U.S. FOOD & DRUG ADMINISTRATION

# BLA 125557: BLINCYTO (BLINATUMOMAB)

## INTRODUCTORY COMMENTS

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# Approved Drugs for Treatment of ALL

- Over 20 drugs are approved by FDA for treatment of acute lymphoblastic leukemia (ALL).
- In most cases, the intended population has been patients with ALL in morphological relapse.
- The endpoints used to denote clinical benefit (or reasonably likely to predict clinical benefit) for treatments of ALL include overall survival or morphological complete remission of long duration.

Complete remission (CR) - Marrow blasts <5%, no extramedullary ALL, neutrophils > 1 Gi/L and platelets >100 Gi/L

CRi - Not a CR due to incomplete recovery of neutrophil and/or platelets counts

# BLINCYTO: PROPOSED INDICATION

*"Treatment of minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia"*

- The proposed intended population includes patients with ALL in morphological complete remission with only molecular evidence of ALL
- The proposed clinical benefit is molecular response.

# STUDY MT103-203 - DESIGN

- Design:  Single-arm trial of blinatumomab
- Key Eligibility: ALL in CR /CRi with MRD $\geq$ 0.1% after 3 blocks of intensive chemotherapy

# ISSUES

1. Study MT103-203 included patients with MRD ≥ 0.1%. Do the available data support the cut-off of MRD ≥ 0.1% as describing a subpopulation of patients with ALL in CR who have a need for pre-emptive therapy?

2. Do the results of MT103-203 demonstrate that for patients with ALL in CR who have MRD ≥ 0.1%, treatment with blinatumomab provides a potential benefit that outweighs the risks from the treatment?

# STUDY 20120148

- Retrospective analysis
- Pooled cohort of patients with ALL in CR/CRi with MRD ≥ 0.01% after intensive chemotherapy
- N=268 for patients in $Ph^{neg}$ BCP ALL in first CR/CRi
- Analysis endpoint - Relapse-free survival (RFS)
- FDA's results:

| Baseline MRD level | N | Median RFS (months) |
|---|---|---|
| ≥ 10% | 15 | 2.0 |
| 1% to < 10% | 70 | 9.7 |
| 0.1% to < 1% | 108 | 10.6 |
| 0.01% to < 0.1% | 75 | 31.3 |

Population with inferior prognosis

# STUDY MT103-203 - Efficacy Results

- Design:  Single-arm trial of blinatumomab
- Key Eligibility: ALL in CR /CRi with MRD $\geq$ 0.1% (historical median RFS - 10.6 months or less)

- Efficacy Endpoint: Absence of detectable MRD using an assay with sensitivity < 0.01% after 1 cycle of blinatumomab
- For Analysis: N=87 patients in CR with MRD $\geq$ 0.1%
- Results: Response in 69 patients (79%; 95% CI: 70%, 88%). Estimated median RFS was 22.3 months.
- Propensity Score Analysis
  - Applicant's conclusion - RFS results favor blinatumomab significantly
  - FDA's conclusion - Confounding issues limit interpretability of results

# STUDY MT103-203 - Safety

- Design:  Single-arm trial of blinatumomab
- Key Eligibility: ALL in CR /CRi with MRD $\geq$ 0.1% (historical median RFS - 10.6 mos or less)
- Efficacy Endpoint: Absence of detectable MRD using an assay with sensitivity < 0.01% after 1 cycle of blinatumomab
- Accrued: N=87 patients in CR with MRD $\geq$ 0.1%
- Results: Response in 69 patients (79%; 95% CI: 70%, 88%). Estimated median RFS was 22.3 months.

- Safety: Toxicity profile similar to that established in patients with relapsed or refractory BCP ALL (including CRS and neurotoxicity)

# ISSUES

1. Study MT103-203 included patients with MRD $\geq$ 0.1%. Do the available data support the cut-off of MRD $\geq$ 0.1% as describing a subpopulation of patients with ALL in CR who have a need for pre-emptive therapy?

2. Do the results of MT103-203 demonstrate that for patients with ALL in CR who have MRD $\geq$ 0.1%, treatment with blinatumomab provides a potential benefit that outweighs the risks from the treatment?


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# BLA 125557 S013

# Blincyto® (blinatumomab)

FDA Presentation

March 7, 2018

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# Proposed Indication:

**For the treatment of patients with minimal residual disease (MRD) positive B-cell precursor-acute lymphocytic leukemia (BCP-ALL)**

# Issues

- **Patient population**: Do the available data support the cut-off of MRD ≥ 0.1% as describing a subpopulation of patients in morphologic complete remission (CR) who have a need for pre-emptive therapy?

- **Response**: Is achieving undetectable MRD in this population sufficiently meaningful to outweigh the risks of treatment with blinatumomab?

# Outline

- MRD as a prognostic indicator of a high-risk population
- Efficacy – MT103-203
- Propensity score analysis
- Safety
- Summary

# What level of MRD identifies a population of patients with BCP-ALL in morphologic CR who might benefit from further therapy?

