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Integrating Immunotherapy in Early-Stage Triple-Negative Breast Cancer: Practical Evidence-Based Considerations

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Abstract

The KEYNOTE-522 study is a practice-changing phase III randomized study that demonstrated that the addition of pembrolizumab to polychemotherapy improves outcomes in patients with high-risk early-stage triple-negative breast cancer (TNBC). This regimen is highly efficacious with unprecedented pathologic complete response (pCR) rates, and clinically meaningful improvements in event-free survival (EFS). However, the combination is also associated with significant high-grade treatment-related toxicity. The backbone regimen deviated from common practice, including the addition of carboplatin, lack of dose dense anthracyclines, and adjuvant capecitabine for residual disease, thus brining important questions regarding real-world translation of these results. This brief report practically addresses some of the most relevant questions physicians and patients face in optimizing care using the best available evidence.

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer that lacks expression of the estrogen and progesterone receptors (ER and PR, respectively) and expression or amplification of HER2/neu. Although TNBC is a heterogeneous group of breast cancers of distinct phenotypes, there are limited biomarkers to guide distinct treatment of early-stage disease. Patients with TNBC often present with stage II or III disease and receive neoadjuvant therapy, historically comprising of anthracycline- and taxane-based chemotherapy, which can produce pathologic complete response (pCR) rates of approximately 40%.[1–3] For patients who achieve pCR, prognosis is excellent, with recurrence rates typically, ˂10%; however, for those who do not achieve a pCR, recurrence rates can approach 50%.[4–6] Although an improvement in pCR in a registration study can lead to accelerated approval by the FDA, an event-free survival (EFS) benefit must still be demonstrated.[7–9] Recent studies in patients with TNBC that included neoadjuvant chemoimmunotherapy combinations have shown clinically significant improvement in EFS despite no or modest improvements in pCR.[3,6] The new approval of the PD-1 inhibitor pembrolizumab in combination with chemotherapy in high-risk early-stage TNBC has brought into question several practical considerations. This brief report deciphers the

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available data to provide clinicians guidance to optimize systemic recommendations for patients with early-stage TNBC.

Experience With Neoadjuvant Chemoimmunotherapy

Immune checkpoint inhibitors (ICIs) and specifically PD-1 and PD-L1 inhibitors, have revolutionized cancer care across multiple cancer histologies, and have recently had their first regular approvals in TNBC. The first study to demonstrate potential benefit of the addition of a PD-1 inhibitor to neoadjuvant chemotherapy was the iSPY2 study, in which the pCR rate almost tripled from 22% to 60%.[10] In this study, pembrolizumab was added only to weekly paclitaxel, and all patients received dose-dense (every 2 weeks) doxorubicin and cyclophosphamide (AC). A number of studies have been reported since then, with some, but not all, showing improvements in pCR in the ICI-containing arms (Table 1).[3,6,10–13] One such study, GeparNUEVO, which evaluated the addition of durvalumab to anthracycline and taxane-based neoadjuvant chemotherapy (with no adjuvant durvalumab prescribed), did not demonstrate a statistically significant improvement in pCR, but did show a clinically and statistically significant improvement in EFS in a planned secondary analysis.[3]

KEYNOTE-173 was a noncomparative multicohort phase I study of pembrolizumab added to various neoadjuvant anthracycline and taxane-based regimens in TNBC. The non–carboplatin-containing arm (the taxane used was nab-paclitaxel) was associated with a pCR rate of 55%. Arms that included nab-paclitaxel with carboplatin had the highest pCR rates (60%–80%). The arms that were eventually incorporated into the registration KEYNOTE-522 study (solvent-based paclitaxel was the taxane used) had pCR rates of 25% (carboplatin area under the curve of 2 [AUC2]) and 50% (carboplatin AUC5) in KEYNOTE-173. A pooled analysis demonstrated that the addition of carboplatin improved pCR rates resulting in the incorporation of carboplatin in the subsequent registration study, KEYNOTE-522.[14]

