AKUT LÖSEMİLERDE İMMUNOTERAPİ

Prof. Dr. Zeynep KARAKAŞ

İ.Ü. İstanbul Tıp Fakültesi

Pediatrik Hematoloji/Onkoloji Bilim Dalı,İSTANBUL

zeynepkar@hotmail.com

Akut lösemiler

- ✓ Çocukluk çağının en sık görülen malignitesi; %80 ALL
- ✓ Çoğu 20 yaşın altında (median 14 yaş).
- ✓ Çocukluk çağı ALL'sinde beş yıllık EFS dramatik olarak arttı. OS: %90
- ✓ Adolesan ve genç erişkinlerde OS:%42-63 arasında
- ✓ Kırk yaşından büyük erişkinlerde: %24-17.7 arasında
- ✓ %15 şanssız hastanın relaps yapacağını öngörebilmekteyiz.

1. Hochberg J et al. Humoral and Cellular Immunotherapy in ALL in Children, Adolescents, and Young Adults. Clinical Lymphoma, Myeloma & Leukemia, 2014,14:3, 6-13.

2. Lee DW et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385: 517-528.

Refrakter ve relaps lösemi

- ✓ **Prognoz hala kötüdür ve tek tedavi seçeneği allojenik kemik iliği naklidir.**
- ✓ **Dirençli hastalarda allojenik kemik iliği naklinin başarısı, kanser hücrelerini aktif olarak yoketmede immün sistemin büyük potansiyeline dikkati çekti.**
- ✓ **Humoral ve hücresel immunoterapi kanser tedavisinde seçenek oldu.**
- ✓ **İmmunoterapi bugün umut vaat eden hedefli antikanser stratejilerden biridir.**

Hochberg J,El-Mallawany NK, Cairo MS. Humoral and Cellular Immunotherapy in ALL in Children, Adolescents, and Young Adults. Clinical Lymphoma, Myeloma & Leukemia, Vol. 14, No. S3, S6-13, 2014

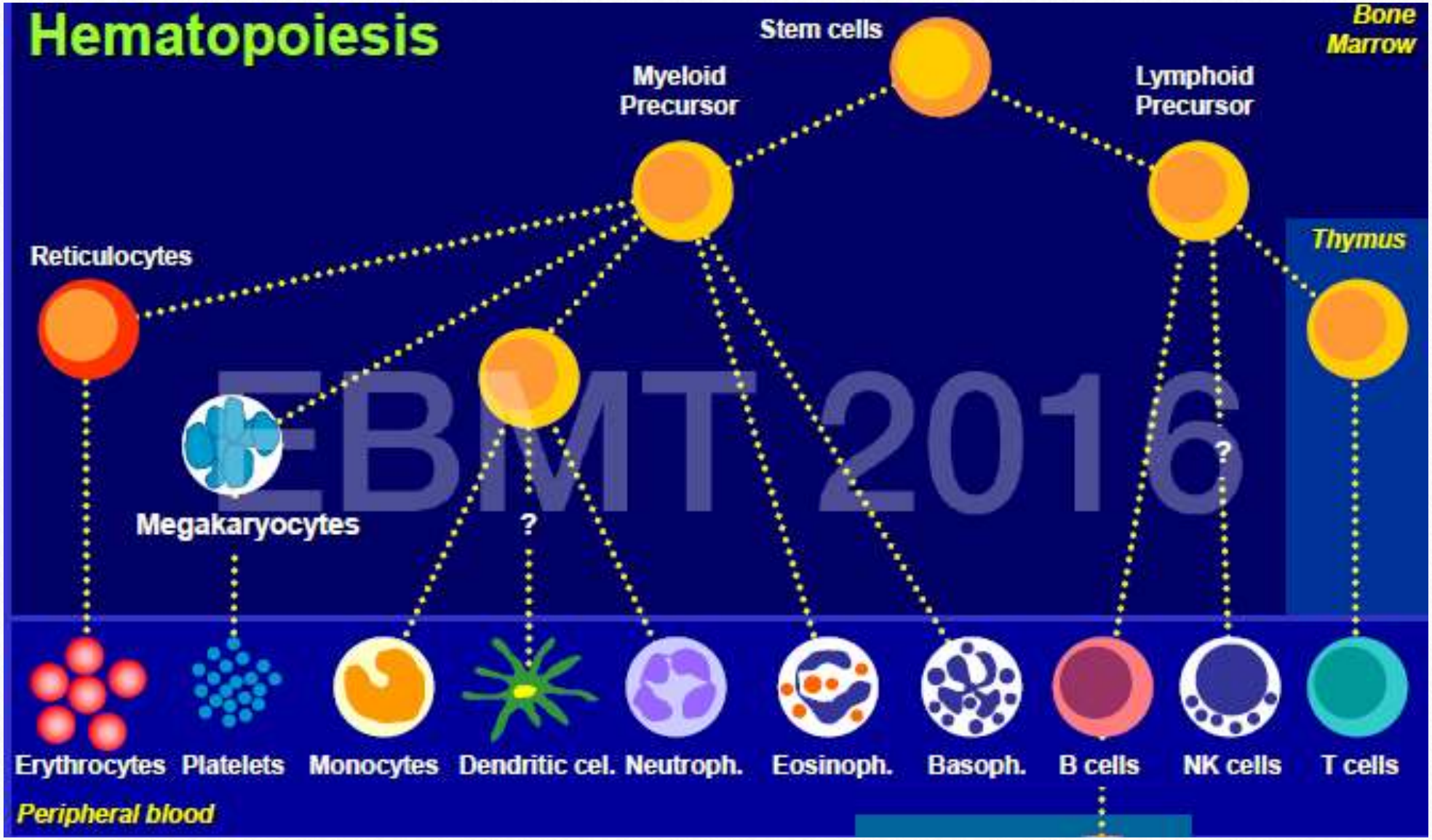
Science dergisi, 2013'ün en önemli gelişmesini 'Kanser immunoterapisi' olarak belirledi.

İMMUNOTERAPİ

Kanserle mücadele için vücudun doğal savunma sistemlerini harekete geçirir, hastalıkla mücadeleyi organizmanın yapmasını sağlar.

Tümörü değil, immün sistemi hedefler.

Kanser tedavisinde farklı bir yol


Hematopoiesis
Bone Marrow
Stem cells
Myeloid Precursor
Lymphoid Precursor
Thymus
Reticulocytes
Megakaryocytes
?
?
EBMT 2016
Erythrocytes
Platelets
Monocytes
Dendritic cel.
Neutroph.
Eosinoph.
Basoph.
B cells
NK cells
T cells
Peripheral blood

TÜMÖRLERE KONAK YANITI

HÜCRESEL İMMÜNİTE

- ✓ Sitotoksik T lenfositler (CTL)
- ✓ NK hücreleri
- ✓ Makrofajlar

HUMORAL İMMÜNİTE

Konak tümör hücrelerine konağın yaptığı antikorlar veya (their constituens for tumour antigens))

TÜMÖRLERE KONAK YANITI/HÜCRESEL İMMÜNİTE

Sitotoksik T lenfositler (CTL)

- ✓ Tümörlere karşı majör immün savunma mekanizmasıdır
- ✓ Virusla ilişkili tümörlerden korur
- ✓ (EBV ilişkili, HPV ilişkili tm ler)

NK hücreleri

- ✓ Önceden duyarlılaşmadan tümör hücrelerini öldürebilir.
- ✓ **IL-2 ve IL-15** ile aktive olduktan sonra tümör hücrelerini parçalayabilir.
- ✓ Hücreleri tümöre dönüştürecek DNA hasarını ve stress antijenlerini tanımlar.

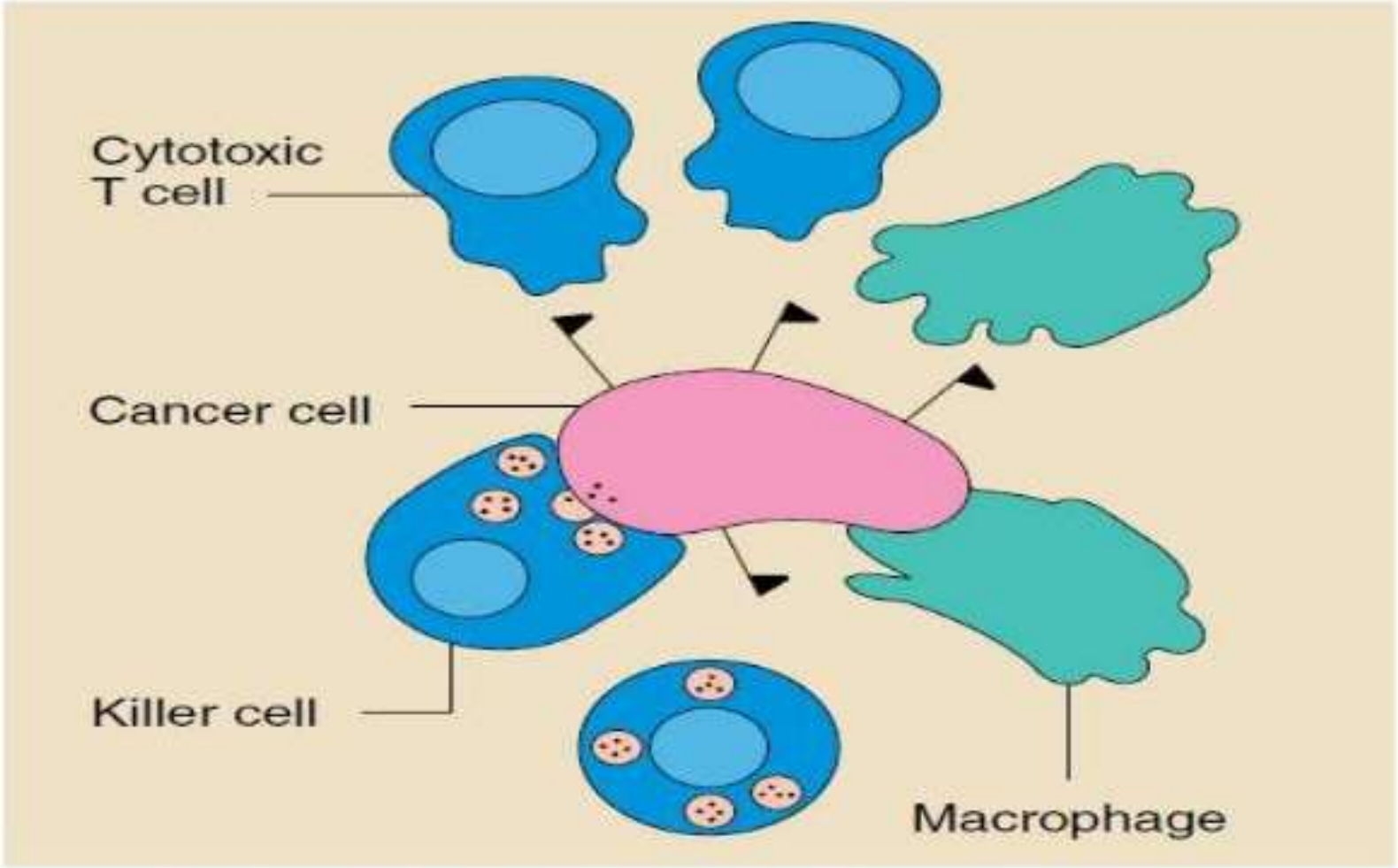
Makrofajlar

- ✓ Aktive makrofajlar in vitro tümör hücrelerine sitotoksiktirler.
- ✓ Mikroplara benzer şekilde tümör hücrelerini öldürebilirler (TNF salgılama..)

T hücreleri ve NK hücreleri tarafından salgılanan İnterferon γ makrofajları uyarır.

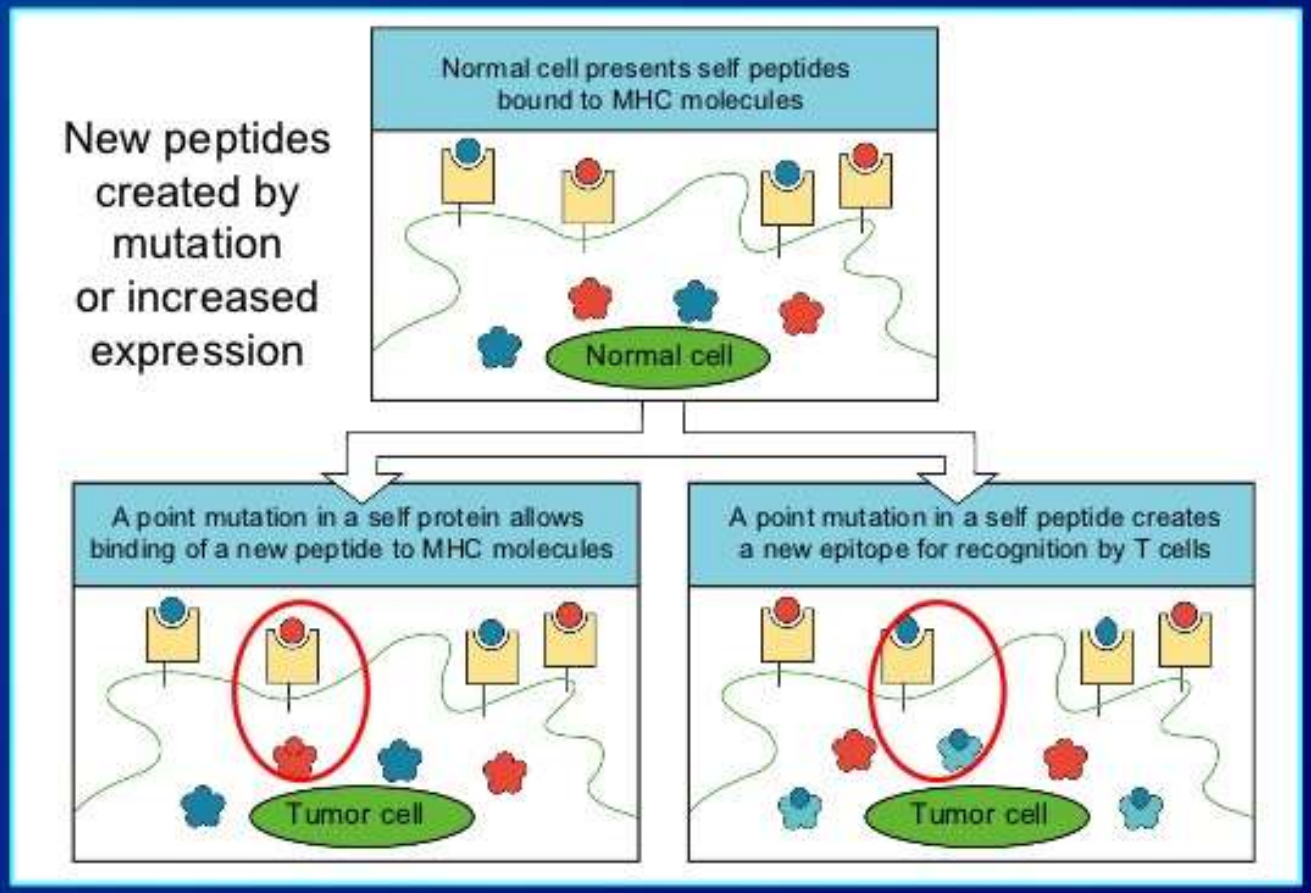
T hücreleri, NK hücreleri ve makrofajlar tümör hücrelerini öldürmede işbirliği yaparlar.

TÜMÖRLERE KONAK YANITI



A cancer cell can rouse several types of immune defenses.

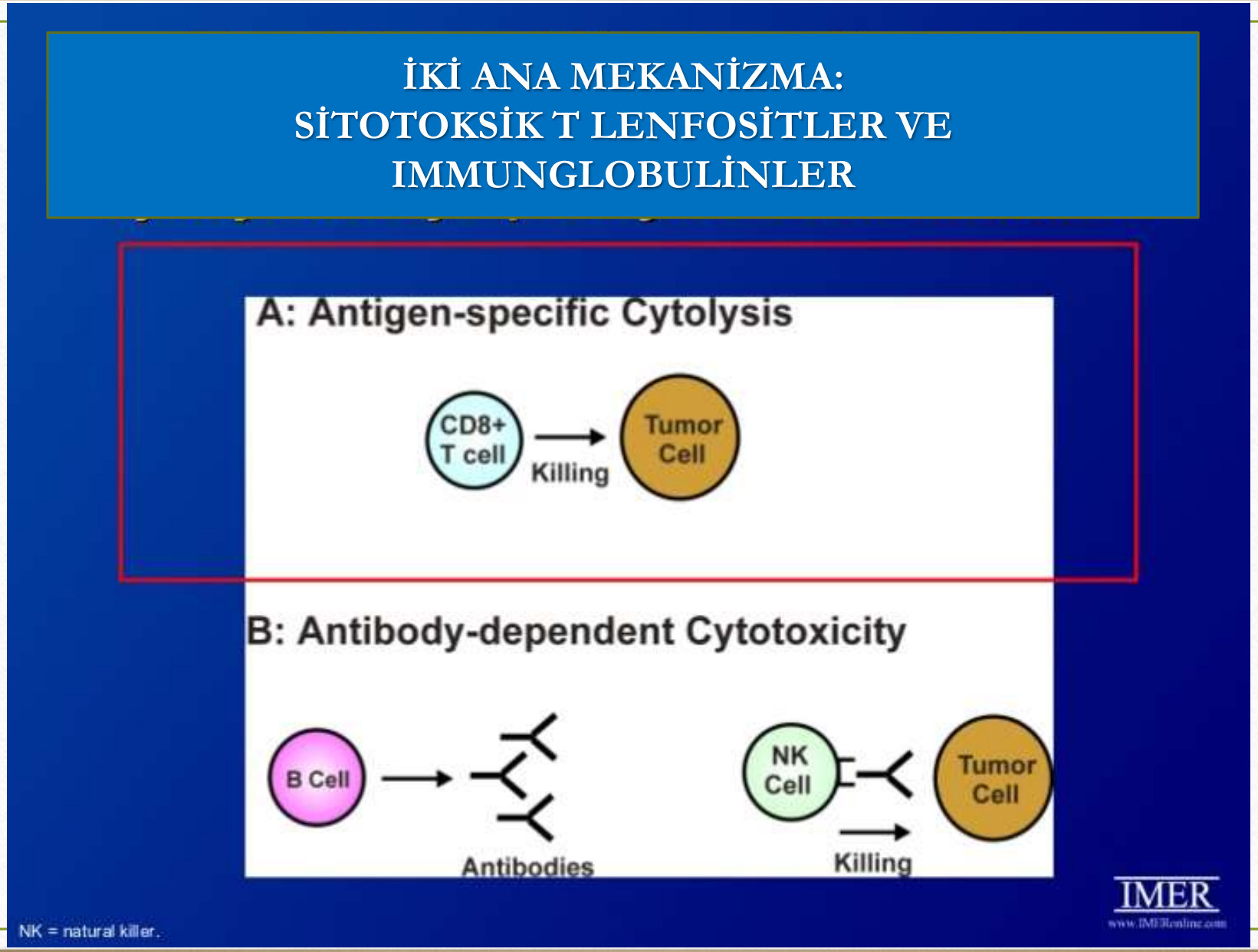
KANSER HÜCRELERİNDEKİ GENETİK DÜZENSİZLİK İMMÜN SİSTEM TARAFINDAN TANINAN ANTİJENLERİ OLUŞTURUR



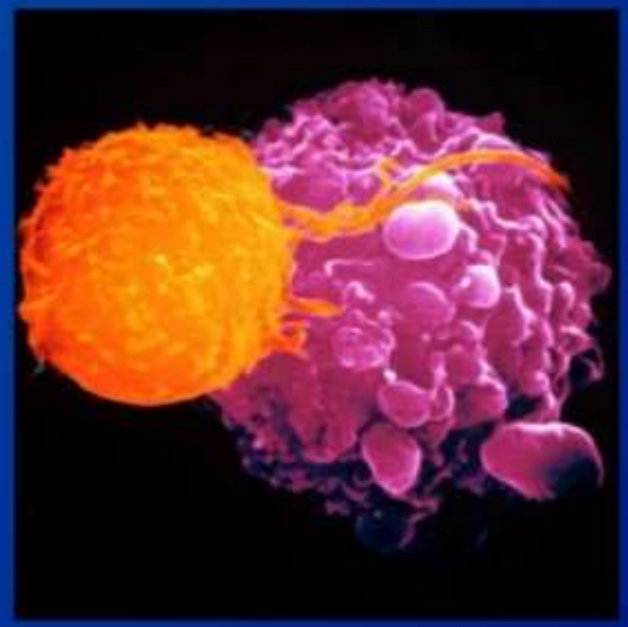
MHC = major histocompatibility complex.
www.immunoweb.com/tu10.htm

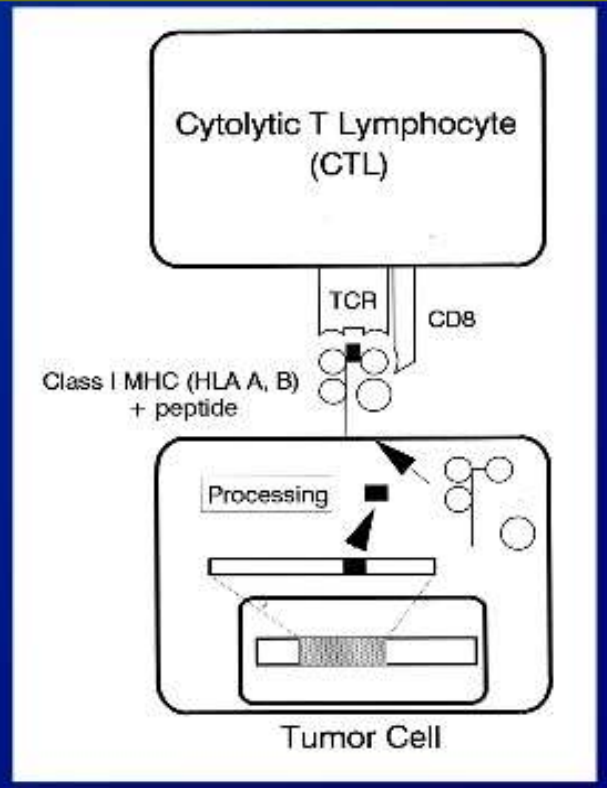
IMER

İKİ ANA MEKANİZMA: SİTOTOKSİK T LENFOSİTLER VE IMMUNGLOBULİNLER



CD +8 sitotoksik T lenfositler antijen eksprese eden tümör hücrelerini öldürür





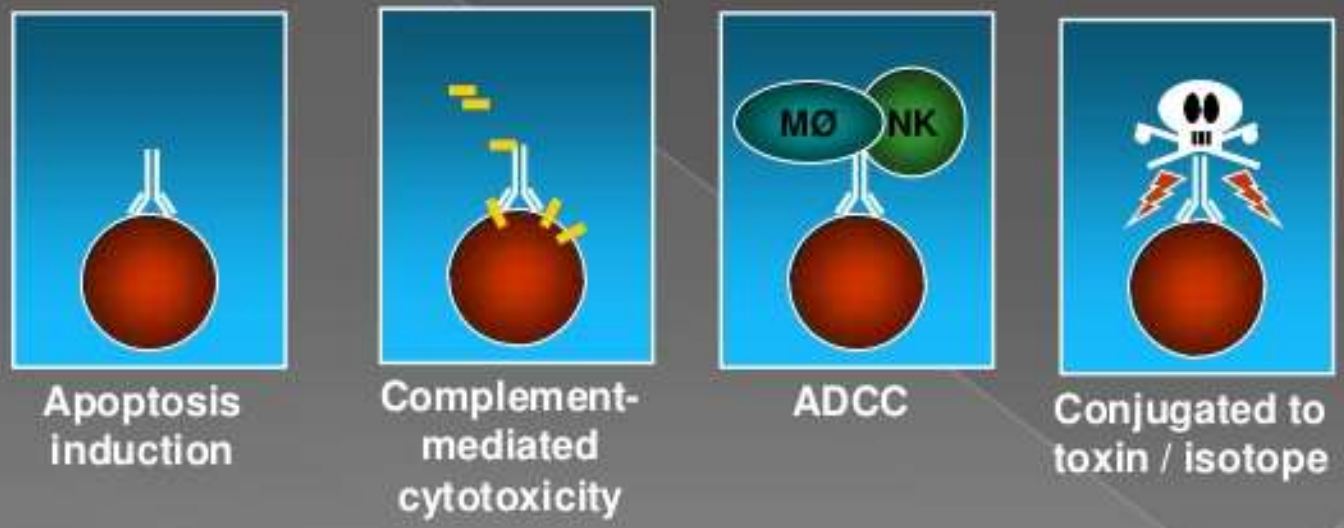
How Do These CD8+ T Cells Initially Become Activated to Fight Tumors?

TCR = T-cell receptor.
Boissonnas et al, 2007.

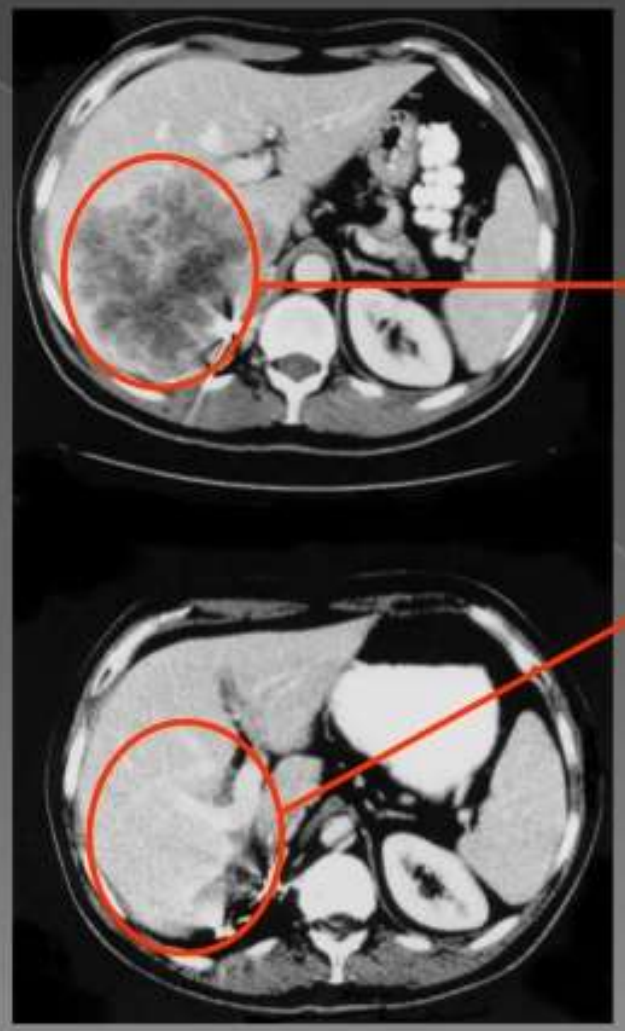
IMER

MONOKLONAL ANTİKORLAR

- Adminstration of monoclonal antibodies which target either tumour-specific or over-expressed antigens.
- Kill tumour cells in a variety of ways:



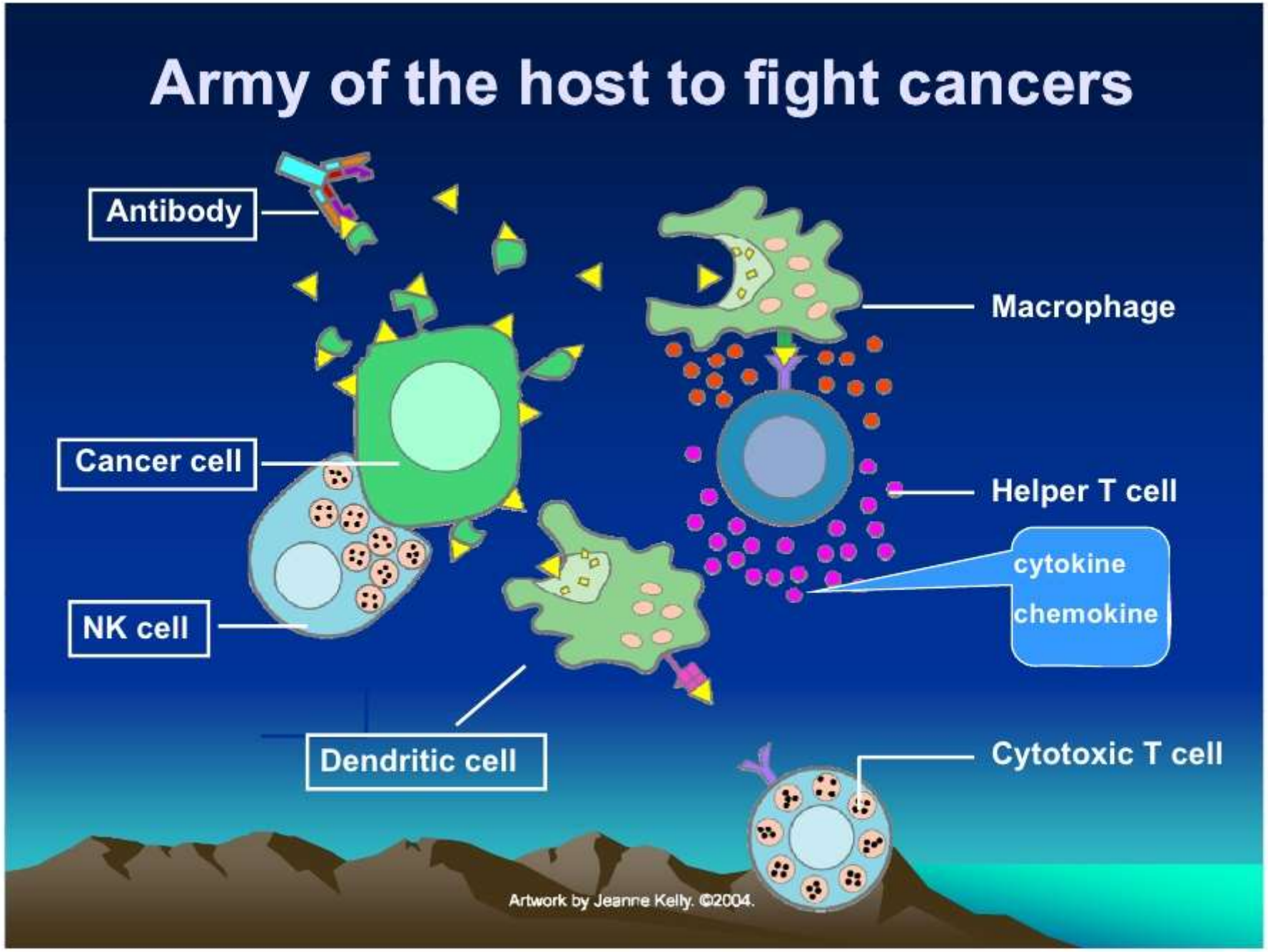
Effective therapies



Complete regression of a large liver metastasis from kidney cancer in a patient treated with IL-2.

Regression is ongoing seven years later

Rosenberg (2001) Nature, 411:381-4


Army of the host to fight cancers
Antibody
Macrophage
Cancer cell
Helper T cell
cytokine
chemokine
NK cell
Dendritic cell
Cytotoxic T cell
Artwork by Jeanne Kelly. ©2004.

Pediatrik Tümörlerde Niçin İmmünoterapi?

Yoğun kemoterapi
Çoklu ilaç tedavisi

→ Çocukluk çağı kanserlerinde daha iyi gidiş

Çözülmemiş konular

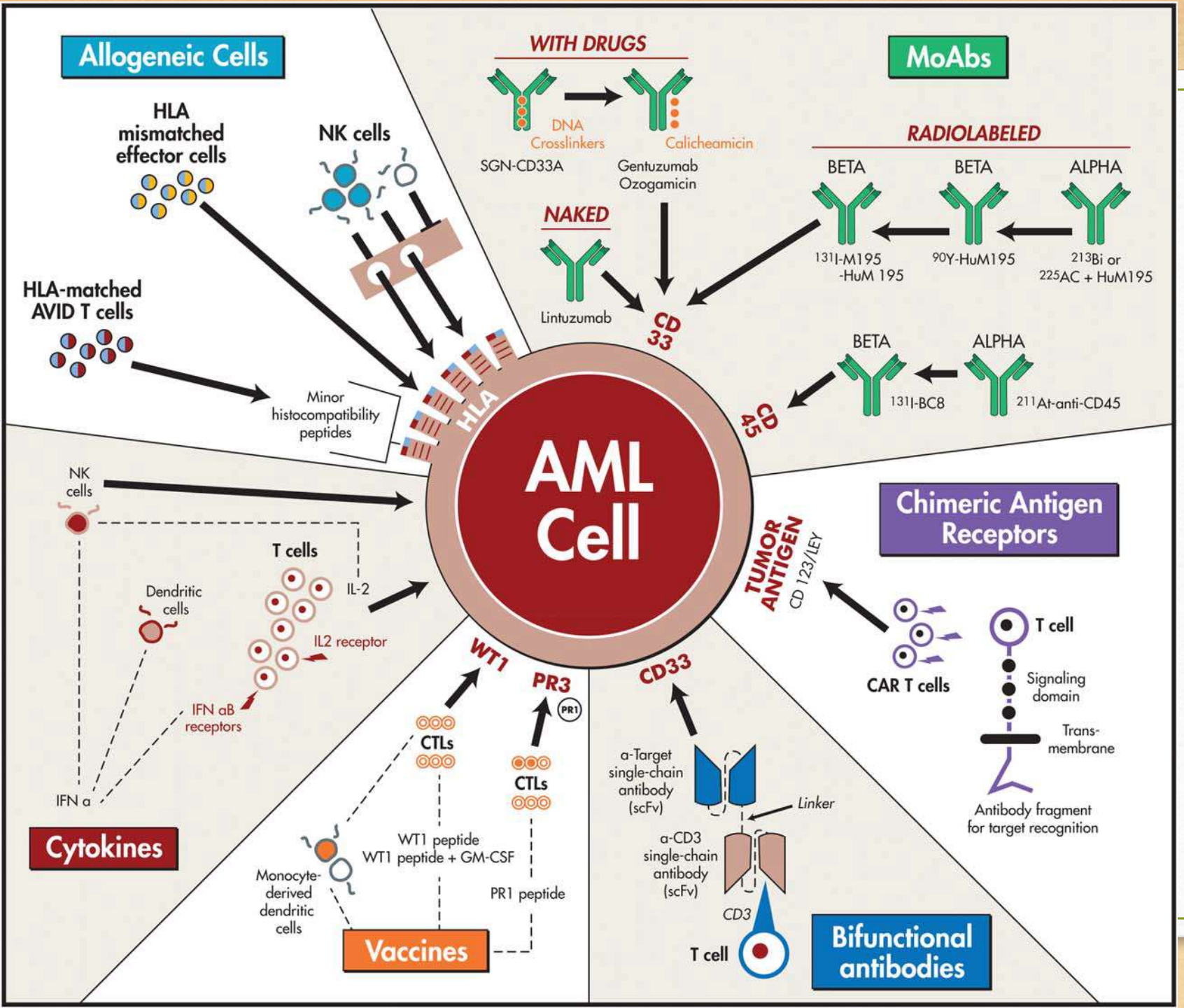
Refrakter ve relaps hastalar nasıl tedavi edilmeli?

Yoğun kemo/radyoterapiye bağlı toksisiteler nasıl yönetilmeli?

