Triple-Negative Breast Cancer

Introduction:

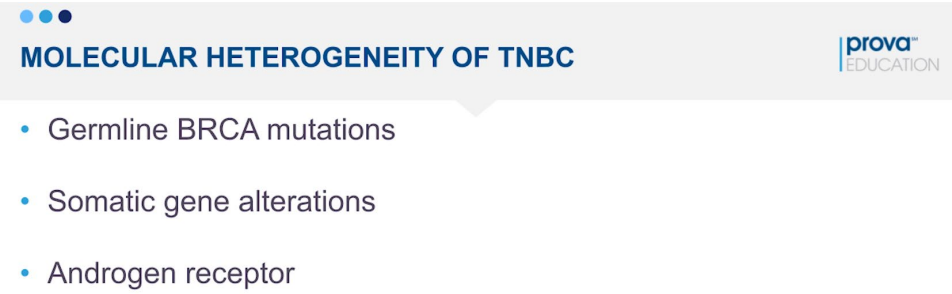
Traditionally, triple-negative breast cancer (TNBC) has been classified as an aggressive malignancy defined by what it is lacking – namely, malignant cells which express the estrogen receptor, progesterone receptor or human epidermal growth factor receptor 2 (HER2). In addition, the median overall survival (OS) for patients with metastatic TNBC typically ranges from 8-13 months. These characteristics present significant therapeutic challenges, as patients with TNBC do not benefit from anti-hormonal or HER2-targeting therapies; consequently, for many years, standard treatment for this patient population has consisted of various combinations of cytotoxic chemotherapy. As a result, novel therapies are needed to face these significant clinical challenges.

With the advance of genomic technologies, efforts are ongoing to molecularly classify this genetically heterogeneous malignancy. It is hoped that the added information concerning molecular drivers for this malignancy will yield targetable therapies for these patients.

TNBC Heterogeneity:

Currently, the molecular heterogeneity of TNBC is categorized based upon the following criteria: the patient's germline *BRCA1/2* mutation status, the presence of somatic mutations which could serve as oncogenic drivers for the disease, and the presence of the androgen receptor. [See Table 1]

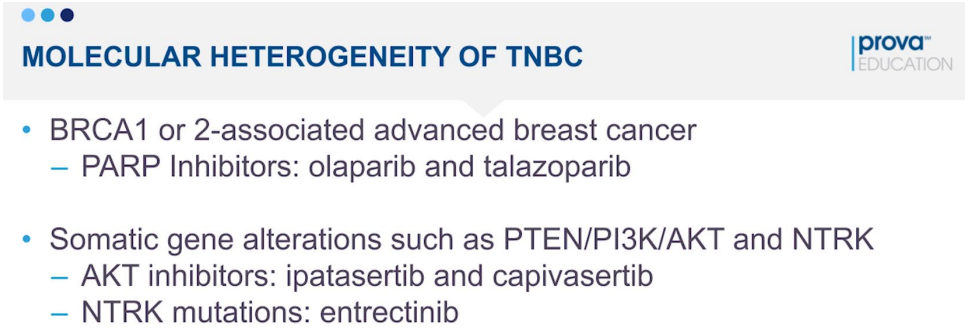
Table 1: Molecular Heterogeneity of TNBC



Germline mutations to *BRCA1/2* impair the patient's ability to repair double-strand DNA breaks, and consequently, makes their disease susceptible to a class of compounds known as poly (ADP-ribose) polymerase (PARP) inhibitors.

Somatic mutations which may be targetable include those in the PI3K/AKT or PTEN pathways. Clinical investigation in the TNBC setting is ongoing for the AKT inhibitors ipatasertib and capivasertib. In addition, a subset of breast cancer patients have mutations to the neurotrophic tyrosine receptor kinase (*NTRK*) gene. Although only approximately 1% of patients with breast cancer have a mutation to *NTRK*, roughly 2/3 of those have TNBC.

Table 2: Treatments Targeting the Molecular Heterogeneity of TNBC



More research needs to be done in order to effectively treat those patients having TNBC which expresses the androgen receptor. Response rates seen for the blockade of this receptor in these patients have frequently been less than 20%.

