

ABSTRACT

Background: NGR-hTNF is a VTA exploiting a tumour-homing peptide (NGR) that selectively binds to aminopeptidase N/CD13 highly expressed on tumour blood vessels. In preclinical models, NGR-hTNF showed antitumour activity both at low and at high doses. **Methods:** Patients (pts) with advanced MPM were treated with low-dose NGR-hTNF given at 0.8 µg/m² as 1-hour intravenous infusion every 3 weeks (q3w). This dose was previously selected in phase I trial based on dynamic imaging changes and preliminary clinical activity. The trial had a 2-stage design with 16 and 27 pts to be enrolled. Progression-free survival (PFS) was the primary endpoint with reassessment performed q3w according to MPM-modified RECIST criteria. **Results:** From May 2007 to January 2008, 43 pts with progressive disease after pemetrexed/platinum-based regimens were enrolled. Globally, 41 pts were treated with 142 cycles (median, 2; range, 1-14). 16 pts (39%) and 10 pts (24%) have received ≥4 and ≥6 doses, respectively. Pts characteristics were: median age 64 years (range, 34-80); M/F 27/14; histology epithelial/non-epithelial (E/NE) 32/9; PS 0/1/2 24/10/7; EORTC prognostic score (EPS) good/poor 32/9. 18 pts (44%; 95% CI, 29-59%) had stable disease with a median duration of 4.4 months (95% CI, 3.5-5.3). Median 3-month PFS were 2.8 months (95% CI, 1.7-3.4) and 43% (95% CI 26-59%), respectively. To date, 7 pts (17%) remain on treatment (range: 3.4-10.5 months) and 24 pts (83%) are still alive (range of follow-up: 0.7-11.5 months). In an exploratory subset analysis, there were no differences in PFS between pts with good and poor EPS, E and NE histology, PS 0 and 1-2, and pts younger and older than the median age. Neither grade 3-4 treatment-related adverse events nor toxicity-related death were observed. Most common grade 1-2 toxicities per patient were transient infusion-related constitutional symptoms, including chills (59%) and fatigue (18%). Currently, an additional cohort of 12 pts is treated with a weekly schedule. **Conclusion:** NGR-hTNF is well tolerated and shows evidence of disease control in chemo-pretreated MPM patients. The drug will be further developed as single agent in this setting.

Background

- A large body of preclinical evidences have shown that tumour necrosis factor-α (TNF-α) has potent antitumour activity. However, its clinical use has been hampered by severe systemic toxicity, with MTD significantly lower than ED in humans¹
- The antivascular effects of TNF-α provided the rationale for developing a vascular targeting strategy aimed at increasing the local antitumour activity
- NGR-hTNF is a novel 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}, including malignant pleural mesothelioma (Figure 2)

Figure 1. Recombinant fusion protein consisting of NGR peptide and human Tumour Necrosis Factor-α (hTNF-α)

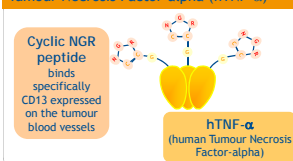
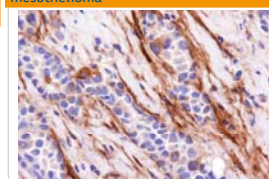
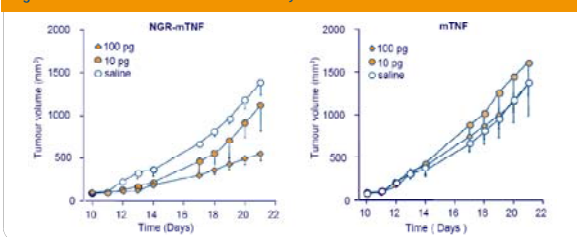


Figure 2. CD13 expression in mesothelioma



- NGR-mTNF was found to have antitumour activity also at doses in the picogram range (equivalent to a dose of 0.2 µg/m² in humans) in preclinical model⁴ (Figure 3)

Figure 3. Preclinical antitumour activity at low doses of NGR-mTNF and mTNF



Phase I trials of NGR-hTNF

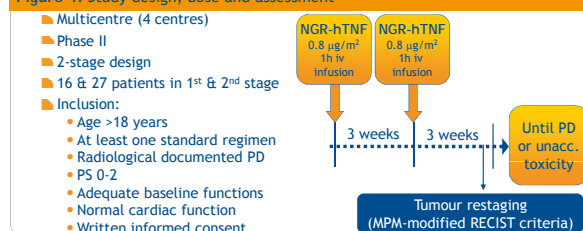
- In a phase I study evaluating a dose-interval ranging from 0.2 to 60 µg/m² the MTD of NGR-hTNF was established at 45 µg/m² when given as single agent once every 3 weeks⁶
- Conversely, a further phase I trial exploring the low-dose range of NGR-hTNF from 0.2 to 1.6 µg/m² selected the dose of 0.8 µg/m² as the optimal biological dose, based on dynamic imaging changes and preliminary antitumour activity⁷

Disease background

- Advanced malignant pleural mesothelioma (MPM) is an aggressive tumour that usually has a poor prognosis⁷
- The combination of pemetrexed and cisplatin has become standard of care in 1st line with median PFS and OS durations of 5.7 and 12.1 months, respectively⁸
- However, the patient population progressing after 1st line chemotherapy has an aggressive disease with median PFS of 1.5 months and disease control rate of 19% registered in 120 patients enrolled in the best supportive care (BSC) arm of a phase III trial⁹
- In this study, treatment with pemetrexed as second-line therapy provided a significant improvement in PFS, whereas improvement in OS was not reported in comparison with the BSC arm (8.4 months versus 9.7 months), possibly because of significant imbalance in post-discontinuation chemotherapy between the two arms

