İmmünosüpresif Tedavilerde Yeni Gelişmeler ve İlişkili İnfeksiyonlar
CAR-T Hücre Tedavisi

Ediz Tütüncü

KLİMİK 2026

1 Mayıs 2026, Antalya

Sunum planı

- “Chimera”
- Tarihçe / gelişim
- TCR yapısı / işleyiş
- CAR-T hücre yapısı / jenerasyonları
- Endikasyon / etkililik
- Uygulama, yan etkiler, ciddiyet skalası, yönetim
- İnfeksiyonlara yatkınlık, ne, ne zaman
- Önleme

Chimera

- 350–340 BC, Apulia

- 850–750 BC, Karkamış

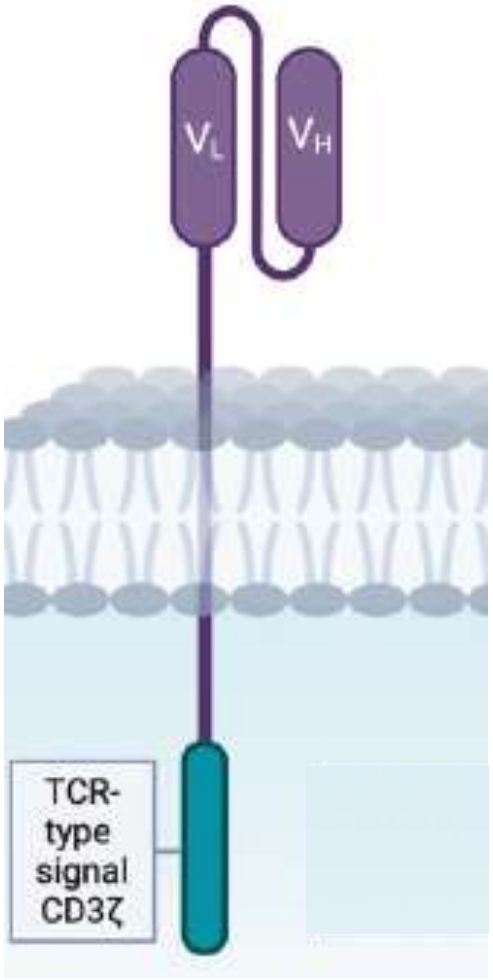
Chimera

- Bellerophon
- Yanartaş

CAR-T hücresi

- Chimeric antigen receptor (CAR)

  Bir kısmı antikor bir kısmı ise TCR yapısında olan hibrid molekül



TCR
T hücre reseptörü

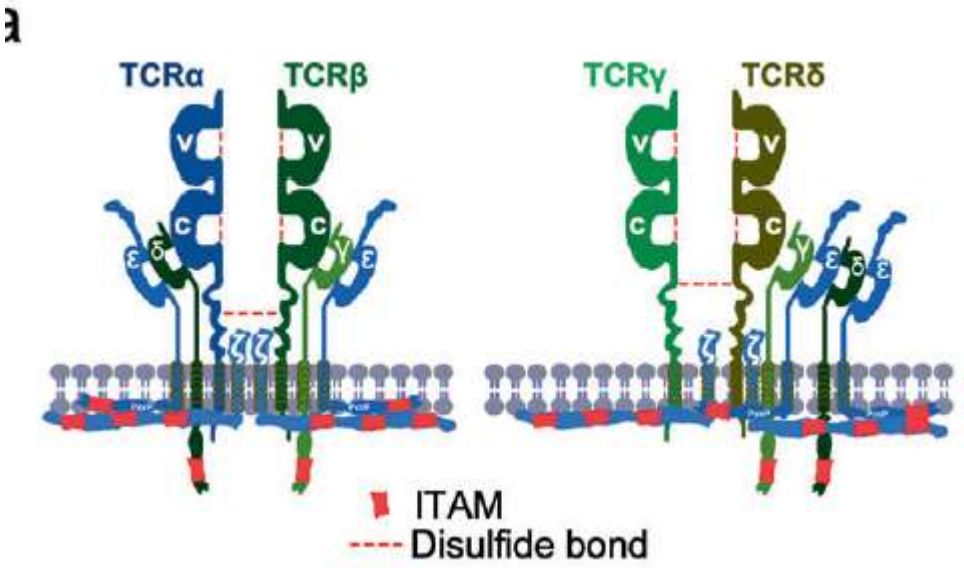
➢T hücreleri etkin bir “antijen bağımlı” hücre aracılı adaptif immün yanıt gelişiminde en önemli hücrelerdir.

Makrofajlar, dendritik hücreler, B lenfositler gibi antijen sunan hücrelerce MHC molekülleri aracılığıyla yabancı peptid molekülleri TCR’e sunulur,

Antijenik peptid ile TCR ilişkisi, T hücre aktivasyonu, klonal ekspansiyonu ve diferansiyasyonunu başlatır.

➢T hücre sinyali, etkin bir T hücre gelişimi, aktivasyonu için şarttır.

TCR



- TCR, alfa ve beta zincirlerinden oluşan bir heterodimer (TCRα/TCRβ),

  Ekstrasellüler bölge, transmembran bölgesi ve kısa bir sitoplazmik kuyruk

  CD3 δ, γ, ε, ζ zincirleri ile multiprotein kompleksleri oluştururlar,

Sinyal 1

- TCR, APC tarafından sunulan peptid antijeni tanır
  - CD8 T hücreleri MHC-I
  - CD4 T hücreleri MHC-II

Sinyal 2 / kostimülasyon

- APC üzerindeki CD80/CD86, T hücresindeki CD28 molekülüne bağlanır
  - Proliferasyon sinyali

Sinyal 3

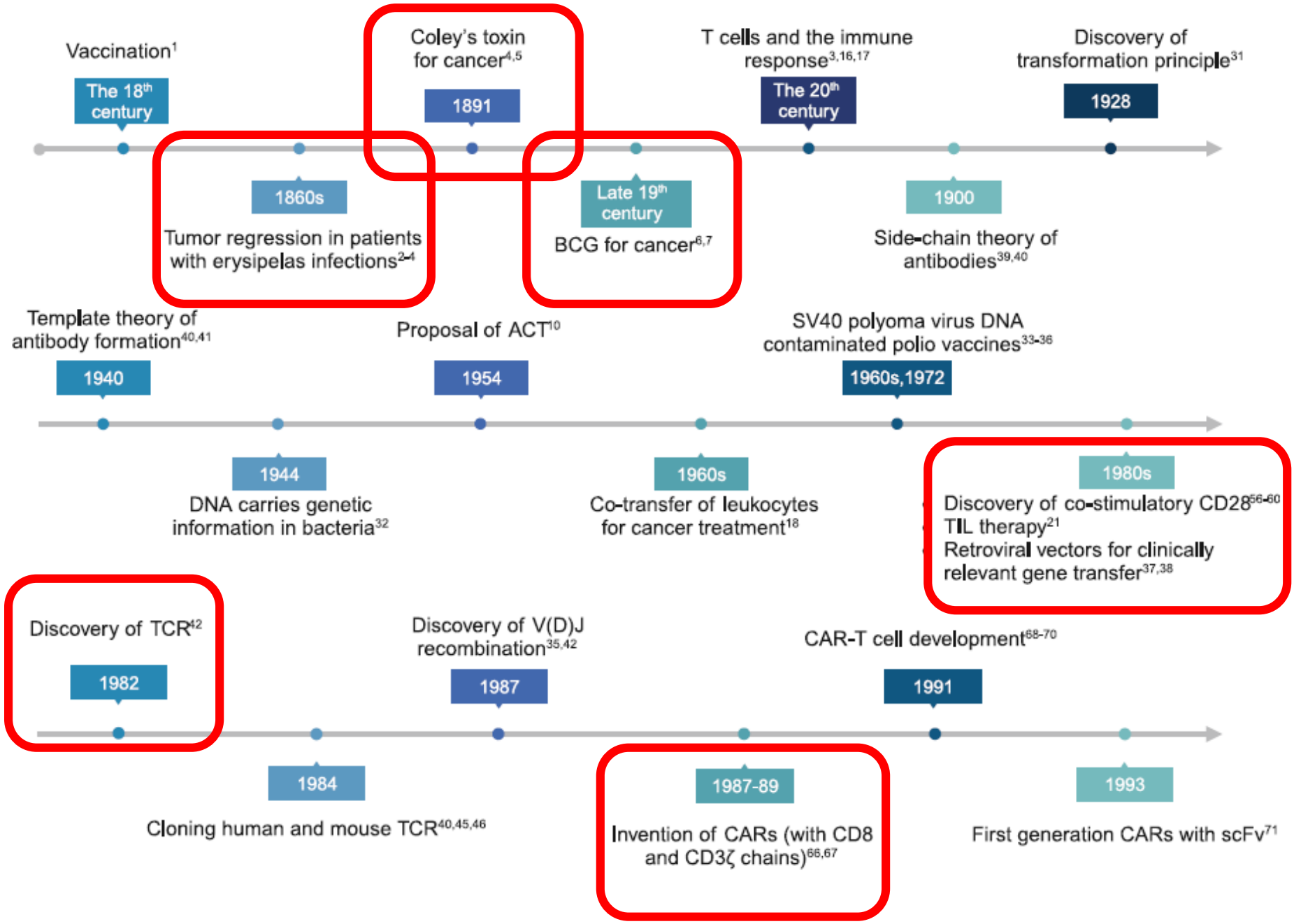
- TCR-Ag- MHC bağlanması ile ITAM içeren CD3 kompleks fosforilasyonu başlar

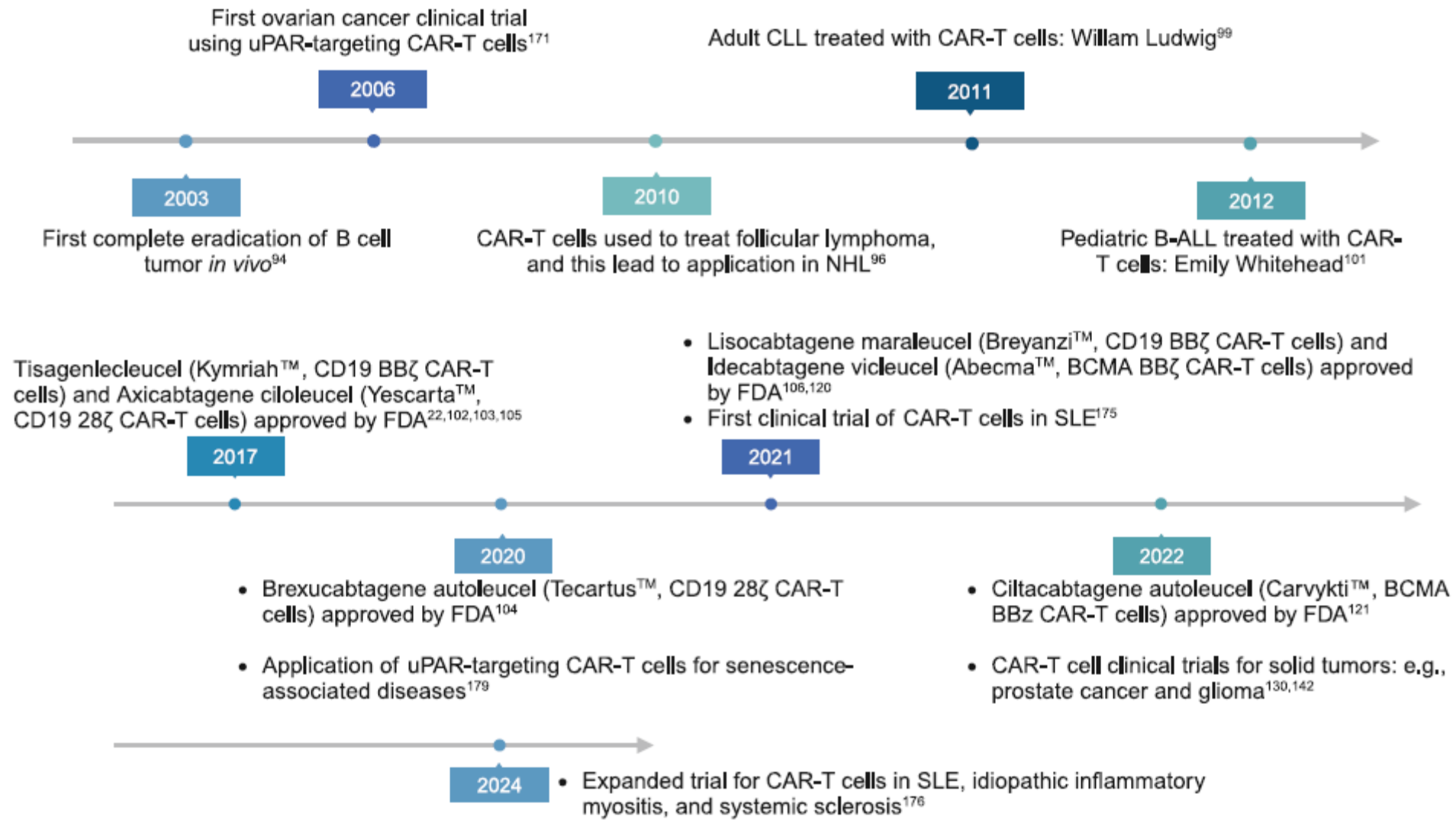
  Kinaz aktivasyonu ve adaptör proteinler aracılığıyla sinyal kaskadı tetiklenir

