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REVIEW

Combination Therapy with Immune Checkpoint Inhibitors and Histone Deacetylase Inhibitors or Alkylating Agents

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Purpose: Immune checkpoint inhibitors (CPIs) have been widely adopted in a number of early and advanced malignancies. Histone deacetylase inhibitors (HDACis) and alkylating agents (AAs) have been suggested to potentiate the actions of CPIs on tumor cells. We conducted a comprehensive literature review to explore the potential synergistic activity between CPIs, AAs, and HDACis.

Patients and Methods: Clinical and non-clinical studies describing outcomes in patients with cancer receiving CPIs and either concomitant or sequential (pre- or post-CPI) AAs or HDACis were identified in PubMed using pre-defined search strings. Manual searches of key oncology congresses were similarly performed. All relevant articles and abstracts were manually screened for relevance, classified according to the specific anticancer agents used (CPIs, AAs, or HDACis), tumor entity, and whether treatment was concomitant or sequential.

Results: Overall, 227 unique clinical studies across a range of tumor types, both solid tumors and hematological malignancies, were identified. One hundred and fifty-nine publications on Phase I and II clinical studies together with 41 publications on Phase III studies were examined. The most commonly investigated tumor types were melanoma, triple-negative breast cancer, non-small cell lung cancer, and Hodgkin lymphoma. The randomized clinical studies identified, all of which reported on the combination of a CPI with an AA, demonstrated superior outcomes in the combination arm compared with CPI or AA monotherapy. Similarly, combination therapy with CPIs and HDACis demonstrated promising activity.

Conclusion: Sequential or concomitant administration of a CPI with an AA or an HDACi may improve outcomes for patients with a range of tumor types. There is a rationale to support further investigation into the potential for synergy between CPIs, alkylating agents and/or HDACis in both the non-clinical and clinical settings.

Plain Language Summary: People being treated for cancer will often receive more than one drug at a time, and the concept of combining cancer drugs is frequently investigated as a potential opportunity to improve outcomes for patients. We reviewed the published literature for clinical trials and work undertaken in laboratories to explore whether combining targeted agents that stop cancer cells from multiplying (known as checkpoint inhibitors) with traditional chemotherapy that kills cancer cells could be a useful approach. We looked at evidence in publications where checkpoint inhibitors were used at the same time as chemotherapy, or given immediately before or after chemotherapy. The most important evidence came from clinical trials where outcomes for patients receiving combinations of treatment were directly compared with those from patients receiving a single treatment. These studies showed superior outcomes for patients who were treated with a combination of cancer drugs compared with patients receiving monotherapy. We also found evidence that adding another class of cancer drug, called histone deacetylase inhibitors, might sensitize tumors to checkpoint inhibitors. These findings provide a rationale for examining alkylating agents and/or histone deacetylase inhibitors combined with checkpoint inhibitors.

Keywords: histone deacetylase inhibitor, checkpoint inhibitor, alkylating agents, synergy, hematological malignancies, solid tumors

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Introduction

Promising early-phase clinical studies with immune checkpoint inhibitors (CPIs) given as monotherapy, and adoption of these agents in a number of indications and settings, have driven further investigation into the use of these agents in combination with chemotherapy in settings including triple-negative breast cancer (TNBC), bladder cancer, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), and various relapsed/refractory lymphomas.[1–9] In addition, the investigation of combination treatment with CPIs has been necessitated as an approach to overcome factors such as acquired resistance to CPIs or delayed efficacy.[10,11] However, it should be noted that studies such as those conducted by Hersh et al and Heynckes et al have highlighted the difficulties of CPI combination therapies in specific tumor entities, together with other unmet medical needs.[12,13]

Combination therapy using a CPI-containing regimen has been shown to improve patient outcomes,[14,15] and the underlying mechanisms for this have been investigated. Agostinetto et al examined the use of immunotherapy in patients with TNBC and suggested that histone deacetylase inhibitors (HDACis) may act synergistically with CPIs through an upregulation of antigen-presenting genes and enhanced tumor recognition and killing.[16] Moreover, Briere et al noted that the HDACi mocetinostat increased tumor antigen presentation, decreased immune suppressive cell types and augmented CPI therapy in a panel of NSCLC cell lines in vitro.[17] It is also possible that chemotherapy may influence the tumor microenvironment and the likelihood of response to CPI-based regimens, with evidence that the functions of natural killer cells may be restored, enabling infiltration of the tumor microenvironment and an increasing sensitivity of tumor cells to natural killer cell-mediated killing.[16,18]

CPIs, alkylating agents (AAs), and HDACis have disparate mechanisms of action (Figure 1), whereby CPIs potentiate the actions of T cells against cancer cells, while AAs induce double-strand breaks in cancer cell DNA, and HDACis induce conformational changes that improve access to the DNA for other drugs together with epigenetic changes.[19–23] The aim of the current analysis was to explore the potential synergistic activity between CPIs, AAs, and HDACis via a comprehensive literature review examining both non-clinical findings and clinical outcomes.

