# AIEOP-BFM ALL 2017

## International investigator-initiated inter-group multi-center open-label randomized clinical trial (Phase III)

**Trial Steering Committee (composed by National Coordinators):**
A. Biondi (AIEOP), J. Starý (CPH), S. Elitzur (INS), A. Kolenova (SPHOS), A. Attarbaschi/ G. Mann (BFM-A), D. Barbaric (ANZCHOG), N. Bodmer/ F. Niggli (BFM-CH), M. Schrappe (BFM-G)

**Sponsor:**
University Medical Center Schleswig-Holstein (Kiel, Germany)

**EudraCT Number: 2016-001935-12**

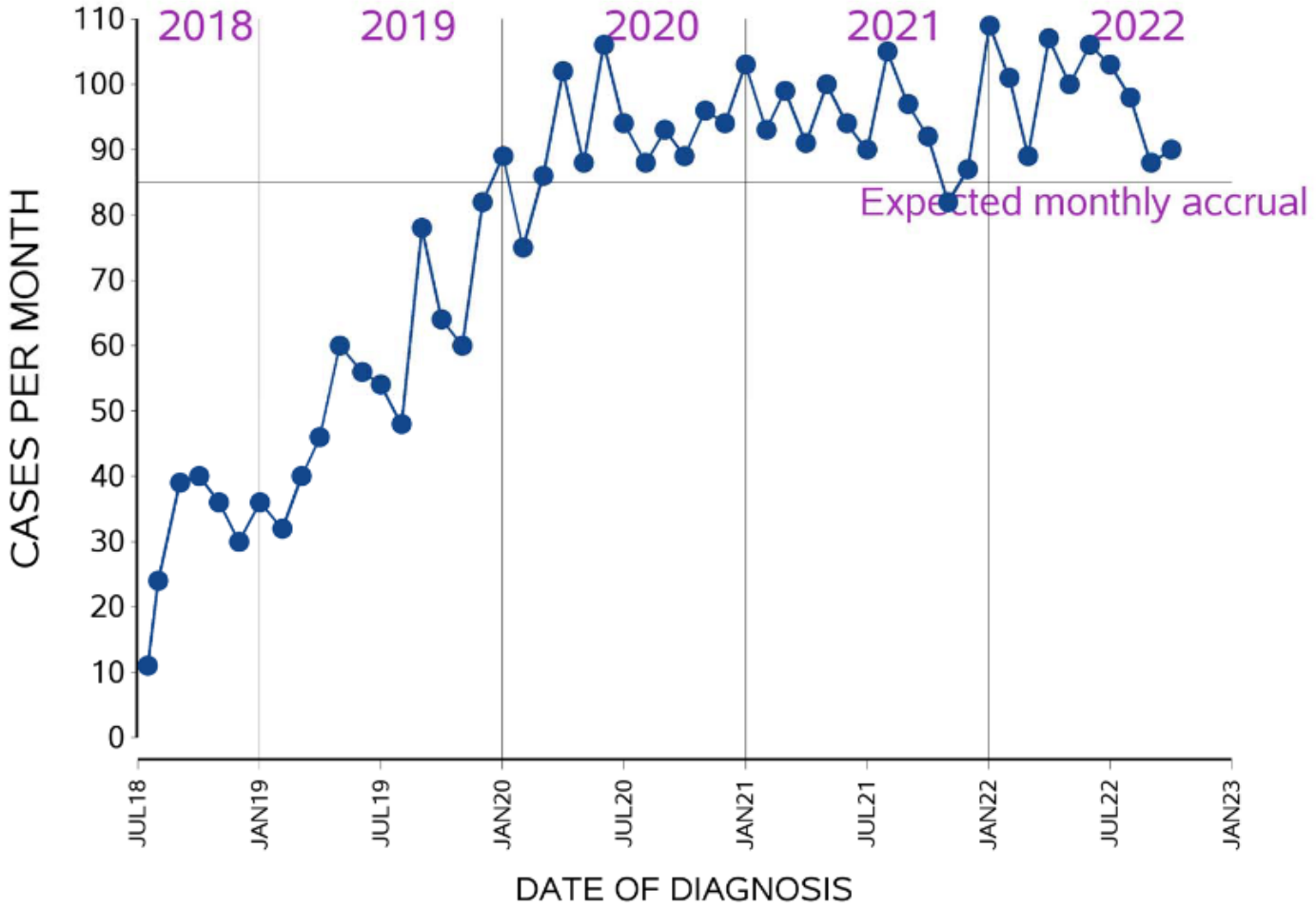
SC-AT-NP-00098 10.23

# AIEOP-BFM ALL 2017

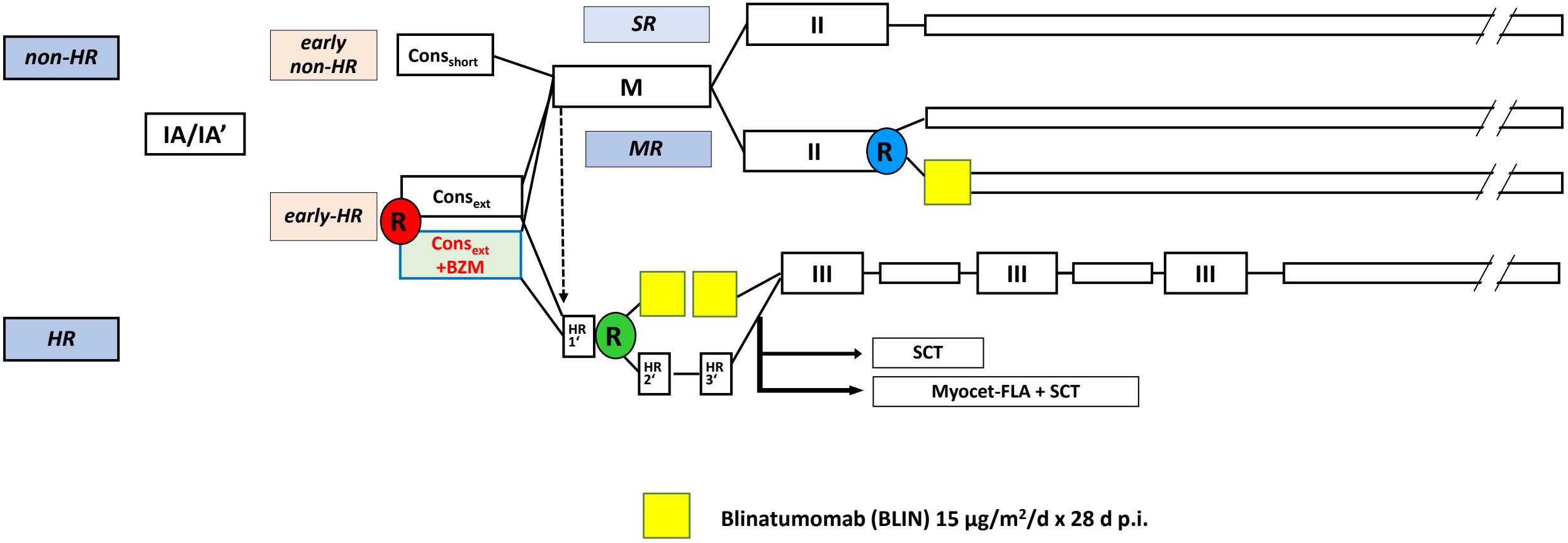
| | |
|---|---|
| **Participating countries (study groups)** | • Australia (part of ANZCHOG)<br>• Austria (BFM-A)<br>• Czech Republic (CPH)<br>• Germany (BFM-G)<br>• Israel (INS)<br>• Italy (AIEOP)<br>• Slovakia (SPHOS)<br>• Switzerland (BFM-CH) |
| **Planned recruitment**<br><br>**Start of enrollment**<br>**Patients enrolled for this report**<br>Closure of enrollment in B-ALL | 5 years, approx. 1000 new pts (per year)<br>all subtypes of ALL, 0-<18 yrs of age<br>7-15-2018<br>up to October 31, 2022<br>August 31, 2023 |

# Enrollment in trial AIEOP-BFM ALL 2017

(up to Oct. 31, 2022)



