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REVIEW ARTICLE

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Recent advances in the treatment of triple-negative breast cancer

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ABSTRACT

Triple-negative is the rarest breast cancer biological subtype of breast cancer, but has the most aggressive course. The resuls of chemotherapy, especially in advanced disease, are unsatisfactory. Numerous clinical trials have been conducted, that resulted in registrations of new drugs decreasing the risk of recurrence and improving the outcome of patients with metastatic disease. The article summarizes the data on modern therapies registered in recent years. The role of pembrolizumab in perioperative treatment in the early stage was indicated, as well as the importance of olaparib in *BRCA* mutation carriers. Additionally, in patients with metastatic the indication for immunotherapy (pembrolizumab and atezolizumab), sacituzumab govitecan and PARP inhibitors (olaparib and talazoparib) in *BRCA* mutation carriers were highlighted.

Keywords: triple-negative breast cancer, immunotherapy, olaparib, talazoparib, atezolizumab, pembrolizumab, sacituzumab govitecan

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Introduction

Triple-negative breast cancer (TNBC) has been difficult to treat for many years. This biological subtype is diagnosed in approximately 10–15% of all breast cancer patients [1]. Young women are more frequently affected, and in up to 20–25% of patients *BRCA* gene mutations are detected (especially *BRCA1*), which has therapeutic implications [2–4].

Triple-negative breast cancer is an aggressive subtype of breast cancer with a high risk of recurrence (especially in the first 3–5 years after diagnosis), regardless of sensitivity to neoadjuvant chemotherapy [5]. Optimization of perioperative chemotherapy (use of regimens with shorter intervals between cycles, preoperative addition of carboplatin or capecitabine in the case of residual disease) reduces the risk of disease relapse [6–8]. However, 20–30% of patients still experience disease recurrence (sometimes very quickly and with high tumor burden, usually involving the lungs) [5]. In such cases standard chemotherapy usually shows limited effectiveness. The overall survival (OS) rate of patients with metastatic TNBC is low, with the median not exceeding 2 years [4, 9].

In recent years, numerous clinical trials have been conducted with new drugs in patients with early and advanced TNBC. This article summarizes the results of studies with drugs registered in the last few years which improve treatment outcomes and are included in the management algorithms for patients with TNBC.

Systemic treatment of early triple-negative breast cancer

Pembrolizumab

The results of the phase-III clinical trial KEYNOTE-522 led to the registration of pembrolizumab. Pembrolizumab is the first immunotherapy in patients with early TNBC, regardless of the expression of the programmed death

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receptor 1 (PD-L1) [10, 11]. The study involved patients with previously untreated stage II or III TNBC, who were randomized to preoperative treatment consisting of 12 cycles of paclitaxel (weekly) with carboplatin (every 1 or 3 weeks), followed by 4 cycles of doxorubicin or epirubicin plus cyclophosphamide (every 3 weeks). In the experimental arm, pembrolizumab was additionally used in both preoperative (8 doses every 3 weeks) and postoperative therapy (9 subsequent doses). No treatment was used for the residual disease. The primary endpoints of the study were pathological complete response (pCR) and event-free survival (EFS) in the entire study population [12].

In the first interim analysis, which involved the first 602 randomized patients of all 1174 patients enrolled in the study, the pCR rate was 64.8% [95% confidence interval (CI) 59.9–69.5] in the pembrolizumab group compared to 51.2% (95% CI 44.1 58.3) in the placebo group (pCR difference 13.6%; 95% CI 5.4–21.8; $p < 0.001$). A benefit of pembrolizumab treatment was demonstrated after 39 months of follow-up (median). The 3-year EFS rate was 84.5% (95% CI: 81.7–86.9) in the pembrolizumab arm versus 76.8% (95% CI 72.2—80.7) in the placebo arm [hazard ratio (HR) = 0.63; 95% CI 0.48–0.82; $p < 0.001$]. The most commonly reported events were distant recurrences (7.7% *vs.* 13.1%, respectively). Reassessment of the pCR in the entire study population indicated the advantage of immunotherapy, but the numerical difference was smaller (7.4%) [10]. Patients are still being monitored.

A pooled analysis of preoperative and postoperative adverse events revealed that grade ≥ 3 complications considered by the investigator to be related to study treatment were found in 77.1% of 783 patients in the pembrolizumab arm and 73.3% of 389 patients in the placebo group. The most common events were nausea, alopecia, and anemia. Discontinuation of study treatment due to adverse events (AEs) was 27.7% in the immunotherapy group and 14.1% in the placebo group. Serious treatment-related AEs occurred in 34.1% of patients in the pembrolizumab group and 20.1% in the placebo group. Deaths resulting from treatment-related adverse events occurred in 4 patients (0.5%) in the pembrolizumab group and 1 patient (0.3%) in the placebo group. The majority of treatment-related complications occurred during preoperative treatment. Adverse events with an incidence of at least 5% higher in the pembrolizumab group than in the placebo group were fever (28.2% *vs.* 18.5%), hypothyroidism (15.1% *vs.* 5.7%), diarrhea (40.6% *vs.* 34.2%), rash (29.9% *vs.* 23.7%), decreased appetite (22.7% *vs.* 16.7%), and hypokalemia (11.2% *vs.* 6.2%) %). It should be emphasized that most adverse events occurred during preoperative chemotherapy [10].

