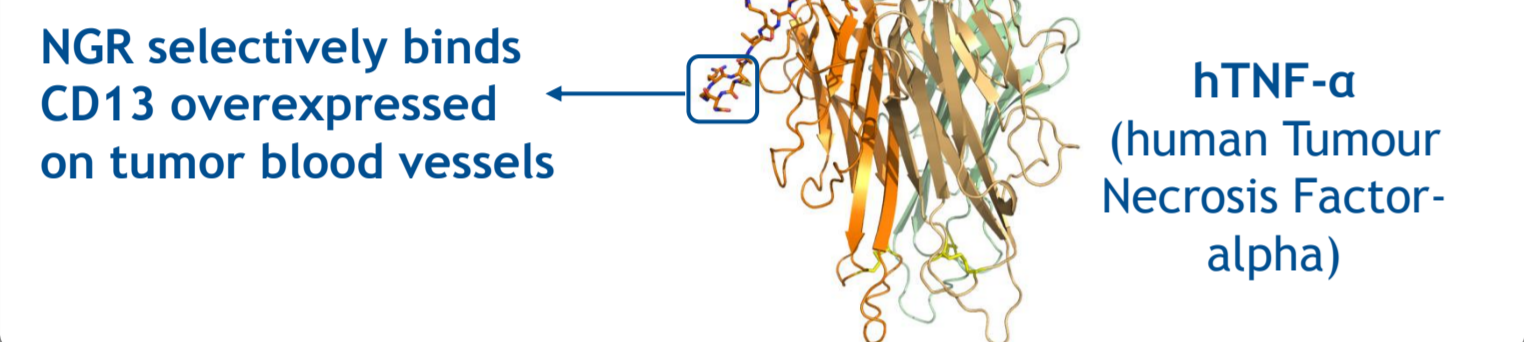


Phase II study of NGR-hTNF in combination with doxorubicin in relapsed ovarian cancer