# AIEOP-BFM ALL 2017: Treatment overview and randomizations for B-ALL



# Risk stratification for B-ALL in trial AIEOP-BFM ALL 2017

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## High risk (HR)

- no complete remission on day 33 or
- positivity for *KMT2A::AFF1,* or
- positivity for *TCF3::HLF1,* or
- hypodiploidy <45 chromosomes, or
- FCM-MRD in BM on day 15 ≥ 10% and not *ETV6::RUNX1* positive, or
- *IKZF1*$^{plus}$ and PCR-MRD at TP1 positive or inconclusive, and not positive for *ETV6::RUNX1*, *TCF3::PBX1* or *KMT2A* rearr. other than *KMT2A::AFF1,* or
- PCR-MRD at TP1 ≥ $5x10^{-4}$ and positive < $5x10^{-4}$ at TP2 (PCR-MRD SER), or
- PCR-MRD at TP2 ≥ $5x10^{-4}$, or
- age < 1 year and any *KMT2A* rearrangement

## Medium risk (MR)

- no HR criteria and no SR criteria

## Standard risk (SR)

- no HR criteria *and*
- PCR-MRD at TP1 negative for all investigated markers with at least one marker with a quantitative range of ≤ $10^{-4}$ or
- inconclusive PCR-MRD result at TP1 and PCR-MRD not positive at TP2 and FCM-MRD in BM d15 < 0.1%

## Combined use of FCM-based and ASO-PCR-based MRD-detection

(FCM: Flow cytometry; ASO RQ-PCR: allele-specific oligonucleotide real-time quantitative PCR)

# Randomization in HR:

Experimental arm (EA): 2 courses of Blinatumomab (28-d continuous infusion) vs. Control arm (CA): 2 courses of chemotherapy (blocks HR-2 and HR-3)

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## Primary study question

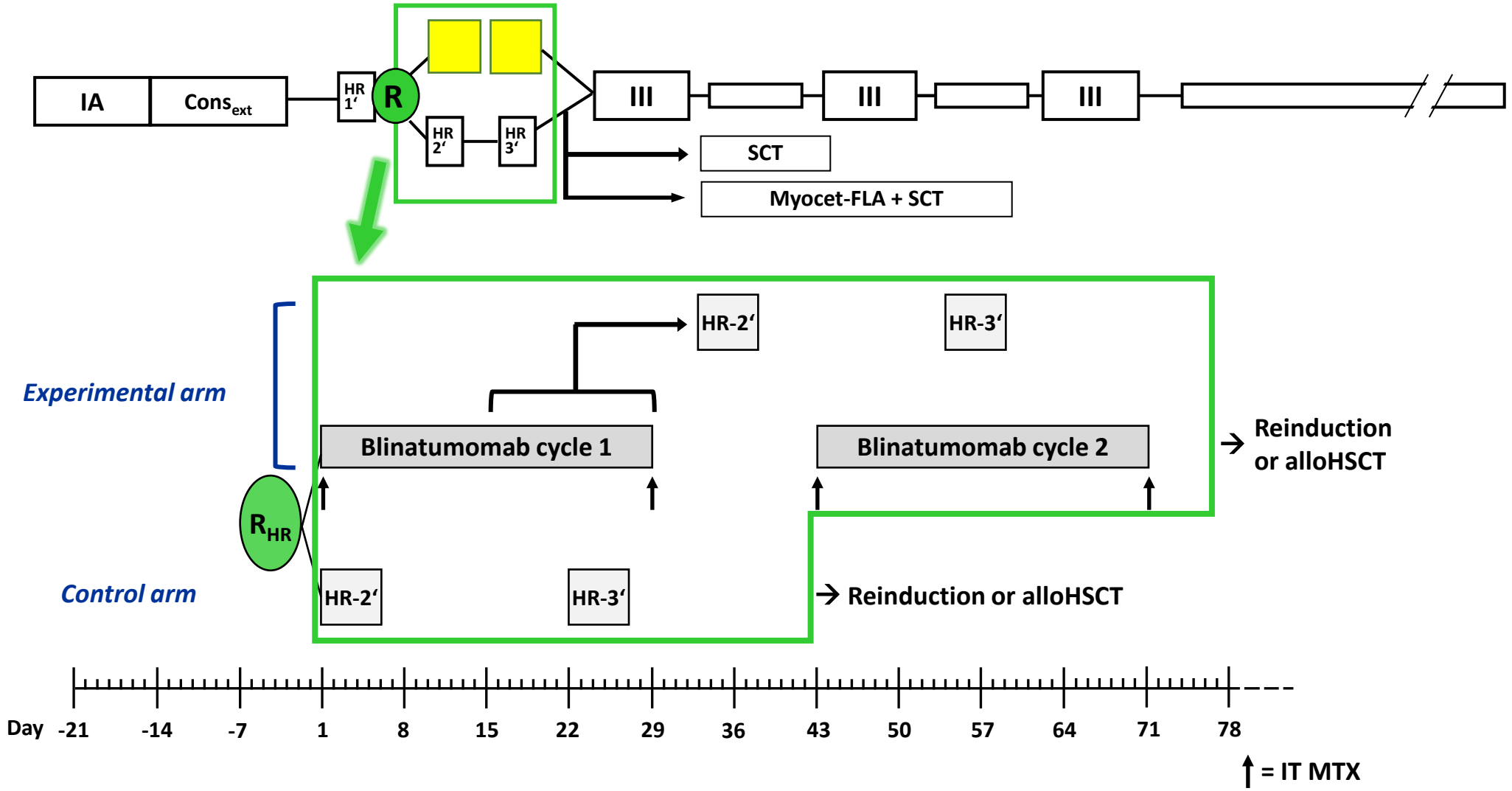
- Can the pEFS from time of randomization be improved by replacing two conventional highly intensive chemotherapy courses by two cycles of post-consolidation immunotherapy with Blinatumomab (15 µg/m²/d for 28 days per cycle) plus 4 doses intrathecal Methotrexate?

