

NGR-hTNF, a vascular targeting agent (VTA), administered as single agent in patients with colorectal cancer (CRC) failing standard regimens: a Phase II study

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ABSTRACT

Background: NGR-hTNF is a VTA consisting of TNF- α fused to the tumour-homing peptide NGR, which is able to selectively bind an aminopeptidase N overexpressed on tumour blood vessels. **Methods:** CRC pts failing standard therapies received low-dose NGR-hTNF given at 0.8 $\mu\text{g}/\text{m}^2$ as 1-hour infusion every 3 weeks (q3w; triweekly cohort). Progression-free survival (PFS) was the primary study objective with restaging performed q6w. A 2-stage design was used, with 16 and 27 pts to be recruited. Ultimately, an additional 13 pts were treated with 0.8 $\mu\text{g}/\text{m}^2$ on a weekly basis (weekly cohort). **Results:** In the triweekly cohort, 111 cycles (range, 1-10) were delivered to 33 pts with radiologically-documented progression after last therapy. Pts characteristics were: median age: 65 years (range, 53-79); M/F 16/17; PS 0/1 26/7. Median number of prior lines was 3 (range, 2-5), whereas 8 pts (25%) had received ≥ 4 lines and 22 (67%) biologicals. No grade 3-4 drug-related toxicity was observed. Predominant grade 1-2 toxicities were short-lived, infusion-related chills (53%). The median PFS was 2.5 months (95% CI, 2.2-2.8) and the PFS rates at 3 and 4.5 months were 31% and 16%, respectively. The disease control rate was 39% (95% CI, 23-55), with one partial response (3%) and 12 stable diseases (36%). In pts with disease control, the median PFS time was 3.8 months and the 3- and 4.5-month PFS rates were 67% and 42%, respectively. With a median follow-up of 18.4 months (95% CI, 18.3-18.5), the median OS time was 13.1 months (95% CI, 8.7-17.5). The proportions of pts alive at 18 and 24 months were 33% and 25%, respectively. Pts who achieved disease control had a median OS of 15.4 months, while those who did not had 9.3 months. Median OS in pts pretreated with < 3 and ≥ 3 regimens were 18.6 and 9.3 months ($p=.03$), respectively, whereas 1-year survival rates in biological-naïve and prior-biological pts were 72% and 41% ($p=.01$), respectively. There was no toxicity exacerbation using the weekly schedule. In this cohort, two patients (15%) had PFS of 10.5 and 11.0 months, which resulted longer than PFS on prior therapy (3.8 and 6.3 months, respectively). **Conclusion:** Based on favourable toxicity profile and disease control in heavily pretreated CRC patients, NGR-hTNF will be further developed in combination with standard chemotherapy.

Background

- Preclinical models have shown that tumour necrosis factor-alpha (TNF- α) has potent 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 novel vascular targeting agent (VTA) that has been rationally designed and prepared by coupling the N-terminus of human TNF- α with the C-terminus of the tumour-homing peptide Cys-Asn-Gly-Arg-Cys (CNGRC) (Figure 1)
- The cell surface receptor for the NGR-containing peptide is a CD13/aminopeptidase N isoform selectively expressed by endothelial cells of newly formed human tumour vessels²⁻⁴, including CRC (Figure 2)

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

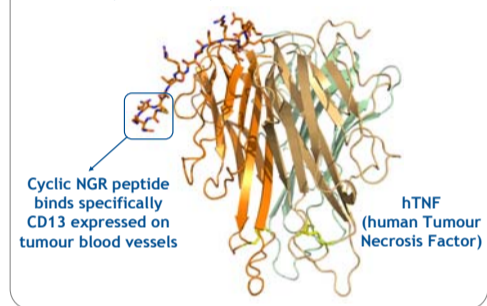
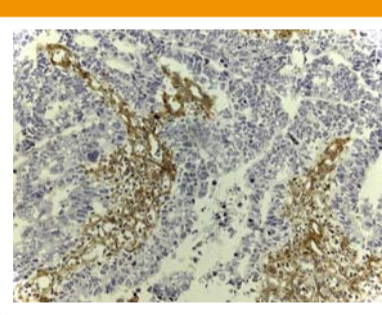
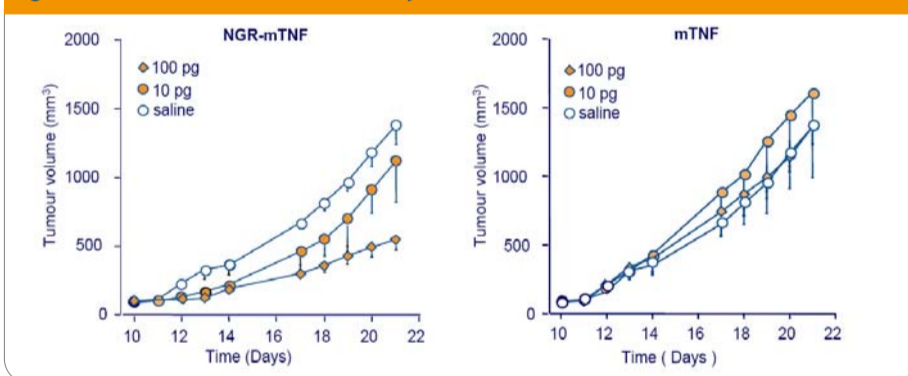