→ Target (hedef) tedaviler

İMMÜNOTERAPİ

- ✓ Adoptif T hücre tedavisi (AIT)
- ✓ Pasif immunoterapi-mAb
- ✓ Aktif immunoterapi-Aşılar



- ✓ Monoklonal antikor tedavisi,
- ✓ Antikorla birleşmiş bispesifik T ve NK hücreleri,
- ✓ Genetik olarak yeniden düzenlenmiş T hücreleri ve
- ✓ Kimerik antijen reseptörlerini hedefleyen NK hücreleri

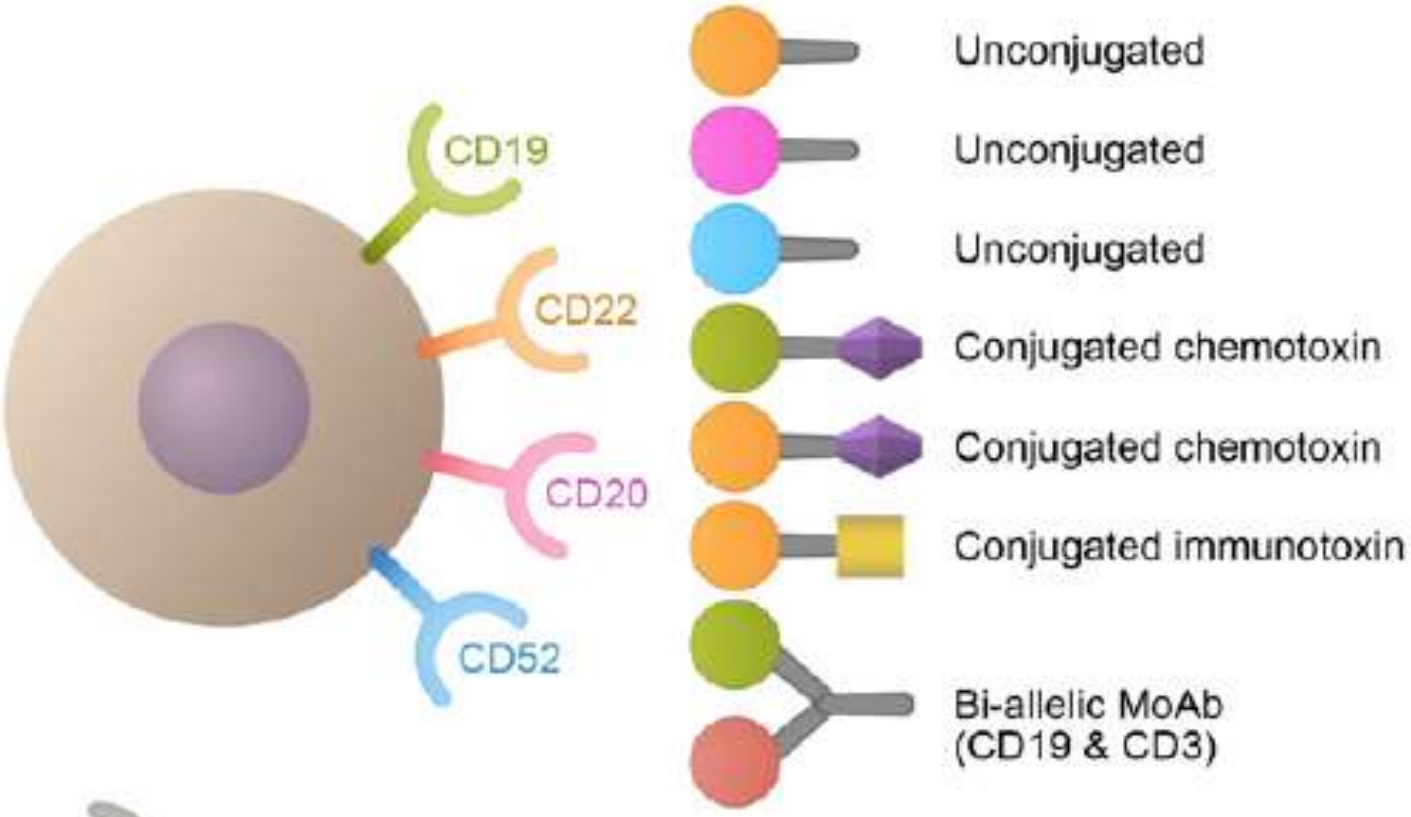
Grosso DA, Hess RC, and Weiss MA. Immunotherapy in Acute Myeloid Leukemia. Cancer August 15, 2015, 2689-2704.

İMMÜNOTERAPİ/GERÇEK HAYAT

- ✓ **İlk başarılı sonuçlar anti-CD20 monoklonal antikorları ile,**
- ✓ **Tek başına veya kombinasyon olarak anti-CD22 ve anti-CD19 antikor ted,**
- ✓ **Hedefli kimerik antijen reseptörleri içeren genetiği değiştirilmiş T ve NK hücreleri dirençli tümör hücrelerini yoketmek için yeni bir alternatif oluşturabilir.**
- ✓ **Humoral ve hücresel kombine immunoterapi çocuk adolesan ve genç erişkinlerdeki yüksek riskli ALL'de tedavi seçeneği olabilir.**

Hochberg J et al. Humoral and Cellular Immunotherapy in ALL in Children, Adolescents, and Young Adults. Clinical Lymphoma, Myeloma & Leukemia, 2014,14:3, 6-13.
Grosso DA et al. Immunotherapy in Acute Myeloid Leukemia. Cancer 15: 2689-2704, 2015.

BLOOD, 25 JUNE 2015 • VOLUME 125, NUMBER 26



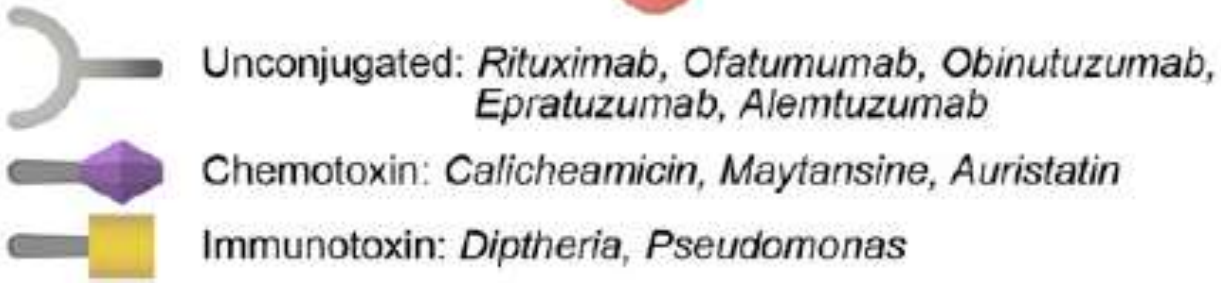


Figure 1. Schema of different monoclonal antibodies.

Jabbour E et al. Monoklonal antibodies in acute lymphoblastic leukemia. Blood,125:26, 4010-16,2015

Humoral İmmünite/Monoklonal antikor tedavileri

- Normal hücreye zarar vermeden tümör hücresine özgül sitotoksisiteye yol açmaktadır.
- Monoklonal antikorlar laboratuvarda üretilen proteinlerdir; tümör hücresini doğrudan öldürür ya da bağışıklık sistemini uyararak onun ölümünü uyarır.
- Bazı monoklonal antikorlar radyoaktif izotop ya da toksine bağlanır. Bu durumda antikor tümör hücresini öldürecek ajanın vericisi konumuna geçer.

Monoklonal antikorların avantajları

Hedef tümör hücresine daha spesifik

Etki mekanizması konvansiyonel kemoterapiden farklı

Genellikle daha güvenli

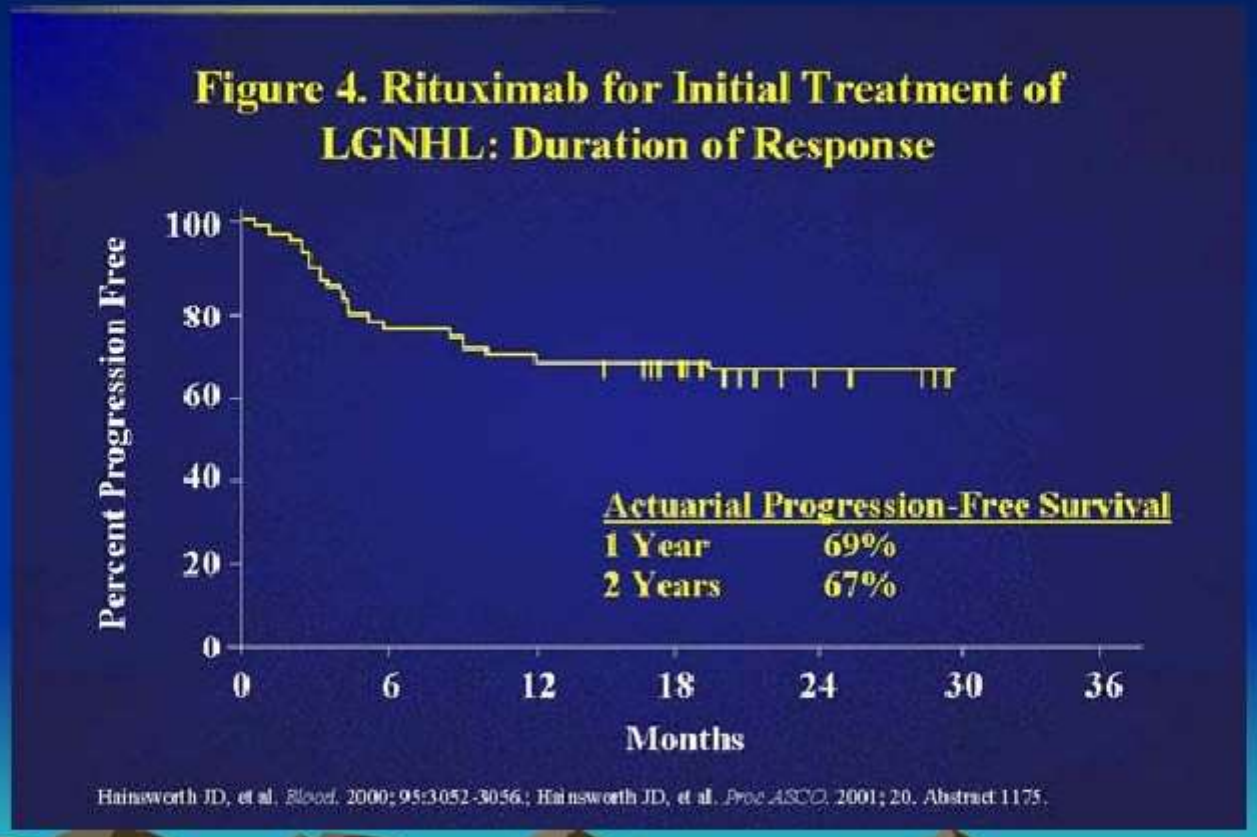
Barth M et al. British J Haematol 2012

Rituximab

- İlk olarak çocukluk çağı B-hücreli lenfomalarda ICE (ifosfamide, carboplatin, ve etoposide) relaps tedavisine eklendi.
- Başarılı sonuçlar standart BFM ve COG B hücreli lenfoma protokollerine girmesini sağladı.
- Kemik iliği ve /veya MSS tutulumu olan hastalarda 3 yıllık yaşam belirgin olarak arttı, bu başarı pediatrik malignitelerde monoklonal antikor tedavisinin gelişmesini sağladı.

Antibody Therapy

Rituximab: The first approved antibody by FDA in clinical trial.
Targeting CD20. low-grade non-Hodgkin lymphoma



Pre B ALL

- B-ALL hastalarının %93 kadarı indüksiyon kemoterapisi ile remisyona girer
- Ancak bunların %50'sinden fazlasında 5 yıl içinde relaps olur.
- Minimal rezidüel hastalık varlığında, büyük yaşlarda ve sitogenetik anomali varlığında ilk remisyonda kemik iliği nakli önerilmektedir.
- Yoğun kemoterapi ve kemik iliği nakline rağmen, pre-B-ALL'de relaps riski yüksektir ve tedavide yeni seçeneklere ihtiyaç vardır.

Vaka:

7 yaşında kız hasta

Solukluk, halsizlik

Derin anemi (Hb: 3…,trombositopeni)

Hepatosplenomegali

PreB ALL, t(17,19) mutasyonu

7.gün steroid yanıtsız,15. ve 33. gün yanıtsız (%7 dirençli hasta)

Donorü vardı ancak KİT olsa bile yaşayan hiç hasta yok.

Blinatumomab için klinik çalışmaya girdi (İsviçre, Faz III)

Remisyona girdi, KİT oldu, yaşıyor.

preB ALL'de Blinatumomab

- ✓ Prekursor B ALL ilik dışı bölgeleri sıklıkla tutan ve öncül B hücrelerinden kaynaklanan ALL türüdür.
- ✓ Erken pro-B lenfoblastlar tipik olarak CD 19, sitoplazmik CD 22 ve CD 34 ekprese eder. Tipik olarak CD 20 taşımazlar, TDT taşıyabilirler.
- ✓ Geç pro-B hücreler genellikle CD19,CD10,CD79a ve TdT taşırlar. Bazen CD20 ve yüzeyel CD22 ekprese edebilirler. PreB hücreleri ise sitoplazmik immunglobulin μ zinciri taşırlar.
- ✓ B hücre immunfenotipi hedefli tedavi için kılavuzdur.
- ✓ B hücre gelişiminin tüm aşamalarında CD19 olması blinatumomab tedavisi için önemlidir.

CD 19: B hücre malnitelerinde ideal tümör hedefi

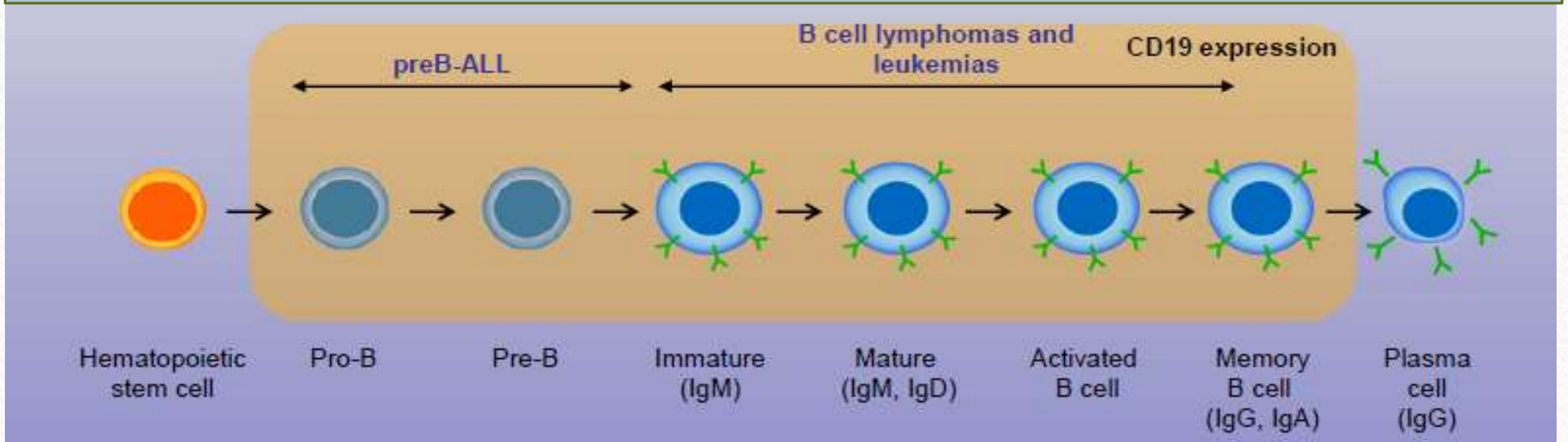
Hematopoietik kök hücrelerde bulunmaz.

CD19 plazma hücreleri dışında B hücre gelişiminin tüm evrelerinde eksprese edilir.

Birçok B hücre malinitelerinde bulunur:

B-ALL, CLL, DLBCL

CD 19 antikorları tümör hücresinin büyümesini önler.

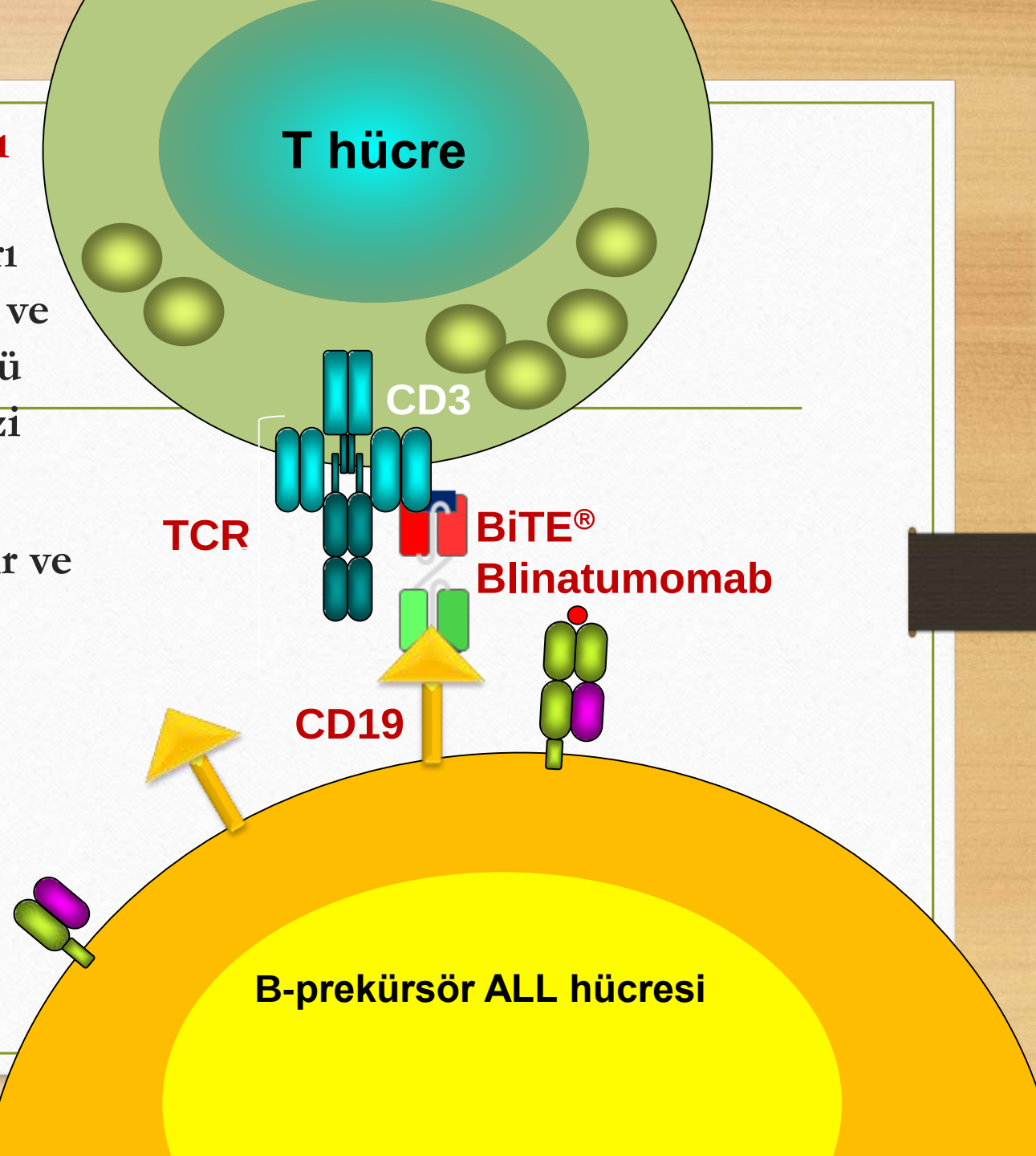


1. Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397
Image adapted from Janeway CA, Travers P, Walport M, et al. *Immunobiology*. 5th ed. New York, NY: Garland Science; 2001:221-293; Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397; and Feldman M, Marini JC. Cell cooperation in the antibody response. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Maryland Heights, Missouri: Mosby;2001:131-146.

Blinatumomab, BiTE® Antikor Yapısı

- ✓ Bispecific T-cell engager (BiTE) antikorları hedef hücrenin yüzey antijenlerine (CD19) ve aktive T cell reseptörlerine (TCRs) iki yönlü bağlanarak sitotoksik T hücre ilişkili sitolizi kolaylaştıran monoklonal antikorlardır.
- ✓ CD 19 B hücre soyunun en erken antijenidir ve bu durum onu B hücre malinitelerinde tedavinin hedefi haline getirmiştir
- ✓ r/r Ph-negatif ALL'de monoterapi olarak

  %43 CR



1. Bargou R, et al. *Science* 2008;321:974–977.
2. Raponi S, et al. *Leuk Lymphoma* 2011;52:1098–1107.
3. Piccaluga P, et al. *Leuk Lymphoma* 2011;52:325–327.
4. Topp MS, et al. *Lancet Oncol* 2015;16:57–66.

Blinatumomab*

- ✓ CD19+ B-hücreleri ve CD3+ T-hücreleri blinatumomab aracılığıyla bağlanınca

  T-hücreleri ve kanser hedef hücreleri arasında sitolitik bir sinaps oluşur:

  Sitotoksik T-hücreleri granzim ve perforin salgılar.

- ✓ Perforinler kalsiyum varlığında hedef B-hücre membranına granzimin girmesi için bir delik açar. Granzimler programlanmış hücre ölümünü (apoptosis) aktive eder; DNA parçalanması, poli-ADP riboz polimeraz (PARP) bölünmesi ve kaspazların aktivasyonu yoluyla apoptoz olur.
- ✓ T-hücreleri ayrıca salgıladığı enflamatuar sitokinler aracılığıyla ek granzim ve perforin oluşumunu sağlar. Aktive olan T hücreleri hücre siklusuna girerek T hücre kompartımanının genişlemesini ve hedef dokularda T hücre sayısının artmasını sağlar.
- ✓ *** Blincyto, Amgen INC, Thousand Oaks, CA,** CD19'a ve T-cell reseptörlerine iki yönlü olarak bağlanan spesifik bir monoklonal antikor olan, çeşitli B hücre malignitelerinde kalıcı remisyon sağlayan tedavi olarak Aralık 2014'de **FDA tarafından onaylanmıştır.**

VİDEO

- ✓ **Blinatumomab klinik çalışmaları 2001 yılında şempanze modelleriyle başladı.**

  İlk insan çalışmaları NHL, KLL'de yapıldı.

Rank	Status	Study
1	Recruiting	**Blinatumomab in Treating Younger Patients With Relapsed B-cell Acute Lymphoblastic Leukemia** **Conditions:** B Acute Lymphoblastic Leukemia; Recurrent Adult Acute Lymphoblastic Leukemia; Recurrent Childhood Acute Lymphoblastic Leukemia **Interventions:** Procedure: Allogeneic Hematopoietic Stem Cell Transplantation; Drug: Asparaginase; Biological: Blinatumomab; Drug: Cyclophosphamide; Drug: Cytarabine; Drug: Dexamethasone; Drug: Etoposide; Other: Laboratory Biomarker Analysis; Drug: Leucovorin Calcium; Drug: Mercaptopurine; Drug: Methotrexate; Drug: Mitoxantrone Hydrochloride; Drug: Pegaspargase; Other: Pharmacological Study; Drug: Therapeutic Hydrocortisone; Drug: Thioguanine; Drug: Vincristine Sulfate
2	Active, not recruiting	**Clinical Study With Blinatumomab in Pediatric and Adolescent Patients With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia** **Condition:** Acute Lymphoblastic Leukemia **Intervention:** Drug: blinatumomab
3	Recruiting	**Study of Blinatumomab in Japanese Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia** **Condition:** Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) **Intervention:** Drug: Blinatumomab
4	Recruiting	**Phase 3 Trial of Blinatumomab vs Standard Chemotherapy in Pediatric Subjects With HR First Relapse B-precursor ALL** **Condition:** Leukemia, Acute Lymphoblastic **Interventions:** Drug: Blinatumomab; Drug: Conventional Consolidation Chemotherapy
5	Available	**Expanded Access Protocol of Blinatumomab in Pediatric and Adolescent Subjects With Relapsed and/or Refractory B-precursor Acute Lymphoblastic Leukemia (ALL)** **Condition:** Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL)

Pediatrik klinik çalışmalar

- **Daha önce KİT yapılmış 9 hastada 28 gün boyunca Blinatumomab 5 veya 15 µg/kg/gün dozunda verilmiş, 7-14 günlük dinlenme döneminin ardından yanıtlılarda aynı doz konsolidasyon tedavisi olarak verilmiştir.**
- **İlk kürden sonra hastaların 4'ü remisyona girmiştir. Hastaların 3'ü 1490 gün sonra sağ ve sağlıklı olup kür oranı %30 'dur.**
- **Bu verilerle çocuklarda relaps/refrakter B-lösemi hastalarında Blinatumomab tedavisinin bir seçenek olabileceği ancak daha fazla bilgiye ihtiyaç olduğu bildirilmiştir.**

- Larry W. Buie LW, Pecoraro JJ, Horvat TZ,Daley RJ. Blinatumomab: A First-in-Class Bispecific T-Cell Engager for Precursor B-Cell Acute Lymphoblastic Leukemia. Annals of Pharmacotherapy 2015, 49(9): 1057–1067

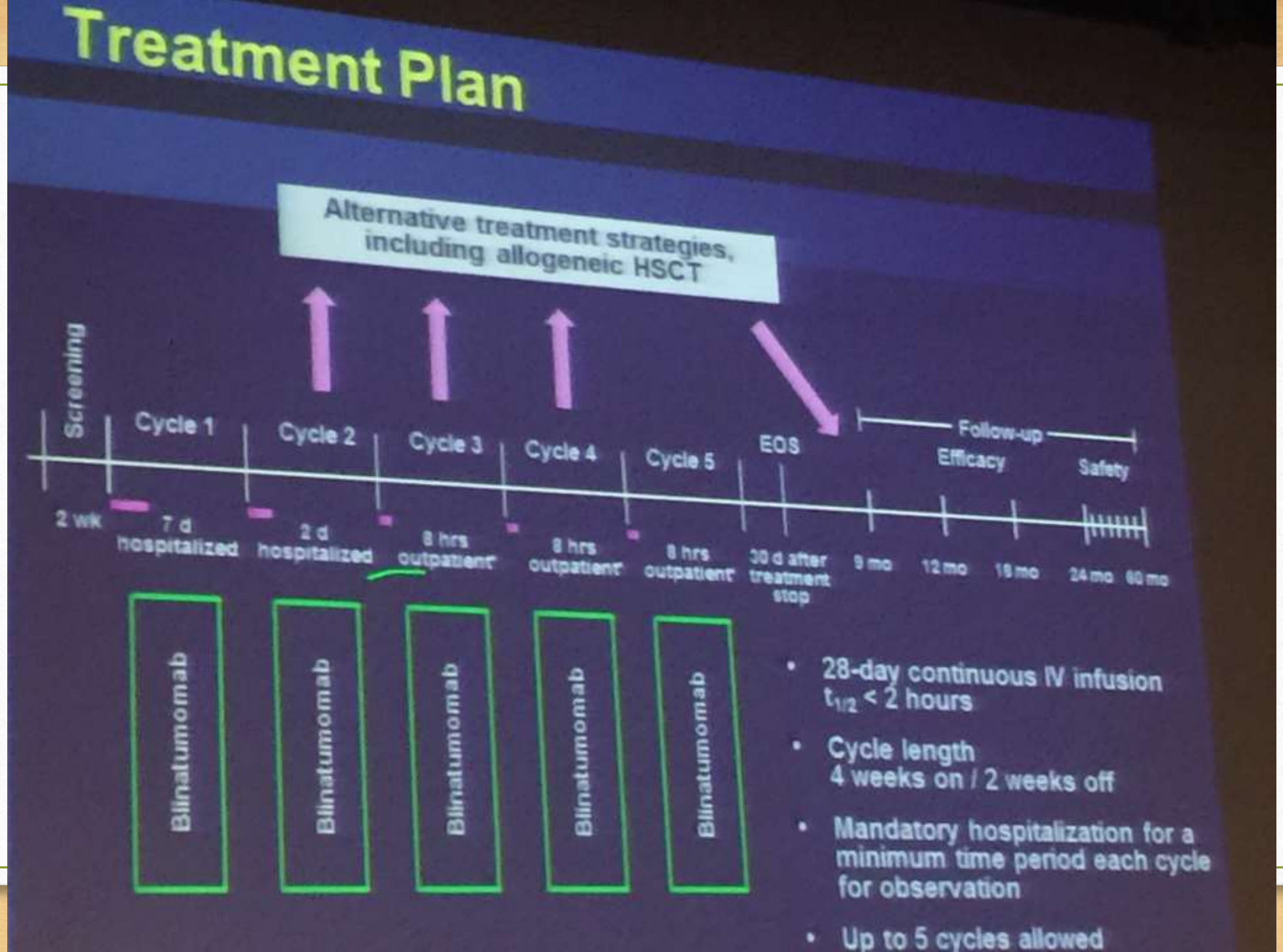
Relaps/Refrakter lösemi/ Faz I/II çalışması

- ✓ **Relaps/refrakter 41 çocuk hastada blinatumomab doz çalışması yapılmıştır.**
- ✓ **Hastalar daha önceden KİT dahil çok yoğun kemoterapi almış hastalar olup doz yaş gruplarına göre ayarlanmıştır**
- ✓ **2-6 yaş ve 7-17 yaş, median 2 kür.**
- ✓ **Hastaların %32'sinde (n:13) tam remisyon sağlanmıış olup 10 hastada MRD negatif bulunmuş ve 9 hasta KİT'e gitmiştir. Tam remisyon sağlanan hastalarda relapsız sağkalım 8.7 ay olarak bildirilmiştir.**

Larry W et al. Blinatumomab: A First-in-Class Bispecific T-Cell Engager for Precursor B-Cell Acute Lymphoblastic Leukemia. Annals of Pharmacotherapy 2015, 49(9): 1057–1067

Shah NN et al. Immunotherapy for pediatric leukemia. Frontiers in oncology,3:1-9,2013

Treatment Plan



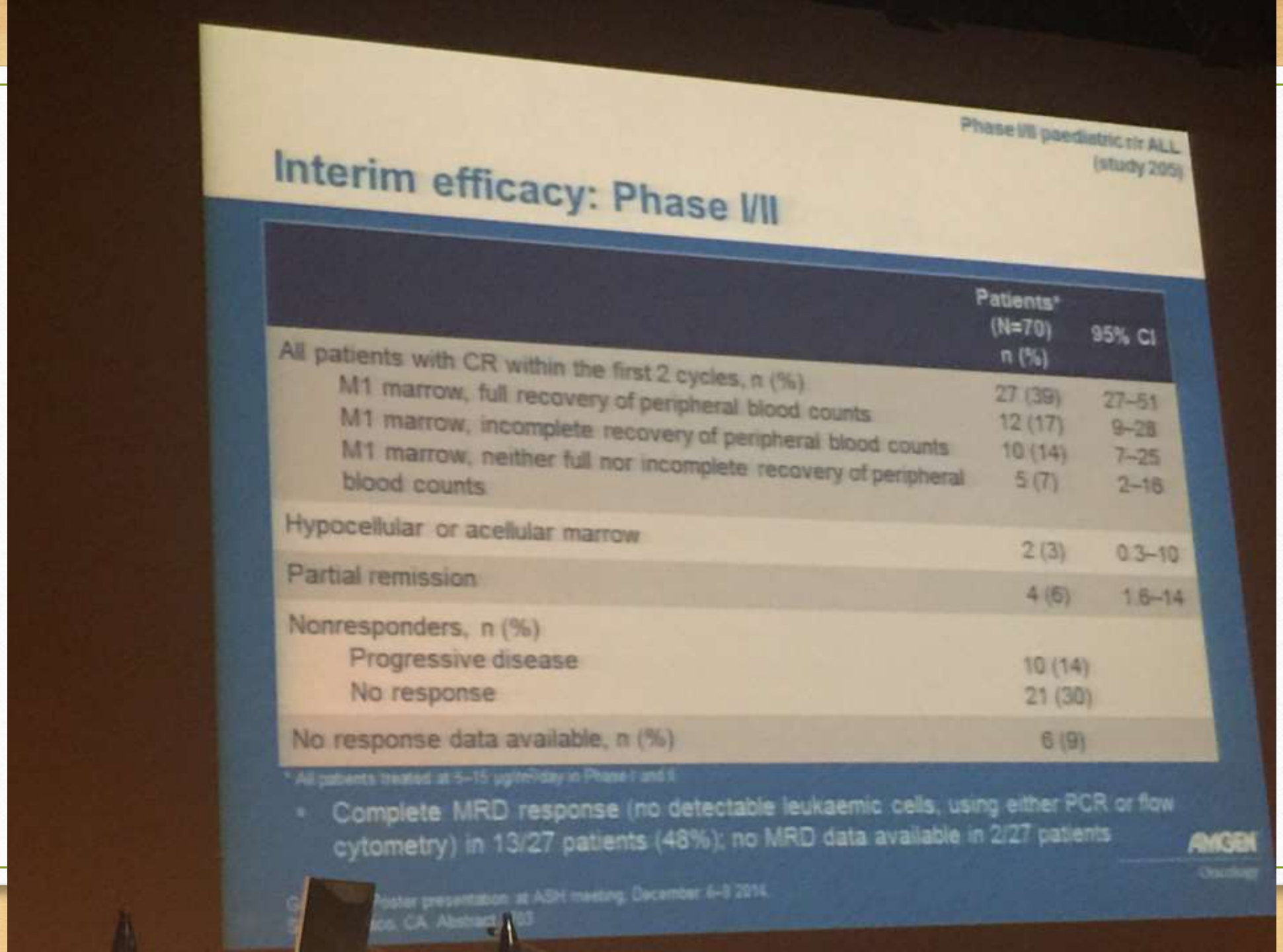
- 28-day continuous IV infusion $t_{1/2} < 2$ hours
- Cycle length
  4 weeks on / 2 weeks off
- Mandatory hospitalization for a minimum time period each cycle for observation
- Up to 5 cycles allowed

Dahil edilme kriterleri

B cell prekürsör ALL
<18 yaş altı
Organ fonksiyonları ve performansı iyi hastalar
Relaps/Rezistan hastalar
Standart indüksiyon veya relaps tedavisine yanıtsız hastalar
≥2. Kİ relapsı
KİT sonrası relaps

