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PODCAST

Should all advanced BRCA-mutated patients in response to first-line platinum-based chemotherapy receive PARPi + bevacizumab as maintenance therapy?

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The best first-line maintenance treatment in patients with high-grade serous ovarian cancer carrying a *BRCA1/2* mutation is still up for debate, as we do not have a clear answer as to what is the best option between a monotherapy with poly ADP ribose polymerase inhibitors (PARPis) and the combination therapy of olaparib and bevacizumab, after a partial or complete response to platinum-based chemotherapy.

While we hope to have in the future molecular markers that go beyond BRCA status and homologous recombination deficiency, that will allow us to better detect patients who will have a poor response to platinum and PARPi, a partial selection of patients is currently possible through their clinical characteristics. A high-risk case with stage IV disease, a partial response to platinum, residual disease after surgery, and pulmonary disease with pleural effusion might gain a higher benefit from the combination therapy. The response to chemotherapy (CA125 normalization) or the KELIM score is also worth consideration, as some data show that it might help predict benefit from bevacizumab maintenance.

Data from PAOLA-1 suggest a higher benefit in terms of progression-free survival and overall survival in low-risk patients (stage III, with no residual after upfront surgery) from the addition of olaparib to bevacizumab. Although it is possible to argue that patients with BRCA tumours are likely to benefit the most from PARPi and might therefore not need bevacizumab in the first line, we still do not have a formal proof of the direct comparison, which will be available with the NIRVANA-1 trial results.

Hopefully, in the future, we will be able to look for signatures of PARPi and platinum resistance such as secondary mutations or reversions of BRCA which might help us optimize and tailor our strategy.

As for the challenges lying ahead in the first-line setting (extending beyond BRCA-mutated patients), PAOLA-1 has shown how patients who relapse after finishing PARPi therapy have a better prognosis than those who relapse during PARPi therapy. This might signify the need for a new definition, such as a PARPi-free interval, and a new therapy paradigm that would see patients who did not progress during the therapy undergo it once again. A validation of this approach through a phase III trial would be paramount.

The optimization of maintenance therapy through locoregional interventions in the case of oligometastatic progression, while currently not validated prospectively, seems to be a viable option to extend the therapy-free interval. By contrast, patients who progress extensively during maintenance are in need of new strategies, because it seems as though platinum-based chemotherapy and current targeted therapies are no longer the optimal option.

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