  Calcineurin, NF-kB, Akt/mTOR yolakları aktive olur
- IL-2 salınımı ile T hücre proliferasyonu ve farklılaşması tetiklenir, efektör T hücre yanıtı

İmmünoterapi

Bireyin immün sisteminin modülasyonu ile infeksiyonlar ve kansere karşı güçlendirilmesi ya da otoimmün hastalıklara karşı immüntolerans geliştirilmesi


Vaccination[1]
The 18th century
Coley's toxin for cancer[4,5]
1891
T cells and the immune response[3,16,17]
The 20th century
Discovery of transformation principle[31]
1928
1860s
Tumor regression in patients with erysipelas infections[2-4]
Late 19th century
BCG for cancer[6,7]
1900
Side-chain theory of antibodies[39,40]
Template theory of antibody formation[40,41]
1940
Proposal of ACT[10]
1954
SV40 polyoma virus DNA contaminated polio vaccines[33-36]
1960s,1972
1944
DNA carries genetic information in bacteria[32]
1960s
Co-transfer of leukocytes for cancer treatment[18]
1980s
Discovery of co-stimulatory CD28[56-60]
TIL therapy[21]
Retroviral vectors for clinically relevant gene transfer[37,38]
Discovery of TCR[42]
1982
Discovery of V(D)J recombination[35,42]
1987
CAR-T cell development[68-70]
1991
1984
Cloning human and mouse TCR[40,45,46]
1987-89
Invention of CARs (with CD8 and CD3ζ chains)[66,67]
1993
First generation CARs with scFv[71]


2003
First complete eradication of B cell tumor *in vivo*[94]
2006
First ovarian cancer clinical trial using uPAR-targeting CAR-T cells[171]
2010
CAR-T cells used to treat follicular lymphoma, and this lead to application in NHL[96]
2011
Adult CLL treated with CAR-T cells: Willam Ludwig[99]
2012
Pediatric B-ALL treated with CAR-T cells: Emily Whitehead[101]
2017
Tisagenlecleucel (Kymriah™, CD19 BBζ CAR-T cells) and Axicabtagene ciloleucel (Yescarta™, CD19 28ζ CAR-T cells) approved by FDA[22,102,103,105]
2020
• Brexucabtagene autoleucel (Tecartus™, CD19 28ζ CAR-T cells) approved by FDA[104]
• Application of uPAR-targeting CAR-T cells for senescence-associated diseases[179]
2021
• Lisocabtagene maraleucel (Breyanzi™, CD19 BBζ CAR-T cells) and Idecabtagene vicleucel (Abecma™, BCMA BBζ CAR-T cells) approved by FDA[106,120]
• First clinical trial of CAR-T cells in SLE[175]
2022
• Ciltacabtagene autoleucel (Carvykti™, BCMA BBz CAR-T cells) approved by FDA[121]
• CAR-T cell clinical trials for solid tumors: e.g., prostate cancer and glioma[130,142]
2024
• Expanded trial for CAR-T cells in SLE, idiopathic inflammatory myositis, and systemic sclerosis[176]

ACT
Adaptif hücre transferi

ACT (adaptive cell transfer), 1954

İnfekte hücreler ya da tümör hücrelerini spesifik olarak tanıyarak yok eden matür T lenfositlerinin / hücresel bağışıklığın indüksiyonu

T hücreleri

Hücre yüzeyinde eksprese edilen antijenleri tanıma, hedef alma, yok etme kabiliyeti,

Uzun yaşam döngüsü, immünolojik hafıza kapasitesi,

Bağışıklık yanıtını amplifiye edebilmeleri,

Genetik mühendislik açısından uygunlukları

BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 13 1957

CANCER—A BIOLOGICAL APPROACH*

III. VIRUSES ASSOCIATED WITH NEOPLASTIC CONDITIONS

BY

Sir MACFARLANE BURNET, M.D., F.R.S.

Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

İmmün sürveyans

Bağışıklık sistemi pek çok tümör hücresi öncüllerini tanıyarak yok edebilir…

Burnet M. Br Med J 1957;1:841

EFFECT OF LEUKOCYTES ON TRANSPLANTABILITY OF HUMAN CANCER

CHESTER M. SOUTHAM, MD, ALEXANDER BRUNSCHWIG, MD,
ARTHUR G. LEVIN, MD,* AND QUIRINO S. DIZON, MD*

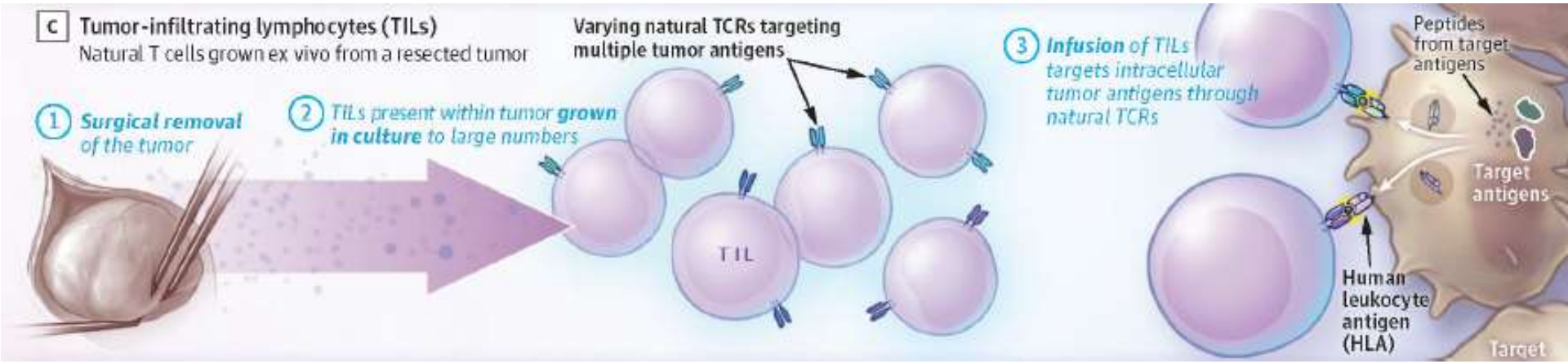
Kanser hastalarından elde edilen lökositler, aynı bireydeki kanser hücrelerinin büyümesi üzerinde spesifik bir inhibitör etki gösterir.

Southam CM et al. Cancer 1966;19:1743

TIL
(Tumor-infiltrating lymphocyte therapy)

Tümör infiltre eden lenfositler

Hastanın tümörünün rezeke edilerek çıkarılması ve doğal olarak tümör dokusunu infiltre eden lenfositlerin ex vivo izolasyonu ve ekspansiyonu sonrası tekrar hastaya verilmesi



Brudno JN et al. JAMA 2024;332:1924

Patel KK et al. Molecular Ther 2025;33:2123

TIL
(Tumor-infiltrating lymphocyte therapy)

Tümör antijenine spesifik doğal lenfosit popülasyonlarının zenginleştirildiği varsayımına dayanır,
Genetik modifikasyon yok.

- Tümör biyopsilerinin elde edilmesinde güçlük,
- Kimi tümörlerde yetersiz TIL popülasyonları,
- Kompleks ve pahalı üretim süreci,
- TIL infüzyonu sonrası uygulanan IL-2'ye bağlı toksisite,
- T hücre tükenmesi ve deplesyonu

Patel KK et al. Molecular Ther 2025;33:2123

THE MAJOR HISTOCOMPATIBILITY COMPLEX-RESTRICTED ANTIGEN RECEPTOR ON T CELLS

I. Isolation with a Monoclonal Antibody*

By KATHRYN HASKINS, RALPH KUBO, JANICE WHITE, MICHELE PIGEON, JOHN KAPPLER,‡ AND PHILIPPA MARRACK

From the Department of Medicine, National Jewish Hospital and Research Center, and the Departments of Microbiology, Biochemistry, Biophysics, and Genetics and Medicine, University of Colorado Health Sciences Center, Denver, Colorado 80206

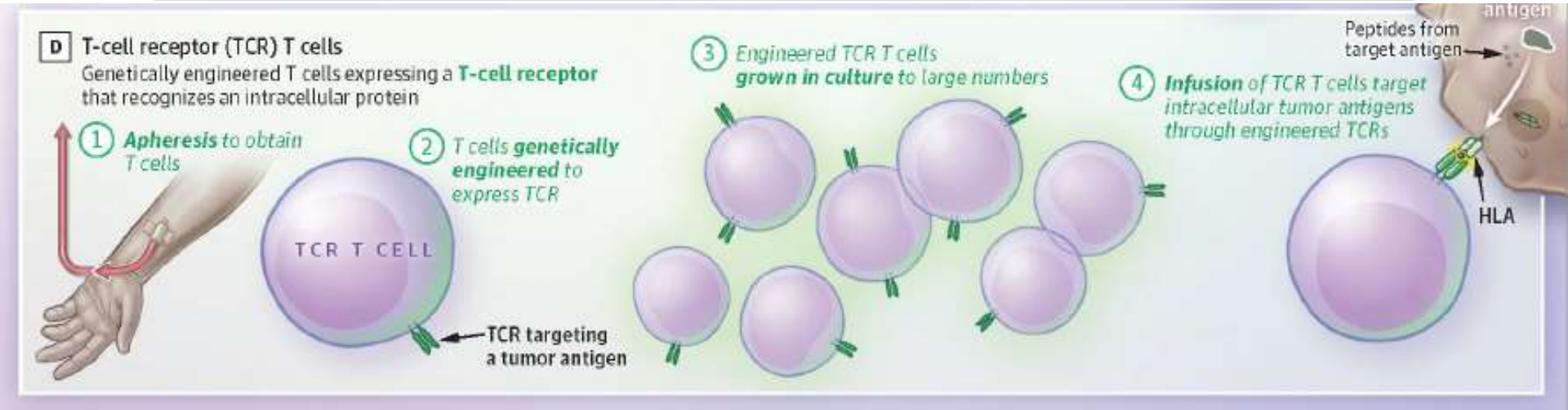
T hücre reseptörü ve fonksiyonlarının tanımlanması

Haskins K et al. J exp med. 1983;157:1149

TCR
(T cell receptor therapy)

T hücre reseptörü tedavisi

Hastadan T hücrelerinin izole edilerek kanser antijenlerini spesifik olarak tanıyacak ve yok edecek sentetik ya da modifiye bir TCR geni eklenerek bu reseptör ile donatılan spesifik T hücre subtiplerinin tasarlanması ve üretilmesi



TCR
(T cell receptor therapy)

TCR, MHC bağımlıdır.

