



# Combining PARP inhibitors and platinum-based chemotherapy in metastatic triple negative and/or BRCA-associated breast cancer

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*Comment on:* Rodler E, Sharma P, Barlow WE, *et al.* Cisplatin with veliparib or placebo in metastatic triple-negative breast cancer and BRCA mutation-associated breast cancer (S1416): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2023;24:162-74.

**Keywords:** Metastatic breast cancer; triple negative; PARP inhibitors; BRCAness; BRCA-like phenotype

Submitted Dec 28, 2022. Accepted for publication Jan 07, 2023. Published online Jul 03, 2023.

doi: 10.21037/tcr-23-365

**View this article at:** <https://dx.doi.org/10.21037/tcr-23-365>

Metastatic triple negative breast cancer (mTNBC) is an aggressive cancer characterized by a poor prognosis compared to other breast cancer subtypes. Even with advances in therapy such as addition of immunotherapy to chemotherapy, median overall survival (OS) remains less than 2 years (1). With substantial unmet need, there has been a lot of interest in expanding the therapeutic armamentarium. Regardless of germline or somatic *BRCA* mutation status, mTNBC can share characteristics with cancers which arise in patients with homologous recombination deficit (HRD). In this setting which has been termed BRCAness (2), DNA double strand breaks are repaired by more error-prone pathways such as non-homologous end joining repair (3). This supports the study of drugs targeting HRD in mTNBC.

In their recent publication in *Lancet Oncology*, Rodler *et al.* (4) present the results of the S1416 trial. This was a well-conducted, randomized trial which recruited 335 participants with mTNBC (>95% of participants) or metastatic estrogen receptor (ER) and/or progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer with known or suspected deleterious germline *BRCA1* or *BRCA2* mutation (<5% of participants). Eligible participants were then assigned to receive 21-day cycles of cisplatin (75 mg/m<sup>2</sup> intravenously

on day 1) in combination with either veliparib (300 mg orally twice a day on days 1–14) or placebo. Participants could have received up to one line of chemotherapy for metastatic disease.

The trial utilized a novel definition of BRCAness. Among patients with wildtype germline *BRCA1/2* mutation, BRCAness was defined as a genomic instability score of 42 or higher, somatic *BRCA1/2* mutation, *BRCA1* promoter methylation, and/or germline mutation in homologous recombination repair (HRR) genes (excluding *BRCA1/2*). Using these criteria, the wildtype germline *BRCA1/2* population was classified into BRCA-like and non-BRCA-like phenotype groups. Among the 82% of patients with available results, 48% were BRCA-like and 52% were non-BRCA-like.

Initial results after a median follow-up of 11.1 months showed that the addition of veliparib was not associated with a significant difference in its primary endpoint of progression-free survival (PFS) for the germline *BRCA1/2*-mutated group [hazard ratio (HR), 0.79; 95% CI, 0.38–1.67; P=0.54] or in the non-BRCA-like group (HR, 0.89; 95% CI, 0.60–1.33; P=0.57). However, there was a statistically significant, but modest magnitude difference in PFS for the BRCA-like group (HR, 0.57; 95% CI, 0.37–0.88; P=0.010). This significant relative effect translated to a 1.7 months

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absolute gain in median PFS, but there was no statistically significant improvement in OS. There was no difference in survival in any subgroup with numerically more events in the veliparib arms in all subgroups other than the BRCA-like group which showed a non-significant improvement in survival with veliparib which differed by 1.8 months at the median.

