Immune targeting of the microenvironment in classical Hodgkin's lymphoma: insights for the hematologist

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Abstract: While up to 80% of patients with Hodgkin's lymphoma (HL) are cured with first-line therapy, relapsed/refractory (R/R) disease remains a clinical challenge and is fatal for many young patients. HL is unique in that the tumor cells (Hodgkin Reed–Sternberg; HRS cells) are a small fraction (<1%) of the tumor bulk, with the remaining tumor composed of the cells of the tumor microenvironment (TME). The support and integrity of the TME is necessary for HRS cell growth and survival. Targeting the programmed death 1 pathway has shown exciting activity in relapsed HL and led to United States Food and Drug Administration approval of the checkpoint inhibitors, nivolumab and pembrolizumab, for R/R HL. Novel combinations with checkpoint blockade therapy (CBT), targeted approaches such as combinations of CBT with brentuximab vedotin or chemotherapy, chimeric antigen receptor T-cells, and the use of CBT to potentially sensitize to subsequent therapy are being investigated as treatment approaches. As understanding of the HL TME grows, hopefully this will increase the number of rational therapeutic targets.

Keywords: Hodgkin, lymphoma, relapsed, refractory, immune, microenvironment, checkpoint, target, therapeutic

Introduction

Classical Hodgkin's lymphoma (HL) remains the most common lymphoma of adolescents and young adults, with an estimated 8500 new cases per year.[1,2] Although up to 80% of HL patients are cured with first-line chemotherapy, either alone or combined with radiation, a cure for patients with relapsed and refractory (R/R) HL remains challenging, and approximately 1150 primarily young patients succumb to this disease annually in the United States (US).[1,3]

Hodgkin Reed–Sternberg (HRS) tumor cells have a unique appearance characterized by a large nucleus, at least one large nucleoli, a large Golgi apparatus, and abundant cytoplasm.[4–6] HRS cells originate from germinal center B-cells, but have lost expression of the B-cell receptor and only faintly express common B-cell markers and transcription factors, such as CD19, CD20, and CD79a.[7,8] Moreover, HL is unique among lymphomas and other tumors in that the HRS tumor cells comprise <1% of the total tumor volume.

HRS cells are dependent upon anti-apoptotic and pro-survival signals from the tumor microenvironment (TME) for growth and survival. The TME is composed of a mixture of immune cells and stroma, including T-lymphocytes, natural killer (NK) cells, monocytes, macrophages, and dendritic cells.[9] In this review we will discuss how novel agents targeting the immune microenvironment have shown efficacy in R/R HL.

Evasion of immune surveillance

The binding of the programmed death receptor 1 (PD-1) immune checkpoint protein on T-cells to its ligand, programmed death ligand-1 (PD-L1) on tumor cells, impairs the immune system's ability to recognize and eliminate tumor cells in many malignancies.[10–13] HRS cells express high levels of PD-L1 due to multiple mechanisms, including the amplification of chromosome 9p24.1 and constitutive activator protein 1 (AP1) signaling.[14,15] In Epstein–Barr virus (EBV)-positive tumors, EBV latent membrane protein 1

