Role of the Receptor for Advanced Glycation End products (RAGE) in blood as a potential biomarker for progression to olaparib: A post hoc analysis of platinum-resistant ovarian cancer (PROC) patients treated in the ROLANDO-GEICO 1601 trial

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Background

Olaparib (OLA) has shown significant activity in combination with pegylated liposomal doxorubicin (PLD) regardless of BRCA status in the ROLANDO-GEICO 1601 trial with an overall disease control rate of 77% and a median PFS at 6 months of 47%[1]. Here we report the results from a translational analysis.

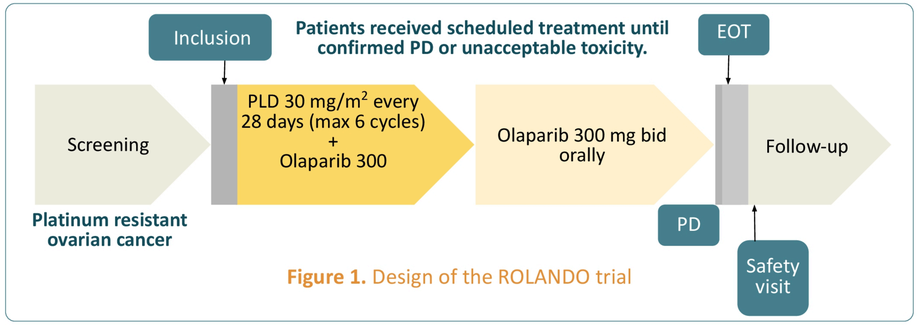


Figure 1. Design of the ROLANDO trial

Methods

- ROLANDO was a single-arm phase II trial including patients with high-grade PROC. Patients received 6 cycles of PLD every 28 days + OLA 300 mg b.i.d. followed by OLA 300 mg b.i.d. monotherapy until progression (PD) or unacceptable toxicity.
- The study analyzed the protein expression levels in blood samples of epithelium-mesenchyme transition and immune response pathways: AURKA, MERTK, AXL, PAI-1, TYRO3, CD36, RAGE, GAS-6, MBL, UPAR, CD31, CALR, LOX-1.
- Expression levels were compared between baseline and +/- 1 month after progression.
- Luminex using the Immuno-oncology checkpoint 14-plex human and the apoptotic cell clearance ProcartaPlex Panels.
- A PCA biplot for comparison among the expression of all 12 proteins was constructed.
- Impact on survival was assessed by Kaplan-Meier test and Cox regression models.

Table 1. Baseline characteristics

Characteristic	RAGE≤100 n=12	RAGE>100 n=10
Median age (range), years	52 (45-75)	59 (43-72)
ECOG; n (%)		
0	3 (25)	6 (60)
1	9 (75)	4 (40)
Histological subtype; n (%)		
Serous	12 (100)	8 (80)
Endometrioid	0 (0)	2 (20)
BRCA; n (%)		
Native or Unknown	10 (83.3)	8 (80)
Mutated	2 (16.7)	2 (20)
CA-125		
>2xULN	10 (83.3)	8 (80)
<2xULN	2 (16.7)	2 (20)
Previous lines; n (%)		
≥2	4 (33.3)	5 (50)
<2	8 (66.7)	5 (50)
Platine previous lines		
≥2	9 (75)	5 (50)
<2	3 (25)	5 (50)
Bevacizumab		
No	2 (16.7)	7 (70)
Yes	10 (83.3)	3 (30)

