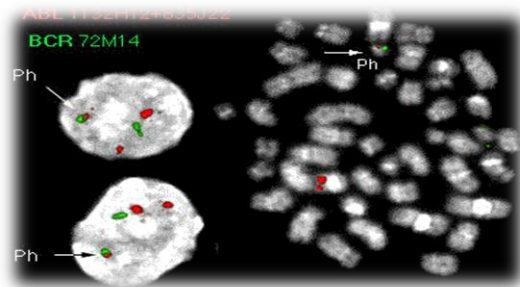
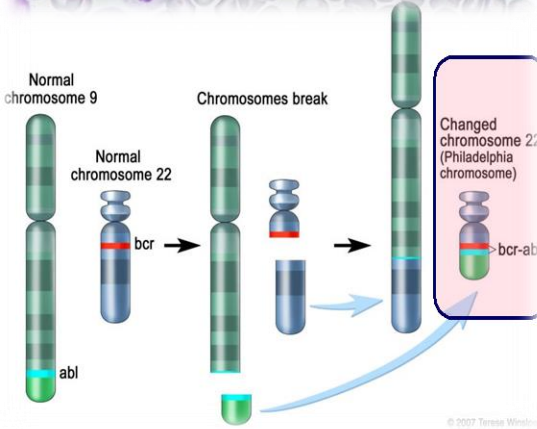
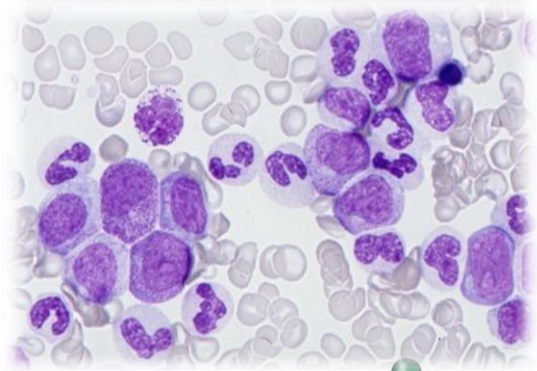
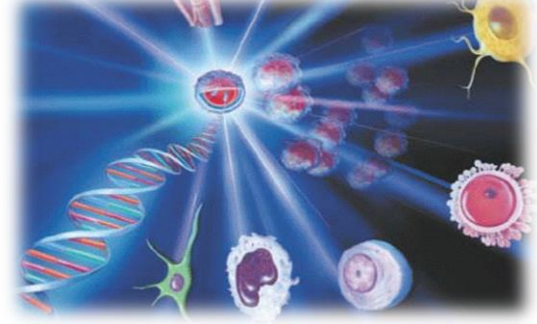


KML Tedavisinde Optimal Yanıt ve Erken Geçiş

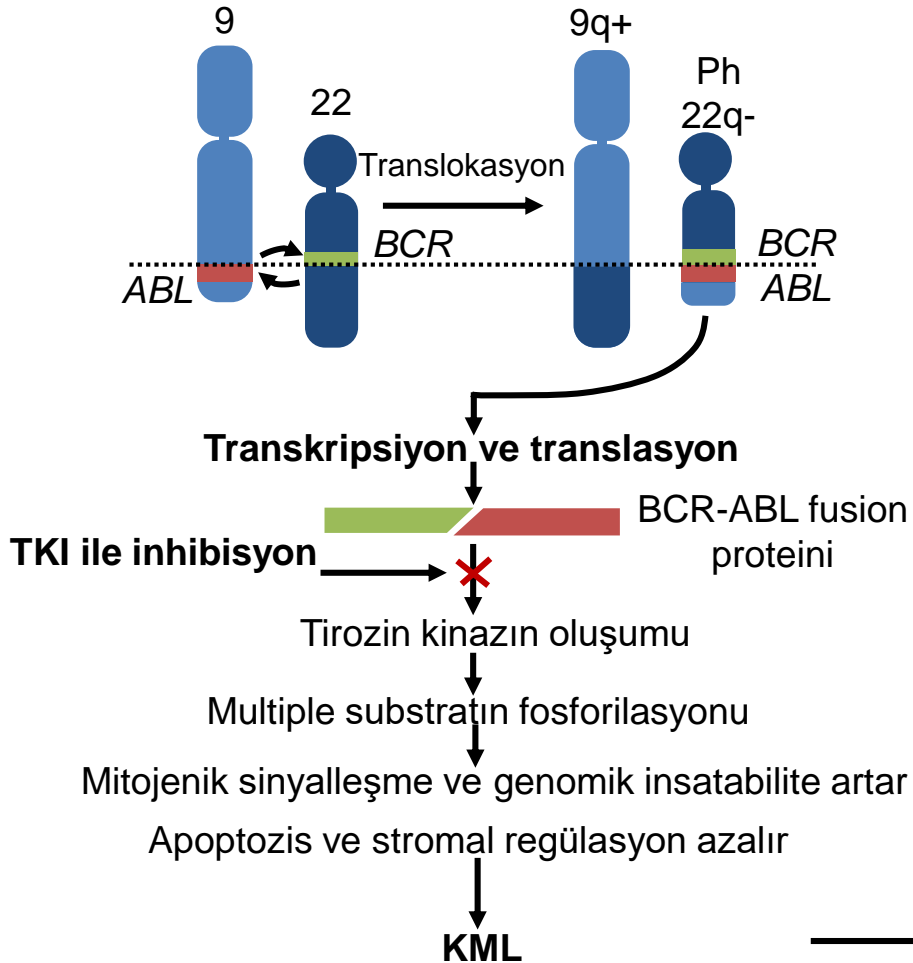


Doç Dr Leylagül KAYNAR

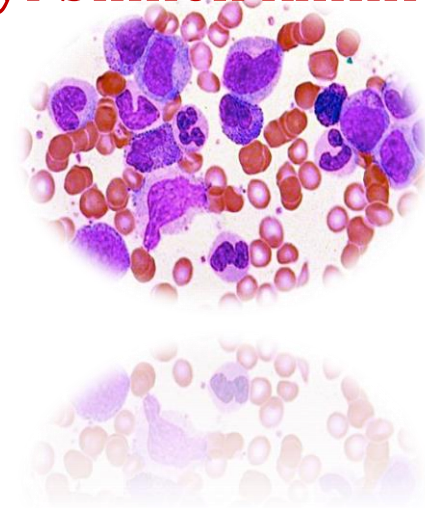


Erciyes Üniversitesi Tıp Fakültesi
Hematoloji Bilim Dalı
Erciyes Transplant Merkezi

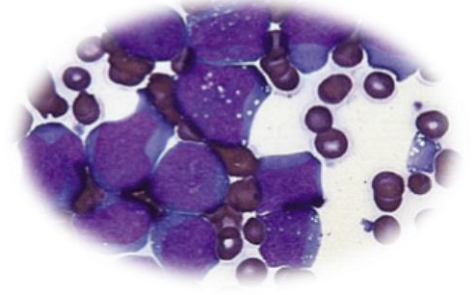
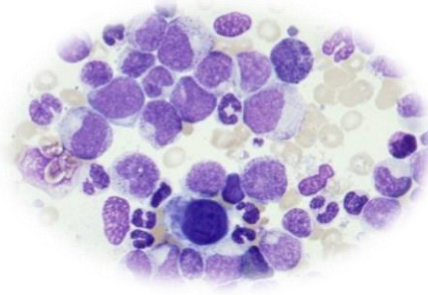
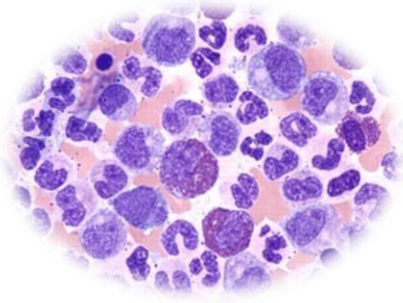
Kronik Myeloid Lösemi



- Kök hücre bozukluğu
- BCR-ABL onkogeni
- Myeloproliferasyon ile karakterize
- İyi bilinen klinik gidiş



KML Doğal Seyri



Kronik

Ortalama süre
5-6 yıl

Akselere

Ortalama süre
6-9 ay

Blastik

Ortalama yaşam süresi
3-6 ay

İleri fazlar

Tedaviye cevap var

Tedaviye azalmış cevap

Tedaviye dirençli



KML tanısı



DUYARLILIK

Hematolojik

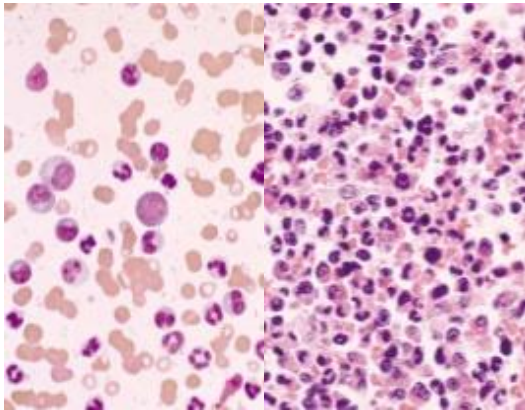
Sitogenetik

Moleküler

Karyotype
(Ph kromozomu)

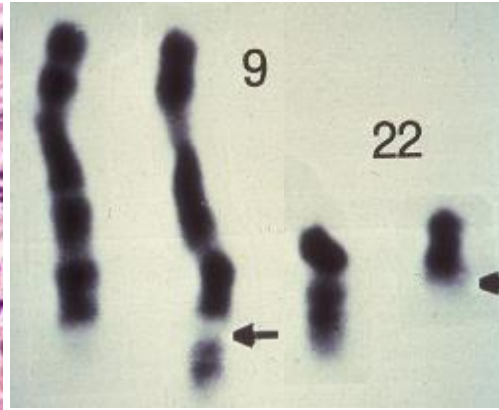
FISH
(BCR-ABL füzyonu)

PCR

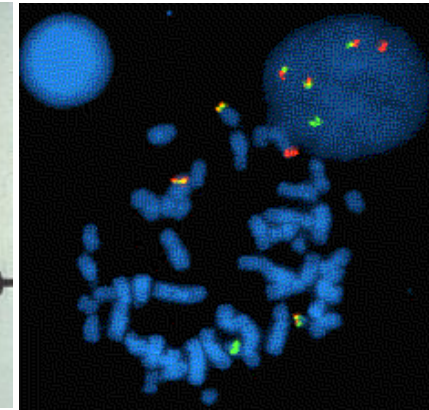


Periferik kan

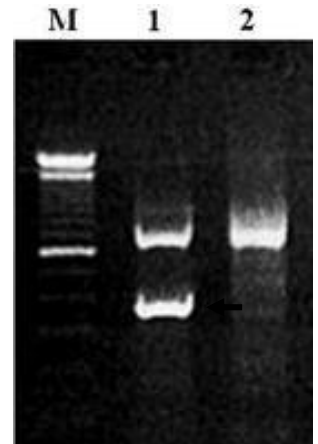
Kemik iliği
(Myeloid hiperplazi)



Kromozomal translokasyon
 $t(9;22)(q34;q11)$



Anormal BCR-ABL
Kırmızı: BCR
Yeşil: ABL
Sarı: fusion



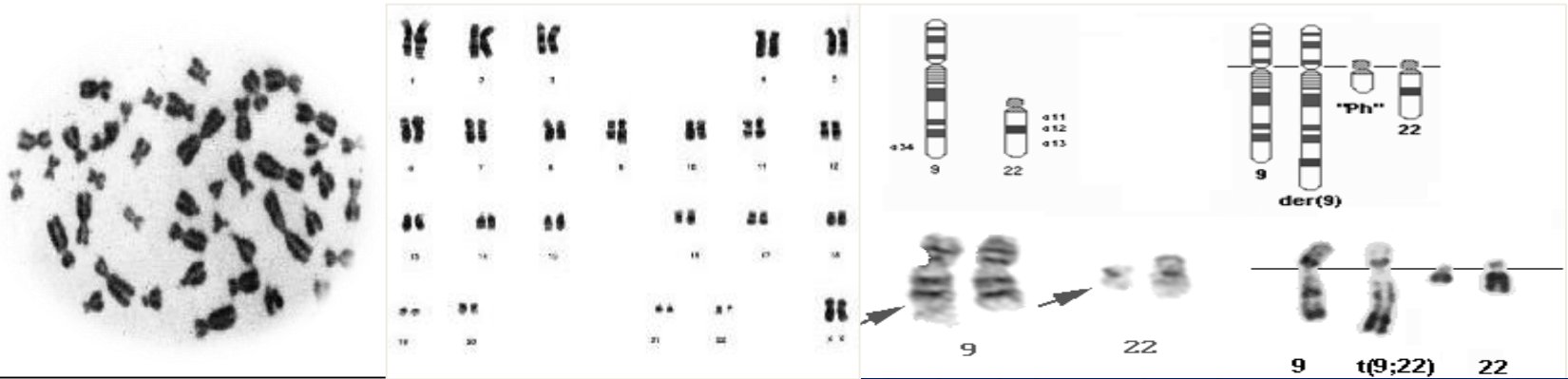
Anormal BCR-ABL
Lane 1: BCR-ABL+
Lane 2: BCR-ABL-

KML'DE TANI

Philedelphia kromozomu: Klasik sitogenetik testi ile tespit edilir. Kİ

Bcr-Abl füzyon geni: FISH ile tespit edilir. PK+ Kİ

Füzyon genin mRNA gen ürünü: PCR ile tespit edilir. PK+Kİ



ABL 1132H12+835J22

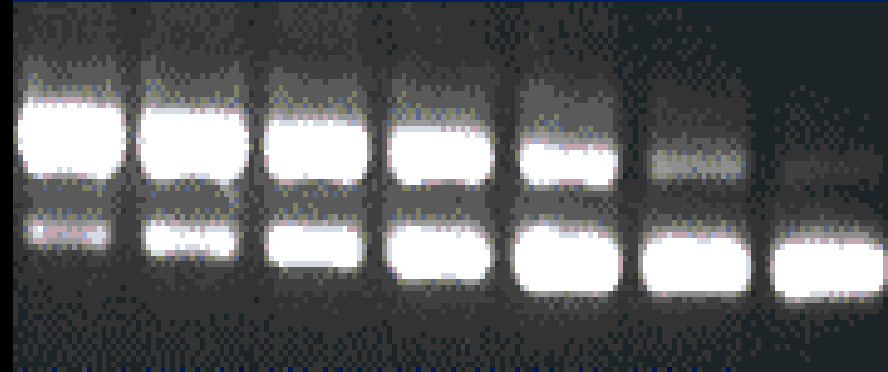
BCR 72M14

Ph

Ph

fluorescence in situ
hybridization

10^6 $10^{5.5}$ 10^5 $10^{4.5}$ 10^4 $10^{3.5}$ 10^3

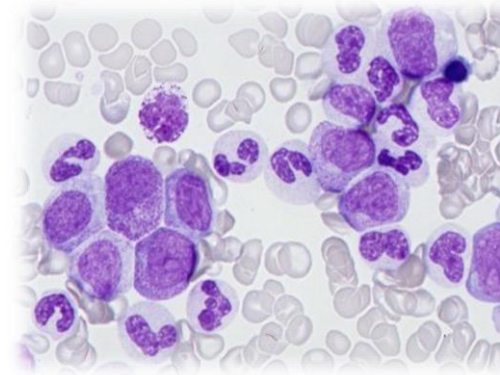
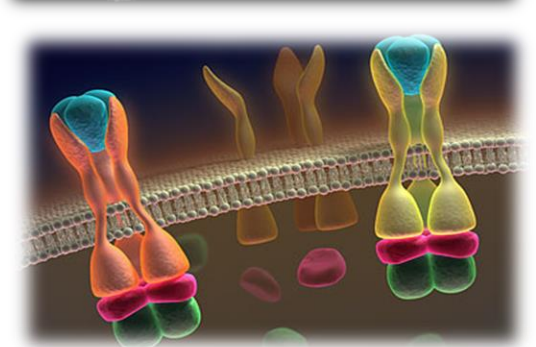
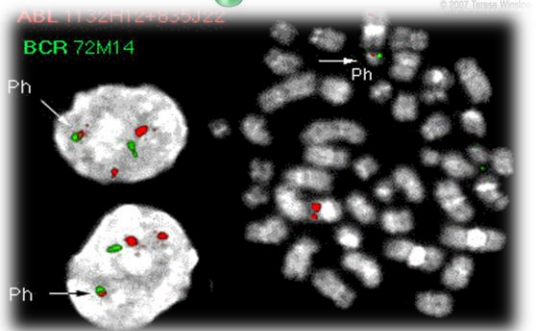
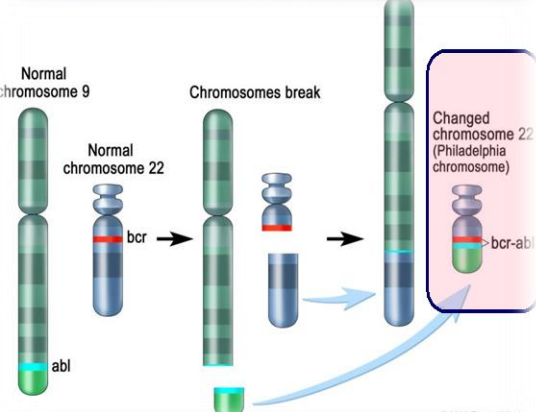
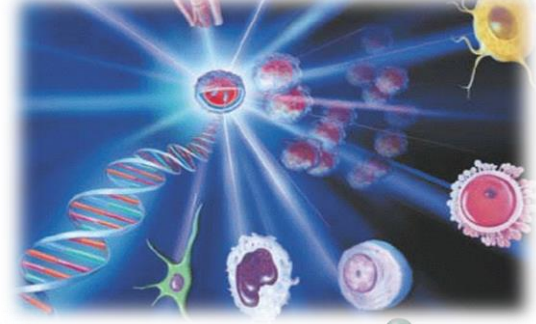


