BLINCYTO® (blinatumomab) for Minimal Residual Disease Positive (MRD+) B-cell Precursor Acute Lymphoblastic Leukemia (ALL)

Oncologic Drugs Advisory Committee
Amgen Inc
March 7, 2018
Introduction

Kathy Kross, MSc
Executive Director, Global Regulatory Affairs
Oncology Therapeutic Area Head
Amgen Inc
# Presentation Overview

<table>
<thead>
<tr>
<th>Section</th>
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</tr>
</thead>
<tbody>
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</tbody>
</table>
Expert Consultant

Richard Simon, DSc
Former Director, Biometric Research Program of the National Cancer Institute
BLINCYTO is indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia in adults and children.
Blinatumomab Mechanism of Action

Anti-CD3 mAb

Blinatumomab (anti-CD19/anti-CD3 BiTE®)

Anti-CD19 mAb

CD19+ leukemia cell

CD3+ cytotoxic T-cell

T-cell cytotoxicity is redirected towards leukemia cells

Contact with leukemia cells leads to cytotoxic T-cell activation

Production of inflammatory cytokines and proliferation of cytotoxic T-cells

Through serial lysis, individual cytotoxic T-cells can induce apoptosis of multiple leukemic cells
# Blinatumomab Regulatory History

<table>
<thead>
<tr>
<th>Date</th>
<th>Milestone</th>
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</thead>
<tbody>
<tr>
<td>2014</td>
<td><strong>Accelerated Approval</strong></td>
</tr>
<tr>
<td>December</td>
<td>• Ph- R/R B-cell precursor ALL</td>
</tr>
<tr>
<td></td>
<td>• 1° Endpoint - hematologic complete remission (CR)</td>
</tr>
<tr>
<td></td>
<td>• Approximately doubled CR rate vs. historical SOC control</td>
</tr>
<tr>
<td>2017</td>
<td><strong>Full Approval</strong></td>
</tr>
<tr>
<td>July</td>
<td>• R/R B-cell precursor ALL in adults and children</td>
</tr>
<tr>
<td></td>
<td>• Broaden indication to include Ph+ R/R ALL</td>
</tr>
<tr>
<td></td>
<td>• Confirmatory phase 3 trial demonstrated significant OS over chemotherapy</td>
</tr>
<tr>
<td></td>
<td>• Reduction of leukemic burden (CR) correlated with OS</td>
</tr>
<tr>
<td>2017</td>
<td><strong>sBLA submitted for MRD+ B-cell ALL</strong></td>
</tr>
<tr>
<td>September</td>
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</table>
Proposed Indication

BLINCYTO is indicated for the treatment of minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia (ALL)
Minimal Residual Disease (MRD) in ALL

- MRD is a direct measurement of ALL disease burden
  - Presence of leukemic cells below the detection of conventional morphologic measures

- MRD+ patients in hematologic CR are not in full remission

- Presence of MRD is the strongest prognostic factor for relapse
  - Outcomes in MRD+ patients are quite poor

- Patients with MRD+ ALL have limited options
  - No approved therapy for MRD+ patients
3 Studies for MRD+ ALL

- **Study 202**: Exploratory Safety/Efficacy
  - Phase 2
  - N=21

- **Study 203 (BLAST)**: Safety/Efficacy
  - Phase 2
  - N=116

- **Study 148**: Historical Comparator
  - N=287

Study 203 vs Study 148
Propensity Score Analysis
Rationale for Blinatumomab Use in MRD+ ALL

- Blinatumomab is efficacious in MRD+ ALL
  - 78% achieved complete MRD response (undetectable MRD) after 1 cycle
  - Median relapse-free survival (RFS)
    - Complete MRD responders 23.6 months vs. non-responders 5.7 months
    - Supported by comparison to historical data (Study 148) in the propensity score analysis

- Clinical outcomes are better for MRD-negative patients

- Adverse events well characterized and managed through product labeling and existing REMS

- Favorable benefit-risk
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Overview of MRD+ ALL

Jerald Radich, MD

Fred Hutchinson Cancer Research Center
Overview of Acute Lymphoblastic Leukemia (ALL)

- ALL is rare ~6,600 new cases (~2,400 adults)
  - Majority of ALL cases are B-lineage, Philadelphia chromosome-negative ALL

- Treatment goals
  - CR achieved in > 80%
  - Overall survival (OS) ~40%

- Patients who do not obtain a CR or relapse have a very low likelihood of survival
  - 5 yr OS < 10%
  - Transplant can salvage some relapsed patients

BCR-ABL MRD and Outcome in CML

Relapse Post-allogeneic Transplant

EFS After Imatinib Therapy

Probability of Clinical Relapse

Days after max PCR 6–12 months

Estimated % Without Event

Mos Since Start of Treatment


Minimal Residual Disease (MRD) Has Great Clinical Utility

- 30-50% of adult patients with ALL who achieve hematologic CR following chemotherapy have evidence of disease using more sensitive tests (MRD)
- MRD reflects ALL disease burden
- MRD is strongest prognostic feature for relapse after achieving CR
Minimal Residual Disease (MRD)  
Presence of Malignant Cells Below Detection Limits of Microscopy

- Morphology (limit 5\%)

MRD Detection Methods
- Flow cytometry (limit $10^{-3}$ to $10^{-4}$)
- PCR of Ig or TCR ($10^{-4}$ to $10^{-5}$)
- NGS of Ig or TCR (limit $10^{-5}$ to $10^{-6}$)

The ALL Patient Experience

- **Day 30 bone marrow**
  - If no CR → alternative RX
  - If CR → continued therapy

- **At relapse**
  - Lower chance for CR with chemo
  - Low chance of transplant working

