Editorial

Neoadjuvant immunotherapy in early-stage triple negative breast cancer

Panayiotis Laouris, Mariana Espirito Santo Rodrigues, Susanne Crocamo Ventilary Costa, Bruno Henrique Rala de Paula^

Early Phase Trials Unit, Division of Oncology, University of Cambridge, Cambridge, UK

Correspondence to: Bruno Henrique Rala de Paula, MSc. Early Phase Trials Unit, Division of Oncology, University of Cambridge, Cambridge, UK. Email: brunobhrp@hotmail.com.

Comment on: Gong Y, Zuo H, Zhou Y, *et al.* Neoadjuvant Pseudomonas aeruginosa mannose-sensitive hemagglutinin (PA-MSHA) and chemotherapy versus placebo plus chemotherapy in patients with HER2-negative breast cancer: a randomized, controlled, double-blind trial. Ann Transl Med 2023;11:243.

Keywords: Neoadjuvant immunotherapy; HER2-negative breast cancer; triple-negative breast cancer (TNBC); pseudomonas aeruginosa mannose-sensitive hemagglutinin (PA-MSHA)

Submitted Apr 20, 2023. Accepted for publication May 30, 2023. Published online Jun 27, 2023.
doi: 10.21037/atm-23-1550
View this article at: https://dx.doi.org/10.21037/atm-23-1550

Breast cancer is the most diagnosed cancer in women globally, with 287,850 new cases and 43,250 new deaths in 2022 in the USA (1). Breast cancers are traditionally categorised based on their immunohistochemical (IHC) expression of classic hormone and growth factor receptors including estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), as well as expression of proliferation marker Ki-67 protein (2). This is because the distinct molecular profile of each breast cancer has broad implications on its prognosis and choice of treatment. According to the 2013 St. Gallen International Breast Cancer Conference, breast cancer can be grouped based on IHC expression, as surrogate intrinsic subtypes, into the following breast cancer molecular subtypes of the above markers: luminal A, luminal B, HER2 overexpression, basal-like triple-negative breast cancer (TNBC) (3).

In the recent years, a subset of HER2-negative subtypes of breast cancer including TNBC have been shown to be amenable to immunotherapy. Immunotherapy describes a broad range of drugs that works broadly by activating the immune system to better recognise and attack cancer cells. Recent evidence shows that in the highly immunogenic tumour microenvironment of TNBC there is an ongoing immune response linked to a greater number of tumour infiltrating lymphocytes (TILs) and higher expression of programmed cell death ligand 1 (PD-L1) (4). TILs are necessary for response to immunotherapy, and therefore a higher PD-L1 expression is thought to occur as an adaptive method of tumour resistance to TILs. Blockade of immune checkpoints such as the PD-L1/programmed cell death 1 (PD-1) checkpoint therefore restores the cytotoxic effect of immune cells in the tumour microenvironment, improving the efficiency of the immune response to the tumour and thus the efficacy of classical chemotherapy through a synergistic effect.

Immune checkpoint inhibitors (ICIs) have been shown to prolong survival in lung cancer, melanoma and more recently breast cancer, and new immune molecule-based therapies are constantly being trialled and approved for breast cancer therapy in many countries. One of the prominent roles anticancer immunotherapies have taken is the additive effect when combined to neoadjuvant chemotherapy treatment in early stage TNBC, allowing beyond disease downstaging, higher rates of breast conservation, but also impacting positively the pathologic

^ ORCID: 0000-0001-6427-229X.

complete response (pCR) rates and survival (5). Recently, atezolizumab, a humanised monoclonal antibody against PD-L1, was approved in the UK in combination with nab-paclitaxel for use in unresectable locally advanced or metastatic TNBC with PD-L1 expression. Additionally, pembrolizumab, another humanised monoclonal antibody that works by blocking PD-1 receptors on lymphocytes, has also been approved as neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer, and in combination with chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer. While further studies are necessary to study these therapies in the long-run and determine the optimal duration and sequence of ICIs in treating early-stage TNBC, their clinical promise is irrefutable.

The study recently published in *Annals of Translational Medicine*, by Gong *et al.* presents a single-centre prospective randomised double-blind phase 2 trial investigating the benefit of neoadjuvant *Pseudomonas aeruginosa* mannose-sensitive haemagglutinin (PA-MSHA) in addition to paclitaxel and carboplatin (PCb) chemotherapy in previously untreated Chinese individuals with early-stage HER2-negative breast cancer (6). This genetically engineered heat-killed strain of *Pseudomonas aeruginosa* that exhibits mannose-sensitive haemagglutination type I fimbriae on its surface has been approved by the State Food and Drug Administration in China for complementary cancer treatment since 1998. PA-MSHA exerts its antiproliferative effects through both direct tumoricidal action as well as through its ability to act as an immunostimulant adjuvant particularly through inducing dendritic cell maturation in a Toll-like receptor 4 (TLR4)-dependent manner, T cell activation and M1 macrophage polarisation (7).

