalıkları önleyici buluşlarda bulundu.

Sonuçlarını yaymak üzere Türkiye'ye döndü. Oysa, kimse ilgilenmedi! Bu durum, Ankara Şeker Fabrikası Araştırma Enstitüsü'nün bir laboratuar armağan etmesine değin sürdü. Aygün, gelecek günlerde ilgi ile karşılanacak sonuçları, artık açıklayacaktı.

Yabancılar buluşlardan, Türk kamuoyundan önce bilgi edinmişler.



Prof. Aygün – Bir Türk yardımcı arıyor..

Kanser konusunda bugüne değin

"Organizmanın savunma hücreleri olan lenfoid sistem ile başka hücre grubu, kanserle birlikte ekildiklerinde, hızla kanser kolonilerine karşı savaşa geçiyor. Böylelikle yok etme çalışması başlıyor. Dr. Aygün bu noktadan hareket ederek, bir antikor yani kanser eritici madde için çalışmalara başlamış".

YANKI DERGİSİ, SAYI:428, 1979

MONOKLONAL ANTİKORLAR

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

MONOKLONAL ANTİKORLAR

- **Konjuge Antikorlar**
  - **Radyo-konjuge antikorlar**
    - Tositumomab (Bexxar)
    - Ibritumomab (Zevalin)
    - Her ikisi de dirençli lenfomlar da kullanılmaktadır.
  - **Toxin-konjuge antikorlar**
    - Gemtuzumab ozogamicin (Mylotarg)

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

YENİ MONOKLONAL ANTİKORLAR

- Epratuzumab
- Matuzumab
- Nimotuzumab
- Zalutumumab
- Pertuzumab
- Mapatumumab
- Lexatumumab
- Volociximab
- Pemtumomab
- Labetuzumab
- ch806
- CP-751,871
- IMC-A12
- VEGF-Trap
- IMC-18F1
- IMC-1121B
- IMC-3G3
- Vitaxin
- CNTO 95

