Emerging Therapies in Non–Small Cell Lung Cancer: Clinical Trials With Novel Agents

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Author's disclosures of potential conflicts of interest are found at the end of this article.

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Abstract

Non–small cell lung cancer (NSCLC) continues to be the leader in cancer-related deaths in the United States. Although local therapies such as surgery and special types of radiation appear to deliver the best chance for cure or remission, systemic therapies such as chemotherapies and novel biologic therapies can be offered in combination with local therapies or alone for patients with metastatic disease. With tremendous improvement in the world of medical research and individualized cancer therapies, the medical oncology community is continuously discovering and targeting a network of molecular markers and genetic mutations in NSCLC in hopes of advancing the current treatment and formulating specifically tailored regimens for all patients with NSCLC. Clinical trials are designed to investigate the efficacy and safety of new drugs to improve survival and quality of life. Emerging treatment approaches, specific mechanisms of action, and drug classes in the development of NSCLC agents will be discussed.

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Although treatment options have significantly improved within the past 2 decades, non–small cell lung cancer (NSCLC) is the most common type of lung cancer, and its survival rate remains a challenge. At the turn of the 21st century, an improved understanding of NSCLC pathophysiology and the identification of genetic mutations have gradually shifted the treatment approach from general chemotherapy to targeted therapy (Figure 1). Driver mutations are identified in approximately 60% of patients with NSCLC, suggesting that targeted therapies may be more effective in this subgroup of patients (Chan & Hughes, 2015). Currently, there is a small number of NSCLC targeted therapies against some of the known genetic mutations. However, there is an unmet need for a large number of patients with NSCLC who harbor

certain types of mutations that do not yet have options and would need to be treated with standard chemotherapy (Borghaei et al., 2015). There is also an increasing number of clinical trials for patients with NSCLC evaluating the potential benefit of new therapies (Table 1).

EMERGING TREATMENT APPROACHES AND PATHWAYS

First-generation genetic alterations such as epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) rearrangements, and Kirsten rat sarcoma (*KRAS*) mutations

Table 1. Summary of Current Phase I/II Clinical Trials for Patients With NSCLC

Class	Agent	Mechanisms of action	Phase	Design
Tumor epigenetics	Entinostat	HDAC inhibitor	I, II	Combination
	Azacitidine	DNA hypomethylation	I	Monotherapy
Tumor metabolism	Ethaselen	Thioredoxin reductase	I	Combination
	LY2606368	Checkpoint kinase 1	I	Combination
Immunotherapy	Gemogenovatucel-T	Tumor peptide vaccine	II	Combination
	JNJ-64041757	Listeria vaccine	I	Monotherapy
	DSP-7888	Wilms tumor 1 vaccine	I	Monotherapy
	AD-MAGEA3 and MG1-MAGEA3	MAGE-A3-expressing Maraba virus	I, II	Monotherapy
	Enoblituzumab	B7-H3 antibody	I	Monotherapy
	Indoximod	Indoleamine 2,3 dioxygenase inhibitor	I, II	Combination
	Avelumab	Programmed cell death ligand 1 inhibitor	II	Combination
	Varlilumab	Anti-CR27 monoclonal antibody	I	Combination
	Autologous gamma delta T-cell therapy (ImmuniCell)	Autologous T lymphocytes	II, III	Monotherapy
	Targeted natural killer (NK) cells	Modified NK cell therapy	II	Monotherapy
	rSIFN-co	Recombinant interferon	I	Monotherapy
Targeted therapy	Tesevatinib	EGFR CNS penetrant	II	Monotherapy
	Famitinib	c-KIT, vascular endothelial growth factor receptor (VEGFR) 2, platelet-derived growth factor receptor, VEGFR3, FMS-like tyrosine kinase (FLT)1, FLT3	II	Monotherapy and combination
	Anlotinib	VEGF1/2/3, fibroblast growth factor receptor (FGFR)2	II, III	Monotherapy
	Entrectinib	NTRK1/2/3, ROS1, ALK	II	Monotherapy
	LY3023414	PI3K, mTOR	II	Combination
	Ibrutinib	Bruton tyrosine kinase	I, II	Monotherapy
	Pacritinib	Janus kinase 2	I, II	Monotherapy
	Binimetinib	MEK	I	Combination
DNA repair	Veliparib	PARP	I, II	Combination
Chemotherapy	Plinabulin	Tubulin depolymerization	I, II	Combination
	PT-112	Platinum based	I, II	Combination
Oncolytic virus	CVA21	CVA21	I	Combination

