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Immune escape mechanisms and therapeutic approaches in cancer: the cancer-immunity cycle

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Abstract: The introduction of immune checkpoint inhibitors has changed the therapeutic possibilities for various cancer types. However, despite the success in some entities, a significant fraction of patients does not respond to immune checkpoint inhibitors. A functioning cancer-immunity cycle is needed as the precondition for a clinically meaningful response to immune checkpoint inhibitors. It is assumed that only if each step of the cycle is activated and functioning properly, immune checkpoint inhibitors induce a meaningful immune response. However, an activated cancer-immunity cycle might not be present equally in each patient and cancer type. Ideally, treatment concepts should consider each single step of the cancer-immunity cycle and provide personalized treatment approaches, allowing the adaption to functioning and malfunctioning steps of the individual patient’s specific cancer-immunity cycle. In the following review, we provide an overview of the single steps of the cancer-immunity cycle as well as the impact of malfunctioning steps on the generation of an effective tumor-specific immune response.

Keywords: cancer-immunity cycle, immune checkpoint inhibitors, immune escape, immune resistance, PD-L1, solid cancer

Introduction
The introduction of immune checkpoint inhibitors (ICIs) has revolutionized therapeutic options for cancer as in several entities durable responses could be achieved.\(^1\)\(^-\)\(^5\) Combinational approaches with chemotherapy or targeted therapies have further increased the fraction of patients profiting from an ICI-based treatment approach.\(^6\)\(^-\)\(^10\) In contrast to other systemic therapies in metastatic cancer, patients responding to ICI can present with durable responses over years.\(^11\)\(^-\)\(^13\) Importantly, ICI are not without side effects. Although severe side effects are only occasionally observed, immune-mediated side effects including myocarditis, hypophysitis, and colitis are potentially life-threatening.\(^14\)\(^-\)\(^18\) Further, ICI bear a potential financial burden to the health system, considering the currently still very high treatment costs. Therefore, ICI should be applied with an optimal cost-effectiveness profile based on reliable, robust biomarkers. Indeed, a significant fraction of patients does not respond and some entities present with primary resistance toward ICI.\(^19\)\(^-\)\(^21\) The so far intensively studied biomarkers include expression of programmed cell death protein ligand 1 (PD-L1), tumor mutational burden (TMB), antigen load, inflammatory blood biomarkers as well as the gut microbiome.\(^22\)\(^-\)\(^25\) So far, no single biomarker showed consistent results across entities, underlining the highly complex orchestra of interactions between the immune system and cancer cells.\(^26\)\(^,\)\(^27\) In the following review, we provide explanation on each step of the cancer-immunity cycle and potential immune escape mechanisms inhibiting a clinically effective immune response.

Overview of the activated cancer-immunity cycle
The cancer-immunity cycle involves several steps initiating a clinically effective T-cell-mediated immune response.\(^26\)\(^,\)\(^28\)
Impaired cancer-immunity cycle due to missing antigen release from the tumor

As a first step in the cancer-immunity cycle tumor-specific antigens must be released from dying tumor cells. The tumor-specific antigens are released after necrosis or apoptosis of the tumor cells. Further, the antigens must be captured by APCs, primarily by dendritic cells (DCs), and transported to the local lymph node to start with antigen presentation to naïve T-cells and T-cell priming. Other types of professional APCs involve macrophages, monocytes, and B cells, whereas thymic epithelial cells and vascular endothelial cells are functioning in antigen presentation as nonprofessional APCs.

An ineffective antigen release, for example, in the absence of dying tumor cells, would prevent an effective antigen presentation and further steps of the cancer-immunity cycle resulting in an ineffective recognition of tumor cells by T-cells (Figure 1(b)). In consequence, if no antigens are released from tumor cells no immune response in form of a T-cell attack can be generated. In addition, a fully and properly proceeded cancer-immunity cycle inducing the killing of cancer cells would start over with the release of additional tumor-associated antigens which would further restart the cancer-immunity cycle and deepen a tumor-specific T-cell response. The frequently observed correlation of high TMB and response to ICI is explained by a higher availability of tumor neoantigens in the presence of a high mutational burden. Cancers with microsatellite instability and in consequence a high TMB frequently present with high response rates to ICI-based therapy. Further, also the configuration of antigens, specifically the antigen-presenting machinery, impacts whether they are taken up by APCs, as human leucocyte antigen (HLA) binding capacity impacts this particular process. Therefore, another immune evasion pattern is constituted by splitting the antigen-presentation system by either acquired mutations in the HLA component β2 microglobulin or by the loss of the HLA alleles, leading to restricted antigen-presentation and T-cell recognition.

