Review

Cancer Immunology and Immunotherapy

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Abstract. Hanahan and Weinberg described six distinct biological properties of cancer cells that enable tumor growth and metastasis. These properties were referred to as the traditional hallmarks of cancer. Recent discoveries further elucidated hallmarks including evasion of immune destruction by tumor cells that disrupt anticancer response pathways. This review discusses cancer immunology and new treatment strategies aimed at restoration of antitumor immune responses.

The traditional hallmarks of cancer include sustained proliferative signaling, evasion from growth suppressors, and resistance to cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Two emerging hallmarks include reprogramming of energy metabolism and evading immune destruction (1). These hallmarks are referred to as enabling characteristics of cancer.

The Molecular Basis of Cancer Immunotherapy

The human immune system mounts natural endogenous response to foreign cells, particularly highly immunogenic cancer cells, through a complex series of steps. These involve presenting of cancer antigens to T-cells via antigen-presenting cells (APCs), priming and activating T-cells in lymph nodes, trafficking and infiltration of T-cells into tumor beds (tumor-infiltrating lymphocytes), recognition of cancer cells by T-cells, development of antigen-specific systemic effector and memory T-cells, and humoral immunity, allowing effector T-cells, other endogenous immune cells and antibodies to tumor to act in concert in order to eliminate cancer cells (2). Typically, major histocompatibility complex (MHC) class-I APCs, for instance dendritic cells (DC), present antigen to cluster of differentiation 8+ (CD8+) T-cells. This leads to the production of cellular cytotoxic immune response against foreign antigens. However, this rarely provides adequate antitumor immunity.

One limitation of cancer immunotherapy is that natural tumor antigens elicit relatively weak T-cell responses since high-affinity T-cells tend to be rendered tolerant to these antigens. Cancer immune responses start with MHC/T-cell receptor (TCR) interactions. Increasing the stability of the MHC-peptide–TCR complex significantly improves immune responses and induces expansion of T-cells specific for the natural tumor epitopes. Therefore, peptides that stabilize the MHC-peptide–TCR complex may provide superior antitumor immunity through enhanced stimulation of specific T-cells (3).

Both weakly and strongly immunogenic antigens on cancer cells enable multiple evasion strategies. This is suspected to be due to modulating factors in the tumor microenvironment that subvert the existing antitumor T-cell response. Important tumor immune modulating factors are described below.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA4), a negative regulator of T-cell activation (4), is expressed in response to immune reaction and inhibits uncontrolled immune responses. CTLA4 prevents the occurrence of chronic autoimmune inflammation. It binds B7 molecules on DCs and other APCs, inhibiting further stimulation and expansion of the immune response. However, in antitumor responses, CTLA4 becomes an inhibitor to development of endogenous immune responses.

This article is freely accessible online.

COI/Funding: LGL is a co-founder of Transtarget, Inc. Otherwise, the authors have nothing to disclose.

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Key Words: Cancer immunology, immunotherapy, checkpoint inhibitor, PD1, PDL1, CTLA4.
Programmed death-1 (PD1), a transmembrane protein expressed on T-cells, B-cells and natural killer (NK) cells, binds to programmed death ligand-1 and 2 (PD-L1/2). When it binds to its ligand, it directly inhibits tumor cell apoptosis, causes peripheral T-effector cell exhaustion, and promotes the conversion of T-effector cells to regulatory T-cells (Tregs) (5). Cancer cells that express PD-L1/2 hinder the killing capacity of effector T-cells by inhibitory signals. The PD-L1–PD1 interaction functions as an immune response brake, or an 'immunostat' in the microenvironment. This interaction deems effector T-cells ineffective and leads to the interruption of the cancer-immune response network.

Tregs [CD4+, CD25+, forkhead box P3+ (FOXP3+), CTLA4+, glucocorticoid induced tumor necrosis factor receptor related protein+ (GITR+)] promote tolerance and suppress T-effector cell function, and their infiltration in tumors is correlated with poor prognosis (6). Tumor and stromal cells in the tumor beds release multiple factors, such as adenosine and C-C motif chemokine ligand 28 (CCL28), which inhibit T-effector cell function and attract Tregs, respectively. Tumor immunosuppression can be targeted by inhibiting or depleting Tregs. Anti-CD25 antibodies and low-dose cyclophosphamide are two therapies that preferentially deplete Tregs (6).

Myeloid-derived suppressor cells (MDSC) are cells of myeloid origin that expand during various pathological conditions, including cancer and inflammation. They are characterized by increased production of reactive oxygen and nitrogen species (7).

Monocytes develop in the bone marrow and transform into macrophages prior to entering tissue. These tissue macrophage populations can then differentiate into either proinflammatory, microbiocidal (M1), or anti-inflammatory (M2) subtypes (8).

Neutrophils are the most abundant circulating phagocytes. They are the first cells to be recruited to sites of inflammation. A subset of neutrophils, however, inhibits T-cell responses through macrophage-1 antigen (MAC1), limiting the damage to host tissue during inflammation (9).

The overall strategy for enhancing the immune responses is to interrupt the suppressive circuit by either inhibition or depletion of a specific cells or cell types.

**Current Cancer Immunotherapy Strategies**

**Cell-based immunotherapy of cancer.** Cellular immunity depends mainly on the ability of DCs to take up and process antigens in the peripheral blood and tissues. Immature DCs are particularly good at antigen ingestion and processing but for a productive T-cell response, they must mature into fully activated DCs which express high levels of cell-surface MHC antigen complexes and co-stimulatory molecules. Very small numbers of activated DCs are efficient at generating immune responses against pathogens (10). In cancer, this process is not robust enough to produce meaningful antitumor responses.

The production of vaccines for cancer came after the introduction of monoclonal antibodies. The first cell-based cancer vaccine, Sipuleucel-T (Provenge), was approved by the US Food and Drug Administration (FDA) in 2010 for the treatment of prostate cancer and is the only cell-based immunotherapy currently available outside clinical trial settings.

