NGR-hTNF plus chemotherapy as first-line therapy of non-small cell lung cancer (NSCLC)

Background and Methods

- NGR-hTNF consists of TNF tumor necrosis factor) fused with the peptide NGR (asparagine-glycine-arginine) that is able to selectively target COX-1-overexpressing tumor blood vessels.
- Overexpression of COX-1 in NSCLC has been associated with very poor prognosis and increased angiogenesis.
- In phase I trial, NGR-hTNF 0.8 µg/m² was safely given in combination with cisplatin.
- For the chemotherapeutic agents, improved overall survival favoring cisplatin-pemetrexed compared with cisplatin-gemcitabine versus cisplatin-pemetrexed.
- For the antiangiogenic agents, there is a restriction of use in patients with squamous histology.

Chemotherapy (CT) according to histology:
- Squamous histology:
  - Cisplatin 80 mg/m² day 1 + Gemcitabine 1,250 mg/m² day 1, 8 (6 cycles)
  - Cisplatin 80 mg/m² day 1 + Pemetrexed 500 mg/m² day 1 (6 cycles)
- Nonsquamous histology:
  - Cisplatin 80 mg/m² day 1 + Pemetrexed 500 mg/m² day 1 (6 cycles)
  - NGR-hTNF + CT (6 cycles)

Baseline patient characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>NGR-hTNF + CT (N=61)</th>
<th>CT alone (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>62 (38-78)</td>
<td>62 (38-77)</td>
</tr>
<tr>
<td>Sex</td>
<td>55 (66%)</td>
<td>58 (68%)</td>
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<tr>
<td>Performance status</td>
<td>ECOG 0 (95%)</td>
<td>ECOG 0 (94%)</td>
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<tr>
<td>median (range)</td>
<td>22 (26%)</td>
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<tr>
<td>Histologic subtype</td>
<td>Nonsquamous (44%)</td>
<td>Nonsquamous (42%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Nonsmoker (40%)</td>
<td>Nonsmoker (43%)</td>
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<tr>
<td>EGFR mutation status</td>
<td>Wild type or unknown</td>
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</tbody>
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Overall efficacy results

- Efficacy results in patients with squamous cell histology

Conclusions

- NGR-hTNF is well tolerated in combination with both chemotherapy regimens, cisplatin/pemetrexed and cisplatin/gemcitabine, regardless of histology.
- There were no pulmonary hemorrhage or bleeding events commonly associated with antiangiogenic or antivascular agents in patients with squamous cell histology.
- Subset analyses suggest a potential clinical benefit for the combination compared with chemotherapy alone in squamous NSCLC in larger sample size trial.

Study design

- Open-label, randomized phase II trial
- Chem-naïve, stage IIB/IV NSCLC
- Brain metastases (if adequately treated)
- Performance status (PS) 0-1
- Primary study endpoint: progression-free survival (PFS)
- Secondary study endpoints: response rate, overall survival, safety

Hypothesis testing: % of patients in PFS

Adverse events by arm

<table>
<thead>
<tr>
<th>Arm A: CT alone</th>
<th>N=69</th>
<th>N=61</th>
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<tbody>
<tr>
<td>PFS rates at 6 months</td>
<td>49% (35-63)</td>
<td>47% (35-63)</td>
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<tr>
<td>OS rates at 12 months</td>
<td>64% (54-74)</td>
<td>67% (58-76)</td>
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Efficacy results in patients with nonsquamous histology

- Progression-free survival (PFS) at 6 months
- Overall survival at 12 months

Subset analyses in patients with nonsquamous histology