ALTERNATİF ANTİKOR HEDEFLERİ

CD19

CD22 Epratuzumab

CD40

CD52

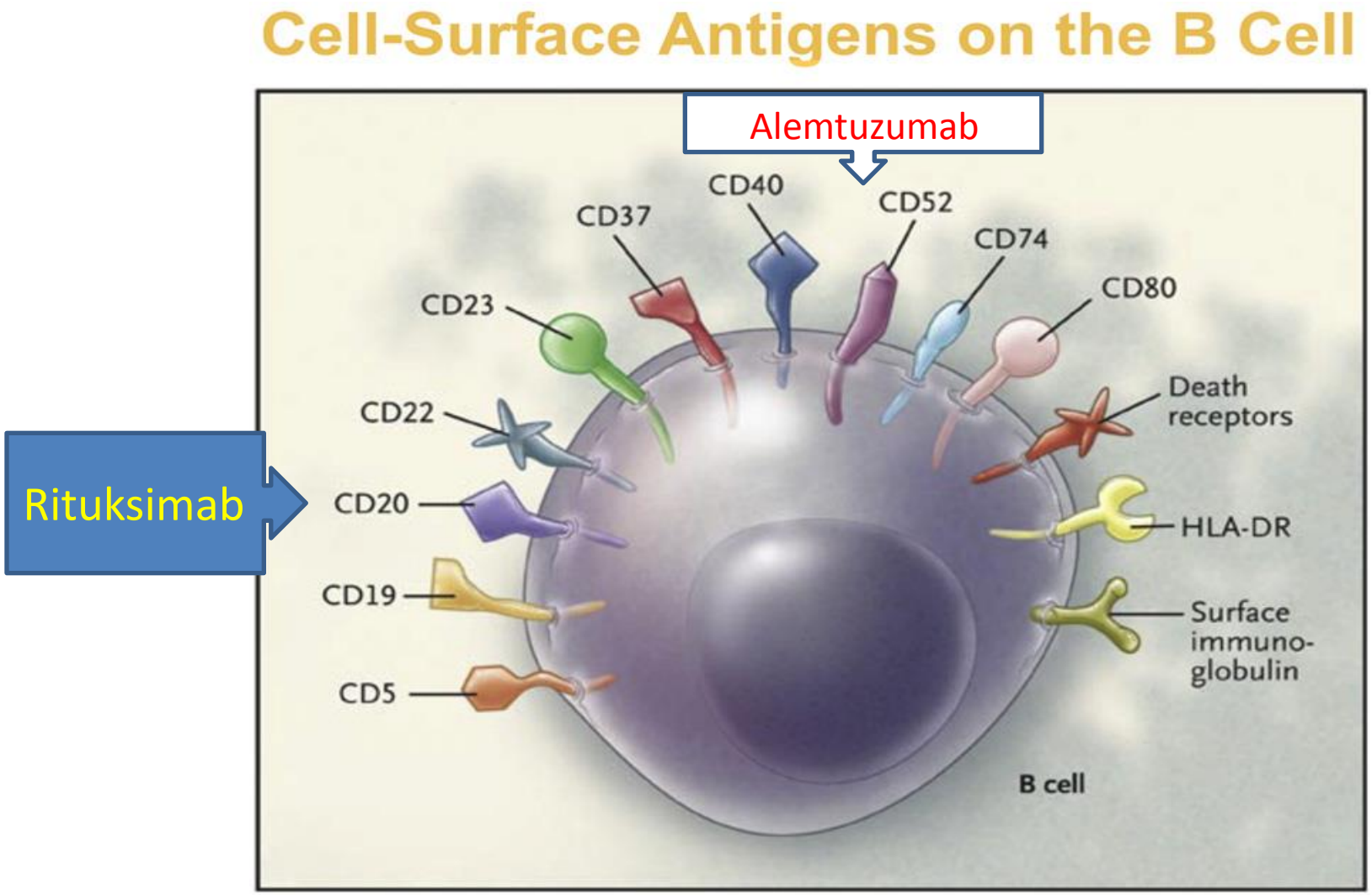
CD80

HLA-DR

B Ly S

VEGF

RITUXIMAB & ALEMTUZUMAB



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

ETKİ MEKANİZMALARI

- Kompleman bağımlı sitoliz (CDC)
- Antikor bağımlı hücresel sitotoksisite
- Apopitosis

Johnson P., Glennie M., Seminars in Oncology. Vol 30, No1, Suppl 2, 3-8

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… 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: normal düzeyler 24. ayda sağlanır…**

RİTUKSİMAB… Ig düzeyleri…

- **Ig düzeyleri düşüyor…**
  - **Ig G : 12 ay**
  - **Ig M: 6 ay**
  - **Ig A : 9 ay sırasında en düşük düzey**

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...

- **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.

