

**NGR-hTNF, a vascular targeting agent (VTA),
in previously treated patients with
malignant pleural mesothelioma (MPM):
A phase II study**

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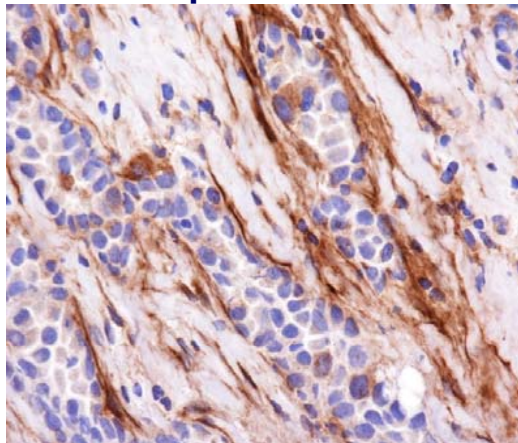
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NGR-hTNF: Structure & target

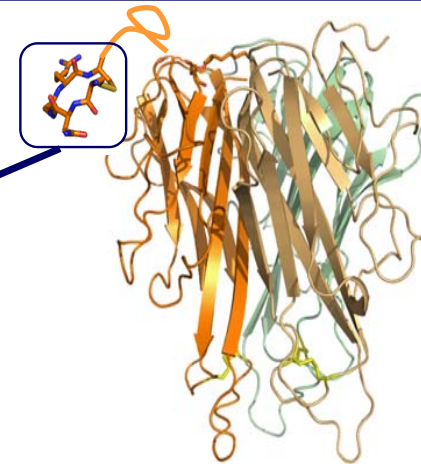
TNF- α has shown potent antitumor and antivascular activity in preclinical models. However, its clinical use has been hampered by severe systemic toxicity, with MTD significantly lower than ED¹

CD13 expression in MPM



Cyclic NGR peptide selectively binds CD13 overexpressed on the tumor vessels

Recombinant fusion protein²

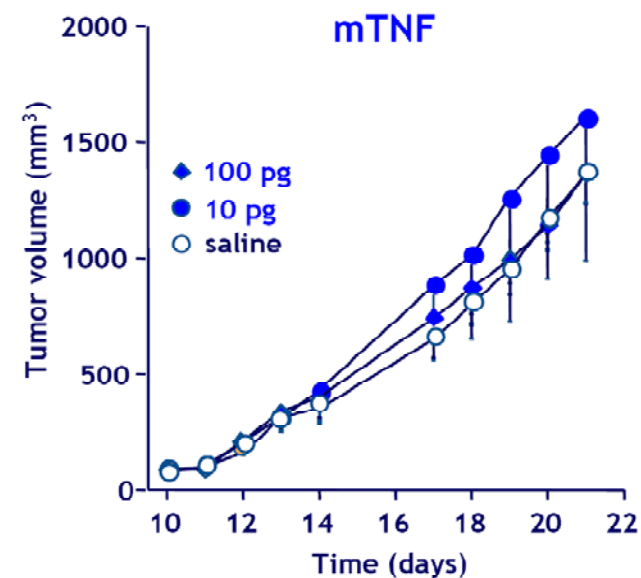
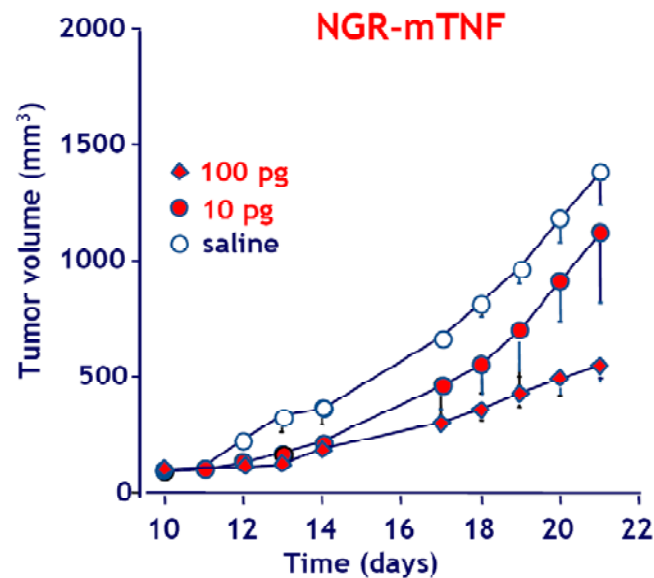


hTNF- α (human tumor necrosis factor-alpha)