**MRD:**
1. An indicator of relapse risk
2. A therapeutic target
MRD Status is Associated With CR and Survival

Probability of Continuous CR

- Probability of Survival

MRD-Positivity is Associated with Poor Outcome in Children and Adults

OS for Pediatric ALL: 5 studies with 2,876 patients

OS for Adult ALL: 5 studies with 779 patients

Meta-Analysis: MRD and EFS in Children and Adults

EFS for Pediatric ALL: 20 studies with 11,249 patients

EFS for Adult ALL: 16 studies with 2,069 patients

HR = 0.23 (0.18 to 0.28)

HR = 0.28 (0.24 to 0.33)

Association of MRD and EFS is Remarkably Similar Across Studies

EFS by ALL Peds Studies (with 95% CIs)

- Imashuku (2003)
- Eckert (2013)
- Stow (2010)
- Bowman (2011)
- Kang (2009)
- Pulsipher (2014)
- Vilmer (2000)
- Foster (2011)
- Borowitz (2015)
- Chen (2012)
- Vora (2013)
- Salah-Eldin (2014)
- Borowitz (2008)
- Sutton (2014)
- Eckert (2012)
- Velden (2012)
- Conter (2010)
- Flohr (2008)
- Meleshko (2011)
- Zhou (2007)

Relative Sample Size
- 0.025
- 0.100
- 0.250
- 0.500

Hazard Ratio
- Favors No MRD
- Favors MRD

EFS by ALL Adult Studies (with 95% CIs)

- Tucunduva (2014)
- Bruggemann (2005)
- Ravandi (2013)
- Stirewalt (2003)
- Mortuza (2002)
- Beldjord (2014)
- Krampera (2002)
- Gokbuget (2012)
- Patel (2009)
- Pane (2005)
- Ribera (2014)
- Holowiecki (2008)
- Bassan (2009)
- Lee (2012)
- Raff (2006)
- Spinelli (2007)
- MA – standard
- MA – Bayesian
Effect of MRD is Independent of Other Covariates

Subset Analysis of EFS for MRD ALL

<table>
<thead>
<tr>
<th>Subset</th>
<th>Favors Absence of MRD</th>
<th>Favors Presence of MRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (95% Exact CI)</strong></td>
<td><strong>Adult</strong></td>
<td><strong>Pediatric</strong></td>
</tr>
<tr>
<td>MRD Detection Method:</td>
<td>0.32 (0.20, 0.51)</td>
<td>0.27 (0.20, 0.36)</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>0.24 (0.18, 0.32)</td>
<td>0.20 (0.11, 0.35)</td>
</tr>
<tr>
<td>PCR</td>
<td>0.29 (0.21, 0.39)</td>
<td>0.30 (0.20, 0.46)</td>
</tr>
<tr>
<td>MRD Cutoff:</td>
<td>0.21 (0.14, 0.32)</td>
<td>0.18 (0.11, 0.29)</td>
</tr>
<tr>
<td>$10^{-4}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt; 10^{-4}$</td>
<td>0.33 (0.24, 0.44)</td>
<td>0.20 (0.15, 0.28)</td>
</tr>
<tr>
<td>MRD Detection Period:</td>
<td>0.25 (0.18, 0.36)</td>
<td>0.20 (0.15, 0.28)</td>
</tr>
<tr>
<td>Induction</td>
<td>0.18 (0.08, 0.41)</td>
<td></td>
</tr>
<tr>
<td>Consolidation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other period</td>
<td>0.28 (0.22, 0.37)</td>
<td>0.17 (0.07, 0.42)</td>
</tr>
<tr>
<td>Cytogenetics:</td>
<td>0.34 (0.22, 0.53)</td>
<td></td>
</tr>
<tr>
<td>Ph-</td>
<td></td>
<td></td>
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<tr>
<td>Ph+</td>
<td></td>
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Pre-Transplant MRD Status Affects Outcome


CR 1 = 90, CR2 = 58, >CR2 = 12.

*MRD status not influenced by adjusting for CR status*
CR: < 5% Blast in Bone Marrow

**Outcomes By Response Status**

- **Multi-agent chemotherapy**
  - **Response Assessment**
    - **CR 90%**
      - **Morphologic Assessment**
        - **CR**
          - **Molecular Assessment**
            - **MRD-**
              - **Implications/Clinical Outcome**
                - Decreased Risk of Relapse
                - Improved Outcomes
                - HSCT option
            - **MRD+**
              - **Implications/Clinical Outcome**
                - Increased Risk of Relapse
                - Poor HSCT Outcomes compared to MRD-
        - **No CR**
          - **Refractory Disease**
            - **Implications/Clinical Outcome**
              - ALL Salvage Treatment
              - Worst Outcome of the 3 Scenarios

**Molecular Assessment**
There is Nothing *Minimal* About Residual Disease

- Presence of MRD is still associated with thousands of leukemia cells. *This leukemia burden is not minimal*

- MRD after standard induction or consolidation is strongly associated with relapse and poorer survival, both in the context of chemotherapy or transplantation. *The clinical consequence of MRD is not minimal*

- We need more options to treat MRD. This is a major unmet need in the care of ALL patients
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Efficacy

Janet Franklin, MD, MPH

Executive Medical Director
Global Development Lead for BLINCYTO
Amgen Inc
Efficacy Overview

- Blinatumomab in Relapsed/Refractory ALL
- MRD+ ALL Clinical Trials
  - Study 202: Exploratory Phase 2
  - Study 203: Phase 2
- Historical Comparisons
  - Study 148
  - Propensity Score Analysis
Relapsed/Refractory (R/R) ALL Development

**Adults**
- Study 206 (Ph 2)  
  N = 36  
  Dose/Schedule
- Study 211 (Ph 2)  
  N = 225  
  Safety/Efficacy
- Study 310  
  N = 1139  
  Historical Comparator (Global)
- Study 311 TOWER (Ph 3)  
  N = 405  
  Safety/Efficacy

**Pediatrics**
- Study 205 (Ph 1/2)  
  N = 49/44  
  Dose/Sched/Safety/Efficacy
- Study 216 ALCANTARA (Ph 2)  
  N = 45  
  Safety/Efficacy Ph+
- Study 228  
  N = 159  
  Historical Comparator (US)
- Study 299  
  N = 198  
  Historical Comparator (EU)
- Study 310  
  N = 1139  
  Historical Comparator (Global)
R/R ALL: CR Correlates with Overall Survival (OS)

