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Combining epigenetic and immune therapy to overcome cancer resistance

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Abstract

Cancer undergoes “immune editing” to evade destruction by cells of the host immune system including natural killer (NK) cells and cytotoxic T lymphocytes (CTLs). Current adoptive cellular immune therapies include CAR T cells and dendritic cell vaccines, strategies that have yet to show success for a wide range of tumors. Cancer resistance to immune therapy is driven by extrinsic factors and tumor cell intrinsic factors that contribute to immune evasion. These extrinsic factors include immunosuppressive cell populations such as regulatory T cells (T_{regs}), tumor-associated macrophages (TAMS), and myeloid-derived suppressor cells (MDSCs). These cells produce and secrete immunosuppressive factors and express inhibitory ligands that interact with receptors on T cells including PD-1 and CTLA-4. Immune checkpoint blockade (ICB) therapies such as anti-PD-1 and anti-CTLA-4 have shown success by increasing immune activation to eradicate cancer, though both primary and acquired resistance remain a problem. Tumor cell intrinsic factors driving primary and acquired resistance to these immune therapies include genetic and epigenetic mechanisms. Epigenetic therapies for cancer including DNA methyltransferase inhibitors (DNMTi), histone deacetylase inhibitors (HDACi), and histone methyltransferase inhibitors (HMTi) can stimulate anti-tumor immunity in both tumor cells and host immune cells. Here we discuss in detail tumor mechanisms of immune evasion and how common epigenetic therapies for cancer may be used to reverse immune evasion. Lastly, we summarize current clinical trials combining epigenetic therapies with immune therapies to reverse cancer immune resistance mechanisms.

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Competing Interests

The authors declare no competing interests.

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Cancer Immune Evasion

Cancer cells avoid the immune response in a process known as “immune editing” or immune evasion[1]. Initially, lymphocytes including cytotoxic T cells and natural killer (NK) cells target cancer cell elimination by secreting perforin and granzyme or by the death ligand/death receptor pathway [2]. Perforin creates pores in the membrane of the target cell, which allows granzyme to enter, triggering apoptosis. Death ligands like TNFα, FasL or TRAIL secreted by or expressed on the surface of cytotoxic T cells or NK cells interact with death receptors on cancer cells to trigger apoptosis[2]. Though these cancer elimination mechanisms are the same in cytotoxic T cells and NK cells, the activation of these two cell types differs. NK cells have non-specific cell targets and are activated when activating receptors are stimulated more than inactivating receptors by ligands expressed by the cancer cell[3]. For instance, MHC class I is an NK cell inhibitory ligand expressed by the cancer cell. On the contrary, cytotoxic T cells are specific to peptides presented by MHC class I molecules, so expression of MHC class I molecules is required for cytotoxic T cell activation. Activation of the cytotoxic function requires TCR-CD3 complex recognition of the specific peptide bound to the MHC class I, as well as two co-stimulatory signals through the CD8 and CD28 molecules[2]. Activation of NK cells results in immediate cytotoxic function, whereas activation of CD8 T cells requires priming by an antigen-presenting cell and then time to develop cytotoxic function. During cancer initiation, cells including natural killer cells and T effector cells fight and kill the cancer cells, but as tumors progress they exhibit mechanisms of immune suppression. These include expression of PD-L1, a ligand for the PD-1 protein on CD3 T cells, that inhibits killer T cell action against tumor cells. In addition, T regulatory cells that express CTLA-4 and normally suppress autoimmunity secrete cytokines to inhibit the action of T and NK cells against tumors[1]. In addition, suppressive immune cell populations can infiltrate tumors to promote immune evasion.

Regulatory T cells

Regulatory T cells (T_{regs}) play a key role in suppressing effector T cell (T_{eff}) immune responses in order to maintain self-tolerance[4]. T_{regs} suppress immune responses through the secretion of cytokines that inhibit effector T cells. These cytokines include IL-35, IL-10, and TGF-β[5]. In the tumor microenvironment, T_{regs} downregulate antitumor immune responses. In many human tumor types, there is increased infiltration of T_{regs} into the tumor microenvironment[6]. In addition, elevated levels of T_{regs} are associated with increased tumor invasion, and a more favorable balance of T effector cells to T regulatory cells is associated with better patient outcomes[7].

Tumor-Associated Macrophages

Macrophages are phagocytic myeloid cells that reside in tissues and act as immune sensors[8]. Tumor-associated macrophages (TAMs) contribute to resistance to immune therapy through

a variety of mechanisms. TAMs include both M1 macrophages (classically activated) and M2 macrophages (alternatively activated), though M2 macrophages are the majority in many tumor types[9]. These TAMs are recruited to tumors in large numbers by chemokines such as CSF1, CCL2, and CXCL12[10]. M2 macrophages promote tumor progression and metastasis, and TAM infiltration is associated with poor prognosis in cancers[11]. TAMs suppress antitumor immunity through the recruitment of MDSCs to the tumor and can suppress the T cell immune response directly through the expression of the immunosuppressive ligand PD-L1[10].

Myeloid Derived Suppressor Cells

Another class of immune cells with an inhibitory effect on the anti-tumor immune response are myeloid derived suppressor cells (MDSCs). MDSCs are associated with the promotion of angiogenesis and tumor invasion and create an immunosuppressive environment that promotes the growth of malignant cells[12]. Activated MDSCs recruit T_{regs} through the secretion of TGF-B and IL-10[13]. MDSCs also inhibit anti-tumor cells such as CTLs, dendritic cells, and NK cells[14], creating a suppressed immune environment that promotes cancer growth[13]. MDSCs express arginase, which inhibits T cell and NK cell proliferation through the depletion of L-arginine[15]. Additionally, MDSCs express high levels of inducible NO synthase (iNOS), which leads to the accumulation of NO and causes T cell anergy through inhibition of the IL-2 pathway. MDSCs produce high concentrations of reactive oxygen species (ROS) which are known to impair TCR signaling and induce T cell apoptosis. MDSCs express high levels of indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan, inducing anergy and cell cycle arrest in T cells. MDSCs can also inhibit T cells through the expression of immunosuppressive ligands such as PD-L1 and death receptor CD95[13]. Increased MDSC frequency is correlated with poor patient prognosis[16] and increased levels of MDSCs in the tumor microenvironment are associated with increased resistance to immune therapies[17].

Cancer immunotherapy

Adoptive cell therapies

As our understanding of the immune system’s capacity for anti-tumor response grows, researchers have developed new strategies to initiate and strengthen the anti-tumor immune response including adoptive T cell therapy, CAR T cell therapy, and dendritic cell vaccines. The anti-tumor immune response depends most basically upon the ability of T cells to infiltrate the tumor while being able to recognize and react to cancer-specific antigens. One method for achieving this is Chimeric Antigen Receptor (CAR) T cell therapy. CAR T cells are engineered to express synthetic receptors specific to cancer cells, allowing for subsequent tumor elimination[18]. CAR T cells have demonstrated success in eradicating specific hematological cancers including acute lymphoblastic leukemia[19]. B cell leukemia patients who were treated with CD19 CAR T cell therapy showed complete eradication of the cancer and significantly improved outcomes. However, clinical results in solid tumors have been less impressive due to difficulty selecting a suitable target antigen and lower T cell infiltration[20]. In addition, while CAR T cell therapy has displayed encouraging results, significant issues remain with regards to toxicity. CAR T cell therapy may cause Cytokine

Release Syndrome (CRS), a spectrum of inflammatory symptoms caused by immune activation of large numbers of lymphocytes that can be very toxic to patients[21].

