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

Introduction	**Kathy Kross, MSc** *Executive Director – Global Regulatory Affairs*
Overview of MRD+ ALL & Unmet Medical Need	**Jerald Radich, MD** *Fred Hutchinson Cancer Center*
Clinical Efficacy & Safety	**Janet Franklin, MD, MPH** *Executive Medical Director – Global Development Lead for BLINCYTO*
Benefit-Risk	**Gregory Friberg, MD** *Vice President – Oncology Global Development*
Clinician's Perspective	**Aaron Logan, MD, PhD** *Division of Hematology/Oncology, UCSF*

Expert Consultant

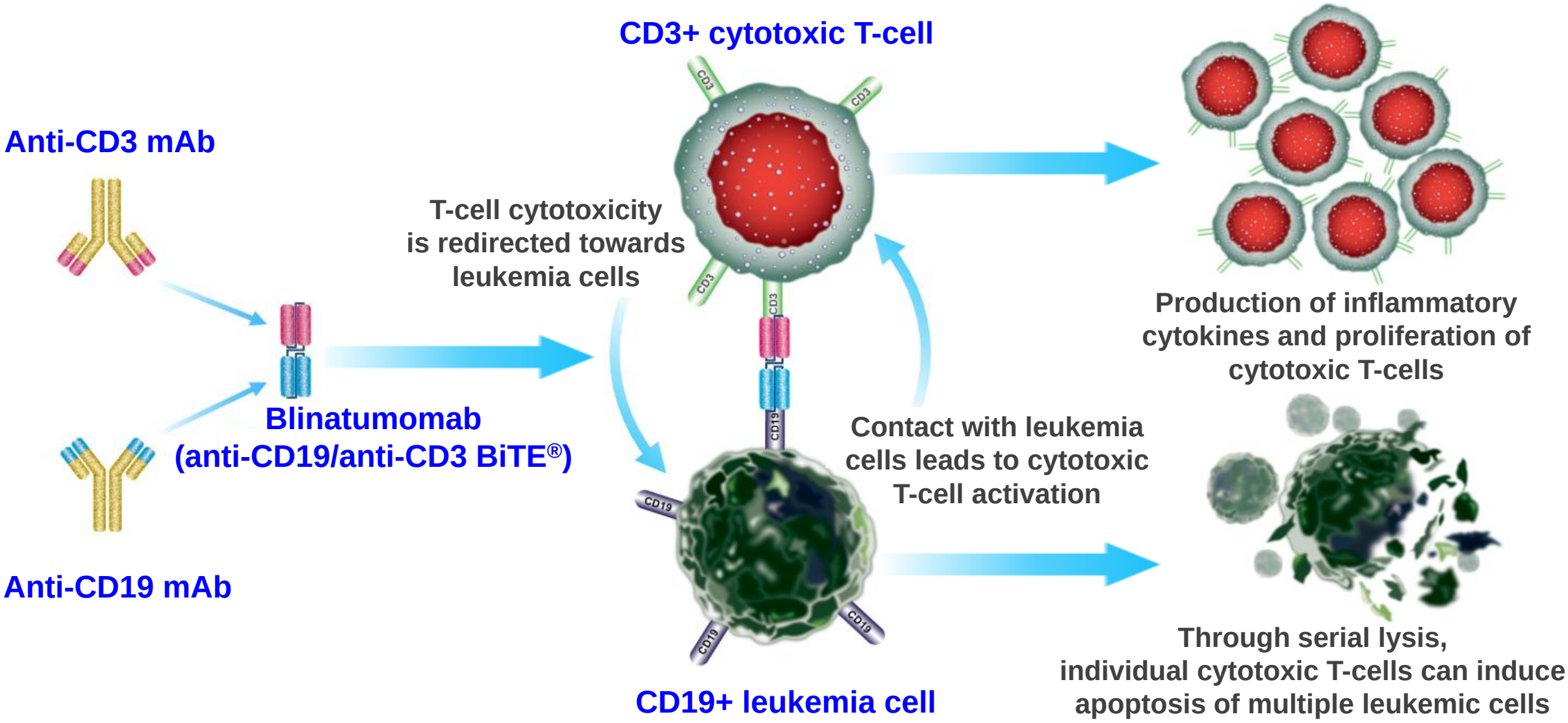
Richard Simon, DSc

Former Director, Biometric Research Program of the National Cancer Institute

BLINCYTO (blinatumomab) – Current Approved Indication

BLINCYTO is indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia in adults and children

Blinatumomab Mechanism of Action



Blinatumomab Regulatory History

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

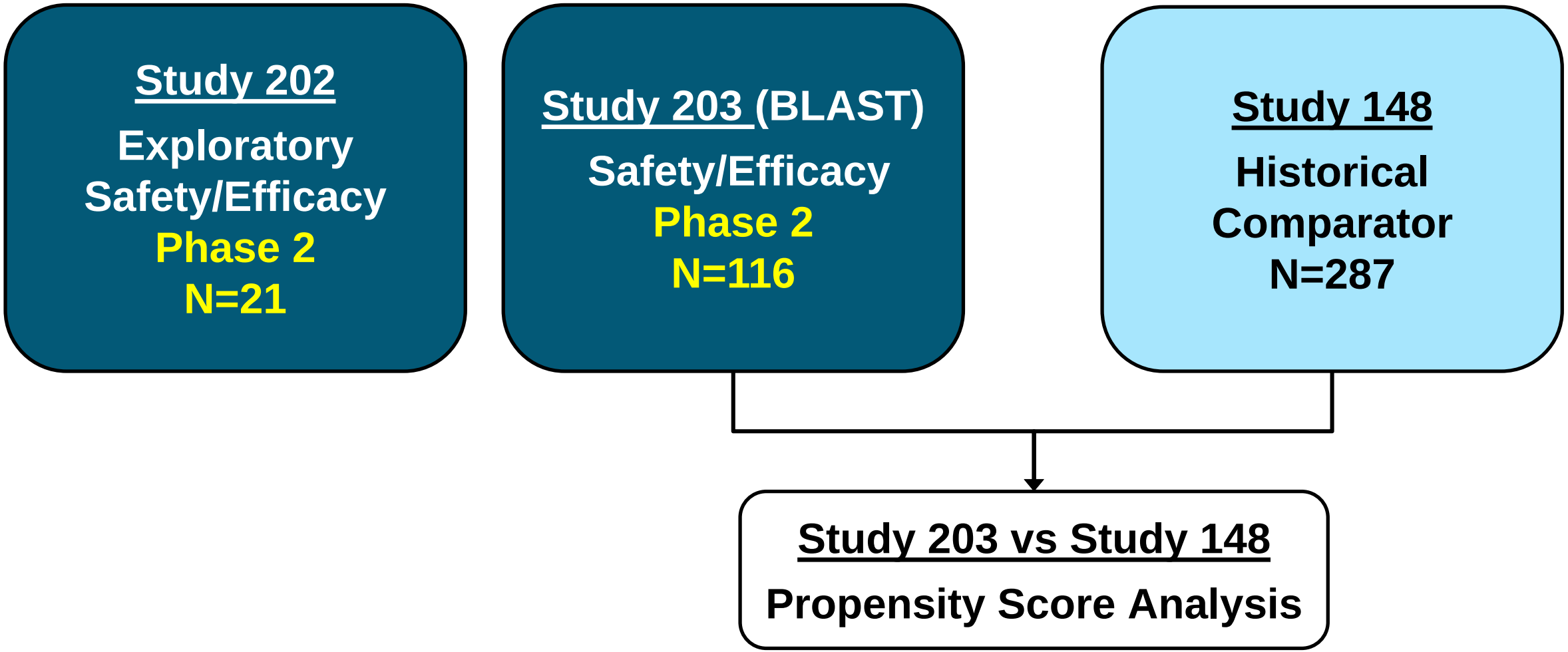
Proposed Indication

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



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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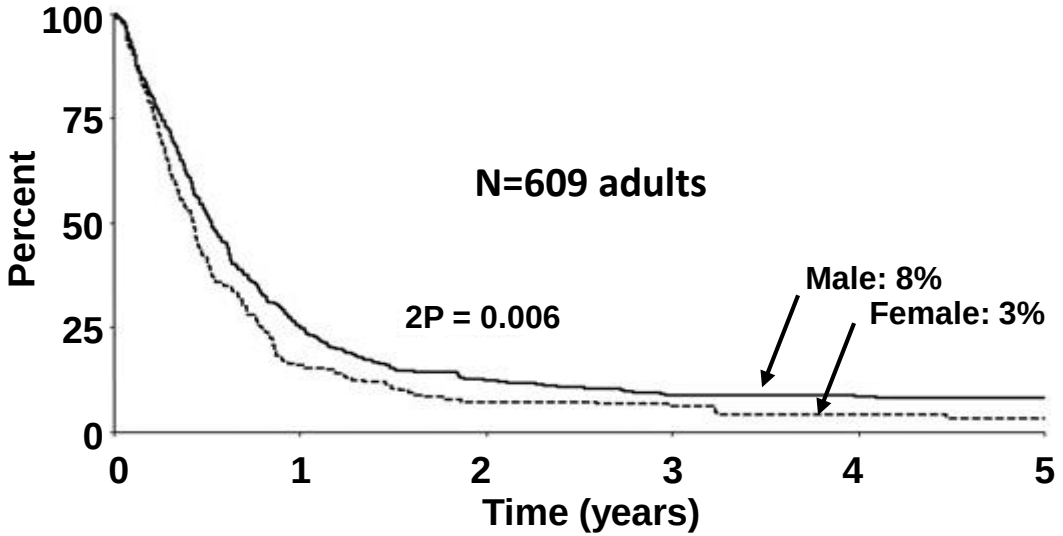
Overview of MRD+ ALL

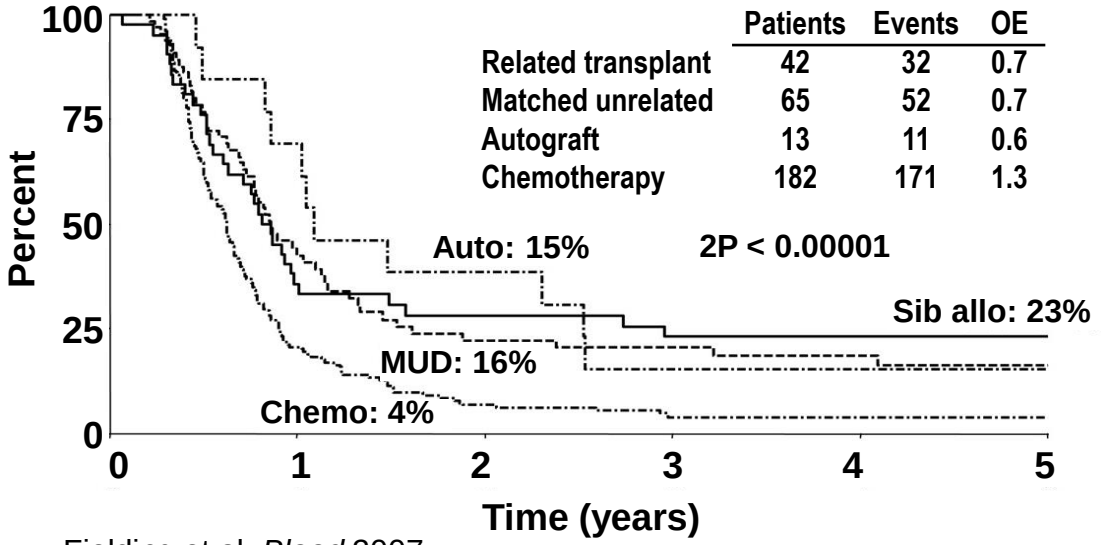
Jerald Radich, MD

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

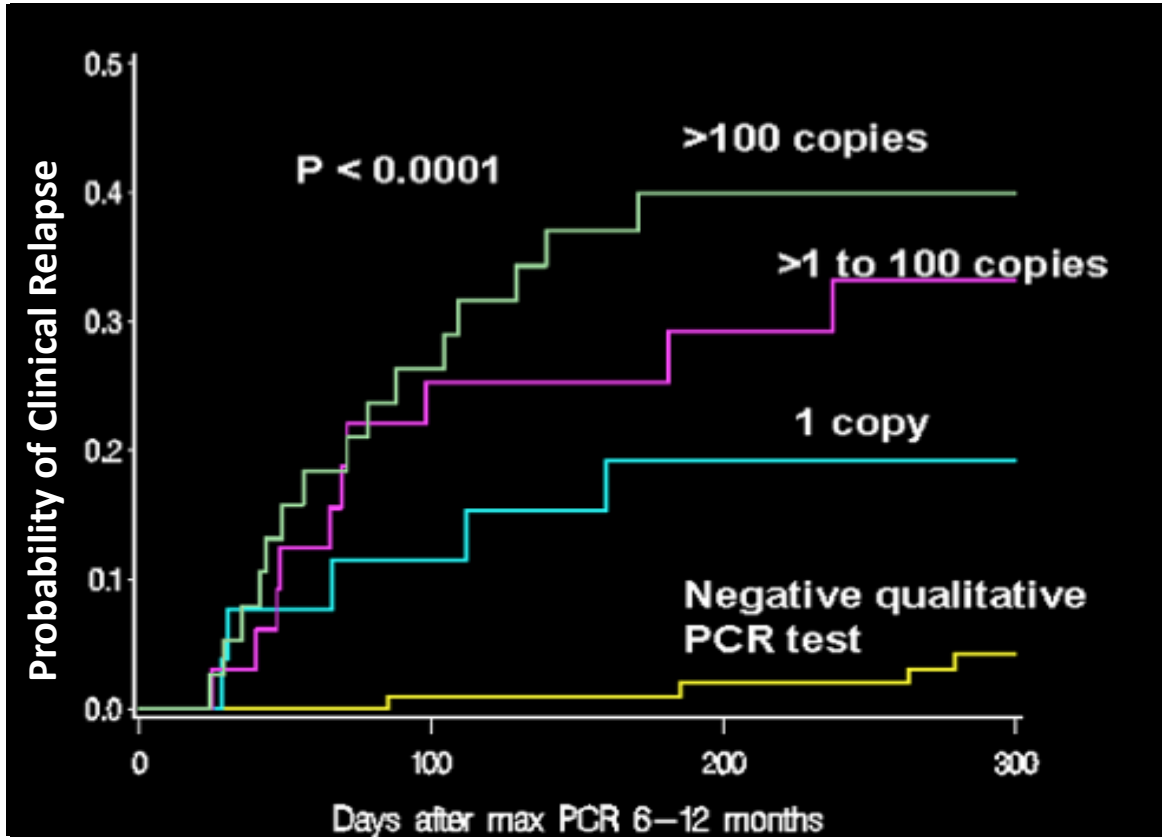




Fielding et al. *Blood* 2007.

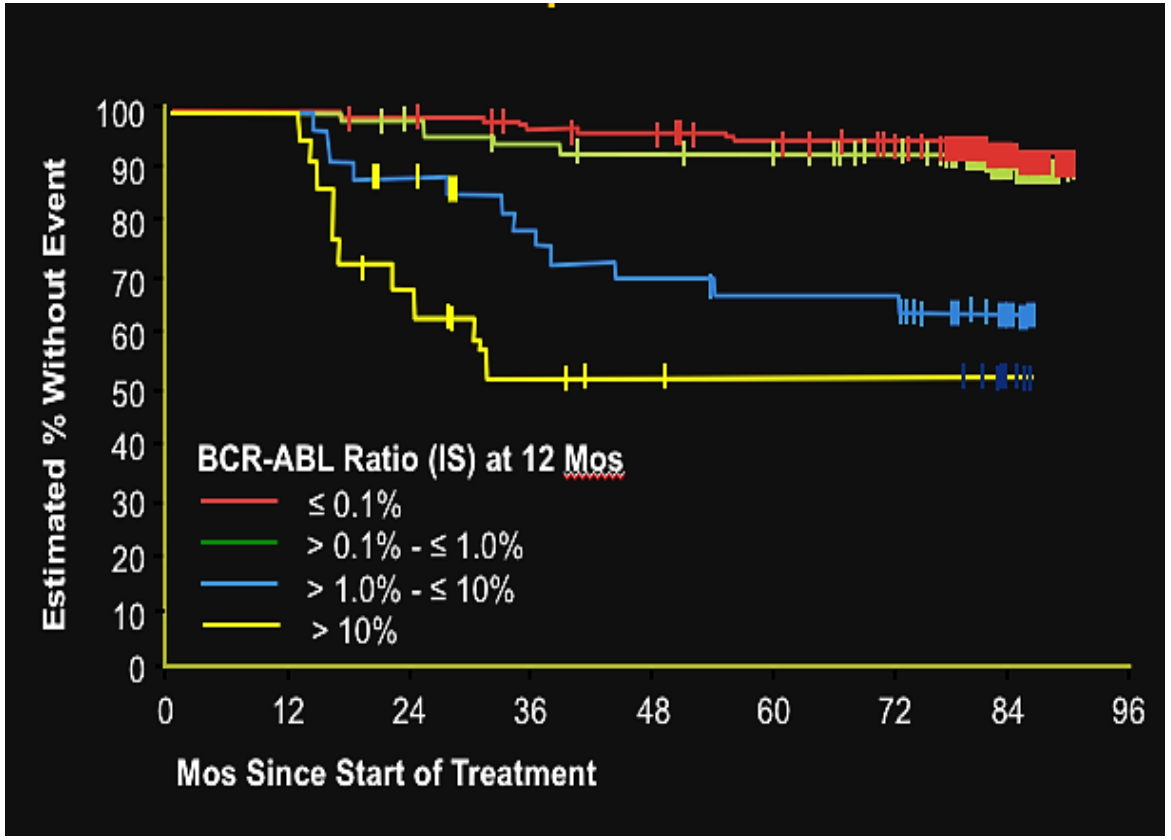
BCR-ABL MRD and Outcome in CML

Relapse Post-allogeneic Transplant



Radich *Blood.* 1997.