Prognostik Risk Skorlama Sistemleri

Study	Calculation	Risk Definition by Calculation
Sokal et al, 1984 ⁷	$\text{Exp } 0.0116 \times (\text{age in years} - 43.4) + 0.0345 \times (\text{spleen} - 7.51) + 0.188 \times [(\text{platelet count} \div 700)^2 - 0.563] + 0.0887 \times (\text{blast cells} - 2.10)$	low risk, < 0.8 intermediate risk, 0.8-1.2 high risk, > 1.2
Euro Hasford et al, 1998 ⁸	$0.666 \text{ when age} \geq 50 \text{ years} + (0.042 \times \text{spleen}) + 1.0956 \text{ when platelet count} > 1,500 \times 10^9 \text{L} + (0.0584 \times \text{blast cells}) + 0.20399 \text{ when basophils} > 3\% + (0.0413 \times \text{eosinophils}) \times 100$	low risk, ≤ 780 intermediate risk, 781-1,480 high risk, > 1,480
EUTOS Hasford et al 2011 ⁹	$\text{Spleen} \times 4 + \text{basophils} \times 7$	low risk ≤ 87 ; high risk > 87

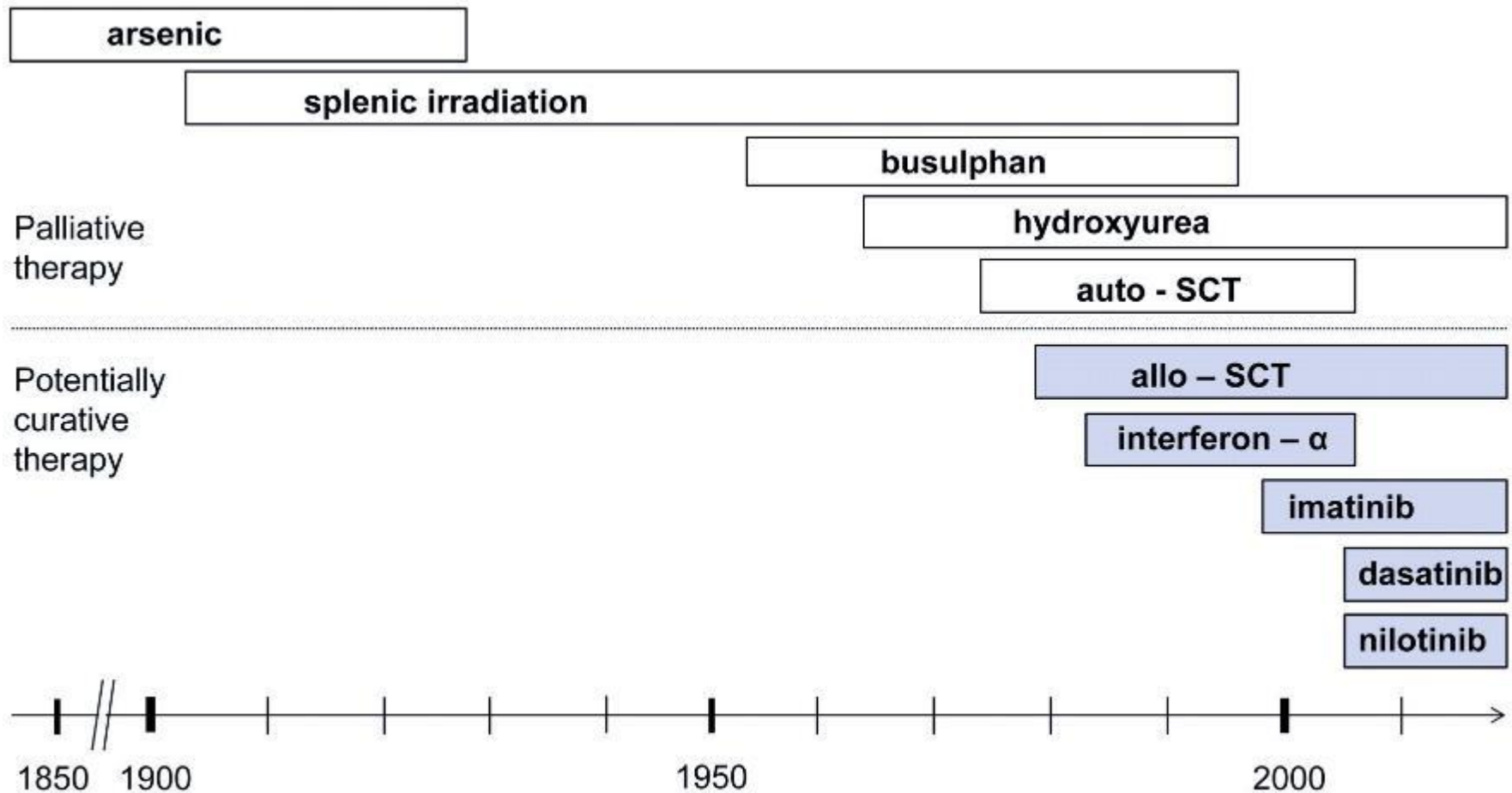
Calculation of relative risk.

Age is in years. Spleen is in centimeters below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are in percent of peripheral blood differential. All values must be collected prior to any treatment. To calculate Sokal and Euro risk score: http://www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html. To calculate EUTOS risk score: http://www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html.



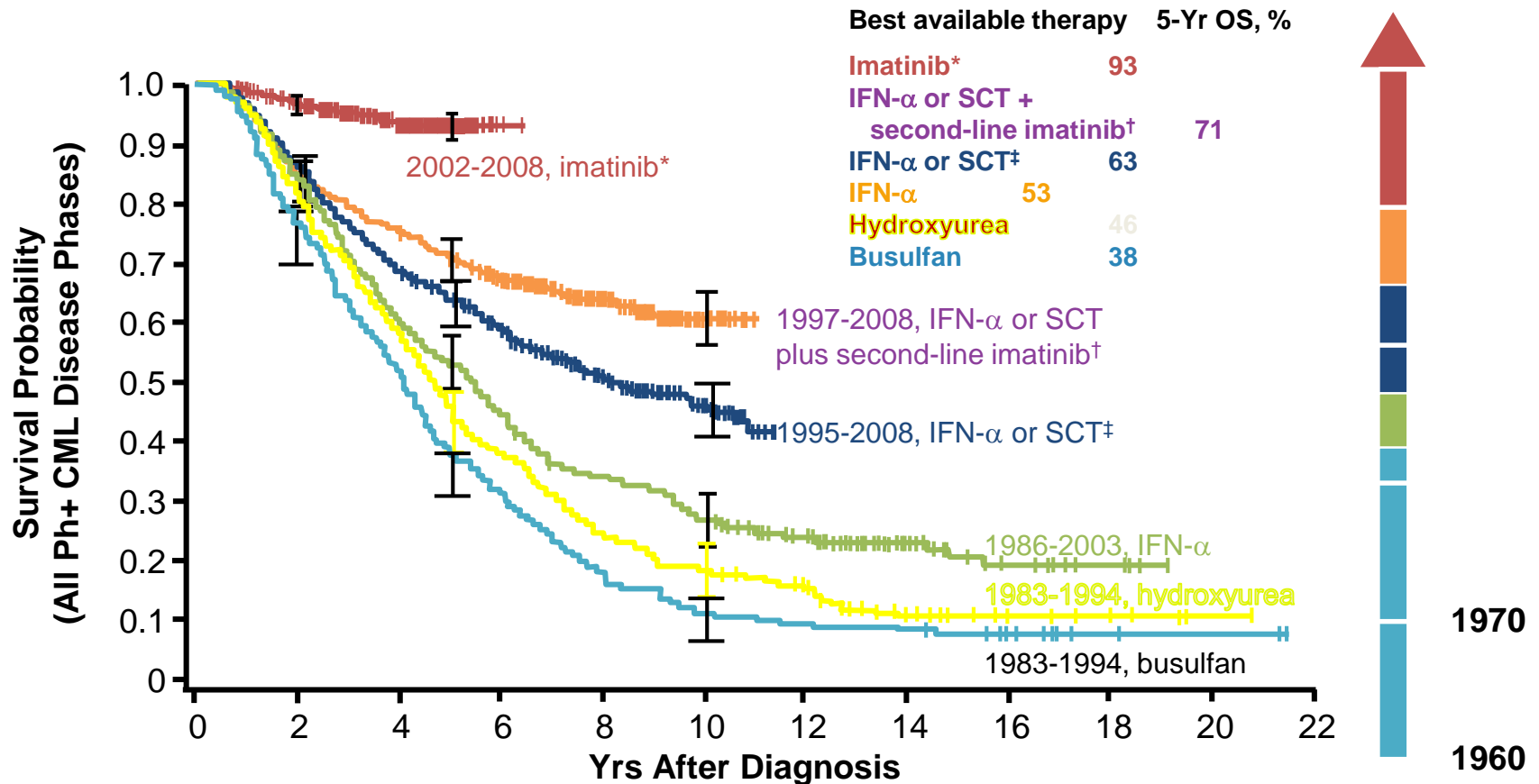
KML – Tedavi

KML'DE DEĞİŞEN TEDAVİ



Pavlů J et al. Blood 2011;117:755-763

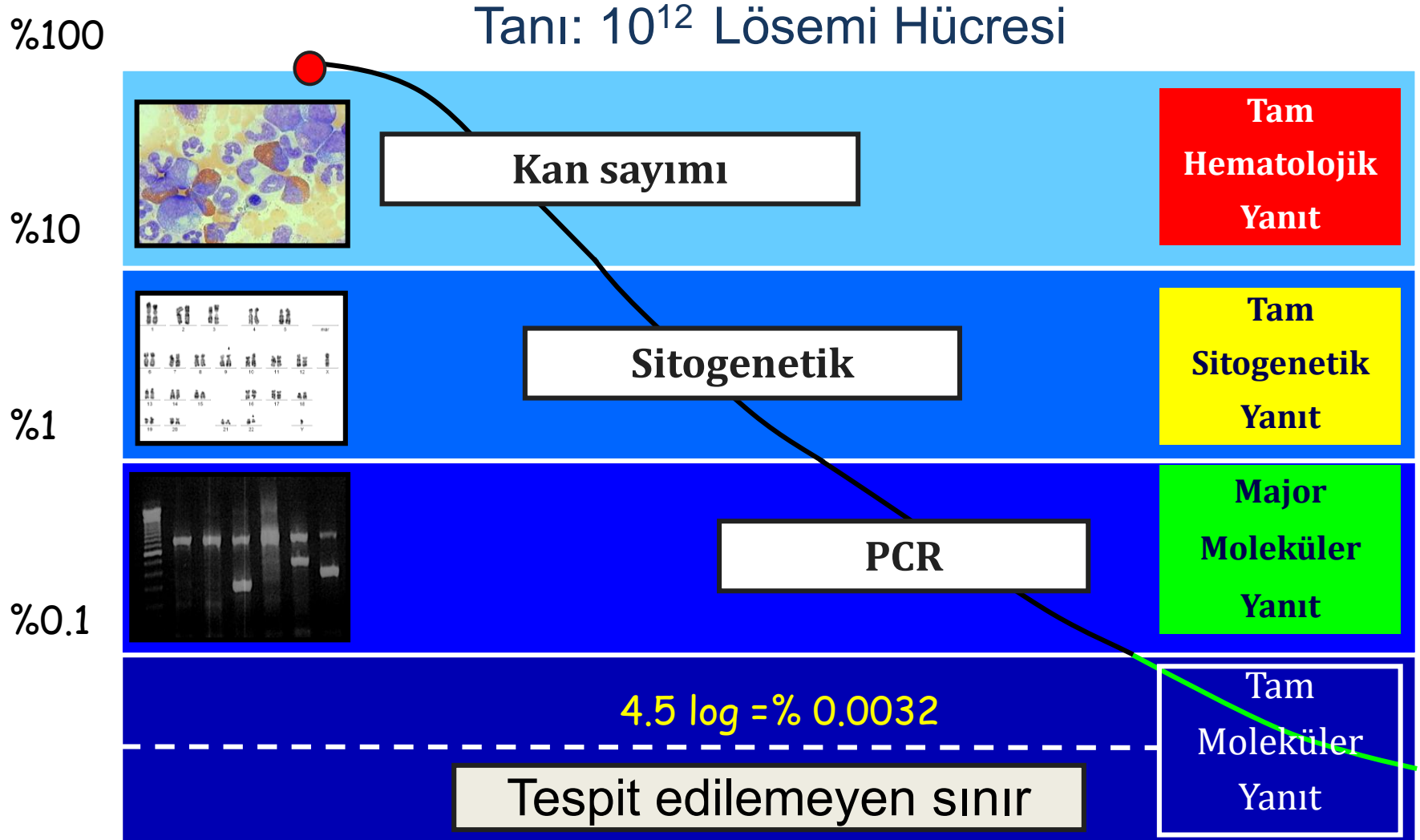
KML'de değişen survival



*CML IV. [†]CML IIIA. [‡]CML III.

Leitner AA, et al. Internist (Berl). 2011;52:209-217.

KML TEDAVİ HEDEFLERİ



HEMATOLOJİK YANIT KRİTERİ

UPDATE
2013

Tam hematolojik yanıt:

- Lökosit sayısı $< 10 \times 10^9/L$ ile birlikte periferik kan sayımlarının tam olarak normal olması,
- Platelet sayısı $< 450 \times 10^9/L$,
- Periferik kanda myelosit, promyelosit veya blast olmaması,
- Palpable SM'nin kaybolması ile birlikte hastalık bulgu ve semptomlarının olmaması.

