

Phase II study of NGR-hTNF, a selective vascular targeting agent (VTA), administered as single agent at low dose in pre-treated patients with hepatocellular carcinoma (HCC)

A. Santoro¹, G. Citterio², L. Rimassa¹, T. Pressiani¹, G. Rossoni², G. Donadoni¹, A. Zanoni¹, F. Caligaris-Cappio², A. Lambiase³, C. Bordignon³

¹Istituto Clinico Humanitas, Rozzano, Milan, Italy; ²Istituto Scientifico San Raffaele, Milan, Italy; ³Molmed, Milan, Italy

ABSTRACT

Background: NGR-hTNF is a VTA exploiting a tumour homing peptide (NGR) selectively binding tumour blood vessels, where NGR-hTNF specific binding relies on dynamic interactions with TNF-receptors and aminopeptidase N/CD13. NGR-hTNF combines activity on tumour vascular permeability and direct anticancer activity, both at low doses and at high doses. **Methods:** Patients with unresectable, recurrent or metastatic HCC were treated with a low dose of NGR-hTNF given at 0.8 µg/m² as 1-hour intravenous infusion every 3 weeks (q3w). This phase II trial had a 2-stage design with 16 and 27 patients to be enrolled in first and second stage, respectively. Progression-free survival (PFS) was the primary endpoint and tumour reassessment according to WHO criteria was performed q3w. Results: Twenty-seven patients with progressive disease following prior loco-regional treatment (59%), systemic therapy (56%), or both (33%), were recruited. Patients characteristics were: median age 67 years (range, 34 to 79); male/female 21/6; PS 0/1 18/9; Child-Pugh score A/B 21/6. Globally, 82 cycles (median, 2; range, 1 to 10) were administered. Main grade 1-2 toxicities per patient were infusion-related constitutional symptoms, including chills (55%) and transient blood pressure increase (11%). Neither grade 3-4 treatment-related adverse events nor toxicity-related deaths were observed. Median PFS duration was 2.3 months (95% CI, 1.7 to 2.9 months). One complete response lasting 6.6+ months was observed in a sorafenib-refractory patient and one partial response lasting 4.4 months was reported in a patient with lung metastases. Stabilizations of disease occurred in an additional 6 patients with a median duration of 3.8 months (range, 2.6 to 5.9 months). Median PFS in stable or responder patients was 4.3 months (95% CI, 2.7 to 5.8 months). **Conclusions:** NGR-hTNF given at 0.8 µg/m² q3w is well tolerated and shows promising antitumour activity in previously treated patients with advanced HCC. The drug will be further developed as single agent in this setting also exploring a weekly schedule of administration.

Background

- tumour necrosis factor- α (TNF- α) has shown in many preclinical models to have potent antivascular and antitumour activity. However, its clinical use has been hampered by severe systemic toxicity, with MTD significantly lower than ED in humans¹
- NGR-hTNF is a selective 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 isoform overexpressed by endothelial cells of newly formed human tumour vessels,²⁻⁴ including hepatocellular carcinoma
- In preclinical models, NGR-hTNF was found to have antitumour activity also when administered at doses in the picogram range (Figure 2), equivalent to a dose of 0.2 µg/m² in humans, the selected starting dose of Phase I trial

Figure 1. NGR-hTNF: a recombinant fusion protein consisting of NGR peptide combined with human Tumour Necrosis Factor- α (hTNF- α)

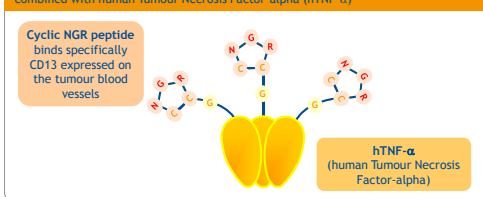
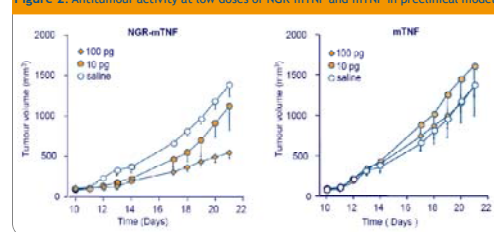


Figure 2. Antitumour activity at low doses of NGR-hTNF and mTNF in preclinical model



Phase I trials

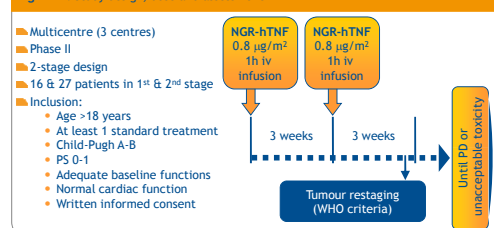
- A phase I study evaluating a dose-interval ranging from 0.2 to 60 µg/m² established the MTD of NGR-hTNF at 45 µg/m² when given as single agent once every 3 weeks⁵
- Conversely, a further phase I trial exploring the low-dose range of NGR-hTNF from 0.2 to 1.6 µg/m² selected the dose of 0.8 µg/m² as the optimal biological dose (OBD), based on dynamic imaging changes and preliminary antitumour activity⁷

