Comprehensive Cancer Center
Tübingen-Stuttgart

# Post ASH 2024 San Diego

## Akute lymphatische Leukämie

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# GMALL Trial 08/2013. Chemotherapy or SCT


Nicola Gökbuget. 961 Chemotherapy or Stem Cell Transplantation in Adult High Risk Ph/BCR::ABL1-Negative ALL Patients with Early MRD Negativity: Results of the Randomized GMALL Trial 08/2013.

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## Chemotherapy or Stem Cell Transplantation in Adult High Risk Ph/BCR::ABL1-Negative ALL Patients with Early MRD Negativity: Results of the Randomized GMALL Trial 08/2013

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GMALL German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

FRANKFURT CANCER INSTITUTE

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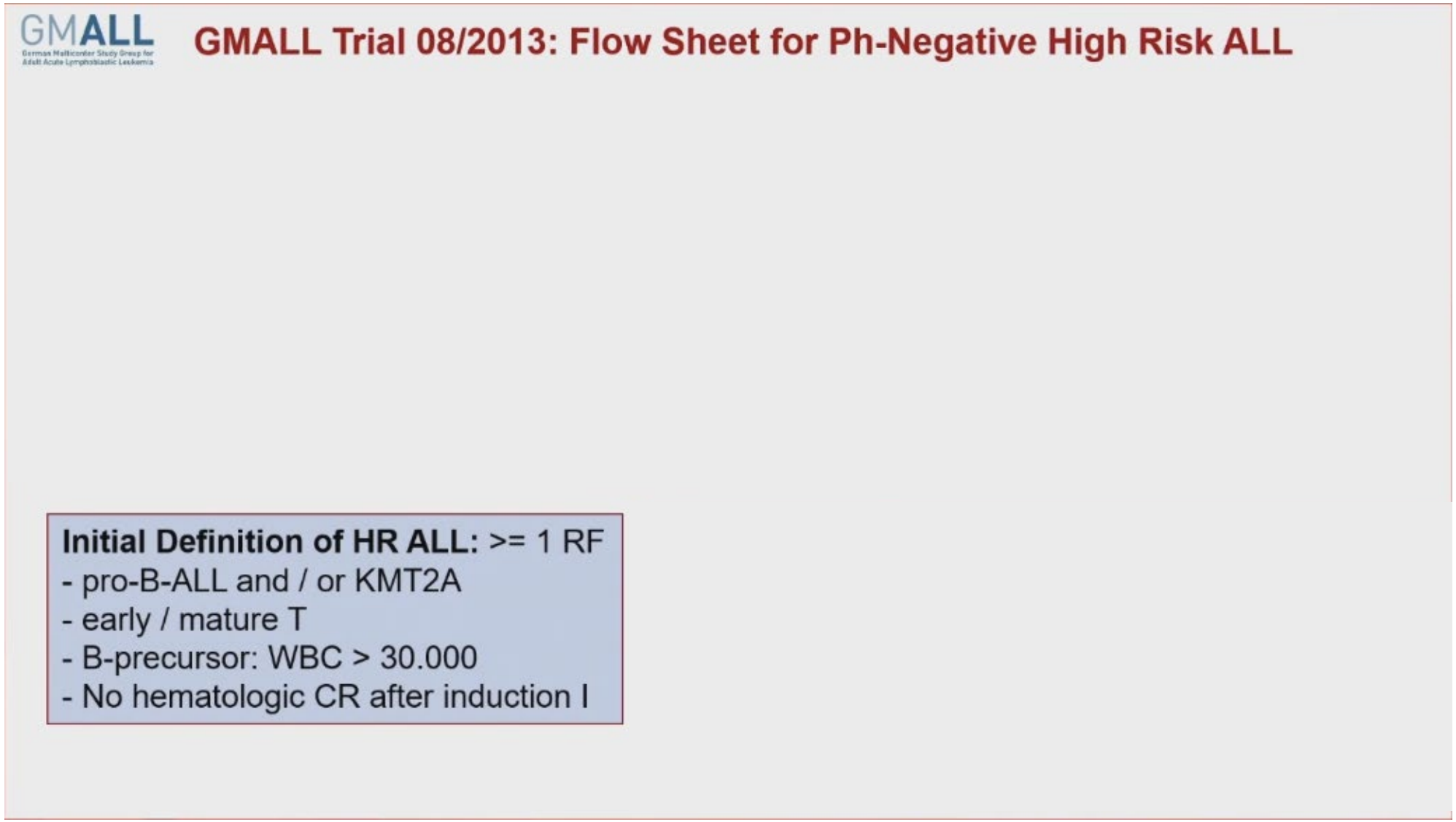


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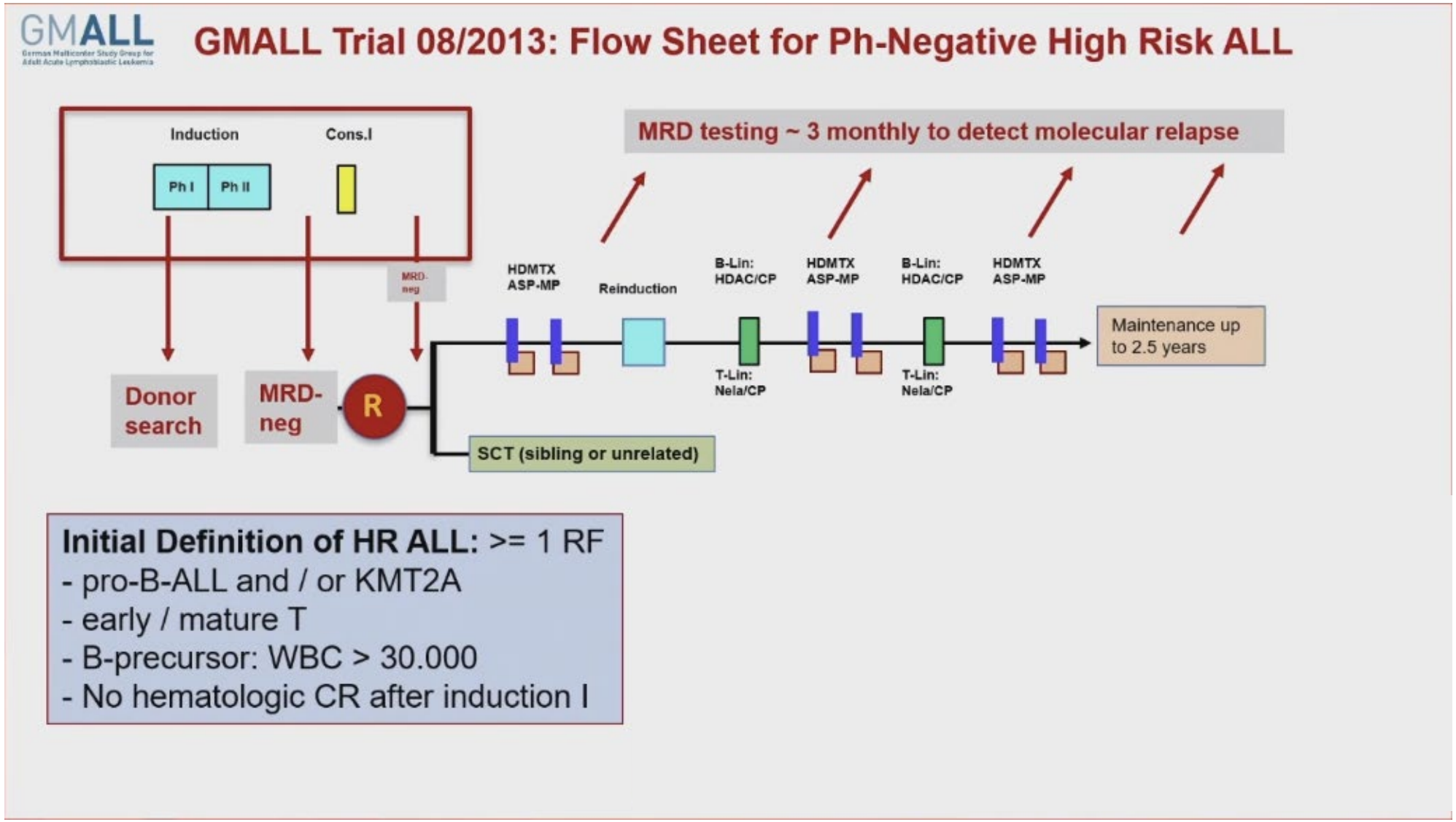


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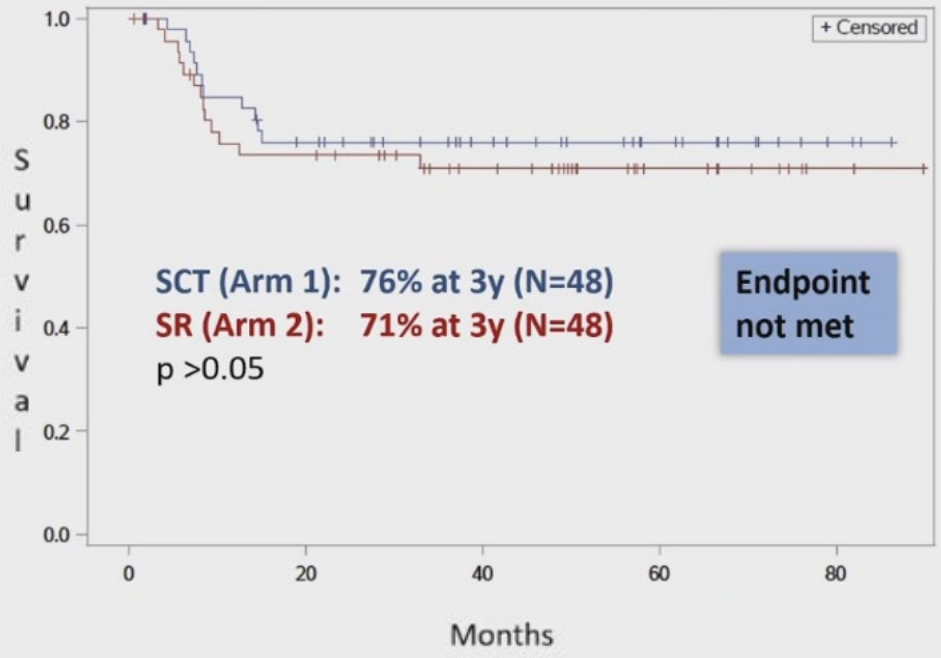
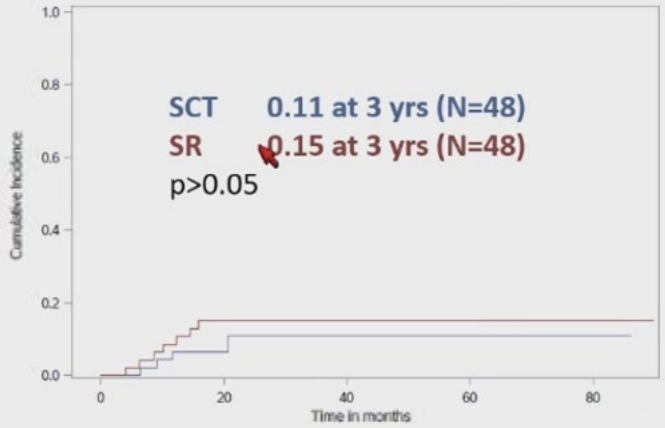
## GMALL 08: Outcome of HR ALL According to Randomisation II