Quality of life (QoL) data were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) and EORTC QLQ-BR23 questionnaires, which were collected from over 80% of patients at week 21 of preoperative treatment and after 24 weeks of postoperative treatment. There were no significant differences between the study groups according to quality-of-life outcomes (global health status, emotional functioning, physical functioning, and breast symptoms, including skin problems) [13].

Taking into account the data showing statistically significant pCR improvement and reducing the risk of recurrence (improvement of the 3-year EFS rate) as well as maintaining the quality of life, pembrolizumab was recommended for perioperative treatment in patients with early TNBC [14, 15].

Olaparib

Patients diagnosed with TNBC are more often carriers of *BRCA* gene mutations compared to other breast cancer subtypes. Considering the unsatisfactory results of treatment in patients with a high risk of recurrence, the OlympiA clinical trial was designed to evaluate the benefits of additional targeted therapy after standard chemotherapy in *BRCA* mutation carriers. The OlympiA study compared patients treated for one year with olaparib {PARP, poly[adenosine diphosphate(ADO)-ribose] polymerase} inhibitor with the placebo group. The study included 1836 randomly assigned patients [including 1509 (82%) patients with TNBC] with residual disease after preoperative chemotherapy or patients who had undergone initial surgery and had lymph node involvement (pN+ disease) or advanced pT2-4N0 disease. In 94% of patients, chemotherapy based on anthracyclines and taxanes was used, and 26% of patients additionally received platinum derivatives [16]. The primary endpoint of the OlympiA study was invasive disease-free survival (IDFS). The secondary endpoints included distant disease-free survival (DDFS) and overall survival (OS).

After a median follow-up of 3.5 years, there was a significant improvement in OS in the olaparib group compared to placebo (HR = 0.68; 98.5% CI 0.47–0.97; $p = 0.009$). After 4 years of follow-up, the difference in OS between treated (olaparib) and untreated (placebo) patients was 3.4% (89.8% *vs.* 86.4%). Similarly, a significant reduction in the risk of relapse was demonstrated (HR for IDFS = 0.63; 95% CI 0.50–0.78) — IDFS after 4 years was 82.7% in the olaparib group and 75.4% in the placebo group as well as a reduction in the risk of distant metastases (HR for DDFS = 0.61; 95% CI 0.48–0.77) — DDFS after 4 years was 86.5% *vs.* 79.1%, respectively. An analysis of the effectiveness of treatment depending on the subtype of breast cancer

was also performed, confirming the benefit of olaparib treatment in patients with TNBC (HR for IDFS = 0.62; HR for DDFS = 0.59; HR for OS = 0.64).

More than 11 months of treatment — out of the planned 12 months — were completed by 76% of patients in the olaparib group versus 82% of patients in the placebo group, and 25% of patients in the olaparib group required a dose reduction versus 5% of patients in the placebo group. Adverse events were more frequent in the experimental arm. The most common AEs were nausea (57% *vs.* 24%), asthenia (40% *vs.* 27%), anemia (24% *vs.* 4%), vomiting (23% *vs.* 8%), headache (20% *vs.* 17%), diarrhea (18% *vs.* 14%), neutropenia (16% *vs.* 6%). AEs leading to drug discontinuation occurred in 11% of patients in the olaparib group and 5% of patients in the placebo group. The most common AEs leading to discontinuation of olaparib were nausea (2%), anemia (2%), fatigue (2%), and neutropenia (1%). Grade ≥ 3 AEs in the olaparib group included anemia (9%), neutropenia (5%), leucopenia (3%), fatigue (2%), and lymphopenia (1%). There was 1 death from cardiac arrest in an olaparib-treated patient and 2 deaths from other cancer in the placebo group (acute myeloid leukemia and ovarian cancer). There were patients requiring blood transfusion during the study (6% in the olaparib group and 1% in the placebo group). There were 5 cases of myelodysplastic syndrome or acute myeloid leukemia (2 in the olaparib group and 3 in the placebo group).

Preliminary data on the quality of life of patients in the OlympiA study indicate that olaparib was well tolerated. A slightly higher incidence of complications did not affect the patients' well-being — no significant difference in fatigue and quality of life was noted. Treatment with olaparib led to a mild increase in nausea and vomiting during treatment, but symptoms resolved after treatment discontinuation. A gradual improvement in physical and emotional functioning, as well as general health, was observed over 24 months after adjuvant chemotherapy [17]. Longer follow-up of patients is planned.

Based on presented results, olaparib was approved for adjuvant treatment in *BRCA* mutation carriers with HER2-negative breast cancer at high risk of recurrence [18], which is also recommended by international expert panels [3, 14, 15].

It should be emphasized that there have been no studies comparing the efficacy of olaparib with capecitabine in patients with early TNBC with residual disease after preoperative chemotherapy. Data on mutation status in *BRCA* genes in patients treated with capecitabine in the CREATE-X study were also not presented [8]. The results of studies in patients with advanced breast cancer, in whom PARP inhibitor therapy was more effective than chemotherapy (including capecitabine) in *BRCA* mutation carriers, can provide hints while deciding on the choice of treatment in the case of residual disease [19, 20].

