.cáncer. XII FORO DE ovario
Y OTROS TUMORES GINECOLÓGICOS

Cambiando el patrón de progresión con el iPARP ¿Cómo actuar ante una oligoprogresión?

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Conflictos de interés

Asesoría, consultoría, honorarios de conferencias y gastos de viaje de AZ, MSD, GSK, Clovis, Pharmamar.

Introduction: Hot spots

- PARPi represent a new standard of care in the upfront treatment of advanced EOC. The majority of patients now receive a PARPi, alone or in combination with bevacizumab, as part of their first-line maintenance therapy.
- Concerns regarding post-PARPi progression treatment have emerged, highlighting an unmet need to define a valid algorithm strategy.
- PARPi and platinum agents share several mechanisms of resistance. The concept of platinum-free interval as a surrogate of platinum sensitivity should be questioned in patients exposed to PARPi.
- The impact on subsequent non-platinum chemotherapy and surgery also remains unclear.
- Understanding of ovarian cancer mechanism of progression may offer an opportunity for more personalized therapy and treatment de-escalation, especially in the case of oligoprogression.

Efficacy of subsequent chemotherapy for patients with EOC progressing on PARP inhibitors

Post-hoc analyses of the SOLO2/ENGOT Ov-21 trial

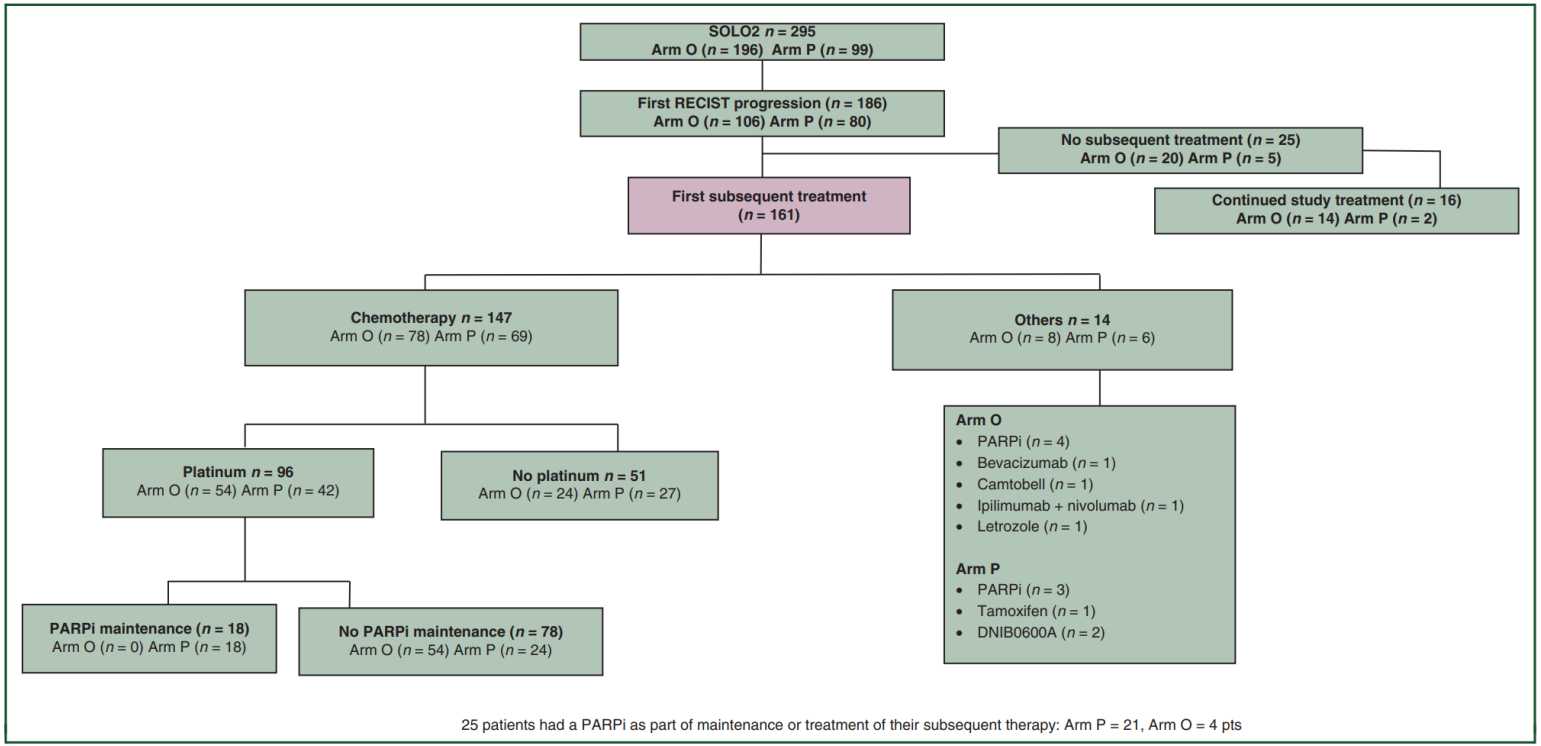

Figure 1. Flow-chart of the study. O, olaparib; P, platinum; PARPi, poly (ADP-ribose) polymerase inhibitor.

Frenel et al JCO 2022

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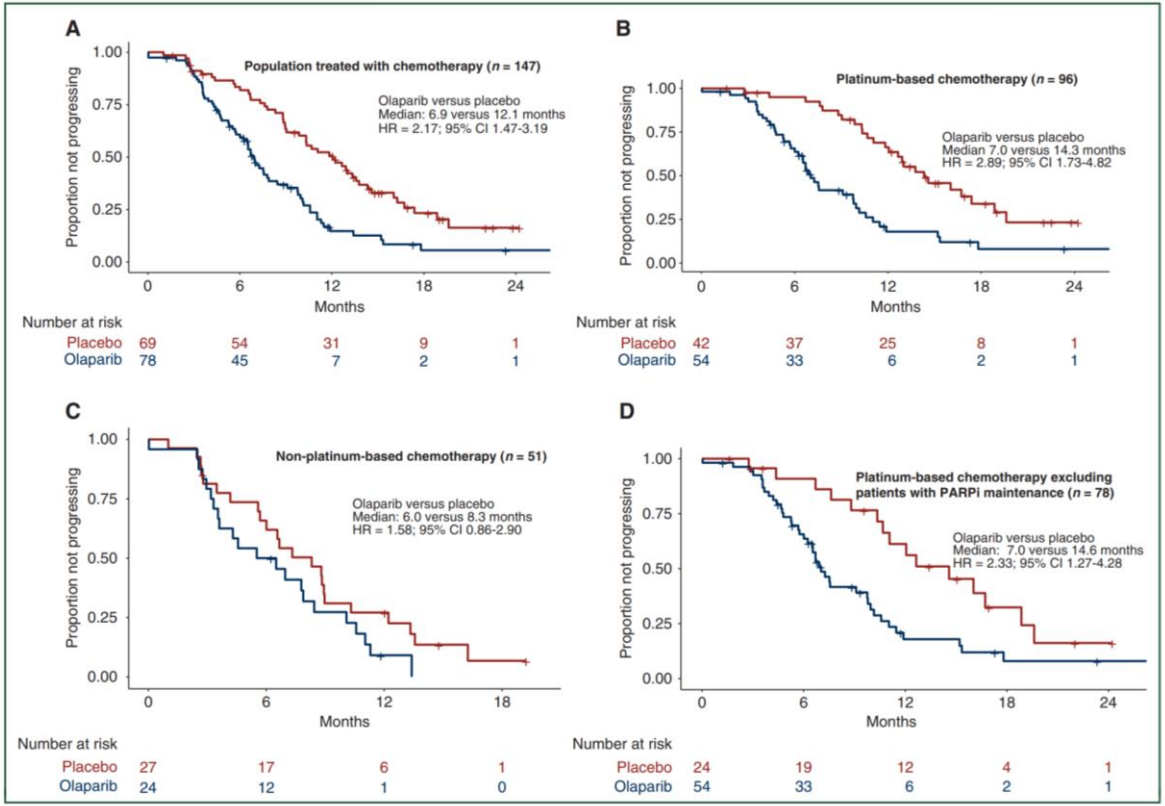

Figure 2. Time to second progression according to subsequent therapy type. CI, confidence interval; HR, hazard ratio; PARPi, poly (ADP-ribose) polymerase inhibitor.

