Review Article

Molecular targeting of low-grade serous and mucinous carcinomas of the ovary or peritoneum

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Abstract: Over the past decade, the strategy for clinical trial design in making progress against epithelial cancers of the ovary/peritoneum/fallopian tube has changed dramatically. The NRG [the Gynecologic Oncology Group (GOG)] Rare Tumor Committee has been a leader in this transformation. No longer does "one size fit all". Rather, separate clinical trials for rare subtypes have been developed, and, in some cases, completed. An enhanced understanding of their pathologic diagnosis, molecular biology, and clinical behavior has galvanized this change. Pathology studies have led to replacement of the International Federation of Gynecology and Obstetrics (FIGO) grading system of low-grade serous carcinoma to the binary grading system, and immunohistochemical studies have assisted in distinguishing mucinous carcinoma of the ovary from colorectal cancer. Historically, conventional chemotherapy has demonstrated very limited activity in both histologic subtypes. Preclinical studies have identified and elucidated genes and pathways in both—*MAP kinase* pathway, *IGF1-R*, the angiogenesis pathway, and possibly, the *PI3K/AKT/mTOR* pathway in low-grade serous carcinoma, and *KRAS*, *HER-2/neu* amplification, *src*, and the angiogenesis pathway in mucinous carcinoma—that may serve as targets for novel therapies. MEK inhibitor (MEKi) therapy has shown promising activity in patients with recurrent low-grade serous carcinoma, and the current emphasis is focused on the second generation of MEKi trials and combinations of MEKi and inhibitors of the PI3K/AKT/mTOR pathway. For mucinous carcinoma, mEOC/GOG 0241 was designed to test both a colorectal cancer-type chemotherapy regimen and anti-angiogenesis therapy but closed prematurely due to slow accrual related to the rarity of this subtype. The experience with targeted therapy is otherwise extremely limited to date. The hope is that lessons learned from the failure of the mEOC/GOG 0241 trial will inform future trials. In summary, there is tremendous potential for progress against these two rare histologic subtypes by leveraging our knowledge of their molecular biology and translating this understanding into improved, novel therapeutics.

Keywords: Ovarian cancer; low-grade serous carcinoma; mucinous carcinoma; targeted therapy

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Introduction

Historically, all women with epithelial ovarian cancer or primary peritoneal cancer, regardless of their tumor's histologic subtype, have been treated similarly within single-institution, investigator-initiated, or cooperative group trials. However, within the past few years, based on our enhanced understanding of the heterogeneity of ovarian or peritoneal cancer related to refinement of pathologic criteria, elucidation of molecular biology, and reports of clinical behavior, separate clinical trials for specific subtypes have been developed and conducted. One of the leaders in this transformation has been the Rare Tumor Committee of the Gynecologic Oncology Group (GOG), which was established in 2005. In 2014, the GOG merged with other cooperative groups to form the new NRG Oncology cooperative group. Since 2005, several clinical trials for rare

ovarian/peritoneal cancer subtypes—clear cell carcinomas, mucinous carcinomas, and low-grade serous carcinomas, and non-epithelial tumors—have been activated.

The overarching principles by which the GOG (NRG) Rare Tumor Committee has operated have included the following: (I) separate clinical trials for distinct histologic subtypes; (II) investigation of novel targeted agents based on promising pre-clinical studies, whenever possible; and (III) inclusion of robust tissue acquisition and translational research components within each trial.

Nevertheless, the study of rare ovarian cancers remains logistically challenging for a variety of reasons. Small patient numbers within each of the subtypes represents a threat to meeting accrual targets. This realization has led to strategies to overcome this limitation, including intergroup trials and international consortia or other collaborations. Additional issues include the implementation of novel trial designs with which to efficiently study these rare tumors and accurate pathologic diagnostic criteria for eligibility. For example, prospective digital pathology review rather than the usual post-hoc central pathology review is necessary for trial screening in most of such investigations. Furthermore, the financial, regulatory, and nursing and data management efforts associated with opening any clinical trials are particularly burdensome when one considers that any single institution may accrue a relatively small number of patients to a multi-institutional or cooperative group trial of a rare tumor.

