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Breast Cancer (EA Comen, Section Editor)

Targeted Therapies for Triple-Negative Breast Cancer

Tomas G. Lyons, MD

Address
Breast Medicine Service, Memorial Sloan Kettering Cancer Center, 300 E. 66th Street, New York, NY, 10065, USA
Email: lyonst@mskcc.org

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Opinion statement

Triple-negative breast cancer (TNBC) is a particularly aggressive subtype of breast cancer. TNBC is a heterogenous subtype of breast cancer that is beginning to be refined by its molecular characteristics and clinical response to a targeted therapeutic approach. Until recently the backbone of therapy against TNBC has been cytotoxic chemotherapy. However, the breast oncology community is now seeing encouraging clinical activity from molecularly targeted approaches to TNBC. Recently, we have seen 3 newly approved targeted therapies for TNBC, including the PARP inhibitors olaparib and talazoparib for germline BRCA mutation associated breast cancer (gBRCAm-BC) and most recently the checkpoint inhibitor, atezolizumab in combination with nab-paclitaxel for programmed death-ligand 1 (PD-L1+) advanced TNBC. Improved biomarkers are needed to inform better patient selection for treatment with checkpoint inhibition. Higher response rates are seen when checkpoint inhibitors are combined with chemotherapy in the first-line setting and the use of these agents at an earlier stage of the disease does show promise. Antibody-drug conjugates are generating much excitement and may allow re-examination of prior cytotoxics that failed in development due to toxicity. Tumor sequencing is identifying potential molecular targets and ongoing studies are evaluating novel small molecule agents in this field such as AKT inhibition and many others. The treatment paradigm of chemotherapy as "one size fits all" approach for management of TNBC is changing based on molecular subtyping. Soon, the term TNBC may no longer be appropriate, as this heterogenous subtype of breast cancer is further refined by its molecular characteristics and clinical response to a targeted therapeutic approach.

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Introduction

Triple-negative breast cancer (TNBC) is characterized by the absence of expression of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2-receptor. TNBC represents approximately 15–20% of all breast cancers and generally has a more aggressive biology, with earlier onset of metastatic disease, visceral metastases, rapidly progressive disease, short response duration to available therapies and inferior survival outcomes [1]. TNBC lacks a standard of care approach guided by tumor biology. However, due to advances in both molecular classification of TNBC and genome sequencing we are identifying potential molecular targets in TNBC [2–4]. Recently, we have seen 3 newly approved targeted therapies for TNBC, including the PARP inhibitors olaparib and talazoparib for germline BRCA mutation associated breast cancer (gBRCAm-BC) and most recently the checkpoint inhibitor atezolizumab in programmed death-ligand 1 (PD-L1+) TNBC. Numerous clinical studies are ongoing investigating a wide range of potential targets in TNBC including PARP inhibition, immune-directed therapy with checkpoint inhibitors, antibody-drug conjugates and molecular targeting e.g. the AKT pathway (see Fig. 1). In this article we review the current data supporting the use of these newer therapeutic agents in TNBC.