***BRCA1/2* Mutations:**

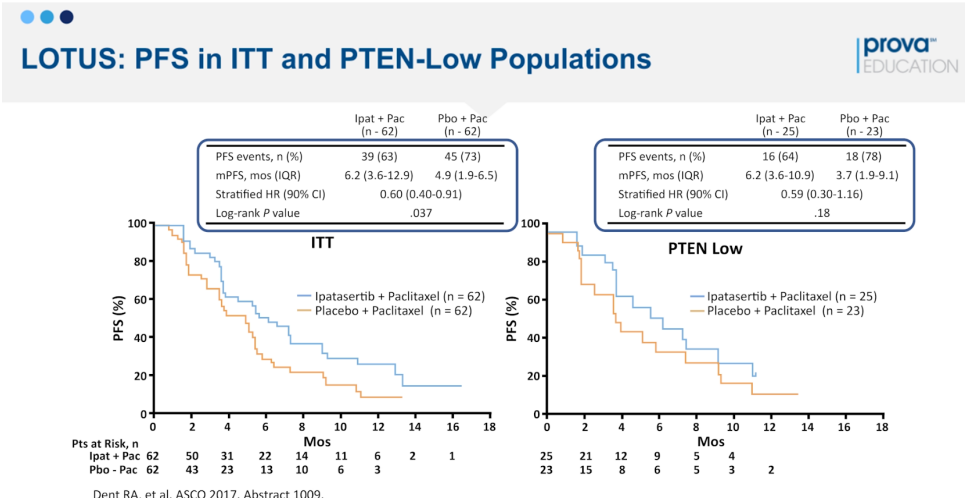
In January 2018, the FDA granted regular approval to olaparib, the first-in-class PARP inhibitor for the treatment of patients having germline *BRCA1/2*-mutant, HER2- metastatic breast cancer who received prior chemotherapy (adjuvant, neoadjuvant, or metastatic setting). This approval was based on the results obtained in the OlympiAD clinical trial (NCT02000622), a study in which eligible participants received either olaparib or physician's choice of chemotherapy (capecitabine, vinorelbine, or eribulin).

In October 2018, a second PARP inhibitor, talazoparib, was approved by the FDA for patients having germline *BRCA1/2*-mutated, HER2-, locally-advanced or metastatic breast cancer. Patient selection for treatment was contingent upon *BRCA1/2*-mutation confirmation using the FDA-approved companion diagnostic. The approval letter cited results obtained in the EMBRACA trial (NCT01945775), which compared talazoparib with physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in patients with *BRCA1/2*-mutant, HER2-, locally-advanced or metastatic breast cancer.

Somatic Mutations:

Promising OS data were presented at the 2018 ASCO conference for the phase 2 LOTUS study (NCT02162719) which evaluated the AKT inhibitor ipatasertib in combination with paclitaxel in treatment-naïve patients with locally-advanced or metastatic TNBC.[1] [See Figure 1] In the Phase 3 CapItello290 study (NCT03997123), another AKT inhibitor, capivasertib, is being evaluated in combination with paclitaxel in treatment-naïve patients with locally-advanced or metastatic TNBC.

Figure 1: LOTUS Trial Results



In August 2019, the FDA granted approval for the use of entrectinib in patients having a solid tumor with confirmed *NTRK* fusions, a rare mutation that occurs in around 0.1% of cases of TNBC. This approval cited results obtained in the STARTRK-2 (NCT02568267), STARTRK-1 (NCT02097810), and ALKA-372-001 (NCT02097810) trials. This approval continued the recent paradigm of tissue-agnostic approvals based on common biomarkers seen across a variety of tumor types. Prior examples of this include the May 2017 approval for pembrolizumab in patients with microsatellite instability-high or mismatch repair-deficient malignancies and the November 2018 approval of larotrectinib for *NTRK* fusion+ solid tumors lacking a known acquired resistance mutation.

Immunotherapies:

TNBC is considered to be one of the most immunogenic breast cancer subtypes. Clinical studies have shown that the enhanced presence of tumor-infiltrating immune cells (TIICs) was associated with improved clinical benefit in these patients.[2] One hallmark for cancer progression is the evasion of malignant cells via immunosuppression in the tumor microenvironment (TME). Considerable research has focused on the role of checkpoint inhibitors in TME immunosuppression, especially the blockade of the programmed cell death-1 (PD-1) receptor/programmed death-ligand 1 (PD-L1) pathway.