Note. Information from ClinicalTrials.gov (2017).

account for a significant proportion of the driver mutations identified in NSCLC (Khanal & Ganti, 2016). Several known targeted agents against B-rapidly accelerated fibrosarcoma (*BRAF*) V600E mutation, MNNG-HOS transforming gene (*MET*) pathway, C-ros oncogene 1 (*ROS1*) rearrangement, rearranged during transfection (*RET*) rearrangement, and human epidermal growth factor receptor 2 (*HER2*, *HER2/neu* or *ErbB2*) pathways offer promising therapeutic options (Figures 1 and 2). Emerging mechanisms of action and focused areas of scientific work that are currently being investigated through phase I and II clinical trials in NSCLC are tumor epigenetics, tumor metabolism, cancer vaccines, checkpoint inhibitors, modified T-cell therapy, cytokines, next-generation EGFR inhibitors, multikinase inhibitors, phosphoinositide 3-kinase isoforms and mechanistic target of rapamycin kinase (PI3K/mTOR) pathway inhibitors, other miscellaneous target inhibitors, DNA repair, new generation chemotherapy, and oncolytic virus (Figures 1 and 2; Dholaria, Hammond, Shreders, & Lou, 2016). Table 1 summarizes the current therapeutic agents on phase I/II clinical trials involving patients with NSCLC (ClinicalTrials.gov, 2017). These drugs aim to offer better alternatives to drugs in their class or are a completely new class of drugs with novel mechanisms of action.

TARGETS AND MECHANISMS OF ACTION

Targeted Therapy

Targeted therapies directly involve specific protein molecules that are responsible for cell cascades of dysregulations or activations of certain genes. Any changes or disruptions in cell pathways with specific protein molecules can cause tumor growth (Croce, 2008). Transcription factors, kinases, and growth factors are some of the many factors involved in signaling systems, leading to cell growth, survival, differentiation, and programmed cell death. Currently, many targeted agents are being investigated, specifically for various oncogenic proteins for potential therapeutic benefit in NSCLC (Figure 1). Some agents focus on a very specific target or pathway, whereas other inhibitors involve multiple targets in the development of NSCLC treatment (Hirsch, Suda, Wiens, & Bunn Jr., 2016) See Table 2 for a summary of commonly known inhibitors and their agents.

EGFR Inhibitors

EGFR inhibitors are the first generation of targeted agents. Gefitinib (Iressa), erlotinib (Tarceva), afatinib (Gilotrif), and osimertinib (Tagrisso) are currently approved as therapeutic agents. ASP8273 (phase III), EGF816 (phase II), and PF-06747775 (phase II) are still under evaluation in clinical trials (Hirsch et al., 2016). Although several EGFR inhibitor agents are current and previously noted, specific EGFR targets, such as EGFR T790M, EGFR (central nervous system [CNS] penetrant), EGFR/MET bispecific monoclonal antibody (mAb), EGFR exon 20, EGFR mAb, and EGFR antibody miR-16, are being explored. Some of the promising agents include tesevatinib, which targets CNS penetration, and AP32788, which targets exon 20 mutations (Dholaria et al., 2016).

The results of preclinical studies on AP32788 were presented at the 2016 American Association for Cancer Research Annual Meeting. The research showed that AP32788 inhibited *EGFR* and *HER2* mutants including exon 20 insertion mutants. Inhibition of EGFR in nontumor cells has been associated with dose-limiting toxicities of EGFR inhibitors in patients. The analysis confirmed that AP32788 irreversibly inactivated EGFR exon 20 with 20-fold selectivity over wild-type EGFR in contrast with other tested EGFR tyrosine kinase inhibitors. The phase I/II clinical trial of AP32788 is now open for patient enrollment in multiple institutions.

