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Systemic treatment in triple-negative breast cancer patients — standard and novel approaches

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Abstract

In recent years, after a long standstill in pharmacotherapy of triple-negative breast cancer (TNBC), several new targeted agents have been registered for treatment of patients with this neoplasm (pembrolizumab, olaparib, talazoparib, sacituzumab govitecan, and trastuzumab deruxtecan).

The standard treatment for patients with early TNBC and operable primary tumors up to 2 cm and negative lymph nodes is primary surgery followed by adjuvant chemotherapy and possible radiotherapy. Patients with higher local and regional stages are candidates for primary chemotherapy followed by radical surgery and adjuvant treatment. Adjuvant olaparib prolongs invasive disease-free survival and overall survival of patients with germline *BRCA1*/2 mutation. Adding pembrolizumab to perioperative systemic treatment increases the pathological complete response rate (pCR) and prolongs event-free survival. However, there are no data on effectiveness and safety of applying combined immunotherapy with adjuvant capecitabine for patients without pCR after preoperative treatment or with adjuvant olaparib for germline *BRCA1*/2 mutation carriers.

Chemotherapy is the standard treatment for advanced TNBC. Palliative treatment with PARP inhibitors (olaparib, talazoparib) in patients with germline *BRCA1*/2 mutation prolongs progression-free survival and increases the overall response rate compared with chemotherapy.

In PD-L1-positive patients, adding pembrolizumab to first-line chemotherapy increases the response rate and prolongs survival. The same endpoints are better for TNBC patients treated with sacituzumab govitecan compared with chemotherapy. Trastuzumab deruxtecan is indicated for the treatment of patients with low human epidermal growth factor receptor 2 (HER2) expression and is more efficient than chemotherapy. In Poland, pembrolizumab, talazoparib, and sacituzumab govitecan are reimbursed from public funds.

Keywords: triple negative breast cancer, pembrolizumab, olaparib, talazoparib, sacituzumab govitecan, trastuzumab deruxtecan, germline *BRCA1*/2 mutation, carboplatin

Introduction

Triple-negative breast cancer (TNBC) is characterized by the lack of expression of specific receptors, considered standard targets for drugs used in this malignancy — hormone therapy and anti-HER2 agents. Expression of both hormone receptors on tumor cells is less than 1% of stained nuclei, and there is also no molecular target for anti-HER2 agents, i.e. neither HER2 overexpression confirmed by immunohistochemistry (IHC) as 3+ score nor gene amplification detected in fluorescence *in situ* hybridization (FISH) in the case of equivocal HER2 status (IHC score 2+) [1].

Several cancers with different molecular characteristics are actually classified as triple-negative breast cancer. Over the decades, enormous effort has been

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put into trying to identify differences between these subtypes to determine optimal treatment. An example is the study by Burstein et al. [2], in which 4 subtypes of TNBC were identified based on the expression of selected genes and classified as the following subtypes:

1) luminal androgen receptor (luminal androgen receptor LAR);
2) mesenchymal (MES);
3) basal-like immune-suppressed (BLIS);
4) basal-like immune-activated (BLIA).

The authors of that study showed that the BLIS subtype had the worst prognosis, while patients with the BLIA subtype had the best prognosis in terms of disease-free survival (DFS) and disease-specific survival (DSS). Moreover, potential targets for molecularly targeted drugs in a given subtype were also indicated: 1) LAR — androgen receptor and transmembrane glycoprotein mucin 1 (MUC1); 2) MES — platelet-derived growth factor receptor-a (PDGFRA) and (c-KIT); 3) BLIS — immunosuppressive protein V-set domain containing T cell activation inhibitor 1 (VTCN1), and 4) BLIA — STAT and cytokine-dependent signaling pathway.

The studies conducted over the last few years have led to the registration of new drugs in the treatment of both early and advanced TNBC. Paradoxically, all new therapies in this disease are directed at molecular targets; these include immunotherapy, poly (ADP-ribose) polymerase inhibitors (PARPis), and monoclonal antibodies conjugates with cytotoxic drugs: anti-TROP2 (sacituzumab govitecan) and anti-HER2 (trastuzumab deruxtecan).

Treatment of patients with early TNBC — current standard

According to the current European and American recommendations for the management of patients with early triple-negative breast cancer, in the case of a resectable tumor up to 2 cm in size, without lymph node metastases, primary surgery should be performed, followed by adjuvant treatment [3, 4]. In patients with a primary tumor larger than 2 cm or with positive lymph nodes, treatment should begin with preoperative chemotherapy, even if the tumor is primarily operable.

ABC study gives some guidelines on the choice of adjuvant chemotherapy in the former group of patients with a relatively low risk of recurrence [5]. The non-inferiority study by Blum et al. [5] compared 6 cycles of adjuvant chemotherapy TC (docetaxel with cyclophosphamide) with regimens containing taxoid and anthracycline. It was a pre-planned stepwise futility analysis of 3 clinical trials, which included 4242 patients without HER2 overexpression. In 31% of patients, TNBC was diagnosed, 41% had no lymph node involvement, and grade 3 (G3) histology was present in 51% of patients. The primary endpoint was invasive cancer-free survival (IDFS), and the threshold for determining futility for TC versus anthracycline- and taxoid-based regimens was IDFS relative risk (RR) greater than 1.18. The 4-year IDFS rate was 88.2% for TC chemotherapy and 90.7% for taxoid and anthracycline-containing chemotherapy [hazard ratio (HR) = 1.23; p = 0.04]. It has, therefore, been shown that the TC regimen should not be treated as an equivalent alternative to anthracycline- and taxoid-containing regimens. The number of deaths in both arms was similar (HR = 1.08; p = 0.60). In a subgroup analysis, in node-negative TNBC patients, the difference in the 4-year IDFS rate was 2.5 percentage points in favor of anthracycline-based regimens.

Currently, there are no data confirming that preoperative chemotherapy prolongs life compared to postoperative chemotherapy in patients with operable cancer [6]. The choice of primary systemic treatment, apart from the possible improvement in operability or enabling breast-conserving surgery (BCS), is mainly determined by chance to confirm the effectiveness of chemotherapy and prognosis. Obtaining a microscopically confirmed complete response, i.e. pathological complete response (pCR) with no residual disease (residual cancer burden, RCB0) is associated with good prognosis compared to the lack of pCR/RCB0 [for TNBC, the 5- and 10-year event-free survival (EFS) rates in pCR patients was 91% and 86%, respectively, in RCBI patients — 80% and 75%, respectively, in RCBII patients — 66% and 61%, respectively, and RCBIII patients — 28% and 25%, respectively] [7]. Importantly, in patients with residual disease after preoperative treatment, postoperative chemotherapy with capecitabine can be used, with a documented impact on prolonging overall survival (OS) time, as demonstrated in the phase III CREATE-X study [8]. The benefit of capecitabine in all patients without HER2 overexpression included both DFS (5-year rate 74% *vs.* 68%; HR = 0.70; p = 0.01) and overall survival (5-year rate 89% *vs.* 84%; HR = 0.59; p = 0.01). The effect of capecitabine on improving the prognosis was particularly pronounced in the group of TNBC patients.

Taxoids and anthracyclines are both used in preoperative chemotherapy. Compared to taxoid-free regimens containing an anthracycline, this treatment allows for a higher pCR rate (RR = 1.48; 95% CI 1.04–2.12), as well as longer disease-free survival (DFS; RR = 0.89; 95% CI 0.80–0.99) and local (LRFS) and regional recurrence-free survival (RRFS; RR = 0.74; 95% CI 0.59–0.94) [9]. Due to better tolerability, anthracyclines and taxoids are used sequentially, instead of simultaneously. The sequence of

anthracycline and taxoid administration has no significant impact on the effectiveness of preoperative chemotherapy. There was only a non-statistically significant trend towards greater benefit if taxoid was administered first — HR for OS = 0.80 (95% CI 0.60–1.08), DFS HR = 0.84 (95% CI 0.65 –1.09), and pCR RR = 1.15 (95% CI 0.96–1.38). There were no significant differences in the frequency of taxoid dose reduction (RR = 0.81; 95% CI 0.59–1.11) or the risk of G3/4 neurotoxicity (RR = 0.95; 95% CI 0.55–1.65) and G3/4 neutropenia (RR = 1.25; 95% CI 0.86–1.82). There are no data on the impact of administration sequence on patients' quality of life [10].