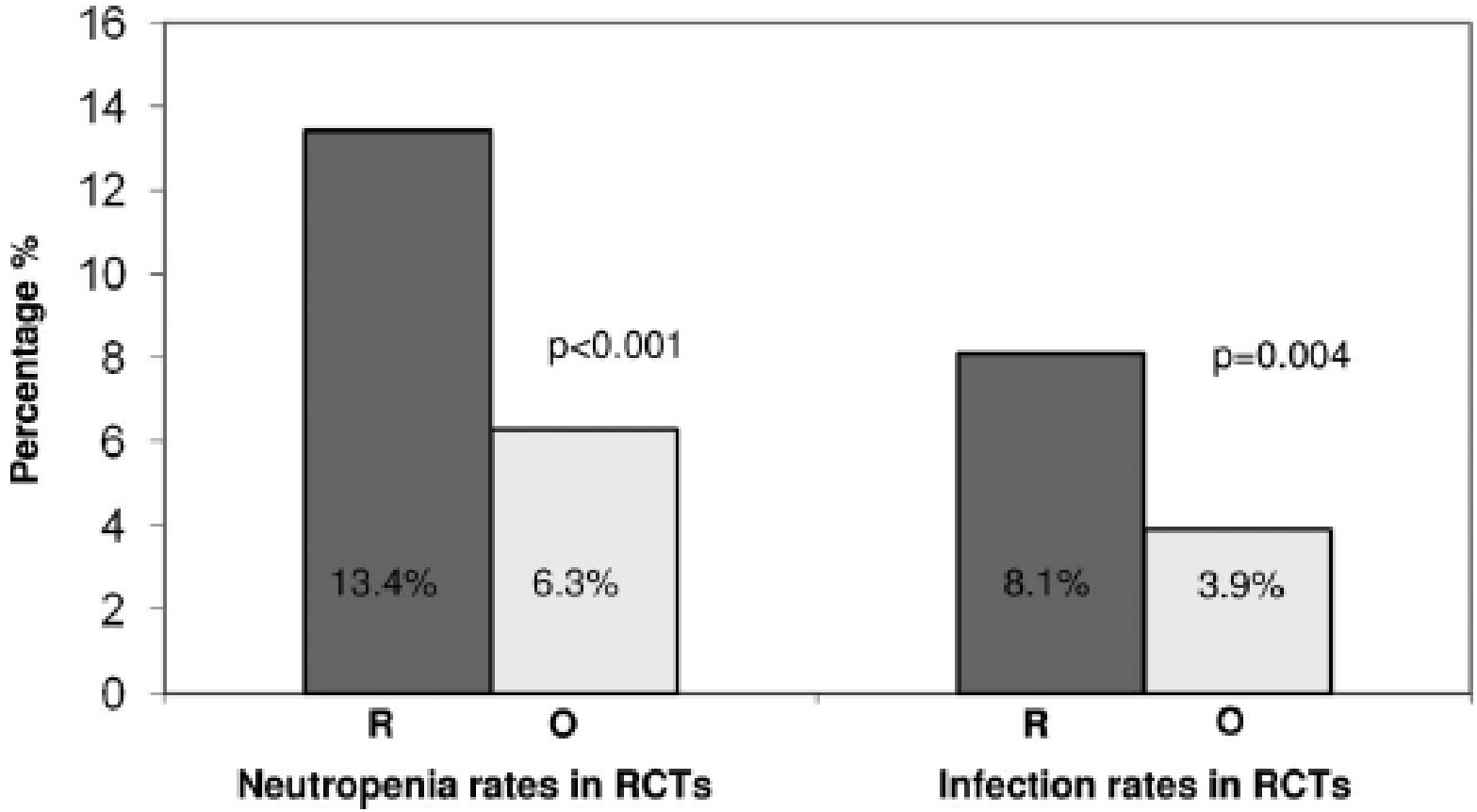
RİTUKSİMAB... İnfeksiyon ne kadar sık ?

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... 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... 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**

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 $\leq 1.5 \times 10^9/L$
- 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... Viral infeksiyonlar

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

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 ?

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 ?

HCV (+) veya HBV taşıyıcılarda re-aktivasyon

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

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… 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… ne yapalım? HBV

IVIg kullanımı:

Sınırlı deneyim…

Viral İnfeksiyon görüldükten sonra etkisiz…

RİTUKSİMAB… ne yapalım? HBV

LAMUVİDİNE

En etkili gibi…

Buna rağmen yanıtsızlık olabiliyor…

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… 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.