EFS After Imatinib Therapy



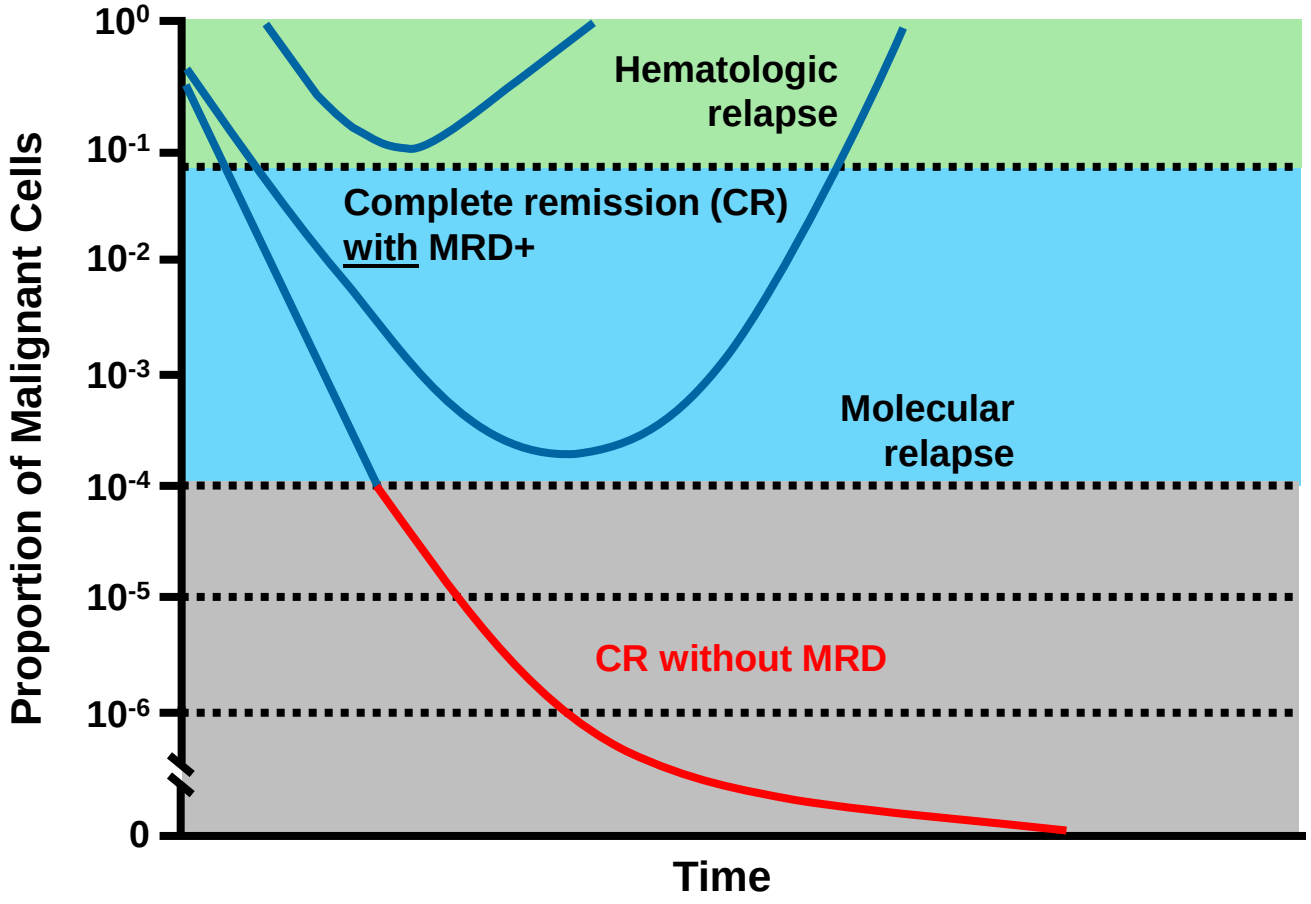
Hughes *NEJM.* 2003.

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



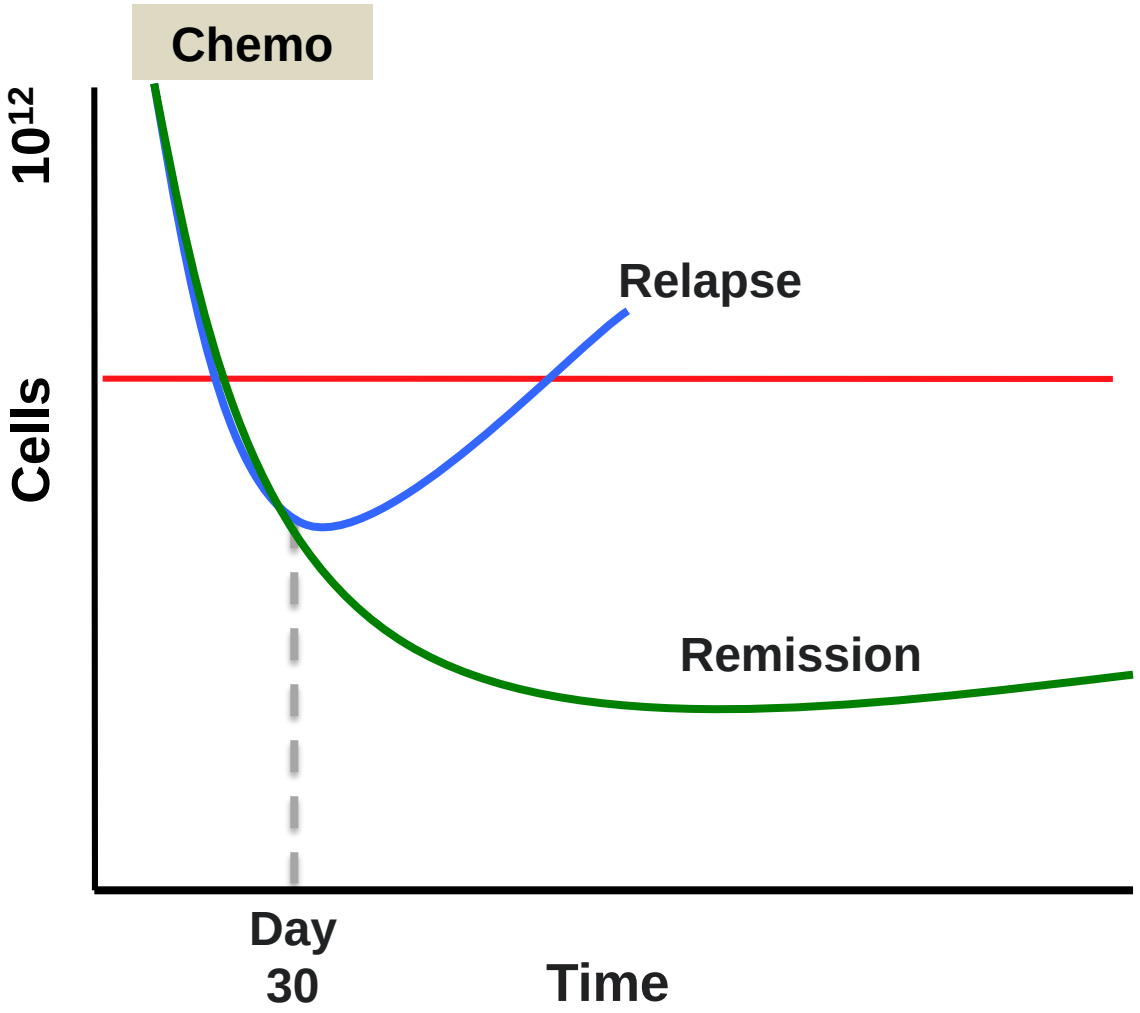
- **Morphology (limit 5%)**

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})**

Adapted from Bruggemann M, et al. *Blood*. 2012;120:4470-4481.

The ALL Patient Experience

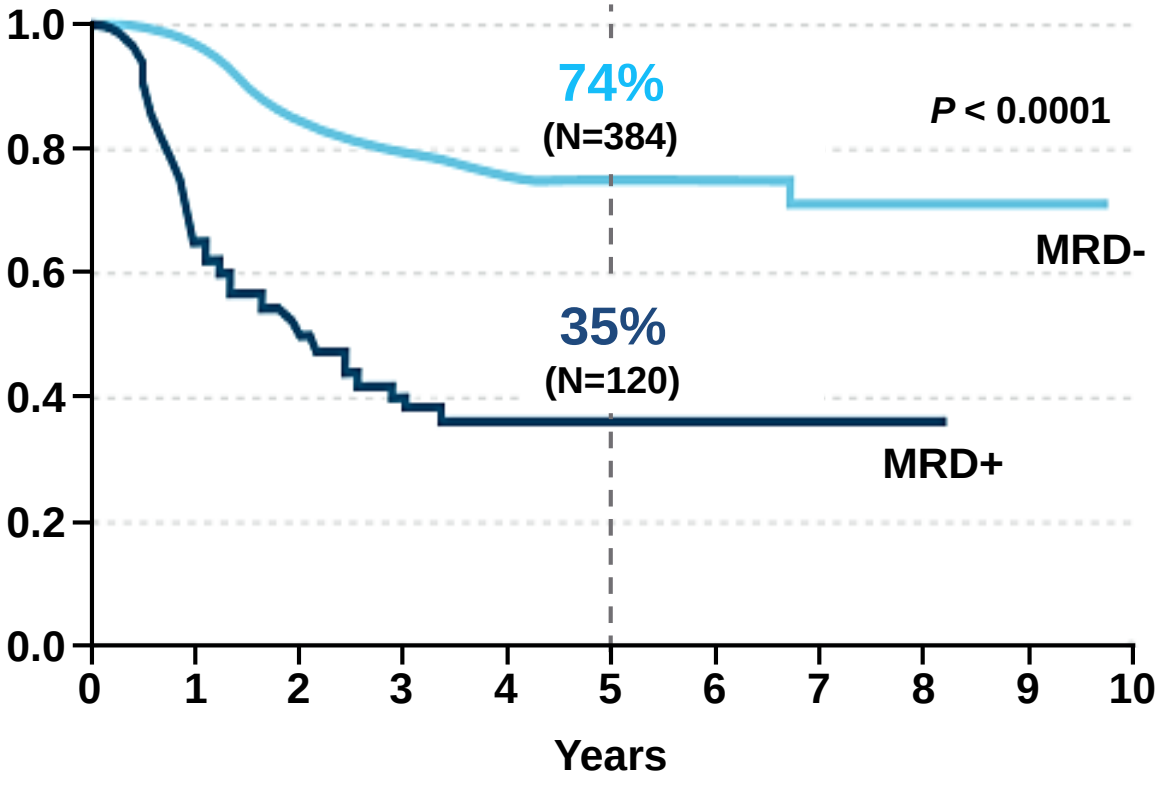


- **Day 30 bone marrow**
  - If no CR → alternative RX
  - If CR → continued therapy
- **At relapse**
  - Lower chance for CR with chemo
  - Low chance of transplant working

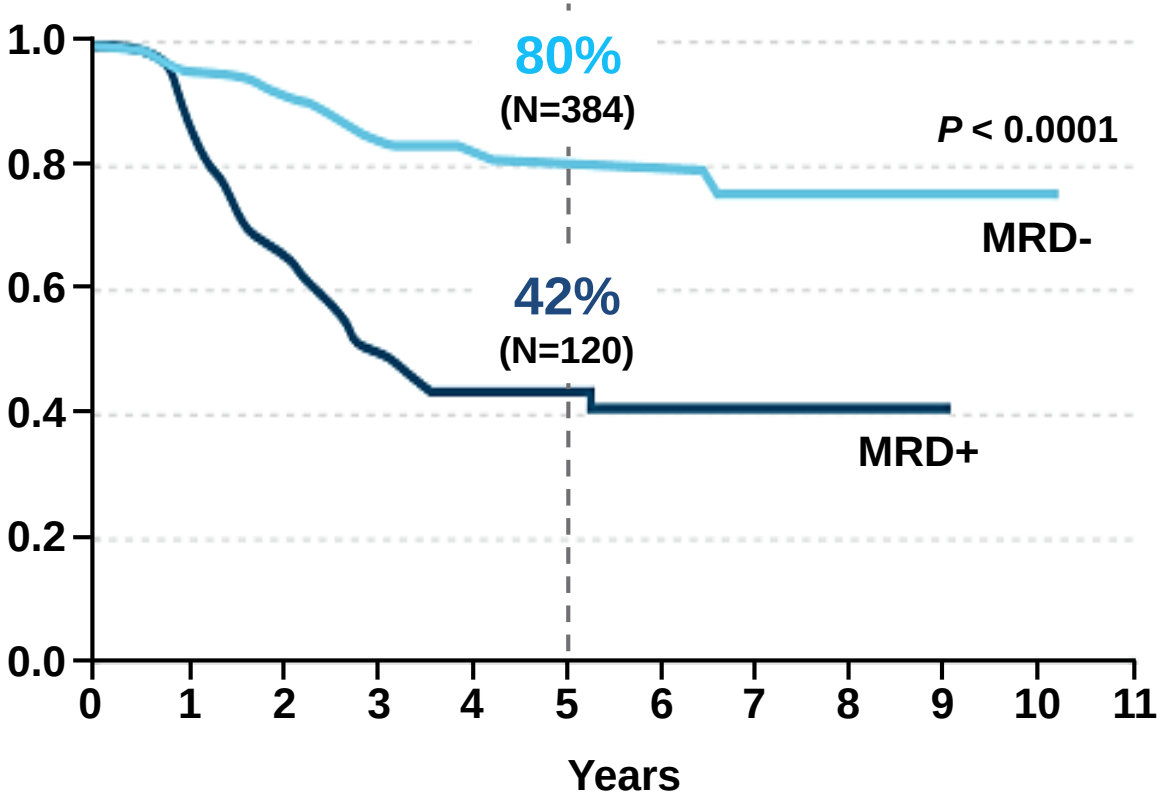
MRD:
1. **An indicator of relapse risk**
2. **A therapeutic target**

MRD Status is Associated With CR and Survival

Probability of Continuous CR



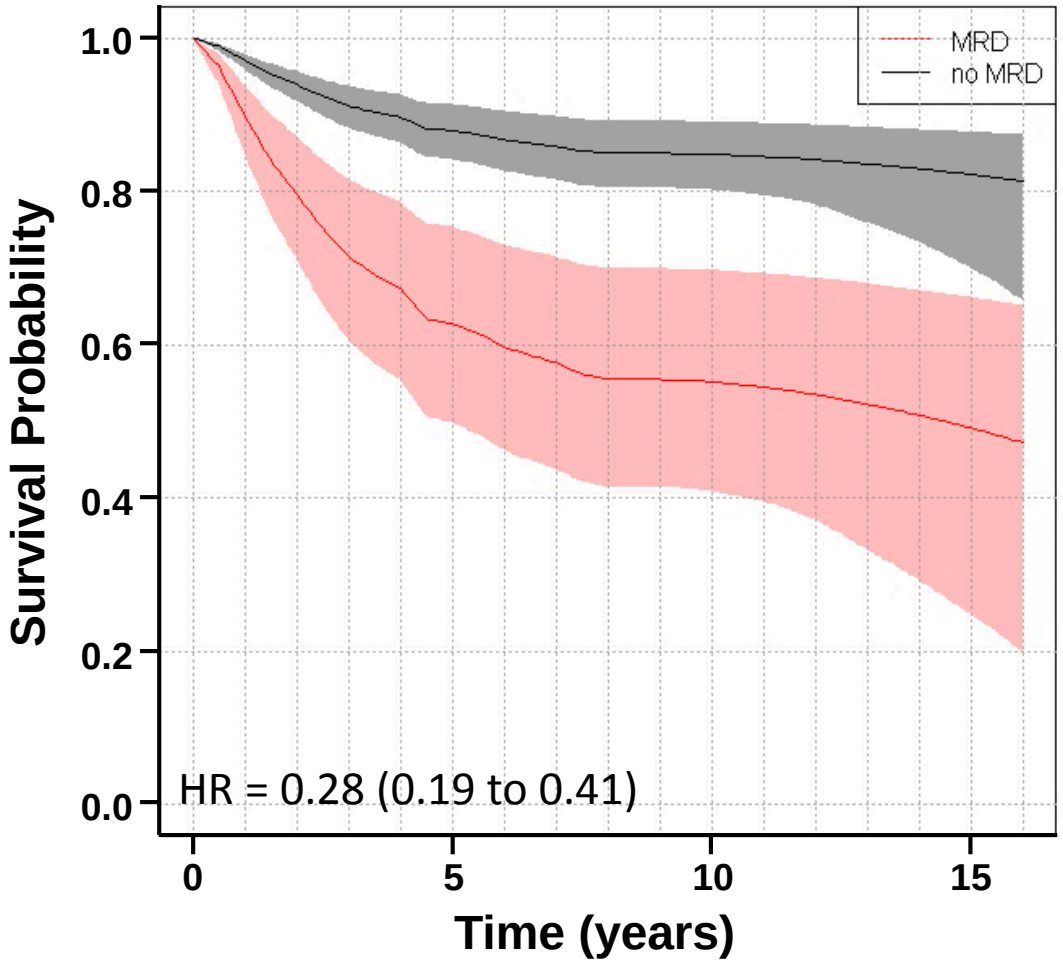
Probability of Survival



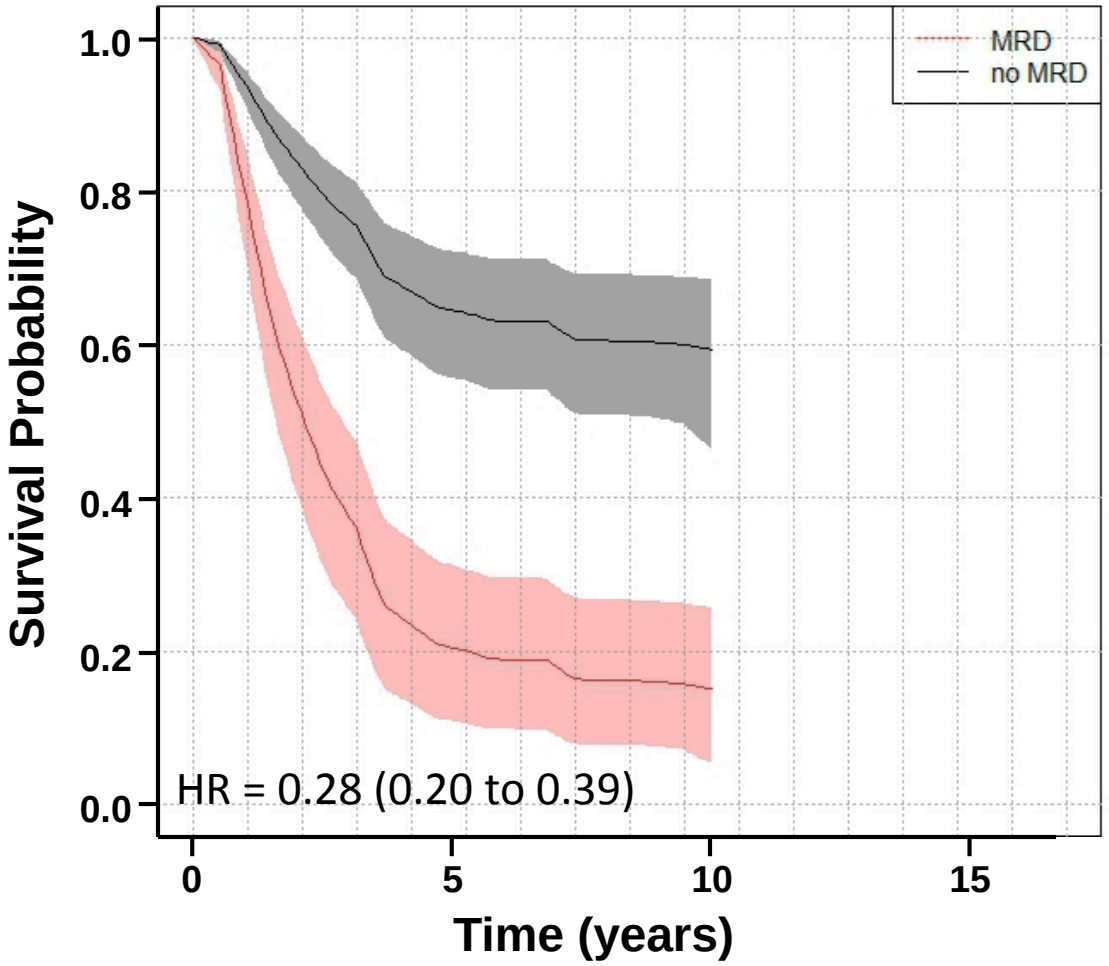
Adapted from Gökbuget N, et al. *Blood*. 2012;120:1868-1876.