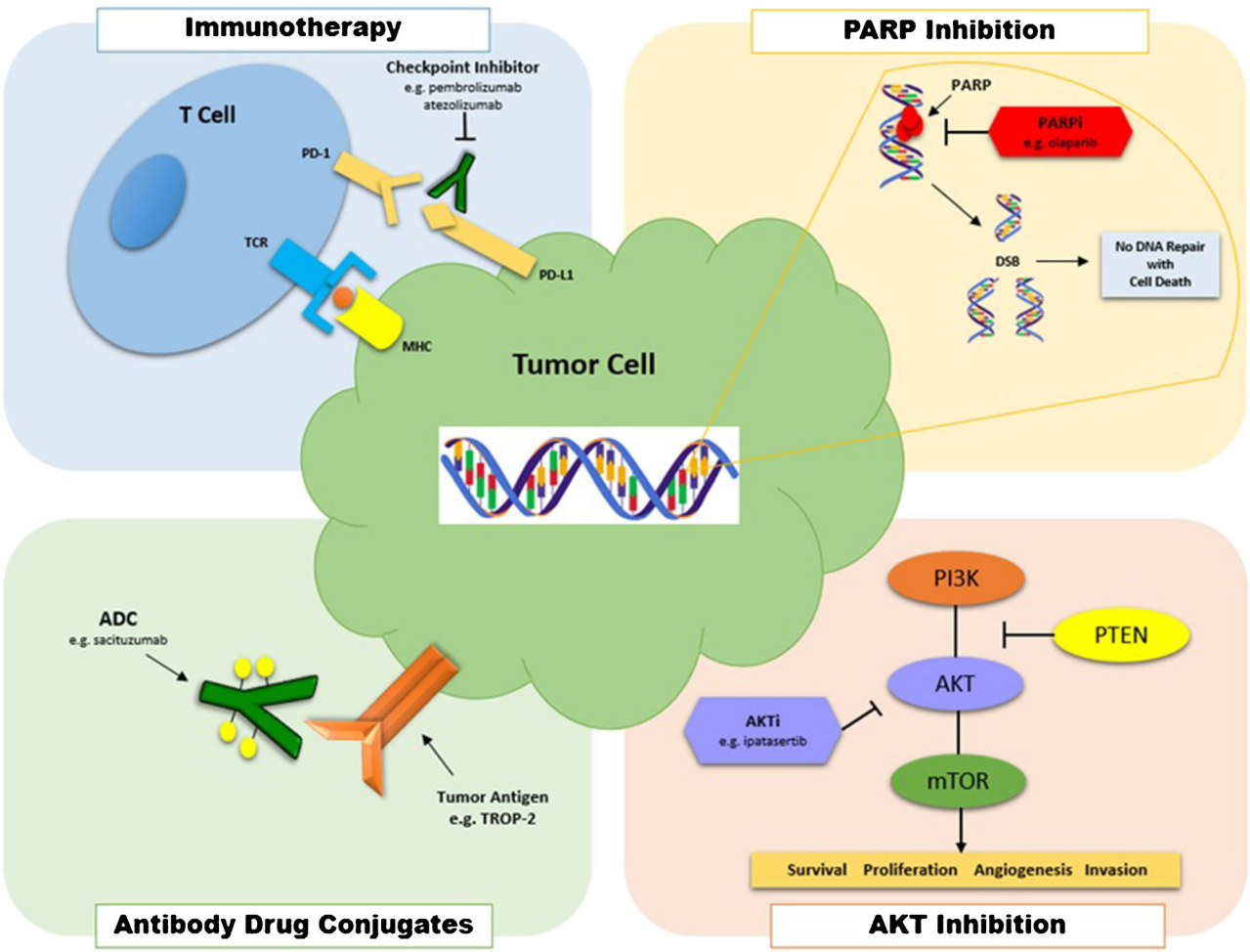

Fig. 1. Emerging therapeutic targets in TNBC

Immunotherapy

Breast cancer has generally not been regarded as an immunogenic tumor. However, tumor-infiltrating-lymphocytes (TILs) have been shown to be present in BC tissues, with a positive association in outcome in both the early-stage and the advanced disease setting in TNBC [5–8]. In addition, tumors with a high mutational burden have superior responses to checkpoint inhibition. TNBC has a higher mutational burden than other BC subtypes [9]. The clinical activity of immune checkpoint inhibitors - cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) and/or programmed death-ligand 1 (PD-L1) has dramatically changed the treatment landscape for many cancers. Many studies are evaluating the role of checkpoint inhibitors in breast cancer, with the most encouraging results to date being in TNBC.

