Specific NK cell activation to treat relapsed/refractory (r/r) Hodgkin Lymphoma (HL) patients – final, updated data on clinical outcome, pharmacokinetics and pharmacodynamics of a phase 1 study investigating AFM13, a bispecific anti-CD30/CD16A TandAb

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Introduction
TandAb – a tetravalent, bispecific antibody molecule
TandAb Features
- comprised solely of scFv domains
- expressed as a single gene product
- the linkers favor an intermolecular head-to-tail dimerization resulting in tetravalent bispecific TandAbs

TandAb Properties
- high affinity: bivalent binding of each target
- very potent cytotoxicity: recruitment of NK- or T-cells
- no renal filtration: not continuous infusion necessary
- high specificity: no off-target activity
- excellent drug-like properties (production and stability)
- off-the-shelf product

AFM13 is a CD30/CD16A TandAb – Recruiting NK cells to kill tumors

Hodgkin Lymphoma with high medical need for efficacious and safe treatment
- Characterized by CD30+ malignant Reed-Sternberg cells
- Chemotherapy ± radiation therapy with a high cure rate but toxic; cardiac toxicity, organ failure, infertility, secondary malignancies
- 20-25% of HL patients relapse, 2nd line chemotherapy and autologous SCT induce durable remission in only 50% of the patients
- First targeted therapy for salvage treatment: brentuximab vedotin (BV), a CD30 – targeting antibody-drug-conjugate: high response rate but limited duration of response and progression free survival
- High medical need for effective and safe therapies → Immunotherapy may be an option

Methods
Phase 1 study: design
- Classical 3+3 dose escalation design: 0.01, 0.04, 0.15, 0.5, 1.5, 4.5, 7.0 mg/kg
- Infusion weekly for 4 weeks; 2nd cycle optional (5 pts.); 4 patients twice weekly regimen
- Inclusion criteria: progressive HL (CD30+); relapsed/refractory disease; > 2 prior treatments
- Objectives: Safety, tolerability, MTD, PK, PD, efficacy
- Twice weekly dosing could be initiated based on PK data

Study assessments
- Safety by CTCAE version 4.02 (clinical examinations, AEs, DLTs, lab); ADAs
- Pharmacokinetics
- Tumor response (“Cheson criteria”, 2007) 3 weeks after the last dose
- Pharmacodynamics (PD): CD30-, NK-cell populations, Cytokines (IFN-y, TNF-a, IL-2, IL-6, IL-10, IL-12)

Results
Tab. 1: Patients

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Safety population (n=28)</th>
<th>CTCAE grade 1/2</th>
<th>CTCAE grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>15 (53.6%)</td>
<td>14 (50.0%)</td>
<td>1 (3.6%)</td>
</tr>
<tr>
<td>Chills</td>
<td>11 (39.3%)</td>
<td>11 (39.3%)</td>
<td>0 (0.0%)</td>
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<td>Headache</td>
<td>8 (28.6%)</td>
<td>8 (28.6%)</td>
<td>0 (0.0%)</td>
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<tr>
<td>Nausea</td>
<td>5 (17.9%)</td>
<td>5 (17.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (17.9%)</td>
<td>5 (17.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (14.3%)</td>
<td>4 (14.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (14.3%)</td>
<td>0 (0.0%)</td>
<td>4 (14.3%)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (14.3%)</td>
<td>4 (14.3%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Efficacy
Fig 3: Change in tumor volume measured by CT-scan;
A: Efficacy population (n=26);
B: Patients refractory to brentuximab vedotin as most recent treatment prior to AFM13 (n=7);
C: Patients treated with AFM doses ≥ 2.5 mg/kg body weight (n=13)

Pharmacodynamics
Fig 4: CD69+ NK-cells relative to total number of NK-cells; dose cohorts ≥0.15 mg/kg

Other PD parameters
- Quantifiable serum cytokine levels could only be measured for IL-6 (n=8), IL-8 (n=4), IL-10 (n=3) and TNF-a (n=7);
No cytokines detected in patients receiving doses <0.5 mg/kg
- ADCC activity through quantification of granocyte B and serum outcome markers TARC, BAT3 and sIL12A did not provide conclusive information

Conclusions
- AFM13 is well tolerated
- AFM13 showed activity in terms of pharmacodynamics and efficacy, incl. BV refractory patients
- Treatment duration and dose regimen need to be optimized
- A phase 2 study in r/r HL is in preparation

Fig. 1: Formation of TandAb
Fig. 2: Mode of action; AFM13 brings NK-cells in close proximity to tumor cell; NK-cells get activated and kill tumor cells
Fig. 3: Change in tumor volume measured by CT-scan
Fig. 4: CD69+ NK-cells relative to total number of NK-cells; dose cohorts ≥0.15 mg/kg
Fig. 5: sCD30 levels in serum; relative change from baseline

Disclosures: Rothe, Sasse, Eichauer, Hummel: No conflict if interest indicated. Topp: Amplon, Honoraria, Research funding. Ravic: Affirmed Therapeutics AG, Heidelberg, Germany