Methods

Figure 4. Study design, dose and assessment



Results

- From May 2007 to January 2008, forty-three patients with advanced MPM, and radiologically documented progressive disease after pemetrexed/platinum-based regimens were enrolled. The last 23 patients were recruited in a 2-month interval. 41 patients received at least one dose of study drug and were included in this analysis
- The median time from completion of 1st line therapy to study treatment start was 3.9 months. Baseline characteristics are summarised in Table 1

Table 1. Baseline characteristics

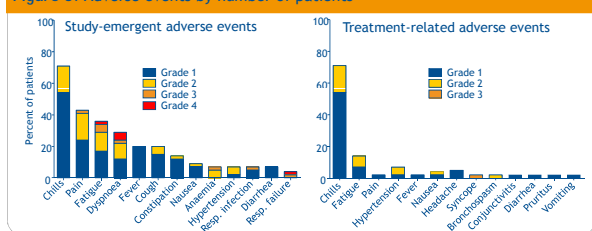
Characteristics	n=41 (%)
Median age, years (range)	64 (54-80)
Gender	
Male	27 (66)
Female	14 (34)
ECOG performance status	
0	24 (59)
1	10 (24)
2	7 (17)
Primary tumour histology	
Epithelial	32 (78)
Nonepithelial	9 (22)
EORTC prognostic score (EPS)+	
Good	32 (78)
Poor	9 (22)
Previous systemic therapy	
Pemetrexed/carboplatin or cisplatin	38 (93)
Gemcitabine/cisplatin	3 (7)
Best response to first-line therapy	
Partial response	5 (12)
Stable disease	24 (59)
Progressive disease/Unknown	12 (29)

* a poor EPS score is based on the presence of at least three of the following factors: male gender; WBC count < 3.3 × 10⁹/L; ECOG PS of 1 or 2; probable histologic diagnosis; sarcomatoid histology

Safety

- 158 cycles were administered (mean 3.9; median 2; range 1 to 16), with 24% and 10% of patients receiving ≥6 and ≥12 cycles, respectively
- Overall, 219 study-emergent adverse events (AEs) were reported and the majority were of grade 1 (64%) or grade 2 (24%) severity. 21 grade 3 (10%) and 6 grade 4 (2%) AEs were noted
- Only 67 AEs (31%) were considered treatment-related and the most frequent were chills, with 42 events (19%) experienced by 29 patients (71%), and fatigue, with 9 events (4%) reported in 6 patients (15%)
- Neither grade 4 AEs nor toxicity-related death were observed in the study population. Only one patient (2%) had a grade 3 treatment-related event (vasovagal syncope)
- At end of therapy, ECOG PS improved or remained stable in 27 patients (66%)

Figure 5. Adverse events by number of patients



Efficacy

- According to an ITT analysis, one patient had PR (Figure 6) and 17 SD, with a median duration of 4.3 months
- Efficacy results are reported in Tables 2-3 and the actuarial PFS curve is shown in Figure 7 (10 patients censored)
- PFS durations of 12.4 and 10.5 months were observed in an elderly patient with PS of 2 and in a chemo-refractory patient with biphasic histology, respectively
- Patients with SD at their 1st restaging (n=18) received a median of 6 cycles (range 3-16) and had 9- and 12-month PFS rates of 27% and 14%, respectively. Three patients are currently on treatment (range 3.3-9 months)
- In a post-hoc subset analysis, no differences in PFS were detected between patients with epithelial and nonepithelial histology, good and poor EORTC prognostic score, ECOG PS 0-1 and 2, and age < and ≥70 years
- With a median duration of follow-up of 8.3 months (95% CI, 6.5 to 10.1 months), 27 patients (66%) are still alive

Table 2. Best overall response

Variable	# pts	Estimate	95% CI
PR	1	2%	0-12
SD	17	42%	28-57
DCR	18	44%	30-59
PD	18	44%	30-59
Not assessed*	5	12%	5-25

PR: partial response; SD: stable disease; DCR: disease control rate; PD: progressive disease; *Five patients withdrew from the study before their first restaging scan for symptomatic deterioration

Figure 6. CT scan PR in a 66-old patient

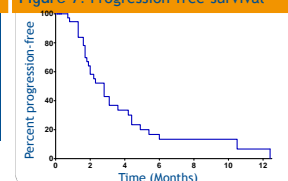


Table 3. Time-related efficacy data

Variable	Estimate	95% CI
Median PFS	2.8 months	2.0-3.6
3-month PFS rate	43%	26-59
Median PFS in SD pts (n=18)	4.4 months	3.5-5.3
3-month PFS rate	88%	71-99
Median OS	NR	
6-month OS rate	74%	60-88

PFS: progression-free survival; SD: stable disease; Pts: patients; OS: overall survival; NR: not reached; CI: confidence interval; *Median follow-up: 8.3 months

Figure 7. Progression-free survival



Conclusions

- NGR-hTNF administered at low dose shows a favourable and manageable toxicity profile, with evidence of disease control in chemo-pretreated MPM patients
- Prolonged PFS durations were also reported in elderly, chemorefractory and PS2 patients
- NGR-hTNF is currently evaluated in a cohort of 14 patients treated with a weekly schedule (7 patients with SD, 6 with PD and 1 too early)
- The mode of action of NGR-hTNF, along with its safety profile, should also facilitate its incorporation into standard chemotherapy regimens

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