ALL CR1: MRD değerlendirilemiyorsa ne yapmalı?

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Akut Lenfoblastik Lösemi

- Çocuklarda görülen en sık kanser (Tüm kanserlerin %23'ü, lösemilerin %76'sı)

  özellikle 15 yaş altında sık

- Erişkin akut lösemilerin %20'si
- Erişkinlerde E/K: 1.2/1
- İnsidansı: 1.5/100.000

Prognostik Faktörler

- Uzun yıllar standart risk faktörleri kullanıldı. Günümüzde tanımlanmış yeni prognostik faktörlerin ise yeni tedavi seçenekleri kullanılabilir olduğunda kullanılması öneriliyor.

Faktörler	Olumlu	Olumsuz
Yaş	<35	>35
Lökosit sayısı	<30.000/mikroL (B) <100.000/mikroL (T)	>30.000/mikroL (B) >100.000/mikroL (T)
Sitogenetik	Hiperdiploidi	Hipodiploidi (<44) Bcr-abl;MLL-AF4
CR eldesi	<4 hafta	>4 hafta
Moleküler remisyon	<%0.01	<%0.01

Table 19-1 Clinical and biologic characteristics of selected genetic subtypes of ALL.

Genetic abnormality	Frequency (%)		Estimated event-free survival (%)		Therapeutics
	Adult	Pediatric	Adult	Pediatric	
B-cell					
Hyperdiploidy >50 chromosomes	6-7	23-29	30-50 at 5 years	80-90 at 5 years	Antimetabolites
Hypodiploid <44 chromosomes	2	1	10-20 at 3 years	30-40 at 3 years	
t(8;14); t(2;8); t(8;22); *c-MYC* overexpression	5	2	50-80 at 3 years	75-85 at 3 years	Short-term intensive multiagent chemotherapy with rituximab
t(12;21)(p13;q22)/*ETV6-RUNX1* fusion	0-3	20-25	Unknown	85-95 at 5 years	Intensive asparaginase
t(1;19)(q23;p13.3)/*TCF3-PBX1* fusion	2-3	4-5	40-70 at 3 years	85-90 at 5 years	High-dose methotrexate
t(9;22)(q34;q11)/*BCR-ABL1* fusion	25-30	2-3	40-60 at 2 years	80-90 at 3 years	ABL1 tyrosine kinase inhibitors (imatinib/dasatinib)
t(4;11)(q21;q23)/*MLL-AF4* fusion	3-7	2	10-20 at 3 years	30-40 at 5 years	*FLT3* inhibitors (PKC412/CEP-701)
BCR-ABL1–like/*IKZF1* alterations	Unknown	15-20	Unknown	40-50 at 5 years	Tyrosine kinase inhibitors in some cases
iAMP21	Unknown	2	Unknown	60-70 at 5 years	Intensive glucocorticoid, asparaginase and vincristine
T-cell					
NOTCH1 mutations	60-70	50	~50 at 4 years	90 at 5 years	? γ-secretase inhibitors
HOX11 overexpression	30	7	70-80 at 3 years	90 at 5 years	
HOX11L2	13	20	~20 at 2 years	~45 at 5 years	
t(9;9)(q34;q34)/*NUP214-ABL1* fusion	5	4	Unknown	Unknown	ABL kinase inhibitors (imatinib/dasatinib)

ALL = acute lymphoblastic leukemia; iAMP21 = intrachromosomal amplification of chromosome 21.

Sitogenetik ve moleküler genetik faktörler

- Yaş ve lökosit sayısının prognostik önemi bu faktörlerin özel genetik anormalliklerle birlikteliği ile açıklanabilir.
- Örn: iyi prognostik özellik sayılan hiperdiploidi (>50) veya ETV6-RUNX1 1-9 yaş grubu arasında sık olup (%25) erişkinlerde nadirdir (%6-7).
- Hipodiploidi (<44), near-hipodiploidi (24-31) ve düşük-hipodiploidi (32-39) hem çocuk hem de erişkinlerde kötü prognostik faktör.
- Ph erişkinlerin %25-30'unda görülmekte olup yaş arttıkça görülme sıklığı artmaktadır.

- PH(+) ve bcr/abl1 füzyonu olan ALL'lerde hem pediyatrik grup hem de erişkinlerde IKZF1 delesyonu bulunuyor (%75-85). Ph(-) grupta ise IKZF1 delesyonu %7-9 oranında görülüyor ve bcr-abl (+) olgularla benzer genetik ekspresyon profili sergiliyor. Konvansiyonel tedavilere yanıtı kötü.

- MLL genini içeren translokasyonlar da (t(4;11), t(11;19), t(9;11) kötü prognostik özellik taşıyıp, CR1 de allo öneriliyor.

Minimal kalıntı hastalık (MRD)

- Morfolojik ve sitogenetik remisyonda olan hasta grubundaki subklinik hastalıktır.

- Relapstan sorumludur.

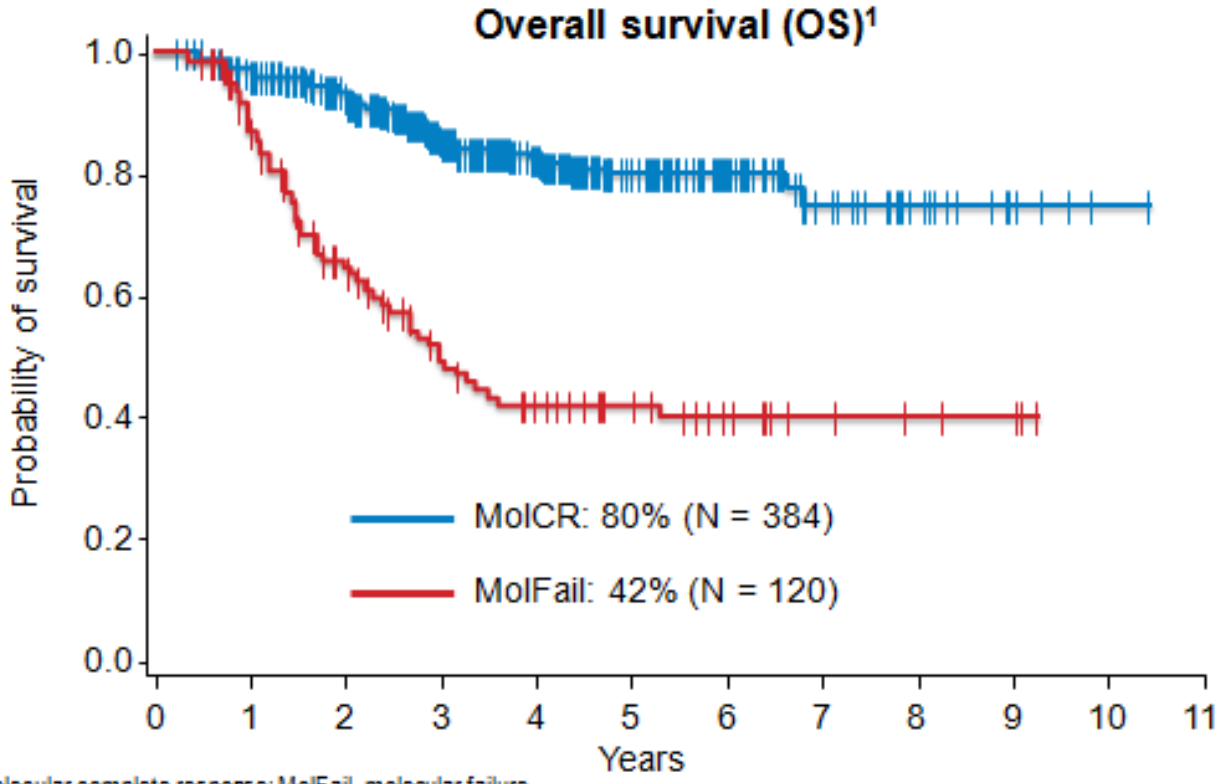
- Malign klonu bulmak için kullanılan MRD yöntemleri:

  PCR ve flow-sitometri

MRD

- Aberran immünofenotipik özelliklerin flow sitometri ile saptanması, füzyon transkriptlerin veya antijen reseptör genlerin PCR ile amplifikasyonu kalıntı hastalığın değerlendirilmesinde konvansiyonel morfolojik yöntemlerden 100 kat daha fazla sensitif (%0.01 veya daha az miktardaki hastalık değerlendirilebiliyor).

Minimal residual disease (MRD) is the most important prognostic factor in ALL



MolCR, molecular complete response; MolFail, molecular failure

- Molecular MRD negativity is associated with significant improvement in DFS[2] and OS[1]
- Molecular MRD status is a predictor of haematological relapse[3]

1. Gökbuget N, et al. *Blood*. 2012;120:1868–1876. 2. Bassan R, et al. *Blood* 2009;113:4153–4162. 3. Raff T, et al. *Blood* 2007;109:910–915.

Farklı metodların karşılaştırılması

	Flow Cytometry	PCR of Fusion Genes (*BCR/ABL*)	PCR of IgH or TCR	High Throughput Sequencing
Sensitivity:	**10^{-3}-10^{-4}**	**10^{-4}-10^{-6}**	**10^{-4}-10^{-5}**	**10^{-5}-10^{-6}**
Applicability:				
Precursor-B	80%-95%	25%-40%	90%-95%	90%-95%
T-ALL	90%-95%	10%-15%	90%-95%	10%-15%

Van Dongen JM,et al. Blood 2015

Farklı metodların karşılaştırılması

	Flow-sitometri	Füzyon genlerin PCR ile tesbiti (BCR/ABL)	IgH/TCR PCR
Pozitif yönleri	•Hızlı	•Spesifik •Sensitif •Hızlı •Stabil hedef	•Spesifik •Sensitif •Yaygın uygulanabilir
Negatif yönleri	•Daha az sensitif •Fenotipik şiftler olabilir •Standardizasyon problemleri	•Sınırlı uygulama	•Zaman alıcı •Klonal evolüsyon

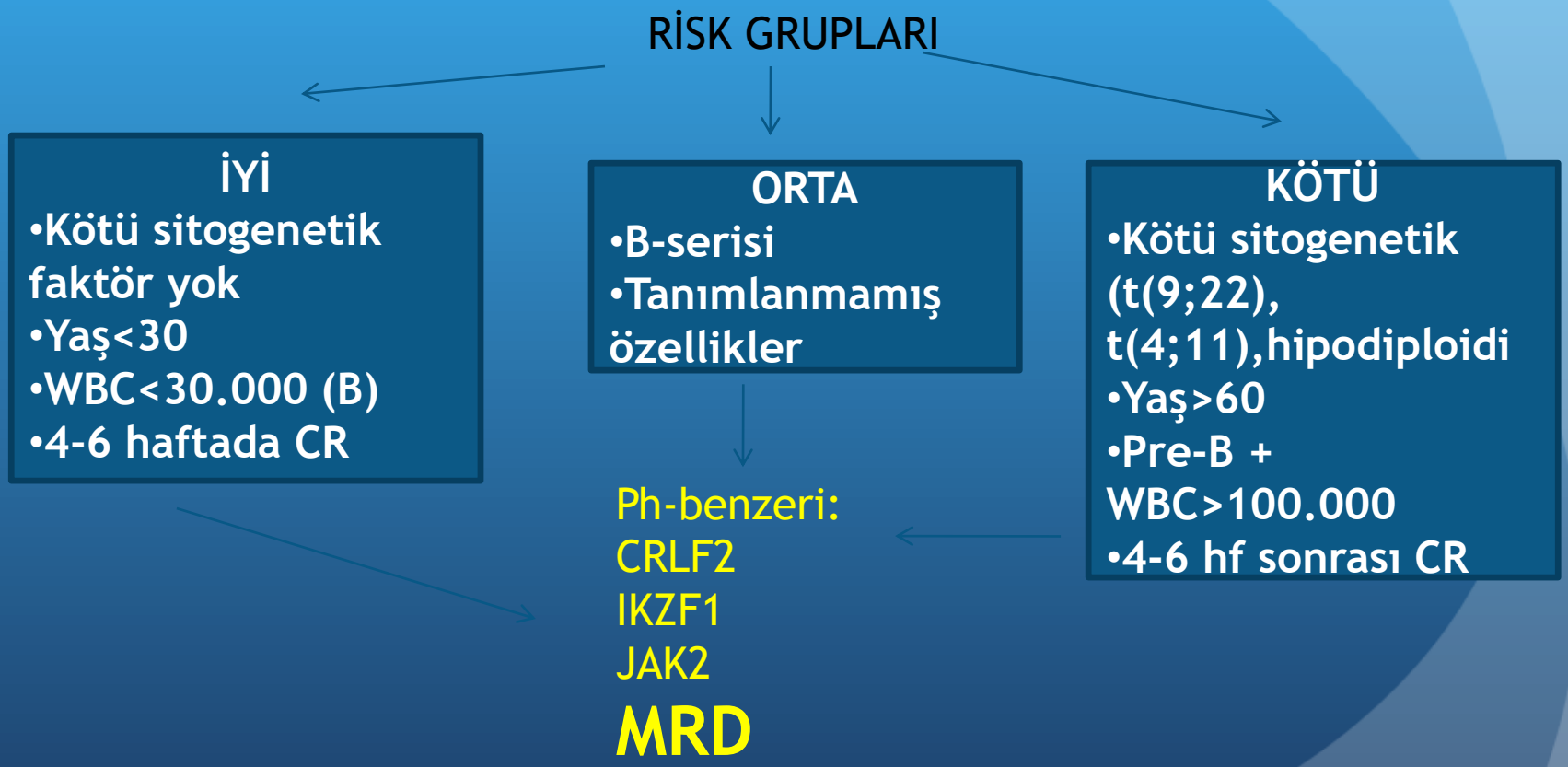
ALL'de neden MRD ?