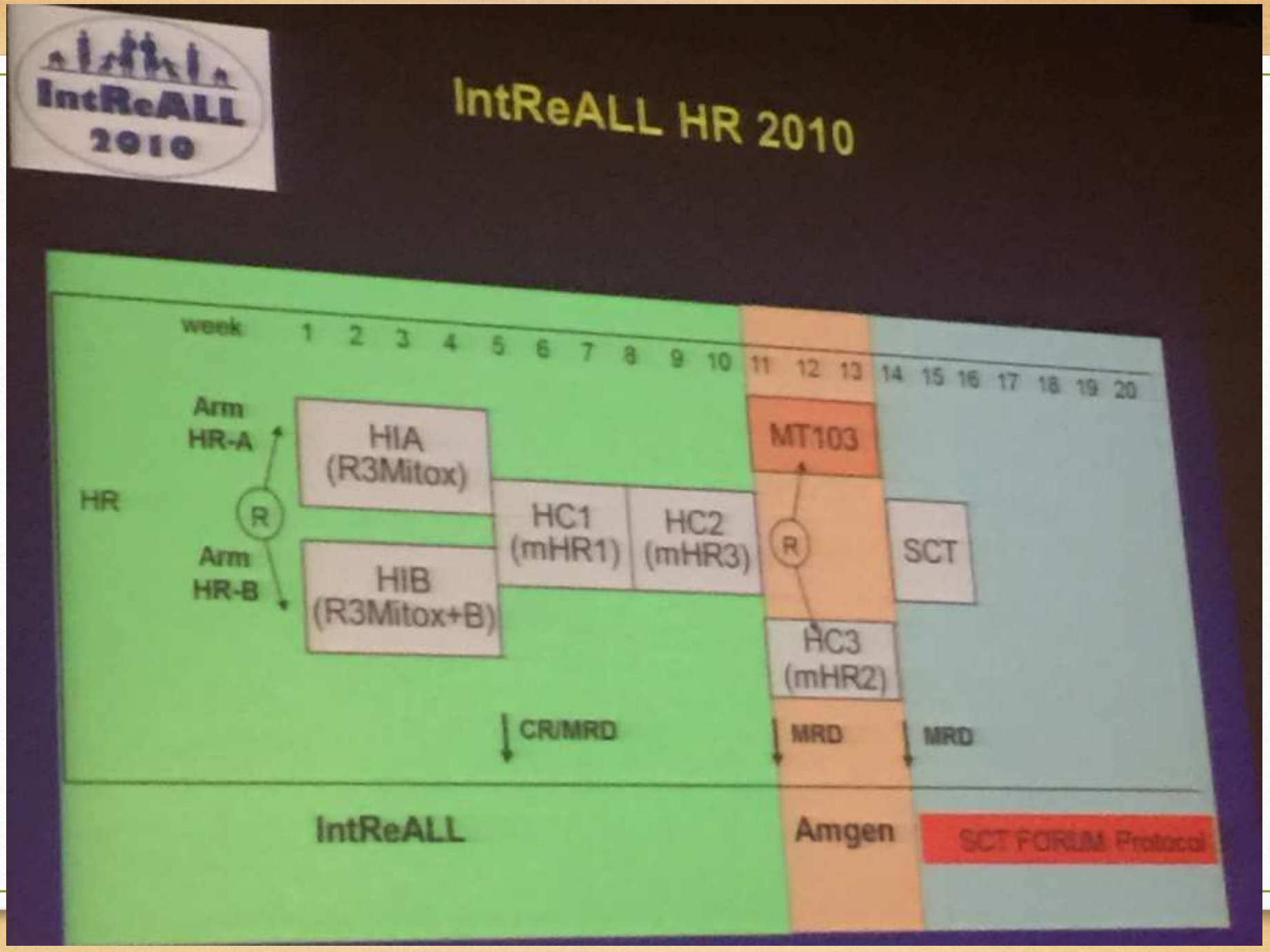
Dışlanma kriterleri

Kronik GVHD
MSS ve testis tutulumu olanlar
MSS patolojisi olanlar

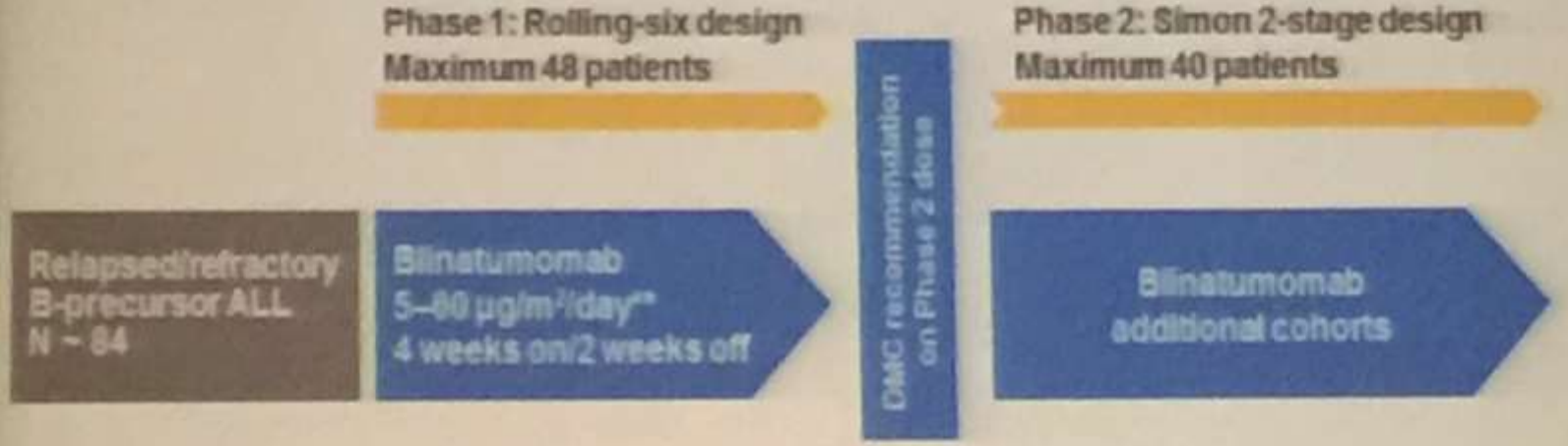

Phase I/II paediatric r/r ALL (study 205)
Interim efficacy: Phase I/II
Patients* (N=70) n (%)
95% CI
All patients with CR within the first 2 cycles, n (%) 27 (39) 27–51
M1 marrow, full recovery of peripheral blood counts 12 (17) 9–28
M1 marrow, incomplete recovery of peripheral blood counts 10 (14) 7–25
M1 marrow, neither full nor incomplete recovery of peripheral blood counts 5 (7) 2–16
Hypocellular or acellular marrow 2 (3) 0.3–10
Partial remission 4 (6) 1.6–14
Nonresponders, n (%)
Progressive disease 10 (14)
No response 21 (30)
No response data available, n (%) 6 (9)
* All patients treated at 5–15 µg/m²/day in Phase I and II
Complete MRD response (no detectable leukaemic cells, using either PCR or flow cytometry) in 13/27 patients (48%); no MRD data available in 2/27 patients
AMGEN
Oncology
Poster presentation at ASH meeting, December 6–9 2014.
CA. Abstract

Prekürsör B-ALL'li çocuklarda Blinatumomab kullanım endikasyonları

- Çoklu relaps olan hastalarda reindüksiyon
- Hematopoietik kök hücre naklinden sonra relaps olan hastalarda tedavi
- Kemik iliği nakli öncesi MRD pozitif olan hastalar


IntReALL 2010
IntReALL HR 2010
week 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
HR
Arm HR-A
Arm HR-B
R
HIA (R3Mitox)
HIB (R3Mitox+B)
HC1 (mHR1)
HC2 (mHR3)
MT103
R
HC3 (mHR2)
SCT
CR/MRD
MRD
MRD
IntReALL
Amgen
SCT FORUM Protocol

Phase 1/2 study of blinatumomab in paediatric* patients with r/r B-cell precursor ALL



Primary endpoint

- Phase 1: Maximum tolerated dose defined by ≤1 of 6 patients experiencing a dose-limiting toxicity (DLT) or maximal administered dose (MAD)
- Phase 2: Rate of CR within the first 2 cycles

Secondary endpoints

- Safety
- PK (Phase 1)
- CR rate in first 2 cycles (Phase 1)
- Time to haematological relapse
- Eligibility for alloSCT after blinatumomab (Phase 2)
- CR duration
- OS
- RFS
- Assessment of immunogenicity
- Cytokine serum concentrations (Phase 1)

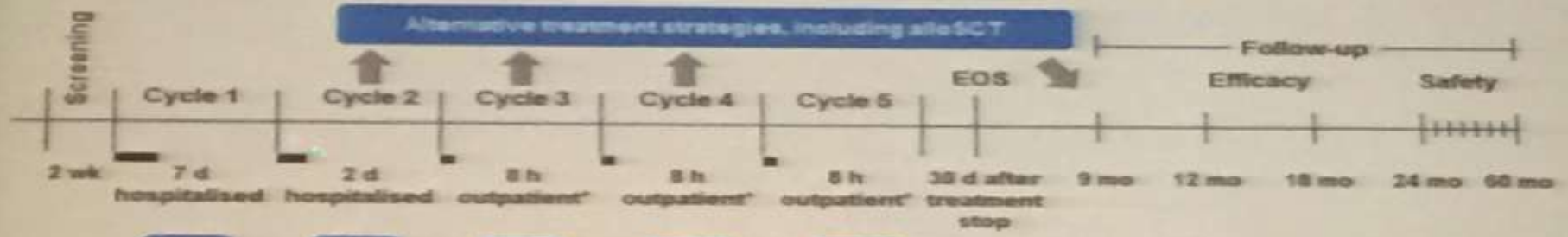
*Blinatumomab is not licensed for use in paediatric patients in the EU

**5 µg/m²/day starting dose, with potential for decrease to 3.75 µg/m²/day or step-wise increase to a maximum of 60 µg/m²/day depending on response

DMC, data monitoring committee; OS, overall survival; PK, pharmacokinetics; RFS, relapse-free survival

von Stackelberg A, et al. Poster presentation at ASH meeting, December 6–9 2014, San Francisco, CA. Abstract 2292;

Treatment plan



- 28-day cIV infusion: $t_{½}$ <2 hours
- Cycle length: 4 weeks on / 2 weeks off
- Mandatory hospitalisation for a minimum time period each cycle for observation
- Up to 5 cycles allowed

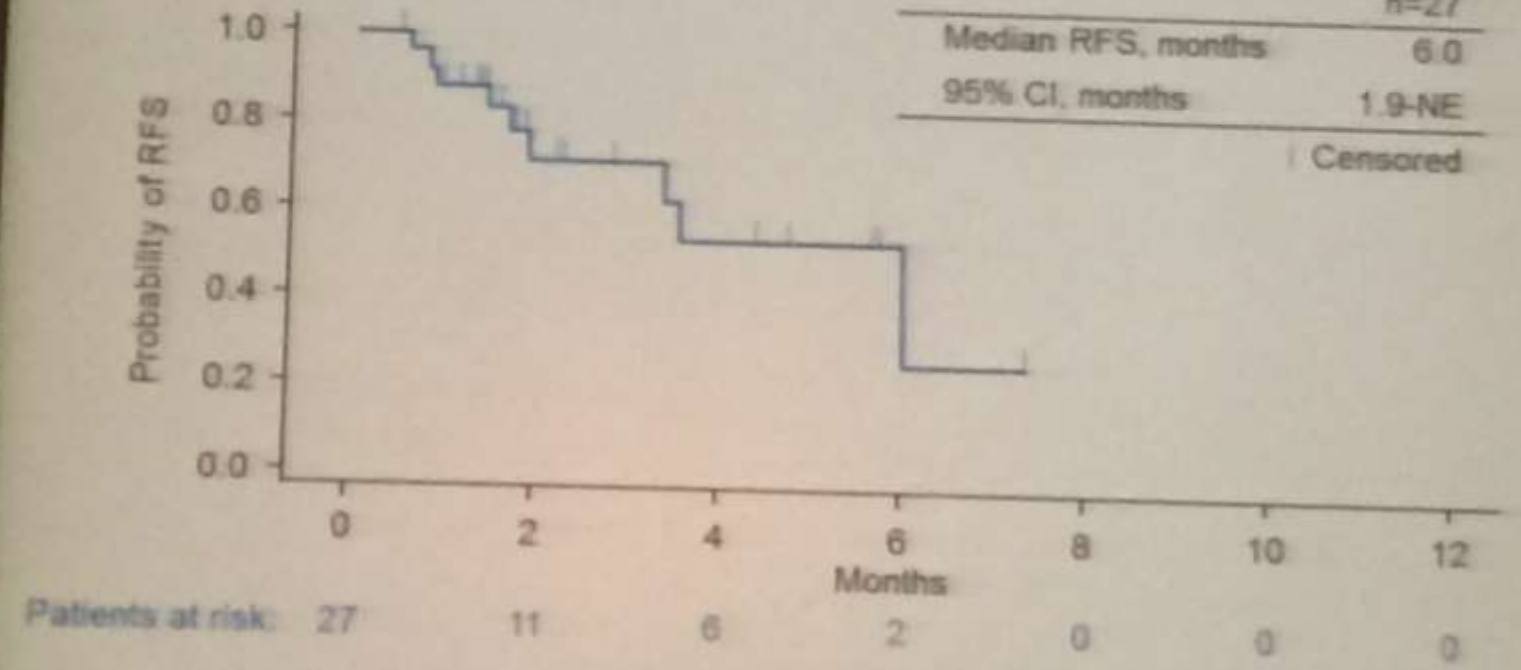
* 8 hrs outpatient observation followed by daily outpatient follow-ups during the subsequent 2 days

d, days; EOS, end of study; h, hours; mo, months; $t_{½}$, half-life; wk, weeks

von Stackelberg A, *et al*. Poster presentation at ASH meeting, December 6–9 2014, San Francisco, CA. Abstract 2292

Relapse-free survival, SCT censored

All patients treated at 5–15 µg/m²/day in Phase 1/2



- Based on the wide CI, there was no difference in RFS for responders vs SCT-censored responders

Dose evaluation cohorts and dose-limiting toxicities (DLTs): Phase 1

Cohort	Dose (µg/m²/day)	Patients (n)	DLTs (n)	Fatal DLTs (n)
1	5	5	0	0
2	15	7	1 CRS with GI haemorrhage	0
3	30	5	2 CRS	1 Grade 4 CRS leading to grade 5 cardiac failure
4	15–30 Stepwise dosing	6	1 Respiratory failure	1 Respiratory failure

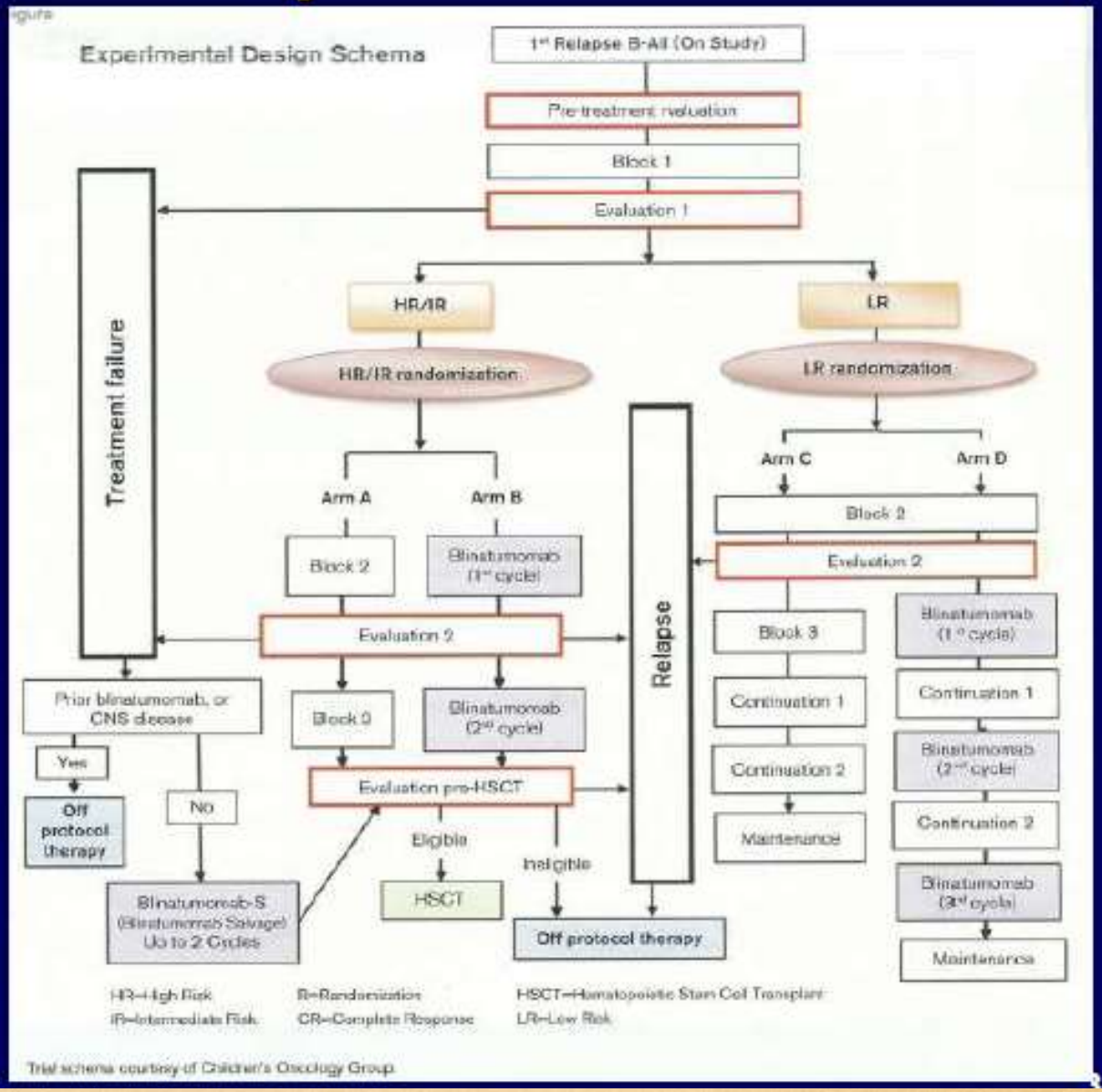
- 23 patients in the dose evaluation part of the study
- MTD: 15 µg/m²/day (based on review of overall toxicity profile by the DMC)
- Recommended stepwise dose to mitigate CRS: 5–15 µg/m²/day
  - → Evaluate in Phase 1 dose expansion part

CRS: cytokine release syndrome; GI: gastrointestinal; MTD: maximum tolerated dose

von Stackelberg A, et al. Poster presentation at ASH meeting, December 6–9 2014, San Francisco, CA. Abstract 2282

Risk stratified randomized phase III testing Blinatumomab in 1st relapse childhood B-ALL

- NCT02101853
- Incorporating Blinatumomab into the anti malignant chemotherapy regimen
- Randomized 1:1 Blina+chemo vs. chemo
- Patients with treatment failures will receive Blina and intermediate and high risk patients will proceed to HSCT
- Primary endpoint: DFS
- Secondary endpoints: Negative MRD; 2nd CR; %of pts. proceeding to HSCT; safety



YAN ETKİ/BLİNATUMOMAP

- Hastaların ≥%5'inde görülen yan etkiler;

- Ateş,titreme,afazi ve ensefalopatidir.
- Börolojik yan etkiler: Grade 3 veya daha ağır, median 7 günde ve hastaların %11-28'inde bildirilmiştir.
- Nörolojik bulgular veya sitokin salınım bulguları gelişen hastalarda kısa süreli dexametazon kullanılır.
- Anemi, nötropeni, trombositopeni, ALT yüksekliği görülebilecek diğer yan etkilerdir.
- Blinatomomab, metabolizması CYP450'ye bağlı olan ilaçlarla etkileşir.

SİTOKİN SALINIM SENDROMU

- Blinatumomab verilmesinden sonra IFN-γ, IL-10, ve IL-6 sitokinleri artar, HLH/MAS'a benzer bulgular gelişir.
- Hipotansiyon, multisistem organ yetmezliği ve hiperferritinemi tedavisinde anti-IL-6 reseptorü olan tocilizumab kullanılabilir.
- **Maliyet:** FDA onaylı doz şemasına göre bir ilaç kürünün maliyeti $95,350, tüm ilaç tedavisi $106,792 olarak hesaplanmıştır.
- Maliyete ilacın yanısıra hastane masrafları, destek tedavilerin maliyeti de eklenecektir.

Blinatumomab/SONUÇ

- FDA tarafından onaylanmış yeni bir BiTE tedavi edici monoklonal antikordur.
- Devam eden Faz III çalışmaları sonrası tedavideki yeri daha iyi belirlenecektir.
- Klinik tecrübeler kısıtlı olsa da Blinatumomab tedavisine MRD pozitif ALL ve relaps/refrakter B-ALL olan hastalar adaydır.
- Bu tedaviye en iyi aday KİT'e gidecek remisyonda ancak MRD pozitif olan hastalardır.
- Bu hastalarda Blinatumomab tedavisi MRD negatif kalıcı bir remisyon sağlayabilir.
- Gelecekteki çalışmalar blinatumomabın tedavideki optimal yerini gösterecektir.
- Süregelen çalışmalarda kemoterapi ile kombine Blinatumomab ve diğer immünoterapiler, Philadelphia pazitif ALL gibi özel hasta gruplarında kullanımı değerlendirilmektedir.
- Blinatumomab tedavisinden sonra optimal KİT zamanı, CAR T hücreleri ile tedavinin yeri hala belirsizdir. Sitokin salınım sendromunu ve nörolojik toksisiteleri birçok hasta tolere eder ve tedaviyle iyileşir.

Fatal adverse events on study
All patients treated at 5–15 µg/m²/day in Phase 1/2

	Patients (N=70)
Any fatal adverse events, n (%)†	6 (9)
Multiorgan failure*	2 (3)
Fungal infection	1 (1)
Respiratory failure*	1 (1)
Sepsis*	1 (1)
Thrombocytopenia	1 (1)

- The above does not include 2 additional patients who died of disease progression, including 1 who died of recurrent leukaemia (both reported by the investigators as AEs)

†Per CTCAE v4.0
*2 patients died in remission following complete MRD response and on-study SCT

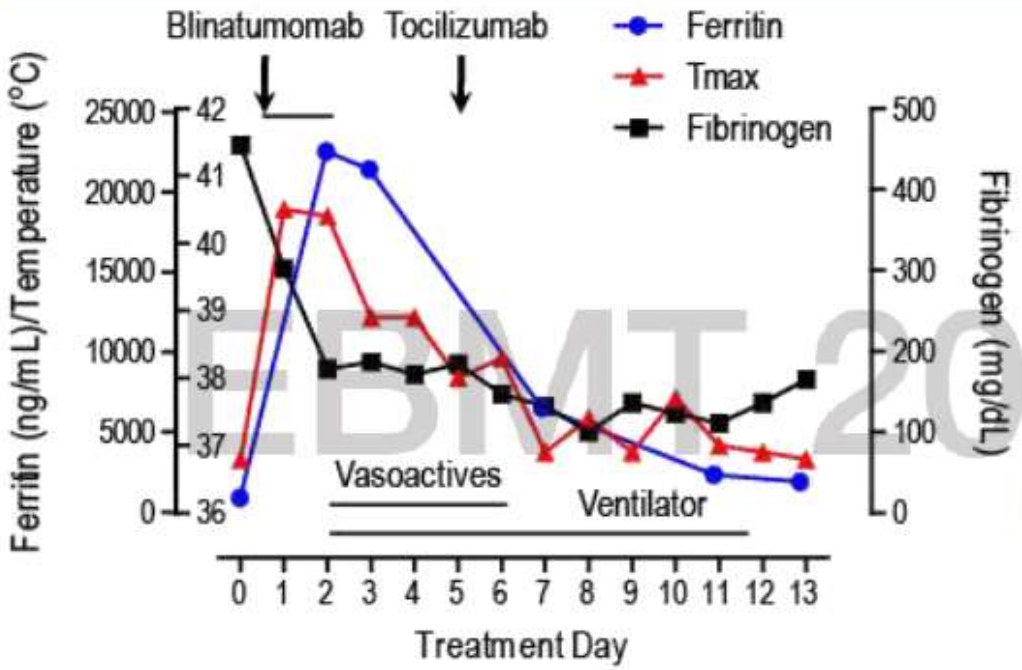
Gore L, et al. Poster presentation at ASH meeting, December 6-9 2014, San Francisco, CA. Abstract 3783

Conclusions

- Phase 1 dose-escalation[1]
  - MTD established as 15 µg/m²/day
  - Two DLTs in higher dose cohorts had fatal outcomes
  - Recommended dose for Phase 2 to avoid CRS: 5–15 µg/m²/day
- Phase 1/2 efficacy[2,3]
  - Blinatumomab has antileukaemic activity in heavily pretreated paediatric patients with r/r ALL, including ability to induce MRD-negative remissions
    - Most patients were refractory or had relapsed after SCT; 91% of patients had relapsed within 6 months of the last salvage treatment
  - Blinatumomab has the potential to provide bridge to SCT
    - 37% of patients with CR within the first two cycles of treatment went on to receive alloSCT
- Phase 1/2 safety
  - Adverse events associated with blinatumomab treatment consistent with previous experience in this disease setting
  - Low incidence of severe CRS and neurological events

1. von Stackelberg A, et al. Poster presentation at ASH meeting, December 6–9 2014; San Francisco, CA. Abstract 2052.
2. Gore L, et al. Poster presentation at ASH meeting, December 6–9 2014; San Francisco, CA. Abstract 3783.
3. Handgretinger R, et al. Poster presentation at ASBMT meeting, February 11–15 2015; San Diego, CA. Abstract 248.

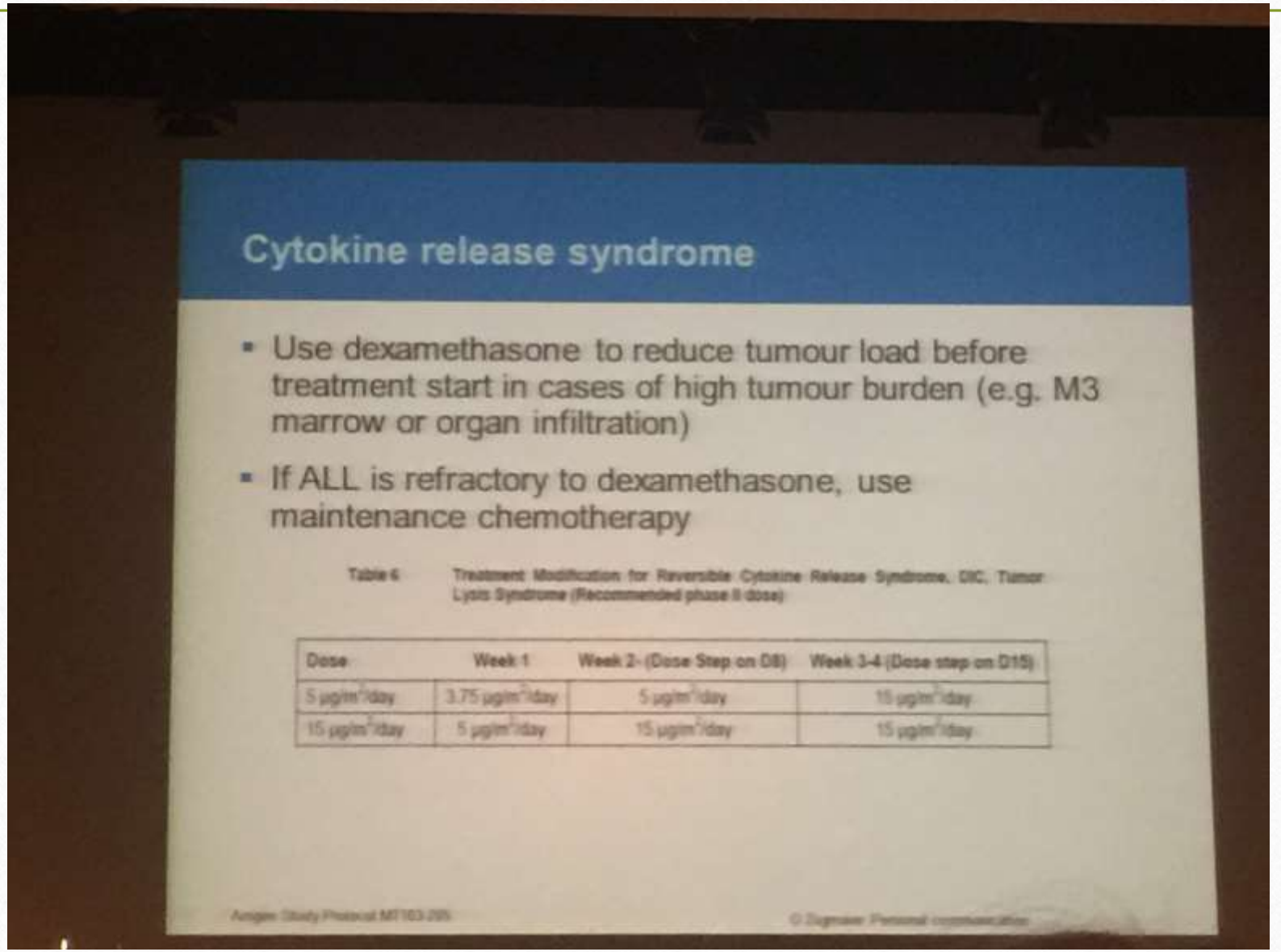
Blinatumomab Causes HLH/MAS as Well, Reversible With Tocilizumab

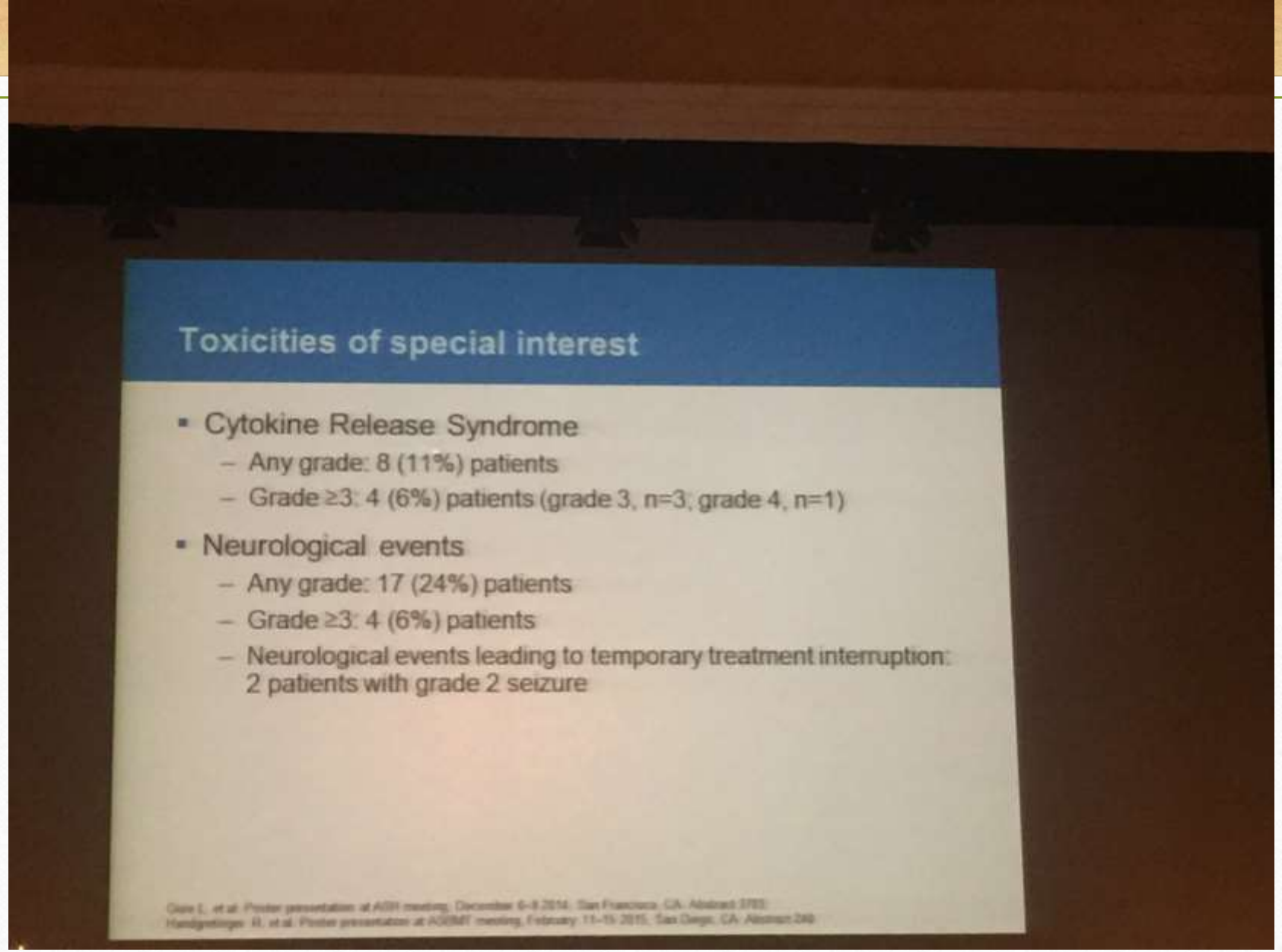


Elevated cytokines

- IL-10 (5338 pg/mL)
- IL-6 (681 pg/mL)
- INF-γ (192 pg/mL)
- IL-2R (4872 pg/mL)

David Teachey, Stephan Grupp. Blood, 2013


Cytokine release syndrome
Use dexamethasone to reduce tumour load before treatment start in cases of high tumour burden (e.g. M3 marrow or organ infiltration)
If ALL is refractory to dexamethasone, use maintenance chemotherapy
Table 6 Treatment Modification for Reversible Cytokine Release Syndrome, DIC, Tumor Lysis Syndrome (Recommended phase II dose)
Dose
Week 1
Week 2- (Dose Step on D8)
Week 3-4 (Dose step on D15)
5 µg/m²/day
3.75 µg/m²/day
5 µg/m²/day
15 µg/m²/day
15 µg/m²/day
5 µg/m²/day
15 µg/m²/day
15 µg/m²/day


Toxicities of special interest
Cytokine Release Syndrome
Any grade: 8 (11%) patients
Grade ≥3: 4 (6%) patients (grade 3, n=3; grade 4, n=1)
Neurological events
Any grade: 17 (24%) patients
Grade ≥3: 4 (6%) patients
Neurological events leading to temporary treatment interruption: 2 patients with grade 2 seizure

Target Antigen	Unkonjuge MoAb	Kaynak	Konjuge MoAb	Kaynak
CD19			SAR3419	İnsan
			Blinatumomab (BiTE)	Fare
CD20	**Rituximab**	Kimerik		
	Ofatumumab	İnsan	90Y-Ibritumomabtiuxetan	Fare
	Obinutuzumab	İnsan	1311-Tositumomab	Fare
	Veltuzumab	İnsan		
	AME-133	İnsan		
			Inotuzumab ozogamicin	İnsan
CD 22			CAT-3888 (BL22)	Fare
CD40	Dacetuzumab	İnsan		
	Lucatumumab	İnsan		
CD52	**Alemtuzumab**	İnsan		
HLA-DR	Apolizumab	İnsan		
	Milatuzumab	İnsan		

Pediatr Blood Cancer 2015;62:1171–1175

Re-Induction Chemoimmunotherapy With Epratuzumab in Relapsed Acute Lymphoblastic Leukemia (ALL): Phase II Results From Children's Oncology Group (COG) Study ADVL04P2

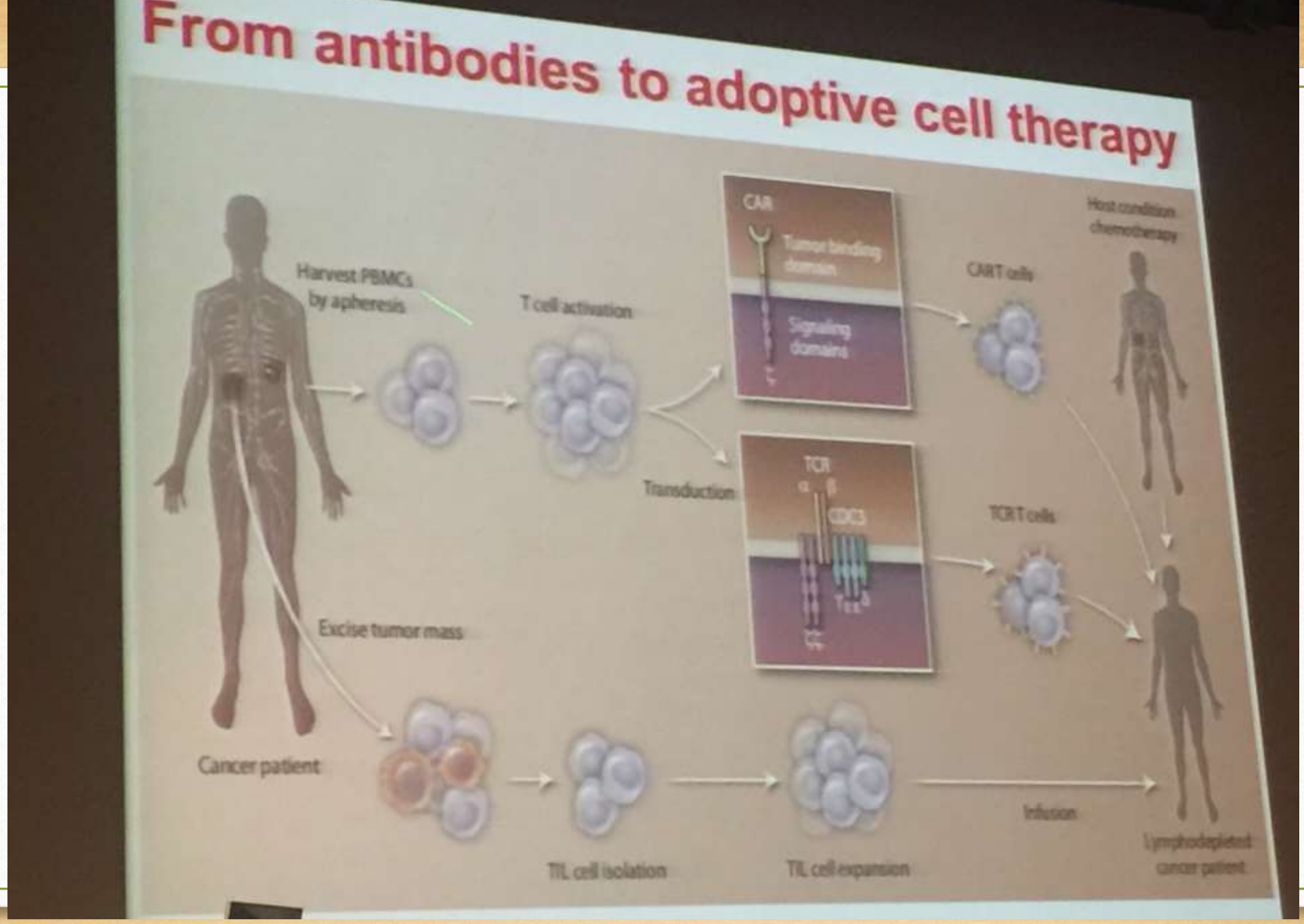
Elizabeth A. Raetz, MD,[1]* Mitchell S. Cairo, MD,[2] Michael J. Borowitz, MD, PhD,[3] Xiaomin Lu, PhD,[4] Meenakshi Devidas, PhD,[4] Joel M. Reid, PhD,[5] David M. Goldenberg, MD, ScD,[6] William A. Wegener, MD, PhD,[6] Hui Zeng, MS,[4] James A. Whitlock, MD,[7] Peter C. Adamson, MD,[8] Stephen P. Hunger, MD,[8] and William L. Carroll, MD[9]

Background. Given the success of immunotherapeutic approaches in hematologic malignancies, the COG designed a phase I/II study to determine whether the addition of epratuzumab (anti-CD22) to an established chemotherapy platform improves rates of second remission (CR2) in pediatric patients with B-lymphoblastic leukemia (B-ALL) and early bone marrow relapse. ***Procedure.*** Therapy consisted of three established blocks of re-induction chemotherapy. Epratuzumab (360 mg/m^2/dose) was combined with chemotherapy on weekly × 4 (B1) and twice weekly × 4 [eight doses] (B2) schedules during the first re-induction block. Remission rates and minimal residual disease (MRD) status were compared to historical rates observed with the identical chemotherapy platform alone. ***Results.*** CR2 was achieved in 65 and 66%, of the evaluable B1 (n = 54) and B2 patients (n = 60), respectively; unchanged from that observed historically without epratuzumab. Rates of MRD negativity (<0.01%) were 31% in B1 ($P = 0.4128$) and 39% in B2 patients ($P = 0.1731$), compared to 25% in historical controls. The addition of epratuzumab was well tolerated, with a similar toxicity profile to that observed with the re-induction chemotherapy platform regimen alone. ***Conclusions.*** Epratuzumab was well tolerated in combination with re-induction chemotherapy. While CR2 rates were not improved compared to historical controls treated with chemotherapy alone, there was a non-significant trend towards improvement in MRD response with the addition of epratuzumab (twice weekly for eight doses) to re-induction chemotherapy. Pediatr Blood Cancer 2015;62:1171–1175.

