# Ph like ALL;tanısal yaklaşım yeni tedavi yolunu mu açıyor?

Dr.Sinem Civriz Bozdağ

AÜTF Hematoloji B.D.

# Yıl 2009…

## yeni bir subtip tanımlandı…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

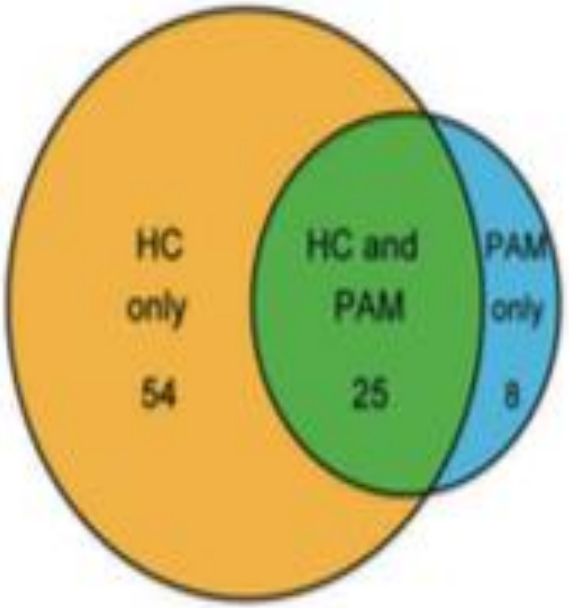
### Deletion of *IKZF1* and Prognosis in Acute Lymphoblastic Leukemia

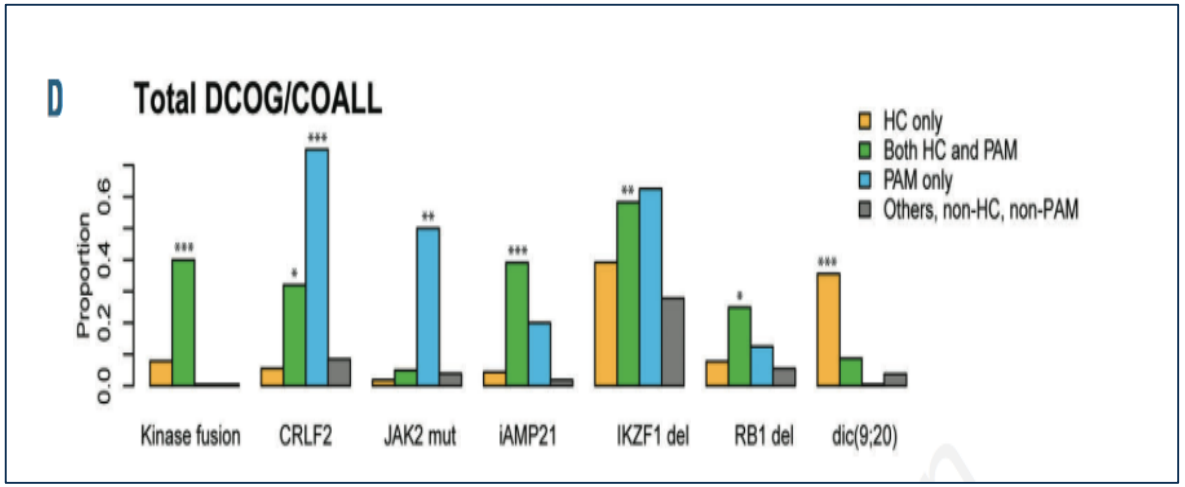
Charles G. Mullighan, M.D., Xiaoping Su, Ph.D., Jinghui Zhang, Ph.D., Ina Radtke, Ph.D., Letha A.A. Phillips, B.S., Christopher B. Miller, B.S., Jing Ma, Ph.D., Wei Liu, Ph.D., Cheng Cheng, Ph.D., Brenda A. Schulman, Ph.D., Richard C. Harvey, Ph.D., I-Ming Chen, D.V.M., Robert J. Clifford, Ph.D., William L. Carroll, M.D., Gregory Reaman, M.D., W. Paul Bowman, M.D., Meenakshi Devidas, Ph.D., Daniela S. Gerhard, Ph.D., Wenjian Yang, Ph.D., Mary V. Relling, Pharm.D., Sheila A. Shurtleff, Ph.D., Dario Campana, M.D., Michael J. Borowitz, M.D., Ph.D., Ching-Hon Pui, M.D., Malcolm Smith, M.D., Ph.D., Stephen P. Hunger, M.D., Cheryl L. Willman, M.D., James R. Downing, M.D., and the Children's Oncology Group

### A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study

*Monique L Den Boer*, Marjon van Slegtenhorst*, Renée X De Menezes, Meyling H Cheok, Jessica G C A M Buijs-Gladdines, Susan T C J M Peters, Laura J C M Van Zutven, H Berna Beverloo, Peter J Van der Spek, Gaby Escherich†, Martin A Horstmann†, Gritta E Janka-Schaub†, Willem A Kamps‡, William E Evans, Rob Pieters‡*

# Farklı yöntemler kullandılar…



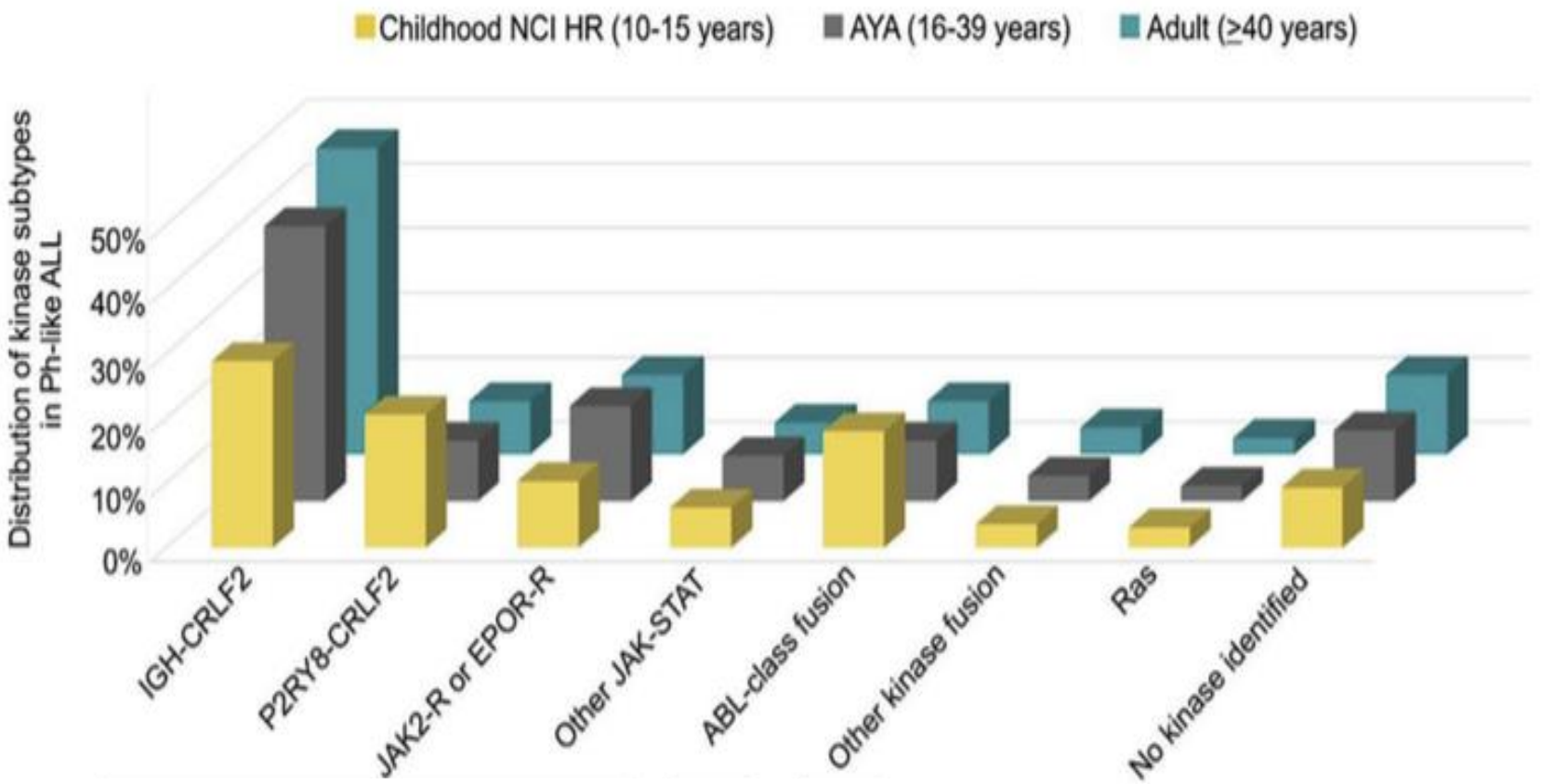

PAM: Prediction analysis of microarray,110 prob set

HC: Hiearchiacal clustering,250 prob set

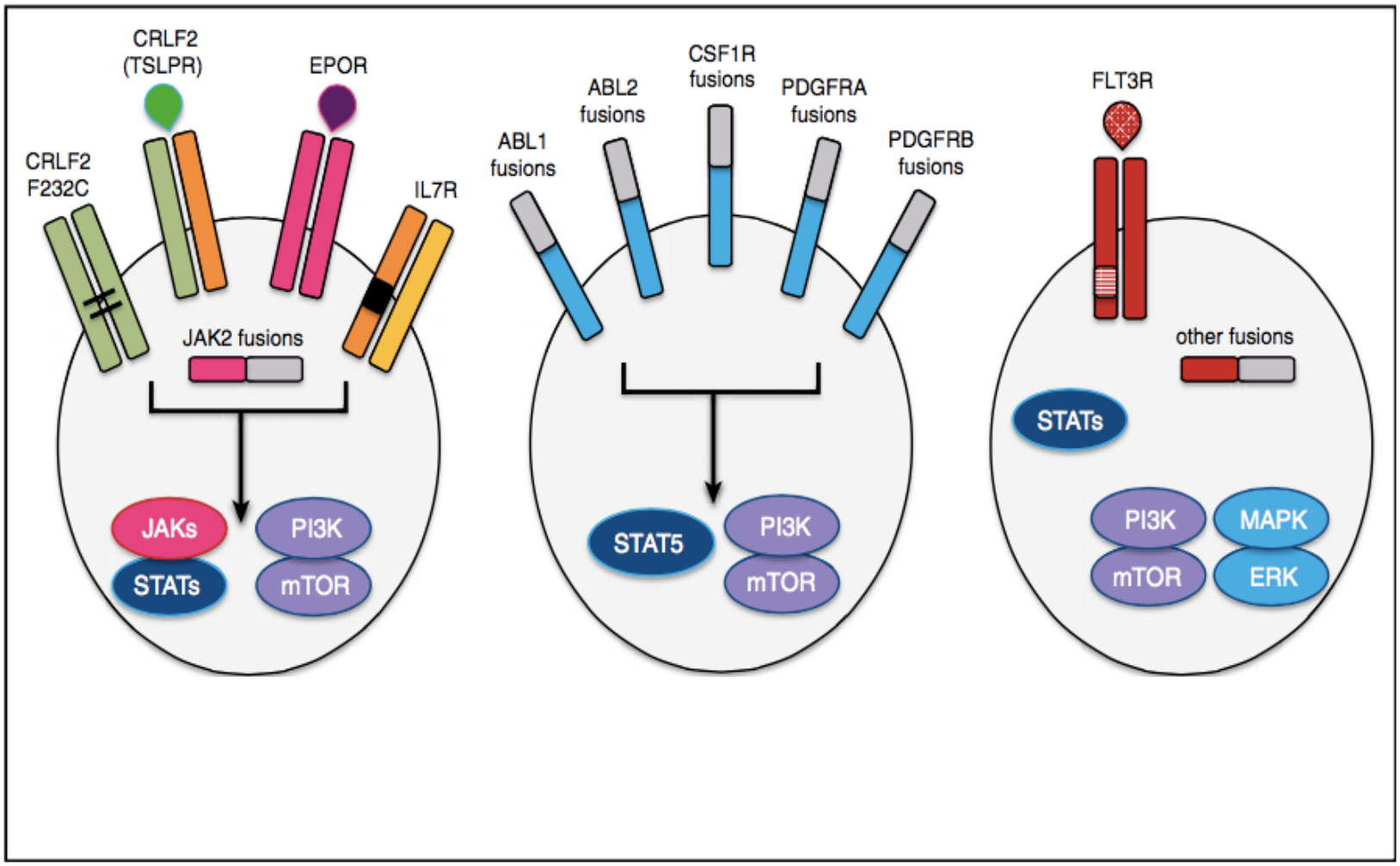
SONUÇ: artmış sitokin reseptör ve tirozin kinaz sinyali ile karakterize bir subtip