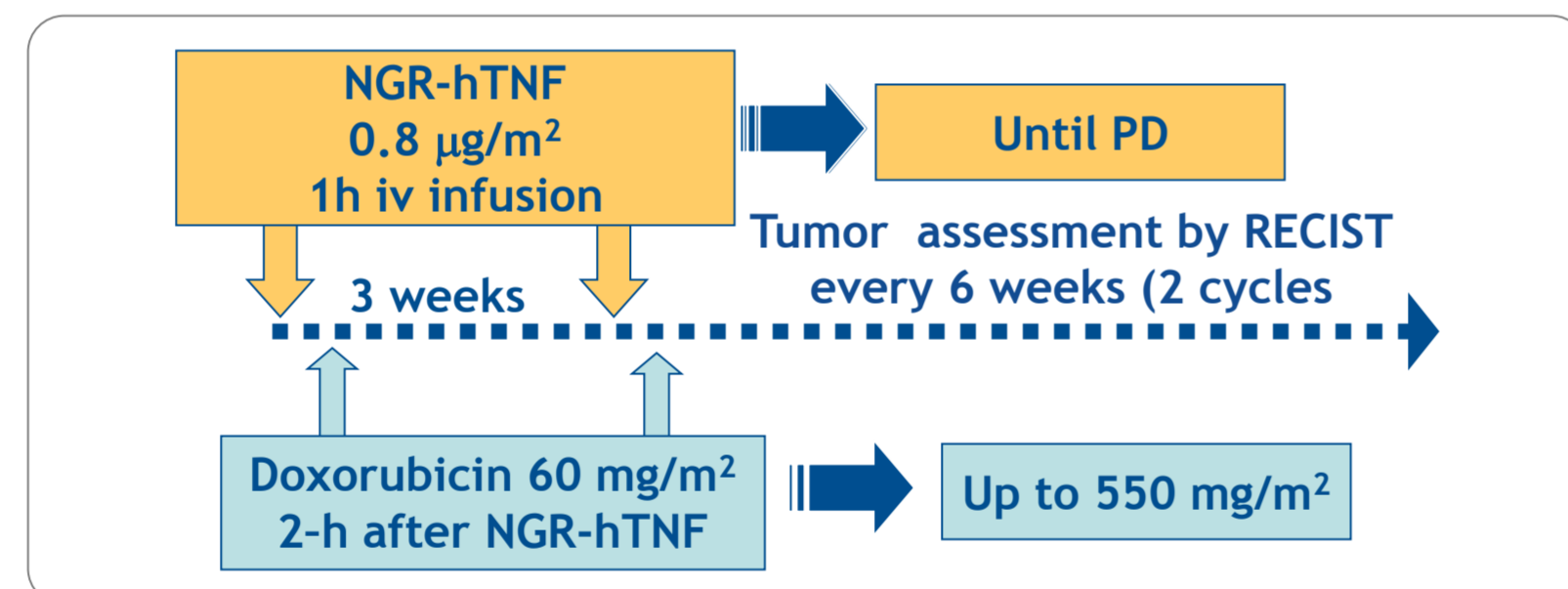
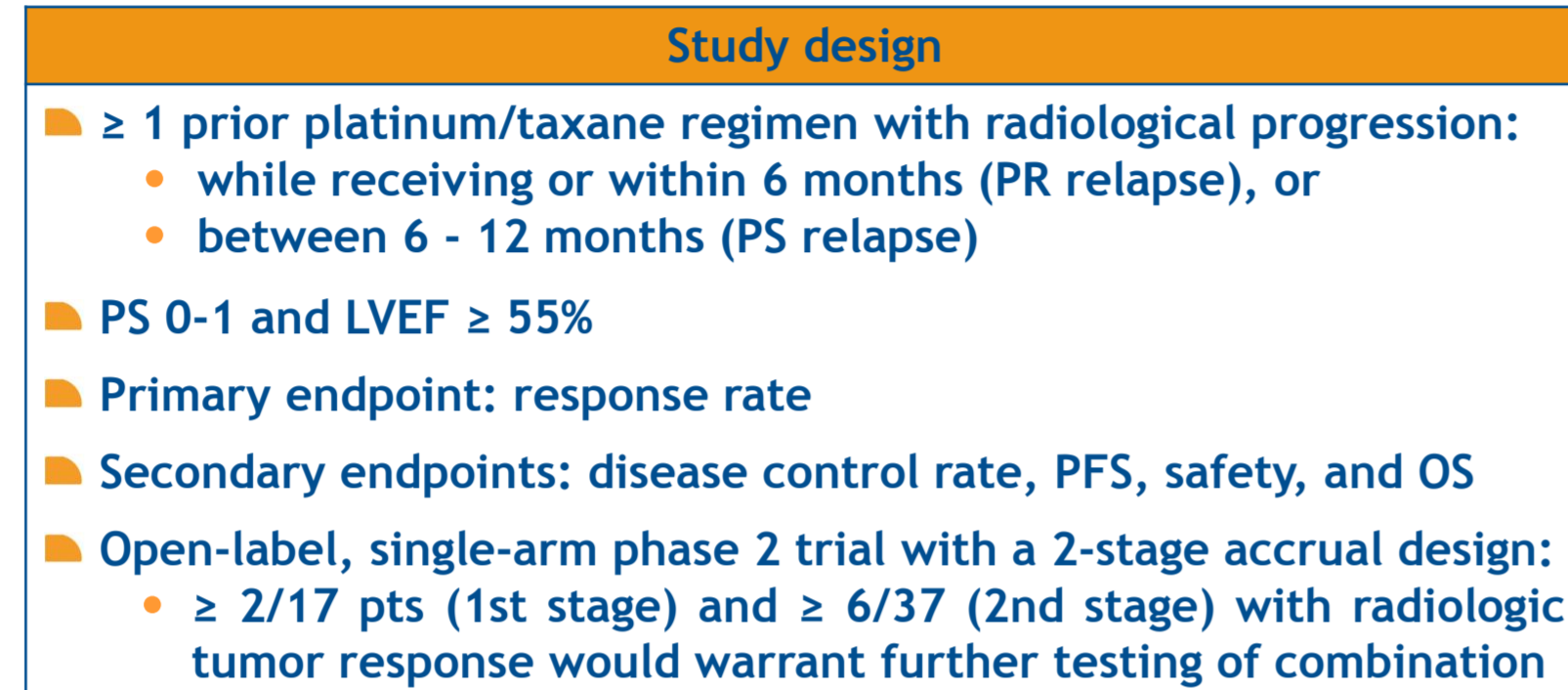
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Background and methods

