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The implication of anti-PD-1 therapy in cancer patients for the vaccination against viral and other infectious diseases

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ABSTRACT

The phenomenon of ‘T cell exhaustion’, a state of T cell dysfunction observed during chronic infections and cancers, has been a major obstacle in mounting appropriate immune responses against infectious agents or tumor antigens. The exhausted T cells are characterized by poor effector functions mainly due to the overexpression of inhibitory receptors such as programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), T cell immunoglobulin and mucin-domain containing 3 (TIM3), lymphocyte activation gene 3 (LAG3), and T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT), commonly referred to as immune checkpoint (ICP) molecules. ICP blockade, especially of PD-1, which can potentially reverse T cell exhaustion and thereby re-stimulate the impaired immune system, is widely used in clinics as a promising therapeutic strategy for various cancers and is more recently being investigated in infectious diseases as well. In fact, cancer patients represent a population of immunocompromised individuals who are more susceptible to infections and associated complications, and thus the need for protective vaccinations against these diseases is of prime importance in this category. When it comes to vaccinating anti-PD-1-treated cancer patients against infectious agents, a special focus should be brought on the revived immune cells, which could be dynamically affected by the antigenic stimulation. However, since cancer patients are not generally included in clinical trials for designing vaccines against infectious diseases, the possible interaction between vaccine immune responses and ICP therapy is largely unexplored. Mechanistically, the reversal of T cell exhaustion by ICP in an otherwise immunocompromised population could be beneficial for the vaccine's efficacy, helping the immune system to mount a robust immune response. Nevertheless, patients with cancer undergoing anti-PD-1 blockade are known to experience immune-related adverse effects (irAEs). The risk of increasing the irAEs due to the overstimulation of the immune system during vaccination is a major concern. Therefore, while

routine vaccination is indispensable for the protection of cancer patients, the impact of PD-1 blockade on vaccine responses against infectious agents requires careful consideration to avoid undesirable adverse effects that could impair the efficacy of anti-cancer treatment.

Keywords: immune checkpoint, PD-1, COVID-19, Influenza, SARS-CoV-2, T cell exhaustion, cancer immunotherapy, vaccination, infection

Abbreviations: AE, adverse events; AP-1, activator protein-1; AU, arbitrary units; COVID-19, coronavirus disease 2019; CP, cancer patients; CRS, cytokine release syndrome; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ERD, enhanced respiratory syndrome; HC, healthy controls; HIV, human immunodeficiency virus; HPV, human papillomavirus; ICI, immune checkpoint inhibitors; ICP, immune checkpoint; IL, interleukin; irAEs, immune-related adverse effects; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; LCK, leukocyte-specific tyrosine kinase; N.R., not reported, NAbT, neutralizing antibody titer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PI3K, phosphoinositide 3-kinase; RAS, rat sarcoma; RSV, respiratory syncytial virus; SARS-CoV, severe acute respiratory syndrome coronavirus; SHP, Src homology phosphatase; TCR, T cell receptor; T_{eff}, effector T cells; T_{fh}, follicular helper T cell; Tregs, regulatory T cells. vs., versus.

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References

1. Introduction

Cancer is a complex ecosystem and a dynamic milieu composed of different cell types interacting with each other partly via soluble factors. Tumor cells are surrounded by stromal cells and various subsets of immune cells that can communicate with them. The complexity of the tumor microenvironment justifies the inter-tumoral and inter-patient heterogeneity that still remains a hurdle in drawing a clear picture of cancer progression and successfully treating each individual patient (Jamal-Hanjani et al., 2015).

In the long history of cancer treatment, the most remarkable milestone during the past decade was the advent of immunotherapy. While conventional chemotherapy and radiotherapy directly target/kill cancer cells and induce immunogenic cell death, cancer immunotherapy is designed to boost and instruct the patient's immune system. In the domain of immunotherapy, immune checkpoint blockades that target cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1)/ programmed cell death-ligand 1 (PD-L1) that reverse the dormant state of the tumor-infiltrating immune cells have proven clinical success in the treatment of some refractory cancers. However, resistance to immune checkpoint (ICP) inhibition may also arise and efforts have been made to identify biomarkers that could help in the prediction of patients who will respond to immunotherapy (S. Wang et al., 2021). A meta-analysis has found that the objective response rates in anti-PD-1/PD-L1 treated patients reached only up to 29% in melanoma, 27% in lung cancer, and 21% in genitourinary cancer patients (Chen et al., 2021). Aside from primary resistance that occurs rapidly in response to treatment, acquired resistance is also observed in the patients with at least 6 months of progression-free initial survival that limits the efficacy of anti-PD-1 therapy (Dobosz et al., 2022). Many factors like the lack of tumor antigen expression and tumor immunogenicity linked to reduced mutation rates, the expression of additional checkpoint molecules by tumor cells, the presence

of certain circulating noncoding RNAs that can regulate tumor immunogenicity, and the reduced diversity of the gut microbiota could contribute to the resistance to immunotherapy and the lack of success of PD-1 blockade (Sun et al., 2020). In parallel, anti-PD-1 treatment has been shown to apply a selective pressure on melanoma tumor cells leading to tumor evasion via mutations in MHC class I or IFN- γ receptor signalling molecules (Zaretsky et al., 2016). All these factors highlight the challenges to overcome for improving the outcomes of PD-1/PD-L1 immunotherapy.

One major factor that correlates with the response to immune checkpoint therapy is the variable density and variety of infiltrating immune cells in different tumors. Some tumors termed “hot tumors” are quite well infiltrated by immune cells to mount a strong inflammatory reaction against tumor antigens that is determinant for the establishment of an efficient anti-tumor response (Duan et al., 2020). However, some tumors that are less immunogenic, termed “cold tumors”, do not succeed to attract immune cells, mainly effector T cells (T_{eff}), or are predominantly infiltrated by regulatory cells, and consequently struggle to mount a robust anti-tumor immune response. Several factors, including the unavailability of some tumor antigens, a weakness in antigen presentation, an impaired T cell activation, and a T_{eff} cell ‘homing deficit’ towards the target, are responsible for the lack of T cell infiltration at the cold tumor sites (Bonaventura et al., 2019). Novel approaches to transform immune-excluded cold tumors into immune-inflamed hot tumors by improving T cell infiltration are currently of enormous interest to maximize the efficacy of cancer immunotherapy.

New cancer therapeutic strategies are emerging with the use of chimeric antigen receptor (CAR)-T cells, personalized cancer vaccines, and also combined therapies merging the effect of multiple ICP blockades or other strategies with ICP inhibition to synergistically improve the therapeutic outcome of cancer medicines (Waldman et al., 2020). Besides, some attractive

strategies lie in the possibility of combining immune checkpoint inhibitors (ICI) with an inflammatory boost stimulus into the tumor to maximize the effect of ICP blockade in the tumor core. Interestingly, influenza virus infection has been correlated with a decrease in cancer-specific mortality in lung cancer patients highlighting the benefit of local inflammation at the tumor site (Newman et al., 2020). A similar synergistic impact is conceivable when administering vaccines against infectious diseases in cancer patients undergoing immune checkpoint therapy. On the other hand, owing to the heterogeneity of tumor microenvironment between tumors and between patients, the risk of some patients developing immune-related adverse events (irAEs) could be increased with a stronger boost of the immune response.

Due to their vulnerable immune status, cancer patients including the ones undergoing ICP therapies are necessarily prioritized for the vaccination campaigns for flu and coronavirus disease 2019 (COVID-19). However, data remain scarce on the possible reciprocal interaction between PD-1 blockade and vaccination. Intuitively, the reversal of T cell exhaustion by PD-1 blockade, that is beneficial to stimulate the anti-tumor immune response, can also amplify vaccine-related immunity. This review discusses the benefits and challenges of vaccinating cancer patients under immunotherapy against viral and other infectious diseases and novel opportunities in designing vaccination strategies combining immune checkpoint inhibitors.

2. PD-1/PD-L1 pathway

PD-1 interacts with its ligands PD-L1 and PD-L2 to maintain immune homeostasis by inducing central and peripheral tolerance. In contrast to the inhibitory effect of PD-1-PD-L1 interaction on T cell receptor (TCR) and costimulatory signals leading to apoptosis, anergy, and exhaustion of T_{eff} cells (Yokosuka et al., 2012), the PD-1/PD-L1 axis induces continuous Foxp3 expression and proliferation in regulatory T cells (Tregs) (Francisco et al., 2009). The tightly regulated expression of these molecules is essential for inhibiting self-reactive T cells and promoting

Treg functions to prevent autoimmune responses (Ghosh et al., 2021). However, the involvement of dysregulated PD-1/PD-L1 pathway is decisive in the reduction of anti-tumor response, and its overexpression on tumor-infiltrating T cells and tumor cells has been associated with poorer prognosis in cancer patients (Zhang et al., 2015). Recently, the PD-1/PD-L1 axis has also been found to be involved in the selective migration of Tregs and T_{eff} through lymphatic endothelial cells in a mouse model of melanoma (Piao et al., 2022).

