

Lenfomalarda Hücresel Tedavilerinin Yeri CAR-T

Dr.Ebru Kızılkılıç

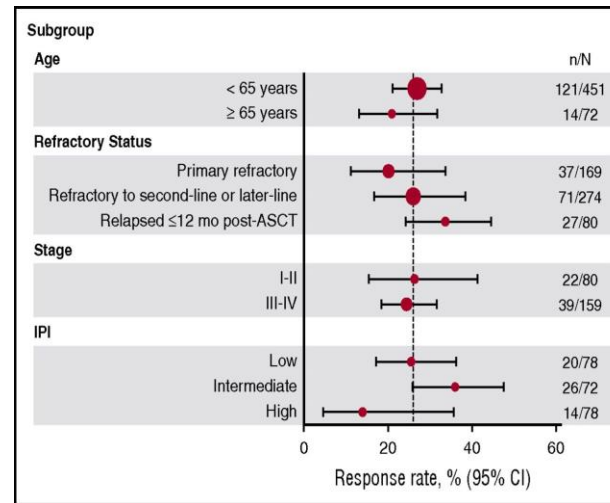
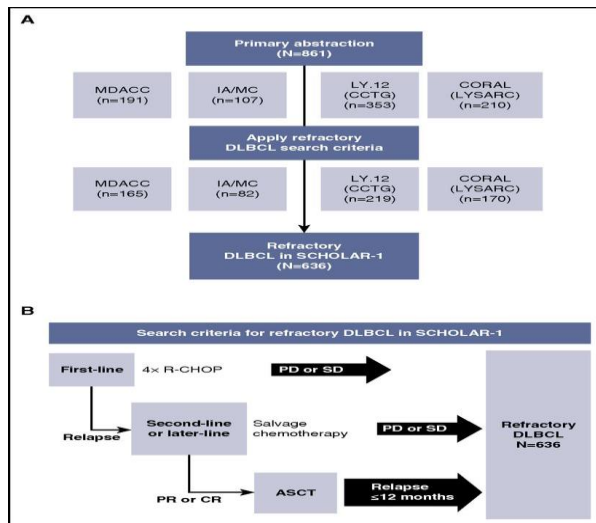
Acıbadem Altunizade Hastanesi Hematoloji Bölümü

Neden R/R DLBCL da hücresel tedavilere ihtiyacımız var?

- Yeni tanı alan NHL %30
- Avrupa'da görülme insidansı 3-4/100.000
- 5 Yıllık survi %62. USA %55.4 Avrupa
- IPI skoruna bağlı olarak %20-%50 R-CHOP refrakter ya da CR sonrası nüks

Neden R/R DLBCL da hücresel tedavilere ihtiyacımız var?

SCHOLAR-1



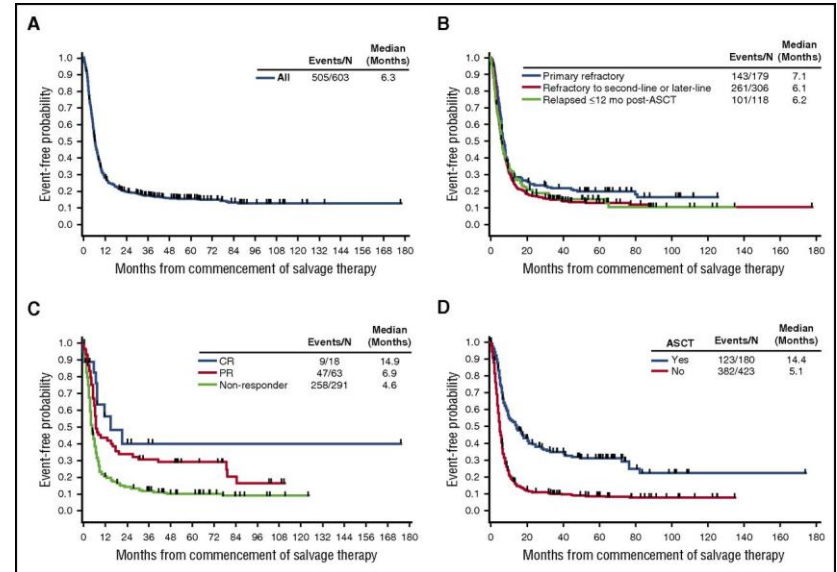
Crump et al Blood 2017; 130 (16):1800-

Neden R/R DLBCL da hücresel tedavilere ihtiyacımız var?

N=636

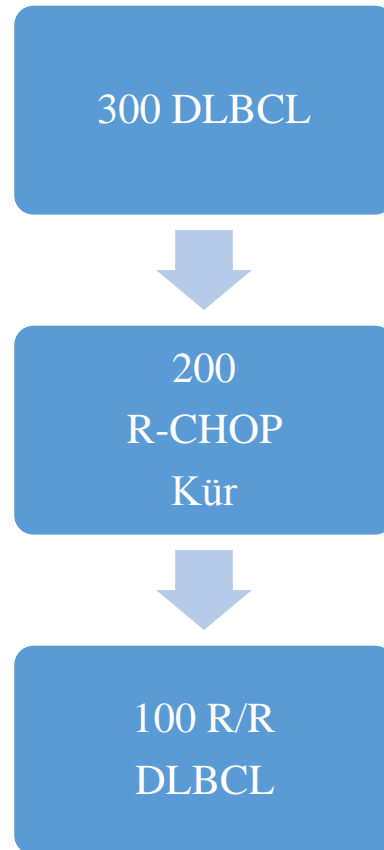
Post-rituximab 2000-2017

- Primer refrakter median 7.1 ay 2 yr OS %24
- >2 ted. Direnç. 6.4 ay. %20
- Relaps <12 ay (post –ASCT) 6.4 ay %19
- Median Overall survival 6.3 ay

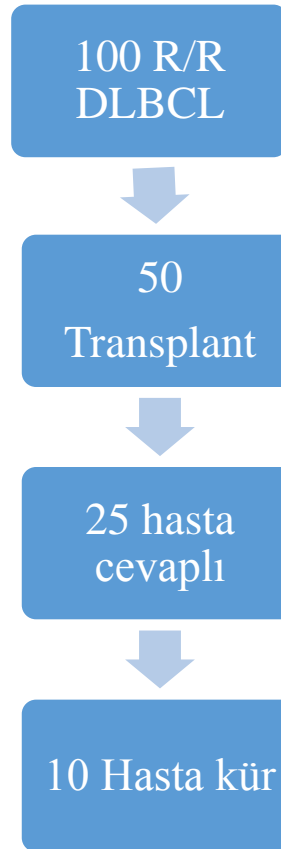


Neden R/R DLBCL da hücresel tedavilere ihtiyacımız var? Otolog nakil ?

KURTARMA KEMOTERAPİSİ	N	RR	Nakil oranı	PFS
R-ICE	202	%64	51	3 yıl % 31
R-DHAP (CORAL)	194	%63	55	3 yıl % 42
R-DHAP (LY12)	304	%45	49	3 yıl %28
R-GDP	306	%44	52	3 yıl % 28
R-DHAP (ORCHARD)	223	%42	37	2 yıl %26
O-DHAP(ORCHARD)	222	%38	33	2 yıl % 24



j. Frenberg. ASH education book.



Neden R/R DLBCL da hücresel tedavilere ihtiyacımız var? Otolog nakil sonrası nüks ?

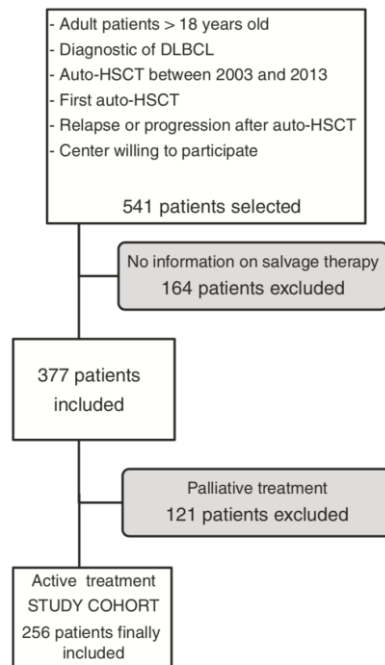


Table 2 Salvage therapy at relapse after 1st auto-HSCT

	<i>n</i>	<i>%</i>
Platinum-containing regimens	133	52
Active intensive combinations (doxorubicin, cytosine arabinoside, ifosfamide, and gemcitabine)	97	38
Active nonintensive combinations	26	10

Barca et.al A retrospective analysis of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation (EBMT) 2019

Neden R/R DLBCL da hücresel tedavilere ihtiyacımız var? Otolog nakil sonrası nüks ?

