HHS Public Access

Author manuscript

Curr Pharmacol Rep. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Curr Pharmacol Rep. 2017 December ; 3(6): 360–373.

Epigenetic Therapeutics and Their Impact in Immunotherapy of Lung Cancer

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Abstract

Lung cancer is the leading cause of cancer-related death in the United States and worldwide. Novel therapeutic developments are critically necessary to improve outcomes for this disease. Aberrant epigenetic change plays an important role in lung cancer development and progression. Therefore, drugs targeting the epigenome are being investigated in the treatment of lung cancer. Monotherapy of epigenetic therapeutics such as DNA methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi) have so far not shown any apparent benefit while one of the clinical trials with the combinations of DNMTi and HDACi showed a small positive signal for treating lung cancer. Combinations of DNMTi and HDACi with chemotherapies have some efficacy but are often limited by increased toxicities. Preclinical data and clinical trial results suggest that combining epigenetic therapeutics with targeted therapies might potentially improve outcomes in lung cancer patients. Furthermore, several clinical studies suggest that the HDACi vorinostat could be used as a radiosensitizer in lung cancer patients receiving radiation therapy. Immune checkpoint blockade therapies are revolutionizing lung cancer management. However, only a minority of lung cancer patients experience long-lasting benefits from immunotherapy. The role of epigenetic reprogramming in boosting the effects of immunotherapy is an area of active investigation. Preclinical studies and early clinical trial results support this approach which may improve lung cancer treatment, with potentially prolonged survival and tolerable toxicity. In this review, we discuss the current status of epigenetic therapeutics and their combination with other antineoplastic therapies, including novel immunotherapies, in lung cancer management.

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Disclosure

The authors have no conflicts of interest to declare.

1. Introduction

Lung cancer is the leading cause of cancer-related death and a major healthcare challenge globally [1]. Non-small cell lung cancer (NSCLC), accounting for about 85% of all cases, is the major histologic subtype. Small cell lung cancer (SCLC) accounts for 10–12% of all lung cancer cases [2]. At the time of diagnosis more than 40% of patients are already in an advanced tumor stage. Despite the recent development of targeted therapies and immunotherapies, the overall prognosis for patient is still poor, with less than 15–18% of patients surviving at 5 years after diagnosis. The primary treatment for the majority of advanced lung cancer patients continues to be cytotoxic chemotherapy [3]. Novel lung cancer treatment strategies using epigenetic therapeutics alone or in combination with other therapies have been preclinically developed and clinically tested over the last decade, with numerous ongoing clinical trials. Epigenetic therapeutics were first shown to be effective in the treatment of hematological malignancies such as acute myeloid leukemia (AML), myeloid dysplastic syndrome (MDS), acute lymphoblastic leukemia (ALL) and some types of lymphoma. Some are approved by the US Food and Drug Administration (FDA) as shown detailed in Supplementary Table 1. Epigenetic therapeutics such as DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis) were first tested as monotherapies, and subsequently as combination therapies. In this review, we discuss the current status of their potential application in lung cancer management with perspectives on combination with other novel therapies, including immunotherapy.

2. Epigenetics in lung cancer

Epigenetic alterations such as DNA methylation and histone modifications are known to be involved in tumor development and tumor progression of lung cancer and other cancers [15].

2.1 DNA-methylation

DNA methylation affects the transcription of genes without altering the DNA nucleotide sequence and is found sparsely but globally in human cells. In eukaryotic DNA, cytosine is methylated and then converted into 5-methylcytosine by DNA methyltransferases (DNMTs) [16]. There are three enzymatically active DNMTs in human cells: DNMT1, 3a and 3b [17–19]. Global hypomethylation is characteristic in the transformation of benign cells to malignant cells and accelerates as cancer progresses. On the other hand, hypermethylation of specific regions, such as the CpG islands of tumor suppressor genes, plays an important role in carcinogenesis for many types of cancers, including lung cancer [20, 21]. Hypermethylation of these sequences can induce inappropriate silencing of growth regulatory genes and tumor suppressor genes. Inactivation of tumor suppressor genes via promoter hypermethylation is an early event in carcinogenesis and reported to be an early sign of lung cancer development [22].

2.1.1 DNA-methyltransferase—inhibitors In the 1960s, Vesely et al. first described the DNMTis azacitidine and decitabine and showed their cancerostatic effect in preclinical leukemia studies [23, 24]. In 1980 Jones et al. discovered that azanucleotides could induce DNA hypomethylation, especially when lower doses were used [25]. Momparler et al.

conducted preclinical and clinical studies proving that azanucleotides were effectively targeting DNA methylation in leukemic cells [26, 27]. After numerous further trials, azacitidine and decitabine were finally approved by the FDA for hematological malignancies (see Supplement Table 1).

