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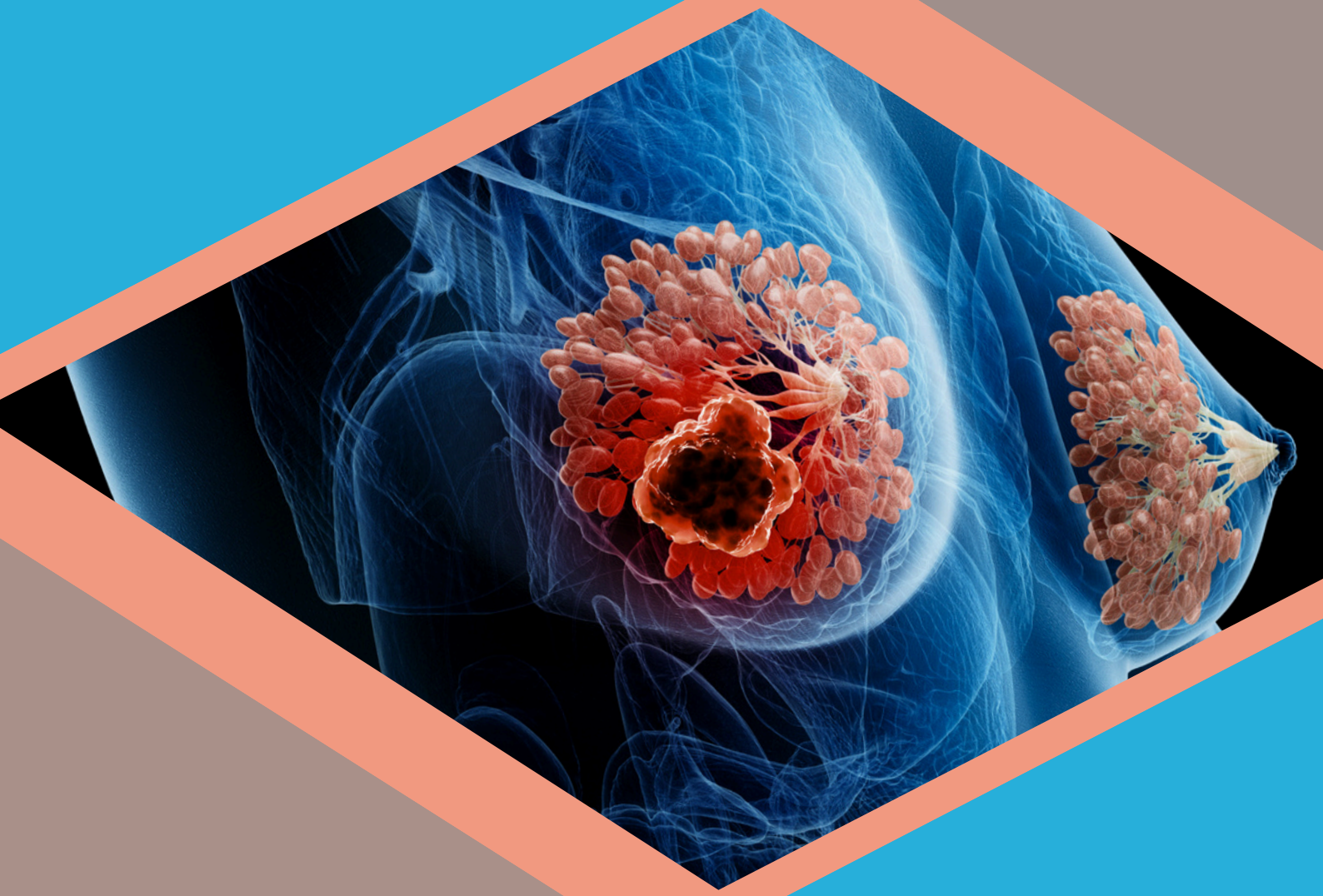

Addressing controversies in breast cancer treatment

Taylor & Francis

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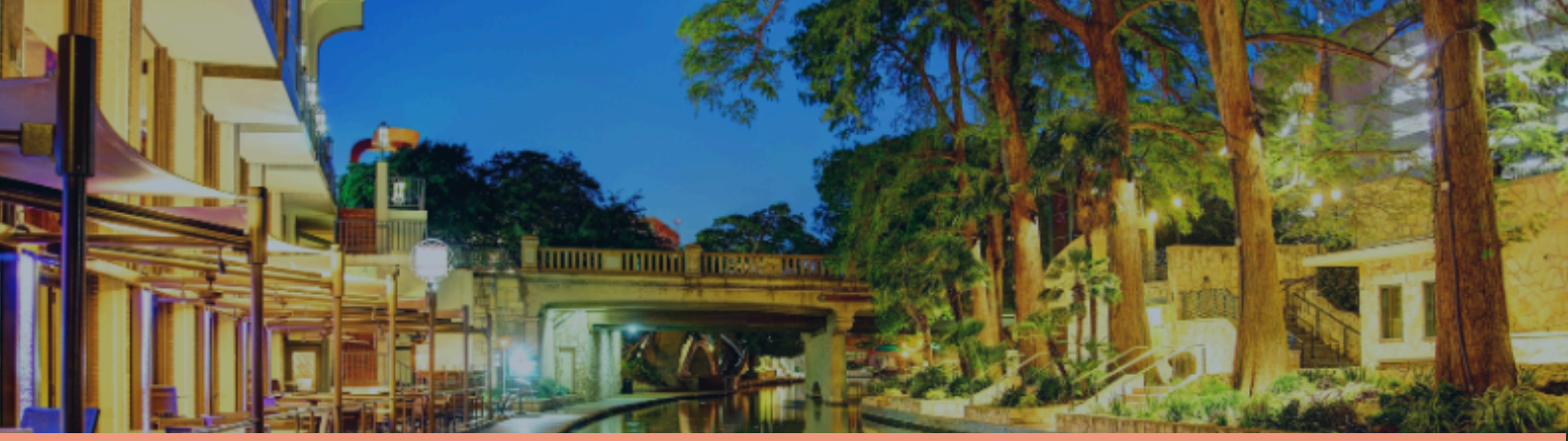

Key insights from SABCS 2024

The most recent SABCS (San Antonio Breast Cancer Symposium®, 10–14th December 2024, TX, USA) continued the tradition of combining principles of multidisciplinary management with basic and translational science that underpin therapeutic strategies in breast cancer.

Discover key presentations in this conference report by John Benson (Cambridge University Hospitals NHS Foundation Trust, UK).

The ‘micro’ and ‘macro’ of breast cancer

Results of the ICARO study were presented at last year’s meeting on behalf of the Oncoplastic Breast Consortium and subsequently published [1]. Findings from this retrospective real-world study have been practice changing and support the omission of routine completion axillary lymph node dissection (ALND) in patients with isolated tumor cells (≤0.2mm) (ITCs) in sentinel nodes following neoadjuvant chemotherapy (NACT) presenting with either clinically node-negative (cN0) or node-positive (cN1) disease. Residual ITCs are found exclusively in only 1.5% of cases but for patients with residual nodal macrometastases (>2mm) and micrometastases (≤2mm and >0.2mm) in the context of NACT, additional nodal deposits are found in up to 60% cases on completion ALND. Results of a follow-on study from the Oncoplastic Breast Consortium examining the significance of residual micrometastases in sentinel nodes after NACT (microNACT) will be presented at SABCS 2024. These may permit further treatment de-escalation to be safely implemented and reduce associated upper limb morbidity.

INSEMA and SOUND trial updates

On a similar theme of de-escalating axillary surgery, the INSEMA trial may provide further evidence to support omission of routine sentinel lymph node (SLN) biopsy in patients with smaller, biologically favorable tumors. Many breast units around the world are now considering omission of surgical

staging of the axilla based on results of the SOUND trial presented at the 18th St. Gallen International Breast Cancer Conference (15–18 March 2023, Vienna, Austria), which is now published [2] . The SOUND trial revealed similar rates of axillary recurrence in each arm of the trial (0.4%) with no statistically significant difference in distant DFS at 5 years [HR 0.84; CI 0.45 – 1.54] for tumors <2cm in patients of mean age 60 years (52–68 years).

Nonetheless, omission of SLN biopsy in women >70 years should be considered; indeed, some international guidelines such as the National Comprehensive Cancer Network (NCCN) have already incorporated this change and state that women aged ≥70 years with T1N0 hormone receptor positive, HER2 negative cancers do not require routine SLN biopsy if in receipt of hormonal therapy. Both SOUND and INSEMA include women <70 years with mean ages of 60 years and 60.2 years respectively. Hence these trials broaden the population of patients potentially suitable for omission of routine SLN biopsy. Although the INSEMA trial has a more complex design than SOUND with a secondary randomization process, the primary objective was to determine whether the omission of SLN biopsy is non-inferior to routine surgical staging of the axilla in terms of invasive disease-free survival.

Tamoxifen guidance

Tamoxifen therapy should be discussed as an option for risk reduction in pre- and postmenopausal women, whilst a similar recommendation applies to raloxifene for postmenopausal women only. Furthermore, American Society of Clinical Oncology (ASCO) guidelines acknowledge aromatase inhibitors (exemestane) as an additional option for breast cancer risk reduction in postmenopausal women. Uptake of chemoprevention strategies for high-risk patients (whether based on genetic predisposition or previous biopsy findings of atypical ductal hyperplasia, lobular neoplasia or ductal carcinoma in situ [ER positive or unknown]) have been modest to date, involving less than 20% of eligible patients. The dose of tamoxifen in the original chemoprevention trials was 20mg daily (based on the conventional dose for adjuvant hormonal therapy).

Tamoxifen has notable side effects including thrombo-embolism and increased risk of uterine malignancy; the Phase III TAM-01 trial reported that low dose tamoxifen (5mg daily) administered for 3 years significantly reduced the chance of invasive disease recurrence [HR 0.36; 95% CI 0.14 – 0.92; p= 0.025] at 10 year follow up and 7 years from treatment cessation [3]. Moreover, the incidence of adverse events was similar for tamoxifen and placebo groups. Information will be presented at SABCS2024 on changes in low-dose tamoxifen usage and uptake of chemoprevention following the publication of TAM-01 and amended guidelines from ASCO and the NCCN.

Balancing treatment benefits and quality of life in older patients

The absolute benefits of adjuvant breast cancer therapies are smaller in older patients who have fewer years of remaining life and potential co-morbidities.

Optimization of therapies must balance oncological benefit with quality-of-life. The Phase III EUROPA trial randomized women over 70 years of age with stage I luminal-type breast cancer to either breast irradiation or endocrine therapy. Results of this trial will provide important information on health-related quality of life for shared decision making between patients and their physicians. Interestingly, with the advent of five fraction regimens (1 week) for breast radiotherapy, the risk-to-benefit ratio for adjuvant treatments has changed and we should no longer necessarily strive for omission of breast irradiation. Ian Kunkler (University of Edinburgh, Scotland) will present the eagerly awaited results of the SUPREMO trial evaluating the benefits of post-mastectomy radiotherapy for 'intermediate risk' patients with 1–3 positive axillary nodes. Benefits of PMRT are well established for patients with ≥4 positive nodes but there exists much variation in practice (and national guidelines) pertaining to fewer than four positive nodes.

Another potentially practice-changing trial will be the NRG Oncology/RTOG 9804 and ECOG-ACRIN ES194 trial, which will address whether endocrine therapy only will suffice for "good risk" cases of ductal carcinoma-in-situ following surgical resection with clear surgical margins.

OlympiA trial progress

Judy Garber (Dana-Farber Cancer Institute, MA, USA) will present long term results of the OlympiA trial that has investigated the benefit of adding a PARP inhibitor (olaparib) to adjuvant therapies in high risk HER2 negative breast cancer patients with pathogenic germline mutations in the BRCA-1 or BRCA-2 genes. These patients with an inherited mutation of these breast cancer predisposition genes have a pre-existing defect in DNA-repair mechanisms that renders cancer cells more susceptible to the effects of a poly(ADP)-ribose polymerase (PARP) inhibitor that further compromises the ability of cancer cells to satisfactorily repair damaged DNA and thereby succumb to apoptotic cell death. At a median follow up of 3.5 years, this trial has previously shown a statistically significant improvement in overall survival for olaparib compared with placebo in germline BRCA1/2 mutation carriers[4].

Author profile:

In addition to serving as a Consultant Breast Surgeon in the Cambridge Breast Unit (UK), John Benson holds academic positions as an Associate Lecturer at the University of Cambridge, a Visiting Professor at the School of Medicine, Anglia Ruskin University and an Honorary Lecturer at the University of East Anglia (UK).

He co-convenes the Advanced Skills in Breast Disease Course, now hosted by Selwyn College Cambridge (UK) after its transition from the Royal College of Surgeons of England. Additionally, he serves as the Module Lead for the Masters in Oncoplastic Breast Surgery, a program jointly run by the University of East Anglia and the Royal College of Surgeons of England. His clinical practice at Addenbrooke's Hospital is exclusively dedicated to managing patients with breast diseases.

SOURCES

1. Montagna G, Laws A, Ferrucci M et al. ICARO study group. nodal burden and oncologic outcomes in patients with residual isolated tumor cells after neoadjuvant chemotherapy (ypN0i+): The OPBC-05/ICARO study. J. Clin. Oncol. doi:10.1200/JCO.24.01052 (2024) (Epub ahead of print).
2. Gentilini OD, Botteri E, Sangalli C et al. Sentinel lymph node biopsy vs no axillary surgery in patients with small breast cancer and negative results on ultrasonography of axillary lymph nodes: the SOUND randomized clinical trial. JAMA Oncol. 9(11), 1557–1564 (2023).
3. Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A et al. Randomized placebo controlled trial of low-dose tamoxifen to prevent recurrence in breast noninvasive neoplasia: a 10-year follow-up of TAM-01 study. J. Clin. Oncol. 41(17), 3116–3121 (2023).
4. Geyer CE Jr, Garber JE, Gelber RD et al. OlympiA Clinical Trial Steering Committee and Investigators. 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. 33(12), 1250–1268 (2022).

Breastfeeding choices for cancer patients: insights from the POSITIVE trial

In this interview, Fedro Peccatori (Istituto Europeo di Oncologia, Milan, Italy) discusses the POSITIVE trial, which is assessing the impact on women with Stage I–III hormone receptor-positive breast cancer taking a break from endocrine treatment to breastfeed. He highlights the importance of discussing breastfeeding with pregnant breast cancer survivors in prenatal counseling and concludes by discussing future work that needs to be done to understand the long-term impact of pausing treatment to breastfeed.

What factors or conditions should be considered when recommending breastfeeding for breast cancer patients post-treatment?

Any woman who wishes to breastfeed after breast cancer should be supported in doing so. Breastfeeding counseling should be non-directive and explore each woman's attitudes, offering support when needed. All reproductive choice options should be discussed as part of preconceptional or prenatal counseling. I really like the idea of having a "birth plan" during pregnancy to address possible issues about breastfeeding after breast cancer well in advance.
The POSITIVE trial evaluates the safety of pausing endocrine treatment in patients with hormone receptor-positive breast cancer who want to become pregnant. It is a prospective, international, multicenter, single-arm trial that enrolled 518 patients who were 42 years or younger across 20 countries over 5 years. Eligible patients had Stage I–III hormone receptor-positive breast cancer and had a strong desire to become pregnant. The trial allowed 18–30 months of endocrine treatment, followed by 3 months of wash out, and up to 2 years' break to allow for conception, delivery and breastfeeding. After that, patients were strongly suggested to restart and complete endocrine treatment.

The analysis of data about breastfeeding from the POSITIVE trial are quite clear: breastfeeding after breast cancer should be supported as it is feasible and safe, at least in the short-run. On the other hand, even if the advantages of breastfeeding for the infant are definitive, women who choose not to breastfeed after breast cancer should be equally supported.

Of note, one of the factors favoring breastfeeding in the POSITIVE cohort was breast-conserving surgery. In the study, we could not explore the reason why women with unilateral mastectomy breastfed less but this is an interesting point to address in the future.

What other endpoints were explored in the trial?

The primary endpoint of the POSITIVE trial was the breast cancer free interval. Secondary endpoints were the distant recurrence-free interval, pregnancy outcomes, offspring outcomes, use of assisted reproductive technology, adherence to endocrine treatment and breastfeeding. Results after a median follow up of 41 months were published in the New England Journal of Medicine and Journal of Clinical Oncology and breastfeeding data are those presented at the European Society for Medical Oncology Congress 2024 that will be eventually published in a peer-reviewed journal [1,2].

How do you hope to see these findings impacting clinical guidelines for breast cancer aftercare?

Given these data, speaking about breastfeeding to women who are pregnant after breast cancer should be an essential part of the prenatal counseling of breast cancer survivors. The POSITIVE trial is the largest prospective series investigating breastfeeding frequency, pattern and impact on breast cancer relapse in women with hormone receptor-positive early breast cancer who temporarily interrupted endocrine treatment to seek pregnancy.
I hope this evidence, together with the evidence coming from patients harboring BRCA pathogenic variants, will be incorporated into clinical guidelines and help women exploit their reproductive choice to achieve real reproductive autonomy.

What are the next steps for the study?

We need to continue the follow-up of patients in the POSITIVE study to understand if the temporary interruption of endocrine treatment is safe in terms of providing a breast cancer free interval and to understand if breastfeeding is safe in the long run. POSITIVE is an academic trial with no support from pharmaceutical companies and we are seeking forward-thinking donors interested in supporting the completion of this practice-changing study.

Interviewee profile:

Fedro Peccatori is the Director of the Fertility and Procreation Unit within the Division of Gynecologic Oncology at the European Institute of Oncology (Milan, Italy). He is a medical and gynecologic oncologist whose clinical activities mainly include the diagnosis and treatment of breast cancer, gynecologic malignancies and tumors in young adults. His main research projects deal with fertility preservation and counseling in young oncological patients, pharmacological protection of ovarian function during chemotherapy, clinical and molecular characterization of pregnancy-associated cancers and research protocols for the treatment of breast and gynecological malignancies.

The opinions expressed in this interview are those of the author and do not necessarily reflect the views of Oncology Central or Taylor & Francis Group.

The POSITIVE study is sponsored and conducted globally by the ETOP IBCSG Partners Foundation in collaboration with the Breast International Group (BIG) and by the Alliance for Clinical Trials in Oncology in North America.

SOURCES

1. Partridge AH, Niman SM, Ruggeri M et al. Interrupting endocrine therapy to attempt pregnancy after breast cancer. N. Engl. J. Med. 388(18), 1645–1656 (2023).
2. Azim HA Jr, Niman SM, Partridge AH et al. Fertility preservation and assisted reproduction in patients with breast cancer interrupting adjuvant endocrine therapy to attempt pregnancy. J. Clin. Oncol. 42(23), 2822–2832 (2024).

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Combining immunotherapy with PARP inhibitors. Is it possible to find the way through?

Georgios I Papageorgiou, Nikolaos Skouteris, Kleopatra Eleftheriou & Christos Kosmas

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COMMENTARY

Combining immunotherapy with PARP inhibitors. Is it possible to find the way through?

Georgios I Papageorgiou[*,a], Nikolaos Skouteris[b], Kleopatra Eleftheriou[c] and Christos Kosmas[b]

[a]2nd Medical Oncology Department, IASO General Clinic, Athens, Greece; [b]Division of Medical Oncology & Hematopoietic Cell Transplant Unit, Department of Medicine, "Metaxa" Cancer Hospital, Piraeus, Greece; [c]Pharmacy Department, IASO General Clinic, Athens, Greece

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1. Introduction

Immune checkpoint inhibitors (ICIs) emerged as the breakthrough of the previous decade in the field of oncology, representing a safe and effective anticancer approach with long-lasting responses in a variety of tumor types [1]. Simultaneously, the parallel introduction of Poly ADP-ribose polymerase inhibitors (PARPi) has achieved the so-called synthetic lethality in certain tumors with pre-existing defects in the DNA damage repair pathway. As both strategies offer encouraging antitumor activity without overlapping toxicities, it is valuable to investigate a possible synergistic activity in the clinical setting [2].

2. Rationale for combining immunotherapy with PARP inhibitors

Various mechanisms have been proposed in favor of combining ICIs with PARPi. First of all, homologous recombination deficient (HRD) tumors might benefit from increased neoantigen load as well as an increased tumor mutational burden when treated with PARPi [3].

Secondly, DNA damage has been shown to induce the activation of the STING and NF-κB pathways, which could in turn increase the effectiveness of ICIs by boosting the production of type I interferon, independently of HRD [4].

Preclinical evidence also suggests that PARPi lead to PD-L1 upregulation in a multiparametric manner; the only drawback lies on the recent knowledge that PD-L1 should not be considered the most robust biomarker to predict ICIs' efficacy [5]. Furthermore, the inhibition of PARP could modify the tumor microenvironment toward a more ICI susceptible state [6].

Altogether, these data provide encouraging preclinical evidence to support the combination of ICIs with PARPi in the clinical setting. Brown et al. provided a preliminary sequencing approach paradigm in 2018; immune-hot tumors should be treated with ICIs monotherapy, while PARPi could be added at disease progression. On the contrary, a short-term induction treatment with PARPi before adding ICIs could be utilized in cases of immune-cold tumors; otherwise, an upfront combination of both drugs could be an alternative approach [3].

Eitherway, PARPi have failed to demonstrate a robust overall survival (OS) benefit when used as a monotherapy [7,8], while they may also negatively affect OS when used in subsequent treatment lines based on recent evidence arising from ovarian cancer [9]. Currently, PARPi seem to benefit only certain patient populations in terms of OS and only when combined with other anticancer agents [10,11]. Meanwhile, ICIs generally provide their optimal efficacy when given upfront in various types of malignancies [12], so the pursue for a possible synergistic activity with targeted treatment is worthwhile.

Currently, numerous Phase II studies aim to investigate this combination in breast cancer with (NCT04837209) or without radiation (NCT03025035), in gastric adenocarcinoma (NCT04209686), in pancreatic cancer (NCT05093231), in head and neck carcinoma (NCT04681469) and in sarcomas (NCT06074692).

In the following sections, we are going to present the most encouraging latest clinical data and discuss the possible reasons behind the failure to confirm the preclinical synergy into the clinical setting. A meticulous study design and methodology is the cornerstone of unveiling the specific populations who could benefit from combinations of PARPi with ICIs.

3. "The good" – An oncoming revolution in endometrial cancer?

The addition of immunotherapy to first-line chemotherapy is already established in advanced endometrial carci-

CONTACT Georgios I Papageorgiou Tel.: +3069 4006 8547; georgeipap@hotmail.gr

This article has been corrected with minor changes. These changes do not impact the academic content of the article.

noma [13]. The DUO-E Phase III trial assessed the addition of durvalumab to first-line chemotherapy, followed by maintenance durvalumab with or without the addition of olaparib. In the intention-to-treat population at the first interim analysis, both arms were found superior versus chemotherapy alone cohort in terms of progression-free-survival (PFS), but only the durvalumab (an anti-PD-L1 monoclonal antibody which blocks the interaction between PD-L1 and PD-1) – olaparib (a PARP1 and PARP2 inhibitor) combination proved its superiority versus control in terms of OS. Furthermore, patients treated with the durvalumab – olaparib combination seem to fare better than the ones treated with durvalumab alone in the maintenance setting, but unfortunately no direct comparison can be drawn between the two arms due to the study design [14].

Based on the prespecified exploratory subgroup analyses, the addition of olaparib seems to benefit the proficient missmatch repair (pMMR) subgroup the most, a finding which is consistent with the paradigm suggested by Brown et al. in 2018 [3]. PD-L1 positive tumors seem to benefit from the addition of durvalumab – with or without olaparib, while patients with mutations in the homologous recombination repair pathway achieved a 70% reduction in the risk of progression or death when treated with durvalumab – olaparib versus control. Additionally, it seems that patients with serous histology derive the most benefit when given olaparib on top of chemoimmunotherapy [14].

4. "The bad" – Disappointing evidence in ovarian cancer & lung cancer; or not exactly?

Although PARPi were first introduced in the field of medical oncology owing to their effectiveness in advanced ovarian cancer, the results of immunotherapy still remain devastating in this tumor type. A variety of mechanisms are linked with resistance to ICIs, defining ovarian cancer as a generally immune-cold tumor [15]. It may be assumed that this disease would not be the most ideal to point out a clinical synergy between PARPi and immunotherapy, although a possible benefit in distinct subgroups (endometrioid histology, other less common histologies, dMMR, MSI-high) could not be ruled out.

Despite the pessimistic preclinical evidence, the DUO-O Phase III trial aimed to investigate the benefit of adding both durvalumab and olaparib to standard-of-care treatment in non-*BRCA* patients with advanced ovarian cancer similarly to the successful DUO-E trial in endometrial cancer; of note, durvalumab was used upfront, while olaparib was added in the maintenance setting. As expected, the first interim analysis revealed a statistically and clinically meaningful benefit in terms of PFS, which was more pronounced in HRD patients. Unfortunately, no safe conclusions arise from this study, as no PARPi was allowed in the control arm as maintenance treatment; for this reason, the benefit of durvalumab addition cannot be quantified [16].

Regarding the data arising from non-small cell lung cancer (NSCLC), the ongoing Phase III KEYLINK-06 trial is investigating the efficacy of pembrolizumab – olaparib versus pembrolizumab – pemetrexed maintenance after first-line standard chemoimmunotherapy in patients with nonsquamous NSCLC. Specifically, in March 2024 the sponsor announced that the combination misses the PFS and OS end points, but the investigators are expecting the data to mature in order to provide a full analysis in the future. Despite the disappointing early results leading to a seemingly negative trial, the design of this trial should serve as the paradigm for designing similar studies in other malignancies, as it aimed to uncover the efficacy of PARPi in the maintenance setting after achieving a benefit from platinum-based chemoimmunotherapy. Furthermore, this study proves that PARPi do not benefit patients with NSCLC as it would be anticipated after response to platinum, even if this is an unanimously platinum-sensitive disease. Perhaps we should look into the subgroup of patients who could derive some benefit from this approach, as it is known that a minority of NSCLC patients respond to platinum rechallenge – which means that their disease is more vulnerable to DNA damage [17]. The same conclusions could be drawn from the KEYLINK-008 Phase III trial in squamous NSCLC that was halted due to futility [18].

5. "The ugly" – The off-label clinical experience in breast cancer

The oncology community is gradually becoming more confident in combining immunotherapy with olaparib in the adjuvant setting of certain triple-negative breast cancer (TNBC) patients, even though no randomized clinical trial has established the superiority of this approach versus standard-of-care practice [19]. The relevant studies incorporating these two drugs separately in everyday clinical practice are thoroughly analyzed in the following paragraphs.

KEYNOTE-522 set a pembrolizumab-based chemoimmunotherapy approach as the standard-of-care choice in nonmetastatic TNBC, as the combination induced increased pathologic complete responses (pCR) and event-free survival rates versus neoadjuvant chemotherapy alone [20], regardless of the PD-L1 score and the pCR outcome [21]. Of note, adjuvant treatment with neither capecitabine nor olaparib was allowed in this study, while another study had already previously proven the benefit

of adding immunotherapy to chemotherapy in metastatic TNBC irrespective of germline *BRCA* (g*BRCA*) status [22].

During the same period of time, the OlympiA trial assessed the use of olaparib for 1 year in the adjuvant setting of high-risk HER2-negative breast cancer with g*BRCA* mutations. Around half of the participants had received neoadjuvant therapy – but not the KEYNOTE-522 regimen as it had not been proven at that time. The second interim analysis showed a statistically significant OS benefit for patients treated with olaparib versus placebo [23].

As the safety of the immunotherapy – olaparib combination has already been shown in the MEDIOLA trial [24], this regimen is increasingly being utilized in the adjuvant setting of TNBC patients carrying g*BRCA* – and other [25] – mutations, who received the KEYNOTE-522 regimen preoperatively without achieving pCR, with the hope of offering an additive or even synergistic effect. Indirect evidence suggests that patients with g*PALB2* mutations also derive benefit from adjuvant olaparib, so this subgroup is also often treated with this off-label regimen in everyday clinical practice [25]. It would be valuable to collect real world data from this off-label approach, or even conduct a relevant randomized clinical trial in TNBC on the basis of the KEYNOTE-522 study, with the exception of permitting the adjuvant use of olaparib where applicable.

The same strategy should be investigated in the perioperative setting of hormone-receptor positive breast cancer with g*BRCA* mutations, given the encouraging preliminary results of the KEYNOTE-756 study [26].

6. Conclusion & future perspective

Although numerous trials have investigated the combination of PARPi with ICIs, there is still insufficient data to establish this combination versus standard-of-care options. One reason is the inclusion of unselected patient populations in most studies. The lack of consensus in defining and precisely measuring HRD in nonovarian tumors is indicative in the prospective study of Kim et al. that was published in 2022; in this case, HRD was defined as the presence of at least one HR related gene mutation [27], while the definition of HRD in ovarian cancers is much more complex and correlated with increased benefit from PARPi [28].

Eventually, the combination of PARPi with immunotherapy could provide an individualized approach for patients with diverse malignancies. For this reason, it is essential to precisely define and measure HRD in each type of malignancy so as to predict the anticipated benefit from PARPi. These drugs may augment the efficacy of immunotherapy, converting immune-cold tumors to hot ones [3]. In addition, the radiosensitising properties of PARPi [29] could be exploited in clinical trials, which could in turn induce the so-called "abscopal effect" when combined with immunotherapy [30]. Consequently, the inclusion of carefully selected patient populations might shed light to the extent of synergy in the clinical setting and also lead to approvals.

Author contributions

All authors contributed equally to this work.