- Hastaların 3/4 ü aktif tedavi alıyor.
- Hastaların yarısı bu tedavilere yanıt veriyor.
- 1/3 hasta 2. transplant oluyor.
- Allo-RIC PFS ve OS 3 yıl %40-50
- NRM % 20-30
- İlk otologdan sonra relaps <12 ay ise 3 yıllık O.S %20

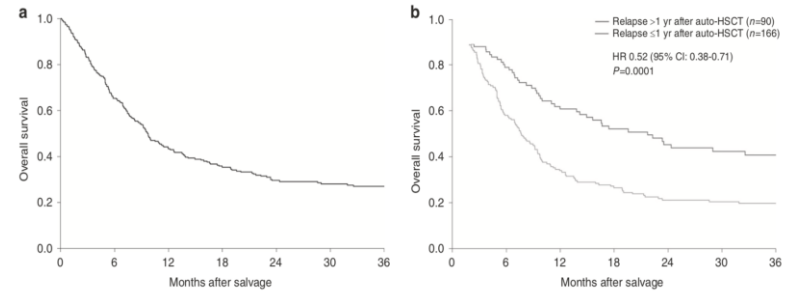


Fig. 2 Overall survival of the whole cohort of patients (a) and overall survival according to the time of relapse after auto-HSCT (b)

REVIEW ARTICLE

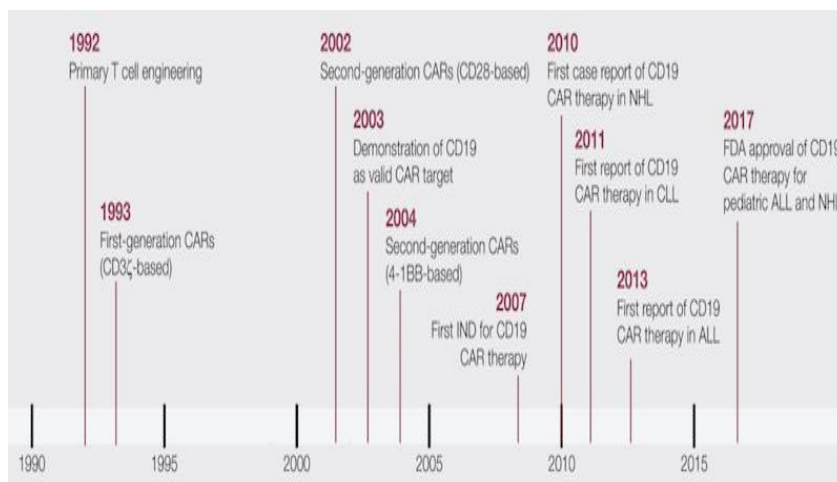
FRONTIERS IN MEDICINE

Chimeric Antigen Receptor Therapy

Carl H. June, M.D., and Michel Sadelain, M.D., Ph.D.

THE AIM OF CANCER IMMUNOTHERAPY IS TO ENHANCE THE IMMUNE RESPONSE against tumor cells. The emergence of immuno-oncology as the first broadly successful strategy to treat metastatic cancer will require clinicians to integrate this new type of medicine with chemotherapy, surgery, radiation therapy, and the use of targeted small molecules. Immuno-oncologic drugs include a broad range of agents, including antibodies, vaccines, adjuvant therapies, cytokines, oncolytic viruses, bispecific molecules, and cellular therapies.¹ Vaccines have generally not proved to be efficacious unless they are used as a preventive agent against virally induced tumors.² The selective targeting of neoantigens created by tumor-specific mutations³ may prove otherwise. Alternatively, adoptive cell-transfer-based therapies bypass the need for active immunization and therefore have potential efficacy in immunologically compromised patients with cancer.

Genetically engineered T cells constitute a powerful new class of therapeutic agents that offer hope for curative responses in patients with cancer. Chimeric antigen receptor (CAR) T cells were recently approved by the Food and Drug Administration (FDA) and are poised to enter the practice of medicine for the treatment of leukemia and lymphoma (see video). Synthetic biology approaches for cellular engineering provide a broadly expanded set of tools to program immune cells for enhanced function. Advances in T-cell engineering, genetic editing, the selection of the most functional lymphocytes, and cell manufacturing have the potential to broaden T-cell-based therapies and foster new applications beyond oncology in infectious diseases, organ transplantation, and autoimmunity. This review addresses the principles of T-cell engineering and synthetic immunity, with a focus on the efficacy and toxic effects of current CAR therapies.



From the Center for Cellular Immunotherapies, Perelman School of Medicine, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia (C.H.J.); and the Center for Cell Engineering, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York (M.S.). Address reprint requests to Dr. June at the Smilow Center for Translational Research, 3400 Civic Center Blvd., Bldg. 421, 8th Fl., Rm. 123, Philadelphia, PA 19104-5156, or at cjune@upenn.edu; or to Dr. Sadelain at the Center for Cell Engineering, 1250 First Ave., Schwartz Bldg., 10th Fl., Rm. S1021, New York, NY 10065, or at m-sadelain@ski.mskcc.org.

N Engl J Med 2018;379:64-73.

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An illustrated glossary and a video showing CAR T cell action are available at NEJM.org

Hücresel tedavilere ihtiyacımız var ama sonuçlar?

- ZUMA-1. :Axicabtagene ciloleucel (YESCARTA)
- FAZ-1-2
- >18 yaş,
- 108 hasta
- Mayıs 2015-eylül 2016- Aug. 2018
- 22 yer- USA-İsrail
- Lenfodeplezyon : -5,-4,-3 endoksan-fludarabine
- CAR-T hücre dozu: $2 \cdot 10^6$ / kg -tek doz
- Median takip süresi :27.1 ay

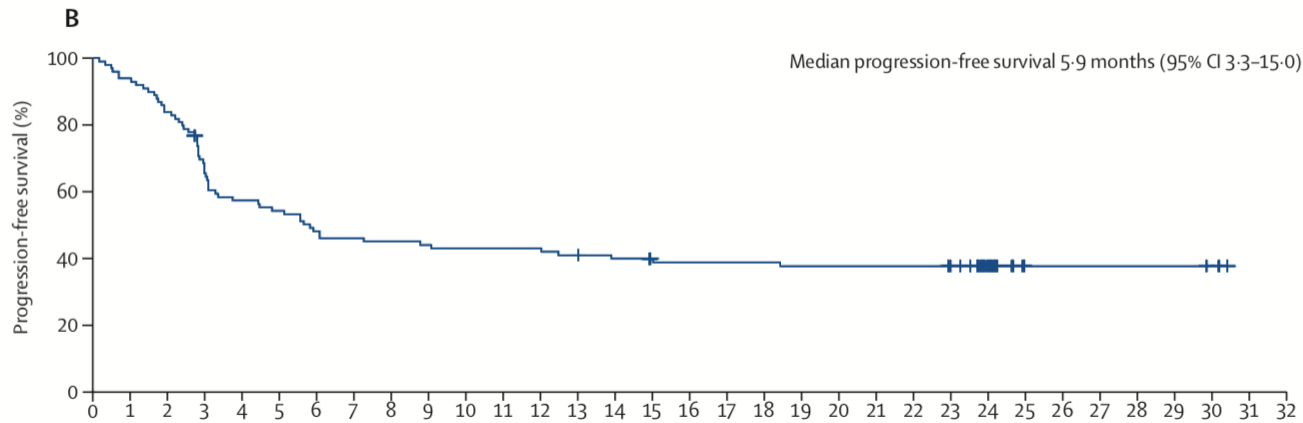
Hücresel tedavilere ihtiyacımız var ama sonuçlar?