This review will focus on two rare subtypes of epithelial ovarian cancer—low-grade serous carcinoma and mucinous carcinoma—and will provide an overview of progress to date and research opportunities for the future.

Low-grade serous carcinoma

Background

The story of the evolution of progress in the study of low-grade serous carcinoma of the ovary/peritoneum really began in the early 1990s when Dr. Silva first proposed the binary grading system for serous carcinoma (1). After over a decade of experience using this system rather than that of the International Federation of Gynecology and Obstetrics (FIGO), the findings were reported in 2004 (2). This seemingly trivial proposal for replacement of the time-honored 3-tier grading system (grade 1-3) with the 2-tier system (low grade and high grade) actually galvanized the medical community to seriously study the significant differences between low- and high-grade serous carcinoma in terms of molecular biology and clinical behavior. Prior to this time, FIGO grade 2 serous carcinoma was not well characterized and was considered by some to be more like FIGO grade 1 and by others to be more associated with FIGO grade 3.

Over the ensuing decade since this initial report, the binary grading system for serous carcinoma has been widely studied and ultimately adopted (3-10). During this same period, the molecular biology of low-grade serous carcinoma has begun to be elucidated (11-31), and the clinical behavior better understood (32-46).

Pathology

The binary grading system for serous carcinoma is based primarily on the assessment of nuclear atypia with the mitotic count used as a secondary criterion (2). In their study of 100 cases of serous ovarian carcinoma—50 low-grade and 50 high-grade—from the MD Anderson Cancer Center files, Malpica *et al.* reported that, in comparison with the FIGO grading system, all but one of the 36 FIGO grade 1 cases were classified as low-grade, and all of the 11 FIGO grade 3 cases were classified as high-grade (2). However, of the 53 FIGO grade 2 cases, 15 were classified as low-grade and 38 as high-grade (2). The results of this study simply underscore the confusion surrounding the FIGO grade 2 category and why migrating to a 2-tier grading system makes so much sense. A further important finding of this study was the coexistence of serous tumor of low malignant potential and low-grade serous carcinoma in 60% of cases. Subsequent reports only further strengthened the observation that the FIGO grading system is flawed and the wisdom surrounding dichotomization of the grading system for serous carcinoma (3,4,6-8). Bodurka *et al.* conducted an ancillary study of GOG Protocol 158 in which 241 cases of serous carcinoma from the paclitaxel/carboplatin arm of the trial, which had been classified using the FIGO grading system, were re-classified using the MD Anderson binary grading system (8). When analyzed using the original FIGO grading system, there was no difference in clinical outcome in patients with grade 2 or 3 tumors in multivariate analysis (8).

Molecular biology

Molecular and genetic investigations over the past decade have brought the biology of low-grade serous carcinoma into much sharper focus. Based on available evidence, we

currently believe that low-grade serous carcinoma may arise following an initial diagnosis of serous tumor of low malignant potential or *de novo* (32-34,47-49). The weight of evidence further suggests that the mitogen-activated protein kinase (MAPK) pathway plays a prominent role in the pathogenesis of both entities. Genomic profiling studies have demonstrated that low-grade serous carcinomas segregate from high-grade serous carcinomas but are similar to serous tumors of low malignant potential (15,17). Compared with high-grade serous carcinomas, low-grade serous carcinomas have a much lower frequency of p53 mutations or p53 expression (18,19), greater expression of estrogen receptor (ER) and progesterone receptor (PR) (21), greater expression of PAX2 (23), overexpression of anterior gradient homolog 3 (AGR3) (50), and overexpression of insulin like growth factor 1 (IGF-1) (51). Although germline BRCA mutations occur in a relatively high proportion of women with high-grade serous carcinoma, low-grade serous carcinoma does not appear to be part of the hereditary breast-ovarian cancer syndrome (52,53).

