

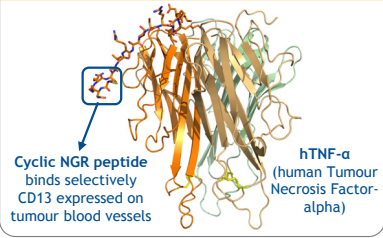
Phase I and pharmacodynamic study of NGR-hTNF administered at high doses in refractory patients with solid tumours

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BACKGROUND AND METHODS

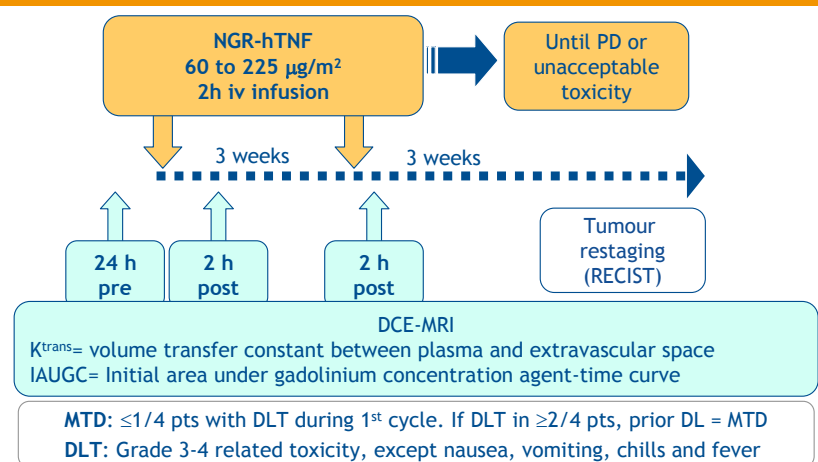
Figure 1. Structure of the NGR-hTNF molecule (1 subunit)



- Tumour necrosis factor-alpha (TNF-α) has shown potent antivascular and antitumour effects in preclinical models, but its clinical development was hampered by severe toxicity¹
- NGR-hTNF consists of TNF-α fused with the tumour-homing peptide NGR²⁻⁴ (Figure 1)
- NGR selectively binds a CD13 overexpressed on tumour blood vessels
- Significant preclinical synergism was displayed between low doses of NGR-hTNF and doxorubicin^{2,4}

- The maximum tolerated dose (MTD) of NGR-hTNF was established in a previous trial⁵ at 45 μg/m² when given as 1-hour infusion every 3 weeks (q3w), with dose limiting toxicity (DLT) being characterised by grade-3 acute infusion reactions
- In the present trial (Fig.2) additional dose escalations were explored by using:
 - Prolonged infusion timing (2 hours)
 - Premedication with paracetamol 1,000 mg
- Four patients enrolled at each of eight dose levels:
 - 60-80-100-125-150-175-200-225 μg/m²

Figure 2. Study design, doses and assessment



- Inclusion criteria:**
 - Age >18 years
 - Resistant to standard therapies
 - ECOG PS 0-1
 - Adequate baseline functions
 - Written informed consent
- PK:** Blood samples collected just prior to and at 20', 60', 90', 120', 180', 240' during the first 3 cycles

RESULTS

- 28 patients enrolled (median age: 57 years)
- ECOG PS 0/1: 12/6
- 73 cycles (range, 1-6)
- Prior regimens ranged from 1 to 6 (median, 3)
- No DLT occurred and MTD has not yet been reached

Figure 3. Adverse events (in >5% of patients)

