

NGR-hTNF, a novel vascular targeting agent (VTA), as second-line therapy in malignant pleural mesothelioma (MPM): Preliminary results of multicenter phase II study

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ABSTRACT

Background: NGR-hTNF is a VTA exploiting a tumor-homing peptide (NGR) that selectively binds to aminopeptidase N/CD13 highly expressed on tumor blood vessels. NGR-hTNF combines direct anticancer activity and effects on tumor vascular permeability. In preclinical models, NGR-hTNF showed antitumor activity either at low doses or at high doses. **Methods:** Patients (pts) with advanced MPM pretreated with first-line chemotherapy received a 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 in first and second stage, respectively. Progression-free survival (PFS) was the primary end-point with reassessment performed q6w. **Results:** From May to December 2007, 42 pts were enrolled and 16 were included into the first-stage analysis: 75% were males; median age 64 years (range, 48-80); PS 0/1/2 7/6/3; 69% had epithelial, 12.5% sarcomatoid, 6% mixed and 12.5% unknown histology. Overall, 58 cycles (median 2, range, 1-9) were completed. Seven pts (44%; 95% CI 20-68%) had a stable disease (SD) with a median duration of 4.4 months (range, 1.6-7.1-). The maximum changes of target lesions in SD pts ranged from 17% shrinkage to 6% growth. The estimated PFS rate at 4.5 months was 37% (95% CI 10-65%) and 3 pts (19%) are still on treatment at 6 months. To date, 26 pts are enrolled in stage 2 (5 SD, 3 PD, 18 too early) and an additional 12 pts are entering into a subsequent cohort of pts treated with a weekly schedule. Main grade 1-2 toxicities per patient were infusion-related constitutional symptoms, including chills (56%) and fatigue (31%). Neither grade 3-4 treatment-related adverse events nor toxicity-related death were observed. **Conclusion:** NGR-hTNF shows a favourable and manageable toxicity profile, with preliminary evidence of long-lasting disease control in chemo-pretreated MPM patients.

Background

- A large number of preclinical studies have shown that tumor necrosis factor-α (TNF-α) has potent antitumor activity. However, its clinical use has been hampered by severe systemic toxicity, with MTD significantly lower than ED in humans.¹
- The antivascular effects of TNF-α provided the rationale for developing a vascular targeting strategy aimed at increasing the local antitumor activity and at enabling systemic administration of therapeutic doses.
- NGR-hTNF is a novel therapeutic vascular targeting agent (VTA) that has been genetically engineered by coupling the N-terminus of human TNF-α with the C-terminus of the tumor-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 tumor vessels,^{2,4} including malignant pleural mesothelioma (Figure 2).

Figure 1. Recombinant fusion protein consisting of NGR peptide combined with human Tumor Necrosis Factor-α (hTNF-α)

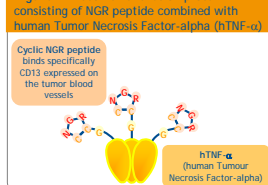
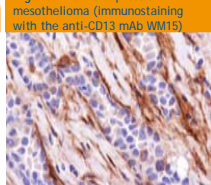
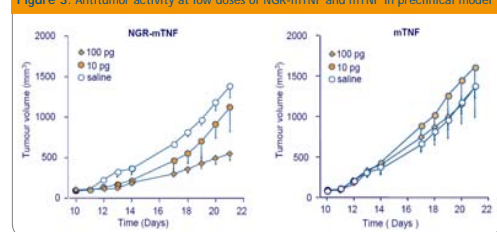


Figure 2. CD13 expression in mesothelioma (immunostaining with the anti-CD13 mAb WM15)



- Recently, in an APN-null mice model⁵ was shown that although aminopeptidase N activity is not essential for embryonic and fetal development including *de novo* blood vessel formation and normal adult function, it is critical for the pathological development of new blood vessels from existing blood vessels in disease.
- NGR-mTNF was found to have antitumor activity also at doses in the picogram range (equivalent to a dose of 0.2 µg/m² in humans) in preclinical model⁶ (Figure 3).

Figure 3. Antitumor activity at low doses of NGR-mTNF and mTNF in preclinical model



Phase I trials

- A phase I study evaluating a dose-interval ranging from 0.2 to 60 µg/m² established the MTD of NGR-hTNF at 45 µg/m² when given as single agent once every 3 weeks.⁶
- 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 (OBD), based on dynamic imaging changes and preliminary antitumor activity.⁷

Disease background

- Advanced malignant pleural mesothelioma (MPM) is an aggressive tumor that usually has a poor prognosis.⁸
- The combination of pemetrexed and cisplatin has become the standard of care in the first-line treatment of MPM with median progression-free (PFS) and overall survival (OS) durations of 5.7 months and 12.1 months, respectively.⁹
- However, patients who have progressed on first-line chemotherapy for mesothelioma have few treatment options, and there are no currently approved second-line therapies.
- In a recently completed phase III study examining pemetrexed as second-line chemotherapy versus best supportive care, a significant longer PFS was demonstrated in the chemotherapy-receiving arm (3.8 versus 1.5 months). However, no improvement in OS was observed (8.4 versus 9.7 months), possibly because of the imbalance in post-discontinuation therapy between the two arms.¹⁰
- Additionally, two separate phase II single-arm trials evaluating in pemetrexed-pretreated patients a combination chemotherapy¹¹ (gemcitabine plus vinorelbine) and a combined targeted therapy¹² (bevacizumab plus erlotinib), have reported median PFS durations of 2.8 and 2.6 months, respectively.

