Today, we are witnessing a revolution in the treatment of cancer using immunotherapy. In the past decade, work from many laboratories and clinicians has unequivocally demonstrated that the immune system can eradicate established cancers and enhance patient survival. However, immunotherapies have distinct tumor response-to-toxicity profiles owing to distinct mechanisms of action. We have previously termed immunotherapies that activate a general systemic immune response as enhancement cancer immunotherapy and those that target a specific dysfunctional immune response, especially within the tumor microenvironment, as normalization cancer immunotherapy. In this perspective, we provide a framework for normalization cancer immunotherapy in the context of melanoma.

INTRODUCTION
The history of cancer immunology is intertwined with the history of melanoma research, sharing in mutual triumphs and failures. One reason why melanoma’s history is so inextricably linked to cancer immunology’s is that melanoma is often considered one of the most immunogenic human cancers, evidenced by significant infiltration of hematopoietic cells, including various types of lymphocytes and myeloid cells, and this has made it a favored target on the forefront of burgeoning immunotherapies. Thus, for the past 40 years, breakthroughs in the field of cancer immunology were often accomplished through the study of melanoma, ultimately resulting in successful immunotherapies that target melanoma cells. The promise of immunotherapy began with great enthusiasm with the discovery of IFNs (Isaacs and Lindenmann, 1957) and the cancer trials that followed shortly thereafter. Melanoma was one of the first human cancers to achieve moderate success with immunotherapy by treatment with IFN-α2b (Goldstein and Laszlo, 1986), eventually becoming the first immunotherapy for melanoma to be approved by the Food and Drug Administration (FDA) in 1996 (Kirkwood et al., 1996). Several years after the discovery of IL-2 (Morgan et al., 1976; Taniguchi et al., 1983), an administered high dose of IL-2 had durable responses in ~10–15% of patients with melanoma (Atkins et al., 1999), clearly revealing that immunomodulation was indeed a viable weapon in the oncologist’s armamentarium. Subsequently, IL-2 therapy for the treatment of metastatic melanoma was approved in 1998 by the FDA (Atkins et al., 1999). The early successes of IFN-α and IL-2 therapy against human cancers, although limited, prompted scientists to identify the targets of immunotherapy cancer antigens. Perhaps not surprisingly, the first human cancer antigen identified was the melanoma antigen, MAGE-1, which provided the much needed evidence that immunity could target cancer cells specifically (van der Bruggen et al., 1991). Melanoma has also served as a critical target for the development of cancer vaccines (Rosenberg et al., 1998); adoptive cell therapy (Rosenberg et al., 1988); and the first FDA-approved oncolytic virus, Talimogene laherparepvec (Andtbacka et al., 2015). Perhaps most importantly, melanoma was the first cancer to be FDA-approved for immunotherapies targeting T-cell regulation, including targets such as CTLA-4 (Hodi et al., 2010) and PD-1 (Topalian et al., 2014, 2012).

However, each of these immunotherapies has very distinct efficacies and toxicity profiles owing to distinct mechanisms of action. We recently proposed the concepts of enhancement cancer immunotherapy and normalization cancer immunotherapy (Sanmamed and Chen, 2018) to better understand tumor response-to-toxicity profiles and guide future therapeutic targets for cancer immunotherapy. Enhancement cancer immunotherapies attempt to boost underlying immune responses, whereas normalization cancer immunotherapies seek to repair a dysfunctional immune response within the tumor microenvironment (TME). The archetypal normalization cancer immunotherapy is PD-1 or PD-L1 (B7-H1) blockade (collectively called anti-PD therapy), which more selectively targets a dysfunctional T-cell response within the TME, resulting in greater tumor response and reduction of systemic toxicities. In this perspective, we do not attempt to provide a comprehensive review of immune responses to melanoma but rather provide a conceptual framework for normalization cancer immunotherapy to be adopted for further immunotherapeutic discovery and rational clinical trial design.

IMMUNE RESPONSES TO CANCER AND SUBSEQUENT IMMUNE ESCAPE
There is unequivocal evidence that endogenous immune responses to cancer occur (Kaplan et al., 1998;
Shankaran et al., 2001; Vesely et al., 2011). Furthermore, cancer antigens are recognized by T cells, leading to tumor cell destruction and sculpting by immunological mechanisms in a process called cancer immunoediting (Matsushita et al., 2012; Schreiber et al., 2011). Ultimately, immune control of cancers may become broken, leading to immune escape where cancers progressively grow and eventually become clinically apparent (Khong and Restifo, 2002). This latter event frequently leads to formation of an immunosuppressive TME that inhibits subsequent naturally occurring immune responses and resistance to immunotherapy (Sharma et al., 2017a; Zitvogel et al., 2006). Thus, escape from immune control is considered a hallmark of cancer (Hanahan and Weinberg, 2011).