KEYNOTE-173 (NCT02622074) & KEYNOTE-522 (NCT03036488):

In the phase 1b KEYNOTE-173 trial, patients with locally-advanced TNBC received the anti-PD-1 antibody pembrolizumab with a variety of different chemotherapy combinations, including either taxane alone followed by anthracycline, or taxane-platinum followed by anthracycline-based therapy.[3] The pathologic complete response (pCR) rate in the study was around 60%, while the 12-month event-free survival (EFS) rates were 100% for those achieving pCR and 88% for those who did not. The investigators concluded that as a neoadjuvant therapy, pembrolizumab + chemotherapy yielded promising antitumor activity with a manageable toxicity profile, which supported the ongoing KEYNOTE-522 trial.

In KEYNOTE-522, the use of pembrolizumab + chemotherapy vs. placebo + chemotherapy as neoadjuvant therapy and pembrolizumab vs. placebo as adjuvant therapy was evaluated in patients with TNBC. Results presented at ESMO 2019 showed that as a neoadjuvant therapy, the addition of pembrolizumab to taxane-platinum followed by doxorubicin-cyclophosphamide (AC) or epirubicin-

cyclophosphamide (EC) led to a significantly improved pCR rate compared to those who did not have immunotherapy.[4] At the first interim analysis (data cutoff: September 24, 2018), 64.8% of the pembrolizumab + chemotherapy patients and 51.2% of the placebo + chemotherapy patients showed a pCR [See Figure 2]; these results were statistically significant, with P=0.00055. At the second interim analysis (data cutoff: April 24, 2019), the 18-month EFS rates were 91.3% and 85.3% respectively for the pembrolizumab + chemotherapy and placebo + chemotherapy patients respectively [See Figure 3]. The EFS data afforded a hazard ratio (HR) of 0.63 (95% CI: 0.43-0.93).

Figure 2:

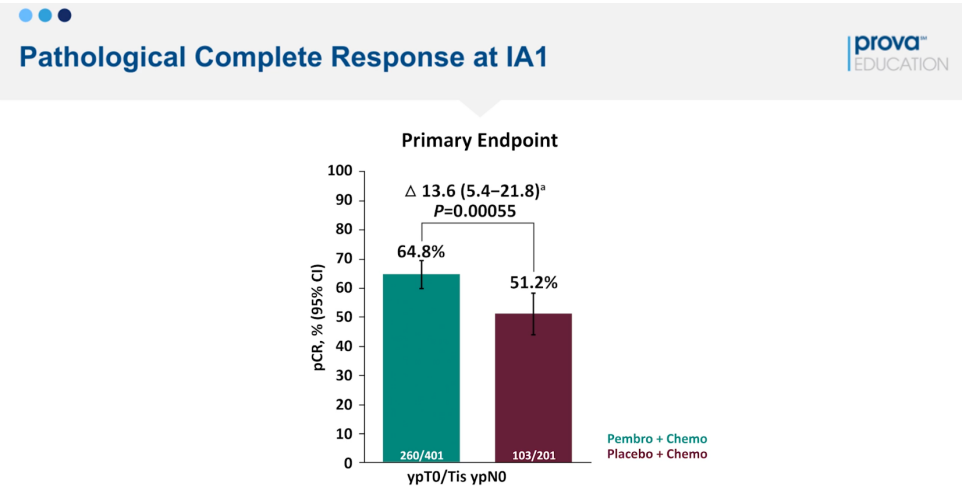
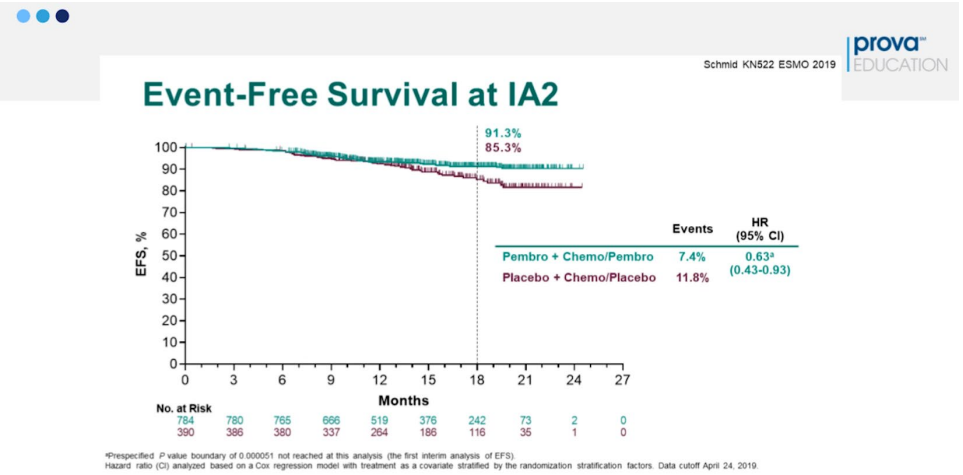