PD-1, also known as CD279, was first discovered by Tasuku Honjo and colleagues in 1992, as a membrane protein that induces apoptosis in 2B4.11 cell line (a murine T-cell hybridoma) and interleukin-3 (IL-3)-deprived LyD9 cell line (a murine hematopoietic progenitor cell line) (Ishida et al., 1992). Further studies carried out in PD-1 deficient mice have revealed the role of PD-1 in the induction of peripheral self-tolerance by negatively regulating immune responses (Nishimura, 1998). However, the nature of this inhibitory pathway became clear with the identification of B7-homologue 1 (B7-H1) -a member of the B7 family that consists of structurally related cell surface ligands that bind to lymphocyte co-stimulatory or co-inhibitory receptors- as the ligand of PD-1 (later named as PD-L1) (Dong et al., 1999; Freeman et al., 2000). The second ligand of PD-1, termed PD-L2, was also discovered immediately after, that shared 40% sequence homology and overlapping functions with PD-L1 (Y. Latchman et al., 2001). Similar to PD-1, PD-L1 deficient mice were also prone to autoimmune diseases (Y. E. Latchman et al., 2004), demonstrating the critical negative regulatory role of the PD-1/PD-L1 pathway on effector T cell immune responses.

Although a low expression is found at the basal level, PD-1 is transcriptionally upregulated on T, B, and natural killer (NK) cells, dendritic cells (DCs), and macrophages upon antigen stimulation. While PD-L2 expression is limited mainly to antigen-presenting cells, PD-L1 is constitutively expressed or induced in numerous cell types including myeloid or lymphoid

immune cells, normal epithelial cells, and cancer cells, conferring a more prominent role for PD-L1 than PD-L2 in tumor immunity (Ghosh et al., 2021). Structurally, PD-1 consists of four domains, an immunoglobulin variable region (IgV), a transmembrane domain, immunoreceptor tyrosine-based inhibitory motifs (ITIMs), and immunoreceptor tyrosine-based switch motifs (ITSMs). The binding of PD-L1 to PD-1 induces the phosphorylation of intracellular ITIMs and ITSMs that further results in the recruitment of tyrosine acid phosphatase Src homology phosphatase 1 (SHP-1) and SHP-2 in close proximity to TCR. SHP-1 and SHP-2 dephosphorylate several targets involved in the TCR signalling pathways (Fig. 1) (Salmaninejad et al., 2019; Sharpe & Pauken, 2018).

One of the main pathways involved in TCR signalling is the PI3K/AKT/mTOR pathway. Either the phosphoinositide 3-kinase (PI3K) can be dephosphorylated and inhibited directly by SHP-1/2, or SHP-1/2 can activate the phosphatase and tensin homolog (PTEN) via dephosphorylating the protein kinase casein kinase 2 (CK2), which further leads to the inhibition of PI3K. Another major pathway of TCR signalling is the RAS/MAPK/ERK pathway involved in cell proliferation and differentiation. SHP-1/2 directly targets rat sarcoma (RAS) that then leads to the inhibition of the RAS/MAPK/ERK pathway. The leukocyte-specific tyrosine kinase (LCK) phosphorylates the proteins zeta chain of T-cell receptor-associated protein kinase (ZAP70), CD3-zeta (CD3 ζ), and protein kinase C θ (PKC θ) that continue to activate TCR signalling. PD-1 signalling can also inhibit the function of LCK via SHP1/2 recruitment, and hence modulate the TCR signalling downstream (Sheppard et al., 2004). In contrast, PD-1 signalling via SHP1/2 is found to upregulate basic leucine zipper ATF-like (BATF), a member of the activator protein-1 (AP-1) transcription factor family, which can counteract the effector T cell transcriptional programs (Quigley et al., 2010). In essence, the overexpression of PD-1/PD-L1 inhibits T cell growth, proliferation, and survival, through all

these mechanisms, conferring them a dysfunctional or ‘exhausted’ phenotype in the tumor microenvironment (Fig. 1) (Salmaninejad et al., 2019; Sharpe & Pauken, 2018).

3. Parallels between cancer and infection: immune checkpoints are altered in both

The phenomenon of T cell exhaustion that represents the functional impairment and terminal deletion of persistently stimulated antigen-specific T cells was first described during chronic viral infections (Gallimore et al., 1998), making the host susceptible to viral immune invasion. Cancer shares many parallels with chronic infections due to the prolonged persistence of the antigens, and the crucial role of exhausted T cells in cancer progression has also been unfolded in later years (Fig. 2). The differentiation of the hyporesponsive tumor-specific CD8⁺ T lymphocytes starts early during tumorigenesis, and continuous antigen encounter and TCR stimulation in the tumor microenvironment are necessary to drive them towards exhaustion (Schieteringer et al., 2016). Several studies have found similar transcriptional signatures in the CD8⁺ T cells in cancer and chronic viral infection (Dolina et al., 2021; Khan et al., 2019). The AP-1 family transcription factors are found to be important drivers of the progression of various cancers due to their pleiotropic effects on cell proliferation, apoptosis, and T-cell activation, anergy or exhaustion (Fig. 1) (Atsaves et al., 2019). Similarly, significant activation of AP-1 family members is observed during viral or bacterial infections to modulate the immune responses against them (Quigley et al., 2010; A. Wang et al., 2013; Yuan et al., 2022). The analogous T cell phenotypes in cancer and infection could explain why cancer patients are more susceptible to antigen invasion when they are exposed to viruses or other infectious agents.

The onset of T cell exhaustion is characterized by the high expression of cell surface inhibitory receptors/ICP such as PD-1 that will inhibit the TCR signalling and effector functions by engaging the PD1-PD-L1 pathway. While few contemporary studies have been emerging

showing the beneficial effect of PD-1-PD-L1 blockade in potentiating tumor immunity, in 2006, Barber et al demonstrated for the first time that the reversal of T cell exhaustion is possible with PD-1-PD-L1 inhibition in chronic lymphocytic choriomeningitis virus (LCMV) infection (Barber et al., 2006). Albeit the clinical application of PD-1 blockade has witnessed major breakthroughs in cancer therapy during the past decade, the advancement of PD-1 blockade for infectious diseases is in its infancy (Hashimoto et al., 2018). The dysregulated expression of PD-1 or PD-L1 has been described during hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infections (Jubel et al., 2020) and more recently in severe COVID-19 patients (Bonam, Chauvin, Levillayer, et al., 2022; Bonam, Chauvin, Mathew, et al., 2022; R Bonam et al., 2022). Bacteria and fungi could also induce PD-L1 on antigen presenting cells and in turn suppress T_{eff} responses by promoting Tregs (Karnam et al., 2021; Periasamy et al., 2011; Stephen-Victor et al., 2017). Of note, experimental studies have shown an enhanced expression of PD-L1 in cancer cells upon exposure to infectious agents and aggravation of cancer *in vivo* when exposed to the infections (Groeger et al., 2022; Ren et al., 2023). A number of clinical trials investigating PD-1 blockade are underway in these diseases and promising data seems to emerge (Awadasseid et al., 2021; Jubel et al., 2020). Besides suggesting the potential of the PD-1/PD-L1 pathway as a biomarker to predict disease progression and treatment outcome, these shreds of evidence emphasize the potential of PD-1 inhibition to tackle drug-resistant pathogens.

4. How does anti-PD-1 therapy modify the immune system? lessons learned from experimental models and cancer patients

As described above, the major mechanism of anti-PD-1 immunotherapy is to reinvigorate the $CD8^+$ T cells that impart cytotoxic effects against tumor cells. Recent combination therapies with PD-1 blockade not only aim to reverse the exhaustion of $CD8^+$ T cells but also to promote

their expansion and survival. The engineered fusion of anti-PD-1 with an IL-15-IL-15R α complex known as IL-15 superagonist (sIL-15) can efficiently induce tumor-specific CD8⁺ T cells and reduce metastasis while overcoming extensive peripheral NK cell activation and toxicity caused by IL-15 alone in various transplantable tumor models in mice (Shen et al., 2022). Similarly, PD-1 blockade + IL-2 combination therapy is also being investigated for cancer. It has been demonstrated recently in a mouse model of LCMV infection that combined anti-PD-1 and IL-2 therapy reverts the stem-like state of PD-1⁺ TCF1⁺ CD8⁺ T cells to support viral clearance (Hashimoto et al., 2022), suggesting the great potential of incorporating cytokines to modulate immune response with ICP therapy. In addition, PD-1 is expressed in tumor-infiltrating CD4⁺ T cells such as follicular helper T cells (Tfh), Tregs, NK cells, B lymphocytes, macrophages, DCs, and monocytes. The impact of PD-1 blockade on these cells has been insufficiently elucidated (Han et al., 2020). Indeed, in parallel to counteracting CD8⁺ T cell exhaustion, PD-1 blockade has been shown to reduce the Treg infiltration in tumors (Dyck et al., 2016). In contrast, some other studies recall the role of anti-PD-1 in the activation of Tregs leading to tumor progression, highlighting the controversial contribution of PD-1⁺ Tregs in cancer (Kamada et al., 2019; Kumagai et al., 2020). A recent study concluded that the unresponsiveness to ICIs combined with chemotherapy and the progression of metastatic triple-negative breast cancer were correlated with CD8⁺ T cell anergy, together with high levels of circulating antibody-secreting cells (ASCs), Tfh, and terminal NK cells before treatment (Egelston et al., 2022). Despite the lack of antigen receptors, the role of NK cells is well-established in anti-tumor immunity mirroring cytotoxic T cells (Laba et al., 2022). Moreover, anti-PD-1 therapy impacts the function and recruitment of Tfh cells (Herati et al., 2022) that provide essential help for B cells to generate antibodies. Potentially, the overactivation of Tfh and B cells could lead to autoreactive antibody production and the development of secondary autoimmunity.

