Phase II trial of NGR-hTNF and doxorubicin in relapsed small-cell lung cancer (SCLC)

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Background and methods

- Tumor necrosis factor-alpha (TNF-α) showed powerful preclinical antitumor activity, but its clinical use was hampered by severe toxicity.
- NGR-hTNF consists of TNF-α fused with the tumor homing peptide NGR (asparagine-glycine-arginine).
- Maximal synergism achieved with 2-hour delay between low-dose NGR-hTNF and doxorubicin dosing.
- Low-dose NGR-hTNF increased both number of tumor cells reached by doxorubicin and intracellular amount of doxorubicin.
- In phase 1 trial, NGR-hTNF 0.8 μg/m² plus doxorubicin 75 mg/m² was selected for phase 2 trial and showed favorable tolerability and promising activity.

**Background and methods**

**Tumor necrosis factor-alpha (TNF-α)** showed powerful preclinical antitumor activity, but its clinical use was hampered by severe toxicity. NGR-hTNF consists of TNF-α fused with the tumor homing peptide NGR (asparagine-glycine-arginine). Maximal synergism achieved with 2-hour delay between low-dose NGR-hTNF and doxorubicin dosing. Low-dose NGR-hTNF increased both number of tumor cells reached by doxorubicin and intracellular amount of doxorubicin. In phase 1 trial, NGR-hTNF 0.8 μg/m² plus doxorubicin 75 mg/m² was selected for phase 2 trial and showed favorable tolerability and promising activity.

**Study design**

- Multicenter, single-arm phase II trial
- Two-stage accrual design
- Primary endpoint: PFS
- Key Inclusion criteria:
  - ≥ 18 years
  - ≥ 1 prior systemic regimen
  - PS 0-2 and LVEF 55%
- Based on RECIST after 6 weeks (2 cycles) of therapy
- Dose escalation from 0.8 up to 550 mg/m²

**Baseline characteristics (n=28)**

| Characteristic |Median age in years (range)| Gender| ECOG performance status
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<tr>
<td>Median age in years (range)</td>
<td>63 (41-76)</td>
<td>Gender</td>
<td>male female</td>
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<td>ECOG performance status</td>
<td>13 (46%)</td>
<td>15 (54%)</td>
<td>13 (46%)</td>
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<td>Prior number of regimens</td>
<td>2 (71%)</td>
<td>8 (29%)</td>
<td>2 (71%)</td>
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<td>Best response to prior therapy</td>
<td>16 (57%)</td>
<td>12 (43%)</td>
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**Conclusions**

- The combination of NGR-hTNF and doxorubicin can be safely given in relapsed SCLC patients
- NGR-hTNF plus doxorubicin showed evidence of activity, which was weakly correlated with prior platinum sensitivity
- Low baseline NLR strongly associated with improved survival in both platinum-resistant and platinum-sensitive patients
- Further development of this combination is of interest

References


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References