Cytokine-Induced Killer (CIK) cells are a similar type of adoptive cell therapy that have proven to be better tolerated than CAR T cell therapy. CIK cells are a heterogenous preparation of natural killer (NK) cells and CD3+ T lymphocytes that possess enhanced cytotoxic activity, allowing them to recognize and kill tumor cells with minimal residual disease[22,23]. Thus far, clinical trials with CIK adoptive cell therapy have shown a recurrence-free survival (RFS) benefit and overall survival (OS) benefit in some cases[24].

Another class of adoptive cell therapy seeks to harness the power of dendritic cells, the immune system's most potent antigen-presenting cells. Dendritic cell vaccines load dendritic cells with antigens which, upon administration, activate antigen-specific T cells to trigger an immune response[25]. In many clinical trials, DC vaccines induce tumor-specific T cell responses, though significant evidence for clinical efficacy of DC vaccines alone is yet to be seen[26]. The combination of DC vaccines with other therapies has shown promise in several clinical trials and is an area of active research.

CTLA-4 Immune Checkpoint and Drug Target

Immune checkpoints are pathways within the immune system that normally maintain self-tolerance but can be co-opted by tumors to evade destruction. By disrupting these pathways with monoclonal antibodies, immune checkpoint therapies can strengthen the anti-tumor immune response and improve patient outcomes[27]. One of the best characterized immune checkpoints is CTLA-4, a receptor on the surface of T cells that acts as a negative regulator of T cell activation when bound to a B7 protein on the surface of an antigen-presenting cell[28]. CTLA-4 also plays a major role in driving the suppressive function of regulatory T cells, ultimately inhibiting effector T cell responses[29]. Blocking the CTLA-4 pathway with anti-CTLA-4 monoclonal antibodies including ipilimumab and tremilimumab leads to more T cell activation and proliferation and reduced T_{reg}-mediated immunosuppression. The anti-CTLA-4 drug ipilimumab produces significant, durable responses in about 20% of melanoma patients but has not shown similar promise in clinical trials for other solid tumors, exhibiting less than 10% response rates[27,30].

PD-1 Immune Checkpoint and Drug Target

Programmed Death 1 (PD-1) checkpoint bears similarities to CTLA-4, ultimately acting as a negative regulator of T cell function. When PD-L1 binds to PD-1, it inhibits T cell proliferation and cytokine production, decreasing the T cell immune response[31]. Monoclonal antibodies blocking PD-1 produce an anti-tumor response in a variety of cancers. Melanoma patients exhibit the best response to anti-PD-1 (about 30% objective response rate) with renal cell carcinoma (30%) and non-small cell lung cancer (about 20%) close behind[27,32]. However, many common solid tumors such as breast, colon, ovarian, and pancreatic cancer have less than a 10% overall response rate to anti-PD-1[27].

In addition to anti-CTLA-4 and anti-PD1 therapies, many other receptors are the subject of ongoing research for cancer therapeutics, including LAG-3, Tim-3, VISTA, ICOS, OX40 and 4–1BB[33]. LAG-3 inhibits TCR signaling by interacting with MHC II[34], and Tim-3

inhibits T cells through the binding of ligands which include Galectin-9, Ceacam1 and HMGB1[35]. VSIG-3 is the ligand for VISTA, which also acts by inhibiting T cells[36]. OX40, 4–1BB and ICOS are all co-stimulatory molecules, therefore interactions with OX40 (CD134) and 4–1BB (CD137) enhance T cell differentiation and cytotoxic function. Antibodies against LAG-3, Tim-3, or VISTA block T cell inhibition (antagonist) whereas antibodies against OX40, 4–1BB or ICOS act as agonists, augmenting T cell function[37]. Therapies targeting these receptors are in the preclinical stages of development and have the potential to yield exciting responses either alone or in combination with anti-CTLA-4 or anti-PD-1.

Resistance to immunotherapy in cancers

The above immune therapies demonstrate significant advances for the treatment of many different types of cancer. However, as noted, none is curative for a majority of patients. Cancer resistance to immune therapy results from a variety of factors within the tumor microenvironment that can either prevent cytotoxic anti-tumor cells from infiltrating or make it unfavorable for these cells to survive and function appropriately upon infiltration. The unfavorable microenvironment is largely due to two main immunological factors: immunosuppressive cytokines and inhibitory immune checkpoints. Suppressive immune cells are the main contributors to this unfavorable tumor microenvironment. Cancer resistance to immunotherapy can also result from tumor cell-intrinsic factors, which can be categorized as primary or acquired resistance. Primary resistance is natural resistance to immunotherapy that can occur prior to treatment (non-responders), while acquired resistance can develop in response to immunotherapy treatment (initial responders who relapse). Mechanisms of primary resistance may include a reduction in antigen expression, changes in cell surface receptor expression, and changes in metabolic pathways[38].

Cancer resistance to immune therapy is epigenetically controlled

Just as cancers are defined by genetic alterations, the epigenetic landscape of cancers is significantly altered compared to normal cells. Cancers exhibit changes in the silencing DNA methylation modification. DNA methylation is the addition of a methyl group to the cytosines of CpG dinucleotides by DNA methyltransferases (DNMTs). Cancers generally exhibit global loss of methylation at repetitive element regions, which are silenced to preserve genome stability in normal cells[39]. Conversely, cancers exhibit a gain of methylation and other suppressive epigenetic modifications at the promoter regions of tumor suppressor genes[39]. Therapies that target DNA methylation have shown promise in many types of cancer. 5-azacytidine (Aza) is a cytidine analog that inhibits DNMTs, triggering their degradation and re-expression of genes silenced by promoter DNA methylation[40]. Aza and another demethylating agent, 5-aza-2’-deoxycytidine (Decitabine or Dac), are approved by the FDA for the treatment of myelodysplastic syndrome[41]. Recent evidence from pre-clinical studies and clinical trials suggests that DNMTis may reverse immune evasion in cancers.

Another epigenetic silencer, histone deacetylases (HDACs), are a family of enzymes that remove acetyl groups from histones. There are four zinc dependent classes of HDACs which

include Class I (HDAC 1, 2, 3, 8), Class IIa (HDAC 4, 5, 7, 9), Class IIb (HDAC 6, 10) and Class IV (HDAC 11) enzymes. The Class III enzymes or sirtuins are non-zinc dependent[42]. HDACs remove negatively charged acetyl groups from the positively charged histone proteins that DNA is wrapped around, compacting the chromatin and silencing genes. Histone deacetylases inhibitors (HDACi) function by interfering with HDACs and like DNMTis can reverse transcriptional inhibition of tumor suppressor genes. The HDACi suberoylanilide hydroxamic acid (SAHA) was approved for the treatment of persistent or cutaneous T cell lymphoma in 2006. Like DNMTis, recent work has shown that HDACis can also stimulate anti-tumor immunity[42,43].

Histone methyltransferase (HMT) enzymes deposit methylation residues on specific lysines of histones, establishing patterns of gene expression, and thus have essential roles in cell cycle regulation and development. HMTs that are overexpressed in cancer include DOT1L, which catalyzes up to three methyl groups to histone H3, lysine 79; G9a, which induces H3K9me; and EZH2, which adds H3K27 methylation. All three of these are silencing marks and inhibiting the HMTs responsible opens up the chromatin to activate gene expression, similar to the effects of DNMTis and HDACis[39].

Tumors undergo immunoediting as an adaptive mechanism to evade the immune system, and a growing body of evidence implicates epigenetic control of this immune resistance. Immunoediting often involves downregulation of MHC I or loss of antigen expression, resulting in an overall loss of antigen presentation. MHC class I genes in human breast cancer are suppressed due to silencing DNA methylation marks at their promoter regions. DNA methylation inhibition reversed MHC I gene promotor methylation and upregulated gene expression in response to interferon[44]. Additionally, Wylie *et al.* found that downregulated expression of immunogenic antigens correlated with immune escape from adoptive cell therapy. Treating with DNA demethylating agents restored expression of these immunogenic antigens[45].