Figure 3:



From these data, the investigators concluded that in the neoadjuvant setting, pembrolizumab plus chemotherapy significantly increased the pCR rate over that of chemotherapy plus placebo in patients with early TNBC. In addition, although EFS data were not mature enough to draw conclusions, they were trending in the right direction with the neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab regimen. In this study, positive clinical response to pembrolizumab was noted, regardless of whether the TIICs were PD-L1+ (i.e. PD-L1 expression on ≥1% of TIICs).

IMpassion130 (NCT02425891):

The Phase 3 IMpassion130 clinical trial evaluated the use of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) in combination with the anti-PD-L1 antibody atezolizumab or placebo in treatment-naïve patients with TNBC.[5]

In the intention-to-treat population, the median progression-free survival (PFS) was 7.2 months for atezolizumab plus nab-paclitaxel and 5.5 months for placebo plus nab-paclitaxel, affording an HR for progression or death of 0.80 (95% CI: 0.69-0.92; P=0.002). [See Figure 4] In the same patient population, the median OS for the same treatment arms were 21.3 months and 17.6 months respectively, providing an HR for death of 0.84; (95%CI: 0.69-1.02; P=0.08). [See Figure 5]

Figure 4:

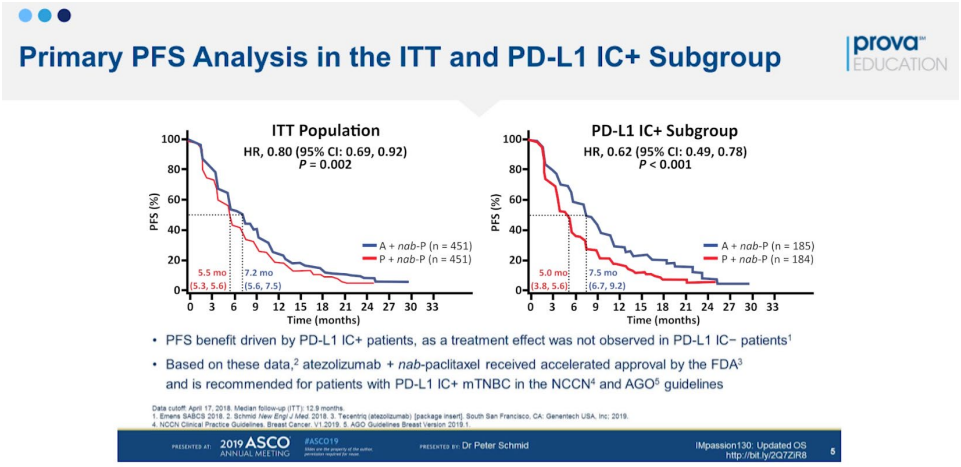
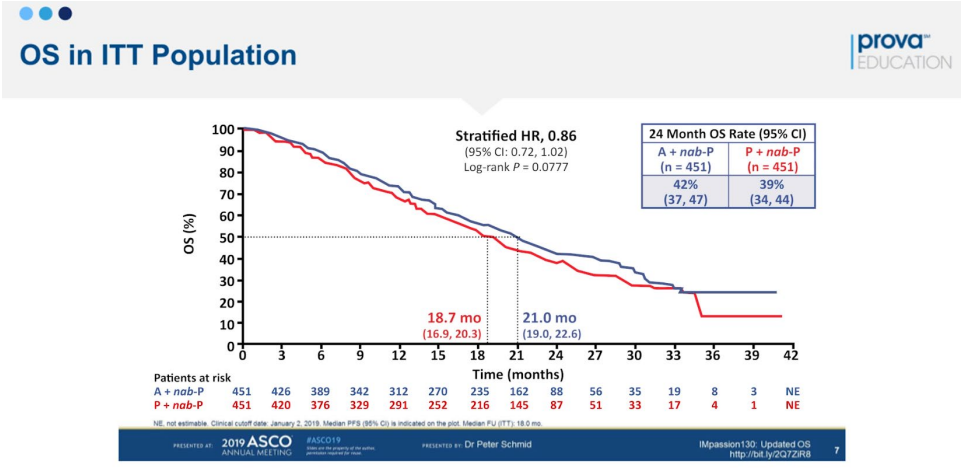