	FAZ 1 VE FAZ 2 (N 108)
Yaş	58 (23-76)
>65 yaş	27- %25
Evre3-4 hastalık	90-%83
IPI skor 3-4 - 5	48- %44
> 3 den fazla tedavi oranı %	76- %74
Post-ASCT nüks.	25- %23

	Investigator-assessed (n=101)	IRC-assessed (n=101)
Objective response*	84 (83%)	75 (74%)
Complete response†	59 (58%)	55 (54%)
Partial response	25 (25%)	20 (20%)
Ongoing response‡	39 (39%)	36 (36%)
Complete response	37 (37%)	35 (35%)
Partial response	2 (2%)	1 (1%)
Median duration of response, months (95% CI)	11.1 (4.2-NE)	NR (10.9-NE)
Median duration of complete response, months (95% CI)	NR (12.9-NE)	NR (NE-NE)
Median overall survival, months (95% CI)	NR (12.8-NE)	NR (12.8-NE)

Locke F et. Al. Lancet. Oncol.
Aralık 2018

Hücresel tedavilere ihtiyacımız var ama sonuçlar?

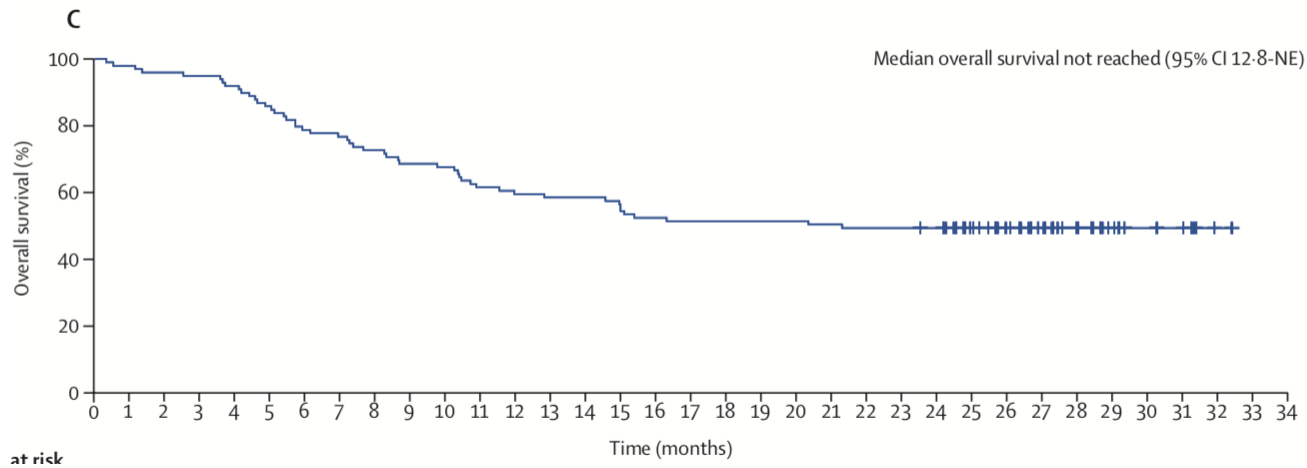


12 ay PFS %44
18 ay PFS % 40

Axi-cell 2 yıllık PFS. %39

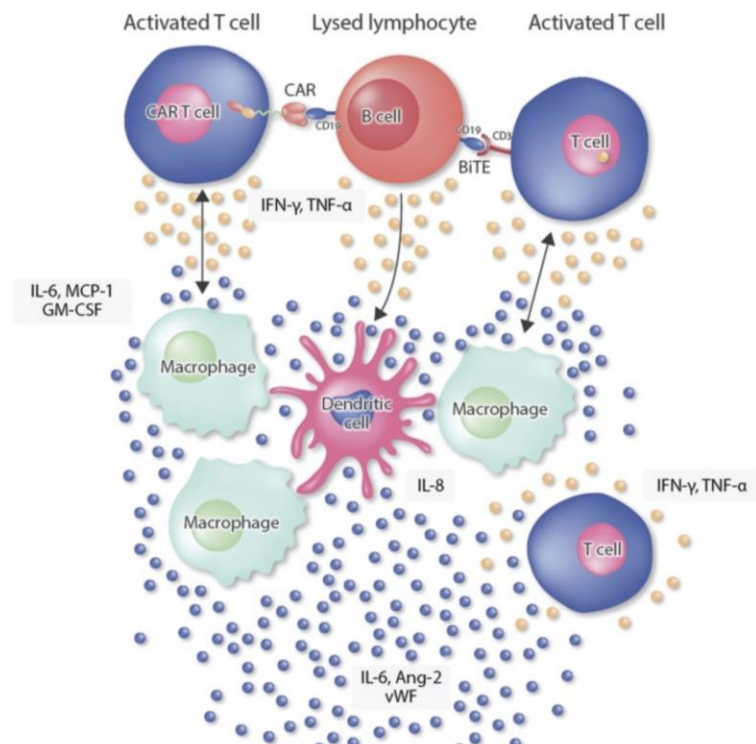
Locke F et. Al. Lancet. Oncol. Aralık 2018

Hücresel tedavilere ihtiyacımız var ama sonuçlar?



12 ay	OS %60
18 ay	OS %53
24 ay	OS %51

Locke F et. Al. Lancet. Oncol. Aralık 2018



General Symptoms

High fever
Malaise
Arthralgia/myalgia
Nausea
Headaches
Rash

Cardiovascular

Tachykardia hypotension
Cardiac arrhythmias

Shock

Pulmonary

Hypoxia

Pulmonary edema due to vascular leakage
Acute respiratory distress syndrome

Hematologic

Prolonged cytopenias

Disseminated intravascular coagulation

Borrega G et al. Hemasphre 2019
April 3(2) :e191

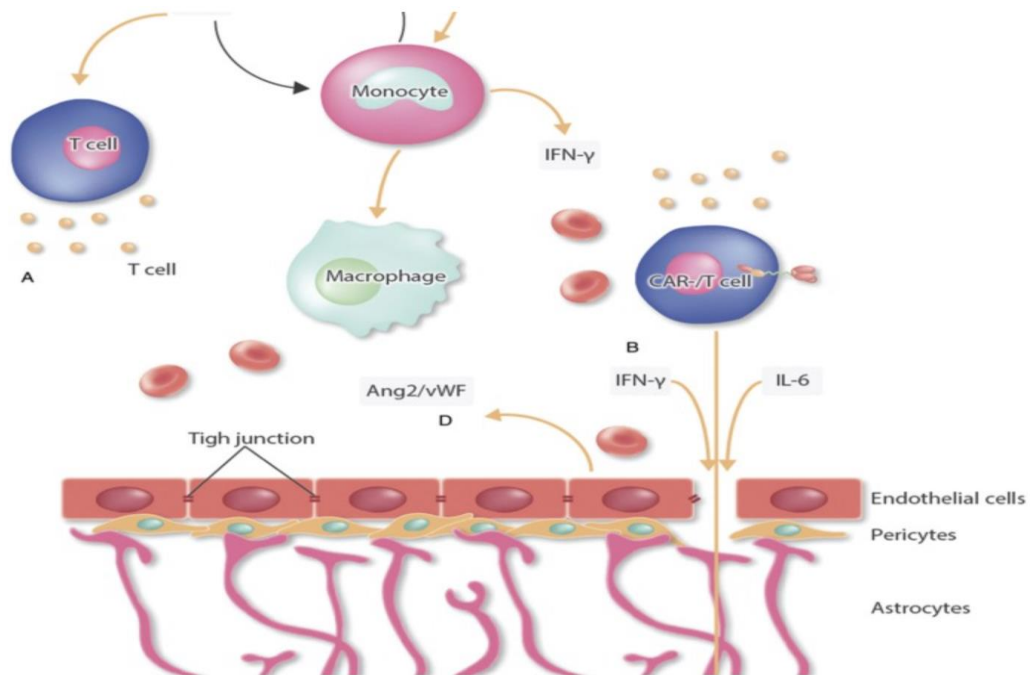
CRS

CRS grading and management approaches




CRS grade 1	<ul style="list-style-type: none">• temperature $>38^{\circ}\text{C}$• flu-like symptoms• nausea	<ul style="list-style-type: none">• infectious workup• broad spectrum antibiotic• supportive measures (antipyretics)
CRS grade 2	<ul style="list-style-type: none">• temperature $>38^{\circ}\text{C}$• hypotension not requiring vasopressors• hypoxia requiring low-flow nasal cannula or blow-by	<ul style="list-style-type: none">• manage fever and symptoms as grade 1• transfer to IMC/ICU• low dose vasopressor• tocilizumab 8mg/kg i.v.
CRS grade 3	<ul style="list-style-type: none">• temperature $>38^{\circ}\text{C}$• hypotension requiring one vasopressor with or without vasopressin• hypoxia requiring high-flow oxygen or facemask	<ul style="list-style-type: none">• manage fever and symptoms as grade 2• repeat tocilizumab• low dose corticosteroids
CRS grade 4	<ul style="list-style-type: none">• temperature $>38^{\circ}\text{C}$• hypoxia requiring positive airway pressure• hypotension requiring multiple vasopressors (excl. vasopressin)	<ul style="list-style-type: none">• manage fever and symptoms as grade 2• high dose corticosteroids• consider further individual treatment