Pembrolizumab in metastatic TNBC

Pembrolizumab, a PD-1 inhibitor, was evaluated in the phase II KEYNOTE-086, single arm study, in advanced TNBC [10]. Cohort A of KEYNOTE-086, evaluated the efficacy and safety of pembrolizumab in 170 patients with previously treated TNBC, regardless of PD-L1 expression. Forty-four percent of patients had three prior lines of chemotherapy in the advanced setting. Sixty-two percent had PD-L1 positive tumors ($n = 105$). The ORR was low at only 4.7%, with 1 patient achieving a complete response (CR) and 7 patients a partial response (PR), in addition to 35 patients having SD. The PFS was similar in both the PD-L1 positive and negative cohorts (2.7 and 1.9 months respectively). There was no significant difference in OS, being 8.9 months in all patients and 8.3 vs 10 months in the PD-L1 positive and negative cohorts respectively.

Cohort B of KEYNOTE-086 evaluated pembrolizumab as first line therapy for patients with PD-L1 positive TNBC. The study enrolled 84 patients, 73 (87%) of which had received prior neoadjuvant or adjuvant chemotherapy. The ORR was 23.1%, with 3 patients achieving a CR and 16 a PR. Twelve of the 19 responses were ongoing at data cutoff, and the median DOR was 8.4 months (range 2.1+ to 13.9+). Median PFS was 2.1 months and median OS was 16.1 months.

Pembrolizumab has also been evaluated in the phase III KEYNOTE-119 (NCT02555657) study. In this trial, 622 patients with advanced TNBC were randomized 1:1 to receive pembrolizumab compared with single-agent physician's choice chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) as second- or third-line therapy. The official results have not been presented but a press release in May 2019 stated that pembrolizumab failed to meet its primary endpoint of OS. Results are due to be presented at an upcoming meeting.

Additional studies are ongoing evaluating pembrolizumab in TNBC, including the KEYNOTE-355 (NCT02819518) and KEYNOTE-522 (NCT03036488) studies.

Atezolizumab in metastatic TNBC

The Impassion130 (NCT02425891) is a phase III randomized study evaluating nab-paclitaxel plus the PD-L1 inhibitor atezolizumab vs nab-paclitaxel plus placebo in patients as first line therapy for metastatic or inoperable locally advanced TNBC [11•]. Prior neoadjuvant or adjuvant therapy was allowed if >12 months from end of therapy. Patients were stratified by PD-L1 which was defined as positive if >1% staining on immune cells. The co-primary endpoints were PFS and OS in ITT and PD-L1+ population. The primary endpoint of PFS was to be assessed in both ITT and PD-L1+ population. First interim OS analysis was to be tested in ITT population and only if significant, would the investigators then test OS in the PD-L1+ population. In total 902 patients were randomized (1:1) with 41% of patients being PD-L1+ in both arms. The median follow-up was 12.9 months. The PFS was improved by just over 1.5 months in the ITT population with the combination of atezolizumab to nab-paclitaxel, 7.2 months vs 5.5 months (HR 0.80; CI 0.69 to 0.92; $P = 0.002$). In the PD-L1+ patients the PFS was improved by 2.5 months with atezolizumab. PFS was 7.5 months vs 5.0 months, respectively (HR, 0.62; 95% CI, 0.49 to 0.78; $P < 0.001$). OS in the ITT population was improved by approx. 4 months with atezolizumab. The median OS was 21.3 months with atezolizumab and 17.6 months with placebo (HR, 0.84; 95% CI, 0.69 to 1.02; $P = 0.08$). However, this was not statistically significant. In the PD-L1+ population the difference in OS was much greater at an impressive 10.5 months, with 54% of patients alive at 2 years. Median OS was 25.0 vs 15.5 months, respectively (HR, 0.62; 95% CI, 0.45 to 0.86). The HR was 0.62 but this could not be formally tested as the OS difference in ITT was not shown to be significant. No new safety signals were seen for either drug. Based on Impassion130, the FDA granted accelerated approval for atezolizumab in combination with nab-paclitaxel for the treatment of patients with unresectable locally advanced or metastatic PD-L1+ TNBC. This marks the first checkpoint inhibitor to be approved for use in breast cancer. We also await the outcome of Impassion131, a similar design phase III trial of atezolizumab + paclitaxel vs paclitaxel + placebo as first line therapy in TNBC, to see if a similar survival benefit is observed in the PD-L1+ population (NCT03125902).