- 1. Prognostik belirteç olarak
- 2. Tedavinin düzenlenmesi: Transplantın rolü
- 3. Tedavi yanıtının ve direncin belirlenmesi
- 4. Güncel tedavilerin etkinliğinin değerlendirilmesi

Erişkin ALL'de MRD'nin prospektif çalışmalarda prognostik önemi

	N	metod	(-) düzeyi	MRD (-) grupta sonuçlar	MRD (+) grupta sonuçlar
Bassan R, 2009	280	RQ-PCR	$\leq 10^{-4}$	OS : %75 DFS: %72	OS : %32 DFS: %14
Gökbuget N, 2012	580	RQ-PCR	$\leq 10^{-4}$	OS : %80 DFS: %89	OS : %42 DFS: %26
Ribera JM, 2014	326	Flow	$<5x10^{-4}$	OS : %56 DFS: %52	OS : %17 DFS: % 0

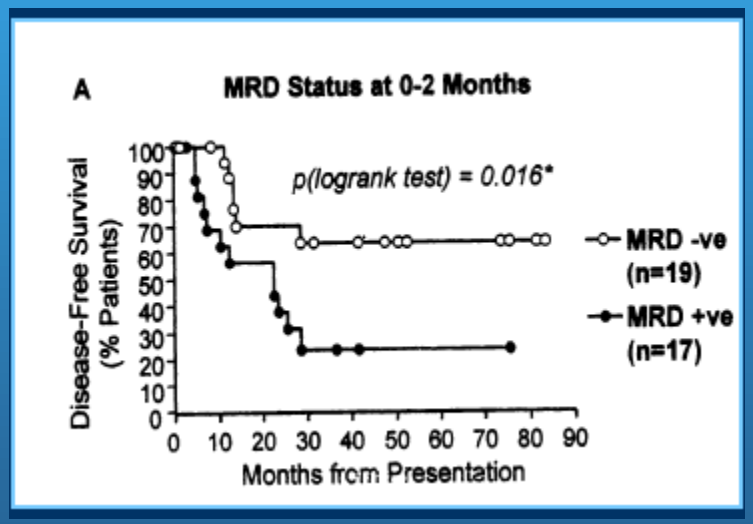
Erişkin ALL'de MRD çalışmaları: Prognostik grupların belirlenmesi

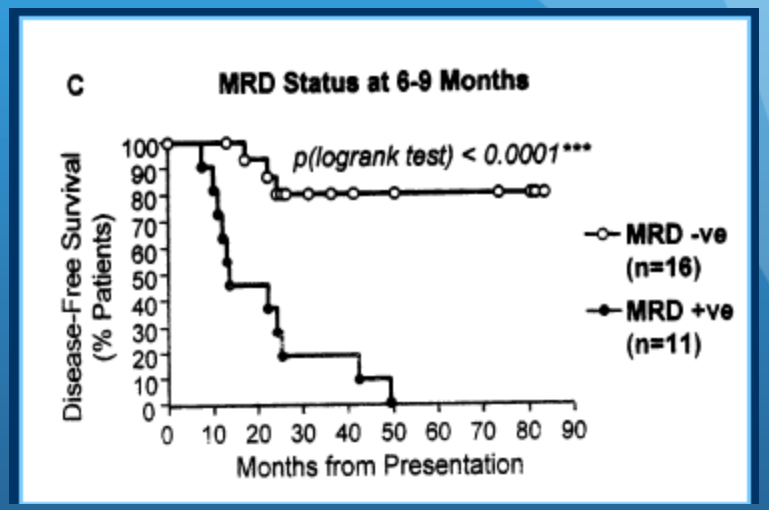


CRLF2:sitokin reseptör benzeri faktör2, IKZF1: Ikaros ailesiçinko parmak pr1

Bassan R,etal. Blood 2009

MRD yüksek risk olguları tanımlamada standart risk faktörlerinden daha değerli





Mortuza FY et al.J Clin Oncol 2002

MRD pozitif grupta SCT sonucu iyileştirir

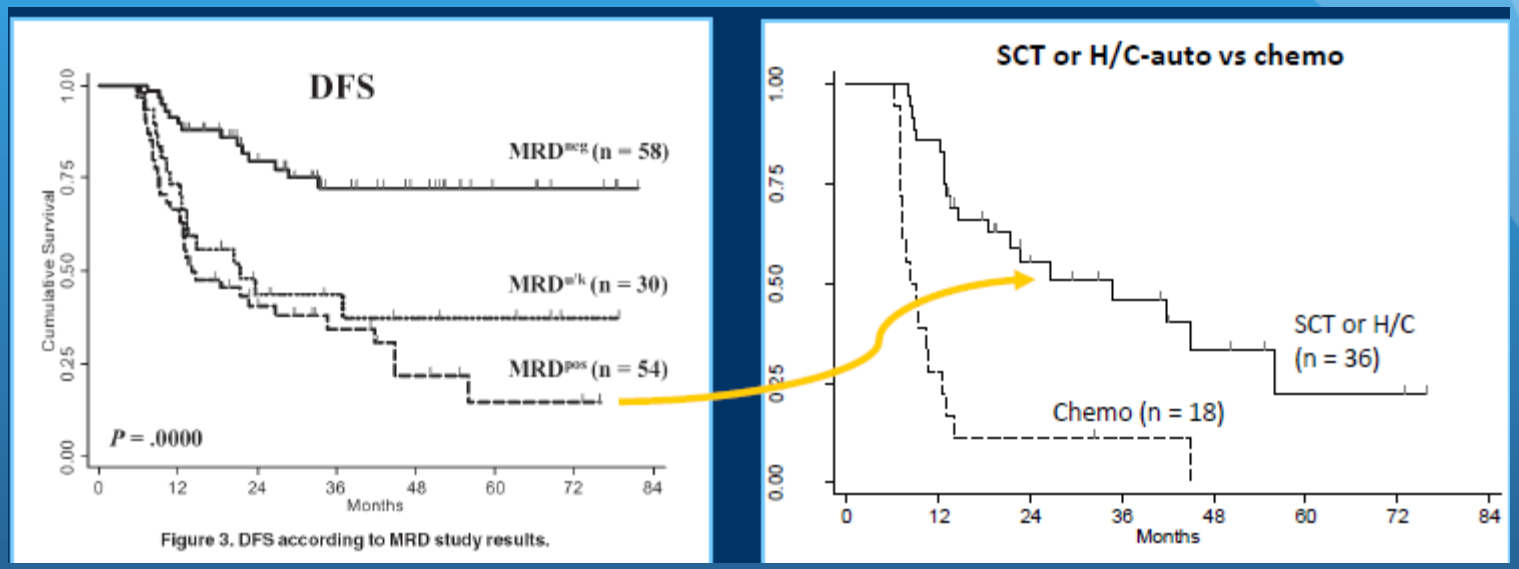
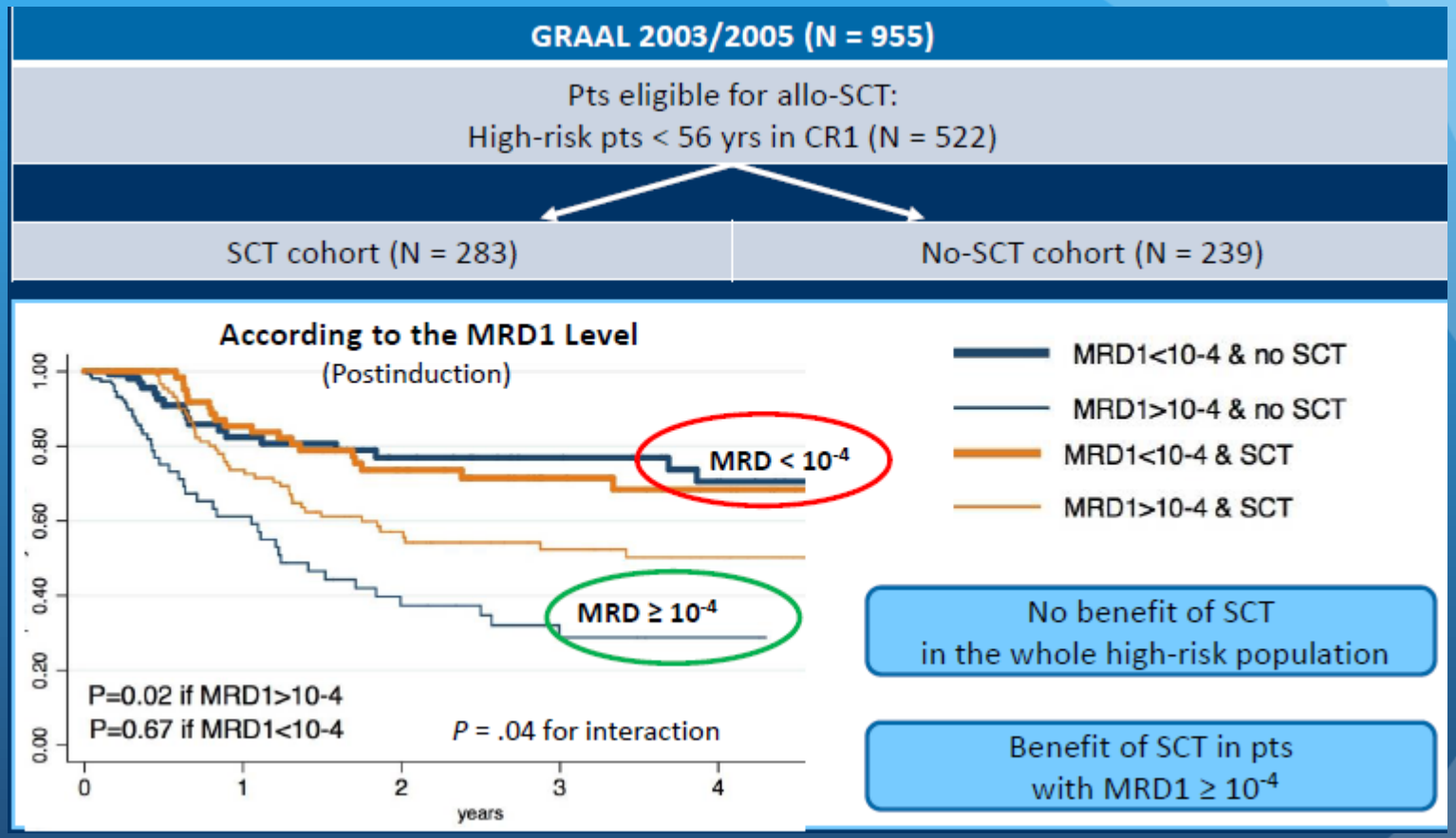


Figure 3. DFS according to MRD study results.