It brings up the issue of irAEs, a parallel downside that occurs in cancer patients during ICI therapy due to the reactivation of the immune system. In addition to autoantibody production, various mechanisms such as inflammatory cell infiltration and pro-inflammatory cytokine production contribute to the development of irAEs. Some of the common irAEs generally appearing during ICP blockade therapy are linked with autoimmune responses like skin disorders, colitis, hepatitis, and thyroiditis (Callahan et al., 2016). The incidence of irAEs reaches 26.82% (21.73–32.6) in any grade and 6.10% (4.85–7.64) in severe grade in a meta-analysis of patients treated with different anti-PD-1/anti-PD-L1 agents (P.-F. Wang et al., 2017). In fact, several studies have demonstrated that the development of irAEs is positively correlated with ICI treatment benefits and improved patient survival. Nevertheless, it is important to note that serious secondary effects that require treatment with immunosuppressants can counteract the efficacy of ICI therapy. Besides, it is necessary to optimally control the profound toxicities that can eventually lead to serious complications and organ failures, to improve the patient's quality of life and survival (Iranzo et al., 2022).

5. Anti-PD-1 therapy in animal models and immune response to the vaccines

Few studies have been carried out in animal models to investigate the repercussion of PD-1 blockade towards immune response to vaccination against infectious agents. High expression levels of immune checkpoint molecules in immune cells are associated with the persistence of chronically-infecting pathogens and disease progression. Consequently, the combination of immune checkpoint blockade has emerged as an attractive strategy to enhance immune responses against pathogens. Human papillomavirus (HPV) infection is a common cause of certain types of cancers including cervical cancer, and head and neck cancers. The combination of HPV vaccination with PD-1 blockade has significantly controlled the tumor burden and improved the survival of C57BL/6 mice bearing HPV-expressing TC-1 tumors (Peng et al.,

2021). Based on one hypothesis of shared immune response at the same site, an interesting study from Newman et al described the improvement of the antitumor response against lung melanoma with an intranasal challenge with influenza virus during PD-1 blockade in mice (Newman et al., 2020). In contrast, influenza virus infection promoted melanoma growth in the skin, highlighting a diversion of the immune cells -particularly anti-tumor CD8⁺ T cells to the site of inflammation rather than at the tumor bed and the anti-cancer response could alternatively be rescued by PD-1 blockade (Kohlhapp et al., 2016). These results stress the prospects of coupling ICI therapy with an inflammatory trigger to reorientate the immune response towards the tumor site in the case of refractory cancers.

Towards the efforts to develop an ideal vaccine for HIV, PD-1 inhibition has been shown to improve the outcome of therapeutic vaccination and increase survival by inducing functional CD8⁺ T cells in a simian immunodeficiency virus infection model of Rhesus macaques (Pan et al., 2018; Rahman et al., 2021). Enhancement of virus-specific T cell responses along with virus control was also observed when anti-PD-L1 was combined with therapeutic vaccination in chronic Friend retrovirus infection model of mice (Knuschke et al., 2021). Blocking the PD-1/PD-L1 axis enhanced HIV-1 Gag-specific CD8⁺ T cell responses following vaccination of mice with dendritic cell-directed lentiviral vaccines (Dai et al., 2012). Another study carried out in HLA transgenic rabbits has demonstrated that synergistic blockade of PD-1 and LAG-3 improved the therapeutic vaccination efficacy of herpes simplex virus (Roy et al., 2019). PD-1 deficiency and PD-1 blockade following *Streptococcus pneumoniae* vaccination also significantly increased the protective IgG responses in mice (McKay et al., 2015). Similarly, PD-1 deficiency in mice augments the germinal center B cell and plasmodium-specific-Tfh cell responses during malaria vaccination, suggesting that PD-1 blockade could be effectively combined with malaria vaccination as well (Liu et al., 2015).

PD-1 blockade may not benefit each and every vaccination against infectious diseases. Management of respiratory syncytial virus (RSV) infection is still an unresolved issue since inactivated RSV vaccine is shown to induce enhanced respiratory syndrome (ERD) upon subsequent viral infection. Cotton rats (*Sigmodon hispidus*) serve as an excellent animal model for RSV infection, and this model replicates the RSV vaccine-induced ERD. Studies carried out in this model have shown that the development of ERD was found to be associated with low levels of pulmonary PD-1 expression (Muralidharan et al., 2019). Hence, in this case, PD-1 blockade would be more detrimental than beneficial and alternative strategies need to be devised to avoid the over-activation of the immune system in response to RSV vaccination. Similarly, PD-1 blockade has been found to exacerbate *Mycobacterium tuberculosis* (TB) infection in Rhesus macaque (Kauffman et al., 2021). It is necessary to take these findings into careful consideration when administering anti-PD-1 therapy to cancer patients who had prior exposure to TB.

6. Anti-PD-1 therapy alters immune responses during vaccination against infectious diseases in humans

Cancer patients are at higher risk of becoming seriously ill if they catch infections (flu, measles, COVID-19, and others), firstly because of their impaired immune system and also because their immune response should concentrate on fighting the tumor rather than resolving the infection-induced chronic inflammation. Vaccine antigens stimulate a number of cells of the innate and adaptive immune systems to generate the cellular and humoral responses post-vaccination. Since PD-1 is expressed in T_{eff} cells, T_{fh} cells, and B cells that are important in generating cellular and antibody responses, anti-PD-1 therapy could dynamically affect the post-vaccination immune responses. Theoretically, PD-1 blockade could be beneficial, augmenting antibody generation or cellular responses to vaccination, and conferring greater

protection from infection. Yet, there are several pitfalls in this assumption including the risk of increasing irAEs due to the hyperstimulation of the immune system in certain patients (Figure 3). Live-attenuated vaccines including measles, rotavirus, and chickenpox vaccines are not recommended for cancer patients due to the risk of viral replication and infection in vulnerable individuals (Ariza-Heredia & Chemaly, 2015). However, influenza vaccines are generally subunit protein vaccines and although they are limited by their low efficacy, it is safe to administer them in immunocompromised individuals in general. Besides, the COVID-19 era popularized the use of mRNA vaccines that are more potent than other vaccine strategies without imposing significant risks on a majority of individuals. Since cancer patients are not included in investigational trials for vaccine development, there is not enough clinical evidence so far to demonstrate the interaction between ICI therapy and different types of vaccines against various pathogens. Only a few retrospective studies have investigated the interaction between ICI therapy and vaccination for influenza and severe acute respiratory syndrome coronavirus (SARS-CoV)-2 in cancer patients (Table 1 and references therein).

6.1. Influenza vaccination in patients undergoing anti-PD-1 therapy: a long-standing debate

Annual influenza vaccination is recommended for cancer patients who are particularly at increased risk of influenza infection-related complications due to their underlying disease or cancer-directed treatments. Despite their immunosuppressive background, several studies have found that cancer patients can mount an immune response against influenza vaccines. However, the immunogenicity differs according to the type of cancer treatment received by the patients, and whether the generated response can fully protect them from influenza infection and associated complications is still controversial. Cancer-induced immunosuppression or the use of conventional cytotoxic or immunosuppressive therapies is expected to counteract the

cellular and humoral immune responses to influenza vaccination. Hence, patients undergoing chemotherapy have been shown to experience lower protection than healthy individuals. In contrast, higher seroprotection and seroconversion rates were demonstrated in ICI-treated cancer patients compared to cytotoxic chemotherapy groups according to a previous study (Keam et al., 2020). Follow-up studies by the same group have also demonstrated higher cell-mediated immune responses for both CD4⁺ and CD8⁺ T cells in ICI-treated individuals compared to chemotherapy groups, consistent with the immune-stimulating capacity of anti-PD-1 therapy (Kang et al., 2020). More recently, Herati et al. have shown that the Tfh-B cell axis was altered during the generation of immune responses to influenza vaccination in anti-PD-1 treated cancer patients (Herati et al., 2022). Tfh cells have been shown to play a major role in the generation of high-affinity antibody responses following seasonal influenza vaccination with evidence of circulating Tfh1 cells communicating with influenza-specific memory B cells and promoting their differentiation into plasmablasts (Ueno, 2019). The increase in Tfh activation and plasmablast frequency suggests an enhanced germinal center activity and B cell maturation, and was associated with an increase in the fold induction of hemagglutinin inhibitory antibody titers compared to baseline in anti-PD-1-treated individuals. Nevertheless, a qualitative functional impairment was observed in the influenza antibodies generated in anti-PD-1 treated patients that resulted in similar endpoint seroprotection rates compared to healthy individuals (Herati et al., 2022).

