

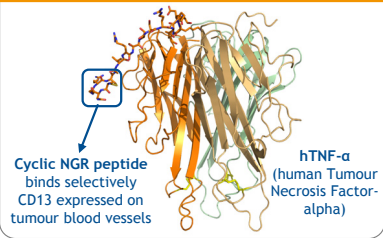
NGR-hTNF in combination with doxorubicin in progressive or recurrent ovarian cancer

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BACKGROUND AND METHODS

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

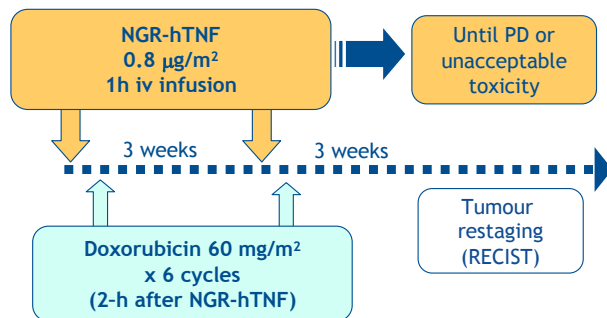


- Tumour necrosis factor-alpha (TNF-α) has shown potent antivascular and antitumour effects in preclinical models, but its clinical development was hampered by severe toxicity¹
- NGR-hTNF consists of TNF-α fused with the tumour-homing peptide NGR²⁻⁴ (Figure 1)
- NGR selectively binds a CD13 overexpressed on tumour blood vessels
- Significant preclinical synergism was displayed between low doses of NGR-hTNF and doxorubicin^{2,4}

Treatment of recurrent ovarian cancer is traditionally based on platinum sensitivity, as assessed by the treatment-free interval (TFI, less or more than 6 months) following a first-line platinum-based chemotherapy

In an earlier phase I trial⁵, the optimal biological low dose of NGR-hTNF was established at 0.8 μg/m² in combination with doxorubicin 60-75 mg/m², and the association showed a very favourable toxicity profile

Figure 2. Study design, doses and assessment



- Multicentre (2 centers) Phase II study
- Two-stage design, assuming that ≥2/17 and ≥6/37 patients with radiologically-confirmed response after the 1st and 2nd study stage, respectively, would warrant additional testing of the combination
- Inclusion criteria:
 - Age >18 years
 - At least one prior platinum/taxane regimen
 - Patients with tumor progression while receiving (refractory), or within 6 months (resistant), or between 6 and 12 months (partially sensitive) after completing a platinum-containing regimen
 - ECOG performance status 0-1
 - LVEF ≥ 55%

RESULTS

- 34 patients have been currently enrolled
- 17 patients recruited in the first study stage were included in the present analysis
- 90 cycles were delivered (median, 6; range, 1-8)
- 7 patients (41%) received 8 cycles

Figure 3. Adverse events (in >10% of patients)

