

# Phase II study of NGR-hTNF, a selective vascular targeting agent (VTA), in previously treated patients with malignant pleural mesothelioma (MPM)

V. Gregorc<sup>1</sup>, G.L. Ceresoli<sup>2</sup>, P. A. Zucali<sup>2</sup>, F.G. De Braud<sup>3</sup>, E. Bajetta<sup>4</sup>, A. Santoro<sup>2</sup>, M.G. Viganò<sup>1</sup>, F. Caligaris Cappio<sup>1</sup>, A. Lambiase<sup>5</sup>, C. Bordignon<sup>5</sup>

<sup>1</sup>Istituto Scientifico San Raffaele, Milan, Italy; <sup>2</sup>Istituto Clinico Humanitas, Rozzano, Milan, Italy; <sup>3</sup>Istituto Europeo di Oncologia, Milan, Italy; <sup>4</sup>IRCCS Fondazione Istituto Nazionale dei Tumori, Milan, Italy; <sup>5</sup>Molmed, Milan, Italy

## Background

- Tumor necrosis factor-alpha (TNF- $\alpha$ ) has potent antivascular and antitumor activity. However, its clinical development has been hampered by severe systemic toxicity.<sup>1</sup>
- NGR-hTNF is a VTA consisting of TNF- $\alpha$  fused with the tumor-homing peptide NGR (Fig. 1).
- NGR selectively binds a CD13 isoform overexpressed in most tumor blood vessels,<sup>2-4</sup> including MPM (Fig. 2).

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

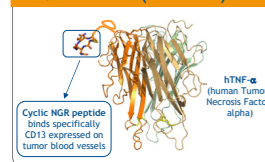
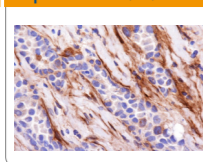


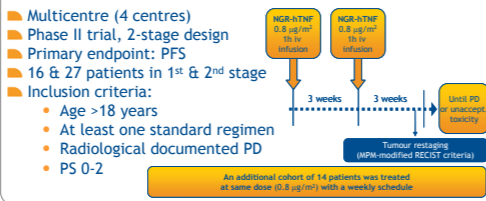
Figure 2. CD13 expression in MPM



- NGR-TNF has shown antitumor activity even at doses in the picogram range<sup>5</sup> (equivalent to 0.2  $\mu\text{g}/\text{m}^2$  in humans)
- Two phase I trials have previously selected 0.8  $\mu\text{g}/\text{m}^2$  and 45  $\mu\text{g}/\text{m}^2$  as optimal-biological and maximum-tolerated dose, respectively.<sup>6,7</sup>
- The combination of pemetrexed and cisplatin is the standard first-line treatment of MPM with median OS of 12.1 months, respectively.<sup>8</sup>
- In a randomised study examining pemetrexed as second-line therapy versus supportive care alone, a longer PFS was demonstrated in the chemotherapy-receiving arm (3.8 v 1.5 months). However, no improvement in OS was observed (8.4 v 9.7 months).<sup>9</sup>
- Currently, there are no widely approved salvage regimen for MPM.

## Methods

Figure 3. Study design, dose, and assessments



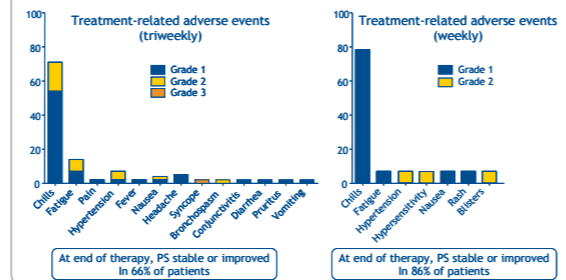
## Results

Baseline characteristics	Triweekly n=43 (%)	Weekly n=14 (%)
Median age, years	64	68
Age range, years	54-80	50-86
Gender		
Male	27 (63)	7 (50)
Female	16 (37)	7 (50)
ECOG performance status		
0	24 (56)	7 (50)
1-2	19 (44)	7 (50)
Primary tumor histology		
Epithelial	34 (79)	11 (79)
Nonepithelial	9 (21)	3 (21)
EORTC prognostic score		
Good	34 (79)	11 (79)
Poor	9 (21)	3 (21)
Previous systemic therapy		
Pemetrexed / platinum	40 (93)	13 (93)
Gemcitabine / cisplatin	3 (7)	1 (7)
Best response to prior therapy		
PR	5 (12)	2 (14)
SD	24 (56)	8 (57)
PD / Unknown	14 (32)	4 (24)
PFS on prior therapy		
$\geq$ 6 months	24 (67)	9 (64)
< 6 months	19 (33)	5 (36)

## Safety

- 171 cycles (range, 1-18) were administered in the triweekly cohort and 248 infusions (range, 4-51) in the weekly cohort.
- Only one grade 3 drug-related adverse event was observed.
- The most common drug-related toxicity was grade 1-2 chills, occurring approx 30 min after the start of first infusions and lasting about 20 min.
- The weekly dosing schedule did not change the toxicity profile (Figure 4).