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ORCID

Georgios I Papageorgiou
https://orcid.org/0000-0002-8370-9802
Nikolaos Skouteris https://orcid.org/0000-0002-5725-8243
Kleopatra Eleftheriou
https://orcid.org/0009-0002-1026-4627
Christos Kosmas https://orcid.org/0000-0001-6790-5785

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov. 2019;18(3):197–218. doi:10.1038/s41573-018-0007-y
2. Classen S, Petersen C, Borgmann K. Crosstalk between immune checkpoint and DNA damage response inhibitors for radiosensitization of tumors. Strahlenther Onkol. 2023;199(12):1152–1163. doi:10.1007/s00066-023-02103-8
3. Brown JS, Sundar R, Lopez J. Combining DNA damaging therapeutics with immunotherapy: more haste, less speed. Br J Cancer. 2018;118(3):312–324. doi:10.1038/bjc.2017.376

   • **Suggests a preliminary sequencing approach between immune checkpoint inhibitors (ICIs) and PARP inhibitors based on preclinical data.**

4. Peyraud F, Italiano A. Combined PARP inhibition and immune checkpoint therapy in solid tumors. Cancers. 2020;12(6):1502. doi:10.3390/cancers12061502
5. Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. J Immunother Cancer. 2019;7(1):278. doi:10.1186/s40425-019-0768-9
6. Yélamos J, Moreno-Lama L, Jimeno J, Ali SO. Immunomodulatory roles of PARP-1 and PARP-2: impact on PARP-centered cancer therapies. Cancers. 2020;12(2):392. doi:10.3390/cancers12020392
7. Matulonis U, Herrstedt J, Oza A, et al. Final overall survival and long-term safety in the ENGOT-OV16/nova Phase III trial of niraparib in patients with recurrent ovarian cancer (LBA 6). Gynecol Oncol. 2023;176:S31–S32. doi:10.1016/j.ygyno.2023.06.508
8. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Eng J Med. 2017;377(6):523–533. doi:10.1056/NEJMoa1706450
9. Hirschl N, Leveque W, Granitto J, et al. PARP inhibitors: strategic use and optimal management in ovarian cancer. Cancers. 2024;16(5):932. doi:10.3390/cancers16050932
10. Ray-Coquard I, Leary A, Pignata S, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Ann Oncol. 2023;34(8):681–692. doi:10.1016/j.annonc.2023.05.005
11. Fizazi K, Azad AA, Matsubara N, et al. First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the Phase III TALAPRO-2 trial. Nat Med. 2024;30(1):257–264. doi:10.1038/s41591-023-02704-x
12. Zhang Z, Shen L, Peng Z. Does first-line immunotherapy impact the efficacy of later treatments: a discussion on the use of second progression-free survival as a research endpoint. J Cancer Res Clin Oncol. 2022;148(10):2921–2924. doi:10.1007/s00432-022-04068-0
    • **ICIs seem to provide their optimal efficacy when given upfront in any tumor type.**
13. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus chemotherapy in advanced endometrial cancer. N Eng J Med. 2023;388(23):2159–2170. doi:10.1056/NEJMoa2302312
14. Westin SN, Moore K, Chon HS, et al. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: the Phase III DUO-E trial. J Clin Oncol. 2024;42(3):283–299. doi:10.1200/JCO.23.02132
    •• **Durvalumab – Olaparib combination is a safe and effective maintenance treatment in advanced endometrial cancer. More research is needed in order to establish this strategy as a standard-of-care.**
15. Pawłowska A, Rekowska A, Kuryło W, et al. Current understanding on why ovarian cancer is resistant to immune checkpoint inhibitors. Int J Mol Sci. 2023;24(13):10859. doi:10.3390/ijms241310859
16. Harter P, Trillsch F, Okamoto A, et al. Durvalumab with paclitaxel/carboplatin (PC) and bevacizumab (BEV), followed by maintenance durvalumab, Bev, and Olaparib in patients (PTS) with newly diagnosed Advanced ovarian cancer (AOC) without a tumor BRCA1/2 mutation (non-tbrcam): results from the randomized, placebo (pbo)-controlled Phase III duo-O trial. J Clin Oncol. 2023;41(Suppl. 17):LBA5506. doi:10.1200/jco.2023.41.17_suppl.lba5506
17. Petrelli F, Coinu A, Cabiddu M, et al. Platinum rechallenge in patients with advanced NSCLC: a pooled analysis. Lung Cancer. 2013;81(3):337–342. doi:10.1016/j.lungcan.2013.06.022
18. Hochmair M, Schenker M, Dols MC, et al. Abstract CT034: results from Phase III KEYLYNK-008: pembrolizumab (pembro) with and without maintenance olaparib (OLA) after first-line (1L) pembro plus chemotherapy (chemo) for metastatic squamous non-small-cell lung cancer (SQNSCLC). Cancer Res. 2024;84(Suppl. 7):CT034. doi:10.1158/1538-7445.am2024-ct034
19. Han HS, Vikas P, Costa RLB, et al. Early-stage triple-negative breast cancer journey: beginning, end, and everything in between. Am Soc Clin Oncol Edu Book. 2023;43:e390464. doi:10.1200/EDBK_390464
    • **The oncology community has started to adopt an off-label olaparib – pembrolizumab use in the adjuvant setting of certain triple-negative breast cancer patients.**
20. Schmid P, Cortes J, Dent R, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. N Eng J Med. 2022;386(6):556–567. doi:10.1056/NEJMoa2112651
21. Schmid P, Cortés J, Dent RA, et al. LBA18 pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: updated EFS results from the Phase III keynote-522 study. Ann Oncol. 2023;34:S1257. doi:10.1016/j.annonc.2023.10.008
22. Emens LA, Molinero L, Loi S, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer: biomarker evaluation of the IMpassion130 study. J Natl Cancer Inst. 2021;113(8):1005–1016. doi:10.1093/jnci/djab004
23. Geyer CE Jr, Garber JE, Gelber RD, 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;33(12):1250–1268. doi:10.1016/j.annonc.2022.09.159
24. Drew Y, Kim JW, Penson RT, et al. Olaparib plus durvalumab, with or without bevacizumab, as treatment in PARP inhibitor-naïve platinum-sensitive relapsed ovarian cancer: a Phase II multi-cohort study. Clin Cancer Res. 2024;30(1):50–62. doi:10.1158/1078-0432.CCR-23-2249
    • **This trial has proved the safety of the combination of olaparib with immunotherapy.**
25. Morganti S, Bychkovsky BL, Poorvu PD, et al. Adjuvant olaparib for germline BRCA carriers with HER2-negative early breast cancer: evidence and controversies. Oncologist. 2023;28(7):565–574. doi:10.1093/oncolo/oyad123
26. Cardoso F, McArthur HL, Schmid P, et al. LBA21 keynote-756: Phase III study of neoadjuvant pembrolizumab (pembro) or Placebo (pbo) + chemotherapy (chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2- breast cancer. Ann Oncol. 2023;34:S1260–S1261. doi:10.1016/j.annonc.2023.10.011

27. Kim H, Ahn S, Kim H, et al. The prevalence of homologous recombination deficiency (HRD) in various solid tumors and the role of HRD as a single biomarker to immune checkpoint inhibitors. J Cancer Res Clin Oncol. 2022;148(9):2427–2435. doi:10.1007/s00432-021-03781-6
28. Telli ML, Timms KM, Reid J, et al. Homologous recombination deficiency (HRD) score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer. Clin Cancer Res. 2016;22(15):3764–3773. doi:10.1158/1078-0432.CCR-15-2477

• This research has defined homologous recombination deficient in ovarian carcinoma.

29. Jannetti SA, Zeglis BM, Zalutsky MR, et al. Poly(ADP-ribose)polymerase (PARP) inhibitors and radiation therapy. Front Pharmacol. 2020;11:170. doi:10.3389/fphar.2020.00170
30. Nabrinsky E, Macklis J, Bitran J. A review of the Abscopal effect in the era of immunotherapy. Cureus. 2022;14(9):e29620. doi:10.7759/cureus.29620

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Jenny Furlanetto, Frederik Marmé & Sibylle Loibl

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Drug Evaluation

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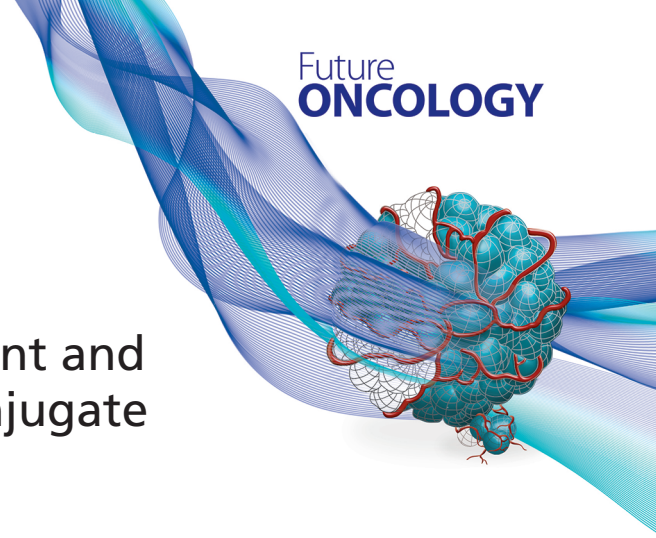

Sacituzumab govitecan: past, present and future of a new antibody–drug conjugate and future horizon

Jenny Furlanetto*,[1], Frederik Marmé[2] & Sibylle Loibl[1,3]

[1]German Breast Group, Neu-Isenburg, 63263, Germany

[2]Medical Faculty Mannheim, Heidelberg University, Universitätsfrauenklinik, Mannheim, 68167, Germany

[3]Centre for Haematology & Oncology, Bethanien, Frankfurt/M, 60389, Germany

*Author for correspondence: Tel.: +49 6102 7480 350; Jenny.Furlanetto@gbg.de

Sacituzumab govitecan (SG) is a new antibody–drug conjugate directed against the cell-surface antigen Trop-2. Characteristics of the linker connecting the payload SN-38 to the antibody allows SG to kill tumor cells expressing Trop-2 and also the adjacent tumor cells (bystander effect). SG showed efficacy and safety in several epithelial tumors. The phase III ASCENT trial led to the approval of SG (10 mg/kg, d1,8 q3w) in patients with advanced or metastatic triple-negative breast cancer (TNBC) who have received ≥2 prior systemic therapies, including ≥1 for metastatic disease. The phase III TROPiCS-02 trial in heavily pretreated advanced hormone receptor (HR)-positive breast cancer has recently shown an improvement in progression-free survival for patients treated with SG compared to single-agent chemotherapy. The phase III post-neoadjuvant SASCIA study in early high-risk TNBC and HR-positive breast cancer is currently recruiting patients.

Plain language summary: Sacituzumab govitecan is a new treatment for metastatic triple-negative breast cancer. Triple-negative means that the three most commonly identified proteins are not found on the surface of cancer cells (estrogen or progesterone receptor and high level of the protein HER2). Metastatic breast cancer indicates that the breast cancer has spread to other parts of the body. Sacituzumab govitecan is a monoclonal antibody, a therapeutic antibody or protein that can attach a specific target on the surface of cancer cells known as Trop-2. The antibody carries a medication known as SN-38, which is released within and around the cancer cells, causing the destruction of cancer cells. The ASCENT trial compared 3 acituzumab govitecan with chemotherapy, which is a treatment that kills cancer cells or stops them from dividing. The trial showed that patients with advanced triple-negative breast cancer who took sacituzumab govitecan lived longer than those who took a different chemotherapy regimen while on the study. The TROPiCS-02 trial showed that also patients with a metastatic cancer expressing estrogen or progesterone receptor, known as hormone-receptor positive breast cancer, derived benefit from sacituzumab govitecan. The SASCIA trial will define if patients with early breast cancer receiving sacituzumab govitecan after surgery might live longer without the recurrence of cancer. Early-stage breast cancer means that the cancer has not spread to other parts of the body and can be completely removed with surgery.

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Keywords: antibody–drug conjugate • early breast cancer • metastatic breast cancer • sacituzumab govitecan

Antibody–drug conjugates

Antibody–drug conjugates (ADCs) are a new class of drugs, composed of a monoclonal antibody usually humanized to reduce immunogenicity [1], bound to a highly potent chemotherapeutic agent (payload) through a linker (cleavable or non-cleavable). The characteristics of the linker are essential in determining where the drug is released (intra or extracellularly). Non-cleavable linkers are highly stable, resistant to proteolytic degradation, which allow cleavage only after antibody degradation within the lysosome, but these have lower membrane permeability [1,2]. Therefore, non-cleavable ADCs act primarily after internalization within cells expressing the target antigen and are best suited to treat cancers that have high and homogenous expression of the target [3]. Cleavable linkers

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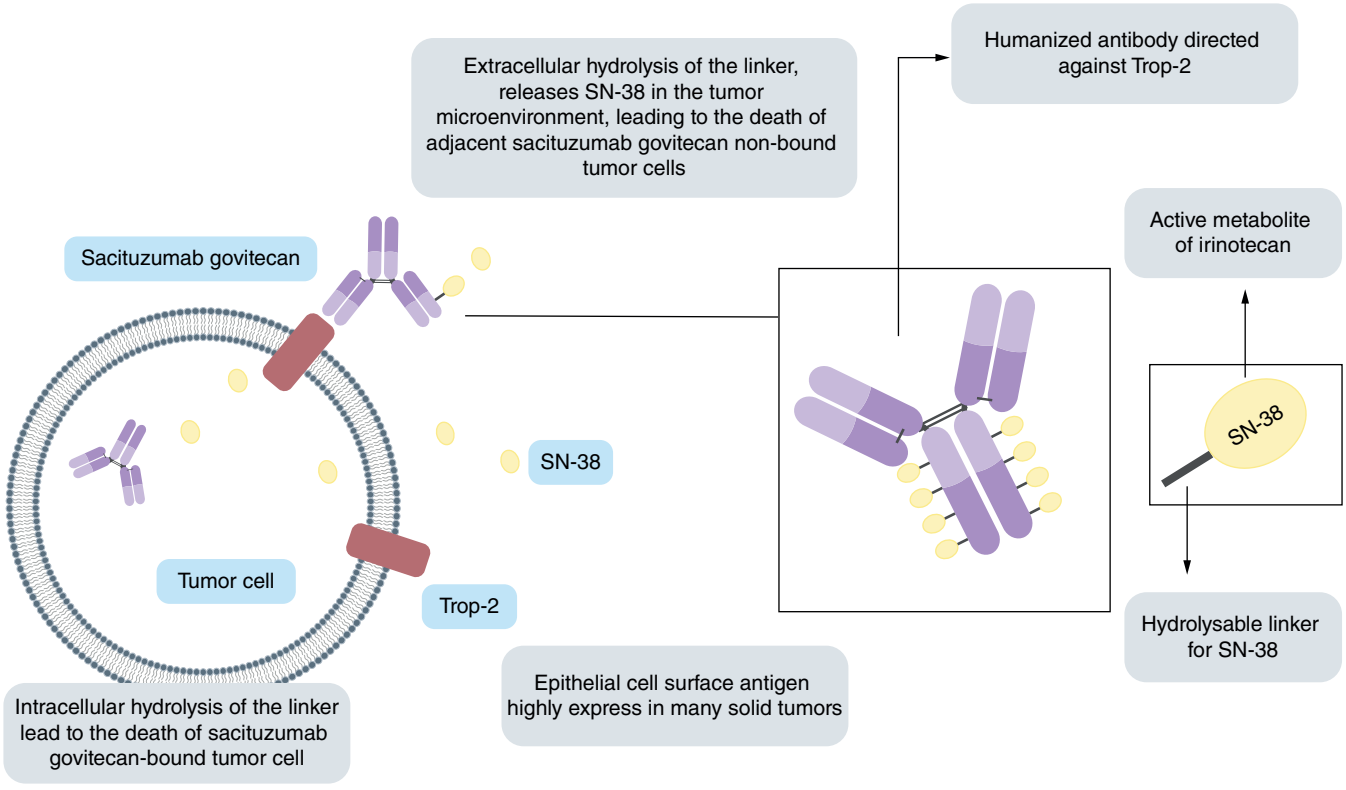

Figure 1. Sacituzumab govitecan mechanism of action.

are characterized by a cleavage occurring either through lysosomal proteases, glutathione reduction or in a pH-dependent fashion [4]. Owing to these properties, the ADC can kill the antigen-expressing cells after internalization and also the neighboring cells, which do not express the target antigen, by the release of the drug in the tumor microenvironment (bystander effect) [5]. The target of the monoclonal antibodies is usually expressed on the tumor cells or as a molecule of the stroma surrounding the tumor. Ideally, targeted antigens should be expressed at low level on normal cells and at high level on tumor cells or tumor microenvironment. The payload is usually an extremely potent anticancer drug, which cannot be administered as a free drug due to its narrow therapeutic index [1]. The conjugation to the monoclonal antibody permits the release of the drug within the tumor cells or in the tumor microenvironment but only to a very limited extent in the bloodstream, significantly reducing toxicity.

Currently, four ADCs are approved by the US FDA for the treatment of solid tumors: trastuzumab emtansine (T-DM1) [6–8], for the treatment of HER2-positive metastatic breast cancer (mBC) pretreated with trastuzumab and a taxane and for HER2-positive early breast cancer with residual disease after neoadjuvant trastuzumab and taxanes; trastuzumab deruxtecan (T-DXd) [9], for HER2-positive mBC progressing on two or more prior anti-HER2-based regimens; enfortumab vedotin (EV) [10], for locally advanced/metastatic urothelial carcinoma previously treated with a PD-(L)1 inhibitor and a platinum-based chemotherapy as (neo)adjuvant or metastatic treatment; and sacituzumab govitecan (SG). The present review mainly focuses on SG, which has been recently approved by the FDA as well as the EMA for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease [11].

Sacituzumab govitecan

SG is an ADC composed of the humanized monoclonal antibody hRS7 and the toxic payload SN-38. SN-38 is the active metabolite of irinotecan (topoisomerase-I inhibitor) (Figure 1). The target of sacituzumab is Trop-2, which was discovered about 40 years ago as a cell surface marker of trophoblast cells [12]. Subsequently, it became evident that the same glycoprotein expressed in several different tumor types had been described under several names (e.g. TACTSTD2, M1S1, GA733-1, EGP-1), and the name given at the time of discovery, Trop-2, was

used from then on [13]. Trop-2 is expressed in many epithelial solid cancers, including breast, gynecologic and gastrointestinal tumors, bladder and prostate cancer and oral squamous cell carcinoma [14]. In breast cancer MCF-7 cells, Trop-2 expression is necessary and sufficient to stimulate transformed cell growth [15]. Trop-2 overexpression might be associated with a less favorable breast cancer phenotype [16]. Especially TNBC is characterized by a high expression of Trop-2. Trop-2 expression levels were evaluated in 150 patients with TNBC using a validated immunohistochemistry assay and histochemical scoring (H-score). Overall, 56% patients had a high H-score (100–200), 26% had a H-score medium (200–300), and 18% had a low H-score (<100) [17,18]. Of the latter, seven patients did not express Trop-2 on immunohistochemistry. Trop-2 overexpression is linked to increased tumor growth and cell migration, contributing to tumor progression [19]. Among patients with breast cancer, Trop-2 activation state has been reported as a determinant of progression, with membrane localization associated with worse survival [20]. A meta-analysis of 15 studies showed that Trop-2 overexpression was significantly associated with poor overall survival (OS) in patients with solid tumors (pooled Hazard Ratio: 1.9; 95% CI: 1.6–2.25) [14]. SG binds to Trop-2 with nanomolar affinity. In contrast to other ADCs, SG is characterized by a moderately cytotoxic payload and high drug-to-antibody ratio (7.6:1) [21]. SN-38 is bound to the monoclonal antibody via the hydrolyzable linker CL2A, which enables SG to act with a double effect. The antibody component of SG binds to Trop-2 expressed on the cell surface of tumor cells, leading to an enrichment of the ADC within the tumor. The SG-Trop-2 complex is internalized via receptor-mediated endocytosis. Via lysosomal degradation the linker is cleaved, releasing the active SN-38, which can kill the tumor cell by blocking DNA replication. However, the time-depended hydrolysis of the linker releases part of SN-38 outside the tumor cells, within the tumor microenvironment, thereby killing adjacent tumor cells not expressing Trop-2 [21,22]. A similar ADC that comprised the same monoclonal anti-TROP2 antibody (hRS7) and SN-38 but a more stable linker leading to a lesser degree of extracellular drug release demonstrated lower activity in a preclinical mouse model, underlining the importance of the linker as part of the ADCs [22].

Dose selection

The phase I 3+3 dose escalation study (NCT01631552) [23] enrolled 25 patients with diverse metastatic epithelial cancers. SG was administered on d1,8 q3w cycles until dose-limiting toxicity or progression. Studied doses were 8, 10, 12 and 18 mg/kg. Most of the patients received acetaminophen, antihistamines and dexamethasone to avoid allergic reactions. However, prophylaxis with antiemetics and anti-diarrheal medications were not allowed. The maximum tolerated dose was 12 mg/kg, with neutropenia being the dose-limiting toxicity, but dose delays and dose reductions were frequent. To increase compliance, the two lower doses, 8 and 10 mg/kg were further investigated. No treatment-related grade 4 toxicities were observed, and grade 3 toxicities were confined to fatigue, neutropenia, leukopenia and diarrhea. The 8 and 10 mg/kg doses were selected for assessment in the phase II study (Recommended Phase II Dose, RP2D), as these dose levels permitted the administration of more cycles with limited toxicity. SG demonstrated activity also in patients who failed or relapsed under prior therapy with a topoisomerase-I inhibitor. The subsequent phase 2 dose-expansion component of the study focused on the accrual of additional patients with diverse metastatic epithelial cancers who progressed after at least 1 prior standard therapy. Enrollment was performed in a sequential manner, first at the 8 mg/kg dose level and then at the 10 mg/kg level given on d1,8 q3w cycles. Overall, 178 patients were enrolled at starting dose levels of 8 and 10 mg/kg, including those who were at these dose levels in the phase 1 trial. Safety of the two doses as well as the time on treatment were not different. However, as 10 mg/kg SG provides better overall response and clinical benefit rates compared to 8 mg/kg, the higher dose was chosen for further investigations in different indications [24].

Pharmacokinetics & pharmacodynamics

In the phase I escalation study, concentration of SG and the antibody IgG increased with increased dose. Most of SN-38 in the serum (>96%) was bound to IgG. At 10 mg/kg, the mean AUC(0-inf) for free SN-38 was 3630 ng·h/ml and the AUC(0-inf) for total SN-38 was 111 000 ng·h/ml, indicating that most of the SN-38 was bound to the antibody. The sample size was small for the 8 mg/kg group, but exposure parameters increased with increasing dose [25]. In serum *in vitro*, 50% of SN-38 was released from the ADC within 24 h. SG cleared with a half-life of approximately 11 to 14 h, reflecting the release of SN-38 from the conjugate [22]. IgG cleared more slowly (half-life, approximately 103–114 h). Clinically, more than 90% of SN-38 is released in 3 days. In xenograft models hRS7-CL2A-SN-38 conjugate (conditionally cleavable) was superior to the highly stable hRS7-CL2E-SN-38 and control conjugate with CL2A linker, owing to enhanced bystander effect [26]. No antibody response against hRS7

Table 1. Summary of the available efficacy results of sacituzumab govitecan in several advanced epithelial tumors.

Cohort[†]	ITT	ORR (%, 95% CI)	CBR (%, 95% CI)	mPFS (months, 95% CI)	mOS (months, 95% CI)	Ref.
TNBC	108	33.3 (24.6–43.1)	45.4 (35.8–55.2)	5.6 (4.8–6.6)	13 (11.2–14.0)	[25,33]
$HR^+/HER2^-$ BC	54	31.5 (19.5–45.6)	44.4 (30.9–58.6)	5.5 (3.6–7.6)	12 (9.0–18.2)	[25,34]
Non-small-cell lung cancer	54	16.7 (7.9–29.3)	24.1 (13.5–37.6)	4.4 (2.5–5.4)	7.3 (5.6–14.6)	[25,35]
Small-cell lung cancer	62	17.7 (9.2–29.5)	24.2 (14.2–36.7)	3.7 (2.4–4.8)	7.1 (5.6–8.1)	[25,36]
Esophageal carcinoma	19	5.3 (0.1–26.0)	21.1 (6.1–45.6)	3.4 (1.9–6.0)	7.2 (4.9–14.7)	[25]
Colorectal cancer	31	3.2 (0.1–16.7)	19.4 (7.5–37.5)	3.9 (1.9–5.6)	14.2 (6.8–19.1)	[25]
Pancreatic adenocarcinoma	16	0 (0–20.6)	0 (0–20.6)	2.0 (1.1–3.5)	4.5 (2.9–7.0)	[25]
Urothelial cancer	45	28.9 (16.4–44.3)	44.4 (29.6–60.0)	6.8 (3.6–9.7)	16.8 (9.0–21.9)	[25,37]
Endometrial	18	22.2 (6.4–47.6)	44.4 (21.5–69.2)	3.2 (1.9–9.4)	11.9 (4.7–nr)	[25]
Castrate-resistant prostate cancer	11	9.1 (0.2–41.3)	27.3 (6.0–61.0)	np	np	[25]

[†]Due to the small size of the cohorts, results on patients with head and neck squamous cell carcinoma (n = 4), gastric cancer (n = %), glioblastoma multiforme (n = 3), hepatocellular carcinoma (n = 2), renal cell carcinoma (n = 1), cervical cancer (n = 1), ovarian cancer (n = 8) are not available.
CBR: Clinical benefit rate; DOR: Duration of response; HR: Hormone receptor; ITT: Intention-to-treat; m: Median; np: Not present; nr: Not reported; nr: Not reached; ORR: Overall response rate; OS: Overall survival; OSP: Overall safety population; PFS: Progression-free survival; TNBC: Triple-negative breast cancer; UC: Urothelial cancer.

IgG or SN-38 was detected, even after multiple cycles [23,24]. The volume of distribution was estimated as 2.72 l for SG and 1.44 l for the naked antibody. These results suggest that SG is distributed more than the unconjugated antibody. SN-38 is highly bound to human plasma proteins, predominantly albumin [27]. The distribution and clearance of the antibody portion of SG is similar to other IgG1 antibodies and is influenced by Trop-2-mediated uptake, pinocytosis and FcRn-receptor mediated uptake and clearance mechanisms *in vivo*. The estimated clearance of SG was 0.132 l/h and that of IgG 0.0143 l/h, suggesting that the ADC is cleared faster than the naked antibody. As long as SN-38 is tied to the antibody, it is protected from glucuronidation. In the liver, SN-38 can be conjugated to UGT1A1 forming the inactive metabolite SN-38G. SN-38 may also be metabolized by CYP3A4.

SG is most efficacious at the high drug-antibody ratio of 7.6:1, which does not affect binding and pharmacokinetics. It delivers up to 136-fold more SN-38 to tumors than irinotecan [28]. SG delivers SN-38 in its most active, non-glucuronidated form, which may explain the lower frequency of severe diarrhea than with irinotecan. Interestingly, antitumor effect of SG was greater in mice-bearing tumors with higher Trop-2 expression, with significantly greater effects with SG vs all other treatments in these mice. However, a clinical benefit was observed both in chemo-sensitive solid tumors with low Trop-2 expression, as well as in chemo-resistant tumors with high Trop-2 expression [29].

IMMU-132-01: phase I/II basket trial in metastatic solid tumors

IMMU-132-01 was a phase I and II multicenter, single-arm, basket study (NCT01631552), which enrolled patients with many different solid epithelial tumors, including patients with mTNBC refractory to or relapsed after at least one standard line of therapy. Patients with brain metastases were enrolled only if stable. In the phase II part, all patients received SG 10 mg/kg administered intravenously on d1,8 q3w cycles. Treatment was given until disease progression, unacceptable toxicity, investigator or patient decision or death. The first analysis was conducted in 69 patients with mTNBC [18]. Most of them were heavily pretreated, with a median of five prior treatment lines. SG was administered for a median of 14 doses with median exposure duration of about 5 months. The overall response rate (ORR) was 30%, with a median time to an objective response of 1.9 months and a median duration of response of 8.9 months. Despite being a heavily pretreated population, median progression-free survival (PFS) was 6 months and overall survival (OS) was 16.6 months favoring SG when compared with previous reports on single agent chemotherapy [30,31]. Patients with moderate/strong Trop-2 staining demonstrated a longer median PFS compared to patients with weak expression (7.1 vs 3.1; p = 0.019). A summary of the efficacy results of the phase I/II basket trials in several advanced epithelial cancers is presented in Table 1. The toxicity profile was manageable, with 41% of the patients experiencing grade 3-4 AEs mainly neutropenia (39%), leukopenia (16%), anemia (14%) and diarrhea (13%). Febrile neutropenia was experienced by 7% of the patients. Dose reduction due to adverse events (AEs) was necessary mainly due to neutropenia for 19% of the patients in the first two cycles, 16% later on. Based on these preliminary results, SG was assigned a 'breakthrough therapy' designation by the FDA in 2016 for the treatment of patients with mTNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease [32]. The analyses conducted in the expanded cohort of 108 patients

confirmed the results previously obtained (Table 1) [33]. Additionally, there was no significant difference in response rates according to patient age, number of previous therapies, or the presence or absence of visceral metastases. Among patients who received previous checkpoint inhibitors, the response rate was 44%. No new safety concerns emerged. Efficacy and safety in mTNBC patients were further evaluated in the phase III confirmatory ASCENT study (NCT02574455) [11].

In the basket trial, a further cohort of 54 patients with hormone receptor (HR)-positive/HER2-negative breast cancer was included. Patients had to have disease progression on endocrine-based therapy and should have received at least one prior chemotherapy for mBC [34]. Overall, 59% of the patients received prior treatment with a CDK4/6 inhibitor and 44% with an mTOR inhibitor. Patients in this cohort received a median of 13.5 doses of SG, with a median duration of exposure of 4.6 months. About one-third of the patients achieved an objective response with a median time to an objective response of 2.1 months. ORR was higher and median PFS, and OS were longer in patients without prior exposure to CDK4/6 inhibitors (ORR in patients without vs with prior CDK4/6 inhibitor, 40.9% vs 25%), although numbers for this comparison are very small. As for patients with mTNBC, SG demonstrated a favorable activity in HR-positive advanced breast cancer (Table 1) with a manageable safety profile when compared to the current standard of care chemotherapy in this setting [38]. Efficacy and safety in patients with HR-positive advanced breast cancer is further evaluating in the ongoing phase III TROPiCS-02 study (NCT03901339) [39].