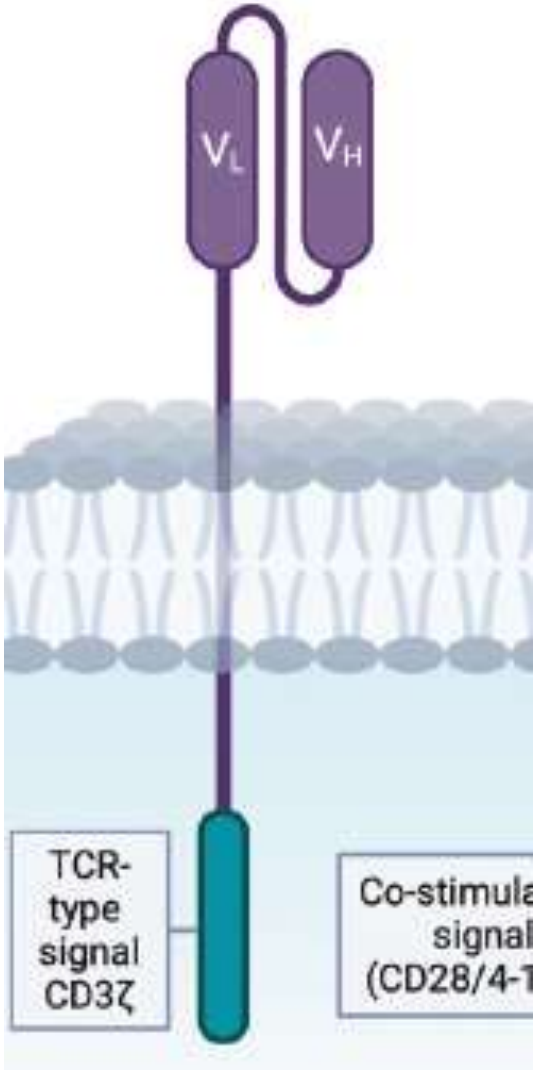
Hücre içi antijenleri tanıma kapasitesi,

Hastanın HLA sınıfı ile tümörün HLA'sı birbiriyle uyumlu olmak zorunda

Antijen sunumu için gerekli olan MHC proteini ekspresyonunun down regülasyonu ile "tumor escape"

Patel KK et al. Molecular Ther 2025;33:2123

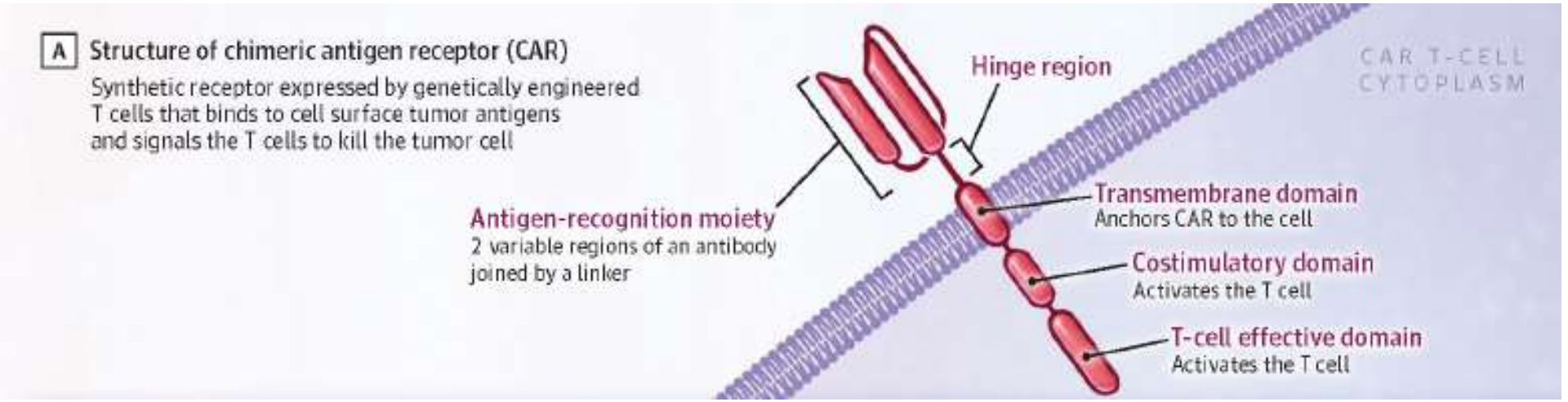
CAR-T hücre



- MHC'den bağımsız,
- T hücre aktivasyonunu sağlayacak stimülasyonları garanti edecek bir yapı

Kısmen antikor kısmen TCR

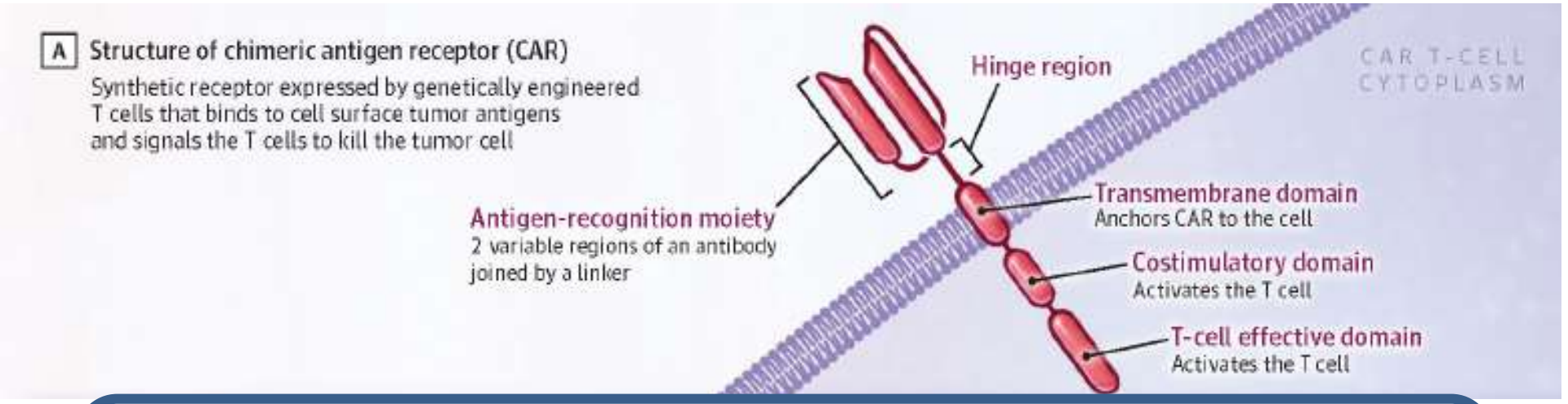
CAR-T hücresi



➢ CAR-T hücreleri, tümör hücresi yüzey antijenini tanıyan sentetik bir reseptörü eksprese eden genetik mühendislik ile tasarlanmış T lenfositlerdir.

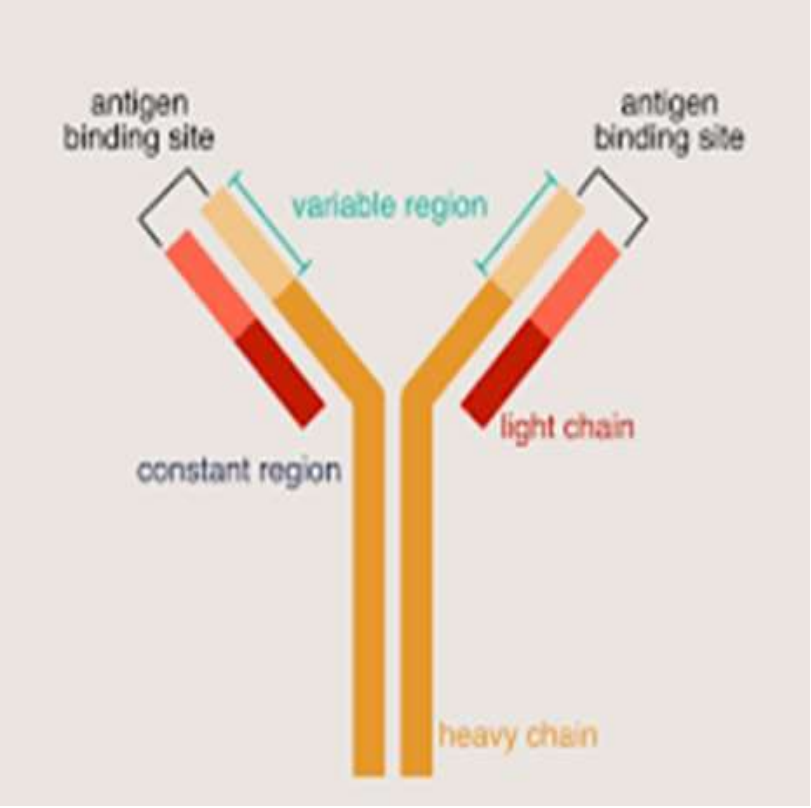
Brudno JN et al. JAMA 2024;332:1924

CAR-T hücresi

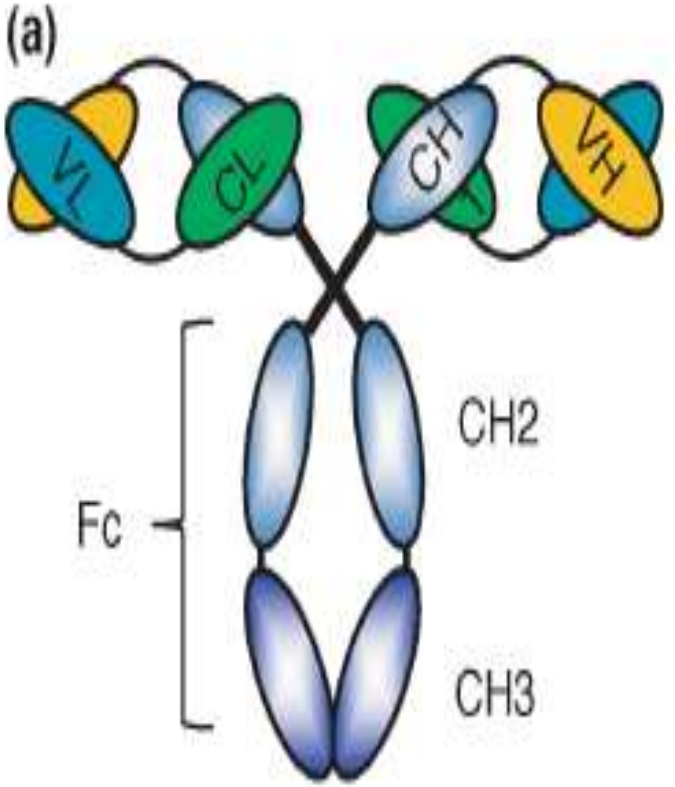


- Antijen tanıyan bölge
  bir antikorun iki değişken bölgesinden geliştirilir

Brudno JN et al. JAMA 2024;332:1924



ünglob



- Hedef antijenin spesifik kısımlarını tanıyan Y şeklinde büyük bir glikoprotein,

  Fab fragmanı farklı bağlanma alanlarına sahip dimerik fonksiyonel bölge (HVR)

  Fc fragmanı daha az değişkendir ve proteinin APC ve immün sistem tarafından tanınmasında

Review Article

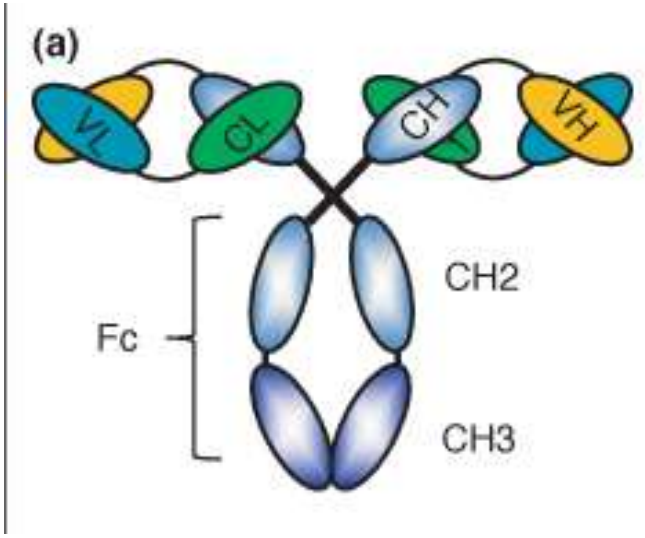
scFv Antibody: Principles and Clinical Application

Zuhaida Asra Ahmad,[1] Swee Keong Yeap,[2] Abdul Manaf Ali,[3] Wan Yong Ho,[1] Noorjahan Banu Mohamed Alitheen,[1] and Muhajir Hamid[1,4]

[1] *Department of Cell and Molecular Biology, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, Selangor, 43400 Serdang, Malaysia*

- İmmünglobülinler

  Doğal, büyük, immünojenik moleküller



ınol 2012;2012:980250

Review Article

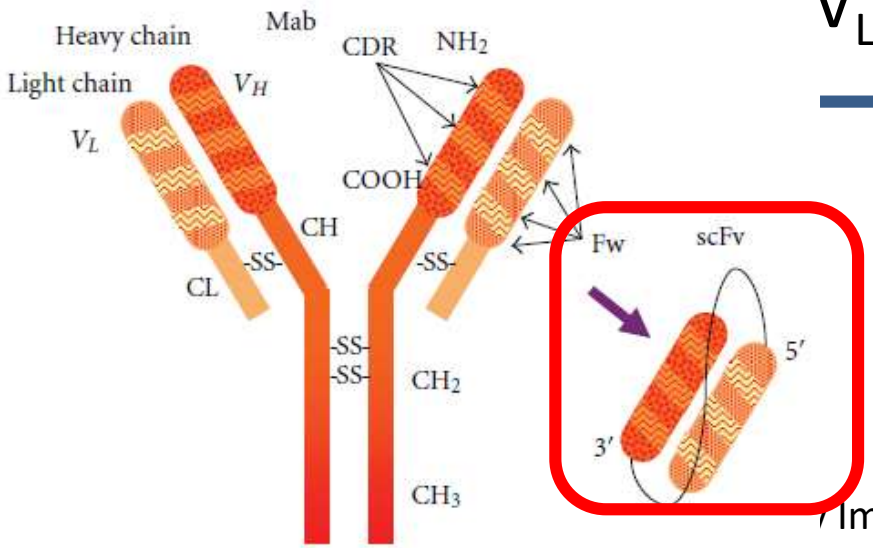
scFv Antibody: Principles and Clinical Application