ALL de Monoklonal antikor kullanımı

- Blinatumumab, İnotumzumab ve Epratumubzumab etkili bulunmuş
- Gelecekte ilk tedavilere eklenebilir
- Kombine immunoterapiler?
- KİT yerine geçebilir?

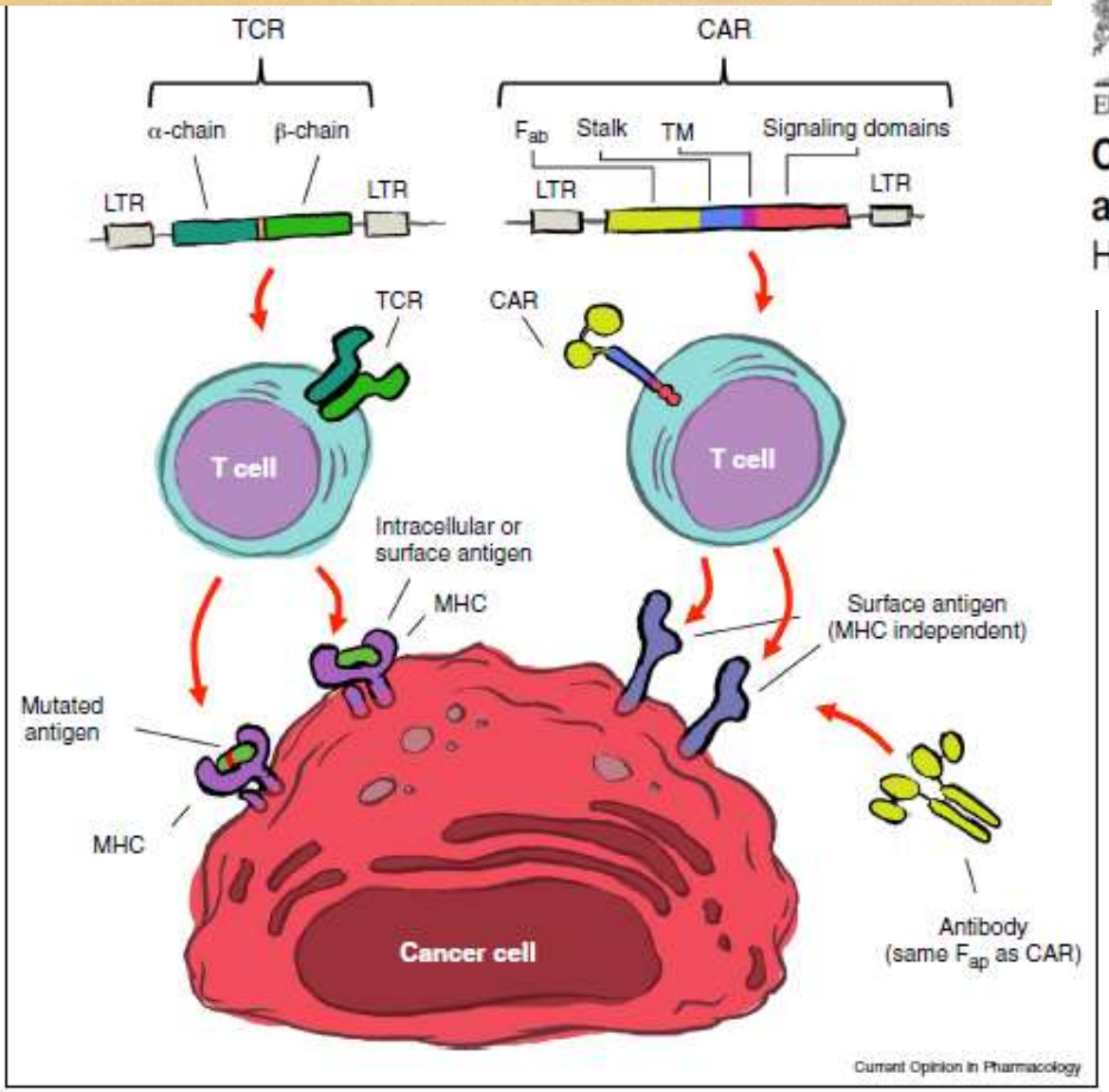
Sellüler tedaviler le kompetisyon?


From antibodies to adoptive cell therapy
Harvest PBMCs by apheresis
T cell activation
CAR
Tumor binding domain
Signaling domains
CAR T cells
Host condition chemotherapy
Transduction
TCR
TCR T cells
Excise tumor mass
Cancer patient
TIL cell isolation
TIL cell expansion
Infusion
Lymphodepleted cancer patient

Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Pharmacology

Cancer gene therapy with T cell receptors and chimeric antigen receptors

Hans J Stauss[1], Emma C Morris[1] and Hinrich Abken[2,3]



Retroviral and lenti-viral vectors encoding TCR or CAR molecules can be used to redirect the specificity of human T cells. CAR molecules recognize proteins that are expressed on the surface of cancer cells. TCR molecules can recognize peptides that are derived from intracellular proteins, including mutated proteins.

T hücreleri kanseri yok eder.

Kanser hücresini tanıması gerek

Genetik mühendislik:

Reseptör transferi: viral ve non viral yöntemlerle)

Viral: Retroviral ve lentiviral vektörler

Non-viral: Sleeping Beauty systemi (mRNA transferi)

CD19'a karşı geliştirilmiş CARTs klinik çalışmalarda başarılı.

Current Opinion in Pharmacology 2015, 24:113–118

ELSEVIER

Experimental Hematology 2015;43:1001–1014

Antileukemic potency of CD19-specific T cells against chemoresistant pediatric acute lymphoblastic leukemia

Alla Dolnikov[a,b,c], Sylvie Shen[a,b,c], Guy Klamer[b,c], Swapna Joshi[c], Ning Xu[a,c], Lu Yang[c], Kenneth Micklethwaite[d], and Tracey A. O'Brien[a,b,c]

[a]*Cord & Marrow Transplant Facility, Kids Cancer Centre, Sydney Children's Hospital, Sydney, Australia;* [b]*Faculty of Medicine, University of New South Wales, Sydney, Australia;* [c]*Children's Cancer Institute Australia, Sydney, Australia;* [d]*Westmead Millennium Institute, University of Sydney, Sydney, Australia*

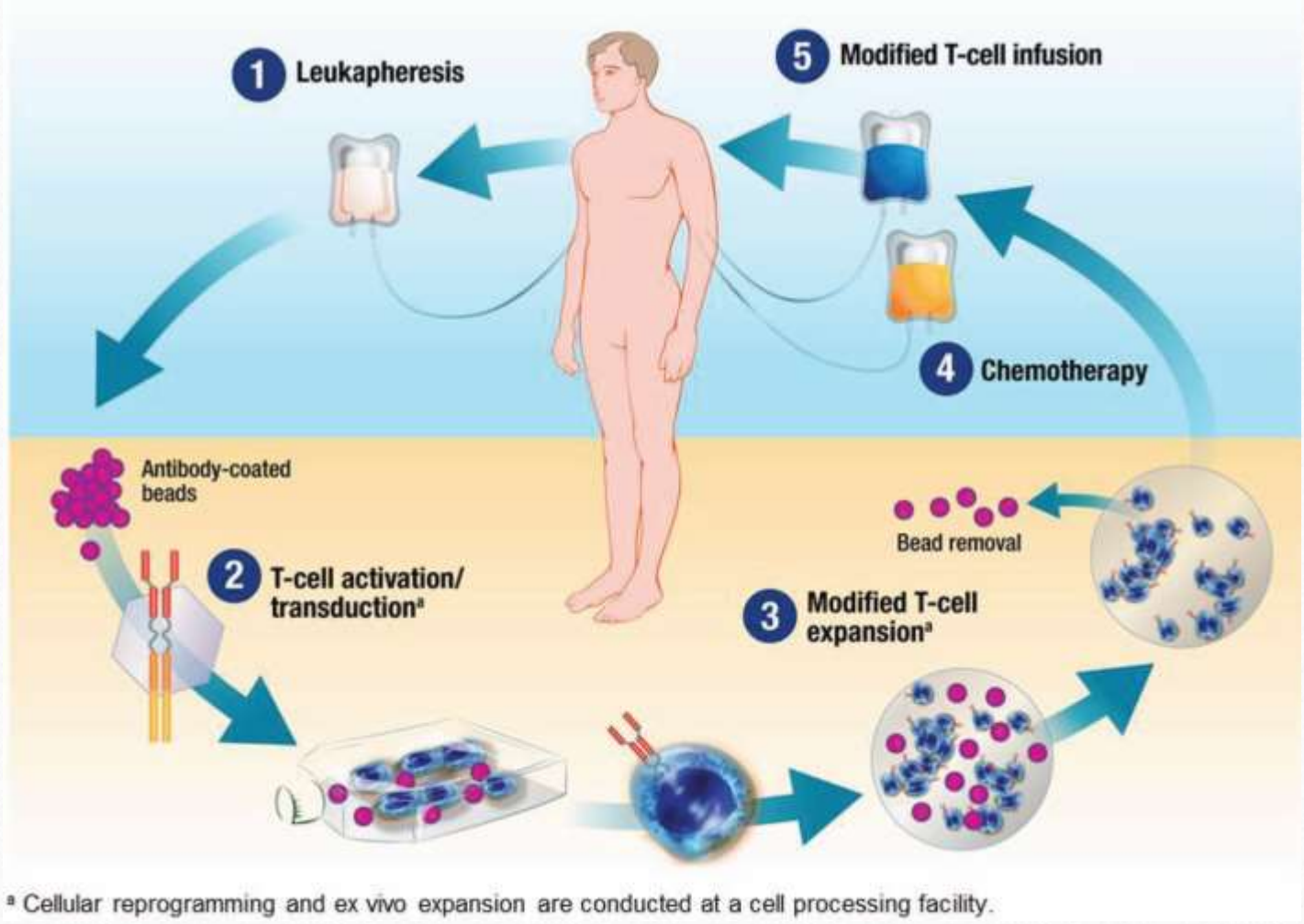
CD19'a karşı Kimerik antijen reseptörleriyle (CARs) genetik olarak modifiye edilmiş T hücreleri (virüs veya manufacturing)

Bu hücrelerin ekspansiyonu (IL-1, IL-15) ile

Sitoredüktif conditioning tümör hücreleri öldürülürmesi artar(Fludarabin ve Siklofosfamidle AZA öneriyor

CART hücre varlığı lösemi yüküyle ilişkili,

Sleeping Bauty sistemi: piggy-Bace transporon temelli sistem



Maude S.L.et al. Chimeric antigen receptor T-cell therapy for ALL. Hematology 2014, 559-564.

bjh review

Current status of chimeric antigen receptor therapy for haematological malignancies

Shannon Maude and David M. Barrett

Abramson Cancer Center and the Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philac PA, USA

British Journal of Haematology, 2016, **172,** 11–22

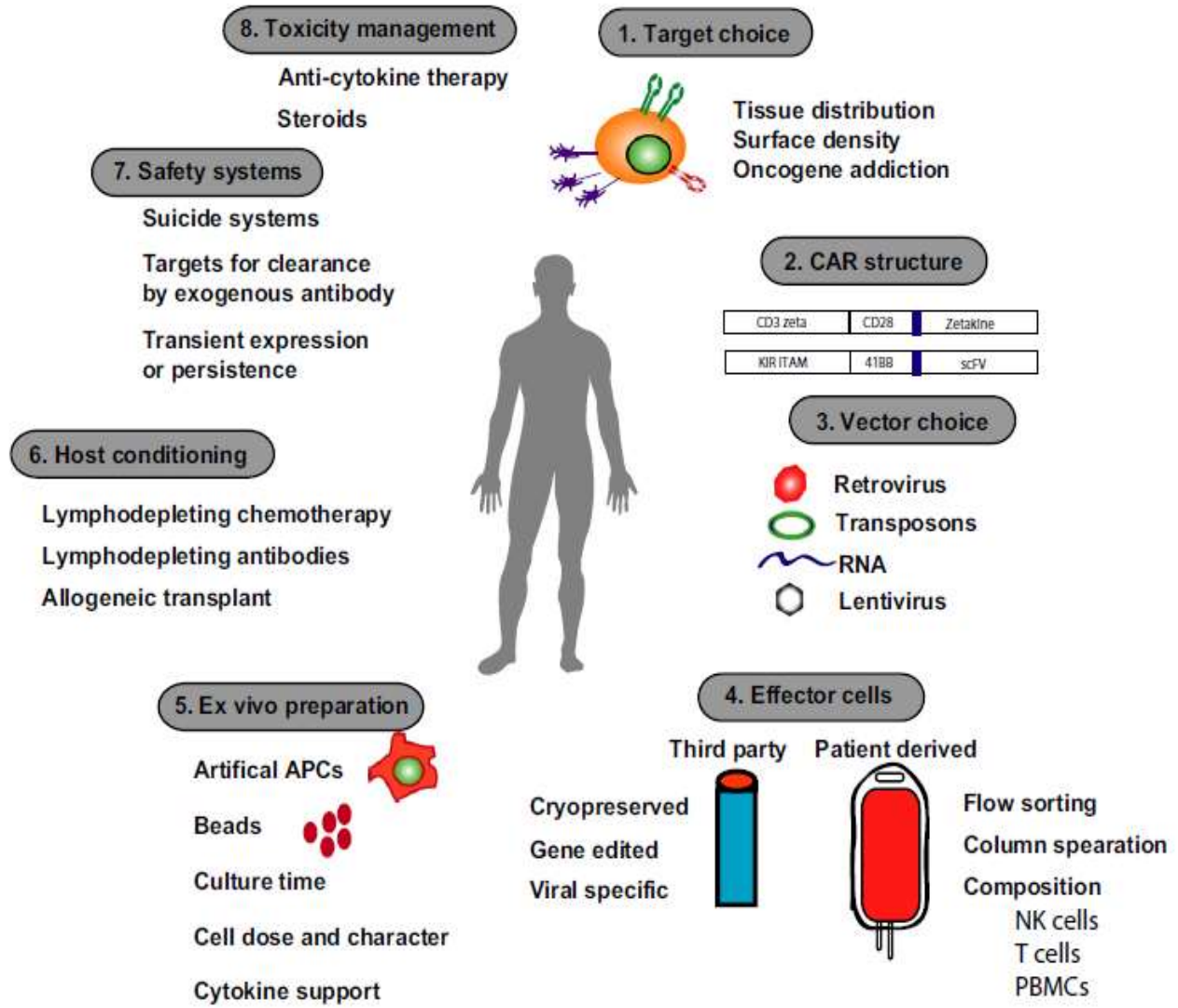
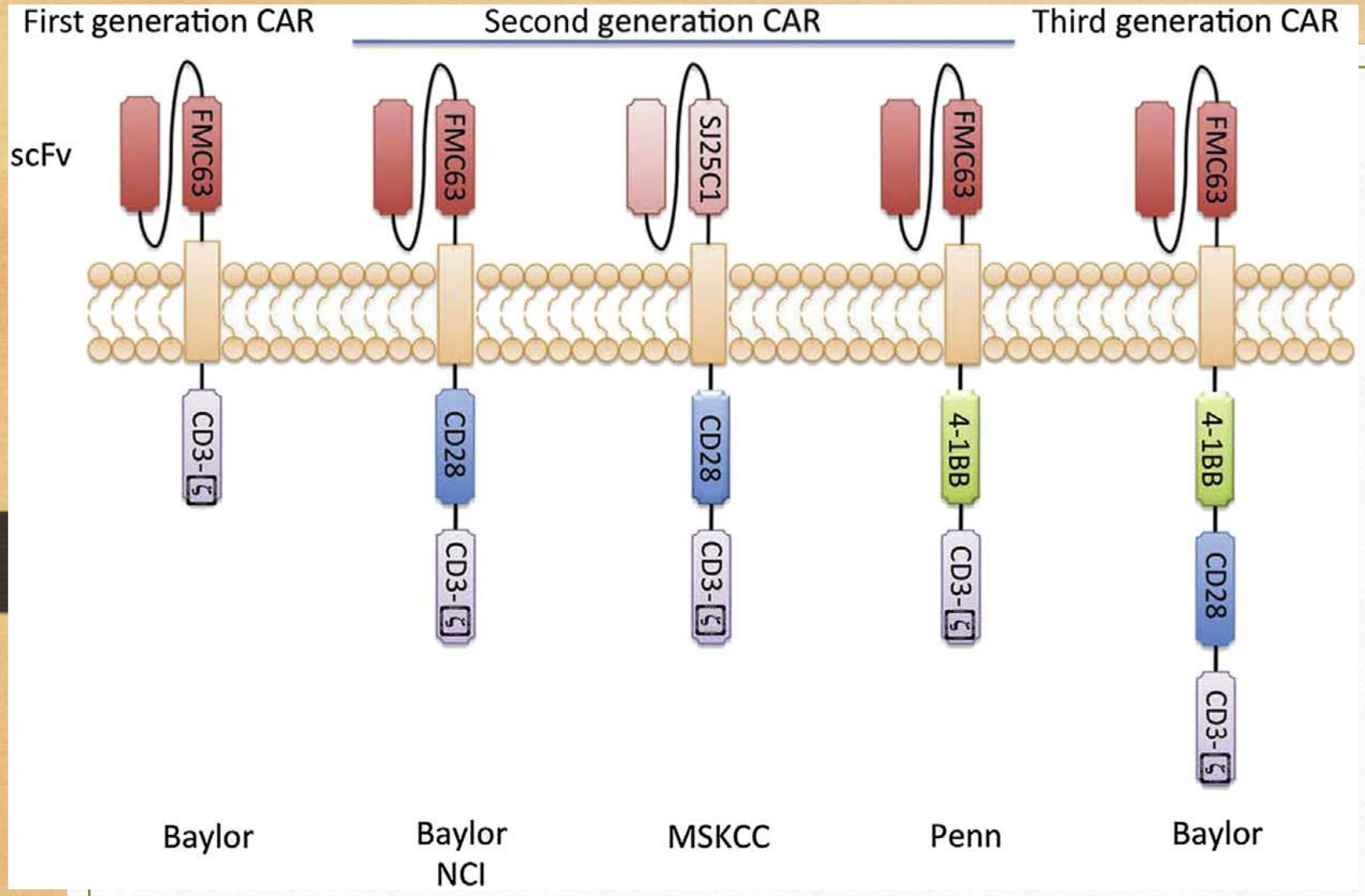


Fig 1. Variables that contribute to CAR design and efficacy. Change in any variable group can dramatically alter the function and efficacy of the overall product, making iterative comparisons in preclinical modelling extremely challenging. CAR, chimeric antigen receptor; APCs, antigen presenting cells; NK cells, Natural Killer cells; PBMCs, peripheral blood mononuclear cells.



Birinci Jenerasyon CARs: Tek sitoplazmik signal içerir CD3-z,

İkinci Jenerasyon CAR: CD3-z ve CD28 veya 41BB
İkinci jenerasyon daha etkili (klinik çalışmalarda)

Üçüncü jenerasyon CAR: CD28, 41BB, ve CD3-z içerir.

Baylor(Baylor College of Medicine): Clinical Trials NCT01853631, NCT00586391;

NCI (National Cancer Institute): Clinical Trials NCT01087294, NCT00924326, NCT01593696; MSKCC (Memorial Sloan-Kettering Cancer Center): Clinical Trials NCT01840566,
NCT01860937, NCT01044069, NCT00466531, NCT01416974;

Penn (Abramson Cancer Center of the University of Pennsylvania): Clinical Trials NCT01747486, NCT01029366, NCT01551043

1. Hochberg J,El-Mallawany NK, Cairo MS. Humoral and Cellular Immunotherapy in ALL in Children, Adolescents, and Young Adults. Clinical Lymphoma, Myeloma & Leukemia, Vol. 14, No. S3, S6-13, 20142152-2650/$ - see frontmatter ª 2014

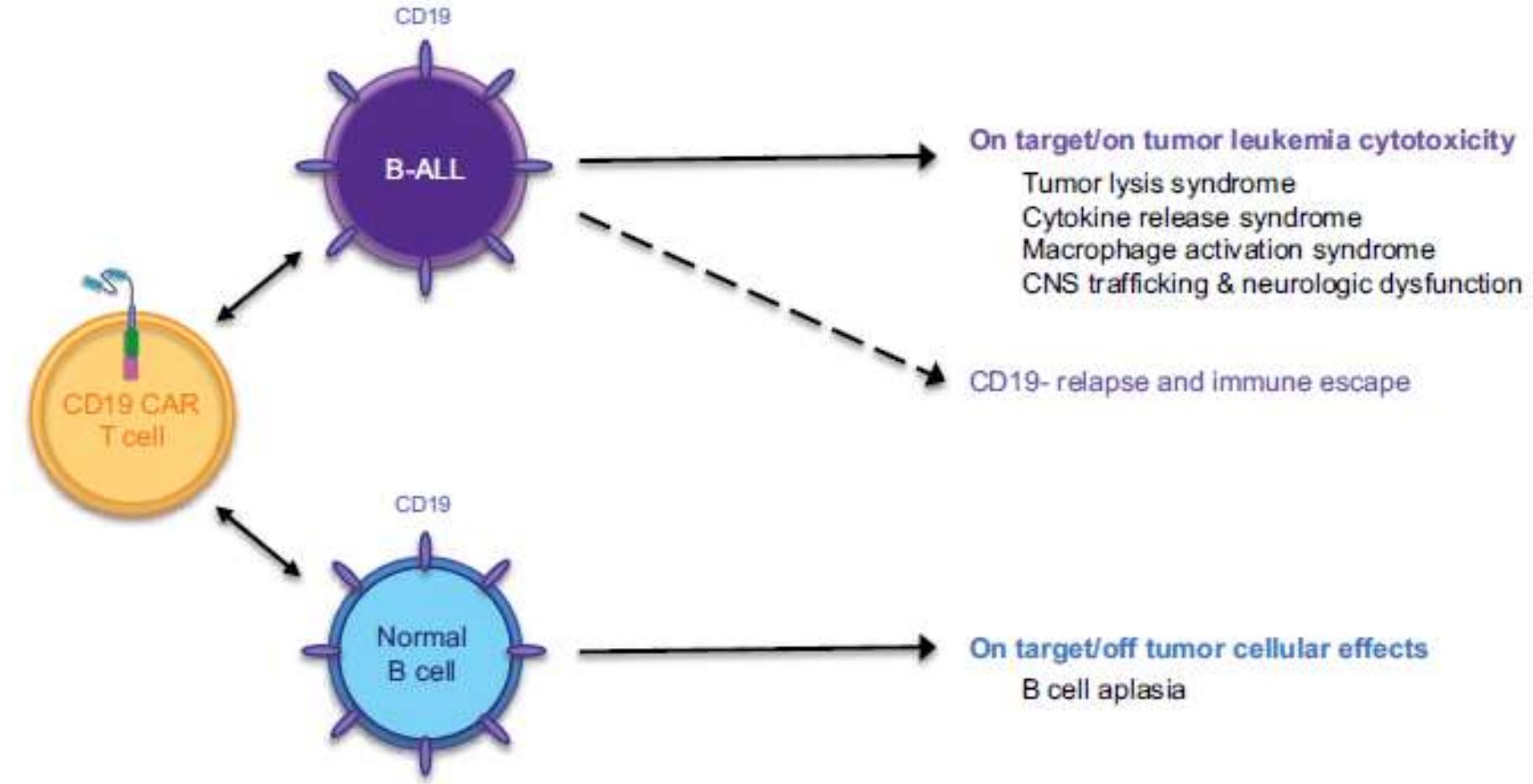
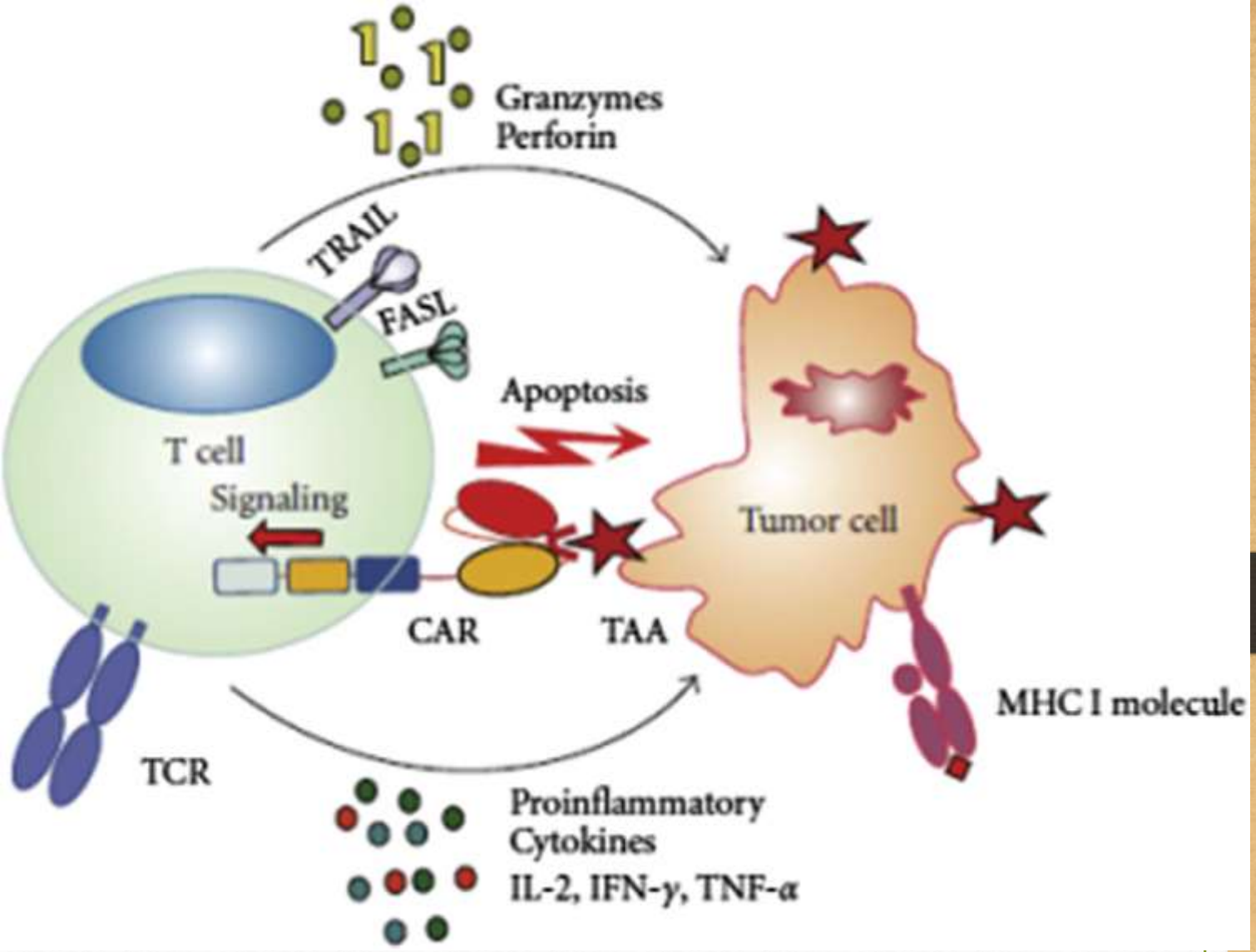


Figure 2. Binding of CD19 CAR T cells to CD19-expressing cells can induce potent on target/on tumor and on target/off tumor sequelae.
B-ALL, B-cell acute lymphoblastic leukemia; CNS, central nervous system.

CAR : Chimeric Antigen Receptor;
FASL :FAS ligand;
IFN : Interferon;
IL : Interleukin;
MHC :Major histocompatibility complex;
TAA :Tumor associated antigen;
TCR: T cell receptor;
TNF :Tumor necrosis factor;
TRAIL :Tumor Necrosis Factor Related Apoptosis-Inducing Ligand.



Cartellieri M et al. Chimeric Antigen Receptor-Engineered T Cells for Immunotherapy of Cancer.
J Biomed Biotechnol 2010;
2010:956304.

Review Series

ACUTE LYMPHOBLASTIC LEUKEMIA

CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia

Shannon L. Maude,[1,2] David T. Teachey,[1,2] David L. Porter,[3] and Stephan A. Grupp[1,2,4]

[1]Division of Oncology, The Children's Hospital of Philadelphia, [2]Department of Pediatrics, [3]Department of Medicine, and [4]Department of Pathology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

BLOOD, 25 JUNE 2015 • VOLUME 125, NUMBER 26

Supported in part by grants from the National Institutes of Health National Cancer Institute (R01CA102646 and R01CA116660), the Leukemia and Lymphoma Society, Weinberg and Leukemia Research Funds, and a Stand Up To Cancer and St. Baldrick's Pediatric Dream Team Translational Research Grant (SU2C-AACR-DT1113). Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research. S.L.M. is a St. Baldrick's Foundation Scholar. D.T.T. is supported by a Research Scholar Grant (RSG-14-022-01-CDD) from the American Cancer Society.

