Comment on 'Population-adjusted indirect treatment comparison of maintenance PARP inhibitor with or without bevacizumab *versus* bevacizumab alone in women with newly diagnosed advanced ovarian cancer'. (*Ther Adv Med Oncol*. 2021 Sep 30;13:17588359211049639)

Ther Adv Med Oncol

2023, Vol. 15: 1–3

DOI: 10.1177/17588359231168509

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Dear Editor,

Hettle *et al.*[1] performed a population-adjusted indirect treatment comparison (ITC) between PAOLA-1 study[2] and PRIMA study[3] by selecting a high-risk group of patients enrolled in the PAOLA-1 study (modified PAOLA-1 study) who were comparable to those in the PRIMA study. They compared the progression-free survival (PFS) of the four arms: the bevacizumab (Bev) arm and the Bev + olaparib arm in the modified PAOLA-1 study, and the placebo arm and niraparib arm in the PRIMA study, and analyzed which regimen was superior. Then, Hettle *et al.* concluded that 'in biomarker-unselected and HRD-positive patients, combination treatment with olaparib plus bevacizumab as maintenance treatment improves for women with newly diagnosed advanced ovarian cancer compared with either bevacizumab or niraparib alone'. However, whether a comparison of two trials by an ITC is appropriate or not needs to be carefully evaluated.

The patients enrolled in the GOG218 study, which tested the superiority of Bev, were high-risk advanced ovarian cancer patients, 94.3% of whom had residual tumor after primary debulking surgery.[4,5] In the GOG218 study, PFS with and without Bev was almost the same up to the start of maintenance therapy. We compared the Kaplan-Meier curves of PFS from the end of first-line chemotherapy in the GOG218 study[5] with the Kaplan–Meier curves of PFS in the biomarker unselected population in the paper by Hettle *et al.*[1] (Figure 1). As a result, the median PFS of the placebo arm in the PRIMA study and the Bev initiation arm and the control arm in the GOG218 study were all about 8 months, and the Kaplan–Meier curves were very similar. On the other hand, when the Bev throughout arm of the GOG218 study was compared with the placebo + Bev arm of the modified PAOLA-1 study, which was the same treatment, the median PFS was 12 months for the former and 16 months for the latter, which was very different. In other words, the patient backgrounds of the PRIMA and GOG218 studies are similar, but the modified PAOLA-1 study appears to have a more favorable prognosis than the GOG218 study.

One reason for this bias is that the PAOLA-1 study was limited to patients who received Bev in combination with chemotherapy in the first-line treatment. One of the severe adverse events of Bev identified in the GOG218 study was intestinal perforation,[4] and risk factors for this include extensive peritoneal dissemination involving the intestinal tract. Other adverse events associated with Bev include thromboembolism and bleeding.[4] In routine practice, Bev tends to be administered to patients who are less likely to experience adverse events from Bev, so the patients enrolled in the PAOLA-1 study had less peritoneal dissemination involving the intestinal tract and fewer thrombosis than those in the PRIMA study,

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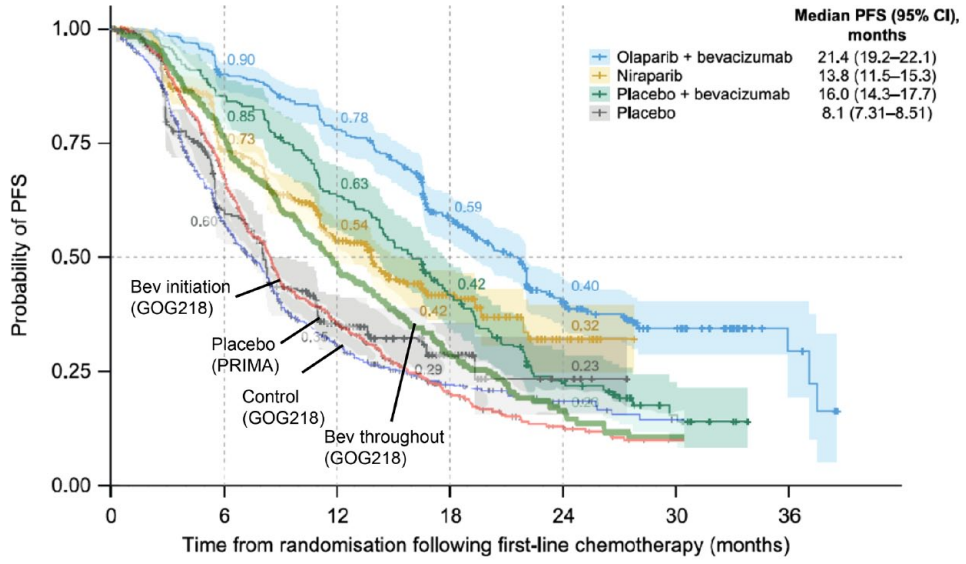

Figure 1. Comparison of Kaplan–Meier curves between GOG218 study, PRIMA study, and PAOLA-1 study.
Figure 4 in the EMA assessment report[5] for the GOG218 study was superimposed on Figure 2 in the paper by Hettle *et al.*[1] Both are open access data.

which may have led to the better outcome of the modified PAOLA-1 study. It is noteworthy that the ITC analysis by Hettle *et al.*[1] was performed without information on the localization and size of the residual tumor after surgery in the PRIMA study.

The phenomenon of a better prognosis in patients treated with Bev when the physician's choice is to use Bev or not was recently observed in a trial examining drug therapy for inoperable cervical cancer. In the GOG240 study,[6] the chemotherapy arm had a median PFS of 5.9 months and a median overall survival (OS) of 13.0 months, which prolonged to 8.2 and 17.0 months, respectively, when Bev was added.[6] On the other hand, in the KEYNOTE 826 study[7] examining the superiority of pembrolizumab, the presence or absence of Bev depended on the physician's choice. In the arm without pembrolizumab, the chemotherapy group had a median PFS of 6.2 months and a median OS of 12.6 months, similar to the chemotherapy arm of the GOG240 study, whereas the chemotherapy + Bev group had a median PFS of 10.2 months and a median OS of 24.7 months,[7] which were obviously longer than those of the Bev arm of the GOG240 study. Thus, physicians are hesitant to use Bev for high-risk patients who are prone to perforation and other adverse events, so in cohorts not randomized with or without Bev, the prognosis for the Bev group tends to be better.

In conclusion, the patients in the modified PAOLA-1 study in the paper by Hettle *et al.*[1] appear to have a more favorable prognostic background than those in the PRIMA study, and their ITC do not suggest which treatment regimen is superior.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Hidekatsu Nakai: Data curation; Funding acquisition; Writing – original draft.

Noriomi Matsumura: Conceptualization; Data curation; Writing – original draft.

Acknowledgment
Not applicable.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported in part by Japan Society for the Promotion of Science (JSPS) KAKENHI grant number 22K09630 (Grant-in-Aid for Scientific Research C for Hidekatsu Nakai).

Competing interests

Noriomi Matsumura received lecture fees from Chugai Pharmaceutical, AstraZeneca, and Takeda Pharmaceutical. Noriomi Matsumura also received a research grant from AstraZeneca. Hidekatsu Nakai has no competing interest.

Availability of data and materials

Not applicable.

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