Molecularly Targeted Therapies in Non–Small-Cell Lung Cancer Annual Update 2014

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Abstract: There have been significant advances in the understanding of the biology and treatment of non–small-cell lung cancer (NSCLC) during the past few years. A number of molecularly targeted agents are in the clinic or in development for patients with advanced NSCLC. We are beginning to understand the mechanisms of acquired resistance after exposure to tyrosine kinase inhibitors in patients with oncogene addicted NSCLC. The advent of next-generation sequencing has enabled to study comprehensively genomic alterations in lung cancer. Finally, early results from immune checkpoint inhibitors are very encouraging. This review summarizes recent advances in the area of cancer genomics, targeted therapies, and immunotherapy.

Key Words: Non–small-cell lung cancer, Targeted therapies, Immunotherapy.

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MOLECULAR GENETICS OF HUMAN LUNG CANCER

Lung cancer has traditionally been classified by histologic subtype and immunohistochemical characteristics. However, this classification has been complicated by the recognition that several clinically actionable somatic genetic alterations can be identified in the distinct histologic subtype of lung cancer and that some of these alterations can be found in more than one histology. Through comprehensive genomic analysis, it is known that all lung cancers carry high rates of somatic mutation, high levels of inter- and intra-chromosomal rearrangement, and copy-number alterations as compared with other tumor types.[1] Exploitation of these genomic aberrations has become an attractive and efficacious treatment strategy and has underscored the need for multiplexed genetic testing as part of the routine care of patients with lung cancer. To stratify patients into clinically relevant subgroups, the combination of histomorphological, immunohistochemical, and genetic analysis is now used routinely for patients with newly diagnosed lung cancer and is the standard of care in newly diagnosed adenocarcinoma in which epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement testing have been incorporated into standard treatment algorithms. In addition, many institutions are now routinely testing for alterations such as ROS proto-oncogene 1 (*ROS 1*), *RET*, B-Raf proto-oncogene (*BRAF*), and v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (*HER2*) which have shown initial promise in tailored cancer treatment.

Lung Adenocarcinoma

Lung adenocarcinoma is one of the best genetically characterized human epithelial malignancies and recent discoveries of targetable driver mutations have highlighted the impressive cadre of molecular alterations present in this disease. The identification of oncogenic activation of particular tyrosine kinases (TK) in some patients with advanced non–small-cell lung cancer (NSCLC) most notably mutations in EGFR[2–4] or rearrangements of the *ALK* gene[5] has led to a paradigm shift and the development of specific molecular treatments for patients. These clinical successes have revolutionized the field and stimulated the investigation into

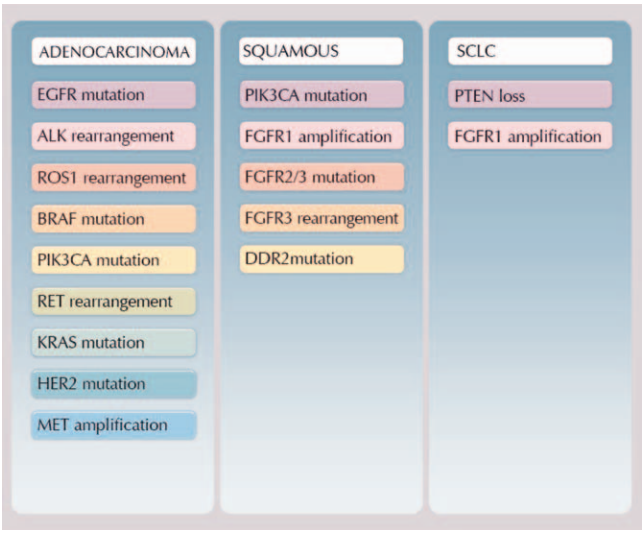

FIGURE 1. Potential targetable oncogenes by histology subtype. *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; *DDR2*, discoidin domain receptor tyrosine kinase 2; *FGFR1*, fibroblast growth factor receptor 1; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *MET*, MET proto-oncogene; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; *PTEN*, phosphatase and tensin homology deleted on chromosome 10; *RET*, ret proto-oncogene; SCLC, small-cell lung cancer.

additional, potential targetable, generation aberrations across all lung cancer histologies (Fig. 1 and Table 1).

For patients with lung adenocarcinoma, the impact of genetic testing has led to changes in the standard diagnostic algorithms with recommendations from the International Association for the Study of Lung Cancer and National Comprehensive Cancer Network that newly diagnosed patients with advanced disease be tested for EGFR mutation and ALK fusion testing. In addition, many institutions are now routinely testing for alterations in genes such as ROS, RET, MET proto-oncogene (*MET*), BRAF, and HER2 which have shown initial promise in tailored cancer treatment.

The need to perform detailed molecular testing of lung cancers began with the correlation of EGFR mutations and sensitivity to gefitinib and erlotinib in lung adenocarcinoma, typically in patients with modest tobacco exposure EGFR TK inhibitors (TKIs) are now the established first-line therapy in patients with NSCLC known to have activating mutations in EGFR.[6,7] The majority of these tumors initially respond to EGFR TKIs, but subsequently develop resistance to therapy, with a median time to progression of 9 months.[8] Recent work has demonstrated the value of additional molecular testing at the time of acquired resistance in EGFR-TKI–responsive patients, as nearly half of patients with disease progression will carry a secondary EGFR mutation, such as T790M, which can now be successfully targeted with third-generation EGFR TKIs such as AZD9291 and CO-1686.[8,9] Additional mechanisms of resistance to EGFR inhibitors have been defined in rebiopsy cohorts, many of which are associated with a potential for response to other targeted agents or with response to other chemotherapies (small cell transformation).[8]

Receptor TK (RTK) gene rearrangements, such as ALK, ROS, and RET, are identified in 1% to 8% of lung adenocarcinomas.[10] Patients whose tumors harbor ALK fusion and ROS1 rearrangements demonstrate a response to crizotinib and other TKIs.[11,2] However, similar to their EGFR counterparts, these patients ultimately recur. This has led to molecular characterization of mechanisms of acquired resistance and the clinical use of ALK and ROS inhibitors with expanded mechanisms of action such as LDK378.

Interestingly, some of the most frequent genomic alterations in adenocarcinoma, such as mutations in tumor protein p53 (TP53), KRAS, and serine/threonine kinase 11 (STK11), have proven difficult to target and therapeutically exploit.[13,14] The mitogen activation pathway (MAPK) is often implicated in the development of lung adenocarcinoma; however, little success has been garnered therapeutically. The most common mechanism for MAPK activation is through substitutions mutations in 12th, 13th, and 61st amino acids of KRAS. Activating KRAS mutations are observed in approximately 20% to 25% of lung adenocarcinomas in the United States and are generally associated with a history of smoking. The presence of a KRAS mutation appears to have at most a limited effect on overall survival (OS) in patients with early-stage NSCLC although some data have suggested that it was associated with inferior prognosis. Efforts to identify specific inhibitors for KRAS-mutated lung cancer have proven challenging with the current focus of targeted therapeutics for patients with KRAS-mutated lung cancer is against downstream effectors of activated KRAS such as mitogen-activated protein kinase kinase (MEK) 1/MEK2, phosphatidylinositol 3-kinase (PI3K), and v-*akt* murine thymoma viral oncogene homolog (AKT). Recent phase II data examining combination use of selumetenib, an inhibitor of MEK1/MEK2, and docetaxel has been shown to have promising activity in KRAS-mutant patient population.[15] Additional work on downstream effectors in the KRAS-mutant pathway is crucial, and currently, several clinical trials using the inhibition of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (pI3KCA), MEK, and phosphatase and tensin homology deleted on chromosome 10 (PTEN) are in progress.

Squamous Cell Lung Cancer

Genotyping alone has improved survival in patients who harbor a targetable mutation such as EGFR mutation and echinoderm microtubule associated protein like 4 (EML4-ALK) fusions. However, there has been limited advancement in targeted approaches in squamous cell carcinoma until recently. Recent genomic profiling in squamous cell carcinoma has highlighted a number of new molecular targets including the fibroblast growth factor receptor (FGFR) family kinases. FGFRs are cell surface TK receptors that mediates cell survival and proliferation. Gene amplification of FGFR1 has been detected in 7% to 25% of squamous tumors, and extensive profiling has identified low-frequency activating mutations and copy-number alterations in all the FGFRs.[16–18] Small molecule inhibitors of FGFR1 are in clinical development, and a case report of a NSCLC patient with tumor regression in response to the FGFR small molecule TKI BGJ398 has

TABLE 1. A Tabulated Summary of Targeted and Biologic Therapies for Non–Small-Cell Lung Cancer

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
EGFR inhibitors (HER1, HER2, and pan-inhibitors)						
http://clinicaltrials.gov/ct2/results?term=cetuximab+lung+cancer&Search=Search	ImClone/Eli Lilly Bristol-Myers Squibb	Cetuximab/Erbitux IMC-C225	Chimeric MoAb	EGFR	FDA approved -Head and neck cancer -Colorectal cancer Phase III studies for NSCLC have been completed and reported.	Rash and other skin toxicities, nail changes, diarrhea, infusion reaction, headache, hypomagnesemia
http://clinicaltrials.gov/ct2/results?term=erlotinib+and+lung+cancer&Search=Search	Genentech/OSI Pharmaceuticals	Erlotinib/Tarceva OSI-774	Reversible small molecule TKI	EGFR	FDA approved -Advanced NSCLC • After failure of at least one prior regimen • Maintenance therapy -In combination with gemcitabine for advanced pancreatic cancer	Skin toxicity, diarrhea
http://clinicaltrials.gov/ct2/results?term=afatinib+and+lung+cancer&Search=Search	Boehringer Ingelheim	Afatinib Gilotrif BIBW-2992	Irreversible small molecule TKI	EGFR, HER2	Approved for the first-line treatment of patients with L858R and Exon 19 EGFR mutations	Rash, diarrhea, fatigue
http://clinicaltrials.gov/ct2/results?term=gefitinib+and+lung+cancer&Search=Search	AstraZeneca	Gefitinib/Iressa ZD 1839	Reversible small molecule TKI	EGFR	Available only as part of a special program called the Iressa Access Program in the United States. Approved for use in patients with EGFR mutations in Europe and Japan.	Skin toxicity, diarrhea, interstitial lung disease
http://clinicaltrials.gov/ct2/results?term=lapatinib+and+lung+cancer&Search=Search	GlaxoSmithKline	Lapatinib/Tykerb GW 572016	Reversible small molecule TKI	EGFR, HER2 (erb-B2)	FDA approved for HER2-overexpressing advanced breast cancer Phase II for NSCLC	Diarrhea, nausea, vomiting, dermatologic (palmar-plantar erythrodysesthesia and rash), fatigue, hepatotoxicity
http://clinicaltrials.gov/ct2/results?term=panitumumab+lung+cancer&Search=Search	Amgen	Panitumumab/ Vectibix ABX-EGF MAb	Human IgG2 MoAb	EGFR	FDA approved for colorectal cancer Phase II for NSCLC	Hypomagnesemia, paronychia, fatigue, nausea, diarrhea, infusion reaction
http://clinicaltrials.gov/ct2/results?term=trastuzumab+and+lung+cancer&Search =Search	Genentech	Trastuzumab Herceptin	Humanized MoAb	HER2	FDA approved for HER2-overexpressing breast cancer Phase II for NSCLC (completed)	Cardiomyopathy, infusion reactions, diarrhea
http://clinicaltrials.gov/ct2/results?term=icotinib+and+lung+cancer&Search=Search	Zhejiang Beta Pharma Inc.	Icotinib Conmana (China) BPI-2009H	Small molecule TKI	EGFR	Approved by the CFDA in China and currently in Phase IV development	Rash, diarrhea
http://clinicaltrials.gov/ct2/results?term=necitumumab+lung+cancer&Search=Search	Eli Lilly/ImClone	Necitumumab NA IMC-11F8	Human IgG1 MoAb	EGFR	Phase III completed. Data to be presented at American Society of Clinical Oncology meeting in June 2014.	Thromboembolic events

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=dacomitinib+and+lung±cancer&Search=Search	Pfizer	Dacomitinib NA PF299804	Irreversible small molecule TKI	Pan-HER	Phase III (ARCHER 1009 and BR26 were completed and did not meet their primary end points. ARCHER 1050 is currently ongoing and is expected to be completed in 2015)	Diarrhea, acne, rash
https://clinicaltrials.gov/ct2/results?term=Sym004&Search=Search	Merck/Symphoge n	NA NA Sym004	A mixture of two monoclonal antibodies directed against nonoverlapping epitopes.	EGFR extracellular domain III	Phase I/II	Rash and diarrhea
http://clinicaltrials.gov/ct2/results?term=pertuzumab+lung+cancer&Search=Search	Genentech/Roche	Pertuzumab Perjeta rhuMAb 2C4	Humanized murine MoAb	Prevents dimerization of HER2 with other HER receptors	FDA approved for HER2-overexpressing metastatic breast cancer in combination with trastuzumab and docetaxel. Currently no ongoing studies in lung cancer. Phase II studies completed.	Fatigue, diarrhea, LVEF decrease
http://clinicaltrials.gov/ct2/results?term=neratinib+lung+cancer&Search=Search	Pfizer (Wyeth)	Neratinib NA HKI-272	Irreversible small molecule TKI	EGFR, HER2	Phase III (breast cancer) Phase II for NSCLC completed	Diarrhea, asthenia, rash
http://clinicaltrials.gov/ct2/results?term=nimotuzumab+lung+cancer&Search=Search	YM BioSciences	Nimotuzumab TheraCIM h-R3	Humanized MoAb	EGFR	Approved in Thailand and Myanmar for relapsed high-grade Glioma Phase II for NSCLC	Rash, diarrhea
http://clinicaltrials.gov/ct2/results?term=BMS-690514+lung+cancer&Search=Search	Bristol-Myers Squibb	NA NA BMS-690514/ EVR1	Small molecule TKI	Pan-HER VEGFR2	Phase II completed. Currently there are no ongoing studies.	Diarrhea, rash, arterial hypertension, pulmonary embolism, angioedema
http://clinicaltrials.gov/ct2/results?term=pelitinib+and+lung+cancer&Search=Search	Pfizer (Wyeth)	Pelitinib NA EKB-569	Irreversible small molecule TKI	EGFR, HER2, HER4	Phase II completed. No ongoing studies currently.	Diarrhea, rash, nausea, asthenia
http://clinicaltrials.gov/ct2/results?term=RO5083945+lung+cancer&Search=Search	Roche	NA NA RO5083945/ GA201	Glyco-engineered anti-EGFR IgG1 MoAb	EGFR (also improved antibody-dependent cellular cytotoxicity)	Phase II. Now closed to accrual.	Infusion reactions, rash, hypomagnesaemia
http://clinicaltrials.gov/ct2/results?term=U3-1287 +AMG888+lung+cancer&Search=Search	Daiichi Sankyo	NA NA U3-1287/ AMG888	Human MoAb	HER3	Phase Ib/II. Closed to accrual.	Rash, anemia, diarrhea
http://clinicaltrials.gov/ct2/results?term=MM121+lung+cancer&Search=Search	Merrimack Pharmaceuticals	NA NA MM121/SAR256212	Human MoAb	HER3	Phase I/II	

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=CO+1686+lung+cancer&Search=Search	Clovis	NA NA CO 1686	Irreversible oral small molecule inhibitor	Mutant forms of EGFR including T790M	Phase II	
https://clinicaltrials.gov/ct2/results?term=AZD9291&Search=Search	AstraZeneca	NA NA AZD 9291	Irreversible oral small molecule inhibitor	Mutant forms of EGFR including T790M	Phase II	
http://clinicaltrials.gov/ct2/results?term=azd8931&Search=Search	AstraZeneca	Momelotinib NA AZD8931	Reversible small molecule inhibitor	EGFR, HER2, HER3	Phase II No ongoing studies for lung cancer	
http://clinicaltrials.gov/ct2/results?term=MEHD7945+A&Search=Search	Genentech	NA NA MEHD7945 A	Humanized dual action IgG1 Moab	EGFR, HER3	Phase II Phase I for lung cancer currently not recruiting	
http://clinicaltrials.gov/ct2/results?term=AV-203+and+cancer&Search=Search	AVEO Pharmaceuticals	NA NA AV 203	Humanized Moab	HER3	Phase I	
http://clinicaltrials.gov/ct2/results?term=ARRY+380+cancer&Search=Search	Array BioPharma	NA NA ARRY 380	Reversible small molecule inhibitor	HER2	Phase I (completed)	Nausea, rash, fatigue
http://clinicaltrials.gov/ct2/results?term=BMS-599626+cancer&Search=Search	Bristol-Myers Squibb/ Ambit Biosciences	NA NA BMS-599626	Reversible small molecule inhibitor	Pan-HER (EGFR, HER2, HER4)	Phase I (completed)	Diarrhea, nausea, rash, musculoskeletal cramps
http://clinicaltrials.gov/ct2/results?term=MM151+cancer&Search=Search	Merrimack Pharmaceuticals	NA NA MM151	Combination of three human MoAb	EGFR	Phase I	
http://clinicaltrials.gov/ct2/results?term=MM-111+cancer&Search=Search	Merrimack Pharmaceuticals	NA NA MM111	Bi-specific antibody fusion protein	HER2-HER3 heterodimer	Phase I/II Phase I for lung cancer	
http://clinicaltrials.gov/ct2/results?term=Zalutumumab+cancer&Search=Search	Genmab	Zalutumumab NA HuMax-EGFr	Human MoAb	EGFR	Not recruiting patients currently.	Rash, fatigue, pyrexia
VEGF and VEGFR inhibitors						
http://clinicaltrials.gov/ct2/results?term=bevacizumab+lung±cancer&Search=Search	Genentech	Bevacizumab Avastin	Humanized MoAb	VEGF-A	FDA approved -Metastatic HER2 negative breast -Metastatic colorectal -Metastatic NSCLC -Phase III testing ongoing in the adjuvant setting (ECOG 1505)	Hypertension, proteinuria, thrombosis, hemorrhage, gastrointestinal perforation

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=sorafenib+lung+cancer&Search=Search	Bayer	Sorafenib Nexavar BAY43-9006	Small molecule TKI	VEGFR-2,3, PDGFR β, KIT, RAF/MEK, FLT-3	FDA approved -Unresectable hepatocellular cancer -Advanced renal cell carcinoma Phase III terminated, phase II ongoing for NSCLC. Being evaluated in KRAS-positive NSCLC.	Rash/desquamation, hand-foot skin reaction, diarrhea, fatigue, hypertension
http://clinicaltrials.gov/ct2/results?term=Sunitinib+lung+cancer&Search=Search	Pfizer	Sunitinib Sutent SU 011248	Small molecule TKI	VEGFR-1,2,3, PDGFR β, KIT, FLT-3, RET	FDA approved -Gastrointestinal stromal tumor -Advanced renal cell carcinoma Phase III for NSCLC. Being evaluated in the maintenance setting for NSCLC and SCLC.	Hypertension, rash, stomatitis, diarrhea, hypothyroidism, hand-foot syndrome
http://clinicaltrials.gov/ct2/results?term=pazopanib+lung+cancer&Search=Search	GlaxoSmithKline	Pazopanib Votrient GW786034	Small molecule TKI	VEGFR-1,2,3, PDGFR α, β, KIT	FDA approved for advanced renal cell carcinoma Ph III for NSCLC	Nausea, hypertension, diarrhea, fatigue, transaminase elevation, vomiting, hair depigmentation.
http://clinicaltrials.gov/ct2/results?term=vandetanib	AstraZeneca	Vandetanib Zactima ZD6474	Small molecule TKI	VEGFR-2, 3, EGFR, RET	FDA approved for -Advanced, unresectable medullary thyroid cancer Phase III studies in NSCLC completed (lung indication not being pursued)	Hypertension, diarrhea, rash
http://clinicaltrials.gov/ct2/results?term=Aflibercept+lung+cancer&Search=Search	Sanofi-Aventis	Aflibercept Zaltrap VEGF-TRAP/ AVE0005	Fusion protein of extracellular domain portions from VEGFR-1 & VEGFR-2 combined with Fc of human IgG	VEGF, placental growth factor	Phase III (VITAL-failed to meet primary end point of OS). Currently not accruing lung cancer patients.	Hypertension, dysphonia, epistaxis, proteinuria, headache, diarrhea
http://clinicaltrials.gov/ct2/results?term=cediranib+lung+cancer	AstraZeneca	Cediranib Recentin AZD2171	Small molecule TKI	VEGFR-1,2,3, PDGFR β, KIT	Phase III Currently no active studies for lung cancer	Diarrhea, dysphonia, hypertension
http://clinicaltrials.go v/ct2/results?term=motesanib+lung+cancer&Search=Search	Amgen	Motesanib NA AMG706	Small molecule TKI	VEGFR-1,2,3, PDGFR β, KIT, RET	Phase III (NSCLC study failed to improve survival). Currently no active studies for lung cancer	Nausea, diarrhea, fatigue, hypertension
http://clinicaltrials.gov/ct2/results?term=BIBF1120+lung+cancer&Search=Search	Boehringer Ingelheim	Nintedanib Vargatef BIBF 1120	Small molecule TKI	VEGFR-1,2,3 PDGFR-α, β FGFR-1,2,3 Src kinases	Ph III completed. Phase III LUME-lung 1 showed a survival benefit. Submitted to the EMEA for approval.	Nausea, vomiting, elevated liver enzymes, diarrhea

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=Ramucirumab+lung+cancer&Search=Search	ImClone/Eli Lilly	Ramucirumab Cyramza IMC-1121B	Human MoAb	VEGFR-2	Approved for gastric cancer. Phase III study (REVEL) completed. Primary end point of overall survival was met in the second-line treatment of advanced NSCLC in combination with docetaxel.	Hypertension, abdominal pain, nausea, anorexia, headache, proteinuria, deepvenous thrombosis.
http://clinicaltrials.gov/ct2/results?term=axitinib+and+lung+cancer&Search=Search	Pfizer	Axitinib Inlyta AG013736	Small molecule TKI	VEGFR-1,2,3 PDGFR β KIT	Not recruiting NSCLC patients. Phase II study for carcinoid tumors ongoing.	Diarrhea, hypertension, fatigue, nausea, hand-foot syndrome, proteinuria
http://clinicaltrials.gov/ct2/results?term=vatalanib+lung+cancer&Search=Search	Novartis/Bayer Schering	Vatalanib NA PTK787/ZK 222584	Small molecule TKI	VEGFR-1,2 PDGFR β KIT	Phase III Phase II for lung cancer	Hypertension, diarrhea, nausea, fatigue, dizziness
http://clinicaltrials.gov/ct2/results?term=tivozanib+cancer&Search=Search	AVEO Pharmaceuticals	Tivozanib Tivopath AV-951	Small molecule inhibitor	Pan VEGFR-1,2,3	Ph III completed. Improvement in OS was not seen. U.S. FDA did not approve tivozanib for lung cancer.	Diarrhea, dysphonia, asthenia, hypertension
http://clinicaltrials.gov/ct2/results?term=linifanib+lung+cancer&Search=Search	Abbott (Abbvie)/ Genentech	Linifanib NA ABT-869	Small molecule TKI	VEGFR, PDGFR	Phase III Phase II for NSCLC	Fatigue, hypertension, proteinuria, hand foot skin reaction
http://clinicaltrials.gov/ct2/results?term=cabozantinib+lung+cancer&Search=Search	Exelixis/ Bristol Myers Squibb	Cabozantinib Cometriq XL184	Small molecule TKI	VEGFR-2, MET, RET	Phase III Phase II for NSCLC. Also being evaluated in patients KIF5B/RET translocations.	Diarrhea, mucositis, anorexia, vomiting, hand-foot skin reaction, hypertension, elevation of liver enzymes
http://clinicaltrials.gov/ct2/results?term=Regorafenib&Search=Search	Bayor	Regorafenib Stivarga BAY73-4506	Diphenylurea multikinase inhibitor	VEGFR-1,2,3, TIE2, PDGFRβ, FGFR, KIT, RET, RAF	Phase III Phase I for lung cancer	Hand-foot skin reaction, extremity pain, hypothyroidism, rash
http://clinicaltrials.gov/ct2/results?term=lenvatinib&Search=Search	Eisai Limited	Lenvatinib NA E7080	Small molecule TKI	VEGFR-2 (also 1,3), FGFR-2, RET	Phase III Phase I for lung cancer. Also being evaluated in patients KIF5B/RET translocations.	Hypertension, fatigue, proteinuria, anorexia, diarrhea, dysphonia
http://clinicaltrials.gov/ct2/results?term=XL647+cancer&Search=Search	Exelixis	NA NA XL647	Irreversible small molecule TKI	VEGFR-2, EGFR, HER2, EphB4	Ph II completed. Currently no active ongoing studies.	Diarrhea, rash, fatigue, nausea, hypertension, anorexia
http://clinicaltrials.gov/ct2/results?term=CT-322+cancer&Search=Search	Adnexus (Bristol-Myers Squibb)	NA NA CT-322	Adnectin (fibronectin-based small protein)	VEGFR-2	Phase II.	Proteinuria, hypertension
http://clinicaltrials.gov/ct2/results?term=foretinib+cancer&Search=Search	Exelixis/ GlaxoSmithKline	Foretinib NA GSK1363089/ XL880	Small molecule TKI	VEGFR-2, MET, Ron	Phase II.	Hypertension, fatigue, nausea, diarrhea, night blindness

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=AEE+788+cancer&Search=Search	Novartis	NA NAAEE 788	Irreversible small molecule TKI	VEGFR-2, EGFR, HER2	Phase I/II. Currently not recruiting patients.	Fatigue, diarrhea, nausea, rash
http://clinicaltrials.gov/ct2/results?term=xl820+cancer&Search=Search	Exelixis	NA NA XL820	Small molecule TKI	VEGFR-2, PDGFR β, KIT	Phase II No active lung trials	Nausea, fatigue, rash
http://clinicaltrials.gov/ct2/results?term=xl999+and+cancer&Search=Search	Exelixis	NA NA XL999	Small molecule TKI	VEGFR, PDGFR, FLT-3, Src, FGFR	Phase II (terminated due to safety concerns)	Cardiac toxicity, diarrhea, asthenia, hypersensitivity
http://clinicaltrials.gov/ct2/show/NCT00952497?term=telatinib±cancer&rank=1	ACT Biotech Inc.	Telatinib NA BAY57-9352	Small molecule TKI	VEGFR-2,3, PDGFR-β, andKIT	Phase I (completed)	Hypertension, hoarseness, anorexia, diarrhea
http://clinicaltrials.gov/ct2/results?term=ombrabulin+cancer	Sanofi-Aventis	Ombrabulin NA AVE8062	Combretastatin A-4 derivative	Tubulin-binding agent that targets the immature neovasculature of tumors	Phase II (completed). Currently no active studies accruing lung cancer patients.	
http://clinicaltrials.gov/ct2/results?term=megf0444a+AND+cancer	Genentech	NA NA MEGF0444A/RG7414	humanized antibody against EGFL7 (epidermal growth factor domain-like 7)	Targets EGFL7. A vascular-restricted secreted protein present in the tracks that surround tumor blood vessels	Ph I completed. Currently not accruing lung cancer patients.	
ALK & ROS1 inhibitors						
http://clinicaltrials.gov/ct2/results?term=crizotinib+lung+cancer&Search=Search	Pfizer	Crizotinib Xalkori PF-02341066	Dual small molecule ATP-competitive inhibitor	ALK, c-Met, ROS1	FDA approved for ALK+ locally advanced or metastatic NSCLC	Nausea, diarrhea, visual disturbances, alanine aminotransferase elevation, fatigue
http://clinicaltrials.gov/ct2/results?term=X-396+cancer&Search=Search	Xcovery	NA NA X-396	Small molecule inhibitor	ALK	Phase I	
http://clinicaltrials.gov/ct2/results?term=LDK378+lung+cancer&Search=Search	Novartis	Ceritinib Zykadia LDK378	Small molecule inhibitor	ALK translocations	Approved by the U.S. FDA for the treatment for patients with ALK-positive metastatic NSCLC after treatment with crizotinib	Nausea, vomiting, diarrhea. Notably visual disturbances were not seen.
http://clinicaltrials.gov/ct2/results?term=AP26113+cancer&Search=Search	Ariad Pharmeceuticals	NA NA AP26113	Small molecule inhibitor	ALK/EGFR	Phase I/II	
http://clinicaltrials.gov/ct2/results?term=ch5424802BCL-2 inhibitors	Chugai Pharmaceuticals	NA NA CHS424802/AF802	Small molecule inhibitor	ALK	Phase I/II	

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=ABT-263&Search=Search	Abbott (Abbvie)& Genentech	Navitoclax NA ABT-263	Small molecule inhibitor (ABT-263 is orally bioavailable)	Bad-like BH3 Mimetic	Phase II for SCLC. Not accruing patients currently.	Diarrhea, back pain, thrombocytopenia
http://clinicaltrials.gov/ct2/results?term=G3139+cancer&pg=1	Genta	Oblimerson Genasense G3139	Antisense oligo-deoxyribonucleotide	Bcl-2	Phase II/III. Not recruiting patients currently	Fever, elevated liver enzymes
http://clinicaltrials.gov/ct2/results?term=Obatoclax&Search=Search	GeminX	Obatoclax NA GX15-070	Small molecule inhibitor	Pan Bcl-2	Ph I/II. Not recruiting patients currently.	Neurotoxicity, cytopenias
http://clinicaltrials.gov/ct2/results?term=AT101+and+cancer&Search=Search	Ascenta	NA NA AT101	Negative enantiomer of gossypol	Pan Bcl-2	Phase II (NSCLC studies terminated, SCLC ongoing)	Gastrointestinal side effects
BCR-ABL/SRC tyrosine kinase/STAT inhibitors						
http://clinicaltrials.gov/ct2/results?term=dasatinib+and+lung+cancer&Search=Search	Bristol-Myers Squibb	Dasatinib Sprycel BMS-354825	Small molecule TKI of SRC-family	Src, BCR-ABL, KIT, PDGFR, FMS or colony-stimulating factor 1 receptor CSF1R	FDA approved for chronic myelogenous leukemia Phase II for NSCLC. Also being studied in NSCLC patients with DDR2 mutations and inactivating BRAF mutations.	Fluid retention, pleural effusion, diarrhea, prolonged QTc, myelosuppression, rash
http://clinicaltrials.gov/ct2/results?term=imatinib+and+lung±cancer&pg=1	Novartis	Imatinib Gleevec STI-571	Small molecule TKI	KIT, PDGFR, BCR-ABL fusion protein	FDA approved for -Gastrointestinal stromal tumor Dermato-fibrosarcoma protuberans -Philadelphia chromosome-positive chronic myelogenous leukemia Ph II for NSCLC	Fluid retention, diarrhea, myelosuppression, rash
http://clinicaltrials.gov/ct2/results?term=saracatinib	AstraZeneca	Saracatinib NA AZD 0530	Small molecule TKI of SRC-family binds the active conformation of the ATP-binding pocket	Src, BCR-ABL (Inhibits Src kinase–mediated osteoclast resorption)	Phase II. Currently not accruing patients.	Leukopenia, febrile neutropenia, asthenia
http://clinicaltrials.gov/ct2/results?term=bosutinib&Search=Search	Pfizer (Wyeth)	Bosutinib NA SKI-606	4-anilino-3-quinolinecarbonitrile dual Src/Abl kinase inhibitor	Src, ABL	Phase II Phase I for lung cancer. Completed	Diarrhea, anorexia, nausea
http://clinicaltrials.gov/ct2/results?term=KX2-391&Search=Search	Kinex Pharmaceuticals	NA NA KX2-391	Small molecule TKI targeting the substrate binding site	c-Src	Phase II Phase I for lung cancer	Hypokalemia, anemia, elevated AST, fatigue, dyspnea, fever, vomiting, constipation, hematuria, lymphopenia

