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Adding adjuvant drugs from distinct breast cancer trials

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ABSTRACT

Studies conducted in perioperative settings have recently expanded the treatment options for early-stage operable breast cancer. These studies have different inclusion criteria, however they are not entirely mutually exclusive. It results that multiple treatment options may be available to the same patient, making the choice of therapy a significant challenge. The concurrent or sequential administration of these therapies has been suggested by expert panels or international guidelines. Yet combining therapeutic strategies that have been independently tested can be problematic. It is possible that the same subset of patients benefits from each therapy individually, meaning that combining them might offer no additional benefit. Moreover, the toxicity of those combinations – short and long-term – has not been assessed in phase 3 trials. Whether these toxicities and dose reductions offset gains is unknown. Here, we offer clinical scenario where this could happen, like combining pembrolizumab plus olaparib in triple-negative breast cancer, or olaparib plus CDK4/6 inhibitors in hormone receptor–positive disease. Although each therapy has shown efficacy in individual trials, the net gain of their combined or sequential use in the peri-operative setting remains unproven in phase 3 trials. This dilemma extends well beyond breast cancer as a growing number of agents continue to be approved in neoadjuvant or adjuvant space. A cautious evidence-driven approach is needed to ensure these strategies truly benefit patients. This could have important policy implications, including regulatory enforcement for combination trials rather than extrapolating from monotherapy data.

1. Introduction

Several studies conducted in perioperative settings have recently expanded the treatment options for early-stage operable breast cancer. While these studies have different inclusion criteria, they are not entirely mutually exclusive. As a result, multiple treatment options may apply to the same patient, making the choice of therapy a significant challenge.

The concurrent or sequential administration of these treatments has been suggested, either by expert panels or international guidelines. We highlight the dangers of combining therapeutic strategies that have been independently tested. It is possible that the patients who benefit from each of these treatments individually are the same – are sharing similar characteristics. In such cases, combining the strategies would not provide any additional benefit. Moreover, the toxicity of those combinations – short and long-term – has not been assessed in phase 3 trials. Whether these toxicities and dose reductions offset gains is unknown.

2. An analogy

To illustrate the clinical scenarios we describe later, consider the analogy where a company tests an energy drink designed to improve performance in a 5000-meter race. The clinical trial is properly conducted and shows a benefit from the drink. A competitor introduces a special energy gel, and again, individuals who take the gel perform better on the 5000-m race than those who do not. A third company creates an energy bar, and once more, participants consuming the bar finish the 5000-m race faster than those without any supplement.

Now, we have three options to improve performance: an energy drink, a gel, and an energy bar. Suppose someone decides to take all three simultaneously: they experience stomach pain and lose the race. This analogy mirrors the clinical scenario where different breast cancer therapies tested independently are combined without evidence. The result could be unnecessary toxicity without any additional benefit.

Importantly, this analogy is not intended to trivialize the seriousness of a breast cancer diagnosis – having breast cancer is a life-changing

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event. Rather, the intent is to provide a directly understandable image that highlights the potential intricacies at play when combining therapies.

3. Case 1: pembrolizumab and olaparib in triple-negative breast cancer

Let's consider a 43-year-old patient with stage II, node-positive, triple-negative breast cancer. This patient carries a germline BRCA1 mutation. She could be offered pembrolizumab in the neoadjuvant phase, followed by adjuvant pembrolizumab, in addition to neoadjuvant chemotherapy. This strategy was tested in the KEYNOTE-522 study, which showed a benefit in event-free survival (EFS) and overall survival [1].

The 18th St. Gallen conference brought together 71 breast cancer experts from 27 countries [2]. When presented with this scenario, the panelists were asked what they would recommend after surgery if residual disease was found, in addition to continuing pembrolizumab that was initiated before surgery according to the KEYNOTE-522 trial?

Note: the presence of residual disease post-surgery would render this patient eligible for one year of adjuvant olaparib. This is based on the phase 3 OlympiA study, which showed a survival benefit compared to placebo in patients with HER2-negative breast cancer, residual disease at surgery for those receiving neoadjuvant therapy, and a germline BRCA1 or BRCA2 mutation [3].

Astonishingly, 62 % of the voters recommended the concurrent use of pembrolizumab and olaparib postoperatively. Additionally, 24 % of the other panelists recommended administering both agents sequentially. Overall, 86 % of the experts would have used both products, either in combination or sequentially [2]. Other experts have considered that this combination was a «reasonable option» [4]. Yet, again, such strategy was never tested in a phase 3 trial.