In addition to vaccine efficacy, concerns were raised about the risk of irAEs in ICI-treated patients as a result of influenza vaccine-induced immune responses in several studies. Despite that, a recent systematic meta-analysis revealed that the vaccinated patients reported a slightly lower rate of irAEs (gastrointestinal, endocrinal, pulmonary, cutaneous or rheumatic) compared to unvaccinated patients (32% versus 41%, respectively), and seroprotection rates were comparable between healthy and ICI-treated cancer patients, confirming that influenza

vaccination increases the survival of patients under PD-1 blockade therapies without having any detrimental effects in terms of safety (Lopez-Olivo et al., 2022; Valachis et al., 2021). Still, some unresolved questions remain regarding the protection of vaccinated cancer patients during the occurrence of flu infection and the reciprocal effect of vaccine-induced immune responses on the anti-tumor response and survival of the patients. It has been shown that seasonal flu infection can convert cold tumors into hot tumors in a mouse model of pulmonary melanoma and the combination of PD-1 blockade resulted in an increase in the antitumor response (Newman et al., 2020). In this context, a commercial unadjuvanted inactivated flu shot (FluVx) could be synergized with PD-L1 blockade to reduce tumor growth while PD-L1 used alone failed to do so (Newman et al., 2020). This attractive strategy may help in treating ICI-resistant tumors. Long-term follow-up studies are required to address these issues in the patients.

6.2. Impact of anti-PD-1 therapy in cancer patients to COVID-19 vaccines

The global threat of the COVID-19 pandemic necessitated the rapid development of vaccines and massive vaccination campaigns prioritizing immunocompromised individuals including cancer patients. However, cancer patients were not included in the clinical trials for vaccine development (Yap et al., 2021) and minimal data has emerged so far regarding the interference between COVID-19 vaccines and ICI therapy. Although cancer patients under active immunotherapy showed seropositivity after the second dose of BNT162b2 (mRNA vaccine) or AZD1222 vaccine (or ChAdOx1, a viral vectored vaccine), the anti-SARS-CoV-2 IgG titers or neutralizing antibody titers were lower compared to healthy controls (Massarweh et al., 2021; Terpos et al., 2022). An additional booster dose compensates for the delayed response to confer similar protection between ICI-treated patients and healthy individuals (Massarweh et al., 2021). Nonetheless, patients treated with immunotherapy developed a stronger anti-SARS-

CoV-2 humoral response as compared to patients treated with chemotherapy or targeted therapies (Fenioux et al., 2022). Another study evaluated the risk factors for negative seroconversion in vaccinated cancer patients as male sex and active treatment (chemotherapy, immunotherapy, biological therapy alone, and chemotherapy plus biological therapy) (Cavanna et al., 2021). Two studies from the same group evaluated the neutralizing antibody (NAbT) levels in patients with solid and haematological tumors and under different therapies including immunotherapies (Fendler, Shepherd, Au, Wu, et al., 2022; Fendler, Shepherd, Au, Wilkinson, Turajlic, et al., 2022). As what was observed in healthy individuals by others, most of the patients with cancer in the cohort exhibited a time-dependent decline in NAbT during follow-up and lacked detectable NAbT against the Variants of Concerns (VOCs) following two vaccine doses, independently of the vaccine type (BNT162b2 or ChAdOx1). However, a third dose of BNT162b2 in solid cancer patients resulted in a significant increase in NAbT against Omicron. On the other hand, patients with haematological malignancies developed an impaired response to VOCs even after a third vaccination. Overall, the proportion of patients with solid cancer, including the patients treated with ICP blockade, who developed NAbT was comparable to individuals without cancer after a third vaccination (Fendler, Shepherd, Au, Wu, et al., 2022). Another recent study in a small cohort has reported that cancer patients mount both humoral and T cell responses to COVID-19 vaccination but was independent of their response to ICI therapy (Sisteré-Oró et al., 2022).

Short-term safety of the BNT162b2 vaccine was assessed in ICI-treated patients at 17–21 days after the first dose and 12–31 days after the second dose. The data revealed that the vaccine-related systemic side effects were comparable between the ICI-treated groups and healthy controls. Moreover, no new irAEs or exacerbations of previously existing irAEs were reported in this study (Ohuchi et al., 2022). Nevertheless, few case studies reported the rare occurrence of some irAEs such as hepatitis, colitis, autoimmune type I diabetes, or cytokine release

syndrome (CRS) in cancer patients undergoing immunotherapy post-COVID-19 vaccination (Au et al., 2021; Lasagna et al., 2022; Ohuchi et al., 2022). Also an exacerbation of some irAEs, for instance, grade 4 skin rash, has been observed in cancer patients under ICP blockade following COVID-19 vaccination (Hussain et al., 2022). A patient with non-small cell lung cancer who developed severe toxic epidermal necrolysis induced by Pembrolizumab was successfully treated with intravenous immunoglobulin (IVIG) therapy, suggesting the potential use of IVIG to treat irAEs (Galeotti et al., 2017; Kian et al., 2022). Hence, to be on the safer side, the interactions between anti-PD-1 immunotherapy and COVID-19 vaccination should be carefully considered from both sides. Recommendations from an international group of medical oncologists highlighted the necessity to avoid the administration of anti-cancer investigational medicinal products (IMP) until 2–4 weeks after the second dose of COVID-19 vaccine, especially for those having a risk of CRS (Au et al., 2021). Vaccine administration should probably be avoided in patients experiencing cancer IMP trial-associated irAEs until the events are markedly resolved.

A prospective multicenter, longitudinal, multi-cohort study known as VOICE (vaccination against COVID in cancer) including patients with solid cancer malignancies undergoing active cancer therapy is underway to assess the immune responses to mRNA-1273 SARS-CoV-2 vaccine from Moderna. This trial intends to follow up on the incidence and severity of COVID-19 after vaccination in these patients, in addition to in-depth studies on the strength and longevity of the antibody and T cell responses to the vaccine and the vaccine side effects (van der Veldt et al., 2021). The initial data emerging from this study confirm the safety and adequate antibody responses to vaccination in a larger cohort of cancer patients undergoing different types of therapy (Oosting et al., 2021), and follow-up studies are ongoing to compare the longevity of this protection. Nevertheless, the existing data seems to guarantee that the benefits outweigh the risks.

7. Concluding remarks

Although it remains necessary that cancer patients should be protected against infectious diseases by vaccination, in view of some rare cases of adverse side effects like CRS (Au et al., 2021), identification of biomarkers to predict the patients with a higher risk of developing side effects is necessary. Indeed, Herati et al. highlighted a correlation between the irAEs and Tfh responses in anti-PD-1-treated cancer patients that can be useful to anticipate the occurrence of deleterious side effects (Herati et al., 2022). Monitoring the level of circulating Tfh numbers could have a predictive value in many other pathologies as well since, they were found to be upregulated in the blood of patients with autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis (Gensous et al., 2018).

The consequences of vaccinating cancer patients who are resistant to immunotherapy is another area that requires in-depth discussion. The complexity of factors and mechanisms underlying resistance to ICI treatment is further enhanced by patient-to-patient variability as well as inter and intra-tumor heterogeneity (Hu-Lieskovan et al., 2021). Various PD-1/PD-L1 independent immune-escape mechanisms could contribute to an immunosuppressive TME (e.g., myeloid-derived suppressor cells, M2 polarized tumor-associated macrophages, N2 neutrophils), which has a major role in the development of immunotherapeutic resistance and hence strategies such as combination therapies to evade these mechanisms are essential (Jenkins et al., 2018). The combination of anti-PD-1 therapy with an intra-tumoral injection of antigenic peptide-coated BCG has been found to improve the anti-tumoral response by reducing immunosuppressive cells and increasing the tumor-infiltrating T cells in cancer models of mice (Ylösmäki et al., 2021). These types of immunomodulatory agents, especially infectious disease vaccines, which can reprogram the TME are in the spotlight for overcoming ICI treatment resistance in recent

years and hence indicate the additional benefit of vaccinating cancer patients who are resistant to anti-PD-1 therapy.

In addition, it is important to consider the vaccine development strategy for cancer patients undergoing immunotherapy. Does the type of immune response generated by different vaccine strategies determine the type and severity of adverse effects observed in cancer patients? The existing Influenza protein subunit vaccines predominantly generate CD4⁺ T cell-mediated humoral responses, whereas the COVID-19 epoch benefited significantly from recent breakthroughs in the mRNA vaccine technology that generates the most potent immune response boosting all arms of the immune system including humoral (CD4⁺ T cell), CD8⁺ T cell and innate immune responses. Global efforts are ongoing in the development of single-shot combo mRNA vaccines for both COVID-19 and the flu. Would this shortcut approach also bypass or minimize the risk of some adverse events in immunocompromised individuals? Moderna and Merck recently released some encouraging results on their Phase IIb clinical trial studying the efficacy of mRNA cancer vaccine combined with Pembrolizumab in melanoma patients (KEYNOTE-942; <https://clinicaltrials.gov/ct2/show/NCT03897881>) (<https://www.science.org/content/blog-post/moderna-and-merck-are-better-right>). The results show a reduced risk of recurrence or death by 44% in patients with advanced melanoma. These promising results open the way for the use of mRNA to treat cancer and, more importantly, to combine mRNA cancer vaccine to mRNA COVID-19 vaccine to promote the anti-cancer response and minimize the side effects. However, unlike other vaccines for infectious diseases, mRNA vaccine for COVID-19 did not undergo rigorous randomized clinical trials and reports on higher risk of cardiac inflammation in vaccinated population are emerging (Pillay et al., 2022). Therefore, careful analysis of all the clinical parameters and adverse events is critical.