Figure 5:



In patients PD-L1+ TIICs, the median PFS values were 7.5 months and 5.0 months for the atezolizumab plus nab-paclitaxel and placebo plus nab-paclitaxel patients respectively, providing an HR of 0.62 (95% CI: 0.49-0.78; P<0.001). Among the patients with PD-L1+ disease, the median OS values were 25.0

months and 18 months, respectively for the same treatment arms, providing an HR of 0.62 (95% CI: 0.45-0.86; not statistically-tested).

This study revealed that the assay used to determine PD-L1-positivity is rather important. If a patient is PD-L1+ by the Ventana SP142 assay, then they were also likely to be positive by one of the other PD-L1 assays (e.g. the Dako 22C3 or the Ventana SP263); however, it was not readily apparent if the same clinical benefit would be present if the tumor was PD-L1- by SP142, yet positive by one of the other assays. Given these data, it is thought that the SP142 antibody was the one which was most likely to provide the greatest benefit with atezolizumab in combination with nab-paclitaxel, and thus should be the assay used for testing the TIICs in these patients prior to therapy initiation.

Discussion:

The only clinical data which support the use of checkpoint inhibitor-based immunotherapy as a standard of care in metastatic TNBC comes from the IMpassion130 trial. The PFS data showed a clear trend for benefit with atezolizumab in both the ITT and PD-L1+ populations, however, statistical significance was only noted in those with PDL1+ TIICs. Highly statistically significant improvement in OS, of approximately 7 months, was only noted in the PD-L1+ population. Although atezolizumab is generally well-tolerated, serious adverse events do often occur with its administration; consequently, if a patient's TIICs were clearly PD-L1-, it may not be advisable for the patient to receive atezolizumab. As an alternative, one might search for germline *BRCA1/2* mutations, and if present, offer FDA-approved PARP inhibitor therapy. In the absence of such anomalies, one might consider doing next-generation sequencing to test for rarer mutations, microsatellite instability, or mismatch repair deficiency. Such analyses could yield mutations which are amenable to targetable therapies. If targetable mutations are not readily apparent, a clinician may consider finding appropriate clinical trials for their patients, or perhaps, treat with standard chemotherapy.

References:

1) R. Dent R, S-A. Im, M. Espie, et al. Overall survival (OS) update of the double-blind placebo (PBO)-controlled randomized phase 2 LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for locally advanced/metastatic triple-negative breast cancer (mTNBC). Presented at: 2018 ASCO Annual Meeting; June 1-5, 2018; Chicago, IL. Abstract 1008

2) L. Emens, C. Cruz, J.P. Eder, et al. Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer - A Phase 1 Study. *JAMA Oncol*. 2019; 5(1): 74–82.

3) P Schmid, YH Park, E Muñoz-Couselo, et al. Abstract PD5-01: KEYNOTE-173: Phase 1b multicohort study of pembrolizumab (Pembro) in combination with chemotherapy as neoadjuvant treatment for triple-negative breast cancer (TNBC). *Cancer Res*. 79(S4):PD5-01; DOI: 10.1158/1538-7445.SABCS18-PD5-01

4) P. Schmid. 'KEYNOTE-522: Phase 3 study of pembrolizumab (pembro) + chemotherapy (chemo) vs placebo (pbo) + chemo as neoadjuvant treatment, followed by pembro vs pbo as adjuvant treatment for early triple-negative breast cancer (TNBC)'. LBA8_PR. *Annals of Oncology*. 2019; 30(S5); LBA8_PR.

5) P. Schmid, S. Adams, H.S. Rugo, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med* 2018;379:2108-2121.