2.1.2 DNMTi-monotherapy in lung cancer—A pilot phase I-II study on decitabine in patients with stage IV NSCLC was conducted by Momparler et al. [28, 29]. One patient was reported to have survived 81 months. This promising finding led to further DNMTi trials in lung cancer patients. Most of these trials combined DNMTis with other agents. To our knowledge, only one monotherapy trial with decitabine was conducted in NSCLC patients; no objective clinical response was observed and severe toxicities occured. Grade 4 neutropenia was observed in 15 patients, and was dose limiting in four patients; grade 3 neutropenia, thrombocytopenia or anemia were frequently reported as well. Two patients with extensive liver metastases experienced grade 3 hepatotoxicity [4] (Table 1). Due to limited efficacy in NSCLC as monotherapy, further trials combined DNMTis with other agents [4, 30].

2.2 Histone modifications

In eukaryotes, 147 base pairs (bp) of DNA are wrapped around an octamer of histones consisting of two copies each of H2A, H2B, H3 and H4 [31]. The resulting nucleosomes are further compacted to form higher-order chromatin structures. There are several types of histone modifications, including acetylation, methylation and ubiquitination. These modifications regulate gene expression by altering the interactions of histones with chromatin-associated proteins, marking regions of transcriptionally active euchromatin and inactive heterochromatin [32]. Histone post-translational modification is not dependent on the cell cycle and is potentially reversible [33, 34]. Histones can be post-translationally modified by histone acetyltransferases (HATs) and histone deacetylases (HDACs) [35]. HDACs are responsible for removing the acetyl-group from lysine residues in histones, inducing a condensed state of inactivated-chromatin (heterochromatin) and transcriptional repression; HATs perform the opposite function by adding acetyl-groups to lysine residues and inducing a euchromatin state and transcriptional activation [36]. There are four classes of HDAC enzymes based on their structures and functions: class I (HDAC 1–3 and 8), II (HDAC 4–7, 9 and 10), III (Sir-2 related - SIRT1-7) and IV (HDAC 11) [37] HDAC expression can be altered in various cancers. Overexpression of HDACs was observed in several solid tumors including lung cancer [38–40]. A synergistic interaction between HDAC-mediated histone deacetylation and DNMT-mediated DNA methylation can collaboratively cause gene silencing [15, 41, 42]. These mechanisms are known to be involved in cancer development [36].

2.2.1 Histone deacetylase inhibitors—HDACis were developed to reverse the gene silencing effect of HDACs and are classified into the following four major classes: 1) hydroxamic acids, 2) amino-benzamides, 3) cyclic peptides and 4) short-chain fatty acids [31]. The most commonly used HDACi in clinical trials with solid tumors and hematological malignancies belong to the first two groups. Three HDACi have been FDA-approved for the treatment of T-cell lymphomas: vorinostat, romidepsin, and belinostat. The HDACi

panobinostat has been FDA-approved for the treatment of multiple myeloma since 2015 (Supplementary Table 1).

2.2.2 HDACi-monotherapy in lung cancer—HDACi monotherapies were investigated in NSCLC and SCLC clinical trials. Romidepsin was tested in three single-arm monotherapy trials. Among them, a phase I trial in patients with neuroendocrine tumors was terminated early due to an increased number of severe cardiac toxicities [43]. Two later trials, one in NSCLC and one in SCLC, did not identify severe cardiac toxicities despite the fact that the dosage was increased in the NSCLC trial [44, 45] (Table 1 and Supplementary Table 3). Romidepsin was ultimately found to be clinically ineffective in a monotherapy setting. Safety and efficacy of entinostat, vorinostat, belinostat and panabinostat were investigated in monotherapy settings in NSCLC patients [6, 7, 9]. Entinostat showed only minimal efficacy, but was reported to be safe and tolerable in NSCLC [6, 7]. Vorinostat did not show any objective antitumor response in NSCLC patients, and severe toxicities were reported [9]. Panobinostat, a pan-deacetylase inhibitor, is the only HDACi that induced tumor-shrinkage as a monotherapy in SCLC. However, the trial was terminated earlier than planned, as only a small percentage of patients responded [46]. Thus, HDACi monotherapy has not proven to be effective in lung cancer.

2.3 Epigenetic therapeutic combinations for the treatment of lung cancer

As the antitumor efficacy of epigenetic monotherapies is low, more recent trials have combined epigenetic therapeutics in an effort to improve outcome. The observation both *in vitro* and *in vivo* that HDAC-mediated histone deacetylation and DNMT mediated DNA methylation collaboratively cause gene silencing supported clinical trials to test the efficacy of combining HDAC inhibition and DNMT inhibition in cancer treatment [15, 19, 41, 42]. Several such trials were terminated earlier than planned. Chu et al. published a clinical trial combining HDAC inhibition with valproic acid and DNMT inhibition with decitabine in NSCLC patients. Unacceptable neurotoxic adverse events were reported and there was no survival benefit [14]. Juergens et al. conducted a phase I/II trial of combined azacitidine and entinostat in NSCLC patients. Median overall survival (OS) and median progression free survival (PFS) were encouraging, 8.6 months and 7.4 weeks respectively, after completion of at least one cycle of epigenetic treatment, although the objective response rate was low [10]. The vast majority of patients (87%) discontinued the therapy due to disease progression [10] (Table 1). Another interesting finding from this study was an increased objective response (21%) of those patients continuing with other chemotherapies. Subsequently, further trials combining chemotherapy with epigenetic agents were conducted.