Safety data on the combination of anti-PD(L)1 therapy and olaparib are available, with evaluations conducted from early-phase to phase III studies [5,6]. However, cross-trial comparisons have limited value due to differences in patient populations. The safety of such a strategy – both short and long-term – in patients with early breast cancer in the adjuvant setting remains untested in phase 3 trials, and therefore uncertain.

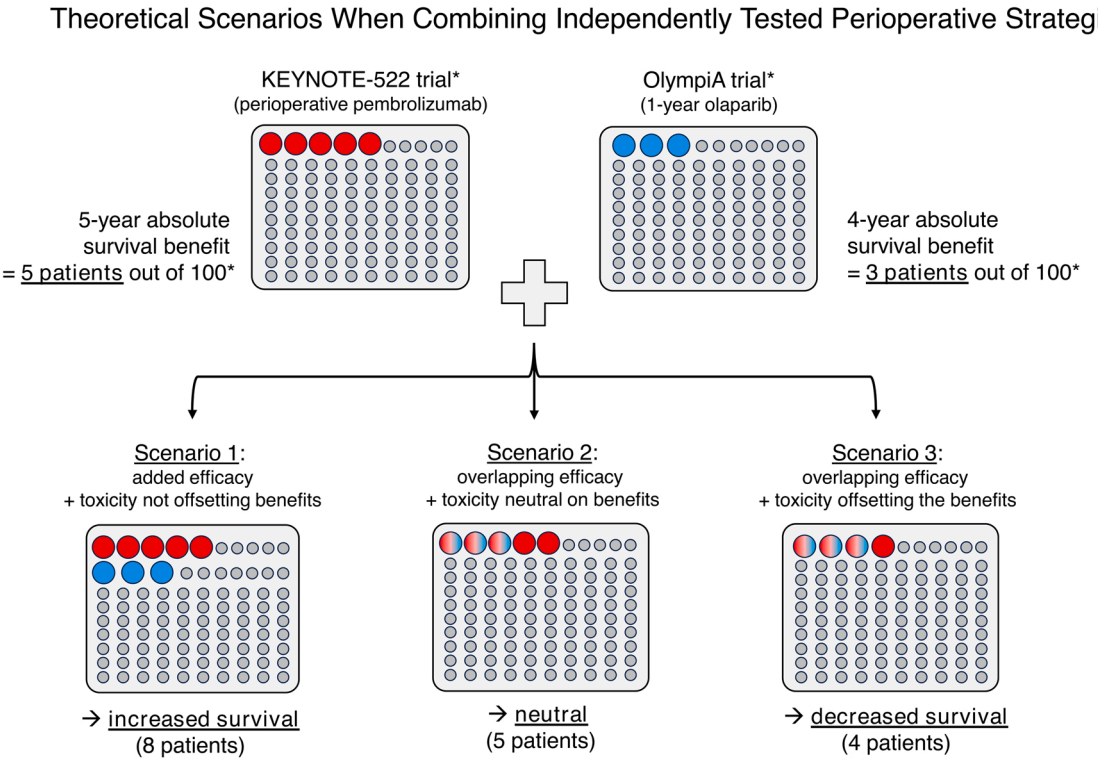
In the **Figure**, based on the 4-year and 5-year absolute survival benefits observed in OlympiA and KEYNOTE-522, respectively [1,3], we present different scenarios: one where the combination provides a net survival benefit, another where there is no additional benefit, and a third where the added toxicity and dose reduction lead to a decrease in survival. In all scenarios, the combination strategy results in increased toxicity, and none of these scenarios have been tested in phase 3 trials. Fig. 1

4. Case 2: olaparib and CDK4/6 inhibitors

Consider now a hormone receptor-positive, HER2-negative breast cancer, and that the patient has residual disease upon surgery. Such patients would be eligible for one year of olaparib in addition to standard of care. Indeed, while the OlympiA study included a minority of hormone receptor-positive patients – around 18 % – the benefit was demonstrated across the entire study population [7].

The same patient could also be potentially eligible for the addition of adjuvant CDK4/6 inhibitors, such as abemaciclib or ribociclib, which have now shown benefits in invasive disease-free survival (iDFS) with 2 and 3 years of treatment, respectively, in the MonarchE and NATALEE trials [8,9].

Although sequential use has not been tested in phase 3 trials, international guidelines do not formally advise against it. For example, the



Each circle represents a patient. The circles representing patients who did not benefit in terms of survival are smaller in size to enhance the readability of the graph.
*: the 5-year absolute survival benefit in KEYNOTE-522 was 4.9 and rounded to 5; the 4-year absolute in OlympiA was 3.4 and was rounded to 3.