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=XL228+cancer&Search=Search	Exelixis	NA NA XL228	Multi-targeted TKI	Src, ABL, IGF-1R, AURORA, FGFR1-3	Phase I (closed)	Nausea, neutropenia, fatigue, hypoglycemia
http://clinicaltrials.gov/ct2/results?term=OPB+51602+cancer&Search=SearchBRAF inhibitors	Otsuka Beijing Research Institute	NA NA OPB 51602	Inhibitor of signal transducer and activator of transcription 3	STAT 3	Phase I	
http://clinicaltrials.gov/ct2/results?term=Vemurafenib+cancer&Search=Search	Plexxikon/ Roche	Vemurafenib Zelboraf PLX4032/ RG7204	Small molecule inhibitor	BRAF (V600E mutation)	FDA approved for metastatic melanoma Being evaluated in BRAFV600E cancers including lung cancer.	Diarrhea, rash, fatigue, skin squamous cell carcinoma
http://clinicaltrials.gov/ct2/results?term=dabrafenib+and+cancer&Search=Search	GlaxoSmithKline	Dabrafenib Tafinlar GSK2118436	Small molecule inhibitor	Mutant BRAF kinase	FDA approved for melanoma. Being evaluated in BRAFV600E cancers including lung cancer.	Pyrexia, rash, skin squamous cell carcinoma, diarrhea
http://clinicaltrials.gov/ct2/results?term=LGX818+cancer&Search=Search	Novartis	NA NA LGX818	Small molecule inhibitor	BRAF kinase inhibitor	Phase I/II in BRAF-mutant or BRAF-dependent tumors. Currently not being evaluated in lung cancer.	
http://clinicaltrials.gov/ct2/results?term=ArQ736+cancer&Search=Search	ArQule	NA NA ArQ736	Small molecule inhibitor	Pan-Raf inhibitor	Phase I completed in patients with BRAF or Nras mutations.	
Epigenetic modulators of gene expression or protein degradation						
Heat Shock Protein (HSP)-90 Inhibitors						
http://clinicaltrials.gov/ct2/results?term=IPI-504+cancer&pg=1	Infinity	Retaspimycin NA IPI-504	Water-soluble geldanamycin derivative	HSP-90	Phase III Phase II for NSCLC (activity in ALK-translocated patients). Also being evaluated in KRAS-mutant NSCLC	Fatigue, nausea, diarrhea, renal failure, liver failure
http://clinicaltrials.gov/ct2/results?term=STA-9090+lung+cancer&Search=Search	Synta Pharmaceuticals	Ganetespib NA STA-9090	Small molecule inhibitor	HSP-90	Phase II/III. Currently being evaluated in ALK-positive disease.	Diarrhea, anemia, fatigue, abdominal pain, elevated alkaline phosphatase, insomnia
http://clinicaltrials.gov/ct2/results?term=AUY922+cancer&Search=Search	Novartis	NA NA AUY922	Isoxazole-based compound (non-geldanamycin)	HSP90	Phase II	Diarrhea, nausea, fatigue, visual symptoms, vomiting
http://clinicaltrials.gov/ct2/results?term=Alvespimycin+cancer&Search=Search	Bristol-Myers Squibb/Kosan Biosciences	Alvespimycin NA KOS-1022/17-DMAG	Benzoquinone antineoplastic antibiotic	HSP-90	Phase II Phase I for lung cancer	Diarrhea, fatigue, headache, joint pain

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=Tanespimycin+cancer&Search=Search	Bristol-Myers Squibb/Kosan Biosciences	Tanespimycin NA KOS-953/ 17-AAG	Benzoquinone antineoplastic antibiotic	HSP-90	Development halted by company (Phase III & Phase I for lung cancer)	Fatigue, lymphopenia
http://clinicaltrials.gov/ct2/results?term=DS+2248+cancer&Search=Search	Daiichi Sankyo	NA NA DS 2248	Benzoquinone antineoplastic antibiotic	HSP-90	Phase I	
HDAC inhibitors						
http://clinicaltrials.gov/ct2/results?term=vorinostat+lung+cancer&pg=1	Merck	Vorinostat Zolinza MK 0683/ SAHA	Hydroxamic acid-type	Class I, II, and IV	FDA-approved cutaneous T-cell lymphoma Phase III in NSCLC terminated	Diarrhea, nausea, fatigue, thrombocytopenia, muscle spasms
http://clinicaltrials.gov/ct2/results?term=Romidepsin+cancer&Search=Search	Astellas/Gloucester Pharmaceuticals	Romidepsin Istodax FK228	Cyclic tetrapeptide (depsipeptide)	Class I specific	FDA-approved cutaneous T-cell lymphoma Phase I/II for NSCLC	Fatigue, rash, thrombocytopenia, nausea
http://clinicaltrials.gov/ct2/results?term=entinostat+lung+cancer&Search=Search	Syndax Pharmaceuticals	Entinostat NA MS-275/ SNDX-275	Benzamide derivative	Class I specific	Phase II in E-cadherin–positive NSCLC.	Pancytopenia, hypophosphatemia, nausea, fatigue
http://clinicaltrials.gov/ct2/results?term=Belinostat+lung+cancer&Search=Search	CuraGen/ Topotarget	Belinostat NA PXD 101	Hydroxamic acid-type	Class I & II isoforms	Phase I/II	Nausea, emesis, fatigue
http://clinicaltrials.gov/ct2/results?term=pivanex+cancer&Search=Search	Titan	Pivanex (pivaloyloxymethyl butyrate) NA AN-9	Aliphatic acid	Class I and IIa specific	Phase II (completed)	Fatigue, nausea, dysgeusia
http://clinicaltrials.gov/ct2/results?term=Valproic+acid+lung+cancer&Search=Search		Valproic acid Depakote	Aliphatic acid	Class I and IIa specific	Phase II	Anemia, neurological toxicity, nausea, hepatic toxicity
http://clinicaltrials.gov/ct2/results?term=Sodium+phenylbutyrate+lung+cancer&Search=Search		Sodium phenylbutyrate	Aliphatic acid	Class I and IIa specific	Phase II (completed)	Neuro-cortical toxicity, hypokalemia, hyponatremia, hyperuricemia, nausea
http://clinicaltrials.gov/ct2/results?term=Panobinostat+lung+cancer&Search=Search	Novartis	Panobinostat Faridak LBH589	Hydroxamic acid-type	Pan-HDAC (all isoforms)	Phase II Phase I for lung cancer	Rash, QT interval prolongation, nausea, diarrhea, hypokalemia, thrombocytopenia
http://clinicaltrials.gov/ct2/results?term=SB939+cancer&Search=Search	S*BIO	NA NA SB939	Small molecule HDAC inhibitor	HDAC	Phase II Phase I for lung (no ongoing trials)	Fatigue, troponin elevation, QTc prolongation
http://clinicaltrials.gov/ct2/results?term=CUDC-101+cancer&Search=Search	Curis	NA NA CUDC-101	Hydroxamic acid	HDAC, HER2, EGFR	Phase Ib	Fatigue, increased creatinine, increased hepatic enzymes

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=PCI-24781+cancer&Search=Search	Pharmacyclics	NA NA PCI-24781	Cyclic tetrapeptide	Class I & II	Phase I/II	
http://clinicaltrials.gov/ct2/results?term=FK-228+lung+cancer&Search=Search	Gloucestor Pharmaceuticals	NA NA FK-228	Cyclic tetrapeptide (depsipeptide)	Class I	Phase IIb Phase I for lung	
http://clinicaltrials.gov/ct2/results?term=CHR-3996+cancer&Search=Search	Chroma Therapeutics	NA NA CHR-3996	Small molecule inhibitor	Class I HDAC isoforms	Phase I (completed)	Fatigue, nausea, vomiting
http://clinicaltrials.gov/ct2/results?term=Givinostat+cancer&Search=Search	Italformaco	Givinostat NA ITF2357	Hydroxamic acid derivative	Class I & II	Currently being studied in hematologic malignancies in Phase II	
Proteasome inhibitors						
http://clinicaltrials.gov/ct2/results?term=bortezomib+and+lung±cancer&Search=Search	Millennium Pharmaceuticals (Takeda Oncology)	Bortezomib Velcade PS-341	Reversible inhibitor	26S proteasome and client proteins (i.e., p27, p53, NFkB, Bcl-2, Bax)	FDA approved for -Multiple myeloma -Mantle cell lymphoma Phase II for NSCLC. Being explored in KRAS-mutant patients.	Asthenia, nausea, diarrhea, constipation, peripheral neuropathy, hypotension, thrombocytopenia
http://clinicaltrials.gov/ct2/results?term=carfilzomib+and+lung±cancer&Search=Search	Onyx Pharmaceuticals	Carfilzomib NA PR-171	Irreversible inhibitor	20S proteasome subunit	Phase II. Currently not recruiting patients. Phase I for lung cancer	Pancytopenia, peripheral neuropathy
http://clinicaltrials.gov/ct2/results?term=mln9708+AND+cancer	Millennium Pharmaceuticals (Takeda Oncology)	NA NA MLN9708	Reversible inhibitor	20S proteasome subunit	Phase I/II Phase I for lung cancer	Anorexia, dehydration, fatigue, nausea, peripheral sensory neuropathy, macular rash, renal failure, and thrombocytopenia
http://clinicaltrials.gov/ct2/results?term=NPI-0052+cancer&Search=Search	Nereus Pharmaceuticals	Salinosporamide A NA NPI-0052	Irreversible inhibitor	20S catalytic core subunit of the proteasome	Phase I for solid tumors ongoing	Fatigue, nausea, neurological toxicity
http://clinicaltrials.gov/ct2/results?term=CEP-18770+cancer&Search=Search	Cephalon and Ethical Oncology Science	NA NA CEP-18770	Slowly reversible	Inhibits chymotrypsin like activity of proteasome	Phase I for solid tumors completed	
FGFR inhibitors						
http://clinicaltrials.gov/ct2/results?term=brivanib+and+cancer&Search=Search	Bristol-Myers Squibb	Brivanib NA BMS-582664	Small molecule TKI	FGFR and VEGFR-2	Phase III Phase II for NSCLC completed.	Hypertension, fatigue
http://clinicaltrials.gov/ct2/results?term=Dovitinib+and+cancer&Search=Search	Novartis	Dovitinib NA TKI-258	Small molecule inhibitor	FGFR-1,2,3, PDGFR, VEGFR-2	Phase II Phase II for lung cancer	Hypertension, anorexia, nausea, vomiting, fatigue, headache

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=GSK3052230+and+cancer&Search=Search	GSK/Five Prime therapeutics	GSK3052230 FP-1039	Soluble fusion protein consisting of a portion of the FGFR1 linked to Fc portion of IgG1	FGF ligand trap (multiple FGFs)	Phase I in patients with FGFR deregulated patients.	Neutropenia, bowel perforation, urticaria, atrial fibrillation
http://clinicaltrials.gov/ct2/results?term=AZD4547+and+cancer&Search=Search	AstraZeneca	NA NA AZD4547	Small molecule inhibitor	FGFR1,2,3	Phase II	
http://clinicaltrials.gov/ct2/results?term=Ponatinib+and+cancer&Search=Search	ARIAD	Ponatinib NA AP24534	Small molecule inhibitor	Pan-FGFR inhibitor Pan-BCR ABL inhibitor RET	Phase II CML NSCLC study on going in patients with RET translocations	Low platelet counts, headache, nausea, joint pain, fatigue, anemia, increased lipase, muscle spasms, rash, pancreatitis
http://clinicaltrials.gov/ct2/results?term=TSU-68+and+cancer&Search=Search	Taiho Pharmaceutical	Orantinib TSU-68 SU6668	Small molecule inhibitor	FGFR, PDGFR, VEGFR	Phase I/II No active trials for lung	Fatigue, AST/ALT elevation, diarrhea
http://clinicaltrials.gov/ct2/results?term=BGJ398+cancer&Search=Search	Novartis	NA NA BGJ398	Small molecule inhibitor	FGFR1,2,3	Phase I in solid tumor patients with FGFR amplifications.	
Hedgehog antagonists						
http://clinicaltrials.gov/ct2/results?term=Vismodegib+and+cancer&Search=Search	Genentech	Vismodegib NA GDC-0449	Small molecule inhibitor	Smoothened receptor in the sonic hedgehog pathway	Phase II study completed in SCLC. Currently no studies on going for NSCLC.	Dysgeusia, hyponatremia, fatigue, muscle spasms
http://clinicaltrials.gov/ct2/results?term=LDE+225+and+cancer&Search=Search	Novartis	NA NA LDE 225	Small molecule inhibitor	Smoothened receptor in the hedgehog pathway	Phase II Phase I for lung cancer	Fatigue, nausea, anorexia, muscle cramps, dysgeusia
http://clinicaltrials.gov/ct2/results?term=IPI-926+and+cancer&Search=Search	Infinity	NA NA IPI-926	Small molecule inhibitor	Smoothened receptor in the hedgehog pathway	Phase II Phase I for solid tumors including lung Cancer (completed)	Fatigue, nausea, transaminitis
http://clinicaltrials.gov/ct2/results?term=PF04449913+cancer&Search=Search	Pfizer	NA NA PF04449913	Small molecule inhibitor	Smoothened receptor in the hedgehog pathway	Phase I	
http://clinicaltrials.gov/ct2/results?term=LY2940680+cancer&Search=Search	Eli Lilly	NA NA LY2940680	Small molecule inhibitor	Smoothened receptor in the hedgehog pathway	Phase I SCLC	
Hormone therapy						
http://clinicaltrials.gov/ct2/results?term=Fulvestrant+lung+cancer&Search=Search	AstraZeneca	Fulvestrant Faslodex ICI 182780	Blocks estrogen activity through receptor	Estrogen receptor	FDA approved for hormone receptor–positive breast cancer Phase II for postmenopausal women with NSCLC	Hot flashes, injection site reaction, headache, gastrointestinal disturbances, back pain

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=Anastrazole+and+lung+cancer&Search=Search	AstraZeneca	Anastrazole Arimidex	Decreases estrogen in postmenopausal women	Aromatase inhibitor	FDA approved for hormone receptor–positive breast cancer Phase II for postmenopausal women with NSCLC has been terminated.	Hot flashes, joint disorders, osteoporosis, nausea, mood changes, hypertension
http://clinicaltrials.gov/ct2/results?term=enobosarm+AND+cancer	GTx Inc	Enobosarm Osterine GTx-024	A selective androgen receptor modulator	Aryl propionamides	Phase III Currently no studies on going for lung cancer	Hair growth/virilization, prostatic hyperplasia, elevated red blood cell counts, decrease in HDL cholesterol, liver function abnormalities
Hypoxia-activated drugs						
http://clinicaltrials.gov/ct2/results?term=TH-302+AND+CANCER&Search=Search	Threshold Pharmaceuticals	NA NA TH-302	Tumor selective hypoxia activated prodrug	2-nitroimidazole moiety is triggered by hypoxic conditions to release DNA-alkylating dibromo isophosphoramide mustard	Phase II Phase I for NSCLC. Currently not recruiting patients.	Skin lesions, mucositis, fatigue, nausea
http://clinicaltrials.gov/ct2/results?term=PR-104+cancer&Search=Search	Proacta	NA NA PR-104	Tumor selective hypoxia activated preprodrug	Converted to a pro-drug which is reduced under hypoxic conditions to a hydroxylamine metabolite, PR-104H, which is a cytotoxic nitrogen Mustard-alkylating agent.	Phase II (Phase II in NSCLC & SCLC terminated)	Cytopenias, nausea, vomiting, fatigue
HIF-1α inhibitors						
http://clinicaltrials.gov/ct2/results?term=PX-478+AND+CANCER&Search=Search	Oncothyreon	PX-478	Small molecule inhibitor	HIF-1α	Phase I	Anemia, fatigue, nausea, elevated AST/ALT
http://clinicaltrials.gov/ct2/results?term=EZN-2968+AND+CANCER&Search=Search	Eon Pharmaceuticals	EZN-2968	HIF-1α mRNA antagonist	HIF-1α	Phase I in solid tumors have been completed.	Vomiting, fatigue
Immunomodulatory agents						
http://clinicaltrials.gov/ct2/results?term=Lenalidomide+lung+cancer&Search=Search	Celgene	Lenalidomide Revlimid CC-5013		Immunomodulatory, anti-inflammatory, antiangiogenic	FDA approved for -Multiple myeloma -Myelodysplastic syndrome Phase II completed for NSCLC	Myelosuppression, rash, thrombosis

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=Thalidomide+lung±cancer&Search=Search	Celgene	Thalidomide Thalomid		Immunomodulatory, anti-inflammatory, antiangiogenic	FDA approved for multiple myeloma Phase II for NSCLC. Currently no active trials.	Somnolence, peripheral neuropathy, dizziness, neutropenia, thrombosis, rash
Immunomodulatory antibodies						
http://clinicaltrials.gov/ct2/results?term=Ipilimumab+and+lung±cancer&Search=Search	Bristol-Myers Squibb	Ipilimumab Yervoy MDX 010	IgG1 human MoAb	CTLA-4	FDA approved -Metastatic melanoma Phase III trials ongoing in squamous NSCLC and phase II in SCLC.	Rash, diarrhea (autoimmune colitis), hypothyroidism, hypophisitis, hepatitis
http://clinicaltrials.gov/ct2/results?term=tremelimumab+AND+cancer	MedImmune	Tremelimumab/ Ticilim Umab NA CP675,206	IgG2 monoclonal antibody	CTLA-4	Phase II (malignant mesothelioma). Phase I in lung cancer.	
http://clinicaltrials.gov/ct2/results?term=BMS-936559&Search=Search	Bristol-Meyers Squibb	NA BMS-936559 MDX-1105	Human IgG4 MoAb	Inhibitor of programmed death-1 ligand	Ph I completed. Currently not accruing patients.	Rash, diarrhea, fatigue, hypothyroidism, hypophysitis, hepatitis
http://clinicaltrials.gov/ct2/results?term=BMS936558+and+cancer&Search=Search	Bristol-Meyers Squibb	Nivolumab NA MDX-1106/ BMS936558/ ONO4538	Human IgG4 MoAb	Inhibitor of programmed death-1: a receptor expressed on activated T-cells, and may suppress antitumor immunity	Phase III in NSCLC	Rash, lymphopenia, arthralgia, myalgia
http://clinicaltrials.gov/ct2/results?term=AMP-224+cancer&Search=Search	GSK/Amplimmune	NA NA AMP-224	Fc-fusion protein	Targets PD-L2, which binds to PD-1	Phase 1 completed.	
http://clinicaltrials.gov/ct2/results?term=BMS-663513+cancer&Search=Search	Bristol-Myers Squibb	Urelumab NA BMS-663513	Humanized MoAb	Agonist of CD-137, aTNF receptor	Phase I in solid tumors	Neutropenia, elevated liver enzymes, rash, pruritus, diarrhea
IAPs antagonist						
http://clinicaltrials.gov/ct2/results?term=HGS+1029+and+cancer&Search=Search	Human Genome Sciences/Aegera	NA NA HGS 1029/ AEG 40826	Small molecule Smac mimetic	IAPs antagonist	Phase I completed	Nausea, anorexia, diarrhea, fatigue, elevated amylase and lipase, supraventricular tachycardia
http://clinicaltrials.gov/ct2/results?term=TL32711+and+cancer&Search=Search	Tetralogic	Birinapant NA TL32711	Small molecule Smac mimetic	IAPs antagonist	Phase I/II. Phase I completed. Currently no ongoing studies for lung cancer	
http://clinicaltrials.gov/ct2/results?term=AT-406+and+cancer&Search=Search	Ascenta Therapeutics	NA NA AT-406	Small molecule Smac (second mitochondria-derived activator of caspases) mimetic	Multi-IAP antagonist (XIAP, c-IAP1, c-IAP2, and ML-IAP)	Phase I	

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=GDC0917+and+cancer&Search=Search	Genentech	NA NA GDC0917	Small molecule peptide Smac mimetic	IAPs antagonist	Phase I completed	
http://clinicaltrials.gov/ct2/results?term=LCL161+and+cancer&Search=Search	Novartis	NA NA LCL161	Small molecule Smac mimetic	IAPs antagonist	Phase II Phase I completed in lung cancer.	
IGF-1R inhibitor						
http://clinicaltrials.gov/ct2/results?term=Figitumumab&Search=Search	Pfizer	Figitumumab CP-751871	IgG2 type human MoAb	IGF-1R	Phase III terminated (further development halted)	Cardiac toxicity, hyperglycemia, asthenia, anorexia, pneumonia, dehydration, early death.
http://clinicaltrials.gov/ct2/results?term=OSI-906&Search=Search	OSI Pharmaceuticals/ Astellas	Linsitinib NA OSI-906/ASP-7487	Small molecule inhibitor	IGF-1R and insulin receptor (IR)	Phase II completed in NSCLC Not accruing patients	Nausea, vomiting, fatigue, hyperglycemia, elevated liver enzymes
http://clinicaltrials.gov/ct2/results?term=AMG479+cancer&Search=Search	Amgen	NA NA AMG-479	IgG1 type human MoAb	IGF-1R	Phase III Phase I/II for lung was terminated	Thrombocytopenia, neutropenia, hyperglycemia, fatigue, rash, elevated LFTs, asymptomatic TSH increase
http://clinicaltrials.gov/ct2/results?term=Cixutumumab+and+cancer&Search=Search	ImClone	Cixutumumab NA IMC-A12	IgG1 type human MoAb	IGF-1R	Phase III completed. Development has been discontinued.	Pruritus, rash, anemia, hyperglycemia, infusion-related reaction
http://clinicaltrials.gov/ct2/results?term=Dalotuzumab+and+lung+cancer&Search=Search	Merck	Dalotuzumab NA MK-0646	IgG1 type humanized MoAb	IGF-1R	Phase II completed. Currently not recruiting patients.	Fatigue, hyperglycemia, nausea, constipation, diarrhea
http://clinicaltrials.gov/ct2/results?term=BIIB022+cancer&Search=Search	Biogen Idec	BIIB022	Human nonglycosylated IgG4 MoAb	IGF-1R	Phase II Phase I for NSCLC	Hypertension, fatigue, dyspnea, QTc prolongation
http://clinicaltrials.gov/ct2/results?term=BMS-754807&Search=Search	Bristol-Myers Squibb	NA NA BMS-754807	Small molecule reversible inhibitor	IGF-1R and IR	Phase I completed. Currently not recruiting patients.	Fatigue, hyperglycemia
http://clinicaltrials.gov/ct2/results?term=AVE1642+cancer&Search=Search	Sanofi-Aventis	NA NA AVE1642	Humanized MoAb	IGF-1R	Phase I/II (no active trials. Company discontinued development)	Hyperglycemia, asthenia, hypersensitivity
http://clinicaltrials.gov/ct2/results?term=R1507&Search=Search	Genmab & Roche	Robatumumab NA R1507	IgG1 type human MoAb	IGF-1R	Phase II (Development is halted)	Fatigue, anorexia, weight loss
Integrins						
http://clinicaltrials.gov/ct2/results?term=EMD121974+cancer&Search=Search	NA Merck Serono	Cilengitide EMD121974	Cyclic peptide	$\alpha_5\beta_3$ and $\alpha_5\beta_5$ integrin	Phase III Phase I/II for NSCLC	Lymphopenia, thrombocytopenia, neutropenia, fatigue, nausea, anorexia

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=Volociximab+cancer&Search=Search	PDL BioPharma & Biogen Idec	Volociximab NA M200	Chimeric MoAb	$\alpha_5 \beta_1$ integrin	Phase II	Fatigue, nausea, constipation, diarrhea, arthralgia
http://clinicaltrials.gov/ct2/results?term=PF-04605412+cancer&Search=Search	Pfizer	NA NA PF-04605412	Human IgG1 MOAb	$\alpha_5 \beta_1$ integrin	Phase I terminated. Currently there are no ongoing studies.	
http://clinicaltrials.gov/ct2/results?term=Vitaxin+cancer&Search=Search	MedImmune	Vitaxin NA MEDI-522	Humanized IgG1 MoAb	$\alpha_5 \beta_1$ integrin	Phase I completed.	Chills, fever, nausea
mTOR inhibitors						
http://clinicaltrials.gov/ct2/results?term=Temsirolimus+lung+cancer&Search=Search	Pfizer (Wyeth)	Temsirolimus Torisel CCI-779	Ester analog of rapamycin	mTORC1	FDA-approved -advanced renal cell carcinoma Phase II for NSCLC	Fatigue, rash, asthenia, hyperglycemia, hyperlipidemia, hypophosphatemia, myelosuppression, nausea, diarrhea
http://clinicaltrials.gov/ct2/results?term=Everolimus+lung+cancer&Search=Search	Novartis	Everolimus Afinitor RAD001	Derivative of the natural macrocyclic lactone sirolimus	mTORC1	FDA-approved -advanced renal cell carcinoma Phase II for NSCLC	Stomatitis, asthenia, pneumonitis, fatigue, infections, diarrhea, neutropenia
http://clinicaltrials.gov/ct2/results?term=Ridaforolimus+lung+cancer&Search=Search	Merck/Ariad	Ridaforolimus Taltorvic AP-23573	Small molecule serine/threonine kinase inhibitor	mTOR	Phase II for NSCLC terminated.	Fatigue, anorexia, mucositis
http://clinicaltrials.gov/ct2/results?term=Sirolimus+and+lung+cancer&Search=Search	Generic drug with multiple manufactures	Sirolimus Rapamune Rapamycin	A macrolide derived from *Streptomyces hygroscopicus*	mTORC1	Phase I/II	Cytopenias, hypoalbuminemia, hyperglycemia, hypercholesterolemia, hypertriglyceridemia
http://clinicaltrials.gov/ct2/results?term=AZD8055+cancer&Search=Search	AstraZeneca	NA NA AZD 8055	ATP-competitive small molecule inhibitor	mTOR C1,2	Phase I/II completed.	Transaminitis
http://clinicaltrials.gov/ct2/results?term=OSI+027+cancer&Search=Search	OSI Pharmaceuticals	NA NA OSI 027	Small molecule inhibitor	mTORC1,2	Phase II completed.	
http://clinicaltrials.gov/ct2/results?term=BEZ+235+and+cancer&Search=Search	Novartis	NA NA BEZ 235	Small molecule inhibitor	PI3K/mTORC1	Phase I/II	
c-Met/HGFR pathway inhibitors						
http://clinicaltrials.gov/ct2/results?term=Tivantinib+lung+cancer&Search=Search	ArQule	Tivantinib NA ARQ197	Small molecule inhibitor	c-MET/ HGFR	Phase III discontinued. Did not meet its primary end point.	Hepatotoxicity
http://clinicaltrials.gov/ct2/results?term=Onartuzumab+lung+cancer&Search=Search	Roche/Genentech	Onartuzumab NA MetMab/RG3638	Humanized monovalent MoAb	c-MET	Phase III in met-positive patients discontinued for lack of benefit.	Peripheral edema

(Continued)

Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=Rilotumumab+cancer&Search=Search	Amgen	Rilotumumab NA AMG 102	Human IgG2 MoAb	HGF (ligand)	Phase III in gastric cancer and gastroesophageal junction malignancies. Phase I/II	Fatigue, constipation, anorexia, nausea, dyspnea
http://clinicaltrials.gov/ct2/results?term=Ficlatuzumab+and±cancer&Search=Search	AVEO Pharmaceuticals	Ficlatuzumab NA AV-299/SCH900105	Humanized IgG1 MoAb	HGF (ligand)	Randomized Phase II	Fatigue, peripheral edema, headache, diarrhea
http://clinicaltrials.gov/ct2/results?term=Amuvatinib+cancer&Search=Search	Astex Pharmaceuticals	Amuvatinib NA MP-470	Small molecule inhibitor	KIT, c-MET, RET, PDGFR, FLT3	Phase II (SCLC). Currently not recruiting patients.	
http://clinicaltrials.gov/ct2/results?term=MGCD265+and+cancer&Search=Search	MethylGene	NA NA MGCD265	Small molecule inhibitor	c-MET, VEGFR1,2,3, Ron, Tie-2	Phase I/II	
http://clinicaltrials.gov/ct2/results?term=MK2461+and+cancer&Search=Search	Merck	NA NA MK2461	Small molecule inhibitor	c-MET	Phase I/II completed	
http://clinicaltrials.gov/ct2/results?term=BMS777607+and+cancer&Search=Search	Bristol-Myers Squibb	NA NA BMS777607	Small molecule inhibitor	c-MET	Phase I completed.	
http://clinicaltrials.gov/ct2/results?term=INCB28060&Search=Search	Incyte	NA NA INCB28060	Small molecule inhibitor	c-MET	Phase I completed	
http://clinicaltrials.gov/ct2/results?term=AMG+208&Search=Search	Amgen	NA NA AMG 208	Small molecule inhibitor	c-MET	Phase I not recruiting patients	
http://clinicaltrials.gov/ct2/results?term=LY2875358&Search=Search	Eli Lilly	NA NA LY2875358	Humanized IgG4 MoAb	c-MET	Phase II	
http://clinicaltrials.gov/ct2/results?term=PF-4217903&Search=Search	Pfizer	NA NA PF-4217903	Small molecule inhibitor	c-MET/HGFR	Phase I (terminated)	
http://clinicaltrials.gov/ct2/results?term=JNJ38877605&Search=Search	Johnson & Johnson	NA NA JNJ38877605	Small molecule inhibitor	c-MET	Phase I (Terminated)	Elevation in creatinine
http://clinicaltrials.gov/ct2/results?term=JNJ38877605&Search=Search	SGX Pharmaceuticals	NA NA	Selective small molecule inhibitor	Met	Phase I (terminated)	Nephrotoxicity, fatigue, pyrexia, nausea, vomiting
Mitogen activated protein/extracellular signal-regulated kinase (MEK) inhibitors						
http://clinicaltrials.gov/ct2/results?term=Trametinib&Search=Search	GlaxoSmithKline	Trametinib Mekinist GSK1120212	Allosteric small molecule inhibitor	MEK 1/2	FDA approved in Melanoma in combination with dabrafenib. Phase II in lung cancer.	Rash, diarrhea, central serous retinopathy
http://clinicaltrials.gov/ct2/results?term=Selumetinib+lung+cancer&Search=Search	AstraZeneca/Array BioPharma	Selumetinib NA AZD6244/ ARRY142880	Allosteric inhibitor	MEK 1 & 2	Phase III Phase II completed in NSCLC (phase I ongoing in KRAS & BRAF mutants)	Rash, diarrhea, nausea, emesis

