Triple negative breast cancer: any closer to cracking the code?

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Purpose of review
Triple negative breast cancer is the most aggressive subtype of breast cancer and has traditionally lacked targeted therapies leading to worse prognosis in most patients.

Recent findings
We will review new targeted therapies for triple negative breast cancer including immunotherapy, antibody-drug conjugates, and poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitors.

Summary
Immunotherapy is now a backbone of PD-L1 positive metastatic triple negative breast cancer in the front-line setting as well as part of neoadjuvant therapy for high risk localized triple negative breast cancer. PARP inhibitors and a new antibody-drug conjugate are additional new therapies that can be used to improve the outcome for localized and metastatic triple negative breast cancers. None of these treatments were available before the review period for this paper.

Keywords
immunotherapy, PARP inhibitors, residual disease after neoadjuvant therapy, targeted therapy, Triple negative breast cancer

Triple negative breast cancer, characterized by the absence of estrogen, progesterone, and HER2 receptors, accounts for about 15% of all breast cancers. These cancers typically have a more aggressive clinical course and unlike HER2 amplified or estrogen receptor positive breast cancers, have eluded targeted agents, until now. The last 2 years have seen the emergence of several new tools for triple negative breast cancer, including immunotherapy, an antibody-drug conjugate and PARP inhibitors, that have each found new indications in the spectrum of triple negative breast cancers. In this review, we will review these new practice changing therapies.

IMMUNOTHERAPY

Since the first study to show survival benefit of ipilumimab in melanoma in 2010, immunotherapy has been progressing in leaps and bounds [1]. Drugs harnessing the immune system are now approved for use in a variety of malignancies from melanoma to lung, genitourinary, and gastroinstestinal cancers. Its use in breast cancer had remained elusive; however, until recently. Here I will review its use in the metastatic setting which was first studied, followed by the early disease state.

Metastatic disease

In 2018, first positive results from use of immunotherapy in breast cancer were reported from the IMpassion 130 trial [2▪]. In this phase 3 randomized trial, patients with previously untreated metastatic triple negative breast cancer were randomized to treatment with nab-paclitaxel or combination of nab-paclitaxel with atezolizumab, an anti-PD-L1 antibody. Each group included 451 patients and both PD-L1 positive and negative patients were included. Atezolizumab plus nab-paclitaxel prolonged progression-free survival (PFS) among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup by about 2.5 months. Overall survival was improved only in patients with PD-L1 positive tumors with overall survival of 15.5 months in the chemotherapy arm vs.

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KEY POINTS

- Immunotherapy has now been approved for use in only patients with triple negative breast cancer both in the metastatic and neoadjuvant settings.
- Adjuvant therapy with PARP inhibitors can increase cure rate for triple negative breast cancer patients with BRCA mutations who have high risk localized disease.
- Targeted chemotherapy agents and/or antibody drug conjugates may provide the most personalized cancer treatment for triple negative breast cancer patients in the future.

25.0 months in the immunotherapy containing arm (hazard ratio, 0.62; 95% confidence interval, CI, 0.45–0.86). This study resulted in a conditional approval for atezolizumab in combination with nab-paclitaxel in PD-L1 positive triple negative breast cancers in the first line metastatic setting.

Subsequently, KEYNOTE 355 assessed use of pembrolizumab in the same setting of previously untreated metastatic triple negative breast cancer patients and was published in 2020 [3▪▪]. Choices of chemotherapy backbone were expanded in this trial to include nab-paclitaxel, paclitaxel, or gemcitabine plus carboplatin. Pembrolizumab was given every 3 weeks at 200 mg dosing. Patients were randomized in a 2 : 1 ratio to receive chemotherapy plus pembrolizumab or placebo. Again, both PD-L1 positive and negative patients were included. A total of 847 patients were randomized with median follow-up of over 2 years in the second interim analysis. Among patients with high levels of PD-L1 expression [combined positive score (CPS) $\geq$10], median progression-free survival was 9.7 months with pembrolizumab–chemotherapy and 5.6 months with placebo–chemotherapy (hazard ratio, HR for progression or death, 0.65, 95% CI 0.49–0.86; $P = 0.0012$). Median progression-free survival was 7.6 and 5.6 months (HR, 0.74, 0.61–0.90; $P = 0.0014$) among patients with CPS of 1 or more and 7.5 and 5.6 months (HR, 0.82, 0.69–0.97; not significant) among the intention-to-treat population. The pembrolizumab benefit increased with level of PD-L1 enrichment. Grade 3–5 treatment-related adverse event rates were 68% in the pembrolizumab–chemotherapy group and 67% in the placebo–chemotherapy group. As a result of this trial, pembrolizumab has been approved in combination with chemotherapy for patients with PD-L1 positive previously untreated metastatic triple negative breast cancer in combination with chemotherapy.

