6. Hematolojik Onkoloji Kongresi

Birinci Tam Remisyondaki ALL - Transplant Şart Mı?

Dr Selami Koçak TOPRAK
Ankara Üniversitesi Tıp Fakültesi Hematoloji BD

21 Eylül 2019, Girne, KKTC

Akut Lenfoblastik Lösemi

2019

Tedavi

pediatric-inspired chemotherapy regimens

assessments for measurable residual disease (MRD)

novel targeted and immune therapeutics

Tedavi yanıtı

Akıbet

DeFilipp Z, et al. Biol Blood Marrow Transplant. 2019. pii: S1083-8791(19)30528-2.

Klasik bilgi

Bizim ilgilendiğimiz yaş grubunda ALL akıbeti kötüdür

Sağkalım > %90

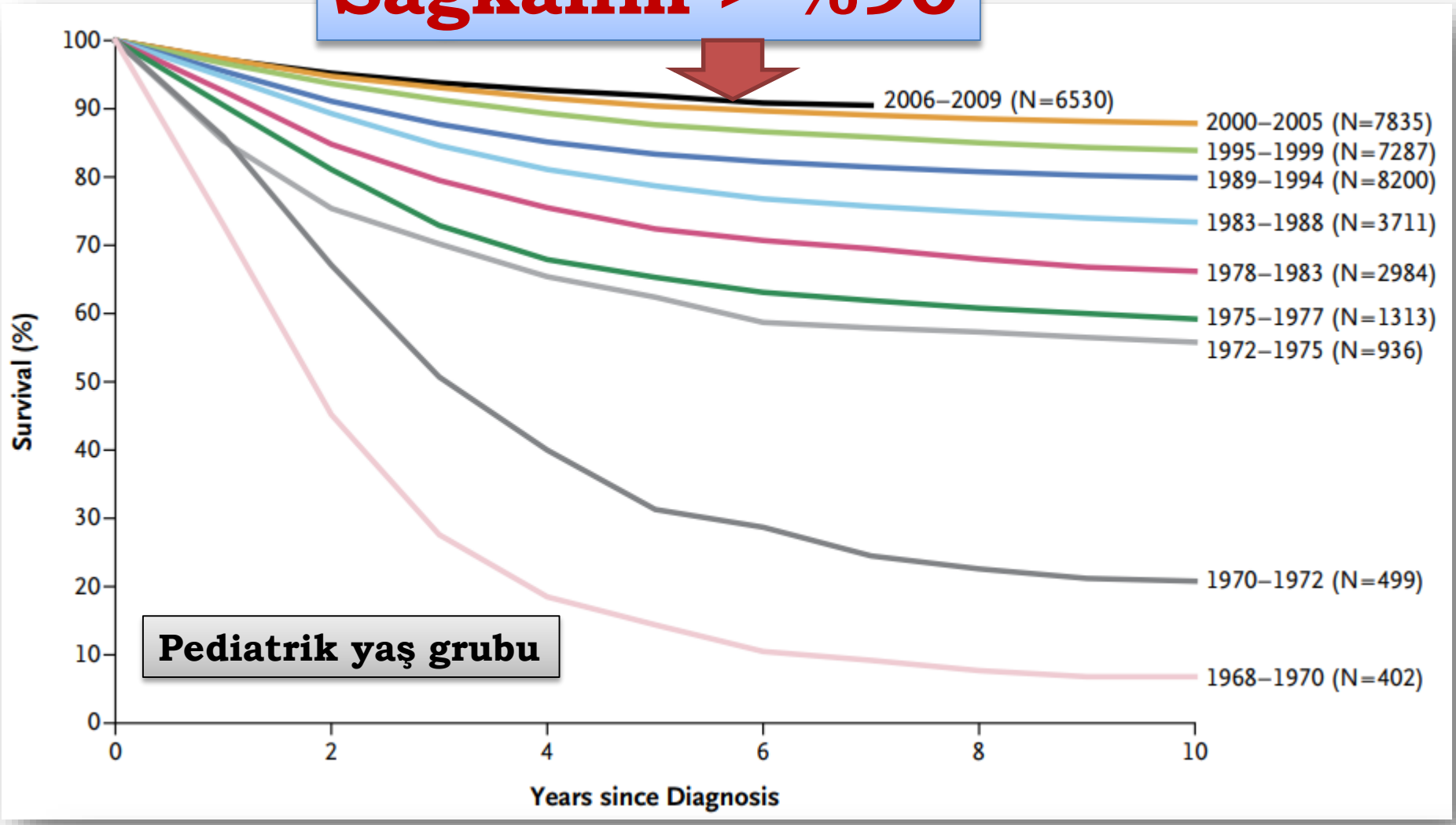


Figure 1. Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.

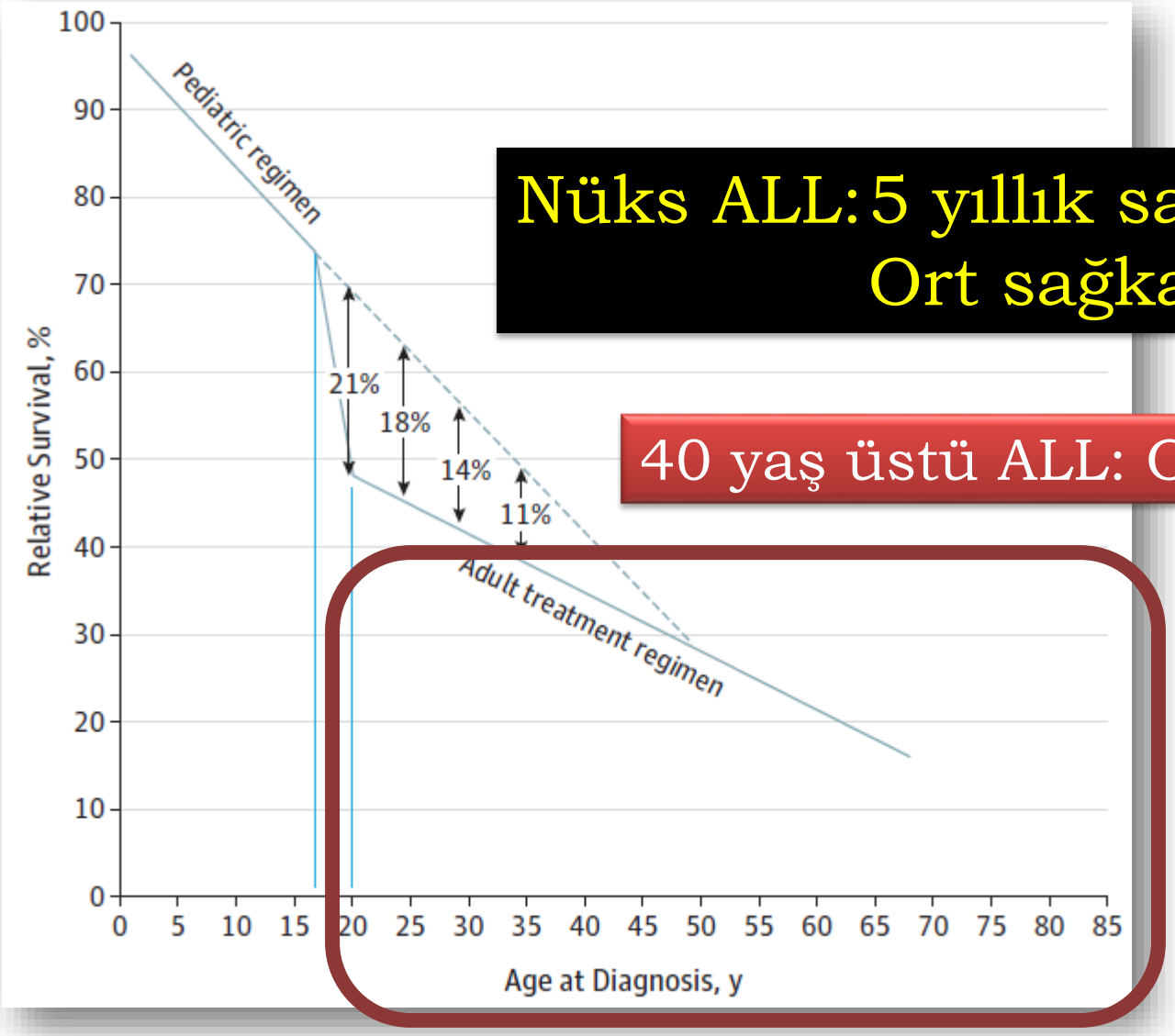
Hunger SP, et al. N Engl J Med. 2015;373(16):1541-52.

