

Phase I and Pharmacodynamic Study of High-Dose NGR-hTNF in Patients with Refractory Solid Tumors

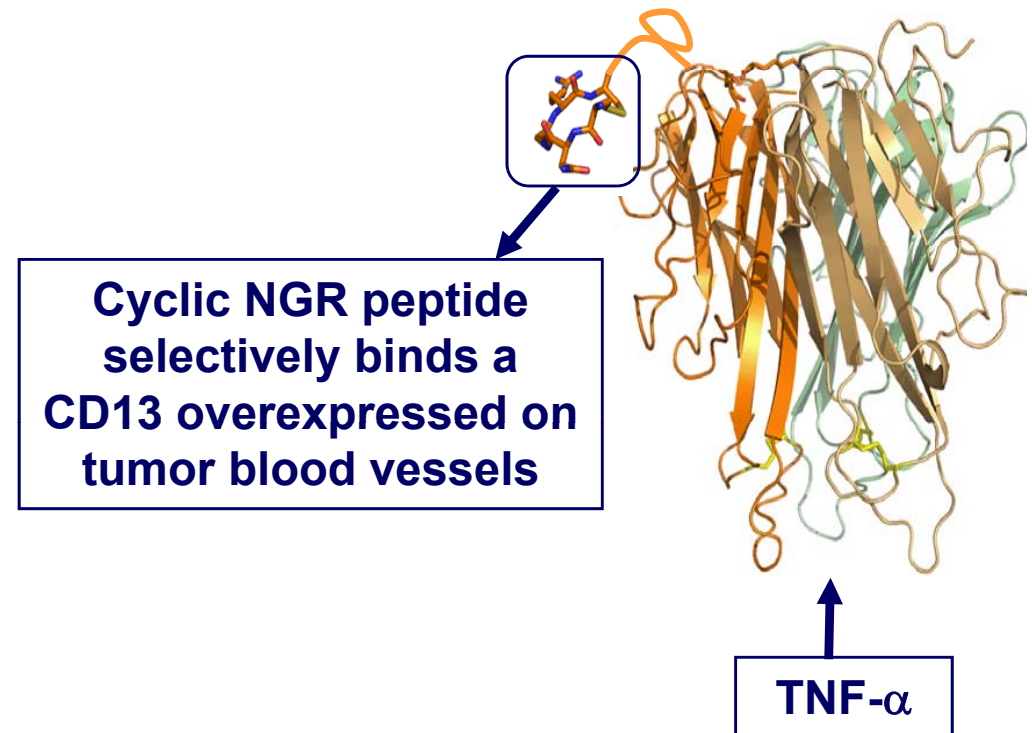
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Phase I and PD study of high-dose NGR-hTNF: Structure and target of NGR-hTNF

- Tumor necrosis factor-alpha (TNF- α) has shown potent antivasular and antitumor effects in preclinical models¹
- However, the early-stage clinical development of TNF- α was hindered by severe toxicity¹
- NGR-hTNF consists of TNF- α fused with the tumor-homing peptide NGR (asparagine-glycine-arginine)²⁻⁴



1. Blick M, et al. *Cancer Res* 1987;47:2986-9
2. Curnis F. et al. *Nat Biotech* 2000;18 (11): 1185-9
3. Corti A. et al. *Methods Mol Med* 2004; 98: 247-64
4. Curnis F. et al. *JCI* 2002; 110: 475-82

Phase I and PD study of high-dose NGR-hTNF: Background

- In a previous phase I trial⁵, maximum tolerated dose (MTD) of NGR-hTNF was established at 45 $\mu\text{g}/\text{m}^2$ when given as 1-hour intravenous infusion every 3 week (q3w)
- Dose limiting toxicity (DLT) were grade 3 infusion related reactions, while common toxicities were transient grade 1-2 chills (83%) and fever (56%)
- In the present trial, we explored further dose escalation using:
 - longer infusion time (2 hours)
 - mild premedication (paracetamol 1,000 mg iv or po)
- 4 patients enrolled at each of 12 dose levels (DLs):
 - 60-80-100-125-150-175-200-225-250-275-300-325 $\mu\text{g}/\text{m}^2$ (q3w)