Disease background

- Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer deaths worldwide. Until recently, there has been no agreed upon standard therapy for the significant majority of HCC patients whose tumours are not amenable to potentially curative therapy⁸
- In a recent phase III trial, Child-Pugh class A patients treated with sorafenib experienced a significantly longer OS and TTP compared with patients receiving placebo. Additionally, a two percent partial response rate was reported in sorafenib-treated patients⁹
- Interestingly, HCC is a highly hypervascular tumour in which neovascularization contributes to growth and metastasis⁹

Methods

Figure 3. Study design, dose and assessment



Results

- From February 2007 to June 2008, twenty-seven HCC patients previously treated with loco-regional and/or systemic therapy were enrolled in this phase II study
- Baseline characteristics are summarized in Table 1

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 class	
A	21 (78)
B	6 (22)
AFP >400 ng/mL	
Yes	9 (33)
No	18 (67)
Prior treatments	
Resection/Transplantation	9 (33)
Ablation	5 (18)
TACE	16 (59)
Sorafenib/Chemotherapy/Hormonal therapy	15 (56)

Safety

- A total of 86 cycles of therapy were administered (range, 1 to 14).
- Neither grade 3-4 treatment-related adverse events nor toxicity-related deaths were observed in the study population.
- Most commonly reported treatment-related adverse events were grade 1-2 chills (55%) and transient blood pressure increase (11%), generally occurring approximately 30 minutes after the start of the first infusions and lasting about 20 minutes. No cumulative toxicities were observed.

Table 2. 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%)	-	-	-

Efficacy

- One complete response (4%) lasting 9.0+ months was observed in a sorafenib-refractory patient and one partial response (4%) was reported in a Child-Pugh class B patient. Additionally, a 28% tumour shrinkage was detected in one out of six patients (22%) experiencing stable disease.
- Efficacy results are reported in Table 3 and the actuarial progression-free survival curve is depicted in Figure 4
- A 76-year-old sorafenib-refractory patient, with a large (6.5 x 5.5 cm) hepatic mass and extensive multifocal lesions, had a dramatic tumour shrinkage starting from the 2nd cycle with complete necrosis of the primary lesion and absence of any foci of contrast-enhancement in the remaining parenchyma. The baseline and post 4th cycle CT scans are shown in Figure 5
- With a median follow-up of 7.6 months, 3- and 6-month overall survival rates were 82% and 60%, respectively.

Table 3. Time-related efficacy data

Variable	Estimate (months)	95% CI
Median PFS in ITT population (n=27)	2.3	1.7-2.9
Median PFS in pts with SD/PR/CR (n=8)	4.3	2.7-5.8
Median duration of SDs (n=6)	3.3	2.6-5.9

PFS=progression-free survival; pts=patients; SD=stable disease; PR=partial response; CR=complete response; CI=confidence interval

Figure 4. Progression-free survival (ITT population)

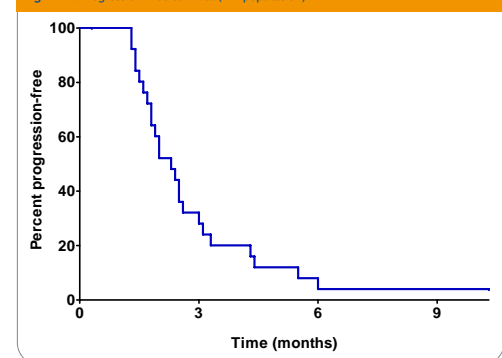
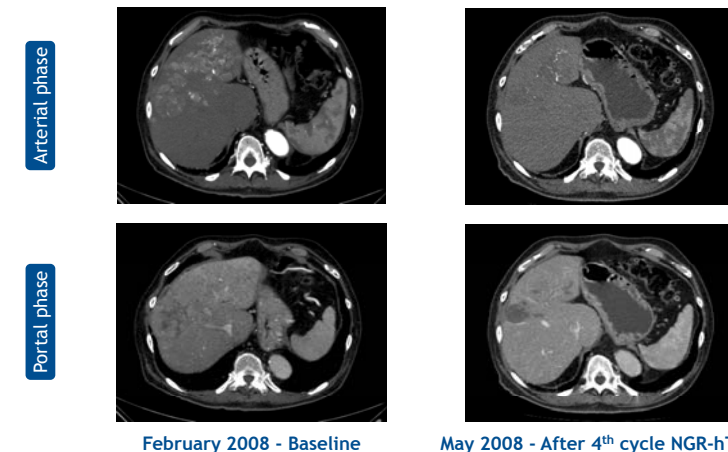


Figure 5. Complete necrosis in a hypervascular, infiltrating HCC after 4 cycles of NGR-hTNF evaluated by contrast-enhanced CT scan in a 76-year-old patient refractory to sorafenib



February 2008 - Baseline

May 2008 - After 4th cycle NGR-hTNF

Conclusions

- NGR-hTNF administered at low dose is safe and shows evidence of antitumour activity in pretreated patients with advanced hepatocellular carcinoma
- Noteworthy, the toxicity profile is limited to reversible and easily manageable constitutional symptoms, such as chills, generally occurring during the administration of first infusions
- NGR-hTNF will be further developed as single agent in pretreated patients, also exploring a weekly schedule of administration
- The mechanism of action of NGR-hTNF, along with its safety profile, should also facilitate the combination with standard regimens

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