



Immune checkpoint inhibition in the treatment of early stage triple negative breast cancer: 2021 update[☆]

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ABSTRACT

There is an emerging body of evidence regarding the use of immunotherapy in early-stage triple negative breast cancer (TNBC), with the recent publication of several phase III and randomised phase II studies examining the role of immune checkpoint inhibitors (ICI) in the neoadjuvant setting in combination with chemotherapy. Evidence to date suggests that the addition of PD-1/PD-L1 inhibitors results in slight increases in the rate of pathologic complete response (pCR) seen at the time of surgery, and improved event free survival (EFS) has now been reported. However, a number of questions remain such as the optimal chemotherapy backbone; whether traditional third generation chemotherapy regimens can safely be de-escalated in the presence of an ICI; and the most appropriate sequencing of treatment in order to best harness a durable immune response and if continuation of post operative ICI is needed if one achieves a pCR. A predictive biomarker is also yet to be established, given that PD-L1 protein expression does not seem discriminatory. Given that long-term clinical outcome improvements seen thus far in early stage trials do not seem to be mediated through small changes in pathological complete response rates, new approaches in early stage trial design are now needed.

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1. Introduction

Immunotherapy has an established role as first-line therapy in combination with chemotherapy in advanced triple negative breast cancer patients who are designated PD-L1 positive using an immunohistochemical (IHC) assay [1–3]. There is now also an emerging body of evidence pertaining to the use of immunotherapy in the early stage TNBC setting [4–9]. The use of immunotherapy in early stage TNBC is attractive on several fronts. There is strong biologic rationale for the use of immune checkpoint inhibitors (ICI) in early stage disease. Whilst breast cancer has not traditionally been considered immunogenic, early stage TNBC demonstrates high levels of immune infiltration [10,11]. Tumour infiltrating lymphocyte (TIL) infiltrate exhibits high expression of PD-1 and other inhibitory checkpoint molecules that serve as targets for ICI therapy. The more robust immune microenvironment seen in early-stage disease may potentially result in greater efficacy of ICI in

comparison to the relatively immune-depleted advanced setting, ideally priming the immune system to eradicate residual micro-metastatic disease after resection of the primary lesion.

Currently reported studies examining the utility of immunotherapy in early stage TNBC pertain to the neoadjuvant setting, where checkpoint inhibitors (PD-1/-L1 inhibitors) have been added to neoadjuvant chemotherapy (NACT) regimens [4–8]. There is pre-clinical rationale suggesting an advantage to deploying immunotherapy in the neoadjuvant compared to the adjuvant setting [12]. Neoadjuvant immunotherapy was demonstrated to have much greater efficacy compared to adjuvant immunotherapy in two mouse models of TNBC [12]. In the presence of neoadjuvant immunotherapy greater antigen creation was demonstrated and a higher quantity of tumour-specific T cells was observed. It is postulated that release of dying tumour antigens may act to prime and expand T cells in the primary tumour that can expand to the periphery. The presence of the primary tumour during immunotherapy exposure resulted in greater expansion of T cells compared to when it had been removed prior to receipt of immunotherapy. The reason(s) for this observation are still unclear, but certainly there appeared to be a beneficial immune-stimulatory response related to the presence of the primary lesion.

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2. Randomized studies in early-stage TNBC with neoadjuvant PD-(L)1 inhibitors

The addition of ICI to neoadjuvant chemotherapy significantly increased the rate of pathological complete response seen at the time of surgery in women with Stage II and III TNBC in two large, randomised, phase III trials: KEYNOTE-522 [5] (pembrolizumab) and IMpassion031 [7] (atezolizumab). In the case of KEYNOTE-522 [5], pCR was a co-primary endpoint with event free survival (EFS [13]. In KEYNOTE-522 [5] an absolute increase in pCR rate of 13.6% was seen in the pembrolizumab arm compared to the control arm at the first interim analysis, which had reduced to 9.2% at the second interim analysis. The pCR rate in the intervention arm remained similar (64.8% and 64% respectively), however the control arm was performing better at the second timepoint, leading to the reduction in the delta change. Recent presentation of the EFS endpoint demonstrated a significant 3-year EFS of increase of 84.5% with pembrolizumab compared with 76.8% with placebo (HR 0.63, 0.48–0.82, $p = 0.0031$) [13]. This data suggests that pCR is a poor surrogate for EFS results in immunotherapy trials.

