

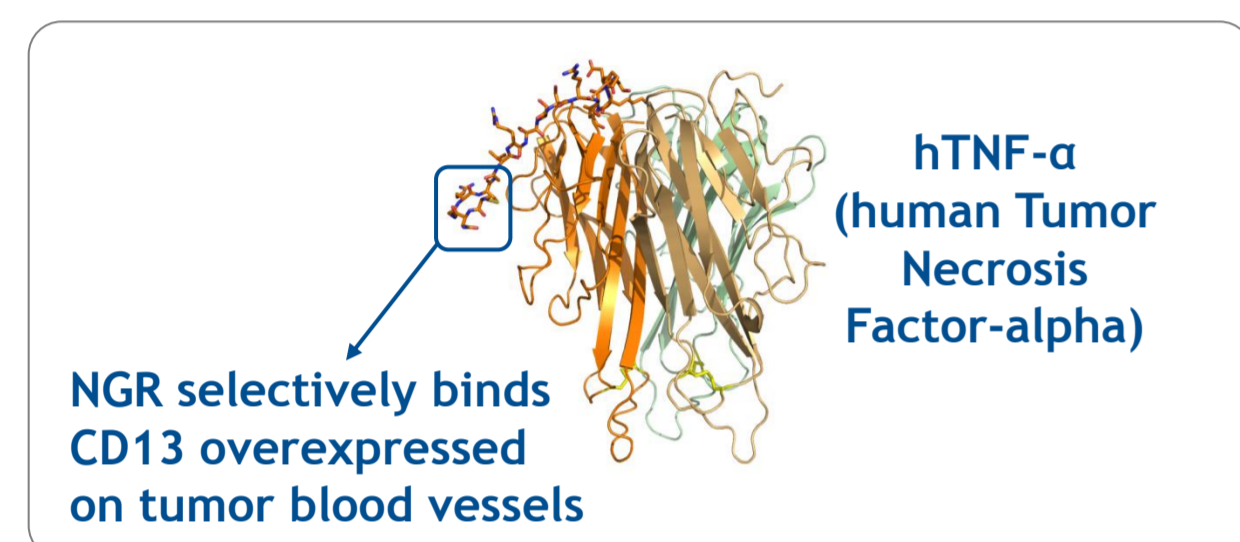
Phase II study of NGR-hTNF plus doxorubicin in relapsed ovarian cancer

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Background and methods

- Tumor necrosis factor-alpha (TNF- α) has shown potent preclinical antitumor effects, but its clinical development was hampered by severe toxicity¹
- NGR-hTNF consists of TNF- α fused with the tumor-homing peptide NGR (asparagine-glycine-arginine)²⁻³

