Antibody–drug conjugate targeting folate receptor α: a new milestone in personalized medicine for high-grade serous ovarian cancer

Antonio Gonzalez-Martin

Medical Oncology Department, Cancer Center Clinica Universidad de Navarra, Madrid, Spain

Correspondence to
Dr Antonio Gonzalez-Martin, Medical Oncology, Clinica Universidad de Navarra, Madrid, Spain; agonzalezma@unav.es

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Patients with recurrent high-grade serous ovarian cancer who are no longer candidates for platinum-based chemotherapy, often referred to as patients with platinum-resistant disease, have represented an unmet medical need since the introduction of platinum chemotherapy decades ago. Unfortunately, the prognosis for these patients is usually poor with a median overall survival of around 12 months, and the activity of the few active agents used in monotherapy is very limited with an overall response rate of 5–15%. Although the addition of bevacizumab improved the overall response rate and the median progression-free survival in the phase III AURELIA trial, this improvement did not translate into an overall survival benefit, potentially explained by the crossover to bevacizumab in the control arm.[1 2]

This bleak scenario began to change with the accelerated approval of mirvetuximab soravtansine-gynx (MIRV) by the US Food and Drug Administration (FDA) on November 14, 2022 for adult patients with folate receptor α (FRα)-positive, platinum-resistant ovarian cancer who received 1–3 prior systemic treatments (bevacizumab required). This approval was based on the results of the single-arm phase II SORAYA study, whose final overall survival data are presented by Coleman et al in this issue of the *International Journal of Gynecological Cancer*.[3]

In the SORAYA study MIRV, an antibody–drug conjugate that targets FRα and induces a cytotoxic effect through an anti-tubulin payload (maytansinoid DM4), was administered to 106 patients with platinum-resistant disease previously treated with 1–3 chemotherapy lines (one of them including bevacizumab). The tumors of these patients had to express a high rate of FRα (≥75% of cells with ≥2+ immunohistochemical staining intensity as defined by the FDA-approved VENTANA FOLR1 (FOLR1-2.1) RxDx assay). The final median overall survival in the efficacy-evaluable population (n=105) was 15.0 months (95% CI 11.5 to 18.7). Additionally, the investigators provided interesting information about the median overall survival according to the number of prior lines and the prior use of poly (ADP-ribose) polymerase (PARP) inhibitors.

The results of the SORAYA study should be interpreted in the context of the MIRASOL study (GOG 3045/ENGOT-Ov55), a phase III study that compared MIRV with the investigator's choice of chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan) in a similar population, with the difference that prior bevacizumab was not mandatory. MIRASOL is the first study to show an overall survival benefit of a targeted therapy over chemotherapy in a phase III trial of platinum-resistant ovarian cancer, reaching a median of 16.46 months with MIRV versus 12.75 months with single-agent chemotherapy (HR 0.67; 95% CI 0.50 to 0.89; p=0.005).[4] The 15.0 months final median overall survival observed in the SORAYA study is consistent with the MIRASOL data and corroborates the efficacy of MIRV in this population.

As with each step forward in personalized medicine, a few new questions arise including the timing for introducing this innovation in the natural history of platinum-resistant patients and the effect of prior therapy, especially targeted therapy.

In this regard, the SORAYA trial has shown that median overall survival in participants with 1–2 prior lines of therapy (n=51) was superior to that in participants with three prior lines of therapy (n=53): 18.7 months (95% CI 13.8 to not estimable (NE)) vs 11.6 months (95% CI 7.1 to 16.7). Although in the MIRASOL study[5] the median overall survival was similar in both populations, 16.46 months (95% CI 12.88 to NR) in those with 1–2 prior lines vs 17.35 months (95% CI 12.81 to 20.24) in patients with three prior lines, it should be recommended to incorporate this drug as early as possible in the treatment history of patients with platinum-resistant high-grade serous ovarian cancer based on the observed increase in overall survival.

As PARP inhibitors have been increasingly adopted as maintenance after response to front-line platinum-based therapy, some concerns have been raised about potential resistance to subsequent therapies.

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However, the SORAYA study has demonstrated a similar overall survival regardless of prior use of PARP inhibitors. The median overall survival was 15.0 months (95% CI 11.5 to NE) in participants who received prior PARP inhibitors (n=50) versus 14.0 months (95% CI 7.1 to NE) in those who did not receive prior PARP inhibitors (n=51). For this sub-group analysis, the MIRASOL trial confirmed the overall survival benefit in patients exposed to PARP inhibitors in favor of MIRV (HR 0.48, 95% CI 0.33 to 0.71) and median overall survival (19.88 months vs 11.37 months), ruling out any concerns about cross-resistance mechanisms.[5]

In terms of safety, the SORAYA trial has not identified new safety signals and the safety profile is consistent with the profile reported in MIRASOL. Grade 3–4 ocular treatment-related adverse events were limited (visual impairment 6%; keratopathy 9%; and dry eye 2%), confirming the efficacy of prophylactic and mitigative procedures for ocular adverse events.

In summary, MIRV is the first targeted therapy to demonstrate a survival benefit over chemotherapy in patients with platinum-resistant ovarian cancer. This achievement represents a new milestone in personalized medicine for high-grade serous ovarian cancer, resulting from the combination of a new class of drug (antibody–drug conjugate) targeting a relevant membrane protein in high-grade serous ovarian cancer (FR-α) identified with a clearly defined biomarker, with an unprecedented overall survival benefit and a manageable safety profile.

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ORCID iD
Antonio Gonzalez-Martin http://orcid.org/0000-0001-8376-9576

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