Triple negative breast cancer – prognostic role of immune-related factors: a systematic review

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Introduction

Triple negative breast cancer

Triple negative breast cancer (TNBC) is defined by ≤1% estrogen receptor (ER) positive tumor cells, progesterone receptor (PR) negativity, and normal HER2-receptor expression (HER2 normal by immunohistochemistry (IHC) or in situ hybridization (ISH) analysis separately or combined). In the literature, TNBC and basal-like breast cancer is often used interchangeably, however, the two terms are not totally overlapping, as basal-like breast cancer can be receptor-positive in rare cases. TNBC constitutes 15–20% of all breast carcinomas [1]. TNBC affects younger women more often and has a worse prognosis than breast cancer in general, due to a combination of more aggressive clinical behavior and lack of molecular targets for therapy [2].

Due to lack of targeted treatment, there is a need for new treatment options, and amongst these there are hopes that the emerging field of immunotherapy will provide efficient treatment strategies for this aggressive cancer.

Prognostic factors in TNBC

Apart from the extensively documented clinico-pathological risk factors such as node-status, tumor size, grade and proliferation rate (ki-67), there are no prognostic and predictive biomarkers suitable for clinical use for TNBC [3]. There is hope that a more detailed knowledge of the interaction between tumor cells and the immune system might lead to clinically useful biomarkers. Among these are tumor infiltrating lymphocytes (TILs) and the prevalence of other cells from the immune system as well as biomarkers related to the immune/tumor interaction, such as PD-L1.

However, in breast cancer, there are differences in the prognostic significance of immune cells according to breast cancer subtype, likewise, the expression and significance of
immune checkpoint markers such as PD-L1 may not have the same significance in TNBC as in other, less aggressive breast cancers [4–8].

**Aim of this review**

The purpose of this review is to give an overview of the composition of cells of the immune system and of biomarkers of immune checkpoint inhibitors in the tumor microenvironment and their significance in TNBC. Hereby elucidating which cells and which biomarkers related to the immune system play the most important role in the interaction between tumor and immune system, it is necessary to investigate the tumor microenvironment to discover which immune cells are present, and what their prognostic and predictive values are. This will clarify if known cancer immune treatments will be effective, but will also potentially inform us of other possible targets for therapy.

**Material and methods**

A search of PubMed was made using the terms ‘triple negative breast cancer’ and ‘tumor infiltrating lymphocytes’, ‘CD8’, ‘CD4’, ‘B cells’, ‘natural killer cells’, ‘macrophages’, ‘myeloid derived suppressor cells’, ‘dendritic cells’, ‘immune checkpoint inhibitor’, ‘CTLA-4’ and ‘PD-L1’. Only articles written in English including at least 50 patients were included, unless there were no studies on the subject except with less than 50 patients.

**Significance of TILs in TNBC**

When considering the inflammatory infiltrate in cancers, TILs have been the main focus of much of recent research. TILs have been shown both in breast cancer in general and in TNBC in particular to be a strong prognostic indicator. Loi et al. were the first to show that each 10% increment in intratumoral and stromal TILs was associated respectively with a 27% and 17% reduced risk of death in the TNBC group of a study including 2009 breast cancer patients. Loi et al. later confirmed these results in a study of 134 TNBCs, where they also showed that a high number of TILs was a significant predictor of distant recurrence, and that each 10% increase in TILs was associated with a 13% reduction in relative risk of distant recurrence [9].

In a meta-analysis of the prognostic value of TILs in TNBC including 8 studies with a total of 2987 patients, it was found that cancers rich in TILs were associated with a 30% reduced risk of recurrence, a 22% reduction in distant recurrence and a 34% reduced risk of death [10].

TILs have also been shown to be predictive of response to neoadjuvant chemotherapy (NAC). Denkert et al. were the first to show a positive association between TILs and response to NAC in a study of over 1000 breast cancer patients [11]. Denkert et al. later confirmed that TILs are also associated with pathological complete remission (pCR) to NAC when looking at the TNBC group alone [12], and these results have been confirmed by others [13].