Also, in order to optimize the effect of vaccination for the cancer patient under ICI treatment, another option could be to inject the shot against the infectious agent closer to the tumor site depending on the type of cancer. This question is rationalized to avoid the diversion of the immune response to the area of vaccine-induced inflammation rather than to the tumor bed. With the development of new vaccine formulations, the mode of administration could be improved/adapted as well. The data emerging from influenza and COVID-19 vaccine studies open several opportunities and challenges towards the development of optimized vaccination strategies against viral and other infectious diseases suitable for cancer patients and more generally for immunocompromised individuals having other comorbidities, to provide the best outcome without compromising the safety or the efficacy of anti-cancer treatment.

The lessons learned from cancer patients under ICI therapy could be extrapolated to look at the importance of ICIs in designing novel vaccines or therapeutic strategies for other infectious diseases as well. Promising data have emerged in animal studies for several difficult-to-treat chronic pathogens such as HIV and hepatitis with ICP blockade therapy. Indeed, HIV patients are at a higher risk of developing cancer and viral hepatitis is common among patients with liver, gastrointestinal, head and neck, and lung cancers (Ramsey et al., 2019). There are reports showing that the application of anti-PD-1 therapy in cancer patients living with HIV or hepatitis infection leads to a decrease in viral loads, thus emphasizing the prospects of PD-1 blockade in treating diseases caused by these pathogens (Tsiakos et al., 2022). The clinical application of these data is progressing with extreme caution due to the potential side effects of ICIs in chronically-infected patients (Hashimoto et al., 2018). Strategies to predict the occurrence of irAEs would help to resolve this problem and to enhance the future of ICI therapy in cancer and infectious diseases.

In conclusion, scrutinizing vaccine-induced responses in ICI-treated cancer patients sheds light on the grey areas in vaccinating immunocompromised individuals and provides futuristic insights into the potential of targeting ICPs in infectious diseases. Nevertheless, some questions remain to be answered. What are the risks and benefits of vaccinating cancer patients resistant to immunotherapy treatment? What is the best window to vaccinate cancer patients undergoing ICP blockade? How can we easily predict the occurrence/exacerbation of irAEs in cancer patients while vaccinating for infectious diseases? The discovery of effective and accurate predictive markers of response to immunotherapy and over-activation of immune responses is urgently needed to address these challenges.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Figure Legends

Fig. 1: PD-1/PD-L1 signalling pathway. PD-L1 expressed on the surface of APCs or cancer cells interacts with its receptor PD-1 on T cells to induce the phosphorylation of the intracellular domains (ITIM, ITSM) of PD-1, which then leads to the recruitment of the tyrosine phosphatases SHP-1 and SHP-2 close to TCR. SHP1/2 dephosphorylates several targets involved in the TCR signalling pathways leading to the modulation of transcriptional programs and metabolic switches, which ultimately result in the inhibition of T cell growth, proliferation, and survival, driving them to an exhausted phenotype. AA, amino acid; AP-1, activator protein 1; APC, antigen presenting cell; BATF; basic leucine zipper ATF-like; CD3 ζ , CD3-zeta; CK2, casein kinase 2; ERK, extracellular signal-regulated kinase; FAO, fatty acid oxidation; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; LCK, leukocyte-specific tyrosine kinase; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T-cells; NF κ B, nuclear factor kappa B; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PI3K, phosphoinositide 3-kinase; PKC θ , protein kinase C θ ; PTEN, phosphatase and tensin homolog; RAS, rat sarcoma; SHP, src homology phosphatase; TCR, T cell receptor; ZAP-70, zeta-chain-associated protein kinase-70. Figure created at BioRender.com.

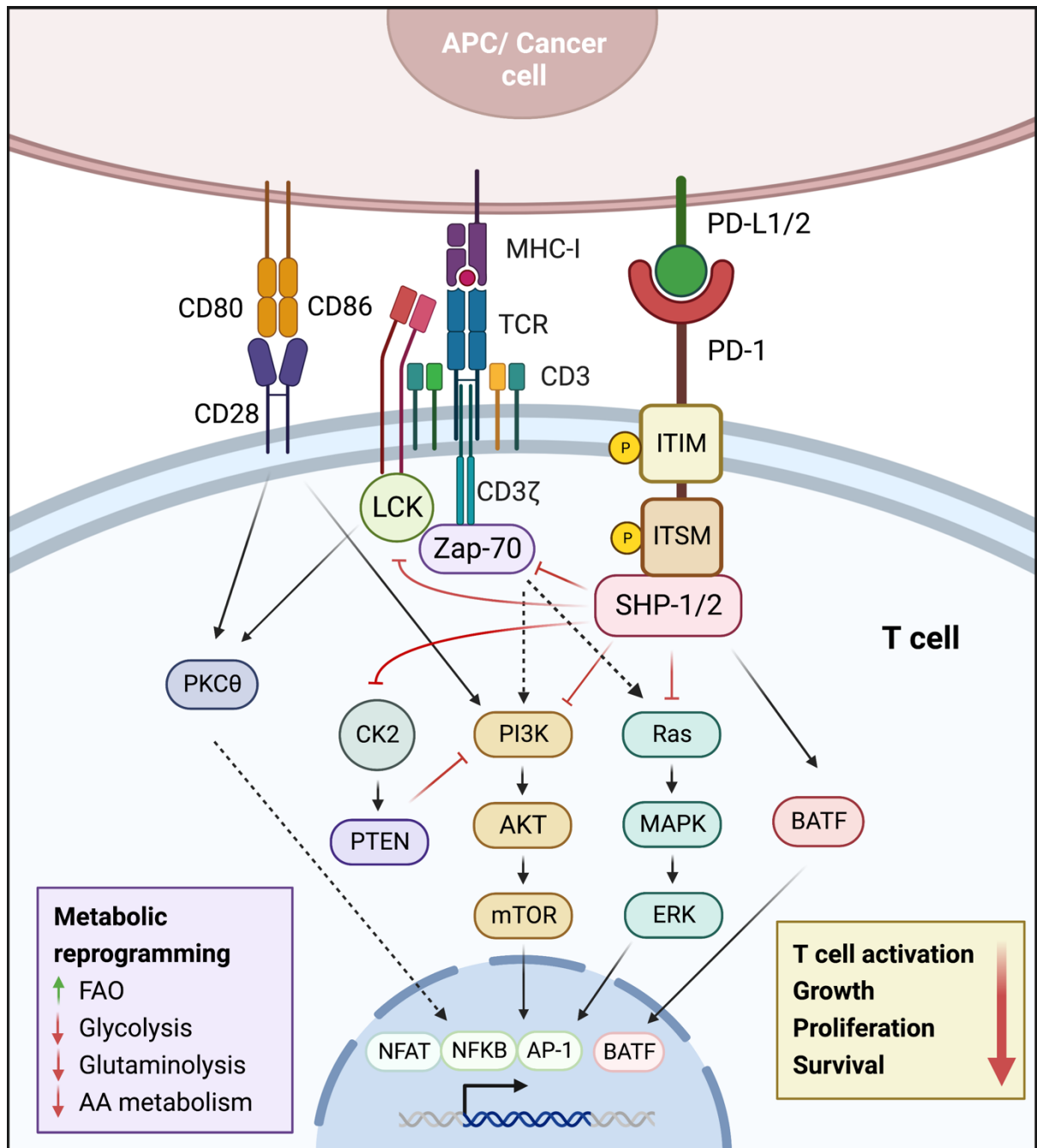


Fig. 2: Parallel phenotypes of cancer and chronic infection. Tumor antigens and chronic pathogenic antigens persistently stimulate antigen-specific cytotoxic T cells which are involved in killing tumor cells or pathogen-infected cells. In both scenarios, these T cells eventually lose their effector functions acquiring an exhausted phenotype, along with a gradual increase in the expression of ICP molecules such as PD-1 that inhibits TCR signalling. ICP, immune checkpoint; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TCR, T cell receptor. Figure created at BioRender.com.