## Study 20120148

| | | |
|---|---|---|
| Non-interventional retrospective analysis | Patients ≥ 15 years old with Philadelphia-negative BCP-ALL in morphologic CR with MRD ≥0.01% after 3 blocks of intensive chemotherapy<br>• N=268 – CR1 cohort | Hematologic relapse-free survival (RFS) |

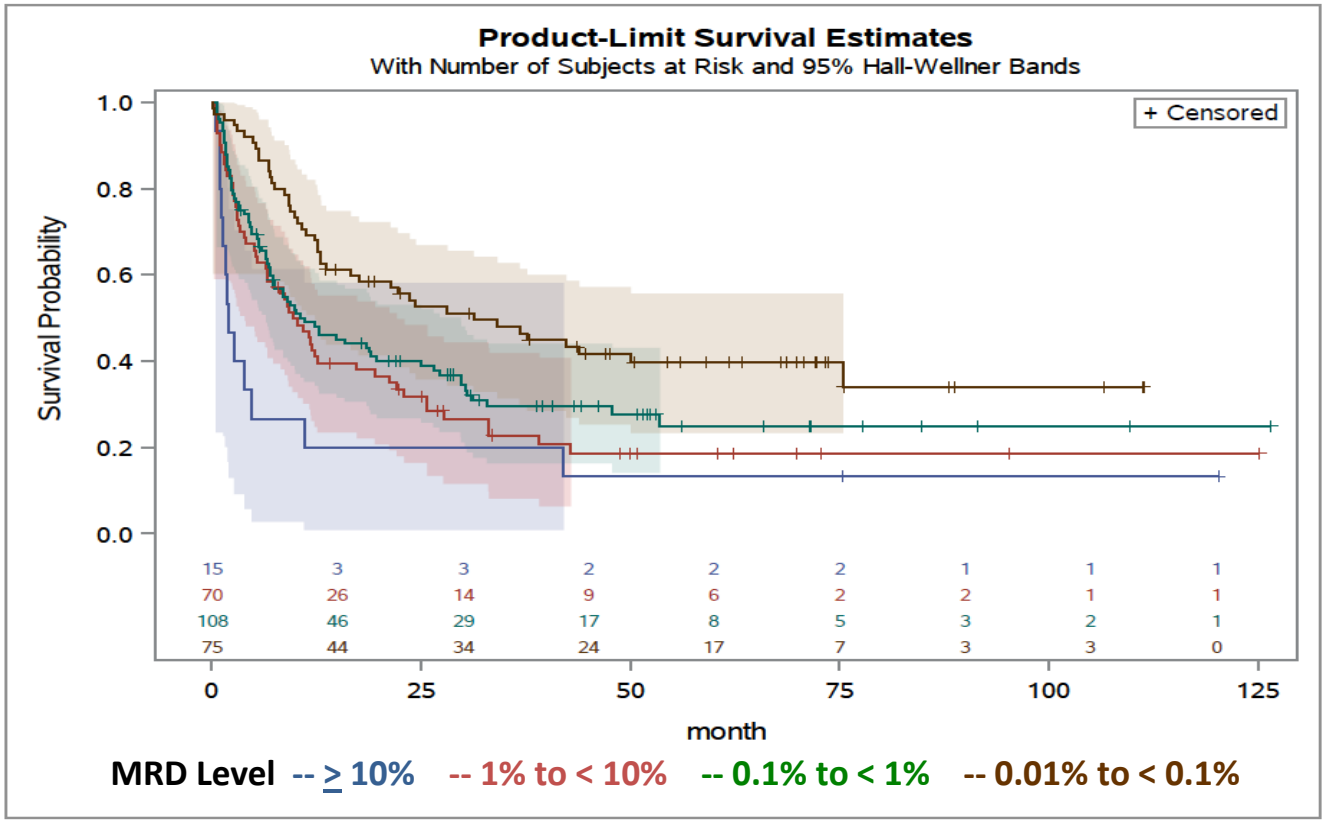
**FDA Analysis Endpoint**: Hematologic RFS by baseline MRD

# Study 20120148 – Patient Characteristics

| | FDA Analysis Set<br>N = 268<br>n (%) |
|---|---|
| Sex | |
| • Female | 111 (41) |
| • Male | 157 (57) |
| Age at diagnosis (years) | |
| • Median | 32.5 years |
| (Range) | (15-65 years) |
| CR number | |
| • CR1 | 268 (100%) |
| MRD status | |
| • Persistent | 215 (80) |
| • Relapse | 51 (19) |
| • Unknown | 2 (1) |
| MRD level at baseline | |
| • ≥ 10% | 15 (6) |
| • 1% - < 10% | 70 (26) |
| • 0.1% - < 1% | 108 (40) |
| • 0.01% - < 0.1% | 75 (28) |
| Allogeneic HSCT after baseline MRD | |
| • Yes | 122 (46) |
| • No | 146 (54) |

Abbreviations: CR1 – first morphologic complete remission; HSCT – hematopoietic stem cell transplantation; MRD – minimal residual disease

# Study 20120148 – Hematologic RFS by MRD Level at Baseline




| Baseline MRD level | N | Median Hematologic RFS (months) |
|---|---|---|
| ≥ 10% | 15 | 2.0 |
| 1% to < 10% | 70 | 9.7 |
| 0.1% to < 1% | 108 | 10.6 |
| 0.01% to < 0.1% | 75 | 31.3 |