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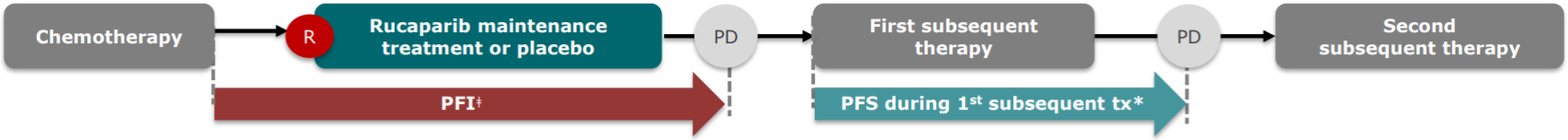
Efficacy of subsequent chemotherapy for patients with EOC progressing on PARP inhibitors

Exploratory analyses of the ARIEL3



	ITT Population			PFI <6 months			PFI 6–≤12 months			PFI >12 months		
	Event rate	Median, mo (95% CI)	Log-rank *P* value	Event rate	Median, mo (95% CI)	Log-rank *P* value	Event rate	Median, mo (95% CI)	Log-rank *P* value	Event rate	Median, mo (95% CI)	Log-rank *P* value
Rucaparib	163/174	7.0 (6.2–7.8)	<0.0001	30/30	5.4 (2.8–7.7)	0.2139	58/61	7.4 (6.1–8.6)	0.0056	75/83	7.1 (6.2–9.7)	0.0017
Placebo	61/76	11.3 (9.9–14.1)		14/16	8.3 (3.3–10.9)		38/46	11.3 (9.4–14.4)		9/14	18.5 (10.3–NA)	

- In the ITT population, 9.2% of patients in the rucaparib group and 25.0% in the placebo group received a PARP inhibitor maintenance therapy following their first subsequent platinum-based chemotherapy