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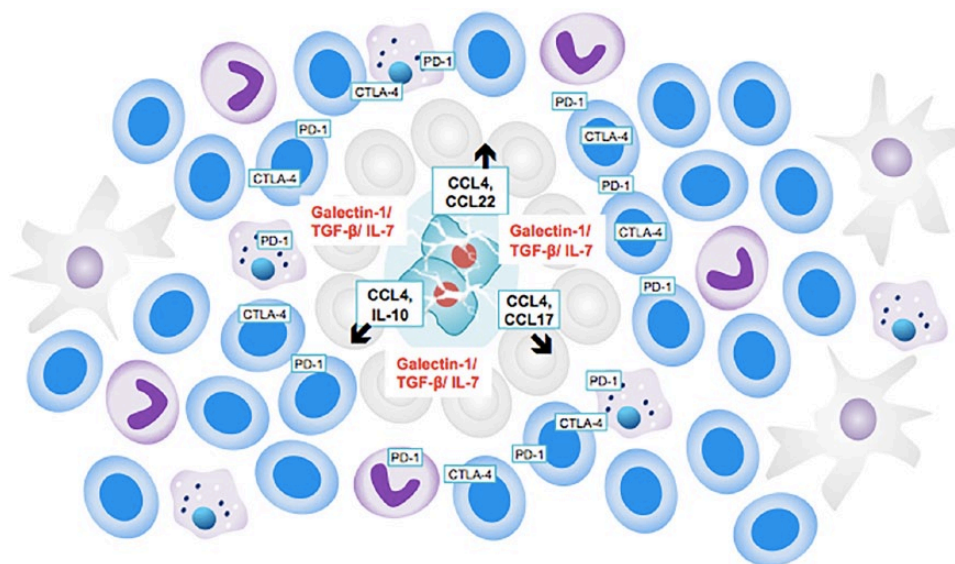
Figure 1. Tumor microenvironment.
Figure 1. HRS cells further escape effector T-cell elimination by altering their own immune microenvironment through the secretion of cytokines and chemokines which attract protective CD4+ T-cells, mast cells, and macrophages, while inhibiting the function of the surrounding natural killer cells and effector T-cells.
HRS, Hodgkin Reed–Sternberg.

(LMP1) is also described as increasing PD-L1 promoter activity *via* JAK3.[16] This PD-1/PD-L1 interaction facilitates HRS cell evasion of immune surveillance and survival within the TME.[17,18]

Genetic aberrancies and loss of HLA class I and II expression are additional immunologic dys-regulations described in HL.[5] Class II transacti-vator (*CIITA*) gene alterations have been identified in HL and lead to overexpression of PD-L1 and PD-L2, as well as downregulation of surface human leukocyte antigen (HLA) class II expression, further reducing tumor cell immuno-genicity.[19] In addition, inactivating mutations in the β-2-microglobulin (*B2M*) gene in HRS cells leads to the loss of HLA (class I) expression.[20] Although HLA class I negative HRS cells could be putatively targeted by NK cells or cytotoxic T-cells, the antigens HLA-G and HLA-E, found in HRS cells, are protective against these mecha-nisms.[5] EBV-positive tumors may alter HLA class I and II signaling, while EBV-negative tumors more commonly lose HLA expression altogether.[21–23]

HRS cells further escape effector T-cell elimina-tion by altering their own immune microenviron-ment (TME) through the secretion of chemokines,

such as CCL4, CCL17/TARC, and CCL22/MDC, that attract protective CD4+ T-cells, mast cells, and macrophages[24] (Figure 1). Eosinophils, monocytes, dendritic cells, NK cells, neutrophils, and activated fibroblasts are also recruited by and interact directly with HRS cells in the TME.[6,25] CD4+ T-cells are hyporespon-sive to T-cell receptor stimulation and suppress the activation and proliferation of effector T-cells.[26] HRS cells and surrounding regulatory T-cells (Tregs), secrete interleukin (IL)-10 to fur-ther inhibit the surrounding NK cells and effector T-cells.[24] Other cytokines involved in tumor expansion and recruitment of CD4+ T-cells and Tregs include IL-7, transforming growth factor-beta (TGF-β), and galectin-1.[27] CD137, which is ectopically expressed by HRS cells leads to enhanced growth of HRS cell lines and escape from immune surveillance *via* IL-13 secre-tion.[28,29] Both autocrine and paracrine growth factor signaling within the TME allow the HRS cells to proliferate and evade the host immunity.[5,25]

This knowledge has contributed to the develop-ment of checkpoint blockade therapy (CBT) for relapsed HL, now approved for this indication, which has been a paradigm shift for the manage-ment of this population.