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=AS+703026&Search=Search	Merck KGaA/EMD Serono	Pimasertib NA AS 703026/ MSC1936369B	Non-competitive small molecule inhibitor	MEK 1/2	Phase I/II	Asthenia, diarrhea, constipation, rash, nausea, vomiting
http://clinicaltrials.gov/ct2/results?term=RDEA119%2F+&Search=Search	Ardea Biosciences	NA NA RDEA119/ BAY 869766	Allosteric inhibitor	MEK 1/2	Phase I/II	Rash, diarrhea, nausea, vomiting, fatigue, and peripheral edema
http://clinicaltrials.gov/ct2/results?term=MEK162&Search=Search	Novartis	NA NA MEK162	Small molecule inhibitor	MEK	Phase II Phase I in Lung Cancer	
http://clinicaltrials.gov/ct2/results?term=PD325901&Search=Search	Pfizer	NA NA PD325901	Small molecule inhibitor	MEK 1/2	Phase I completed	Ocular toxicity, neurological toxicity
http://clinicaltrials.gov/ct2/results?term=AZD8330&Search=Search	AstraZeneca/Array BioPharma	NA NA AZD8330	Small molecule inhibitor	MEK 1	Phase I completed	
http://clinicaltrials.gov/ct2/results?term=GDC-0973&Search=Search	Genentech	Cobemetinib NA GDC-0973/ XL518	Small molecule inhibitor	MEK 1	Phase III Phase II lung cancer	
Inhibitors of mitosis						
Aurora kinase inhibitors						
http://clinicaltrials.gov/ct2/results?term=AZD+1152&Search=Search	AstraZeneca	NA NA AZD 1152	Small molecule inhibitor	Aurora B	Phase II/III (heme focus) Phase I in solid tumors terminated	Neutropenia
http://clinicaltrials.gov/ct2/results?term=MLN+8237&Search=Search	Millennium Pharmaceuticals (Takeda Oncology)	Alisertib NA MLN 8237	Small molecule serine/ threonine protein kinase inhibitor	Aurora A	Phase I/II	Myelosuppression, mucositis, nausea, fatigue
http://clinicaltrials.gov/ct2/results?term=AT9283&Search=Search	Astex	NA NA AT9283	Multi-targeted kinase inhibitor	Aurora A and B, JAK 2 and 3 Tyk2, RSK2, Ret, Mer, Yes and GSK3 beta	Phase II (multiple myeloma) Phase I (completed)	Neutropenia
http://clinicaltrials.gov/ct2/results?term=Danusertib&Search=Search	Nerviano	Danusertib NA PHA739358	Small-molecule 3-aminopyrazole inhibitor	Pan-aurora (aurora B dominant)	Phase II (prostate and heme)	
http://clinicaltrials.gov/ct2/results?term=ENMD-2076&Search=Search	Entremed	NA NA ENMD-2076	Multi-targeted kinase inhibitor	Aurora kinase A, VEGFR, Flt-3, FGFR3	Phase II (ovarian) Phase I (multiple myeloma)	
http://clinicaltrials.gov/ct2/results?term=MK5108&Search=Search	Merck	NA NA MK5108	Small molecule inhibitor	Aurora A kinase	Phase I (completed)	Cytopenias
http://clinicaltrials.gov/ct2/results?term=GSK1070916&Search=Search	GlaxoSmithKline	NA NA GSK1070916	ATP-competitive inhibitor	Aurora kinase B & C	Phase I (completed)	

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=AS703569&Search=Search	Merck KGaA/EMD Serono	NA NA AS703569	Multi-targeted kinase inhibitor	Aurora kinase-A & B, KIT, BTK, LYN, ABL, Akt, and Flt-3	Phase I (completed)	
http://clinicaltrials.gov/ct2/results?term=PF-03814735&Search=Search	Pfizer	NA NA PF-03814735	ATP-competitive, reversible inhibitor	Aurora A & B	Phase I (completed)	Dairrhea, nausea, anorexia
http://clinicaltrials.gov/ct2/results?term=SNS-314&Search=Search	Sunesis	NA NA SNS-314	ATP-competitive selective inhibitor	Pan-aurora kinase inhibitor (A, B, & C)	Phase I (completed)	Nausea, fatigue, constipation
http://clinicaltrials.gov/ct2/results?term=AMG900&Search=Search	Amgen	NA NA AMG900	Small molecule inhibitor	Pan-aurora kinase (A, B, and C)	Phase I	
http://clinicaltrials.gov/ct2/results?term=TAK901&Search=Search	Millennium Pharmaceuticals (Takeda Oncology)	NA NA TAK901	Small molecule inhibitor	Aurora kinase A	Phase I (completed)	
http://clinicaltrials.gov/ct2/results?term=MK0457&Search=Search	Merck	Tozasertib NA MK0457	Small molecule serine/threonine protein kinase inhibitor	Aurora kinase family	Phase II (halted due to cardiac risk)	Neutropenia, nausea, mucositis
http://clinicaltrials.gov/ct2/results?term=CYC116&Search=Search	Cyclacel	NA NA CYC116	Small molecule inhibitor	Pan-aurora	Phase I (terminated)	
Checkpoint kinase (Chk) inhibitor						
http://clinicaltrials.gov/ct2/results?term=LY2603618&Search=Search	Eli Lilly/Array BioPharma	NA NA LY2603618	Inhibitor of Chk, potentiating DNA targeting therapies	Chk 1	Phase II (not recruiting patients)	
http://clinicaltrials.gov/ct2/results?term=AZD7762&Search=Search	AstraZeneca	NA NA AZD7762	ATP-competitive inhibitor of Chk, potentiating DNA-targeting therapies	Chk1/2	Phase I (completed)	
http://clinicaltrials.gov/ct2/results?term=SCH900776&Search=Search	Schering-Plough	NA NA SCH900776	Inhibitor of Chk, potentiating DNA targeting therapies	Chk 1	Phase II in liquid tumors. Phase I completed in solid tumors.	
Kinesin protein inhibitors						
http://clinicaltrials.gov/ct2/results?term=SB-715992&Search=Search	GlaxoSmithKline	Ispinesib NA SB-715992	KSP inhibitor	Mitotic kinesin spindle protein Eg5	Phase II	Neutropenia, fatigue, anemia, elevated creatinine, lymphopenia, hyperglycemia (no neuropathy like Taxanes)
http://clinicaltrials.gov/ct2/results?term=LY-2523355&Search=Search	Eli Lilly/KyowaHakko Kirin	NA NA LY-2523355	Allosteric inhibitor of Eg5	Mitotic kinesin spindle protein Eg5	Phase II (NSCLC) (completed)	Neutropenia, fatigue, nausea, rash

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=SB-743921&Search=Search	GlaxoSmithKline	NA NA SB-743921	KSP inhibitor	Mitotic kinesin spindle protein Eg5	Phase I (completed)	Neutropenia, hypophosphatemia, transaminitis
http://clinicaltrials.gov/ct2/results?term=GSK-923295&Search=Search	GlaxoSmithKline	NA NA GSK-923295	KSP inhibitor	Centromere-linked kinesin-like motor protein CENP-E (kinesin 7)	Phase I (completed)	Fatigue, vomiting, hyponatemia, transaminase elevation
http://clinicaltrials.gov/ct2/results?term=ARRY-520&Search=Search	Array BioPharma	NA NA ARRY-520	KSP inhibitor	Mitotic kinesin spindle protein Eg5	Phase I	Cytopenias, nausea, vomiting, fatigue, hyponatremia
http://clinicaltrials.gov/ct2/results?term=MK0731&Search=Search	Merck	NA NA MK0731	KSP inhibitor	Mitotic kinesin spindle protein Eg5	Phase I (completed)	Neutropenia, diarrhea, nausea, mucositis, anorexia
http://clinicaltrials.gov/ct2/results?term=ARQ-621&Search=Search	ArQule	NA NA ARQ-621	Allosteric inhibitor of Eg5	Mitotic kinesin spindle protein Eg5	Ph I (completed)	
http://clinicaltrials.gov/ct2/results?term=AZD4877&Search=Search	AstraZeneca	NA NA AZD4877	KSP inhibitor	Mitotic kinesin spindle protein Eg5	Ph II (discontinued from development)	Neutropenia
Polo-like kinase inhibitor						
http://clinicaltrials.gov/ct2/results?term=BI-2536&Search=Search	Boehringer Ingelheim	NA NA BI-2536	ATP competitive small molecule inhibitor	Plk1 (serine threonine kinase)	Phase II (completed in SCLC)	Neutropenia, fatigue, nausea
http://clinicaltrials.gov/ct2/results?term=BI-6727&Search=Search	Boehringer Ingelheim	Volasertib NA BI-6727	Dihydropteridinone derivative (binds to ATP-binding pocket)	Plk1 (serine threonine kinase)	Phase II (completed)	Anemia, neutropenia, thrombocytopenia, fatigue
http://clinicaltrials.gov/ct2/results?term=GSK461364&Search=Search	GlaxoSmithKline	NA NA GSK461364	ATP-competitive inhibitor	Plk1 (serine threonine kinase)	Phase I (completed)	Fatigue, anemia, abdominal pain
http://clinicaltrials.gov/ct2/results?term=NMS1286937&Search=Search	Nerviano Medical Sciences	NA NA NMS1286937	Small molecule inhibitor	Plk1 (serine threonine kinase)	Phase I (completed)	
Notch pathway inhibitors						
http://clinicaltrials.gov/ct2/results?term=RO+4929097&Search=Search	Roche	NA NA RO 4929097	Gamma secretase inhibitor	Γ-secretase inhibitor (Pan-notch)	Phase II	Asthenia, nausea, diarrhea, hypophosphatemia, pruritus.
http://clinicaltrials.gov/ct2/results?term=MK0752&Search=Search	Merck	NA NA MK0752	Gamma secretase inhibitor	γ secretase inhibitor (Pan-notch	Phase I/II Phase I in lung cancer	Abdominal cramps, diarrhea, nausea, fatigue
http://clinicaltrials.gov/ct2/results?term=PF03084014&Search=Search	Pfizer	NA NA PF03084014	Gamma secretase inhibitor	γ secretase inhibitor (Pan-notch)	Phase I (completed)	Gastrointestinal toxicity (reduced with steroids)
http://clinicaltrials.gov/ct2/results?term=REGN421&Search=Search	Regeneron	NA NA REGN421	Human MoAb	Delta-4 ligand	Phase I	

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
Osteoclast function modifiers						
http://clinicaltrials.gov/ct2/results?term=zoledronate+and+lung±cancer&Search=Search	Novartis	Zoledronate Zometa NA	Farnesyl pyrophosphate	Osteoclast inhibitor	FDA approved for -Osteoporosis -Cancer-related bone metastases (multiple myeloma and solid tumors)	Hypocalcemia, osteonecrosis of jaw, renal toxicity
http://clinicaltrials.gov/ct2/results?term=Denosumab+lung+cancer&Search=Search	Amgen	Denosumab Xgeva/ Prolia AMG-162	Fully human monoclonal antibody	RANK ligand inhibitor (transmembrane protein important for osteoclast activity and survival)	FDA approved for -Osteoporosis -Prevention of skeletal-related events in patients with bone metastases from solid tumors	Hypocalcemia, osteonecrosis of jaw, serious infections, skin reactions
http://clinicaltrials.gov/ct2/results?term=etidronate+AND+cancer	Procter & Gamble Pharmaceuticals	Etidronate Didronel	Bisphosphonate-ATP requiring small molecule	Osteoclast inhibitor	FDA approved for symptomatic Paget disease, hypercalcemia from cancer Phase III for bone metastasis	Esophagitis, arthralgias, hypersensitivity reactions
http://clinicaltrials.gov/ct2/results?term=Alendronate+cancer&Search=Search	Novartis	Alendronate Fosamax	Nitrogen containing bisphosphonate targets farnesyl pyrophosphate synthase	Osteoclast inhibitor	FDA approved for osteoporosis Phase III for bone metastasis	Esophagitis, osteonecrosis of jaw, delayed healing, hypersensitivity reaction, bone/muscle pains
http://clinicaltrials.gov/ct2/results?term=MK-0822+and+cancer&Search=Search	Merck	Odanacatib NA MK-0822	Anti-cathepsin K (decreases bone resorption)	Cathepsin K (osteoclast-specific enzyme)	Phase III for osteoporosis No open cancer-specific trials	
http://clinicaltrials.gov/ct2/results?term=AAE-581&Search=Search	Novartis	Balicatib NA AAE-581	Anti-cathepsin K		Phase II for osteoporosis (completed) No open cancer trials	
PI-3K/AKT inhibitors						
AKT inhibitors						
http://clinicaltrials.g ov/ct2/results?term=MK2206+lung+&Search=Search	Merck	NA NA MK2206	Non–ATP- competitive allosteric Akt	Akt	Phase II	Rash, mucositis, Gastrointestinal toxicity
http://clinicaltrials.gov/ct2/results?term=AG+1343+lung&Search=Search	Agouron Pharmaceuticals	Nelfinavir Viracept AG 1343	Protease inhibitor	Akt	Phase II in combination radiotherapy trials.	Diarrhea, rash, fatigue, leukopenia
http://clinicaltrials.gov/ct2/results?term=perifosine+lung&Search=Search	Keryx/AOI Pharmaceuticals	Perifosine NA KRX-0401	Alkylphospholipid	Akt	Phase I/II (NSCLC trial suspended)	Nausea, vomiting, diarrhea, fatigue
PI-3K inhibitors						
http://clinicaltrials.gov/ct2/results?term=BEZ235&Search=Search	Novartis	Dactolisib NA BEZ235	Small molecule inhibitor	PI-3K (pan-class 1), mTOR complexes 1/2	Phase I/II	Nausea, emesis, diarrhea, fatigue, anemia

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=BKM120+lung+cancer&Search=Search	Novartis	Buparlisib NA BKM120	Small molecule ATP-competitive inhibitor	PI-3K (pan-class 1)	Phase II	Rash, hyperglycemia, altered mood, Pruritus
http://clinicaltrials.gov/ct2/results?term=Rigosertib+lung+cancer&Search=Search	Onconova Therapeutics	Rigosertib Estybon ON01910	Non–ATP-competitive small molecule inhibitor	PI-3K inhibitor downregulates cyclin D1, induces NOXA, BIM, and JNK	Phase III Phase II in squamous tumors including lung cancer	Fatigue, anorexia
http://clinicaltrials.gov/ct2/results?term=XL147&Search=Search	Exelixis	NA NA XL147	Small molecule inhibitor	PI-3K (class 1 isoforms)	Phase I completed	Rash, arterial thrombosis, transaminitis, hyperglycemia
http://clinicaltrials.gov/ct2/results?term=BGT226&Search=Search	Novartis	NA NA BGT226	Dual small molecule Inhibitor	PI-3K and mTOR	Phase I (completed)	
http://clinicaltrials.gov/ct2/results?term=PX-866&Search=Search	Oncothyreon	NA NA PX-866	Irreversible small molecule inhibitor (Wortmanin analog)	PI-3K, lowersp-mTOR, p-S6 ribosomal protein	Phase I/II	Diarrhea, nausea, vomiting
http://clinicaltrials.gov/ct2/results?term=GDC-0941&Search=Search	Genentech	Pictilisib NA GDC-0941	Small molecule inhibitor	PI-3K (class 1 isoforms)	Phase II squamous NSCLC	Nausea, fatigue, diarrhea, dysgeusia, headache, pleural effusion
http://clinicaltrials.gov/ct2/results?term=PF-04691502&Search=Search	Pfizer	NA NA PF-04691502	Dual molecule inhibitor	PI-3K and mTOR	Phase II Phase I for lung cancer	
http://clinicaltrials.gov/ct2/results?term=XL765&Search=Search	Exelixis	NA NA XL765	Dual selective oral inhibitor	PI-3K (class 1) and mTOR	Phase I (completed)	Nausea, diarrhea, transaminitis, rash, anorexia, fatigue
http://clinicaltrials.gov/ct2/results?term=BAY80-6946&Search=Search	Bayor	NA NA BAY80-6946	Highly selective reversible inhibitor	Pan-class I PI-3K	Phase II Phase I (NSCLC)	Fatigue, nausea, diarrhea, mucositis, dysgeusia, anemia
PDGFR α inhibitors						
http://clinicaltrials.gov/ct2/results?term=Ramucirumab&Search=Search	Imclone LLC	Ramucirumab NA IMC-3G3	Human IgG1 MoAb	PDGFRα	Phase II	Fatigue
http://clinicaltrials.gov/ct2/results?term=MEDI-575&Search=Search	MedImmune	NA NA MEDI-575	MoAb	PDGFRα	Phase II (currently not accruing patients)	
PARP inhibitors						
http://clinicaltrials.gov/ct2/results?term=BSI-201&Search=Search	Sanofi-Aventis (BiPar Sciences)	Iniparib NA BSI-201	Small lipophilic molecule inhibitor	PARP-1	Phase III (squamous) (ECLIPSE) (completed, no benefit noted and further development discontinued)	Nausea, fatigue

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=Rucaparib&Search=Search	Pfizer	Rucaparib NA AG014699/ PF-01367338	Small molecule inhibitor	PARP-1	Phase II Phase I for NSCLC	Fatigue, thrombocytopenia, hypophosphatemia, lymphopenia
http://clinicaltrials.gov/ct2/results?term=Veliparib&Search=Search	Abbott/AbbVie	Veliparib NA ABT 888	Small molecule inhibitor	PARP-1, 2	Phase II	Fatigue, neutropenia (with chemotherapy)
http://clinicaltrials.gov/ct2/show/NCT01788332?term=AZD2281&rank=29	AstraZeneca	Olaparib NA AZD2281	Small molecule inhibitor	PARP	Phase II	Nausea, fatigue, anemia
http://clinicaltrials.gov/ct2/results?term=MK4827&Search=Search	Merck	Niraparib NA MK4827	Small molecule inhibitor	PARP-1, 2	Phase I Phase III breast cancer	Fatigue, nausea, myelosuppression
http://clinicaltrials.gov/ct2/results?term=BMN673&Search=Search	Biomarin	NA NA BMN673	Small molecule inhibitor	PARP-1, 2	Phase III breast cancer Phase I solid tumors including SCLC	
SMAC mimetics						
http://clinicaltrials.gov/ct2/results?term=TL32711&Search=Search	Tetralogic	Birinapant NA TL32711	Small molecule Smac mimetic	Antagonizes IAPs	Phase I	
http://clinicaltrials.gov/ct2/results?term=AT-406&Search=Search	Ascenta Therapeutics	NA NA AT-406	Small molecule Smac mimetic	Antagonizes IAPs	Phase I	
Survivin inhibitors						
http://clinicaltrials.gov/ct2/results?term=LY2181308&Search=Search	Pharmaceuticals & Eli Lilly Isis	NA NA LY2181308	Antisense oligonucleotide	Blocks survivin	Phase II	PTT prolongation, headache, lymphopenia, fever, fatigue, nausea
http://clinicaltrials.go v/ct2/results?term=YM155&Search=Search	Astellas	NA NA YM155	Small molecule inhibitor	Suppresses survivin	Phase II	Hypertension, neutropenia, fatigue, nausea, stomatitis, fever
Telomerase inhibitors						
http://clinicaltrials.gov/ct2/results?term=GRN163L&Search=Search	Geron Corporation	Imetelstat NA GRN163L	Competitive telomerase RNA template antagonist	Telomerase	Phase I (completed)	PTT prolongation, gastrointestinalside effects, fatigue, anemia, GGT elevation, peripheral neuropathy
http://clinicaltrials.gov/ct2/results?term=KML001&Search=Search	University of Maryland	Sodium metaarsenite NA KML001	Oral arsenic agent	Telomerase	Phase I	
TRAIL receptor agonists						
http://clinicaltrials.gov/ct2/results?term=PRO95780&Search=Search	Genentech	Apomab/drozitumab NA PRO95780	Human IgG1 MoAb	TRAIL-R2/DR)	Phase II (no active studies)	Neutropenia, elevated liver enzymes, supra ventricular tachycardia, pulmonary embolism

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=HGS-ETR1&Search=Search	Human Genome Sciences	Mapatumumab NA HGS-ETR1	Human MoAb	TRAIL-R1/DR4	Phase I (completed)	Fatigue, nausea, hypotension, transaminitis.
http://clinicaltrials.gov/ct2/results?term=HGS-ETR2&Search=Search	Human Genome Sciences	Lexatumumab NA HGS-ETR2	Human MoAb	TRAIL-R2/DR5	Phase I completed in pediatric solid tumors. No currently active studies in Lung Cancer	Fatigue, transaminitis.
http://clinicaltrials.gov/ct2/results?term=AMG-655+&Search=Search	Amgen	Conatumumab NA AMG-655	Human MoAb	TRAIL-R2/DR5	Phase II. Open label extension study in multiple solid tumors currently ongoing.	Fever, fatigue, gastrointestinal toxicity
http://clinicaltrials.gov/ct2/results?term=AMG951+&Search=Search	Amgen/Genentech	Dulanermin NA AMG951 (rhApo2L/TRAIL)	Recombinant human MoAb	DR4 and DR5	Phase II (completed)	Arthralgia, myalgias, nausea, transaminitis
VDAs						
http://clinicaltrials.gov/ct2/results?term=ASA404&Search=Search	Antisoma & Novartis	Vadimezan NA ASA404	Small molecule VDA	Induces TNF-α, serotonin, and nitric oxide	Phase III (development halted as no benefit seen in NSCLC study)	
http://clinicaltrials.gov/ct2/results?term=NGR-hTNF&Search=Search	MolMed	NA NA NGR-hTNF	CNGRC peptide-TNF α conjugate (NGR-hTNF is a first-in-class compound based on the combination of a tumor homing peptide (NGR) with the hTNF	Membrane-bound metalloprotease CD13 expressed on endothelial cells	Phase III mesothelioma, phase II SCLC (completed), phase II NSCLC (completed)	Infusion-related chills
http://clinicaltrials.gov/ct2/results?term=BNC105P&Search=Search	Bionomics Limited	NA NA BNC105P	VDA	Inhibits tubulin polymerization and acts as a VDA	Phase II (mesothelioma in Australia) Phase I (completed)	Fatigue, rash, infusion reaction
http://clinicaltrials.gov/ct2/results?term=Combretastatin-A4+phosphate&Search=Search	OxiGENE	Combretastatin-A4 phosphate/CA4P Zybrestat NA	Small molecule VDA	Reversible tubulin depolymerizing agent. Disrupts E-cadherin	Phase II (completed)	Hypertension, reversible cardiac ischemia, pulmonary embolism
http://clinicaltrials.gov/ct2/results?term=NPI-2358&Search=Search	Nereus Pharmaceuticals	Plinabulin NA NPI-2358	Small molecule VDA	Disrupts the endo thelial tubulin cytoskeleton	Phase I/II (completed)	Nausea, vomiting, diarrhea, fatigue, fever, tumor pain
http://clinicaltrials.gov/ct2/results?term=OXi4503&Search=Search	OXiGENE	Combretastatin A1 Diphosphate NA OXi4503	Small molecule VDA	Tubulin-binding agent	Phase I (completed)	Hypertension, tumor pain, fatigue, cytopenias, nausea
http://www.medicinova.com/html/research_cancer.html	MediciNova	NA NA MN-029	Binds reversibly to the colchicine-binding site on tubulin.	Disrupts the endothelial tubulin cytoskeleton	Phase I (completed)	Nausea, vomiting, hypotension, fatigue, diarrhea

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Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=ZD6126&Search=Search	AstraZeneca	NA NA ZD6126	Small molecule VDA	Disrupts the endothelial tubulin cytoskeleton	Phase I (terminated)	Anorexia, constipation, dyspnea, fatigue
Vaccines						
http://clinicaltrials.gov/ct2/results?term=Belagenpumatucel-L&Search=Search	NovaRx	Belagenpumatucel-L Lucanix	TGF-β2 antisense gene-modified allogeneic whole tumor cell vaccine	CTL Response against NSCLC cells	Phase III (completed). Primary end point of OS was not met. In a predefined subset analyses, improved survival was noted in patients with squamous cell carcinoma	Mild reactions-local (pain, redness, swelling) -systemic (fever, fatigue, muscle pain)
http://clinicaltrials.gov/ct2/results?term=Stimuvax&Search=Search	Merck KGaA/EMD Serono	BLP25 Liposome Vaccine Stimuvax	Synthetic peptide derived from the mucin 1 (Muc-1) antigen	CTL response against Muc-1-expressing tumor cells	Phase III. No survival benefit noted with 75% of the planned patients events occurring.	Cough, fatigue, dyspnea
http://clinicaltrials.gov/ct2/results?term=MAGE-A3&Search=Search	GlaxoSmithKline	NA NA GSK1572932A/ MAGE-A3	Antigen-specific cancer immunotherapeutic	CTL response against MAGE-A3–positive tumors	Phase III (MAGRIT). Completed. Coprimary end points note met. No clear subset likely to benefit identified.	Mild reactions -Local (pain, redness, swelling) -Systemic (fever, fatigue, muscle pain)
http://clinicaltrials.gov/ct2/results?term=GSK+249553&Search=Search	GlaxoSmithKline	Astuprotimut-R NA GSK 249553	Antigen-specific cancer immunotherapeutic	MAGE-3–positive tumors	Phase III	Mild grade 1 or 2 local or systemic reactions
http://clinicaltrials.gov/ct2/results?term=PANVAC-VF&Search=Search	Therion Biologics	PANVAC-VF NA NA	Delivered through two viral vectors—recombinant vaccinia and recombinant fowlpox—containing transgenes to Muc-1 and carcinoembryonic antigen	Epthelial Muc-1 and carcinoembryonic antigen	Phase III Phase I for lung cancer	Injection site reaction
http://clinicaltrials.gov/ct2/results?term=Montanide+&Search=Search	Bioven Sdn. Bhd (bioven)	Recombinant human EGF-rP64K/ Montanide ISA 51 NA	rEGF linked to the Neisseria meningitidis-derived recombinant immunogenic carrier protein P64k (rP64K) and mixed with immunoadjuvant Montanide ISA 51	Antibody-mediated inhibition of endogenous EGF binding to its receptor, EGFR	Phase II. Also recruiting mesothelioma patients.	
http://clinicaltrials.gov/ct2/results?term=TG+4010+&Search=Search	Transgene	NA NA TG 4010 (MVA-MUC1-IL2)	Modified vaccinia Ankara virus vector with Muc1 and IL-2 sequences	CTL response against Muc1	Phase II/III	Influenza-like symptoms

(Continued)

Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=HSPPC-96&Search=Search	Antigenics	Oncophage Vitespen HSPPC-96	Autologous tumor vaccine made by extractingheat shock protein gp96 and its associated peptides	Autologous tumor cells	Phase III (completed or terminated) Phase II feasibility study completed in NSCLC	
http://clinicaltrials.gov/ct2/results?term=CeaVac+Monoclonal+antibody+3H1+anti-idiotype+vaccine&Search=Search	Titan Pharmaceuticals	CeaVac monoclonal antibody 3H1 anti-idiotype vaccine NA	Recombinant MoAb that mimics a specific epitope of the CEA	Tumors that express CEA	Phase III (colorectal-completed) Phase II completed for NSCLC	
http://clinicaltrials.gov/ct2/results?term=AG3340&Search=Search	Agouron Pharmaceuticals/ Pfizer	Prinomastat NA AG3340	Small molecule, nonpeptidic, hydroxymate MMP inhibitor	MMPs 2, 3, 9, 13, and 14	Phase III completed. Showed no benefit (no active trials)	
http://clinicaltrials.gov/ct2/results?term=1650-G+Vaccine&Search=Search	University of Kentucky	NA NA 1650-G Vaccine	Allogenic cellular vaccine	CTL response against NSCLC cells	Phase II (completed)	
http://clinicaltrials.gov/ct2/results?term=CG8123+%28GVAX%29&Search=Search	Cell Genesys	NA NA CG8123 (GVAX)	GM-CSF gene-modified autologous whole tumor vaccine	CTL response against tumor cells	Phase II (terminated)	
http://clinicaltrials.gov/ct2/results?term=L-Vax&Search=Search	AVAX Technologies	NA NA L-Vax	Dinitrophenyl-modified autologous NSCLC vaccine	CTL response against NSCLC cells	Phase I/II (study has been suspended)	
http://clinicaltrials.gov/ct2/results?term=Monoclonal+antibody+11D10+antiidiotype+vaccine&Search=Search	NCI/RTOG/SWOG	Monoclonal antibody 11D10 anti-idiotype vaccine	MoAb against an idiotype that mimics a HMFG membrane epitope	Cells expressing HMFG membrane epitope	Phase II (NSCLC completed) (limited-stage SCLC)	
http://clinicaltrials.gov/ct2/results?term=EP-2101&Search=Search	Epimmune	NA NA EP-2101	Multi-epitope DNA vaccine, emulsified in montanide ISA-51	Tumors expressing CEA, HER2/neu, p53, and MAGE 2/3	Phase I (completed)	
http://clinicaltrials.gov/ct2/results?term=Mutant+p53+peptide+pulsed+dendritic+cell&Search=Search	NCI	NA NA Mutant p53 peptide pulsed dendritic cell	Autologous dendritic cells pulsed with a mutant p53 peptide	Tumor cells expressing mutant p53	Phase II (completed)	
http://clinicaltrials.gov/ct2/results?term=INGN-225&Search=Search	Introgen Therapuetics	Ad.p53-DC NA INGN-225	Autologous dendritic cells transduced with a recombinant adenovirus encoding p53 peptide	Tumor cells expressing mutant p53	Phase II (SCLC)	
http://clinicaltrials.gov/ct2/show/NCT00019006?term=Ras+peptide+cancer+vaccine&rank=1	NCI	Ras peptide cancer vaccine NA		Mutated K-Ras	Phase II (completed)	
http://clinicaltrials.go v/ct2/results?term=S-3304&Search=Search	Shionogi	NA NA S-3304	Noncytotoxic inhibitor of MMP	MMP-2 MMP-9	Phase I/II	Gastrointestinal toxicities, including dairrhea