The results of studies with new drugs are summarized in Table 1. The introduction of pembrolizumab and olaparib to the treatment of patients with early TNBC will reduce the risk of recurrence of a very aggressive breast cancer subtype. Adding both therapies to the currently used treatment regimen results in longer therapy time. The need to determine the *BRCA* mutation status in patients with TNBC should be emphasized [21]. The use of immunotherapy prompts consideration of specific complications that may be different from the side effects of chemotherapy that clinicians may anticipate in patients with TNBC.

Systemic treatment in metastatic triple-negative breast cancer

Studies conducted in recent years in patients with metastatic TNBC led to the development of a new management algorithm. The key role is played by PD-L1 expression tests (with a specific test depending on the type of planned immunotherapy) and *BRCA* gene status assessment, which should be ordered in the case of TNBC recurrence. The results of these tests are of key

Table 1. Results of clinical trials with new therapies in patients with early triple-negative breast cancer

Study	Randomization	Number of patients	Inclusion criteria	Treatment regimen	DFS	OS	Remarks
KEYNOTE-522	2:1	1174	Stage II–III	Chemotherapy ± pembrolizumab	ESF: HR = 0.63	Data still collected	pCR: 64.8% *vs.* 51.2%
OlympiaA	1:1	1836 (TNBC 1509)	*BRCA* mutation, residual disease, or ≥ pT2 or pN+	± olaparib	iDFS: HR = 0.62	HR = 0.64	

Chemotherapy: paclitaxel + carboplatin followed by doxorubicin/epirubicin + cyclophosphamide; DFS — disease-free survival; iDFS — invasive disease-free survival; EFS — event-free survival; OS — overall survival; pCR — pathological complete response; TNBC — triple-negative breast cancer; HR — hazard ratio

importance in determining the therapeutic path for patients. In the first-line treatment of patients with TNBC with PD-L1 expression, immunotherapy (atezolizumab or pembrolizumab) in combination with chemotherapy is preferred. PARP inhibitors (olaparib or talazoparib) should be considered in *BRCA* mutation carriers. In the second-line treatment, sacituzumab govitecan is preferred. In the remaining patients, standard chemotherapy should be used. This management requires determination of predictive factors [4].

Atezolizumab

Atezolizumab was the first immunotherapy registered for patients with advanced breast cancer [22]. The pivotal study IMpassion130 involved 902 patients with metastatic or unresectable locally advanced TNBC. Patients who had previously undergone perioperative chemotherapy (including taxane-based chemotherapy) were eligible for the study, provided that their treatment had been completed ≥ 12 months before randomization. Screening tests included PD-L1 expression determination using the Ventana SP142 test, which was found in 41% of TNBC patients. In first-line treatment, nab-paclitaxel was used either in monotherapy or in combination with atezolizumab. The primary endpoints of the study were progression-free survival (PFS) and OS assessed in the entire population and the group of patients with PD-L1 expression. The results of the study showed a significant improvement in PFS in the entire group of patients receiving immunotherapy (7.2 versus 5.5 months, HR = 0.80; 95% CI 0.69–0.92; p = 0.0025) and, above all, in the group with PD-L1 expression (7.5 *vs.* 5.0 months, HR = 0.62; 95% CI 0.49–0.78; p < 0.0001). The first and final OS analysis showed no improvement after immunotherapy in the entire study population (21 *vs.* 18.7 months, HR = 0.86; 95% CI 0.75–1.02; p = 0.077), which resulted in abandoning the determination of the OS benefit in patients with PD-L1 expression. Additional analysis indicated a clinically significant benefit of atezolizumab in the PD-L1 positive group (OS: 25.4 *vs.* 17.9 months, HR = 0.67; 95% CI 0.53–0.86). The overall response rate (ORR) was also higher in the immunotherapy group (59% *vs.* 43%; HR = 1.96; p = 0.002) [23].

The most common AEs in patients treated in the IMpassion130 study were alopecia, asthenia, nausea, and diarrhea. Complications (grades 3–4) were reported in 51% of patients in the immunotherapy group and 43% of patients in the control group. Among patients with grade ≥ 3 AEs, the most common were neutropenia (8% in both groups), peripheral neuropathy (6% in the atezolizumab group *vs.* 3% in the control group), and asthenia (4% in the atezolizumab group *vs.* 3% in the placebo group). As a result of adverse events, treatment with at least one drug was discontinued in 19% of patients receiving combination therapy and in 8% of patients receiving chemotherapy alone (neuropathy was the most common cause). Typical immunotherapy side effects occurred in the experimental arm: rash (36% *vs.* 26% in the control arm), thyroid disorders (hypothyroidism — 18% *vs.* 4% and hyperthyroidism — 5% *vs.* 1%), and pneumonia (4% *vs.* 1%) [23].

The EORTC-C30 and BR23 questionnaires were used to assess the quality of life of patients treated in the IMpassion130 study. Treatment with atezolizumab did not affect the quality of life in the entire population and in patients with TNBC with PD-L1 expression [24].