Adaptive immune resistance

Upon tumor cell recognition and immune activation, tumor cells often counter an ongoing immune attack with upregulation or recruitment of immunosuppressive moieties, resulting in a dysfunctional immune response locally within the TME (Figure 1a). This concept has been termed adaptive immune resistance or adaptive resistance (Kim et al., 2018; Taube et al., 2012). The first demonstration of adaptive immune resistance in human patients identified colocalization of tumor-infiltrating lymphocytes expressing IFN-γ and melanoma cells expressing B7-H1 (PD-L1) (Taube et al., 2012). Furthermore, activated T cells express immune inhibitory receptor PD-1, and subsequent engagement of PD-1 on activated T cells with B7-H1 (PD-L1) expressed on tumor cells results in T-cell dysfunction and impaired immune responses to cancer (Dong et al., 2002, 1999). Overcoming this dysfunctional immune response is critical to obtaining effective immunotherapies.

NORMALIZATION VERSUS ENHANCEMENT CANCER IMMUNOTHERAPY

Melanoma therapies have advanced rapidly in the past decade and may be broadly divided into tumor-targeting therapies and immune-modulating
therapies. Tumor-targeted therapies include more conventional chemotherapy and radiation and kinase inhibitors such as vemurafenib, dabrafenib, and trametinib, which target the tumor cell for death. In contrast, immunotherapies are immune-modulating where the target is a component of the immune system, and the effective response is tumor detection and eradication or control by antitumor immunity. Distinct immunotherapies have distinct tumor response-to-toxicity profiles (Figure 1b). For example, among the previously FDA-approved immunotherapies for metastatic melanoma, only anti-PD therapy has a favorable objective tumor response-to-systemic toxicity ratio. Although IFN-α, IL-2, and anti–CTLA-4 boost general immune activation (enhancement), anti–PD-1 therapies more selectively target a dysfunctional immune response triggered within the TME (normalization).

Enhancement cancer immunotherapies

Most cancer immunotherapeutic strategies attempt to boost the antitumor immune response by targeting the fundamental cellular and molecular mechanisms that are physiologically required or necessary in generating an immune response: antigen uptake, processing, and presentation by antigen-presenting cells; migration of antigen-presenting cells to lymphoid organs; T-cell activation and costimulation; trafficking of activated T cells to the TME; T-cell recognition of tumor cells and tumor cell death; and generation of antigen-specific memory T cells. We will limit our discussion to FDA-approved immunotherapies for metastatic melanoma including IL-2, anti–CTLA-4, and anti-PD therapy. However, there is great promise of emerging immunotherapies against melanoma such as adoptive cell transfer (Chandran et al., 2017), chimeric antigen-receptor T cells (Wiesinger et al., 2019), melanoma neoantigen vaccines (Ott et al., 2017), and oncolytic viruses (Andtbacka et al., 2015). Vaccines would be characterized as enhancement immunotherapy, whereas adoptive cell transfer, chimeric antigen-receptor T cells, and oncolytic viruses uniquely perform both tumor-targeting and immunomodulatory functions that predominately enhance ongoing immune response.

The major limiting factor for cancer immunotherapies, especially enhancement immunotherapies, is immune-related adverse events (irAEs) (Postow et al., 2018). Rare objective responses and significant systemic toxicity limited the success of IFN-α and IL-2 therapy. Type I IFNs are known to be important for dendritic cell maturation, activation, migration, and survival, resulting in enhanced adaptive immune responses (Decker et al., 2005). IFN-α2b was FDA-approved as an adjuvant therapy in high-risk resected melanoma in 1996 (Kirkwood et al., 1996). As IFN-α2b was approved as adjuvant therapy after surgical resection, there are no objective responses to be measured. Meta-analysis of phase III randomized clinical trials did show a modest increase in overall survival (Wheatley et al., 2003). However, patients receiving IFN-α2b had significant systemic toxicity, limiting its use as an adjuvant therapy.