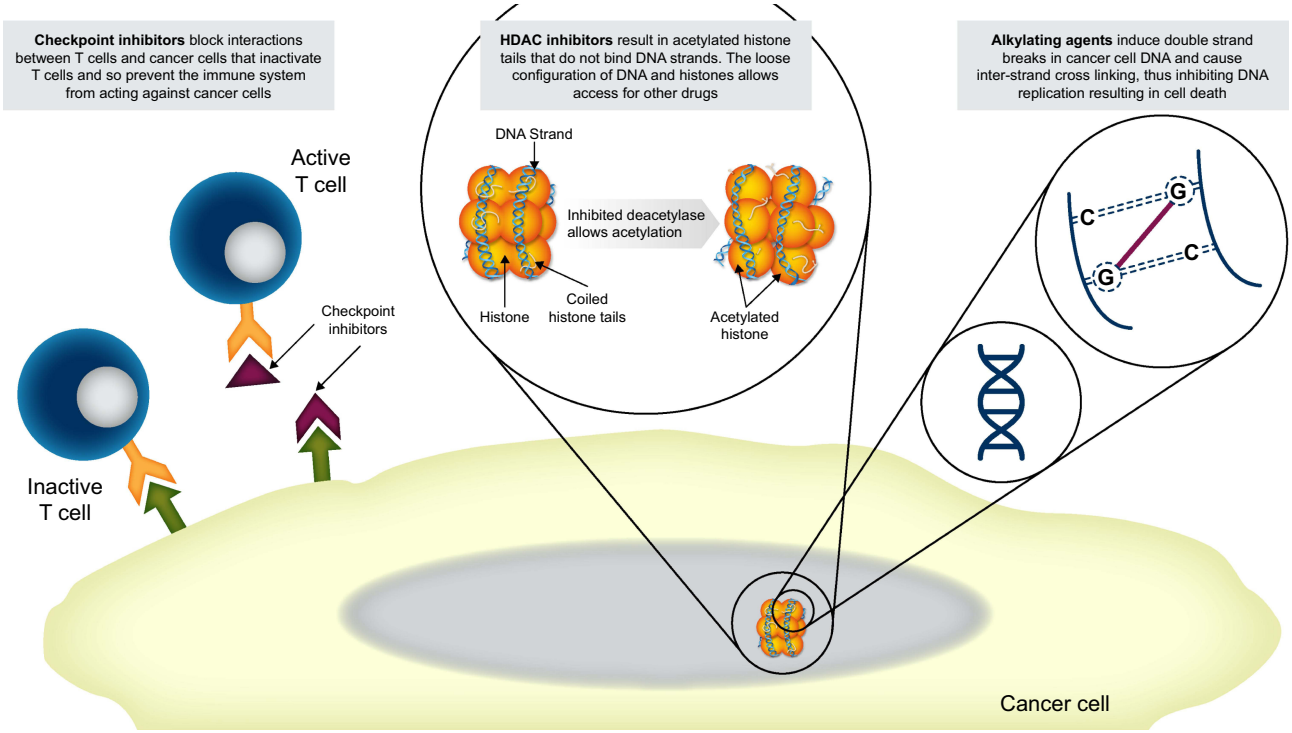

Figure 1 Checkpoint inhibitors, alkylating agents, and histone deacetylase inhibitors have disparate mechanisms of action.[19–23]
Abbreviation: HDAC, histone deacetylase.

Materials and Methods

Non-clinical experiments and clinical studies describing outcomes in patients with cancer involving CPIs and either concomitant or sequential (pre- or post-CPI) AAs or HDACis were identified in PubMed using pre-defined search strings. All approved and pipeline CPIs were included within the search strings, details of which are included in Supplementary Appendix A, with no language limits applied to the searches up to a cut-off date of 31 July 2022.

A manual search of Clinicaltrials.gov and abstracts presented at key oncology and hematology conferences from January 2019 to July 2022 was conducted. Conferences searched included the American Association for Cancer Research (AACR), American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), American Society for Hematology (ASH), European Hematology Association (EHA), and the International Conference on Malignant Lymphoma (ICML).

All articles and abstracts identified were collated into an Excel spreadsheet and screened manually for relevance to the research question. Full text articles and abstracts were subsequently obtained for all potentially relevant publications. Potentially relevant publications were then classified according to the type of CPI administered, whether administration was concomitant or sequential, whether the CPI was administered alongside AAs or HDACis, and tumor type. The analysis included both studies where a CPI was added to an AA or HDACi treatment regimen, and those where an AA or HDACi was added to CPI therapy. Tumor types for which only a single publication was identified were excluded from further analysis owing to the challenges of drawing conclusions relating to CPI backbone therapy from a limited pool of data. Clinical outcomes were examined by disease entity, with data extracted from publications for those tumor types where at least two clinical studies were identified. Data extracted from relevant publications included the combination regimen used, comparator arms in randomized studies, whether the use of CPIs with AAs or HDACis was concomitant or sequential, the phase of the studies identified, and the findings from the primary endpoints of the studies including response rates, progression-free survival (PFS), and overall survival (OS).

Results

Studies Identified

A total of 440 articles and conference abstracts were identified together with 357 Clinicaltrials.gov entries. A total of 221 publications were excluded because they were review articles or treatment guidelines (n=85), did not report on studies where CPIs were combined or administered sequentially with AAs or HDACis (n=80), were publications of study protocols (n=28), examined genetic factors or resistance mechanisms (n=16), were cost-effectiveness studies not reporting efficacy data (n=7), or focused on non-oncological indications (n=5). Publications detailing case studies, case series, registry/database studies, or non-clinical studies were screened, however, findings were considered in the context of those from prospective clinical trials.

The remaining publications described non-clinical studies (n=14), case studies or series (n=5), Phase I and II studies (n=159) (which were predominantly open-label and non-comparative), and Phase III studies (n=41) (Table 1). Overall, 227 unique clinical studies across a range of tumor types, both solid tumors and hematological malignancies were considered relevant, and publications on these studies were manually screened.

The most commonly investigated tumor types were melanoma, TNBC and NSCLC (Table 1). Several studies also examined activity and tolerability in a variety of subtypes of lymphoma, including HL. Given the paucity of published evidence for some tumor types, such as pancreatic cancer, renal cell cancer, cervical cancer, and sarcoma, this review will focus on those tumor types for which there is a body of published evidence, particularly comparative clinical evidence.