Population with inferior prognosis

# Efficacy Analysis

## Study MT103-203

# Study MT103-203

- Single-arm, open-label, multicenter Phase 2
- Population - Adults ≥ 18 years old BCP-ALL who were MRD-positive* in morphologic CR or CR without platelet recovery after at least 3 intensive chemotherapy blocks

  *MRD ≥ 0.1% in an assay with sensitivity at least 0.01%
- Primary endpoint – Undetectable MRD** after one cycle of blinatumomab

  **In an MRD assay with sensitivity at least 0.01%
- Secondary endpoint – Hematologic RFS at 18 months

# MT103-203 – Patient Characteristics

| | Applicant's Primary Endpoint Full Analysis Set N = 113 n (%) | FDA Efficacy Analysis Set N = 87 n (%) |
|---|---|---|
| Age | | |
| • Median | 45 years | 42 years |
| • (Range) | (18-76 years) | (18-76 years) |
| Disease Status | | |
| • CR1 | 68 (60) | 61 (70) |
| • CR2 | 30 (27) | 25 (29) |
| • CR3 | 1 (1) | 1 (1) |
| • CRi | 14 (12) | 0 |
| MRD at baseline (central lab) | | |
| • > 10% | 9 (8) | 7 (8) |
| • 1% - < 10% | 44 (39) | 35 (40) |
| • 0.1% - < 1% | 51 (45) | 45 (52) |
| • < 0.1% | 3 (3) | 0 |
| • Below LLOQ | 5 (4) | 0 |
| • Not quantifiable | 1 (1) | 0 |
| Best MRD assay sensitivity | | |
| • 0.01% | 8 (7) | 7 (8) |
| • 0.005% | 20 (18) | 13 (15) |
| • 0.001% | 85 (75) | 67 (77) |
| HSCT after blinatumomab | | |
| • Yes | 87 (77) | 69 (79) |
| • No | 26 (23) | 18 (21) |

Abbreviations: CR – complete remission, CRi – complete remission with incomplete count recovery, LLOQ – lower limit of quantitation, MRD – minimal residual disease

# MT103-203 – Primary Endpoint Results
## MRD After 1 Cycle of Blinatumomab

| | Applicant's Primary Endpoint Full Analysis Set N = 113 n (%) | FDA Efficacy Analysis Set N=87 n (%) |
|---|---|---|
| **Response**: | | |
| Undetectable MRD in assay with sensitivity ≤0.01% (95% CI) | 88 (77.9%) (69.1%,85.1%) | 69 (79.3%) (70.4%, 87.6%) |

Abbreviation: CI – confidence interval

# MT103-203 – Secondary Endpoint Results
## 18-Month Hematologic RFS

| | Applicant Censored at HSCT or Post-Blinatumomab Salvage Therapy N=110 | FDA Not Censored at HSCT or Post-Blinatumomab Salvage Therapy N=87 |
|---|---|---|
| Number of events | 21 (19.1%) | 47 (54.0%) |
| Relapse | 18 (16.4%) | 29 (33.3%) |
| Secondary leukemia | 1 (0.9%) | - |
| Death | 2 (1.8%) | 18 (20.7%) |
| KM estimates (95% CI) | | |
| 18-month hematologic RFS | 53.6% (33.1%, 70.3%) | 58.5% (47.4%, 68.0%) |
| Median hematologic RFS (months) | NA (6.3, NA) | 22.3 (15.0, NA) |

# Issue

Is achieving undetectable MRD reasonably likely to predict long-term benefit for patients in morphologic CR?

FDA review of event-free survival (EFS) or RFS and overall survival (OS) by MRD status:

- Berry, et al (2017) published meta-analysis
- Propensity Score Analysis

# Berry, 2017 – Meta-analysis: Association of MRD with Clinical Outcome in Patients with ALL

| Characteristic | All Studies Included | | B-Cell ALL Studies | |
|---|---|---|---|---|
| Number of Studies | 39 | | 11 | |
| Year Published | 2000-2015 | | 2007-2015 | |
| Number of Patients | 13,637 | | 5,209 | |
| Population | | | | |
| Pediatric | 20 | 51% | 9 | 82% |
| Adult | 16 | 41% | 2 | 18% |
| Mixed | 3 | 8% | 0 | 0% |
| MRD Method | | | | |
| PCR | 23 | 59% | 7 | 64% |
| FC | 12 | 31% | 4 | 36% |
| Mixed | 4 | 10% | 0 | 0% |
| MRD Timing | | | | |
| Induction | 24 | 62% | 11 | 100% |
| Consolidation | 4 | 10% | 0 | 0% |
| Other | 11 | 28% | 0 | 0% |
| MRD Cut-Off | | | | |
| 0.01% | 17 | 44% | 7 | 64% |
| 0.04% | 1 | 3% | 0 | 0% |
| 0.05% | 2 | 5% | 0 | 0% |
| 0.1% | 15 | 38% | 4 | 36% |
| 0.5% | 1 | 3% | 0 | 0% |
| 1% | 2 | 5% | 0 | 0% |
| Missing | 1 | 3% | 0 | 0% |

Abbreviations: FC – flow cytometry; PCR – polymerase chain reaction
Source: Berry et al. (2017) eTable 1.