- Randomized controlled TOWER Study (Study 311) results:
  - Confirmed blinatumomab reduces disease burden compared to standard of care (SOC) chemotherapy
  - Established disease reduction correlates with overall survival
  - Demonstrated significant OS benefit over chemotherapy
    
    \[ \text{HR} = 0.71 \ [95\% \ CI: \ 0.55, \ 0.93], \ P = 0.012 \]
  - Predicted by earlier single-arm study and historical comparisons
MRD+ ALL Development Program

**Study 202**
- Exploratory Safety/Efficacy
- Phase 2
- N=21

**Study 203 (BLAST)**
- Safety/Efficacy
- Phase 2
- N=116

**Study 148**
- Historical Comparator
- N=287

Study 203 vs Study 148
Propensity Score Analysis
# Study 202: Key Outcomes – Final Analysis

<table>
<thead>
<tr>
<th>Key Outcomes</th>
<th>N=20</th>
</tr>
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<tbody>
<tr>
<td>MRD response, n (%)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Allo HSCT after blinatumomab, n (%)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>50.8</td>
</tr>
<tr>
<td>Alive and in remission, n (%)</td>
<td>10 (50)</td>
</tr>
</tbody>
</table>

- 10 patients still in remission 5 years after start of blinatumomab treatment
  - 5 of these patients never received a transplant
MRD+ ALL Development Program

Study 202
Exploratory Safety/Efficacy Phase 2
N=21

Study 203 (BLAST)
Safety/Efficacy Phase 2
N=116

Study 148
Historical Comparator
N=287

Study 203 vs Study 148
Propensity Score Analysis
Study 203: Phase 2 Study in MRD+ ALL

- Larger multi-center and multi-country study to assess efficacy and safety in patients with MRD+ ALL
  - To confirm MRD response rate of 80% in Study 202\textsuperscript{a,b}

- Conducted in EU due to availability of centralized MRD assay

- Investigators uncomfortable with randomizing MRD+ patients who had already received 3+ blocks of intensive chemotherapy

Study 203: Patient Population

◆ Key Inclusion criteria
  – ≥ 3 prior intensive chemotherapy blocks
  – MRD level ≥ 10^{-3}
    • Reliable assay sensitivity was limited to 10^{-4} in 2009
    • Allowed measurement of at least a 10-fold reduction in leukemic burden
    • Allowed for feasible study to evaluate time-based endpoints
  – Age ≥ 18 years in 1st or later CR with MRD+ B-cell precursor ALL

◆ Key Exclusion criteria
  – History of CNS pathology
  – Presence of extramedullary disease
  – Prior Allogeneic HSCT

CR defined as < 5% blasts in bone marrow after at least ≥ 3 intensive chemotherapy blocks (e.g., GMALL induction I-II/consolidation I, induction/intensification/consolidation, or three blocks of Hyper CVAD).
Study 203: Endpoints

- **Primary Endpoint**
  - Proportion of patients achieving complete MRD response (undetectable disease) after 1 cycle of blinatumomab

- **Key Secondary Endpoint**
  - Hematologic RFS among Ph- patients at 18 months\(^a\)

- **Secondary Endpoints**
  - Overall survival
  - Incidence of adverse events

- **All endpoints were pre-specified in statistical analysis plan**

\(^a\): Censored at HSCT or post-blinatumomab chemotherapy.
Study 203: Treatment Overview

Blinatumomab is administered as a continuous IV infusion at a dose of 15 µg/m²/day (approximately equivalent to the blinatumomab fixed dose of 28 µg/day) over 4 weeks followed by a treatment-free period of 2 weeks (1 cycle = 6 weeks). Subjects were eligible to receive up to 4 cycles of treatment. CSF prophylaxis given periodically throughout treatment; HSCT = hematopoietic stem cell transplantation.

- **Cycle 1**: blinatumomab 15 µg/m²/day x 28 days
- **Primary endpoint assessment**
- **Up to 3 Additional Cycles Permitted**: blinatumomab 15 µg/m²/day x 28 days per cycle
- **2-year follow-up for efficacy**
- **5-year follow-up for survival**
- **100-day allogeneic HSCT-related mortality assessment**
- **Patients eligible for allogeneic HSCT**

FSE: November, 2010
LSE: January, 2014

5-year follow-up: January, 2019
## Study 203: Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=116</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68 (59)</td>
</tr>
<tr>
<td>Female</td>
<td>48 (41)</td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>45 (18–76)</td>
</tr>
<tr>
<td>Age, n (%)</td>
<td></td>
</tr>
<tr>
<td>18 to &lt; 35 years</td>
<td>36 (31)</td>
</tr>
<tr>
<td>35 to &lt; 55 years</td>
<td>41 (35)</td>
</tr>
<tr>
<td>55 to &lt; 65 years</td>
<td>24 (21)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>15 (13)</td>
</tr>
<tr>
<td><strong>Median time from last prior treatment, months (range)</strong></td>
<td>2.0 (0–55)</td>
</tr>
<tr>
<td>Relapse history, n (%)</td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>75 (65)</td>
</tr>
<tr>
<td>CR2</td>
<td>39 (34)</td>
</tr>
<tr>
<td>CR3</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Baseline MRD levels, n (%)</td>
<td></td>
</tr>
<tr>
<td>10^{-1} to &lt; 1</td>
<td>9 (8)</td>
</tr>
<tr>
<td>10^{-2} to &lt; 10^{-1}</td>
<td>45 (39)</td>
</tr>
<tr>
<td>10^{-3} to &lt; 10^{-2}</td>
<td>52 (45)</td>
</tr>
<tr>
<td>Other(^{a})</td>
<td>10 (9)</td>
</tr>
</tbody>
</table>

