

Phase II study of two doses of NGR-hTNF, a vascular targeting agent (VTA), combined with capecitabine/oxaliplatin (XELOX) in colorectal cancer (CRC) patients failing standard regimens

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Abstract 6066

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ABSTRACT

Background: NGR-hTNF is a VTA exploiting a tumor-homing peptide (NGR) that selectively binds an aminopeptidase N expressed on tumor vessels. In preclinical models, NGR-hTNF showed synergism with chemotherapy even at low doses. Two phase I trials previously selected 0.8 µg/m² and 45 µg/m² as optimal-biological and maximum-tolerated dose, respectively. **Methods:** Two sequential cohorts of 12 CRC patients (pts) failing standard therapies were planned to receive 2 doses of NGR-hTNF given at 0.8 µg/m² (LD) or 45 µg/m² (HD) as 1-hour intravenous infusion every 3 weeks (q3w). XELOX consisted of oxaliplatin 100 mg/m² plus capecitabine 825 mg/m² twice-daily for 14 days q3w. Primary study objective was safety (≤ 2/12 pts with grade 3-4 toxicity related to NGR-hTNF). Secondary aims included tolerability and clinical activity. Tumor restaging was done q6w. **Results:** From January 2008 to March 2009, 12 pts (median age, 57 years, range 40-74; M/F 7/5; PS 0/1 11/1) were enrolled in the LD cohort and 11 pts (median age, 54 years, range 43-65; M/F 7/4; PS 0/1 8/3) in the HD cohort. All pts had previously received oxaliplatin and fluoropyrimidines. The median number of prior regimens was 3 (range, 1-4) in LD and 2 (range, 2-4) in HD. Globally, 44 cycles (median, 3; range, 2-6) and 24+ cycles (median, 2; range, 1-4+) were delivered in LD and HD, respectively. The combination was well tolerated. No grade 3-4 study drug-related toxicities were observed in both cohorts, most common grade 1-2 toxicity being short-lived, infusion-time related chills (58% in LD and 54% in HD). In the LD cohort, 1 partial response, 5 stable diseases (SD) lasting for a median time of 5.0 months (range, 3.0-8.6), and 6 progressions (PD) were observed. Maximal change in target lesions of SD pts ranged from 0% growth to 46% shrinkage. The median PFS was 3.4 months (range, 1.5-9.4), whereas the median ratio between PFS on current study and on prior therapy was 0.92. In the HD cohort, there are currently 3 SD, 6 PD, and 2 too-early, as best response. **Conclusions:** Both NGR-hTNF doses were safely administered in combination with XELOX in heavily pretreated CRC pts, without worsening of chemo-associated toxicity.

Background

- In preclinical models, tumor necrosis factor-α (TNF-α) has shown potent antitumor activity. However, its clinical use was hampered by severe systemic toxicity, with MTD significantly lower than ED in humans¹
- NGR-hTNF is a vascular targeting agent (VTA) that has been rationally designed and prepared by fusing the N-terminus of recombinant human TNF-α with the C-terminus of the cyclic tumor-homing peptide Cys-Asn-Gly-Arg-Cys (NGR) (Figure 1)
- The receptor for the NGR-containing peptide is a CD13 (aminopeptidase N) isoform selectively expressed by endothelial cells of newly formed human tumour vessels, including CRC (Figure 2)²⁻⁴

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

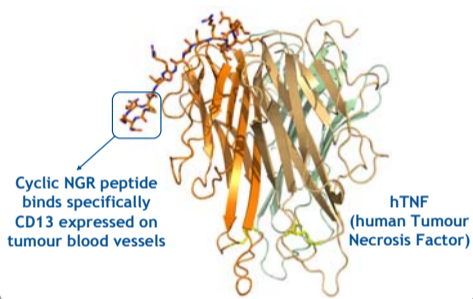
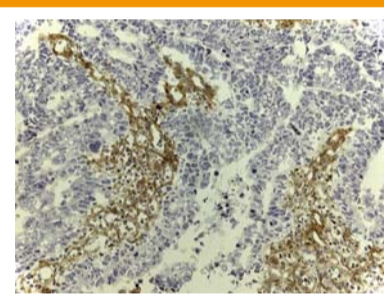
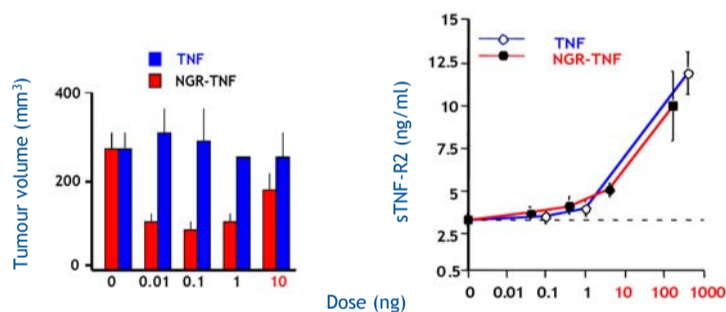


