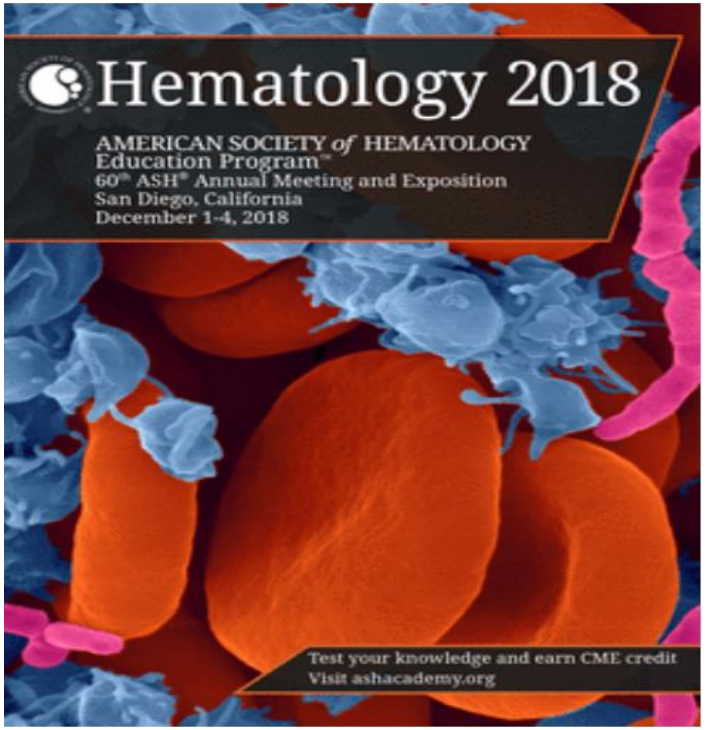

2018 YILI HEMATOLOJİK HASTALIKLARA NE GETİRDİ?

Dr. Vildan Özkocaman

Uludağ Üniversitesi Tıp Fakültesi

Hematoloji Bilim Dalı, Bursa

YENI ANTIKOAGÜLANLAR

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Oral faktör Xa inhibitörleri

Rivaroxaban (Xarelto, 10.15.20 mg/günde 1-2)

Apixaban (Eliquis tb, 2.5, 5 mg) 2x1

Oral trombin inhibitörleri

Dabigatran

(Pradaxa 150 mg 2x1, 110 mg 2x1, 75 mg 2x1)

- Kalça ve diz cerrahisi
- Atriyal Fibrilasyon, VTE prof.

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YENI ANTIKOAGÜLAN ILAÇLAR

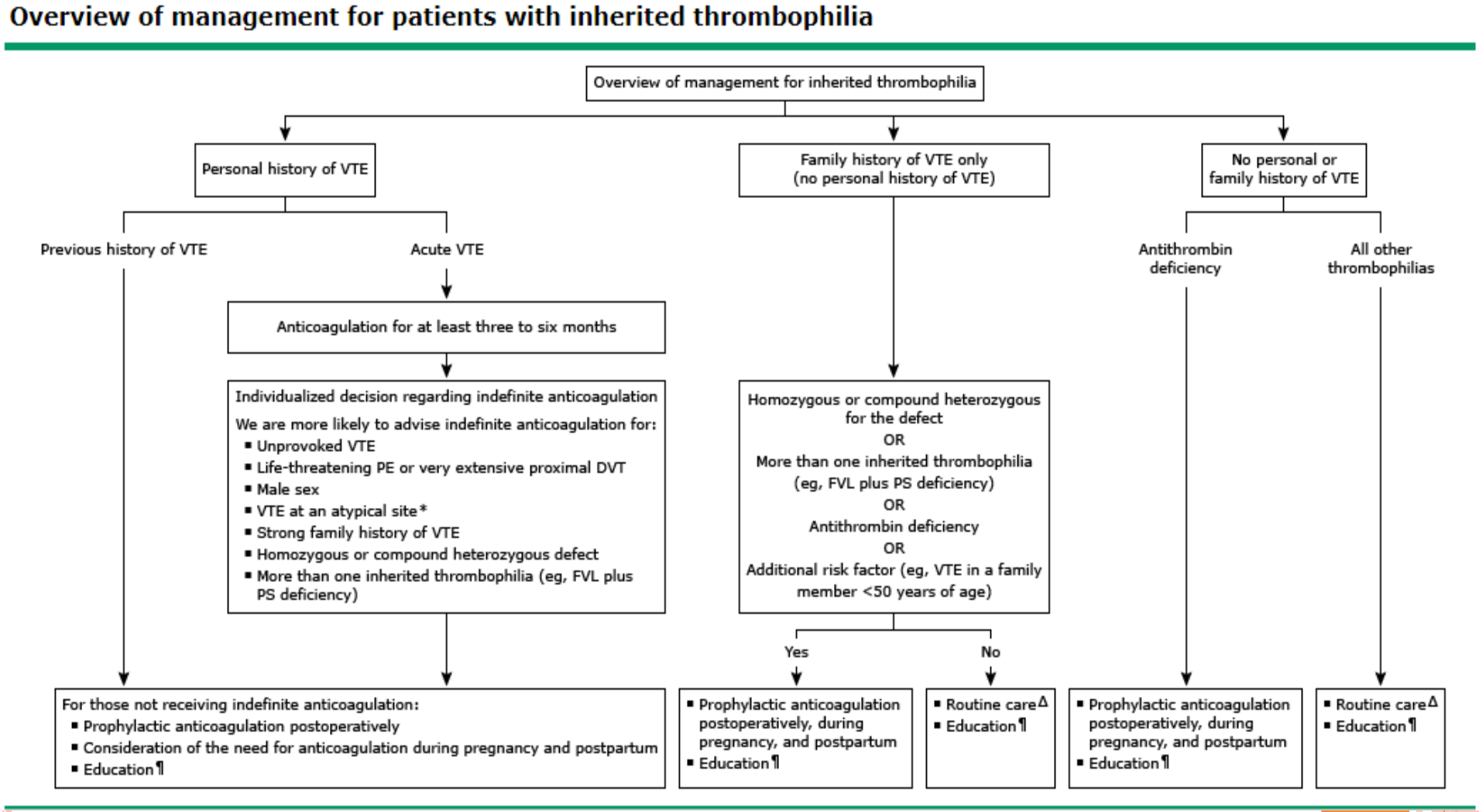
Avantajları

- Hızlı antikoagülan etki
- Parenteral forma ihtiyaç yok
- Yarılanma ömrü kısa
- Rutin laboratuvar izlemine ihtiyaç yok
- Yiyecek ve ilaç etkileşimi az-yok
- Vitamin K alınımında bir sınırlama yok

Dezavantajları

- Kısa yarılanma ömrü, bir iki doz atlanmasında etki kaybı
- Antidot yok. Ciddi kanama ve acil durumda algoritma yok
- Geçerliliği ispatlanmış izlem metodu yok
- Özel durumlarda (obezite, yaşlılık, renal yetersizlik) doz ayarlaması ve yönetim algoritması yok
- Pahalı ilaçlar

KALITIMSAL TROMBOFİLİLİ HASTALARIN TEDAVİ ALGORİTMASI



TROMBOZ VE TEDAVİSİ

KANSERLİ HASTALARDA TROMBOZ PROFİLAKSİSİ

- **Rivaroxaban Thromboprophylaxis in High-Risk Ambulatory Cancer Patients Receiving Systemic Therapy: Results of a Randomized Clinical Trial (CASSINI)**

- VTE önemli oranda azalttı
- Majör kanama düşük

Glikokortikoid tedavi ile VTE riski

- **Association of Risk of Incident and Recurrent Venous Thromboembolism with Oral Glucocorticoid Treatment**

Fernanda Andrade Orsi,
Willem M Lijfering, Geert-Jan Geersing, Frits Richard Rosendaal,Olaf Dekkers,
Saskia le Cessie and
Suzanne Cannegieter

Oral Glikokortikoid tedavi ile VTE riski

- 2-3 kat artmış VTE
- 2547 hasta
- 363 ü oral GK reçetelenmiş en az 1 kere
- İlk VTE riski: 3.5-kat artmış

- Tedavi başlanmadan önce: 2.5
- İlk 7 gün içinde: 5.3
- 6 ay sonra: 1.6
- Doz bağımlı ilişki: GK tedavi ve VTE riski

Direkt oral antikoagülanlar cerrahi öncesi yönetim

- **Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) Study: A Perioperative Management Plan for Patients with Atrial Fibrillation Who Are Receiving a Direct Oral Anticoagulant**

James Douketis, Alex Spyropoulos, Joanne M Duncan, Marc Carrier, Gregoire Le Gal,
Alfonso J Tafur, Thomas Vanassche, Peter Verhamme, Sudeep P Shivakumar, Peter L. Gross, Agnes Yuet Ying Lee, Erik Yeo,
Susan Solymoss, Jeannine Kassis,
Genevieve Le Templier, Stephen Kowalski,
Mark Blostein, Vinay Shah, Elizabeth MacKay, Cynthia M. Wu, Nathan Clark, Shannon M. Bates, Fred Spencer, Eleni Arnaoutoglou, Michiel Coppens, Donald Arnold, Joseph A Caprini,
Na Li, Karen Moffat, Syed Summer and Sam Schulman

Direkt oral antikoagülanlar cerrahi öncesi ve sonrası yönetim

Apixaban, ***dabigatran***, ***rivaroxaban***

Perioperatiy tedavi -DOACs AF

Electif cerrahi- Belirsiz

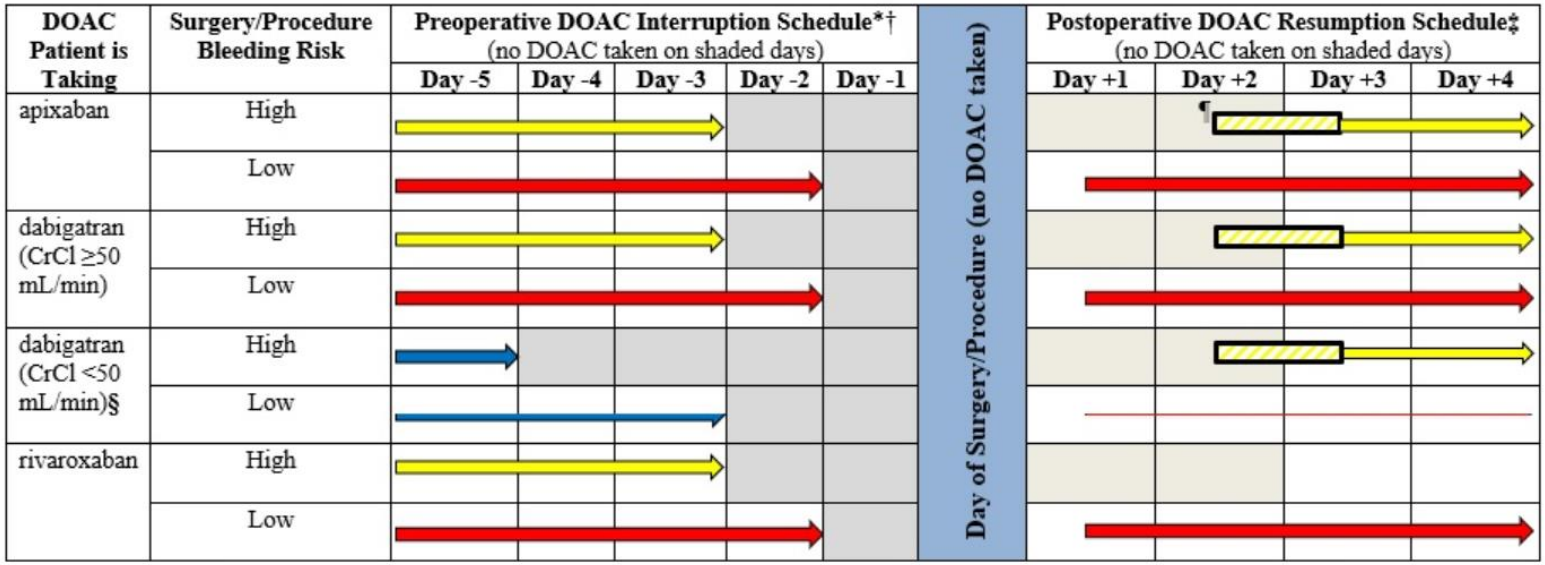
<u>Bununla ilgili çalışma yok</u>

- DOAC ne zaman kesileceği-periop zamanlama-ne zaman tekrar başlanacağı
- Koagülasyon testlerine ihtiyaç? Heparin köprüsüne ihtiyaç?

Majör kanama (1%) ve arterial TE (0.5%)

DIREKT ORAL ANTIKOAGÜLANLAR CERRAHI ÖNCESI VE SONRASı YÖNETIM

Figure 1. Perioperative DOAC Management Protocol



KANAMA RISKI YÜKSEK CERRAHI IŞLEMLER

High Bleed Risk Surgery/Procedures

1) any surgery requiring neuraxial anaesthesia
   - neuraxial anaesthesia/injection
   - epidural anaesthesia/injection
2) major intracranial or neuraxial surgery
   - brain cancer resection
   - laminectomy or neuraxial tumour resection
   - intracranial (subdural, epidural) bleed evacuation
3) major thoracic surgery
   - lobectomy, pneumonectomy
   - esophagectomy
4) major cardiac surgery
   - coronary artery bypass
   - valve replacement or repair
5) major vascular surgery
   - aortic aneurysm repair
   - aortobifemoral bypass, popliteal bypass
   - carotid endarterectomy
6) major abdominopelvic surgery
   - hepatobiliary cancer resection
   - pancreatic cancer or pseudocyst resection
   - colorectal and gastric cancer resection
   - diverticular disease resection
   - inflammatory bowel disease resection
   - renal cancer resection
   - bladder cancer resection
   - endometrial cancer resection
   - ovarian cancer resection
   - radical prostatectomy
7) major orthopedic surgery
   - hip arthroplasty or hip fracture repair
   - knee arthroplasty or tibial osteotomy
   - shoulder arthroplasty
   - metatarsal osteotomy
8) other major cancer or reconstructive surgery
   - head and neck cancer surgery
   - reconstructive facial, abdominal, limb surgery

Direkt oral antikoagülanlar cerrahi öncesi ve sonrası yönetim

Standart protokol:

1. DOAC farmakokinetik özellikleri
2. **İşlem ilişkili kanama riski**
3. CrCl

4. Cerrahi kanama riski düşük olgularda
   1 gün önce ve sonra ilaca ara vermek
5. Cerrahi kanama riski yüksek olgularda
   2 gün önce ve sonra ilaca ara vermek

6. Dabigatran ile CRCL< 50 ml/dk ---daha uzun ara verilmesi

7. Preop koag. Testlerine ve DMAH köprüsüne ihtiyaç yok

Olgular major kanama ve trombo-emboli riski için post-op 30 gün boyunca haftalık izlemde kalmalı

Atrial fibrilasyonlu DOC kullanan periop antikoagülan değerlendirimi

- **Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) Study: A Perioperative Management Plan for Patients with Atrial Fibrillation Who Are Receiving a Direct Oral Anticoagulant**

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Atrial fibrilasyonlu DOC kullanan periop antikoagülan değerlendirimi

	Apixaban	Dabigatran	Rivaroxaban	Total
# of pts	1257	668	1082	3007
Age (y, mean±SD)	73.1±9.15	72.38±9.93	71.97±9.3	71.53±9.39
Male (%)	64.04	68.56	67.01	66.11
High bleed risk (%)	32.3	34.13	34.47	33.49
Major bleed (%)	1.35	0.90	1.85	1.43
Arterial TE (%)	0.16	0.60	0.37	0.33

ÇİFT ANTİPLATELET TEDAVİ YAN ETKİLERİNİ DÜZELTMEDE SOĞUKTA DEPO PLATELETLER

Cold-Stored Platelets to Reverse Dual Antiplatelet Therapy

Moritz Stolla, Anthony Vargas,
Shawn Bailey, Lydia Fang,
Esther Pellham, Irena Gettinger,Todd Christoffel, Jill Corson,
Barbara Osborne and Lynda
Fitzpatrick

ÇİFT ANTİPLATELET TEDAVİ YANETKİLERİNİ DÜZELTMEDE SOĞUKTA DEPO PLATELETLER

- Dual antiplatelet therapy (DAPT)
- ***ASA*** and ***P2Y12 inhibitors***
- Akut koroner sendromlu hastalarda
- Major kanama komplikasyonu
- Acil cerrahi öncesi aşırı kanama durumunda antidotu ya da etkili tedavisi yok

ÇİFT ANTİPLATELET TEDAVİ YANETKİLERİNİ DÜZELTMEDE SOĞUKTA DEPO PLATELETLER

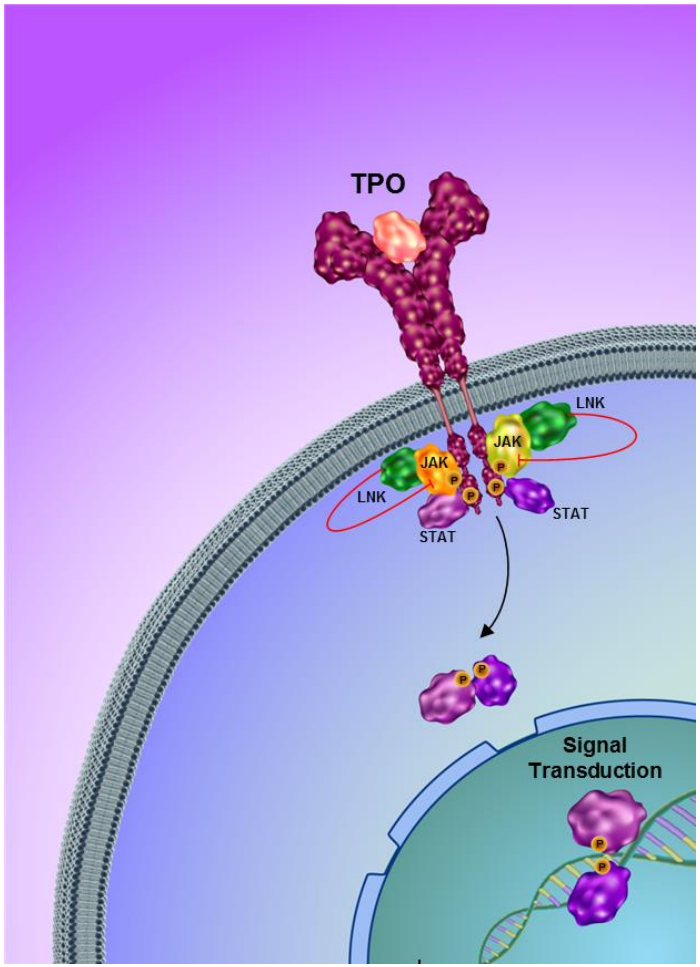
- ***Room temperature-stored platelet transfusions*** (RSP)
- Aspirin etksini geri çevirebilir

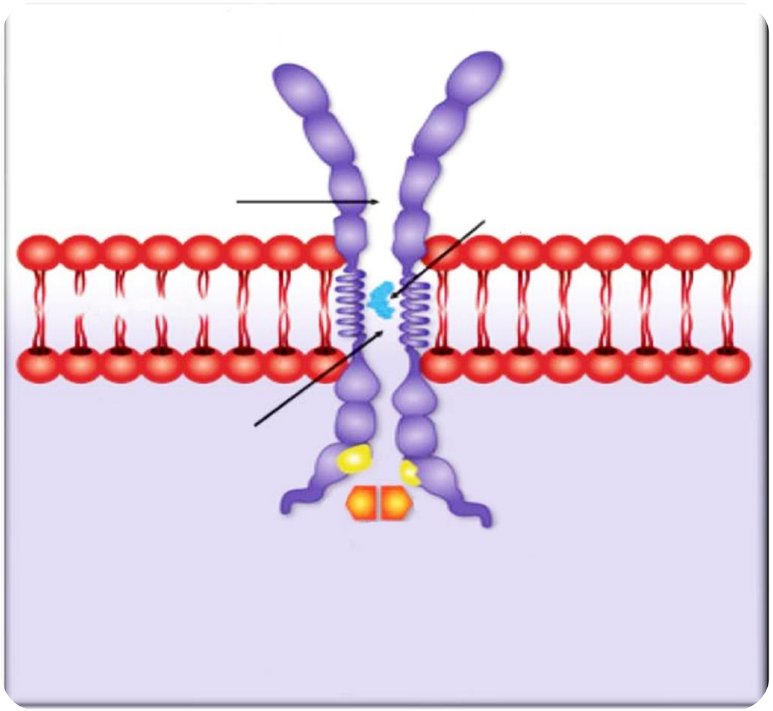
- ***Cold-stored platelets*** (CSP)
- 2.5---6 gün
- Transfüzyon ihtiyacını kaldırma amacı