Checkpoint inhibition combined with chemotherapy in the neoadjuvant setting

Pembrolizumab has also been investigated in the neoadjuvant setting. The KEYNOTE-173, is a phase Ib study of pembrolizumab plus chemotherapy as neoadjuvant therapy for locally advanced TNBC [12]. Patients were enrolled into 1 of 2 cohorts; cohort A - pembrolizumab plus weekly nab-paclitaxel (125 mg/m2) followed by pembrolizumab plus doxorubicin and cyclophosphamide (AC) every three weeks and cohort B - pembrolizumab plus weekly nab-paclitaxel (100 mg/m2) and carboplatin (AUC 6) followed by pembrolizumab plus AC. The pathological complete response (pCR) rate (defined as no invasive residual disease in the breast and lymph nodes; ypT0TisN0)

Table 1. Selection of ongoing Phase II/III studies of checkpoint inhibitors in TNBC

Drug	Trial Identifier	Phase	BC Subtype	Neoadjuvant	Adjuvant	1st line metastatic	≥2nd line metastatic	Target Accrual Status
Pembrolizumab	KEYNOTE-119 (NCT02555657)	III	TNBC				Pembrolizumab vs single agent chemotherapy of physicians choice*	600 Ongoing
	KEYNOTE-355 (NCT02819518)	III	TNBC			Pembrolizumab + P or NP or GC vs placebo + P or NP or GC		858 Recruiting
	KEYNOTE-522 (NCT03036488)	III	TNBC	Pembrolizumab + PC-AC or EC vs Placebo + PC-AC or EC				855 Ongoing
	(NCT02954874)	III	TNBC		Pembrolizumab in patients with residual disease (>1 cm and/or positive nodes) post standard NACT			1000 Recruiting
Atezolizumab	IMpassion131 (NCT0312590)	III	TNBC			Atezolizumab + P vs placebo + P		540 Recruiting
	Impassion031 (NCT0319793)	III	TNBC	Atezolizumab + NP-AC vs Placebo + NP-AC				204 Recruiting
	NCT03281954	III	TNBC	Atezolizumab + PC-AC or EC vs Placebo + PC-AC or EC				1520 Recruiting
Durvalumab	DORA (NCT0316761)	II	TNBC				Durvalumab + olaparib vs olaparib in TNBC patients following response to platinum	60 Planned

Pembro, pembrolizumab; BC, breast cancer; TNBC, triple-negative breast cancer; ER+, estrogen receptor positive; HER2+, human epidermal receptor positive; pCR, pathological complete response; NP, nab-paclitaxel; P, paclitaxel; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; GC, gemcitabine and carboplatin; NACT, neoadjuvant chemotherapy

*choice of chemotherapy incudes, capecitabine, eribulin, gemcitabine and vinorelbine

was 60% (90% CI, 30–85) in cohort A ($n = 10$) and 90% (90% CI, 61–100) in cohort B (n = 10). There were no new safety signals observed with the combination of pembrolizumab and chemotherapy.

Pembrolizumab was also evaluated in the phase II, neoadjuvant, adaptively randomized, multicenter I-SPY2 trial [13]. The goal of this trial design is to efficiently identify promising agents to take to phase III with a high probability of success. A total of 249 patients were randomized, 69 to receive pembrolizumab in combination with weekly paclitaxel and 180 patients to weekly paclitaxel alone in the control arm, and all patients then continued to receive neoadjuvant AC, followed by surgery. Pembrolizumab was not continued in the adjuvant setting. Forty patients in the pembrolizumab arm had ER+ disease and 29 had TNBC. It is worth noting that the results are estimated pCR rates, as raw pCR rates are biased due to the adaptive design of the trial. If the predicted probability of success in a phase III trial of 300 patients was >85%, then the drug would graduate from the trial. Findings showed that the estimated pCR rate (ypT0/Tis and ypN0) was significantly higher with the addition of pembrolizumab in patients with TNBC than in the control arm; (60% vs 20%; HR 0.60; 95% CI 0.43–0.78), with a > 99% probability of success in a phase III study. A phase III study is currently underway (KEYNOTE-522 NCT03036488). See Table 1 for a selection of ongoing studies.