## Secondary study questions

- Can treatment-related life-threatening complications and mortality during the intensified consolidation phase of high-risk treatment be reduced when replacing two intensive chemotherapy courses by two cycles of immunotherapy with Blinatumomab?
- What is the proportion of patients with insufficient MRD response to Blinatumomab as defined in the protocol as compared to the MRD response after the HR-2' block in the control arm?

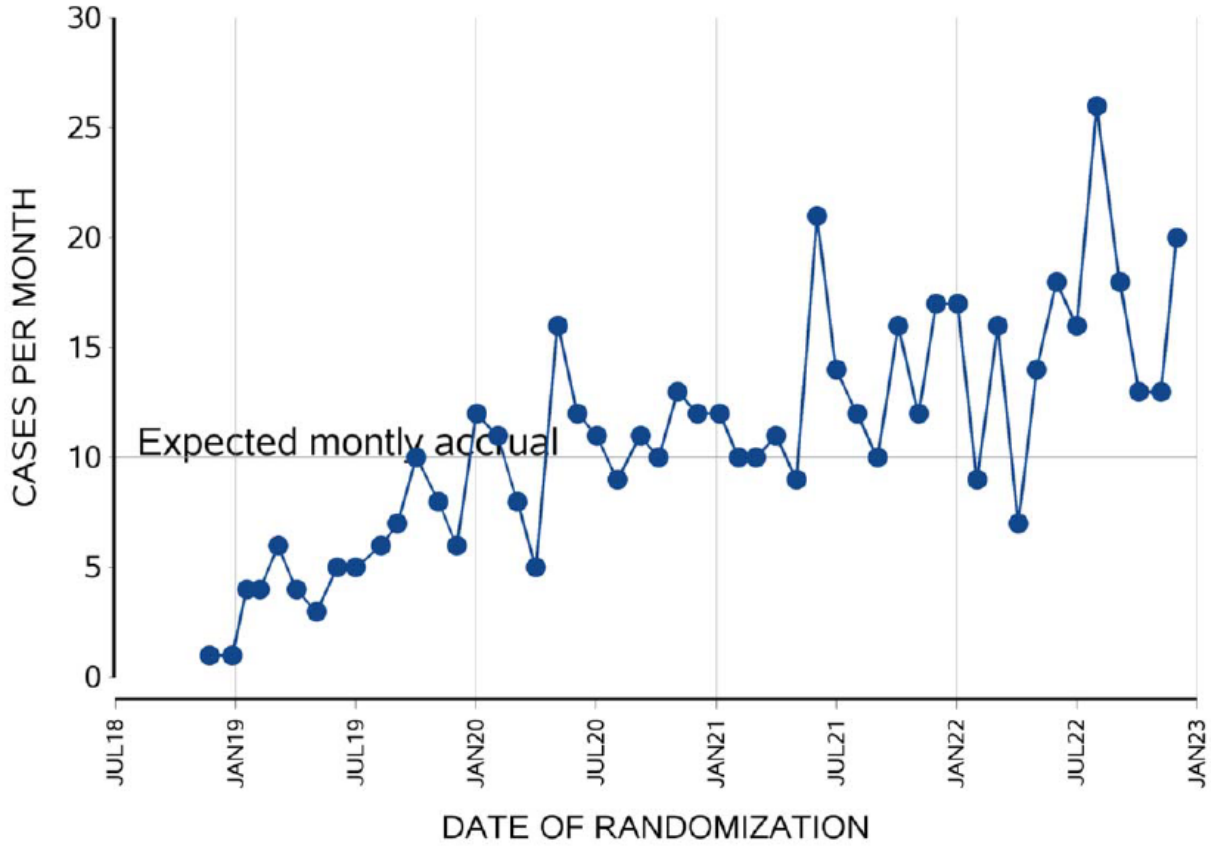
# AIEOP-BFM ALL 2017: Randomization R-HR (B-ALL)