¹Cancer Res 1987;47:2986-9

²Nat Biotechnol 2000;18 (11): 1185-9

NGR-hTNF: Preclinical activity at low dose



Antitumor activity was shown also at low doses in the picogram range (100 pg), equivalent to 0.2 $\mu\text{g}/\text{m}^2$ in humans (phase I trial starting-dose)

J Clin Invest 2002; 110: 475-82

NGR-hTNF: Early clinical development

- **Phase I¹:**
 - **DLs: 0.2 - 60 $\mu\text{g}/\text{m}^2$**
 - **DLTs: gr. 3 dyspnea and acute infusion reaction (60 $\mu\text{g}/\text{m}^2$)**
 - **MTD: 45 $\mu\text{g}/\text{m}^2$**

- **Phase I low-dose range²:**
 - **DLs: 0.2 - 1.6 $\mu\text{g}/\text{m}^2$**
 - **No DLTs/MTD**
 - **0.8 $\mu\text{g}/\text{m}^2$ selected as the optimal biological dose based on safety, DCE-MRI changes, soluble TNF-receptor kinetics, and preliminary activity**

¹ASCO 2008 - Abs 3521

²ASCO 2007 - Abs 3540

NGR-hTNF in MPM: Disease background

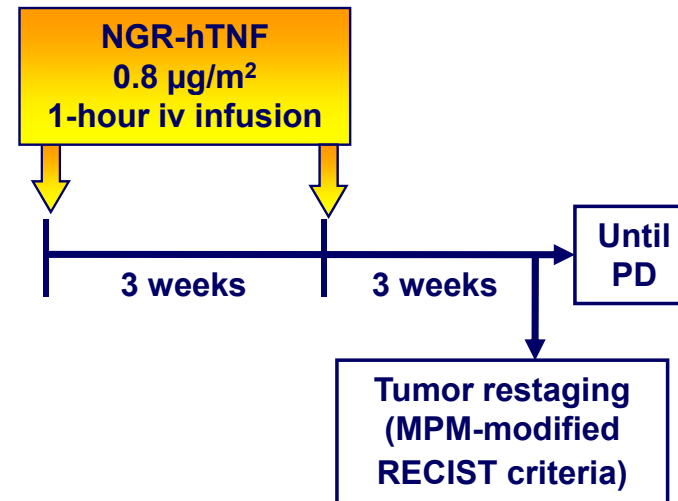
- **Advanced MPM is a devastating disease with increasing incidence worldwide**
- **The pemetrexed-cisplatin combination is standard of care in 1st line with median PFS and OS of 5.7 and 12.1 months, respectively¹**
- **However, patients progressing after 1st line have an aggressive disease with median PFS of 1.5 months and DCR of 19% reported in the no-treatment arm of a phase III trial²**
- **Neither regulatory-approved nor widely-accepted 2nd line therapy are currently available**

¹JCO 2003 ; 21:2636-2644

²JCO 2008 ; 26:1698-1704

NGR-hTNF in MPM: Study design

- Multicenter, open-label phase II trial
- Two-stage design:
 - 16 and 27 pts after 1st and 2nd stage
- Primary endpoint : 3-month PFS rate
 - 7 (44%) and 13 (48%) patients progression-free at 3 months after 1st and 2nd stage
- Key inclusion criteria:
 - Age >18 years
 - At least 1 prior systemic regimen
 - Radiologically-documented PD
 - PS 0-2
 - Written informed consent