- TNF- α has shown potent preclinical antivasular and antitumor effects, but its clinical development was hampered by severe toxicity¹
- NGR-hTNF consists of TNF- α fused with the tumor-homing peptide NGR²⁻³



- In preclinical model,⁴ low-dose NGR-TNF given 2 hours before doxorubicin increased both number of tumor cells reached by doxorubicin and intracellular amount of drug
- In phase I trial,⁵ the optimal biological low dose of NGR-hTNF was established at 0.8 $\mu\text{g}/\text{m}^2$ in combination with doxorubicin 75 mg/m^2 , with a favorable safety profile
- Recurrent 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 PR relapse,⁶ the Gynecologic Oncology Group (GOG) retrospectively analyzed 11 phase 2 trials on 407 patients. Median 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 rate strongly correlated with OS
- In PS relapse,⁷ the combination of trabectedin and pegylated liposomal doxorubicin (PLD) recently yielded median PFS and OS of 7.4 and 23 months, respectively



Baseline characteristics (n=37)

Median age in years (range)	57 (35 - 72)
ECOG performance status (PS)	32 (86%) / 5 (14%)
<ul style="list-style-type: none"> 0 / 1 	
Prior number of systemic regimens	30 (81%) / 7 (19%)
<ul style="list-style-type: none"> 1 / ≥ 2 platinum- or taxane-based 	
PFS on prior treatment	9.7 (7.4 - 11.6)
<ul style="list-style-type: none"> median in months (95% CI) 	
Treatment-free interval (TFI) after last treatment	4.6 (3.1 - 5.7)
<ul style="list-style-type: none"> median in months (95% CI) 	
Patients with PR relapse (< 6 months)	25 (68%)
Patients with PS relapse (6 - 12 months)	12 (32%)
Baseline neutrophil-to-lymphocyte ratio (NLR)	2 (1 - 17)
<ul style="list-style-type: none"> median (range) 	

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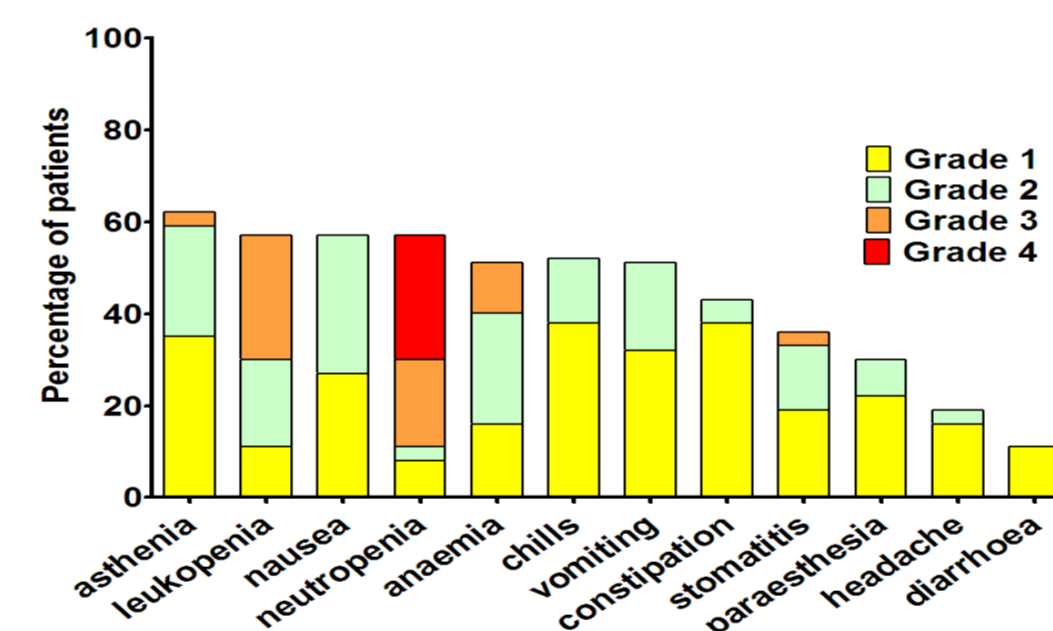
Acknowledgements (MolMed)

