

# Risk of severe hematologic toxicities in cancer patients treated with PARP inhibitors: results of monotherapy and combination therapy trials

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## Dear editor

The tolerability profile of PARP inhibitors often includes hematologic toxicities, and the characterization of these adverse events is important to allow effective management by clinicians. Zhou et al<sup>1</sup> recently carried out a meta-analysis of the incidence and relative risks of severe neutropenia, thrombocytopenia, and anemia events in 12 randomized controlled trials of PARP inhibitors, either as monotherapy or in combination with chemotherapy or radiotherapy. The authors concluded that olaparib resulted in a higher incidence of severe (common terminology criteria for adverse events [CTCAE] grade  $\geq 3$ ) neutropenia when compared with niraparib and veliparib; however, these conclusions are based on inappropriate and incomplete comparisons of hematologic toxicity with olaparib or veliparib in combination with myelotoxic chemotherapy versus niraparib monotherapy. While both monotherapy and combination therapy olaparib studies are discussed in the paper, the neutropenia analysis is based on olaparib data solely from studies in combination with paclitaxel or paclitaxel plus carboplatin. In order to inform the practicing clinician of the relative risk of hematologic toxicity associated with different PARP inhibitors, direct comparison needs to be conducted based on monotherapy, where applicable, as per the approved drug indication, otherwise the reader is given misleading information.

Consistent with the known myelotoxicity of carboplatin and paclitaxel, the observed incidence of severe neutropenia in studies of olaparib monotherapy is considerably lower than the figure Zhou et al<sup>1</sup> have derived from combination trials (olaparib combination arm, 49.1%; chemotherapy control arm, 36.5%). In each of three pivotal registration trials of olaparib monotherapy, the incidence of severe (CTCAE grade  $\geq 3$ ) neutropenia was less than 10% (SOLO2 and OlympiAD data include decreased granulocyte count, decreased neutrophil count, febrile neutropenia, granulocytopenia, neutropenia, neutropenic infection [OlympiAD only] and neutropenic sepsis). In Study 19 (NCT00753545), a randomized controlled trial of 265 platinum-sensitive recurrent ovarian cancer patients, the incidence of severe neutropenia was 3.7% for olaparib treated-patients (placebo arm, 0.8%).<sup>2</sup> In the SOLO2 study (NCT01874353), which recruited 295 platinum-sensitive recurrent ovarian cancer patients with a *BRCA* mutation, the incidence was 5.1% (placebo arm, 4.0%),<sup>3</sup> while 9.3% of the 205 *BRCA*-mutated metastatic breast cancer patients treated with olaparib monotherapy in the

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OlympiAD trial (NCT02000622) experienced grade  $\geq 3$  neutropenia compared with 26.4% of 97 patients in the chemotherapy comparator arm.

These grade  $\geq 3$  neutropenia data compare favorably against the niraparib monotherapy data (19.6% incidence compared with 1.7% in the control arm) and veliparib combination therapy data (29.9% incidence compared with 10.3% in the control arm) discussed by Zhou et al,<sup>1</sup> which suggest that it is inaccurate to conclude that olaparib resulted in higher incidence of neutropenia when compared with niraparib and veliparib.<sup>4</sup>

## Acknowledgment

We thank Elin Pyke, MChem, of Mudskipper Business Ltd, for medical writing assistance, funded by AstraZeneca.

## Disclosure

IA, TM, and SRT are employees of AstraZeneca, and TM and SRT own stock. The authors report no other conflicts of interest in this communication.

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