SİTOGENETİK YANIT KRİTERİ

(en az 20 metafaz incelenmeli: Ph + metafaz sayısı)



Sitogenetik Yanıt:

- **Tam:** Ph+0
- **Kısmi:** Ph+ %1-35
- **Majör:** Ph+ %0-35
(Kısmi + Tam)
- **Minör:** Ph+>%35



Sitogenetik Yanıt:

- **Tam:** Ph+ %0
- **Majör:** Ph+ %1-35
- **Minör:** Ph+ %36-65
- **Minimal:** Ph+ %66-95
- **Yok:** Ph+> %95

MOLEKÜLER YANIT KRİTERİ

Majör Moleküler Yanıt:

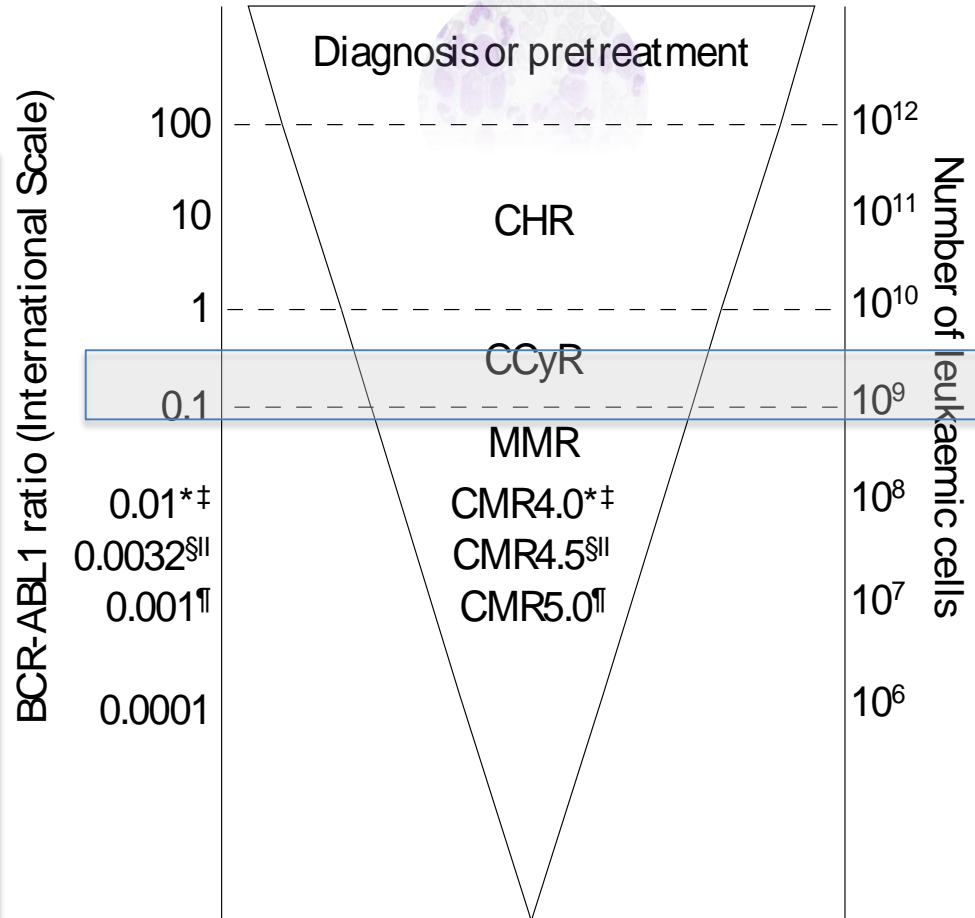
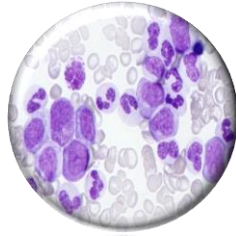
- Q-PCR ile BCR-ABL transkriptleri $\leq \% 0.1$ (IS) veya BCR-ABL mRNA'sında Q-PCR $\geq 3\log$ azalma (IS yok ise)

Tam Moleküler Yanıt:

- Standart bazalin en az 4.5 log aşağısını ölçme duyarlılığına sahip Q-PCR (IS) ile BCR-ABL RNA'sının tespit edilemesi

ELN “Moleküler olarak tespit edilemeyen lösemi” teriminin kullanılması önerilmektedir.

KLM'de Tedavi Hedefleri



IS'ya göre tedavi edilmemiş hastada ortalama BCR-ABL seviyesi %100,

1 log azalma = IS %10

2 log azalma = IS %1 = CCyR

3 log azalma = IS'da % 0.1 MMY

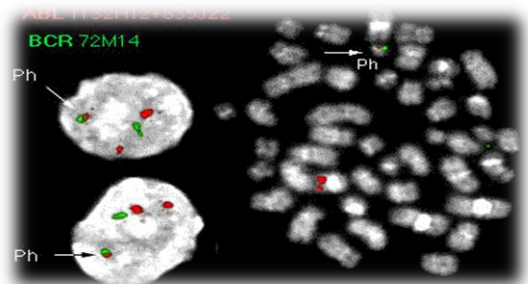
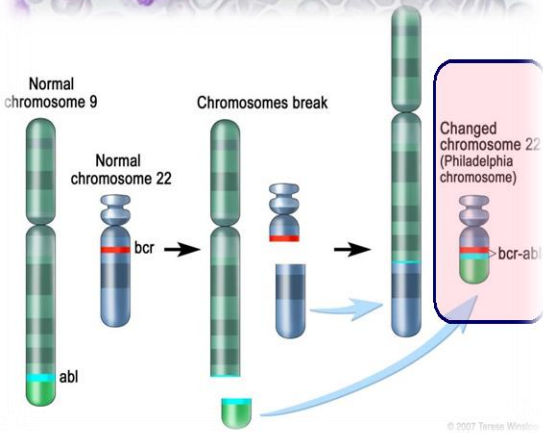
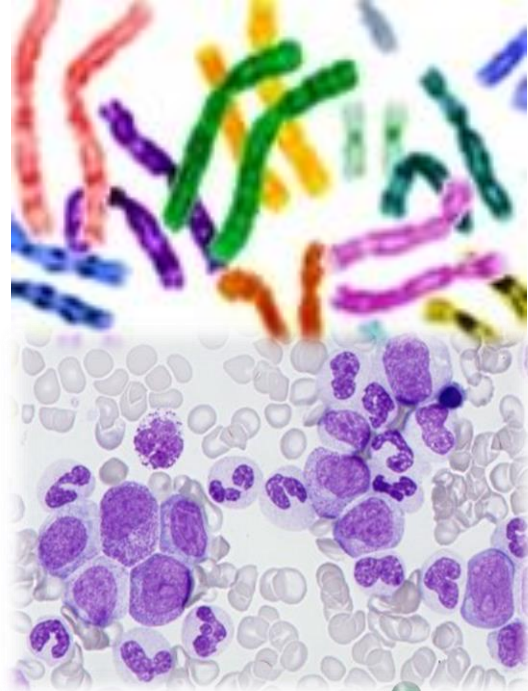
4 log azalma = IS % 0.01

4.5 log azalma = IS %0.0032

5 log azalma = IS %0.001

KLM'de Tedavi Hedefleri

- Tam hematolojik yanıt (CHR)
- Sitogenetik yanıt (CCyR)
- Moleküler yanıt (MMR)



KML – SİTOGENETİK YANIT

Sitogenetik yanıtın önemi

- Sitogenetik cevaba ulaşılması İMB ile tedavi edilen hastalarda uzun dönem survivalın önemli bir prognostik göstergesidir.
- IRIS çalışmasında
6.ayda herhangi bir Cy yanıt,
12 . ayda MCyR elde edilenlerde bu hedefe ulaşamayanlara göre daha iyi PFS elde edildi.

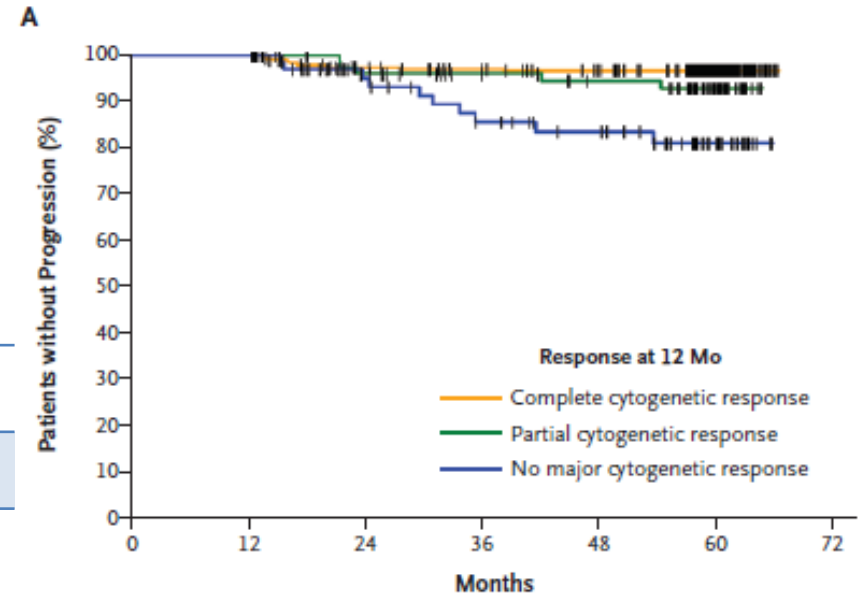
Five-Year Follow-up of Patients Receiving
Imatinib for Chronic Myeloid Leukemia

N Engl J Med 2006;355:2408-17.

Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia

- Median 60 aylık takipte PFS
- 12. Ayda MCyR'a ulaşamayanlara göre CCyR/PCyR'a ulaşanlarda daha iyi

12. Ay Cy	CCyR	MCyR	MCyR YOK
PFS	%97	%93	%81



IRIS

- 3. ayda minör CyR
- 6. veya 12. ayda PCyR
- 18. ayda CCyR gözlem süresince stable CCyR ile birlikte.

Imatinib for Newly Diagnosed Patients With Chronic Myeloid Leukemia: Incidence of Sustained Responses in an Intention-to-Treat Analysis

Hugues de Lavallade, Jane F. Apperley, Jamshid S. Khorashad, Dragana Milojkovic, Alistair G. Reid, Marco Bua, Richard Szydlo, Eduardo Olavarria, Jaspal Kaeda, John M. Goldman, and David Marin

Results

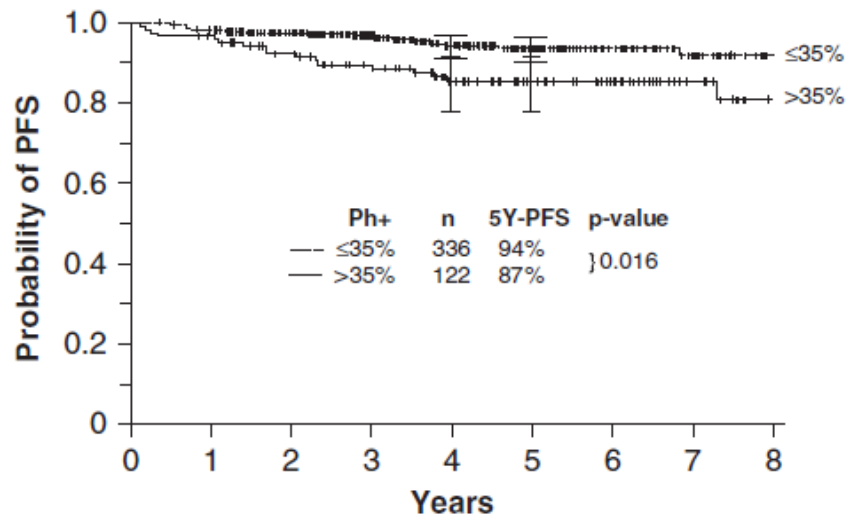
At 5 years, cumulative incidences of complete cytogenetic response (CCyR) and major molecular response (MMR) were 82.7% and 50.1%, respectively. Estimated overall survival and PFS were 83.2% and 82.7%, respectively. By 5 years, 25% of patients had discontinued imatinib treatment because of an unsatisfactory response and/or toxicity. The 5-year probability of remaining in major cytogenetic response while still receiving imatinib was 62.7%. Patients achieving a CCyR at 1 year had a better PFS and overall survival than those failing to reach CCyR, but achieving a MMR conferred no further advantage. The identification of a kinase domain mutation was the only factor predicting for loss of CCyR.

1 yıl imatinib tedavisi sonrası elde edilen CCyR
OS ve PFS için majör prognostik faktördür.

5 yıllık OS %98 x %74 $p=0.03$

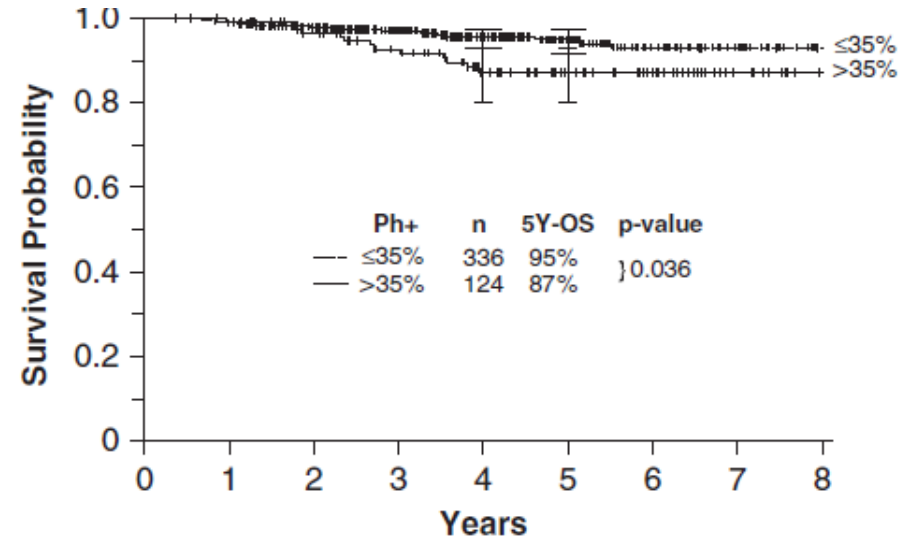
Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML)

B Hanfstein^{1,23}, MC Müller^{1,23}, R Hehlmann¹, P Erben¹, M Lauseker², A Fabarius¹, S Schnittger³, C Haferlach³, G Göhring⁴,



Patients at risk (n)

Ph+	≤35%	324	285	235	174	123
	>35%	118	104	91	70	52



Patients at risk (n)

	≤35%	327	286	236	177	126
	>35%	121	108	94	72	53

5 yıllık OS 3. ayda PCyR -----5 yıllık OS %95, PCyR yok ise %87

6. ayda CCyR -----5 yıllık OS %97, PCyR yok ise %91

The achievement of an early complete cytogenetic response is a major determinant for outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors

Elias Jabbour,¹ Hagop Kantarjian,¹ Susan O'Brien,¹ Jenny Shan,¹ Alfonso Quintas-Cardama,¹ Stefan Faderl,¹

- IMT400, IMT800 ve 2. kuşak TKI
- 3, 6, ve 12. Aylarda CCyR'a ulaşanlar önemli derecede daha iyi 3 yıllık EFS ve OS
- EFS (%98, %97 %98'e karşın %83, %72, %67 p<0.001)
- OS (%99, %99, %99'e karşın %95, %90, %94 p<0.001)
- İkinci kuşak tirozin kinaz inhibitörleri imatinibe göre daha yüksek oranda CCyR ve MMR'ı indükler.
- **Erken CCy'a ulaşmak halen MMR'a ulaşılsın ya da ulaşılmamasın hala KML sonucunu belirleyen majör belirteçtir.**

Early responses predict better outcomes in patients with newly diagnosed chronic myeloid leukemia: results with four tyrosine kinase inhibitor modalities

Preetesh Jain, Hagop Kantarjian, Aziz Nazha, Susan O'Brien, Elias Jabbour, Carlos Guillermo Romo, Sherry Pierce,