To facilitate the use of TILs as a prognostic marker in the clinical setting, an International TILs Working Group published guidelines to allow for a more standardized evaluation of this parameter [14], with minor modifications added in 2017 [15]. However, despite these efforts, interobserver variance is still deemed too great to allow for TIL evaluation to be introduced in routine clinical practice [16].

**Subpopulations of TILs**

With regards to subtypes of TILs the strongest evidence for effect on outcome has been found for T-lymphocytes. T-lymphocytes are the most predominant type of lymphocytes in the tumor microenvironment, constituting up to 75% of TILs [17]. In the following, we discuss subtypes of TILs with different impacts on prognosis. A recurring paradox in this area is that despite the functional heterogeneity of TIL subtypes, the very general parameter of TIL evaluation on H and E (Hematoxylin Eosin) stains is still a strong prognostic factor [14]. Also, some TIL subtypes are known to downregulate the immune system. However, their presence in some cancers seems to infer a better prognosis [18,19]. This somewhat arbitrary effect is taken as a sign that the presence of these cells is an expression of a robust immune response, including natural feedback mechanisms [14].

**CD8**+T lymphocytes

CD8+ T-lymphocytes differentiate into cytotoxic T-lymphocytes (CTLs) upon recognition of antigen and play a key role in the adaptive immunological defense against foreign agents and tumor cells. In TNBC, as in many other cancer types, tumors rich in CD8+ T-lymphocytes are associated with a better prognosis (Table 1) [10,20–22]. CD8+ infiltrates are seen in 60% of TNBCs [23]. Some evidence suggests that the effect of CD8+ T-cells is more powerful in hormone receptor negative breast cancers. In a study of 1854 breast cancer samples, Baker et al. [4] only found independent prognostic significance of CD8+ T-cells in ER-negative breast cancers (p = .03), whereas the same could not be shown for ER positive tumors.

**CD4**+ T helper cells

CD4+ T helper cells can differentiate into a variety of subtypes upon activation, and their function is to modulate the activity and differentiation of the immune system through modulation of, e.g., B-cells, CD8+ T-cells and macrophages [24]. The main subgroups that have been investigated are T-helper cells (TH1), follicular T helper cells and regulator T-lymphocytes.

TH1 are the principal source of interferon-γ, and follicular T-helper cells (Tfh) are a relatively newly described subgroup of CD4+ T-cells. Both subgroups have shown improved survival in some hormone receptor positive breast cancers, but, as yet, not in TNBC [17].

Regulator T-lymphocytes (Tregs) are a subgroup of CD4+ T-lymphocytes with the immune phenotype CD4+, CD25+, Fox3P+. In breast cancer, TNBCs have the highest...
Table 1. Prognostic value of T-lymphocyte subtypes.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Phenotype</th>
<th>Evaluation method</th>
<th>CD8+</th>
<th>CD4 + TH1</th>
<th>CD4 + Tfh</th>
<th>CD4 + Treg (FOXP3+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1902 of which 261</td>
<td>Basal-like</td>
<td>IHC for CD8</td>
<td>CD8-high associated with better breast cancer specific survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahmoud et al. [20]</td>
<td>Basal-like and ER/PR/HER2 +/-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>TNBC</td>
<td>IHC for CD8 and FOXP3</td>
<td>CD8-high better pCR rates (41 vs 18%, p = .03)</td>
<td></td>
<td></td>
<td>Low CD8+/FOXP3- ratio associated with lower pCR (44 vs 14%, p = .002)</td>
</tr>
<tr>
<td>Miyashita et al. [21]</td>
<td>TNBC</td>
<td>IHC for CD8 and CD4</td>
<td>Better DFS with high intratumoral CD8+ TILs: 0.48 (CI: 0.27–0.83, p = .01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>232</td>
<td>TNBC</td>
<td>IHC for CD8 and CD4</td>
<td>Recurrence rate for CD8+ high, ER-negative: 0.70 (CI: 0.5–1.0, p = .03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matsumoto et al. [22]</td>
<td>TNBC</td>
<td>IHC for CD8 and CD4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1953, of which 268</td>
<td>ER negative</td>
<td>IHC for CD8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baker et al. [23]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>ER/PR/HER2 +/-</td>
<td>Flow cytometry and gene expression analysis</td>
<td>Prognostic significance in TNBC not yet shown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gu-Trantien et al. [17]</td>
<td>ER/PR/HER2 +/-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>164</td>
<td>TNBC</td>
<td>IHC, immunofluorescence, NanoString gene expression</td>
<td>Prognostic significance in TNBC not yet shown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeung et al. [18]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3992, of which 630</td>
<td>ER/PR/HER2 +/-, basal-like or TNBC, non basal-like</td>
<td>IHC</td>
<td>High Treg associated with improved survival (HR: 0.33, 95% CI 0.17–0.66, p = .002)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu et al. [28]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
amounts of FOXP3+ cells (70%) compared to other types of breast cancer [23]. The function of Tregs in the normal immune environment is to regulate and suppress immune responses to prevent autoimmune reactions. Traditionally, it has been believed that, in the tumoral environment, regulatory T-cells can suppress the effect of other effector cells, thus preventing an effective immune response to tumor [25]. Previously, it was thought that high levels of Tregs were associated with a worse prognosis. However, several recent studies have shown the opposite in a variety of cancers, including TNBC (Table 1) [18,26–28]. It is, as yet, unknown what the exact mechanism behind this positive effect of Tregs is, but in colorectal cancer, certain subsets of Tregs were associated with a better prognosis than others [29]. A similar study has not, to our knowledge, been performed in breast cancer, but Syed et al. showed the accumulation of a subset of Treg cells with immunosuppressive characteristics in breast cancer tumor microenvironment, compared to normal tissue [30].