Figure 4. Toxicity



## Efficacy

- After the 8<sup>th</sup> cycle, one patient achieved a PR lasting for further 9.4 months (Figure 5).
- Overall efficacy results are listed in Table 1 and progression-free and overall survival curves are depicted in Figures 6 and 7, respectively.

Figure 5. Objective response in a 66-old patient

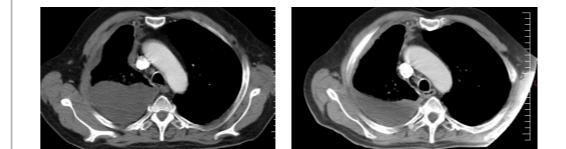


Table 1. Overall efficacy results

Variable	Triweekly (n=43)	Weekly (n=14)	All (n=57)
Best response, %			
PR	2	-	2
SD	42	50	44
Disease control rate (PR+SD)	44	50	46
PD	37	50	40
Non-assessable	19	-	14
PFS, months			
Median	2.8	3.0	2.8
(CI 95%)	(1.9-3.7)	(1.9-4.1)	(2.2-3.4)
6-month rate	13	36	19
PFS in pts with disease control, months			
Median	4.4	9.1	4.7
(CI 95%)	(4.0-4.8)	(4.7-13.4)	(4.0-5.4)
OS, months			
Median	11.6	NR	12.1
(CI 95%)	(5.6-17.6)	-	(8.4-15.7)

PR=partial response; SD=stable disease; DCR= disease control rate; PD=progressive disease; PFS=progression-free survival; SD=stable disease; OS=overall survival; CI=confidence interval; NR=not reached after a median follow-up of 12.4 months; Median follow-up for the entire study population: 17.9 months.

- In multivariate Cox analyses, male gender (p=.034) and age older than median value (p=.019) were associated to longer PFS, whereas PS of 0 (p=.001) and epithelial histology (p=.008) were associated to longer OS.

## CONCLUSIONS

- NGR-hTNF shows a favourable toxicity profile, with evidence of disease control in MPM patients previously treated with a pemetrexed-based chemotherapy.
- Overall study results included a DCR of 46% maintained for a median of 4.7 months, a median PFS of 2.8 months, and a median OS of 12.1 months.
- These results warrant further randomised evaluation of NGR-hTNF in this setting.

Figure 6. Progression-free survival

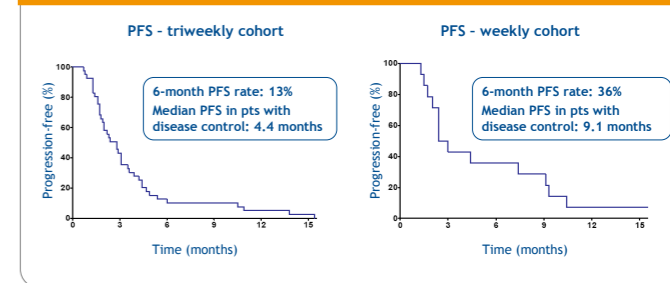
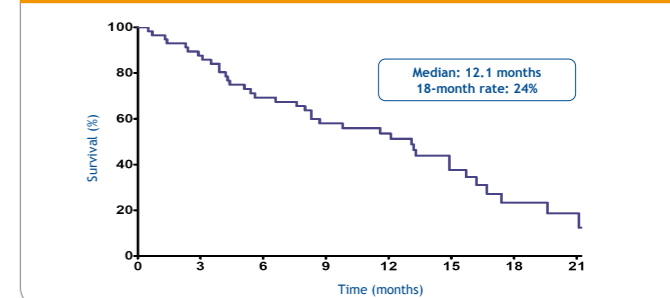


Figure 7. Overall survival (entire study population)



## References

- Blick M, et al. *Cancer Res* 1987;47:2986-9.
- Curnis F, et al. *Nat Biotech* 2000;18 (11): 1185-9
- Corti A, et al. *Methods Mol Med* 2004; 98: 247-64
- Rangel R, et al. *PNAS* 2007; 104: 4588-4593
- Curnis F, et al. *J Clin Invest* 2002; 110: 475-82
- van Laarhoven H et al. *ASCO* 2008; Abs 3521
- Gallo-Stampino C, et al. *ASCO* 2007; Abs 3540
- Vogelzang NJ et al. *JCO* 2003; 21: 2636-2644
- Jassem J et al. *JCO* 2008; 26:1698-1704

## Acknowledgements

- Istituto San Raffaele: G. Rossini, A. Zanoni
- Istituto Clinico Humanitas: R. Finotto
- Istituto Europeo di Oncologia: S. Boselli
- Istituto Nazionale dei Tumori: B. Formisano
- MolMed: F. Fontana, S. Colombi, A. Troysi, E. Lungagnani