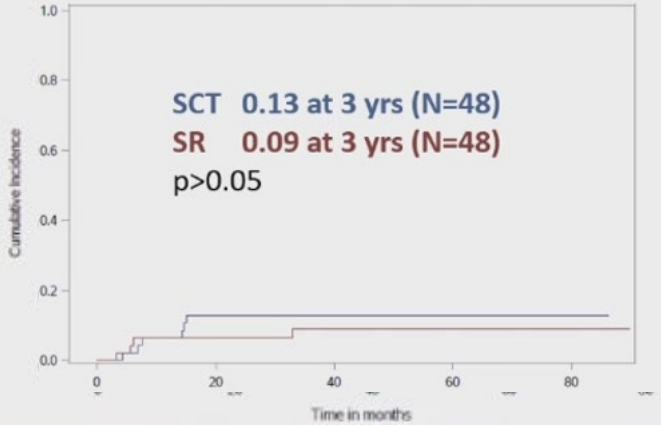
### Disease Free Survival




### Hematologic Relapse Risk




### Treatment-Related Mortality

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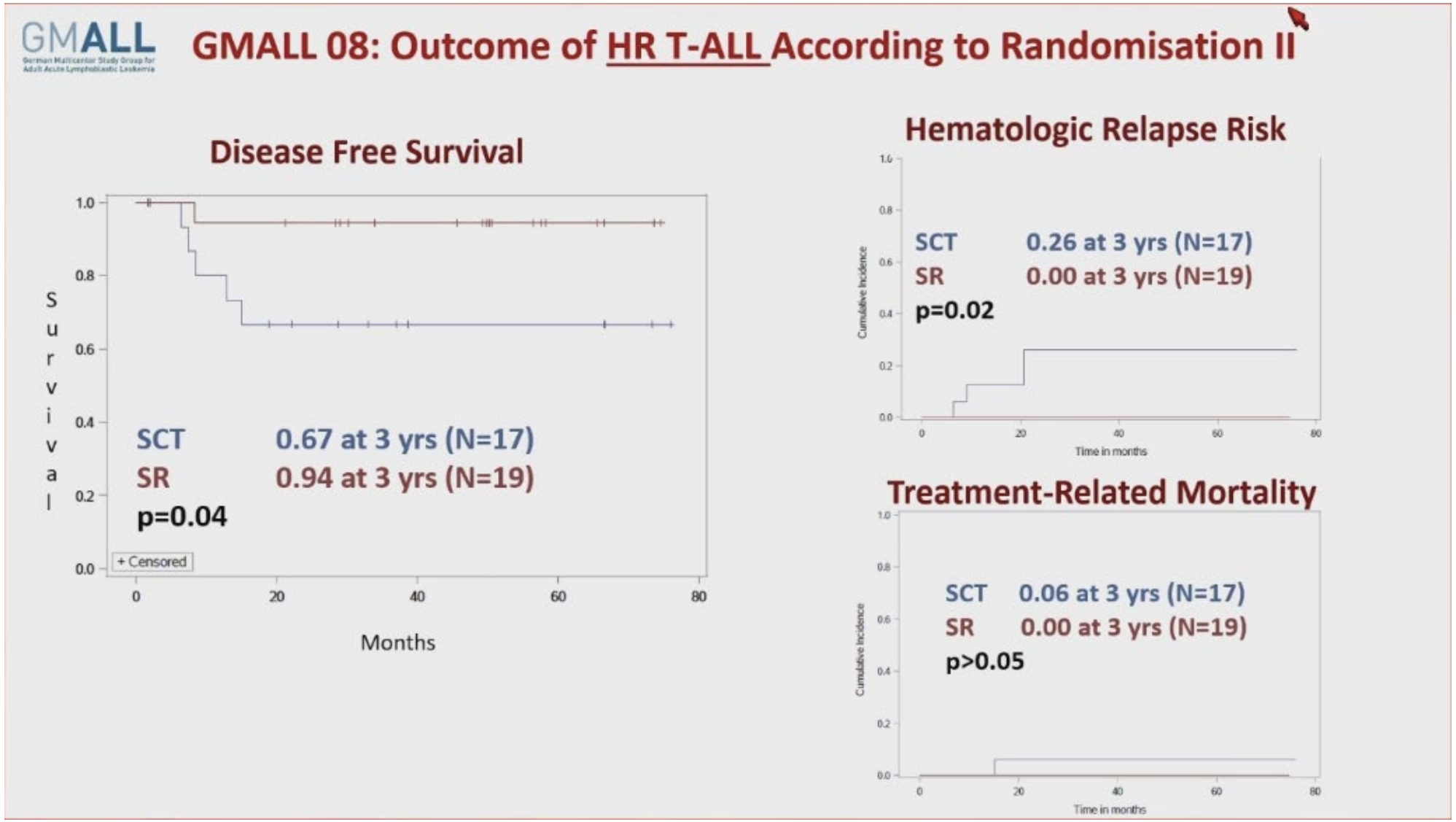


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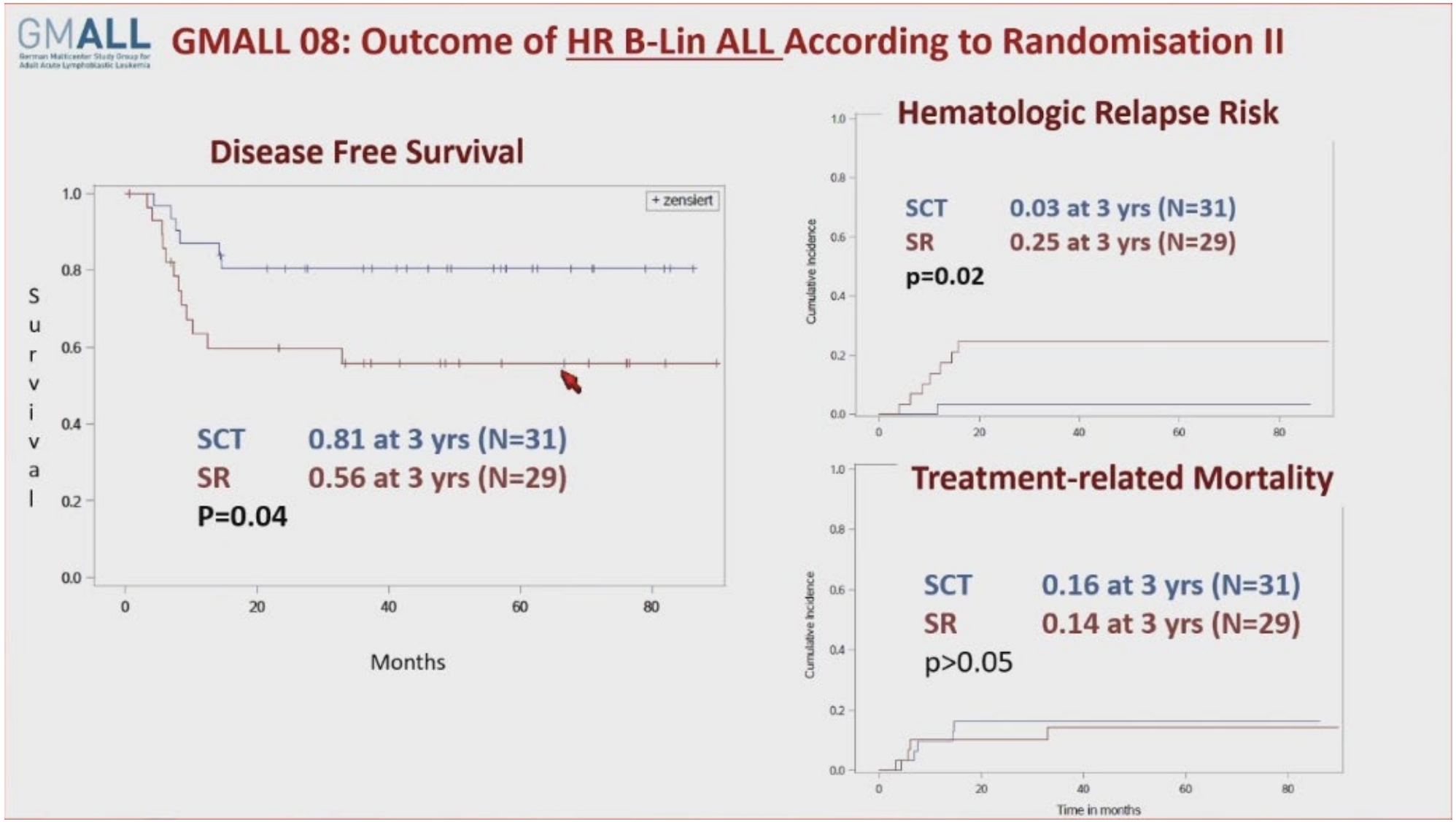


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## GMALL 08: Outcome of Molecular and Hematologic Relapse after Randomization II

**Alive: 2/14**

| B-precursor (N=9) | | T-ALL (N=5) | |
|---|---|---|---|
| **Mol Relapse** | **7** | **MolRelapse** | **4** |
| SR Therapy (N=6) | | SR Therapy (N=1) | |
| - Cyt relapsed/died: | 5 | SCT/alive: | 1 |
| - SCT/alive: | 1 | | |
| SCT (N=1) | | SCT (N=3) | |
| Cyt relapsed/died: | 1 | Cyt relapsed/died: | 3 |
| **Direct Cyt Relapse:** | **2** | **Direct Cyt Relapse** | **1** |
| SR Therapy (N=2) | | SCT (N=1) | 1 |
| Died: | 2 | Died: | 1 |

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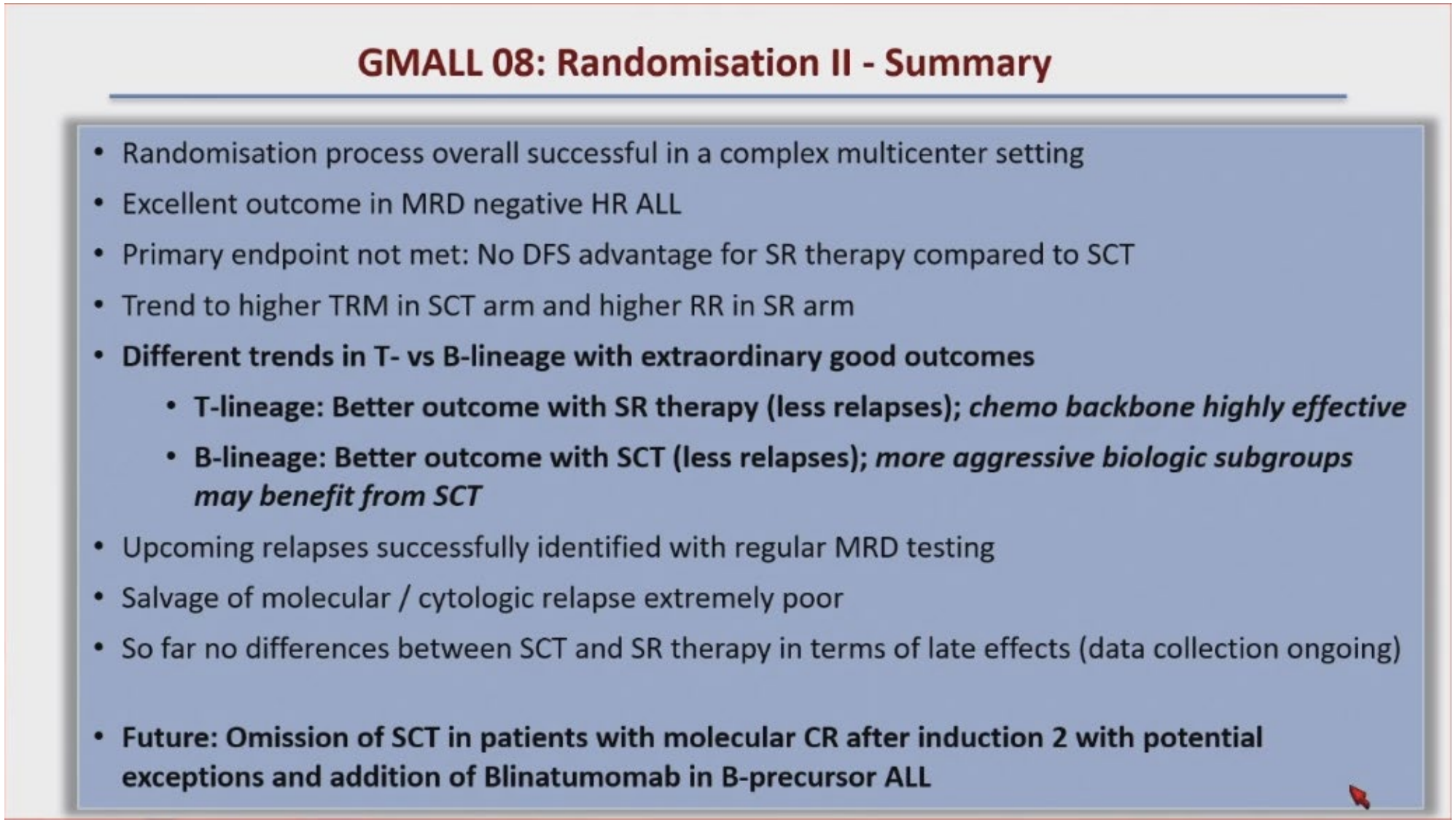


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# GMALL Trial 08/2013. Outcome Ph+ALL


Heike Pfeifer. 840 Update on GMALL Trial 08/2013 Shows Durable Favorable Outcome of Newly Diagnosed Adult Philadelphia-Positive Acute Lymphoblastic Leukemia (Ph+ALL) with Imatinib, Dose-Reduced Induction Followed By Stem Cell Transplantation .