Antibody-based therapies in patients with acute lymphoblastic leukemia

Shira Dinner[1] *and Michaela Liedtke*[2]

[1]*Division of Hematology/Oncology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; and* [2]*Division of Hematology, Department of Medicine, Stanford University School of Medicine, Stanford, CA*

Traditionally, the management of acute lymphoblastic leukemia (ALL) has relied on intensive multiagent cytotoxic chemotherapy followed by either prolonged maintenance or allogeneic stem cell transplantation. With this approach, >90% of children and ~40% of adults will survive, while the remaining patients succumb to their disease or treatment-related toxicity.



Nüks ALL: 5 yıllık sağkalım < %10
Ort sağkalım ≈ 6 ay

40 yaş üstü ALL: OS %30-40 ve ↓

Siegel SE, et al. JAMA Oncol. 2018;4(5):725-734.
Paul S, et al. Clin Adv Hematol Oncol. 2019;17(3):166-175.
Guerra VA, et al. Ther Adv Hematol. 2019;10:2040620719849496.

Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies

Nicola Gökbuget, Michael Kneba, Thorsten Raff, Heiko Trautmann, Claus-Rainer Bartram, Renate Arnold, Rainer Fietkau, Mathias Freund, Arnold Ganser, Wolf-Dieter Ludwig, Georg Maschmeyer, Harald Rieder, Stefan Schwartz, Hubert Serve, Eckhard Thiel, Monika Brüggemann and Dieter Hoelzer, on behalf of the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia


Nicola Gokbuget, MD

Blood. 2012;120(9):1868-76.

Hastaların yaklaşık **%40-50**'si
(bilinen kötü risk özellikleri taşımayan **standart riskli hastalar da dahil**)
nüks olmaktadır.
Nihayetinde bu hastaların sağ kalımı %10'un altına inmektedir

Reduction of relapse rate is therefore the main aim of treatment optimization in ALL.

One approach is to **identify patients in clinical complete remission with high risk of relapse** as candidates for early treatment intensification, including allogeneic stem cell transplantation.

Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies

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Nicola Gokbuget, MD

Blood. 2012;120(9):1868-76.

Response to standard induction treatment has been proven to be the most important factor in predicting outcome and risk of relapse.

Response to standard induction treatment

İki belirgin prognostik etken öne çıkmaktadır

- **CR'nin sitolojik konfirmasyonu**
- **CR'nin elde edilme zamanı önemli**

Minimal kalıntı hastalık
Ölçülebilir kalıntı hastalık

Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies

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Nicola Gokbuget, MD

Blood. 2012;120(9):1868-76.

15-55 yaş grubu ALL hastasında

Konsolidasyon tedavisi sonrası

MRD (+) olan
- 5 yıllık nükssüz sağ kalım **%25**

MRD (-) olan
- 5 yıllık nükssüz sağ kalım **%67**

GMALL

Received: 24 October 2018 | Accepted: 31 October 2018
DOI: 10.1002/ajh.25338

WILEY AJH

CRITICAL REVIEW

Am J Hematol. 2019;94(2):257-265.

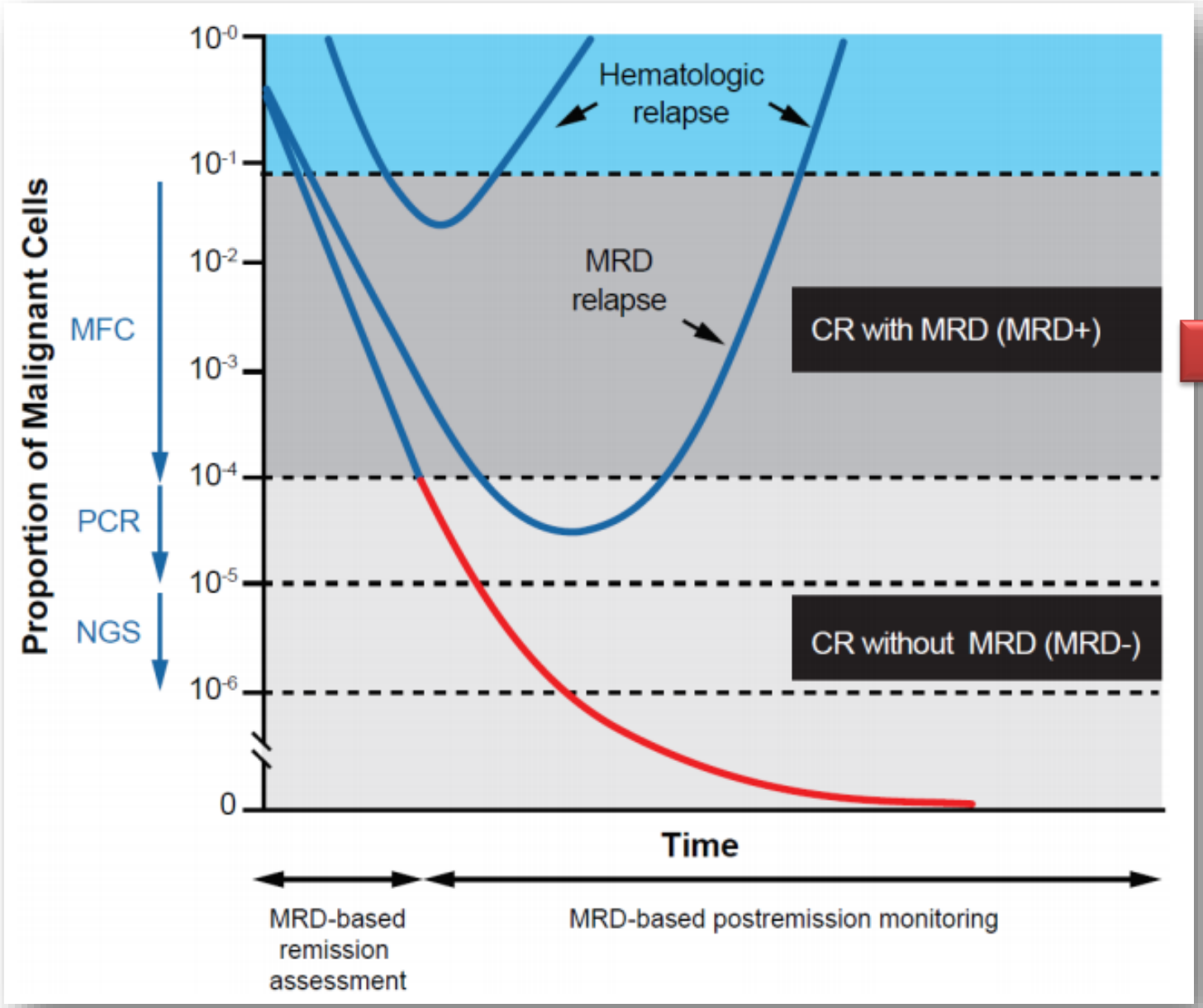
Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts

Nicholas J. Short[1] | Elias Jabbour[1] | Maher Albitar[2] | Marcos de Lima[3] | Lia Gore[4] | Jeffrey Jorgensen[1] | Aaron C. Logan[5] | Jae Park[6] | Farhad Ravandi[1] | Bijal Shah[7] | Jerald Radich MD[8] | Hagop Kantarjian[1]

ARTIK BİLİYORUZ

İlk sıra tedaviden sonra saptanan
"ölçülebilir kalıntı hastalık" (ya da minimal kalıntı hastalık), ALL'de nüks ve sağ kalımın güçlü bir belirleyicisi/işaretidir

Bu durumun
- klinik pratikte kullanımı ya da
- tedavi kararındaki yeri



Short NJ, et al. Am J Hematol. 2019;94(2):257-265.

ALL'de

Response category	BM blasts	ANC per µL	Platelets per µL
CR	≤ 5%	> 1,000	> 100,000
CR with partial haematological recovery (CRh)	≤ 5%	> 500[a]	> 50,000[a]
CR with incomplete haematological recovery (CRi)	< 5%	< 1,000[b] **or**	< 100,000[b]
CR with incomplete platelet recovery (CRp)	< 5%	> 1,000	< 100,000
MRD response/MRD-negativity	< 0.01% and < 10^{-4}		

[a]But not achieving CR. [b]But not achieving CRh. ANC, absolute neutrophil count

Post-remisyon MRD durumu, post-remisyon tedavi stratejisini belirlemeli

Örneğin: İlk remisyonda MRD (+) ise alloTX'e gitmek gibi

MRD (+) olan hastalar için
5 yıllık nükssüz sağ kalım
- Allo-tx ile **%44**
- Allo-tx yoksa **%11**

Ne yazık ki, erken nüks nedeni ile ancak %50'den daha az hasta allo-tx'e gidebilmekte

Gökbuget N, et al. Blood. 2012;120(9):1868-76.

Ama alloTx'e MRD (+) mi gitmeli, yoksa????

Birinci tam remisyondaki Philadelphia kromozomu **negatif** ALL'de hematopoietik kök hücre nakli

Rutin MRD değerlendirmesi öncesi çalışmalar

Genellikle 1980-90'lı yıllardaki çalışmalar

1. tam remisyondaki hastalar

Donor vs no donor çalışmalar

MSD vs YOK

Allo-Tx

Otolog / konvansiyonel KT

Bordeaux-Grenoble-Marseille-Toulouse study
GOELAL02 trial
HOVON-18/37 trial

Allo-Tx vs otolog-Tx

Lösemisiz sağ kalım açısından allo-Tx kolu üstün

Rutin MRD değerlendirmesi öncesi çalışmalar

Genellikle 1980-90'lı yıllardaki çalışmalar

1. tam remisyondaki hastalar

Donor vs no donor çalışmalar

MSD vs YOK

Allo-Tx

Otolog / konvansiyonel KT

LALA-87 study
LALA-94 study

1. TR sonrası

Allo-Tx

Otolog / konvansiyonel KT

	OS (10 yıllık)	p
Allo-Tx yapılan	%46	0,004
Allo-Tx yapılamayan	%31	

Rutin MRD değerlendirmesi öncesi çalışmalar

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1. tam remisyondaki hastalar

Donor vs no donor çalışmalar

MSD vs YOK

Allo-Tx

Otolog / konvansiyonel KT

LALA-87 study
LALA-94 study

1. TR sonrası

Allo-Tx

Otolog / konvansiyonel KT

	OS (10 yıllık)
Yüksek risk	**p 0,009**
Standart risk	**p 0,006**

Rutin MRD değerlendirmesi öncesi çalışmalar

Genellikle 1980-90'lı yıllardaki çalışmalar

1. tam remisyondaki hastalar

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Allo-Tx

Otolog / konvansiyonel KT

LALA-87 study
LALA-94 study

1. TR sonrası

Allo-Tx

Otolog / konvansiyonel KT

Ph (+) ve Ph (-)

Her iki grupta da
allo-Tx yapılması 3 yıllık lösemisiz sağ kalım açısından ÜSTÜN

Rutin MRD değerlendirmesi öncesi çalışmalar

Genellikle 1980-90'lı yıllardaki çalışmalar

1. tam remisyondaki hastalar

Donor vs no donor çalışmalar

MSD vs YOK

Allo-Tx

Otolog / konvansiyonel KT

MRC UKALL XII/ECOG 2993

n=1646

Std risk
Yüksek risk

2 faz ind tedavisi

MSD vs YOK

Allo-Tx

Otolog / 2,5 yıl konvansiyonel KT

Rutin MRD değerlendirmesi öncesi çalışmalar

Genellikle 1980-90'lı yıllardaki çalışmalar

1. tam remisyondaki hastalar

Donor vs no donor çalışmalar

MSD vs YOK

Allo-Tx

Otolog / konvansiyonel KT

MRC UKALL XII/ECOG 2993

Ph negatif

	OS (5 yıllık)	p
Allo-Tx yapılan	%53	0,001
Allo-Tx yapılamayan	%45	

Rutin **MRD değerlendirmesi dönemi** çalışmaları

Blood. 2009 Apr 30;113(18):4153-62. doi: 10.1182/blood-2008-11-185132. Epub 2009 Jan 13.

Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL).

Bassan R[1], Spinelli O, Oldani E, Intermesoli T, Tosi M, Peruta B, Rossi G, Borlenghi E, Pogliani EM, Terruzzi E, Fabris P, Cassibba V, Lambertenghi-Deliliers G, Cortelezzi A, Bosi A, Gianfaldoni G, Ciceri F, Bernardi M, Gallamini A, Mattei D, Di Bona E, Romani C, Scattolin AM, Barbui T, Rambaldi A.