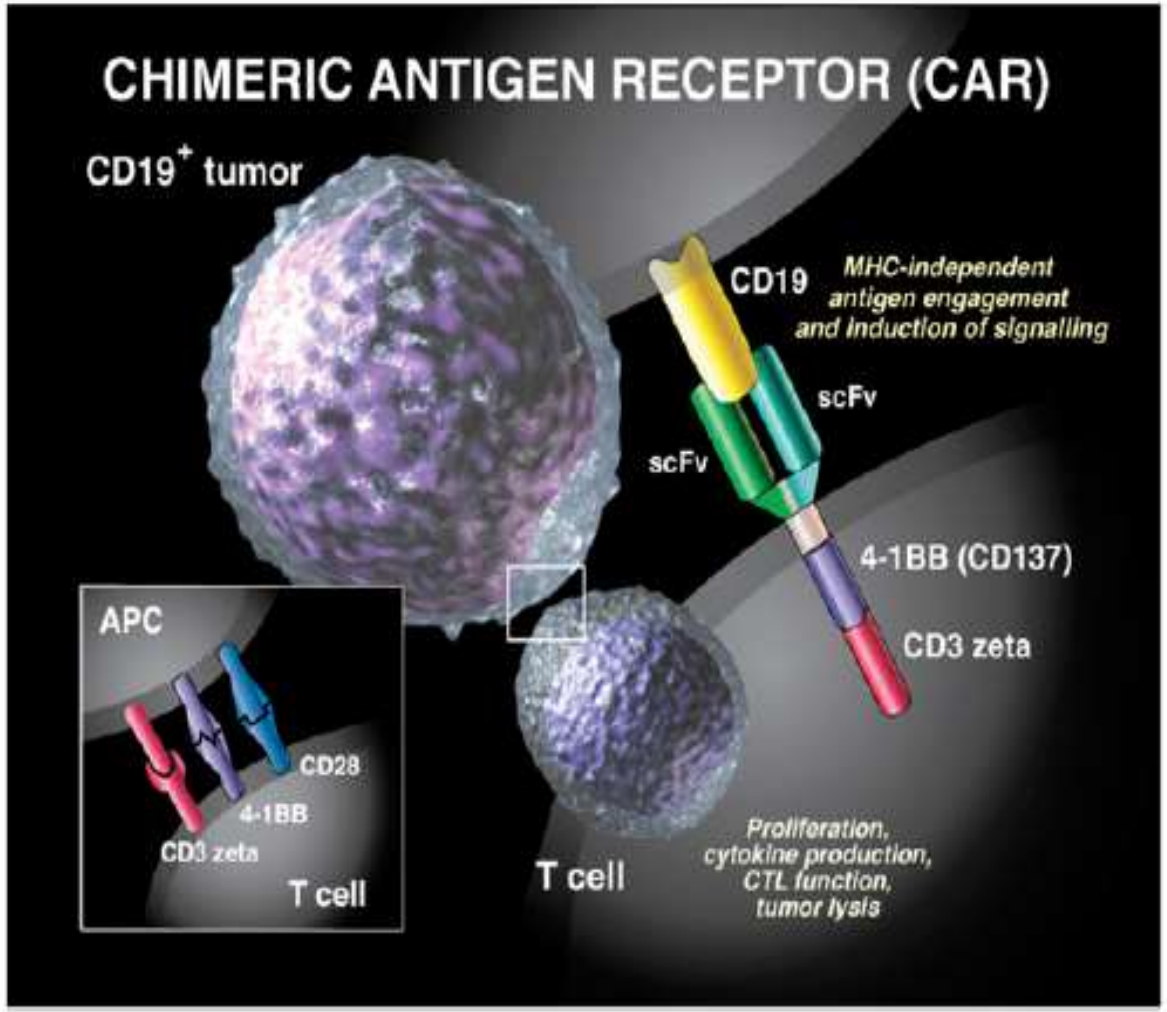


Figure 2. Second-generation CAR used in current clinical studies at Penn and CHOP. CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex. Reprinted with permission from Barrett et al.[77] © Sue Seif

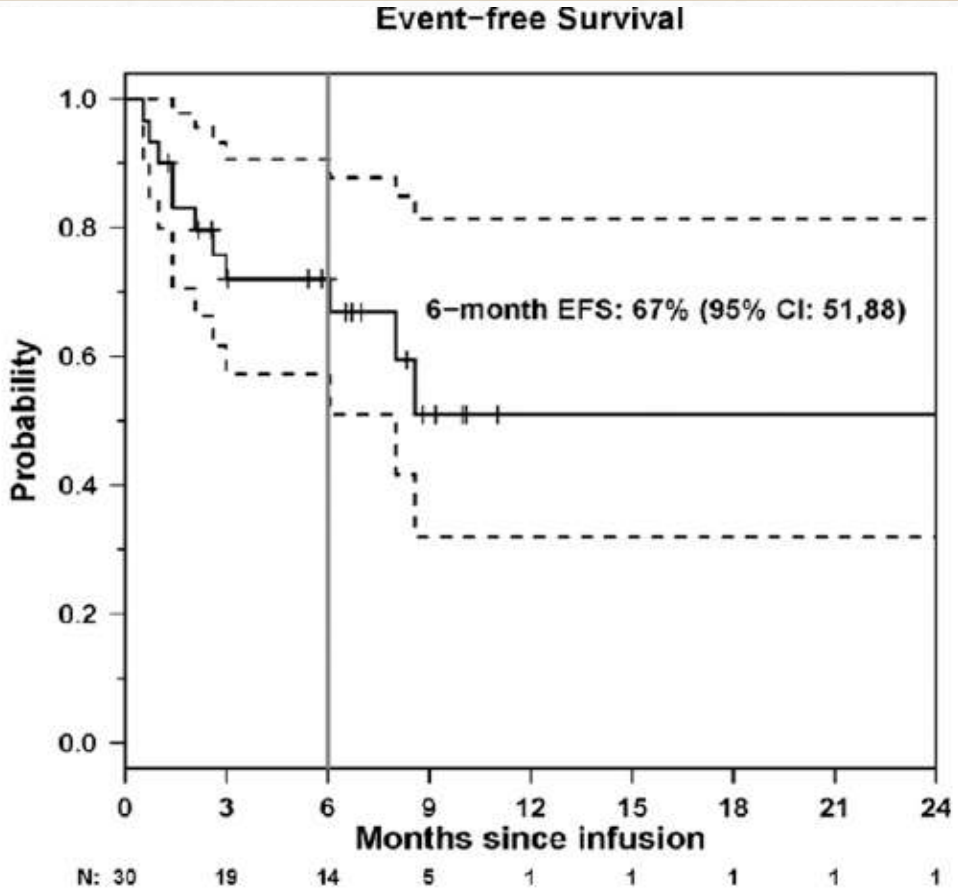
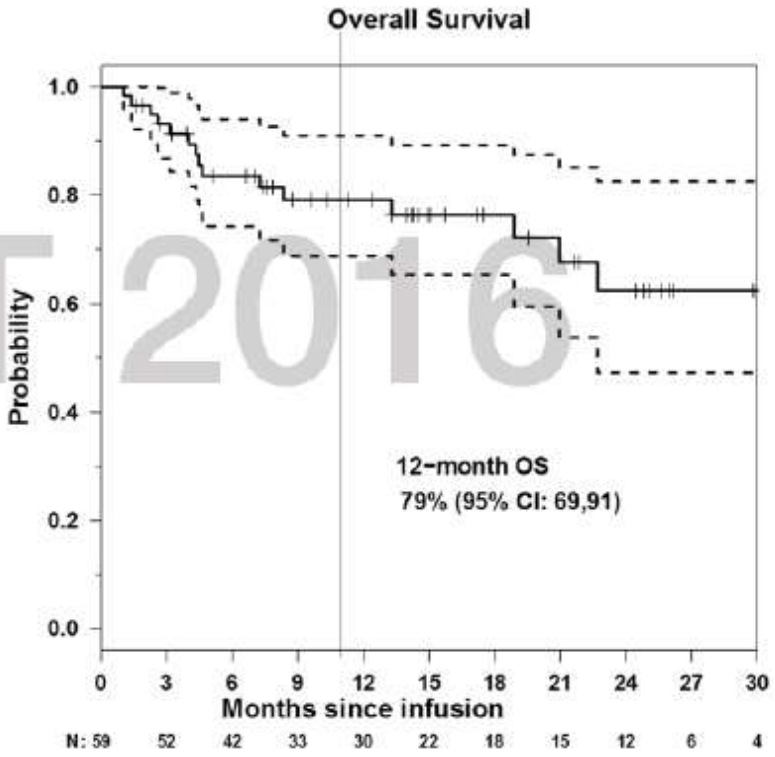


Figure 3. Event-free survival in 30 children and adults treated with CTL019 therapy. Of this group, 5 patients who entered a CR went on to further therapy, 3 of whom received an allogeneic bone marrow transplant. The fourth had refractory T-cell ALL aberrantly expressing CD19, entered remission after CTL019, and subsequently underwent donor lymphocyte infusion. She remains in remission >1 year later. The fifth patient developed myelodysplastic syndrome and received therapy for this condition (this was scored as an event, but she did receive further therapy in ALL remission and was counted among the 5). The rest have not received further therapy to consolidate their remissions. EFS, event-free survival. Figure adapted from Maude et al[26] with permission.

93% CR rate for r/r ALL after CTL019

>200 patients with CLL, ALL, NHL, MM have gotten CTL019

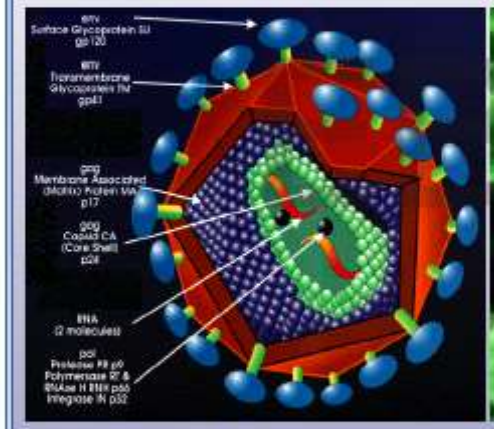
- 59 r/r pediatric ALL pts:
  55 in CR at 1 mo (93%)
  median f/u 12 mo
- 6 went to subsequent transplant, 1 to DLI
- 6 mo RFS: 76% (95%ci 65-89%)
  12 mo RFS: 55% (95%ci 42-73%)
- No relapses past 1 year
- 18 patients in remission beyond 1 year,
  13 without further therapy



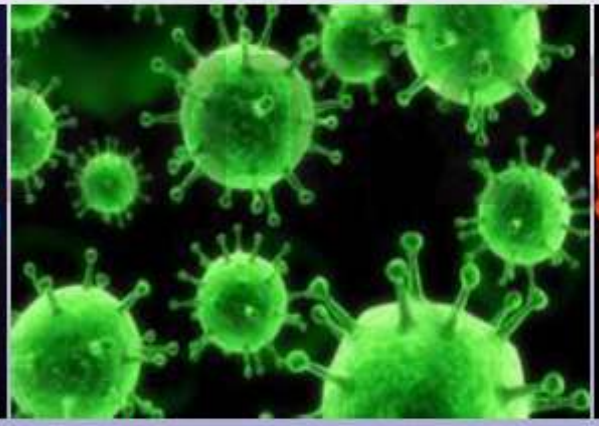
CTL019 Toxicities

- **B-cell aplasia**
  - observed in all responding patients to date
  - managed with IVIg replacement therapy
- **Cytokine release syndrome (CRS in 88% of pts)**
  - reversible, on-target toxicity
  - Controlled with anti-IL-6 therapy (tocilizumab used in 27%)
  - Severity related to tumor burden: Treat MRD as outpatient?
- **Macrophage activation syndrome (HLH / MAS)**
- **Neurotoxicity**
  - Seizures in <5%
  - Significant confusion, aphasia in 15-20%
  - Occurs in a small number of patients and after CRS

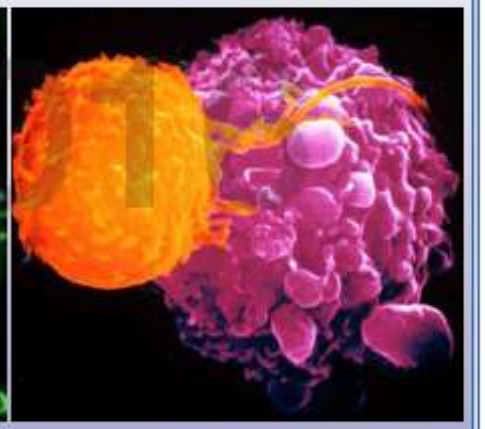
CART19 (CTL019) Cells For Relapsed, Refractory ALL



Structure of a Lenti-virus



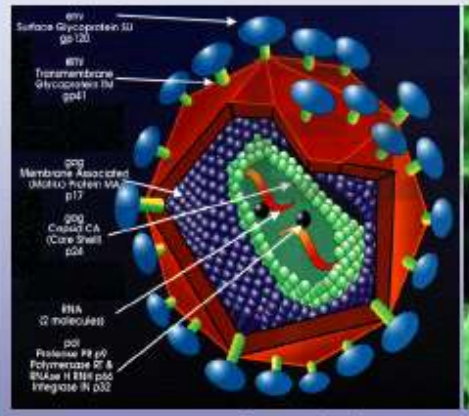
Lenti-viruses used for T-cell transduction



Transduced T-cell attacks a tumor cell

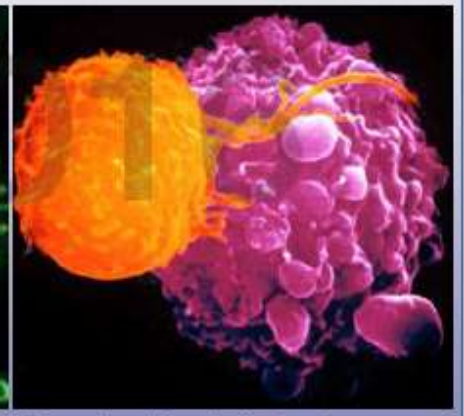
UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

CART HÜCRELERİ
KİT'DEN ÖNCEMİ?,SONRA MI?, SIRASINDA MI?



Structure of a Lenti-virus

Lenti-viruses used for T-cell transduction



Transduced T-cell attacks a tumor cell

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

For ALL, anything has to be better than DLI…
CAR T cells AFTER allogeneic SCT

- Response of relapsed ALL to DLI 0-20%
- Of responding patients, most responses transient.
- Overall survival extremely poor.

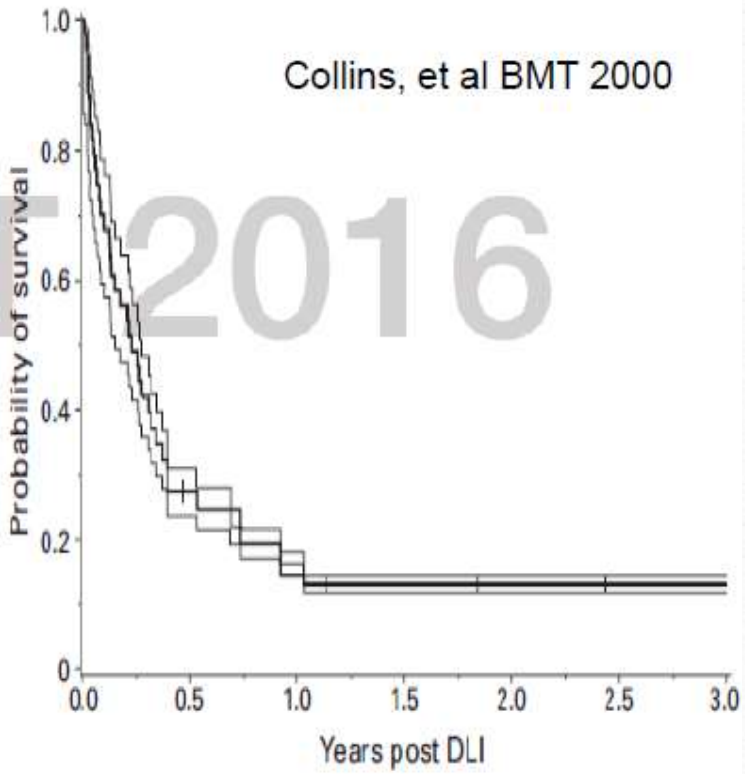


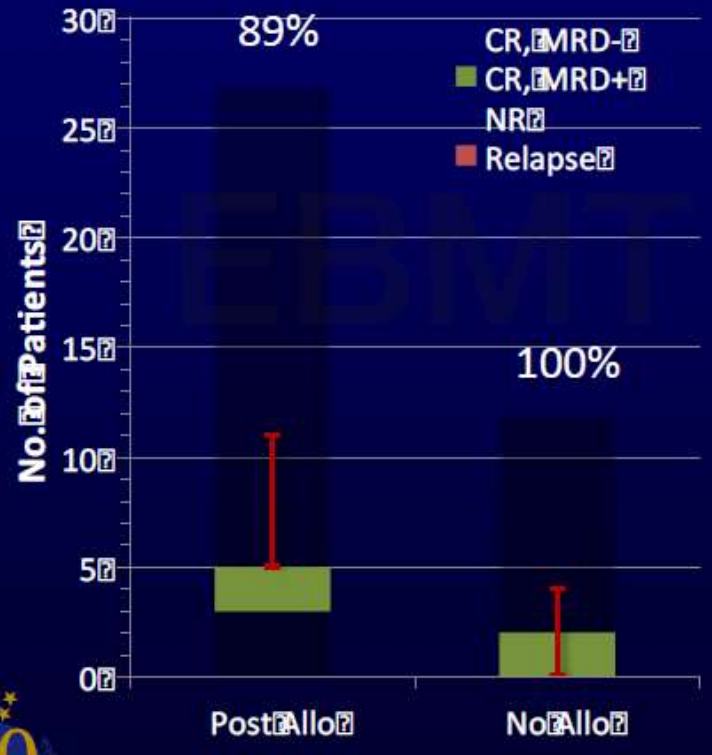
Figure 1 Actuarial survival with 95% confidence intervals in 44 ALL patients treated with DLI

After: CAR T cells highly effective in relapsed ALL

- 27 patients post-allo SCT
- T cells collected from patient
  - 6 months post-SCT
- Median donor chimerism 100%
- No GVHD to date
- Dramatically superior to DLI

Maude, Grupp et al, unpublished (Dec 2015)

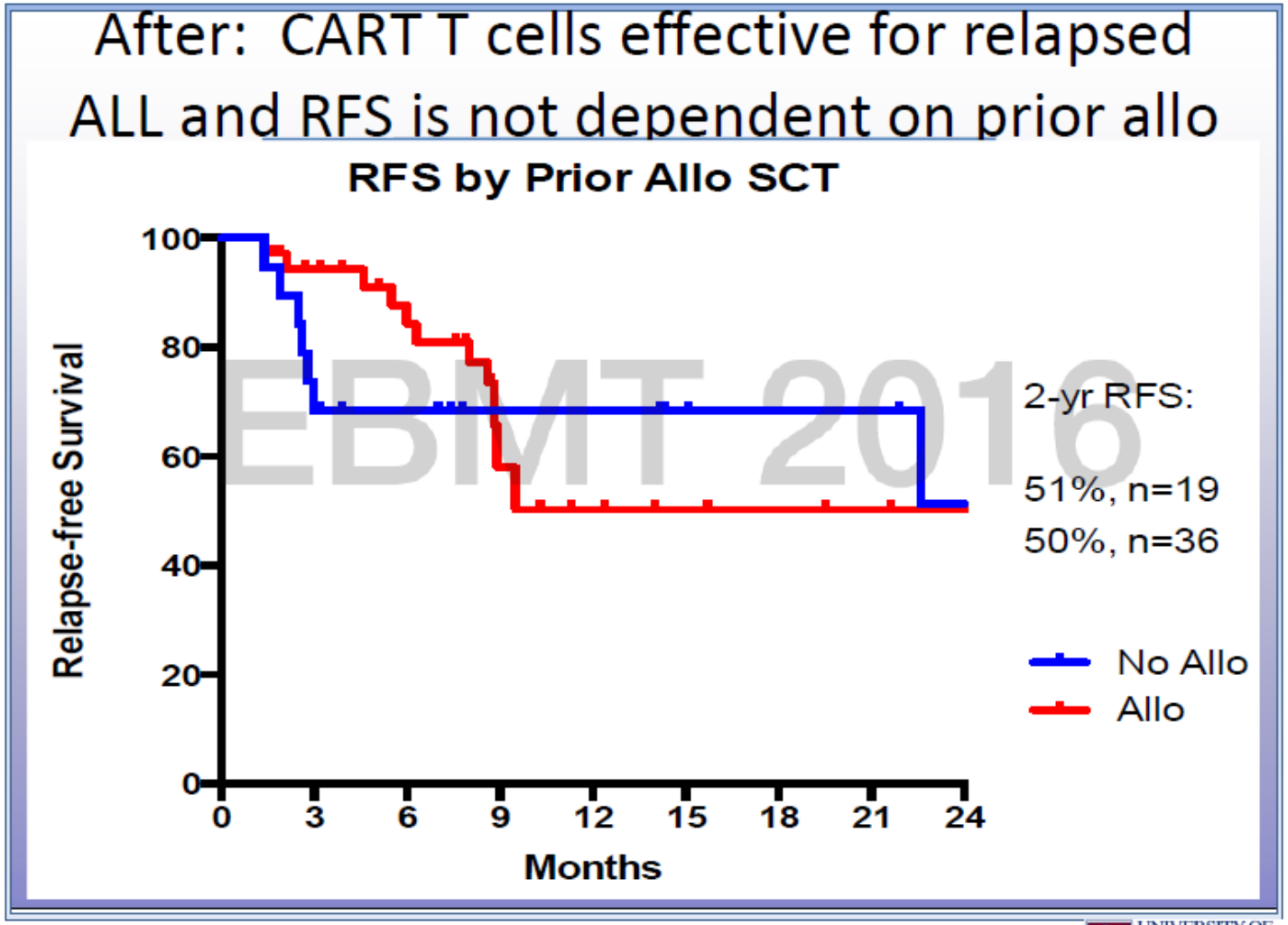
After: CAR T cell response is not dependent on prior allo



Maude, Grupp et al, unpublished (Dec 2015)

- 27 patients post-allo SCT
- T cells collected from patient
  - 6 months post-SCT
- Median donor chimerism 100%
- No GVHD to date
- Dramatically superior to DLI

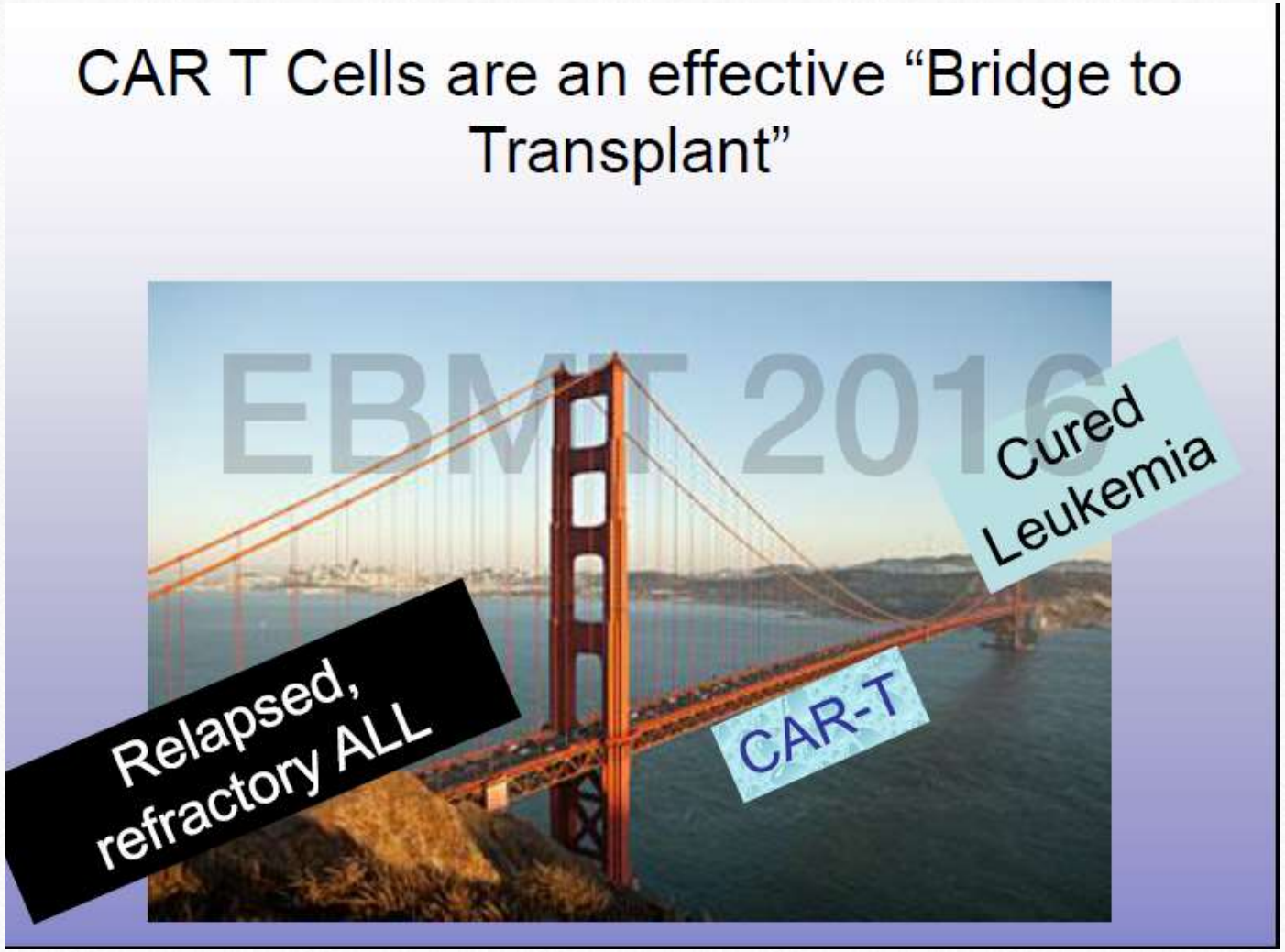
After: CART T cells effective for relapsed ALL and RFS is not dependent on prior allo



Maude, Grupp et al, unpublished (Dec 2015)

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

CAR T Cells are an effective “Bridge to Transplant”

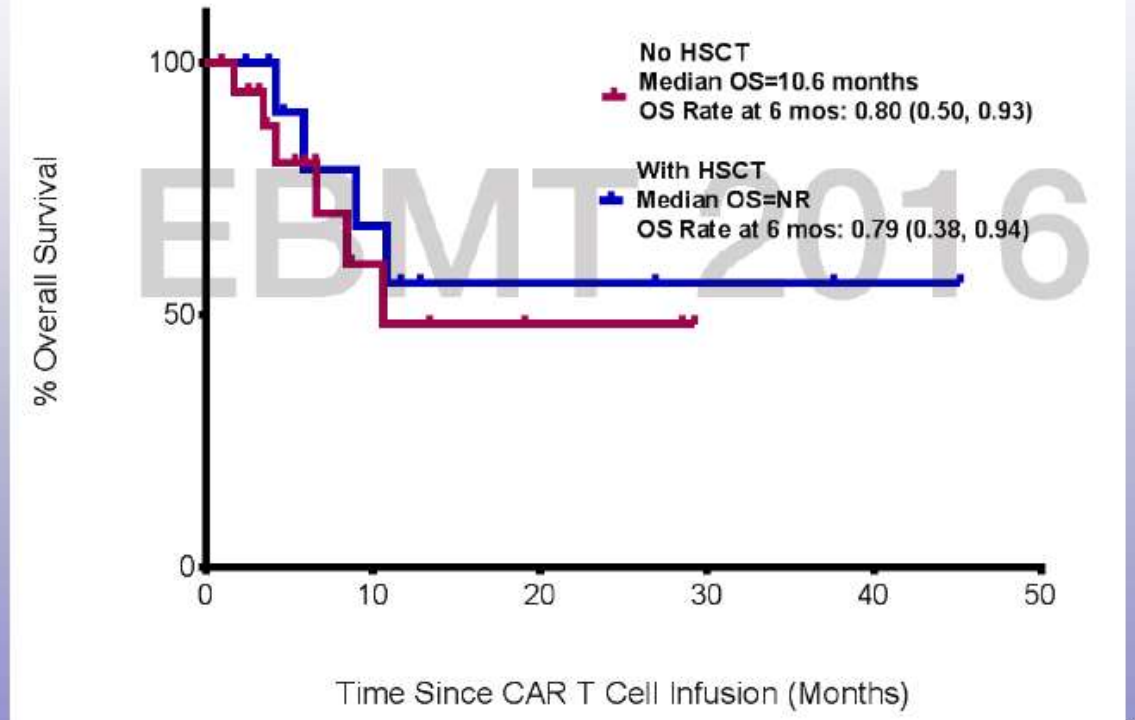


Before: Is transplant after CAR T cells necessary?

Relapse after CAR T cells

- In CLL, no patient with CR has relapsed with follow-up 6-65 months (Penn)
- In ALL, ~1/3 of patients relapse after CTL019 (CHOP)
  - 2/3 of relapses have CD19 negative ALL (Grupp)
- 49% (18/37) patients relapsed after CART19 (MSK)
  - 3/18 (16%) with CD19 negative ALL
  - 4/18 (22%) despite allogeneic SCT after CAR T cells.
- Other strategies, transplant or otherwise, are needed to prevent relapse of ALL after CAR T cells.

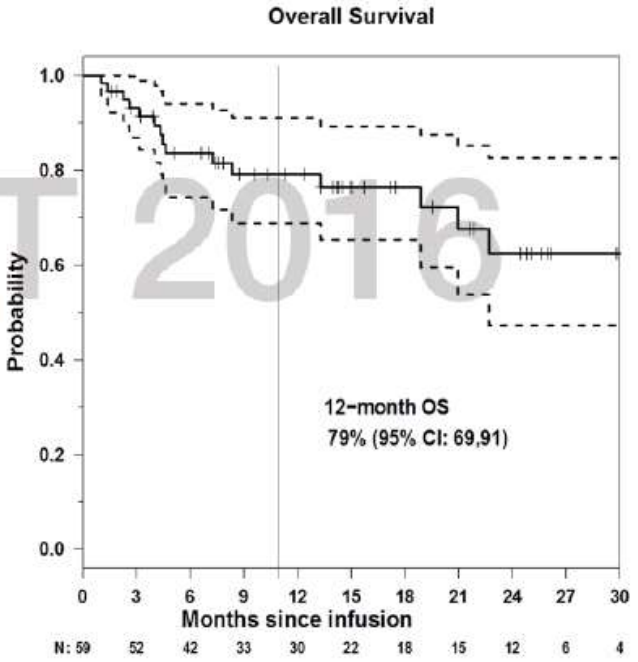
Instead: Overall survival similar with or without allo SCT after CAR T Cells (MRD-CR Patients)



Park et al, ASH 2015 abst 682

Instead: Long-term remission for r/r ALL after CTL019

- 59 r/r pediatric ALL pts:
- 55 in CR at 1 mo (93%)
- Median f/u 12 mo
- 6 mo RFS: 76% (95%ci 65-89%)
- 12 mo RFS: 55% (95%ci 42-73%)
- No relapses past 1 year
- 18 patients in remission beyond 1 year,
- 13 without further therapy
- 6 went to subsequent transplant, 1 to DLI



Maude, Grupp, unpublished

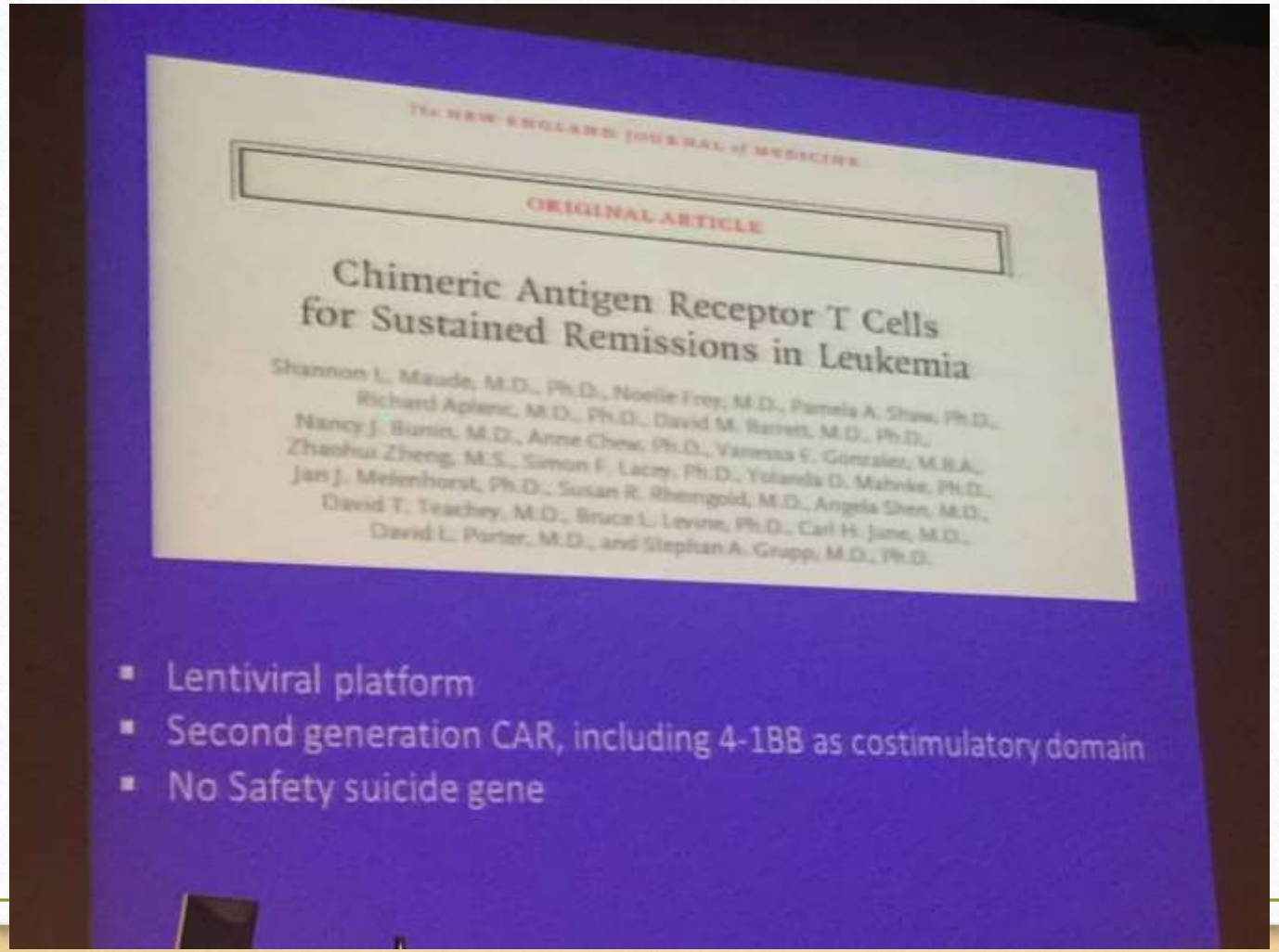
Summary: CTL019 for B cell malignancies

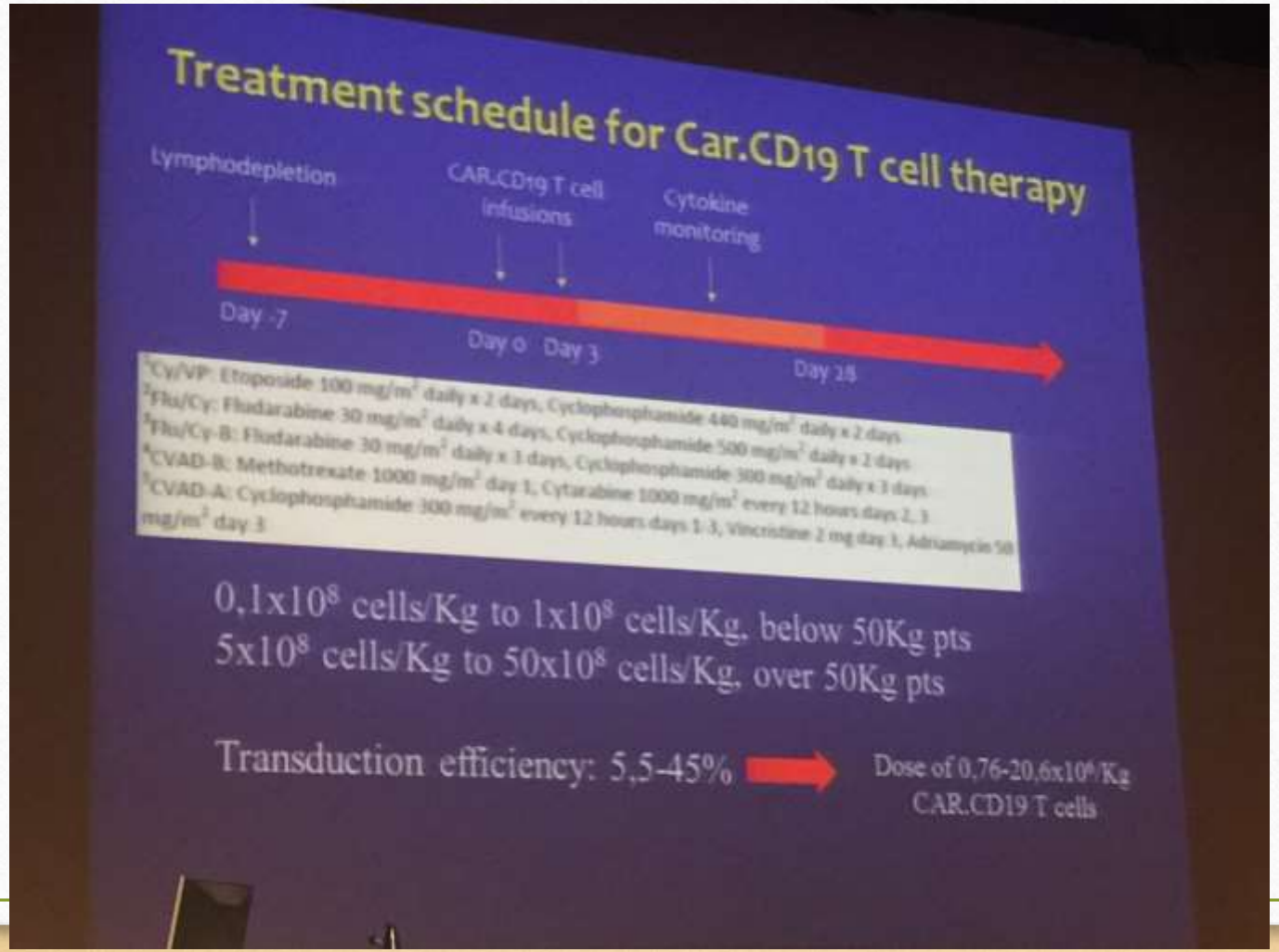
- Massive CTL019 expansion (1000 – 10,000 fold *in vivo*)
  - E:T ratio 1:1000-93,000
- Eradication of bulky tumor
- Overall response rate 21/43 CLL (49%)
- Overall CR rate ALL ~90%
- CTL019 cells persist for >60 months after a single treatment
  - Persisting cells remain functional
- Relapse of ALL (particularly CD19-) is a major problem after CAR T cell therapy
  - Need for combination or alternative therapy (i.e. anti-CD22)
  - Role for consolidative allogeneic SCT? Is CAR T cell therapy a "bridge to transplant"?