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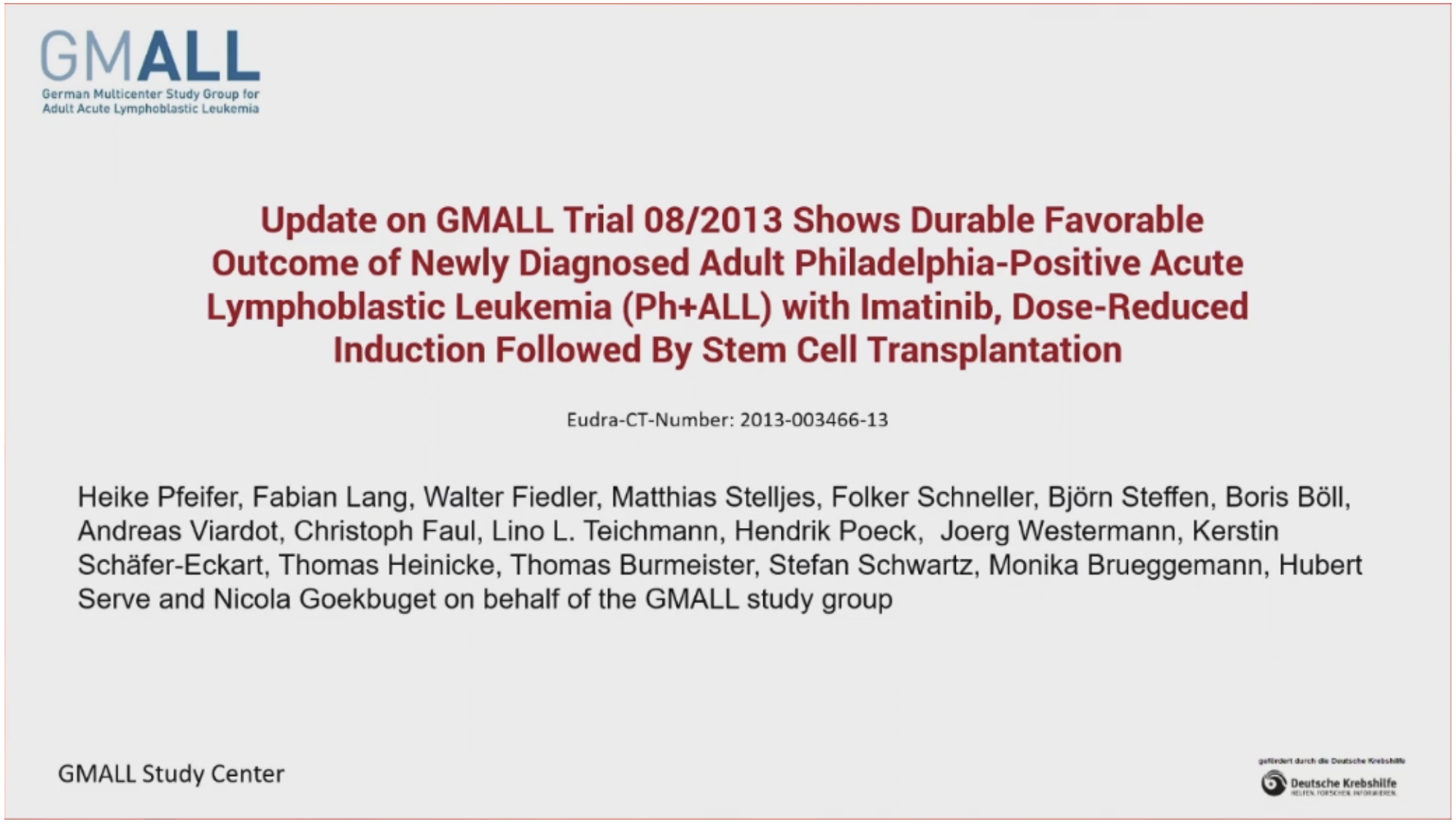


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# GMALL Trial 08/2013. Outcome Ph+ALL

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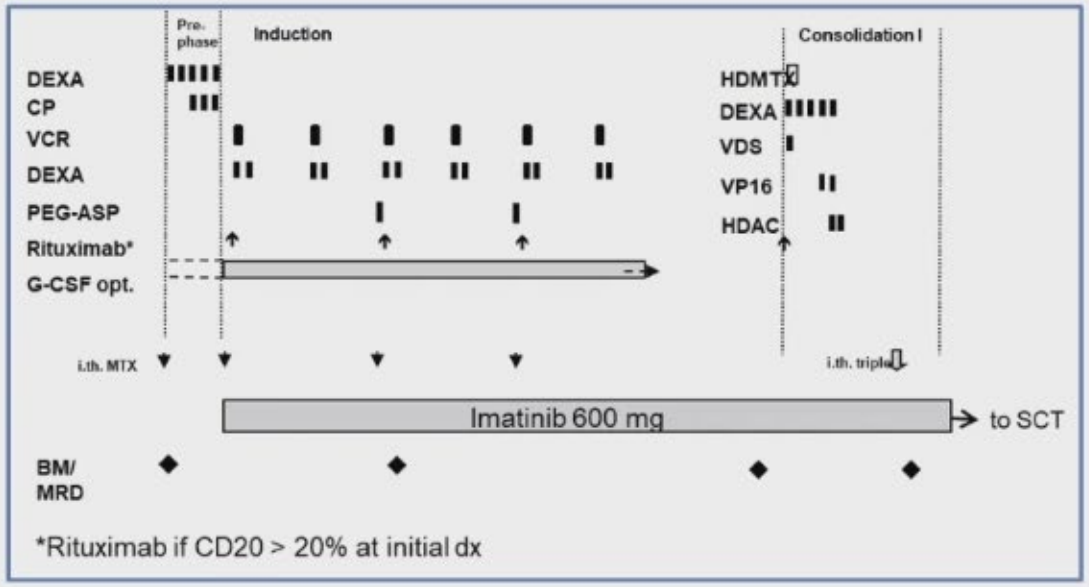
German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

## Induction und Consolidation I for Ph+ ALL within GMALL08/2013 trial

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## Overall Response after Induction and Consolidation Ph+ALL within GMALL 08/2013

| | after Induction I | pre Consolidation I | after Consolidation I |
|---|---|---|---|
| Evaluable | 165 | **174** | 174 |
| cytology | | | |
| **CR/CRu** | **85%** | **96%** | **94%** |
| PR | 9% | 2% | 0% |
| Failure | 4% | 1% | 2% |
| **Early Death** | **1%** | **1%** | **3%**** |

* incl. 3 pro-B-ALL
** 4 Death in CR

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## MRD Response after Induction and Consolidation for Ph+ALL within GMALL 08/2013

| | After Induction I | Pre Consolidation I | After Consolidation I |
|---|---|---|---|
| **MRD Total** | **174** | **150** | **144** |
| **MRD Evaluable** | **139 (80 %)** | **150 (87%)** | **144 (87%)** |
| **Mol CR** | **9 %** | **24 %** | **42%** |
| **Mol Fail** | **81%** | **58%** | **38%** |
| $\geq 10^{-2}$ | | | 17% |
| $<10^{-2} \geq 10^{-3}$ | | | 41% |
| $<10^{-3} \geq 10^{-4}$ | | | 43% |
| **Mol IMR** | **25%** | **18%** | **21 %** |

- MolCR: MRD negative with at least 10.000 ABL1 copies
- MolFail: MRD positive, quantifiable, with Ratio >1E-04
- Mol IMR: MRD positive below <1E-04 (with at least 10 000 ABL1 copies)

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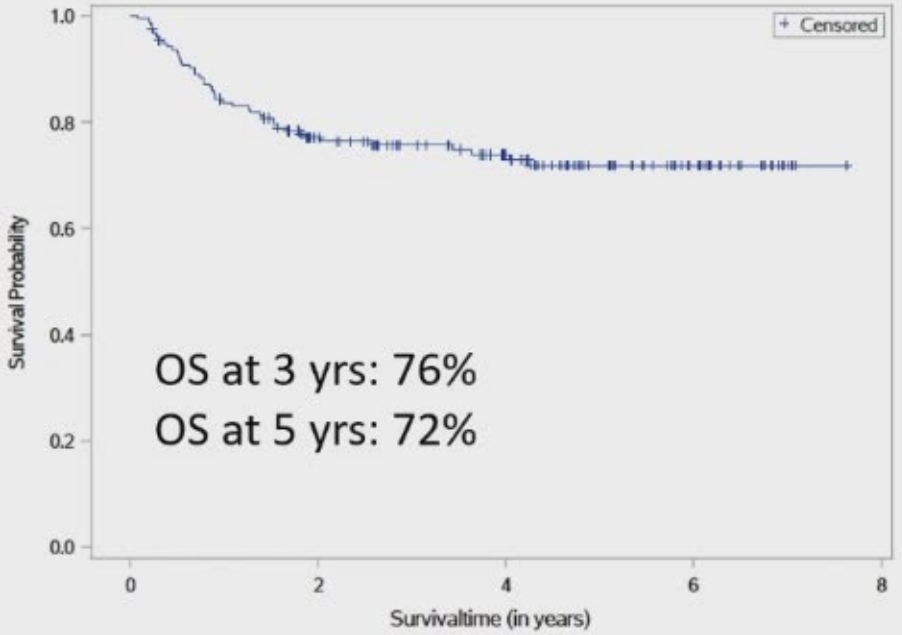
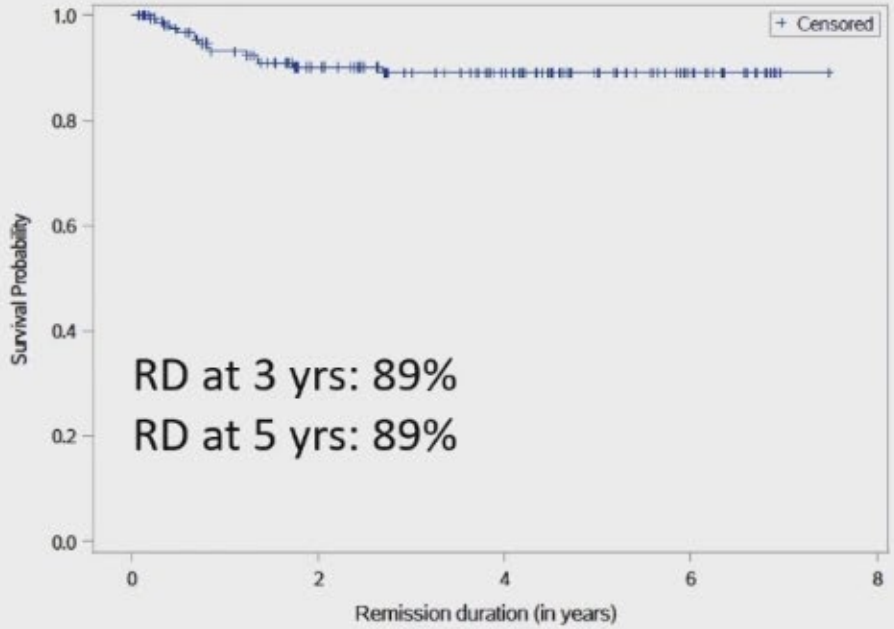
## Overall Survival and Remission Duration for Ph+ALL within GMALL 08/2013

### Overall Survival all (n=174)




### Remission Duration all (n=168)

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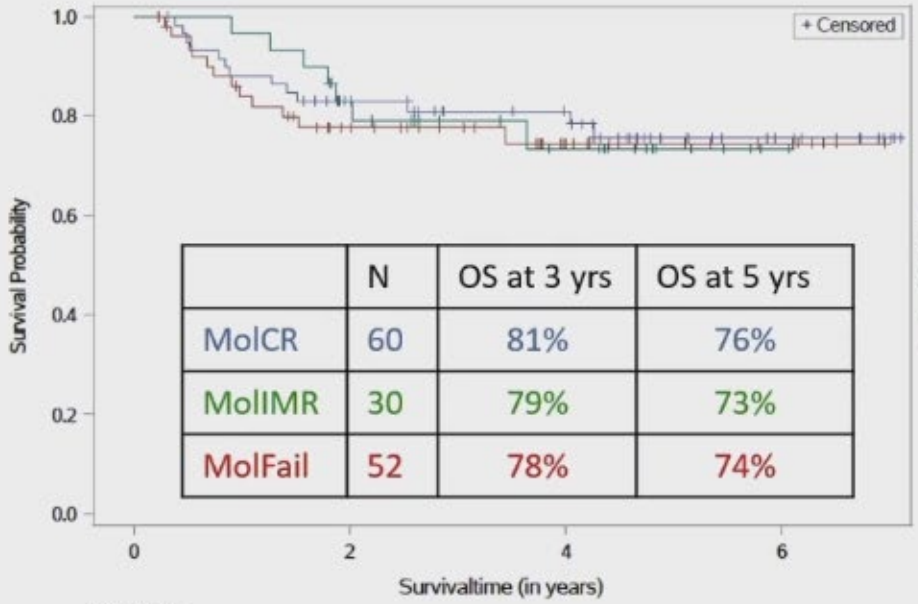
## Outcome for Patients with CR after Cons I According to MRD Response for Ph+ALL within GMALL 08/2013