While pembrolizumab was shown the KEYNOTE 355 trial to work with several chemotherapy backbones, atezolizumab results were not able to be replicated with paclitaxel instead of nab-paclitaxel. In the IMpassion 131 trial, a phase III double-blind, placebo-controlled, randomized trial of first-line paclitaxel with or without atezolizumab, addition of atezolizumab to weekly paclitaxel failed to improve PFS or overall survival in the PD-L1 positive patients, which were about 45% of the total tested population, similar to the previous trials [4▪]. The approval for atezolizumab for treatment of triple negative breast cancer patients has since been withdrawn as a result of the negative IMpassion 131 trial. The reason for the difference in outcomes between pembrolizumab and atezolizumab is unclear at this time.

Neoadjuvant therapy

After encouraging results of immunotherapy in the advanced setting, trials were set up to assess benefit of adding immunotherapy in the early disease setting in triple negative breast cancer patients. Most patients with triple negative breast cancer receive neoadjuvant chemotherapy to assess response and guide therapy. Therefore KEYNOTE-522 set out to assess benefit of addition of immunotherapy in this setting [5▪▪].

Over 600 patients with previously untreated stages II or III triple-negative breast cancer were randomized to receive neoadjuvant therapy with pembrolizumab or placebo in combination with carboplatin and paclitaxel followed by cyclophosphamide plus an anthracycline given in a nondose-dense scheduling. After surgery, pembrolizumab was continued for up to 9 additional cycles in the immunotherapy arm. Patients were not selected based on PD-L1 expression. Pathologic complete response was 65% in the pembrolizumab–chemotherapy group vs. 51% in the chemotherapy group. After a median follow-up of 15.5 months, DFS was 93% in the immunotherapy arm vs. 88% in the chemotherapy group. Across all treatment phases, the incidence of treatment-related adverse events of grade 3 or higher was 78% in the pembrolizumab–chemotherapy group and 73% in the placebo–chemotherapy group. As of June 2021, pembrolizumab was approved by the FDA for treatment of high-risk early triple negative breast cancers in combination with chemotherapy and followed as a single agent in the adjuvant setting.

Patients were eligible for the KEYNOTE-522 trial regardless of PD-L1 positivity. No appreciable difference was seen in response in PD-L1 negative vs. positive patients in the KEYNOTE-522 trial but it's important to note that majority of the patients were PD-L1 positive. More than 80% of patients were PD-

L1 positive which is more than what would have been expected in non-selected patients (40–45% were positive for PD-L1 in trials in the metastatic setting). Another question at this point is the chemotherapy backbone. We know from earlier trials that dose dense AC is superior to regular dose AC but the latter was chosen as back bone for this trial assuming due to the every three week dosing of pembrolizumab. In addition, the additional value of carboplatin is unclear at this time.

Nevertheless, neoadjuvant therapy per the KEYNOTE 522 trial with immunotherapy combined with AC-T carboplatin is a great option for patients with locally advanced triple negative breast cancer. It is unclear however, which patients need immunotherapy and who would achieve a pathologic complete response from the backbone of dose dense AC followed by paclitaxel alone. Side effects were more common in the immunotherapy arm including deaths due to side effects (three vs. one patient in the immunotherapy compared to the chemotherapy arm).

Similar results have been reported for the combination of atezolizumab with chemotherapy in the neoadjuvant setting. The IMpassion031 trial was a randomized, double-blind, phase 3 trial, in which patients received atezolizumab vs. placebo in combination with weekly nab-paclitaxel for 12 weeks followed by every 2 weeks doxorubicin and cyclophosphamide before surgery. Pathologic complete response was improved in both the overall population and the PD-L1 positive tumors. In the PD-L1-positive population, pathologic complete response was 69% in the atezolizumab plus chemotherapy group vs. 49% in the chemotherapy arm. Atezolizumab has not yet been approved for this indication and may not be in the future due to conflicting results in the metastatic setting [6].