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

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



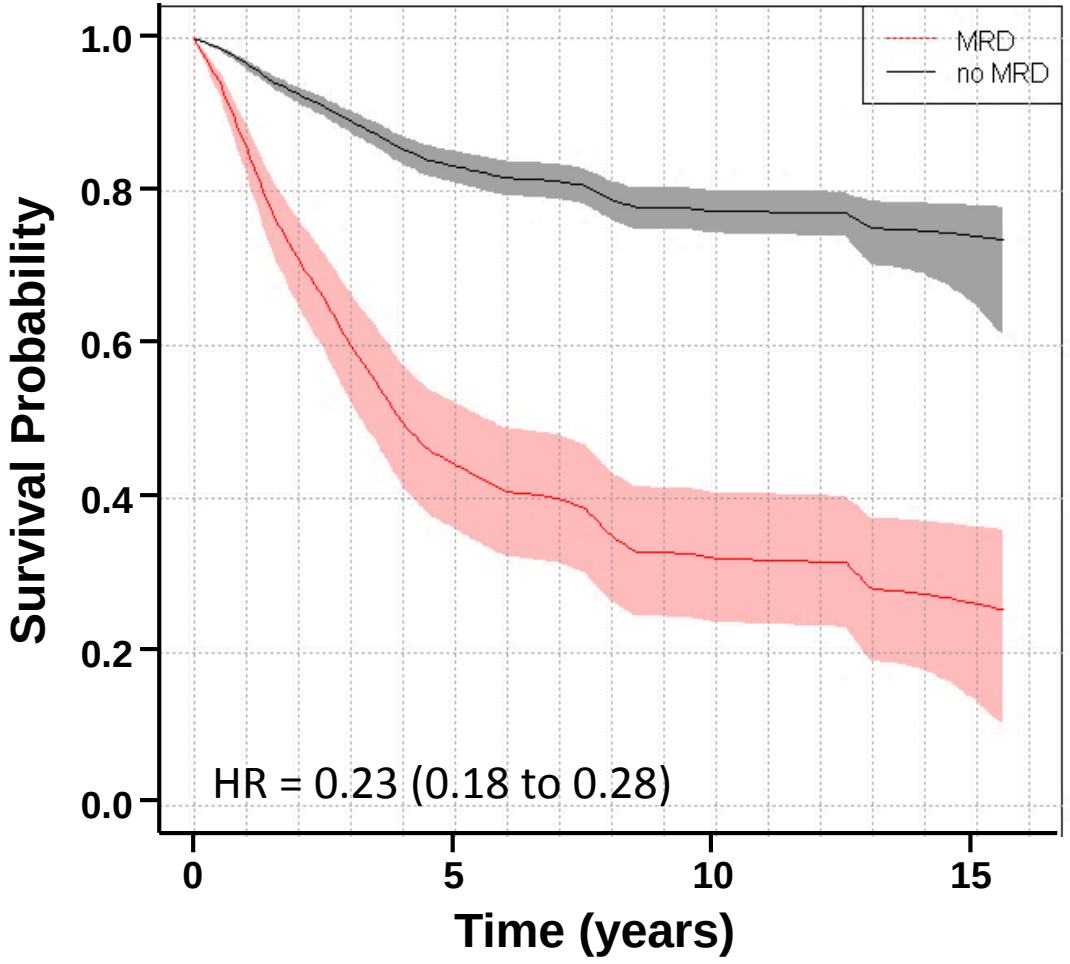
OS for Adult ALL: 5 studies with 779 patients



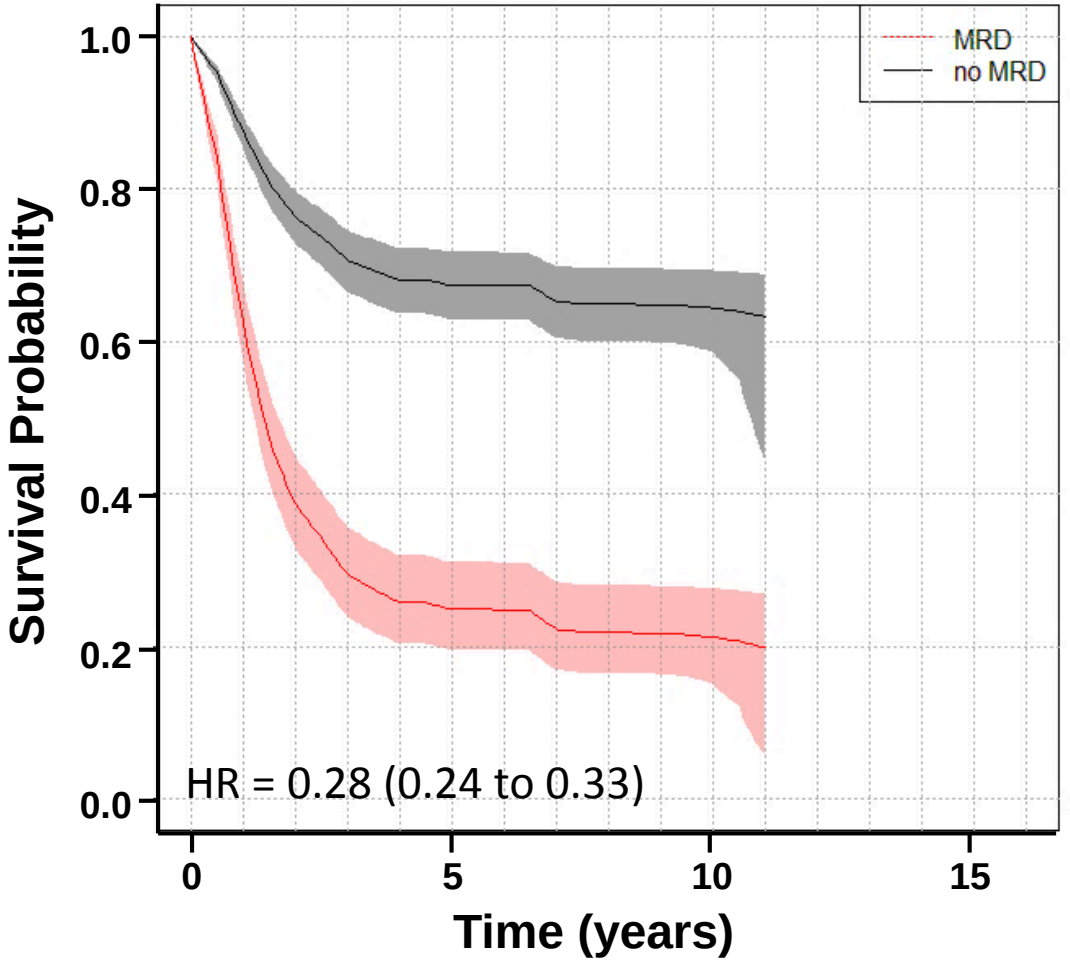
Adapted from Berry DA, et al. *JAMA Oncol.* 2017;3(7):e170580. doi:10.1001/jamaoncol.2017.0580.

Meta-Analysis: MRD and EFS in Children and Adults

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



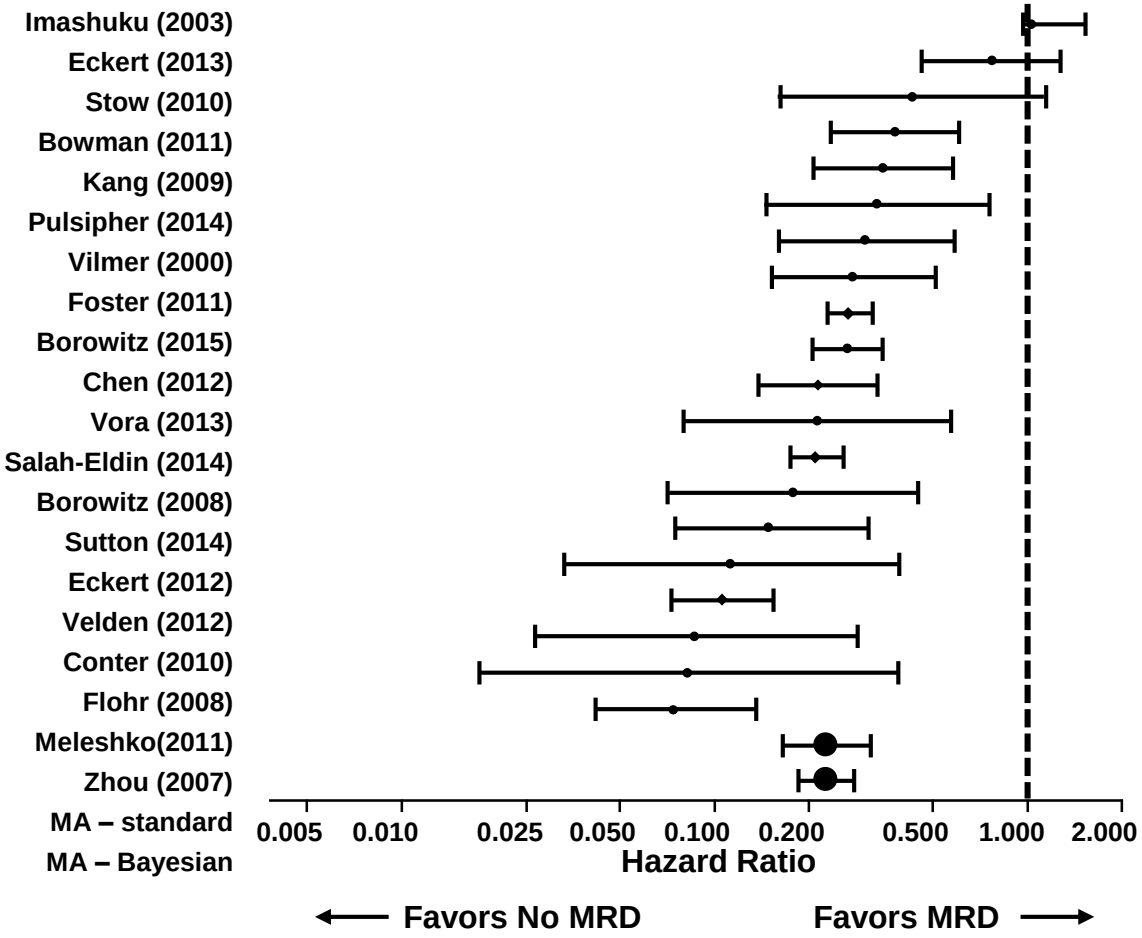
EFS for Adult ALL: 16 studies with 2,069 patients



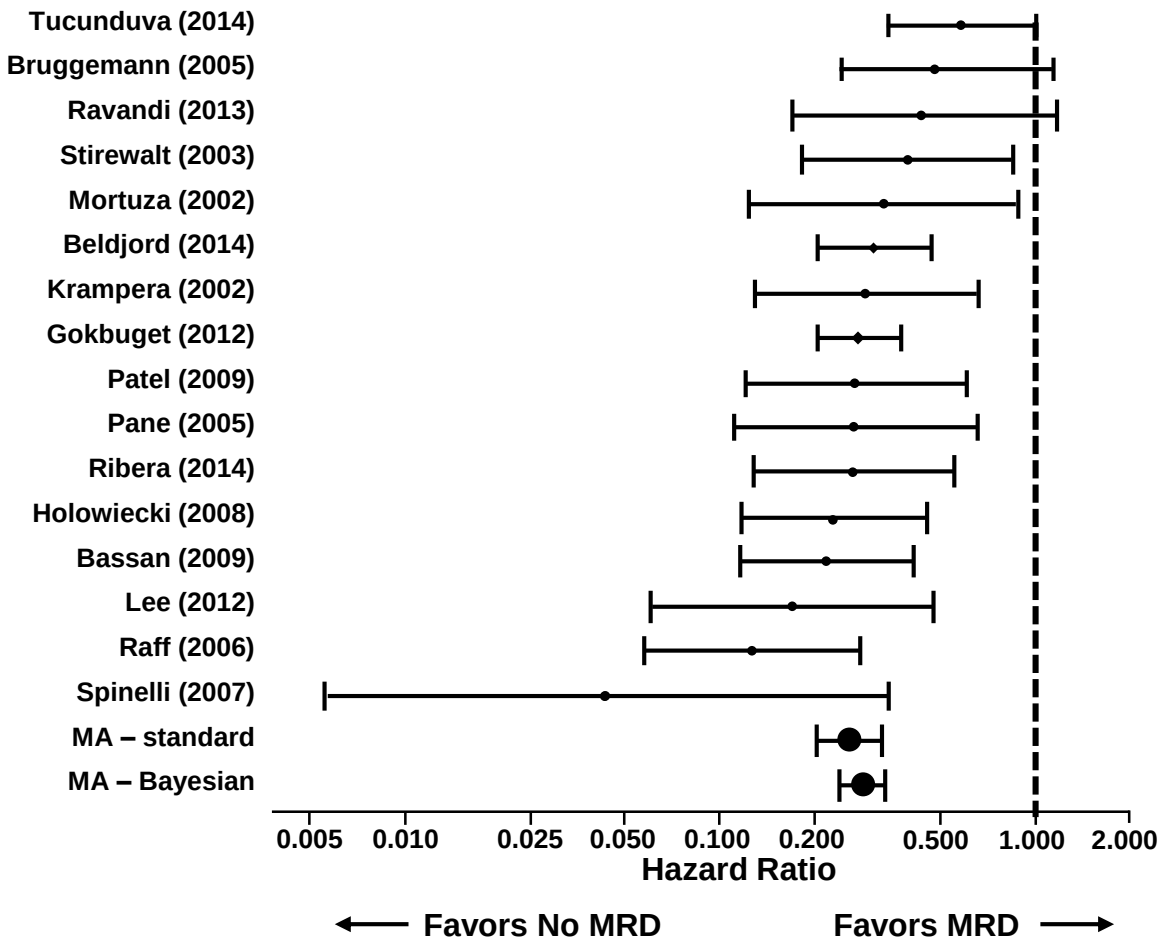
Adapted from Berry DA, et al. *JAMA Oncol.* 2017;3(7):e170580. doi:10.1001/jamaoncol.2017.0580.

Association of MRD and EFS is Remarkably Similar Across Studies

EFS by ALL Peds Studies (with 95% CIs)



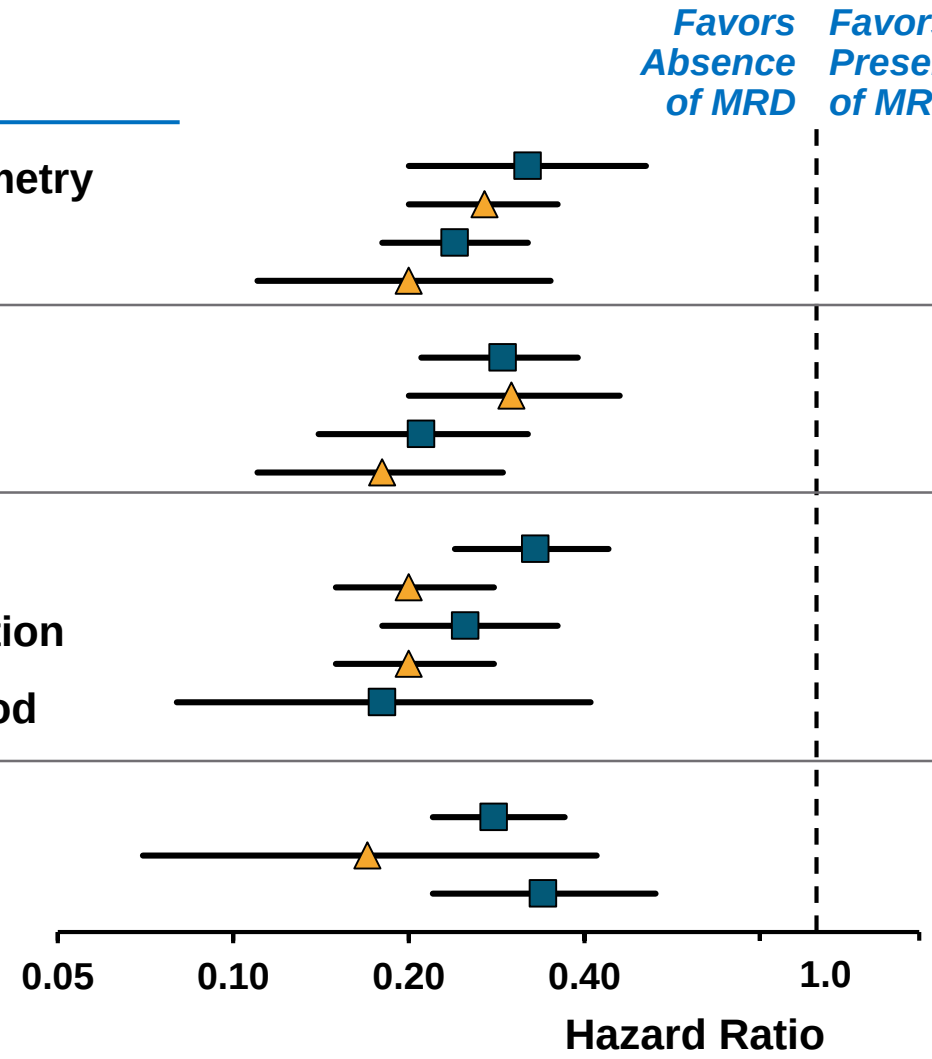
EFS by ALL Adult Studies (with 95% CIs)



Relative Sample Size • 0.025 • 0.100 • 0.250 ● 0.500

Effect of MRD is Independent of Other Covariates

Subset Analysis of EFS for MRD ALL

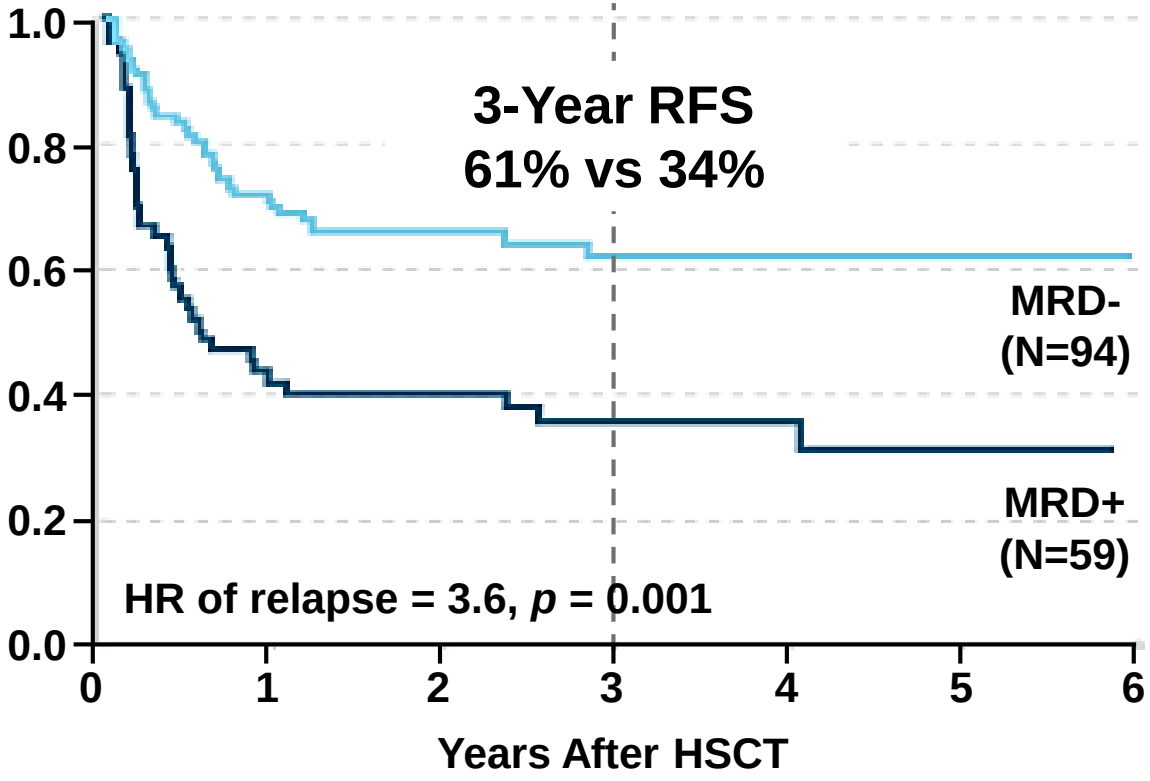


Subset		HR (95% Exact CI) Adult	HR (95% Exact CI) Pediatric
MRD Detection Method:	Flow cytometry	0.32 (0.20, 0.51)	0.27 (0.20, 0.36)
	PCR	0.24 (0.18, 0.32)	0.20 (0.11, 0.35)
MRD Cutoff:	10^{-4}	0.29 (0.21, 0.39)	0.30 (0.20, 0.46)
	$< 10^{-4}$	0.21 (0.14, 0.32)	0.18 (0.11, 0.29)
MRD Detection Period:	Induction	0.33 (0.24, 0.44)	0.20 (0.15, 0.28)
	Consolidation	0.25 (0.18, 0.36)	0.20 (0.15, 0.28)
	Other period	0.18 (0.08, 0.41)	–
Cytogenetics:	Ph-	0.28 (0.22, 0.37)	0.17 (0.07, 0.42)
	Ph+	0.34 (0.22, 0.53)	–