Chimeric antigen receptor T-cell (CAR-T cell) is a T-cell that expresses a transduced single-chain variable fragment (scFV) that targets a tumor-associated antigen on tumors. Expressing the scFV on the surface of the T-cells converts every T-cell into an antigen-specific killer T-cell. Bispecific antibodies combine the benefits of different binding specificities of two monoclonal antibodies into a single construct, enabling approaches retargeting of effector cells to tumor targets. Advances in antibody engineering and antigen profiling of malignant cells have led to the development of a multitude of bispecific antibodies. Most are focused on retargeting T-cell via anti-CD3 binding for redirected tumor killing. There have been significant advances in the design and application of bispecific antibodies for intravenous and local injection in the past 25 years. Since the recent revival of bispecific antibodies, there has been multiple, ongoing phase I/II and III trials, and a few promising clinical outcomes (11).

**Antibody-based immunotherapy of cancer.** Monoclonal antibodies are proteins produced by B-cells that bind to a specific antigen. They are currently one of the most successful form of cancer immunotherapy. We should differentiate between monoclonal antibody-based cancer therapy and monoclonal antibody-based immunotherapy of cancer. This can be illustrated by the differences in their mechanisms of action. Anti-neoplastic agents such as bevacizumab block ligand–receptor interaction, thereby affecting growth or survival pathways, where monoclonal antibodies such as rituximab cause antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity. Antibody-dependent cellular phagocytosis is also relevant. On the other hand, other monoclonal antibodies work as vehicles to selectively deliver chemotherapy or radiation as immunoconjugates to the cancer cells with minimum systemic exposure to these cytotoxins (ibrutinomab tiuxetan, trastuzumab and emtansine).

The use of monoclonal antibodies has expanded dramatically in recent years to include multiple targets. The evolution of antibody-based immunotherapy has focused on stimulating persistent immunity, activating stimulatory receptors and modulating the amplitude of immune responses, as well as the production of immunoconjugates and bispecific antibodies. Monoclonal antibodies are manufactured to target antigens that are both abundant and accessible, and unique to cancer cells. These antigens include cell surface receptors such as CD20 (rituximab) and CD30 (brentuximab and vedotin), as well as growth factors such as epidermal growth factor receptor (cetuximab), human epidermal growth factor...
receptor 2 (trastuzumab) and vascular endothelial growth factor [VEGF (bevacizumab)], and antigens expressed by tumor support structures such as the stroma and extracellular matrix, fibroblast activation protein (sibrotuzumab) and tenascin (81C6) (12). When bound to surface antigens of tumor cells, monoclonal antibodies prompt the uptake and destruction of those cells, in doing so, exposing intracellular antigens that were inaccessible to the antibodies or APCs beforehand. APCs then gain access to these intratumoral antigens and produce tumor-infiltrating cytotoxic T-lymphocytes (13), leading to a persistent adaptive immune response against the tumor. In addition to antibodies targeting tumor surface antigens, antibodies targeting T-cell stimulatory receptors are being manufactured. Stimulation with OX40, 4-1BB, and CD27 not only induces proliferation and cytokine production in T-cells, but also inhibits proliferation and differentiation of Tregs (10); these agents are currently in trials (OX40 in colorectal cancer: NCT02559024; 4-1BB in combination with pembrolizumab in solid tumors: NCT02179918; and anti-CD27 in combination with nivolumab in solid tumors: NCT02335918).

Antibodies are also being used to enhance the strength of the immune response. As mentioned earlier, activated T-cells and tumor cells express CTLA4 receptors as an immune-suppressive mechanism to protect against autoimmunity and to escape elimination. Antagonism of these receptors has shown antitumor benefit. For example, ipilimumab inhibits the receptor CTLA4, permitting persistent T-cell activation. Similarly, PD1 is expressed on activated T- and B- cells and when bound to by PD1 ligand they become deactivated (10-12). Tumor cells tend to overexpress PD1 ligands, allowing them to deactivate this response.

Monoclonal antibody immunoconjugates include conjugates with radionuclide, drugs, toxins or enzymes to enhance toxic effects against tumor cells. 90Y-Ibritumomab and 131I-tositumomab are two radionuclides conjugated with antibodies to CD20 leading to improved response rates (RR) and progression-free survival (PFS) in patients with non-Hodgkin’s lymphoma (11). Brentuximab vedotin, a conjugate of an antimitotic drug with CD30 antibodies, was approved for clinical use against relapsed or refractory Hodgkin’s lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma (12).

Bispecific antibodies are constructed to have dual affinity (Figure 1) (13). The most common constructs are directed at an activating receptor on T-effector cells and at the tumor antigen. Similarly, bispecific T-cell engagers directly stimulate T-cells by binding to CD3 along with tumor antigens CD19 or epithelial cell adhesion molecule. The US FDA recently approved blinatumumab, with an scFV region directed at CD3 and a scFV directed at CD19, for use in CD19+ acute lymphoblastic leukemia. This approval has re-ignited interest in the use of bispecific antibodies.

Cytokine-based immunotherapy of cancer. Perhaps the best known examples of cytokine-based immunotherapy in cancer are the use of interleukin-2 (IL2) and interferon alpha (IFNα) in melanoma and renal cell carcinoma (RCC).

In 1976, IL2 was first identified as a T-cell growth factor. IL2 promotes proliferation, differentiation, and recruitment of T- and B-cells, NK cells, and thymocytes. This stimulates lymphokine-activated killer cells and tumor-infiltrating lymphocytes, allowing the human body to respond to malignant (14).

Atkins et al. reviewed 270 patients with metastatic melanoma treated with IL2 who had enrolled into eight clinical trials conducted between 1985 and 1993. Tumor responses were seen in 16% of patients, with complete responses (CR) in 17 (6%) and partial responses (PR) in 26 (10%). Median overall survival (OS) for the whole cohort was 12 months. The authors concluded that high-dose IL2 can produce durable responses in patients with metastatic melanoma and that it should be considered a therapeutic option for appropriately selected patients (15).