Melanoma

Histone Deacetylase Inhibitors

Non-Clinical Studies

In the B16F10 murine melanoma model, the combination of panobinostat with an anti-programmed cell death protein-1 (PD-1) agent significantly improved survival when compared with outcomes in control mice ($P<0.05$).[41] This study conducted by Woods et al demonstrated that class I HDACis including panobinostat, vorinostat, and entinostat

Table 1 Summary of Phase II and III Studies Examining the Combination of Checkpoint Inhibitors with Alkylating Agents or HDAC Inhibitors

Trial	Phase	N	CPI	Study Design	Tumor Type	Key Findings
SENSITIZE[24]	Ib/II	23	PEM	Pembrolizumab + domatinostat	Advanced stage melanoma	• Preliminary efficacy: 1 PR, 2 SD • Domatinostat-induced alterations of tumor microenvironment
ENCORE 601[25]	II	53	PEM	Pembrolizumab + entinostat	Melanoma	• ORR: 19% (1 CR and 9 PRs; 95% CI: 9, 32%) • CBR: 32% (7 SD; 95% CI: 20, 46%) • Median PFS: 4.2 months
PEMDAC[26]	II	29	PEM	Pembrolizumab + entinostat	Metastatic uveal melanoma	• ORR: 14% (4 PR; 95% CI: 3.9, 31.7%) • CBR: 28% (4 SD) • Median PFS: 2.1 months; 1-year PFS: 17% • Median OS: 13.4 months; 1-year OS: 59%
Phase II[27]	II	64	IPI	Ipilimumab + temozolomide	Metastatic melanoma	• ORR: 31% (10 CR, 10 PR) • Median PFS: 5 months; PFS at 6 months: 45% • Median OS: 24.5 months
Phase II in Japanese patients[28]	II	15	IPI	Ipilimumab + dacarbazine	Metastatic melanoma	• Survival rate at 1 year: 67% (90% CI: 42.3, 85.8) • ORR: 13% (95% CI: 1.7, 40.5) • CBR: 40% (95% CI: 16.3, 67.7) • Study terminated early due to severe liver toxicity
Phase II[12]	II	72	IPI	Ipilimumab + dacarbazine Ipilimumab	Metastatic melanoma	• ORR: 14.3% (95% CI: 4.8, 30.3) vs 5.4% (95% CI: 0.7, 18.2) • Median OS: 14.3 months (95% CI: 10.2, 18.8) vs 11.4 months (95% CI: 6.1, 15.6) • 1-, 2-, and 3-year OS: 62% vs 45%, 24% vs 21%, 20% vs 9%
Phase III[29]	III	502	IPI	Ipilimumab + dacarbazine Placebo + dacarbazine	Advanced melanoma	• ORR: 15.2% vs 10.3%; P=0.09 • 1-, 2-, and 3-year OS: 47.3% vs 36.3%, 28.5% vs 17.9%, 20.8% vs 12.2% • Median OS: 11.2 months (95% CI: 9.4, 13.6 months) vs 9.1 months (95% CI: 7.8, 10.5 months)
Phase III[30]	III	502	IPI	Ipilimumab + dacarbazine Placebo + dacarbazine	Advanced melanoma	• ORR: 50% (3 CR, 17 PR) vs 35% (7 PR) • 5-year OS: 18.2% (95% CI: 13.6, 23.4%) vs 8.8% (95% CI: 5.7, 12.8%); P=0.002 • Median OS: 11.2 months (95% CI: 9.5, 13.8 months) vs 9.1 months (95% CI: 7.8, 10.5 months; HR, 0.69; 95% CI: 0.57, 0.84)
Q-TWIST analysis[31]	III	502	IPI	Ipilimumab + dacarbazine Placebo + dacarbazine	Stage III/IV melanoma	• Q-TWiST difference: 0.50 months (P=0.0326) favoring ipilimumab after 1 year • Q-TWiST difference: 1.5 months with 2 years of follow-up (P=0.0091), 2.36 months at 3 years (P=0.005) and 3.28 months at 4 years (P=0.0074)
MORPHEUS platform[32]	Ib/II	29	ATEZ	Atezolizumab + entinostat Fulvestrant	HR+ breast cancer	• ORR: 6.7% (95% CI: 0.17, 31.95) vs 0% (95% CI: 0, 23.16) • Duration of response: 2.5 months for atezolizumab + entinostat • Median PFS: 1.8 months (95% CI: 1.5, 3.6) vs 1.8 months (95% CI: 1.5, 2.7) • 40.0% and 21.4% of patients had Grade 3/4 AEs; no Grade 5 AEs
NeoPACT[33]	II	117	PEM	Pembrolizumab + carboplatin + docetaxel	TNBC	• pCR: 60% (95% CI: 51, 70%) • Residual cancer burden: 71% (95% CI: 62, 80%) • 2-year event-free survival: 88% in all patients; 98% in pCR group and 82% in no pCR group
GeparNuevo[34]	II	174	DUR	Durvalumab + nab-paclitaxel Placebo + nab-paclitaxel	TNBC	• pCR: 53.4% (95% CI: 42.5, 61.4%) vs 44.2% (95% CI: 33.5, 55.3%) • Odds Ratio: 1.45 (95% CI: 0.80, 2.63, unadjusted Wald P=0.224).
IMpassion031[2]	III	333	ATEZ	Atezolizumab + nab-paclitaxel + doxorubicin + cyclophosphamide Placebo + nab-paclitaxel + doxorubicin + cyclophosphamide	TNBC	• pCR: 95 (58%, 95% CI: 50, 65) patients vs 69 (41%, 95% CI: 34, 49) patients (rate difference 17%, 95% CI: 6, 27; one-sided P=0.0044 [significance boundary 0.0184]) • PD-L1-positive population, pCR: 53/77 (69%, 95% CI: 57, 79) patients vs 37/75 (49%, 95% CI: 38, 61) patients (rate difference 20%, 95% CI: 4, 35; one-sided P=0.021 [significance boundary 0.0184]).
ENCORE-601[35]	Ib/II	77	PEM	Pembrolizumab + entinostat	Metastatic NSCLC	• ORR: 7 of 76 (9.2%, 95% CI: 3.8, 18.1%) – did not reach the prespecified threshold for the lower bound of the 95% CI • Median DOR: 10.1 months • Median PFS: 2.8 months (95% CI: 1.5, 4.1) • PFS at 6 months: 22% • Median OS: 11.7 months (95% CI: 7.6, 13.4)

(*Continued*)

Table 1 (Continued).