ALK Inhibitors

ALK inhibitors such as crizotinib (Xalkori), alectinib (Alecensa), ceritinib (Zykadia), and brigatinib (Alunbrig) are currently approved by the US Food and Drug Administration (FDA). Lorlatinib (phase II), X-396 (phase III), TSR-011 (phase II), and entrectinib (phase II) are being studied in trials. On April 28, 2017, the FDA granted accelerated approval to the targeted therapy brigatinib for patients with metastatic NSCLC with the *ALK* gene alterations who progressed on or are intolerant to crizotinib. Brigatinib is the fourth *ALK*-targeted agent and the third approved for this use after crizotinib. The new approval is based on clinically meaningful and durable overall response rates (ORRs) in patients with locally advanced or metastatic *ALK*-positive NSCLC whose disease progressed with crizotinib. In the noncomparative, two-arm, open-label, mul-

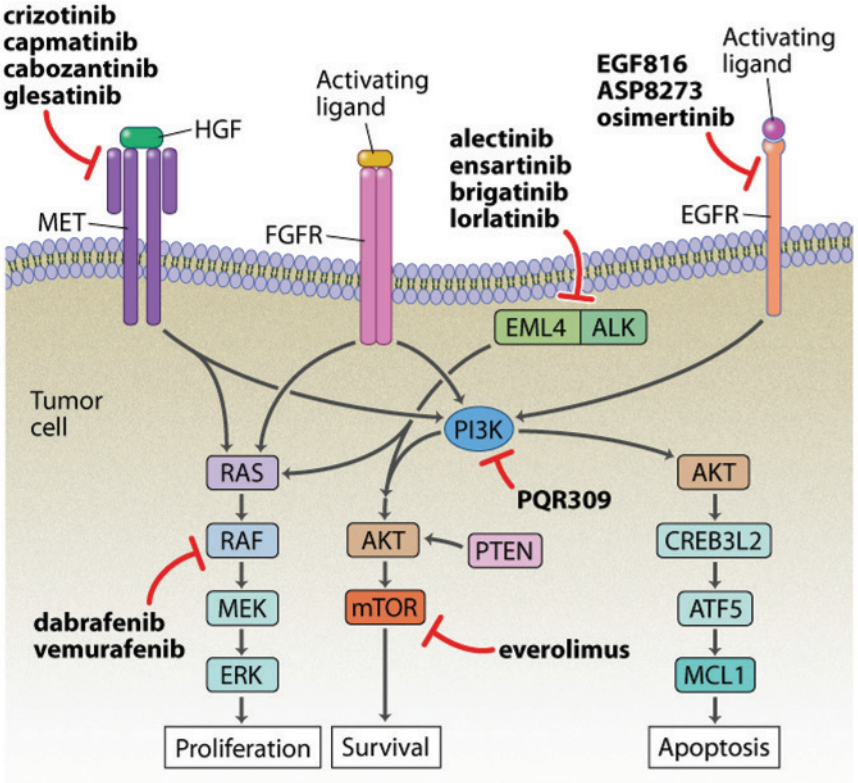

Figure 1. Molecular targets and inhibiting agents are being studied in phase I/II trials as potential therapy for patients with lung cancer. HGF = hepatocyte growth factor; FGFR = fibroblast growth factor receptor; ERK = extracellular signal-regulated kinase; PTEN = phosphatase and tensin homolog; ATF5 = activating transcription factor 5. Information from Dholaria, Hammond, Shreders, and Lou (2016). Illustration by DNA Illustrations.

ticenter ALTA clinical trial, 222 patients were randomly assigned to brigatinib orally at doses of either 90 mg once daily (112 patients) or 180 mg once daily following a 7-day lead-in at 90 mg once daily (110 patients). Assessed by an independent review committee, the objective response rate was 48% (95% confidence interval [CI], 39%–58%) in the 90-mg arm and 53% (95% CI, 43%–62%) in the 180-mg arm. After a median follow-up of 8 months, median duration of response was 13.8 months in both arms. Notably, all patients had tumors with a documented *ALK* rearrangement, determined on the basis of an FDA-approved test or another fluorescence in situ hybridization (FISH) test (Gettinger et al., 2016).

ROS1 Inhibitors

ROS1 inhibitors are being assessed in clinical trials. Crizotinib is currently approved, but cabozantinib (Cometriq, Cabometyx; phase II), ceritinib (phase II), lorlatinib (phase II), entrectinib (phase II), and DS-6051b (phase I) are currently being investigated in ongoing trials. Although acquired resistance to targeted therapies is challenging, existing agents may be repurposed to overcome drug resistance, and cabozantinib has been identified as a promising treatment of *ROS1*-rearranged NSCLC after disease progression on crizotinib (Chong et al., 2017).

