Efficacy of HSV-TK\(^+\) suicide gene donor lymphocytes after haploidentical transplantation (haplo-HSCT): preliminary results of randomized TK008 study

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High rate of infectious mortality in T-cell depleted haplo

non-relapse mortality

ALL

AML

CR>2

CR1

ALWP haplo survey
Ciceri et al, Blood 2009
Engineering of donor T cells: HSV-TK

Sources: adapted from Bonini et al., Science 1997; Bonini et al., Nat. Med. 2003; Recchia et al., PNAS 2006; Ciceri et al., Blood 2007
TK007 phase II trial: very low infectious mortality after TK-cells

Days after SCT

Non-relapse mortality

60%

14%

No IR
IR TK treated
TK007 phase II trial: overall survival in TK-cells treated acute leukemias
Long-term Overall Survival is free of chronic GvHD and immune-suppressive treatment

Survival free of immunosuppressive therapy (IST, n=49)
TK008: Study design

Key inclusion criteria
- AML-ALL at high-risk in first CR
- AML-ALL in ≥ second CR
- secondary AML in CR
- advanced-stage AML/ALL
- lack of HLA-matched relat/unrel donor

Stratification
- disease status (1st vs > 1st vs relapse)
- performance status (0 vs 1)
- country

Primary endpoint
- DFS/PFS

Key secondary endpoints
- OS, NRM, CIR, IR, GvHD

Statistics
- n=170 patients
- HR=0.55; 1-β=80%; α=0.05
- 1-year DFS, 30% vs 52%
- 91 events (deaths + relapses/PD)

Dose of MM-TK cells: 1x10^7/Kg
- Up to 4 monthly doses to reach IR CD3+ cell count ≥ 100/µL
- Starting 21 to 49 days after HSCT
- In absence of IR and/or GvHD

Haplo-HSCT*
plus MM-TK cells
n=127

R (3:1)
n=43

Haplo-HSCT**

* T-depleted (T cells, 1x10^4/Kg)
**T-depleted (T cells, 1x10^4/Kg)
or
**Unmanipulated BM/PB + HD CTX
T-REPLETE HAPLO CLIMBING: UNMANIPULATED BM AS CONTROL ARM
TK008: Patient disposition

- 24 patients randomly assigned to the experimental arm
  - analysis on an ITT basis (cut-off: 8 May 2014)
  - an additional 9 patients randomly assigned to control arm

- 19 patients treated with MM-TK cells
  - 5 patients untreated due to: poor mobilization (n=1), early relapse (n=1), spontaneous immune reconstitution (n=1) and too early (n=2)

- 15 patients with MM-TK-related immune reconstitution (IR)
  - 4 patients without IR due to: grade 3 GvHD resolved with ganciclovir (n=1), early death for liver failure (n=1) and too early (n=2)

- Median follow-up time: 1.2 years (95% CI, 0.6 to 1.8)
## TK008: patients, TK cells dose

### Patient and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median in years (range)</td>
<td>39 (19-67)</td>
</tr>
<tr>
<td>Male</td>
<td>71%</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>92%</td>
</tr>
<tr>
<td>AML</td>
<td>75%</td>
</tr>
<tr>
<td>CR1 / ≥ CR2 / Relapse</td>
<td>50% / 29% / 21%</td>
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</tbody>
</table>

### Treatment with MM-TK cells

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first dose, median in days (95% CI)</td>
<td>28 (25-35)</td>
</tr>
<tr>
<td>Number of doses, median</td>
<td>2 (1.8-2.2)</td>
</tr>
<tr>
<td>Cumulative dose, median per 10^7/kg</td>
<td>2.4 (2.0-2.9)</td>
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</tbody>
</table>

### Time to IR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>From HSCT, median in days (95% CI)</td>
<td>105 (68-125)</td>
</tr>
<tr>
<td>From first dose</td>
<td>69 (33-95)</td>
</tr>
<tr>
<td>From last dose</td>
<td>27 (23-33)</td>
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</table>
TK008: Leukemia Relapse

Cumulative incidence of relapse or progression

- All patients (n=24)
  - 16% (±8)

Cumulative incidence of relapse or progression according to the dose of MM-TK cells (n=19)

- Dose < 3.0 x 10^7/Kg (n=14)
- Dose ≥ 3.0 x 10^7/Kg (n=5)
  - 22% (±12)