Author information

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MRD sonucuna göre tedavi kararı verilen ilk prospektif çalışma

Sadece Ph (+) ve MLL (+): Hızlıca allo-Tx'e yönlendirildiler

Geri kalanlar

16. haftada PCR ile MRD düşük/negatif olanlar

22. haftada PCR ile MRD negatif olanlar

KT ile devam ettiler

Geri kalanlar

Bu kriterleri karşılamayanlar

Allo-Tx ile devam ettiler

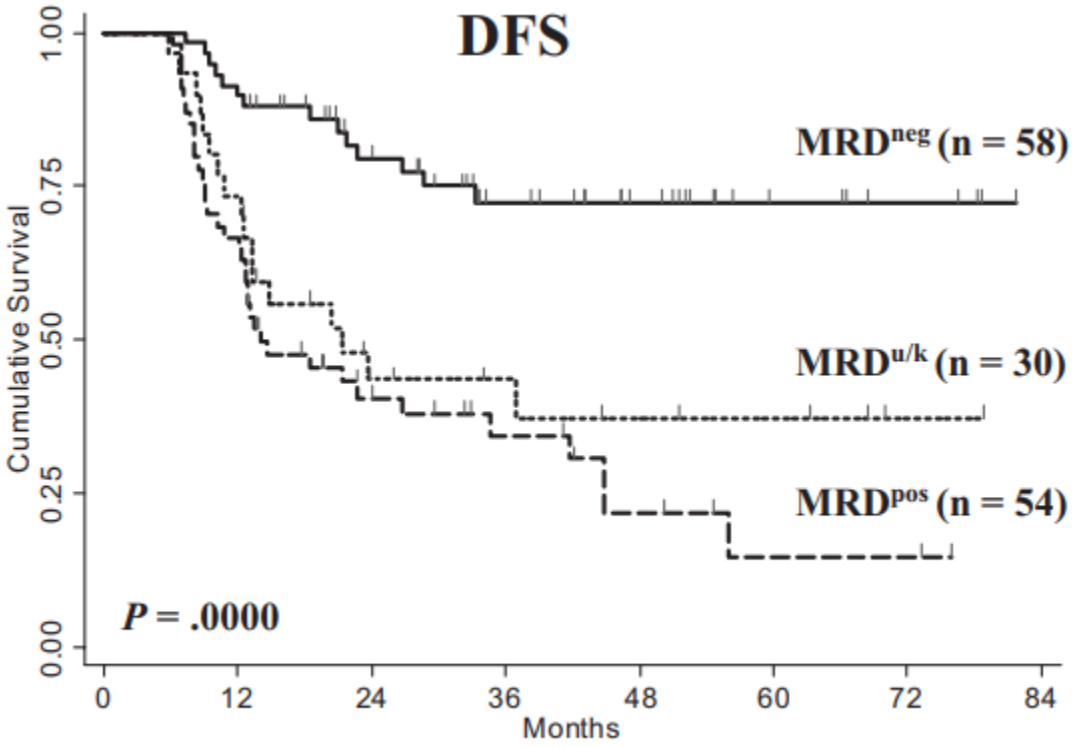


Figure 3. DFS according to MRD study results.

Hastalıksız sağ kalım MRD negatif grupta (allo-Tx YOK) belirgin yüksek

J Clin Oncol. 2014 May 20;32(15):1595-604. doi: 10.1200/JCO.2013.52.2425. Epub 2014 Apr 21.

Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial.

Ribera JM[1], Oriol A[2], Morgades M[2], Montesinos P[2], Sarrà J[2], González-Campos J[2], Brunet S[2], Tormo M[2], Fernández-Abellán P[2], Guàrdia R[2], Bernal MT[2], Esteve J[2], Barba P[2], Moreno MJ[2], Bermúdez A[2], Cladera A[2], Escoda L[2], García-Boyero R[2], Del Potro E[2], Bergua J[2], Amigo ML[2], Grande C[2], Rabuñal MJ[2], Hernández-Rivas JM[2], Feliu E[2].

Yüksek riskli, Ph negatif hastalar

14. günde blast < %10 (erken morfolojik yanıt)

Konsolidasyon sonu MRD < $5x10^{-4}$

KT ile devam ettiler

Geri kalanlar

Bu kriterleri karşılamayanlar

Allo-Tx ile devam ettiler

	5 yıllık DFS		OS
Allo-Tx	%32	p=0,002	%37
KT	%55		%59

Çoklu değişkenli analizde MRD olmaması, DFS ve OS için tek etkili faktör

Blood. 2015 Apr 16;125(16):2486-96; quiz 2586. doi: 10.1182/blood-2014-09-599894. Epub 2015 Jan 13.

Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia.

Dhédin N, Huynh A, Maury S, Tabrizi R, Beldjord K, Asnafi V, Thomas X, Chevallier P, Nguyen S, Coiteux V, Bourhis JH, Hichri Y, Escoffre-Barbe M, Reman O, Graux C, Chalandon Y, Blaise D, Schanz U, Lhéritier V, Cahn JY, Dombret H, Ifrah N; GRAALL group.

GRALL-2003 ve GRALL-2005

n=522
Yaş:15-55
Ph (-) yüksek riskli

Pediatric protocol

En az bir konvansiyonel yüksek risk varsa

MSD ya da URD varsa → Allo-Tx ile devam ettiler

MSD ya da URD yoksa → KT ile devam ettiler

Nükssüz sağ kalım açısından
allo-Tx yapılan ve yapılamayanlar arasında FARK YOK

Blood. 2015 Apr 16;125(16):2486-96; quiz 2586. doi: 10.1182/blood-2014-09-599894. Epub 2015 Jan 13.

Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia.

Dhédin N, Huynh A, Maury S, Tabrizi R, Beldjord K, Asnafi V, Thomas X, Chevallier P, Nguyen S, Coiteux V, Bourhis JH, Hichri Y, Escoffre-Barbe M, Reman O, Graux C, Chalandon Y, Blaise D, Schanz U, Lhéritier V, Cahn JY, Dombret H, Ifrah N; GRAALL group.

GRALL-2003 ve GRALL-2005

n=522
Yaş:15-55
Ph (-) yüksek riskli

Pediatric protocol

En az bir konvansiyonel yüksek risk varsa

MSD ya da URD varsa

Allo-Tx ile devam ettiler

MSD ya da URD yoksa

KT ile devam ettiler

İndüksiyon sonrası MRD > 10^{-3} olup allo-Tx yapılanlarda ise lösemisiz sağ kalım, tx yapılamayan gruba göre anlamlı uzun

p=0,001

İndüksiyon sonrası MRD yanıtlılarda bu fark kaybolmakta

Bone Marrow Transplantation
https://doi.org/10.1038/s41409-018-0373-4

REVIEW ARTICLE

Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

Sebastian Giebel[1] · David I. Marks[2] · Nicolas Boissel[3] · Frederic Baron[4] · Sabina Chiaretti[5] · Fabio Ciceri[6] · Jan J. Cornelissen[7] · Michael Doubek[8] · Jordi Esteve[9] · Adele Fielding[10] · Robin Foa[5] · Norbert-Claude Gorin[11,12] · Nicola Gökbuget[1,3] · Helene Hallböök[13] · Dieter Hoelzer[14] · Elena Paravichnikova[15] · Josep-Maria Ribera[16] · Bipin Savani[17] · Anita W. Rijneveld[7] · Christoph Schmid[18] · Ulla Wartiovaara-Kautto[19] · Mohamad Mohty[10,11] · Arnon Nagler[10,20] · Hervé Dombret[3]