High-dose bolus IL2 has also led to durable, high-quality remissions in RCC, although this was also in a minority of patients. In a retrospective analysis from the National Cancer Institute, Klapper et al. reported that out of 259 patients with metastatic RCC who were treated with high-dose IL2, 23 (9%) had CR and 30 (12%) had achieved PR (16). Similar results were seen in another series of 212 patients treated with high-dose IL2, with an overall response rate (ORR) of 20%. This included 16 patients with a CR and a median survival of 10 years or more (17). IL2 is, however, associated with severe toxicity including hypotension, arrhythmia, metabolic acidosis, fever, nausea and vomiting, dyspnea, edema, oliguria/renal failure and neurotoxicity (18).

IFNα was the first recombinant cytokine used to treat metastatic melanoma. IFNα is thought to increase phagocytic activity of macrophages and augment cytoxicity of lymphocytes for malignant cells (19).

Adjuvant IFNα therapy is considered in patients with RCC at high risk for recurrence following initial surgical resection. The most extensive data come from a meta-analysis of four randomized trials published between 1990 and 2008, including 8122 patients (20). Disease-free survival (DFS) with IFNα was significantly prolonged, with a hazard ratio (HR) for recurrence of 0.82. OS data available from 12 out of 14 trials was significantly improved with IFNα, with a HR for death of 0.89. The activity of monotherapy with IFNα in metastatic RCC has also been evaluated in several large trials (21). Although the ORR was as high as 15%, most responses were PR and rarely persisted beyond 1 year. In a meta-analysis that included four studies involving a total of 644 patients, treatment with IFNα was superior to that of controls (odds ratio for death at 1 year 0.56, and an overall HR for death of 0.74) (22).
Immunological escape is the phenomenon whereby cancer cells have acquired the ability to evade the adaptive immune system. One of the most important known mechanisms allowing escape from immune surveillance is the up-regulation of expression of immune checkpoint molecules such as CTLA4 and PD1 (previously known as CD279). CTLA4, which was discovered in 1987, acts as a negative regulator of T-cell activation (4). Cancer cells that express PD-L1/2 also hinder the T-effector cell killing capacity by inhibitory signals. The PD1–PD-L1/2 interaction deems T-effector cells incompetent and leads to the interruption of the cancer-immunity cycle. This inhibitory pathway is a hardwired into the immune system to maintain self-tolerance and modulate the amplitude of immune responses and is often referred to as immune checkpoints. Blocking immune checkpoints is among the most promising approaches to activating therapeutic antitumor immunity (23).

**Checkpoint Inhibitors in Melanoma**

*Anti-CTLA4.* Ipilimumab is the first immune checkpoint inhibitor to be approved for the treatment of metastatic melanoma (24). In two large phase III trials, ipilimumab significantly prolonged OS. In the first study, 676 previously treated patients with advanced melanoma were randomly assigned in a 3:1:1 ratio to receive ipilimumab plus glycoprotein 100 (GP100) vaccine (n=406), ipilimumab alone (n=137), or GP100 alone (n=136). OS was significantly increased with the use of ipilimumab (25). In the second trial, 502 previously untreated patients with metastatic melanoma were assigned in a 1:1 ratio to ipilimumab plus dacarbazine or to placebo plus dacarbazine. OS rates consistently favored the ipilimumab arm;
Anti-PD1. Pembrolizumab and nivolumab are PD1 inhibitors which were first approved for melanoma by FDA on September 4, 2014 and December 22, 2014 respectively (28).

In a phase I/II dose-escalation cohort expansion study, 107 patients were treated at various doses of nivolumab between 0.1 to 10 mg/kg every 2 weeks. The median OS was 16.8 months. Objective response was observed in 33 out of 107 patients (31%) (29).

These results led to three phase III trials. The CheckMate 066 phase III trial enrolled 418 previously untreated patients with wild-type B-raf (BRAF) melanomas. Patients were randomly assigned to nivolumab/placebo (n=210) or dacarbazine/placebo (n=208). The OS was significantly increased in the nivolumab arm, with a 1-year survival rate of 72.9% vs. 42.1%. The ORR was 40.0% in the nivolumab arm vs. 13.9% in the dacarbazine arm (30).

The CheckMate 037 phase III trial enrolled patients previously treated with anti-CTLA4 and BRAF inhibitor. They were randomly assigned in a 2:1 ratio to either nivolumab or chemotherapy (either dacarbazine or carboplatin plus paclitaxel). An interim analysis on 167 patients (120 on nivolumab and 47 on chemotherapy) showed that objective response were significantly more common in patients on nivolumab (38 out of 120; 31.7%) vs. those on chemotherapy (five out of 47; 10.6%) (31).

The KEYNOTE-001 trial, a phase I study, enrolled 655 patients with advanced melanoma. A total of 342 had been previously treated with ipilimumab and the rest were ipilimumab-naïve. The OS was 67% (63% vs. 71%, respectively) at 12 months and 50% (46% vs. 53%, respectively) at 24 months (32). Although PDL1 expression correlated with increased responsiveness, the absence of PDL1 did not preclude a response (33).

KEYNOTE-002, a phase II trial, had 540 patients with ipilimumab-refractory advanced melanoma. They were randomly assigned to 2 or 10 mg/kg pembrolizumab, or chemotherapy (either dacarbazine plus paclitaxel, paclitaxel, carboplatin, dacarbazine, or temozolomide). PFS and ORR were significantly improved in the pembrolizumab arms. The most common treatment-related adverse events were fatigue, pruritis, and rash (34).

KEYNOTE-006, a three-armed phase III trial, enrolled 834 patients with advanced melanoma. Patients were randomized 1:1:1 to pembrolizumab (at 10 mg/kg) every 2 weeks, every 3 weeks, or four doses of ipilimumab (3 mg/kg) every 3 weeks. Estimated 12-month OS rates were 74.1%, 68.4%, and 58.2%, respectively (35).

Combination of anti-PD1 and anti-CTLA4. The CheckMate 067 phase III trial evaluated the efficacy of combined anti-CTLA4 and anti-PD1. In this trial, 945 treatment-naïve patients were randomly assigned in a 1:1:1 ratio to combination of nivolumab (1 mg/kg every 3 weeks) plus ipilimumab (3 mg/kg every 2 weeks) for four doses followed by nivolumab (3 mg/kg every 2 weeks), or nivolumab alone (3 mg/kg every 2 weeks), or ipilimumab alone (3 mg/kg every 3 weeks for four doses). All three arms included placebo treatments. The median PFS in the combination arm was superior to that with ipilimumab alone, with 11.5 months vs. 2.9 months, respectively, and an HR of 0.42. The ORR for the combination, nivolumab alone, and ipilimumab alone were 57.6%, 43.7%, and 19.0%, respectively. The CR rates were 11.5, 8.9, and 2.2%, respectively. These results, however, were at the costs of serious adverse effects (36).