Time (years)
TK008 & TK007: Leukemia relapse
Effect of TK cell dose

Cumulative incidence of relapse or progression according to the dose of MM-TK cells (n=49)

- ≤ 1.0 x 10^7/Kg (n=15)
- 1.1 to 2.9 x 10^7/Kg (n=26)
- ≥ 3.0 x 10^7/Kg (n=8)

- 69% (±12)
- 22% (±9)
TK008: Non-relapse mortality

Cumulative incidence of non-relapse mortality

- All patients (n=24)
- Patients with IR (n=15)

Cumulative Incidence

Time (years)

0 1 2 3 4

0.0 0.2 0.4 0.6 0.8 1.0

10% (±7)

0%
UNMANIPULATED BM HAPLO

non-relapse mortality  relapse incidence

![Graph showing non-relapse mortality and relapse incidence.]

- CR3/Adv 61±5%
- CR1/2 28±4%

Years after transplantation
TK008 experimental arm
CD3+ T-cells immune reconstitution

CD3+ cells > 100/mcl (median 118 days)

TK1001A
TK1002A
TK1005A
TK1007A
TK1011A
TK1012A
TK1014A

CD3+ cells/mL

0 25 50 75 100 125 150 175 200 225 250 275 300

500 1000

days post tx

0

50

100

150

200

250

300

500

1000
TK008: GvHD

**Grade 2 / 3 acute GvHD**
- Onset from HSCT, median in days (95%CI): 6 / 1
- Duration of GvHD: 90 (26-153)
- Duration of ganciclovir treatment: 11 (6-27)
- Fully resolved / Ongoing: 14 (8-30)

**Chronic GvHD**
- 6 / 1
- 1 (ongoing)

**Cumulative incidence of grade 2 to 4 acute GvHD**

**Reduction of LNGFR^+ cells after 14-day ganciclovir therapy in patients with grade 2 to 3 acute GvHD**

- Pre-ganciclovir: 58 (±99)
- Post-ganciclovir: 9 (±13)

**p=0.06**
TK008 & TK007: GvHD kinetics

Time to GvHD resolution (n=16)

- 19% of patients GvHD-free at 7 days
- Median 13 days
- 56% at 14 days
- 69% at 21 days
- 75% at 28 days
- 82% at 35 days
- 82% at 42 days
- 91% at 49 days
- 100% at 56 days

Percent of patients vs. Time (days)
TK008 & TK007: DFS and OS
Effect of TK cell dose

DFS/PFS according to the dose of MM-TK cells (n=49)

OS according to the dose of MM-TK cells (n=49)
TK008: Overall survival

OS for all patients (n=24)

OS for patients with IR (n=15)
TK008: Disease-free survival

DFS/PFS for all patients (n=24)

DFS/PFS for patients with IR (n=15)
TK008: Overall Survival is free of chronic GvHD and immune-suppressive treatment

Survival free of immunosuppressive therapy (IST, n=24)
Haploidentical SCT is not inferior to matched donors
ITT outcome analysis: 8 years, 249 pts

The OS / TRM / RI according to donor source (MRD vs MUD vs haplo-HCT) were comparable (p=ns) in pts transplanted in CR.
Conclusions

- TK-cells therapy represents the largest clinical experience of immune gene therapy
- TK-cells therapy is provided by a centralized manufacturing and is feasible on a multicentre and multinational trial
- TK-cells infusions abate non-relapse mortality through a fast immune recovery in haploidentical transplant recipients
- HSV-TK suicide gene machinery effectively controls GvHD in 100% of affected patients in a fast time window; no additional long-term immune-suppressive treatment is anymore necessary in patients
- TK-cells abate leukemia relapse with a dose-dependent effect
- TK008 trial prospectively provide comparison evidence on the impact of immune gene therapy on long term leukemia cure without chronic GvHD
- Leukemia-free survival of patients receiving TK-cells is largely superior over expected trial design outcomes
Chiara Bonini, Arnon Nagler, Evangelia Yannaki, Maria Teresa Lupo Stanghellini, Attilio Bondanza, Giacomo Oliveira, Raffaella Greco, Eduardo Olavarria, Eva M Weissinger, Michael Stadler, Donald Bunjes, Dietger Niederwieser, Lutz Uharek, Wolfgang Bethge, John DiPersio, Michele Donato, Andrew Pecora, Antonio Lambiase, Claudio Bordignon
Thank you very much for your attention

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