Received: 1 August 2018 / Revised: 8 October 2018 / Accepted: 10 October 2018

Table 1 Indications for HSCT in younger adults with Ph-negative ALL

Study group	Age (years)[a]	AlloHSCT	AutoHSCT	Method for MRD assessment	Preferred timing of alloHSCT
CELL (Czechia)	<65	At least one: •MRD $\geq 10^{-3}$ after induction •MRD $\geq 10^{-4}$ after consolidation	Option, if MRD negativity before 1st consolidation	PCR	After 1st cycle of consolidation
FALL (Finland)	<45	At least one: •WBC $>100 \times 10^9$/L •11q23 aberrrations •Hypodiploidy •B-lineage: – No CR after first course of induction – MRD $\geq 10^{-3}$ on day 79 •T-lineage: – Bone marrow blast count ≥25% on day 15 and ≥5% after block A of consolidation – MRD $\geq 10^{-3}$ after block B of consolidation	No	PCR and/or FC	After 1st cycle of consolidation
GIMEMA (Italy)	<65	At least one: •MRD positivity after consolidation •WBC $>100 \times 10^9$/L •Early/mature T-ALL, pro-B-ALL •t(4;11) •*MLL* rearrangement	Option, if MRD negativity after consolidation	PCR	After 1st cycle of consolidation

GMALL (Germany)	<55	At least one: •Common/pre-B-ALL and WBC $>30 \times 10^9$/L •Pro-B-ALL/*MLL* rearrangement •Early/mature T-ALL •No CR after induction I •MRD $\geq 10^{-4}$ after consolidation I	No	PCR	After 1st cycle of consolidation
GRAALL (France)	<60	At least one: •MRD $\geq 10^{-3}$ after induction •MRD $\geq 10^{-4}$ after consolidation	No	PCR	After consolidation
HOVON (The Netherlands)	<40	At least one: •MRD $\geq 10^{-4}$ during/after consolidation •No CR after first course of induction •Adverse cytogenetics •WBC $>30 \times 10^9$/L in B-ALL or WBC $>100 \times 10^9$/L in T-ALL	No	FC	After intensification 1
PALG (Poland)	<55	At least one: •MRD $\geq 10^{-3}$ after induction •MRD $\geq 10^{-4}$ during/after consolidation •WBC $>30 \times 10^9$/L in B-ALL or WBC $>100 \times 10^9$/L in T-ALL •*MLL* rearrangement •CNS involvement	Option, if all: •MRD $<10^{-3}$ after induction •MRD $<10^{-4}$ after consolidation	FC after induction PCR after consolidation	After consolidation
PETHEMA (Spain)	<55 (60 if "fit")	At least one: •MRD $>10^{-3}$ after induction •MRD $>10^{-4}$ during/after consolidation	No	FC	After 1st cycle of consolidation (if MRD$>10^{-3}$ after induction) After consolidation (if

Table 1 (continued)

Study group	Age (years)[a]	AlloHSCT	AutoHSCT	Method for MRD assessment	Preferred timing of alloHSCT
					MRD $>10^{-4}$ after consolidation)
RALL (Russia)	<55	B-cell ALL, at least one: •Age >30 years •WBC $>30 \times 10^9$/L •t(4;11), t(1;19) •MRD positivity during/after consolidation T-cell ALL: •*MLL* rearrangement	•T-cell ALL, except for *MLL* rearrangement	FC or PCR	After consolidation
SVALL (Sweden)	<65	At least one: •Leukemic blast count ≥5% after induction •MRD $\geq 10^{-3}$ after consolidation •Optionally for MLL rearrangement and hypodiploidy with low MRD level	No	B-cell ALL: FC T-cell ALL: PCR	After consolidation
UKALL (UK)	<40	At least one: •High initial WBC •Adverse cytogenetics •MRD $\geq 10^{-3}$ after two cycles of induction	No	PCR	After 2 cycles of induction

Avrupa'dan 11 farklı grup, 11 farklı davranış şekli

Yaş: 60-65 ↓

All-Tx için en önemli kriter MRD

FALL (Finland)	<45	At least one: •WBC $>100 \times 10^9$/L •11q23 aberrrations •Hypodiploidy •B-lineage: – No CR after first course of induction – MRD $\geq 10^{-3}$ on day 79 •T-lineage: – Bone marrow blast count ≥25% on day 15 and ≥5% after block A of consolidation – MRD $\geq 10^{-3}$ after block B of consolidation
GMALL (Germany)	<55	At least one: •Common/pre-B-ALL and WBC $>30 \times 10^9$/L •Pro-B-ALL/*MLL* rearrangement •Early/mature T-ALL •No CR after induction I •MRD $\geq 10^{-4}$ after consolidation I
GIMEMA (Italy)	<65	At least one: •MRD positivity after consolidation •WBC $>100 \times 10^9$/L •Early/mature T-ALL, pro-B-ALL •t(4;11) •*MLL* rearrangement

Avrupa'dan 11 farklı grup, 11 farklı davranış şekli

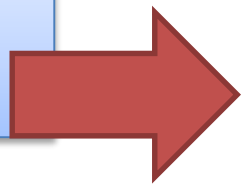
Yaş: 60-65 ↓

All-Tx için en önemli kriter MRD

MRD eşik değeri de farklı
MRD tetkik etme zamanı da farklı

Çoğunluk için ANLAMLI olan
İnd sonrası > 10^{-3}
Konso sonrası > 10^{-4}

Flowsitometrik yöntemler
PCR tabanlı yöntemler



Daha anlamlı kabul edilmekte

Avrupa'dan 11 farklı grup, 11 farklı davranış şekli

Yaş: 60-65 ↓

All-Tx için en önemli kriter MRD

4 grup MRD negatif olanlara otolog Tx de önermekte

European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

Ne öneriyor?

Ph negatif ALL'de allo-Tx nüksü önlemede etkili bir tedavi yöntemidir

Ph negatif ALL'de, 1. TR'de allo-Tx yüksek nüks riski olan hastalara önerilir

Yüksek nüks riski olan:
En güçlü belirleyici MRD'dir

Ph negatif ALL'de, 1. TR'de allo-Tx MRD olan hastalara önerilmelidir

MRD, ind sonrası **< 10^{-3} olmalıdır**
MRD, kons sonrası **olmamalıdır**

MRD hariç diğer etkenler: Tanıdaki lökosit sayısı, ek mutasyonlar, kötü immünofenotip, vb merkezin deneyimine göre değişebilir

European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

Ne öneriyor?

Yoğun KT protokolleri (pediatric inspired) uygulanıp MRD negatif olan
Başka risk etkenleri olsa bile

Allo-Tx önerilmeyebilir

Uygun verici

MSD – MUD tercih edilir

Yüksek nüks riski olanlarda bunlar yoksa

olabilir

MM related (haplo dahil)

MM unrelated

European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

Ne öneriyor?

