Progress in the Therapy of Ph+ ALL

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Incidence of Some Important Cytogenetic-Molecular Abnormalities in ALL

Ph+ 2-5%
Hyperdiploid >50
TEL-AML 25%

Ph+ 25%
Hyperdiploid >50
TEL-AML 2%

Pui. NEJM. 2004;350, 1535-1548
## Selected Trials in Ph+ ALL Prior to Tyrosine Kinase Inhibitors (TKIs)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ph+ N(%)</th>
<th>CR %</th>
<th>Median EFS/CRD (months)</th>
<th>Median OS (months)</th>
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<tbody>
<tr>
<td>Bloomfield</td>
<td>29 (17)</td>
<td>46</td>
<td>7</td>
<td>11</td>
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<tr>
<td>Gotz</td>
<td>25</td>
<td>76</td>
<td>NA</td>
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<tr>
<td>Larsen</td>
<td>30 (27)</td>
<td>70</td>
<td>7</td>
<td>11</td>
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<tr>
<td>GFCH</td>
<td>127 (29)</td>
<td>59</td>
<td>5</td>
<td>NA</td>
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<tr>
<td>Secker-Walker</td>
<td>40 (11)</td>
<td>83</td>
<td>13</td>
<td>11</td>
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<tr>
<td>Wetzler</td>
<td>67 (29)</td>
<td>79</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Faderl</td>
<td>67 (13)</td>
<td>*55, 90</td>
<td>*8, 10.8</td>
<td>11.3, 16.5</td>
</tr>
<tr>
<td>Dombret</td>
<td>154</td>
<td>67</td>
<td></td>
<td>19% at 3 years</td>
</tr>
<tr>
<td>Arico</td>
<td>326</td>
<td>82</td>
<td>28% at 5 years</td>
<td>40% at 5 years</td>
</tr>
<tr>
<td>Schrappe</td>
<td>61 (1)</td>
<td>75</td>
<td>38% at 5 years</td>
<td>49% at 5 years</td>
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</tbody>
</table>
UKMRCALLXII/ECOG2993 – Overall survival

Median age 40, range 15-60 years

<table>
<thead>
<tr>
<th></th>
<th>At risk:</th>
<th>TIME IN YEARS</th>
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<tbody>
<tr>
<td>Sib allo HSCT</td>
<td>45</td>
<td>35 29 25 19 18</td>
</tr>
<tr>
<td>MUD allo HSCT</td>
<td>31</td>
<td>23 12 12 11 11</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>82</td>
<td>43 23 19 15 12</td>
</tr>
</tbody>
</table>
Overall Survival by Availability of Sibling Donor


Median age 40, range 15-60 years
City of Hope - Overall Survival

Median age 36, range 2-57 years

In the Era of TKIs, Can We Do Away With Allogeneic Hematopoietic Stem Cell Transplant?
Imatinib - Survival by Regimen

Median follow-up 4 years (range, 13 to 78 mos)

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>No. Fail</th>
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<tbody>
<tr>
<td>Hyper-CVAD</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>Hyper-CVAD + imatinib</td>
<td>48</td>
<td>21</td>
</tr>
</tbody>
</table>