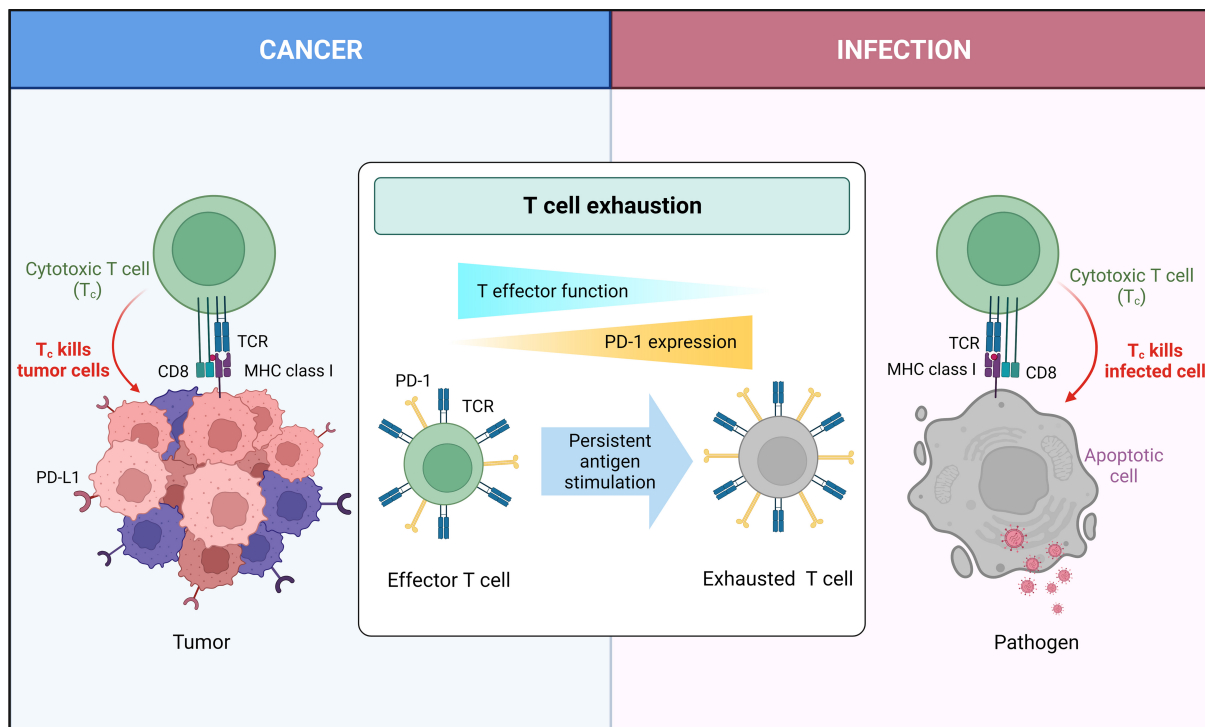


Fig. 3: Impact of anti-PD-1 immunotherapy on vaccination (flu/COVID-19)-induced immune responses in cancer patients. Treating cancer patients with anti-PD-1 immunotherapy reverses the CD8⁺ T cell exhaustion and reduces Treg infiltration in tumors. Besides, anti-PD-1 therapy in cancer patients induces higher levels of circulating Tfh activation/proliferation and plasmablast differentiation in response to vaccination compared to healthy individuals. This results in a higher fold induction of humoral antibody responses, with lower affinity possibly due to their impaired glycosylation status at the baseline. Hence the endpoint seroprotection rates are found to be comparable between healthy and anti-PD-1 treated patients in studies of flu or COVID-19 vaccination. Although vaccine-related side effects are similar between healthy and anti-PD-1-treated patients, the risk of irAEs such as autoimmunity and cytokine release syndrome might increase in some patients. ASC, antibody secreting cells; ICOS, inducible T-cell Co-stimulator; PD-1; programmed cell death protein 1; Tfh, follicular helper cell. Figure created at BioRender.com

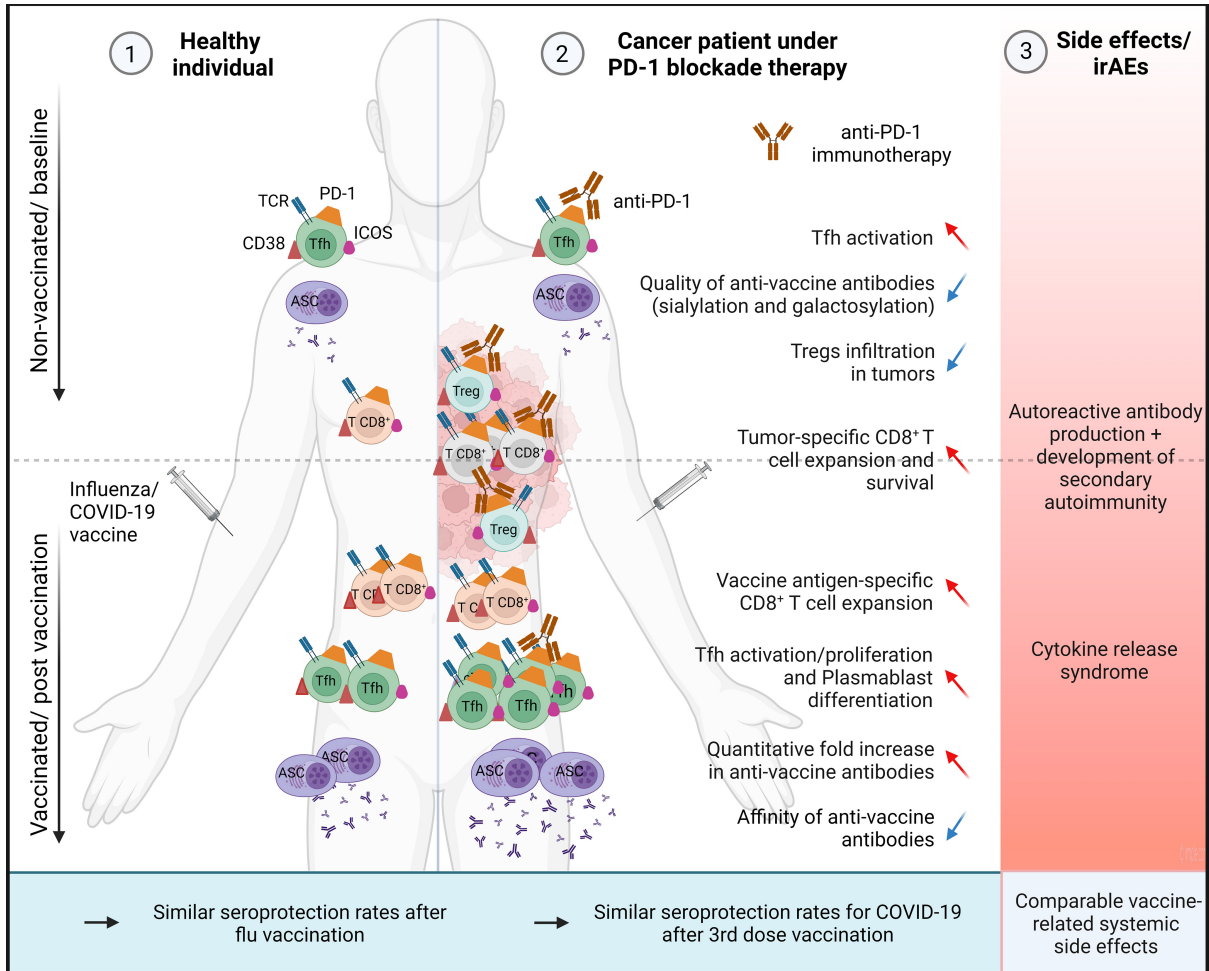


Table 1. Summary of studies testing the safety and efficacy of vaccination against viral diseases in cancer patients undergoing immunotherapy with immune checkpoint inhibitors.

Abbreviations: AE, adverse event; AU, arbitrary units; CNS, central nervous system; CP, cancer patients; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HC, healthy controls; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; N.R., not reported; NAbT, neutralizing antibody titer; NSCLC, non-small cell lung carcinoma; OS, overall survival, PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; Tfh, follicular helper T cells; vs., versus; WT, wildtype.

Table 1

Cancer type	ICI agent	vaccine	AEs/safety	Efficacy/seroconversion	Ref
SARS-COV-2					
Different types of solid cancers (mainly breast and gastrointestinal; <i>n</i> = 257) and HC	Immunotherapy (8.56%)	2 doses of BNT162b2 or mRNA-1273 (Moderna)	No grade 3 or 4 AEs	68.18% seropositivity rate in immunotherapy group; 75.88% in whole CP and 100% in HC	(Cavanna et al., 2021)
Different types of solid cancers (mainly breast and lung cancers; <i>n</i> = 816) and HC (<i>n</i> = 274)	Immunotherapy (16.8%)	2 doses BNT162b2	Severe-grade AEs, 1st dose: 3.5%; 2nd dose: 1.3%	93.3% responders in ICI-treated CP vs HC 100%	(Di Noia et al., 2021)
Different types of solid cancers (mainly gastrointestinal and lungs; <i>n</i> = 102) and HC (<i>n</i> = 78)	ICI (22%); chemotherapy+ICI (14%)	2 doses of the BNT162b2 mRNA vaccine	N.R.	After the 2nd dose, seroconversion in the patient group (90%) vs HC (100%). Median IgG titer in the ICI patients (3020 AU/mL) and chemotherapy+ICI (310 AU/mL) vs HC (7160 AU/mL). The lowest IgG titers observed with chemotherapy + Immunotherapy and with immunotherapy + biological therapy	(Massarweh et al., 2021)
Different types of solid cancers (<i>n</i> = 64) and hematological cancers (<i>n</i> = 83)	ICI: 25.4%; ICI + chemotherapy: 11.3%	56.0% received BNT162b2 (2 doses) and 44.0% received mRNA-1273 (2 doses)	N.R.	ICI group: high seropositivity (55.2%), intermediate seropositivity (37.9%), no seroconversion (6.9%); ICI + chemotherapy group: high seropositivity (36.8%), intermediate seropositivity (57.9%), no seroconversion (5.3%)	(Figueiredo et al., 2021)
Different types of solid cancers and hematological cancers; CoV+: Patients with prior SARS-CoV-2 infection (<i>n</i> = 154); CoV-: Patients without prior SARS-CoV-2 infection (<i>n</i> = 89)	Immunotherapy, solid cancers: CoV- (9.2%), CoV+ (10.7%); hematologic cancers: CoV- (17.8%), CoV+ (18.2%)	1 or 2 doses BNT162b2	N.R.	Seroconversion in all CoV- patients; 1st dose: 61%, 2nd dose: 85.7%	(Fong et al., 2021)

