

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

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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. 1A).
- NGR selectively binds a CD13 isoform overexpressed in most tumor blood vessels²⁻⁴, including NSCLC (Fig. 1B).

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

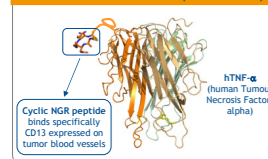
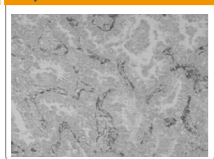
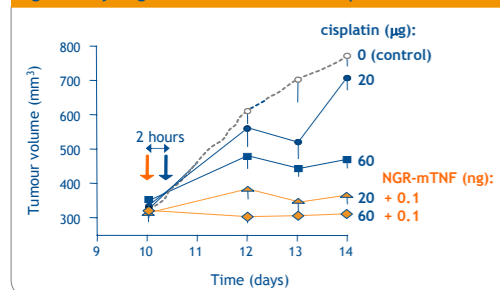


Figure 1B. CD13 expression in NSCLC



- Low doses of NGR-mTNF significantly increased the antitumor activity of cisplatin, with maximal synergism observed with a 2-hour delay between NGR-TNF and cisplatin administration⁵ (Fig. 2)

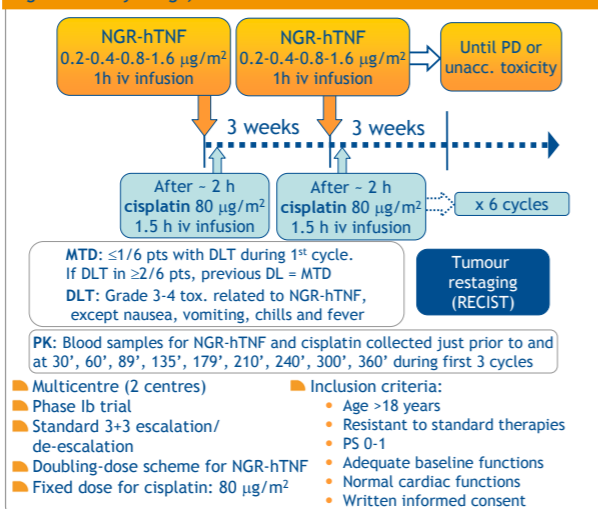
Figure 2. Synergism of NGR-mTNF with cisplatin



- Two phase I trials have previously selected 0.8µg/m² and 45 µg/m² as optimal-biological and maximum-tolerated dose, respectively^{6,7}.

Methods

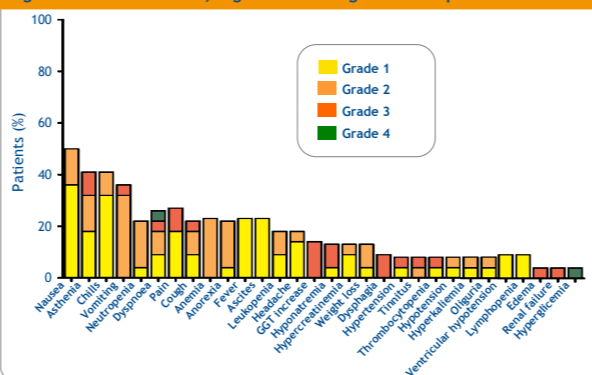
Figure 3. Study design, doses and assessments



Safety

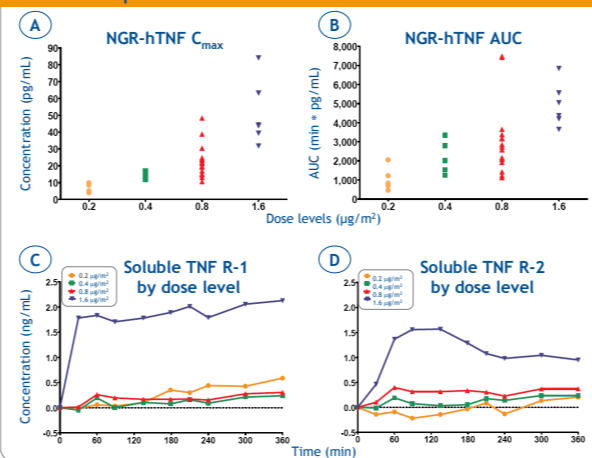
- 77 cycles of NGR-hTNF (mean, 3.5; median, 2; range, 1-10).
- 67 cycles of cisplatin (mean, 3.0; median, 2; range, 1-10).
- As expected exploring low doses of NGR-hTNF, MTD was not reached.
- No DLTs at 0.2 µg/m² (n=4), 0.4 µg/m² (n=3), and 1.6 µg/m² (n=3)
- At 0.8 µg/m², a MPM patient with lung metastases, pre-treated with 3 regimens, had a short-lived grade 3 acute infusion reaction.
- This cohort was expanded to 6 patients, without any further DLT, and to 12 patients for activity assessment
- Only 6% of AEs were related to NGR-hTNF and the most frequent was chills: 9 patients (41%) over 18 cycles (23%)
- These events were infusion-related, short-lived, and easily manageable
- No apparent exacerbation of cisplatin-associated toxicity (Fig. 4)

Figure 4. Adverse events, regardless of drug relationship



Pharmacokinetics and pharmacodynamics

Figure 5. Pharmacokinetic profile of NGR-hTNF and of soluble TNF receptors R-1 and R-2



- Both NGR-hTNF C_{max} and AUC increased proportionally with dose ($r^2=0.91$, $p<.0001$ and $r^2=0.67$, $p=.001$, respectively) (Figure 4, A and B).
- Overall, there was no apparent PK interactions between NGR-hTNF and cisplatin.
- At doses of 0.2-0.4-0.8 µg/m², the levels of soluble TNF receptors R-1 and R-2 were scattered around baseline values.
- Stimulation of both receptors was only observed after 1.6 µg/m² ($p=.001$ and $p=.0001$, respectively) (Figure 4, C and D)
- A significant correlation at first cycle was detected between AUC of NGR-hTNF and both AUC and E_{max} of sTNF-R2 (Spearman $r=0.64$, $p=.005$ and $r=0.61$, $p=.008$, respectively)

Results

- At dose level of 0.8 µg/m², a lung cancer patient pretreated with cisplatin, had a partial response, lasting 7.2 months. A further lung cancer patient, pretreated with 6 regimens including cisplatin, had a significantly tumor shrinkage (-28%) maintained for 7.1 months. Additionally, 4 patients had stable disease for a median time of 6.4 months.
- The median progression-free survival in the intent-to-treat population (n=22), in patients previously treated with platinum (n=12), and in the 0.8 µg/m² dose cohort (n=12), were 2.7, 4.3, and 4.7 months, respectively.
- Patients characteristics and preliminary antitumor activity observed are outlined in Table 1.

CONCLUSION

- The combination of NGR-hTNF at 0.8 µg/m² with cisplatin at 80 mg/m² showed a favourable toxicity profile and promising activity in heavily pre-treated patients, and will be further developed in platinum-sensitive tumors.

Table 1. Patients characteristics and preliminary antitumor activity by dose levels

DL (µg/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	-
	8	Colorectal	60	1	6	-	PD/4.5	5	SD	4.6
0.8	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
	21	Hepatic duct	60	0	2	Platinum	SD/4.2	1	NA	-
1.6	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=nonassessable; SFTP=solitary fibrous tumor of the pleura; NSCLC=non-small cell lung

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