Nerofe™: A novel Human Peptide Hormone for Treatment of Cancer
(Phase 1 results)

Nerofe Compound Highlights

**Description**
- Novel human peptide hormone (84AA, API 14AA)
- Novel mechanism of action
- FDA orphan drug status
- Low cost of production
- Excellent safety profile.
- Relatively high half-life (more than 4h in human)
- Phase 1 ongoing

**Activities**
- Nerofe affects cancer cells:
  - Directly through T1/ST2 receptor which is overexpressed in those cells.
  - Indirectly through endothelial cells by regulating angiogenesis
  - Indirectly through immune cells by regulating cytokine secretion.
- Nerofe is therefore effective in treatment for cancer.

**Triple action in cancer treatment**
- Cytotoxic for cancer and inflamed cells.
- Modulates immune system response.
- Inhibits angiogenesis through inhibition of secretion of major pro-angiogenic cytokines.

Pre-Clinical results

**Breast Cancer**
Babal/C females were inoculated with 4 million EMT6 cells (mammary gland carcinoma) SC. The mice were then treated with Nerofe while a control group was treated with Saline. The tumor size was periodically measured every three days as described in fig 2.

![Fig 2: Nerofe’s effect on Tumor growth in Balb/C mice injected S.C. with EMT6 murine carcinoma cells](image)

Phase 1 Clinical Trial status

**Background**
This apoptosis factor (NEROFE™) is a 14-a.a. modified form of a hormone-like peptide present in the human thymus, which plays a key role in immune system regulation. Nerofe is acting through novel MOA mediated by T1/ST2 receptor.

**Methods**
This ongoing, single-center, first-in-human, 3+3 dose-escalation study of this factor given I.V. at 6 mg/m²-96 mg/m² over 5 3-pt cohorts (3 times a week; 28-day cycle) examines the MTD, safety, PK profile, and anti-tumor activity in patients with advanced solid tumors. Patients undergo tumor assessments every other cycle. Samples for PK are taken on days 1 of cycles 1 and 2.
Results

To date, 15 patients with advanced/metastatic solid tumors have been enrolled (3+3 protocol).

- **Toxicity:**
  MTD has not been reached. Treatment was well-tolerated with no cumulative toxicity.

- **Pharmacokinetic analysis:**
  AUC, Cmax and t½, were calculated and were dose-dependent and approximately linear.

- **Efficacy:**
  5 of 15 evaluable patients have been treated for at least 3 cycles and were considered SD through this period.
  One patient suffering from spinal cord neoplasia (treated for +11M) was walking with the use of a treadmill when entering the trial, because of the tumor pressing on her spinal cord. Halfway in treatment was walking freely again. A biopsy taken from her prior treatment showed 30% dividing cells (Ki67 positive), following treatment only 10% dividing cells were present. Scar tissue and bleeding were observed in that biopsy – suggesting an anti-angiogenesis process took place.

- **Mode of Action (MOA)**
  - **Strong anti-angiogenic effect**
    Nerofe administration was associated with orders of magnitude decreases in plasma levels of Angiopoietin-1, PDGF AA, TGF-β1 and VEGF in all patients in cohorts 3 and 4. This effect wasn’t observed on the same extent on the lower treatment dosage, suggesting a Nerofe dosage dependent induction of anti-angiogenesis.

<table>
<thead>
<tr>
<th>Percent change in serum level of angiogenesis factor during treatment</th>
<th>Angiopoietin-1</th>
<th>FGF acidic</th>
<th>FGF Basic</th>
<th>PDGF-AA</th>
<th>PDGF-BB</th>
<th>VEGF-D</th>
<th>TGF-β1</th>
<th>VEGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>906%</td>
<td>1201%</td>
<td>195%</td>
<td>1379%</td>
<td>2271%</td>
<td>265%</td>
<td>18%</td>
<td>117%</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>-90%</td>
<td>-59%</td>
<td>-76%</td>
<td>-82%</td>
<td>-95%</td>
<td>-47%</td>
<td>-80%</td>
<td>-40%</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>-77%</td>
<td>-26%</td>
<td>-34%</td>
<td>-79%</td>
<td>-82%</td>
<td>-62%</td>
<td>-59%</td>
<td>-54%</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>-50%</td>
<td>-27%</td>
<td>-13%</td>
<td>-73%</td>
<td>-78%</td>
<td>-72%</td>
<td>-20%</td>
<td>-63%</td>
</tr>
</tbody>
</table>

+1/↓: number of patients in which levels raised/dropped following treatment

Fig 3: percent change of serum angiogenesis factors during treatment

- **Strong anti-proliferative effect**
  In 3 patients with elevated serum EGF levels, levels decreased normal values.

- **Immmuno-modulatory effect**
  In Cohorts 3 and 4 major pro-inflammatory cytokines serum levels increased significantly, an effect not seen on the lower treatment dosages, suggesting a Nerofe dosage dependent induction immune system response to the tumor.

<table>
<thead>
<tr>
<th>Percent change in cytokine level during treatment</th>
<th>GM-CSF (20)</th>
<th>IL-12p70 (33)</th>
<th>IL-2 (48)</th>
<th>IL-21 (52)</th>
<th>TNF-a (75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>2173%</td>
<td>469%</td>
<td>-100%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Cohort 2</td>
<td>-97%</td>
<td>-76%</td>
<td>-100%</td>
<td>-61%</td>
<td>-5%</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>11%</td>
<td>83%</td>
<td>84%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Cohort 4</td>
<td>5613%</td>
<td>477%</td>
<td>242%</td>
<td>1326%</td>
<td>74%</td>
</tr>
</tbody>
</table>

Fig 4: percent change of serum cytokines during treatment

- **Selective biomarker for efficacy**
  Patients whose tumor were positively stained for T1/ST2 receptor stayed in trial with SD significantly longer than patients who had a tumor that was negatively stained.

Conclusions

Nerofe administered at doses up to 96 mg/m² is safe, well-tolerated and demonstrates interesting anti-angiogenic activity in combination with increased immune cytokines. Tumor T1/ST2 expression may be a biomarker for sensitivity to Nerofe. Dose-escalation continues in this trial.

Patents

Strong IP protection:
1. One NCE patent granted in USA and other countries.
2. One patent for anti-angiogenic and anti-metastatic activity of Nerofe.
3. One patent for active derivatives of Nerofe.

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