In 2003, Singer *et al.* reported their study of 182 ovarian tumors, including 51 serous tumors of low malignant potential and 21 low-grade serous carcinomas (13). *KRAS* mutations were reported in 33% of serous tumors of low malignant potential and in 35% of low-grade serous carcinomas, and *BRAF* mutations were found in 28% and 33%, respectively. Subsequent reports of low-grade serous carcinoma, however, seemed to confirm a 20-40% frequency of *KRAS* mutations but a much lower frequency of *BRAF* mutations—2-6% (24,54). Based on their findings, Wong *et al.* concluded that the low frequency of *BRAF* mutations in advanced stage low-grade serous carcinomas compared with serous tumors of low malignant potential suggested that the former are more likely derived from serous tumors of low malignant potential without *BRAF* mutations (24). A more recent study appeared to confirm these observations (28). In other words, the presence of a *BRAF* mutation in an advanced stage serous tumor of low malignant potential may somehow protect against the development of a subsequent low-grade serous carcinoma. In a study of 23 patients with an original diagnosis of serous tumor of low malignant potential who subsequently recurred with low-grade serous carcinoma, patients with *KRAS G12V* mutations had shorter survival times than those with either *KRAS G12D*, wild-type, or rare *KRAS* variants (HR =4.77; P=0.023) (29). And, although it appears that aberrations of the PI3K/AKT/mTOR pathways are relatively rare in low-grade serous carcinoma (27), there is some evidence that dual blockade of the *MAP kinase* and PI3K/AKT/mTOR pathways may be associated with enhanced activity compared with MAP kinase pathway blockade alone (see below).

Clinical behavior

Surgery is a major modality of treatment in low-grade serous carcinoma, as it is in all histologic subtypes. For most patients, primary surgery, including surgical staging for patients with apparent early-stage disease and cytoreductive surgery for those with metastatic disease, is the initial treatment. Fertility-sparing surgery is an option for selected young patients. For selected women with extensive metastatic disease or significant co-morbidities, neoadjuvant chemotherapy with interval cytoreductive surgery may be recommended. In such cases, either fine needle aspiration/core biopsy or a minimally invasive surgical procedure to establish an accurate diagnosis is performed prior to starting chemotherapy.

Several predominant themes have emerged from studies of the clinical course of low-grade serous carcinoma of the ovary or peritoneum. In an ancillary study of GOG protocol 182, Fader *et al.* reported the details regarding 189 patients with FIGO grade 1 serous carcinoma (a surrogate for low-grade serous carcinoma) (40). On multivariate analysis, only residual disease status following primary surgery was significantly associated with overall survival (OS). Patients with microscopic residual disease had a significantly longer median progression-free survival (PFS) (33.2 months) and OS (96.9 months) compared with those with residual 0.1-1.0 cm disease (14.7 and 44.5 months, respectively) and more than 1.0 cm of residual disease (14.1 and 42.0 months, respectively). The overall pattern of these results closely resembles that of epithelial ovarian cancer in general. In a second study from the same dataset, serum CA 125 values were analyzed (42). Although pre-treatment CA 125 was not prognostic of outcome, patients with CA 125 levels that normalized after 1-3 cycles of chemotherapy were 60-64% less likely to experience disease progression as compared to those whose CA 125 levels never normalized or normalized after four cycles (P≤0.024). Normalization of CA 125 levels before the second cycle was negatively associated with death, with an HR of 0.45 (P=0.025).

Previs *et al.* reported the Duke experience with 81 women with low-grade serous carcinoma of the ovary (44). On multivariate analysis, obesity (HR =2.8) and optimal tumor debulking (HR =0.05) were significant predictors

of OS. Additionally, obesity was not associated with worse disease-specific survival, suggesting that mortality of obese patients may have been attributable to other comorbidities.