Phase I and PD study of high-dose NGR-hTNF: Study objectives and MTD definition

■ Primary endpoint

- To determine the optimal biologic dose (OBD) of NGR-hTNF by evaluating both the safety in terms of MTD and the antivasular effect in terms of changes documented with dynamic imaging

■ Secondary endpoints

- To assess the PK profile of NGR-hTNF and to monitor the plasma levels of soluble TNF-receptors (sTNF-R1 and sTNF-R2)
- To document the preliminary antitumor activity

■ MTD definition

- if $\leq 1/4$ patients with DLT during first cycle → further dose escalation
- if $\geq 2/4$ patients with DLT during first cycle → prior DL declared as MTD

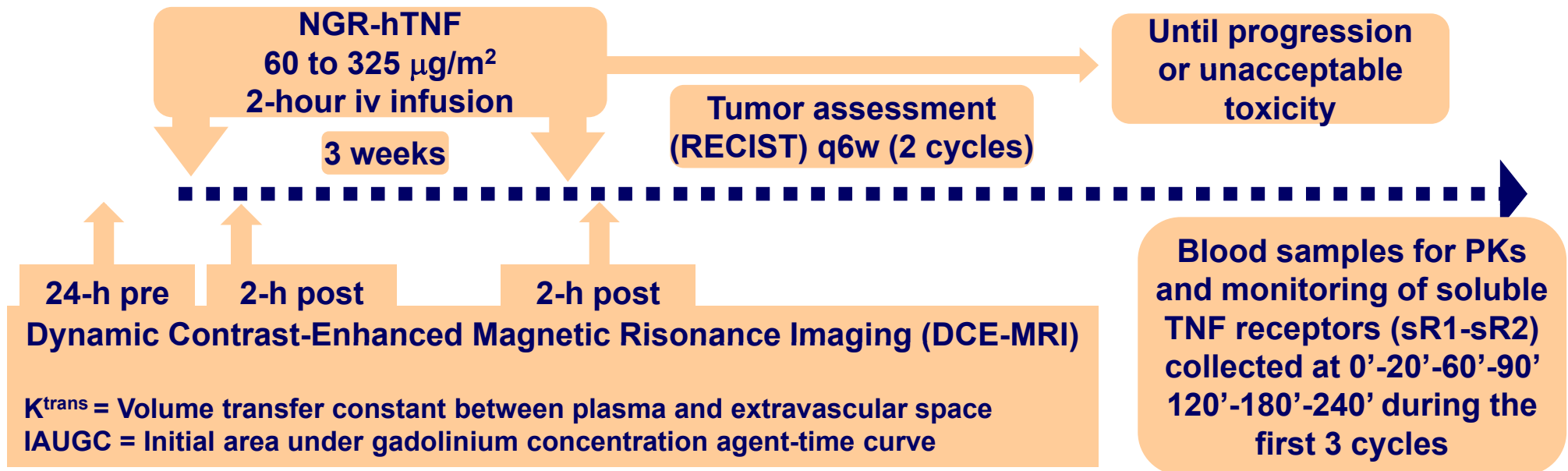
■ DLT definition

- grade 3-4 drug-related toxicity
- exceptions → nausea/vomiting, chills, and fever (quickly controlled with therapy)

Phase I and PD study of high-dose NGR-hTNF: Study design

■ Inclusion criteria

- patients (≥ 18 years) with solid tumors refractory to standard therapies
- performance status (PS) 0-1