Results

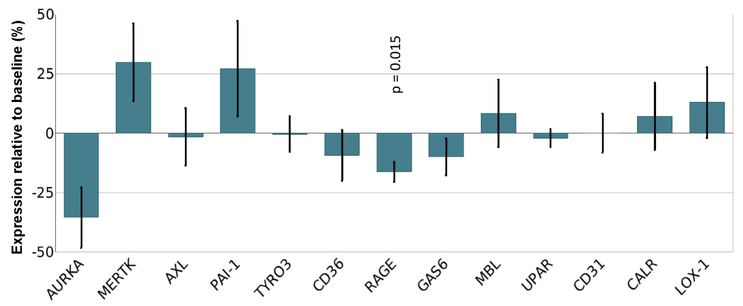


Figure 2. Change in expression levels at PD respect to baseline

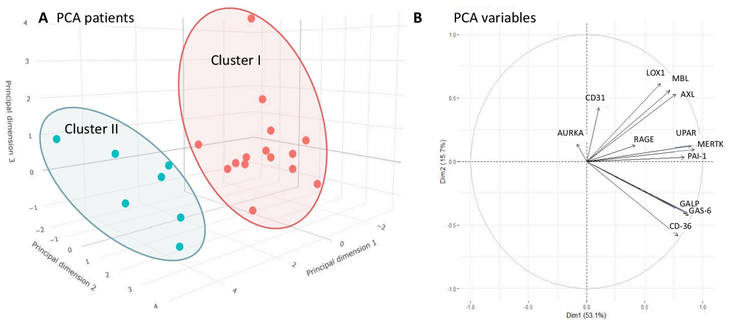


Figure 3. PCA analysis A) PCA clustering of patients accoridng to their protein expression level profile; B, biplot with correlation between protein expression levels

- From 2017 to 2020, 31 patients were included and 22 patients had analyzable blood samples at baseline, 9 of them had paired samples at PD.
- Among the determined biomarkers, only RAGE expression was significantly reduced at progression when compared to baseline, mean expression levels of 99,3 pg/ml (standard deviation [SD]: 31.4) vs 82,2 pg/ml (SD: 26.6) (p=0.015, paired t test) (**Figure 2**).
- Patients with higher RAGE levels were older (median age 59 years), and had less previous treatment lines (≤2 in 80% of patients) (**Table 1**).
- In the PCA biplot expression of RAGE at baseline was positively correlated with CD31, GAS6, PAI1, CALR and MERTK and negatively related with AURKA (**Figure 3**).

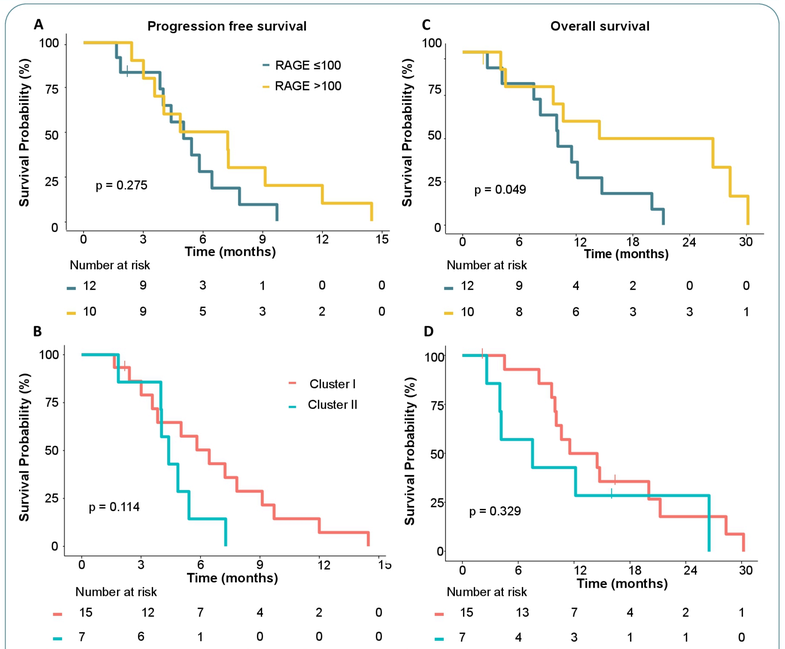


Figure 4. Subgroup analysis of PFS according to RAGE at baseline (A) and PCA analysis (B). Subgroup analysis of PFS according to RAGE at baseline (C) and PCA analysis (D)

- Patients with RAGE >100 pg/mL at baseline showed better survival outcomes, with a median OS 20.5 months (95% CI: 9.6NR) vs 10.1 months (95% CI: 8.2-NR) (p=0.049, Cox) (**Figure 4**).

Conclusions

- Progressive reduction of levels of RAGE in blood could be a predictive biomarker of progression to OLA in the PROC setting.
- Higher levels of RAGE at baseline in blood is a potential favorable prognostic factor for survival.

References

1. Perez-Fidalgo et al. ESMO Open 2021 Aug;6(4):100212

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