Zuhaida Asra Ahmad,[1] Swee Keong Yeap,[2] Abdul Manaf Ali,[3] Wan Yong Ho,[1] Noorjahan Banu Mohamed Alitheen,[1] and Muhajir Hamid[1,4]

[1] *Department of Cell and Molecular Biology, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, Selangor, 43400 Serdang, Malaysia*

- Fv fragmanı, Ig molekülünün antijen bağlama özelliğine sahip en küçük birimi

Bir pep V_L zincirleri



J Immunol 2012;2012:980250

Review Article

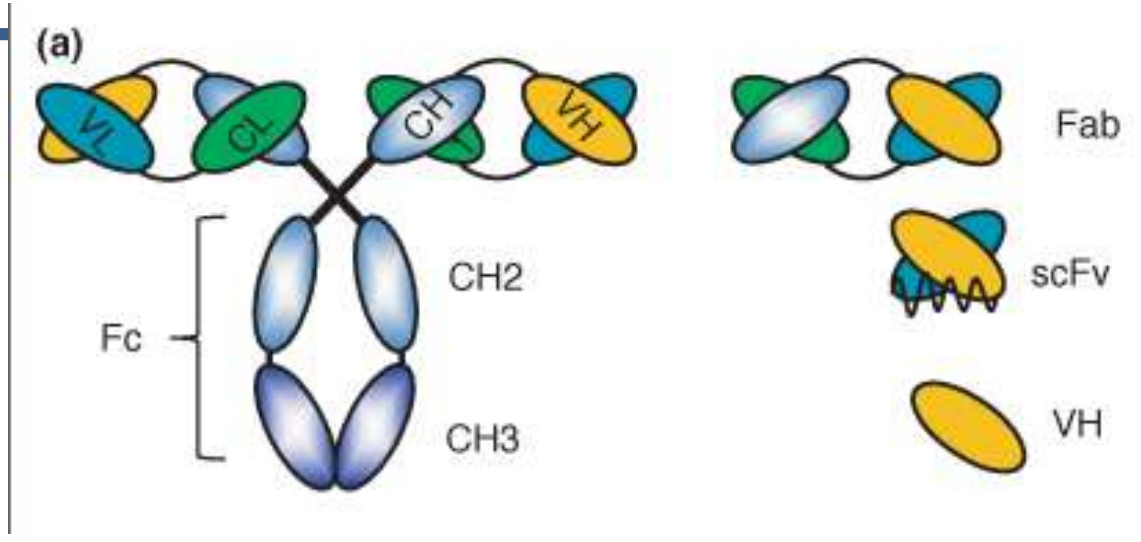
scFv Antibody: Principles and Clinical Application

Zuhaida Asra Ahmad,[1] Swee Keong Yeap,[2] Abdul Manaf Ali,[3] Wan Yong Ho,[1] Noorjahan Banu Mohamed Alitheen,[1] and Muhajir Hamid[1,4]

[1] *Department of Cell and Molecular Biology, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, Selangor, 43400 Serdang, Malaysia*

- Solid tümörler gibi yoğun dokulara daha kolay penetrasyon

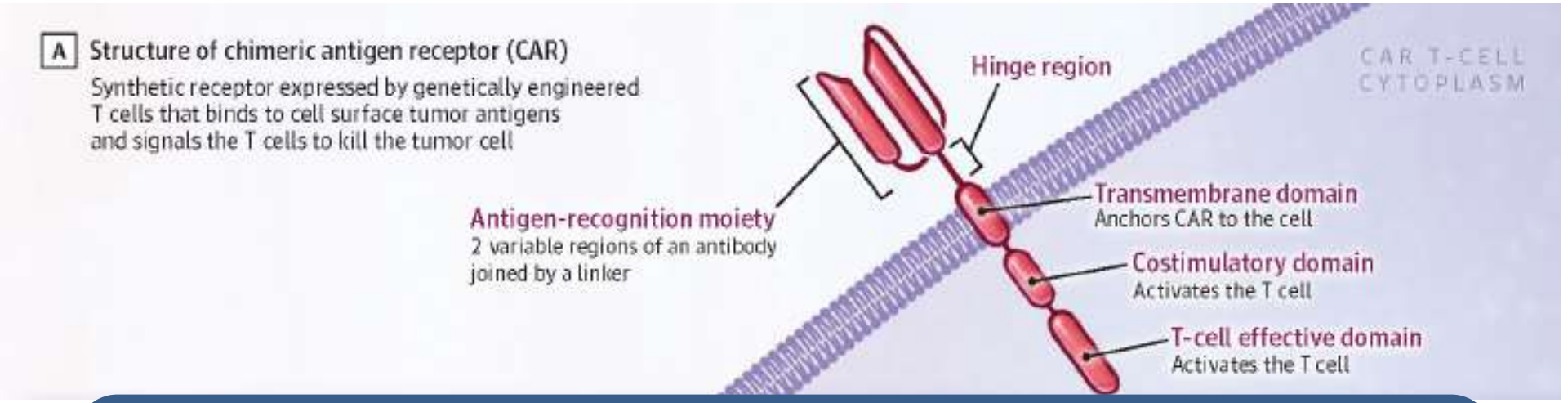
  mAb < Fab < scFv



nol 2012;2012:980250

Although multiple smaller antigen-binding fragments of the immunoglobulin (Fab, scFv, VH, or VL) have been developed, obviously the sdAb is the simplest variant of all. The sdAb can have occasionally an agonistic or antagonistic effect on its target. However, the absence of the immunoglobulin constant domains deprives the sdAb from the natural effector functions of antibodies (such as complement activation). Therefore, it is necessary to equip the sdAb with an engineered Fc or with novel accessory effector moieties (enzymes, toxins, . . .) to generate man-made, tailored effector functions and to obtain more potent next-generation therapeutics.

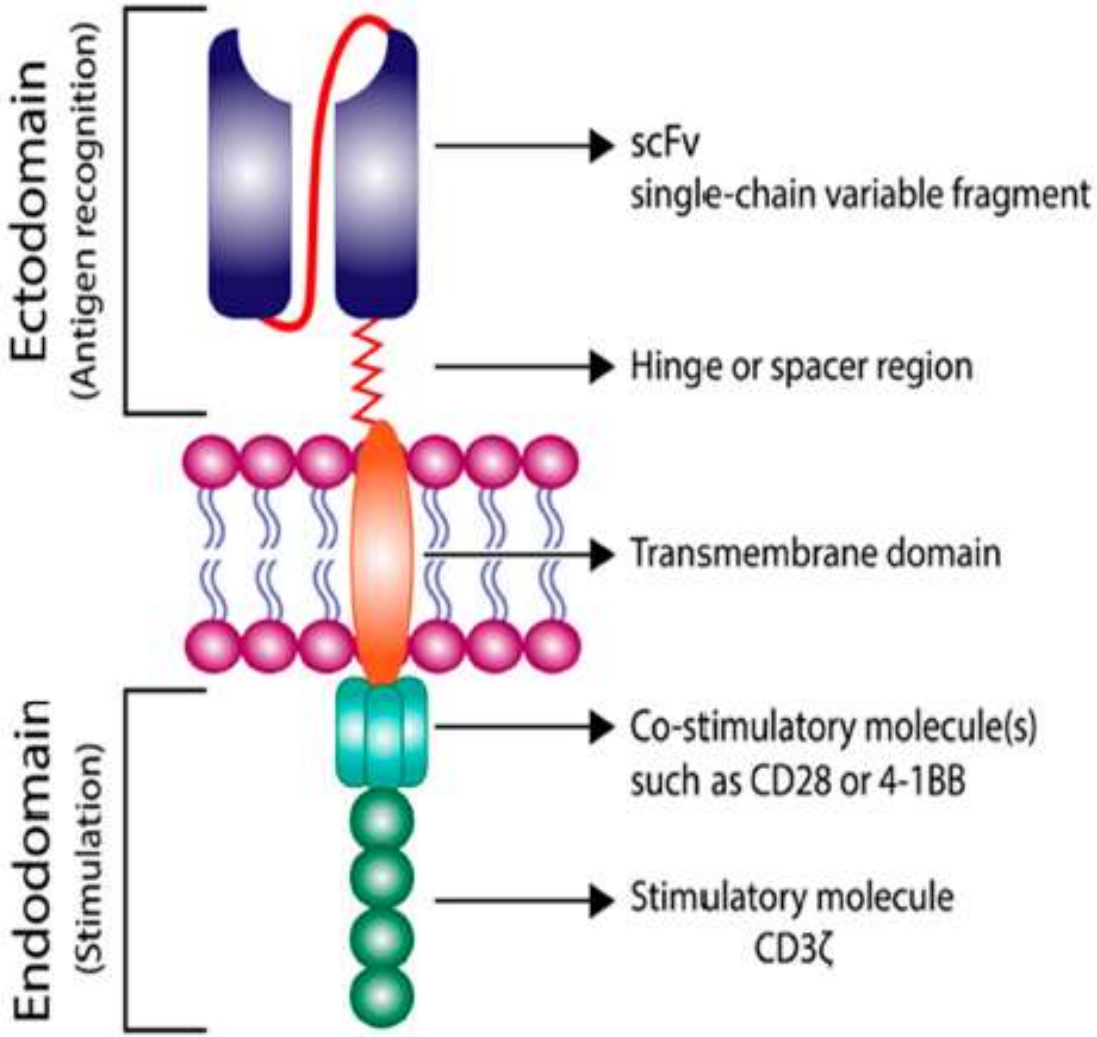
CAR-T hücresi



- Antijen tanıyan bölge
  bir antikorun iki değişken bölgesinden geliştirilir

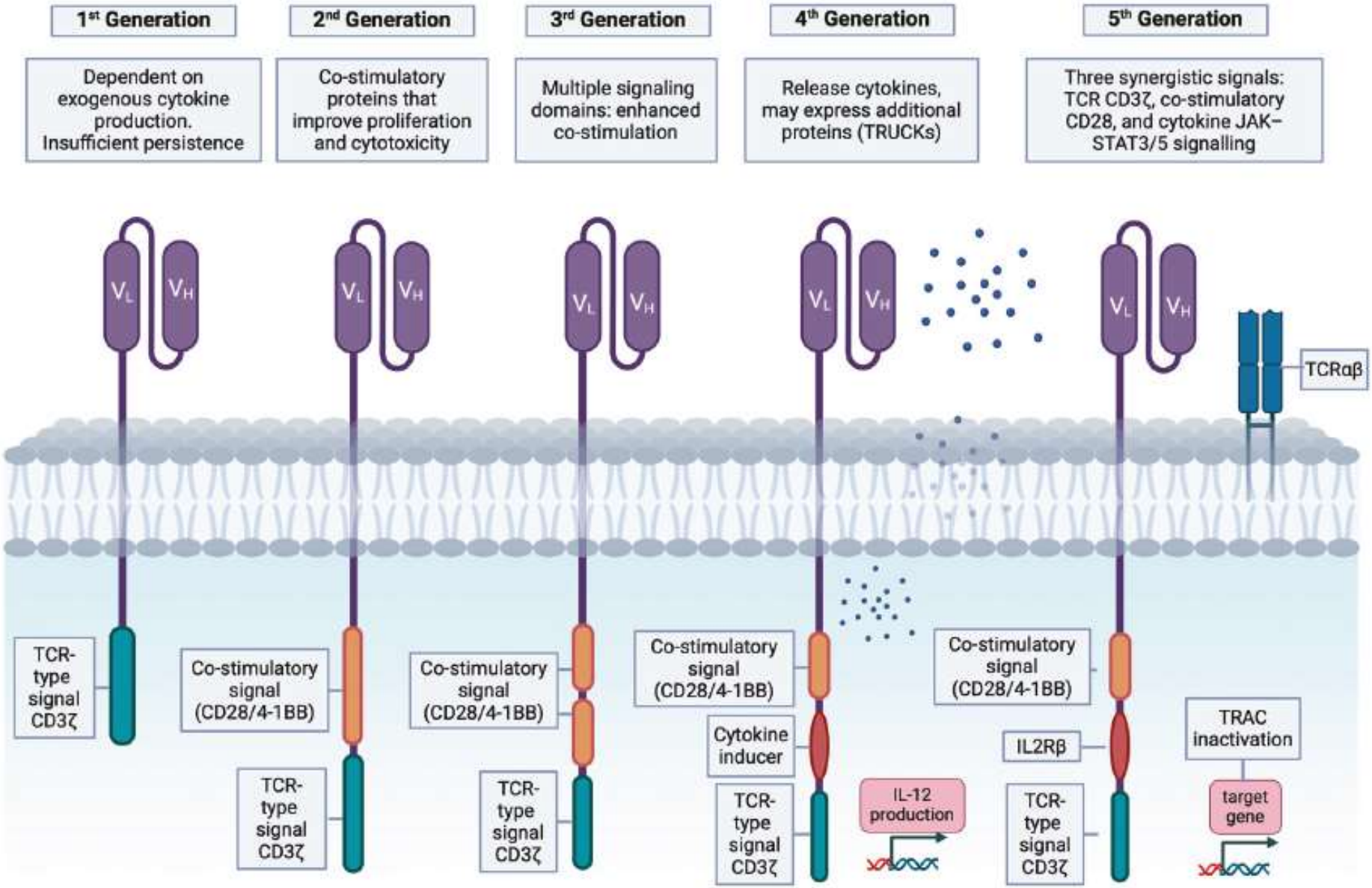
- T hücresini aktive eden, T hücrelerinden geliştirilmiş intrasellüler bölge
  CD3ζ T-hücre aktivasyon bölgesi,
  Kostimülatör bölge CD28 ya da 4–1BB