PARP inhibition

Poly (ADP-ribose) polymerase enzymes are essential for DNA damage repair. Cancers with defective homologous recombination DNA repair, such has BRCA1 and BRCA2 mutated breast cancer are targets for inhibition with PARP inhibitors (PARPi). The prevalence of a BRCA mutation is approximately 20% in an unselected TNBC population [14]. There are currently several PARPi in clinical development, including olaparib, veliparib, niraparib, rucaparib and talazoparib.

Olaparib

Early phase II studies of olaparib in gBRCAm-BC showed encouraging response rates [15–17]. OlympiAD was a randomized, open-label, phase III trial evaluating olaparib monotherapy compared with physician's choice conventional chemotherapy (capecitabine, eribulin or vinorelbine) [18•]. Patients could have received neoadjuvant or adjuvant platinum chemotherapy if more than 12 months at elapsed since last dose. In addition, prior use of platinum in the metastatic setting was allowed if the patients had not progressed on platinum. Three hundred and two patients having received no more than 2 prior therapies in the advanced setting were randomized in a 2:1 ratio to olaparib or chemotherapy. After a median follow-up of 14.5 months, progression-free survival (PFS) was significantly prolonged with olaparib vs. chemotherapy (7.0 months vs. 4.2 months; HR 0.58 [95% CI 0.43 to 0.8]; $p < 0.001$). The response rate in the olaparib group was also increased (59.9% vs. 28.8%). At planned interim analysis, there was no difference in overall survival (OS) between the 2 groups. There were no new safety signals observed. Health related quality of life measures favored olaparib over treatment of physician's choice. Olaparib was the first PARPi to demonstrate superior efficacy and better tolerability compared

with standard chemotherapy for gBRCAm-BC and has resulted in FDA approval in this patient subgroup.

Talazoparib

Talazoparib is another PARPi undergoing evaluation in breast cancer. The EMBRACA study tested talazoparib as monotherapy in patients with gBRCAm-BC compared to physician choice therapy (capecitabine, eribulin, gemcitabine, or vinorelbine) [19•]. In this open-label, phase III study, 287 patients were randomized to talazoparib at 1 mg daily and 144 patients to chemotherapy. All patients had gBRCAm-BC, HER2-negative advanced disease and could have received no more than 3 prior lines of chemotherapy in the advanced setting. Patients could have received neoadjuvant or adjuvant platinum chemotherapy if more than 6 months at elapsed since last dose. In addition, patients could have received but not have progressed on a platinum in the metastatic setting. The median PFS, which was the primary endpoint, was significantly improved with talazoparib compared with the chemotherapy arm (8.6 months vs 5.6 months, HR = 0.542, $P < .0001$). In addition, the ORR was superior for talazoparib (62.6% vs 27.2%, HR = 4.99, $P < .0001$). An interim analysis of overall survival appeared to show a positive trend in favor of talazoparib, although these data are immature. Quality-of-life measurements revealed that in the talazoparib arm, patients had a significant delay in the time to clinical deterioration, which was 24.3 months for patients on talazoparib, vs 6.3 months for those on standard-of-care chemotherapy. Based on the results from the EMBRACA study, talazoparib has also received FDA approval for patients with gBRCAm-BC.

