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Expert Opinion

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The role of secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer: what do the trials tell us?

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In the current issue of the *Journal of Gynecologic Oncology*, Dr. Ehmann and colleagues discuss the clinical context of the findings of GOG-0213, relative to those recently presented (American Society of Clinical Oncology [ASCO] 2020), particularly focusing on the discordance in overall survival (OS) findings [1]. To this effect, they have labeled GOG-0213 as a "negative trial" and have sought to contrast the trial's design and findings to DESKTOP-III and SOC-1. It is important to note at the outset that the manuscripts from DESKTOP-III and SOC-1 have yet to be peer-reviewed and data presented in the opinion reflect those published in abstract form and presented at the virtual ASCO meeting in May 2020. However, the context of the question asked by the authors also underscores the primary reason why the question is best addressed in a randomized trial—namely, an inherent sense that it should have been "positive."

In their preamble, the authors quote a meta-analysis by Bristow, et al., which demonstrated that complete cytoreductive surgery is the "strongest independent factor" for OS, and linearly related the degree of resection to added months of OS [2]. It is important to state that the strong selection bias in the index trials cannot be overcome by any meta-analytical technique; hence, the importance of the 5 attempted randomized clinical trials addressing secondary cytoreduction in platinum-sensitive recurrent ovarian cancer.

The authors summarize the findings from the available data of the 3 trials for which we have information. Two additional trials, EORTC-55963 (closed for futility, NCT00006356) and SOCceR (ongoing) are not included in their review. There are some important observations to be made in rebuttal to the opinion:

1. Surgical candidacy: The authors rightly point out that the 3 trials used different methodology to provide guidance for surgical candidacy. As outlined in the published manuscript and provided in the online Protocol document, the goal of patients participating in the surgical objective of GOG-0213 was complete gross resection (CGR) [3]. Presence of extra-abdominal organ disease, ascites (by radiographic determination) and carcinomatosis were among factors considered reflective of poor surgical candidacy. Both DESKTOP-III and SOC-1 used structured algorithms to provide guidance, though with the same goal–CGR. Interestingly, the rate of CGR by each of these techniques is numerically (67%–76.7%) and statistically similar [4,5]. It is important to recall

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that DESKTOP-II, the trial that validated the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) score, noted that patients who were AGO score negative still had a CGR rate of 63% and that surgery performed at high volume recruiting centers did not have a more favorable outcome compared with low volume centers [6].

2. Patient selection strategy: A commonly presented conclusion when addressing the outcomes of the three trial is that proper patient selection is important. The argument for this contention resides in the observation that if surgery is undertaken and is not able to render a post-operative outcome of CGR, patients fair poorly. However, that outcome does not address whether surgery should be considered in the first place. In other words, patients not going on to surgery do not run the risk of incomplete resection. All 3 trials demonstrate (and to the same degree), that patients achieving CGR do better than patients not achieving CGR, however only GOG-0213 demonstrates parity of the CGR cohort to all patients undergoing non-surgical treatment.
3. Individualization: Another often stated contrast between the trials is that only in GOG-0213 were patients enrolled by physician discretion. In their opinion, the authors state that DESKTOP-III and SOC-I used "strictly defined criteria." This is clearly an overstatement. Indeed, we do not know the number of patients meeting AGO or iMODEL criteria who were not placed on trial. However, from DESKTOP-II, we do have a hint of what this proportion might be as 113/261 (42%), AGO score positive patients did not undergo surgery. Why? There are many factors that account for this including, patient acceptance, medical safety of surgery, and poor likelihood for CGR. As stated in their publication of DESKTOP-I, the criteria were developed to be used as guidance for high probability for CBR; to isolate selection criteria to an algorithm alone undermines its intent [7]. For instance, no patients included in the development of the AGO score had undergone neoadjuvant chemotherapy. Would this factor alone dissuade consideration of surgery in a patient with an isolated nodal recurrence? Further, in the SOC-1 trial, patients not meeting the iMODEL score were allowed to undergo further evaluation with positron emission tomography-computed tomography scanning where 2 physicians could override the criteria to enroll the subject. In this case, 11% of patients in the SOC-1 trial were enrolled by physician-directed individualization. It is clear that in each of these trials, consideration of disease status, patient desire and medical fitness was appropriately weighed prior to trial enrolment.
4. Differential outcomes in the surgical arm: As stated the median progression-free survival (PFS), OS, and 3-year OS rate among the three trials are similar, highlighting the remarkable consistency of surgical outcomes among these three trials. Perhaps most striking is the morphology of the Kaplan-Meier survival curves, which result from similar time-dependent event rates. One would expect far greater differences for these endpoints and curve morphology should there have been factors such as case selection or quality of surgical outcomes at play.
5. Patient demographics: As raised by Ehmann et al. [1], GOG-0213 did have a more diverse patient population, which was highlighted to bolster the potential impact of racial and ethnic impact particularly as it relates to underlying gBRCA populations. However, work performed specifically in the Asian population has supported similar rates of gBRCA mutation carriers in high-grade serous ovarian cancer as the US population [8]. Further, OS analysis specifically addressing the Asian and non-Asian populations showed no difference in treatment effect between cohorts and no deviation from the results in the overall intent-to-treat population. The impact of this factor alone on the results of GOG-0213 is judged to be insignificant. However, since gBRCA status is an important prognostic variable, imbalance not controlled for by simple