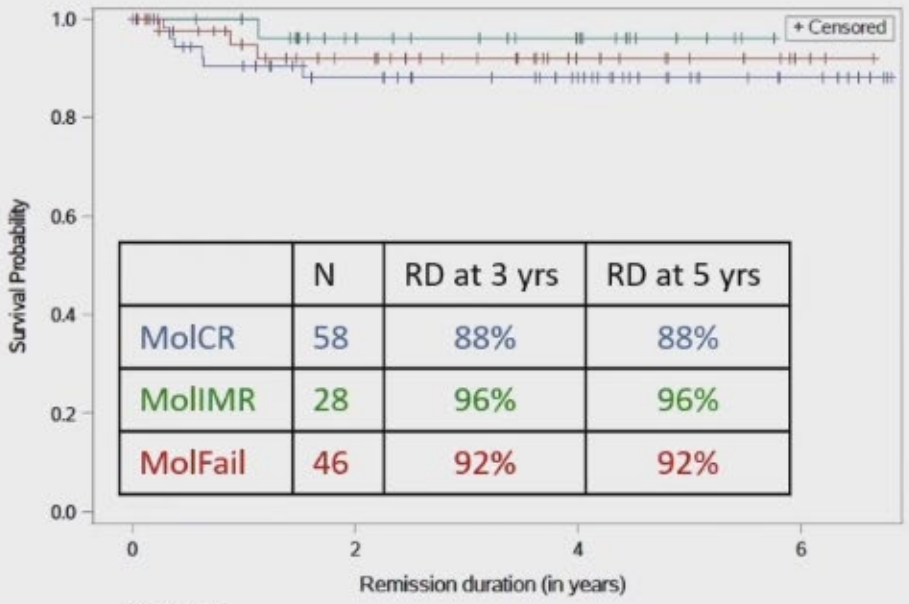
### Overall Survival all




| | N | OS at 3 yrs | OS at 5 yrs |
|---|---|---|---|
| MolCR | 60 | 81% | 76% |
| MolIMR | 30 | 79% | 73% |
| MolFail | 52 | 78% | 74% |

p>0.05

### Remission Duration all




| | N | RD at 3 yrs | RD at 5 yrs |
|---|---|---|---|
| MolCR | 58 | 88% | 88% |
| MolIMR | 28 | 96% | 96% |
| MolFail | 46 | 92% | 92% |

p>0.05

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# GMALL Trial 08/2013. Outcome Ph+ALL

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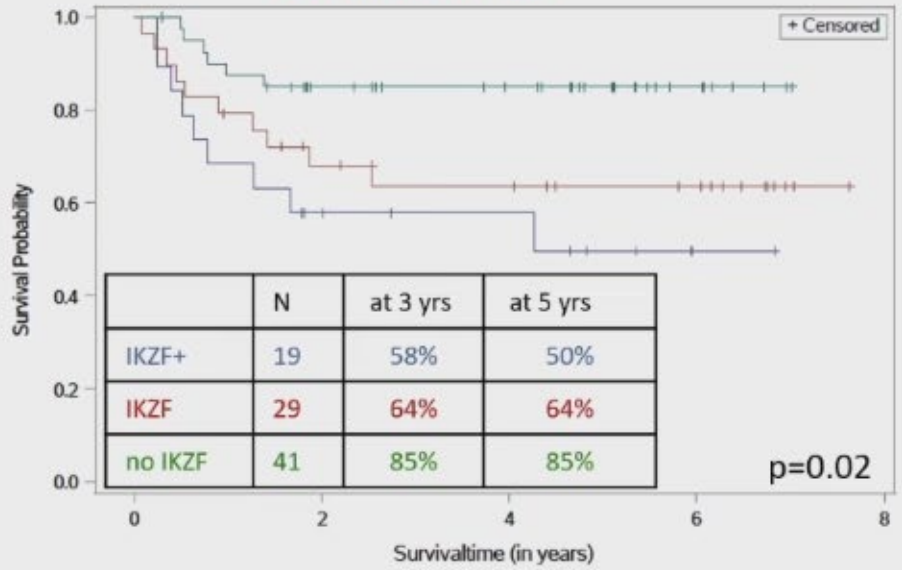
## Outcome **According to IKZF Signature** For Ph+ALL within GMALL 08/2013

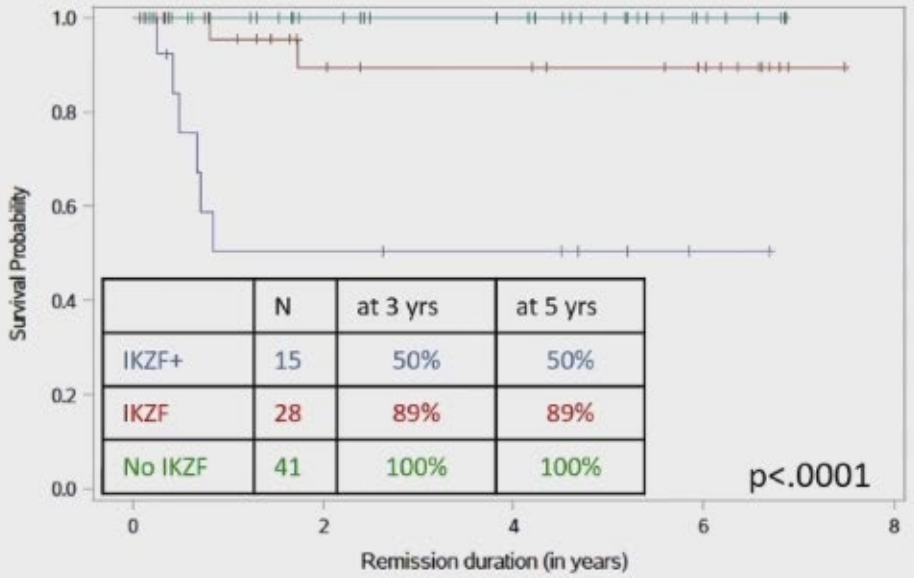
### Overall Survival




| | N | at 3 yrs | at 5 yrs |
|---|---|---|---|
| IKZF+ | 19 | 58% | 50% |
| IKZF | 29 | 64% | 64% |
| no IKZF | 41 | 85% | 85% |

p=0.02

### Remission Duration




| | N | at 3 yrs | at 5 yrs |
|---|---|---|---|
| IKZF+ | 15 | 50% | 50% |
| IKZF | 28 | 89% | 89% |
| No IKZF | 41 | 100% | 100% |

p<.0001

IKZF+ vs IKZF

Relapse rate: 40% vs 7%

Death in CR: 7% vs 29%

- method: MLPA P335
- IKZF + defined as: IKZF deletion +CDKN2A- and/ or PAX5 deletions

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## Summary

- Dose reduced induction including PEG-ASP in combination with Imatinib was feasible and yielded high response rates with a molecular CR rate of 43% already after CI.
- A very high SCT realization rate (98%) was obtained at approximately 3 months from diagnosis likely contributing to the favorable overall outcome with a low relapse rate.
- Nevertheless, a relevant TRM especially in a higher patient age (>45 yrs) was observed, leading to recommendations for dose-reduced TBI-based conditioning regimens in older patients
- IKZF+positive patients showed a higher relapse rate despite allogeneic SCT
- Randomized prospective trials are required to define the future role of SCT considering
  - Response
  - Risk factors
  - Standardized SCT procedures

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# Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients


Sabina Chiaretti. 835 Efficacy and Toxicity of Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients of All Ages. Intermediate Analysis of the Gimema ALL2820

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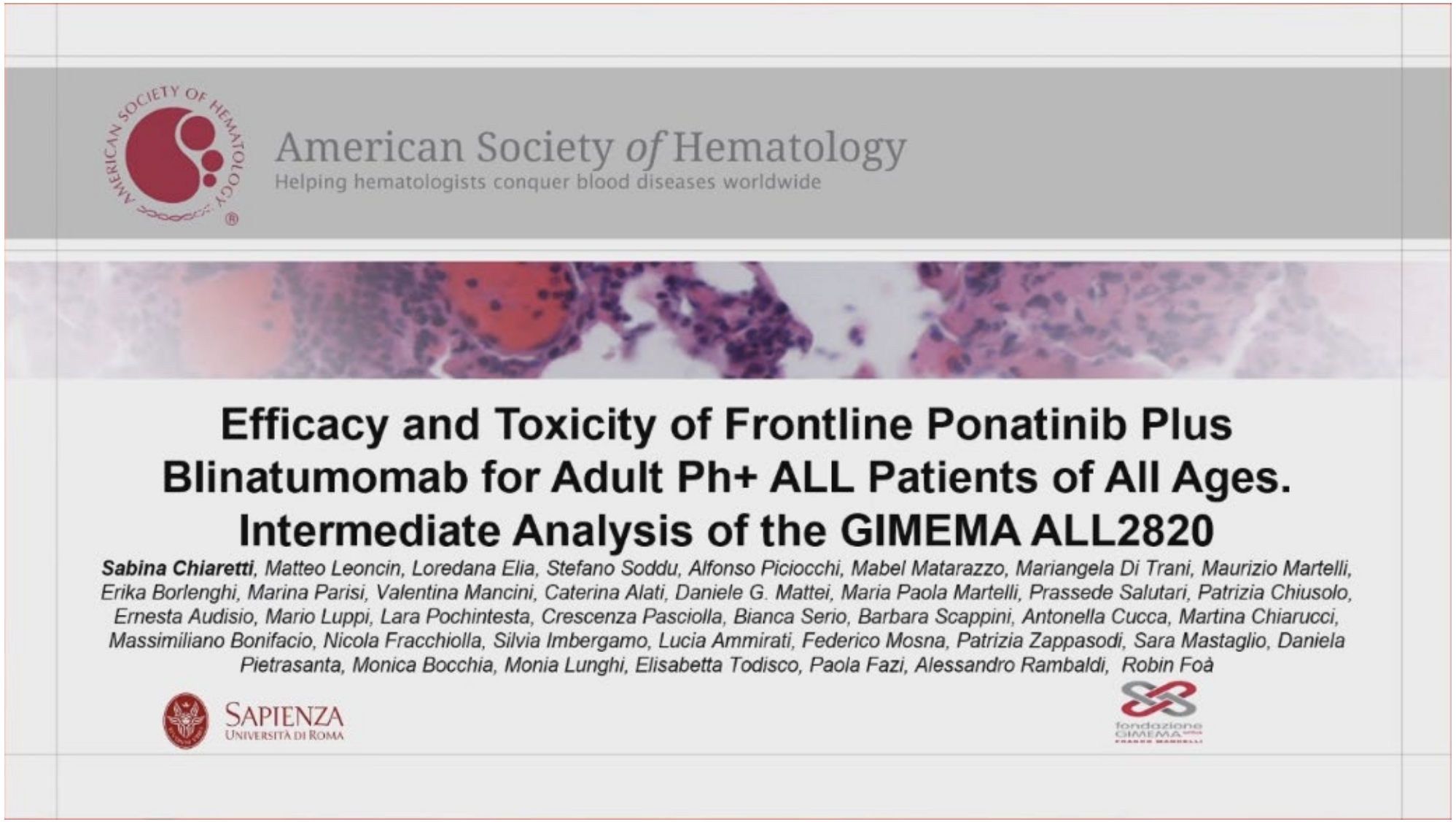


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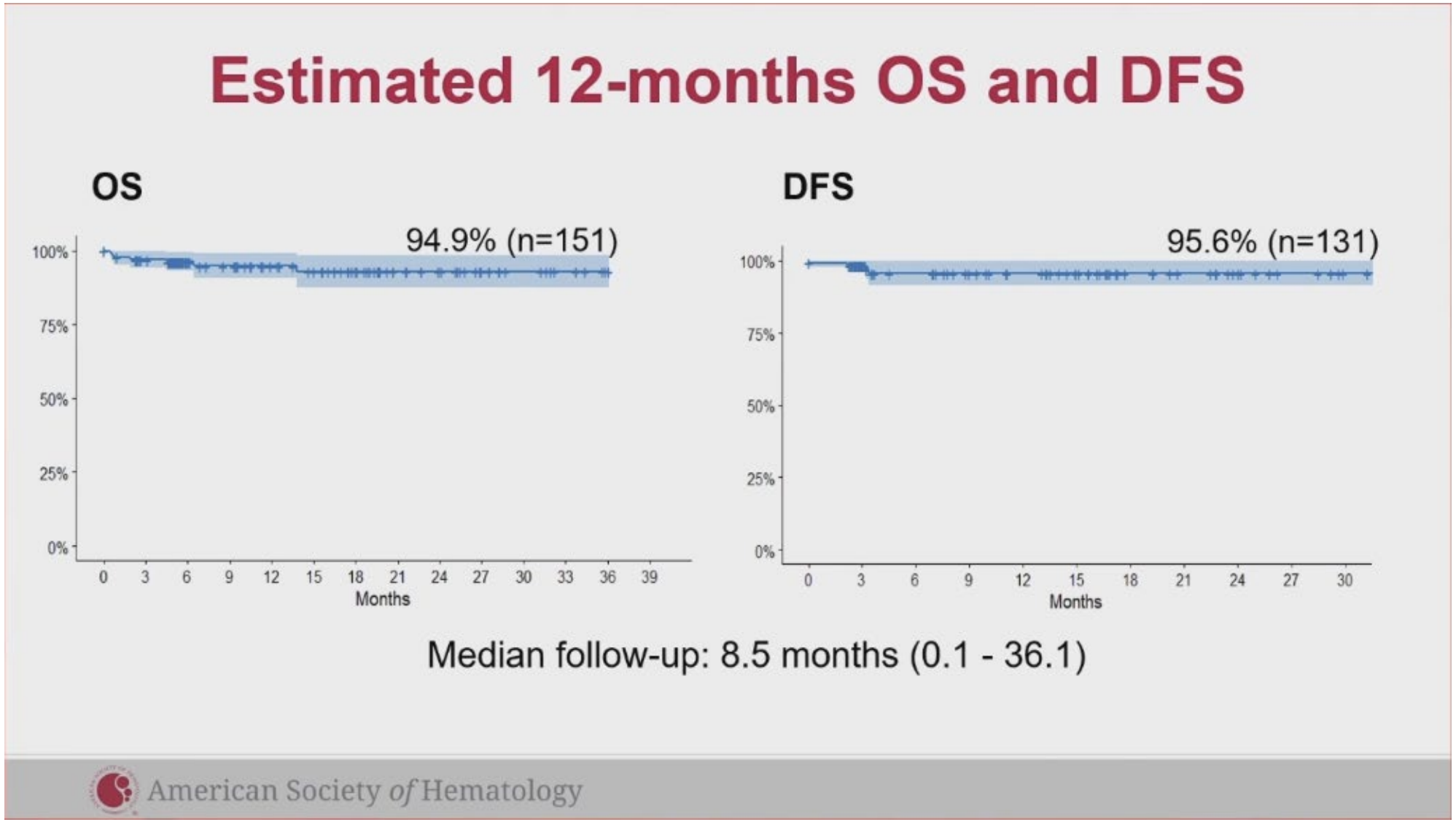