$p<0.001$

## Trials With Frontline Imatinib

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Median age (range)</th>
<th>Imatinib and chemo schedule</th>
<th>CR %</th>
<th>Relapse %</th>
<th>EFS % (years)</th>
<th>Survival % (years)</th>
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</thead>
<tbody>
<tr>
<td>Thomas</td>
<td>45</td>
<td>51 (17-84)</td>
<td>Concurrent</td>
<td>93</td>
<td>22</td>
<td>68* (3)</td>
<td>55 (3)</td>
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<tr>
<td>Yanada</td>
<td>80</td>
<td>48 (15-63)</td>
<td>Concurrent</td>
<td>96</td>
<td>26</td>
<td>51 (2)</td>
<td>58 (20)</td>
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<tr>
<td>Lee</td>
<td>20</td>
<td>37 (15-67)</td>
<td>Concurrent</td>
<td>95</td>
<td>32</td>
<td>62 (2)</td>
<td>59 (2)</td>
</tr>
<tr>
<td>Lee</td>
<td>29</td>
<td>36 (18-55)</td>
<td>Alternating</td>
<td>79</td>
<td>4</td>
<td>78 (3)</td>
<td>78 (3)</td>
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<tr>
<td>Wassmann</td>
<td>45</td>
<td>41 (19-63)</td>
<td>Concurrent</td>
<td>*</td>
<td>*</td>
<td>61 (2)</td>
<td>43 (2)</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>46 (21-65)</td>
<td>Alternating</td>
<td>*</td>
<td>*</td>
<td>52 (2)</td>
<td>36 (2)</td>
</tr>
<tr>
<td>de Labarthe</td>
<td>45</td>
<td>45 (16-59)</td>
<td>Concurrent</td>
<td>96</td>
<td>19</td>
<td>51 (1.5)</td>
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<td>Delannoy</td>
<td>30</td>
<td>66 (58-78)</td>
<td>Alternating</td>
<td>72</td>
<td>60</td>
<td>58 (1)</td>
<td>66 (1)</td>
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<tr>
<td>Vignetti</td>
<td>30</td>
<td>69 (61-83)</td>
<td>+Prednisone</td>
<td>100</td>
<td>48</td>
<td>48 (1)</td>
<td>74 (1)</td>
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<td>Ottmann</td>
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<td>68 (54-79)</td>
<td>Chemo→Concurrent</td>
<td>96</td>
<td>41</td>
<td>29 (1.5)</td>
<td>35 (1.5)</td>
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<tr>
<td></td>
<td>27</td>
<td></td>
<td>Imatinib→Concurrent</td>
<td>50</td>
<td>54</td>
<td>57 (1.5)</td>
<td>41 (1.5)</td>
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Imatinib Significantly Enhances Long-term Outcomes in Ph+ ALL: The UKALLXII/ECOG2993 trial

Overall Survival

Median age 42, range 16-64 years

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<tr>
<th></th>
<th>Imatinib</th>
<th>No Imatinib</th>
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<tbody>
<tr>
<td>SCT</td>
<td>59% 3 yr OS</td>
<td>40% 5 yr OS</td>
</tr>
<tr>
<td>No SCT</td>
<td>28% 3 yr OS</td>
<td>19% 5 yr OS</td>
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</tbody>
</table>

HyperCVAD + Dasatinib

Intensive phase

100
R 1 R 2 R 3 R 4 R 5 R 6 R 7 R 8

70

Maintenance phase

100
R R

24 months

Risk-adapted intrathecal CNS prophylaxis

Hyper-CVAD
MTX-cytarabine

Dasatinib 70 mg daily continuously 2nd course
Vincristine + prednisone

R Rituximab
Long-term Follow-up of HyperCVAD + Dasatinib

Median age 55, range 21-80 years

Ravandi F, et al. Cancer. 2015 Dec 1;121(23):4158-64
HyperCVAD + Dasatinib: Survival - Transplanted Patients Excluded

Median age 55, range 21-80 years

Ravandi F, et al. Cancer. 2015 Dec 1;121(23):4158-64
HyperCVAD + Dasatinib: Outcome by Transplant and Age

Median age 55, range 21-80 years

Chemotherapy Plus Nilotinib: Korean Society of Hematology

Median age 47, range 17-71 years
How Can We Do Better?

• Early and continuous therapy with TKI

• Predict relapse by monitoring MRD and change or intensify therapy

• Minimize chemotherapy especially in the elderly and unfit patients

• Use a more potent TKI and reduce chemo dose in combination regimens
How Can We Do Better?

• Early and continuous therapy with TKI

• Predict relapse by monitoring MRD and change or intensify therapy

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• Use a more potent TKI and reduce chemo dose in older patients
Kaplan Meier Plot of 10-year Overall Survival by Cohort

Median age 42, range 16-64 years

EFS for Cohort 5 Chemo + Imatinib Only Versus Related-Donor SCT Versus Unrelated-Donor SCT

Median age 10, range 1.3 – 21 years

P = .1438

- Cohort 5 chemo (n = 25)
- Related BMT (n = 21)
- Unrelated BMT (n = 11)
Children’s Oncology Group – EFS of Patients Treated with Imatinib