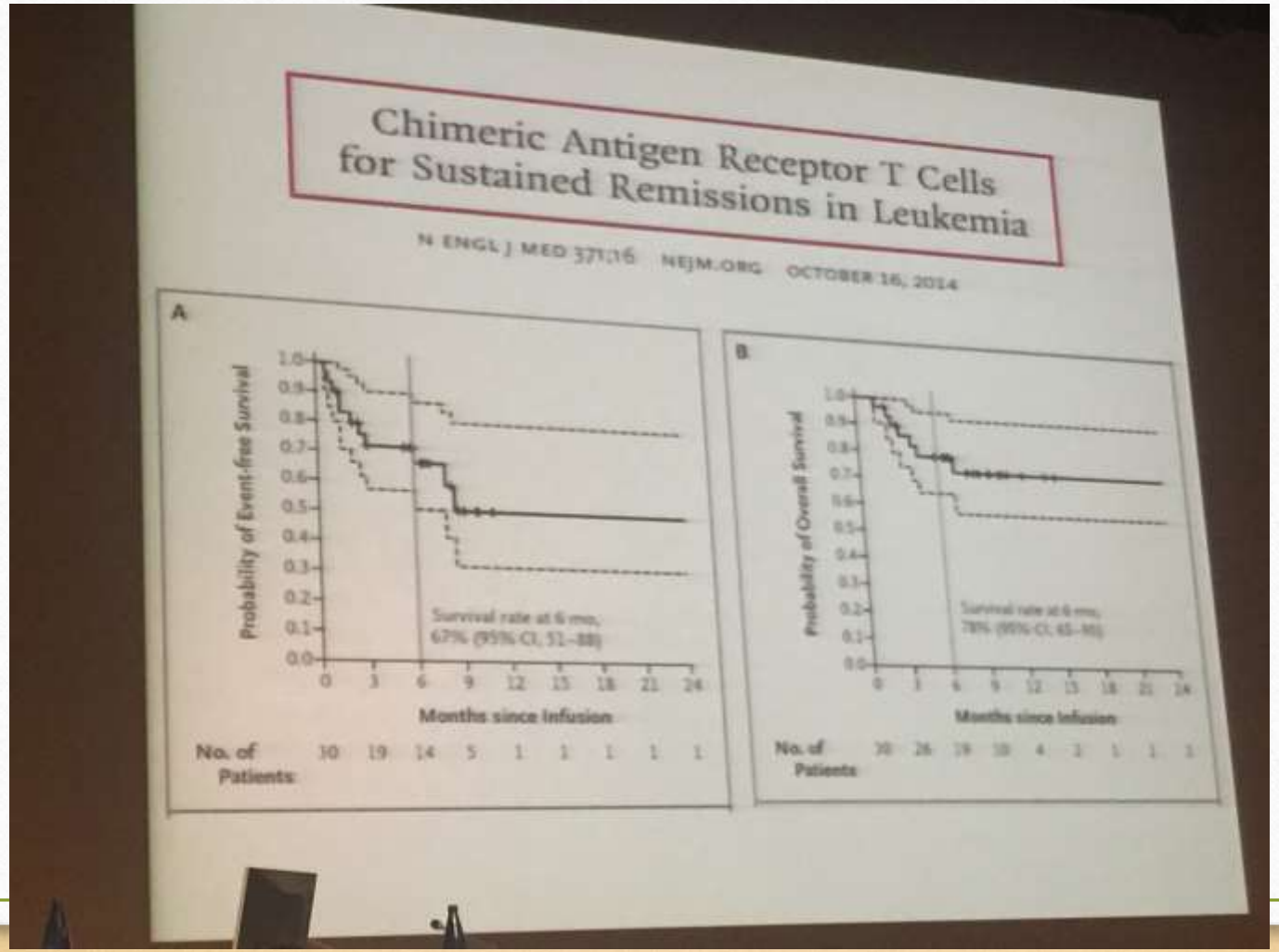
1. Porter D, et al. ASH 2013; Abstracts 873 and 4162.

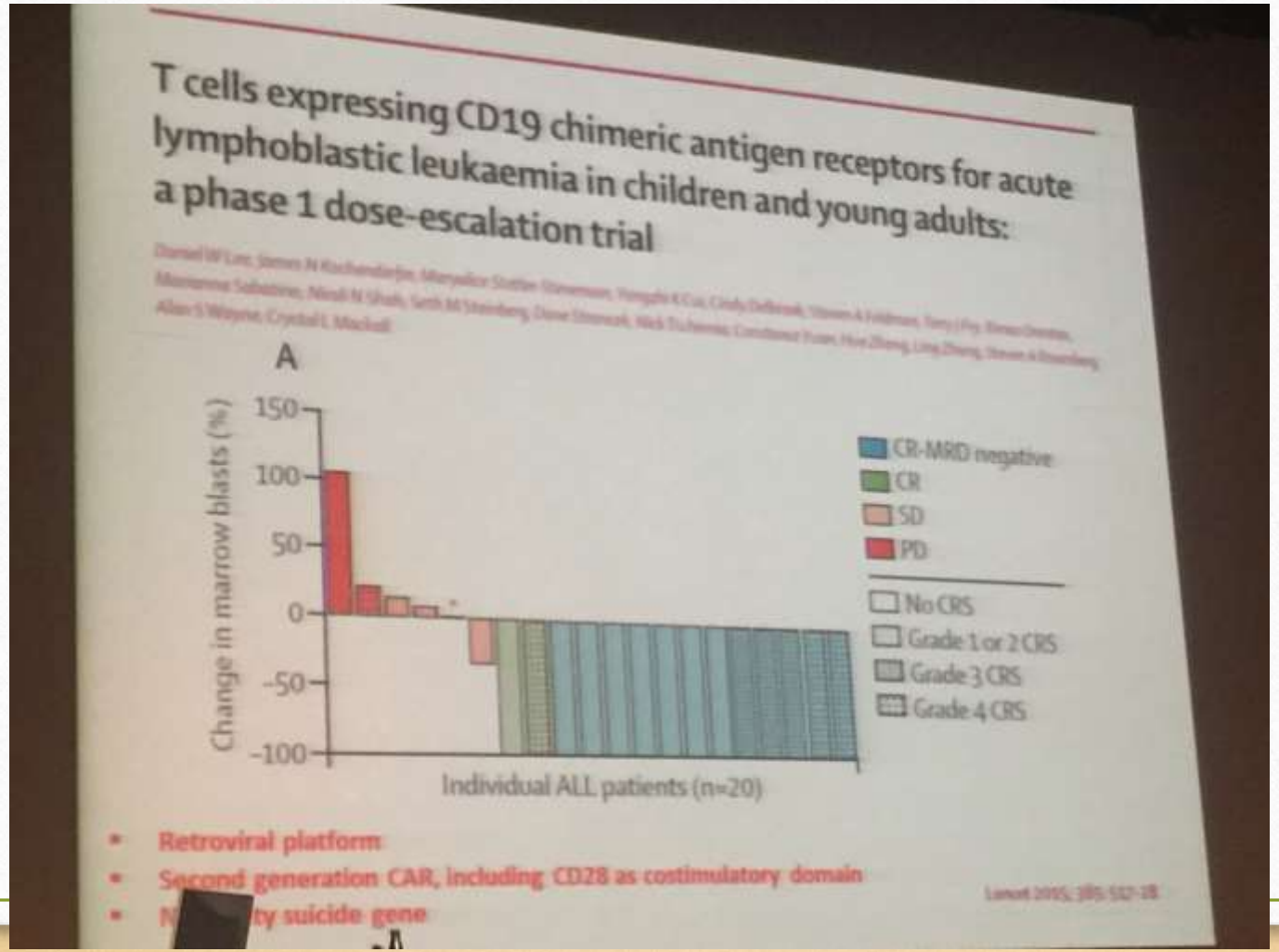
Summary: CTL019 for B cell malignancies

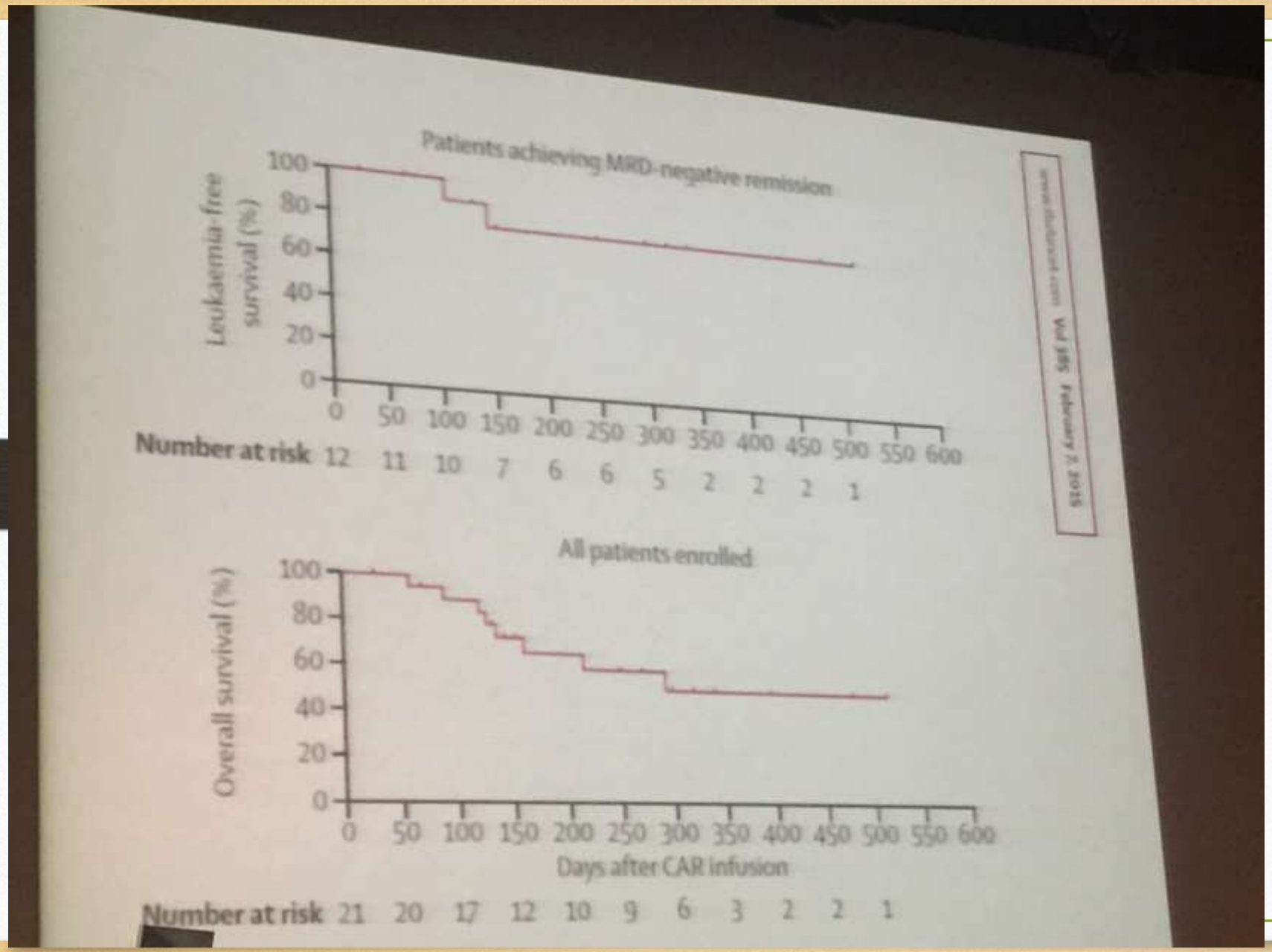
- CAR T cells for relapsed ALL AFTER transplant dramatically more effective than DLI
- Response, OS and RFS not dependent on prior allo SCT.
- CAR T cells BEFORE (as a bridge to) transplant may or may not be necessary
  - No difference in OS, RFS or relapse between patients who have and do not have subsequent transplant.
  - Limited data
  - Select patients at highest risk for relapse to proceed to allogeneic SCT?
- For some patients, CAR T cells may be an effective alternative INSTEAD of transplant.
- CAR therapy holds great promise for patients with advanced, relapsed and/or refractory CLL, ALL, NHL, MM

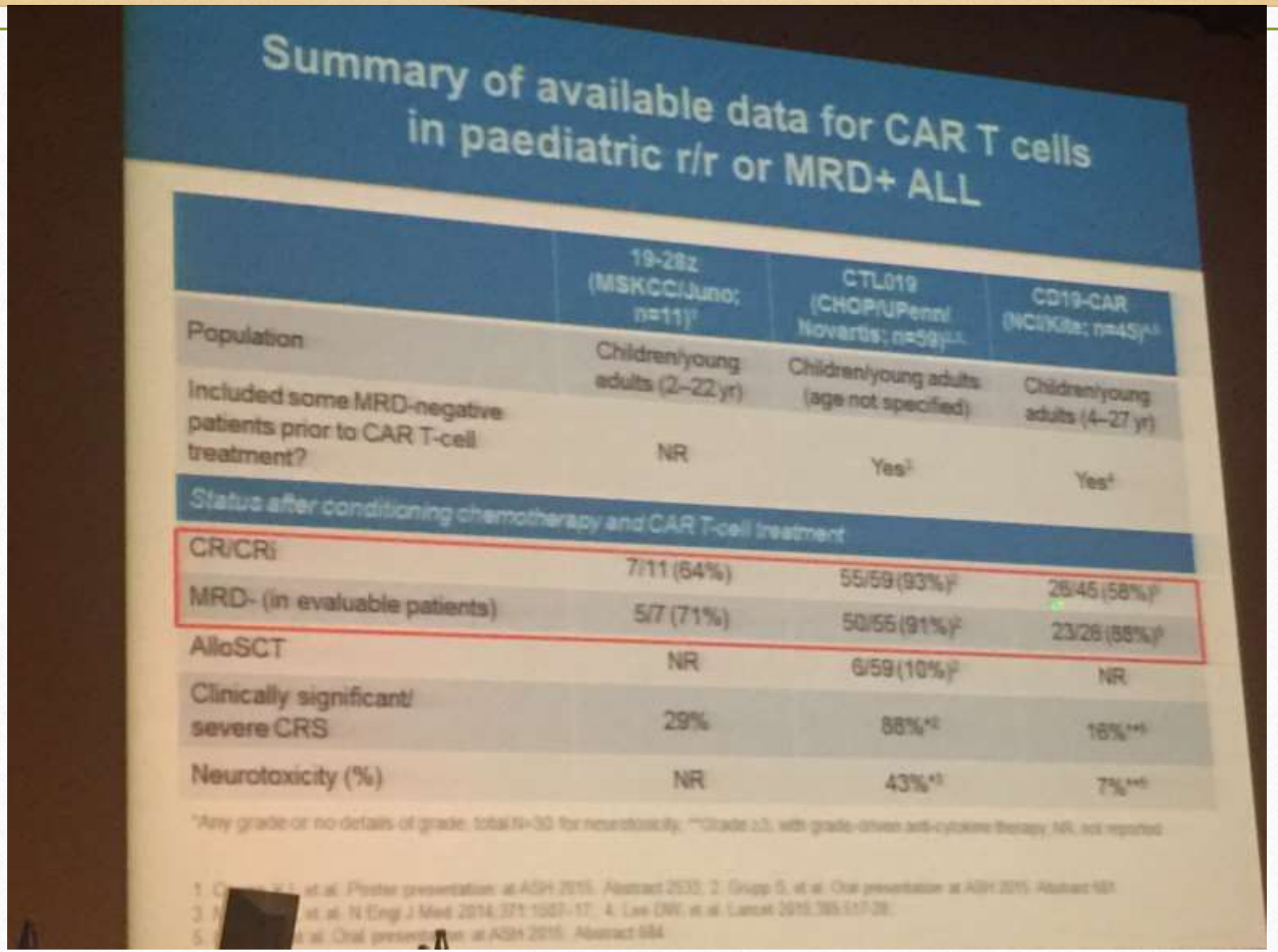

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia
Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.
Lentiviral platform
Second generation CAR, including 4-1BB as costimulatory domain
No Safety suicide gene


Treatment schedule for Car.CD19 T cell therapy
Lymphodepletion
CAR.CD19 T cell infusions
Cytokine monitoring
Day -7
Day 0
Day 3
Day 28
[1]Cy/VP: Etoposide 100 mg/m² daily x 2 days, Cyclophosphamide 440 mg/m² daily x 2 days
[2]Flu/Cy: Fludarabine 30 mg/m² daily x 4 days, Cyclophosphamide 500 mg/m² daily x 2 days
[3]Flu/Cy-B: Fludarabine 30 mg/m² daily x 3 days, Cyclophosphamide 300 mg/m² daily x 3 days
[4]CVAD-B: Methotrexate 1000 mg/m² day 1, Cytarabine 1000 mg/m² every 12 hours days 2, 3
[5]CVAD-A: Cyclophosphamide 300 mg/m² every 12 hours days 1-3, Vincristine 2 mg day 3, Adriamycin 50 mg/m² day 3
0,1x10⁸ cells/Kg to 1x10⁸ cells/Kg, below 50Kg pts
5x10⁸ cells/Kg to 50x10⁸ cells/Kg, over 50Kg pts
Transduction efficiency: 5,5-45%
Dose of 0,76-20,6x10⁶/Kg CAR.CD19 T cells


Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia
N ENGL J MED 371;16 NEJM.ORG OCTOBER 16, 2014
A
Probability of Event-free Survival
Survival rate at 6 mo, 67% (95% CI, 51–88)
Months since Infusion
No. of Patients: 30 19 14 5 1 1 1 1 1
B
Probability of Overall Survival
Months since Infusion
No. of Patients: 30 26 19 10 4 3 1 1 1


T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial
A
Change in marrow blasts (%)
150
100
50
0
-50
-100
Individual ALL patients (n=20)
CR-MRD negative
CR
SD
PD
No CRS
Grade 1 or 2 CRS
Grade 3 CRS
Grade 4 CRS
Retroviral platform
Second generation CAR, including CD28 as costimulatory domain
ty suicide gene


Patients achieving MRD-negative remission
Leukaemia-free survival (%)
100
80
60
40
20
0
0 50 100 150 200 250 300 350 400 450 500 550 600
Number at risk 12 11 10 7 6 6 5 2 2 2 1
All patients enrolled
Overall survival (%)
100
80
60
40
20
0
0 50 100 150 200 250 300 350 400 450 500 550 600
Days after CAR infusion
Number at risk 21 20 17 12 10 9 6 3 2 2 1



Summary of available data for CAR T cells in paediatric r/r or MRD+ ALL

	19-28z (MSKCC/Juno; n=11)[1]	CTL019 (CHOP/UPenn/ Novartis; n=59)[2,3]	CD19-CAR (NCI/Kite; n=45)[4,5]
Population	Children/young adults (2–22 yr)	Children/young adults (age not specified)	Children/young adults (4–27 yr)
Included some MRD-negative patients prior to CAR T-cell treatment?	NR	Yes[3]	Yes[4]
Status after conditioning chemotherapy and CAR T-cell treatment			
CR/CRi	7/11 (64%)	55/59 (93%)[3]	26/45 (58%)[4]
MRD- (in evaluable patients)	5/7 (71%)	50/55 (91%)[3]	23/26 (88%)[4]
AlloSCT	NR	6/59 (10%)[3]	NR
Clinically significant/ severe CRS	29%	88%*[3]	16%**[5]
Neurotoxicity (%)	NR	43%*[3]	7%**[5]

*Any grade or no details of grade; total N=30 for neurotoxicity. **Grade ≥3, with grade-driven anti-cytokine therapy. NR, not reported.

1. [illegible] et al. Poster presentation at ASH 2015. Abstract 2533. 2. Grupp S, et al. Oral presentation at ASH 2015. Abstract 681.
3. [illegible] et al. N Engl J Med 2014;371:1507–17. 4. Lee DW, et al. Lancet 2015;385:517–28.
5. [illegible] et al. Oral presentation at ASH 2015. Abstract 684.

İmmün tedavide alışılmamış toksisiteler

SİTOKİN SALGILANMA SENDROMU

Hem Blinatumomab hrm de CAR T –hücre infüzyonundan sonra görülür.

Tümör yüküyle direkt ilişkilidir.

Erken oluşur (Tedaviden sonraki ilk 3-5 günde)

Sıklıkla ciddi, bazen yaşamı tehdir edicidir.

NÖROLOJİK BULGULAR

Genellikle kısa, genellikle uzun süreli sekel bırakmadan kendiliğinden iyileşir.

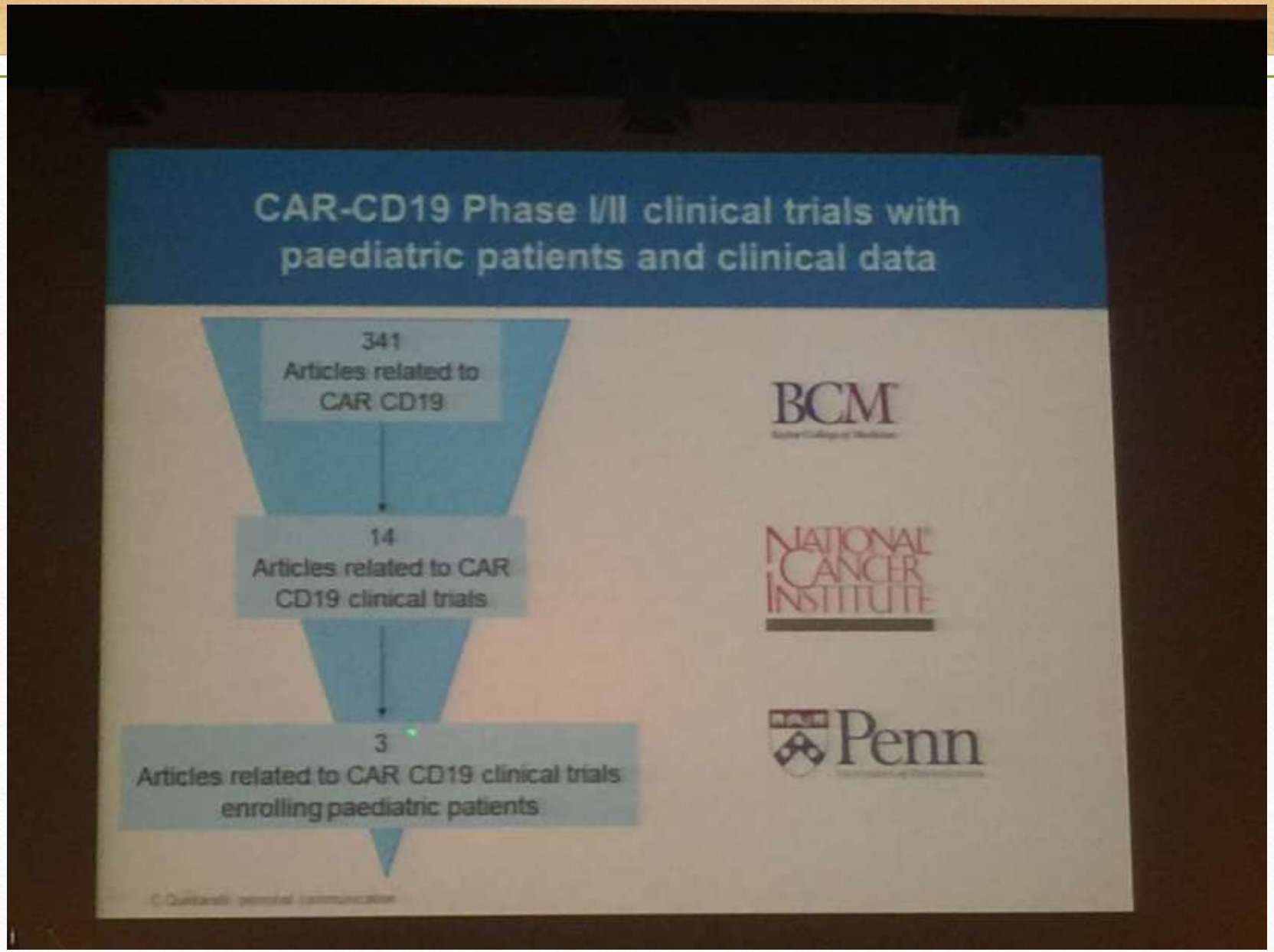
Blinatumomab tedavisinden sonra oluşur, ciddiyeti erişkinlerden azdır.

Recruiting trials for CAR CD19 in the paediatric setting

Region	Number of studies	Enrolling centre	CAR construct	Clinical trial identifier	Phase
East Asia	5	Shanghai Tongji Hospital	2nd generation	NCT02537977	I/II
		Shanghai GeneChem Co	4-1BB/;	NCT02672501	I/II
		Shenzhen Second People's Hospital	CD28/;	NCT02456350	I
		Sinobioway Cell Therapy Co	?	NCT02735682	I/II
		Chinese PLA General Hospital	4-1BB/;	NCT01864889	I
North America	8	Seattle Children's Hospital	4-1BB/;	NCT02028455	I/II
		Baylor College of Medicine	CD28/; vs 4-1BB/CD28/;	NCT01853631	I
		MD Anderson Cancer Center	CD28/;	NCT02529813	I
		Baylor College of Medicine	CD28/;	NCT02050347	I
		National Cancer Institute	CD28/;	NCT01593696	I
		MSKCC	CD28/;	NCT01865837	I
		MSKCC	CD28/; (EBV-CTL)	NCT01430390	I
		Kite Pharma	CD28/;	NCT02625480	I/II
		UPenn/Novartis	4-1BB/;	NCT02435849	II
Europe	2	Uppsala University, Sweden (Adults)	3rd generation	2013-001393-19	I/II
		Novartis Pharma multicentre trial	4-1BB/;	2013-003205-25	II

EBV-CTL, Epstein-Barr virus-specific cytotoxic T lymphocyte

https://clinicaltrials.gov/; https://www.clinicaltrialsregister.eu


CAR-CD19 Phase I/II clinical trials with paediatric patients and clinical data
341
Articles related to CAR CD19
14
Articles related to CAR CD19 clinical trials
3
Articles related to CAR CD19 clinical trials enrolling paediatric patients
BCM
NATIONAL CANCER INSTITUTE
Penn

CAR-CD19 Phase I/II clinical trials with paediatric patients and clinical data

BCM

Infusion of donor-derived CD19-redirected virus-specific T cells for B-cell malignancies relapsed after allogeneic stem cell transplant: a phase 1 study

Penn

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

NATIONAL CANCER INSTITUTE

T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial

CAR CD19 trials with clinical results: construct and manufacturing specifications

	NCI/Kite Pharma[1]	CHOP/UPenn/Novartis[2]	Baylor College of Medicine[3]
Type of construct	CD28/ζ	4-1BB/ζ	CD28/ζ
Type of vector	γRetrovirus	Lentivirus	γRetrovirus
Starting material	Patient-derived fresh apheresis	Patient-derived fresh/frozen apheresis	Frozen PBMC
Purification of cells	CD3+	–	EBV/CMV CTL
Cytokine during production	IL2	IL2	IL2
Activation	CD3/CD28 paramagnetic beads	CD3/CD28 paramagnetic beads	EBV/CMV-infected cells
Total days of production	11	12	40 ± 12
Status before infusion	Fresh	Frozen	Frozen

CMV: cytomegalovirus; IL2: interleukin-2

1. Lee DW, et al. Lancet. 2015;385:517-28. 2. Maude SL, et al. N Engl J Med. 2014;371:1507-17. 3. Cruz CR, et al. Blood. 2013;122:2965-73.

CAR CD19 trials with clinical results: clinical trial specifications

	NCI/Kite Pharma[1]	CHOP/UPenn/Novartis[2]	Baylor College of Medicine[3]
Trial Phase	I	I/II	I
Patient cohort	Children/young adults (up to 30 yr) with r/r B-cell leukaemia or lymphoma	Children/young adults and adults with r/r B-cell leukaemia: T-ALL CD19+ (1 patient)	Relapsed or high-risk B-cell malignancies after HSCT
Patients (N)	21	25/30 were paediatric	3/8 were paediatric
Lympho-depletion	Fludarabine/ cyclophosphamide	Etoposide/cyclophosphamide Fludarabine/cyclophosphamide Methotrexate/cytarabine Cyclophosphamide/vincristine/ Adriamycin	None
Prophylactic therapy	Intrathecal chemotherapy before infusion	None	None

HSCT, [illegible]

1. Lee DW, et al. Lancet 2015;385:517–28. 2. Maude SL, et al. N Engl J Med 2014;371:1507–17.
3. Cruz CR, et al. Blood 2013;122:2965–73.

CAR CD19 trials with clinical results: outcomes

	NCI/Kite Pharma[1]	CHOP/UPenn/ Novartis[2]
Morphological CR at 1 month	14/20 (70%)	27/30 (90%)
MRD- by Flow	12/20 (60%)	22/28 (79%)
Sustained remission**	10*/20 (50%)	19/30 (63%)
EFS	9/20 (45% at 12 months)	20/30 (67% at 6 months)
OS	10/20 (52% at 10 months)	23/30 (78% at 6 months)
Relapse CD19+	8/10 (80%)	3/7 (43%)
Study-related deaths	None	None
Grade 1–2 CRS	10/21 (48%)	22/30 (73%)
Grade 3–4 CRS	6/21 (28%)	8/30 (27%)

Baylor College of Medicine[3]

1) CR x 3 months
2) Progressive disease
3) CR x 2 months

*Patients who underwent HSCT after CAR T-cell infusion
**At end of study
CR, complete remission; CRS, cytokine release syndrome; EFS, event-free survival;
MRD-, minimal residual disease negative; OS, overall survival

1. Lee DW, et al. Lancet 2015;385:517–28; 2. Maude SL, et al. N Engl J Med 2014;371:1507–17; 3. Cruz CR, et al. Blood 2013;122:2965–73.

