

Phase I study of NGR-hTNF, a vascular targeting agent (VTA), in combination with cisplatin in refractory patients with solid tumours

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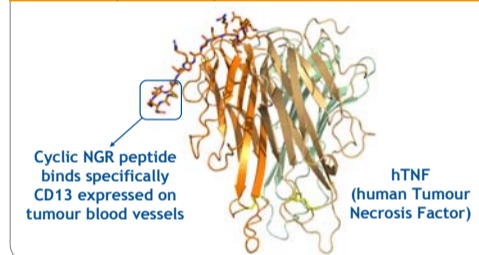
ABSTRACT

Background: NGR-hTNF is a VTA consisting of TNF- α fused to the tumour-homing peptide (NGR) able to selectively binds an aminopeptidase N overexpressed on tumour blood vessels. Low-dose NGR-hTNF displayed significant preclinical synergism with cisplatin. **Methods:** Pts with resistant/refractory solid tumours received NGR-hTNF given with a low-dose, doubling-dose scheme (0.2-0.4-0.8-1.6 $\mu\text{g}/\text{m}^2$) as 1-hour intravenous infusion, in combination with a fixed-dose of cisplatin 80 mg/m^2 . Both drugs were given every 3 weeks. A 3+3 design was followed. Any grade 3-4 toxicity related to NGR-hTNF was defined dose-limiting toxicity (DLT). Sampling for pharmacokinetics (PK) and pharmacodynamics (soluble TNF-receptors, sTNF-R1 and 2) was done during the first 3 cycles. **Results:** 22 pts (median age, 60 years; M/F 14/8; PS 0/1 12/10) with various solid tumours were evaluated over 77 cycles (range, 1-10). The median number of prior regimens was 3 (range, 1-6) and 12 pts (55%) were platinum-pretreated. NGR-hTNF Cmax and AUC increased dose-proportionally ($r^2=0.91$, $p<.0001$ and $r^2=0.67$, $p=.001$, respectively). No shedding of sTNF-Rs was noted up to 0.8 $\mu\text{g}/\text{m}^2$. Higher and faster peaks of sTNF-R1 ($p=.001$) and sTNF-R2 ($p=.0001$) were observed at 1.6 $\mu\text{g}/\text{m}^2$ than at lower doses. A correlation was detected between first-cycle NGR-hTNF exposure and sTNF-R2 AUC ($r=0.64$, $p=.005$), while no relationship was noted for sTNF-R1. The combination was safely administered without PK interaction or worsening of platinum toxicity. Consistently with the low doses tested, MTD was not reached. No DLTs were recorded at 0.2 $\mu\text{g}/\text{m}^2$ ($n=4$), 0.4 $\mu\text{g}/\text{m}^2$ ($n=3$) and 1.6 $\mu\text{g}/\text{m}^2$ ($n=3$). At 0.8 $\mu\text{g}/\text{m}^2$, a transient grade 3 infusion reaction was registered. This cohort was expanded to 6 pts for safety check with no further DLT, and to 12 pts for activity assessment. At this dose, 2 lung cancer pts, both platinum-pretreated, achieved a partial response (-79%) and a significant tumour shrinkage (-28%), lasting 7.2 and 6.7 months, respectively. An additional 4 pts had stable disease for a median time of 6.4 months. The median progression-free survival for all pts ($n=22$), for pts enrolled at 0.8 $\mu\text{g}/\text{m}^2$ ($n=12$), and for platinum-pretreated pts ($n=9$) were 2.7, 4.7, and 4.3 months, respectively. **Conclusion:** The combination of NGR-hTNF 0.8 $\mu\text{g}/\text{m}^2$ with cisplatin is well-tolerated and shows promising activity.

Background

- In preclinical models, tumour necrosis factor-alpha (TNF- α) has shown 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 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 vessels^{2,4}

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



- NGR-mTNF was found to have activity even at doses in the picogram range (equivalent to a dose of 0.2 $\mu\text{g}/\text{m}^2$ in humans) in preclinical model⁴, without induction of soluble TNF receptors shedding (Figure 2)
- Additionally, low doses of NGR-mTNF significantly increased the antitumour activity of cisplatin, with maximal synergism being observed with a 2-hour delay between NGR-TNF and cisplatin administration⁵ (Figure 3)