# Berry, 2017 – Meta-analysis: Association of MRD with Clinical Outcome in Patients with ALL

**Outcomes in the Subgroup of B-Cell ALL Studies**

| Outcome | Population | Number of Studies | HR[a] (95% BCI) |
|---|---|---|---|
| EFS | Pediatric | 9 | 0.21 (0.14, 0.30) |
| EFS | Adult | 2 | 0.28 (0.17, 0.46) |
| OS | Pediatric | 2 | 0.18 (0.09, 0.38) |
| OS | Adult | 0 | - |

Source: Berry et al. (2017) eTable 2.

[a] HR for MRD-negative vs. MRD-positive

- Studies had different binary cut-offs for MRD-negativity
  - The data do not identify a specific MRD cut-off for defining a group likely to have good long-term prognosis.
- Patients' hematologic disease status and number of prior relapses not specified
  - The data do not distinguish a specific patient population for whom MRD-negativity results in long-term benefit.

# Propensity Score Analysis

- **Objective** – To describe the blinatumomab treatment effect on relapse-free and overall survival in patients with MRD-positive ALL
- **Patient population**
  - Cohorts from Study 148 and Study 203
  - ≥ 18 years old
  - Ph-negative BCP-ALL
  - First CR/CRi
  - After at least 3 intensive chemotherapy blocks
  - MRD ≥ 0.1%
  - Time to relapse >14 days from the date of MRD detection (Study 148 cohort)
- **Endpoints** – Hematologic RFS and OS

# Propensity Score Analysis
## Characteristics of Study Population

| | 20120148<br>Direct Comparison Analysis Set<br>N=182 | MT103-203<br>CR1/CRi1 Subset<br>N=73 |
|---|---|---|
| Sex | | |
| • Female | 102 (56) | 41 (56) |
| • Male | 80 (44) | 32 (44) |
| Age at MRD | | |
| • Median | 32.5 years | 46 years |
| (Range) | (18-65 years) | (18-76 years) |
| WBC at diagnosis | | |
| • >30 Gi/L | 51 (28) | 13 (18) |
| • ≤30 Gi/L | 130 (71) | 51 (70) |
| • Unknown | 1 (1) | 9 (12) |
| MRD at baseline | | |
| • >10% | 13 (7) | 3 (4) |
| • 1% - < 10% | 56 (36) | 25 (34) |
| • 0.1% - < 1% | 113 (58) | 38 (52) |
| • 0.01% - < 0.1% | 0 | 6 (8) |
| • Unknown | 0 | 1 (1) |
| Time from diagnosis to baseline MRD | | |
| • Median | 8 months | 6 months |
| (Range) | (1-60 months) | (2-67 months) |
| HSCT after MRD baseline | | |
| • Yes | 80 (44) | 57 (78) |
| • No | 102 (56) | 16 (22) |

# Statistical Evaluation of Propensity Score Analyses

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# Propensity Score Analysis

- Objective of Propensity Score Analysis
- Propensity Score Analysis Results
- Limitations in the Data for Propensity Score Analysis
- Limitations of Interpretation

# Objective of Propensity Score Analysis

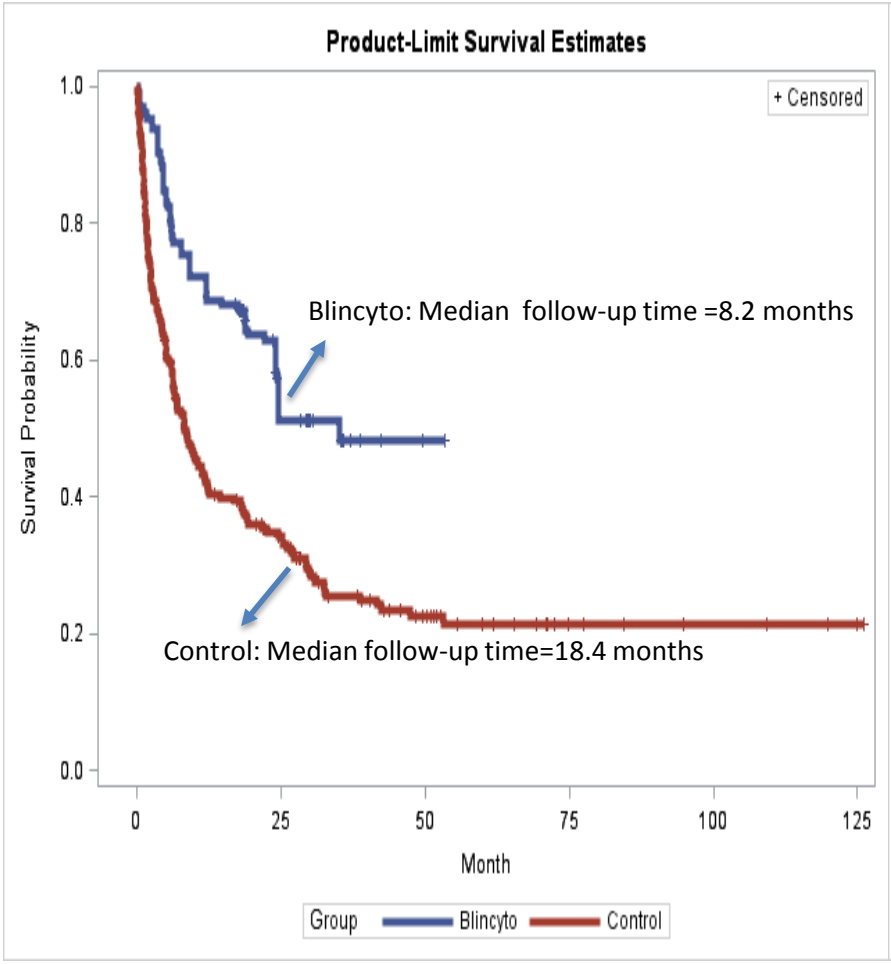
- Propensity Score Analysis
  - Mimics randomization
  - Useful for in comparing to historical controls
- Study Objective: Compare Study MT103-203 vs historical control Study 20120148
  - Efficacy Endpoints: RFS and OS
  - Propensity Score Adjustment
    - Selected baseline factors are balanced by using a weight function sIPTW*