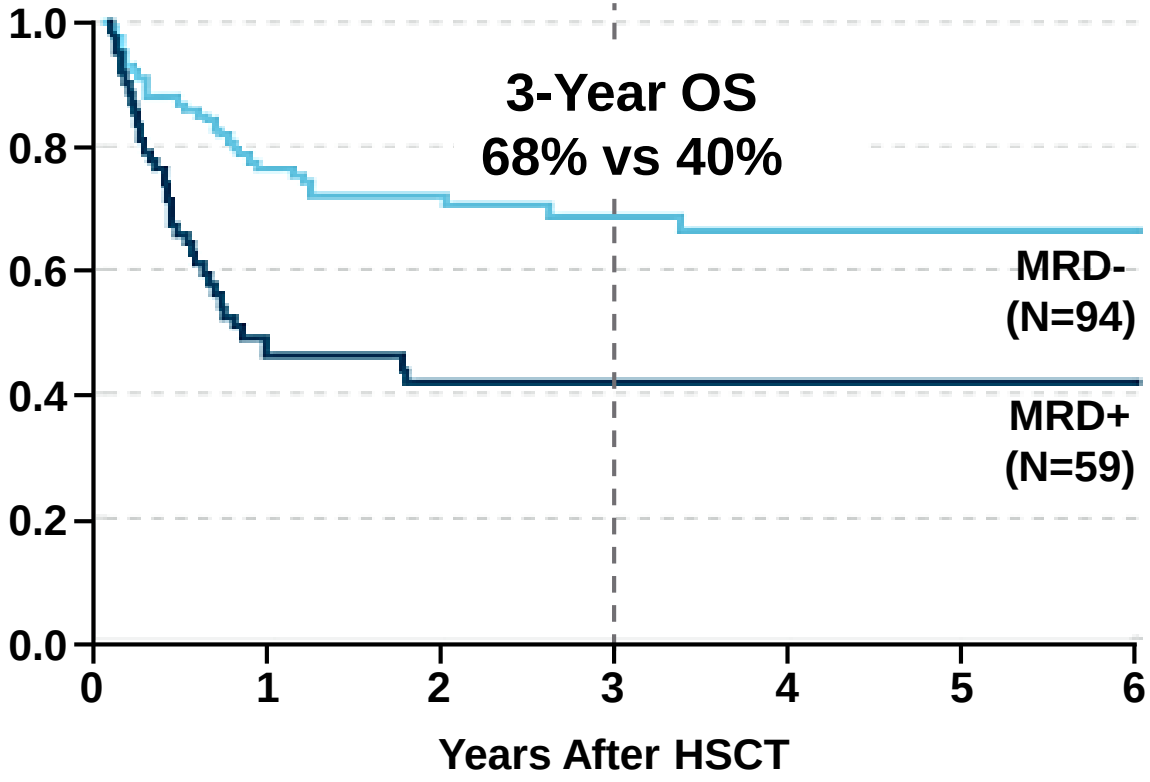
Adapted from Berry DA, et al. *JAMA Oncol.* 2017;3(7):e170580. doi:10.1001/*jamaoncol*.2017.0580.

Pre-Transplant MRD Status Affects Outcome

Probability of RFS



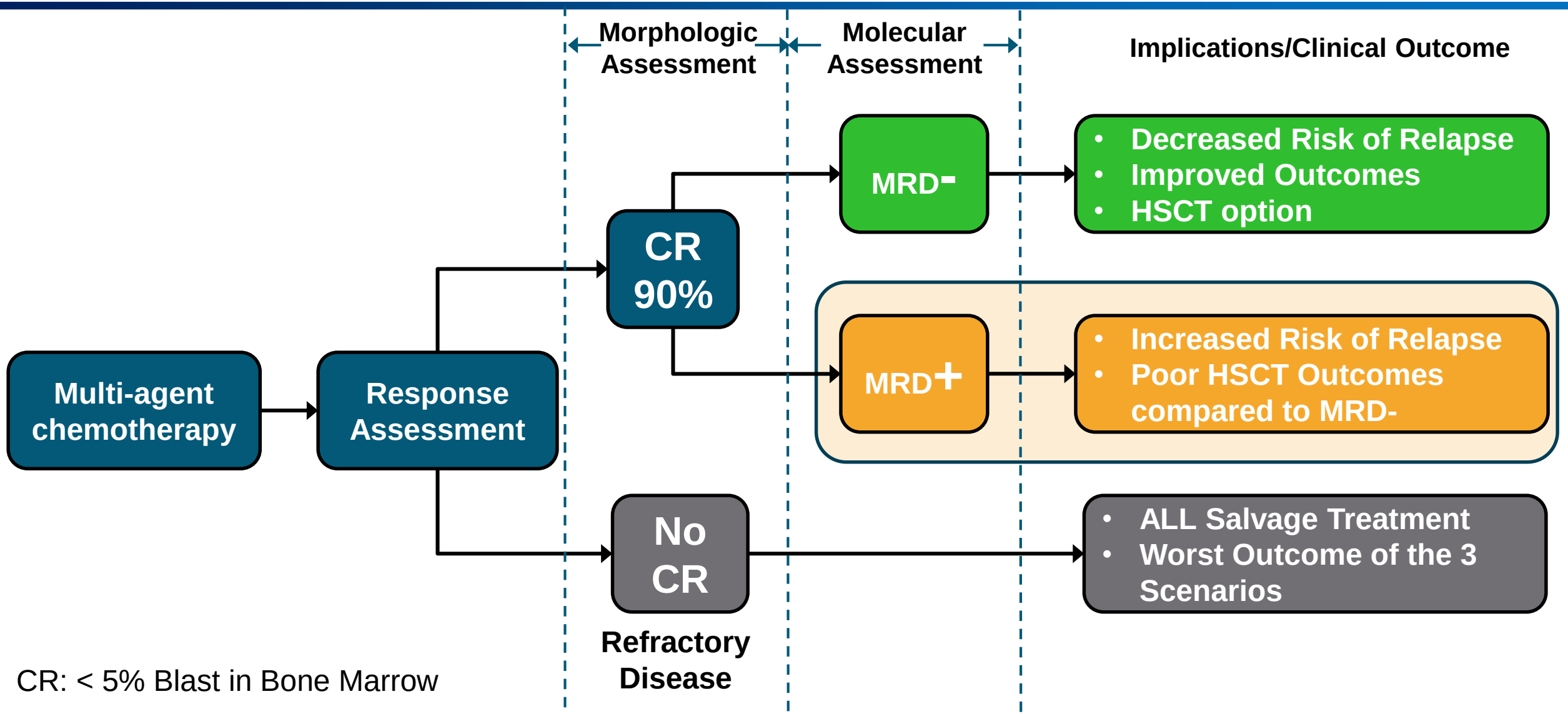
Probability of OS



CR 1 = 90, CR2 = 58, >CR2 = 12.
MRD status not influenced by adjusting for CR status

Bar M, et al. *Leuk Res Treatment*. 2014;2014:421723.

Outcomes By Response Status



CR: < 5% Blast in Bone Marrow

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 311 TOWER (Ph 3)
  N = 405
  Safety/Efficacy
- Study 211 (Ph 2)
  N = 225
  Safety/Efficacy
- Study 216 ALCANTARA (Ph 2)
  N = 45
  Safety/Efficacy Ph+
- Study 310
  N = 1139
  Historical Comparator (Global)

Pediatrics

- Study 205 (Ph 1/2)
  N = 49/44
  Dose/Sched/Safety/Efficacy
- Study 299
  N = 198
  Historical Comparator (EU)
- Study 228
  N = 159
  Historical Comparator (US)

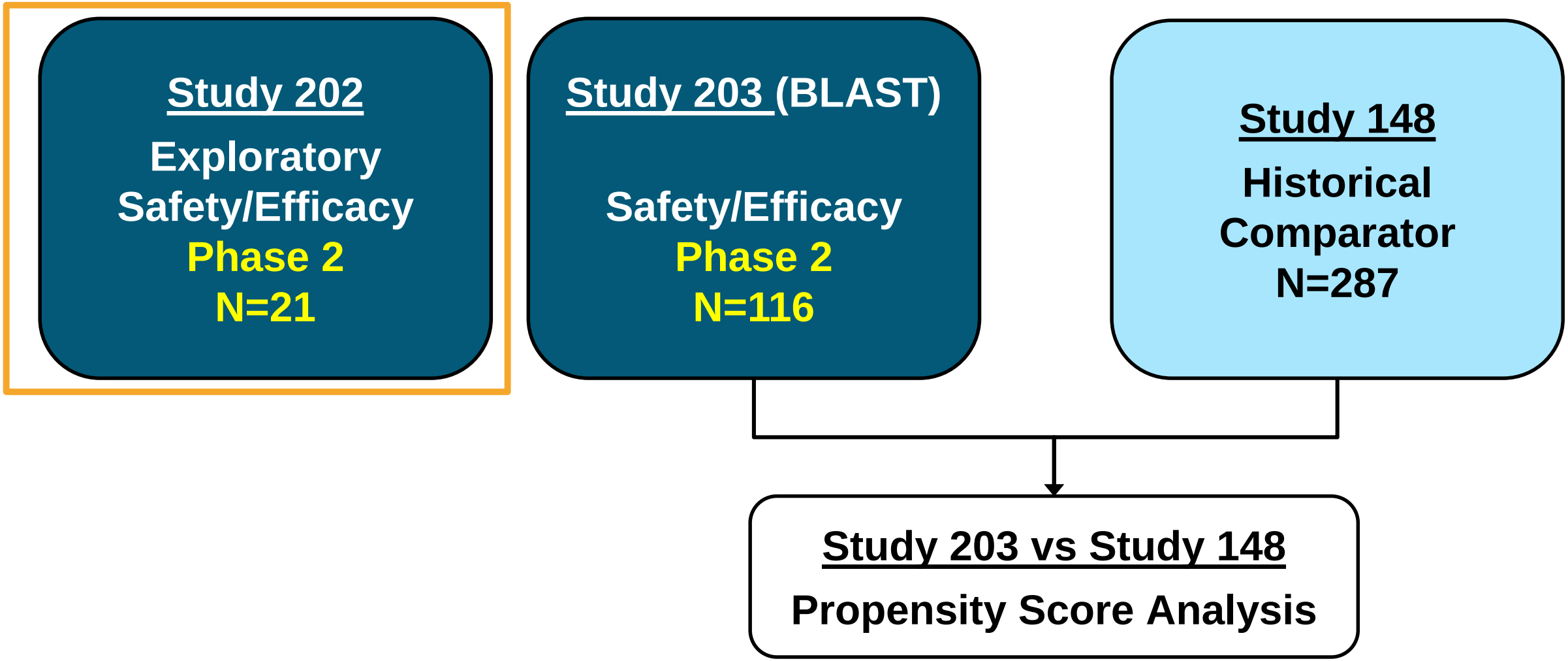
Clinical Study

Historical Comparator

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 (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

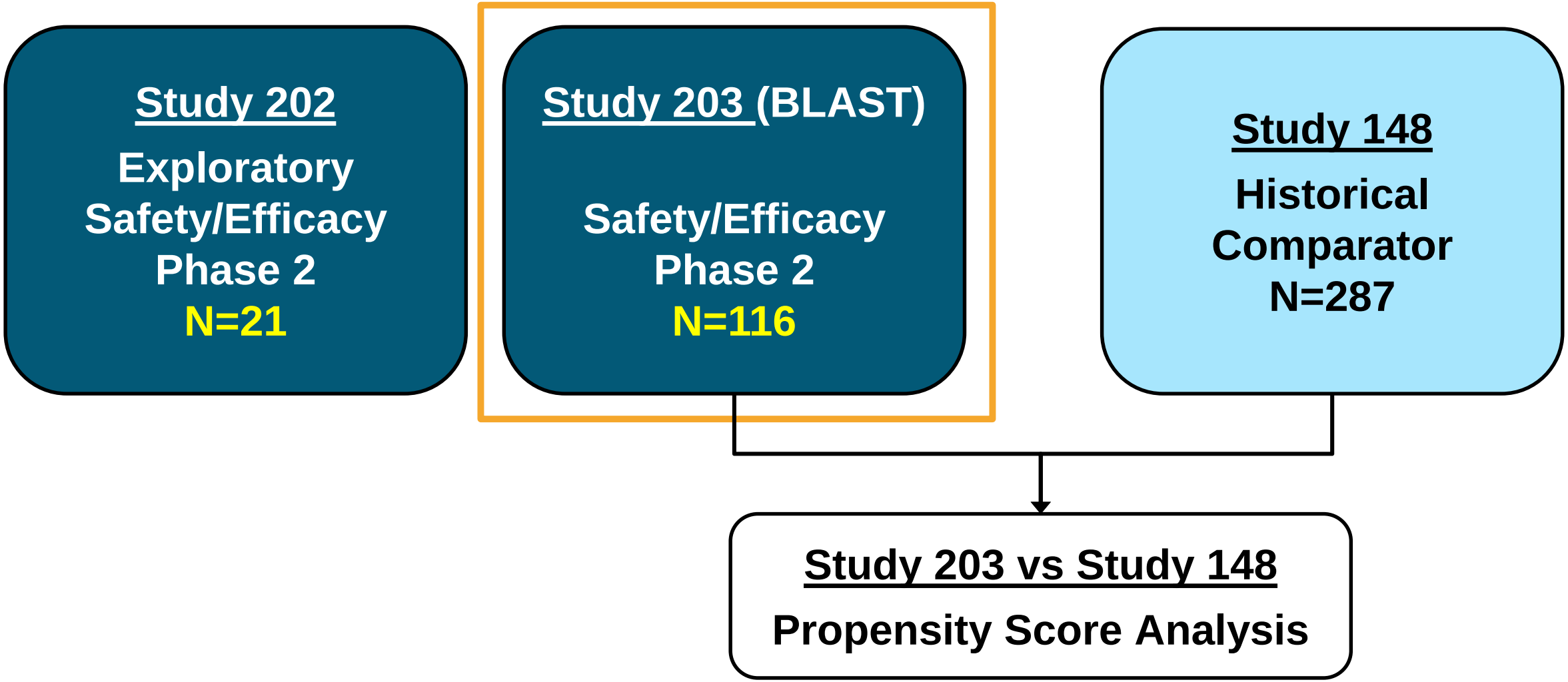


Study 202: Key Outcomes – Final Analysis

Key Outcomes	N=20
MRD response, n (%)	16 (80)
Allo HSCT after blinatumomab, n (%)	9 (45)
Median follow-up, months	50.8
Alive and in remission, n (%)	10 (50)

- **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 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[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**

a. Topp MS, et al. *J Clin Oncol.* 2011;29:2493-2498.
b. Gokbuget N, et al. *Haematologica.* 2017;102:132-135.

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

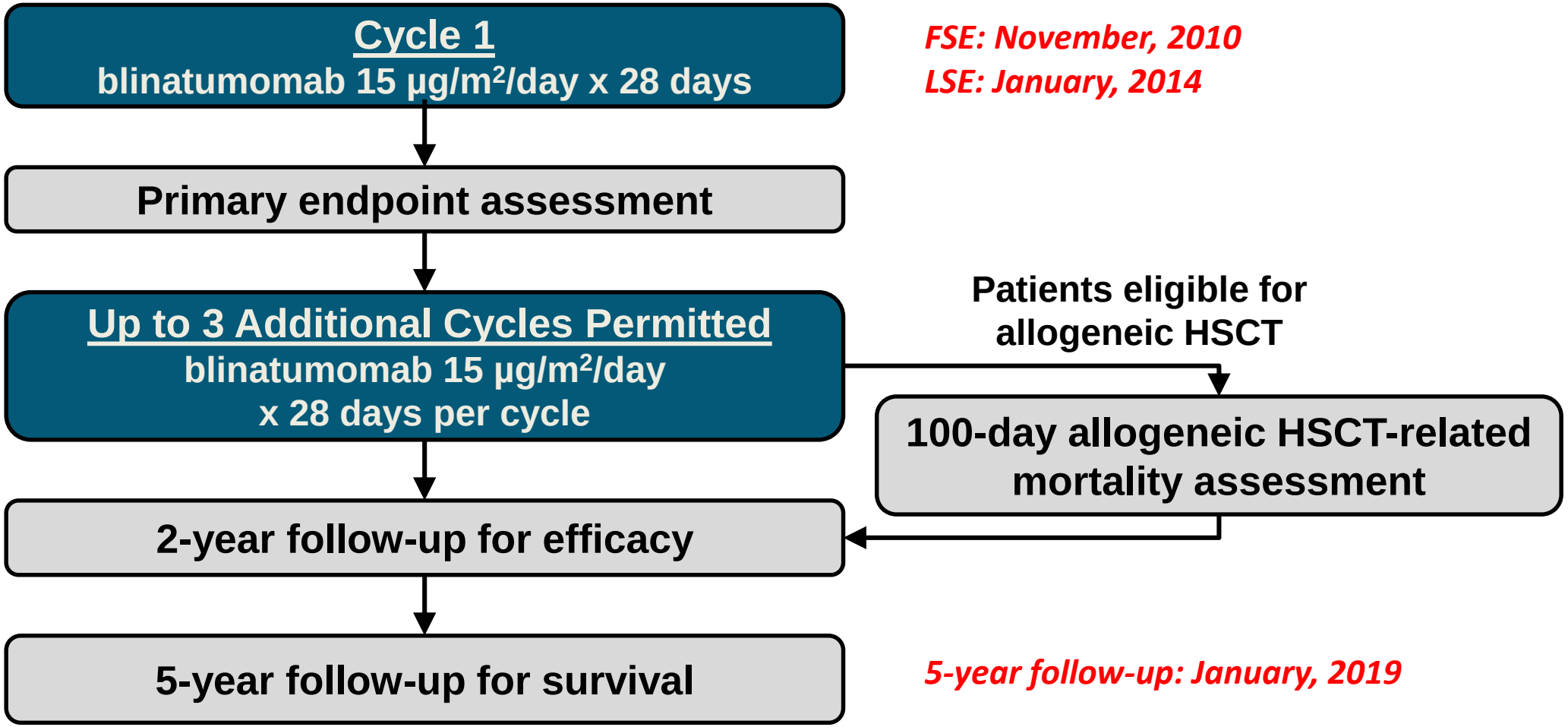
CR defined as < 5% blasts in bone marrow after at least ≥ 3 intensive chemotherapy blocks (e.g., GMALL induction I-II/consolidation I, induction/intensification/consolidation, or three blocks of Hyper CVAD).