(Continued)

Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=CEA+%286D%29&Search=Search	NCI	Recombinant fowl pox or vaccinia-CEA(6D)/TRICOM NA	Recombinant fowl pox/ vaccinia virus vector encoding CEA and a triad of costimulatory molecules (B7-1, ICAM-1, and LFA-3) (TRICOM)	CEA-expressing tumors	Phase II (terminated)	
http://clinicaltrials.gov/ct2/results?term=CCL21&Search=Search	NCI	NA NA CCL21	Adenovirus CCL21 gene modified autologous dendritic cells		Phase II	
http://clinicaltrials.gov/ct2/results?term=DRibble+vaccine&Search=Search	Providence Health Services/The Wayne D. Kuni and Joan E. Kuni Foundation	DRibble vaccine NA	Autologous tumor vaccine	Autologous tumor cells	Phase II	
http://clinicaltrials.gov/ct2/results?term=Ad100-gp96Ig-HLA+A1&Search=Search	University of Miami, Sylvester Cancer Center	NA NA Ad100-gp96Ig-HLA A1	Irradiated NSCLC cells, manipulated to express and secrete heat shock protein gp96-Ig fusion protein	CTL response against NSCLC cells	Phase I	
http://clinicaltrials.gov/ct2/results?term=MAGE-12+peptide+vaccine+&Search=Search	NCI	MAGE-12 peptide vaccine (emulsified in Montanide ISA-51) NA	Peptide vaccine	MAGE-12 antigen-positive tumors	Phase I (completed) (all solid tumors-completed)	
http://clinicaltrials.gov/ct2/results?term=pVAX%2FL523S+&Search=Search	Corixa Corporation	pVAX/L523S and Ad/L523S NA	Recombinant DNA and Adenovirus Expressing L523S protein		Ph I (no updates available)	
http://clinicaltrials.gov/ct2/results?term= Semi- allogeneic +human+fibroblasts+%28MRC-5%29+transfected&Search=Search	University of Pittsburgh	Semiallogeneic human fibroblasts (MRC-5) transfected NA	Fibroblasts transfected with DNA from autologous tumor	Autologous tumor cells	Phase I	
http://clinicaltrials.gov/ct2/results?term=WT-1+%28Wilm's+tumor%29+analog+peptide+vaccine&Search=Search	Memorial Sloan Kettering Cancer Center	WT-1 analog peptide vaccine NA	Peptide vaccine	WT gene expressing tumors	Phase II for mesothelioma. Phase1 completed for NSCLC	
Antisense oligonucleotides						
file://localhost/ttp/::clinicaltrials.gov:ct2:results%3Fterm=Oblimerson+&Search=Search	Genta	Oblimerson Genasense G3139	Antisense oligo-deoxyribonucleotide	Bcl-2	Currently not under development for lung cancer.	Fever, elevated liver enzymes
http://clinicaltrials.gov/ct2/results?term=Custirsen&Search=Search	OncGenex	Custirsen NA OGX 011	Antisense oligonucleotide	Clusterin	Phase III	

(Continued)

Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=LY2181308&Search=Search	Isis Pharmaceuticals & Eli Lilly	NA NA LY2181308	Antisense oligonucleotide	Blocks survivin	Phase II (completed)	PTT prolongation, headache, lymphopenia, fever, fatigue, nausea
http://clinicaltrials.gov/ct2/results?term=ISIS+2503&Search=Search	Isis Pharmaceuticals	NA NA ISIS 2503	Antisense oligonucleotide	H-ras	Currently no studies for lung cancer	
http://clinicaltrials.gov/ct2/results?term=ISIS+5132&Search=Search	Isis Pharmeceuticals	NA NA ISIS 5132	Antisense oligonucleotide against c-Raf kinase mRNA expression	Raf-1	Currently no studies for lung cancer	Mild hematologic toxicity, asthenia, fever
Therapeutic antibody engineering (novel targets, antibody–drug conjugates, antibody fragments)						
http://clinicaltrials.gov/ct2/results?term=Catumaxomab&Search=Search	Trion Pharma	Catumaxomab Removab	Rat-murine hybrid monoclonal antibody binding to EpCAM and CD3 antibody	EpCAM/CD3	Phase III (phase I studies in solid tumors terminated) -Approved in Europe for malignant ascitis	Fever, Nausea,Vomiting
http://clinicaltrials.gov/ct2/results?term=GC-1008&Search=Search	Genzyme	Fresolimumab NA GC-1008	Human IgG4 MoAb	Pan-neutralizing TGF-β	Phase II (mesothelioma)	
http://clinicaltrials.gov/ct2/results?term=Bavituximab&Search=Search	Peregrine Pharmaceuticals	Bavituximab Tarvacin UNII-Q16CT95N25 3G4	Chimeric IgG1 MoAb	Membrane phosphatidylserine complexed with β2-glycoprotein I on tumor vasculature	Ph II	Nausea, fatigue, headache, alopecia, anemia, hypertension
http://clinicaltrials.gov/ct2/results?term=ALD518&Search=Search	Alder Pharmaceuticals	ALD518	Anti-IL-6 antibody	To treat anemia, cachexia, and fatigue	Phase II (completed)	
http://clinicaltrials.gov/ct2/results?term=ACE-011&Search=Search	Acceleron and Celgene	Sotatercept NA ACE-011	Fully human soluble activin receptor type 2A IgG-Fc fusion protein	Activin antagonist (Increases haemoglobin and also increases bone mineral density)	Phase II (all solid tumor studies terminated)	Headache, paresthesia, dizziness, fatigue, hypertension
http://clinicaltrials.gov/ct2/results?term=Sonepcizumab%2F+&Search=Search	Lpath/ Merck-Sereno	Sonepcizumab/ ASONEP	Humanized MoAb	Shingosine-1-phosphate	Phase I (completed)	Infusion reaction
http://clinicaltrials.gov/ct2/show/NCT00635596?term=MT110&rank=1	Micromet AG	MT110	EpCAM/ CD3 bispecific antibody construct (BiTE)	EpCAM/ CD3	Ph I (not recruiting participants)	Fever, elevated liver enzymes
http://clinicaltrials.gov/ct2/results?term=CVX-045&Search=Search	Pfizer	CVX-045	Human MoAb	Thrombospond in-1 Mimetic	Phase I (completed)	Fatigue, gastrointestinal upset, dyspnea, headache, dizziness, anemia

(Continued)

Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=AGS-22M6E&Search=Search	Astellas Pharmaceuticals	NA NA AGS-22M6E	Monoclonal antibody-drug conjugate	Anti-Nectin-4 monoclonal antibody-conjugated to the cytotoxic agent monomethyl auristatin E	Phase I	
Therapeutic viruses						
http://clinicaltrials.gov/ct2/results?term=Seneca+Valley+virus-001+&Search=Search	NCI	NA NA Seneca Valley virus-001 (NTX-010)	Picornavirus	Replication competent anticancer virus	Phase II (SCLC)(completed accrual)	
http://clinicaltrials.gov/ct2/show/NCT01708993?term=Reolysin&rank=3	Oncolytics Biotech	NA Reolysin NA	Oncolytic reovirus	Replicates selectively in cells with activated Ras pathway causing cell lysis	Phase II	Chills, fever, headache, runny nose, fatigue, and myelosuppression
Miscellaneous therapeutic agents						
http://clinicaltrials.gov/ct2/results?term=Iloprost+CANCER&Search=Search	Actelion	Iloprost Ventavis (inhaled) ACT-213105	Oral PGI2 (prostacyclin) analogue	Multiple effects including activation of PPAR	FDA approved for pulmonary arterial hypertension Phase II completed for lung cancer prevention	Headache, flushing
http://clinicaltrials.gov/ct2/results?term=TLK286&Search=Sear ch	Telik	Canfosfamide Hydrochloride Telcyta TLK286	Cancer cell-activated chemotherapeutic	Activated byglutathione S-transferase P1-1 (overexpressed in many tumors)	Ph III (completed)	Nausea, vomiting, fatigue, microscopic hematuria, anemia
http://clinicaltrials.gov/ct2/results?term=Isotretinoin+cancer&Search=Search	NCI	Isotretinoin Several brand names Including Accutane Roaccutane	Retinoid	Exact mechanism of action unknown. Isotretinoin may down-regulate the telomerase enzyme, inhibiting "cellular immortalization and tumorigenesis	Ph II (completed)	Dryness of the skin, acne flare and skin rash, raised liver enzyme, hyperlipidemia, birth defects
http://clinicaltrials.gov/ct2/results?term=endostatin&Search=Search	Simcere pharmaceuticals	Endostar NA YH-16	Recombinant human endostatin	Angiogenesis inhibitors	Phase III/ IV. Phase II study in stage III NSCLC.	Pneumonia, pulmonary embolism
http://clinicaltrials.gov/ct2/show/NCT01748825?term=MK-1775&rank=3	Merck	MK-1775	Sensitizes p53 negative cells to DNA damage by abrogation of G2 checkpoint	WEE1 inhibitor	Phase I/II.	
http://clinicaltrials.gov/ct2/results?term=CHR-2797&Search=Search	Chroma Therapeutics	Tosedostat CHR-2797	Small molecule aminopeptidase inhibitor	M1 family of aminopeptidases	Phase I/II. All studies have either completed accrual, terminated or suspended	

(Continued)

Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=PF-3512676&Search=Search	Pfizer	NA NA PF-3512676/CPG 7909	Synthetic agonist of toll-like receptor 9 (TLR9)	TLR9	Phase III terminated due to lack of efficacy	Sepsis
http://clinicaltrials.gov/ct2/results?term=PF-00562271&Search=Search	Pfizer	PF-00562271	Reversible focal adhesion kinase (FAK) inhibitor	FAK	Phase I (completed)	Headache, nausea, peripheral neuropathy, diarrhea, fatigue, edema
http://clinicaltrials.gov/ct2/results?term=ZD4054&Search=Search	AstraZeneca	Zibotentan NA ZD4054	Endothelin A Receptor (ETAR) antagonist	ETAR	Phase II	
http://clinicaltrials.gov/ct2/results?term=AZD+6918&Search=Search	AstraZeneca	AZD 6918	Small molecule inhibitor	Tropomyosin-related kinases (Trk)	Phase I (Development discontinued)	
http://clinicaltrials.gov/ct2/results?term=Eribulin+mesylate+lung+cancer&Search=Search	Eisai Inc.	Eribulin mesylate E7389	Non-taxane microtubule dynamics inhibitor		Phase II (completed)	Fatigue, cytopenias
http://clinicaltrials.gov/ct2/results?term=Triapine+lung+cancer&Search=Search	Vion Pharmaceuticals, NCI	Triapine	Ribonucleotide reductase inhibitor (enhancing the activity of gemcitabine)		Phase II (completed)	
http://clinicaltrials.gov/ct2/results?term=Epofolate&Search=Search	Bristol-Meyers Squibb	Epofolate BMS-753493	Folate conjugate of epothilone analog BMS-748265		Phase I (terminated)	Fatigue, nausea, elevated liver enzymes, diarrhea
http://clinicaltrials.gov/ct2/results?term=Efatutazone&Search=Search	Daiichi Sankyo	Efatutazone NA CS 7017/ RS5444	PPARγ agonist	Peroxisome proliferator-activated receptor (PPAR)-γ	Phase I	Fluid retention
http://clinicaltrials.gov/ct2/results?term=PD++0332991+lung+cancer&Search=Search	Pfizer/Onyx	NA NA PD 0332991	Small molecule inhibitor	CDK 4/6 inhibitor	Phase II	
http://clinicaltrials.gov/ct2/results?term=Celecoxib+lung+cancer&Search=Search	Pfizer	Celecoxib Celebrex or Celebra for Arthritis Onsenal for polyps	Eicosanoid	Cyclooxygenase-2 inhibitor	Phase II	
http://clinicaltrials.gov/ct2/results?term=apricoxib	Tragara Pharmaceuticals	Aprecoxib CS-706. TG01 Capoxigem	A benzenesulfonamide nonsteroidal anti-inflammatory drug	Small molecule selective Cox-2 inhibitor	Phase II (completed)	
http://clinicaltrials.gov/ct2/results?term=QBI-139&Search=Search	Quintessence Biosciences	QBI-139	Variant of human pancreatic ribonuclease 1	Causes destruction of RNA	Phase I	
http://clinicaltrials.gov/ct2/results?term=CVX-060&Search=Search	Pfizer	CVX-060	Antiangiogenic COVX-Body	A Selective angiopoietin-2 (ANG-2) binding	Phase I (completed)	Fatigue, proteinuria

(Continued)

Table 1. (*Continued*)

Hyperlink	Trial Sponsor(s)	Generic Name Trade Name Other Name(s)	Type	Target(s)	Current Phase of Development	Prototypic Side Effects
http://clinicaltrials.gov/ct2/results?term=AZD1480&Search=Search	AstraZeneca	NA NA AZD1480	Small molecule inhibitor	JAK2 kinase	Phase I (terminated in solid tumors)	
http://clinicaltrials.gov/ct2/results?term=GSAO&Search=Search	NCI	4-(N-(S-glutathionylacetylamino) phenylarsonous acid (GSAO)	Synthetic tripeptide trivalent arsenical	Angiogenesis inhibitor that targets the mitcohondria actively dividing but not quiescent endothelial cells arresting their proliferation and causing apoptosis	Phase I (terminated)	
http://clinicaltrials.gov/ct2/results?term=chol-FUS1&Search=Search	Introgen Therapeutics	DOTAP: chol-FUS1	Lipid-based nanoparticles	Fus1 tumor suppressor gene	Phase I (completed). Phase II initiated in NSCLC.	Fever, hypophosphatemia
http://clinicaltrials.gov/ct2/results?term=LY+2510924&Search=Search	Eli Lilly	NA NA LY 2510924	Peptide antagonist	Antagonizes the CXCR4 peptide.	Phase II (completed enrollment in ES-SCLC	

In this sixth annual update of the table, the current status of targeted drugs in clinical development for lung cancer is detailed. Only compounds that have entered clinical trials at the time of writing are included. In this version, we have attempted to make this reference tool dynamic and allow it to evolve as the information evolves. To facilitate this, we have attached a hyperlink with each category. Clicking on the hyperlink will take the reader to the clinicaltrials.gov website for each compound and update the reader on the current status of the ongoing clinical trials. We have also "de-listed" some of the drugs whose development has been discontinued in lung cancer from this version of the table. Drugs whose development has been discontinued in the past year included to update the reader as to their current status. As in the previous updates, the compounds are grouped by their mechanism of action. Under each class, they are listed in the order of their phase of clinical development, with those in the latest phase of development being listed first. The categories are listed alphabetically, except for the first three categories (EGFR, VEGFR, and ALK inhibitors) since drug(s) from each of these category are approved for the treatment of patients with NSCLC. The five new categories added in the previous update have been maintained in this current update and consist of immunomodulatory antibodies, SMAC mimetics, antisense oligonucleotides, therapeutic antibody engineering, and therapeutic viruses. These new categories are listed at the end of the table. Also at the end of the table are drugs that do not fall into a specific category. These are listed under "miscellaneous therapeutic agents." In the last column, the commonly reported toxicities are listed. This list of toxicities is not intended to be comprehensive, but only the prototypic or most commonly seen "class effect" toxicities are noted. The toxicity column has been left blank for compounds very early in development for which mature toxicity data are not yet available. The phase of the trial in also listed in the last but one column. The phase of development in lung cancer has been specified only if it differs from the overall phase of development of the agent. Compounds still in phase I development are also included. However, only those compounds enrolling lung cancer patients are listed. When available, the generic name, trade name(s) and other accepted name(s) or numbers used to refer to an agent are also listed.

ABL, ABL proto-oncogene; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; ARCHER, Advanced Research for Cancer targeted pan-HER therapy; AST, aspartate aminotransferase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CEA, carcinoembryonic antigen; CFDA, China Food and Drug Administration; CNGRC, cyclic peptide Cys-Asn-Gly-Arg-Cys; CTL, Cytotoxic T lymphocyte; CTLA-4, cytotoxic T-lymphocyte antigen-4; DR, death receptor; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EMEA, European Medicines Agency; ES-SCLC, extensive-stage small-cell lung cancer; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; FLT, fms-related tyrosine kinase; GGT, gamma-glutamyl transferase; HDAC, histone deacetylase; HDL, high-density lipoprotein; HGFR, hepatocyte growth factor receptor; HIF, hypoxia-inducible factor; HMFG, human milk fat globule; hTNF, human tumor necrosis factor; IAPs, inhibitor of apoptosis proteins; ICAM, intercellular adhesion molecule; IGF-1R, insulin growth factor-1 receptor; IGF1R, insulin-like growth factor 1 receptor; IgG2, immunoglobulin G2; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; KSP, kinesin spindle protein; LFA, leukocyte function antigen; LFT, liver function test; LVEF, left ventricular ejection fraction; NCI, National Cancer Institute; MAGFIT, MAGE-3 as adjuvant non-small cell lung cancer immunotherapy; MEK, MAP kinase-ERK kinase; MoAB, monoclonal antibody; MMP, matrix metalloproteinase; mRNA, messenger RNA, mTOR, mammalian target of rapamycin; NGR, Asn-Gly-Arg tripeptide; NSCLC, non–small-cell lung cancer; OS, overall survival; PARP, Poly(ADP-ribose) polymerase; PD-1, programmed death 1; PDGFR, platelet derived growth factor receptor; PDGFR α, platelet derived growth factor α; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferators activated receptor; PTT, partial thromboplastin time; RAF, v-raf murine leukemia viral oncogene homolog; rEGF, epithelial growth factor receptor; REVEL, Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy; RTOG, Radiation Therapy Oncology Group; SCLC, small-cell lung cancer; SMAC, second mitochondria-derived activator of caspase; SWOG, Southwest Oncology Group; TKI, tyrosine kinase inhibitor; TNF, tumor necrosis alpha; TRAIL, TNF-related apoptosis-inducing ligand; TRICOM, triad of costimulatory human molecules B7-1, ICAM-1, and LFA-3; TSH, thyroid-stimulating hormone, VDA, vascular disrupting agent; VEGFR, vascular endothelial growth factor receptor; VEGFR2, vascular endothelial growth factor receptor 2; VITAL, (Ziv-)Aflibercept Versus Placebo in Patients With Second-Line Docetaxel for Locally Advanced or Metastatic Non–Small-Cell Lung Cancer trial; WT, Wilm' tumor.

been presented.[19] In addition, a number of different mutations have been identified in FGFR2 and FGFR3, including a recurrent fusion of FGFR3 and transforming, acidic coiled-coil containing protein 3 (TACC3), which provides much needed insight into the oncogenic pathways operating in SCC and makes a strong case for applying FGFR inhibitors in this disease.[20–22] Targetable alterations in lung squamous cell carcinomas also include members of the PI3K pathway, discoidin domain receptor tyrosine kinase 2 (*DDR2*), and potentially the nuclear factor, erythroid 2-like 2 (NFE2L2)/kelch-like ECH-associated protein 1 Keap1)/cullin 3 (CUL3) antioxidant response pathway. In contrast to lung adenocarcinomas, there does not seem to be a substantial cohort of nonsmokers with squamous cell lung cancer and the disease appears to be more genomically homogeneous.

Small-Cell Lung Cancer

With the development of targeted agents, the treatment paradigm of NSCLC continues to evolve; however, the discovery of a clinically actionable mutation in small-cell lung cancer (SCLC) remains elusive. SCLC remains an exceptionally aggressive malignancy with limited treatment options in the relapsed/refractory setting. SCLC has a high mutation rate, likely secondary to tobacco carcinogen exposure in this patient population. This high rate of mutation makes the identification of pathologically relevant driver mutations difficult. Genomic sequencing has confirmed a high prevalence of difficult to target TP53 and retinoblastoma 1 (RB1) inactivation mutations. Next-generation sequencing (NGS) has been applied to the SCLC genome in hopes of identifying new therapeutic targets, and recent work has showcased the identification of significantly mutated genes in SCLC cell lines. These aberrations include genetic alterations affecting histone-modifying enzymes CREB binding protein (CREBBP), E1A binding protein p300 (EP300), and LFF as well as PTEN mutations, FGFR1 and SOX2 amplification. Recent work on SOX2 demonstrates the prevalence of SOX2 amplification in SCLC cell lines with expression of SOX2 strongly correlated with increased gene copy number and clinical stage leading the authors to postulate if SOX2 is a genuine SCLC driver mutation.[23,24]

EPIGENETIC THERAPY IN THE TREATMENT OF LUNG CANCER

The contributions of epigenetic dysregulation to carcinogenesis through aberrant DNA methylation and altered chromatin configuration continue to be expanded.[25] The cancer epigenome contains a variety of tumor-specific alterations which define subgroups of disease, alter transcriptional patterns, and may reflect therapeutic sensitivities.[26–28]

Recent genomic sequencing efforts have further underscored the inextricable connections between genetic and epigenetic mechanisms of carcinogenesis, including alternative mechanisms leading to loss of individual tumor suppressor gene function and cooperation of defects affecting key signaling pathways. A signature example in lung cancer is the CDKN2A locus, encoding both the p16 tumor suppressor (a key regulator of cell-cycle progression from G1- to S-phase) and alternate reading frame (ARF) (which can sequester mouse double minute 2 homolog (MDM2) leading to stabilization of the tumor suppressor p53). Comprehensive genomic analysis of squamous cell lung cancers by the Cancer Genome Atlas (TCGA) Research Network has demonstrated CDKN2A loss of function in the large majority of cases, the most common mechanisms being homozygous deletion in 29%, site-specific promoter hypermethylation leading to gene silencing in 21%, and missense or truncating mutation in 18%.[27]

The TCGA has also demonstrated, across tumor types, high rates of genetic alterations in key epigenetic regulators. These include members of the mixed-lineage leukemia gene family of histone methyltransferases, mutated in 20% and 18% of squamous and nonsquamous lung cancers, respectively.[29] Chromatin-modifying enzymes which add and remove histone modifications, termed "writers" and "erasers", affect the state of chromatin compaction of DNA making it more or less accessible for the transcription of genes which play various roles in the transformation of a cancer cell (Fig. 2). Beyond the vast changes in DNA methylation that characterize cancer, these enzymes contribute to an altered landscape of transcriptional regulation not only in the hematologic malignancies for which epigenetic therapy has found early success but also in a broad range of solid tumors including lung cancers.[25,29] Mutations of the isocitrate dehydrogenase genes, found across many tumor types, most notably gliomas and sarcomas but also including a small percentage of lung cancers, result in a CpG island methylator phenotype with therapeutic implications.[29,30] Multiple CpG island methylator phenotype–like states have been described, and the molecular abnormalities responsible for these phenotypes are beginning to be defined; to date, these include alterations in genes affecting the metabolism of methylated cytosines and mutations in DNA methyltransferases.[30,31]

Historically, identification and demonstration of re-expression of individual tumor suppressor genes have provided the rationale for the clinical development of DNA hypomethylating agents and histone deacetylase inhibitors in various hematologic malignancies.[32] In fact, of course, hundreds of genes are affected by these therapies. Many of the described "hallmarks of cancer," broad programs of normal cellular functions subverted during carcinogenesis, are altered by epigenetic reprogramming.[33] Epigenetically directed therapies have the potential to concurrently affect multiple relevant pathways critical to cancer proliferation, survival, and metastatic capacity. Site-specific hypermethylation of promoters for genes controlling stem cell maturation has been implicated as a mechanism contributing to replicative immortality and clonogenic potential in cancer.[34,35] Promoter demethylation by DNA methyltransferase inhibitors such as azacitidine can markedly reduce replicative capacity in cancer cell lines, associated with reversal of a program of cancer-specific changes in methylation.[36] Mutations in epigenetic regulators such as the polycomb-repressive complex protein polycomb ring finger oncogene BMI-1 (BMI-1) and the histone methyltransferase EZH2 can enhance clonogenic potential of cancer cells.[35] In addition, genetic alterations of chromatin regulatory genes with established roles in proliferation, inhibition of apoptosis and senescence, and promotion of genomic instability have been described.[35]

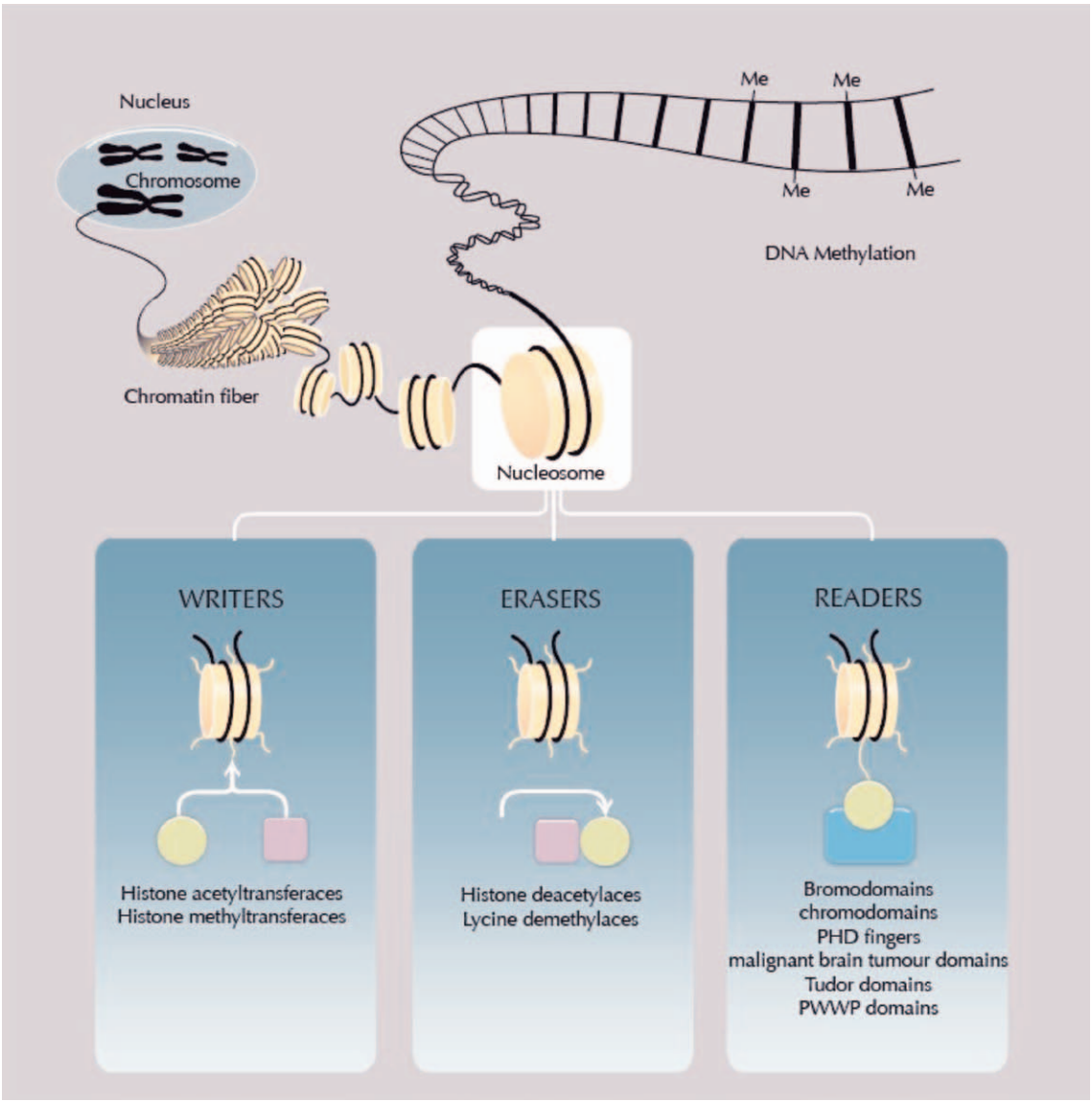

FIGURE 2. Chromatin-modifying enzymes. MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal–regulated kinase; PHD, plant homeodomain; PI3K, phosphatidylinositol 3-kinase; PWWP, proline-tryptophan-tryptophan-proline.

In addition to affecting key elements of carcinogenesis, epigenetic therapy may have a role in the treatment of acquired resistance to mutationally targeted therapy. For example, inhibition of the histone demethylase KDM5A has been shown to preferentially eliminate clonogenic survivors to EGFR TK therapy in EGFR-mutant NSCLC cell lines.[37]

Although epigenetic therapy regimens using DNA hypomethylating agents or histone deacetylase inhibitors have become standard-of-care therapies in myelodysplastic syndrome and peripheral T-cell lymphoma, these treatments have only begun to be clinically investigated in lung cancer or other solid tumors. Combinatorial epigenetic therapy consisting of the DNA hypomethylating agent azacitidine and the histone deacetylase inhibitor entinostat has been shown to result in rare objective responses in lung cancer.[38] Data from this initial study suggest that combinatorial epigenetic therapy may prime lung cancers for improved responses to subsequent therapy, notably including immunotherapy. Preclinical models suggest that multiple pathways down-regulated in tumors as a mechanism of immune escape and evasion may be re-expressed in response to epigenetic therapy and may augment the effectiveness of programmed death 1 (PD-1) immune checkpoint blockade.[39] Thus epigenetic therapy may prime tumors to respond to immunotherapeutic strategies by overcoming tumor mechanisms including increased antigen presentation, up-regulation of programmed death receptor ligand 1 (PD-L1) expression, and augmentation of interferon and cytokine signaling within the tumor.[40]

In addition to next-generation hypomethylating agents and histone deacetylase inhibitors, there are a host of novel epigenetic therapies targeting chromatin modifying enzymes now being translated into clinical testing in lung cancer and other solid tumors. EZH2 inhibitors are currently in early

phase clinical development and may be of relevance in the treatment of lung cancers including SCLCs, in which EZH2 seems to be frequently overexpressed. A DOT1-like histone H3K79 methyltransferase inhibitor is being developed for acute leukemias defined by alterations in mixed-lineage leukemia, a gene family of histone methyltransferases also commonly mutated or otherwise genetically altered in lung cancer. Beyond targeting chromatin-modifying enzymes that write or erase histone marks, bromodomain and extra-terminal histone-binding proteins possess what may be termed a "reading" function focused on histone acetylation; trials of inhibitors of the protein–protein interaction have been initiated in SCLC.[41–43] The evolving knowledge of the prevalence and array of identifiable defects in chromatin regulators and DNA-methylation phenotypes suggests a large number of potential targets and strategies for epigenetic therapy beyond those which have formed the basis of much clinical investigation of epigenetic therapies to date. Thoracic oncologists can expect an expanding portfolio of novel epigenetically targeted agents with potential for clinical application to lung cancer during the next several years.