Boer J,Haematologica 2015

# Ph like ALL


Childhood NCI HR (10-15 years)
AYA (16-39 years)
Adult (≥40 years)
Distribution of kinase subtypes in Ph-like ALL
50%
40%
30%
20%
10%
0%
IGH-CRLF2
P2RY8-CRLF2
JAK2-R or EPOR-R
Other JAK-STAT
ABL-class fusion
Other kinase fusion
Ras
No kinase identified

# Ph like ALL



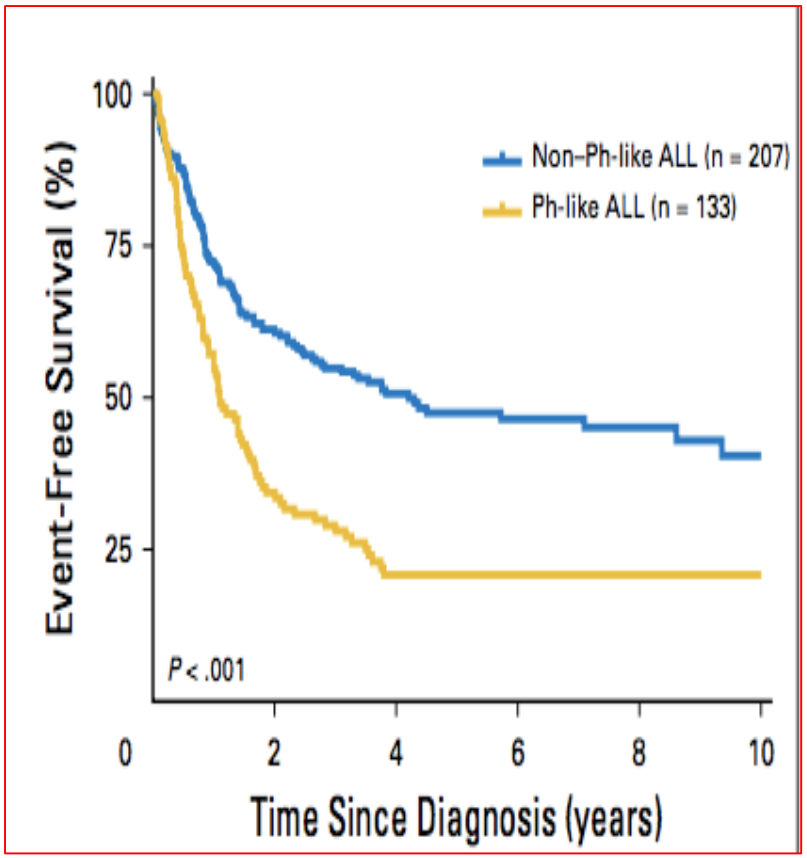

TASİAN S,Blood 2017

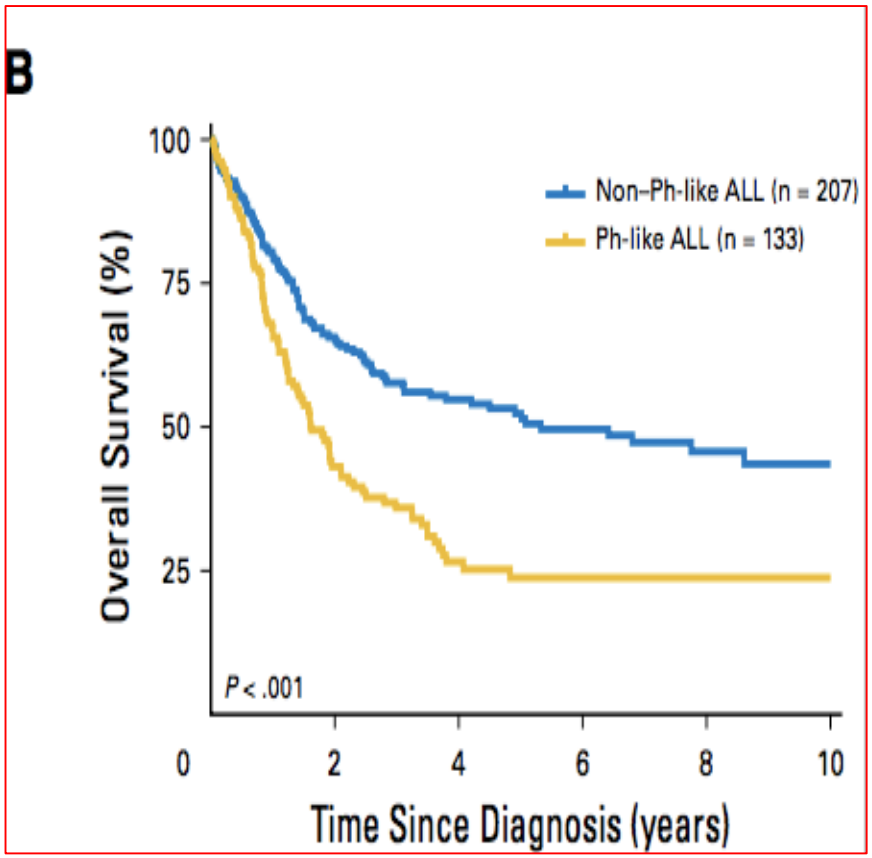
# DSÖ 2016 REVİZYONU

| **B-lymphoblastic leukemia/lymphoma** |
| --- |
| B-lymphoblastic leukemia/lymphoma, NOS |
| B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities |
| B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1* |
| B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged |
| B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1* |
| B-lymphoblastic leukemia/lymphoma with hyperdiploidy |
| B-lymphoblastic leukemia/lymphoma with hypodiploidy |
| B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH* |
| B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1* |
| *Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like* |
| *Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21* |
| **T-lymphoblastic leukemia/lymphoma** |
| *Provisional entity: Early T-cell precursor lymphoblastic leukemia* |
| *Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma* |

Arber D, Blood 2016

# Diğer subtiplere göre kötü sağkalım




Roberts K,JCO 2017

# Kötü sağkalım oranları!!

| Study | Age (years) | Total (Ph-like) | Frequency Ph-like | Outcomes (Ph-like vs. B-other) |
|---|---|---|---|---|
| Jain et al. [20] | 15–39 | 80 (33) | 42% | 5-yr OS (all ages) 23% vs. 59% (p = 0.006) |
| | 40–84 | 68 (16) | 24% | |
| Herold et al. [19] | 16–20 | 26 (5) | 19% | 5-yr DFS (all ages) 19% vs. 57% (p = 0.001) |
| | 21–39 | 68 (12) | 18% | 5-yr OS (all ages) 22% vs. 64% (p = 0.006) |
| | 40–55 | 45 (4) | 9% | |
| | 55–84 | 67 (5) | 7% | |
| Boer et al. [24] | 16–20 | 24 (6) | 25% | 5-yr EFS (all ages) 24% vs. 42% (NR) |
| | 21–39 | 48 (9) | 19% | 5-yr OS (all ages) 33% vs. 50% (NR) |
| | 40–71 | 55 (6) | 11% | |
| Roberts et al. [23] | 21–39 | 344 (96) | 28% | 5-yr EFS 24% vs. 61% (p < 0.0001) |
| | 40–59 | 304 (62) | 20% | 5-yr EFS 21% vs. 39% (p = 0.0021) |
| | 60–86 | 150 (36) | 24% | 5-yr EFS 8% vs. 33% (p = 0.47) |
| Roberts et al. [21] | 1–15 | 853 (108) | 13% | 5-yr EFS 58% vs. 84% (p < 0.001) |
| | 16–20 | 372 (77) | 21% | 5-yr EFS 41% vs. 83% (p < 0.001) |
| | 21–39 | 168 (46) | 27% | 5-yr EFS 24% vs. 63% (p < 0.001) |
| Loh et al. [17] | 1–31 | 572 (81) | 14% | 5-yr EFS 63% vs. 86% (p < 0.0001) |
| Reshmi et al. [18] | 1–31 | 1389 (284) | 20% | NR |