IM400, IM800, Nilotinib, Dasatinib; EFS, OS, TR

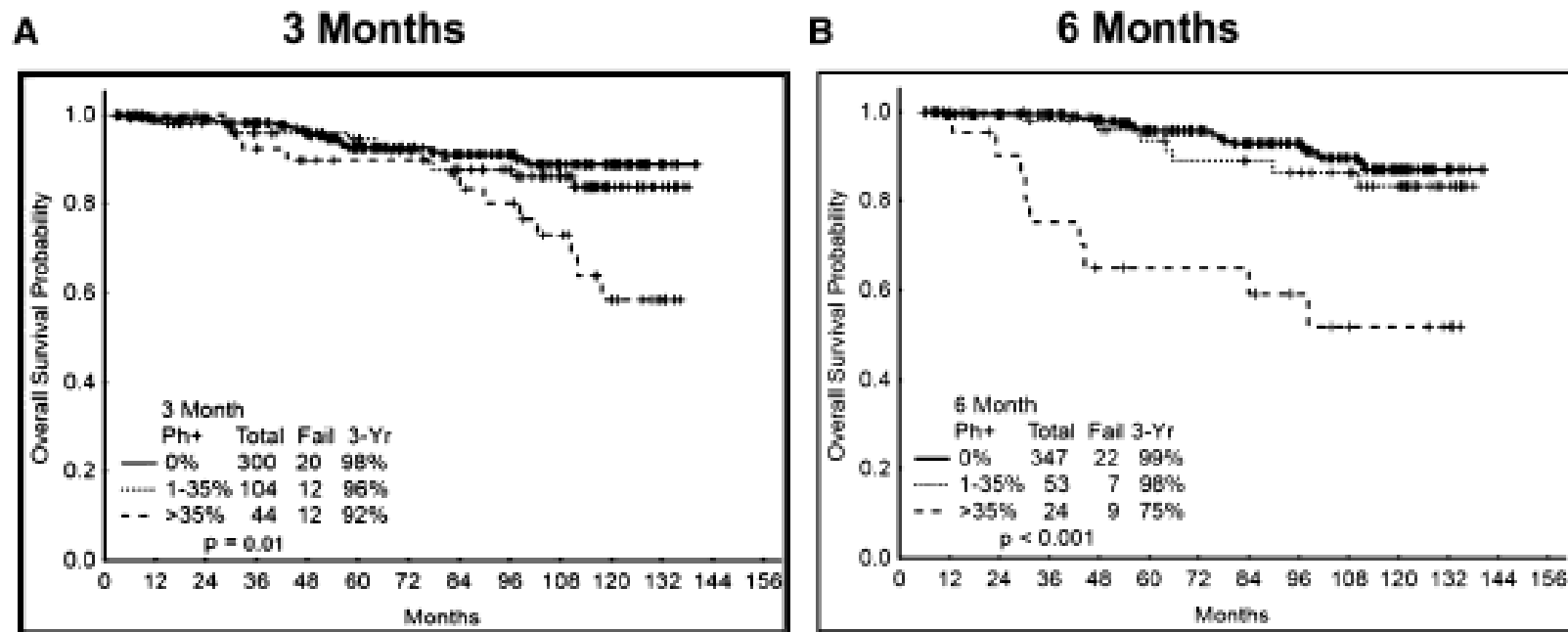
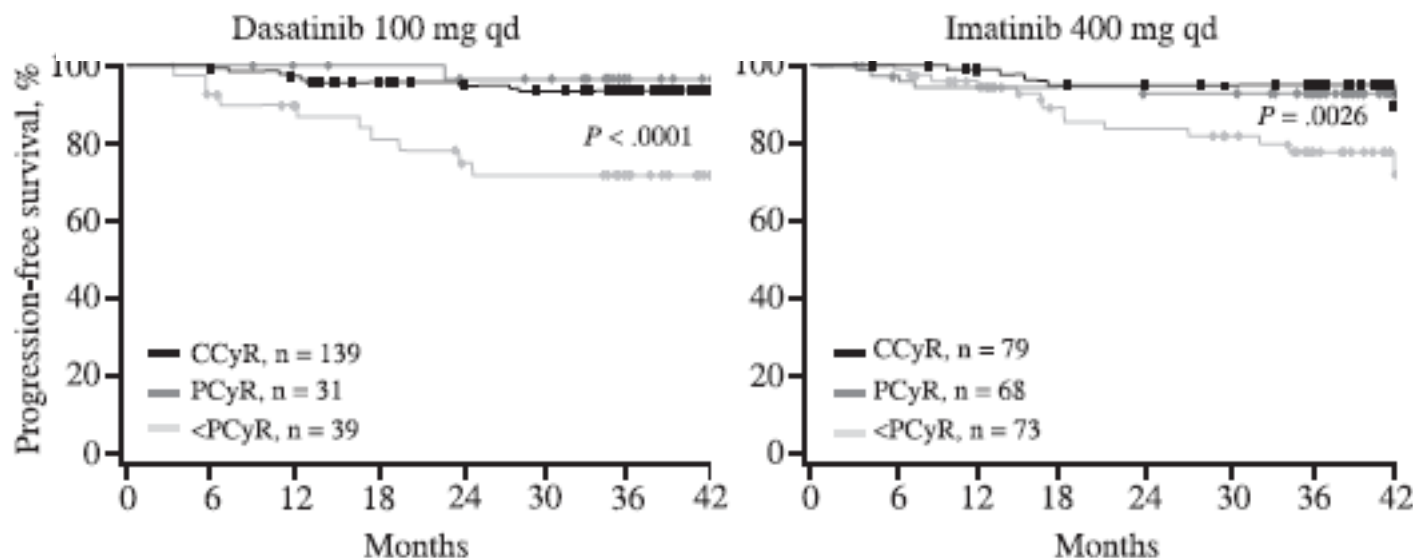


Figure 5. OS according to cytogenetic response at 3 and 6 mo. (A) OS by cytogenetic response at 3 mo. (B) OS by cytogenetic response at 6 mo.

IM400 ile genç sokal risk skoru yüksek hastalarda
daha az stg yanıt oranları ile birlikte

Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION)

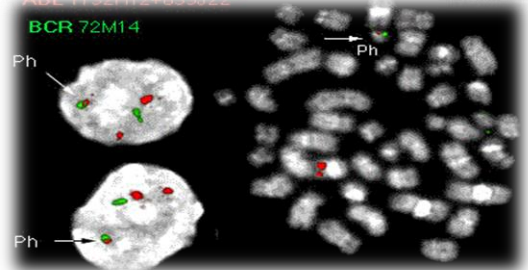
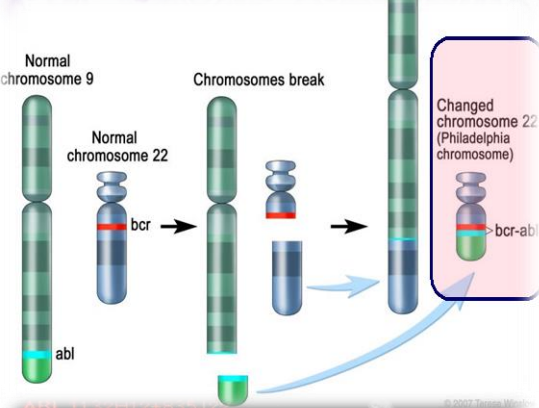
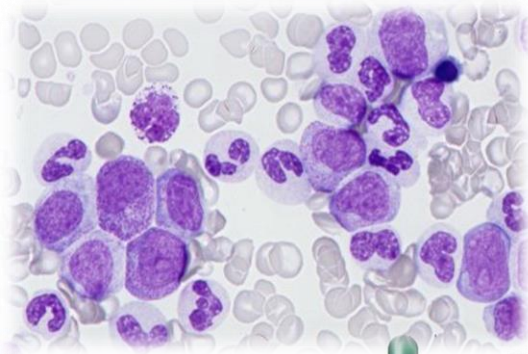
Elias Jabbour,¹ Hagop M. Kantarjian,¹ Giuseppe Saglio,² Juan Luis Steegmann,³ Neil P. Shah,⁴ Concepción Boqué,⁵



- DASISION landmark analizinde 1. Sıra dasatinib / imatinib ile
- 3. ve 6. Ayda MCyR önemli derecede prediktör
- 3 yıllık PFS %94 iken 3 ve 6 aylarda MCyR'a ulaşamayan hastalar için %71 ve %84'dür.

Sitogenetik yanıtın önemi

- ✂ Erken sitogenetik cevaba ulaşılması TKI inhleri ile tedavi edilen hastalarda uzun dönem survivalın en önemli prognostik göstergesidir.
- ✂ CCYR'a ulaşılması daha iyi PFS ve OS ile birlikte.

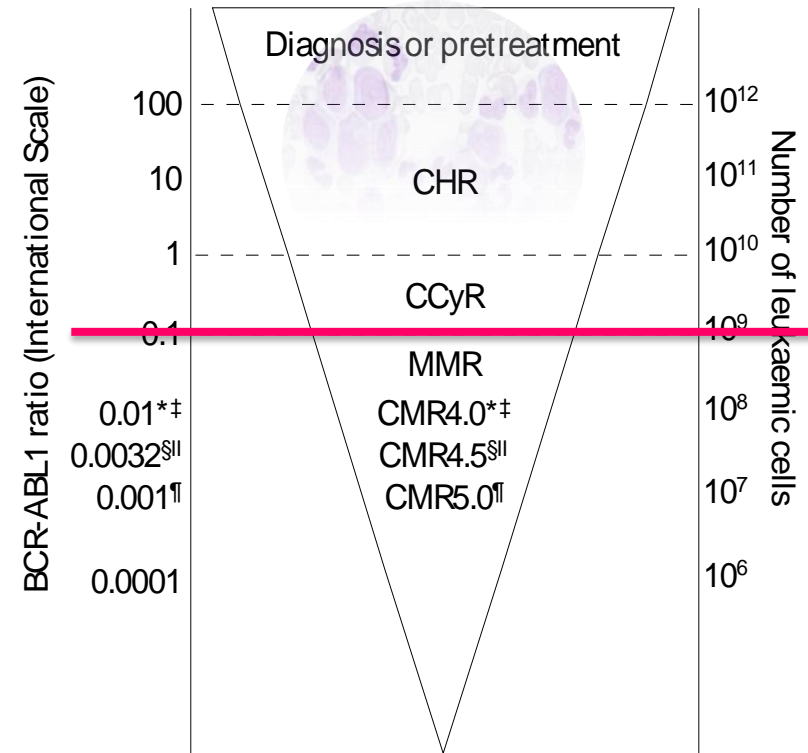


KML

MOLEKÜLER YANIT

Moleküler yanıt

- TKI tedavisi sonrası
Tam sitogenetik yanıtı
yakalayan hastalar için
MMR'a ulaşılması
gerçekten gerekli mi?



Imatinib for Newly Diagnosed Patients With Chronic Myeloid Leukemia: Incidence of Sustained Responses in an Intention-to-Treat Analysis

Hugues de Lavallade, Jane F. Apperley, Jamshid S. Khorashad, Dragana Milojkovic, Alistair G. Reid, Marco Bua, Richard Szydlo, Eduardo Olavarria, Jaspal Kaeda, John M. Goldman, and David Marin

Results

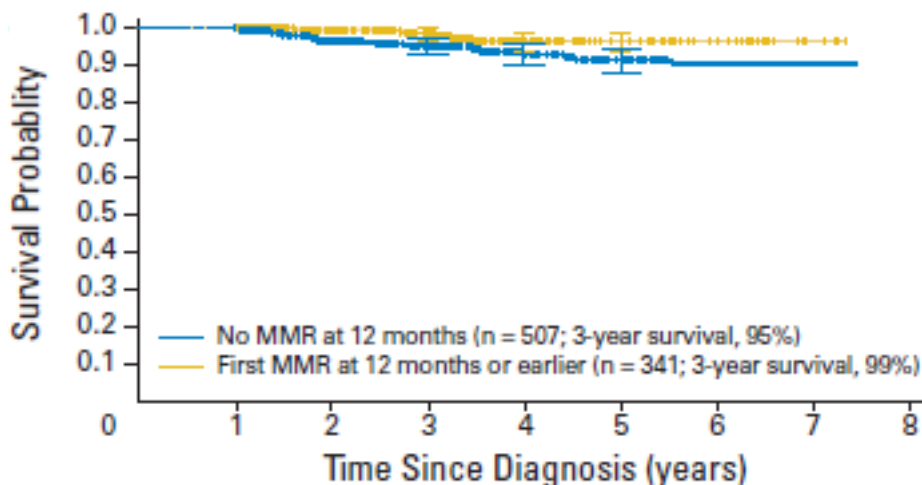
At 5 years, cumulative incidences of complete cytogenetic response (CCyR) and major molecular response (MMR) were 82.7% and 50.1%, respectively. Estimated overall survival and PFS were 83.2% and 82.7%, respectively. By 5 years, 25% of patients had discontinued imatinib treatment because of an unsatisfactory response and/or toxicity. The 5-year probability of remaining in major cytogenetic response while still receiving imatinib was 62.7%. Patients achieving a CCyR at 1 year had a better PFS and overall survival than those failing to reach CCyR, but achieving a MMR conferred no further advantage. The identification of a kinase domain mutation was the only factor predicting for loss of CCyR.

1 yıl imatinib tedavisi sonrası elde edilen CCyR OS ve PFS için majör prognostik faktördür.

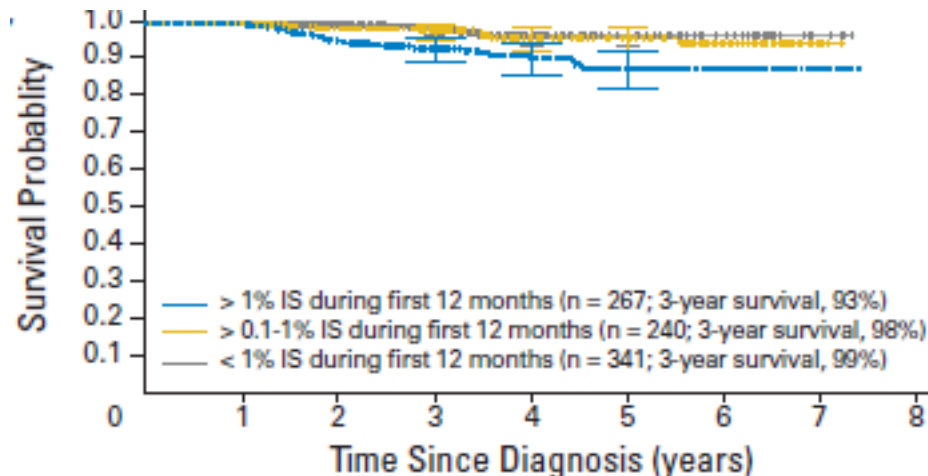
Ancak ek olarak MMR'a ulaşmanın ek katkısı gösterilememiştir.

Tolerability-Adapted Imatinib 800 mg/d Versus 400 mg/d Versus 400 mg/d Plus Interferon- α in Newly Diagnosed Chronic Myeloid Leukemia

Rüdiger Hehlmann, Michael Lauseker, Susanne Jung-Munkwitz, Armin Leitner, Martin C. Müller, Nadine Pletsch, Ulrike Proetel, Claudia Haferlach, Brigitte Schlegelberger, Leopold Balleisen, Mathias Hänel, Markus Pfirrmann, Stefan W. Krause, Christoph Nerl, Hans Pralle, Alois Gratwohl, Dieter K. Hossfeld, Joerg Hasford, Andreas Hochhaus, and Susanne Sauße



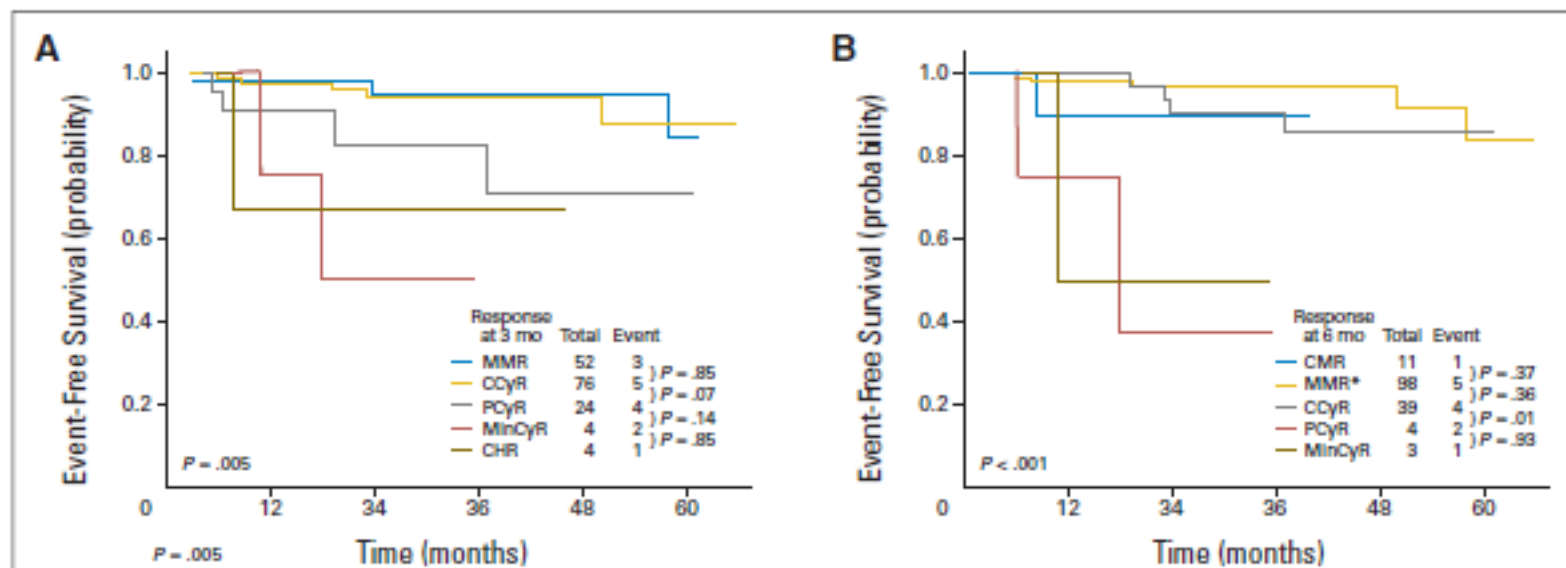
Patients at risk (n)



12. Ayda MMR'a ulaşanlarda 3 yıllık OS daha iyi
Ancak CCyR'a ulaşanlarda MMR'a ulaşip ulaşmamak OS'ı etkilememekte

Front-Line Therapy With Second-Generation Tyrosine Kinase Inhibitors in Patients With Early Chronic Phase Chronic Myeloid Leukemia: What Is the Optimal Response?

