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# B cells and the coordination of immune checkpoint inhibitor response in patients with solid tumors

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## ABSTRACT

Immunotherapy profoundly changed the landscape of cancer therapy by providing long-lasting responses in subsets of patients and is now the standard of care in several solid tumor types. However, immunotherapy activity beyond conventional immune checkpoint inhibition is plateauing, and biomarkers are overall lacking to guide treatment selection. Most studies have focused on T cell engagement and response, but there is a growing evidence that B cells may be key players in the establishment of an organized immune response, notably through tertiary lymphoid structures. Mechanisms of B cell response include antibody-dependent cellular cytotoxicity and phagocytosis, promotion of CD4+ and CD8+ T cell activation, maintenance of antitumor immune memory. In several solid tumor types, higher levels of B cells, specific B cell subpopulations, or the presence of tertiary lymphoid structures have been associated with improved outcomes on immune checkpoint inhibitors. The fate of B cell subpopulations may be widely influenced by the cytokine milieu, with versatile roles for B-specific cytokines B cell activating factor and B cell attracting chemokine-1/CXCL13, and a master regulatory role for IL-10. Roles of B cell-specific immune checkpoints such as TIM-1 are emerging and could represent potential therapeutic targets. Overall, the expanding field of B cells in solid tumors holds promise for the improvement of current immunotherapy strategies and patient selection.

## INTRODUCTION

The first clinical observations hinting at a host-dependent antitumor immunity date back from more than 150 years ago, with reports of disappearing cutaneous melanomas in the event of hypodermatitis.<sup>1</sup> Evidence of metastases disappearing without any systemic therapy has since been reported in the context of various solid tumors including cutaneous or kidney cancers.<sup>2–3</sup> The development of anticancer therapies harnessing immunity has been first proposed through the use of bacterial strains. Coley's toxins have sometimes resulted in cure in solid

tumors,<sup>4</sup> while adjuvant intravesical BCG in non-muscle invasive bladder cancer remains standard of care up to this day.<sup>5</sup> Since the 1980s, cytokine-based therapies using interferon or interleukin (IL)-2 were associated with durable remissions<sup>6,7</sup> and could still be a relevant contemporary option in melanoma or renal cell carcinoma.<sup>8</sup>

Modern takes on immunotherapy involve immune checkpoint inhibitors,<sup>9</sup> of which most used in routine care target the programmed cell death (PD)-1<sup>10</sup> or cytotoxic T lymphocyte antigen (CTLA)-4<sup>11</sup> axis. A minority of patients will experience objective tumor response though, and biomarkers including checkpoint expression or gene expression signatures remain scarce with little predictive power.<sup>12–13</sup> Agents targeting novel checkpoints have yet to demonstrate their ability to overcome resistance to PD-1 or CTLA-4 inhibition.<sup>9</sup> While the activity of immune checkpoint inhibitors was mostly dissected through the lens of CD8+T cell response,<sup>14–16</sup> other immune factors are likely to shape the anti-tumor immunity.

The role of B cells has long been established in the defense against pathogens, although respective implication of B cell subtypes in antitumor immunity has only been recently studied. The versatility of the B lineage may, however, be of key importance to generate efficient and sustained immune responses against solid tumors: antibody secretion by plasma cells and plasmablasts allows for antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis of opsonized cells<sup>17</sup>; multiple types of memory B cells may provide long-lasting immunity through pools of highly specific IgG memory cells, as well as unswitched IgM memory B cells that can replenish B cell subpopulations on repeated

antigenic stimulation<sup>18–20</sup>; cross-talks between T and B cells appear essential not only for T CD4 but also for T CD8 expansion and activation.<sup>21–24</sup> Here, we will review current evidence about the B cell role in antitumor immunity and response to checkpoint inhibitors, and how their determinants could inform patient selection for systemic therapies.