Epigenetic regulation of MHC-I antigen presentation by the polycomb repressive complex can lead to immunotherapy resistance[46]. Burr *et al.* showed that an important function of polycomb repressive complex 2 (PRC2) is its ability to mediate the silencing of the MHC-I antigen processing pathway, which leads to the evasion of T-cell mediated immunity. *Siebenkäs et al.* showed that both colon and ovarian cancer cells have lower expression of the antigen processing and presentation machinery, preventing tumor detection by CD8 T cells. Treating with DNMT inhibitors increased expression of both the antigen processing and presentation genes and cancer testis antigens (CTAs)[47]. Specific molecules that were upregulated upon treatment included B2M, CALR, CD58, PSMB8, and PSMB9[47]. Siebenkäs *et al.* thus demonstrate how treatment with DNMT inhibitors might sensitize patients to immunotherapy by upregulating the expression of antigen processing and presentation molecules. Similarly, Gameiro *et al.* utilized HDAC inhibitors to upregulate silenced antigen processing and presentation machinery in prostate and breast cancer cells. Gameiro *et al.* demonstrate that exposure to HDAC inhibitors can reverse the ability of tumors to evade immune attack. After HDACi treatment, the tumor cells exhibited increased sensitivity to T-cell mediated lysis[48]. Thus, repressive histone modifications and DNA

methylation silence antigen processing and presentation in cancers to promote immune evasion.

The high rate of proliferation of tumor cells also contributes to immune evasion through transcriptional mechanisms. The high rate of cell proliferation in tumors leads to an increase in their mutation burden and copy number load, as well as global loss of methylation within late-replicating domains[49]. Immunomodulatory pathway genes concentrated within these late-replicating methylation domains gain promoter methylation and are transcriptionally suppressed in many solid tumors. Furthermore, methylation loss in these domains corresponds to immune evasion in both lung cancer and melanoma[49].

Cancer cells may also evade the immune system through direct epigenetic silencing of Fas. Fas is an apoptotic effector molecule within the TNF receptor family and is also a downstream target of the p53 tumor suppressor[50]. Maecker *et al.* demonstrate that epigenetic silencing of Fas promotes growth and prevents apoptosis of tumor cells derived from mouse embryonic fibroblasts. When cells were treated with the HDACi Trichostatin A, tumor growth was suppressed and chemosensitivity was restored[50].

Lastly, epigenetic inactivation of follistatin-like 1 (FSTL1) promotes immune evasion. Zhou *et al.* demonstrate the role that FSTL1 plays in the pathogenesis of nasopharyngeal carcinoma (NPC). In many NPC cell lines, FSTL1 was downregulated via promoter hypermethylation. Furthermore, the expression of FSTL1 suppressed cell proliferation and migration of NPC cells, and treatment with FSTL1 increased secretion of the IL-1β and TNF-α cytokines in macrophage cultures. This suggests that FSTL1 may activate macrophages and reduce immune evasion.

The immune cell response to cancer is also regulated by epigenetic mechanisms. One example is the de novo DNA methylation of the Tcf7 gene promoter by DNMT3a on CD8+ T cells following activation and proliferation. Typically CD8+ T cells differentiate into the early effector cell stage after activation, followed by further differentiation into either memory precursor or terminal effector cells[51]. Ladle et. al demonstrated that DNMT3a establishes methylation patterns within the Tcf7 promoter which leads to the differentiation of terminal effector CD8 T cells. Ladle et. al also found that DNMT3a KO mice have the ability to clear infections and have improved CD8 T cell memory. Youngblood *et al.* investigated the effects of DNA methylation patterns on naïve and effector gene expression in CD8 T cells. Following infection, memory precursor CD8 T cells gained de novo DNA methylation to suppress expression of naïve genes[52]. Deleting DNMT3a during an early stage of differentiation reduced the methylation of naïve genes, resulting in quicker re-expression of these genes to accelerate memory cell development. Overall this work demonstrates that epigenetic repression of naïve genes in CD8 can be reversed in cells that develop into memory CD8 T cells. Ghoneim *et al.* demonstrated that inhibition of DNA methylation in activated CD8 T cells allows retention of effector function even during chronic stimulation[53]. During both effector and exhaustion stages of an immune response, de novo methylation patterns restricted CD8 T cell expansion even after anti-PD-1 treatment[53]. These methylation programs were associated with the exhaustion stage and were an acquired

form of resistance in PD-1^{hi} CD8 T cells, which could be reversed by inhibiting DNA methylation.

Due to the intrinsic and extrinsic resistance mechanisms outlined above, most patients do not respond to immune checkpoint therapy alone[27]. As a result, many current studies focus on combination therapies that seek to enhance the effectiveness of immune therapy for a wider range of patients.

Combination of epigenetic drugs with immunotherapies

Pre-clinical studies combining HMTs with immune therapy have shown effectiveness in several tumor types. Increased expression of EZH2 leads to an increase in H3K27me3, loss of antigen presentation, and reduced immunogenicity in melanoma[55]. Addition of an EZH2 inhibitor to anti-CTLA-4 or IL-2 treatment reversed many of these immunosuppressive effects and significantly improved immune therapy in preclinical models[55]. BET (bromo and extra terminal) proteins are a family of proteins that epigenetically regulate the transcription of oncogenes[56]. EZH2 components silence chemokine expression in mouse models of ovarian cancer and inhibition of EZH2 sensitizes the cancers to immune checkpoint blockade therapy[57]. In an ovarian cancer model, treatment with the BET inhibitor JQ-1 decreased PD-L1 expression on tumor cells, tumor-associated dendritic cells, and macrophages[58]. In oral squamous cell carcinoma, JQ-1 downregulated the expression of PD-L1 and combining JQ-1 and with knockdown of PD-L1 was synergistic[59]. In a Myc-driven lymphoma mouse model, BETi treatment inhibited PD-L1 expression[60]. Combining JQ-1 and anti-PD-L1 was significantly more effective than treatment with either drug alone[60].

DNMTis upregulate immune signaling in both tumor and host immune cells (Figure 1). Low doses of DNMTis upregulate immune signaling, including the interferon response [61,62,63–66], cancer/testis antigens (CTAs), and antigen processing and presentation in breast, colon, lung, and ovarian cancer cell lines[62,67]. DNMTis activate a canonical interferon signaling pathway through upregulation of dsRNA, specifically hypermethylated endogenous retroviruses (ERVs) that activate dsRNA sensors TLR3 and MDA5[61]. DNMTis increase expression and reduced methylation of ERVs, which make up 8% of the genome. The interferon response caused by DNMTis is abrogated by inhibiting dsRNA sensors MDA5 and TLR3, proving that transcription of dsRNA species caused the interferon response[61,65]. The DNMTi upregulation of ERVs and subsequent interferon response can be increased by adding HDACi[68], inhibitors of H3K9 methyltransferases[69], or Vitamin C, which is a cofactor for the TET DNA demethylases[70]. DNA methylation silences expression of the CCL5 cytokine in tumor cells, which is required for T cell infiltration in ovarian cancers. Treatment with DNMTi can reverse this silencing and bring in CTLs[71]. DNMTis also affect host immune cells, specifically effector T cells. Inhibiting de novo methylation in effector T cells prevented their exhaustion[51,72] and synergized with immune checkpoint blockade in a mouse model of viral infection[72].

Epigenetic drugs have also been studied in combination with adoptive T cell therapy. Treatment of mice with the DNMTi decitabine improved the efficacy of adoptive T cell immunotherapy, showing greater inhibition of tumor growth and an increased cure rate[73].

Similarly, the combination of the HDACi LAQ824 with adoptive T cell therapy resulted in significantly improved antitumor immune activity in recipient mice[74].