İMMÜN TROMBOSITOPENI

ITP

ITP-TPO MIMETIKLER-ELTROMBOPAQ





ITP-ELTROMBOPAQ

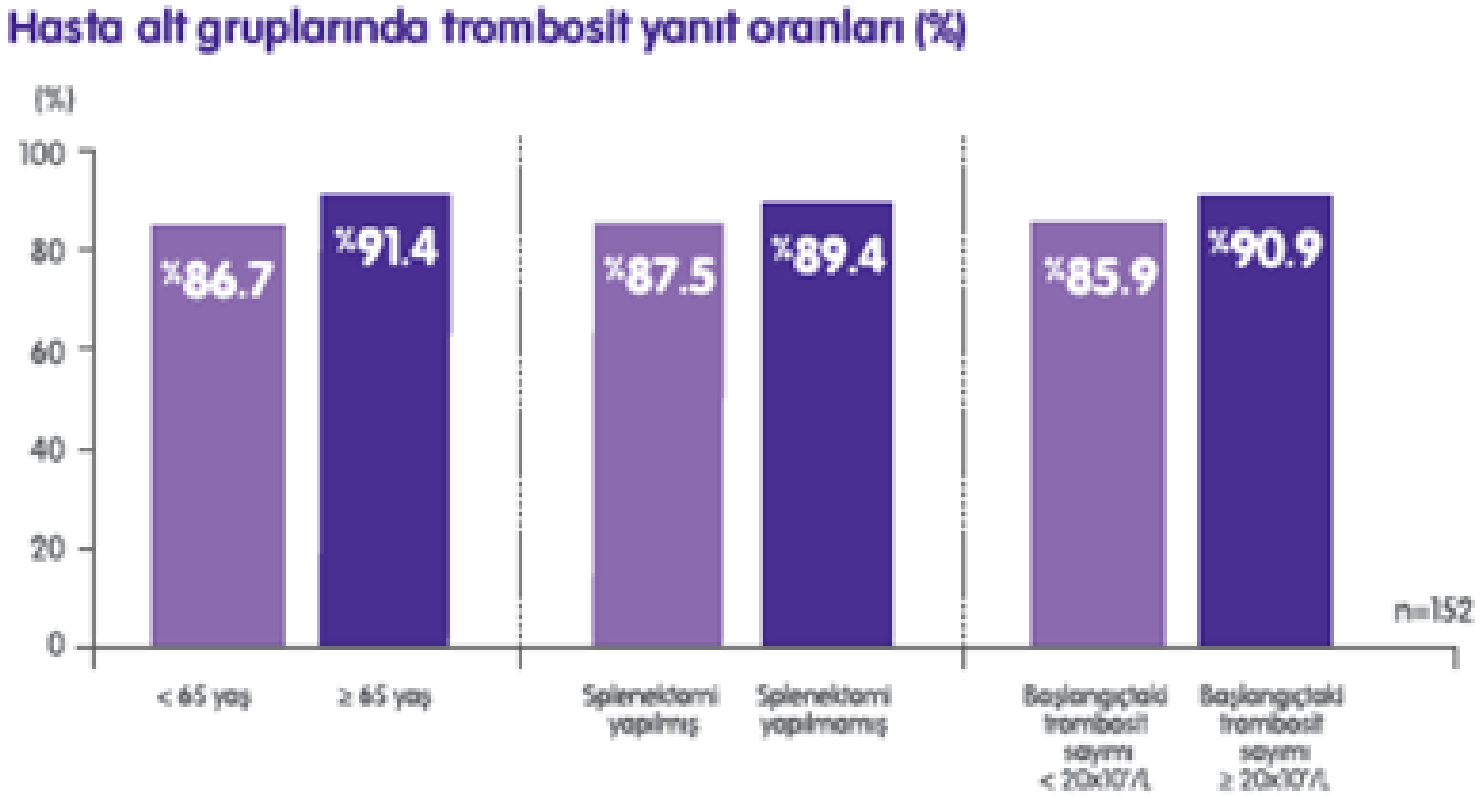
- **TERAPÖTİK ENDİKASYONLAR**

  REVOLADE

- Splenektomi sonrası nüks eden veya
- Splenektominin kontrendike olduğu
- Steroid ve immunsupresif tedavilere dirençli
- Kanama riski bulunan

Trombosit Sayımı	Dozun Ayarlanması Veya Yanıt
En az 2 haftalık tedaviyi takiben <50.000/μL	Günlük doz 25 mg basamaklarla maksimum 75 mg/gün'e çıkarılmalıdır.
≥50.000/μL ile ≤150.00/μL	Kanamanın önlenmesi veya azaltılması için gerekli trombosit sayımlarının sağlanması için en düşük dozda eltrombopag ve/veya eşzamanlı İTP tedavisi kullanılmalıdır.
>150.000/μL ile 250.000/μL	Günlük doz 25 mg basamaklarla azaltılmalıdır. Bu değişiklik ve sonraki herhangi bir doz ayarlamasının etkisinin değerlendirilmesi için 2 hafta bekleyiniz.
>250.000/μL	Eltrombopag tedavisini kesiniz; trombosit izlem sıklığını haftada iki kereye çıkarınız. Trombosit sayımı ≤100.000/μL düzeyinde olduğunda tedaviyi günlük dozu 25 mg azaltarak yeniden başlatınız.

HASTALARIN %88'INDE TROMBOSIT YANITI GÖZLENMIŞTIR



ITP-Fostamatinib

- **Two-Year Safety and Efficacy Outcomes with Fostamatinib in Adult Patients with Immune Thrombocytopenia (ITP): Open-Label Extension to Phase 3 Trial Program**

Anne-Marie Duliege, Donald M. Arnold, Ralph Boccia, Michael Boxer, Nichola Cooper, Quentin A Hill, Darla K Liles, Michelle Sholzberg, Hany Zayed, Sandra Tongand James B. Bussel

ITP-FOSTAMATINIB

SYK inhibitor

Fostamatinib

Perzistan ve kronik ITP

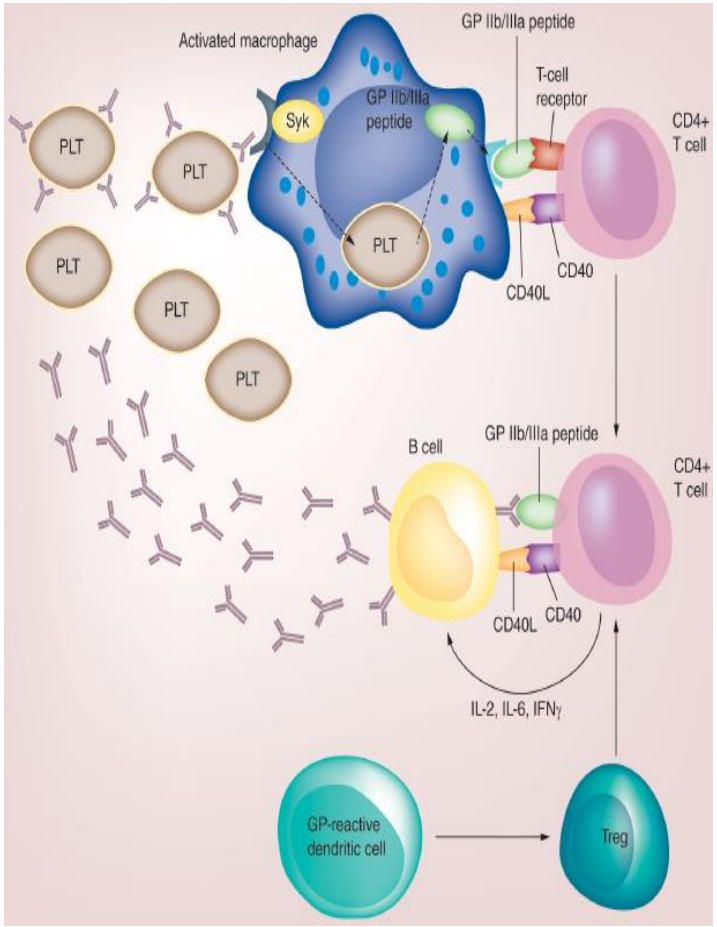
---

*≥1 tedaviye dirençli ve 30,000/μL altı trombosit sayısı

*3 yıl ve üzeri izlem, fostamatinib ile

*≥50,000/μL ve üzeri 12 ay stabil trombosit sayısına ulaşım ve idame sağlanmış

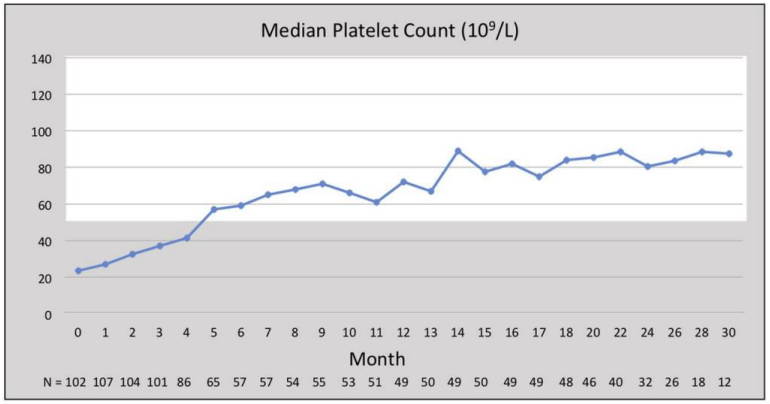
•SYK sinyali antikorla kaplı trombositlerin fc reseptör bağlantısının fagositozunda kritik bir öneme sahiptir



Fostamatinib disodium tablet (TAVALISSE)-------FDA onayı: 17.04.2018

Immunotherapy 2018; 10(1): 9–25

ITP-FOSTAMATINIB



Most Common AEs	Mild	Moderate	Severe	Total (n=123)
Diarrhea	12.2%	14.6%	0.8%	27.6%
Hypertension	8.1%	8.9%	0	17.1%
Petechiae	10.6%	3.3%	1.6%	15.4%
Epistaxis	8.1%	5.7%	0	13.8%
Upper respiratory tract infection	7.3%	2.4%	0	9.8%
Headache	6.5%	3.3%	0	9.8%
Nausea	8.9%	0	0	8.9%
Dizziness	8.9%	0	0	8.9%
Vomiting	7.3%	0	0	7.3%
Fatigue	6.5%	0.8%	0	7.3%
Contusion	6.5%	0.8%	0	7.3%

- 12 hf kullanım ile cevap yoksa kesilmesi (%36)
- Stabil cevap:
- %78---12. ayda (Tr: 72000)
- %56-----24. ayda (Tr: 80000)

- Toplam cevap: %46

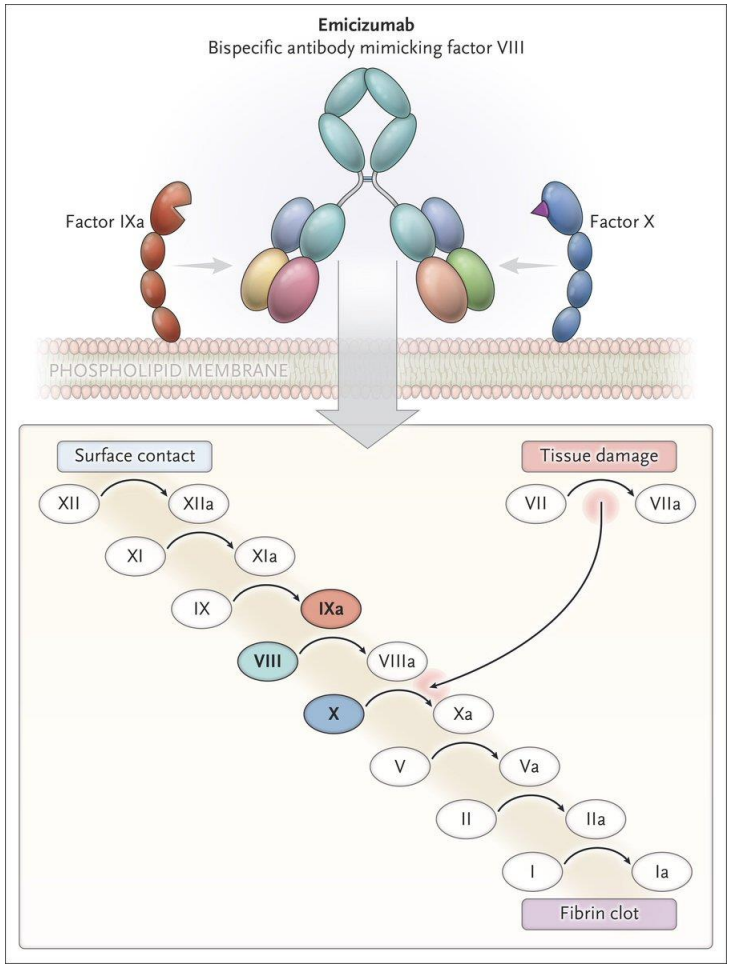
HEMOFİLİ
EMICIZUMAB

- Emicizumab - a bispecific humanize monoklonal antikor

s.c

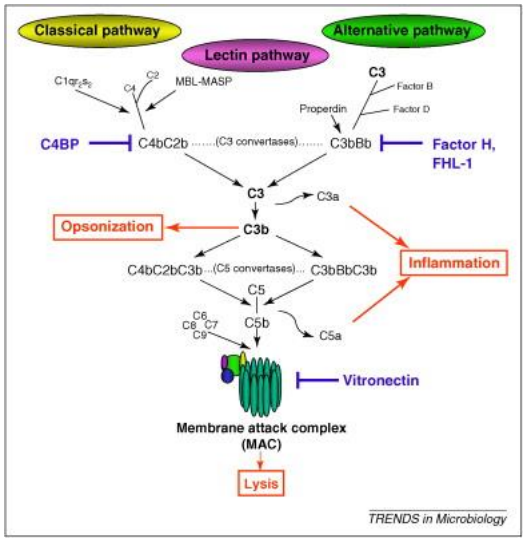
Köprü-FIXa ve FX

- Emicizumab (HEMLIBRA, Roche)
- Hemofili-A , Profilaksi de , inhibitörlü +/_
- FDA onayı: 04.10.2018



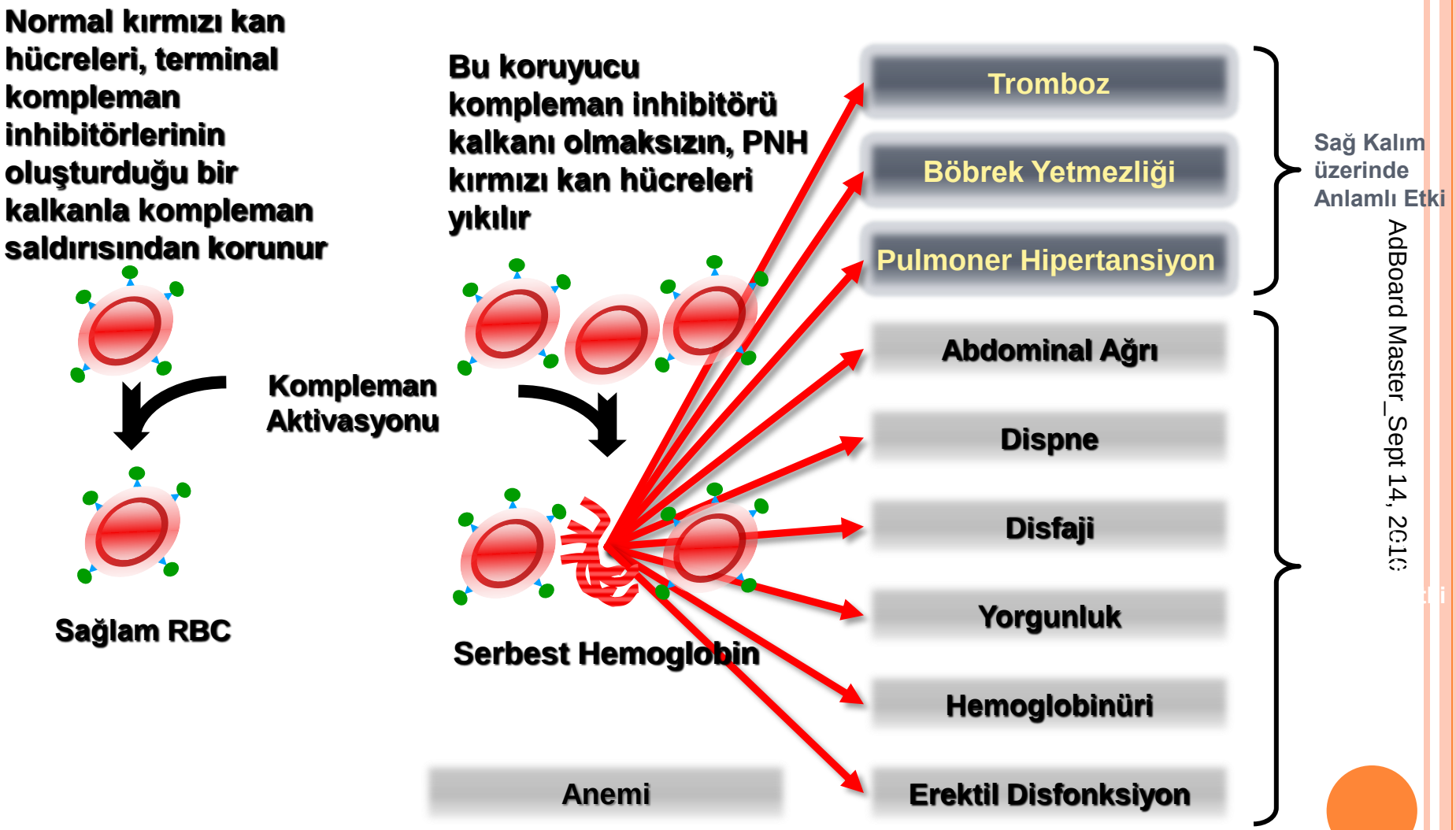
KOMPLEMAN ILIŞKILI ANEMI

- Anti CD5 monoclonal antikor (***ravulizumab***)
- C5 specific N-acetylglucosamine conjugated small interfering RNA (***cemdisiran***), hf, s.c
- ***Coversin***,günlük, s.c
- ***Compstatin***
- ***C3, c3b***



Paroksismal nokturnal hemoglobinüri (PNH)

Kronik Hemoliz ve Serbest Hemoglobinin Neticeleri



1. International PNH Interest Group. *Blood.* 2005;106:3699-3709. 2. Brodsky R Paroksismal Nokturnal Hemoglobinüri. In: Hematology - Basic Principles and Practices. 4th ed. R Hoffman; EJ Benz; S Shattil et al, eds. Philadelphia, PA: Elsevier Churchill Livingstone; 2005; p. 419-427. 3. Rother RP et al. *JAMA.* 2005;293:1653-1662. 4. Socie G et al. *Lancet. 1*996;348:573-577. 5. Hill A et al. *Br J Haematol.* 2007;137:181-92. 6. Lee JW et al. *Hematologica* 2010. 95 (s2): Abstract #505 and 506. 7. Hill A et al. *Br J Haematol*. 2010; May;149(3):414-25. 8. Hillmen P et al. *Am. J. Hematol*. 2010; 85:553–559.

PNH-FLAER

- Akım sitometride kullanılan floresan aerolisin (FLAER) de günümüzde kullanılan test
- Spesifik olarak GPI çıpasına bağlanan FLAERE kullanılarak lökositlere GPI ile bağlı antijenler belirlenebilmekte
- GPI antijenleri için en uygun saptama yönteminin FLAER olduğuna dair kanıtlar artmakta
- FLAER çok güçlü bir sensitiviteye sahiptir ve %0,01 oranındaki PNH klonlarını saptayabilir
- FLAER küçük anormal granülositlerin saptanmasında CD59 ‘dan daha hassas belirleme özelliğine sahip

ANLAŞILMASI KOLAY RAPOR VERILMESI ÖNEMLIDIR…

1. PNH Klonu tespit edildi – **evet** veya hayır
2. WBC'deki PNK Klonunun büyüklüğü **(Granülositlerde % 88.9 ve monositlerde % 90.1)**
3. Tip I **(%47.3)**, Tip II **(%19.9)** ve Tip III **(32.8)** hücre dağılımlı RBC'de PNH Klonu büyüklüğü
4. PNH klonunun akış sitometrisi **grafiği** sağlandı

[redacted]

Phone: 877-PNH-FLOW
Fax: 207-941-8287
www.dahlchase.com

FLOW CYTOMETRY REPORT – PNH EVALUATION

Name: PNH, Positive
DOB: 7/31/1973 Sex: M MR #: 123456789
Facility: Ordering Facility
Dept: Outpatient

Pathology Number: F-07-20349
Date of Procedure: 6/15/2007
Date of Accession: 6/15/2007

Physician: Ordering Provider, M.D.
Ordering Facility
Street Name
City, State Zip code
(999) 123-4567

Copies to: Other providers/clinicians

TISSUE/SPECIMEN: Peripheral Blood in Heparin

DIAGNOSIS: SIGNIFICANT PNH CLONE IDENTIFIED

Comment: Flow cytometric analysis shows a significant PNH clone (greater than 1% GPI-deficient cells) within the RBCs, granulocytes and monocytes. These findings are consistent with a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH). Any potential difference in clone size between the white blood cells and the red blood cells may be due to hemolysis and/or recent transfusion.

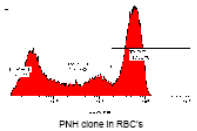
Reference: Richards et al: Diagnosis and Management of PNH, Blood 2005, 106 (12)

Flow Results: ***Immunophenotypic analysis*** was performed using gating antibodies CD45, CD15, CD33, CD64, GPI-linked antibodies CD59, CD14, CD24, as well as fluorescent Aerolysin (FLAER).

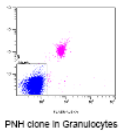
Red Blood Cells: Type I cells: 47.3% (normal CD59 expression)
Type II cells: **19.9% (partial CD59 deficiency)**
Type III cells: **32.8% (complete CD59 deficiency)**

Monocytes with FLAER/CD14 Deficiency: 90.1%

Granulocytes with FLAER/CD24 Deficiency: 88.9%



PNH clone in RBC's



PNH clone in Granulocytes

The markers used for this flow cytometric analysis are labeled as Analyte Specific Reagents (ASR) and are used for clinical purposes. The performance characteristics of these markers have been determined by DCDS-Flow Cytometry Laboratory. Their use has not been approved by the U.S. Food and Drug Administration; the FDA has determined that such approval is not necessary.