Trial	Phase	N	CPI	Study Design	Tumor Type	Key Findings
KEYNOTE-189[36]	III	616	PEM	Pembrolizumab + pemetrexed + cisplatin/carboplatin Placebo + pemetrexed + cisplatin/carboplatin	Advanced NSCLC	• Median OS: 22.0 (95% CI: 19.5, 24.5) months vs 10.6 (95% CI: 8.7, 13.6) months (HR: 0.56; 95% CI: 0.46, 0.69) • Estimated 2-year OS: 45.7% vs 27.3% • Median PFS: 9.0 (95% CI: 8.1, 10.4) months vs 4.9 (95% CI: 4.7, 5.5) months (HR: 0.49; 95% CI: 0.41, 0.59) • Estimated 2-year PFS: 22.0% vs 3.4% • ORR: 48.3% (5 CR, 193 PR) vs 19.9% (1 CR, 40 PR) • Median DOR: 12.5 (range: 1.1, 34.9) months vs 7.1 (range: 2.4, 27.8) months
KEYNOTE-407[37]	III	559	PEM	Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel Placebo + carboplatin + paclitaxel/nab-paclitaxel	Metastatic NSCLC	• Median OS: 17.1 (95% CI: 14.4, 19.9) months vs 11.6 (95% CI: 10.1, 13.7) months (HR: 0.71; 95% CI: 0.58, 0.88) • OS rates: 12 months, 64.7% vs 49.6%; 18 months, 48.0% vs 36.5%; 24 months, 37.5% vs 30.6% • Median PFS: 8.0 (95% CI: 6.3, 8.4) months vs 5.1 (95% CI: 4.3, 6.0) months (HR: 0.57; 95% CI: 0.47, 0.69) • PFS rates: 12 months, 35.8% vs 17.7; 24 months, 18.6% vs 6.3% • ORR: 62.6% (6 CR, 168 PR) vs 38.4% (9 CR, 99 PR) • Median DOR: 8.8 (range: 1.3, 28.4) months vs 4.9 (range: 1.3, 28.3) months
POSEIDON[38]	III	1013	DUR +TREM	Tremelimumab + durvalumab + platinum-based chemotherapy Durvalumab + platinum-based chemotherapy Platinum-based chemotherapy	Metastatic NSCLC	• Median PFS: 6.2 months (95% CI: 5.0, 6.5) vs 5.5 (95% CI: 4.7, 6.5) months vs 4.8 (95% CI: 4.6, 5.8) months for T + D + CT vs D + CT vs CT • 12-month PFS rate: 26.6% vs 24.4% vs 13.1% • Median OS: 14.0 months (95% CI: 11.7, 16.1) vs 13.3 (95% CI: 11.4, 14.7) months vs 11.7 (95% CI: 10.5, 13.1) months for T + D + CT vs D + CT vs CT • 24-month OS rate: 32.9% vs 29.6% vs 22.1%
Phase II[39]	II	22	PEM	Pembrolizumab + entinostat	HL	• AEs: thrombocytopenia (32%) • 12-month PFS: 74%
CHECKMATE-205[40]	II	51	NIV	Nivolumab + doxorubicin + vinblastine + dacarbazine	Advanced HL	• CR rate: 69% • 21-month PFS: 80% (95% CI: 66, 89)

Abbreviations: AE, adverse event; ATEZ, atezolizumab; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; DUR, durvalumab; HDAC, histone deacetylase; HL, Hodgkin lymphoma; HR, hazard ratio; HR+, hormone receptor positive; IPI, ipilimumab; nab-paclitaxel, nanoparticle albumin–bound paclitaxel; NIV, nivolumab; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; pCR, pathological CR; PEM, pembrolizumab; PFS, progression-free survival; PR, partial response; Q-TWIST, quality-adjusted time without symptoms of disease or toxicity of treatment; SD, stable disease; TNBC, triple-negative breast cancer; TREM, tremelimumab.

upregulated the expression of PD-ligand (PD-L) 1 and, to a lesser degree, PD-L2 in human and murine melanoma cell lines as well as human melanoma xenografts. This upregulation was shown to be robust and durable, lasting over 96 hours.[41]

Clinical Studies

The open-label Phase II ENCORE-601 study evaluated pembrolizumab in combination with entinostat in patients with unresectable or metastatic melanoma previously treated with a PD-1-blocking antibody who had experienced progression on or after therapy.[25] Overall, 53 patients were enrolled, and the confirmed overall response rate (ORR) was 19% (1 complete response [CR] and 9 partial responses [PRs]; 95% confidence interval [CI]: 9, 32%), exceeding the threshold for success defined in the study protocol. Median PFS was 4.2 months and the tolerability profile of the combinations studied was acceptable.[25] Similarly, the Phase II PEMDAC trial of pembrolizumab and entinostat in a cohort of 29 patients with metastatic uveal melanoma reported manageable toxicities, durable objective responses, and prolonged survival (median OS: 13.4 months) in a subset of three patients with *BAP1* wild-type tumors.[26]

The Phase Ib/II SENSITIZE study combined domatinostat with pembrolizumab in patients with advanced melanoma refractory to prior CPI therapy.[24,42] Preliminary findings from the Phase Ib part of the study in a total of 40 patients revealed a manageable tolerability profile with signals of clinical activity.[42] The pharmacokinetic (PK) profile was dose dependent, and analysis of tumor biopsies showed domatinostat-induced alteration of the tumor microenvironment,

including infiltration of CD8+ T cells, the presence of PD-1/PD-L1-positive cells, and changes in gene expression levels.[24]

In another early-phase clinical study in 10 therapy-naïve patients with unresectable stage III/IV melanoma treated with ipilimumab and nivolumab in combination with mocetinostat, eight of nine patients treated with 70 mg mocetinostat achieved objective radiological responses.[43]

Alkylating Agents

Non-Clinical Studies

Combination therapy consisting of limb infusion of melphalan with cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blockade revealed improved survival, and tumor-specific immunity in murine models of melanoma when compared with treatment with either melphalan or CTLA-4 blockade alone.[44]

Combination Therapy Clinical Studies

Several clinical studies have demonstrated promising activity in patients with melanoma when treated with ipilimumab in combination with dacarbazine or temozolomide.[12,27–31] A Phase II study of ipilimumab plus temozolomide in 64 patients reported a 6-month PFS of 45% and a median OS of 24.5 months.[27] Overall, 10 (15.6%) patients achieved a CR and 10 (15.6%) a PR.[27] In a Phase II study in 72 chemotherapy-naïve patients with advanced melanoma, the ORR was 14.3% (95% CI: 4.8, 30.3) with ipilimumab plus dacarbazine vs 5.4% (95% CI: 0.7, 18.2) with ipilimumab alone. Median OS was 14.3 months (95% CI: 10.2, 18.8) vs 11.4 months (95% CI: 6.1, 15.6), respectively; and 12-month, 24-month, and 36-month survival rates were 62%, 24%, and 20% vs 45%, 21%, and 9%, respectively, for combination vs ipilimumab alone.[12]