Figure 2. CD13 expression in CRC



- NGR-mTNF showed activity even at doses in the nanogram range in preclinical model⁴, without induction of soluble TNF receptors shedding (Figure 3)
- Additionally, low doses of NGR-mTNF significantly increased the activity of a variety of chemotherapeutics, with maximal synergism being observed with a 2-hour delay between NGR-TNF and chemotherapy administration⁵

Figure 2. Low doses of NGR-TNF do not induce sTNF-R2 shedding while triggering antitumour effects



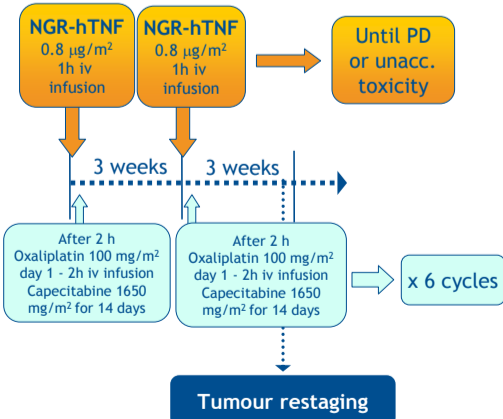
Early clinical development of NGR-hTNF

- In a phase I study evaluating a dose-interval ranging from 0.2 to 60 µg/m², the MTD of NGR-hTNF was established at 45 µg/m² 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 µg/m² selected the dose of 0.8 µg/m² as the optimal biological dose, based mainly on dynamic imaging changes and preliminary antitumour activity⁶

Methods

Figure 4. Study design, dose and assessment

- 2 sequential cohorts
- 0.8 µg/m² (LD, low-dose cohort)
- 45 µg/m² (HD, high-dose cohort)
- Fixed dose for oxaliplatin 100 mg/m² day 1 every 3 weeks and capecitabine 825 mg/m² twice-daily (total daily dose of 1,650 mg/m²) for 14 days, every 3 weeks
- Inclusion:
 - Age > 18 years
 - Resistant to standard therapies
 - PS 0-1
 - Adequate baseline functions
 - Written informed consent



Objective: ≤ 2/12 pts with DLT during 1st cycle
DLT: Grade 3-4 tox. related to NGR-hTNF, except nausea, vomiting, chills and fever

PK: Blood samples collected just prior to and at 30', 60', 89', 135', 179', 210', 240', 300', 360' during first 3 cycles

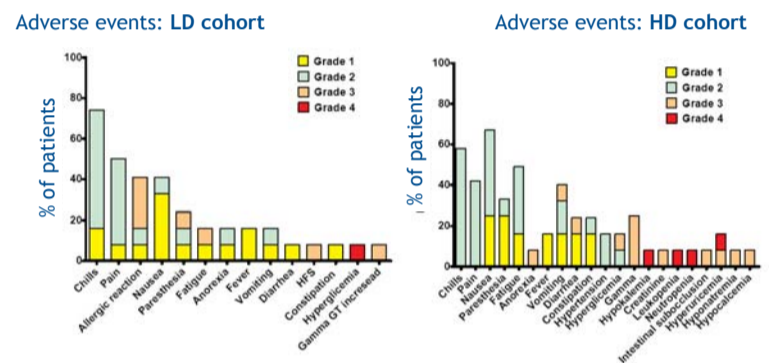
Results

- 12 patients enrolled in the LD cohort between January and June 2008:
 - Median age: 57 years; range, 40-74
 - Males/Females: 7/5
 - PS 0/1: 11/1
- 12 patients recruited in the HD cohort between July 2008 and May 2009:
 - Median age: 56 years; range, 43-65
 - Males/Females: 7/4
 - PS 0/1: 8/4
- Median number of prior regimens was 3 (range, 1-4) in the LD cohort and 2 (range, 0-4) in the HD cohort
- All patients had previously received fluoropyrimidines, oxaliplatin and/or irinotecan
- 9 patients (75%) in the LD cohort and 10 (83%) in the HD cohort were previously treated with at least one biological agent
- Globally, 44 cycles (median, 3; range, 2-6) and 31+ cycles (median, 2; range, 1-4+) were delivered in the LD and HD cohorts, respectively