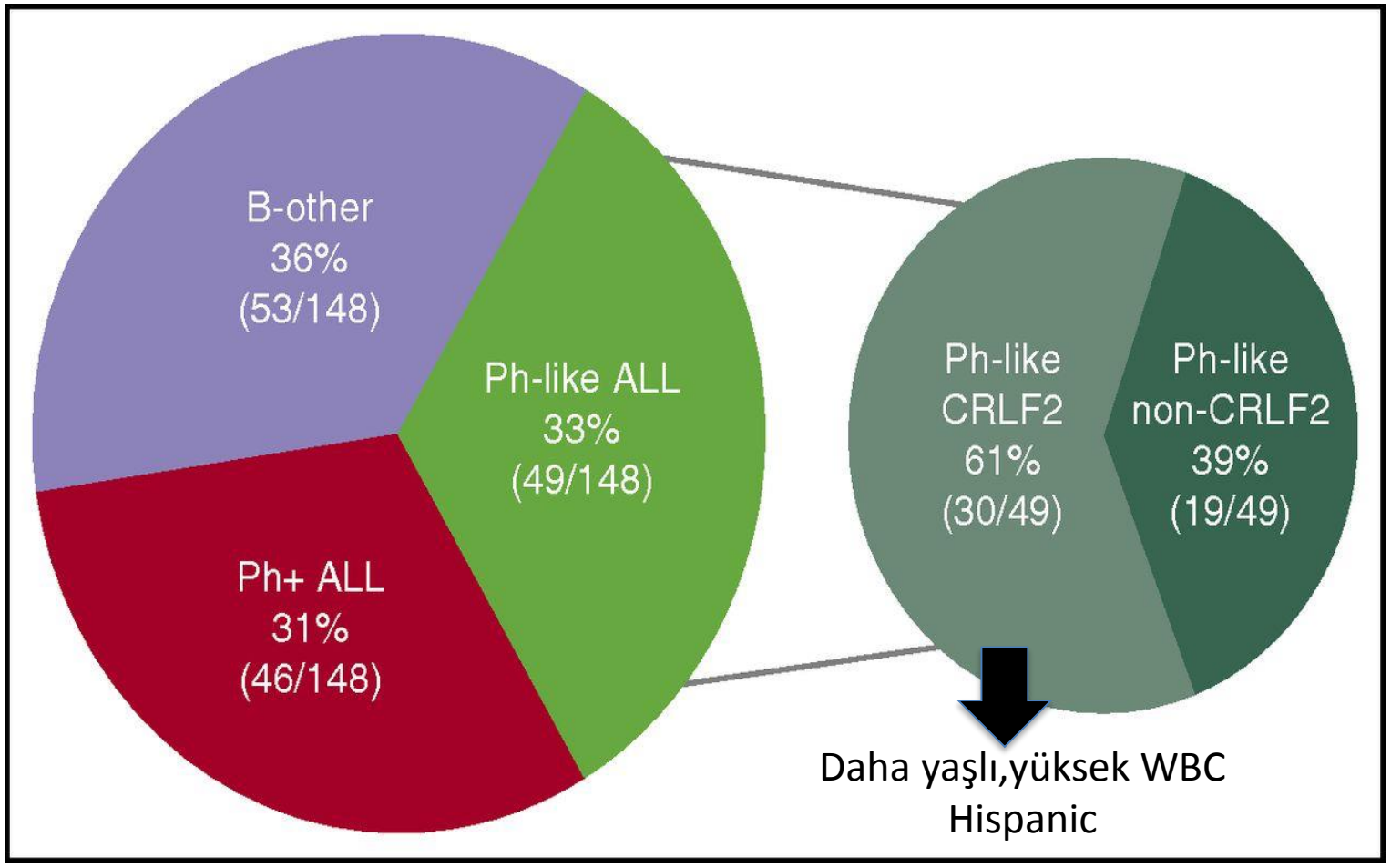
# Sık mı görülüyor?

| Clinical Trial | Age (years) | Risk Group | Ph-like ALL Prevalence (%) No. | | Treatment Outcome | | Reference |
|---|---|---|---|---|---|---|---|
| P9906 | 1–18 | high-risk | 31 | 68 | 5-yr EFS | 25.9% ± 10% | Mullighan[1] |
| COALL 92/97 | 0–18 | all | 19 | 28 | 5-yr DFS | 59.5% | Den Boer[2] |
| DCOG-ALL-8/9 | 0–18 | all | 15 | 10 | 5-yr DFS | 57.1% | Den Boer[2] |
| AALL0232 | 1–18 | high-risk | 14 | 81 | 5-yr EFS | 62.6% ± 6.9% | Loh[6] |
| DCOG-ALL-8/9/10 | 1–18 | all | 16 | 94 | 5-yr CIR | 32% | van der Veer[7] |
| Multiple trials | | | | | | | Roberts[8] |
| | 1–15 | standard-risk | 10 | 33 | — | — | |
| | 1–15 | high-risk | 12.7 | 108 | 5-yr EFS | 58.2% ± 5.3% | |
| | 16–20 | all | 20.6 | 77 | 5-yr EFS | 41.0% ± 7.4% | |
| | 21–39 | all | 27.4 | 46 | 5-yr EFS | 24.1% ± 10.5% | |
| HOVON | 16–71 | all | 17 | 21 | 3-yr EFS | ~25% | Boer[9] |
| GMALL | 15–65 | all | 13 | 26 | 5-yr DFS | 24% | Herold[10] |
| University Pennsylvania | | | | | | | Tasian[11] |
| | 18–39 | all | 25.9 | 7 | — | — | |
| | 40–88 | all | 18.3 | 11 | — | — | |
| Multiple trials | | | | | | | Roberts[12] |
| | 21–39 | all | 27.9 | 96 | 5-yr EFS | 24.1% | |
| | 40–59 | all | 20.4 | 62 | 5-yr EFS | 21.4% | |
| | 60–86 | all | 24 | | 3-yr EFS | 8% | |
| MD Anderson | 15–84 | a ll | 33.1 | 49 | 5-yr OS | 23% | Jain[13] |
| St. Jude Total XV | 1–18 | all | 11.6 | 40 | 5-yr EFS | 90.0% ± 4.7% | Roberts[14] |

# Kimlerde daha sık görülür?

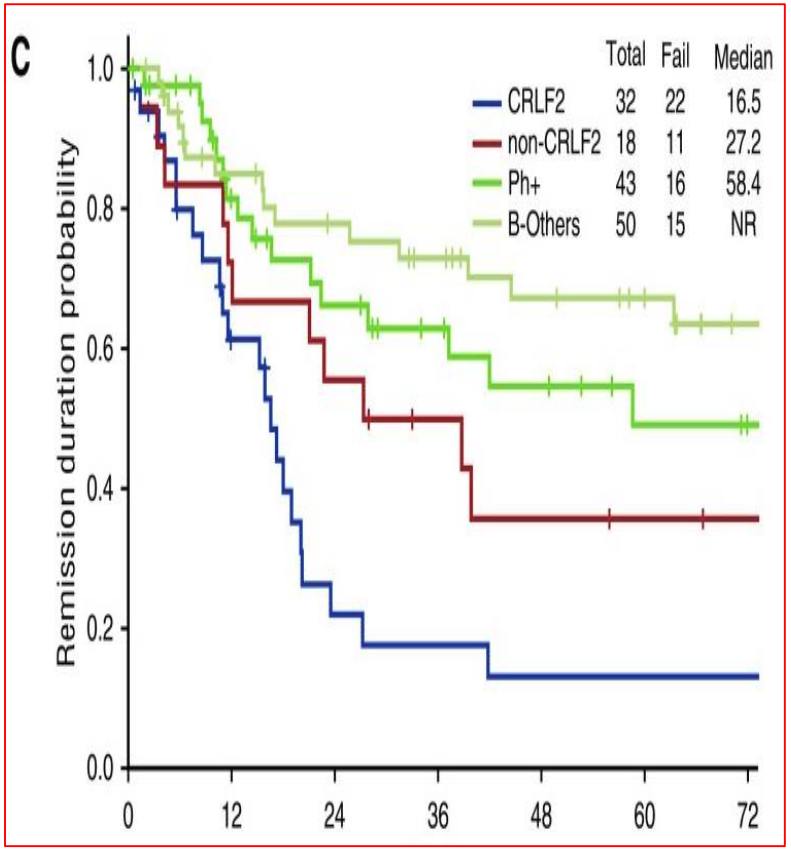
- Hispanic populasyon
- Erkeklerde daha sık
- GATA3 mutasyon daha sık
- Down sendromu olanlarda daha sık
- Daha yüksek lökosit sayısı??

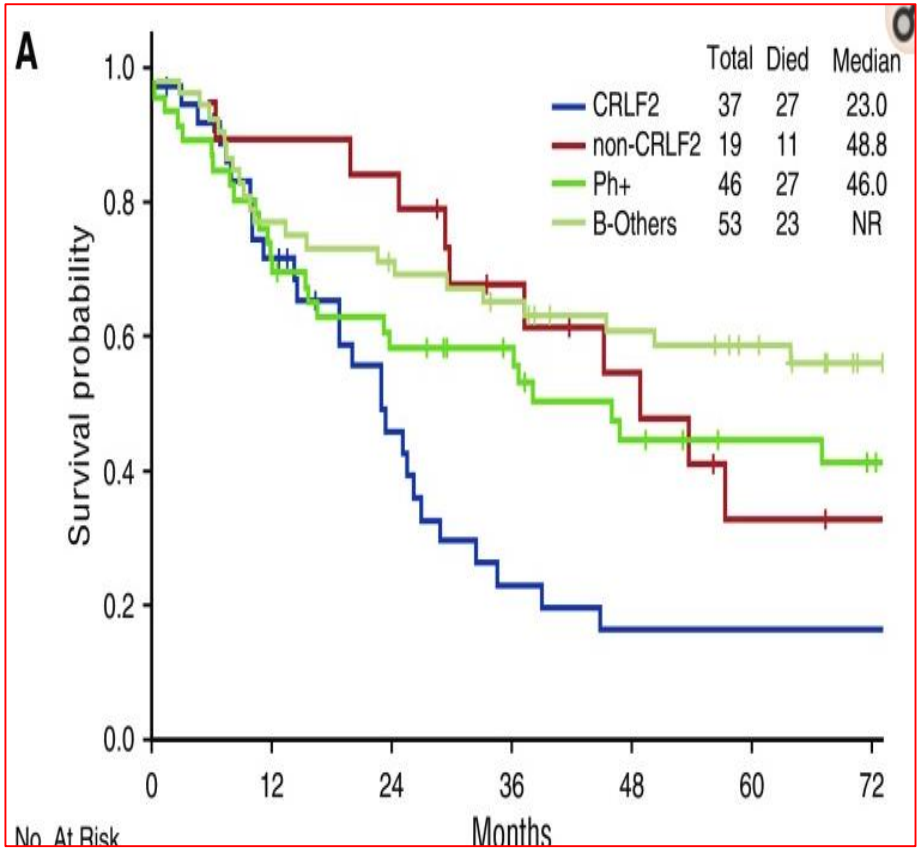
# CRLF2 oldukça sık!!