10. 16. 22. haftalarda MRD (PCR ile) bakılmış. 280 olgunun 234'ünde CR elde edilmiş. Başlangıçtaki klinik risk faktörlerinden bağımsız MRD 5 yıllık OS sonuçlarını göstermiş ve SCT ile sonuçlarda anlamlı iyileşme görülmüş.

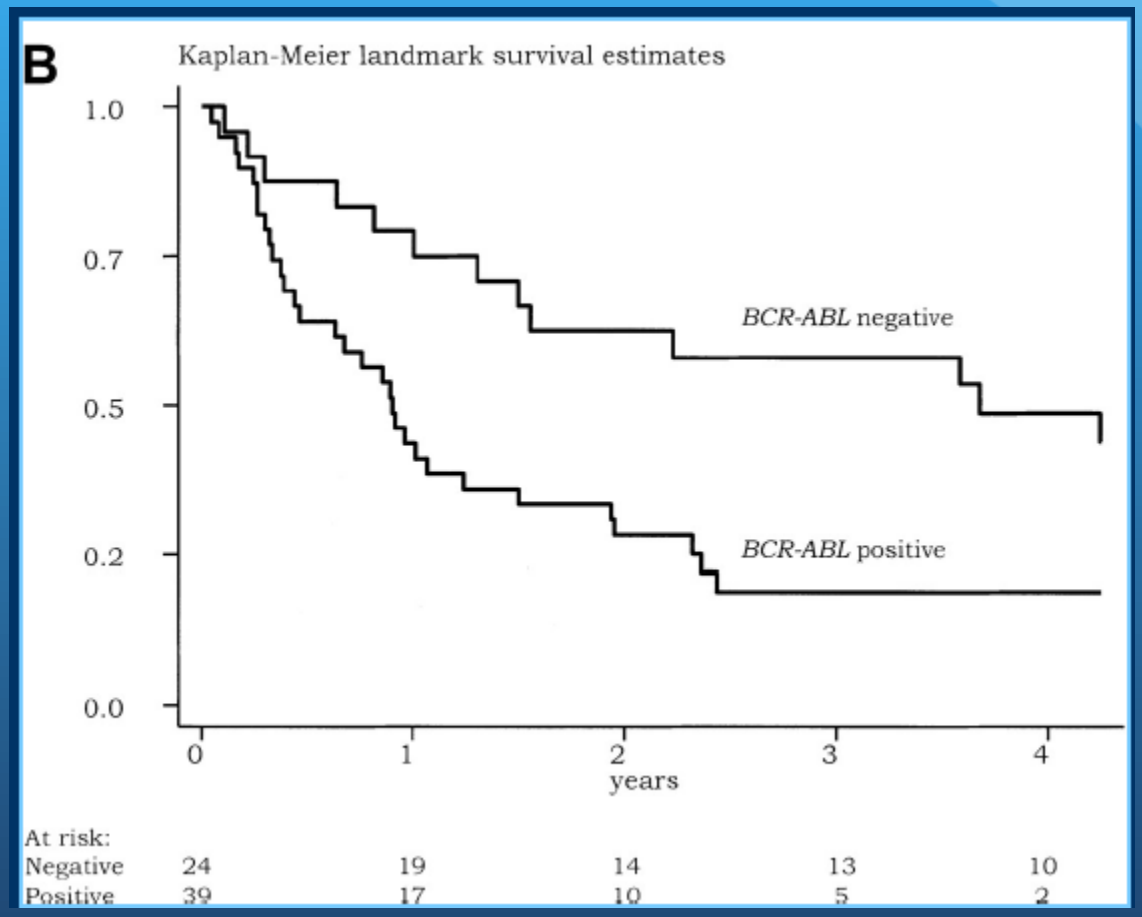
Bassan R,et al. Blood.2009

MRD (+) grupta SCT yararı?



Dhedin N et al. 55. ASH 2013, Abstract 552.

Ph(+) ALL'de Transplant öncesi MRD seviyesi Allo-SCT sonrası DFS'ı tahmin eder



Dombret H, et al. Blood. 2002

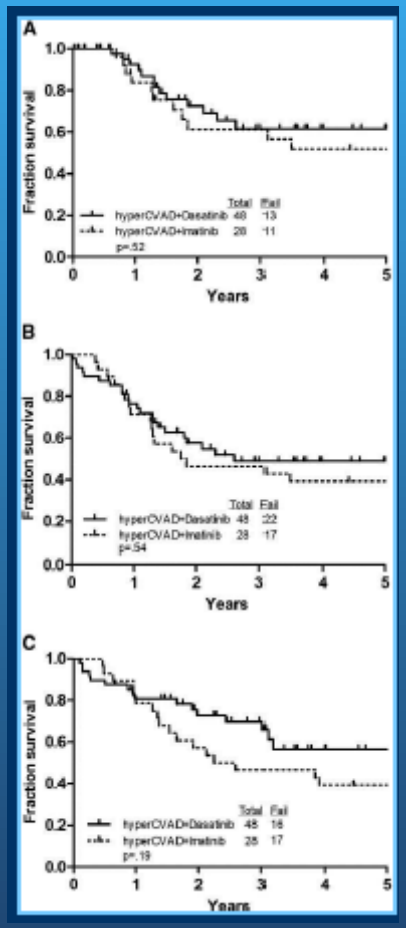
Ph(+) ALL: KT+TKİ MR'u sağlar

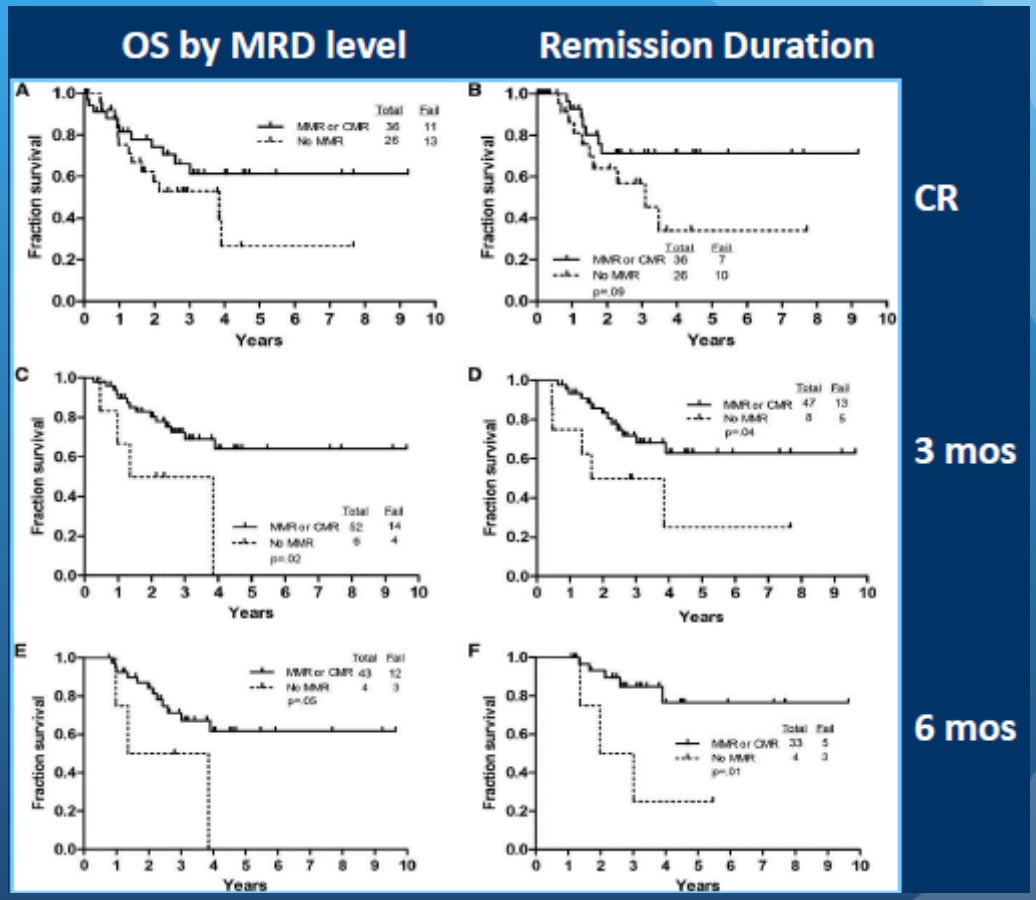
Group	N	Age	Time-Point	% PCR Negative
MDACC	20	< 75	After consolidation	60
Korea	20	< 67	After 1st consolidation	70
JALSG	77	< 63	Day 63	50
GMALL	92	< 65	After 2 inductions	52
GRALL	45	< 60	After 2 inductions	29 neg 64 MMR
MDACC **Dasatinib**	33	< 79	After consolidation	61 neg 21 MMR

JALSG = Japan adult leukemia study group; GMALL = German multicenter study group for acute lymphoblastic leukemia; GRALL = group research in acute lymphoblastic leukemia; MDACC = MD Anderson cancer center; MMR = major molecular response

1.Fielding AK.Blood.2010; 2. Thomas DA,et al. Blood.2004; 3. Lee KH,et al. Leukemia,2005; 4. Yanada M,et al. J Clin Oncol.2006; 5. Wassmann B, et al. Blood.2006; 6. De Labarthe A, et al. Blood 2007; 7.Ravandi F,et al.Blood 2010

Ph (+) ALL: Allo-SCT uygulanmamış 76 olgunun Hyper-CVAD + TKİ sonuçları





Tedavi sonrası bcr-abl MRD düzeyleri

Ravandi F,et al. Blood 2013

İlk konsolidasyon sonrası moleküler başarısızlık olan hastalarda 5 yıllık sonuçlarda Allo etkisi

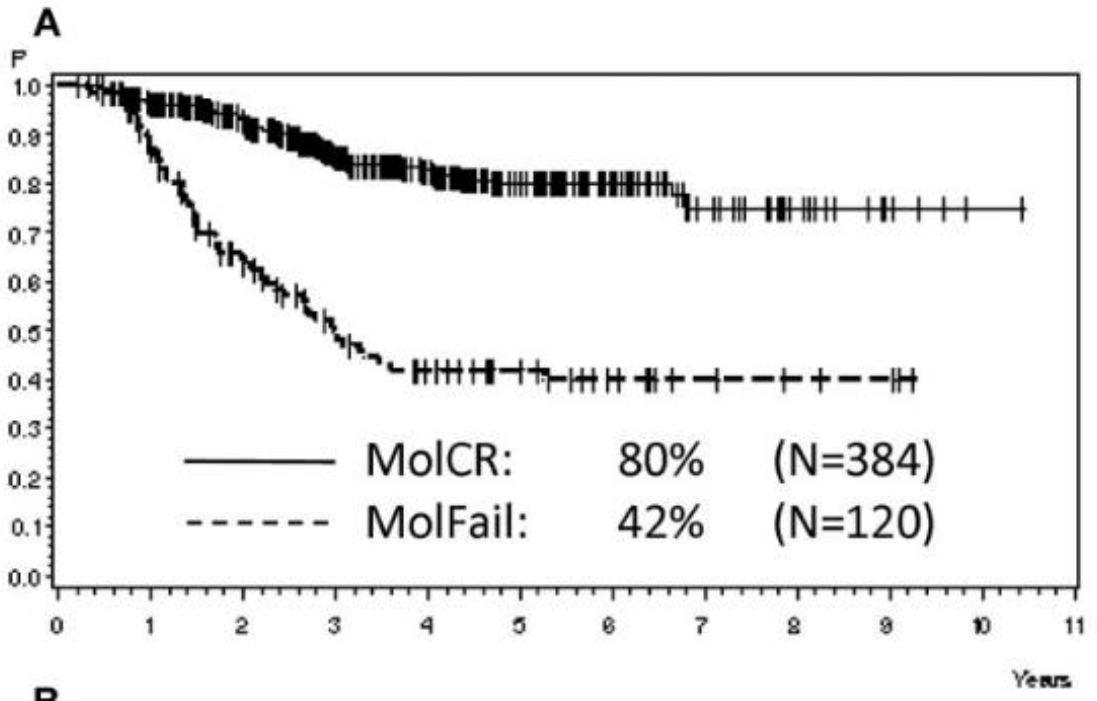
Table 3. Effect of SCT on 5-year outcome of patients in the SR and HR groups with molecular failure after consolidation (week 16)