Of note, in the BRCA-like group, patients were allowed to continue veliparib (or placebo) after chemotherapy was discontinued and outcomes appeared to differ only after most patients stopped chemotherapy. This raises the question of whether the benefit of veliparib reflects maintenance therapy after chemotherapy rather than benefit from the combination of chemotherapy with a poly-ADP ribose polymerase (PARP) inhibitor. It should also be noted that in an era of immunotherapy in programmed cell death ligand 1 (PD-L1) positive mTNBC (typically around 30–40% of all mTNBC), the observation that only 4% of patients received an immune checkpoint inhibitor as a previous treatment means that the results of the S1416 trial are more difficult to generalize to contemporary treatment. Pembrolizumab in combination with chemotherapy has now been established as the standard of care either in the neoadjuvant setting and as first-line therapy for PD-L1 positive mTNBC (1,5). The impact of prior treatment with immunotherapy on benefit from PARP inhibitors delivered in later lines remains unknown.

As expected, the addition of veliparib did increase toxicity consistent with the known adverse event profile of this drug. There was excess hematologic toxicity for all three blood cell lines as well as a modest increase in gastrointestinal adverse events. The effect of this increased toxicity was that there was an almost 5-times higher odds of discontinuation of treatment for reasons other than progressive disease for the combination of veliparib and chemotherapy compared to placebo with chemotherapy [Mantel Haenszel odds ratio (OR), 4.93, 95% CI: 3.16–7.67;  $P=0.004$ ]. This difference in treatment discontinuation also resulted in unbalanced censoring of patients between the 2 arms with more prevalent censoring of the veliparib arm. The effect of this potential informative censoring is unclear.

Surprisingly, there was a no impact of the addition of veliparib to platinum-based chemotherapy in the germline *BRCA1/2*-mutated group (6-9). The reasons for this are not clear. Prior trials had shown that the addition of PARP inhibitors to chemotherapy increased response rate and had a modest impact on PFS (10). One possible reason is the low statistical power in this group. The trial was

designed with an expected total sample size of 63 *BRCA1/2* mutation carriers. However, only 37 patients were positive for germline *BRCA1/2* mutation. Another explanation is that in some trials, PARP inhibitors were continued beyond chemotherapy and PFS curves appeared to separate after participants stopped chemotherapy (9). This questions whether the observed effect reflects maintenance use of PARP inhibitors rather than the combination of PARP inhibitors with chemotherapy (11).

Irrespective of the statistical significance of these data which may have been limited by statistical power, neither the improvement in PFS nor in OS were of a clinically meaningful magnitude. Specifically, the gains reported failed to meet the threshold for clinically meaningful benefit defined by professional societies. The American Society of Clinical Oncology and the European Society for Medical Oncology (ESMO) have developed tools to quantify the magnitude of clinical benefit of drugs for the treatment of solid tumors. For instance, the ASCO Cancer Research Committee (ASCO-CRC) published targets for clinically meaningful benefit using a single cut-off in clinical trials for 4 cancer types (pancreatic cancer, lung cancer, triple-negative breast cancer, and colon cancer). Thresholds for clinically meaningful benefit were defined as OS improvements ranging from 2.5 to 6 months and PFS improvements ranging from 3 to 5 months. Therefore, the addition of veliparib to chemotherapy would not meet the threshold for clinically meaningful benefit defined by these scales (12-16).

It is important to highlight that the scientific community has not agreed on a definition of BRCAness for patients with breast cancer. The definition of BRCA-like in the S1416 trial was novel, but questions remain. In order to define a reproducible subgroup of patients who may benefit from specific targeted therapy, there is a need for a standardized, reliable and sensitive quantitative assay to define BRCAness. Considering that 76% of wildtype germline *BRCA1/2*-mutated patients presented with a genomic instability score of at least 42, one critical aspect highlighted by these data is the need to validate the threshold of genomic instability score(s) needed to identify clinically meaningful antitumor activity of PARP inhibitors (17-20).