3. Epigenetic therapeutics combined with non-immune therapies in lung cancer

To improve therapeutic efficacy in lung cancer, clinical trials with combinations of epigenetic therapeutics with chemotherapeutics, radiotherapy, targeted therapy and more recently immunotherapy have been conducted.

3.1. Epigenetic therapeutics combined with chemotherapy

In preclinical studies, taxanes and platinum-based agents led to an increased antitumor effect when combined with HDACi [47, 48]. This was investigated in clinical trials combining HDACi with chemotherapeutics. Ramalingam et al. published a trial combining carboplatin and paclitaxel with vorinostat or placebo in 94 NSCLC patients. Among them, twenty completed the vorinostat arm and, showed a prolonged PFS (6 vs 4.1 months), a prolonged OS (13 vs. 9.7 months) and an improved response rate (RR) of 34% compared to 12% in the placebo arm. The 1-year OS was 51% in the vorinostat group and 33% in the placebo group [45]. Toxicities were substantial with 3 deaths occurring in the vorinostat arm [49, 50], Table 2a. Jones et al. reported partial response (PR) in 1 out of 5 lung cancer patients treated with panobinostat, paclitaxel, and carboplatin [50]. A recent phase I study combining belinostat with carboplatin and paclitaxel, presented at the 2016 World Conference on Lung Cancer by Waqar et al., demonstrated encouraging antitumor efficacy. In 13 out of 23 patients RR was available. PR was seen in 35%, stable disease (SD) in 17% and only one patient had a progressive disease (PD) [51]. Compared to carboplatin/paclitaxel alone, the combination with an HDACi appears promising [49].

Unfortunately, the results of most clinical trials combining HDACi with chemotherapy in lung cancer have been negative. Some of these trials were terminated early due to toxicities. Trials with published outcome data are limited, and several trials are still ongoing (Table 2a). While combined treatment of lung cancer patients with either belinostat or vorinostat with carboplatin and paclitaxel shows preliminary efficacy, larger trials must be performed and ongoing trials need to be completed to confirm efficacy. In a neoadjuvant phase-I trial combining the proteasome inhibitor bortezomib with vorinostat, necrosis was detected in 6 out of 20 patients who completed the treatment. Additionally Jones et al. reported reduced SUV-uptake in PET-CT scans performed after treatment completion but before surgery [52]. Erasmus et al. reported that a reduction of SUV-uptake could predict operability and survival [53]. It remains unclear if the necrosis was related to the treatment or caused by the tumor itself. Furthermore the tumor size was not reduced by this neoadjuvant treatment. Toxicities were dose-limiting in two patients (Table 2a).

3.2 Epigenetic therapeutics combined with targeted therapies

There are several ongoing and completed trials combining epigenetic drugs with targeted therapies (Table 2a). A trial combining the HDACi belinostat with the erlotinib was terminated due to intolerable toxicities. The full publication of this study is still pending. Witta et al. published a phase II, two-arm trial combining entinostat or placebo with erlotinib in 132 advanced NSCLC who previously experienced chemotherapy treatment failure. The trial population was not preselected by actionable EGFR mutation. The combined therapy of erlotinib and entinostat did not result in improved clinical outcome in this unselected patient population. Han et al. published a phase I/II trial combining gefitinib and vorinostat in patients with both EGFR-mutant and EGFR-wildtype advanced NSCLC. Subgroup analysis found that vorinostat potentially improves the efficacy of gefitinib in EGFR-mutant NSCLC [78, 82]. However, only 13 patients in this study were EGFR-mutant. Larger trials will be needed to validate the finding. A preclinical study demonstrated that the combined use of vorinostat and osimertinib could reverse BIM deletion polymorphism–mediated osimertinib

resistance in EGFR-mutant NSCLC cells. Therefore, the authors suggest the future development of selective HDAC inhibitors to overcome osimertinib resistance [83]. To our knowledge, combined epigenetic therapy and ALK-inhibitor therapy trials have not yet been conducted. A preclinical study by Fukuda et al. demonstrated that HDAC inhibition with quisinostat could overcome crizotinib resistance by mesenchymal-epithelial transition. This preclinical finding might support related clinical studies in NSCLC with ALK rearrangement [84].

3.3 Epigenetic therapeutics combined with radiation therapy

Preclinical studies combining HDACi and radiation therapy in lung cancer, colon cancer, breast cancer, and other cancers demonstrated increased anti-tumor efficacy [85–87]. The combination of HDACi with radiotherapy was investigated in three recent lung cancer trials [88–90]. Vorinostat was used as a radiosensitzer in a phase-I study, enrolling twelve NSCLC patients with brain metastases. The combination of vorinostat with radiation therapy was reported to be safe and the median OS was 36 weeks. A recently published study by Choi et al. enrolled 17 NSCLC patients with up to 4 brain metastases and used vorinostat as a radiosensitizer before sterotactic radiotherapy of the brain metastases. Dose-limiting toxicities did not occur (Supplementary Table 3) [89]. Further studies are ongoing.