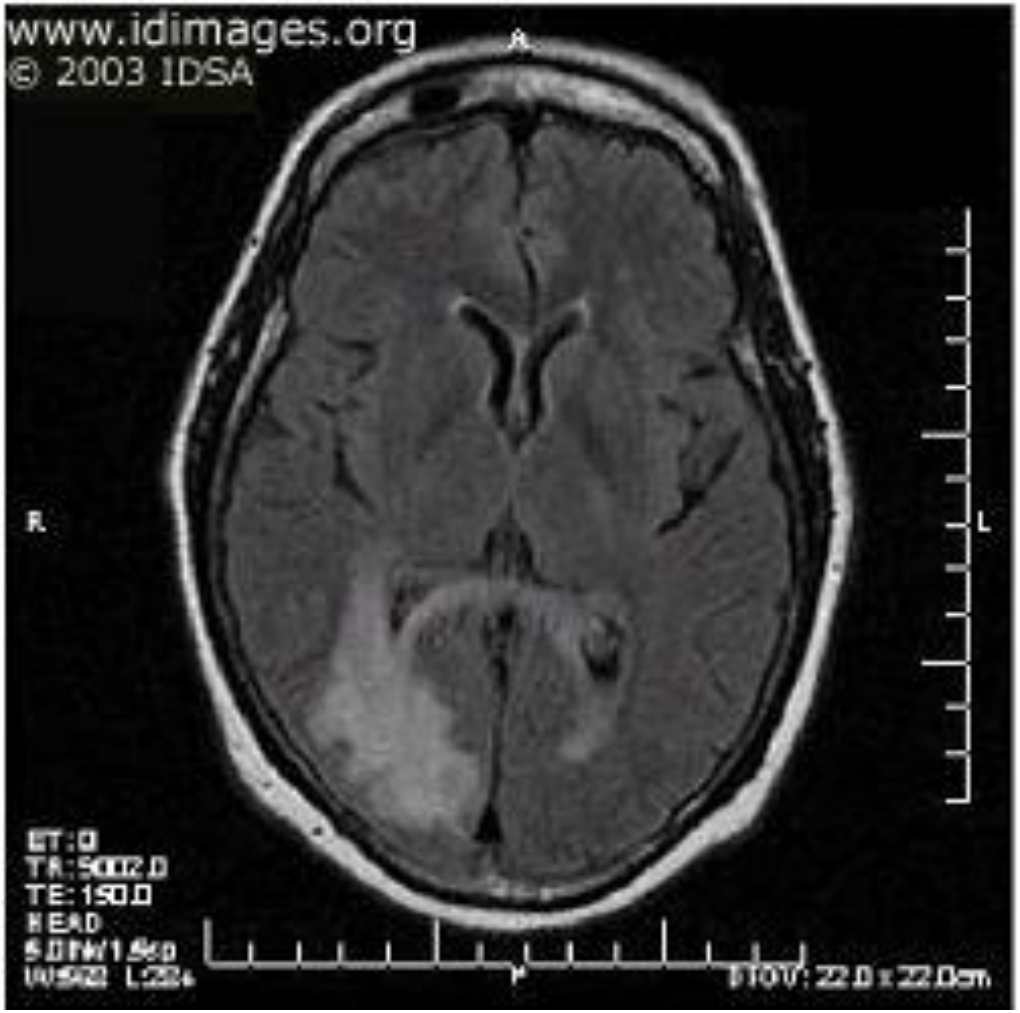
Pfreundschuh M, Tru¨mper L, Osterborg A, et al. CHOPlike chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379–391.

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..