Schultz K R et al. JCO 2009;27:5175–5181
SWOG0805 - Treatment Regimen

A

Intensive phase

100

1 2 3 4 5 6 7 8

Maintenance phase

100

Risk-adapted intrathecal CNS prophylaxis

Hyper-CVAD

MTX-cytarabine

Hyper-CVAD

MTX-cytarabine

24 months

Dasatinib 50 mg po bid/ 100 mg daily

Vincristine + prednisone

Vincristine + prednisone

B

Intensive phase

100

1 2 3 4 5 6 7 8

Maintenance phase

100

Risk-adapted intrathecal CNS prophylaxis

Hyper-CVAD

MTX-cytarabine

Hyper-CVAD

MTX-cytarabine

24 months

Dasatinib 70 mg po daily

Vincristine + prednisone

Vincristine + prednisone

SWOG0805: Continuous TKI Therapy

Induction + Consolidation + Maintenance + Transplant

Dasatinib
Survival Outcomes

Median age 44, range 22-60 years
Patient Disposition and Response

94 patients enrolled and evaluable (60 untreated; 34 one prior cycle)

81 CR, 2 CRi (86%)
2 (2%) CR could not be confirmed
8 (9%) resistant
1 (1%) missing data

41 (49%) received protocol-specified allogeneic SCT in first CR

42 (52%) no protocol-specified allogeneic SCT in first CR

8 (20%) Non-protocol SCT in first CR

3 (36%) died after relapse
5 (63%) alive in CR

1 (2%) missing data
3 (7%) relapsed and are alive
6 (15%) died after relapse
31 (76%) alive in CR

23 (55%) alive in CR

4 (10%) alive after relapse
15 (36%) died after relapse

Median age 44, range 22-60 years
SWOG0805: Outcomes With HSCT

(A) Relapse-free survival (B) Overall survival

(C, D) landmark analysis HCT versus no HCT

Median age 44, range 22-60 years

How Can We Do Better?

• Early and continuous therapy with TKI

• **Predict relapse by monitoring MRD and change or intensify therapy**

• Minimize chemotherapy especially in the elderly and unfit patients

• Use a more potent TKI and reduce chemo dose in older patients
MDACC MRD study: Population Studied

- April 2001 to March 2011
- 122 patients with Ph+ ALL treated on
  HyperCVAD + Imatinib (n=54)
  HyperCVAD + Dasatinib (n=68)
- 115 (94%) achieved CR
- 101 achieved CR with one course and had at least 1 MRD assessment
- 25 underwent alloSCT in first CR – excluded
- FINAL N=76

Comparison of Outcomes for the Patients Treated on the 2 Regimens (A) CRD, (B) DFS, (C) OS

Outcome by Achievement of Negative Flow at Various Time Points

A. OS by MFC status at CR

B. CRD by MFC at CR

C. OS by MFC at 3 months

D. CRD by MFC at 3 months

E. OS by MFC at 12 months

F. CRD by MFC at 12 months

Outcome by Achievement of MMR or Better at Various Time Points

A. OS by level of BCR-ABL/ABL at CR
B. CRD by level of BCR-ABL/ABL at CR
C. OS by level of BCR-ABL/ABL at 3 months
D. OS by level of BCR-ABL/ABL at 6 months
E. OS by level of BCR-ABL/ABL at 9 months
F. OS by level of BCR-ABL/ABL at 12 months

Multivariate Analysis of Predictors of Long-term Outcome

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>MMR</td>
<td>0.248</td>
<td>0.110 - 0.559</td>
<td>0.001</td>
</tr>
<tr>
<td>MRD positive by <em>IgH</em></td>
<td>1.651</td>
<td>0.714 - 3.819</td>
<td>0.242</td>
</tr>
<tr>
<td>MRD positive by flow</td>
<td>1.464</td>
<td>0.583 - 3.679</td>
<td>0.418</td>
</tr>
<tr>
<td>positive CD20</td>
<td>0.486</td>
<td>0.211 - 1.118</td>
<td>0.090</td>
</tr>
<tr>
<td>fusion protein = p210</td>
<td>0.532</td>
<td>0.179 - 1.582</td>
<td>0.256</td>
</tr>
<tr>
<td>Cyto = Ph+ alone or + other</td>
<td>0.665</td>
<td>0.220 - 2.010</td>
<td>0.470</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.996</td>
<td>0.989 - 1.002</td>
<td>0.212</td>
</tr>
<tr>
<td>Blast % BM</td>
<td>0.984</td>
<td>0.962 - 1.007</td>
<td>0.162</td>
</tr>
<tr>
<td>Age</td>
<td>1.014</td>
<td>0.985 - 1.045</td>
<td>0.347</td>
</tr>
<tr>
<td>Time to CR</td>
<td>0.971</td>
<td>0.897 - 1.051</td>
<td>0.460</td>
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<tr>
<td>log.WBC</td>
<td>2.083</td>
<td>1.050 - 4.133</td>
<td>0.036</td>
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</table>