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/m^2/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.

Study 203: Baseline Patient Characteristics

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

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

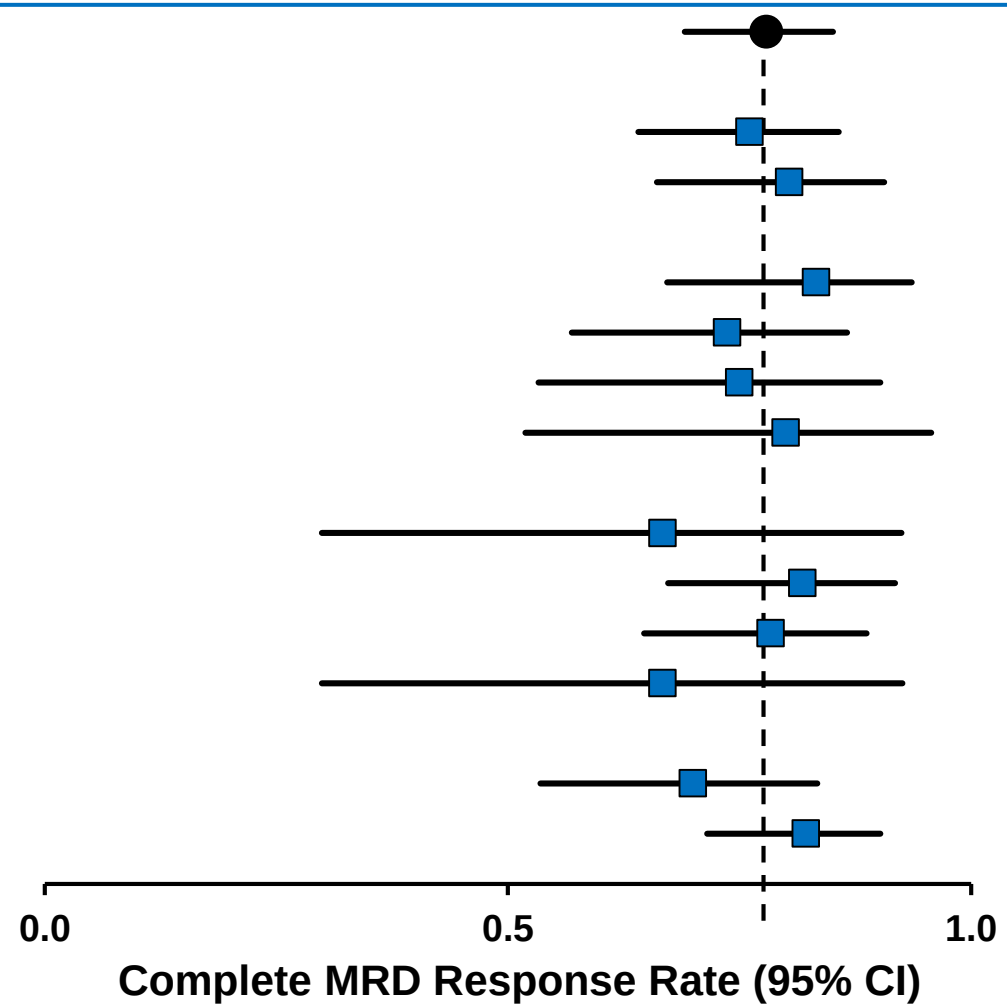
Evaluations	Primary Endpoint FAS[a] N=113 n (%)	95% CI
Patients with evaluable MRD	**112 (99)**	
Complete MRD response at end of Cycle 1 *(undetectable with an assay sensitivity of at least 10^{-4})*	**88 (78)**	**69–85**

- **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)

Primary EP FAS	n/N	%	(95% Exact CI)
Overall	88/113	78	(69, 85)
Gender			
Male	51/67	76	(64, 86)
Female	37/46	80	(66, 91)
Age			
18 to < 35	30/36	83	(67, 94)
35 to < 55	28/38	74	(57, 87)
55 to < 65	18/24	75	(53, 90)
≥ 65	12/15	80	(52, 96)
MRD Level at Baseline			
10^{-1} to < 1	6/9	67	(30, 93)
10^{-2} to < 10^{-1}	36/44	82	(67, 92)
10^{-3} to < 10^{-2}	40/51	78	(65, 89)
Other	6/9	67	(30, 93)
Remission Status			
CR 2/3	28/40	70	(53–83)
CR 1	60/73	82	(72–90)



Complete MRD response = defined by the absence of MRD with an assay with a minimum sensitivity of 10^{-4} after 1 cycle of blinatumomab.

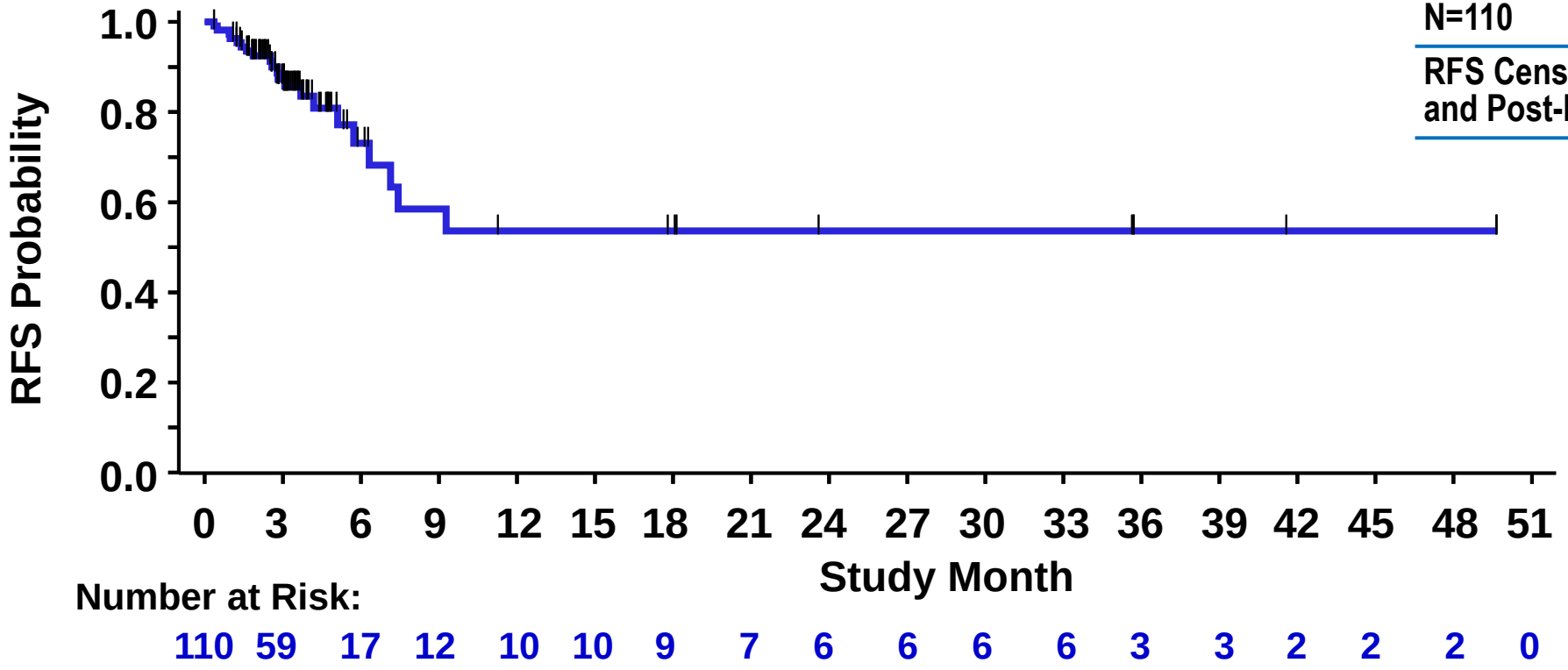
Study 203: Key Secondary Endpoint – RFS at 18 Months Exceeds Pre-specified Threshold of 28%

- 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)

		RFS at 18 months*	95% CI
Primary	Censored at HSCT or post-blinatumomab chemotherapy	54%	33, 70
Sensitivity	Uncensored at HSCT or post-blinatumomab chemotherapy	53%	44, 62

*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

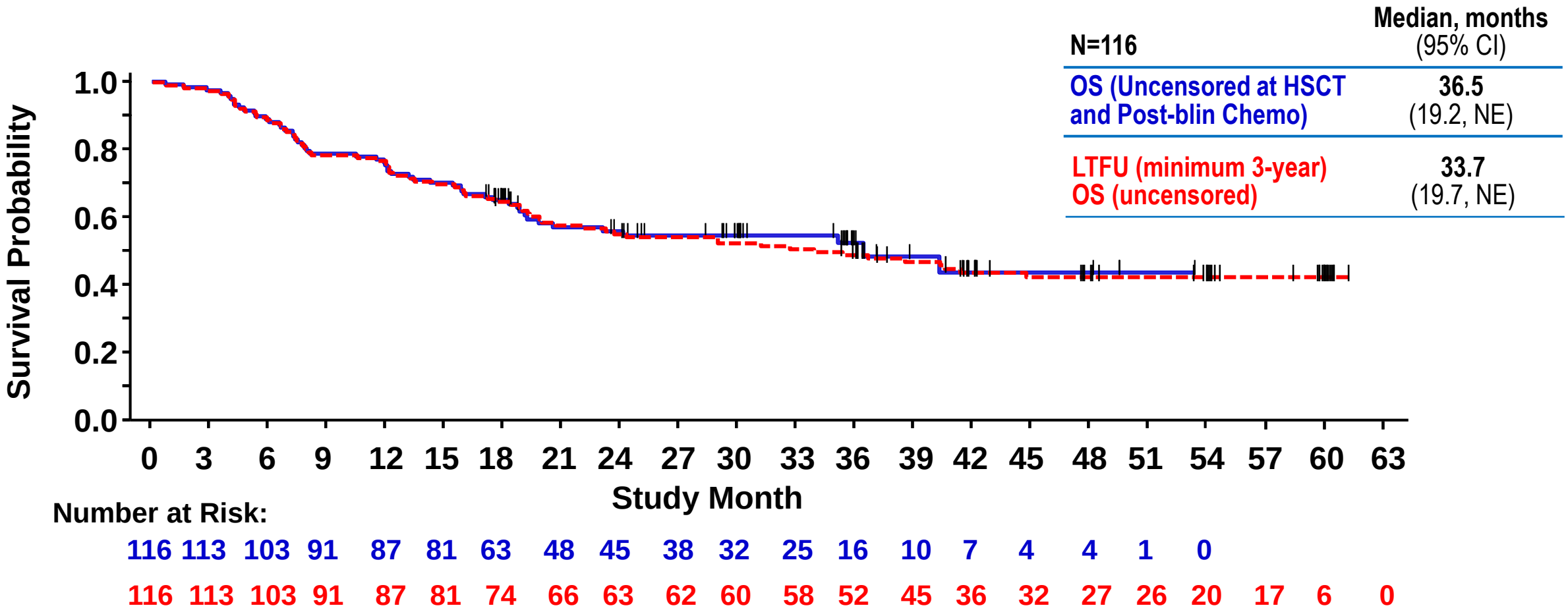


N=110	Median, months (95% CI)
RFS Censoring at HSCT and Post-blin Chemo	NE (6.3, NE)

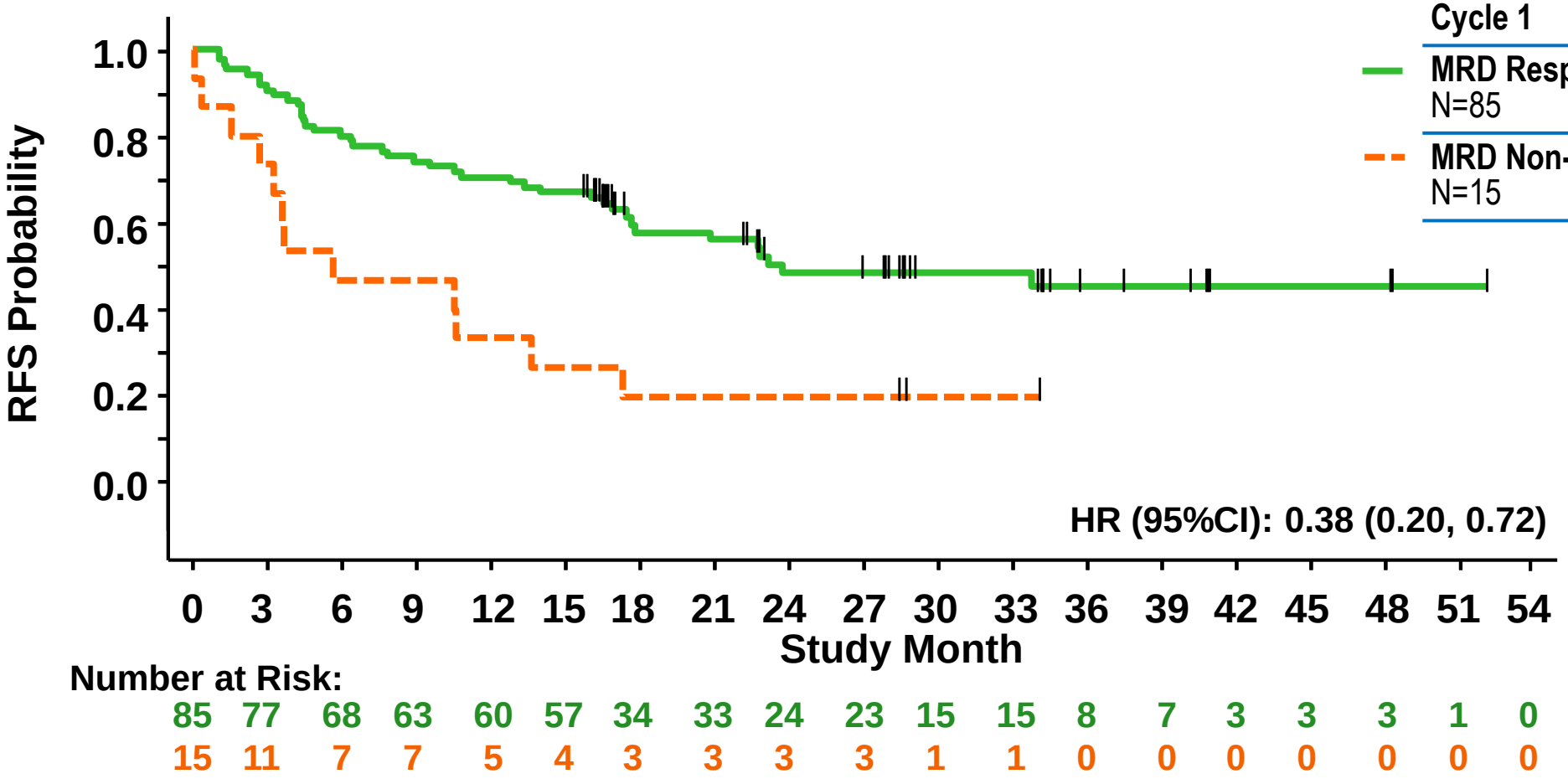
- **74 of 110 (67%) patients were transplanted in continuous remission**

Philadelphia Chromosome-Negative Patients in Hematologic CR.

Study 203: Secondary Endpoint – OS (uncensored)



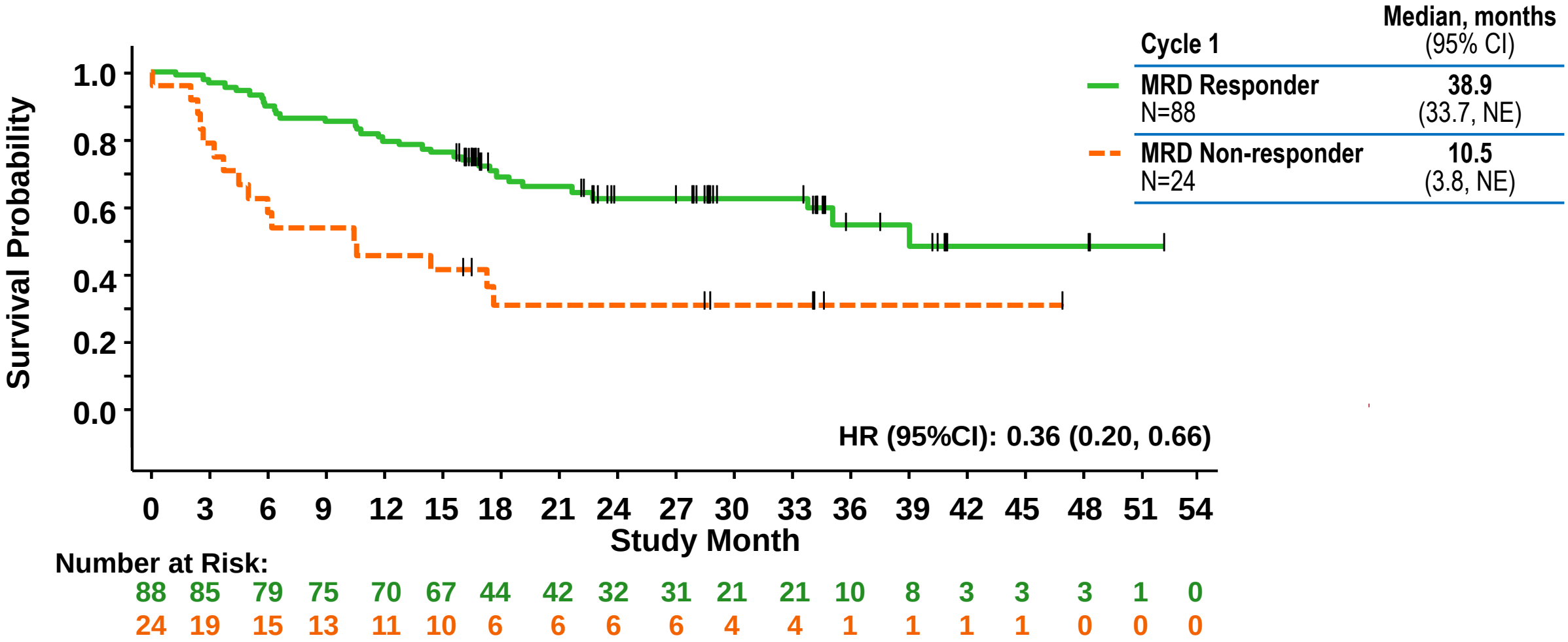
Study 203:
Landmark Analysis − Impact of MRD Response on RFS



Cycle 1	Median, months (95% CI)
MRD Responder N=85	23.6 (17.4, NE)
MRD Non-responder N=15	5.7 (1.6, 13.6)

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.