Summary of available data for CAR T cells in paediatric r/r or MRD+ ALL

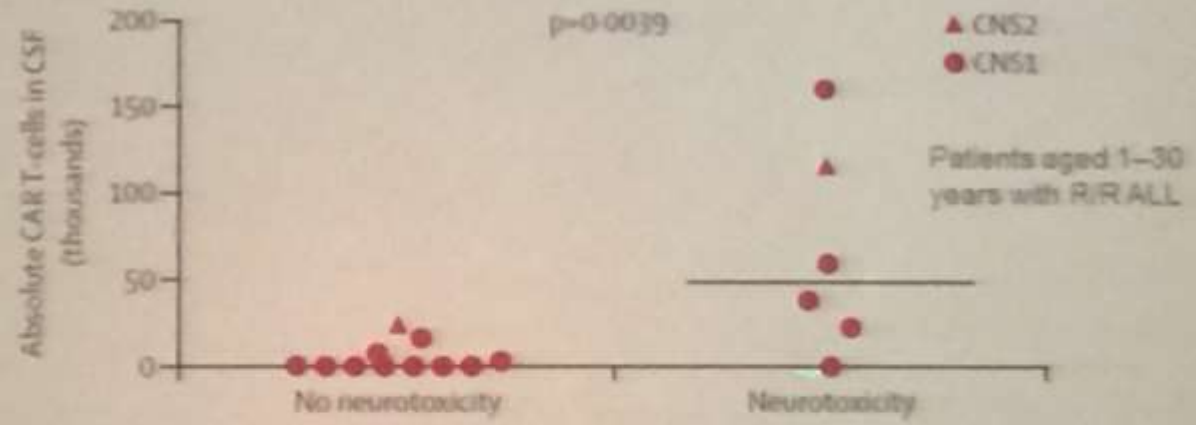
	19-28z (MSKCC/Juno; n=11)[1]	CTL019 (CHOP/UPenn/ Novartis; n=59)[2,3]
Population	Children/young adults (2–22 yr)	Children/young adults (age not specified)
Included some MRD-negative patients prior to CAR T-cell treatment?	Not reported	Yes[2]
CR/CRi	7/11 (64%)	55/59 (93%)[2]
MRD-negativity (in evaluable patients)	5/7 (71%)	50/55 (91%)[2]
Allogeneic HSCT	NR	6/59 (10%)[2]
Clinically significant/severe CRS	29%	88%*[3]
Neurotoxicity (%)	NR	43%*[3]

*Any grade or no details of grade; total N=30 for neurotoxicity

1. Gunset KJ, et al. Poster presentation at ASH 2015. Abstract 2533. 2. Grupp S, et al. Oral presentation at ASH 2015. Abstract 681.
3. Maude SL, et al. N Engl J Med 2014;371:1507–17

T-cell mediated inflammation of the CNS is a possible cause of the neurological events seen with T-cell engaging immunotherapy

Association between KTE-C19 levels in the CSF and neurotoxicity in R/R ALL[1]



- 19-28z CAR T cells: detected in the CSF of 3/4 patients with neurological AEs in whom CSF samples were available[2]

AE, adverse event; CSF, cerebrospinal fluid

1. Lee DW, et al. Lancet 2015;385:517–28.

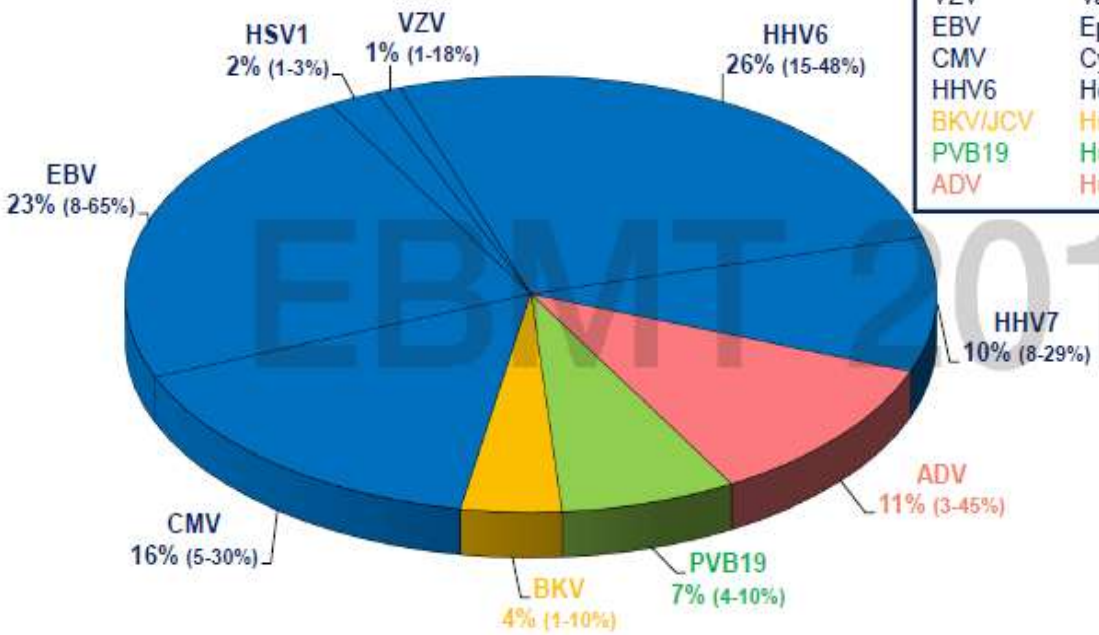
Mabs vs CARs

- Geçici etki
- Vücutta sınırlı dağılım
- Hedef molekülde yüksek ekspresyon ihtiyacı

- Hücre ömrünün uzamasının kalıcılığı
- Solid dokulara aktif geçiş
- Düşük antijen varlığında tümör hücrelerini tanıma
- Hedefi tanıdıktan sonra çoklu litik aktiviteler

Frequency of detection of DNA viruses after HSCT

HSV1	Herpes simplex virus 1
HSV2	Herpes simplex virus 2
VZV	Varicella-zoster virus
EBV	Epstein-Barr virus
CMV	Cytomegalovirus
HHV6	Herpesvirus 6
BKV/JCV	Human Polyomaviruses 1 and 2
PVB19	Human Parvovirus B19
ADV	Human Adenovirus (A-G, 1-67)

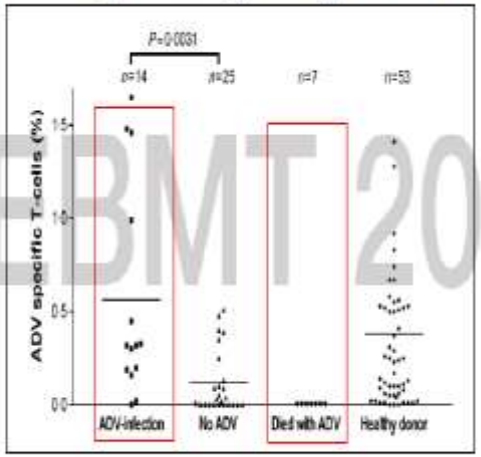


- 80% of viral infection/reactivation after HSCT caused by Herpes viruses
- 75% of patients positive for ≥ 1 virus (up to 5 viruses reported)
- overall mortality of viral infection after transplantation 17-35%

modified from Lion, ESH-EBMT, 2014; Papadopoulou et al., Sci Transl Med 2014

Best therapeutic option - adoptive T-cell therapy

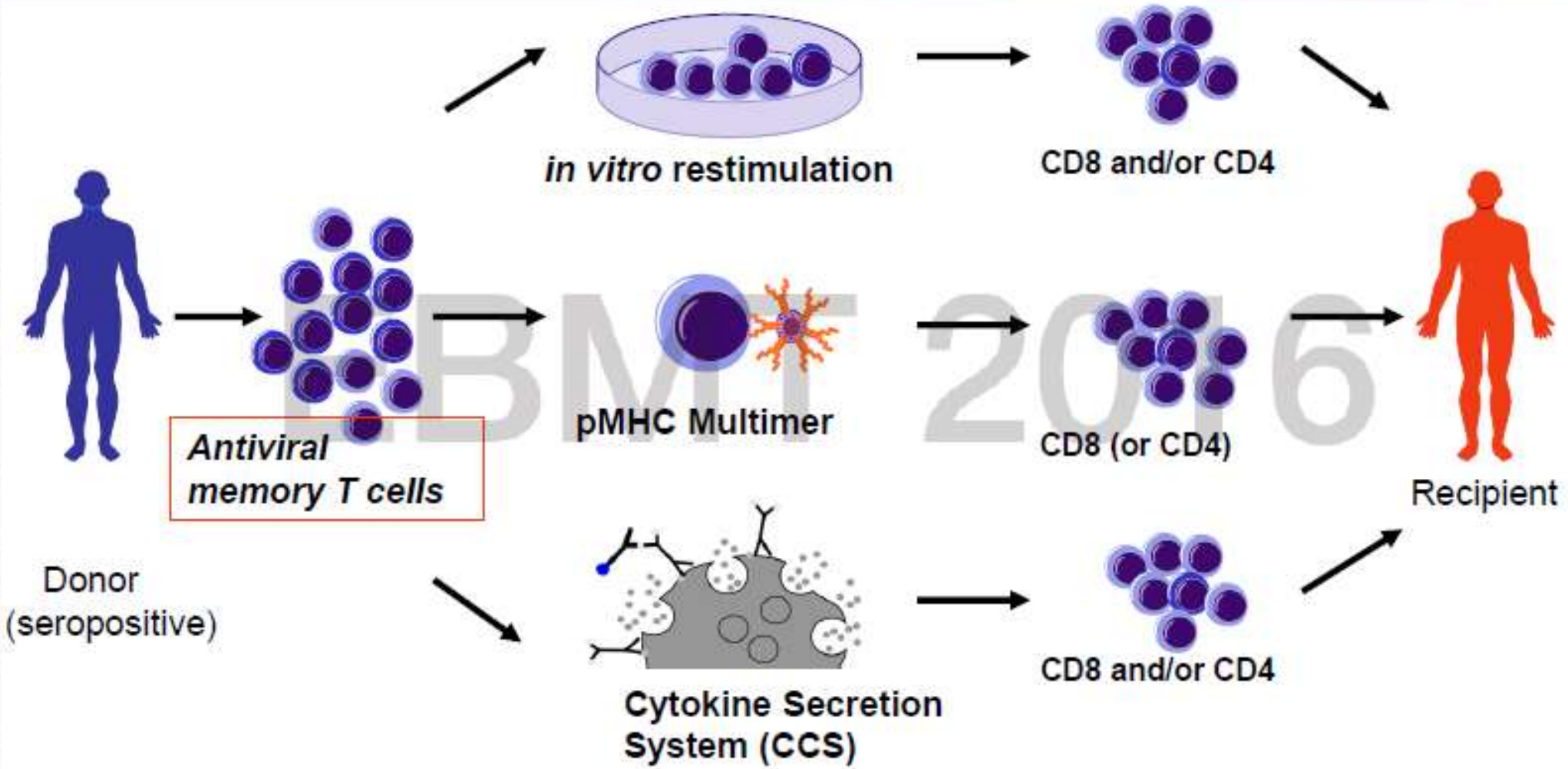
- antiviral drugs limit but do not clear infection and associated with severe side effects
- elimination of viruses only achieved by recovery of cellular immunity



➡ *Can adoptively transferred virus-specific T cells effectively **restore immunity** and **control established infection** or **virus-induced malignancies** after transplantation?*

YES, they can!

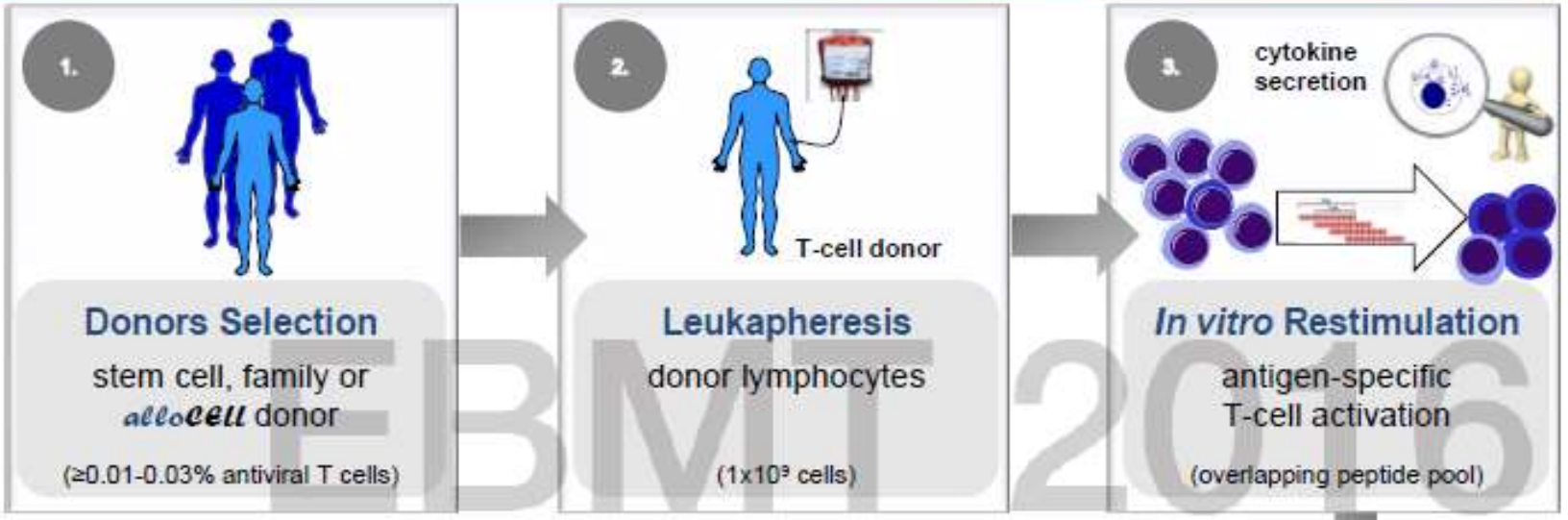
Status quo:
Methods to generate clinical-grade virus-specific T cells



Feuchtinger et al. (2006) Br J Haematol
Barker et al. (2010) Blood
Peggs et al. (2011) Lancet
Icheva et al. (2013) J Clin Oncol
Feucht et al. (2015) Blood

Moosmann et al. (2010) Blood
Feuchtinger et al. (2010) Blood
Quasim et al. (2011) Br J Haematol
Tischer et al. (2014) J Transl Methods

Manufacturing of clinical-grade virus-specific T cells for adoptive immunotherapy post transplantation



Manufacturing license, MHH

2014	**CMV** (pp65, first ATMP at MHH)
2015	**EBV, ADV, CMV/ADV** (EBNA1/Consensus, Hexon, pp65/Hexon)
2015	**CMV /EBV/ADV/others** (pp65/EBNA1/Consensus/Hexon/others)

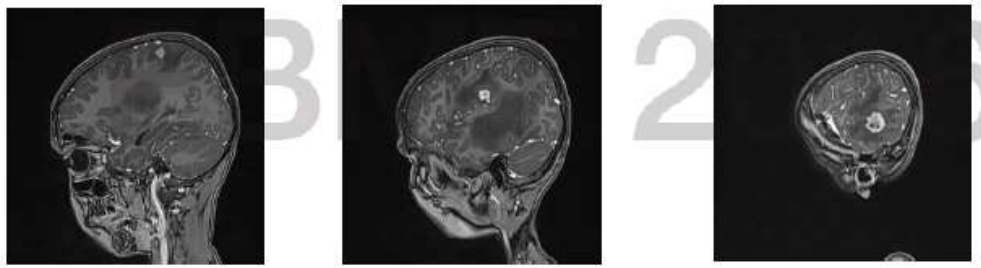
Tischer, Priesner et al., JIM 2014

MHH

Patient 1: EBV-specific T-cell transfer from third party donor in a patient with primary CNS PTLD

Patrick Hundsdörfer
Karlheinz Seeger
Charité Berlin

- 11-year-old boy after Liver-tx 2005 (Alagille syndrome)
- Tacrolimus + MMF
- 04/2015 headache and vomiting



- diffuse large B cell lymphoma, CD20+, EBV+
- systemic Rituximab + intrathecal Rituximab + AraC + MTX + prednisone
- consolidating treatment with EBV-specific T cells

Patient 1: EBV-specific T-cell transfer from third party donor in a patient with primary CNS PTLD

Donor Recruitment

- EBV-seropositive mother with insufficient numbers of EBV-specific T cells
- 8 potential donors from *allocell* (≥ 5/10 HLA match)

	HLA-										
	A	A	B	B	C	C	DRB1	DRB1	DQB1	DQB1	Match
patient	*03	*03	*07	*14	*07	*08	*15	*01	*05	*05	5/10
donor	*03	*11	*07	*07	*07	*07	*15	*16	*05	*06	

- negative crossmatch

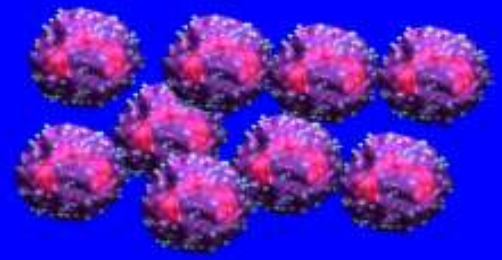
Pretesting for EBV-specific T-cell enrichment using cytokine secretion assay (CSA)

Antigen	% $CD3^+/IFN\text{-}\gamma^+$	$\%CD4^+/IFN\text{-}\gamma^+$	$\%CD8^+/IFN\text{-}\gamma^+$
EBNA-1/Consensus Pool (before enrichment)	1.25	0.44	2.48
EBNA-1/Consensus Pool (after enrichment)	48.35	16.83	68.71

Manufacturing and adoptive T-cell transfer

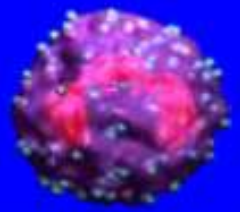
- EBNA-1- and Consensus-specific T cells (25 x 10^3 CD3+ T cells/kg bw; 50% CD3+IFN-γ+ T cells
- manufacturing of 1 T-cell product which was given as 5 T-cell doses (1 fresh, 4 cryopreserved, > 4 weeks)
- no acute or delayed side effects
- detection of EBV-specific T cells in patient's blood with and/or without expansion

Goal: Explore Methods to Expand NK Cells for Clinical Use in Humans with Cancer



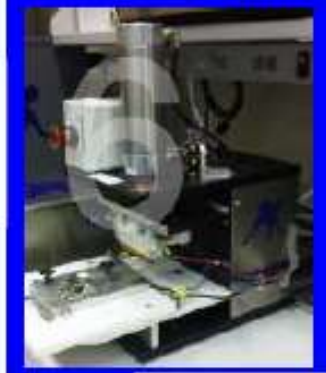
Developed a method to expand highly-activated clinical grade NK Cells using EBV-LCL feeders under GMP Conditions

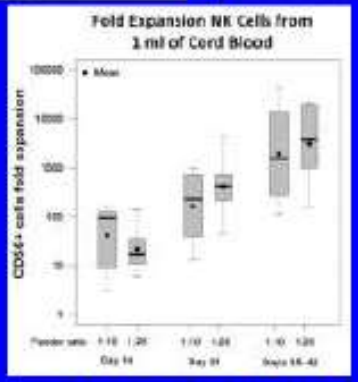
M. Berg and R. Childs et al Cytotherapy 2009
R. Childs and M. Berg M. Hematology ASH Educ Program 2013
R. Childs and M. Carlsten M. Nature Reviews Drug Discovery 2015



NK Cell

Developed a method to expand NK cells from a minute fraction of selectively accessed cord blood





S. Vasu and R. Childs Cytotherapy 2015

Automated the NK Cell expansion method using the Miltenyi Prodigy instrument

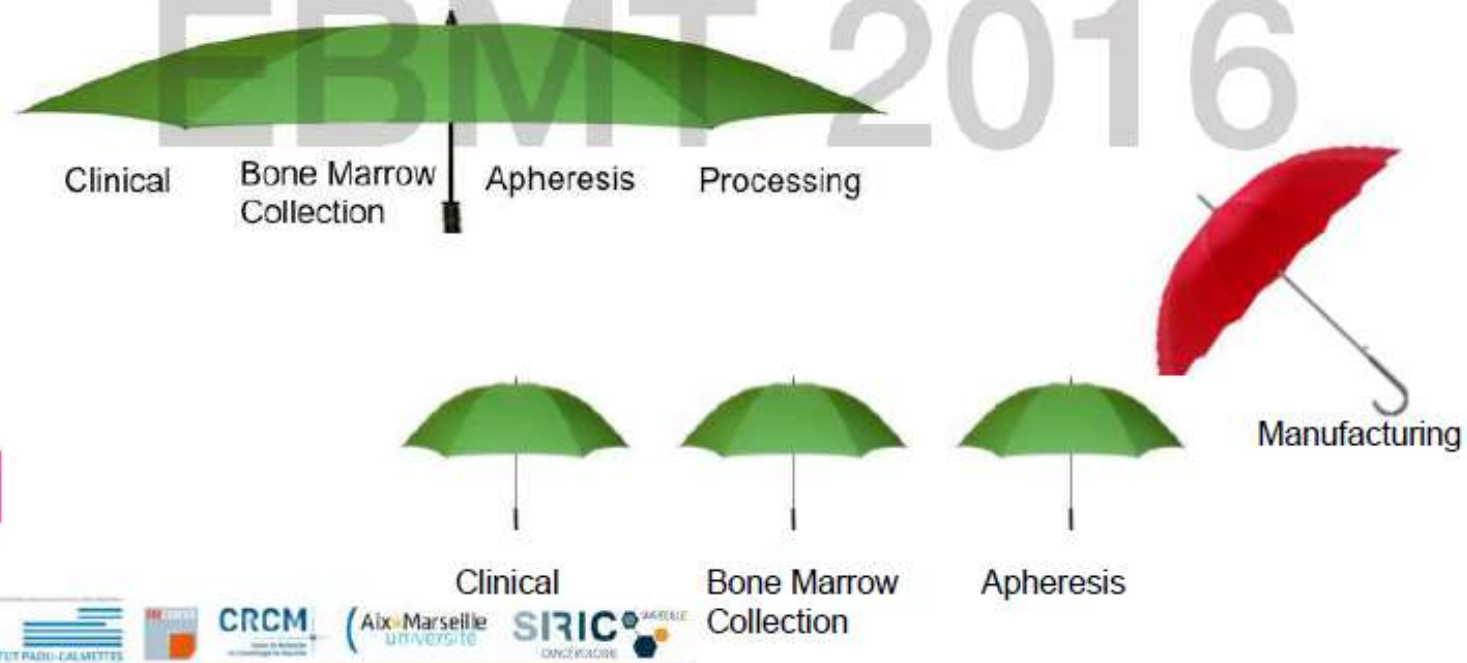
M. Granzin et al. Cytotherapy 2015

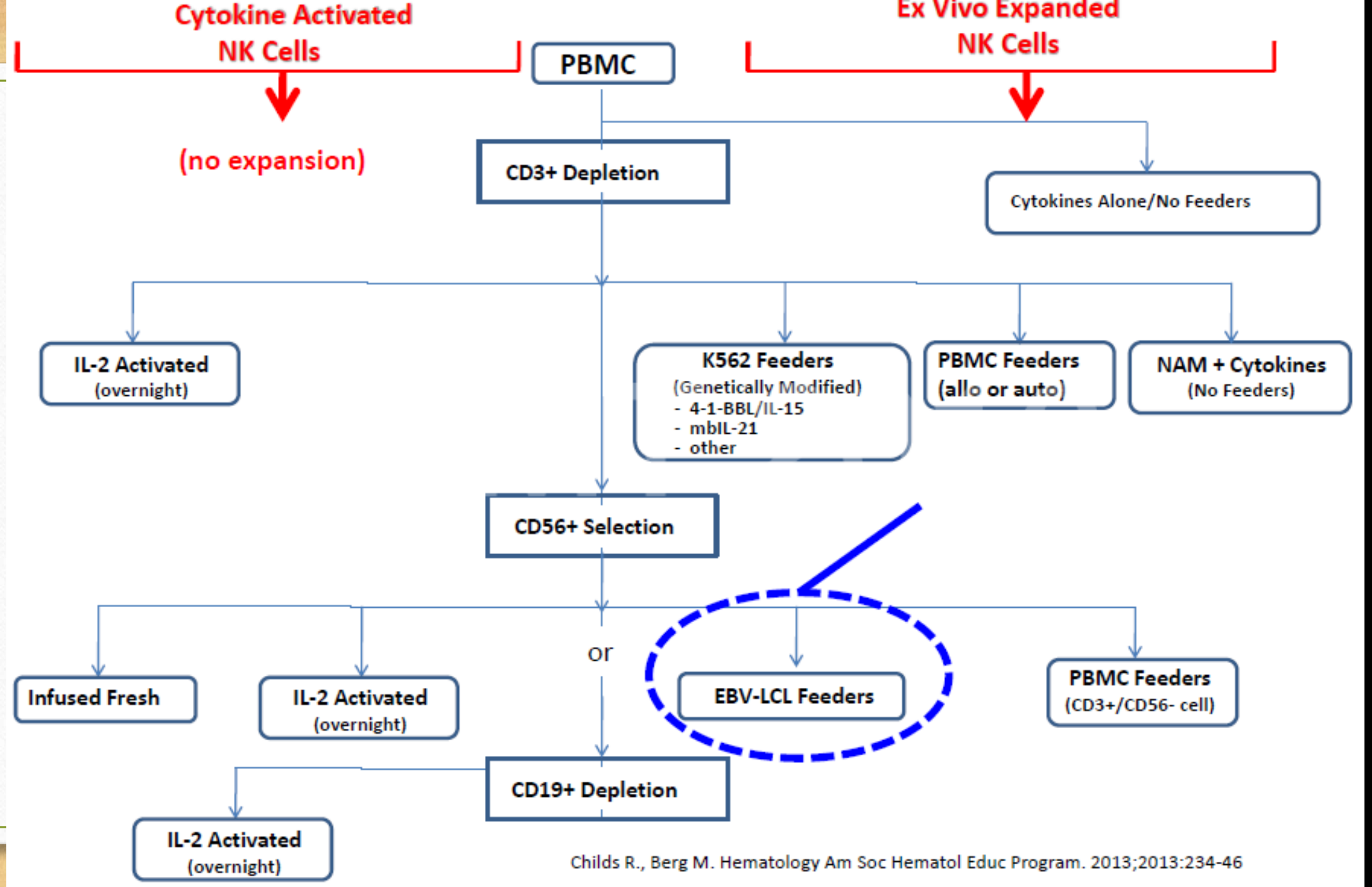
Demonstrated IL-21 dramatically enhances NK cell expansion using EBV/ LCL feeder cells

M. Granzin et al Submitted for publication 2016

SWOT : Threats (1)

- **Manufacturing, production and distribution of cellular therapies of somatic cell therapies and gene therapies by industry – similarly to manufacturing of drugs - challenges the FACT-JACIE model.**





Childs R., Berg M. Hematology Am Soc Hematol Educ Program. 2013;2013:234-46

Cytotherapy, 2015; 17: 1009–1014

International Society for Cellular Therapy
ISCT®

REVIEWS

Quality compliance in the shift from cell transplantation to cell therapy in non-pharma environments

JOAQUIM VIVES, IRENE OLIVER-VILA & ARNAU PLA

Banc de Sang i Teixits, Barcelona, Spain

Abstract

Along with academic and charitable organizations, transfusion centers have ventured into the stem cell field, with the aim of testing of novel cell-based therapeutics in a clinical setting for future marketing approval. The fact that quality management structures, which are required for compliance with good scientific practice regulations, were originally designed for product development in corporate environments represents a major challenge for many developers. In this *Commentary*, challenges that non-pharmaceutical institutions must overcome to translate cell-based products into clinical therapies will be discussed from a quality standpoint. Furthermore, our development experience for a mesenchymal stromal cell–based therapy will be shared as a case study.

Key Words: *cell-based therapeutics, Good Laboratory Practices, Good Manufacturing Practices, product development, quality compliance*

1	Active, not recruiting	**A Pediatric Trial of Genetically Modified Autologous T Cells Directed Against CD19 for Relapsed CD19+ Acute Lymphoblastic Leukemia** **Condition:** B Cell Leukemia **Intervention:** Biological: Autologous CD19 CAR+ EGFTt + T cells
2	Recruiting	**A Pediatric and Young Adult Trial of Genetically Modified T Cells Directed Against CD19 for Relapsed/Refractory CD19+ Leukemia** **Condition:** CD19+ Acute Leukemia **Intervention:** Biological: Patient Derived CD19 specific CAR T cells also expressing an EGFRt
3	Recruiting	**T-Lymphocytes Genetically Targeted to the B-Cell Specific Antigen CD19 in Pediatric and Young Adult Patients With Relapsed B-Cell Acute Lymphoblastic Leukemia** **Condition:** Relapsed B-Cell Acute Lymphoblastic Leukemia **Interventions:** Procedure: leukapheresis or collection of PBMCs; Drug: cyclophosphamide based chemotherapy regimens; Biological: modified T cells
4	Recruiting	**Therapy for Pediatric Relapsed or Refractory Precursor B-Cell Acute Lymphoblastic Leukemia and Lymphoma** **Conditions:** Recurrent B-Cell Childhood Acute Lymphoblastic Leukemia; Recurrent Childhood B-Lymphoblastic Lymphoma **Interventions:** Drug: dexamethasone; Drug: vincristine sulfate; Biological: rituximab; Drug: clofarabine; Drug: cyclophosphamide; Drug: etoposide; Biological: aldesleukin; Drug: pegaspargase; Drug: methotrexate; Drug: mercaptopurine; Drug: cytarabine; Drug: mitoxantrone; Drug: teniposide; Drug: vinblastine; Biological: natural killer cell infusion; Other: laboratory biomarker analysis; Drug: therapeutic hydrocortisone; Procedure: allogeneic hematopoietic stem cell transplantation
5	Recruiting	**Salvage Therapy With Chemotherapy and Natural Killer Cells in Relapsed/Refractory Paediatric T Cell Lymphoblastic Leukaemia and Lymphoma** **Condition:** Relapsed/Refractory Paediatric T Cell Lymphoblastic Leukaemia and Lymphoma **Intervention:** Biological: Expanded haploidentical natural killer cells (NKAEs)

Intervention: Biological: Expanded haploidentical natural killer cells (NKAEs)

---

6 **Completed** **Pilot Study of Haploidentical Natural Killer Cell Infusions for Poor Prognosis Non-AML Hematologic Malignancies**

Conditions: Acute Lymphoblastic Leukemia; Chronic Myelogenous Leukemia; Juvenile Myelomonocytic Leukemia; Myelodysplastic Syndrome; Non-Hodgkin's Lymphoma

Interventions: Other: NK Cell Infusion; Biological: Immunotherapy; Device: Miltenyi Biotec CliniMACS device; Drug: Interleukin-2 (IL-2); Drug: Clofarabine; Drug: Cyclophosphamide; Drug: Etoposide

---

7 **Completed** **Pilot Study of Expanded, Donor Natural Killer Cell Infusions for Refractory Non-B Lineage Hematologic Malignancies and Solid Tumors**

Conditions: Leukemia, Myeloid, Acute; Leukemia, Lymphocytic, Acute, T-Cell; Juvenile Myelomonocytic Leukemia Lymphoblastic; T-cell Lymphoblastic Lymphoma; Myelodysplastic Syndrome

Interventions: Procedure: Haploidentical donor derived natural killer cell infusion; Drug: Chemotherapy; Device: CliniMACS

---

8 **Recruiting** **Anti-CD22 Chimeric Receptor T Cells in Pediatric and Young Adults With Recurrent or Refractory CD22-expressing B Cell Malignancies**

Conditions: Follicular Lymphoma; ALL; NHL; Large Cell Lymphoma

Intervention: Biological: CD22-CAR

---

9 **Completed** **Efficacy and Safety Study of StemEx®, to Treat Subjects With High Risk Hematologic Malignancies, Following Myeloablative Therapy**

Conditions: Hematologic Malignancies; Acute Myeloid Leukemia; Lymphoid Leukemia; Chronic Myeloid Leukemia; Hodgkin's Disease; Non-Hodgkin's Lymphoma; Myelodysplastic Syndromes

Intervention: Drug: StemEx®

---

10 **Completed** **Late Effects of Treatment for Sarcomas in Children**

Condition: Sarcoma

Published in final edited form as:
Pediatr Blood Cancer. 2015 August ; 62(8): 1468–1472. doi:10.1002/pbc.25555.

Natural Killer Cell Therapy in Children with Relapsed Leukemia

Jeffrey E. Rubnitz, MD, PhD, **Hiroto Inaba, MD, PhD**, **Guolian Kang, MS**, **Kwan Gan, RN**, **Christine Hartford, MD**, **Brandon M. Triplett, MD**, **Mari Dallas, MD**, **David Shook, MD**, **Tanja Gruber, MD, PhD**, **Ching-Hon Pui, MD**, and **Wing Leung, MD, PhD**
Departments of Oncology, Bone Marrow Transplantation and Cellular Therapy, Biostatistics, and Pathology, St. Jude Children's Research Hospital; and Department of Pediatrics, University of Tennessee Health Science Center, College of Medicine, Memphis, Tennessee

Abstract

Background—Novel therapies are needed for children with relapsed or refractory leukemia. We therefore tested the safety and feasibility of haploidentical natural killer cell therapy in this patient population.

Procedure—Twenty-nine children who had relapsed or refractory leukemia were treated with chemotherapy followed by the infusion of haploidentical NK cells. Cohort 1 included 14 children who had not undergone prior allogeneic hematopoietic cell transplantation (HCT), whereas Cohort 2 included 15 children with leukemia that had relapsed after HCT.

Results—Twenty-six (90%) NK donors were KIR mismatched (14 with one KIR and 12 with 2 KIRs). The peak NK chimerism levels were >10% donor in 87% of the evaluable recipients. In Cohort 1, 10 had responsive disease and 12 proceeded to HCT thereafter. Currently, 5 (36%) are alive without leukemia. In Cohort 2, 10 had responsive disease after NK therapy and successfully proceeded to second HCT. At present, 4 (27%) are alive and leukemia-free. The NK cell infusions and the IL-2 injections were well-tolerated.

Conclusions—NK cell therapy is safe, feasible, and should be further investigated in patients with chemotherapy-resistant leukemia.

Acknowledgments

Supported in part by the National Institutes of Health Cancer Center Support (C
U01 GM092666, and RO1 CA115422, a Center of Excellence Grant from the S
Foundation of Memphis, and the American Lebanese Syrian Associated Charit
American Cancer Society Professor.