The results obtained in the IMpassion131 study were a surprise. The design of this study was similar to the IMpassion130 study, while paclitaxel was added to atezolizumab in place of nab-paclitaxel. The primary endpoint of the study was PFS in the entire study population and patients with PD-L1 expression. The secondary endpoint was OS. PD-L1 expression was found in 45% of TNBC patients. There was no improvement in PFS in patients with PDL1 expression (median PFS: 6 *vs.* 5.7 months; p = 0.20) and in the entire study group (median PFS: 5.7 *vs.* 5.6 months; p = 0.86). There was also no difference in OS. Median OS among patients with PD-L1 expression was 22.1 months in the atezolizumab group and 28.3 months in the group treated with paclitaxel (worse result in the group with immunotherapy similar to entire study population — 19.2 and 22.8 months, respectively) [25]. The research is ongoing to explain the reasons for the different outcomes of atezolizumab treatment.

According to the current registration, atezolizumab can be used in combination with nab-paclitaxel in the first-line treatment of patients with metastatic TNBC with PD-L1 expression determined by the SP142 test [22].

Pembrolizumab

Another important study on immunotherapy in patients with metastatic TNBC was the KEYNOTE-355 study. Patients with primary metastatic TNBC and recurrence after at least 6 months from the end of radical treatment (surgery or adjuvant chemotherapy) were eligible for the study. As in the immunotherapy studies discussed above, pembrolizumab was used in combination with chemotherapy in the first-line treatment of advanced TNBC. Chemotherapy included nab-paclitaxel, paclitaxel, or gemcitabine with carboplatin. The study aimed to evaluate the effect of adding pembrolizumab to chemotherapy on treatment outcomes. In total 847 patients were randomly assigned to combination therapy or chemotherapy alone. The study assessed PD-L1 expression status using the Dako 22C3 assay, with a positive combined score (CPS) ≥ 10 in 38%

of tumors. The primary endpoints of the study were PFS and OS in patients with TNBC and CPS ≥ 10 or CPS > 1 in the entire study population. Better treatment results were reported in patients with high PD-L1 expression receiving pembrolizumab with chemotherapy. In patients with TNBC and PD-L1 expression with CPS ≥ 10, median PFS was significantly higher in the group with immunotherapy added to chemotherapy compared to the group receiving chemotherapy alone (median PFS — 9.7 versus 5.6 months; HR = 0.65 95% CI 0.49–0.86; p = 0.0012). The use of immunotherapy in this group also resulted in a significant improvement in OS (median OS — 23.0 versus 16.1 months; HR = 0.93; 95% CI 0.55–0.95; p = 0.0185). However, there was no improvement in treatment outcomes in the subgroup with CPS > 1 and in the entire study population receiving pembrolizumab with chemotherapy [26].

The most common AEs included anemia (49% of patients in the experimental group and 46% of patients in the chemotherapy group), neutropenia (41% and 38%, respectively), and nausea (39% and 41%). Grade ≥ 3 complications occurred in 68% of patients treated with pembrolizumab and 67% of patients treated with chemotherapy; most commonly reported were neutropenia (30% each) and anemia (16% and 15%, respectively). Two deaths were reported in the experimental arm due to acute kidney injury and pneumonia. Immune-related adverse events (irAEs) were reported in 27% of patients in the pembrolizumab group and 6% in the chemotherapy arm; grade ≥ 3 irAEs occurred in 5% of patients receiving immunotherapy [26].

A comparison of the quality of life with the use of the QLQ-30 and BR23 questionnaires after 15 weeks of treatment showed similar results. The addition of pembrolizumab did not affect the quality of life (including global health status, emotional or physical functioning) [27].

In conclusion, significant improvement in PFS and OS and maintenance of quality of life were demonstrated in patients with high PD-L1 expression undergoing combination therapy. Based on the results of the KEYNOTE-355 study, pembrolizumab was registered for use in combination with chemotherapy in the first-line treatment of locally recurrent unresectable or metastatic TNBC in patients with PD-L1 expression with a CPS ≥ 10 [11]. The assessment of PD-L1 expression, when pembrolizumab therapy is considered, should be performed using the 22C3 test.

Olaparib

The first of the studies evaluating the effectiveness of a PARP inhibitor in patients with breast cancer was the OlympiAD study, which compared olaparib with standard chemotherapy in *BRCA* germline mutation carriers suffering from advanced HER2-negative breast cancer. Thus, the study involved two groups of patients diagnosed with TNBC and hormone-dependent breast cancer (almost 50% of patients each). Patients could previously receive no more than 2 lines of chemotherapy due to metastatic disease (33% of patients had not previously used palliative chemotherapy, 40% had received one line of chemotherapy, and further 27% received 2 lines). A small number of patients had previously received platinum derivatives (7% in neoadjuvant treatment and 19% in palliative setting). In the OlympiAD study, 205 patients were randomized to olaparib and 97 to physician's choice chemotherapy (capecitabine, eribulin, or vinorelbine). The primary endpoint of the study was PFS, and the secondary endpoints were OS and safety [28].