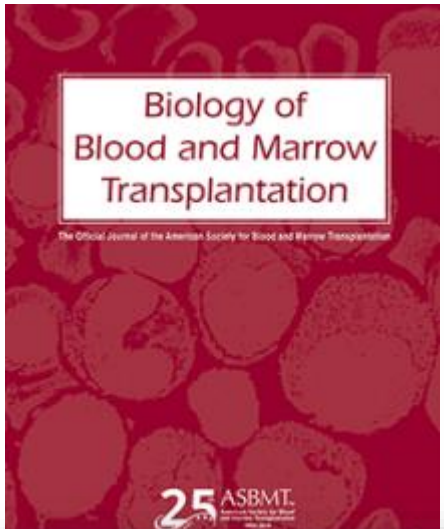
Bugünkü konumuzdan bağımsız ama

Genç hastalarda TBI tabanlı ablatif hazırlık tedavisi

- TBI-Cy
- TBI-etopozid

Yaşlı/komorbiditesi olanlarda

- TBI tabanlı RIC



ASTCT

formerly ASBMT

American Society for
Transplantation and Cellular Therapy

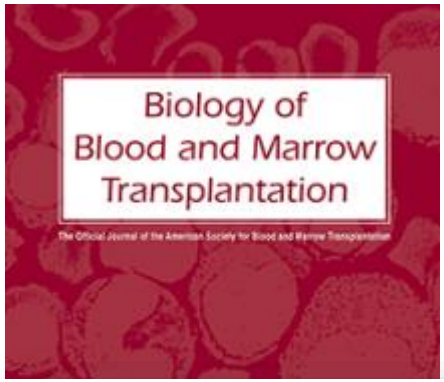
Biol Blood Marrow Transplant. 2019 Aug 22. pii: S1083-8791(19)30528-2. doi: 10.1016/j.bbmt.2019.08.014. [Epub ahead of print]

Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Updated 2019 Evidence-Based Review from the American Society for Transplantation and Cellular Therapy.

DeFilipp Z[1], Advani AS[2], Bachanova V[3], Cassaday RD[4], Deangelo DJ[5], Kebriaei P[6], Rowe JM[7], Seftel MD[8], Stock W[9], Tallman MS[10], Fanning S[11], Inamoto Y[12], Kansagra A[13], Johnston L[14], Nagler A[15], Sauter CS[10], Savani BN[16], Perales MA[10], Carpenter PA[17], Larson RA[9], Weisdorf D[3].

Table 1. Transplant Indications

	Recommendation	Grade of Recommendation	Highest Level of Evidence
Ph-negative disease			
Should allo-HCT be offered for standard-risk ALL adults in CR1?	Unclear	A	1++
Should allo-HCT be offered for high-risk ALL adults in CR1?	Yes	A	1++



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formerly ASBMT

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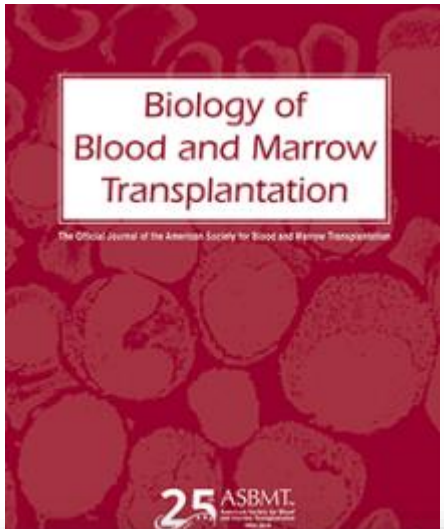
Table 1. Transplant Indications

	Recommendation	Grade of Recommendation	Highest Level of Evidence
Adolescents and young adults with Ph-negative disease			
Should allo-HCT be considered for AYA with otherwise standard-risk, MRD-negative ALL in CR1 if treated with pediatric-inspired regimens?	No	A	1++
Should allo-HCT be considered for AYA in CR1 with high-risk features or persistent MRD after induction?	Yes	A	1++



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Otolog Tx önerilmiyor

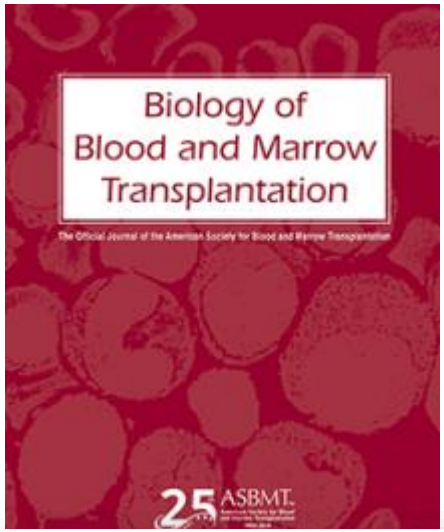

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Table 2. Disease- and Transplant-related Factors

	Recommendation	Grade of Recommendation	Highest Level of Evidence
Measurable residual disease			
Should the presence of MRD positivity be considered an indication to offer allo-HCT?	Yes	B	2++

Biology of Blood and Marrow Transplantation

Conditioning regimen			
Should a myeloablative regimen be the preferred conditioning intensity in fit patients?	Yes	C	2+
Should the preferred myeloablative regimen include TBI?	Yes	C	2+
Are RIC regimens an acceptable alternative for adults considered unfit for myeloablative regimens?	Yes	D	2+
Alternative donors			
Can umbilical cord blood and haploidentical relatives be considered as alternative donor options?	Yes	C	2+
Graft source			
Should PBSC, BM, and UCB be considered graft options for allo-HCT?	Yes	B	1+
Is there a preferred graft source for HLA-matched donor allo-HCT?	No	B	1+

Birinci tam remisyondaki Philadelphia kromozomu **pozitif** ALL'de hematopoietik kök hücre nakli

Best Pract Res Clin Haematol. 2018 Dec;31(4):357-360. doi: 10.1016/j.beha.2018.09.004. Epub 2018 Sep 20.

Allogeneic transplantation for patients with Philadelphia chromosome positive acute lymphoblastic leukemia: Is it imperative in the tyrosine kinase inhibitor era?

Litzow MR[1].

Author information

1 Division of Hematology and Blood and Marrow Transplant, Mayo Clinic, 200 1st Street South West, Rochester, MN 55905, USA. Electronic address: litzow.mark@mayo.edu.

	Erişkin	Çocuk
Ph kromozomu varlığı	%30-40	%2-3

Ph kromozomu varlığı	**Erişkin > 60 yaş** **%50**

Curr. Treat. Options in Oncol. (2019) 20:4
DOI 10.1007/s11864-019-0603-z

CrossMark

Leukemia (PH Wiernik, Section Editor)

Treatment of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

Iman Abou Dalle, MD
Elias Jabbour, MD
Nicholas J. Short, MD
*Farhad Ravandi, MD**

Ph kromozomu varlığı

Düşük yanıt oranları

Yüksek nüks oranları

< %25 uzun dönem sağ kalım

Ort sağ kalım max 8 ay (std KT ile)

Tek potansiyel küratif seçenek allo-Tx idi yıllarca

Uzun dönem sağ kalım oranları max %35 gibi

Azımsanmayacak morbidite-mortalite ile birlikte

Litzow MR. Best Pract Res Clin Haematol. 2018 Dec;31(4):357-360.

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GRAAPH-2005 trial

Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia

Yves Chalandon, Xavier Thomas, Sandrine Hayette, Jean-Michel Cayuela, Claire Abbal, Françoise Huguet, Emmanuel Raffoux, Thibaut Leguay, Philippe Rousselot, Stéphane Lepretre, Martine Escoffre-Barbe, Sébastien Maury, Céline Berthon, Emmanuelle Tavernier, Jean-François Lambert, Marina Lafage-Pochitaloff, Véronique Lhéritier, Sylvie Chevret, Norbert Ifrah and Hervé Dombret, for the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL)

Blood 2015 125:3711-3719; doi: https://doi.org/10.1182/blood-2015-02-627935

İmatinib + indirgenmiş yoğunluklu KT komb.

