Introduction

With current front-line treatment regimens of chemotherapy alone or in combination with radiation, over 80% of patients with Hodgkin lymphoma achieve long-term cure.1 For those patients with relapsed or refractory disease, approximately 50% are cured with high-dose salvage chemotherapy and autologous hematopoietic stem cell transplantation. However, patients who relapse after stem cell transplant (SCT) have traditionally had a poor prognosis. The antibody-drug conjugate brentuximab vedotin, an anti-CD30 monoclonal antibody coupled to a microtubule polymerization inhibitor monomethyl auristatin E, was the first drug approved by the US Food and Drug Administration (FDA) for relapsed classical Hodgkin lymphoma after autologous SCT. Overall response rates from a phase II trial are 75% with a complete response rate of 34%,2 but long-term remissions are rare. Research over the past 3 decades has unveiled multiple regulatory pathways that act to dampen immune activation and prevent autoimmunity. For example, in lymphoid organs, T cells express the surface molecule cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which competes with CD28 for binding to the costimulatory molecules B7-1 and B7-2 on antigen-presenting cells and results in inhibitory signaling.3 In peripheral tissues, target cells express PD-1 ligands that can engage PD-1 on T cells to induce T cell exhaustion and impaired effector responses.4 Taking advantage of these inhibitory pathways, many cancers also express PD-1 ligands and thereby suppress antitumor immunity.4 Recent efforts in developing immune checkpoint inhibitors—antibodies against CTLA-4 or PD-1/PD-L1—have led to their approval in several malignancies including relapsed or refractory Hodgkin lymphoma, in which response rates of PD-1 inhibitors nivolumab or pembrolizumab exceed 60%.5 Despite this success, complete remissions and durable responses are still uncommon, and thus current research efforts seek to expand the therapeutic potential of PD-1 blockade through novel immunotherapy combinations. In this review, we will highlight our understanding of the biology of the PD-1 pathway in Hodgkin lymphoma, recent clinical trials establishing the therapeutic efficacy of PD-1 blockade in relapsed and refractory disease, and promising combination strategies incorporating PD-1 inhibitors under current investigation.

Biology of PD-1 and checkpoint inhibition

Encoded by the PDCD1 gene, PD-1 is a type 1 transmembrane protein belonging to immunoglobulin superfamily of receptors that contains an extracellular IgV domain, a transmembrane domain, and an intracellular domain bearing an immune receptor tyrosine-based inhibitory motif (ITIM).6 PD-1 was established as a negative regulator of T cell responses through experiments showing development of a lupus-like syndrome in mice deficient for PD-1 (Table 1).7 This phenotype is less severe than CTLA-4-mice, which develop a fatal lymphoproliferative disorder by 3 to 4 weeks of age.8,9 PD-1 is not expressed on naive T cells but is
induced during antigen-mediated T cell activation. Clearance of the activating antigen leads to downregulation of PD-1 expression, but persistent antigen such as in chronic viral infection or cancer leads to sustained and high expression of PD-1. Several transcription factors regulate PD-1 expression in activated T cells, including NFATC1, FOXO1, T-bet, and BLIMP1, and epigenetic regulation such as through alterations in DNA methylation patterns or histone modifications may also play a role.

PD-1 recognizes 2 ligands: PD-L1 (also known as B7-H1; CD274) is expressed by a wide variety of cell types including both hematopoietic and nonhematopoietic cells, while PD-L2 (BD7-DC; CD273) expression tends to be more restricted to dendritic cells, macrophages, and B cells. Unlike PD-1-deficient mice, mice lacking PD-L1 and PD-L2 do not develop a spontaneous lupus-like syndrome but have increased susceptibility to autoimmunity in various disease models. Ligand binding of PD-1 leads to recruitment of the protein tyrosine phosphatase Src homology domain-containing phosphatase 2 to the T cell receptor complex, resulting in the dephosphorylation of signaling molecules such as ZAP70 and dampening of T cell signaling. Consequently, this attenuated signaling causes T cell exhaustion, or the progressive loss of effector functions and potential. Early studies showed that various cancer cells express PD-L1 on the surface and that tumor infiltrating lymphocytes often express PD-1, suggesting that the PD-1/PD-L1 pathway can be exploited by tumors to suppress the antitumor immune response and allow for tumor growth.