High-dose IL-2 therapy was met with initial excitement as it provided a response rate of 16% and long-term survival in some patients with metastatic melanoma (Atkins et al., 1999). However, the toxicity from IL-2 therapy was severe, often requiring admission to medical intensive care units to manage life-threatening organ failure (Schwartz et al., 2002). A pooled analysis from multiple phase II and phase III clinical trials of patients with metastatic melanoma treated with high-dose IL-2 shows an objective response rate of 14% (92 of 722 patients) and a rate of grade 3–4 toxicities of 40% (286 of 722 patients) (Figure 1b) (Agarwala et al., 2002; Atkins et al., 1999; Parkinson et al., 1990; Rosenberg et al., 1994; Sammamed and Chen, 2018; Schwartzentruber et al., 2011; Tarhini et al., 2007). IL-2 is a critical growth factor for T cells, allowing for expansion of T cells after antigen stimulation. Therefore, recombinant IL-2 therapy generates a broad stimulation of the immune system with significant toxicity and relatively poor antitumor responses. This is most likely owing to the greater number of self-reactive or non–tumor-specific T cells that expand than the fewer tumor-specific T cells that expand in response to IL-2 therapy.

In 2011, the modern revolution of cancer immunotherapy began with the approval of anti–CTLA-4 (ipilimumab) mAb for metastatic melanoma (Hodi et al., 2010; Robert et al., 2011). The function of CTLA-4 is to control self-reactive T cells, typically through regulatory T cells (Tregs) (Kuehn et al., 2014; Tivol et al., 1995; Waterhouse et al., 1995; Wing et al., 2008). Accumulated data now supports that the main effect of anti–CTLA-4 therapy in patients with melanoma is through modulation of Treg function, including Treg depletion (Arce Vargas et al., 2018; Romano et al., 2015). Pooled data analysis from multiple phase II and phase III clinical trials of patients with metastatic melanoma treated with anti–CTLA-4 shows an objective response rate of 14% (222 of 1,561 patients) and a rate of grade 3–4 toxicities of 25% (392 of 1,561 patients) (Figure 1b) (Ascierto et al., 2017; Hodi et al., 2016, 2010; Larkin et al., 2015; Ribas et al., 2015; Robert et al., 2015b; Sammamed and Chen, 2018; Weber et al., 2009). Similar to IL-2, the toxicity of anti–CTLA-4 exceeds that of tumor responses, likely owing to targeting of Tregs in peripheral lymph organs rather than within the TME.

Normalization cancer immunotherapies

In contrast to high-dose IL-2 and anti–CTLA-4 therapy, blockade of the PD-1/PD-L1 pathway results in greater tumor efficacy with reduced systemic side effects, suggesting a very distinct mechanism of action (Figure 1b). Since its FDA approval for melanoma in 2014 (Topalian et al., 2014), it is now well established that the PD-1/B7-H1 (PD-L1) axis is a major pathway resulting in dysfunctional immune responses within the local TME (Zou et al., 2016). Pooled data analysis from multiple phase II and phase III clinical trials of patients with metastatic melanoma treated with anti–PD-1 shows an objective response rate of 34% (598 of 1,773 patients) and a rate of grade 3–4 toxicities of 14% (256 of 1,773 patients) (Figure 1b) (Larkin et al., 2018, 2015; Ribas et al., 2015; Robert et al., 2015a, 2015b; Sammamed and Chen, 2018; Topalian et al., 2014). For the first time in the history of oncology, a medical therapy had greater tumor efficacy than...
systemic toxicity. Importantly, anti-PD therapy appears to be targeting a mechanism widely shared by cancers, as it has been approved for 18 different cancer indications and shows efficacy in more than 25 different malignancies, which will likely result in future FDA approvals (Ribas and Wolchok, 2018). In contrast, anti–CTLA-4 monotherapy has failed to show efficacy or gain FDA approval for cancers beyond melanoma (Beer et al., 2017; Lynch et al., 2012). This is likely owing to minimal expression of B7-H1 in noninflamed tissues and more selective upregulation of B7-H1 within the local TME, allowing for a more precise, tumor-specific immune response with less systemic immune activation when targeting the PD pathway.

Combination anti–PD-1 and anti–CTLA-4 therapy is also approved for melanoma and shows an increased objective response rate and significant toxicity (Hodi et al., 2016; Larkin et al., 2015). Pooled analysis from phase I, II, and III clinical trials of patients with metastatic melanoma treated with combination anti–PD-1/anti–CTLA-4 show a response rate of 58% (679 of 1,171 patients) and a rate of grade 3–4 toxicity of 60% (699 of 1,171 patients) (Figure 1b) (Hodi et al., 2018, 2016; Larkin et al., 2015; Sznol et al., 2017). A recent analysis showed a benefit of 4-year overall survival in patients with melanoma treated with combination nivolumab/ipilimumab versus nivolumab alone (Hodi et al., 2018). It is unclear if the increased toxicity with combination blockade limits the benefit of increased objective responses. Careful dosing and sequential therapy may help maximize objective responses while ameliorating systemic toxicity.