Veliparib

A phase II study of single agent veliparib demonstrated a PFS of 5.2 months with RR of 14% and 36% for BRCA1 and BRCA2 patients respectively [20]. Results of combining veliparib with carboplatin and paclitaxel in the randomized phase II BROCADE study in patients with gBRCAm-BC have been published in abstract form [21]. The combination resulted in a significantly improved ORR compared with carboplatin/paclitaxel and placebo (77.8% vs. 61.3% $p = 0.027$). The PFS was 14.1 months for the veliparib arm vs. 12.3 months for placebo, which was not statistically significant. There was no increase in toxicity reported between the 2 arms. A confirmatory phase III 'BROCADE 3' study is currently ongoing (NCT02163694).

PARP inhibition in early stage breast Cancer

The OlympiA trial (NCT020032823), is a phase III randomized study, evaluating olaparib at a dose of 300 mg twice daily for 1 year in patients with gBRCA1/2 mutation with residual disease post neoadjuvant chemotherapy or patients with node positive TNBC or node-negative TNBC with a tumor measuring ≥2 cm following adjuvant chemotherapy or ER+ patients with ≥4 nodes following surgery and adjuvant chemotherapy.

Veliparib in combination with neoadjuvant chemotherapy was evaluated in unselected TNBC patients as part of the I-SPY 2 study [22]. The predicted pathological complete response rate (pCR) was 51% versus 26% in the control arm. However, results of the phase III BRIGHTNESS study, of the addition of veliparib to carboplatin vs. carboplatin vs. placebo followed by standard chemotherapy in the neoadjuvant setting in patients with TNBC failed to show an improvement in pCR for the combination of veliparib and carboplatin vs. carboplatin (53% and 58% respectively) [23].

Lastly, talazoparib was tested as monotherapy in the neoadjuvant setting for patients with a gBRCAm-BC (NCT02282345). This phase II study enrolled 20 women with stage I–III gBRCAm-BC [24]. Seventeen of the women had triple-negative disease. Patients were treated with 6 months of talazoparib followed by surgery and with appropriate adjuvant chemotherapy (1 patient withdrew consent after 5 months of therapy). The study's primary endpoint was residual cancer burden (RCB) or pCR. Results showed that 53% of patients (10 of 19) achieved a pCR, or a score of RCB0; combined, 63% (12 of 19) received a score of RCB0 and RCB1. A larger single arm Phase II study is currently ongoing (NCT03499353).

PARP inhibitors combined with immunotherapy

Combining PARPi with immunotherapy is an attractive scientific strategy with minimal additional toxicity expected and may result in enhanced clinical activity given the greater genomic instability in BRCA mutated cancers.

The MEDIOLA trial is a phase I/II open-label basket study of olaparib and durvalumab (anti-PD-L1 checkpoint inhibitor) in patients with advanced solid tumors [25]. The cohort with HER2 negative and gBRCAm-BC was recently presented. Patients could not have received a PARP inhibitor or immunotherapy, prior anthracycline and taxane was required and prior platinum therapy was allowed. Patients received single agent olaparib for 4 weeks with the addition of durvalumab 1.5 g IV every 4 weeks introduced at week 4. A total of 25 patients were enrolled, 12 (48%) having ER positive disease and 13 (52%) having TNBC. The ORR was 67% in patients with no prior therapy ($n = 6/9$), 67% in patients with 1 prior therapy (n = 6/9), 20% in patients with 2 prior therapies ($n = 1/5$) and 0% patients with 3+ prior therapies ($n = 0/2$).

The DORA study is a phase II trial evaluating olaparib plus durvalumab as a maintenance therapy following response to platinum chemotherapy in unselected TNBC (NCT03167619).

Antibody-drug conjugates

Antibody-drug conjugates (ADCs) are a novel anticancer treatment that permit the targeted delivery of a potent cytotoxic 'payload' to cancer cells through the specific binding of an antibody to a selective cancer cell surface molecule. Recent years have seen a number of ADCs enter clinical studies across many cancer types including TNBC. A number of ADCs are being investigated in TNBC. Early results are encouraging with confirmatory studies ongoing or planned.