Applying these observations and subsequent proof-of-concept studies to patients, PD-1 inhibitors have been introduced into the clinic in several cancer types with varying efficacy. PD-1 blockade was first successfully applied to metastatic melanoma with objective response rates approximately 40% and with durable responses in many patients. These advances soon led to the expansion of anti-PD-1 agents to nonsmall-cell lung cancer, renal cell carcinoma, bladder cancer, head and neck squamous cell cancers, and tumors exhibiting mismatch repair deficiency, with approvals for other solid tumors likely in the near future.

Role of PD-1 in Hodgkin lymphoma

Classical Hodgkin lymphoma is characterized by rare clonal, multinucleated Reed-Sternberg cells that are situated within a milieu of infiltrating inflammatory cells. In most patients, Reed-Sternberg cells robustly express PD-L1 or PD-L2, which are encoded by genes within the chromosomal region 9p24.1. For example, one study showed that 105 of 108 patients (97%) with newly diagnosed Hodgkin lymphoma had alterations of the PD-L1 and PD-L2 loci, including 56% with copy gain and 36% with amplification. These genetic alterations may have prognostic significance, as 9p24.1 amplifications were associated with advanced stage disease and shortened progression-free survival.

Multiple signaling pathways have been shown to regulate PD-L1 and PD-L2 expression in Reed-Sternberg cells (Fig. 1A), although our understanding of these mechanisms is limited. Treatment of classical Hodgkin lymphoma cell lines with MEK/ERK inhibitors in vitro downregulated PD-L1 expression, suggesting that ERK/MAPK signaling promotes PD-L1 expression. Chromosome 9p24.1 also contains the JAK2 locus, and inhibition of JAK2 decreased PD-L1 transcription. Furthermore, in Epstein-Barr virus (EBV)-associated Hodgkin lymphoma cells with normal PDL1 copy number, EBV-latent membrane protein (LMP1) induced PD-L1 expression through the AP-1 and JAK-STAT pathways.

In addition to phenotypically characterizing Reed-Sternberg cells, PD-L1 and PD-L2 have functional consequences on immune suppression of antitumor responses. Reed-Sternberg cells typically account for less than 5% of cells within the tumor, which predominantly consist of T cells as well as macrophages, eosinophils, B cells, plasma cells, neutrophils, and fibroblasts. Interestingly, T cells from Hodgkin lymphoma tissue samples as well as peripheral blood from patients expressed PD-1, and increased PD-1 expression on intratumoral T cells has been associated with poor prognosis. Another recent study suggests that high expression of PD-1/PD-L1 on leukocytes within the tumor microenvironment, but not PD-L1/PD-L2 on Reed-Sternberg cells, is associated with inferior overall survival. Importantly, patient Hodgkin lymphoma cells treated with antibodies inhibiting PD-1/PD-L1 signaling showed increased IFN-γ production, suggesting that antitumor responses of Hodgkin lymphoma infiltrating T cells are suppressed by the PD-1 axis. Preclinical data also support a role for PD-1 blockade in other hematological malignancies, providing a rationale for assessing the clinical activity of PD-1 inhibition in patients. The exact mechanism of action for PD-1 inhibition in Hodgkin lymphoma is poorly characterized (Fig. 1B). In some solid tumors such as melanoma and nonsmall-cell lung cancer, high levels of nonsynonymous mutational burden have been associated with improved objective responses and more durable clinical benefit with immune checkpoint inhibitors. These observations suggest that anti-PD-1 activity relies on the recognition of neoantigens created by these nonsynonymous mutations. However, Reed-Sternberg cells are rare within the tumor environment and are less likely to harbor a high mutational load. In addition, one proposed mechanism of action for checkpoint inhibition is CD8+ T cell recognition of neoantigens presented on major histocompatibility complex (MHC) class I on tumor cells. Correspondingly, loss of MHC class I such as from mutations in beta-2-microglobulin (B2M) have been associated with acquired resistance to PD-1 blockade in melanoma. Yet, Reed-Sternberg cells frequently harbor inactivating mutations in B2M, resulting in loss of expression of the MHC class I complex which is critical for engagement with CD8+ T cells. Moreover, decreased MHC class I expression was associated with poorer clinical outcomes independent of PD-L1 and PD-L2 amplification. This suggests that CD8+ T cell effector responses may not be solely responsible for the clinical efficacy of checkpoint inhibitors. Others have proposed that in Hodgkin lymphoma,
PD-L1 may be involved in transmitting trophic signals that promote tumor growth independent of regulating the immune response to the tumor.39