Major trials utilizing checkpoint inhibitors in melanoma are summarized in Table I.

Immunotherapy in Non-Small Cell Lung Cancer (NSCLC)

Historically, NSCLC was considered to be non-immunogenic, based on several failed attempt to treat patients with NSCLC using agents such as IL2, IFN, and Bacillus Calmette-Guerin (37). However, with the development of anti-CTLA4 and PD1–L1 inhibition therapy, immunotherapy is changing the landscape of NSCLC treatment.

Anti CTLA4. A total of 204 patients with stage IIIB/IV chemotherapy-naïve NSCLC were randomly assigned 1:1:1 to receive carboplatin/paclitaxel/placebo (control, n=66) or carboplatin/paclitaxel/ipilimumab [four doses of ipilimumab followed by two doses of placebo (concurrent, n=70) or two doses of placebo followed by four doses of ipilimumab (phased arm, n=68)]. This study met its primary endpoint of improved immune-related PFS for phased ipilimumab vs. the control (hazard ratio=0.72; p=0.05) but not for concurrent ipilimumab (HR=0.81; p=0.13). Phased ipilimumab also improved PFS per World Health Organization criteria (HR=0.69) (38). Chemotherapy exposure prior to ipilimumab administration may have potentially enhanced T-cell activation resulting in improved endpoints in the phased arm (39).

Anti-PD1. Nivolumab and pembrolizumab were approved by the US FDA for NSCLC, with the indication being for patients with advanced (metastatic) NSCLC whose disease progressed after first-line platinum-based treatment.

In a phase I study of 306 patients with advanced solid tumors, nivolumab resulted in 22 (17%) out of 129 patient with NSCLC achieving an objective response with a median duration of response of 17.1 months. RR and OS were similar in patients with squamous and non-squamous histologies (40).

CheckMate 063, a phase II study, enrolled 117 patient with advanced squamous NSCLC with ≥2 prior therapies and
Table I. Checkpoint inhibitors in melanoma.

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Agent(s)</th>
<th>Phase</th>
<th>No. of patients</th>
<th>OS (95% CI)</th>
<th>ORR (95% CI)</th>
<th>CR</th>
<th>PR</th>
<th>Grade 3-4 AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodi et al. (25)</td>
<td>Ipilimumab + GP100</td>
<td>III</td>
<td>403</td>
<td>At 2 years: 21.6%</td>
<td>5.7% (3.7-8.4%)</td>
<td>0.2%</td>
<td>5.5%</td>
<td>10-15%</td>
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<tr>
<td></td>
<td>Ipilimumab</td>
<td>III</td>
<td>137</td>
<td>At 2 years: 23.5%</td>
<td>10.9% (6.3-17.4%)</td>
<td>1.5%</td>
<td>9.5%</td>
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</tr>
<tr>
<td>Robert et al. (26)</td>
<td>Ipilimumab</td>
<td>III</td>
<td>250</td>
<td>At 2 years: 47.3%</td>
<td>15.2%</td>
<td>1.6%</td>
<td>13.6%</td>
<td>56.3%</td>
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<tr>
<td></td>
<td>Nivolumab</td>
<td>III</td>
<td>107</td>
<td>At 2 years: 62%</td>
<td>31%</td>
<td>NA</td>
<td>NA</td>
<td>22%</td>
</tr>
<tr>
<td>Topalian et al. (29)</td>
<td>Nivolumab</td>
<td>I/II</td>
<td>210</td>
<td>At 2 years: 43%</td>
<td>40.0% (33.3-47%)</td>
<td>7.6%</td>
<td>32.4%</td>
<td>11.7%</td>
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<tr>
<td>Robert et al.,</td>
<td>Nivolumab</td>
<td>III</td>
<td>120</td>
<td>Not reported;</td>
<td>31.7% (23.5-40.8%)</td>
<td>3.3%</td>
<td>28.3%</td>
<td>5%</td>
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<tr>
<td>CheckMate066 (30)</td>
<td></td>
<td></td>
<td></td>
<td>6-months PFS: 48%</td>
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<td>Weber et al.,</td>
<td>Nivolumab</td>
<td>III</td>
<td>210</td>
<td>At 1 year: 72.9%</td>
<td>43.7% (38.1-49.3%)</td>
<td>8.9%</td>
<td>34.8%</td>
<td>16.3%</td>
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<tr>
<td>CheckMate037 (31)</td>
<td></td>
<td></td>
<td></td>
<td>(65.5-78.9%)</td>
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<tr>
<td>Larkin et al.,</td>
<td>Ipilimumab + Nivolumab</td>
<td>III</td>
<td>314</td>
<td>Not reported;</td>
<td>57.6% (52-63.2%)</td>
<td>11.5%</td>
<td>46.2%</td>
<td>55.0%</td>
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<tr>
<td>CheckMate067 (36)</td>
<td></td>
<td></td>
<td></td>
<td>Median PFS: 11.5(8.9-16.7) months</td>
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<tr>
<td></td>
<td>Nivolumab</td>
<td></td>
<td>316</td>
<td>6.9 (4.3-9.5) months</td>
<td>43.7% (38.1-49.3%)</td>
<td>8.9%</td>
<td>34.8%</td>
<td>16.3%</td>
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<tr>
<td></td>
<td>Ipilimumab</td>
<td></td>
<td>315</td>
<td>2.9 (2.8-3.4) months</td>
<td>19% (14.9-23.8%)</td>
<td>2.2%</td>
<td>16.8%</td>
<td>27.3%</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>I</td>
<td>655</td>
<td>At 1 year: 67%</td>
<td>34%</td>
<td>6%</td>
<td>28%</td>
<td>14%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>At 2 years: 50%</td>
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<tr>
<td>Duad et al.,</td>
<td>Pembrolizumab</td>
<td>II</td>
<td>180</td>
<td>Not reported;</td>
<td>21% (15-28%)</td>
<td>2%</td>
<td>3%</td>
<td>11%</td>
</tr>
<tr>
<td>KEYNOTE001 (32)</td>
<td></td>
<td></td>
<td></td>
<td>6-Month PFS: 34%</td>
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<tr>
<td>Ribas et al.,</td>
<td>Pembrolizumab</td>
<td>III</td>
<td>181</td>
<td>38% (31-45%)</td>
<td>26% (19-32%)</td>
<td>19%</td>
<td>23%</td>
<td>14%</td>
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<tr>
<td>KEYNOTE002 (34)</td>
<td>2 mg/kg</td>
<td>II</td>
<td>180</td>
<td>Not reported;</td>
<td>21% (15-28%)</td>
<td>2%</td>
<td>3%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
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<td></td>
<td>6-Month PFS: 34%</td>
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<tr>
<td>Robert et al.,</td>
<td>Pembrolizumab q2wk</td>
<td>III</td>
<td>279</td>
<td>At 1 year: 74.1%</td>
<td>33.7%</td>
<td>5.0%</td>
<td>28.7%</td>
<td>13.3%</td>
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<tr>
<td>KEYNOTE006 (35)</td>
<td>10 mg/kg</td>
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<tr>
<td></td>
<td>Pembrolizumab q3wk</td>
<td></td>
<td>277</td>
<td>At 1 year: 68.4%</td>
<td>32.9%</td>
<td>6.1%</td>
<td>26.8%</td>
<td>10.1%</td>
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<tr>
<td></td>
<td>Ipilimumab</td>
<td></td>
<td>278</td>
<td>At 1 year: 58.2%</td>
<td>11.9%</td>
<td>1.4%</td>
<td>10.5%</td>
<td>19.9%</td>
</tr>
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</table>