Similarly, a Phase III study of 502 untreated patients with metastatic melanoma demonstrated that OS was significantly longer with ipilimumab plus dacarbazine vs dacarbazine alone (11.2 months vs 9.1 months, respectively). Survival rates at 1 year (47.3% vs 36.3%), 2 years (28.5% vs 17.9%), and 3 years (20.8% vs 12.2%) were also all higher with combination treatment vs dacarbazine alone (hazard ratio [HR] for death, 0.72; $P<0.001$).[29] Although little difference between groups was observed during the first year following treatment of patients with stage III/IV melanoma with dacarbazine in combination with either ipilimumab or placebo, after 2-, 3- and 4-years' follow-up of patients with extended survival, the benefits of adding dacarbazine for advanced melanoma continued to persist.[31] The long-term survival benefits of adding ipilimumab to a backbone of dacarbazine were assessed in a Phase III trial that examined 5-year survival rates in treatment-naïve patients with advanced melanoma.[30] This study noted that the 5-year survival rate was 18.2% (95% CI: 13.6%, 23.4%) for patients treated with ipilimumab plus dacarbazine vs 8.8% (95% CI: 5.7%, 12.8%) for those who received placebo plus dacarbazine ($P=0.002$), highlighting the durable survival benefit of the addition of ipilimumab in this patient population.[30] However, a Phase II study of ipilimumab plus dacarbazine in 15 Japanese patients with previously untreated, unresectable or metastatic melanoma considered this combination not to be tolerable due to high-grade liver toxicity, despite resulting in an ORR of 13% (2/15) and a disease control rate of 40% (6/15). There were no new safety signals and the overall safety profile was similar to previous studies, except for hepatotoxicity.[28]

Sequential Therapy Clinical Studies

Dacarbazine has also been studied as part of a sequential treatment regimen with CPIs; however, at present, only data from case studies or series rather than randomized controlled trial data are available.[45,46] Kan et al reported findings from four patients with advanced melanoma found to be refractory to nivolumab treatment.[45] These patients received dacarbazine followed by pembrolizumab, with two patients achieving a PR.[45] Saito et al reported the case of a 65-year-old woman who discontinued nivolumab treatment owing to adverse events (AEs), but experienced regression of both her primary tumor and lung metastases following three courses of dacarbazine therapy.[46]

Breast Cancer

HDACis

Non-Clinical Studies

A study examining the combination of entinostat with either anti-PD-1 or anti-CTLA-4 in a murine human epidermal

growth factor receptor 2 positive (HER2+) metastatic breast cancer model demonstrated that this treatment approach did not reduce pulmonary metastases or improve survival.[47]

Clinical Studies

Within the MORPHEUS platform of multiple, global, open-label, randomized Phase Ib/II trials, the anti-PD-L1 monoclonal antibody, atezolizumab was investigated in combination with the HDACi, entinostat in 15 patients with locally advanced or metastatic hormone receptor positive (HR+) HER2 negative (HER2-) breast cancer.[32] Limited efficacy for this combination was observed, with an ORR of 6.7% (95% CI: 0.17, 31.95), a duration of response of 2.5 months, and a median PFS of 1.8 months. The observed safety profile was consistent with each agent's known safety profile.[32]

AAs

Non-Clinical Studies

In a murine model of estrogen receptor-positive, progesterone receptor-positive, HER2+ (ER+/PR+/HER2+) breast cancer (EMT-6/P), the addition of low-dose cyclophosphamide to CTLA-4 blockade inhibited tumor growth; however, administration of bolus cyclophosphamide impaired the efficacy of CTLA-4 blockade.[48] This study also demonstrated that concomitant or sequential administration of gemcitabine with CTLA-4 blockade was similarly effective, with no significant differences in outcome with either form of administration.[48] A single-cell atlas study investigated CPI in combination with platinum, doxorubicin, taxol, vinorelbine and cyclophosphamide chemotherapy in models of TNBC and non-Hodgkin lymphoma (NHL).[49] The findings from this study indicated that intermittent medium-dose cyclophosphamide in combination with a CPI was more effective than other combinations, with the addition of vinorelbine further increasing efficacy by controlling local and metastatic neoplastic growth.[49]

Combination Therapy Clinical Studies

Clinical data from the Phase II NeoPACT study demonstrated that combination treatment with pembrolizumab plus carboplatin-based triplet chemotherapy produced good pathological CR rates in TNBC.[33] A total of 117 patients with TNBC were enrolled in this multicenter, single-arm trial to receive neoadjuvant therapy with carboplatin in combination with docetaxel and pembrolizumab. Pathological CR and residual cancer burden 0+1 rates were found to be 60% (95% CI: 51%, 70%) and 71% (95% CI: 62%, 80%), respectively, and 2-year event-free survival was 88%. Treatment-related AEs led to discontinuation of trial drug in 12% of patients, with immunologic AEs observed in 28% of patients (Grade ≥3, 6%), demonstrating that the regimen was generally well tolerated with no new safety signals.[33]

Sequential Therapy Clinical Studies

Durvalumab was administered 2 weeks prior to the commencement of cyclophosphamide treatment in the multicenter, prospective, randomized, double-blind, placebo-controlled Phase II GeparNuevo trial. There was a numerically, but not statistically, significant increase in the pathological CR rate in patients with TNBC who received combination therapy compared with those who received chemotherapy alone.[34] Similarly, in the Phase III IMpassion031 trial, administration of neoadjuvant atezolizumab with nab-paclitaxel, followed by combination treatment with cyclophosphamide-containing chemotherapy was shown to be beneficial in patients with early-stage TNBC.[2] Pathological CR occurred in 95/165 (58%, 95% CI: 50, 65) patients in the atezolizumab plus chemotherapy group and 69/168 (41%, CI: 34, 49) patients in the placebo plus chemotherapy group (rate difference 17%, 95% CI: 6, 27; one-sided P=0.0044 [significance boundary 0.0184]).[2]