The KEYNOTE-522 study was a registration phase III study evaluating the combination of weekly paclitaxel 1 + carboplatin (AUC1.5 weekly or AUC 5 every 3 weeks) followed by AC every 3 weeks, with or without pembrolizumab in a 2:1 randomization.[6] After surgery, all patients received 9 cycles of pembrolizumab irrespective of pCR result. As we consider the results, it is important to note that the neoadjuvant chemotherapy backbone used was not a standard regimen and that adjuvant capecitabine was not allowed. Although carboplatin can certainly improve pCR rates, confirmatory studies to evaluate its effect on EFS have yet to be reported. Recent post hoc analysis from the BRIGHTNESS study suggested an EFS benefit (hazard ratio [HR], 0.57; 95% CI, 0.36–0.91; P=.018) with the addition of carboplatin to an anthracycline-taxane based regimen, but this was an exploratory analysis and data remain limited.[15] On the other hand, several studies have shown that every-2-week (dose-dense) AC is superior to every-3-week AC, and that the addition of capecitabine to the treatment of patients with residual disease after neoadjuvant chemotherapy can improve both EFS and overall survival (OS); neither dose-dense AC nor adjuvant capecitabine were used in the KEYNOTE-522 study.[16,17]

An initial analysis of KEYNOTE-522 demonstrated that the addition of pembrolizumab resulted in an improvement in pCR from 51.2% to 64.8%, although the pCR benefit was more modest in the final analysis (55.6% vs 63% in the control arm versus pembrolizumab arms, respectively).[6] Nevertheless, a clinically and statistically significant 3-year EFS improvement from 76.8% to 84.5% (HR, 0.63; 95% CI, 0.48–0.82; $P<.001$) was observed in the control versus pembrolizumab arm, respectively.[18] PD-L1 status was not predictive of benefit for pembrolizumab treatment. Among patients achieving a pCR, 3-year EFS rates were high irrespective of arm (92.5% vs 94.4% in the control vs pembrolizumab arm, respectively). Conversely, in those without pCR, EFS rates were disappointingly low in both groups, albeit higher in the pembrolizumab arm (67.4% vs 56.8% in the control arm). Although EFS benefit was seen across all subgroups, it was less clear in patients aged ≥65 years (HR, 0.79; 95% CI, 0.4–1.56) or in those with poor performance status (HR, 0.81; 95% CI. 0.41–1.62).

Notably, the pembrolizumab-containing regimen was associated with significant toxicity, with 77.1% of patients developing high-grade (ie, grade ≥3) treatment-related adverse events (trAEs), including a 0.5% rate of treatment-related death. It is important to note that most of the high-grade toxicity observed was due to chemotherapy; indeed, the control arm had a high-grade trAE rate of 73.3%. Significant toxicity rates were also observed in the adjuvant pembrolizumab phase with a 6.3% rate of high-grade trAE and a 0.3% rate of treatment-related death. As expected, pembrolizumab increased the risk of immune-related toxicity, with 33.5% of patients experiencing immune-mediated adverse events, of which 12.9% were high-grade immune trAEs. In the pembrolizumab arm, 22.3% of patients experienced thyroid abnormalities or thyroiditis, 5.7% severe skin reactions, 4.5% adrenal insufficiency or unspecified hypophysitis, and 2.2% pneumonitis.[18] On July 26, 2021, the FDA granted full approval for pembrolizumab in high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

Practical Considerations in Integrating ICIs in Clinic

Who Should Be Treated With the KEYNOTE-522 Regimen?