EGFR MUTATION–POSITIVE NSCLC

The approach toward lung cancer therapeutics has undergone a major paradigm shift in the last 10 years. The impetus to move toward larger and more frequent biopsies and perform upfront genotyping at the time of diagnosis came in large part with the recognition that between 10% and 20% of U.S. lung cancer patients had tumors carrying an EGFR mutation, a biomarker of oncogene addiction that correlates strongly with response to EGFR TKIs.[44] There are several subtypes of EGFR mutations, but the two most frequent, L858R and del19, comprise 90% of the cases and are also the most tightly associated with robust response to therapy.[45] In this review, L858R and del19 mutations will be collectively referred to as "common mutations." We will review the current treatment recommendations for EGFR-mutant patients and the pivotal studies that shape the basis for the recommendations.

Advanced-Stage Disease: First Line

When EGFR mutations were first discovered, several single-arm phase II studies were quickly performed confirming that patients with advanced lung cancer and common EGFR mutations did very well with first-line gefitinib and erlotinib therapy, with response rates (RRs) of 60% to 75% and median progression-free survival (PFS) of approximately 9 to 10 months.[46–48] Although these results were two-to-three fold better than what was achieved with the current standard-of-care platinum-doublet chemotherapy regimens, there was still some skepticism about whether a randomized trial would favor an EGFR TKI or not because EGFR-mutant patients seemed to do better on chemotherapy than EGFR wild-type patients. However, this debate was settled when the IPASS study was published.

Iressa Pan-Asia Study (IPASS) was a large randomized trial of approximately 1200 patients done in Asia, where EGFR mutations are two to three times more common than in western countries.[6] All the subjects were nonsmokers with adenocarcinoma, both of which are clinical features that have been associated with increased incidence of EGFR mutations. Patients did NOT have to have an EGFR mutation to enter the trial, but among the subset that had tissue available for EGFR mutation testing, approximately 60% were positive for common EGFR mutations. The IPASS design compared first-line gefitinib with first-line chemotherapy with carboplatin and paclitaxel for up to six cycles with a primary end point of PFS. The results showed that in the overall intention-to-treat population, gefitinib had an improved PFS compared with chemotherapy with a hazard ratio (HR) of 0.74 and a 95% confidence interval (CI) of 0.65 to 0.85 (Table 2). However, when examining the subset of patients with tissue available for genotyping, it became clear that the overall positive results for gefitinib were exclusively due to the contribution from the EGFR-mutant cohort of patients, who had an even more impressive PFS benefit from first-line gefitinib (HR, 0.48; 95% CI, 0.36–0.46). Conversely, the EGFR wild-type patients showed that front-line EGFR TKI was a harmful strategy for them with HR of 2.85 (95% CI, 2.1–4.0). In addition to a PFS benefit, patients with EGFR mutations treated with gefitinib had an improved quality of life compared with those treated with chemotherapy.[49] Hence, practice changed significantly with the IPASS publication in two major ways: (1) the importance of early genotyping was appreciated and giving first-line EGFR TKIs to patients with EGFR mutations became an accepted therapeutic strategy and (2) because the wild-type patients did so poorly with first-line gefitinib in lieu of chemotherapy, it became obvious that if one did not know the mutation status for a patient, then EGFR TKIs should not be given, at least in the first-line setting.

After IPASS, several other randomized trials were completed in rapid succession, each confirming similar benefits from first-line gefitinib or erlotinib, primarily for patients with common EGFR mutations (Table 2).[7,50–53] The European Randomized Trial of Tarceva versus Chemotherapy (EURTAC) study was especially important from this collection of studies as it was the first such trial performed in a western population.[52] In EURTAC, Spanish and Italian EGFR-mutant patients (common mutations only) treated with first-line erlotinib had improved PFS compared with investigator-choice chemotherapy (either cisplatin/docetaxel or cisplatin/gemcitabine) (HR, 0.37; 95% CI, 0.25−0.54). None of the studies examining first-line gefitinib or erlotinib have demonstrated a survival advantage for the genotype-directed therapy, presumably because EGFR mutants have a very robust RR and PFS when EGFR TKIs are given in the second-line or later-line setting and thus allowing them to "catch up" to the benefit achieved with first-line therapy.

More recently, two randomized studies were completed with the second-generation EGFR TKI afatinib as first-line therapy for EGFR mutation–positive patients.[54,55] In contrast to the first-generation drugs erlotinib and gefitinib, second-generation EGFR TKIs are "irreversibly binding" meaning that instead of adenosine triphosphate (ATP)-competitive binding at the receptor, the drug forms a direct chemical covalent bond with the EGFR receptor. In addition, afatinib binds all the ErbB receptors, not just EGFR. Lux-lung 3 was a global study comparing afatinib with cisplatin/pemetrexed, and Lux-lung 6 was performed in China only, comparing afatinib with

TABLE 2. Summary of Randomized Trials Examining Genotype-Customized First-Line EGFR TKI Therapy

Study	Treatment	N	Response Rate	Median PFS, mo	HR for PFS (95% CI)	Median OS, mo	HR for OS (95% CI)
IPASS[6,54]	Gefitinib	132	71%	9.6	0.48 (0.36–0.64)	21.6	1.00 (0.76–1.33)
	Carbo/Pac	129	47%	6.3		21.96	
WJTOG 3405[7a]	Gefitinib	86	62%	9.2	0.49 (0.35–0.71)	NR	NR
	Cis/doce	86	31%	6.3		NR	
NEJ 002[8]	Gefitinib	114	74%	10.4	0.36 (0.25–0.51)	30.5	No ratio provided $p = 0.31$
	Carbo/pac	114	31%	5.5		23.6	
OPTIMAL[a50]	Erlotinib	83	83%	13.1	0.16 (0.10–0.26)	NR	NR
	Carbo/gem	82	36%	4.6		NR	
EURTAC[a51]	Erlotinib	86	58%	9.7	0.37 (0.25–0.54)	19.3	1.04 (0.65–1.68)
	Carbo or cis/gem or doce	87	15%	5.2		19.5	
Lux-Lung 3[52]	Afatinib	230	69%	11.1	0.58 (0.43–0.78)	28.2	0.88 (no CI provided)
	Cis/pem	115	44%	6.9		28.2	
Lux-Lung 3: Afatinib arm, common mutations only[a]		203	75%	13.6	0.47 (0.34–0.65)	31.5	0.78 (0.58–1.06)
Lux-Lung 3: Cis/pem arm, common mutations only[a]		104	43%	6.9		28.6	
Lux-Lung 3: Afatinib arm, exon 19 del only[56]		112	NR	NR	0.28 (0.18–0.44)	33.3	0.54 (0.36–0.79)
Lux-Lung 3: Cis/pem arm, exon 19 del only		57	NR	NR		21.1	
Lux-Lung 6[53]	Afatinib	242	74%	11.0	0.28 (0.20–0.39)	23.1	0.93 (no CI provided)
	Cis/gem	122	31%	5.6		23.5	
Lux-Lung 6: Afatinib arm, common mutations only[a]		216	NR	11.0	0·25 (0.18–0.35)	23.6	0.83 (0.62–1.09)
Lux-Lung 6: Cis/gem arm, common mutations only[a]		108	NR	5.6		23.5	
Lux-Lung 6: Afatinib arm, exon 19 del only[56]		124	NR	NR	0·20 (0·13 0·33)	31.4	0.64 (0.44–0.94)
Lux-Lung 6: Cis/gem arm, exon 19 del only		62	NR	NR		18.4	

[a]Only L858R and del 19 mutants were included in this study.

CI, confidence interval; EURTAC, European Randomized Trial of Tarceva Versus Chemotherapy; HR, hazard ratio; IPAS, Iressa Pan-Asia Study; NEJ, North East Japan; NR, no mature data reported; OPTIMAL, Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer; PFS, progression-free survival; OS, overall survival; WJTOG, West Japan Thoracic Oncology Group.

cisplatin/gemcitabine. Similar to the prior studies, the afatinib trials showed a superior PFS, RR, and quality of life for genotype-directed treatment, particularly among the 90% of trial participants with common EGFR mutations. As a result, afatinb was Food and Drug Administration (FDA) approved in 2013 as first-line therapy for patients with L858R and deletion 19 EGFR mutations. At the 2014 American Society of Clinical Oncology (ASCO) meeting, we also learned that among exon 19 deletion mutants, first-line afatinib seems to improve OS compared with first-line chemotherapy.[56] Although these results were from a post hoc subgroup analysis, the survival benefit was large (approximately 1 year) and was replicated in both Lux-lung 3 and Lux-lung 6 with highly significant *p* values (Table 2). The L858R patients did not have a survival advantage with afatinib, similar to the results from other studies with gefitinib and erlotinib.

Because of this collection of research, the current standard approach in the Unites States is to test all patients with newly diagnosed advanced adenocarcinoma for EGFR mutations and, if positive for a common mutation, to treat with either afatinib or erlotinib.[57] If patients are symptomatic from their cancer and cannot wait for the results of mutation testing to return, chemotherapy should be started as EGFR TKIs should only be given in the first-line setting to patients known to have an EGFR mutation. There are uncommon mutations that are still considered sensitizing to EGFR TKIs such as L861Q, G719X, and S768I. However, it is important to note that the exon 20 insertion/deletion mutations are typically not sensitive to erlotinib, gefitinib, and afatinib.[58]

Advanced-Stage Disease: Special Considerations for EGFR-Mutant Patients

There are several considerations in the management of EGFR-mutant patients that are unique compared with historical approaches for treating lung cancer: (1) When to start EGFR TKIs if chemotherapy was given before mutation

test result availability, (2) Should EGFR TKIs be continued beyond progression, and (3) How to work-up EGFR mutation–positive lung cancer with acquired resistance to the first EGFR TKI. There are no definitive randomized trials that give us direction about these issues, but clinical experience is now large and consensus recommendations are emerging. For patients who were unable to wait for EGFR mutation test results before starting first-line chemotherapy, it is always difficult to know when and how to start an EGFR TKI after the mutation is discovered. Options range from beginning the TKI immediately after the test results returns to not until the patient progresses and second-line therapy is indicated. One popular approach is to complete four to six cycles of the first-line chemotherapy (assuming the patient is tolerating therapy and is not progressing through it) and then switch to the EGFR TKI, similar to a maintenance approach; however, no clinical trials have addressed this specific situation.[58]

A more common question is under what circumstances to continue an EGFR TKI when the patient is progressing on therapy. The discussion arises because it has been observed that even when EGFR mutants are radiographically progressing through an EGFR therapy, removal of that therapy can hasten a clinically significant flare in the disease in up to 25% of cases, leading to hospitalization and/or death in approximately 1 week in the initial publication.[59] The disease flare is thought to be due to a mix of clones within the tumor, some of which are still sensitive to the EGFR TKI and remain under control even while other clones are growing. Removal of the suppressive TKI can allow many more cells to divide compared with keeping the suppressive TKI on board.

EGFR mutants have two distinctive patterns of progression not historically distinguished in lung cancer treatment paradigms: (1) progression in only one site while the rest of the disease remains stable, and (2) very slow and indolent progression in multiple anatomic locations. There is mounting evidence suggesting that if progression is only in one location, then local treatment (surgery or radiation) followed by continued EGFR TKI therapy can yield good outcomes.[60,61] In one study using this approach, EGFR-mutant patients had controlled disease for a median of 6 months after the locally directed therapy before further progression was noted.[60] In addition, clinical experience is accumulating supporting the notion that patients who are having slow and indolent progression while on an EGFR TKI can achieve significant additional time on therapy after meeting Response Evaluation Criteria in Solid Tumors (RECIST) criteria for progression.[62,63] One single institution experience documented that 88% of EGFR patients received ongoing EGFR TKI beyond RECIST-defined progression and the median time until a change in therapy was necessary from that point was 10 months.[63]

Once a patient is progressing sufficient to demand a change in systemic therapy, there is an additional question of whether one should stop the EGFR TKI and switch to chemotherapy or continue the EGFR TKI along with adding chemotherapy. Again, the observation of a clinically significant flare in disease if the EGFR TKI is stopped has fueled interest in this question. Prospective randomized studies are in process which will provide further guidance, but retrospective studies suggest that RRs may be higher if the EGFR TKI is continued while chemotherapy is added.[64]

Considering a biopsy at the time of progression on the initial EGFR TKI is an emerging standard for EGFR mutants.[56] Initially this was a maneuver primarily done for research purposes to gain a better understanding of the range of molecular mechanisms of acquired resistance and to consider customizing clinical trial options for patients. It then became appreciated that a small portion of patients would have a transformation from adenocarcinoma harboring an EGFR mutation to SCLC with the same EGFR mutation as an escape mechanism from their EGFR TKI.[65,66] This transformation, although rare, facilitated broader clinical interest in repeat biopsies because the biopsy might indicate a new therapeutic direction. In the current era, data are rapidly accumulating that third-generation EGFR TKIs may have high activity among those with acquired resistance by virtue of the T790M mutation in exon 20, the single mutation that accounts for 50% to 65% of acquired resistance (see later in the article).[67,68] This provides yet an additional and compelling clinical indication for biopsy at the time of acquired resistance.

Treatment of Acquired Resistance

Even though initial therapy with an EGFR TKI is quite effective, acquired resistance still develops after 10 to 15 months. When the second-generation EGFR TKIs were developed, there was great hope that these would be highly effective for patients with acquired resistance because laboratory studies showed that these compounds had a high level of activity against T790M in vitro.[69] Unfortunately, in clinical trials, all three second-generation EGFR TKIs tested (neratinib, afatinib, and dacomitinib) have had disappointing results with RRs in the single digits.[70–72] The explanation behind the discordant preclinical and clinical results is thought to be that the second-generation drugs have a high degree of wild-type EGFR potency, therefore dose escalation is limited by rash, diarrhea, and other side effects resulting from wild-type EGFR inhibition. Hence, in patients, it seems difficult to achieve drug concentrations sufficient to inhibit T790M.

The first successful clinical trial for EGFR acquired resistance was a phase I trial examining the combination of afatinib and cetuximab.[73] This trial expanded when activity was observed to ultimately include 93 patients. The RR was 32%, significantly higher than the 7% observed with single agent afatinib. However, the toxicity of this regimen is not insignificant, with 18% of patients having grade 3 acneiform rash (rash that limits activities of daily living and covers >30% of the body surface area). Interestingly, the preclinical evidence for this combination suggested that T790M mutants would preferentially benefit[74]; however, the clinical observation has been that response is roughly equal regardless of T790M status.

A new class of third-generation EGFR TKIs have recently entered clinical study.[67,68] These differ from the prior generations of EGRF TKIs because although they have potent inhibition of both activating EGFR mutations and T790M, wild-type inhibition is close to zero, allowing dose escalation to concentrations that can effectively overcome acquired

resistance. Two compounds have had mature results presented in abstract form thus far, CO-1686 and AZD9291. Both have demonstrated RRs of approximately 60% among those with biopsy-proven T790M. Mature PFS is not yet available, but responses appear to be durable for at least 6 months in most patients in the preliminary data. As suspected, rash and diarrhea are extremely uncommon during therapy with third-generation EGFR TKIs. CO-1686 causes hyperglycemia, which is typically controlled with oral medications.

Early-Stage Disease

Whenever there is a successful strategy for treating advanced-stage disease, such as EGFR TKIs for patients with EGFR mutations, there is interest in moving the therapy from late-stage disease to early-stage disease with the hope of increasing cure rates. Studies are just beginning that will look at incorporation of EGFR TKIs into multimodality therapy for stage III disease. However, two studies have been completed offering preliminary data about adjuvant erlotinib. The Surgically resected EGFR mutant lung cancer with adjuvant erlotinib cancer treatment (SELECT) study was a single-arm multicenter study of 2 years of adjuvant erlotinib for patients with common EGFR mutations.[75] One hundred patients were treated (stage I $n = 45$, stage II $n = 27$, and stage III $n = 28$) and the primary end point of 2-year disease-free survival (DFS) was 89% (by stage I: 96%, stage II: 78%, and stage IIIA: 91%), which was significantly improved compared with the predefined historical control 2-year DFS for EGFR mutants followed with observation alone. In addition, after a median duration of follow-up of more than 3 years, of the 29 patients that recurred, only four recurred while one erlotinib and 25 recurred after erlotinib was completed, raising speculation that duration of therapy may be important. The Surgically resected EGFR mutant lung cancer with adjuvant erlotinib cancer treatment (RADIANT) study was a randomized study of 2 years of adjuvant erlotinib versus placebo that enrolled a broader population of lung cancer patients among which 16% harbored EGFR mutations.[76] Although the overall study was negative, the subgroup analysis of EGFR mutants suggested that erlotinib provided a DFS advantage with HR of 0.61 (95% CI, 0.38–0.98), but no OS advantage in this preliminary study. A more definitive prospective randomized trial including only EGFR mutants and powered to examine OS is set to begin this year.

HER-2/3–POSTIVE NSCLC

The Role of HER2 and HER3 in NSCLC

HER2 and HER3 (also known as ERBB2 and ERBB3, respectively) are members of the HER/ERBB RTK family, which also includes EGFR and HER4. Although these receptors all mediate cell proliferation and survival through downstream MAPK and PI3K pathways, they vary with regard to the ability to bind ligand and the presence of an active TK domain. For example, HER2 has no known high-affinity ligand and therefore uses homo- or heterodimerization for activation, and HER3 has no TK activity and relies on heterodimerization to induce downstream signaling. The most powerful signaling heterodimer is that of HER2 and HER3, which can function as an oncogenic unit.[77]

Oncogenic *HER2* kinase domain mutations were first reported in NSCLC in 2004.[78] Since that time, several studies have found the rate of kinase domain *HER2* mutations in NSCLC to be approximately 2% to 4%.[79–81] These mutations are most commonly in-frame insertions in exon 20 with duplication of amino acids YVMA at codon 775; infrequently, insertions in other codons or point mutations can be found that lead to constitutive activation of downstream pathways resulting in cell growth and survival. More recently, extracellular domain mutations were detected in *HER2* and found to be oncogenic, including a S310F mutation in exon 8 detected in one of 188 lung adenocarcinomas,[82] a S310Y mutation in one of 63 squamous cell lung cancers,[83] and 1 S310F and 1 S310Y mutation in 258 lung adenocarcinomas sequenced by the Cancer Genome Atlas Network. Across these studies, the frequency of extracellular domain mutations appears to be less than 1%.

In contrast to *HER2*, there have been no reports of mutations in the *HER3* gene. However, HER3 has been implicated as an escape mechanism for drugs that inhibit signaling through EGFR and HER2.[84,85] Attempts at therapeutically targeting both HER2 and HER3 are ongoing.

Clinical Features of Patients with *HER2*-Mutated NSCLC

Patients with *HER2*-mutant NSCLC have distinct clinicopathologic characteristics, similar to those whose tumors harbor *EGFR* mutations. In the largest reported study of 65 patients with *HER2*-mutant NSCLC to date, the median age of diagnosis was 60.4 years (range, 31–86), 69% were female, 52% were never-smokers, and all tumors were adenocarcinomas.[81] Although *HER2* mutations are relatively rare in lung cancer, the rate of detection can be enriched by testing never-smoker patients with adenocarcinoma or adenosquamous histology without an *EGFR* mutation, in which case the frequency is approximately 14%.[79] *HER2* mutations are mutually exclusive with point mutations in *EGFR, KRAS, BRAF,* neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*)*, PIK3CA, MEK1,* and *AKT*, as well as rearrangements in *ALK*.[80]

Preclinical and Clinical Data for Therapeutics Targeting HER2 and HER3

Both small molecular inhibitors and monoclonal antibodies targeting HER2 are under investigation. Currently, there are limited data for patients treated on prospective clinical trials; however, preclinical studies and retrospective data from patients treated with off-label, commercially available agents show promise in targeting HER2 in those with *HER2*-mutant NSCLC. Below are several compounds under investigation.

Trastuzumab

In contrast to breast cancer, HER2 overexpression or amplification does not predict for benefit from trastuzumab in lung cancer. However, the presence of a *HER2* mutation may be a predictive biomarker for response to trastuzumab in NSCLC. In a retrospective study of 16 patients with *HER2*-mutant

NSCLC, a total of 22 anti-HER2 treatments were assessed.[81] Of the patients who received trastuzumab-based regimens (trastuzumab combined with carboplatin, paclitaxel, carboplatin/paclitaxel, vinorelbine, or docetaxel), the RR was 60% (nine of 15 regimens tested) and disease control rate was 100%. One patient received trastuzumab alone and had a partial response (PR).

Afatinib

Afatinib is an irreversible small molecular inhibitor of EGFR and HER2 that is approved for use in the first-line setting for patients with *EGFR*-mutant NSCLC. In lung cancer cell lines harboring a *HER2* insertion mutation in the TK domain, afatinib was effective at inhibiting survival, whereas erlotinib was not.[86] Interestingly, afatinib was also effective at inhibiting survival in cell lines transformed with the *HER2* extracellular domain mutation.[82] The clinical activity of afatinib in *HER2*-mutant NSCLC has been evaluated in the same retrospective study discussed above.[81] Three patients who had progressed after receiving trastuzumab-based therapy were treated with afatinib, which resulted in 100% disease control rate (one PR and two stable disease [SD]). In the only prospective study with afatinib in this population, five patients with NSCLC harboring a *HER2* kinase domain mutation were treated with afatinib, followed by the option to add weekly paclitaxel at 80 mg/m^2 to afatinib at progression.[87] Of the three patients evaluable for response (two patients withdrew early due to toxicity), two had a PR to afatinib alone and one had SD with afatinib and a PR once paclitaxel was added.

Dacomitinib

Dacomitinib is an irreversible pan-HER TKI. A phase II study including patients with NSCLC and *HER2* amplification or mutation with any number of prior lines of therapy treated patients with dacomitinib 45 or 30 mg with the option to escalate to 45 mg once daily.[88] Of the 16 evaluable patients in the *HER2* cohort, there were two with a PR, both of whom had a *HER2* mutation. Final results from this study are pending.

Neratinib

Preclinical mouse models of *HER2*-mutant lung cancer have demonstrated that HER2 inhibition plus mammalian target of rapamycin (mTOR) inhibition results in significant tumor shrinkage over either alone.[89] On the basis of this and other preclinical data, the combination of neratinib, an irreversible pan-HER small molecule inhibitor, and temsirolimus, an mTOR inhibitor, was studied in a phase I trial including patients with multiple tumor types.[90] Six patients of the 60 on the trial had *HER2*-mutant NSCLC. Among them, two had a PR (one of whom had prior trastuzumab) and the remainder had an SD.

MM-111

MM-111 is a bispecific fully human antibody targeting HER2 and HER3. In preclinical studies of HER2-overexpressing cancer cells, MM111 inhibits cell proliferation, particularly when used in combination with other HER2 inhibitors such as trastuzumab.[91] A phase I trial in multiple tumor types with HER2 positivity is testing MM-111 combined with various HER2-targeted agents and chemotherapeutics to determine the maximally tolerated dose, safety, and efficacy. This drug has not yet been tested in patients with *HER2*-mutant NSCLC.

MEHD 7945 A

In contrast to the previously discussed compounds, MEHD 7945 A does not target HER2, but instead is a dual-action human immunoglobulin G1 (IgG1) monoclonal antibody that targets EGFR and HER3. In cell lines and xenograft models of tumors resistant to the EGFR inhibitors cetuximab or erlotinib, MEHD 7945 A was able to overcome resistance and inhibit tumor growth.[92] Clinically, the safety and activity of MEHD 7945 A were studied in a phase I trial in multiple tumor types.[93] Nine patients with NSCLC were included, of which two had SD as their best response. The final report from this study is pending.

MM-121

Unique compared with the other drugs discussed here, MM-121 is a monoclonal antibody that only targets HER3. It is being developed in combination with other targeted agents or chemotherapeutics, which is not surprising given the lack of known alterations in HER3 in human cancers. Specifically, MM-121 is being tested in combination with erlotinib, with early signals of clinical benefit in patients with *EGFR*-mutant NSCLC and erlotinib resistance.[94]

ALK-POSITIVE NSCLC

Chromosomal rearrangements of ALK are present in 3% to 7% of NSCLC. The resulting ALK fusions, such as EML4-ALK, function as potent oncogenic drivers and lead to a state of oncogene addiction. In the clinic, this phenomenon underlies the marked responsiveness of ALK-positive tumors to small molecule ALK TK inhibition. Crizotinib, a multitargeted TKI of ALK, ROS1 and cMET, was the first ALK inhibitor tested in the clinic and helped to establish ALK as a therapeutic target in NSCLC.[12] To date, nine other ALK inhibitors have now entered clinical development, with promising early results in both crizotinib-naive and crizotinib-resistant disease. In this study, we review the latest data on crizotinib and select next-generation ALK inhibitors in TKI-naive patients with ALK-positive NSCLC.

5.1 Crizotinib

Phase I and II studies have shown that crizotinib is highly active in patients with advanced, ALK-positive NSCLC. In the phase I trial (PROFILE 1001), the objective RR (ORR) among 143 evaluable patients was 61% and median PFS was 9.7 months.[95] Updated results from the phase II study of crizotinib (PROFILE 1005) were recently reported in the U.S. FDA label. Among 765 patients with advanced, ALK-positive NSCLC, the ORR was 48% and median duration of response was 11 months;[96] the follow-up of these phase II patients was too short to evaluate PFS. On the basis of RRs observed in the phase I and II studies, along with its favorable side effect profile, crizotinib was granted accelerated approval by the FDA in August 2011 for patients with advanced, ALK-positive NSCLC. This approval occurred almost exactly 4 years after the first report of ALK rearrangements in NSCLC.[97]

Recently, the results of the first prospective, randomized phase III trial comparing crizotinib with standard chemotherapy in advanced, ALK-positive NSCLC (PROFILE 1007) were reported.[11] In this study, 347 ALK-positive patients who had failed one prior platinum-based chemotherapy regimen were randomized 1:1 to receive either crizotinib as their second-line therapy, or pemetrexed or docetaxel chemotherapy. Compared with standard single-agent chemotherapy, treatment with crizotinib resulted in a significantly longer PFS and a tripling of the ORR. The median PFS with crizotinib was 7.7 months by independent radiology review compared with 3 months with chemotherapy. Consistent with previous single-arm studies, the RR with crizotinib was 65%, as opposed to 20% with chemotherapy, thus confirming the significant antitumor activity of crizotinib in advanced ALK-positive NSCLC.

In this study, crizotinib was more active than either pemetrexed or docetaxel chemotherapy in ALK-positive NSCLC.[11] Consistent with previous studies in unselected patients with advanced NSCLC, the efficacy of second-line docetaxel in ALK-positive NSCLC was minimal, with a median PFS of 2.6 months and an ORR of 6.9%.[98] In contrast, pemetrexed showed greater activity than expected based on previous second-line studies.[99] Median PFS was 4.2 months in ALK-positive patients as compared with 3.5 months in unselected NSCLC patients with adenocarcinoma histology. The RR to pemetrexed was also higher in this study at 29.3% as compared with 12.8% in the general population of lung adenocarcinomas.[100] Although these findings suggest that patients with ALK-positive NSCLC may be more responsive than average to pemetrexed-based chemotherapy, the benefit of pemetrexed seems to be less than that originally suggested by small retrospective studies,[101,102] and importantly, significantly less than that with crizotinib.

In a prespecified interim analysis, OS was found to be similar between the crizotinib and chemotherapy arms with a median OS of 20.3 and 22.8 months, respectively.[11] This analysis was immature with a total of 96 deaths (40% of the required events) and censoring of more than 70% of patients in either treatment arm. In addition, the analysis was likely confounded by the high crossover rate of patients in the chemotherapy group. Approximately 90% of patients who were treated with chemotherapy and had disease progression crossed over to receive crizotinib. This issue has similarly complicated the analysis of OS in multiple randomized phase III studies of EGFR TKIs in advanced EGFR-mutant NSCLC. In these studies where the crossover rate from chemotherapy to targeted therapy ranged from 64% to 95%, no difference in OS was demonstrated despite substantial improvements in PFS with the targeted therapy.

Several important issues regarding the role of crizotinib in ALK-positive NSCLC remain to be addressed. In many countries, crizotinib is an approved therapy for patients with advanced, ALK-positive NSCLC with no requirement for prior treatment. As a result, crizotinib can be prescribed as first-line therapy. Although the first-line use of EGFR TKIs in advanced EGFR-mutant NSCLC has been established in multiple randomized phase III studies, there is limited data on the use of crizotinib in the first-line setting. In the original phase I study, there were 24 patients who received crizotinib as their first systemic therapy.[95] In this small cohort, the ORR was 64% and median PFS was 18.3 months, suggesting that first-line crizotinib may be at least equivalent if not more effective than crizotinib in the second-line setting and beyond. A randomized phase III trial comparing crizotinib with platinum/pemetrexed chemotherapy in newly diagnosed, advanced ALK-positive NSCLC (ClinicalTrials.gov number, NCT01154140) has recently completed enrollment, and results may be reported at ASCO 2014. A similar phase III trial in Asia comparing first-line crizotinib with platinum/pemetrexed chemotherapy in ALK-positive NSCLC patients (ClinicalTrials.gov number NCT01639001) is ongoing.

Next-Generation ALK Inhibitors: Alectinib and Ceritinib

Alectinib (RO5424802) is a highly potent and selective TKI targeting ALK, but not ROS1 or cMET.[103] Alectinib was first evaluated in a phase I/II study in Japan and enrolled a total of 70 Japanese patients with advanced, ALK-positive NSCLC who were crizotinib naive.[104] In contrast to the PROFILE 1001/5/7 studies which used ALK fluorescence in situ hybridization (FISH) only, patients were identified as ALK-positive using ALK immunohistochemistry (IHC), followed by ALK FISH for confirmation. In the phase II portion of the study, the ORR with alectinib dosed at 300 mg twice-daily was remarkably high at 94%. With a median follow-up of only 7.6 months, median PFS is not yet known, but durable responses exceeding 12 months have been reported.