MET Inhibitors

MET inhibitors are not currently approved, but agents such as crizotinib (phase II), cabozantinib (phase II), INC280 (phase II), and MGCD265 (phase II) are potential therapeutic agents being investigated. A synergistic effect of crizotinib (a MET inhibitor) and trametinib (Mekinist) was observed in MET-amplified NSCLC cell lines in a study by Chiba and colleagues (2016). Findings from the group indicate that the mitogen-activated protein kinase (MAPK) pathway is biologically important for MET-amplified NSCLC, and the au-

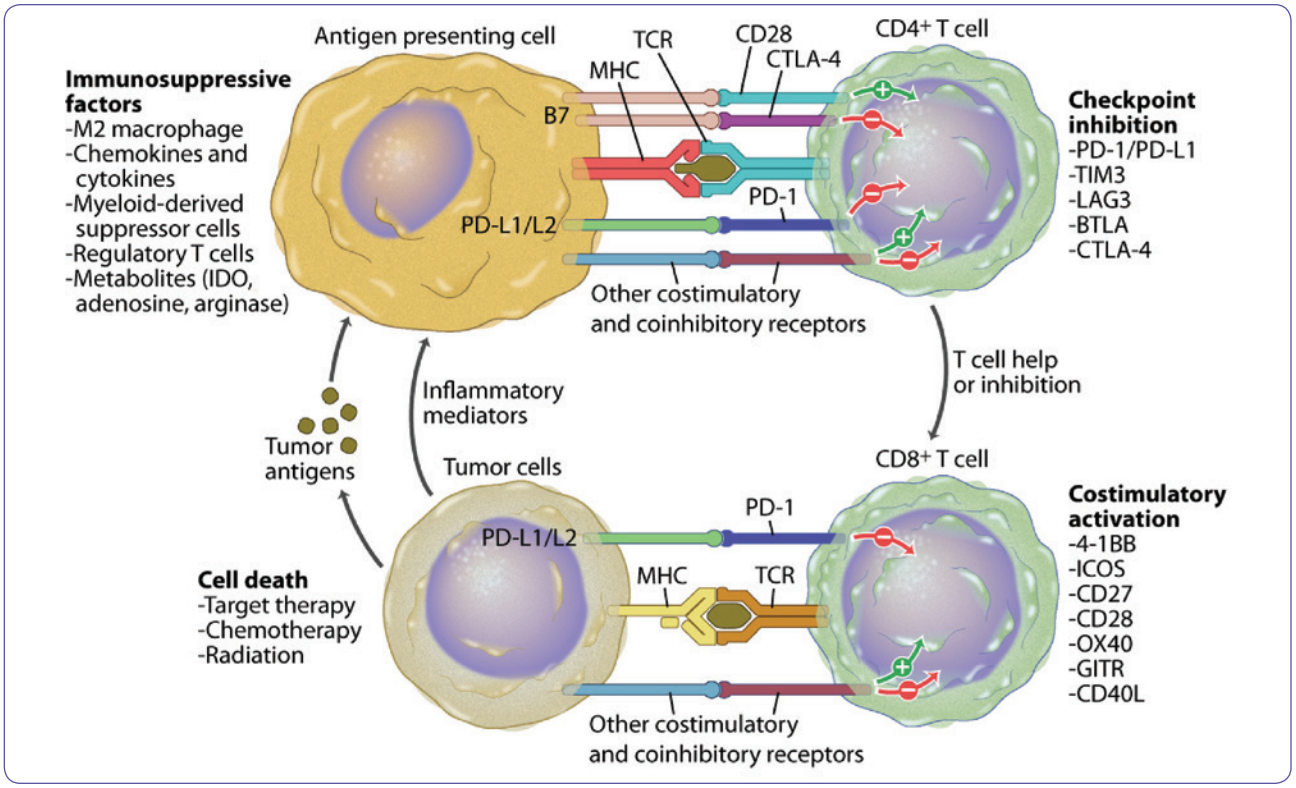

Figure 2. Multifaceted immunotherapy approaches to target cancer cells. IDO = indoleamine 2,3-dioxygenase; MHC = major histocompatibility complex; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; TCR = T-cell receptor; PD-1 = programmed cell death protein 1; TIM3 = T-cell immunoglobulin and mucin-domain containing-3; BTLA = B and T lymphocyte associated; LAG3 = lymphocyte-activation gene 3; CAR = chimeric antigen receptor; ICOS = inducible costimulatory. Information from Dholaria et al. (2016). Illustration by DNA Illustrations.

thors strongly encourage the development of combination therapy with a MET inhibitor and a MEK inhibitor against MET-amplified NSCLC (Chiba et al., 2016).

