The commentary entitled “Turning the concept of synthetic lethality on its head” by Parkes and Kennedy not only clearly highlighted our recent work on the genetic interaction between BRCA2 and PARP1 but also raised some valid questions (1,2). We would like to clarify that while our findings suggest that loss of PARP1 and BRCA2 can result in synthetic viability, it does not challenge the dogma of synthetic lethality by PARP inhibition in BRCA2-deficient cells. We found that although Brca2^ko/ko mouse embryonic stem (ES) cells fail to survive, we could rescue their lethality by treating Brca2 heterozygous (Brca2^km/km) cells with olaparib prior to Cre-mediated deletion of the conditional allele. Interestingly, these “rescued” Brca2^km/km cells were found to be sensitive to olaparib, consistent with the concept of synthetic lethality. We obtained similar results in mouse hematopoietic stem cells (HSC), when mice carrying Brca2 conditional alleles were treated with olaparib and then the conditional alleles were deleted in the HSC. Like in the case of ES cells, we obtained viable Brca1^km/km HSC, but they were still sensitive to olaparib. Our observations led us to conclude that the order of loss of PARP1 and BRCA2 is important. The two opposite outcomes i.e., synthetic viability and synthetic lethality are dependent on the order in which BRCA2 and PARP1 are lost. In BRCA2-deficient cells, PARP inhibition results in synthetic lethality. In contrast, in Parp1 deficient or PARP inhibited cells, when Brca2 is deleted, it results in cell viability. When PARP is inhibited or its levels are reduced, the cells are able to protect the replication fork from MRE11-mediated degradation, which contributes to cell viability when BRCA2 is deleted. Whether PARP inhibitor pretreatment can result in synthetic viability of other BRCA2 deficient cells, especially mammary epithelial cells remain to be explored. However, we did observe a significant increase in epithelial tumors in Parp1 heterozygous mice when Brca2 was deleted using Cre under the control of K14 promoter.

The effect of PARP inhibition on the viability of Brca1^km/ks ES cells is not known. However, it was shown by Chaudhuri et al. that Parp1 deficiency protects stalled replication forks in Brca1^km/ks B-cells (3). Among other questions that currently remain unanswered, the mechanism of survival of cells by a short pretreatment of PAPR or MRE11 inhibitors is quite interesting. It is puzzling how these cells continue to survive even after PARP1 or MRE11 activity is restored. Although we do not fully understand, we proposed that MRE11 or PARP inhibition results in transient protection of the replication fork, which allows the survival of Brca2^km/km ES cells. However, because of the presence of chromosomal aberrations and increased sister chromatid exchange, these cells may acquire secondary mutations that enable them to overcome the growth arrest even after the fork protection is lost. These secondary mutations are essential for their subsequent survival.

Our findings do not challenge the importance of olaparib in treating BRCA2-deficient tumors. Our study has revealed that PARP inhibitors are not as innocuous in homologous recombination proficient cells as suggested by previous studies. Our conclusions are supported by a recent showing a significant increase in sister chromatid exchange
in BRCA2 proficient cells by PARP inhibitors (4). Because PARP inhibition in Brca2 heterozygous cells can contribute to cell viability, our findings raise concerns about the long term effect of PARP inhibitors as well as its use for cancer prevention in BRCA2 mutation carriers.

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**Footnote**

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

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