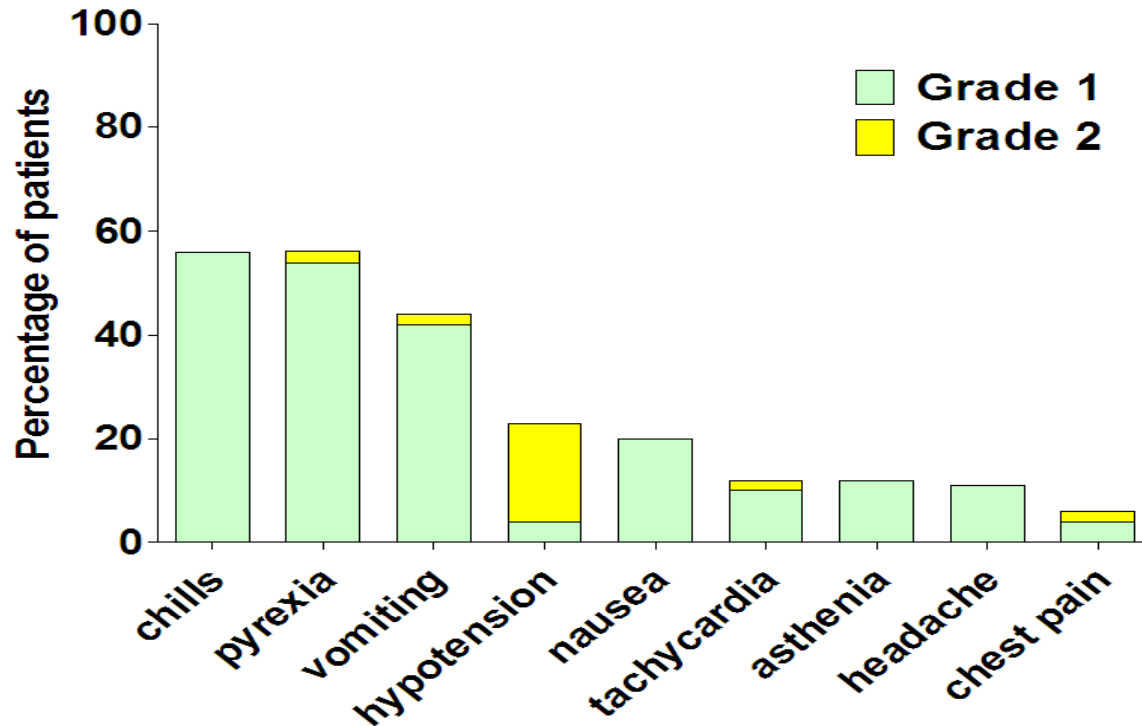
Phase I and PD study of high-dose NGR-hTNF: Baseline characteristics (n=48)

Median age in years (range)	61 (23 - 76)
Gender	
Male	37 (77%)
Female	11 (23%)
ECOG performance status (PS)	
0	23 (48%)
1	25 (52%)
Prior number of systemic regimens	
Median	3
Range	1-7
Tumor types	
Colorectal cancer	28
Mesothelioma	8
Liver cancer	5
Neuroendocrine	3
Soft-tissue sarcomas	2
Gastric cancer	2