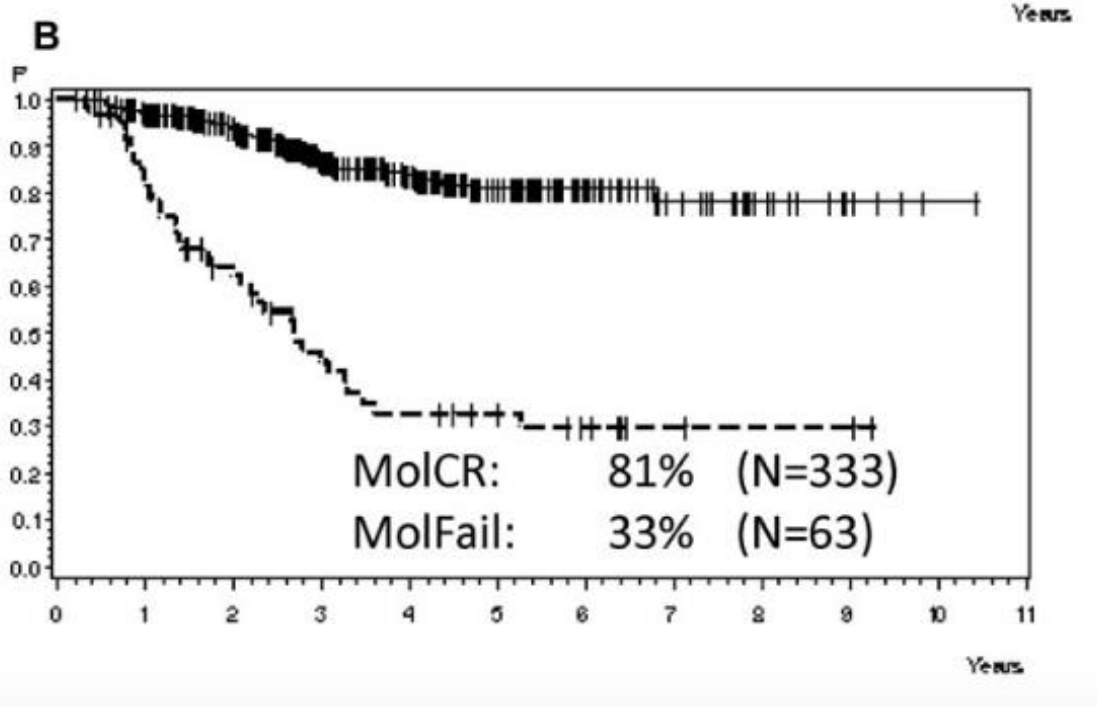
		No SCT		SCT		
Parameter	**N**	**n**	**% ± SD**	**n**	**% ± SD**	***P***
Continuous complete remission	120	63	12 ± 5	57	66 ± 8	< .0001
Continuous complete remission (landmark analysis)	60	35	17 ± 7	25	73 ± 10	.0001
Disease-free survival	120	63	11 ± 4	57	44 ± 8	< .0001
Disease-free survival (landmark analysis)	60	35	16 ± 7	25	50 ± 10	.004
Overall survival	120	63	33 ± 7	57	54 ± 8	.06

Gökbuget N ve ark., 2012

SR ve HR grubunda 16. haftadaki moleküler remisyon durumuna göre sağkalım olasılığı

Gökbuget N ve ark, 2012





MRD özet:

- Konsolidasyon sonrası moleküler CR elde edilemeyenlerde relaps riski yüksektir (%80)
- Moleküler başarısızlık ve moleküler relaps hızlı hematolojik relaps ve düşük sağkalım süresi ile ilişkilidir.
- Moleküler başarısızlık allo sonrası sağkalımı kısaltır
- HSCT öncesi yüksek MRD seviyesi artmış relaps oranı ile ilişkilidir
- Ph(+) ALL'de allo-SCT öncesi ve sonrasında MRD (+)'liği düşük DFS ile birliktelik gösterir.
- Bu nedenle bazı araştırıcılar transplant sonrası PFS'ı iyileştirmede imatinib ve diğer TKİ'ni MRD eradikasyonunda kullanmaktadırlar.

- Konvansiyonel remisyon indüksiyon tedavisi ile <%0.01 moleküler remisyon elde edilen olgularda sonuçlar çok iyi olup standart risk ALL gibi tedaviye devam edilebilir.
- Remisyon indüksiyon sonrası >%1 lösemik hücre varlığı allo-SCT için aday olabilir.

Öte yandan;

- Pediyatrik olgularda MRD güçlü bir prognostik faktör olup standart bir yaklaşım olmuştur.
- Ancak erişkinlerde henüz standart bir yaklaşım olamamıştır; Neden?

**Erişkinlerde prognostik önemini değerlendirebilmek için geniş seriler bulunamaması, her merkezin farklı rejim kullanıyor olması, hasta sayısının az olması.

**Teslerin yapıldığı laboratuarlar arasında tutarsızlıklar olması

- Bu sorulara rağmen tedavide yeni moleküllerin (BİTE antikorlar gibi) keşfi ile MRD erişkinlerde de giderek artan oranda kullanılmaya başlanmıştır.

- Düşük risk olgular bu sayede belirlenip aşırı tedaviden kaçınılabilir mi?
- Yüksek risk olgular daha iyi tanımlanıp daha yoğun tedaviler seçilebilir mi?

Güncel tedaviler: Blinatumomab Faz II MRD (+) ALL çalışması

B-precursor ALL in haematological CR with molecular failure or relapse after ≥3 cycles of chemotherapy

N = 21

ENROL

Blinatumomab
15 µg/m²/d CIV
4 weeks on/2 weeks off
(CIV by minipump)

- Molecular CR patients may receive 3 consolidation cycles
- Molecular SD patients may receive 1 more cycle to achieve molecular CR

Primary endpoint: molecular* CR

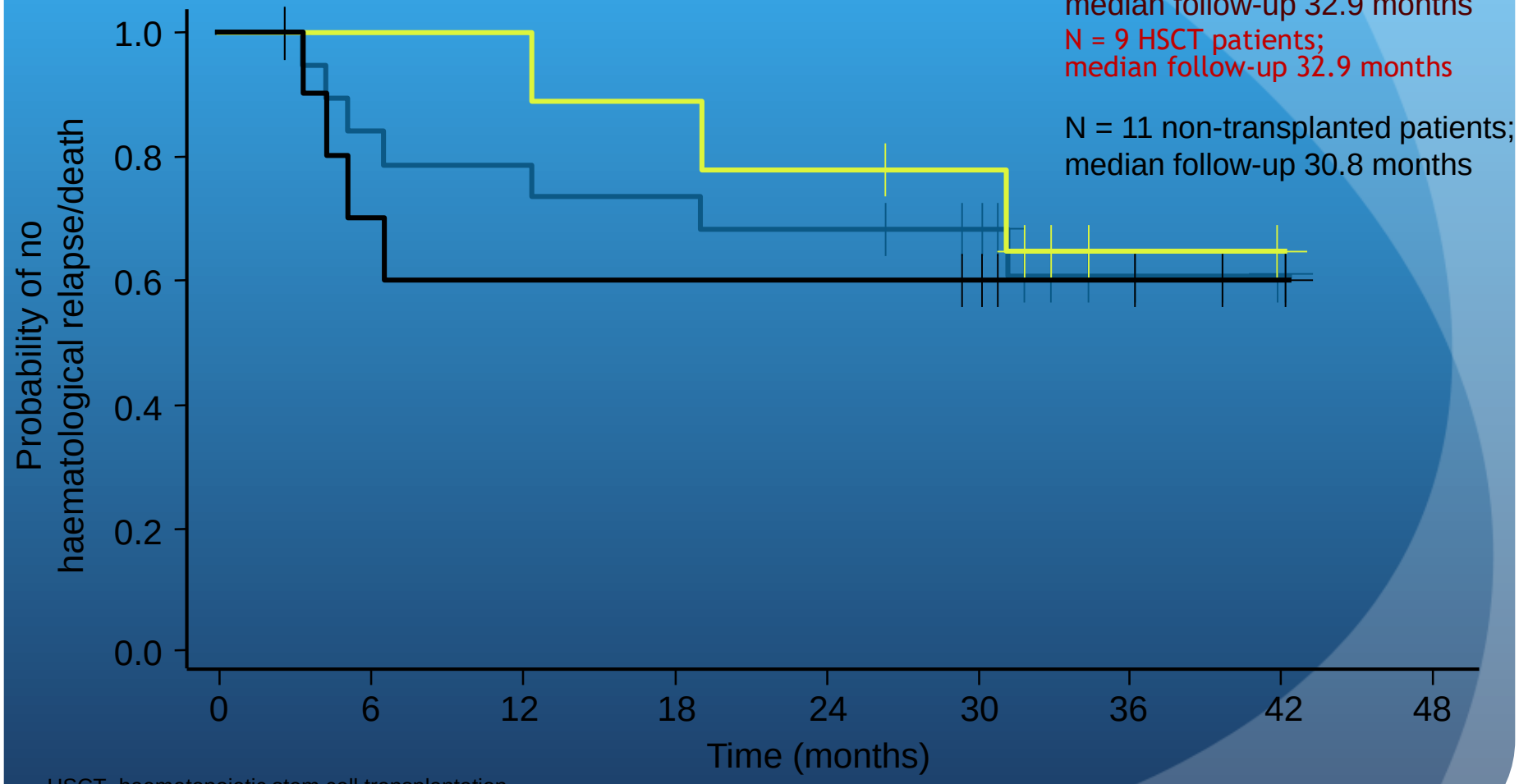
Secondary endpoints:
- Time to haematological relapse
- Incidence and severity of adverse events

*Assessed by Q-PCR central lab, Ig/TCR rearrangement, Ph+ or t(4;11)

CIV, continuous intravenous infusion; CR, complete response; SD, stable disease

Topp M, et al. *J Clin Oncol* 2011;29:2493–2498.

MRD (+) ALL'de Blinatumomab uzun süreli LFS sağlar



HSCT, haematopoietic stem cell transplantation

Topp M, et al. *Blood* 2012;120:5185–5187.