Brudno JN et al. JAMA 2024;332:1924

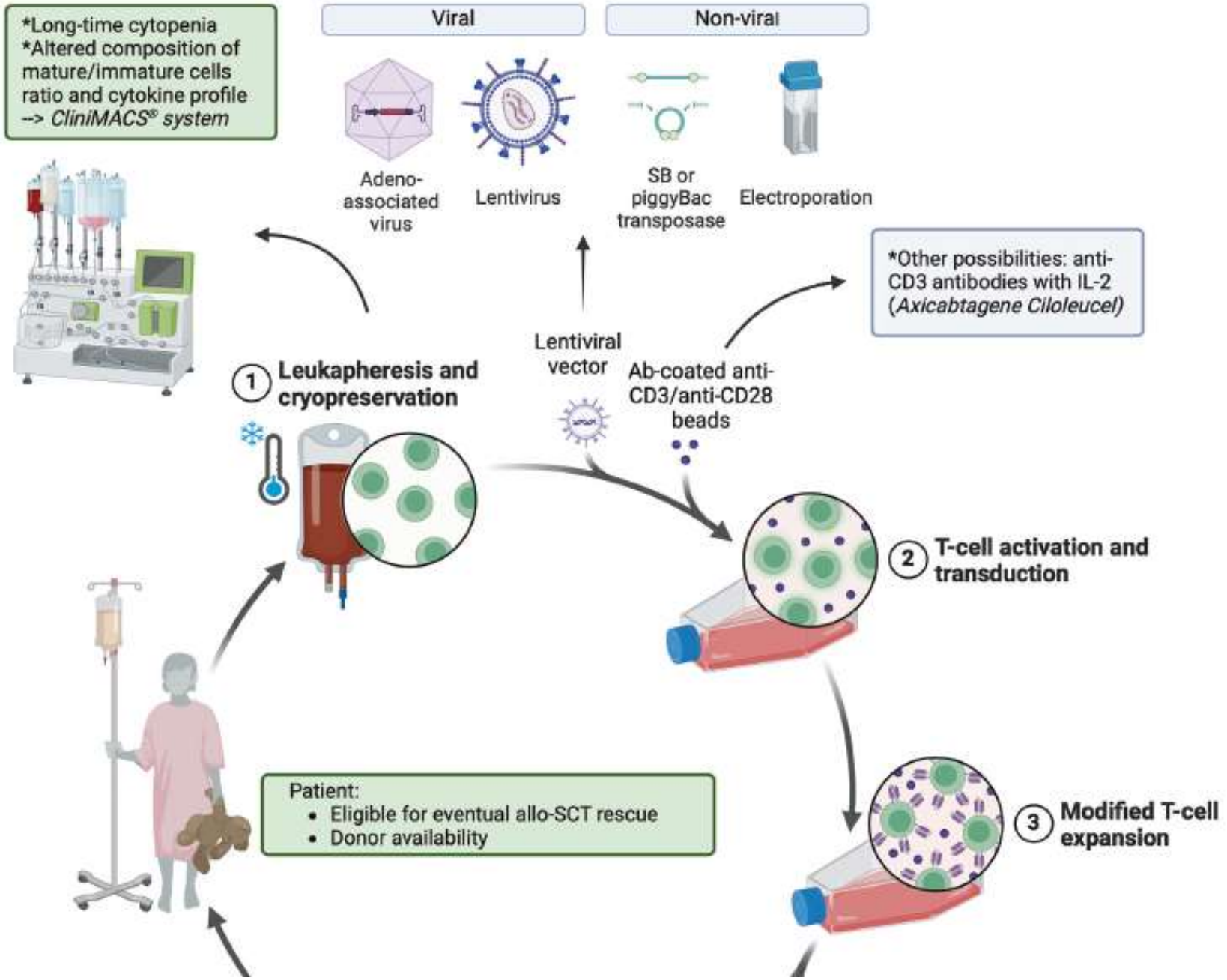


➢ scFv antijen spesifisitesi sağlarken, kostimülatör bölgeler efektör T hücre aktivasyonu için (proliferasyon, sitotoksisite ve persistans) gereklidir.

Chen YJ et al. Cancers 2023;15:663

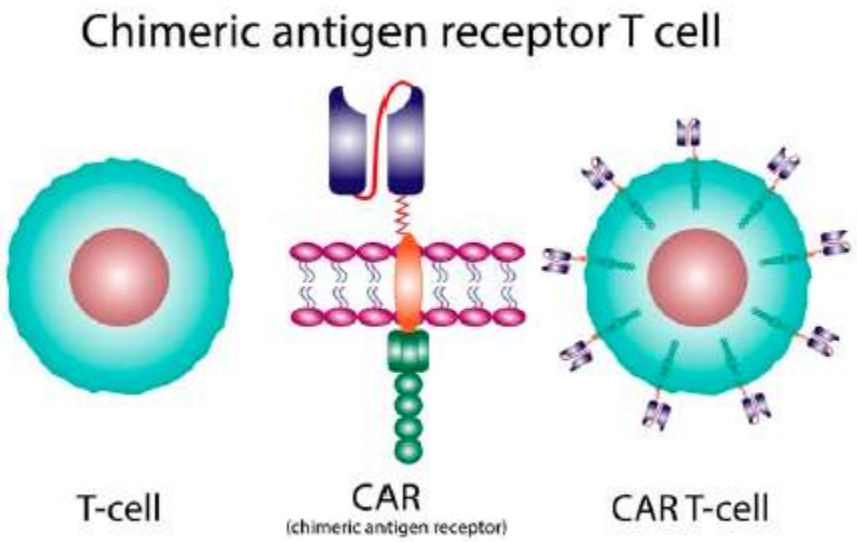


Zugasti I et al. Signal Transduct Target Ther 2025;10:210



Zugasti I et al. Signal Transduct Target Ther 2025;10:210

(a)



➢ CAR molekülünün antijen tanımlayan bölgesi tümör hücresindeki antijene bağlandığında CAR-T hücresi aktive olarak hücreyi yok eder.

Chen YJ et al. Cancers 2023;15:663

- Lökoferez

  ALC > 0,2 10^9/L

- CAR-T hücre hazırlanma süreci

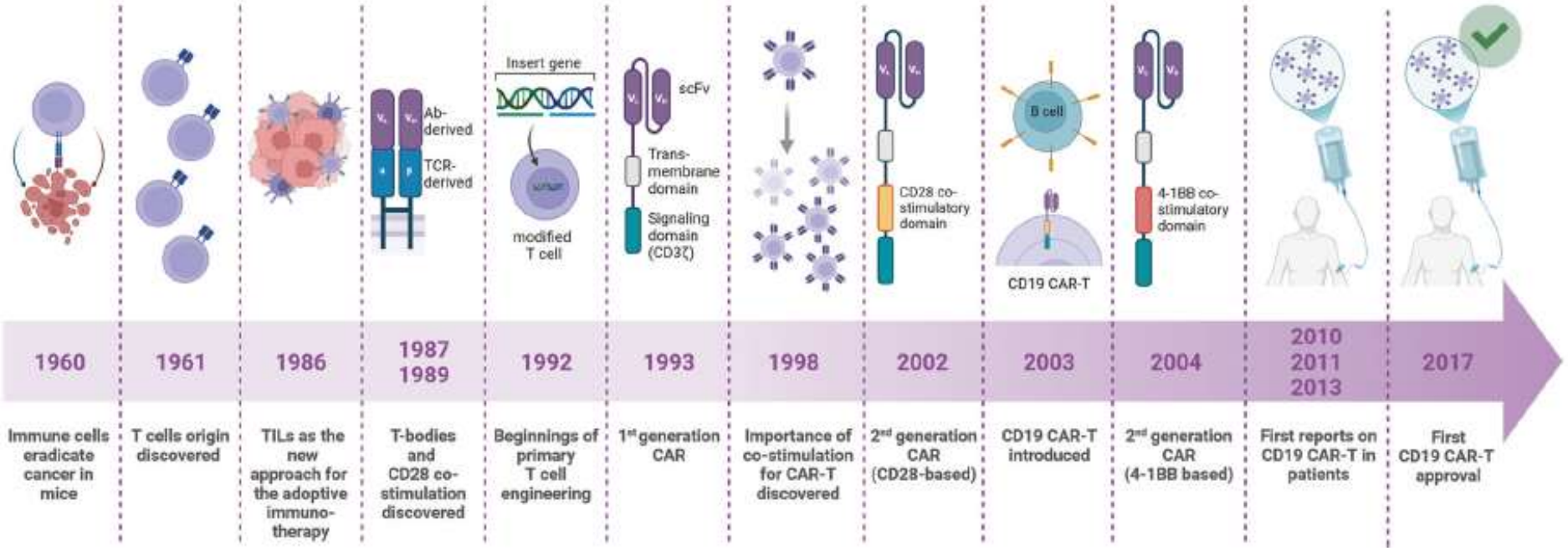
  3-6 hafta

- Bridging therapy

  Lökoferezle CAR-T uygulaması arasındaki 4-6 haftada

  Fludarabin siklofosfamid

  Tümör yükünü azaltmak



Zugasti I et al. Signal Transduct Target Ther 2025;10:210

William Ludwig, 2010
Refrakter KLL

Emily Whitehead, 2012
B ALL

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

Faz 2, R/R B-ALL (n=75)
12. ay sağkalım %76, event-free %50

Maude SL et al. N Engl J Med. 2018;378:439

Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial

Theodore W. Laetsch, MD[1,2]; Shannon L. Maude, MD, PhD[1]; Susana Rives, MD, PhD[3]; Hidefumi Hiramatsu, MD, PhD[4]; Henrique Bittencourt, MD, PhD[5,6]; Peter Bader, MD[7]; André Baruchel, MD[8]; Michael Boyer, MD[9]; Barbara De Moerloose, MD, PhD[10]; Muna Qayed, MD[11]; Jochen Buechner, MD, PhD[12]; Michael A. Pulsipher, MD[13,14]; Gary Douglas Myers, MD[15]; Heather E. Stefanski, MD, PhD[16]; Paul L. Martin, MD, PhD[17]; Eneida Nemecek, MD[18]; Christina Peters, MD[19]; Gregory Yanik, MD[20]; Seong Lin Khaw, MBBS(Hons), PhD[21]; Kara L. Davis, DO[22]; Joerg Krueger, MD[23]; Adriana Balduzzi, MD[24]; Nicolas Boissel, MD, PhD[25]; Ranjan Tiwari, MSc[26]; Darragh O'Donovan, PhD[27]; and Stephan A. Grupp, MD, PhD[1,2]

R/R B-ALL (n=79), median izlem 38 ay
Relaps free survival %52

Laetsch TW et al. J Clin Oncol. 2023;41:1664

CAR-T Cell Product Name and FDA Approved Date	Indication(s)	Target Antigen
Kymriah® (tisagenlecleucel) - Approved by FDA in 2017	• Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. • Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. • Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.	CD19
Yescarta® (axicabtagene ciloleucel) - Approved by FDA in 2017	• Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. • Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. • Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.	CD19
Tecartus® (brexucabtagene autoleucal) - Approved by FDA in 2020	• Adult patients with relapsed or refractory mantle cell lymphoma (MCL). • Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).	CD19
Breyanzi® (lisocabtagene maraleucel) - Approved by FDA in 2021	Adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), highgrade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have: • refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or • refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or • relapsed or refractory disease after two or more lines of systemic therapy.	CD19
Abecma® (idecabtagene vicleucel) - Approved by FDA in 2021	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.	BCMA
Carvykti® (ciltacabtagene autoleucel) - Approved by FDA in 2022	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.	BCMA