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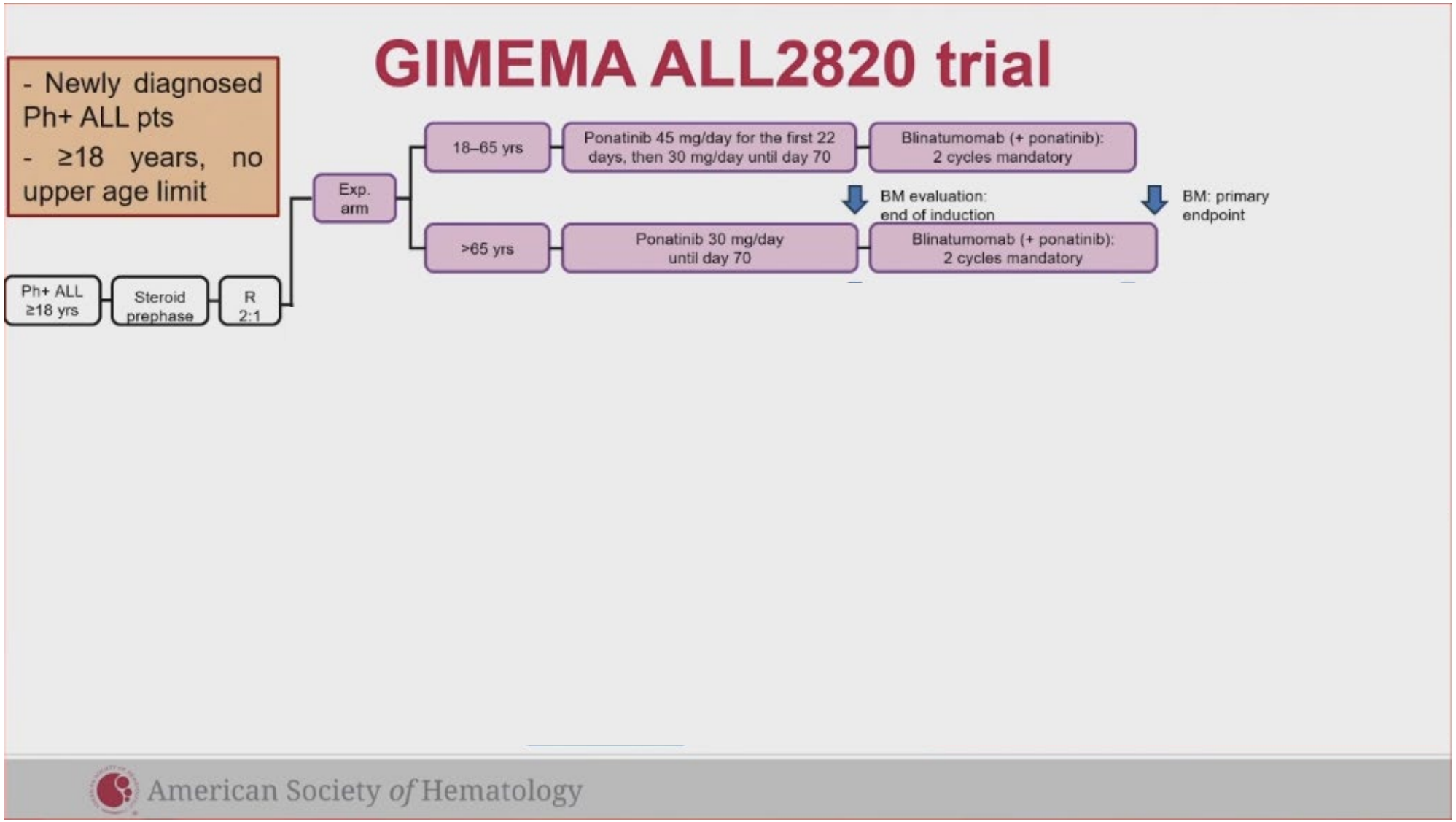


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# Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients

## Experimental arm: hematologic & molecular responses

| End of induction (d +70) | n=137 |
|---|---|
| CHR | 131 (96%) |
| Deaths | 4 (3%) |
| Off treatment | 2 (1%) |

| | No molecular responses (%) | CMR | PNQ | Overall molecular responses (%) |
|---|---|---|---|---|
| End of induction (d +70) | 71/131 (54) | 40/131 | 20/131 | 60/131 **(46)** |
| After 2 cycles of blinatumomab | 30/117 (26) | 59/117 | 27/117 | 86/117 **(74)** |

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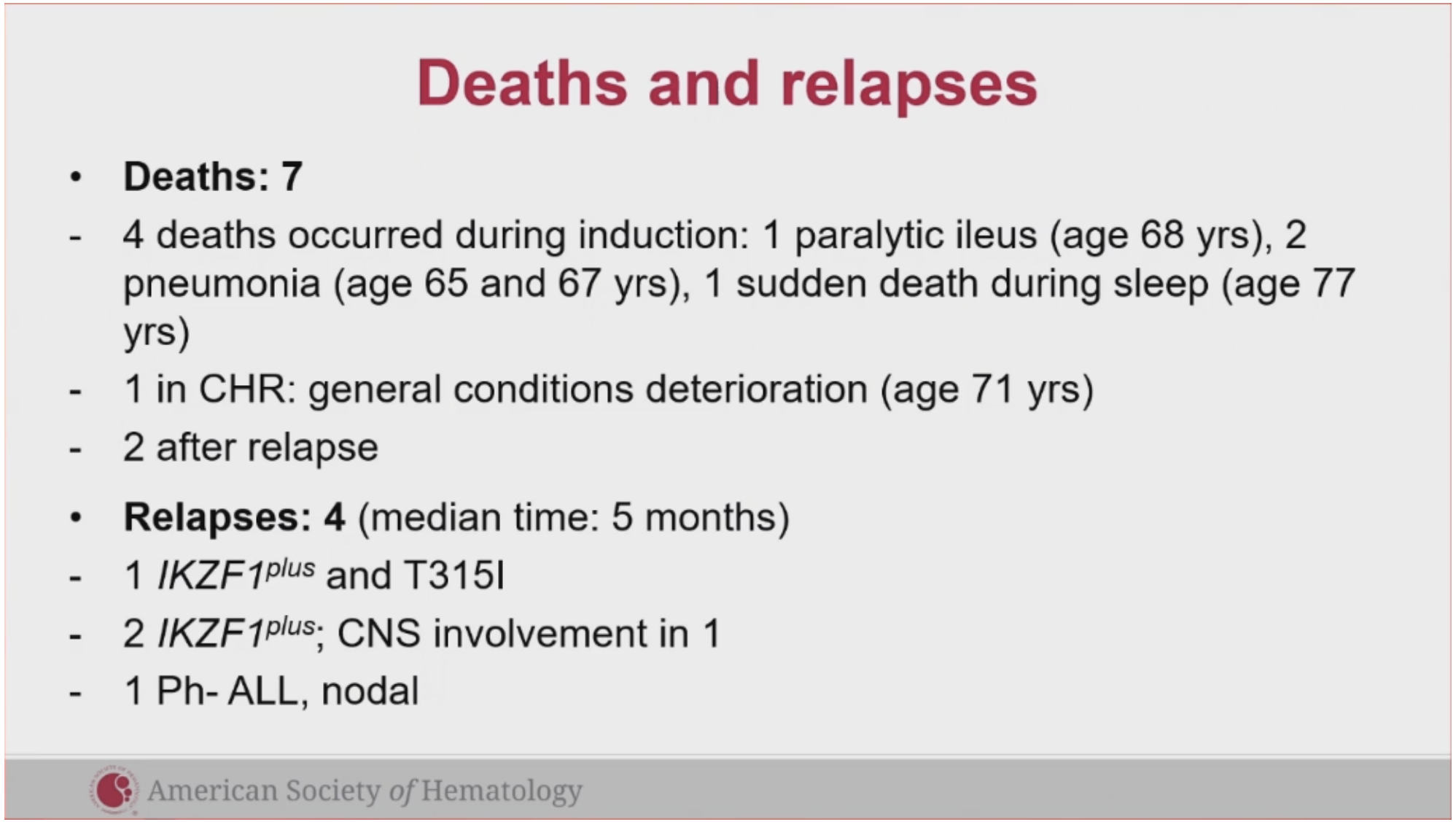


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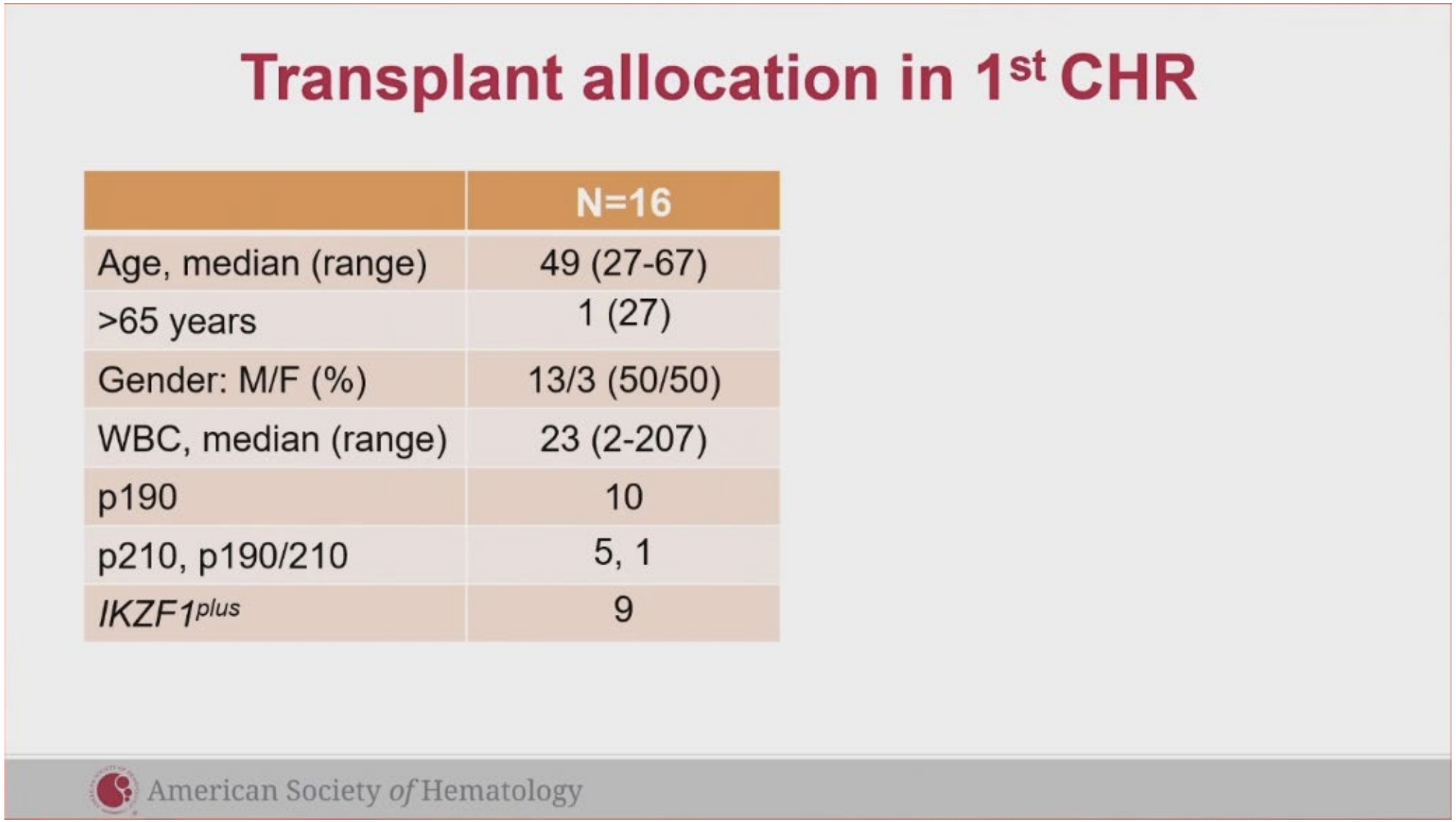


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# Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients

## Transplant allocation in 1st CHR

| | N=16 |
|---|---|
| Age, median (range) | 49 (27-67) |
| >65 years | 1 (27) |
| Gender: M/F (%) | 13/3 (50/50) |
| WBC, median (range) | 23 (2-207) |
| p190 | 10 |
| p210, p190/210 | 5, 1 |
| *IKZF1plus* | 9 |

**Reasons for transplant**

- MRD persistence (n=7)
- *IKZF1plus* (n=9)
- Both (n=5)

**So far, no relapses nor transplant-related deaths**

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# Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients

## Conclusions

- The combination of ponatinib in induction followed by a consolidation with blinatumomab has further improved the results achieved in the D-ALBA trial.
- This strategy was effective and feasible: 12-months OS and DFS are 94.9% and 95.6%.
- SAEs, leading to interruption or discontinuation were rare and mostly observed in the elderly population.
- The biologically-driven allo-SCT allocation has further reduced the rate of allografts. No fatal events have so far been recorded.
- Given these results, a strategy for TKI discontinuation after an optimal time on TKI needs to be implemented*.