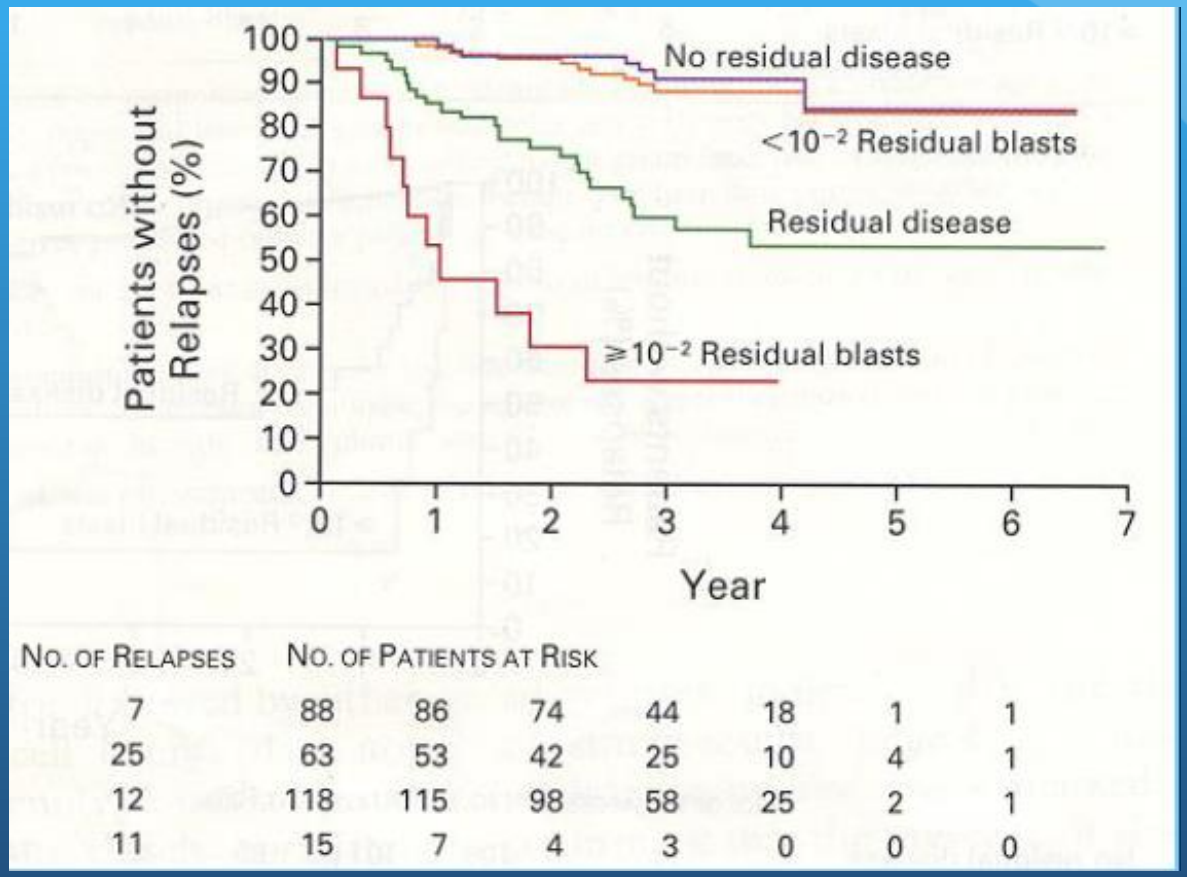
Pediyatrik grupta MRD'nin önemi

- Çocuklarda tedavinin 19.günü MRD (+)'liği olan grupta EFS (-) olan gruptan başlangıçtaki risk faktörlerinden bağımsız olarak kötü olduğu gösterilmiş.

- Örn: Düşük risk grupta olmasına rağmen MRD≥%1 olan grupta 10 yıllık EFS %69.2

  Standart risk grupta olup MRD<%1 olan grupta 10 yıllık EFS %82.9

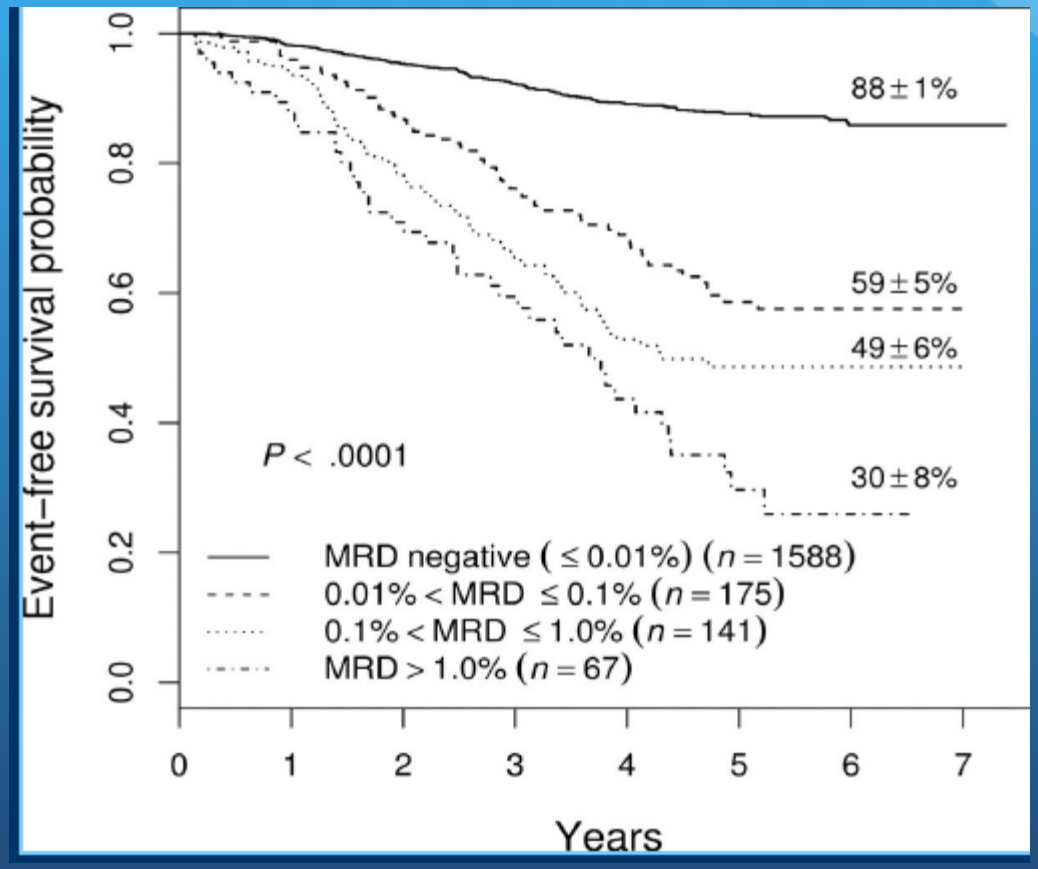
Pediyatrik ALL'de MRD sonucu tahminde yardımcı



No. of Relapses	No. of Patients at Risk						
7	88	86	74	44	18	1	1
25	63	53	42	25	10	4	1
12	118	115	98	58	25	2	1
11	15	7	4	3	0	0	0

Cave H et al. N Engl J Med 1998

Pediyatrik ALL'de İndüksiyon sonu MRD EFS için önemli prognostik faktör



Borowitz MJ,et al. Blood 2008.

MRD'de sorunlar

- MRD klinik çalışmalarda bir son nokta olarak mı kullanılmalı?
- Hızlı relapsı görmek için mi MRD'yi takip etmeli?
- Zamanlama: Ne zaman? Ne kadar sıklıkla?
- Klinik olarak hangi MRD seviyesi daha önemli?
- Periferik kandan MRD Kİ'den MRD'nin yerini alabilir mi?

HENÜZ KONSENSUS YOK!

ALL’ de kür açısından önemli bir hedef

- Hem çocuk hem de erişkinlerde bağımsız prognostik bilgi sağlar.
- Tedavinin yönlendirilmesinde MRD düzeyinin dahil edilmesinin öneminin kanıtlanmasında yeterli veri mevcut
- Özel sitogenetik alt gruplar için tedavinin etkinliğinin değerlendirilmesinde önemli görüş sağlar
- Yüksek risk olguların kurtarılmasında tedavinin erken yoğunlaşırılması için iyi bir rasyonel sağlar:

  Allo: Tx öncesi MRD durumuna göre etkinliğinin tartılması

  Ph (+) ALL için TKİ kullanımı

  Güncel tedavi modalitelerinin kullanımı

Bassan R,et al. Blood.2009

Erişkinde Tedavi

- Pek çok ajan birlikte kullanılmakla birlikte en iyi kombinasyonun ne olduğu hala net değildir.
- Çocuklara göre sonuçlar daha kötü

  Pediyatrik grupta OS: >%80

  Erişkinlerde OS: %30-45
- Erişkinlerde relaps oranları yüksek
- Relaps olan olgularda standart tedavi ile remisyon oranları %20-30
- Relaps sonrası toplam sağkalım 3-5 ay
- Rejimler bir merkezden diğerine değişiklik göstermektedir.
- Rejimler hastaların yaşına/ WBC sayısına/ genotipik özelliklerine göre değişmektedir

- Pediyatrik protokollerin erişkinlerde kullanıma girmesi ile CR oranları %75-90'ları bulmuş olmakla birlikte kür oranı sadece %30-40 arasındadır. Bu nedenle agresif yaklaşımlar, CR1 de allogeneik kök hücre nakli uygulamaları araştırılmıştır.

- Relaps oranlarının %50-75 arasında olması konsolidasyon rejimlerinde pekçok varyasyonlar yapılmasına, MRD eradikasyonu için ek çaba sarfetmeye itmiştir.

Riske yönelik erişkin ALL tedavisi

- 1. İleri yaş adölesan ve genç erişkinlere pediyatrik protokollerin uygulanması
- 2. Ph(+) ALL'de imatinib veya dasatinibin ilk sıra tedaviye eklenmesi
- 3. CR1'de allogeneik kök hücre naklinin uygulanması sağkalımda anlamlı iyileşme sağlayabilir.

1. Pediyatrik protokollerin yeri

Country	Regimen	Age Range (years) [Median P, A]	Patients (n)	CR (%)	EFS (%) (years)
Retrospective					
United States[30]	CCG (P) CALGB (A)	16-20 [16, 19]	197 124	90 90	63 (7) 34 (7)
France[31]	FRALLE93 (P) LALA94 (A)	15-20 [16, 18]	77 100	94 83	67 (5) 41 (5)
Italy[32]	AIEOP (P) GIMEMA (A)	14-18 [15, 16]	150 95	94 89	80 (2) 71 (2)
United Kingdom[33]	ALL97 (P) UKALLXII/E2993 (A)	15-17 [NR, NR]	61 67	98 94	65 (5) 49 (5)
United States[34]	Hyper-CVAD (A) (includes modified ± rituximab)	13-21 [19]	83	98	62 (4) 70 (4)*
Prospective					
United States[35,36]	DFCI 91-01, 9501 DFCI	15-18 18-50	51 74	94 82	78 (5) 73 (2)
Spain[37]	PETHEMA ALL-96	15-18 19-30	35 46	94 100	60 (6) 63 (6)
France[11]	GRAALL-2003	15-45	172	95	58 (3.5)
Canada[38]	Modified DFCI	18-60	85	89	63 (5)*
United States[39]	Augmented BFM	12-40	85	93	74 (3)*

Deborah A. Clin Adv Hemat Oncol 2014;12:13-17.

Chemotherapy

Clinical Study

Chemotherapy 2014;60:219–223
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Is the BFM Regimen Feasible for the Treatment of Adult Acute Lymphoblastic Leukemia? A Retrospective Analysis of the Outcomes of BFM and Hyper-CVAD Chemotherapy in Two Centers

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Key Words
Acute lymphoblastic leukemia · BFM chemotherapy · Hyper-CVAD chemotherapy

Abstract
Multiple induction regimens have been developed for adult patients with acute lymphoblastic leukemia (ALL). However, there have been no prospective randomized trials that directly compare these regimens. In this study, we wanted to evaluate the outcome of 50 adult ALL patients treated with BFM (i.e. Berlin-Frankfurt-Munster, n = 20) and hyper-CVAD (n = 30) protocols between March 2006 and October 2012. The median age was 25 years in the BFM group and 30.5 years in the hyper-CVAD group with a male/female ratio of 15:5 and 17:13, respectively. Forty-five percent of the patients in the BFM group and 30.3% in the hyper-CVAD group were <25 years old. The majority of cases were B cell in origin (80% in the BFM group and 70% in the hyper-CVAD group). Complete remission after induction therapy was achieved in 95 and 96% of the patients, respectively. The median follow-up time was 37 months. The 5-year survival rate was higher in the BFM group than in the hyper-CVAD group (59 vs. 34%). There were also no complications which could cause a delay during the hyper-CVAD regimen. Both chemotherapies were well tolerated. None of the patients died from drug-related toxicity. Only mild liver enzyme elevations were seen as toxicity in the BFM group; these did not cause any delay in therapy. The BFM regimen seems to be feasible for adult patients with ALL in terms of tolerability and efficacy, especially in young adults.
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Introduction