Therapeutically, a cancer vaccination approach is a possible strategy to overcome the lack of antigen release and presentation and is currently widely under investigation. So far, vaccines have shown some clinical benefit in carcinoma in situ or minimal residual disease. However, in more advanced tumor stages, therapeutic vaccines have not shown clinical efficacy as monotherapy due to predominating immune evasion mechanisms. A vaccination approach to increase DC antigen presentation and T-cell activation in consequence, is the transfer of extracorporal activated DCs. Similar to tumor antigen-based vaccination approaches, DC vaccination failed to have meaningful clinical activity as a monotherapy, however, the combination with ICI in selected patients with proven restriction of DC-based antigen presentation could potentially deliver profit. Further, the combination with chemotherapy and/or radiotherapy might induce the availability of tumor antigens due to the induction of apoptosis/necrosis. In consequence, more tumor antigens are released and available for DC transport and T-cell activation. In line, the combination with chemotherapy and ICI has shown to be clinically more active than ICI alone across several cancer types. The so-called ‘abscopal effect’ refers to the observation that after radiation of a single progressing cancer lesion other distant cancer lesions show response to ICI as well. In detail, the radiotherapy induces tumor cell death which further leads to the release of cancer antigens. Therefore, the implementation of combinations with chemotherapy, radiotherapy, or other vaccination strategies are currently extensively investigated.

Further, other novel immune modulating therapeutics include histone deacetylase (HDAC) inhibitors which have been identified to increase
Figure 1. (a) The cancer-immunity cycle displaying all pivotal steps to generate an effective tumor-specific immune response. (b) Impaired cancer-immunity cycle due to missing antigens. (c) Impaired cancer-immunity cycle due to impaired T-cell priming in the local lymph node – no matching T-cell receptors. (d) Impaired cancer-immunity cycle due to impaired T-cell priming in the local lymph node – immune checkpoint signaling. (e) Impaired cancer-immunity cycle due to systemic factors inhibiting tumor-specific T-cells in the bloodstream. (f) Impaired cancer-immunity cycle due to immune checkpoint signaling in the local tumor microenvironment.
the expression of PD-L1, major histocompatibility complex (MHC) class I/II molecules as well as cancer germline mutations and therefore antigen-based tumor immunogenicity.63,64 HDAC inhibitors have shown clinical meaningful results in hematological malignancies such as B-cell lymphomas and their combination with ICI is currently investigated to promote immune responses and potentially show effects in solid tumors as well (Table 1).63 In terms of safety, HDAC inhibitors are associated with specific class-related side effects such as cardiac effects, that is, the prolongation of QTc interval and in rare cases incidences of arrhythmias, and their management has to be elucidated.65

Impaired cancer-immune cycle due to impaired T-cell priming in the local lymph node

The presentation of tumor-specific antigens to naïve T-cells triggers the priming and activation of effector T-cells. Importantly, the distribution of effector T-cells and regulatory T-cells is critically influencing the effectiveness of the immune response.29 As most tumor antigens derive from self-antigens, tumor-specific antigens could potentially not get properly recognized by APCs or T-cells as ‘foreign’ enough and could be considered as ‘self’. This would lead to the priming and activation of regulatory T-cells rather than effector T-cells. Therefore, this process must be accompanied by immunogenic signals like proinflammatory cytokines (i.e. interleukin-1, interferon α, tumor-necrosis factor α) and costimulatory factors (i.e. CD27, OX40) to promote immunity and not lead to tolerance against the specific antigens.29,66–68