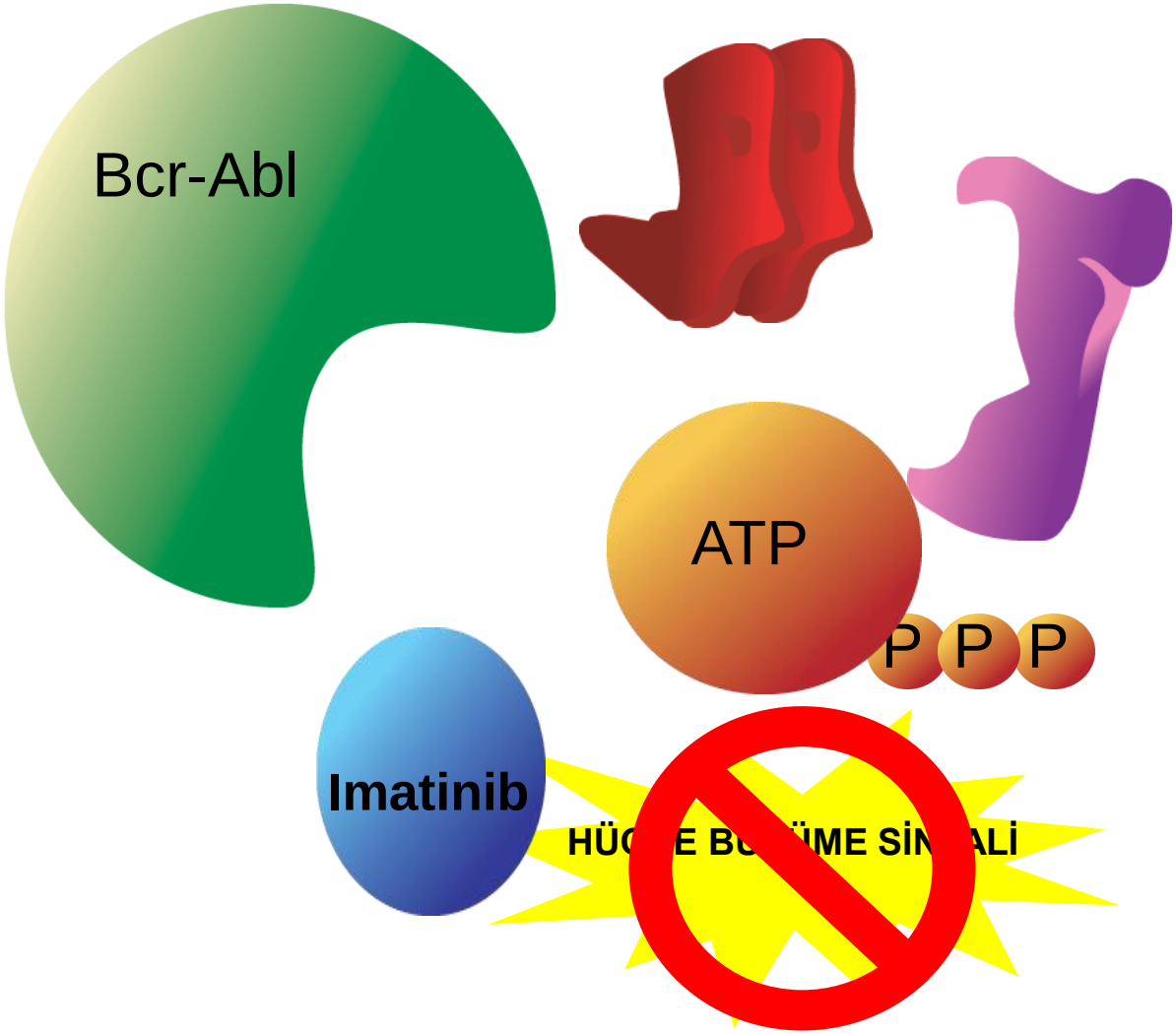
RİTUKSİMAB... Progresif Multifokal Lökoensefalopati



RİTUKSİMAB… Progresif Multifokal Lökoensefalopati

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

KÜÇÜK MOLEKÜLLER (Nib'ler)