A total of 75 patients were randomised with a 1:1 ratio to the experimental (37 patients) and control (38 patients) arms of the study and treated in parallel. Both groups were treated with paclitaxel 80 mg/m^2 and carboplatin (area under the time curve =2) chemotherapy on days 1, 8 and 15 every 28 days for 4 cycles. In addition to this standard regime, the patients in the experimental arm received a subcutaneous injection of PA-MSHA on the upper arm every other day, from the first day of neoadjuvant chemotherapy up to 3 days prior to surgery. Median follow-up duration was 95 months. Clinical response was assessed every 2 days using the Response Evaluation Criteria in Solid Tumours (RECIST) and the objective response rate (ORR) was measured as the primary endpoint.

In this study, Gong *et al.* demonstrate a significantly higher ORR in the PA-MSHA group (86.5%) compared to the control group (60.5%) (95% confidence interval 5.9-43.5%, P=0.011). The study's secondary endpoints, comprising of pCR rate, survival outcomes and immunological index remained unchanged. PA-MSHA therapy had a similar safety profile to the control group and no added toxicity. However, there was a greater number of patients with immune-related adverse events (irAEs) in the treatment group (56.8%) compared to the control group (13.2%), and those exhibiting these effects benefitted from much-improved outcomes to those who didn't, suggesting that irAEs could act as a clinical biomarker of benefit from PA-MSHA treatment.

One of the strengths of this study is that it is the first randomised controlled trial to evaluate the effects of neoadjuvant PA-MSHA on early-stage HER2-negative breast cancer, and it presents a statistically significant improvement in ORR with the suggested treatment regime. Additionally, the use of randomisation and double blinding might have contributed to reduce bias.

On the other hand, there are a few aspects that require attention in interpreting the results. Although the intention-to-treat and parallel arm design closely mimics the real clinical setting, there is a question of whether the subcutaneous administration protocol of PA-MSHA induced clinically meaningful benefit. Moreover, it would be useful to further understand if the patients' quality of life during the study changed compared to the control arm.

In clinical practice, neoadjuvant therapy for breast cancer is a decision taken based on a combination of factors, but the specific molecular subtype play a major role. The demographic of this study, however, comprises several molecular breast cancer subtypes, with most participants with luminal subtype (77.3%), which is usually not responsive to neoadjuvant chemotherapy, and stage III breast cancer (64.0%). The inclusion of patients with more

than one molecular subtype of breast cancer allows for subgroup analysis to be conducted to investigate the effect of molecular subtype of breast cancer on treatment success. Indeed, the study demonstrates a statistically significant ORR difference of 31.0% (95% confidence interval: 7.8–50.5%, P=0.009) between experimental and control arm response in a total of 58 patients with luminal breast cancer, but no such significant difference in results in a total of 17 patients with TNBC. Despite this, it would be ideal to focus on a larger and perhaps more homogeneous population for future studies with this regimen. Furthermore, exploratory analysis could be considered to find an optimal subgroup population for PA-MSHA treatment. The study's protocol could be further enhanced by considering additional parameters in the subgroup analysis. These include tumour mutation burden and neoantigen load, intratumoral TIL (iTIL) and stromal TIL (sTIL) density, immune gene signatures and predictive immune biomarkers that determine the response of conventional ICIs, such as PD-L1 expression. This is especially important given the heterogeneity feature of TNBC and associated challenge of selecting the subpopulation of patients predicted to benefit most from treatment.

The lack of a statistically significant improvement in the pCR of the experimental arm compared to the control arm (16.2% *vs.* 10.5%, P=0.516) is an important caveat of this study, considering that pCR is a US Food and Drug Administration approved surrogate endpoint for disease-free survival and overall survival in randomised clinical trials testing neoadjuvant treatments in early-stage breast cancer (8). pCR is defined as the absence of residual invasive cancer upon evaluation of the resected breast tissue and regional lymph nodes. Compared to ORR which measures the proportion of patients who experience a reduction in tumour size regardless of the extent of reduction, pCR is a more stringent endpoint as it requires complete local eradication of the invasive tumour. pCR acts as a quantitative surrogate endpoint for long-term outcomes and this has enabled its applicability in risk stratification and selection of subsequent adjuvant treatment (8). Conversely, ORR may be a less reliable predictor of long-term outcomes than pCR, as some patients who have a partial response may still experience disease progression or recurrence. On the other hand, other studies have shown that obtaining a pCR is not necessary for achieving important survival benefits, as demonstrated by the use of endocrine treatments in patients with luminal-like breast cancers (9).