In conclusion, despite its limitations, the results of the S1416 trial are a welcome addition to the literature. The modest effect of PARP inhibitors in unselected mTNBC has been described before (21) and S1416 is confirmatory of this. However, S1416 raises the question of whether it may be possible to identify a subgroup of patients with mTNBC

and with characteristics of BRCAness who may benefit from the addition of PARP inhibitors to chemotherapy. Further research especially in the validation of an appropriate companion diagnostic for PARP inhibitors in patients with BRCA1/2 wildtype status is required. Thereafter, an appropriately designed randomized trial will be needed to evaluate the therapeutic role of PARP inhibitors in this group of patients. Such a trial may need to evaluate both the value of concurrent chemotherapy and PARP inhibition and the utility of PARP maintenance therapy in this setting.

### Acknowledgments

*Funding:* None.

### Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Translational Cancer Research*. The article has undergone external peer review.

*Peer Review File:* Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-365/prf>

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-365/coif>). EA reports that he received grant from Novartis paid to institution (Princess Margaret Cancer Centre) outside the submitted work. The other author has no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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### References

1. Cortes J, Rugo HS, Cescon DW, et al. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. *N Engl J Med* 2022;387:217-26.
2. Lips EH, Mulder L, Oonk A, et al. Triple-negative breast cancer: BRCAness and concordance of clinical features with BRCA1-mutation carriers. *Br J Cancer* 2013;108:2172-7.
3. Boussios S, Rassy E, Moschetta M, et al. BRCA Mutations in Ovarian and Prostate Cancer: Bench to Bedside. *Cancers (Basel)* 2022;14:3888.
4. Rodler E, Sharma P, Barlow WE, et al. Cisplatin with veliparib or placebo in metastatic triple-negative breast cancer and BRCA mutation-associated breast cancer (S1416): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2023;24:162-74.
5. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med* 2020;382:810-21.
6. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med* 2017;377:523-33.
7. Hurvitz SA, Gonçalves A, Rugo HS, et al. Talazoparib in Patients with a Germline BRCA-Mutated Advanced Breast Cancer: Detailed Safety Analyses from the Phase III EMBRACA Trial. *Oncologist* 2020;25:e439-50.
8. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol* 2019;30:558-66.
9. Diéras V, Han HS, Kaufman B, et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2020;21:1269-82.
10. Desnoyers A, Nadler M, Wilson BE, et al. Associations with response to Poly(ADP-ribose) Polymerase (PARP) inhibitors in patients with metastatic breast cancer. *NPJ Breast Cancer* 2022;8:43.
11. Tung N, Garber JE. PARP inhibition in breast cancer: progress made and future hopes. *NPJ Breast Cancer* 2022;8:47.
12. Cherny NI, de Vries EGE, Dafni U, et al. Comparative Assessment of Clinical Benefit Using the ESMO-

- Magnitude of Clinical Benefit Scale Version 1.1 and the ASCO Value Framework Net Health Benefit Score. *J Clin Oncol* 2019;37:336-49.
13. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 2015;26:1547-73.
  14. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received. *J Clin Oncol* 2016;34:2925-34.
  15. Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. *J Clin Oncol* 2015;33:2563-77.
  16. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol* 2014;32:1277-80.
  17. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med* 2018;24:628-37.
  18. Abbotts R, Dellomo AJ, Rassool FV. Pharmacologic Induction of BRCAness in BRCA-Proficient Cancers: Expanding PARP Inhibitor Use. *Cancers (Basel)* 2022;14:2640.
  19. De Summa S, Pinto R, Sambiasi D, et al. BRCAness: a deeper insight into basal-like breast tumors. *Ann Oncol* 2013;24 Suppl 8:viii13-21.
  20. Oshi M, Gandhi S, Wu R, et al. Development of a novel BRCAness score that predicts response to PARP inhibitors. *Biomark Res* 2022;10:80.
  21. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol* 2011;12:852-61.

**Cite this article as:** Molto Valiente C, Amir E. Combining PARP inhibitors and platinum-based chemotherapy in metastatic triple negative and/or BRCA-associated breast cancer. *Transl Cancer Res* 2023;12(7):1887-1890. doi: 10.21037/tcr-23-365