There was a statistically significant improvement in PFS in the group of patients treated with olaparib compared to the group treated with physician's choice standard cytotoxic drugs (7.0 months *vs.* 4.2 months; HR = 0.58; 95% CI 0.43–0.80; p < 0.001). The PFS benefit was greater in patients with TNBC compared to other patients (HR for PFS = 0.43). The overall response rate was higher in the PARP inhibitor arm, e.g. 59.9% in the olaparib arm and 28.8% in the standard chemotherapy arm. In contrast, OS results were similar in both arms of the study. The median OS rate was 19.3 months in the olaparib arm and 17.1 months in the chemotherapy arm (HR = 0.90; 95% CI 0.66–1.23; p = 0.513). The OS results did not depend on the biological subtype of breast cancer, but there was a clinical improvement in OS in patients who were treated with olaparib in the first line (OS: 22.6 *vs.* 14.7 months; HR = 0.51; 95% CI 0, 29–0.90) [19].

Adverse events of olaparib were most commonly of grade 1 or 2 and rarely led to discontinuation of treatment. Nausea, anemia, vomiting, fatigue, cough, decreased appetite, back pain, and headache were reported with a slightly higher incidence (≥ 5%) in the olaparib arm compared to the standard arm. Conversely, neutropenia, elevated liver enzymes, alopecia, and hand-foot syndrome were more common (≥ 5%) in the chemotherapy arm compared to olaparib. Grade ≥ 3 AEs were reported in 38% of patients in the olaparib arm and 49% of patients in the chemotherapy arm, with causality suspected in 24.4% and 34.1% of patients, respectively. The most common grade ≥ 3 AE in patients treated with olaparib was anemia, and in patients receiving chemotherapy — neutropenia (three episodes of febrile neutropenia were reported). The treatment discontinuation rate due to AEs was 5% in the olaparib arm and 8% in the chemotherapy arm [19].

Patients assessed olaparib therapy better than chemotherapy (QLQ-C30 questionnaire). A comparison of general health and quality of life between the study

arms indicated a better outcome in patients receiving PARP inhibitors. The median time to deterioration of health status and quality of life was not reached in the olaparib group but was 15.3 months in patients using standard cytotoxic drugs (HR = 0.44; p = 0.004). Among the subscales evaluating symptoms and functioning using the QLQ-C30 questionnaire, only nausea and/or vomiting were more frequently reported during olaparib treatment compared to chemotherapy [29].

Based on the above results of the OlympiAD study (significant improvement in PFS and quality of life), olaparib was approved for use in *BRCA* mutation carriers suffering from advanced HER2-negative breast cancer [18].

Talazoparib

The second study that evaluated the efficacy of a PARP inhibitor versus chemotherapy in *BRCA* germline mutation carriers with HER2-negative advanced breast cancer (44% with TNBC) was the EMBRACA study. Patients who could previously receive no more than 3 lines of palliative treatment were eligible (no previous chemotherapy — 38%, 1 line — 37%, 2 lines — 20%, 3 lines — 5% of patients). The patients were randomly assigned to two groups — 287 received talazoparib and 144 received physician's choice chemotherapy (capecitabine — 44%, eribulin — 40%, gemcitabine — 10%, vinorelbine — 7%). In total 18% of patients had previously received platinum derivatives. The study showed an improvement in PFS in patients using talazoparib with medians of 8.6 and 5.6 months, respectively (HR = 0.54; 95% CI 0.41–0.71; p < 0.001; in a subgroup of TNBC patients HR = 0.60) [30]. The ORR was also higher in the talazoparib group compared to the control arm (62.6% *vs.* 27.2%; odds ratio 5.0; p < 0.001) [30]. However, there was no difference in OS in the whole group, depending on the treatment used — the median OS was 19.3 months in the talazoparib group and 19.5 months in the chemotherapy group (HR = 0.848; 95% CI 0.670–1.073; p = 0.17) [20].

The most common AEs occurring in > 30% of patients were anemia, fatigue, nausea, neutropenia, and headache in the talazoparib group and nausea, fatigue, and neutropenia in the chemotherapy group. Adverse events (grade 3–4) occurred in 70% of patients in the talazoparib group and 64% of patients in the chemotherapy group. Myelotoxicity (grades 3–4) was reported in 57% of patients in the talazoparib arm and 39% of patients in the chemotherapy arm. Blood transfusions were frequent in the PARP inhibitor arm, with 39% of patients receiving at least one blood transfusion in the talazoparib group versus 6% of patients receiving chemotherapy. Adverse events led to discontinuation of treatment in 6% of patients treated with talazoparib and 9% of patients in the chemotherapy group [20].

Important conclusions can be drawn from analyzes of the quality of life assessed using the QLQ-C30 and QLQL-BR23 questionnaires. Significant improvements in general health and quality of life from baseline were observed in the talazoparib group, while there was a significant decrease in quality of life in the chemotherapy group. There was also a significant improvement in breast-related symptoms (BR23) in patients receiving a PARP inhibitor, which was not seen in patients receiving chemotherapy. It should be noted that treatment with talazoparib resulted in a significant delay in the time to clinically significant deterioration of health status and quality of life as well as breast-related symptoms [20, 31].

The results of the EMBRACA study, which showed a statistically significant improvement in PFS and quality of life, contributed to the registration of talazoparib for use in *BRCA* mutation carriers suffering from advanced HER2-negative breast cancer [32].