TARGETED THERAPY

Poly (adenosine diphosphate–ribose) polymerase inhibitors

Poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitors target cancers with defects in homologous recombination repair by synthetic lethality. Olaparib, a PARP inhibitor, was initially shown to have activity in patients with metastatic breast cancer and a germ line mutation in 2017 [7]. In the OlympiAD trial, progression-free survival was significantly longer in the olaparib group compared with chemotherapy of the physician's choice in previously treated patients who had not received more than 2 prior lines of therapy. Although not restricted to triple negative breast cancer patients, about 50% of patients were triple negative. Since the approval of Olaparib, talozaparib has also obtained approval in this setting after publication of the results of the EMBRACA trial in 2018 [8].

Similar to immunotherapy, after showing efficacy in the metastatic setting, PARP inhibitors have now been tested in the early-stage disease in the OlympiA trial [9▪▪]. Given lack of data for combination of chemotherapy and PARP inhibitors, they were tested in the adjuvant setting after completion of either neoadjuvant or adjuvant chemotherapy instead of in combination with chemotherapy. OlympiA was a phase 3, double-blind, randomized trial involving patients with human epidermal growth factor receptor 2 (HER2)–negative early breast cancer with BRCA1 or BRCA2 germline pathogenic or likely pathogenic variants and high-risk clinicopathological factors. Patients were randomly assigned in a 1 : 1 ratio to 1 year of oral olaparib or placebo. The primary end point was invasive disease-free survival.

Patients were selected for high-risk disease. If triple negative, they either had residual invasive disease after neoadjuvant therapy or had lymph node positive or tumors larger than 2 cm if not given neoadjuvant chemotherapy. A total of 1836 patients underwent randomization and over 80% ended up being triple negative. After a median follow-up of 2.5 years, the 3-year invasive disease-free survival was 86% in the olaparib group and 77% in the placebo group (HR 0.58; 99.5% CI, 0.41–0.82; $P < 0.001$). Olaparib was associated with fewer deaths than placebo but this difference was not statistically significant at time of publication. Safety data were consistent with known side effects of olaparib, with nausea and fatigue being most common.

Olaparib has now been approved for use as a result of the OlympiA trial in patients with early germline BRCA mutations who are high risk for relapse and represents an alternative to additional chemotherapy after surgery. Although not compared directly to capecitabine, another option in this setting, previous OlympiAD trial that tested PARP inhibitors in the metastatic setting, did allow capecitabine in the chemotherapy arm which ended up being about 45% of the chemotherapy chosen. It is hard to extrapolate to the adjuvant setting but in addition to possible increased efficacy, olaparib is generally better tolerated than capecitabine as well making it the most likely first option for these patients as of this year.

Sacituzumab govitecan

Triple negative breast cancer is defined by the absence of markers. Other than PD-L1 and BRCA

mutations, no other markers were previously identified that could be targeted in this group. One drug recently has brought us a step closer to that goal.

Sacituzumab govitecan-hziy is the second antibody–drug conjugate approved in breast cancer (after ado-trastuzumab emtansine for HER2 positive disease) [10▪]. It combines a humanized monoclonal antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2), with SN-38 (an active metabolite of irinotecan and a topoisomerase inhibitor). These two components are linked by a cleavable linker. Sacituzumab govitecan-hziy enables delivery of high concentrations of SN-38 to tumors. In a phase I/II randomized trial, patients with advanced triple negative breast cancer who had been treated with at least two prior lines of chemotherapy were enrolled in a single arm trial to receive sacituzumab govitecan-hziy on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxic effects. A total of 108 patients received sacituzumab govitecan-hziy at a dose of 10 mg per kilogram of body weight. In this heavily pretreated patients with metastatic breast cancer, response rate was 33% for a median duration of 7.7 months. Although not compared to other regimens and study did not test cancers for expression of Trop-2 antigen, it is a more targeted approach than traditional chemotherapy. It was approved by the FDA in June of 2020. Hope is that many more targeted drugs are yet to come.

CONCLUSION

Triple negative breast cancer continues to lack the number of targeted therapies available in ER+ or HER2+ breast cancers. However, the past two years have seen treatments show promise in triple negative breast cancer that have yet to work in other types of breast cancer, such as immunotherapy, flipping the paradigm. PD-L1 positive and BRCA mutation positive triple negative breast cancer patients now have additional options. As we continue to understand different subtypes of triple negative breast cancer, hope is that more targeted therapies will be developed that move us more away from traditional chemotherapy for the treatment of this aggressive type of breast cancer.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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