In the initial systematic study of metastatic low-grade serous carcinoma of the ovary by Gershenson *et al*., in which 112 women with stages II-IV low-grade serous carcinoma were retrospectively analyzed, major features included a relatively young age at diagnosis (median age =43 years), prolonged OS (median OS =82 months) compared with high-grade ovarian cancers, and relative chemoresistance as reflected by the surrogate marker of persistent tumor at the completion of primary treatment (48% of patients) (32). After adjusting for other variables, persistent disease after primary chemotherapy was associated with a shorter PFS time (HR =2.64; P=0.03). The theme of relative chemoresistance, thought to be related to the indolent nature of low-grade serous carcinoma, was subsequently also observed in reports of patients treated with neoadjuvant chemotherapy (34), patients with primary peritoneal low-grade serous carcinoma (36), and patients with recurrent disease (35). Nevertheless, chemotherapy generally remains the standard therapy for women with low-grade serous carcinoma until such time that it is replaced by evidence-based alternative treatment. In addition, in the report of chemotherapy for recurrent low-grade serous carcinoma, 60% of women had stable disease (SD) for a period of time. Whether the frequency of stable disease is more related to tumor biology or a therapeutic effect remains unresolved.

For some women, hormonal therapy may offer a greater benefit than chemotherapy with less associated toxicity (39). In a report of 64 women with recurrent low-grade serous carcinoma who received 89 separate hormonal therapy regimens, 9% of patient-regimens resulted in an objective response, and 62% of patient-regimens resulted in SD (39). In addition, ER/PR expression data were available in 50 patients in this study. Patients with ER+/PR- tumors had a shorter time to progression (HR =1.8) than patients with ER+/PR+ tumors; however, this observation approached but did not reach statistical significance (P=0.056). Thus, hormonal therapy remains a reasonable and potentially active treatment for women with metastatic low-grade serous carcinoma.

Given the realization that cytotoxic chemotherapy has limited activity in low-grade serous carcinoma, a search for more effective systemic therapies is warranted. As with most cancer types, investigators have principally focused on the study of targeted therapies over the past few years. Coupled with these efforts is the continued study of the molecular biology of low-grade serous carcinoma through additional basic science and translational research studies.

Table 1 Low-grade serous carcinoma of the ovary/peritoneum: molecular biomarkers/potential targets

Gene or pathway	Frequency	Potential active agents	References
KRAS	20-40%	MEKi	(13,24,27-29,54)
BRAF	2-6%	BRAFi	(13,24,27-29,54)
IGF-1R	Overexpressed compared to SBOT and HGSC	IGF-1Ri	(51)
Angiogenesis	–	Anti-angiogenesis agents, e.g., bevacizumab, etc.	(43,55)
PI3K/AKT/mTOR	Rare	PI3Ki AKTi mTORi	(27)

Abbreviations: SBOT, serous borderline tumor; HGSC, high-grade serous carcinoma.

Targeted therapeutics

Based on preclinical research findings, potential genes or pathways for targeting low-grade serous carcinoma include the MAPK pathway, IGFR-1, the angiogenesis pathway, and possibly the PI3K/AKT/mTOR pathway (*Table 1*). The MAPK signaling pathway is one of the most activated and best characterized in cancer (56). The MAPK cascade is triggered by the binding of a ligand that ultimately leads to phosphorylation of *ERK* (57,58). Thus, *MEK* is a good candidate for targeted therapy, and a number of MEK inhibitors (MEKi) have been developed in the past few years (59,60). Preclinical studies of ovarian cancer demonstrated significant growth inhibition in cell lines with *KRAS* or *BRAF* mutations compared with cell lines with wild-type cells (61,62). In view of the cumulative data indicating mutations within the MAPK pathway, as discussed above, exploration of MEKi in patients with low-grade serous carcinoma was a natural progression.

In a landmark GOG phase II trial (GOG 0239), Farley

et al. demonstrated promising results with a MEKi, selumetinib (54). Fifty two women with recurrent low-grade serous carcinoma were enrolled in this trial and treated with the MEKi, selumetinib 50 mg twice daily. The overall response rate (ORR) was 15%, with one complete response (CR) and seven partial responses (PRs). Another 65% of patients in the trial had SD. The median PFS was 11.0 months. The most common toxicities were gastrointestinal (GI) [13], dermatologic [9], and metabolic [7]. Three patients experienced grade 4 toxicities—one each cardiac, pain, and pulmonary. Mutational analysis was conducted on formalin-fixed, paraffin-embedded (FFPE) tumor samples from 34 patients in this trial. The primary tumor accounted for 82% of the cases. In these 34 cases, there were 2 (6%) *BRAF* mutations and 14 (41%) *KRAS* mutations. In this study, there was no correlation between mutations of *BRAF* or *KRAS* and objective response. Subsequently, the promising results of this trial in the context of the relatively low response rates of low-grade serous carcinoma to either chemotherapeutic or hormonal agents prompted further investigations.