In preclinical mouse models of cancer, DNMTi and/or HDACi treatment sensitizes tumors to immune therapy (Figure 1). DNMTis plus HDACis increase ERVs in a mouse model of ovarian cancer (ID8)[75], activating interferon signaling and recruiting CD8+ T cells to kill the tumors[76]. DNMTi treatment sensitizes mouse melanoma to subsequent anti-CTLA4 therapy[61,77,78] and mouse ovarian cancer to anti-PD-1 therapy[76]. HDACi improved effectiveness of anti-PD-1 treatment in melanoma and lung adenocarcinoma, causing slower tumor progression and increased survival compared to control and single agent treatments[43,79]. In another murine model, the DNMTi decitabine in combination with anti-CTLA4 immune blockade decreased tumor burden and improved survival of mice with ovarian cancer[73]. The combination of DNMTis, HDACis, anti-PD1, and anti-CTLA4 together showed significantly improved treatment outcomes in mice, with over 80% of tumor bearing mice being cured[80]. HDACi and DNMTis inhibited MDSC function in this study[80]. These results strongly support the combination of immune checkpoint therapies with DNMTi and/or HDACi in cancer treatment.

Clinical trials combining epigenetic and immune therapy

Many clinical trials are currently testing combinations of epigenetic drugs with immune therapy, most commonly HDACi and DNMTi. While effective for MDS/AML (DNMTi) and cutaneous T cell lymphoma (HDACi), epigenetic drugs have thus far shown limited effectiveness in the treatment of solid tumors as single agents. For example, when non-small cell lung cancer (NSCLC) patients were treated with azacytidine and entinostat, a DNMTi and an HDACi, respectively, only 4% of the patients exhibited an objective response[81]. Combining epigenetic drugs with conventional chemotherapy improves effectiveness of these therapies. In NSCLC patients, the combination of vorinostat, an HDACi, with carboplatin and paclitaxel enhanced the efficacy of the chemotherapeutic drugs and lead to improved patient survival[82]. Similarly, the DNMTi azacytidine partially reverses platinum resistance, improving the efficacy of carboplatin in patients with epithelial ovarian cancer[83–85]. These results point to the potential of epigenetic drugs to improve the efficacy of conventional therapies, though further study is required.

Epigenetic drugs have shown exciting initial results when used in combination with immune checkpoint inhibitor therapies. Following the aforementioned study in patients with NSCLC, several patients who had received DNMTi and HDACi therapy took part in a trial for immune checkpoint therapy with an anti-PD-1 inhibitor. Of the six patients, five survived six months without cancer progression[66]. Based on the strong preclinical data for DNMTi upregulation of interferon signaling and reversal of immune evasion, many clinical trials combining DNMTi and immune checkpoint blockade cancer are ongoing or completed (see Table 1 for a complete list of trials combining epigenetic therapy with immune therapy in cancer). Trial NCT02664181 combines THU (tetrahydrouridine, a cytidine deaminase inhibitor) with oral decitabine and nivolumab (anti-PD-1) in non-small cell lung cancer. In this trial THU is used to stabilize decitabine as it works by blocking cytidine deaminase, an enzyme that rapidly breaks down decitabine. NCT02900560 combines oral azacytidine and

pembrolizumab (anti-PD-1) in epithelial ovarian cancer. Trial #NCT03206047 tests the combination of guadecitabine (SGI-110, a pro-drug form of decitabine), atezolizumab (anti-PD-L1), and a CDX-1401 vaccine (dendritic cell vaccine against the cancer testis antigen NY-ESO-1). NY-ESO-1 antigen is expressed at higher levels on cancer cells than normal cells but can be demethylated and further upregulated by DNMTi treatment. Other clinical trials combining DNMTi and immune checkpoint blockade are being run in a wide range of cancers to determine their safety and efficacy (Table 1). These include diffuse large B cell lymphoma (NCT02951156), lung cancer (NCT02546986), ovarian cancer (NCT02901899), colorectal cancer (NCT02260440), acute myeloid leukemia (NCT02845297, NCT02397720), metastatic melanoma (NCT02816021, NCT02608437), and myelodysplastic syndromes (NCT02599649, NCT02530463, NCT02890329, NCT02508870, NCT02117219, NCT02775903).

Several clinical trials are currently testing HDACi in combination with immunotherapy based on preclinical results showing that HDACi can prime the tumor to respond to immune therapy. NCT03765229 utilizes the HDACi entinostat (MS275) in combination with pembrolizumab (anti-PD-1) in melanoma. This trial will assess whether entinostat can cause the tumor to become less resistant to an immune system attack by making it more visible to the immune system. It will also investigate whether entinostat in combination with pembrolizumab shrinks the tumor in patients who had no immune cells within the tumor environment prior to treatment. The same combination therapy (entinostat and pembrolizumab) is being tested in myelodysplastic syndrome, non-small cell lung cancer, and colorectal cancer (NCT02936752, NCT02437136, NCT02909452, NCT02697630). In lung cancer, salivary gland cancer, and renal cell carcinoma, the HDACi vorinostat is being tested in combination with pembrolizumab (NCT02638090, NCT02538510, NCT02619253). The HDAC6i ACY241 is being tested in combination with pembrolizumab in non-small cell lung cancer (NCT02635061). Other HDACi and immune checkpoint blockade combinations are in trials for melanoma (NCT02032810), triple negative breast cancer (NCT02708680), non-small cell lung cancer (NCT02805660), and epithelial ovarian cancer (NCT02915523).

Lastly, combination of DNMTi and HDACi with immune therapy has gone to clinical trials based on preclinical success in cell lines and mouse models. Trial #NCT02512172 in colorectal cancer patients combines oral azacytidine with the HDACi romidepsin and anti-PD-1. Other trials combine DNMTi, HDACi, and checkpoint blockade in gastrointestinal cancers (NCT03812796), non-small cell lung cancer (NCT00387465, NCT01928576), and advanced colorectal cancer (NCT02512172).

Conclusions and future directions

Immunotherapy has proven an exciting and productive area of research for the treatment of many cancers. As our understanding of the anti-tumor immune response grows, so will our ability to harness the human immune system for the elimination of cancer. Many of the immune therapies discussed here are effective in a minority of patients. Future research will focus on improving existing immune therapies and critically assessing combination therapy to significantly improve patient outcomes. Because of their effect on the anti-tumor immune

response, both HDACi and DNMTi are promising therapeutic agents to reverse tumor immune resistance and to sensitize tumors to immune therapy in a wide variety of solid tumors. We eagerly await results of ongoing clinical trials (Table 1), which will provide information on safety, efficacy, and potential biomarkers for these combinations. Utilizing epigenetic therapies to reverse tumor immune resistance and sensitize to curative immune therapy may prove to be a safe and effective way to treat multiple types of cancer, reaching large numbers of patients.