Elias Jabbour, Hagop M. Kantarjian, Susan O'Brien, Jianqin Shan, Alfonso Quintás-Cardama, Guillermo Garcia-Manero, Mary Beth Rios, and Jorge E. Cortes



3, 6, 12 ve 18. ayda CCyR'a ulaşanlarda EFS'yi MMR'a ulaşılıp ulaşılmaması etkilemez

Results

Overall, 155 patients (93%) achieved complete cytogenetic response (CCyR), including 146 (87%) with major molecular response (MMR; complete in 46 patients [28%]). According to the ELN definitions, the rates of suboptimal response were 0%, 2%, 1%, and 12% at 3, 6, 12, and 18 months of therapy, respectively. There was no difference in EFS and CCyR duration between patients who achieved CCyR with and without MMR across all the landmark times of 3, 6, 12, and 18 months.

VOLUME 29 · NUMBER 32 · NOVEMBER 10 2011

JOURNAL OF CLINICAL ONCOLOGY

Molecular Responses in Patients with Chronic Myelogenous Leukemia in Chronic Phase Treated with Imatinib Mesylate

Jorge Cortes,^{1,2} Moshe Talpaz,² Susan O'Brien,¹ Dan Jones,³

Table 3. Significance of achieving molecular response in sustaining a complete cytogenetic remission

Best Bcr-Abl/Abl ratio	No. evaluable	No. who lost complete cytogenetic remission to		P	n
		PR/Minor/≥90%	Total (%)		
≥0.05%	68	12 + 4*/5+1*/3	25 (37)	<0.0001	
<0.05%	166	6 + 2*/0/1	9 (5)		
>0 and <0.05%	74	5/0/0	5 (7)	0.48	
Undetectable	82	1 + 1*/0/1	3 (4)		

* Patients lost complete cytogenetic remission only transiently.

Moleküler yanıt seviyesine ulaşamıyanların %37'si ile

MMR'a ulaşanların %5'i ve CMR'a ulaşanların %4'ü

CCyRlarını kaybetti

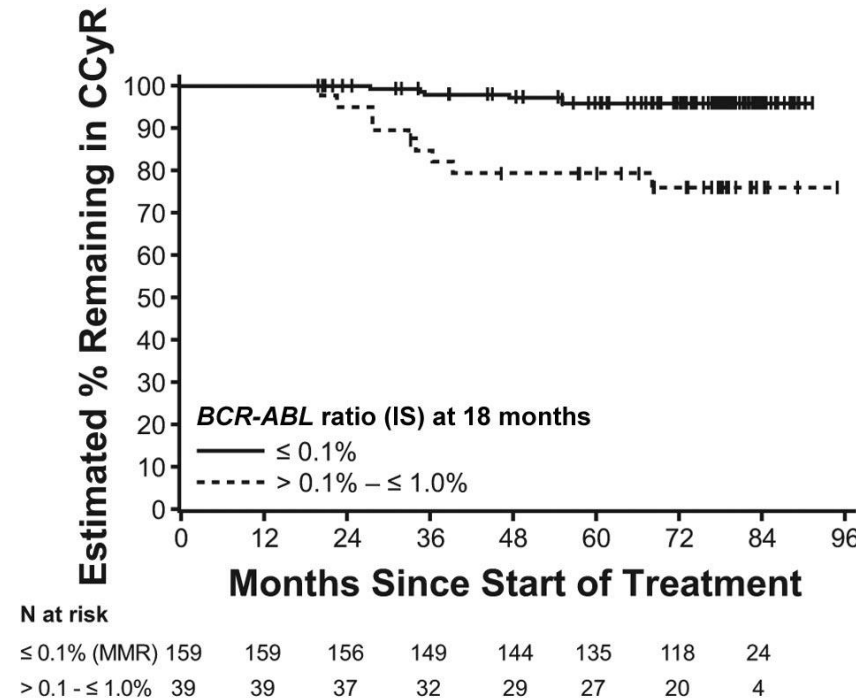
Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS)

*Timothy P. Hughes,¹ *Andreas Hochhaus,² Susan Branford,³ Martin C. Müller,⁴ Jaspal S. Kaeda,⁵ Letizia Foroni,⁶

IRIS 7 yıllık takibinde; bu sürede

CCyR kaybetme ihtimali

18. Ayda **MMR olanlarda** %3, **CCyR olup MMR yok ise** %26



Time to loss of CCyR at 18-month landmarks by molecular response.

GIMEMA çalışmasında da benzer sonuçlar bildirmişlerdir.

MMR elde edilmesi;

1- 12-18. ayda MMR'a ulaşılması daha uzun süre
CCyR birlikte,

IRIS; MMR ve PFS

IRIS 5 yıllık takibinde;

12. ay		
	CCyR+<MMR	CCyR+MMR
PFS	%97	%89

IRIS 84 aylık takibinde;

18. ay		
	MMR	<MMR
EFS P=0.01	%95	%89

IRIS çalışması 7. yılında tedavinin her hangi bir zamanında MMR'a ulaşan hastalarda progresyonun çok nadir olduğu gösterilmiştir.

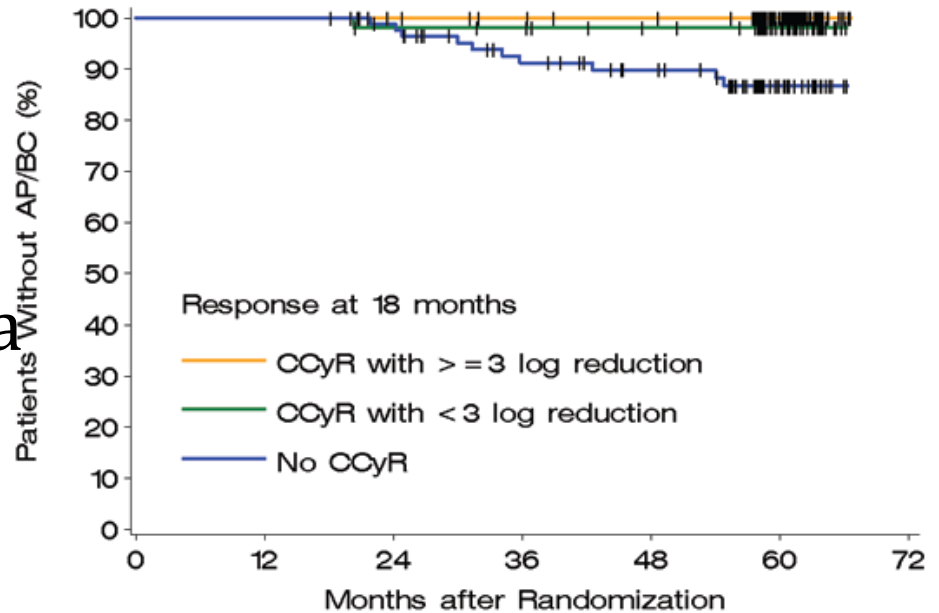
MMR elde edilmesi;

- 1- 12-18. ayda MMR'a ulaşılması daha uzun süre CCyR birlikte,
- 2- Daha düşük oranda PFS ve EFS ile birlikte,

Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia

Brian J. Druker, M.D., François Guilhot, M.D., Stephen G. O'Brien, I

- IRIS'in 5 yıllık takibinde 12. ve 18. ayda CCyR ve MMR'ı olan hiçbir hasta akselere veya blastik faza ulaşmamış.



12. ayda CCyR ve BCR-ABL1 seviyesinde en az 3 log azalma olan hastalar için

24. Ayda tahminin PFS %100, 12. ayda CCyR olup ve BCR-ABL1 seviyesinde 3 logdan az azalma olanlarda %95.

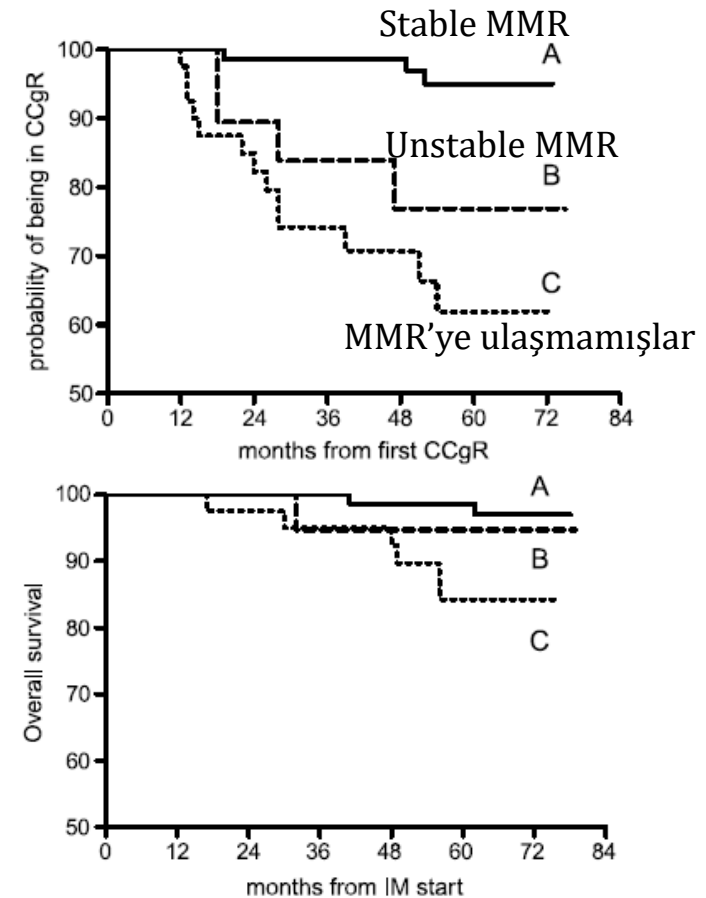
Majör moleküler yanıt

- 1- 12-18. ayda MMR'a ulaşılması daha uzun süre CCyR birlikte,
- 2- Daha düşük oranda PFS ve EFS ile birlikte,
- 3- Daha düşük oranda AP/BP'a dönüşüm ile birlikte,

Treatment of Philadelphia-Positive Chronic Myeloid Leukemia with Imatinib: Importance of a Stable Molecular Response

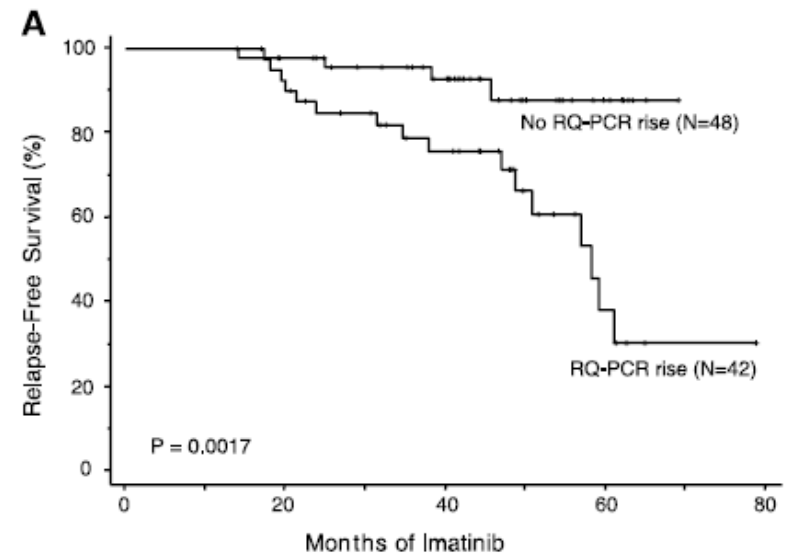
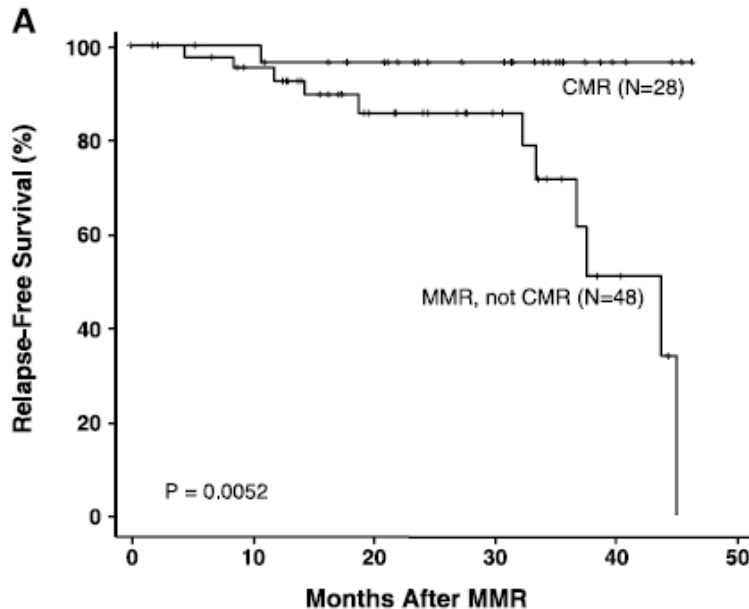
Francesca Palandri,¹ Ilaria Iacobucci,¹ Simona Soverini,¹ Fausto Castagnetti,¹ Angela Poerio,¹

- Stable MMRLı hastalar, stabil olmayan MMRLı ve hiç MMRL'si olmayan hastalar ile karşılaştırıldığında önemli derecede daha düşük CCyR kaybetme riskine sahiptirler
- (A%4 x B%21 p=0.03)
- (A%4 x C%33 p< 0.0001).



A Half-Log Increase in BCR-ABL RNA Predicts a Higher Risk of Relapse in Patients with Chronic Myeloid Leukemia with an Imatinib-Induced Complete Cytogenetic Response

Richard D. Press.¹ Chad Galderisi.¹ Rui Yan.¹ Carole Rempfer.¹ Stephanie G. Willis.²



- CMR'a ulaşan hastalarda RFS daha iyi

- MR'de 0.5 logluk artış RFS'ı etkilemekte

Majör moleküler yanıt

- 1- 12-18. ayda MMR'a ulaşılması daha uzun süre CCyR birlikte,
- 2- Daha düşük oranda PFS ve EFS ile birlikte,
- 3- Daha düşük oranda AP/BP'a dönüşüm ile birlikte,
- 4- MMR'ye ulaşıldıktan sonra MMR kaybı artmış hastalık relaps riski ile birlikte.

Time...

slips through my hands



Imatinib produces significantly superior molecular responses compared to interferon alfa plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase

S Branford¹, Z Rudzki¹, A Harper¹, A Grigg², K Taylor³, S Durrant⁴, C Arthur⁵, P Browett⁶, AP Schwart⁷, D Ma⁸, JF Seymour⁹, K Bradstock¹⁰, D Joske¹¹, K Lynch¹², I Gathmann¹³ and TP Hughes¹

- İMB'e erken MR'in prognostik önemi ilk olarak IRIS alt grup analizinde ortaya konulmuştur.
- 3. aya kadar BCR-ABL1'de 1 log azalma yok

veya

- 6. aya kadar BCR-ABL1'de 2 log azalma yok ise

hastalık progresyon insidansı önemli derecede daha yüksek...