- Marina Mantori
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- Gloria Rossoni
- Antonella Troysi
- Elena Lungnanani

Safety

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

Study-emergent AEs (>10% of patients)



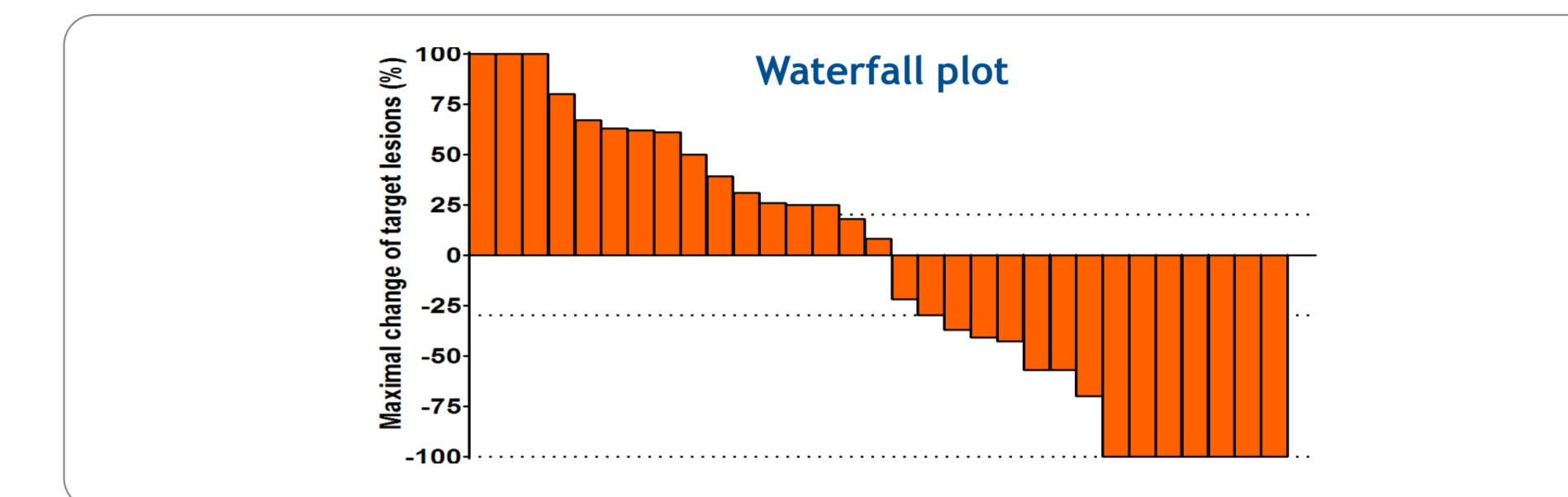
Conclusions

- NGR-hTNF and doxorubicin can be safely given in relapsed OC with a very favorable tolerability profile
- Disease control was achieved in half of patients with PR and in most of patients with PS relapse and was maintained for a median time of 5 and 7.8 months, respectively
- Low baseline NLR associated with improved outcome especially in patients with PR relapse
- Based on tolerability and activity, NGR-hTNF in combination with PLD is currently compared with PLD alone in a randomized phase II trial in PR disease (NGR018 trial-www.clinicaltrials.gov NCT01358071)