In the early 1980s, acute lymphoblastic leukemia (ALL) was a rarely curable disease with an overall survival (OS) of about 10% [1]. Combination chemotherapy is the primary treatment modality for ALL patients. Multiple induction regimens have been developed. CALBG 9111, hyper-CVAD, GMALL 05/93, French GRAALL-2003 (for younger adults) and BFM (i.e. Berlin-Frankfurt-Munster, for children and adolescents) are the most-used regimens [2–6]. However, there have been no prospective randomized trials that directly compare these. After adapting combinations used in pediatric groups, integrating stem-cell transplantation into front-line therapy

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2. Ph(+) ALL'de TKİ eklenmesi

TABLE 3
Imatinib Plus Chemotherapy as First-Line Therapy for Ph+ ALL: Summary of Selected Studies

Study	Study description	No. % total	Response, %	Median CRD	CCR/DFS/TTP	Survival/EFS
Thomas[37]	Imatinib+CVAD	20	100% CR	NA	NA	NA
Yanada[38]	Phase 2, Imatinib+intensive chemo	80	71% PCR negative; 96% CR	5.2 mo	NA	OS 1 y: 73.3% allogeneic HSCT; 84.8% no HSCT
Wassmann[39]	Phase 2, concurrent or alternating imatinib with chemo	92	Concurrent: 95% CR, 52% PCR negative. Alternating: 19% PCR negative	NA	NA	OS 1 y Alternating: 72%; Concurrent: 61%
Lee[52]	Imatinib+Allo SCT	29	23% CR, 86.2% received SCT after 1st CR	NA	78.1% DFS	78.1% OS

CCyR indicates complete cytogenic response, CHR, complete hematological response, CMR, complete marrow response, CR, complete remission; CCR continuous complete remission; CRD complete remission duration; EFS event free survival; MCyR major cytogenic response, MaHR major hematological response, NA, data not available; CCR/DFS/TTP

Author, year	Group	TKI-mg/day	*n*	CR (%)	Transplant rate (%)	Overall survival (time)
Young adults						
Thomas, 2004 [11]	MDACC	I-400	20	93	50	75% (20 months)
Yanada, 2006 [12]	JALSG	I-600	80	96	61	75% (12 months)
Wassmann, 2006 [13]	GMALL	I-400, I-600	92	95	77	43% (24 months)
de Labarthe, 2007 [14]	GRAALL	I-600	45	96	48	65% (18 months)
Chalandon, 2008 [15]	GRAALL	I-800	118	100 (DIV), 96 (I-HCVAD)	85	68% (DIV) 54% (I-HCVAD) (24 months)
Ribera, 2010 [16]	PETHEMA	I-400	30	90	70	30% (48 months)
Bassan, 2010 [17]	NILSG	I-600	59	92	63	38% (60 months)
Fielding, 2010 [18]	UKNRCI/ECOG	I-600	145	95	44	43% (36 months)
Mizuta, 2011 [19]	JALSG	I-600	100	97	53	65% (36 months)
Ribera, 2011 [20]	PETHEMA	I-600	25	100	92	65% (24 months)
Ravandi, 2010 [21]	MDACC	D-100	35	94	18*	64% (24 months)
Lee, 2011 [22]	Korea	D-100	30	100	80	83% (12 months)
Kim, 2011 [23]	KAAWP	N-400 bid	50	90	73	66% (24 months)
Elderly patients						
Vignetti, 2007 [24]	GIMEMA	I-800	30	100	N/A	74% (12 months)
Ottmann, 2007 [25]	GMALL	I-600	55	96 (I), 50 (chemo)	N/A	42% (24 months)
Rousselot, 2010 [26]	EWALL	D-140, D-100 (70 years)	71	90	N/A	Median 27 months
Foa, 2011 [27]	GIMEMA	D-140	53	100	N/A	69%† (20 months)
Children						
Schultz, 2009 [28]	COG	I-340, mg/m^2	50‡	—	29*	80% (36 months)
Rives, 2011 [29]	SHOP	I-260, mg/m^2	16	100	94	79% (36 months)

TKI, tyrosine kinase inhibitor; CR, complete remission; MDACC, M. D. Anderson Cancer Center; JALSG, Japanese Acute Leukemia Study Group; GMALL, German Multicenter Adult Acute Lymphoblastic Leukemia; GRAALL, French Group for Research in Adult Acute Lymphoblastic Leukemia; PETHEMA, Programa Español de Tratamientos en Hematología; NILSG, Northern Italy Leukemia Study Group; UKNRCI/ECOG, UK National Cancer Research Institute/US Eastern Cooperative Oncology Group; KAAWP, Korean Adult ALL Working Party; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; EWALL, European Working Group on Adult ALL; COG, Children's Oncology Group; SHOP, Sociedad Española de Hematologia y Oncologia Pediátrica; I, imatinib; D, dasatinb; N, nilotinib; DIV, dexamethasone, imatinib and vincristine; HCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone; N/A, not available.

*Not prescribed by the protocol.

†Median age 54 years.

‡Cohort with continuous exposure to imatinib.

Ribera JM. Leuk lymphoma 2013;54:21-27.

- Pekçok çalışmada standart tedaviye eklenen TKİ'lerinin hızla MRD'ı da azaltabileceği gösterilmiştir.
- Bcr/abl1 (+) ALL'de MRD kanıtı olmaksızın allo-SCT uygulandığında DFS'ın anlamlı ölçüde uzadığı gösterildiği için yüksek risk ALL grubunda allo öncesi veya sonrası sonrası eklenen TKİ ile OS'nin anlamlı ölçüde uzattığı da söylenebilir.

- Günümüzde TKİ+KT sonrası uygun hastalarda allo-SCT standart yaklaşım olmuştur.

3. CR1'de Allo

- Allo'nun ALL'deki etkinliği ilk olarak 1973'te rapor edilmiştir. Özellikle t(9;22) ve t(4;11) pozitif ALL'de kür için optimal tedavi yaklaşımı olarak kabul edilebilir.
- En erken veriler Hollanda'dan. 54 ALL olgusu (15-51 yaş) ve 15 lenfoblastik lenfoma olgusu (indüksiyon ve konsolidasyon KT'si uygulanmış). 30 hastaya allo, 22 hastaya otolog.
- 5.yılda DFS %58±11 olup sonuçlar tx uygulanmayan olgulardan istatistiksel olarak farklı bulunmamış.

LALA-94 çalışması

Allogeneic stem cell transplantation improves the outcome of adults with t(1;19)/*E2A-PBX1* and t(4;11)/*MLL-AF4* positive B-cell acute lymphoblastic leukemia: results of the prospective multicenter LALA-94 study

N Vey[1], X Thomas[2], C Picard[3], T Kovascovicz[4], C Charin[2], JM Cayuela[5], H Dombret[5], N Dastugue[6], F Huguet[6], C Bastard[7], A Stamatoulas[7], M Giollant[8], O Tournilhac[8], E Macintyre[9], A Buzyn[9], D Bories[10], M Kuentz[10], F Dreyfus[11], A Delannoy[12], S Raynaud[13], N Gratecos[13], D Bordessoule[14], S de Botton[14], C Preudhomme[14], O Reman[15], X Troussard[15], A Pigneux[16], C Bilhou[16], JP Vernant[17], C Boucheix[18] and J Gabert[3], For The GET-LALA Group the Swiss Group for Clinical Cancer Research (SAKK)

Standard-risk ALL
- Patients with T-cell ALL in CR after one course of induction
- Patients with B-cell ALL and:
  - Absence of CNS involvement
  - Absence of t(9;22), t(1;19), t(4;11) or their molecular equivalents
  - Absence of 11q23 rearrangements
  - WBC <30 G/l
  - CD10+/CD19+, or CD20+/CD19+ (if CD10−) in the absence of myeloid markers
  - CR achieved after one course of induction

High-risk ALL
- Non standard-risk ALL without Ph+/*BCR-ABL* or CNS involvement
- Patients without immuno-phenotypic or karyotypic analysis

Ph+ ALL
- Patients with t(9;22) or *BCR-ABL*
- CNS-positive ALL
- Patients with CNS involvement

Abbreviations: ALL, acute lymphoid leukemia; WBC, white blood cells.

LALA-87 ve LALA-94 geniş grup çalışmasında standart risk allo SCT'tan anlamlı fayda görmemiş.
LALA-94: Ph(-) yüksek risk olgularda ise allo OS'de anlamlı uzama sağlamış

	E2A-PBX1	*MLL-AF4*	*Other B-cell*
Number of patients	24	34	325
Initial randomization			
Idarubicine	14 (58%)	16 (47%)	159 (49%)
Daunorubicine	10 (42%)	18 (53%)	166 (51%)
Cleared marrow blasts by day 8	4/13 (31%)	7/24 (29%)	31/144 (21%)
Response to induction 1			
CR	21 (87%)	26 (76%)	246 (75%)
Failure	1 (4%)	4 (12%)	71 (23%)
Death	2 (9%)	4 (12%)	8 (2%)
Response to induction 2			
Evaluable	1	4	60
CR	0	2 (50%)	35 (58%)
CR rate	21 (87%)	28 (82%)	281 (86%)
Post-remission treatment			
Allo-SCT	8	12	44
Auto-SCT	5	10	34
Chemotherapy	7	5	163
Relapse	10/24 (42%)	14/28 (50%)	140 (43%)
Death	11 (46%)	22 (65%)	165 (51%)

Abbreviations: CR, complete response; SCT, stem cell transplantation.

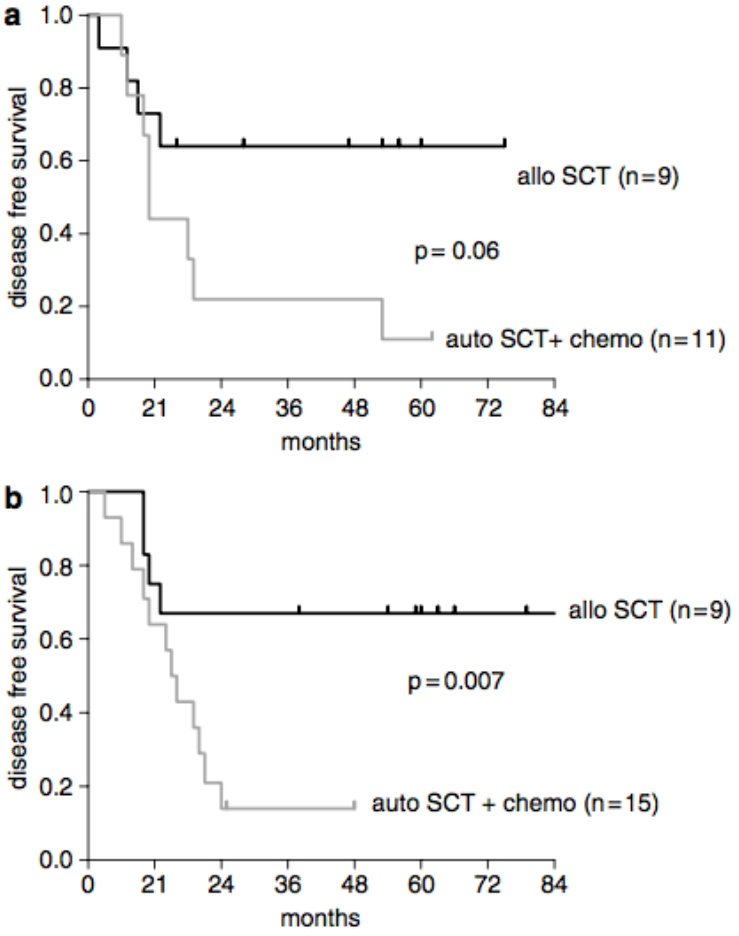


Figure 2 DFS according to treatment allocation in (**a**) patients with t(1;19)/*E2A-PBX1* and (**b**) patients with t(4;11)/*MLL-AF4*.

Yüksek risk ALL'de allo donörü varsa CR1de allo DFS'ı iyileştirir.