Phase I and PD study of high-dose NGR-hTNF: Treatment exposure and safety

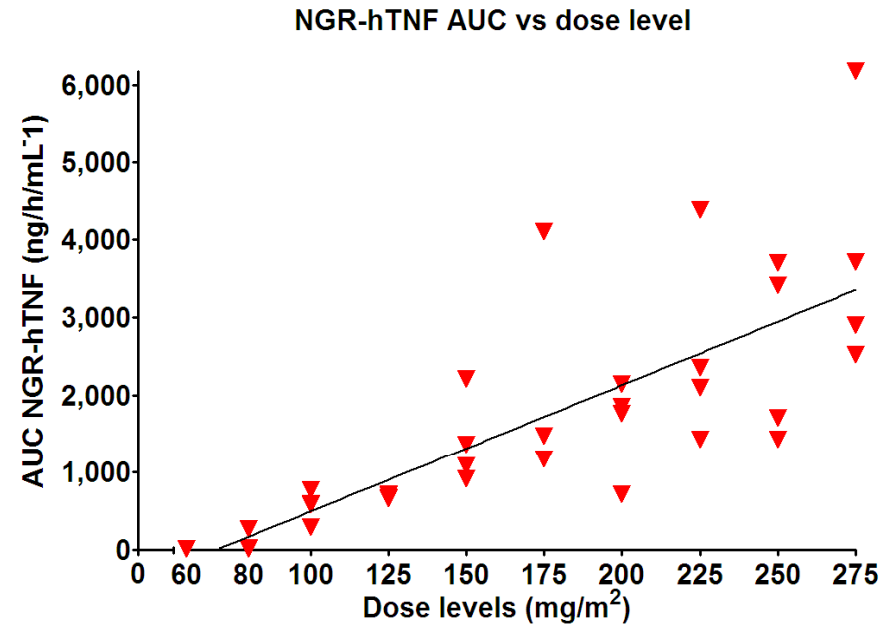
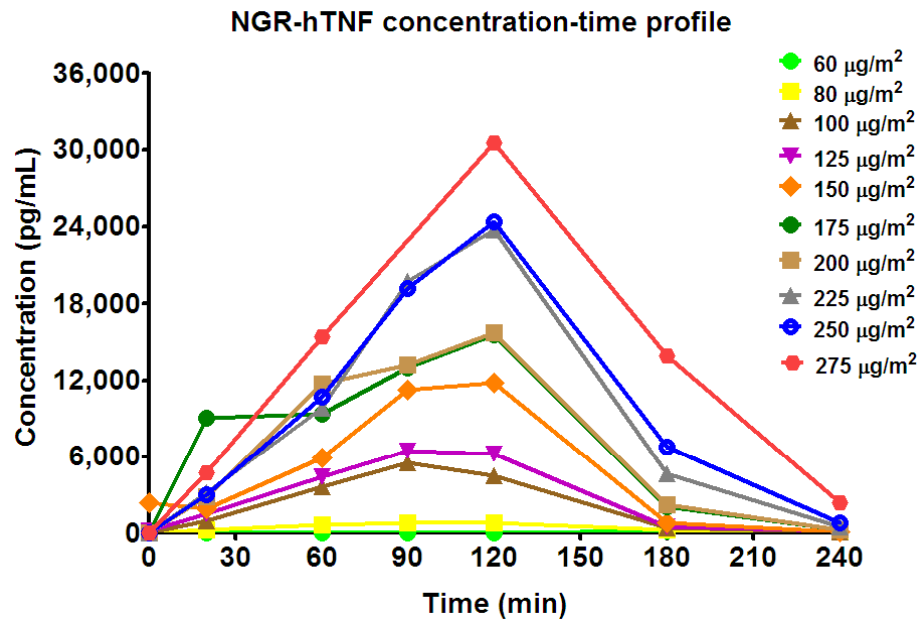
- 117 cycles delivered (range 1 - 6)
- No objective response observed. Twelve patients (25%) had stable disease as best response (median duration, 12.1 weeks; range 10-20)