Solid tumors (mainly breast; $n = 134$) and hematological cancers ($n = 66$)	ICI (16%)	2 doses of BNT162b2 (55%); mRNA-1273 (31%); AD26.COV2.S (10%); mRNA unknown (2%)	No AEs reported in 194/428 vaccination episodes. Mostly low-grade AEs were reported in others.	Seroconversion in ICI-treated CP (97%); no significant difference in seroconversion when comparing solid-tumor patients to HC, but significantly reduced in patients with hematological cancers	(Thakkar et al., 2021)
Different types of solid cancers (mainly gastrointestinal; $n = 232$) and HC ($n = 261$)	Immunotherapy (36%)	2 doses BNT162b2	AEs in CP were similar to that observed in HC	Seroconversion after 1st dose: immunotherapy-treated CP (30%) vs HC (84%); after 2nd dose: immunotherapy-treated CP (90%) vs. HC (N.R.)	(Goshen-Lago et al., 2021)
Different types of solid cancers (mainly breast; $n=110$) and HC ($n=25$)	ICI (16%)	Antibody response 4 weeks after the first injection of the BNT162b2 (Pfizer-BioNTech)	N.R.	Seroconversion in CP (55%) vs in HC (100%). The potential confounding factors associated with "no seroconversion" were: age >65 years ($P = 0.008$) and treatment by chemotherapy ($P = 0.003$), while treatment by immunotherapy was not affecting seroconversion.	(Palich, Veyri, Marot, et al., 2021)
Solid cancers (mainly breast, $n = 223$) and HC ($n = 49$)	ICI (13%)	3-4 weeks after the 2nd injection of the BNT162b2	N.R.	Seroconversion in patients (94%) vs. in HC (100%). Anti-Spike antibody titers: in non-chemotherapy (896 AU/ml), vs. in chemotherapy (227 AU/ml), vs. in HC (2517 AU/ml)	(Palich, Veyri, Vozy, et al., 2021)
Different types of solid cancers ($n = 47$)	Nivolumab (4%)	CoronaVac (Sinovac inactivated COVID-19 vaccine)	AEs any grade after first dose: 18.9%; after second dose: 23.1%	100% seroconversion in Nivolumab-treated patients vs 63.8% in all the CP	(Karacin et al., 2021)
Different types of solid cancers (mainly skin for cohort B ($n = 131$); mainly breast for cohort C ($n = 229$); mainly respiratory tract for cohort D ($n = 143$)) and HC (cohort A)	immunotherapy anti-PD-1 or PD-L1 (cohort B, 17%); chemotherapy (cohort C, 30%); chemoimmunotherapy (cohort D, 19%)	mRNA-1273 (Moderna)	Most irAEs were low grade except for 3 patients who developed grade 3 effects.	D28 post 1st vaccination: cohort A (no cancer, 66%); cohort B (immunotherapy, 37%); cohort C (chemotherapy, 32%); cohort D (chemoimmunotherapy, 33%) 2nd dose: cohort A (100%); cohort B (99%); cohort C (97%); cohort D (100%)	(Oosting et al., 2021) (NCT04715438)

Solid cancers (<i>n</i> = 861) Cohort A: no cancer (<i>n</i> = 246); Cohort B: immunotherapy (<i>n</i> = 135); Cohort C: chemotherapy (<i>n</i> = 246); Cohort D: chemo-immunotherapy (<i>n</i> = 246)	Against PD-1 or PD-L1 ICI (cohort B); chemoimmunotherapy (cohort D)	2 doses of the mRNA-1273 vaccine and 28 days after a third mRNA-1273 for inadequate responders (<i>n</i> =46)	After the 3rd vaccination, no serious AEs and no new irAEs.	Immunogenicity after the second vaccination: 51% in cohort A, 32% in cohort B, 42% in cohort C, and 25% in cohort D; At 6 months: 95% in cohorts A and B, 84% in cohort C, and 100% in cohort D; against omicron: in 38% in cohort A, 67% in cohort B, 50% in cohort C, and 13% in cohort D; after 3rd dose for inadequate responders, seroconversion for Omicron: 63% of patients in cohort B, 77% in cohort C, and 44% in cohort D.	(Oosting et al., 2022)
Different types of solid cancers (<i>n</i> = 447) and hematological cancers (<i>n</i> = 138) and HC (<i>n</i> = 25)	ICI (anti-PD-(L)1 ± anti-CTLA-4, 24% among solid CP)	BNT162b2 (74%) AZD1222 (26%)	Active irAEs secondary to ICI: 9% among solid CP	After 2 doses: seroconversion of 85% in solid CP vs 59% in haematological CP; seroconversion in CP (WT, 87%; Alpha, 70%; Beta, 62%; Delta, 63%) vs HC (WT, 100%; Alpha, 96%; Beta, 86%; Delta, 85%). Detectable S-reactive T cells in solid CP (77%) vs. hematological CP (80%) vs. HC (80%)	(Fendler et al., 2021)
Solid cancers (<i>n</i> = 115) and hematological cancer (<i>n</i> = 84)	Anti-PD-L1+/- CTLA-4 (28%)	2 doses BNT162b2 or ChAdOx1 (Astrazeneca); 3rd dose BNT162b2 only	N.R.	After 2nd dose: seroconversion in solid CP (WT, 97%; Delta, 56%; Omicron, 37%); Following 3rd dose, solid CP (WT, 99%; Delta, 97%; Omicron, 90%)	(Fendler, Shepherd, Au, Wilkinson, CAPTURE consortium, et al., 2022; Fendler, Shepherd, Au, Wilkinson, Turajlic, et al., 2022; Fendler, Shepherd, Au, Wu, et al., 2022)
Different types of solid cancers (mainly digestive and breast; <i>n</i> = 163)	Immunotherapy (9%)	2 or 3 doses of the BNT162b2 (BioNTech; Pfizer)	No severe AEs observed after the 3rd dose.	Humoral response at a threshold greater than 1000 AU/ml at 1st dose 46%; 2nd dose 86% in immunotherapy group	(Fenioux et al., 2022)

Solid cancers (Vienna cohort; <i>n</i> = 26) and solid cancers and hematological cancers (Meran cohort; <i>n</i> = 413); HC (<i>n</i> = 41)	Vienna cohort: Immune checkpoint inhibition (30.8%); Chemotherapy + ICI (19.2%); Meran cohort: Immune checkpoint inhibition (7.7%); Chemotherapy + ICI (0.1%)	3 doses BNT162b2 (73.1%); 3 doses mRNA-1273 (11.5%)	Low grade AEs after the third dose.	After 3rd dose, the anti-S concentration median of 2500 AU/ml in patients with solid cancers in Vienna cohort; patients with solid tumours, median anti-S concentration of 18624 AU/ml in Meran cohort	(Mair, Berger, Mitterer, et al., 2022)
Solid tumors (Vienna cohort; <i>n</i> = 111) and solid cancers and hematological cancers (Meran cohort; <i>n</i> = 484); and HC	Vienna cohort: Immune checkpoint inhibition (27%); Chemotherapy + ICI (14.4%); targeted therapy +ICI (3.6%); Meran cohort: Immune checkpoint inhibition (6%); Chemotherapy + ICI (8.7%)	Vienna cohort: BioNTech/Pfizer (BNT162b2, 58.3%), Moderna (mRNA-1273, 25.0%), or AstraZeneca (AZD1222, 16.7%); Meran cohort: BNT162b2 (100%)	In the Meran cohort, no serious AEs after vaccination were observed.	Vienna cohort: Median anti-spike antibody levels were 57.7 AU/mL in solid CP after 2 doses; Meran cohort: After 2 doses, solid CP (median, 246.4 AU/mL) vs hematological CP (median, 139.3 AU/mL). After the 1st dose, lowest median levels were observed in CP under chemotherapy (157.7 AU/mL) or chemotherapy+ICI (118.7 AU/mL) and the highest median levels in CP with no ongoing antineoplastic treatment (634.3 AU/mL)	(Mair, Berger, Berghoff, et al., 2022)
Thoracic cancer (NSCLC, SCLC, MPM; <i>n</i> = 306), HC (<i>n</i> = 18)	ICI (15.7%); chemo-immunotherapy (<i>n</i> = 62)	BNT162b2 mRNA vaccine	No specific safety concerns irAES in ICI-treated patients.	Seroconversion was 88.5% after 3rd dose in CP. Anti-Spike IgG titers were significantly reduced in patients treated with chemotherapy or immunotherapy compared to HC. No significant differences were seen between chemotherapy- and immunotherapy-treated patients.	(Gounant et al., 2022)
Solid cancers (mainly lung and breast; <i>n</i> = 50)	% ICI among total CP (50%), those receiving 2 vaccine doses (56.5%) or booster dose (44.4%)	BNT162b2 (42%) and mRNA-1273 (58%)	N.R.	No statistical differences in NAbT against D614G, Delta and Omicron in ICIs-treated patients vs non-PD-1/PD-L1-treated patients after 2 or 3 doses	(Zeng et al., 2022)
Influenza					