Part of anthracycline-containing chemotherapy (usually AC or EC regimen) can be administered in dose-dense manner, i.e. shortening the intervals between infusions to 2 weeks with the supportive use of human granulocyte colony-stimulating factor (G-CSF). Most data on the beneficial impact of this approach on prognosis come from studies assessing the effectiveness of adjuvant chemotherapy. In the case of preoperative chemotherapy, no improvement in prognosis was demonstrated, but a beneficial effect of dose density on increasing the pCR rate was observed in patients with low hormone receptor (HR) expression (OR = 1.36; p = 0.007) [11].

Another form of preoperative chemotherapy escalation is adding a platinum derivate to taxoids. The results of the 2018 meta-analysis by Poggio et al. [12] showed that for all patients with triple-negative breast cancer, this approach allows for an increase in the pCR rate from 37% to 52% (OR = 1.96; p < 0.001). There was also a trend towards improvement in EFS, but without affecting overall survival. The update of the cited work published in 2021, after a longer follow-up, showed a significant benefit from the addition of platinum in the entire group of TNBC patients in terms of prolonged EFS (HR = 0.70; 95% CI 0.56–0.89), but with no statistically significant impact on OS (HR = 0.82; 95% CI 0.64–1.04) [13].

It is worth emphasizing that in a publication from 2018, Poggio et al. [12] showed a clear benefit of adding a platinum derivative in terms of pCR in patients without a germline *BRCA* mutation (pCR rate 57% *vs.* 33%; OR = 2.72; p < 0.001), but this was not observed in patients harboring this mutation (pCR rate 58% *vs.* 54%; OR = 1.17; p = 0.711). A meta-analysis by Poggio et al. included two studies that analyzed the impact of adding a platinum compound on the survival of patients depending on the presence of a germline *BRCA* mutation, i.e. BrighTNess [14] and GeparSixto [15]. The frequency of germline *BRCA* mutation in radically treated TNBC patients was 15–17%. In both studies, subgroup analysis results suggested a benefit in terms of EFS and DFS from adding a platinum compound in patients without mutations. However, the results differed in *BRCA* mutation carriers. The results of the BrighTNess study indicated an EFS benefit from adding a platinum compound, while the GeparSixto study showed no benefit from adding platinum to preoperative chemotherapy in patients with germline mutations – neither in terms of pCR rate nor DFS.

It should be noted that combining platinum with taxoid is undoubtedly associated with greater G3–4 hematological toxicity (for neutropenia: OR = = 3.19; 95% CI 1.55–6.54, for thrombocytopenia: OR = 8.32; 95% CI 2.88–23.98 and for anemia: OR = = 15.01; 95% CI 4.86–46.30) [12].

The discussion about the appropriateness of adding carboplatin to preoperative chemotherapy returned at the 2022 San Antonio Breast Cancer Symposium (SABCS). Gupta et al. [16] presented the results of a single-center, randomized phase III study conducted in India, which included 720 TNBC patients. Stratification did not include age but only menopausal status and cancer stage. In the experimental arm, in addition to paclitaxel and the AC/EC regimen, patients also received carboplatin [area under the curve (AUC) 2] added to paclitaxel. Almost 70% of patients were under 50 years of age. The primary endpoint was DFS, and the secondary endpoint — among others — OS. The study was negative for the primary endpoint with the 5-year DFS rates of 70.6% and 64.5%, respectively for patients treated with and without carboplatin (HR = 0.79; 95% CI 0.61–1.02; p = 0.073). Nevertheless, a subgroup analysis was performed, whose results suggested a benefit from adding carboplatin in patients under 50 years of age, both in terms of DFS and OS — 74.5% *vs.* 62.3% (interaction test p = 0.003) and 76.8% *vs.* 65.7% (interaction test p = 0.004). The study did not take *BRCA* gene status into account.

Based on the above data, it can be concluded that adding carboplatin to taxoid administered preoperatively may be justified in patients who accept more severe treatment toxicity, are younger, and have no germline *BRCA* mutation; the benefit of such escalation in patients with the mutation is not confirmed.

After surgery, depending on indications, patients are referred for adjuvant radiotherapy, and, as already mentioned, in the absence of pCR, adjuvant treatment with capecitabine should be considered. It has also been shown that the use of platinum derivatives instead of capecitabine at this stage of treatment is not associated with greater effectiveness but with more severe toxicity [17].

A schematic summary of the standard management in patients with early TNBC using perioperative chemotherapy is presented in Figure 1.

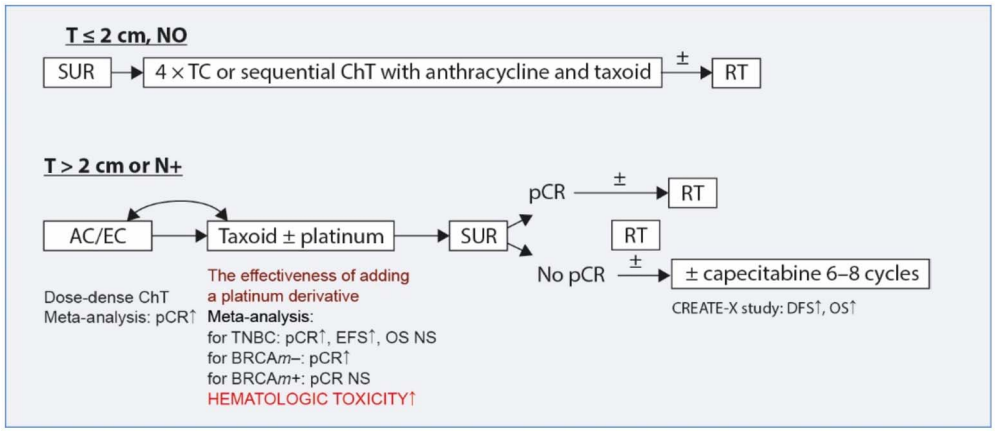

Figure 1. Schematic summary of standard treatment in patients with early triple-negative breast cancer (TNBC) using perioperative chemotherapy; ↑ — statistically significantly greater benefit from a given therapy; AC/EC — chemotherapy according to the doxorubicin and cyclophosphamide or epirubicin and cyclophosphamide regimen; BRCAm– — patients without germline *BRCA* mutation; BRCAm+ — patients with germline *BRCA* mutation; SUR — radical surgical procedure; DFS — disease-free survival; EFS — event-free survival; N — involvement of regional lymph nodes; NS — not significant; OS — overall survival; pCR — pathological complete response; RT — adjuvant radiotherapy; T — primary tumor; TC — chemotherapy according to the docetaxel and cyclophosphamide regimen

Treatment of patients with early TNBC — what is new?

Novel options for perioperative treatment in TNBC patients include immunotherapy added to preoperative chemotherapy and continued after surgery, as well as adjuvant treatment with a PARPi in patients with a germline *BRCA* mutation.

The scope of new drug studies and registrations (data as of June 2023) in early TNBC is presented in Figure 2.

Immunotherapy

So far, the only immune checkpoint inhibitor (ICI) registered for perioperative treatment of TNBC is pembrolizumab. Registration was based on the results of the phase III KEYNOTE-522 study [18]. It included TNBC patients with cT1c breast tumor and lymph node involvement (cN1–N2) or with cT2–T4 tumor regardless of lymph node status (cN0–N2). Patients were assigned to two arms in a 2:1 ratio and received chemotherapy with pembrolizumab (n = 784) or chemotherapy with placebo (n = 390). Sequential chemotherapy was used: first 12 weeks of treatment with carboplatin and paclitaxel, then four cycles of AC or EC every 3 weeks. After surgery, patients could undergo adjuvant radiotherapy depending on indications and continued pembrolizumab or placebo as adjuvant treatment, for a total of 17 cycles. The co-primary endpoints were the pCR rate (ypT0/Tis ypN0) and EFS in the population included in the treatment (time to progression preventing radical surgical treatment, relapse, subsequent malignancy, or death). The germline *BRCA* mutation status was not determined in the study participants. Notably, carboplatin was mandatory in all patients despite the previously mentioned controversies. Additionally, the study did not allow the use of capecitabine as an adjuvant treatment in patients without pCR.