Lung Cancer

HDACis

Non-Clinical Studies

There are few non-clinical studies examining CPIs in combination with HDACis in lung cancer; however, findings from a study by Hicks et al suggest that exposure of a diverse array of human carcinoma cells to a clinically relevant dose of

either the pan-HDACi vorinostat or the class I HDACi entinostat may increase the sensitivity of lung and prostate cancer xenografts to the antibody-dependent cellular cytotoxicity of avelumab.[50]

Clinical Studies

Findings for the combination of PD-1 inhibitors with HDACis in NSCLC have been mixed, with further research required to fully evaluate this treatment approach. A Phase I/Ib study of vorinostat plus pembrolizumab resulted in a disease control rate of 58% in a CPI pre-treated patient population (n=33), demonstrating preliminary anti-tumor activity.[51] In addition, tumor response data from a Phase Ib study of citarinostat plus nivolumab suggest that this combination may be a feasible treatment option in patients with advanced NSCLC (n=17); however, given the totality of the safety profile, including Grade 3 nausea lasting for more than 72 hours despite treatment and a fatal (Grade 5) cardiac arrest considered related to study treatment, further research may be needed to understand the use of this combination.[52] Findings from the ENCORE 601 Phase II study in anti-PD-L1-experienced patients recorded an ORR of 9.2% (95% CI: 3.8, 18.1) in 71 evaluable patients treated with entinostat plus pembrolizumab, which did not meet the protocol prespecified threshold for promising activity. Median duration of response was 10.1 months (95% CI: 3.9, not-estimable [NE]), PFS at 6 months was 22%, median PFS was 2.8 months (95% CI: 1.5, 4.1), and median OS was 11.7 months (95% CI: 7.6, 13.4).[35]

AAs

Combination Therapy Clinical Studies

Both SCLC and NSCLC have been targets for clinical studies investigating CPI combination therapy, with the combination of CPIs with platinum-based chemotherapy found to improve patient outcomes resulting in significantly longer PFS, higher ORR, and improved patient quality of life when compared with chemotherapy alone.[4,5,36–38,53–63] For example, the Phase III KEYNOTE-189 study investigated the effects of adding pembrolizumab to a backbone of pemetrexed and platinum-based chemotherapy in patients with previously untreated NSCLC.[36] Compared with chemotherapy alone, pembrolizumab plus chemotherapy improved OS (HR: 0.56 [95% CI: 0.46, 0.69]), PFS (HR: 0.49 [95% CI: 0.41, 0.59]), and ORR (19.9% vs 48.3%).[36] In addition, findings from the Phase III KEYNOTE-407 study, in which treatment-naïve patients with NSCLC received paclitaxel and platinum-based chemotherapy with or without pembrolizumab demonstrated significantly improved OS (median, 17.1 months [95% CI: 14.4, 19.9] vs 11.6 months [95% CI: 10.1, 13.7]; HR: 0.71 [95% CI: 0.58, 0.88]) and PFS (median, 8.0 months [95% CI: 6.3, 8.4] vs 5.1 months [95% CI: 4.3, 6.0]; HR: 0.57 [95% CI: 0.47, 0.69]) in those patients who received combination therapy vs those on chemotherapy alone.[37]

In contrast, an open-label, randomized, Phase II trial conducted in SCLC demonstrated a significant improvement in OS but not PFS when patients received pembrolizumab in combination with cisplatin/carboplatin plus etoposide vs pembrolizumab monotherapy.[6] Furthermore, neoadjuvant toripalimab in combination with platinum-based chemotherapy in patients with potentially resectable NSCLC allowed an R0 resection (microscopically margin-negative resection) rate of 100% without serious surgical complications in Phase II trials.[4,5]

Two recent Phase II studies combining atezolizumab plus carboplatin-based chemotherapy showed positive outcomes in patients with NSCLC, with a median OS of 13.6 and 18.9 months, and median PFS of 8.9 and 7.4 months reported by each study, respectively.[64,65] Moreover, a Phase III trial of 550 patients who received nivolumab in combination with carboplatin-based chemotherapy demonstrated significant improvements in PFS compared with the placebo plus carboplatin arm.[55] Furthermore, the IMpower Phase III studies showed that the addition of atezolizumab to carboplatin-based chemotherapy led to improvements in OS and PFS compared with chemotherapy alone in SCLC and NSCLC, with more long-term survivors among patients receiving combination therapy, and no new safety signals.[66–71] Interim findings from a study of camrelizumab in combination with cisplatin-based chemotherapy also indicated improvements in ORR (86.7%) compared with chemotherapy alone (57.1%).[56] In addition, a large multicenter, Phase II, single-arm study of durvalumab in combination with neoadjuvant cisplatin-based chemotherapy demonstrated the tolerability of this regimen with an encouraging 1-year event-free survival of 73.3% (n=55) in patients with NSCLC.[72]

The Phase III open-label POSEIDON study examined the combination of tremelimumab and durvalumab plus platinum-based chemotherapy vs durvalumab plus chemotherapy vs chemotherapy alone for the first-line treatment of metastatic NSCLC.[38] PFS was significantly improved with durvalumab plus chemotherapy vs chemotherapy alone (HR: 0.74 [95% CI: 0.62, 0.89]; P=0.0009; median, 5.5 vs 4.8 months, respectively); however, this trend for improved OS did not reach statistical significance (HR: 0.86 [95% CI: 0.72, 1.02]; P=0.0758; median, 13.3 vs 11.7 months, respectively; 24-month OS, 29.6% vs 22.1%, respectively). The addition of tremelimumab to durvalumab plus chemotherapy resulted in a further significant improvement in PFS (HR: 0.72 [95% CI: 0.60, 0.86]; P=0.0003; median, 6.2 vs 4.8 months, respectively) and OS (HR: 0.77 [95% CI: 0.65, 0.92]; P=0.0030; median, 14.0 vs 11.7 months, respectively; 24-month OS, 32.9% vs 22.1%, respectively) as compared with chemotherapy alone.[38]