Normalization cancer immunotherapy beyond melanoma

Melanoma has long been considered an immunogenic tumor owing to evidence that a significant subset of melanomas (~40–50%) is infiltrated with lymphocytes and that some melanomas, albeit rare, spontaneously regress (Ferradini et al., 1993; van Houdt et al., 2008). Therefore, at least two types of immune dysfunctions in melanoma could be identified, one with infiltration of lymphocytes (hot tumor) and another without (cold tumor). The immune evasion mechanisms in the hot tumors may be caused by the overexpression of B7-H1 as well as other immune suppressors. The cold tumors seem to restrict T-cell access, and therefore, appear noninflamed.

This concept of hot versus cold tumors extends to all solid cancers. Importantly, anti-PD therapy appears to be targeting a mechanism widely shared by cancers, as it has been approved for 18 different cancer indications and shows efficacy in many more malignancies (Ribas and Wolchok, 2018). For most of these FDA-approved indications, anti-PD therapy shows a significant tumor response-to-toxicity profile (Table 1). Listed in Table 1 are pooled analyses from landmark clinical trials with FDA-approved PD therapies as monotherapy. Additional anti-PD mAbs that are currently in clinical trials, have been approved in combination with other therapies, or have not yet been approved by the FDA are excluded. This is a rapidly expanding therapeutic landscape, with more than 3,000 active cancer clinical trials involving PD therapy (Tang et al., 2018). This analysis is a single snapshot in time that will undoubtedly change with updated objective response rates and toxicity rates owing to longer follow-up and additional data from ongoing clinical trials. Nevertheless, these data underscore the benefit of targeted local immune dysfunction within the TME.

Immune-related adverse events in cancer immunotherapy

In addition to distinct tumor responses, enhancement cancer immunotherapy (anti–CTLA-4) and normalization cancer immunotherapy (anti–PD) have distinct irAEs (Postow et al., 2018). For example, the most common cutaneous irAE from ipilimumab is a spongiotic, eczematous eruption (Lacouture et al., 2014), whereas lichenoid dermatoses with expression of PD-1 on alveolar macrophages may contribute to the development of pneumonitis during anti-PD therapy (Igarashi et al., 2016).

Melanoma is unique, where development of vitiligo as an irAE is related to the cancer target as opposed to the mechanism of immunotherapy (Hua et al., 2016). Shared melanoma antigens with normal melanocytes predispose the development of T cells recognizing and destroying normal melanocytes in patients with melanoma treated with cancer immunotherapy. Vitiligo may develop during immunotherapy to other cancers as well (Kosche et al., 2018), but with a much lower frequency than melanoma. Overall, the development of irAEs do not confer any treatment benefit with the exception of vitiligo during melanoma treatment (Hua et al., 2016).

Antigen quality over antigen quantity for successful cancer immunotherapy

The development of vitiligo during cancer immunotherapy of melanoma is reflective of immune detection of cancer antigens. Without immune detection of tumor-specific antigens, there can be no immune response to cancers. Therefore, it has been hypothesized that cancers with greater tumor mutational burden will have a greater number of potential neoantigens and thereby a higher success rate for cancer immunotherapy (Snyder et al., 2014). For example, cutaneous malignancies such as
as melanoma and cutaneous squamous cell carcinoma have high mutational load owing to UV exposure and have a high response rate to anti-PD therapy. However, tumor mutational burden does not always predict response to normalization cancer immunotherapy (Cristescu et al., 2018). Among the 18 cancer indications FDA-approved with PD therapy, the two cancers with the lowest mutational burden have some of the highest response rates (Hodgkin lymphoma and primary mediastinal large B-cell lymphoma) (Table 1) (Armand et al., 2019, 2018). In addition to hematologic malignancies, tumor mutational burden as a predictive biomarker of response also does not correlate with virally induced solid cancers. For example, both head and neck squamous cell carcinoma and Merkel cell carcinoma can either be due to viral transformation (lower mutational burden) or carcinogen induction (higher mutational burden) (Goh et al., 2016; Stransky et al., 2011). Nevertheless, both subtypes show similar responses to anti-PD therapy (Ferris et al., 2016; Nghiem et al., 2019). Therefore, the quality of the antigens targeted is more important than the quantity of antigens. This underlies the importance of targeting the mechanism of immune escape within the TME with normalization cancer immunotherapy, regardless of tumor mutational burden or cancer subtype.