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

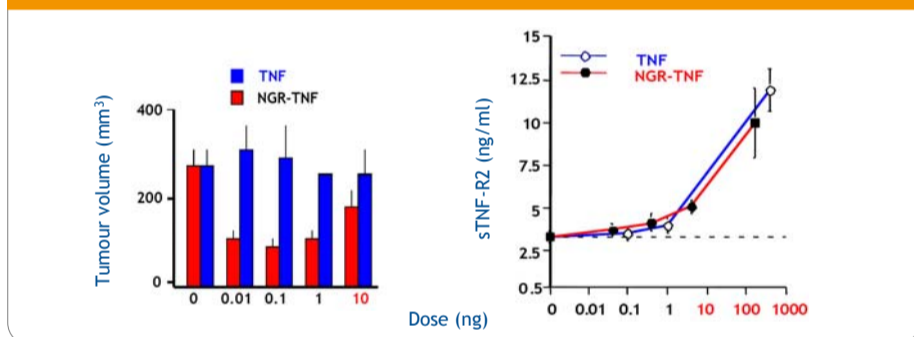
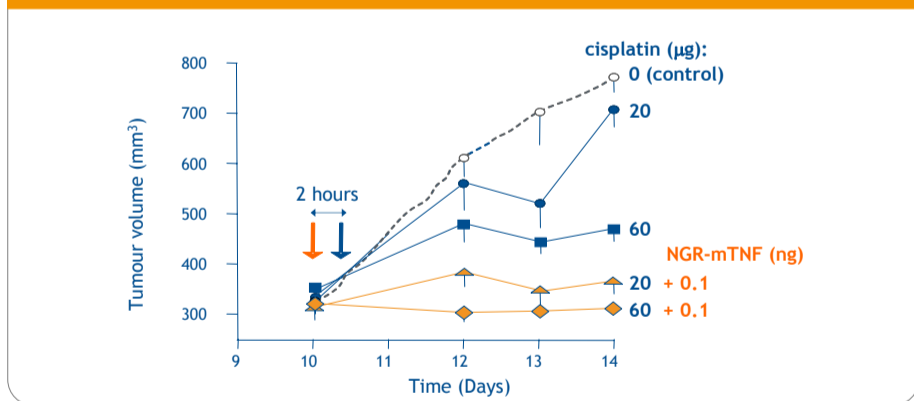


Figure 3. Synergistic antitumour activity of NGR-mTNF with cisplatin



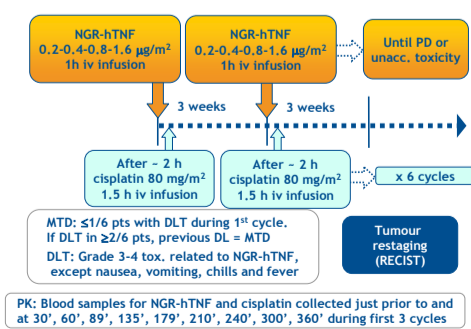
Phase I trials

- 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 weeks⁶
- 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 activity⁷

Methods

Figure 4. Study design, dose and assessment

- 2 centres
- Standard 3 + 3 escalation
- Doubling-dose scheme for NGR-hTNF
- Fixed dose for cisplatin: 80 mg/m^2
- Inclusion:
 - Age >18 years
 - Resistant to standard therapies
 - PS 0-1
 - Adequate baseline functions
 - Normal cardiac function
 - Written informed consent



Results

- 22 patients resistant or refractory to standard treatments enrolled
- Baseline characteristics: M/F 14/8; PS 0/1 12/10; median age 60 years (47-75)
- Median number of prior regimens: 3 (range 1-6)

- 9 patients (41%) pretreated with ≥ 4 regimens
- 12 patients (55%) pretreated with a platinum-based regimen

Safety

- 77 cycles of NGR-hTNF (range 1-10) and 67 of cisplatin (range 1-10) administered
- Only 6% of AEs were considered NGR-hTNF-related, and the most frequent was chills, experienced by 9 patients (41%) (Table 1).
- These events were infusion-related, short-lived, and easily manageable
- Neither grade 4 treatment-related AEs nor toxicity-related deaths were observed
- At 0.8 $\mu\text{g}/\text{m}^2$, a MPM patient with lung metastases, pretreated with 3 regimens, had a short-lived grade 3 acute infusion reaction. Though the AE was not surely dose-related, the cohort was expanded to 6 patients for safety, with no subsequent DLT observed
- Considering that dose level 0.8 $\mu\text{g}/\text{m}^2$ was previously selected for phase II development as single-agent in the low-dose range, the cohort has been further expanded to 12 patients, for preliminary activity evaluation

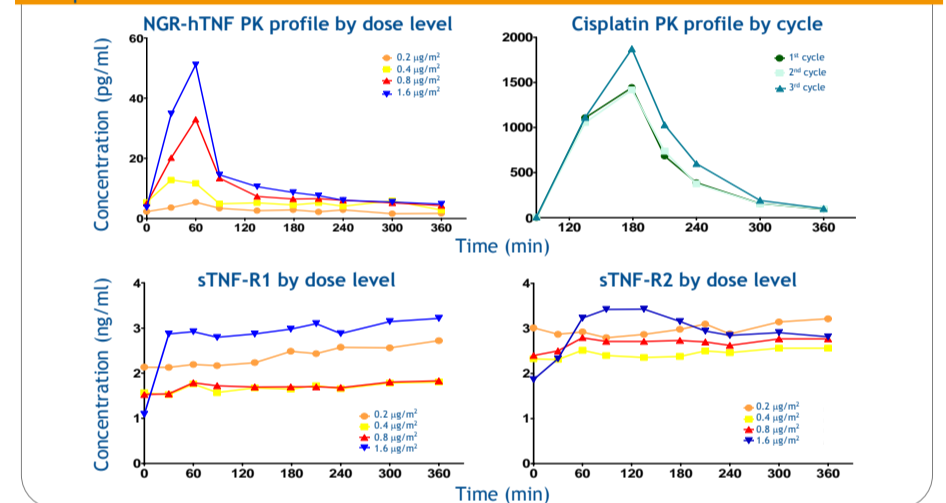
Table 1. Adverse events related to NGR-hTNF by number of patients