\(^{a}\) 3 (3%) patients < 10^{-3}, 5 (4%) patients below the lower limit of quantitation, and 1 (1%) patient unknown.
Study 203: Primary Endpoint
78% Achieved a Complete MRD Response

<table>
<thead>
<tr>
<th>Evaluations</th>
<th>n (%)</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Patients with evaluable MRD</td>
<td>112 (99)</td>
<td></td>
</tr>
<tr>
<td>Complete MRD response at end of Cycle 1</td>
<td>88 (78)</td>
<td>69–85</td>
</tr>
</tbody>
</table>

- 78% complete MRD response rate (95% CI: 69, 85)
- The lower bound of 69% exceeds the pre-specified threshold of 44%

a. Patients receiving ≥ 1 dose of blinatumomab who had an MRD assay available with a sensitivity <10^-4 at the central lab.
Study 203: Complete MRD Response After Cycle 1 by Baseline Characteristics (Primary Endpoint FAS)

<table>
<thead>
<tr>
<th>Primary EP FAS</th>
<th>n/N</th>
<th>%</th>
<th>(95% Exact CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>88/113</td>
<td>78</td>
<td>(69, 85)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51/67</td>
<td>76</td>
<td>(64, 86)</td>
</tr>
<tr>
<td>Female</td>
<td>37/46</td>
<td>80</td>
<td>(66, 91)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to &lt; 35</td>
<td>30/36</td>
<td>83</td>
<td>(67, 94)</td>
</tr>
<tr>
<td>35 to &lt; 55</td>
<td>28/38</td>
<td>74</td>
<td>(57, 87)</td>
</tr>
<tr>
<td>55 to &lt; 65</td>
<td>18/24</td>
<td>75</td>
<td>(53, 90)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>12/15</td>
<td>80</td>
<td>(52, 96)</td>
</tr>
<tr>
<td>MRD Level at Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^{-1} to &lt; 1</td>
<td>6/9</td>
<td>67</td>
<td>(30, 93)</td>
</tr>
<tr>
<td>10^{-2} to &lt; 10^{-1}</td>
<td>36/44</td>
<td>82</td>
<td>(67, 92)</td>
</tr>
<tr>
<td>10^{-3} to &lt; 10^{-2}</td>
<td>40/51</td>
<td>78</td>
<td>(65, 89)</td>
</tr>
<tr>
<td>Other</td>
<td>6/9</td>
<td>67</td>
<td>(30, 93)</td>
</tr>
<tr>
<td>Remission Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR 2/3</td>
<td>28/40</td>
<td>70</td>
<td>(53–83)</td>
</tr>
<tr>
<td>CR 1</td>
<td>60/73</td>
<td>82</td>
<td>(72–90)</td>
</tr>
</tbody>
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Complete MRD response = defined by the absence of MRD with an assay with a minimum sensitivity of 10^{-4} after 1 cycle of blinatumomab.
Primary analysis of RFS was censored at HSCT or post-blinatumomab chemotherapy

Pre-specified threshold of 28% based on historical data: RFS after 1 year was 17.5% (14 out of 80 patients)

<table>
<thead>
<tr>
<th>Primary</th>
<th>RFS at 18 months*</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Censored at HSCT or post-blinatumomab chemotherapy</td>
<td>54%</td>
<td>33, 70</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Uncensored at HSCT or post-blinatumomab chemotherapy</td>
<td>53%</td>
</tr>
</tbody>
</table>

*18-month time point utilized to ensure RFS endpoint was examined at a minimum of 1-year following the duration of blinatumomab treatment.
Study 203: Key Secondary Endpoint – RFS

♦ 74 of 110 (67%) patients were transplanted in continuous remission

Philadelphia Chromosome-Negative Patients in Hematologic CR.
Study 203: Secondary Endpoint – OS (uncensored)

Survival Probability

Study Month

Number at Risk:

0.0 0.2 0.4 0.6 0.8 1.0

OS (Uncensored at HSCT and Post-blin Chemo)

Median, months (95% CI)

N=116

OS (Uncensored at HSCT and Post-blin Chemo) 36.5 (19.2, NE)

LTFU (minimum 3-year) OS (uncensored) 33.7 (19.7, NE)
Study 203: Landmark Analysis − Impact of MRD Response on RFS

Landmark analysis at day 45 performed to correct immortal bias, excluding patients with RFS < 45 days.
Day 45 pre-specified because all patients had MRD measurement by day 45 according to study protocol.
Not censored for HSCT.

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Median, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD Responder N=85</td>
<td>23.6 (17.4, NE)</td>
</tr>
<tr>
<td>MRD Non-responder N=15</td>
<td>5.7 (1.6, 13.6)</td>
</tr>
</tbody>
</table>

HR (95%CI): 0.38 (0.20, 0.72)
Study 203: Landmark Analysis – Impact of MRD Response on OS

Landmark analysis at day 45 performed to correct immortal bias, excluding patients with OS < 45 days. Day 45 pre-specified because all patients had MRD measurement by day 45 according to study protocol.
MRD+ ALL Development Program

- **Study 202**
  Exploratory Safety/Efficacy
  Phase 2
  N=21

- **Study 203 (BLAST)**
  Safety/Efficacy
  Phase 2
  N=116

- **Study 148**
  Historical Comparator
  N=287

- **Study 203 vs Study 148**
  Propensity Score Analysis
Study 148: Historical Comparator Study Design

**High-Level Study Details**

- **Purpose:**
  - Understand historical outcomes of ALL patients with quantifiable MRD
  - Provide comparator for study 203

- **Primary Endpoints**
  - RFS
  - OS

- **Patients in CR1 or CR2 with MRD+ ALL**
- **Initial diagnosis between 2000-2014**
- **8 countries in Europe**

**Key Inclusion Criteria**

- **Presence of MRD:**
  - $\geq 10^{-4}$ by PCR
  - $\geq 10^{-3}$ by flow cytometry

