

Multipl Myelom'da Hücresel Tedaviler

DOÇ. DR. ÖMÜR GÖKMEN SEVİNDİK

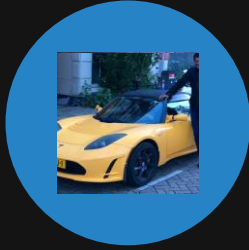
TÜRK AFEREZ DERNEĞİ KONGRESİ – İSTANBUL 2019



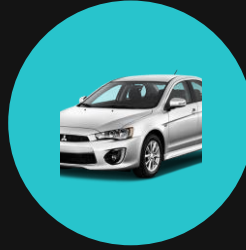
MEDİPOL
MEGA
ÖZEL
MEDİPOL MEGA
HASTANELER
KOMPLEKSİ



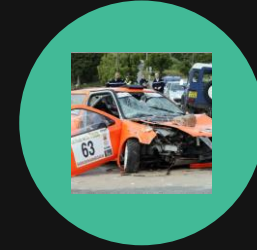
Eriřim ve paha problemlerini göz ardı ettiğinizde multipl myelom tedavisinde CAR-T/NK hücre tedavilerini ařağıdaki tedavi ařamalarının hangisinde kullanmayı uygun görürsünüz?



A) İLK NÜKS

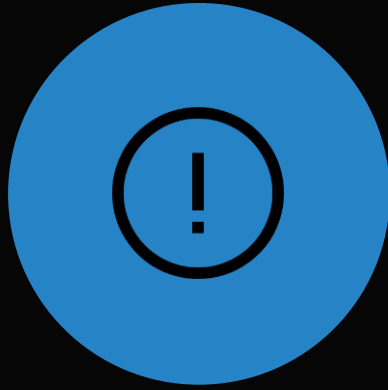


B) 2. VEYA 3. NÜKS

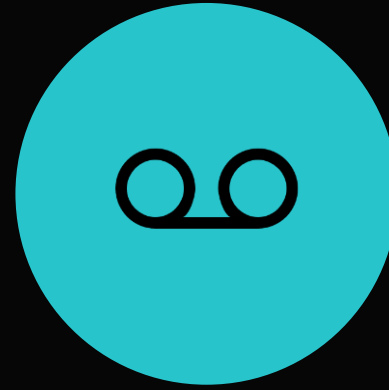


**C) RUTİN TEDAVİ SEÇENEKLERİNİ
TÜKETMİř İLERİ NÜKS**

Eriřim ve paha problemlerini göz ardı ettiğinizde multipl myelom tedavisinde CAR-T/NK hücre tedavilerinin gelecekte otolog kök hücre naklinin yerini alabileceğini düşünüyor musunuz?



A) EVET



B) HAYIR

Sunum Planı

Myelom'da İmmünoterapi Dayanağı

CAR-T Hücre Tedavisi Kavramsal Konsept Kanıtları

CAR-T Hücre Tedavisi Klinik Faz Çalışmaları

CAR Temelli Hücresel Tedavilerde Gelecek Konsepti

Özet

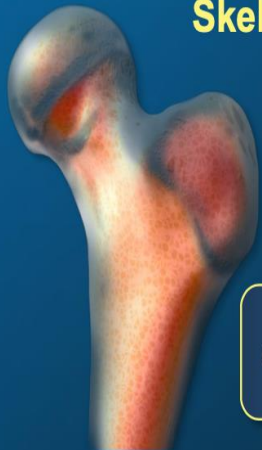
Multiple Myeloma Pathophysiology

Complex Cellular, Cytokine and Bone Marrow Matrix

Plasma Cell Transformation^{1,2}

Myeloma Stem Cell
Clonal evolution
Inter-clonal relationship
Genomic instability
Dysregulation of cyclins, oncogenes, tumor suppressors

Skeletal

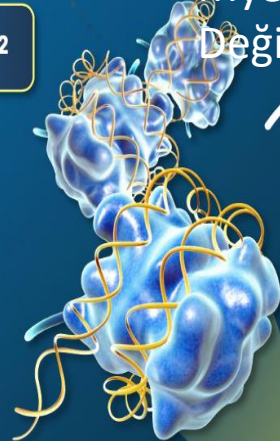


Macrophage, Osteoblast-Osteoclast Dysregulation^{1,7,14}

Macrophage dysfunction
Increased osteoclastic activity
Osteoblast-osteoclast dissociation

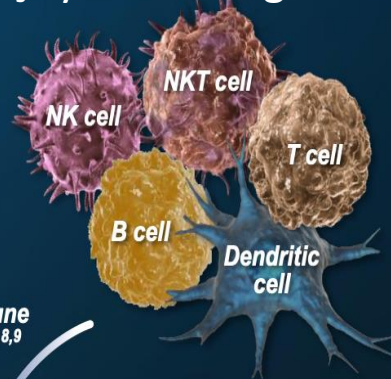
Plasmacytomas

Myelom'da Hiçbir Şey Göründüğü Kadar Basit Değildir!!



Multiple myeloma tumor cells

Failure of immune surveillance^{3-6,8,9}



Immune Dysregulation^{3-6,8,9,12}

Abnormal Cellular numbers
Compromised immune function / immunosuppression
Myeloid-derived suppressor cells
Defective T cell activation
Defective NK cell functions

Infections

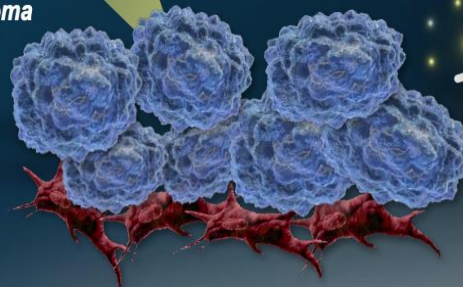
Disrupted Production of Cytokines and Growth Factors^{5,8,10,11}

Abnormal cytokine
proTNF- α production files

Blood Counts

Aberrant Stromal Structure^{1,5,13}

ICAM1/VCAM1 interactions^{10,11,13}



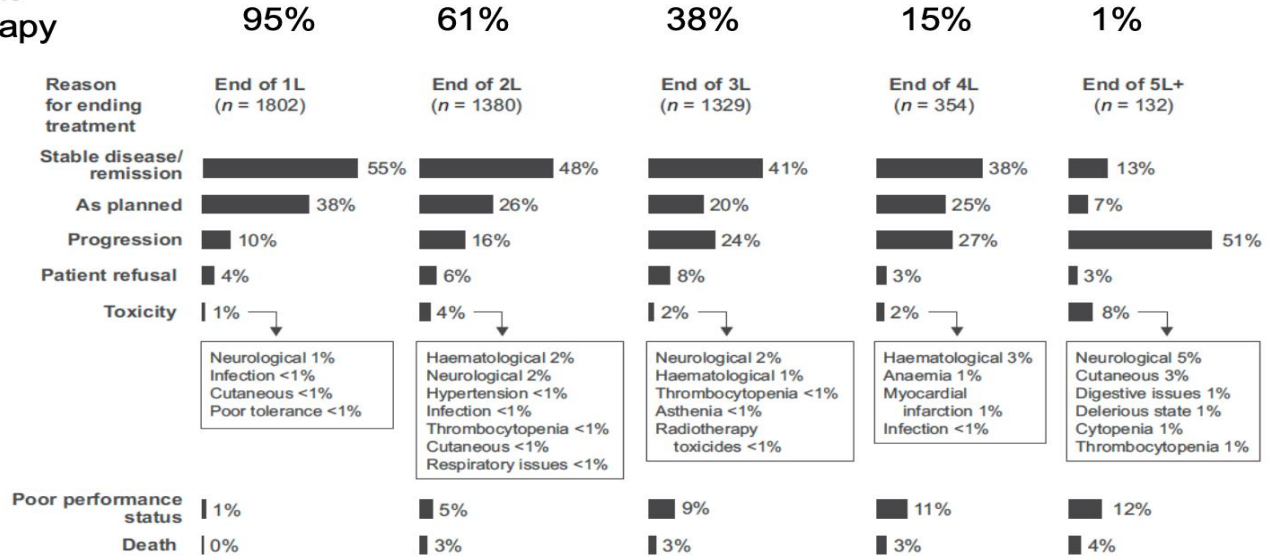
Tumor Microenvironment

ICAM1, intercellular adhesion molecule 1; NK, natural killer; NKT, natural killer T cell; PD-1, programmed death 1; TNF- α , tumor necrosis factor- α ; VCAM1, vascular cell adhesion molecule 1.

1. Raab MS, et al. *Lancet*. 2009;374:324-339. 2. Morgan GJ, et al. *Nat Rev Canc*. 2012;12:335-348. 3. Katodritou E, et al. *Am J Hematol*. 2011;86:967-973. 4. Braga WM, et al. *Clin Dev Immunol*. 2012;2012:293479. 5. Pratt G, et al. *Br J Haematol*. 2007;138:563-579. 6. Rosenblatt J, et al. *J Immunother*. 2011;34:409-418. 7. Kyle RA, et al. *N Engl J Med*. 2004;351:1860-1873. 8. Cook G, Campbell JD. *Blood Rev*. 1999;13:151-162. 9. Bernal M, et al. *Hum Immunol*. 2009;70:854-857. 10. Gupta D, et al. *Leukemia*. 2001;15:1950-1961. 11. Jourdan M, et al. *Eur Cytokine Netw*. 1999;10:65-70. 12. Favaloro J, et al. *Leuk Lymphoma*. 2014;12:1-8. 13. Damiano JS, et al. *Blood*. 1999;93:1658-1667. 14. Oranger A, et al. *Clin and Dev Immunology*. 2013;2013:289458

Gerçek Yaşam Pratiğinde Hasta Sonlanımı

Proportion of patients reaching line of therapy



YENİ PARADİGMAMIZ EN 'İYİ' TEDAVİ SEÇENEKLERİNİ İNDÜKSİYON VE İLK NÜKSTE KULLANMAK!

*Data from 4997 patient charts in Belgium, France, Germany, Italy, Spain, Switzerland, and the UK.

The proportion of patients who had received each line are from the cross-sectional review; data on durations of treatment and treatment-free intervals are from the retrospective review.

1L-5L = first line-fifth line treatment; CI = confidence interval; m = month.

Yong K, et al. Br J Haematol. 2016;175:252-264.

Curing Multiple Myeloma (MM) with Total Therapy (TT)

Bart Barlogie, Alan Mitchell, Frits van Rhee, Joshua Epstein, Shmuel Yaccoby, Maurizio Zangari, Christoph Heuck, Antje Hoering, Gareth J. Morgan, and John Crowley

Blood 2014 124:195

Curing myeloma at last: defining criteria and providing the evidence

Bart Barlogie, Alan Mitchell, Frits van Rhee, Joshua Epstein, Gareth J. Morgan, and John Crowley

Blood 2014 124:3043-3051; doi: <https://doi.org/10.1182/blood-2014-07-552059>

Kür Var!



Blood Cancer Journal

Altmetric: 97

[More detail >>](#)

Article | [OPEN](#)

Defining cure in multiple myeloma: a comparative study of outcomes of young individuals with myeloma and curable hematologic malignancies

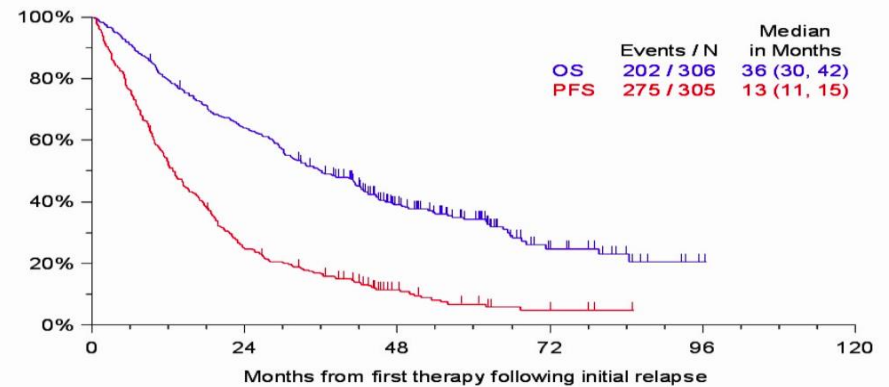
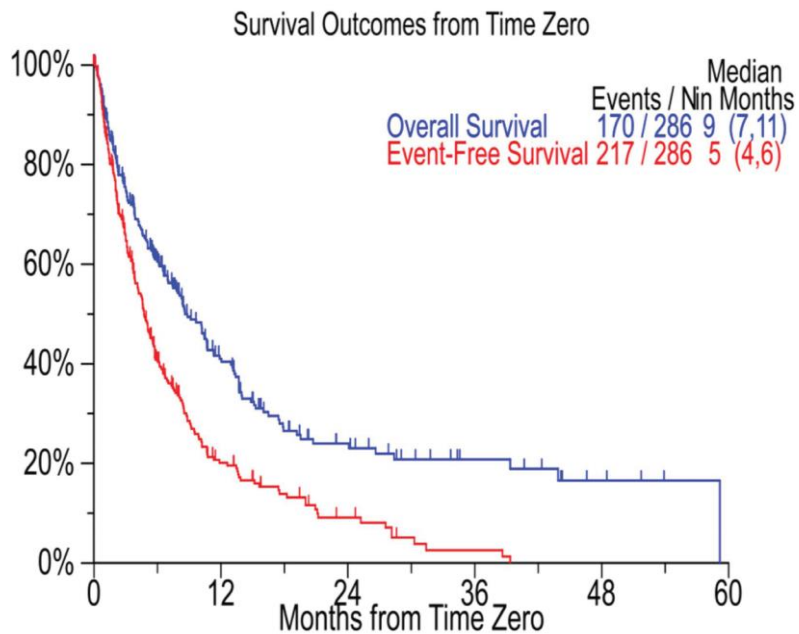
Praful Ravi, Shaji K. Kumar, James R. Cerhan, Matthew J. Maurer, David Dingli, Stephen M. Ansell & S. Vincent Rajkumar [✉](#)

curable diseases. We are confident that when we see cure, we will know it.

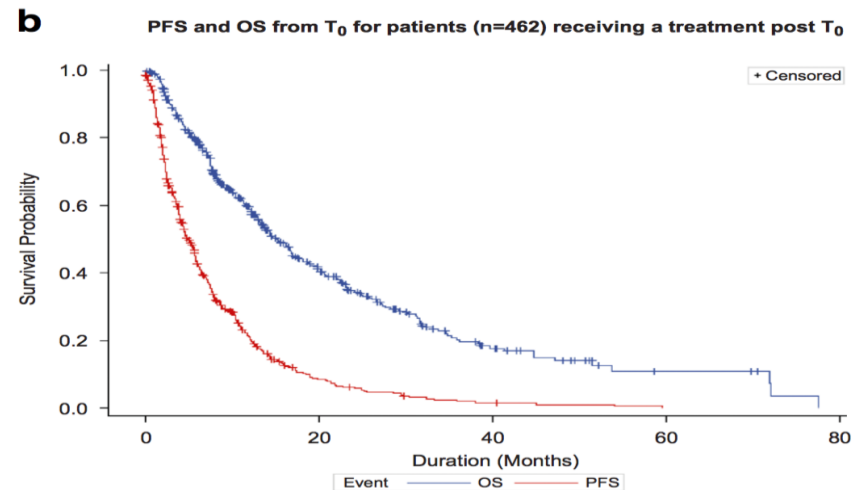
Kür Yok. Olsa Bilirdik!



Nüks Ne Kadar Kötü?