The KEYNOTE-522 study enrolled patients with stage II or III TNBC, and therefore, any patient meeting these criteria should be considered. However, can the data we have currently help optimize and balance treatment recommendations in specific patient populations? As mentioned, PD-L1 status was not helpful in discriminating benefit to pembrolizumab. The EFS subgroup analysis demonstrated benefit regardless of nodal status; however, patients with stage II disease appeared to have a lesser improvement in pCR compared with those with stage III (pCR rate improved by 7.8%–11% in stage II, but 24.6%–25.6% in stage III).[19] This is important to note because all patients sustaining pCR had high EFS rates, irrespective of receiving neoadjuvant pembrolizumab. Most importantly, the KEYNOTE-522 results need to be considered in the context of its toxicity; a 77.1% high-grade trAE rate is very high, and ideally alternative less toxic treatment regimens should be considered, especially in patients in whom the benefit of pembrolizumab is less clear. Subgroup analysis, albeit exploratory and with relatively small numbers, demonstrated less

apparent benefit in those with a performance status of 1 and in those who were aged ≥65 years, with HRs crossing "1".[19] These are also subgroups of patients more likely to experience significant toxicity, and clinicians must carefully consider whether to prescribe the KEYNOTE-522 regimen to individual patients. In our internal institutional guidance, we note that standard dose-dense AC/paclitaxel may be considered in older patients and/or those with a performance status >0, especially those with node-negative disease (Figure 1).

Should We Use Carboplatin?

The KEYNOTE-522 regimen used carboplatin in combination with paclitaxel and its efficacy data reflects this specific combination. Thus, it is unknown if a deviation from this regimen would result in inferior net benefit. Although IMpassion031 and GeparNUEVO suggest an EFS benefit using regimens that do not include carboplatin, these were phase II studies, and are insufficient to support omission of carboplatin from the KEYNOTE-522 regimen.[3,6,12] Although limited data suggest possible EFS benefits for carboplatin, definitive studies are still pending.[15] Although physicians must make treatment decisions on an individual basis considering the toxicity of this agent, we do not recommend routinely excluding the incorporation of carboplatin.

Should We Use Dose-Dense AC?

Dose density is associated with improved EFS and OS benefits in anthracycline- and taxane-based regimens that did not include either platinums or ICIs, or additional therapies for patients with residual disease.[16] The KEYNOTE-522 regimen did not include dose-dense AC, and thus the benefits observed with this regimen, which are unprecedented in early-stage TNBC, are independent of dose density. Indeed, it is unclear how dose density would significantly improve outcomes with all of these additional therapies. There are practical considerations of reconciling an every-2-week AC regimen with an every-3-week one, which would increase the complexity of the regimen, in terms of not only additional visits but also uncertainty regarding duration of pembrolizumab, because AC would finish several weeks earlier. Although studies evaluating dose density suggest acceptable toxicity profiles compared with non–dose-dense chemotherapy, the toxicity and feasibility of dose density after 3 months of carboplatin and paclitaxel with pembrolizumab is unknown.[16] For these reasons, and given the benefit of the KEYNOTE-522 regimen as a whole, we favor an every-3-week approach, although dose-dense AC may still be considered as a potential benefit cannot be excluded.

Is There a Role for Other ICIs?

Although data from IMpassion031, which included atezolizumab, closely resemble those from KEYNOTE-522, it was a phase II study. The ALEXANDRA/IMpassion030 study, is a phase III adjuvant study comparing the addition atezolizumab to standard paclitaxel and dose-dense AC (without carboplatin) to the chemotherapy alone, and is expected to provide more definitive data.[20] For now, however, we have insufficient data to recommend using ICIs other than pembrolizumab.

Is Adjuvant Pembrolizumab After pCR Needed?