Chen YJ et al. Cancers 2023;15:663

CAR T-cell product	Antigen target	Indications	Malignancy response of complete or partial remission, %	Overall survival estimates
Tisagenlecleucel	CD19	Pediatric and young adult B-cell acute lymphoblastic leukemia[3,4]	82	63% Overall survival at 3 y
		Large B-cell lymphoma[5,6]	53	Median overall survival, 11.1 mo
		Follicular lymphoma[7,8]	86.2	87.7% Estimated overall survival at 24 mo
Axicabtagene ciloleucel	CD19	Large B-cell lymphoma[9–11]	83	42.6% Estimated overall survival at 5 y
		Follicular lymphoma[12,13]	94	76% Estimated overall survival at 36 mo
Brexucabtagene autoleucel	CD19	Mantle cell lymphoma[14,15]	91	Median overall survival, 46.6 mo
		Adult B-cell acute lymphoblastic leukemia[16,17]	71	Median overall survival, 25.4 mo
Lisocabtagene maraleucel	CD19	Large B-cell lymphoma[18,19]	73	50.5% Estimated overall survival at 2 y
		Chronic lymphocytic leukemia[20]	48	Median overall survival, 43 mo
		Follicular lymphoma[21]	97	93% Overall survival at 12 mo
		Mantle cell lymphoma[22]	83	Median overall survival, 18.2 mo
Idecabtagene vicleucel	BCMA	Multiple myeloma[23,24]	73	Estimated median overall survival, 19.4 mo
Ciltacabtagene autoleucel	BCMA	Multiple myeloma[25,26]	98	70.4% Overall survival at 27 mo

2024;332:1924

CAR T-cell product	Antigen target	Indications	Malignancy response of complete or partial remission, %	Overall survival estimates	Proportion with adverse effects, %			
					Cytokine release syndrome[b]	Neurologic toxicity[c]	Severe infections[d]	Prolonged cytopenias[e]
Tisagenlecleucel	CD19	Pediatric and young adult B-cell acute lymphoblastic leukemia[3,4]	82	63% Overall survival at 3 y	77	39	24	35
		Large B-cell lymphoma[5,6]	53	Median overall survival, 11.1 mo	57	20	19	34
		Follicular lymphoma[7,8]	86.2	87.7% Estimated overall survival at 24 mo	49	37	9.3	Neutropenia: 15.5%; thrombocytopenia: 16.5%; anemia: 3.1%
Axicabtagene ciloleucel	CD19	Large B-cell lymphoma[9–11]	83	42.6% Estimated overall survival at 5 y	93	64	28	38
		Follicular lymphoma[12,13]	94	76% Estimated overall survival at 36 mo	78	56	15	33
Brexucabtagene autoleucel	CD19	Mantle cell lymphoma[14,15]	91	Median overall survival, 46.6 mo	91	63	32	26% at more than 90 d
		Adult B-cell acute lymphoblastic leukemia[16,17]	71	Median overall survival, 25.4 mo	89	60	25	36
Lisocabtagene maraleucel	CD19	Large B-cell lymphoma[18,19]	73	50.5% Estimated overall survival at 2 y	42	30	12	37
		Chronic lymphocytic leukemia[20]	48	Median overall survival, 43 mo	85	45	17	54
		Follicular lymphoma[21]	97	93% Overall survival at 12 mo	58	15	5	22
		Mantle cell lymphoma[22]	83	Median overall survival, 18.2 mo	61	31	15	40
Idecabtagene vicleucel	BCMA	Multiple myeloma[23,24]	73	Estimated median overall survival, 19.4 mo	84	18	22	Neutropenia: 41%; thrombocytopenia: 48%
Ciltacabtagene autoleucel	BCMA	Multiple myeloma[25,26]	98	70.4% Overall survival at 27 mo	95	22[f]	20	Neutropenia: 30%; thrombocytopenia: 41%

Sitokin salınım sendromu (CRS)

- Anti-CD19 CAR T hücreleri alıcıda 1000 kat kadar çoğalarak başta IL-6 ve IFN-γ olmak üzere sitokin yanıtını tetikler,

- Yüksek proinflamatuvar sitokin düzeyleri ateş, taşipne, taşikardi, hipoksi, hipotansiyon, koagülopati tablosu ile seyreden CRS'a yol açabilir,

- İnfüzyondan ortalama 2-7 gün sonra, 3 haftaya kadar
- İnsidans %57-93

İmmün efektör hücre ilişkili nörotoksisite sendromu (ICANS)

- CAR T hücrelerinin kan beyin bariyerini geçmesiyle ensefalopati, afazi, bilinç bulanıklığı, tremorlar, fokal motor defektler, nöbetler, serebral ödemle karakterize

- Median başlangıç zamanı 4 gün, 30 güne kadar
- İnsidans %20-70

BRIEF COMMUNICATION OPEN

Check for updates

Secondary malignancy of T-cell origin after CAR T-cell therapy: EMA's conclusions from the evaluation of 38 suspected cases

Philipp Berg[1], Charlotte Bakker[2]✉, Moritz Sander[3], Nicklas Hasselblad Lundstrøm[3], Karin Erneholm[3,4], Flora Musuamba Tshinanu[5], Olga Kholmanshikh[5], Filip Van Nuffel[5], Susanne Müller[1], Gabriele Ruppert-Seipp[1], Gabriele D. Maurer[1,4], Justina Januskiene[2], Maria Mantziri[2], Bianca Mulder[4,6], Frederika A. van Nimwegen[6], Daiana Vasilcanu[7] and Ulla Wändel Liminga[4,7]

- T hücre kökenli sekonder maligniteler
  - 11 Nisan 2024, 42500 CAR-T hastası
  - 38 T hücre malignitesi (~ 1/1000)

Berg p et al. Gene Ther 2025; doi: 10.1038/s41434-025-00586-x.

AEs

- Hemofagositik lenfohistiyositoz,
- B hücre aplazisi,
- Sitopeniler,
- DIC
- İnfeksiyonlar

Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline

Bianca D. Santomasso, MD, PhD[1]; Loretta J. Nastoupil, MD[2]; Sherry Adkins, RN, MS[2]; Christina Lacchetti, MHSc[3]; Bryan J. Schneider, MD[4]; Milan Anadkat, MD[5]; Michael B. Atkins, MD[6]; Kelly J. Brassil, PhD, RN[2]; Jeffrey M. Caterino, MD, MPH[7]; Ian Chau, MD[8]; Marianne J. Davies, DNP[9]; Marc S. Ernstoff, MD[10]; Leslie Fecher, MD[4]; Pauline Funchain, MD[11]; Ishmael Jaiyesimi, DO, MS[12]; Jennifer S. Mammen, MD, PhD[13]; Jarushka Naidoo, MD[14]; Aung Naing, MD[2]; Tanyanika Phillips, MD[15]; Laura D. Porter, MD[16]; Cristina A. Reichner, MD[17]; Carole Seigel, MBA[18]; Jung-Min Song, MSN, RN, CNS[11]; Alexander Spira, MD, PhD[19]; Maria Suarez-Almazor, MD[2]; Umang Swami, MD[20]; John A. Thompson, MD[21]; Praveen Vikas, MD[22]; Yinghong Wang, MD[2]; Jeffrey S. Weber, MD, PhD[23]; Kathryn Bollin, MD[24]; and Monalisa Ghosh, MD[25]

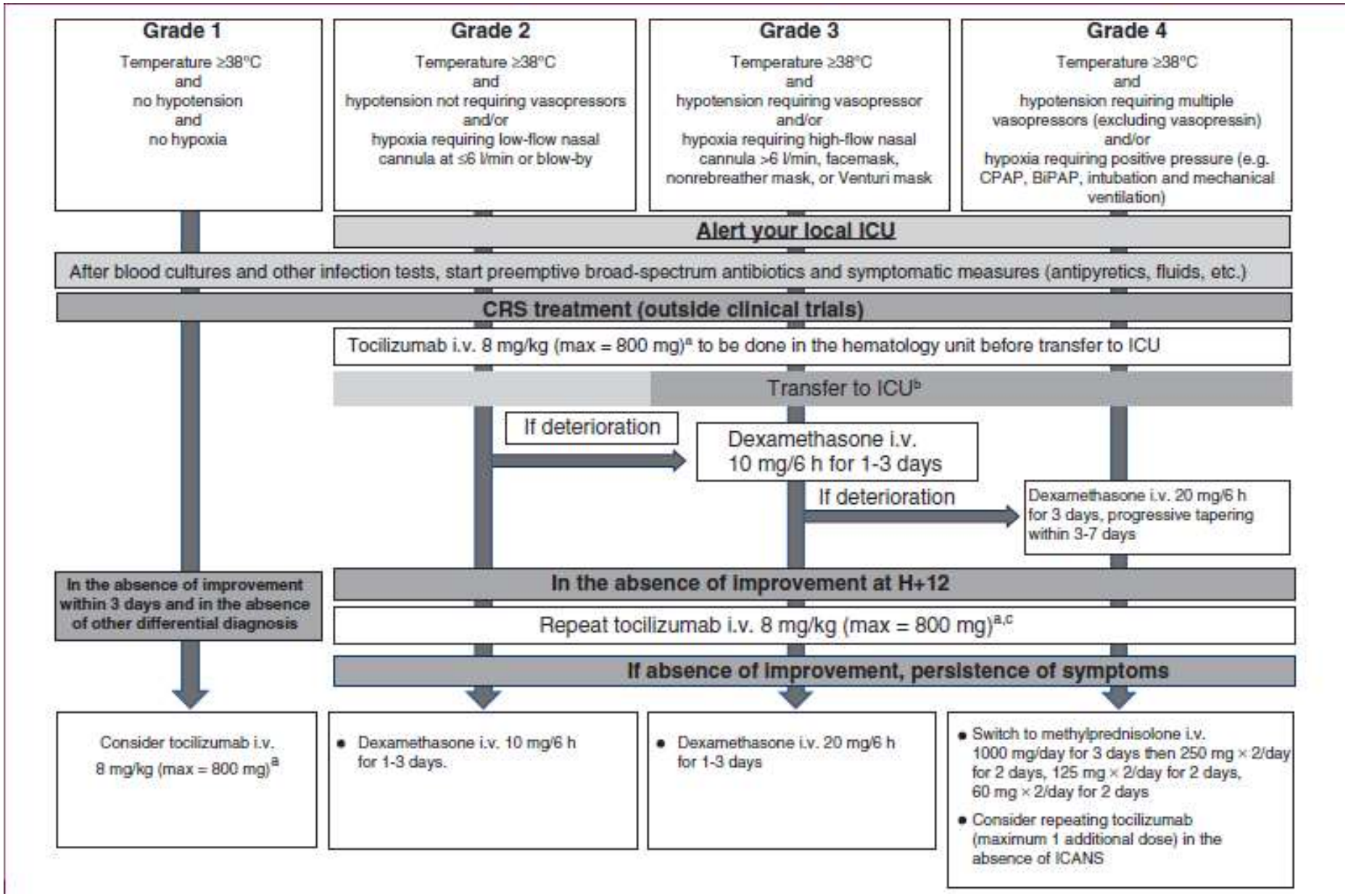
Santomasso BD et al. J Clin Oncol 2021;39:3978