The first interim analysis was performed after enrollment of 602 patients, and the median follow-up was 15 months. The pCR rate was significantly higher in the pembrolizumab-treated group (65% *vs.* 51%, $p < 0.001$). Additionally, there was a lower risk of breast cancer-related events in patients receiving immunotherapy (EFS: HR = 0.63; 95% CI 0.43–0.93). After 39 months of follow-up, there was a significant difference in the 3-year EFS rate in favor of immunotherapy (85% *vs.* 77%; HR = 0.63; $p < 0.001$) [19]. In an analysis with a higher number of patients, there was still a difference in the pCR rate in favor of immunotherapy, but with a smaller absolute difference (63% *vs.* 56%). Subgroup analysis indicated a benefit from immunotherapy in terms of EFS, regardless of the programmed death ligand 1 (PD-L1) expression.

Most adverse events were reported during the preoperative treatment. What is noteworthy is the frequency of G3 and higher adverse events (AEs), which was almost 80% in patients in both groups. This probably resulted from toxicity of multidrug chemotherapy.

The most common immunotherapy-related adverse events (irAEs) of at least grade 3 severity were skin complications, infusion hypersensitivity, and adrenal insufficiency. There were three deaths in the experimental arm (due to pulmonary embolism, sepsis, and pneumonia). In the group of patients receiving chemotherapy with placebo, death in 1 patient was reported due to therapy complications [18].

Based on the KEYNOTE-522 study, pembrolizumab was registered in combination with

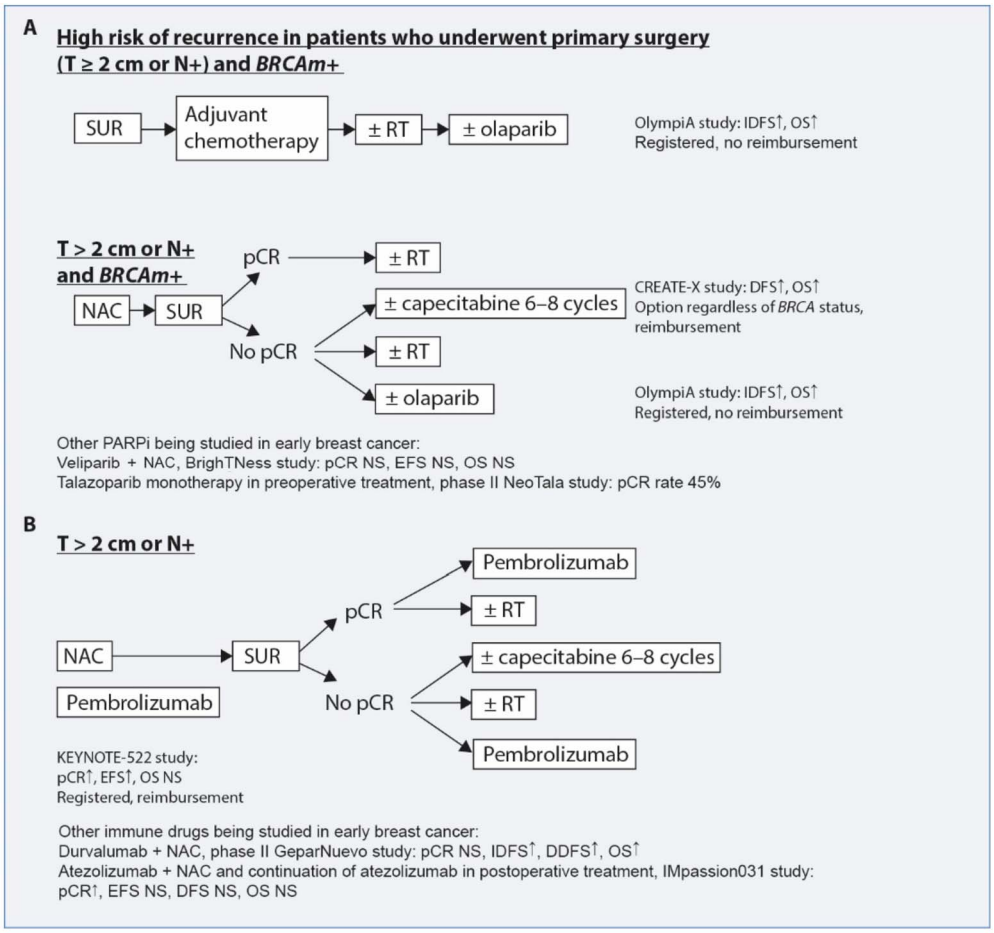

Figure 2. New trials and drug registrations in early triple-negative breast cancer (TNBC) (as of June 2023); **A.** PARP inhibitors; **B.** Immunotherapy; ↑ — statistically significantly greater benefit from a given therapy; BRCAm+ — patients with germline *BRCA* mutation; SUR — radical surgical procedure; DFS — disease-free survival; EFS — event-free survival; IDFS — invasive disease-free survival; N+ — involvement of regional lymph nodes; NAC — neoadjuvant/preoperative chemotherapy; NS — not significant; OS — overall survival; PARPi — PARP inhibitor; pCR — pathological complete response; T — primary tumor

chemotherapy as a neoadjuvant treatment; then it can be continued as monotherapy in adjuvant treatment after surgery in patients with locally advanced or early TNBC at high risk of recurrence. In Poland, from July 1, 2023, the drug is reimbursed from public funds for this indication.

Pembrolizumab was not the only immune checkpoint inhibitor evaluated in the perioperative treatment setting. The aim of the double-blind, randomized phase III study IMpassion031 was to evaluate the effectiveness of atezolizumab added to preoperative chemotherapy [20]. In that study, nab-paclitaxel (12 administrations) and a dose-dense AC regimen were used sequentially. Immunotherapy was continued postoperatively as an adjuvant treatment (up to a year in total). The study included 333 patients with tumors larger than 2 cm, regardless of lymph node status. The co-primary endpoints were the pCR rate in all patients included in the study and in patients with PD-L1 expressing tumor-infiltrating immune cells (IC) $\geq$ 1%. It was shown that the addition of atezolizumab to preoperative chemotherapy resulted in a significantly higher pCR rate (58% *vs.* 41%, p = 0.0044, with a significance threshold of 0.0184) in the entire population included in the study. Interestingly, the difference in pCR rate in patients with PD-L1 expression did not reach statistical significance (69% *vs.* 49%, p = 0.021, with a significance threshold of 0.0184). After approximately 39 months of follow-up, the results regarding EFS, DFS, and OS were presented, and no significant differences were found [21].

It is worth noting the phase II GeparNuevo study [22], which aimed at assessing the value of adding durvalumab to preoperative chemotherapy (12 administrations of nab-paclitaxel, then EC every 2 weeks, n = 174).

Immunotherapy was not continued after surgery, but postoperative local and systemic treatment was allowed according to the local standards. It was

a double-blind, randomized study. The primary endpoint was the pCR rate, and the secondary endpoints included IDFS, distant metastasis-free survival (DDFS), and OS. There was no significant difference in the pCR rate, but there was a significant difference in favor of durvalumab in terms of the 3-year IDFS rate (86% *vs.* 77.2%; HR = 0.48; p = 0.036), DDFS rate (92% *vs.* 78.4%; HR = 0.31; p = 0.005), and OS rate (95% *vs.* 84%; HR = 0.24; p = 0.006). It should be emphasized that the study was not designed to demonstrate a difference in survival and the obtained results are exploratory. Some patients received postoperative chemotherapy. Nevertheless, the observed benefits, which require confirmation in a properly planned phase III trial, raise hope that short-term preoperative immunotherapy may prove to be a valuable and sufficient option in TNBC patients.