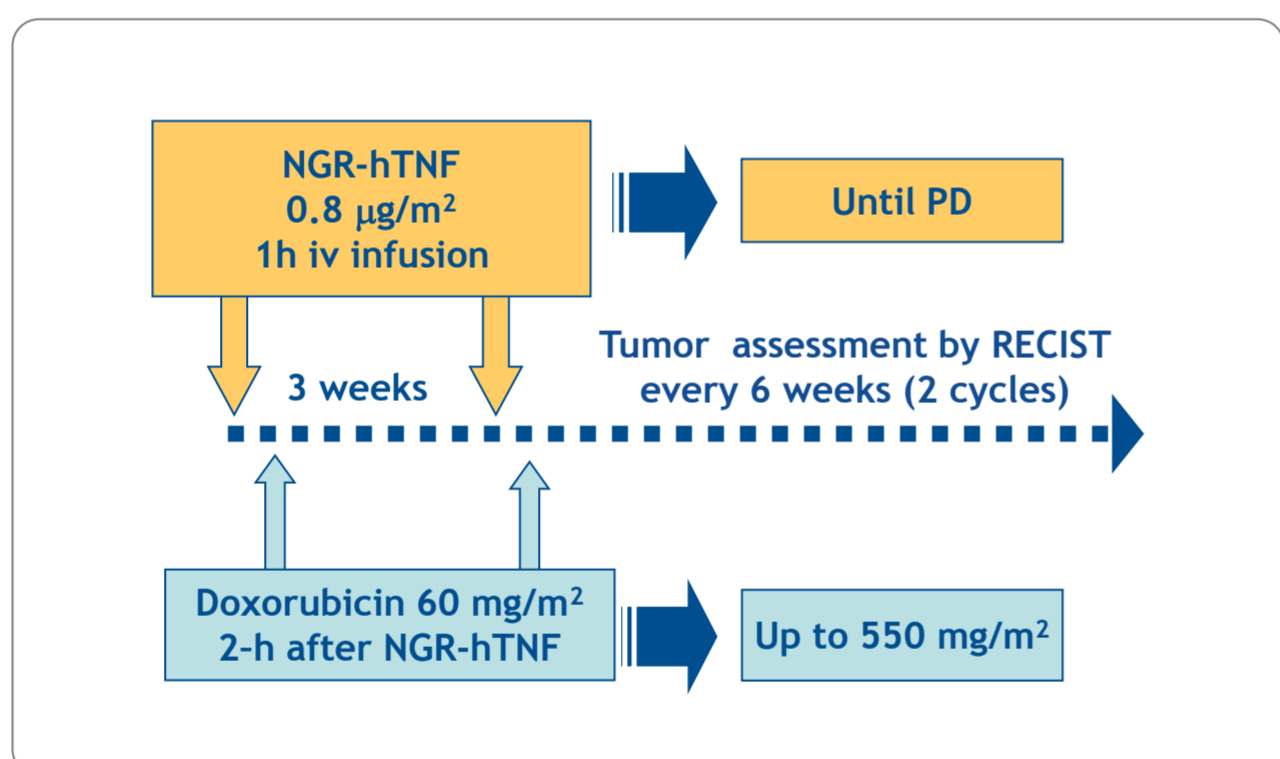


- In preclinical models,⁴ low-dose NGR-TNF given two hours before doxorubicin increased both number of tumor cells reached by doxorubicin and intracellular amount of doxorubicin
- Synergism with doxorubicin was observed in immunocompetent mice, but not in nude mice lacking functionally mature T lymphocytes²
- In phase I trial,⁴ the optimal dose of NGR-hTNF was established at 0.8 $\mu\text{g}/\text{m}^2$ in combination with doxorubicin, with a safe profile

- Ovarian cancer (OC) patients who progress while receiving first-line platinum-based therapy or within 6 months of its completion have refractory/resistant (PR) relapse
- Patients who progress between 6 and 12 months have partially-sensitive (PS) relapse
- In refractory/resistant relapse,⁵ the Gynecologic Oncology Group (GOG) analyzed retrospectively several phase 2 trials on 407 patients. Overall response rate was 14% and disease control rate was 39%. Median PFS was 2.4 months while median OS was 10.2 months. Disease control strongly correlated with OS
- In PS relapse,⁶ the combination of trabectedin and pegylated liposomal doxorubicin (PLD) recently yielded median PFS and OS of 7.4 and 23 months, respectively

Study design

- One or more prior platinum/taxane regimen with radiological progression:
 - while receiving or within 6 months (PR relapse) or
 - between 6 - 12 months (PS relapse)
- PS 0-1 and LVEF \geq 55%
- Primary endpoint: response rate (CR+PR)
- Secondary endpoints: disease control rate (CR+PR+SD), PFS, OS, and safety
- Open-label, single-arm phase 2 trial with a two-stage accrual design:
 - \geq 2/17 pts (first stage) and \geq 6/37 (second stage) with radiologic response would warrant further testing of combination



Baseline characteristics (n=37)

Median age in years (range)	57 (35 - 72)
ECOG performance status (PS)	32 (86%) / 5 (14%) 0 / 1
Prior regimens	1 / \geq 2
PFS on prior treatment	30 (81%) / 7 (19%) median in months (95% CI) 9.7 (7.4 - 11.6)
Treatment-free interval (TFI)	4.6 (3.1 - 5.7) median in months (95% CI)
PR relapse (< 6 months)	25 (68%)
PS relapse (6 - 12 months)	12 (32%)
Baseline lymphocyte count (per mL)	1.6 (1.2-2.2) median (25th-75th percentile)