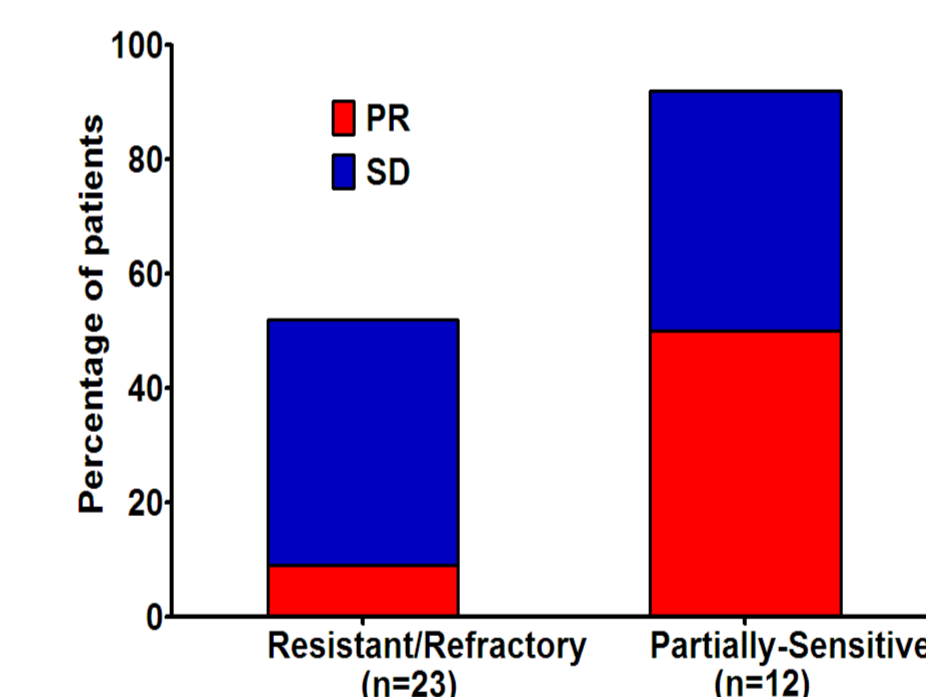
Results

Best overall response	n=35*	%	95% CI
Partial response (PR)	8°	23	11 - 40
Stable disease (SD)	15	43	26 - 61
Disease control (PR + SD)	23	66	48 - 81
Progressive disease (PD)	12	34	19 - 52