Patient Outcomes Based on Molecular Response

A

<table>
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<tr>
<th></th>
<th>Median RFS</th>
<th>4-year RFS rate</th>
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<tbody>
<tr>
<td>CMR</td>
<td>29 (34)</td>
<td>NR</td>
</tr>
<tr>
<td>MMR</td>
<td>10 (12)</td>
<td>NR</td>
</tr>
<tr>
<td>No MMR</td>
<td>46 (54)</td>
<td>26.1 mos</td>
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P = .04

B

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<th>Median RFS</th>
<th>4-year RFS rate</th>
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<tbody>
<tr>
<td>CMR</td>
<td>51 (60)</td>
<td>125.7 mos</td>
</tr>
<tr>
<td>MMR</td>
<td>16 (19)</td>
<td>26.1 mos</td>
</tr>
<tr>
<td>No MMR</td>
<td>18 (21)</td>
<td>12.1 mos</td>
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P = .002

C

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<th>4-year OS rate</th>
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<td>29 (34)</td>
<td>NR</td>
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<tr>
<td>MMR</td>
<td>10 (12)</td>
<td>NR</td>
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<tr>
<td>No MMR</td>
<td>46 (54)</td>
<td>46.7 mos</td>
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P = .11

D

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<td>51 (60)</td>
<td>126.5 mos</td>
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<tr>
<td>MMR</td>
<td>16 (19)</td>
<td>38.6 mos</td>
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<tr>
<td>No MMR</td>
<td>18 (21)</td>
<td>20.4 mos</td>
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P = .005

## Impact of CMR on Outcome

### Molecular response at 3 months

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>3-year OS rate (%)</th>
<th>P</th>
<th>3-year RFS rate (%)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>CMR</td>
<td>51 (60)</td>
<td>79</td>
<td></td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>23 (27)</td>
<td>56</td>
<td>0.006</td>
<td>42</td>
<td>0.002</td>
</tr>
<tr>
<td>No MMR</td>
<td>11 (13)</td>
<td>45</td>
<td></td>
<td>36</td>
<td></td>
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Chemotherapy Plus Nilotinib: Korean Society of Hematology

Median age 47, range 17-71 years

NGS MRD in ALL: Prognostic Impact

- NGS MRD performed pre-SCT in 41 children with B-ALL
- Discrimination better with NGS than with MFC

Prospective monitoring for post-SCT MRD was also superior with NGS

Pulsipher MA et al, *Blood*, 2015, 125(22), 3501-3508
MRD: Duplex Sequencing

a) Randomized duplex tag

b) PCR duplicates both strands of duplex

αβ family

βα family

C) Single-strand consensus sequences (SSCSs)

Duplex consensus sequences (DCSs)

True mutation

Identification of Low-Level Mutations with Duplex Sequencing

Conventional NGS: artifactual errors obscure low-level variants

Duplex Sequencing: errors removed, revealing single true mutation

IKZF1 Deletions in Ph+ ALL

- 83 adults with Ph+ ALL (57 treated with TKI)
- *IKZF1* deletion in 63%

How Can We Do Better?

- Early and continuous therapy with TKI
- Predict relapse by monitoring MRD and change or intensify therapy
- Minimize chemotherapy especially in the elderly and unfit patients
- Use a more potent TKI and reduce chemo dose in older patients
TKI with Minimal Chemotherapy

Median age 54, range 24-77 years

A. Overall survival (OS)

B. Disease-free survival (DFS), from day +85

TKI Induction Followed by Intensive Chemotherapy and HSCT

Median age 45.9, range 16.9–59.7 years

TKI with Limited Chemotherapy

Median age 69, range 59-83 years

Low vs. High Intensity Induction

Median age 47, range 21-60 years

Role of Stem Cell Transplant in CR1 and Influence of MRD

Median age 47, range 21-60 years

How Can We Do Better?