Sequential Therapy Clinical Studies

A recent Phase II study examined the sequential administration of durvalumab immediately after platinum-based doublet chemotherapy in 42 patients. This study reported a 1-year PFS rate from registration of 75.0% (60% CI: 69.0, 80.0) and 1-year OS rate from registration of 97.7% (95% CI: 84.6, 99.7).[73]

Hodgkin Lymphoma

HDACis

Clinical Studies

Combination therapy with PD-1 inhibitors and vorinostat induced positive responses in patients with HL, including those refractory to prior PD-1 treatment. As part of a Phase I study, 32 patients with HL, 78% of whom had prior PD-1 blockade, and 56% of whom were PD-1 refractory, received vorinostat in combination with pembrolizumab. Among anti-PD-1-naïve/sensitive patients, the ORR and CR rates were 93% and 64%, respectively. Among PD-1 refractory patients, the ORR and CR rates were 56% and 6%, respectively.[74] In a second Phase I study of patients with lymphoma treated with vorinostat plus pembrolizumab, the two evaluable patients with HL both responded to treatment, achieving PRs despite being previously refractory to PD-1 blockade.[75]

Early data from a Phase II trial of the combination of entinostat plus pembrolizumab demonstrated good tolerability, with an ORR of 100% among five patients with HL, including a PR in a patient who had previously received both entinostat and pembrolizumab as monotherapy.[76] In a second Phase II trial, 22 eligible patients with HL treated with entinostat plus pembrolizumab achieved an ORR of 86% and a CR rate of 45%.[39] Interestingly, responding patients included nine who had received prior anti-PD-1-antibody therapy and three who had received prior HDACi therapy.[39]

AAs

Combination Therapy Clinical Studies

In a pilot study, concurrent combination therapy with pembrolizumab plus adriamycin, vinblastine and dacarbazine (AVD) for untreated HL was shown to be well tolerated without any dose delays, serious AEs, or immune-related AEs ≥ Grade 2. All six patients enrolled achieved an objective response, with 3/6 achieving a CR by interim scan, and 3/6 a PR with a Deauville score of 4.[77] Similarly, the combination of a PD-1 inhibitor with other alkylating chemotherapy agents in Phase II studies produced favorable outcomes in patients with HL with manageable tolerability profiles. A high ORR of 80% was recorded in 41 adult patients with relapsed-refractory (R/R) HL who received up to three 28-day cycles of bendamustine and nivolumab, with 44% of patients achieving a CR.[78] In another study, 61.5% (8/13) of patients treated with camrelizumab plus gemcitabine and oxaliplatin achieved a CR and 30.8% (4/13) a PR, resulting in an ORR of 92.3% at the first tumor response evaluation.[79] The combination of pembrolizumab with COPDAC-28 (cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine) in pediatric patients with high-risk HL resulted in 68% of patients having a positron emission tomography (PET)-negative response at end of treatment.[80] Finally, the combination of nivolumab with doxorubicin, dacarbazine and brentuximab vedotin resulted in an ORR of 93% (95% CI: 82.7, 98.0) with 88% (95% CI: 75.9, 94.8) of patients achieving a CR.[81]

Sequential Therapy Clinical Studies

Sequential therapy with CPIs followed by AAs has also been studied. Fifty-one patients with newly diagnosed HL, treated with nivolumab followed by nivolumab plus AVD (N-AVD) demonstrated a 21-month PFS rate of 83% and a complete metabolic response rate of 75% at end of treatment, with no new safety signals.[40] Similarly, a Phase II study in 30 patients with R/R HL who received sequential treatment with pembrolizumab and AVD showed that, following pembrolizumab monotherapy, 11/30 patients (37%) achieved complete metabolic response (CMR), and an additional 7/28 (25%) patients with quantifiable PET scans had >90% reduction in metabolic tumor volume; all patients achieved CR after 2 cycles of AVD and maintained their responses at the end of treatment.[82]

Combination and Sequential Therapy Clinical Studies

Both concomitant or sequential treatment with PD-1 inhibitors and doxorubicin, vinblastine, and AVD result in favorable outcomes in patients with HL. Adult patients with unfavorable HL (defined as Stage IA, IB, IIA, or IIB disease in association with risk factors such as extranodal disease or involvement of ≥3 nodal areas) were randomized in a Phase II trial to receive either concomitant treatment with 4 cycles of N-AVD or sequential treatment with 4 doses of nivolumab, 2 cycles of N-AVD, and 2 cycles of AVD at standard doses, followed by 30Gy involved-site radiotherapy.[1] Among 101 patients eligible for primary endpoint analysis, 46/51 (90%; 95% CI: 79, 97%) patients receiving concomitant therapy and 47/50 (94%; 95% CI: 84, 99%) patients receiving sequential therapy achieved a CR after study treatment. With a median follow-up of 13 months, 12-month PFS was 100% for patients receiving concomitant treatment and 98% (95% CI: 95, 100%) for patients receiving sequential therapy.[1]

Discussion

The aim of this review was to identify and examine data relating to the combination of CPIs with either AAs or HDACis following analysis of several published articles and abstracts. Non-clinical studies have demonstrated the efficacy of this treatment approach in tumor models and suggest that caution may be required when determining dose and dosing of AAs with CPIs.