Sacituzumab govitecan

Sacituzumab govitecan is a conjugate composed of a monoclonal antibody that binds to trophoblast-cell surface antigen 2 (TROP-2) on the surface of tumor cells, the small molecule SN-38 (govitecan, an active metabolite of topoisomerase I), and a linker.

The ASCENT pivotal study involved 529 patients with metastatic or inoperable locally advanced TNBC. Patients had to have received previously at least 2 lines of chemotherapy (one of them could be neoadjuvant chemotherapy provided that relapse occurred within 12 months of therapy completion). In total 61 patients with stable brain metastases were also recruited. The effectiveness of sacituzumab govitecan was compared with the investigator's choice chemotherapy (eribulin — 54% of patients, vinorelbine — 20%, capecitabine — 13%, or gemcitabine — 12%). The primary endpoint of the study was median PFS in a cohort of 468 patients without brain metastases. The secondary endpoints of the study were OS in patients without brain metastases, PFS and OS in the overall population, ORR, safety, and quality of life. Patients treated in the study had previously received various cytostatics (mean 4 lines) — all patients were treated with taxoids, and the majority also received anthracyclines (82%) and carboplatin (66%). In addition, 7% of patients had previously been treated with PARP inhibitors and 27% had received immunotherapy. The results of the ASCENT study showed a statistically significant benefit from treatment with the new conjugate [33]. The final results of the ASCENT study were recently presented. The median PFS rate was 5.6 months in the conjugate arm and 1.7 months in the chemotherapy arm (HR = 0.39;

Table 2. Results of clinical trials with new therapies in patients with advanced triple-negative breast cancer (TNBC)

Study	Randomization	Number of patients	Inclusion criteria	Treatment regimen	PFS (months)	OS (months)	ORR (%)
IMpassion-130	1:1	902 (369 PD-L1 + 41%)	TNBC first line; DFI > 12 months	Nab-paclitaxel ± atezolizumab	7.5 *vs.* 5.0 (HR = 0.62)*	25.4 *vs.* 17.9*	58.9% *vs.* 42.6%*
IMpassion-131	2:1	651 (292 PD-L1 + 45%)	TNBC first line; DFI > 12 months	Paclitaxel ± atezolizumab	6.0 *vs.* 5.7 (HR = 0.82, NS)*	22.1 *vs.* 28.3 (HR = 1.11; NS)*	63% *vs.* 55%*
KEYNOTE-355	1:1	847 (323 PD-L1 + 38%)	TNBC first line; DFI > 6 months	Chemotherapy ± pembrolizumab	9.7 *vs.* 5.6 (HR = 0.66)*	23 *vs.* 16.1 (HR = 0.73)*	52.7% *vs.* 40.8%*
OlympiaAD	2:1	302	*BRCA* mutation, previously ≤ 2 lines of palliative chemotherapy	Olaparib *vs.* chemotherapy	7.0 *vs.* 4.2 (HR = 0.58)** (TNBC = 0.43)	19.3 *vs.* 17.1 (HR = 0.90)** (TNBC HR = 0.93)	59.9% *vs.* 28.8%**
EMBRACA	2:1	432	*BRCA* mutation, previously ≤ 3 lines of palliative chemotherapy	Talazoparib *vs.* chemotherapy	8.6 *vs.* 5.6 (HR = 0.54)** (TNBC HR = 0.60)	19.3 *vs.* 19.5 (HR = 0.848)** (TNBC HR = 0.899)	62.6% *vs.* 27.2%**
ASCENT	1:1	529	*BRCA* mutation, previously at least 1 line of palliative chemotherapy	Sacituzumab govitecan *vs.* chemotherapy	5.6 *vs.* 1.7 (HR = 0.39)	12.1 *vs.* 6.7 (HR = 0.48)	35% *vs.* 5%

*Results in the population with positive PD-L1 expression; **results in the entire group of patients with HER2-negative breast cancers; DFI — disease-free interval; HR — hazard ratio; NS — not significant; ORR — objective response rate; OS — overall survival; PD-L1+ — positive expression of programmed cell death ligand 1; PFS — progression-free survival; TNBC — triple-negative breast cancer

95% CI 0.31–0.49; $p < 0.0001$). The benefit of therapy with conjugate was observed in all analyzed subgroups. OS results also significantly improved — the median OS rate was 12.1 months in the sacituzumab group and 6.7 months in the chemotherapy group (HR = 0.48; 95% CI 0.39–0.59; $p < 0.0001$). Statistically significant improvement in the ORR (35% *vs.* 5%) and clinical benefit rate (45% *vs.* 9%) was also confirmed [34].

The most common treatment-related AEs of any grade were neutropenia (63% in the conjugate group and 43% in the chemotherapy arm), diarrhea (59% *vs.* 12%), nausea (57% *vs.* 26%), alopecia (46% *vs.* 16%), fatigue (45% *vs.* 30%), and anemia (34% *vs.* 24%). The most common grade ≥ 3 adverse events were neutropenia (51% in the sacituzumab group and 33% in the chemotherapy arm), leukopenia (10% *vs.* 5%), diarrhea (10% *vs.* < 1%), anemia (8% *vs.* 5%), and febrile neutropenia (6% *vs.* 2%) [33].