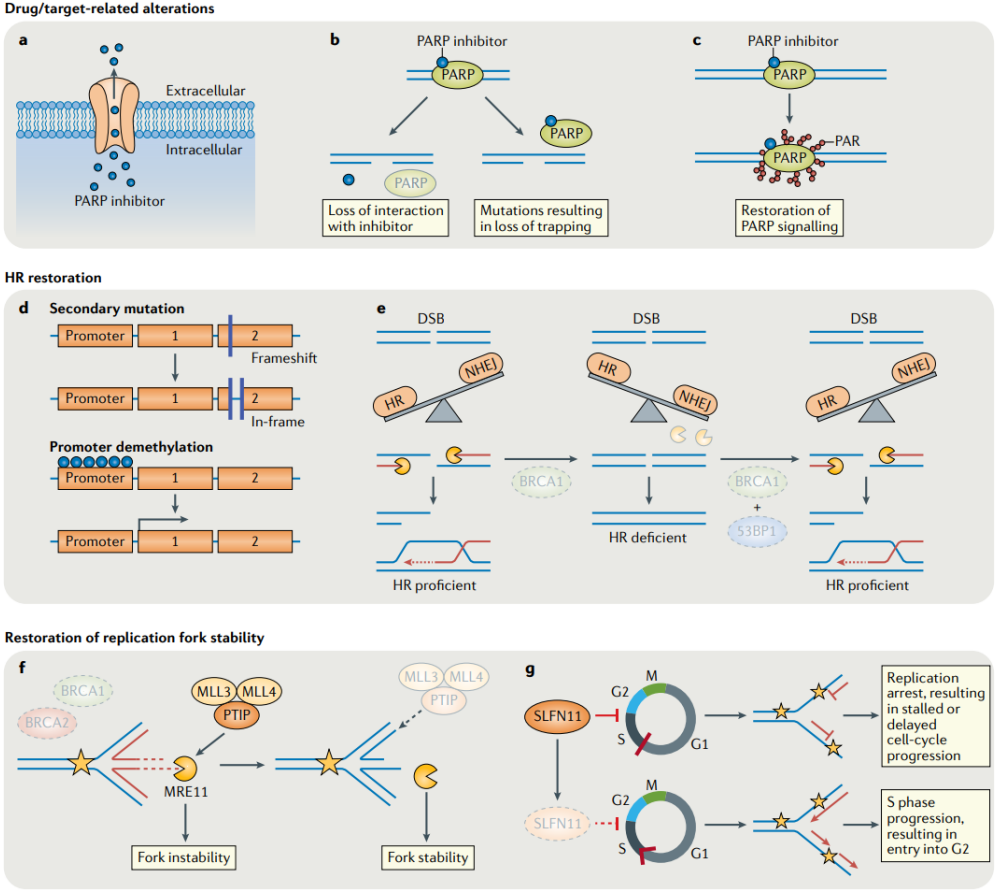
Data cutoff date: 4 April 2022.
*Progression free survival from the start of first subsequent therapy to disease progression. ‡From date of last chemotherapy prior to randomisation to date of PD on ARIEL3 treatment. CI, confidence interval; ITT, intent-to-treat; mo, months; NA, not applicable; PD, disease progression; PFI, progression-free interval; PFS, progression-free survival; R, randomisation.

Efficacy of subsequent chemotherapy for patients with EOC progressing on PARP inhibitors

Mechanism of resistance to PARP inhibitors

Resistance occurs via one of three general mechanisms:

- Alterations related to the drug/target
- Restoration of homologous recombination (HR)
- Restoration of replication fork stability



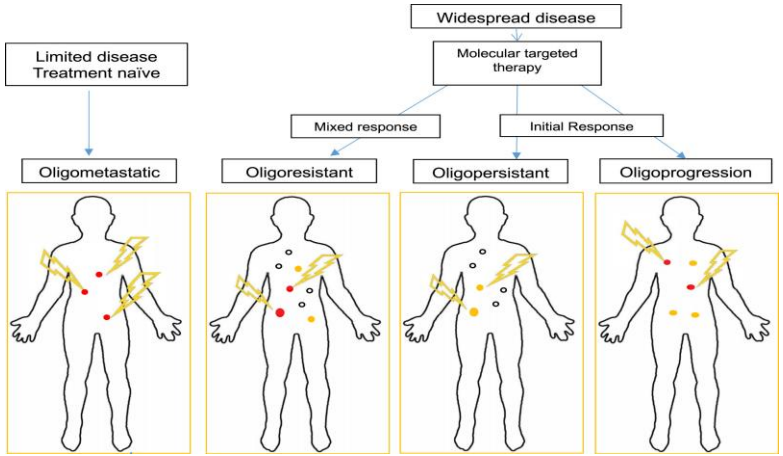
Dias et al Nature Review 2021

Oligometastatis/Oligoprogression in patients with OC under PARPi maintenance

Nomenclature in the metastatic state

- Oligometastasis is considered as metastatic disease confined to a limited number of sites (often described as up to three or five sites) and can be synchronous or metachronous with the primary tumour presentation.

- Oligoprogression develops on a background of polymetastatic disease. OPD occurs following an initial response to systemic treatment where disease progression only occurs in a limited number of sites with the potential for the development of sub-clones of drug resistance.



Patel et al Clin Oncol 2019

Oligoprogression in patients with OC under PARPi maintenance

Strategies of management

- The rationale is based on the supposed PARPi resistance developed in some clones from the original tumor growing as discrete nodules, whereas the rest of the disease is still under control.

