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MEK Inhibitors for the Treatment of Low-Grade Serous Ovarian Cancer: Expanding Therapeutic Options for a Rare Ovarian Cancer Subtype

David M. Gershenson, MD¹; Charlie Gourley, MBChB, PhD²; and James Paul, BSc³

The introduction of the binary grading system for ovarian serous carcinoma in 2004, replacing traditional three-tier grading systems, and its subsequent acceptance into the WHO classification system a decade later led to a remarkable acceleration in studies of low-grade serous ovarian carcinoma (LGSOC).^{1,2} Early observational studies identified the demographic and clinical characteristics of LGSOC compared with high-grade serous ovarian carcinoma (HGSOC), including its rarity (LGSOC comprises < 10% of all serous carcinomas), younger age at diagnosis, relative chemotherapy resistance, responsiveness to endocrine therapy, and prolonged overall survival.³⁻⁶ Similar to those with HGSOC, most patients present with advanced disease, and > 70% relapse.^{3,7}

Concomitantly, molecular biology investigations identified its high frequency of estrogen and progesterone receptor expression and the influence of the mitogen-activated protein kinase (MAPK) signaling pathway on its pathogenesis.^{5,8-20} LGSOC and HGSOC develop along discrete developmental pathways, with LGSOC having a high frequency of MAPK pathway mutations and HGSOC having ubiquitous p53 mutations, DNA repair defects, and copy number abnormalities.¹¹⁻²³ Multiple reports have indicated that *KRAS* mutations occur in 16% to 44% of LGSOCs, *BRAF* mutations in 2% to 20%, and *NRAS* mutations in up to 26%.¹¹⁻²¹

As with most rare tumor subtypes, few effective therapeutic options exist for women with LGSOC. As noted, the efficacy of chemotherapy is limited. Other options include endocrine therapy and bevacizumab.^{5,10,24-27} MEK inhibitors are orally bioavailable, non-ATP competitive, small-molecule inhibitors of MEK1/2. Once MEK inhibitors became available for clinical development, it was logical to study them in LGSOC. The initial phase II trial examined selumetinib in recurrent LGSOC.¹⁹ The objective response rate (ORR) was 15%, with 65% of patients having stable disease, and median progression-free survival (PFS) was 11.0 months. DNA from 34 patients was analyzed for *KRAS* and *BRAF* mutations. There were two *BRAF* mutations (6%) and 14 *KRAS* mutations (41%); however, no correlation between response and mutational status was found.

Subsequently, two large randomized clinical trials of MEK inhibitors in recurrent LGSOC were launched. MILO/ENGOT-ov11, featured in the report by Monk et al²⁸ that accompanies this editorial, compared binimetinib with physician's choice of chemotherapy (PCC). Between June 2013 and April 2016, 341 patients were accrued. GOG 0281 was a phase II/III trial comparing trametinib with PCC (pegylated liposomal doxorubicin or weekly paclitaxel, topotecan, letrozole, or tamoxifen).²⁹ Between February 2014 and April 2018, 260 patients were enrolled.

On the basis of an interim analysis of 303 patients, enrollment in MILO was discontinued, because the PFS hazard ratio (HR) crossed the predefined futility boundary. Median PFS was 9.1 months for binimetinib and 10.6 months for PCC by blinded independent central review (BICR; HR, 1.21; $P = .807$); in the updated analysis, corresponding median PFS times were 10.4 and 11.5 months, respectively (HR, 1.15; $P = .748$). Conversely, GOG 0281 met its primary end point, with a median PFS of 13.0 months for trametinib and 7.2 months for PCC (HR, 0.48; $P < .001$). In the MILO trial, the ORR by BICR was 16% for binimetinib and 13% for PCC; however, in the updated analysis, the ORR by local investigator assessment was 24% in both groups. In GOG 0281, the ORRs were 26% and 6.2% for trametinib and PCC, respectively.

How do we interpret these disparate results? The MILO trial failed to meet its primary end point, possibly because of the better-than-anticipated outcome in the PCC group, whereas GOG 0281 was the first positive randomized trial in women with recurrent LGSOC. There are potential explanations to consider, while keeping in mind the limitations of cross-study comparisons. First, in the design of the MILO trial, median PFS for PCC was estimated to be 7 months based on two retrospective studies, and the design aimed to detect an HR of 0.60, corresponding to a median PFS of 11.7 months, in the binimetinib arm.^{4,5} Eligibility was limited to \leq three lines of prior chemotherapy regimens, with no limit to the number of lines of prior hormonal therapy. As noted in Table 1 of the report by Monk et al,²⁸ only 28% of all patients in MILO received \geq three prior systemic regimens (range, 1-8 prior regimens).