4. Epigenetic therapeutics combined with immunotherapy

4.1 Lung cancer immunity and immunotherapy

NSCLC has been historically considered to be non-immunogenic. In recent years the role of the immune system in cancer development and progression, and in lung cancer in particular, has been better understood [91, 92]. Both the innate and the adaptive immune systems are involved in destroying cancer cells and inhibiting cancer cell growth [93]. Immature dendritic cells (DC), existing in most human cancers, capture cancer cell antigens [94, 95]. Once activated, DCs present cancer antigens within the major histocompatibility complex (MHC) to naïve T-cells in tumor-draining lymph nodes and induce a T-cell response. Cytotoxic CD8+ T-cells are then enabled to spot and destroy cancer cells [3]. Dysfunction of the immune system is well-known to be involved in cancer development and progression through different mechanisms [93, 96, 97]. Recent publications have demonstrated that various immunological mechanisms play an important role in NSCLC. Impairment of T-cell proliferation and an immunosuppressive microenvironment contribute to lung cancer growth [98–100]. One of the major mechanisms of T-cell suppression is the so-called immune checkpoint. Several immune checkpoints have been discovered including CTLA-4/B7, PD-L1/PD-1, LAG-3, TIM-3 [101].

Programmed death receptor-1 (PD-1) is expressed by cytotoxic T-cells infiltrating NSCLCs. The increased expression and activation of PD-1 has a wide immunosuppressive effect [102]. The upregulation of programmed death receptor ligand-1 (PD-L1) on NSCLC cells correlates with the suppression of activating tumor-infiltrating DCs and T-cells [103–105]. These recent findings in cancer immunity brought forth the development of novel immunotherapies in lung cancer and other malignancies. Some of the most promising drugs target immune checkpoints such as PD-1/PD-L1 and CTLA-4. An increased OS in NSCLC

patients treated with anti-PD-1 or anti-PD-L1 in second-line therapy and also in selected patients in first-line therapy was demonstrated [91, 106–108]. Nivolumab (anti-PD1), pembrolizumab (anti-PD1), and atezolizumab (anti-PDL1) have been approved as a 2nd line NSCLC therapy. Pembrolizumab has been approved as 1st line treatment in metastatic NSCLC. In May 2017, pembrolizumab in combination with carboplatin and pemetrexed was granted accelerated approval for metastastic nonsquamous NSCLC as 1st line treatment (Supplementary Table 4).

4.2 Preclinical studies of combined epigenetic therapeutics and immunotherapy

Only a minority of patients treated with immunotherapy shows a long-term benefit [18, 107, 109]. To enhance clinical efficacy, combinations of epigenetic therapies with immunotherapies were studied in lung cancer and other cancers [110]. Several preclinical studies suggest that epigenetic reprogramming enhances immune recognition and response against cancer cells and reverse immune evasion [111, 112]. HDACi and DNMTis significantly augment the effector T-cell tumor-infiltration by removing or inhibiting myeloid-deprived suppressor cells (MDSC) and other immune suppression components [113–115].

Preclinical studies demonstrate that combining epigenetic drugs with immunotherapy could lead to alteration of multiple pathways, changing the phenotype of cancer cells and facilitating long-lasting adaptive- and innate- immune responses [111, 113, 116]. The HDACis vorinostat and romidepsin enhance T-cell chemokine expression and augment response to PD-1 immunotherapy in lung adenocarcinoma. *In vivo* experiments with this combined treatment result in nearly complete lung cancer eradication [113]. A mouse-model with colon carcinomas and mammary carcinomas treated by combining azacitidine, entinostat and anti-PD-1 or anti-CTLA-4 therapy revealed a remarkable improvement in treatment outcomes and cure of more than 80% of tumor-bearing mice [116]. Furthermore, epigenetic therapies have been reported to increase tumor antigen expression. Weiser et al. reported that treatment with the DNMTi decitabine alone as well as the sequential treatment with decitabine and the HDACi depsipeptide increase the expression of cancer testis antigen NY-ESO-1 and facilitate the recognition of thoracic cancer cells by CD8+ T-cells specific for NY-ESO-1 [117].

4.3 Clinical combinations of epigenetic therapeutics with immunotherapy

Wrangle et al followed up 6 patients who previously received epigenetic therapy with azacitidine and entinostat within a trial mentioned above [10] and subsequently treated with anti-PD-1 or anti-PD-L1. Of these 6 patients, 3 partial responses and two stable diseases were observed after immune checkpoint blockade [112, 118–120]. These recent preclinical and clinical discoveries support the rationale of several clinical combination therapy study designs. Combinations of epigenetic drugs and immunotherapies are currently under investigation in multiple lung cancer trials (Table 2b). To date, only limited outcome data is available from such trials.