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

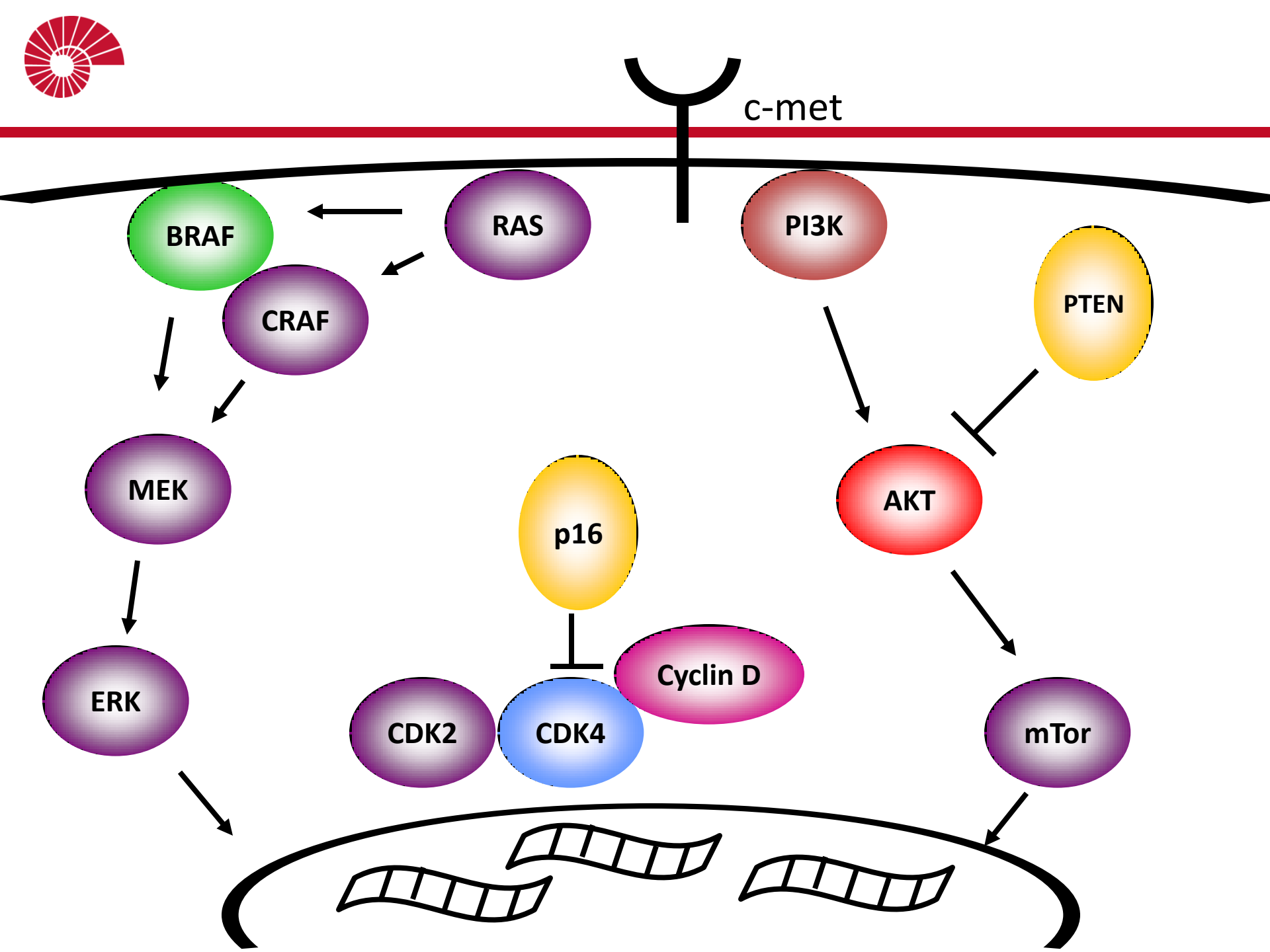
KÜÇÜK MOLEKÜLLER (Nib'ler)