treated patient with nivolumab. Objective response was seen in 17 (14.5%) patients and the median time to response was 3.3 months. A total of 26% of patients had stable disease (SD) of median duration 6.0 months. Grade 3-4 treatment-related adverse events were reported in 17%, including fatigue, pneumonitis, and diarrhea (41).

CheckMate 017, a randomized, open-label, international phase III trial in which 272 patients with advanced squamous NSCLC who had disease progression during or after initial platinum-based doublet chemotherapy were randomly assigned to either nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m² every 3 weeks). The 1 year OS rate was 42% with nivolumab vs. 24% with docetaxel. The RR was 20% with nivolumab vs. 9% with docetaxel (p=0.008). PDL1 expression was neither prognostic nor predictive of benefit. Grade 3 or 4 treatment-related adverse events were reported in only 7% of the nivolumab group as compared with 55% of the docetaxel group (42).

CheckMate 057, an open-label phase III study of 582 patients with advanced non-squamous NSCLC whose disease progressed on or after platinum-based doublet chemotherapy, randomized patients to nivolumab or docetaxel. Nivolumab demonstrated superior OS (HR=0.73) and improved ORR (19.2% vs. 12.4%). PDL1 expression was associated with benefit from nivolumab (43).

KEYNOTE-001, a phase I trial, treated 495 patients with advanced NSCLC with pembrolizumab. The ORR was 19.4%, and the median duration of response was 12.5 months. PDL1 expression in 50% or more tumor cells was selected as the cutoff from the training group. Among patients with an expression score of 50% or more in the validation group, the RR was 45.2%. Common adverse events attributed to pembrolizumab were fatigue, pruritus, and low appetite (44).

KEYNOTE-010 was a randomized phase II/III trial enrolling 1034 patients: 345 were allocated to 2 mg/kg pembrolizumab, 346 to 10 mg/kg pembrolizumab, and 343 to docetaxel. OS was significantly longer for both pembrolizumab groups vs. docetaxel. Among patients with PDL1 expression of 50% or more in the treatment group, the RR was 45.2%. Common adverse events attributed to pembrolizumab were fatigue, pruritus, and low appetite (44).
Table II. Checkpoint inhibitors in non small cell lung cancer (NSCLC).

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Agent(s)</th>
<th>Phase</th>
<th>No. of patients</th>
<th>OS (95% CI)</th>
<th>ORR (95% CI)</th>
<th>CR</th>
<th>PR</th>
<th>Grade 3-4 AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch et al. (38)</td>
<td>Concurrent Ipilimumab</td>
<td>II</td>
<td>70</td>
<td>Median OS=9.7 months</td>
<td>21%</td>
<td>0%</td>
<td>21%</td>
<td>41%</td>
</tr>
<tr>
<td>Topalian et al. (40)</td>
<td>Phased Ipilimumab</td>
<td>II</td>
<td>68</td>
<td>12.2 Months</td>
<td>32%</td>
<td>0%</td>
<td>32%</td>
<td>39%</td>
</tr>
<tr>
<td>Rizvi et al.</td>
<td>Nivolumab</td>
<td>II</td>
<td>117</td>
<td>Median OS=8.2 (6.1-10.9) months</td>
<td>14.5% (8.7-22.2%)</td>
<td>0</td>
<td>14.5%</td>
<td>17%</td>
</tr>
<tr>
<td>Brahmer et al.</td>
<td>Nivolumab</td>
<td>III</td>
<td>135</td>
<td>Median OS=9.2 (7.3-13.3) months</td>
<td>20%</td>
<td>1%</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>Paz-Ares et al.</td>
<td>Nivolumab</td>
<td>III</td>
<td>292</td>
<td>Median OS=12.2 (9.7-15) months</td>
<td>19.2%</td>
<td>NA</td>
<td>NA</td>
<td>10.5%</td>
</tr>
<tr>
<td>Rizvi et al.</td>
<td>Nivolumab + Erolitinib</td>
<td>I</td>
<td>21</td>
<td>Not reported; 24-Week PFS=47%</td>
<td>19%</td>
<td>NA</td>
<td>NA</td>
<td>19%</td>
</tr>
<tr>
<td>Antonia et al.</td>
<td>Nivolumab + chemotherapy</td>
<td>I</td>
<td>56</td>
<td>Not reported; 24-Week PFS=36-71%</td>
<td>33-50%</td>
<td>NA</td>
<td>NA</td>
<td>45%</td>
</tr>
<tr>
<td>Garon et al. KEYNOTE001 (44)</td>
<td>Pembrolizumab</td>
<td>I</td>
<td>495</td>
<td>Median OS=12 (9.3-14.7) months</td>
<td>19.4% (16-23.2%)</td>
<td>NA</td>
<td>NA</td>
<td>9.5%</td>
</tr>
<tr>
<td>Brahmer et al. KEYNOTE010 (45)</td>
<td>Pembrolizumab</td>
<td>II/III</td>
<td>345</td>
<td>Median OS=10.4 months</td>
<td>18%</td>
<td>0%</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Herbst et al. (46)</td>
<td>Atezolizumab</td>
<td>I</td>
<td>53</td>
<td>Median OS=12.7 months</td>
<td>18%</td>
<td>0%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Rizvi et al. (48)</td>
<td>Durvalumab</td>
<td>II</td>
<td>149 evaluable</td>
<td>Not reported; 24-Week PFS=45%</td>
<td>23%</td>
<td>NA</td>
<td>NA</td>
<td>11%</td>
</tr>
<tr>
<td>Brahmer et al. (49)</td>
<td>BMS-936559</td>
<td>I</td>
<td>75 NSCLC</td>
<td>Not reported</td>
<td>14%</td>
<td>NA</td>
<td>NA</td>
<td>6%</td>
</tr>
</tbody>
</table>