Electronic Signature
Pathologist/Technologist
Date

Positive PNH

Page 1 of 1

AdBoard Master_Sept 14, 2010

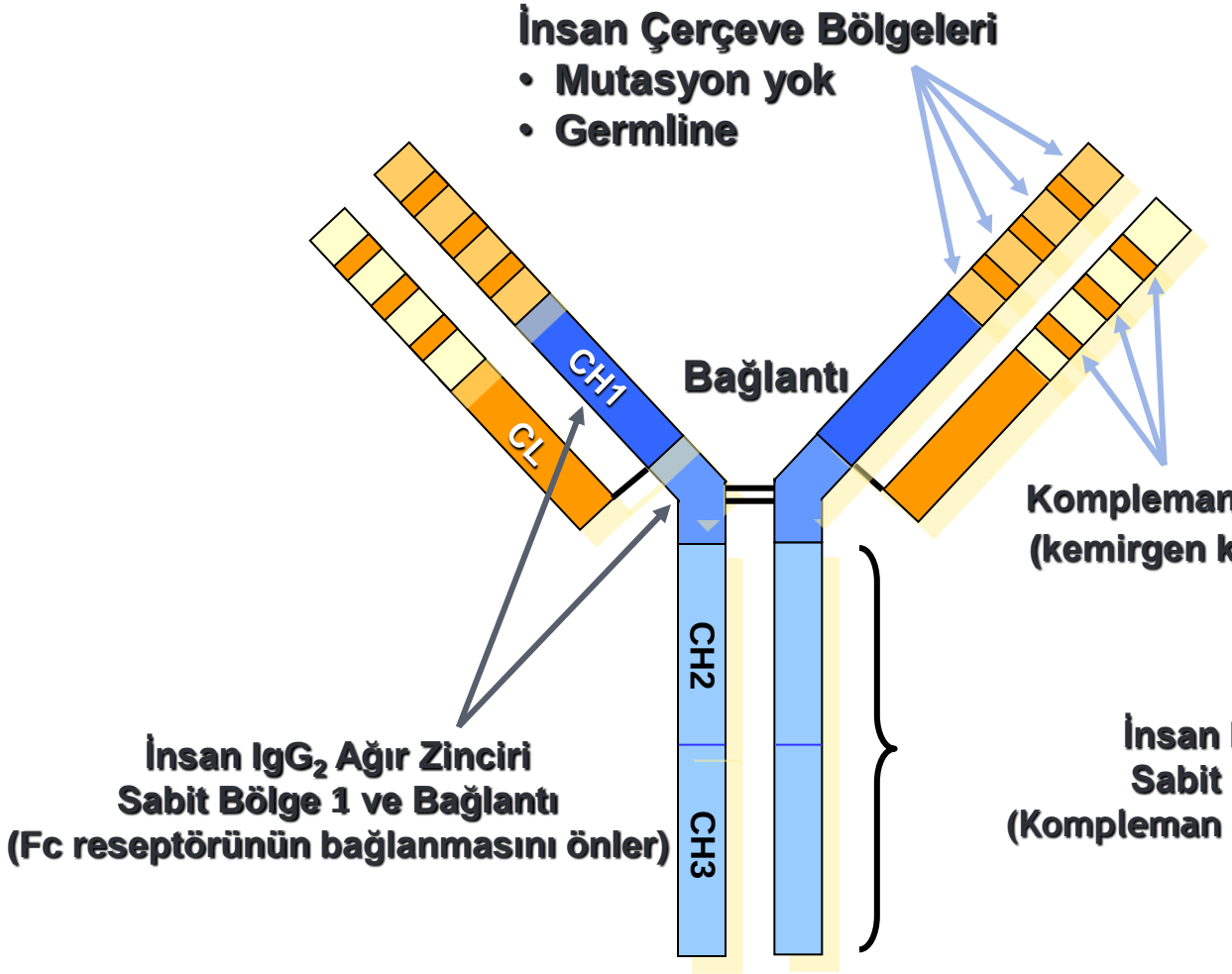
PNH TANıSı IÇIN YÜKSEK RISK ALTıNDAKI HASTALARıN BELIRLENMESI:

- -Coombs negatif hemolitik anemi
- -Hemoglobinüri
- -Aplastik anemi
- -Miyelodisplastik sendrom, refrakter anemi
- -Açıklanamayan sitopeniler
- -Açıklanamayan tromboz (venöz veya arteriyel)

PNH TEDAVİSİ

- Subklinik PNH:
  - Spesifik tedaviye gerek yok
- PNH/Kemik iliği yetersizliği sendromu:
  - Aplastik Anemi, Düşük riskli MDS
  - Kemikiliği yetersizliğine odaklanılmalı
  - PNH klonu olan olgularda ekulizumab yararlı
- Klasik PNH
  - Eculizumab ile tedavi
  - Cevap yetersiz ise
    - Kemik iliği transplantasyonu
    - Steroidler
    - Splenektomi
    - Destek tedavi

SOLIRIS® (EKULIZUMAB) İNSANDA ILK OLARAK ANTI-C5 SINIFI ANTIKOR OLARAK ELDE EDILDI



PNH- ECULİZUMAB TEDAVISI

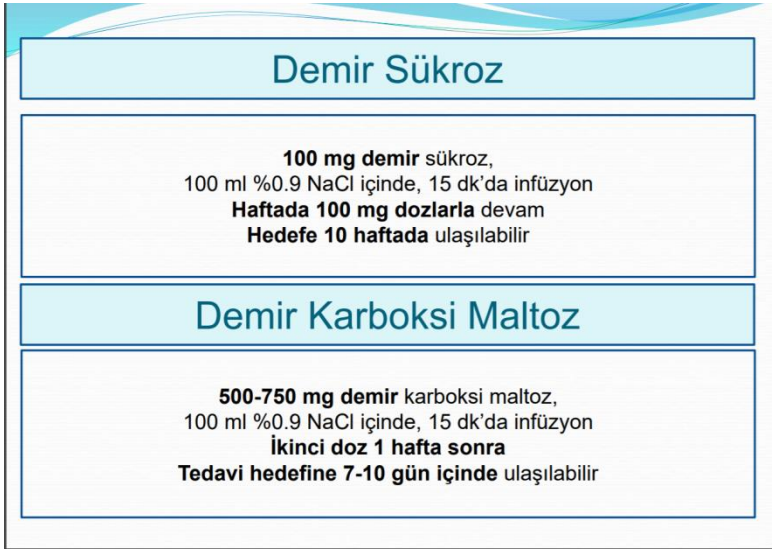
- Yaşam kalitesinde artış
- İlacın iyi tolere edilmesi
- Refrakterlik ya da tolerans bulgusu yok
- Trombozda azalma (Primer antikoagülan kesildiğinde de etkili)
- Eculizumabla MDS/AML ‘ye dönüşüm yok
- Transfüzyon ihtiyacında azalma
- Survival avantajı sağlamakta
- Komplikasyonları azaltmakta ve yaşam süresini iyileştirmektedir

Demir eksikliği anemisi-tedavi

İNTRAVENÖZ DEMIR TEDAVISI

- Oral demir tedavisinin tolere edilememesi
- Devam eden kan kaybının oral demirle kısa sürede yerine koyulamayacağı durumlar
- Oral demirin emiliminin bozulduğu durumlar
  - Çölyak hastalığı
  - H.pylori enfeksiyonu,kronik atrofik gastrit
  - İnflamatuar barsak hastalıkları
  - Gastrik cerrahi
- Demir hemostazını bozan kronik inflamasyonun bulunması (hepsidin artar)
- Kronik böbrek yetmezliği- diyaliz
- İntramusküler demir enjeksiyonu önerilmemektedir.
  - Ağrılı
  - Kalçada boyama
  - Emilimi değişken
  - Sarkom gelişimi

İNTRAVENÖZ DEMIR TEDAVISI



Demir karboksimaltoz:
Doz: 750-1000 mg
İnfüzyon hızı: 15 dakika

Ticari isim: Ferinject

- IV demir tedavisi İBH ilişkili DEA de birinci sıra tedavi olarak rehberlere girmiştir

- KBY de diyaliz bağımlı olan ve olmayan tüm hastalar için IV demir standart tedavidir.

Oral emilim bozukluğu (hepsidin artışı)

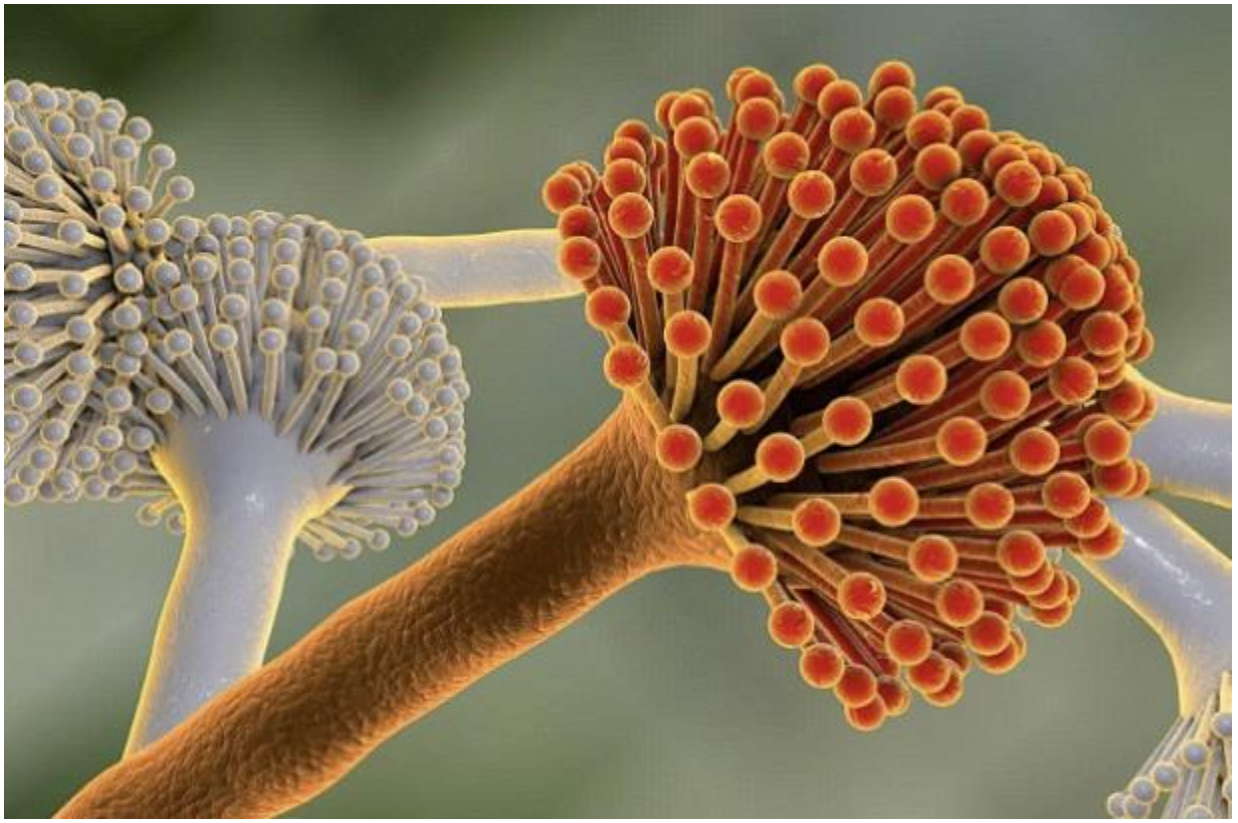
-Kalsiyum içeren preparatlar

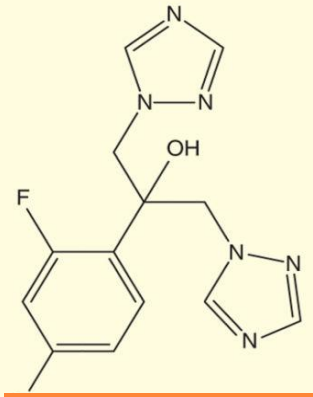
-Kronik kan kaybı

-Epo tedavisi alan hastalarda fonksiyonel demir eksikliği

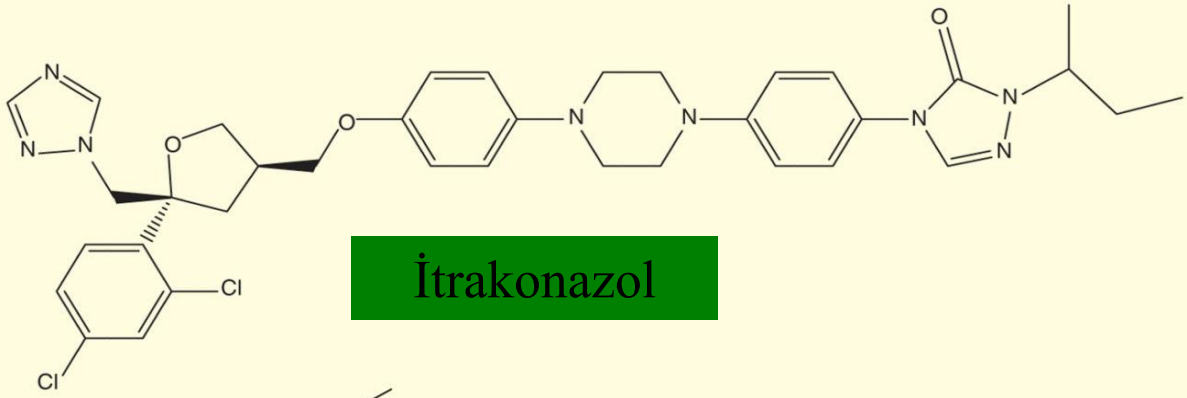
İMMÜNSÜPRESİF HASTADA

FUNGAL PROFILAKSI

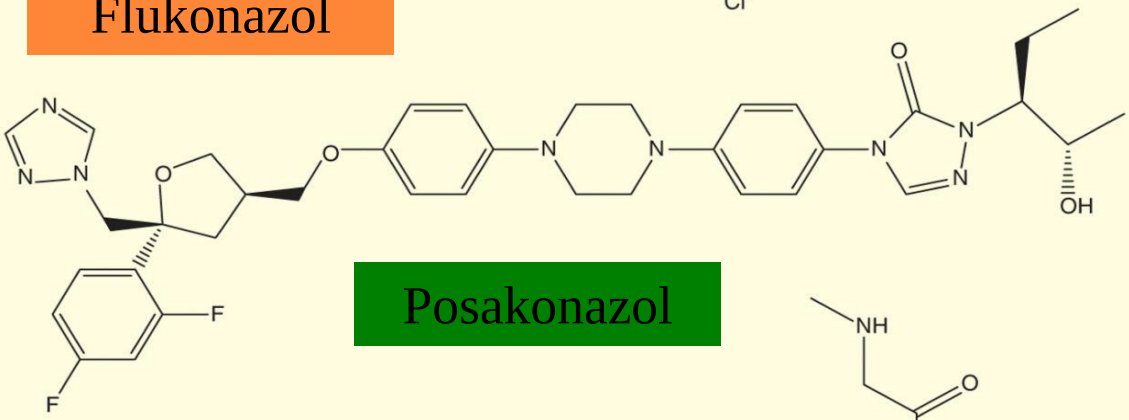




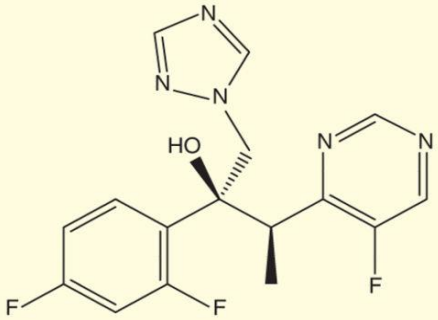
Flukonazol



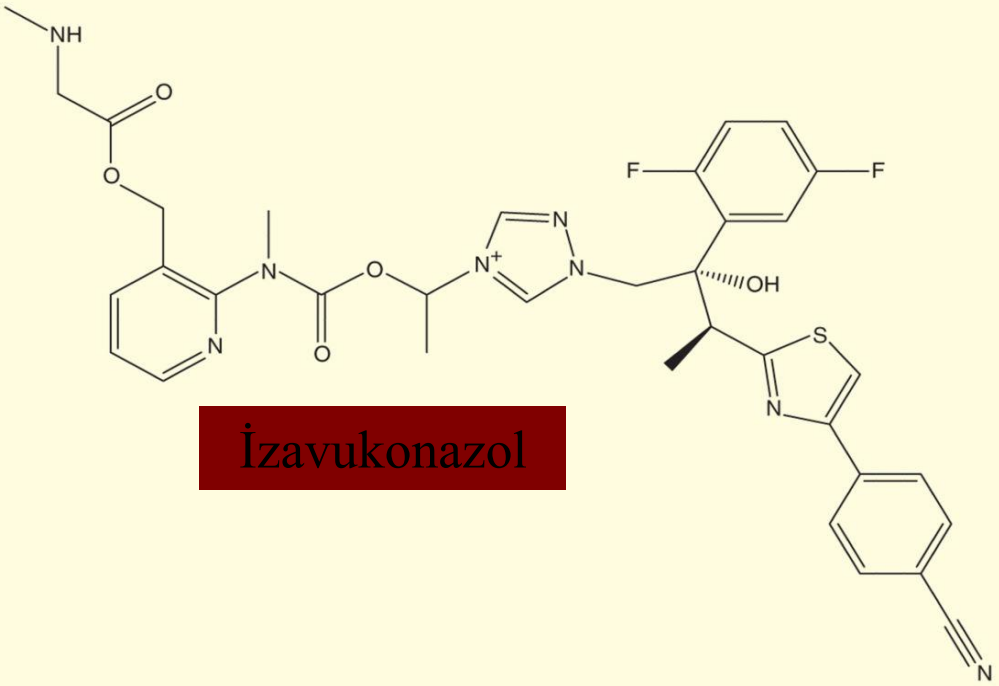
İtrakonazol



Posakonazol



Vorikonazol



İzavukonazol

Multipl miyelom

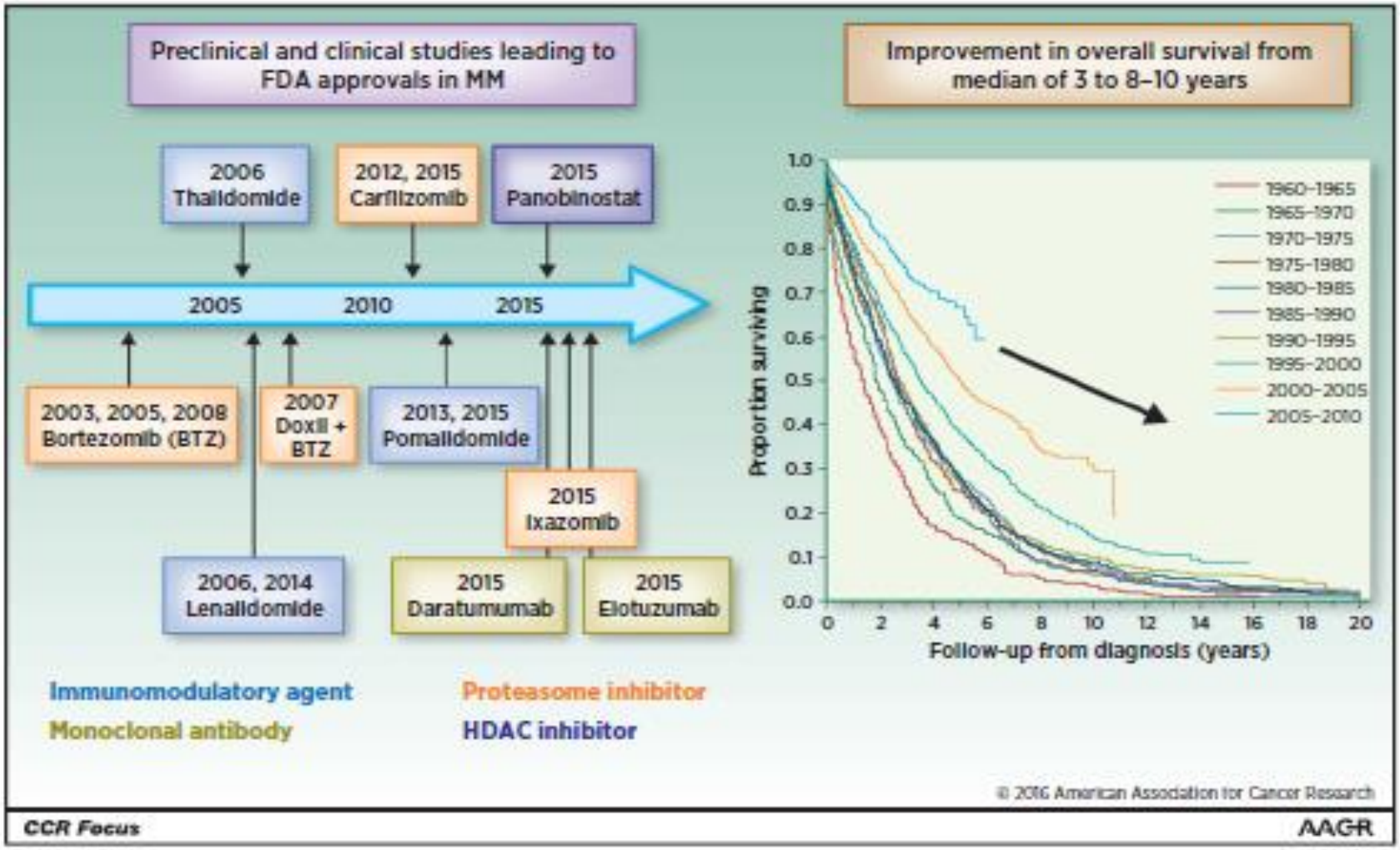
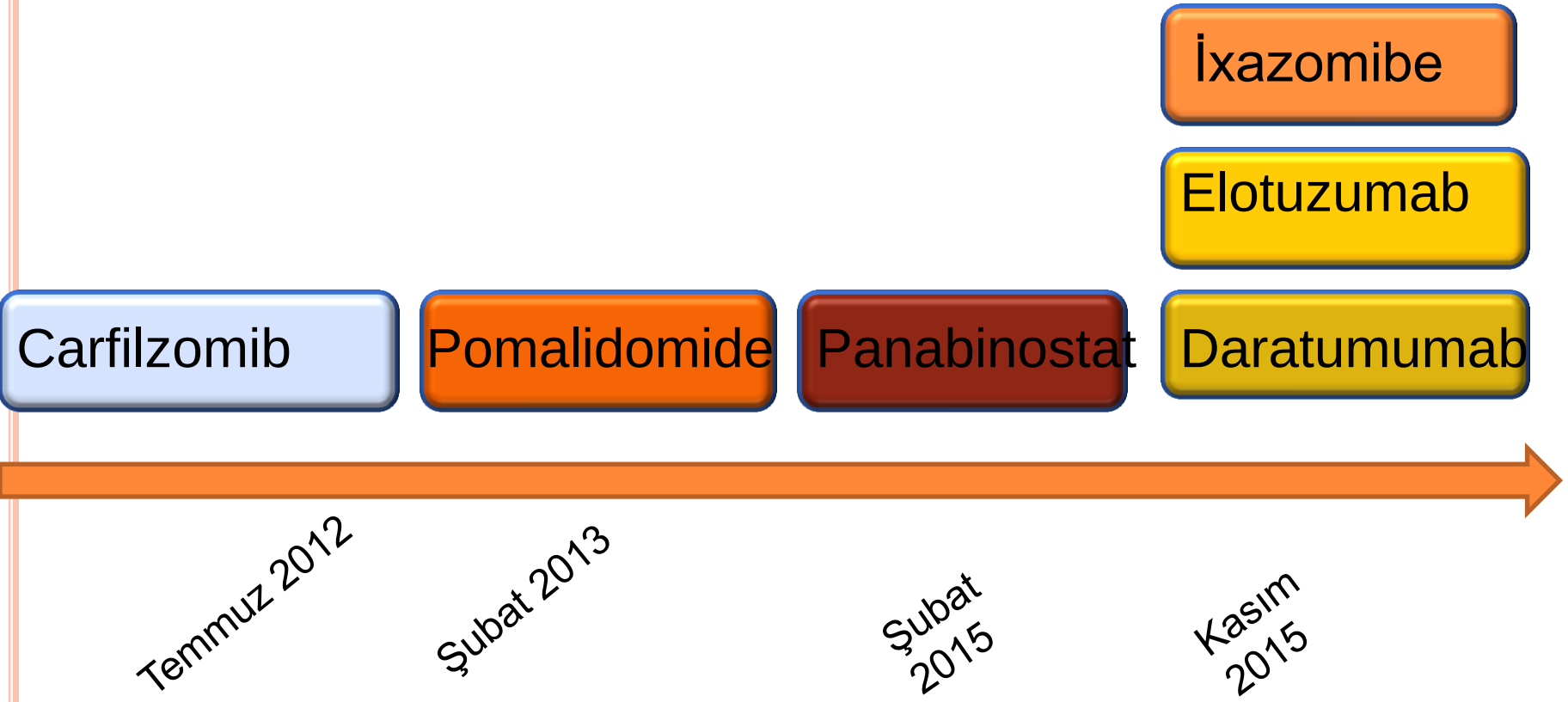
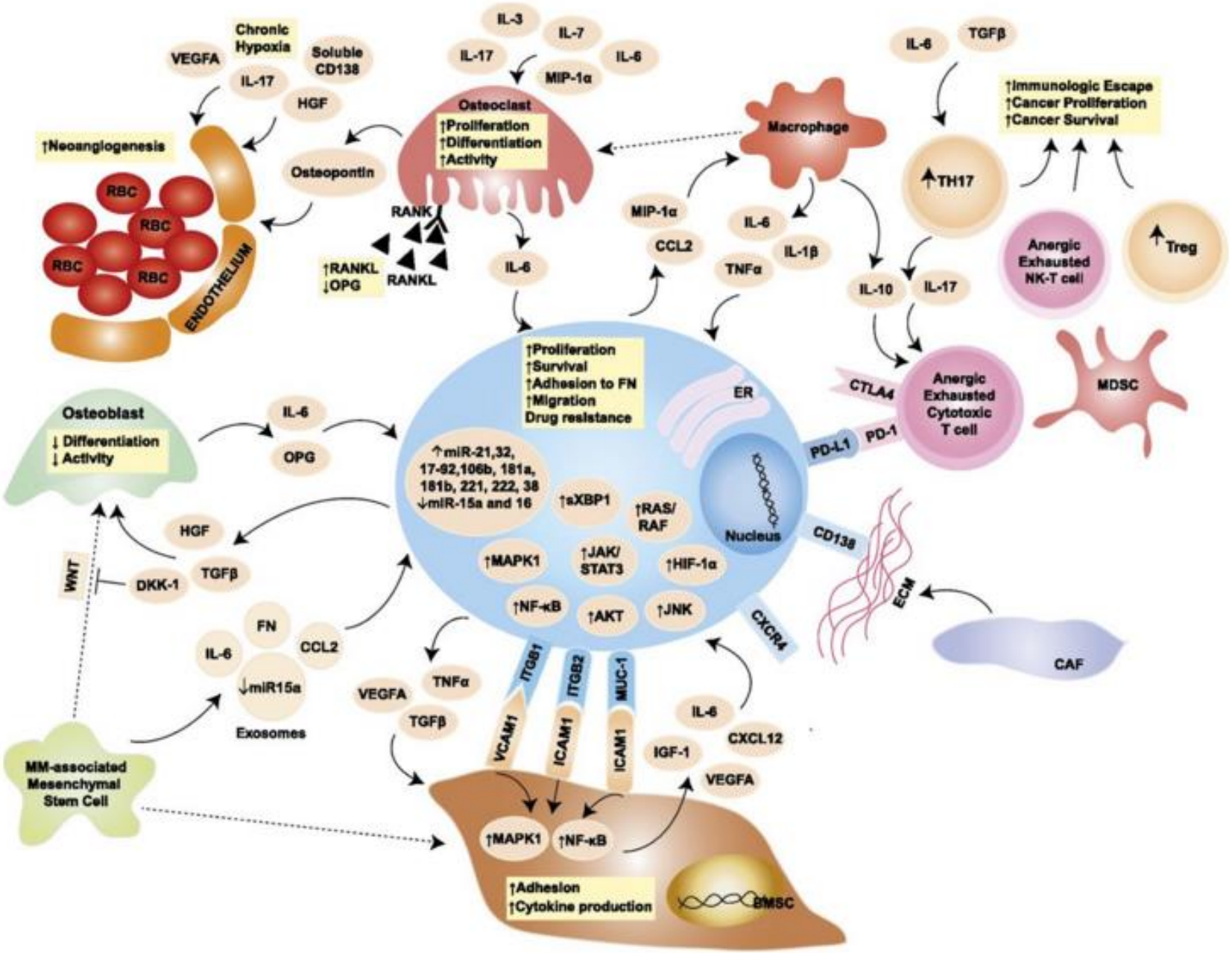