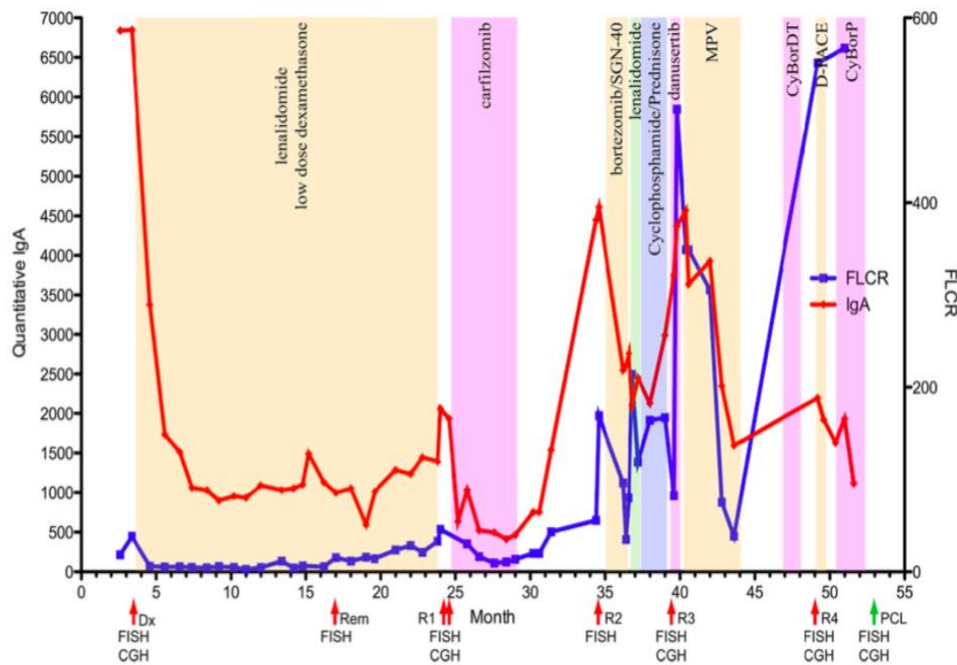


From 1st relapse

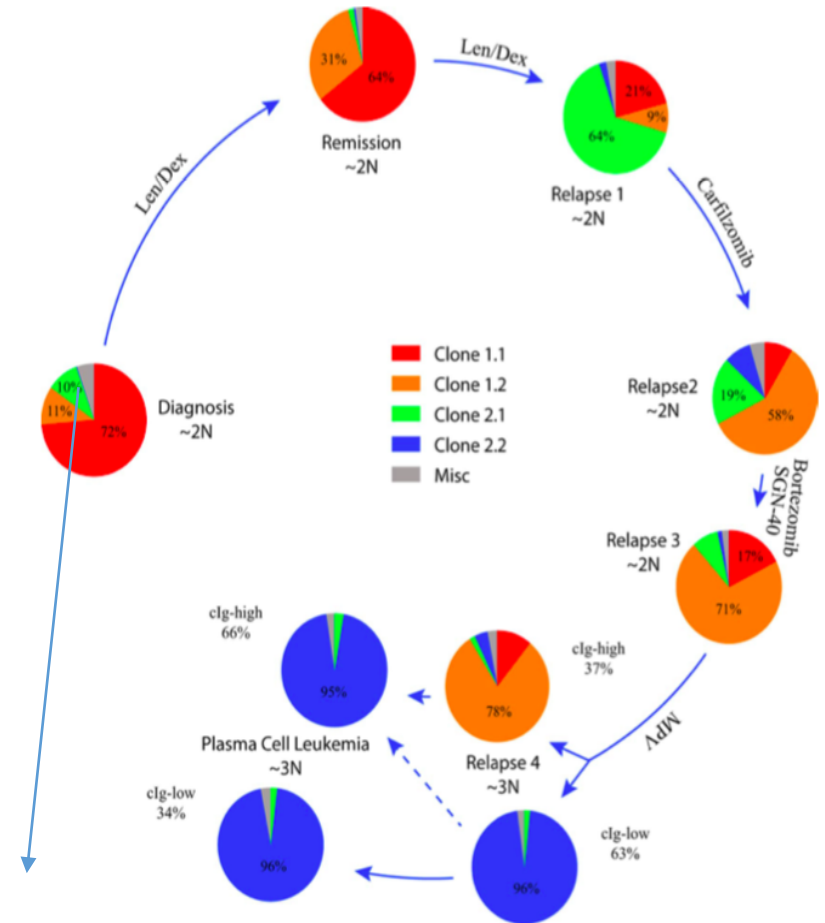


Kumar SK, Leukemia. 2012 26(1):149, Kumar SK, Leukemia. 2017 31: 2443

Neden Yeni Hedefler

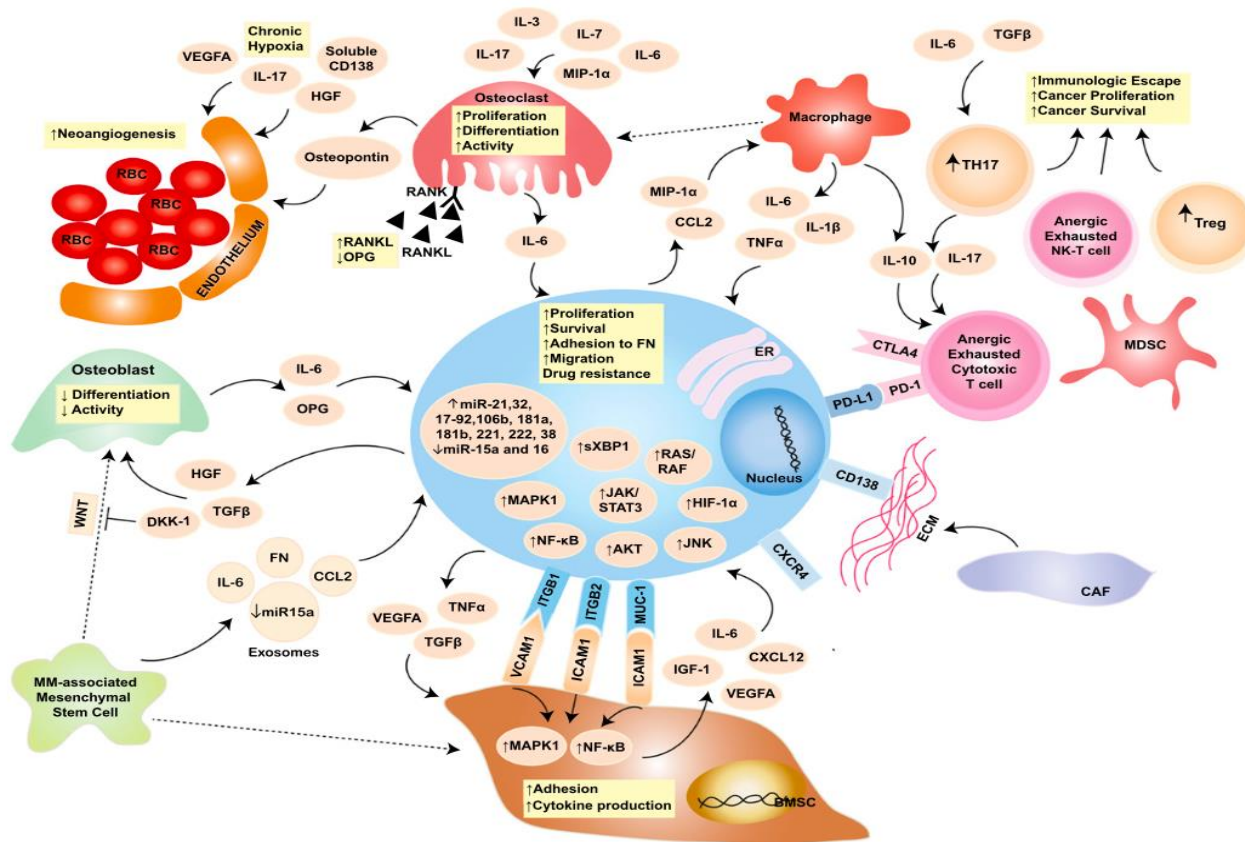


Houston we have a PROBLEM!!

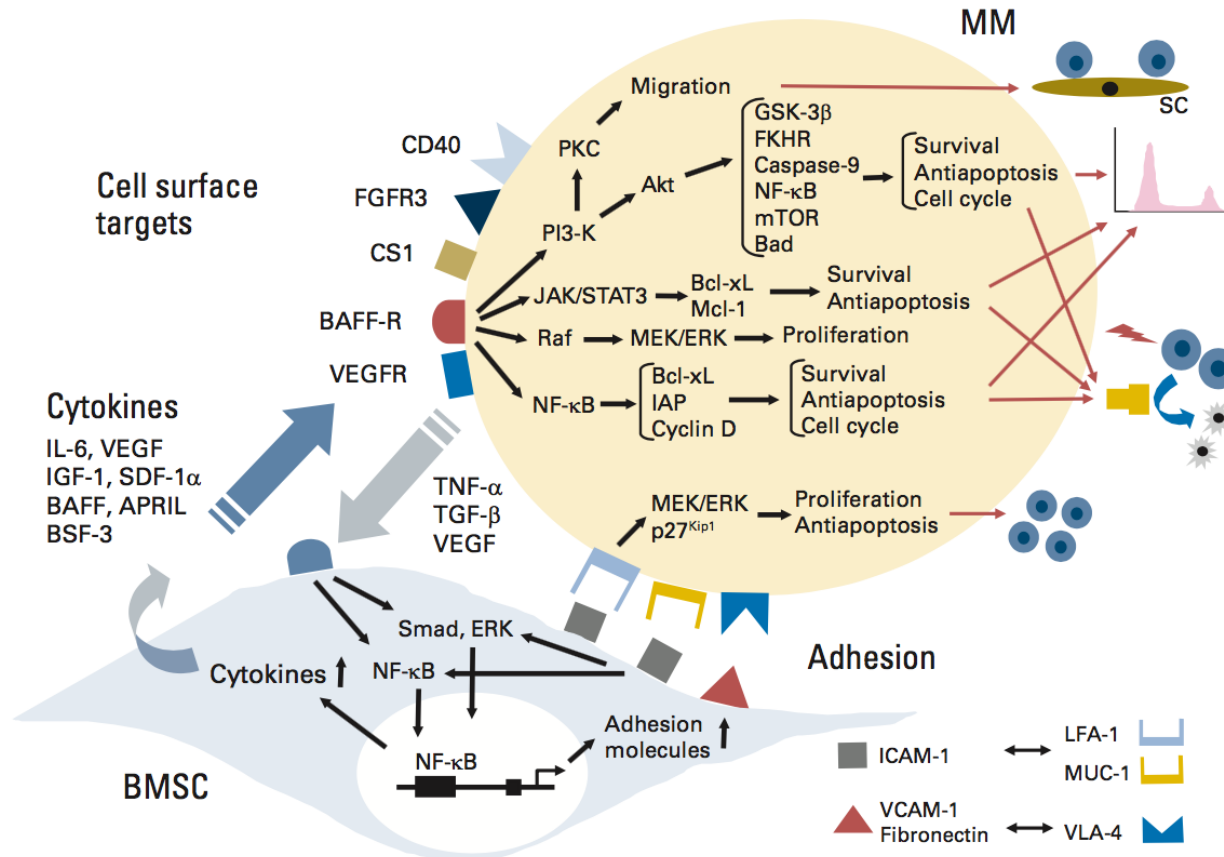


Keats, JJ. Blood. 2012 120(5):1067

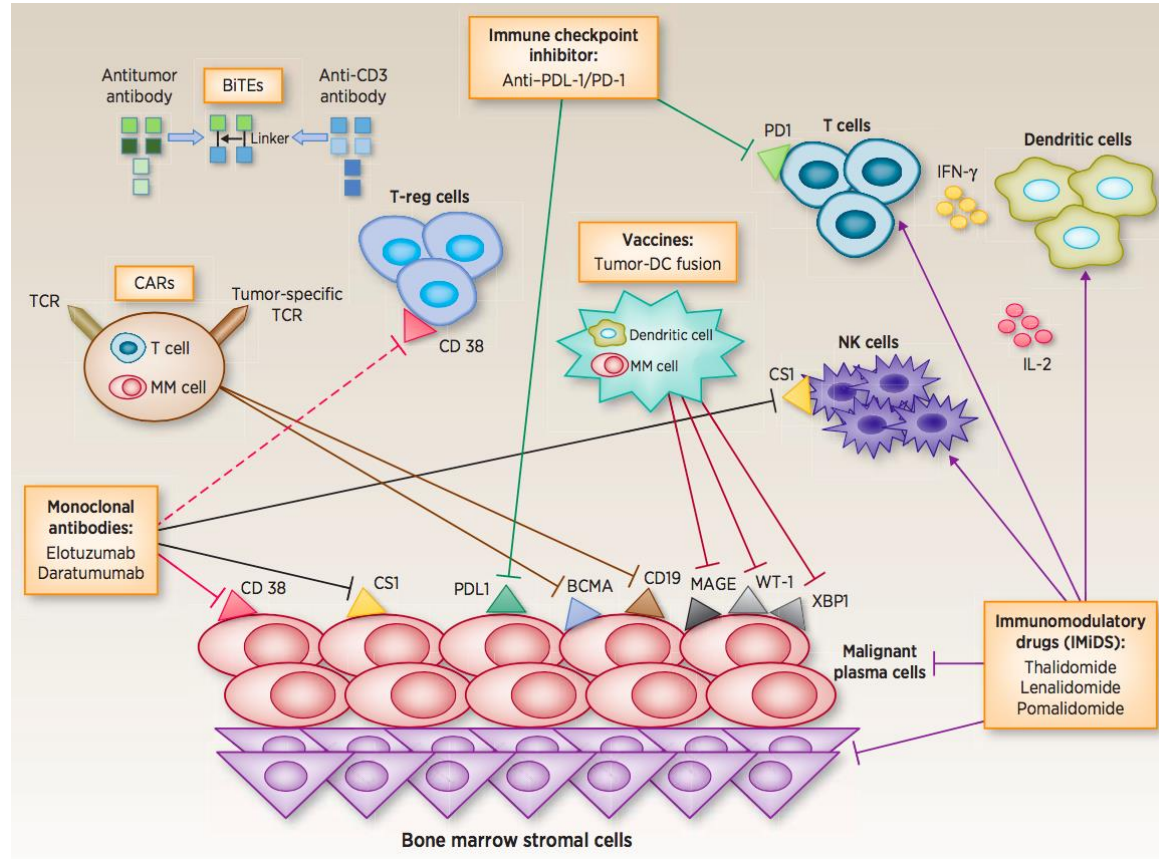
Miyelom Kemik İliği Mikroçevre Etkileşimi ve Tümör İmmün Kaçışı



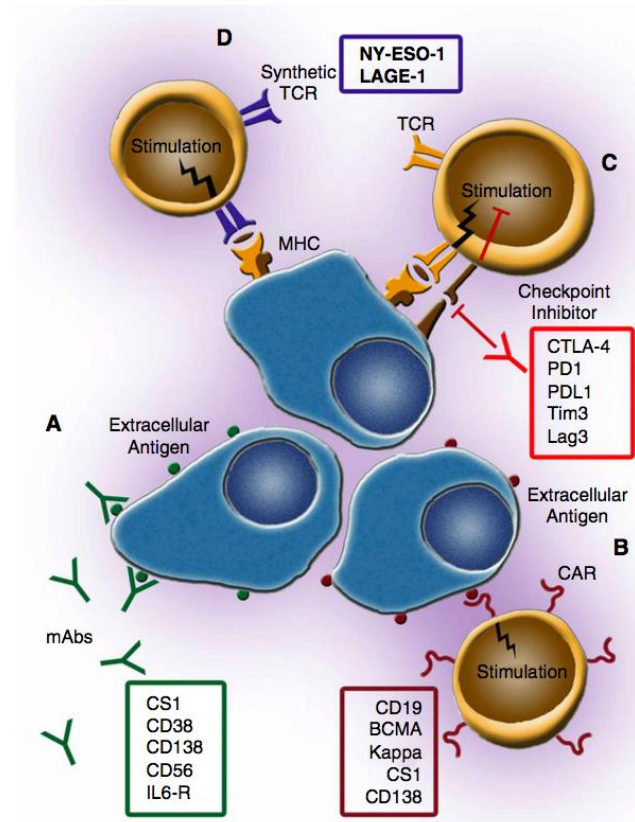
Miyelom'da Hedeflenebilir Yolaklar



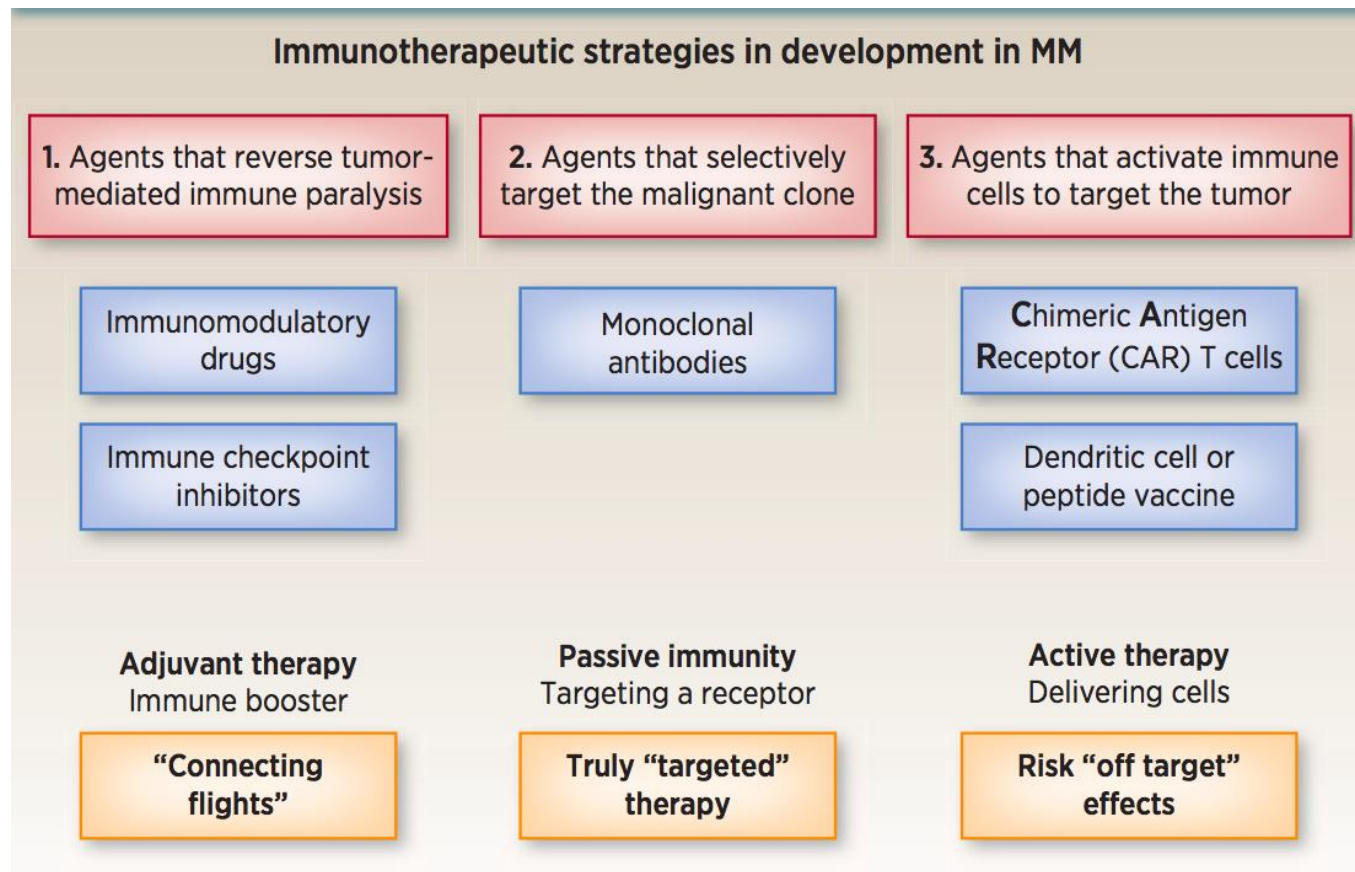
Miyelom'da Hedefe Yönelik İmmünoterapi Seçenekleri