We analyzed molecular responses in 55 newly diagnosed chronic-phase chronic myeloid leukemia (CML) patients enrolled in a phase 3 study (the IRIS trial) comparing imatinib to interferon-alfa plus cytarabine (IFN + AraC). *BCR-ABL/BCR%* levels were measured by real-time quantitative RT-PCR and were significantly lower for the imatinib-treated patients at all time points up to 18 months, $P < 0.0001$. The median levels for imatinib-treated patients continued to decrease and had not reached a plateau by 24 months. A total of 24 IFN + AraC-treated patients crossed over to imatinib. Once imatinib commenced, the median *BCR-ABL/BCR%* levels in these patients were not significantly different to those on first-line imatinib for the equivalent number of months. The incidence of progression in imatinib-treated patients, defined by hematologic, cytogenetic or quantitative PCR criteria, was significantly higher in the patients who failed to achieve a 1 log reduction by 3 months or a 2 log reduction by 6 months, $P = 0.002$. A total of 49 patients were screened for *BCR-ABL* kinase domain mutations. Mutations were detected in two imatinib-treated patients who crossed over from IFN + AraC and both lost their imatinib response. In conclusion, first-line imatinib-treated patients had profound reductions in *BCR-ABL/BCR%*, which significantly exceeded those of IFN + AraC-treated patients and early measurements were predictive of subsequent response.

Leukemia (2003) 17, 2401-2409

Delayed achievement of cytogenetic and molecular response is associated with increased risk of progression among patients with chronic myeloid leukemia in early chronic phase receiving high-dose or standard-dose imatinib therapy.

Quintás-Cardama A¹, Kantarjian H, Jones D, Shan J, Borthakur G, Thomas D, Kornblau S, O'Brien S, Cortes J.

Author information

Abstract

Patients not in complete cytogenetic response (CCyR) continuously face the competing possibilities of eventually achieving a cytogenetic response versus progressing. We analyzed the probability of achieving a CCyR, major molecular response, and progression in 258 patients with chronic myeloid leukemia in early chronic phase at 3, 6, and 12 months from imatinib start. The initial imatinib dose was 800 mg/day in 208 (81%) and 400 mg/day in 50 (19%) patients. For patients not in CCyR, the probability of achieving CCyR ($P = .002$) or major molecular response ($P = .004$) significantly decreased, whereas the risk of progression increased ($P = .16$) at each time point. Patients with a BCR-ABL1/ABL1 ratio greater than 1% to 10% after 3 months of imatinib had a 92% probability of achieving CCyR with continued therapy, similar to the 98% for those with 1% or less, but their risk of progression (11%) was almost 3-fold that of patients with a BCR-ABL1/ABL1 transcript ratio of 1% or less (4%) and similar to that of patients with transcript levels more than 10% (13%). These results suggest that patients not in CCyR after 12 months on imatinib have a higher risk of progression. This risk is discernible as early as 3 months into imatinib therapy by molecular analysis and may provide the rationale to institute therapies that render higher rates of early response.

- 3. ayda

BCR-ABL1 \leq %10 olanlara göre kıyaslandığında,

BCR-ABL1 $>$ %10 (IS) olan hastalar

CCyR veya MMR'ye ulaşma ihtimali daha düşük ve
progresyon ihtimali daha yüksek

Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML)

B Hanfstein^{1,23}, MC Müller^{1,23}, R Hehlmann¹, P Erben¹, M Lauseker², A Fabarius¹, S Schnittger³, C Haferlach³, G Göhring⁴,

Table 1. Five-year overall survival of patients grouped according to molecular response at 3 and 6 months, *P*-values comparing neighboring groups, hazard ratios comparing with the best or better response group

BCR-ABL ^{IS}	At 3 months (n = 692)			At 6 months (n = 789)		
	Pts (%) 5Y-OS	P-value (log-rank)	Hazard ratio (CI)	Pts (%) 5Y-OS	P-value (log-rank)	Hazard ratio (CI)
≤ 1%	218 (31%) 97.2%	n.s.	1	498 (63%) 96.9%	0.002	1
> 1%–10%	283 (41%) 93.9%		1.5 (0.6–4.0)	196 (25%) 89.6%		3.1 (1.5–6.6)
> 10%	191 (28%) 87.0%	0.012	3.6 (1.4–8.8)	95 (12%) 87.9%	n.s.	4.3 (1.9–9.7)
≤ 1%	218 (31%) 97.2%	0.049	1	498 (63%) 96.9%	<0.001	1
> 1%	474 (69%) 91.0%		2.3 (1.0–5.6)	291 (37%) 89.0%		3.5 (1.8–6.9)
≤ 10%	501 (72%) 95.2%	<0.001	1	694 (88%) 94.6%	0.007	1
> 10%	191 (28%) 87.0%		2.7 (1.5–5.1)	95 (12%) 87.9%		2.5 (1.3–5.1)

Abbreviations: BCR-ABL^{IS}, BCR-ABL transcript ratio according to the international scale; CI, 95% confidence interval; pts, number of patients; 5Y-OS, 5-year overall survival.

Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML)

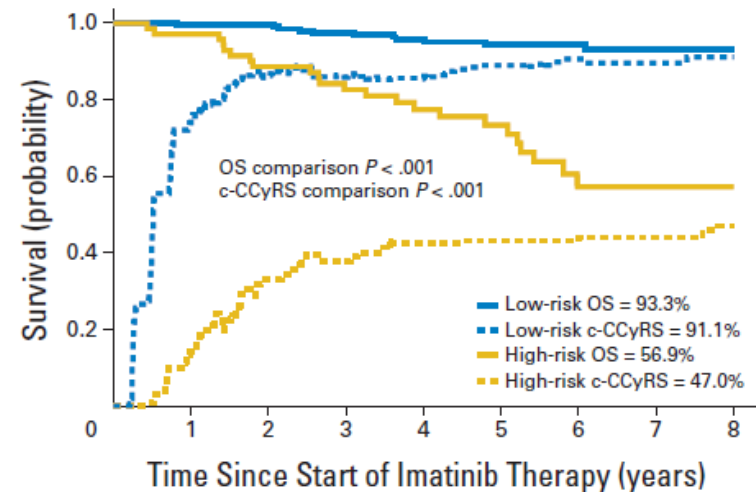
B Hanfstein^{1,23}, MC Müller^{1,23}, R Hehlmann¹, P Erben¹, M Lauseker², A Fabarius¹, S Schnittger³, C Haferlach³, G Göhring⁴,

- CML IV çalışması (imt ile tedavi edilen 1303 yeni tanı hasta) ,
- 3. ayda BCR-ABL >%10 ve 6. ayda BCR-ABL >%1 olan hastalar 5. yılda önemli oranda daha düşük OS ve PFS ile birlikte
- 3. ayda BCR-ABL >%10 ---- 5 yıllık OS %87,
BCR-ABL≤%10 ---- 5 yıllık OS %95 (p<0.0001)
- 6. ayda BCR-ABL >%10 ---- 5 yıllık OS %87.9,
BCR-ABL≤%10 ----5 yıllık OS %97 (p<0.0001)

Assessment of *BCR-ABL1* Transcript Levels at 3 Months Is the Only Requirement for Predicting Outcome for Patients With Chronic Myeloid Leukemia Treated With Tyrosine Kinase Inhibitors

David Marin, Amir R. Ibrahim, Claire Lucas, Gareth Gernard, Libai Wang, Richard M. Szydlo,

- Birinci sıra İMB ile tedavi edilen
- 282 CP-CML'li hasta,



3. AY BCR-ABL (IS)

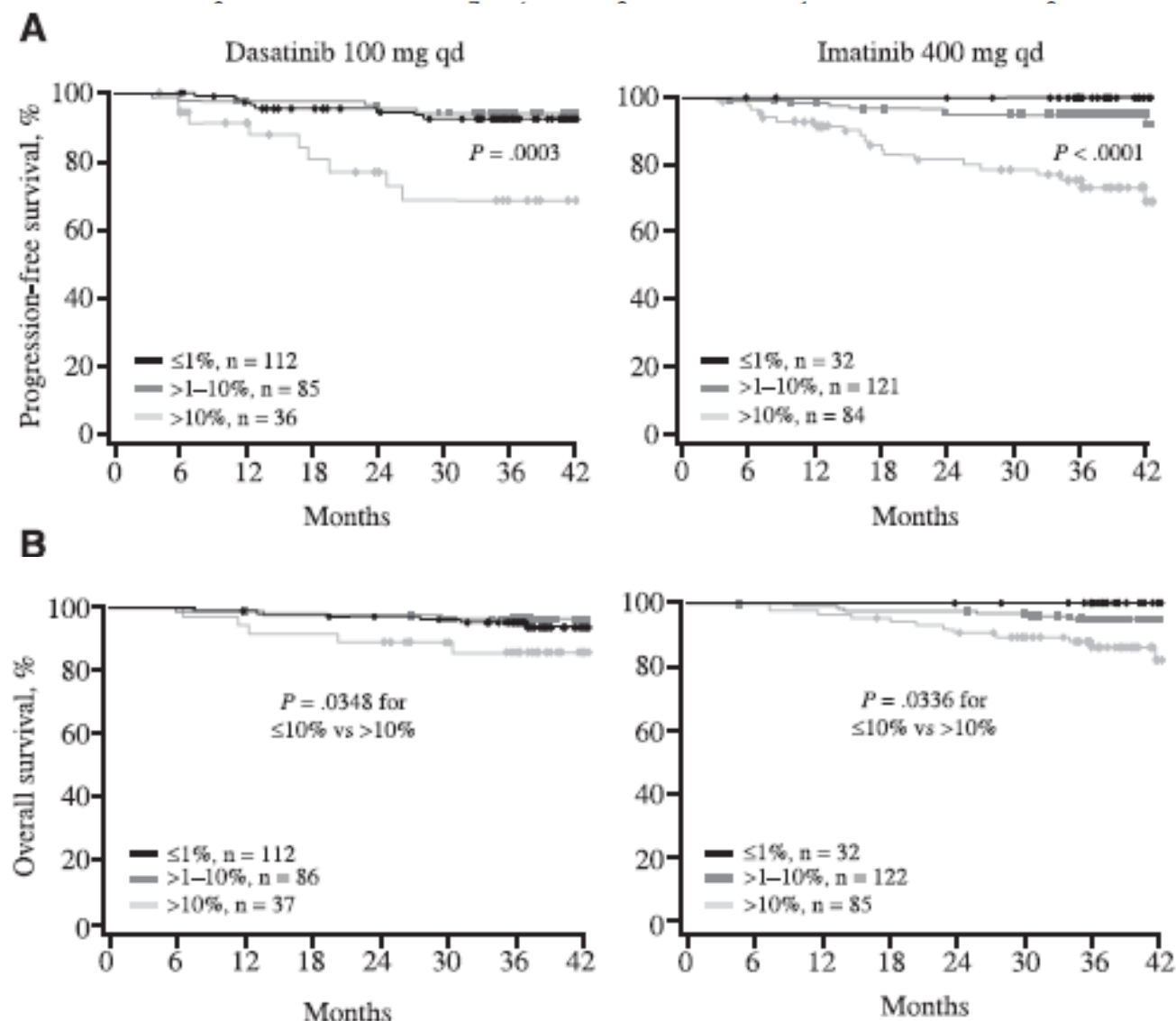
		≤%9.84	>%9.84
8. YIL	OS	%93.3	%56.9
	PFS	%92.8	%57
	EFS	%65	%6.9

2. Kuşak TKI lar için dönüm noktaları geçerli mi?

- DASISION ve ENESTnd çalışmalarının landmark analizi de yeni tanı alan CP CML hastalarında dasatinib ve nilotinib ile birinci sıra tedavide erken moleküler yanıtın prognostik önemini göstermiştir.

Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION)

Elias Jabbour,¹ Hagop M. Kantarjian,¹ Giuseppe Saglio,² Juan Luis Steegmann,³ Neil P. Shah,⁴ Concepción Boqué,⁵



Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION)

Elias Jabbour,¹ Hagop M. Kantarjian,¹ Giuseppe Saglio,² Juan Luis Steegmann,³ Neil P. Shah,⁴ Concepción Boqué,⁵

BLOOD, 23 JANUARY 2014

Final Study Results of the Phase 3 Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056)

Jorge E. Cortes, MD¹, Giuseppe Saglio, MD², Michele Baccarani, MD³, Hagop M. Kantarjian, MD¹, Jiří Mayer, MD⁴, Concepción

[December 6, 2014; Blood: 124 \(21\)](#)

		DASATİNİB		İMATİNİB	
		3. Ayda BCR-ABL		3. Ayda BCR-ABL	
		≤%10	>%10	≤%10	>%10
3. YIL	PFS (p<0.0001)	%93	%68	%96	%75
	OS (p=0.0348) (p=0.0036)	%96	%86	%96	%88
	AP/BP transformasyon	%3	%13	%3	%13
5.YIL	PFS p=0.0014/ p=0.0001	%89	%72	%93	%72
	OS p= 0.0028 / p= 0.0003	%94	%81	%95	%81
	AP/BP transformasyon	%3	%14	%3	%15

Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib

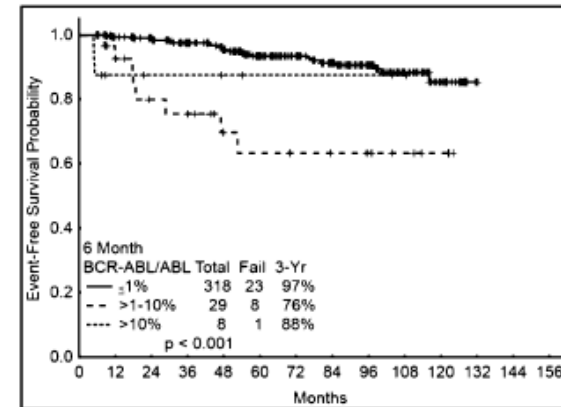
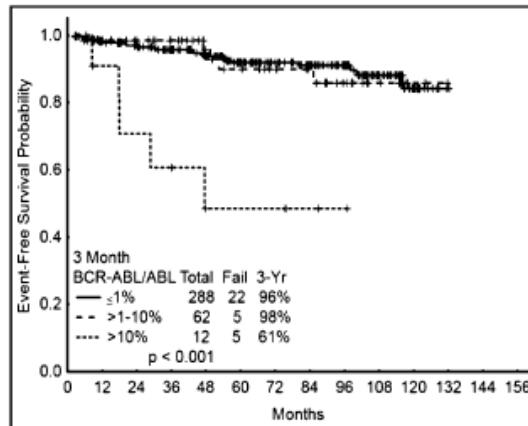
Timothy P. Hughes,^{1,2} Giuseppe Saglio,³ Hagop M. Kantarjian,⁴ François Guilhot,⁵ Dietger Niederwieser,⁶

- ENESTnd çalışmasında
- 3.ayda BCR-ABL>%10 daha düşük moleküler cevap, artmış progresyon riski ve daha düşük OS ile birlikte

	NİLOTİNİB 2X300MG		NİLOTİNİB 2X400MG		İMATİNİB	
	3. Ayda BCR-ABL		3. Ayda BCR-ABL		3. Ayda BCR-ABL	
	≤%10	>%10	≤%10	>%10	≤%10	>%10
2 yılda MMR'ye ulaşma p<0.0001	%80	%29	%75	%29	%58	%20
3 yıllık PFS p*	%95.2	%82.9	%89	%66.9	%97.7	%82.6
4 yıllık OS p*	%96.7	%86.7	%96.9	%92.7	%98.9	%83.6

Early responses predict better outcomes in patients with newly diagnosed chronic myeloid leukemia: results with four tyrosine kinase inhibitor modalities

Preetesh Jain, Hagop Kantarjian, Aziz Nazha, Susan O'Brien, Elias Jabbour, Carlos Guillermo Romo, Sherry Pierce,