OS: Overall survival, CI: confidence interval, ORR: objective response rate, CR: complete response, PR: partial response, PFS: progression-free survival; AEs: adverse events, NA: not available.

Anti-PDL1. Atezolizumab, durvalumab and BMS-936559 are three different antibodies to PDL1 that have been evaluated in NSCLC.

The efficacy of atezolizumab in NSCLC was reported from a phase I dose-escalation study that enrolled 53 patients with NSCLC. The ORR was 23%. An additional 17% of patients had SD lasting 24 weeks or longer (46).

The POPLAR study, a randomized phase II trial, compared atezolizumab to standard second-line docetaxel in 287 patients with advanced NSCLC who had failed platinum-based therapy. The median OS was 12.6 months with atezolizumab vs. 9.7 months with docetaxel (HR=0.73, p=0.04). Results correlated with PDL1 status (47).

A phase I/II trial evaluating durvalumab enrolled 198 patients (116 with non-squamous and 82 with squamous histology). In all, 149 were evaluable for response with 24 weeks or more of follow-up; the ORR was 14% (23% in those with PDL1+ disease), and the disease control rate at 24 weeks was 24%. The ORR was higher in patients with squamous (21%) than non-squamous (10%) histology (48).

BMS-936559 was evaluated in a phase-I study for advanced cancer; 75 out of 207 patients had NSCLC. Of 49 evaluable patients with NSCLC, 10% achieved PR, and another 12% had SD of 24 weeks or more (49).

Major trials utilizing checkpoint inhibitors in NSCLC, including ongoing trials (i.e. Checkmate 012), which have not been introduced in the text are summarized in Table II.

Immunotherapy in Head and Neck Squamous Cell Carcinoma (HNSCC)

HNSCC is a perfect target of checkpoint blockade therapy as it is known to have high tumor PDL1 expression and strong presence of tumor-infiltrating lymphocytes in the tumor microenvironment. Furthermore, its genomic makeover is highly mutated in tobacco- and alcohol-related HNSCC and can carry foreign DNA in human papilloma virus (HPV)-related HNSCC.
Anti-PD1. The largest available data of immunotherapy in HNSCC is from an expansion cohort of a phase II/II, KEYNOTE-012 (50). A total of 132 patients with recurrent/metastatic HNSCC were treated with pembrolizumab (200 mg every 3 weeks). The ORR was 17.7%, with 7 CRs and 27 PRs; 33 (17%) patients achieved SD. The ORR was 21.9% in those with HPV+ disease and 15.9% in those with HPV− disease. The median OS was 8.5 months. Treatment-related adverse events occurred in 122 (64%) patients, of which 23 (12%) were grade 3-4.

KEYNOTE-055, a phase II trial, enrolled patients with recurrent metastatic HNSCC whose disease had progressed after platinum and cetuximab therapy (51). Preliminary analyses presented at American Society of Clinical Oncology 2016 focused on the first 50 patients enrolled (52). Nine patients had a confirmed PR, for an ORR of 18.0%. The SD rate was 18.0% (n=9). Six (12.0%) patients experienced grade 3-5 treatment-related adverse events. On August 5, 2016, the US FDA granted accelerated approval of pembrolizumab for recurrent metastatic HNSCC progressing on platinum chemotherapy.

Additional studies are underway. KEYNOTE-040 is a phase III randomized study of pembrolizumab vs. investigator’s choice treatment (methotrexate, docetaxel, or cetuximab) for recurrent or metastatic HNSCC (NCT02252042) and KEYNOTE-048 is yet another phase III randomized trial in which patients with recurrent or metastatic HNSCC will be randomly assigned to receive pembrolizumab alone, or pembrolizumab plus a platinum-based drug (cisplatin or carboplatin) with 5-fluorouracil, or cetuximab plus a platinum-based drug (cisplatin or carboplatin) with 5-fluorouracil (NCT02358031).

CheckMate 141 is a phase III trial evaluating nivolumab vs. investigator’s choice (methotrexate, docetaxel, or cetuximab) for recurrent or metastatic HNSCC (NCT02252042) and KEYNOTE-048 is yet another phase III randomized trial in which patients with recurrent or metastatic HNSCC will be randomly assigned to receive pembrolizumab alone, or pembrolizumab plus a platinum-based drug (cisplatin or carboplatin) with 5-fluorouracil, or cetuximab plus a platinum-based drug (cisplatin or carboplatin) with 5-fluorouracil (NCT02358031).