Figure 2. CD13 expression in CRC



- NGR-mTNF was found to have antitumour activity in preclinical model⁴ (Figure 3) even at doses in the picogram range (equivalent to a dose of 0.2 $\mu\text{g}/\text{m}^2$ in humans)

Figure 3. Preclinical antitumour activity at low doses of NGR-mTNF and mTNF



Early clinical development of NGR-hTNF

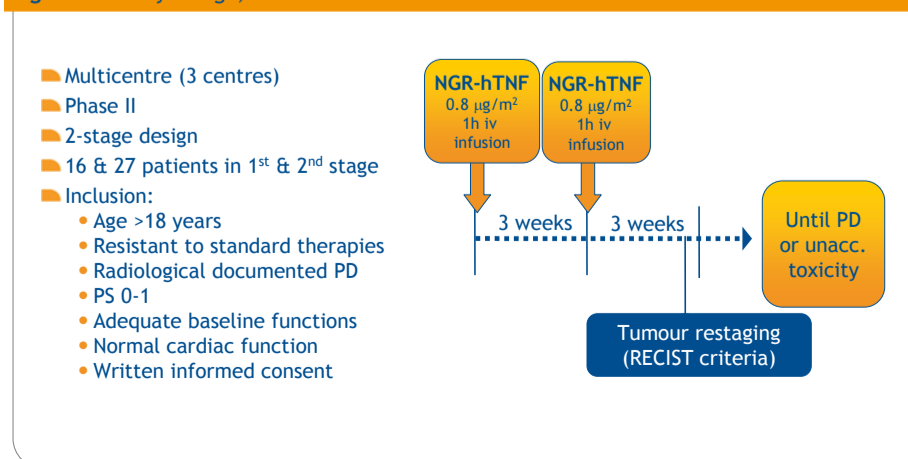
- In a phase I study evaluating a dose-interval ranging from 0.2 to 60 $\mu\text{g}/\text{m}^2$, the MTD of NGR-hTNF was established at 45 $\mu\text{g}/\text{m}^2$ when given as single agent once every 3 weeks⁵
- A further trial exploring the low-dose range of NGR-hTNF from 0.2 to 1.6 $\mu\text{g}/\text{m}^2$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

Disease background

- Despite recent advances in metastatic CRC treatment, which include irinotecan- or oxaliplatin-based first-line regimens, and increasing use of targeted agents, most patients develop resistance to these therapies
- Recently, two monoclonal antibodies have shown to be effective in unselected disease refractory to standard chemotherapy^{7,8}
- A significant increase of median PFS versus BSC was reported for patients treated with cetuximab⁷ (1.9 vs 1.8 months) and with panitumumab⁸ (2.0 vs 1.8 months). Similar results were registered in terms of disease control rate (39% vs 11%, in the first study and 37% vs 10%, in the second study). However, there is a need for new treatment options in this setting

Methods

Figure 4. Study design, dose and assessment



- Multicentre (3 centres)
- Phase II
- 2-stage design
- 16 & 27 patients in 1st & 2nd stage
- Inclusion:
 - Age >18 years
 - Resistant to standard therapies
 - Radiological documented PD
 - PS 0-1
 - Adequate baseline functions
 - Normal cardiac function
 - Written informed consent

Results

- Thirty-three colorectal cancer patients resistant or refractory to standard treatments, including biological agents, were enrolled in this phase II study
- Baseline characteristics are summarised in Table 1