Preliminary results of an ongoing trial combining pembrolizumab and entinostat in NSCLC patients and melanoma patients (ENCORE 601) were recently presented as posters at the

Society for the Immunotherapy of Cancer Annual Meeting in 2016 and Annual ASCO meeting in 2017 respectively [121, 122]. Out of 22 enrolled NSCLC patients, 17 were evaluable. Of eleven anti-PD-1/PD-L1 naïve patients, one PR, one SD and nine PD were reported. The prior preclinical finding of reduced immunosuppressive myeloid driver suppressor cells and regulatory T-cells could be verified in blood samples of the study patients [116, 121]. Of the remaining six patients who had received prior anti-PD-1/PD-L1 therapy and were now receiving combination therapy, three had SD and the other three had PD. Grade 3/4 treatment-related adverse events included hypophosphatemia (9%), neutropenia (5%), anemia (5%), acute respiratory failure (5%), elevated alkaline phosphatase (5%), and immune-mediated hepatitis (5%) [121]. Syndax Pharmaceuticals recently announced the interim analysis of this trial. The pre-specified objective response threshold to advance into the second stage of the Phase 2 trial was met [123]. At least 2 out of 20 NSCLC patients, previously progressive on anti-PD-1 or anti-PD-L1 therapy or 3 out of 13 NSCLC patients previously naïve to anti-PD-1 or anti-PD-L1 therapy responded objectively, defined as either a PR or complete response (CR) to entinostat/pembrolizumab treatment [123]. Encouraging signals have emerged from preliminary interim analyses, although most clinical trials in this field are still ongoing. The completion of ENCORE 601 and other ongoing trials will provide data to answer weather clinical efficacy could be confirmed for combining epigenetic and immunotherapies (Table 2b).

5. Discussion

This review focuses on epigenetic therapeutics and their impact on novel therapies including immunotherapy of lung cancer. FDA-approval of these drugs for MDS, AML, ALL and lymphomas treatment encouraged the exploration of the efficacy of epigenetic therapy studies in lung cancer patients. The efficacy of monotherapies in lung cancer was very limited; and when higher doses were applied severe toxicities were observed. The discovery of a possible synergistic effect of different groups of epigenetic therapeutics led to multiple lung cancer trials combining DNMTis and HDACis [10, 14] (Table 1). Again, substantial toxicities occurred and led to the early termination of numerous trials. Most of the dual-agent epigenetic therapy trials completed in lung cancer did not result in a survival benefit. Prolonged survival and PFS were achieved in some lung cancer patients in a clinical trial combining azacitidine and entinostat [10].

An additive effect of epigenetic therapies and chemotherapy was found in 21% of patients who subsequently continued with chemotherapies [10]. Several clinical trials were initiated to verify this improved effect. Ramalingam et al. described a trend toward improvement in median PFS and OS in the vorinostat-group [49]. Unfortunately, the synergistic effect was accompanied by added toxicities, which led to death in several patients [49]. Several other trials with the same approach are to be completed in the near future and might shed light on an optimal regimen when epigenetic therapeutics are combined with chemotherapy in lung cancer patients (Table 2a).

Some combined targeted therapy and epigenetic therapy trials were designed before the necessity of EGFR mutation testing for effective targeted therapy was known. Therefore, the clinical impact of these combinations remains unclear. The clinical efficacy of such

combinations should be investigated in a preselected cohort of EGFR-mutated NSCLC patients. At least one such trial currently enrolls EGFR-mutant NSCLC patients (Table 2a). Preclinical data suggest that HDACi could reverse the acquired resistance to 3rd generation EGFR inhibitors and ALK inhibitors in NSCLC patients with actionable EGFR or ALK mutations. These findings need to be verified in clinical trials designed to test this strategy. Another promising approach is the combination of epigenetic therapies with radiotherapy. Only a few trials investigated this approach, but the available data suggests a survival benefit and tolerable toxicities.

Immune checkpoint blockade and other emerging immunotherapy are changing the landscape of lung cancer therapeutics. Positive signals from preclinical and clinical NSCLC studies suggested the efficacy of epigenetic therapeutics in combination with immunotherapy. Several clinical NSCLC studies combining HDACis, DNMTis, or both with anti-PD-L1 therapy and anti-PD-1 therapy with or without anti-CTLA-4 are recruiting patients (Table 2b). Preliminary results of some of those studies including ENCORE 601 support that this approach is clinically meaningful. To date, there are still gaps in the understanding of how epigenetic therapeutics can improve the efficacy of immunotherapies. Further understanding of epigenetic modulation not only in cancer cells, but also in the tumor microenvironment and immune system will help to optimize the clinical trial design and lung cancer management.

Epigenetic therapies have the potential for improving outcomes for lung cancer patients. These therapies can impact varieties of genes and pathways in cancer cells as well as other cells. Currently there is no reliable predictive biomarker for epigenetic therapies. Bringing these therapies to treat lung cancer and other cancers will require further studies confirming efficacy, minimizing side effects, and optimizing management. The most encouraging developments come from combination therapy, particularly with immunotherapy. Advancement of our understanding of tumor epigenetics and immunology, insight from previous and ongoing studies, and continuing the search for new ways to optimize treatment regimens will help us integrate epigenetic treatment into real world management of lung cancer and change the outcome of this disease.