## Mechanisms of B cell-mediated antitumor immunity

### The pivotal role of B cells in immune activation

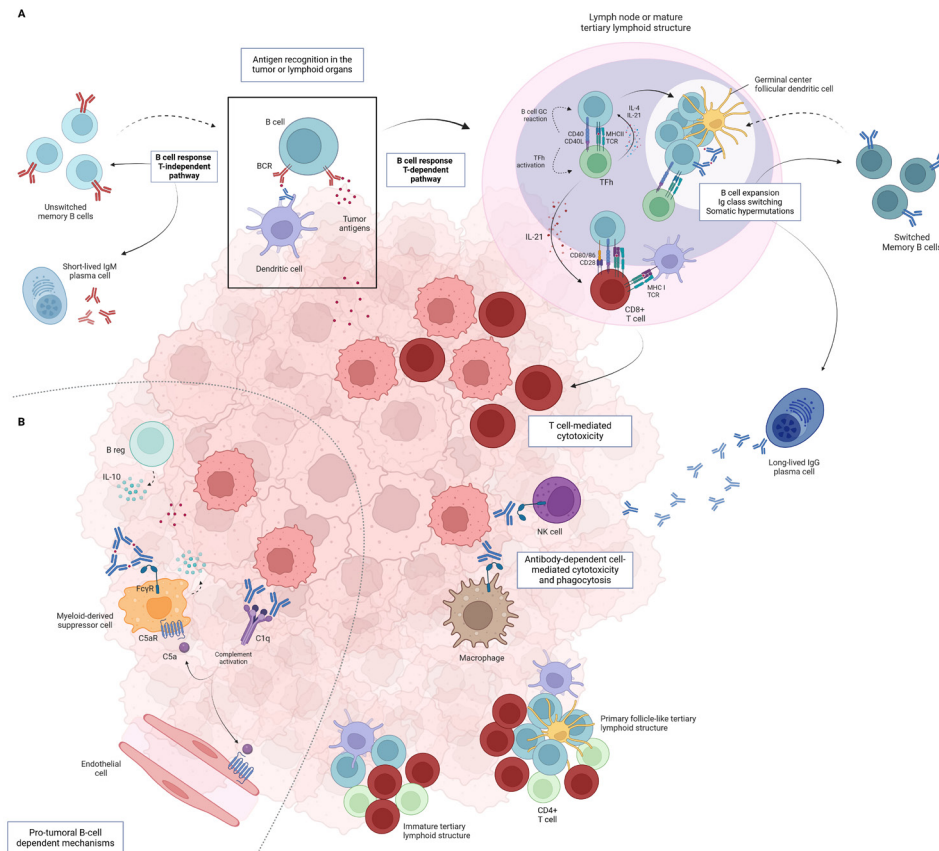
The roles of B cells in immunity have been largely described, ranging from the production of antibodies that drive humoral immunity to maintenance of T cells. The maturation process of B cells begins with antigen recognition by the B cell Receptor (BCR), after which activated B cells will interact with CD4<sup>+</sup> follicular helper T cells (TFh) in lymphoid organs or tertiary lymphoid structures (TLS). Antigen presentation through the B cell major histocompatibility complex (MHC) II to the T cell receptor allows for TFh activation; costimulatory signals from the CD40/CD40L axis, as well as the secretion of IL-4 and IL-21 by activated TFh will allow the activated B cell to enter the germinal center reaction.<sup>25–26</sup> The germinal center reaction consists of B cell expansion and somatic hypermutation in the variable region of the immunoglobulin gene within the germinal center dark zone, allowing for the generation of centrocytes with variable antigen affinity. In the light zone, centrocytes undergo positive selection in the presence of TFh and follicular dendritic cells (FDC), where immunoglobulin class switch recombination ultimately occurs. These centrocytes then differentiate into long-lived antibody-producing plasma cells or switched memory B cells that govern long-term immunity.<sup>18</sup> Other pathways involve T-independent B cell activation without immunoglobulin class switching nor somatic hypermutation; this process allows for quicker generation of short-lived plasma cells and unswitched (IgM<sup>+</sup>) memory B cells. Despite lesser antigen specificity compared with germinal center B cells, unswitched B cells remain more versatile with broader antigen recognition and lower activation thresholds, and retain the ability to reinitiate germinal center reaction on repeated antigen exposition.<sup>18–27–28</sup>

Interactions between B and T cells within lymphoid organs and secondary lymphoid structures are key for antitumor T cell-mediated cytotoxicity (figure 1).<sup>29</sup> B cells can induce antigen-specific CD8<sup>+</sup> and CD4<sup>+</sup> T cell activation, respectively, through MHC class I or II, as repeatedly shown in the context of cancer, bacterial or viral infections,<sup>23–30–32</sup> along with costimulation signals involving CD80/CD28<sup>31</sup> and CD40/CD40L.<sup>25</sup> Previously described interactions between B cells and TFh, by inducing IL-21 secretion, also promote the maintenance of the CD8<sup>+</sup> immune response.<sup>24–33</sup> More recently, it has been shown that B and T cell relationships may also involve B cells in later maturation stages, as evidenced by the secretion of T-attracting chemokines by plasmablasts which promotes cytotoxic immunity in melanoma.<sup>34</sup>

Humoral immunity is another key feature of B cell-mediated antitumor immunity. Antibodies secreted by B cells may recognize and bind neoantigens that emerge from mutations or aberrant post-transcriptional modifications.<sup>35</sup> Those can be found on the surface of tumor cells, in the tumor microenvironment on immunogenic cell death, or may even be targeted intracellularly by IgA.<sup>36</sup> Other self-peptides may also be recognized, including normal peptides overexpressed in specific cancer settings such as metalloproteinases, viral epitopes in virus-associated tumors, or peptides that underwent aberrant post-translational modifications.<sup>35–37–39</sup> Opsonization with immunoglobulins has been demonstrated notably in melanoma and renal cell cancer,<sup>40–41</sup> allowing for ADCC by natural killer cells and phagocytosis (ADCP) by macrophages. Crescioli *et al* reported an overall decrease of the peripheral memory B cell compartment and circulating memory B cells, and an increase of antibody-secreting plasmablasts in stage IV melanoma patients compared with healthy volunteers, which was in line with a higher proportion of IgG in melanoma lesions compared with normal tissue.<sup>41</sup> In renal cell carcinoma, Meylan *et al* demonstrated that intratumor plasma cells were correlated with higher levels of tumor-coating IgG, as well as with tumor cell apoptosis likely due to a macrophage-dependent process.<sup>40</sup> Other Ig isotypes such as IgA may also elicit antitumor activation of myeloid cells such as in ovarian cancers.<sup>36</sup> Neoantigen-binding antibodies may not only elicit ADCC or ADCP but also T cell-mediated cytotoxicity via distinct mechanisms. In murine experiments using an allogeneic tumor rejection model, based on the injection of B16F10 melanoma cells derived from C57BL/6 mice into 129S1 mice, dendritic cells could uptake antibody-coated tumor antigens and elicit T cell activation through antigen presentation.<sup>42</sup> Non-specific antibody binding may also occur through polymeric immunoglobulin receptors (pIgR) that allow transcytosis of IgA into the gastrointestinal mucosa in physiological conditions; in ovarian cancers that universally express pIgR, non-specific IgA transcytosis elicited modification of cancer cells transcriptional programs, notably increasing interferon  $\gamma$ -related pathways, increasing T cell cytotoxicity and tumor control.<sup>36</sup>