Fig. 1. Theoretical Scenarios When Combining Independently Tested Perioperative Strategies. Legend: Each circle represents a patient. The circles representing patients who did not benefit in terms of survival are smaller in size to enhance the readability of the graph. *: The 5-year absolute survival benefit in KEYNOTE-522 was 4.9 and rounded to 5; the 4-year absolute in OlympiA was 3.4 and was rounded to 3.

National Comprehensive Cancer Network (NCCN) guidelines state: "In patients eligible for both adjuvant olaparib and abemaciclib, the optimal choice of therapy and sequencing remains unknown". In contrast, the European Society of Medical Oncology explicitly advises against combining these agents due to overlapping toxicities, but allows for their sequential use, noting that "Olaparib and abemaciclib should not be combined due to overlapping toxicities, but may be considered sequentially, with olaparib first [V, A]."

5. Conclusion

Combining cancer drugs (either concurrently or sequentially) in the adjuvant setting, based on studies where these drugs were tested in isolation, assumes that the beneficial effects will add up. However, it is plausible that this approach may result in none to minimal benefit if the same patients are those benefiting from each strategy. The strategy to use more drugs, resulting in more toxicity and higher costs, ultimately does not automatically benefit patients. This holds particularly true in settings where most patients do not directly benefit from additional therapy such as the adjuvant setting. While a growing number of agents continue to receive approval in this setting, a cautious evidence-driven approach is needed to ensure that combination strategies provide meaningful gain. This could have important policy implications, such as encouraging regulatory bodies to mandate combination trials that directly address those questions rather than relying on extrapolations from monotherapy data.

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CRediT authorship contribution statement

Timothée Olivier: Writing – review & editing, Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Vinay Prasad:** Writing – review & editing, Validation, Conceptualization.

Declaration of Competing Interest

Dr Vinay Prasad reported receiving research funding from Arnold Ventures LLC through a grant made to UCSF; royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press; and consulting fees from UnitedHealthcare and OptumRX. He also reported receiving revenue from Patreon, YouTube, and Substack for the podcasts Plenary Session, VPZD, and Sensible Medicine; for the newsletters Sensible Medicine, The Drug Development Letter, and VP's Observations and Thoughts; and for the YouTube channel Vinay Prasad MD MPH. Dr Timothée OIivier has no conflicts of interest to declare.

References

[1] Schmid P., Cortes J., Dent R., et al. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer. New England Journal of Medicine. 0(0). doi:10.1056/NEJMoa2409932.

[2] M. Untch, M. Banys-Paluchowski, S.Y. Brucker, et al., Treatment of early breast cancer: The 18th St. Gallen International breast cancer consensus conference against the background of current german treatment recommendations, Geburtshilfe Frau 83 (9) (2023) 1102–1116, https://doi.org/10.1055/a-2121-2495.

[3] C.E. Geyer, J.E. Garber, R.D. Gelber, et al., Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high risk, early breast cancer, Ann. Oncol. (2022), https://doi.org/10.1016/j.annonc.2022.09.159.

[4] N.V. Desai, D. Zakalik, M.R. Somerfield, N.M. Tung, Q and A: a new standard of care for germline BRCA1 and/or BRCA2 mutation carriers with early-stage breast cancer, JCO Oncol. Pract. 18 (6) (2022) 427–429, https://doi.org/10.1200/OP.21.00770.

[5] S.M. Domchek, S. Postel-Vinay, S.A. Im, et al., Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study, Lancet Oncol. 21 (9) (2020) 1155–1164, https://doi.org/10.1016/S1470-2045(20)30324-7.

[6] A. Es, P. Sh, G. Jc, et al., Pembrolizumab plus olaparib for patients with previously treated and biomarker-unselected metastatic castration-resistant prostate cancer: the randomized, open-label, phase III KEYLYNK-010 Trial, J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 41 (22) (2023), https://doi.org/10.1200/JCO.23.00233.

[7] A.N.J. Tutt, J.E. Garber, B. Kaufman, et al., Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer, N. Engl. J. Med. 384 (25) (2021) 2394–2405, https://doi.org/10.1056/NEJMoa2105215.

[8] P. Rastogi, J. O'Shaughnessy, M. Martin, et al., Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes, J. Clin. Oncol. (2024), https://doi.org/10.1200/JCO.23.01994. Published online January 9.

[9] Dennis Slamon, Oleg Lipatov, Zbigniew Nowecki, et al., Ribociclib plus endocrine therapy in early breast cancer, N. Engl. J. Med. 390 (12) (2024) 1080–1091, https://doi.org/10.1056/NEJMoa2305488.