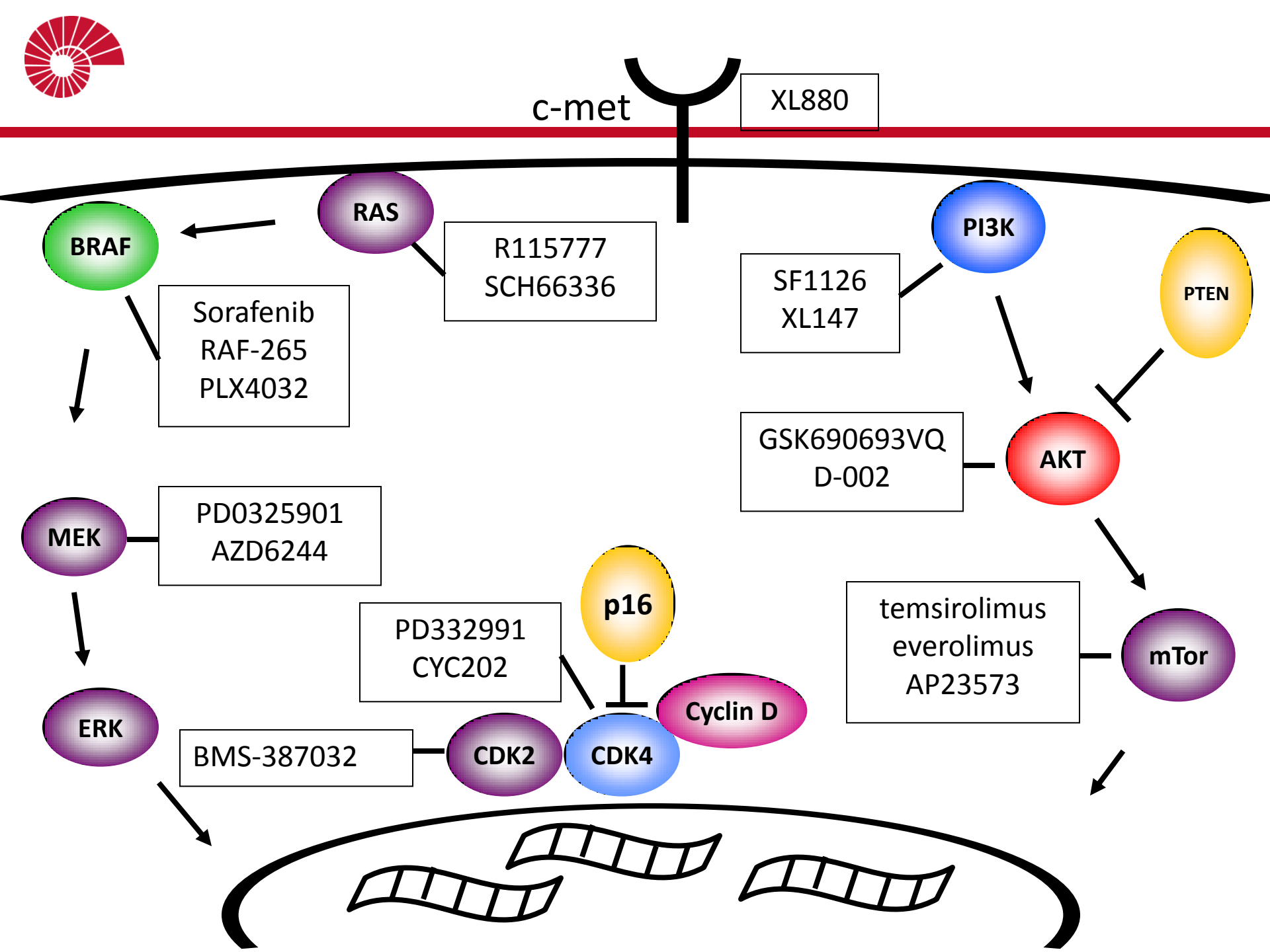
KÜÇÜK MOLEKÜLLER (Nib'ler)

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 KÜÇÜK MOLEKÜLLÜ 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)


c-met
BRAF
RAS
CRAF
PI3K
PTEN
MEK
AKT
p16
ERK
Cyclin D
CDK2
CDK4
mTor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XL880
RAS
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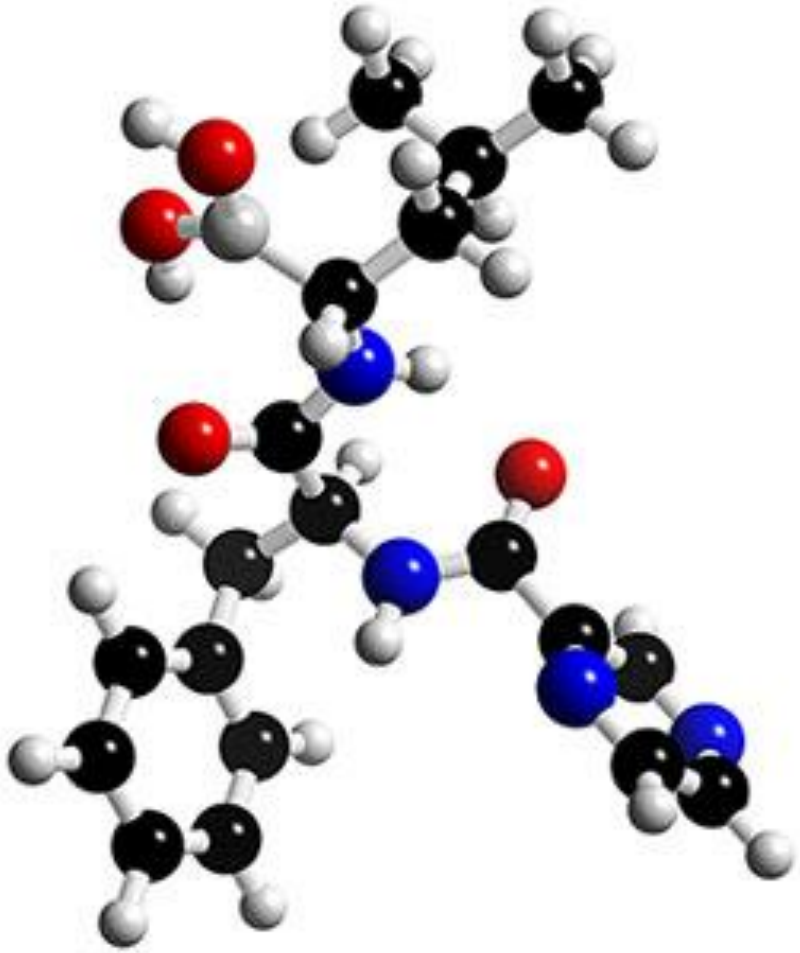
SCH66336
BRAF
Sorafenib
RAF-265
PLX4032
PI3K
SF1126
XL147
PTEN
GSK690693VQ
D-002
AKT
MEK
PD0325901
AZD6244
p16
PD332991
CYC202
Cyclin D
temsirolimus
everolimus
AP23573
mTor
ERK
BMS-387032
CDK2
CDK4