**PRINCIPLES OF NORMALIZATION CANCER IMMUNOTHERAPY**

Because the mechanisms of immune suppression are largely developed within the TME, a deep understanding of the TME is critical to identify pathways selectively upregulated within the TME and resultant dysfunctional immunity against cancers. Therefore, the goal of normalization cancer immunotherapy is to reset or reprogram a previously effective immune response against cancers by targeting unique

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**Table 1. Approved Anti-PD Monotherapies for Cancer**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Objective Response</th>
<th>Grade 3–5 Toxicity</th>
<th>Drug (Target; FDA Approval)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>34%</td>
<td>14%</td>
<td>Pembrolizumab (PD-1; 2014) Nivolumab (PD-1; 2014)</td>
<td>Larkin et al., 2018, 2015; Ribas et al., 2015; Robert et al., 2015a, 2015b; Sannamed and Chen, 2018; Topalian et al., 2014</td>
</tr>
<tr>
<td>NSCLC</td>
<td>26%</td>
<td>23%</td>
<td>Pembrolizumab (PD-1; 2015) Nivolumab (PD-1; 2015) Atezolizumab (PD-L1; 2016) Durvalumab (PD-L1; 2018)</td>
<td>Antonia et al., 2017; Borghaei et al., 2015; Brahmer et al., 2015; Fehrenbacher et al., 2016; Reck et al., 2016</td>
</tr>
<tr>
<td>RCC</td>
<td>25%</td>
<td>19%</td>
<td>Nivolumab (PD-1; 2015) Avelumab (PD-L1; 2019) (combined with Axitinib)</td>
<td>Motzer et al., 2015</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>70%</td>
<td>18%</td>
<td>Nivolumab (PD-1; 2016) Pembrolizumab (PD-1; 2017)</td>
<td>Armand et al., 2018; Chen et al., 2019</td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>20%</td>
<td>12%</td>
<td>Atezolizumab (PD-L1; 2016) Nivolumab (PD-1; 2017) Avelumab (PD-L1; 2017)</td>
<td>Balar et al., 2017; Necchi et al., 2017; Patel et al., 2018; Powles et al., 2017; Sharma et al., 2017b</td>
</tr>
<tr>
<td>HNSCC</td>
<td>15%</td>
<td>13%</td>
<td>Pembrolizumab (PD-1; 2016) Nivolumab (PD-1; 2016)</td>
<td>Ferris et al., 2016; Mehra et al., 2018</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>41%</td>
<td>20%</td>
<td>Avelumab (PD-L1; 2017) Pembrolizumab (PD-1; 2018)</td>
<td>Kaufman et al., 2016; Nghiem et al., 2019</td>
</tr>
<tr>
<td>MSI-hi</td>
<td>33%</td>
<td>15%</td>
<td>Pembrolizumab (PD-1; 2017)</td>
<td>Le et al., 2020</td>
</tr>
<tr>
<td>Colorectal carcinoma (MSI-hi)</td>
<td>31%</td>
<td>20%</td>
<td>Nivolumab (PD-1; 2017)</td>
<td>Overman et al., 2017</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>19%</td>
<td>21%</td>
<td>Nivolumab (PD-1; 2017) Pembrolizumab (PD-1; 2018)</td>
<td>El-Khoueiry et al., 2017; Zhu et al., 2018</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>12%</td>
<td>18%</td>
<td>Pembrolizumab (PD-1; 2017)</td>
<td>Fuchs et al., 2018</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>15%</td>
<td>12%</td>
<td>Pembrolizumab (PD-1; 2018)</td>
<td>Chung et al., 2019</td>
</tr>
<tr>
<td>PMBCL</td>
<td>45%</td>
<td>23%</td>
<td>Pembrolizumab (PD-1; 2018)</td>
<td>Armand et al., 2019</td>
</tr>
<tr>
<td>SCLC</td>
<td>14%</td>
<td>11%</td>
<td>Nivolumab (PD-1; 2018) Atezolizumab (PD-L1; 2019) (combined with chemotherapy) Pembrolizumab (PD-1; 2019)</td>
<td>Antonia et al., 2016, NCT02628067, NCT02054806</td>
</tr>
<tr>
<td>cSCC</td>
<td>47%</td>
<td>12%</td>
<td>Cemiplimab (PD-1; 2018)</td>
<td>Migden et al., 2018</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>10%</td>
<td>12%</td>
<td>Pembrolizumab (PD-1; 2019)</td>
<td>Shah et al., 2019</td>
</tr>
</tbody>
</table>

Not included are endometrial carcinoma ( pembrolizumab; PD-1; 2019) and triple negative breast cancer (atezolizumab; PD-L1; 2019) that are approved in combination with chemotherapy or targeted therapy.