Figure 1

Bench-to-bedside translation of novel agents in myeloma. Early advances in myeloma therapy included melphalan and prednisone, followed by combination chemotherapy and then high-dose melphalan, rescued first by bone marrow and more recently by peripheral blood stem cell transplantation. Importantly, remarkable progress has been made in the past 12 years due to the FDA approval of the proteasome inhibitors bortezomib, carfilzomib, and ixazomib; the immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide; the histone deacetylase (HDAC) inhibitor panobinostat; as well as the monoclonal antibodies elotuzumab and daratumumab (left). All of these recent therapies have been initially evaluated and achieved responses in relapsed refractory multiple myeloma (MM), and then moved into clinical trials earlier in the disease course where their efficacy improved. Moreover, their use in combination—that is, lenalidomide, bortezomib, and dexamethasone—can achieve unprecedented frequency and extent of response when used as initial therapy. They have been integrated into the treatment paradigm of transplant candidates and nontransplant candidates as initial and maintenance therapies. As a consequence of

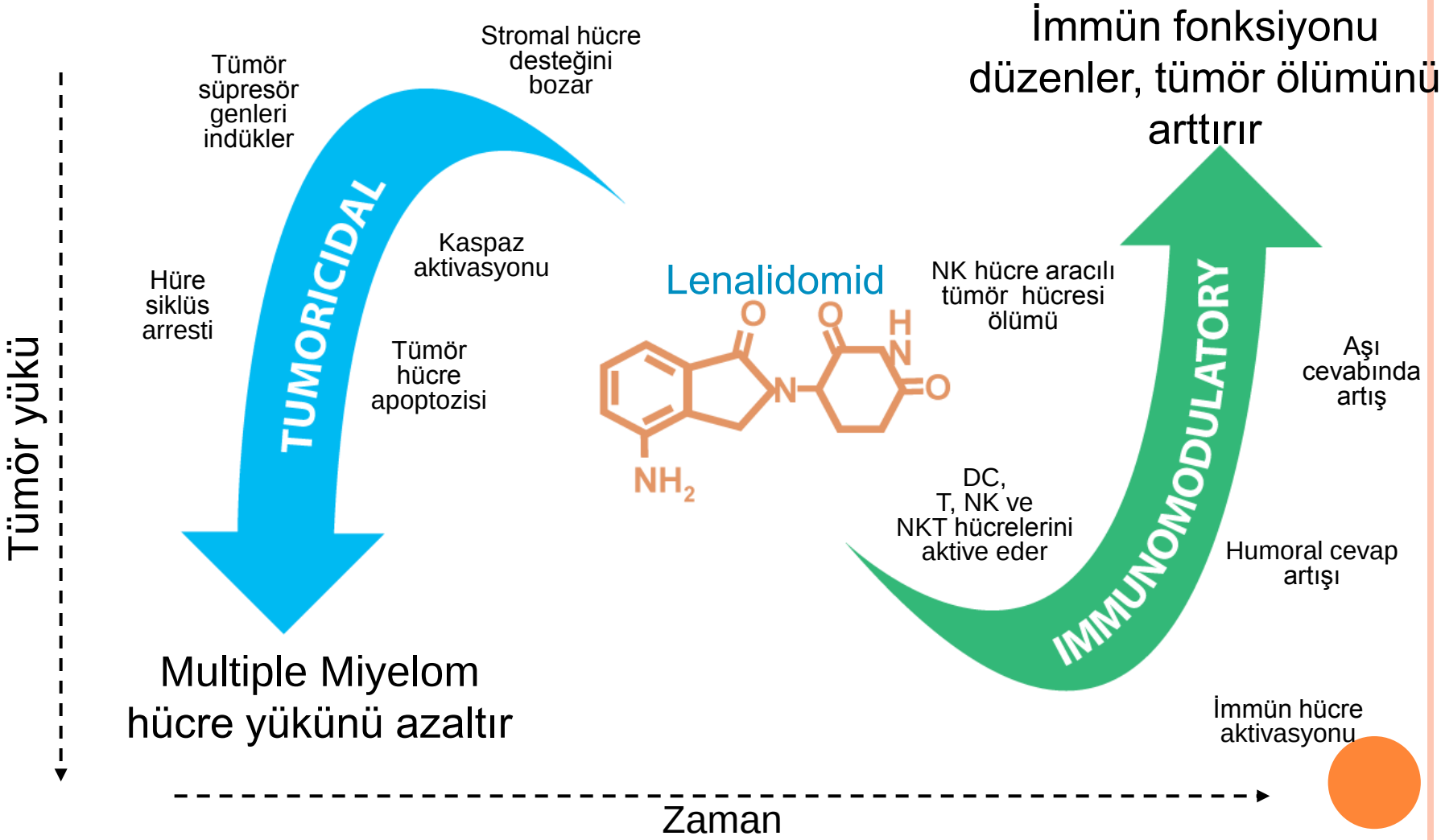
Multipl miyelom





Bianchi G Blood 2015

LENALIDOMIDIN IMMUNOMODÜLATÖR VE TÜMÖROSIDAL ETKILERI



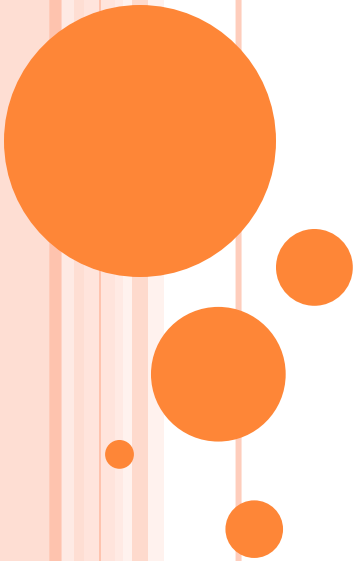
Referanslar slide notlarında yer almaktadır.

İMMÜN KONTROL NOKTALARI NELERDİR

- Bu aşamada devreye giren düzenleyici mekanizmalar içinde en fazla incelenmiş olanlar

- **Sitotoksik T lenfosit ilişkili antijen-4**
- CTLA-4----------CD80/86

- **Programlanmış hücre ölüm proteini-1**
- PDCD-1----------CD274
- PDCD-1 ligand-1----------PD-L1
- PCDD-1 ligand-2 arası bağlantılardır



KLL

KLL-

- Different/long-term side-effects: chemo-related side-effects, secondary malignancy, infusion reactions, immuno-suppression, bleeding, arrythmia, TLS, colitis/pneumonitis etc etc
- Practicalities: iv, oral, long-term until PD, requiring hospital admission
- Cost: only cure (or death) is cheap
- Last not least: Different biology

MRC CLL1 n=660

MRC CLL2 n=640

MRC CLL3 n=418

LRF CLL4 n=777

NCRI ADM/ARC n=565

NCRI RIALTO n=565

NCRI FLAIR1 n=754

NCRI FLAIR2 n=822

1978 1983 1988 1993 1998 2003 2008 2014 2019

Chlorambucil

Chlorambucil Prednisolone

Fludarabine

Fludarabine Cyclophos

Campath

Fludarabine Cyclophos Rituximab

Ofatumumab

Chlorambucil Obinutuzumab

Bendamustine (Rituximab)

Chlorambucil Ofatumumab

Idelalisib Rituximab

Ibrutinib

Venetoclax Obinutuzumab

Venetoclax

Ibrutinib Obinutuzumab

Acalabrutinib ±obinutuzumab

Zanbrutinib

SNS-62

AZD6738

Ibrutinib +TGR-1202

Venetoclax

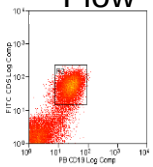
Tirabrutinib

Acalabrutinib

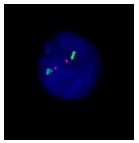
CAR-T

Morphology

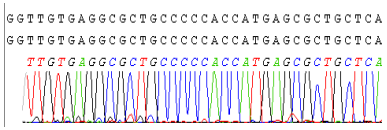
Flow



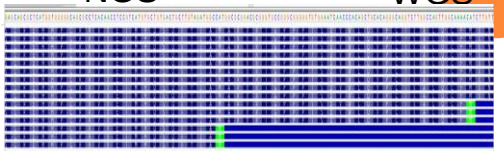
FISH



Sanger



NGS

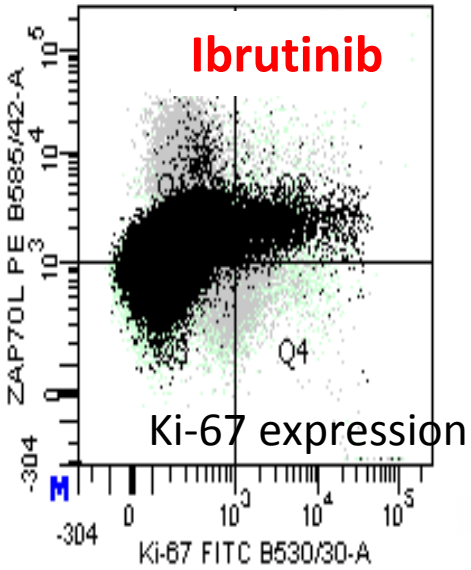


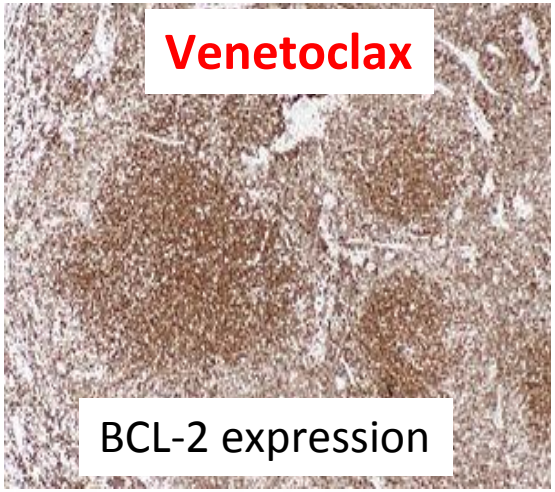
WGS

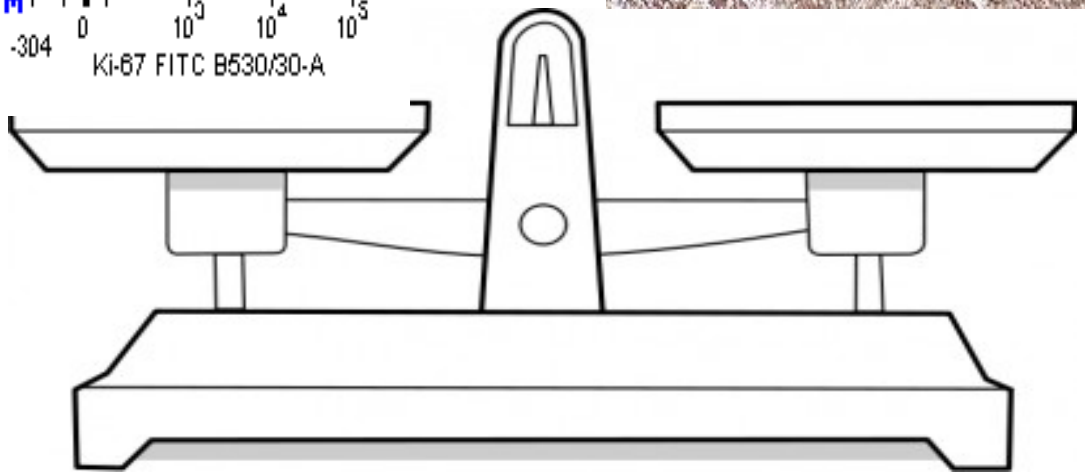
KLL PATOFIZYOLOJISI: PROLIFERATION VE APOPTOSIS

Proliferation

Apoptosis







KLL

- **Ibrutinib + Rituximab**

FCR a PFS ve OS üstünlüğü

<70 yaş altı- iyi tolere

- **Venotoklax+R**
  - MRD-

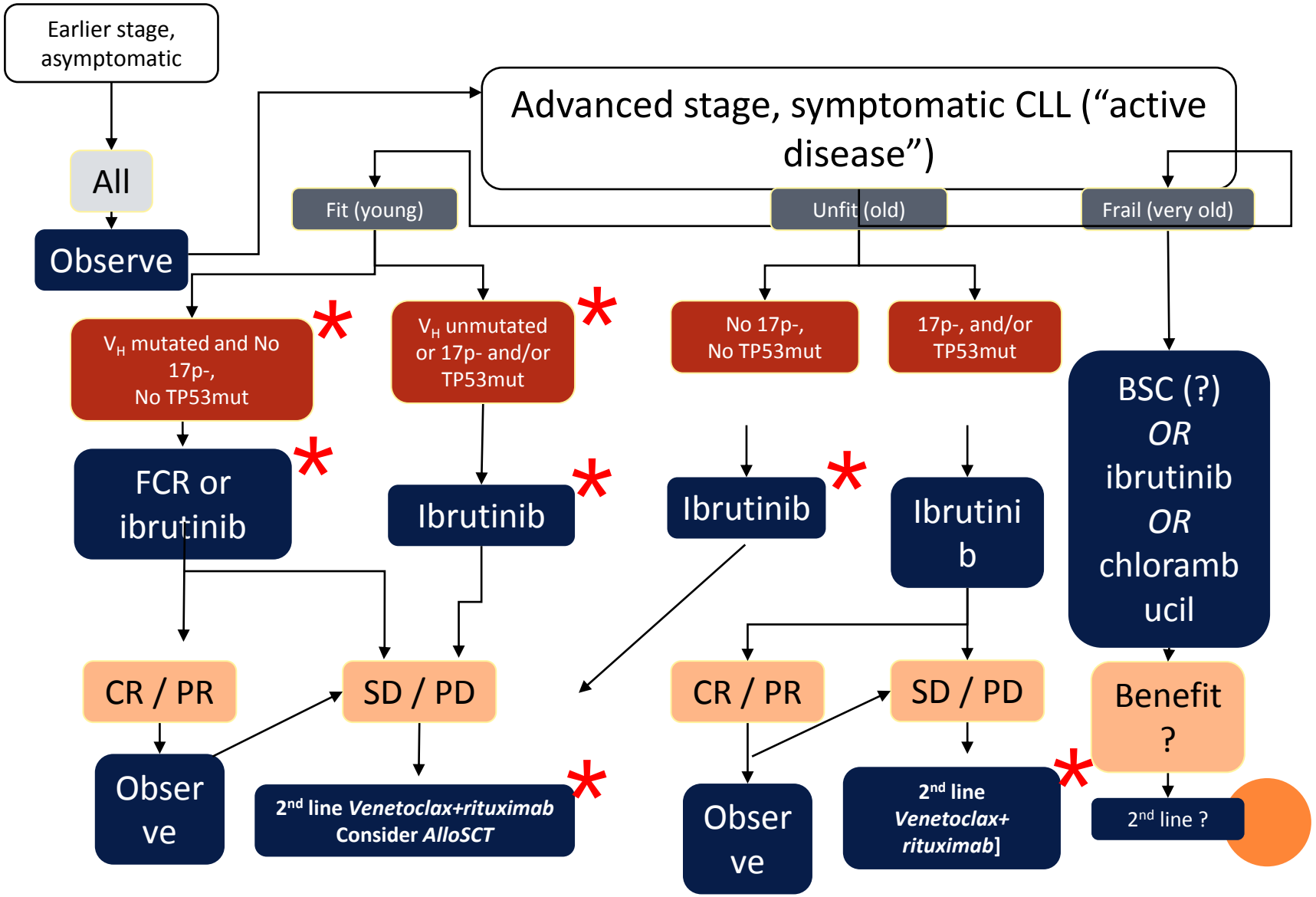
İbrutinib+Venotoklax

RR-KLL

MRD avantajı

- **FCR**
- Brentiksumab+ R

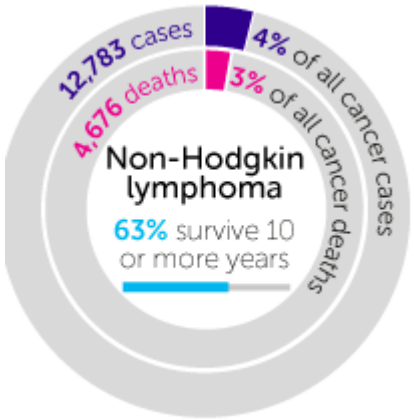
KLL TEDAVİSİ ALGORİTMA-ŞUBAT 2019



KLL: SONUÇ

1. MRD eredikasyonu
2. Yeni hedeflenmiş tedaviler dramatik olarak sonuçları değiştirmiştir (sürekli kullanım ile)
3. Kombine kullanımlar
4. Rezistan mutasyonlar
5. Kür? (muhtemel)