We thank Elaine Coustan-Smith and Dario Campana for performing minimal residual disease analyses, our clinical, laboratory, and research office colleagues for data collection; and the many patients and parents who participated in the transplantation and cellular therapy research program.

bjh research paper

Immunotherapy with the trifunctional anti-CD20 x anti-CD3 antibody FBTA05 (Lymphomun) in paediatric high-risk patients with recurrent CD20-positive B cell malignancies

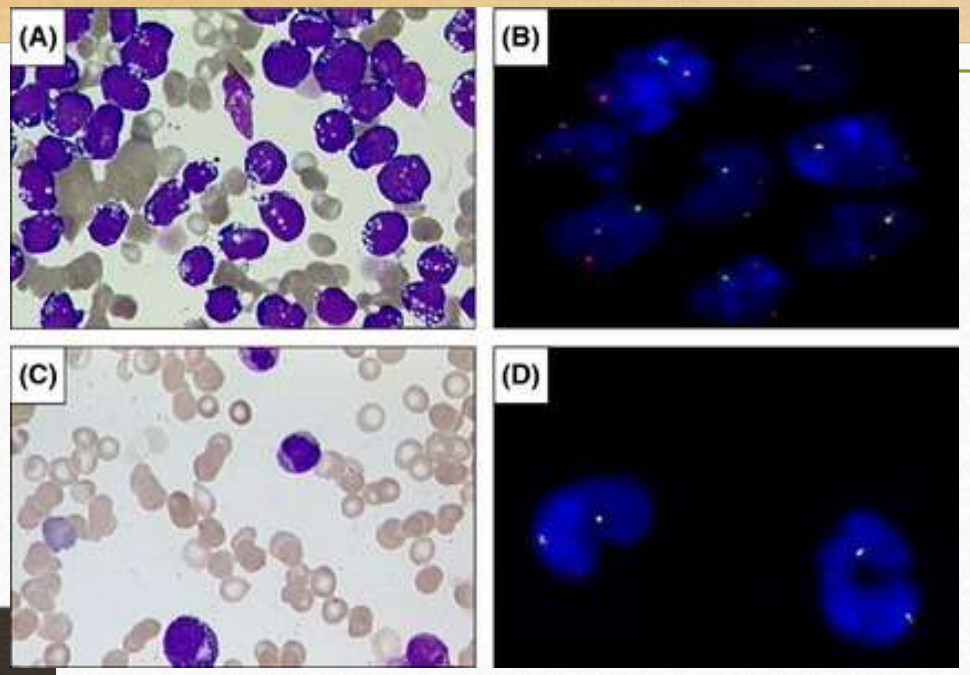
Friedhelm R. Schuster,[1,*] Michael Stanglmaier,[2,*] Wilhelm Woessmann,[3] Beate Winkler,[4] Meinolf Siepermann,[1] Roland Meisel,[1] Paul G. Schlegel,[4] Jürgen Hess,[5] Horst Lindhofer,[2,5] Arndt Borkhardt[1] and Raymund Buhmann[6,7]

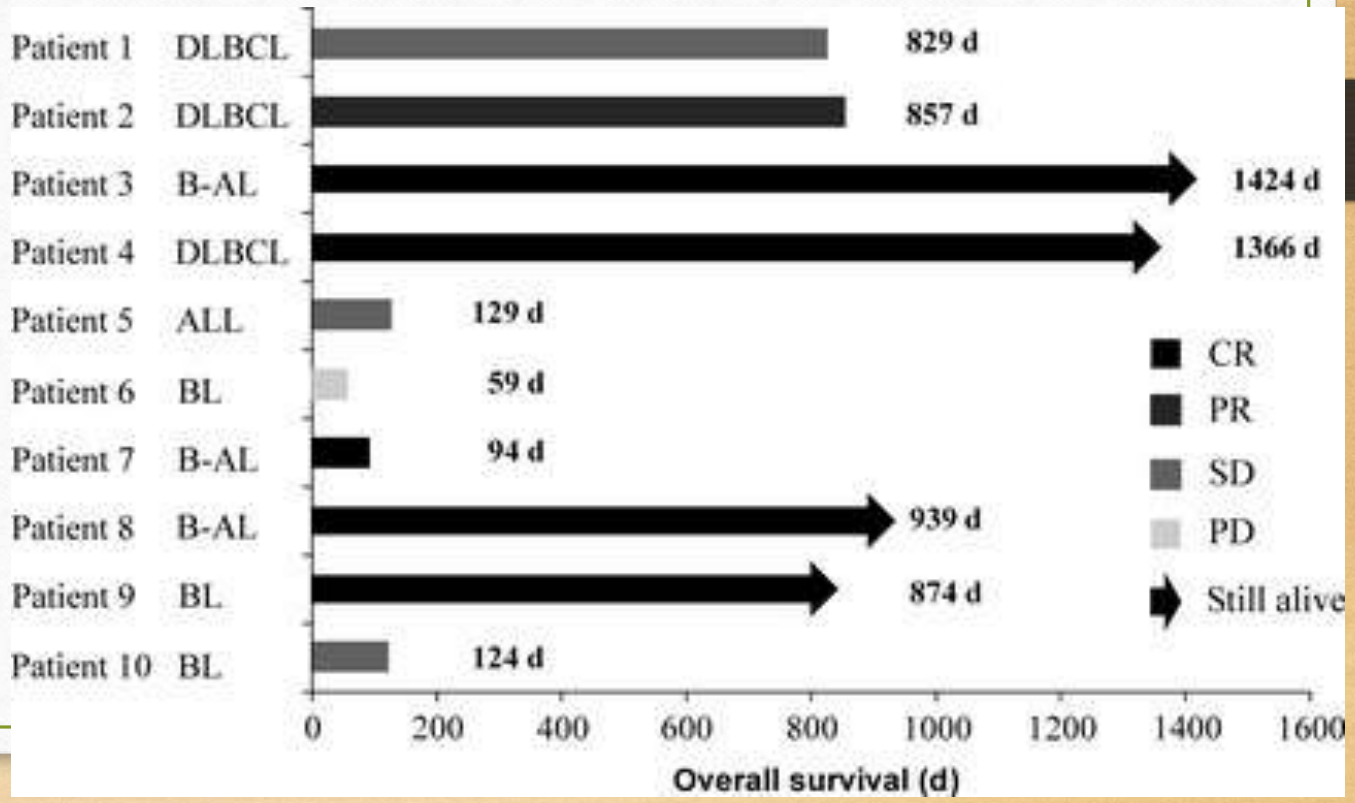
[1]Department of Paediatric Oncology, Haematology and Immunology, University of Duesseldorf, Duesseldorf, [2]TRION Research GmbH, Martinsried, [3]Department of Paediatric Haematology and Oncology, Justus-Liebig University, Giessen, [4]Department of Paediatric Haematology, Oncology and Stem cell Transplantation, University of Wuerzburg, Wuerzburg, [5]TRION Pharma GmbH, Munich, [6]Department of Medicine III and Transfusion Medicine, University Hospital Grosshadern, LMU, and [7]Helmholtz Zentrum Munich, German Research Centre for Environmental Health, Munich, Germany

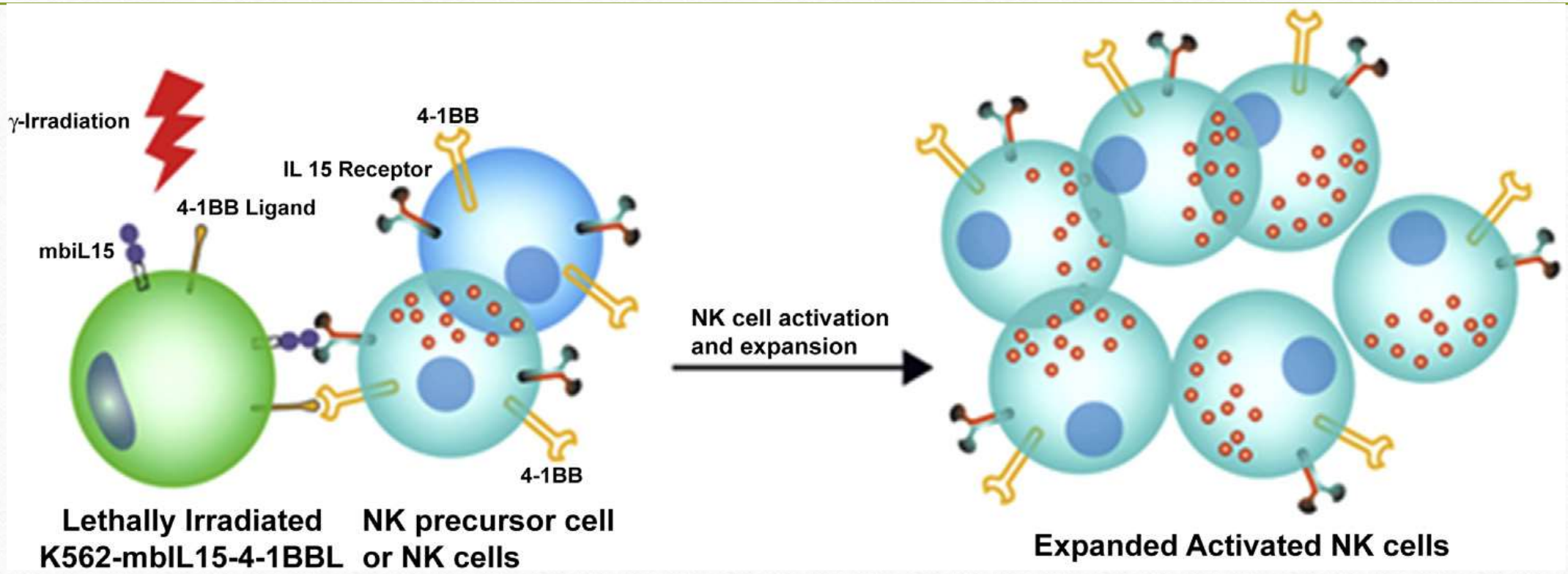
Received 14 July 2014; accepted for publication 4 November 2014

Summary

Children with B cell malignancies refractory to standard therapy are known to have a poor prognosis and very limited treatment options. Here, we report on the treatment and follow-up of ten patients diagnosed with relapsed or refractory mature B-cell Non Hodgkin Lymphoma (B-NHL), Burkitt leukaemia (B-AL) or pre B-acute lymphoblastic leukaemia (pre B-ALL). All children were treated with FBTA05 (now designated Lymphomun), an anti-CD3 x anti-CD20 trifunctional bispecific antibody (trAb) in compassionate use. Within individual treatment schedules, Lymphomun was applied (a) after allogeneic stem cell transplantation (allo-SCT, $n = 6$) to induce sustained long-term remission, or (b) stand alone prior to subsequent chemotherapy to eradicate residual disease before allo-SCT ($n = 4$). Nine of ten children displayed a clinical response: three stable diseases (SD), one partial remission (PR) and five induced or sustained complete remissions (CR). Five of these nine responders died during follow-up. The other patients still maintain CR with a current overall survival of 874–1424 days (median: 1150 days). In conclusion, despite the dismal clinical prognosis of children refractory to standard therapy, immunotherapy with Lymphomun resulted in a favourable clinical outcome in this cohort


(A)
(B)
(C)
(D)


Patient 1 DLBCL
Patient 2 DLBCL
Patient 3 B-AL
Patient 4 DLBCL
Patient 5 ALL
Patient 6 BL
Patient 7 B-AL
Patient 8 B-AL
Patient 9 BL
Patient 10 BL
829 d
857 d
1424 d
1366 d
129 d
59 d
94 d
939 d
874 d
124 d
CR
PR
SD
PD
Still alive
0
200
400
600
800
1000
1200
1400
1600
Overall survival (d)



Cartoon Illustrating Mechanism of Peripheral Blood NK Expansion by K562-mbIL15-41BBL

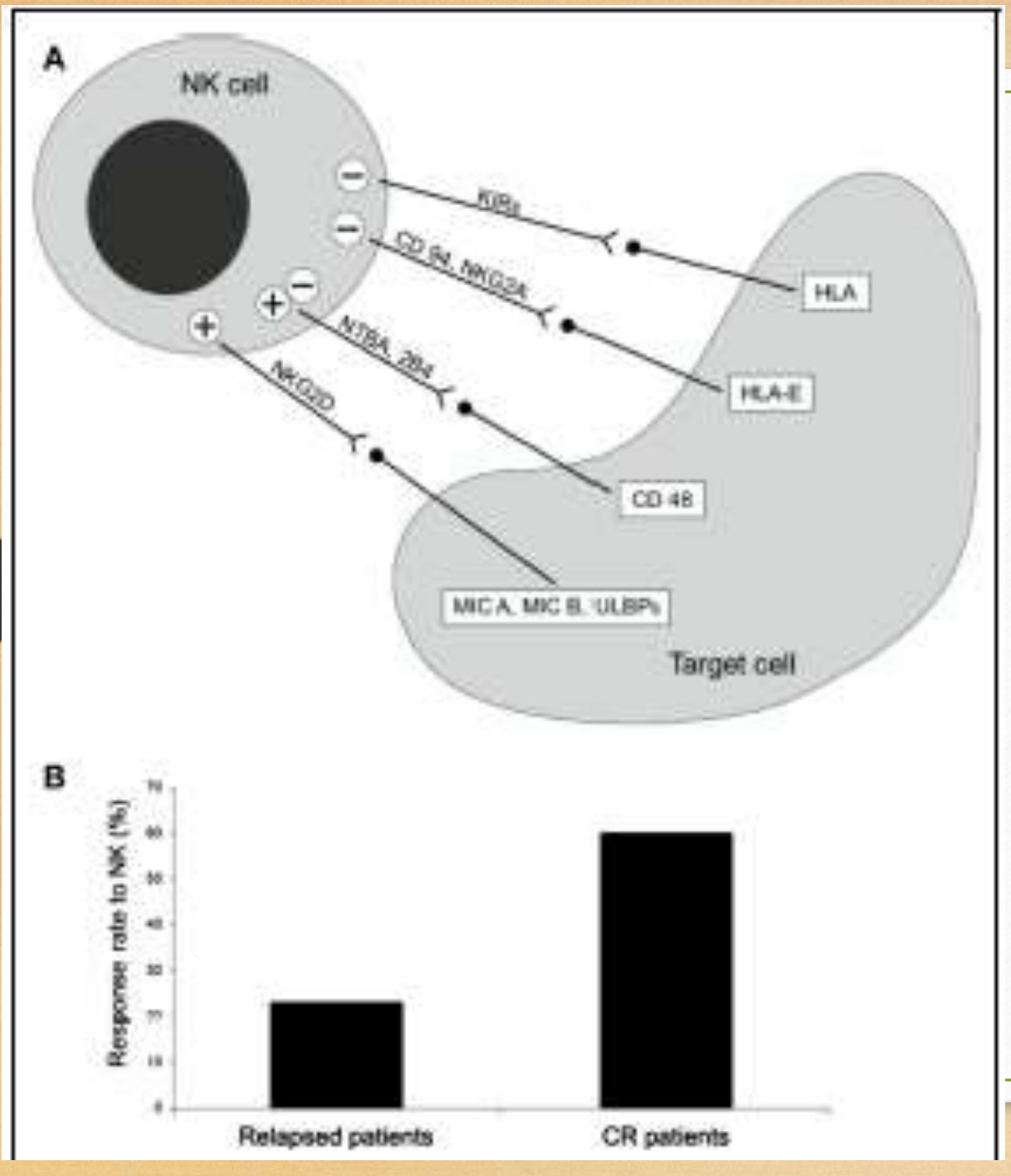


FIGURE 1 | (A) Receptors and ligand involved in NK cell-mediated cytotoxicity. **(B)** Percentage of long-term CR patients after NK cell infusion. Thirteen AML patients, five with active disease, two in molecular relapse, and six in morphological complete remission (CR) were treated with alloreactive NK cells, after fludarabine/cyclophosphamide immunosuppressive chemotherapy. Only one of the five patients with active disease achieved transient CR, whereas the other four patients had no clinical benefit. On the contrary, five out of eight patients showed a response, which in some cases was long-lasting CR [adapted from Curti et al. (5)].

Alloreactive natural killer cells for the treatment of acute myeloid leukemia: from stem cell transplantation to adoptive immunotherapy

*Loredana Ruggeri[1], Sarah Parisi[2], Elena Urbani[1] and Antonio Curti[2]**

frontiers in Immunology

MINI REVIEW
published: 15 October 2015
doi: 10.3389/fimmu.2015.00479

TABLE 1 | Clinical trials with expanded allogeneic NK cells in haploidentical SCT.

Diseases	Phase of trials	Cells	Combined therapy	Institute
High-risk solid tumors	Ongoing phase 2	*Ex vivo* expanded NK cells	Haploidentical HSCT, RIC and IL-2	Samsung Medical Center, Korea
Hematological malignancies	Ongoing	Phase-1 IL-2-activated NK cells	Haploidentical HSCT and RIC	Institut Paoli-Calmette, France
Leukemia and myeloproliferative disease	Ongoing phase 1/2	Haploidentical HSCT, TBI and chemotherapy	*Ex vivo* expanded NK cells	M.D. Anderson Cancer Center, USA
ALL	Ongoing phase 2	K562-mb 15–41 BBL and IL-2 stimulated NK cells	Haploidentical HSCT and chemotherapy	National University Health System, Singapore
AML and ALL	Ongoing phase 1/2	*Ex vivo* expanded	NK-cells haploidentical HSCT	Asan Medical Center, Korea
Relapsed/refractory pediatric acute leukemia	Ongoing phase 2	Activated and expanded NK cells	Haploidentical HSCT and salvage chemotherapy	Hospital Universitario La Paz, Spain
Myelodisplastic syndrome and leukemia	Completed phase 1/2	IL-2-activated NK cells	Haploidentical HSCT, chemotherapy and IL-2	M.D. Anderson Cancer Center, USA

Leukemia (2015) 29, 1 – 10

www.nature.com/leu

REVIEW

Cell-based strategies to manage leukemia relapse: efficacy and feasibility of immunotherapy approaches

A Rambaldi[1], E Biagi[2], C Bonini[3], A Biondi[2] and M Introna[1]

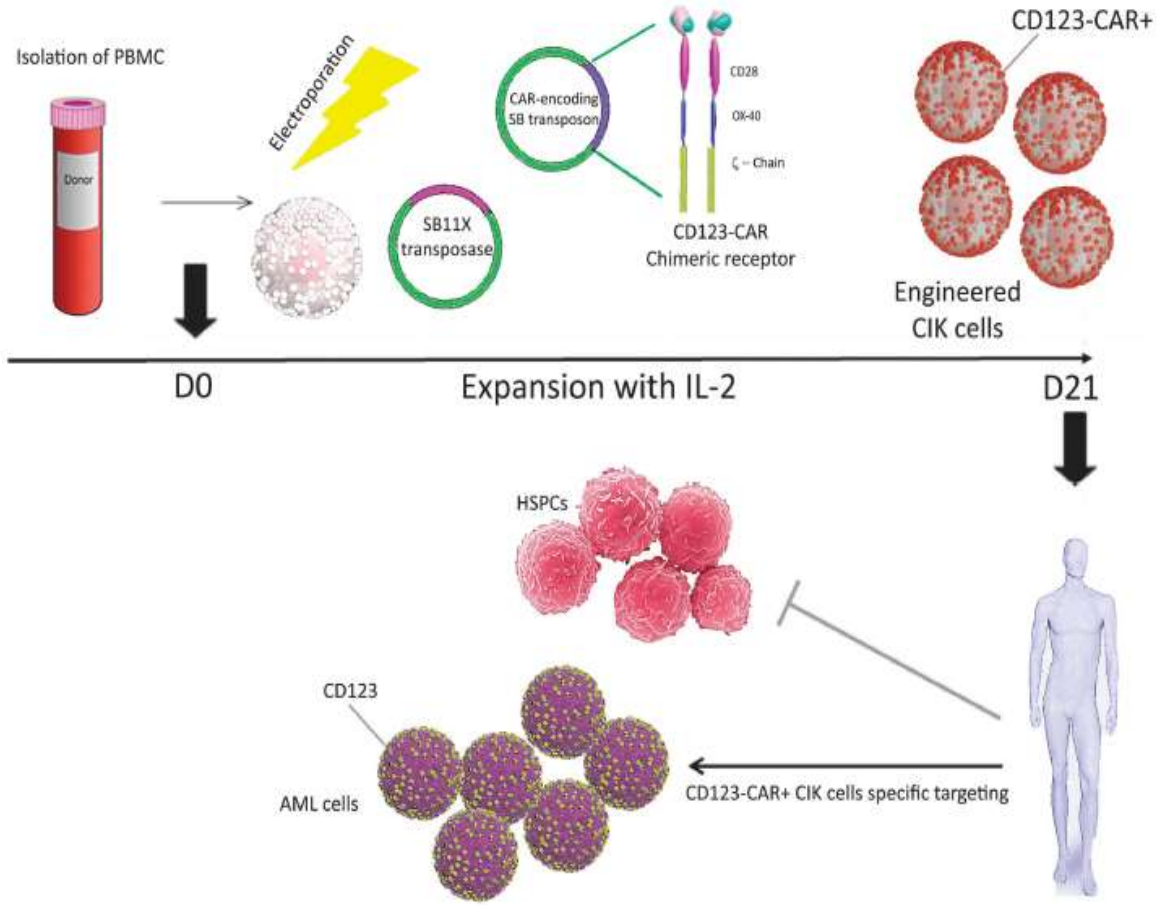
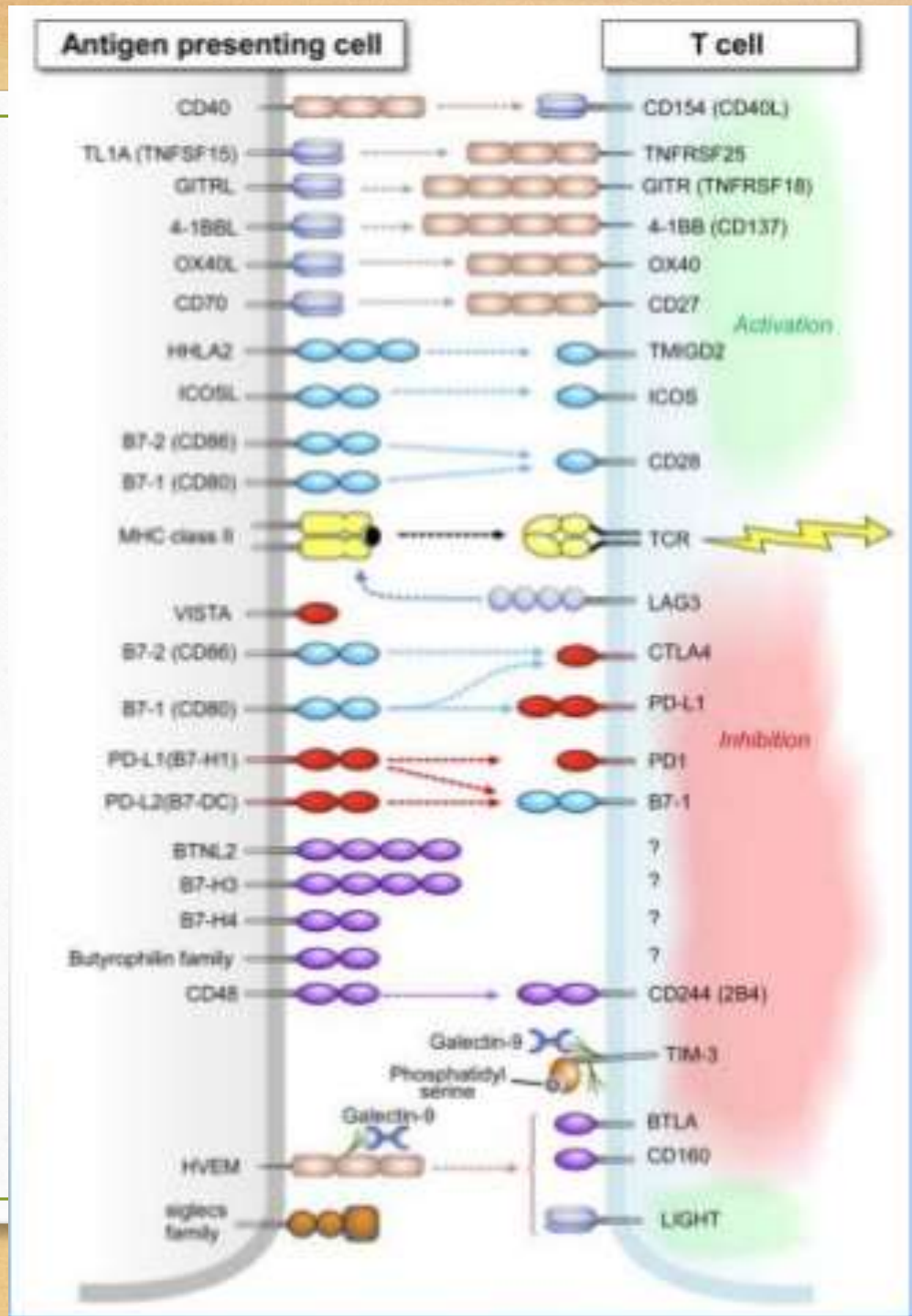


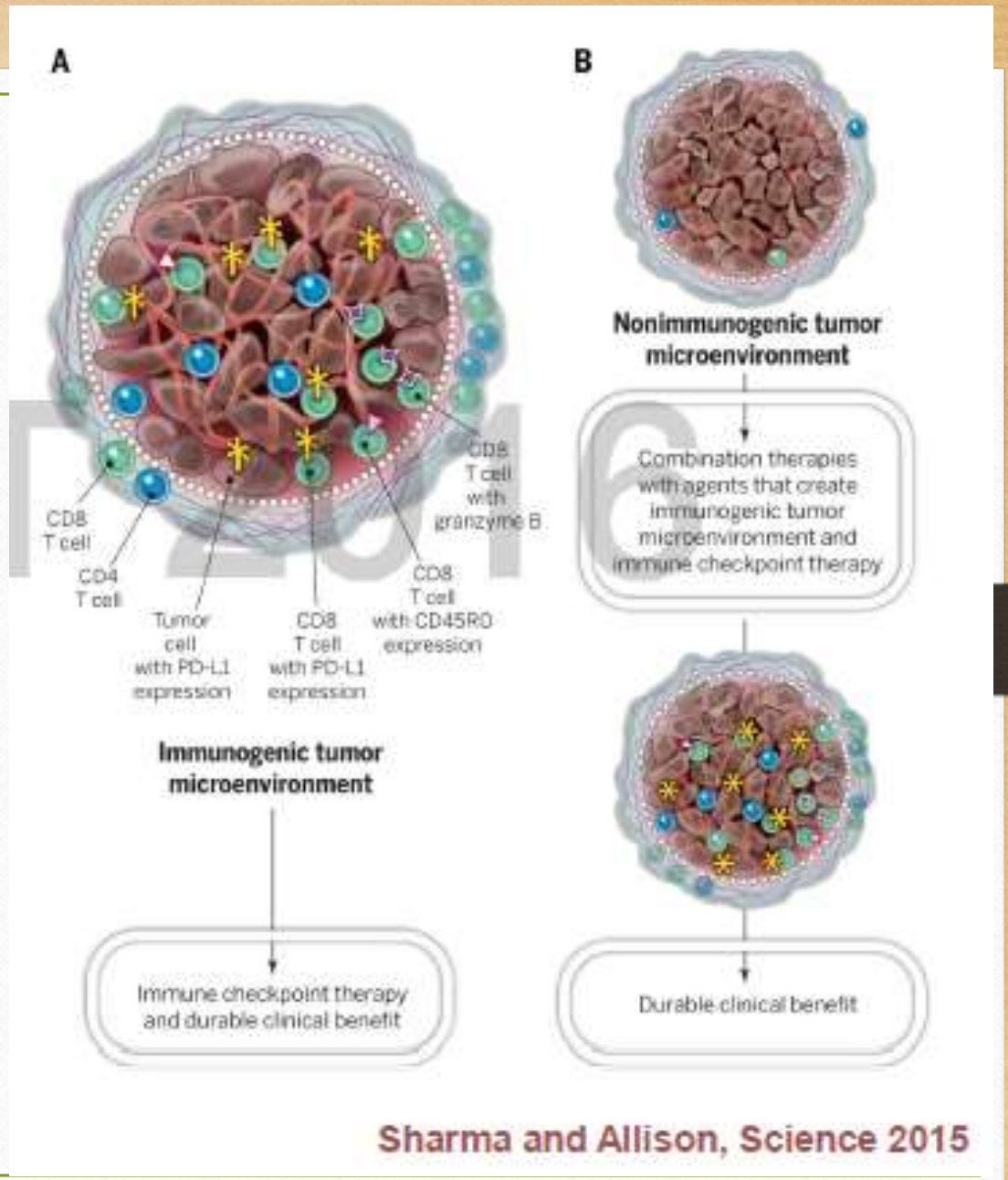
Figure 1. Design of CIK cell differentiation and modification protocol to induce the ectopic expression of anti-CD123 CAR by SB system for the clinical application. Peripheral blood mononuclear cells (PBMCs) from healthy donors are isolated and modified at day 0 by electroporation with the SB system composed of the SB11X transposase-encoding plasmid and the anti-CD123 CAR-encoding SB transposon. The SB11X transposase catalyzes the integration reaction of the third-generation (CD28-OX40-ζ chain) anti-CD123 CAR into the genome of the electroporated cells. After nucleofection, the cells are cultured for 21 days in the presence of IL-2, following the CIK cell differentiation protocol and becoming at the end CIK cells engineered to stably express anti-CD123 CAR. As a future clinical application, anti-CD123 CAR$^+$ CIK cells will be injected into the patients, where they will specifically target CD123$^+$ AML cells while sparing the hematopoietic stem cell compartment.



This target list just keeps growing

Future development: combination therapy

- Blockade of several immune checkpoints
- Cancer vaccines
- Adoptive T cell transfer
- Targeted therapies
- Oncolytic viruses
- Chemotherapy (immunogenic cell death)
- Radiotherapy



Sharma and Allison, Science 2015

Pediyatrik AML

- **CD33 antikor-ilaç konjugasyonu (Gentuzumab ozogamisin) geçtiğimiz yıllarda AML tedavisinde başarıyla kullanılmıştır.**

- **Bu deneyimden sonra AML hücresinin değişik antijenlerine karşı antikorlarla preklinik ve erken klinik çalışmalar yapılmıştır.**
- **Hedefli Kimerik antijenik reseptör ekprese eden T hücreleriyle veya,**
- **Modifiye T hücre reseptör genleriyle oluşturulan yeniden düzenlenmiş T hücreleriyle adoptif immunoterapi ve kanser aşıları dirençli AML hastalarında geliştirilen yeni stratejilerdir(7).**

- Buckley SA, Walter RB. Update on Antigen-Specific Immunotherapy of Acute Myeloid Leukemia. Curr Hematol Malig Rep 1065-75,2015

Cytotherapy, 2015; 17: 330–335

International Society for Cellular Therapy ISCT

CrossMark

Safety and tolerability of allogeneic dendritic cell vaccination with induction of Wilms tumor 1–specific T cells in a pediatric donor and pediatric patient with relapsed leukemia: a case report and review of the literature

SHOJI SAITO[1,2], RYU YANAGISAWA[1,2], KENTARO YOSHIKAWA[1,2], YUMIKO HIGUCHI[1], TERUTSUGU KOYA[1], KIYOSHI YOSHIZAWA[1], MIYUKI TANAKA[2], KAZUO SAKASHITA[2], TAKASHI KOBAYASHI[1], TAKASHI KURATA[2], KOICHI HIRABAYASHI[2], YOZO NAKAZAWA[2], MASAAKI SHIOHARA[2], YOSHIKAZU YONEMITSU[3], MASATO OKAMOTO[4], HARUO SUGIYAMA[5], KENICHI KOIKE[2] & SHIGETAKA SHIMODAIRA[1]

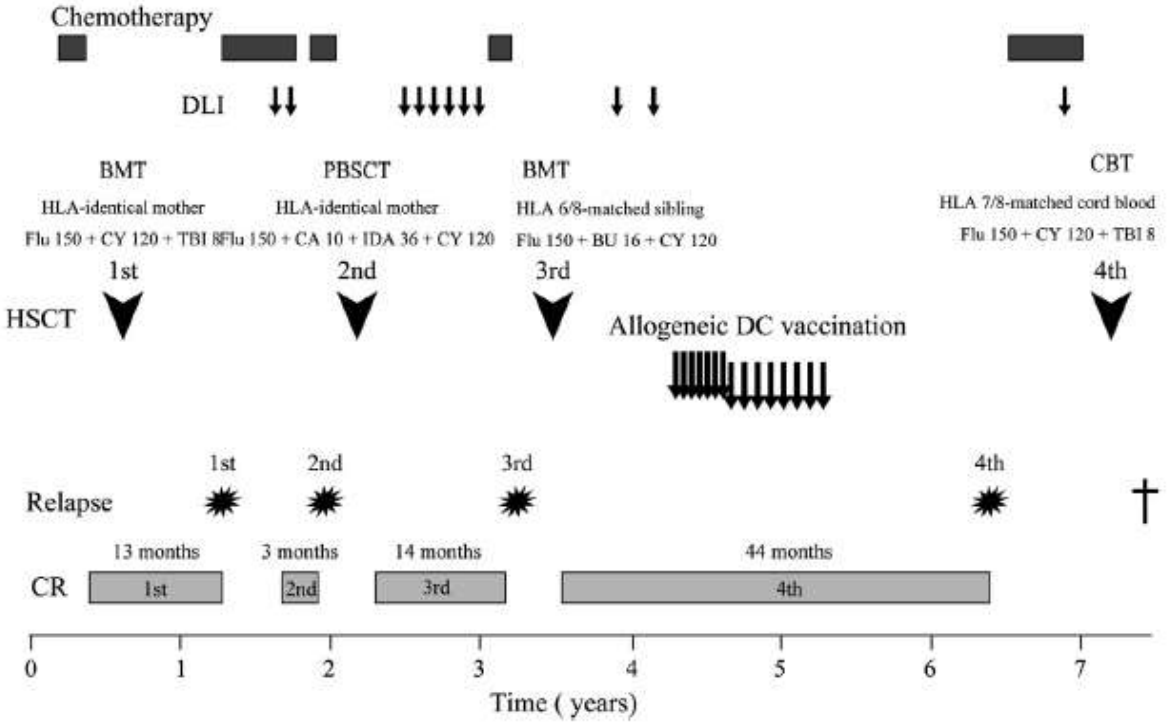
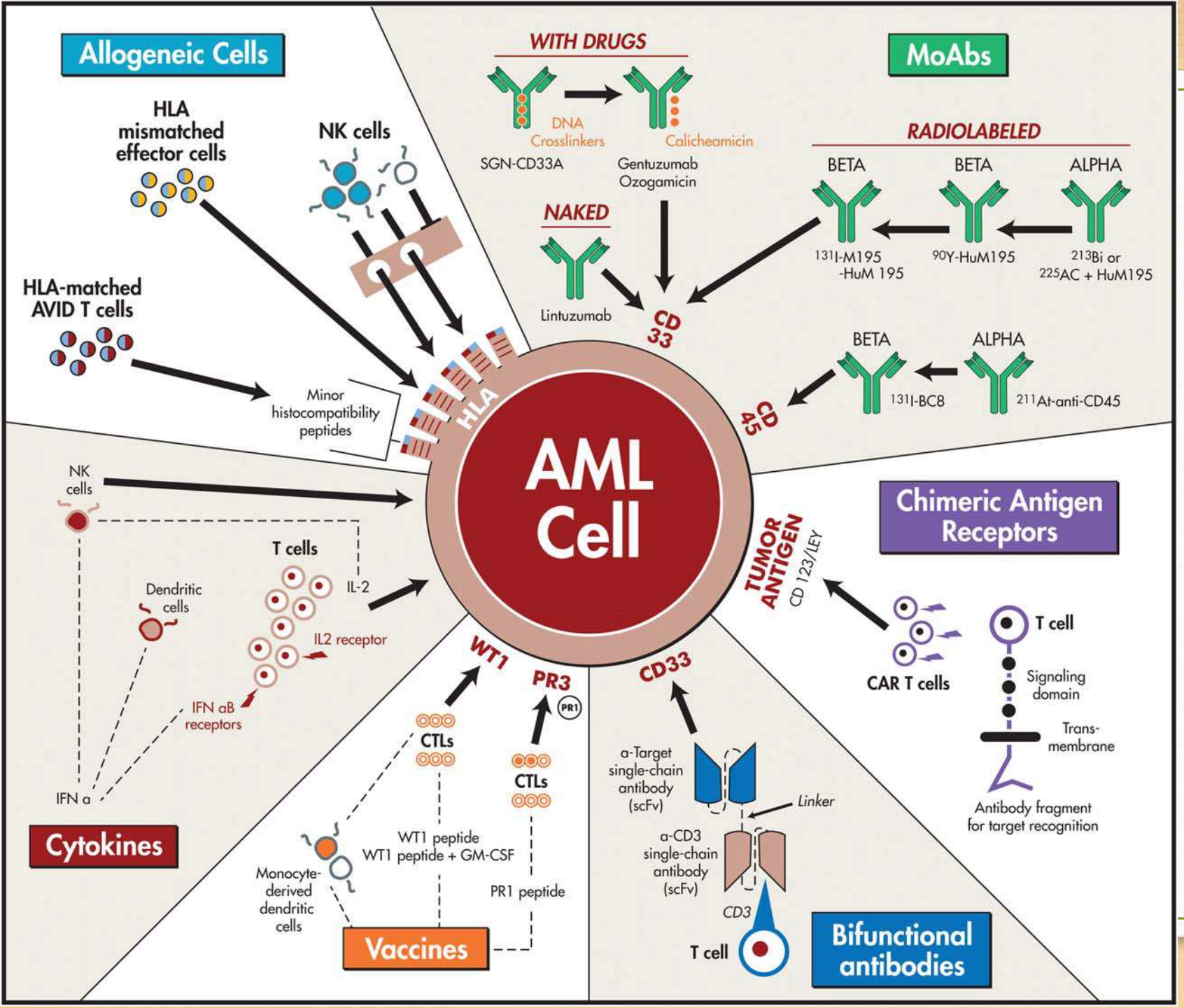


Figure 1. Clinical course of the patient. Allogeneic DC vaccination initiated 13 months after the third HSCT. BMT, bone marrow transplantation; CBT, cord blood transplantation; Flu 150, fludarabine 150 mg/m^2; CY 120, cyclophosphamide 120 mg/kg; TBI 8, total body irradiation 8 Gy; CA 10, cytarabine 10 g/m^2; IDA, idarubicin 36 mg/m^2; BU 16, busulfan (intravenously) 16 mg/kg.

In conclusion, this report suggests that allogeneic DC vaccination is a safe, tolerable and even feasible option even for pediatric patients and pediatric donors. Because there are currently few effective therapies for patients who have a relapse after allogeneic HSCT, future trials should consider this treatment for patients with relapsing leukemia.



Grosso DA, Hess RC, and Weiss MA. Immunotherapy in Acute Myeloid Leukemia. Cancer August 15, 2015,2689-2704.

Teşekkürler