## 2 cycles Blinatumomab or courses HR-2' + HR-3'



# AIEOP-BFM ALL 2017: Randomization in **HR-B-ALL (R-HR)**

## Enrollment



# Patients and methods (1)

- 728 pts with HR B-ALL enrolled from July 15, 2018 to October 31, 2022 *
- 619 pts were eligible for randomization
- **572 pts were randomized** (92.4% of those eligible)
- Reasons for non-eligibility were:
  - Event (death or relapse) before randomization was due (26),
  - Down syndrome (25; scheduled for a non-randomized intervention with BLIN),
  - presence of *TCF3::HLF* (3; could receive any alternative therapy including BLIN),
  - discontinuation/substantial change of preceding therapy (23) or
  - other protocol exclusion criteria (32).
- One pt assigned to the experimental arm (EA) and 4 pts assigned to the control arm (CA) received the other arms, respectively.

* Data frozen in May 2023

# Patients and methods (2)

- For this report on randomization of Blinatumomab (BLIN) vs intensive chemotherapy (HR-2, HR-3), **medically relevant adverse reactions of special interest (ARSI)** were analyzed (intent-to-treat analysis)
- +/- life-threatening ARSI
- Only events during the randomized treatment phase were analyzed (before the next treatment element was started)

# Results in R-HR: overview

| | All ARSI | | | | | Life-threatening ARSI | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control (HR-2, HR-3) | | Experimental (BLIN cycles 1+2) | | P (Fisher exact test) | Control (HR-2, HR-3) | | Experimental (BLIN cycles 1+2) | | P (Fisher exact test) |
| | N | %* | N | %* | | N | %* | N | %* | |
| N of pts with ARSI | 61 | 22.8 | 29 | 10.3 | <0.001 | 14 | 5.2 | 0 | 0 | <0.001 |
| N of ARSI | 71 | 26.5 | 33# | 11.7 | | 15 | 5.6 | 0 | 0 | |

* related to 268 pts in control arm, and 281 pts in experimental arm

NOTE: 16 pts switched in/after the first BLIN cycle to the HR blocks due to toxicity or poor response to BLIN

# 3 of the 33 ARSI in the EA were related to HR blocks (observed in 3 of the 16 pts that switched to HR blocks).

# Results in R-HR (1)

| | All ARSI | | | | Life-threatening ARSI | | | |
|---|---|---|---|---|---|---|---|---|
| | Control (HR-2, HR-3) | | Experimental (BLIN cycles 1+2) | | Control (HR-2, HR-3) | | Experimental (BLIN cycles 1+2) | |
| | N | % * | N | % * | N | % * | N | % * |
| Infections | 20 § | 7.5 | 1 | 0.4 | 9 | 3.4 | 0 | 0 |
| Immune system disorders | 27 | 10.1 | 7 # | 2.5 | 3 | 1.1 | 0 | 0 |