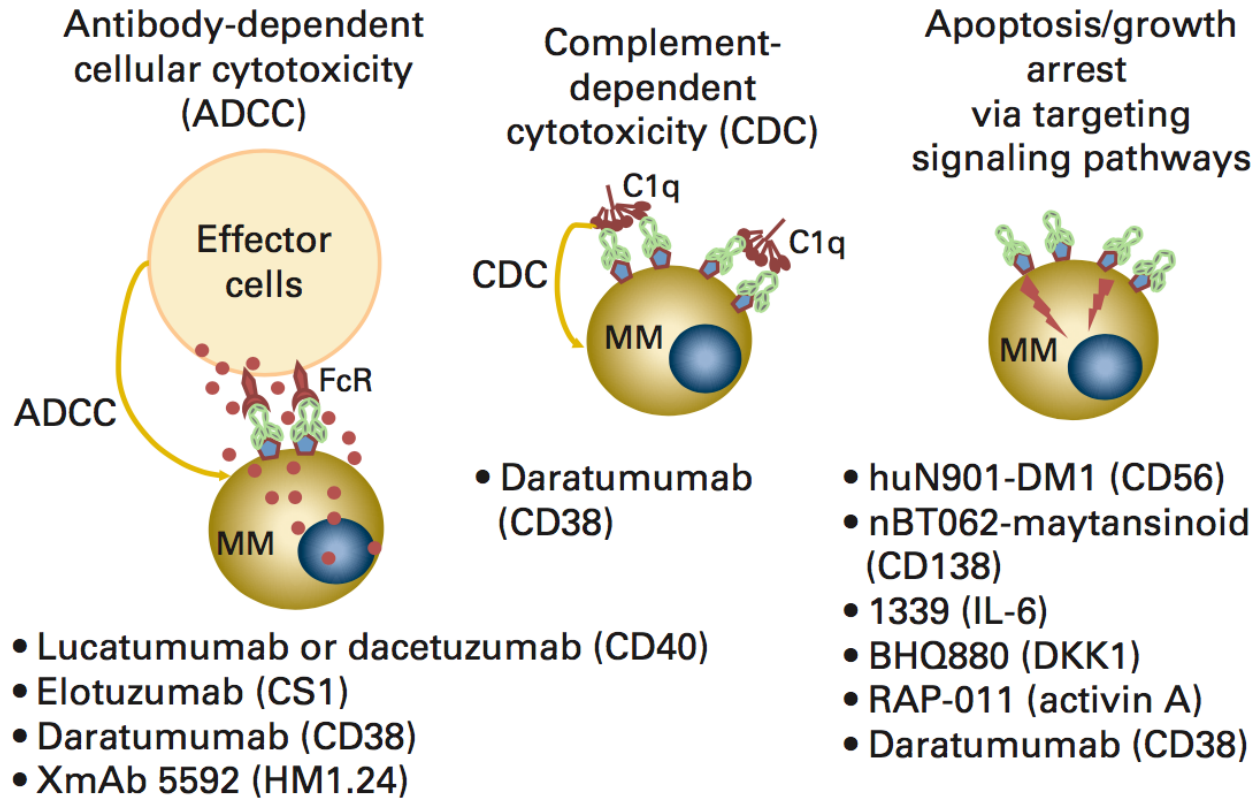
Miyelom'da Hedefe Yönelik İmmünoterapi Seçenekleri



Miyelom'da İmmünoterapi Stratejileri



Miyeloma'da İmmünoterapi – Monoklonal Antikorlar



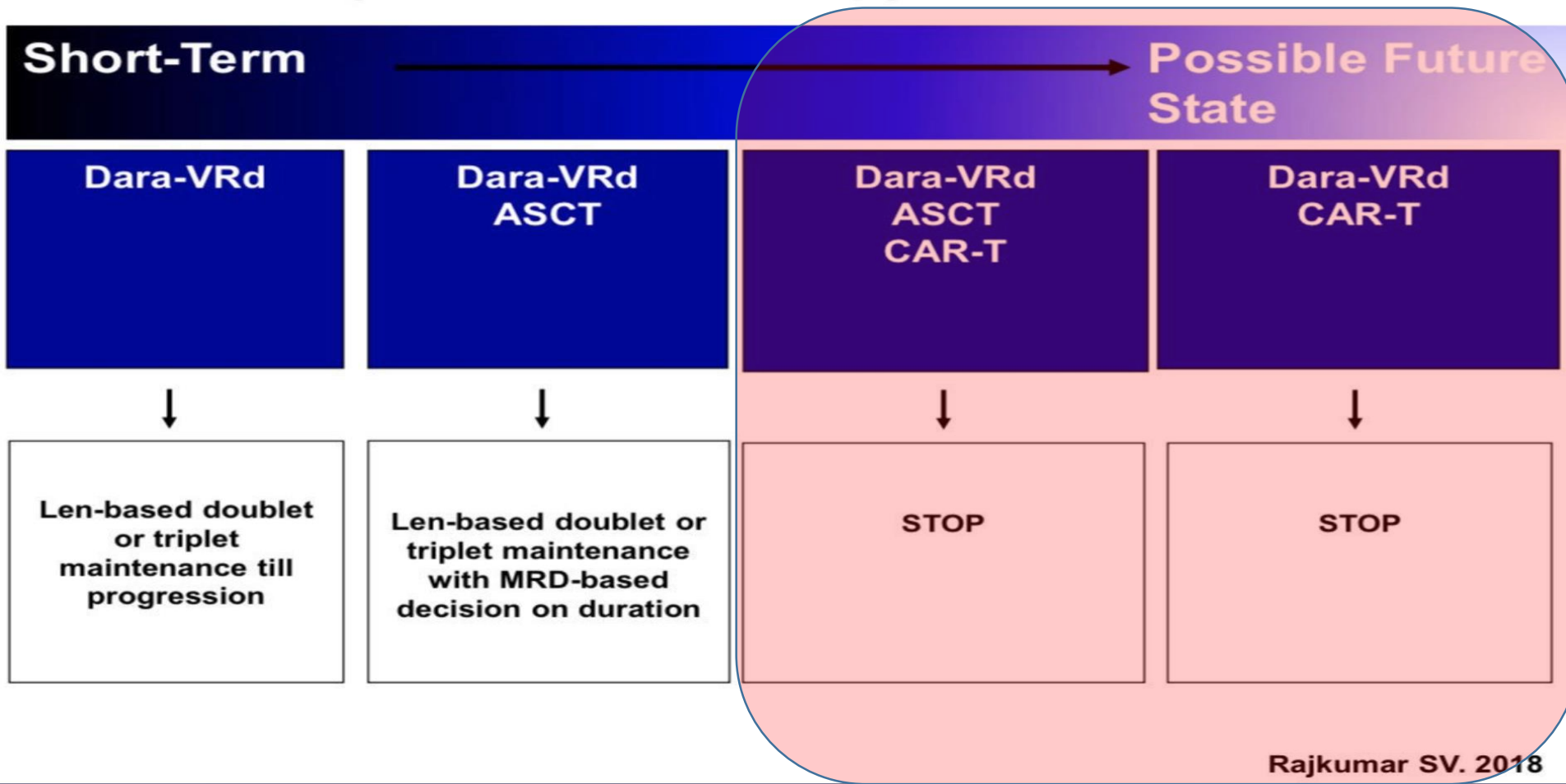


Mühim olan darphaneyi soyamak değil, darphaneyi soyarken para basmak.

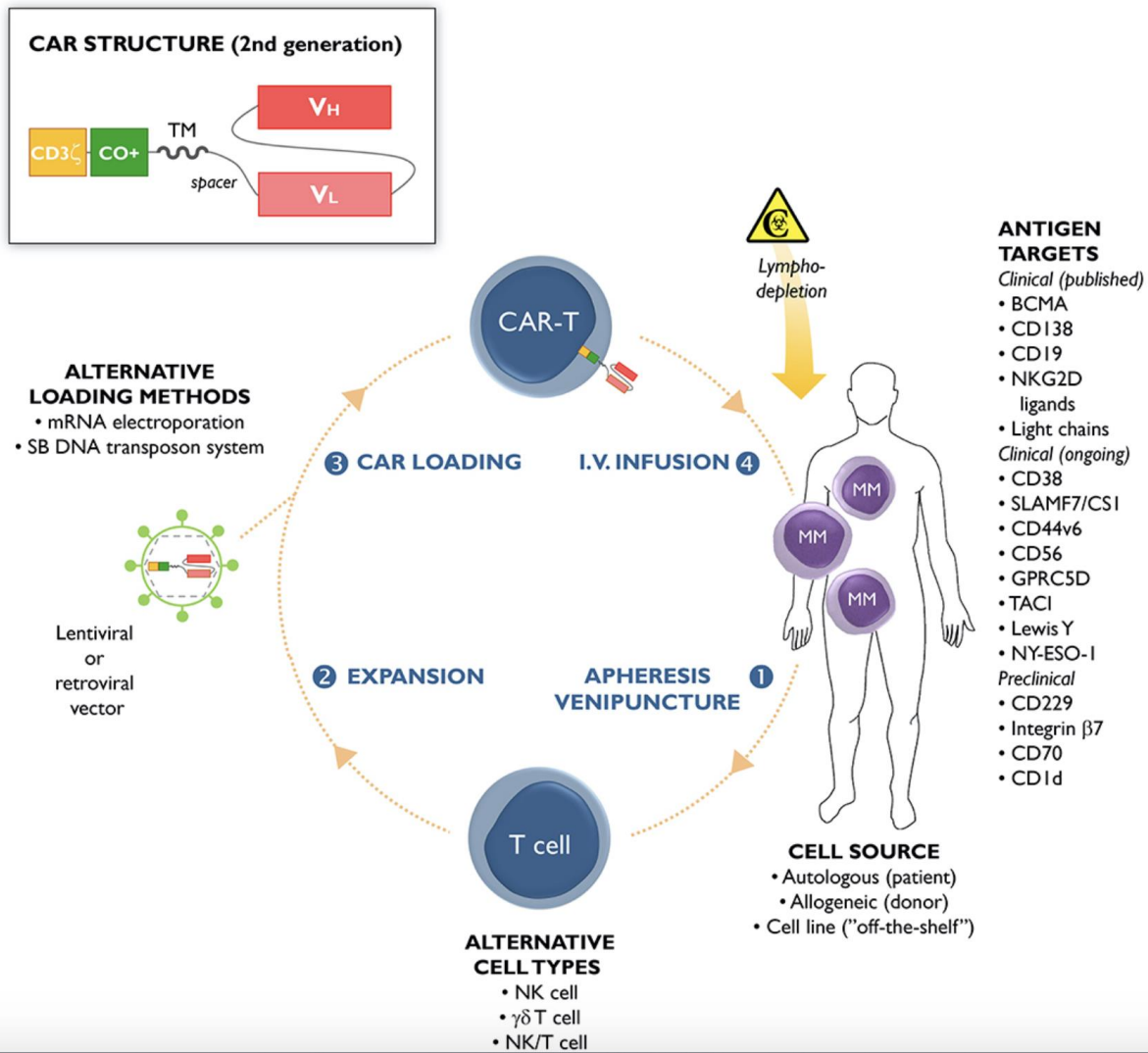
Nice İnnovatif ve **Erişilebilir** Miyelom Tedavilerine!

Şimdiye kadar tümörü statik immün hücrelerce yok etmeye çalışırken, artık dinamik, kendini çoğaltabilen immün hücreleri aracı olarak kullanıyoruz..

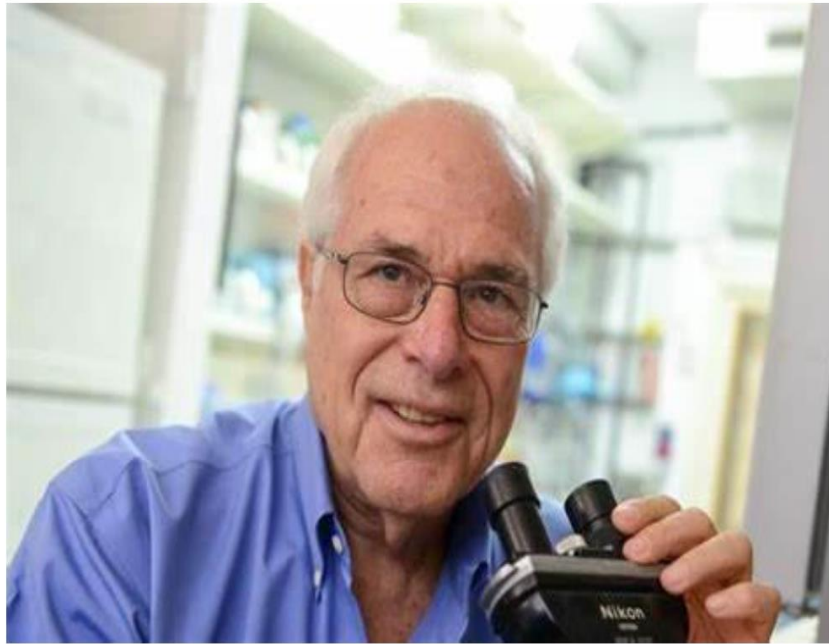
Myeloma Initial Therapy: Future State



CAR-T Hücresi Tedavisi



◆ Zelig Eshhar



NEW RESEARCH IN

Physical Sciences

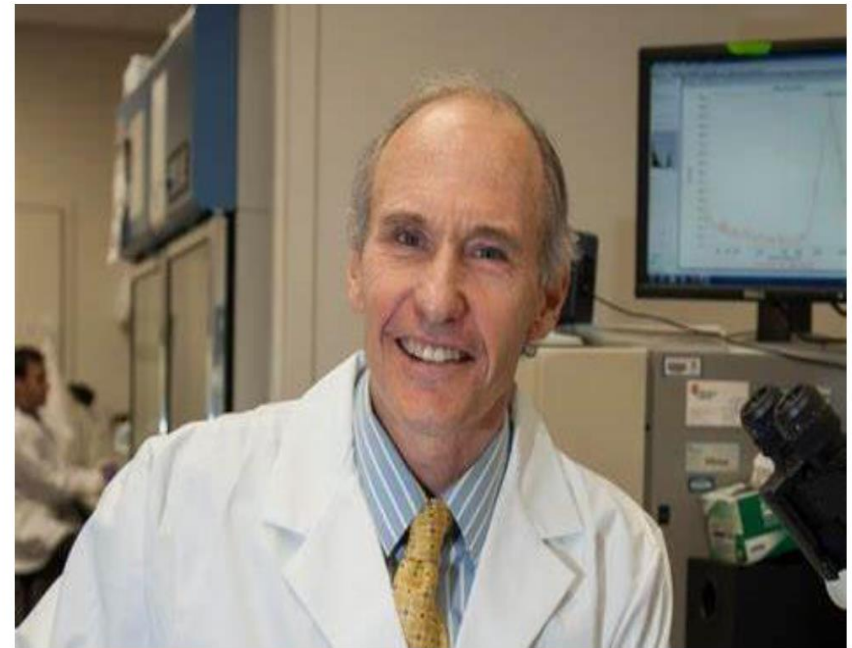
Social Sciences

Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

G Gross, T Waks and Z Eshhar

PNAS December 1, 1989, 86 (24) 10024-10028; <https://doi.org/10.1073/pnas.86.24.10024>

◆ Carl H. June



T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia

Michael Kalos^{1,2,*}, Bruce L. Levine^{1,2,*}, David L. Porter^{1,3}, Sharyn Katz⁴, Stephan A. Grupp^{5,6}, Adam Bagg^{1,2} and Carl H. June...