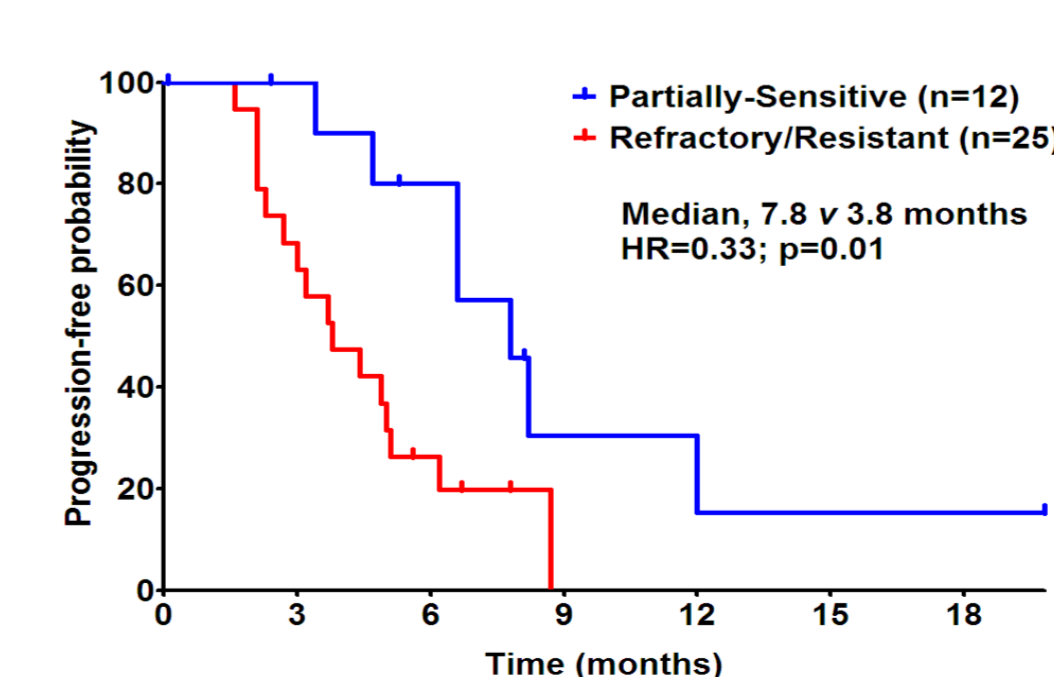
*2 patients discontinued treatment for symptomatic deterioration before tumor reassessment
 ° 6 patients had PR during the first study stage (n=17) and the trial met its primary endpoint



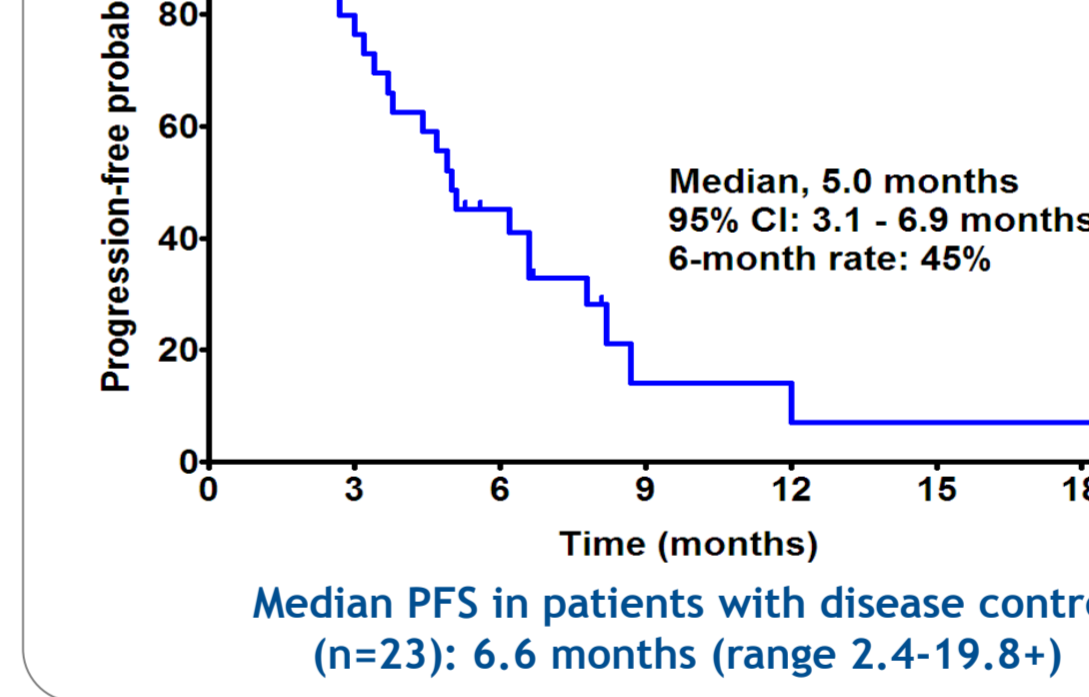
Disease control rate by platinum sensitivity