Recently, the results of the quality-of-life analysis in patients treated in the ASCENT study were published. According to assessment of health and quality of life, physical functioning, severity of fatigue and pain, treatment with sacituzumab govitecan obtained higher scores. Only for nausea, vomiting, and diarrhea, conjugate treatment was more burdensome than chemotherapy. The median time to first clinically significant deterioration in quality of life was greater for sacituzumab govitecan compared to chemotherapy in terms of physical functioning (22.1 *vs.* 12.1 weeks, $p < 0.001$), role (11.4 *vs.* 7.1 weeks, $p < 0.001$), fatigue (7.7 *vs.* 6.0 weeks, $p < 0.05$), and pain (21.6 *vs.* 9.9 weeks, $p < 0.001$) [35].

Based on the results of the ASCENT study, sacituzumab govitecan was registered for the treatment of patients with metastatic TNBC after at least one line of palliative therapy [36].

The results of studies with new drugs in patients with metastatic TNBC are summarized in Table 2.

Discussion

The treatment of patients with TNBC has changed significantly in recent years. Many new drugs have been approved for both early and metastatic TNBC. Registered indications are summarized in Table 3.

Treatment of patients with early TNBC is predominantly based on preoperative chemotherapy consisting of anthracyclines and taxanes, often as part of intensified regimens and with the addition of carboplatin. Intensive chemotherapy translates into achieving pCR in up to half of the treated patients. In the case of residual disease, capecitabine is additionally used.

Table 3. Registered indications of new therapies in triple-negative breast cancer (TNBC) based on the summary of product characteristics

Early TNBC		Dosage
Pembrolizumab	Pembrolizumab in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence	Neoadjuvant pembrolizumab in combination with chemotherapy with 8 doses of 200 mg *i.v.* every 3 weeks followed by adjuvant treatment with pembrolizumab as monotherapy with 9 doses every 3 weeks (or in neoadjuvant with 4 doses of 400 mg *i.v.* every 6 weeks, followed by 5 doses of 400 mg every 6 weeks)
Olaparib	Olaparib in monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2--mutations who have HER2-negative, high-risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy	300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg for up to 1 year
Advanced TNBC		**Dosage**
Atezolizumab	Atezolizumab in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease	840 mg *i.v.* every 2 weeks, or 1 200 mg *i.v.* every 3 weeks, or 1 680 mg *i.v.* every 4 weeks in combination with nab-paclitaxel (100 mg/m^2 *i.v.* on days 1, 8, and 15 of each 28-day cycle)
Pembrolizumab	Pembrolizumab in combination with chemotherapy is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumors express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease	Pembrolizumab in combination with chemotherapy 200 mg *i.v.* every 3 weeks or 400 mg *i.v.* every 6 weeks
Olaparib	Olaparib in monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with anthracycline and taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments	300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg
Talazoparib	Talazoparib as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should be previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced, or metastatic setting unless patients were not suitable for these treatments	1 mg (one 1 mg capsule) once daily
Sacituzumab govitecan	Sacituzumab govitecan as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease	10 mg/kg body weight *i.v.* on day 1 and day 8 of 21-day treatment cycles

CPS — combined positive score; PD-L1 — programmed cell death ligand 1; PFS — progression-free survival; TNBC — triple-negative breast cancer

The results of recent studies have led to the registration and recommendation of two drugs in patients with early TNBC. The first one is pembrolizumab used in perioperative treatment in patients with disease stages II–III. The drug is used in early TNBC regardless of PD-L1 expression status. The second is olaparib, recommended in a narrower group of patients (carriers of *BRCA* gene mutations) with residual disease or undergoing primary surgery with lymph node metastases or ≥ pT2. Due to the change in management principles, there are now definitely fewer patients starting treatment with surgery. The period when preoperative treatment is used additionally allows for obtaining information about the status of the *BRCA* gene, and thus the test result is known at the time of qualification for surgical treatment and later when making a decision on possible treatment of the residual disease. There are no unequivocal recommendations on the choice of management in residual disease (capecitabine, olaparib) when immunotherapy (pembrolizumab) was used in perioperative treatment. According to the latest recommendations, the treatment of patients with stage II–III TNBC has been extended to 12–18 months, depending on the management plan.

On the other hand, the choice of treatment in the case of recurrence of the disease varies greatly. According to the recommendations, making a decision on palliative treatment requires determination of PD-L1 expression and *BRCA* gene status. The choice of the test to determine PD-L1 expression depends on the planned treatment (two tests are used to qualify for therapy with atezolizumab or pembrolizumab, due to differences between them). The following scenarios are recommended in the first line of TNBC treatment:

— if PD-L1 expression is positive (about 40% of patients) — immunotherapy (pembrolizumab or atezolizumab) + chemotherapy (paclitaxel, nab-paclitaxel or gemcitabine with carboplatin; in the case of atezolizumab therapy, only nab-paclitaxel);
— if a *BRCA* mutation is present (20–25% of patients) — a PARP inhibitor (olaparib or talazoparib; talazoparib has been reimbursed in Poland since November 2022[37]);
— if there is no PD-L1 expression and *BRCA* mutation — chemotherapy.