+ See all authors and affiliations

Science Translational Medicine 10 Aug 2011:

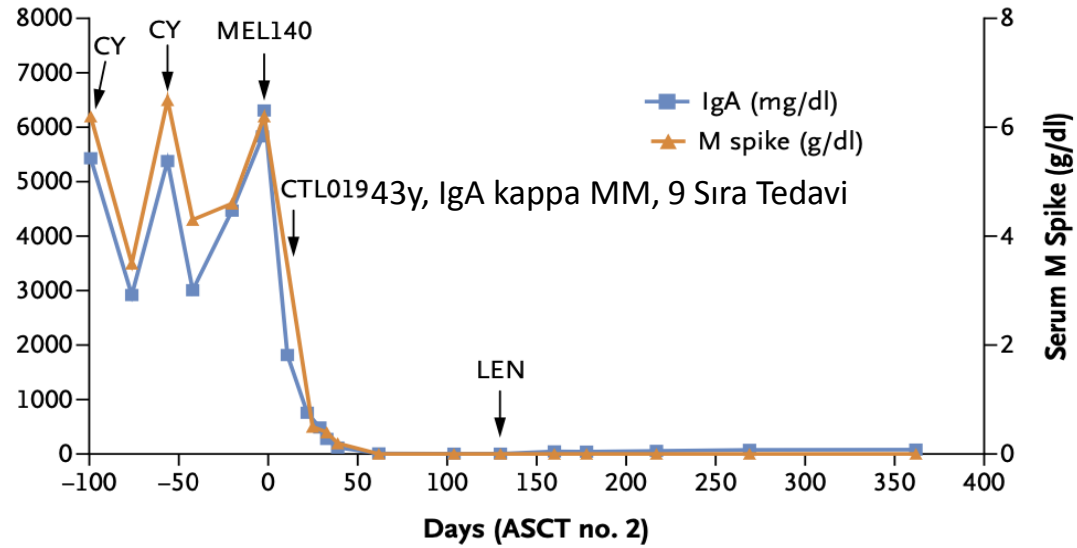
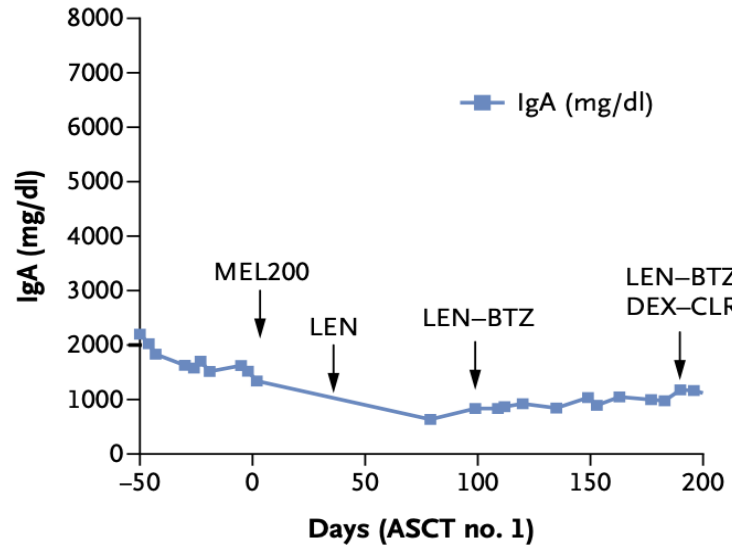
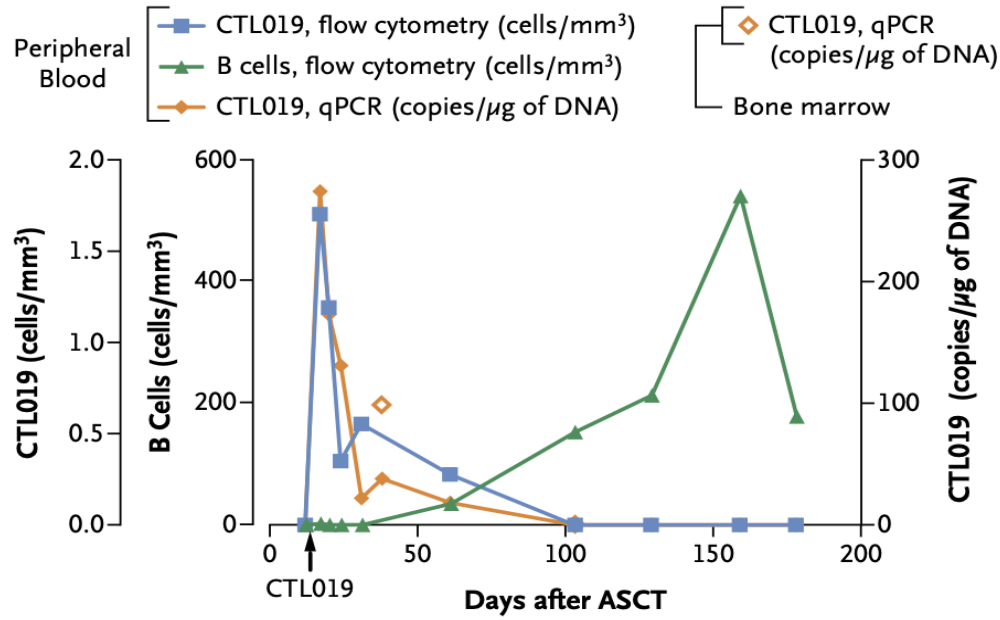
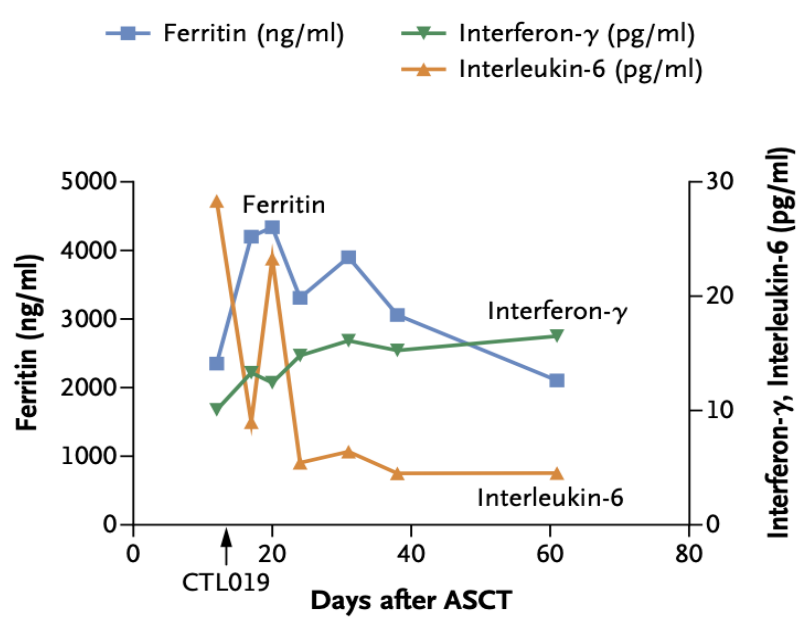
Vol. 3, Issue 95, pp. 95ra73

DOI: 10.1126/scitranslmed.3002842

BRIEF REPORT

Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma

Alfred L. Garfall, M.D., Marcela V. Maus, M.D., Ph.D., Wei-Ting Hwang, Ph.D.,
Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., J. Joseph Melenhorst, Ph.D.,
Zhaohui Zheng, M.S., Dan T. Vogl, M.D., Adam D. Cohen, M.D.,
Brendan M. Weiss, M.D., Karen Dengel, R.N., B.S.N., Naseem D.S. Kerr, M.P.H.,
Adam Bagg, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., and
Edward A. Stadtmauer, M.D.

A**B****C**

Anti-CD19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma

Alfred L. Garfall, ... , Marcela V. Maus, Carl H. June

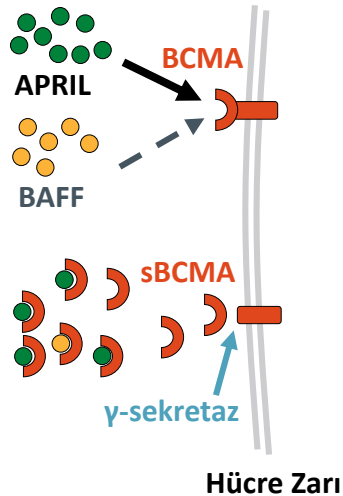
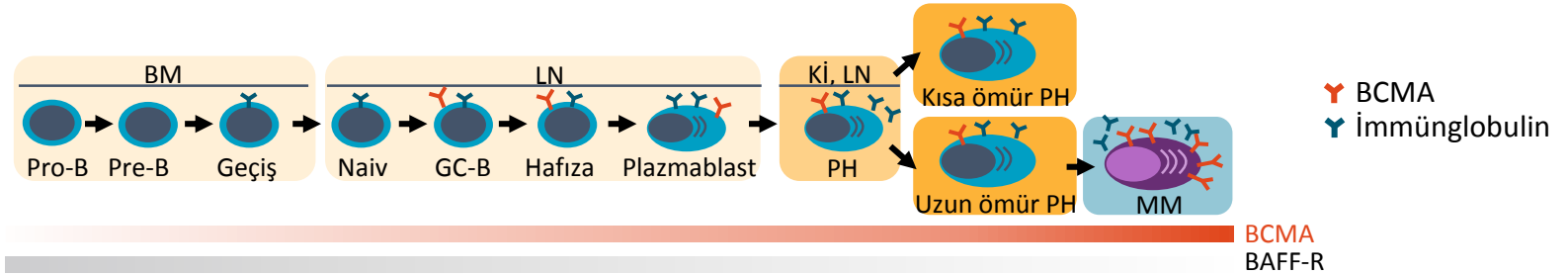
JCI Insight. 2019;3(8):e120505. <https://doi.org/10.1172/jci.insight.120505>.

Table 1. Patient characteristics and clinical responses

ID	Age/Sex	Poor-prognosis features	Prior lines of therapy	Mel. dose (mg/m ²) ^A	PFS, prior ASCT	PFS, ASCT + CTL019	Response, day 100 after ASCT ^B
1	48 F	Complex karyotype, t(4;14), del17p, +1q21	10	140	181	479	SCR
2	58 M	Complex karyotype, BRAFV600E	7	200	341	42	PD
3	65 F	Plasma cell leukemia	3	140	210	182	VGPR
5	64 F	t(4;14), +1q, <PR to induction	7	140	127	249	VGPR
6	53 M	BRAF V600E mutation	2	140	100	76	PD
7	62 F	N/A ^C	6	140	342	223	VGPR
8	57 F	t(4;14), +1q	4	200	334	187	PR
9	62 M	+1q, t(4;14)	4	140	266	92	PD
10	68 F	del(17p), +1q	10	140	249	155	PR
12	59 M	N/A ^C	6	200	325	323	VGPR

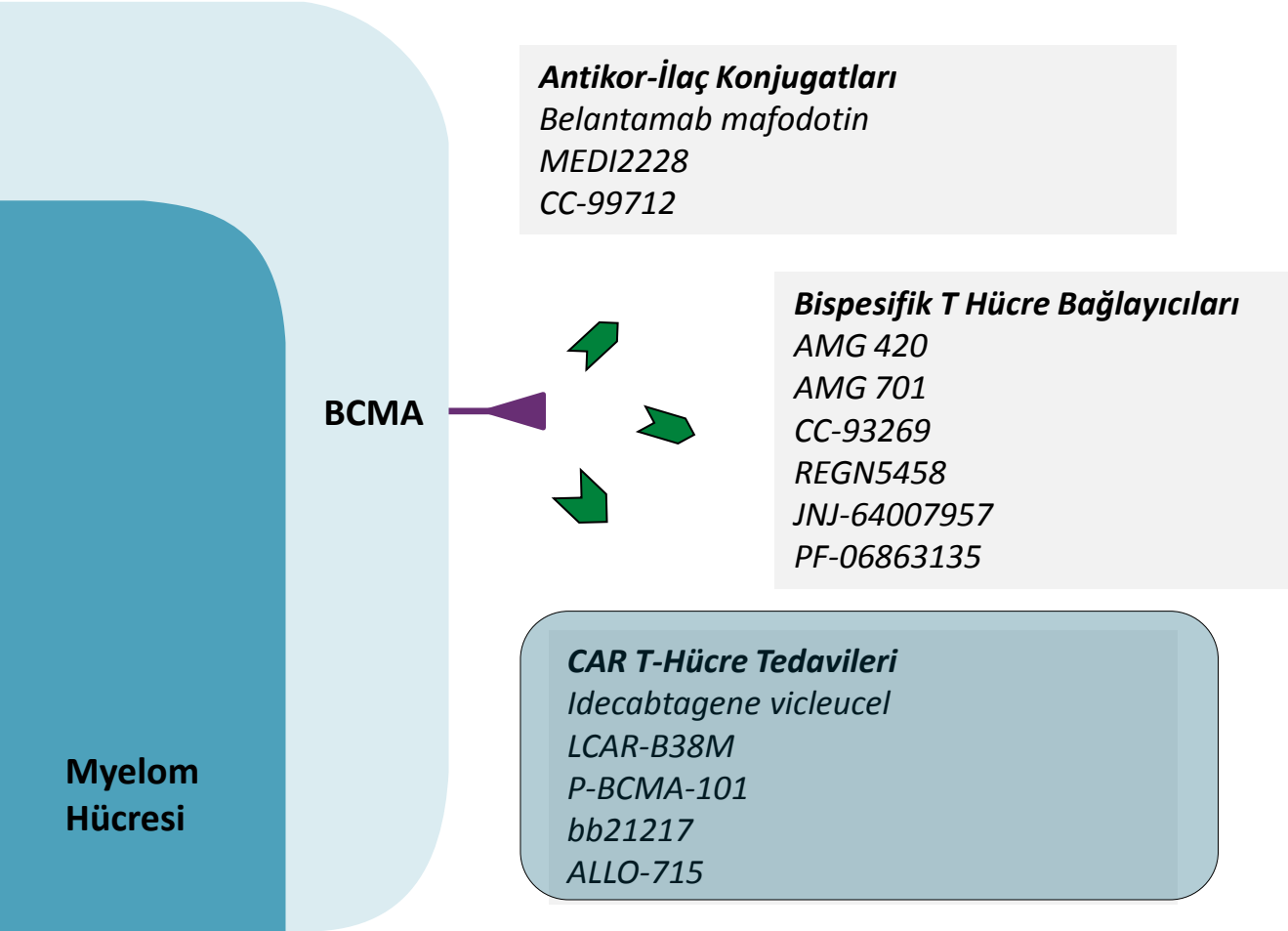
^ADose with ASCT + CTL019. All subjects received melphalan at 200 mg/m² dose with prior ASCT. ^BResponses are graded according to International Myeloma Working Group definitions. ^CCytogenetic data not available. Mel., melphalan; PFS, progression-free survival; VGPR, very good partial response; PR, partial response; PD, progression of disease; SCR, stringent complete response.

Myelom Tedavisinde Yeni Hedef BCMA



- BCMA: Spesifik olarak plazma hücrelerinde ve myelom hücrelerinde ifade edilmekte
- TNF süper ailesinin hücre yüzey reseptörü
- Myelom hücrelerinde normal plazma hücrelerinden daha fazla ifade edilmekte
- Diğer dokularda ifadesi yok
- B hücre olgunlaşmasında ve farklılaşmasında anahtar role sahip
- Myelom hücre büyümesini, sağkalımını, kemoterapi direncini ve kemik iliği mikroçevresinde immün baskılanmayı tetiklemekte
- BCMA ifadesi MGUS durumundan ileri myeloma doğru artmakta
- Ek ligandları arasında APRIL ve BAFF mevcut

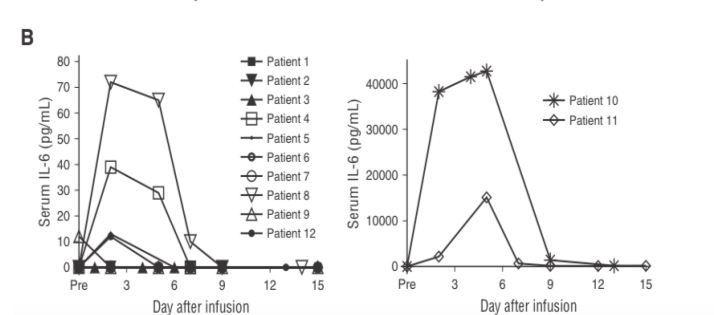
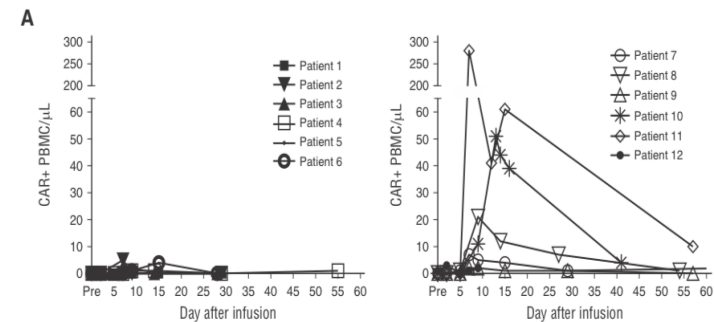
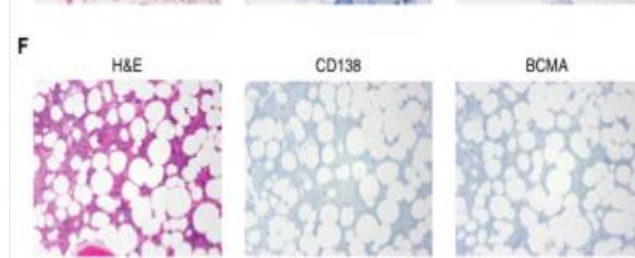
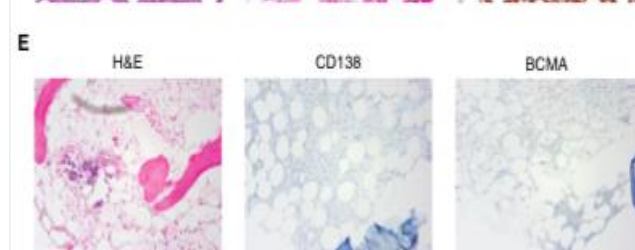
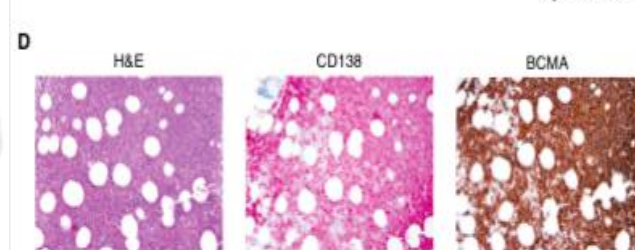
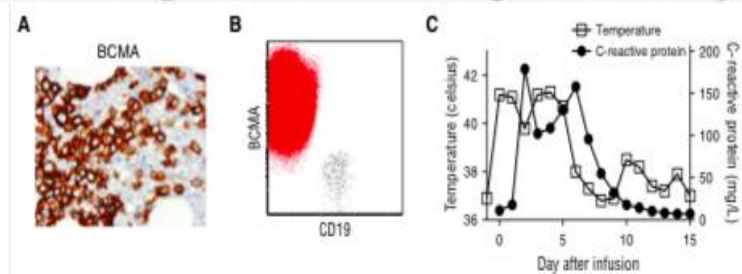
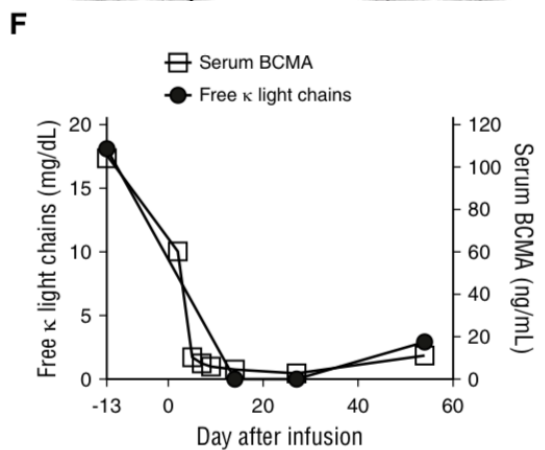
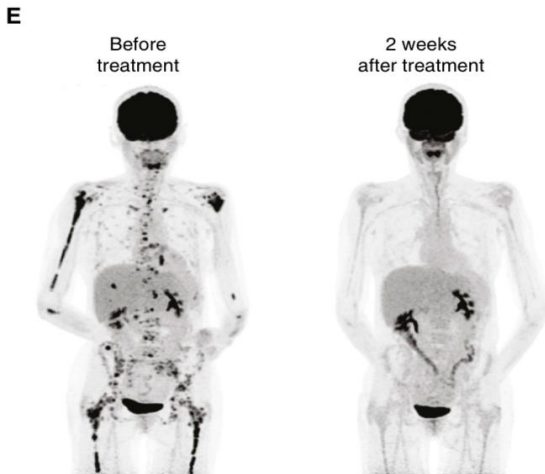
BCMA'ı Hedefleyen Tedaviler