Three ongoing phase II or III clinical trials have emerged from this experience. Each of these trials includes a different MEKi. The MILO trial (NCT01849874) is an open-label phase III protocol that randomizes patients with recurrent low-grade serous carcinoma to either chemotherapy [physician's choice of pegylated liposomal doxorubicin (PLD), paclitaxel, or topotecan] or MEK162. A second trial (NCT01936363) has a randomized phase II design and includes the MEKi, pimasertib, with either placebo or SAR245409 (a PI3K/mTOR inhibitor). GOG 0281 is a randomized phase II/III trial (NCT02101788) that has been activated through NRG Oncology. This trial includes a randomization between standard of care (physician's choice of letrozole, tamoxifen, PLD, weekly paclitaxel, or topotecan) and MEKi monotherapy, trametinib. This trial also includes a robust translational research component, with fresh and archival FFPE tissue for next generation sequencing and proteomics as well as cell-free DNA and pharmacokinetic studies.

As noted above, the angiogenesis pathway may also be a target in patients with low-grade serous carcinoma. Bidus *et al*. reported three patients with apparent recurrent low-grade serous carcinomas (one with primary peritoneal low-grade serous carcinoma, one with ovarian low-grade serous carcinoma, and another with a mixed low-grade serous-endometrioid carcinoma) treated with bevacizumab, a monoclonal antibody against the vascular endothelial growth factor A (VEGF-A) (55). All three patients experienced a sustained response—two PRs and one CR. Subsequently, Grisham *et al*. reported on 17 patients with low-grade serous carcinoma of the ovary or peritoneum who received bevacizumab (43). Two patients were treated with single-agent bevacizumab and the others with a combination of bevacizumab and chemotherapy. Fifteen patients were evaluable for response, and six (40%) had a PR. An additional five (33.3%) had SD lasting 3 months or longer.

To date, there have been no clinical trials exploring the role of IGF1-R targeted therapy in women with low-grade serous carcinoma. Likewise, although an agent targeting the PI3K/AKT/mTOR pathway in combination with a MEKi was administered to a proportion of women on one of the three trials above (NCT01936363), the results of this trial are pending, and no AKT inhibitor, PI3K inhibitor, or mTOR inhibitor monotherapy trials specifically for patients with low-grade serous carcinoma have been developed.

Mucinous carcinoma

Background

As with low-grade serous carcinoma, our understanding of the pathologic diagnosis, molecular biology, and clinical behavior of mucinous carcinoma has significantly expanded over the past decade or so. Historically, mucinous carcinoma has been treated similarly to all other epithelial ovarian cancer subtypes. Our new knowledge has sharpened our focus on potential methods of improving treatment for women with this histologic subtype. However, its previously unanticipated extreme rarity has been an impediment to the development of prospective clinical trials.

Pathology

Mucinous tumors appear to represent a spectrum, from benign to borderline to invasive. The pathology of mucinous tumors of the ovary is complex and beyond the scope of this article. However, a few salient points are noted. Ovarian mucinous carcinoma is divided into intraepithelial (non-invasive) carcinoma and invasive carcinoma. Intraepithelial mucinous carcinoma is characterized by the presence of marked atypia but without stromal invasion. Invasive mucinous carcinoma is characterized by stromal invasion more than 5 mm or more than 10 mm (2). Invasive mucinous carcinoma is further divided into two types: (I) expansile (confluent) and (II) infiltrative (63,64). The prognosis of the infiltrative type is significantly worse than

that of the expansile type.