**sITPW=stabilized Inverse Probability of Treatment Weight**

# KM Plots for RFS and OS Ignoring HSCT

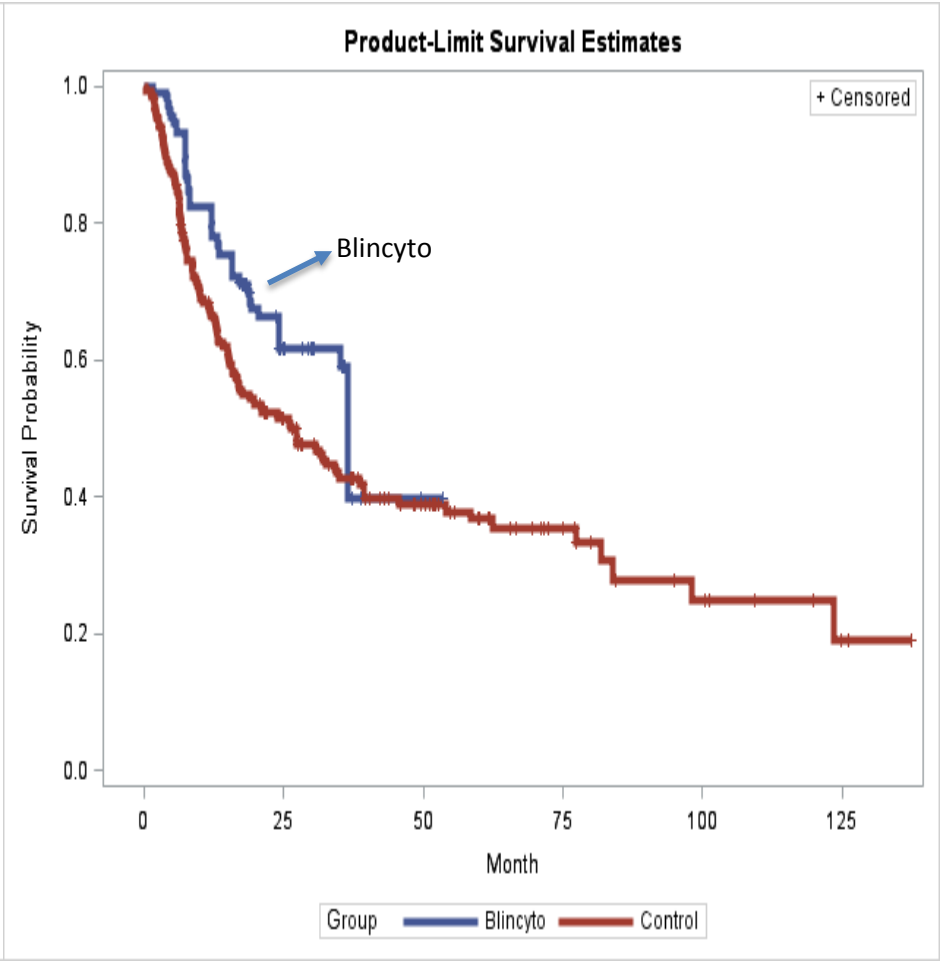
## Propensity Score Weighted for Each Patient (sIPTW)

### RFS




HR (95% CI)=0.50 (0.32-0.78)

### OS



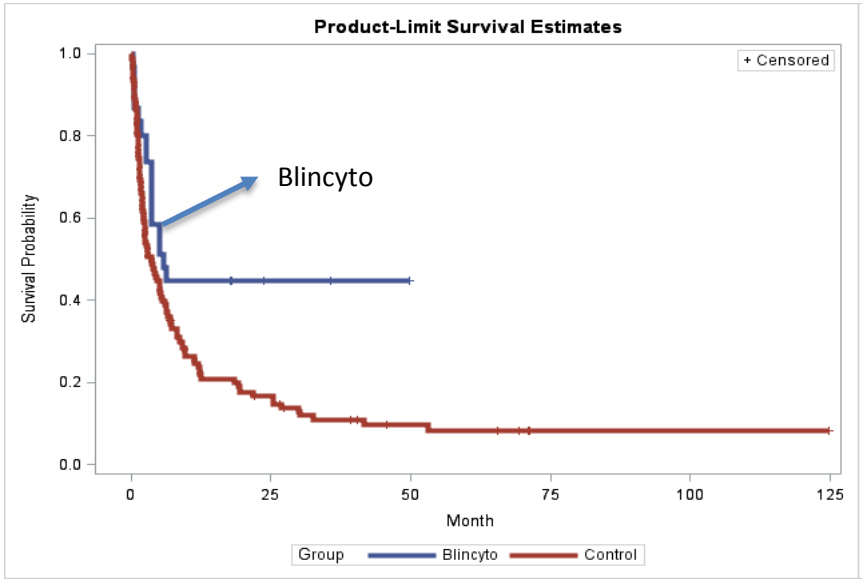

HR (95% CI) =0.76 (0.47-1.24)