There are some controversies about use of the perioperative treatment regimen in clinical practice proposed in the KEYNOTE-522 study. The use of carboplatin in all patients is questionable, especially considering the high toxicity of preoperative chemotherapy observed in the study. The actual value of continuing immunotherapy after surgery, especially in pCR patients, also requires confirmation in further studies. Finally, the most important doubt is related to the non-use of adjuvant chemotherapy with capecitabine in patients who did not achieve the pCR. It is also unknown whether postoperative immunotherapy should be replaced with olaparib in patients with germline *BRCA* mutations.

Perhaps information about the value of capecitabine in patients undergoing immunotherapy will be provided by the results of the ongoing NSABPB-59/GeparDouze study [23], which is assessing the value of adding atezolizumab in perioperative treatment. Preoperative chemotherapy that was used in the NSABPB-59/GeparDouze study was the same as in the KEYNOTE-522 study, but after enrolling over 600 patients, a protocol amendment was introduced allowing for administration of adjuvant chemotherapy with capecitabine if the pCR was not achieved.

PARP inhibitors

Considering breast cancer, currently (as of June 2023), PARP inhibitors are only applicable in patients harboring germline *BRCA1*/2mutation without HER2 overexpression. As mentioned, among TNBC patients there are several percent carriers of such mutations.

Olaparib was registered for perioperative treatment based on the results of the phase III OlympiA study [24]. It aimed to evaluate the value of adjuvant treatment with olaparib in patients with early breast cancer, at high risk of recurrence, without HER2 overexpression, and with a pathogenic or probably pathogenic germline *BRCA1*/2 mutation. The study included 1836 patients who were assigned to two arms, with olaparib for a year (300 mg twice daily) or placebo. During this therapy, it was possible to use adjuvant hormone therapy and adjuvant bisphosphonate treatment. Concomitant adjuvant chemotherapy was not allowed. In patients after primary surgery, postoperative chemotherapy was required (at least 6 cycles of anthracyclines or taxoids, or drugs from both groups, platinum was allowed), and it had to be completed before olaparib or placebo therapy commencement. Adjuvant chemotherapy was not allowed in patients who received preoperative chemotherapy. In addition, it was necessary to complete local treatment, and radiotherapy had to be completed 2 to 12 weeks before study treatment initiation.

The primary endpoint of the OlympiA study was IDFS, and secondary endpoints included DDFS and OS. TNBC was diagnosed in 82% of patients included in the study. The inclusion criteria for TNBC patients were as follows: primary tumor size of at least 2 cm or axillary lymph node involvement and adjuvant chemotherapy or neoadjuvant therapy but without achieving the pCR. Among the patients included in the study, 72% were carriers of a germline *BRCA1* mutation, half underwent preoperative chemotherapy, 93% received anthracyclines and taxoids, platinum compounds were used in 26%, and 62% of patients were premenopausal.

Adjuvant treatment with olaparib increased the 3-year invasive disease-free survival rate (86% *vs.* 77%; HR = 0.58; p < 0.001). After a longer follow-up, not only a sustained beneficial effect was demonstrated in terms of 4-year IDFS (83% *vs.* 75.4%; HR = 0.63), but also an improvement in the 4-year OS rate (90% *vs.* 86, 4%; HR = 0.68; p = 0.009) [25].

The most important controversy regarding adjuvant treatment with olaparib is related to the impossibility of postoperative use of capecitabine in patients who did not achieve the pCR after preoperative chemotherapy. This problem is particularly important in TNBC patients, for whom the presence of residual disease is associated with a significant and considerable worsening of the prognosis, and currently, the only options with a proven beneficial effect on overall survival are postoperative capecitabine-based chemotherapy or treatment with olaparib. Capecitabine in this indication is reimbursed in Poland, and currently (June 2023) olaparib is not reimbursed from public funds in this indication. Of course, the impact on prognosis improvement of both treatments cannot be directly compared, and it is not known which option is more effective. In the OlympiA study, half of the patients received preoperative chemotherapy, and most of them were diagnosed with TNBC. The absolute benefit of olaparib in this subgroup in terms of the 4-year overall survival

rate was 7.57 percentage points (86% *vs.* 78.5%) and in terms of the 4-year invasive disease-free survival rate — 9.47 percentage points (77% *vs.* 67.6%). In the CREATE-X study, one-third of patients had TNBC, but their *BRCA* mutation status was unknown [8]. In that subgroup, the absolute benefit in terms of the 5-year overall survival rate was 9 percentage points (79% *vs.* 70%), and in terms of the 5-year disease-free survival rate 14 percentage points (70% *vs.* 56%). Since both methods improve the prognosis but cannot be combined due to untested toxicity and lack of data on additive effectiveness, the question arises whether it would be beneficial to use both therapies sequentially in patients with a high recurrence risk, starting from capecitabine. Obviously, the use of olaparib after chemotherapy with capecitabine is associated with a long time from surgery to PARPi therapy initiation. On the other hand, the effectiveness of olaparib was also demonstrated in the subgroup of patients receiving adjuvant chemotherapy in the OlympiA trial (4-year IDFS rate: HR = 0.618; 95% CI 0.425–0.888) [25]. Of course, the use of this type of sequence is also based on the assumption of the additive effect of both drugs, but such an assumption seems to have a rational basis.

As mentioned earlier, additional uncertainty is related to the possible combination of immunotherapy and PARP inhibitors in perioperative treatment. In the cited pivotal studies of pembrolizumab and olaparib, there are no data allowing for assessment of effectiveness and safety of combining these methods.

So far, only olaparib has been registered for treatment of patients with early breast cancer, but other drugs from this group have also been evaluated in perioperative treatment. The phase III BrighTNess study aimed to assess the value of adding carboplatin together with veliparib or alone to paclitaxel used in sequential preoperative chemotherapy in TNBC patients [26]. Treatment with veliparib was not associated with an additional benefit, either in the overall group or in *BRCA* mutation carriers. In turn, the single-arm phase II NEOTALA study assessed the effectiveness and safety of talazoparib in preoperative treatment in 48 patients with a germline *BRCA1*/2 mutation [27]. All patients were diagnosed with TNBC, the pCR was achieved in 45% of patients, and the toxicity of PARP inhibitor monotherapy was moderate.

Treatment of patients with metastatic/advanced TNBC

Standard chemotherapy

Until recently, systemic treatment of advanced TNBC was limited only to standard chemotherapy. The only controversial issues concerned presumably greater activity of platinum derivatives compared to other cytotoxic drugs. The study that largely verified this hypothesis was TNT [28]. The aim of this randomized phase III study was, among others, a comparison of effectiveness of carboplatin and docetaxel in palliative treatment in molecularly unselected patients with advanced TNBC. The study included 376 patients previously treated with an anthracycline. The primary endpoint was the objective response rate (ORR). Molecular testing was performed to identify biomarkers associated with the effectiveness of individual drugs, including, among others, the presence of germline and somatic *BRCA1*/2 mutations, methylation status of *BRCA1* in tumor cells, *BRCA1* mRNA expression, and mutational signatures indicating a DNA damage repair (DDR) deficiency (DDR-d) by homologous recombination. Germline *BRCA1* mutations were found in 8.2% of patients, *BRCA2* in 3% of patients, and in 16% of study participants, the test was not performed. Somatic *BRCA1*/2 mutations were found in 4% of breast tumors examined.

In unselected TNBC patients no significant differences were found in the effectiveness of carboplatin and docetaxel, neither in the objective response rate (31.4% *vs.* 34%, p = 0.66), nor in progression-free survival (PFS) and overall survival. Similarly, there was no difference in the response rate in patients without a germline mutation (28% *vs.* 34.5%, p = 0.30). However, in carriers of a germline mutation, carboplatin turned out to be significantly more effective than docetaxel in terms of objective responses (68% *vs.* 33%, p = 0.03) and PFS (median 6.8 months *vs.* 4.4 months, p = 0.002). There was no difference in OS.

The results of the TNT study indicate that advanced TNBC has a poor prognosis with median PFS for first-line chemotherapy of approximately 4 months and median overall survival of approximately 1 year.

New drugs

All newly registered drugs in palliative care of TNBC patients are targeted at molecular targets, even though this subtype of breast cancer was originally distinguished by the negation of traditional targets for anticancer drugs, i.e. hormone receptors and HER2 overexpression. Progress in pharmacotherapy was made possible by finding new targets or redefining old drug targets.