Treatment with checkpoint blockade

The PD-1 inhibitors nivolumab and pembrolizumab are now US Food and Drug Administration (FDA) approved for the treatment of relapsed HL. Nivolumab is US FDA approved for the treatment of adult patients with HL that have relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and the anti-CD 30 antibody drug conjugate (ADC) brentuximab vedotin (BV) or after three or more lines of systemic therapy that includes autologous HSCT.[30] In a phase I dose-escalation trial, 23 patients with R/R HL were treated with nivolumab 3 mg/kg every 2 weeks with an objective response rate (ORR) of 87%. A total of six (26%) of these patients achieved a complete response (CR). Responses were durable for many, lasting over 1 year in eight patients.[31] A larger, follow-up phase II study of patients with recurrent HL receiving nivolumab after failure of autologous stem cell transplantation (ASCT) and subsequent BV showed an ORR of 66.3% at a median follow up of 8.6 months. The CR and partial response (PR) rates were 8.8% and 57.5%, respectively. At 6 months the progression-free survival (PFS) was 76.9%, and the overall survival (OS) rate was 98.7%. Evaluable patients who achieved CR were more likely to have higher level 9p24·1 alterations, whereas those with progressive disease were more likely to have lower level 9p24·1 alterations. Patients whose HRS cells exhibited *PD-L1/PD-L2* amplification and increased PD-L1 expression, based upon fluorescence *in situ* hybridization, were also more likely to attain CR. However, the majority of patients with 9p24·1 polysomy or PD-L1 expression in the lower quartile achieved a PR. Nivolumab was well tolerated, with the most common adverse events (AEs) of any grade including fatigue, infusion reactions, and rash. The most common grade 3–4 AEs were neutropenia and increased lipase levels.[32]

Pembrolizumab, a second PD-1 inhibitor, has also showed similar activity in R/R HL. The KEYNOTE-013 phase I study included heavily pretreated R/R HL patients, all of whom progressed after treatment with BV. Of 31 total patients, 55% had at least five prior therapies, and 71% had prior ASCT. With pembrolizumab 10 mg/kg given every 2 weeks the ORR was 65%, with a CR rate of 16%. At 24 weeks the PFS was 69% and at 52 weeks PFS was 46%.[33] In the following KEYNOTE-087 phase II study, 210 patients with R/R HL were divided into three categories, based upon: whether they progressed after ASCT and subsequent BV (1), ASCT without subsequent BV (2), or salvage chemotherapy and BV (ASCT ineligible due to chemoresistant disease (3).[34] All patients received pembrolizumab 200 mg every 3 weeks, with an ORR of 69% and a CR rate of 22.4%. Transplant-ineligible patients had an ORR of 64.2%, while the transplanted groups had ORR 73.9% and 70.0% respectively. In additional subgroup analysis, the trial also found that the ORRs were similar for patients who had already received at least three lines of therapy as compared with those who had not (68.7% *versus* 71.4%). Median OS was not reached, but at 9 months the OS was 97.5% and PFS was 63.4%. Most of the patients' tumors were PD-L1 positive, but clinical activity was still seen in patients with low PD-L1 expression. The most common AEs of all grade were hypothyroidism (12.4%) and pyrexia (10.5%), but the most common grade 3/4 AEs were neutropenia (2.4%), dyspnea (1%), and diarrhea (1%). Overall, treatment was well tolerated, and this study led to US FDA approval of pembrolizumab for HL relapsed after three or more prior lines of therapy.[35]

The combination of nivolumab with ipilimumab, a CTLA-4 inhibitor, typically provides higher ORR and OS rates in solid tumors as compared with PD-1 monotherapy due to the synergism in their mechanisms of action.[36,37] CTLA-4 inhibitors affect the immune-priming phase by supporting T-cell activation and proliferation, while PD-1 inhibitors allow for effector T-cell function against tumor. Together these actions help the immune system to recognize the tumor as foreign and mount an attack. However, as a result of immune enhancement, combination checkpoint blockade often results in greater immune-related toxicity.[36,38,39] Checkmate 039 examined this combination in 65 patients with R/R hematologic malignancies and found that for the 31 patients with HL, the efficacy and toxicity profile of the combination was similar to that seen with anti-PD-1 therapy alone. Of note, these patients were predominantly transplant-naïve. However, there was no clear additive or synergistic benefit for dual checkpoint blockade in this study.[40]