In IMpassion031 [7] the difference in pCR rate between the two arms was greater, at 17%, however the pCR rates in both arms (58% in the atezolizumab arm vs 41% in the control arm) were more modest compared to KEYNOTE-522, most likely due to the lack of carboplatin. A very early look at the EFS endpoint revealed a hazard ratio in favour of atezolizumab. GeparNuevo [4] enrolled 174 patients and whilst it was considered a statistically significant negative study in the overall population, with the pCR increase of 53.4% vs 44.2%, there was a higher pCR in the subset that had a window “run-in” (61% vs 41.4%), which will be discussed further at a later point in this article. Recently the long term survival results have been reported with significant improvement in all survival endpoints, independent of PD-L1 IHC result and window cohort [14]. This is of interest given that the GeparNeuvo [4] population was slightly lower risk, with higher numbers of node negative patients and no post-operative immunotherapy compared with KEYNOTE-522 [5].

The outlier in terms of phase III trials is the NeoTRIPaPDL1 study [8] (atezolizumab), which did not demonstrate an increase in pCR rates with the addition of immunotherapy (44% in the atezolizumab arm vs 41% in the control arm, not statistically significant), although noting that pCR was not its primary endpoint. The primary endpoint was EFS and is yet to be reported as results are immature. Given the above two trials, we await the results with interest in this higher risk population, where Stage III patients comprised nearly 50% of the trial population.

Two other randomised phase II studies I-SPY2 [6] and NCI-10013 [9] also contribute to body of evidence in this arena. Both I-SPY2 [6] and NCI-10013 [9] demonstrated improvements in pCR with the addition of immunotherapy to neoadjuvant chemotherapy.

Interrogation of the treatment regimens and study populations of these trials may shed light on the differing results [Table 1]. However, it does seem clear now that changes in pCR observed in trials incorporating ICI do not correspond to changes in survival endpoints. This is an important lesson and we may need to rethink how we go forward in developing immunotherapy approaches in breast cancer.

3. The role of the chemotherapy backbone

The most suitable chemotherapy backbone to which a checkpoint inhibitor should be added in the neoadjuvant setting remains unclear. One suggested reason for the discrepancy in outcomes between NeoTRIPaPDL1 [8] and the other two studies is the omission of an anthracycline in NeoTRIPaPDL1. The potential

immunomodulatory properties of anthracyclines have been described in the TONIC trial [15], where an upregulation of genes involved in PD-1–PD-L1 and T cell cytotoxic pathways was observed after induction chemotherapy with doxorubicin, thus suggesting anthracyclines may potentiate responses to ICI therapy.

The study population in NeoTRIPaPDL1 [8], however, was higher-risk, with a greater proportion of higher T-stage and lymph node-positive patients. Almost half of participants had Stage III disease in comparison to the other two trials where patients with Stage III disease comprised less than a third of participants. It is probably unsurprising that higher tumour burden resulted in lower pCR rates as greater tumour burden has been shown to be immunosuppressive and thus may negatively influence response to an ICI [16]. It seems unlikely that the addition of an anthracycline would have significantly mitigated this factor. The control group in NeoTRIPaPDL1 [8] also performed better than would be expected given the disease characteristics of participants, the cause of which is not entirely clear, although carboplatin-containing regimens did appear to result in higher pCR rates overall across studies, without altering the difference in pCR rates between treatment arms. Variations in anthracycline scheduling (dose-dense or not), and in the specific taxane employed were also seen across the trials, reflective of the fact that the ‘optimal’ neoadjuvant chemotherapy regimen in TNBC in standard-of-care patients is still itself a matter for some debate. Ultimately it seems counter-intuitive to escalate chemotherapy when it is being given in combination with a checkpoint inhibitor. Chemotherapy causes haematopoietic stress and depletes T lymphocytes, diminishing immune responses and potentially detrimentally affecting response to ICI therapy.

Importantly, the addition of ICI may offer the opportunity to safely de-escalate the chemotherapy backbone in suitable patients. In particular, sparing young women the potential long-term effects of an anthracycline would be desirable. How to best select these patients still requires refinement. Of note, NCI-10013 [9] demonstrated a pCR rate of 56% in the intervention arm (carboplatin and paclitaxel with atezolizumab for 12 weeks), a rate compatible with that seen in IMpassion031, however without the use of an anthracycline. The trial population was similar, suggesting that in a susceptible population the use of an ICI may negate the need for an anthracycline.

It seems unlikely that the specific ICI agent used influences response given that positive results have been demonstrated with the use of both PD-1 and PD-L1 inhibitors.