ASSOCIATED CONTENT

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By contrast, in the two studies used to estimate median PFS in the PCC group, the proportions of patients who received at least three prior systemic regimens were 62% (range, 1-11 prior regimens) and 56% (range, 1-14 prior regimens), respectively.^{4,5} Moreover, 48.1% of patients in GOG 0281 had at least three prior systemic regimens and thus represented a more heavily pretreated and possibly poorer prognostic group compared with that studied in MILO. Altogether, this perhaps explains the better-than-expected outcome in the MILO PCC arm, which in turn may have made it more difficult to demonstrate a potential benefit of MEK inhibition in this study.

Another possible explanation is the difference in the PCC arms, where GOG 0281 allowed letrozole and tamoxifen as options. However, it should be noted that patients receiving letrozole did well, and overall PFS results were statistically significant even when patients receiving tamoxifen, who did particularly poorly, were excluded. Alternatively, it may simply be that trametinib has greater efficacy compared with binimetinib in recurrent LGSOC. Fernández et al³⁰ compared four different MEK inhibitors (trametinib, selumetinib, binimetinib, and refametinib) in novel LGSOC patient-derived cell lines and found trametinib to have the greatest antiproliferative effects. A single dose of trametinib had a greater impact on cellular proliferation than 10-fold higher doses of the other drugs. It also had the greatest impact on cellular viability and was most capable of inducing apoptosis. Similar findings have been reported in lung cancer cell lines and tumor models.^{31,32} Whether this preclinical superiority translates into greater clinical efficacy has not been directly tested. One might counter with the argument that the MILO updated analysis of 341 patients revealed median PFS by BICR of 10.4 months and ORR by local investigator assessment of 24% for binimetinib, which were not that different from results in GOG 0281 (ie, median PFS, 13.0 months; ORR, 26%). However, the latter trial included a more heavily pretreated group. It is also worth highlighting the fact that 76% of patients receiving binimetinib had grade ≥ 3 adverse events, and 31% had adverse events leading to permanent discontinuation of study drug. There were several rare but serious adverse events, such as decreased ejection fraction and retinal vein occlusion, underscoring the fact that MEK inhibitors can be somewhat complicated to manage and require careful monitoring.

Finally, what is the significance of the mutational analysis in the MILO²⁸ trial? The selumetinib trial failed to demonstrate a correlation between *KRAS/BRAF* mutations and ORR, and the mutational analysis for GOG 0281 is ongoing. The authors note a putative association between *KRAS*

mutation status and response. Although this is interesting, this observation must be considered hypothesis generating at present. First, 47 mutations in total were examined, and the single statistically significant result would be less impressive after an appropriate adjustment for this number of comparisons. It is also not clear that the association is restricted to the binimetinib arm, because the corresponding odds ratio in the PCC arm is of a similar magnitude (3.40 v 2.13) and not obviously different, given the overlap of the respective 95% CIs (95% CI, 1.53 to 7.66 v 0.67 to 7.81). Admittedly, the PCC result is not statistically significant, but the sample size is 50% of that for binimetinib, with power correspondingly reduced. Although the ORR for binimetinib in the *KRAS*-mutant group is an impressive 44%, this is in the context of the updated local response rate in all biomarker-assessed patients, which is already high at 27% overall (Table 3 by Monk et al²⁸), and the fact that this subgroup was selected after examination of multiple others as outlined previously.

It would have been interesting to have examined the predictive value (in the sense of allowing selection between binimetinib and PCC) of *KRAS* mutation status by estimating the relative effect of binimetinib versus PCC in the *KRAS*-mutant and wild-type groups separately and using a test for interaction to determine whether these differed significantly. We do understand that the numbers available mean the power to detect even the most marked interaction is heavily compromised, but nonetheless, this is the approach required to assess the predictive value of this biomarker. This more generally emphasizes the difficulties associated with exploratory retrospective analysis of predictive biomarkers in clinical trials and perhaps suggests a requirement to more seriously consider prospectively incorporating putative biomarkers into the design of trials where this is feasible and scientifically justified.³³

In summary, although not meeting its primary end point, the MILO study demonstrates that MEK inhibition results in disease control in a significant number of patients and is a strategy that should be seriously considered in this difficult-to-treat disease. More importantly, although there are questions still to be answered regarding the extent to which various MAPK mutations confer MEK inhibitor sensitivity, it is clear that the molecular biology of some LGSOCs results in their addiction to this pathway and exceptional responses to MEK inhibition.³⁴ Such outcomes may not be achievable with standard-of-care chemotherapy. Meanwhile, the search for the optimal predictive biomarker for MEK inhibitor sensitivity continues.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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