

Phase II study of NGR-hTNF, a selective vascular targeting agent (VTA), in previously treated patients with advanced hepatocellular carcinoma (HCC)

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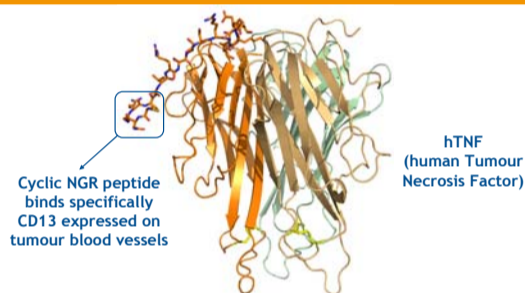
ABSTRACT

Background: HCC is a highly vascularised and poor-prognosis tumor with median survival of 6 months in untreated pts with advanced-stage disease, class C according to Barcelona Clinic Liver Cancer (BCLC). NGR-hTNF is a VTA consisting of TNF- α fused to the tumor-homing peptide NGR, which binds an aminopeptidase N overexpressed on tumor vessels. **Methods:** Advanced-stage HCC pts received NGR-hTNF 0.8 $\mu\text{g}/\text{m}^2$ infused over 1-hour every 3 weeks (q3w). Progression-free survival (PFS) was the primary study aim with restaging performed q6w. A two-stage design was used with 16 and 27 pts to be enrolled. Subsequently, an additional 12 pts were treated with 0.8 $\mu\text{g}/\text{m}^2$ on a weekly basis (weekly cohort). **Results:** Pts with documented progression after loco-regional treatments (59%), systemic therapies (56%; range, 1-3 regimens), or both (33%) received 90 cycles (range, 1-18+). Pt characteristics were: median age 65 years (range, 34-79); M/F 21/6; PS 0/1 18/9; Child-Pugh (C-P) A/B 21/6, BCLC B/C 5/22. No grade 3-4 drug-related toxicities were observed. Main grade 1-2 toxicities were short-lived, infusion-related chills (55%). The median PFS was 2.3 months (95% CI, 1.7-2.9). The disease control rate (DCR) was 30% and the confirmed response rate was 8%. A complete response (4%) lasting 11.5+ months was observed in a 76-year-old sorafenib-refractory, C-P B pt. A partial response (4%) with a 78% tumor reduction was reported in a further C-P B pt. Additionally, a 28% tumor shrinkage was detected in one out of 6 patients (22%) experiencing stable disease. Pts who achieved disease control received a median of 5 cycles (range, 4-18+) and had a median PFS of 4.3 months (range, 3.0-12.8+). With a median follow-up of 14.0 months (95% CI, 12.7-15.3), 8 pts (30%) were still alive and the median overall survival (OS) time was 9.1 months (range, 1.3-21.3+). The survival rates at 12 and 18 months were 34% and 22%, respectively. In the weekly cohort, there was no worsening of toxicity and the DCR was 33%. The subset of 12 sorafenib-pretreated pts reported a response rate of 8% and a DCR of 33%, whereas the median PFS and OS were 2.3 and 9.5 months, respectively. **Conclusions:** NGR-hTNF is well tolerated and appears to have promising antitumor activity in previously treated HCC patients. The drug will be further developed in this setting.