### Tissue-based organization of B cell response

Close interactions between B and T cells have been shown essential for the generation of an effective cytotoxic CD8<sup>+</sup> response, which is reflected by the colocalization of B and T cells found in several tumor types. In ovarian cancer tissues with low dendritic cell infiltration, the most common tissue-resident APC, B cells are found in close proximity to T cells, which suggests that they may exert antigen presentation.<sup>43</sup> In a murine 4T1 breast cancer model, simultaneous transfer of both activated B cells and T cells from tumor-draining lymph nodes led to more significant tumor regression compared with the transfer of either population.<sup>44</sup> The importance of intratumor CD4<sup>+</sup>, CD8<sup>+</sup>T cells, and B cells colocalization has



**Figure 1** BCR in solid tumors. (A) Coordination of the antitumor immune response by B cells. Antigen recognition by the B-cell receptor triggers a T cell-dependent or T cell-independent B cell response. The T cell-dependent response involves B and T-cell crosstalks within secondary or tertiary lymphoid structures. Interactions between B-cells and TFh through the CD40/CD40L axis allows for TFh activation, as well as initiation of a B cell germinal center reaction. Activation of TFh cells promotes T CD8+ activation and expansion in the T cell zone, ultimately prompting efficient T cell-mediated cytotoxicity. The germinal center reaction involves a positive selection of high-affinity, class-switched B cells that will differentiate into long-lived switched (IgG+) memory B cells or IgG+ plasma cells. The humoral response exerts antitumor effects through antibody-dependent cytotoxicity and phagocytosis. The T-independent response allows for swift generation of IgM+ plasma cells or unswitched (IgM+) memory B cells, which harbor lower somatic hypermutation rates and lower antigen affinity compared with their switched (IgG+) counterparts; unswitched memory B cells have the ability to reinitiate a B-cell response and a germinal center reaction on repeated antigenic stimulation. (B) Modulation of the immune response by B cells. Tumor infiltration by regulatory B cells secreting immunosuppressive cytokines such as IL-10 allows for an immunosuppressive microenvironment. Immune complexes involving immunoglobulins and tumor antigens may promote activation of myeloid-derived suppressor cells. Complement activation by immunoglobulins may also promote MDSC activation and angiogenesis, inducing a protumoral microenvironment. BCR, B cell receptor; Ig, immunoglobulin; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; TCR, T cell receptor complex; TFh, T CD4+ follicular helper.

been recapitulated in lung adenocarcinoma models in which neoantigen-specific B cells were necessary to activate TFh, which in turn activated effector CD8+ T cells by IL-21 secretion.<sup>24</sup>

A more organized B cell-centered immune response may arise within tumor tissues in the form of TLS that aggregate multiple immune cell types.<sup>45–47</sup> Early TLSs are mostly composed of B and T cell aggregates and lack FDC, while primary follicle-like TLS involve CD21+CD23+ FDC. The organization of a mature, or secondary follicle-like TLS is similar to that of a secondary lymphoid organ, with the presence of a germinal center allowing B cell maturation and differentiation into high-affinity plasma cells of

switched memory B cells (figure 1). A mature TLS is evidenced by the presence of germinal center FDCs, coexpressing CD21+ and CD23+, and may be surrounded by plasma cells secreting tumor-directed IgG or IgA antibodies.<sup>40 48 49</sup> These TLS have been identified across a wide spectrum of cancers at all disease stages, with variations in abundance between cancer types and between patients.<sup>50–52</sup> It is suggested that patients whose tumor-associated TLS are mature and present a high density of B cells harbor more effective antitumor immunity, while immune regulatory phenotypes have been mostly described in the absence of structured TLS.<sup>53–56</sup>