HER2 Inhibitors

HER2 inhibitors, such as ado-trastuzumab emtansine (Kadcyla; phase II), afatinib (phase II), and dacomitinib (phase 2), are actively being studied for potential benefit in patients with NSCLC. Afatinib treatment displayed moderate efficacy in patients with *HER2* mutations (Song, Yu, Shi, Zao, & Zhang, 2016).

BRAF Inhibitors

BRAF inhibitors with potential benefit currently in clinical trials include vemurafenib (Zelboraf; phase II), dabrafenib (Tafinlar; phase II), and dabrafenib plus trametinib (phase II). Preliminary vemurafenib activity was observed in NSCLC and in other diseases (Hyman et al., 2015). The use of vemurafenib and dabrafenib—agents that block MAPK signaling in patients with melanoma and the *BRAF* V600E mutation—has been associated with prolonged survival and progression-free survival. The frequency of *BRAF* V600E mutation in lung adenocarcinoma is 1.5% to 2.8%. Treatment of *BRAF* V600E–mutant lung adenocarcinomas with dabrafenib is currently under evaluation in a phase II trial and could represent another milestone in individualized therapy for patients with lung cancer. The trials are still ongoing as further investigation is needed (Sanchez-Torres, Viteri, Molina, & Rosell, 2013).

RET Inhibitors

RET inhibitors are not currently approved, but several potential agents, such as cabozantinib (phase II), alectinib (phase II), apatinib (phase II), vandetanib (Caprelsa; phase II), ponatinib

Table 2. Quick Reference on the Inhibitors and Actionable Mutations

Inhibitor	Actionable mutation	Agents
EGFR	Mutations in exon 19-21; T790M	Gefitinib[a], erlotinib,[a] afatinib[a], osimertinib[a]
ALK	Fusion	Crizotinib[a], alectinib[a], ceritinib[a], brigatinib[a]
ROS1	Fusion	Crizotinib[a], cabozantinib, ceritinib
MET	Amplification	Crizotinib, cabozantinib
HER2	Mutation	Trastuzumab, afatinib, dacomitinib, lapatinib
BRAF	Mutation	Vemurafenib, dabrafenib
RET	Fusion	Cabozantinib, alectinib, apatinib, vandetanib
PIK3CA	Mutation	Buparlisib, alpelisib
NTRK1	Mutation	Entretinib, cabozantinib
MAP2K1	Mutation	Selumetinib, trametinib, cobimetinib
PI3K/mTOR dual	Signaling pathway	LY3023414
Multikinase	> 1 mutations	Famitinib, anlotinib, entrectinib
FGFR1	Amplification	Nintedanib, ponatinib
DDR2	Mutation	Dasatinib
PTEN	Mutation	Buparlisib

Note. [a] FDA approved for the mutation in NSCLC. Information from Hirsch et al. (2016); Khanal & Ganti (2016).

(Iclusig; phase II), and lenvatinib (Lenvima; phase II), are being explored in clinical trials. Alectinib demonstrated preliminary antitumor activity in patients with advanced *RET*-rearranged NSCLC, most of whom had received prior RET inhibitors. Larger prospective studies with longer follow-up are needed to assess the efficacy of alectinib in *RET*-rearranged NSCLC and other *RET*-driven malignancies (Lin et al., 2016).

NTRK1 Inhibitors

Neurotrophic receptor tyrosine kinase 1 (NTRK1) inhibitors have potential therapeutic benefit and are being investigated in trials. They are entrectinib (phase II), LOXO-101 (phase II), cabozantinib (phase II), and DS-6051b (phase I).

