NGR-hTNF, a vascular targeting agent (VTA), in previously treated patients with malignant pleural mesothelioma (MPM): A phase II study

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TNF-α has shown potent antitumor and antivasular activity in preclinical models. However, its clinical use has been hampered by severe systemic toxicity, with MTD significantly lower than ED\(^1\).

CD13 expression in MPM

Recombinant fusion protein\(^2\)

Cyclic NGR peptide selectively binds CD13 overexpressed on the tumor vessels

\(^1\)Cancer Res 1987;47:2986-9
NGR-hTNF: Preclinical activity at low dose

Antitumor activity was shown also at low doses in the picogram range (100 pg), equivalent to 0.2 μg/m² in humans (phase I trial starting-dose)

J Clin Invest 2002; 110: 475-82
NGR-hTNF: Early clinical development

- **Phase I**\(^1\):
  - DLs: 0.2 - 60 µg/m\(^2\)
  - DLTs: gr. 3 dyspnea and acute infusion reaction (60 µg/m\(^2\))
  - MTD: 45 µg/m\(^2\)

- **Phase I low-dose range**\(^2\):
  - DLs: 0.2 - 1.6 µg/m\(^2\)
  - No DLTs/MTD
  - 0.8 µg/m\(^2\) selected as the optimal biological dose based on safety, DCE-MRI changes, soluble TNF-receptor kinetics, and preliminary activity

\(^1\)ASCO 2008 - Abs 3521
\(^2\)ASCO 2007 - Abs 3540
NGR-hTNF in MPM: Disease background

- Advanced MPM is a devastating disease with increasing incidence worldwide

- The pemetrexed-cisplatin combination is standard of care in 1\textsuperscript{st} line with median PFS and OS of 5.7 and 12.1 months, respectively\textsuperscript{1}

- However, patients progressing after 1\textsuperscript{st} line have an aggressive disease with median PFS of 1.5 months and DCR of 19% reported in the no-treatment arm of a phase III trial\textsuperscript{2}

- Neither regulatory-approved nor widely-accepted 2\textsuperscript{nd} line therapy are currently available

\textsuperscript{1}JCO 2003; 21:2636-2644
\textsuperscript{2}JCO 2008; 26:1698-1704
NGR-hTNF in MPM: Study design

- Multicenter, open-label phase II trial
- Two-stage design:
  - 16 and 27 pts after 1st and 2nd stage
- Primary endpoint: 3-month PFS rate
  - 7 (44%) and 13 (48%) patients progression-free at 3 months after 1st and 2nd stage
- Key inclusion criteria:
  - Age >18 years
  - At least 1 prior systemic regimen
  - Radiologically-documented PD
  - PS 0-2
  - Written informed consent

NGR-hTNF 0.8 µg/m²
1-hour iv infusion

3 weeks 3 weeks

Until PD

Tumor restaging (MPM-modified RECIST criteria)

A subsequent cohort of 12 patients treated at 0.8 µg/m² with a weekly schedule

- 43 patients enrolled in the triweekly cohort from May 2007 to January 2008
- 14 patients enrolled in the weekly cohort from February 2008 to June 2008
# NGR-hTNF in MPM: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Triweekly cohort n=43 (%)</th>
<th>Weekly cohort n=14 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>64 (54-80)</td>
<td>68 (50-86)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (63)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (37)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (56)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>1-2</td>
<td>19 (44)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Primary tumor histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial</td>
<td>34 (79)</td>
<td>11 (79)</td>
</tr>
<tr>
<td>Nonepithelial</td>
<td>9 (21)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>EORTC prognostic score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>34 (79)</td>
<td>11 (79)</td>
</tr>
<tr>
<td>Poor</td>
<td>9 (21)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Prior systemic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemetrexed / platinum</td>
<td>40 (93)</td>
<td>13 (93)</td>
</tr>
<tr>
<td>Gemcitabine / cisplatin</td>
<td>3 (7)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Best response to prior therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>5 (12)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>SD</td>
<td>24 (56)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>PD / Unknown</td>
<td>14 (32)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>PFS on prior therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6 months</td>
<td>24 (67)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>19 (33)</td>
<td>5 (36)</td>
</tr>
</tbody>
</table>
NGR-hTNF in MPM: Safety