3 yıllık EFS 3. ayda

BCR-ABL ≤ %1 -- %96

BCR-ABL > %1 - ≤ %10 -- %98

BCR-ABL > %10 -- %61

3 yıllık EFS 6. ayda

BCR-ABL ≤ %1 -- %97

BCR-ABL > %1 - ≤ %10 -- %98

BCR-ABL > %10 -- %88

- Çalışmalar

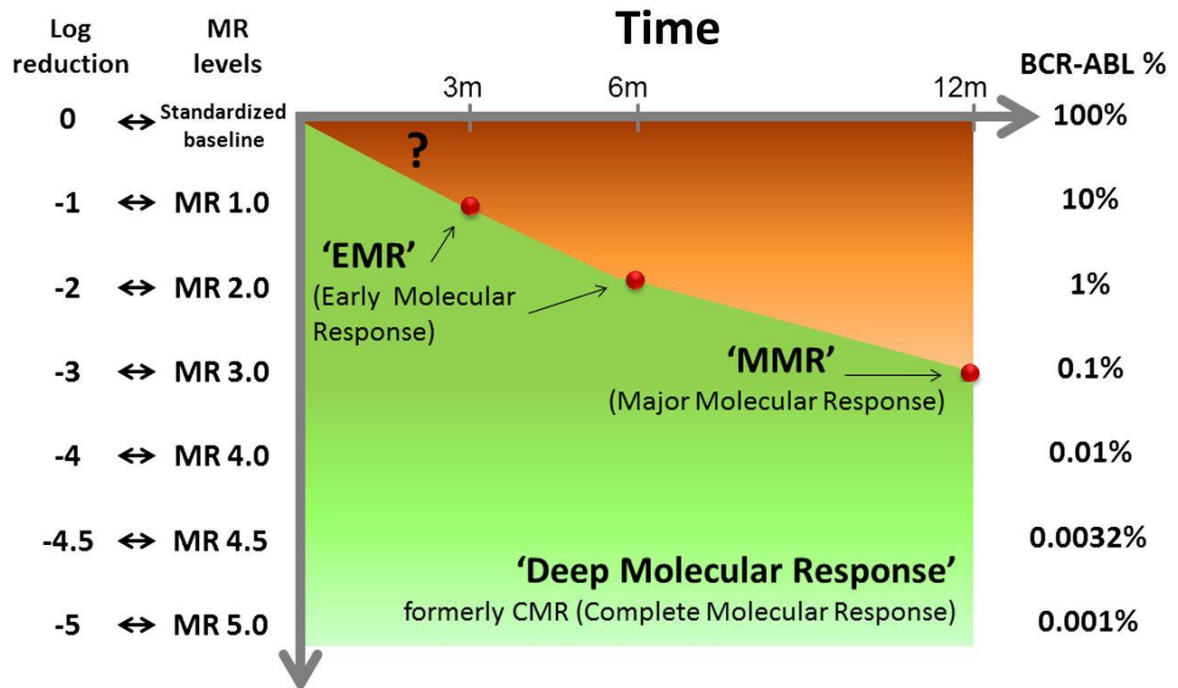
3 ay sonra BCR-ABL \leq %10 ve
6 ay sonra \leq %1 transkript seviyelerinin
uzun dönem sonuçlar için etkili prognostik
indikatör olduğunu gösterdi

Majör moleküler yanıt

- 1- 12-18. ayda MMR'a ulaşılması daha uzun süre CCyR birlikte,
- 2- Daha düşük oranda PFS ve EFS ile birlikte,
- 3- Daha düşük oranda AP/BP'a dönüşüm ile birlikte,
- 4- MMR'ye ulaşıldıktan sonra MMR kaybı artmış hastalık relaps riski ile birlikte.
- 5- 3. ve 6. aylardaki erken moleküler yanıtlar daha iyi survival ile birlikte.

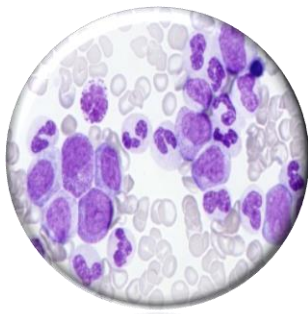
KLM'de Yeni Tedavi Hedefleri

- Erken tam sitogenetik yanıt (CCyR)
- Hızlı moleküler yanıt (MMR)
- Daha hızlı derin kalıcı moleküler yanıtlar (MR4, MR4.5 ve MR5)

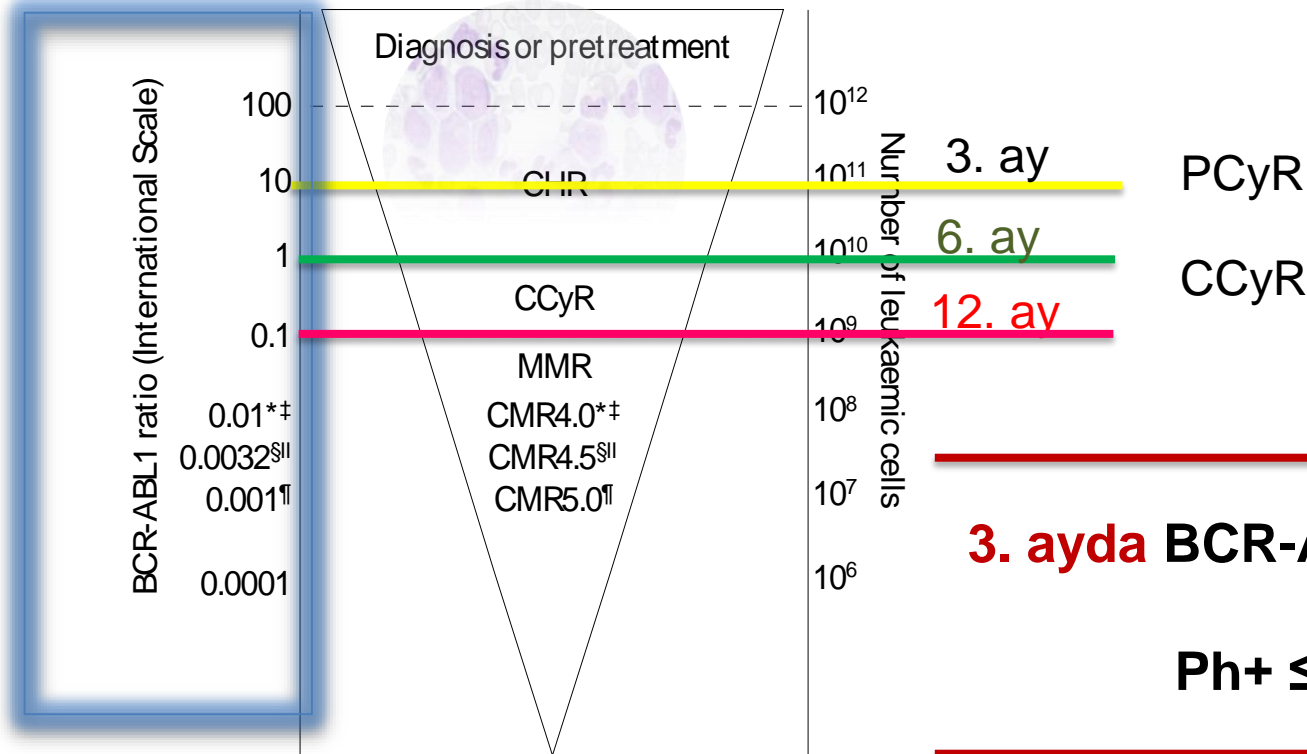


Optimal yanıt

- Optimal yanıt:
Aynı tedaviye devam edilmeli
En iyi uzun dönem sonuçlar ve
neredeyse normal survival
- 3. ayda BCR-ABL1 \leq %10 veya Ph+ \leq %35
- 6. ayda BCR-ABL1 \leq %1 veya Ph+ 0 (CCyR)
- 12. ayda BCR-ABL1 \leq %0.1 (MMR)



Optimal yanıt hedefleri:



3. ayda BCR-ABL1 \leq %10 ve/veya

Ph+ \leq %35

6. ayda BCR-ABL1 \leq %1 ve/veya

Ph+ 0 (CCyR)

12. ayda BCR-ABL1 \leq %0.1 (MMR)

Yanıtsızlık (primer veya sekonder)

- Yanıtsız kabul edilen hastalar progrese olma ve ölüm için yüksek riskli

Tedavi değiştirilmeli

- Yanıtsızlık primer veya sekonder olabilir.

Yanıtsızlık

- 3. ayda THY olmaması veya $Ph+ > \%95$
- 6. ayda BCR-ABL1 $> \%10$ veya $Ph+ > \%35$
- 12. ayda BCR-ABL1 $> \%1$ veya $Ph+ \geq \%1$

Sekonder yanıtsızlık tanımları

1. Tam hematolojik yanıt kaybı
2. Tam sitogenetik yanıt kaybı
3. Doğrulanmış majör moleküler yanıt kaybı
(ardışık 2 testte $>0.1\%$, bir tanesi $\geq 1\%$)
4. BCR-ABL1 mutasyonu
5. Ph + hücrelerde klonal kromozom anormallikleri;
majör yol

Uyarı

- Orta kategorideki cevabı işaret eder.
- Cevap ve sonuç daha iyi olabilir,
ancak diğer cevabı veya sonucu hangi tedavinin iyileştireceği ile ilgili spesifik tedavi önerisi yaptıracak net veri mevcut değil.

Uyarı:

- Tanı anında yüksek risk veya CCA/Ph+, majör yol
- 3. ayda BCR-ABL1 >%10 veya Ph+ %36-95
- 6. ayda BCR-ABL1 %1-10 veya Ph+ %1-35
- 12. ayda BCR-ABL1 %0.1-1

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Baccarani et al, Blood 2013;122:872-884

Response definitions for any TKI **first line,
and 2nd line in case of intolerance, all patients (CP, AP, and BC)**

Time	Optimal response	Warning	Failure
Baseline		High risk Major route CCA/Ph+	
3 mos.	BCR-ABL ^{IS} ≤10%* Ph+ ≤35% (PCyR)	BCR-ABL ^{IS} >10%* Ph+ 36-95%	No CHR* Ph+ >95%
6 mos.	BCR-ABL ^{IS} <1%* Ph+ 0% (CCyR)	BCR-ABL ^{IS} 1-10%* Ph+ 1-35%	BCR-ABL ^{IS} >10%* Ph+ >35%
12 mos.	BCR-ABL ^{IS} ≤0.1%* (MMR)	BCR-ABL ^{IS} 0.1-1%*	BCR-ABL ^{IS} >1%* Ph+ >0%
Then, and at any time	MMR or better	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+

*and/or **in 2 consecutive tests, of which one ≥1%

IS: BCR-ABL on International Scale

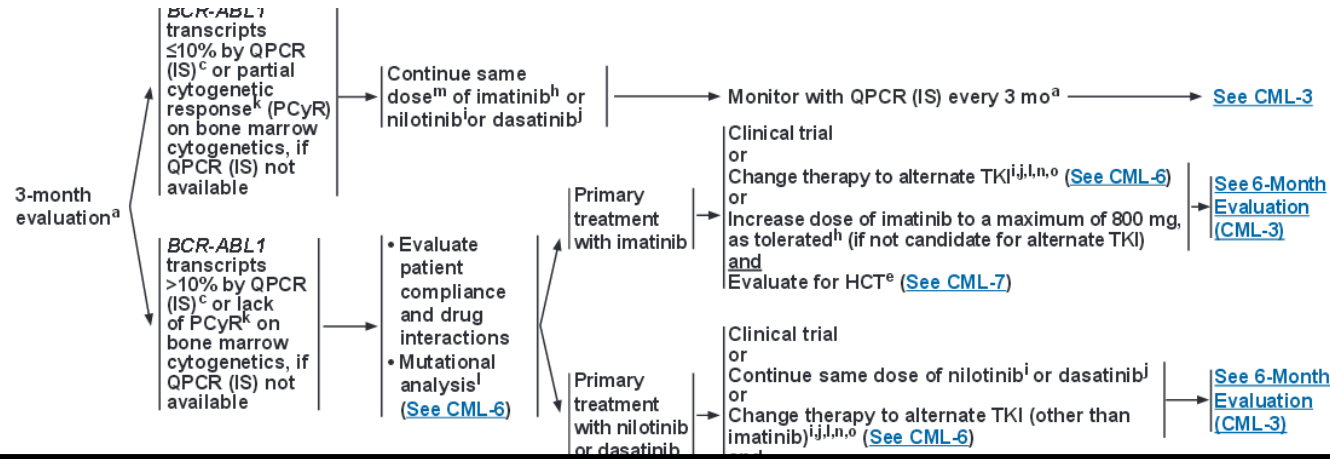
Baccarani et al, Blood 2013;122:872-884

Line	Event	TKI, standard dosage ¹					Transplantation					
Chronic phase												
			Imatinib 400 mg/qd	Nilotinib 300 mg/bid	Dasatinib 100 mg/qd	Bosutinib 500 mg/qd	Ponatinib 45 mg/qd	Search for		alloSCT		Chemotherapy
								HLA type + sibs	unrelated donor	consider	recommended	
1 st	Baseline		X	X	X			X ²				
2 nd	Intolerance to 1 st TKI		Any other TKI approved 1 st line									
	Failure 1 st line of	imatinib		X ⁸	X	X	X	X				
		nilotinib			X	X	X	X	X	X		
		dasatinib		X ⁸		X	X	X	X	X		
3 rd	Intolerance to/failure of two TKI		Any remaining TKI							X		
Any	T315I mutation						X	X	X	X		
Accelerated or blast phase												
In newly diagnosed, TKI naïve patients	start with		X ³		X ⁴			X	X			
	no optimal response, BP										X ⁷	X ⁵
TKI pre-treated patients			Any other TKI			X ⁶				X ⁷	X ⁵	

NCCN Guidelines Version 1.2016

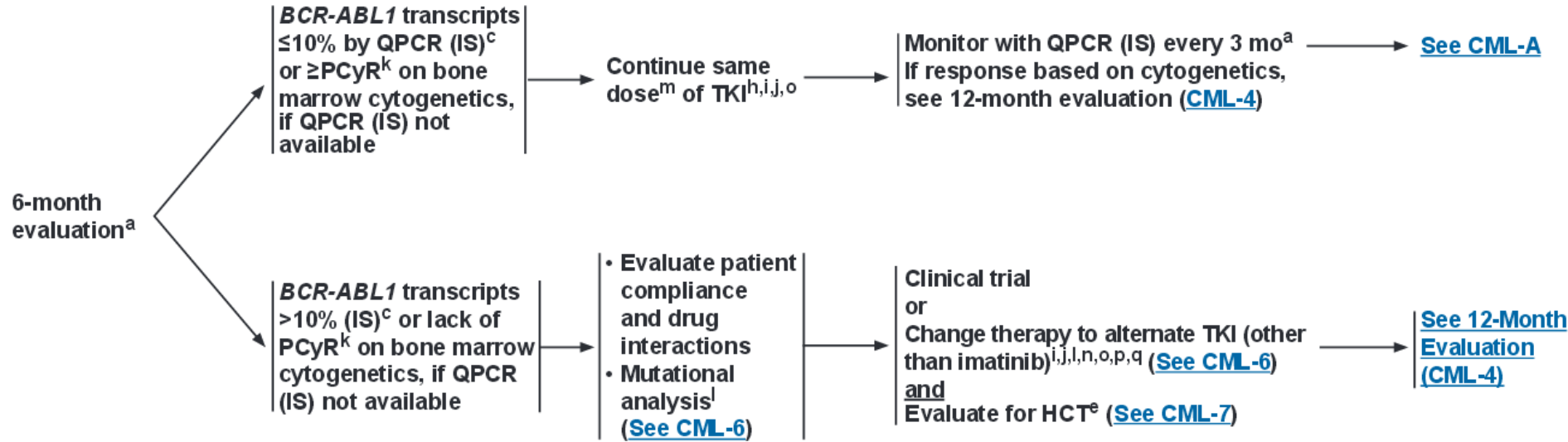
Chronic Myelogenous Leukemia

NCCN Evidence Blocks™



Takip	Yanıt	Tedavi önerileri
	BCR-ABL ≤ %10 (IS) veya ≥PCyR	Aynı doz TKI'ya devam
3.ay	BCR-ABL >%10 (IS) veya PCyR yok	<p>Primer tedavi: imatinib Alternatif TKI'ya geç veya İmatinibi 800mg'a kadar artır tolere edebilir ise (hasta diğer TKI'lar için aday değil ise)</p> <p>Primer tedavi: dasatinib veya nilotinib Aynı doz TKI'ya devam veya Alterne TKI'ya geç (İmatinib dışında)</p>