Background

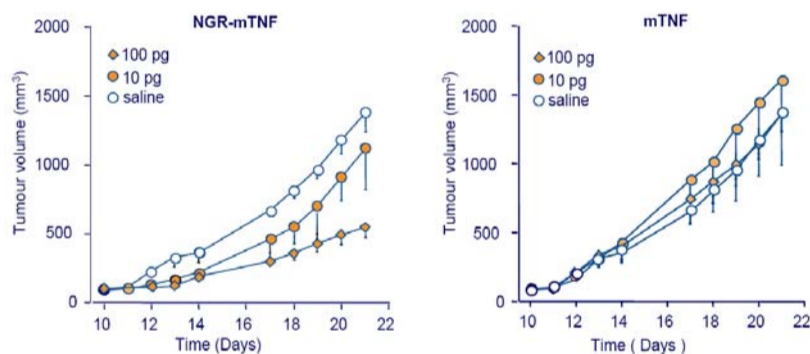
- A large body of preclinical evidences have shown that tumour necrosis factor-alpha (TNF- α) has potent antitumour activity. However, its clinical use was hampered by severe systemic toxicity, with MTD significantly lower than ED in humans¹
- NGR-hTNF is a novel vascular targeting agent (VTA) that has been genetically engineered by coupling the N-terminus of human TNF- α with the C-terminus of the tumour-homing peptide Cys-Asn-Gly-Arg-Cys (NGR) (Figure 1)
- The cell surface receptor for the NGR-containing peptide is a CD13/aminopeptidase N (APN) isoform selectively expressed by endothelial cells of newly formed human tumour vessels²⁻⁴

Figure 1. Structure of the NGR-hTNF molecule (1 subunit)



- In preclinical models,⁴ NGR-mTNF was found to have antitumour activity also at doses in the picogram range (100 pg) (Figure 2), equivalent to a dose of 0.2 $\mu\text{g}/\text{m}^2$ in humans, the selected starting dose in phase I trial

Figure 2. Preclinical antitumour activity at low doses of NGR-mTNF and mTNF



Early clinical development of NGR-hTNF

- In phase I study evaluating a dose-interval ranging from 0.2 to 60 $\mu\text{g}/\text{m}^2$ the MTD of NGR-hTNF was established at 45 $\mu\text{g}/\text{m}^2$ when given as single agent once every 3 weeks⁵
- A further trial exploring the low-dose range of NGR-hTNF from 0.2 to 1.6 $\mu\text{g}/\text{m}^2$ selected the dose of 0.8 $\mu\text{g}/\text{m}^2$ as the optimal biological dose, based on dynamic imaging changes and preliminary antitumour activity⁶

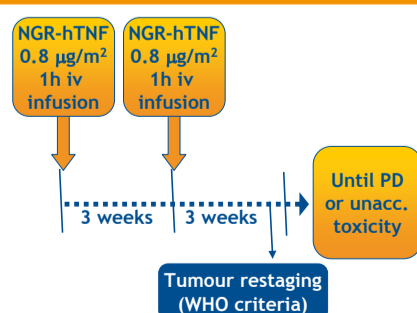
Disease background

- HCC is the 3rd leading cause of cancer deaths worldwide with increased incidence in the Western world
- Until recently, there has been no agreed upon standard therapy for the majority of HCC patients whose tumors are not amenable to potentially curative therapy⁷
- In a recent phase III trial, Child-Pugh A patients treated with sorafenib experienced a significantly longer OS and TTP compared with patients receiving placebo. Additionally, a 2% partial response rate was reported in sorafenib-treated patients⁸
- Interestingly, HCC is a highly hypervascular tumour in which neovascularisation contributes to growth and metastasis⁹

Methods

Figure 3. Study design, dose and assessment

- Multicentre (3 centres)
- Phase II
- 2-stage design
- 16 & 27 patients in 1st & 2nd stage
- Inclusion:
 - Age >18 years
 - At least one standard treatment
 - Child-Pugh A-B
 - PS 0-1
 - Adequate baseline functions
 - Normal cardiac function
 - Written informed consent



Safety

- 95 cycles were administered with a median of 2 (range, 1 to 23)
- No grade 3-4 treatment-related adverse events were observed
- The most common treatment-related adverse events were grade 1-2 chills (55%), and transient blood pressure increase (11%), generally occurring during the first infusions

Table 1. Treatment-related adverse events occurring in > 5% of patients

Event	Grade 1	Grade 2	Grade 3	Grade 4
Chills	9 (33%)	6 (22%)	-	-
Blood pressure increase	3 (11%)	-	-	-
Fatigue	2 (7%)	-	-	-