Jain N,Blood 2017

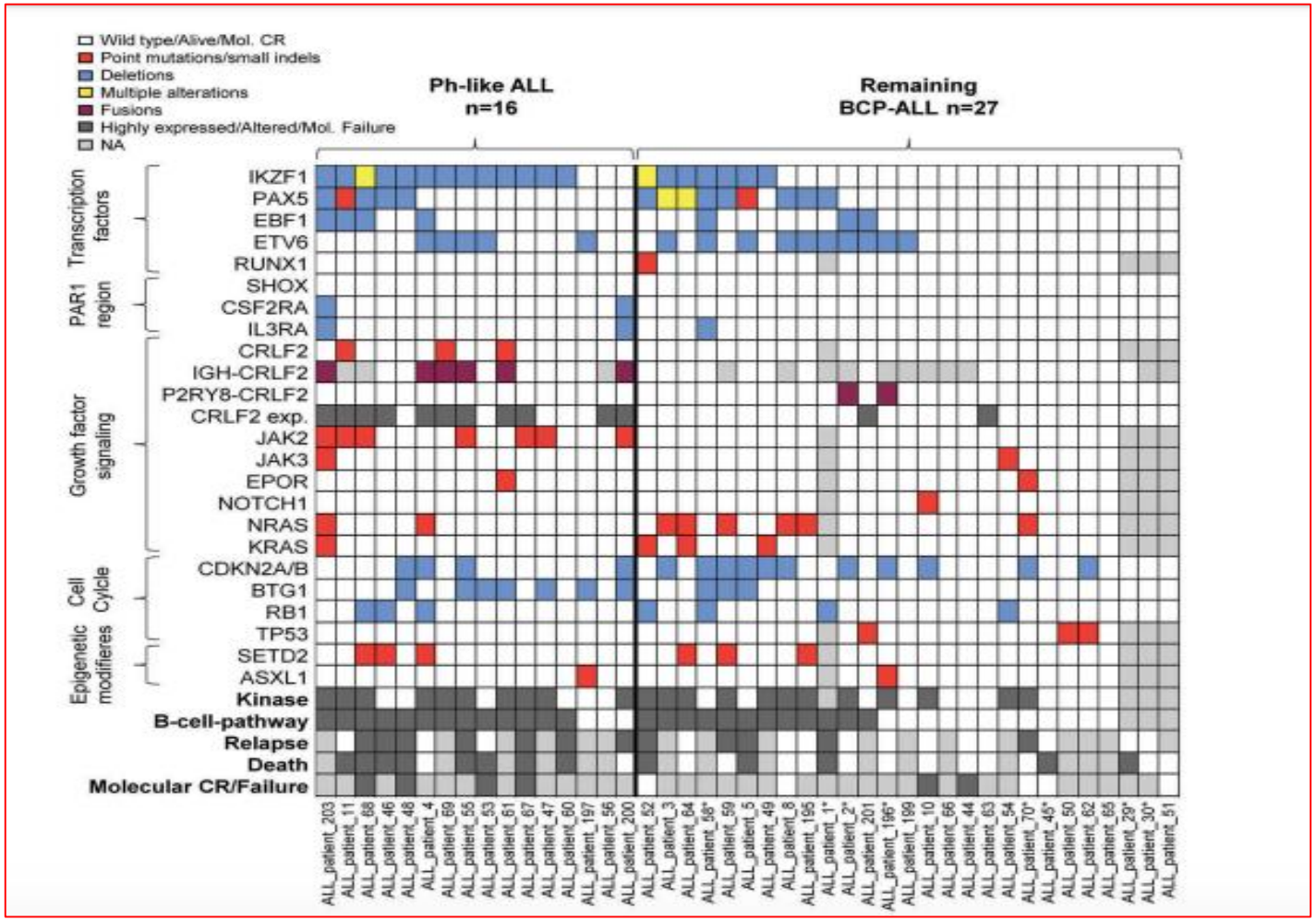
# CRLF2 mutasyonu olanlarda remisyon süresi ve sağkalım kısa!!