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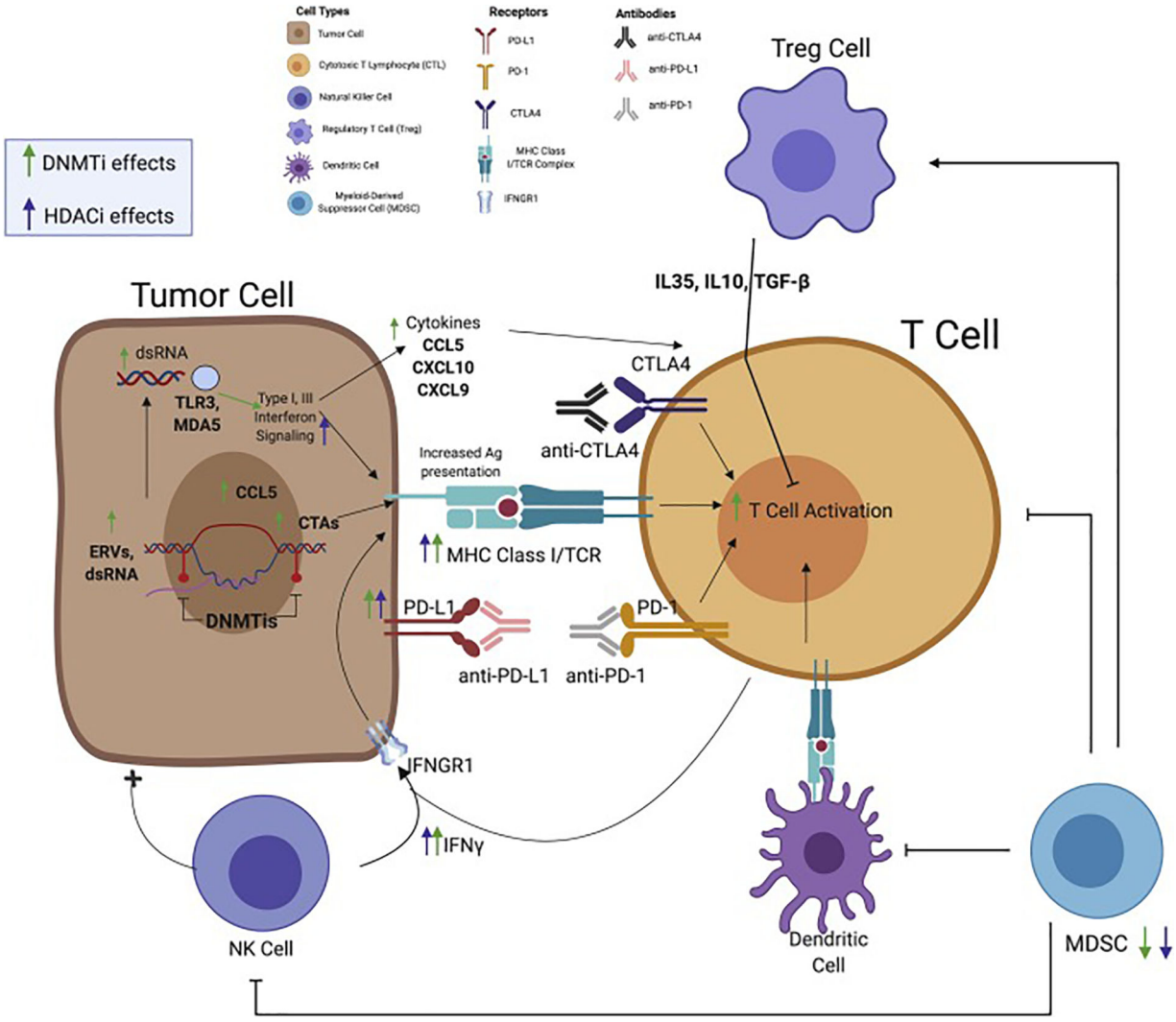

Figure 1. DNMTi and HDACi promote anti-tumor immune signaling.

DNMTi treatment removes methylation from endogenous double-stranded RNA species, including ERVs, which activate Type I and III interferon signaling through sensors including TLR3 and MDA5. This signaling in turn leads to increased expression of antigen processing and presentation machinery including MHC I on the cell surface. DNMTis also upregulate cancer testis antigens (CTAs) and the cytokine CCL5 by demethylation of their promoter regions. HDACi increase antigen processing and presentation and PD-L1 expression, along with DNMTi. DNMTi increase T cell activation against tumor cells and both DNMTi and HDACi repress MDSCs, promoting an anti-tumor immune microenvironment.

Table 1.

Completed and ongoing clinical trials utilizing epigenetic modifiers in cancer.

Trial number	Status	Title	Drug and Schedule	Study Type	Notes
NCT03812796	Recruiting	Epigenetic Modulation of the immunE response in GastrointEstinal Cancers	Phase IIA: Domatinostat in an oral tablet given at varying doses. Given Avelumab intravenously at 10 mg/kg every two weeks. Phase IIB: Patients treated with domatinostat at safe combination dose found in phase IIA. Given Avelumab intravenously at 10 mg/kg every two weeks.	Phase 2 GI cancer - microsatellite stable colorectal or gastroesophageal cancer	
NCT02664181	Completed	Rational EpigenetiC Immunotherapy for SEcond Line Therapy in Pateients with NSCLC: Precise Trial	Experimental: Oral THU (10 mg/kg) followed by oral decitabine (0.2 mg/kg) 60 minutes after THU occuring consectuively for two days weekly. Nibolumab adminstered at 3 mg/kg intravenously every two weeks until progression. Active Comparator: Nivolumab 3 mg/kg intravenously every two weeks until progression.	Phase 2 Lung Cancer, Non-small cell lung cancer	
NCT02900560	Recruiting	Study of Pembrolizumab With of Without CC-486 in Patients with Platinum-Resistance Ovarian Cancer	Cohort 1: Oral Azacitidine (CC-486) at 100 mg once a day for 21 days and then 7 days off. Given with Pembrolizumab at 200 mg intravenously every 21 days. Cohort 2: Oral Azacitidine (CC-486) at 100 mg twice a day for 21 days and then 7 days off. Given with Pembrolizumab at 200 mg intravenously every 21 days Cohort 3: Oral Azacitidine (CC-486) at 300 mg once a day for 14 days and then 14 days off. Given with Pembrolizumab at 200 mg intravenously every 21 days. Cohort 4: Oral Azacitidine (CC-486) at 300 mg once a day for 21 days and then 7 days off. Given with Pembrolizumab at 200 mg intravenously every 21 days.	Phase 2 Epithelial Ovarian Cancer	
NCT03206047	Suspended (Other-Pending Phase 2 Portion of Study)	Atezolizumab, Guadecitabine, and CDX-1401 Vaccine in Treating Patients With Recurrent Ovarian, Fallopian Tube or Primary Peritoneal Cancer	Cohort 1: Atezolizmab administered intravenously over 30–60 minutes on day 1 and 15. Treatment regimen repeats every 28 days for 24 courses. Cohort 2: Guadecitabine administered subcutaneously on days 1–5. Treatment repeats every 28 days for up to 6 courses. Atezolizumab administered intravenously over 30–60 minutes on day 8 and day 22. Treatment regimen repeats every 28 days for up to 24 courses. Cohort 3: Guadecitabine and Aztezolizumab administered in the same manner as cohort 2. Addition of CDX-1401 vaccine intravenously occurs on day 15 and poly ICLC subcutaneously on days 15 and 16. Treatment repeats every 28 days for up to 6 courses.	Phase 1 Platinum-Resistant: Fallopian Tube Carcinoma, Ovarian Carcinoam, Primary Peritoneal Carcinoma Recurrent: Fallopian Tube Carcinoma, Ovarian Carcinoma, Primary Peritoneal Carcinoma	
NCT02951156	Active, Not recruiting	Avelumab in Combination Regimens That Include An Immune Agonist, Epigenetic Modulator, CD20 Antagonist and/or Conventional Chemotherapy in Patients with Relapsed or Refractory Diffuse Large B cel Lymphoma	Phase 1b (Arm A): Azelumab, Utomilumab, Rituzimab Phase 1b (Arm B): Avelumab, Utomilumab, Azacitidine Phase 1b (Arm C): Avelumab, Rituxima, Bendamustine Phase 3 (Arm D): Selected regimen from Phase 1b component. Phase 3 (Arm E): Choice of investigator to do either rituximad/ bendamustine or rituximab/gemcitabine/oxaliplatin.	Phase 3 Diffuse Large B-Cell Lymphoma	
NCT03765229	Recruiting	An Exploratory Study of Pembolizumab Plus Entinostat in Non-inflamed Stage III/IV Melanoma	Entinostat at 5 mg administered orally occuring once weekly of a 21 day cycle starting on day 1 of study treatment; Pembrolizumab at 200 mg administered intravenously every 3 weeks starting at cycle 2 (occurs after research tumor biopsy at the end of cycle 1)	Phase 2 Melanoma	Combination therapy of both entionstat and pembrolizumab will continue if patient has