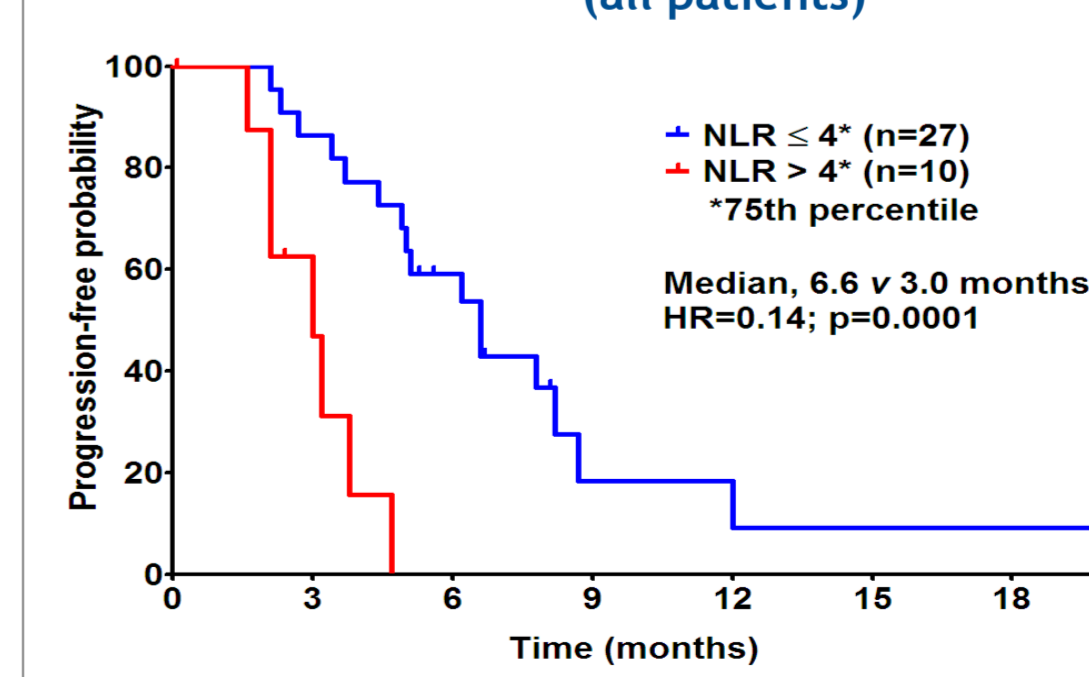
PFS by platinum sensitivity



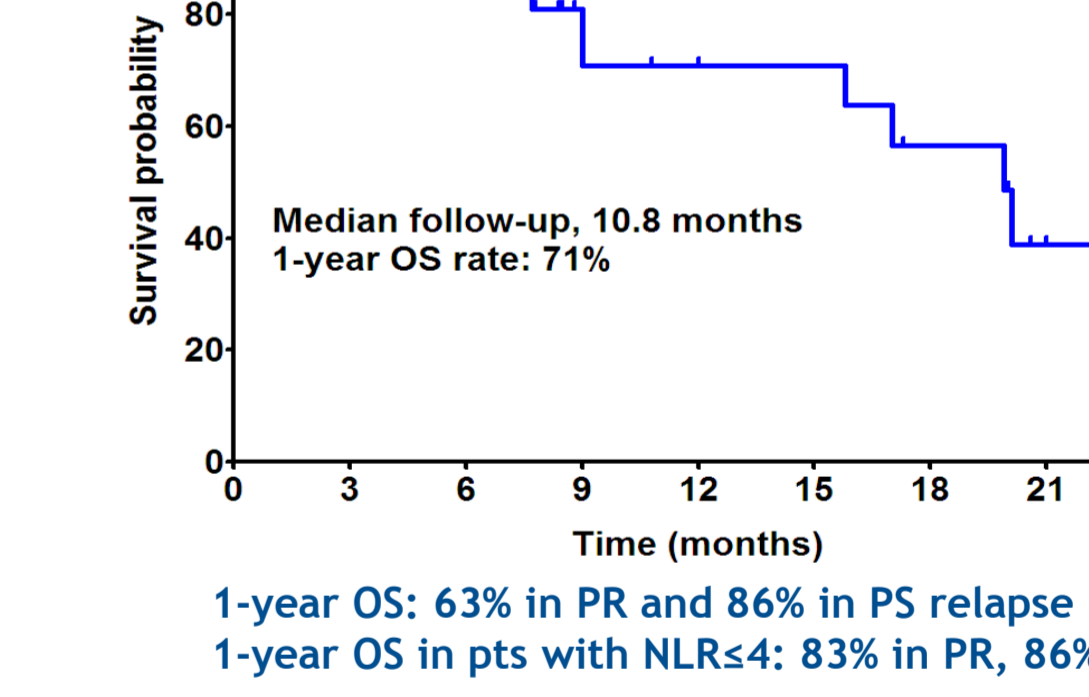
Progression-free survival



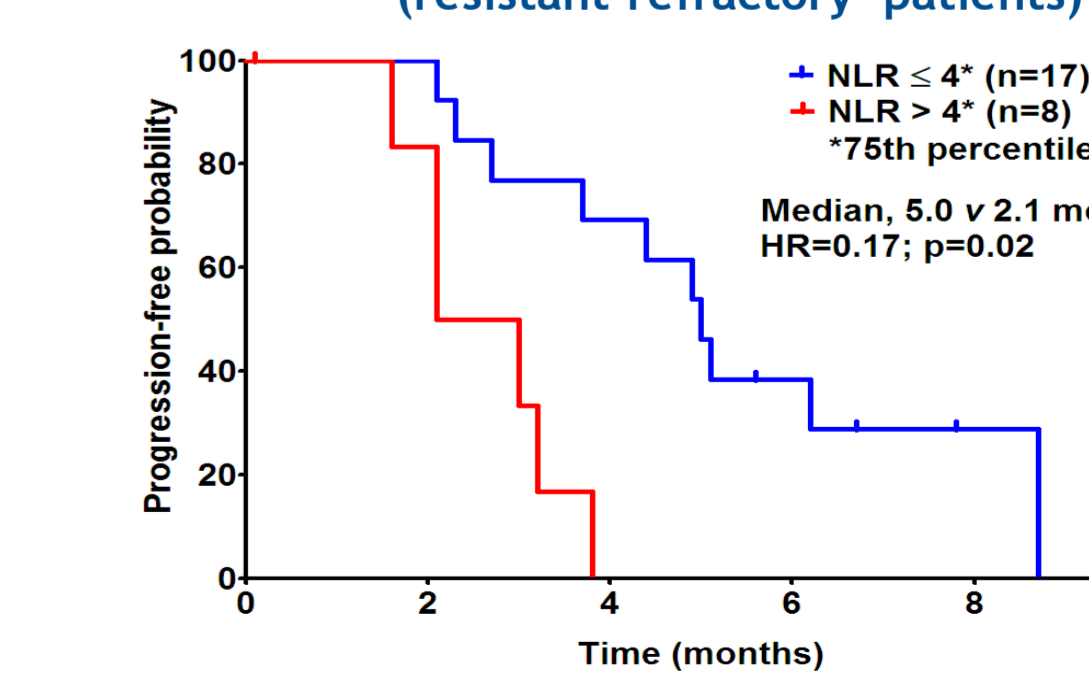
PFS by neutrophil-to-lymphocyte ratio (all patients)



Overall survival



PFS by neutrophil-to-lymphocyte ratio (resistant-refractory patients)



The baseline neutrophil-to-lymphocyte ratio (NLR) is an index of host immune response to tumor⁸