NHL



SEER Stat Fact Sheets: Non-Hodgkin Lymphoma

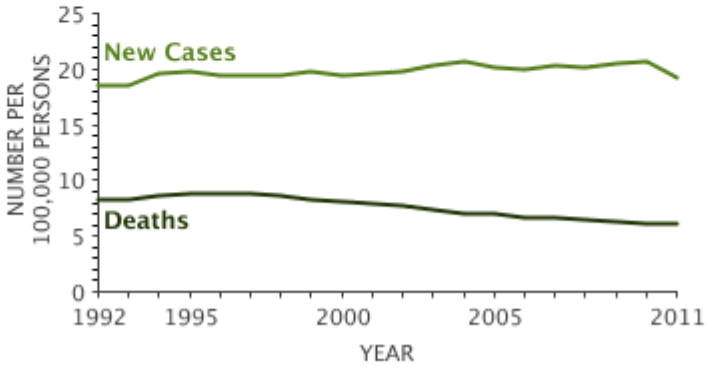
Expand All | Collapse All

Statistics at a Glance

Show Less

At a Glance

Estimated New Cases in 2014	70,800
% of All New Cancer Cases	4.3%
Estimated Deaths in 2014	18,990
% of All Cancer Deaths	3.2%

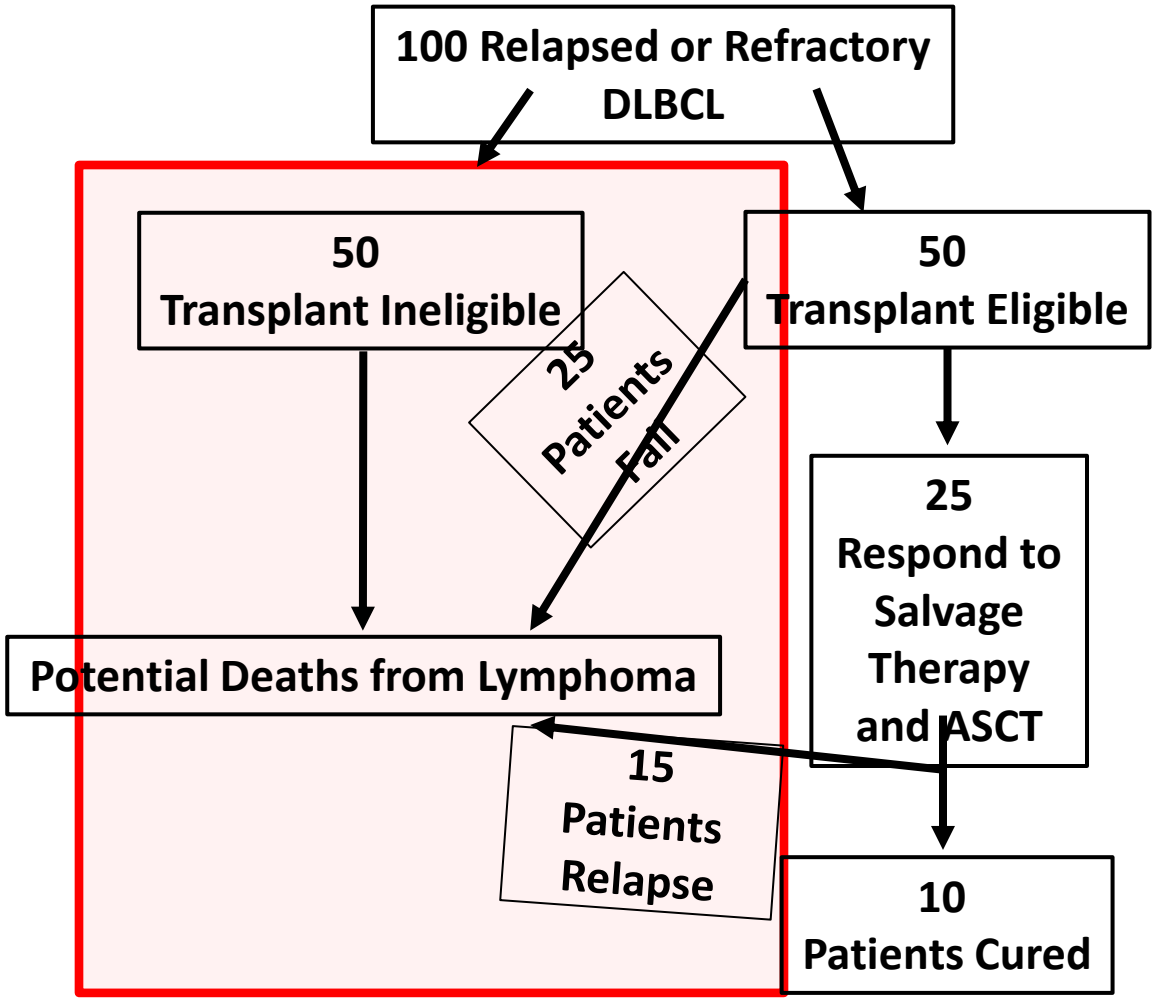


Percent Surviving 5 Years
69.3%
2004–2010

Lenfomalar

- NHL, DBBH
- Double HİT
- Triple HİT
- ----------
- Yüksek dereceli lenfomalar
- MYC-BCL-2-BCL-6

OTOLOG SONRASI TEDAVİLER İLE NHL



*Estimates based on Gisselbrecht et al. J Clin Onc 2010 28:27, 4184-4190.

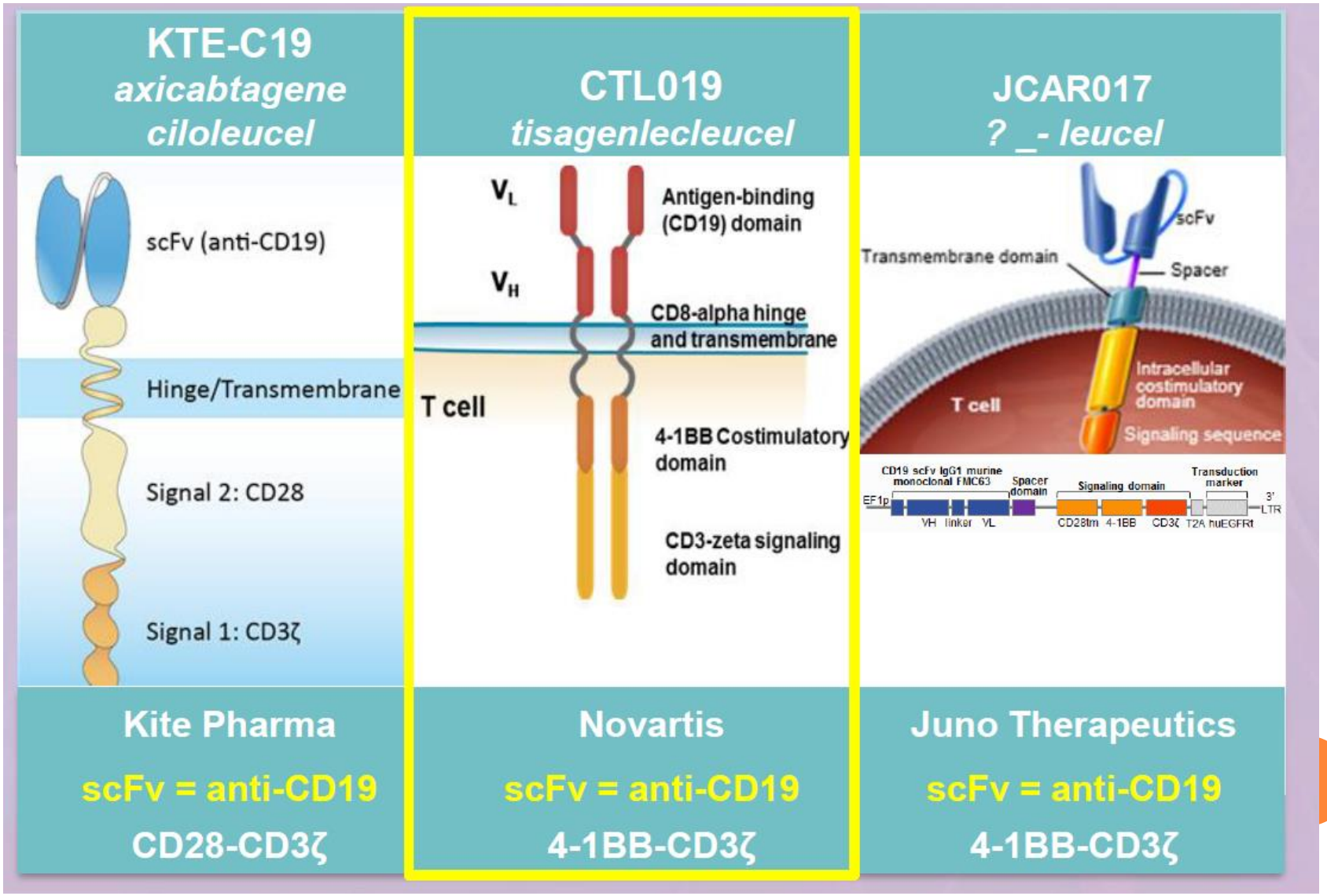
*Assumes all patients received rituximab as part of primary

YENİ TEDAVİ

SİNYAL YOLAKLARINI HEDEFLEYEN

CAR T CELL

CD19-Directed CAR T Cells



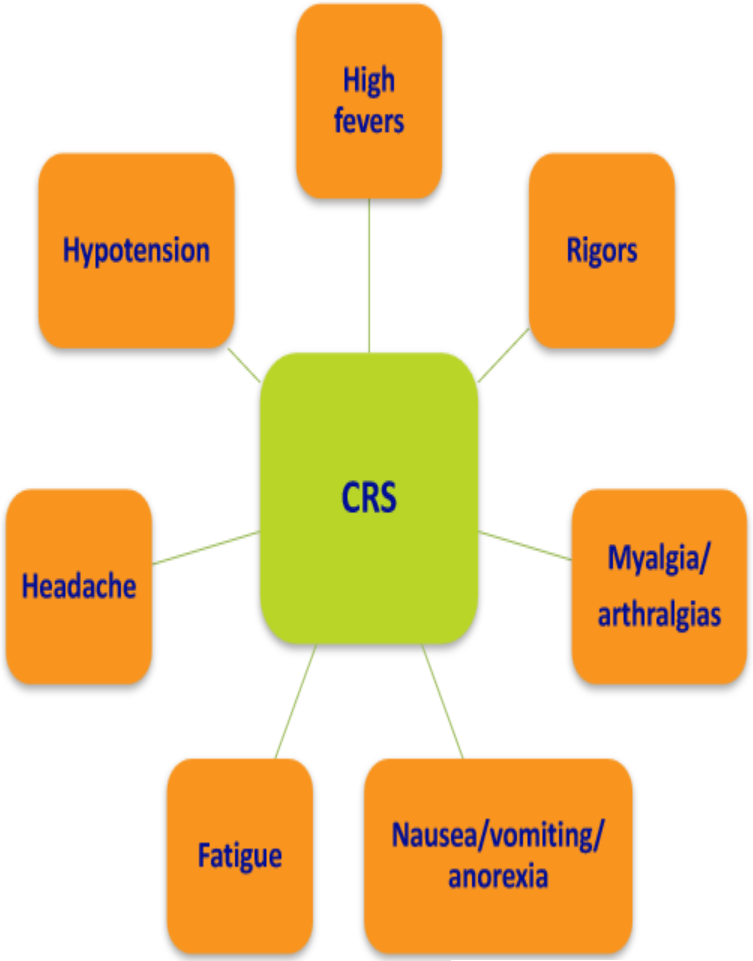
Summary of Pivotal CAR-T Trials in R/R DLBCL

	JULIET (N=93)	TRANSCEND-NHL-001 (N=102)	ZUMA-1 (N=108)
Agent	Tisagenlecleucel	Lisocabtagene maraleucel	Axicabtagene ciloleucel
Median prior therapies (range)	3 (1-6)	3 (1-8)	NR (1-5+)
ORR	52%	75%	82%
CR	40%	55%	58%

Borchmann P et al. Proc EHA 2018;Abstract S799; Abramson JS et al. Proc ASCO 2018;Abstract 7505; Locke FL et al. Proc ASCO 2018;Abstract 3003; Locke FL et al. Proc ASCO 2018;Abstract 3039

Cytokine Release Syndrome (CRS) and Neurotoxicity in Key Pivotal CAR-T Trials

Grade 3/4 AEs	JULIET	TRANSCEND NHL 001	ZUMA-1
CRS	22%	1%	12%
Neurologic	12%	13%	29%



Borchmann P et al. Proc EHA 2018;Abstract S799; Abramson JS et al. Proc ASCO 2018;Abstract 7505; Locke FL et al. Proc ASCO 2018;Abstract 3003

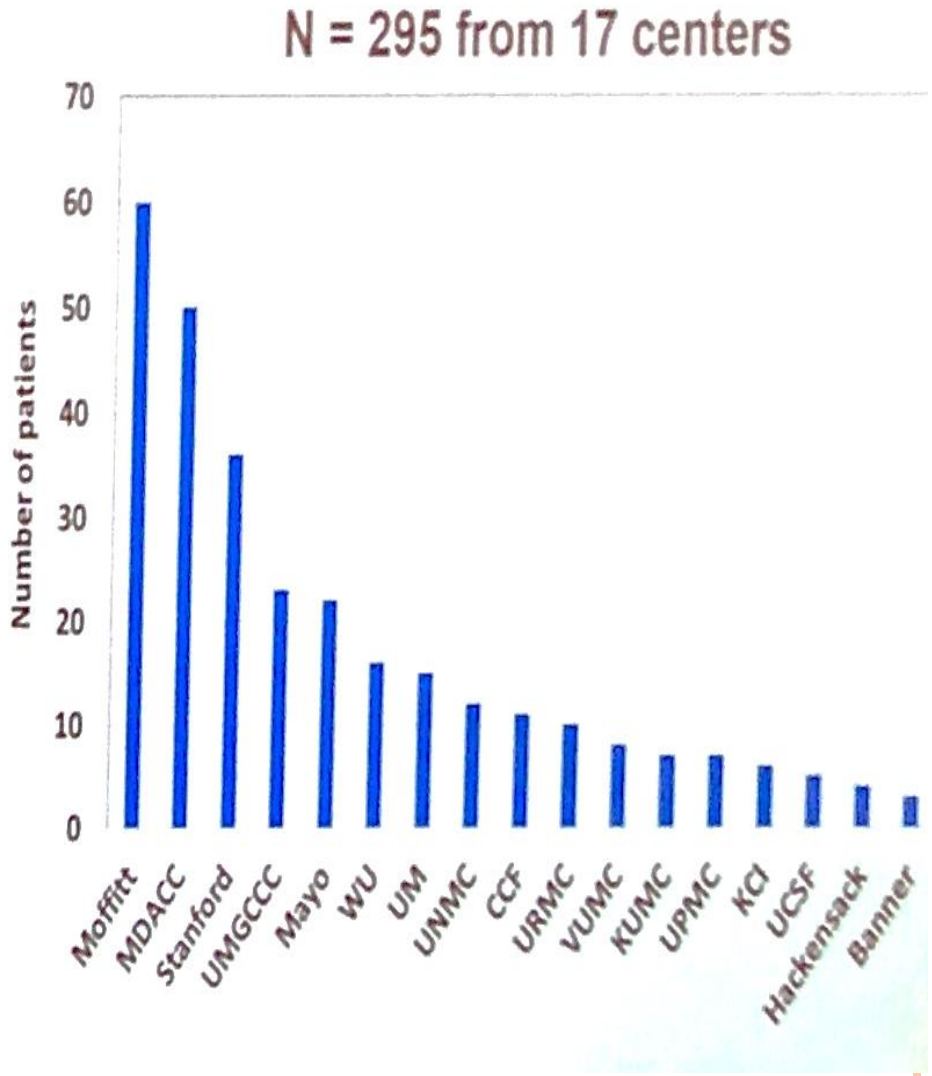
Safety of Axicabtagene Ciloleucel CD19 CAR T-Cell Therapy in Elderly Patients with Relapsed or Refractory Large B-Cell Lymphoma

	(N = 17)	(N = 44)
Median age, (range) years	68 (64-77)	48 (24-64)
Male	11 (65)	27 (61)
Female	6 (35)	17 (39)
Histological subtypes		
DLBCL including HGBCL	13 (76)	29 (66)
TFL	4 (24)	4 (9)
PMBCL	0	11 (25)
Response at Day 30 after Axi-cel		
CR, N (%)	8 (47)	21 (48)
PR, N (%)	5 (29)	12 (27)
SD, N (%)	1 (6)	3 (7)
PD, N (%)	3 (18)	8 (18)
Adverse events, N (%)		
CRS grade 0	3 (18)	4 (9)
CRS grade 1-2	11 (65)	35 (80)
CRS grade 3 or higher	3 (18)	5 (11)
CRES grade 0	7 (41)	13 (30)
CRES grade 1-2	5 (29)	14 (32)
CRES grade 3 or higher	5 (29)	17 (39)
Median hospitalization period	19 days	15 days

Dahlia Sano et al. Blood 2018;132:96

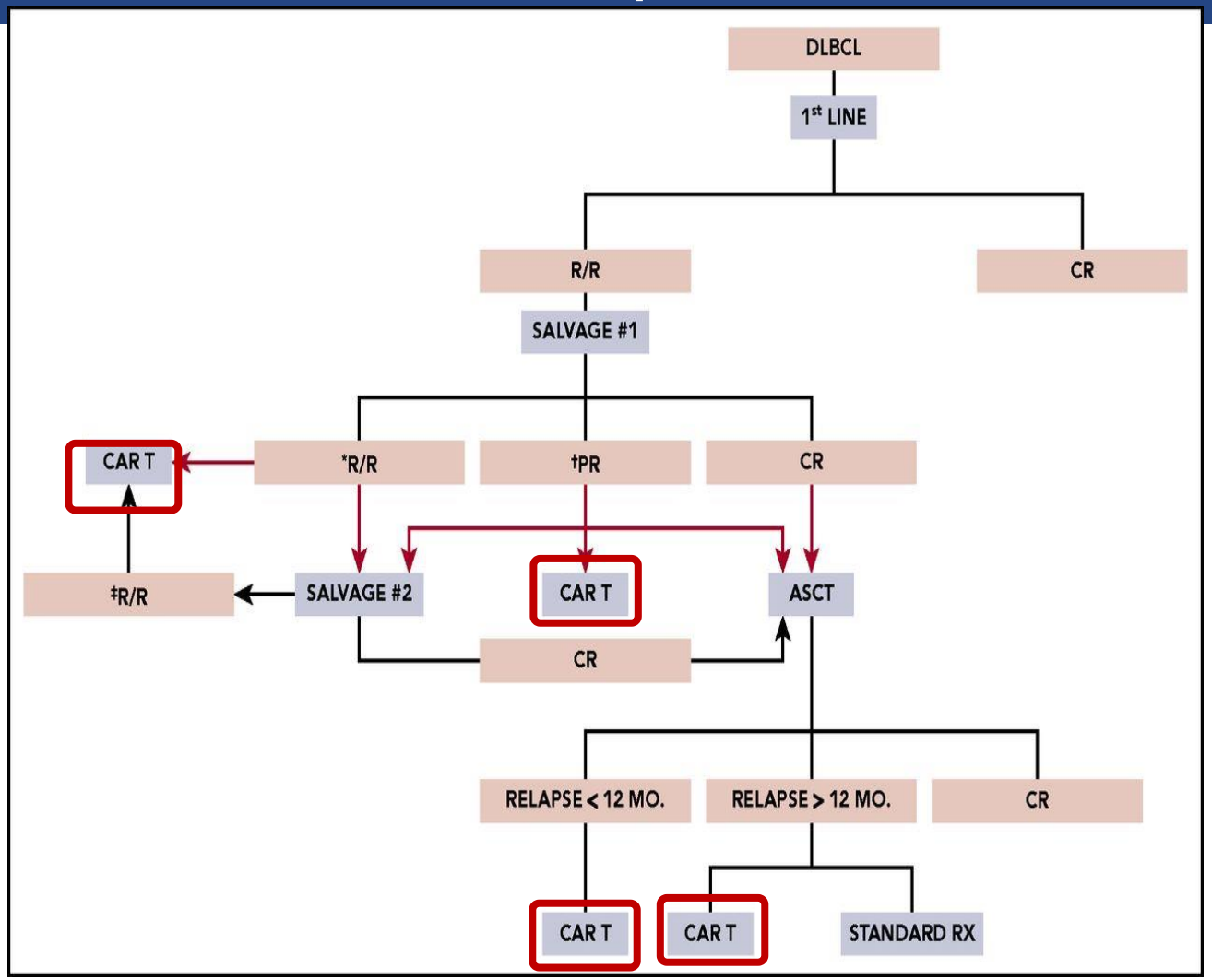
"Real-world" Axi-cel

- **Objective:** Delineate the characteristics and real world outcomes of patients undergoing standard of care axi-cel.
- Retrospective analysis of data from **17 US academic centers**.
- All patients **leukapheresed as of August 31, 2018** with intention to manufacture commercial axi-cel were included in these analyses.



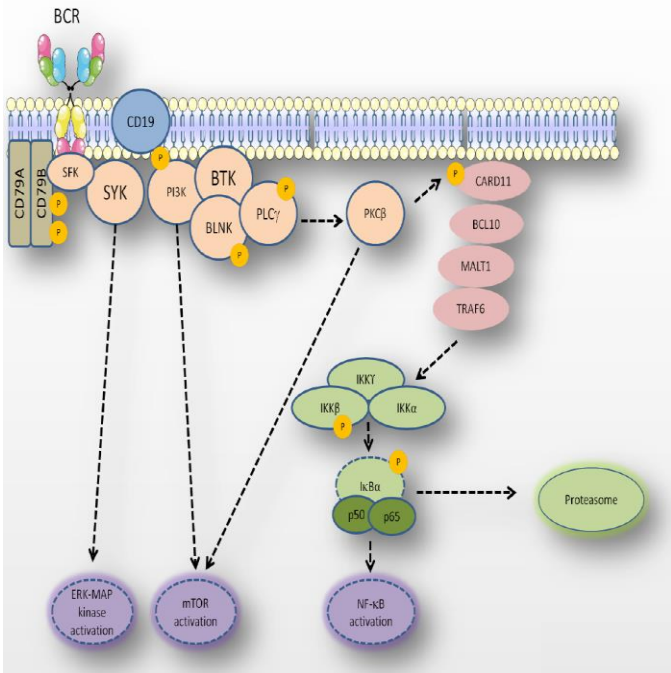
Nastoupil ASH 2018 Abstract 91 Saturday, December 1, 2018: 9:30 AM
Pacific Ballroom 20 (Marriott Marquis San Diego Marina)

Proposed schema for use of anti-CD19 CAR T-cell therapy in clinical practice.