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Curr Pharmacol Rep. Author manuscript; available in PMC 2018 December 01.

Table 1

Epigenetic therapeutics (mono- and combined) in NSCLC patients

Epigenetic agent		Phase	Total patient #	Patient # with NSCLC	Response rate	CR/PR	SD	OS month	Side effects	Study status	NCT number	Reference
DNMTi												
decitabine		1	EC, LC, pleural meso (35)	20	-		-	-	grade 4 neutropenia (15), grade 3 leukopenia, thrombocytopenia or anemia in (20) of 35, (2) of 35, and (3) of 35 patients	completed	NCT00019825	[4]
HDACi												
belinostat		1	-	-	-		-	-	not yet published	completed	NCT00413075	[5]
entinostat		1	refractory solid tumors and lymphomas (27)	2	better in lower dose		1/2	-	frequent hypophosphatemia	completed	NCT00020579	[6, 7]
romidepsin		2	19	16	no objective responses		9	-	grade 3 anemia (3), grade 3/4 neutropenia (4), grade 4 thrombocytopenia (1), grade 3 hypoxia (3), pneumonitis (1), tumor pain (1), thrombosis (1), cellulitis at injection site (2), pulmonary embolism (1)	completed	NCT00020202	[8]
vorinostat		2	16	16	2 progressed after 1 cycle (2), included in further analyses (14)		-	7.1	9 SAE: neutropenia (3), pulmonary embolism (2), hyperglycemia (1), thrombosis (1), dyspnea (1), cerebrovascular accident (1), 16 AE: neutropenia (6), hyperglycemia (5), lymphopenia (3), fatigue (4), pneumonia (1)	completed	NCT00138203	[9]
DNMTi	**HDACi**											
azacitidine	entinostat	1/2	45	45	see next columns	1/1	10		therapy cycle 1: grade 3: hematologic toxicities (9), gastrointestinal symptoms (6), electrolyte disturbances (3), general symptoms (5), grade 4:	completed	NCT00387465	[10]

Epigenetic agent		Phase	Total patient #	Patient # with NSCLC	Response rate	CR/PR	SD	OS month	Side effects	Study status	NCT number	Reference
									hematologic toxicities (3); therapy cycle ≥2: grade 3: hematologic toxicities (9), gastro intestinal (1), endocrine (1), general symptoms (5); grade 4: hematological toxicities (3)			
azacitidine	entinostat	-	-	Stage I NSCLC	-	-	-		not yet published	terminated	NCT01207726	[11]
azacitidine	entinostat	1	-	Stage I NSCLC	-	-	-		not yet published	terminated	NCT01886573	[12]
azacitidine	entinostat	-	-	-	-	-	-		not yet published	terminated	NCT01935947	[13]
decitabine	valproic acid	1	8	8	-	-	1		grade 3 neurotoxicity (2)	terminated earlier (initially 25 planned)	NCT00084981	[14]

Abbreviations: AE: adverse event; CR: complete response; DNMTi: DNA methyltransferase inhibitor; EC: esophageal cancer; HDACi: histone deacetylase inhibitor; LC: lung cancer; meso: mesothelioma; NCT Number: ClinicalTrials.gov identifier; NSCLC: non-small cell lung cancer; OS: overall survival; PR: partial response; SAE: serious adverse event; SD: stable disease; (−): data not available.

Table 2

th non-immune therapies in NSCLC patients

	Phase	Total patient #	Patient # with NSCLC	Response rate	CR/PR	PFS month	SD	OS month	Side effects	Study status	NCT number	Reference
py												
	1	-	-	-	-	-	-	-	not yet published	-	NCT00901537	[54]
r paclitaxel	1	-	-	-	-	-	-	-	not yet published	completed	NCT01478685	[55]
py												
carboplatin	1	23	23	35%	8	-	4	-	fatigue (91%), nausea (78%), constipation (74%), anemia (65%), diarrhea (65%), alopecia, arthralgia, decreased appetite, insomnia, neutropenia (61%), dizziness, vomiting (57%), headache (52%)	completed	NCT01310244	[51]
are chemotherapy	1	aimed 7	aimed 7		-	-	-	-	not yet published	terminated	NCT01090830	[56]
	1	-	-	-	-	-	-	-	not yet published	terminated	NCT00907179	[57]
- etoposid	1	6	4		-	-	-	-	dose-limiting toxicity (2), grade 4 thrombocytopenia and grade 4 febrile neutropenia (1)	terminated because of inacceptable toxicities	NCT00958022	[58]
metrexed	1	-	-	-	-	-	-	-	not yet published	active, not recruiting	NCT01336842	[59]
rboplatin, bevacizumab	1	22	4	-	3		11	-	neutropenia (90%, 67% grade 4), thrombocytopenia (90%), anemia (76%), fatigue (71%), diarrhea (52%), vomiting (48%)	completed	NCT00556088	[50]