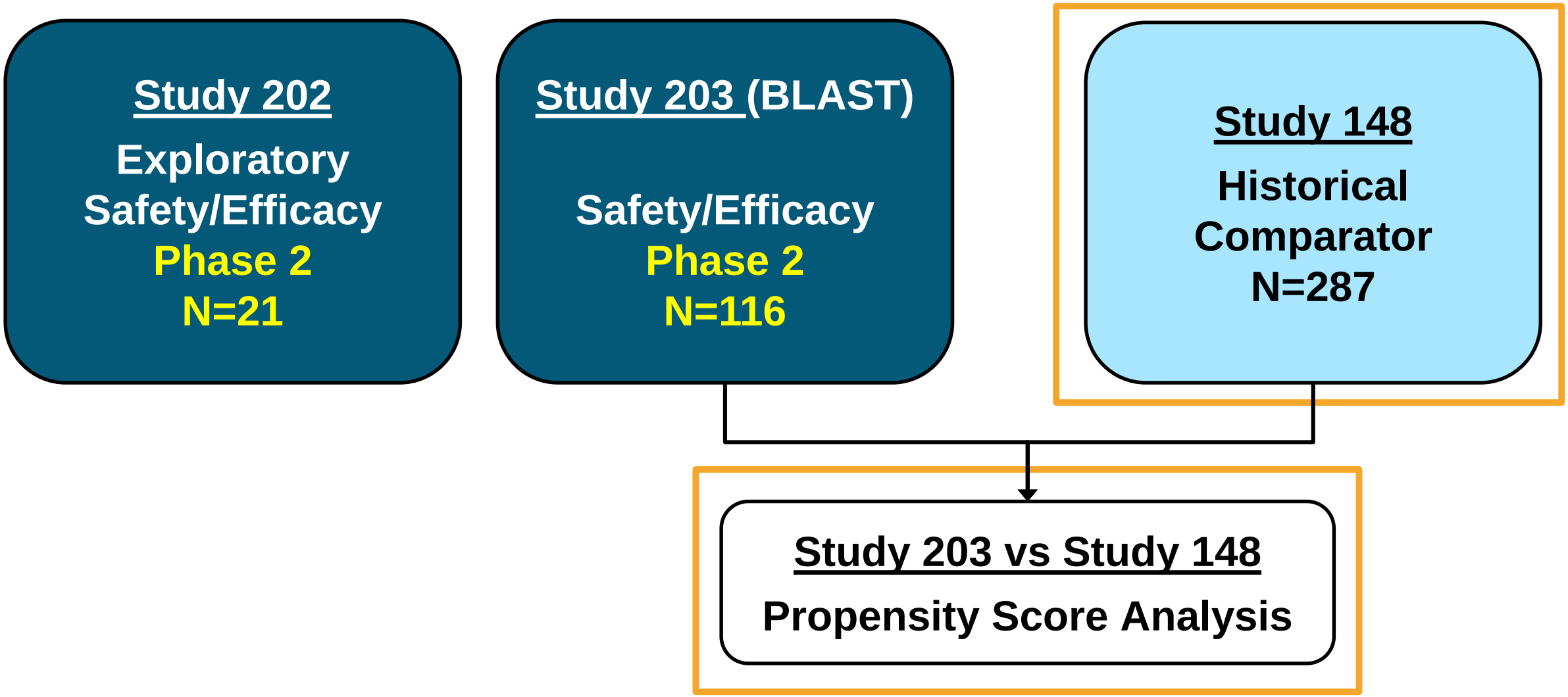
Study 203:
Landmark Analysis − Impact of MRD Response on OS



Cycle 1	Median, months (95% CI)
MRD Responder N=88	38.9 (33.7, NE)
MRD Non-responder N=24	10.5 (3.8, NE)

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 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:**
  - ≥ 10^{-4} by PCR
  - ≥ 10^{-3} by flow cytometry
- **Ph- B-precursor ALL**
- **3+ intensive chemotherapy blocks**
- **Age ≥ 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

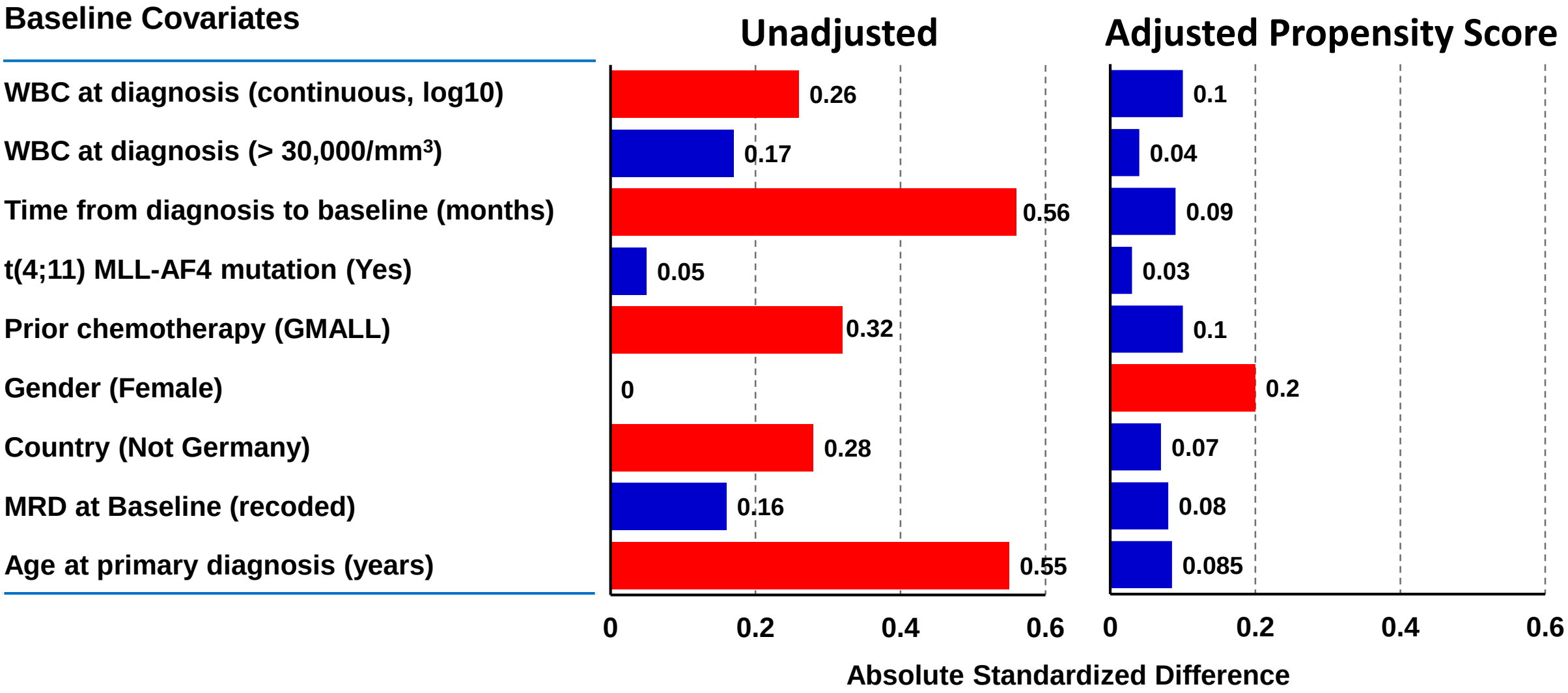
Study 203 (BLAST) N=73	Study 148 (Historical Comparator) N=182
◆ Ph- B-precursor ALL in CR after 3+ intensive chemotherapy blocks ◆ ≥ 18 years of age at MRD baseline date ◆ In first remission (CR1) ◆ MRD at ≥ 10^{-3}	

Propensity Score Analysis (PSA) Overview

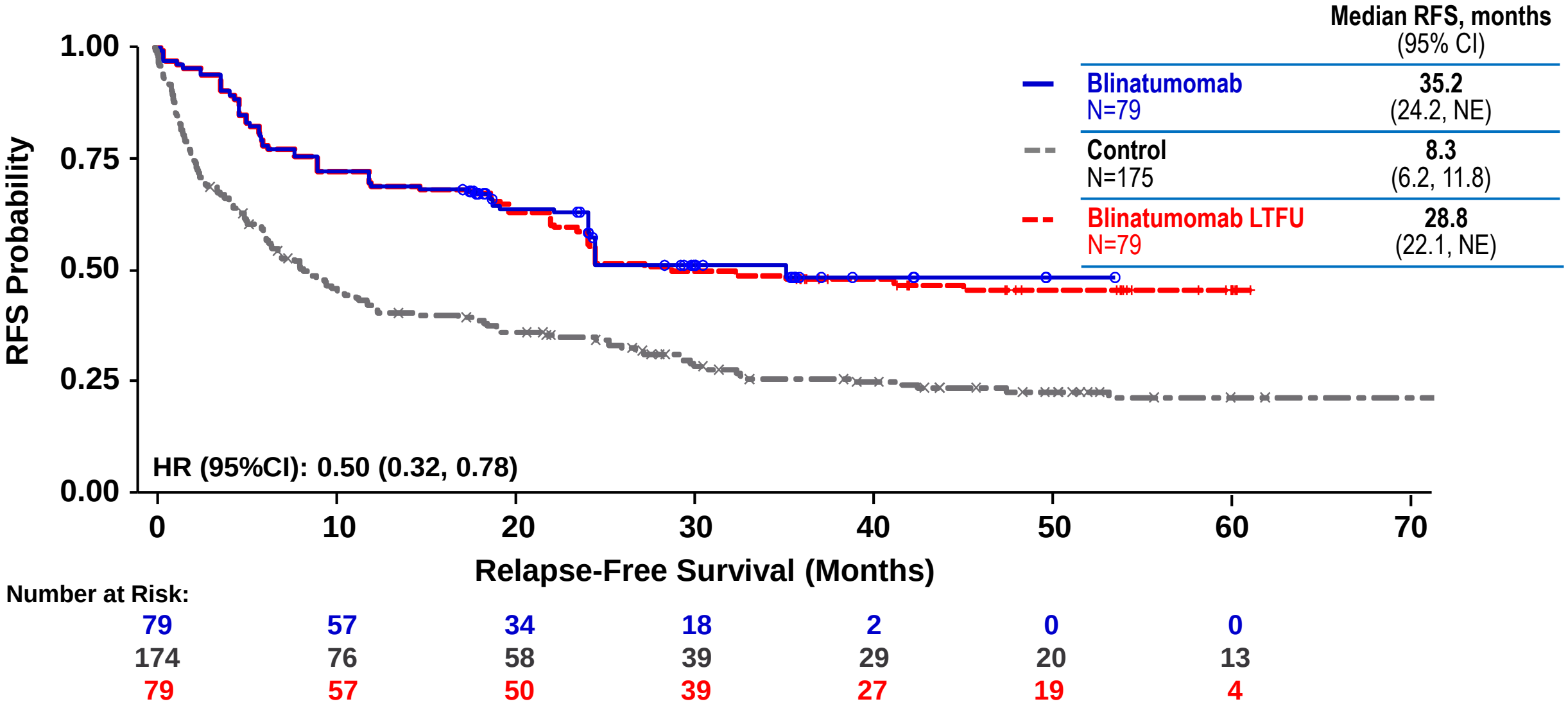
- **PSA attempts to mimic the effect of randomization by creating a balance between treated and untreated patients**
  - The propensity score captures how differences in baseline covariates contribute to a patient's probability of being in one group or the other
  - Individual subjects are weighted by 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.

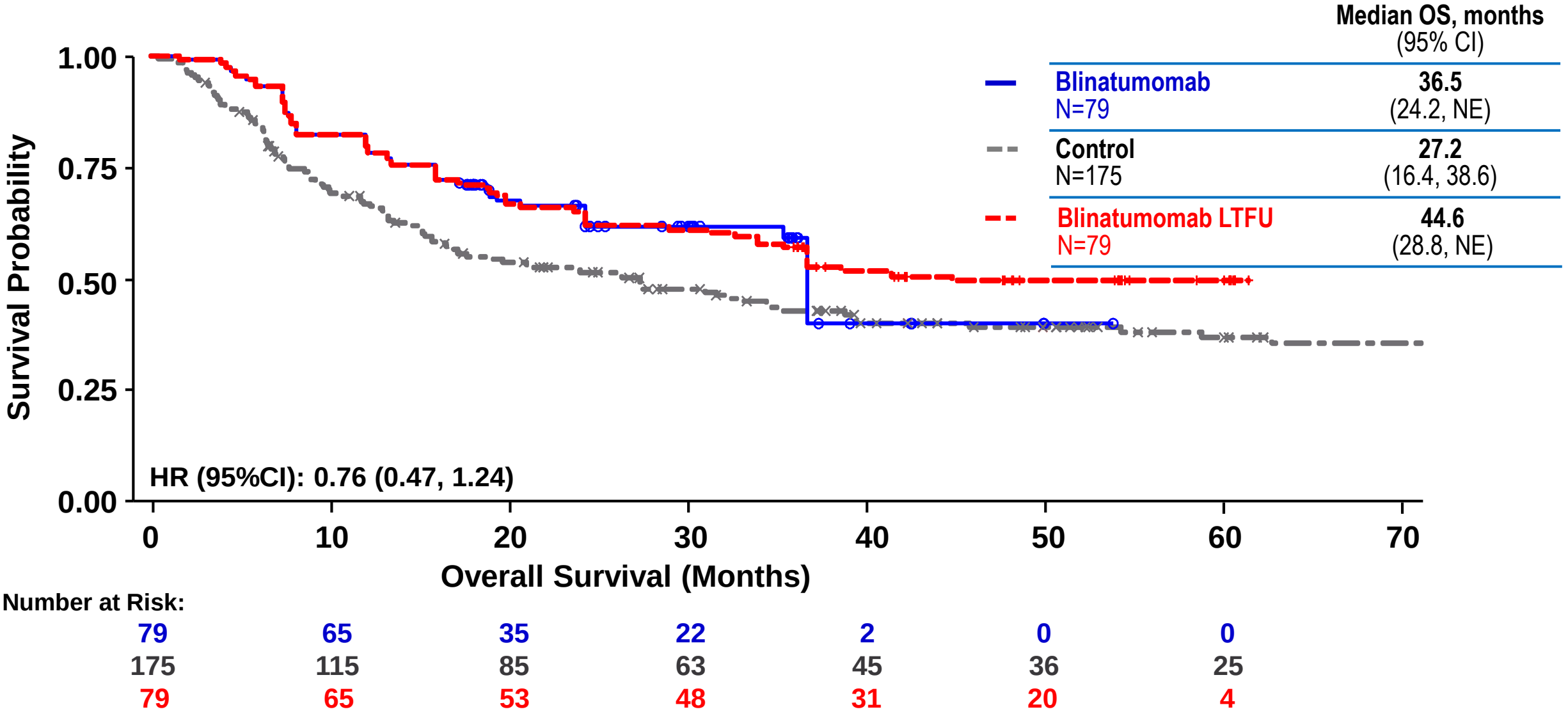
Baseline Covariate Balance Before and After Adjustment



Propensity Score Analysis: Relapse-Free Survival (Primary Analysis Set)

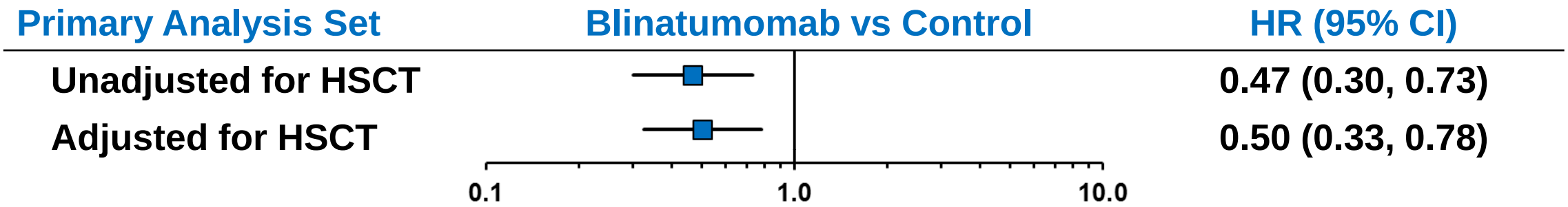


Propensity Score Analysis: Overall Survival (Primary Analysis Set)



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



Propensity Score Analysis: A High Percentage of Blinatumomab-Treated Patients Went to HSCT

	Propensity Score Analysis	
	Study 203 N=73	Historical (Study 148) N=182
Patients with HSCT, %	78	44
Patients ≥ 35 Years of Age, %	68	38

Summary of Blinatumomab Efficacy in MRD+ ALL

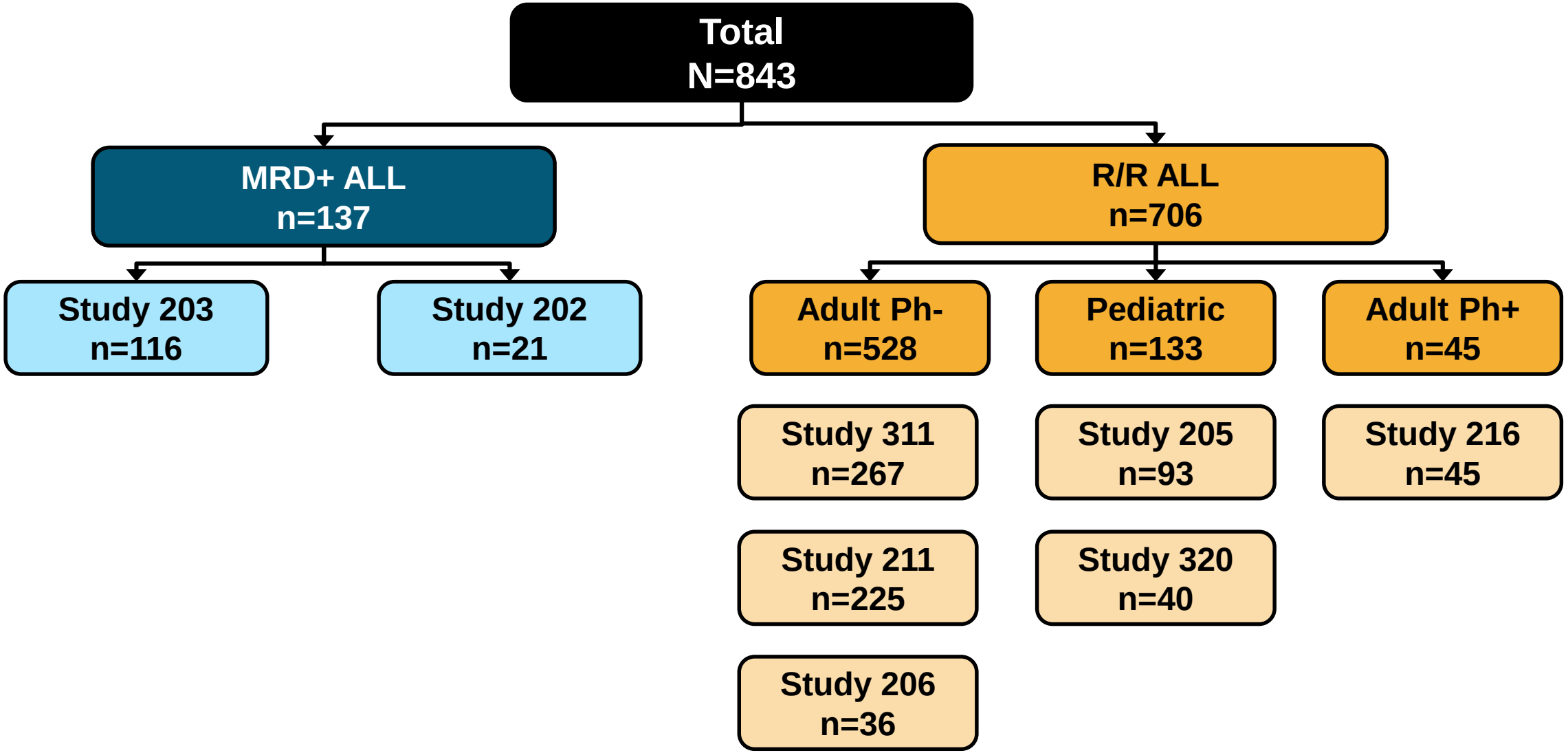
- **MRD-positivity reflects measurable disease burden**
- **Blinatumomab is able to induce MRD-negativity**
  - 78% of patients achieved complete MRD response after first cycle
- **Complete MRD responders had improved RFS and OS compared to non-responders**
- **Propensity score analysis demonstrated 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