UKALL/ECOG 2993 çalışması

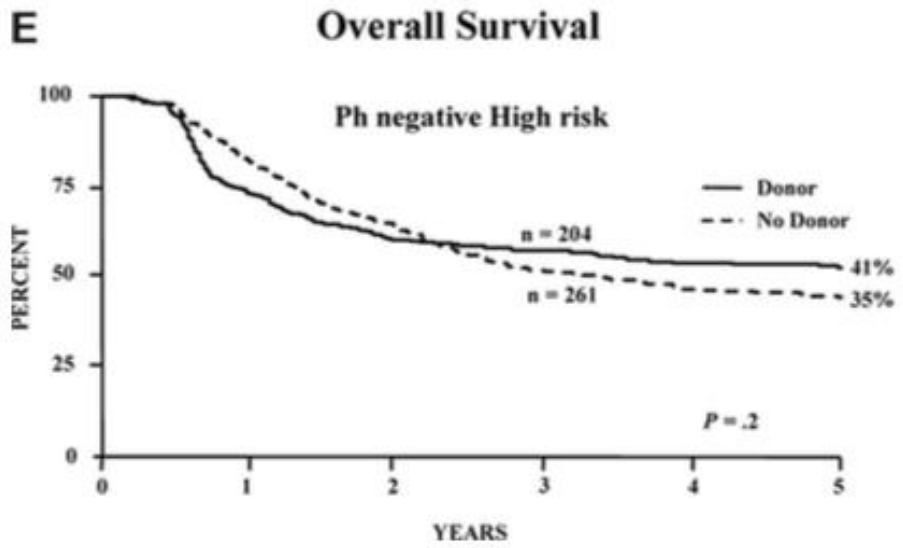
In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993)

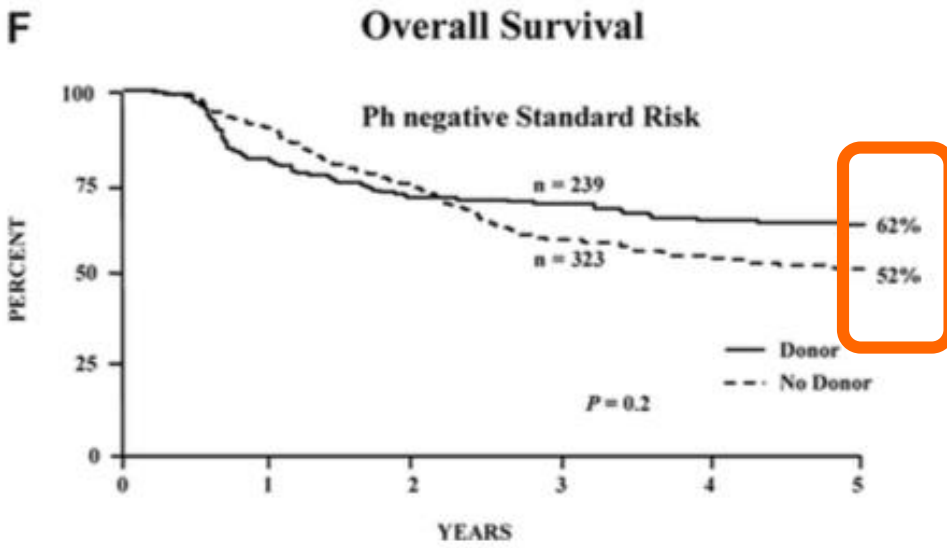
Anthony H. Goldstone,[1] Susan M. Richards,[2] Hillard M. Lazarus,[3] Martin S. Tallman,[4] Georgina Buck,[2] Adele K. Fielding,[5] Alan K. Burnett,[6] Raj Chopra,[7] Peter H. Wiernik,[8] Letizia Foroni,[5] Elisabeth Paietta,[8] Mark R. Litzow,[9] David I. Marks,[10] Jill Durrant,[2] Andrew McMillan,[11] Ian M. Franklin,[12] Selina Luger,[13] Niculae Ciobanu,[14] and Jacob M. Rowe[15]

1913 hasta (yaş: 15-59) 1993-2006 çalışmaya dahil edilmiş. 50 yaş altı donörü olan her hasta allo SCT'a yönlendirilmiş.

Yüksek risk grubu: 1. yaş>35
2. WBC>30.000 (B), 100.000 (T)
3. Ph(+)

Medyan izlem süresi: 4 yıl



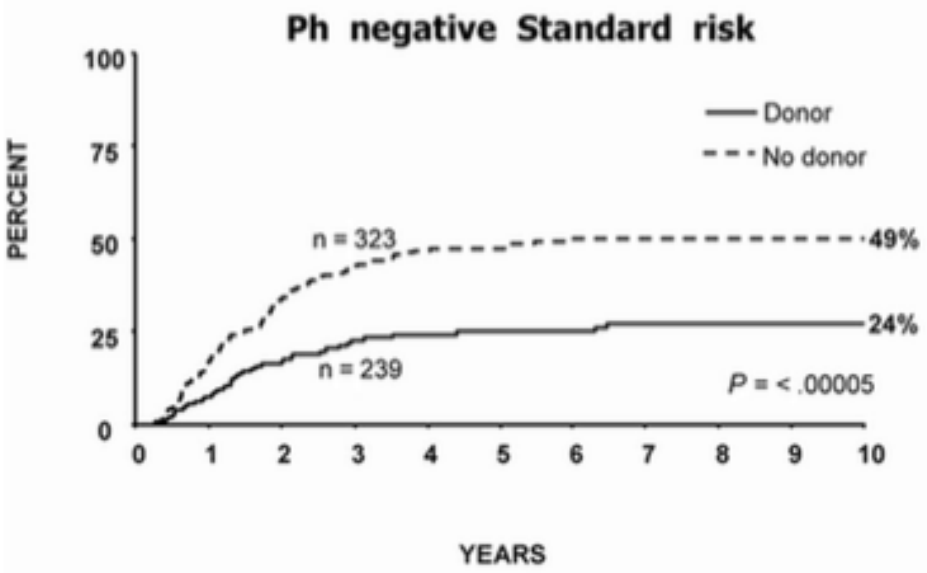


LALA çalışmaları tersine bu çalışmada standart risk ALL olgularının allo-SCT'tan anlamlı fayda gördüğü gösterilmiş.

>35 yaş ALL yüksek risk grupta yüksek tx ilişkili mortalite nedeni ile CR1de allo olumlu yönde istatistiksel anlamlılık sağlamamış.

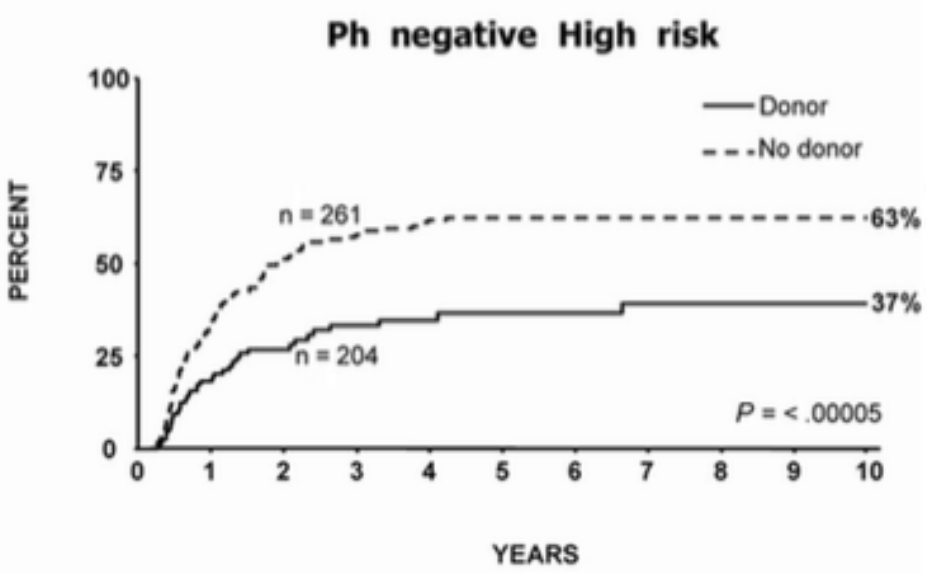
A

Relapse Rate



B

Relapse Rate



C

Non-Relapse Mortality (%)

	3 months	6 months	1 year	2 years
High Risk				
Donor	1.5	7.3	26.0	35.8
No Donor	1.2	2.0	10.3	13.6
Standard Risk				
Donor	0.4	3.4	17.6	19.5
No Donor	0.3	1.2	5.3	6.9

Table 2. Published trials in adult ALL that included > 100 patients and assignment to HCT

Study	Patients	TRM/NRM	Relapse	Survival
Ribera et al, PETHEMA[8]	N = 156 Ph−; age, 15-50 y; 72 donor; 84 no donor	10% donor; 2% no donor	@5 y: 62% and 51%	@5 y: DFS: 37% donor, 46% no donor; OS: 40% donor, 49% no donor
Goldstone et al, MRC-ECOG[9]	N = 1031; age, 15-64 y (allo 15-59 y); 443 donor; 588 no donor	@2 y: high-risk: 36% donor, 14% no donor; standard-risk: 20% donor, 7% no donor	@10 y: high-risk: 37% donor, 63% no donor; standard-risk: 49% donor, 24% no donor	@5 y: OS: high-risk: 41% donor, 35% no donor; standard-risk: 62% donor, 52% no donor
Cornelisson et al, HOVON[10]	N = 257; age, 15-55 y; 96 donor; 161 no donor	@5 y: 16% donor, 3% no donor	@5 y: 24% donor, 55% no donor	@5 y: DFS: 60% donor, 42% no donor ($P = .01$)
Kako et al, JALSG[11]	N = 649; age, 15-54 y; 241 chemotherapy; 408 HCT	NR	NR	@10 y: OS: standard-risk: chemotherapy, 40%; HCT, 54%; high-risk: chemotherapy, 25%; HCT, 38%

NR indicates not reported; PETHEMA, Programa Español de Tratamiento en Hematología; MRC, Medical Research Council of the United Kingdom; and ECOG, Eastern Cooperative Oncology Group.

HOVON çalışmasında OS standart risk ALL'de Allo-SCT lehine

- Meta analizlerde ilk CR'da allo-SCT ile KT ve otolog kök hücre nakilleri ile karşılaştırldığında tüm mortalitede azalma olduğu da gösterilmiş.

- Subgrup analizlerde :

*__Standart risk__ ALL'de ALLO-SCT ile OS avantajı (+)

*__Yüksek risk__ olgularda ALLO-SCT ile istatistiksel olarak anlamlı OS avantajı var.

