

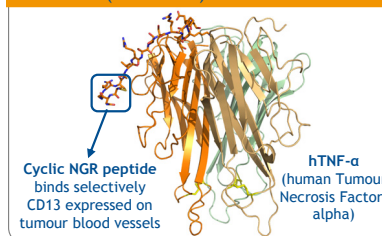
NGR-hTNF in combination with doxorubicin in relapsed small-cell lung cancer (SCLC)

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BACKGROUND AND METHODS

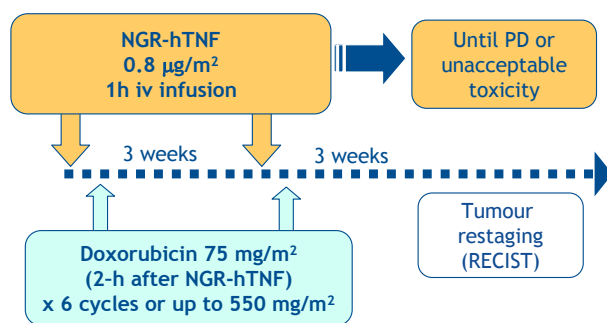
Figure 1. Structure of the NGR-hTNF molecule (1 subunit)



- TNF-α showed powerful antitumour activity in preclinical models, but its clinical use was associated to severe toxicity¹
- NGR-hTNF consists of TNF-α fused with the tumour-homing peptide NGR²⁻⁴ (Figure 1)
- Maximal preclinical synergism noted with 2-hour delay between low-dose NGR-hTNF and doxorubicin dosing^{2,4}

- Despite initial responsiveness to chemotherapy, SCLC is categorized by rapid progression to refractory disease
- Patients who progress while receiving first-time therapy (or within 3 months of its completion) are believed to have refractory (resistant) disease. Patients who progress more than 3 months are considered to have sensitive relapsed disease
- A Phase I trial selected NGR-hTNF 0.8 µg/m² plus doxorubicin 75 mg/m² for Phase II development and showed a very favourable tolerability profile⁵

Figure 2. Study design, doses and assessment



- Multicentre (4 centres) Phase II study
- Two-stage design, with 16 & 27 patients after 1st and 2nd study stage
- Inclusion criteria:
 - At least one prior platinum-based chemotherapy
 - ECOG performance status 0-2
 - LVEF ≥ 55%

RESULTS

- 28 patients enrolled
- 26 patients evaluated (two patients too early)
- 113 cycles administered (median, 3; range, 1-10)
- 8 patients (31%) received 6 or more cycles

Figure 3. Non-haematol. adverse events (>10% of pts)

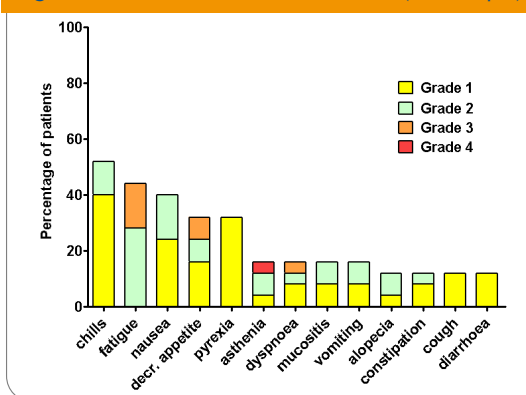


Table 1. Patients characteristics

	n=26 (%)
Median age, years (range)	61 (45-72)
Gender	
male	19 (68)
female	9 (32)
ECOG performance status	
0	13 (50)
1-2	13 (50)
Prior chemotherapeutic regimens	
1	19 (73)
2-3	7 (27)
Best response to prior therapy	
Complete response (CR)	1 (4)
Partial response (PR)	12 (46)
Stable disease (SD)	3 (12)
Progressive disease (PD) / Unknown	10 (38)
Sensitivity to platinum-based therapy	
Refractory/resistant disease	15 (58)
Sensitive relapsed disease	11(42)

Table 2. Efficacy results

	N=26 (%)
Best overall response	
Partial response (PR)	6 (23)
Stable disease (SD)	8 (31)
Progressive disease (PD)	9 (35)
Non-assessable	3 (11)
Disease control rate (PR + SD)	14 (54)
Median PFS, months	3.2
6-month rate	35%
Median PFS in patients with disease control (range)	6.3 (2.7-7.9)
Median PFS in patients with refractory/resistant disease 6-month rate	2.7 27%
Median PFS in patients with sensitive relapsed disease 6-month rate	4.1 49%
Median PFS in pts with PR (range)	8.2 (5.0-12.0)
Median PFS in pts with SD (range)	4.9 (3.0-15.8)