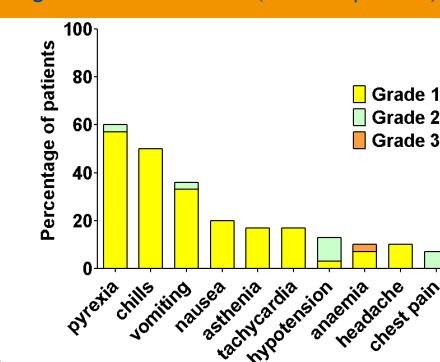


Table 1. Patients characteristics

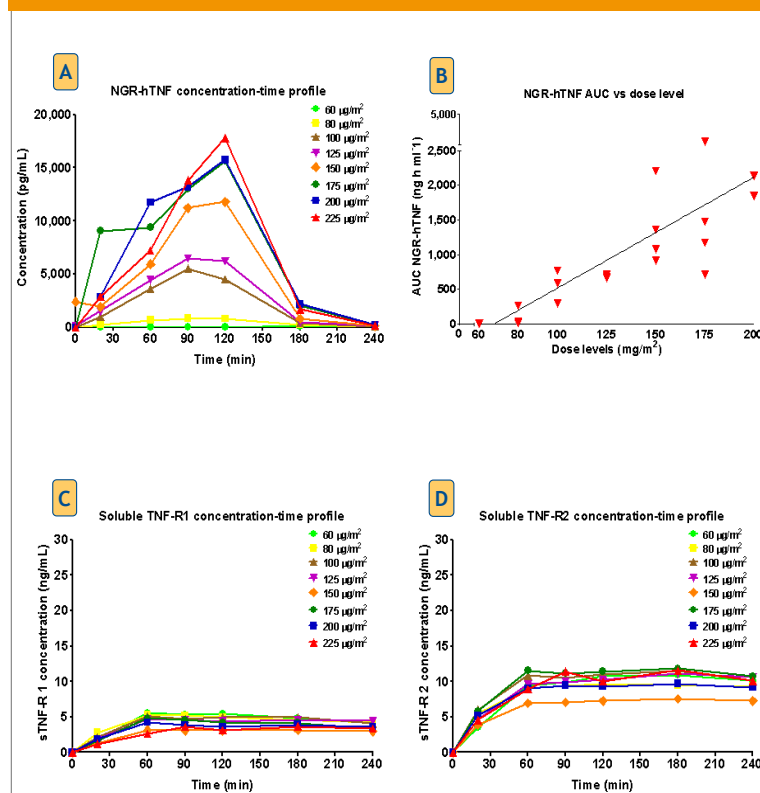
DL (μg/m ²)	Pt #	Tumour type	Age	PS	# prior regimens	Cycles
60	1	Liver	66	1	1	2
	2	Liver	47	0	1	6
	3	Colorectal	48	0	4	2
	4	Colorectal	70	0	2	4
80	5	Colorectal	59	0	3	2
	6	Colorectal	37	1	3	2
	7	Colorectal	71	0	2	2
	8	Colorectal	65	0	4	4
100	9	Colorectal	69	1	5	2
	10	Liver	45	1	1	2
	11	Colorectal	68	0	3	2
	12	Gastric	64	1	5	2
125	13	Colorectal	60	0	3	6
	14	Colorectal	49	1	3	2
	15	Colorectal	43	0	4	2
	16	Liver	23	1	4	2
150	17	Neuroendocrine	27	0	3	2
	18	Colorectal	76	1	3	2
	19	Mesothelioma	61	1	3	2
	20	Neuroendocrine	29	0	1	4
175	21	Sarcomas	55	1	1	2
	22	Mesothelioma	67	1	2	6
	23	Mesothelioma	50	1	2	1
	24	Colorectal	63	1	5	1
200	25	Sarcomas	32	1	3	1
	26	Sarcomas	53	1	5	2
	27	Mesothelioma	67	1	3	2
	28	Colorectal	62	0	3	1

DL=dose level; PS=performance status

CONCLUSIONS

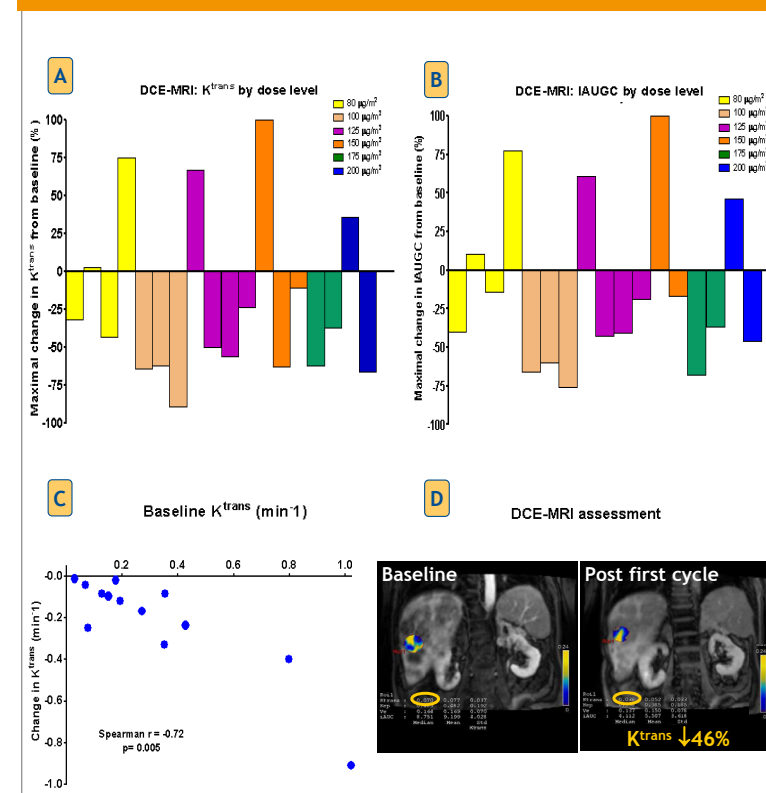
- NGR-hTNF can be safely delivered at doses higher than MTD using a mild pre-medication and a longer infusion time
- NGR-hTNF at high doses induces low increase of receptor shedding and early antivascular effects
- Further dose escalations are currently ongoing at doses ranging from 225 to 325 μg/m²

Figure 4. PKs and kinetics of soluble TNF receptors



- C_{max} and AUC of NGR-hTNF increased dose-proportionally (p<.0001 for both) (Figures 4A-4B).
- The levels of sTNF-R2 peaked significantly higher than those of sTNF-R1:
 - Median = 10.8 vs 5.2 ng/mL (p= 0.002, Mann-Whitney test - Figures 4C-4D)
- The changes in sTNF-Rs, however, did not significantly differ across dose levels
- The plateau observed in the shedding kinetics of sTNF-Rs suggests that the use of high doses of NGR-hTNF can overcome this counterregulatory mechanism

Figure 5. Dynamic contrast-enhanced MRI (DCE-MRI)



- K^{trans} significantly decreased in 13/18 (72%) patients assessed by DCE-MRI (Figure 5A), which is consistent with a reduction in tumour blood flow in response to NGR-hTNF:
 - Median baseline K^{trans} = 0.16 min⁻¹
 - Median post-dosing K^{trans} = 0.10 min⁻¹ (p=0.03, Wilcoxon test)
- These dose-unrelated reductions (median, -56%; p=0.0002) were noted in patients with CRC (n=7), HCC, MPM and STS (n=2 for each)
- Similar results were observed for IAUGC (Figure 5B)
- Greater decreases were achieved in patients with higher baseline K^{trans} (Figure 5C), thus suggesting an increased antivascular effect in malignancies with extensive abnormal vasculature

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