Cyclophosphamide 300 mg/m² · Fludarabine 30 mg/m² QD for 3 days

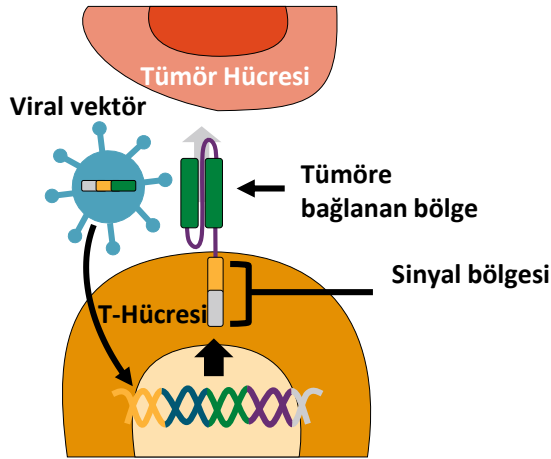
→ CAR-BCMA T cells Single infusion

CART-BCMA

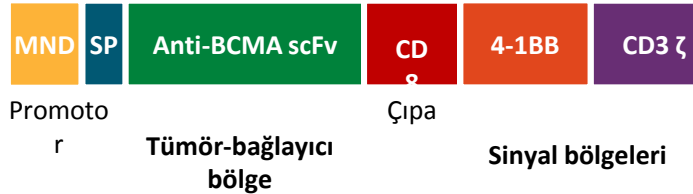


Ali SA, Blood. 2016(128)13:1688

Idecabtagene Vicleucel: BCMA-Hedefli CAR T-Hücre



Idecabtagene CAR dizaynı

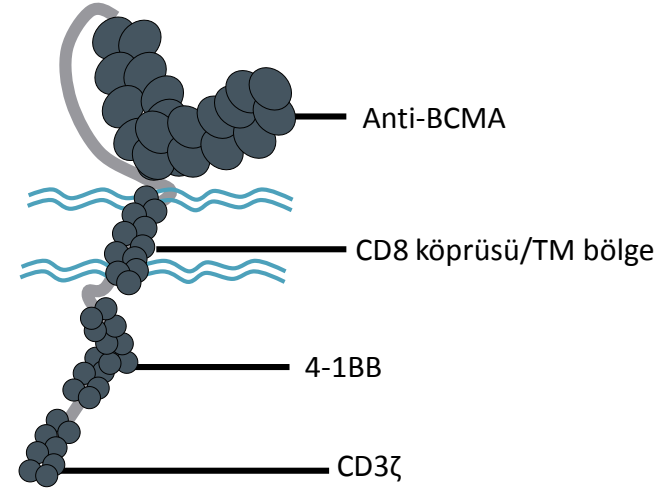


Hücre Dışı Bölge

Hedefleyici bölge
Destek/TM Bölge

Hücre içi bölge

Ko-stimülatuar bölge
T-Hücre aktivasyon bölgesi

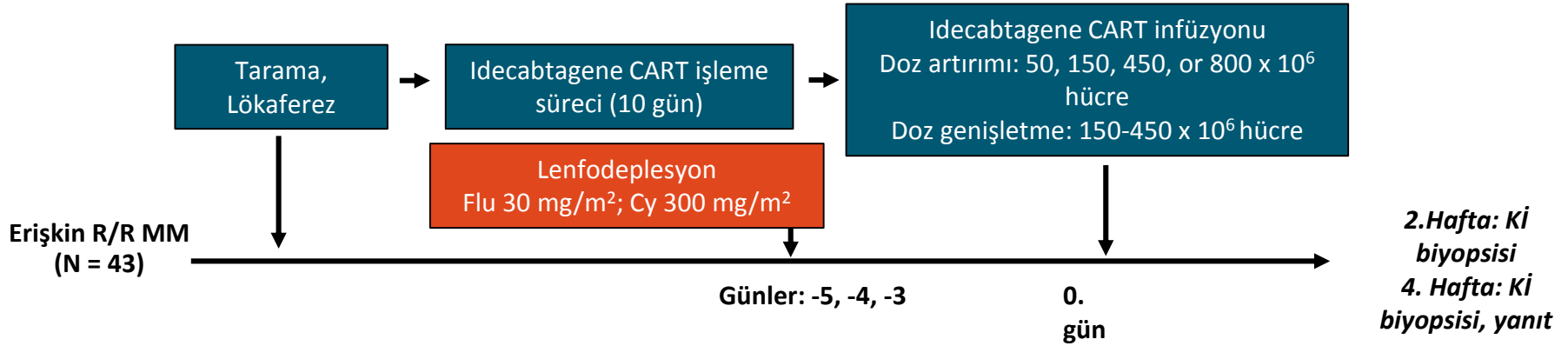


Idecabtagene: İkinci Jenerasyon CAR yapısı

- Lentiviral vektör ile kodlanmış edilmiş BCMA hedefli otolog CAR T ürünü
- Hedefleyici bölge: **Anti-BCMA**
- Ko-stimülatuar bölge: **4-1BB**
- T-Hücre aktivasyon bölgesi: **CD3 ζ**

MM'da Faz I CRB-401 Idecabtagene Vicleucel Çalışması: Çalışma Dizaynı

- Çok merkezli, R/R MM'da açık etiketli faz I çalışma (N = 43; veri kesim tarihi: Mart 29, 2018)
 - Doz artırım (n = 21): ≥ 3 sıra tedavi (PI, IMiD içeren) veya çift refrakter, $\geq 50\%$ BCMA+
 - Doz genişletme (n = 22): Daratumumab maruziyeti, son tedaviye direnç, BCMA ifadesinden bağımsız



- Birincil sonlanım: Güvenlilik ve tolerabilite
- İkincil sonlanım: IMWG kriterlerine göre yanıt durumu

CRB-401: Bazal Karakteristikler

Parametre	Doz Artırım (n = 21)	Doz Genişletme (n = 12)
Medyan yaş, yıl (aralık)	57 (37-74)	64 (46-75)
Erkek, n (%)	13 (62)	8 (67)
Tanıdan geçen medyan süre, yıl (aralık)	4 (1-16)	6 (1-36)
ECOG PS, n (%)		
▪ 0	8 (38)	2 (17)
▪ 1	11 (52)	10 (83)
▪ 2	2 (10)	0
Yüksek risk SG,* n (%)	8 (38)	7 (58)
Medyan takip, ay (aralık)	15 (5.1-22.8)	7.0 (1.5-8.1)
Medyan önceki tx sayısı, n (range)	7 (3-14)	8 (3-23)
Önceki OKHN, n (%)	21 (100)	11 (92)
▪ 0	0	1 (8)
▪ 1	15 (71)	8 (67)
▪ > 1	6 (29)	3 (25)

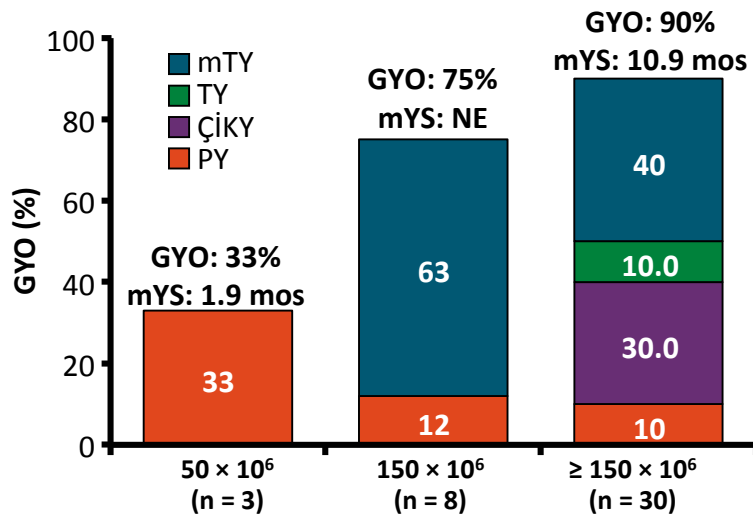
*del(17p), t(4;14), t(14;16).

Raje. NEJM. 2019;380:1726.

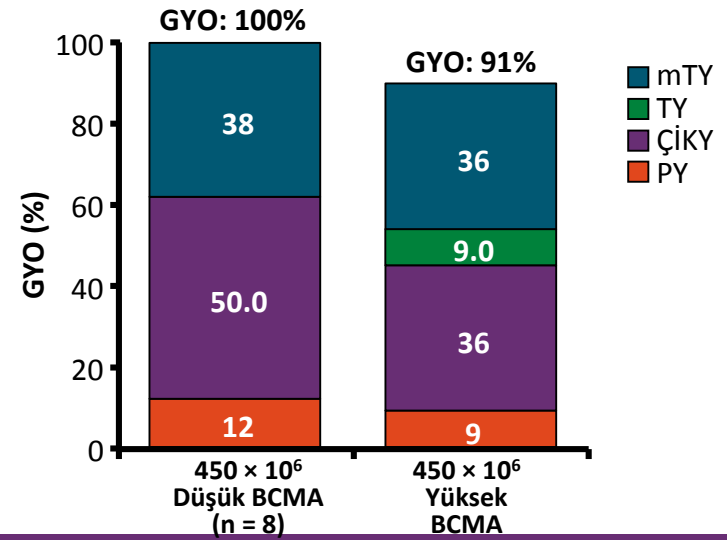
Parametre, n (%)	Doz Artırım (n = 21)		Doz Genişletme (n = 12)	
	Maruz	Refrakter	Maruz	Refrakter
Önceki tedaviler				
▪ Bortezomib	21 (100)	13 (62)	12 (100)	7 (58)
▪ Karfilzomib	19 (90)	12 (57)	11 (92)	7 (58)
▪ Lenalidomid	21 (100)	17 (81)	12 (100)	7 (58)
▪ Pomalidomid	19 (90)	14 (67)	12 (100)	31 (94)
▪ Daratumumab	15 (71)	9 (43)	12 (100)	12 (100)
▪ Bort/Len	21 (100)	12 (57)	12 (100)	5 (42)
▪ Bort/Len/Car/ Pom/Dara	15 (71)	3 (14)	11 (92)	3 (25)

CRB-401: Doz ve BCMA İfadesine Göre Yanıtlar

Doza Göre Tümör Yanıtı

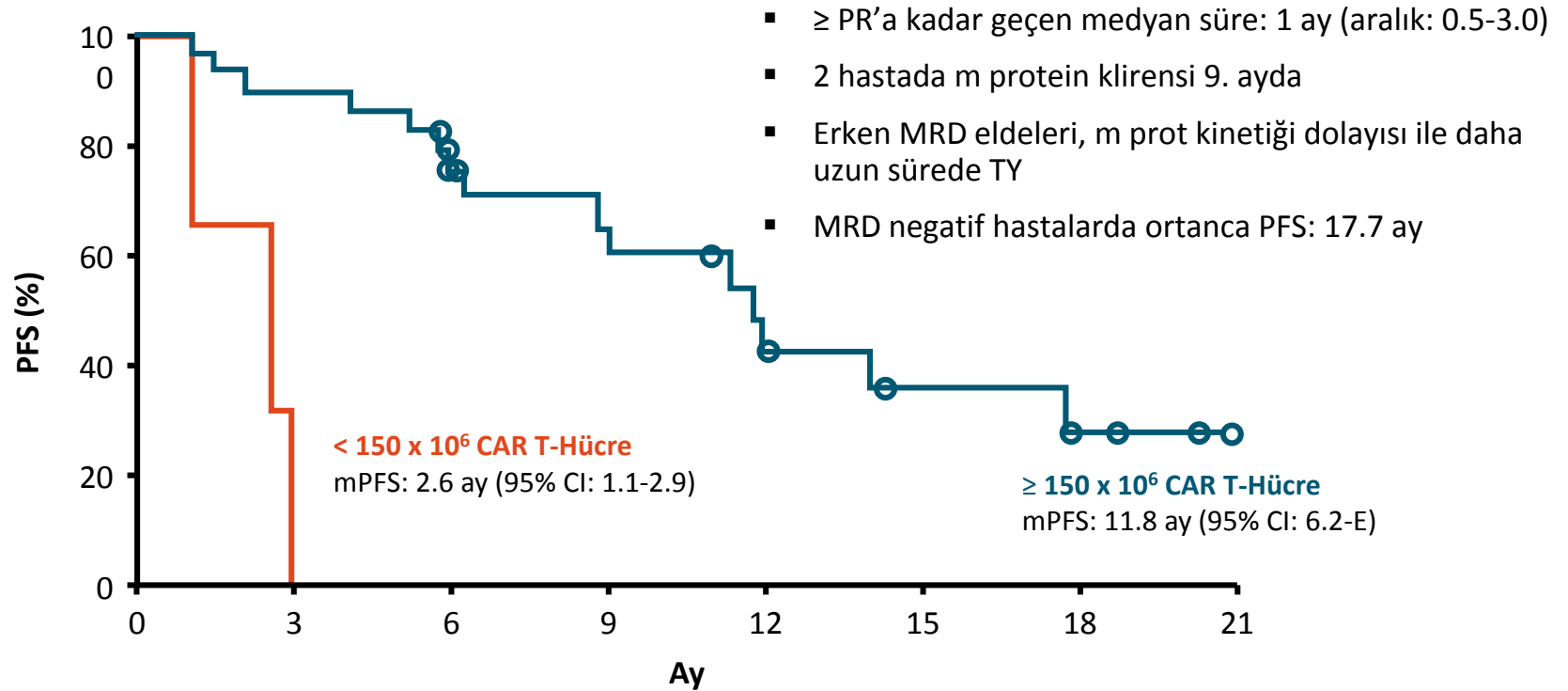


BCMA İfadesine Göre Yanıt



Yanıt	50 × 10 ⁶	150 × 10 ⁶	450 × 10 ⁶	800 × 10 ⁶	Total
MRD değerlendirilebilen yanıtlı hastalar	0	4	11	1	16
MRD neg -NGS (10 ⁻⁴)-	0	4 (100)	11 (100)	1 (100)	16 (100)

CRB-401: PFS



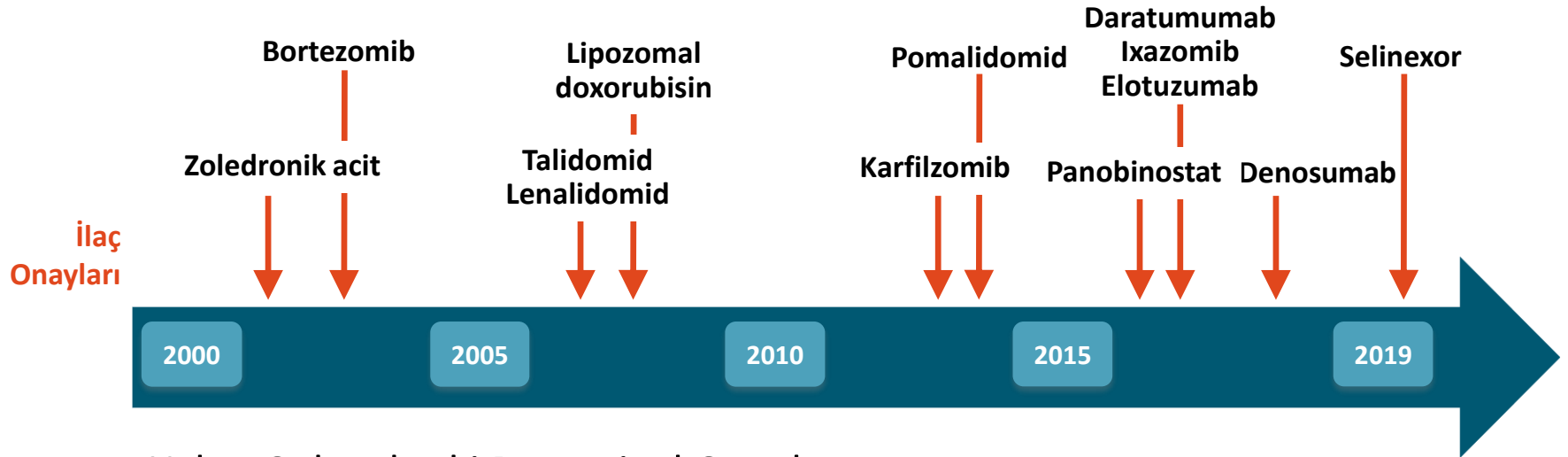
CRB-401: YE'ler

YE'ler, n (%)	Tüm Hastalar (N = 33)		
	Herhangi bir derece	Derece 3	Derece 4
SSS (Sit. Sal. Send)	25 (76)	2 (6)	0
Nörotoksisite	14 (42)	0	1 (3)
Nötropeni	28 (85)	2 (6)	26 (79)
Trombositopeni	19 (58)	5 (15)	10 (30)
Anemi	19 (58)	15 (45)	0
Enfeksiyon	12 (36)	2 (6)	0