Table 1. Baseline characteristics

Characteristics	n=33 (%)
Median age, years (range)	65 (53-79)
Gender	
Male	16 (48)
Female	17 (52)
ECOG performance status	
0	26 (79)
1	7 (21)
Primary diagnosis	
Colon cancer	23 (70)
Rectal cancer	10 (30)
Sites of disease	
Median	3
Range	1 - 6
1 or 2	11 (33)
≥ 3	22 (67)
Liver	25 (76)
Lung	24 (73)
Circulating tumor cells (CTC)	
< 3 cells/7.5 mL	15 (46)
≥ 3 cells/7.5 mL	13 (39)
Unknown	5 (15)
Prior lines of systemic therapy	
2 lines	15 (46)
3 lines	10 (30)
≥ 4 lines	8 (24)
Best response to prior therapy	
Partial response	6 (18)
Stable disease	12 (36)
Progressive disease/Unknown	15(46)

Safety

- A total of 111 cycles of therapy were administered with a median of 2 (range, 1 to 10)
- No grade 3-4 treatment-related adverse events were observed
- The most common treatment-related adverse events were grade 1-2 chills (53%), and transient blood pressure increase (9%), generally occurring during the first infusions

Table 2. Treatment-related adverse events occurring in >5% of patients

Event	Grade 1	Grade 2	Grade 3	Grade 4
Chills	4 (12%)	13 (41%)	-	-
Blood pressure increase	3 (9%)	-	-	-
Fatigue	2 (6%)	-	-	-
Nausea	2 (6%)	-	-	-

Efficacy

- In the 1st stage of the study (n=16), one patient achieved a PR lasting 5 months and 9 patients (56%) had SD as best response. Median and 3-month PFS in this cohort were 2.9 months and 47%, respectively
- Efficacy results after the 2nd stage (n=33) are reported in Tables 3-4, and the Kaplan-Meier plots for PFS and OS are depicted in Figures 4-5

Table 3. Best overall response

Variable	# pts	%
PR	1	3
SD	12	36
DCR	13	39
PD	18	55
Not assessed*	2	6

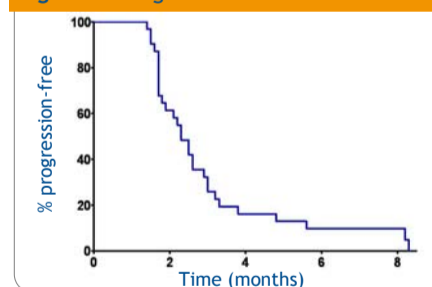
PR= partial response; SD=stable disease; DCR=disease control rate; PD=progressive disease; *Two patients withdrew from the study before their first restaging scan for symptomatic deterioration

Table 4. Time-related efficacy data

Variable	Median (months)
PFS (ITT, n=33)	2.5
PFS in patients with SD (n=13)	3.8
OS (ITT, n=33)	13.1
OS in patients with SD (n=13)	15.4

PFS=progression-free survival; SD=stable disease; OS=overall survival.

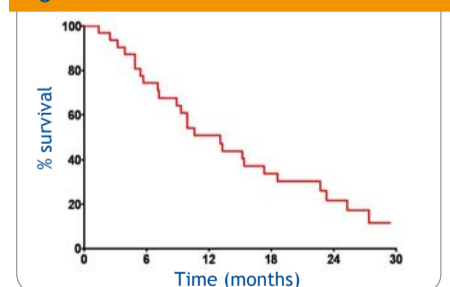
Figure 5. Progression-free survival



EXPLORATORY ANALYSES

- In univariate analyses, no correlations were found between either PFS or OS and all variables assessed including age, gender, PS, baseline CTCs, outcomes on prior therapy, number of prior treatment lines, and previous therapy with biologicals.
- In a further subset analysis, median OS in biological-naïve and prior-biological cohorts were 22.7 and 10.6 months, respectively.

Figure 6. Overall survival



WEEKLY SCHEDULE

- In an additional cohort (n=13) receiving a weekly schedule at the same dose, there was no worsening of toxicity profile. Most common drug-related toxicity was grade 1-2 chills experienced by 7 patients (54%)
- Two patients (15%) had PFS times of 10.5 and 11.0 months, which resulted longer than PFS on prior therapy (3.8 and 6.3 months, respectively).

Conclusions

- NGR-hTNF administered at low dose is well tolerated and shows preliminary evidence of disease control in heavily pretreated patients with advanced CRC
- NGR-hTNF is currently developed in combination with standard chemotherapy

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