Summary of Blinatumomab Exposure

	MRD+ ALL N=137	R/R ALL N=706
Treatment exposure – days, median	55.5	39.9
Number of started cycles, median	2.0	2.0

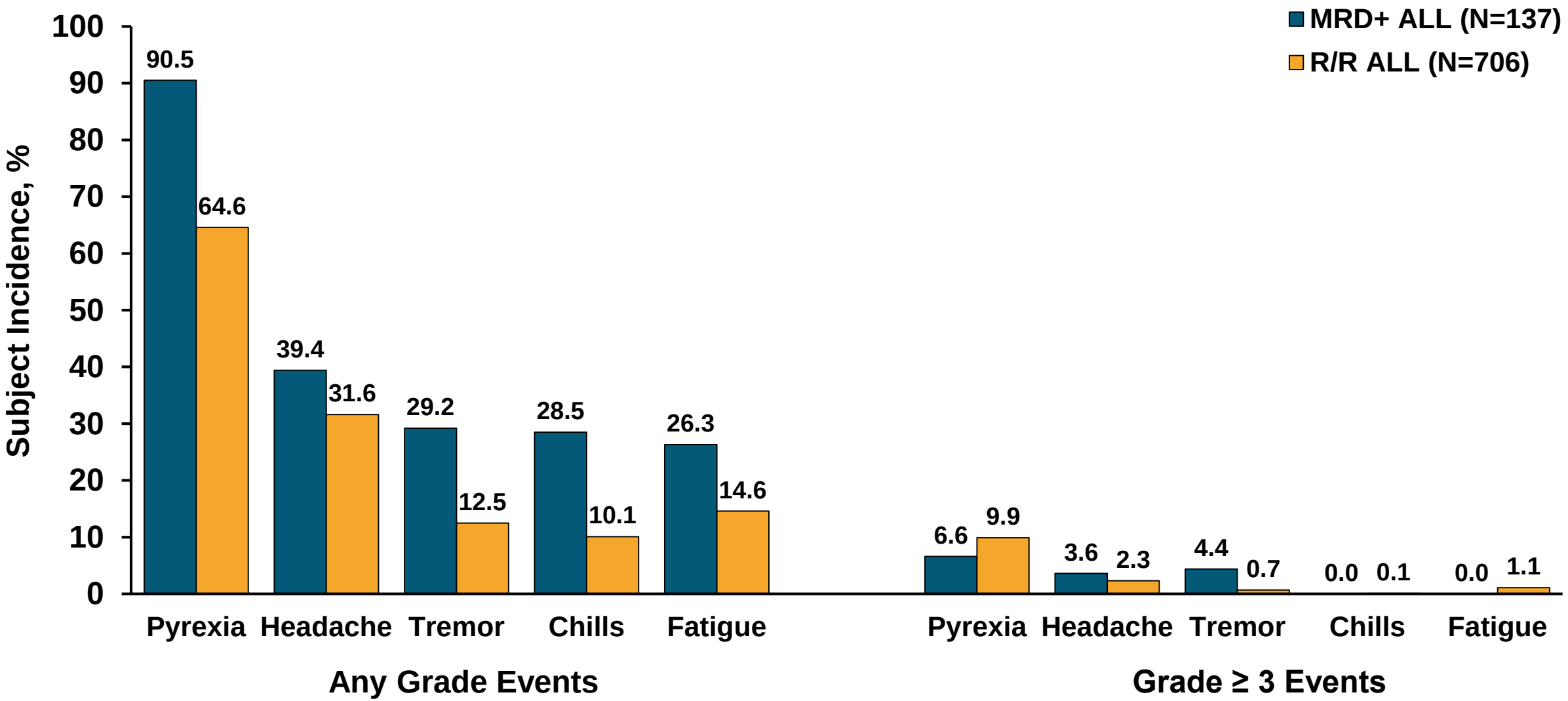
A single cycle of blinatumomab treatment consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval.

Summary of Adverse Events

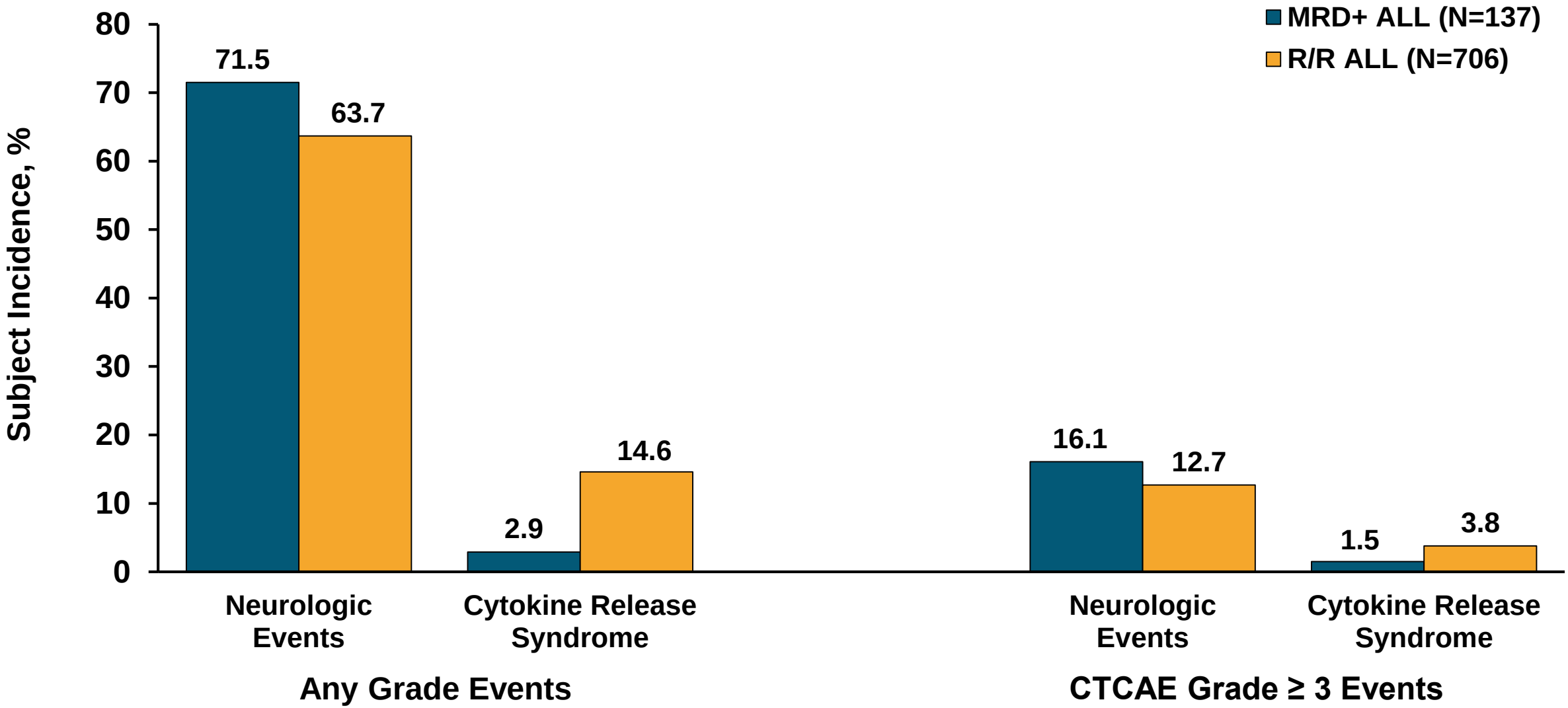
	Subject Incidence, %	
	MRD+ ALL N=137	R/R ALL N=706
All adverse events	100.0	99.2
Serious adverse events	60.6	61.5
Grade ≥ 3 adverse events	64.2	83.6
Fatal adverse events*	1.5	15.7
Adverse events leading to permanent discontinuation	16.8	14.0

*Within 30 days of blinatumomab treatment.

Common Adverse Events (≥ 25% in MRD+ ALL)



Key Adverse Reactions



Neurologic Events (MRD+ ALL)

	MRD+ ALL N=137	
	Any Grade Event	Grade ≥ 3 Event
Incidence	71.5%	16.1%
Time to onset, median	2.0 days	4.0 days
Resolution	95.9%	100%
Duration, median	10.0 days	4.0 days

- Most common events (≥ 10%): headache, tremor, insomnia, aphasia, and dizziness
- No fatal neurologic events

Cytokine Release Syndrome (MRD+ ALL)

	MRD+ ALL N=137
Overall incidence, n (%)	4 (2.9%)
CTCAE grade ≥ 3 events, n (%)	2 (1.5%)
Fatal events	0%
Time to onset, median	2.0 days
Resolution	100%
Duration	< 1 day to 2 days

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

Introduction	**Kathy Kross, MSc** *Executive Director – Global Regulatory Affairs*
Overview of MRD+ ALL & Unmet Medical Need	**Jerald Radich, MD** *Fred Hutchinson Cancer Center*
Clinical Efficacy & Safety	**Janet Franklin, MD, MPH** *Executive Medical Director – Global Development Lead for BLINCYTO*
Benefit-Risk	**Gregory Friberg, MD** *Vice President – Oncology Global Development*
Clinician's Perspective	**Aaron Logan, MD, PhD** *Division of Hematology/Oncology, UCSF*

Benefit-Risk

Gregory Friberg, MD

VP Global Development, Oncology

Amgen Inc

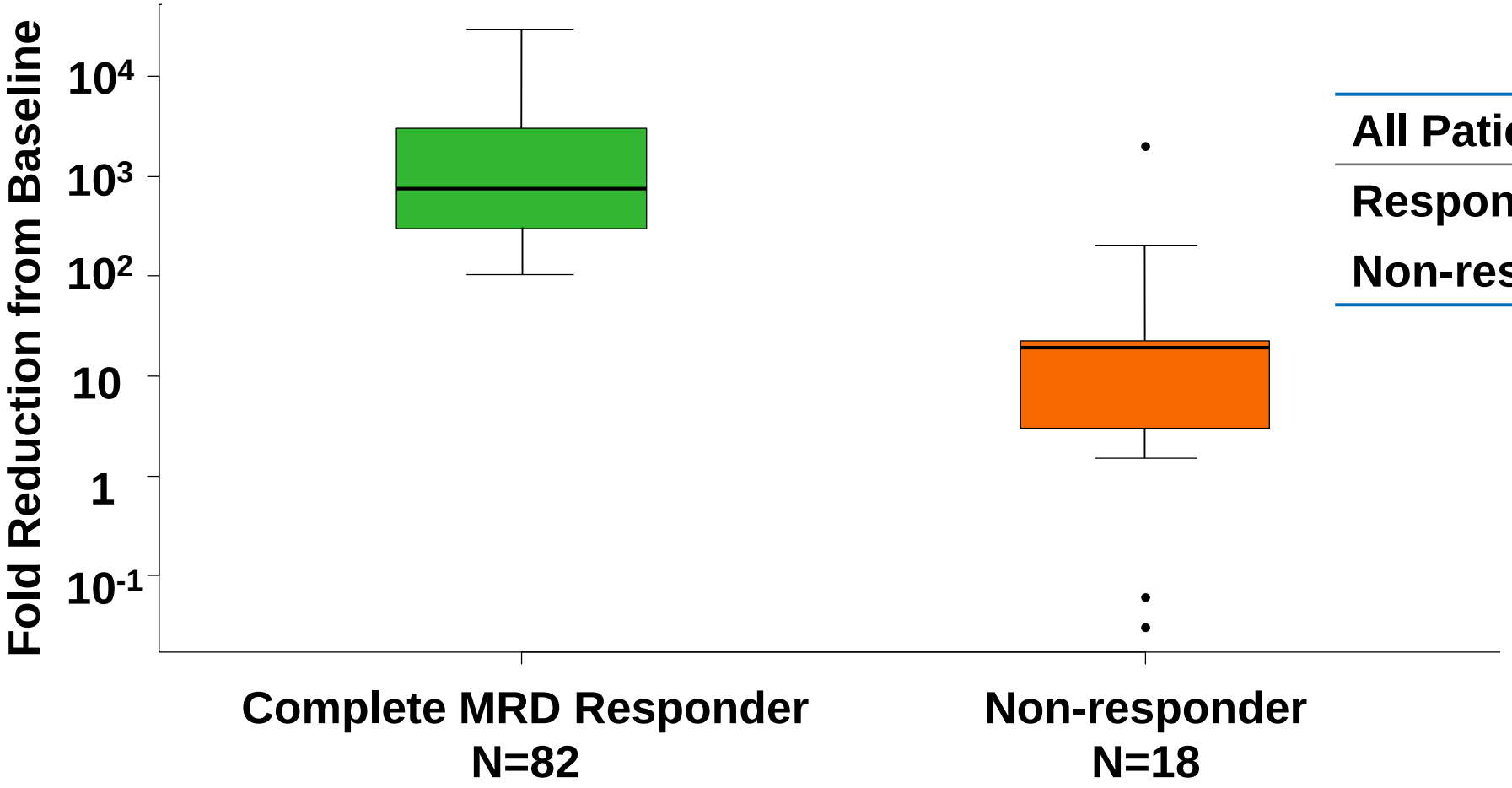
Hematologic Complete Remission is No Longer the Best Measure of a Full Remission

- **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



	Median Reduction
All Patients	550-fold
Responders	750-fold
Non-responders	20-fold

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**

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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**

Cycle	Started Cycle n (%)
1	116 (100)
2	75 (65)
3	33 (28)
4	20 (17)

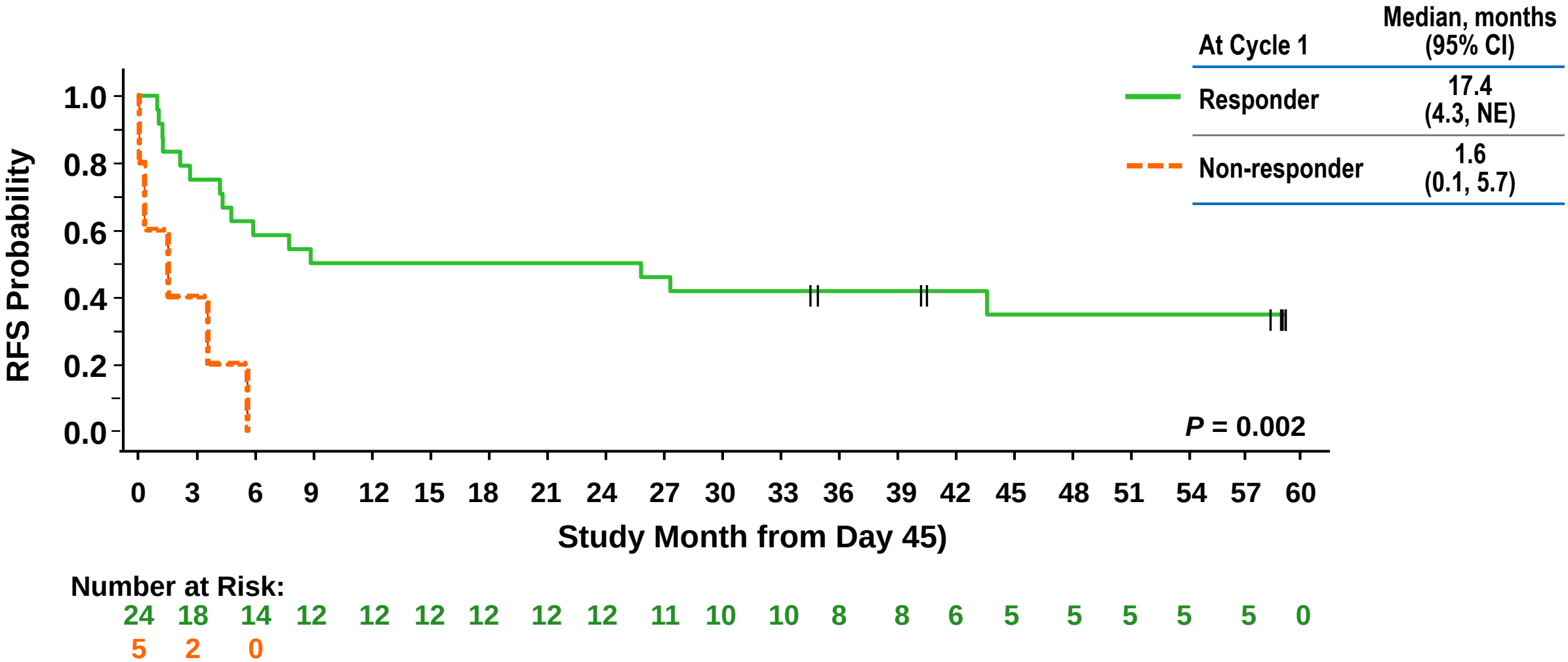
Study 203: Responders by Number of Cycles Received

- 2 patients achieved complete MRD response after 2 cycles of blinatumomab

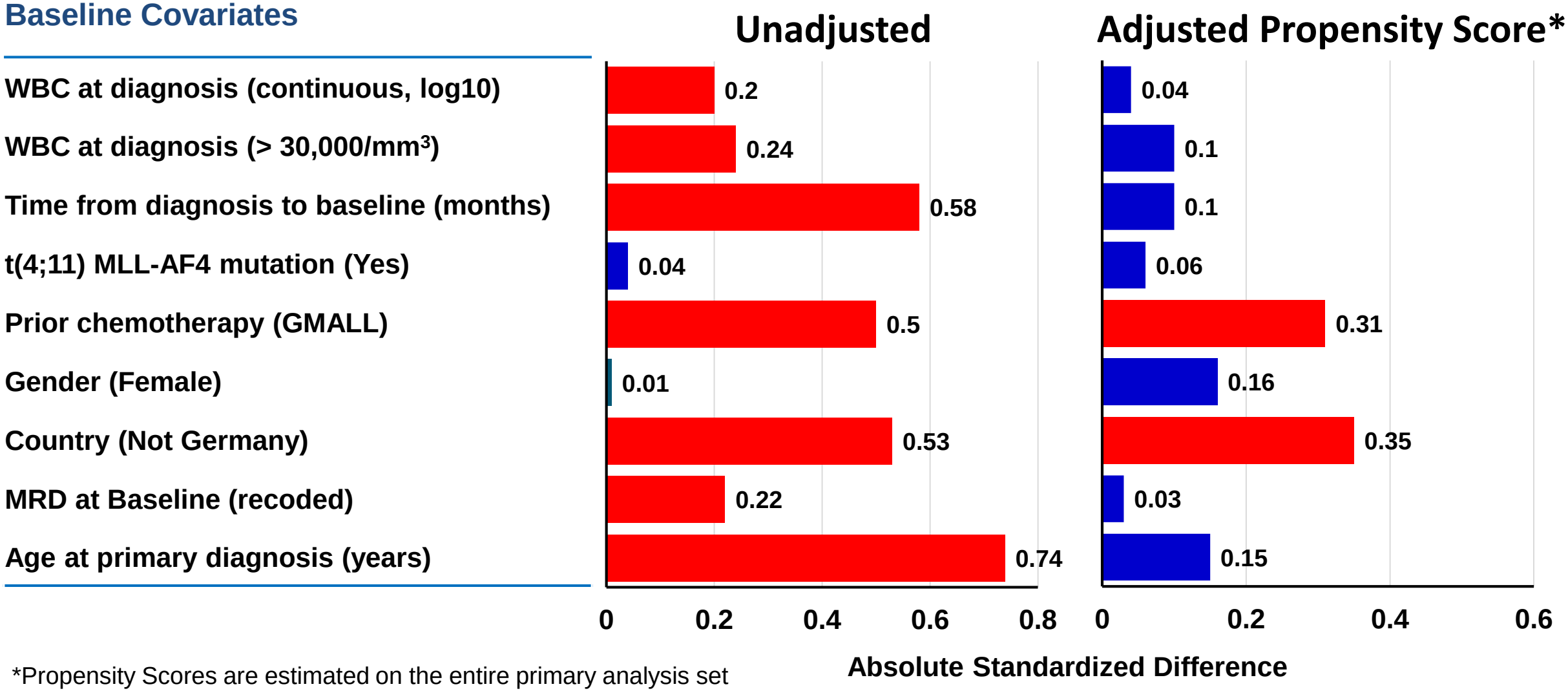
Prim EP FAS N=113		Additional Responders		
	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Complete MRD Responder, n(%)	88 (77.9)	2 (1.8)	0	0

