Title

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Journal

Clinical Advances in Hematology and Oncology, 11(10)

ISSN

1543-0790

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Publication Date

2013-10-01

Peer reviewed

Treatment Paradigms in Advanced Non–Small-Cell Lung Cancer

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Abstract: Lung cancer is the most common cause of cancer-related death worldwide, owing to its metastatic spread at the time of diagnosis. As a result, chemotherapy is the standard of care for the majority of patients. In recent years, the role of chemotherapy has expanded to include maintenance therapy and approved second- and third-line treatments. Nonetheless, traditional chemotherapy has modestly improved outcomes in patients with advanced non–small-cell lung cancer (NSCLC). Research efforts have been redirected toward the integration of molecularly-targeted agents into a treatment algorithm with unprecedented survival rates in selected patients. This article will provide an update on the multiple systemic regimens available to treat NSCLC, and discuss emerging molecular-based therapies.

Keywords
Non–small-cell lung cancer, molecularly targeted therapy, chemotherapy, maintenance therapy

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, contributing to an estimated 1.4 million deaths every year.[1] This high mortality rate results from the inability to detect lung cancer in its early stage. As a consequence, the majority of patients are diagnosed with advanced disease, for which no curative therapy exists. Platinum-based chemotherapy has been the mainstay of treatment for several decades, and has been shown to prolong survival, palliate symptoms, and enhance quality of life. However, the benefits of this treatment are short-lived. Over the past 2 decades, unprecedented advances in the treatment of metastatic non–small-cell lung cancer (NSCLC) have occurred. The successful alignment of our increased knowledge of the molecular biology of lung cancer with drug development has launched a new era of "precision medicine." Moreover, maintenance therapy and treatment beyond the first line are now common practice. This review summarizes recent advances in the treatment of NSCLC, provides a treatment algorithm, and discusses promising new therapies currently in development.

First-Line Therapies

Molecularly-Targeted Regimens

The first druggable molecular target in NSCLC was the epidermal growth factor receptor (EGFR). When ligands bind to this receptor, the intracellular pathway is activated, leading to cell growth, proliferation, and activation of additional signaling pathways.[2] Mutations in EGFR lead to constitutive activation of the receptor, resulting in uncontrolled cellular proliferation, tumor growth, and metastases.[3,4] The incidence of EGFR mutations varies by smoking status, ethnic background, and tumor histology.[5] By tumor histology, EGFR mutations occur in 30% of adenocarcinomas and in 7% of non-adenocarcinomas. Two mutations—deletions in exon 19 and L858R—are responsible for the majority of EGFR mutations in NSCLC, and confer sensitivity to EGFR-tyrosine kinase inhibitors (TKIs).[6]

The first trial to demonstrate a benefit for an EGFR-TKI in the frontline setting was IPASS (Iressa Pan-Asia Study). This landmark study compared carboplatin plus paclitaxel with gefitinib (Iressa, AstraZeneca) in patients with advanced NSCLC.[7] As shown in Table 1, a significantly longer progression-free survival (PFS) was observed in the subset of patients with EGFR-mutated tumors who received gefitinib (hazard ratio [HR], 0.48; *P*<.001) compared with patients who received chemotherapy. However, in patients with a wild-type EGFR tumor, PFS was longer in the chemotherapy arm (HR, 2.85; *P*<.001). These findings, along with the results of 4 other randomized clinical trials (Table 1), convincingly demonstrate the benefit of an EGFR-TKI as the treatment of choice for patients with EGFR-mutated tumors, with all studies showing significantly increased objective response rates (ORR) and prolonged PFS.[8-14] Overall survival (OS) was not improved, owing to crossover. In May 2013, erlotinib (Tarceva, Astellas Pharma Inc) and a companion EGFR diagnostic test were approved by the US Food and Drug Administration (FDA) for the first-line treatment of patients whose tumors harbor an EGFR mutation.

Afatinib (Gilotrif, Boehringer Ingelheim), a second-generation irreversible EGFR-TKI, has also shown benefit in the first-line setting. Two phase 3 trials comparing afatinib with a platinum doublet in patients with EGFR-mutated tumors produced results similar to those with first-generation EGFR-TKIs (Table 1).[15,16] The median PFS for the afatinib arms were 11.1 months (HR, 0.58; *P*<.001) and 11 months (HR, 0.28; *P*<.0001). Response rates significantly favored afatinib. Based on these data, afatinib was approved on July 12, 2013 for the first-line treatment of patients with advanced-stage lung cancer whose tumors harbor an EGFR exon 19 deletion or L858R mutation. To evaluate whether there is an optimal EGFR-TKI, a randomized trial comparing afatinib with erlotinib (LUX-LUNG 8) is ongoing.