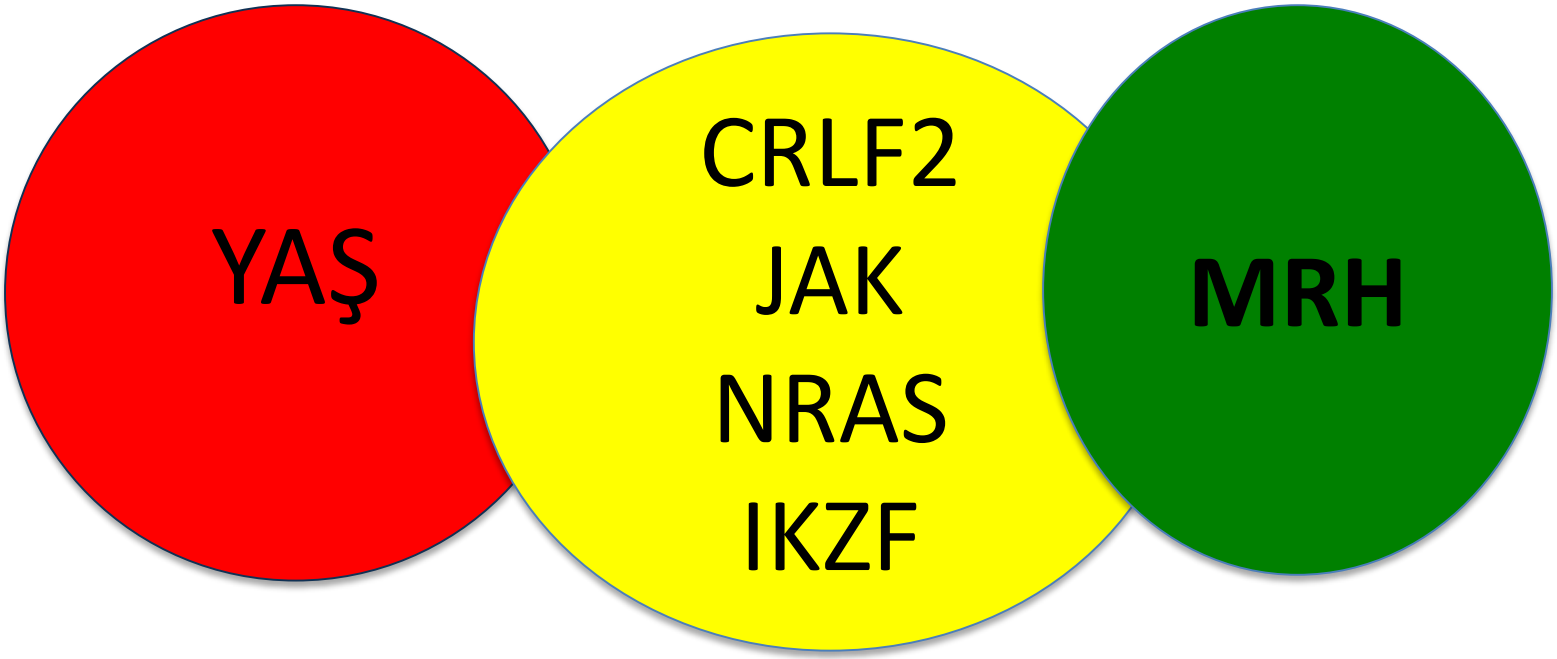

Jain N,Blood 2017

# IKZF,CRLF2 ve JAK mutasyonları sık ve birarada!!!




Herold T,JCO 2017

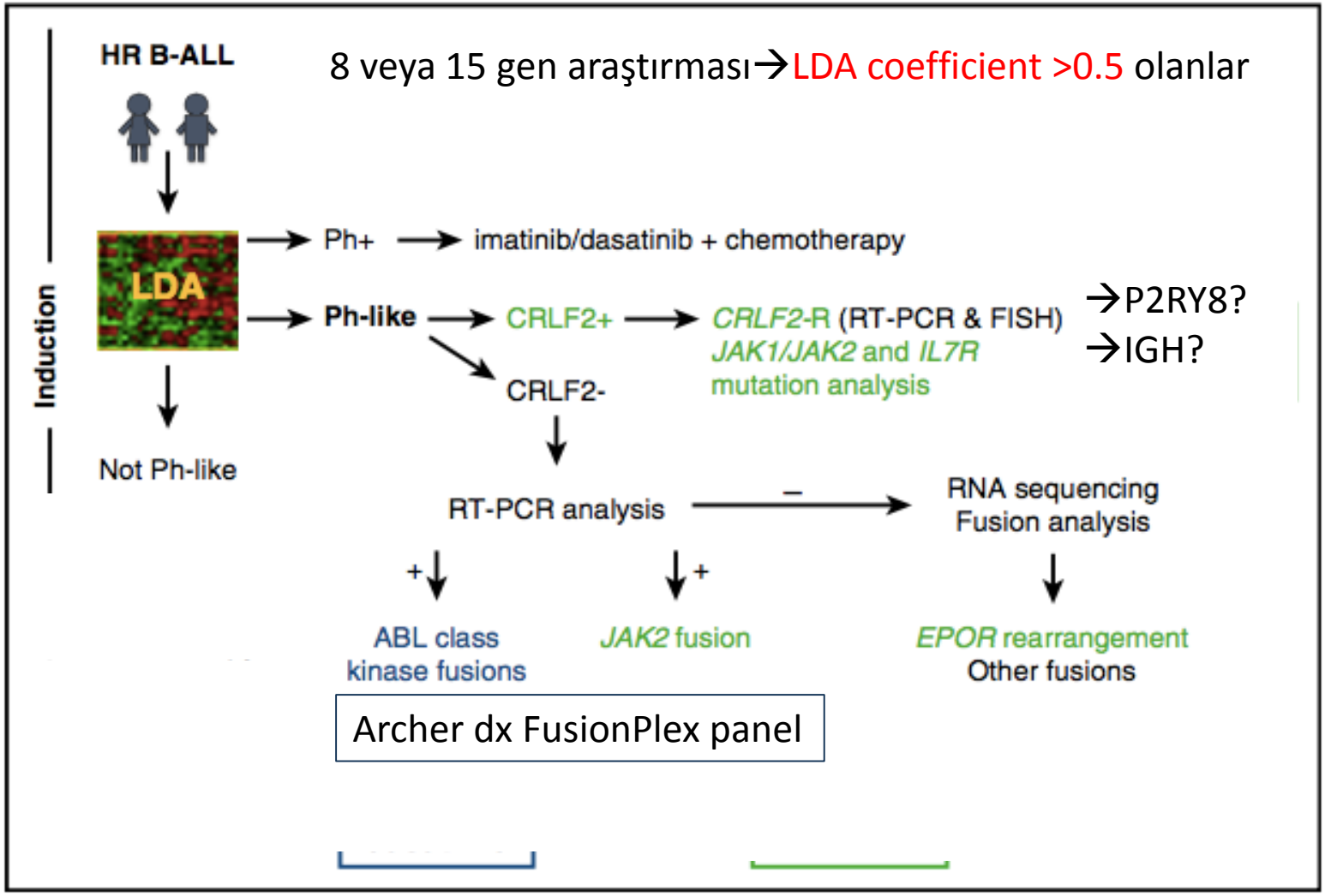
# PROGNOZ




Roberts K,JCO 2017
Herold T,Haematologica 2017

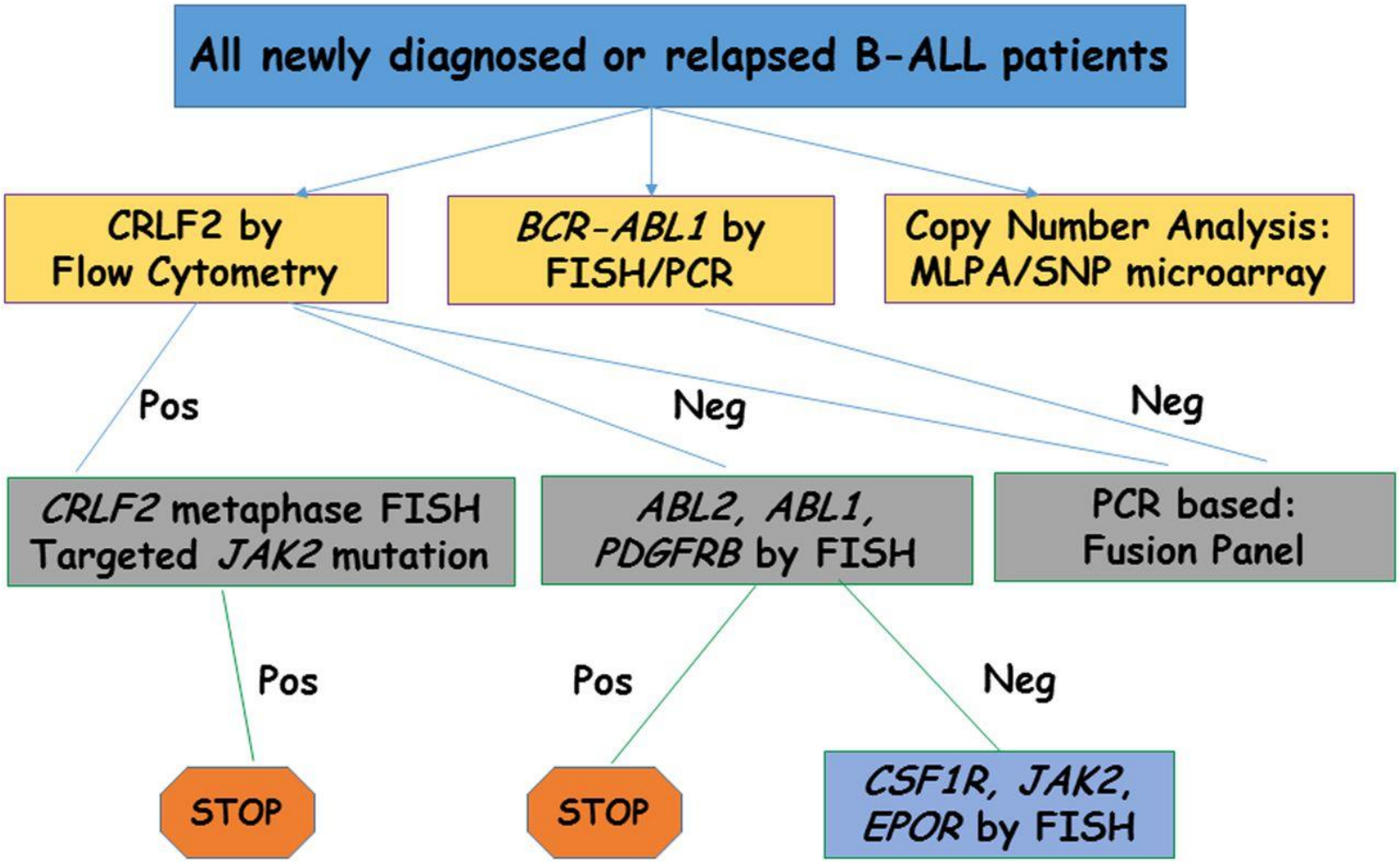
TANI

# -St.Jude yaklaşımı-




Tasian ,Blood 2017

# Testing Algorithm For Ph-Like B-ALL
# MD Anderson Trial



# Alman yaklaşımı

1-CRLF2 ekspresyon analizi

2-ABL and Janus Activated Kinase (JAK) yolağını aktive eden ve ABL1, ABL2, CSF1R, PDGFRB and JAK gibi genleri içereren füzyonların FISH analizi

3-ABL ve JAK füzyon partnerlerinin identifikasyonu için füzyon spesifik RT-PCR

Fasan A,Blood 2015

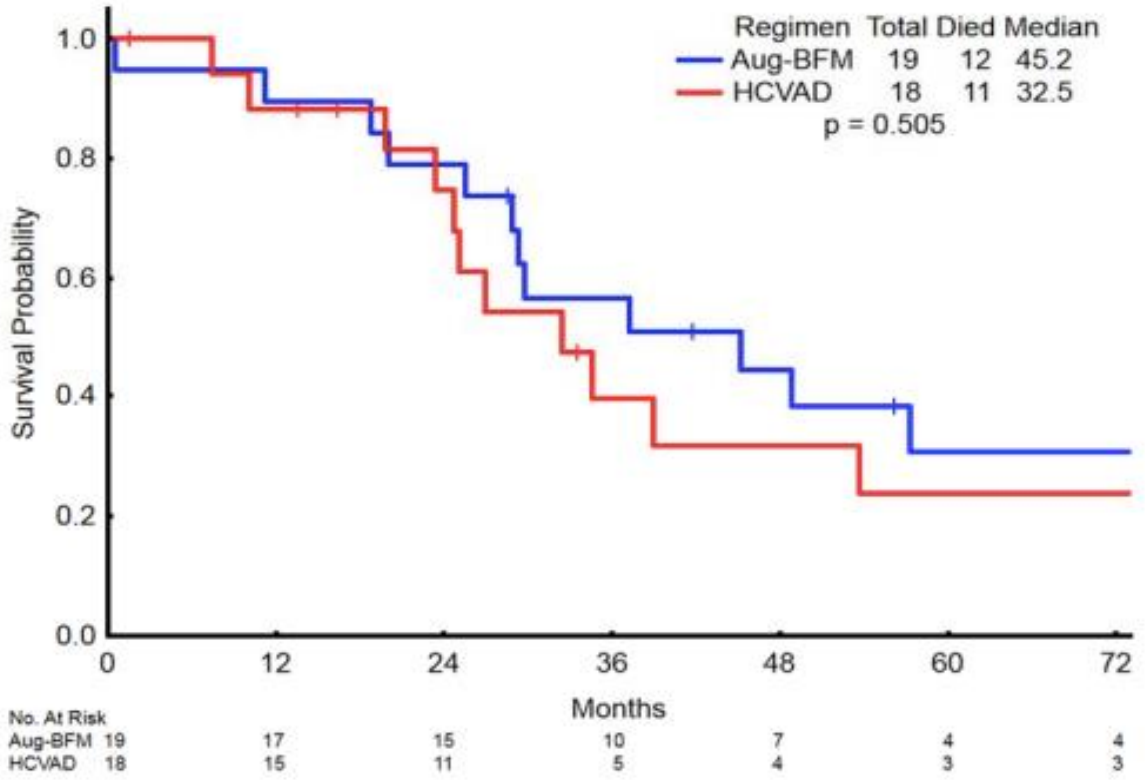
# TEDAVİ

# GMALL/Pediatrik rejim

## -MRH fazla-

| | Ph-like ALL | Remaining BCP-ALL | *P*-value |
|---|---|---|---|
| **Response to induction** | | | |
| Evaluable | N=19 | N=40 | |
| Complete remission | 19 (100%) | 40 (100%) | n.a. |
| Molecular remission (n=31 evaluable) | 4/12 (33%) | 19 (79%) | 0.02 |
| **Long-term outcome** | | | |
| Continuous complete remission | 5 (26%) | 24 (60%) | 0.03 |
| Death in complete remission | 2 (11%) | 3 (7%) | |
| Relapse | 12 (63%) | 13 (32%) | 0.05 |
| Median time to relapse (days) | 122 (25-844) | 555 (96-1248) | 0.03 |

# Pediatrik rejim vs Erişkin rejim




Jain N,Blood 2017

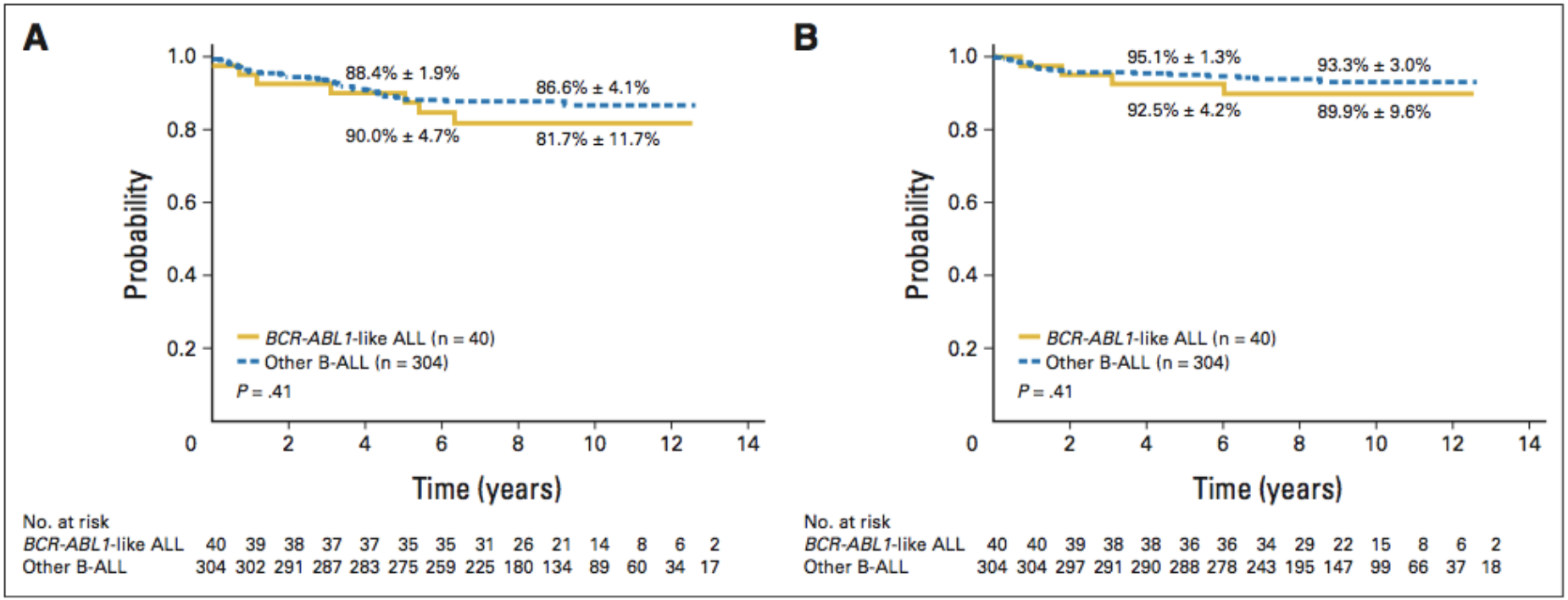
# Total Therapy XV/St.Jude

## -MRH (+)liği daha sık-

| Variable | *BCR-ABL1*–Like ALL | | | | |
|---|---|---|---|---|---|
| | Yes | | No | | |
| | No. | % | No. | % | *P* |
| MRD on day 19 | | | | | |
| < 5% | 30 | 9.84 | 275 | 90.16 | .009 |
| ≥ 5% | 9 | 26.47 | 25 | 73.53 | |
| MRD at the end of induction | | | | | |
| < 0.01% | 24 | 8.60 | 255 | 91.40 | .001 |
| ≥ 0.01% | 16 | 25.81 | 46 | 74.19 | |