- **Ph- B-precursor ALL**
- **3+ intensive chemotherapy blocks**
- **Age $\geq 15$ years at ALL diagnosis**
- **No extramedullary disease**
- **No blinatumomab within 18 months of MRD detection**
- **No alloHSCT prior to MRD detection**
**Study 148 and 203 Aligned to Allow Propensity Score Analysis**

- Aligned inclusion criteria to those common in Studies 148 and 203

<table>
<thead>
<tr>
<th>Study 203 (BLAST)</th>
<th>Study 148 (Historical Comparator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=73</td>
<td>N=182</td>
</tr>
</tbody>
</table>

- Ph- B-precursor ALL in CR after 3+ intensive chemotherapy blocks
- ≥ 18 years of age at MRD baseline date
- In first remission (CR1)
- MRD at ≥ 10⁻³
Propensity Score Analysis (PSA) Overview

- PSA attempts to mimic the effect of randomization by creating a balance between treated and untreated patients
  - The propensity score captures how differences in baseline covariates contribute to a patient’s probability of being in one group or the other
  - Individual subjects are weighted by the propensity to be treated by blinatumomab to allow balancing of the two populations
- Balance between the weighted\(^a\) populations is assessed based on their baseline covariates

\(a\). IPTW (Inverse Probability to be Treated Weighted) analyses applies these weights within a regression setting.
Baseline Covariate Balance Before and After Adjustment

Baseline Covariates

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Unadjusted</th>
<th>Adjusted Propensity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC at diagnosis (continuous, log10)</td>
<td>0.26</td>
<td>0.1</td>
</tr>
<tr>
<td>WBC at diagnosis (&gt; 30,000/mm³)</td>
<td>0.17</td>
<td>0.04</td>
</tr>
<tr>
<td>Time from diagnosis to baseline (months)</td>
<td>0.56</td>
<td>0.09</td>
</tr>
<tr>
<td>t(4;11) MLL-AF4 mutation (Yes)</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>Prior chemotherapy (GMALL)</td>
<td>0.32</td>
<td>0.1</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>0.28</td>
<td>0.07</td>
</tr>
<tr>
<td>Country (Not Germany)</td>
<td>0.16</td>
<td>0.08</td>
</tr>
<tr>
<td>MRD at Baseline (recoded)</td>
<td>0.55</td>
<td>0.085</td>
</tr>
<tr>
<td>Age at primary diagnosis (years)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Propensity Score Analysis: Relapse-Free Survival (Primary Analysis Set)

**Median RFS, months (95% CI)**

- **Blinatumomab**
  - N=79
  - 35.2 (24.2, NE)

- **Control**
  - N=175
  - 8.3 (6.2, 11.8)

- **Blinatumomab LTFU**
  - N=79
  - 28.8 (22.1, NE)

**HR (95% CI):** 0.50 (0.32, 0.78)

**Number at Risk:**

<table>
<thead>
<tr>
<th></th>
<th>79</th>
<th>57</th>
<th>34</th>
<th>18</th>
<th>2</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>174</td>
<td>76</td>
<td>58</td>
<td>39</td>
<td>29</td>
<td>20</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>57</td>
<td>50</td>
<td>39</td>
<td>27</td>
<td>19</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>
Propensity Score Analysis: Overall Survival (Primary Analysis Set)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinatumomab</td>
<td>36.5 (24.2, NE)</td>
</tr>
<tr>
<td>N=79</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>27.2 (16.4, 38.6)</td>
</tr>
<tr>
<td>N=175</td>
<td></td>
</tr>
<tr>
<td>Blinatumomab LTFU</td>
<td>44.6 (28.8; NE)</td>
</tr>
<tr>
<td>N=79</td>
<td></td>
</tr>
</tbody>
</table>

HR (95% CI): 0.76 (0.47, 1.24)

Number at Risk:

<table>
<thead>
<tr>
<th>Months</th>
<th>79</th>
<th>65</th>
<th>35</th>
<th>22</th>
<th>2</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>79</td>
<td>175</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>115</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>35</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>22</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Propensity Score Analysis: Blinatumomab Demonstrated Longer RFS Regardless of HSCT

- Isolating the contribution of HSCT to survival is difficult in ALL trials
- Transplantation is a post-baseline time-dependent variable rather than a baseline confounder
- RFS was significantly longer for blinatumomab vs control, with and without adjustment for transplant

<table>
<thead>
<tr>
<th>Primary Analysis Set</th>
<th>Blinatumomab vs Control</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted for HSCT</td>
<td></td>
<td>0.47 (0.30, 0.73)</td>
</tr>
<tr>
<td>Adjusted for HSCT</td>
<td></td>
<td>0.50 (0.33, 0.78)</td>
</tr>
</tbody>
</table>
## Propensity Score Analysis: A High Percentage of Blinatumomab-Treated Patients Went to HSCT

<table>
<thead>
<tr>
<th></th>
<th>Study 203 N=73</th>
<th>Historical (Study 148) N=182</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with HSCT, %</td>
<td>78</td>
<td>44</td>
</tr>
<tr>
<td>Patients ≥ 35 Years of Age, %</td>
<td>68</td>
<td>38</td>
</tr>
</tbody>
</table>
Summary of Blinatumomab Efficacy in MRD+ ALL

- MRD-positivity reflects measurable disease burden
- Blinatumomab is able to induce MRD-negativity
  - 78% of patients achieved complete MRD response after first cycle
- Complete MRD responders had improved RFS and OS compared to non-responders
- Propensity score analysis demonstrated significantly prolonged RFS and a positive OS trend compared to historical controls
- Almost twice as many patients with MRD+ ALL treated with blinatumomab went on to HSCT compared to historical controls
  - 78% vs. 44%, respectively
Safety
Introduction – Safety in MRD+ ALL

- Consistent with the established safety profile in R/R B-precursor ALL
- Key safety risks – managed by the label & communication REMS
  - Neurologic events
  - Cytokine release syndrome
  - Preparation and administration errors
- No new safety risks identified
Blinatumomab Clinical Trials in ALL
Safety Analysis Set