### Mechanisms of B cell modulation of antitumor immune response

Despite their key roles in coordinating effective anti-tumor immunity, B cells can be involved in immune tolerance in specific settings. As such, humoral responses do not always correlate with effective antitumor immunity. Polyreactive, aspecific IgG<sub>1</sub> antibodies have been notably reported in melanoma without antitumor activity.<sup>41</sup> Conversely, some antibody isotypes could drive immune suppression and thus harbor a protumoral role.<sup>57</sup> Karagiannis *et al* notably showed immunoregulatory functions for IgG<sub>4</sub> antibodies and IgG<sub>4</sub>+B cells in melanoma. Here, IgG<sub>4</sub> inhibited FcγRI activation on macrophages, and therefore, inhibited potential IgG<sub>1</sub> antitumor properties.<sup>58–59</sup> The formation of immune complexes in premalignant and malignant stroma may also drive chronic inflammation as shown in skin squamous cell carcinoma, by driving protumoral myeloid infiltration.<sup>60</sup> Immune complexes may also trigger the activation of the classical complement pathway which can contribute to tumor progression. The anaphylatoxin C5a, released from the cleavage of C5 downstream of the complement cascade can promote the recruitment of myeloid-derived suppressor cells that will impair efficient antitumor immune response<sup>61–62</sup>; C5a may also lead to increased angiogenesis by direct interaction with C5aR-expressing endothelial cells.<sup>63</sup> Conversely, complement components may harbor context-dependent antitumor roles, notably through interactions with tumor vasculature or tumor-infiltrating immune cells,<sup>64–65</sup> although the implication of the humoral response in these mechanisms is yet to be explored.

Specific regulatory populations of B cells (Bregs) have been also described, which are functionally defined by their capacity to inhibit effector cells such as CD8+T cells and NK cells.<sup>57–66</sup> Their action is mediated by inhibitory cytokines including IL-10, which secretion is a hallmark of B regulatory cells, as well as IL-35 or TGF-β.<sup>67–70</sup> Secretion of IL-10 by regulatory B cells may impair MHC I and II expression on the surface of tumor or antigen-presenting cells,<sup>71–72</sup> thus limiting antigen recognition and induction of immune responses. IL-10 and TGF-β also promote Treg activation and expansion,<sup>73–74</sup> and drive tumor-associated macrophages (TAMs) towards a protumoral phenotype.<sup>75</sup> These TAMs have been shown to harbor transcriptional programs favoring tumor invasion, involving notably expression of various matrix metalloproteinase genes, and could reinforce the immunosuppressive contexture by IL-10 or TGF-β production.<sup>76</sup> Unlike expression of FoxP3 by regulatory T cells (Treg), there is no unique single surface marker or transcription factor to identify B cells harboring regulatory functions, supporting the idea that Bregs are not confined to a specific lineage but instead may arise from B cells at various developmental stages in response to specific stimuli.<sup>66–77</sup>

It is yet unclear whether other specific B cell subpopulations may induce immune tolerance. Double negative B cells, lacking the CD27 memory marker and IgD expression, have been described as displaying an exhausted

phenotype with potential for aberrant auto-immune reactions, respectively, in the context of chronic infections and autoimmune disease.<sup>78</sup> Emerging evidence showed that expansion of double negative B cells in lung cancer was inversely related to the proportion of mature B cells.<sup>79</sup> In nasopharyngeal carcinoma, double negative B cells were shown to harbor alterations in pathways involved in mRNA processing, questioning their ability to induce antitumor responses.<sup>80–81</sup> Senescence mechanisms in B cells have also been partially described, with a decrease in class-switching capabilities and impaired effective immune response associated with ageing,<sup>82–83</sup> but those have not yet been described in solid tumors in contrast with T cell immunosenescence.<sup>84</sup>

### B cells as predictive markers in the era of immune checkpoint inhibitors

#### B cells and immune checkpoint inhibitors activity in solid tumors

Consistent with their role in T cell activation and TLS formation, B cell infiltration has been associated with improved prognosis in several solid tumor types such as melanoma,<sup>85</sup> breast cancer,<sup>86</sup> lung adenocarcinoma<sup>87</sup> or oral squamous cell carcinoma<sup>88</sup> before the era of modern immune checkpoint inhibition. Multiple studies since evaluated B cells as potential predictors of response to immune checkpoint inhibition, evaluating B cell infiltration, B cell-derived gene signatures, TLS, or circulating B cell subtypes (table 1).

The impact of B cell infiltration has been mostly studied in melanoma, where it has been associated with improved response rates to immune checkpoint inhibitors in both localized neoadjuvant and metastatic settings with PD-1 blockade as monotherapy or PD-1 and CTLA-4 combined inhibition.<sup>89–90</sup> Predictive histological scores have been explored in distinct melanoma and renal cell carcinoma cohorts, integrating B cell infiltration and features such as T CD8+ coinfiltration to improve response prediction.<sup>53–56</sup> The association between improved outcomes and B cell infiltration has since been demonstrated in several tumor types, including metastatic urothelial carcinomas treated with dual PD-L1 and CTLA-4 inhibition,<sup>91</sup> or triple negative breast cancers treated with neoadjuvant PD-L1 plus chemotherapy.<sup>92</sup> Molecular studies using RNA-sequencing yielded similar results in patients treated with PD-1 or PD-L1 inhibition across various tumor types, including melanoma, urothelial or lung cancers, where B cell signatures were associated with improved outcomes. Such association was also confirmed in rare tumors usually displaying lower susceptibility to immune checkpoint inhibitors such as soft tissue sarcomas.<sup>93</sup>