While most studies have focused on PD-L1 and PD-L2 expression by Reed-Sternberg cells, these cells comprise only a small population within the tumor, and so it is possible that other inflammatory cells within the tumor microenvironment may also play a role in immune suppression. Interestingly, tumor-associated macrophages have been shown to express PD-L1, and increased levels of tumor-associated macrophages are associated with poor clinical outcomes in patients with advanced disease.40,41 In fact, recent data suggest that the majority of PD-L1 in Hodgkin lymphoma tumors is expressed by tumor-associated macrophages, which are in close contact with PD-L1+ Reed-Sternberg cells as well as PD-1+ CD4+ T cells.42 In other models, tumor-associated macrophages have been shown to express PD-1, and blockade of PD-1 enhances macrophage phagocytosis to restrict tumor growth. Thus, PD-1 inhibition in Hodgkin lymphoma may also target tumor-associated macrophages within the immune environment.

Clinical experience of anti-PD-1 monotherapy in Hodgkin lymphoma

As preliminary data suggested that Reed-Sternberg cells express PD-1 ligands and that PD-1 blockade may have activity in Hodgkin lymphoma, several clinical trials have assessed the safety and efficacy of PD-1-blocking antibodies in patients (Table 2). Nivolumab is a fully human IgG4 antibody targeting PD-1 that has been approved for the treatment of advanced stage melanoma, nonsmall-cell lung cancer, renal cell carcinoma, and other malignancies. In a phase I trial of 23 heavily pretreated patients with relapsed or refractory Hodgkin lymphoma treated with nivolumab 3mg/kg every 2 weeks, the overall response rate was 87%, with a complete response rate of 17%.43 The rate of progression-free survival at 24 weeks was 86%. Analysis of pretreatment specimens demonstrated increased expression of PD-L1 and PD-L2 in Reed-Sternberg cells as well as phospho-STAT3 expression suggestive of active JAK-STAT signaling.

Moreover, a second multicenter phase II study (CheckMate 205) of 80 patients with classical Hodgkin lymphoma who had failed to respond to autologous stem cell transplantation or had relapsed after brentuximab vedotin further demonstrated the therapeutic benefit of nivolumab.44 With a median follow-up of 8.9 months, there was an objective response rate of 66.3% with a complete response seen in 9% of patients. The toxicity profile of nivolumab was similar to those established from studies of nivolumab in other malignancies, with the most common adverse events being fatigue, infusion reaction, and rash. These studies demonstrate that PD-1 blockade with nivolumab is safe and effective in Hodgkin lymphoma, leading to FDA approval (May 2016) and European Medicines Agency (EMA) approval.

| Drug       | Trial | Phase | N  | ORR, % | CR, % | 6-mo PFS, % |
|------------|-------|-------|----|--------|-------|--------------|
| Nivolumab  | Ansell et al43 | I     | 23 | 87     | 17    | 86           |
|            | Younes et al44  | II    | 80 | 66     | 9     | 77           |
| Pembrolizumab | Armand et al45  | Ib    | 31 | 65     | 16    | 69           |
|            | Chen et al46    | II    | 210| 69     | 22    | 72           |