**Natural killer cells**

Natural killer cells (NK) recognize and eliminate foreign cells lacking the MHC class 1 molecule, necessary for activation of CD8+ lymphocytes [31]. Studies of breast cancers in general and TNBC cell lines in particular, have shown that tumor cells are capable of downregulating their 'visibility' to NK cells through modulation of their receptors and inhibitory factors in the microenvironment [32,33]. Studies of breast cancer have shown NK cells to be associated with a better prognosis, but there has been little research regarding differences between breast cancer subtypes (Table 2) [34,35].

**B-cells**

B-lymphocytes have not been shown to have the same degree of significance as T-lymphocytes, with studies showing both worse, better, or unaffected prognoses [36,37]. However, some evidence suggests that the B-lymphocyte population in the basal-like subtype might have more significance than in other types of breast cancer, where Iglesia et al. showed that metastasis- and DFS correlated better with B-cell gene expression signatures for basal-like and HER-2 enriched cancers, than for other subtypes (Table 2) [38].

**Other cells from the immune system**

**Tumor-associated macrophages**

Tumor-associated macrophages (TAMs) play a key role in regulating the interaction between the immune system and cancer [39]. Two subtypes are relevant, M1 and M2, where M1 is an efficient antigen presenter and produces inflammatory cytokines, whereas M2 macrophages participate in dampening of inflammation, angiogenesis and tumor progression [40].

In breast cancer in general and in TNBC, TAMs are mostly associated with a worse prognosis (Table 2) [37,41,42]. Campbell et al. showed that proliferating macrophages are associated with hormone-receptor negativity ($p = 0.00001$ for ER and $p = 0.002$ for PR), and with basal-like cancer, but not with HER2 status [42].

Also, the composition of macrophage subtypes seems to be different in TNBC. Stewart et al. showed that basal-like breast cancer cells had a greater ability than the less aggressive luminal breast cancer type, to drive macrophage differentiation in cell cultures, and to induce polarization towards both M1 and M2 phenotype, creating a population of macrophages distinct from the population found in cell cultures with breast cancer cells of a less aggressive type [43].

Evidence also suggests that the prevalence of the M2-phenotype is more prevalent in TNBC/basal-like breast cancers than in hormone receptor positive breast cancers, as shown by Medrek et al. in a study of 144 breast cancer samples, where high densities of CD163+ macrophages in tumor stroma (CD163 is a biomarker for M2 macrophages) were associated with TNBC/basal-like cancers, higher grade and larger size. However, the study only included 15 patients with TNBC/basal-like tumors [5].