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

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.

ANTİBİYOPROFLAKSİ ?

ANTİBİYOPROFLAKSİ ?

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Prevention and Treatment of Cancer-Related Infections

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OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	FEVER & NEUTROPENIA RISK (See FEV-2)	ANTIMICROBIAL PROPHYLAXIS [d,e,f,g,h,i]
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 • 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 • 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 • 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)

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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 • 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 • 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 • 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)

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OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	FEVER & NEUTROPENIA RISK (See FEV-2)	ANTIMICROBIAL PROPHYLAXIS [d,e,f,g,h,i]
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 • 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 • 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 • 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)

ANTİBİYOPROFLAKSİ ?

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OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	ANTIFUNGAL PROPHYLAXIS[f,l]	DURATION
INTERMEDIATE TO HIGH	ALL	Consider: • Fluconazole[m] or Micafungin • Amphotericin B products[n] (category 2B)	Until resolution of neutropenia
	MDS (neutropenic) AML (neutropenic)	Consider: • Posaconazole[m] (category 1) • Voriconazole[m], Fluconazole[m], Micafungin, or Amphotericin B products[n] (all category 2B)	
	Autologous HCT with mucositis[j]	Consider: • Fluconazole[m] or Micafungin (both category 1)	
	Autologous HCT without mucositis	Consider no prophylaxis (category 2B)	
	Allogeneic HCT (neutropenic) See Antipneumocystis Prophylaxis (INF-6)	Consider: • Fluconazole[m] or Micafungin (both category 1) • Voriconazole[m], Posaconazole[m], or Amphotericin B product[n] (all category 2B)	Continue during neutropenia and for at least 75 d after transplant
	Significant GVHD[k] See Antipneumocystis Prophylaxis (INF-6)	Consider: • Posaconazole[m] (category 1) • Voriconazole[m], Echinocandin, Amphotericin B products[n], or Micafungin (all category 2B)	Until resolution of significant GVHD

ANTİBİYOPROFLAKSİ ?

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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

ANTİBİYOPROFLAKSİ ?

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PREVENTION OF CYTOMEGALOVIRUS (CMV) REACTIVATION OR DISEASE

OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/ THERAPY EXAMPLES	SURVEILLANCE PERIOD[p]	PREEMPTIVE THERAPY[g,q,r]
High risk for CMV	Allogeneic hematopoietic cell transplant recipients	• Typically for 1 to 6 months after transplant • GVHD requiring therapy	First-line therapy[s] Valganciclovir (PO) or Ganciclovir (IV)[t] → Foscarnet (IV) or Cidofovir (IV)
	Alemtuzumab	For a minimum of 2 months after alemtuzumab	

KANSERDE MOLEKÜLER TSUNAMİ…?

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…!

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…