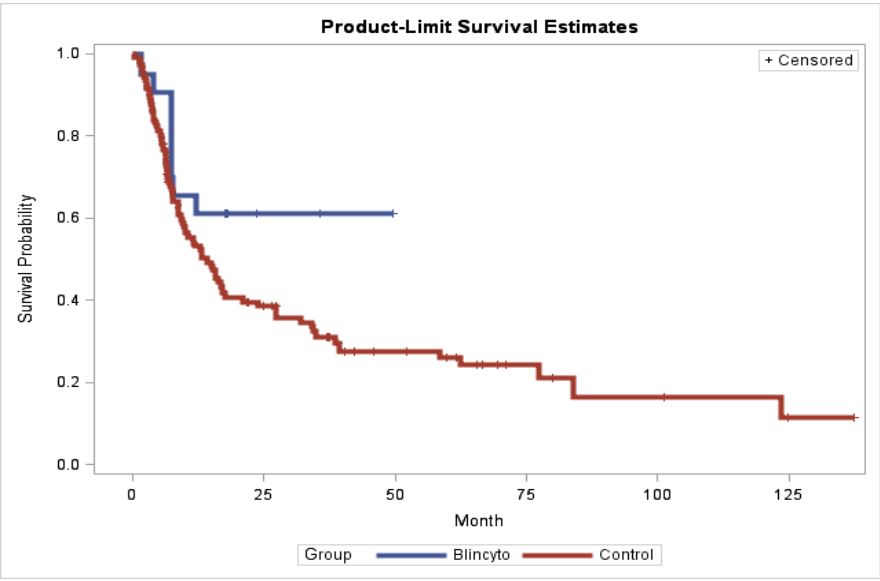
# Exploratory Subgroup Analyses by HSCT (Y/N)