ICANS



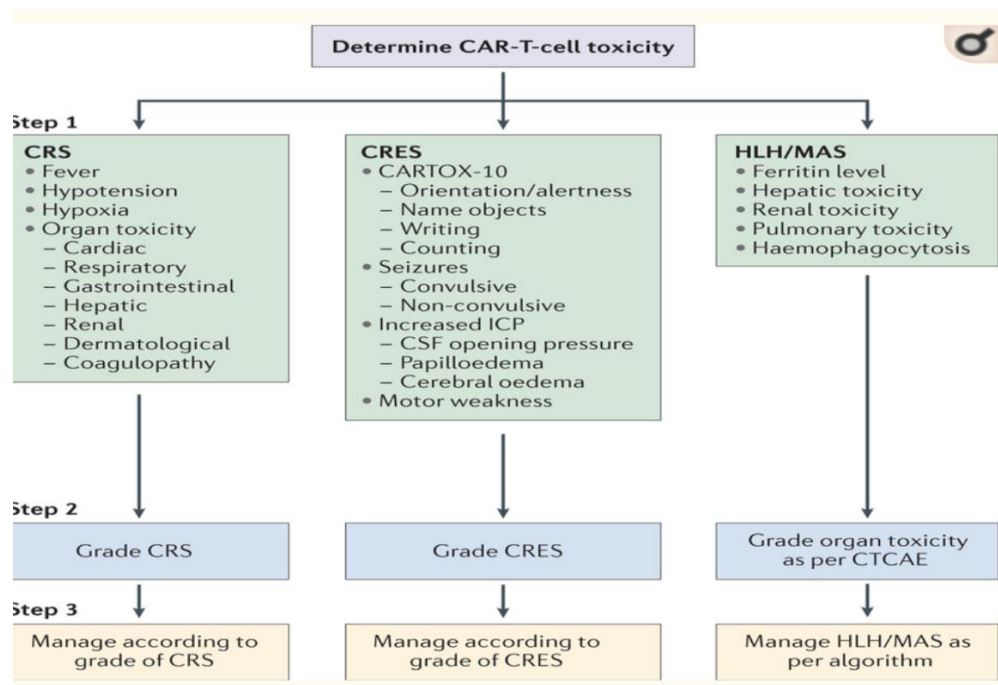
immune effector cell-associated neurotoxicity syndrome (ICANS)

- Başağrısı, halsizlik, afazi, letarji,
- Nöbetler, intrakraniyal basınç artışı
- Cerebral ödem, koma
-  ICANS %64 MRI normal
- MRI: T2 FLAIR vazojenik ödem

CRS grading and management approaches



ICANS grade 1	<ul style="list-style-type: none"> • awakens spontaneously • fatigue • ICE: 7-9 points 	<ul style="list-style-type: none"> • supportive care • IV hydration • neurology consultation • EEG/MRI • consider antiepileptic drug
ICANS grade 2	<ul style="list-style-type: none"> • awakens to voice • delirius/somnolent • ICE: 3-6 points 	<ul style="list-style-type: none"> • supportive care as grade 1 • consider ICU transfer • consider antiepileptic drug, if not started • low dose corticosteroids (i.e. dexamethasone 10mg)
ICANS grade 3	<ul style="list-style-type: none"> • awakens to tactile stimulus • ICE: 0-2 points • local edema on imaging • seizure, that resolves with intervention 	<ul style="list-style-type: none"> • Supportive care as grade 2 • ICU transfer • continuous corticosteroids (i.e. dexamethasone 10mg every 6 hours) and antiepileptic drugs • repeat MRI
ICANS grade 4	<ul style="list-style-type: none"> • comatose • ICE: 0 • cerebral edema • life-threatening (>5min) seizure • motor weakness 	<ul style="list-style-type: none"> • supportive care as grade 3 • high dose corticosteroids specific neurointensive treatment (status epilepticus, brain edema) • consider further individual treatment



Hücresel tedavilere ihtiyacımız var ama yan etkiler?

	Any
Any	108 (100%)
Pyrexia	94 (87%)
Anaemia	73 (68%)
Hypotension	63 (58%)
Nausea	63 (58%)
Fatigue	57 (53%)
Decreased appetite	55 (51%)
Headache	50 (46%)
Diarrhoea	48 (44%)
Neutropenia	48 (44%)
Hypoalbuminaemia	43 (40%)
Hypocalcaemia	43 (40%)
Tachycardia	43 (40%)
Chills	40 (37%)
Encephalopathy	40 (37%)
Febrile neutropenia	39 (36%)
Hyponatraemia	38 (35%)
Thrombocytopenia	38 (35%)
Vomiting	37 (34%)
Hypokalaemia	36 (33%)
Decreased neutrophil count	36 (33%)
Hypoxia	34 (31%)
Tremor	33 (31%)

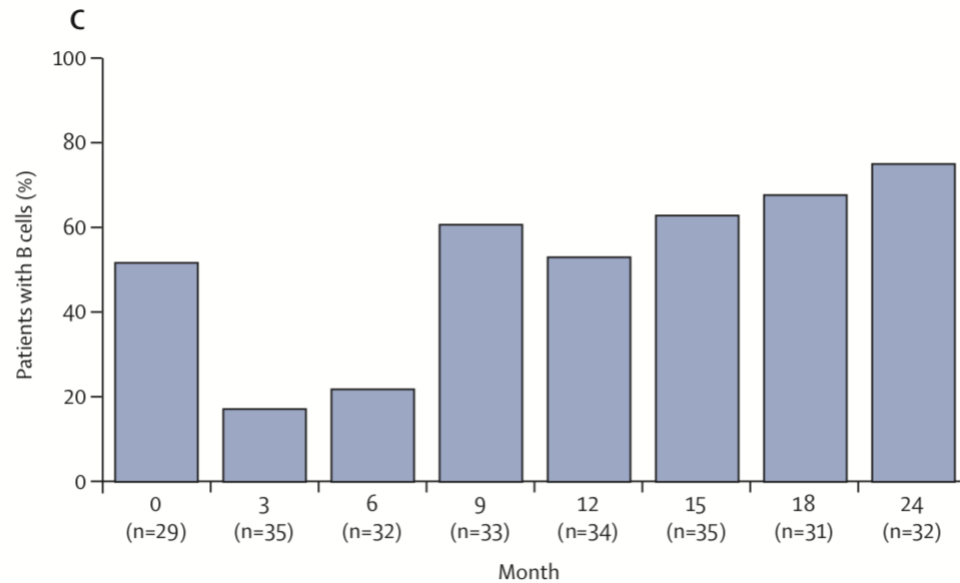
Decreased white blood cell count	33 (31%)
Constipation	32 (30%)
Decreased platelet count	32 (30%)
Cough	31 (29%)
Hypophosphataemia	31 (29%)
Confused state	29 (27%)
Dizziness	23 (21%)
Dyspnoea	23 (21%)
Increased alanine aminotransferase	22 (20%)
Decreased lymphocyte count	22 (20%)
Peripheral oedema	21 (19%)
Sinus tachycardia	21 (19%)
Hyperglycaemia	20 (19%)
Hypomagnesaemia	20 (19%)
Leucopenia	20 (19%)
Aphasia	19 (18%)
Increased aspartate aminotransferase	19 (18%)
Somnolence	18 (17%)
Hypertension	17 (16%)
Muscular weakness	17 (16%)
Pleural effusion	17 (16%)
Weight loss	17 (16%)

Locke F et. Al. Lancet. Oncol. Aralık 2018

Hücresel tedavilere ihtiyacımız var ama yan etkiler?