• Early and continuous therapy with TKI

• Predict relapse by monitoring MRD and change or intensify therapy

• Minimize chemotherapy especially in the elderly and unfit patients

• Use a more potent TKI and reduce chemo dose in older patients
Tyrosine Kinase Domain Mutations at Relapse

• 13 patients with available mutation analysis at relapse

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Patients (N)</th>
</tr>
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<tbody>
<tr>
<td>T315I</td>
<td>4</td>
</tr>
<tr>
<td>F359V</td>
<td>1</td>
</tr>
<tr>
<td>V299L</td>
<td>2</td>
</tr>
</tbody>
</table>
Distribution of BCR-ABL1 Tyrosine Kinase Domain Mutations in 36 Patients in First Relapse

- Sanger sequencing: n = 24
  - 12.5% (T315I)
  - 12.5% (F317L)
  - 75% (V299L, Compound without T315I, No mutation)

- Relapses: n = 36
  - T315I (n = 18)
  - F317L (n = 1)
  - V299L (n = 1)
  - Compound without T315I (n = 1)
  - No mutation (n = 3)
  - No sequencing (n = 12)

Low-Intensity Chemotherapy + Dasatinib: T315I Prior to Initiation of Therapy

- Screening for T315I mutation performed by ASO qRT-PCR in 43 pts
- T315I mutation detected in 10 (23%)
Potency of Ponatinib Against Clinically-Relevant Mutations In Vitro

• Clinically achievable ponatinib concentrations (40 nM with ≥30 mg/d)1 suppressed the emergence of any single mutation in vitro2

<table>
<thead>
<tr>
<th>BCR-ABL1</th>
<th>Ponatinib IC(_{50}), nM</th>
</tr>
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<tbody>
<tr>
<td>Native BCR-ABL1</td>
<td>0.5</td>
</tr>
<tr>
<td>F317L</td>
<td>1.1</td>
</tr>
<tr>
<td>H396P</td>
<td>1.1</td>
</tr>
<tr>
<td>M351T</td>
<td>1.5</td>
</tr>
<tr>
<td>T315A</td>
<td>1.6</td>
</tr>
<tr>
<td>M244V</td>
<td>2.2</td>
</tr>
<tr>
<td>Q252H</td>
<td>2.2</td>
</tr>
<tr>
<td>Y253F</td>
<td>2.8</td>
</tr>
<tr>
<td>G250E</td>
<td>4.1</td>
</tr>
<tr>
<td>Y253H</td>
<td>6.2</td>
</tr>
<tr>
<td>F317V</td>
<td>10.0</td>
</tr>
<tr>
<td>F359V</td>
<td>10.0</td>
</tr>
<tr>
<td>T315I</td>
<td>11.0</td>
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<tr>
<td>E255K</td>
<td>14.0</td>
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<tr>
<td>E255V</td>
<td>36.0</td>
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<tr>
<td>Parental Ba/F3 cells</td>
<td>1713.0</td>
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Hyper-CVAD with Ponatinib in Ph+ ALL:
A) 2-year EFS, B) 2-year OS

Median age 51, range 27-75 years

Jabbour E, et al. Lancet Oncology, 2015, 16(15), 1547–1555
Hyper-CVAD with Ponatinib: Overall Survival With and Without Censoring for alloHSCT

Median age 51, range 27-75 years

Jabbour E, et al. Lancet Oncology, 2015, 16(15), 1547–1555
<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>CR*</td>
<td>61/61 (100)</td>
</tr>
<tr>
<td>CCyR**</td>
<td>52/52 (100)</td>
</tr>
<tr>
<td>MMR</td>
<td>68/70 (97)</td>
</tr>
<tr>
<td>CMR</td>
<td>55/70 (79)</td>
</tr>
<tr>
<td>MRD***</td>
<td>68/69 (99)</td>
</tr>
<tr>
<td>Early death</td>
<td>0 (0)</td>
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</tbody>
</table>

* 1 pt in CR at start
** 5 pts were diploid at start
*** 1 pt had no sample sent for MRD
Hyper-CVAD + Ponatinib: Updated Survival