For patients with a germline *BRCA1*/2 mutation, constituting approximately 12% of the TNBC population, two PARP inhibitors have been registered for use in monotherapy, of which talazoparib is reimbursed from public funds in Poland (as of June 2023).

Another drug registered and reimbursed in our country is sacituzumab govitecan, a cytotoxic drug conjugate with an antibody targeting the TROP-2 membrane receptor. This receptor is expressed in cancer cells in almost all patients, which means there is no need to determine it when planning treatment.

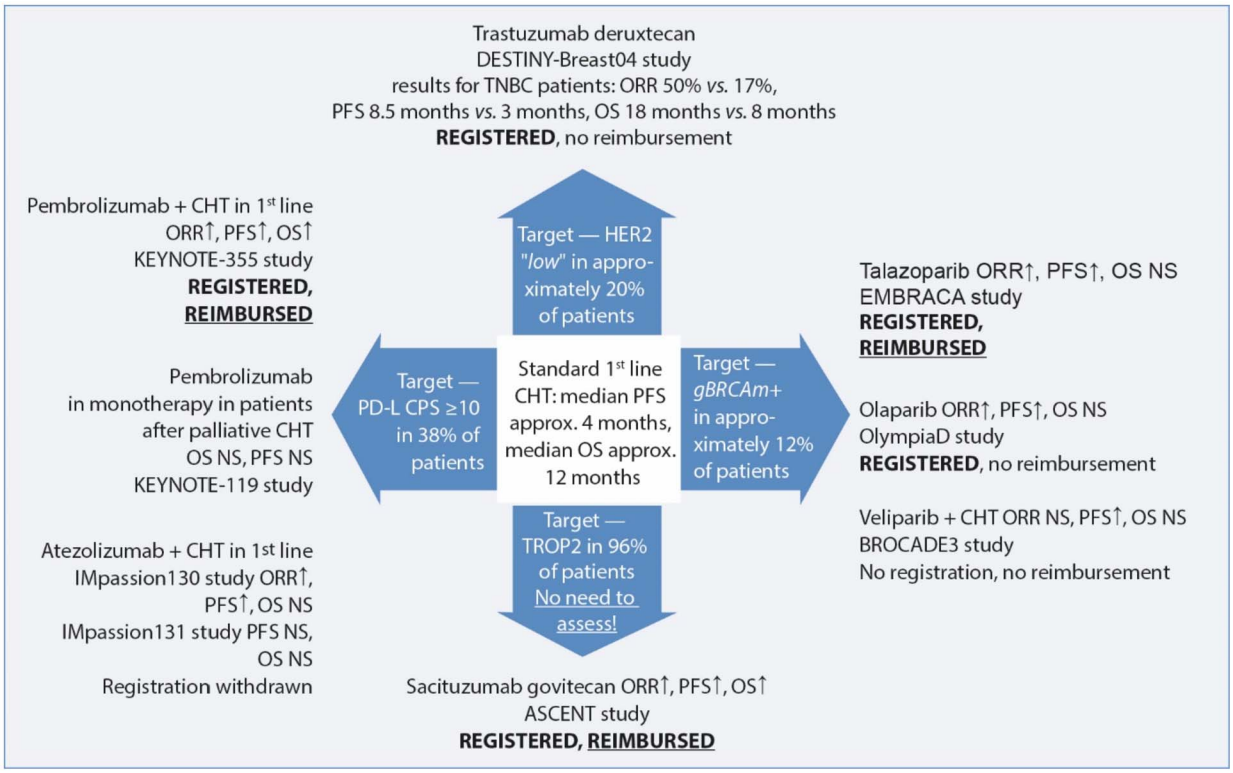

Figure 3. New options for targeted treatment in patients with advanced triple-negative breast cancer (TNBC) (as of June 2023); ↑ — statistically significant greater benefit from a given therapy; CHT – chemotherapy; gBRCAm+ — patients with germline *BRCA* mutation; HER2 "low" — low HER2 expression (immunohistochemical reaction 1+ or 2+ and no *HER2* amplification); NS — not significant; ORR — objective response rate; OS — overall survival; PFS — progression-free survival

Pembrolizumab in combination with first-line chemotherapy is also registered and reimbursed from July 1, 2023, but only in patients with confirmed PD-L1 expression and a combined positive score (CPS) of at least 10.

The latest registration concerns trastuzumab deruxtecan in patients with low HER2 expression. The DESTINY-Breast04 study included very few patients with tumors without HR expression. However, even in 20% of TNBC patients, low HER2 expression can be expected [29]. New options for targeted treatment in patients with advanced TNBC (as of June 2023) are summarized in Figure 3.

PARP inhibitors

In the treatment of patients with metastatic/advanced breast cancer with a germline *BRCA1/2* mutation and without HER2 overexpression, talazoparib and olaparib have been registered so far, of which talazoparib is reimbursed in Poland (as of June 2023).

A pivotal study with talazoparib was the randomized phase III EMBRACA study, [30] aimed at comparing the effectiveness of talazoparib (1 mg daily, orally) and the investigator's choice chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). The primary endpoint of the study was PFS, and secondary endpoints included OS and ORR. The study included 431 patients who could have previously received no more than three lines of palliative chemotherapy and had previously been treated with a taxoid and anthracycline unless they had contraindications to such therapy. Previous treatment with a platinum derivative was allowed as long as no progression was observed during therapy and up to 8 weeks after its completion. Previous hormone therapy was possible without restrictions, and patients with stable brain metastases could also participate in the study. Triple-negative breast cancer was diagnosed in 44% of patients participating in the study, germline *BRCA1*mutation was present in 45% of patients (the remaining had the *BRCA2* mutation), 18% of patients had previously received platinum-based chemotherapy, and 75% of patients had received at most first-line palliative chemotherapy.

Talazoparib turned out to be significantly more effective than chemotherapy in terms of PFS (8.6 months *vs.* 5.6 months; HR = 0.54; $p < 0.001$) and the objective response rate (63% *vs.* 27%; OR = 5.0; $p < 0.001$). After a longer follow-up (median 45 months), there was no difference in OS (median 19.3 months *vs.* 19.5 months; HR = 0.85; $p = 0.17$), in the subgroup analysis, these results were

consistent for patients with TNBC and hormone-sensitive BC [31]. Hematological toxicity of G3–4 severity (mainly anemia) occurred more frequently in patients taking talazoparib (55% *vs.* 38%). Non-hematological toxicity of G3–4 severity occurred with a similar frequency, i.e. 32% and 38%, respectively. Talazoparib treatment was discontinued due to toxicity in 6% of patients [30].

OlympiAD, a pivotal study of olaparib, had a similar design to the EMBRACA study [32]. It included 302 patients with advanced cancer with a germline *BRCA1*/2 mutation and without HER2 overexpression, who have so far received up to two lines of palliative chemotherapy. Patient characteristics were similar: 49% of patients had TNBC, germline *BRCA1* mutation was present in 56% of patients, 28% had previously received platinum-based chemotherapy, and 71% of patients had received at most one line of palliative chemotherapy.

It was shown that olaparib prolonged PFS compared to standard chemotherapy (median 7 months *vs.* 4.2 months; HR = 0.58; p < 0.001) and increased the objective response rate (60% *vs.* 29%). In the OlympiAD study, there was also no significant difference in OS in patients receiving a PARP inhibitor compared to patients receiving standard chemotherapy (median 19.3 months *vs.* 17 months, HR = 0.90; p = 0.513) [33]. In the subgroup analysis, there was no effect on OS in both patients with triple-negative and hormone-sensitive breast cancer. Perhaps a greater benefit from olaparib administration could have occurred in patients who had not previously undergone palliative chemotherapy at all (HR = 0.51; 95% CI 0.29–0.90).

The toxicity of olaparib reported in the OlympiAD study was similar to that caused by talazoparib. Olaparib treatment was discontinued due to toxicity in 5% of patients.