- 108 hastanın 52 sinde grade >3 yan etki % 48
- Grade >3. CRS. 12 hasta %12
- Grade>3 nörolojik olay 35 hasta % 32
- Grade >3 enfeksiyon 30 hasta %28
- 50 hasta progresif hastalık ex.
- 4 hasta yan etki ilişkili ölüm.

Hücresel tedavilere ihtiyacımız var ama yan etkiler?



%31 hasta IVIG

Axi-cel

- FDA 18 Ekim 2017
- EMA 23 Ağustos 2018
- Axicabtagene ciloleucel erişkin relaps/refrakter DLBCL ve PMBCL hastalarında iki ya da daha fazla sistemik tedavi sonrası kullanılır.

Tüm dünyada >1000 hasta axicel tedavisi aldı

Tisagenlecleucel

- JULIET

- Faz 2

- 10 ülke, 27 yer

- >18 yaş, relaps-refrakter DLBCL

- 238 hasta refere edildi, 165 dahil edildi, 111 hasta infüzyon aldı.

Table 1. Demographic and Clinical Characteristics of the Patients in the Full Analysis Set at Baseline.*

Characteristic	Patients (N=111)
Median age (range) — yr	56 (22–76)
Age ≥65 yr — no. (%)	25 (23)
ECOG performance status — no. (%)†	
0	61 (55)
1	50 (45)
Disease stage at study entry — no. (%)‡	
Stage I	8 (7)
Stage II	19 (17)
Stage III	22 (20)
Stage IV	62 (56)
Bone marrow involvement at study entry — no. (%)	8 (7)
Diagnosis on central histologic review — no. (%)	
Diffuse large B-cell lymphoma, not otherwise specified	88 (79)
Transformed follicular lymphoma	21 (19)
Other	2 (2)
Double- or triple-hit rearrangement: MYC plus BCL2, BCL6, or both — no./total no. (%)§	19/70 (27)
Cell of origin of cancer — no. (%)	
Germinal center B-cell type	63 (57)
Non-germinal center B-cell type	45 (41)
Missing data	3 (3)
No. of previous lines of antineoplastic therapy — no. (%)¶	
1	5 (5)
2	49 (44)
3	34 (31)
4–6	23 (21)
Relapse after last therapy — no. (%)	50 (45)
Refractory diffuse large B-cell lymphoma — no. (%)**	61 (55)
Previous autologous hematopoietic stem-cell transplantation — no. (%)	54 (49)

Schuster SJ et.al N Engl J med 2019 Jan.

Tisagenlecleucel

- JULIET

- %92 hasta infüzyon öncesi kemoterapi aldı.

(Gemcitabine, etoposide, dexametazon, rituximab, cisplatin, ibrutinib, lenalidomid)

- %73 hasta lenfodeplezyon , Flu-Cy %20 bendamustin

- 111 hasta , tek doz , median $3 \times 10^8/\text{kg}$ (0.1-6)

Tisagenlecleucel

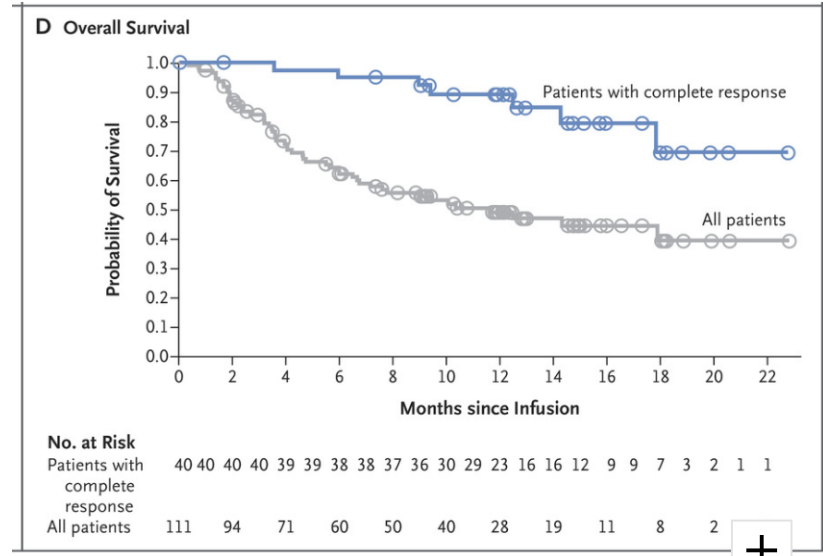
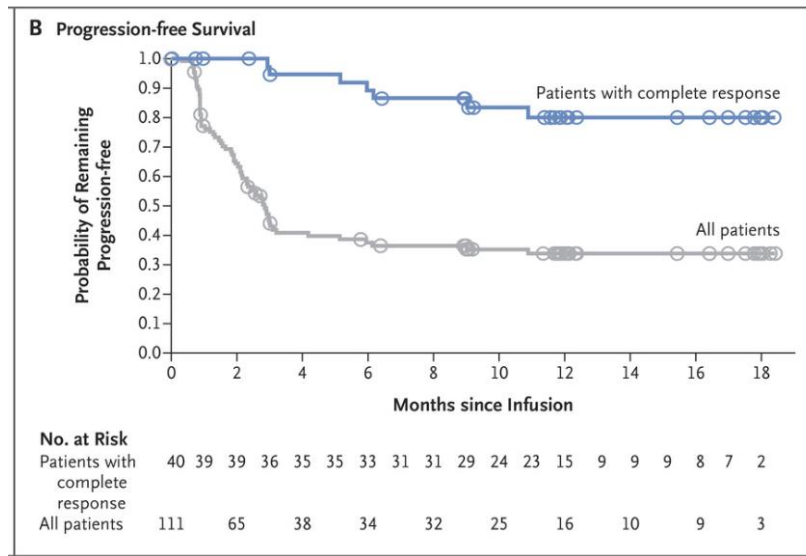
Response Rate, n (%)	Fludarabine based (n=68)	Non-fludarabine based (n=18)	No lymphodepleting chemotherapy (n=7)
Best overall response rate (CR + PR)	37 (54)	9 (50)	2 (29)
CR	28 (41)	7 (39)	2 (29)
PR	9 (13)	2 (11)	0
SD	10 (15)	3 (17)	1 (14)
PD	16 (24)	4 (22)	4 (57)
Unknown	5 (7)	2 (11)	0

Table S5. Best Overall Response and Overall Response Rate After Tisagenlecleucel Infusion From the Efficacy Analysis Set of the Independent Review Committee Assessment

Response Rate, n (%)	Patients (N=93)	
Best overall response rate (CR + PR)	48 (52)	(95% CI, 41%-62%)
CR	37 (40)	
PR	11 (12)	
SD	14 (15)	
PD	24 (26)	
ORR (CR + PR) at 3 months	35 (38)	
CR	30 (32)	
PR	5 (5)	
Overall response rate (CR + PR) at 6 months	30 (33)	
CR	27 (29)	
PR	3 (3)	

Schuster SJ et.al N Engl J med 2019 Jan.

Tisagenlecleucel



Schuster SJ et.al N Engl J med 2019 Jan.

Tisagenlecleucel

- JULIET
- 3. ayda % 38 hasta ORR %32 CR
- 6.ayda %33 hasta ORR %29 CR
- CRS%58
- Nörolojik bulgular %12
- %30 hasta IVIG ihtiyacı

- FDA 1 Mayıs 2018
- EMA Ağustos 2018
- Tisagenlecleucel (Kymriah) , en az iki ya da daha fazla sıra tedavi almış DLBCL da onaylandı

Lisocabtagene Maraleucel (liso-cel;JCAR017)

- TRANSCEND-NHL-001
- DLBCL (de novo ya da FL transforme)
- High grade B hücreli Lenfoma(double/triple hit)
- DLBCL (CLL ya da MZL transforme)
- PMBCL
- FL3B
- MCL

Abramson SJ et al. EHA 2018abstract
S800

Transfusion Medicine Reviews (2019)
journal

Lisocabtagene Maraleucel (liso-cel;JCAR017)

	FULL (N=102)	CORE (N=73)
Yaş	61(20-82)	20-82
Double-triple L	19. (%19)	16(%22)
Önceki kemoterapiler	3 (1-8)	3(2-8)
CNS	2	1
kemorefrakter	71. (%70)	49 (%67)
HSCT	41 (40)	28(38)
Allogeneik	5	0
Otolog	38(%37)	28 (%38)

- ORR %82,
- CR%55
- 8. ayda hastaların %40 remisyonda
- 1 yıllık os %59
- CRS%37

Abramson SJ et al. Transfusion Medicine Reviews journal 2019.