Event	Grade 1	Grade 2	Grade 3	Grade 4
Chills	7 (32%)	2 (9%)	-	-
Vomiting	1 (4%)	1 (4%)	-	-
Dyspnea	-	-	1 (4%)	-
Headache	1 (4%)	-	-	-

Pharmacokinetics and Pharmacodynamics

- Both NGR-hTNF Cmax and AUC increased proportionally with dose ($r^2=0.91$, $p<.0001$ and $r^2=0.67$, $p=.001$, respectively)
- Overall, there was no apparent PK interactions between NGR-hTNF and cisplatin
- At doses of 0.2-0.4-0.8 $\mu\text{g}/\text{m}^2$, the levels of soluble TNF receptors 1 and 2 were scattered around baseline values
- Stimulation of both receptors was only observed after 1.6 $\mu\text{g}/\text{m}^2$ ($p=.001$ and $p=.0001$, respectively)
- A significant correlation at first cycle was detected between AUC of NGR-hTNF and both AUC and Emax of sTNF-R2 (Spearman $r=0.64$, $p=.005$ and $r=0.61$, $p=.008$, respectively)

Figure 5. Pharmacokinetic profile of NGR-hTNF, cisplatin and soluble TNF receptors R1 and R2



Antitumour activity

- At dose level of 0.8 $\mu\text{g}/\text{m}^2$:
 - A NSCLC patient, pretreated with platinum, had a PR
 - A NSCLC patient, pretreated with 6 regimens including cisplatin, had a significant tumour shrinkage (-28%), maintained for 7.1 months
- 4 patients had SD for a median time of 6.4 months
- Median PFS:
 - ITT population: 2.7 months
 - Patients pretreated with platinum: 4.3 months
 - Dose level of 0.8 $\mu\text{g}/\text{m}^2$: 4.7 months

Table 2. Patient characteristics and preliminary antitumour activity by DL

DL ($\mu\text{g}/\text{m}^2$)	Pt #	Tumour type	Age	PS	# of prior regimens	Prior platinum-based regimen	BOR to last regimen/ TTP (months)	Cycles	BOR	Duration of SD/PR (months)
0.2	1	Mesothelioma	59	1	2	Platinum	PD/1.5	1	NA	-
	2	Colorectal	56	0	5	-	SD/11.6	2	PD	-
	3	Melanoma	47	0	1	Platinum	SD/8.0	2	PD	-
	4	Melanoma	58	1	1	Platinum	SD/5.6	1	NA	-
0.4	5	Lung	52	1	3	Platinum	PD/3.1	1	NA	-
	6	Sarcoma	49	0	1	-	SD/10.6	2	PD	-
	7	Mesothelioma	55	1	3	Platinum	PD/0.5	2	PD	-
0.8	8	Colorectal	60	1	6	-	PD/4.5	5	SD	4.6
	9	Mesothelioma	65	1	3	Platinum	PD/1.2	1	NA	-
	10	Sarcoma	48	0	2	-	NA/4.9	4	SD	4.0
	11	NSCLC	60	0	6	Platinum	PD/2.5	8	SD	6.7
	12	Colorectal	69	0	4	-	PD/3.7	2	PD	-
	13	NSCLC	73	0	1	Platinum	PR/8.9	10	PR	7.2
	17	Colorectal	65	1	5	-	PD/2.7	2	PD	-
	18	Colorectal	70	1	5	-	PD/2.3	1	NA	-
	19	Colorectal	58	1	5	-	PD/2.6	2	PD	-
	20	Pancreas	75	0	3	-	SD/5.2	6	SD	6.7
1.6	21	Hepatic duct	60	0	2	Platinum	SD/4.2	1	NA	-
	22	Gastric	57	0	4	Platinum	PD/2.4	6	SD	6.4
	14	Carcinoid	67	1	1	Platinum	SD/9.8	5	SD	3.6
	15	SFTP	51	0	4	-	SD/12.6	7	SD	5.0
	16	NSCLC	62	0	4	Platinum	PD/1.1	2	PD	-

DL=dose level; PS=performance status; BOR=best overall response; TTP=time to progression; SD=stable disease; PR=partial response; PD=progressive disease; NA=non-assessable; SFTP=solitary fibrous tumour of the pleura; NSCLC=non-small cell lung

Conclusions

- NGR-hTNF administered at low doses in association with cisplatin was well tolerated without apparent PK interaction or exacerbation of platinum-associated toxicity
- As expected for using a low-dose range of NGR-hTNF, MTD was not reached
- Combination of NGR-hTNF 0.8 $\mu\text{g}/\text{m}^2$ with cisplatin 80 mg/m^2 showed promising activity also in platinum-pretreated patients and will be further developed in selected tumour types

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