- Local treatment (surgery or stereotactic body radiotherapy) of OPD sites may slow or prevent propagation of drug-resistant clones:
  - increasing the likelihood to prolong therapeutic benefit from the current line of systemic therapy,
  - or the response to subsequent treatments.

- In ovarian cancer, OLP under PARPi may still benefit from PARPi maintenance after local treatment instead of stopping the PARPi and undergoing new line of chemotherapy.

PARIS 2022 ESMO congress

Is re-introduction or continuation of PARP inhibitors after local therapy for oligo-metastatic progression in patients with relapsed ovarian cancer relevant?

Thibault GAUDUCHON[1], Maria KFOURY [2], Domenica LORUSSO [3], Anne FLOQUET [4], Jole VENTRIGLIA [5], Hélène SALAUN [6], Malak MOUBARAK [7], Romain RIVOIRARD [8], Laura POLASTRO [9], Laure FAVIER [10], Benoit YOU [11], Dominique BERTON [12], Thibault DE LA MOTTE ROUGE [13], Laura MANSI [14], Cyril ABDEDDAIM [15], Karine PRULHIERE [16], Laurence LANCRY LECOMTE [17], Magali PROVANSAL [18], Cécile DALBAN [19], Isabelle RAY-COQUARD [1-20]

Methods

- **Design**: international multicenter retrospective study
- **Goal**: to evaluate the role of PARPi continuation or reintroduction in patients with HGOC after local treatment (LT) for oligometastatic progression under parpi
- **Primary endpoint**: median PFS with PARPi therapy after local therapy (PFS post-LT)
- **Secondary objectives** : Tolerability and OS

Patient characteristics

- **74 patients** in 20 centers (between April 2020 and November 2021)
- Median age : **61 years old**
- **65%** of BRCA mutated (43% BRCA1)
- **92%** had received > 2 lines of prior systemic chemotherapy
- **Initial PARPi**: olaparib (61%), Niraparib (32%) and rucaparib (7%)
- PARPi median time before LT : **16,6 months** (3.7 to 39.0)

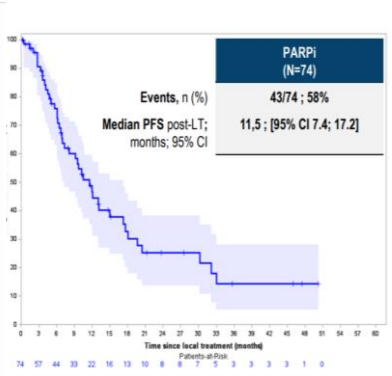
Main progression sites	Local therapy
lymph nodes (42%)	radiotherapy (44%)
peritoneum (27%)	surgery (43%)
liver (11%)	both (7%)
other visceral (16%) [1]	Percutaneous Thermal Ablation (4%) [2]
Abdominal wall (4%)	Chemoembolization (1%)

[1] Spleen, Lung, Adrenal Glands and Brain

[2] cryotherapy, radiofrequency or microwave

Results

- **Median follow up** of 14.8 months [95% CI 11.8 - 22.8]
- **Median PFS** post-LT[1] : 11.5 months
- **1-year OS rate** : 90.7% [95% CI 79.1; 96.0]
- 5 patients (6.8%) discontinued PARPi due to toxicity [2]



[1] PFS post local treatment

[2] hematological toxicity (N=2), asthenia and anorexia (N=2), myelodysplastic syndrome (N=1)

Gauduchon et al ESMO 2022

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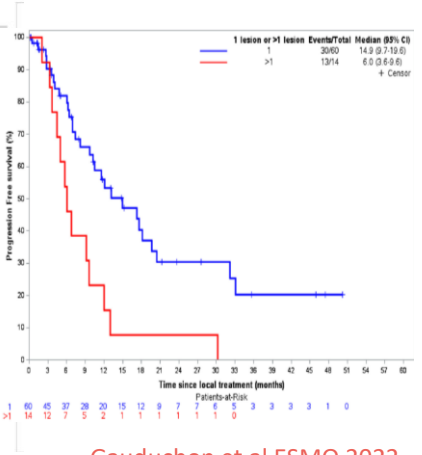