# Total Therapy XV/St.Jude

## -MRH bazlı yaklaşım olmalı!!-




N:40

1-18 YAŞ

Roberts K,JCO 2014

# ALLOJENEİK HEMATOPOİETİK KÖK HÜCRE NAKLİ GEREKLİ Mİ?

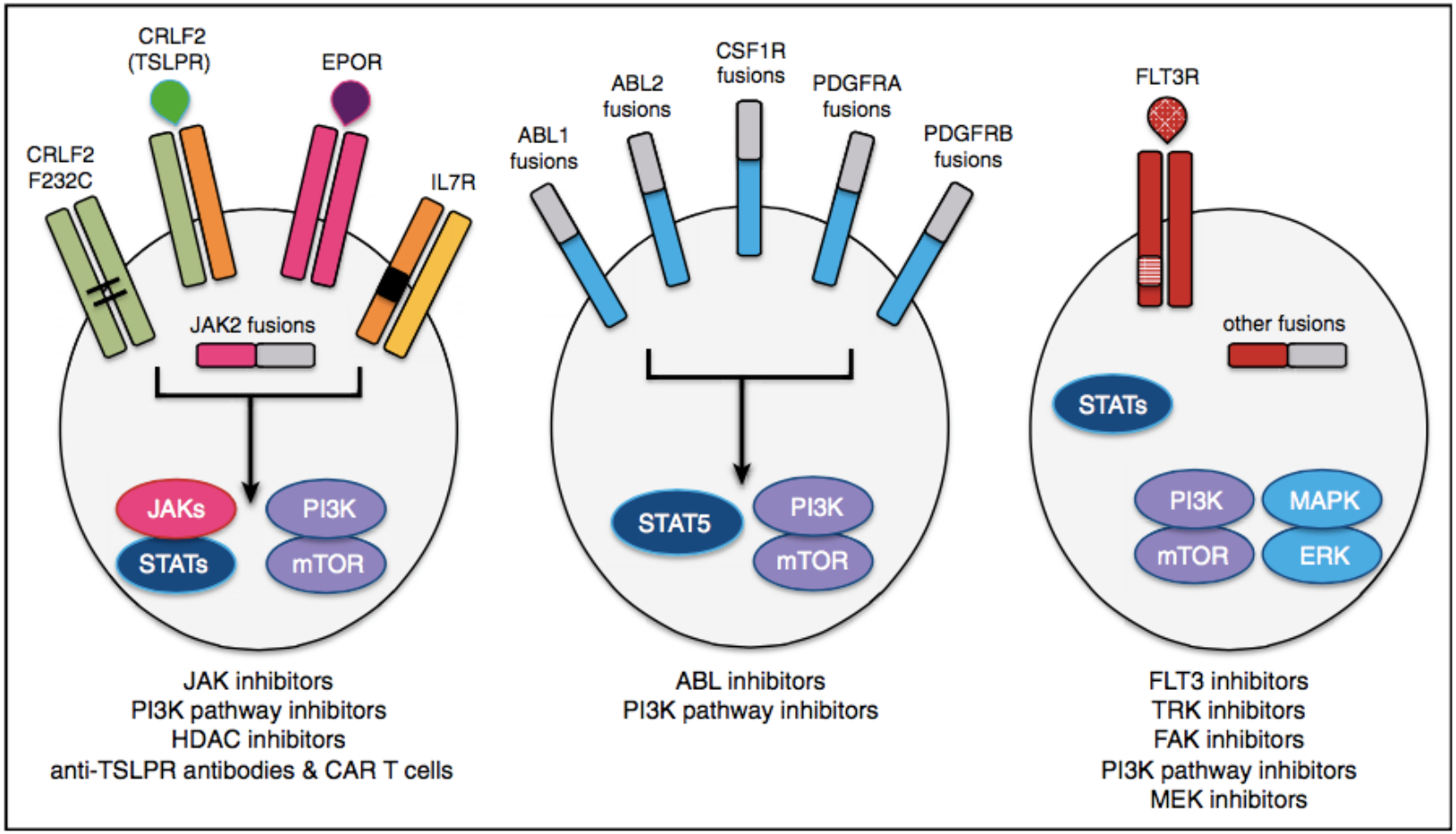
- MRH(+)→AHKHN endike…
- MRH(+)→ immunoterapi →MRH(-)???

- MRH(-)→APKHN endike mi??
  →hangi mutasyon var fark eder mi??

- Pediatrik bazlı tedavi almamış hastalarda MRH statusundan bağımsız AHKHN yapılmalı mı??

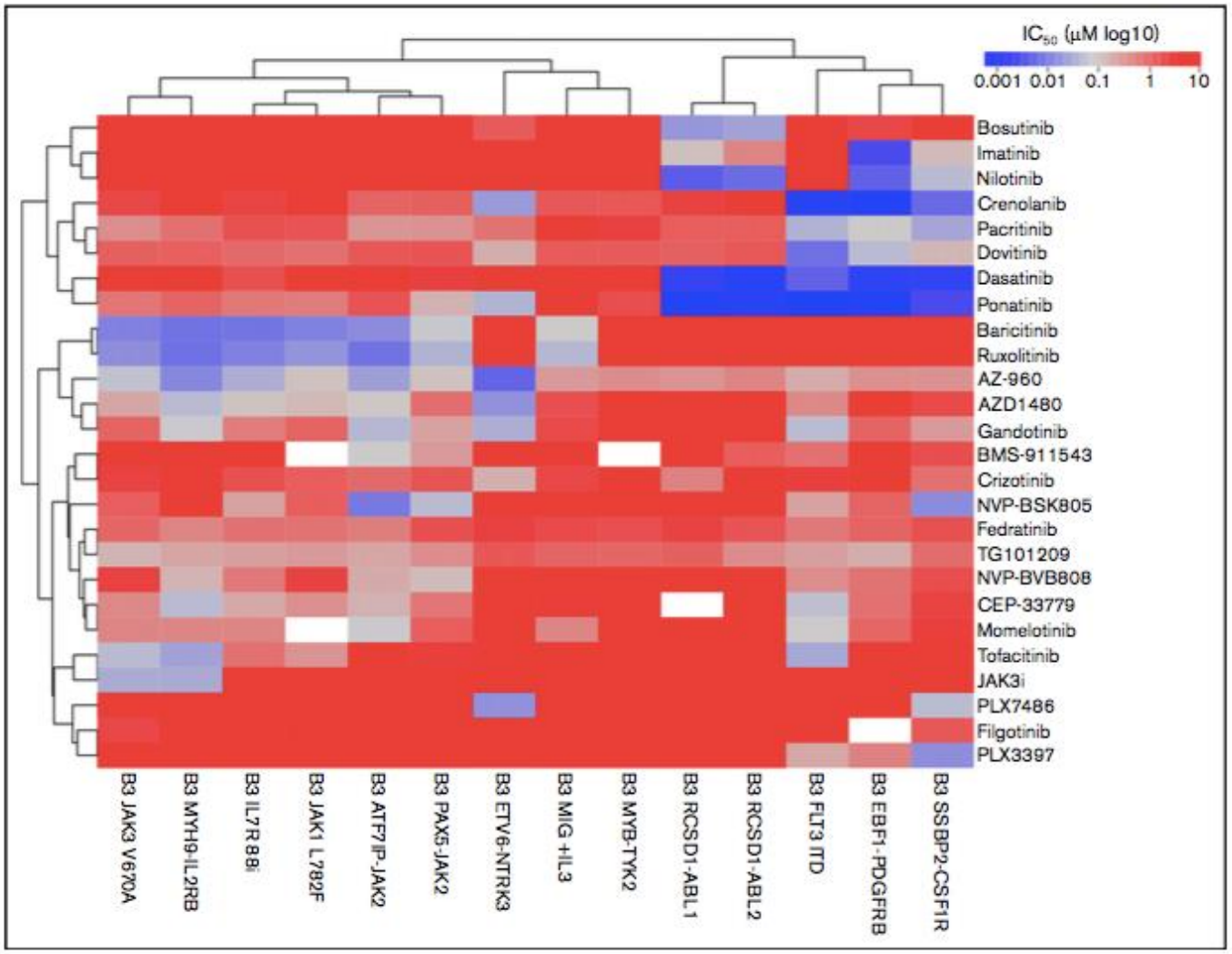
- Nakil sonrası idame gerekli mi???

# Hedefe yönelik tedaviler..




TASİAN S,Blood 2017

# Hedefe yönelik tedaviler..




Roberts K,Blood Adv 2017

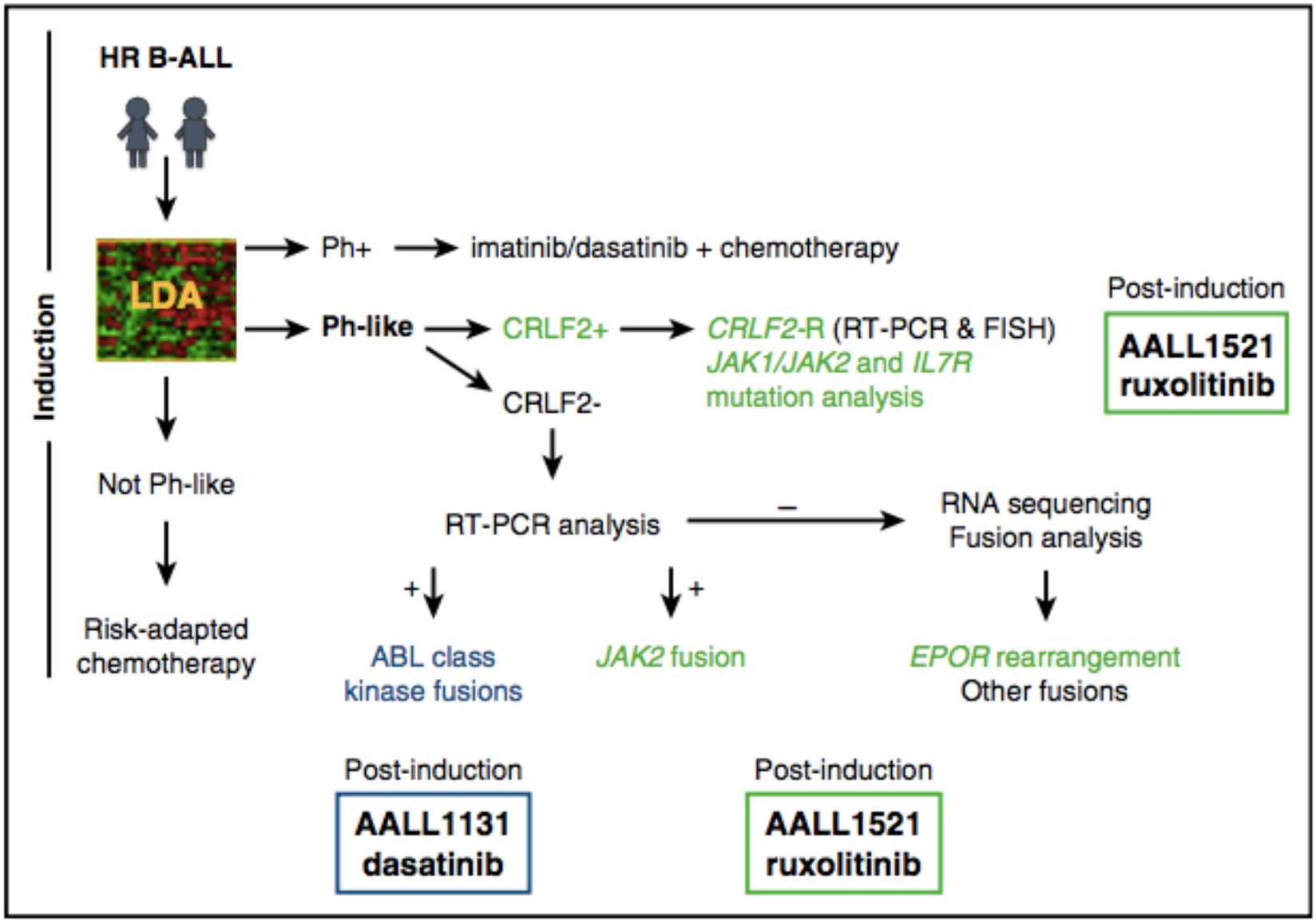
# Abl class!