CONCLUSIONS

- The combination of NGR-hTNF and doxorubicin can be safely administered in relapsed SCLC patients
- NGR-hTNF plus doxorubicin showed evidence of antitumour activity, which appeared to be weakly correlated with platinum-sensitivity
- Further development of this combination in relapsed SCLC is of interest

Figure 4. Best overall response and waterfall plot

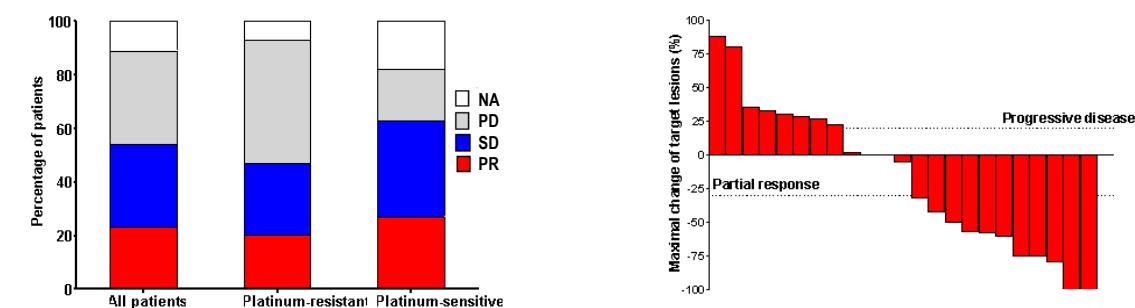


Figure 5. Progression-free survival (PFS)

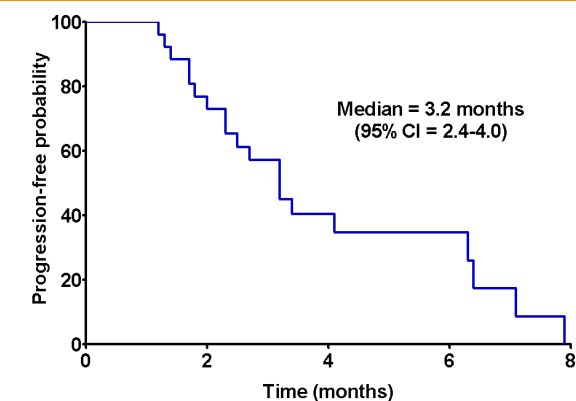
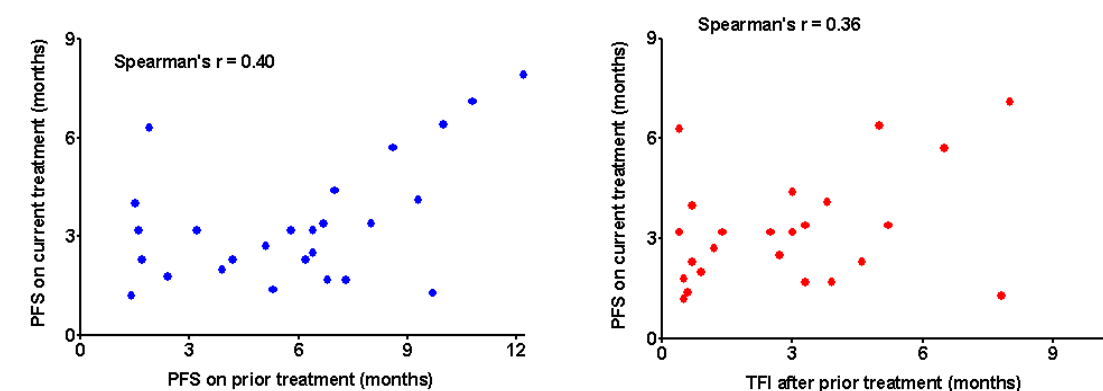


Figure 6. Correlations with prior treatment



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
- Curnis F, et al. *J Clin Invest* 2002; 110: 475-82.
- Gregorc V et al. *BJC* 2009; 101: 219-224

Acknowledgements

M. Mantori, S. Colombi, A. Troysi, E. Lungagnani (MolMed)