*related to 268 pts in control arm, and 281 pts in experimental arm

§ bacterial infections most frequent but also some fungal infections (n=3), and some without clear data on origin

# Cytokine release syndrom (CRS) ≥ grade 2 in 5 pts;
allergic reactions to asparaginase in 2 pts after having been switched to CA

# Results in R-HR (2)

| | All ARSI | | | | Life-threatening ARSI | | | |
|---|---|---|---|---|---|---|---|---|
| | Control (HR-2, HR-3) | | Experimental (BLIN cycles 1+2) | | Control (HR-2, HR-3) | | Experimental (BLIN cycles 1+2) | |
| | N | %* | N | %* | N | %* | N | %* |
| Nervous system disorders | 6 # | 2.2 | 21 # | 7.5 | 1 | 0.4 | 0 | 0 |
| Gastrointestinal disorders | 6 § | 2.2 | 0 | 0 | 1 | 0.4 | 0 | 0 |
| Hepato-biliary disorders | 2 | 0.7 | 0 | 0 | 1 | 0.4 | 0 | 0 |

# 2 in CA, and 17 in EA were seizures grade 2 or 3

§ 5 out of 6 were diagnosed with acute pancreatitis

*related to 268 pts in control arm, and 281 pts in experimental arm

# Conclusions

- This first randomized trial in newly diagnosed pts with HR B ALL confirms the favorable toxicity profile previously reported with Blinatumomab in pediatric patients with 1st relapse (Locatelli F et al, JAMA 2021; Brown P et al, JAMA 2021; Hogan LE et al, J Clin Oncol 2022).
- If upcoming analyses of outcome data in trial AIEOP-BFM ALL 2017 will not show any inferiority of the EA in terms of anti-leukemia efficacy, blinatumomab replacement of some of the intensive chemotherapy blocks will become the new standard of care for treatment in newly diagnosed patients with HR B-ALL.

# Acknowledgments
# Trial AIEOP-BFM ALL 2017


**Dept. of Pediatrics, University Medical Center Schleswig-Holstein, Campus Kiel**
Anja Möricke, Julia Alten, Lile Bauer, Lennart Lenk, Jana Brazdova, Saskia Sonnenberg, Simon Vieth, Gunnar Cario

**Dept. of Pediatric Hematology/ Oncology, Medical School Hannover**
Martin Stanulla
Christian Kratz

**Reference Laboratories**
Giuseppe Basso †, Giovanni Cazzaniga, Giuseppe Gaipa, Michael Dworzak, Jan Trka, Monika Brüggemann, Matthias Ritgen, Brigitte Schlegelberger, Oskar Haas, Anke Bergmann, Doris Steinemann, Wolf-Dieter Ludwig, Beat Schäfer, Joelle Tchinda, Shai Izraeli, Renate Panzer-Grümayer, Rolf Köhler, Stefan Koehrer, Claus R. Bartram

**AIEOP-BFM Trial Steering Committee**
Andrea Biondi, Georg Mann/Andishe Attarbaschi, Jan Stary, Felix Niggli/Nicole Bodmer, Sara Elitzur, Draga Barbaric, Alexandra Kolenova, Martin Schrappe

**Task Force**
Franco Locatelli, Andishe Attarbaschi, Arend Stackelberg, Birgit Burkhardt, Rita Beier, Anja Möricke, Gunnar Cario, Valentino Conter, Luciano dalla Pozza, Carmelo Rizzari, Claudia Rössig, Jean-Pierre Bourquin

**AMGEN:**
Gerhard Zugmaier

**Statistical analysis**
Maria Grazia Valsecchi, Michaela Vossen-Gajcy, Daniela Silvestri, Martin Zimmermann

ALL-SCT-BFM and PedFORUM team: Christina Peters

**National ALL 2009 & 2017 Study Committees**

**Participating centers**