Sacituzumab Govitecan

Sacituzumab govitecan is an ADC that combines a fully human IgG1 monoclonal antibody against the tumor-associated trophoblast antigen 2 (Trop-2) and SN-38 (7-ethyl-10-hydroxycamptothecin), which is a topoisomerase I–inhibiting drug. Irinotecan is the prodrug of SN-38. However, SN-38 has a 100- to 1000-fold higher potency than irinotecan. Therefore, sacituzumab govitecan can deliver higher levels of SN-38 to the cancer cells. Trop-2 is overexpressed in many epithelial cancers and has been shown to be expressed in >80% of TNBC. A phase I dose-finding trial in advanced solid cancers, including metastatic TNBC showed encouraging activity. The single arm phase II study of sacituzumab govitecan enrolled 69 patients with heavily pretreated (median 5 lines) TNBC [26]. Results demonstrated an ORR of 30% (19 PRs and 2 CRs). Median PFS was 6.0 months, and median OS was 16.6 months. Trop-2 expression was positive in 88% (48/69) of patients. Grade ≥ 3 adverse events included neutropenia (39%), leukopenia (16%), anemia (14%), and diarrhea (13%); the incidence of febrile neutropenia was 7%. Based on these results the phase III randomized ASCENT trial has commenced and enrolled patients with TNBC who have progressed on ≥2 lines of therapy (NCT02574455). Patients are randomized to sacituzumab govitecan vs physicians' choice chemotherapy (capecitabine, eribulin, gemcitabine and vinorelbine).

Ladiratuzumab Vedotin

Ladiratuzumab vedotin is an ADC composed of a humanized IgG1 and monoclonal antibody targeting LIV-1 and the microtubule inhibitor MMAE. LIV-1 is a transmembrane protein with zinc transporter and metalloproteinase activity. LIV-1 is expressed in more than 90% of breast tumors and has limited expression in normal tissues. A phase 1 study consisted of a dose escalation phase ($n = 81$) and a phase 1b expansion phase ($n = 63$) with metastatic TNBC [27]. The recommended dose for the expansion phase was 2.5 mg/kg, with a maximum dose of 200 mg per cycle. Patients enrolled had received ≥2 cytotoxic regimens (with a median of 4) in the metastatic setting. Ninety percent of metastatic breast tumor samples screened were LIV-1 positive, including moderate to high in 68% of screened TNBC patients. The most frequent toxicities observed included alopecia (40.7%), neutropenia (24.7%) and peripheral neuropathy (19.8%). In the TNBC cohort the ORR was 25.0%, SD rate of 33%, CBR of 28%, and DCR of 58% and median PFS was 13 weeks. Enrollment in the TNBC cohort is ongoing and further evaluation of ladiratuzumab vedotin as monotherapy and in combination with checkpoint inhibitor in TNBC is planned.

Trastuzumab Deruxtecan (DS-8201a)

Trastuzumab deruxtecan is an ADC that targets HER2. It consists of an antibody component which is a humanized immunoglobulin G1 (IgG1) monoclonal antibody produced with reference to the amino acid sequence of trastuzumab,

and a cytotoxic payload exatecan derivative – which is a topoisomerase I inhibitor. This ADC is being investigated in HER2 positive breast cancer and is showing very promising results in patients with refractory HER2+ disease despite prior trastuzumab and T-DM1 based therapy [28]. The phase I study of trastuzumab deruxtecan also enrolled patients with HER2-low breast cancer (defined as IHC 1+/ISH negative or 2+/ISH negative) [29]. Results of this cohort have been presented in abstract form and demonstrated impressive results in heavily pretreated HER2 low breast cancer. TNBC patients were also eligible for enrollment in the study. Thirty-four patients with HER2 low tumors were enrolled. The ORR was 50% (17/34), DCR was 85.3% (29/34) and median PFS had not been reached. The drug is generally well tolerated with GI and hematologic adverse events being the most frequently reported. This drug is generating great excitement not only for HER2 positive disease but also as potential therapeutic option for HER2 low tumors of which TNBC patient may be candidates. Enrollment in larger monotherapy studies in HER2 low breast cancer are ongoing.