Given the promising results with PD-1 inhibition, new strategies to leverage the immune system and alter the tumor microenvironment in HL are actively being investigated. Combinations of chemotherapy plus immunotherapy and targeted

agents with immunotherapy are currently in clinical trials. The ECOG-ACRIN sponsored phase I clinical trial, E4412, examined the safety and efficacy of treatment with the combinations of BV 1.8 mg/kg + ipilimumab at 1 mg or 3 mg (arms a–c), and nivolumab 3 mg/kg + BV at 1.2 mg/kg or 1.8 mg/kg (arms d–f) in patients with R/R HL. In arms a–c for 19 patients the therapy was well tolerated with no dose-limiting toxicities noted during dose escalation. There were four grade 3–4 AEs: rash, vomiting, neuropathy, and thrombocytopenia. The ORR for 12 evaluable patients was 67% with a CR of 42%. With a median follow up of 0.66 years, the median PFS was 0.74 years and the OS was not reached.[41] For the 19 patients who received BV + nivolumab, the regimen was generally well tolerated and highly active. A patient who was heavily pretreated developed grade 5 pneumonitis and four additional patients experienced grade 3 AEs: rash, pruritis, typhlitis, and neutropenia. A total of 18 patients were evaluable for response, with an ORR of 89% and a CR rate of 61%.[42] The 6-month PFS was 93%, with a median follow up of 0.84 years, and the median OS was not reached.

Interim results of an additional phase I/II study of the combination of BV (1.8 mg/kg) and nivolumab for R/R HL recently showed an ORR of 82% and a CR rate of 61%, which is similar to the prior results. Grade 3 or higher events occurred in 31% of patients.[43] The combination of BV + nivolumab in both studies demonstrates a higher ORR than seen in the phase II trials of nivolumab or BV monotherapy, and a significantly higher CR rate.[31,32,44] Longer follow up will provide further data on the durability of CRs and PRs. Correlative tumor biopsies and next generation sequencing are also being explored for a greater understanding of the role of the effect of CBT on the HL TME.

The strategy of dual checkpoint blockade combined with ADC was presented at the American Society of Hematology (ASH) meeting in 2018. The arms g–i of protocol E4412, which combined ipilimumab and nivolumab with BV, showed an ORR of 82%, with a CR of 68% in 22 patients with R/R HL. For patients who received at least three cycles of therapy, the ORR was 95% with a CR rate of 84%. This study is now a randomized phase II study comparing the doublet regimen of BV/nivolumab with the triplet of BV/nivolumab/ipilimumab in patients with R/R HL (ClinicalTrials.gov identifier: NCT01896999);[45] it is open through the Cancer Trials Support Unit. Additionally, there are trials currently investigating the combination of nivolumab and chemotherapy for R/R HL. The chemotherapeutic agents being studied include gemcitabine, bendamustine, ifosfamide, carboplatin, and etoposide (ClinicalTrials.gov identifiers: NCT03016871, NCT03739619).

Beyond checkpoint: other novel targets

While chimeric antigen receptor (CAR) T-cells have transformed the treatment of relapsed diffuse large B-cell lymphoma, they have yet to make a significant impact in the R/R HL space. Whether this is due to the immune protective nature of the TME in HL or to the choice of target antigen (most of the patients treated by CD30 CARs have received prior treatment with CD30 targeting agents such as BV) has yet to be determined. There are two trials that have recently described the effect of CD30-targeted CAR T-cells. In the first study, 16 patients with R/R HL (all previously treated with BV) and 2 patients with non-Hodgkin's lymphoma were conditioned with bendamustine/fludarabine and treated with a CD30-targeted CAR (ATLCAR.30). Overall, four patients were excluded from analysis due to CR prior to infusion of the CAR. Of the 14 remaining patients, 3 developed cytokine release syndrome (CRS), 1 with grade 1 which resolved spontaneously, and 2 with grade 2, responding to tocilizumab. There was no neurotoxicity observed. The ORR was 7 (50%): CR was 6 (43%) and there was 1 (7%) PR. At a median follow up of 138 days, the median PFS was 129 days. At 1 year, two patients remained in CR.[46] Similarly, in the RELY-30 trial, CD30 CAR T-cells were infused in patients after receiving the lymphodepleting combination of cyclophosphamide and fludarabine. Of eight patients, six (75%) had a CR lasting up to 6 months, while the other two patients progressed. This methodology of CAR T-cell delivery was also found to be well tolerated, with four patients experiencing grade 1 CRS and six patients developing a transient maculopapular rash.[47] No other toxicity was reported. Both CAR T-cell products were found to be well tolerated and effective in these studies. A longer duration of follow up and greater patient numbers are required to get a true sense of the tolerability and durability of this therapy.