**Dendritic cells**

Dendritic cells (DCs) are professional antigen presenting cells (APCs) that participate in the activation of adaptive immune cells, e.g., T-cells. However, tumor infiltrating DCs often show an aberrant phenotype with lower expression of costimulatory molecules, blunted antigen cross representation and upregulation of regulatory molecules, pointing towards factors in the tumor environment blunting the stimulatory effect of DCs, turning them towards a protumorigenic effect. A subgroup of DCs often seen in tumors are the plasmacytoid dendritic cells (pDCs), which are often associated with a worse prognosis, tumor tolerance and upregulation of Treg [6,44–47]. In breast cancers, higher numbers of pDC were found in TNBC than in less aggressive tumor types in 151 patients with non-metastatic cancer (Table 2) [6]. Clinical trials in breast cancer patients with dendritic cell vaccines are ongoing, some in combination with chemotherapy, but so far results have been negligible [48].

**Myeloid-derived suppressor cells**

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of immature myeloid cells. Their main function is to inhibit the immune system through secretion of inhibitory cytokines and other substances [49]. Circulating MDSCs in peripheral blood have been shown to be elevated in breast cancer patients in all stages of the disease, and to be positively correlated with stage and metastasis [50,51]. Most of the research of MDSCs in the tumor microenvironment has been performed in murine models, and very little research exits on MDSCs in human breast cancer tissue, but one study showed MDSCs to be expanded in breast cancer tumor tissue as opposed to normal tissue and was not particularly associated with hormone receptor negativity. However, this study only included 23 breast cancer patients [52].
### Table 2. Other cells from the immune system.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Phenotype</th>
<th>Evaluation method</th>
<th>NK-cells</th>
<th>B-cells</th>
<th>Macrophages</th>
<th>Dendritic cells (DC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascierto et al. [35]</td>
<td>14, of which 9 TNBC</td>
<td>ER/PR/HER2 +/-</td>
<td>IHC and gene expression profiling</td>
<td>Increased expression of NK-activating genes in patients without recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahmoud et al. [37]</td>
<td>1902, of which 288 basal-like</td>
<td>ER/PR/HER2 +/-</td>
<td>IHC</td>
<td></td>
<td>Total CD20+ B-cell count independently associated with outcome (HR = 0.75, CI = 0.58–0.96)</td>
<td></td>
</tr>
<tr>
<td>Iglesia et al. [39]</td>
<td>855, of which 140 basal-like</td>
<td>Classified according to gene expression profiles</td>
<td>Gene expression analysis</td>
<td></td>
<td>B-cells associated with improved metastasis free survival in basal-like</td>
<td></td>
</tr>
<tr>
<td>Murri et al. [43]</td>
<td>168, of which 35 ER/PR negative</td>
<td>ER/PR +/-, HER2 not evaluated</td>
<td>IHC</td>
<td></td>
<td>No significant effect of macrophages in multivariate analysis</td>
<td></td>
</tr>
<tr>
<td>Campbell et al. [44]</td>
<td>216, of which 29 basal-like</td>
<td>ER/PR/HER2 +/-</td>
<td>IHC</td>
<td></td>
<td>Proliferating macrophages associated with 75% increased risk of death (p = .048)</td>
<td></td>
</tr>
<tr>
<td>Medrek et al. [5]</td>
<td>144, of which 15 TNBC/basal-like</td>
<td>ER/PR/HER2 +/-</td>
<td>IHC and gene expression profiling</td>
<td></td>
<td>Macrophages an independent risk factor for BCSS (HR = 0.12, CI = 0.02–0.72, p = 0.02)</td>
<td></td>
</tr>
<tr>
<td>Treilleux et al. [49]</td>
<td>255</td>
<td>ER/PR/HER2 +/-</td>
<td>IHC</td>
<td></td>
<td>OS at 58 months: 93% vs 73% (p = .05) for plasmacytoid DC high tumors</td>
<td></td>
</tr>
<tr>
<td>Sisirak et al. [6]</td>
<td>60, of which 12 TNBC</td>
<td>ER/PR/HER2 +/-</td>
<td>IHC and flow cytometry</td>
<td></td>
<td>Dendritic cells associated with TNBC</td>
<td></td>
</tr>
</tbody>
</table>
Immune checkpoints as a prognostic factor and treatment target

The function of immune checkpoints in the non-cancerous environment is to regulate the proliferation and activities of cytotoxic cells to prevent autoimmune reactions. In the cancerous environment, these mechanisms are adopted by cancer cells to render immune cells anergic, and unable to eliminate tumor cells.