Inhibition of the PIK3/AKT/mTOR pathway

Activation of the PIK3/AKT/mTOR pathway is a relatively frequent event in TNBC, through activation of *PIK3CA* or *AKT1* and loss of *PTEN*, which can result in hyperactivation of AKT pathway [30]. Targeting the AKT pathway is an attractive option in TNBC. The phase II LOTUS trial randomized patients with advanced TNBC to first line treatment with paclitaxel in combination with the AKT inhibitor ipatasertib ($n = 62$) or placebo (n = 62) [31]. The combination of paclitaxel/ipatasertib demonstrated an improvement in median PFS 6.2 months vs 4.9 months in the paclitaxel/placebo arm (HR 0.60, 95% CI: 0.37–0.98, $p = 0.037$). In the subset of patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors ($n = 42$), the benefit of ipatasertib was even greater - PFS 9.0 months vs. 4.9 months (HR, 0.44; 95% CI, 0.20–0.99). Interim survival data from the study was recently presented in abstract form and showed a trend in improved median OS of 23.1 months with paclitaxel/ ipatasertib vs 18.4 months with paclitaxel/ placebo [33]. Ipatasertib has been generally well tolerated, with diarrhea being the most frequent treatment-related adverse event. The randomized phase III placebo-controlled study IPATunity130 is currently enrolling patients with *PIK3CA*/*AKT1*/*PTEN*-altered TNBC to first line paclitaxel ± ipatasertib.

The Phase II PAKT study with a similar design to the LOTUS study, investigated the addition of the AKT inhibitor capivasertib to paclitaxel as first-line therapy in 140 patients with metastatic TNBC [32]. The addition of capivasertib resulted in significantly longer PFS (median PFS 5.9 months vs 4.2 months; HR 0.74) and OS (median OS 19.1 months vs 12.6 months; HR 0.61). The most common grade ≥ 3 adverse events were diarrhea, infection, neutropenia, rash, and fatigue.

Lastly, the combination of paclitaxel and ipatasertib is also being evaluated as neoadjuvant therapy in the randomized placebo-controlled phase II FAIRLINE study for stage I-III TNBC (NCT02301988).

Conclusions

Chemotherapy has been the backbone therapy for advanced TNBC for many years, however, we are now entering a new era in TNBC management with a number of novel therapeutic agents driving the field forward. Immunotherapy with checkpoint inhibition holds great promise with the first approved immunotherapy agent, atezolizumab in TNBC. Moving forward, we need to identify biomarkers that will allow enrichment of studies so patients may achieve even greater benefit and possibly carve out a subgroup of patients who only need single agent immunotherapy and might avoid the toxicity of chemotherapy. It will be important to develop combination immunotherapy studies, to enhance the immune response so a greater proportion of TNBC patients may benefit not just PD-L1+ patients. PARP inhibition has shown benefit over chemotherapy both in outcome and quality of life in gBRCAm-BC. Use of PARP inhibitors in early stage disease is an important next step and may lead to greater cure rates for patients with gBRCAm-BC. Antibody-drug conjugates are generating much excitement and may allow re-examination of prior cytotoxics that failed in development due to toxicity. Tumor sequencing is identifying potential molecular targets and ongoing studies are evaluating novel small molecule agents in this field such as AKT inhibition and many others.

It is with great hope and optimism that we look to the numerous ongoing and future trials that will further our understanding of the biology TNBC and pave the way to an increased number of treatment options and improved outcomes for our patients.

Compliance with Ethical Standards

Conflict of Interest
Tomas G. Lyons declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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This study resulted in the FDA approval of the first checkpoint inhibitor in breast cancer.

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