Median age 47, range 21-80 years
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ponatinib N=61</th>
<th>Dasatinib N=72</th>
<th>Imatinib N=54</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>61/61 (100)</td>
<td>63/67 (94)</td>
<td>42/45 (93)</td>
</tr>
<tr>
<td><strong>CCyR</strong></td>
<td>52/52 (100)</td>
<td>53/57 (93)</td>
<td></td>
</tr>
<tr>
<td><strong>MMR</strong></td>
<td>68/70 (97)</td>
<td>65/70 (93)</td>
<td></td>
</tr>
<tr>
<td><strong>MMR after induction</strong></td>
<td>36/55 (65)</td>
<td>37/62 (60)</td>
<td>20/38 (53)</td>
</tr>
<tr>
<td><strong>CMR</strong></td>
<td>55/70 (79)</td>
<td>45/70 (64)</td>
<td>26 (52)</td>
</tr>
<tr>
<td><strong>MRD- by flow</strong></td>
<td>68/69 (99)</td>
<td>67/70 (96)</td>
<td></td>
</tr>
<tr>
<td><strong>1-yr OS rate</strong></td>
<td>84%</td>
<td>79%</td>
<td>79%</td>
</tr>
<tr>
<td><strong>1-yr CRD rate</strong></td>
<td>100%</td>
<td>94%</td>
<td>79%</td>
</tr>
<tr>
<td><strong>Early death</strong></td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
Ponatinib Plus Steroids in Elderly and Unfit

Figure 1: BCR-ABL/ABL ratio at 24w defining CMR as BCR-ABL >0.01 with a sensitivity of at least 10,000 molecules of ABL.

Figure 2: Kaplan-Meier plot representing OS.

Median age 68, range 27 - 85
Monoclonal Antibodies in Pre-B ALL

- Blinatumomab
- Epratuzumab
- Inotuzumab
- Alemtuzumab
- Rituximab
- Ofatumomab
- Obinutuzumab

Lymphoblast
Blinatumomab in Ph-Positive ALL

Single-Agent Blinatumomab

R/R Ph+ ALL to 2+ generation TKI (N = 45):
- T315I (n = 10)
- ≥2 TKI (n = 27)
- Prior ponatinib (n = 23)

Primary endpoint
(CR/CRh during first 2 cycles):
- CR/CRh: 16 (36%)
- T315I: 4 (40%)
- ≥ 2 TKI: 11 (41%)
- Prior ponatinib: 8 (35%)

Secondary endpoints:
- Complete MRD response: 14 (88%)
- Proceed to allo-HSCT: 7 (44%)
- Median RFS: 6.7 mo (median follow-up: 9 mo)
- Median OS: 7.1 mo (median follow-up: 8.8 mo)

Martinelli G et al. JCO 2017: 35(16), 1795–1802
**Blinatumomab + Ponatinib**

**Induction phase**
- 30 mg for 1 cycle (4 weeks)

**Consolidation phase: C2-C4**
- 15 mg in CMR for 2 cycles (2 weeks each)

**Maintenance phase**
- 15 mg for 5 years

- **Blinatumomab**
- **IT MTX, Ara-C**
- **Ponatinib 30 mg**
- **Ponatinib 15 mg**
Inotuzumab + Bosutinib

**Cycle 1**

D1: 0.8 mg/m²  
D8: 0.5 mg/m²  
D15: 0.5 mg/m²

**Cycle 2-6***

D1: 0.5 mg/m²  
D8: 0.5 mg/m²  
D15: 0.5 mg/m²

*After CR / CCyR / MRD neg: 1.0 mg/m² Q4 wks

Bosutinib continuously daily until PD or toxicity

**Inotuzumab**

- Inotuzumab

**Bosutinib daily (3 dose levels)**

- 300mg
- 400mg
- 500mg

Jain N, et al. Abstract 143
Potential Role of Autologous SCT: CALGB-10001
Potential Role of Autologous SCT: GRAAPH-2003

Median age 45, range 16 – 59 years

Chimeric Antigen Receptor (CAR) – T cell Therapy
Recurring Kinase Alterations in Ph-like ALL

Conclusions

• Better tools available for treatment of Ph+ ALL

• MRD detection can help predict patients more likely to relapse

• Using more potent TKIs and with age-adjusted chemotherapy long term survival without transplant possible