Data published on multiple histologic cohorts showed that SG has antitumor efficacy in non-small-cell lung cancer [35], small-cell lung cancer [36], and metastatic urothelial carcinoma [37] (Table 1). Efficacy and safety data on the overall cohort of patients with epithelial tumors were recently published (overall safety population) and includes previously unpublished disease cohorts (e.g. gastrointestinal, pancreatic, endometrial and renal cell carcinoma) [25]. SG showed antitumor activity and a good tolerability in patients with different refractory metastatic epithelial cancers. In patients with gastrointestinal tumors, response rate was low, possibly due to previous irinotecan exposure. This was not the case for patients with small-cell lung cancer, which respond despite previous therapy with irinotecan. The highest response rates were achieved in patients with endometrial carcinoma. Median PFS and OS were similar in the different cohorts but were longer in patients with colorectal cancer. Toxicity was in line with previous reports and was manageable with dose reductions/delays and supportive treatment such as growth factor support or antidiarrheal medications. Only 8% of the patients discontinued treatment due to AEs. Patients homozygous for the *UGT1A1*28* allele showed higher risk for neutropenia but not diarrhea. Results are in line with the analysis of the ASCENT study [11]. Even if the assessment of *UGT1A1* genotype is not generally recommended, patients with known *UGT1A1* homozygous *28/*28 genotype should be carefully monitored [40]. In the basket study, *UGT1A1* genotype was available for 81.4% of the patients, and 9.3% were found to be homozygous for the 28* allele. An overview of ongoing studies in solid tumors is presented in Table 2.

On the basis of the results of the subsequent TROPHY-U-01 (NCT03547973) [41] single-arm, phase II, multicenter trial, in April 2021, the FDA granted accelerated approval to SG for patients with locally advanced or metastatic urothelial cancer who previously received a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor [42]. The phase 3 confirmatory trial TROPiCs-04 (NCT04527991) is ongoing.

Phase III trials in metastatic breast cancer

Triple-negative breast cancer

The ASCENT study was a phase III confirmatory, multicenter, randomized trial in patients with mTNBC who received at least 2 previous lines of chemotherapy for unresectable, locally advanced or mBC [11]. Patients with disease recurrence within 12 months of completing (neo)adjuvant chemotherapy were included after only 1 regimen in the metastatic setting [43]. Patients were randomized 1:1 to receive either SG at a dose of 10 mg/kg of body weight or treatment of physician's choice (TPC, capecitabine, gemcitabine, vinorelbine, eribulin) as defined before randomization. Treatment was given until disease progression or unacceptable toxicities. Patients were stratified according to the number of prior lines (2 vs 3 or >3). Patients with stable brain metastasis were eligible, but not analyzed for the primary endpoint, which was centrally assessed PFS in patients without baseline brain metastases. Secondary endpoints included OS, investigator assessed PFS, objective response and safety. A total of 529 patients participated in the trial, and 61 had baseline brain metastases. Median age was 54 years. All patients had received previous taxanes. The trial was halted early in March 2020 due to compelling evidence of efficacy. The objective response for the group treated with SG was 35% (4% complete response, 31% partial response) vs 5% for patients treated with TPC ($p < 0.0001$). The centrally assessed median PFS for patients treated with SG was 5.6

Table 2. Overview of studies with sacituzumab govitecan in solid tumors (as of 17.01.2022).

	Indication	Designation	Phase	Drug	Sample size (n)	Primary endpoint	Status
Breast	HER2$^-$ BC, residual disease after NACT	SASCIA (NCT04595565)	III	SG vs TPC (capecitabine, platinum-based chemotherapy) for 8 cycles or observation	1200	Invasive DFS	Recruiting
	HER2$^-$ BC, residual disease after NACT	ASPRIA (NCT04434040)	II	Atezolizumab + SG for 6 cycles	40	Undetectable circulating tumor DNA after 18 wks	Recruiting
	Localized TNBC, neoadjuvant	NeoSTAR (NCT04230109)	Umbrella, II	1°cohort: SG 4 cycles → standard TPC 2°cohort: SG + pembrolizumab 4 cycle → standard CT of PC SG +/- pembrolizumab in HR+ BC and IBC	100	pCR with SG	Active, not recruiting
	Refractory/relapsed mTNBC	ASCENT (NCT02574455)	III	SG vs TPC (eribuline, capecitabine, gemcitabine, vinorelbine) until PD or unacceptable toxicity	529	PFS	Completed
	HER2$^-$ mBC with brain metastasis	NCT04647916	II	SG ≤2 years until disease progression or unacceptable toxicity	44	Intracranial ORR	Recruiting
	mTNBC, at least prior treatment, Chinese	NCT04454437	II	SG until PD or unacceptable toxicity	80	ORR	Active, not recruiting
	HER2$^-$ mBC, PD1 negative	NCT04468061	II	SG+/-Pembrolizumab Patients with CR after at least 24 wks of therapy may be eligible for pembrolizumab and/or SG after PD	110	PFS	Recruiting
	mTNBC, at least 2 prior treatment	VERU-111 (NCT05008510)	II	Sabizabulin vs SG Sabizabulin + SG vs SG	216	PFS	Not yet recruiting
	Advanced TNBC, at least 2 prior treatment	NCT05113966	II	Trilaciclib + SG	45	PFS	Recruiting
	Advanced TNBC	InCITe (NCT03971409)	II	Avelumab → avelumab + binimetinib Anti-OX40 Antibody → Anti-OX40 Antibody + avelumab Utomilumab → utomilumab + avelumab Binimetinib → binimetinib + liposomal doxorubicin SG → SG + avelumab liposomal doxorubicin → liposomal doxorubicin + avelumab until PD or unacceptable toxicity	150		Recruiting
	Advanced TNBC, at least 2 prior treatment	NCT04927884	I/II	SG + chemoimmunotherapy (cyclophosphamide, N-803, PD-L1 t-haNK)	79	MTD, best ORR safety	Recruiting

ANC: Absolute neutrophil count; BC: Breast cancer; CPI: Checkpoint inhibitor; CR: Complete response; CRPC: Castration-resistant prostate cancer; CT: Chemotherapy; DFS: Disease-free survival; DLT: Dose-limiting toxicity; HRD: Homologous recombination deficiency; HNSCC: Head and neck squameous cell carcinoma; IBC: Inflammatory breast cancer; m: Metastatic; MIBC: Muscle invasive bladder cancer; MTD: Maximum tolerated dose; NSCLC: Non-small cell lung cancer; ORR: Overall response rate; OS: Overall survival; pCR: Pathologic complete response; PD: Progressive disease; PD1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; PSA: Prostate-Specific Antigen; SCLC: Small cell lung cancer; SG: Sacituzumab govitecan; SmPC: Summary of Product Characteristics; TEAE: Treatment-emergent adverse event; TPC: Treatment of Physician's Choice; UC: Urothelial cancer; UGT1A1: Uridine diphosphate-glucuronosyl transferase 1.

Table 2. Overview of studies with sacituzumab govitecan in solid tumors (as of 17.01.2022) (cont.).

	Indication	Designation	Phase	Drug	Sample size (n)	Primary endpoint	Status
	Advanced TNBC	Morpheus-TNBC (NCT03424005)	Umbrella, I/II	1°line PD-L1-positive: atezolizumab + nab-paclitaxel vs atezolizumab + nab-paclitaxel + tocilizumab vs atezolizumab + SG vs capecitabine; 2°line chemo-naïve: atezolizumab + ipatasertib vs atezolizumab + SGN-LIV1A vs atezolizumab + selicrelumab + bevacizumab vs atezolizumab + chemotherapy (gemcitabine + carboplatin or eribulin)	280	ORR AEs	Recruiting
	mBC	NCT04039230	I/II	SG + talazoparib	75	DLT	Recruiting
	Locally recurrent or mBC HER2-	ASSET (NCT05143229)	I	Alpelisib + SG	18	Recommended phase II dose	Not yet recruiting
	$HR^+/HER2^-$ mBC	TROPiCS-02 (NCT03901339)	III	SG vs TPC (eribulin, capecitabine, gemcitabine, vinorelbine)	400	PFS	Active, not recruiting
	$HR^+/HER2^-$ mBC, Asian	NCT04639986	III	SG vs TPC (eribulin, capecitabine, gemcitabine, vinorelbine)	330	PFS	Recruiting
	$HR^+/HER2^-$ mBC	NCT04448886	II	SG+/-pembrolizumab. Patients with CR may receive pembrolizumab and/or SG after PD	110	PFS	Recruiting
Endometrial	Persistent or recurrent endometrial carcinoma with elevated Trop-2	NCT04251416	II	SG until disease progression or unacceptable toxicity	50	ORR	Recruiting
Lung	Advanced NSCLC with PD on/after platinum-based chemotherapy and anti-PD-1/PD-L1	EVOKE-01 (NCT05089734)	III	SG vs docetaxel until PD or unacceptable toxicity	520	OS	Recruiting
	Advanced NSCLC	EVOKE-02 (NCT05186974)	II	SG + pembrolizumab SG + pembrolizumab + carboplatin SG + pembrolizumab + cisplatin	164	ORR, DLTs	Not yet recruiting
	mNSCLC	Morpheus Lung (NCT03337698)	I/II	Experimental arms with several different investigational products, including atezolizumab + SG	435	% of patients with OR	Recruiting
	Advanced SCLC and HRD cancers resistant to PARP inhibitors	NCT04826341	I/II	SG + berzosertib until PD or unacceptable toxicity	70	MTD,ORR overall and HRD cohort	Recruiting
Prostrate	mCRPC progressing on abiraterone or enzalutamide	NCT03725761	II	SG for a minimum of 3 cycles	55	PSA rate	Suspended (accrual goal met)

ANC: Absolute neutrophil count; BC: Breast cancer; CPI: Checkpoint inhibitor; CR: Complete response; CRPC: Castration-resistant prostate cancer; CT: Chemotherapy; DFS: Disease-free survival; DLT: Dose-limiting toxicity; HRD: Homologous recombination deficiency; HNSCC: Head and neck squameous cell carcinoma; IBC: Inflammatory breast cancer; m: Metastatic; MIBC: Muscle invasive bladder cancer; MTD: Maximum tolerated dose; NSCLC: Non-small cell lung cancer; ORR: Overall response rate; OS: Overall survival; pCR: Pathologic complete response; PD: Progressive disease; PD1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; PSA: Prostate-Specific Antigen; SCLC: Small cell lung cancer; SG: Sacituzumab govitecan; SmPC: Summary of Product Characteristics; TEAE: Treatment-emergent adverse event; TPC: Treatment of Physician's Choice; UC: Urothelial cancer; UGT1A1: Uridine diphosphate-glucuronosyl transferase 1.

Table 2. Overview of studies with sacituzumab govitecan in solid tumors (as of 17.01.2022) (cont.).

	Indication	Designation	Phase	Drug	Sample size (n)	Primary endpoint	Status
Urothelial	mUC progressing on platinum-based chemotherapy and PD1/L1 inhibitors	NCT04724018	I	Dose escalation and de-escalation of SG + enfortumab vedotin	24	MTD DLTs	Not yet recruiting
	mUC	TROPHY U-01 (NCT03547973)	II	SG (previous treated with platinum-based and/or CPIs; SG (ineligible for platinum-based therapy and PD after immune CPIs); SG + pembrolizuman; cisplatin followed by SG for 6 cycles → maintenance with avelumab followed by SG (platinum naive); SG + cisplatin + avelumab (platinum naive)	321	ORR	Recruiting
	Advanced, PD after platinum-based/anti- PD-1/PD-L1 therapy	TROPiCS-04 (NCT04527991)	III	SG vs TPC (paclitaxel, docetaxel, vinflunine)	600	OS	Recruiting
	Cisplatin-ineligible MIBC and mUC	MORPHEUS-UC (NCT03869190)	Umbrella, I/II	Arms with several different investigational products, including atezolizumab + SG	735	ORR pCR for MIBC	Recruiting
	Cisplatin ineligible mUC	NCT04863885	I/II	Phase I: SG + ipilimumab + nivolumab Phase II: SG + ipilimumab + nivolumab for 4 cycles followed by nivolumab until PD or unacceptable toxicity	46	MTD ORR	Recruiting
Brain	Recurrent glioblastoma	NCT04559230	II	SG until PD or unacceptable toxicity	40	PFS	Not yet recruiting
	Glioblastoma or metastatic brain tumors from breast	NCT03995706	0	GG 1 cycle before surgery; SG after brain surgery until PD	20	SG-metabolites/serum concentration	Recruiting
Solid tumors	mNSCLC/HNSCC/endometrial (Trop-2+)	TROPiCS-03 (NCT03964727)	II	SG until PD or unacceptable toxicity	200	ORR	Recruiting
	Advanced esophageal squamous-cell/cervical carcinoma, gastric adenocarcinoma	NCT05119907	II	SG until PD or intolerable toxicity	180	ORR	Recruiting
	m solid tumors benefiting from SG	NCT04319198	Rollover Study	As in the parental study	200	Long-term safety	Enrolling by invitation
	Advanced tumors/TNBC, Japanese	ASCENT-J02 (NCT05101096)	I/II	SG dose escalation in solid tumors; SG dose escalation in solid tumors in subjects with UGT1A1 polymorphism; SG dose escalation in mTNBC	61	TEAEs, laboratory abnormalities, DLT, ORR	Recruiting
	m epithelial cancer	NCT01631552	I/II	SG with dose escalation until PD or unacceptable toxicity	515	TEAEs, ORR, interruption discontinuation,	Completed
	Advanced TNBC/mUC/Ovarian	SEASTAR (NCT03992131)	I/II	Rucaparib and lucitanib vs rucaparib + SG	329	TEAEs, DLT, ORR	Active, not recruiting
	Advanced, moderate liver impairment	NCT04617522	I	SG dose escalation	24	Safe starting dose	Recruiting
	mNSCLC, mTNBC	NCT05006794	I	GS-9716 dose escalation GS-9716 + docetaxel GS-9716 + SG	205		Recruiting

ANC: Absolute neutrophil count; BC: Breast cancer; CPI: Checkpoint inhibitor; CR: Complete response; CRPC: Castration-resistant prostate cancer; CT: Chemotherapy; DFS: Disease-free survival; DLT: Dose-limiting toxicity; HRD: Homologous recombination deficiency; HNSCC: Head and neck squameous cell carcinoma; IBC: Inflammatory breast cancer; m: Metastatic; MIBC: Muscle invasive bladder cancer; MTD: Maximum tolerated dose; NSCLC: Non-small cell lung cancer; ORR: Overall response rate; OS: Overall survival; pCR: Pathologic complete response; PD: Progressive disease; PD1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; PSA: Prostate-Specific Antigen; SCLC: Small cell lung cancer; SG: Sacituzumab govitecan; SmPC: Summary of Product Characteristics; TEAE: Treatment-emergent adverse event; TPC: Treatment of Physician's Choice; UC: Urothelial cancer; UGT1A1: Uridine diphosphate-glucuronosyl transferase 1.

(95% CI: 4.3–6.3) compared to 1.7 (95% CI: 1.5–2.6) months in TPC arm (hazard ratio 0.41, 95% CI: 0.32–0.52; $p < 0.001$). Investigator-assessed PFS was consistent with central assessment. The median OS was 12.1 (95% CI: 10.7–14.0) months in SG arm compared to 6.7 (95% CI: 5.8–7.7) months in TPC arm (hazard ratio 0.48, 95% CI: 0.38–0.59; $p < 0.001$). The benefit of SG over chemotherapy was observed in all predefined subgroups, including patients ≥65 years [44], patients previously treated with PD1/PD-L1 inhibitors, or with liver metastases. In patients ≥65 years improvement in median PFS with SG vs TPC was comparable with that of the overall population (7.1 vs 2.4 months; hazard ratio 0.22, 95% CI: 0.12–0.40) as was OS (15.3 vs 8.2 months; hazard ratio 0.37, 95% CI: 0.22–0.64), with increased ORR (50% vs 0) [44]. In the exploratory analysis conducted in patients with known brain metastases at baseline (n = 61), SG showed a numerically better tumor response compared TPC (clinical benefit rate 9% vs 3%), with more patients having a stable disease with SG (47% vs 31%). Median PFS was in favor of SG (2.8 vs 1.6, hazard ratio 0.65, 95% CI: 0.35–1.22), with better PFS rate at 3 and 9 months. Median OS was not improved by the use of SG (6.8 vs 7.5 months, hazard ratio 0.87, 95% CI: 0.47–1.63). Data should be taken with caution, due to the small number of patients with brain metastases enrolled [45]. Efficacy of SG was further analyzed in patients who recurred ≤12 months after (neo)adjuvant chemotherapy and received 1 line of therapy in the metastatic setting, prior to study enrollment (SG n = 33, TPC n = 32). Also in the subset of patients with early relapse, SG improved PFS (5.7 vs 1.5 months; hazard ratio 0.41, 95% CI: 0.22–0.76) and OS (10.9 vs 4.9 months; hazard ratio 0.51, 95% CI: 0.28–0.91) compared to TPC, with increased ORR (30% vs 3%) [43]. These data support the use of SG as second-line treatment option in patients with mTNBC. In the TPC arm of the ASCENT trial, 54% of the patients received eribulin, 20% vinorelbine, 13% capecitabine and 12% gemcitabine. When efficacy of SG was evaluated against each agent individually, SG maintained its benefit compared to all of the included chemotherapies. ORR of SG was 35% vs 5% with eribulin, 4% with vinorelbine, 6% with capecitabine, and 3% with gemcitabine respectively. Median PFS of SG was 5.6 compared to 2.1, 1.6, 1.6, and 2.7 months. Median OS was 12.1 months vs 6.9, 5.9, 5.2, and 8.4 months [46]. Based on the results of the ASCENT trial, in April 2021 the FDA granted regular approval to SG (Trodelvy, Immunomedics Inc.) for patients with unresectable locally advanced or mTNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease. The recommended SG dose is 10 mg/kg once weekly on d1,8 q3w cycles until disease progression or unacceptable toxicity [47]. Finally, SG was also approved by the EMA in November 2021 for the same indication. General instructions for SG administration are provided in Table 3.

The biomarker analyses assessing the value of Trop-2 expression and germline *BRCA1/2* mutation on SG treatment were recently published [17]. The clinical benefit of SG was observed irrespective of Trop-2 expression. However, higher efficacy of SG was seen in patients with medium/high H-score compared to a low H-Score. Patients with high, medium and low H-scores had a median PFS of 6.9 months (95% CI: 5.8–7.4 months), 5.6 months (95% CI: 2.9–8.2 months), and 2.7 months (95% CI: 1.4–5.8 months), respectively. Median OS was 14.2 months (95% CI: 11.3–17.5 months), 14.9 months (95% CI: 6.9 months-not evaluable), and 9.3 months (95% CI: 7.5–17.8 months), respectively. The ORR with SG according to the H-scores was 44%, 38%, and 22%, respectively. Data should be taken with caution due to the small number of patients in the low H-score group (n = 59). As SN-38 leads to DNA double-strand breaks it was assumed that patients with *BRCA1/2* mutations might be more sensitive to SG. However, SG demonstrated similar efficacy regardless of germline *BRCA1/2* mutation. In *BRCA1/2* mutated patients, the median PFS was 4.6 vs 2.5 months in SG treated vs TPC treated patients, respectively; median OS was 15.6 vs 4.4 months. In *BRCA1/2* wild-type patients, the median PFS was 4.9 and 1.6 months respectively; median OS was 10.9 vs 7 months. In *BRCA1/2*-mutant patients, ORR was 19% vs 6% in SG-treated vs TPC-treated patients. In *BRCA1/2* wild-type patients, the ORR was 33% vs 6% in SG-treated vs TPC-treated patients, respectively. The number of patients with germline *BRCA1/2* mutations is too small to derive conclusions. The tumor of patients included in the ASCENT trial had to be triple-negative on their latest tumor biopsy and therefore the trial also included a number of patients that had HR-positive tumors at their initial diagnosis but whose tumors had lost HR expression during their evolution. This subset of patients has also been investigated separately, demonstrating results absolutely comparable to the overall population (PFS hazard ratio 0.48; OS hazard ratio 4.44) [49]. Ongoing studies with SG in solid tumors are presented in Table 2.

HR-positive breast cancer

The TROPiCS-02 trial is a phase III, open-label, randomized, multicenter trial of SG vs treatment of physician's choice in patients with HR+/HER2- mBC who have received at least two but not more than four prior lines of chemotherapy [39]. Patients must be aged ≥18 years, have histologically confirmed HR+/HER2- mBC,

Table 3. General instructions for sacituzumab govitecan administration.

Patients' information
■ Inform patients about the most common side effects (i.e. infusion-related reactions, neutropenia, nausea, vomiting, diarrhea, alopecia) and on the possible interventions
■ Ask for concomitant medications: inhibitors or inducers of UGT1A1 are expected to increase or decrease SN-38 exposure, respectively, and should be used with caution.
Dosage
■ 10 mg/kg body weight administered as an intravenous infusion once weekly on day 1 and day 8 of 21-day treatment cycles.
Investigations
Administer SG only if:
■ Day 1: ANC $\geq$1500/mm^3
■ Day 8: ANC $\geq$1000/mm^3
No testing of Trop-2 or *UGT1A1* status is required.
Premedication
Infusion-related reactions:
■ Antipyretics and H1 and H2 blockers should be administered before each SG infusion
■ Corticosteroids may be administered prior to subsequent infusions if the subject had experienced an infusion-related reaction with a previous infusion.
Antiemetic prophylaxis:
■ Patients should be premedicated prior to each infusion with a standard two-drug regimen (5-HT3 antagonist and dexamethasone)
■ A 3-drug regimen including a NK-1 antagonists may be considered in patients with persistent nausea and vomiting
■ Anticipatory nausea can be treated with olanzapine.
Diarrhea and cholinergic syndrome:
■ Routine prophylaxis for diarrhea is not recommended
■ In case of acute diarrhea or early cholinergic syndrome patients should be treated with atropine. Prophylaxis with atropine should be used for future infusions
■ At the onset of delayed diarrhea, infections should be ruled out. In case of negative results, loperamide should be start.
Infusion
■ First infusion: administer over a period of 3 h
■ Subsequent infusions: administer over a period of 1 to 2 h if prior infusions were well tolerated.
Adverse reactions
■ Observe patients during each infusion and for at least 30 min after each infusion for signs or symptoms of infusion-related reactions
■ Treat all toxicities with the maximum supportive measures to avoid complications (follow the latest available version of SG SmPC for adverse reactions management)
■ Dose should not be re-escalated after a dose reduction for adverse reactions
■ In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, in particular severe neutropenia, and appropriate treatment instituted
■ Patients with known reduced UGT1A1 activity should be closely monitored for adverse reactions. When unknown, no testing of *UGT1A1* status is required as the management of adverse reactions including the recommended dose modifications will be the same for all patients.

ANC: Absolute neutrophil count; SG: Sacituzumab govitecan; SmPC: Summary of Product Characteristics.
Reference: [48].

relapsed/refractory to two to four prior systemic chemotherapy regimens for mBC, including at least one prior anticancer hormonal treatment and at least one CDK4/6 inhibitor in any setting. Overall, 543 patients were randomized 1:1 to receive SG or treatment of physician's choice (eribulin, capecitabine, gemcitabine or vinorelbine). The co-primary endpoints of the study are PFS and ORR. Secondary/exploratory endpoints include OS, duration of response, safety, quality of life as well as blood and tumor biomarkers. Results on the primary endpoints were recently presented [50]. The median age of the patients enrolled was 56 years. Overall, patients received a median of three prior chemotherapy regimens for mBC, 86% prior endocrine therapy in the metastatic setting for $\geq$6 months, 60% and 38% received prior CDK4/6 inhibitors for $\leq$12 and >12 months, respectively, 95% had visceral metastases. SG significantly improved the median PFS compared to treatment of physician's choice (5.5 vs 4 months, hazard ratio 0.66, 95% CI: 0.53–0.83; p = 0.0003) in this very heavily pretreated population. The observed benefit was consistent in all the subgroups including patient with visceral metastases, aged $\geq$65 years and receiving more than 3 prior regimens for mBC. ORR was higher with SG (21% vs 14%) and median duration

of response was 7.4 vs 5.6 months, respectively. A trend in improvement for OS was observed with SG (13.9 vs 12.3 months, hazard ratio, 0.84; p = 0.143), but further follow-up is needed as the data is not yet mature [50]. A similar trial is ongoing in an Asian population only (NCT04639986, Table 2).

Compliance & toxicity

In line with the known safety profile of SG, the most common treatment-related adverse events (TRAEs) of any grade with SG compared to TPC in the ASCENT trial were neutropenia (63% vs 43%), diarrhea (59% vs 12%), nausea (57% vs 26%), alopecia (46% vs 16%), fatigue (45% vs 30%), and anemia (34% vs 24%). The most frequent TRAEs grade ≥3 were neutropenia (51% vs 33%), leukopenia (10% vs 5%), diarrhea (10% vs <1%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%). Neuropathy grade ≥2 did not occur in the SG arm and was low in the TPC arm (1%). Only one patient developed grade 3 pneumonitis, whereas no grade 1 or 2 interstitial lung disease was reported in the SG arm. No cases of pneumonitis were reported in the TPC arm. Febrile neutropenia was reported for 6% of patients in the SG arm and in 2% in the TPC arm. No severe cardiovascular toxicities occurred. Serious AEs were reported for 25% of patients with SG vs 8% with TPC [11]. Median time to onset of neutropenia grade ≥3 was 21 days in the SG arm, 14 days in the TPC arm with a median duration of 6 days. Myeloid growth factor was used in neutropenia management as secondary prophylaxis and as treatment in 29% and 30% of patients, respectively, in the SG arm and 10% and 17% in the TPC arm. Median time to onset of diarrhea grade ≥3 was 19 days vs 27 days, with a median duration of 5 days vs 1 day. Premedication or concomitant medication was used in diarrhea management in 55% and 10% of patients in the SG and TPC arms, respectively [51]. Median relative total dose intensity with SG was 99.7%. Dose reductions (22% vs 26%) and treatment discontinuations (5% in both groups; due to AEs 4.7% vs 5.4%, none due to neutropenia or diarrhea) were similar in both arms, and did not have any impact on SG efficacy [51]. In both arms three fatal events occurred due to AEs. None of those were considered to be related to SG [11].

Polymorphisms in the gene encoding *UGT1A1* are associated with SN-38 glucuronidation. Patients harboring *UGT1A1* polymorphisms might be at higher risk of hematologic toxicity. In the ASCENT trial, 97% of patients in the SG arm had genotype data at baseline. Of those, 45% were wild-type (*UGT1A1* genotype *1/*1) with normal enzymatic activity, 38% were heterozygous (*1/*28) with reduced activity and 14% were homozygous (*28/*28), with severely reduced activity. Patients with *UGT1A1* homozygous *28/*28 genotype were at higher risk for neutropenia, febrile neutropenia and diarrhea. Also, treatment discontinuations occurred more frequently. However, the prevalence of a homozygous *28/*28 genotype was relatively low. Therefore, the recommendations for treatment and toxicity management are not changed [51]. More data with this respect are expected from the ongoing trials. In patients ≥65 years, SG retained a manageable safety profile, which was comparable with the overall population. Key grade ≥3 TRAEs in patients aged ≥65 years with SG compared to TPC were neutropenia (45% vs 40%), anemia (14% vs 6%), leukopenia (10% vs 4%), diarrhea (10% vs 0%) and febrile neutropenia (8% vs 0%). The use of granulocyte-colony stimulating factor was 53% in the SG vs 29% in the TPC arm and of antidiarrheal medication was 65% vs 13%. Treatment discontinuations due to TRAEs were low, without any treatment-related deaths. Dose reductions were more frequent in older patients, but equally distributed among both arms [44]. The safety profile in patients with brain metastases was similar as in the overall population [45]. Trop-2 expression did not affect toxicity, and SG demonstrates a manageable safety profile consistent with that of the ASCENT overall study population [52]. No new safety signals emerged from the TROPiCS-02 trial [50]. Early toxicity management is essential to maintain an optimal exposure to SG and guidelines should be followed [53].