Immunotherapy, which mainly focuses on blocking immune-regulating proteins that suppress the anticancer tumor response, has proven effective in many different cancer types, including melanoma and lung cancer [53–55].

There are currently numerous ongoing clinical studies involving breast cancer patients and various immunotherapeutic treatment strategies [56]. The most established forms of immunotherapy are centered around the Programmed Death 1 receptor (PD-1) and its ligand PD-L1, and also CTLA-4.

**CTLA-4**

CTLA-4 blockade is effective in the treatment of melanoma, but is not yet well researched in breast cancer [56,57]. CTLA-4 can be expressed by cancer cells and plays a key role in ‘switching off’ the immune response of T-cells by progressively blocking the co-stimulatory signals from APCs, needed by T-cells to react to the antigens they are presented to [56,58]. In breast cancer, CTLA-4 has been shown to be an independent predictor of shorter DFS (hazard ratio (HR) 2.176, 95% CI 1.084–4.437, p = .029) and OS (HR 2.820, CI 1.337–5.950, p = .007) in 130 patients (see Table 3) [59], but differences in CTLA-4 expression in subtypes of breast cancer have not been described.

**PD-1 and PD-L1**

PD-1 is expressed in activated T-lymphocytes, but also in B-lymphocytes, mononuclear cells, NK cells and some DCs [60]. When PD-1 binds to its ligand PD-L1, it serves to down-regulate T-cell activity, thus playing an important role in harnessing autoimmune reactions in the normal body [61]. PD-L1 is expressed in a variety of solid tumors, including breast cancer, colorectal cancer, melanoma and lung cancer [62–65].

PD-L1 is commonly expressed in TNBC. In a study including 35 triple-negative, non-basal-like tumors and 69 basal-like tumors, high expression of PD-L1 was found in 31% and 33%, respectively [62]. Mittendorf et al. found higher expression of PD-L1 in TNBC, than in other cancer types, using RNA sequencing (p = .001) [66], but there have been conflicting results as to whether there is a positive correlation between basal-like/hormone-receptor negative cancers and PD-L1 expression compared to other breast cancer subtypes [7,8,67,68].

Another area with conflicting results is the impact of high expression of PD-L1 on prognosis, with recent evidence pointing towards PD-L1 expression being associated with improved survival (Table 3) [69]. This somewhat arbitrary effect is thought to be explained by high expression of PD-L1 being an indicator of a more robust immune response to tumor. However, other studies have reported worse outcomes with high PD-L1 expression, as described below. A meta-analysis including 5 studies composing 2546 patients with breast cancer of all types found association between shorter OS and PD-L1 overexpression (HR = 1.76, 95% CI 1.09–2.82, p = .02), but also found association between TNBC and higher levels of PD-L1 expression [8]. However, one of the studies included in this meta-analysis also studied outcome in subtypes, concluding that PD-L1 was a significant

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Phenotype</th>
<th>Evaluation method</th>
<th>CTLA4</th>
<th>PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al. [61]</td>
<td>130</td>
<td>ER/PR/HER2 +/-</td>
<td>IHC</td>
<td>CTLA4 expression inde-</td>
<td>PD-L1 expression associated with better DFS (p = .04)</td>
</tr>
<tr>
<td>Botti et al. [72]</td>
<td>238</td>
<td>TNBC</td>
<td>IHC</td>
<td></td>
<td>PD-L1 expression associated with worse OS (HR = 1.76, CI 1.09–2.82, p = .02)</td>
</tr>
<tr>
<td>Zhang et al. [8]</td>
<td>2546 (metaanalysis)</td>
<td>ER/PR/HER2 +/-</td>
<td>–</td>
<td></td>
<td>PD-L1 expression associated with better DFS (p = .02)</td>
</tr>
<tr>
<td>Wang et al. [64]</td>
<td>443, of which 34 TNBC, non-basal-like, 69 basal-like</td>
<td>ER/PR/HER2 +/-</td>
<td>IHC</td>
<td></td>
<td>Stromal PD-L1 expression associated with better DFS (p = .05)</td>
</tr>
<tr>
<td>Li et al. [73]</td>
<td>136</td>
<td>TNBC</td>
<td>IHC</td>
<td></td>
<td>High PD-L1 expression and low TILs independent prognostic factor of RFS and OS (for RFS: HR = 4.7, CI 1.6–12.7, p = .01; for OS: HR = 8.4, CI 2.3–30.3, p = .02)</td>
</tr>
<tr>
<td>Mori et al. [74]</td>
<td>248</td>
<td>TNBC</td>
<td>IHC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
predictor of OS in the basal-like subtype (HR: 2.60, CI: 1.016–6.652, \( p = .046 \)) [7].

