Editorial Commentary

Alterations in the MAPK pathway: promising biomarkers for MEK1/2 inhibition

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Low-grade serous ovarian carcinoma (LGSOC) is a distinct subtype of ovarian cancer that presents unique challenges in terms of treatment due to intrinsic chemoresistance. LGSOC, in comparison to high-grade serous ovarian carcinoma, has a high prevalence of mutations in KRAS (20–40%), NRAS (26%) and BRAF (5–10%) (1,2). Patients with activating mutations in canonical mitogen-activated protein kinase (MAPK) pathway components are reported to respond more frequently to targeted agents, such as MEK inhibitors, compared to patients without a mutation in the MAPK pathway (3,4). MEK inhibitors are a class of targeted therapies designed to block the activity of MEK1 and MEK2. These are proteins that play a crucial role in the MAPK signaling cascade and can contribute to uncontrolled cell growth, resistance to apoptosis and increased angiogenesis (5).

The post-hoc tumor tissue analysis from the phase 3 ENGOT-ov11/MILO study evaluated the efficacy of binimetinib, a potent MEK1/2 inhibitor, in treating recurrent LGSOC (6). The study enrolled 341 patients between June 2013 and April 2016, who were randomized 2:1 to receive either binimetinib or physician's choice of chemotherapy (PCC). The most commonly altered gene was *KRAS* (33%), which is in accordance with literature (7-10).

The study found that patients with a *KRAS* mutation (*KRAS*mut) treated with binimetinib were 3.4 times more likely to respond [complete remission (CR) or partial remission (PR)] compared to patients without a *KRAS* mutation (*KRAS*wt) [95% confidence interval (CI): 1.57–7.67]. Among patients treated with binimetinib, 44% of *KRAS*mut patients achieved a CR/PR compared to 19% of *KRAS*wt patients.

The study also found that patients who harbor MAPK pathway alterations (*NRAS*, *BRAF*, *NF1*, *RAF1* mutations) and are treated with binimetinib have longer progression-free survival (PFS) compared to those without MAPK pathway alterations [hazard ratio (HR) 0.50; 95% CI: 0.31–0.79]. A similar trend towards improved PFS was observed among patients harboring a MAPK pathway alteration treated with PCC (HR 0.82; 95% CI: 0.43–1.59). This is in line with other evidence suggesting that women with low-grade serous ovarian tumors containing a *KRAS* or *BRAF* mutation experience a more favorable outcome compared to those with tumors that lack these activating MAPK pathway mutations (11).

In vitro and *in vivo* data indicate that patients harboring the KRAS G12V mutation may be more sensitive to MEK inhibition compared to other *KRAS* variants. Despite this, the study found no difference in PFS in patients with KRAS G12V mutation (n=19) versus patients with other *KRAS*

variants (n=26).

In the GOG-281/LOGS phase 2/3 trial, patients with recurrent LGSOC were treated with trametinib, a MEK1/2 inhibitor, versus PCC. PFS and overall response rate (ORR) were both markedly higher in patients with a *KRAS*, *BRAF* or *NRAS* mutation compared to patients with wild-type *KRAS*, *BRAF* and *NRAS* (3). This confirms the findings of the post-hoc tumor analysis of the MILO/ENGOT-ov11 trial. Additionally, the GOG-281/LOGS trial found that this mutation profile might be predictive for ORR, but not for PFS.

Similar impact of a *KRAS* mutation on ORR were described in the ENGOT-ov60/GOG-3052/RAMP201 study including patients with recurrent LGSOC (12). The initial results of this study showed that avutometinib, a dual RAF/MEK inhibitor, in monotherapy or in combination with defactinib, a FAK inhibitor, had a higher ORR in *KRAS*mut patients (monotherapy 10% *vs.* combination 60%) compared to *KRAS*wt patients (monotherapy 6% *vs.* combination 29%). Based on these results, the study will continue as a randomized phase 3 clinical trial of the combination of avutometinib and defactinib versus PCC.

In conclusion, this post-hoc analysis identifies alterations in the MAPK pathway as possible biomarkers to select patients for MEK1/2 inhibitor treatment in the future. MEK inhibitors could be an effective treatment option for LGSOC patients with alterations in the MAPK pathway and not limited to *KRAS*. Biomarker research is crucial in identifying the right patient population to select for targeted agents, making this type of translational research important in LGSOC.

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