Victor A. Chow et al. Blood 2018;132:777-781

Yeni tedavi hedefleri-NHL



BCR signature:

- SYK inh
- PI3K inh
- PKC-β inh
- BTK: ibrutinib
- mTOR inh

Apoptosis:

- BH3 mimetic

Epigenetic

- HDAC inhibitors
- EZH2 inhibitors

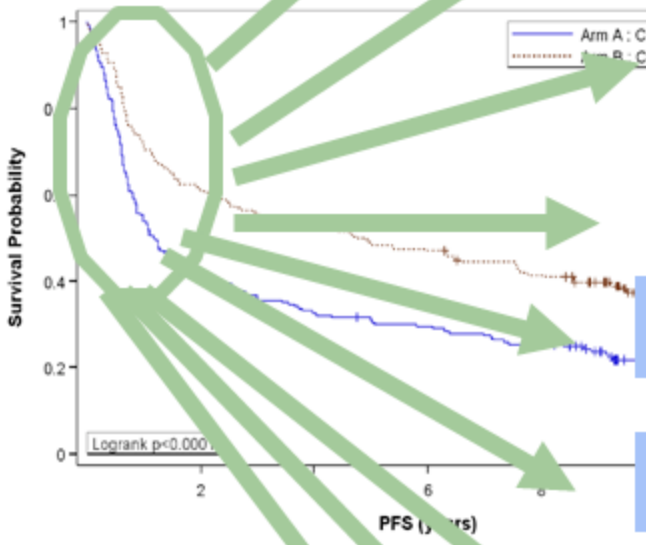
Nuclear export

- Selinexor

Agent	Target	Status	Overall Response	Subtype DLBCL	References
Ibrutinib	BTK	Phase I/ II	37%	ABC	(Wilson et al ; 2015)
Fostamatinib	SYK	Phase II	3% 22%	DLBCL	(Flinn et al, 2016) (Friedberg et al, 2010)
Lenalidomide	immunomodulator	Phase II	42% 52%	DLBCL ABC	(Zinzani et al, 2015 (Hernandez-Ilizaliturri et al, 2011)
Bortezomid + chemo	NF kB	Phase II	83%	ABC	(Dunleavy et al, 2009)
Tazemetostat	EZH2	Phase II	60%	DLBCL	(Italiano et al, 2018)
Everolimus	m TOR	Phase II	30%	GCB	(Witzig et al, 2011)
Temsirolimus	mTOR	Phase II	28%	DLBCL	(Smith et al, 2010)
CUDC 907	PI3K delta +HDAC	Phase II	37%	GCB/Myc	(Oki et al, 2017)
obinutuzumab	CD20	Phase II	32%	DLBCL	(Morschhauser et al, 2013)
MOR00208	CD 19	Phase II	29%	DLBCL	(Jurczak et al, 2016)
Blinatumumab	B specific CD19/CD3	Phase II	43%	DLBCL	(Viadrot et al, 2016)
Polatuzumab vedotin	CD79b	Phase I	25%	DLBCL	(Palanca et al, 2015)
Nivolumab	Anti PD1	Phase I	36%	DLBCL	(Lesokhin et al, 2016)
Selinexor	Exportin XPO1	Phase I/IIb	32%	DLBCL	(Kuruvilla et al, 2017)
Ublituximab + 1202+ benda	CD20	Phase II/III		DLBCL	(Lunning et al, 2017)

Dunleavy K, et al. *Blood.* 2009;113(24):6069-6076. Italiano A, et al. *Lancet Oncol.* 2018;19(5):649-658. Witzig TE, et al. *Leukemia.* 2011;25(2):341-347. Smith SM, et al. *J Clin Oncol.* 2010;28(31):4740-4746. Oki Y, et al. *Haematologica.* 2017;102(11):1923-1930. Morschhauser FA, et al. *J Clin Oncol.* 2013;31(23):2912-2919. Jurczak W, et al. *J Med Case Rep.* 2016;10(1):123. Viadrot A, et al. *Blood.* 2016;127(11):1410-1416. Palanca MA, et al. *Lancet.* 2015;16(6):706-715. Lesokhin AM, et al. *J Clin Oncol.* 2016;34(23):2698-2704. Kuruvilla J, et al. *Blood.* 2017;129(24):3175-3183.

DLBCL: Moving Forward CHOP: Ongoing Trials in First Li



Lenalidomide

R2-CHOP / R-
Studies

BTKi / ibrutinib

>> Activity
Ph III no d

Bortezomib

>> Activity in non-
2 ph III studies R-

BCL2 / ABT-199

Ongoing Ph II G-CHO

PKCb / enzastaurin

PRELUDE trial–no diff

mTOR

PILLAR2 trial rand ma
post R-CHOP,

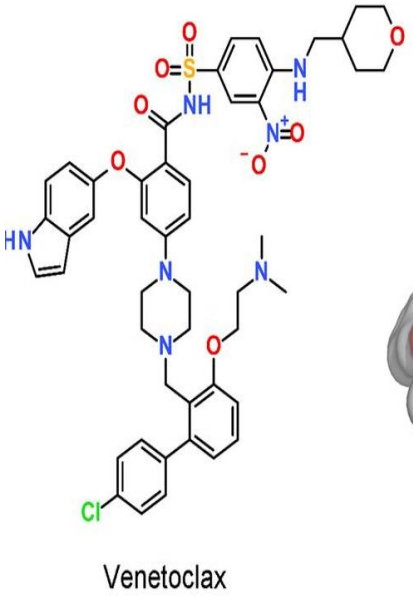
PI3K

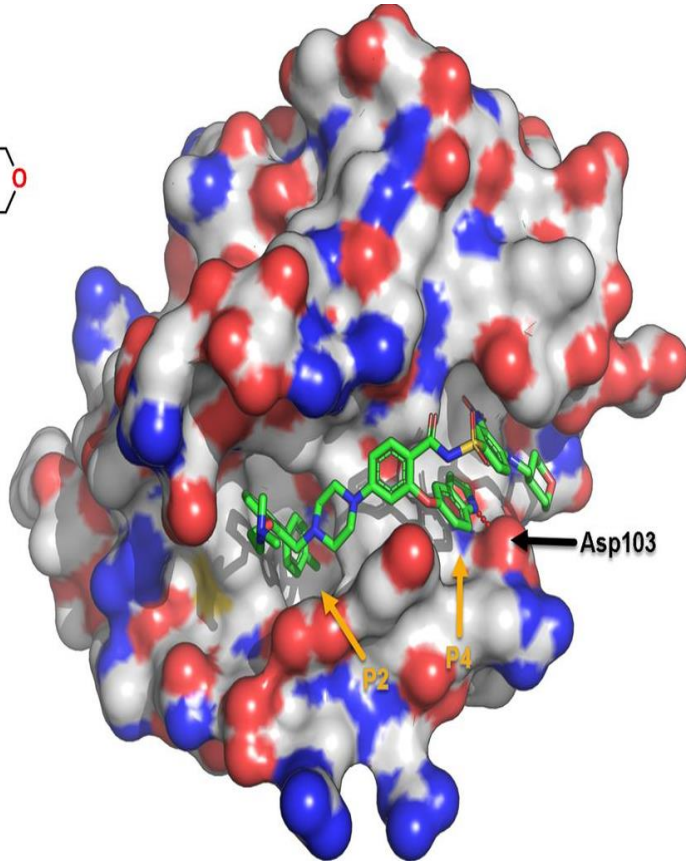
Idelalisib, IPI-1

Epigenetics

Azacytidine

Venetoclax





Venetoclax indicated for the treatment of patients with CLL/SLL, with or without 17p deletion, who have received at least one prior therapy

SdV Sept 2018

(Ruefli-Brasse and Reed, Biochemical Journal 2017;474:3643-3657)

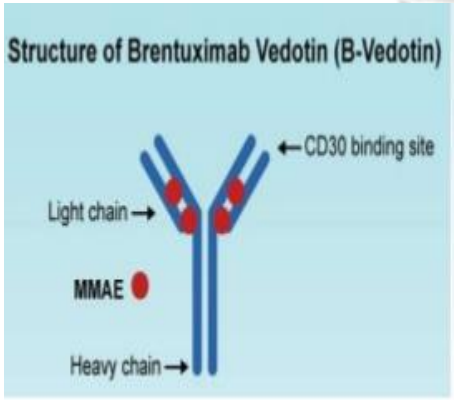
Hodgkin lenfoma

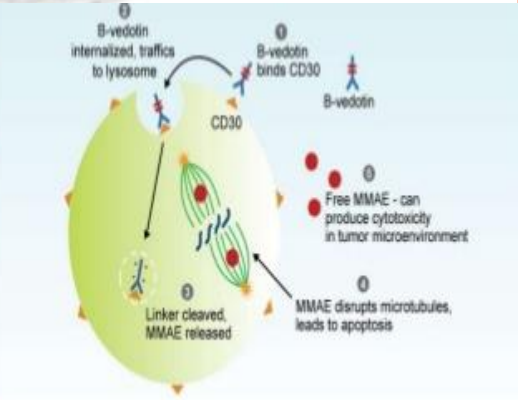
Hodgkin lenfoma

- ABVD
- Interim PET-CT cevabı
- Risk e göre tedavi
  - escBEACOPP-----BV-ADV
- Yeni ilaçlar
  - Brentuximab vedotin (Adcetris)
  - Immune check points inhibitors (PD1 BLOKAJI, Nivolumab)

BRENTİKSUMAB VEDOTİN (BV)
ANTI-CD30

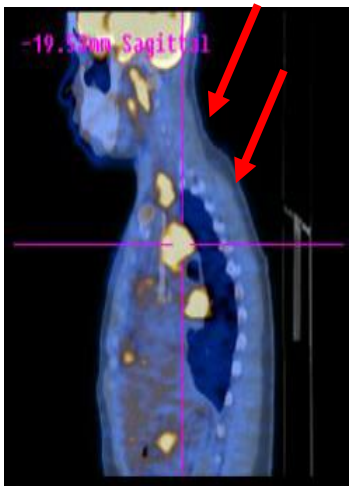
- 1- OKİT sonrası nüks Hodgkin Lenfoma da
  - Ağustos 2011 de FDA onaylı (Hodgkin hastaları için; yaklaşık 35 yılda onay alınan ilk ilaç)
- 2- OKİT e aday olmayan en az 2 multiajan kemoterapiye cevapsızlık sonrası
- 3- En az bir multiajan kemoterapi rejimi sonrası nüks sistemik Anaplastik Large Cell Lenfoma (ALCL)
- ----------
- Refrakter Hodgkin Hastalığı
  - 6.7 ay med, CR: %32, PR: %41 (%73)
- ALCL
  - 12,6 ay med. CR: %57, PR: %29 (%86)





PET/CT SCANS BEFORE AND AFTER ABVD x 2

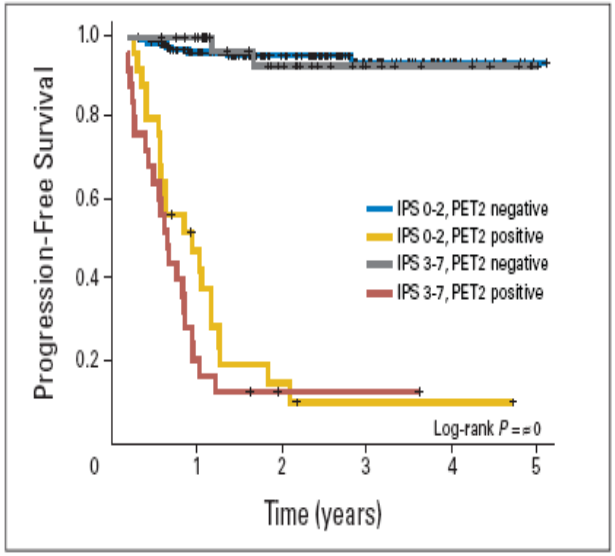
Baseline: Before ABVD



Cervical LAD

Mediastinal LAD

After ABVD x 2: PET-negative



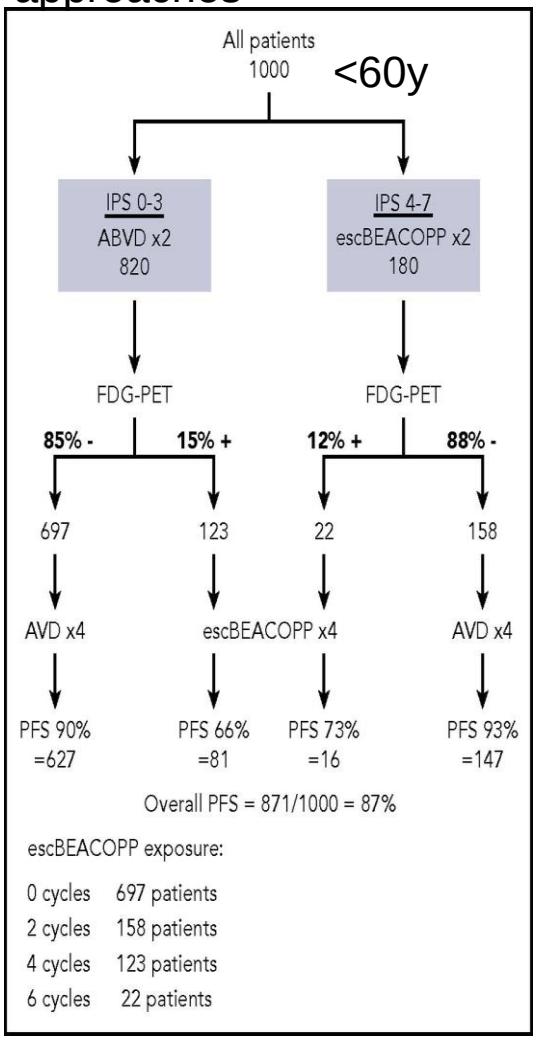
EARLY RESPONSE is predictive of outcome

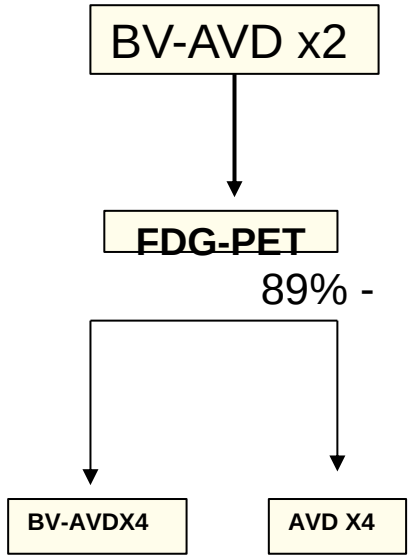
Interim PET/CT response adapted strategies after ABVD x 2

(Gallamini A. et al. JCO 2007)

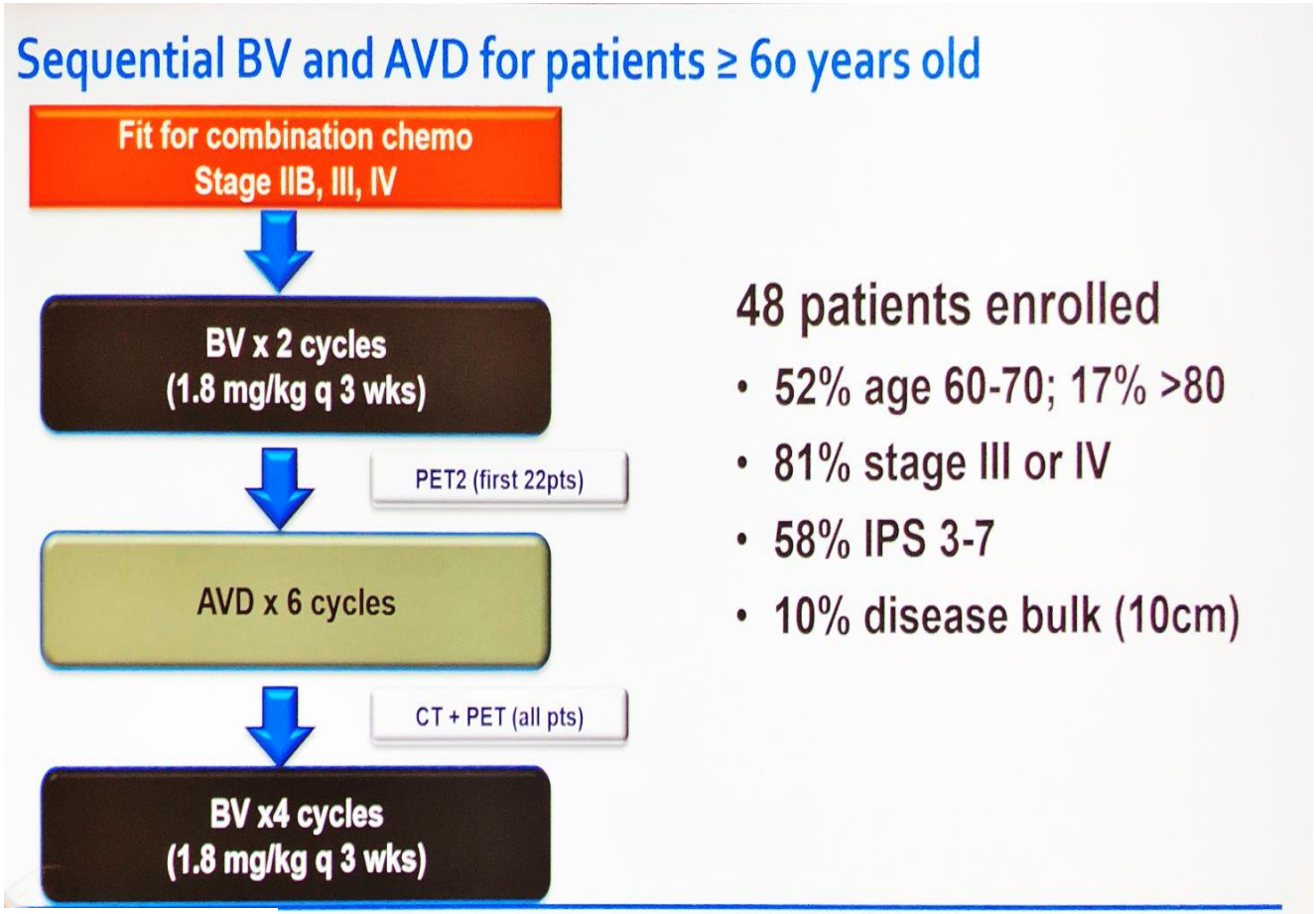
Merging of different risk-adapted approaches.

RATHL/AHL2011 approaches





Sean H. Lim, and Peter W. M. Johnson Blood 2018;131:1679-1688

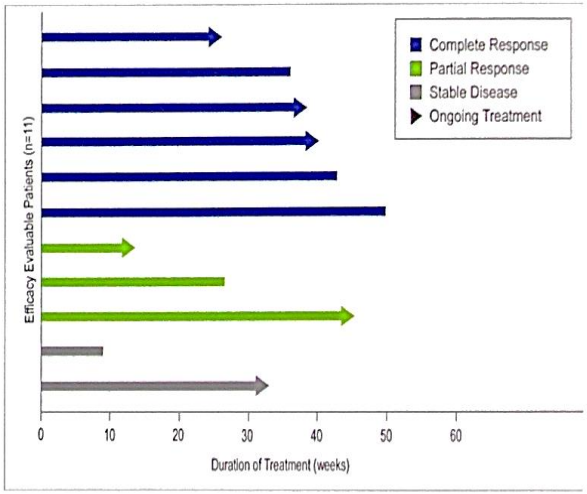


Evens A et al *J Clin Oncol 36:3015-3022. © 2018*

Nivolumab+BV as frontline therapy in elderly pts with HL

82% ORR, 55% CR among efficacy evaluable patients (n=11)

Best Responses Evaluable Patients (n=11)	N (%)
Complete response	6 (55)
Partial response	3 (27)
Stable disease	2 (18)
Progressive disease	0
Overall response rate (CR+PR)	9 (82)
Disease control rate (CR+PR+SD)	11 (100)



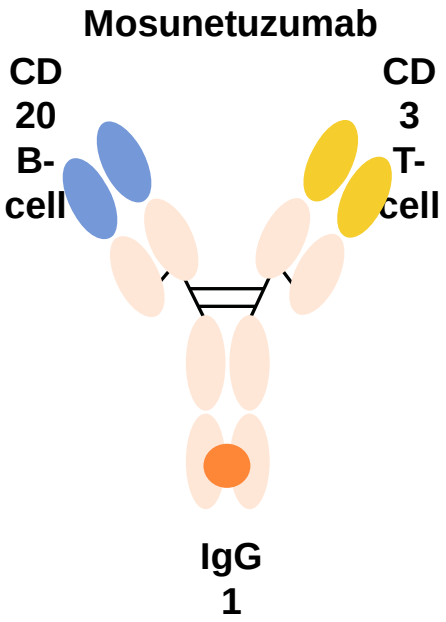
Median follow-up: 8 months

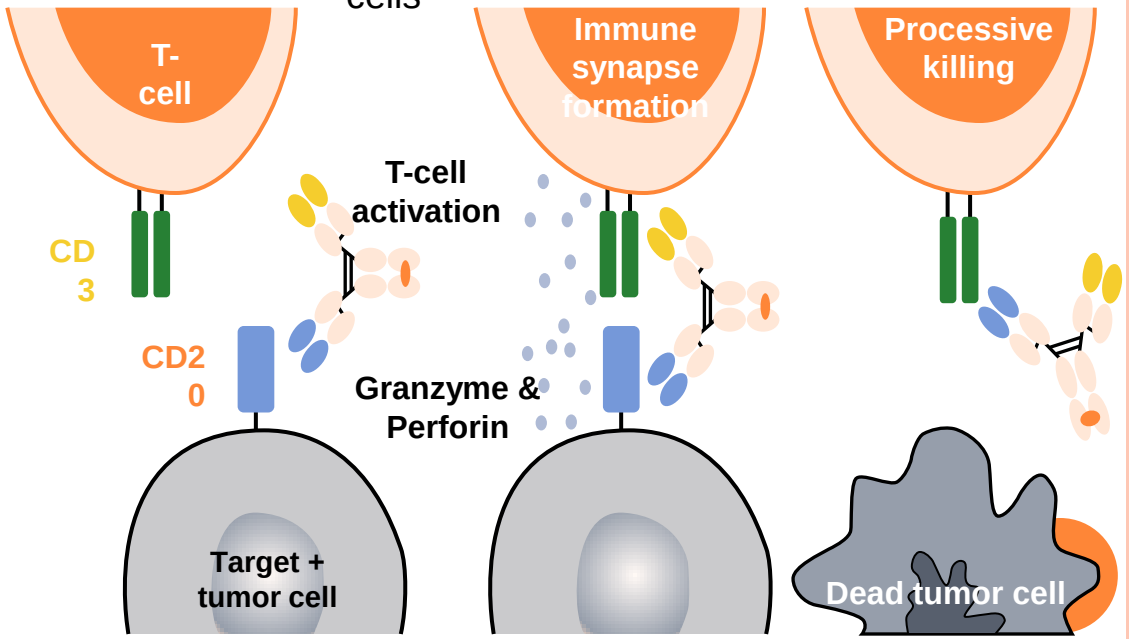
Friedberg J., et al. ISHL 2018

Mosunetuzumab: a bispecific antibody targeting CD3 and CD20

- **Full-length humanized IgG1 antibody**
  - Longer half-life than fragment-based drug formats
  - PK properties enable once weekly to q3w dosing
  - Does not require *ex-vivo* T-cell manipulation
  - Off the shelf, readily available treatment

- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells
  - Conditional agonist: T-cell activation dependent on B-cell engagement
  - Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells





ADCC, antibody-dependent cell-mediated cytotoxicity

Sun et al. Sci Transl Med 2015

MDS

MDS

- Oral rigosertib ve
- + AZA
- İlk basamakta

- Yüksek riskli-MDS ----cesaret verici

- Luspatercept
- Düşük ve orta risk MDS
- Tx ihtiyacı

- Aza =Aza + Len, VPA or Ida

- Aza +/- Nivo
- Aza + Rigo

- Aza + Apr246 80-100% cevap:p53 mut MDS/AML
- Eltrombopag düşük risk MDS: 50% cevap
- Luspatercept : 38%
- Imetelstat: 37% (RA + RS)

ALL

Erişkin ALL

Alt Tip	Tedavi	% Kür
Burkitt	B-NHL GMALL + R HCVAD +R EPOCH +R GRAALL +R	80-90%
B-Lineage Ph- B-Lineage PH+ PH-like	Intensive Chemo +/- SCT	~50% ~50% ?
T-Lineage ALL Cortical Early/Mature	Intensive Chemo Intensive Chemo + SCT	50-70% 30-40%
Age Groups AYA Elderly	Pediatric insp.	60-70% 30%

* AYA: Adolescents and Young Adults

Efficacy and Safety of CD19 CAR-T Cell Therapy for B-cell ALL in a Large Cohort Including patients with EMD, HLB, BCR-ABL (+) Mutation, TP53 Mutation, and Post-Transplant Relapse

Zhang X, et al. ASH 2018;Abstract 280

Results

Day 30 after CAR-T infusion	Patients (n)
CR or CRi	92% (76/83)
- Extramedullary Disease - Central nervous system lymphoma - High Leukemia Burden - TP53 - BCR-ABL - After allo HCST	82% (14/17) 82% (8/11) 77% 88% (7/8)
Cytokine Release Syndrome	Gr. 0-II 82% Gr. III-IV 16%
Severe CNS toxicity	12%
CAR-T-related deaths	N=1

Efficacy and Safety of CD19 CAR-T Cell Therapy for B-cell ALL in a Large Cohort Including patients with EMD, HLB, BCR-ABL (+) Mutation, TP53 Mutation, and Post-Transplant Relapse

Zhang X, et al. ASH 2018;Abstract 280

Sonuçlar

- Tam cevap oranları yüksek
- CRS ve nörotoksite tedavi edilebilir
- TP53+:
- Tx SONRASI NÜKS
  - 2. Allo-SCT

Erişkin ALL de hedeflenmiş tedaviler

Tyrosine Kinase Inhibitors

Ph+/ BCR-ABL ALL

Imatinib, Dasatinib, Nilotinib, Bosutinib Ponatinib

Ph-/bcr-abl-like ALL

ABL1, ABL2; Dasatinib, JAK2; Ruxolitinib

Antibody therapy

Anti-CD20 Rituximab, Ofatumomab
Anti-CD22 Inotuzumab Ozogamicin
Anti-CD19 T cell-activating therapies
Blinatumomab,
Chimeric Antigen Receptor T-cells (CAR T cells)

Immune Checkpoint Inhibitors

Ph + ALL DE TEDAVİ SEÇENEKLERİ

Chemotherapy combined with a TKI

- Intensive + SCT
- Less intensive, SCT ?
- No Chemo, (only corticosteroids) SCT ?

Tyrosine Kinase Inhibitors

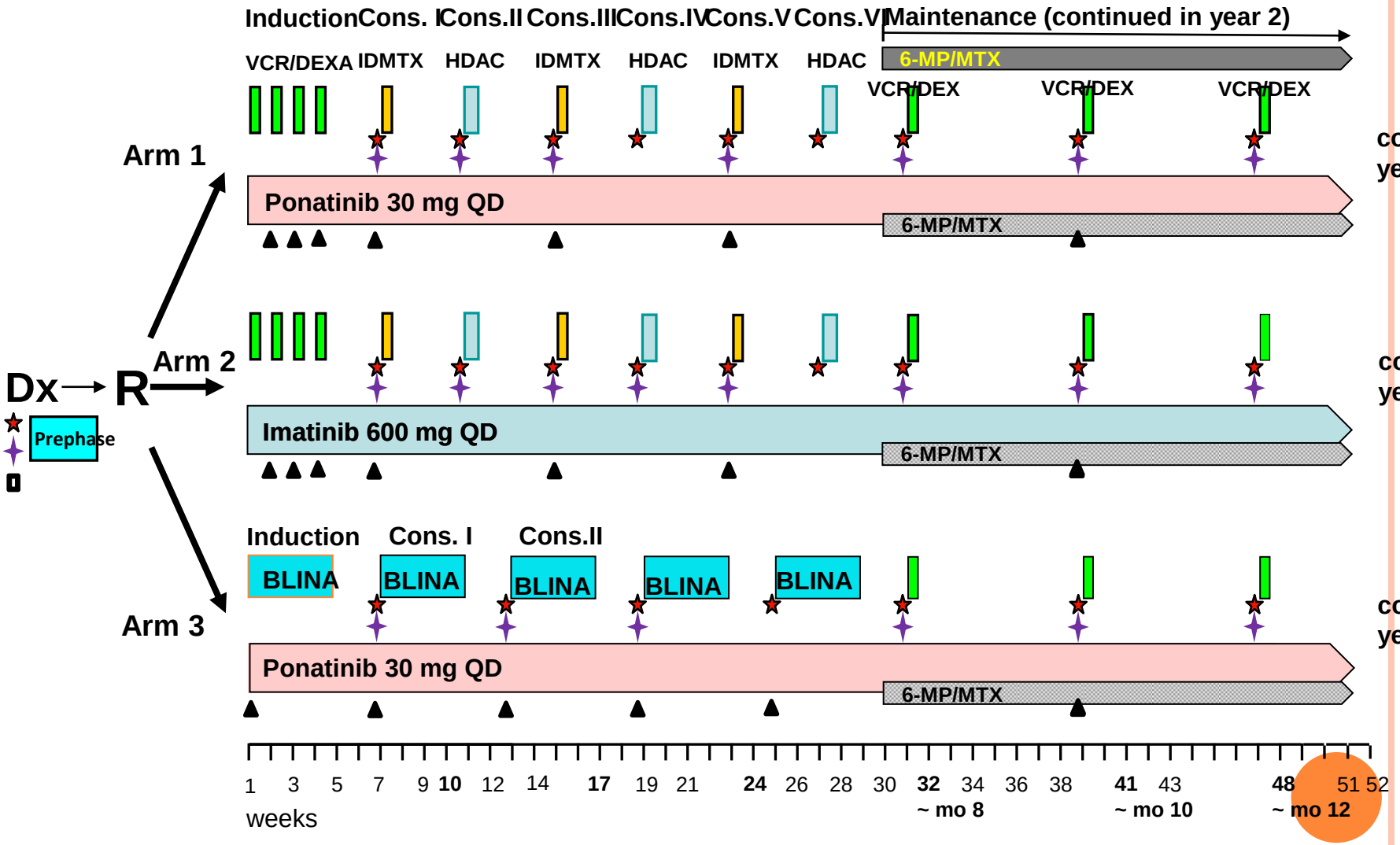
- Imatinib
- Dasatinib, Nilotinib
- Bosutinib, Ponatinib

Immunotherapy

- Inotuzumab with Tki in comb.
- Blinatumomab, mono
- (eradicates resistant mutations!)

Randomised Study Imatinib vs. Ponatinib + Blinatumomab in elderly de novo Ph+ALL

EWALL PH03: Study Design



☆ PB: BCR-ABL1/ABL1 (RT-PCR)

✦ BM: BCR-ABL1/ABL1 (RT-PCR) and Ig gene rearrangement (PCR)

TKD mutation testing if BCR-ABL1 positive

Intrathecal MTX

▲ Intrathecal triple therapy

Ottmann et. al.

ASH 2018
BLINATUMOMAB İÇİN YENİ NE VAR?

- Blina Frontline in elderly pts. (~75 y.o.) followed by POMP Maintenance
- Blina Frontline combined with Hyper-CVAD
- Blina in MRD positive pts., follow up

BLINATUMOMAB VE TRANSPLANT IN ROLÜ

- in MRD pts. high rate of conversion to MRD negativity
- superior outcome, still most pts. receive SCT after Blina
- ~25% of non-SCT pts. remain in CCR

→ How to select MRD neg. pts for SCT vs. not

→ <u>Future:</u>

When Blinatumomab is frontline, do we still need SCT?

ASH 2018
CAR-T-cell Tedavisinde yeni ne var?

Extramedullary Disease

- Efficacy in Extramedullary disease #280
- A novel generation of EMD Wang, 2018

Updates

- Anti-CD19 CAR-T-cells in Pediatric + AYA pts. #895
- Anti-CD19 CAR-T-cells in Adults #897

Attempts to avoid CD19-negative relapse

- Cocktail of CD19/CD22 #277
- Bicistronic CD19/CD22 CAR-T # 279
- Sequential CD22 Targeting #282

New approaches

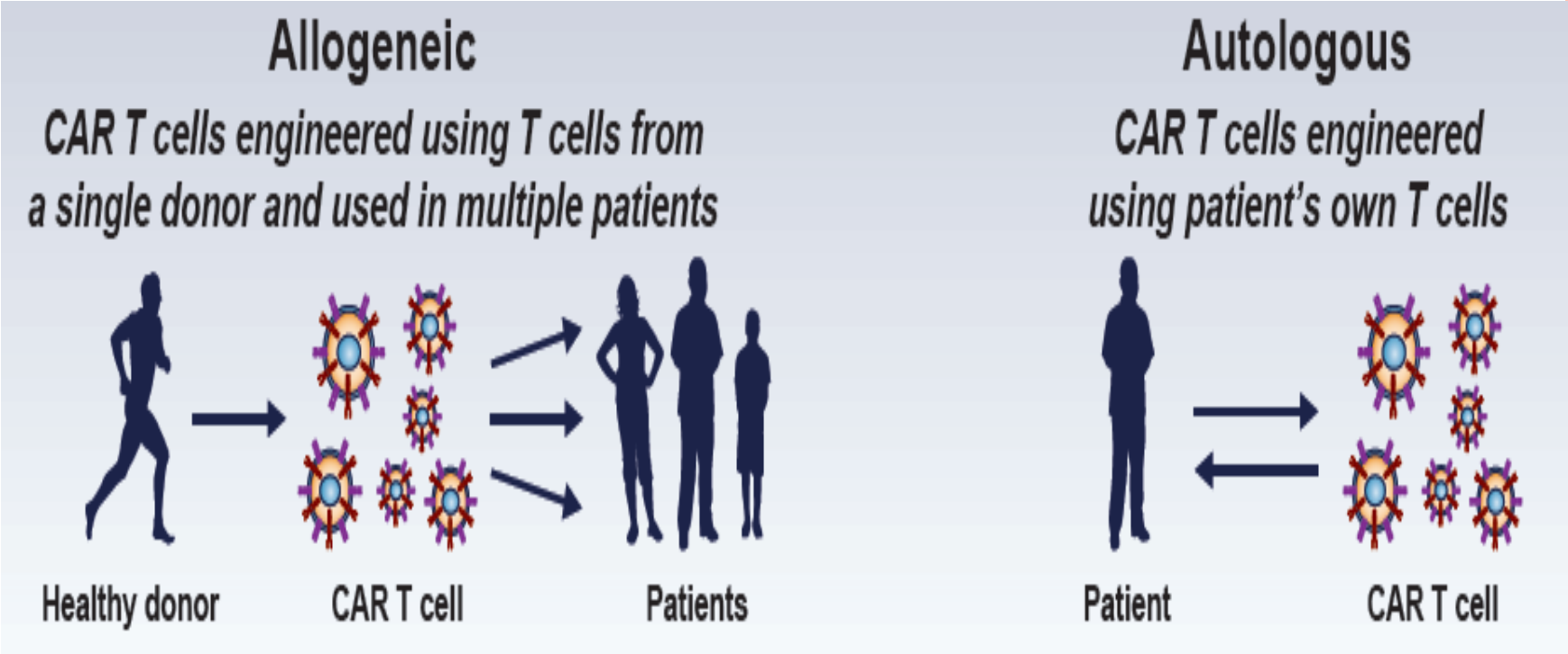
- Checkpoint Inhibitor Augment CD19 CAR-T-cells #895
- UCART19, Allogeneic CAR-T-cells #896
- CD19 CAR-T-cells alone/with ibrutinib #299

Combination of CAR T-cells with Immune Checkpoint Inhibitors e.g. Pembrolizumab, Nivolumab, Ibrutinib

- Etkinlik artıyor
- CRS ve neurotoxite azalıyor

Autologous vs Allogeneic CAR T Cell Therapy

Various approaches to CAR T-Cell Therapy



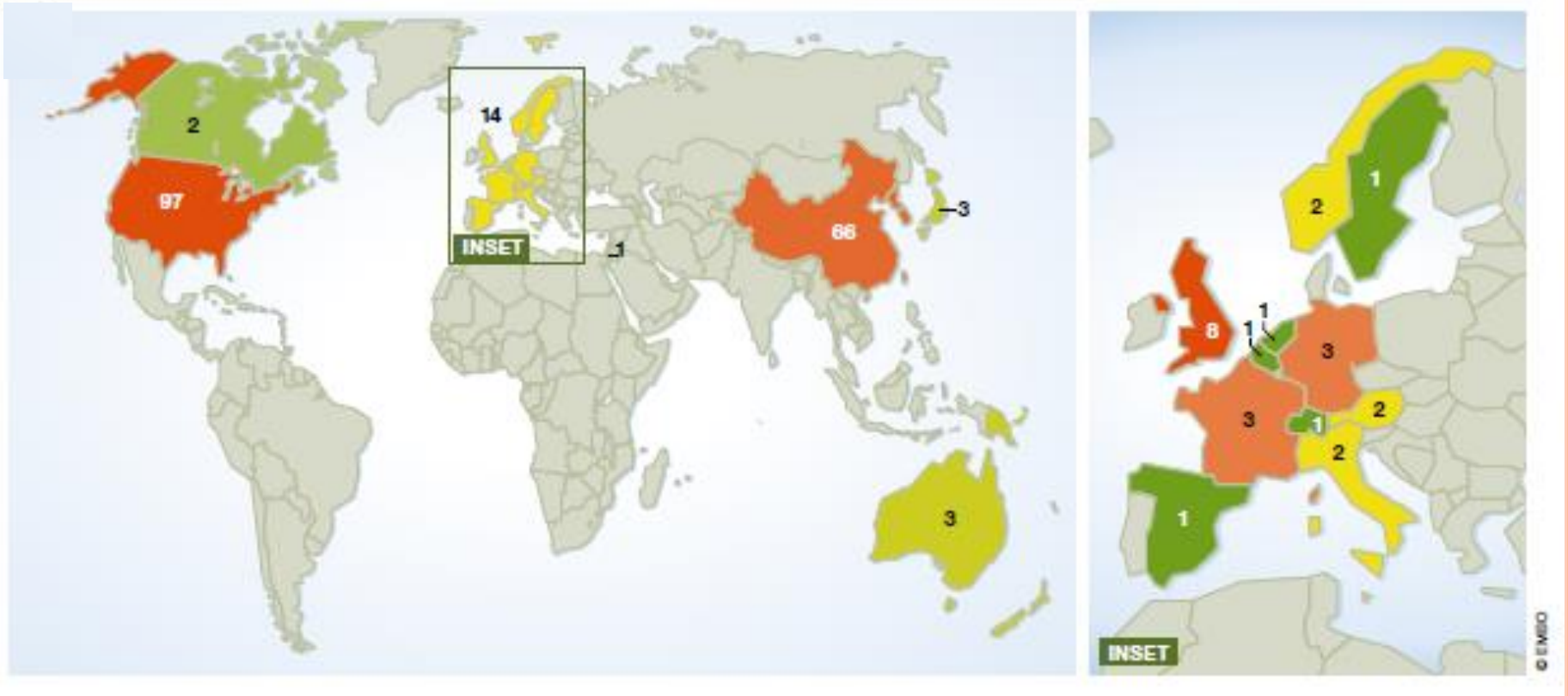
ASH 2017: Phase 1 results of UCART19 in adults with CD19+ R/R B-ALL[1]
Updated oral abstract 887, Monday, December 11, 2017: 7:15 PM

1. Benjamin R et al. ASH 2017. Abstract 887.

Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts

Hartmann, J. et al._EMBO Molecular Medicine_(9):1179-1326_2017

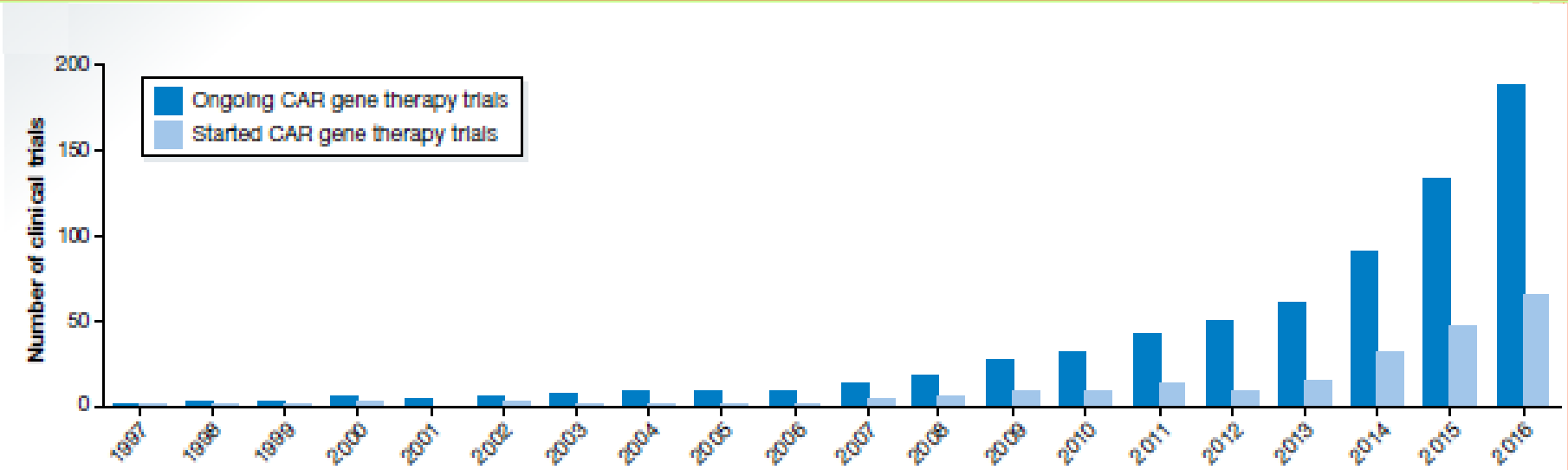
CAR T cell trials over geographical distribution



Geographical distribution of worldwide ongoing CAR T cells clinical trials (left) and distribution of trial sites of the ongoing European studies (right). Five studies are multi-centric, of which four are multi-country trials in Europe (Dataset EV5). Long-term follow-up studies are not included. Color code indicates the prevalence of trials from low (green) to high (red).

Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts

Hartmann, J. et al._EMBO Molecular Medicine_(9):1179-1326_2017



Approaches and cost of CAR T cells

Tisagenlecleucel (Novartis)
B-cell ALL children
425.000 US Dollar

Axicabtagen-Ciloleucel (Roche)
DLBCL
375.000 US Dollars

Miltenyi/Academic
CliniMACS Prodigy ®
Fully automated
Costs 150.000-180.000 € ?

Academic Approaches
Single university institution

CAR-T Therapy Displays Favorable Gains in Health Outcomes and Competitive Cost-Effectiveness When Compared with Past Innovative Cancer Treatments

Baumgardner J, et al. ASH 2018: Abstract 322

Background

- Negative trend in pharmaceutical oncology treatments

  marginal improvements in survival with significant increases in costs in incremental QALYs and cost/QALY

→ CAR-T Therapy vs. up-to-date innovations for both hematologic and non-hematologic cancers in terms of cost-utility

Conclusion

- CAR-T therapy improved health outcomes (measured in QALYs) to a greater extent than both treatments for hematologic cancers and non-hematologic cancers
- CAR-T Cell Therapies represent a break and offers the same Cost-Utility ratio as the other innovations.

→ Hope is to cure patients with a single CAR T-cell infusion !?