Similarly, the next-generation ALK inhibitor ceritinib (LDK378) has also demonstrated high RRs in crizotinib-naive ALK-positive NSCLC. In preclinical studies, ceritinib is also more potent and selective than crizotinib, targeting ALK and ROS1 but not cMET.[105] In a global phase I study, ceritinib was highly active in patients with advanced, ALK-positive NSCLC.[106] Among 34 patients who had not received an ALK inhibitor and who received ceritinib at doses of 400 mg or higher, the ORR was 62%, and median PFS was 10.4 months. Of note, in contrast to the phase I study of alectinib, this study included both Asian and white patients. In addition, the ceritinib study required only ALK FISH testing to demonstrate ALK rearrangement, as opposed to both ALK IHC and ALK FISH. Thus, these two factors, ethnicity and diagnostic testing, could explain the differences in efficacy seen between alectinib and ceritinib in the TKI-naive ALK-positive population.

ROS1-, RET-, AND NTRK1-POSITIVE NSCLC

Biology

Gene fusions result from large-scale inter- or intrarearrangements or chromosomal deletions that join pieces of two disparate genes and result in chimeric messenger RNA transcripts and proteins. The gene fusions described here contain sequences from the 5' region of an unrelated partner gene and the 3' region of genes encoding RTKs: ROS1, RET, and neurotrophic tyrosine kinase, receptor, type 1 (NTRK1). These gene fusions always have an intact kinase domain encoded by the 3' gene region, but contain varying 5' sequences from other genes. These partner genes typically provide two critical

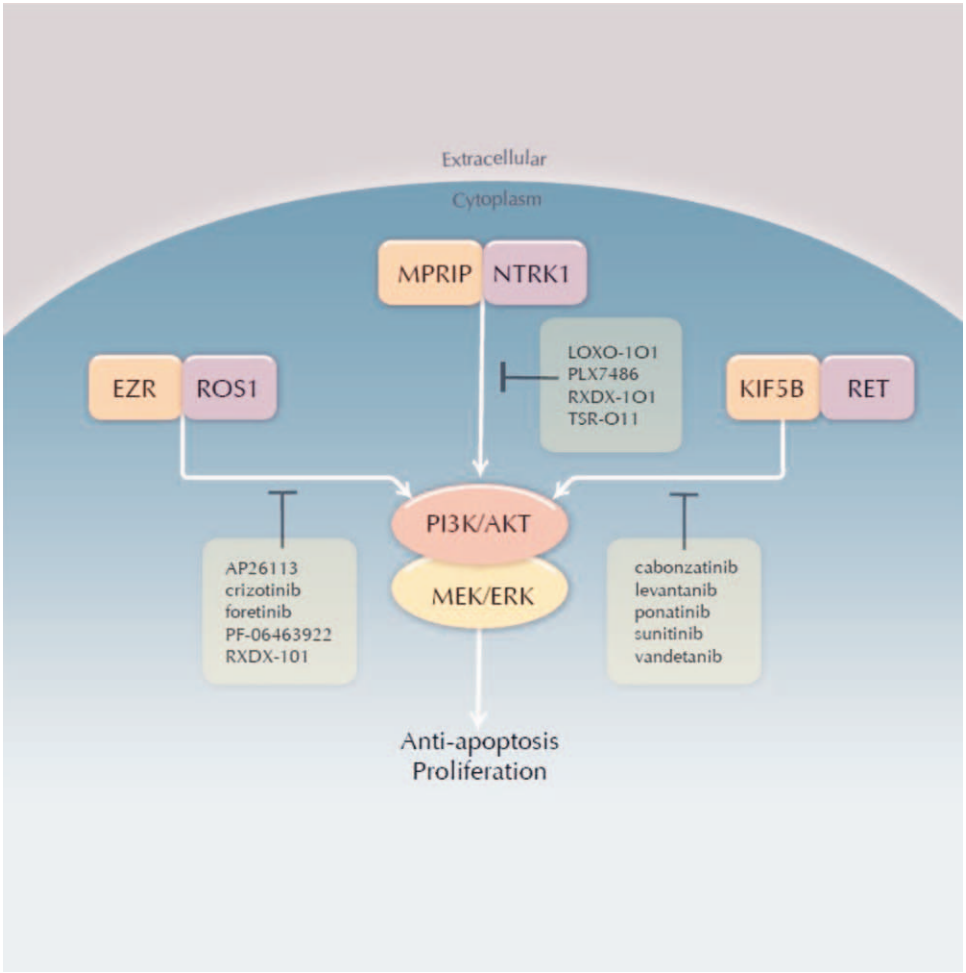

FIGURE 3. ROS1, NTRK1, and RET inhibitors. MPRIP, myosin phosphatase Rho interacting protein; NTRK1, neurotrophic tyrosine kinase, receptor, type 1; EZR, ezrin; ROS, ROS proto-oncogene 1; AKT, v-*akt* murine thymoma viral oncogene homolog; KIF, kinesin family member 5B; and RET, ret proto-oncogene.

components: a promoter that allows sufficient transcription of the novel gene and sequences that encode oligomerization domains. ROS1, RET, and transforming tyrosine kinase protein (TRKA) (encoded by the NTRK1 gene) are not highly expressed in most lung adenocarcinomas, but their upstream partner joins a promoter that drives sufficient expression in the tumor cell.[108–110] The typical mode of activation for these RTKs cannot occur because they lack the extracellular domains harboring the ligand-binding domain; however, the oligomerization domain, for example coiled-coil domains encoded by the partners kinesin family member 5B (KIF5B), coiled-coil domain containing 6 (CCDC6), ezrin (EZR), tropomyosin 3 (TPM3), and myosin phosphatase Rho interacting protein (MPRIP) facilitate dimerization of the fusion protein.[97,111,112] It is currently unknown whether different fusion partners, which can target the fusion proteins to different cellular compartments, induce differential tumor behavior, including drug sensitivity.[113] Activation of the kinase domain initiates a downstream signaling cascade that ultimately activates MAPK and AKT signaling, which leads to cellular proliferation among other tumorigenic properties.[112,114,115] This dominant signaling role makes targeted inhibition of these oncogenes an attractive therapeutic strategy (Fig. 3).

Incidence

Multiple studies have investigated the incidence of the oncogenic fusions using a variety of techniques, including FISH, IHC, NGS of RNA and DNA, and polymerase chain reaction; however, an approved companion diagnostic is not yet available for these oncogenes.[108,111,112,114,116–118] Typically, these oncogene fusions do not overlap with other dominant oncogenes, but unbiased studies have demonstrated overlap of ROS1 fusions and EGFR, KRAS, and BRAF mutations, similar to dual oncogenes observed in ALK-positive cases.[117–122] The incidence of ROS1, RET, and NTRK1 gene fusions seems to be in the range of 1% to 3% although the reported incidence is higher in studies using enriched cohorts (i.e., negative for other oncogenes).[108,111,112,114,116–118] Although associations have been drawn with age, sex, and smoking history, there is no reliable clinical selection for oncogenic fusions and

thus these factors should not be used as criteria for selection of patients to undergo testing.[111,112,114,116,123,124] Although these gene fusions are widely associated with adenocarcinoma histology, this is not an ideal selection criteria as squamous cell and other histologies have been associated with ROS1, RET, and NTRK1 fusions.[108,116,117,125,126]

ROS1, RET, and NTRK in Other Disease Types

Although these oncogenic fusions occur infrequently in lung cancer, interest in these targets is bolstered by their occurrence in other malignancies. ROS1 has been detected in gastric cancer, colorectal cancer, Spitzoid neoplasms, and numerous others.[113,119,127,128] RET fusions have long been identified in papillary thyroid cancer but have also been identified in chronic myelomonocytic leukemia (CMML) and others.[128–130] An oncogenic NTRK1 fusion was first detected in a colorectal cancer specimen, later found to be prevalent in papillary thyroid cancers, and now identified in multiple other tumor types.[128,129,131–133] Many TRKA inhibitors have activity against two homologous RTKs, transforming tyrosine kinase protein B (TRKB) (NTKR2), and transforming tyrosine kinase protein C (TRKC) (NTRK3). These genes are also involved in gene fusions across multiple cancer types, perhaps broadening the appeal of these pan-TRK inhibitors.[134–137]

INHIBITORS OF ROS1, RET, AND TRK.

ROS1

Crizotinib (Pfizer) has been approved for use in ALK-positive NSCLC. ROS1 has high homology to ALK and many ALK inhibitors also display ROS1 inhibition.[113] An expanded phase I trial is the first trial to report clinical outcomes of ROS1-positive NSCLC patients treated with crizotinib (NCT00585195). The most recent update of 35 patients demonstrated an ORR of 60% and a 6-month PFS rate of 76%, very similar to studies of the same drug in ALK-positive NSCLC patients.[95,138] Foretinib (XL-880, GlaxoSmithKline) is a multikinase inhibitor with activity against ROS1, as well as RET, MET, *AXL* receptor tyrosine kinase (AXL), and other kinases, that has a planned ROS1 cohort in an upcoming clinical trial (NCT01068587).[139] Ceritinib (LDK378, Novartis) is a potent second-generation ALK inhibitor that displays weaker ROS1 inhibition[105]; however, this drug is not currently in clinical trials enrolling ROS1-positive NSCLC patients. AP26113 (Ariad) is currently in clinical trials for ALK-positive NSCLC and also has activity against ROS1 but is currently not yet enrolling ROS1-positive NSCLC patients (NCT01449461). PF-06463922 (Pfizer) is a next-generation ALK/ROS1 inhibitor that is currently enrolling crizotinib-naive or TKI-resistant ROS1 patients (NCT01970865).[140]

RET

Multiple RET inhibitors are undergoing clinical trials in RET-positive NSCLC patients, and many of these drugs are multikinase inhibitors. A clinical trial of cabozantinib (XL184, Exelixis), a RET inhibitor (in addition to MET and vascular endothelial growth factor receptor 2 [VEGFR2]) is currently accruing RET-positive NSCLC patients (NCT01639508). Early results from this trial demonstrated confirmed PRs in two patients and prolonged SD (31 weeks) in a third patient demonstrating early clinical activity of this RET inhibitor in RET gene fusion positive patients.[141] A phase II clinical trial of vandetanib (AstraZeneca), a dual RET and EGFR inhibitor, in RET-positive NSCLC is currently accruing patients (NCT01823068). A patient treated off-protocol with vandetanib 300 mg once-daily showed a clinical response.[142] An additional patient treated with off-protocol vandetanib showed prolonged SD of 6 months on drug.[143] Lenvantinib (E7080, Eisai) is multikinase inhibitor (VEGFR1-3, fibroblast growth factor receptors 1-3 [FGFR1-3], stem cell factor receptor [SCFR], and platelet derived growth factor receptor [PDGFR]) with activity against RET and is currently enrolling patients in a phase II clinical trial (NCT01877083).[144] Clinical trials of ponatinib (AP24534, Ariad), a multikinase inhibitor with RET activity, in RET-positive NSCLC are planned (NCT01935336).[145,146] Sunitinib (Pfizer) is another multikinase inhibitor currently in a phase II clinical trial of never smokers with lung adenocarcinoma and has a secondary end point to evaluate benefit in patient with RET gene fusions (NCT01829217).

TRK

LOXO-101 (Loxo) is a selective pan-TRK inhibitor (TRKA, TRKB, and TRKC) that is planned to shortly enter first in man phase I clinical trials. RXDX-101 (Ignyta) is a pan-TRK inhibitor that also has ALK/ROS1 activity with reported central nervous system penetration and is currently in phase I clinical trials. TSR-011 (Tesaro) is an ALK inhibitor with approximately 10 selectivity over the TRK family of RTKs and is currently in a phase I clinical trial (NCT0204848).[147] PLX7486 (Plexxikon), a pan-TRK inhibitor with additional activity against Fms, is currently in clinical trials as a single agent and in combination with chemotherapy in patients with solid tumors (NCT01804530). This study will also evaluate cancer-related pain as TRKA signaling can modulate pain: Mutations in the NTRK1 gene are the cause of the autosomal recessive syndrome of congenital insensitivity to pain with anhydrosis.[148] A major focus of next-generation ALK inhibitors has been to improve CNS penetration to more effectively treat the brain metastases that occur frequently in patients demonstrating disease progression on crizotinib[149]; however, CNS penetration may not be a desired effect of pan-TRK inhibitors. Inhibition of TRKB has been linked to ataxia and other serious neurologic side effects, mimicking the phenotype of the mutant stargazer (stg) mice, which demonstrate ataxia and lack brain-derived neurotrophic factor, the TRKB cognate ligand.[150,151]

Resistance

Resistance mechanisms to cognate inhibitors of ROS1 are similar to mechanisms of drug resistance observed for tumors bearing ALK fusions or EGFR mutations. The first described mechanism of resistance was a patient with a ROS1 kinase domain mutation.[152] This mutation, G2032R, is analogous to the ALK G1202R and adjacent to the D1203N and S1206Y mutation located at the solvent front; all these mutations induce resistance to crizotinib.[153–155] Preclinical data suggests that foretinib and PF-06463922 can inhibit ROS1

G2032R and that AP26113 can overcome the predicted ROS1 gatekeeper mutation, L2026M.[139,140,156] Resistance mechanisms to RET inhibitors have yet to be described in NSCLC patients; however, ponatinib has demonstrated activity against oncogenic RET carrying substitutions at the predicted gatekeeper residue, V804.[145,146] TRKA harbors a bulky tyrosine residue at the conserved gatekeeper position perhaps making this position a less likely site of mutation to decrease inhibitor binding. Bypass signaling has also recently been described in a ROS1-positive cell line model of drug resistance. The lung adenocarcinoma cell line with SLC34A2-ROS1, HCC78, with in vitro induced resistance to a ROS1 kinase inhibitor, switched oncogene dependence away from ROS1 to EGFR.[157] This mechanism of resistant suggests the need for combination strategies to prevent or overcome resistance.

BRAF-MUTANT NSCLC

BRAF, an oncogene encoding a RAS-regulated kinase that promotes cell growth, has generated recent interest in oncology.[158,159] The majority of BRAF mutations promote kinase activation, enhancing the ability of kinase to directly phosphorylate MEK.[159] The BRAF exon 15 mutation in which glutamine is substituted for a valine at residue 600 (V600E) destabilizes the inactive kinase conformation, leading to continual downstream phosphorylation in the MAPK signaling cascade. BRAF mutations are found in approximately 50% of melanomas, and treatment for metastatic melanoma using selectively targeted BRAF V600E inhibitors has elicited high RRs.[160] Yet, colorectal cancers harboring the same BRAF mutation rarely respond to BRAF inhibitor monotherapy.[161] Clinical investigation targeting specific BRAF mutations in NSCLC is ongoing.

Prevalence of BRAF Mutations in NSCLC

In 2002, two studies identified BRAF mutations in 1.6% to 3% of NSCLC.[159,162] Based on these findings and improved genotyping techniques, a 2011 U.S. study examined tissue from 697 patients with lung adenocarcinoma of which BRAF mutations in codons V600, D594, and G469 occurred in 3% of NSCLC cases.[163] An analysis looking at the gene more broadly conducted in Italy in 2011 identified BRAF mutations in 4.9% of patient cases.[164] In contrast to melanoma where 90% of BRAF mutations are V600E, approximately half of the BRAF mutations in the general NSCLC population are non-V600E.[165] A comprehensive genomic study for squamous cell lung cancer identified BRAF mutations in 4% of cases, all of which were non-V600E.[27] The V600E mutation has been associated with a more destructive tumor, with a poor prognosis (significantly shorter DFS and OS).[164] V600E mutations have been reported as significantly more common in females than males (8.6% versus 0.9%) and were less strongly associated with cigarette smoking.[164] BRAF mutations in an Asian population were detected at a lower frequency (1.3%).[166]

Clinical Data with BRAF Inhibitors

Vemurafenib, a V600E BRAF inhibitor used in melanoma, has been associated with antitumor activity in NSCLC.[167] Dabrafenib has been more rigorously evaluated. In an interim analysis of a single-arm trial, the overall RR for single agent dabrafenib was 54%, and it was generally well tolerated.[168] As a result, the FDA granted breakthrough status to dabrafenib for V600E mutation–positive NSCLC in January 2014. During a clinical trial of the Src family TKI dasatinib for advanced NSCLC, a profound antitumor effect was seen in one patient, and that patient was subsequently found to have a kinase-inactivating non-V600E BRAF mutation, ^{Y472C}BRAF.[169] When studying dasatinib in NSCLC cell lines with an endogenous inactivating BRAF mutation, the cell lines experienced senescence, which was reversed with transfection of active BRAF.[169]

Selected Ongoing Trials with BRAF Inhibitors

Currently, a phase II, nonrandomized, open-label study of dabrafenib as a monotherapy and in combination with trametinib, a mitogen-activated protein kinase inhibitor, is recruiting stage IV NSCLC participants with BRAF V600E mutations (NCT01336634). A study evaluating dasatinib in subjects with advanced cancers harboring a DDR2 mutation or an inactivating BRAF mutation is currently enrolling (NCT01514864). A phase II, open-label, second-line study of GSK1120212, which is closed to enrollment, compared trametinib with docetaxel in stage IV NSCLC with a mutation in KRAS, NRAS, BRAF, or MEK1 gene (Clinicaltrials.gov No.: NCT01362296).

KRAS-MUTANT NSCLC

Biology and Nomenclature

In lung cancer, KRAS (chromosome 12p12.1) is the principal member of the Ras family (which also includes HRAS [11p15.5] and NRAS [1p13.1]) involved in tumorigenesis. The HRAS and KRAS genes were initially identified from studies of two cancer-causing viruses, the Harvey sarcoma virus and the Kirsten sarcoma virus. These viruses were originally discovered in rats by Jennifer Harvey and Werner Kirsten, hence the name Rat sarcoma (Ras).[170] NRAS is so named for its initial identification in human neuroblastoma cells. All RAS proteins undergo complex, multi-step post-translational modification including farnesylation, geranylgeranylation, and palmitoylation.

KRAS activation begins with stimulation of various upstream receptors, most EGFR in lung cancer. Adaptor proteins interact with the intracellular domain of EGFR and recruit guanine nucleotide exchange factors that interact with RAS to promote the exchange of guanosine diphosphate (GDP) for guanosine triphosphate (GTP). With binding of GTP, activated KRAS phosphorylates downstream signaling cascade proteins until GTP is converted to GDP through a GTPase activity intrinsic to the Ras family enzymes. The end effect is that KRAS kinase and signaling capacity is higher when the enzyme is bound to GTP instead of GDP. Key downstream effectors include the RAF/ MEK/extracellular signal–regulated kinase (ERK) cascade (controlling cellular proliferation), PI3K/AKT/mTOR cascade (controlling survival), and pathways affecting tumor invasion and vesicle trafficking (Fig. 4).

Role in Tumorigenesis

KRAS acquires tumorigenic properties when mutations arise that decrease its intrinsic GTPase activity. The resulting

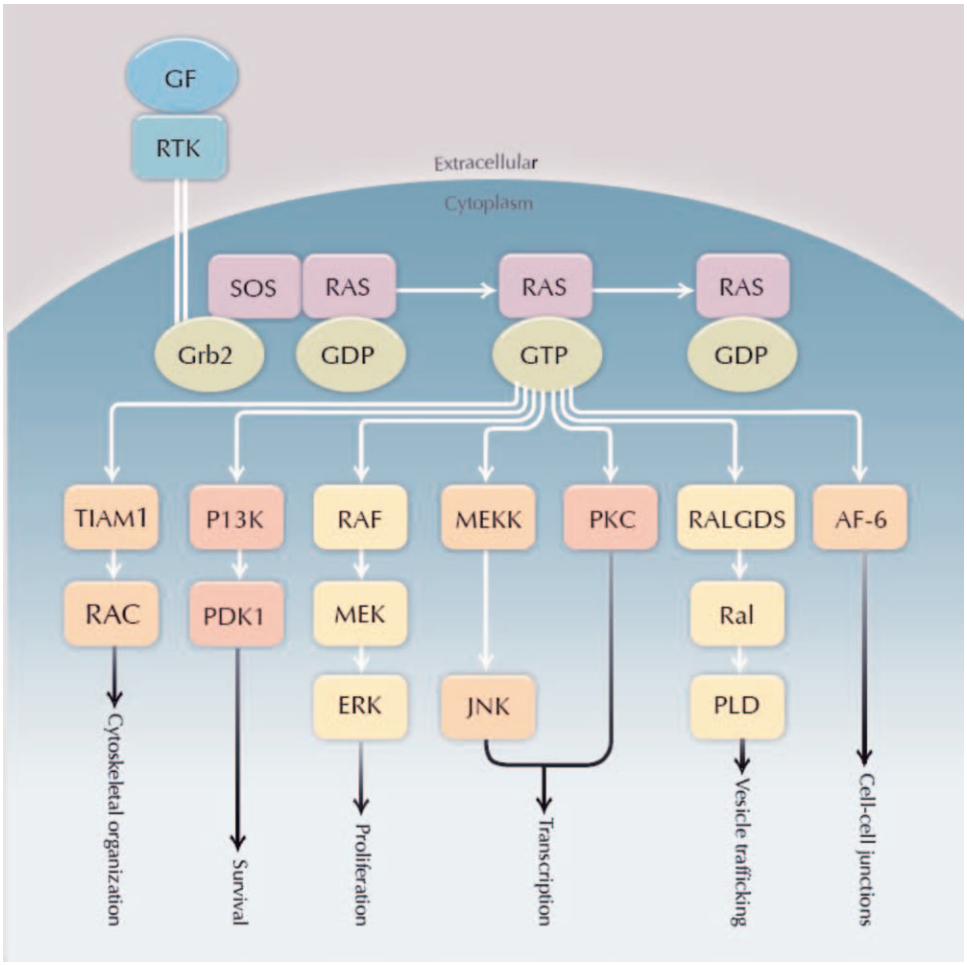

FIGURE 4. KRAS Mutations in NSCLC. ERK, extracellular signal-regulated kinase; GDP, guanosine 5′-diphosphate; GF, growth factor; GTP, guanosine 5′-triphosphate; JNK, Jun N-terminal kinase; MEK, MAP (mitogen-activated protein) kinase; PDK1, phosphoinositide-dependent kinase-1; PI3K, phosphatidylinositol 3-kinase; PKC, Protein kinase C; RAS, rat sarcoma; RTK, receptor tyrosine kinase; SOS, son of sevenless.

RAS proteins are locked in the GTP-bound conformation independent of upstream signals. This causes marked up-regulation of RAS kinase activity and downstream growth and mitotic signaling. Overall, RAS mutations occur in approximately 30% of all human cancers, with KRAS mutations the most common and best characterized.[171] KRAS mutations result in single amino acid substitutions primarily at residues G12, G13, or Q61. In addition to lung cancer, KRAS mutations occur in 70% to 90% of pancreas cancer, 30% to 40% of colorectal cancer, 30% of biliary tract cancer, 20% of melanoma, 15% of endometrial cancer, and 15% of ovarian cancer.[172]

In lung cancer, KRAS mutations occur commonly at codon 12 (within exon 2) (>80%), occasionally at codon 13, and rarely at codon 61. Approximately 80% of codon 12 mutations are guanine/thymidine (purine for pyrimidine) nucleotide transversions,[173] which are considered the characteristic mutation related to tobacco smoke exposure. KRAS mutations in lung tumors from never smokers are typically guanine/adenine (G/A) (purine for purine) transversions. The two most common mutations in NSCLC, G12C (approximately 40% of cases), and G12V (approximately 20%), arise from guanine/thymidine transversions.[174] Other principal mutations include G12D (17%), G12A (7%), and G12S (5%).[175]

Clinical Significance

KRAS mutations occur in approximately 20% to 30% of NSCLC.[176,177] KRAS mutations occur predominantly in adenocarcinoma histology, have been reported rarely in squamous cell carcinoma, but have not been observed in SCLC.[178,179] In contrast to EGFR mutations and ALK and ROS1 fusions mutations, KRAS mutations are associated with smoking.[180] Among lifetime nonsmokers with lung cancer, KRAS mutations occur only in 2% to 6% of cases.[173,181] KRAS mutations are mutually exclusive of EGFR, ALK, and ROS1 aberrations.

The prognostic role of KRAS mutations is not clear. In a meta-analysis of 24 studies incorporating various disease stages, treatments, and KRAS mutation detection methods, KRAS mutations were associated with worse survival (HR, 1.35; 95% CI, 1.16–1.56).[182] However, in a pooled analysis of 1543 patients with resected early-stage NSCLC (of whom 300 had KRAS

mutations), there was no difference in OS between KRAS-mutant and KRAS wild-type cases.[173] No significant benefit from adjuvant chemotherapy was noted for wild-type cases or codon 12 mutations; among the 24 codon 13 mutation cases, adjuvant chemotherapy was deleterious (HR, 5.78; 95% CI, 2.06–16.2).

In advanced NSCLC, KRAS mutations predict resistance to EGFR TKIs.[181] However, the mutual exclusivity of KRAS and EGFR mutations and the strong association between EGFR mutations and sensitivity to EGFR TKIs limit the clinical utility of KRAS mutations as a selection biomarker in current clinical practice. In contrast to colorectal cancer, in NSCLC, KRAS mutations are not clearly associated with resistance to the anti-EGFR monoclonal antibody cetuximab.[183]

Treatment of KRAS-Mutant NSCLC

At the present time, there are no targeted therapies clinically available for NSCLC patients with KRAS mutations. High affinity binding to the GTP substrate has hindered the development of therapeutic agents that inhibit KRAS directly. In late 2013, initial reports of KRAS G12C inhibitors that bind to an allosteric site specific to the mutant molecule were published,[184,185] but such drugs are likely years away from clinical use.

Therapeutic strategies against KRAS-mutant cancers that have been investigated clinically include inhibition of post-translational modification, inhibition of effector pathways, and synthetic lethality.

Post-translational Modification

To date, this strategy has had little clinical efficacy. Farnesyl transferase inhibitors have failed to inhibit KRAS due to alternative prenylation by geranylgeranyl transferase.[186] Combined farnesyl transferase inhibitors and geranylgeranyl transferase inhibitor therapy has been associated with excessive toxicity.[187]

Effector Pathway Inhibition

Several clinical trials have evaluated MEK inhibition alone or in combination with other therapies for KRAS-mutant lung cancer. In a phase II clinical trial of docetaxel ± the MEK inhibitor selumetinib (AZD6244; AstraZeneca) for previously treated advanced KRAS-mutant NSCLC, selumetinib was associated with improved PFS (5.3 versus 2.1 months; 80% CI, 0.42–0.79; $p = 0.14$) and a trend toward improved OS (9.4 versus 5.2 months; 80% CI, 0.56–1.4; $p = 0.21$).[15] Another phase II trial randomizing patients to selumetinib alone or in combination with erlotinib has completed enrollment (NCT01229150). Other MEK inhibitors under study specifically in KRAS-mutant NSCLC include MEK162 (Novartis) combined with erlotinib (NCT01859026) and trametinib (GSK1120212; GlaxoSmithKline) monotherapy (NCT01362296).

A possible benefit of BRAF inhibition in KRAS-mutant NSCLC was suggested in the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination trial. In that study, 11 of 14 (79%) patients with KRAS/BRAF mutations had disease control at 8 weeks with sorafenib.[188] However, in preclinical models, BRAF inhibitors appear ineffective against RAS-mutant cells, paradoxically potentiating RAF/MeK/ERK signaling.[189] This phenomenon, which has been attributed to v-*raf* murine sarcoma viral oncogene homolog C (CRAF) activation, is evident clinically in the development of KRAS-mutant cutaneous squamous cell carcinomas in melanoma patients treated with BRAF inhibitors.[190,191]

A number of recent and ongoing clinical trials have focused on the PI3K/AKT/mTOR signaling cascade. Specific agents under investigation in KRAS-mutant NSCLC include the mTOR inhibitor ridaforolimus (IPI-504; Infinity Pharmaceuticals, Cambridge, MA) (NCT00818675), the mTOR inhibitor everolimus in combination with the HSP90 inhibitor retaspimycin (NCT01427946), everolimus in combination with trametinib (NCT00955773), and the dual PI3K-mTOR inhibitor BEZ235 (Novartis) in combination with MEK162 (Novartis) (NCT01337765, NCT01363232).

The ras homolog family member A (RHOA)-focal adhesion kinase (FAK) axis has emerged as a critical mediator of RAS signal transduction. In transgenic and orthotopic mouse models of KRAS-mutant lung adenocarcinoma, FAK inhibition resulted in inhibition of tumor growth and prolongation of survival,[192] leading to an ongoing multicenter phase II trial of the FAK inhibitor defactenib (VS-6063; Verastem, Needham, MA) in previously treated advanced KRAS-mutant NSCLC (NCT01951690).

In a randomized phase II clinical of erlotinib ± the c-MET inhibitor tivantinib (ARQ-197; ArQule, Woburn, MA), an exploratory analysis revealed that the small cohort with KRAS mutations achieved a PFS HR of 0.18 (95% CI, 0.05–0.70).[193] This benefit was hypothesized to be related to a putative feedback loop through which EGFR acts as a downstream mediator of KRAS signaling, interactions between hepatocyte growth factor (HGF) (the MET ligand) and KRAS, or non–MET-mediated pathways. A subsequent randomized phase II clinical trial of erlotinib-positive ARQ-197 versus single-agent chemotherapy in previously treated advanced KRAS-mutant NSCLC (NCT0139578) has completed accrual.