SPECIAL ARTICLE

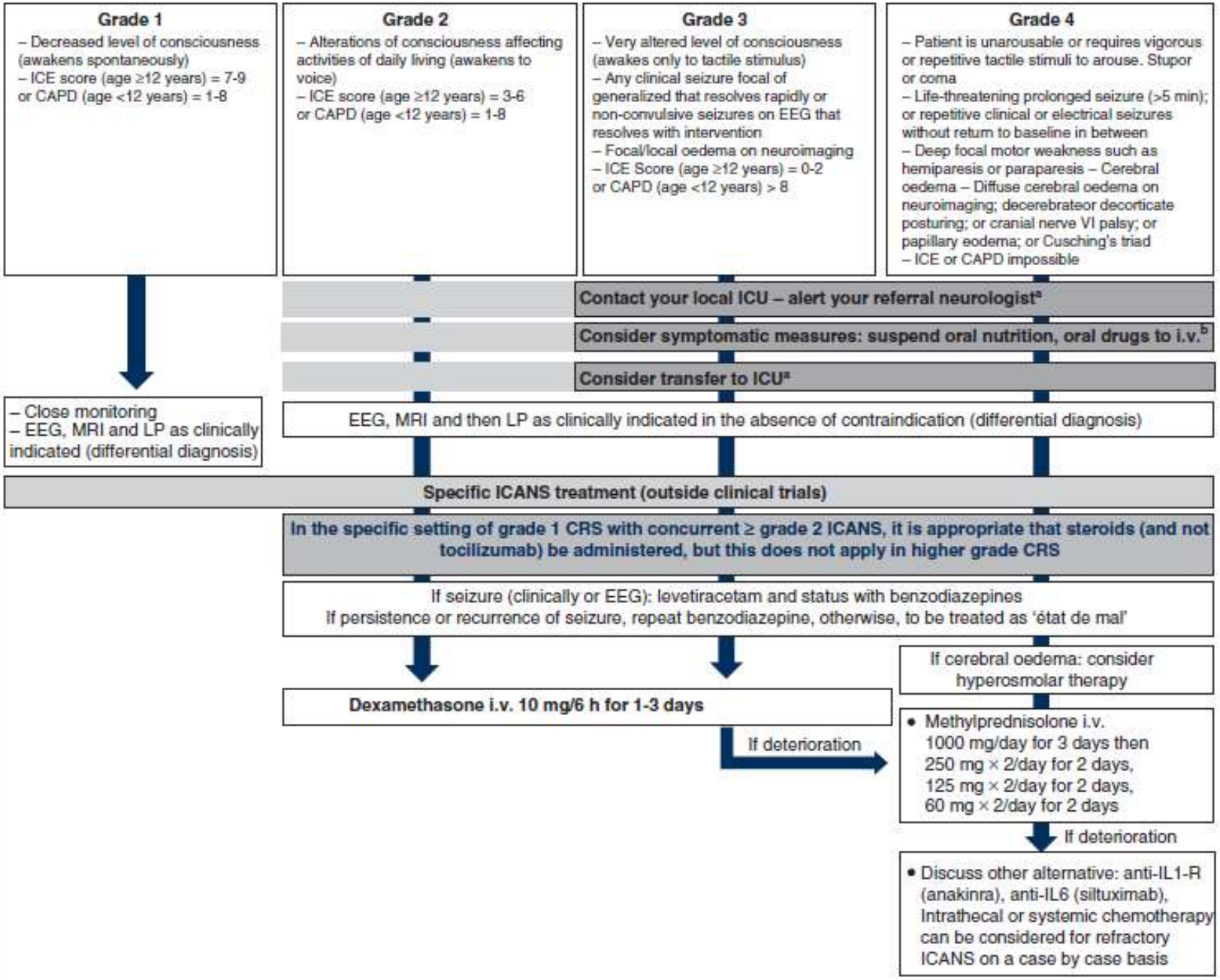
Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)

P. J. Hayden[1†], C. Roddie[2,3*†], P. Bader[4], G. W. Basak[5], H. Bonig[6], C. Bonini[7], C. Chabannon[8], F. Ciceri[9], S. Corbacioglu[10], R. Ellard[11], F. Sanchez-Guijo[12], U. Jäger[13], M. Hildebrandt[14], M. Hudecek[15], M. J. Kersten[16], U. Köhl[17,18], J. Kuball[19], S. Mielke[20], M. Mohty[21], J. Murray[22], A. Nagler[23], J. Rees[3,24], C. Rioufol[25], R. Saccardi[26], J. A. Snowden[27], J. Styczynski[28], M. Subklewe[29], C. Thieblemont[30], M. Topp[15], Á. U. Ispizua[31], D. Chen[3,32], R. Vrhovac[33], J. G. Gribben[32], N. Kröger[34], H. Einsele[15] & I. Yakoub-Agha[35]

Hayden PJ et al. Ann Oncol 2022;33:259



Hayden PJ et al. Ann Oncol 2022;33:259



Hayden PJ et al. Ann Oncol 2022;33:259

Overview of infectious complications among CAR T- cell therapy recipients

Swarn Arya[1] and Zainab Shahid[1,2*]

[1]Infectious Disease Service, Memorial Sloan Kettering Cancer Center, New York, NY, United States,
[2]Department of Medicine, Weill Cornell School of Medicine, New York, NY, United States

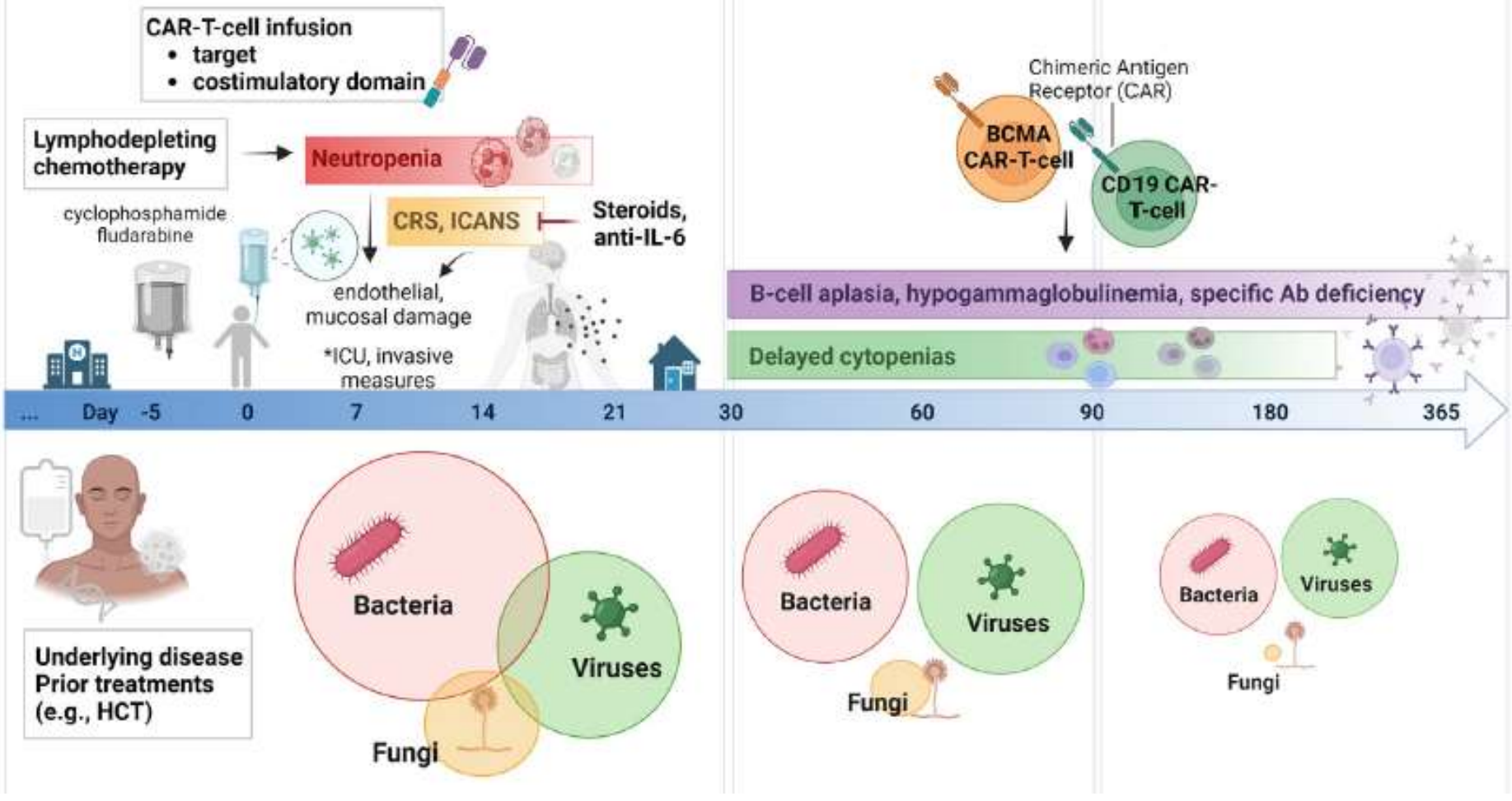
- >30 gün nötropeni %30,
- >90 gün nötropeni %10-20,
- CD4 T hücre lenfopenisi 1. yılda %35,
- B hücre aplazisi / hipogamaglobülinemi

- Otolog/allo HCT
- Bridging therapy
- Tocilizumab / deksametazon

Arya S et al. Front Oncol. 2024;14:1398078

Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies

Eleftheria Kampouri[1,2] | Jessica S. Little[3,4] | Kai Rejeski[5,6] | Oriol Manuel[2] | Sarah P. Hammond[4,7] | Joshua A. Hill[1,8,9]



Overview of infectious complications among CAR T- cell therapy recipients

Swarn Arya[1] and Zainab Shahid[1,2*]

[1]Infectious Disease Service, Memorial Sloan Kettering Cancer Center, New York, NY, United States,
[2]Department of Medicine, Weill Cornell School of Medicine, New York, NY, United States

- İlk 30 gün bakteriyel infeksiyonlar,
- >30 gün viral infeksiyonlar
- Fungal infeksiyonlar, CMV reaktivasyonu nadir

- CD-19 CAR-T tedavisi sonrası %19-69,
- BCMA CAR-T tedavisi sonrası %42-69,
- İnfeksiyon ilişkili mortalite %1

Arya S et al. Front Oncol. 2024;14:1398078

Table 12. Infection prophylaxis post-CAR-T

	EBMT/EHA recommendation	Comments
Neutropenia	G-CSF to shorten duration of neutropenia from day +14 or after resolution of CRS or ICANS Can consider starting earlier, e.g. day 5,[a] if patient is at high risk of infection, e.g. ALL, post-allo-HCT, high-dose steroids. For persistent neutropenia ($<0.5 \times 10^9$/l) following day +28, consider G-CSF	Avoid if patient has CRS or ICANS
Antibacterial prophylaxis	Not routinely recommended[b]	Can be considered in case of prolonged neutropenia and should be based on local guidelines, e.g. with levofloxacin or ciprofloxacin
Anti-viral	Valaciclovir 500 mg bid or aciclovir 800 mg bid	Start from LD conditioning until 1-year post-CAR T-cell infusion AND until $CD4^+$ count $>0.2 \times 10^9$/l
Anti-pneumocystis	Co-trimoxazole 480 mg once daily or 960 mg three times each week To start from LD conditioning until 1-year post-CAR-T cell infusion AND until $CD4^+$ count $>0.2 \times 10^9$/l Where there is prolonged myelosuppression, postpone start after ANC $>0.5 \times 10^9$/l	Can be started later depending on centre guidelines In case of co-trimoxazole allergy (or cytopenias precluding use of co-trimoxazole), pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered
Systemic anti-fungal prophylaxis	Not recommended routinely; consider posaconazole (300 mg/day) or fluconazole (200 mg/day) or micafungin (50 mg i.v./day) in patients with severe (ANC $<0.5 \times 10^9$/l) or prolonged (>14 days) neutropenia and/or in patients on long-term or high-dose (>72 h) corticosteroids or in patients post-allo-HCT	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis should be considered
i.v. Immunoglobulin	Routine in children. Consider in adults with serious/ recurrent infections with encapsulated organisms and hypogammaglobulinemia (<4 g/l)	Clinical evidence does not support routine use in adults following allo-HCT

Hayden PJ et al. Ann Oncol 2022;33:259

How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies

Joshua A. Hill[1-4] and Susan K. Seo[5,6]