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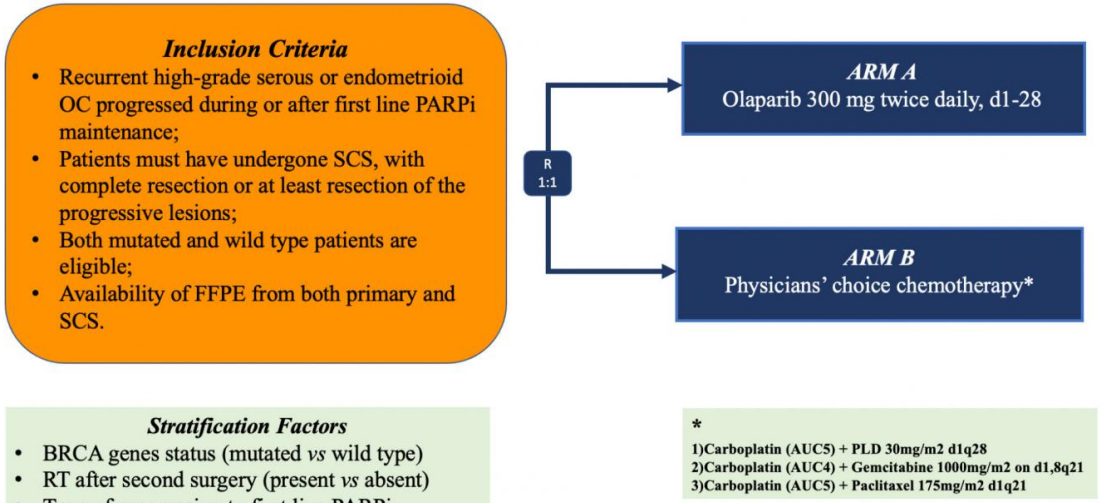
Phase III randomized, open-label MITO 35b study

Olaparib beyond progression compared with platinum chemotherapy after secondary cytoreductive surgery in patients with recurrent ovarian cancer



Key inclusion criteria

- Patients with high-grade serous or endometroid ovarian, fallopian tube, or primary peritoneal cancer recurrent or progressive after first-line PARPi maintenance
- Only one previous line of a platinum-based chemotherapy not containing bevacizumab
- Patients must have undergone secondary cytoreductive surgery. The cytoreduction must result in complete resection (absence of macroscopic residual tumor) or at least resection of the progressive lesion(s) occurring during maintenance
- Patients must have received first-line maintenance therapy with a PARPi for at least 6 months; patients who experience disease relapse after the end of 24 months maintenance therapy are eligible
- Documented BRCA1/2 status. Both mutated and wild type patients are eligible. Patients with unknown status of BRCA genes must agree to undergo analysis of their germline and somatic BRCA status (testing must be completed prior to randomization in the study)
- Patients must start the experimental treatments in the current study within 3–8 weeks from second surgery
- Patients must provide archival tumor samples formalin-fixed, paraffin-embedded (FFPE) from both the primary and secondary surgeries for paired analysis. A quality control analysis of samples will be performed before randomization

Schettino et al.Int J Gynecol Cancer 2022

Conclusions

The Dandelion Dilemma Revisited for Oligoprogression: Treat the Whole Lawn or Weed Selectively

- The increasing use of PARPis in clinical practice highlights an emerging clinical issue, to overcome resistance.
- Oligoprogression after PARPi represents a new scenario and further data are needed before getting any definitive conclusion.
- Future research should focus on mutational analysis of surgically resected lesions to understand the molecular pattern of oligometastatic disease progression, such as PARPi resistance, and to propose a tailored target therapy.
- Effective de-escalation strategies might help to personalize patient care, reduce toxicity, improve the quality of life, and optimize treatment outcomes in specific patient subpopulation.

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Gracias