A subsequent cohort of 12 patients treated at 0.8 µg/m² with a weekly schedule

- 43 patients enrolled in the triweekly cohort from May 2007 to January 2008
- 14 patients enrolled in the weekly cohort from February 2008 to June 2008

NGR-hTNF in MPM: Baseline characteristics

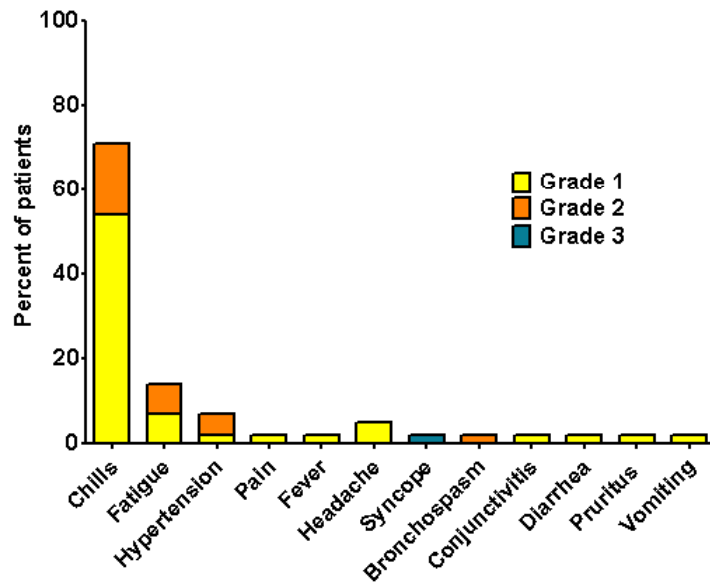
Characteristics	Triweekly cohort n=43 (%)	Weekly cohort n=14 (%)
Median age, years (range)	64 (54-80)	68 (50-86)
Gender		
Male	27 (63)	8 (57)
Female	16 (37)	6 (43)
ECOG performance status		
0	24 (56)	7 (50)
1-2	19 (44)	7 (50)
Primary tumor histology		
Epithelial	34 (79)	11 (79)
Nonepithelial	9 (21)	3 (21)
EORTC prognostic score		
Good	34 (79)	11 (79)
Poor	9 (21)	3 (21)
Prior 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		
≥ 6 months	24 (67)	9 (64)
< 6 months	19 (33)	5 (36)

NGR-hTNF in MPM: Safety

- **Drug-exposure:**
 - **171 cycles (range, 1-18) in the triweekly cohort**
 - **262 infusions (range, 4-65) in the weekly cohort**
- **One grade 3 drug-related adverse event (triweekly cohort)**
- **Most common drug-related toxicity: grade 1-2 chills, transiently occurring during first infusions**
- **The weekly dosing schedule did not change the toxicity profile**

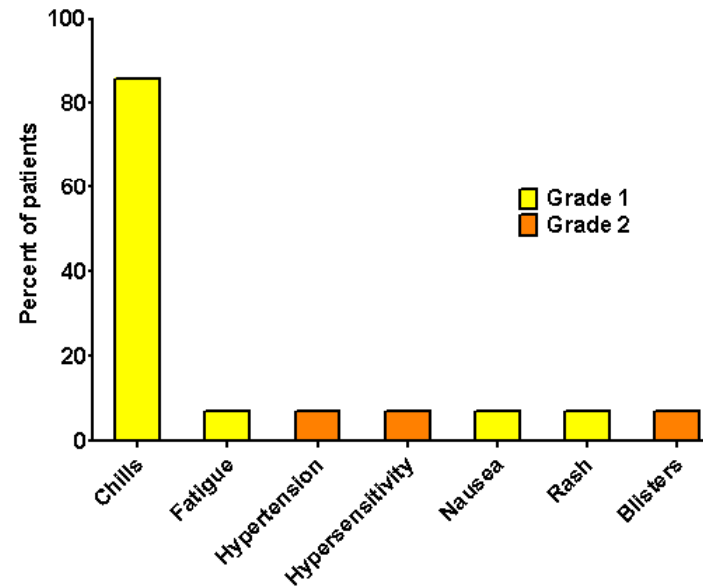
NGR-hTNF in MPM: Treatment-related adverse events