In the patient population defined above, veliparib or placebo in combination with carboplatin and paclitaxel were also evaluated in the phase III BROCADE3 trial [34]. If chemotherapy was discontinued due to toxicity, patients could continue treatment with a PARP inhibitor until progression. It was shown that veliparib added to chemotherapy prolonged progression-free survival (median 14.5 months *vs.* 12.6 months; HR = 0.71; p = 0.0016). However, despite its relatively low toxicity, the preparation has not yet been registered due to its limited effectiveness compared to PARP inhibitors used in monotherapy.

Sacituzumab govitecan

Sacituzumab govitecan was registered for the treatment of TNBC patients based on the results of the phase III randomized ASCENT study [35]. This study aimed to compare the effectiveness of an anti-TROP-2 antibody conjugate with the active metabolite of irinotecan SN38 (10 mg/kg body weight IV on days 1 and 8 every 21 days) to the investigator's choice chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine). The study included 468 patients with advanced TNBC after previous treatment with taxane and at least two lines of palliative chemotherapy. The primary endpoint was PFS (patients with stable brain metastases were excluded from the main analysis), and secondary endpoints included OS, response rate, and safety. A germline *BRCA1*/2 mutation was found in 7% of patients included in the study. The median number of previous lines of systemic treatment was 3; 71% of patients had received two to three lines of chemotherapy, 82% of patients had previously received anthracycline, 7% a PARP inhibitor, and 27% immunotherapy.

The new drug turned out to be significantly more effective compared to standard chemotherapy, both in terms of PFS (median 5.6 months *vs.* 1.7 months; HR = 0.41; p < 0.001) and OS (median 12 months *vs.* 6.7 months; HR = 0.48; p < 0.001), and the objective response rate (35% *vs.* 5%). In the subgroup of approximately 60 patients with stable brain metastases, median PFS (2.8 months *vs.* 1.6 months), OS (6 months *vs.* 7.5 months), and the objective response rate (3% *vs.* 0%) suggest that sacituzumab govitecan may have similar activity to chemotherapy in these patients [36].

Treatment-related toxicity of at least grade 3 severity was higher in patients in the experimental arm, and more hematological complications were recorded (neutropenia 51% *vs.* 33%, febrile neutropenia 6% *vs.* 2%). Diarrhea was also a problem and occurred in 10% of patients [35]. It should be remembered that, as in the case of irinotecan, atropine is used to treat this side effect. G3 pneumonia occurred in a patient receiving sacituzumab. There were three deaths related to adverse events in each arm, and none were associated with the sacituzumab govitecan treatment.

Irinotecan derivative SN-38, with which the anti-TROP-2 antibody is conjugated, is metabolized by uridine diphosphate glucuronosyl transferase (UGT1A1). In some patients (approximately 20% of the Black population, 10% of the white population, and 2% of the East Asian population), there is a genetically determined reduced activity of this enzyme. These people may experience severe side effects, and it is advisable to modify the dose of the drug. Similarly, severe toxicity may occur in patients taking concurrently UGT1A1 inhibitors (e.g. propofol, ketoconazole, EGFR kinase inhibitors). On the other hand, in patients taking concomitantly UGT1A1 inducers (e.g. carbamazepine, phenytoin, rifampicin, ritonavir, tipranavir), exposure to the active metabolite may be much lower than expected, which may result in lower efficacy [37].

An exploratory analysis was performed to assess the effectiveness of the conjugate in subgroups of patients with high, medium, and low TROP-2 expression and in patients without and with a germline *BRCA1*/2 mutation. TROP-2 expression in cancer cell membranes was assessed immunohistochemically in 290 tumors (H-score: range 0–300). The receptor was not detected in only 4% of patients, low expression occurred in 16% of patients (H-score: 0–99), moderate expression in 26% (H-score: 100–200), and high expression in 54% of patients (H-score: 201–300). The *BRCA* gene status was assessed in 292 patients, and germline mutations were detected in 12%. Sacituzumab was shown to be active in all groups evaluated [38].

In February 2023, the US Food and Drug Administration (FDA) registered sacituzumab govitecan also for patients with unresectable or metastatic hormone-sensitive breast cancer based on the results of the TROPICS02 study [39].

Immunotherapy

Pembrolizumab was registered in patients with advanced TNBC based on the results of the double-blind, randomized phase III KEYNOTE-355 study [40]. It aimed at evaluating the value of pembrolizumab added to first-line palliative chemotherapy with nab-paclitaxel (32%), paclitaxel (13%), or KG regimen (55%). The study included 847 patients with advanced TNBC who had not previously received palliative chemotherapy. The study could include patients with a relapse that occurred at least 6 months after completion of radical treatment, and the presence of stable brain metastases was also allowed. If taxoid, gemcitabine, or a platinum derivative were used in the perioperative chemotherapy regimen, recurrence had to occur at least 1 year after treatment completion.

The primary endpoints were PFS and OS assessed hierarchically in patients with PD-L1 expression $\geq$ 10, in patients with PD-L1 expression $\geq$ 1, and finally in all subjects included in the study. PD-L1 expression was expressed as the combined positive score (CPS), i.e. the ratio of the number of cells with PD-L1 expression (tumor cells, lymphocytes, and macrophages infiltrating the tumor) to the number of all tumor cells (regardless of PD-L1 expression) multiplied by 100. In 25% of patients, PD-L1 expression was less than 1, and 38% had PD-L1 expression greater than or equal to 10.

In patients with CPS $\geq$ 10 receiving pembrolizumab, a significant prolongation of PFS (median 9.7 months *vs.* 5.6 months; HR = 0.65; p = 0.0012; threshold of statistical significance equal to 0.00411) and OS (median 23 months *vs.* 16.1 months; HR = 0.73; p = 0.0185; threshold of statistical significance equal to 0.0227) were shown. No statistically significant difference in PFS and OS was observed in patients with lower PD-L1 expression or in all patients (formally, the research hypotheses were not evaluated in the latter group). The objective response rate was 53% *vs.* 41%, 45% *vs.* 39%, and 41% *vs.* 37%, respectively.

Treatment-related adverse events of at least grade 3 severity occurred in approximately 70% of patients in both arms. Immune-related AEs of this severity were observed in 5% of patients treated with pembrolizumab, mainly skin, lungs, thyroid gland, and intestine toxicity. In patients receiving immunotherapy, two deaths were reported due to treatment complications: one due to renal failure and one due to pneumonia.

Pembrolizumab was registered in combination with first-line chemotherapy in patients with advanced TNBC with PD-L1 expression in the tumor tissue and a CPS $\geq$ 10. The drug is reimbursed from public funds in Poland for this indication from July 1, 2023.

In addition to the KEYNOTE-355 study, other studies have also assessed the value of immunotherapy.

The phase III randomized KEYNOTE-119 study compared the effectiveness of pembrolizumab monotherapy with chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in the second or third line of palliative treatment of TNBC patients [41]. The primary endpoint was OS assessed in patients with PD-L1 expression and a CPS $\geq$ 10, in patients with a CPS $\geq$ 1, and in all patients. Pembrolizumab was not more effective than chemotherapy.

Another immunological drug with conflicting results is atezolizumab. The phase III IMpassion130 trial assessed the value of this antibody added to nab-paclitaxel (nab-P) in the first-line treatment [42]. The primary endpoints were PFS in all patients and patients with PD-L1 expression, and OS assessed in all patients and, if a significant difference was found, also in patients with PD-L1 expression. PD-L1 expression was assessed in tumor-infiltrating immune cells as a percentage of the tumor area involved (expression < 1% was considered negative and expression $\geq$ 1% was positive).

There was a benefit from adding atezolizumab to chemotherapy in terms of PFS in all patients (median 7.2 months *vs.* 5.5 months; HR = 0.80; p = 0.002) and in patients with PD-L1 expression (7.5 months *vs.* 5 months; HR = 0.62; p < 0.001). Atezolizumab did not prolong OS in all patients (median 21 months *vs.* 18.7 months; HR = 0.87; p = 0.077). In an exploratory analysis (formally, no hypothesis testing was planned in this group), a difference was found in OS in patients with PD-L1 expression (median 25.4 months *vs.* 18 months; HR = 0.67; 95% CI 0.53–0.86) [43].