Table 1. Selected ongoing clinical trials in R/R HL.

ClinicalTrials.gov identifier and drug(s)	Outcome	Further study
NCT01896999 (E:4412), ipilimumab/nivolumab/BV	ORR 82%, CR 68% all-comers, ORR 95%, CR 84% if >3 cycles	Randomized phase II of ipilimumab/nivolumab/BV *versus* nivolumab/BV, recruiting
NCT03016871, nivolumab ±ifosfamide/carboplatin/etoposide (NICE)	Recruiting	
NCT03739619, gemcitabine/bendamustine/nivolumab	Recruiting	
NCT02690545, ATLCAR.30 for CD30+	Prelim ORR 50%, 43% CR, still recruiting	
NCT02917083, CD30 CAR T-cells (RELY 30)	Preliminary 75% CR, still recruiting	
NCT03209973, tislelizumab	ORR 85.7%, CR 61.4%	
NCT02824029, ibrutinib	Recruiting	
NCT02362035, acalabrutinib/pembrolizumab	Recruiting	

BV, brentuximab vedotin; CAR, chimeric antigen receptor; CR, complete response; HL, Hodgkin's lymphoma; ORR, objective response rate; R/R, relapsed/refractory

Novel PD-1 antibodies have also been described. Tislelizumab, a humanized immunoglobulin (Ig) G4, presented early data at the ASH. In a multicenter, phase II trial of 70 patients in China the ORR was 85.7% with a CR rate of 61.4% at a median follow up of 7.9 months. The medication was generally well tolerated, with the rate of AEs being similar to that of other PD-1 inhibitors.[48] It is unclear whether the higher CR rate seen with this agent compared with other single-agent PD-1 inhibitors is a function of the drug itself, the patient population, or other factors. Further study is warranted.

Checkpoint blockers may also resensitize HL patients to subsequent therapy. In a multicenter, retrospective study of 81 R/R HL patients who had received a median of four therapies prior to CBT, the ORR post-CBT was 62% with a 42% CR. Responses were independent of the post-CBT treatment regimen and included both patients who responded and did not respond to CBT. Among patients with a CR or PR to CBT itself, the ORR to post-CBT was 42%, in contrast with an ORR of 20% for nonresponders to CBT.

It is hypothesized that the CBT may sensitize the lymphoma to the subsequent therapy and that the response to post-CBT correlates with the response to CBT itself in the HL population.[49] Larger, prospective studies are needed to confirm this intriguing hypothesis.

For patients who relapse on immune-based therapy, novel targeted therapy remains an active area of investigation. Bruton's tyrosine kinase (BTK) inhibition has been shown to suppress phosphoinositide 3-kinase (PI3K), mammalian target of rapamycin (mTOR), FAS (also known as CD95 or Apo-1; a tumor necrosis factor receptor) and nuclear factor kappa B (NF-κB) in HL cell lines.[50] Ibrutinib, a BTK inhibitor, is currently being studied in the phase II setting for R/R HL (ClinicalTrials.gov identifier: NCT02824029). Acalabrutinib, a second generation BTK inhibitor, is undergoing a phase Ib/II proof-of-concept study in combination with pembrolizumab (ClinicalTrials.gov identifier: NCT02362035; Table 1). While none of these agents may have sufficient single-agent activity, they hold the promise of combining with chemotherapy or immunotherapy, particularly as their

spectrum of toxicity is different from that of both chemotherapy and immunotherapy, and to offer more options for patients with multiple R/R disease.