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Trial number	Status	Title	Drug and Schedule	Study Type	Notes
					clinical beenfit from therapy for up to 27 weeks.
NCT00387465	Completed	Azacitidine and Entinostat in Treating Patients with Recurrent Advanced Non-Small Cell Lung Cancer	Phase 1: Azacitidine at 30 mg/m2 administered subcutaneously. Entinostat at 7 mg orally on day 3 and 10 of each cycle. Phase 1: Azacitidine at 40 mg/m2 administered subcutaneously. Entiostat at 7 mg orally on days 3 and 10 of each cycle. Phase 2: Azacitidine at 40 mg/m2 administed subcutaneously on days 1–6 and 8–10. Entiostat at 7 mg administered orally on day 3 and 10. Treatment repeats every 28 days.	Phase 1/ Phase 2 Recurrent Non-small Cell Lung Cancer, Stage IIIA NSCLC, Stage IIIB NSCLC, Stage IV NSCLC	
NCT02437136	Active, Not recruiting	Ph1b/2 Dose-Escalation Study of Entinostat With Pembrolizumab in NSCLC with Expansion Cohorts in NSCLC, Melanoma, and Colorectal Cancer	Cohort 1: Ph 2 NSCLC (squamous or adeno). Patients not pre-treated with PD-1 or PD-L1 blocking antibody. Given entinostat and pembrolizumab Cohort 2: Ph 2 NSCLC. Patients pre-treated with PD-1/PD-L1 blocking antibody. Given entinostat and pembrolizumab. Cohort 3: Ph 2 Melanoma. Patients pre-treated with PD-1/PD-L1 blocking antibody. Given entinostat and pembrolizumab. Cohort 4: Ph 2 Mismatch Repair-Proficient CRC. Patients not pre-treated with PD-1 or PD-L1 blocking antibody. Given entiostat and pembrolizumab.	Phase 1/Phase 2 Non-small Cell Lung Cancer, Melanoma, Mismath Repair-Proficient Colorectal Cancer	
NCT02936752	Recruiting	Entinostat and Pembrolizumab in Treating Patients With Myelodysplastic Syndrom After DMNTi Therapy Failure	Patients receive low dose of oral entinostat on days 1 and 8 or a higher dose on days 1, 8, and 15. Pembrolizumab given intravenously over 30 minutes on day 1 of courses 2 and courses after. Treatment repeats every 21 days for up to 4 courses.	Phase 1 Blasts 21–20 Percent of bone Marrow Nucleated Cells, Myelodysplastic Syndrome, Previously treated Myelodysplastic syndrome	
NCT02546986	Active, Not recruiting	Safety and Efficacy Study of CC-486 with MK-3475 to Treat Locally Advanced or Metastatic Non-Small Cell Lung Cancer	Experimental Arm: Patients receive oral Azacitidine at 300 mg daily on days 1–14 of the 21 day cycles. Pembrolizumab adminstered intravenously for 30 minnutes on day 1 of the 21 day cycles. Control Arm: Patients receive pembrolizumab intravenously for 30 minutes on day 1 of the 21 day cycles. Oral placebo will be adminstered on days 1–14 of the 21 day cycles.	Phase 2 Non-small Cell Lung Carcinoma	
NCT02909452	Active, Not recruiting	Continuation Study of Entinostat in Combination with Pembrolizumab in Patients with Advanced Solid tumors	Entinostat at 1 mg given daily with pembrolizumab given every three weeks. Entinostat at 5 mg given once weekly with pembrolizumab given every three weeks. Entinostat at 10 mg given bi-weekly with pembrolizumab given every three weeks.	Phase 1 Neoplasms (Glandular and Epithelial), Neoplasms by histologic type, brnchial neoplasms, lung neoplasms, respiratory tract neoplams, thoracic neoplasms, digestive system neoplasms, endocrine gland neoplasms, NSCLC, lung diseases, breast disease, renal neoplasm, solid tumors	
NCT02697630	Active, Not recruiting	Efficacy Study of Pembrolizumab with Entinostat to Treat Metastatic Melanoma of the Eye (PEMDAC)	Pembrolizumab at 200 mg adminstered intravenoulsy every third week. Entinostat at 5 mg administered orally once weekly.	Phase 2 Metastatic Uveal Melanoma	

Trial number	Status	Title	Drug and Schedule	Study Type	Notes
NCT02538510	Active, Not recruiting	Pembrolizumab and Vorinostat in Treating Patients with Recurrent Squamous cell Head and Neck Cancer or Salivary Gland Cancer that is Metastatic and/or Cannot be removed by surgery	Receive vorinostat orally or via PEG on days 1–5 and pembrolizumab intravenously over 30 minutes on day 1. Treatment courses repeat every 21 days for up to 2 years	Phase 1/Phase 2 Head and Neck Squamous Cell Carcinoma, Recurrent Nasal Cavity and Paranasal Sinus Squamous Cell Carcinoma, Recurrent Nasopharynx Carcinoma, Recurrent salivary Gland Carcinoma, Squamous Cell Carcinoma Metastatic in Neck with Occult primary, Stage III Major salivary Gland carcinoma, Stage III nasal cavity and paranasal sinus squamous cell carcinoma, Stage III nasopharynheal carcinoma, Stage IV nasopharyngeal carcinoma, Stage IVA major salivary gland carcinoma, Stage IVA nasal cvity and paranasal sinus squamous cell carcinoma, Stage IVB major salivary gland carcinoma, Stage IVB Nasal cavity and Paranasal sinus squamous cell Carcinoma, Stage IVC major salivary gland carcinoma, Stage IVC nasal cavity and Paranasal sinus Squamous cell carcinoma	
NCT02638090	Recruiting	Pembro and Vorinostat for Patients with Stage IV Non-small Cell Lung Cancer (NSCLC)	Phase 1 (Dose Escalation): Level 1 - Vorinostat at 200 mg given orally daily with pembrolizumab at 200 mg adminstered intravenously every 3 weeks. Level 2 - Vorinostat at 400 mg given orally daily with pembrolizumab at 200 mg adminstered intravenously every 3 weeks. Phase 1b (Expansion): Level 1-Pembrolizumab plus vorinostat given at maximum tolerated dose. Arm A: Pembrolizumab adminstered at 200 mg intravenously every 3 weeks. Arm B: Pembrolizumab plus vorinostat treatment given at maximum tolerated dose.	Phase 1/Phase 2 Lung cancer, Non-small Cell Lung Cancer	
NCT02619253	Recruiting	Phase I/Ib study of Pembrolizumab with Vorinostat for Patients with Adavanced Renal or Urothelial Cell Carcinoma	Dose Finding cohort: Patients will be given oral vorinostat daily for 14 days with pembrolizumab at 200 mg intravenously. Two doses of vorinostat will be tested 100 and 200 mg. Each cycle is every 21 days. Expansion Cohort: After determining which dose of vorinostat should be used in the dose finding cohort, patients with prior treatments are enroleed in three different cohorts. 15 anti-PD1 naive renal and urothelial patients, 15 anti-PD1 resistane renal and urothelial pateitns and 15 patients with androgen-sensitive or castration-resistance prostate cancer. Each cohort will then receive the established vorinostat dose along with 200 mg pembrolizumab intravenously.	Phase 1 Renal Cell Carcinoma, Urinary Bladder Neoplasms	