Total
N=843

MRD+ ALL
n=137

- Study 203
  n=116
- Study 202
  n=21

R/R ALL
n=706

- Adult Ph-
  n=528
  - Study 311
    n=267
  - Study 211
    n=225
- Pediatric
  n=133
  - Study 205
    n=93
  - Study 320
    n=40
- Adult Ph+
  n=45
  - Study 216
    n=45
Summary of Blinatumomab Exposure

<table>
<thead>
<tr>
<th></th>
<th>MRD+ ALL (N=137)</th>
<th>R/R ALL (N=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment exposure – days, median</td>
<td>55.5</td>
<td>39.9</td>
</tr>
<tr>
<td>Number of started cycles, median</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

A single cycle of blinatumomab treatment consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval.
## Summary of Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Subject Incidence, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MRD+ ALL N=137</td>
<td>R/R ALL N=706</td>
<td></td>
</tr>
<tr>
<td>All adverse events</td>
<td>100.0</td>
<td>99.2</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>60.6</td>
<td>61.5</td>
<td></td>
</tr>
<tr>
<td>Grade ≥ 3 adverse events</td>
<td>64.2</td>
<td>83.6</td>
<td></td>
</tr>
<tr>
<td>Fatal adverse events*</td>
<td>1.5</td>
<td>15.7</td>
<td></td>
</tr>
<tr>
<td>Adverse events leading to permanent discontinuation</td>
<td>16.8</td>
<td>14.0</td>
<td></td>
</tr>
</tbody>
</table>

*Within 30 days of blinatumomab treatment.*
Common Adverse Events (≥ 25% in MRD+ ALL)

- **Any Grade Events**:
  - Pyrexia: 90.5%
  - Headache: 64.6%
  - Tremor: 39.4%
  - Chills: 31.6%
  - Fatigue: 29.2%

- **Grade ≥ 3 Events**:
  - Pyrexia: 6.6%
  - Headache: 9.9%
  - Tremor: 12.5%
  - Chills: 10.1%
  - Fatigue: 14.6%

**MRD+ ALL (N=137)**

**R/R ALL (N=706)**
Key Adverse Reactions

MRD+ ALL (N=137)  
R/R ALL (N=706)

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade Events</th>
<th>CTCAE Grade ≥ 3 Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic Events</td>
<td>71.5%</td>
<td>16.1%</td>
</tr>
<tr>
<td>Cytokine Release Syndrome</td>
<td>63.7%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Neurologic Events</td>
<td>2.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Cytokine Release Syndrome</td>
<td>14.6%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>
# Neurologic Events (MRD+ ALL)

<table>
<thead>
<tr>
<th>MRD+ ALL</th>
<th>N=137</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade Event</td>
<td>Grade ≥ 3 Event</td>
</tr>
<tr>
<td>Incidence</td>
<td>71.5%</td>
</tr>
<tr>
<td>Time to onset, median</td>
<td>2.0 days</td>
</tr>
<tr>
<td>Resolution</td>
<td>95.9%</td>
</tr>
<tr>
<td>Duration, median</td>
<td>10.0 days</td>
</tr>
</tbody>
</table>

- Most common events (≥ 10%): headache, tremor, insomnia, aphasia, and dizziness
- No fatal neurologic events
<table>
<thead>
<tr>
<th></th>
<th>MRD+ ALL N=137</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence, n (%)</td>
<td>4 (2.9%)</td>
</tr>
<tr>
<td>CTCAE grade ≥ 3 events, n (%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Fatal events</td>
<td>0%</td>
</tr>
<tr>
<td>Time to onset, median</td>
<td>2.0 days</td>
</tr>
<tr>
<td>Resolution</td>
<td>100%</td>
</tr>
<tr>
<td>Duration</td>
<td>&lt; 1 day to 2 days</td>
</tr>
</tbody>
</table>
Summary of Safety in MRD+ ALL

- Majority of adverse events were managed with supportive care, with or without treatment interruption
- Consistent with the established safety profile in the current indication of R/R ALL
- No new safety risks
- Mitigated by product labeling and existing REMS
# Presentation Overview

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Kathy Kross, MSc</td>
</tr>
<tr>
<td></td>
<td><em>Executive Director – Global Regulatory Affairs</em></td>
</tr>
<tr>
<td>Overview of MRD+ ALL &amp; Unmet Medical Need</td>
<td>Jerald Radich, MD</td>
</tr>
<tr>
<td></td>
<td><em>Fred Hutchinson Cancer Center</em></td>
</tr>
<tr>
<td>Clinical Efficacy &amp; Safety</td>
<td>Janet Franklin, MD, MPH</td>
</tr>
<tr>
<td></td>
<td><em>Executive Medical Director – Global Development Lead for BLINCYTO</em></td>
</tr>
<tr>
<td>Benefit-Risk</td>
<td>Gregory Friberg, MD</td>
</tr>
<tr>
<td></td>
<td><em>Vice President – Oncology Global Development</em></td>
</tr>
<tr>
<td>Clinician’s Perspective</td>
<td>Aaron Logan, MD, PhD</td>
</tr>
<tr>
<td></td>
<td><em>Division of Hematology/Oncology, UCSF</em></td>
</tr>
</tbody>
</table>
Benefit-Risk

Gregory Friberg, MD
VP Global Development, Oncology
Amgen Inc
Hematologic Complete Remission is No Longer the Best Measure of a Full Remission

- **MRD is widely used in clinical practice**
  - Marker of leukemic persistence
  - Indicator of incomplete response

- **MRD+ predicts disease recurrence and death**
  - For newly diagnosed population
  - For patients receiving transplant

- **MRD-negativity is correlated with improved survival**
  - In context of therapies studied in Berry meta-analysis
Blinatumomab is an Active Anti-Leukemic Therapy