CheckMate 141 is a phase III trial evaluating nivolumab vs. investigator’s choice (methotrexate, docetaxel, or cetuximab) in recurrent/metastatic HNSCC. A total of 361 patients were randomized, 240 to nivolumab and 121 to other drugs. A 30% reduction in risk of death was observed with a median OS of 7.5 months for those treated with nivolumab and 5.1 months for those treated with methotrexate, docetaxel or cetuximab. The ORR for patients treated with nivolumab with PDL1 expression ≥1%, ≥5%, and ≥10% was 18.2%, 25.9%, and 32.6%, respectively, compared to 3.3%, 2.3%, and 2.9% for those treated with methotrexate, docetaxel or cetuximab. Grade 3-4 treatment-related adverse events occurred in 13.6% and 35.1% of patients on nivolumab, and investigator’s choice, respectively (53).

Anti-PDL1. Twenty-nine patients with 29 HNSCC were treated with durvalumab in a phase I study (54). Preliminary clinical activity in patients with HNSCC was observed with a manageable safety profile and the data supported continued clinical development of durvalumab in HNSCC.

Immunotherapy for RCC

Table III summarizes the major trials utilizing checkpoint inhibitors in RCC.

Anti-PD1. In a phase I study with expansion cohorts (55), a total of 34 previously treated patients with advanced RCC were given nivolumab (1 or 10 mg/kg) every 2 weeks. Out of the 34 patients, 10 (29%) achieved objective response with median response duration of 12.9 months; nine additional patients (27%) had SD lasting 24 weeks or more. Three out of five patients who stopped therapy while in response continued to respond for 45 weeks or more.

A phase II study also demonstrated the promising antitumor activity of nivolumab and its manageable safety profile (56). A total of 168 patients with metastatic clear-cell RCC previously treated with VEGF inhibitors were randomly assigned to 0.3 (n=60), 2 (n=54) or 10 mg/kg (n=54) nivolumab once every 3 weeks. A total of 118 patients (70%) had received more than one prior systemic regimen. Respective ORRs were 20%, 22%, and 20%.

In the phase III CheckMate 025 trial, 821 patients with advanced clear cell RCC who had been treated with one or two regimens of anti-angiogenic therapy were randomly assigned to nivolumab (3 mg/kg every 2 weeks) or everolimus (10 mg/day). The trial was stopped early based on the interim analysis as the median OS was 25.0 months with nivolumab and 19.6 with everolimus (HR=0.73). The ORR was greater with nivolumab than with everolimus (25% vs. 5%). PDL1 expression was not associated with benefit from nivolumab (57).

Anti-PD1 and CTLA4. In a phase I study, patients with metastatic RCC (favorable/intermediate Memorial Sloan Kettering Cancer Center score; Karnofsky score ≥80%; untreated or any number of prior therapies) were randomized to receive nivolumab plus ipilimumab by two different schedules. A total of 44 patients were randomized. The ORR was 29%–39%. Most common adverse events were elevated lipase (16%, n=7), elevated alanine aminotransferase (11%, n=5), diarrhea (9%, n=4), colitis (5%, n=2), or elevated amylase (5%, n=2). No grade 3-4 pneumonitis was seen (58).

Anti-PDL1. In a phase Ia study, 70 patients with metastatic RCC were treated with atezolizumab. The ORR was 15% and the median OS was 28.9 months. There were no grade 4 or 5 adverse events (59). This result lead to the study of atezolizumab in further phase II (NCT01984242) and phase III (NCT02420821) clinical trials in advanced RCC.

Immunotherapy in Urothelial Carcinoma

Anti-PD1. In KEYNOTE-012, a phase Ib study, 33 patients with recurrent, metastatic, or persistent urothelial cancer of the
A phase II trial was therefore conducted to evaluate the response to PD1 blockade in patients with tumors with and without MMR deficiency (63). This also matched the fact that patients with MMR-deficient colorectal cancer have 10 to 100 times as many somatic mutations as those with MMR-proficient tumors (66, 67) and tumors with higher number of somatic mutations, such as melanoma and lung cancer, had higher RR to PD1 blockade. A phase II trial was therefore conducted to evaluate the response to PD1 blockade in patients with tumors with and without MMR deficiency (63).

In a phase II study, 310 patients with locally advanced and metastatic urothelial carcinoma whose disease had progressed on platinum-based chemotherapy were given atezolizumab. The ORR for IHC 0/1 cases was 16% (six PRs). Drug-related adverse events, of which fatigue was the most common (five patients, 2%), occurred in 50 (16%) out of 310 treated patients (62). An open-label randomized phase III trial, the KEYNOTE-045 study is currently underway.

Anti-PDL1. In an extended phase I study evaluating atezolizumab in pw metastatic urothelial cancer of the bladder, the ORR for IHC 2/3 cases was 46% (six CRs, 15 PRs), and for IHC 0/1 cases was 16% (six PRs). Drug-related adverse events occurred in 64% out of 87 patients evaluable for safety (most often fatigue, asthenia, nausea); 8% had grade 3-4 adverse events; 12% of patients had immune-related adverse events. No therapy-related deaths were seen (61).

In a phase II study, 310 patients with locally advanced and metastatic urothelial carcinoma whose disease had progressed on platinum-based chemotherapy were given atezolizumab. PDL1 expression status was defined by the percentage of PDL1+ immune cells in stroma by a prototype immuno-histochemistry (IHC) assay. Objective response were observed in seven (25%) patients (62). This study led to the May 18, 2016 US FDA approval of atezolizumab for advanced urothelial cancer progressing on platinum-containing chemotherapy.

Checkpoint Inhibitors in Colorectal Cancer

In a phase I study of approximately 300 patients with advanced solid tumors, only one (3%) out of 33 patients with colorectal cancer responded to nivolumab (63, 64). This patient’s tumor was studied extensively, and was found to be mismatch repair (MMR)-deficient (65). This also matched the fact that patients with MMR-deficient colorectal cancer have 10 to 100 times as many somatic mutations as those with MMR-proficient tumors (66, 67) and tumors with higher number of somatic mutations, such as melanoma and lung cancer, had higher RR to PD1 blockade. A phase II trial was therefore conducted to evaluate the response to PD1 blockade in patients with tumors with and without MMR deficiency (63).