- Inokuchi K, Wakita S, Hirakawa T, et al. RCSD1- ABL1-positive B lymphoblastic leukemia is sensitive to dexamethasone and tyrosine kinase inhibitors and rapidly evolves clonally by chromosomal translocations. Int J Hematol. 2011; 94(3):255-260.

- Lengline E, Beldjord K, Dombret H, Soulier J, Boissel N, Clappier E. Successful tyrosine kinase inhibitor therapy in a refractory B-cell precursor acute lymphoblastic leukemia with EBF1- PDGFRB fusion. Haematologica. 2013;98(11): e146-e148.

- Schwab C, Ryan SL, Chilton L, et al. EBF1- PDGFRB fusion in pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL): genetic profile and clinical implications. Blood. 2016; 127(18):2214-2218.

- Frech M, Jehn LB, Stabla K, et al. Dasatinib and allogeneic stem cell transplantation enable sustained response in an elderly patient with RCSD1-ABL1-positive acute lymphoblastic leukemia. Haematologica. 2017;102(4):e160–e162.




Tasian ,Blood 2017

**Table 2. Current clinical trials of TKI-based therapies in children and adults with Ph-like ALL**

| Ph-like ALL alterations | Kinase inhibitor | Disease status | Age, y | Clinical trial |
|---|---|---|---|---|
| ABL class | Dasatinib | Newly diagnosed | 1-30 | NCT01406756 (COG AALL1131) |
| ABL class | Dasatinib | Newly diagnosed | 1-18 | NCT03117751 (SJCRH Total XVII) |
| ABL class | Dasatinib | Relapsed | ≥10 | NCT02420717 (MDACC) |
| CRLF2/JAK pathway | Ruxolitinib | Newly diagnosed | 1-21 | NCT02723994 (COG AALL1521) |
| CRLF2/JAK pathway | Ruxolitinib | Newly diagnosed | 1-18 | NCT03117751 (SJCRH Total XVII) |
| CRLF2/JAK pathway | Ruxolitinib | Relapsed | ≥10 | NCT02420717 (MDACC) |

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American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

# Efficacy of Tyrosine Kinase Inhibitors in Ph-like Acute Lymphoblastic Leukemia harboring ABL-class Rearrangements

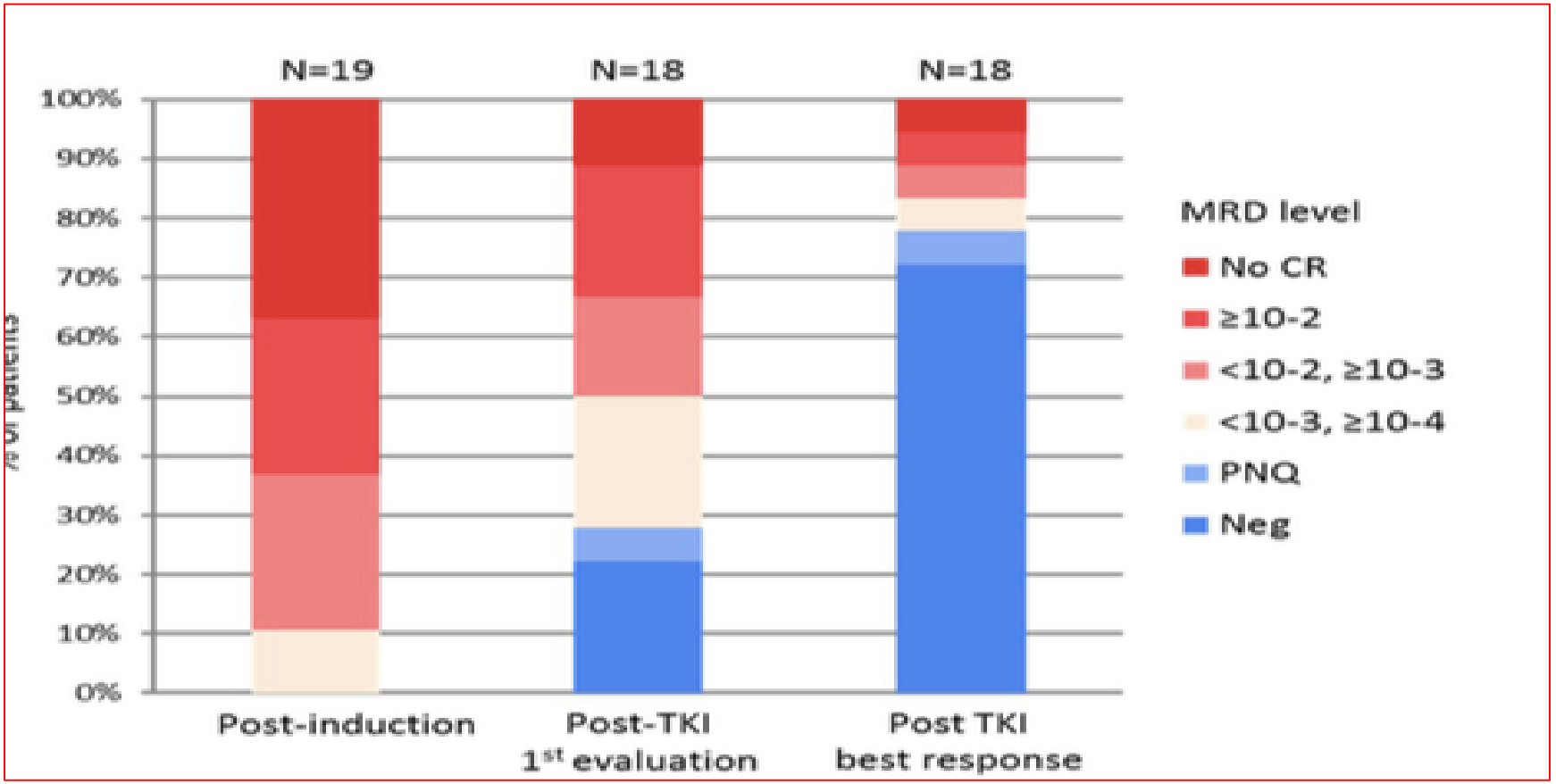
| Pt | Fusion gene | Sex | Age | WBC ($x10^9$/L) | IKZF1 | Front-line trial | Prednisone response (D8) | MRD response to induction† | Time to TKI initiation (days*) | TKI (dose, mg daily) | Treatment combined with TKI | First MRD post-TKI (days**) | Best MRD in CCR (days**) | HSCT‡ | Survival (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patients in first line** | | | | | | | | | | | | | | | |
| #1 | EBF1-PDGFRB | M | 16 | 167 | del | FRALLE-2000B | Poor | $2x10^{-1}$ | 55 | Imatinib (400) | Chemo | $5x10^{-3}$ (21) | Neg (50) | Y | Alive in CR1 (62) |
| #2 | EBF1-PDGFRB | M | 11 | 154 | wt | FRALLE-2000B | Poor | $2x10^{-2}$ | 44 | Imatinib (300) | Chemo | Neg (44) | Neg (44) | N | Alive in CR1 (50) |
| #3 | EBF1-PDGFRB | M | 5 | 23 | wt | FRALLE-2000A | Poor | No CR (35%) | 39 | Imatinib (NA) | Chemo | $>10^{-2}$ (18) | Neg (45) | N | Alive in CR1 (50) |
| #4 | EBF1-PDGFRB | M | 15 | 31 | wt | EORTC 58081-AR1 | Good | $5x10^{-3}$ | 137 | Imatinib (500) | Chemo | Neg (109) | Neg (109) | N | Alive in CR1 (43) |
| #5 | EBF1-PDGFRB | M | 17 | 6 | wt | CAALL-01 | Good | No CR (60%) | 38 | Imatinib (550) | Chemo | $4x10^{-4}$ (48) | +<10-4 (62) | Y | Alive in CR1 (23) |
| #6 | EBF1-PDGFRB | M | 36 | 45 | wt | GRAALL-2014 | Poor | $8x10^{-3}$ | 44 | Imatinib (400) | Chemo | +<$10^{-4}$ (35) | Neg (78) | Y | Alive in CR1 (23) |
| #7 | NUMA1-PDGFRB | M | 61 | 4 | wt | VCR-DEX-Ritux | Good | $1x10^{-3}$ | 39 | Dasatinib (100) | Chemo | Neg (67) | Neg (67) | N | Alive in CR2 (36) |
| #8 | ETV6-PDGFRB | F | 72 | 16 | wt | EWA | | | | | | $2x10^{-3}$ (91) Neg (120) | 1x10-4 (252) Neg (120) | N | Alive in CR1 (29) |
| #9 | ATF7IP-PDGFRB | F | 54 | 13 | wt | GRAA | | | | | | $1x10^{-4}$ (15) | Neg (77) | N | Death in CR2 (16) |
| #10 | NUP214-ABL1 | M | 16 | 30 | del | EORTC 5 | | | | | | No CR (23) $>10^{-2}$ (71) | No CR (23) 1x10-2 (114) | Y | Alive in CR1 (45) |
| #11 | NUP214-ABL1 | M | 17 | 114 | del | FRALL | | | | | | $1x10^{-2}$ (26) | Neg (54) | Y | Alive in CR1 (43) |
| #12 | NUP214-ABL1 | F | 24 | 11 | del | FRALL | | | | | | Neg (65) | Neg (65) | Y | Alive in REL1 (29) |
| #13 | NUP214-ABL1 | F | 31 | 70 | del | GRAA | | | | | | NA | NA | N | Death in REL1 (9) |
| #14 | NUP214-ABL1 | M | 18 | 18 | wt | GRAALL-2014 | NA | No CR (9%) | 70 | Dasatinib (100) | Chemo | $8x10^{-2}$ (14) | Neg (125) | Y | Alive in CR1 (11) |
| #15 | RCSD1-ABL1 | F | 26 | 29 | wt | GRAALL-2014 | Good | $6x10^{-3}$ | 69 | Dasatinib (NA) | Chemo | $2x10^{-3}$ (85) | 5x10-4 (125) | Y | Alive in CR1 (27) |
| #16 | LSM14A-ABL1 | M | 36 | 390 | del | VCR-DEX-Ritux | Poor | No CR (7%) | 49 | Dasatinib (NA) | Chemo | No CR (15) | NA | N | Death, REF (2) |
| #17 | ZC3HAV1-ABL2 | M | 27 | 30 | del | GRAALL-2014 | NA | $9x10^{-4}$ | 58 | Imatinib (600) | Chemo | $2x10^{-4}$ (44) | Neg (175) | Y | Alive in CR1 (8) |
| #18 | MEF2D-CSF1R | M | 34 | 89 | wt | GRAALL-2014 | Poor | $1x10^{-2}$ | 20 | Imatinib (NA) | Chemo | $1x10^{-4}$ (96) | Neg (147) | N | Death in REL1 (13) |
| #19 | ZMYM2-FGFR1 | M | 23 | 53 | wt | GRAALL-2005 | Poor | No CR (55%) | 67 | Ponatinib (30) | Chemo | $2x10^{-2}$ (39) | 2x10-3 (175) | N | Death in REL3 (37) |
| **Patients in relapse** | | | | | | | | | | | | | | | |
| #20 | ETV6-ABL1 | M | 12 | NA | del | FRALLE-2000B | Good | +<$10^{-4}$ | REL1 | Dasatinib (100) | Chemo | Neg (25) | Neg (25) | Y | Alive in CR2 (124) |
| #21 | ETV6-ABL1 | M | 14 | 570 | del | FRALLE-2000B | Poor | $2x10^{-2}$ | REL1 | Imatinib (NA) | Chemo | $1x10^{-3}$ (21) | +<10-4 (49) | Y | Alive in CR2 (59) |
| #22 | RANBP2-ABL1 | F | 20 | 6 | del | GRAALL-2005R | Good | <$10^{-4}$ | REL2, REF | Dasatinib (140) | Chemo | $7 x10^{-2}$ (60) | 8x10-3 (87) | N | Death in REL3 (29) |
| #23 | ETV6-ABL1 | F | 61 | 10 | wt | EWALL-BB | Poor | No CR (75%) | REL1 | Imatinib (400) | Chemo | $5x10^{-3}$ (34) | Neg (245) | N | Death in REL2 (28) |
| #24 | NUP214-ABL1 | F | 15 | 237 | del | EORTC 58081-VHR | Poor | $>10^{-2}$ | REL3 | Dasatinib (140) | Chemo, DLI | $3x10^{-2}$ (27) | NA | N | Death in REL5 (60) |