The choice of chemotherapy is limited by the drugs used in the primary treatment. TNBC recurrences occur in the first years after radical treatment with standard cytotoxic drugs active in TNBC (anthracyclines, taxoids, carboplatin, capecitabine). According to the recommendations, anthracyclines or taxoids (previously used) may be reintroduced if relapse occurred at least one year after completion of chemotherapy with these drugs (taking into account the lifetime cumulative dose of anthracyclines) [4, 15, 21]. Other drugs to be used include vinorelbine, gemcitabine, cyclophosphamide, and eribulin. In turn, in the second and subsequent treatment lines, the recommendations clearly indicate the use of sacituzumab govitecan [4, 15], which has been reimbursed in Poland since November 2022 [37]. In subsequent treatment lines other cytotoxic drugs should be used, taking into account the low treatment response rate. The treatment algorithm for patients with TNBC is shown in Figure 1.

The new drugs discussed above for TNBC patients have positive scores on the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). Drugs used in early TNBC (pembrolizumab and olaparib) received the highest score A due to a significant reduction of recurrence risk and the absence of a significant increase in toxicity and deterioration of patients' quality of life. On the other hand, in palliative treatment, PARP inhibitors (olaparib and talazoparib) and sacituzumab govitecan scored 4 points on the scale (maximum score — 5). PARP inhibitors significantly prolong PFS and improve patients' quality of life with less treatment toxicity. Sacituzumab govitecan prolongs median PFS and OS with slightly higher toxicity but maintained quality of life. Atezolizumab scored 3 points because the drug improves PFS, but OS analysis was additional. Pembrolizumab scored 3 points, but the score needs to be changed due to the need to take into account the significant OS improvement [38].

The evolution of treatment options for TNBC patients is still highly awaited. Modern drugs significantly improve the prognosis compared to standard chemotherapy. Further studies are needed, especially in patients with metastatic TNBC, to conclude that long-term treatment is also possible for this subtype of metastatic breast cancer.

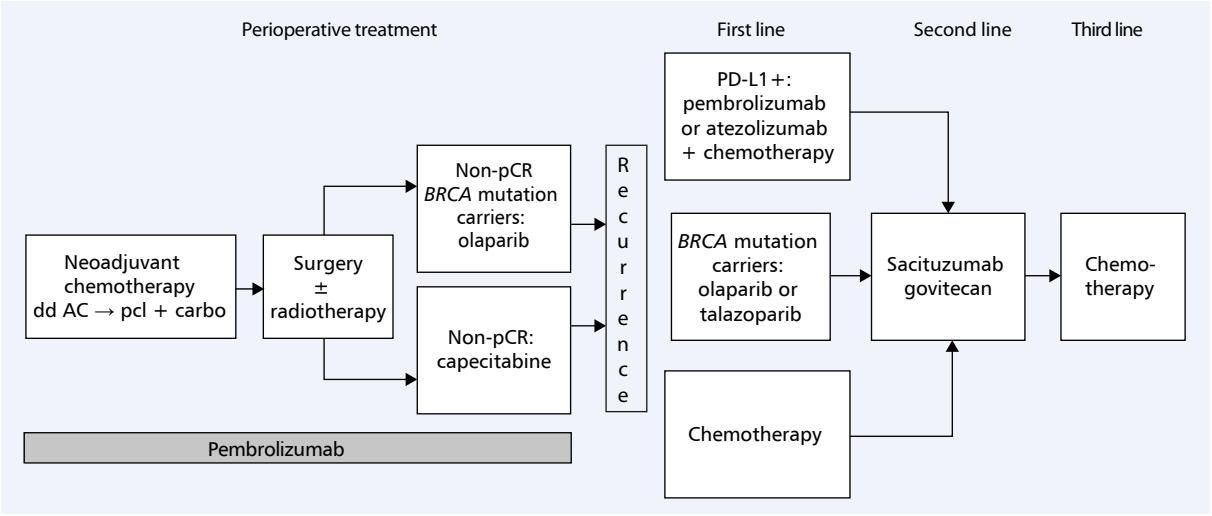

Figure 1. Treatment algorithm for patients diagnosed with triple-negative breast cancer; dose dense (dd) doxorubicin with cyclophosphamide (AC) — AC regimen with shortening of the intervals between cycles; pcl — paclitaxel; carbo — carboplatin; non-pCR — no pathological complete response; PD-L1— programmed cell death ligand 1

Article Information and Declarations

Conflict of interest

KP: honorarium for consultations/lectures/training/clinical trials and compensation for participation in scientific congresses from Roche, Novartis, Eli Lilly, Pfizer, MSD, AstraZeneca, Gilead, Teva, and Egis.
AJ-G.: honorarium for consultations/lectures/training/clinical trials from AstraZeneca, Novartis, Roche, Gilead, Eli Lilly, Amgen, Pfizer, MSD.
MK: honorarium for consultations/lectures/training/clinical trials and compensation for participation in scientific congresses from MSD, Bayer, Novartis, Eli Lilly, Pfizer, Roche, Vipharm, Angelini, AstraZeneca.
AN: no conflict of interest.
ZN: honorarium for lectures/clinical studies from Roche, MSD, Novartis, Eli Lilly, and AstraZeneca.

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