References

- Blick M, et al. *Cancer Res* 1987;47:2986-9
- Curnis F, et al. *Nat Biotech* 2000;18 (11): 1185-9
- Curnis F, et al. *JCI* 2002; 110: 475-82
- Gregorc V et al. *BJC* 2009; 101: 219-224
- Rose PG et al. *Gyn Oncol* 2010; 117:324-329
- Poweda A et al. *Ann Oncol* 2011; 22:39-48

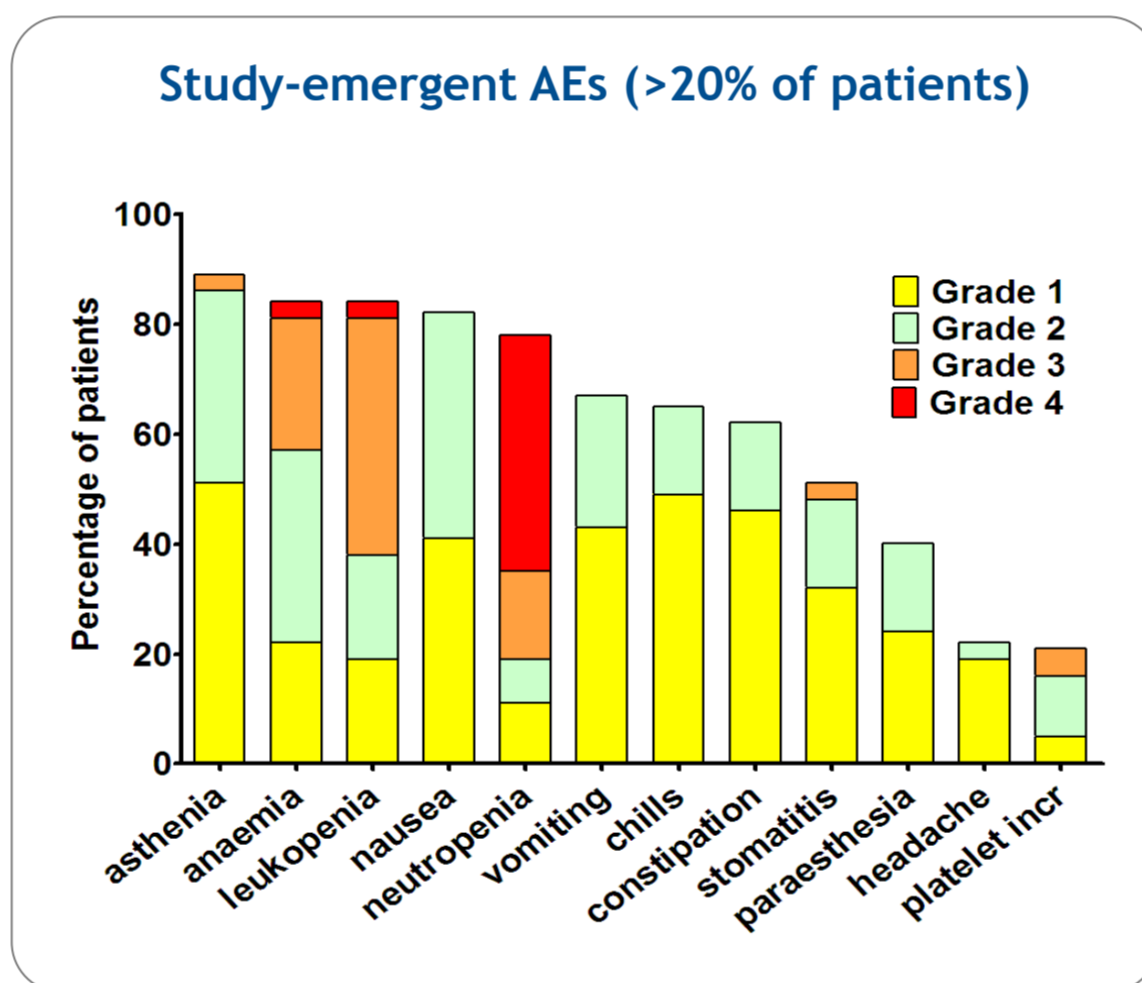
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Results