- No DLT occurred and MTD has not yet been reached

Treatment-related adverse events (worst grade in > 5% of patients)



Phase I and PD study of high-dose NGR-hTNF: Pharmacokinetics

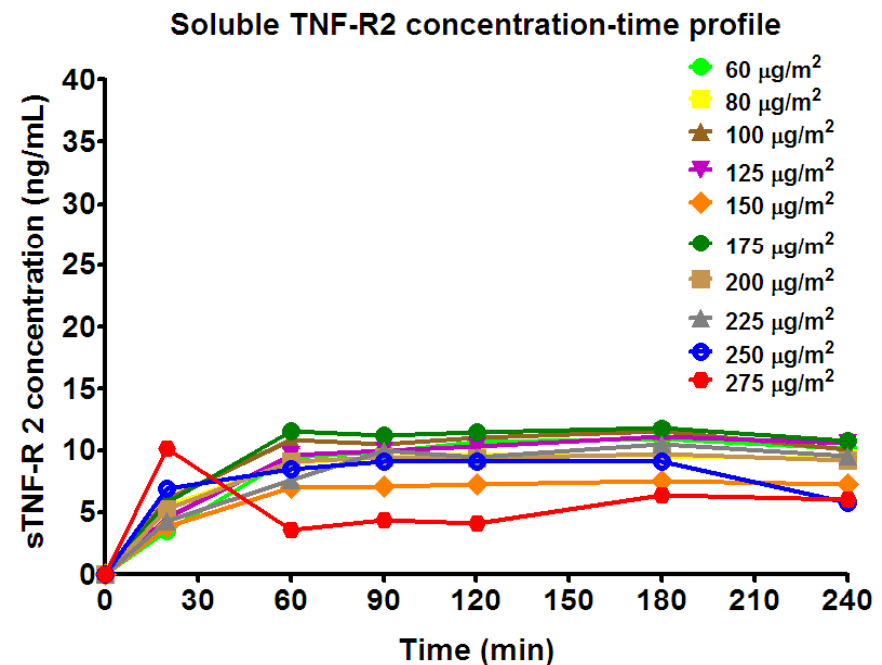
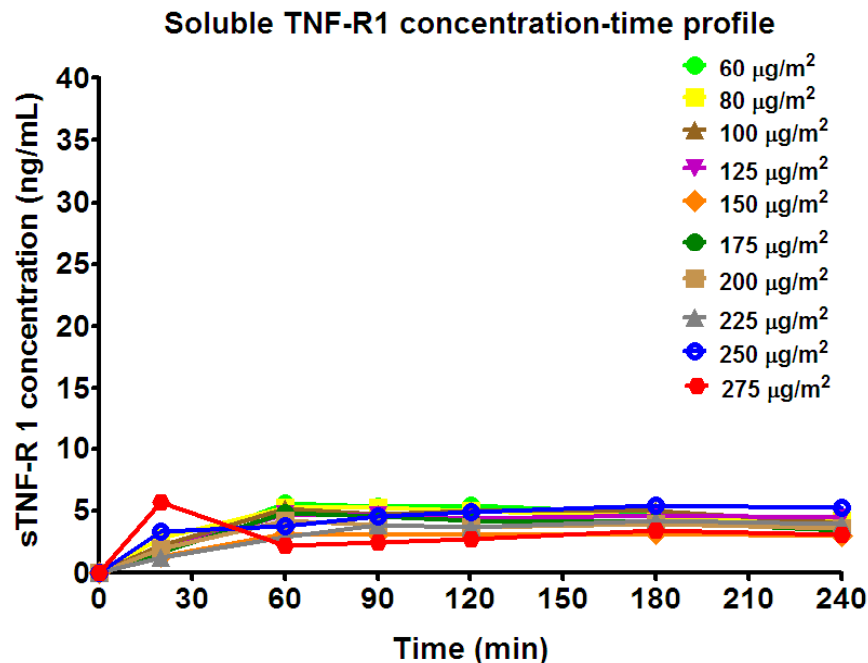
Both C_{max} and AUC of NGR-hTNF increased proportionally with dose ($p=0.0001$ and $p=0.0003$, respectively)