Safety

- In both cohorts, no grade 3 to 4 adverse events (AEs) related to NGR-hTNF
- Only 27 (16%) of AEs related to NGR-hTNF
- Most common related AEs were grade 1-2 chills experienced by 9 patients (75%) during 17 cycles (39%) in the LD cohort and by 7 patients (58%) over 10 cycles (32%) in the HD cohort
- These AEs were infusion-related, short-lived, and easily manageable
- No differences in either frequency or severity of AEs between the two NGR-hTNF doses were detected (Figure 5)

Figure 5. Adverse events - irrespective of drug relationship - by % of patients



Antitumour activity

- In the low-dose cohort (0.8 µg/m²):
 - One patient (8%) had a partial response and 5 patients (42%) had stable disease as best response for a median duration of 5.0 months (range, 3.0 - 5.5)
- In the high-dose cohort (45 µg/m²):
 - Four patients (33%) had stable disease as best response for a median time of 3.3 months (range, 2.3 - 6.1)

Table 1. Patient characteristics and preliminary antitumour activity by dose level (DL)

DL (µg/m ²)	Pt N°	Gender / Age / PS	N° of prior regimens	Prior oxaliplatin based regimen	Last regimen	BOR to last regimen/ TTP (months)	N° of cycles	BOR	SD/PR duration (months)
0.8	1	F/67/0	1	Folfox	Triplebiologicals + Folfox	PR/14.2	6	SD	5.5
	2	M/59/0	2	Folfox	Irinotecan	SD/4.6	2	PD	-
	3	F/51/0	4	Folfox	Irinotecan + Cetuximab	PD/1.1	2	PD	-
	4	M/63/0	2	Folfox	Folfiri	PD/1.1	6	SD	3.8
	5	F/55/0	3	Folfox	Irinotecan + Cetuximab	SD/16.6	2	PD	-
	6	M/52/0	2	Folfox	Folfiri	PD/2.1	2	PD	-
	7	F/66/0	4	Folfox	Irinotecan + Cetuximab	NE/0.7	6	SD	5.0
	8	F/54/0	1	-	Folfiri	SD/5.8	4	PR	2.3
	9	M/71/0	2	Folfox	Folfiri	PR/9.7	6	SD	5.0
	10	M/40/0	3	Folfox	Irinotecan + Cetuximab	SD/8.8	2	PD	-
	11	M/74/0	3	Xelox	Folfox	NE/1.5	2	PD	-
	12	M/51/1	4	Folfox	Irinotecan + Cetuximab	PD/2.8	4	SD	3.0
45	1	F/65/0	2	Folfox	Folfiri + Panitumumab	SD/7.7	2	PD	-
	2	M/60/0	3	Xelox	Irinotecan + Cetuximab	PD/5.2	2	PD	-
	3	M/58/1	2	Folfox	Folfiri	PR/14.3	4	SD	6.1
	4	M/51/1	2	Xelox	Folfiri + Bevacizumab	PD/1.9	2	PD	-
	5	F/54/0	2	Folfox	Folfiri + Axitinib	PD/1.9	2	PD	-
	6	M/45/0	4	Capecitabine	Capecitabine + Bevacizumab	SD/5.5	4	SD	3.6
	7	F/43/0	3	Xelox	Folfiri + Cetuximab	SD/6.4	3	SD	3.0
	8	M/52/1	2	Folfox	Irinotecan	PD/NA	2	PD	-
	9	M/65/1	0	-	-	NA	2	PD	-
	10	F/63/0	4	Folfox	Irinotecan + Cetuximab	PD/6.0	4	NA	-
	11	M/43/0	2	Xelox	Folfiri + Axitinib	PD/2.4	1	PD	-
	12	M/62/0	0	-	-	NA	3	SD	2.3

DL=dose level; PS=performance status; BOR=best overall response; TTP=time to progression; SD=stable disease; PR=partial response; PD=progressive disease; NA=not assessed; Triplebiologicals=bevacizumab+cetuximab+irinotecan; Folfox=FUFA+oxaliplatin; Folfiri=FUFA+irinotecan; Xelox=capecitabine+oxaliplatin

Conclusions

- Both NGR-hTNF doses were well tolerated in combination with XELOX in CRC patients already pretreated with an oxaliplatin-based regimen
- No apparent worsening of chemo-associated toxicity was observed
- In two heavily pre-treated patients the PFS of the experimental treatment was substantially longer than the PFS on the previous regimen: this may constitute a hint of activity of low dose NGR-hTNF. There seems to be no effect of high dose NGR-hTNF
- This combination deserves further development in less heavily pretreated patients

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