- Drug-exposure:
  - 171 cycles (range, 1-18) in the triweekly cohort
  - 262 infusions (range, 4-65) in the weekly cohort

- One grade 3 drug-related adverse event (triweekly cohort)

- Most common drug-related toxicity: grade 1-2 chills, transiently occurring during first infusions

- The weekly dosing schedule did not change the toxicity profile
NGR-hTNF in MPM: Treatment-related adverse events

At the end of therapy, PS stable or improved in 61% of patients

At the end of therapy, PS stable or improved in 79% of patients
### NGR-hTNF in MPM: Best overall response

<table>
<thead>
<tr>
<th></th>
<th>Triweekly (n=43)</th>
<th>Weekly (n=14)</th>
<th>All (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response (PR)</td>
<td>2%</td>
<td>-</td>
<td>2%</td>
</tr>
<tr>
<td>Stable disease° (SD)</td>
<td>42%</td>
<td>50%</td>
<td>44%</td>
</tr>
<tr>
<td>Disease control rate (PR + SD)</td>
<td>44%</td>
<td>50%</td>
<td>46%</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>37%</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Non-assessable*</td>
<td>19%</td>
<td>-</td>
<td>14%</td>
</tr>
</tbody>
</table>

*As best response at any time

*8 patients were withdrawn before first restaging due to symptomatic deterioration (n=6) and early death (n=2)

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January 2008

June 2008
## NGR-hTNF in MPM: Efficacy results (ITT analyses)

<table>
<thead>
<tr>
<th></th>
<th>Triweekly (n=43)</th>
<th>Weekly (n=14)</th>
<th>All (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-free survival (PFS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>2.8</td>
<td>3.0</td>
<td>2.8</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(2.3-3.3)</td>
<td>(1.9-4.1)</td>
<td>(2.3-3.3)</td>
</tr>
<tr>
<td>3-month rate°</td>
<td>37%</td>
<td>50%</td>
<td>41%</td>
</tr>
<tr>
<td>6-month rate°</td>
<td>11%</td>
<td>36%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>PFS in patients with disease control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>4.4</td>
<td>9.1</td>
<td>4.7</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(4.0-4.8)</td>
<td>(4.7-13.4)</td>
<td>(4.0-5.4)</td>
</tr>
<tr>
<td><strong>Overall survival (OS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>11.6</td>
<td>NR*</td>
<td>12.1</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(5.6-17.6)</td>
<td>-</td>
<td>(7.2-17.0)</td>
</tr>
</tbody>
</table>

°Kaplan-Meyer estimates

*NR=not reached after a median follow-up of 12.5 months
NGR-hTNF in MPM: Progression-free survival

- Triweekly cohort
  - 6-month PFS rate = 11%
  - Median PFS in patients with disease control = 4.4 months
  - Events/N = 39/43

- Weekly cohort
  - 6-month PFS rate = 36%
  - Median PFS in patients with disease control = 9.1 months
  - Events/N = 13/14
NGR-hTNF in MPM: Overall survival

Median OS = 12.1 months
Follow-up = 17.9 months
Events/N = 40/57
NGR-hTNF in MPM: Post-hoc analysis

In multivariate Cox analyses:

- Male gender (p=.02) associated to longer PFS
- PS of 0 (p=.003) and epithelial histology (p=.03) associated to longer OS
NGR-hTNF in MPM:
Conclusions

- NGR-hTNF 0.8 µg/m² (q3w or weekly) is well tolerated in MPM patients previously treated with a pemetrexed-based chemotherapy

- Overall results included a DCR of 46%, maintained for a median time of 4.7 months, and a median OS of 12.1 months

- NGR-hTNF will be further developed in advanced MPM and these time-related outcomes need to be evaluated in a randomized setting

NGR-hTNF is currently developed either as single agent or in combination in: CRC, HCC, SCLC, NSCLC, and OC
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