Safety

- 177 cycles in combination (median 4, range 1-8)
- 18 patients (49%) had \geq 6 cycles and 12 patients (32%) completed 8 cycles
- No treatment discontinuations for adverse events (AEs)
- Grade 1-2 chills in 19 patients (51%) on NGR-hTNF infusion
- 2 patients (5%) with grade 1 cardiac events



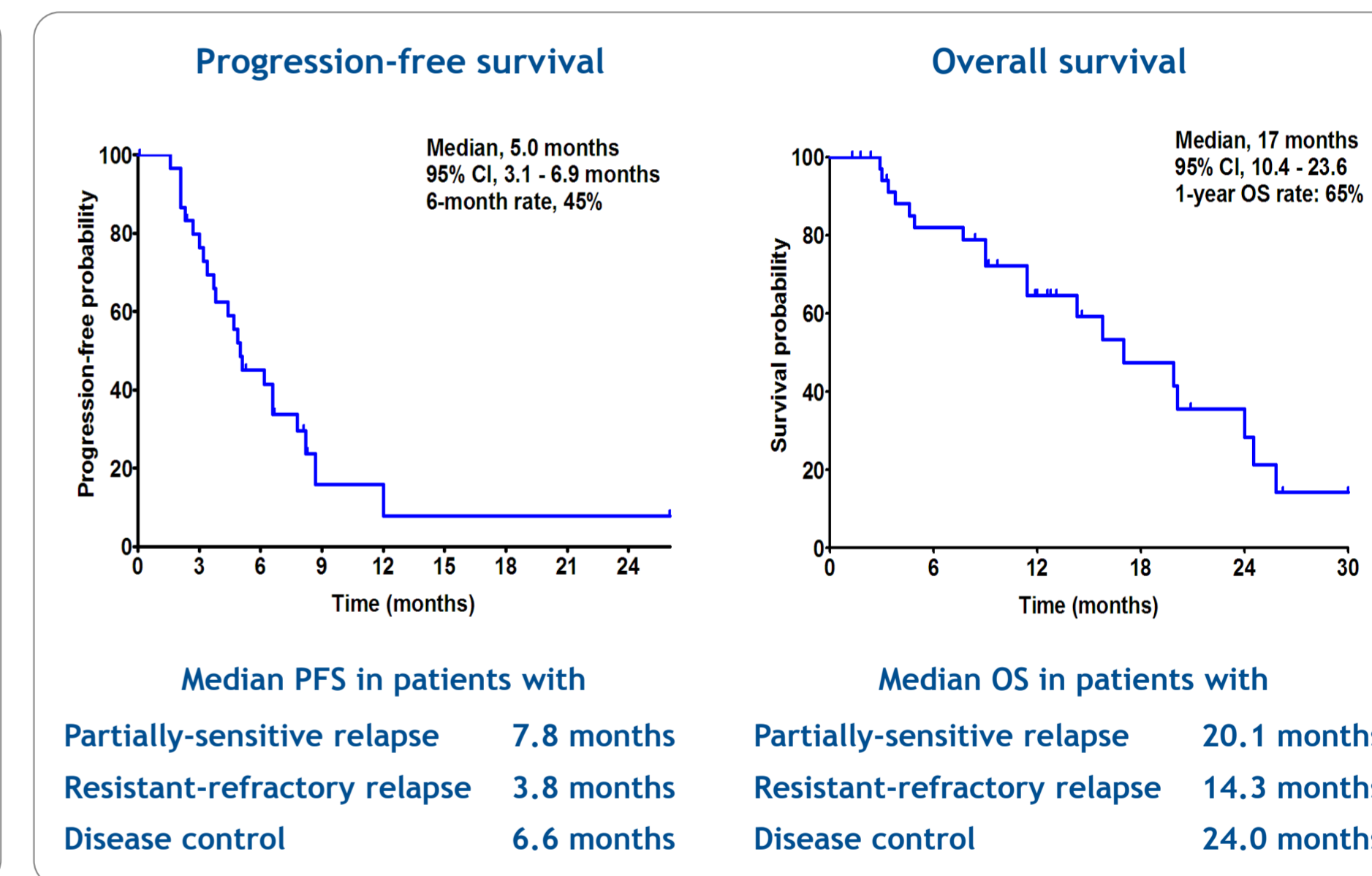
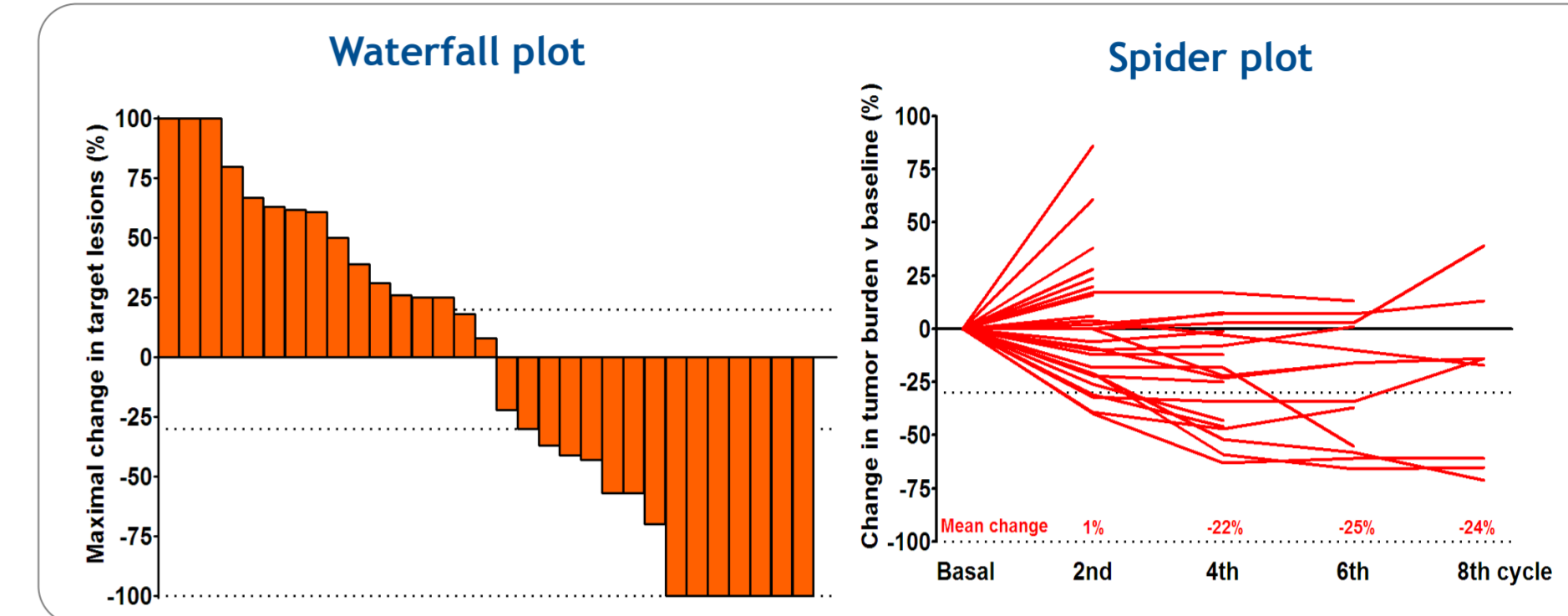
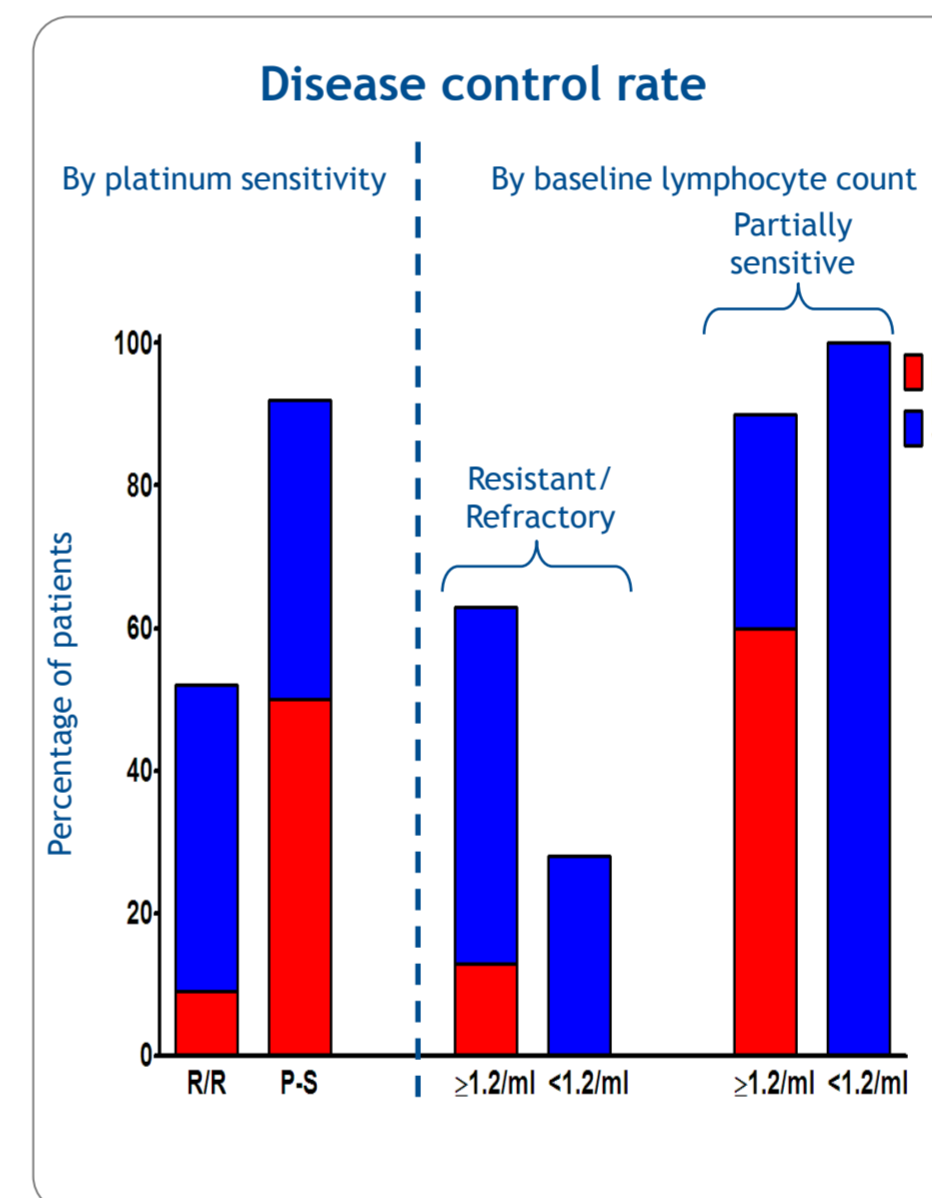
Conclusions

- NGR-hTNF and doxorubicin can be safely given in relapsed OC with a favorable tolerability profile
- Disease control was achieved in half of patients with resistant/refractory and in most of patients with partially-sensitive relapse and was maintained for a median time of 5.0 and 7.8 months, respectively
- Resistant/refractory patients with baseline lymphocyte counts higher than the first quartile experienced median PFS of 4.9 months and median OS of 15.8 months
- Based on tolerability and activity, NGR-hTNF in combination with PLD is currently compared with PLD alone in a randomized phase II trial in resistant/refractory disease

Best response

	n=35*	%
Partial response (PR)	8°	23
Stable disease (SD)	15	43
Disease control (PR + SD)	23	66
Progressive disease (PD)	12	34

* Two patients withdrew before first reassessment
° Six patients had PR during the 1st stage (n=17) and the trial met its overall primary endpoint



Antitumor activity according to the baseline peripheral blood lymphocyte count