Another randomized, phase III IMpassion131 study assessed the value of adding atezolizumab to

first-line chemotherapy with paclitaxel [44]. Taking into account the results of IMpassion 130, the primary endpoint was PFS evaluated hierarchically in patients with PD-L1 expression and then in all patients. The secondary endpoint was OS. There was no effect of atezolizumab on either PFS or OS. For this reason, despite the previous registration of atezolizumab for palliative treatment in TNBC patients, it was ultimately withdrawn.

Taking into account the results of these studies, the question of the value of immunotherapy in palliative treatment seems unresolved definitely. There are no data demonstrating the value of immunotherapy in patients previously undergoing palliative chemotherapy. In contrast, adding an immunological drug to first-line chemotherapy provides conflicting results. Such therapy may be beneficial in selected patients, but there are no good predictive factors. Currently, the qualification criterion for pembrolizumab treatment is high PD-L1 expression. On the other hand, there is no consistency in the method of this factor assessment.

The biomarker analysis conducted in patients included in the IMpassion130 study showed that the benefit of adding atezolizumab to nab-paclitaxel may be seen in patients with tumor-infiltrating lymphocytes (TILs) CD8+ in the tumor and stroma and PD-L1 expression [45]. Germline *BRCA1*/2 mutations were detected in 14.5% of patients participating in the study, and their presence did not determine the PFS benefit of adding atezolizumab to nab-paclitaxel in patients with PD-L1 expression.

In a representative sample of patients from the IMpassion131 study (471 out of 651), molecular subtypes of tumors were assessed as part of the exploratory analysis according to the Burstein classification mentioned above [46]. The BLIA subtype was identified in 30% of the tumors examined, BLIS in 41%, LAR in 24%, and MES in 5%. The results of the analysis indicated the benefit of adding atezolizumab to paclitaxel in terms of PFS in patients with the BLIA subtype (HR = 0.66; 95% CI 0.45–0.97). Interestingly, in the KEYNOTE-119 study, biomarker assessment also indicated that high lymphocyte infiltration in the tumor was associated with greater effectiveness of pembrolizumab, but not chemotherapy [47]. All these observations suggest greater effectiveness of immunotherapy in patients with a rich infiltration of immune cells in the tumor microenvironment. This gives hope that finding a better way to select patients for immunotherapy will help to use better drugs from this group.

Trastuzumab deruxtecan

The drug is used in breast cancer patients if the HER2 receptor is present in cancer cell membranes. A situation in which HER2 expression is demonstrated but the criteria for overexpression are not met is called low HER2 expression (HER2-low). This applies to patients with an immunohistochemical reaction of 1+ or 2+ and no gene amplification [29].

The randomized phase III Destiny-Breast04 trial included 557 patients with advanced breast cancer with low HER2 expression and any expression of hormone receptors [48]. These were patients who had previously received one or two lines of chemotherapy (palliative or perioperative if the time to recurrence was shorter than 6 months) and at least one line of hormone therapy if the presence of hormone receptors was detected in the tumor. Stable brain metastases were allowed. Patients were allocated to two arms in a 2:1 ratio and received trastuzumab deruxtecan (5.4 mg/kg body weight every 3 weeks) or the investigator's choice chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel). The primary endpoint was PFS in patients with hormone receptor expression, and the secondary endpoints included PFS in all patients, OS in patients with hormone receptor expression and in the entire population. The vast majority of patients included in the study (89%) expressed hormone receptors. A significant prolongation of PFS (median 10 months *vs.* 5.4 months; HR = 0.51; $p < 0.001$) and OS (median 24 months *vs.* 17.5 months; HR = 0.64; $p = 0.003$) was demonstrated in this group after use of trastuzumab deruxtecan as compared to standard chemotherapy. The benefit of the experimental therapy was also observed in all patients. The study included only 58 patients without the expression of hormone receptors, i.e. with TNBC. However, as compared to standard chemotherapy, median PFS in this group was 8.5 months *vs.* 3 months (HR = 0.46; 95% CI; 0.24–0.89), and OS 18 months *vs.* 8 months (HR = 0.48; 95% CI 0.24–0.95).

A higher objective response rate was observed in patients receiving trastuzumab deruxtecan compared with chemotherapy. This concerned the entire population included in the study, patients with the expression of hormone receptors and patients without their expression (52% *vs.* 16%, 53% *vs.* 16%, and 50% *vs.* 17%, respectively).

Adverse events of at least grade 3 severity occurred in a slightly lower percentage of patients receiving the conjugate (53% *vs.* 67%). In 12% of patients treated with trastuzumab deruxtecan interstitial pneumonitis occurred, and 3 patients died because of it. Left ventricular dysfunction was observed in 4.6% of patients receiving anti-HER2 drug, and G2/G3 reduced ejection fraction in 12% and 1.5% of patients, respectively.

The results of the Destiny-Breast04 study became the basis for the registration of trastuzumab deruxtecan in early 2023 as monotherapy in palliative treatment of breast cancer patients with low HER2 expres-

sion who have previously received palliative or adjuvant chemotherapy if relapse occurred during its duration or within 6 months of its completion.

Targets for molecularly targeted drugs in patients with triple-negative cancer

BRCA mutations

PARP inhibitors are approved for the treatment of breast cancer patients with pathogenic or likely pathogenic germline *BRCA1*/2 mutations. Such mutations occur in approximately 5% of unselected breast cancer patients and in 15–17% of TNBC patients [28]. The risk of their occurrence is greater in patients with a family history of breast cancer, younger than 50 years of age, with synchronous or metachronous disease of the contralateral breast or ovarian cancer, and in ethnic groups with a high incidence of the so-called founder mutations [49]. Patients with germline *BRCA1* mutations are predisposed to TNBC, and the median age of onset is approximately 41 years. Hormone receptor-positive cancers are more likely to develop in *BRCA2* mutation carriers, and the median age is approximately 49 years. In patients with infiltrating breast cancers, somatic *BRCA1*/2 mutations can also be found, which are twice as rare as germline mutations [28, 50]. In the case of somatic mutations, the phenotype of the tumors is usually the same as in carriers of germline mutations, but the age of disease onset is typically like in women with sporadic cancer (approximately 62 years).

Currently, a 2-stage molecular test to detect a germline *BRCA* mutation is recommended in Poland [51]. The results of the study by Kowalik et al. [52] published in 2018 were used to establish such an algorithm. It aimed to assess the value of next-generation sequencing (NGS) in detecting germline *BRCA1*/2 mutations in the Polish population. The authors included 2931 patients referred for genetic testing at the oncology center in Kielce. In the first stage, patients were screened using the high-resolution melting polymerase chain reaction (HRM-PCR) method to identify founder mutations and the most common ones in the Polish population. In total 103 (3.5%) mutations were detected, including 53 (51%) in healthy carriers and 50 (49%) in patients diagnosed with cancer. In the second stage, in 454 (16%) individuals without founder mutations and meeting strict clinical and family burden criteria, sequencing of all *BRCA1*/2 exons was performed using the NGS technique. In total 58 mutations (12.8%) were detected, of which 40 (8.8%) were pathogenic, 14 (3.1%) were of unknown clinical significance, and 4 (0.9%) were determined as non-pathogenic. In conclusion, the screening allowed for the detection of 64% of pathogenic germline mutations, and for detection of remaining mutations, the NGS technique was necessary.

Figure 4 summarizes current recommendations for testing patients and their family members for germline *BRCA1*/2 mutation and the potential application of knowledge about the mutation burden in diagnostic, therapeutic, and preventive management.

It should be mentioned that the results of another open, non-randomized phase II study indicate the activity of olaparib in patients with advanced breast cancer with somatic *BRCA1*/2 mutations (median PFS 6.3 months; ORR 50%) and with germline *PALB2* mutations (median PFS 13.3 months; ORR 82%) [50]. However, these encouraging results require confirmation. Then, in breast cancer patients, PARP inhibitors could be indicated in a broader group, as in the case of ovarian or prostate cancers.