NSCLC (n = 23) Age matched HC (N.R.)	PD-1/PD-L1 inhibitor	Trivalent influenza vaccination	All grade irAEs: 52.2%, grade 3/4: 26.1%. This is significantly higher than general experience at the same center (all grades: 25.49%, grade 3/4: 9.8%)	No major difference observed in the generation of antibody titers between CP vs. HC.	(Rothschild et al., 2017)
N.R. (n = 28)	Anti-PD-1	Afluria (Seqirus)	No grade 3/4 local or systemic AEs reported, grade 2 AEs: 7%.	Anti-PD-1 therapy did not adversely affect anti-influenza IgG or IgM responses. Influenza infection was documented in only one CP and there were no influenza related hospitalizations.	(Kanaloupitis et al., 2017)
Lung cancer (n = 23), age-matched HC (n = 11)	Nivolumab (95.7%) Pembrolizumab (4.3%)	Trivalent, inactivated, non-adjuvanted influenza vaccine	All grade irAEs: 52.2%, severe grade 3/4 irAEs: 26.1%, higher than the rate in a non-study population in the same institute (all grades: 25.5%, grade 3/4: 9.8%)	Seroprotection rates were comparable between CP vs. HC (A/H1N1: 77.8% vs. 100%; A/H3N2: 77.8% vs. 90.0%; B/Brisbane: 50% vs. 36.4%). However, the seroconversion factor was significantly higher in CP compared to HC reflecting lower baseline levels in CP.	(Läubli et al., 2018)
Advanced solid cancers (n = 300)	Mixed, ICI (98%)	26.3% were vaccinated with trivalent (two type A viruses, H1N1 and H3N2, and one type B virus, B/Brisbane) or quadrivalent (adding a type B virus, B/Phuket) inactivated virus vaccine (split vaccine)	Incidence of influenza syndrome was higher among vaccinated vs. non vaccinated (24.1% vs. 11.8%, p = 0.009), especially in the elderly, but no differences were observed in anti-cancer outcome	Vaccination was not clinically effective in advanced CP treated with ICI	(Bersanelli et al., 2018)

NSCLC (n = 127)	Nivolumab	Trivalent inactivated influenza vaccine (33.1%)	The incidence of irAEs was comparable between vaccinated vs. non-vaccinated CP (26% vs. 22%)	N.R.	(Wijn et al., 2018)
Solid cancers (n = 147), lung cancer (52%), melanoma (11%), primary CNS lymphoma (7%)	Anti-PD-1 + ipilimumab (combination, 12%), anti-PD-1 only (88%)	Inactivated influenza vaccine	irAE rates were 18% (all grades) or 7% (grade 3) in CP treated with anti-PD-1 alone, which were similar to results previously reported in clinical trials of ICIs.	N.R.	(Chong et al., 2018)
Solid cancers (n = 534), lung (37%), melanoma (34%), GU (18%), breast (7.2%), and lymphoma (3.4%)	93% received single agent ICI	N.R. (72.1%)	Rates of irAEs were not significantly different between vaccinated and unvaccinated CP (37.4% vs. 42.6%, p = 0.067)	Vaccination did not significantly improve PFS (vaccinated 47.2 m vs. unvaccinated 43.2 m, p = 0.0621) but improved OS (vaccinated 72 m vs. 62 m unvaccinated, p < 0.001)	(Gopalakrishnan et al., 2018)
NSCLC (n = 117)	PD-1/PD-L1 inhibitor monotherapy	Mixed (28%)	Rates of irAEs were comparable between vaccinated vs non-vaccinated CP (67% vs. 63%, p = 0.720)	N.R.	(Reddy et al., 2019)
NSCLC (n = 285)	ICI, N.R.	N.R. (15.8%)	The need for steroids for the treatment of irAEs was slightly less in vaccinated CP compared to non-vaccinated CP (4% vs. 11%).	N.R.	(Roberts et al., 2019)

Solid cancers (n = 370), mostly lung cancer (46%) and melanoma (19%)	Ipilimumab (CTLA-4 inhibitor), or pembrolizumab or nivolumab (anti-PD-1 agents)	Quadrivalent/trivalent non adjuvanted inactivated influenza vaccine	irAE rates, any grade: 20%, grade 3/4: 8%. No grade 5 events observed. irAE rates were comparable to results from published clinical trials.	Influenza was diagnosed in only 2/370 CP	(Chong et al., 2020)
NSCLC (n = 25) urothelial carcinoma (n = 5)	Single agent ICIs targeting PD-1 (nivolumab; n = 7, pembrolizumab; n = 8) or PD-L1 (atezolizumab; n = 15)	N.R.	No grade 4–5 irAEs observed, grade 1–3: 50%, a proportion usually observed in single-agent ICI-treated CP	Seroprotection rates in CP receiving nivolumab (H1N1: 71%, H3N2: 57%), pembrolizumab (H1N1: 63%, H3N2: 63%), and atezolizumab (H1N1: 67%, H3N2: 67%).	(Bayle et al., 2020)
Solid cancers (n = 24)	Single agent ICI therapy: nivolumab (58%), pembrolizumab (29%), atezolizumab (4%), avelumab (4%), durvalumab (4%)	Inactivated influenza vaccine (Fluarix® quadrivalent or Fluzone® quadrivalent)	29% of CP experienced new irAEs (any grade). All who experienced irAEs were within the first year of ICI therapy, possibly a natural incidence than from vaccination	N.R.	(Gwynn et al., 2020)
Different types (n = 136, mostly lung cancer)	ICIs (33.8), cytotoxic agents (66.2)	Seasonal quadrivalent influenza vaccine	9% incidence of irAE (grade 1) in ICI treated CP	Seroprotection rates were significantly higher in ICI-treated CP (76% to 89%) than in chemotherapy (48% to 70%)	(Keam et al., 2020)
Different types (n = 40, mostly lung cancer)	ICI, n = 11 (nivolumab, 64%; pembrolizumab, 36%); cytotoxic chemotherapy, n = 29	Seasonal quadrivalent influenza vaccine	N.R.	Seroprotection rate was higher in ICI-treated CP (73%) compared to chemotherapy (66%-59%). Cell-mediated immune responses were also stronger in ICI-treated CP.	(Kang et al., 2020)

Different types (n = 162), mainly melanoma (56.2%), and NSCLC (13.6%)	Pembrolizumab, single agent (95.1%) or combined (4.9%)	43.2% received at least one inactivated influenza vaccination without adjuvant	irAEs (any grade) in the vaccinated group trended to be lower compared with the nonvaccinated group (25.7% vs 40.2%; P = 0.07)	N.R.	(Failing et al., 2020)
Solid cancers (n = 303), mostly melanoma (47.8%) and NSCLC (31.0%)	Nivolumab (69.0%) Pembrolizumab (28.4%) Atezolizumab (2.6%)	N.R. (22.1%)	Incidence of irAE (any grade) was comparable between non-vaccinated and vaccinated groups (43% vs. 44.8%, p-value = 0.850)	Survival rate in the vaccinated group was higher compared to non-vaccinated group	(Valachis et al., 2021)
Solid cancers (n = 1188)	Single agent (ICI, 94.4%), combinations (ICI+ICI, 5.6%)	Mixed (48.9%)	Only mild and rare vaccine-related AEs were observed (grades 1–2: 1.5%,).	ILI complications (11.8% vs 38.3%, p=0.002) and frequency of ILI-related intravenous therapies (11.8% vs 29.8%, p=0.027) were significantly less in vaccinated CP vs. non-vaccinated. ILI lethality was 0% in vaccinated and 4.3% in unvaccinated CP.	(Bersanelli et al., 2021)
metastatic melanoma (n = 176)	ICI, N.R.	N.R. (51.1% vaccinated vs 48.9% unvaccinated CP)	IrAEs were higher in vaccinated group compared to the unvaccinated group (67% vs 40%; p=0.0005)	Vaccinated CP had longer PFS than unvaccinated but not overall survival OS	(Erickson et al., 2021)
Mixed (n = 133), mostly lung cancer and melanoma	Single agent pembrolizumab, nivolumab, atezolizumab, or durvalumab	N.R. (39.8%)	There was no statistical difference in irAEs between vaccinated vs. non-vaccinated CP (30% vs. 45%, p = 0.15)	N.R.	(Vutukuri et al., 2021)

<p>Cohort 1: renal cell carcinoma or urothelial carcinoma (n = 39); Cohort 2: Melanoma (n = 57)</p>	<p>Cohort 1: anti-PD-1 (n= 29), non-anti-PD-1 (n = 10); Cohort 2: anti-PD-1 (n = 30), HC (n = 27)</p>	<p>Seasonal quadrivalent inactivated influenza vaccination</p>	<p>Higher circulating Tfh responses in anti-PD-1 treated CP are predictive of irAEs</p>	<p>All groups achieved similar endpoint seroprotection. However, fold induction of antibody responses was significantly higher in anti-PD-1 treated CP compared to others, reflecting lower baseline and qualitative impairment of antibodies in the former group.</p>	<p>(Herati et al., 2022)</p>
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