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.

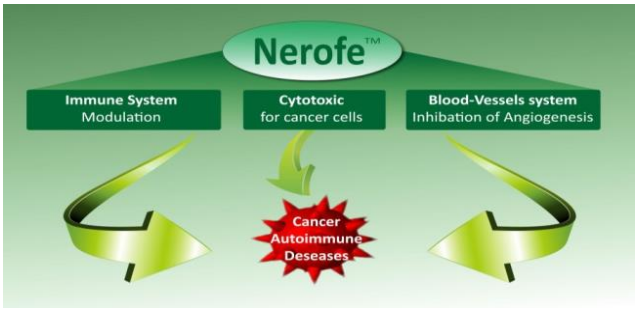

Fig 1: Nerofe's Triple Action in Cancer Treatment

Pre-Clinical results

Breast Cancer

Balb/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.

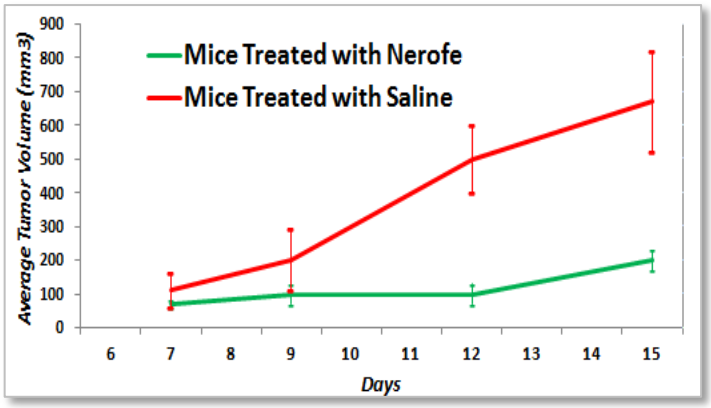

Fig 2: Nerofe's effect on Tumor growth in Balb/C mice injected S.C. with EMT6 murine carcinoma cells

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/m^2-96 mg/m^2 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 $t_{½}$ 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 shown 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 Angiopoeitin-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.

Percent change in serum level of angiogenesis factor during treatment

	Angiopoeitin-1		FGF acidic		FGF Basic		PDGF-AA		PDGF-BB		VEGF-D		TGF-β1		VEGF	
Cohort 1		906%		1201%		195%		1379%		2271%		265%		18%		117%
Cohort 2	2↓	-90%	2↓	-62%	2↓	-74%	2↓	-92%	2↓	-95%	1↓	-47%	2↓	-80%	2↓	-40%
Cohort 3	2↓	-77%	3↓	-26%	2↓	-34%	2↓	-79%	2↓	-82%	3↓	-62%	2↓	-59%	3↓	-54%
Cohort 4	3↓	-50%	2↓	-27%	2↓	-13%	3↓	-73%		-78%	2↓	-72%	2↓	-20%	2↓	-63%

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

Fig 3: percent change of serum angiogensis factors during treatment

○ Strong anti-proliferative effect

In 3 patients with elevated serum EGF levels, levels decreased normal values.

○ *Immuno-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.

	GM-CSF (20)	L-12p70 (33	IL-2 (48)	IL-21 (52)	TNF-a (75)
Cohort 1	2173%	469%		-100%	4%
Cohort 2	-97%	-76%	-100%	-61%	-5%
Cohort 3	11%	83%		84%	31%
Cohort 4	5613%	477%	242%	1326%	74%

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.

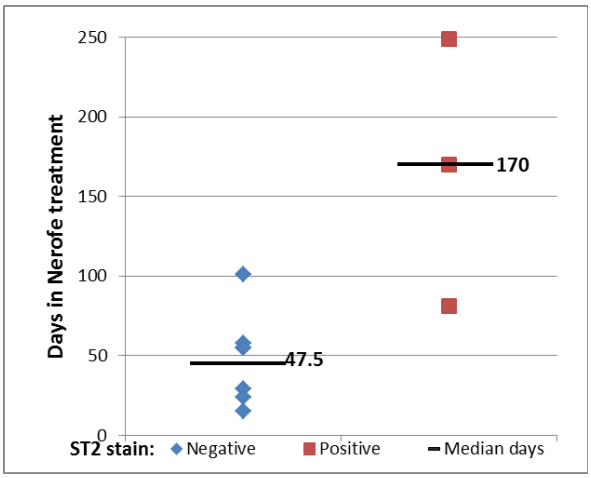

Fig 5: Time of SD is related to T1/ST2 tumor staining

Conclusions

Nerofe administered at doses up to 96 mg/m^2 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.

Contacts

Dr. Yoram Devary, CTO, Immune System Key
ydevary@immunesk.com
+972 502 597032
www.ImmuneSK.com