Furthermore, within the local lymph node matching T-cell receptors (TCRs) for each mature T-cell have to be activated.69 If no matches are present, that is, due to a low TCR repertoire diversity, no immune response can be generated (Figure 1(c)). Indeed, the TCR repertoire has been identified as a potential multidimensional biomarker for response assessment of immunotherapeutics as a richer diversity of the TCR repertoire was associated with beneficial outcome in metastatic melanoma patients treated with the cytotoxic T-lymphocyte antigen 4 (CTLA4) inhibitor ipilimumab.70,71 Moreover, immune checkpoint blockade has shown to impact the TCR repertoire diversity and therefore to boost the antitumor immunity at this specific step in the cancer-immunity cycle.72 Further, the binding affinity between tumor antigen–MHC complexes and TCRs plays an important role in the activation of antitumor activity. TCRs binding to tumor-specific antigens have been described to have a significantly lower binding affinity than TCRs binding to viral antigens.73 This observation implies an acquired tolerance to self-antigens that consequently dampens the antitumor activity of ‘native’ T-cells.

Adoptive T-cell therapy is a potential therapeutic approach to overcome the lack of insufficient effector T-cell activation by reinfusing genetically modified autologous T-cells into the patient.29 Chimeric antigen receptor (CAR) T-cells targeting a tumor surface antigen have shown clinical benefit in hematologic malignancies for instance in forms of leukemia or lymphoma.74–76 A similar approach with targeting recombinant antigen-specific TCR α and β chains is under investigation and aims to bypass immune tolerance by molecularly engineered higher affinities for the targeted antigens.77 This method aims to supply the immune system with large quantities of specifically tumor-antigen targeting T-cells. So far, this approach has not achieved sufficient clinical efficacy in solid tumors and is under further investigation.78 Specifically, acquired resistance to transferred monospecific T-cells as a result of antigenic drift as well as potential severe and life-threatening side effects, that is, cytokine release storm, have to be addressed before aiming for wider clinical usage in solid tumors.79 Cytokine release syndrome (CRS) manifests as a strong systemic immune reaction with hypotension, hyperpyrexia, and acute respiratory distress as a consequence of released cytokines by immune cells.80 Further, bispecific and trispecific T-cell engager (BiTE, TriTE) as well as bsicpecific and trispecific killer cell engager (BiKE, TriKE) multispecific antibodies (msABs) are linkers between endogenous cytotoxic T/NK cells and antigens expressed by cancer cells with two or three binding domains, respectively.81,82 The consecutive binding of the cytotoxic T/NK cells and the cancer antigens leads to T-cell proliferation and potentiation of the T-cell-mediated immune response and increased tumor specificity.82 MsABs are currently under clinical investigation in Phase I–III trials and bear the potential to overcome escape mutations and to access personalized immunotherapy approaches (NCT04631601, NCT03319940, NCT03214666; Table 1).81,83 In addition, also cytokines and costimulatory
Table 1. Examples of ongoing clinical trials of novel immune-modulating agents targeting steps of the cancer-immunity cycle.