Synthetic Lethality

With synthetic lethality, KRAS-mutant cancer cells are selectively killed by means of inhibition of a second protein. In KRAS-mutant cell lines, RNAi-based synthetic lethal screens have identified several potential targets. A number of these, including cyclin-dependent kinase 4 (CDK4), STK33, TBK1, and Polo-like kinase 1 (PLK1), encode protein kinases and may therefore be amenable to small molecule inhibition.[194]

NSCLC WITH PI3K PATHWAY ALTERATIONS

PI3K signaling plays important roles in metabolism, growth, survival, and motility. The class IA PI3Ks are most clearly associated with human cancer and are activated by growth factor stimulation through RTKs. Class IA PI3Ks are composed of a regulatory subunit and catalytic subunit. The regulatory subunit, p85, is encoded by PIK3R1, PIK3R2, and PIK3R3, whereas the catalytic subunit has three isoforms such as p110α, p110β, and p110δ encoded by PIK3CA, PIK3CB,

and PIK3D, respectively. Binding of p85 to phosphotyrosine residues on RTKs releases the inhibition of p110 by p85 and causes localization of PI3K to the plasma membrane, where it can phosphorylate phosphatidylinositol 4,5-bisphosphate to produce phosphatidylinositol 3,4,5 trisphosphate (PIP3), which in turn propagates intracellular signaling by means of AKT and pyruvate dehydrogenase lipoamide kinase isozyme 1 (PDK1) and other PIP3-dependent signaling pathways. PTEN dephosphorylates PIP3 to phosphatidylinositol 4,5-bisphosphate and thus inhibiting PI3K-dependent signaling and acting as a tumor suppressor. PI3K can also be activated by RAS or by G-protein–coupled receptors which bind directly to the catalytic subunit. PI3K–AKT signaling regulates multiple downstream pathways including the bcl2 family members, forkhead transcription factors, MDM2/p53, mTORC1/2, and nuclear factor kappa-light-chain-enhancer of activated B cells (NFKB) pathways, to promote cell survival and inhibit apoptosis.[195–197]

Genetic Alterations in PI3K Pathway

Genetic alterations of elements in the PI3K pathway have been described in lung cancer and other tumor types. PIK3CA encodes the gene for the p110α isoform of the catalytic subunit ofPI3K. Both copy-number gains and mutations in PIK3CA have been identified in lung cancer. PIK3CA copy-number gains occur in approximately 20% of lung cancers, with higher frequency in squamous cell carcinomas.[198–200] Somatic mutations in PIK3CA have also been described and promote the activation of the PI3K signaling pathway.[201] Mutations in PIK3CA are clustered in two hotspot regions in exons 9 and 20 encoding the helical and kinase domains of the protein, respectively. These mutations lead to increased lipid kinase activity and constitutive PI3K–AKT signaling.[201] The mechanism of action is different based on mutation type; for example, the helical domain mutants E545K and E542K interfere with the inhibitory interaction between the regulatory subunit p85 and the catalytic unit p110α, whereas the kinase domain mutant H1047R is located near the activation loop and leads to constitutive signaling through the kinase.[195] PIK3CA mutations have been reported in 1% to 5% of NSCLC cell lines and tumors.[198,202] Kawano et al.[202] found PIK3CA mutations in 6.5% of lung squamous cell carcinomas and less often in lung adenocarcinomas (1.5%). PIK3CA mutations often do not exist in isolation, and coexistence with other mutations, such as KRAS, NRAS, BRAF, and EGFR, is common.[203–205] A study among patients with lung adenocarcinoma in the United States reported 70% of cases with PIK3CA mutation had a coexisting driver mutation, with the most frequent partner being KRAS.[205]

The tumor suppressor gene PTEN encodes a lipid phosphatase that negatively regulates the PI3K/AKT pathway, and loss of PTEN leads to constitutive PI3K–AKT signaling. Somatic PTEN deletions and mutations, and inactivation of PTEN by epigenetic mechanisms such as methylation or microRNA silencing, are seen in multiple cancers.[206] PTEN mutations occur in approximately 5% of lung cancers and are significantly associated with squamous cell rather than adenocarcinoma histology (10.2% versus 1.7%).[207] Reduction or loss of PTEN expression has been reported in up to 70% of NSCLC, both adenocarcinoma and squamous cell.[208]

Other mutations in elements of the PI3K pathway have also been reported. For example, a somatic mutation in AKT, E17K, constitutively activates the protein kinase.[209] The AKT1 E17K mutation was found in 5.5% (two of 36) squamous cell lung cancers, but not (zero of 53) in lung adenocarcinoma.[210] PIK3R1 mutations causing truncations or in-frame deletions have also been reported and are thought to relieve the inhibitory effect of p85 on p110, thereby activating PI3K signaling.

Drug Development

There are multiple PI3K inhibitors in development, with specificity ranging from pan-PI3K inhibitors to isoform-selective PI3K inhibitors and dual PI3K/MTOR inhibitors. As a class, common adverse events have been hyperglycemia (which is thought to be due to the role PI3K plays in the insulin signaling pathway), maculopapular rash, and gastrointestinal issues such as nausea, vomiting, dyspepsia, diarrhea, and stomatitis. In addition to the phase I studies of PI3K inhibitors that enrolled all tumor types, there are many ongoing trials with a focus on lung cancer, both as monotherapy and in combination with other agents. There have been multiple phase I/Ib studies combining various PI3K inhibitors with MEK inhibitors which have enrolled expansion cohorts of patients with KRAS-mutated lung cancer; efficacy results from these trials are awaited. In nonmolecularly selected lung cancer populations, currently ongoing trials include GDC0941 in combination with carboplatin, paclitaxel, with or without bevacizumab, and BKM120 in combination with docetaxel or carboplatin/pemetrexed. BKM120 is also being tested singly and in combination with EGFR inhibitors in molecularly selected cohorts. GDC0032 is also being tested in combination with chemotherapy agents including docetaxel and paclitaxel.

Preclinical data have suggested that cancers harboring activating mutations in PIK3CA may be among the most sensitive to single-agent PI3K pathway inhibitors.[195] In general, the clinically observed activity of PI3K inhibitors as monotherapy has been modest, and it is not entirely clear how well molecular alterations in PI3K pathway correlate with antitumor effect.[211] In one institution's cumulative phase I experience, patients with PI3K mutations who were enrolled in phase I trials with PI3K/AKT/MTOR inhibitors had a higher PR rate than wild-type PI3K patients on their best phase I therapy.[203] However, the RRs reported (18% for PI3K-mutated patients versus 8% for wild-type, with H1047R mutations faring best with a 38% PR rate),[203] still leave much room for improvement and are not comparable with the RRs achieved with the landmark-targeted therapies used for EGFR or ALK inhibition. The frequent coexistence of other driver mutations may mean that single-agent PI3K inhibition may not be sufficient if the coexisting driver is not effectively targeted as well. In addition, signaling feedback loops may be activated that promote growth by means of alternative pathways; for example, mTORC1 inhibition leads to the activation of PI3K pathway through a feedback loop, limiting single-agent mTORC1 efficacy.[195] Finally, it remains unclear whether the drugs in development thus far are achieving an adequate therapeutic

window; observed pathway inhibition in various trials has ranged from 30% to 90%, and it is possible that at the dosing levels achieved there may not be sufficient pathway inhibition to have an antitumor effect.[211]

MET-POSITIVE NSCLC

The MET/HGF pathway has been identified as a potential therapeutic target in multiple solid tumors, including NSCLC.[212–214] The MET gene on chromosome 7q21-31 encodes the HGF receptor (HGFR), which is a single-chain heterodimer consisting of a 50-kDa extracellular α-chain and a 140-kDa transmembrane β-chain. Binding of the HGF ligand leads to dimerization of the receptor and phosphorylation of the intracellular TK domain.[215] This results in activation of downstream signaling pathways, such as PI3K–AKT and RAS–MAP–kinase, which are involved in cell survival and apoptosis, cell proliferation and differentiation, cytoskeletal function, angiogenesis, and other cellular functions.[216,217] There is also crosstalk between MET and other RTKs, including EGFR/ERBB family of receptors, which can result in HGF-independent activation of the MET pathway.[212,213,218] Ligand-mediated MET is tightly controlled through recruitment of Casitas B-lineage Lymphoma (CBL) (E3 ubiquitin ligase), which binds to the regulatory site of the juxtamembrane domain of HGFR and leads to ubiquination of HGFR into clathrin-coated vesicles, with ultimate degradation.[219]

Aberrant signaling of the MET pathway can occur through overexpression of HGF or HGFR, decreased degradation of HGFR, MET amplification, or MET mutations.[212,213] In NSCLC, the most common mechanism for aberrant MET signaling is overexpression of HGF and HGFR. HGFR overexpression is associated with poor prognosis and has been reported to occur in up to 61% of NSCLC,[220,221] including 25% to 67% of patients with adenocarcinoma of the lung.[220] The prevalence of de novo MET amplification is low (≤5%)11 to 15 but is also associated with poor prognosis.[221] Importantly, MET amplification has been identified as a mechanism for acquired resistance to EGFR TK inhibition in a subset (5%–20%) of patients with activating EGFR mutations through ERBB3-dependent activation of the PI3K pathway.[85,222,223] It is also seen that amplification can be de novo without resistance. Both somatic and germline MET mutations have been identified in multiple solid tumors.[212] In NSCLC, mutations in the extracellular semaphorin domain (exon 2) and intracellular juxtamembrane domain (exon 14–15, including exon skipping), which can affect ligand binding and receptor downregulation, respectively, have been described.[220,224,225] In a recently reported series that included 106 patients with NSCLC who underwent MET mutational analysis, approximately 4% were found to be MET-mutation positive (exon 14–15).[226]

Both in vitro and in vivo preclinical models have established the utility of MET pathway inhibitors to suppress HGF-dependent and HGF-independent MET phosphorylation and activation of downstream pathways, resulting in inhibition of both tumor growth and metastasis.[212] Dual inhibition of EGFR and MET in in vivo tumor xenograft models has been shown to be additive and potentially synergistic in NSCLC, including in tumors with acquired resistance to EGFR TKIs.[227,228] Recently we have also shown that MET can synergize with its family member Recepteur d'Origine Nantais (RON).[229] MET targeting strategies have included inhibitors of the HGF-HGFR binding, including HGF antagonists, HGFR inhibitors, and decoy MET, as well as small molecule inhibitors of the intracellular TK domain.[212–214] The preclinical experience has led to clinical testing of both single-agent and combination strategies to inhibit the MET pathway in NSCLC.

Monoclonal Antibodies Targeting HGF and HGFR

AMG 102 (rilotumumab) and AV 299 (ficlatuzumab) are monoclonal antibodies targeting HGF. Rilotumumab is a fully humanized monoclonal antibody that has been shown to improve the activity of chemotherapy in preclinical and clinical testing in tumors that overexpress MET.[230,231] In phase I testing as a single agent, rilotumumab was well tolerated with most common treatment-related adverse events including fatigue (13%), constipation (8%), and nausea (8%).[232] A phase I/II trial is currently ongoing evaluating rilotumumab with erlotinib in previously treated patients with NSCLC (NCT01233687). Ficlatuzumab is a human anti-HGF IgG1 monoclonal antibody.[233] In phase I testing, ficlatuzumab was well tolerated with no additional safety signals identified when combined with an EGFR TKI.[234] In a randomized phase II trial comparing gefitinib with gefitinib plus ficlatuzumab in never or former light smokers with previously untreated adenocarcinoma of the lung, there was no significant difference in RR (40% versus 43%) or PFS (4.7 versus 5.6 months) between the two groups (gefitinib versus gefitinib + ficlatuzumab, respectively).[235] Interestingly, in subgroup analysis, patients with activating mutations in the EGFR gene and low MET expression appeared to gain the most benefit from the combination (overall RR 70% versus 44% and median PFS 11.0 versus 5.5 months).[235]

MetMab (Onartuzumab) and LY-2875358 are monoclonal antibodies directed against the MET receptor. MetMab is a humanized, monovalent monoclonal antibody that inhibits HGF/MET binding without inducing MET dimerization.[236,237] In contrast, LY-2875358 is a bivalent MET receptor antibody that can inhibit both HGF-mediated signaling by binding to the MET receptor and HGF-independent activation of the MET pathway by inducing internalization and degradation of MET.[238] LY-2875358 has confirmed antitumor activity in in vivo and in vitro models.[239,240] A phase I trial as a single agent and in combination with erlotinib has been reported with no dose-limiting toxicities, serious, or grade III adverse events.[241] Currently, LY-2875358 is being evaluated in two phase II trials, including a randomized phase II with erlotinib versus erlotinib alone in patients with advanced-stage EGFR-mutated NSCLC (NCT01897480), as well as a single-agent or combined with erlotinib in patients with MET diagnostic positive NSCLC that has progressed on erlotinib.

Onartuzumab has been evaluated in a randomized phase II trial in patients with recurrent NSCLC in combination with erlotinib versus erlotinib alone.[242] There was no significant difference in the primary PFS end point in the intention-to-treat population (HR, 1.09; $p = 0.69$). However, in the prespecified MET-positive population (defined by a score of 2 to 3+ by IHC

[≥50% of cells with strong or moderate or higher staining using CONFIRM SP44 anti-MET monoclonal antibody]) the combination arm was associated with improved PFS (HR, 0.53; p = 0.04) and OS (HR, 0.37; p = 0.002).[242] A phase III trial evaluating this combination versus erlotinib alone in MET-positive patients with advanced-stage NSCLC who have received prior chemotherapy is ongoing (MetLung; NCT01456325).

MET TKIs

Targeting the MET TK has the potential to inhibit both HGF-dependent and HGF-independent signaling through the MET pathway. There are a number of MET TKIs currently undergoing testing in early-phase clinical trials.[213] Although crizotinib is FDA-approved for ALK-translocated NSCLC, it also has in vitro activity against MET. In a case report, a patient with advanced-stage MET-amplified (MET/CEP7 ratio >5.0) and ALK-negative NSCLC was reported achieved a rapid and durable response after treatment with crizotinib.[243]

Cabozantinib (XL184) is an ATP-competitive inhibitor of MET, VEGFR, and RET with documented phase II activity in an unselected pretreated cohort of 60 patients with advanced NSCLC (overall RR 10%; disease control rate 40%).[244] The combination of cabozantinib with erlotinib was also shown to be active in a phase IB trial of patients with previously treated NSCLC, the majority of who had received prior erlotinib.[245] In this trial, two of 53 patients had confirmed MET gene copy-number gain and both achieved tumor shrinkage with the combination.

On the basis of a promising randomized phase II trial, the phase III MARQUEE trial was initiated to test the combination of tivantinib (ARQ 197), a non–ATP-competitive TKI of MET, with erlotinib in previously treated patients with advanced NSCLC. This trial was stopped at the interim analysis because the primary OS end point was not met. Recent in vitro studies demonstrated that tivantinib is a cytotoxic drug affecting microtubule dynamics with activity in cell lines independent of MET activity. It is feasible that tivantinib is a weak MET inhibitor and has differential activity in different tumors.[246–248]

FGFR-POSITIVE NSCLC

Dysregulation of FGFR family signaling has been described in a broad range of cancers, including lung, breast, prostate, myeloma, sarcoma, bladder, and endometrial cancers, among others.[249–254] Amplification, translocation, and point mutations involving FGFR family members have all been described across the various tumor types, and each of these genetic alterations occurs in lung cancer.

The FGF/FGFR family consists of 18 FGF ligands which bind to four homologous FGFR RTKs (FGFR 1, 2, 3, and 4). A typical FGFR is composed of an extracellular domain with three IG-like domains, a transmembrane domain, and a split TK domain. Binding of FGF ligand to FGFRs induces receptor dimerization, which leads to transphosphorylation of a tyrosine in the activation loop of the TK domain. Activation leads to downstream signaling via the PI3K/AKT and RAS/MAPK pathways which are central to growth, survival migration, and angiogenesis.[249–254]

Amplification

Amplification at 8p12 was observed in multiple studies of squamous cell lung cancer,[16,18,255] and FGFR1 has been identified as a potential candidate gene in this region. Weiss et al.[18] identified focal amplifications in FGFR1 corresponding to the 8p12 amplification in a study of 155 primary squamous cell lung cancer specimens, which they validated in an independent set of 153 squamous cell lung cancers. Similarly, Dutt et al.[16] reported FGFR1 amplification in approximately 20% of squamous cell lung cancers and rarely in adenocarcinoma (3%). Inhibition of FGFR1 in amplified cell lines and in mouse models with FGFR1-amplified engrafted tumors showed growth inhibition and induced apoptosis.

It remains unclear whether FGFR1 amplification is a prognostic marker in lung cancer. Weiss et al. reported that FGFR1 amplification (copy number >9 by FISH) had a trend toward worse survival compared with patients who lacked FGFR1 amplification (copy number = 2 by FISH). Multiple studies have investigated the potential prognostic role of FGFR1 among patients with squamous cell lung cancer; some have reported no effect of FGFR1 amplification on survival,[256,257] whereas others have reported inferior survival with FGFR1 amplification,[18,258,259] and one reported potential improved survival.[260] Comparison across studies is limited by the heterogeneity in definitions of amplification, and there is not yet a defined standard in the field.

Fusions

In addition to FGFR1 amplification, fusions involving FGFR3 have recently been reported in lung cancer.[20–22] Fusions involving FGFR3 have been reported in other cancers including glioblastoma and bladder cancer.[261] Kim et al.[20] performed whole exome sequencing of lung squamous cell cancers from Korean patients and identified an in-frame fusion of FGFR3 with TACC3. Overall two of 148 Korean lung squamous cell cancers had this fusion; probing the TCGA data set revealed another four of 178 samples with the FGFR3-TACC3 fusion.[20] Majewski et al.[21] used kinome-centered RNA sequencing on 95 lung cancer samples and identified two squamous cell lung cancers with FGFR3-TACC3 fusions. FGFR3 fusions resulted in overexpression of fusion proteins and enhanced proliferation of cells and activation of downstream MAPK–ERK pathways.[22] Studies in bladder cancer and glioblastoma have invoked various hypotheses for the transforming capacity of FGFR3-TACC3, including constitutive activation and signaling via downstream MAPK pathway,[262] localization to the mitotic spindle, causing chromosomal missegregation and aneuploidy,[263] or loss of a 3'UTR miR-99a binding site resulting in enhanced expression of the fusion transcripts.[264] Importantly, multiple studies have shown sensitivity of FGFR3 fusion cell lines and xenograft models to FGFR inhibitors.[22,262,263]

Point Mutations

Point mutations in FGFR have also been identified as potentially oncogenic, in particular mutations in FGFR2 and FGFR3. Analysis of whole exome data from TCGA identified five FGFR2 and six FGFR3 mutations from 178 tumor/normal pairs.[265] The observed mutations fell within both the

extracellular and kinase domains of FGFR2 and FGFR3 and included previously identified mutations in other tumor types and novel mutations. Some of these mutations were transforming in anchorage-independent growth assays and xenograft assays. In particular, extracellular domain mutations W290C and S320C in FGFR2 and S249C in FGFR3, as well as kinase domain mutations K660E and K660N in FGFR2, significantly increased colony formation in anchorage-independent growth assays as compared with wild type (in contrast, FGFR2 E471Q and T787K, and FGFR3 S435C and K717M were not transforming). The transforming ability of the specific FGFR2 and FGFR3 mutations was inhibited by multiple of the small molecule FGFR inhibitors currently in clinical development.[265]

Drugs

Many FGFR inhibitors are in development and have multitargeted activity and inhibit other kinases in addition to FGFR, most notably VEGFR, PDGFR, FLT3, RET, KIT, among others.[261] Selective FGFR inhibitors are also in development and preliminary results have been reported for some of these trials. A phase I study of BGJ398 is enrolling patients with advanced solid malignancies with FGFR1 or FGFR2 amplification or FGFR3 mutation. A preliminary report in 2012 reported 26 patients having been treated, including 10 with FGFR1 amplified breast cancer and three with FGFR1-amplified lung squamous cell cancer. The most frequent adverse events included diarrhea, fatigue, nausea, and hyperphosphatemia, with dose-limiting toxicities of grade 3 elevations in transaminases and grade 2 corneal events. Hyperphosphatemia may be a class effect due to blockade of FGF23 signaling but seems controllable with phosphate binders and diuretics. One patient with lung cancer and FGFR1 amplification (FGFR1/CEP8 ratio of 2.6 by FISH) had a confirmed PR.[266] A phase I study of AZD4547, with selection for FGFR1 and FGFR2 amplification in the later phases of the study has completed accrual, and final results are pending. In a preliminary report, dose-limiting toxicities included hyperphosphatemia, renal failure, mucositis, and increased transaminases. A preliminary report in 2013 reported on 21 patients with FGFR1- or FGFR2-amplified tumors on study. One patient with FGFR1-amplified lung squamous cancer had a PR,[267] with another patient with FGFR1-amplified lung squamous cancer having a prolonged period of SD. Although some are selecting for specific FGFR family alterations, others are more inclusive and enroll specific tumor types without molecular characterization required a priori. Class specific effects of the selective FGFR inhibitors are thought to include hyperphosphatemia and tissue calcification due to FGF23 blockade; although this is a class-specific adverse event, increases in FGF23, phosphate, and vitamin D levels may also serve as potential biomarkers for effective FGFR inhibition.[282] Most of these studies are with single agents although a few are testing in combination with various chemotherapy regimens.

MITOTIC/CYCLIN INHIBITORS IN LUNG CANCER

Disrupting cell division has been a cornerstone of cancer drug development. Mitotic inhibitors are among the most widely developed agents in oncology and have been used in lung cancer treatment for more than three decades. These agents bind tubulin and prevent polymerization to microtubules, hence, preventing cell division. Multiple mitotic inhibitors have been developed and many are still standard therapies in lung cancer treatment including paclitaxel, docetaxel, vinorelbine, and etoposide. These agents are routinely combined in platinum regimens in the adjuvant, locally advanced, and metastatic NSCLC; and platinum/etoposide remains the established treatment for limited- and extensive-stage SCLC.

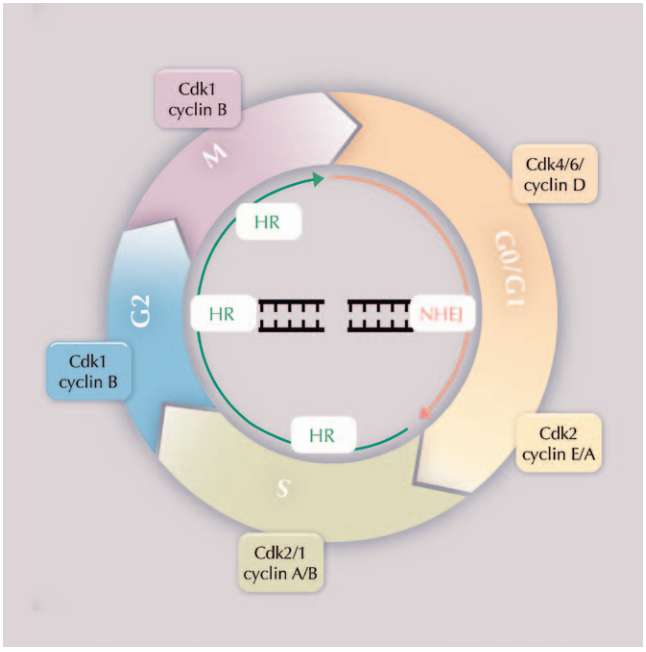

FIGURE 5. Mitotic/cyclin inhibitors. NHEJ, non-homologous end joining; HR, homologous recombination.

More recent advances in targeting cell cycling have come with the development of cell cycle checkpoint inhibitors. Cell cycle check points are important in maintaining genomic stability and preventing cancer development in normal cells (Fig. 5).[268] These checkpoints help in cellular surveillance of DNA damage by causing cycle arrest and permitting DNA repair. However, these checkpoints also protect cancer cells from the effects of DNA-damaging agents such as cisplatin/carboplatin and gemcitabine and from the effects of radiation. CDKs are key regulators of sequential progression through the G1, S, G2, and M phases of the cell cycle. Checkpoint kinase inhibitors disrupt the ability of cancer cell to repair this damage and have recently shown promising activity as single agents in selected patient populations and in combination with DNA-damaging therapies in broader tumor settings.[269,270] Many of these novel agents are being developed in lung cancer treatment.

LY2606368

LY2606368 is an oral small molecule selective ATP-competitive inhibitor of the checkpoint kinase 1 (CHK1), and to a lesser extent CHK2. CHK1 and 2 regulate DNA damage response by inhibiting CDK1 preventing the entry into mitosis.[271] This leads to cell cycle arrest, DNA repair, and apoptosis

of damaged cells.[272] LY2606368 has been shown to potentiate DNA-damaging agents and has potent antitumor activity as a single agent in preclinical studies.[273] LY2606368 is currently in a phase I study in patients with advanced refractory squamous NSCLC, head and neck cancer, and anal cancer (N = 150; NCT01115790).

Palbociclib (PD-0332991)

Palbociclib (Pfizer) is an oral CDK4/6 inhibitor, inhibiting retinoblastoma (Rb) protein phosphorylation in early G1 and disrupting cell cycle progression to S phase. Palbociclib has recently shown remarkable activity in a randomized phase II trial in patients with advanced hormone-positive breast cancer.[274] One hundred sixty-five women were randomized 1:1 to 2.5 mg of letrozole orally daily ± 125 mg palbociclib daily for 3 weeks followed by 1 week off. The primary end point was investigator-assessed PFS. Palbociclib/letrozole was associated with a significant improvement in PFS compared with letrozole alone (20.2 versus 10.2 months; HR, 0.488; 95% CI, 0.32–0.75; one-sided p = 0.0004). The most common toxicities in the palbociclib/letrozole arm were neutropenia, leukopenia, fatigue, and anemia. Palbociclib is in planned investigation in CDK4/6-amplified recurrent squamous lung cancer as part of the National Cancer Institute–sponsored biomarker driven "Master" protocol.

LY2835219

LY2835219 (Eli Lilly) is an oral selective ATP-competitive inhibitor of CDK4/6 which has entered into phase I study in NSCLC (NCT02079636). Ninety-nine patients will be enrolled across multiple cohorts including combinations with pemetrexed (nonsquamous only), gemcitabine, ramicirumab, and trametinib. Development in other tumors including breast cancer, colorectal cancer, melanoma, glioblastoma multiforme, and mantle cell lymphoma is ongoing.

AZD1775

TP53 mutations are the most common genomic alterations in lung cancer, occurring in an estimated 51% of squamous lung cancers and 34% of adenocarcinomas (Catalogue of Somatic Mutations in Cancer [COSMIC]). These mutations render the G1 checkpoint defective, making these cancers more dependent on the S/G(2) cell cycle checkpoint for repair and resistant to DNA-damaging agents. This resistance can be overcome in the presence of S/G(2) inhibitors.[271] The WEE1 kinase coordinates cell cycle progression and DNA damage checkpoints. AZD1775 (Astra-Zeneca) is an oral ATP-competitive inhibitor of WEE1 (concentration that inhibits 50% 5 nM; EC50 80 nM versus pCDK1Y15).[275] WEE1 inhibition leads to unregulated CDK1 (and 2) activity, overriding S/G2 checkpoints leading to mitotic catastrophe and cell death in DNA damaged cells. This activity may be most pronounced in p53-mutated (G1-deficient) cells in combination with platinum-based and gemcitabine-based regimens. A phase I trial of AZD1775 + cisplatin, + carboplatin, and +gemcitabine in more than 180 patients with refractory solid tumors has recently been completed; and early activity and safety have been reported in combination with carboplatin/paclitaxel in patients with p53-mutated platinum-sensitive recurrent ovarian cancer.[276] AZD1775 has entered into trials in p53-mutated lung cancer: a first-line randomized phase trial of carboplatin/pemetrexed ± AZD1775 in patients with nonsquamous NSCLC (NCT02087241); and a second-line randomized phase II trial of docetaxel ± AZD1775 in patients with nonsquamous and squamous histologies (NCT02087176). Trials are also ongoing in p53-mutated platinum-sensitive and platinum-resistant recurrent ovarian cancer.

Volasertib (PLK-1 ONO01910)

PLK1 is important for cellular recovery from G2/M arrest due to DNA damage. Overexpression of PLK1 leads to chromosomal instability and is seen in many tumors including NSCLC.[277] Volasertib is an i PLK1 inhibitor in development in NSCLC. Recent data were presented from a study of 131 patients with recurrent nonsquamous NSCLC randomized 1:1:1 to volasertib 300 mg/m^2, volasertib 300 mg/m^2 and pemetrexed 500 mg/m^2, or pemetrexed alone IV day 1 every 3 weeks.[278] The median PFSs (primary end point) for these cohorts were: 1.4,

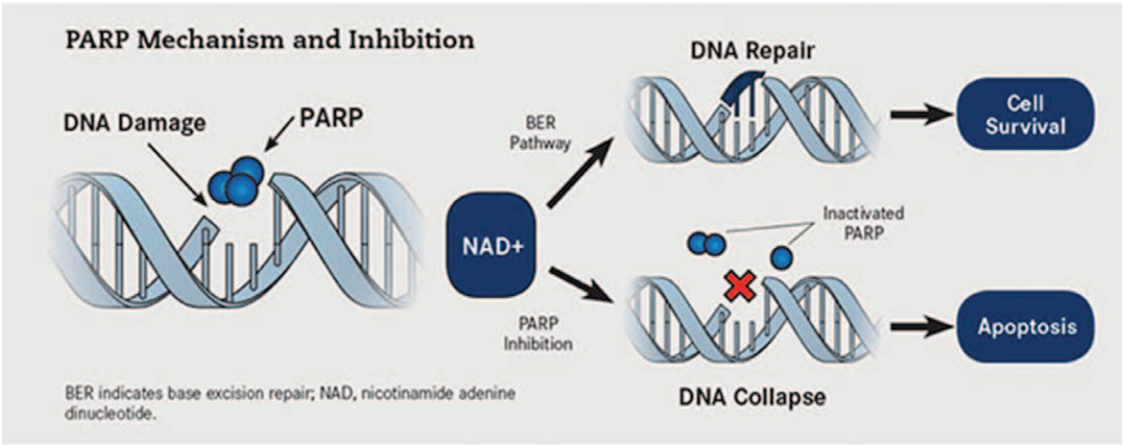

FIGURE 6. PARP inhibition: Mechanism of action (reproduced from Oncology Live, 2013, permission requested). BER, base excision repair; NAD, nicotinamide adenine dinucleotide; PARP, Poly(ADP-ribose) polymerase.

3.3, and 5.3 months, respectively. The ORRs were 8.1%, 21.3%, and 10.6%, respectively. Grade 3/4 toxicity was primarily limited to fatigue (all arms) and neutropenia (volasertib/pemetrexed, 11%). Development of volasertib is ongoing in acute myeloid leukemia and urothelial cancer.

Alisertib (MLN8237)

The aurora kinases play important roles in mitosis. Aurora kinase A promotes mitosis through activation of CDK1, and its overexpression has been linked to taxane resistance. Aurora kinase B is linked to cytokinesis, and its inhibition leads to dysfunctional chromosomal alignment and segregation. Several aurora kinase inhibitors (A and B) are in development.