Preclinical data further suggest the potential of other novel immune-based strategies. CD137 enhances HRS cell growth and aids in immune escape.[28] Blocking the interaction of CD37 with its ligand may prevent tumor proliferation and also enhance anti-tumor immunity. Monoclonal antibodies against glucocorticoid-induced tumor necrosis factor-related protein and OX40 (CD134) may also increase effector T-cell function, and may be a strategy either alone or combined with other agents.[51] Clinical trials with these agents have not yet begun.

Conclusion

HL is a unique disease in which a small number of malignant tumor cells subsist within an immunosuppressive TME. This microenvironment where HRS cells are dependent upon anti-apoptotic and pro-survival signals in the surrounding milieu to survive is a critical therapeutic target. Many questions remain unanswered regarding the interactions between the HRS cells and the TME. Targeting the PD-1/PD-L1 checkpoint has shown promise, but further study is needed in order to identify additional therapeutic targets, and to better understand resistance mechanisms. Ongoing studies involving BV combined with doublet immunotherapy, novel checkpoint blocking agents, CAR T-cell therapy, tyrosine kinase inhibitors, and using checkpoint inhibitors to resensitize to chemotherapy may provide some insight. However, patients who relapse beyond checkpoint blockade continue to have limited treatment options, and continued investigation into novel TME-based strategies is needed.

Conflict of interest statement

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References

1. Cancer stat facts: Hodgkin lymphoma. NIH, Natl Cancer Institute, SEER data [Internet], https://seer.cancer.gov/statfacts/html/hodg.html (accessed 11 March 2019).

2. Brugières L and Brice P. Lymphoma in adolescents and young adults. *Prog tumor Res* 2016; 43: 101–114.

3. Ansell SM. Hodgkin lymphoma: diagnosis and treatment. *Mayo Clin Proc* 2015; 90: 1574–1583.

4. Grover NS and Savoldo B. Targeting immune system alterations in Hodgkin lymphoma. *Curr Hematol Malig Rep* 2017; 12: 358–369.

5. Liu Y, Sattarzadeh A, Diepstra A, *et al.* The microenvironment in classical Hodgkin lymphoma: an actively shaped and essential tumor component. *Semin Cancer Biol* 2014; 24: 15–22.

6. Wein F and Küppers R. The role of T cells in the microenvironment of Hodgkin lymphoma. *J Leukoc Biol* 2016; 99: 45–50.

7. Hertel CB, Zhou X, Hamilton-Dutoit SJ, *et al.* Loss of B cell identity correlates with loss of B cell-specific transcription factors in Hodgkin/Reed–Sternberg cells of classical Hodgkin lymphoma. *Oncogene* 2002; 21: 4908–4920.

8. Schwering I, Bräuninger A, Klein U, *et al.* Loss of the B-lineage-specific gene expression program in Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma. *Blood* 2003; 101: 1505–1512.

9. Ansell SM. Targeting immune checkpoints in lymphoma. *Curr Opin Hematol* 2015; 22: 337–342.

10. Ma L-J, Feng F-L, Dong L-Q, *et al.* Clinical significance of PD-1/PD-Ls gene amplification and overexpression in patients with hepatocellular carcinoma. *Theranostics* 2018; 8: 5690–5702.

11. Qin A, Coffey DG, Warren EH, *et al.* Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer. *Cancer Med* 2016; 5: 2567–2578.

12. Ricklefs FL, Alayo Q, Krenzlin H, *et al.* Immune evasion mediated by PD-L1 on glioblastoma-derived extracellular vesicles. *Sci Adv* 2018; 4: eaar2766.

13. Vu HL, Rosenbaum S, Purwin TJ, *et al.* RAC1 P29S regulates PD-L1 expression in melanoma. *Pigment Cell Melanoma Res* 2015; 28: 590–598.