SASCIA: phase III trial in early breast cancer

Patients with TNBC without a pathological complete response (pCR) have a 5-year event-free survival rate of about 50% [54–56]. The association between pCR and prognosis is less pronounced in HR-positive/HER2-negative patients. However, the CPS+EG scoring system for prognosis after NACT, taking into account clinical stage (C), post treatment pathological stage (PS), estrogen receptor status (E) and grade (G), leads to an improved estimate of prognosis, allowing to select patients at high risk of relapse for post-neoadjuvant therapy [57]. Patients with TNBC without a pCR [54–56] after NACT as well as HR-positive/HER2-negative patients with a CPS+EG score ≥3 or 2 with metastatic lymph nodes after NACT have a high risk of recurrence. In high-risk patients, post-neoadjuvant therapy can significantly improve survival [58–61]. Based on the high activity of SG in heavily pretreated patients with mTNBC and HR-positive/HER2-negative breast cancer [11,62], even after prior immune-checkpoint inhibitors or

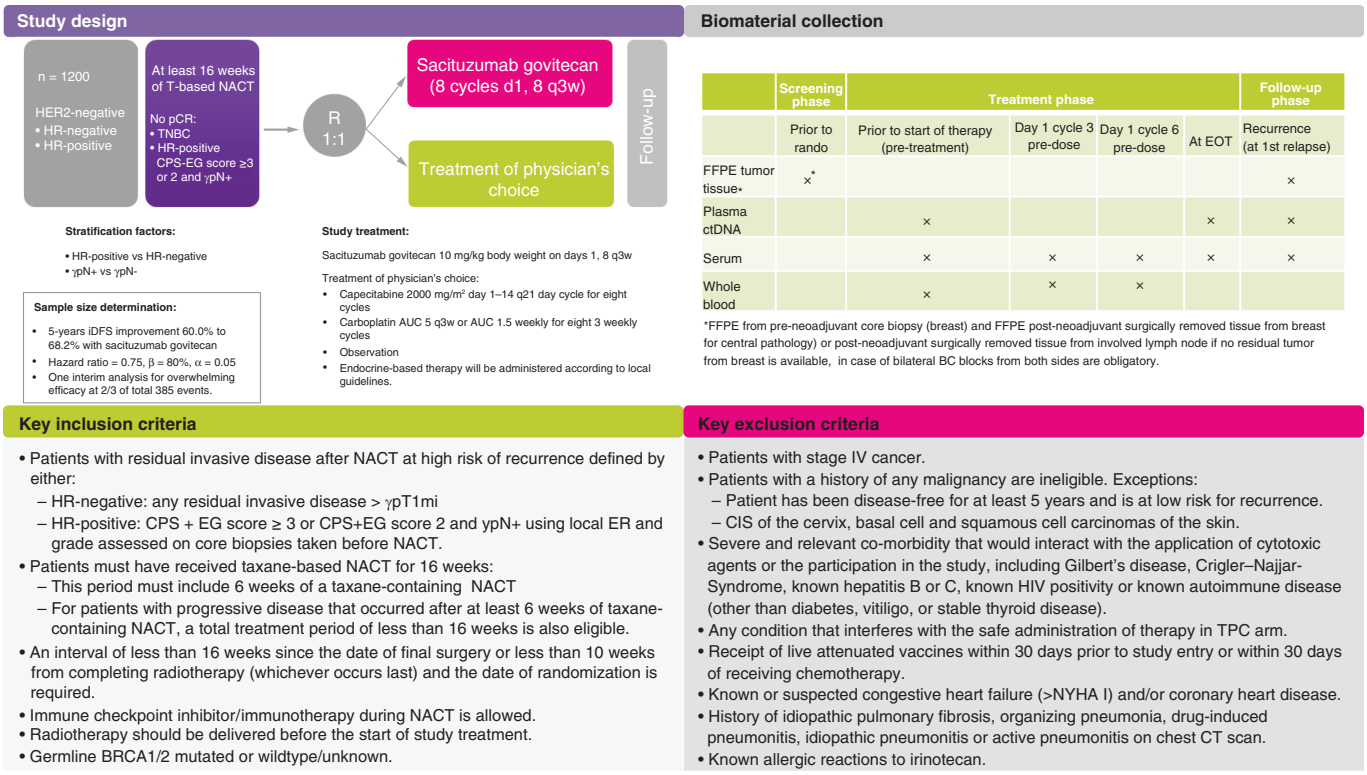

Figure 2. SASCIA study overview.
AUC: Area under the curve; CPS-EG: Clinical stage and post-treatment pathologic stage-estrogen receptor (ER) and grade (G); CT: Computed tomography; d: Day; FFPE: Formalin-fixed, paraffin-embedded; iDFS: Invasive disease-free survival; NACT: Neoadjuvant chemotherapy; q3w: Every 3 weeks; NYHA: New York Heart Association Functional Classification; TNBC: Triple-negative breast cancer; TPC: Treatment of physician´s choice.

CDK4/6 and mTOR inhibitors, SG might be an ideal therapy against the resistant residual disease after standard NACT regardless of HR status.

The phase III, prospective, multi-center, randomized, open-label, parallel group, SASCIA trial evaluates the use of SG in primary HER2-negative breast cancer patients at high risk of relapse after standard neoadjuvant treatment (Figure 2) [63]. Patients are defined as being of high risk of recurrence if diagnosed with TNBC and having residual disease (>ypTmi) after NACT or as HR-positive with CPS+EG score ≥3 or >2 with metastatic lymph nodes after NACT. SASCIA will randomize 1200 patients with centrally confirmed HER2-negative (Immunohistochemistry score 0-1 or FISH negative according to ASCO/CAP guideline), HR-positive (≥1% positive stained cells) or HR-negative breast cancer assessed preferably on tumor tissue from post-neoadjuvant residual invasive disease. Patients are allocated 1:1 to receive either SG or TPC (capecitabine or platinum-based chemotherapy) for 8 cycles, including observation. In patients with HR-positive breast cancer, endocrine-based therapy is administered according to local guidelines. The addition of a CDK4/6 inhibitor to endocrine therapy is allowed. The primary endpoint of the trial is invasive disease-free survival. Secondary endpoints include overall survival (key secondary objective), distant disease-free survival, safety, compliance, patient-reported outcome and quality of life. The trial comprises a wide translational research program, including the assessment of predictive markers for SG treatment and the analysis of circulated tumor DNA dynamics as early predictors of response (Figure 2). At the safety interim analysis including 88 randomized patients [64], SG showed a higher rate of AEs compared to TPC, which were in line with the known safety profile of SG. All patients had AEs G1-4 in SG arm vs 86.0% in TPC arm, and 66.7% vs 20.9% G3-4. The observed difference in G3-4 AEs was almost exclusively due to hematologic toxicities (55.6% vs 0%), whereas the rate of non-hematologic AEs was similar between the treatment arms (33.3% vs 28.15). Dose reductions occurred at identical rates in both treatment arms (SG: 26.7% vs TPC: 28.1%). Overall, 13.6% patients under SG discontinued therapy prematurely; 66.7% had ≥1 dose delay, due to hematological (46.7%) and non-hematological AEs (6.7%). Treatment discontinuations occurred in 9.4% in the TPC arm.

It should be considered that TPC includes patients who were only observed and received no further treatment. Moreover, AEs due to SG therapy were well manageable using the recommended supportive measures. Therefore, the study continues as planned. No other trial examines the administration of SG in the post-neoadjuvant setting. Currently, only one further trial with SG is ongoing in the early setting, the phase II NeoSTAR umbrella trial (Table 2) [65]. Patients with early TNBC were randomized to receive SG for 4 cycles followed by definitive surgery. Additional neoadjuvant therapy was foreseen if residual disease was confirmed at pre-surgical biopsy. Recently, preliminary results on the NeoSTAR trial were presented. Overall, 50 patients were randomized. The pathologic complete response rate with SG monotherapy was 30%, with a radiological response rate of 42%.

Conclusion & future directions

SG showed high activity in heavily pretreated patients and was efficacious in a population of patients with early relapse who may be resistant to chemotherapy. SG showed a favorable safety profile, also in older patients. The most common adverse events related with SG were neutropenia and diarrhea, which might be controlled with the early onset of appropriate supportive treatment. A careful monitoring and toxicity management according to guidelines is essential to guarantee an adequate treatment exposure. Ongoing studies will highlight the efficacy and safety of SG in other solid tumors and different settings. As resistance might occur due altered expression of the target antigen, the processing of the internalized ADC or against the toxic payload itself, additional ADCs should be explored. A further anti-Trop2 ADC, datopotamab deruxtecan (Dato-DXd) has shown promising results. Dato-DXd consist of an a humanized anti-TROP2 IgG1 monoclonal antibody, linked to a topoisomerase I inhibitor payload (exatecan derivative) via a tetrapeptide-based cleavable linker. The safety profile differs from that of SG, with low frequency of hematologic toxicity and diarrhea and with nausea and stomatitis being the most common AEs [66]. Interestingly, preliminary data on Dato-DXd suggests efficacy also in patients pretreated with SG, proving that a sequential treatment with ADCs having the same target or a similar payload might be effective. This might be due to the differences in the antibody itself or to the payload, being deruxtecan much more potent compared to govitecan or additionally to the payload concentration. In the absence of comparative data, the choice of ADCs should be guided by the toxicity profile, activity and patients preference. Further effort should be made in the selection of patients who can derived the most benefit by the treatment with the developed ADCs. The assessment of the target on a mRNA level instead of on a protein level by immunohistochemistry is an explored option. Moreover, combination therapy leading to enhance activity and improved outcome needs to be explored in the future.

Author contributions

All authors made a substantial contribution to the conception of the work; all authors drafted the work and revised it critically for important intellectual content; all authors approved the final version of the manuscript to be published; all authors agreed to be 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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Executive summary

Sacituzumab govitecan

- Sacituzumab govitecan (SG) is an antibody–drug conjugate composed of the humanized monoclonal antibody hRS7 and SN-38 (active metabolite of irinotecan) as the toxic payload.
- SN-38 cannot be administered as free drug due to its high toxicity. SN-38 is bound to the monoclonal antibody via the hydrolyzable linker CL2A, which ensures that an active concentration of SN-38 is maintained in the tumor tissue.
- The target of SG is Trop-2, expressed in many epithelial tumors, especially, triple-negative breast cancer (TNBC).
- Trop-2 overexpression is associated with poor overall survival (OS). SG can kill tumor cells with/without Trop-2 expression due to a bystander effect.

Dose selection

- The maximum tolerated dose of SG was 12 mg/kg, with neutropenia being the dose-limiting toxicity.
- The 8 and 10 mg/kg doses permitted the administration of more cycles with minimal toxicity and had a similar safety profile.
- The dose of 10 mg/kg was chosen for further investigation providing better overall response and clinical benefit rate.

Phase I/II basket trial in metastatic solid tumors

- SG demonstrated high activity in heavily pretreated patients with TNBC and hormone receptor (HR)-positive/HER2-negative breast cancer and a favorable safety profile.

Phase III studies in metastatic breast cancer

- The ASCENT trial led to the approval of SG (10 mg/kg on d1,8 q3w) in patients with advanced TNBC who have received ≥2 prior systemic therapies, ≥1 for metastatic disease.
- TROPiCS-02 evaluates SG vs treatment of physician's choice in patients with HR+/HER2- metastatic breast cancer who received ≥2 prior lines of chemotherapy.

Toxicity

- The most common treatment-related adverse events of any grade with SG were neutropenia, diarrhea, nausea, alopecia, fatigue and anemia.
- Patients with *UGT1A1* homozygous *28/*28 genotype were at higher risk for neutropenia, febrile neutropenia and diarrhea. Recommendations for treatment dosing in patients with *UGT1A1* mutation are not changed.
- Early toxicity management is essential to maintain an optimal exposure to SG.

The SASCIA trial: phase III study in early breast cancer

- SASCIA is a phase III, multi-center, randomized, open-label study evaluating SG vs treatment of physician's choice in primary HER2-negative breast cancer patients at high risk of relapse after standard neoadjuvant treatment.
- The primary endpoint is invasive disease-free survival, with OS being the key secondary endpoint.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Beck A, Goetsch L, Dumontet C, Corvaïa N. Strategies and challenges for the next generation of antibody-drug conjugates. *Nat. Rev. Drug Discov.* 16, 315–337 (2017).
2. Criscitiello C, Morganti S, Curigliano G. Antibody-drug conjugates in solid tumors: a look into novel targets. *J. Hematol. Oncol.* 14(1), 20 (2021).
3. Kovtun YV, Audette CA, Ye Y *et al.* Antibody-drug conjugates designed to eradicate tumors with homogeneous and heterogeneous expression of the target antigen. *Cancer Res.* 66(6), 3214–3221 (2006).
4. Tsuchikama K, An Z. Antibody–drug conjugates: recent advances in conjugation and linker chemistries. *Protein Cell* 9, 33–46 (2018).
5. Li F, Emmerton KK, Jonas M *et al.* Intracellular released payload influences potency and bystander-killing effects of antibody-drug conjugates in preclinical models. *Cancer Res.* 76(9), 2710–2719 (2016).
6. Verma S, Miles D, Gianni L *et al.* Trastuzumab emtansine for HER2- positive advanced breast cancer. *N. Engl. J. Med.* 367, 1783–1791 (2012).
7. Krop IE, Kim S-B, González-Martín A *et al.* Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 15, 689–699 (2014).
8. von Minckwitz G, Huang C-S, Mano MS *et al.* Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N. Engl. J. Med.* 380, 617–628 (2019).
9. Modi S, Saura C, Yamashita T *et al.* Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N. Engl. J. Med.* 382, 610–621 (2020).

10. Rosenberg JE, O'Donnell PH, Balar AV *et al.* Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. *J. Clin. Oncol.* 37, 2592–2600 (2019).
11. Bardia A, Hurvitz SA, Tolaney SM *et al.* ASCENT clinical trial investigators. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N. Engl. J. Med.* 384(16), 1529–1541 (2021).

•• **Phase III confirmatory study showing an improvement in PFS and OS with sacituzumab govitecan compared to single-agent chemotherapy for patients with metastatic triple-negative breast cancer.**

12. Lipinski M, Parks DR, Rouse RV, Herzenberg LA. Human trophoblast cell-surface antigens defined by monoclonal antibodies. *Proc. Natl. Acad. Sci. USA* 78, 5147–5150 (1981).
13. Shvartsur A, Bonavida B. Trop2 and its overexpression in cancers: regulation and clinical/therapeutic implications. *Genes Cancer* 6, 84–105 (2015).
14. Zeng P, Chen MB, Zhou LN, Tang M, Liu CY, Lu PH. Impact of TROP2 expression on prognosis in solid tumors: a systematic review and meta-analysis. *Sci. Rep.* 6, 33658 (2016).

• **TROP2 overexpression is associated with poor survival in human solid tumors.**

15. Trerotola M, Cantanelli P, Guerra E *et al.* Upregulation of Trop-2 quantitatively stimulates human cancer growth. *Oncogene* 32(2), 222–233 (2013).
16. Huang H, Groth J, Sossey-Alaoui K, Hawthorn L, Beall S, Geradts J. Aberrant expression of novel and previously described cell membrane markers in human breast cancer cell lines and tumors. *Clin. Cancer Res.* 11(12), 4357–4364 (2005).
17. Bardia A, Tolaney SM, Punie K *et al.* Biomarker analyses in the phase III ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer. *Ann. Oncol.* S0923-534(21)02047-0 (2021).

• **Sacituzumab govitecan benefits patients with previously treated mTNBC expressing high/medium Trop-2 compared with standard of care chemotherapy and regardless of germline BRCA1/2 mutation status.**

18. Bardia A, Mayer IA, Diamond JR *et al.* Efficacy and safety of anti-Trop-2 antibody drug conjugate sacituzumab govitecan (IMMU-132) in heavily pretreated patients with metastatic triple-negative breast cancer. *J. Clin. Oncol.* 35(19), 2141–2148 (2017).
19. Goldenberg DM, Stein R, Sharkey RM. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. *Oncotarget* 9(48), 28989–29006 (2018).
20. Lin H, Huang JF, Qiu JR *et al.* Significantly upregulated TACSTD2 and Cyclin D1 correlate with poor prognosis of invasive ductal breast cancer. *Exp. Mol. Pathol.* 94(1), 73–78 (2013).
21. Cardillo TM, Govindan SV, Sharkey RM *et al.* Sacituzumab govitecan (IMMU-132), an anti-Trop-2/SN-38 antibody-drug conjugate: characterization and efficacy in pancreatic, gastric, and other cancers. *Bioconjug Chem.* 26(5), 919–931 (2015).
22. Goldenberg DM, Cardillo TM, Govindan SV, Rossi EA, Sharkey RM. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). *Oncotarget* 6(26), 22496–22512 (2015).
23. Starodub AN, Ocean AJ, Shah MA *et al.* First-in-human trial of a novel anti-trop-2 antibody-SN-38 conjugate, sacituzumab govitecan, for the treatment of diverse metastatic solid tumors. *Clin. Cancer Res.* 21(17), 3870–3878 (2015).
24. Ocean AJ, Starodub AN, Bardia A *et al.* Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate for the treatment of diverse epithelial cancers: safety and pharmacokinetics. *Cancer* 123(19), 3843–3854 (2017).
25. Bardia A, Messersmith WA, Kio EA *et al.* Sacituzumab govitecan, a trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. *Ann. Oncol.* 32(6), 746–756 (2021).
26. Govindan SV, Cardillo TM, Sharkey RM, Tat F, Gold DV, Goldenberg DM. Milatuzumab-SN-38 conjugates for the treatment of CD74+ cancers. *Mol. Cancer Ther.* 12(6), 968–978 (2013).
27. CAMPTOSAR® (Irinotecan) Injection, intravenous infusion. Prescribing information. Last update: April 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020571s048lbl.pdf
28. Sharkey RM, McBride WJ, Cardillo TM *et al.* Enhanced delivery of SN-38 to human tumor xenografts with an anti-Trop-2-SN-38 antibody conjugate (sacituzumab govitecan). *Clin. Cancer Res.* 21(22), 5131–5138 (2015).
29. Cardillo TM, Mostafa AA, Rossi D *et al.* Abstract 3193: treatment of high Trop-2-expressing triple-negative breast cancer (TNBC) with sacituzumab govitecan (IMMU-132) overcomes homologous recombination repair (HRR) rescue mediated by Rad51. *Cancer Res.* 77(13), 3193 (2017).
30. Andre F, Zielinski CC. Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents. *Ann. Oncol.* 23(6), vi46–vi51 (2012).
31. Hurvitz S, Mead M. Triple-negative breast cancer: advancements in characterization and treatment approach. *Curr. Opin. Obstet. Gynecol.* 28, 59–69 (2016).
32. ESMO, FDA grants breakthrough therapy designation for sacituzumab govitecan for the treatment of TNBC; https://www.esmo.org/oncology-news/archive/fda-grants-breakthrough-therapy-designation-for-sacituzumab-govitecan-for-the-treatment-of-tnbc
33. Bardia A, Mayer IA, Vahdat LT *et al.* Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N. Engl. J. Med.* 380(8), 741–751 (2019).

34. Kalinsky K, Diamond JR, Vahdat LT *et al.* Sacituzumab govitecan in previously treated hormone receptor-positive /HER2-negative metastatic breast cancer: final results from a phase I/II, single-arm, basket trial. *Ann. Oncol.* 31(12), 1709–1718 (2020).
35. Heist RS, Guarino MJ, Masters G *et al.* Therapy of advanced non-small cell lung cancer with an SN-38-anti-Trop-2 drug conjugate, sacituzumab govitecan. *J. Clin. Oncol.* 35, 2790–2797 (2017).
36. Gray JE, Heist RS, Starodub AN *et al.* Therapy of small cell lung cancer (SCLC) with a topoisomerase-I-inhibiting antibody-drug conjugate (ADC) targeting Trop-2, sacituzumab govitecan. *Clin. Cancer Res.* 23, 5711–5719 (2017).
37. Tagawa ST, Faltas BM, Lam ET *et al.* Sacituzumab govitecan (IMMU-132) in patients with previously treated metastatic urothelial cancer (mUC): results from a phase I/II study. *J. Clin. Oncol.* 37, 354 (2019).
38. Kazmi SM, Chatterjee D, Alexis K *et al.* Real-world 1-year survival analysis of patients with metastatic breast cancer with liver or lung metastasis treated with eribulin, gemcitabine or capecitabine. *Ann. Oncol.* 30, v133 (2019).
39. Rugo HS, Bardia A, Tolaney SM *et al.* TROPiCS-02: a phase III study investigating sacituzumab govitecan in the treatment of HR+/HER2- metastatic breast cancer. *Future Oncol.* 16(12), 705–715 (2020).
40. Sacituzumab govitecan – FDA Access on September 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761115s000lbl.pdf
41. Tagawa ST, Balar AV, Petrylak DP *et al.* TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. *J. Clin. Oncol.* 39(22), 2474–2485 (2021).
42. U.S. Food & Drug Administration, FDA grants accelerated approval to sacituzumab govitecan for advanced urothelial cancer; www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sacituzumab-govitecan-advanced-urothelial-cancer
43. Carey LA, Loirat D, Punie K *et al.* Assessment of sacituzumab govitecan (SG) in patients with prior neoadjuvant/adjuvant chemotherapy in the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC). *J. Clin. Oncol.* 39(15), 1080 (2021).
44. Kalinsky K, Oliveira M, Traina MT *et al.* Outcomes in patients (pts) aged ≥65 years in the phase 3 ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC). *J. Clin. Oncol.* 39(15), 1011–1011 (2021).
45. Diéras V, Weave R, Tolaney SM *et al.* Subgroup analysis of patients with brain metastases from the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in metastatic triple-negative breast cancer. *Cancer Res.* 81(4), PD13-07 (2021).
46. O'Shaughnessy J, Punie K, Oliveira M *et al.* Assessment of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) cohort by agent in the phase 3 ASCENT study of patients (pts) with metastatic triple-negative breast cancer (mTNBC). *J. Clin. Oncol.* 39(15), 1077 (2021).
47. U.S. Food & Drug Administration, FDA grants regular approval to sacituzumab govitecan for triple-negative breast cancer; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-sacituzumab-govitecan-triple-negative-breast-cancer
48. SG Summary of Product Characteristics, version 24 November 2021. https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf
49. O'Shaughnessy J, Brufsky A, Rugo HS *et al.* Analysis of patients (pts) without an initial triple-negative breast cancer (TNBC) diagnosis (Dx) in the phase III ASCENT study of sacituzumab govitecan (SG) in brain metastases-negative (BMNeg) metastatic TNBC (mTNBC). *Ann. Oncol.* 32(Suppl. 5), S457–S515 (2021).

- **Patients without TNBC at initial diagnosis had a significant survival benefit with sacituzumab govitecan vs treatment of physician's choice, with a manageable safety profile. Outcomes were similar to those of the ASCENT trial's overall population.**

50. Rugo HS, Bardia A, Marmé F *et al.* Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer. *J. Clin. Oncol.* 40(Suppl. 17), LBA1001 (2022).
51. Rugo HS, Tolaney SM, Loirat D *et al.* Impact of UGT1A1 status on the safety profile of sacituzumab govitecan in the phase 3 ASCENT study in patients with metastatic triple-negative breast cancer. *Cancer Res.* 81(4), PS11-09 (2021).

- **Patients with UGT1A1 homozygous *28/*28 genotype treated with sacituzumab govitecan are at modestly higher risk for neutropenia and diarrhea and should be monitored closely.**

52. Hurvitz SA, Tolaney SM, Punie K *et al.* Biomarker evaluation in the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer. *Cancer Res.* 81(4), GS3-06 (2021).
53. Spring LM, Nakajima E, Hutchinson J *et al.* Sacituzumab govitecan for metastatic triple-negative breast cancer: clinical overview and management of potential toxicities. *Oncologist* 26(10), 827–834 (2021).
54. Hahnen E, Lederer B, Hauke J *et al.* Germline mutation status, pathological complete response, and disease-free survival in triple-negative breast cancer: secondary analysis of the GeparSixto randomized clinical trial. *JAMA Oncol.* 3(10), 1378–1385 (2017).
55. Sikov WM, Berry DA, Perou CM *et al.* Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J. Clin. Oncol.* 33, 13–21 (2015).
56. Petrelli F, Coinu A, Borgonovo K *et al.* The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. *Breast Cancer Res. Treat.* 144, 223–232 (2014).

57. Marmé F, Lederer B, Blohmer JU *et al.* Utility of the CPS+EG staging system in hormone receptor positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. *Eur. J. Cancer* 53, 65–74 (2016).

58. Masuda N, Lee SJ, Ohtani S *et al.* Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N. Engl. J. Med.* 376, 2147–2159 (2017).

59. von Minckwitz G, Huang CS, Mano MS *et al.* Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N. Engl. J. Med.* 380, 617–628 (2019).

60. Piccart-Gebhart M, Holmes E, Baselga J *et al.* Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J. Clin. Oncol.* 34, 1034–1042 (2016).

61. von Minckwitz G, Procter M, de Azambuja E *et al.* Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N. Engl. J. Med.* 377, 122–131 (2017).

62. Bardia A, Diamond JR, Vahdat LT *et al.* Efficacy of sacituzumab govitecan (anti-Trop-2-SN-38 antibody-drug conjugate) for treatment-refractory hormone-receptor positive (HR+)/HER2- metastatic breast cancer (mBC). *J. Clin. Oncol.* 36, 1004 (2018).

63. Marmé F, Stickeler E, Furlanetto J *et al.* Phase III postneoadjuvant study evaluating sacituzumab govitecan, an antibody drug conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment: SASCIA. *J. Clin. Oncol.* 39(15), TPS602 (2021).

64. Marmé F, Hanusch C, Furlanetto J *et al.* Safety interim analysis (SIA) of the phase III postneoadjuvant SASCIA study evaluating sacituzumab govitecan (SG) in patients with primary HER2-negative breast cancer (BC) at high relapse risk after neoadjuvant treatment. *Ann. Oncol.* 33(Suppl. 3), S148–S164 (2022).

65. Spring L, Tolaney SM, Desai NV *et al.* Phase 2 study of response-guided neoadjuvant sacituzumab govitecan (IMMU-132) in patients with localized triple-negative breast cancer: results from the NeoSTAR trial. *J. Clin. Oncol.* 40(Suppl. 16), 512 (2022).

66. Krop I, Juric D, Shimizu T *et al.* Datopotamab deruxtecan (Dato-DXd) in advanced/metastatic HER2 negative breast cancer: triple negative breast cancer results from the phase 1 TROPION-PanTumor01 study. *Cancer Res.* 82(Suppl. 4), GS1-05 (2022).

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Ruiliang Chen, Yushuai Yu, Jie Zhang, Chuangui Song & Chuan Wang

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META-ANALYSIS

Efficacy and safety of neoadjuvant therapy for HR-positive/HER2-negative early breast cancer: a Bayesian network meta-analysis

Ruiliang Chen [a,b,c*], Yushuai Yu [c,d*], Jie Zhang [a,b,c#], Chuangui Song [c,d#] and Chuan Wang [a,b,c#]

[a]Department of Breast Surgery, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, China; [b]Department of General Surgery, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, China; [c]Breast Cancer Institute, Fujian Medical University, Fuzhou, Fujian Province, China; [d]Department of Breast Surgery, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, Fujian Province, China

ABSTRACT

Background: Neoadjuvant treatment for hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer is controversial and requires a comprehensive analysis for optimal therapy assessment. Therefore, a two-step Bayesian network meta-analysis (NMA) was performed to compare the efficacy and safety of different neoadjuvant regimens.

Research design and methods: Phase II/III randomized clinical trials comparing various neoadjuvant therapies for HR+/HER2- breast cancer were included. NMA and pairwise meta-analyses were conducted using Stata (version 14), R (version 4.2.3), and Review Manager 5.4.

Results: Twenty-eight studies (5,625 patients) were eligible. NMA of objective response rate (ORR) indicated the highest SUCRA for chemotherapy (CT) and chemotherapy with anthracycline (CT(A)). Pathologic complete response (PCR) NMA demonstrated significant PCR improvement with chemotherapy regimens containing programmed cell death protein-1 and programmed cell death ligand-1 inhibitors (PD-1i/PD-L1i) and poly ADP-ribose polymerase inhibitors (PARPi). Combined analysis considering both the ORR and safety highlighted CT(A)'s efficacy and toxicity balance.

Conclusions: CT(A) and CT showed improved ORR compared with alternative regimens. CT(A) combined with PD-1/PD-L1 or PARP inhibitors significantly increased PCR rates. Comprehensive assessment of both ORR and safety indicated that CT(A) represents an optimal neoadjuvant therapy for HR+/HER2- breast cancer, whereas AI + CDK4/6 inhibitors rank solely behind chemotherapy.

Registration: PROSPERO Registration: CRD42024538948. International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) registration number INPLASY202440092.

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1. Introduction

Breast cancer (BC) is the most common cancer globally, accounting for approximately 11% of all new cancer cases, and is the leading cause of cancer-related deaths among women [1]. The hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) subtype is predominant, comprising approximately 65% of cases in women aged <50 years and 75% in those aged >50 years [2]. Recognized as a systemic disease, BC treatment increasingly incorporates neoadjuvant therapies. This approach aims to render inoperable tumors operable, favor breast preservation over mastectomy, and establish a basis for further treatment to enhance prognosis [3–6]. However, the efficacy of neoadjuvant therapy in HR+/HER2- BC is subject to debate because of its relatively low benefit compared to other breast cancer types [7,8]. The introduction of new agents, including CDK4/6 inhibitors (CDK4/6i), PARP inhibitors (PARPi), and PD-1/PD-L1 inhibitors (PD-1i/PD-L1i) has the potential to improve treatment outcomes in this patient group.

Several clinical trials have shown positive results highlighting the potential benefits of innovative therapeutic strategies. For example, the incorporation of pembrolizumab (PD-1i), olaparib (PARPi), or durvalumab (PD-L1i) into neoadjuvant chemotherapy (NAC) has been found to significantly enhance pathological complete response (PCR) rates in patients with HR+/HER2- BC [9–11]. The TBCRC 002 trial demonstrated that adding bevacizumab (VEGFi) to both neoadjuvant endocrine therapy (NET) and NAC improved the objective response rate (ORR) and PCR rates but also increased treatment toxicity [12]. CDK4/6 Inhibitors combined with endocrine therapy (ET) significantly improve survival prognosis in patients with advanced or metastatic HR+/HER2- BC [13]; however, their effectiveness in neoadjuvant treatment settings is still being explored [14,15]. Additionally, a meta-analysis published in 2016 showed that NET had similar clinical remission and breast-conserving surgery (BCS) rates to NAC in patients with HR+ breast cancer and that NET was significantly less toxic [16]. With more drugs and therapies emerging, the clinical value of neoadjuvant therapy for HR+ BC is evolving.

CONTACT Chuan Wang dr_chuanwang@fjmu.edu.cn Department of Breast Surgery, Fujian Medical University Union Hospital No, 29 Xin Quan Road, Gulou District, Fuzhou, Fujian Province 350001, China
*These authors have contributed equally to this work and share first authorship.
#Jie Zhang, Chuangui Song, and Chuan Wang are co-corresponding authors

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Specifically, employing neoadjuvant therapy to shrink tumors, boost surgery and BCS rates, or achieve higher PCR rates with more effective drug combinations is noteworthy. Consequently, in the current treatment context, the quest for and advancement of potent neoadjuvant treatment approaches are becoming increasingly important.

Network meta-analyses (NMA) enable the integration of direct and indirect comparisons between a broad range of treatment options, thereby providing a comprehensive evaluation of their relative efficacy. This approach offers indispensable insights into clinical decision-making. Previous NMAs focusing on neoadjuvant therapy for HR+ BC, although valuable, were mainly confined to endocrine therapy regimens and did not include chemotherapy, targeted therapy, or immunotherapy. Furthermore, these analyses primarily assessed ORR and safety without including PCR in their outcomes. The lack of differentiation based on HER2 expression status in patients with HR+ BC, coupled with the inclusion of only a limited set of clinical trials that did not encompass the most recent studies, may have limited their ability to provide a comprehensive evidence base for current clinical practice [17,18].