EFS benefit in those achieving pCR was almost identical between the control and experimental arms (92.5% vs 94.4%, respectively). This analysis of EFS rate in patients achieving pCR in KEYNOTE-522 was exploratory and was not powered to make a definitive conclusion. However, this should be considered in the context of the wealth of data demonstrating the association of pCR with high EFS rates for individuals achieving pCR.[5] Furthermore, although most of the toxicity of the KEYNOTE-522 regimen was seen in the neoadjuvant portion of treatment, the toxicity of single-agent pembrolizumab given adjuvantly was not negligible, with a 6.3% rate of high-grade trAEs, and a 0.3% rate of treatment-related death.[21] It is also notable that the GeparNUEVO investigators reported an improvement in EFS without an adjuvant phase of durvalumab.[3] Given the unclear benefit of adjuvant pembrolizumab in those achieving pCR, and the demonstrated toxicity in the adjuvant phase of treatment, clinicians may discuss potential benefits versus toxicity with individuals to determine whether to continue adjuvant pembrolizumab.

What Adjuvant Therapies Should Be Given to Patients With Residual Disease?

This is a significant area of unmet need given the high rate of recurrence and death in patients not achieving pCR. In KEYNOTE-522, patients who did not achieve a pCR had 3-year EFS rates of 56.8% and 67.4% in the control and experimental arms, respectively. Given that patients included in the study received adjuvant pembrolizumab irrespective of pCR, a benefit for adjuvant pembrolizumab cannot be excluded in those not achieving pCR. The question then becomes how to incorporate other adjuvant therapies.

Several studies have demonstrated the benefit of adjuvant capecitabine, although these studies involved patients who did not receive neoadjuvant immunotherapy.[17,22] The KEYNOTE-522 regimen did not include capecitabine; however, a recent sensitivity analysis that excluded the 44 patients who received off-protocol adjuvant capecitabine demonstrated similar outcomes despite whether capecitabine was used.[21] These data need to be interpreted with significant caution given the very small number of patients who took capecitabine. Although there are additive toxicities that the individual patient receiving combination pembrolizumab and capecitabine may experience, new treatment-emergent toxicities have not been observed.[23] Given the high rates of recurrence in patients who do not achieve pCR, it is reasonable to prescribe concurrent capecitabine with adjuvant pembrolizumab, despite the absence of data.

Another adjuvant consideration in patients with residual disease concerns those with germline *BRCA* mutations. The Olympia study demonstrated that adjuvant olaparib, a PARP inhibitor, significantly improved EFS in patients with a germline *BRCA1* or *BRCA2* mutation who have residual disease after neoadjuvant chemotherapy.[24] Although patients in the Olympia study did not receive neoadjuvant immunotherapy, the separation in EFS occurred early on, suggesting that the introduction of olaparib should not be delayed. Although adjuvant olaparib was not part of the KEYNOTE-522 protocol, the addition of adjuvant olaparib in patients with residual disease and a germline *BRCA* mutation is an attractive consideration because it targets a different pathway. The combination of olaparib and pembrolizumab has been studied, and toxicities described are consistent with

the profile of the individual drug.[25] Thus, administration of olaparib, along with standard pembrolizumab, is reasonable in patients with germline *BRCA* mutations and residual disease after the KEYNOTE-522 regimen.

How Should Adjuvant Radiotherapy Be Sequenced With Adjuvant Systemic Therapies?

Radiotherapy will be recommended for almost all patients who present with node-positive disease, although anticipated data from the NSABP B-51 study may identify a subset of patients who convert from node-positive to node-negative disease after preoperative therapy who do not benefit from radiotherapy.[26,27] Yet the KEYNOTE-522 protocol called for adjuvant radiotherapy "as indicated" and did not specify its timing in relation to the adjuvant portion of the pembrolizumab. Additionally, rates of locoregional failure were not reported in KEYNOTE-522, but it is known from the NeoCT meta-analysis that patients with TNBC who do not achieve a pCR with neoadjuvant therapy have local failure rates as high as 25% at 5 years.[5] Thus, although radiotherapy may be delivered concurrently with pembrolizumab in this setting, the toxicity and locoregional impact of delivering concurrent versus sequential radiotherapy with adjuvant pembrolizumab was not specifically studied, and patients should be counseled about the potential for increased toxicity when both modalities are used together. Given the uncertainties about the role and timing of capecitabine, this therapy will be generally delayed until after radiotherapy even when used in combination with pembrolizumab, but there are no specific data to guide this approach.