A second molecular target in NSCLC is the gene rearrangement of the anaplastic lymphoma kinase (ALK) gene with the echinoderm microtubule-associated protein-like 4 (EML4-ALK) gene. The ALK fusion protein product leads to constitutive activation of multiple pathways responsible for growth, proliferation, and survival.[17] ALK fusion proteins are found in approximately 4% of all NSCLCs.[18-20] Clinically, the ALK rearrangement is associated with adenocarcinoma, a younger age at diagnosis, and a lack of smoking history.[17]

A phase 1 study of crizotinib (Xalkori, Pfizer), a small molecular ALK inhibitor, demonstrated an ORR of 61% and a median PFS of 9.7 months in 143 heavily pretreated patients with ALK-positive tumors.[21,22] Because of its therapeutic benefit, crizotinib was approved for the treatment of patients with ALK-positive tumors. Recently, the PROFILE 1007 (A Phase III Trial of Crizotinib Versus Standard of Care in Patients With Advanced Non–Small-Cell Lung Cancer With a Specific Alteration of the Anaplastic Lymphoma Kinase Gene) trial confirmed the therapeutic benefit of crizotinib over standard second-line chemotherapy with docetaxel or pemetrexed (Alimta, Eli Lilly; Table 1).[23] This study demonstrated a median PFS of 7.7 months in the crizotinib group compared with 3 months in the chemotherapy group (HR, 0.49; *P*<.001). Patients who received crizotinib had a 65% ORR, compared with 20% for patients who received chemotherapy (*P*<.0001). A preliminary survival analysis did not detect a difference in OS between the 2 groups.

Given the proven benefit of EGFR and ALK inhibitors, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend testing all patients with adenocarcinoma for EGFR mutations and ALK gene fusion.[24,25] To assist clinicians and pathologists in selecting patients for this therapy, a comprehensive molecular testing guideline was published.[26]

Chemotherapy Regimens

Despite recent advances in targeted therapies for subsets of patients with oncogene-driven lung adenocarcinomas, chemotherapy remains the standard of care for patients with advanced-stage NSCLC. Over the last 2 decades, combination chemotherapy options for lung cancer patients have increased. Paclitaxel, docetaxel, gemcitabine, and vinorelbine are all acceptable platinum partners in the first-line setting. In fact, no significant differences in PFS and OS were demonstrated among 4 commonly used regimens, with a median PFS of 3.6 months, an OS of 7.9 months, and a 1-year survival rate of 33% (Table 1).[27] Importantly, doublet regimens have demonstrated activity and tolerability in elderly patients and in patients with a poor performance.[28,29] Thus, more and more patients now have the opportunity to benefit from chemotherapy.

Since there are several options, choosing a regimen is predominantly based on toxicity profile and schedule of administration, in association with other patient factors.

One additional cytotoxic chemotherapeutic agent—pemetrexed—has shown a benefit in advanced lung cancer. Pemetrexed was originally approved as monotherapy in the second-line setting. Upon its evaluation with cisplatin in untreated patients, it was shown to improve OS and offer less toxicity.[30] In a preplanned analysis, a statistically significant treatment-by-histology interaction was demonstrated, wherein patients with non-squamous cell tumors who were treated with pemetrexed plus cisplatin achieved a median survival of 11.8 months, compared with 10.4 months for patients with squamous cell histology who were treated with the same regimen (HR, 0.81; *P*=.005; Table 1).[30] Histologic analyses of 2 additional randomized phase 3 trials confirmed the differential efficacy of pemetrexed for OS by histologic subtype.[31,32] Hence, a new treatment paradigm emerged for histology-based therapy of NSCLC with pemetrexed. To determine whether a histologic treatment effect existed with other platinum doublets, retrospective analyses of several large phase 3 trials were performed, but no interaction was observed.[33,34] The molecular mechanism responsible for this unique histologic benefit with pemetrexed is under investigation.