TROP-2

Membrane receptor TROP-2, which was originally discovered in trophoblast cells, is a molecular target for sacituzumab govitecan [53]. Currently, 4 proteins from this family are known (TROP-1, -2, -3, and -4) that are expressed in normal and malignant trophoblast cells. TROP-2 is a transmembrane protein that, when activated, causes the release of intracellular calcium stores and participates in the activation of intracellular signaling pathways. The protein is expressed in cells of many types of cancer, including the majority of breast cancers (>90%). It has been shown that in patients with various cancers, TROP-2 expression is much higher in tumor tissue compared to healthy tissue, and in many cases, it is associated with worse prognosis. The receptor participates in tumorigenesis through various mechanisms.

Sacituzumab govitecan is a conjugate of an antibody (IgG1 kappa) directed against TROP-2 and a topoisomerase I inhibitor SN-38 [35]. The linker between both elements can be hydrolyzed both before internalization of the receptor-bound drug and inside the cell. SN-38, thanks to its release in the intercellular space and passing beyond the cell membrane from inside the target cell, can cause a cytotoxic effect in neighboring cells (even if there is no TROP-2 expression in their cell membrane). This phenomenon is called the "bystander" effect.

HER2

The "bystander" effect is also characteristic of therapy with trastuzumab deruxtecan [48]. Thanks to this property, the drug turned out to be effective in the treatment of cancers with low HER2 expression, and a newly defined molecular target, i.e. HER2-low, appeared in breast cancer therapy. This target is more often present in luminal cancers [29]. It was noticed that the level of HER2 expression may change over time. HER2 expression may be increased by cross-transmission of activation between HER2-dependent

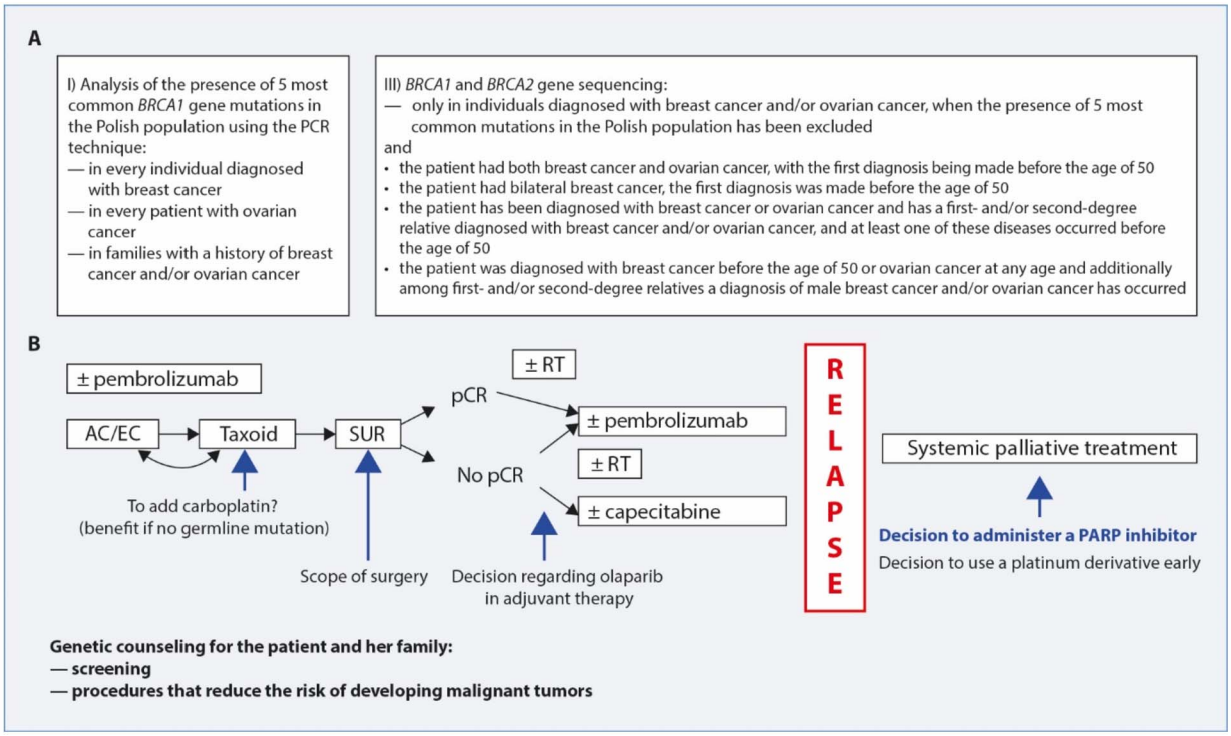

Figure 4. A. Recommendations for testing breast cancer patients and their family members for germline *BRCA1/2* mutations (in accordance with the module I of the National Cancer Control Program of the Ministry of Health [51]). The boxes present the indications for 2-stage genetic testing; **B.** Potential use of knowledge about mutation burden in diagnostic, therapeutic, and preventive procedures. The arrows indicate moments in the therapeutic plan at which knowledge of germline *BRCA* mutation carrier-state may influence treatment choice; AC/EC — chemotherapy according to the doxorubicin and cyclophosphamide or epirubicin and cyclophosphamide regimens; SUR — radical surgical procedure; pCR — pathological complete response; RT — adjuvant radiotherapy

and hormonal receptor-dependent signaling pathways. The phenomenon is intensified under the influence of hormone therapy and is considered one of the mechanisms of hormone resistance. HER2 expression may be increased after chemotherapy or radiotherapy (activation of the NF-kB-dependent pathway), as a result of epigenetic changes or after stimulation with stressors. Cancers with variable low HER2 expression should not be perceived as a separate disease entity; this molecular target and level of its expression rather result from various factors affecting the tumor during the course of the disease. It is estimated that approximately 20% of patients with classic TNBC have low HER2 expression.

Conclusions

Chemotherapy is the basic method of systemic treatment in patients with triple-negative breast cancer. Addition of platinum derivatives to preoperative chemotherapy has been shown to be beneficial in patients without germline *BRCA1/2* mutations. However, in palliative treatment of mutation carriers, platinum-based chemotherapy shows an advantage over a taxoid.

New drugs registered for TNBC patients are, in fact, targeted therapies. Olaparib has been approved as monotherapy or in combination with hormonal therapy in the adjuvant treatment of breast cancer patients with germline *BRCA1/2* mutations, without HER2 overexpression, and with high risk of relapse. An unresolved issue about such treatments is the lack of data on the effectiveness and safety of adjuvant treatment with capecitabine if the patient did not achieve the pCR after preoperative chemotherapy.

Two drugs are registered for palliative treatment in patients with the above-mentioned mutations and without HER2 overexpression: talazoparib and olaparib. Both are indicated for use as monotherapy in patients previously treated with an anthracycline and a taxoid (unless there were contraindications) and undergoing hormone therapy in case of positive HR expression. Currently (June 2023), talazoparib is reimbursed in Poland under the drug program of the Ministry of Health in the first, second, or third treatment lines in TNBC patients and in the second or third treatment lines in patients with HR expression.

Sacituzumab govitecan is indicated for palliative treatment of TNBC patients who have previously received at least two lines of systemic therapy, including at least one for advanced disease. In Poland, the drug is reimbursed under the drug program of the

Ministry of Health in the second, third, or fourth treatment lines.

The only immune checkpoint inhibitor approved for the treatment of TNBC patients is pembrolizumab, which may be used in perioperative treatment. There are some controversies about the type of preoperative chemotherapy, which was combined with immunotherapy in a pivotal study, as well as the lack of data on safety of combining pembrolizumab with adjuvant chemotherapy with capecitabine in patients without pCR after preoperative treatment, and with olaparib in patients with a *BRCA* mutation. In the palliative setting, pembrolizumab is added to first-line chemotherapy in patients with high PD-L1 expression (CPS $\geq$ 10). For both indications, pembrolizumab is reimbursed under the Ministry of Health drug program from July 1, 2023.

Trastuzumab deruxtecan has been registered for palliative treatment in breast cancer patients with low HER2 expression who have previously received palliative or adjuvant chemotherapy if recurrence occurred during its course or within 6 months of its completion. This agent is not reimbursed in Poland for now (in June 2023).

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S.D.-S.: concept and design of the analysis, data collection and analysis, manuscript preparation; PP: data collection and analysis, manuscript preparation.

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Supplementary material

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