| Step of the cancer-immunity cycle | Mechanism of action/therapeutic target | Malignancy | Clinical trial phase | Examples of clinical trials (NCT number) |
|-----------------------------------|----------------------------------------|------------|---------------------|------------------------------------------|
| 1/2/3                             | Neoantigen vaccination                  | Solid tumors, hematologic malignancies | Phase I, II, III | NCT04397926, NCT05192460, NCT03956056 |
| 1/2/3                             | Dendritic cell (DC) vaccination         | Solid tumors, hematologic malignancies | Phase I, II, III | NCT04567069, NCT03730948, NCT05195619 |
| 1/2                               | Histone deacetylase (HDAC) inhibitors   | Solid tumors, hematologic malignancies | Phase I, II, III | NCT04231448, NCT03592472, NCT04651127 |
| 4/5                               | Chimeric antigen receptor (CAR) T-cells | Solid tumors, hematologic malignancies | Phase I, II, III | NCT04257175, NCT05020392, NCT03651128 |
| 4/5                               | T-cell receptor (TCR) T-cells           | Solid tumors, hematologic malignancies | Phase I, II     | NCT03778814, NCT03441100, NCT05066165 |
| 4/5                               | Bispecific T-cell engager [BiTEs] antibodies | Solid tumors, hematologic malignancies | Phase I, II, III | NCT04631601, NCT04827745, NCT03319940 |
| 4/5                               | Trispecific T-cell engager [TriKEs] antibodies | Solid tumors, hematologic malignancies | Phase I, II     | NCT03214666, NCT03577028, NCT05013554 |
| 5                                 | Cytokines involved in T-cell priming (i.e. interferon alpha, chemokines) | Solid tumors, hematologic malignancies | Phase I, II, III | NCT02506153, NCT04081389, NCT04943679 |
| 5                                 | Costimulatory factors for T-cell priming (i.e. CD27, CD40, OX40) | Solid tumors, hematologic malignancies | Phase I, II | NCT03077474, NCT04081688, NCT03442005 |
| 6                                 | Interleukin-6 (IL-6) inhibitors          | Solid tumors | Phase I, II | NCT03999749, NCT04452214 |
| 6                                 | Interleukin 1β (IL-1β) inhibitors       | Solid tumors | Phase I | NCT04581343 |
| 1/7                               | Poly (ADP-ribose) polymerase (PARP) inhibitors | Solid tumors, hematologic malignancies | Phase I, II, III | NCT02484404, NCT03061188, NCT03598270 |
| 1/7                               | Cyclin-dependent kinase (CDK) 4/6 inhibitors | Solid tumors | Phase I, II | NCT03041311, NCT04000529, NCT04213404 |
| 7                                 | Vascular endothelial growth factor (VEGF)-tyrosine kinase inhibitor (TKI) | Solid tumors | Phase I, II, III | NCT05000294, NCT04493203, NCT04879368 |

(Continued)
factors involved in T-cell priming and activation can be therapeutically targeted and are under clinical investigations (NCT03307746, NCT03323398, NCT02506153; Table 1).84 Another important immune escape mechanism taking place in the local lymph node is the control of T-cell activation by additional inhibitory immune checkpoints as they can prevent the activation of T-cells in the lymph node by binding to their ligands (Figure 1(d)).29

The CTLA4 inhibitory antibody ipilimumab blocks CTLA4 and therefore prevents the interaction with its ligands CD80 and CD86 in the local lymph node. In consequence, the negative regulation and prohibition of T-cell activation is blocked resulting in the expansion of T-cells. The disinhibited T-cell expansion also leads to development of autoreactive T-cells explaining the in comparison higher amount of immune-related toxicities associated with ipilimumab therapy.85 Nevertheless, the clinical responses have aroused the pursuit of other targetable immune checkpoints and led to the implementation of programmed cell death protein 1 (PD-1) and PD-L1 targeting monoclonal antibodies, that is, pembrolizumab, nivolumab, and atezolizumab which are now in broad clinical practice as approved first-line monotherapies or combination therapies in different metastatic solid cancers.86 Immune checkpoint inhibition specifically targets the mechanism in cancers that inhibit an effective immune response rather than nonspecific activation of the immune system potentially leading to autoimmunity or unwanted severe side effects. Importantly, dual immune checkpoint blockade with the CTLA-4-targeting agent ipilimumab in combination with the PD-1-targeting agent nivolumab has shown complementary modes of action and therefore beneficial effects in clinical trials and is nowadays an approved first-line regimen in solid tumors.87,88 Noteworthy, the dual checkpoint blockade with ipilimumab and nivolumab is associated with a higher incidence of immune-related adverse events compared to ICI monotherapy, including rash, colitis, diarrhea, pneumonitis, and hepatitis and a clinical as well as laboratory–chemical observation during therapy is important.89