İmatinib + HyperCVAD komb (STANDART KOL)

2 siklus ile maj mol yanıt olanlar

donör **var** vs **yok**

Allo-Tx

Otolog-Tx

n=268
Yaş: 47

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Yves Chalandon, Xavier Thomas, Sandrine Hayette, Jean-Michel Cayuela, Claire Abbal, Françoise Huguet, Emmanuel Raffoux, Thibaut Leguay, Philippe Rousselot, Stéphane Lepretre, Martine Escoffre-Barbe, Sébastien Maury, Céline Berthon, Emmanuelle Tavernier, Jean-François Lambert, Marina Lafage-Pochitaloff, Véronique Lhéritier, Sylvie Chevret, Norbert Ifrah and Hervé Dombret, for the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL)

Blood 2015 125:3711-3719; doi: https://doi.org/10.1182/blood-2015-02-627935

İmatinib + indirgenmiş yoğunluklu KT komb.

İmatinib + HyperCVAD komb (STANDART KOL)

	CR	p
İmatinib + ind KT	%98	0,006
İmatinib + HyperCVAD	%91	

n=268
Yaş: 47

	Maj Mol yanıt	p
İmatinib + ind KT	%66	NS
İmatinib + HyperCVAD	%64	

5 yıllık EFS ve OS: FARKLI DEĞİL

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Blood 2015 125:3711-3719; doi: https://doi.org/10.1182/blood-2015-02-627935

İmatinib + indirgenmiş yoğunluklu KT komb.

İmatinib + HyperCVAD komb (STANDART KOL)

Allo-TX akıbeti?

Allo-Tx yapılanlarda nükssüz sağ kalım anlamlı fazla (p=0.036)
Allo-Tx yapılanlarda OS anlamlı fazla (p=0,02)

n=268
Yaş: 47

İlk sıra tedavi sonrası yanıt elde edilenlerde allo-Tx YARARLI

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GRAAPH-2005 trial

Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia

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Blood 2015 125:3711-3719; doi: https://doi.org/10.1182/blood-2015-02-627935

İmatinib + indirgenmiş yoğunluklu KT komb.

İmatinib + HyperCVAD komb (STANDART KOL)

Allo-TX akıbeti?

Ama ilk sıra tedavi sonrası tam yanıt (CR) sağlananlara bakarsak

n=268
Yaş: 47

Bu grupta nükssüz sağ kalım
allo-Tx yapılsın ya da yapılmasın FARKLI DEĞİL

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Retrospektif analiz

n=167

Outcomes of Adult Philadelphia Positive Acute Lymphoblastic Leukemia Patients Treated with Pediatric Multi–Agent Chemotherapy and Imatinib and the Impact of Residual Disease Monitoring on Survival

Solaf Sami Kanfar, Steven M. Chan, Vikas Gupta, Aaron D. Schimmer, Andre C. Schuh, Hassan Sibai, Karen W.L. Yee, and Mark D. Minden

Blood 2016 128:3976;

TKI-modified version of the Dana Farber Cancer Institute (DFCI) pediatric ALL protocol.

	5 yıllık nükssüz sağ kalım	**p**
Allo-Tx	%75	**0,033**
Allo-Tx YOK	%55	

	OS (ort)	**5 yıllık OS**	p
Allo-Tx	3,3 yıl	%40	**NS**
Allo-Tx YOK	5,3 yıl	%50	

blood advances

Blood Adv. 2016 Dec 27; 1(3): 250–259.
Published online 2016 Dec 19. doi: 10.1182/bloodadvances.2016001495

PMCID: PMC5642915
NIHMSID: NIHMS867643
PMID: 29046900

US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL

Farhad Ravandi,[✉1] Megan Othus,[2] Susan M. O'Brien,[3] Stephen J. Forman,[4] Chul S. Ha,[5] Jeffrey Y. C. Wong,[4] Martin S. Tallman,[6] Elisabeth Paietta,[7,8] Janis Racevskis,[7,8] Geoffrey L. Uy,[9] Mary Horowitz,[10] Naoko Takebe,[11] Richard Little,[11] Uma Borate,[12] Partow Kebriaei,[13] Laura Kingsbury,[2] Hagop M. Kantarjian,[1] Jerald P. Radich,[14] Harry P. Erba,[15] and Frederick R. Appelbaum[16]

18-60 yaş arası
Yeni tanı Ph (+) ALL
Dasatinib + HyperCVAD (8 siklusa kadar)

İlk CR'de

MSD / MUD olanlar: Allo-Tx + 100. günden itibaren dasatinib devam
Diğer grup: Vinc/pred (2 yıl) + dasatinib (süre?)

blood advances

Blood Adv. 2016 Dec 27; 1(3): 250–259.
Published online 2016 Dec 19. doi: 10.1182/bloodadvances.2016001495

PMCID: PMC5642915
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Tüm hastalar için:

3 yıllık OS	EFS	Nükssüz sağ kalım
%69	%55	%62

Allo-Tx hastaları için:

12 aylık OS	Nükssüz sağ kalım
%87	%71
p 0,037	p 0,038

Dasatinib + KT ve takiben alloTx etkili bir yöntemdir

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Blood. 2015 Aug 6;126(6):746-56. doi: 10.1182/blood-2015-03-636548. Epub 2015 Jun 11.

Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia.

Kim DY[1], Joo YD[2], Lim SN[2], Kim SD[1], Lee JH[1], Lee JH[1], Kim DH[3], Kim K[3], Jung CW[3], Kim I[4], Yoon SS[4], Park S[4], Ahn JS[5], Yang DH[5], Lee JJ[5], Lee HS[6], Kim YS[6], Mun YC[7], Kim H[8], Park JH[8], Moon JH[9], Sohn SK[9], Lee SM[10], Lee WS[10], Kim KH[11], Won JH[11], Hyun MS[12], Park J[13], Lee JH[13], Shin HJ[14], Chung JS[14], Lee H[15], Eom HS[15], Lee GW[16], Cho YU[17], Jang S[17], Park CJ[17], Chi HS[17], Lee KH[1]; Adult Acute Lymphoblastic Leukemia Working Party of the Korean Society of Hematology.

Yeni tanı Ph (+) ALL
Nilotinib + çoklu KT kombinasyonu

17-71 yaş
n=90

Hematolojik tam yanıt alanlar

MRD de takip edilmiş

Konsolidasyon + idame **vs** allo-Tx

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Hematolojik tam yanıt alanlar

	2 yıllık OS	p
Allo-Tx	%80	0,227
Non-alloTx	%72	

Farklı değil

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Moleküler tam yanıt alanlar

	2 yıllık moleküler nükssüz sağ kalım	p
Allo-Tx	%65	0,783
Non-alloTx	%53	

Farklı değil

Lancet Oncol. 2015 Nov;16(15):1547-1555. doi: 10.1016/S1470-2045(15)00207-7. Epub 2015 Sep 30.

Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study.