4. Sequencing of immunotherapy in the neoadjuvant setting

The sequencing of ICI therapy deserves consideration in the early-stage setting. In GeparNuevo [4] whilst there was not a statistically significant benefit to the addition of durvalumab in the overall population, patients in the window cohort achieved a significantly higher pCR rate when treated with durvalumab compared with placebo than patients in the non-window cohort. This raised the possibility that there may be immunological interactions that occurred in the window period, with stimulation of lymphocyte migration from the stroma into tumour-cell nests that potentiated a greater response to durvalumab when a checkpoint inhibitor is given prior to introduction of immunosuppressive chemotherapy. An increase in iTILs (immune TILs) during this window period correlated with an increase in pCR, offering weight to the biologic rationale behind this phenomena [4]. This may represent a key factor in increasing responses to neoadjuvant immunotherapy and further trials are ongoing in this regard, including the phase II Neo-N study (ACTRN12619001308189).

Table 1
Neoadjuvant Immunotherapy in early TNBC – Key Trials.

Trial	Primary endpoint(s)	Outcome	N	Neoadjuvant treatment			Adjuvant treatment			PD-L1+ (%)		Anatomic Stage (%)	
				ICI	Anthracycline	Taxane	Platinum	PD-L1 assessment	PD-L1+ (%)	II	III		
Phase III trials													
KEYNOTE-522 [5]	pCR	+	1174	PD-1 (pembrolizumab)	Yes (non-dd)	Paclitaxel	Yes	Pembro/placebo (1 yr)	22C3 CPS > 1	82.5	75.0	24.9	
	EFS (ITT population)	+†						No capecitabine					
Impassion031 [7]	pCR (ITT and PD-L1 + populations)	+	333	PD-L1 (atezolizumab)	Yes (dd)	Nab-paclitaxel	No	Atezolizumab (1 yr)	SP142 ≥ 1%	46	76.5	23.5	
								Capecitabine if RD					
NeoTRIPaPDL1 [8]	EFS (ITT population)	Immature	280	PD-L1 (atezolizumab)	No	Nab-paclitaxel	Yes	AC/EC/FEC	SP142 ≥ 1+	56	51	49	
Randomized Phase II trials													
CeparNuevo [4]	pCR (ITT population)	-*	174	PD-L1 (durvalumab)	Yes (dd)	Nab-paclitaxel	No	N/A	SP263 ≥ 1%	87.3	N/A	N/A	
I-SPY2 [6]	pCR (ITT population)	+	250	PD-1 (pembrolizumab)	Yes (dd or non-dd)	Paclitaxel	No	Clinician's discretion	N/A	N/A	N/A	N/A	
NCI 10013 [9]	pCR (ITT population)	+	67	PD-L1 (atezolizumab)	No	Paclitaxel	Yes	ddAC	N/A	N/A	66.3	33.8	
	ATI	-											

Key: ICI = immune checkpoint inhibitor; pCR = pathologic complete response; EFS = event free survival; ITT = intention-to-treat; dd = dose-dense scheduling; †recent presentation of EFS data – publication of results awaited; 3-year EFS 84.5% with pembrolizumab and 76.8% with placebo (HR 0.63, 0.48–0.82, p = 0.0031). 3-year distant recurrence free survival HR 87% vs 80.7%, HR0.61, 0.46–0.82). 3-yr OS 89.7% vs 86.9% HR 0.72, 0.51–1.02); *recent presentation of survival data [15] - 3-year iDFS 84.9% with durvalumab vs 76.9% with placebo (HR 0.54, 95%CI 0.27–1.09, p = 0.0559); 3-year DDFS 91.4% vs 79.5% (HR 0.37, 95%CI 0.15–0.87, p = 0.0148); 3-year OS 95.1% vs 83.1% (HR 0.26, 95%CI 0.09–0.79, p = 0.0076).

5. Trial endpoints - pCR

A pathological complete response to neoadjuvant treatment has previously been demonstrated to correlate with excellent long term outcomes in TNBC [17,18]. However, whilst achieving a pCR provides excellent prognostic information at the individual level, there remains controversy about whether increasing the pCR rate definitively correlates with improved long-term outcomes. The additional patients achieving a pCR with the addition of a novel therapy may be those who were likely to go on to have favourable outcomes regardless of the additional therapy. In the setting of early TNBC, it has been demonstrated that there are a subset of patients with residual disease and high TILs who have outcomes similar to those who achieve a pCR [19]. If these patients comprise the bulk of the additional complete responses seen then there may be little to no impact on long term survival.