Trial number	Status	Title	Drug and Schedule	Study Type	Notes
NCT02901899	Recruiting	Guadecitabine and Pembrolizumab in Treating Patients with Recurrent Ovarian, Primary Peritoneal, or Fallopian tube Cancer	Patients receive guadecitabine subcutaneously on days 1–4 and pembrolizumab intravenously over 30 minutes on day 5. Treatment courses repeat evry 21 days.	Phase 2 Recurrent - Fallopian Tube Carcinoma, Ovarian Carcinoma, Primary Peritoneal Carcinoma	
NCT02512172	Active, Not recruiting	A Study of Enhancing Response to MK-3475 in Advanced Colorectal Cancer	Patients given oral azacitidine at 300 mg on days 1–14 or 21 for every 28 days. Given pembrolizumab at 200 mg intravenously on days 1 and 15 every 28 days Patients given Romidepsin at 14 mg/m2 on days 1,8, and 15. Given pembrolizumab at 200 mg intravenously on days 1 and 15 every 28 days. Patients given oral azacitidine at 300 mg on days 1–14 or 21 and romidepsin at 7 mg/m2 on days 1,8 and 15. Given pemrbolizumab at 200 mg intravenously on days 1 and 15 every 28 days.	Phase 1 Colorectal Cancer	Romidepsin - Chemotherapy drug approved by FDA for treatment of cutaneous T-cell lymphoma
NCT02260440	Active, Not recruiting	A Phase 2 Study of Pembrolizmab (MK-3475) in Cominaiton with Azacitidine in Subjects With Chemorefractory Metastatic Colorectal Cancer	Pembrolizumab given at 200 mg every 21 days. Azacitidine given at 100 mg daily subcutaneously on days 1–5 every 21 days. 9 cycles of treatment.	Phase 2 Colorectal Cancer	
NCT02845297	Recruiting	Study of Azacitidine in Combination with Pembrolizumad in Replased/ Refractory Acute Myeloid Leukemia (AML) Patients and in Newly Diagnosed Older (>= 65 years) AML Patients	Cohort 1 (Safety Run in Phase) : Treatment of relapsed and refractory AML Patients. Given pembrolizumab intravenously and azacitadine intravvenoulsy or subcutaneously. Cohort 2: Treatment of newly diagnost AML patients (>= 65 years). Given pembrolizumab intravenously and azacitadine intravenously or subcutaneously.	Phase 2 Acute Myeloid Leukemia	
NCT02816021	Recruiting	Study of Oral Azacitidine (CC-486) in Combination with Pembrolizumab (MK-3475) in Patients with Metastatic Melanoma	Arm A - Metastatic Melanoma PD-1 Naive: 3 week treatment cycles. Oral azacitidine given for days 1–15 of every cycle. Pemrbolizumab administered intravenously every 3 weeks and after the oral dose of azacitidine on concurrent treatment days. Arm B - Metastatic Melanoma Post PD-1 Progression: 3 week treatment cycles. Oral azacitidine given for days 1–15 of every cycle. Pembrolizumab adminstered intravenously every 3 weeks and after oral dose of azacitidine on concurrent treatment days.	Phase 2 Melanoma and other malignant neoplasms of skin, metastatic melanoma	
NCT01928576	Recruiting	Phase II Anti-PD1 Epigentic Therapy Study in NSCLC	Arm C: Nivolumab at 3 mg/kg given every 2 weeks until disease progression. Arm D: Treatment occurs every 28 days for 6 cycles. Azacitidine given at 40 mg.m2 on days 1–5 and days 8–10. Entinostat at 5 mg given on days 3 and 10. Nivolumab given at 3 mg/kg on days 1 and 15. Followed by nivolumab at 3 mg/kg given every 2 weeks until disease progression.	Phase 2 Non-small Cell Lung Cancer	
NCT02397720	Recruiting	Nivolumab and Azacitidine with or without Ipilimumab in Treating Patients with Refractory/Relapsed or Newly Diagnosed Acute Myeloid Leukemia	Arm I: Azacitidine adminstered intravenously over 1 hours or subcutaneously on days 1–7 or days 1–4 and days 7–9. Received nivolumab intravenously over 60 minutes on days 1 and 14 (courses 1–4) or on day 1 (course 5 and the courses following). Treatment courses repeat every 28 days. Arm II: Receive azacitidine and nivolumab as in Arm I. Receive ipilimumab intravenously over 90 minutes on day 1 and then every 6 or 12 weeks.	Phase 2 Acute Bilineal Leukemia, Acute Biphenotypic Leukemia, Acute Myeloid Leukemia arising from previous myelodysplastic syndrome, chronic myelomonocytic leukemia, myelodysplastic syndrome, recurrent acute myeloid leukemia, refractory acute myeloid leukemia, secondary acute	

Trial number	Status	Title	Drug and Schedule	Study Type	Notes
				myeloid leukemia, therapy-related actue myeloid leukemia	
NCT02599649	Completed	Lirilumab and Nivolumab with 5-Azacitidine in Patients with Myelodysplastic Syndromes (MDS)	Low or Intermediate-1 MDS Group: Lirilumab adminstered at 3 mg/kg intravenously over 60 minutes one time during every 28 day cycle. Low or Intermediate-MDS Group: Nivolumab adminstered at 3 mg/kg intravenously over 60 minutes every 2 weeks during cycles 1–8. Lirilumab adminstered at 3 mg/kg intravenously over 60 minutes one time during every 28 day cycle. High Risk MDS Group: Azacitidine adminstered at 75 mg/m2 intravenously over 60 minutes on days 1–7 of the 28 day cycle. Lirilumab adminstered at 3 mg/kg intravenously over 60 minutes on day 7 of each cycle. High Risk MDS Group: Azacitidine adminstered at 75 mg/m2 intravenously over 60 minutes on days 1–7 of each 28 day cycle. Lirilumab adminstered at 3 mg/kg intravenously over 60 minutes on day 7 of each cycle. On days 7 and 21 of cycles 1–9 nivolumab is adminstered at 3 mg/kg intravenously over 60 minutes. On day 7 of cycle 10 and beyond, nivolumab adminstered intravenously over 60 minutes.	Phase 2 Leukemia	
NCT02530463	Recruiting	Nivolumab and Ipilimumab with 5-azacitidine in Patients with Myelodysplastic Syndromes (MDS)	Cohort 1 (Hypomethylating failure MDS cohort): Nivolumab adminstered intravenously at 3 mg/kg every 2 weeks for 6 cycles. After 6 cycles, use of Azacitidine is permitted to test concept of re-sensitization. Cohort 2 (Hypomethylating failure MDS cohort): Ipilimumab adminstered intravenously at 3 mg/kg every 3 weeks for 6 cycles. After 6 cycles, use of Azacitidine is permitted to test concept of re-sensitization. Cohort 3 (Hypomethylating failure MDS cohort): Nivolumab adminstered intravenously at 3 mg/kg on days 1 and 15. Ipilimumab adminstered intravenously at 3 mg/kg on day 1. After 6 cycles, use of Azacitidine is permitted to test concept of re-sensitization. Cohort 4 (Previously untreated MDS cohort): Azacitidine admintered intravenously at 75 mg/m2 for 5 days every 4 weeks. On day 6 nivolumab adminstered intravenously at 3 mg/kg every 2 weeks. Cohort 5 (Previously untreated MDS cohort): Azacitidine adminstered intravenously at 75mg/m2 for 5 days every 4 weeks. On day 6 ipilimumab adminstered intravenously at 3 mg/kg every 4 weeks. Cohort 6 (Previously untreated MDS cohort): Azacitidine adminstered intravenously at 75 mg/m2 for 5 days every 4 weeks. On day 6 and day 20 nivolumab adminstered intravenously at 3 mg/kg and ipilimumab adminstered on day 6 intravenously at 3 mg/kg.	Phase 2 Leukemia, Myelodysplastic syndrome	
NCT02635061	Recruiting	Selective HDAC6 Inhibitor ACY 241 in Combination with Nivolumab in Pateitns with Unresectabe Non-smell Cell Lung Cancer	ACY-241 adminstered in combination with nivolumab.	Phase 1 Non-small Cell Lung Cancer	
NCT02890329	Recruting	Ipilimumab and Decitabine in Treating Patients with Relapsed or Refractory Myelodysplastic Syndrome or Acute Myeloid Leukemia	Arm A (Post allo-HCT): Priming phase - patients are administered decitabine intravenously over 60 mintes on days 1–5 out of 28 days. Induction phase - patients are adminstered decatibine intravenously over 60 minutes on days 1–5 and ipilimumab is adminstered intravenously over 90 minutes on day 1. Treatment repeats every 28 days for up to 4 cycles. Maintenance phase - patients adminstered decitibine intravenously over 60 minutes on days 1–5 and ipilimumab is adminstered intravenously over 90 minutes on day 1. Treatment repeats every 4–8 weeks for up to 4 cycles.	Phase 1 Blasts 5% of more of bone marro nucleated cells, hemtopoietic cell transplant recipient, myelodysplastic syndrome, previously treated myelodysplastic syndrome, recurrent acute myeloid leukemia, recurrent acute	