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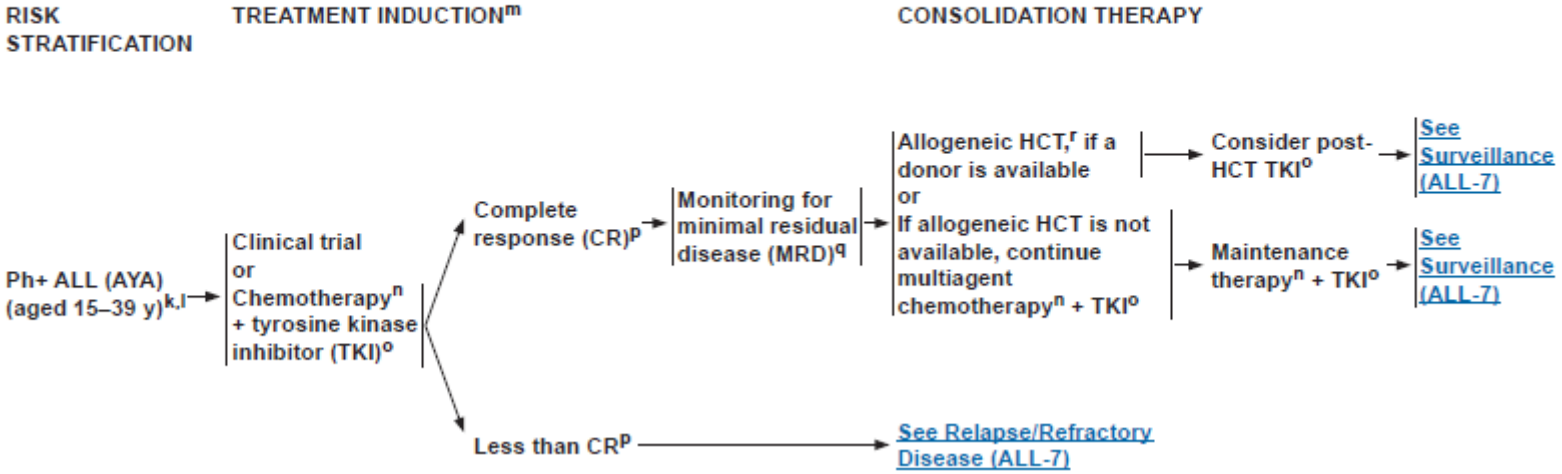

[k]Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.
[l]For additional considerations in the management of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult Oncology.
[m]All ALL treatment regimens include CNS prophylaxis.
[n]See Principles of Chemotherapy (ALL-D).
[o]See Discussion section for use of different TKIs in front-line therapy.
[p]See Response Criteria (ALL-E).
[q]See Minimal Residual Disease Assessment (ALL-F).
[r]Emerging data suggest that for younger patients (aged ≤21 y), allogeneic HSCT may not offer an advantage over chemotherapy + TKIs; Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children's Oncology Group study. J Clin Oncol 2009;27:5175-5181.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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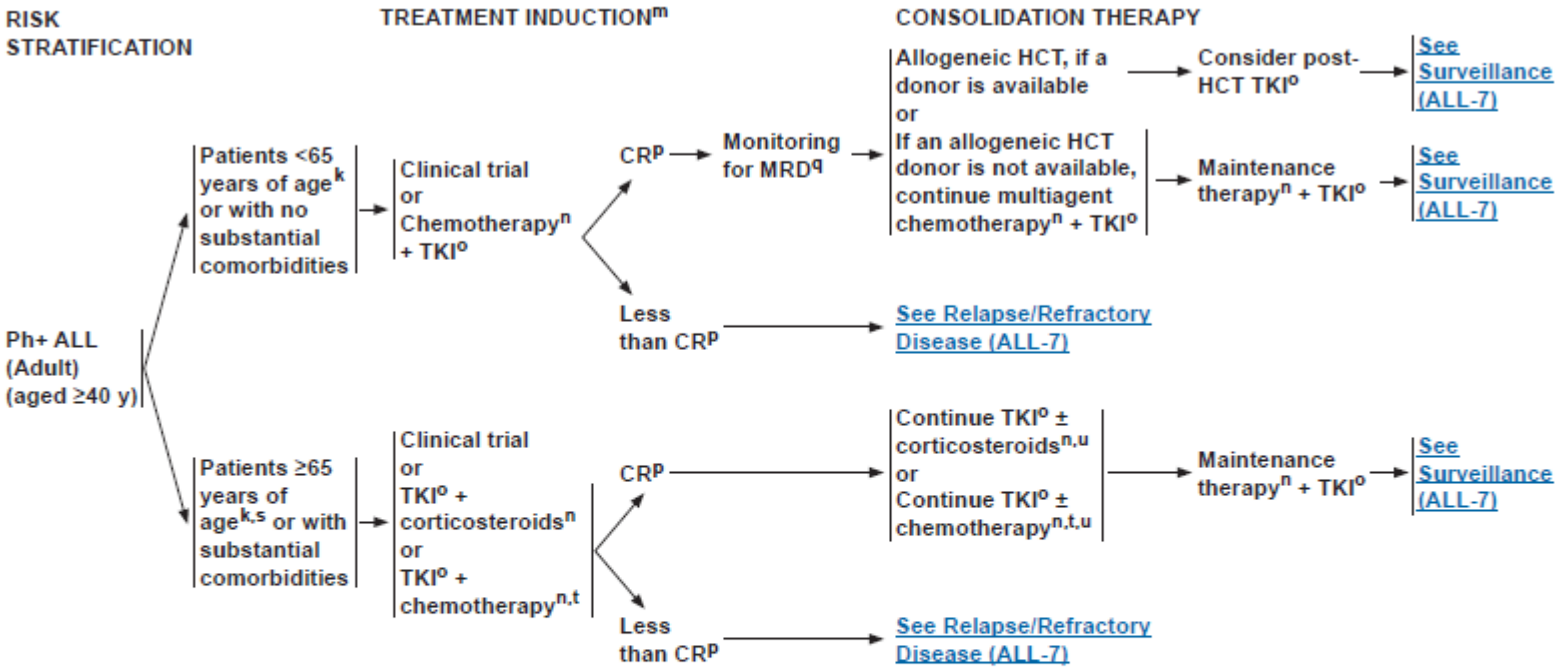

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[q]See Minimal Residual Disease Assessment (ALL-F).
[s]For additional considerations in the management of senior adult patients with ALL, see the NCCN Guidelines for Older Adult Oncology.
[t]Consider dose modifications appropriate for patient age and performance status.
[u]Allogeneic HCT may be considered based on performance status, comorbidities, availability of appropriate transplant donor, and transplant center expertise in treating older patients with allogeneic HCT.

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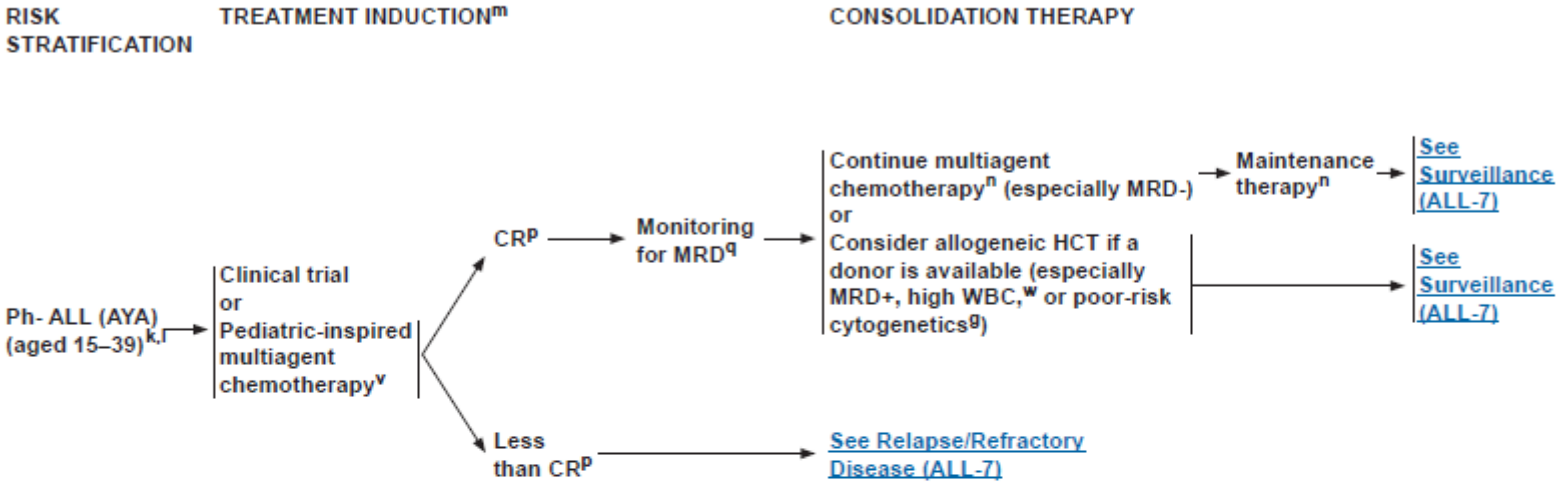

[g]Cytogenetic risk groups are defined as follows:
Good risk: Hyperdiploidy (51–65 chromosomes and/or DNA index >1.16; cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome); t(12;21)(p13;q22): ETV6-RUNX1;
Poor risk: Hypodiploidy (<44 chromosomes and/or DNA index <0.81); t(v;11q23): MLL rearranged; t(9;22)(q34;q11.2): *BCR-ABL* (defined as high risk in the pre-TKI era); Complex karyotype (5 or more chromosomal abnormalities).

[k]Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.

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[p]See Response Criteria (ALL-E).

[q]See Minimal Residual Disease Assessment (ALL-F).

[v]See Principles of Chemotherapy (ALL-D). All regimens include induction/delayed intensification (especially for pediatric-inspired regimens) and maintenance therapy.

[w]High WBC count (≥30 x 10^9/L for B lineage or ≥100 x 10^9/L for T lineage) is considered a high-risk factor based on some studies in ALL. Data demonstrating the effect of WBC counts on prognosis are less firmly established for adults than for the pediatric population.

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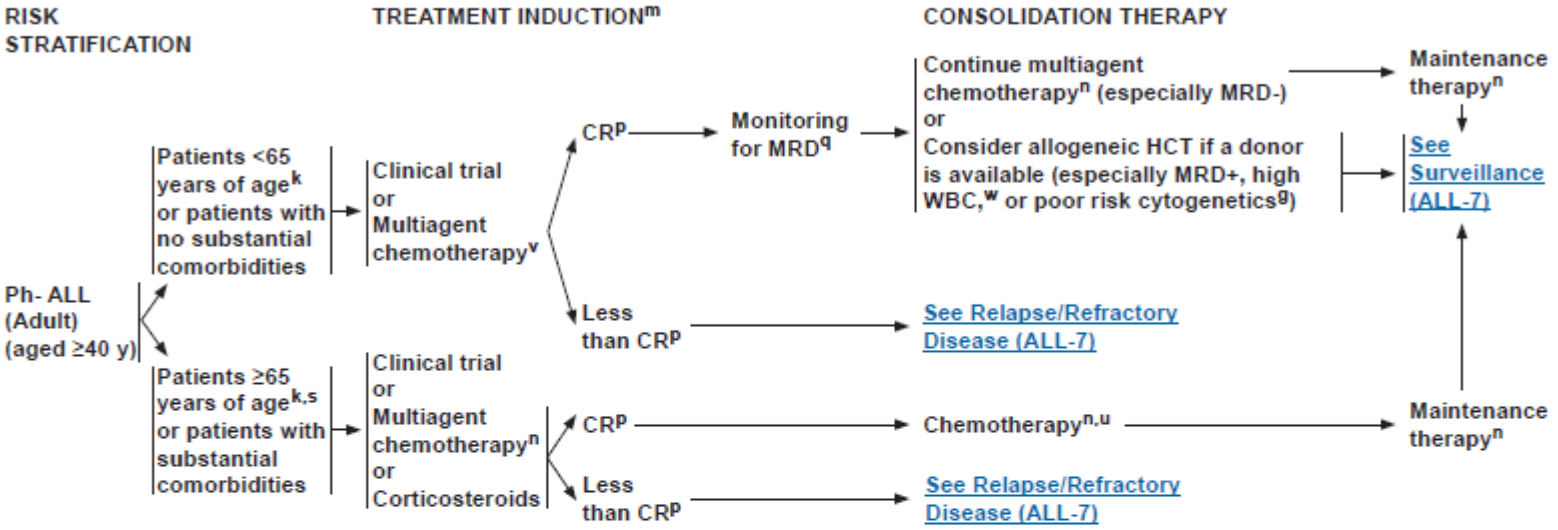

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ÖNERİ

AKHN için performansı uygun olan tüm hastalarda ve olası akraba vericilerinde tanı anında HLA doku grubu belirlenmelidir. Tüm yüksek riskli ALL olgularında TR1 de HLA uyumlu kardeş veya akraba dışı vericiden AKHN önerilir. Standard risk ALL olgularında TR1 sağlanması ve tam uyumlu kardeş verici olması halinde AKHN seçeneği hasta ile birlikte değerlendirilmelidir. Standard risk ALL hastalarında indüksiyon tedavisi sonrası bir dönemde minimal kalıntı hastalık saptanabilen olgularda AKHN yapılabilir. TR2 sonrası kardeş veya akraba dışı HLA uyumlu vericiden AKHN yapılması önerilir. AKHN planlanan olgularda Tüm Vücut Işınlaması (TBI) temelli hazırlama rejimi tercih edilmelidir.

TEŞEKKÜR EDERİM