The greatest challenge in the pathologic diagnosis of mucinous carcinoma is distinguishing a primary ovarian tumor from a tumor metastatic to ovaries, typically arising in the (GI) tract. Immunohistochemistry may be helpful in distinguishing a primary mucinous carcinoma of the ovary from GI tumors metastatic to ovaries but is somewhat limited. In a study by Vang *et al*., a CK7+/CK20+ profile was the most common profile in primary ovarian tumors (74%), upper GI tract tumors (78%), and endocervical tumors (88%) but was occasionally observed in lower GI tumors (65). A CK7-/CK20+ profile was the most common profile in lower intestinal tract tumors (79%) and was uncommon in upper GI tract tumors (9%) and rarely observed in primary ovarian tumors (4%). A CK7+/CK20– profile was seen in some primary ovarian tumors (23%), upper GI tract tumors (13%), but not in lower GI tumors. Zaino *et al*. reviewed 44 cases classified as primary mucinous carcinomas within the context of a large phase III trial (66). The cases were reviewed independently by three pathologists. The pathologists reclassified the majority (57-63%) of mucinous carcinomas as metastatic to the ovary rather than as a primary ovarian tumor.

Molecular biology

Similar to low-grade serous carcinoma, primary mucinous carcinoma of the ovary has several molecular alterations that may serve as targets for systemic therapy. Approximately 43% (32-56% in various studies) of mucinous carcinomas have a *KRAS* mutation (67,68).

HER-2/neu amplification has also been observed in mucinous carcinoma of the ovary. McAlpine and colleagues found that 18.2% of 33 mucinous carcinomas contained *HER-2/neu* amplification (69). In a study of mucinous carcinomas from 49 Asian women, Chao *et al*. observed an 18.4% frequency of *HER-2/neu* positivity (70).

Another potential therapeutic target in mucinous carcinoma is *src* (71,72). And finally, based on experience with treatment of colorectal cancer, the angiogenesis pathway is also a potential target (73). In addition, angiogenesis biomarkers such as microvessel density have been observed to be increased in mucinous ovarian carcinoma compared with other histologic subtypes (74,75).

Clinical behavior

The same surgical principles as outlined above for low-grade serous carcinoma apply to mucinous carcinoma as well. However, based on a retrospective review of 107 patients with mucinous carcinoma of the ovary, Schmeler *et al*. have made the case that routine lymphadenectomy may not be necessary (76).

For women with stage IA mucinous carcinoma of the ovary, the prognosis is good. There is no definite evidence that adjuvant chemotherapy is beneficial in this subset. Whether patients with stage IC mucinous carcinoma require adjuvant therapy remains controversial. For all patients with stages II-IV mucinous carcinoma, standard therapy has consisted of paclitaxel/carboplatin ×6 cycles, or a variation on this theme (intraperitoneal chemotherapy, dose-dense paclitaxel regimen, etc.). Over the past decade, however, it has become increasingly clear that advanced stage or recurrent mucinous carcinoma has a significantly worse prognosis compared with serous carcinoma (77-83).

The Hellenic Cooperative Oncology Group reported their experience with 141 patients with stage III and IV epithelial ovarian cancer treated with primary platinum-based chemotherapy (77). The outcomes of 47 patients with mucinous carcinoma were compared with those of 97 serous carcinoma patients. The ORR was 38.5% in patients with mucinous carcinoma and 70% in patients with serous carcinoma. However, there were no significant differences in time to progression or OS. Hess *et al*. reported their experience with 81 women with advanced epithelial ovarian cancer who underwent primary platinum-based chemotherapy (78). Comparing the outcomes of 27 patients with mucinous carcinoma with 54 patients with other histologic subtypes, they found that that the mucinous carcinoma patients had significantly inferior response rate (26.3% *vs*. 64.9%), median PFS rate (5.7 *vs*. 14.1 months), and median OS rate (12.0 *vs*. 36.7 months). Three additional pooled analyses have documented significantly worse outcomes in women with mucinous carcinoma compared with those with serous carcinoma (79-81). In a study of The Surveillance, Epidemiology, and End Results (SEER) database, Schiavone reported on 40,571 women treated between 1988 and 2007 for epithelial ovarian cancer (82). The database included 4,811 patients with mucinous carcinoma; those with advanced stage disease had inferior cancer-specific survival compared with patients with serous carcinoma.