*Dragani et al, Haematologica in press

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# Blinatumomab and Ponatinib for Adults with Ph+ ALL


Nicholas J. Short. 837 Blinatumomab and Ponatinib for Adults with Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Updated Results and Predictors of Relapse.

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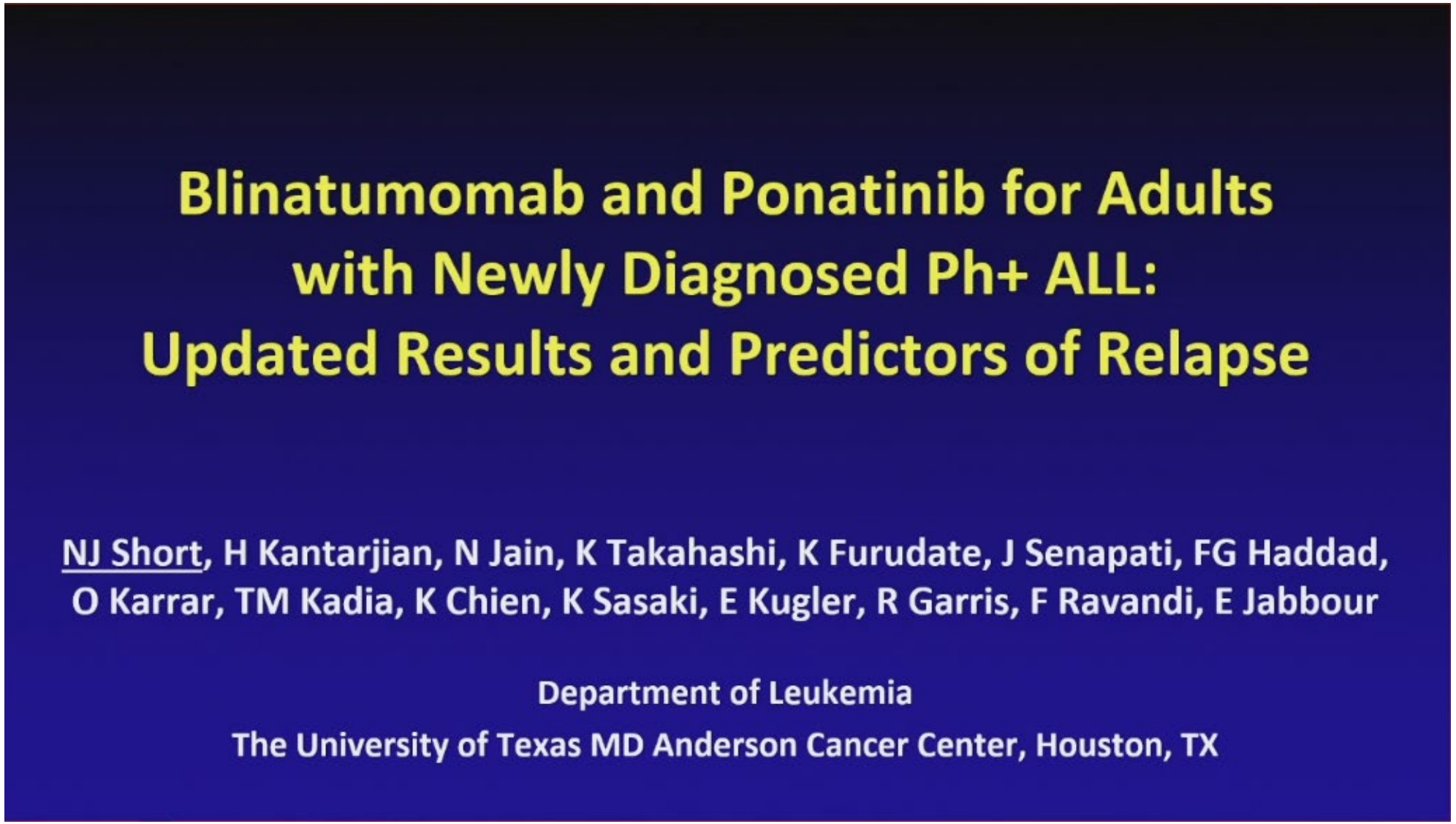


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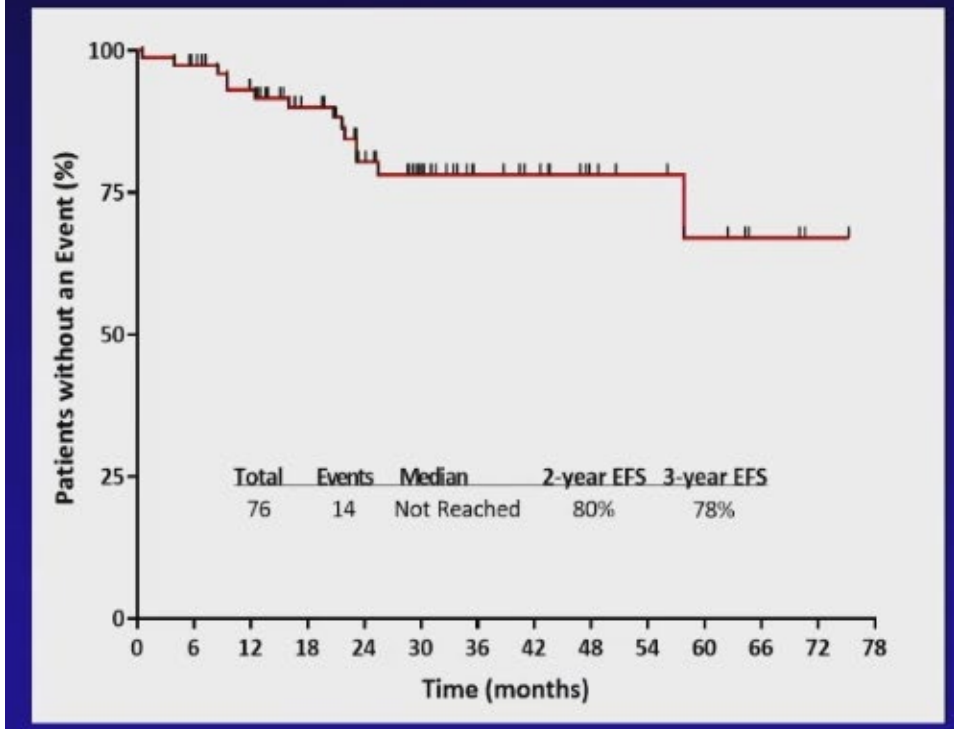
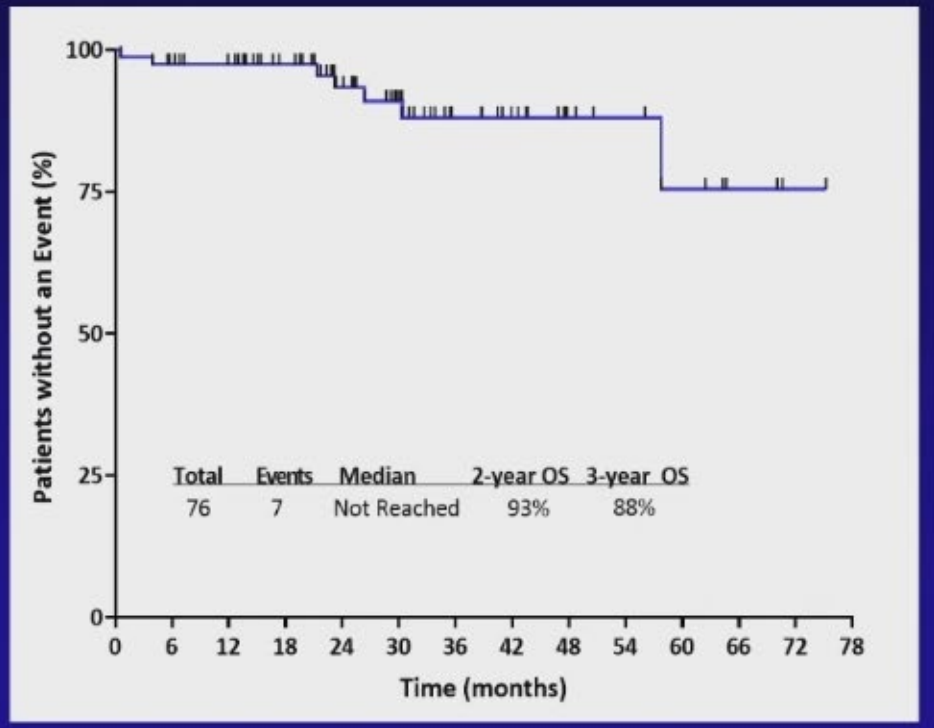
## Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes

Median follow-up: 29 months (range, 5-75 months)

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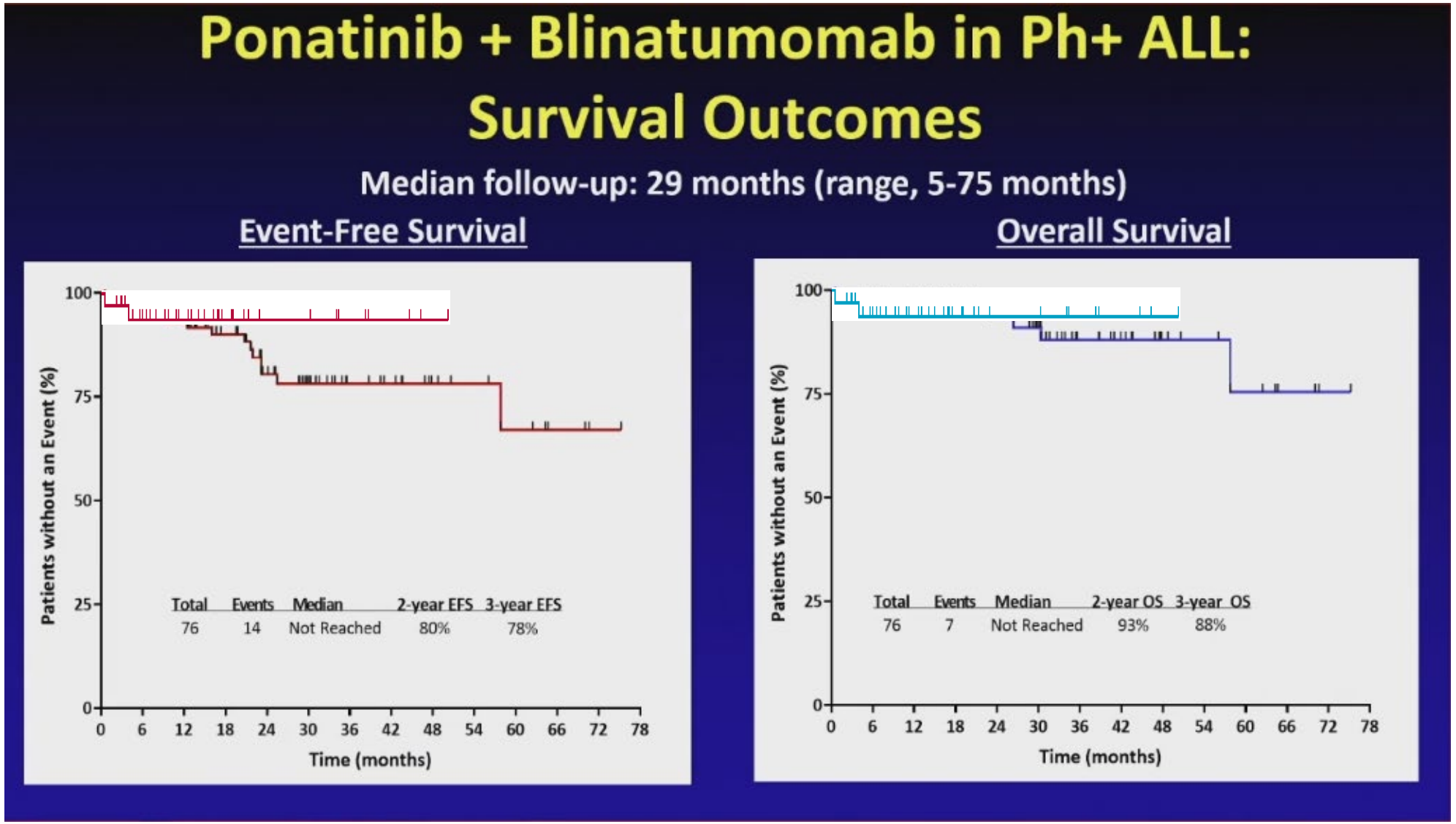