Abbreviations: cSCC, cutaneous squamous cell carcinoma; FDA, Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; MSI-hi, microsatellite instability high tumors, including colorectal, endometrial, and gastrointestinal cancers; NSCLC, non–small cell lung cancer; PMBCL, primary mediastinal large B-cell lymphoma; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

Overall grade 3–5 toxicity for cemiplimab is 42%, whereas treatment-related grade 3–5 toxicity was 12%.
immune evasion mechanisms that pre-
dominately reside within the TME. The
normalization effect includes at least
two aspects—restoring existing
dysfunctional immunity in the TME and
preventing newly recruited immune
cells from losing their functions (i.e.,
becoming dysfunctional).

There are three major principles for
normalization cancer immunotherapy
to be successful (Figure 2). First, iden-
tify an immune tumor escape mecha-
nism that occurs during tumor
progression. This escape mechanism
is largely developed and associated
with tumor progression but not part of
normal physiological immune sup-
pressive mechanisms required for
control of immune responses. One
such example is CTLA-4, which is
required for the control of autoim-
nunity under physiological conditions.
Genetic ablation or antibody blockade
of CTLA-4 leads to severe autoimmune
adverse events (Kuehn et al., 2014).
Second, selectively modulate a
dysfunctional immune response within
the TME for therapeutic intervention.
Most of the tumor evasion mechanism
occurs in the TME. In addition, selec-
tive manipulation of immune re-
sponses in the TME could allow a more
focused immune response so that se-
vere adverse events can be prevented.
Third, manipulate only those mecha-
nisms that are dominant in the TME. As
multiple immune evasion mechanisms
could occur simultaneously in the
TME, it is obviously important to
identify the dominant mechanism or
mechanisms in patients for therapeutic
intervention. Currently, the only
immunotherapy approved for mel-
noma or any other cancer that best fits
the principles of normalization cancer
immunotherapy is anti-PD therapy.

However, anti-PD therapy is far from
perfect, with only a subset of patients

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**Figure 2. Targeting the tumor microenvironment: principles of normalization cancer immunotherapy.** The left panel represents T-cell activation by DCs in the
lymph node where the function of anti–CTLA-4 and high-dose IL-2 acts to enhance T-cell activation. The right panel represents T cells within the TME, where
anti-PD therapy acts to block PD-1/PD-L1 interactions. The three guiding principles of normalization cancer immunotherapy are listed at the bottom. DC,
dendritic cell; MHC, major histocompatibility complex; TAM, tumor-associated macrophage; TCR, T-cell receptor; TME, tumor microenvironment; Treg,
regulatory T cell.
responding and some patients experiencing significant toxicity, albeit less than other immunotherapies. Clearly there are other mechanisms of adaptive immune resistance to be interrogated, including other immune inhibitory molecules (Wang et al., 2019a, 2019b; Yao et al., 2013). In addition to other immune inhibitory molecules expressed within the TME as a mechanism of resistance to PD therapy, tumor intrinsic adaptations may occur that evade immune-mediated tumor cell destruction (Sharma et al., 2017a). For example, mutations in antigen processing and presentation machinery (Zaretsky et al., 2016) or IFN-γ signaling pathways (Shin et al., 2017) result in resistance to PD therapy. Despite these occurrences of tumor intrinsic resistance, normalization cancer immunotherapy is still a powerful approach to restore a normal antitumor immune response locally within the TME so as to maximize tumor eradication and limit systemic toxicity.

FUTURE CONSIDERATIONS FOR CANCER IMMUNOTHERAPY

Careful interrogation of the TME is critical to addressing the numerous defects or dysfunction of antitumor immunity to help determine the mechanisms. As new potential therapeutics are developed and future clinical trials are embarked on, it is critical to focus efforts on those that try to restore an already powerful antitumor immune response within the TME based on mechanisms of tumor-specific immune evasion rather than general immune activation.

REFERENCES


Normalization Cancer Immunotherapy for Melanoma