MPH-miyelofibroz-Tedavide yenilikler

- Ruxolitinib (JAK—2 İNH) ORAL AJAN
- Ropeginterferon alpha
- Kombinasyon tedavileri
- Yeni ilaçlar

Figure 5: Best change from Baseline in spleen volume

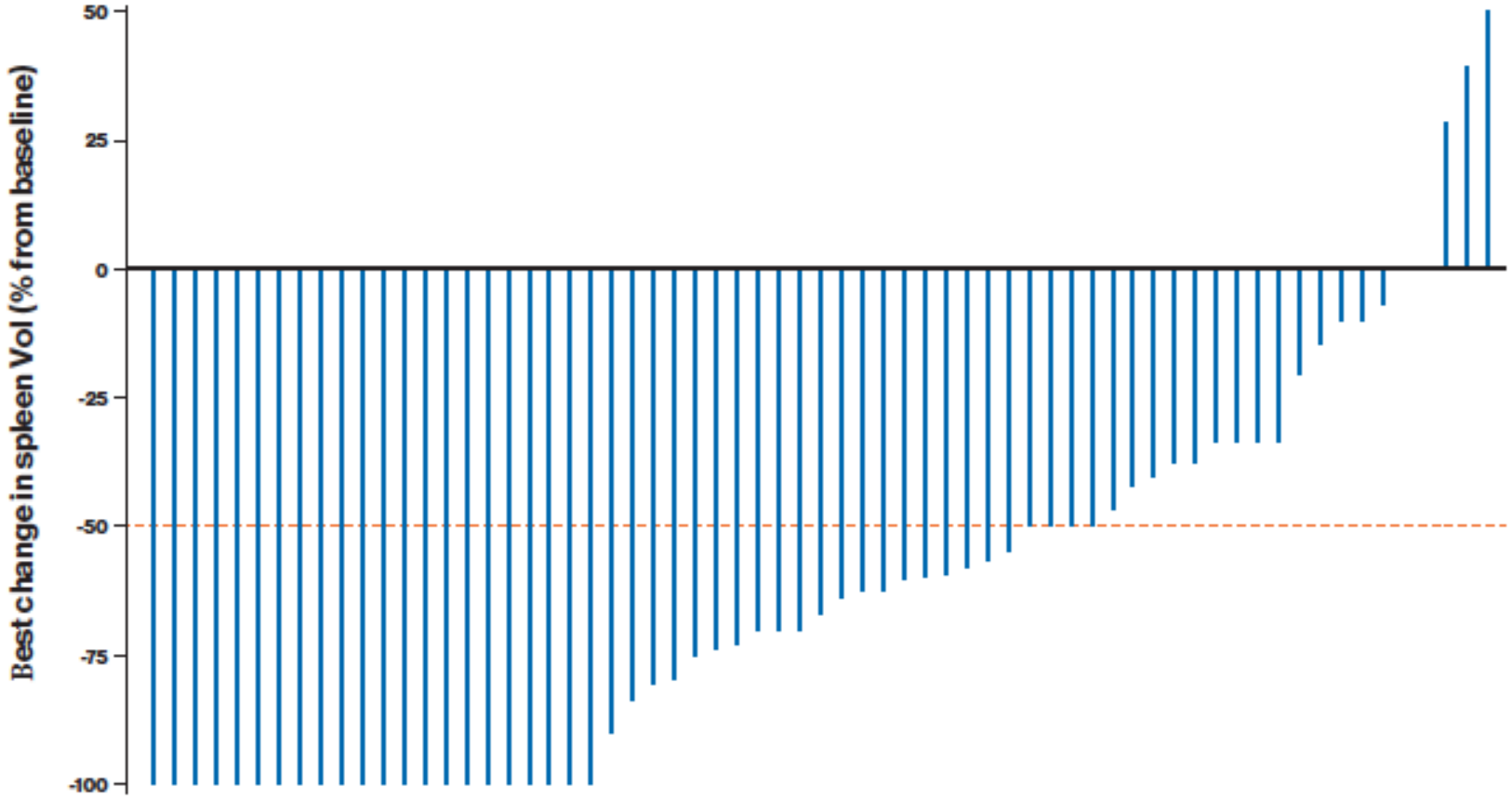
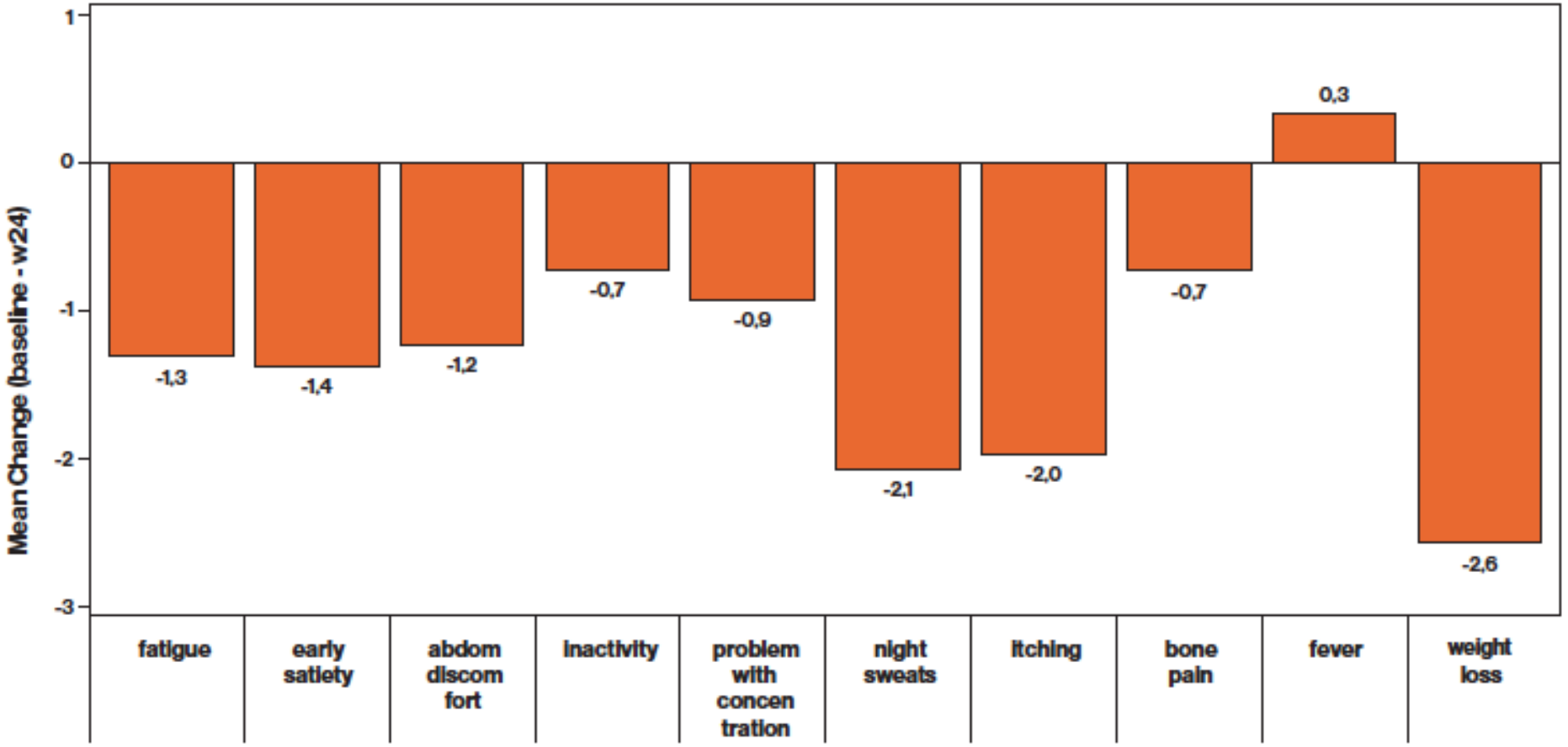


Figure 2: MPN symptoms score



Imetelstat Is Effective Treatment for Patients with Intermediate-2 or High-Risk Myelofibrosis Who Have Relapsed on or Are Refractory to Janus Kinase Inhibitor Therapy: Results of a Phase 2 Randomized Study of Two Dose Levels

John Mascarenhas, MD[1], Rami S. Komrokji[2], Michele Cavo, MD[3], Bruno Martino, MD[4], Dietger Niederwieser, MD[5], Andreas Reiter, MD[6], Bart L Scott, MD[7], Maria R. Baer, MD[8], Ronald Hoffman, MD[9], Olatoyosi Odenike, MD[10],
Jacqueline Bussolari, PhD[11], Eugene Zhu, PhD[11], Fei Huang, PhD[11], Esther Rose, MD[11], Laurie Sherman, BSN[11],
Souria Dougherty, BS, MBA[11], Faye M. Feller, MD[11] and Jean-Jacques Kiladjian, MD, PhD[12]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai; MPN-RC (US), [2]H Lee Moffitt Cancer Center (US), [3]"Seràgnoli" Institute of Hematology, University of Bologna (IT), [4]Grande Ospedale Metropolitano-G.O.M. Bianchi-Melacrino-Morelli (IT), [5]University Hospital Leipzig (DE), [6]University Hospital Mannheim (DE), [7]Fred Hutchinson Cancer Research Center (US), [8]University of Maryland Greenebaum Comprehensive Cancer Center (US), [9]Tisch Cancer Institute, Mount Sinai School of Medicine (US), [10]University of Chicago (US), [11]Janssen Research & Development, LLC (US), [12]Hôpital Saint-Louis, Université Paris (FR)

Funded by Janssen Research & Development and Geron Corporation

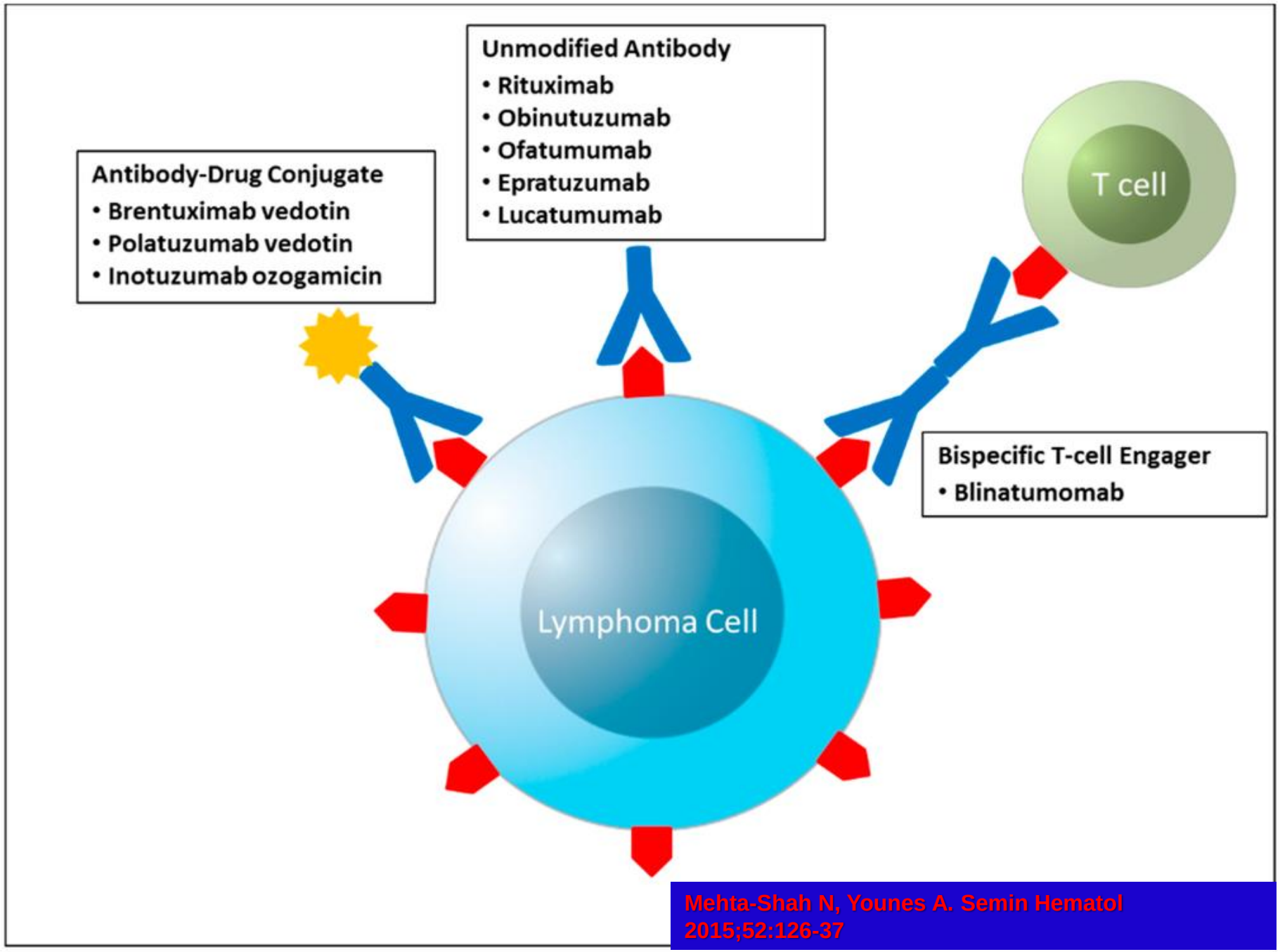
Abstract #685

MPH-SONUÇLAR

- Telomeraz inhb.
- Imetelstat at 9.4 mg/kg IV every 3 weeks
- ve yüksek risk Mf
- Rr- jak-2 inhb.

[1]Kuykendall, et al. *Ann Hematol* 2018;97:435-441.

[2]Newberry, et al. *Blood* 2017;130:1125-1131.

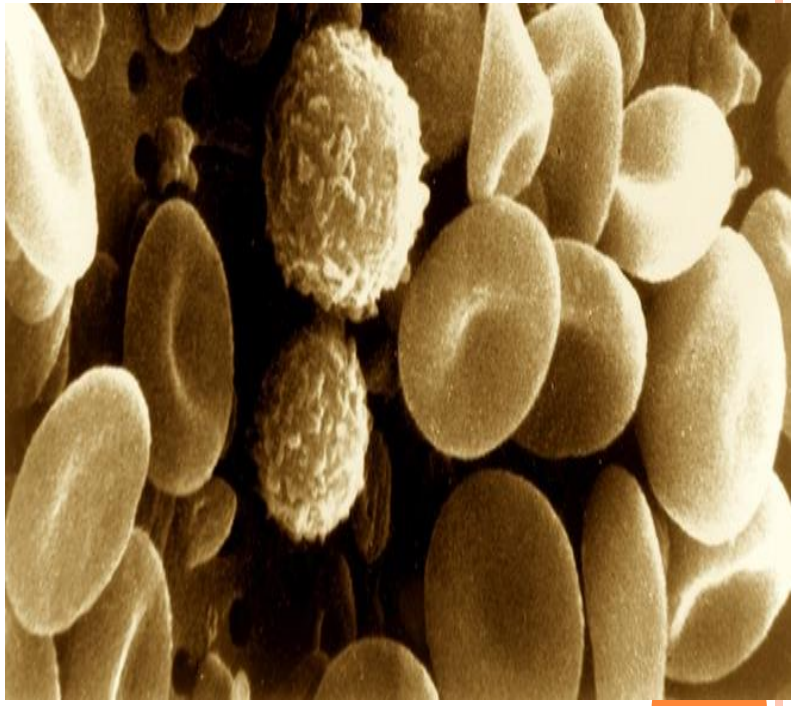


Mehta-Shah N, Younes A. Semin Hematol 2015;52:126-37

Hematopoetik kök hücre

- Farklı hücre tiplerine dönüşebilme
- Kendisini yenileyebilme

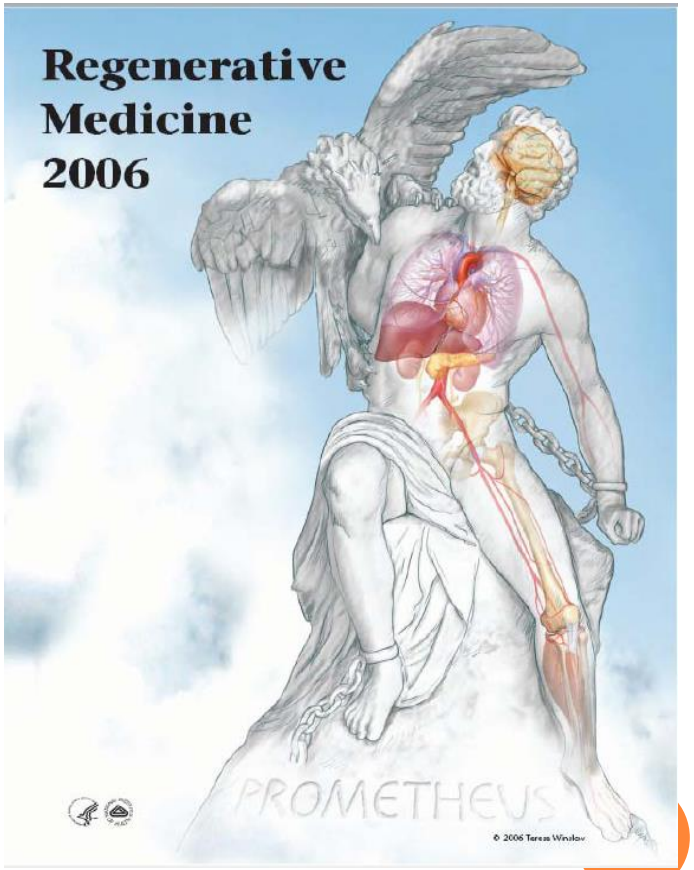
- CD34+ kök hücreler
  - Kemik iliğinde %1-4
  - Çevre kanında %0.06-%1



- Mezenşimal kök hücre
  - Transplantasyon
  - Rejeneratif tıp
  - Otoimmün hastalıklar

İmmünsupressif

Doku uyumuna gerek yok



2018-FDA ONAYı ALAN ILAÇLAR

AML-ALL

- Gilteritinib (xospata)
- FLT3 mut.-rrAML----------FDA onayı-28.11.2018
- ----------
- Venotooclax (Venclexta)
- > 75 yaş , Yeni tanı AML, AZA, Dec,tabine, low doz ARA-C kombine, indüksiyonda
- ----------FDA onayı- 21.11.2018
- ----------
- Glasdegib (Daurismo, Phizer)
- LDAC+Kombine
- ----------
- Ivosidenib (Tibsovo)
- RR- AML, IDH1 mut+
- ----------
- Blinatumomab (Blincyto)
- B –ALL, CR ½ MRD > %0.1

LENFOMA

- CD20 poz. B hücreli NHL
- Rituksan, biobenzer, Truxima=rituksimab---------- FDA onayı-8.11.2018
- ----------
- Brentixumab Vedotin (ADCETRİS)
- Sistemik anaplastik large cell lenfoma/CD30 exp. Lu periferal T hücreli lenfomalar
- (Tedavi edilmemiş, kombinasyonda)----------FDA onayı-16.11.2018
- ----------
- Duvelisib (COPIKTRA)
- Rr FL, rr KLL/SLL----------FDA onayı- 24.09.2018
- ----------
- Moxetumomab pasudotox (LUMOXİTİ)
- RR Hairy cell lösemi de Anti-CD22, 2. sıra sistemik kt,

LENFOMA

- Mogamulizumab
- Sezary/ rr Mycozis Fungoides
- 1.sistemik tedavi sonrası----------FDA onayı: 08.08.2018

- Pembrolizumab (Keytruda)
- Primer med. Lafge B cell lenfoma (PMLCL)
- 2/üzeri sıra tedavi RR----------FDA onayı: 13.06.2018
- ----------
- Tisagenlecleucel (KYMRIAH, Novartis)
- Modifiye otolog T hücre immünoterapi
- CD 19 a yönlenmiş----------FDA onayı: 01.05.2018
- ----------
- Brentixumab Vedotin (ADCETRİS)
- Hodgkin E vre III-IV ilk basamak (KT ile kombinasyonda) ----FDA onayı: 20.03.2018
- ----------
- Venotoclax (Venclexta)
- 17p +/- KLL/SLL----------FDA onayı: 08.06.2018

TTP/PNH/ITP

- **TTP**
- Caplacizumab-vndp----------FDA onayı: 06.02.2019
- ----------

- **PNH**
- Ravalizumab----------FDA onayı: 21.12.2018
- ----------

- **ITP**
- Fostamatinib disodium tablet (TAVALISSE)-------FDA onayı: 17.04.2018

TROMBOSITOPENI/ANEMI

- Primer Hemofagositik Lenfo Histiyositoz (HLH),
- Emapalumab (GAMİFANT)
- Mo-Ab
- IFN-Gama yı nötralize eder
- Erişkin/pediatrik----------FDA onayı: 20.11.2018
- ----------
- Kronik Karaciğer hastalığı/Trombositopeni/Prosedüre hazırlık
- Avatrombopag (Doptelet)----------FDA onayı:21.05.2018
- ----------
- Kronik Karaciğer Hastalığı /medikal, dental prosedürler/Trombositopeni
- Lusutrombopag (Mulpleta)----------FDA onayı: 31.07.2018
- ----------
- KRY, anemi/diyaliz+/_, HIV li zidovudin
- Retacrit epoetin alfa=biobenzer
- (Epoetin alfa, Epogen in biobenzeri)----------FDA onayı: 15.05.2018

SONUÇ

-Monoklonal tedavi yaklaşımları

-Refrakter ve krn ITP de tedavi yaklaşımları

-MRD nin prognostik önemi

-Relaps –refrakter Akut lösemide tedavi seçenekleri

-Mezenşimal kök hücre ve kullanımı

-Hemofilide yenilikler

-İnvaziv mantar enfeksiyonları profilaksisi

-Tromboz genetiği

-CAR-T cell

-KML-TKI kullanımına son verilebilir mi?


2018 YILI HEMATOLOJİK HASTALIKLARA NE GETİRDİ?

SONUÇ

Kanseri tedavi etmek için

Sadece kanser hücre mekanizmaları değil

Bireyin immün sistemini baskılayan, kanserin bu silahını elinden alan bir dönem başlamış bulunuyor

Anti-tümöral immün yanıtın daha iyi anlaşılması ve yönetimi----------yakın geleceğin en ilginç alanlarından birini oluşturacaktır


Teşekkürler