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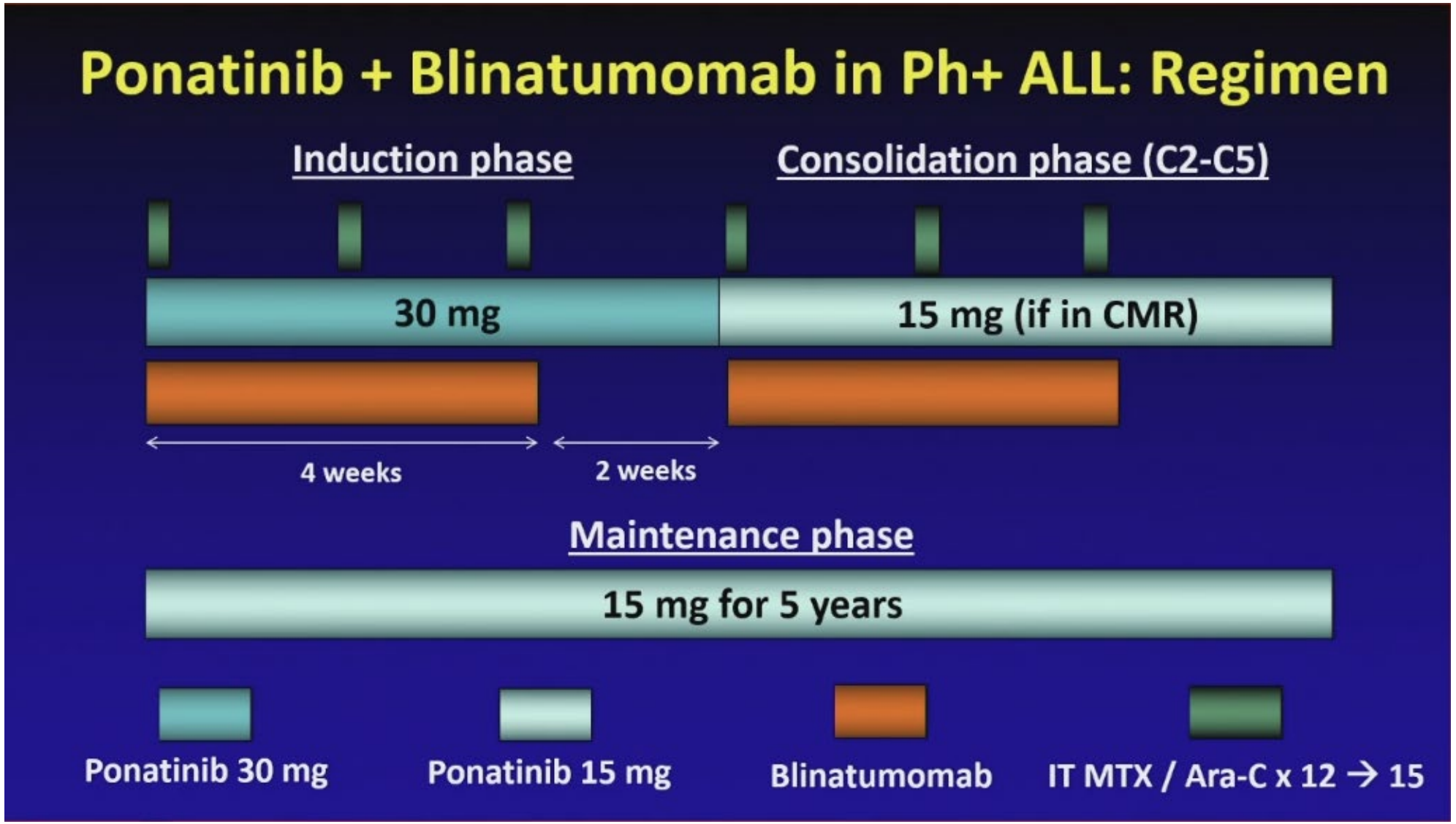


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## Ponatinib + Blinatumomab in Ph+ ALL: Response Rates

| Response, n/N (%) | N = 76 |
|---|---|
| CR/CRi* | 52/53 (98) |
| *CR* | 51/53 (96) |
| *CRi* | 1/53 (2) |
| Early death | 1/53 (2) |
| MMR** | 64/66 (97) |
| CMR** | 57/69 (83) |
| After 1 cycle | 41/69 (59) |
| NGS MRD negative | 55/57 (96) |
| After 1 cycle | 17/36 (47) |

* 23 pts in CR at start
** 10 pts were in MMR, 7 were in CMR, and 2 were NGS MRD negative at start

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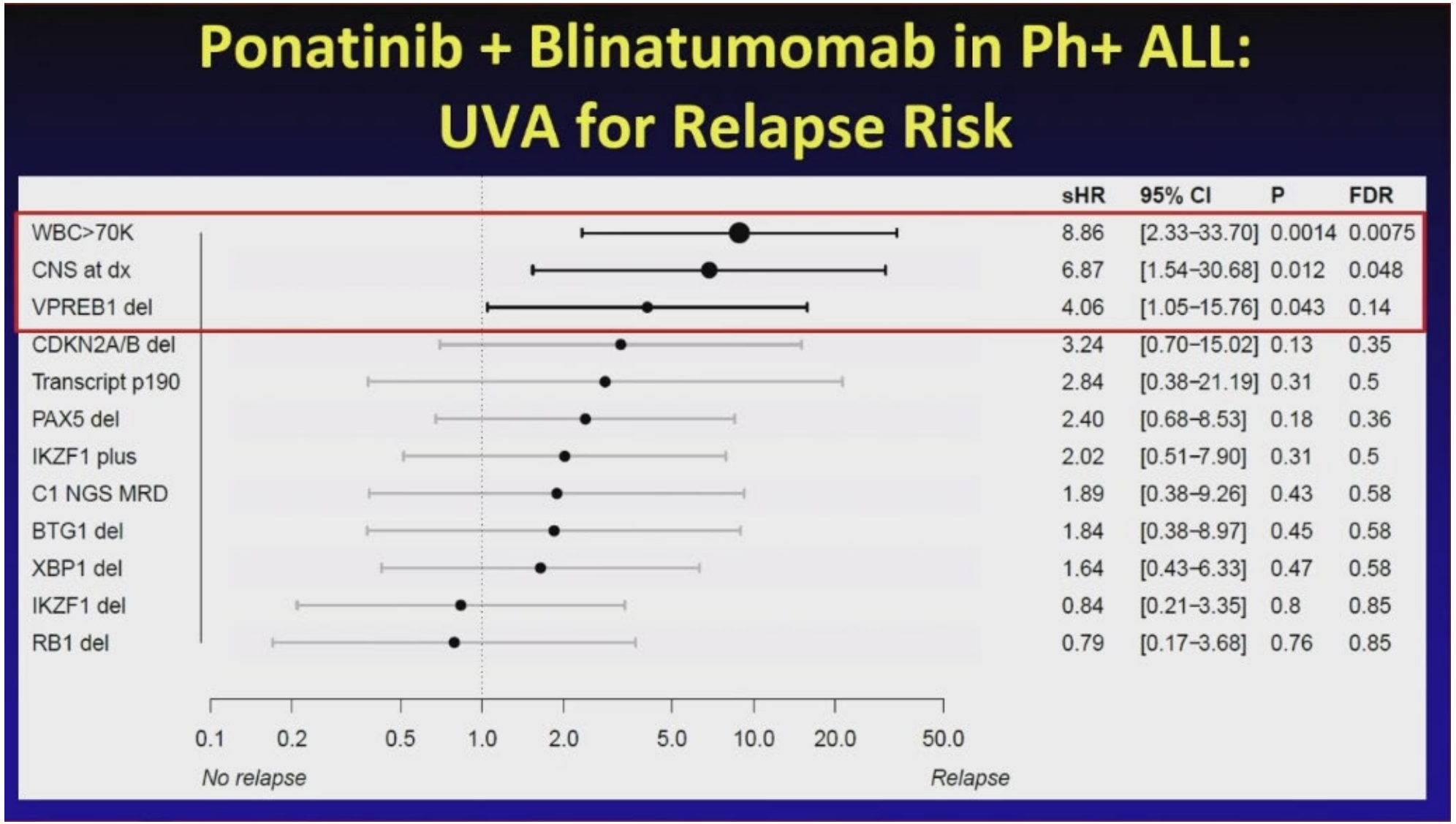


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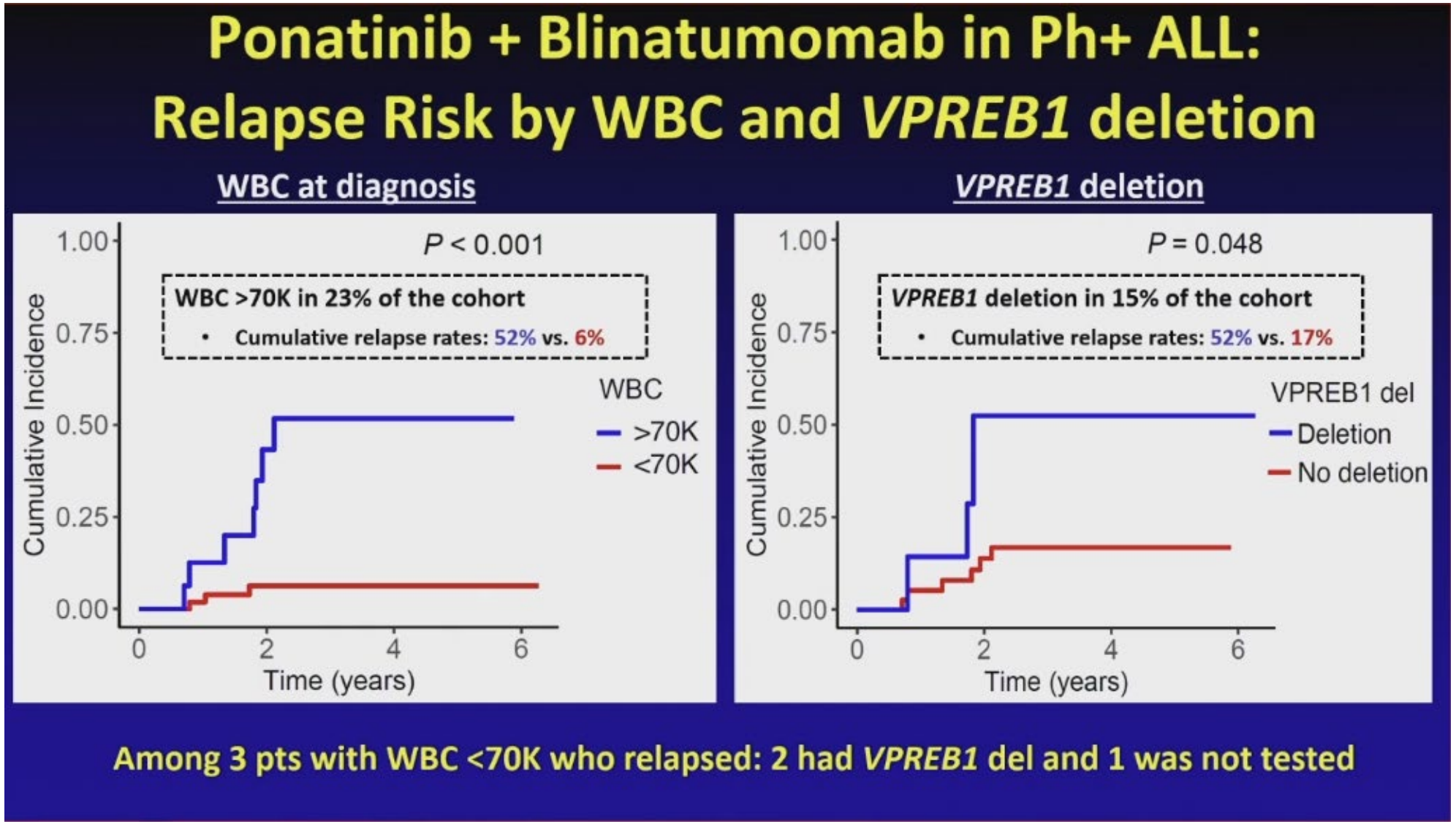