Attempts to add a third cytotoxic agent to a platinum doublet were unsuccessful, with trials showing increased toxicity without an increase in survival. The addition of a targeted agent to a platinum regimen has also been unsuccessful, with the exception of the addition of bevacizumab (Avastin, Genentech). The Eastern Cooperative Oncology Group (ECOG) 4599 trial randomized untreated patients with non-squamous histology to paclitaxel plus carboplatin or paclitaxel/carboplatin and bevacizumab followed by bevacizumab maintenance. Bevacizumab plus paclitaxel/carboplatin led to significant improvements in ORR (35% vs 15%; *P*<.001), median PFS (6.2 months vs 4.5 months; HR, 0.66; *P*<.001), and OS (12.3 months vs 10.3 months; HR, 0.79; *P*=.003).[35] These results have been confirmed in the phase 3 POINTBREAK (A Randomized, Open-Label, Phase 3, Superiority Study of Pemetrexed [Pem] + Carboplatin [Cb] + Bevacizumab [B] Followed by Maintenance Pem + B Versus Paclitaxel [Pac] + Cb + B Followed by Maintenance B in Patients With Stage IIIB or IV Non-Squamous Non-Small Cell Lung Cancer) study, as illustrated in Table 1.[36] This study randomized 900 patients with advanced non-squamous NSCLC to either 4 cycles of bevacizumab/pemetrexed/carboplatin induction followed by bevacizumab/pemetrexed maintenance or bevacizumab/paclitaxel/carboplatin induction followed by bevacizumab maintenance. However, with the exception of toxicity, the pemetrexed-containing regimen did not offer a therapeutic advantage. The primary endpoint of superiority regarding OS was not met. The arm containing pemetrexed had a slightly better median PFS at 6.0 months compared with 5.6 months in the carboplatin/paclitaxel/bevacizumab arm. Whether this level of improvement is clinically meaningful is questionable. Currently, paclitaxel/carboplatin plus bevacizumab followed by bevacizumab maintenance is the standard of care for bevacizumab-eligible patients (non-squamous histology, no history of hemoptysis, and no tumor cavitation).

Our European colleagues showed a survival improvement with a different 3-drug combination. The FLEX (First-Line Erbitux in Lung Cancer) study evaluated cetuximab (Erbitux, ImClone)—a monoclonal antibody to EGFR—plus vinorelbine/cisplatin followed by cetuximab maintenance versus vinorelbine/cisplatin. Cetuximab plus vinorelbine and cisplatin led to an increased ORR (39% vs 26%; *P*=.010) and a marginally significant improvement in OS compared with vinorelbine/cisplatin (11.3 months vs 10.1 months; HR, 0.87; *P*=.044; Table 1).[37] The PFS was identical in the 2 arms at 4.8 months. A confirmatory trial evaluating cetuximab in combination with paclitaxel and carboplatin vs paclitaxel/carboplatin is ongoing through the Southwest Oncology Group (SWOG). More than 1000 out of 1750 patients have been randomized.

Maintenance Therapies

Four to 6 cycles of combination therapy is generally sufficient to control metastatic disease by producing either an objective response or disease stabilization. Historically, a "watch and wait" approach was used with non-progressing patients. Over the past 5 years, data have emerged establishing a role for maintenance therapy in these patients. There are 2 approaches to maintenance chemotherapy: 1) continuation maintenance, in which one of the agents used during first-line treatment is continued, and 2) switch maintenance, in which a new agent is administered after a platinum doublet.

Two pivotal studies supporting the role for pemetrexed as maintenance therapy are described in Table 1.[31,38,39] The first study randomized non-progressing patients following treatment with standard non-pemetrexed doublets to pemetrexed or placebo. Patients with non-squamous cell lung cancer who received pemetrexed had a median PFS of 4.3 months vs 2.6 months (HR, 0.50; *P*<.0001) and a median OS of 13.4 months vs 10.6 months (HR, 0.79; *P*=.012) compared with patients who received a placebo.[31] These results led to the approval of pemetrexed as a maintenance agent in patients with non-squamous histology. As pemetrexed plus platinum became popular in the first-line setting for patients with non-squamous