Dose levels from 60 to 275 $\mu\text{g}/\text{m}^2$ (n=40)
Plasma levels baseline-normalized

Phase I and PD study of high-dose NGR-hTNF: Kinetics of soluble TNF receptors (sTNF-Rs)

- Levels of sTNF-R2 peaked significantly higher than those of sTNF-R1: median, 10.2 ng/mL vs 5.3 ng/mL ($p=0.0001$, Mann-Whitney test)
- However, changes in sTNF-Rs did not differ across dose levels



Dose levels from 60 to 275 $\mu\text{g}/\text{m}^2$ (n=40)
Plasma levels baseline-normalized
Soluble receptors might block bioavailability and activity of TNF⁶

Phase I and PD study of high-dose NGR-hTNF: DCE-MRI changes after first cycle

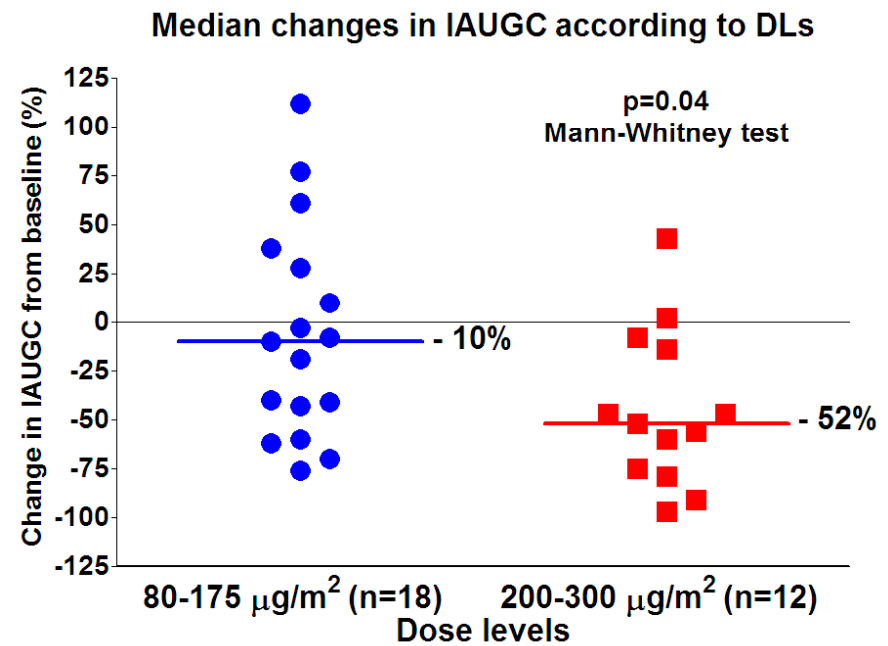
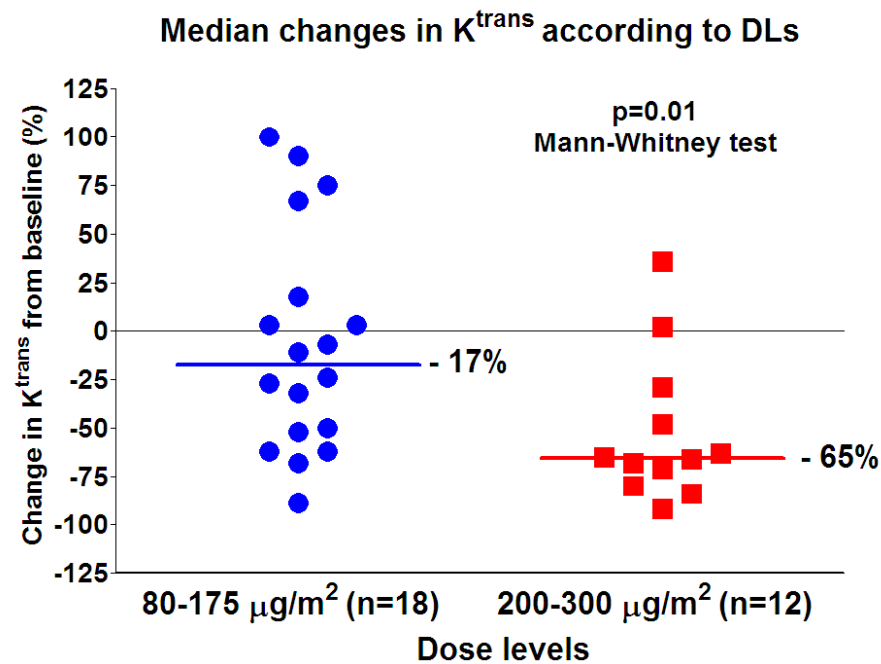
■ Median K^{trans} and IAUGC values significantly decreased after first dosing

■ Baseline K^{trans}	0.15 min ⁻¹
■ Post-dosing K^{trans}	0.08 min ⁻¹ (p=0.006, Wilcoxon test)
■ Change vs baseline	- 48% (95% CI, -2% to -65%)
■ Baseline IAUGC	10.4 mM/L/sec
■ Post-dosing IAUGC	7.2 mM/L/sec (p=0.02, Wilcoxon test)
■ Change vs baseline	- 40% (95% CI, -8% to -55%)

Dose levels from 80 to 300 µg/m² (n=30)

Phase I and PD study of high-dose NGR-hTNF: DCE-MRI changes after first cycle by DLs

Greater decreases observed at the higher dose levels tested



Dose levels from 80 to 300 $\mu\text{g}/\text{m}^2$ (n=30)