ORR = overall response rate, CR = complete response, PFS = progression-free survival.
Preclinical models suggested that while PD-1 blockade alloreactive donor T cells that recognize recipient antigens as a cause of morbidity and mortality after allogeneic stem cell transplantation. Graft-versus-host disease (GVHD) is a PD-1 therapy on toxicities related to allogeneic hematopoietic advanced Hodgkin lymphoma, one concern is the effect of anti-PD-1 inhibitors have expanded the treatment armamentarium for these patients. A phase III trial is currently underway comparing pembrolizumab versus brentuximab vedotin in patients who had failed brentuximab vedotin after transplant, PD-1 inhibitors have expanded the treatment armamentarium for these patients. A phase III trial is currently underway comparing pembrolizumab versus brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma, with an overall response rate of 69%, compete response rate of 22.4%, and a 6-month progression-free survival of 63.4%. Thus, treatment outcomes with single agent nivolumab and pembrolizumab are comparable, and response rates are similar between patients who have and have not received prior brentuximab vedotin (Table 3). Importantly, while previously there were no approved options for patients who had failed brentuximab vedotin after transplant, PD-1 inhibitors have expanded the treatment armamentarium for these patients. A phase III trial is currently underway comparing pembrolizumab versus brentuximab vedotin in patients with relapsed or refractory classical Hodgkin lymphoma (NCT02684292).

Several antibodies targeting PD-L1 have also been developed for clinical use. Avelumab is a fully human IgG1 monoclonal antibody that selectively binds to PD-L1. Early data from a phase I study of avelumab in patients with heavily pretreated Hodgkin lymphoma suggest that avelumab has an acceptable toxicity profile and has clinical activity, with a 54.8% overall response rate among 31 patients. Thus, anti-PD-L1 therapy is also a promising strategy in Hodgkin lymphoma.

While checkpoint inhibitors have shown promising results in advanced Hodgkin lymphoma, one concern is the effect of anti-PD-1 therapy on toxicities related to allogeneic hematopoietic stem cell transplantation. Graft-versus-host disease (GVHD) is a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation and is mediated by alloreactive donor T cells that recognize recipient antigens as foreign. Preclinical models suggested that while PD-1 blockade can augment graft-versus-tumor effects, it may also result in higher rates of acute GVHD and accelerate GVHD lethality. Retrospective analyses have assessed outcomes for patients with advanced lymphoma treated with anti-PD-1 therapy before or after allogeneic hematopoietic SCT. In a study of 39 patients (of which 31 patients had Hodgkin lymphoma) who underwent allogeneic hematopoietic stem cell transplantation after receiving a PD-1 inhibitor, the 1-year cumulative incidence of acute grade 2 to 4 and grade 3 to 4 GVHD were 44% and 23%, respectively, with a 1-year cumulative incidence of chronic GVHD of 41%. There were 3 treatment-related deaths attributed to early acute GVHD, and the incidence of grade 4 GVHD was slightly higher than prior studies (13%), although there did not appear to be any increased risk of relapse. Another retrospective study of 20 Hodgkin lymphoma patients treated with nivolumab after relapse following allogeneic hematopoietic stem cell transplantation showed an acceptable rate of GVHD of 30% (6 patients, all of whom had previously had GVHD). In contrast, a separate study of 31 patients with relapsed lymphoma after allogeneic hematopoietic stem cell transplantation and treated with pembrolizumab or nivolumab showed a higher GVHD rate of 55%, with eight deaths attributed to new-onset GVHD. These data should be interpreted with caution as they were retrospective in nature, patients were treated with heterogeneous conditioning regimens, and they were compared to historical controls, among other limitations. Nevertheless, anti-PD-1 therapy appears to be feasible before or after hematopoietic stem cell transplantation but may carry a risk of increased early immune toxicities, and therefore further prospective studies are warranted.

Prospective combination immunotherapy with PD-1 inhibition in Hodgkin lymphoma

Despite the clinical success of PD-1 agents in Hodgkin lymphoma, many patients never achieve complete remissions or eventually relapse, with no standard treatment options currently approved after failing SCT, brentuximab vedotin and anti-PD-1 therapy. Consequently, many clinical studies are underway to either incorporate anti-PD-1 agents into earlier phases of treatment in combination with standard chemotherapy regimens. Other studies are rationally combining PD-1 inhibitors with active agents in Hodgkin lymphoma for potentially synergistic effects (Table 4). With chemotherapy

For the past several decades, combination chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) has been the standard regimen for most patients with advanced Hodgkin lymphoma. In the second-line for relapsed or refractory disease, several salvage chemotherapy regimens have been used, such as ifosfamide, carboplatin, and etoposide (ICE). While these regimens are established for initial or second-line treatment, it is not known whether immunotherapy with PD-1 inhibition has a role in earlier treatment strategies. Notably, there is a strong rationale for combining immunotherapy with chemotherapy, as chemotherapeutic agents can trigger immunogenic tumor cell death that leads to the release of danger