The impact of specific B cell subpopulations infiltrates is still being investigated. Studies conducted in melanoma and urothelial carcinoma patients treated with immune checkpoint inhibitors highlighted an association between survival and presence of antibody-producing plasma cells and plasmablasts.<sup>34–90–94</sup> In non-small cell lung carcinoma patients treated with atezolizumab, an increased plasma cell signature was related to longer survival and

**Table 1** B cells and outcomes of patients with solid tumors treated with immune checkpoint inhibitors

Histology	N	Treatment	B cell quantification	Study compartment	Marker	Outcomes	Ref
Renal cell carcinoma	28	Anti PD-1 Anti PD-1+anti CTLA-4 anti PD-1+anti VEGFR	Bulk RNA sequencing	Tissue	B cell signature	Higher response rate	53
Melanoma	44	Anti PD-1	Flow cytometry	Blood	IgM Memory B cells	Higher response rate, longer progression-free survival and overall survival	101
	41	Anti PD-1 Anti PD-1+anti CTLA-4	Bulk RNA sequencing	Tissue	B cell signature BCR diversity and clonal expansion	Higher response rate	53
	12	Anti PD-1 Anti PD-1+anti CTLA-4	Mass cytometry	Tissue	Memory B cells	Higher response rate	53
	70	Anti PD-1 Anti CTLA-4	Bulk RNA sequencing	Tissue	Memory B cell signature	Higher response rate and longer progression-free survival	96
	32	Anti PD-1	Single-cell RNA sequencing	Tissue	Plasmablasts Naïve B cells	Higher response rate	34
	41	Anti PD-1	Immunohistochemistry	Tissue	Plasmablasts	Higher response rate	34
	64	Anti PD-1 Anti PD-1+anti CTLA-4	Bulk RNA sequencing	Tissue	Plasma cells Naïve B cells BCR clonality	Higher response rate	90
	535	Anti CTLA-4	Bulk RNA sequencing	Tissue	TLS signature	Longer overall survival	56
	177	Anti CTLA-4	Immunofluorescence	Tissue	B cell infiltration CD8+CD20+ TLS	Longer overall survival	56
Urothelial Carcinoma	28	Anti PD-L1+anti CTLA-4	Immunohistochemistry /immunofluorescence	Tissue	B cells TLS	Higher response rate Higher response rate, longer relapse-free survival and overall survival	91
	21	Anti PD-L1	Bulk RNA sequencing	Tissue	Memory B cell signature	Higher response rate and longer progression-free survival	96
	29	Anti-PD1	Immunohistochemistry	Tissue	Antibody-secreting cells	Longer progression-free survival	94
Non-small cell lung cancer	43	Anti PD-1 Anti PD-L1+platinum	Bulk RNA sequencing	Tissue	B Cell signature	Longer progression-free survival	160
	891	Anti PD-L1	Bulk RNA sequencing	Tissue	Plasma cell signature	Higher response rate and longer overall survival	95
	254	Anti PD-L1	Immunofluorescence	Tissue	TLS	Longer overall survival	95
	122	Anti PD-1	Flow cytometry	Blood	IgM Memory B Cells	Higher response rate and progression-free survival	100
Triple negative breast cancer	22	Anti PD-L1+taxane	Single-cell RNA sequencing	Tissue	B Cells	Higher response rate	92
Soft tissue sarcoma	47	Anti PD-1	Bulk RNA sequencing	Tissue	B cell signature	Higher response rate and longer overall survival	93
Pan-tumor*	39	Anti PD(L)-1 Anti PD-1+anti CTLA-4	Flow cytometry	Blood	Increased Naïve B Cells on therapy Increased IgG Memory B Cells	Higher disease control rate lower disease control rate	102

\*Non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma, gastric and cholangio-carcinoma. BCR, B cell receptor; TLS, tertiary lymphoid structure.



higher response rates; such association was, however, not reported with germinal center or follicular B cell signatures.<sup>95</sup> Tumor-directed antibodies, which may constitute potential surrogates of plasma cell infiltration, may also inform response to immunotherapy, in patients with renal cell carcinoma, the presence of IgG-stained tumor cells was associated with improved survival on nivolumab alone or in combination with ipilimumab.<sup>40</sup>

The respective role of in situ naïve and memory B cells remains less clear. Intratumor switched memory B cells have been associated with increased responses to PD-1 inhibition in melanoma<sup>53</sup> and renal cell carcinoma,<sup>53</sup> while a memory B cell signature was linked to higher response rates and survival benefits for patients with metastatic urothelial carcinoma and melanoma treated with PD-(L)1 inhibitors.<sup>96</sup> These reports contrast with other cohorts including patients with melanoma, in which the naïve B cell compartment was most positively associated with outcomes.<sup>34,90</sup> The impact of the rarer double negative B cells has not been directly studied in the context of immune checkpoint inhibition, although some reports hint at a potentially immunotolerant role in nasopharyngeal carcinoma.<sup>80,81</sup>