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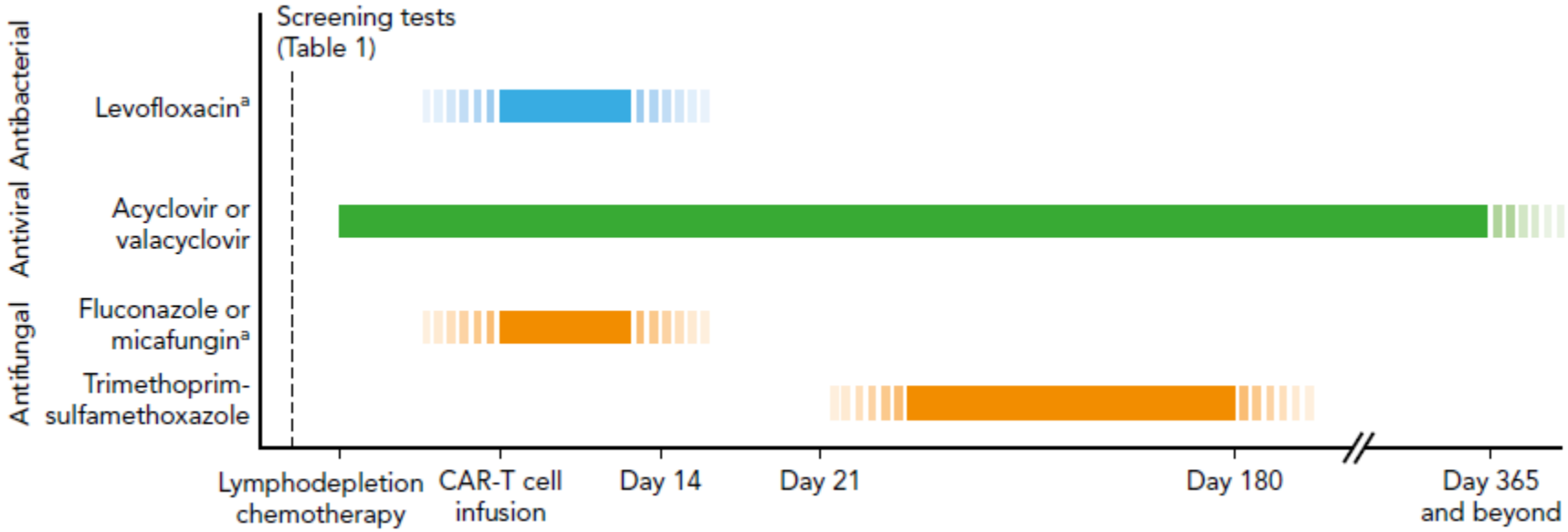

Hill JA et al. Blood 2020;136:925

How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies

Joshua A. Hill[1-4] and Susan K. Seo[5,6]

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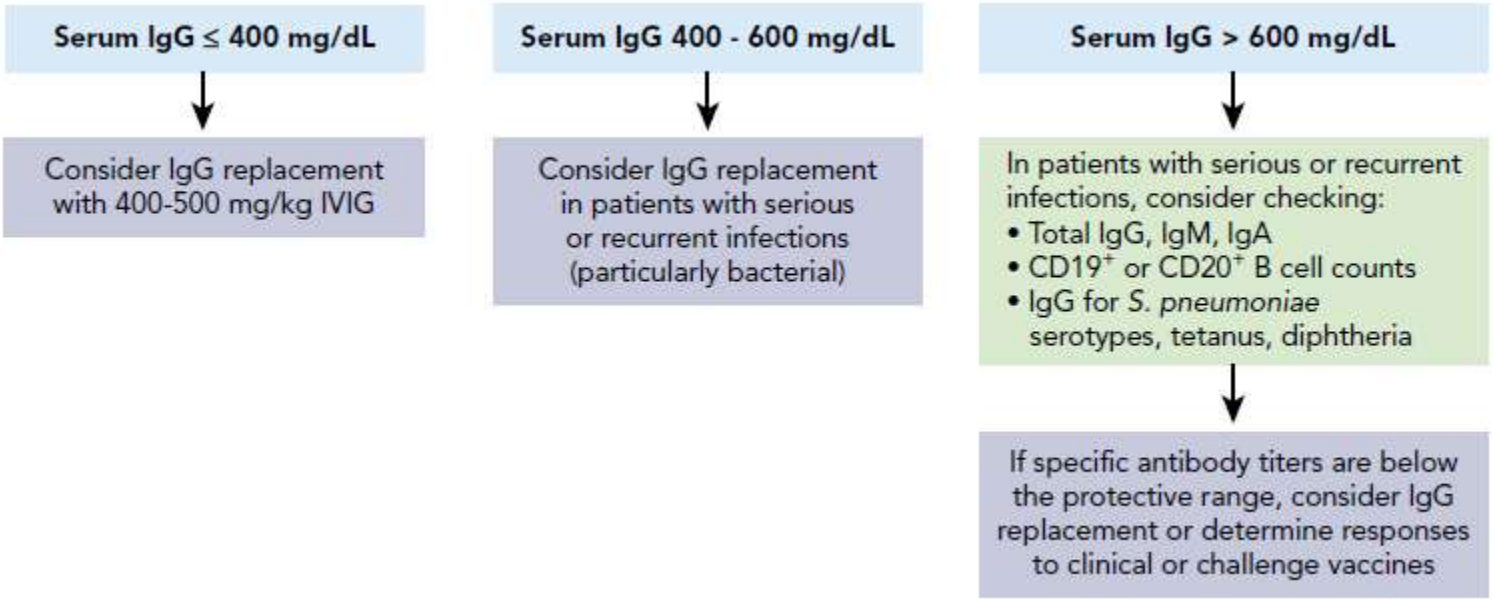

Hill JA et al. Blood 2020;136:925

	EBMT/EHA (Europe)	Spanish group (Spain)	SFGM-TC (France)	Fred Hutch (US)	Dana Farber (US)	CHUV Lausanne (Switzerland)	LMU Munich (Germany)
Antibacterial prophylaxis	NR	NR	NR	FQ during neutropenia[a]	Levofloxacin 500 mg/day during neutropenia[a]	NR	Risk adapted[b]; FQ during neutropenia[a]
Antifungal prophylaxis	Consider fluconazole, posaconazole,[c] or micafungin if severe or prolonged >14 days neutropenia,[a] and/or long-term or high dose (>3 days) of steroids or post-allo-HCT	Fluconazole (400 mg/day) during neutropenia[a]	Consider fluconazole or micafungin if severe neutropenia[a] >14 days, steroids >3 days, post-allo-HCT	Fluconazole (200 mg/day) during neutropenia[a]	No antifungal prophylaxis	Fluconazole (200 mg/day) during neutropenia[a]	No antifungal prophylaxis
Anti-mold prophylaxis	See above	Posaconazole 300 mg/day,[c] nebulized liposomal amphotericin B or micafungin if ≥4 lines of prior treatment, pre-CAR-T-cell infusion severe neutropenia[a], higher dose of CAR-T-cells ($>2\times10^7$), previous IFI, tocilizumab, and/or steroids	Posaconazole (300 mg/day[c]) if post-allo-HCT or steroids or previous IFI	Posaconazole (300 mg/day[c]) if neutropenia[a] >20 days or steroids >3 days for at least 4 weeks after last dose of steroid (and after neutropenia resolution[a])	No anti-mold prophylaxis	Posaconazole (300 mg/day[c]) if post-allo-HCT or steroids or previous IFI	Risk-adapted[b] (posaconazole[c] or micafungin during neutropenia[a] or extended steroid exposure)
Anti-PjP prophylaxis	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	TMP/SMX DS 3×/week Start 1 week pre-infusion (pause during neutropenia), continue until CD4 >200 cells/mm^3	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	TMP/SMX DS 2×/day on 2 consecutive days/week Start 21–28 days post-infusion, continue for at least 6 months	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for at least 6 months or until CD4	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for at least 6 months or until CD4	TMP/SMX 1DS 3×/week Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3
Antiviral prophylaxis	Acyclovir 800 mg 2×/day or valacyclovir 500 mg 2×/day Start at LD chemotherapy, continue for 1 year and until CD4 >200 cells/mm^3	Acyclovir 400–800 mg 2×/day At least 60–100 days after infusion	Acyclovir 800 mg 2×/day or valacyclovir 500 mg 2×/day Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	Acyclovir 800 mg 2×/day or valacyclovir 500 mg 2×/day Start at lymphodepleting chemotherapy, continue for at least 1 year	Acyclovir 400 mg 3×/day or valacyclovir 500 mg 2×/day Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3	Valacyclovir 500 mg 2×/day for 6–12 months	Acyclovir 400 mg 2×/day Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3
CMV monitoring	As clinically indicated	NR	Consider in CMV seropositive patients at high risk Weekly monitoring	Patients treated with >3 days of steroids Weekly until 1 month after last dose of steroid	Strongly consider monitoring for patients receiving >5 doses dexamethasone	Consider in CMV seropositive patients at high risk Weekly/biweekly monitoring	NR

Table 2. Antimicrobial management and infection monitoring in patients with CRS and/or ICANS

Management and monitoring
• Empiric broad-spectrum antibiotics according to fever and neutropenia guidelines*
• ID consultation should be obtained to guide escalation and de-escalation of antimicrobial therapy, particularly in high-risk patients†
High-risk patients are those who meet any of the below criteria o Receiving >1 dose of tocilizumab o Requiring >3 days of ≥10 mg dexamethasone per day within a 7-day period o Receiving 1 or more doses of methylprednisolone ≥1 g per day o Receiving second-line agents for management of CRS or ICANS (eg, anakinra, siltuximab)
• Antibiotic de-escalation should be addressed on a daily basis with consideration for the type of immunosuppressive therapies that have been administered.
• Consider weekly CMV monitoring with serum polymerase chain reaction testing in high-risk patients who are CMV seropositive‡
• Consider using mold-active azole prophylaxis with posaconazole in high-risk patients§

Hill JA et al. Blood 2020;136:925

Table 13. Eligibility criteria for vaccination in patients receiving CD19-targeted CAR T-cell therapy

Agent	EBMT/EHA recommendations		Comments
	Pre-CAR-T	Post-CAR-T	
Influenza vaccine	Preferably vaccinate 2 weeks before LD In B-cell aplasia low likelihood of serological response	>3 months after CAR-T patients should be vaccinated irrespective of immunological reconstitution	Where there is incomplete immune reconstitution[a] or ongoing immunosuppression, there is a high likelihood of lower vaccine responses. Consensus view is that vaccination may still be beneficial to reduce rates of infection and improve clinical course. Consider boost upon B-cell recovery
SARS-CoV-19	Preferably vaccinate before CAR-T therapy In B-cell aplasia low likelihood of serological response	>3 months after CAR T-cell infusion	Limited data is available on vaccine response after CAR-T, and early reports suggest impaired serological responses.[84] However, SARS-CoV-19 vaccine-induced protection relies heavily on T-cell-mediated immunity, therefore B-cell aplasia does not seem to be a contraindication; no T-cell threshold has been defined. Post-vaccination response monitoring is desirable. Guidance on re-vaccination post-CAR-T and frequency/dosing of booster vaccines will vary between countries. National guidelines should be followed in this area of rapidly evolving clinical practice
Killed/inactivated vaccines		>6 months after CAR-T and >2 months after immunoglobulin replacement	Contraindications include concurrent immunosuppressive or cytotoxic therapy
Live and non-live adjuvant vaccines		1 year after CAR-T and fully immune reconstituted[a]	Contraindications include <2 years post-allo-HCT, <8 months after completion of immunoglobulin replacement

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Clinical problem	Ranges and frequency of occurrence	Possible solution
Potential for long period between cell collection and CAR T-cell infusion allows progression of malignancy and may result in deaths	Varies per CAR T-cell product: Range of median reported cell processing times[a] for FDA-approved products: 13–54 d	Allogeneic CAR T cells derived from healthy donors can be manufactured in advance, cryopreserved, stored, and delivered for infusion into patients on demand. This process can decrease the time from the decision to treat to the cell infusion to just a few days (5–9 d).[36,37]
Change in antigen expression by the cancer can cause cancer progression or relapse	Varies per CAR T-cell product, eg, tisagenlecleucel for pediatric leukemia: 91%, axicabtagene ciloleucel for large B-cell lymphoma: 28%, and idecabtagene vicleucel: 4%	CAR T cells directed at multiple malignancy-associated antigens may be able to target an antigen that continues to be expressed by the malignant cell despite loss of expression of 1 or more other target antigens. Patients with relapsed or refractory malignancy after CAR T cells targeting 1 antigen may be able to receive CAR T cells targeting a different antigen as salvage therapy.
CAR T cells with a more differentiated phenotype with loss of tumor-killing functions lead to low efficacy	Not reported	Modified CAR protein structure and cell-processing techniques to produce more naive, more functional CAR T cells Use of CAR T cells as an earlier line of malignancy therapy, so that patient T cells are less affected by prior chemotherapy treatments
Severe[b] cytokine release syndrome and neurologic toxicities	Varies per CAR T-cell product. Severe CRS range: 0%-47% Severe neurologic toxicity range: 2%-32%	Continued prospective evaluation of anticytokine, small-molecule, and low-dose glucocorticoids for prevention and early intervention for these adverse effects
		Development of less-toxic CAR T-cell therapies
Risk of second malignancies	Myeloid malignancies: 2%-10%[38,39] T-cell malignancies: 22 cases reported out of >27 000 doses administered[40]	Use of CAR T cells as an earlier line of malignancy therapy may decrease exposure to prior chemotherapies that can lead to secondary myeloid malignancies Long-term monitoring for second malignancies, including T-cell malignancies

Brudno JN et al. JAMA 2024;332:1924

Sonuç olarak

Teşekkürler…