randomization could impact the performance of the arms among the trials. More work is planned to explore this avenue. Further, since gBRCA status is an important predictive variable relative to poly (ADP-ribose) polymerase inhibitor (PARPi) treatment, imbalances due to subsequent treatment with PARPi's will need to be carefully considered [9]. However, during the conduct of these trials, PARPi availability was limited and likely contributed a minimal degree.

6. Unknown variables: There are, however, a number of variables that are difficult to assess for impact. Cross-over to surgery in subsequent lines of therapy is unknown but, unlike the SOC-1 trial, likely minimal. Factors for subsequent surgery entail other considerations such as intestinal complications of advancing disease, however, these effects would be expected in both arms of the trial. Only in SOC-1, was it a patient desire and investigator intent to offer crossover surgery to control patients as well as post-progression surgery in patients randomized to secondary cytoreduction. This latter observation will likely challenge the interpretation of OS in that trial, a co-primary, hierarchical endpoint.

While the aforementioned list of cross-trial contrasts demonstrates more similarities than differences, there are a number of important characteristics that have not been previously fully addressed:

1. Post-progression survivorship: The most important variable to consider in a trial evaluating OS is the anticipated post-progression survivorship of the cohort. When GOG-0213 was written, OS estimates for this cohort was expected at a median 22 months; more than 2.5 times lower than was observed. This is critically important because the duration of time available to a patient randomized to an intervention predicates what treatments may be available to them during the follow-up period. It just so happens that all three trials were conducted during a time when treatment for platinum-sensitive recurrent ovarian cancer was changing, offering a greater variety of options, such as maintenance therapy; options that at the least extended PFS and at most OS. Indeed, GOG-0213 was designed to first address the impact of bevacizumab added to paclitaxel and carboplatin followed by maintenance bevacizumab until progression on OS. Demonstration of that endpoint highlights that the choice of post-surgical therapy and the potential for several subsequent lines of therapy could have affected the primary endpoints, positively or negatively depending their use and balance in each trial [10].
2. Interaction between the interventions: It may be naïve to discount that surgery and post-surgical treatment are independent factors to survivorship. Unless conducted in a bifactorial manner, the impact of this effect cannot be adequately assessed. GOG-0213 did evaluate both the surgical and chemotherapy objectives when initially launched. Many more patients (about 4 of 5 enrolling) were eligible only for the chemotherapy objective in GOG-0213 due to disease distribution and medical fitness for surgery. The remaining 107 patients were randomized in a bifactorial fashion to first surgery (or not) and then to bevacizumab (or not). While substantially underpowered to formally address individual arm interactions, there does appear to be an interaction between the two treatment modalities but mostly detrimental in the absence of post-operative bevacizumab use.
3. Preoperative disease volume: While all three trials appear to have similar surgical outcomes but disparate control arm outcomes, there may be an imbalance of patients presenting with “high-risk” disease where surgical effort may have contributed to a

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differential benefit in the trial population. If this were the case, one might expect that both arms in GOG-0213 (as representing lower disease volumes) would appear superior to DESKTOP-III and SOC-1, and more aligned with each other. This was not the case, thus a closer evaluation of preoperative disease volume, genomic status of the patient population and post-randomization treatment paradigms are important planned analyses of future work.

The final point to recall is that GOG-213 is a superiority trial with a null hypothesis that pre-chemotherapy surgery would not provide longer OS than chemotherapy alone. We were unable to reject this hypothesis. Thus, it is not a "negative" trial as is purported, but a failed "superiority" trial. The nuance is important because it reflects how hypotheses are formulated and formally tested. We await more data to help clarify its role, if any, in this setting.

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