

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

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Background

- Tumor necrosis factor-alpha (TNF- α) has potent antivascular and antitumor activity. However, its clinical development has been hampered by severe systemic toxicity.¹
- NGR-hTNF is a VTA consisting of TNF- α fused with the tumor-homing peptide NGR (Fig. 1).
- NGR selectively binds a CD13 isoform overexpressed in most tumor blood vessels,²⁻⁴ including CRC (Fig. 2).

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

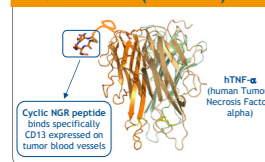
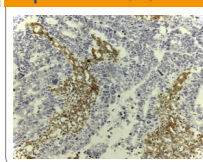


Figure 2. CD13 expression in CRC

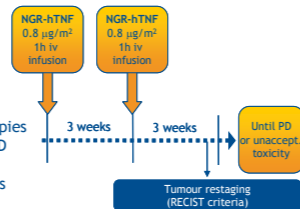


- NGR-TNF has shown antitumor activity even at doses in the picogram range⁵ (equivalent to 0.2 $\mu\text{g}/\text{m}^2$ in humans)
- Two phase I trials have previously selected 0.8 $\mu\text{g}/\text{m}^2$ and 45 $\mu\text{g}/\text{m}^2$ as optimal-biological and maximum-tolerated dose, respectively.
- Despite recent advances in the treatment of metastatic CRC, which include irinotecan- or oxaliplatin-based first-line regimens, and an increasing use of targeted agents, most patients develop resistance to these therapies.
- A median PFS significantly longer than supportive care alone was reported in unselected patients treated with either cetuximab⁷ (1.9 vs 1.8 months) or panitumumab⁸ (2.0 vs 1.8 months). However, there is a need for new options in this setting.

Methods

Figure 3. Study design, dose and assessments

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



Results

Baseline characteristics	n=33 (%)
Median age, years	65
Age range, years	53-79
Gender	
Male	16 (48)
Female	17 (52)
ECOG performance status	
0	26 (79)
1	7 (21)
Sites of metastatic diseases	
Median (range)	3 (1-6)
Liver	25 (76)
Lung	24 (73)
Circulating tumor cells (CTC)	
< 3 cells/7.5 mL	17 (52)
\geq 3 cells/7.5 mL	14 (42)
Unknown	2 (6)
Prior lines of systemic therapy	
Median (range)	3 (2-5)
2 lines	15 (46)
3 lines	10 (30)
4 lines	8 (24)
Prior use of biological agents	
Yes	22 (67)
No	11 (33)

Safety

- 111 cycles administered (mean, 3.4; median, 2; range, 1 to 10).
- Neither grade 3-4 drug-related adverse events nor toxicity-related deaths were observed in the study population.
- The most common drug-related adverse events were grade 1-2 chills, generally occurring approximately 30 min after the start of the first infusions and lasting about 20 min.

Table 1. Drug-related toxicity occurring in >5% of patients

	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

Table 2. Best overall response

	N°of patients	%
Partial Response (PR)	1	3
Stable disease (SD)	12	36
Disease control rate (DCR)	13	39
Progressive disease (PD)	17	51
Not assessed*	3	9

*Two patients withdrew from the study before their first restaging scan for symptomatic deterioration and one patient before study treatment start.

Table 3. Efficacy results

	Estimate (months)	95% CI
Median PFS	2.5	2.2-2.8
Median PFS in patients with PR/SD	3.8	1.4-6.1
Median OS	13.1	7.9-18.3
Median OS in patients with PR/SD	15.4	8.9-21.4

PFS=progression-free survival; ITT= intent-to-treat; SD=stable disease; PR=partial response; OS= overall survival; CI=confidence interval

EXPLORATORY ANALYSES

- In both univariate and multivariate analyses, no correlations were found between PFS and all variables assessed including age, gender, PS, baseline CTCs, outcome on prior therapy, and number of prior treatment lines.
- A baseline CTC level < 3 (p=.02) was significantly associated to better OS in both univariate and multivariate analyses.
- In a subset analysis, the median OS in biological-naïve and prior-biological cohorts were 22.7 and 9.9 months, respectively (p=.05, log-rank test).

WEEKLY SCHEDULE

- In an additional cohort of 13 patients receiving a weekly dosing schedule at 0.8 $\mu\text{g}/\text{m}^2$, there was no worsening of toxicity profile.
- Most common drug-related toxicity was grade 1-2 chills experienced by 7 patients (54%) over 19 infusions (14%).
- Two patients (15%) had PFS times of 10.5 and 11.0 months, which were longer than PFS on prior therapy (3.8 and 6.3 months, respectively).

For the overall study population (n=46) including both triweekly and weekly cohorts, the actuarial curves of PFS and OS are depicted in Figure 4 and 5, respectively.

CONCLUSIONS

- NGR-hTNF shows a favourable toxicity profile, with evidence of disease control in heavily pre-treated CRC patients.
- NGR-hTNF is currently evaluated in combination with standard chemotherapy regimens in this setting.

Figure 4. Progression-free survival

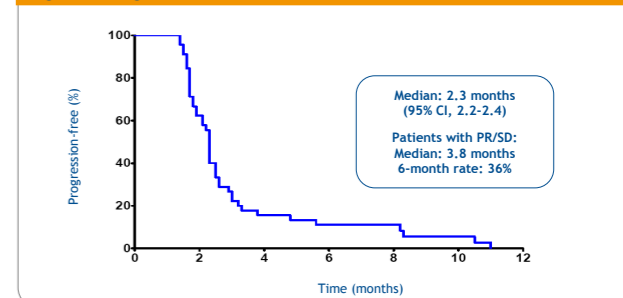
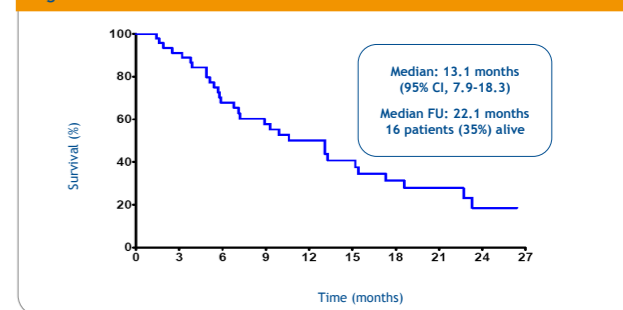


Figure 5. Overall survival



References

- Blick M, et al. *Cancer Res* 1987;47:2986-9.
- Curnis F, et al. *Nat Biotech* 2000;18 (11): 1185-9
- Corti A, et al. *Methods MolMed* 2004; 98: 247-64
- Curnis F, et al. *J Clin Invest* 2002; 110: 475-82
- van Laarhoven H et al. *ASCO* 2008; Abs 3521
- Gallo-Stampino C, et al. *ASCO* 2007; Abs 3540
- Jonker DJ et al. *NEJM* 2007; 357:2040-8
- Van Cutsem E et al. *JCO* 2007; 25:1658-1664

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