Table 1. Selected Phase 3 Trials in Non–Small-Cell Lung Cancer

Trial	Treatment Regimen	N	Selection	Median PFS	HR (95% CI) *P*-Value	Median OS	HR (95% CI) *P*-Value
Selected Randomized Phase 3 Trials With Molecularly-Targeted Agents							
Mok, 2009[7] (IPASS)	Carboplatin/paclitaxel Gefitinib	129 132	EGFR+	6.3 m 9.5 m	0.48 (0.36-0.64) *P*<.001	21.9 m 21.6 m	1.0 (0.76-1.33) *P*=.99
Maemondo, 2010[8,9] (NEJ002)	Carboplatin/paclitaxel Gefitinib	110 114	EGFR+	5.4 m 10.8 m	0.30 (0.22-0.41) *P*<.001	26.6 m 27.7 m	0.887 (0.634-1.241) *P*=.48
Mitsudomi, 2010[10,11] (WJTOG3405)	Cisplatin/docetaxel Gefitinib	86 86	EGFR +	6.6 m 9.6 m	0.520 (0.378-0.715) *P*<.001	39 m 36 m	1.185 (0.767-1.829) *P*=.443
Zhou, 2011[12,13] (OPTIMAL)	Carboplatin/gemcitabine Erlotinib	72 82	EGFR+	4.6 m 13.1 m	0.16 (0.10-0.26) *P*<.0001	22.69 m 28.85 m	1.04 (0.69-1.58) *P*=.6915
Han, 2012[14] (First-SIGNAL)	Cisplatin/gemcitabine Gefitinib	150 159	Unselected	6.4 m 5.8 m	1.198 (0.944-1.520) *P*=.138	22.9 m 22.3 m	0.932 (0.716-1.213) *P*=.604
Sequist, 2013[15] (LUX-LUNG 3)	Cisplatin/pemetrexed Afatinib	115 230	EGFR+	6.9 m 11.1 m	0.58 (0.43-0.78) *P*<.001	Pending	Pending
Wu, 2013[16] (LUX-LUNG 6)	Cisplatin/gemcitabine Afatinib	122 242	EGFR+	5.6 m 11 m	0.28, (0.20-0.39) *P*<.0001	Pending	Pending
Shaw, 2013[23] (PROFILE 1007)	Pemetrexed or docetaxel Crizotinib	174 173	ALK+	3.0 m 7.7 m	0.49 (0.37-0.64) *P*<.001	22.8 m 20.3 m	1.02 (0.68-1.54) *P*=.54
Selected Randomized Phase 3 Trials With Cytotoxic Chemotherapy							
Schiller, 2002[27] (ECOG 1594)	Cisplatin/gemcitabine Cisplatin/docetaxel Carboplatin/paclitaxel Cisplatin/paclitaxel	288 289 290 288	Unselected	4.2 m* 3.7 m* 3.1 m* 3.4 m*	*P*=.001 *P*=NS *P*=NS	8.1 m 7.4 m 8.1 m 7.8 m	*P*=NS *P*=NS *P*=NS
Scagliotti, 2008[30]	Cisplatin/gemcitabine Cisplatin/pemetrexed	488 512	Non-squamous	4.7 m 5.3 m	0.90 (0.79-1.02) *P*=NS	10.4 m 11.8 m	0.81 (0.70-0.94) *P*=.005
Sandler, 2006[35] (ECOG 4599)	Carboplatin/paclitaxel Carboplatin/paclitaxel/bevacizumab	433 417	Non-squamous	4.5 m 6.2 m	0.66 (0.57-0.77) *P*<.001	10.3 m 12.3 m	0.79 (0.67-0.92) *P*=.003
Patel, 2013[36] (POINTBREAK)	Pemetrexed/carboplatin/bevacizumab→pemetrexed/bevacizumab Paclitaxel/carboplatin/bevacizumab→bevacizumab	292 298	Unselected	6.0 m 5.6 m	0.83 (0.71-0.96) *P*=.012	12.6 m 13.4 m	1.00 (0.86-1.16) *P*=.949
Pirker, 2009[37] (FLEX)	Cisplatin/vinorelbine + placebo Cisplatin/vinorelbine + cetuximab	568 557	EGFR+	4.8 m 4.8 m	0.943 (0.825-1.077) *P*=.39	10.1 m 11.3 m	0.871 (0.762-0.996) *P*=.044