There is now growing evidence that an organized B-cell response with intratumor TLS, rather than the presence of individual B cell subtypes, could be associated with better outcomes to immune checkpoint inhibitors. Previously described studies highlighting the predictive role of plasma cells or tumor-directed immunoglobulins also demonstrated that such markers could be surrogates of intratumor TLS.<sup>40,95</sup> In melanoma or renal cell carcinoma, B cells infiltration associated with improved outcomes was also consistently associated with the presence of TLS.<sup>53,56</sup> Association between TLS and response to immune checkpoint inhibition has notably been reported in lung cancer, as well as in sarcoma.<sup>91,93</sup> The TLS maturity stage may be a more stringent predictor of response to immunotherapy. In patients with various metastatic solid tumors subtypes treated mostly (90%) with PD-1 or PD-L1 inhibition alone, mature TLS were associated with increased response rates and survival.<sup>97</sup> A similar association has been demonstrated in dedicated series including localized lung cancers treated with neoadjuvant chemimmunotherapy, and metastatic esophageal cancers treated with immune checkpoint inhibition.<sup>98,99</sup>

Few studies explored the interplay between circulating B cells and immune checkpoint inhibition, which could be a promising strategy for non-invasive and dynamic evaluation of the immune contexture. High levels of baseline unswitched memory B cells, which may reinitiate germinal center reactions on repeated antigenic stimulation, have been described as predictors of outcomes in patients treated with PD-1 inhibitors for metastatic non-small cell lung carcinoma<sup>100</sup> or renal cell carcinoma.<sup>101</sup> In the latter cohort, the baseline circulating memory B cells were also associated with TFh, known to promote B cell maturation and T CD8+ lymphocyte expansion, in a peripheral immune landscape that remained consistent

during the course of treatment. These observations contrast with another pan-tumor cohort, in which baseline B cell levels did not impact outcomes, but in which an increase in naïve B cells was associated with better disease control on PD-1 inhibition.<sup>102</sup> These discrepancies across studies highlight the limited level of evidence currently available regarding circulating B cell subpopulations and outcomes on immune checkpoint inhibition, owing to small cohorts and non-uniform measurement methods, which have yet to be replicated in larger and more homogeneous studies.

### B cells as potential mediators of immune checkpoint inhibitors toxicity

Approximately 20% of patients treated with anti-PD-1 monotherapy develop grade 3 or higher treatment-related adverse events, and up to 50% with dual checkpoint inhibition.<sup>103</sup> Toxicity mechanisms involving T CD8+ lymphocyte activation are thought to be similar to those that drive immune response,<sup>104</sup> but data remain scarce regarding the specific role of B cells. A few studies described potential mechanisms of B cell-mediated toxicity, either through the expansion of B autoreactive populations or modified cytokine expression profiles.

Immune-related adverse events were notably associated with an increase in plasmablasts, which may express autoreactive antibodies, in a cohort of patients with metastatic melanoma treated with immune checkpoint inhibitors.<sup>105</sup> Likewise, specific autoreactive antibodies have been described in patients treated with immune checkpoint inhibitors and presenting with hypophysitis or pneumonitis.<sup>106</sup> Toxicity may also be promoted by the expansion of CD21<sup>low</sup> B cell subtypes: these autoreactive B cells harbor strong antigen presentation capabilities and are understood to trigger T cell-mediated inflammation in autoimmune diseases or chronic infections.<sup>105,107</sup> Impaired regulatory B cell functions have also been described in patients with non-small cell lung cancer harboring immune-related toxicities, which identification may help improve patient monitoring.<sup>108</sup> Novel efforts focus on genomic polymorphisms that may impact immune signaling. A polymorphism in the IL-7 gene has been recently identified as a potential predictor of immune-related toxicities in melanoma patients.<sup>109</sup> While IL-7 is necessary for lymphocyte maintenance, variant IL-7 expression by B cells has been associated with increased T cell clonality and expansion of terminally activated TEMRA CD8+T cells. The increased toxicity in this population was also associated with increased responses to immune checkpoint inhibition, hinting at a global impact on immune activation.

The understanding of B cell-mediated autoimmunity in cancer remains to be fully characterized as several mechanisms may be in play, including activation of autoreactive clones by immune checkpoint inhibitors, or recognition of neoantigens homologous to non-cancer antigens. Large-scale integrative studies exploring genetic polymorphisms, systemic immune cell and cytokine contexture,

such as the PREMIS trial (NCT03984318), may help better understand the determinants of immune-related adverse events and help improve patient management.