### Table 3

| Outcome of PD-1 Inhibitors in Patients With and Without Prior Brentuximab Vedotin Treatment | Drug                  | N  | ORR, % | CR, % |
|-----------------------------------------------------------------------------------------|-----------------------|----|--------|-------|
| Post-ASCT and brentuximab vedotin                                                        | Nivolumab            | 80 | 66     | 9     |
| Post-ASCT and no prior brentuximab vedotin                                               | Pembrolizumab        | 69 | 72     | 21    |
| Post-ASCT and brentuximab vedotin                                                        | Nivolumab            | 63 | 68     | 22    |
| Post-ASCT and brentuximab vedotin                                                        | Pembrolizumab        | 60 | 67     | 21    |

ASCT = autologous stem cell transplant; CR = complete response; N = number of patients; ORR = overall response rate.
signals, Toll-like receptor (TLR) ligands, ATP, and other immunomodulatory factors. These signals are recognized by innate immune effectors such as dendritic cells that can stimulate T cells or inhibit immunosuppressive pathways, resulting in control of tumor growth. Thus, it is possible that PD-1 blockade may synergize with chemotherapy, especially in tumors that are chemotherapy-sensitive. Current studies are underway to add nivolumab to salvage regimens such as ICE (NCT03016871) or incorporate nivolumab into frontline therapy, either currently or after A(B)VD (NCT03004833, NCT03033914). The combination of nivolumab with frontline chemotherapy appears to be well-tolerated as recently reported from a cohort of CheckMate 205, in which untreated patients with newly diagnosed advanced stage Hodgkin lymphoma were given four doses of nivolumab followed by nivolumab plus chemotherapy (doxorubicin, vinblastine, dacarbazine). Ten patients (20%) had serious adverse events, most commonly febrile neutropenia, and common immune-mediated adverse events included hypothyroidism (16%) and elevated transaminases (8%), consistent with prior experience with nivolumab and doxorubicin, vinblastine, and dacarbazine chemotherapy separately.

**Combined with brentuximab vedotin**

In the relapsed or refractory setting after autologous stem cell transplantation, brentuximab vedotin has an overall response rate of 75% and complete response rate of 34%. Brentuximab vedotin has also been used as consolidation therapy after transplant for patients with high risk of relapse, with improvements in progression-free survival in a phase III trial. As above with chemotherapy, brentuximab vedotin may target malignant cells to augment cytotoxicity and tumor antigen release, thereby stimulating an immune response which can be further boosted by checkpoint inhibition. Multiple clinical trials combining brentuximab vedotin and nivolumab are underway, and preliminary results are promising with objective response rates of 85% and complete response rates exceeding 60%.

**Combined with ibrutinib**

Ibrutinib is an oral inhibitor of Bruton tyrosine kinase (BTK), which is a key enzyme downstream of the B-cell receptor. Ibrutinib is currently approved in the treatment of multiple hematologic malignancies including chronic lymphocytic leukemia, mantle cell lymphoma and Waldenström macroglobulinaemia. While ibrutinib has been shown to have modest clinical activity in other hematologic malignancies such as diffuse large B-cell lymphoma, its activity in Hodgkin lymphoma has not been reported in prospective clinical trials. Nevertheless, there is some evidence that ibrutinib may also be effective in Hodgkin lymphoma. For instance, 2 patients with progressive Hodgkin lymphoma after multiple therapeutic regimens including autologous or allogeneic hematopoietic stem cell transplantation demonstrated complete or near-complete responses with ibrutinib treatment. Interestingly, in mice, ibrutinib enhanced the therapeutic effect of anti-PD-L1 treatment in several cancer models, including those that are intrinsically insensitive to ibrutinib treatment. In addition to inhibiting BTK, ibrutinib has also been shown to target other tyrosine kinases including interleukin-2-inducible T cell kinase (ITK), which is critical for the survival of Th2 cells. Therefore, ibrutinib may skew T cells to a Th1 phenotype which have increased antitumor properties, perhaps explaining the combinatorial effect of ibrutinib and checkpoint blockade. Evaluating these potentially synergistic effects in patients, clinical trials combining immune checkpoint blockade with ibrutinib or second-generation BTK inhibitors are currently underway (NCT02362035, NCT02940301).