Furthermore, it seems unlikely that improvements in EFS/OS in the presence of immunotherapy would be mediated through pCR increases as immunotherapy does not exert its effect via tumour reduction, as is the case for cytotoxic chemotherapy. This assumption now seems to have been validated. Studies in other solid organ tumours have not demonstrated a strong correlation between reduction of tumour burden and long-term outcomes in the presence of immunotherapy. It thus follows that an improvement in pCR in the presence of immunotherapy cannot definitively be assumed to translate to improved survival, and conversely a lack of improvement in pCR rates does not rule out longer-term benefits. Therefore, in the setting of early stage disease where the aim of therapy is clearly curative, survival data is required before such treatment is integrated into standard of care. EFS data from NeoTRIPaPDL1 [8] is still immature, and Impassion031 [7] was not powered to detect an EFS benefit. However, there has been an encouraging presentation recently with regards to KEYNOTE-522, demonstrating that the trial has met its dual primary endpoint of EFS [20]. Concerns about the robustness of the pCR endpoint for predicting longer term outcomes in this setting was one of the main reasons cited by the FDA when they declined an initial application for early approval of neoadjuvant pembrolizumab [21], but approval has now been received since presentation of the EFS data.

6. Toxicity considerations

The addition of checkpoint inhibitors to neoadjuvant chemotherapy does appear to add a small but significant toxicity burden, primarily in the form of immune related adverse events (irAEs). Whilst most immune related adverse events are highly manageable, some do require protracted courses of corticosteroids to achieve resolution, which in turn exposes patients to the inherent side effects of steroid treatment [22]. Some irAEs also result in the requirement for permanent medical intervention such as endocrinopathies requiring hormone replacement. Of note, in KEYNOTE-522 [5] at last study assessment 19% of patients who had received pembrolizumab had an unresolved irAE, with some 14% on thyroid replacement therapy, with around 3% experiencing severe endocrine toxicity such as adrenal insufficiency as well as hypopituitarism, the latter themselves having long term potentially life shortening sequelae. In the same study there have been four deaths potentially attributable to a pembrolizumab-related irAE, and thus whilst the rates of severe adverse events are small, these agents are clearly not without trade-off. Effects on decreasing fertility are not yet known but are possible given the link between autoimmunity and infertility. Discussion with patient advocates on risk vs. benefit and the evaluation of high-quality patient reported outcomes from the phase III studies will

be essential in the future as we learn to incorporate these agents in the early stage setting. Reassuringly data published so far has indicated that the addition of ICI to neoadjuvant therapy does not interfere with other components of definitive treatment, in particular delivery of chemotherapy and adjuvant radiotherapy [5]. Of note, if the inclusion of an ICI allows de-escalation of chemotherapy then further analysis will be required to determine whether this reduces the overall burden of treatment, both acutely and in the longer term.

In the setting of early stage disease, particularly where there is a high likelihood of favourable outcomes from a breast cancer point of view, clinicians must be particularly mindful of these potential long term toxicities and counsel patients appropriately. Follow up duration must also be explicitly considered in order to capture later onset irAEs, as it is clear that these can present some time after cessation of checkpoint inhibitor therapy [22]. Whether there is a correlation between irAEs and tumour response and long term outcomes is also worthy of further exploration in the breast cancer context.

7. The role of biomarkers in the early stage setting

As in the advanced setting, a predictive biomarker is highly desirable and is an area of active exploration. Rates of PD-L1 positivity varied across studies, likely due at least in part to the different assays used [23–25]. However, it seems clear that PD-L1 positivity is associated with benefit to PD-1/PD-L1 inhibitors in the advanced setting with the chemotherapy treatment regimens that were evaluated [1–3]. What is clear is that a greater proportion of patients are PD-L1 positive in early stage compared to advanced disease [11,26], reflective of the more intact immune microenvironment. In contrast to the advanced setting, PD-L1 appears not to be predictive of immunotherapy benefit in the neoadjuvant setting, although it does appear to be prognostic. Higher pCR rates were seen across studies in the PD-L1 positive population regardless of chemotherapy backbone and the PD-L1 assay used [4,5,7,8]. One hypothesis is that the current PD-L1 assays used are not sensitive enough to identify all the responsive population in the neoadjuvant setting.

In terms of other biomarkers under consideration, TILs have been established to be predictive of response to neoadjuvant chemotherapy in TNBC independent of ICI [27–31]. Early-stage TNBC is highly infiltrated, with >90% of patients having some TIL evident [27]. Whilst TIL may be unlikely to add independent predictive value for immunotherapy, further analyses are ongoing of trial datasets both at baseline as well as in the residual disease. It is possible that a very low level of TIL (i.e. 1% or 5%) may be all that is needed to engage PD-1/PD-L1 inhibitors in early stage TNBC. TMB and immune gene expression profiles (GEP) have been examined as potential biomarkers. These have been evaluated in the phase II GeparNuevo cohort and appear independently predictive of benefit [32]. TMB however remains fraught with many technical limitations and is yet to be standardized [33]. Whether there is a way to escalate treatment for those with an unfavourable baseline biomarker profile and/or PD-L1 negative, such as adding a CTLA-4 or LAG3 inhibitor, should also be explored.