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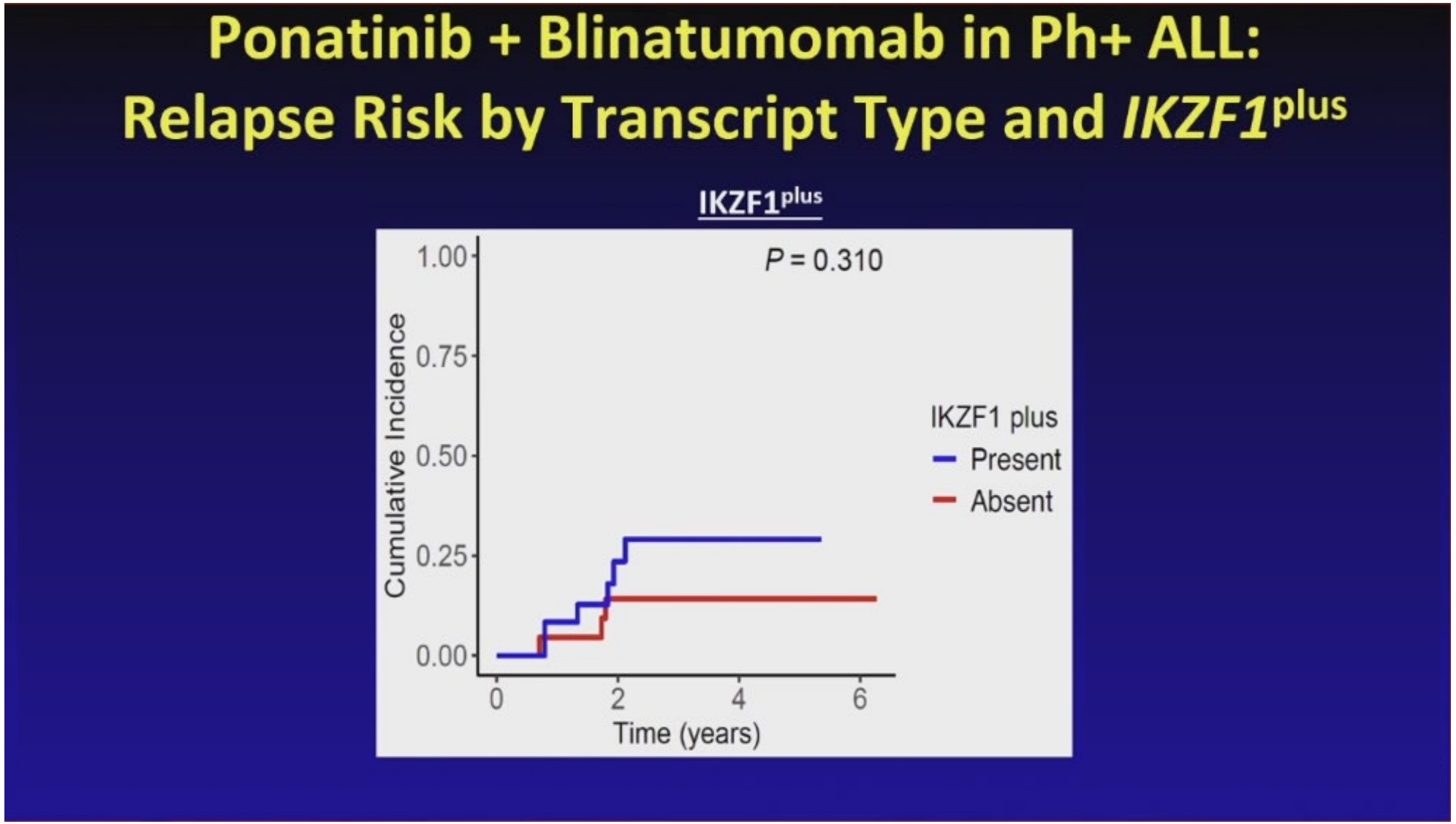


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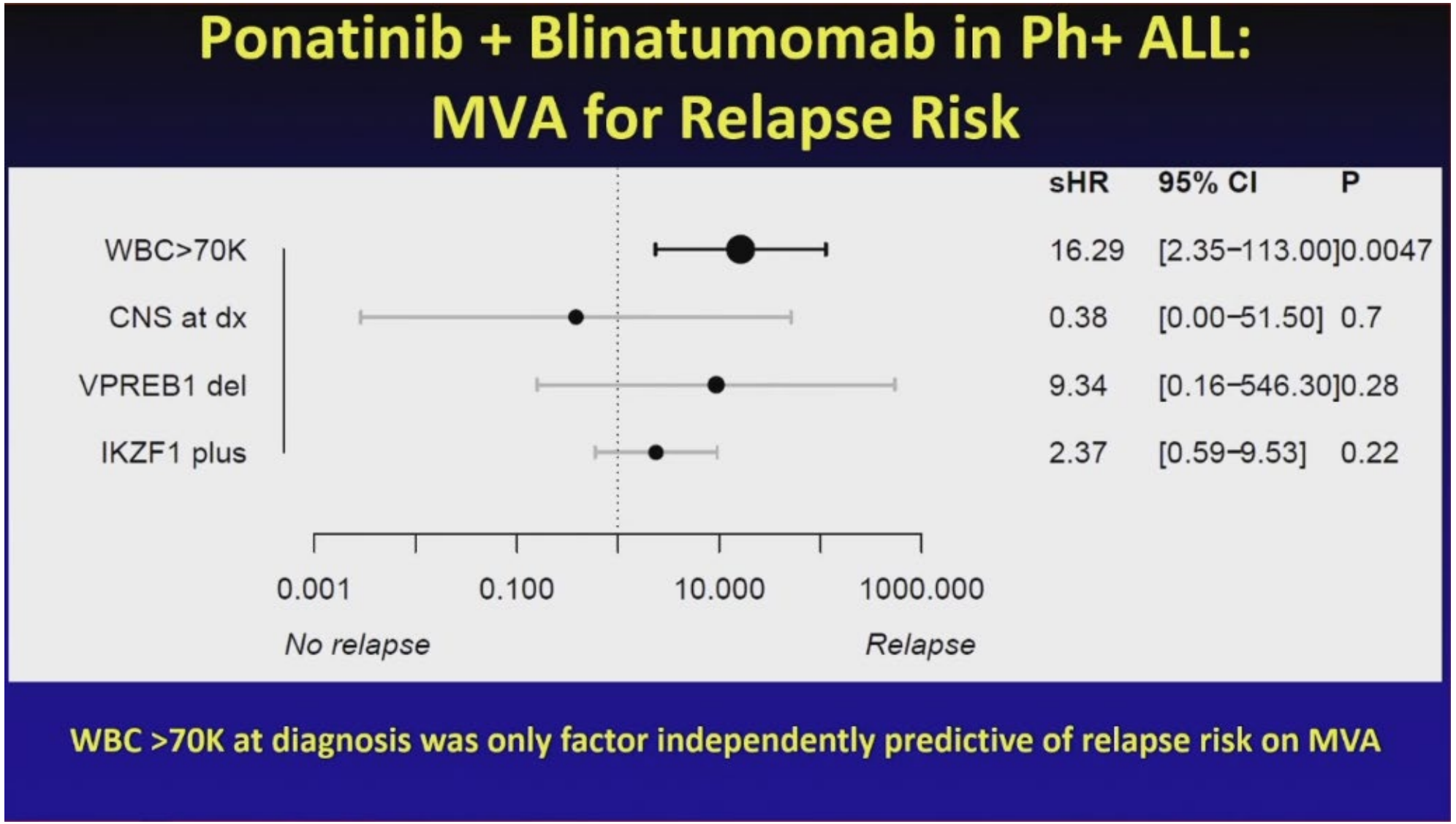


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# Blinatumomab and Ponatinib for Adults with Ph+ ALL

## Ponatinib + Blinatumomab in Ph+ ALL: Conclusions

- Chemotherapy-free combination of ponatinib + blinatumomab achieves deep responses in pts with newly diagnosed Ph+ ALL
  - CR/CRi 98%, CMR 83%, NGS MRD negativity 96%
- Durable remissions without HSCT in first remission
  - Estimated 3-year RFS 78%; 3-year OS 88%
  - Only 2 pts (3%) underwent HSCT in first remission
  - 10 relapses to date (13% relapse rate; half in CNS)
- WBC >70K only factor predictive for relapse; ? role of *VPREB1* deletion
  - Very high-risk feature → CIR rate ~50%
- Novel strategies needed for pts with high-risk Ph+ ALL

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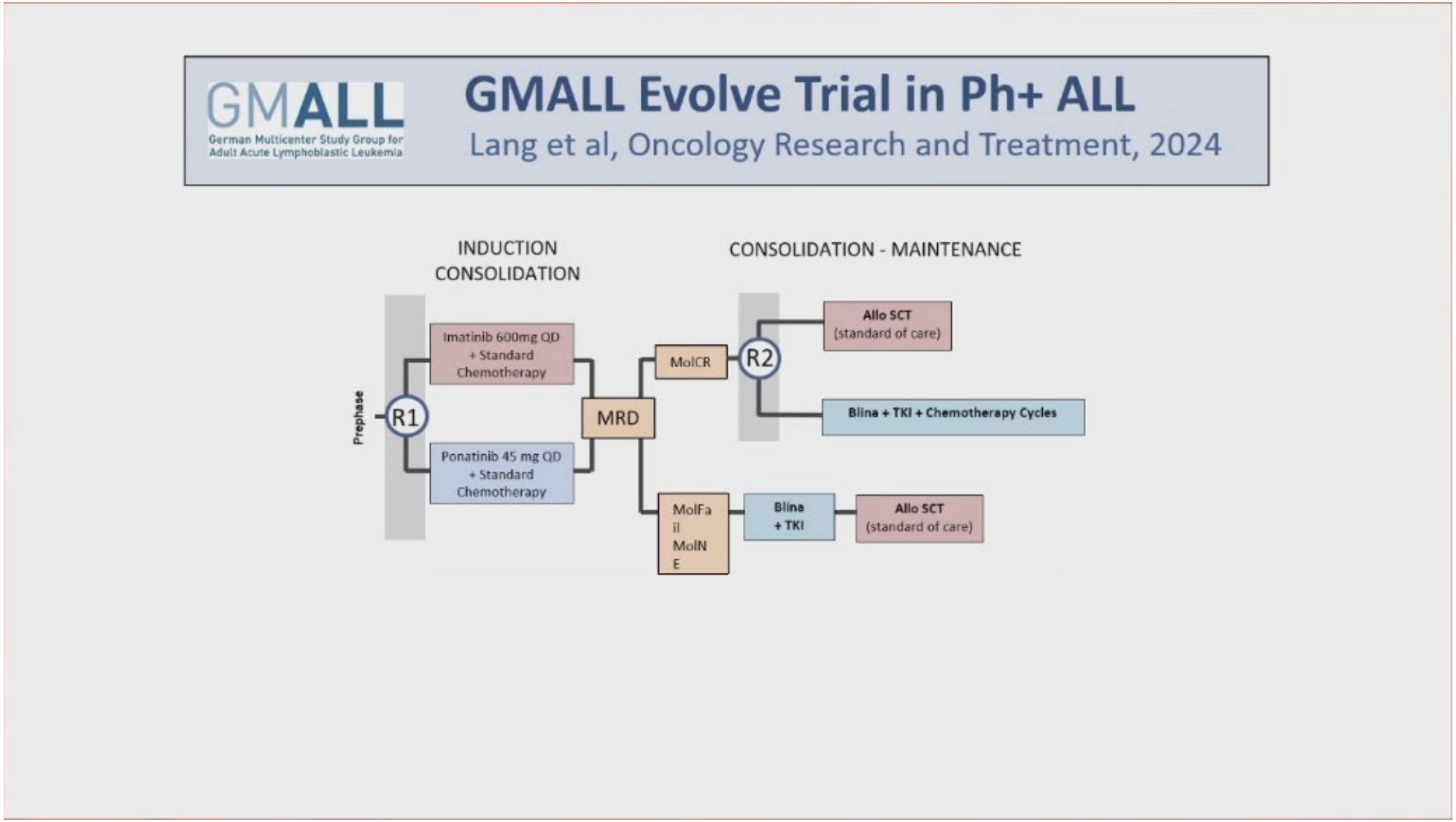
# GMALL Trial 08/2013. Outcome Ph+ALL




Heike Pfeifer. 840 Update on GMALL Trial 08/2013 Shows Durable Favorable Outcome of Newly Diagnosed Adult Philadelphia-Positive Acute Lymphoblastic Leukemia (Ph+ALL) with Imatinib, Dose-Reduced Induction Followed By Stem Cell Transplantation .

# Vielen Dank für Ihre Aufmerksamkeit



Universitätsklinikum Tübingen