Interestingly, Wang et al. reported no effect on outcome for high expression of PD-L1 in general in breast tumors, except for the basal-like subtype, where it was associated with better recurrence free survival (RFS) (HR = 0.39, CI = 0.22–0.86, \( p = .018 \)) [62]. Other studies, exclusively including TNBC have also found diverging results, with Botti et al. showing better DFS for tumors expressing PD-L1 in 238 TNBCs (\( p = .04 \)), while there was no effect on OS [69] and Li et al. showing only association between stromal PD-L1 expression and DFS (\( p = .04 \)), while there was no effect on OS or with regards to tumoral expression of PD-L1 [70]. Mori et al. found no effect on OS with PD-L1 alone in TNBC, but high expression of PD-L1 in combination with low numbers of TILs was an independent prognostic factor of both RFS and OS (for RFS: HR = 4.7, CI 1.6–12.7, \( p = .0067 \); for OS: HR = 8.4, CI 2.3–30.3, \( p = .019 \)) [71]. Clinical trials targeting the PD-1-PD-L1 pathway to treat TNBC patients are ongoing, and preliminary results have been promising [72,73].

A high expression of PD-L1 is associated with higher chance of response to PD-L1 blockade in several tumor types. However, even tumors with very low expression do respond, but less frequently. Selecting patients for treatment with PL-L1 blockade based on PD-L1 expression, and if so, which cut-point to use, is therefore debated [54].

Discussion

Biomarkers related to the immune system have been demonstrated to be of prognostic significance in many tumor types, including breast cancer. However, even TILs, the most thoroughly evaluated parameter, is not yet ready for clinical use, due to interobserver variability and lack of standardization.

The composition of immune cells in the tumor microenvironment of TNBC in some ways resemble that of breast cancer in general, however, there are differences in the prevalence and prognostic significance of several of the cells, and the exact impact on prognosis is not yet known. The composition of the cellular tumor microenvironment is therefore currently mostly of scientific interest, and is not yet ready to be utilized as prognostic indicators in the clinical setting.

The immune checkpoint markers are also correlated with other known prognostic factors, and multivariate analyses taking other known prognostic factors into account has, in some cases, not been performed in past research, but are needed to assess the true value of immune biomarkers in the prognostic evaluation of patients.

More research in this area may be important for our understanding of the role of the immune system in different tumor types. Moreover, treatments targeting the immune system are being developed, and the immune biomarkers may become essential as predictive factors for selecting patients that are likely to benefit from treatment. It remains to be determined which markers, and which cut-points, are optimal. Research in PD-L1 and other biomarkers has, so far given diverse and sometimes contradictory results. This might be due to different cut-off points and methods of evaluation, but also because of different qualities in the antibodies utilized in histological evaluation. Perhaps the future direction of research in this area should focus on expression of biomarkers on a molecular level, as this could lead to more uniform results, which will potentially lead to a better understanding of prognosis and of which patients may benefit from immunotherapy.

Immunotherapy would seem to be a promising treatment modality in TNBC. First, TILs are generally more predominant in this subgroup [74,75]. Secondly, the hormone receptor negative/basal-like subtypes have been considered the most likely candidates to benefit from immunotherapy, due to their high levels of mutations, resulting in a larger number of neo-antigens, which have been shown to be immunogenic [76–79]. TNBC has few targeted treatment options, and further research into immunotherapy for this disease may lead to significant improvements in the treatment and prognosis for these patients.

Disclosure statement

The authors report no conflicts of interest.

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References