SSS Parametreleri	N = 33
Medyan başlangıç zamanı, gün (min-maks)	
▪ Herhangi bir derece	2 (1-25)
▪ Derece ≥ 3	5 (4-6)
Medyan süre, gün (min-maks)	
▪ Herhangi bir derece	5 (1-32)
▪ Derece ≥ 3	2 (2-2)

- Tosilizumab kullanımı: n = 7 (21%)
- Kortikosteroid kullanımı: n = 4 (12%)

2000'den İtibaren Onaylanan Myelom Tedavileri

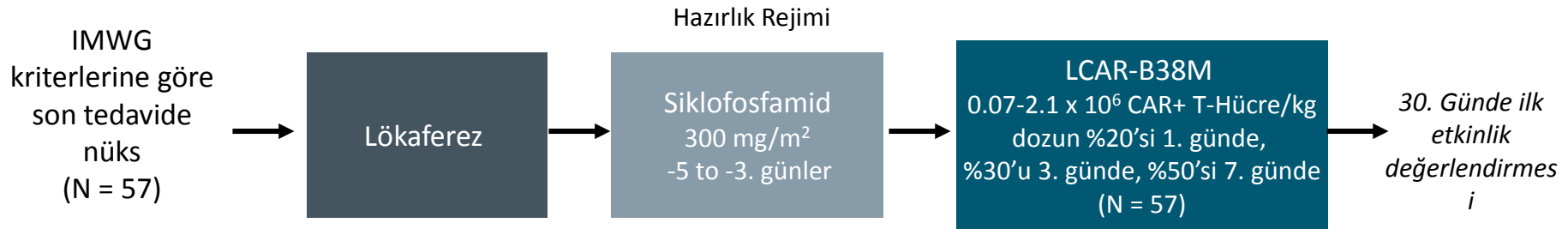


Yakın Gelecekteki Potansiyel Onaylar:

- Melflufen
- Belantamab mafodotin (GSK2857916)
- **Idcabtagene vicleucel (bb2121)**

R/R MM'da Faz I LEGEND-2 Çalışması, LCAR-B38M*: Çalışma Dizaynı

- Araştırmacı inisiyatifli, çok merkezli, tek kollu, açık etiketli faz I trial

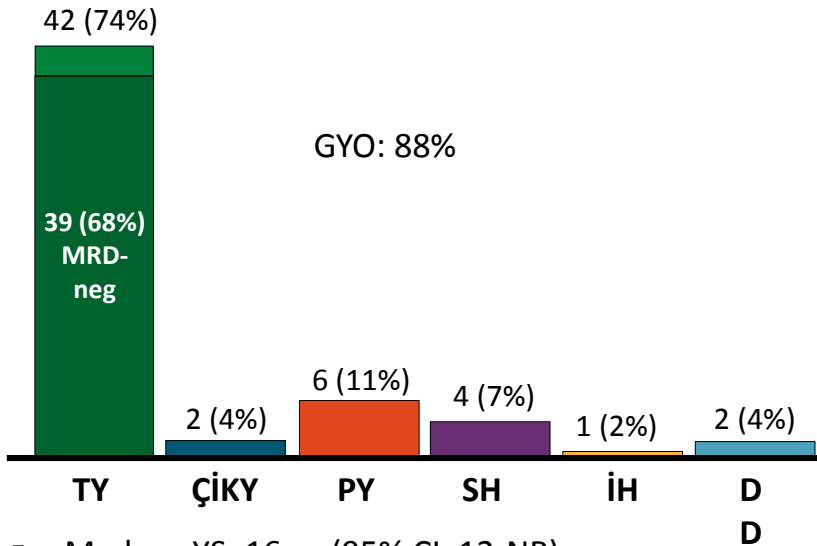


- Birincil sonlanım: Güvenlilik
- İkincil sonlanım: Antimyelom yanıtlar (IMWG kriterlerine göre)

*Lentiviral vektör bazlı 4-1BB ko-stimülatuar bölge; BCMA yakalayan bölge iki farklı epitope birlikte yakalayabiliyor.

LEGEND-2: Yanıtlar

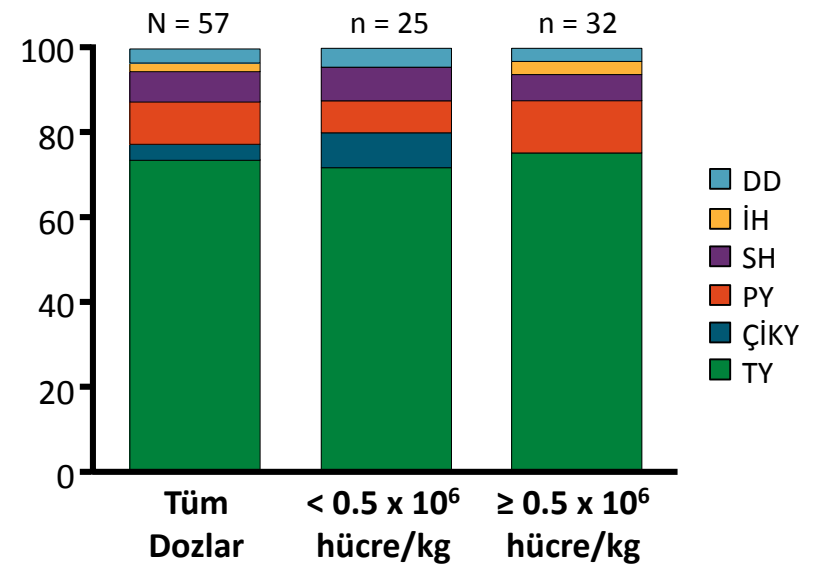
En İyi GYO (N = 57)



- Medyan YS: 16 ay (95% CI: 12-NR)
- MRD-neg TY'de Medyan YS : 22 ay (95% CI: 14-NR)
- İlk yanıt kadar geçen medyan süre: 1 ay (aralık: 0.4-3.6)

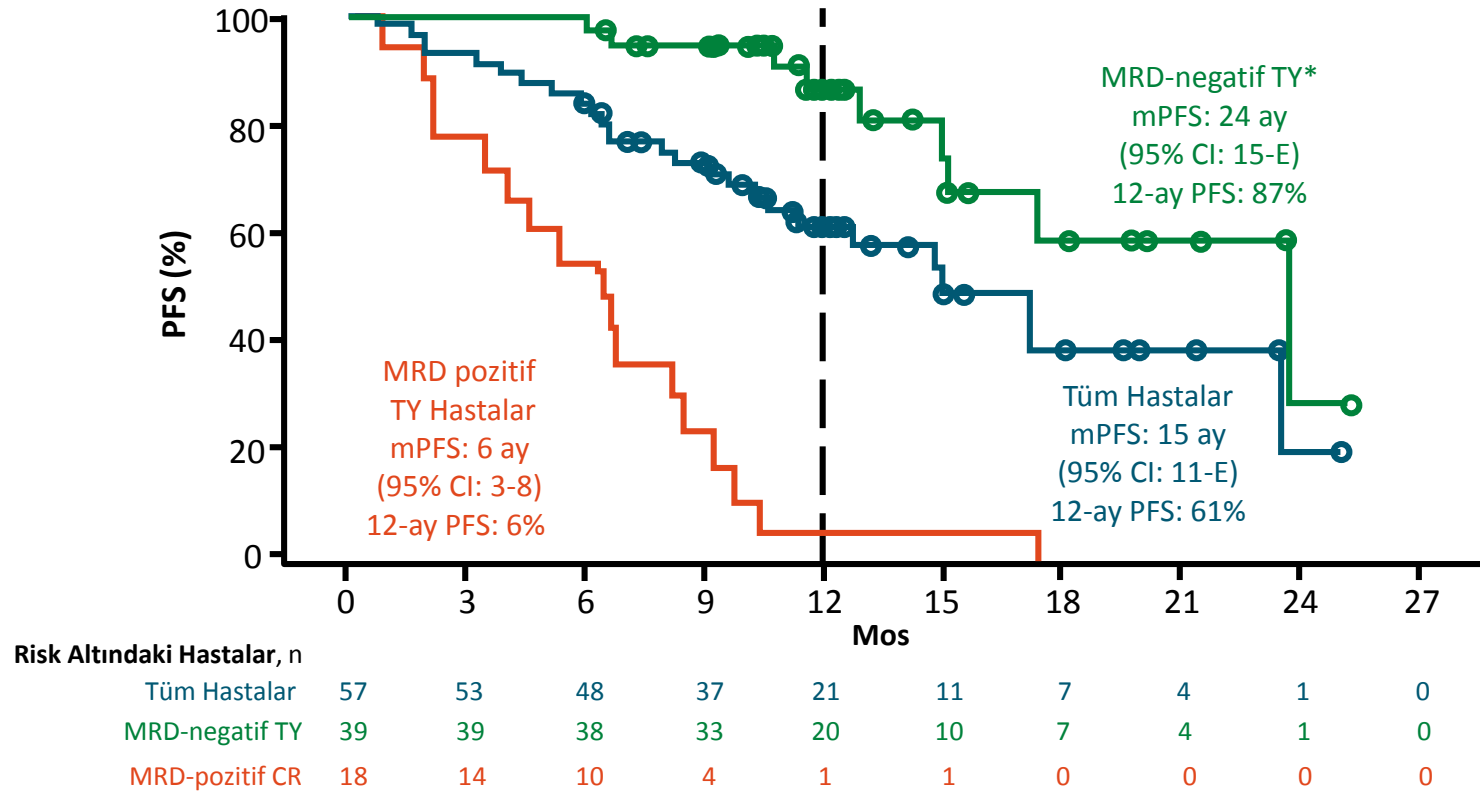
Zhao. ASH 2018. Abstr 955.

Doza Göre En İyi GYO (N = 57)



- BCMA < 40% (n = 26/53): 92%
- BCMA ≥ 40% (n = 27/53): 82%

LEGEND-2: PFS



Zhao. ASH 2018. Abstr 955.

*30/39 hasta halen remisyonda.

bb21217: R/R MM'da BCMA Hedefli CAR-T Hücre

■ bb21217

- Idecabtagene vicleucel (bb2121) ile aynı yapıyı kullanıyor
- PI3K inhibitörü bb007 ile kültüre edilerek daha hafıza-benzeri fenotipte T hücresi zenginleştirilmesi sağlanıyor
- Zenginleştirilmiş CAR-T hücrelerinin daha uzun süre fonksiyon göstereceği düşünülüyor
- Fonksiyonel CAR-T'lerin süregenliği yanıt süresi açısından da önemli bir belirleyici.

927 Updated Results from an Ongoing Phase 1 Clinical Study of bb21217 Anti-Bcma CAR T Cell Therapy

Program: Oral and Poster Abstracts

Type: Oral

Session: 653. Myeloma: Therapy, excluding Transplantation: Novel Therapy for Relapsed Myeloma

Hematology Disease Topics & Pathways:

Biological, multiple myeloma, Diseases, Therapies, CAR-Ts, Plasma Cell Disorders, Lymphoid Malignancies

Monday, December 9, 2019: 6:45 PM

Valencia A (W415A), Level 4 (Orange County Convention Center)

Jesus G. Berdeja, MD¹, Melissa Alsina, MD², Nina D. Shah, MD³, David S. Siegel⁴, Sundar Jagannath, MD⁵, Deepu Madduri, MD^{5}, Jonathan L. Kaufman, MD⁶, Nikhil C Munshi, MD⁷, Jacalyn Rosenblatt, MD⁸, Jagoda K. Jasielec, MD⁹, Yi Lin, MD, PhD¹⁰, Ashley Turka^{11*}, Lyh Ping Lam, PharmD, RPh^{11*}, Monica Massaro, MPH^{11*}, Timothy B. Campbell, MD, PhD^{12*}, Kristen Hege¹², Fabio Petrocca, MD^{11*} and Noopur S. Raje, MD¹³*

22 hasta, medyan 7 sıra tedavi (4-17), 19u dara, 13'ü bort/len/karf/pom/dara

Medyan 23 hafta takip, 13/22 sit. sal. Send, 5 nörotoksisite

%83 GYO, daha uzun erimli yanıtlar(?)

Sunumu bekliyor olacağız...

R/R MM'da BCMA Hedefli Çalışmalar

Çalışma	Faz	Planlanan N	Birincil Sonlanım(lar)		Tedavi
KarMMa-3 (NCT03651128)	III	381	PFS		Idecabtagene vicleucel vs standard triplet regimens (DPd, DVd, or IRd)
KarMMa-2 (NCT03601078)	II	181	ORR, CR	Erken NÜKS!!!!	Idecabtagene vicleucel
KarMMa (NCT03361748)	II	150	ORR		Idecabtagene vicleucel
CARTIFAN-1 (NCT03758417)	II	60	ORR		LCAR-B38M (JNJ-4528)
CARTITUDE-1 (NCT03548207)	I/II	118	Safety, ORR		LCAR-B38M (JNJ-4528)
PRIME (NCT03288493)	I/II	180	Safety, ORR, DoR		P-BCMA-101
EVOLVE (NCT03430011)	I/II	200	Safety, ORR		JCARH125
CRB402 (NCT03274219)	I	74	Safety		bb21217
UNIVERSAL (NCT04093596)	I	90	Safety		ALLO-715