8. Future directions

Of note, there is currently little evidence about the utility of adjuvant immunotherapy in early TNBC. Neoadjuvant trials that include ICI continued into the adjuvant setting are not necessarily designed to delineate whether the adjuvant portion is beneficial over and above the neoadjuvant component. In mouse models a short course of neoadjuvant immunotherapy induced long-term

survivors in a proportion of treated mice, suggesting that if someone is going to generate a sufficient immune response this may occur after only a few doses of ICI therapy [12]. The response may not be enhanced by a longer duration of treatment, which may just add to potential toxicity. Certainly given the mechanism of action of immunotherapy, efficacy seems unlikely to be ‘dose dependent’, as is seen with conventional cytotoxic agents. Pre-clinical models also suggest that removal of antigen (ie the primary tumour) prior to the use of immunotherapy may affect T cell expansion, further raising questions about whether ICI is likely to be effective in this context [12]. Trials looking at adding ICI to adjuvant chemotherapy in those who have upfront surgery and have high risk features, are ongoing, as well as in those who have residual disease post standard NACT.

Furthermore, the optimal treatment regimen to offer in the post-operative setting in someone who has neoadjuvant chemotherapy plus immunotherapy and has residual disease is currently unclear and we will not have these answers for many years. Many clinicians currently offer capecitabine to patients with residual disease post NACT, as per the CREATE-X trial [34]. This was not allowed in KEYNOTE-522 (all patients received adjuvant pembrolizumab/placebo), but was permitted in IMpassion031 concurrently with atezolizumab/placebo. Based on current information we are not able to determine whether adjuvant capecitabine is additive to an ICI approach in the adjuvant setting. Patients carrying a germline *BRCA 1 or 2* variant also require special consideration in light of the recent OLYMPIA [35] results demonstrating an invasive disease free survival benefit to olaparib in the adjuvant setting in women with high-risk HER2-negative early breast cancer. In this setting we feel that there is a definitive role olaparib, however it is unclear if combination with an ICI in the setting of residual disease post-neoadjuvant chemotherapy will be better than single agent. Given results of other neoadjuvant immunotherapy studies, we speculate that it does seem that the majority of the benefit of immunotherapy is achieved in the pre-operative stage and that residual disease may be both chemotherapy and PD-1/PD-L1 inhibitor resistant. However it is plausible that combining post-operative immunotherapy with a non cross-resistant agent may be beneficial in further improving outcomes in patients with residual disease in the adjuvant setting. We await data from clinical trials of adjuvant and residual disease immunotherapy in the near future.

As a greater number of women are exposed to immunotherapy in the early stage setting, the question arises as to the best treatment regimen for women who develop disease recurrence after exposure to PD-1/PD-L1 agents. It is unclear whether patients whose recurrent disease is PD-L1 positive will respond to re-treatment with ICI therapy. Certainly it will be important to explore therapies that amplify T cell responses, and employ combinations with less myelosuppressive chemotherapy in order to try and derive responses. Clearly this will require further consideration, particularly in clinical trial development.

9. Conclusions

There is strong biologic rationale for the utilisation of immunotherapy in the setting of early stage TNBC which has prompted its inclusion in clinical trials in combination with neoadjuvant chemotherapy. Whilst further peer reviewed data is awaited, results to date are encouraging for the efficacy of ICI therapy in this context, resulting in USA FDA approval of pembrolizumab for this indication, with small increases in pCR and significant impressive improvements in EFS. Optimisation of chemotherapy regimens and consideration of the sequencing of ICI agents with chemotherapy remains an important question. Clinicians must also be cognisant of the potential long-term adverse events of these agents, particularly

if their use becomes more commonplace more research is needed in these aspects, and long term follow up (i.e. 10 years) of early stage studies is needed. It seems clear at present that the incorporation of preoperative ICI with neoadjuvant chemotherapy results in more patients with early stage TNBC achieving a pCR, and improved outcome of those with residual disease. If immunotherapeutic agents do enter into standard of care for early stage TNBC future quandaries will arise about the optimal treatment for those who do not achieve a pCR and when women already exposed to these drugs relapse, as it is currently unclear whether there will be the potential for a second response, or rather whether this will further restrict useful treatment options in this space.

Declaration of competing interest

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