**Table 4**

| Trial Intervention | Phase | Status; Estimated Completion Date | ClinicalTrials.gov NCT Reference |
|--------------------|-------|----------------------------------|----------------------------------|
| Combined with chemotherapy |      |                                   |                                  |
| Nivolumab and A(V)D in early-stage unfavorable HL | II | Recruiting; December 2020 | NCT03004833 |
| A(B)VD followed by nivolumab as frontline therapy | II | Recruiting; January 2020 | NCT03033914 |
| Nivolumab with ICE as second-line therapy | II | Recruiting; April 2019 | NCT03016871 |
| Pembrolizumab with ICE as second-line therapy | II | Recruiting; February 2020 | NCT03077828 |
| Pembrolizumab and combination chemotherapy in untreated patients |      |                                   |                                  |
| Nivolumab plus brentuximab vedotin vs brentuximab alone in relapsed/refractory HL | II | Recruiting; July 2023 | NCT02138499 |
| Nivolumab and brentuximab vedotin with or without ipilimumab in relapsed/refractory HL | I/II | Recruiting; June 2018 | NCT01896999 |
| Nivolumab and brentuximab vedotin in older patients with untreated HL | II | Recruiting; May 2024 | NCT02758717 |
| Nivolumab and brentuximab vedotin after SCT in patients with relapsed/refractory HL | II | Recruiting; April 2019 | NCT03057795 |
| Combined with BTK inhibitors |      |                                   |                                  |
| Ibrutinib and nivolumab in relapsed or refractory HL | II | Recruiting; May 2020 | NCT02940301 |
| ACP-196 (acalabrutinib) with pembrolizumab | II | Ongoing; April 2021 | NCT02862005 |
| Combined with immunomodulatory agents |      |                                   |                                  |
| Nivolumab and lenalidomide in relapsed or refractory NHL or HL | I/II | Suspended; April 2020 | NCT03015896 |
| Pembrolizumab and lenalidomide in relapsed NHL and HL | I/II | Recruiting; August 2023 | NCT02875067 |
| Combined with HDAC inhibitors |      |                                   |                                  |
| Pembrolizumab and vorinostat in relapsed or refractory DLBCL, FL, or HL | I | Recruiting; July 2019 | NCT03150329 |
| Pembrolizumab and ISRT for early-stage relapsed or primary refractory HL | II | Recruiting; June 2020 | NCT03179917 |

**References**

1. ABVD = adriamycin, bleomycin, vinblastine, dacarbazine, AVD = doxorubicin, vinblastine, and dacarbazine, BTK = Bruton tyrosine kinase, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, HDAC = histone deacetylase, ICE = Involved-site radiation therapy, NHL = non-Hodgkin lymphoma, SCT = stem cell transplant.
Combined with immunomodulatory drugs

Previous studies have suggested a potential role for CTLA-4 inhibition in Hodgkin lymphoma, with early reports demonstrating CTLA-4 expression in tumor infiltrating T cells.66 Data for CTLA-4 inhibition in patients is limited, although a phase I study of the CTLA-4 inhibitor ipilimumab in patients with hematologic malignancies progressing after allogeneic hematopoietic stem cell transplantation reported complete responses for 2 of 14 Hodgkin lymphoma patients.68 As combined checkpoint blockade has shown efficacy in solid malignancies,69 several studies are assessing combinations of ipilimumab and nivolumab in hematologic malignancies. Preliminary data from CheckMate 039 (NCT01592370) suggest an overall response rate of 74% and complete response rate of 19% with combined ipilimumab and nivolumab in primarily transplant-naïve Hodgkin lymphoma patients.69 These responses are comparable to anti-PD-1 monotherapy in the relapsed/refractory setting, and so the role of combined checkpoint blockade remains unclear.