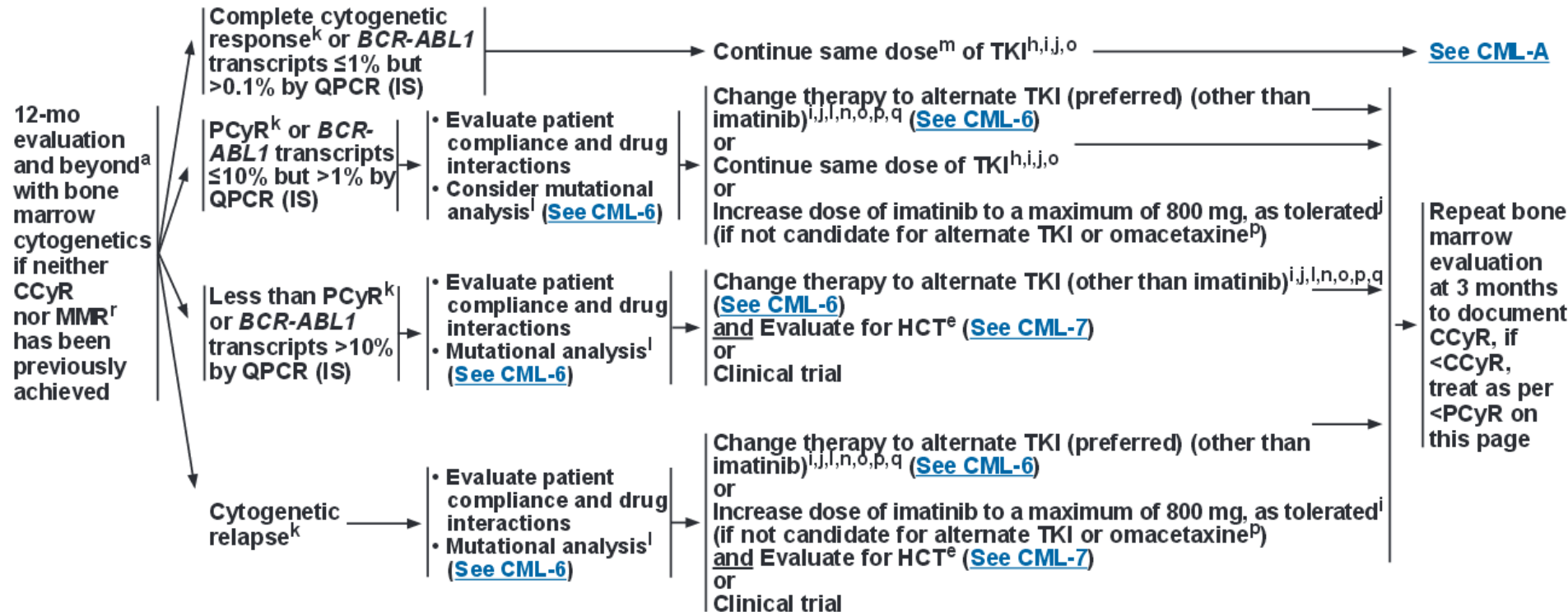
6-MONTH FOLLOW-UP THERAPY^a



Takip	Yanıt	Tedavi önerileri
6. Ay	$BCR-ABL \leq \%10$ (IS) veya \geq PCyR	Aynı doz TKI'ya devam
	$BCR-ABL > \%10$ (IS) veya PCyR elde edilememesi	Alternatif TKI'ya geç

NCCN Guidelines Version 1.2016 Chronic Myelogenous Leukemia NCCN Evidence Blocks™

12-MONTH FOLLOW-UP THERAPY AND BEYOND^a



12-MONTH FOLLOW-UP THERAPY AND BEYOND^aComplete cytogenetic
response^k or *BCR-ABL1*

Takip

Yanıt

Tedavi önerileri

12. ay

CCyR veya
BCR-ABL ≤ %1 fakat >%0.1 (IS)

- Aynı doz TKI'ya devam

PCyR veya
BCR-ABL ≤ %10 fakat >%1 (IS)

- Aynı doz TKI'ya devam veya
- Alternatif TKI'ya geç (imatinib dışında) veya
- İmatinibi 800mg'a kadar artır; (hasta diğer TKılar ve omexataxin için aday değil ise)

PCyR'den daha az veya
BCR-ABL > %10 (IS)

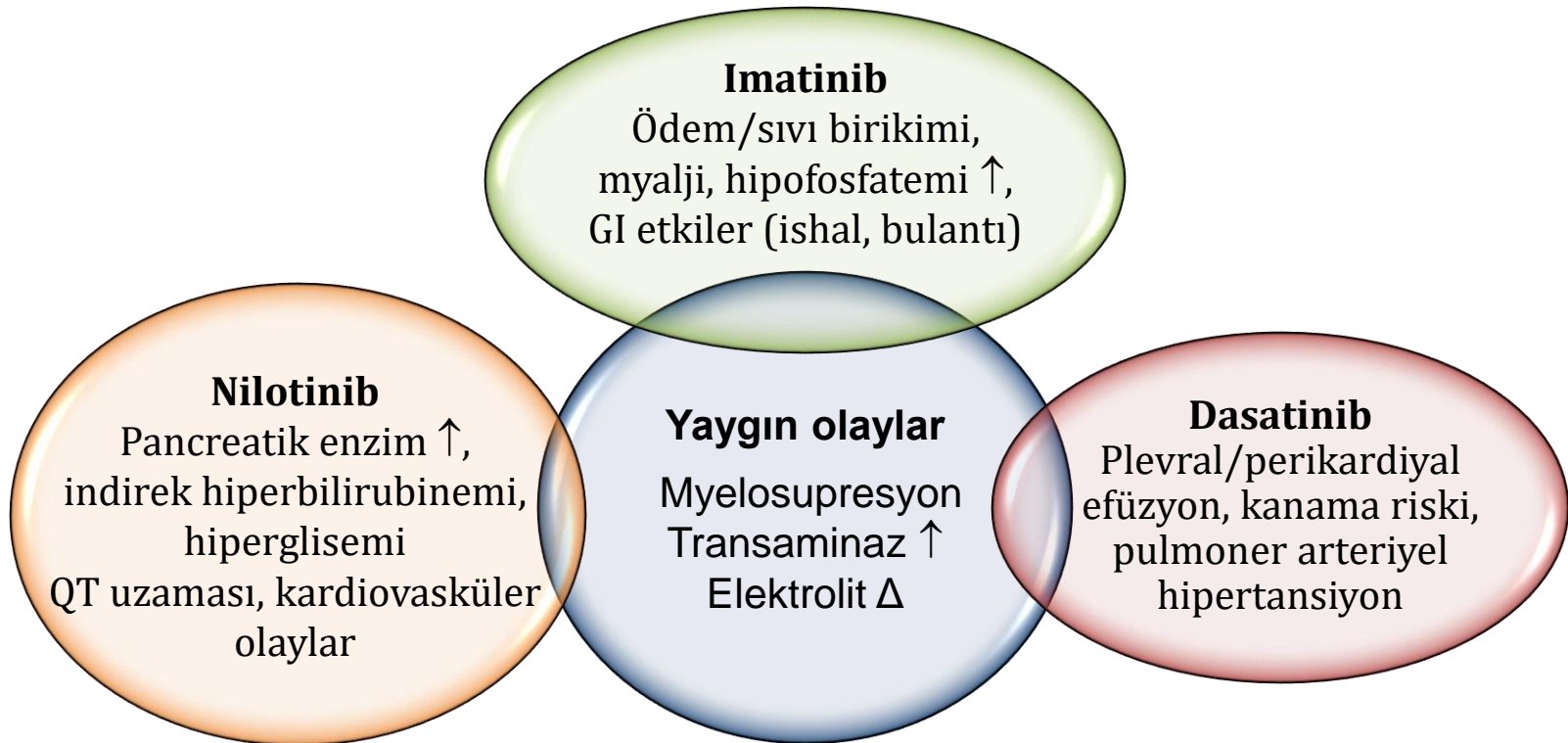
- Alternatif TKI'ya geç (imatinib dışında)

Sitogenetik relaps

- Alternatif TKI'ya geç (imatinib dışında) veya
- İmatinibi 800mg'a kadar artır tolere edebilir ise (hasta diğer TKılar ve omexataxin için aday değil ise)

KML'de yan etkileri ile birlikte 1. sıra tedavi seçenekleri

- ✓ Hala imatinib 1.basamakta etkili bir tedavi,
- ✓ 2. kuşak ilaçlar yüksek riskli hastalarda tercih edilebilir.
- ✓ Seçilecek ajan: hastanın risk skoruna, doktorun tecrübesine, yaş, hastanın tedaviyi tolere edebilme kabiliyetine, ek komorbid durumların varlığı



2. Kuşak TKI ödeme endikasyonları (SUT)



A) Direnç gelişmesi durumu;

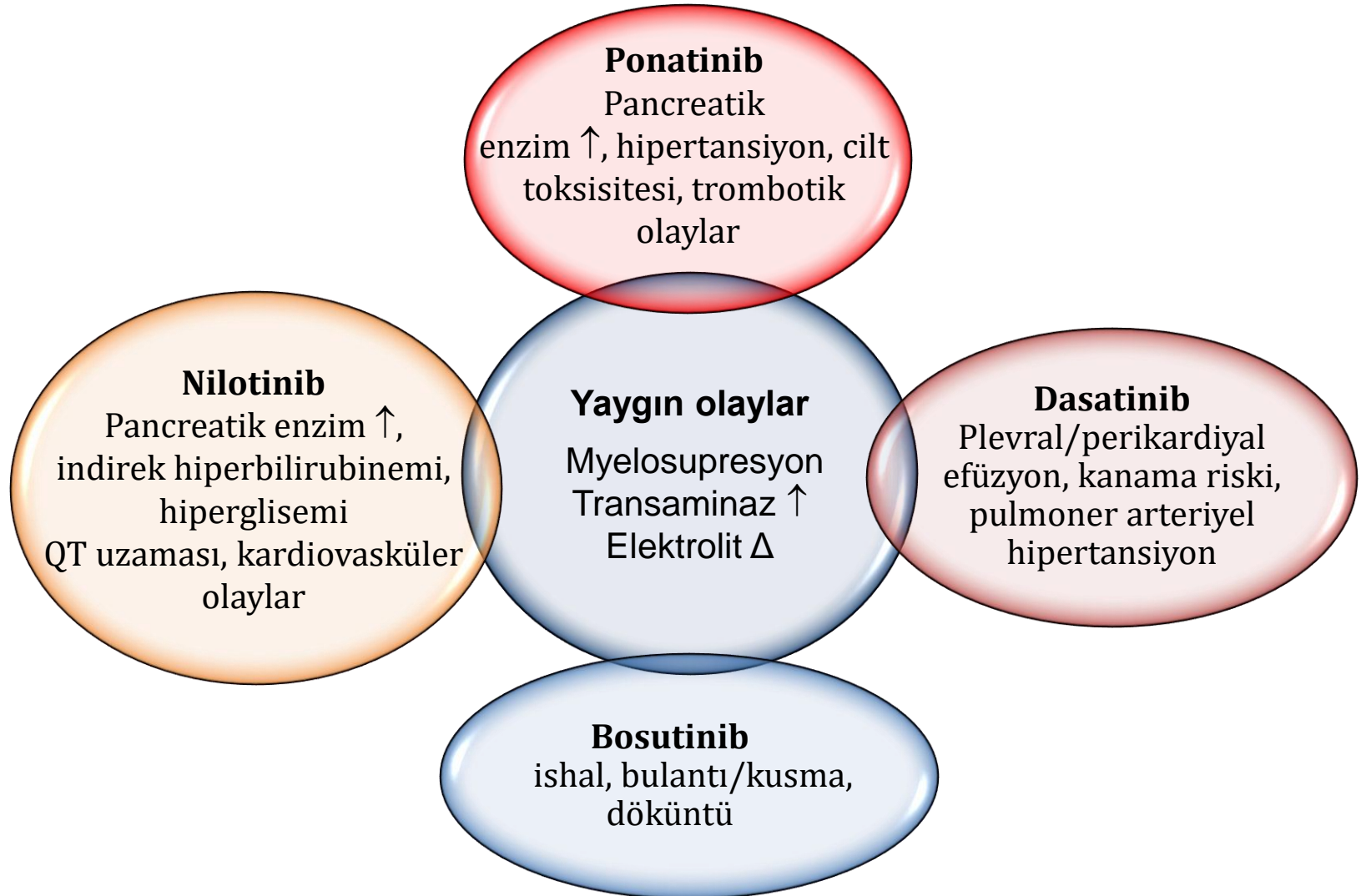
- » 3. ayda tam hematolojik yanıt olmaması veya Ph kromozomu $> \%95$,
- » 6. ayda BCR-ABL $> \%10$ (IS) olması veya Ph kromozomu $> \%35$,
- » 12. ayda BCR-ABL (IS) $> \%1$ olması veya Ph kromozomu pozitifliği,

Tedavi sırasında herhangi bir zamanda aşağıdaki durumlardan herhangi birinin oluşması;

- » Tam hematolojik yanıt kaybı
- » Tam sitogenetik yanıt kaybı
- » En az 2 ölçümle doğrulanmış MMY kaybı ($> \%1$ in üzerinde olması)
- » Mutasyon
- » Ph kromozomu pozitifliği ile birlikte klonal karyotipik anormallik

B) İntolerans gelişmesi durumu; Grade 3-4 yan etki oluşması

KML'de yan etkileri ile birlikte ikinci sıra tedavi seçenekleri



Mutasyon analizi yapılması önerilen durumlar

Kronik faz

- 3. ve 6. ay: Yetersiz başlangıç cevabı (CCyR elde edememe veya $BCR-ABL \leq 10\%$ (IS) olmaması)
- 12. ay: TSY elde edilememesi
- 18. ay: TSY elde edilememesi
- Herhangi bir zamanda: THY, TSY veya MMY kaybı
- Herhangi bir zamanda: $BCR-ABL > 10 \times (> 1 \log)$

Hızlanmış faz veya blastik evreye ilerleme

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Baccarani et al, Blood 2013;122:872-884

**Response definitions to 2nd line therapy in case of failure of imatinib
(can be used provisionally, NOT for the response to 3rd line treatment).**

Time	Optimal response	Warnings	Failure
Baseline		No CHR Loss of CHR on imatinib Lack of CyR to 1 st line TKI High risk	
3 mos.	BCR-ABL ^{IS} ≤10%* Ph+ <65%	BCR-ABL ^{IS} >10%* Ph+ 65-95%	No CHR, or Ph+ >95%, or New mutations
6 mos.	BCR-ABL ^{IS} ≤10%* Ph+ <35% (PCyR)	BCR-ABL ^{IS} ≤10%* Ph+ 35-65%	BCR-ABL ^{IS} >10%* Ph+ >65%* New mutations
12 mos.	BCR-ABL ^{IS} <1%* Ph+ 0 (CCyR)	BCR-ABL ^{IS} 1-10%* Ph+ 1-35%	BCR-ABL ^{IS} >10%* Ph+ >35%* New mutations
Then, and at any time	MMR or better	CCA/Ph- (-7 or 7q-) or BCR-ABL ^{IS} >0.1%	Loss of CHR, or Loss of CCyR or PCyR New mutations Loss of MMR** CCA/Ph+

*and/or

**in 2 consecutive tests, of which one ≥1%

IS: BCR-ABL on International Scale

Allojenik nakil endikasyonları

- 1) Tanı anında AP veya BP (TKİ +/-KT sonrası)
- 2) Başlangıç imatinib cevabına göre:
 - Primer dirençli (gençse, 20 yaş altı)
 - T315I mutasyonlu nüksler (ponatinib ve/veya allo-Tx)
- 3) İkinci sıra TKİ tedavisine göre:
 - İntolerans
 - TSY elde edilememesi (öz.le yüksek riskli mutasyonlarda)
 - TSY kaybı