	Axicabtagene ciloleucel Axi-cel	Tisagenlecleucel Tisa-cel	Lisocabtegene maraleucel Liso-cel
Co-stim. domain	CD28	4-1BB	4-1BB
Vector	Retrovirüs	Lentivirus	Lentivirus
T-cell	Bulk	Bulk	CD4:CD8 1/1
Minimum A. Lenfosit sayısı (afarez için)	>100/mikrolitre	>300/mikrolitre	Minumum değer yok
Apheresis ürünü (üretime gönderilen)		dondurulmuş	
Öncesinde kemoterapi	Pivotal çalışmada yok	%93	%72
Lymphodepletion	FLU 500-CYS 30	FLU 250/CYS 25 ya da bendamustin	FLU 300-CY 30
Hedef car-t doz	2X10 ⁶	3X 10 ⁸	1X10 ⁸
Onay	FDA/EMA DLBCL HGBCL, Transforme FL,PMBCL	FDA/EMA Pediyatrik B ALL,DLBCL,HGBCL, Transforme FL	

	Axicabtagene ciloleucel Axi-cel	Tisagenlecleucel Tisa-cel	Lisocabtagene maraleucel Liso-cel
CRS oranı	% 93	%58	%37
CRS Grade 3-4	%13	%23	%1
CRS Başlangıcı median	2 gün	3 gün	5 gün
Tocilizumab kullanımı	%43	%15	%17
Nörotoksisite	%64	%21	%25
Ciddi nörotoksisite	%28	%12	%15

Abramson SJ et al. Transfusion
Medicine Reviews journal 2019.

Table 4 CAR T-cell therapies for non-Hodgkin lymphoma							
Author, Year	Patients, n	CAR T-cell Product	3 + CRS	3 + NT	ORR	PFS (y)	OS (y)
Kochenderfer et al, ⁶¹ 2015	4 DLBCL 4 PMBCL 4 CLL 1 tCLL 1 SMZL	CD19/CD28	NR	NR	80%	NR	NR
Turtle et al, ⁶² 2016	11 DLBCL 11 tIndolent 4 MCL 6 FL	CD19/4-1BB (delivered in a fixed 1:1 CD4/CD8 ratio)	13%	28%	72%	NR	NR
Neelapu et al, ³¹ 2017	77 DLBCL 8 PMBCL 16 tFL (should probably report response rates and survival stats based separated by histology)	CD19/CD28 (axicabtagene ciloleucel)	13%	28%	82%	44% (1)	59% (1)
Schuster et al, ⁶³ 2017	14 DLBCL 14 FL	CD19/4-1BB (CTL019)	18%	11%	64%	43% (2) 71% (2)	NR
Schuster et al, ³⁰ 2018	88 DLBCL 21 tFL	CD19/4-1BB (CTL019, tisagenlecleucel)	22%	12%	52%	NR	49% (1)

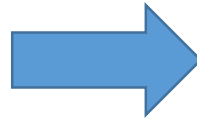
Hunter BD et al. Hemat.oncol Clin North. 2019 Aug.

CAR-T direnç mekanizmaları

- Hedef antijen kaybı

- T- hücre yorulması

- İmmun kaçış
checkpoint.inh



immun

immunomodülatuar ilaçlar

- Persistans kaybı
hedef moleküller

Multiple

Allogeneik CAR-T

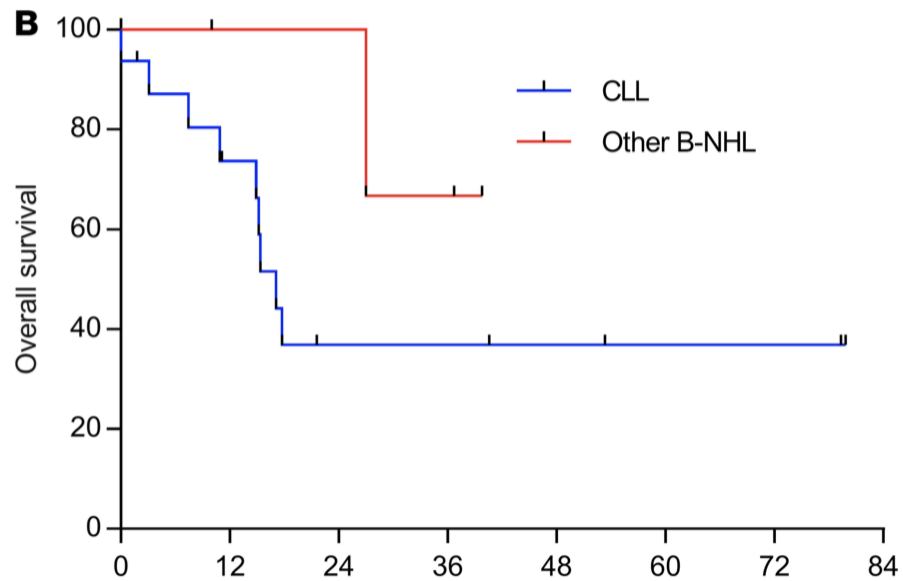
CAR-T sonrası allojeneik nakil ?

- 32 ALL/18 NHK/13 CLL
- MAC%74 ALL %39 NHL
- CAR-T den sonra median süre ALL 72 gün , NHL/KLL 39 gün
- GVHD oranı akut grade 3-4 %25 kronik GVHD %10
- Nötrofil düzelmesi median 18.5 gün
- Trombosit düzelmesi: median 12 gün
- %22 viral ya da fungal enfeksiyon.(ilk 100 gün)
- 100 günlük NRM %16 ALL, %15 /KLL
- 1 yıl NRM % 22 ALL, %33 NHL/KLL

R/R CLL de CAR-T tedavisi

- Faz 1. CD28 domain CAR-T.
- Doz: 3×10^7
- 16 R/R CLL, 4 İndolent B-NHL
- Tüm hastalarda CRS, grade 3-4 % 10
- Nörolojik bulgular %10

R/R CLL de CAR-T tedavisi



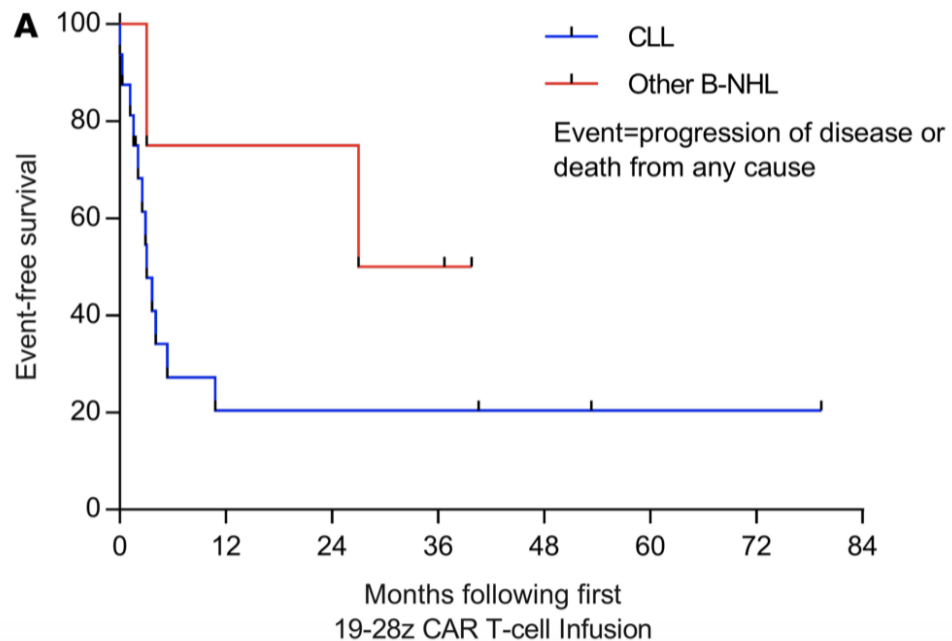


Figure 3. Survival outcomes. EFS (**A**) and OS (**B**) are depicted for patients with CLL (blue lines) and patients with other B-NHL (red lines), measured from the time of first 19-28z CAR T cell infusion, using the Kaplan-Meier method. B-NHL, B cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; EFS, event-free survival; OS, overall survival.