th non-immune therapies in NSCLC patients

	Phase	Total patient #	Patient # with NSCLC	Response rate	CR/PR	PFS month	SD	OS month	Side effects	Study status	NCT number	Reference
+ carboplatin +	1/2	25	25	-	-	-	-	-	not yet published	terminated	NCT00702572	[60]
	1/2	-	-	-	-	-	-	-	not yet published	terminated	NCT00697476	[61]
+ platinum-based agent	1	61 (10 completed)	61	-	-	-	-	-	39 SAE, 61 AE (most frequent anemia and asthenia)	completed	NCT00423449	[62]
	1	12	3	-	-	-	-	-	not separately documented for LC		NCT00565227	[63]
paclitaxel	2	62 (20 completed in vorinostat-arm) 32 (12 completed in placebo-arm)	94	34% (vorinostat-arm) vs 12%	-	6 vs 4.1		13 vs 9.7	29 SAE (vorinostat-arm):febrile neutropenia (2), anemia (2), cardiac disorders (3), gastrointestinal disorders (10), death (3), other general disorders (9), 100% other AE in vorinostat-arm: anemia (43), constipation (23), diarrhea (20), nausea (37), vomiting (25), PD (20), fatigue (52), leukocyte amount decreased (28), thrombocyte count decreased (36), anorexia (35), hyperglycemia (29), peripheral neuropathy (29), and others	completed	NCT00481078	[49]
hase 1), carboplatin	1/2	12 (vorino-stat-arm 4)	12 (vorino-stat-arm 4)	-	-	-	-	-	SAE 3/4: nausea (1), sepsis (1), platelet count decreased (1), hypotension (1), dehydratation (1), neutrophil count	terminated	NCT01413750	[64]

th non-immune therapies in NSCLC patients

	Phase	Total patient #	Patient # with NSCLC	Response rate	CR/PR	PFS month	SD	OS month	Side effects	Study status	NCT number	Reference
									decreased (1), platelet count decreased (1), WBC decreased (1) AE 4/4: anemia (2), blurred vision (1), diarrhea (2), and others			
+ paclitaxel	2/3	126 (vorino-stat-arm), completed 43	126 (vorino-stat-arm)	-	-	-	-	-	SAE 63 (vorinostat-arm) vs 45, AE 114 vs 117	-	NCT00473889	[65]
	1	aimed 23	-	-	-	-	-	-	not yet published	terminated	NCT00094978	[66]
	1	21	neo-adjuvant (21)	6 patients > 60% necrosis	-	-	-	-	most common toxicities included: grade 1 fatigue (14/20, 70%), grade I nausea (8/20, 40%), grade 1 neuropathy (4/20, 20%), and grade 1 diarrhea (4/20, 20%). DLT (2)	completed	NCT00731952	[52]
	2	18	18	-	-	1.5	5	4.7	grade 3 toxicities: thrombocytopenia (7), lymphopenia (3), fatigue (4), hyponatremia (3), dizziness (2), vomiting (2), syncope (2), neuropathy (2), grade 4 toxicities: thrombocytopenia (1), fatigue (1)	completed	NCT00798720	[67]
erapy												
	1	30	2	*	1	>4 in NSCLC, n/a for SCLC	2	-	not separately documented for LC, conjunctivitis, infusion reaction (2/5)	completed	NCT00996515	[68]

th non-immune therapies in NSCLC patients											
	Phase	**Total patient #**	**Patient # with NSCLC**	**Response rate**	**CR/PR**	**PFS month**	**SD**	**OS month**	**Side effects**	**Study status**	**NCT number**	**Reference**
TOR inhibitor CC-223	1b	-	-	-	-	-	-	-	not yet published	completed, Celgene	NCT01545947	[69]
erapy												
	1/2	-	5 (preliminary)	-		-	-	-	grade 3 diarrhea (3), grade 2 diarrhea(1), grade 2 rash (1), grade 1 diarrhea (1), grade 1 nausea (1),	terminated after 5 patients due to severe toxicities	NCT01188707	[70]
	2	132	132	prolonged OS with high expression of E-cadherin	-	-	-	9.4 (patients with high levels of e-cadherin) vs5.9	Fatigue (32), rash (35), diarrhea (30), dermatitis acneiformis (12), dyspnea (11), anemia (7), asthenia (7), hypokalemia (7), abdominal pain (7), hypoxia (4), pleural effusion (4), pneumonia (3), hypophosphatemia (3), syncope (1),	completed	NCT00750698	[71]
	1	42	35	-	3	2.5	14	7.4	most common AEs were fatigue and nausea (grades 1–3) and rash and anorexia (grades 1–2), not specified for LC	completed	NCT00738751	[72]
	1	-	-	-	-	-	-	-	not yet published	completed	NCT01005797	[73]
se 1)	1/2	17	17	-		3.3, prolonged PFS >6	7	-	nausea, vomiting, and fatigue (each 82%), diarrhea (65%), anorexia (53%), and rash (41%)	completed	NCT01302808	[74]
	1/2	33 EGFR mutant NSCLC	33	-	-	-	7	no significant difference	anemia (20), diarrhea (19), rash (12), fatigue (16), nausea (11), anorexia (12),	completed	NCT00503971	[75]