Results

Table 2. Baseline characteristics

Characteristics	n=27 (%)
Median age, years (range)	67 (34-79)
Gender	
Male	21 (78)
Female	6 (22)
ECOG performance status	
0	18 (67)
1	9 (33)
Child-Pugh status	
A	20 (74)
B-C	7 (26)
AFP >400 ng/mL	
Yes	12 (44)
No	15 (56)
Prior treatments	
Resection/Transplantation	9 (33)
Ablation	5 (18)
TACE	16 (59)
Sorafenib/Chemotherapy/Hormonal therapy	15 (56)

Efficacy

- One complete response (4%) lasting 15.8+ months (Figure 4) and one partial response (4%) lasting 4.4 months were observed
- An additional 6 patients (22%) had stable disease (SD) as best response, yielding a disease control rate (DCR) of 30%
- The median PFS was 2.3 months (range, 1.3-15.8+) in ITT population (Figure 5) and 4.3 months (range, 3.0-15.8+) in patients with disease control
- After a median follow up time of 26.1 months, the median OS was 8.9 months (range, 1.3-28.3+) and the 1-year and 2-year survival rates were 27% and 17%, respectively (Figure 6)

Figure 4. Complete response in a hypervascular, infiltrating HCC in a sorafenib-refractory patient

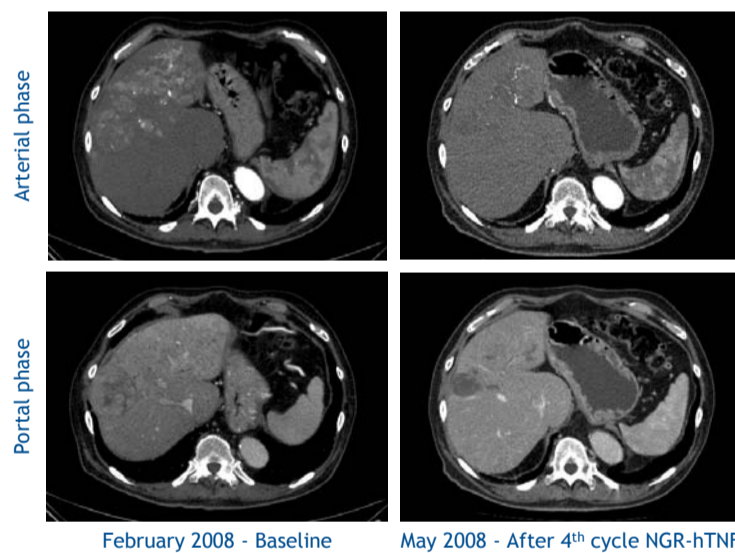


Figure 5. Progression-free survival

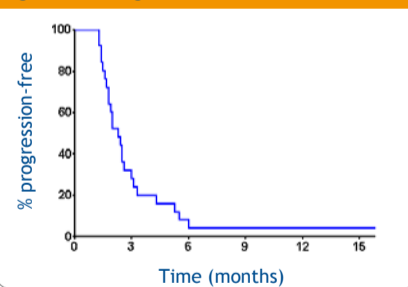
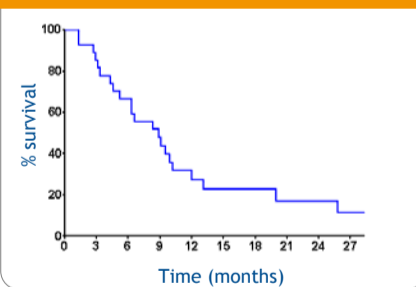


Figure 6. Overall survival



- In a subsequent cohort (n=13) treated with a weekly schedule, the DCR was 33%
- The subset of 12 sorafenib-pretreated patients enrolled in the current study had a response rate of 8% and a DCR of 33%, whereas the median OS was 9.5 months

Conclusions

- NGR-hTNF is well tolerated and shows preliminary evidence of activity in pretreated patients with advanced HCC
- The drug will be further developed in combination in this setting

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