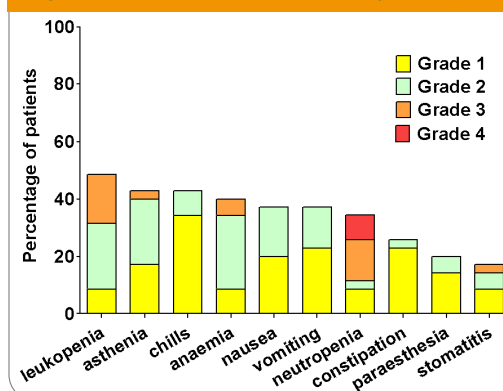


Table 1. Patients characteristics

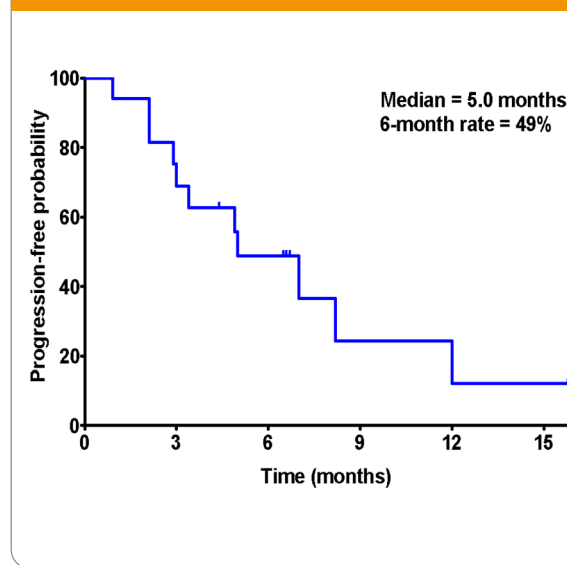
	n=17 (%)
Median age, years (range)	61 (45-72)
ECOG performance status	
0	16 (94)
1	1 (6)
Prior chemotherapy regimens	
1	14 (82)
2-5	3 (18)
Platinum-based	17 (100)
Taxane-based	17 (100)
Best response to prior therapy	
Complete response (CR)	5 (29)
Not evaluable disease (NED)	3 (18)
Partial response (PR)	2 (12)
Stable disease (SD)	4 (24)
Progressive disease (PD)	3 (18)
Progression-free survival (PFS) on prior therapy	
Median, months (95% CI)	10.8 (6.0-12.3)
Treatment-free interval (TFI), months	
Median (95% CI)	3.9 (2.1-7.8)
< 6 months (refractory/resistant)	11 (65)
6 -12 months (partially sensitive)	6 (35)

Table 2. Overall outcomes

	N=17
Best overall response	
PR	6 (35%)
TFI < 6 months	2 (18%)
TFI 6 - 12 months	4 (66%)
SD	6 (35%)*
Disease control rate (PR + SD)	12 (70%)
PD/ nonassessable	5 (30%)
Median PFS, months (95% CI)	5.0 (2.3-7.7)
Median PFS in pts with TFI < 6 months (95% CI)	4.9 (2.1-7.7)
Median PFS in pts with TFI 6 - 12 months (range)	12.0 (5.8-18.2)
Median PFS in pts with disease control (range)	7.0 (3.0-15.8)
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)

(*): Four patients with TFI <6 months and two patients with TFI >6 to <12 months. After a median follow-up of 11.5 months, 15 patients (88%) are still alive

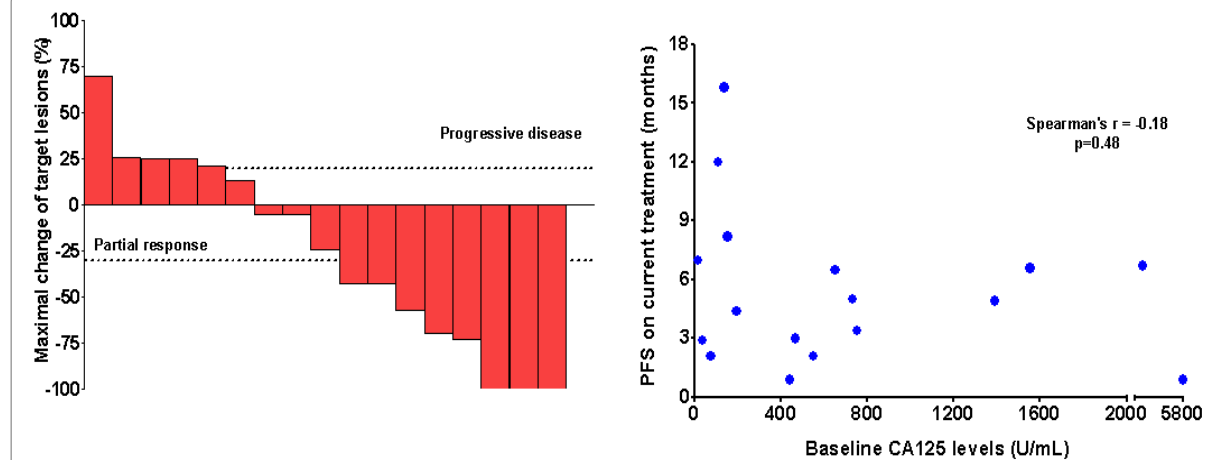
Figure 4. Progression-free survival



CONCLUSIONS

- NGR-hTNF can be safely administered in combination with doxorubicin in recurrent ovarian cancer patients
- The primary trial endpoint (at least six responses on 37 patients) was already met after the first study stage (n=17)
- Antitumor activity seems to be correlated with platinum sensitivity and not with baseline CA125 levels
- Tolerability and efficacy of NGR-hTNF plus doxorubicin deserves further randomised evaluation in resistant/refractory patients against a standard nonplatinum monotherapy (e.g., pegylated liposomal doxorubicin)

Figure 5. Waterfall plot and correlation between progression-free survival (PFS) and CA125



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