Other immunomodulatory drugs such as lenalidomide act through several potential mechanisms, with possible direct effects on malignant cells and indirect activity through modulation of the tumor microenvironment.70 Lenalidomide is currently approved for the treatment of multiple myeloma and myelodysplastic syndrome with deletion of chromosome 1q, and it is also active in several B cell malignancies.71,72 A phase II clinical trial of lenalidomide in 38 relapsed or refractory classical Hodgkin lymphoma patients demonstrated an objective overall response rate of 19%,63 providing a rationale for studying lenalidomide in combination with other agents. In preclinical models of multiple myeloma, lenalidomide treatment modulated PD-1 and PD-L1 expression on effector and tumor cells, and also enhanced checkpoint inhibitor-induced cytotoxicity of multiple myeloma cells.49 Thus, these data suggest that immunomodulatory agents like lenalidomide may have synergistic effects with PD-1 blockade, a hypothesis which is being tested in clinical trials combining pembrolizumab or nivolumab with lenalidomide in patients with Hodgkin or non-Hodgkin lymphoma (NCT02875067, NCT03015896). Of note, recent trials in multiple myeloma combining pembrolizumab with lenalidomide have also been reported to induce an abscopal effect, or the regression of lesions at distant sites outside the field of radiation.

Combined with radiotherapy

Radiotherapy is often used with curative intent in the treatment of localized malignancies, such as in early-stage Hodgkin lymphoma or bulky tumors. Not only does radiotherapy exert a direct cytotoxic effect on malignant cells, it also modulates the tumor microenvironment and antitumor immune responses.81 For example, radiation treatment causes the release of tumor antigens and danger signals, as well as proinflammatory cytokines and chemokines. This promotes the migration and maturation of antigen-presenting cells, which stimulate cytotoxic T cell responses against the tumor. In rare cases, radiotherapy has been reported to induce an abscopal effect, or the regression of lesions at distant sites outside the field of radiation.

Combined with HDAC inhibitors

Histone deacetylases (HDACs) are a family of enzymes that deacetylate lysine residues on histone and nonhistone proteins, and they regulate several pathways implicated in oncogenesis such as cell cycle progression, apoptosis, angiogenesis, and immunity.74 Epigenetic changes have been implicated in the malignant phenotype of Reed-Sternberg cells, and previous studies revealed that Hodgkin lymphoma cell lines and primary tumor tissue highly express class I and II HDACs.75,76 Several HDAC inhibitors have been developed for clinical use, and preclinical studies demonstrated cytotoxic effects of HDAC inhibitors on Hodgkin lymphoma cells.77,78 In a phase II study of 129 heavily pretreated patients with relapsed or refractory Hodgkin lymphoma, treatment with panobinostat, a pan-HDAC inhibitor, resulted in an overall response rate of 27% and complete response rate of 4%.79 Interestingly, HDAC inhibitors can induce a wide array of immunologic changes in malignant cells and the tumor microenvironment, including expression of PD-1 or PD-L1 ligands. For example, correlative studies from the above phase II trial found decreased expression of PD-1 on peripheral blood T cells with panobinostat treatment.80 In vitro studies of melanoma cell lines and patient tumors, HDAC inhibition upregulated PD-L1 and PD-L2 expression, and combined treatment with panobinostat and anti-PD-1 in vivo in mouse studies promoted tumor regression and survival to a greater extent than monotherapy.81 HDAC inhibition also synergized with anti-PD-1 treatment in a lung cancer model.82 Overall, these data suggest that combining HDAC inhibition with PD-1 blockade may improve clinical responses through both direct cytotoxic effects as well as regulation of antitumor immunity, which is being tested in clinical trials (ie, NCT03150329 combining vorinostat, a HDAC inhibitor currently approved in cutaneous T cell lymphoma, and pembrolizumab).

Concluding remarks

The advent of immune checkpoint inhibitors has vastly improved treatment options for many cancer types. While the pathologic cells of Hodgkin lymphoma, Reed-Sternberg cells, robustly overexpress PD-1 ligands, the interplay between Reed-Sternberg cells and the immune microenvironment as well as the mechanism of action for PD-1 inhibitors in this disease are still mysterious. Nevertheless, PD-1 inhibitors as monotherapy in the relapsed or refractory setting have shown remarkable clinical responses. Ongoing clinical investigation with novel combinations of PD-1 inhibitors will hopefully reveal promising strategies to improve cure rates in Hodgkin lymphoma.
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