Future Considerations

The approval of neoadjuvant pembrolizumab and polychemotherapy has changed the treatment paradigm for patients with early-stage TNBC. New data to further help optimize patient care are on the horizon. The SWOG-1418 study is evaluating the use of single-agent pembrolizumab versus observation in patients with residual disease.[28] Although patients may not have received neoadjuvant ICIs in SWOG-1418, these data will help our understanding of pembrolizumab, specifically in the adjuvant setting. As noted, the use of atezolizumab with a potentially less toxic chemotherapy regimen in IMpassion031 was associated with improvement in pCR, and although initial EFS data are promising, they are derived from a secondary analysis of this phase II study. We await results from the phase III ALEXANDRA/IMpassion030 study.[20] The GeparDouze/NSABP B-59 is another large phase III study evaluating the addition of atezolizumab to paclitaxel with carboplatin and AC (dose-dense or every 3 weeks).[29]

As we continue to refine the use of ICIs in patients with early-stage TNBC, there are several considerations that may help optimize patient care. First, we need better tools to select patients, enabling us to identify those who will do very well with chemotherapy alone from those who will benefit from the addition of pembrolizumab. Clearly PD-L1 status alone in early-stage disease is insufficient as a predictive biomarker, and translational work to better understand the immunologic tumor microenvironment and help us identify responders is critical. Second, for patients with residual disease, understanding primary resistance pathways and identifying novel treatments are critical. Finally, the KEYNOTE-522 regimen represents a ceiling treatment; it is very effective, but also very toxic. Thus, de-escalation

approaches are now warranted. Biomarker discovery and leveraging the neoadjuvant setting to risk-stratify patients will be central to improving patient outcomes and attenuating toxicity.

As we await the next generation of studies, we must tailor therapy to individual patients with thoughtful consideration of evidence-based data, escalating and de-escalating therapies according to risk of disease and toxicity of treatment. It is critical to understand not only the data but also our individual patients with TNBC, involving them in treatment discussions to individually optimize care.

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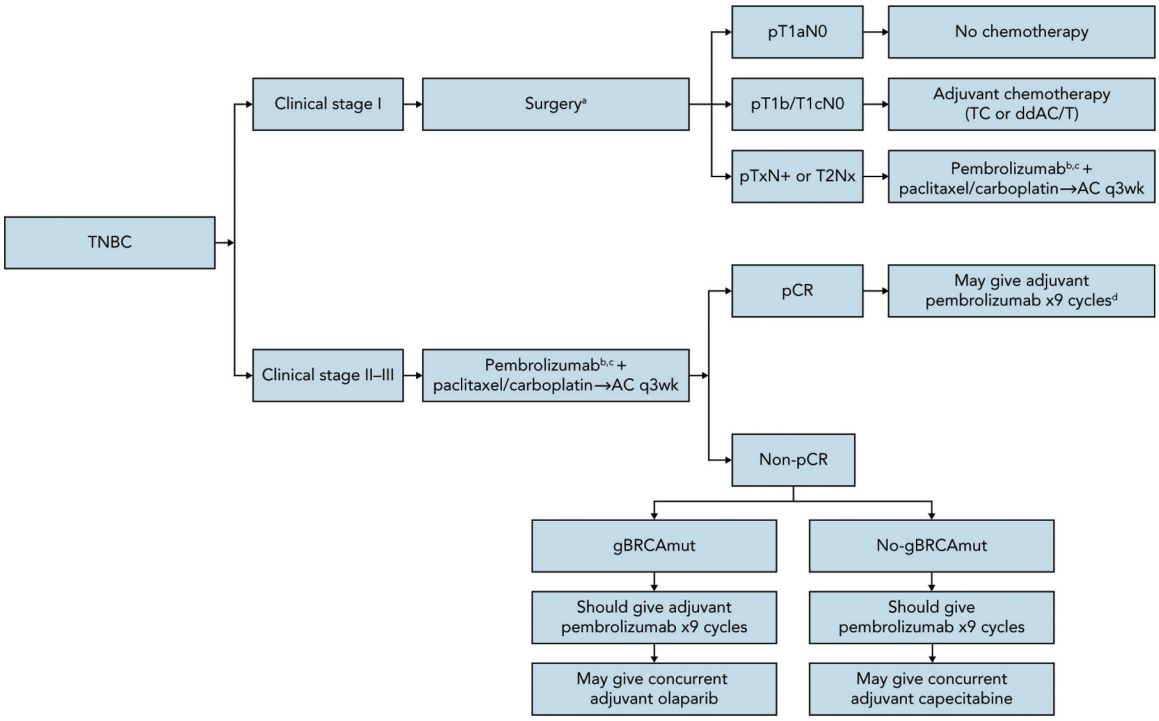