Experience with patients with recurrent mucinous carcinoma of the ovary also indicates a worse outcome compared with other histologic subtypes. Pignata reported 20 patients with recurrent mucinous carcinoma and

Table 2 Mucinous carcinoma of the ovary: molecular biomarkers/potential targets

Gene or pathway	Frequency	Potential active agents	References
KRAS	43% (32-57%)	MEKi	(67,68)
HER-2/neu	18%	Trastuzumab, pertuzumab, etc.	(69,70)
Angiogenesis	–	Anti-angiogenesis agents, e.g., bevacizumab, etc.	(74,75)
Src kinase	Overexpression compared to serous carcinoma	Src kinase inhibitors	(71,72)

388 patients with recurrent cancer of other histologic subtypes—all with platinum-sensitive disease treated with platinum-based chemotherapy (83). The response rate for the mucinous carcinoma patients was significantly worse—36.4% *vs*. 62.6% (P=0.04). Thus, novel therapies for women with mucinous carcinoma of the ovary are clearly needed.

Targeted therapeutics

Based on preclinical research findings, potential genes or pathways for targeting mucinous carcinoma include *HER-2/neu* amplification, *KRAS*, *src*, and the angiogenesis pathway (*Table 2*). However, there is very limited information on experience with targeted therapy in women with mucinous carcinoma of the ovary.

McAlpine *et al*. reported one patient with recurrent mucinous carcinoma of the ovary who experienced a dramatic response to the anti HER2 monoclonal antibody, trastuzumab, in combination with various chemotherapeutic agents (69). Related to the high frequency of *KRAS* mutations in colorectal cancer, targeting of the *MAP kinase* pathway has not produced promising results to date (31,59). For example, Hochster *et al*. conducted a phase II study of selumetinib plus irinotecan as second-line therapy in patients with *KRAS*-mutated colorectal cancer (84). Three patients (9.7%) had a PR, and 16 patients had stable disease for ≥4 weeks. To date, there have been no trials of a MEKi in patients with recurrent mucinous carcinoma of the ovary. Likewise, there have not yet been any trials of *src* inhibitors in this patient population.

The mEOC/GOG 0241 trial was designed to study the activity of a colorectal cancer-type regimen in women with newly diagnosed metastatic mucinous carcinoma of the ovary. This was a phase III trial that randomized women to either the control arm of paclitaxel/carboplatin ×6 cycles *vs*. the combination of capecitabine/oxaliplatin ×6 cycles. Additionally, there was a secondary randomization to bevacizumab or no bevacizumab to test the activity of anti-angiogenesis therapy. The trial was opened in both the UK and US but suffered from slow accrual related to the rarity of ovarian mucinous carcinoma and was closed prematurely.

Summary

In summary, while our understanding of low-grade serous carcinoma of the ovary/peritoneum and mucinous carcinoma of the ovary has expanded significantly over the past decade, the experience with targeted therapy for these rare histologic subtypes is still quite limited. However, the good news is that our approach to the treatment of ovarian/peritoneal/fallopian tube cancer has been transformed during the same period. No longer are we continuing to pursue the "one size fits all" strategy. Currently, for low-grade serous carcinoma, the emphasis is on defining the activity of MEKi therapy, or, in some cases, combinations of MEKi and inhibitors of the PI3K/AKT/mTOR pathway. On the other hand, the extreme rarity of mucinous carcinoma of the ovary combined with the failure of mEOC/GOG 0241 has, for the time being, put a damper on separate targeted agent trials for women with this subtype. The hope is that lessons learned from this experience will inform the design and conduct of future trials. In summary, there is tremendous potential for progress against these two rare histologic subtypes by leveraging our knowledge of their molecular biology and translating this understanding into improved, novel therapeutics.

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