To address these limitations and provide an up-to-date evidence synthesis, we conducted a systematic assessment of the efficacy (assessing both ORR and PCR) and safety of various neoadjuvant regimens for HR-positive, HER2-negative, and early-stage breast cancer. This expanded approach not only overcomes the shortcomings identified in previous studies but also broadens the analysis to provide a nuanced and contemporary guide for clinical decision-making, reflecting the latest developments in treatment options and methodologies.

2. Patients and methods

The protocol has been registered on the international database of prospectively registered systematic reviews (PROSPERO CRD42024538948). Our study was also registered on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) under the registration number INPLASY202440092. More information about the review can be found at the following link: https://inplasy.com/. The protocol for this network meta-analysis has not been previously published in peer- reviewed journals.

2.1. Search strategy

This NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement (PRISMA 2020). We conducted a comprehensive systematic search of databases, such as PubMed, Embase, and the Cochrane Central Register of Clinical Trials. Additionally, we extensively searched for online articles from the American Society of Clinical Oncology, European Society for Medical Oncology, and San Antonio Breast Cancer Symposium. Our search strategy utilized predefined keywords: (neoadjuvant OR preoperative) AND (treatment OR therapy OR chemotherapy OR endocrine therapy OR target therapy) AND (breast OR mammary) AND (cancer OR carcinoma OR malignant OR neoplasm OR tumor) AND (hormone receptor-positive OR HR-positive OR HR+ OR estrogen receptor-positive OR ER+ OR ER-positive OR progesterone receptor-positive OR PR-positive OR PR+ OR Luminal) AND (HER-2- OR HER2- OR ERBB2- OR HER-2 negative OR HER2 negative OR ERBB2 negative OR human epidermal growth factor receptor 2 negative). The search included English-language studies without date restrictions, and we thoroughly checked the cited references in eligible studies for relevant articles.

2.2. Selection criteria

The prespecified inclusion criteria were as follows: (i) Phase II or III randomized clinical trials (RCTs) that focused on neoadjuvant therapy for HR+/HER2- BC; (ii) trials comparing two or more treatment arms; and (iii) availability of relevant outcome measures, such as ORR, PCR, grade 3–5 side effects data, and dropout events. The exclusion criteria were as follows: (i) case reports, case series, systemic reviews, retrospective studies, or non-randomized studies, and (ii) duplicate publications or redundant data from the same clinical trial. The selection process involved screening titles and abstracts for relevance, followed by a detailed evaluation of the full-text articles to ensure eligibility. Any disagreements or discrepancies in the study selection were resolved through discussion and consensus among the reviewers.

2.3. Data extraction

Two authors independently extracted and recorded data from eligible trials using a predefined procedure. The extracted items included the first author, publication year, trial name, country of origin, sample size of analyzed participants, tumor stage, menopause status, neoadjuvant therapy regimens, and treatment duration. Primary (ORR and PCR) and secondary (dropout rates due to adverse events) endpoints were also recorded.

2.4. Definition of outcomes

ORR was defined as the sum of partial and complete responses according to the Modified Response Evaluation Criteria in Solid Tumors (version 1.1) by MRI, US, or physical examination. PCR was defined as the absence of invasive residual cancer in the breast tissue and lymph nodes (ypT0/is ypN0) according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition. Dropout events were defined as the cause of patient withdrawal from the trial due to adverse events. The side effects considered in this study included anemia, neutropenia, thrombocytopenia, vomiting/nausea, diarrhea, stomatitis, mucositis, skin and subcutaneous tissue disorders, sensory neuropathy, hepatic toxicity, and fatigue. Side effects were graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4.0.

2.5. Study design

For ORR analysis, the treatments were classified into 13 experimental arms according to the prescribed drugs. Similarly, for the PCR analysis, the treatments were

categorized into 15 experimental arms. The 13 experimental arms for ORR were subsequently grouped into four strategy groups. In the NMA subgroup targeting the postmenopausal population, the treatment regimens were segregated into 11 experimental arms for the ORR analyses. For the PCR analysis, the regimens were organized into seven distinct experimental arms. Unfortunately, the number of clinical studies concentrating on premenopausal populations is too limited to allow for a comprehensive NMA. In the integrated evaluation of effectiveness and safety, treatment arms for which dropout rate data were missing were excluded from the analysis. The details of all arms are summarized in Supplemental File 1.

2.6. Statistical methods

In the analysis of direct and indirect comparisons, effect sizes were pooled using odds ratios (OR) and 95% confidence intervals (95% CI) because the outcomes were dichotomous variables. Direct evidence was integrated through a pairwise meta-analysis using Review Manager software (version 5.4). Heterogeneity was assessed using the Mantel-Haenszel chi-square test and I^2 test. We defined an I^2 above 50% as indicating a large between-study heterogeneity. The results of the direct comparison were calculated using either a fixed or random-effects model based on the value of I^2. For the Bayesian network meta-analysis, Markov chain Monte Carlo (MCMC) methods were employed using Stata (version 14) and R (version 4.2.3). Three Markov chains were run simultaneously for 50,000 iterations, with different initial values. Given the heterogeneity observed across the different clinical trials, a random-effects model was used to estimate each outcome. The ranking of the different treatments was determined using the network rank and surface under the cumulative ranking (SUCRA), where higher SUCRA values indicated higher ORR/PCR rates. The combined analysis of efficacy and safety was ranked by summing 50% of the SUCRA values for both efficacy (ORR) and safety (dropout rate) for each group.

We assessed the risk of bias in the included RCTs using the Cochrane Risk of Bias (ROB) 2.0 tool [19], which was used to examine the following five dimensions: (1) randomization process, (2) bias of the intended intervention, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of reported outcomes. Disagreements between authors were resolved through discussion. Publication bias was evaluated by analyzing the symmetry of the funnel plot features, which was generated using STATA. The symmetrical and focused arrangement of points within the funnel plots suggested the absence of significant bias. Asymmetry in the funnel plots prompted further evaluation using Egger's test.

2.7. Ethical approval

No ethical approval was required as data in this study is from previously published studies in which informed consent was obtained by primary investigators.

3. Results

3.1. Overview of literature search and study characteristics

The NMA included 28 eligible articles with a total of 5,625 patients. Among these, 18 articles focused on ORR [12,14,15,20–34], whereas 20 articles examined PCR [9–12,14,15,21–27,35–41]. Study selection followed the PRISMA flowchart shown in Figure 1 The PRISMA checklist is presented in Supplemental File 2. Six articles provided data from subgroup analyses of HR+/HER2- breast cancer. One article met the eligibility criteria for the present NMA based on abstracts published by ASCO. All eligible studies were RCTs conducted between January 2005 and June 2023. These trials included the JBCRG-09, IMPACT, and SWOG S0800 studies, which are three-arm RCTs, and the NEO-ORB and PALLET studies, which are four-arm RCTs. The remaining studies were two-arm RCTs. The comprehensive details of the included studies are provided in Supplemental File 3. Figure 2 depicts the NMA plot of ORR, dropout rates, and PCR in the experimental arms as well as the NMA plot of ORR in the different strategy groups.

3.2. Bias assessment

The overall risk of bias across all included trials was low (the chart of bias assessment is shown in Supplemental File 4). Of the 28 trials, 19 explicitly described the randomization methodology, while the rest of the studies mentioned randomization but did not explicitly describe the random assignment process. Most of the trials (15 of 28) employed an open-label design. Six studies employed blinding techniques for both the participants and personnel. Four of the 28 trials did not analyze the results of intention-to-treat populations, potentially leading to minimal attrition bias. All the included studies provided complete outcome data. None of these experiments indicated a high risk of detection or reporting biases. The funnel plots indicated no publication bias (Supplemental File 5).

3.3. ORR of experimental arms and different strategy groups

Two direct comparisons were conducted among the eligible studies. The CT(A) group was directly compared with the control group in six studies. A random-effects model was used because of the high heterogeneity observed ($p = 0.01$, $I^2 = 66\%$). CT(A) demonstrated a significantly higher ORR than the control groups (OR: 1.80, 95% CI: 1.02–3.18, $p = 0.04$; Figure 3a). Two studies directly compared CT(A) with ET, and a fixed-effects model was used because of moderate heterogeneity ($p = 0.17$, $I^2 = 47\%$). CT(A) exhibited a superior ORR compared to ET (OR: 3.29, 95% CI: 1.94–5.58, $p < 0.00001$; Figure 3b).

In the network meta-analysis, CT and CT(A) demonstrated the highest ORR, with posterior probabilities of 78.2% and 77.3%, respectively (Figure 4a), indicating their potential as effective treatment options. The AI + VEGF inhibitor group closely followed with a posterior probability of 64.6%. Conversely, the AI ± GnRHa and SERM ± GnRha exhibited the worst outcomes. Compared to ET alone, ET combined with targeted therapies, including CDK4/6, VEGF, EGFR, and PI3K inhibitors, showed higher ORR rankings. CT(A) was significantly better than AI ±

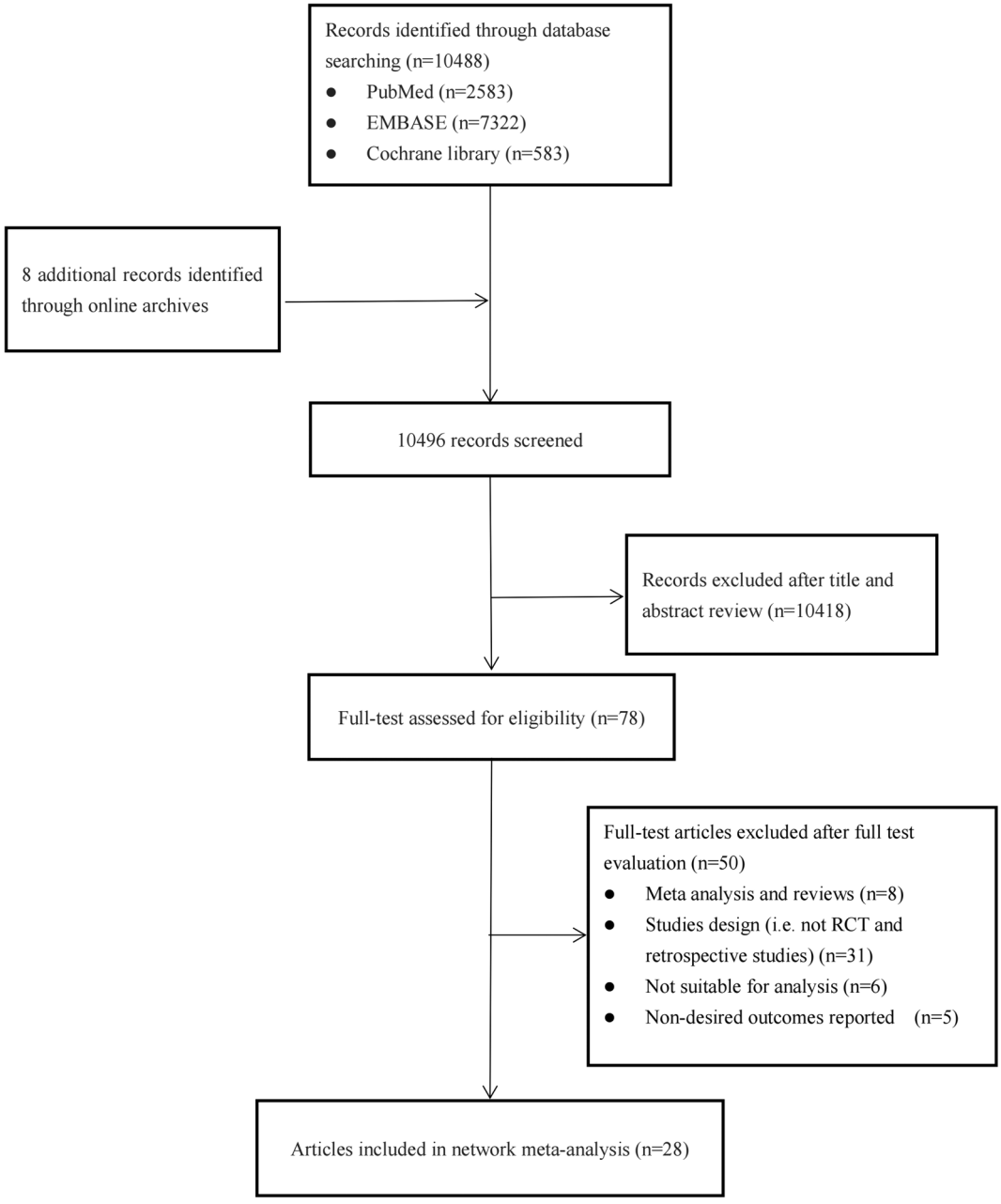

Figure 1. Flowchart illustrating the study selection process for inclusion in the network meta-analysis.

GnRha and SERM ± GnRha (OR: 2.15, $p < 0.05$; OR: 3.99, $p < 0.05$, respectively; Table 1).

SUCRA results for the four strategy groups are shown in Figure 4c. Chemotherapy alone emerged as the top-ranked strategy by a considerable margin. Chemotherapy alone was significantly superior to ET alone (OR, 2.60; $p < 0.05$; Figure 6). Additionally, the addition of targeted therapy to ET significantly enhanced ORR (OR: 1.39, $p < 0.05$; Figure 6).

3.4. PCR of experimental arms

In the pairwise meta-analysis, CT(A) combined with immune checkpoint inhibitors (ICIs) demonstrated significantly higher PCR rates compared to CT(A) alone (OR: 2.33, 95% CI: 1.31–4.15, $p = 0.004$), with low heterogeneity ($p = 0.96$, $I^2 = 0\%$; Figure 3c). This finding is consistent with the results observed for CT(A) + PD-1/PD-L1 inhibitors in the indirect comparison. CT(A) combined with PARP inhibitors-containing therapy showed significantly higher PCR rates compared to CT(A) alone (OR: 2.59, 95% CI: 1.29–5.21, $p = 0.007$), with low heterogeneity ($p = 0.51$, $I^2 = 0\%$; Figure 3d).

Based on the PCR-SUCRA analysis (Figure 4b), combining CT(A) with PARPi or PD-1i/PD-L1i showed potential benefits in the neoadjuvant treatment of HR+/HER2- breast cancer [SUCRA value of CT(A)+PARPi: 88.1; SUCRA value of CT(A) +PD-1i: 81.0; SUCRA value of CT(A)+PARPi+PD-L1i: 80.2]. The inclusion of PD-1i/PD-L1i or PARPi in chemotherapy regimens significantly improves the PCR rate compared to CT(A) alone [SUCRA value of CT(A): 50.6; CT(A)+PARPi versus CT(A), OR: 4.44, 95% CI: 0.69–28.57; CT(A)+PD-1i versus CT(A), OR: 2.37, 95% CI: 0.86–6.50; Table 2].

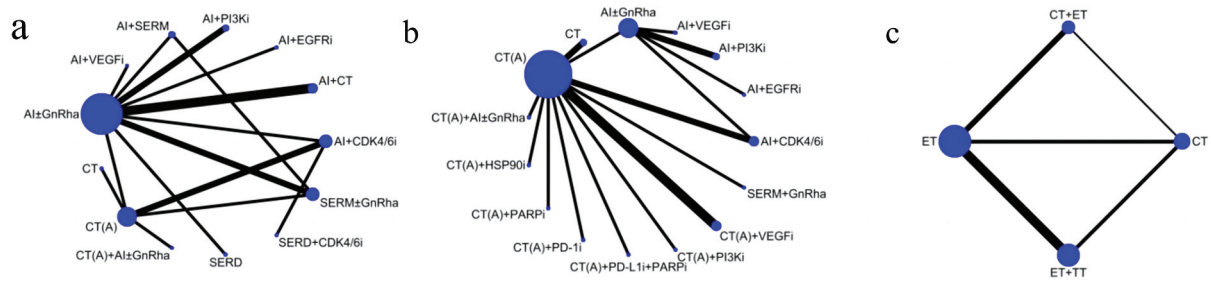

Figure 2. Network diagrams depicting ORR and PCR rate among eligible experimental arms and ORR in eligible strategy groups.

Notes: a ORR in eligible experimental arms; b PCR in eligible experimental arms; c ORR in strategy groups.

Experimental arms: CT = Chemotherapy without Anthracyclines, CT(A) = Chemotherapy containing Anthracyclines, AI±GnRha = Aromatase inhibitor plus Gonadotropin-releasing hormone agonist or not, AI+CDK4/6i = AI plus Cyclin dependent kinase 4/6 inhibitor, AI+EGFRi = AI plus Epidermal growth factor receptor inhibitor, AI+PI3Ki = AI plus Phosphoinositide 3-kinase inhibitor, AI+VEGFi = AI plus vascular endothelial growth factor inhibitor, AI+SERM = AI plus selective estrogen receptor modulator, SERD = Selective estrogen receptor downregulator, SERM±GnRha = SERM plus GnRha or not, CT(A)+H90i = CT(A) plus the Heat Shock Protein 90 inhibitor, CT(A)+PARPi = CT(A) plus poly ADP-ribose polymerase inhibitor, CT(A)+PD-1i = CT(A) plus Programmed Death Receptor 1 inhibitor, CT(A)+PD-L1i+PARPi = CT(A) plus programmed cell death-Ligand 1 and PARPi.

Strategy groups: CT = Chemotherapy alone; ET = Endocrine therapy alone; ET+TT = Endocrine therapy plus targeted therapy. ET+TT = Endocrine therapy plus chemotherapy.

3.5. NMA of postmenopausal subgroup

In the postmenopausal subgroup analysis, the SUCRA value indicated that CT(A) had the highest ORR, with a 70% posterior probability, suggesting it to be the most effective treatment option. Similarly, for PCR outcomes, SUCRA analysis identified CT(A) and AI+CT as leading strategies, with CT(A) achieving a SUCRA value of 77.7 and AI+CT closely following at 77.1, highlighting their superior efficacy. Detailed information and graphs pertaining to the subgroup analysis are available in Supplemental File 7.

3.6. Safety

Owing to the constraints in conducting individual NMA for each side effect, we employed dropout rates as a surrogate outcome indicator, which was expected to reflect the safety of various regimens. The analysis was performed using 11 ORR experimental arms (Figure 4d). AI + CDK 4/6i did not result in a higher discontinuation rate than AI alone. It should be noted that the clinical value of certain drugs, such as VEGFi and PI3Ki, has diminished owing to a substantial rate of treatment discontinuation. To provide a more comprehensive evaluation, we integrated ORR with dropout rates to objectively assess the clinical value of each experimental arm (Figure 5). CT(A) showed an excellent balance between efficacy and adverse events. AI+CDK4/6i also showed high clinical value in reducing toxicity and improving curative effects. Unfortunately, the included trials did not provide information on the dropout rates for Selective estrogen receptor downregulator (SERD)+CDK4/6i, CT(A)+PARPi, or PD-1i/PD-L1i in HR+/HER2- BC. This limitation restricts our ability to conduct a more comprehensive assessment of the safety profiles of these treatments.

The most frequently observed toxicities are shown in Supplementary File 6. Overall, the incidence of toxicity was lower with ET than chemotherapy. In comparison with AI ±GnRha, AI+CDK4/6i was associated with a higher occurrence of neutropenia (40.45%). Both EGFRi and VEGFi exhibit a high incidence of adverse events such as diarrhea, skin and subcutaneous tissue disorders, hepatic toxicity, and fatigue. Specifically, EGFR inhibitors result in diarrhea in over 13% of patients and skin and subcutaneous tissue disorders in more than 11% of patients. Comparable incidence rates of grade 3–5 hematological adverse events were observed on CT and CT(A), particularly neutropenia (55.38%) and febrile neutropenia (15.25%). Stomatitis, mucositis (3.72%), sensory neuropathy (3.70%), and fatigue (2.85%) were more prevalent on CT(A) than on CT.

4. Discussion

This increased choice of agents in the neoadjuvant setting has prompted us to define the optimal neoadjuvant therapy for HR+/HER2- breast cancer. Therefore, we employed a network meta-analysis to combine direct and indirect evidence based on available clinical data and to verify the effectiveness (ORR and PCR) and acceptability (dropout rate) of each treatment. Although HR+/HER2- BC is less responsive to neoadjuvant therapy than other breast cancer subtypes and PCR is difficult to obtain, it can still benefit from this approach, particularly in terms of improving objective tumor remission and breast conservation rates [42,43]. Therefore, for patients with BC seeking symptom alleviation, improved quality of life, and opportunities for breast-conserving surgery, the ORR may be a more suitable indicator of treatment effectiveness.

In our study, a comprehensive analysis of both ORR and safety demonstrated that CT(A) achieved the best balance between efficacy and toxicity. Neoadjuvant chemotherapy remains the cornerstone of breast cancer treatment owing to its effectiveness in downstaging tumors, increasing BCS rates, and providing valuable insights into postoperative strategies [6,44]. Consistent with our findings, a recent meta-analysis demonstrated that anthracycline- and taxane-based chemotherapy regimens remain the preferred approach for neoadjuvant treatment of early-stage operable BC, offering greater benefits than de-anthracycline-based chemotherapy regimens [45]. Therefore, for patients diagnosed with HR+/HER2- BC requiring tumor downstaging to facilitate breast-conserving surgery, neoadjuvant chemotherapy should be routinely recommended according to the NCCN guidelines. Despite the well-established benefits of neoadjuvant

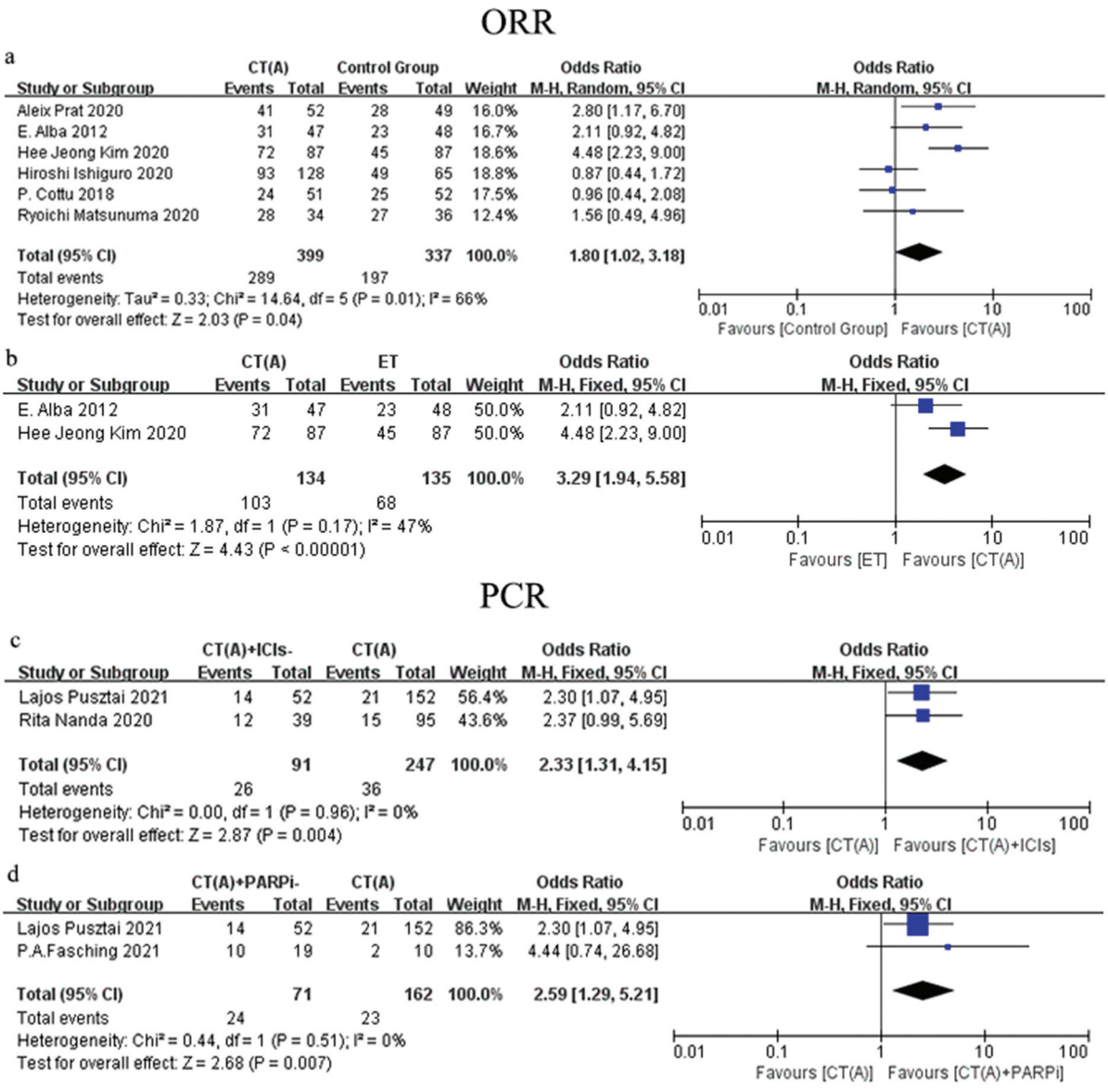

Figure 3. Paired meta-analyses on ORR and PCR rate.

(a) CT(A) versus Control Groups; (b) CT(A) versus ET; (c) CT(A) + immune checkpoint inhibitor-containing therapy versus CT(A); (d) CT(A) + PARPi-containing therapy versus CT(A).

chemotherapy, treatment-related toxicity and drug resistance are issues that must be addressed. Further research is needed to address these obstacles and optimize neoadjuvant breast cancer treatment.

Another clinical scenario involves testing the efficacy of neoadjuvant endocrine therapy, thus aiming for a treatment paradigm that avoids chemotherapy. In our study, CDK4/6 inhibitors + AI ranked only after chemotherapy in the combined assessment of ORR and safety. This underscores the significant potential of AI+CDK4/6 inhibitors in the neoadjuvant treatment of HR+/HER2- breast cancer. Extensive prior research has demonstrated that CDK4/6 inhibitors can inhibit the hyperphosphorylation of retinoblastoma proteins, leading to G1 cell cycle arrest and subsequent suppression of cellular proliferation [46,47]. Consequently, CDK4/6 inhibitors have shown significant efficacy in treating advanced or metastatic HR+/HER2- BC by delaying the emergence of endocrine resistance and halting tumor progression [13,48–50]. Moreover, several meta-analyses have consistently reported that CDK4/6 inhibitors + ET significantly improved the rate of complete cell cycle arrest (CCCA) compared with ET alone, which may have favorable prognostic implications [51–54]. Furthermore, CDK4/6 inhibitors plus AI have the potential to induce tumor shrinkage with slightly better BCS rates than NAC [54]. In terms of both breast cancer-specific survival and recurrence-free survival, CDK4/6 inhibitors + AI were found to be at least equally effective as NAC [22]. Combining CDK4/6 inhibitors with ET was found to increase the incidence of adverse events, especially neutropenia and elevated alanine aminotransferase (ALT) levels, compared with ET alone [14,15,55]. However, compared to standard chemotherapy, CDK4/6 inhibitors + ET exhibited a better safety profile. Therefore, CDK4/6 inhibitors + AI may serve as a less toxic substitute for chemotherapy in individuals afflicted with high-

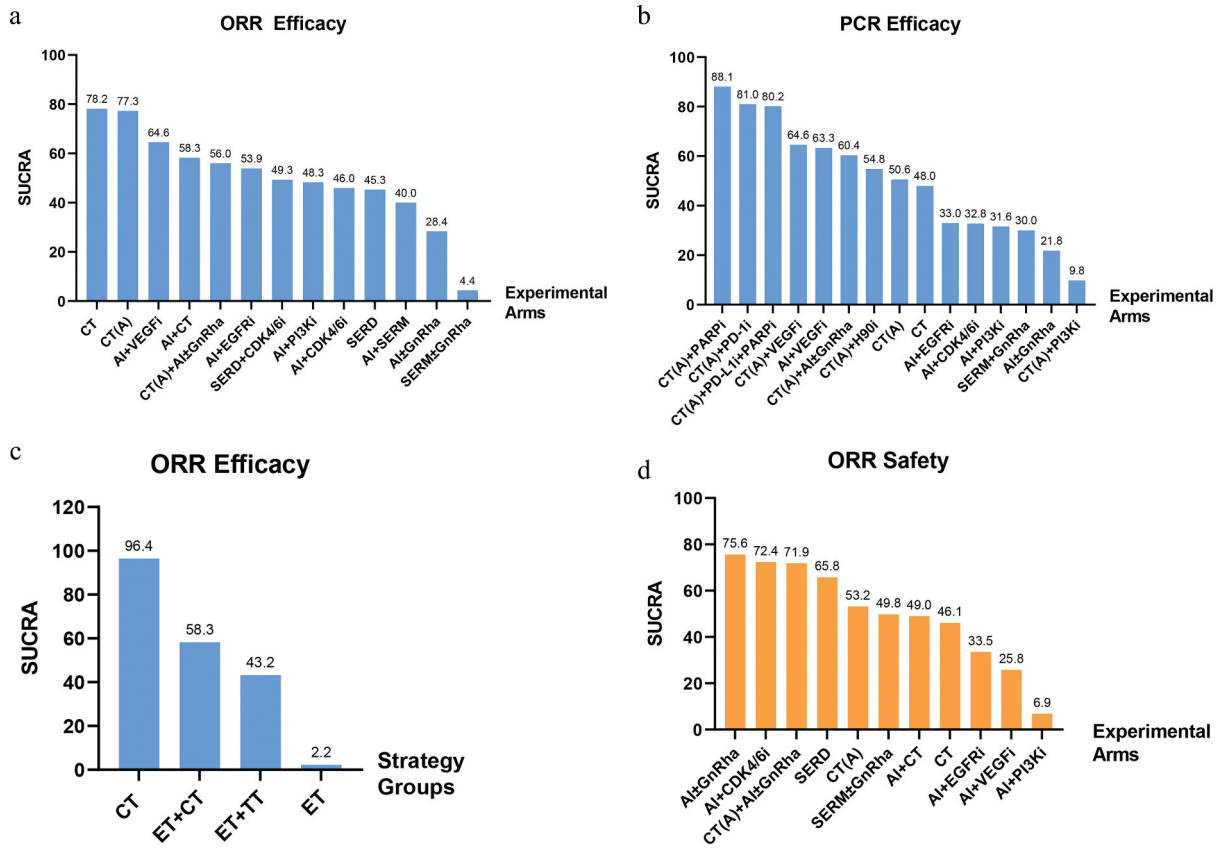

Figure 4. Efficacy (ORR and PCR) and safety (dropout rates) ranking for experimental arms and strategy groups.