Trial number	Status	Title	Drug and Schedule	Study Type	Notes
			Arm B (Transplant naive Patients): Priming phase - patients are adminstered decitabine intravenously over 60 mintes on days 1–5 out of 28 days. Induction phase - patients are adminstered decitabine intravenously over 60 minutes on days 1–5 and ipilimumab is adminstered intravenously over 90 minutes on day 1. Treatment repeats every 28 days for up to 4 cycles. Maintenance phase - patients are adminstered decitabine intravenously ver 60 minutes on days 1–5 and ipilimumab is adminstered intravenously over 90 minutes on day 1. Treatment repeats every 4–8 weeks for up to 4 cycles.	myeloid leukemia with myelodysplasia-related changes, refractory acute myeloid leukemia, secondary acute myeloid leukemia, untreated adult acute myeloid leukemia	
NCT02608437	Unknown	A Study Investigating SGI-110 in Combination with Ipilimumab in Unresectable or Metastatic Melanoma Patients (NIBIT-M4)	SGI-110 administered at 30 mg/m2 subcutaneously on days 1–5 for 2 day cycles. Ipilimmab adminstered at 3 mg/kg intravenously over 90 minutes every 3 weeks for 4 cycles.	Phase 1 Metastatic Melanoma	
NCT02032810	Active, Not recruiting	Phase I of Histone Deacetylase (HDAC) Inhibitor Panobinostat with Ipilimumab with Unresectable III/IV Melanoma	Patients assigned a dose of panobinostat (5, 10, 15, 20 mg). Dose depends on time point patients enters study. Patients given ipilimumab at 3 mg/kg.	Phase 1 Skin Cancer, Melanoma	
NCT02508870	Suspended	A study of Atezolizumab Adminstered Alone or in Combination with Azacitidine in Participants with Myelodysplastic Syndromes	Cohort A (HMA R/R MDS): Patients adminstered atezolizumab at 1200 mg intravenously every 3 weeks (21 day cycles) Treatment will continue for up to 17 cycles. Cohort B (HMA R/R MDS): Induction - Patients adminstered atezolizumab at 840 mg intravenously on days 8 and 22 of 28 day cycles. Azacitidine adminstered at 75 mg/m2 subcutaneously on days 1–7 of 28 day cycles for 6 cycles. Maintenance - Patients who completed induction treatment will be adminstered atezolizumab at 1200 mg intravenously Q3W (21 day cycles) for up to 8 additional cycles. Cohort C1 (HMA Naive MDS): Patients adminstered atezolizumab at 840 mg intravenously on days 8 and 22 of 28 day cycles. Azacitidine adminstered at 75 mg/m2 subcutaneously on days 1–7 of 28 day cycles. Cohort C2 (HMA Naive MDS): Patients enrolled in Cohort C1 fulfil dose limiting toxicity, additional patients will be adminstered atezolizumab at 840 mg intravenously on days 8 and 22 of 28 day cycles. Azacitidine admintered at 75 mg/m2 subcutaneously on days 1–7 of 28 day cycles. Cohort A2 (HMA R/R MDS): If atezolizumab alone or in combination with azacitidine is safe and tolerable. Patients will be randomly assigned to be adminstered atezolizumab at 1200 mg intravenously Q3W (21 day cycle) Treatment will continue up to 17 cycles. Cohort B2 (HMA R/R MDS): If atezolizumab alone or in combination with azacitidine is safe and tolerable, patients will be randomly assigned to be administered atezolizumab at 840 mg intravenously on days 8 and 22 of each 28 day cycles and azacitidine admininistered at 75 mg/m2 subcutaneously on days 1–7 of 28 day cycles for 6 cycles during inducation. Patients who complete induction treatment with be adminstered atezolizumab at 1200 mg intravenously Q3W (21 day cycle) for up to 8 cycles.	Phase 1 Myelodysplastic syndromes	
NCT02708680	Active, Not recruiting	Randomized Phase 2 study of Atezolizumab and Entinostat in pateitns with aTN Breast Cancer with Phase 1b Lead In	Active Comparator: Entinostat given orally at RP2D in combination with atezolizumab. Placebo Comparator: Placebo given orally in ocmbination with atezolizumab.	Phase 1 Breast Cancer	
NCT02117219	Completed	Phase 1 Study to Evaluate MEDI4736 in Subjects with Myelodysplastic Syndrome	Patients adminstered durvalumab intravenously. Azacitidine will be adminstered subcutaneously in combination with durvalumab. Tremelimumab adminstered intravenously. Durvalumab adminstered	Phase 1 Myelodysplastic Syndrome	

Trial number	Status	Title	Drug and Schedule	Study Type	Notes
			intravenously in combination with tremelilmumab. Patients adminstered durvalumab intravenously. Tremelimumab adminstered intravenously. Azacitidine will be adminstered subcutaneously in combination with durvalumab and tremelimumab.		
NCT02775903	Active, Not recruiting	An Efficacy and Safety Study of Azacitidine Subcutaneous in Combination with Durvalumab(MEDI4736) in Previously Untreated Subjects with Higher-Risk Myelodysplastic Syndromes (DS) or in Eldery Subjects with Acute Myeloid Leukemia (AML)	Experimental: Azacitidine adminstered at 75 mg/m2 subcutaneously for 7 days every 4 weeks. Durvalmab adminstered intravenously at 1500 mg on day 1 every 4 weeks. Active Comparator: Azacitidine adminstered at 75 mg/m2 subcutaneously every 7 days for 4 weeks.	Phase 2 Acute Myeloid Leukemia, Myelodysplastic Syndromes	
NCT02805660	Active, Not recruiting	Phase 1/2 Study of Mocetinostat and Durvalumab in Patients with Advanced Solid Tumors and NSCLC	Mocetinostat adminstered orally three times weekly. Durvalumab adminstered at 1500 mg intravenously in 28 day cycles with mocetinostat.	Phase 1/ Phase 2 Advanced Cancer	
NCT02915523	Active, Not recruiting	Phase 1b/2 Study of Avelumab with or without Entinostat in Patietns with Advanced Epithelial Ovarian Cancer	Active Comparator: Avelumab adminstered intravenously on day 1 of each 14 day cycle. Entinostat adminstered on day 1 and day 8 of each cycle at maxium tolerated does (MTD)/ RP2D determined in phase 1b part of study. Placebo Comparator: Avelumab adminstered intravenously on day 1 of each 14 day cycle. Placebo adminstered on day 1 and day 8 of each cycle.	Phase 1/ Phase 2 Epithelial Ovarian Cancer, Peritoneal Cancer, Fallopian Tube Cancer	