**Impaired cancer-immune cycle due to systemic factors inhibiting tumor-specific T-cells in the blood stream**

Activated effector T-cells have to travel *via* the blood stream to the local tumor site. However, factors within the blood stream could impact the sustainability of activated T-cells (Figure 1(e)). Systemic inflammation is triggered by cytokines, immune cells, and acute phase proteins. The
circulation of immune cells, that is, neutrophils, can be increased as a result of cancer-mediated myelopoiesis. Further, neutrophils were described to dampen the T-cell-mediated antitumor response by the secretion of inhibitory factors such as arginase, nitric oxide synthase (NOS), and phagocytosis-associated oxidases (PHOXs), which further generates reactive oxygen species (ROS) and inhibits T-cell activation. In line, elevated systemic inflammation markers as for example the neutrophil-to-lymphocyte ratio (NLR) and the acute phase protein C-reactive protein (CRP) correlated with poor treatment response and worse overall survival in different solid cancers. Importantly, the clinical use of steroids was shown to be associated with higher levels of neutrophils and NLR counts and a simultaneously worse outcome in non-small-cell lung cancer (NSCLC) patients treated with ICI. Further, CRP and different cytokines were shown to impact the generated tumor specific immune response, resulting in impaired response to immune modulating therapies. Elevated systemic CRP levels were found to negatively correlate with levels of CD4+ infiltrating lymphocytes in the tumor microenvironment indicating a close link of local and systemic inflammatory responses. Elevated CRP serum levels were further associated with expression of PD-L1 which contributes to immunosuppression in the tumor microenvironment. Circulating proinflammatory cytokines such as interleukin-6 (IL-6), IL-1, tumor necrosis factor alpha (TNF-α) and transforming growth factor beta (TGF-β) are on the one hand triggering CRP expression and on the other hand were also described to upregulate PD-L1 expression themselves.

The inhibition of proinflammatory cytokines might be a possible way of potentiating the antitumor immune response. Here, the inhibition of IL-6 was reported to have a beneficial effect on the efficacy of anti-PD-L1 therapy in preclinical studies and is now investigated in a phase I-II clinical trial in combination with PD-1 targeting therapy (NCT04191421). Another preclinical study showed a decline in monocyte recruitment and macrophages differentiation accompanied with a high proportion of IL-12 secreting DCs cherishing the antitumor immunity by activation of CD8+ T-cells in the tumor microenvironment in IL-1β deficient mice. Therefore, the blocking of IL-1β, that is, with the anti-IL-1β antibody canakinumab is currently under investigation in clinical trials as combinational immunotherapy with anti-PD-1 therapy in NSCLC patients (NCT03631199). Regarding the safety profile of canakinumab, its usage in rheumatologic diseases has already revealed its tolerable side effect profile with infections, especially of the upper respiratory tract, as most common adverse event. In conclusion, many targets for systemic inflammatory molecules are under preclinical and clinical investigation and will potentially form components in the future immunotherapy.