Several key clinical trials use both pCR and ORR as endpoints to evaluate neoadjuvant immunotherapy with ICIs, in early stage TNBC but results so far showed no significant benefit, except in the KEYNOTE-522 trial (10). The KEYNOTE-522 trial was a randomized, double-blind, phase 3 trial that evaluated the addition of pembrolizumab, a PD-1 inhibitor, to neoadjuvant chemotherapy for patients with TNBC. In this study, the addition of pembrolizumab to chemotherapy resulted in a higher rate of pCR than chemotherapy alone (64.8% *vs.* 51.2%, P=0.00055). Remarkably, two randomised neoadjuvant trials of antibodies against PD-L1, GeparNuevo which tested durvalumab plus chemotherapy in early-stage TNBC and NeoTRIP Michelangelo which tested atezolizumab plus chemotherapy in early-stage TNBC, failed to show a statistically significant increase in pCR with the neoadjuvant immunotherapy in addition to chemotherapy (11,12). They are underpowered compared to the KEYNOTE-522 trial. The i-SPY2 trial is a platform trial that evaluated the efficacy of multiple neoadjuvant treatment regimens in different breast cancer subtypes, including TNBC (13). This trial includes several experimental arms that tested the efficacy of different immunotherapy agents in combination with standard neoadjuvant chemotherapy. The trial used pCR as the primary endpoint and has shown promising results with several immunotherapy agents, including pembrolizumab and atezolizumab. A summary of the results of these studies can be found in *Table 1*.

In conclusion, the study conducted by Gong *et al.* provides insights into the use of novel neoadjuvant immunotherapy strategies in breast cancer treatment. While the study has limitations, the results are intriguing and suggest that the role of PA-MSHA in addition to neoadjuvant chemotherapy for HER2-negative breast cancer patients should be further investigated, especially in terms of further stratifying PA-MSHA treatment based on biomarkers, as well as exploring its effect in combination with other immunotherapy agents and targeted therapies.

Table 1 Summary of clinical trials on neoadjuvant immune checkpoint inhibitors on early-stage triple negative breast cancer

Study or trial	Experimental arm	Control arm	Drug target	Number of patients enrolled	Median time to follow-up (in months)	Primary outcomes	pCR (%)	Reference
KEYNOTE-522 (Phase 3)	Neoadjuvant pembrolizumab + carboplatin/paclitaxel	Neoadjuvant carboplatin/ paclitaxel	PD-1	1,174 (784 experimental *vs.* 390 control)	15.5	pCR	64.8% experimental *vs.* 51.2% control	(10)
GeparNuevo (Phase 2)	Neoadjuvant durvalumab plus anthracycline/taxane based chemotherapy	Neoadjuvant anthracycline/ taxane based chemotherapy	PD-L1	174 (88 experimental *vs.* 86 control)	43.7	pCR	53.4% experimental *vs.* 44.2% control	(11)
NeoTRIP Michelangelo (Phase 3)	Neoadjuvant atezolizumab, carboplatin and nab-paclitaxel	Neoadjuvant carboplatin and nab-paclitaxel	PD-L1	280 (138 experimental *vs.* 142 control)	60[†]	EFS	48.6% experimental *vs.* 44.4% control	(12)
i-SPY2 (Phase 2)	Neoadjuvant pembrolizumab plus anthracycline/taxane based chemotherapy	Neoadjuvant anthracycline/ taxane based chemotherapy	PD-1	250 (69 experimental *vs.* 181 control)	33.6	pCR	22% experimental *vs.* 60% control	(13)

[†], 5-year EFS. pCR, pathologic complete response; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; EFS, event-free survival.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1550/coif). The authors have 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.

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
2. Loibl S, Poortmans P, Morrow M, et al. Breast cancer. Lancet 2021;397:1750-69.
3. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013;24:2206-23.
4. Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol 2018;19:40-50.
5. Potter DA, Herrera-Ponzanelli CA, Hinojosa D, et al. Recent advances in neoadjuvant therapy for breast cancer. Fac Rev 2021;10:2.
6. Gong Y, Zuo H, Zhou Y, et al. Neoadjuvant Pseudomonas

aeruginosa mannose-sensitive hemagglutinin (PA-MSHA) and chemotherapy versus placebo plus chemotherapy in patients with HER2-negative breast cancer: a randomized, controlled, double-blind trial. Ann Transl Med 2023;11:243.
7. Huang M, He F, Li D, et al. PA-MSHA induces inflamed tumor microenvironment and sensitizes tumor to anti-PD-1 therapy. Cell Death Dis 2022;13:931.
8. LeVasseur N, Sun J, Gondara L, et al. Impact of pathologic complete response on survival after neoadjuvant chemotherapy in early-stage breast cancer: a population-based analysis. J Cancer Res Clin Oncol 2020;146:529-36.
9. Burstein HJ. Systemic Therapy for Estrogen Receptor-Positive, HER2-Negative Breast Cancer. N Engl J Med 2020;383:2557-70.
10. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020;382:810-21.
11. Loibl S, Schneeweiss A, Huober J, et al. Neoadjuvant durvalumab improves survival in early triple-negative breast cancer independent of pathological complete response. Ann Oncol 2022;33:1149-58.
12. Gianni L, Huang CS, Egle D, et al. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple-negative, early high-risk and locally advanced breast cancer: NeoTRIP Michelangelo randomized study. Ann Oncol 2022;33:534-43.
13. Nanda R, Liu MC, Yau C, et al. Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer: An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial. JAMA Oncol 2020;6:676-84.

Cite this article as: Laouris P, Rodrigues MES, Costa SCV, Rala de Paula BH. Neoadjuvant immunotherapy in early-stage triple negative breast cancer. Ann Transl Med 2023;11(10):338. doi: 10.21037/atm-23-1550