### A developing role for immune checkpoint expression on B cells

Expression of immune checkpoints and their relationship with antitumor response have been lesser studied in B cells, although current evidence confirms inhibitory roles for the PD(L)-1 axis. Mechanisms of PD-(L)1 immune suppression involve impaired BCR engagement<sup>110 111</sup> and decreased interactions between B and T cells that are necessary for B cell-driven CD4+ and CD8+ expansion.<sup>112</sup> More ambivalent roles for the PD(L)-1 axis have been described with regard to germinal center formation and crosstalk with TFh. Notably, expression of PD-1 and PD-L1 has been associated with germinal center B cell survival, leading to increased production of plasma cells. Though, this survival mechanism impaired negative B cell selection, yielding plasma cells with lesser affinity and flawed humoral response, comforting its overall inhibitory role in B cell-mediated immunity.<sup>113</sup>

Specific B cell checkpoints may also be at play in B cell-driven immunity. Notably, the surface receptor TIM-1 has been recently described as a potential hallmark of B cell regulation.<sup>114–116</sup> In murine models of melanoma, tumor growth was associated with an expansion of TIM-1+B cells in draining lymph nodes.<sup>117</sup> Likewise, responders to PD-1 targeted therapy demonstrated decreased tumor infiltrating TIM-1+B cells over time. Loss of TIM-1 on B cells in several solid tumors models impaired tumor growth through enhanced antigen presentation, and expression of type I interferon signatures promoting T cell responses. As such, TIM-1 could be an essential B cell-restrained immune checkpoint and a promising therapeutic target.

### Cytokines as correlates of B cell fate and immune contexture

The cytokine contexture is key to shape immune activation or tolerance, potentially impacting immune cell activation and lineage fate.<sup>118</sup> Cytokines may be secreted by immune, stromal or tumor cells, and can be assessed at tissue or systemic levels, making them potentially versatile biomarkers of immune response (table 2). Some have been described as directly involved in B cell expansion and activation, such as B cell attracting chemokine (BCA)-1 also known as CXCL13, or B cell activating factor (BAFF). So far, published cohorts provided mixed signals about their respective role in prognosis or response to immune checkpoint inhibition. For instance, high BCA-1/CXCL13 tissue levels have been associated with adverse outcomes in prostate cancer,<sup>119</sup> and soluble BCA-1/CXCL13 with shorter survival in patients with kidney cancer treated with anti-PD-1 nivolumab.<sup>101 120</sup> Inverse associations have been described regarding prognosis in ovarian cancer,<sup>121</sup> or response to immune checkpoint inhibitors in urothelial carcinoma,<sup>94 122</sup> while reports remain conflicting in breast cancer.<sup>123–125</sup> The pleiotropy of BCA-1/CXCL13 may explain differential effects across cancer subtypes.

Antitumor roles may be exerted not only through B cell activation, but also through cytotoxic CXCR5+T cells as well as promotion of TLS formation.<sup>126–128</sup> Conversely, BCA-1/CXCL13 may promote Bregs expansion<sup>129</sup> and act as a growth factor in CXCR5-expressing tumor cells.<sup>130</sup> Similarly controversial roles have been described for BAFF, which has been associated with improved response to immune checkpoint inhibitors in melanoma<sup>131 132</sup> but not in kidney cancer.<sup>101</sup> Antitumor immune effects of BAFF have been described through B cell expansion,<sup>131 133 134</sup> T cell memory and TH1 polarization,<sup>131</sup> while maintenance of a FOXP3+Treg pool<sup>131</sup> and increased competitiveness for clonal antitumor B cell expansion<sup>134 135</sup> could be responsible for its detrimental effects.

Other key cytokines have been broadly associated with acquisition of B regulatory phenotypes and immune tolerance, such as IL-10 as previously described, which is generally expressed by B regulatory cells but may also be secreted by tumor cells and other immune cells.<sup>68 136</sup> Consistently, high IL-10 expression was associated with poor outcomes in patients with colorectal, lung cancer, or melanoma.<sup>72 136–138</sup> While prostimulatory roles of IL-10 of T CD8+ and NK cells have been otherwise suggested at high concentrations,<sup>137 139 140</sup> recombinant pegylated IL-10 in solid tumors did not improve antitumor immune responses.<sup>141 142</sup> Levels of TNF- $\alpha$  may also play a role in the engagement toward regulatory function in B cells as depicted in squamous cell carcinoma,<sup>143</sup> but this role has not yet been confirmed in clinical cohorts, prompting further research regarding TNF- $\alpha$  involvement in B cell fate.<sup>144</sup>

Chronic inflammation has been largely associated with protumoral myeloid infiltration and T cell dysfunction. These immune states are usually reflected by high levels of inflammatory cytokines,<sup>145–147</sup> with recent evidence of a potential association with specific B cell features. Data from patients with kidney cancer treated with immune checkpoint inhibitors as monotherapy notably demonstrated inverse relationships between unswitched memory B cell subpopulations, which were associated with longer survival, and protumoral inflammatory cytokines IL-6 and IL-8.<sup>102</sup> High IL-6 levels have been previously linked with myeloid tissue signatures and resistance to immune checkpoint inhibitors in kidney cancer and melanoma,<sup>13 145 148</sup> while IL-8 expression has been associated with high neutrophil infiltration and poor outcomes in melanoma, lung or kidney cancer.<sup>149</sup> These associations differ from our previously limited understanding of IL-6, IL-8 and B cells interactions: IL-6 was first described as a B cell stimulating factor with potential autoimmune implications<sup>150</sup>; IL-8 is expressed by germinal center immune cells to promote B and T cell interactions, but could also limit B cell expansion in distinct settings.<sup>151 152</sup> A better understanding of the relationship between B cells and inflammatory cytokines could help leverage soluble factors as potential biomarkers or therapeutic targets.