Ortanca 2.5 ayda
%78 MRH negatifliği
9 hasta APKHN
5 Relaps hastanın hepsi TR,2'si MRH (-)

Tanasi, Blood 2019

blood
American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

**Efficacy of Tyrosine Kinase Inhibitors in Ph-like Acute Lymphoblastic Leukemia harboring ABL-class Rearrangements**

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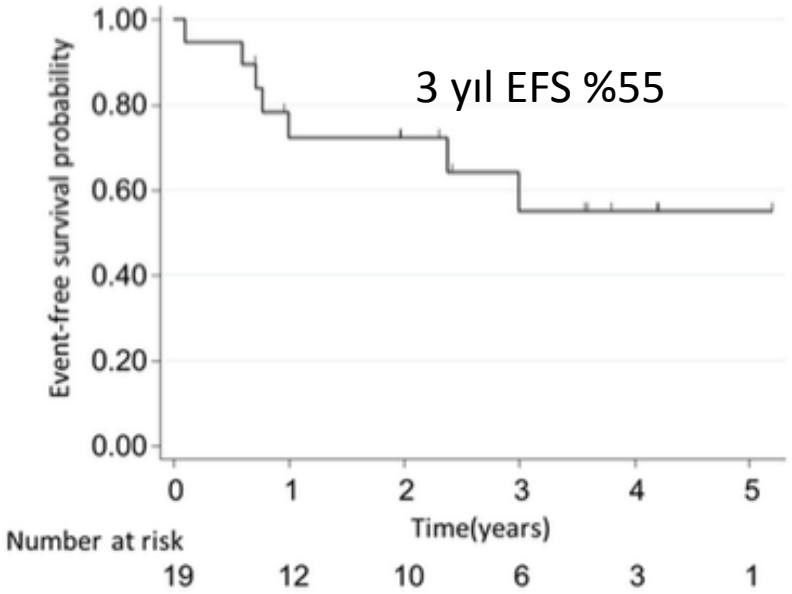


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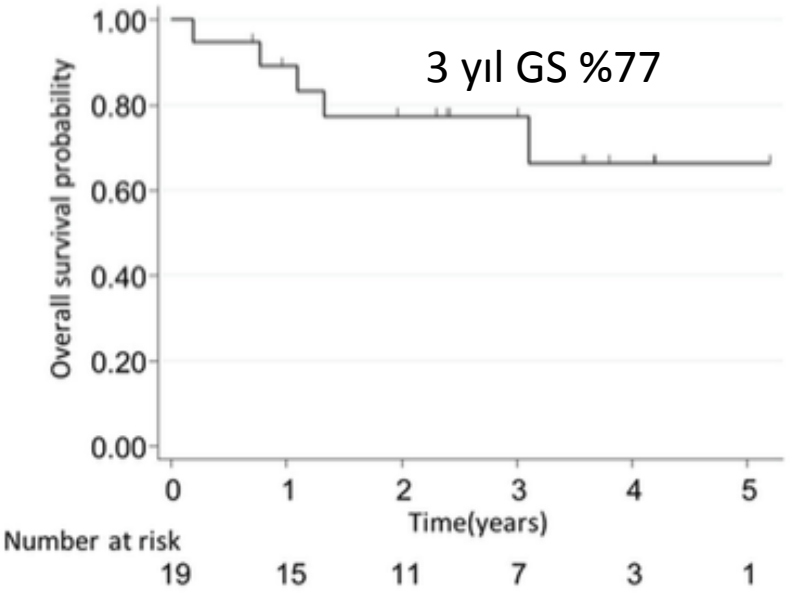


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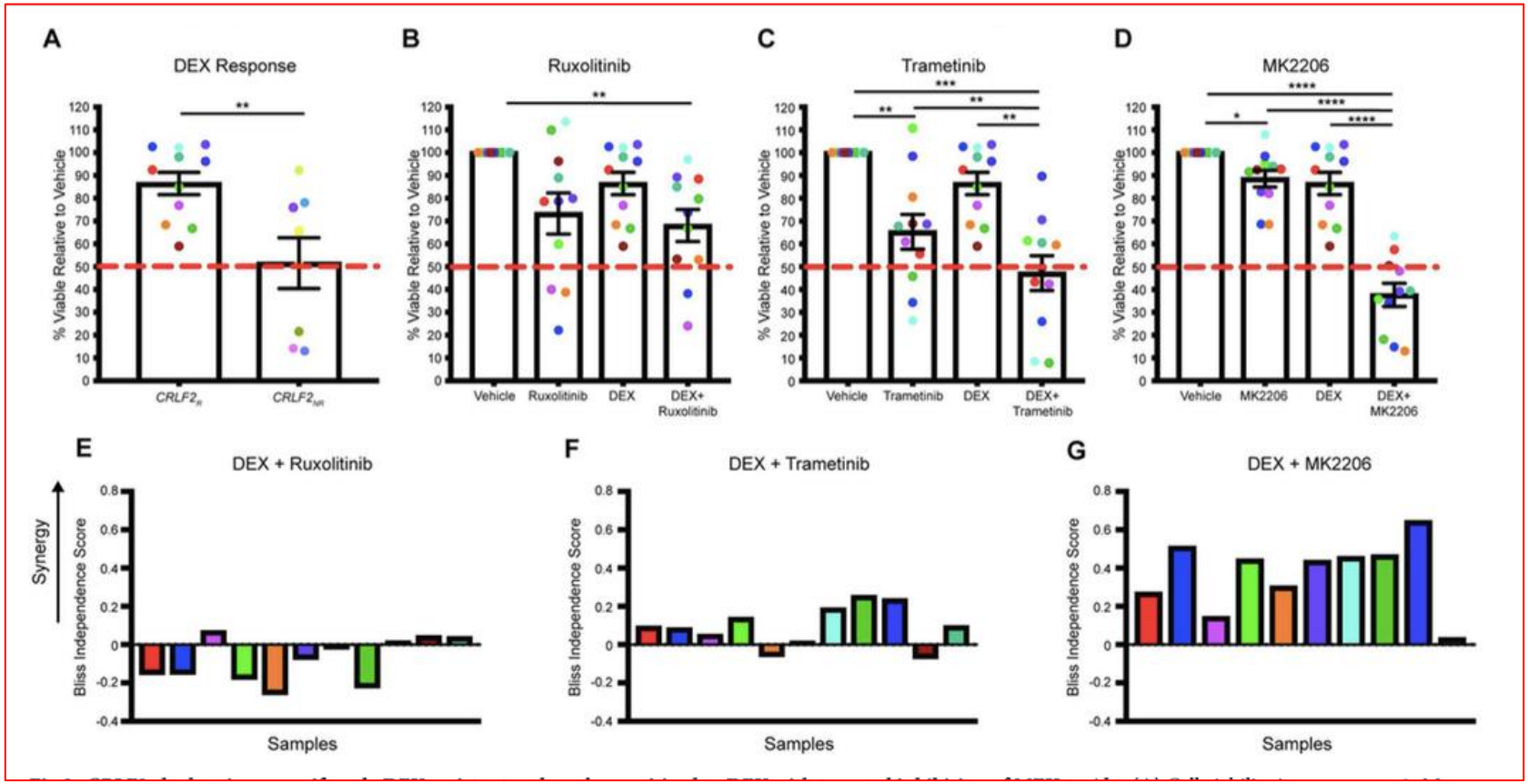
# *CRLF2* rearrangement in Ph-like acute lymphoblastic leukemia predicts relative glucocorticoid resistance that is overcome with MEK or Akt inhibition

**Lauren K. Meyer[1], Cristina Delgado-Martin[1], Shannon L. Maude[2], Kevin M. Shannon[1], David T. Teachey[2], Michelle L. Hermiston[1]***



| Drug | Phase of Clinical Studies development | Ph-Like ALL Target | Method of Action |
|---|---|---|---|
| Birinapant (TetraLogic) | In vitro and in vivo studies | TNF- α –dependent | SMAC mimetic |
| CHZ868 (Novartis) | In vitro and in vivo studies (not for clinical use) | *JAK2*-mutated | Type 2 JAK2 inhibitor |
| Dasatinib (Bristol-Myers Squibb) | Phase 2 and 3 clinical trials in progress | SRC/ABL class tyrosine kinase fusions | Type 2 SRC/ABL class tyrosine kinase inhibitor |
| Gedatolisib (Pfizer) | In vitro and in vivo studies | PI3K and mTOR-activated pathways | Dual inhibitor of PI3K- α , PI3K- γ and mTOR |
| Givinostat (Italfarmaco) | In vitro and in vivo studies | CRLF2+ | Class 1 and class 2 HDAC inhibitor |
| JQ1 (Roche) | In vitro and in vivo studies | CRLF2+ | BET inhibitor |
| Ponatinib (Ariad) | Single case study | SRC/ABL class tyrosine kinase fusions | Type 3 SRC/ABL class tyrosine kinase inhibitor |
| Ruxolitinib (Incyte) | Phase 2 clinical trials in progress | *JAK2*-mutated | Type I JAK2 inhibitor |
| Rapamycin (Pfizer) | In vitro and in vivo studies | mTOR-activated pathways | Inhibitor of mTOR |
| Luminespib (Novartis) | In vitro and in vivo studies | CRLF2+ | HSP90 inhibitor |
| Selumetinib (Astra-Zeneca) and AZD1480 (InvivoGen) | In vitro studies | CRLF2+ | MEK 1/2 inhibitor and ATP-competitive JAK2 inhibitor |
| TSLPR CAR T cells (National Cancer Institute) | In vitro and in vivo studies | CRLF2+ | Allogeneic TSLPR CAR T cells |



Kotb A,Exp Hematol 2018

# SONUÇ OLARAK…

- Ph like ALL  artmış sitokin reseptör ve tirozin kinaz sinyali ,ABL veya JAK STAT yolağını kullanmasıyla karakterize bir subtiptir.
- IKZF, CRLF2, JAK mutasyonları sıktır.
- Kötü prognostiktir.
- MRH bazlı yaklaşım ve erken APKHN planlanması önemlidir!!!
- Hedefe yönelik tedaviler:ruksolitinib,dasatinib..