Foliküler Lenfomada CAR-T

- 21 hasta.
- 8 R/R FL, 13 t FL
- Flu-cy
- 2×10^6
- 1:1 CD4+:CD8+ CAR- T hücre ve 4-1BB
- %88 CR FL 24 ay takipte
- %46 CR tFL 38 ay takip
- CRS %50 FL %39 tFL.
- Nörotoksisite %50 FL %23 tFL

Sekonder CNS Lenfomada CAR-T

- 8 hasta. /Tisagenlecleucel
- Median yaş 50. (17-79)
- Alınan tedaviler 5 (3-6) 1 hasta allo.tx
- 2 hasta sistemik hastalık ve CNS tutulumu (infüzyon sırasında)
- Tüm hastalar direkt CNS tedavine dirençli
- 3 hasta parankimal, 3 hasta leptomeningeal, 2 hasta ise parankimal-leptomeningeal
- 1 hasta grade 1 nörotoksisite,
- 2 hasta PR .

Ibrutinib- CAR-T

- 17 p pozitif BCL-2 inhibitör dirençli KLL
- SLL tanısı ardından hızlı progresyon 17 p pozitif
- Allo tx sonrası relaps.
- BCL-2 inhibitör yanıtızsız.
- Ibrutinib sonrası PR
- CAR-T sonrası kemik iliği CR, MRD negatif
- 2 ay sonra Allo TX.

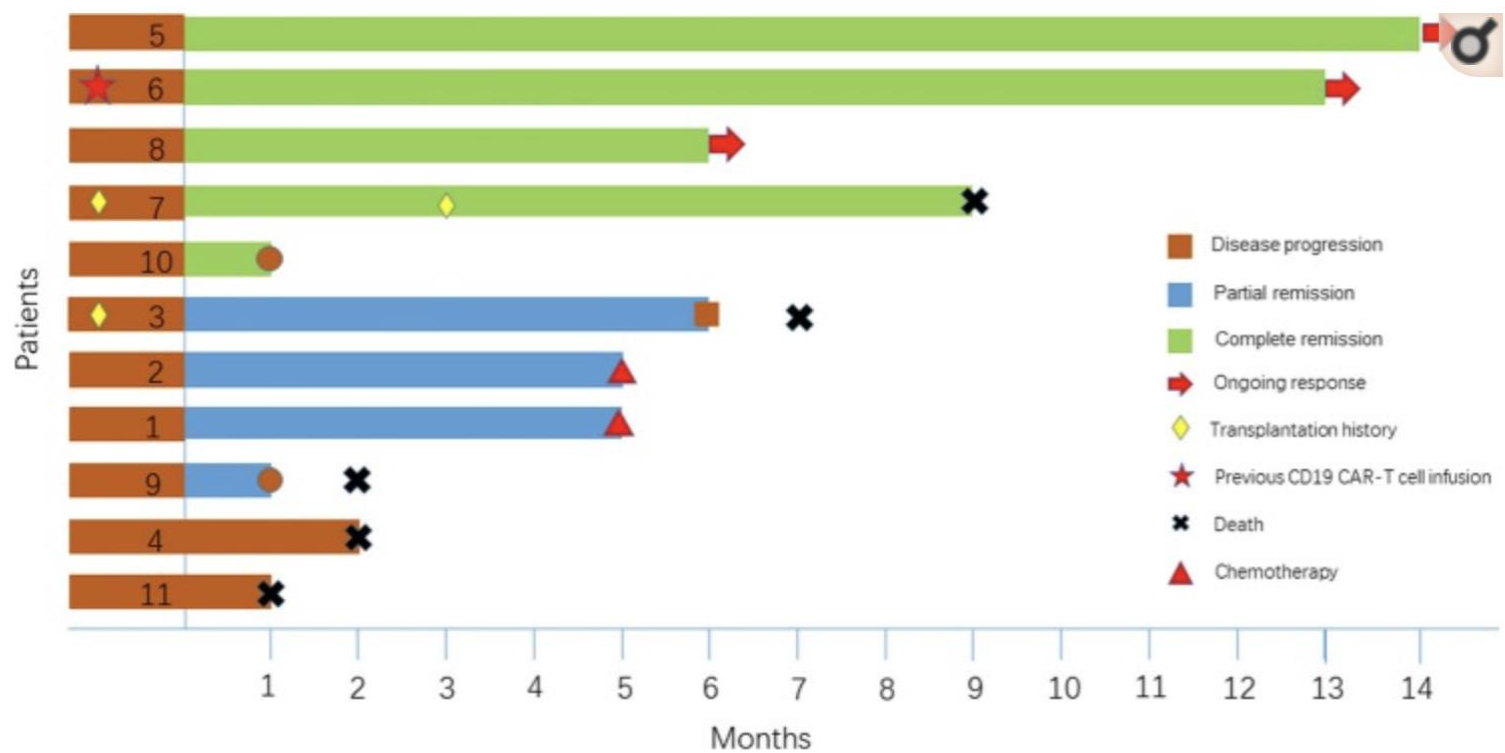
HIV-Agresif B hücreli lenfomada CAR-T

- 2 hasta
- HIV ilişkili Agresif B hücreli lenfoma
- R-EPOCH sonrası relaps.
- Yüksek doz tedavi için komorbiditeleri uygun değil
- axi-cell
- 2 hasta da CR

CAR-T ve Nivolumab

- 11 R/R NHL (10 DLBCL- 1 burkitt)
- 4-1BB domain-Lentiviral CAR-T. CY-FLU.
lenfodeplezyon
- 3 mg/kg PD-1 inh. CAR-T infüzyonundan 3 gün sonra
- Grade 1-2 CRS%25
- 1 hastada nörotoksisite

Cao Y et al. Front Oncol 2019 Aug 19;9:767



CAR-T ve kutanöz T hücreli lenfomalar



Challenge	A T cell aplasia	B Fratricide	C Product contamination
Mechanism	<p>"On-target off-tumor" toxicity Normal T cells → T cell aplasia - Immunodeficiency Tumor T cells → Tumor eradication</p>	<p>killing</p>	<p>CAR construct transduction CART product CAR tumor contamination</p>
Possible solution	<ul style="list-style-type: none"> Targeting T cell subsets Hematopoietic Stem Cell Transplant (HSCT) Short-lived CAR T cells Incorporation of a safety switch 	<ul style="list-style-type: none"> Gene editing, knocking out antigen on CAR T cell surface Targeting downregulated antigens Using NK cells 	<ul style="list-style-type: none"> Using allogeneic T cells Using NK cells