- Approved in 2014 for relapsed or refractory ALL
  - Demonstrated to reduce leukemic burden
  - Significantly improved overall survival
- Study 203 patients were MRD+ after at least 3 intensive blocks of chemotherapy
  - Nearly 4 out of 5 patients achieved a complete MRD response
  - More than half achieved 18-month RFS
- Survival favorable compared to historical MRD+ patients
  - RFS benefit robust in sensitivity analyses
Complete MRD Responders had Nearly a Three Log Median Reduction in Leukemic Burden

Complete MRD Responder  
N=82

Non-responder  
N=18

Fold Reduction from Baseline

$10^{-1}$  
$10$  
$10^2$  
$10^3$  
$10^4$

Median Reduction

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fold Reduction</td>
<td>550-fold</td>
<td>750-fold</td>
<td>20-fold</td>
</tr>
</tbody>
</table>

Note: 3 subjects without MRD response data were removed from the analysis. Using conservative estimates (only measure to lower level of detection in complete responders).
Blinatumomab Safety Profile

- Established safety profile
  - Includes neurologic events, cytokine release syndrome, and medication errors

- Consistent with relapsed/refractory ALL population
  - No new risks identified in MRD+ ALL

- Mitigated by product labeling and existing REMS
  - Hematologists are experienced in managing adverse reactions
Therapeutic Options are Needed for ALL Patients with MRD after Chemotherapy

- MRD+ ALL remains a significant unmet need
  - Dire prognosis with limited options

- Blinatumomab dramatically lowers leukemic burden
  - High complete MRD response rate
  - Improved RFS versus historic control
  - Established and manageable safety profile

- Blinatumomab has a positive benefit-risk for MRD+ ALL
# Presentation Overview

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</thead>
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</tr>
<tr>
<td>Benefit-Risk</td>
<td>Gregory Friberg, MD&lt;br&gt;Vice President – Oncology Global Development</td>
</tr>
<tr>
<td>Clinician’s Perspective</td>
<td>Aaron Logan, MD, PhD&lt;br&gt;Division of Hematology/Oncology, UCSF</td>
</tr>
</tbody>
</table>
A Clinician’s Perspective

Aaron Logan, MD, PhD
UCSF
Supportive Slides

Oncologic Drugs Advisory Committee

Amgen Inc

March 7, 2018
Study 203: Treatment Exposure Duration

- Median number of cycles received: 2

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Started Cycle n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>116 (100)</td>
</tr>
<tr>
<td>2</td>
<td>75 (65)</td>
</tr>
<tr>
<td>3</td>
<td>33 (28)</td>
</tr>
<tr>
<td>4</td>
<td>20 (17)</td>
</tr>
</tbody>
</table>
2 patients achieved complete MRD response after 2 cycles of blinatumomab

<table>
<thead>
<tr>
<th>Prim EP FAS N=113</th>
<th>Additional Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1</td>
</tr>
<tr>
<td>Complete MRD Responder, n(%)</td>
<td>88 (77.9)</td>
</tr>
</tbody>
</table>
Study 203: RFS in non-HSCT Patients
Stratified by MRD Response (Landmark Analysis at Day 45)

<table>
<thead>
<tr>
<th>MRD Response</th>
<th>Median, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>17.4 (4.3, NE)</td>
</tr>
<tr>
<td>Non-responder</td>
<td>1.6 (0.1, 5.7)</td>
</tr>
</tbody>
</table>

At Cycle 1

Number at Risk:

| Study Month from Day 45 | 24  | 18  | 14  | 12  | 12  | 12  | 12  | 12  | 11  | 10  | 10  | 8   | 8   | 6   | 5   | 5   | 5   | 5   | 5   | 5   | 0   |

P = 0.002
Baseline Covariate Balance in Blinatumomab vs. Control Before and After Adjustment Among HSCT Subjects

<table>
<thead>
<tr>
<th>Baseline Covariates</th>
<th>Unadjusted</th>
<th>Adjusted Propensity Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC at diagnosis (continuous, log10)</td>
<td>0.2</td>
<td>0.04</td>
</tr>
<tr>
<td>WBC at diagnosis (&gt; 30,000/mm³)</td>
<td>0.24</td>
<td>0.1</td>
</tr>
<tr>
<td>Time from diagnosis to baseline (months)</td>
<td>0.58</td>
<td>0.31</td>
</tr>
<tr>
<td>t(4;11) MLL-AF4 mutation (Yes)</td>
<td>0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>Prior chemotherapy (GMALL)</td>
<td>0.5</td>
<td>0.16</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Country (Not Germany)</td>
<td>0.53</td>
<td>0.35</td>
</tr>
<tr>
<td>MRD at Baseline (recoded)</td>
<td>0.22</td>
<td>0.15</td>
</tr>
<tr>
<td>Age at primary diagnosis (years)</td>
<td>0.74</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Propensity Scores are estimated on the entire primary analysis set.
Study 203: Pre-Transplant MRD Status Affects RFS

Subjects who underwent HSCT in Complete Remission (Key Sec EP FAS and Prim EP FAS)

KM Plot of RFS From Time of HSCT Stratified by MRD Response

At Cycle 1

- **Responder**: Median, months 25.7 (95% CI: 17.3, NE)
- **Non-Responder**: Median, months 11.4 (95% CI: 1.1, 38.1)

\[ P = 0.049 \]

Number at Risk:

|  | 61 | 57 | 51 | 49 | 46 | 41 | 37 | 33 | 31 | 30 | 28 | 25 | 21 | 18 | 17 | 13 | 12 | 9  | 7  | 5  | 0  |
|   | 10 | 8  | 7  | 6  | 5  | 4  | 3  | 3  | 3  | 3  | 3  | 3  | 2  | 2  | 1  | 1  | 1  | 1  | 0  |   |   |   |
Study 203: Pre-Transplant MRD Status Affects OS

KM Plot of OS From Time of HSCT Stratified by MRD Response

<table>
<thead>
<tr>
<th>MRD Responder</th>
<th>MRD Non-responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>Median, months</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>NE</td>
<td>16.1</td>
</tr>
<tr>
<td>(25.7, NE)</td>
<td>(1.1, NE)</td>
</tr>
</tbody>
</table>