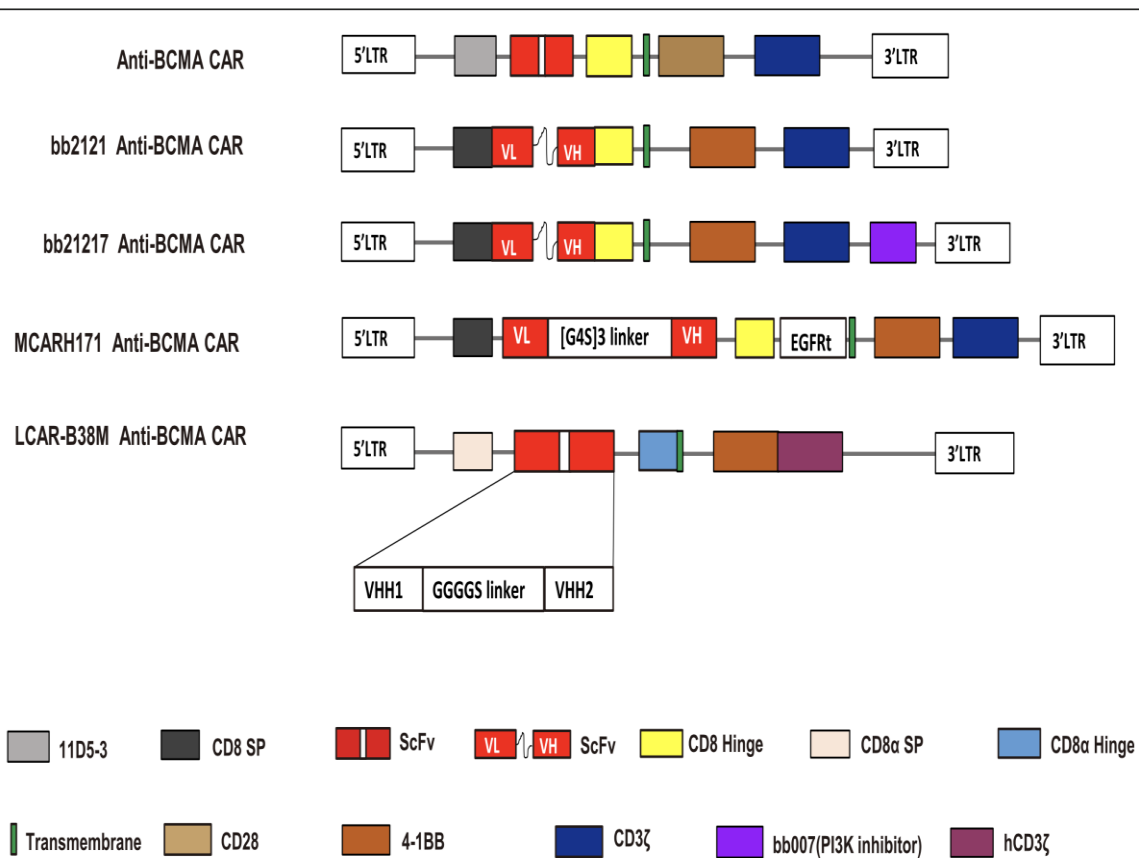
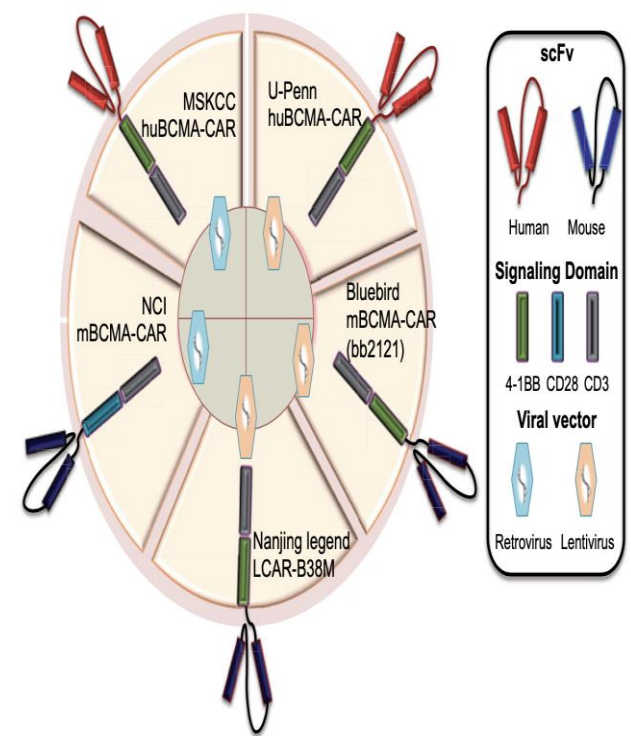
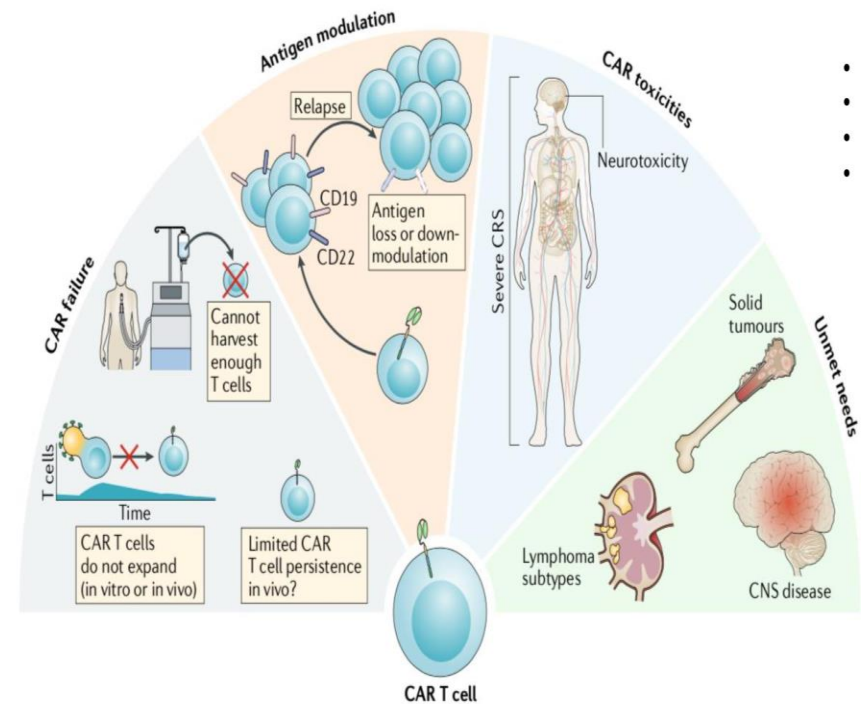
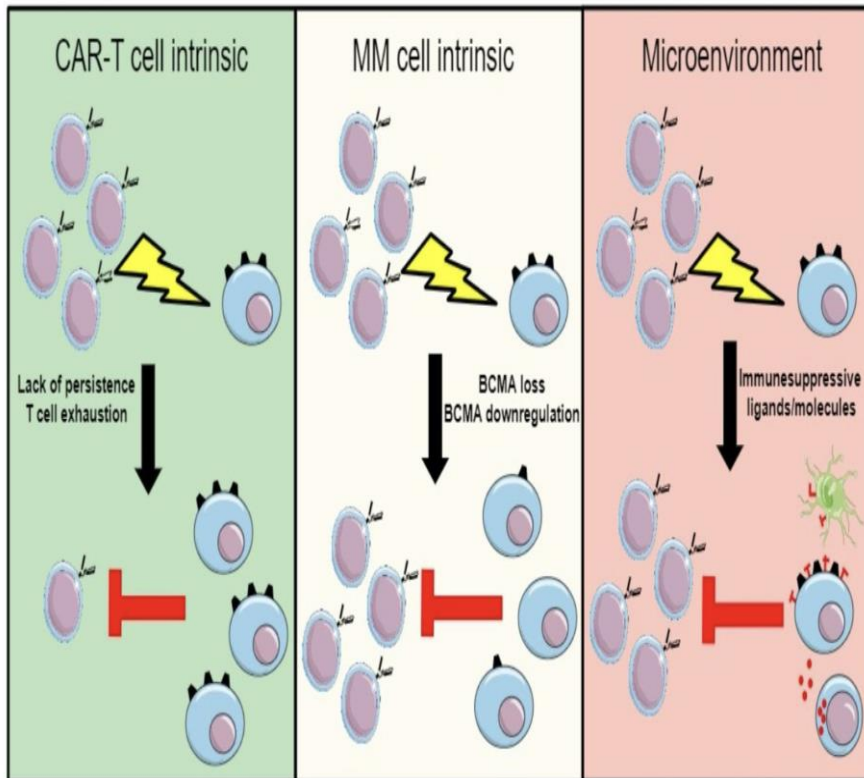


Fig. 1 The schematic diagram of representative structures of BCMA-targeted chimeric antigen receptors (CAR). The BCMA CARs contain a single-chain of BCMA antibody variable fragment (ScFv), a transmembrane domain, a hinge region, a co-stimulation domain (4-1BB, CD28 or OX40), and a CD3ζ domain. Additional sequences (such as PI3K inhibitor) are added to enhance identification of CAR+ T cells. LCAR-B38M CAR contains two epitopes of BCMA ScFv, VHH1 and VHH2. PI3K: phosphoinositol 3 kinase



Kullanımı Kısıtlayan veya Etkiyi Azaltan Faktörler



- No GVHD
- Allogeneic OTS
- Less risk of CRS
- Alternate killing mechanisms mitigate antigen escape

bb21217: R/R MM'da BCMA Hedefli CAR-T Hücre

■ bb21217

- Idecabtagene vicleucel (bb2121) ile aynı yapıyı kullanıyor
- PI3K inhibitörü bb007 ile kültüre edilerek daha hafıza-benzeri fenotipte T hücresi zenginleştirilmesi sağlanıyor
- Zenginleştirilmiş CAR-T hücrelerinin daha uzun süre fonksiyon göstereceği düşünülüyor
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927 Updated Results from an Ongoing Phase 1 Clinical Study of bb21217 Anti-Bcma CAR T Cell Therapy

Program: Oral and Poster Abstracts

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Session: 653. Myeloma: Therapy, excluding Transplantation: Novel Therapy for Relapsed Myeloma

Hematology Disease Topics & Pathways:

Biological, multiple myeloma, Diseases, Therapies, CAR-Ts, Plasma Cell Disorders, Lymphoid Malignancies

Monday, December 9, 2019: 6:45 PM

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22 hasta, medyan 7 sıra tedavi (4-17), 19u dara, 13'ü bort/len/karf/pom/dara

Medyan 23 hafta takip, 13/22 sit. sal. Send, 5 nörotoksisite

%83 GYO, daha uzun erimli yanıtlar(?)

Sunumu bekliyor olacağız...

CAR-T Hücre Kokteyli

A combination of humanised anti-CD19 and anti-BCMA CAR T cells in patients with relapsed or refractory multiple myeloma: a single-arm, phase 2 trial



Zhiling Yan*, Jiang Cao*, Hai Cheng, Jianlin Qiao, Huanxin Zhang, Ying Wang, Ming Shi, Jianping Lan, Xiaoming Fei, Lai Jin, Guangjun Jing, Wei Sang, Feng Zhu, Wei Chen, Qingyun Wu, Yao Yao, Gang Wang, Jing Zhao, Junnian Zheng†, Zhenyu Li†, Kailin Xu†

Summary

Background Anti-B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T-cell therapy has been shown to have activity in patients with relapsed or refractory multiple myeloma. Reports have suggested that a small subgroup of less differentiated myeloma clones express CD19 and anti-CD19 CAR T-cell therapy has shown activity in some of these patients. We aimed to assess the activity and safety of a combination of humanised anti-CD19 and anti-BCMA CAR T cells in patients with relapsed or refractory multiple myeloma.

Lancet Haematol 2019
Published Online
August 1, 2019
[http://dx.doi.org/10.1016/S2352-3026\(19\)30115-2](http://dx.doi.org/10.1016/S2352-3026(19)30115-2)
See Online/Comment
<http://dx.doi.org/10.1016/>

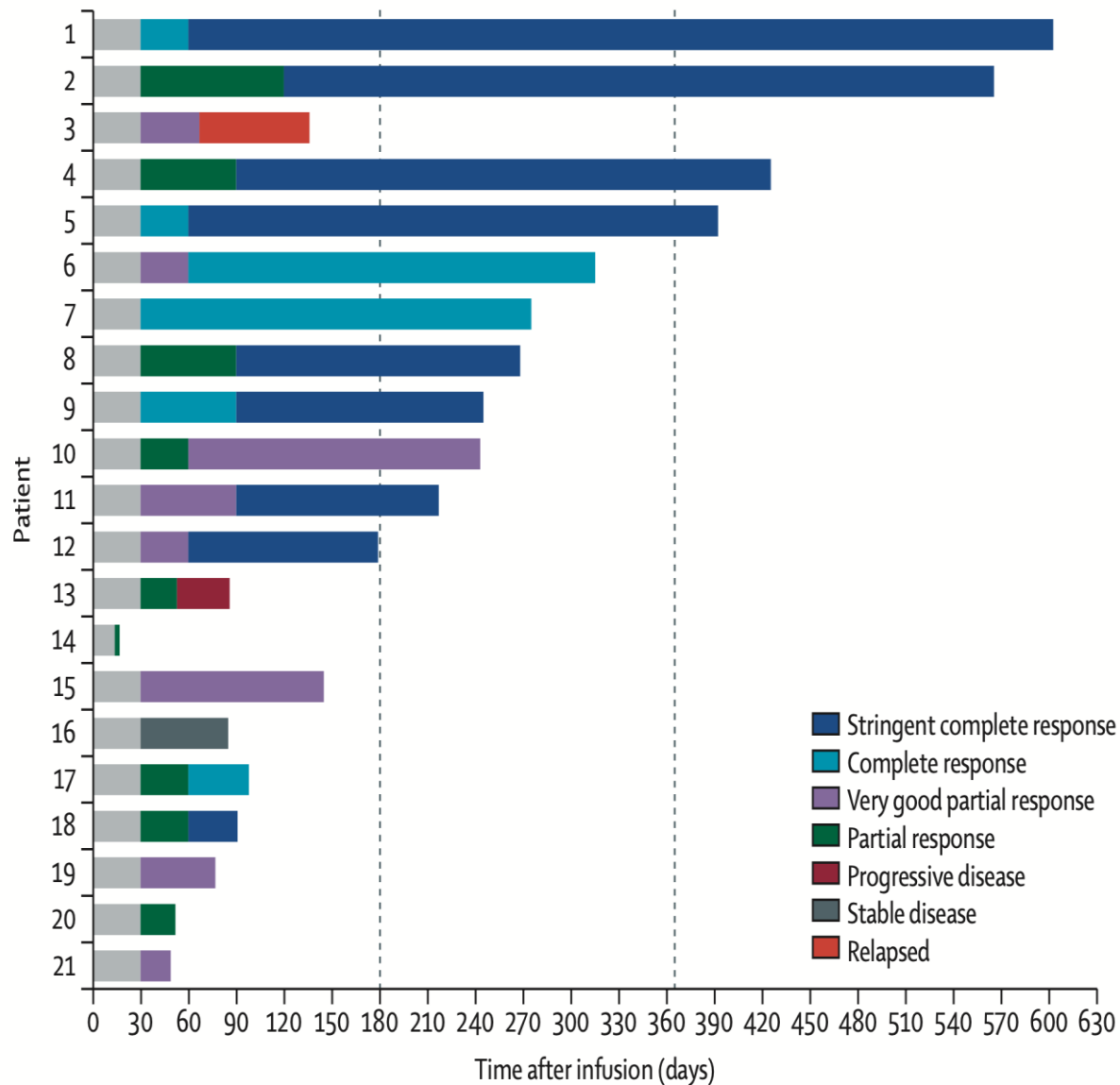


Figure 2: Response assessment after infusion of CART cells
Dotted lines mark 6 months and 12 months after infusion.

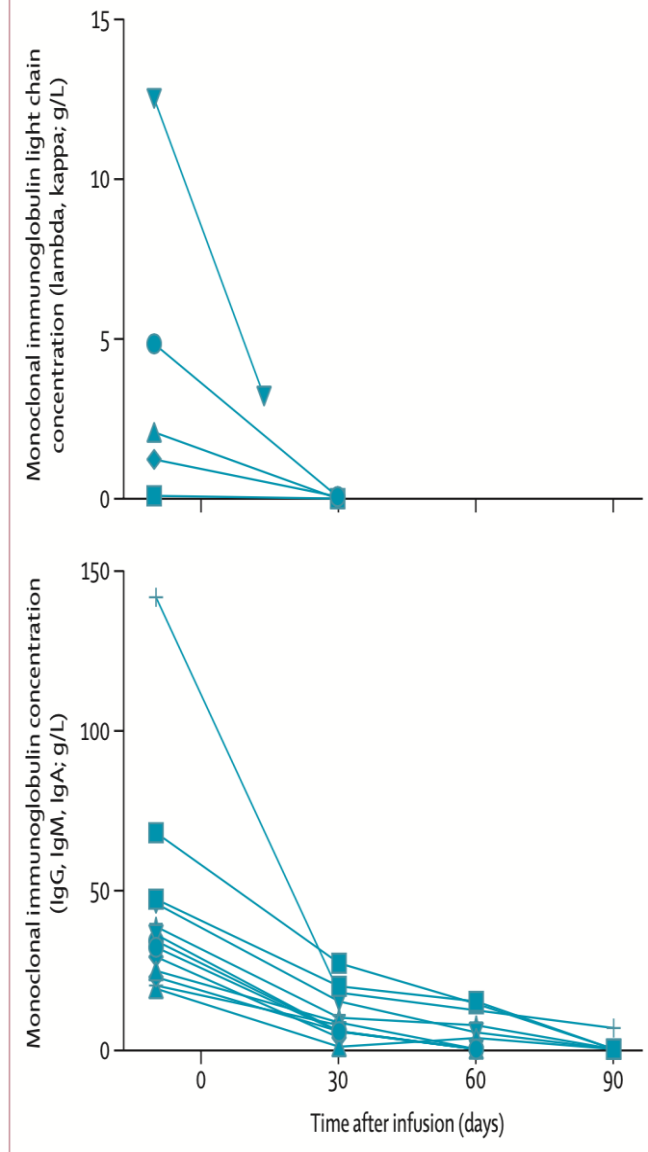


Figure 3: Changes in monoclonal immunoglobulin concentration from baseline
Each line represents a single patient.

MM'da CAR-T Hücre Tedavisinde Değişik Hedefler

	Target	Agents
→	CD38	Daratumumab, Isatuximab, MOR202
→	CS1 (SLAMF7) CARAMBA çalışması	Elotuzumab Numerous CAR T cells
→	BCMA	GSK2857916 (ADC) Numerous BiTEs Numerous CAR T cells
→	CD138	BT-062 (ADC)
	GPRC5D	CAR, BiTE
	CD229	CAR

Target	Agents
→ NKG2D Ligands	
→ Lewis Y Antigen	
→ Surface Ig	Baylor kappa light-chain CAR
ICAM1 (CD54)	BI-505 (mAb)
CD48A	SGN-CD48A (ADC)
CD46	ADC

CD44v6 EURECART Çalışması

→ = CAR T cells in clinical trials

930 A Bispecific CAR-T Cell Therapy Targeting Bcma and CD38 for Relapsed/Refractory Multiple Myeloma: Updated Results from a Phase 1 Dose-Climbing Trial

Program: Oral and Poster Abstracts

Type: Oral

Session: 653. Myeloma: Therapy, excluding Transplantation: Novel Therapy for Relapsed Myeloma

Hematology Disease Topics & Pathways:

Biological, Diseases, Adult, Therapies, Lymphoma (any), Adverse Events, CAR-Ts, Elderly, Biological Processes, Technology and Procedures, Cell Lineage, Study Population, Clinically relevant, Lymphoid Malignancies

