# The Randomized Controlled Trial shows no Survival Difference between HAploidentical Related and Single HLA-Loci Mismatched UnreLatEd Donor Transplantation in Patients with High Risk AML/ALL/MDS

Friedrich Stölzel[1,10], Lutz P Müller[2], Gesine Bug[3], Martin Kaufmann[4], Wolfgang Bethge[5], Matthias Stelljes[6], Tobias A.W. Holderried[7], Udo Holtick[8], Carina Rave[9], Jan Moritz Middeke[10], Judith Schaffrath[2], Julia Riemann[3], Sonja Martin[4], Christoph Faul[5], Christian Reicherts[6], Kristina Hölig[10,11], Gero Hütter[11], Sabine Edemir[2], Fabian Lang[3], Desiree Kunadt[10], Kristin Riedel[10], Falk Heidenreich[9,10], Kristin Lilpopp[9], Alexander H. Schmidt[9], Henning Baldauf[9], Martin Bornhäuser[10], Johannes Schetelig[9,10]

1 University Hospital Kiel, Germany
2 University Hospital Halle, Germany
3 University Hospital Frankfurt (Main), Germany
4 Robert Bosch Hospital Stuttgart, Germany
5 University Hospital Tübingen, Germany
6 University Hospital Münster, Germany
7 University Hospital of Cologne, Germany
9 DKMS Group, Dresden, Germany
10 University Hospital TU Dresden, Germany
11 DKMS Collection Center, Germany

## ACT 1 – Prolog

**High Risk AML/ALL/MDS Patient**

1:1 (stratified)

**Haplo**
**Haploidentical Donor PBSCT with PTCY+Tacro/MMF**

**mmuD**
**9/10 partially matched UD (one mismatch at HLA-A, -B, -C, DRB1) PBSCT with ATG, CSA+MTX**

- **Endpoint:** Overall Survival
- **Non-Inferiority Margin:** Hazard Ratio=1.18 (Haplo vs mmUD), i.e. max. 6% survival disadvantage of Haplo
- **Sample Size:** 98 (stopped early, 266 planned)
- **Accrual:** 5 years (from Feb 2018 to Apr 2023)
- **Follow-Up:** min: 1 year, median: 40 months

## ACT 2 – Eligibility

- AML (high-risk CR1, non-favorable AML mit MDS/MPN history, non-favorable tMN, relapsed refractory)
- MDS (RAEB-T, (very) high-risk IPSS-R)
- ALL (high risk/very high risk in CR1, second remission)
- 2 donors (mmUD and haplo)
- Age ≥ 18
- Fit for transplant

- HLA-identical sibling or 8/8 potentially matched donor by optimatch list
- Second allo HCT

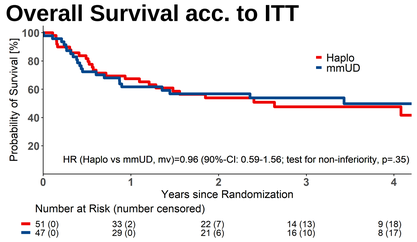
## ACT 3 – Patient Characteristics

| Characteristic | | Haplo (N=51 by ITT) | mmUD (N=47 by ITT) | p |
|---|---|---|---|---|
| **Sex** female | | 53% (27) | 51% (24) | 1.0 |
| **Age** (Median, IQR, range) | | 60 (54-67, 22-71) | 62 (56-68, 32-75) | .4 |
| **Diagnosis** | AML | 69% (35) | 60% (28) | .7 |
| | MDS | 20% (10) | 26% (12) | |
| | ALL | 12% (6) | 15% (7) | |
| **Fit for myeloablative conditioning** | | 33% (17) | 36% (17) | .9 |
| **ECOG** | 0 | 36% (18) | 30% (14) | .5 |
| | 1 | 56% (28) | 55% (26) | |
| | 2 | 8% (4) | 15% (7) | |
| **Disease risk** | low | 14% (6) | 7% (3) | .5 |
| | intermediate | 33% (14) | 39% (16) | |
| | high/very high | 52% (22) | 53% (22) | |
| **Donor age** (Median, IQR, range) | | 36 (30-47, 22-61) | 34 (26-39, 19-56) | .03 |

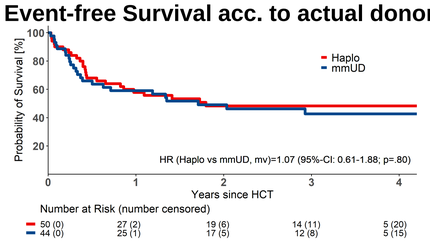
- 4 patients not transplanted (2/1 died in haplo/mmUD arm, 1 withdrawal in haplo arm)
- 6 patients crossed-over from haplo to mmUD and 8 patients from mmUD to haplo

## ACT 4 – Result

**Overall Survival acc. to ITT**




**Event-free Survival acc. to actual donor type**




| Event-Rate (95%-CI) | Haplo | mmUD | p |
|---|---|---|---|
| **OS**@4ys after Rando | 48% (32-62%) | 50% (33-64%) | 1.0 (log-rank) |
| **OS**@4ys after HCT | 42% (23-61%) | 49% (32-63%) | .9 (log-rank) |
| **Relapse**@4ys after HCT | 17% (8-29%) | 30% (16-45%) | .2 (Gray) |
| **NRM**@4ys after HCT | 35% (22-49%) | 27% (15-41%) | .5 (Gray) |
| **GRFS**@4ys after HCT | 32% (20-46%) | 33% (19-47%) | .9 (log-rank) |
| **aGvHD II-IV**@d150 after HCT | 40% (26-53%) | 34% (20-48%) | .5 (Gray) |
| **cGvHD**@2ys after HCT | 52% (37-65%) | 48% (32-62%) | .7 (Gray) |

## ACT 5 – Epilog

- First prospective randomized controlled trial comparing mmUD with ATG vs. haplo with PTCy
- Randomization poorly accepted (strong patient preferences either in favor of or against a family donor)
- For both donor options similar OS, EFS, GRFS and similar cumulative incidences of relapse, NRM, aGvHD, cGvHD and adverse events
- Non-inferiority of haplo with PTCy could not be demonstrated for OS within pre-defined boundaries.
- Median time to HCT 8 days shorter with haplo than with mmUD (35 vs 43 days)
- Results suggest that both donor types should be considered, if no HLA-matched donor is not available.
- Findings support choosing between haplo and mmUD donors based on secondary criteria such as urgency for a transplant, donor age, permissiveness of HLA mis-matches, CMV serostatus, and donor sex.

## Thank you

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