14. Yamamoto R, Nishikori M, Kitawaki T, *et al.* PD-1-PD-1 ligand interaction contributes

to immunosuppressive microenvironment of Hodgkin lymphoma. *Blood* 2008; 111: 3220–3224.

15. Chen BJ, Chapuy B, Ouyang J, *et al*. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. *Clin Cancer Res* 2013; 19: 3462–3473.

16. Green MR, Rodig S, Juszczynski P, *et al*. Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. *Clin Cancer Res* 2012; 18: 1611–1618.

17. Péricart S, Tosolini M, Gravelle P, *et al*. Profiling immune escape in Hodgkin's and diffuse large B-cell lymphomas using the transcriptome and immunostaining. *Cancers (Basel)* 2018; 10: E415.

18. Roemer MGM, Advani RH, Redd RA, *et al*. Classical Hodgkin lymphoma with reduced β2M/MHC class I expression is associated with inferior outcome independent of 9p24.1 status. *Cancer Immunol Res* 2016; 4: 910–916.

19. Steidl C, Shah SP, Woolcock BW, *et al*. MHC class II transactivator CIITA is a recurrent gene fusion partner in lymphoid cancers. *Nature* 2011; 471: 377–381.

20. Reichel J, Chadburn A, Rubinstein PG, *et al*. Flow sorting and exome sequencing reveal the oncogenome of primary Hodgkin and Reed–Sternberg cells. *Blood* 2015; 125: 1061–1072.

21. Diepstra A, Niens M, Vellenga E, *et al*. Association with HLA class I in Epstein–Barr-virus-positive and with HLA class III in Epstein–Barr-virus-negative Hodgkin's lymphoma. *Lancet (London, England)* 2005; 365: 2216–2224.

22. Diepstra A, van Imhoff GW, Karim-Kos HE, *et al*. HLA class II expression by Hodgkin Reed–Sternberg cells is an independent prognostic factor in classical Hodgkin's lymphoma. *J Clin Oncol* 2007; 25: 3101–3108.

23. Nijland M, Veenstra RN, Visser L, *et al*. HLA dependent immune escape mechanisms in B-cell lymphomas: implications for immune checkpoint inhibitor therapy? *Oncoimmunology* 2017; 6: e1295202.

24. Liu WR and Shipp MA. Signaling pathways and immune evasion mechanisms in classical Hodgkin lymphoma. *Blood* 2017; 130: 2265–2270.

25. Steidl C, Connors JM and Gascoyne RD. Molecular pathogenesis of Hodgkin's lymphoma: Increasing evidence of the importance of the microenvironment. *J Clin Oncol* 2011; 29: 1812–1826.

26. Ishida T, Ishii T, Inagaki A, *et al*. Specific recruitment of CC chemokine receptor 4-positive regulatory T cells in Hodgkin lymphoma fosters immune privilege. *Cancer Res* 2006; 66: 5716–5722.

27. Chiu J, Ernst DM and Keating A. Acquired natural killer cell dysfunction in the tumor microenvironment of classic Hodgkin lymphoma. *Front Immunol* 2018; 9: 267.

28. Rajendran S, Ho WT and Schwarz H. CD137 signaling in Hodgkin and Reed–Sternberg cell lines induces IL-13 secretion, immune deviation and enhanced growth. *Oncoimmunology* 2016; 5: e1160188.

29. Pang WL, Ho WT and Schwarz H. Ectopic CD137 expression facilitates the escape of Hodgkin and Reed-Sternberg cells from immunosurveillance. *Oncoimmunology* 2013; 2: e23441.

30. Opdivo (nivolumab) injection. Prescribing information. Princeton, NJ: Bristol-Myers Squibb, 2018.

31. Ansell S, Armand P, Timmerman J, *et al*. Nivolumab in patients (pts) with relapsed or refractory classical Hodgkin lymphoma (R/R cHL): clinical outcomes from extended follow-up of a phase 1 study (CA209–039). *Blood* 2015; 126: 583.