Methods

- Multicenter, two-stage, phase II study with 16 and 27 patients to be enrolled after the first and second stage, respectively.
- NGR-hTNF given at 0.8 µg/m² as 1-hour intravenous infusion every 3 weeks until progressive disease or unacceptable toxicity.
- Primary endpoint: Progression-free survival (PFS) with restaging performed every 6 weeks according to MPM-modified RECIST criteria. Secondary objectives: disease control rate, overall survival and safety.
- Key inclusion criteria:
 - No more than one systemic therapeutic regimen
 - ECOG Performance Status 0-2
 - Adequate baseline bone marrow, hepatic and renal function. Normal cardiac function and absence of uncontrolled hypertension
 - No clinical signs of CNS involvement
 - Written informed consent to participate in the study

Results

- From May 2007 to January 2008, forty-three patients with advanced MPM and radiologically assessed 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 the present analysis. Baseline characteristics are summarized in Table 1.

Table 1. Baseline characteristics

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

Safety

- A total of 151 cycles of therapy were administered with a median of 2 (range, 1 to 16). To date, 39% and 24% of patients have received ≥4 and ≥6 doses, respectively.
- Neither grade 4 adverse events nor toxicity-related death were observed in the study population. Only one patient (2%) had a grade 3 treatment-related adverse event (vasovagal syncope).
- The most common treatment-related adverse events (Table 2) were grade 1-2 chills (63%) and fatigue (24%), generally occurring approximately 30 minutes after the start of the first infusions and lasting about 20 minutes. No cumulative toxicities were observed.
- At end of therapy, ECOG PS improved or remained stable in 27 patients (66%).

Table 2. Treatment-related adverse events occurring in > 5% of patients

Event	Grade 1	Grade 2	Grade 3	Grade 4
Chills	18 (44%)	8 (19%)	-	-
Fatigue	4 (10%)	6 (14%)	-	-
Blood pressure increase	2 (6%)	1 (2%)	-	-

Efficacy

- According to an intent-to-treat analysis, 18 patients (44%) had stable disease (SD) as best overall response.
- Five patients (12%) are still on treatment (range, 4.6 to 11.7 months).
- PFS durations of 11.7 and 9.5 months were observed in an elderly male patient with PS 2 and in a chemo-refractory male patient with biphasic histology, respectively.
- An additional chemo-refractory patient with sarcomatoid histology had a shrinkage (17%) of the pleural lesion documented by CT scan.
- Preliminary efficacy results are reported in Table 3 and 4. Figure 4 shows the actuarial PFS curve (13 patients censored).
- Median duration of follow up was 6.1 months (95% CI, 5.3 to 6.8 months; range, 0.7 to 12.9 months).
- For patients achieving SD at their first restaging (n=18), the 6-month and 9-month PFS rates were 44% and 35%, respectively.
- In an exploratory 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 (Table 5).

Table 3. Best overall response

Variable	No. of patients	%	95% CI
Stable disease (SD)	18	44	30-59
Progressive disease (PD)	18	44	30-59
Not assessed*	5	12	5-25

*Five patients withdrew from the study before their first restaging scan for symptomatic deterioration.

Table 4. Time-related efficacy data

Variable	Estimate	95% CI
Median PFS in ITT population (n=41), months	2.8	2.0-3.6
3-month PFS rate, %	43	26-59
Median PFS in patients with SD (n=18), months	5.0	3.8-6.2
3-month PFS rate, %	87	71-100
Median OS (median follow up: 6.1 months)	NR	-
3-month OS rate, %	88	78-98

PFS=progression-free survival; ITT= intent-to-treat; SD=stable disease; OS= overall survival; CI=confidence interval; NR=not reached

Figure 4. Progression-free survival (ITT population)

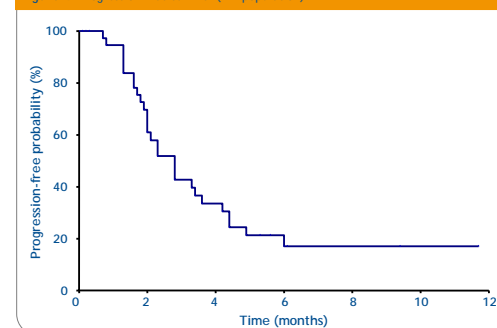


Table 5. Post-hoc subset analysis according to clinical characteristics

Characteristics	No. of pts (%)	HR for PFS	p-value
Histology			
Epithelial	32 (78)		
Nonepithelial	9 (22)	0.98	.97
EORTC prognostic score			
Good	32 (78)		
Poor	9 (22)	0.95	.92
ECOG PS			
0-1	34 (83)		
2	7 (17)	0.84	.72
Age, years			
<70	32 (78)		
≥70	9 (22)	1.12	.78

EORTC=European Organization for Research and Treatment of Cancer; ECOG=Eastern Cooperative Oncology Group; PS=performance status; HR=hazard ratio (a value of 1.0 denotes no difference in the rate of events between the two groups); PFS=progression-free survival.

Conclusions

- NGR-hTNF administered at low dose is safe and shows a favourable and manageable toxicity profile, with evidence of disease control in chemo-pretreated MPM patients.
- Notwithstanding the small-sized samples analysed, it is notable that prolonged progression-free survival durations were also reported in poor-prognosis subsets, including elderly and PS 2 patients.
- NGR-hTNF as single-agent is currently evaluated in a cohort of 12 patients by using a weekly schedule of administration.
- The mode of action of NGR-hTNF, along with its favourable safety profile, should also facilitate its incorporation into standard chemotherapy regimens for MPM.

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