Study 203: RFS in non-HSCT Patients

Stratified by MRD Response (Landmark Analysis at Day 45)

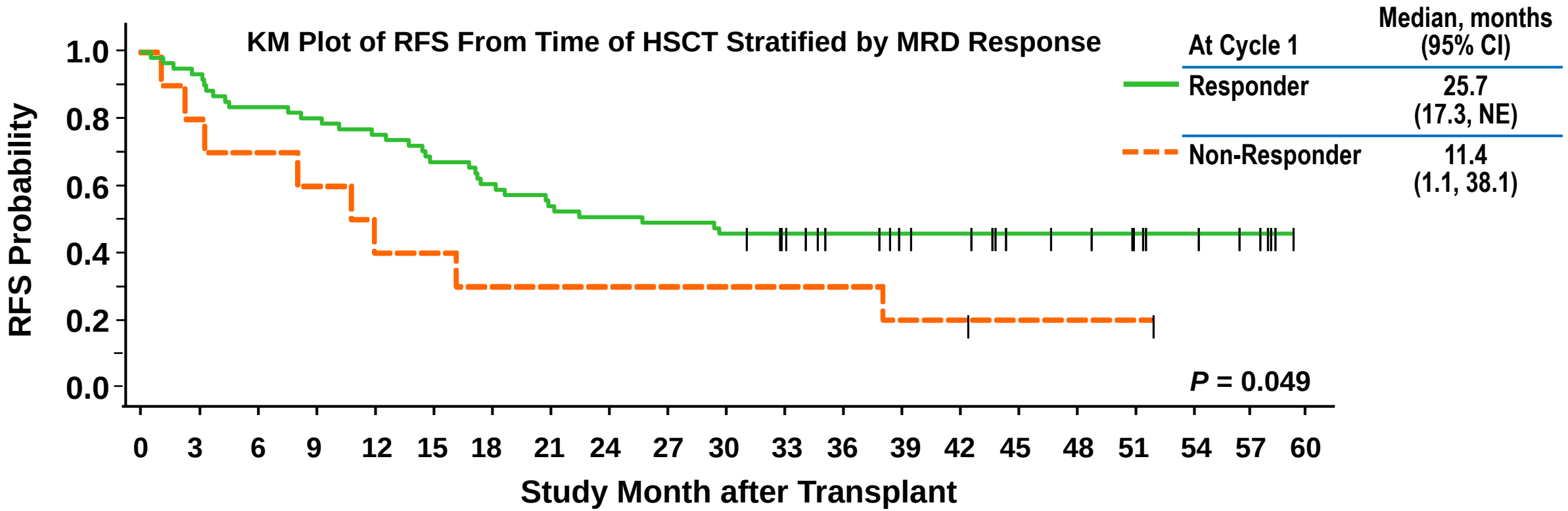


Baseline Covariate Balance in Blinatumomab vs. Control Before and After Adjustment Among HSCT Subjects



*Propensity Scores are estimated on the entire primary analysis set

Study 203: Pre-Transplant MRD Status Affects RFS

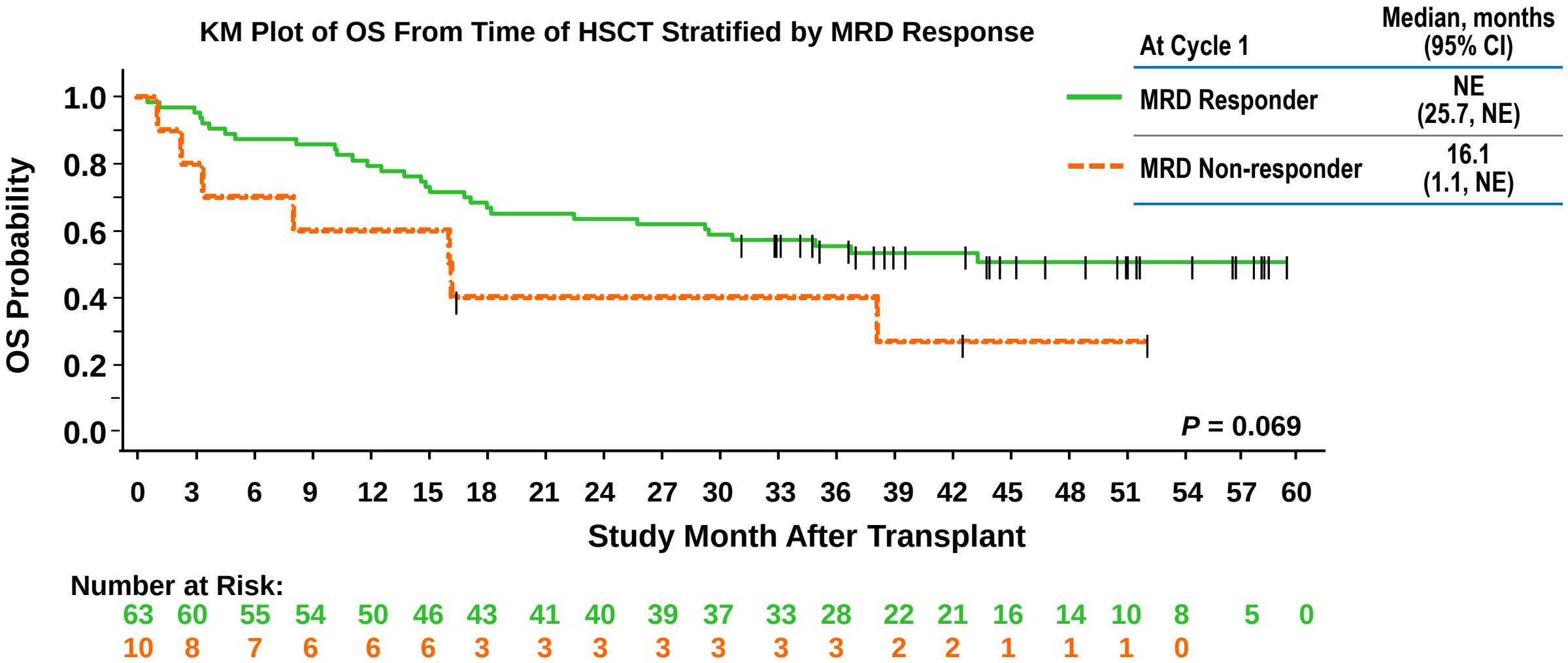


Number at Risk:

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	3	2	2	1	1	1	0		

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

Study 203: Pre-Transplant MRD Status Affects OS



At Cycle 1	Median, months (95% CI)
MRD Responder	NE (25.7, NE)
MRD Non-responder	16.1 (1.1, NE)

Study 203: HSCT Treatment-Related Mortality

- **100-day HSCT treatment-related mortality rate: 7.9% (6/76 patients)**
  - Below published rate of 28%[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%[b] and 32% to 54%[c]

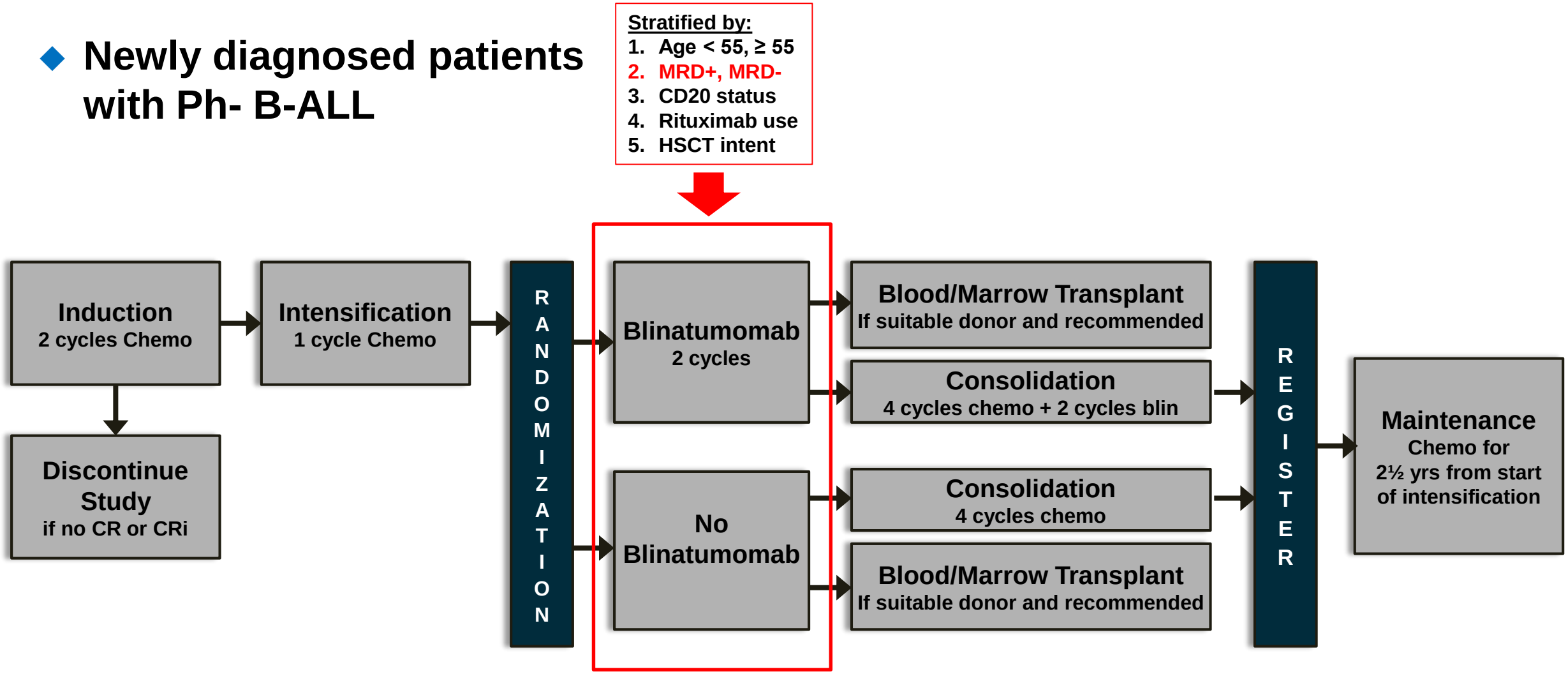
a. Bishop et al, 2008
b. Wingard et al, 2011; Bishop et al, 2008.
c. Bassan and Hoelzer, 2011.

Study 203: HSCT Treatment-Related Mortality Summary

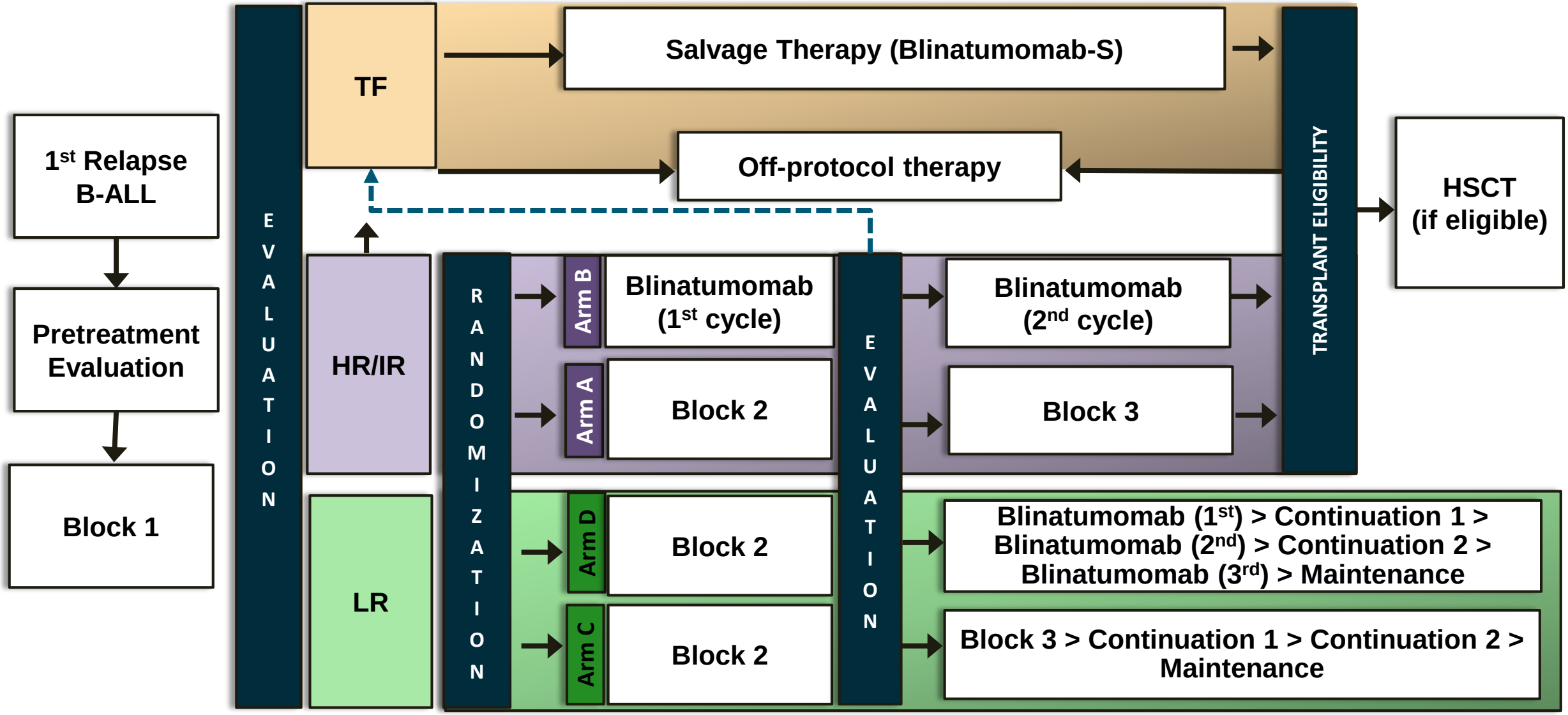
- **Cause of death for the 21 patients who died without documented relapse following HSCT:**
  - Infection (primarily sepsis and pneumonia) = 13
  - Digestive hemorrhage = 1
  - Subacute cerebral injury = 1
  - “Features to suggest VOD” = 1
  - Acute respiratory distress syndrome = 1
  - Probable heart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

ECOG1910 – Study Schema

- **Newly diagnosed patients with Ph- B-ALL**

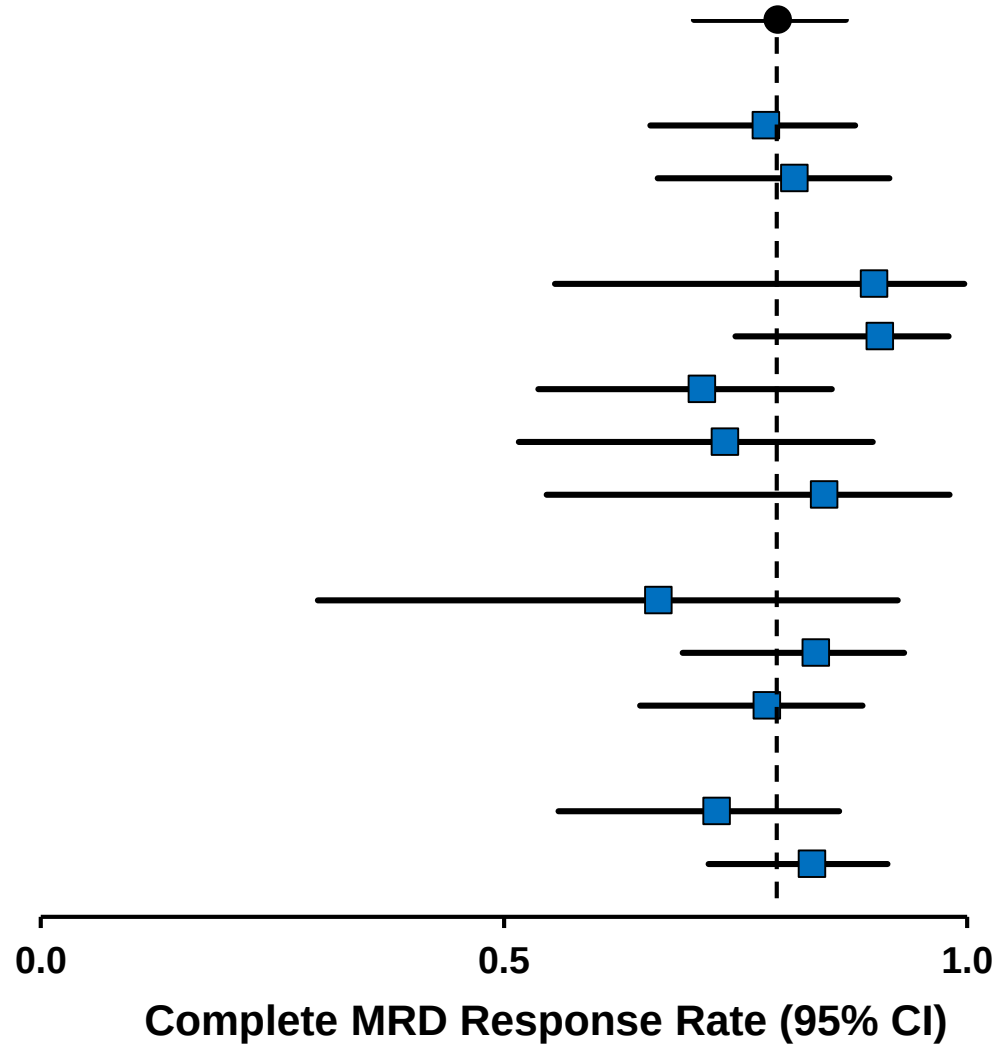


COGAALL1331 – Study Schema



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

Primary EP Efficacy Set	n/N	%	(95% Exact CI)
Overall	82/103	79.6	(70.5, 86.9)
Gender			
Male	47/60	78.3	(65.8, 87.9)
Female	35/43	81.4	(66.6, 91.6)
Age			
18 to < 22	9/10	90.0	(55.5, 99.7)
22 to < 35	20/22	90.9	(70.8, 98.9)
35 to < 55	23/35	71.4	(53.7, 85.4)
55 to < 65	17/23	73.9	(51.6, 89.8)
≥ 65	11/13	84.6	(54.6, 98.1)
MRD Level at Baseline			
10^{-1} to < 1	6/9	66.7	(29.9, 92.5)
10^{-2} to < 10^{-1}	36/43	83.7	(69.3, 93.2)
10^{-3} to < 10^{-2}	40/51	78.4	(64.7, 88.7)
Remission Status			
CR 2/3	27/37	73.0	(55.9, 86.2)
CR 1	55/66	83.3	(72.1, 91.4)



Study 203: OS in non-HSCT Patients

Stratified by MRD Response (Landmark Analysis at Day 45)