Jabbour E[1], Kantarjian H[2], Ravandi F[2], Thomas D[2], Huang X[3], Faderl S[2], Pemmaraju N[2], Daver N[2], Garcia-Manero G[2], Sasaki K[2], Cortes J[2], Garris R[2], Yin CC[4], Khoury JD[4], Jorgensen J[3], Estrov Z[2], Bohannan Z[2], Konopleva M[2], Kadia T[2], Jain N[2], DiNardo C[2], Wierda W[2], Jeanis V[2], O'Brien S[2].

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3 Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
4 Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Yeni tanı Ph (+) ALL
Ponatinib + HyperCVADkombinasyonu

Tam remisyon elde edilenler

Ponatinib idame ile devam edilmişler

Merkez/dr kararına göre allo-Tx serbest bırakılmış

2 yıllık EFS: %81

Lancet Oncol. 2015 Nov;16(15):1547-1555. doi: 10.1016/S1470-2045(15)00207-7. Epub 2015 Sep 30.

Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study.

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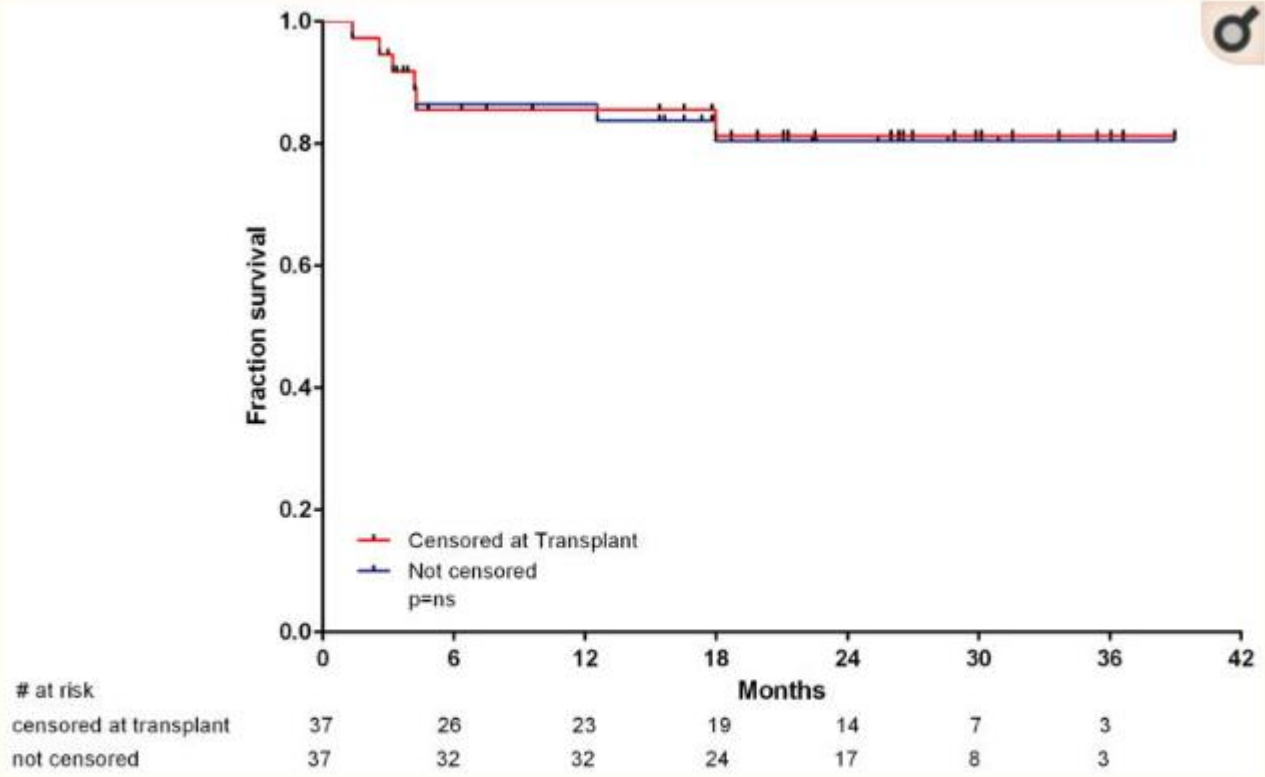

Figure 4

Outcome with and without censoring for ASCT.

OS, allo-Tx yapılan ya da yapılmayan grupta benzer

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Blood. 2016 Jul 28;128(4):504-7. doi: 10.1182/blood-2016-03-707562. Epub 2016 May 27.

Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia.

Short NJ[1], Jabbour E[2], Sasaki K[2], Patel K[3], O'Brien SM[4], Cortes JE[2], Garris R[2], Issa GC[1], Garcia-Manero G[2], Luthra R[3], Thomas D[2], Kantarjian H[2], Ravandi F[2].

Author information

1 Division of Cancer Medicine.
2 Department of Leukemia, and.
3 Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX; and.
4 Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA.

Yeni tanı Ph (+) ALL
TKI+ HyperCVADkombinasyonu

Çok dikkat çekici

	OS	p
İlk üç ay içinde CMR (+)	127 ay	**0,009**
İlk üç ay içinde CMR (-)	38 ay	

Çoklu değişkenli analizde, OS için tek anlamlı kriter

Kayıt çalışması: EBMT

Haematologica. 2015 Mar;100(3):392-9. doi: 10.3324/haematol.2014.116954. Epub 2014 Dec 19.

Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia.

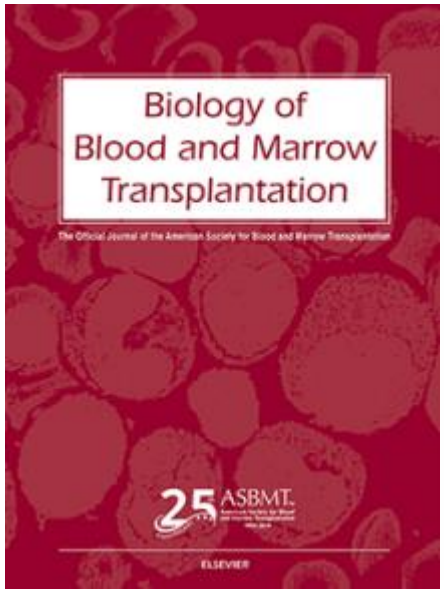
Brissot E[1], Labopin M[2], Beckers MM[3], Socié G[4], Rambaldi A[5], Volin L[6], Finke J[7], Lenhoff S[8], Kröger N[9], Ossenkoppele GJ[10], Craddock CF[11], Yakoub-Agha I[12], Gürman G[13], Russell NH[14], Aljurf M[15], Potter MN[16], Nagler A[17], Ottmann O[18], Cornelissen JJ[19], Esteve J[20], Mohty M[21].

n=473
Ph (+) ALL
İlk sıra tedavi ile tam remisyon elde edilenler

2000-2010 yılları
MSD/MUD

Allo-Tx'e gidenlerin akıbeti?

Allo-Tx öncesi TKI eklemek: OS ↑, nüks insidansını ↓



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American Society for
Transplantation and Cellular Therapy

Ph-positive disease			
Should allo-HCT be offered for Ph+ ALL in CR1 who receive tyrosine kinase inhibitors?	Yes	B	1+
Should allo-HCT be offered for Ph+ ALL in CR1 who receive tyrosine kinase inhibitors who obtain complete molecular remission?	Unclear	B	2++