th non-immune therapies in NSCLC patients												
	Phase	Total patient #	Patient # with NSCLC	Response rate	CR/PR	PFS month	SD	OS month	Side effects	Study status	NCT number	Reference
									vomiting (9), xerosis cutis (8), xerostomia (6), conjuncitivis (5), epigastralgia (4), leukopenia (3), neutropenia (3), mucositis (4), pneumonitis (1).			
se 2)	1/2	16 (1 completed)/ 9 discontinued due to PD	16	-	-	-	-	-	only 1 patient completed the study	terminated	NCT00251589	[76]
	1	EGFR mutant NSCLC	aimed 18	-	-	-	-	-	not yet published	recruiting	NCT02151721	[77]
	1/2	52/43	52/43	see next columns	16	3.2	6	19	toxicities (grade 1–3) in phase I (15) in phase 2 (43)	completed	NCT01027676	[78]
	1	35	15		1	2.2	5	-	fatigue (8/15), rash (8/15), nausea (8/15), anorexia (7/15), diarrhea (6/15), hand-foot syndrome (5/15), others	completed	NCT00635791	[79]
py												
	1/2	20	-	-	-	-	-	-	not yet published	completed	NCT01628471	[80]
celecoxib	1	34	-	-	-	-	-	-	not yet published	completed	NCT00037817	[81]

ith immune therapies in NSCLC patients											
	Phase	Patients #	Patients # with NSCLC	Response rate	PR	SD	Side Effects	Estimated completion	Study Status	NCT Number	Reference
	2	12 (in 2016), aimed 90	12	-	-	-	not yet published	-	recruiting	NCT02546986	[124]

Curr Pharmacol Rep. Author manuscript; available in PMC 2018 December 01.

b Epigenetic therapies combined with immune therapies in NSCLC patients

Epigenetic agents			Phase	Patients #	Patients # with NSCLC	Response rate	PR	SD	Side Effects	Estimated completion	Study Status	NCT Number	Reference
HDACi	**Immunotherapy**												
ACY 241	nivolumab + ipilimumab		1b	not yet completed, aimed 41	aimed 41	-	-	-	not yet completed	2017	recruiting	NCT02635061	[125]
entinostat	pembrolizumab		1b/2	NSCLC and melanoma, 22	not yet completed 22	-	1 (PD-1 naive)	3 (PD-1 naive), 2 (prior PD-1 treatment)	not yet completed, first 22 patients 5 study related AE; 2017: treatment-related AEs occurred in 5 patients (most common: nausea and fatigue (2); grade 3/4 fatigue and rash (1).	2019	recruiting	NCT02437136	[122]
entinostat	pembrolizumab		1	NSCLC	aimed 30, not yet completed	-	-	-	not yet published	2018	recruiting	NCT02909452	[126]
entinostat	nivolumab + ipilimumab			solid tumors mainly BC	not yet completed	-	-	-	not yet completed	2018	recruiting	NCT02453620	[127]
vorinostat	pembrolizumab		1/2	aimed 100, not completed	aimed 100, not completed	-	-	-	not yet completed	2017	recruiting	NCT02638090	[128]
DNMTi	**HDACi**	**Immunotherapy**											
azacitidine	entinostat	nivolumab	1	not completed	-	-	-	-	not yet published	Aug-18	recruiting	NCT01928576	[129]
DNMTi	**others**	**Immunotherapy**											
azacitidine	epacadostat	pembrolizumab	1/2	solid tumors and NSCLC	not completed	-	-	-	not yet published	2021	recruiting	NCT02959437	[130]
decitabine	tetra-hydrouridine	nivolumab	2	not completed	NSCLC	-	-	-	not yet published	2019	not yet recruiting	NCT02664181	[131]
azacitidine	paclitaxel	1 (1+3, 3 mono, or 3+ durvalumab)	2	-	advanced NSCLC	-	-	-	not yet published	2018	recruiting	NCT02250326	[132]

Abbreviations: AE: adverse event; CR: complete response; DLT: dose limiting toxicities; DNMTi: DNA methyltransferase inhibitor; HDACi: histone deacetylase inhibitor; LC: lung cancer; n/a: not available; NCT Number: ClinicalTrials.gov identifier; NSCLC: non-small cell lung cancer; OS: overall survival; PD: progressive disease; PR: partial response; PFS: Progression free survival; SAE: serious adverse event; SCLC: small-cell lung cancer; SD: stable disease; WBC: white blood cells. (−): data not available.

* not separately documented for lung cancer.

Abbreviations: AE: adverse event; BC: breast cancer; CR: complete response; CRS: cytokine release syndrome; EC: esophageal cancer; HL: Hodgkin's lymphoma; LC: lung cancer; NCT Number: ClinicalTrials.gov identifier; NHL: Non-Hodgkin's lymphoma; NSCLC: non-small cell lung cancer; PD: progressive disease; PR: partial response; SD: stable disease. (−): data not available.