Comment on: “Cost-Effectiveness of Niraparib Versus Routine Surveillance, Olaparib and Rucaparib for the Maintenance Treatment of Patients with Ovarian Cancer in the United States”

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Dear Editor,

We read with interest the article by Guy et al. [1] detailing a cost-effectiveness model comparing niraparib, a poly(ADP-ribose) polymerase inhibitor (PARPi), to routine surveillance and two other PARPis approved for maintenance treatment of recurrent ovarian cancer, olaparib and rucaparib. The authors concluded from their analysis that niraparib was less expensive and more cost effective than olaparib and rucaparib, and the incremental cost-effectiveness ratio (ICER) fell within an acceptable range compared to routine surveillance. However, we noted several fundamental problems with the lack of comparability of populations, as well as methodological flaws and violations of statistical assumptions within the model. Although we found the authors' methods flawed overall, in this letter, we comment only on the main problems with the comparison between niraparib and rucaparib.

The authors mention that the analysis of niraparib vs. rucaparib is “a naïve side-by-side comparison” of results from the ENGOT-OV16/NOVA study for niraparib [2] and the ARIEL3 study for rucaparib [3]. A naïve indirect comparison or analysis of two treatment groups as if they were from a single trial without adjustment for potential between-trial variability is not a recommended method of analysis because the homogeneity assumption is nearly impossible to meet [4]. For the homogeneity assumption to be met, the

groups being compared should not have been selected with different inclusion/exclusion criteria or undergone data collection via different methodologies [4]. Throughout their paper, the authors violate this assumption, rendering the model and results invalid.

First, the niraparib and rucaparib populations analyzed within the cost-effectiveness model are dissimilar. Somatic *BRCA*-mutant (*BRCA*mut) patients were included in the “non-germline *BRCA* (non-*gBRCA*)” group for the niraparib data [2], but they were classified in the *BRCA*mut group for the rucaparib data [3]. This dissimilarity leads to bias in assessing efficacy because somatic *BRCA*mut patients have been shown to respond comparably to *gBRCA*mut patients (and better than wild-type *BRCA* patients) in the maintenance and treatment settings of recurrent ovarian cancer [2, 3, 5, 6]. For the non-*gBRCA* group, the median progression-free survival (mPFS) of 9.3 months based on a blinded independent central review (BICR) was used for niraparib, whereas a weighted average of the wild-type *BRCA*/genomic high loss of heterozygosity and wild-type *BRCA*/loss of heterozygosity low mPFS numbers (8.2 months) was used for rucaparib because ARIEL3 did not report a mPFS for non-*gBRCA* patients at the time of the primary analysis. These data have been reported recently for rucaparib [7] and show higher mPFS for the non-*gBRCA* population (11.1 months for BICR-assessed mPFS and 8.6 months for investigator-assessed mPFS) than that calculated by Guy et al. [1].

Furthermore, the efficacy assessments used for the model are also not comparable. Their model included the BICR-assessed mPFS for niraparib *gBRCA* (21.0 months) [2] vs. investigator-assessed mPFS (16.6 months) for rucaparib [3]. In three phase III studies investigating PARPis for maintenance treatment of recurrent ovarian cancer, mPFS was longer in BICR-assessed than investigator-assessed progression-free survival (PFS) [2, 3, 8]. Moreover, results from these three studies demonstrate that inconsistency in efficacy assessments used in the model by Guy et al. leads to bias in

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the overall results. Given that BICR-assessed PFS data have been reported for all three PARPis, those data should have been used consistently across all treatment groups in the analysis. Thus, the more appropriate comparator for rucaparib is the BICR-assessed PFS for patients with *BRCAmut* disease: 26.8 months. In the case of rucaparib, the BICR-assessed mPFS is almost 10 months longer than investigator-assessed mPFS [3].

The adverse event (AE) data used in the treatment cost calculations were also not presented uniformly for each agent. For example, the authors only included the rates of grade 3–4 niraparib-associated thrombocytopenia (33.8%) in their cost analysis [1]. In contrast, they present dose interruption or reduction data for any-grade (i.e., grades 1–5) rucaparib-associated thrombocytopenia (18.0%). The correct comparator should have been the rate of grade 3–4 rucaparib-associated thrombocytopenia (5.1%) [3]. Across the AE data, the authors presented the rates of dose interruption or reductions for any-grade AEs for rucaparib instead of the grade 3–4 AE rates they presented for niraparib.

We also identified methodologic issues and inappropriate assumptions within the model itself. For example, the authors assumed that overall survival duration is two times that of PFS, based on what was seen in a phase II study (Study 19) of olaparib in recurrent ovarian cancer [8]. The relationship between overall survival and PFS has not been demonstrated sufficiently in the literature. In fact, the National Institute for Health and Care Excellence negatively critiqued the use of the overall survival calculation from Study 19 in their own review of the authors' model [9].

Additionally, the cost/efficacy data in their ICER calculation are mismatched. The analysis presents PFS data for niraparib based on the starting dose of 300 mg once daily; however, the cost data were calculated for the step-down dose of niraparib 200 mg once daily (based on the dose reduction rate observed with niraparib). Therefore, the ICER calculation uses different data scenarios for niraparib in the numerator than that in the denominator:

$$\text{ICER} = \frac{\Delta \text{Costs (based on step-down niraparib dose)}}{\Delta \text{Efficacy (PFS based on starting niraparib dose)}}$$

Although their cost analysis was based on the rate of dose reductions for niraparib, the dose reduction rate for rucaparib was not similarly considered; thus, Guy et al. compare the starting dose for rucaparib against the modal dose for niraparib, which is not a valid comparison.

In summary, we observed several comparability problems that violate homogeneity assumptions, as well as inconsistent data presentation and previously documented methodological flaws within the Guy et al. model. All of our observations seriously call into question the validity of the conclusions the authors draw from their analysis, including

whether niraparib is in fact the most cost-effective agent. It is essential when making comparisons between trials that proper statistical methods are employed, data are selected carefully and consistently, and proper adjustments are made to ensure the control of inter-trial variability.

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Compliance with Ethical Standards

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Conflict of interest Katrine Wallace, Sandra Goble, Jeff Isaacson, Lara Maloney, Terri Cameron, and Josh Bedel are employees of Clovis Oncology, Inc., and may own or have stock options in the company.

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