32. Younes A, Santoro A, Shipp M, *et al*. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol* 2016; 17: 1283–1294.

33. Armand P, Shipp MA, Ribrag V, *et al*. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin Lymphoma after brentuximab vedotin failure. *J Clin Oncol* 2016; 34: 3733–3739.

34. Chen R, Zinzani PL, Fanale MA, *et al*. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin Lymphoma. *J Clin Oncol* 2017; 35: 2125–2132.

35. KEYTRUDA®(pembrolizumab) injection. Prescribing information. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., 2014.

36. Wolchok JD, Chiarion-Sileni V, Gonzalez R, *et al*. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017; 377: 1345–1356.

37. Hammers HJ, Plimack ER, Infante JR, *et al*. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell

carcinoma: the CheckMate 016 study. *J Clin Oncol* 2017; 35: 3851–3858.

38. Larkin J, Chiarion-Sileni V, Gonzalez R, *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015; 373: 23–34.

39. Antonia SJ, López-Martin JA, Bendell J, *et al.* Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol* 2016; 17: 883–895.

40. Ansell S, Gutierrez M, Shipp M, *et al.* A phase 1 study of nivolumab in combination with ipilimumab for relapsed or refractory hematologic malignancies (CheckMate 039). *Blood* 2016; 128: 183.

41. Diefenbach C, Hong F, Cohen J, *et al.* Preliminary Safety and Efficacy of the Combination of Brentuximab Vedotin and Ipilimumab in Relapsed/ Refractory Hodgkin Lymphoma: A Trial of the ECOG-ACRIN Cancer Research Group (E4412). *Blood* 2015; 126: 585.

42. Diefenbach CS, Hong F, David K, *et al.* Safety and efficacy of combination of brentuximab vedotin and nivolumab in relapsed/refractory Hodgkin lymphoma: A trial of the ECOG-ACRIN Cancer Research Group (E4412). Updated results presented at Lugano Meeting. *Hematol Oncol* 2017; 35: 84–85.

43. Herrera AF, Moskowitz AJ, Bartlett NL, *et al.* Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood* 2018; 131: 1183–1194.

44. Younes A, Gopal AK, Smith SE, *et al.* Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 2012; 30: 2183–2189.

45. Diefenbach C, Hong F, Ambinder R, *et al.* A phase I study with an expansion cohort of the combinations of ipilimumab, nivolumab and brentuximab vedotin in patients with relapsed/ refractory Hodgkin lymphoma: A trial of the ECOG-ACRIN Research Group (E4412: Arms G-I). Results updated at ASH. *Blood* 2018; 132(Suppl. 1): 679.

46. Grover NS, Park SI, Ivanova A, *et al.* Clinical responses to CAR.CD30-T cells in patients with CD30+ lymphomas relapsed after multiple treatments including brentuximab vedotin. *Blood* 2018; 132(Suppl. 1): 681.

47. Ramos CA, Bilgi M, Gerken CP, *et al.* CD30-chimeric antigen receptor (CAR) T cells for therapy of Hodgkin lymphoma (HL). *Blood* 2018; 132(Suppl. 1): 680.

48. Song Y, Gao Q, Zhang H, *et al.* Tislelizumab (BGB-A317) for relapsed/refractory classical Hodgkin lymphoma: Preliminary efficacy and safety results from a phase 2 study. *Blood* 2018; 132(Suppl 1): 682.

49. Carreau NA, Pail O, Armand P, *et al.* Checkpoint blockade therapy may sensitize Hodgkin lymphoma to subsequent therapy. Updated results presented at ASH. *Blood* 2018; 132(Suppl. 1): 1626.

50. Muqbil I, Aboukameel A, Mohammad R, *et al.* Bruton tyrosine kinase inhibition in classical Hodgkin lymphoma cell lines and animal models. *Blood* 2017; 130(Suppl. 1): 1536.

51. Zappasodi R, de Braud F and Di Nicola M. Lymphoma immunotherapy: Current dtatus. *Front Immunol* 2015; 6: 448.