Non-clinical studies suggest that the administration of certain HDACis induces a durable upregulation of the expression of PD-L1 and PD-L2 in melanoma cell lines and patient tumors.[41] Similarly, signals of efficacy together with changes in the tumor microenvironment have been noted in patients with melanoma refractory to prior CPI therapy when treated with a combination of a CPI and an HDACi.[24] Although clinical studies conducted to date to examine the benefits of combining CPIs and HDACis for the treatment of melanoma are early-phase and non-comparative, the findings from these demonstrate objective responses, potentially owing to epigenetic changes that enhance the sensitivity of tumor cells to CPIs. Similarly, findings from non-clinical and clinical studies suggest that the combination of a CPI with AAs, or sequential administration of these agents could potentially be an effective strategy to improve outcomes in patients with metastatic melanoma.[12,28–31,45,46]

Published non-clinical and clinical evidence suggest there are limited benefits to combining CPIs with HDACis for the treatment of breast cancer.[47] It should be noted, however, that HR+ HER2- breast cancer is particularly unresponsive to CPI, and the only breast cancer subtype in which CPIs have been approved so far is TNBC.[83] In contrast, non-clinical studies suggest that the addition of low- or medium-dose cyclophosphamide or gemcitabine to a CPI inhibits tumor growth in murine breast cancer models.[48] These findings concur with those from clinical studies, where data suggest that the combination of a CPI with platinum-based chemotherapy or administration of a CPI prior to AA therapy improves CR rates in patients with breast cancer compared with AA treatment alone.[34]

Published non-clinical evidence suggests that the epigenetic effects of HDACis may potentiate CPI efficacy in lung cancer xenografts.[50] Clinical findings, however, are less well defined, with a limited pool of studies and no definitive data demonstrating a benefit for this combination across studies.[35,51,52] The majority of clinical studies in lung cancer investigated a range of CPIs in combination with platinum-based chemotherapy and reported enhanced outcomes, including longer PFS and OS, and improved response rates when compared with chemotherapy alone. In addition, the inclusion of a second CPI with a different target may further improve outcomes for this group of patients.[4,5,36–38,53–63,73]

Combination therapy for patients with HL using CPIs plus vorinostat or entinostat resulted in good response rates, including in patients previously refractory to CPI treatment or who progressed following treatment with one or both of the agents given as combination therapy.[39,74–76] It would appear likely, therefore, that the epigenetic effects of HDACis potentiated the efficacy of CPIs in these studies. The administration of a CPI with AA monotherapy or combination therapy resulted in good rates of CR and PR, including in patients with R/R HL and pediatric patients.[77–81] Similarly, high ORRs and reductions in metabolic tumor volume were observed in patients with HL who received a CPI prior to the administration of AA therapy.[40,82]

The majority of clinical studies identified used concomitant dosing of a CPI with either an AA or an HDACi, often in patients who progressed following prior therapies. Several studies examining CPIs plus HDACis note that the epigenetic properties of HDACis may alter the tumor microenvironment, including in patients refractory to prior CPI therapy in some tumor types.[41] It is possible that such alterations may potentiate tumor responses to CPI treatment. However, the combination of a CPI with an HDACi was shown to have limited benefits in patients with HR+ HER2- breast cancer.[47] Available sequential studies suggest both concomitant and sequential administration are effective. Anti-PD-1 agents were the most studied class of CPIs and were predominantly combined with AAs. However, superior efficacy, when compared to single-agent administration, has been observed for all classes of CPIs when combined with certain AAs or HDACis.

The comparative clinical studies identified, all of which reported on the combination of a CPI with an AA, demonstrated superior outcomes in the combination arm compared with the monotherapy arm, regardless of which agent was present in the control arm.[29]

The studies examined in this review article indicate potential interactions between CPIs and AAs or HDACis when administered in combination. Some studies have aimed to elucidate the mechanisms underlying their observations, for example, non-clinical studies of panobinostat in combination with PD-1 blockade in melanoma noted an upregulation of PD-L1 and PD-L2,[41] while domatinostat in combination with pembrolizumab was observed to induce alterations in the tumor microenvironment.[24] Moreover, certain HDACis, including vorinostat and entinostat, have been suggested to increase the sensitivity of tumor xenografts to avelumab.[50] Across tumor types, the combination of CPIs with AAs appears to provide beneficial outcomes; however, not all HDACi and CPI combinations appear to be similarly effective. For example, the combination of entinostat with an anti-PD-1 or CTLA-4 agent, or atezolizumab in non-clinical breast cancer models, or with pembrolizumab in patients with NSCLC,[35] demonstrated limited efficacy,[32,47] despite the combination of entinostat and pembrolizumab appearing to be effective in patients with HL.[39,76] Thus, further non-clinical and clinical studies are required to more accurately examine the mechanisms underlying any potential synergy between these disparate agents to more fully understand how they might interact and potentiate each other's mechanisms of action. There is also a need to more fully examine which CPIs, AAs and HDACis provide the best combination regimen to ensure optimal outcomes for each tumor type.

Strengths of this analysis include the wide scope of articles reviewed during the literature search and the inclusion of studies detailing comparative data for combination and non-combination regimens. Limitations include the narrative nature of this article whereby no systematic meta-analysis of the published data has been conducted.

Conclusion

In conclusion, the findings from this literature review suggest that the sequential or concomitant administration of a CPI with an AA or an HDACi may improve outcomes for patients with a range of tumor types. In addition, there are indications of epigenetic effects of HDACis that may re-sensitize refractory tumors to CPIs. Thus, there is a rationale to support an investigation into the potential for synergy between CPIs and alkylating agents and/or histone deacetylase inhibitors in both non-clinical and clinical settings.

Abbreviations

AA, alkylating agent; AACR, American Association for Cancer Research; AE, adverse event; ASCO, American Society of Clinical Oncology; ASH, American Society for Hematology; ATEZ, atezolizumab; AVD, adriamycin + vinblastine + dacarbazine; CI, confidence interval; CMR, complete metabolic response; COPDAC-28, cyclophosphamide, vincristine,

prednisone/prednisolone, dacarbazine; CPI, checkpoint inhibitor; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; EHA, European Hematology Association; ER+, estrogen receptor positive; ESMO, European Society for Medical Oncology; HDAC, histone deacetylase; HER2+/-, human epidermal growth factor receptor 2 positive/negative; HL, Hodgkin lymphoma; HR, hazard ratio; HR+, hormone receptor positive; ICML, International Conference on Malignant Lymphoma; IPI, ipilimumab; N-AVD, nivolumab and AVD; NE, not-estimable; NHL, non-Hodgkin lymphoma; NIV, nivolumab; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1/2, PD-ligand-1/2; PEM, pembrolizumab; PET, positron emission tomography; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; PR+, progesterone receptor positive; R0, microscopically margin-negative resection; R/R, relapsed-refractory; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer; TREM, tremelimumab.

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Author Contributions

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