(a) ORR ranking for experimental arms; (b) PCR rates experimental arms; (c) Dropout rates ranking for strategy groups; (d) ORR ranking for strategy groups.

Notes: The larger the SUCRA, the higher the ranking. SUCRA: surface under the cumulative ranking curve.

risk HR+/HER2- BC seeking tumor reduction. The ongoing ADAPT cycle trial is evaluating the efficacy of CDK4/6 inhibitors in combination with ET versus CDK4/6 inhibitors in combination with chemotherapy in high-risk Luminal BC. The results of this trial may offer sufficient evidence to consider avoiding chemotherapy as neoadjuvant therapy.

Our investigation indicated that NET alone, encompassing the AI, SERD, and SERM treatments, generally demonstrated lower ORR and PCR rates, positioning it less favorably in the efficacy rankings. Despite this, its significantly better safety profile compared to other treatments underscores the value of NET, particularly when considering patient well-being and treatment tolerance. Notably, two NMA studies of neoadjuvant therapy for HR+ breast cancer demonstrated that NET yielded a response rate similar to that of neoadjuvant chemotherapy, but with less toxicity [17,18]. The WSG ADAPT-HR+/HER2- endocrine trial demonstrated that after receiving four weeks of NET, patients with c/pN0–1 and a low-risk genetic profile (RS 0–11), as well as patients with a similar lymph node burden but an intermediate-risk genetic profile (RS 12–25) and endocrine sensitivity (Ki-67 < 10% after NET), could achieve significant efficacy from ET alone [56]. The long-term invasive disease-free survival with this approach was comparable to that with chemotherapy. However, the applicability of NET in patients with larger tumors or extensive lymph node involvement remains to be definitively established, suggesting the need for future research to adopt a more nuanced patient stratification approach. This would enable the identification of those who could derive the greatest benefits from NET. In conclusion, NET offers a safer and adaptable alternative treatment for specific patient groups, especially those who are unable or unwilling to undergo intense chemotherapy due to the risk of side effects. Extending the NET treatment period could be an effective strategy for optimizing outcomes and maintaining the quality of life.

For breast cancer patients aiming for complete tumor eradication, reduced recurrence risk, and enhanced prognosis, PCR has greater significance. However, achieving PCR in HR+/HER2- BC is notably challenging. Hence, more treatment strategies must be considered to enhance PCR rates in HR+/HER2- BC patients.

Our study ranked CT(A) + PD-1i and CT(A) + PARPi + PD-L1i as the two top-performing treatments using NMA with PCR rates as the primary endpoint. This result suggests that in the pursuit of maximizing efficacy, the addition of ICIs or PARPi to neoadjuvant treatment regimens may present greater opportunities. Farkona et al. recently revealed that adding ICIs to chemotherapy can enhance endogenous anticancer immunity by increasing the release of tumor-specific antigens induced by chemotherapy [57]. Evidence from the TONIC trial suggests that combining anthracycline-based chemotherapy with ICIs yields the most robust response among evaluated chemotherapy regimens [58,59]. Furthermore, chemoimmunotherapy has demonstrated remarkable efficacy as

Table 1. Indirect comparison of ORR among experimental arms and indirect comparison of ORR among strategy groups.

CT	Cross-comparison odds ratios (ORs) and their respective 95% CIs for ORR among different experimental arms								Cross- comparison ORs and their respective 95% CIs for ORR among different strategy groups			
1.15 (0.42,3.15)	CT(A)								CT			
1.35 (0.23,8.06)	1.17 (0.27,5.13)	AI+VEGFi							1.56 (0.76,3.17)	CT+ET		
1.58 (0.36,7.05)	1.37 (0.46,4.14)	1.17 (0.24,5.69)	AI+CT						1.87 (1.23,2.85)	1.20 (0.60,2.42)	ET+TT	
1.54 (0.28,8.55)	1.33 (0.33,5.36)	1.14 (0.15,8.68)	0.97 (0.16,5.73)	CT(A)+AI±GnRha					2.60 (1.73,3.91)	1.67 (0.86,3.24)	1.39 (1.07,1.81)	ET
1.69 (0.32,8.92)	1.47 (0.39,5.52)	1.26 (0.22,7.14)	1.07 (0.25,4.48)	1.10 (0.16,7.51)	AI+EGFRi							
1.79 (0.40,8.03)	1.55 (0.51,4.74)	1.33 (0.23,7.57)	1.13 (0.27,4.75)	1.16 (0.20,6.92)	1.06 (0.21,5.29)	SERD+CDK4/6i						
1.91 (0.49,7.42)	1.65 (0.66,4.13)	1.41 (0.33,6.04)	1.20 (0.41,3.50)	1.24 (0.23,6.55)	1.13 (0.31,4.10)	1.07 (0.29,3.91)	AI+PI3Ki					
1.89 (0.57,6.26)	1.64 (0.85,3.15)	1.40 (0.32,6.21)	1.19 (0.39,3.65)	1.23 (0.26,5.72)	1.12 (0.29,4.24)	1.06 (0.43,2.61)	0.99 (0.39,2.51)	AI+CDK4/6i				
2.00 (0.40,9.88)	1.73 (0.50,6.01)	1.48 (0.28,7.94)	1.26 (0.32,4.92)	1.30 (0.20,8.40)	1.18 (0.25,5.53)	1.12 (0.24,5.26)	1.05 (0.31,3.52)	1.06 (0.30,3.71)	SERD			
2.15 (0.49,9.38)	1.87 (0.64,5.48)	1.60 (0.32,7.96)	1.36 (0.38,4.84)	1.40 (0.24,8.13)	1.27 (0.29,5.50)	1.21 (0.29,5.08)	1.13 (0.37,3.42)	1.14 (0.37,3.49)	1.08 (0.27,4.33)	AI+SERM		
2.47 (0.74,8.31)	2.15 (1.09,4.22)	1.84 (0.49,6.84)	1.56 (0.65,3.74)	1.61 (0.34,7.56)	1.46 (0.47,4.56)	1.38 (0.44,4.34)	1.30 (0.70,2.40)	1.31 (0.65,2.64)	1.24 (0.44,3.51)	1.15 (0.46,2.89)	AI±GnRha	
4.60 (1.32,15.97)	3.99 (1.91,8.32)	3.41 (0.80,14.57)	2.90 (1.00,8.45)	2.99 (0.62,14.43)	2.72 (0.75,9.90)	2.57 (0.75,8.82)	2.41 (1.01,5.76)	2.44 (1.06,5.62)	2.30 (0.69,7.72)	2.14 (0.85,5.35)	1.86 (1.00,3.44)	SERM±GnRha

Notes: The results are presented as the odds ratio (OR) and 95% confidence intervals (CIs) for ORR among the experimental arms (lower left quarter) and as the OR and 95% CIs for ORR among the strategy groups (upper right quarter). ORs > 1 favor the column-defining treatment (i.e. The ORs of CT compared with CT(A) were 1.15, which favor CT treatment). Light blue boxes represent the treatment regimens. Orange boxes mean ORs are statistically significant ORs.

Table 2. Indirect comparison of PCR rate among experimental arms.

CT(A)+PARPi		Cross-comparison odds ratios (ORs) and their respective 95% CIs for PCR among different experimental arms												
1.87 (0.23,15.57)	CT(A)+PD-1i													
1.93 (0.24,15.39)	1.03 (0.26,4.03)	CT(A)+PD-L1i+PARPi												
3.34 (0.50,22.46)	1.78 (0.60,5.29)	1.73 (0.63,4.71)	CT(A)+VEGFi											
2.88 (0.04,200.31)	1.53 (0.03,79.30)	1.49 (0.03,75.16)	0.86 (0.02,39.89)	AI+VEGFi										
3.55 (0.41,30.84)	1.89 (0.43,8.42)	1.84 (0.44,7.68)	1.06 (0.33,3.44)	1.23 (0.02,65.33)	CT(A)+AI±GnRha									
4.20 (0.47,37.57)	2.24 (0.48,10.40)	2.17 (0.50,9.51)	1.26 (0.37,4.29)	1.46 (0.03,78.54)	1.18 (0.24,5.83)	CT(A)+H90i								
4.44 (0.69,28.57)	2.37 (0.86,6.50)	2.30 (0.92,5.75)	1.33 (0.88,2.00)	1.54 (0.03,70.01)	1.25 (0.42,3.75)	1.06 (0.33,3.37)	CT(A)							
5.05 (0.59,42.93)	2.69 (0.63,11.61)	2.61 (0.65,10.58)	1.51 (0.49,4.70)	1.76 (0.03,91.84)	1.42 (0.31,6.47)	1.20 (0.25,5.77)	1.14 (0.40,3.27)	CT						
16.82 (0.11,2472.62)	8.97 (0.08,1026.26)	8.70 (0.08,976.42)	5.04 (0.05,525.95)	5.85 (0.04,839.54)	4.74 (0.04,552.24)	4.01 (0.03,474.08)	3.79 (0.04,388.37)	3.33 (0.03,384.62)	AI+EGFRi					
9.79 (0.89,107.91)	5.22 (0.85,32.26)	5.06 (0.86,29.76)	2.93 (0.61,14.08)	3.40 (0.08,151.77)	2.76 (0.42,17.88)	2.33 (0.35,15.71)	2.20 (0.48,10.03)	1.94 (0.31,12.27)	0.58 (0.01,58.92)	AI+CDK4/6i				
13.31 (0.48,366.99)	7.10 (0.38,132.37)	6.89 (0.38,124.47)	3.99 (0.25,63.97)	4.63 (0.17,123.13)	3.75 (0.19,72.20)	3.17 (0.16,62.43)	3.00 (0.19,46.67)	2.64 (0.14,49.99)	0.79 (0.01,52.93)	1.36 (0.09,20.72)	AI+PI3Ki			
13.01 (0.66,258.30)	6.94 (0.54,88.60)	6.73 (0.55,82.92)	3.90 (0.36,41.82)	4.52 (0.05,396.55)	3.66 (0.28,48.51)	3.10 (0.23,42.12)	2.93 (0.28,30.34)	2.58 (0.20,33.51)	0.77 (0.00,138.49)	1.33 (0.08,21.56)	0.98 (0.03,36.00)	SERM+GnRha		
19.14 (0.93,392.26)	10.21 (0.77,135.33)	9.90 (0.77,126.72)	5.73 (0.51,64.05)	6.65 (0.34,131.11)	5.39 (0.39,74.00)	4.56 (0.32,64.27)	4.31 (0.40,46.50)	3.79 (0.28,51.13)	1.14 (0.02,60.47)	1.96 (0.19,20.57)	1.44 (0.36,5.66)	1.47 (0.05,41.33)	AI±GnRha	
48.82 (2.87,829.21)	26.05 (2.46,276.30)	25.26 (2.47,257.87)	14.62 (1.66,128.50)	16.97 (0.21,1342.75)	13.75 (1.25,151.70)	11.63 (1.03,131.97)	10.99 (1.30,92.94)	9.67 (0.89,104.65)	2.90 (0.02,475.76)	4.99 (0.36,68.40)	3.67 (0.11,118.81)	3.75 (0.16,89.00)	2.55 (0.10,62.37)	CT(A)+PI3Ki

Notes: The results are presented as OR and 95% CIs for the PCR rate (lower left quarter) and as OR and 95% CIs for the ORR (upper right quarter). For PCR rate, ORs > 1 favor the column-defining treatment (i.e. The ORs of CT(A) compared with CT were 1.13, which favor CT(A) treatment). Light blue boxes represent the treatment regimens. Orange boxes mean ORs are statistically significant ORs.

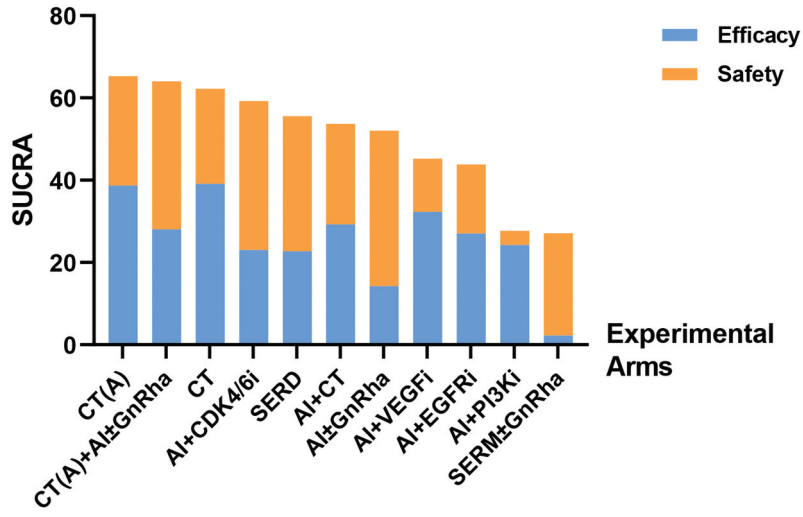

Figure 5. Experimental arms ordered by their overall probability as the best treatment in terms of both ORR and dropout rates.

Notes: Cumulative percentages after normalization to a range of 0–100, are indicated in the key. Each regimen received a score of 50 points for ORR and 50 points for safety based on the SUCRA data (with a total maximum score of 100).

a neoadjuvant therapy for early-stage triple-negative BC, resulting in a significant increase in PCR rates [60–62]. In the context of HR+HER2- BC, the I-SPY2 adaptive trial demonstrated that the addition of pembrolizumab to sequential taxane, anthracycline, and cyclophosphamide therapy more than doubled the PCR rates compared to NAC alone (30% vs 13%). Data from this trial also revealed that the inclusion of durvalumab and olaparib alongside paclitaxel significantly enhanced PCR rates in high-risk HR+/HER2- BC (64% vs 22%). The incorporation of ICIs into chemotherapy did not impede the administration of chemotherapy, and the observed adverse events were consistent with the well-established safety profiles of individual components [9,11]. Additionally, CT(A) plus PARP inhibitors achieved the highest ranking in the PCR SUCRA analysis, with a value of 88.1. In the GeparOLA study involving 29 HR-positive patients, paclitaxel + olaparib achieved a PCR rate of 52.6% compared to 20.0% with paclitaxel + carboplatin [10]. We also observed a significant improvement in PCR rates with CT(A) + PARPi + PD-L1i therapy. This raises questions regarding the relationship between PARP and PD-L1 inhibitors. Preclinical research suggests that impaired nucleotide and base excision repair resulting from PARP inhibitors can increase mutational and neoantigenic loads, potentially enhancing sensitivity to ICIs [63,64]. However, data from clinical trials on the synergistic effects of PARP inhibitors and ICIs are inconclusive [65]. Although the use of ICIs and PARPi has significantly enhanced PCR rates, evidence regarding their influence on patient prognosis remains sparse. Therefore, the crucial question of whether these advancements have resulted in improved survival outcomes requires further in-depth research.

Emerging therapies such as CDK4/6 inhibitors, PARP inhibitors, and ICIs show promise for neoadjuvant HR+/HER2- BC treatment but remain in the early research phases. Currently, three selective CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, have received FDA approval for treating patients with HR+ metastatic breast cancer (MBC). However, its use in neoadjuvant therapy remains under investigation. Similarly, the PARP inhibitors olaparib and talazoparib have been approved for hereditary or suspected hereditary, germline BRCA-mutated, HER2-negative MBC, but not yet for neoadjuvant applications. As for immunotherapy, no ICIs have been FDA-approved for HR +/HER2- breast cancer treatment to date [66]. Consequently, the current primary recommendation for neoadjuvant therapy in patients with HR+/HER2- BC in clinical practice is chemotherapy, with NET serving as an alternative for those who cannot tolerate chemotherapy. However, a recent study identified four distinct molecular subtypes of HR+/HER2- BC: canonical luminal, immunogenic, proliferative, and receptor tyrosine kinase (RTK)-driven [67]. These subtypes have unique biological and clinical characteristics, highlighting the need for tailored therapeutic approaches. Neoadjuvant therapeutic trials targeting each subtype are a significant avenue for future research.

It should be noted that NMA has certain limitations. First, the scarcity of patient-specific treatment data in existing clinical trials for HR+ HER2- BC neoadjuvant therapy complicates the execution of detailed subgroup meta-analyses. This limitation hinders the identification of patient groups that would benefit the most from neoadjuvant treatment. Second, the limited detailed information on grade 3–4 adverse events owing to insufficient data in some studies and variations in recorded adverse event types across different studies might have introduced bias into our pooled analysis, potentially leading to deviations from the actual outcomes. Furthermore, data on dropout rates owing to adverse effects are challenging to obtain for certain treatment strategies, which complicates the assessment of their safety profiles. Finally, owing to the scarcity of data regarding the long-term survival of patients with HR+/HER2- BC receiving different treatments, our study opted for ORR and PCR rates as the principal indicators of treatment efficacy. Future research is needed to clarify the connection between these indicators and survival outcomes as well as to conduct prognosis-based network meta-analyses.

5. Conclusions

Neoadjuvant chemotherapy, with or without anthracycline, showed an improved ORR compared with alternative regimens. CT(A) in combination with PD-1/PD-L1 inhibitors or PARP inhibitors significantly increased PCR rates. A comprehensive assessment of both ORR and safety indicated that CT(A) represents an optimal neoadjuvant therapy for HR+/HER2- breast cancer, whereas AI + CDK4/6 inhibitors rank solely behind chemotherapy.

Abbreviations

BC	Breast Cancer
MBC	Metastatic Breast Cancer
HR+/HER2-	Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative
ER+	Estrogen Receptor Positive
CT	Chemotherapy
CT(A)	Chemotherapy (Anthracycline-based)
CDK4/6i	Cyclin-Dependent Kinase 4 and 6 Inhibitors
PARPi	Poly (ADP-Ribose) Polymerase Inhibitors
PD-1i	Programmed Cell Death Protein 1 Inhibitors
PD-L1i	Programmed Death-Ligand 1 Inhibitors
NAC	Neoadjuvant Chemotherapy
NET	Neoadjuvant Endocrine Therapy
ORR	Objective Response Rate
PCR	Pathological Complete Response
VEGFi	Vascular Endothelial Growth Factor Inhibitors
EGFRi	Epidermal Growth Factor Receptor Inhibitors
PI3Ki	Phosphoinositide 3-Kinase Inhibitors
BCS	Breast-Conserving Surgery
NMA	Network Meta-Analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized Clinical Trials
NCI-CTC	National Cancer Institute Common Terminology Criteria
AJCC	American Joint Committee on Cancer
SUCRA	Surface Under the Cumulative Ranking
ROB	Risk of Bias
ICIs	Immune Checkpoint Inhibitors
AI	Aromatase Inhibitors
SERD	Selective Estrogen Receptor Downregulator
SERM	Selective Estrogen Receptor Modulator
GnRHa	Gonadotropin-Releasing Hormone Agonists
NCCN	National Comprehensive Cancer Network
CCCA	Complete Cell Cycle Arrest
ALT	Alanine Aminotransferase
RTK	Receptor Tyrosine Kinase
FDA	Food and Drug Administration

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Declaration of interest

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Author contributions

R Chen and Y Yu contributed equally to this study. C Song and R Chen conceived this study. R Chen, Y Yu, and J Zhang had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Y Yu and C Wang designed the search strategy. R Chen and J Zhang screened the abstracts and full texts, acquired the data, and determined the risk of bias in the studies. R Chen and Y Yu performed the data analysis. R Chen and Y Yu wrote the first drafts of the manuscript. C Wang, J Zhang, and C Song critically revised the manuscript. All the authors approved the final version of the manuscript.

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Data availability statement

All data generated or analyzed in this study are included in the published article and supplementary information files.

ORCID

Ruiliang Chen http://orcid.org/0009-0004-5608-1273

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca A Cancer J Clinicians. 2021;71 (3):209–249. doi: 10.3322/caac.21660
2. Burstein HJ. Systemic therapy for estrogen receptor-positive, HER2-negative breast cancer. N Engl J Med. 2020;383 (26):2557–2570. doi: 10.1056/NEJMra1307118
3. Kotteas E, Bielo LB, Valenza C, et al. Treatment optimization in early triple negative breast cancer. Expert Rev Anticancer Ther. 2023;23 (10):1107–1116. doi: 10.1080/14737140.2023.2268840
4. An J, Peng C, Tang H, et al. New advances in the research of resistance to neoadjuvant chemotherapy in breast cancer. Int J Mol Sci. 2021;22(17):9644. doi: 10.3390/ijms22179644
5. Untch M, Konecny GE, Paepke S, et al. Current and future role of neoadjuvant therapy for breast cancer. Breast. 2014;23(5):526–537. doi: 10.1016/j.breast.2014.06.004
6. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol. 2008;26(5):778–785. doi: 10.1200/JCO.2007.15.0235
7. Prat A, Galván P, Jimenez B, et al. Prediction of response to neoadjuvant chemotherapy using core needle biopsy samples with the prosigna assay. Clin Cancer Res. 2016;22(3):560–566. doi: 10.1158/1078-0432.CCR-15-0630
8. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. JCO. 2012;30(15):1796–1804. doi: 10.1200/JCO.2011.38.8595
9. 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 (5):676–684. doi: 10.1001/jamaoncol.2019.6650

•• **A prospective phase II randomized trial investigating the effect of pembrolizumab in combination with neoadjuvant chemotherapy on achieving pathologic complete response in patients with HR+/HER2- breast cancer**

10. Fasching PA, Link T, Hauke J, et al. Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study). Ann Oncol. 2021;32(1):49–57. doi: 10.1016/j.annonc.2020.10.471

• **A prospective phase II randomized trial comparing the efficacy of neoadjuvant paclitaxel/olaparib with paclitaxel/carboplatinum in patients with early HR+/HER2- breast cancer.**

11. Pusztai L, Yau C, Wolf DM, et al. Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: results from the adaptively randomized I-SPY2 trial. Cancer Cell. 2021;39(7):989–998.e5. doi: 10.1016/j.ccell.2021.05.009

•• **A prospective phase II randomized trial investigating the efficacy of combining durvalumab with olaparib and paclitaxel as neoadjuvant therapy for high-risk HR+/HER2- breast cancer.**

12. Vaklavas C, Roberts BS, Varley KE, et al. TBCRC 002: a phase II, randomized, open-label trial of preoperative letrozole with or without bevacizumab in postmenopausal women with newly diagnosed stage 2/3 hormone receptor-positive and HER2-negative breast cancer. Breast Cancer Res. 2020;22(1):22. doi: 10.1186/s13058-020-01258-x

13. Spring LM, Wander SA, Andre F, et al. Cyclin-dependent kinase 4 and 6 inhibitors for hormone receptor-positive breast cancer: past, present, and future. Lancet. 2020;395(10226):817–827. doi: 10.1016/S0140-6736(20)30165-3

14. Prat A, Saura C, Pascual T, et al. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial. The Lancet Oncology. 2020;21(1):33–43. doi: 10.1016/S1470-2045(19)30786-7

•• **A prospective phase II randomized trial comparing the efficacy of ribociclib plus letrozole with neoadjuvant chemotherapy for postmenopausal women diagnosed with HR+/HER2- breast cancer.**

15. Johnston S, Puhalla S, Wheatley D, et al. Randomized phase II study evaluating palbociclib in addition to letrozole as neoadjuvant therapy in estrogen receptor–positive early breast cancer: PALLET trial. JCO. 2019;37(3):178–189. doi: 10.1200/JCO.18.01624

• **A prospective phase II randomized trial evaluating the efficacy of adding palbociclib to letrozole as neoadjuvant therapy for HR+/HER2- early breast cancer.**

16. Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. JAMA Oncol. 2016;2(11):1477–1486. doi: 10.1001/jamaoncol.2016.1897

17. Zhang T, Feng F, Yao Y, et al. Efficacy and acceptability of neoadjuvant endocrine therapy in patients with hormone receptor-positive breast cancer: a network meta-analysis. J Cell Physiol. 2019;234(8):12393–12403. doi: 10.1002/jcp.28068

18. Wang W, Liu C, Zhou W, et al. Network meta-analysis of the effectiveness of neoadjuvant endocrine therapy for postmenopausal, HR–positive breast cancer. Sci Rep. 2016;6(1):25615. doi: 10.1038/srep25615

19. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi: 10.1136/bmj.l4898

20. Hurvitz SA, Bardia A, Quiroga V, et al. Neoadjuvant palbociclib plus either giredestrant or anastrozole in oestrogen receptor-positive, HER2-negative, early breast cancer (coopERA breast cancer): an open-label, randomised, controlled, phase 2 study. The Lancet Oncology. 2023;24(9):1029–1041. doi: 10.1016/S1470-2045(23)00268-1

21. Alba E, Calvo L, Albanell J, et al. Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study. Ann Oncol. 2012;23(12):3069–3074. doi: 10.1093/annonc/mds132

•• **A prospective phase II randomized trial comparing the outcomes of chemotherapy with AI as neoadjuvant treatment in HR+/HER2- breast cancer patients.**

22. Cottu P, D'Hondt V, Dureau S, et al. Letrozole and palbociclib versus chemotherapy as neoadjuvant therapy of high-risk luminal breast cancer. Ann Oncol. 2018;29(12):2334–2340. doi: 10.1093/annonc/mdy448

• **A prospective phase II randomized trial comparing the efficacy of letrozole and palbociclib combination therapy with chemotherapy as neoadjuvant treatment for high-risk HR+/HER2- breast cancer.**

23. Kim HJ, Noh WC, Lee ES, et al. Efficacy of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy in pre-menopausal patients with oestrogen receptor-positive and HER2-negative, lymph node-positive breast cancer. Breast Cancer Res. 2020;22(1):54. doi: 10.1186/s13058-020-01288-5

24. Ishiguro H, Masuda N, Sato N, et al. A randomized study comparing docetaxel/cyclophosphamide (TC), 5-fluorouracil/epirubicin/cyclophosphamide (FEC) followed by TC, and TC followed by FEC for patients with hormone receptor-positive HER2-negative primary breast cancer. Breast Cancer Res Treat. 2020;180(3):715–724. doi: 10.1007/s10549-020-05590-w

25. Mayer IA, Prat A, Egle D, et al. A phase II randomized study of neoadjuvant letrozole plus alpelisib for hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (NEO-ORB). Clin Cancer Res. 2019;25(10):2975–2987. doi: 10.1158/1078-0432.CCR-18-3160

26. Guarneri V, Generali DG, Frassoldati A, et al. Double-blind, placebo-controlled, multicenter, randomized, phase IIB neoadjuvant study of letrozole-lapatinib in postmenopausal hormone receptor–positive, human epidermal growth factor receptor 2–negative, operable breast cancer. JCO. 2014;32(10):1050–1057. doi: 10.1200/JCO.2013.51.4737

27. Saura C, Hlauschek D, Oliveira M, et al. Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with oestrogen receptor-positive, HER2-negative, early-stage breast cancer (LORELEI): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Oncology. 2019;20(9):1226–1238. doi: 10.1016/S1470-2045(19)30334-1

28. Nakayama T, Sagara Y, Takashima T, et al. Randomized phase II study of anastrozole plus tegafur-uracil as neoadjuvant therapy for ER-positive breast cancer in postmenopausal Japanese women (neo-ACET BC). Cancer Chemother Pharmacol. 2018;81(4):755–762. doi: 10.1007/s00280-018-3544-5

29. Masuda N, Sagara Y, Kinoshita T, et al. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. The Lancet Oncology. 2012;13(4):345–352. doi: 10.1016/S1470-2045(11)70373-4

30. Lerebours F, Rivera S, Mouret-Reynier MA, et al. Randomized phase 2 neoadjuvant trial evaluating anastrozole and fulvestrant efficacy for postmenopausal, estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer patients: results of the UNICANCER CARMINA 02 French trial (UCBG 0609). Cancer. 2016;122(19):3032–3040. doi: 10.1002/cncr.30143

31. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the immediate preoperative anastrozole, tamoxifen, or combined with tamoxifen (IMPACT) multicenter double-blind randomized trial. JCO. 2005;23(22):5108–5116. doi: 10.1200/JCO.2005.04.005

32. Matsunuma R, Watanabe T, Hozumi Y, et al. Preoperative concurrent endocrine therapy with chemotherapy in luminal B-like breast cancer. Breast Cancer. 2020;27(5):819–827. doi: 10.1007/s12282-020-01077-0

33. Sato N, Masuda N, Morimoto T, et al. Neoadjuvant exemestane or exemestane plus docetaxel and cyclophosphamide tailored by clinicopathological response to 12 weeks' exemestane exposure in patients with estrogen receptor-positive breast cancer: a multicenter, open-label, phase II study. Cancer Med. 2019;8(12):5468–5481. doi: 10.1002/cam4.2423