Alisertib (Millennium) is an oral aurora kinase A inhibitor. A phase I/II trial of alisertib in patients with refractory SCLC, NSCLC, breast cancer, head and neck cancer, and gastroesophageal cancer was recently presented.[279] Patients received the recommended phase II dose of 50 mg orally twice a day for 1 week every 3 weeks. The ORR in 23 patients with NSCLC was 4% with a median PFS of 3.1 months. However, in the SCLC ($n = 47$) cohort, the ORR was 21% (including 3 patients [ORR 27%] with refractory relapsed disease) with a PFS of 2.8 months. Grade 3/4 toxicities (all patients) included neutropenia (38%), anemia (10%), stomatitis (8%), and thrombocytopenia (6%). A randomized phase II study of paclitaxel ± alisertib in patients with relapsed SCLC (NCT02038647), and a trial of alisertib and erlotinib in patients with EGFR-WT NSCLC (NCT01471964) are in progress. Several other A and B, and pan-aurora, kinase inhibitors are in early development in solid and hematologic cancers.

POLY (ADENOSINE DIPHOSPHATE-RIBOSE) POLYMERASE INHIBITORS IN LUNG CANCER

Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) includes a family of 17 proteins that play important roles in DNA repair.[280] In addition to its function in DNA repair, PARP proteins also play major roles in a number of other cellular processes such as transcription, epigenetic regulation, mitosis, and inflammation, which have all been recognized in recent years. PARP 1 and 2 are considered to be highly relevant for DNA repair. After single-strand DNA damage, PARP is recruited as the first step of the repair process (Fig. 6).[281] Subsequently, multiple ADP–ribose units are added to the complex in a NAD-dependent manner. This confers a net negative charge that induces conformational changes and attracts a number of key repair proteins such as DNA ligase III, X-ray cross-complementing gene 1, etc., which ultimately work to repair the DNA damage. In situations of catastrophic DNA damage, massive recruitment of PARP leads to depletion of NAD, resulting in necrotic cell death. Thus the extent of PARP activation could be the determinant of successful DNA repair or cell death. Unrepaired single-strand damage leads to double-strand DNA damage that is repaired by the homologous recombination repair pathway. In subjects with breast cancer, early onset (BRCA) 1 or 2 mutations, the homologous recombination pathway is deficient and there is an overwhelming reliance on PARP for DNA repair.[282]

PARP Inhibition

PARP inhibition was initially studied in cancer in combination with agents that induce DNA repair such as platinum compounds, alkylating agents, and ionizing radiation.[283] Suppression of DNA repair with PARP inhibitors in conjunction with these agents results in enhanced anticancer activity in several preclinical models. In patients with deficient homologous recombination pathway, PARP inhibition results in robust anticancer activity due to the reliance of these cells on PARP for DNA repair.[282] This effect, referred to as "synthetic lethality," has formed the basis for the evaluation of PARP inhibitors as monotherapy in breast and ovarian cancer patients who have BRCA 1 or 2 mutations. In lung cancer, BRCA mutations are rare and hence PARP inhibitors are unlikely to be effective as monotherapy. A small subset of lung cancer patients are known to have "functional" BRCA deficiency and could be candidates for the monotherapy approach even though this has not been tested in clinical trials. Approximately 10% of NSCLCs harbor a mutation in ataxia telangiectasia mutated (ATM) gene, a condition with known deficiency in homologous recombination.[27] Another mechanism referred to as "PARP trapping" has recently been described to account for the anticancer effects of PARP inhibition.[284] Retention of the PARP inhibitor–DNA complex confers cytotoxicity to cells and the extent of PARP trapping is variable among the presently available PARP inhibitors, contributing to potential differences in efficacy of these agents based on this effect.

A number of novel PARP inhibitors are presently in clinical development for the treatment of cancer. Iniparib, which was initially considered to be a PARP inhibitor, had been tested in phase III studies in breast cancer and squamous cell lung cancer in combination with platinum-based chemotherapy.[285] These studies failed to demonstrate survival benefit, and by then, it was also clear that the mechanism of action of inparib was not related to PARP inhibition. Recently, the use of olaparib, a potent small molecule inhibitor of PARP, as maintenance therapy in platinum-sensitive ovarian cancer was associated with a significant improvement in PFS compared with placebo (8.4 versus 4.8 m, $p < 0.001$).[286] In another phase II study, olaparib demonstrated an RR of approximately 40% in ovarian cancer patients with BRCA mutation.[287] Veliparib, a small molecule PARP inhibitor, improved the pathological complete RR for patients with breast cancer in the neo-adjuvant therapy setting. From these lines of evidence, it is clear that PARP inhibitors represent a novel approach for the treatment of cancer.

PARP Inhibitors under Development in Lung Cancer

Small-cell lung cancer

Increasing evidence suggests that PARP inhibition might be a novel strategy for the treatment of SCLC.[288] Objective responses have been reported with BMN-673, a highly potent PARP inhibitor when given as monotherapy to patients with SCLC that had progressed on standard chemotherapy. Biological rationale for the sensitivity of SCLC might be due to the higher PARP 1 expression and other DNA repair proteins in SCLC tumor samples. On the basis of the synergy

between alkylating agents and PARP inhibitors, a phase II study is presently evaluating the combination of temozolamide in combination with veliparib, a PARP inhibitor, for patients with relapsed/refractory SCLC (NCT01638546). The Eastern Cooperative Oncology Group is conducting a randomized phase II study of cisplatin and etoposide with either veliparib or placebo for first-line therapy of patients with extensive stage SCLC (EA2511) (NCT01642251). Veliparib is given at a dose of 100 mg twice-daily on days 1 to 7 of each treatment cycle to synchronize with the administration of cisplatin (day 1) and etoposide (days 1–3). This ongoing study will enroll a total of 135 patients with the primary end point of comparing median PFS between the two arms.

Non–small-cell lung cancer

Because platinum-based chemotherapy is the standard treatment for majority of patients with NSCLC, the use of PARP inhibitors in combination with platinum compounds has been studied extensively in preclinical studies. A phase I study of carboplatin, paclitaxel, and veliparib in patients with advanced solid organ malignancies noticed good tolerability and promising activity in advanced NSCLC.[289] Subsequently, a randomized phase II study of carboplatin and paclitaxel with either veliparib or placebo for first-line therapy of advanced NSCLC was conducted. Accrual to this study has been completed and the results are awaited (NCT01560104). The same combination is presently being tested in conjunction with radiation therapy for patients with surgically unresectable, locally advanced NSCLC by the Southwest Oncology Group (NCT01386385).

Olaparib, another PARP inhibitor, is also under extensive evaluation in NSCLC. A European study will administer olaparib in combination with cisplatin and radiotherapy to patients with unresectable stage III NSCLC (NCT01562210). It is also being studied as maintenance therapy for advanced NSCLC following combination chemotherapy in a randomized study (NCT01788332). More recently, a phase Ib/II study has been initiated to evaluate the combination of olaparib with gefitinib in patients with advanced NSCLC that harbor an EGFR mutation (NCT01513174).

IMMUNE CHECKPOINT INHIBITORS

Lung cancer has not traditionally been viewed as an immune responsive tumor. Immune checkpoint inhibitors have recently demonstrated promising results in lung cancer patients. In particular inhibitors to cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and PD-1 and PD-L1 have shown promise in early studies and are currently in clinical trials in both SCLC and NSCLC. This review provides an update on immune checkpoint inhibitors currently in development in lung cancer patients.

Anti-CTLA-4 Inhibitors

Ipilimumab is a fully human IgG1 antibody to CTLA4 that inhibits the binding of CTLA4 to its ligands (CD80 or B7-1 and CD86 or B7-2). Inhibition augments T-cell activation and proliferation resulting in T-cell infiltration of tumor cells and tumor regression.[290] It is approved by FDA for the treatment of melanoma.[291] Ipilimumab was evaluated in a randomized phase II trial that compared six cycles of standard chemotherapy (carboplatin and paclitaxel) with two different schedules of ipilimumab in 204 patients with stage IV NSCLC.[292] In the concurrent schedule ipilimumab was given with cycle 1 to 4 of chemotherapy followed by two doses of placebo, in the phased schedule placebo was given with the first two cycles of chemotherapy and ipilimumab was added with cycle 3 to 6. Eligible patients were given maintenance ipilimumab or placebo every 12 weeks until progression. The primary end point was immune relate PFS (irPFS). This end point was chosen to better capture the unique pattern of response to immune therapy including regression of index lesions in the face of new lesions and initial progression followed by tumor stabilization or regression.[293,294] The phased arm demonstrated an improvement in irPFS compared with chemotherapy (5.7 versus 4.6 months; HR, 0.72; $p = 0.05$), and OS (12.2 versus 8.3 months). The concurrent arm did not result in an improvement in irPFS (5.5 months; HR, 0.81; $p = 0.81$) or OS (9.7 months). There was also a higher World Health Organization best overall RR in the phased arm compared with chemotherapy or concurrent (32%, 18%, and 21%, respectively). Treatment-related adverse events were similar across treatment groups (concurrent, 41%; phased, 39%; and control, 31%). However, grade 3/4 immune-related adverse events were higher in the concurrent (20%) and phased (15%) arms compared with the control (6%). Two treatment-related deaths were reported including one in the concurrent arm due to septic shock secondary to epidermal necrolysis, and one death occurred in the control arm as a result of neutropenic sepsis. In a preplanned subset analysis patients with squamous cell carcinoma had a significantly improved irPFS (HR, 0.55; 95% CI, 0.27–1.12) and OS (HR, 0.4; 95% CI, 0.22–1.03) when treated with the phased schedule. This was not observed in nonsquamous NSCLC patients or for any histology treated with the concurrent schedule. On the basis of these promising results, a randomized phase III trial is underway comparing standard chemotherapy with or without phased ipilimumab in patients with squamous cell NSCLC (NCT01285609).

The same trial enrolled 103 patients with extensive-stage SCLC and noted an improvement in ifPFS in patients treated with the phased ipilimumab schedule compared with chemotherapy alone (6.4 versus 5.3 months; HR, 0.64; $p = 0.03$) with a nonsignificant trend toward improvement in RR (57% versus 49%) and OS (12.9 versus 9.9 months).[295] This was not seen in the concurrent treatment arm (PFS 3.9 months, RR 30% and OS 9.1 months). Treatment-related and immune-related grade 3/4 adverse events were more common in ipilimumab-containing arms (concurrent 43% and 21%; phased 50% and 17%; and control 30% and 9%). One treatment-related death due to hepatotoxicity was seen in the concurrent-treatment group. On the basis of these data, a randomized phase III trial of platinum-based chemotherapy (carboplatin or cisplatin and etoposide for four cycles) with or without phased ipilimumab in patients with extensive-stage SCLC is underway (NCT01450761). Tremelimumab is a fully human IgG2 antibody. A phase II trial failed to show an improvement in PFS when maintenance tremelimumab was compared with best supportive care (BSC) in patients with disease control (CR/PR or SD) after four cycles of platinum-based chemotherapy (20.9% versus 14.3% patients progression free at 3 months).[296]

Nine (20.5%) of the tremelimumab patients experienced a grade 3/4 adverse effects the most common being diarrhea and colitis (9.1%). Studies with tremelimumab in combination with anti-PD-L1 therapy and gefitinib in patients with NSCLC are ongoing (NCT02000947; NCT02040064).

Anti-PD-1 Antibodies

Nivolumab (BMS-936558), a human monoclonal IgG4 antibody, was the first anti-PD-1 antibody to demonstrate activity in NSCLC patients. PD-1 is an inhibitory T-cell receptor that is engaged by it ligands PD-L1 (or B7-H1) and PD-L2 (or B7-DC) predominantly within the tumor microenvironment.[297,298] Promising activity was seen in a dose-escalation trial that included 129 NSCLC patients treated with nivolumab 1, 3 or 10 mg/kg IV every 2 weeks in an 8-week cycle.[299] An RR of 17.1% was noted in the NSCLC population with no significant difference between squamous (16.7%) and nonsquamous (17.6%) patients. Drug-related adverse events were seen in 53% of patients, 6% of which were grade 3/4 including gastrointestinal, pulmonary (pneumonitis), hepatitis, and infusion reactions.[300] On subset analysis, no significant difference was seen in patients who were EGFR mutation positive or wild type or KRAS positive or wild type.[301] There was a difference in RR between different dose levels; 3% for the 1 mg/kg cohort compared with 24.3% and 20.3% for the 3 and 10 mg/kg cohort, respectively. On the basis of these data, the 3 mg/kg dose was selected for further study, including a single-arm phase II trial of nivolumab in squamous cell lung cancer patients (NCT01721759) and two randomized phase III trials comparing nivolumab with second-line chemotherapy (docetaxel) in squamous and nonsquamous NSCLC patients (NCT01673867; NCT01642004). All three trials have completed accrual and results are anticipated. In patients enrolled in the phase I trial with tumor samples available for assessment, PD-L1 expression by IHC was associated with a response to therapy, whereas no responses were observed in patients with tumors that were PD-L1 negative.[299] A phase III trial is ongoing comparing first-line nivolumab to investigator-choice chemotherapy in patients with PD-L1–positive tumors (NCT02041533). Promising results were seen in melanoma patients when nivolumab was combined with ipilimumab,[300] and a phase I trial is currently evaluating nivolumab alone or in combination with ipilimumab in select tumor types including SCLC (NCT01928394). In addition, a phase I trial is ongoing evaluating nivolumab in combination with first-line platinum-based chemotherapy in NSCLC patients (NCT01454102). Initial data presented at ASCO in 2013 indicated a fairly high rate of grade 3/4 AEs (49%) for combination of nivolumab and chemotherapy.[302]

MK3475 is a humanized IgG4 anti-PD1 antibody that is also being evaluated in NSCLC patients. Preliminary results from a phase I trial with MK-3475 10 mg/kg administered every 2 or 3 weeks reported a 24% response in the first 38 evaluable patients using immune-related response criteria and a 21% RR using conventional RECIST response criteria.[303] This response was higher in patients with tumors that were positive for expression of PD-L1 (67% versus 4%). Median PFS had not been reached at the time of initial data cut off. Treatment-related adverse events, the majority of which were grade 1/2 were noted in 53% of patients including fatigue (16%), rash (16%), and pruritus (16%). Grade 3 pulmonary edema was reported in one patient and two patients experienced grade 2 pneumonitis. Ongoing trials are comparing two different schedules of MK-3475 with standard chemotherapy (docetaxel) as second-line therapy in patients with tumors that are positive for PD-L1 expression (NCT01905657). In addition, MK-3475 is being combined with standard chemotherapy and immunotherapy in an ongoing phase I trial (NCT02039674; NCT01840579).

Anti-PD-L1 Antibodies

BMS-936559, a fully human IgG4 molecule, was the first anti-PD-L1 antibody to demonstrate activity in NSCLC patients. An RR of 10% was observed in 49 patients enrolled in a phase I trial evaluating multiple different dose levels with no significant difference between squamous and nonsquamous NSCLC patients.[304] Despite initial promising results, this agent is not being further explored in lung cancer patients at this time.

MPDL3280A is a human IgG1 monoclonal antibody to PD-L1. A phase I trial that included 85 NSCLC treated with MPDL3280A reported an RR of 23%.[305] Preliminary data reported that the RR was higher in tumors that were IHC3 positive (83%), defined as 10% of tumors staining positive for expression of PD-L1 and in former and current smokers (11 of 43) compared with never smokers (1 of 10).[306] Treatment-related adverse events occurred in 66% of patients, of which 11% were grade 3/4 including fatigue, nausea, dyspnea, and emesis. Trials of MPDL3280A are ongoing in patients with tumors that are positive for expression of PD-L1, are ongoing including a single-arm phase II trial of MPDL3280A (NCT01846416; NCT02031458), and a randomized phase III trial comparing MPDL3280A with standard chemotherapy (docetaxel) (NCT02008227). In addition, an upcoming phase I trial is combining MPDL3280A with or erlotinib in NSCLC patients (NCT02013219).

MEDI-4736 is a fully human antibody specific for PD-L1. Binding of MEDI-4736 relieves B7-H1–mediated suppression of T-cell activation in vitro. An ongoing phase I dose-escalation study including patients with NSCLC is evaluating different dose levels of MEDI-4736 including 0.1, 0.3, and 1 mg/kg every 2 or 3 weeks. Data reported on the first 11 patients enrolled indicated toxicities similar to other agents in this class and responses observed in NSCLC patients.[307] A phase Ib trial is evaluating MEDI-4736 in combination with tremelimumab in NSCLC patients (NCT02000947).

LUNG CANCER VACCINES

Cancer vaccines are based on immune system stimulation through the use of tumor cell antigens. Once the immune system is activated, it may trigger a response to cells harboring these antigens, potentially leading to elimination of the malignancy.[308] The two broad types of vaccines being evaluated in patients with NSCLC are the tumor cell–based and the antigen-based vaccines. Because the antigens are usually poorly immunogenic by themselves, they are combined with potent adjuvants that stimulate the immune response to the vaccine without intrinsic antigenic effect.[309]

Tumor cell vaccines

Belagenpumatucel-L

Belagenpumatucel-L is an allogeneic tumor cell vaccine made of four irradiated NSCLC cell lines (H460, H520, SKLU1, and RH2) modified with transformed growth factor-β2 antisense plasmid.[310] Antisense gene inhibition with decreased cellular expression of transformed growth factor-β2 increases the immunogenicity of the vaccine. In a randomized phase II trial, 75 patients with NSCLC stages II to IV were randomized to one of three doses (1.25, 2.5, or 5.0×107 cells per injection) of the vaccine administered once every 1 or 2 months for a maximum of 16 injections. The treatment was well tolerated and the two high-dose cohorts had a significant improvement in OS compared with low dose. In the phase III Phase III Lucanix™ Vaccine Therapy in Advanced Non-small Cell Lung Cancer (NSCLC) Following Front-line Chemotherapy (STOP) trial, 532 patients with NSCLC stage IIIA to IV were randomized to belagenpumatucel or placebo after frontline therapy.[311] The study did not meet the primary end point with a median OS of 20.3 and 17.3 months in the vaccine and placebo arms, respectively (HR, 0.94; $p = 0.59$).

Among the 490 patients with stage IIIB or IV who were randomized within 12 weeks from completion of frontline therapy, there was a 7.4-month improvement in OS for the vaccine arm, which did not reach statistical significance (20.7 versus 13.4 months; HR, 0.75; $p = 0.083$). In the subset of 99 patients with stage IIIB or IV non-adenocarcinoma, the median OS was significantly higher for the vaccine arm (19.9 versus 12.3 months; HR, 0.55; $p = 0.036$). Therefore, although the study did not meet the end point, the authors suggested that selected subset analyses support the continued development of belagenpumatucel-L in NSCLC.

Tergenpumatucel-L

Tergenpumatucel-L consists of three allogeneic lung tumor cell lines (derived from adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) that were engineered to express the α-galactosyltransferase enzyme, which is one of the major causes of hyperacute rejection induced with porcine xenografts transplanted into baboons.[312] In a phase II trial, 28 patients with advanced NSCLC received tergenpumatucel-L 300 million cells per injection every 2 weeks for eight doses.[313] The treatment was well tolerated without serious adverse events. Eight patients (29%) achieved SD for 4 or more months, with five of 16 (31%) responding to subsequent therapy. The median and 1-year OS were 11.3 months and 46%, respectively. An ongoing phase III study is comparing tergenpumatucel-L to docetaxel in patient with previously treated NSCLC.

Antigen-Associated Vaccines

Melanoma-associated antigen-A3

The melanoma-associated antigen-A3 (MAGE-A3) is an antigen with expression limited to nonmalignant cells, except for placental trophoblasts and testicular germ cells. MAGE-A3 is expressed in approximately 35% of patients with NSCLC. MAGE-A3 vaccine is composed of the protein plus the adjuvant AS15. In a phase II trial, patients with completely resected MAGE-A3–positive stage IB or II NSCLC were randomized to the vaccine (90 patients) administered in 13 doses over 27 months or placebo (60 patients).[314] Although the treatment was well tolerated, there were no statistically significant differences in disease-free interval, DFS, or OS. Nevertheless, the trend favoring the vaccine arm for disease-free interval (HR, 0.75), DFS (HR, 0.76), and OS (HR, 0.81) led to the large phase III trial MAGE-A3 as Adjuvant non-small cell lunG cancer ImmunoTherapy (MAGRIT), where patients with resected stage IB to IIIA NSCLC and MAGE-A3–positive tumors were randomized to placebo or vaccine after adjuvant chemotherapy. The press release from GlaxoSmithKline on March 30, 2014, indicated that the trial enrolled 2312 patients worldwide and did not meet the primary end point of extending DFS.

Mucin-1

Liposomal BLP-25 (tecemotide) is a peptide-based vaccine consisting of a synthetic mucin 1 (MUC-1) lipopeptide combined with the adjuvant monophosphoryl lipid A and three lipids forming a liposomal product. In a phase II study, 171 patients with stage IIIB or IV NSCLC and no progressive disease (PD) after first-line therapy were randomized to BSC or vaccine with 1000 μg weekly for 8 weeks followed by administrations every 6 weeks until tumor progression.[315] The vaccine was preceded by one dose of cyclophosphamide 300 mg/m^2. This low-dose cyclophosphamide, administered 3 days before the immunotherapy, does not have significant antitumor activity in NSCLC and was used to increase the immune response. The study did not meet the primary end point with median OS increasing from 13 months in the BSC arm to 17.4 months in the vaccine group ($p = 0.66$). The greatest benefit for the vaccine was in the subset analysis of patients with locoregional stage IIIB disease, where the post hoc analysis showed that both median (not reached versus 13.3 months) and 2-year OS (60% versus 36.7%) favored the experimental arm. The Stimulating Targeted Antigen Responses To NSCLC trial was a large international, randomized, double-blind, clinical study that randomized patients with stage III NSCLC who did not have PD after chemoradiotherapy, compared with tecemotide or placebo.[316] After the primary treatment, 829 and 410 patients were randomized to tecemotide and placebo, respectively. The study did not meet the primary end point of improving OS, with the median OS increasing from 22.3 months in the placebo to 25.6 months in the tecemotide arm (HR, 0.88; $p = 0.12$). Subset analysis of patients receiving concurrent chemoradiotherapy showed an improved median OS for the 538 patients receiving tecemotide compared with the 268 patients randomized to placebo (30.8 versus 20.6 months; HR, 0.78; $p = 0.016$). A randomized phase III trial comparing tecemotide with placebo in patients with stage III NSCLC treated with concurrent chemoradiotherapy (Stimulating Targeted Antigen Responses To NSCLC trial 2) started in March 2014. A phase III trial (Tecemotide liposome vaccine trial In Asian NSCLC Patients: Stimulating Immune REsponse [INSPIRE] with an almost identical design is being conducted in Asia.

TG4010 is a vaccine composed of the modified vaccinia virus Ankara containing the sequence for the MUC-1 antigen

and interleukin-2. In a phase II trial, two schedules of cisplatin plus vinorelbine and TG4010 were evaluated, including concurrent therapy upfront and TG4010 followed by the combination at progression.[317] Because only two of the initial 21 patients in the sequential arm achieved SD for more than 6 months, this strategy did not meet criteria by the two-stage Simon design for further evaluation. In the concurrent arm, 13 of 37 evaluable patients (35%) achieved PR, with a median OS of 12.7 months and 1-year OS of 53%. In the phase IIB trial, 148 patients with stage IIIB with malignant pleural effusion or stage IV NSCLC were randomized to cisplatin plus gemcitabine alone or in combination with TG4010.[318] The primary end point of the study of PFS at 6 months was met, with a significant prolongation in the vaccine arm compared with chemotherapy alone (43.2% versus 30%, $p = 0.01$). The experimental arm was also associated with increased in RR (41.9% versus 28.4%) and median OS (23.3 versus 12.5 months). A confirmatory phase IIB/III trial (TIME) started in January 2012 and allows a chemotherapy choice among multiple platinum-based doublets.

OPTIMAL TRIAL DESIGN IN THE ERA OF GENOMICS

Advancements in NGS technologies have resulted in a dramatic shift in the clinical trials paradigm such that cancer, once defined by many pathologically defined tumor types, is considered to be a disease of the genome consisting of copious small molecular subsets. This has motivated tailoring therapy with molecularly targeted agents and resulted in re-examination of clinical trials conduct in light of the rarity of certain genetic aberrations, the desire to bring new drugs to market more quickly, and financial resources. Here, we outline some current issues with the design of clinical trials with respect to the bench-to-bedside approach of drug development.

Early Drug Development

National and international efforts such as TCGA and the International Cancer Genomics Consortium have catalogued genetic aberrations of dozens of tumor types across thousands of candidate genes, resulting in massive public data sets and innumerable hypotheses for new therapeutic targets.[319–321] When paralleled by the advancement and reduction in costs for the associated technologies and the scientific successes of targeted agents such as imatinib and crizotinib in phase I trials, the number of phase I studies enrolling patients by molecular abnormality is increasing, as is the size of their expansion cohorts, even though there is little statistical design literature to support this approach.[12,321–327] The expansion cohort has gradually morphed from an opportunity to learn more about the safety of a novel agent to one in which efficacy data are becoming of increasing importance despite a general lacking of any expectation of statistical design for them. Often, the total sample size of the expansion cohort may exceed the sample size anticipated in the phase II setting, where one would otherwise formally test a prespecified hypothesis with clearly stated type I and type II error rates. The problem with not incorporating a trial design in this setting is that any expansion cohort may be deemed a success from being subjected to many subset analyses by histopathology, genetic mutation, and/or outcomes. Statistically, this type of "sampling to a foregone conclusion" will result in false-positive findings; as this practice becomes more common and omics-based tests are more likely to impact this setting, discussions about whether these cohorts truly serve the "phase I intent" should be revisited. Consideration of unambiguous rules for stopping and study success should also be given to expansion cohorts in light of the historically low RR on phase I trials and the goal of minimizing exposure to ineffective or toxic drugs.

Phase II and Phase III Studies

To prevent premature advancement of genomic tests for guiding treatment decisions, one of the significant recent advancements in the design of oncology clinical trials has been the development of a 30-point checklist to determine the readiness of omics-based tests for guiding patient care in clinical trials by the National Cancer Institute.[328] The criteria apply to any trial in which the investigational use of a laboratory test will impact therapy and cover a wide range of topics from establishing standards for sample collection to acquiring strong evidence in support of the test to feasibility, ethics, and legal issues. It is important to note that several of the checklist criteria also apply to studies of single biomarkers, or panels of biomarkers, measured by conventional methods as opposed to high-throughput methods.

Assuming that the criteria from the checklist described above are met, the next step is determining the optimal trial design for evaluation of a therapy in the phase II or phase III setting. This choice of design may vary depending on the situation, but the fundamental statistical principles for power and type I error rate considerations still apply for each phase of development. An enrichment design is appropriate when there is strong evidence that a molecularly targeted agent improves outcomes among patients diagnosed with a cancer harboring a particular biomarker; this type of trial enrolls only those patients who test positive for the marker of interest, and in this setting, the biomarker is referred to as a selection marker.[329,330] The efficiency of the enrichment design depends on proportion of patients with the marker of interest and the level of efficacy among patients without the marker of interest. The results obtained from these types of trials may not necessarily be generalizable to populations of patients with different tumor types characterized by the same marker.

If there is evidence that a therapy may benefit the marker-positive and marker-negative patients, one can use marker status as a stratification factor in a randomized trial to ensure that the treatment assignment is equal within marker subsets. If the goal is to demonstrate that a new agent has a dramatically different effect on outcome in one marker group than in another, then it would also be appropriate to power and test for a marker by treatment interaction—this is statistically the only way in which one may declare a candidate marker as "predictive." It is not appropriate to declare a marker as predictive simply by observing differential relative outcomes between the two groups of patients. If this latter situation is likely the case, then another design option may be powering the study for an overall treatment effect as well as for tests of efficacy within each of the marker subgroups. With this type

of design, treatment assignment depends on marker status, so it is critical that test results be returned within a reasonable timeframe so that randomization may take place, and the planned marker subgroup analyses should be specified in the protocol a priori. In the event that the marker analysis must be done retrospectively, for example, due to feasibility issues or issues with assay development, one may still be able to obtain meaningful results in favor of prediction.[331,332]

At this time, randomized designs remain the standard procedure and are being implemented to validate the clinical utility of a single biomarker, but implementation of these studies can be challenging for two reasons: first, the rarity of some tumors can dramatically hinder study accrual and make for longer study durations, and second, at this time, we often proceed with designing a study under the assumption that the molecularly targeted population is characterized by the same response to standard of care as the entire population when establishing a null hypothesis for the control group. The latter may not actually be the case, and in the event that a genetic aberration confers better outcomes than a design had planned, a randomized study may be underpowered to detect the improvement in outcome for which it was designed. To counter these concerns, nonrandomized designs may appropriate in some settings but come with the caveat that response or duration of response are really the only reliable efficacy end points and are generally more common in earlier phases of drug development, with confirmatory experience to follow after registration since drugs often look promising in preliminary studies and do not always translate to improvements in clinical outcomes.[333]

Predictive oncology has also spurred the research community to re-evaluate the target effect sizes incorporated in statistical designs. The bar is much higher now. The dramatic improvement in efficacy with drugs such as crizotinib and erlotinib in targeted populations has demonstrated that large effect sizes are possible, and that the relatively resource-intense approach of designing studies to detect small differences that may not be clinically meaningful does not parallel the goals of rapid discovery and efficiency of the cancer genome era.

Platform Studies

The era of genomics has also motivated the oncology community to re-examine the way that phase II and III studies are conducted such that "platform designs" are quickly becoming the new standard. These trials enroll thousands of patients to a single protocol for genomic screening and treatment assignment to a substudy based on the genetic characteristics of their disease. Examples of such efforts currently under development are the The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST), Southwest Oncology Group 1400 (LUNG-MAP), Molecular Profiling based Assignment of Cancer Therapeutics (M-PACT), and Molecular Analysis for Therapy Choice (MATCH) trials. Although each of these differs in terms of the statistical designs and end points used by each of the trials encapsulated by the overarching platform, it is believed that these now serve as the new model for trial conduct and will result in more rapid drug discovery and more definitive trials. These studies also have the advantage of profiling all the tumors in a standard manner in a single protocol, but come with some hurdles as well, such as securing drug supply across multiple sponsors and some uncertainty about the ability to accrue a sufficient number of patients with each aberration of interest.

Summary

Some research areas that are likely to further influence the design and conduct of clinical trials in the era of genomics include studies of intratumoral heterogeneity, epigenetics, mechanisms of resistance, and clonal evolution. Presumably more "trials of $n = 1$" will surface, but it is important to recall that "the pleural of anecdote is not data" and that, while playing a role in hypothesis generation, these types of experiences are not comparable with prospectively designed studies. Moving forward, many of the fundamental principles of trial design, such as adequately powering a study and controlling the false-positive rate, will remain even as our design change. With national and international collaborations that carefully consider all aspects of the research process, transformative clinical trials will continue to impact patient care.

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