NSCLC and reported an improvement in progression-free survival and overall survival in the erlotinib treatment group. Currently, maintenance pemetrexed or erlotinib following platinum-based chemotherapy in patients with advanced NSCLC are approved by the U.S. FDA. However, maintenance therapy is not without toxicity and, at this time, should be considered on an individual patient basis.

Targeted Therapies for Select Molecular Cohorts of NSCLC As the efficacy of traditional cytotoxic chemotherapeutic agents plateaued in NSCLC, there was a critical need to define novel therapeutic treatment strategies. These novel strategies have largely been based on the identification of somatic driver mutations within the tumor. These driver mutations occur in genes encoding signaling proteins that, when aberrant, drive initiation and maintenance of tumor cells. Importantly, driver mutations can serve as Achilles' heels for tumors, if their gene products can be targeted therapeutically with small-molecule inhibitors. For example, *EGFR* mutations have been detected in 10–15% of North American patients diagnosed with NSCLC. *EGFR* mutations are associated with younger age, light (<10 pack-year) and nonsmokers, and adenocarcinoma histology. Approximately 90% of these mutations are exon 19 deletions or exon 21 L858R point mutations within the EGFR TK domain, resulting in hyperactivation of both EGFR kinase activity and downstream signaling. Lung tumors that harbor activating mutations within the EGFR kinase domain display high sensitivity to small-molecule EGFR TKIs. Erlotinib and afatinib are FDA-approved oral small-molecule TKIs that inhibit EGFR. Outside the United States, gefitinib also is available. Several large, international, phase III studies have demonstrated improved response rates, progression-free survival, and overall survival in patients with *EGFR* mutation–positive NSCLC patients treated with an EGFR TKI as compared with standard first-line chemotherapy regimens **(Table 107-13)**.

Although response rates with EGFR TKI therapy are clearly superior in patients with lung tumors harboring activating EGFR kinase domain mutations, the EGFR TKI erlotinib is also FDA approved for second- and third-line therapy in patients with advanced NSCLC *irrespective* of tumor genotype. The reason for this apparent discrepancy is that erlotinib was initially evaluated in lung cancer *before* the discovery of *EGFR* activating mutations. In fact, *EGFR* mutations were initially identified in lung cancer by studying the tumors of patients who had dramatic responses to this agent. With the rapid pace of scientific discovery, additional driver mutations in lung cancer have been identified and targeted therapeutically with impressive clinical results. For example, chromosomal rearrangements involving the anaplastic lymphoma kinase (*ALK*) gene on chromosome 2 have been found in ~3–7% of NSCLC. The result of these *ALK* rearrangements is hyperactivation of the ALK TK domain. Similar to EGFR, *ALK* rearrangements are typically (but not exclusively) associated with younger age, light (<10 pack-year) and nonsmokers, and adenocarcinoma histology. Remarkably, *ALK* rearrangements were initially described in lung cancer in 2007, and by 2011, the first ALK inhibitor, crizotinib, received FDA approval for patients with lung tumors harboring *ALK* rearrangements.

In addition to *EGFR* and *ALK*, other driver mutations have been discovered with varying frequencies in NSCLC, including *KRAS*, *BRAF*, *PIK3CA*, *NRAS*, *AKT1*, *MET*, *MEK1* (*MAP2K1*), *ROS1*, and *RET*. Mutations within the *KRAS* GTPase are found in approximately 20% of lung adenocarcinomas. To date, however, no small-molecule inhibitors are available to specifically target mutant *KRAS*. Each of the other driver mutations occurs in less than 1–3% of lung adenocarcinomas. The great majority of the driver mutations are mutually exclusive, and there are ongoing clinical studies for their specific inhibitors. For example, the BRAF inhibitor vemurafenib and the RET inhibitor cabozantinib have already demonstrated efficacy in patients with lung cancer harboring *BRAF* mutations or *RET* gene fusions, respectively. Most of these mutations are present in adenocarcinoma; however, mutations that may be linked to future targeted therapies in squamous cell carcinomas are emerging. In addition, there are active research efforts aimed at defining novel targetable mutations in lung cancer as well as defining mechanisms of acquired resistance to small-molecule inhibitors used in the treatment of patients with NSCLC.

Second-Line Chemotherapy and Beyond Second-line therapy for advanced NSCLC was almost never recommended until a seminal study in 2000 showed that docetaxel improved survival compared to supportive care alone. As first-line chemotherapy regimens improve, a substantial number of patients will maintain a good performance status and a desire for further therapy when they develop recurrent disease. Currently, several agents are FDA approved for second-line use in NSCLC including docetaxel, pemetrexed, erlotinib (approved for second-line therapy regardless of tumor genotype), and crizotinib (for patients with *ALK* -mutant lung cancer only). Most of the survival benefit for any of these agents is realized in patients who maintain a good performance status.

Immunotherapy For more than 30 years, the investigation of vaccines and immunotherapies in lung cancer has yielded little in the way of meaningful benefit. Recently, however, this perception has changed based on preliminary results of studies using monoclonal antibodies that activate antitumor immunity through blockade of immune checkpoints. For example, ipilimumab, a monoclonal antibody directed at cytotoxic T lymphocyte antigen-4 (CTLA-4), was studied in combination with paclitaxel plus carboplatin in patients with both SCLC and NSCLC. There appeared to be a small but not statistically significant advantage to the combination when ipilimumab was instituted after several cycles of chemotherapy. A randomized phase III trial in SCLC is under way to validate these data. Antibodies to the T cell programmed cell death receptor 1 (PD-1), nivolumab and pembrolizumab, have been shown to produce responses in lung cancer, renal cell cancer, and melanoma. Many of these responses have had very long duration (i.e., >1 year). Monoclonal antibodies to the PD-1 ligand (anti-PDL-1), which may be expressed on the tumor cell, have also been shown to produce responses in patients with melanoma and lung cancer. Preliminary studies in melanoma suggest that the combination of ipilimumab and nivolumab could produce higher response rates compared to either agent alone. A similar strategy is being investigated in SCLC patients. Further evaluation of these agents in both NSCLC and SCLC is ongoing in combination with already approved chemotherapy and targeted agents.

Supportive Care No discussion of the treatment strategies for patients with advanced lung cancer would be complete without a mention of supportive care. Coincident with advances in chemotherapy and targeted therapy was a pivotal study that demonstrated that the early integration of palliative care with standard treatment strategies improved both quality of life and mood for patients with advanced lung cancer. Aggressive pain and symptom control is an important component for optimal treatment of these patients.

TABLE 107-13 RESULTS OF PHASE III TRIALS COMPARING CHEMOTHERAPY AND FIRST-LINE EGFR TKI IN *EGFR* MUTATION–POSITIVE PATIENTS

Study	Therapy	No. of Patients	ORR (%)	PFS (months)
IPASS	CbP	129	47	6.3
	Gefitinib	132	71	9.3
EURTAC	CG	87	15	5.2
	Erlotinib	86	58	9.7
OPTIMAL	CG	72	36	4.6
	Erlotinib	82	83	13.1
NEJOO2	CG	114	31	5.4
	Gefitinib	114	74	10.8
WJTOG3405	CD	89	31	6.3
	Gefitinib	88	62	9.2
LUX LUNG 3	CP	115	23	6.9
	Afatinib	230	56	11.1

Abbreviations: CbP, carboplatin and paclitaxel; CD, cisplatin and docetaxel; CG, cisplatin and gemcitabine; CP, cisplatin and paclitaxel; ORR, overall response rate; PFS, progression-free survival.