P = 0.069

Number at Risk:

<table>
<thead>
<tr>
<th>Study Month After Transplant</th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60</td>
<td>63 60 55 54 50 46 43 41 40 39 37 33 28 22 21 16 14 10 8 5 0</td>
</tr>
</tbody>
</table>
Study 203: HSCT Treatment-Related Mortality

- 100-day HSCT treatment-related mortality rate: 7.9% (6/76 patients)
  - Below published rate of 28%\textsuperscript{a}

- Incidence of death in continuous CR following HSCT during follow-up: 27.6% (21/76 patients)
  - Below published 2-year treatment-related mortality rates of 45%\textsuperscript{b} and 32% to 54%\textsuperscript{c}

\textsuperscript{a} Bishop et al, 2008
\textsuperscript{b} Wingard et al, 2011; Bishop et al, 2008.
\textsuperscript{c} Bassan and Hoelzer, 2011.
Study 203: HSCT Treatment-Related Mortality Summary

- Cause of death for the 21 patients who died without documented relapse following HSCT:
  - Infection (primarily sepsis and pneumonia) = 13
  - Digestive hemorrhage = 1
  - Subacute cerebral injury = 1
  - “Features to suggest VOD” = 1
  - Acute respiratory distress syndrome = 1
  - Probable heart attack = 1
  - Unknown = 3
ECOG1910 – Study Schema

- Newly diagnosed patients with Ph- B-ALL

Induction
2 cycles Chemo

Discontinue Study
if no CR or CRi

Intensification
1 cycle Chemo

Randomization

Stratified by:
1. Age < 55, ≥ 55
2. MRD+, MRD-
3. CD20 status
4. Rituximab use
5. HSCT intent

Blinatumomab
2 cycles

Blood/Marrow Transplant
If suitable donor and recommended

Consolidation
4 cycles chemo + 2 cycles blin

Consolidation
4 cycles chemo

Blood/Marrow Transplant
If suitable donor and recommended

Maintenance
Chemo for 2½ yrs from start of intensification
COGAALL1331 – Study Schema

1st Relapse B-ALL

Pretreatment Evaluation

Block 1

1st Relapse Evaluation

TF

Salvage Therapy (Blinatumomab-S)

Off-protocol therapy

HR/IR

Blinatumomab (1st cycle)

Block 2

Arm B

Arm A

Blinatumomab (2nd cycle)

Block 3

Arm D

Arm C

Blinatumomab (1st) > Continuation 1 > Blinatumomab (2nd) > Continuation 2 > Blinatumomab (3rd) > Maintenance

Blinatumomab (1st) > Continuation 1 > Continuation 2 > Maintenance

Block 3 > Continuation 1 > Continuation 2 > Maintenance

TRANSPLANT ELIGIBILITY

HSCT (if eligible)

OFF-PROTOCOL THERAPY

CONTINUATION 1

CONTINUATION 2

MAINTENANCE
Study 203: Complete MRD Response After Cycle 1 by Clinical Characteristics (Primary EP Efficacy Set)

<table>
<thead>
<tr>
<th>Primary EP Efficacy Set</th>
<th>n/N</th>
<th>%</th>
<th>(95% Exact CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>82/103</td>
<td>79.6</td>
<td>(70.5, 86.9)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47/60</td>
<td>78.3</td>
<td>(65.8, 87.9)</td>
</tr>
<tr>
<td>Female</td>
<td>35/43</td>
<td>81.4</td>
<td>(66.6, 91.6)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to &lt; 22</td>
<td>9/10</td>
<td>90.0</td>
<td>(55.5, 99.7)</td>
</tr>
<tr>
<td>22 to &lt; 35</td>
<td>20/22</td>
<td>90.9</td>
<td>(70.8, 98.9)</td>
</tr>
<tr>
<td>35 to &lt; 55</td>
<td>23/35</td>
<td>71.4</td>
<td>(53.7, 85.4)</td>
</tr>
<tr>
<td>55 to &lt; 65</td>
<td>17/23</td>
<td>73.9</td>
<td>(51.6, 89.8)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>11/13</td>
<td>84.6</td>
<td>(54.6, 98.1)</td>
</tr>
<tr>
<td>MRD Level at Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^{-1} to &lt; 1</td>
<td>6/9</td>
<td>66.7</td>
<td>(29.9, 92.5)</td>
</tr>
<tr>
<td>10^{-2} to &lt; 10^{-1}</td>
<td>36/43</td>
<td>83.7</td>
<td>(69.3, 93.2)</td>
</tr>
<tr>
<td>10^{-3} to &lt; 10^{-2}</td>
<td>40/51</td>
<td>78.4</td>
<td>(64.7, 88.7)</td>
</tr>
<tr>
<td>Remission Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR 2/3</td>
<td>27/37</td>
<td>73.0</td>
<td>(55.9, 86.2)</td>
</tr>
<tr>
<td>CR 1</td>
<td>55/66</td>
<td>83.3</td>
<td>(72.1, 91.4)</td>
</tr>
</tbody>
</table>
Study 203: OS in non-HSCT Patients
Stratified by MRD Response (Landmark Analysis at Day 45)

**At Cycle 1**

<table>
<thead>
<tr>
<th>Median, months</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD Responder</td>
<td>38.9</td>
</tr>
<tr>
<td></td>
<td>(11.9, NE)</td>
</tr>
<tr>
<td>MRD Non-responder</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>(2.4, 32.3)</td>
</tr>
</tbody>
</table>

**OS Probability**

\[ P = 0.020 \]

**Number at Risk:**

\[
\begin{array}{cccccccccccccccccccccc}
\end{array}
\]

\[
\begin{array}{cccccccccccccccccccccc}
   & 14 & 10 & 8 & 6 & 5 & 4 & 4 & 4 & 4 & 4 & 3 & 3 & 3 & 3 & 3 & 3 & 3 & 3 & 3 & 3 & 0 \\
\end{array}
\]