Figure 1.

Guidance in integrating chemoimmunotherapy in early-stage TNBC.

Abbreviations: AC, doxorubicin/cyclophosphamide; ddAC, dose-dense doxorubicin/cyclophosphamide and paclitaxel; g*BRCA*mut, germline *BRCA* mutation; NACT, neoadjuvant chemotherapy; pCR, pathologic complete response; PR, partial response; TC, docetaxel and cyclophosphamide; TNBC, triple-negative breast cancer.

[a]If indication for NACT may consider ddAC/T, patients with stage I disease were not eligible for KEYNOTE-522.

[b]Consider ddAC/T in older patients or those with ECOG performance status >0, especially those with smaller lymph node–negative tumors.

[c]Pembrolizumab as per KEYNOTE-522; other PD-1/PD-L1 agents not approved.

[d]May consider omission in discussion with patient.

Table 1.

Summary of Randomized Studies of Neoadjuvant Chemoimmunotherapy in Early-Stage TNBC

Study	Chemotherapy Regimen	Immunotherapy Agent	Phase (n; IO:control)	pCR Control Arm	pCR IO Arm	3-y EFS Control Arm	3-y EFS IO Arm
KEYNOTE-522[6]	Paclitaxel (weekly)/carboplatin (AUC1.5 weekly or AUC5 q3wk) q3wk ×4 cycles Doxorubicin/ Cyclophosphamide q3wk ×4 cycles	Pembrolizumab	III (n=602; 2:1)	55.6%	63%	76.8%	84.5%
IMpassion 031[12]	Nab-paclitaxel (weekly) ×12 wk Doxorubicin/ Cyclophosphamide q2wk ×4 cycles	Atezolizumab	III (n=455; 1:1)	58%	69%	Immature	
NeoTRIPaPD-1[11]	Nab-paclitaxel (weekly)/carboplatin AUC2 weekly ×2 q3wk, ×8 cycles	Atezolizumab	III (n=280; 1:1)	40.8%[a]	43.5%[a]	Not reported	
ETCTN10013[13]	Paclitaxel (weekly)/carboplatin (AUC5 q3wk) q3wk ×4 cycles	Atezolizumab	II (n=67; 2:1)	18.8%	55.6%	Not reported	
GeparNUEVO[3]	Nab-paclitaxel (weekly) ×12 wk Epirubicin/ Cyclophosphamide q2wk ×4 cycles	Durvalumab	II (n=174; 1:1)	44.2%[a]	53.4%[a]	76.9%	84.9%
iSPY2[10]	Paclitaxel weekly ×12 Doxorubicin/Cyclophosphamide q2wk ×4 cycles	Pembrolizumab (only during paclitaxel)	II (n=250; adaptive)	22%	60%	Not reported	

Abbreviations: AUC, area under the curve; EFS, event-free survival; IO, immunotherapy; pCR, pathologic complete response.

[a]Not statistically significant.

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