Monday, December 9, 2019: 7:30 PM

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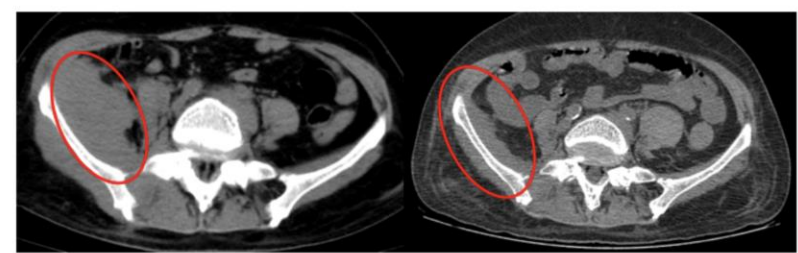
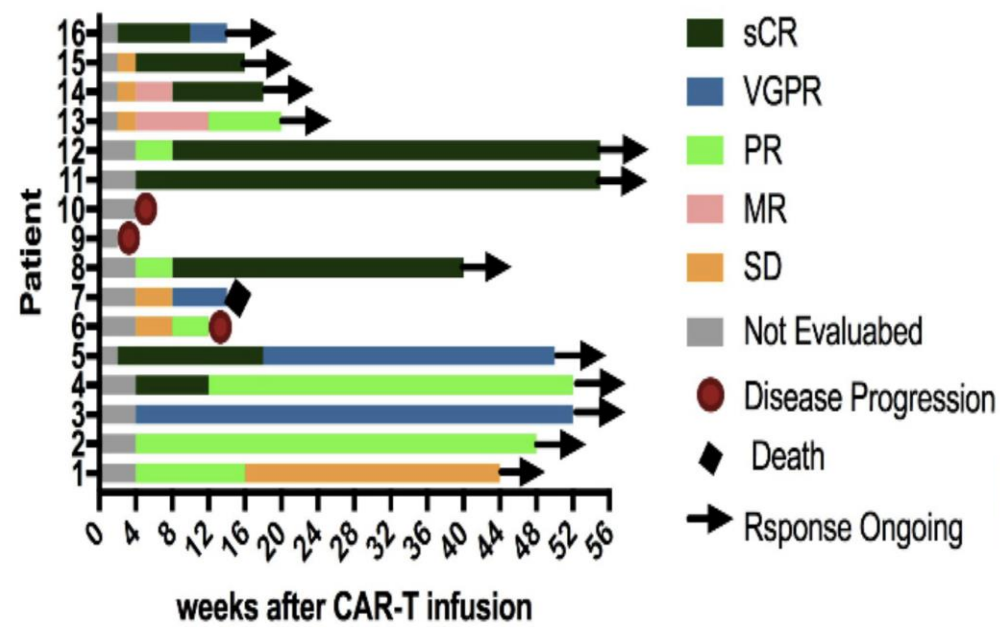
Chenggong Li^{1,2}, Heng Mei^{1,2*}, Yu Hu, MD, PhD^{1,2*}, Tao Guo, MD, PhD^{1,2*}, Lin Liu, MD, PhD^{1,2*}, Huiwen Jiang^{1,2*}, Lu Tang^{1,2*}, Yaohui Wu, MD, PhD^{1,2*}, Lisha Ai, MD, PhD^{1*}, Jun Deng, MD, PhD^{1,2*} and Dan Jin^{3*}*

¹Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

²Hubei Clinical Medical Center of Cell Therapy for Neoplastic Disease, Wuhan, China

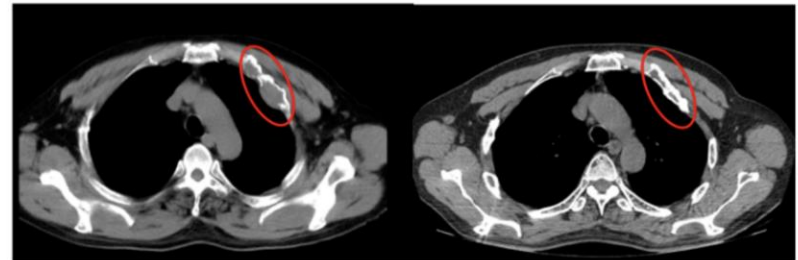
³Cellyan Therapeutics Co., LTD, Wuhan, China

Clinical Efficacy after anti-BM38 CAR-T Infusion



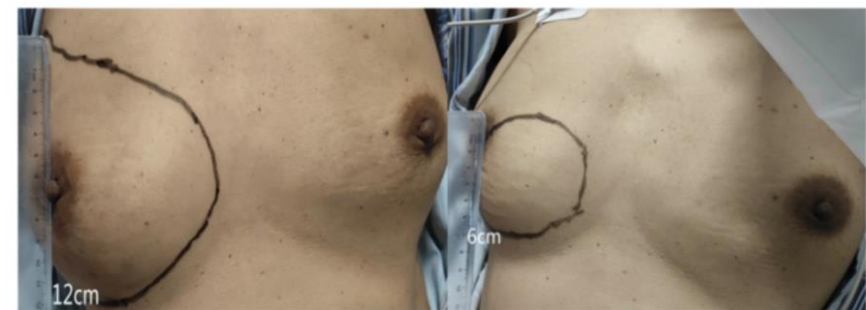
Before infusion of pt7

2 months After infusion



Before infusion of pt11

28 days After infusion



Before infusion of pt15

21 days After infusion

136 Optimal Dual-Targeted CAR Construct Simultaneously Targeting Bcma and GPRC5D Prevents Bcma-Escape Driven Relapse in Multiple Myeloma

Program: Oral and Poster Abstracts

Type: Oral

Session: 652. Myeloma: Pathophysiology and Pre-Clinical Studies, excluding Therapy: Modeling Cellular Immunity and Tumor Microenvironment in Multiple Myeloma

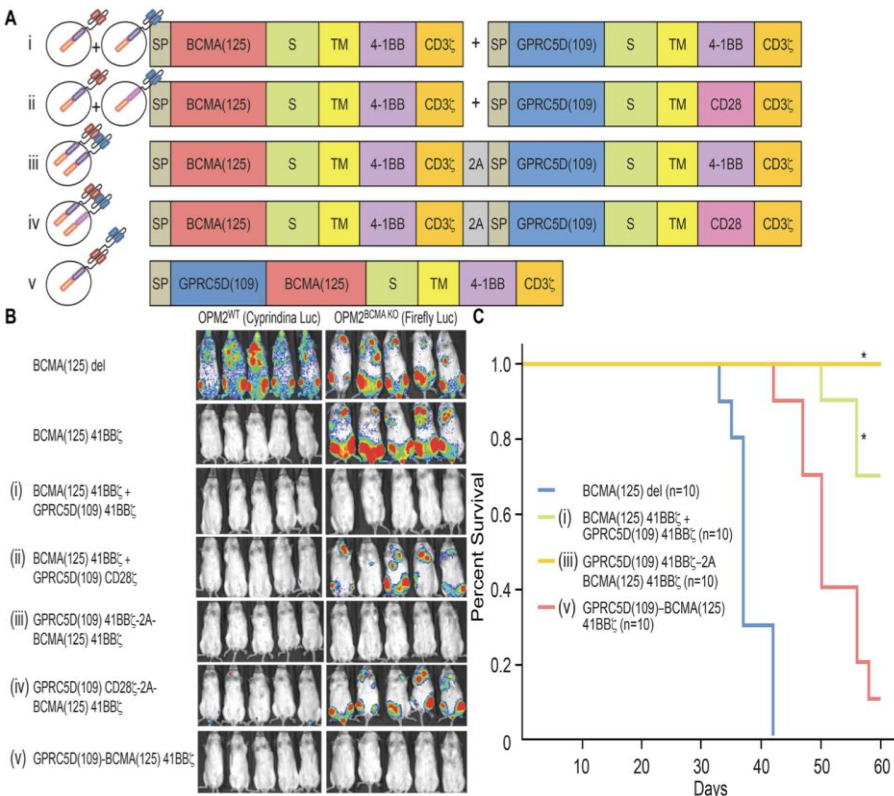
Hematology Disease Topics & Pathways:

Biological, Diseases, multiple myeloma, Therapies, CAR-Ts, Plasma Cell Disorders, immunotherapy, Lymphoid Malignancies

Saturday, December 7, 2019: 10:15 AM

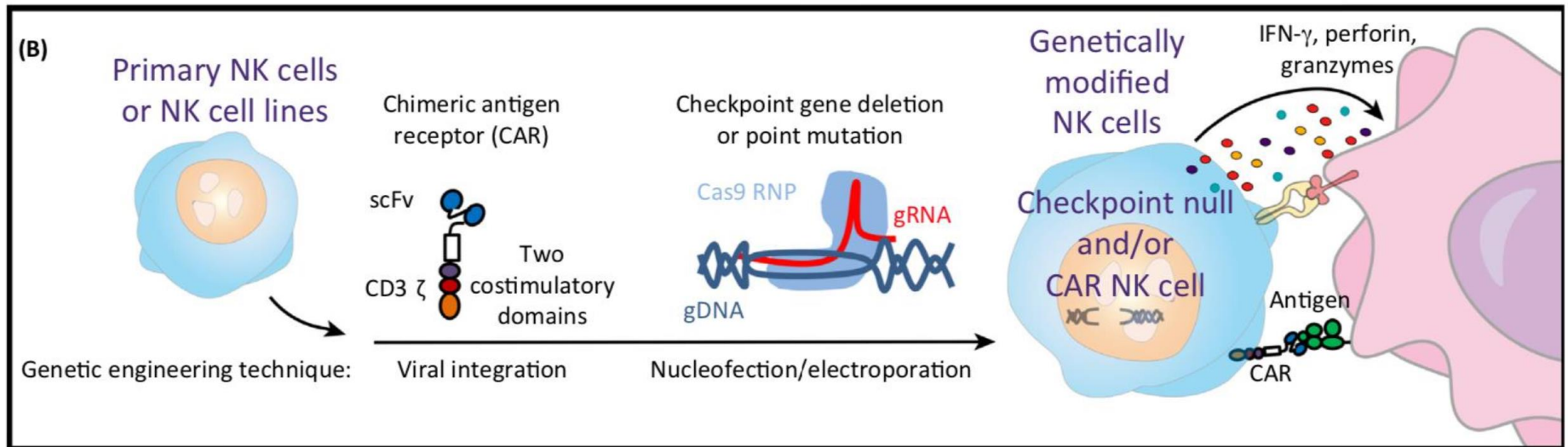
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Carlos Fernandez de Larrea, MD, PhD^{1,2}, Mette Staehr, PhD^{2*}, Andrea Lopez^{2*}, Yunxin Chen, MBBS^{2,3*}, Terence J Purdon, MS^{2*}, Khong Y. Ng, PhD^{4*}, Hans Wendel, MD^{4*}, Renier J. Brentjens, MD, PhD^{2,5} and Eric L Smith, MD, PhD^{2,6}



(A) BCMA/GPRC5D dual-targeted CAR strategies evaluated for the treatment of MM. (i, ii) parallel manufacturing for simultaneous 50:50 infusion (iii-iv) 2 CARs expressed by 1 T cell approaches via 2A bicistronic "self-cleaving" peptide containing vector, codon optimized to avoid DNA recombination (v) Tandem-scFv, "single stalk" CAR. SP: signal peptide; S: spacer; TM: transmembrane. **(B) 4-1BB only containing dual-targeted approaches have enhanced efficacy against BCMA-negative MM cells.** 5-10% OPM2^{BCMA KO} (firefly luciferase⁺) cells were spiked into bulk OPM2^{BCMA KO} (membrane-tethered cyprindina luciferase⁺) cells for IV injection of 2x10⁶ total cells into NSG mice. Day 14, mice were randomized for treatment with 5 x 10⁵ gene modified human T cells with either 1 of the 5 dual-targeted approaches in Fig 1A, BCMA(125)/4-1BBζ mono-targeted CAR, or BCMA(125) scFv non-signaling CAR (del) as controls. BLI, d28 shown. **(C) Dual 4-1BB containing approaches are superior to tandem scFv-single stalk design.** BCMA heterogeneous MM bearing mice, as in (Fig 1B), were treated with 2.5 x 10⁵ gene modified cells (approaches Fig 1A i, iii, v, and BCMA(125) non signaling del CAR as control). Kaplan-Meier survival curve, days post-OPM2 injection. *p < 0.05 compared to tandem-scFv single stalk CAR.

CAR-NK Hücre Üretimi



Trends in Immunology

Souza-Fonseca-Guimaraes F, Cursons J, Huntington ND. **Trends in Immunology** 2019

The therapeutic role of natural killer cells in multiple myeloma

Ghulam Rehman Mohyuddin¹  | Muzaffar H. Qazilbash²

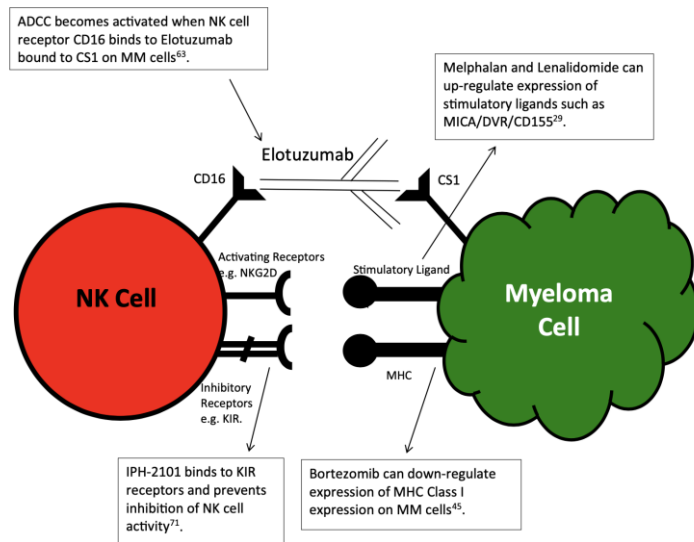


FIGURE 1 Receptors on myeloma cells and NK cells that are targets for several MM pharmacological agents

TABLE 1 Summary of trials of MM involving NK cell products, and ongoing clinical trials across hematological malignancies involving NK cells

Study name/number	Number of patients	Disease	Source of NK cells	Outcomes
Shi et al ⁹⁰	10	MM	Haploidentical KIR ligand mismatched NK cells combined with autologous transplant	CR = 5, PR = 1, SD = 2, 2 = PD
Szmania et al ⁹²	8	MM	Expanded NK cells either autologous or haploidentical	7 evaluable patients, PR = 1, PD = 6
Shah et al ⁹⁶	12	MM	Cord blood derived NK cells combined with autologous transplant	VGPR or greater = 10, PR = 2
NTC01729091	60	MM	Cord blood derived NK cells combined with autologous transplant, Elotuzumab and Lenalidomide	Ongoing
NCT03056339	36	B Lymphoid Malignancies	Cord blood derived CAR engineered NK cells	Ongoing
NCT00995137	14	B Acute Lymphoblastic Leukemia	Haploidentical NK cells	Ongoing
NCT01974479	20	B Acute Lymphoblastic Leukemia	Haploidentical NK cells redirected against CD19	Suspended
NCT02944162	10	Acute Myeloid Leukemia	Allogenic CAR engineered NK cells targeting CD33	Ongoing
NCT02892695	10	Lymphoid Malignancies	Allogenic CAR engineered NK cells targeting CD19	Ongoing
NCT02742727	10	CD7 ⁺ Relapsed Leukemia/Lymphoma	Allogenic CAR engineered NK cells targeting CD7	Ongoing

MM, multiple myeloma; CAR, chimeric antigen receptor; NK, natural killer.

ÖZET

CAR-T cell therapy for multiple myeloma: a consensus statement from The European Myeloma Network

by Philippe Moreau, Pieter Sonneveld, Mario Boccadoro, Gordon Cook, M^a Victoria Mateos, Hareth Nahi, Hartmut Goldschmidt, Meletios A. Dimopoulos, Paulo Lucio, Joan Bladé, Michel Delforge, Roman Hajek, Heinz Ludwig, Thierry Facon, Jesus F. San Miguel, and Hermann Einsele

Haematologica 2019 [Epub ahead of print]

Citation: Philippe Moreau, Pieter Sonneveld, Mario Boccadoro, Gordon Cook, M^a Victoria Mateos, Hareth Nahi, Hartmut Goldschmidt, Meletios A. Dimopoulos, Paulo Lucio, Joan Bladé, Michel Delforge, Roman Hajek, Heinz Ludwig, Thierry Facon, Jesus F. San Miguel, and Hermann Einsele. CAR-T cell therapy for multiple myeloma: a consensus statement from The European Myeloma Network.

Haematologica. 2019; 104:xxx

doi:10.3324/haematol.2019.224204

CAR-T cell therapy is still an **experimental therapy**, mostly developed by pharmaceutical companies. Academic research programs are urgently needed either with or without collaboration with biotech companies or big pharma to improve efficacy and safety, in particular to improve persistence of CAR-T cells, avoid antigen loss and reduce CRS/neurotoxicity.¹⁰⁻¹¹ This is not anything new in Myeloma, an example of disease in which the close collaboration between the pharmaceutical companies and the European cooperatives group has resulted in outcomes improvement.

The development of academic programs, with high prioritization rate, in order to reduce the cost of CAR-T cells proposed by pharmaceutical companies and to increase the academic knowledge on CAR-T cell therapy, to propose new collaborations with pharmaceutical companies, and to design EU clinical trials based on the combination of CAR-T with current or new anti-myeloma strategies, is crucial.

The definition of consensus guidelines and educational programs for autologous CAR-T cell therapy could be expanded to other immunotherapeutic approaches, such as bispecific antibodies, conjugates, NK-cell therapy or allo-CAR-Ts. In the near future, hopefully several strategies targeting BCMA and other plasma cell antigens will become available for the treatment of myeloma patients, and expert clinical judgement about the right time for each patient to use a CART or a bispecific antibodies or antibody drug conjugates will require a deep knowledge of myeloma disease. Educational programs under the guidance of myeloma experts will contribute not only to improve the outcome of our patients but also to a more efficient use of the available resources.

Etkiyi Azaltan Faktörlerin Üstesinden Gelmek

- Daha erken basamaklarda CAR-T Hücre tedavilerini kullanmak
- T Hücre alt popülasyonlarında zenginleştirmeye gitmek (Hafıza-benzeri T Hc'leri gibi)
- Eş-zamanlı CD19'u hedeflemek
- BCMA ifadesini artırmak (gama sekretaz inh..)
- Eş zamanlı diğer antijenleri de hedeflemek
- Allo-CAR, u-CAR konseptlerinin geliştirilmesi
- CAR-NK potansiyelini değerlendirmek(?)

PAHA'YI ve TOKSİSİTEYİ AZALTMAK!!!

CAR T may allow patients to step off the “treadmill” of continuous treatment



*Current paradigm of myeloma therapy:
continuous treatment until progression*

Ama ZOR bir koşu!



One treatment (then observation)

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