Triweekly cohort



At the end of therapy, PS stable or improved in 61% of patients

Weekly cohort



At the end of therapy, PS stable or improved in 79% of patients

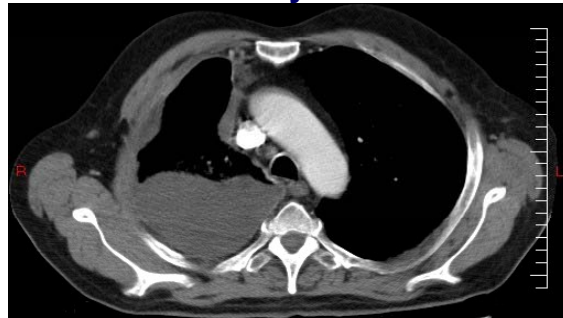
NGR-hTNF in MPM: Best overall response

	Triweekly (n=43)	Weekly (n=14)	All (n=57)
Partial response (PR)	2%	-	2%
Stable disease[°] (SD)	42%	50%	44%
Disease control rate (PR + SD)	44%	50%	46%
Progressive disease (PD)	37%	50%	40%
Non-assessable*	19%	-	14%

[°]As best response at any time

*8 patients were withdrawn before first restaging due to symptomatic deterioration (n=6) and early death (n=2)

January 2008



June 2008

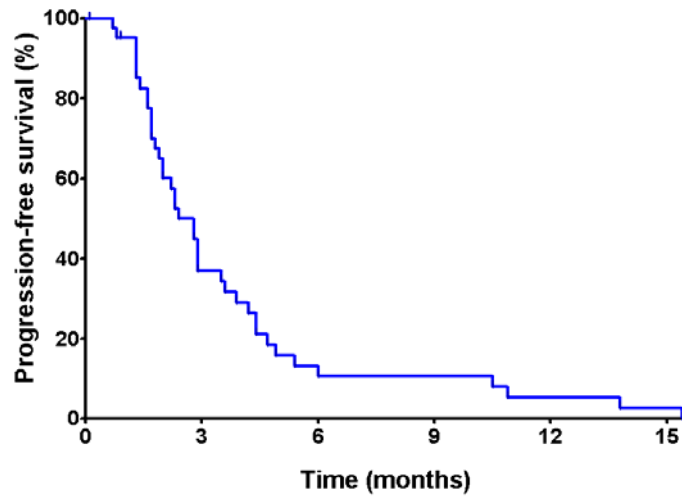


NGR-hTNF in MPM: Efficacy results (ITT analyses)

	Triweekly (n=43)	Weekly (n=14)	All (n=57)
Progression-free survival (PFS)			
Median, months	2.8	3.0	2.8
(95% CI)	(2.3-3.3)	(1.9-4.1)	(2.3-3.3)
3-month rate[°]	37%	50%	41%
6-month rate[°]	11%	36%	17%
PFS in patients with disease control			
Median, months	4.4	9.1	4.7
(95% CI)	(4.0-4.8)	(4.7-13.4)	(4.0-5.4)
Overall survival (OS)			
Median, months	11.6	NR*	12.1
(95% CI)	(5.6-17.6)	-	(7.2-17.0)
[°] Kaplan-Meier estimates *NR=not reached after a median follow-up of 12.5 months			

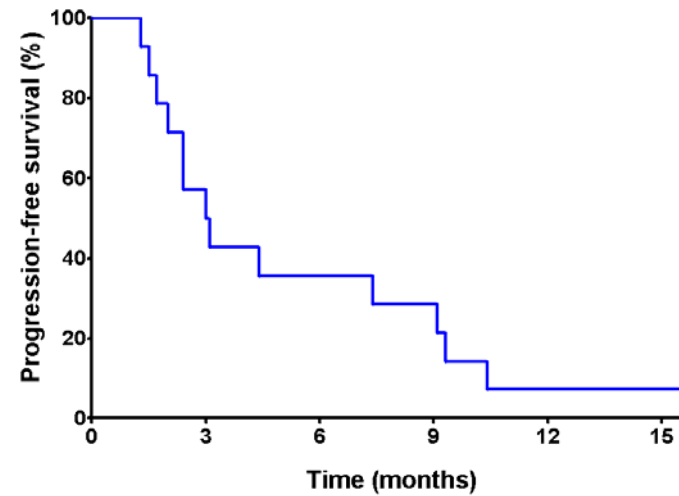
NGR-hTNF in MPM: Progression-free survival