PIK3CA Inhibitors

Phosphatidylinositol 3-kinase (*PIK3CA*)–mutated NSCLC represents a clinically and genetically heterogeneous subgroup in adenocarcinomas as well as in squamous cell carcinomas, with a higher prevalence of these mutations in squamous cell carcinoma. *PIK3CA* mutations have no negative impact on survival after surgery or systemic therapy. However, *PIK3CA*-mutated lung cancer frequently develops in patients with prior malignancies. PI3K inhibitors, including the pan-PI3K inhibitor buparlisib (BKM120) and the PI3Kα-selective inhibitor alpelisib (BYL719), are currently in clinical development and may be effective as anticancer agents. Early data from the clinical trials involving PI3K inhibitors showed promising antitumor activities and acceptable safety parameters. Additional PIK3CA inhibitors being studied, such as PQR309 (phase I), are promising as researchers continue to explore safety and benefit (Massacesi et al., 2016).

MAP2K1 Inhibitors

MAP2K1 inhibitors such as selumetinib (phase III), trametinib (phase II), and cobimetinib (Cotellic; phase I) are currently being studied (Hirsch et al., 2016). Novel connection between miR-449a and MAP2K1 demonstrated a new, potential therapeutic target for the treatment of NSCLC (You et al., 2015).

Multikinase Inhibitors

Instead of targeting a single kinase domain, multikinase inhibitors aimed at several mechanisms of action are being investigated. Famitinib, anlotinib,

entrectinib, and pexidartinib are some promising agents on the horizon. In particular, famitinib is generally well tolerated and demonstrates a wide spectrum of antitumor activities (Zhou et al., 2013). Cells proliferate using the signaling cascade of small molecules of protein kinases. The research interest in the area of multikinase inhibition has been attractive, with their critical involvement in the regulation of cell proliferation and survival. In particular, the mutational activation and/or overexpression of upstream signaling components are being studied.

PI3K/mTOR Pathway Dual Inhibitors

The PI3K pathway has an important role in cell metabolism, growth, migration, survival, and angiogenesis. Drug development aimed at targetable genetic aberrations in the PI3K/A/mTOR pathway has been investigated, with observations that alterations in this pathway induce tumor formation and that inappropriate PI3K signaling is a frequent occurrence in human cancer (Rodon, Dienstmann, Serra, & Tabernero, 2013).

Two known targets are PI3K and PI3K/mTOR (Janmaat, Rodriguez, Gallegos-Ruiz, Kruyt, & Giaccone, 2006). LY3023414, an oral agent currently being investigated, is a small-molecule inhibitor of class I PI3K isoforms and mTOR in the PI3K/mTOR signaling pathway with potential antineoplastic activity. LY3023414 inhibits both certain PI3K isoforms and mTOR in an adenosine triphosphate–competitive manner, which may inhibit both the PI3K/mTOR signaling pathway and the proliferation of tumor cells overexpressing PI3K and/or mTOR. The PI3K/mTOR pathway is upregulated in a variety of tumor cells and plays a key role in promoting cancer cell proliferation and survival, motility, and resistance to chemotherapy and radiotherapy. This dual inhibitor agent may be more potent than an agent that inhibits either PI3K or mTOR alone. In addition, LY3023414 may inhibit DNA-dependent protein kinase (DNA-PK), thereby inhibiting the ability of tumor cells to repair damaged DNA. DNA-PK is activated upon DNA damage and plays a key role in repairing double-stranded DNA breaks.

Miscellaneous Target Inhibitors

Researchers in oncology are constantly investigating other types of inhibitors or targets in order to develop therapeutic drugs for NSCLC. Among the many targets, there is special interest and potential promise in the HER2 pathway. *HER2* mutations represent a distinct subset of NSCLC. Next-generation sequencing showed that *HER2* mutations commonly co-existed with other driver genes. Afatinib treatment displayed moderate efficacy in patients with *HER2* mutations (Song et al., 2016).

TUMOR EPIGENETICS

Tumor epigenetics is the study of somatically heritable changes to molecular processes that influence the flow of information between the DNA of cancer cells and their gene-expression patterns (Feinberg, Koldobskiy, & Göndör, 2016). This includes comparative investigation of tumor cell vs. normal cell in the nucleus, DNA methylation, histone modification, and the consequences of genetic mutations in genes encoding epigenetic regulators (Feinberg et al., 2016).

Multiple mechanisms of action within the drug class of tumor epigenetics are being investigated through various ongoing trials (Table 1; Dholaria et al., 2016). Currently explored mechanisms of actions are histone deacetylase (HDAC) inhibition, DNA hypo-methylation, and DNA methylation/histone deacetylation/lysine demethylation (Dholaria et al., 2016).