RFS

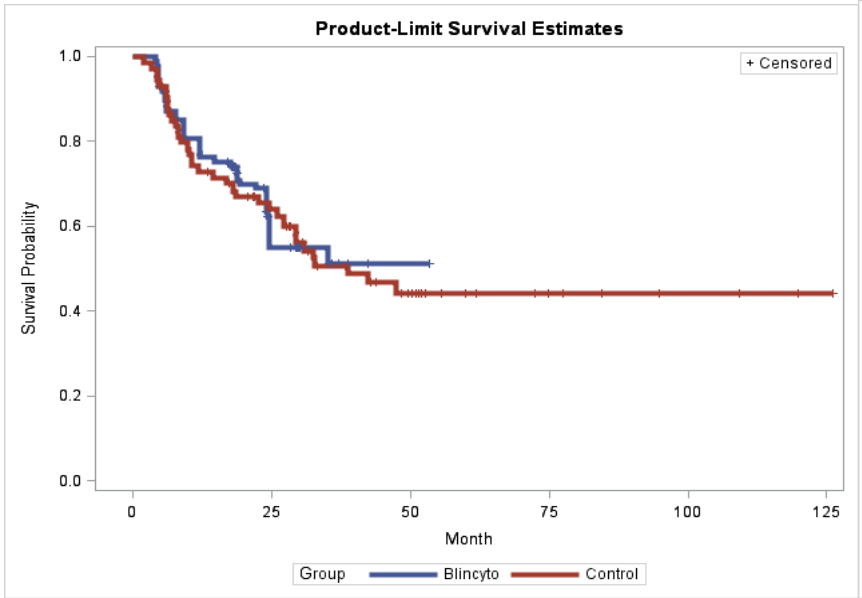
OS

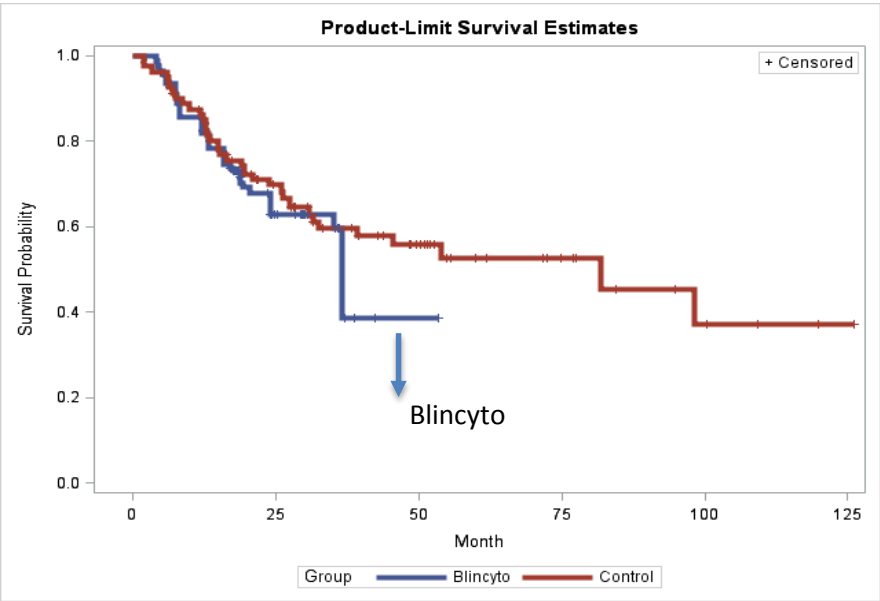
No Transplant




Transplant



# Data Analyses Limitations

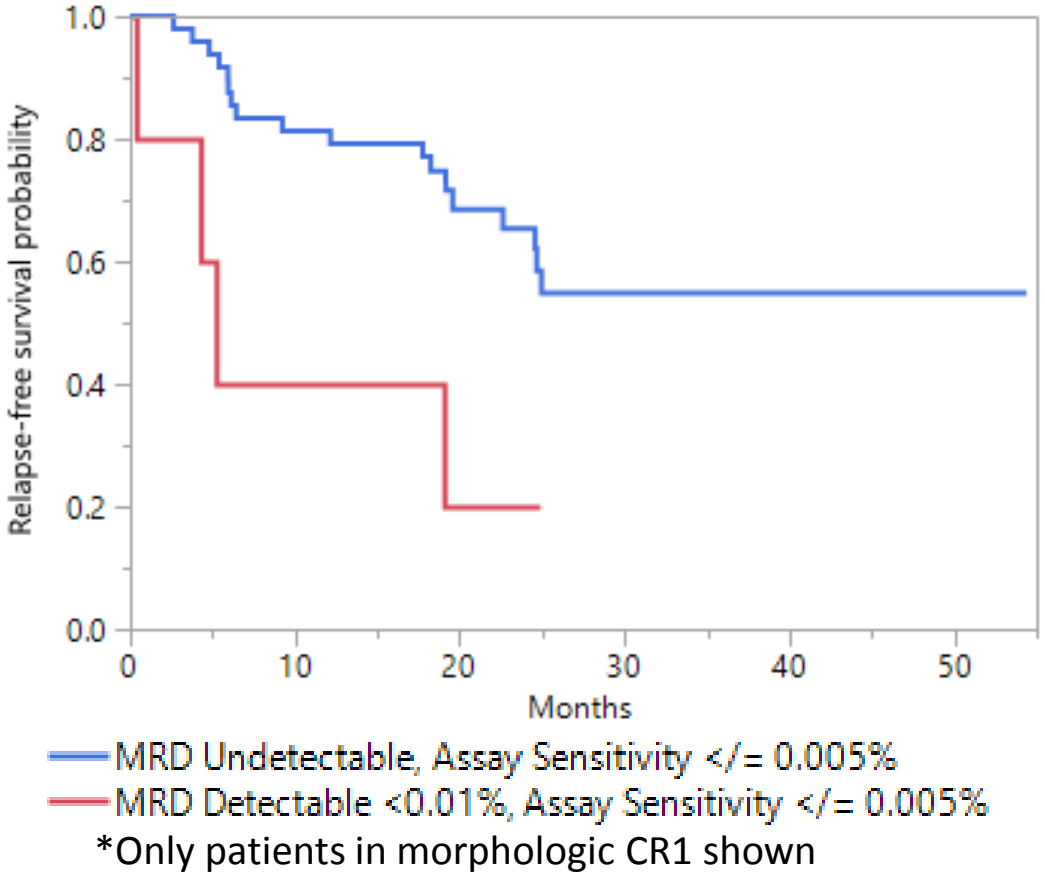
- 35% of Blincyto patient data excluded
  - Patients in CR2 are included in current indication
  - Patients in CR2 of Study 203 removed to match historical control
- Confounding due to subsequent treatment
  - Study 203: 78% of Blincyto patients received HSCT
    - Study starting: 2010
  - Study 148: 44% of control patients received HSCT
    - Study starting : 2000
- Different median follow-up times
  - 8.2 months in Study 203
  - 18.4 months in Study 148

# Propensity Score Analysis Summary

- In general, randomized trials are preferred. However, in select cases, propensity score analysis may be a valid method for making comparisons to historical data.

- In this study, the interpretation of the propensity score adjusted analysis is not clear due to the following limitations:
  - Inappropriate data matching (exclusion of data)
  - Confounding from HSCT
  - Different follow-up times

# MT103-203 – Hematologic RFS for Patients with MRD <0.01% after Cycle 1 by MRD Level




*Only patients in morphologic CR1 shown

- 74% of patients achieved conversion to MRD <0.005%
- Analysis limited by small number of patients with detectable MRD <0.01% (n=5)

# Efficacy Summary

- MT103-203:
  - Undetectable MRD, assay sensitivity ≤0.01%: 79% (95% CI: 70,88)
    - Undetectable MRD, assay sensitivity ≤0.005%: 74%
    - Achievement of undetectable MRD at any level has not been validated as a surrogate for clinical benefit (EFS or OS)
  - Median hematologic RFS: 22.3 months (95% CI: 15,NA)
    - Difficult to interpret RFS in a single-arm trial
- Propensity Score Analysis:
  - Applicant conclusion: Patients treated with blinatumomab had a greater hematologic RFS than those in the historical control
  - FDA conclusion: Interpretability is confounded by multiple factors