**Table 2** Cytokines reportedly associated with distinct B cell contexture in selected solid tumors

Cytokine	Tumor type	Model	Outcomes	Immune cell contexture	Ref
BCA-1/CXCL13	Kidney cancer	Human	Shorter overall survival with ICI	Decreased peripheral memory B cells peripheral T follicular helper	101
	Melanoma, lung, ovarian cancer	Murine	Decreased responses with ICI	Increased IL-10+regulatory B cells	129
	Ovarian cancer	Human	Improved prognosis	Increased B cell infiltration CD8+T cell infiltration TLS presence	121
	Urothelial carcinoma	Human	Longer progression-free and overall survival with ICI	Increased B cell infiltration CD8+T cell infiltration TLS presence	94 122
	Breast cancer	Human	Longer disease-free survival	Increased T cell infiltration TLS presence	125 128
BAFF	Kidney cancer	Human	Shorter overall survival with ICI	Decreased peripheral memory B cells peripheral T follicular helper	101
	Melanoma	Human, murine	Longer overall survival with ICI	Increased B cell antigen presentation TH1 cells infiltration T cell memory acquisition FOXP3 expression on T cells	131
IL-10	Melanoma	Human, cell cultures	Tumor growth	Increased Tumor-associated macrophages Decreased T cell infiltration and activation	71 76 136
	Colon cancer	Cell cultures	Tumor growth	Decreased CD8+T cell activation MHC I and II expression	72
	Squamous skin carcinoma	Murine	Tumor regression	Increased CD8+T cell infiltration and activation	139
TNF- $\alpha$	Squamous skin carcinoma	Murine	Tumor growth	Increased B regulatory cells expansion	143
IL-6	Kidney cancer	Human	Shorter overall survival with ICI	Decreased peripheral memory B cells peripheral T follicular helper	101
	Melanoma, colon	Human, murine	Lower response rates with ICI Higher autoimmunity	Decreased CD8+T cell infiltration Increased TH17 cells, neutrophil, macrophage infiltration	145 148
IL-8	Kidney cancer	Human	Shorter overall survival with ICI	Decreased peripheral memory B cells peripheral T follicular helper	101
	Melanoma, lung, kidney cancer	Human	Shorter overall survival with ICI	Increased neutrophil and monocyte infiltration Decreased T cell infiltration	149

ICI, immune checkpoint inhibitors; MHC, major histocompatibility complex; TLS, tertiary lymphoid structures.

## Perspectives

The multifaceted involvement of B cells in antitumor immunity, promoting T cell-dependent and independent response, could be used to identify potential biomarkers and therapeutic targets. Easily accessible surrogate markers of B cell activation, such as peripheral cytokines, may provide dynamic insights into immune contexture at a patient level. Additional insights into B cell response may be provided by their BCR repertoire, which clonality and diversity could inform potential sensitivity to immune checkpoint inhibition.<sup>53 90</sup>

Accurately picturing the antitumor immunity landscape remains, however, a challenging endeavor. Mitigation of an efficient immune response may occur owing to metastatic niches with distinct resident immune cells and potential inpatient tumor heterogeneity.<sup>153</sup> Reliable assessment of B cell infiltration and TLS by conventional pathology may be impacted by tissue sampling despite efforts to standardize practice.<sup>49</sup> Marker genes or proteins

used for B cell subtyping still differ across studies, while bulk molecular signatures have yet to demonstrate their ability to accurately discriminate B cell subtype infiltration when compared with standard pathological assessments.<sup>90</sup> As such, prospective validation will be essential to implement a pragmatic B cell-derived biomarker into clinical practice.

To further refine the patient selection, what has been mostly reported in the context of single-agent anti-PD1 has to be more widely demonstrated in the setting of combinations, which have become standard of care in multiple solid tumors.<sup>9</sup> So far, ancillary studies of pivotal combination trials in kidney cancer, involving dual checkpoint inhibition or targeted therapies plus immune checkpoint inhibitors, did not yet identify specific immune states amenable to guide therapy.<sup>154 155</sup> Sustained translational research efforts, thus, remain essential to identify contemporary relevant predictors of outcomes.

The potential for therapeutic implications, with regard to B cells, may not be limited to patient selection. Novel insights into B cell-specific checkpoints such as TIM-1 may accelerate development of B cell-specific therapies. Cytokines impacting B cell development could be used to modulate the immune response; such proof of concept has been shown in autoimmune diseases with BAFF inhibitors,<sup>156</sup> although indiscriminate cytokine-directed therapies are still stuttering in solid tumors with no contemporary positive phase 3 trials.<sup>141 157</sup> Promising avenues may also reside in adoptive transfer of engineered B cells to confer long lasting tumor immunity, a therapeutic area that is still in its infancy.<sup>44 158 159</sup> Overall, the field of B cells is swiftly growing in patients with solid tumors and may be one of the keys to continue improving immune-based approaches in cancer.

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