TUMOR METABOLISM

Tumor metabolism refers to the alterations in cellular metabolism pathways that are evident in cancer cells compared with most normal tissue cells. Metabolic alterations in cancer cells are complex and include aerobic glycolysis, reduced oxidative phosphorylation, and the increased generation of biosynthetic intermediates needed for cell growth and proliferation. Many prior studies on this subject show strong limitations to establish and validate the tumor micro- and macroenvironments.

The microenvironment of tumors is composed of cancer cells of various metabolic profiles, which support local metabolic exchanges and interact with cancer cell metabolism. The macroenvironment includes the different tissues of the organism that are capable of exchanging various signals on a larger scale. Very few targets were identified within the tumor metabolism pathways as these studies are difficult to perform and adequate imaging methods are limited (Amoedo, Obre, & Rossignol,

2017). Tumor metabolism is targeted through various mechanisms of action in several clinical trials utilizing thioredoxin reductase, dUTPase, pegylated arginine deiminase, checkpoint kinase 1, and glutaminase (Dholaria et al., 2016).

DNA REPAIR

DNA repair refers to the correction of DNA lesions that threaten genome integrity. As DNA replication errors or environmental agents that damage DNA can introduce mutations if not corrected, multiple cellular DNA repair mechanisms exist to remove damaged regions of chromosomes to prevent these potentially deleterious effects. A critical pathway for the repair of DNA damage is called homologous recombination repair (HRR). It is a pathway for the repair of DNA damage caused by cisplatin or poly-ADP ribose polymerase (PARP) inhibitors. Because HRR may be impaired by multiple mechanisms in cancer, targeting this pathway is of great interest to investigators (Birkelbach et al., 2013).

CHEMOTHERAPY

Advances in the chemotherapy arena are explored with tubulin-depolymerization; platinum-based, micellar nanoparticle–encapsulated cisplatin; and folic acid–tubulysin conjugate (Dholaria et al., 2016). Some of these agents currently being studied include plinabulin, PT-112, NC-6004, and EC-1456. Plinabulin is a potential neoplastic compound that selectively targets and binds to the colchicine-binding site of tubulin, thereby interrupting the equilibrium of microtubule dynamics. This disrupts mitotic spindle assembly, leading to cell-cycle arrest at M phase and blockage of cell division. In addition, plinabulin may also inhibit growth of proliferating vascular endothelial cells, thereby disrupting the function of tumor vasculature that further contributes to a decrease in tumor cell proliferation (Gridelli et al., 2009).

ONCOLYTIC VIRUS

Coxsackievirus A21 (CVA21 [Cavatak]) is targeting the specific virus for a promising drug in NSCLC (Dholaria et al., 2016). Characterization of CVA21 and the receptor-based mechanism of the virus suggest CVA21 as a virotherapy against malignancies that overexpress those receptors. There is limited information on this virus, as it is being translated from the animal studies to early phase I trials in human subjects (Bradley et al., 2014).

CONSIDERATIONS FOR THE ADVANCED PRACTITIONER AND GENERAL APPROACH

At least a decade ago, cancer histology alone guided treatment decisions in NSCLC, but now molecular profiling is of paramount importance to deliver the most effective treatment. The driver mutation analysis plays a critical role in selecting the correct targeted therapy with the best chance of hope for patients with NSCLC. Advanced practitioners are instrumental in educating and guiding patients and their family members from the start of the diagnosis, to analysis of genetic biomarkers, and throughout the course of each biologic and nonbiologic therapy. Each step and measure during the management of NSCLC, if carefully taken, can greatly diminish the level of anxiety and stress for patients.

CONCLUSION

With rapid medical and scientific advances in the discovery of biologic targets and the development of associated therapies, we often encounter a complex situation when treating patients with NSCLC. We understand that recruiting patients with rare mutations to well-designed, multicenter trials to further validate the use of targeted agents remains a challenge. Yet, the 21st century has so far been marked with an incredible escalation of new novel drugs that weren't previously available to our patients. This is a challenging yet exhilarating century, with so much potential for growth and extraordinary service to our patients.

Disclosure

The author has no potential conflicts of interest to disclose.

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