34. Sato N, Masuda N, Morimoto T, et al. Neoadjuvant endocrine therapy with exemestane followed by response-guided combination therapy with low-dose cyclophosphamide in postmenopausal patients with estrogen receptor-positive breast cancer: a multicenter, open-label, phase II study. Cancer Med. 2018;7(7):3044–3056. doi: 10.1002/cam4.1600
35. Nahleh ZA, Barlow WE, Hayes DF, et al. SWOG S0800 (NCI CDR0000636131): addition of bevacizumab to neoadjuvant nab-paclitaxel with dose-dense doxorubicin and cyclophosphamide improves pathologic complete response (pCR) rates in inflammatory or locally advanced breast cancer. Breast Cancer Res Treat. 2016;158(3):485–495. doi: 10.1007/s10549-016-3889-6
36. Yu KD, Wu SY, Liu GY, et al. Concurrent neoadjuvant chemotherapy and estrogen deprivation in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (CBCSG-036): a randomized, controlled, multicenter trial. Cancer. 2019;125(13):2185–2193. doi: 10.1002/cncr.32057
37. Kümmel S, Paepke S, Huober J, et al. Randomised, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neoadjuvant treatment in patients with operable triple-negative or luminal B/HER2-negative breast cancer (GENEVIEVE). Eur J Cancer. 2017;84:1–8. doi: 10.1016/j.ejca.2017.06.037
38. Tung N, Arun B, Hacker MR, et al. TBCRC 031: randomized phase II study of neoadjuvant cisplatin versus doxorubicin-cyclophosphamide in Germline BRCA Carriers with HER2-Negative breast cancer (the INFORM trial). JCO. 2020;38(14):1539–1548. doi: 10.1200/JCO.19.03292
39. Lang JE, Forero-Torres A, Yee D, et al. Safety and efficacy of HSP90 inhibitor ganetespib for neoadjuvant treatment of stage II/III breast cancer. NPJ Breast Cancer. 2022;8(1):128. doi: 10.1038/s41523-022-00493-z
40. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med. 2012;366(4):299–309. doi: 10.1056/NEJMoa1111065
41. Bear HD, Tang G, Rastogi P, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med. 2012;366(4):310–320. doi: 10.1056/NEJMoa1111097
42. Guarneri V, Broglio K, Kau SW, et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. JCO. 2006;24(7):1037–1044. doi: 10.1200/JCO.2005.02.6914
43. Toi M, Nakamura S, Kuroi K, et al. Phase II study of preoperative sequential FEC and docetaxel predicts of pathological response and disease free survival. Breast Cancer Res Treat. 2008;110(3):531–539. doi: 10.1007/s10549-007-9744-z
44. Gralow JR, Burstein HJ, Wood W, et al. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. JCO. 2008;26(5):814–819. doi: 10.1200/JCO.2007.15.3510
45. Braybrooke J, Bradley R, Gray R Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. The Lancet. 2023;401(10384):1277–1292. doi: 10.1016/S0140-6736(23)00285-4
46. VanArsdale T, Boshoff C, Arndt KT, et al. Molecular pathways: targeting the cyclin D-CDK4/6 axis for cancer treatment. Clin Cancer Res. 2015;21(13):2905–2910. doi: 10.1158/1078-0432.CCR-14-0816
47. Lin Z, Zhang X, Zhao F, et al. Bisphenol S promotes the cell cycle progression and cell proliferation through ERα-cyclin D-CDK4/6-pRb pathway in MCF-7 breast cancer cells. Toxicol Appl Pharmacol. 2019;366:75–82. doi: 10.1016/j.taap.2019.01.017
48. Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. Breast Cancer Res. 2016;18(1):17. doi: 10.1186/s13058-015-0661-5
49. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. N Engl J Med. 2020;382(6):514–524. doi: 10.1056/NEJMoa1911149
50. Li J, Huo X, Zhao F, et al. Association of cyclin-dependent kinases 4 and 6 inhibitors with survival in patients with hormone receptor-positive metastatic breast cancer: a systematic review and meta-analysis. JAMA Netw Open. 2020;3(10):e2020312. doi: 10.1001/jamanetworkopen.2020.20312
51. Hurvitz SA, Martin M, Press MF, et al. Potent cell-cycle inhibition and upregulation of immune response with abemaciclib and anastrozole in neoMONARCH, phase II neoadjuvant study in HR(+)/HER2(-) breast cancer. Clin Cancer Res. 2020;26(3):566–580. doi: 10.1158/1078-0432.CCR-19-1425
52. Hong K, Yao L, Sheng X, et al. Neoadjuvant therapy of cyclin-dependent kinase 4/6 inhibitors combined with endocrine therapy in HR+/HER2− breast cancer: a systematic review and meta-analysis. Oncol Res Treat. 2021;44(10):557–567. doi: 10.1159/000518573
53. Guan Y, Shen G, Fang Q, et al. Cyclin-dependent kinase 4 and 6 inhibitors in combination with neoadjuvant endocrine therapy in estrogen receptor-positive early breast cancer: a systematic review and meta-analysis. Clin Exp Med. 2023;23(2):245–254. doi: 10.1007/s10238-022-00814-3
54. Zhang M, Song J, Guo S, et al. Adjuvant and neoadjuvant therapy with cyclin-dependent kinase 4 and 6 inhibitors in hormone receptor-positive, human epidermal growth factor receptor 2-negative early breast cancer: a systematic review and meta-analysis. Endocr Relat Cancer. 2023;30(8). doi: 10.1530/ERC-22-0365
55. Curigliano G, Gómez Pardo P, Meric-Bernstam F, et al. Ribociclib plus letrozole in early breast cancer: a presurgical, window-of-opportunity study. Breast. 2016;28:191–198. doi: 10.1016/j.breast.2016.06.008
56. Nitz UA, Gluz O, Kümmel S, et al. Endocrine therapy response and 21-gene expression assay for therapy guidance in HR+/HER2− early breast cancer. JCO. 2022;40(23):2557–2567. doi: 10.1200/JCO.21.02759
57. Farkona S, Diamandis EP, Blasutig IM. Cancer immunotherapy: the beginning of the end of cancer? BMC Med. 2016;14(1):73. doi: 10.1186/s12916-016-0623-5
58. Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4–dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med. 2007;13(9):1050–1059. doi: 10.1038/nm1622
59. Voorwerk L, Slagter M, Horlings HM, et al. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. Nature Med. 2019;25(6):920–928. doi: 10.1038/s41591-019-0432-4
60. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382(9):810–821. doi: 10.1056/NEJMoa1910549
61. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet (London, England). 2020;396(10257):1090–1100. doi: 10.1016/S0140-6736(20)31953-X
62. Foldi J, Silber A, Reisenbichler E, et al. Neoadjuvant durvalumab plus weekly nab-paclitaxel and dose-dense doxorubicin/cyclophosphamide in triple-negative breast cancer. NPJ Breast Cancer. 2021;7(1):9. doi: 10.1038/s41523-021-00219-7
63. Esteva FJ, Hubbard-Lucey VM, Tang J, et al. Immunotherapy and targeted therapy combinations in metastatic breast cancer. The Lancet Oncology. 2019;20(3):e175–e186. doi: 10.1016/S1470-2045(19)30026-9
64. Lassen U. Combining PARP inhibition with PD-1 inhibitors. The Lancet Oncology. 2019;20(9):1196–1198. doi: 10.1016/S1470-2045(19)30509-1
65. Peyraud F, Italiano A. Combined PARP inhibition and immune checkpoint therapy in solid tumors. Cancers (Basel). 2020;12(6):1502. doi: 10.3390/cancers12061502
66. Huppert LA, Gumusay O, Idossa D, et al. Systemic therapy for hormone receptor-positive/human epidermal growth factor receptor 2-negative early stage and metastatic breast cancer. Ca A Cancer J Clinicians. 2023;73(5):480–515. doi: 10.3322/caac.21777
67. Jin X, Zhou YF, Ma D, et al. Molecular classification of hormone receptor-positive HER2-negative breast cancer. Nature Genet. 2023;55(10):1696–1708. doi: 10.1038/s41588-023-01507-7

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REVIEW

Current usage of pembrolizumab in triple negative breast cancer (TNBC)

Harriet O'Rourke[a], Christopher Hart[a] and Richard H. De Boer[b]

[a]Department of Medical Oncology, St Vincent's Hospital, Fitzroy, Victoria, Australia; [b]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

ABSTRACT

Introduction: The use of immune checkpoint inhibitors (ICI) targeting the PD-1/PD-L1 pathway has changed the landscape in the treatment of triple negative breast cancer (TNBC). The ICI pembrolizumab in combination with chemotherapy now forms a standard of care for the treatment of advanced PD-L1 positive TNBC and as part of neoadjuvant therapy for high-risk early-stage disease. Evidence in this space is rapidly advancing.

Areas covered: This review aims to highlight the evolving role of immunotherapy in TNBC management and to discuss current challenges. The studies in this review were searched from PubMed and ClinicalTrials.gov.

Expert opinion: The KEYNOTE-522 trial demonstrated that the addition of peri-operative pembrolizumab to neoadjuvant chemotherapy improves patient outcomes in early-stage TNBC. However, critical questions remain including how to select which patients truly gain benefit from the addition of pembrolizumab; the optimal duration of therapy, and the optimal adjuvant therapy depending on pathologic response.

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Triple negative breast cancer; TNBC; pembrolizumab; neoadjuvant; metastatic; immunotherapy; biomarker

1. Introduction

Triple negative breast cancer (TNBC) is a highly aggressive histological subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This lack of receptors and consequent lack of endocrine and targeted therapeutic options has made the treatment of TNBC challenging, with chemotherapy historically the only available treatment [1]. Despite conventional chemotherapy, TNBC is associated with high rates of distant metastasis and poor survival. Immune checkpoint inhibitors (ICIs) targeting the programmed cell death 1 (PD-1) and its ligand (PD-L1) pathway have emerged as a promising therapeutic option, demonstrating substantial clinical benefit in both early and advanced TNBC. This review aims to highlight the evolving role of immunotherapy (IO) in the treatment of TNBC.

1.1. Biologic rationale for immunotherapy in TNBC: the immune landscape

While most breast cancers, particularly hormone receptor-positive subtypes, are considered immunologically 'cold,' TNBC is characterized by higher immunogenicity, displaying higher enrichment by tumor-infiltrating lymphocytes (TILs) and higher levels of PD-L1 expression than other subtypes [2]. Recognition of this distinct tumor microenvironment has led to the use of immune-checkpoint inhibitors in both early and advanced TNBC.

The anti-PD-1 monoclonal antibody pembrolizumab received accelerated FDA approval for the treatment of advanced PD-L1-positive TNBC based on the evidence of the phase 1b KEYNOTE-012 trial, in which durable responses were seen in a cohort of women with heavily pre-treated advanced TNBC [1]. Subsequent studies have shown clinical benefits in both early and advanced TNBC. The use of ICI is particularly promising because of the potential for durable responses due to immunologic memory. Combining ICI with chemotherapy appears to have a synergistic effect and significantly improves response rates. The underlying mechanism for this synergy may be that chemotherapy enhances tumor-antigen release and thereby stimulates the anti-tumor response of ICIs [3].

2. Role of ICI in advanced TNBC

2.1. First line pembrolizumab in metastatic TNBC

Pembrolizumab plus chemotherapy was established as a standard of care for the first-line treatment of patients with advanced PD-L1-positive TNBC in the landmark KEYNOTE-355 trial [4]. Adults enrolled in the study had untreated metastatic or locally recurrent inoperable TNBC, where completion of prior curative intent (neo)adjuvant systemic therapy was more than 6 months before first disease recurrence. Patients were randomly assigned to receive pembrolizumab plus chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine/carboplatin) or placebo plus chemotherapy. They were stratified according to the type of chemotherapy, baseline tumor PD-L1 expression (combined positive score (CPS)>1 or CPS < 1), and whether or not they had previously received the same class of chemotherapy in either the neoadjuvant or adjuvant setting. The addition of pembrolizumab to chemotherapy

CONTACT Richard H. De Boer Richard.DeBoer@petermac.org Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria 3050, Australia

Article highlights

- Pembrolizumab in combination with chemotherapy improves overall survival in PD-L1 positive patients with untreated advanced TNBC.
- The addition of peri-operative pembrolizumab to neoadjuvant carboplatin-containing chemotherapy (anthracycline/cyclophosphamide/paclitaxel/carboplatin) improves rates of pathological complete response and 5-year event-free survival (independent of pCR) in patients with high-risk early-stage TNBC, regardless of PD-L1 status.
- Other ICIs have been investigated in advanced and early-stage TNBC with mixed results.
- Reliable predictive biomarkers are needed to guide patient selection for ICI therapy and minimize immune-related and financial toxicity. Currently, there are no validated predictive biomarkers for use of peri-operative pembrolizumab in early-stage disease.
- The necessity for continuing adjuvant pembrolizumab after neoadjuvant chemoimmunotherapy is currently unknown and under investigation: could patients with a pCR safely have adjuvant immunotherapy de-escalated?
- Residual invasive disease (non-pCR) after neoadjuvant ICI indicates resistance, a poorer prognosis, and the need to escalate adjuvant treatment. The optimal adjuvant therapy for these patients is unknown but may include chemotherapy, PARP inhibitors, ICIs, and antibody-drug conjugates, alone or in combination.

resulted in substantial clinical benefit in the CPS > 10 subgroup, with both improved progression-free survival (PFS, HR 0.65, 95% CI 0.49–0.86; $p = 0.0012$) and overall survival (OS) (median OS 23.0 months versus 16.1 months, HR for death 0.73; 95% CI 0.55–0.95; $p = 0.0185$). At 24 months, 48.2% of patients treated with pembrolizumab/chemotherapy were alive compared with 34.0% in the placebo/chemotherapy group [4].

An exploratory analysis demonstrated a consistent OS benefit with the addition of pembrolizumab to chemotherapy in patients whose tumors expressed PD-L1 with a CPS of 10–19 and a CPS of > 20.

However, there was no overall survival benefit in patients with a CPS < 1 or 1–9. These data supported the use of PD-L1 as a predictive biomarker to guide the use of ICI, and a PD-L1 CPS threshold of 10 for the use of pembrolizumab in advanced TNBC.

2.2. Other ICIs in advanced TNBC

Other ICIs have been investigated in advanced TNBC with mixed results. IMpassion130 was a phase 3 randomized trial that evaluated the benefit of adding atezolizumab to nab-paclitaxel in untreated patients with metastatic or unresectable locally advanced TNBC [5]. The PD-L1 positive patients in the chemoimmunotherapy arm had a meaningful overall survival benefit of 7.0-months (25.0 m vs 18.0 m, HR 0.71, 95% CI 0.54–0.93). Notably, there was no significant OS benefit in the intention to treat population, which included all patients regardless of PD-L1 expression. As in the KEYNOTE-355 study, this supports the use of PD-L1 as a predictive biomarker. The confirmatory IMpassion131 trial evaluated the benefit of adding atezolizumab to paclitaxel in patients with untreated advanced TNBC, however it failed to show an improvement in PFS or OS [6]. The reasons for the inconsistent outcomes between the IMpassion130 and IMpassion131 trials are uncertain. One proposed explanation is that the immunosuppressive effects of steroid use required for premedication with paclitaxel in the IMpassion131 trial may have mitigated the effect of atezolizumab. Another potential contributing factor was a difference in the populations between the trials, where those in the IMpassion131 were of lower risk with lower metastatic disease burden. The lack of benefit in the IMpassion131 study led the FDA to withdraw approval for atezolizumab in the US, but atezolizumab in combination with nab-paclitaxel is approved and remains a first-line treatment of advanced TNBC in Europe.

2.3. Biomarkers in advanced TNBC

Current data suggest that a pre-existing immune-enriched tumor microenvironment (PD-L1 positive) is required to benefit from ICI in advanced TNBC [7]. PD-L1 is currently the only prospectively validated biomarker for guiding management of combination chemoimmunotherapy in the first-line treatment of advanced TNBC. However, there are several issues with PD-L1 as a biomarker. Firstly, PD-L1 assessment has technical limitations due to its heterogeneous and dynamic expression, and samples from primary tumors have higher rates of PD-L1 expression than metastases [8]. Secondly, there are currently two methods used to determine PD-L1 status, and they are not interchangeable [9].

KEYNOTE-355 defined PD-L1 status by the combined positive score (CPS), which is the number of all PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. A CPS cutoff of 10 or greater is used to define PD-L1 positivity [4]. The IMpassion trials used the immune cell (IC) area score, defined as the tumor area covered by immune cells (lymphocytes, macrophages, dendritic cells, and granulocytes) that stain positive for PD-L1 [5,6,10]. They defined PD-L1 positivity as an IC score of 1% or greater. These trials also used different immunohistochemistry assays to assess PD-L1 expression: the 22C3 assay in KEYNOTE-355 and the SP142 assay in the IMpassion trials. Regardless of the method used, PD-L1 remains an imperfect biomarker as not all PD-L1 positive patients derive a benefit from ICI therapy. There is a current unmet need to identify those patients who are most likely to respond to ICI and optimize the efficacy of ICI to expand its use beyond those advanced TNBC tumors that are PD-L1 positive.

2.4. Toxicity in advanced TNBC

Combination chemoimmunotherapy has demonstrated an acceptable safety profile in advanced TNBC. As expected, the rates of immune-related adverse events (IRAEs) in KEYNOTE-355 were higher in the pembrolizumab-containing immunotherapy but were most often low-grade, manageable, and most commonly thyroid dysfunction [4]. IRAEs occurred in 26.5% of the pembrolizumab-chemotherapy group compared to 6.4% in the placebo-chemotherapy group, and these events were grade 3 or 4 in 5.3% of patients compared to zero patients, respectively. The most common IRAEs were hypothyroidism (15% versus 3%) and hyperthyroidism (5% and 1%). There are other less common but serious IRAEs, including grade > 3 pneumonitis (1%); colitis (<1%); and severe skin reactions (2%). There were no deaths due to IRAEs [4].

2.5. Challenges in advanced TNBC

Advanced TNBC remains a devastating diagnosis with high mortality. Current strategies being investigated to improve outcomes include combining ICIs with antibody drug conjugates (such as pembrolizumab plus sacituzumab govitecan in the ASCENT04 trial [11]) or PARP inhibitors (avelumab plus talazoparib in the JAVELIN PARP Medley trial [12]). With the shift toward using IO in the early-stage setting, how best to treat patients who develop metastatic TNBC after prior treatment with ICI is an area that requires further investigation.

3. Role of ICI in early-stage TNBC

3.1. Neoadjuvant therapy in early-stage TNBC

Early-stage TNBC is associated with high rates of early recurrence and high mortality. Neoadjuvant chemotherapy has become the preferred approach to stage II and III TNBC as it improves the likelihood of tumor resectability and breast conserving surgery, and because it allows an assessment of the pathological response [13]. This provides important prognostic information and helps to tailor subsequent adjuvant therapy.

A pathological complete response (pCR) is defined as no invasive residual disease in the breast or the lymph nodes after completing neoadjuvant therapy. pCR is well established as a surrogate goal of neoadjuvant chemotherapy, as it is a marker for systemic therapy sensitivity and associated with improved event-free and overall survival in patients with TNBC [14,15]. As a result, pCR is a useful surrogate endpoint in clinical trials. The addition of anti-PD-1/PD-L1 immune checkpoint inhibitors to standard neoadjuvant chemotherapy has recently been shown to improve pCR, and also improve event-free survival (EFS) irrespective of pCR [16].

The degree of response to neoadjuvant therapy can be evaluated and designated by the residual cancer burden (RCB) score. Lower RCB scores (RCB-0 = pCR, or RCB-1 = minimal residual disease) are associated with reduced risk of recurrence compared to higher scores (RCB-2 and RCB-3 = extensive residual disease) [17].

3.2. Benefits of neoadjuvant immune-checkpoint inhibition (ICI)

Pre-clinical studies have demonstrated improved immune responses to neoadjuvant versus adjuvant ICIs [18]. When primary cancer is in situ, it provides a source of tumor antigens which improves the priming of the immune system, expansion of T cells, and anti-tumor effect of ICIs [19]. Thus, by giving ICI in the neoadjuvant setting when the bulk of the primary cancer is present, the T cell response is enhanced and there is greater potential for the elimination of micro-metastatic tumor deposits, preventing relapse after surgery [20–22]. There are a few randomized trials comparing neoadjuvant with adjuvant immunotherapy.

The ALEXANDRA/IMpassion030 phase 3 clinical trial evaluated the addition of atezolizumab to adjuvant chemotherapy (paclitaxel + dose-dense AC/EC), followed by maintenance atezolizumab, in patients with resected stage II-III TNBC [23]. An interim analysis (presented at SABCS in December 2023) demonstrated no improvement in invasive DFS with the addition of adjuvant atezolizumab and increased adverse events in the chemoimmunotherapy arm. Accrual was ceased and the immunotherapy component discontinued due to futility. Several studies have evaluated the efficacy of neoadjuvant ICI in TNBC, with mixed results.

3.3. Pembrolizumab in early TNBC

Pembrolizumab plus neoadjuvant chemotherapy (NACT) was established as a new standard of care following the results of the landmark phase III KEYNOTE-522 trial, in which the addition of the ICI led to improved rates of pCR and EFS in patients with high-risk early TNBC [24]. Here, patients with untreated stage II or III TNBC (cT1c N1–2 or cT2–4 N0–2, as defined by the AJCC 7th edition) were randomized to receive either pembrolizumab or placebo every 3 weeks combined with NACT consisting of weekly paclitaxel with 3-weekly carboplatin followed by doxorubicin-cyclophosphamide (AC) (or epirubicin-cyclophosphamide, EC) every 3 weeks. Following definitive surgery, patients received the same pembrolizumab or placebo every 3 weeks in the adjuvant setting for up to nine cycles, to complete 12 months of therapy. Adjuvant capecitabine or PARP inhibitor was not allowed. The first interim analysis in 2020 showed an improvement in pCR: 64.8% versus 51.2% (estimated treatment difference, 13.6% points; 95% CI, 5.4 to 21.8; $p < 0.001$).

In 2022, Schmid and colleagues [25] published follow-up data on EFS, defined as the time from randomization to the date of disease progression that precluded definitive surgery, local or distant recurrence, occurrence of a second primary cancer, or death from any cause. At a median follow-up of 39.1 months, the 36-month EFS was 84.5% in the pembrolizumab-chemotherapy arm compared with 76.8% in the placebo-chemotherapy arm (HR 0.63, 95% CI, 0.48–0.82, $p < 0.001$). Subgroup analysis demonstrated a benefit in patients regardless of PD-L1 score, stage, and nodal status [25]. This improvement in pCR and EFS with the addition of pembrolizumab in early TNBC led to the FDA approval of pembrolizumab and established it as a standard of care.

Updated findings were presented at the European Society for Medical Oncology (ESMO) 2023 Annual Congress with 5-year EFS data, which is particularly important given that most relapses of TNBC occur within this time period. These 5-year data demonstrated that the EFS benefit was maintained (HR 0.63, 95% CI 0.49–0.81) with the addition of immunotherapy: 81.3% in the pembrolizumab-chemotherapy arm versus 72.3% in the placebo-chemotherapy arm. While overall survival data are still immature, there was a significant benefit in distant recurrence-free survival (HR 0.64, 95% CI 0.49–0.84) [26].

A preplanned exploratory analysis demonstrated that the 5-year EFS was high in all patients who achieved a pCR, and higher in those who received immunotherapy: 92.2% in the pembrolizumab-chemotherapy arm versus 88.2% in the placebo-chemotherapy arm (HR 0.65, 95% CI 0.39–1.08). Residual disease (non-pCR) was a poor prognostic factor, regardless of whether immunotherapy was received: 62.6% 5-year EFS in the pembrolizumab-chemotherapy arm versus 52.3% in the

placebo-chemotherapy arm (HR 0.72, 95% CI 0.54–0.96). We have known that patients who have a pCR have a better outcome, compared with those with residual disease who have higher rates of recurrence. However, these data demonstrate benefit of pembrolizumab regardless of pathologic response: even amongst patients who do not have a pCR, those who received combination chemoimmunotherapy do substantially better (absolute improvement in EFS of 10% at 5 years) [26]. This suggests that neoadjuvant IO has additional long-term anti-tumor effects, beyond achieving a pCR.

3.4. Other neoadjuvant immune-checkpoint inhibitors in early TNBC

Pembrolizumab is the only ICI currently approved for the treatment of early-stage TNBC. However, other ICIs have been investigated in this setting, with mixed results. The phase III IMpassion031 randomized controlled trial demonstrated an improved pCR with the addition of atezolizumab to NACT (nab-paclitaxel + AC) for patients with stage 2–3 TNBC [27]. As in KEYNOTE-522, this benefit in pCR with the addition of neoadjuvant ICI was seen in patients regardless of PD-L1 status. However, the addition of atezolizumab failed to significantly improve 3-year EFS, DFS or OS [28]. The 3-year EFS was numerically higher in the atezolizumab arm at 81% versus placebo arm at 76% but not statistically significant (HR 0.76, 95% CI 0.47–1.21). Why neoadjuvant pembrolizumab but not atezolizumab has shown survival benefit is unclear. Key differences in the KEYNOTE-522 and IMpassion031 studies in terms of the chemotherapy regimen (most notably the absence of carboplatin and the optional use of adjuvant chemotherapy in patients with non-pCR in IMpassion031), sample size and trial design may have contributed. Longer follow-up is required.

Other trials have shown inconsistent results, with several studies showing no significant improvement in pCR with the addition of ICI to NACT.

The phase III NeoTRIP study evaluated the addition of atezolizumab to neoadjuvant chemotherapy (carboplatin and nab-paclitaxel) in patients with early high-risk and locally advanced TNBC [29]. After surgery, patients received four cycles of adjuvant anthracycline regimen (AC), regardless of pCR. This study found no improvement in pCR rates nor in 5-year EFS with the addition of atezolizumab compared with chemotherapy alone [30]. Subsequent biomarker analysis (NeoTRIPaPDL1) identified a baseline imbalance in TILs between arms that may have resulted in smaller differences of pCR [31]. Administering the anthracycline-component in the adjuvant setting may also have contributed to lower rates of pCR in the NeoTRIP trial compared with other studies.

The randomized phase II GeparNuevo trial randomized patients with cT1b-T4N0–3 TNBC to receive neoadjuvant durvalumab or placebo every 4 weeks added to nab-paclitaxel weekly for 12 weeks, then AC, before surgery, without any subsequent adjuvant ICI [32]. There was a unique window phase for the first 117 patients who received a 2-week lead-in with durvalumab monotherapy, although this was ceased and chemoimmunotherapy commenced concurrently for subsequent patients in the trial due to concerns about delaying receipt of chemotherapy. The addition of durvalumab to NACT did not result in a significant increase in the pCR rate. It did, however, show an improvement in invasive DFS (iDFS), distant DFS (DDFS), and OS independent of pCR [33]. This may suggest that pCR is an insufficient endpoint for efficacy of neoadjuvant chemoimmunotherapy. A key aspect to this trial was the decision not to include any ICI in the adjuvant setting, which differentiates it from the KEYNOTE-522 trial.

3.5. Toxicity of ICI in early-stage TNBC

The use of neoadjuvant ICI carries risks of immune-related adverse toxicities that while uncommon, can be life-threatening or permanent, such as insulin-dependent diabetes or hypoadrenalism. Furthermore, the impact of ICI on fertility is not yet clear and is an important consideration for this cohort of TNBC patients who are often young, female and of child-bearing age. Financial toxicity is also significant. Given that a substantial proportion of patients can be cured with NACT alone, it is a relatively small percentage for whom ICI is critical to achieve a cure and so many patients are exposed to an unnecessary risk of immune-related toxicity. This highlights the need for the determination of reliable biomarkers to predict responses to anti-PD-1/PD-L1 checkpoint inhibitors and improve patient selection for immunotherapy.

3.6. Biomarkers in early TNBC

In advanced TNBC, PD-L1 status (CPS >10) is predictive of benefit from pembrolizumab. In early TNBC, PD-L1 status is prognostic but not predictive: patients who are PD-L1 positive have higher rates of pCR, regardless of whether or not they receive immunotherapy, but the efficacy of neoadjuvant ICI in terms of pCR is independent of PD-L1 expression, as shown in the KEYNOTE-522, IMpassion031 and GeparNuevo trials.

Tumor-infiltrating lymphocytes (TILs) are associated with improved prognosis (DFS, distant DFS, and OS) in early TNBC and are an independent predictor of response to chemotherapy [7,34]. TILs are a measure of quantifying immune T cell infiltration. Higher quantity of TILs indicates the presence of an existing anti-tumor immune response, and is associated with smaller tumor size, less nodal involvement and higher level of PD-L1 expression [35]. Conversely, samples from breast cancer metastases show lower quantity of TILs than in the primary tumor, suggesting progressive disease is associated with increased immune suppression [36]. The expression of programmed death-ligand 1 (PD-L1) by tumor cells is an adaptive mechanism of tumor resistance to TILs [35]. By inhibiting the PD-1/PD-L1 checkpoint, immune-checkpoint inhibitors can increase the anti-tumor T cell response. However, numerous studies have demonstrated that TILs are prognostic but not predictive of benefit with ICIs.

3.7. Patient selection: which patients benefit most from neoadjuvant ICI?

As there are currently no validated predictive biomarkers to guide patient selection for neoadjuvant ICI, this instead relies on an assessment of clinical risk [37,38]*****. In the KEYNOTE-522 trial patients with either node positive

disease or T2 and higher tumors were included and derived benefit. Therefore, at present it seems reasonable that neoadjuvant ICI be considered in all node positive TNBC patients and high-risk node-negative patients, balancing the individual risks of toxicity and benefit.

4. Unanswered questions on the optimal adjuncts and schedule of ICI in early-stage TNBC

4.1. Adjuvant ICI

The optimal duration of ICI therapy in early TNBC is unknown. One area of keen interest is investigating the necessity of adding adjuvant ICI following neoadjuvant ICI. All patients in KEYNOTE-522 and IMpassion031 received adjuvant ICI to complete a total of 12 months of immunotherapy, regardless of whether they achieved a pCR. However, continued ICI carries significant financial cost and risk of immune-mediated toxicity, so administering the minimum duration of ICI should be the aim. In the GeparNuevo trial, patients received only neoadjuvant ICI without subsequent adjuvant therapy, and still demonstrated a DFS and OS benefit [32]. This suggests that adjuvant therapy may not be required. At present, the necessity for continuing adjuvant pembrolizumab after neoadjuvant ICI and chemotherapy is uncertain, both in patients who do and do not achieve a pCR. Several studies are currently underway, including the Optimice-pCR trial which aims to answer the question of whether patients who achieve a pCR from neoadjuvant chemoimmunotherapy with pembrolizumab can safely have adjuvant therapy de-escalated with observation instead of adjuvant pembrolizumab [36].