Triweekly cohort



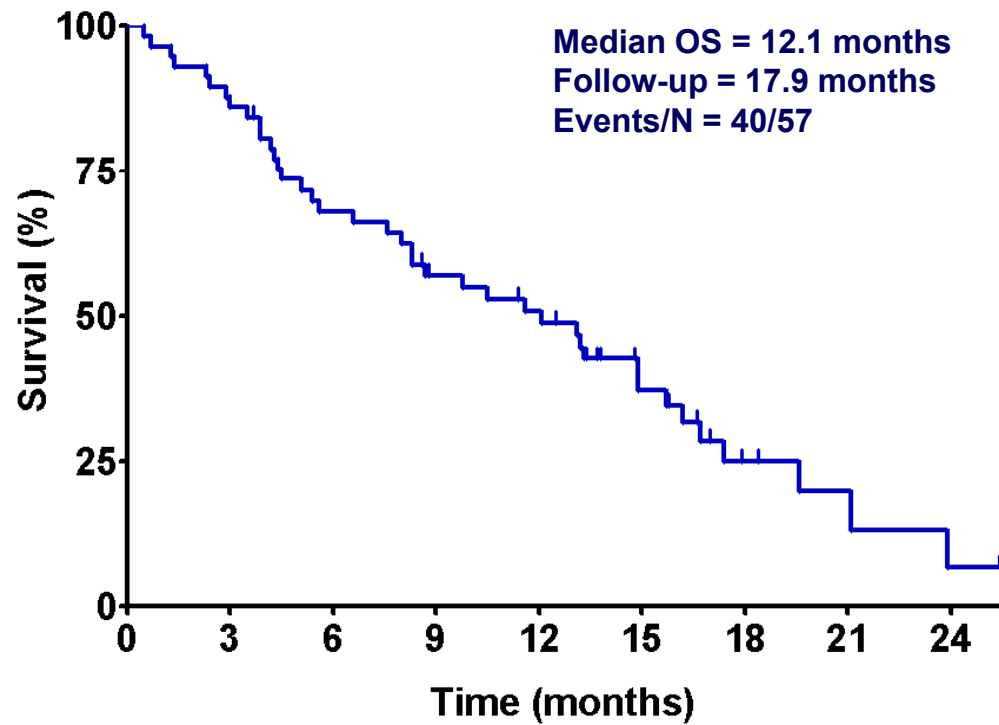
- 6-month PFS rate = 11%
- Median PFS in patients with disease control = 4.4 months
- Events/N = 39/43

Weekly cohort



- 6-month PFS rate = 36%
- Median PFS in patients with disease control = 9.1 months
- Events/N = 13/14

NGR-hTNF in MPM: Overall survival



NGR-hTNF in MPM: Post-hoc analysis

In multivariate Cox analyses:

- **Male gender (p=.02) associated to longer PFS**
- **PS of 0 (p=.003) and epithelial histology (p=.03) associated to longer OS**

NGR-hTNF in MPM: Conclusions

- **NGR-hTNF 0.8 $\mu\text{g}/\text{m}^2$ (q3w or weekly) is well tolerated in MPM patients previously treated with a pemetrexed-based chemotherapy**
- **Overall results included a DCR of 46%, maintained for a median time of 4.7 months, and a median OS of 12.1 months**
- **NGR-hTNF will be further developed in advanced MPM and these time-related outcomes need to be evaluated in a randomized setting**

**NGR-hTNF is currently developed either as single agent or in combination in:
CRC, HCC, SCLC, NSCLC, and OC**

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