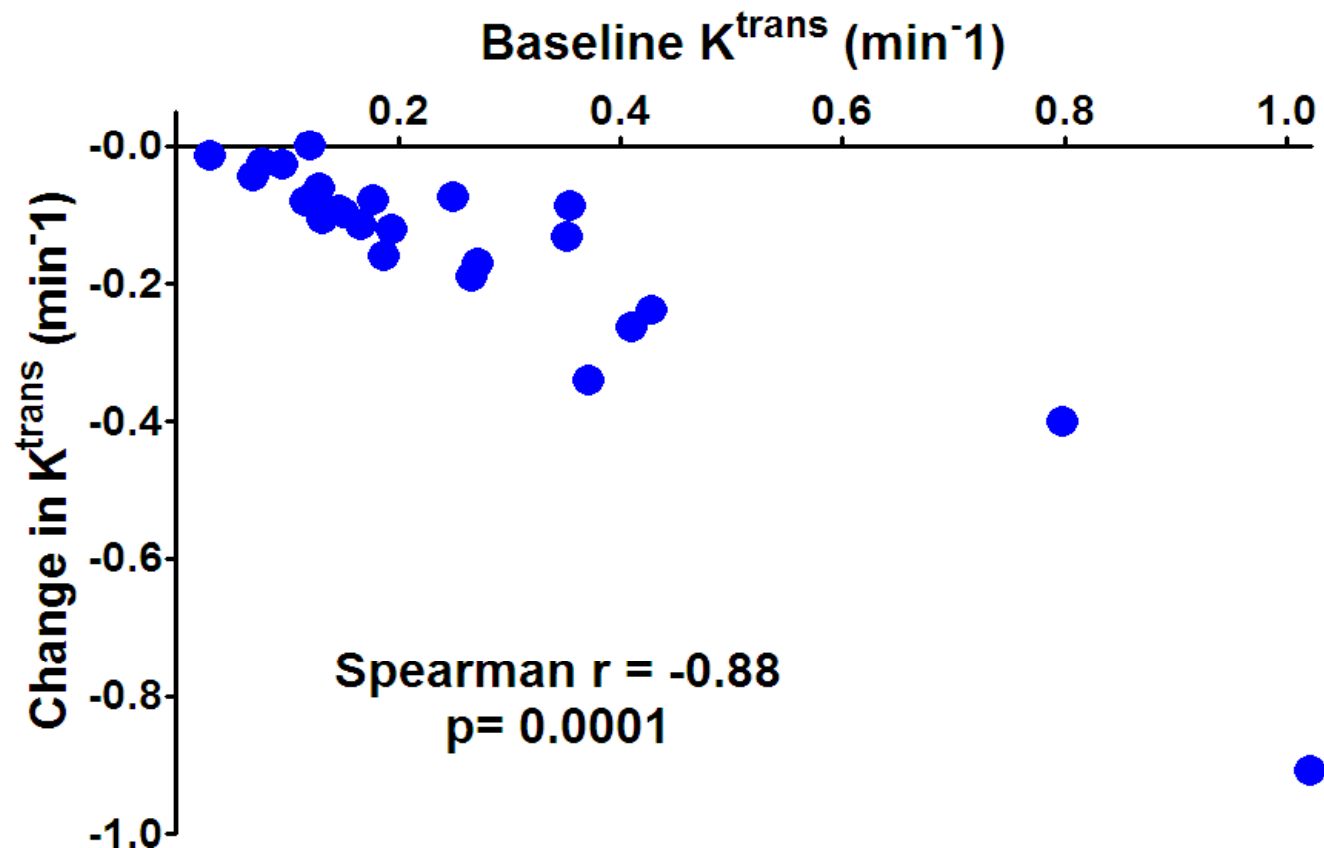
Phase I and PD study of high-dose NGR-hTNF: DCE-MRI reductions over time

■ In 24 patients (80%) median K^{trans} and IAUGC values were reduced

■ Baseline K^{trans}	0.18 min ⁻¹
■ Post-dosing K^{trans}	0.07 min ⁻¹ (p=0.0001, Wilcoxon test)
■ Maximal change vs baseline	- 62% (range, -24% to -92%)
■ Baseline IAUGC	12.4 mM/L/sec
■ Post-dosing IAUGC	5.7 mM/L/sec (p=0.0001, Wilcoxon test)
■ Maximal change vs baseline	- 50% (range, -3% to -97%)

Dose levels from 80 to 300 $\mu\text{g}/\text{m}^2$ (n=24)

Phase I and PD study of high-dose NGR-hTNF: DCE-MRI by baseline values



Dose levels from 80 to 300 $\mu\text{g}/\text{m}^2$ (n=24)

Phase I and PD study of high-dose NGR-hTNF: Conclusions

- **NGR-hTNF can be safely given at doses higher than MTD using a mild premedication and a longer infusion time**
- **The nonoverlapping toxicity profile with cytotoxic agents should facilitate the combination with chemotherapy**
- **High doses of NGR-hTNF induce low receptor shedding and early antivasular effects**
- **The plateau in shedding kinetics of soluble receptors suggests that high doses can overcome this counterregulatory mechanism**
- **Antivasular effects assessed by DCE-MRI were registered in 80% of patients with an apparent dose relationship**
- **The correlation between baseline K^{trans} and extent of reductions suggests increased antivasular effects in tumors with extensive abnormal vasculature**
- **Further dose escalation is warranted**