4.2. Clinical benefit from neoadjuvant ICI in patients with non-pCR

As discussed, the randomized phase II GeparNuevo trial showed that the addition of durvalumab to NACT resulted in a non-significant increase in pCR rate. However, it demonstrated a significant and clinically meaningful improvement in 3-year invasive DFS (iDFS), distant DFS (DDFS) and overall survival (95.2% versus 83.5% (HR 0.24, 95% CI 0.08–0.72, $p = 0.006$) [32]. Similar to the data seen in KEYNOTE-522, this suggests that neoadjuvant chemoimmunotherapy can induce long-term anti-tumor effects with clinical benefit even in patients without a pathologic response.

4.3. Management of residual invasive disease after neoadjuvant ICI

Residual invasive disease after neoadjuvant therapy confers a poor prognosis and identifies patients who are at higher risk of recurrence and require escalation of adjuvant therapy. In the KEYNOTE-522 trial, pembrolizumab was continued postoperatively, irrespective of the pathological response to neoadjuvant therapy, but no other adjuvant treatments were given. The optimal adjuvant therapy for patients with residual disease is unknown but may include chemotherapy, PARP inhibitors, immunotherapy, and antibody-drug conjugates (ADCs) – alone or in combination. Positive circulating tumor DNA (ctDNA) at/after surgery following neoadjuvant chemoimmunotherapy has been associated with a poor prognosis and together with pathological response may help guide escalation of adjuvant therapies [28].

4.4. Adjuvant capecitabine

NACT is standard practice for patients with early TNBC to allow an assessment of residual invasive disease and tailor adjuvant therapy in these patients who are at highest risk of recurrence. The phase III CREATE-X trial demonstrated an overall survival benefit with adjuvant capecitabine compared to observation in patients who had residual invasive disease after NACT for stage I-IIIB HER2-negative breast cancer (HR 0.52, 95% CI 0.39–0.90) [39]. 32.2% of patients in this study had TNBC, and these patients had improved DFS and OS with adjuvant capecitabine. As such, it is now recommended therapy for patients with early-stage TNBC with residual disease after NACT. However, with the survival benefit of neoadjuvant followed by adjuvant pembrolizumab demonstrated in the KEYNOTE-522 trial, the role of adjuvant capecitabine is less clear. Patients with residual invasive disease (non-pCR) in KEYNOTE-522 did not receive adjuvant capecitabine, as it was not considered standard treatment at the time of trial design. In light of these evolving data, clinicians are faced with the decision of whether to combine adjuvant capecitabine with pembrolizumab for patients with residual invasive disease after neoadjuvant treatment with the KEYNOTE-522 protocol. While there is currently no randomized data to show that this combination is superior to single-agent therapy, it seems reasonable in this cohort due to their high risk of recurrence, although the potential benefit must be weighed against the risk of toxicity in the individual patient. Data in the metastatic TNBC setting showed no new safety signals with the combination of pembrolizumab and capecitabine [40,41]. Further research is needed in this space to define the optimal adjuvant therapy regimen.

4.5. Adjuvant PARP inhibitors in BRCA variants

Another approach that has been explored to improve outcomes for patients with early TNBC at high risk of recurrence is the use of poly-adenosine diphosphate-ribose polymerase (PARP) inhibitors. The OlympiA trial demonstrated longer invasive disease-free survival, distant DFS and OS with the adjuvant PARP inhibitor olaparib compared to placebo, for patients with high-risk, HER2-negative early breast cancer with pathogenic or likely pathogenic variants in germline BRCA1 or BRCA2. The trial included patients who received either adjuvant or neoadjuvant chemotherapy: those who received NAC were required to have residual invasive disease [42].

Data from the OlympiA and CREATE-X trials show that adjuvant monotherapy with olaparib or capecitabine offer a meaningful survival benefit. However, the role of these adjuvant therapies in the context of neoadjuvant and adjuvant ICI is not established. There is currently no randomized

data to guide the combination or sequence of adjuvant therapy for these patients with germline BRCA mutations and residual disease after neoadjuvant chemoimmunotherapy for TNBC. Information about germline BRCA status has not been provided in the KEYNOTE-522 trial. Until further data are available, clinical judgment is required. It is not recommended to combine adjuvant capecitabine with olaparib due to overlapping side effects, particularly cytopenias. However, with the improved survival demonstrated with adjuvant olaparib, it seems reasonable to combine it with adjuvant pembrolizumab for those patients with residual disease after neoadjuvant chemotherapy and pembrolizumab for TNBC with germline BRCA mutations. There is biological rationale for combining PARP inhibitors and ICI, which have been shown to have a synergistic benefit in preclinical models [43]. Safety data for combining PARPi and ICIs has been demonstrated in the metastatic setting and the combination is generally well tolerated [44,45]. Studies are underway to investigate the role of more potent PARPi such as talazoparib, and the potential role for neoadjuvant PARPi [46].

4.6. Adjuvant antibody-drug conjugates

Another approach being investigated to improve outcomes in patients with residual disease is the adjuvant use of antibody-drug conjugates (ADCs). ASCENT-05 [47] is a phase 3 randomized trial underway to evaluate the effect of adjuvant therapy with the combination of the ADC sacituzumab govitecan (SG) and pembrolizumab in patients with residual disease after neoadjuvant therapy for TNBC, that may have included a neoadjuvant ICI. SG is a Trop-2-directed ADC that contains the irinotecan active metabolite SN-38 (a topoisomerase I inhibitor). It has been approved for treatment in pre-treated metastatic TNBC after it demonstrated a PFS and OS benefit and is currently being investigated in untreated patients [48]. There is preclinical data that supports the combination of irinotecan and ICI having synergistic antitumor activity via the reduction in regulatory T cells and augmentation of MHC class I-mediated tumor antigen presentation [49].

TROPION-Breast03 [50] is a phase 3 randomized trial assessing the efficacy of the novel ADC datopotamab deruxtecan (Dato-DXd) with or without durvalumab in patients with residual disease after neoadjuvant therapy for TNBC, that may have included a neoadjuvant ICI. Dato-DXd is another Trop-2-directed ADC, this linked to the topoisomerase I inhibitor deruxtecan (DXd).

5. Defining the optimal chemotherapy backbone in early-stage TNBC

5.1. Could a less toxic chemotherapy backbone be used in combination with ICI?

There is currently no consensus on the most effective chemotherapy regimen for high-risk early TNBC, and the necessity of platinum therapy is particularly contentious. An important question is whether a less toxic chemotherapy component could be used in combination with ICI therapy in patients with lower clinical risk. Such patients may include those with node negative TNBC and a high level of preexisting immune activation as evidenced by high TILs and/or PD-L1 expression [51].

5.2. Could carboplatin be omitted?

The addition of carboplatin to neoadjuvant paclitaxel followed by 3-weekly AC demonstrated an improvement in pCR and EFS in the BrighTNess trial [52]. However, this addition of carboplatin to an anthracycline-containing regimen has come at the expense of increasing toxicity. KEYNOTE-522 used carboplatin as part of the NACT regimen, but IMpassion031 and GeparNuevo did not. While the necessity for carboplatin as part of the NAC backbone is uncertain, it was used in the KEYNOTE-522 and thus forms the current standard of care for neoadjuvant chemoimmunotherapy in TNBC. Further studies are needed to determine biomarkers that may guide the escalation or de-escalation of the cytotoxic chemotherapy backbone.

5.3. Could anthracycline be omitted?

Anthracyclines carry risk of cardiotoxicity, myelosuppression, and secondary hematological malignancies. Several studies have looked at the benefit of adding ICI to an anthracycline-free neoadjuvant chemotherapy protocol. NeoPACT was a single-arm phase II study that used a non-anthracycline neoadjuvant regimen of carboplatin, docetaxel, and pembrolizumab in patients with stage I-III TNBC, with no adjuvant pembrolizumab [53]. This regimen resulted in a pCR rate of 58% and estimated 3-year EFS of 86% in all patients; 98% in patients who had a pCR and 68% in patients with non-pCR. These results are comparable to studies evaluating anthracycline-containing chemoimmunotherapy regimens, such as the KEYNOTE-522 trial with pCR rate of 64.8% and 3-year EFS of 84.5% in all patients. The NeoPACT trial provides data to support the potential use of neoadjuvant chemoimmunotherapy where anthracycline-containing regimens are contraindicated, but further research is necessary.

6. Future directions & challenges in early TNBC

Combining ICI with NACT has proved to be a promising strategy to improve outcomes in early TNBC. However, the optimal duration of ICI, the best chemotherapy backbone and best schedule of therapy remain unknown. Outcomes are particularly poor for those patients who fail to respond to immune checkpoint inhibitors and have high residual cancer burden after neoadjuvant therapy, known as primary resistance (41). Understanding and overcoming mechanisms of immunotherapy resistance is critical to improve patient outcomes in early TNBC. Further studies may inform strategies in these patients including the combination and escalation of adjuvant therapies, guided by pathological response and potentially other biomarkers including ctDNA.

7. Conclusion

Pembrolizumab in combination with chemotherapy now forms a standard of care for treatment of advanced PD-L1 positive TNBC, and as part of neoadjuvant therapy for high-risk early TNBC. Despite significant progress, challenges remain in optimizing the role of immunotherapy in treating TNBC. Reliable predictive biomarkers are needed to guide patient selection, improve clinical outcomes, and minimize risk of toxicity. Further studies are needed to answer these urgent questions.

8. Expert opinion

Triple negative breast cancer remains a challenging cancer to treat. In the early breast cancer setting it disproportionately impacts on younger patients, has high relapse rates, and relapses early rather than late: usually within the first 2–3 years after diagnosis. Traditionally, no targeted therapy was effective, and clinicians relied on chemotherapy. Although there have been advances in chemotherapy regimens such as adopting a neo-adjuvant approach, the use of dose dense anthracyclines and the addition of carboplatin, results have still lagged behind the other breast cancer subtypes, namely hormone receptor positive and HER2 positive. This, plus the fact that triple negative cancers are seen as being more 'immunogenic,' has led to several large studies in patients with early TNBC, where immunotherapy (IO) was added to chemotherapy. While the results have been variable and immunotherapy is potentially toxic and expensive, the KEYNOTE-522 study with pembrolizumab has hit its statistical targets and with longer follow-up is appearing to finally be a breakthrough in improving outcomes for these patients. This will hopefully translate into its adoption and an overall improvement in disease outcomes for patients with TNBC. Nevertheless, the cost will be a restraining factor in its widespread use, and there remains critical questions, in particular how best to choose the patients most likely to benefit. It does not make sense that PDL1 expression, which is the most used biomarker, seems not to have a role here. Also, there were limitations of the design of the KEYNOTE-522 trial where patients were randomized to receive either chemotherapy alone versus chemotherapy plus 12 months of immunotherapy. What was needed was a third arm where the immunotherapy was stopped at surgery if there was a pathological complete response. If this arm had similar outcomes to the 12-month arm, then a lot of unnecessary treatment, time, toxicity, and cost could potentially be saved. Thankfully, there are now trials being done to answer this question, but the results will still be a number of years away, and until then clinicians will face a dilemma in whether to continue IO after a pathological CR has been achieved with the neo-adjuvant component of the regimen.

In the metastatic setting, several IO trials in patients with advanced TNBC have been successfully completed, but again, not all trials have achieved statistically valid results. As a point of contrast to the early-stage setting, it appears that the ICIs only work if the patient's tumor tests positive to PDL-1 staining, often at modest/high levels. A major problem is that each ICI is accompanied by a different testing platform/antibody and a different way of measuring the score, which makes it difficult for clinicians and for pathology departments. This has been partially alleviated by the fact that at present only one agent – pembrolizumab – is being widely used in Australia in the metastatic setting, although this may change as other agents come through the trials.

If one speculates on how this area will evolve in the next few years, one hopes that there will be a wider range of agents available to choose from. More importantly, there will be better ways to select which patients truly gain benefit from the addition of pembrolizumab and the optimal duration of therapy, versus those patients who will have a high chance of cure using standard chemotherapy alone. Another development might be the development of immunotherapy agents or regimens that reduce or even eliminate the need for chemotherapy at all.

Abbreviations list

AC	doxorubicin-cyclophosphamide
ADC	antibody drug conjugate
CI	confidence interval
CPS	combined positive score
ctDNA	circulating tumor DNA
Dato-DXd	datopotamab deruxtecan
DDFS	distant disease-free survival
DFS	disease-free survival
DRFS	distant recurrence-free survival
DXd	deruxtecan
EC	epirubicin-cyclophosphamide
EFS	event free survival
ER	estrogen receptor
ESMO	European Society for Medical Oncology
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
FDA	Food and Drug Administration
IC	immune cell
ICI	immune checkpoint inhibitor
iDFS	invasive disease-free survival
IRAE	immune-related adverse events
NACT	neoadjuvant chemotherapy
OS	overall survival
PARP	poly-adenosine diphosphate-ribose polymerase
PARPi	poly-adenosine diphosphate-ribose polymerase inhibitor
pCR	pathological complete response
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PR	progesterone receptor
RCB	residual cancer burden
SABCS	San Antonio Breast Cancer Symposium
SG	sacituzumab govitecan
TIL	tumor-infiltrating lymphocyte
TNBC	triple negative breast cancer

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Nanda R, Chow LQM, Dees EC, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase IB keynote-012 study. J Clin Oncol. 2016;34(21):2460–2467. doi: 10.1200/JCO.2015.64.8931
2. Geurts V, Kok M. Immunotherapy for metastatic triple negative breast cancer: current paradigm and future approaches. Curr Treat Options Oncol. 2023;24(6):628–643. doi: 10.1007/s11864-023-01069-0
3. Galluzzi L, Buqué A, Kepp O, et al. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell. 2015;28(6):690–714. doi: 10.1016/j.ccell.2015.10.012
4. Cortes J, Rugo HS, Cescon DW, et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. N Engl J Med. 2022;387(3):217–226. doi: 10.1056/NEJMoa2202809

•• **Major phase III landmark trial that demonstrated an overall survival benefit and established combination chemoimmunotherapy as a standard of care for untreated metastatic TNBC.**

5. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379(22):2108–2121. doi: 10.1056/NEJMoa1809615
6. Miles D, Gligorov J, André F, et al. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. Ann Oncol. 2021;32(8):994–1004. doi: 10.1016/j.annonc.2021.05.801
7. Blackley EF, Loi S. Targeting immune pathways in breast cancer: review of the prognostic utility of TILs in early stage triple negative breast cancer (TNBC). Breast. 2019;48 (Suppl 1):S44–S48. doi: 10.1016/S0960-9776(19)31122-1
8. Rozenblit M, Huang R, Danziger N, et al. Comparison of PD-L1 protein expression between primary tumors and metastatic lesions in triple negative breast cancers. J Immunother Cancer. 2020;8(2):e001558. doi: 10.1136/jitc-2020-001558
9. Rugo HS, Loi S, Adams S, et al. PD-L1 immunohistochemistry assay comparison in atezolizumab plus nab-paclitaxel–treated advanced triple- negative breast cancer. J Natl Cancer Inst. 2021;113(12):1733–1743. doi: 10.1093/jnci/djab108
10. Emens LA, Adams S, Barrios CH, et al. First-line atezolizumab plus NAB-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: Impassion130 final overall survival analysis. Ann Oncol. 2021;32(8):983–993. doi: 10.1016/j.annonc.2021.05.355

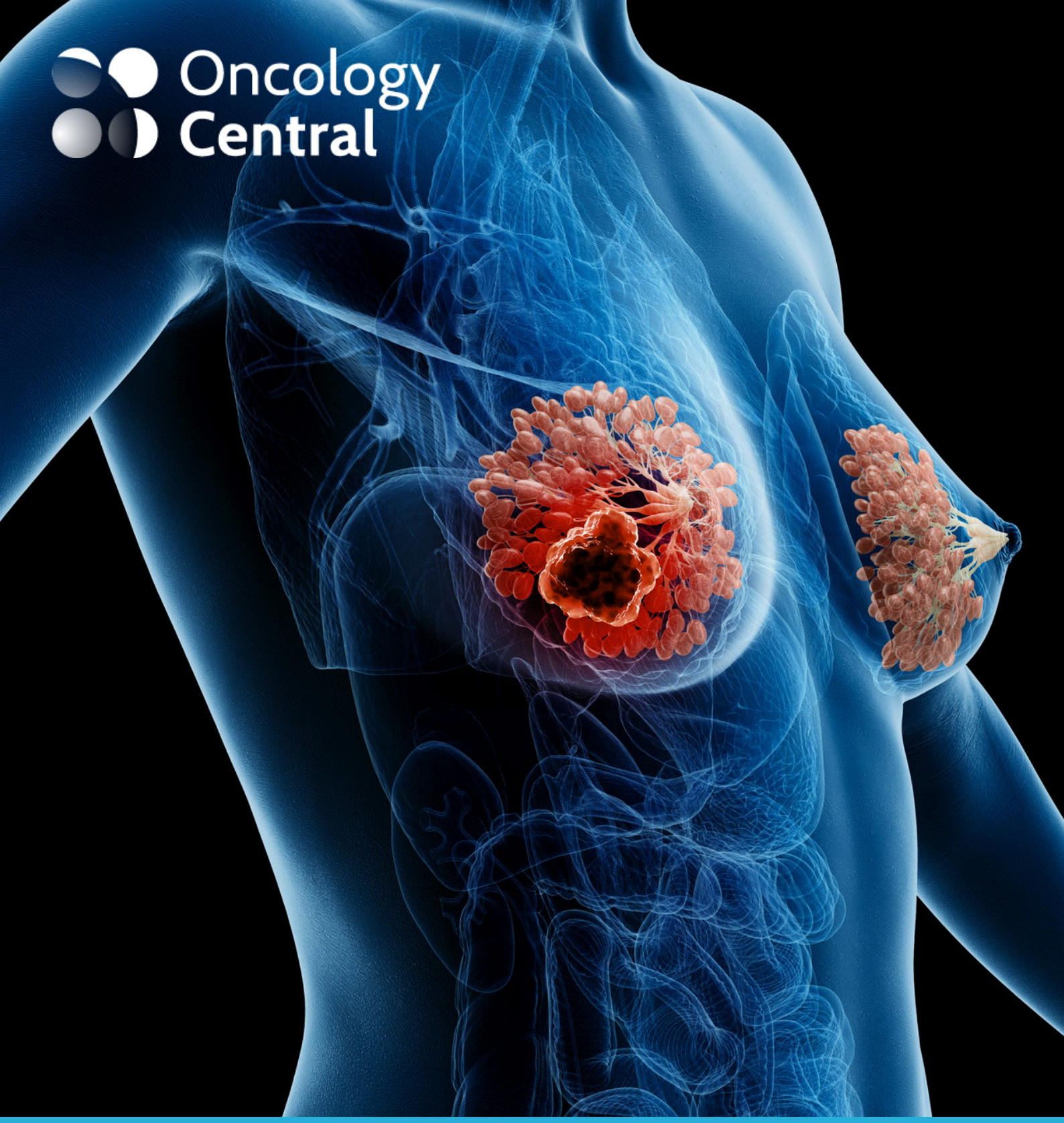
•• **Major phase III trial that demonstrated an overall survival benefit of combining ICI with chemotherapy in untreated metastatic TNBC.**

11. Study of sacituzumab govitecan-hziy and pembrolizumab versus treatment of physician's choice and pembrolizumab in patients with previously untreated, locally advanced inoperable or metastatic triple-negative breast cancer (ASCENT-04) [Internet]. Bethesda (MD): National Library of Medicine Clinicaltrials.gov; 2024 Feb 22 [cited 2024 Feb 28]. Available from: https://clinicaltrials.gov/study/NCT05382286
12. Yap TA, Bardia A, Dvorkin M, et al. Avelumab plus talazoparib in patients with advanced solid tumors: the JAVELIN PARP medley nonrandomized controlled trial. JAMA Oncol. 2023;9(1):40–50. doi: 10.1001/jamaoncol.2022.5228
13. Bonadio RC, Tarantino P, Testa L, et al. Management of patients with early-stage triple-negative breast cancer following pembrolizumab-based neoadjuvant therapy: what are the evidences? Cancer Treat Rev. 2022;110:102459. doi: 10.1016/j.ctrv.2022.102459
14. Sikov WM, Polley M-Y, Twohy E, et al. CALGB (Alliance) 40603: long-term outcomes (LTOs) after neoadjuvant chemotherapy (NACT) ± carboplatin (Cb) and bevacizumab (Bev) in triple-negative breast cancer (TNBC). J Clin Oncol. 2019;37(Suppl 15):591–591. doi: 10.1200/JCO.2019.37.15_suppl.591
15. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164–172. doi: 10.1016/S0140-6736(13)62422-8
16. Pusztai L, Denkert C, O'Shaughnessy J, et al. Event-free survival by residual cancer burden after neoadjuvant pembrolizumab + chemotherapy versus placebo + chemotherapy for early TNBC: exploratory analysis from KEYNOTE-522. J Clin Oncol. 2022;40(16_suppl):503. doi: 10.1200/JCO.2022.40.16_suppl.503
17. Yau C, Osdoit M, van der Noordaa M, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol. 2022;23(1):149–160. doi: 10.1016/S1470-2045(21)00589-1
18. Liu J, Blake SJ, Yong MC, et al. Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. Cancer Discov. 2016;6(12):1382–1399. doi: 10.1158/2159-8290.CD-16-0577
19. Loi S, Drubay D, Adams S, et al. Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. J Clin Oncol. 2019;37(7):559–569. doi: 10.1200/JCO.18.01010
20. Krishnamoorthy M, Lenehan JG, Maleki Vareki S. Neoadjuvant immunotherapy for high-risk, resectable malignancies: scientific rationale and clinical challenges. J Natl Cancer Inst. 2021;113(7):823–832. doi: 10.1093/jnci/djaa216
21. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. Science. 2020;367(6477). doi: 10.1126/science.aax0182
22. Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018;24(11):1655–1661. doi: 10.1038/s41591-018-0198-0
23. Ignatiadis M, Bailey A, McArthur H, et al. Adding atezolizumab to adjuvant chemotherapy for stage II and III triple-negative breast cancer is unlikely to improve efficacy: interim analysis of the ALEXANDRA/IMpassion030 phase 3 trial. [cited 2024 Feb 22]. Available from: https://atgproductions.net/atgclients/sabcs/2023_SABCS_Abstract_Report-12-3-23.pdf
24. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382(9):810–821. doi: 10.1056/NEJMoa1910549
25. Schmid P, Cortes J, Dent R, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. N Engl J Med. 2022;386(6):556–567. doi: 10.1056/NEJMoa2112651

•• **Major phase III trial demonstrating EFS benefit with the addition of peri-operative immune checkpoint inhibitor to neoadjuvant chemotherapy in early-stage TNBC.**

26. Schmid P, Cortés J, Dent RA, et al. LBA18 pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: updated EFS results from the phase III KEYNOTE-522 study. Ann Oncol. 2023;34:S1257. doi: 10.1016/j.annonc.2023.10.008

27. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020;396(10257):1090–1100. doi: 10.1016/S0140-6736(20)31953-X
28. Barrios CH, Harbeck N, Zhang HA, et al. Final analysis of the placebo-controlled randomised phase 3 Impassion031 trial evaluating neoadjuvant atezolizumab plus chemotherapy followed by open-label adjuvant atezo in patients with early-stage triple-negative breast cancer. Ann Oncol. 2023;8(1 suppl_4):101220. doi: 10.1016/j.esmoop.2023.101571
•• **Phase III randomized trial that failed to show an EFS benefit with the addition of ICI to neoadjuvant chemotherapy for early-stage TNBC, despite showing an improvement in pCR.**
29. Gianni L, Huang C, 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(5):534–543. doi: 10.1016/j.annonc.2022.02.004
30. Gianni L, Huang C, Egle D, et al. LBA19 event-free survival (EFS) analysis of neoadjuvant taxane/carboplatin with or without atezolizumab followed by an adjuvant anthracycline regimen in high-risk triple negative breast cancer (TNBC): NeoTRIP michelangelo randomized study. Ann Oncol. 2023;34:S1258–S1259. doi: 10.1016/j.annonc.2023.10.009
31. Bianchini G, Huang CS, Egle D, et al. LBA13 tumour infiltrating lymphocytes (TILs), PD-L1 expression and their dynamics in the NeoTRIPaPDL1 trial. Ann Oncol. 2020;31:S1145–S6. doi: 10.1016/j.annonc.2020.08.2241
32. Loibl S, Untch M, Burchardi N, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;30(8):1279–1288. doi: 10.1093/annonc/mdz158
•• **Randomized phase II trial that demonstrates the addition of ICI to neoadjuvant chemotherapy leading to an improvement in DFS and OS, independent of pCR.**
33. 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(11):1149–1158. doi: 10.1016/j.annonc.2022.07.1940
34. Denkert C, Loibl S, Noske A, et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol. 2010 Jan 1;28(1):105–113. doi: 10.1200/JCO.2009.23.7370
35. Ali HR, Glont SE, Blows FM, et al. PD-L1 protein expression in breast cancer is rare, enriched in basal-like tumours and associated with infiltrating lymphocytes. Ann Oncol. 2015;26(7):1488–1493. doi: 10.1093/annonc/mdv192
36. Szekely B, Bossuyt V, Li X, et al. Immunological differences between primary and metastatic breast cancer. Ann Oncol. 2018;29(11):2232–2239. doi: 10.1093/annonc/mdy399
37. Rizzo A, Ricci A. Biomarkers for breast cancer immunotherapy: PD-L1, TILs, and beyond, expert opin investig drugs. Expert Opin Investig Drugs. 2022;31(6):6, 549–555. doi: 10.1080/13543784.2022.2008354
38. Vs P. Observation in people with triple-negative breast cancer who had a pathologic complete response after chemotherapy plus pembrolizumab [Internet]. Bethesda (MD): National Library of Medicine Clinicaltrials.gov; 2024 Feb 20 [cited 2024 Feb 25]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05812807
39. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376(22):2147–2159. doi: 10.1056/NEJMoa1612645
40. Shah AN, Flaum L, Helenowski I, et al. Phase II study of pembrolizumab and capecitabine for triple negative and hormone receptor-positive, HER2–negative endocrine-refractory metastatic breast cancer. J Immunother Cancer. 2020;8(1):e000173. doi: 10.1136/jitc-2019-000173
41. Page DB, Pucilowska J, Bennetts L, et al. Abstract P2-09-03: updated efficacy of first or second-line pembrolizumab (pembro) plus capecitabine (cape) in metastatic triple negative breast cancer (mTNBC) and correlations with baseline lymphocyte and naïve CD4+ T-cell count. Cancer Res. 2019;79(4_Supplement):P2–09–03–P2–09–03. doi: 10.1158/1538-7445.SABCS18-P2-09-03
42. Tutt AN, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1-or BRCA2-mutated breast cancer. N Engl J Med. 2012;384(25):2394–2405. doi: 10.1056/NEJMoa2105215
43. Wu Z, Cui P, Tao H, et al. The synergistic effect of PARP inhibitors and immune checkpoint inhibitors. Clin Med Insights Oncol. 2021 Feb 25;15:1179554921996288.
44. Vinayak S, Tolaney SM, Schwartzberg L, et al. Open-label clinical trial of niraparib combined with pembrolizumab for treatment of advanced or metastatic triple-negative breast cancer. JAMA Oncol. 2019;5(8):1132–1140. doi: 10.1001/jamaoncol.2019.1029
45. Domchek SM, Postel-Vinay S, Im SA, 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. 2020;21(9):1155–1164. doi: 10.1016/S1470-2045(20)30324-7
46. Litton JK, Beck JT, Jones JM, et al. Neoadjuvant talazoparib in patients with germline BRCA1/2 mutation-positive, early-stage triple-negative breast cancer: results of a phase ii study. Oncology. 2023 Oct 3;28(10):845–855. doi: 10.1093/oncolo/oyad139
47. Study of sacituzumab govitecan-hziy and pembrolizumab versus treatment of physician's choice in patients with triple negative breast cancer who have residual invasive disease after surgery and neoadjuvant therapy (ASCENT-05) [Internet]. Bethesda (MD): National Library of Medicine Clinicaltrials.gov; 2024 Feb 13 [cited 2024 Feb 22]. Available from: https://clinicaltrials.gov/study/NCT05633654
48. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in metastatic triple-negative breast cancer. N Engl J Med. 2021 Apr;384(16):1529–1541.
49. Iwai T, Sugimoto M, Wakita D, et al. Topoisomerase I inhibitor, irinotecan, depletes regulatory T cells and up-regulates MHC class I and PD-L1 expression, resulting in a supra-additive antitumor effect when combined with anti-PD-L1 antibodies. Oncotarget. 2018;9(59):31411–31421. doi: 10.18632/oncotarget.25830
50. A study of dato-DXd with or without durvalumab versus investigator's choice of therapy in patients with stage I-III triple-negative breast cancer without pathological complete response following neoadjuvant therapy (TROPION-Breast03) [Internet]. Bethesda (MD): National Library of Medicine Clinicaltrials.gov; 2024 Feb 13 [cited 2024 Feb 22]. Available from: https://www.clinicaltrials.gov/study/NCT05629585
51. Dixon-Douglas J, Loi S. Immunotherapy in early-stage triple-negative breast cancer: where are we now and where are we headed? Curr Treat Options Oncol. 2023;24(8):1004–1020.
• **Proposes a strategy for assessing clinical risk combined with biomarkers to guide neoadjuvant therapy, and pCR or RCB to guide adjuvant therapy.**
52. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (brightness): a randomized, phase 3 trial. Lancet Onco. 2018;19(4):497–509. doi: 10.1016/S1470-2045(18)30111-6
53. Sharma P, Stecklein SR, Yoder R, et al. Clinical and biomarker findings of neoadjuvant pembrolizumab and carboplatin plus docetaxel in triple-negative breast cancer: NeoPACT phase 2 clinical trial. JAMA Oncol. 2024 Feb 1;10(2):227–235. doi: 10.1001/jamaoncol.2023.5033
• **Demonstrates the potential to de-escalate chemotherapy and omit anthracycline.**



Contact us

Editorial Department

Senior Editor
Jade Parker
j.parker@oncology-central.com

Business Development and Support

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