# Safety Analysis

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# Safety Population

- Patients with BCP-ALL in CR/CRi with detected MRD treated with blinatumomab on MT103-203 (N=116) or MT102-202 (N=21)
- MT102-202
  - Single-arm exploratory trial
  - Patients ≥ 18 years old with BCP-ALL in CR/CRi
  - MRD ≥ 0.01% after standard induction/ consolidation therapy for ALL
- For context: Safety data for patients with relapsed or refractory (R/R) ALL treated with blinatumomab

# Safety Population
## Fatal Treatment-Emergent Adverse Events

- 2 deaths (2%) within 30 days of blinatumomab

- Causes of death:
  - Atypical pneumonia
  - Subdural hemorrhage

# Safety Population
## Post-Transplant Mortality

Relapsed/refractory population

TOWER (blinatumomab vs standard of care)

- Day-100 mortality: 12% vs 0%
- Postmarketing study required

MRD-positive populations:

Study MT103-203

- 90 patients proceeded to HSCT
- Day-100 mortality: 10%

Study MT103-202

- Post-transplant follow-up not recorded

# Safety Population

## TEAE with Withdrawal or Interruption

| TEAE[a] | MRD+ ALL N=137 % | R/R ALL N=706 % |
|---|---|---|
| TEAE with withdrawal | 17 | 14 |
| • Encephalopathy | 4 | 2 |
| • Seizure | 4 | 1 |
| • Tremor | 4 | <1 |
| • Dysphasia | 2 | <1 |
| TEAE with interruption | 28 | 31 |
| • Pyrexia | 6 | 3 |
| • Tremor | 4 | 2 |
| • Encephalopathy | 3 | 3 |
| • Aphasia | 3 | 1 |
| • Hypertransaminasemia | 3 | 1 |
| • Arrhythmia | 3 | 1 |
| • Overdose | 3 | 1 |
| • Cytokine release/infusion reaction (CRS) | 2 | 3 |
| • Hypotension | 2 | <1 |
| • Chills | 2 | <1 |
| • Hypotension | 1 | <1 |
| • Neutropenia | 0 | 2 |
| • Seizure | 0 | 2 |
| • Sepsis | 0 | 2 |

[a]Includes grouped terms

# Safety Population
## Adverse Events of Special Interest

| Adverse Event of Special Interest[a] | Any Grade | | Grade ≥ 3 | |
|---|---|---|---|---|
| | MRD+ ALL N=137 % | R/R ALL N=706 % | MRD+ ALL N=137 % | R/R ALL N=706 % |
| Any AE | 100 | 100 | 66 | 86 |
| CRS | 7 | 15 | 3 | 3 |
| Nervous System Disorders[b] | 69 | 57 | 15 | 13 |
| • Headache | 40 | 32 | 4 | 2 |
| • Tremor | 31 | 13 | 4 | 1 |
| • Dysphasia | 12 | 4 | 1 | 1 |
| • Encephalopathy | 10 | 13 | 4 | 4 |
| • Seizure | 4 | 4 | 4 | 1 |
| Fever | 91 | 66 | 7 | 10 |
| Sepsis | 2 | 14 | 1 | 12 |

[a]Includes grouped terms
[b]System Organ Class

# Summary

- Study 20120148:
  - Patients with MRD ≥ 0.1% had median hematologic RFS ≤ 10.6 months
- Study MT103-203 Results:
  - Undetectable MRD, assay sensitivity ≤0.01%: 79% (95% CI: 70, 88)
    - Undetectable MRD, assay sensitivity ≤0.005%: 74%
  - Median hematologic RFS: 22.3 months (95% CI: 15, NA)
- Propensity score analysis:
  - Applicant conclusion: Hematologic RFS difference favors patients treated with blinatumomab
  - FDA conclusion: Limitations affect the interpretability and no conclusions can be drawn
- Safety in MRD-positive ALL population:
  - Fatal adverse events – 2%
  - Overall safety profile similar to R/R ALL
  - Risk for neurotoxicity and CRS remains

# Questions to ODAC

**Discussion question:**

- Study MT103-203 included patients with MRD ≥ 0.1%. Do the available data support the cut-off of MRD ≥ 0.1% as describing a subpopulation of patients with ALL in CR who have a need for pre-emptive therapy?

**Voting question:**

- Do the results of MT103-203 demonstrate that for patients with ALL in CR who have MRD ≥0.1%, treatment with blinatumomab provides a potential benefit that outweighs the risks from the treatment?


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# Back-Up Slides

# Evaluation of Treatment by HSCT Interaction with Propensity Score Adjustment

| Endpoint | HSCT | HR (95% CI) (MT103-203 vs control) |
|---|---|---|
| RFS | No HSCT | 0.27 (0.14, 0.52) |
| | HSCT | 0.90 (0.53, 1.53) |
| OS | No HSCT | 0.61 (0.40, 0.94) |
| | HSCT | 1.04 (0.61,1.76) |