



# Mirvetuximab soravtansine: an oasis in the desert?

Luisa Bonilla ,<sup>1</sup> Lawrence Kasherman ,<sup>2</sup> Luis Manso,<sup>3</sup> Ainhoa Madariaga <sup>3</sup>

<sup>1</sup>Health Sciences North, Sudbury, Ontario, Canada

<sup>2</sup>Department of Medical Oncology, Illawarra Cancer Care Centre, Wollongong, New South Wales, Australia

<sup>3</sup>Department of Medical Oncology, 12 de Octubre University Hospital, Madrid, Comunidad de Madrid, Spain

## Correspondence to

Dr Ainhoa Madariaga, Medical Oncology, 12 de Octubre University Hospital, Madrid, Comunidad de Madrid, Spain; ainhoa.madariaga@salud.madrid.org

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Three common facts arise in discussions about ovarian cancer nowadays. First, systemic therapy was introduced approximately five decades ago and remained largely unchanged for four of those decades. Second, only a fraction of patients possess a reliable predictive marker of response to therapy, which involves the presence of germline or somatic *BRCA1/2* pathogenic variants and homologous recombination deficiency. Thirdly, in platinum resistant disease, contemporary treatment options have failed to demonstrate overall survival improvements.<sup>1,2</sup> In light of these challenges, the development of mirvetuximab soravtansine-gynx (MIRV) marks a milestone, akin to discovering a glass of water after a 50-year journey through the desert. But as we celebrate this advancement, we must also question: Is this truly the oasis we've been seeking, or merely a glimpse of what's yet to come?

Antibody–drug conjugates (ADCs) have emerged as a groundbreaking class of therapeutics revolutionizing oncology in recent years. In the review article by Bogani and colleagues, they meticulously explore the development of MIRV, an ADC targeting folate receptor  $\alpha$  (FR $\alpha$ ), in ovarian cancer.<sup>3</sup> The authors discuss the results of the pivotal MIRASOL trial (NCT04209855), where MIRV was compared to single-agent chemotherapy in patients with FR $\alpha$ -high platinum-resistant ovarian cancer.<sup>4</sup> The trial results highlight MIRV's achievement as the first agent to demonstrate improved overall survival in patients with platinum-resistant ovarian cancer selected by a biomarker.

The trajectory of MIRV underscores the importance of establishing robust and practical methods to measure FR $\alpha$  expression. Bogani and colleagues explain how, during the transition from prior phase I/II studies to the FORWARD-I phase III trial (NCT02631876)—which was the first phase III study evaluating MIRV versus chemotherapy in platinum-resistant FR $\alpha$ -positive ovarian cancer—there was a shift in the approach to determining FR $\alpha$  expression.<sup>3</sup> The adoption of a simpler scoring system (10x) in FORWARD-I presented discordances with the original PS2 scoring, ultimately diluting MIRV's efficacy and resulting in a failure to demonstrate significant outcome differences. Nonetheless, the persistence and determination exhibited by investigators in launching the MIRASOL study with the initial

biomarker are admirable, particularly because similar obstacles have discontinued many promising agents in the past. Questions persist regarding the optimal cut-off and measures for FR $\alpha$ -directed therapies. The ongoing REFRAme-01 study (NCT05870748), assessing luveltamab tazevibulin in a similar setting, has a FR $\alpha$  tumor proportion score  $\geq 25\%$  cut-off inclusion, reaching a broader patient population. It is likely that FR $\alpha$  cutoffs will vary depending on the FR $\alpha$  targeting agent, combination strategies, and disease setting.

Some considerations are warranted when discussing MIRASOL trial data.<sup>4</sup> First, its restricted patient population, limited to those treated with  $\leq 3$  prior lines of therapy, and the fact that only approximately 36% of patients are considered FR $\alpha$ -high,<sup>3</sup> narrows its catchment area. Additionally, the control arm of the trial consisted of single-agent chemotherapy, and 38% of MIRASOL participants did not receive prior bevacizumab.<sup>4</sup> Many may argue that in these patients, the control should include an antiangiogenic. Indeed, an investigator-initiated randomized phase II trial assessing ADCs in a similar population included bevacizumab in the control arm.<sup>5</sup> In addition, the publication of patient-reported outcome analyses are awaited. It is noteworthy that the management of MIRV emergent adverse events, notably ocular toxicity, requires interdisciplinary collaborations and rigorous monitoring, and its impact on patient quality of life needs to be addressed. The multidisciplinary toxicity management and patient-reported outcomes results need to be considered, especially as we move towards studies assessing MIRV as a maintenance strategy.

A remaining concern pertains around access. While both the US Food and Drug Administration and the European Medicines Agency have increased cancer agent approvals over the past decade, ensuring broader access remains elusive. Approval does not guarantee access, particularly in reimbursement terms, which vary significantly across Western countries and pose even greater challenges in low- and middle-income nations. While contemporary oncology therapies entail high research and development costs with complex manufacturing processes, achieving equity in cancer treatment access and biomarker

## Editorial

utilization remains a pressing challenge requiring innovative solutions.

**Twitter** Lawrence Kasherman @LKasherman and Ainhoa Madariaga @AinhoaMada

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### ORCID iDs

Luisa Bonilla <http://orcid.org/0000-0002-5620-2141>

Lawrence Kasherman <http://orcid.org/0000-0001-7576-8565>

Ainhoa Madariaga <http://orcid.org/0000-0001-7166-9762>

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