**Impaired cancer-immunity cycle due to immune checkpoint signaling in the local tumor microenvironment**

Within the local tumor microenvironment, the composition of the vascular structures and the cytokine gradient impacts the efficacy of T-cell influx ('homing') and further the antitumor immune response. Pathologically composed and activated endothelial cells were shown to hamper the effective influx of T-cells. Once arrived in the local tumor microenvironment, the tumor specific activated T-cells face several immune-suppressive factors. Tumor cells themselves or tumor-infiltrating lymphocytes can express immune checkpoints such as PD-1 and their ligands (PD-L1) inhibiting the immune response and acting as an ‘immunostat’ (Figure 1(f)). Further immune checkpoints expressed on tumor cells are lymphocyte-activation gene 3 (LAG3) or T-cell immunoglobulin and mucin-domain containing-3 (TIM3). In addition, immune-modulating molecules such as indoleamine 2,3-dioxygenase (IDO) as well as cytokines (i.e. IL-6, IL-10, TGFβ) released by tumor cells can prevent effective T-cell action and even generate intratumoral T-cell exhaustion. Strategies to prevent or reverse T-cell exhaustion by a multimodal and combinatorial therapy approach are, therefore, needed. Further, myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment as well as tumor-associated macrophages, specifically M2 macrophages, can add to the immune suppression and the evasion of tumor cells. Importantly, the composition of tumor-infiltrating lymphocyte subsets forming the local inflammatory microenvironment, including CD8+ and CD3+ effector T-cells, CD45RO+ memory T-cells and FOXP3+ regulatory T-cells, determines the capacity of either antitumor or tumor-promoting inflammatory responses. FOXP3+ regulatory T-cells function as immune-suppressive immune cells by secreting inhibitory cytokines (i.e. IL-10, TGF-β).
The application of ICI targeting the individual route of immune evasion of a given patient needs to be addressed. The combination with chemotherapy was shown to potentially increase PD-L1 expression on tumor cells and thereby improve the response potential to PD-1 axis directed ICI therapy and combinational therapies are in clinical use for different solid cancers.\textsuperscript{111–113} Besides chemotherapy, also combinational inhibition of vascular endothelial growth factor (VEGF) with antiangiogenic agents such as the antibody bevacizumab or VEGF-targeting tyrosine kinase inhibitors (TKIs) may potentially boost the antitumor immune response of anti-PD-1 blockade by facilitating T-cell infiltration into the tumor microenvironment and is under investigation (NCT03396926, NCT04879368; Table 1). Further, combinational approaches with the epidermal growth factor receptor (EGFR)-targeting antibody cetuximab with PD-1-targeting ICIs are postulated to have synergistic effects in antitumor immunity.\textsuperscript{114} In addition, targeting the Wnt/β-catenin signaling pathway in combination with PD-1 targeting ICI has been suggested to improve T-cell priming and T-cell infiltration into the tumor microenvironment since the Wnt/β-catenin pathway was associated with modulation of dendritic cells, tumor-associated macrophages as well as regulatory T-cell infiltration and is tested in early clinical trials (NCT01351103).\textsuperscript{115} Also immune-suppressive cytokines can be specifically targeted and are under investigation in early clinical trials such as antibodies targeting IDO (i.e. NCT03854032, NCT03915405) IL-6/IL-6R (i.e. NCT04191421, NCT04691817), IL-10 (i.e. NCT03382912, NCT02009449), and TGFβ (i.e. NCT04429542) as combinational immunotherapies in advanced solid cancers.\textsuperscript{116} In addition, preclinical and clinical studies suggest a combinational approach of inhibiting DNA damage repair (DDR) pathways with, that is, poly(ADP-ribose) polymerase (PARP) inhibitors or cyclin-dependent kinase 4/6 (CDK4/6) inhibitors with PD-1/PD-L1-axis targeting agents since a dysfunctioning DDR has been postulated to play a role in the activation of the host’s immune system.\textsuperscript{117} PARP inhibitors, for example, have been described to enhance the antitumor immunity via STING pathway activation leading to an increased chemokine recruitment and further induced cytotoxic T-cell functioning.\textsuperscript{118} In line, mismatch repair (MMR) deficiency is an established biomarker for the use of ICI therapy since MMR-deficiency leads to new somatic mutations and an increase in neoantigens reinforcing the cancer-immunity cycle.\textsuperscript{119} Further, other cell types within the inflammatory microenvironment of tumors like the innate natural killer (NK) cells, tumor-associated macrophages as well as cancer-associated fibroblasts can be therapeutically addressed (Table 1). Finally, replicative oncolytic viral vectors that are locally injected into tumors providing local immunostimulating signals are currently under early clinical investigation (NCT05076760; Table 1). Various combinational immunotherapy approaches are currently under investigation in clinical trials (i.e. NCT04301778, NCT02829723) and might improve the generated antitumor immune response.\textsuperscript{27,120,121} Importantly, new class-specific immune-related side effects may occur with novel immune-modulating or combinational therapeutics, therefore, clear treatment guidelines and clinical experience are needed to assure the safety and quality of life of patients. Table 1 summarizes immune-modulating therapeutic approaches under clinical investigation targeting the cancer-immunity cycle as monotherapy or combinational therapy with ICI.

Conclusion

All steps of the cancer-immunity cycle can show impaired functioning, resulting in its ineffective sequence and in consequence the reduction of the tumor-specific immune response. Indeed, immune escape and resistance mechanisms might overpower ICI monotherapy and combinational therapies targeting several steps in the cancer-immunity cycle might be needed to achieve a meaningful immune response in cancer patients. A personalized biomarker approach is warranted to identify the impairment of a given patient. Based on the biomarker analysis, targeted combinational treatments should be applied. Many promising therapeutic strategies for novel immune-modulating therapies as well as their combinations and optimal sequences are currently in clinical examinations. However, severe immune-related side effects may be the result of disinhibiting the brakes of the immune system and their management has to be contemplated. To conclude, in the future, understanding the patient’s specific configuration of immune system–cancer cell interactions as well as the specific underlying immune escape mechanism will be needed to guide personalized treatment options of immunotherapy in cancer patients.
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