There were three cohorts in the study, MMR-deficient colorectal cancer (n=11), MMR-proficient colorectal cancer (n=21) and MMR-deficient cancer of types other than colorectal cancer (n=9), and all cohorts were given pembrolizumab at 10 mg/kg i.v. every 2 weeks. These patients had metastatic disease and were all heavily treated. The immune-related ORR in MMR-deficient colorectal cancer was 40%, and the immune-
related PFS rate at 20 weeks was 78%. The corresponding rates in the MMR-deficient colorectal cancer cohort were 71% and 67%. In the MMR-proficient colorectal cancer cohort, the immune-related ORR was 0%, and the immune-related PFS rate at 20 weeks was 11%. The authors of this study concluded that MMR status predicted clinical benefit from immune checkpoint blockade with pembrolizumab.

**Immunotherapy for Hematological Malignancies**

**Hodgkin’s lymphoma.** Studies have shown Reed–Sternberg cells to utilize the PD1 pathway in order to avoid immune detection. In Hodgkin’s disease, alterations in chromosome 9p24.1 results in overexpression of PDL1/PDL2 and promotes their induction through Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling (68, 69). Hodgkin’s disease thus has a unique sensitivity to PD1 inhibition.

In a phase I study, 23 patients with relapsed or refractory Hodgkin’s lymphoma received nivolumab. The RR was 87%, with CR in four (17%), PR in 16 (70%), and SD in three patients (13%). Of the four patients with CR, three had not previously received the antibody to CD30, brentuximab (70). Updated results revealed that 10 out of the 20 initial responders (14 PR, six CR) had durable responses per protocol. Out of the 10 patients with durable responses, two maintained their responses of CR after discontinuing nivolumab due to toxicities. Overall, three patients discontinued nivolumab due to adverse events (71).

A phase Ib multicenter multi-cohort trial of pembrolizumab in patients with hematologic malignancies enrolled patients with relapsed/refractory classical Hodgkin’s lymphoma. ORR among the 31 evaluable patients was 65%. Five patients (16%) achieved CR, 15 (48%) had PR, and seven (23%) had SD as their best response (72).

A phase I (ECOG-ACRIN) study of the combination of brentuximab vedotin, ipilimumab and nivolumab was carried out on patients with relapsed/refractory Hodgkin’s lymphoma. There was 67% objective response seen in 12 evaluable patients for the combination of brentuximab and ipilimumab with a CR of 42% (five out of 12 patients). Overall, the regimen of brentuximab and ipilimumab was well tolerated (73).

**Multiple myeloma (MM).** In preclinical studies, the PD1–PDL1 axis was thought to mediate the resistance of MM to therapy. Tamura et al. showed that the bone marrow microenvironment induces B7 homolog 1 (B7-H1) expression on myeloma cells and this was associated with aggressive behavior, including increased proliferative potential and resistance to chemotherapy, in addition to the T-cell inhibitory effect via the B7-H1–PD1 pathway (74). Paiva et al. prospectively studied 107 patients, including 20 with monoclonal gammapathy of undetermined significance, 87 with MM and nine with normal bone marrow, and showed that patients with persistent minimal residual disease after treatment as well as at relapse showed up-regulation of PDL1/PD1 (75).

Lesokhin et al. presented the preliminary results of an open-label study utilizing nivolumab in patients with relapsed/refractory lymphoid malignancies. The ORR and CR rates in patients with B-cell non-Hodgkin’s lymphoma were 28% and 7%, respectively, including an ORR of 36% in patients with diffuse large B-cell lymphoma, and 40% in patients with follicular lymphoma. In patients with T-cell non-Hodgkin’s lymphoma, the ORR was 17% (no CR), including an ORR of 40% in five patients with peripheral T-cell lymphoma. No objective response was observed in MM. However, 67% had SD (76).

**KEYNOTE-023 study** is an open-label, phase I, multicenter, non-randomized, dose-escalation trial evaluating the safety, tolerability, and efficacy of pembrolizumab in combination with lenalidomide and low-dose dexamethasone in patients with relapsed refractory MM. The preliminary results were presented and showed that 13 out of 17 patients responded to treatment. The ORR was 76%, with four patients achieving a very good PR and nine a PR. No death or treatment discontinuation for toxicity was observed (77).

Badros et al. presented preliminary results from a phase II study of 24 patients with relapsed refractory MM who had received pembrolizumab and 40 mg dexamethasone weekly. Objective response (modified International Myeloma Working Group’s criteria) were observed in 11 out of 22 evaluable patients (50%) including: near CR I three, very good PR in two, and PR in six); additionally, three patients had minimal response, six had SD and in two disease progressed. At a median follow-up of 16 weeks, 17 of 22 patients continued on the study (78).

**Chronic lymphocytic leukemia (CLL).** The MCI 485 trial is a phase II trial to evaluate pembrolizumab in patients with relapsed/refractory CLL and relapsed low-grade B-cell non-Hodgkin’s lymphoma. The relapsed/refractory CLL arm enrolled 16 patients with relapsed/refractory CLL (including five patients with Richter’s syndrome). Based on investigator assessment, four out of five patients with Richter’s syndrome had responded to therapy. Pembrolizumab was tolerated in patients with relapsed CLL and with Richter’s syndrome. Early efficacy observed in heavily pretreated patients with Richter’s syndrome indicated PD1 inhibition as being a potentially promising novel therapy approach (79).

**Primary mediastinal large B-cell lymphoma (PMBCL).** KEYNOTE-013, a phase Ib study evaluating pembrolizumab in solid tumors and non-Hodgkin's lymphoma, included an independent PMBCL cohort for proof of concept. The preliminary results reported 10 patients with relapsed refractory PMBCL who were treated with pembrolizumab; nine patients were evaluable for response. The ORR was 44% (4/9), with one patient achieving a CR and three achieving a PR (80).
Conclusion

Different anticancer immunotherapy treatment modalities have the potential to eventually cure and end all forms of cancer. Such great promise and hope is now emerging from a remarkable amount of data that has accumulated in this field in a very short period of time. Looking ahead to a more promising future for patients with cancer, we must improve our understanding of the mechanism of action of checkpoint inhibitors and search for more therapeutic biomarkers that are able to predict who would benefit the most from such treatments.

References