CAR-T ve kutanöz T hücreli lenfomalar

	Target antigen	CAR construct	Modifications	Models	Clinical trials	Ref
CAR T cells	CD4	α CD4 CD28 41BB CAR	–	<i>in vitro</i> : KARPAS-299; Sézary syndrome, PTCL <i>in vivo</i> : KARPAS-299	–	
	CD5	α CD5 CD28 CAR	–	<i>in vitro</i> : MOLT-4, CCRF-CEM, Jurkat, HuT78, SUP-T1; T-ALL <i>in vivo</i> : Jurkat	–	
		α CD5 41BB CAR	–	<i>in vitro</i> : CCRF-CEM, Jurkat <i>in vivo</i> : Jurkat	–	
	CD7	α CD7 CD28 CAR	CD7 CRISPR/Cas9 KO	<i>in vitro</i> : MOLT-4, CCRF, Jurkat, HuT78, SUP-T1; T-ALL <i>in vivo</i> : CCRF-CEM	NCT03690011	
		α CD7 41BB CAR	CD7 protein expression blocker (PEBL)	<i>in vitro</i> : MOLT-4, CCRF-CEM, Jurkat, Loucy, KG1a <i>in vivo</i> : CCRF-CEM; ETP-ALL PDX		
		α CD7 C CD28 41BB AR	CD7, TRAC CRISPR/Cas9 KO	<i>in vitro</i> : MOLT-4, MOLT-3, HSB-2, T-ALL <i>in vivo</i> : CCRF-CEM; T-ALL PDX		
	CD30	α CD30 CD28 CAR	–	<i>in vitro</i> : KARPAS-299, HDLM-2, L428, L540, KH-M2, L1236 <i>in vivo</i> : KARPAS-299	NCT03049449, NCT01316146, NCT02690545, NCT02917083	
	CD37	α CD37 41BB CAR	–	<i>in vitro</i> : FEPD, HuT78, PTCL	–	
	CCR4	α CCR4 41BB CAR	–	<i>in vitro</i> : HH, HuT78, ML, HuT102, JB-6, Karpas299, SUDHL-1, SR-786, SUP-M2, DEL, Mac-1, Mac-2A, Mac-2B <i>in vivo</i> : ATL41214	–	
	TRBC1	α TRBC1 CD28-OX40 CAR	–	<i>in vitro</i> : T-PLL, PTCL-NOS, ATLL <i>in vivo</i> : Jurkat	NCT0359054	
	TRBC2	α TRBC2 CD28-OX40 CAR	–	<i>in vitro</i> : Loucy, MOLT13, BE13 <i>in vivo</i> : Loucy	–	
CAR NK cells	CD3	α CD3 41BB CD28 CAR	NK-92 cells	<i>in vitro</i> : KARPAS-299, CCRF-CEM, Jurkat; PTCL, Sézary syndrome <i>in vivo</i> : Jurkat	–	
	CD4	α CD4 CD28 41BB CAR	NK-92 cells	<i>in vitro</i> : KARPAS-299, HL60, CCRF-CEM; Sézary syndrome, T-ALL <i>in vivo</i> : KARPS-299	–	
	CD5	α CD5 41BB CD28 CAR	NK-92 cells	<i>in vitro</i> : MOLT-4, CCRF-CEM, Jurkat; T-ALL, Sézary syndrome <i>in vivo</i> : Jurkat	NCT03081910	
	CD7	α CD7 CD28 41BB CAR	NK-92 cells		NCT02742727	

Scarfo I et al. Front Oncol.2019 Apr.16;9;259

DLBCL da tedavi maliyet analizi

Table 6. Cost and cost-effectiveness studies for CAR T cells in DLBCL treatment.

Study	Location	Intervention of interest	Indication	Comparator therapy	Mean total cost (2019 USD)	ICER (2019 USD)	Conclusion	Comments
Tico, et al. [142]	USA	Axicabtagene ciloleucel	R/R B-cell lymphoma in patients ineligible for autologous HCT	Salvage chemotherapy	Axicabtagene ciloleucel, \$817,000; chemotherapy, \$155,000	\$136,000/QALY	Cost-effective assuming a cure for patients who exhibited complete response after five years	Authors advise collecting additional information regarding long-term response rates
Roth, et al. [143]	USA	Axicabtagene ciloleucel	R/R large B-cell lymphoma	Salvage chemotherapy	Axicabtagene ciloleucel, \$550,000; chemotherapy, \$170,000	\$58,000/QALY	Cost-effective	Funded by the manufacturer of axicabtagene ciloleucel
NICE [144]	United Kingdom	Axicabtagene ciloleucel	DLBCL after ≥ 2 systemic therapies	Salvage chemotherapy ± rituximab	Total discounted cost not reported due to confidential commercial arrangement	In excess of \$63,000/QALY	Potentially cost-effective given available data	Authors advise additional data are required regarding long-term outcomes and usage of IVIG
NICE [145]	United Kingdom	Tisagenlecleucel	R/R DLBCL after ≥ 2 systemic therapies	Salvage chemotherapy	Total discounted cost not reported due to confidential commercial arrangement	Range: \$55,000/QALY to \$70,000/QALY	Potentially cost-effective given available data	Significant uncertainty; authors advise that additional data regarding outcomes and IVIG are required for more robust estimates
Whittington, et al. [146]	USA	Axicabtagene ciloleucel	Refractory DLBCL	Chemotherapy	Axicabtagene ciloleucel: public payers, \$459,700–\$554,700; commercial, \$554,000–\$648,900; chemotherapy, public, \$108,600–\$151,200; commercial, \$114,500–\$157,000	Public: \$82,400–\$230,900/QALY; commercial: \$100,400–\$289,000/QALY	Additional outcomes data are required for more precise estimates	Wide ranges in cost and ICER values are due to differences in long-term survival estimates from the five utilized models
Lin, et al. [147]	USA	Axicabtagene ciloleucel	R/R adult DLBCL	Salvage chemotherapy and HCT	Axicabtagene ciloleucel, \$659,000–\$677,000; chemotherapy and HCT, \$175,000	\$133,000–\$200,000/QALY	Potentially cost-effective given available data	Significant uncertainty in estimates using presently available data
		Tisagenlecleucel	R/R adult DLBCL	Salvage chemotherapy and HCT	Tisagenlecleucel, \$538,000–\$547,000; chemotherapy and HCT, \$175,000	\$174,000–\$348,000/QALY	Potentially cost-effective given available data	Significant uncertainty in estimates using presently available data

Abbreviations: CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; HCT, hematopoietic cell transplant; ICER, incremental cost-effectiveness ratio; IVIG, intravenous immunoglobulin; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; R/R, relapsed/refractory; USD, US dollars

Table 5. Cost and cost-effectiveness studies for hematopoietic cell transplant in DLBCL treatment.

Study	Location	Intervention of interest	Indication	Comparator therapy	Mean total cost (2019 USD)	ICER (2019 USD)	Conclusion
Kymes, et al. [115]	USA	G+P	Stem cell mobilization for autologous HCT in patients with relapsed DLBCL	G-CSF alone	G+P, \$104,000; G-CSF alone, \$75,000	\$16,000/QALY	Cost-effective
Maziarz, et al. [116]	USA	Allogeneic HCT	Refractory or relapsed DLBCL after chemotherapy or autologous HCT	–	First year after HCT administration, per-patient: \$490,787	–	Significant economic burden following allogeneic HCT

Abbreviations: G+P, G-CSF plus plerixafor; G-CSF, granulocyte-colony stimulating factor; HCT, hematopoietic cell transplant; DLBCL, diffuse large B-cell lymphoma; ICER, incremental cost-effectiveness ratio; USD, US dollars; QALY, quality-adjusted life year

Harkins RA et. Al. Expert Review of Pharmacoeconomics and Outcomes Research 22 october

CAR-T –Lenfoma da bizi neler bekliyor?

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Neelapu SS et al. N Engl J Med. (2017)

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1. Cahill KE, Leukam MJ, Riedell PA.
Leuk Lymphoma. 2019 Nov 21:1-9. doi: 10.1080/10428194.2019.1691201. [Epub ahead of print]
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2. Lopci E, Meignan M.
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3. Schuster SJ, Bartlett NL, Assouline S, Yoon SS, Bosch F, Sehn LH, Cheah CY, Shadman M, Gregory CB, Ku M, Wei MC, Yin S, Kwan A, Younes K, Hernandez C, Li CC, O'Hear C, Budd LE

CAR-T –Lenfoma da bizi neler bekliyor?

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Locations:			• The west area of the First Affiliated Hospital of University of Science & Technology China Hefei, Anhui, China		
2	<input type="checkbox"/>	Not yet recruiting	Study Evaluating the Efficacy and Safety With CAR-T Immunotherapy for CD19 Positive Lymphoma	• Lymphoma	• Biological: The Chimeric Antigen Receptor T Cell Immunotherapy (CAR-T)
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3	<input type="checkbox"/>	Unknown †	Study Evaluating the Efficacy and Safety With CAR-T for Recurrent or Refractory Diffuse Large B Cell Lymphoma	• Lymphoma	• Biological: CD19-targeted CAR-T cells
Locations:			• The First Affiliated Hospital of Anhui Medical University Hefei, Anhui, China		
4	<input type="checkbox"/>	Recruiting	A Study of C-CAR066 in Subjects With r/r B Cell Lymphoma Who Received CD19 CAR-T Therapy	• B Cell Lymphoma	• Biological: CD20-directed CAR-T cells
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6	<input type="checkbox"/>	Recruiting	MC-19PD1 CAR-T in Relapsed or Refractory B Cell Lymphoma	• Lymphoma	• Biological: MC-19PD1 CAR-T cells