Trial	Treatment Regimen	N	Selection	Median PFS	HR (95% CI) *P*-Value	Median OS	HR (95% CI) *P*-Value
Selected Maintenance Therapy Phase 3 Trials							
Ciuleanu, 2009[31] (JMEN)	Pemetrexed Placebo	441 222	Unselected	4.3 m 2.6 m	0.5 (0.42-0.61) *P*<.0001	13.4 m 10.6 m	0.79 (0.65-0.95) *P*=.012
Paz-Ares, 2012[38,39] (PARAMOUNT)	Cisplatin/ pemetrexed→pemetrexed Cisplatin/ pemetrexed→placebo	359 180	Non-squamous	4.1 m 2.8 m	0.62 (0.49-0.79) *P*<.0001	13.9 m 11.0 m	0.78 (0.64-0.96) *P*=.02
Cappuzzo, 2010[40] (SATURN)	Erlotinib Placebo	438 451	Unselected	12.3 wks 11.1 wks	0.71 (0.62-0.82) *P*<.0001	12.0 m 11.0 m	0.81 (0.70-0.95) *P*=.0088
Kabbinavar, 2010[41,42] (ATLAS)	Bevacizumab + erlotinib Bevacizumab + placebo	370 373	Unselected	4.8 m 3.7 m	0.722 (0.592-0.881) *P*=.0012	15.9 m 13.9 m	0.90 (0.74-1.09) *P*=.2686
Perol, 2012[43]	Cisplatin/gemcitabine→ erlotinib Cisplatin/gemcitabine→ placebo	155 155	Unselected	2.9 m 1.9 m	0.69 (0.54-0.88) *P*=.003	11.4 m 10.8 m	0.87 (0.68-1.13) *P*=.3043
	Cisplatin/gemcitabine →gemcitabine Cisplatin/gemcitabine →placebo	154 155	Unselected	3.8 m 1.9 m	0.56 (0.44-0.72) *P*<.001	12.1 m 10.8 m	0.89 (0.69-1.15) *P*=.3867
Barlesi, 2013[44] (AVAPERL)	Pemetrexed/cisplatin/ bevacizumab→pemetrexed/ bevacizumab Pemetrexed/cisplatin/ bevacizumab→bevacizumab	128 125	Non-squamous	7.4 m 3.7 m	0.48 (0.35-0.66) *P*<.001	NR 12.8 m	0.75 (0.47-1.19) *P*=.219
Selected Second- and Third-Line Phase 3 Trials							
Shepherd, 2000[45]	Docetaxel (75 mg/m^2) Docetaxel (100 mg/m^2) Best supportive care	55 49 100	Unselected	10.6 wk* 10.6 wk* 6.7 wk*	*P*=.037 *P*=.004	7.5 m 5.9 m 4.6 m	*P*=.01 *P*=.78
Fossella, 2000[46]	Docetaxel (75 mg/m^2) Docetaxel (100 mg/m^2) Vinorelbine/ifosfamide	125 125 123	Unselected	17%† 19%† 8%†	*P*=.031 *P*=.013	5.7 m 5.5 m 5.6 m	*P*=.025 *P*>.05
Scagliotti, 2009[32]	Pemetrexed Docetaxel	205 194	Non-squamous	3.1 m 3.0 m	0.82 (0.66-1.02) *P*=.076	9.3 m 8.0 m	0.78 (0.61-1.00) *P*=.048
Shepherd, 2005[48] (BR21)	Erlotinib Placebo	488 243	Unselected	2.2 m 1.8 m	0.61 (0.51-0.74) *P*<.001	6.7 m 4.7 m	0.7 (0.58-0.85) *P*<.001
Garassino, 2012[49] (TAILOR)	Erlotinib Docetaxel	109 110	EGFR Wild-type	2.4 m 3.4 m	0.69 (0.52-0.93) *P*=.014	Pending	Pending
Okano, 2010[50] (DELTA)	Erlotinib Docetaxel	109 90	EGFR Wild-type	1.3 m 2.9 m	1.452 (1.09-1.939) *P*=.01	9.0 m 10.1 m	0.98 (0.69-1.39) *P*=.907

ALK, anaplastic lymphoma kinase; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; m, months; wk, weeks; NR, not reached; NS, not significant; OS, overall survival; PFS, progression-free survival.

*Time to progression.

†Percent survival at 26 weeks.

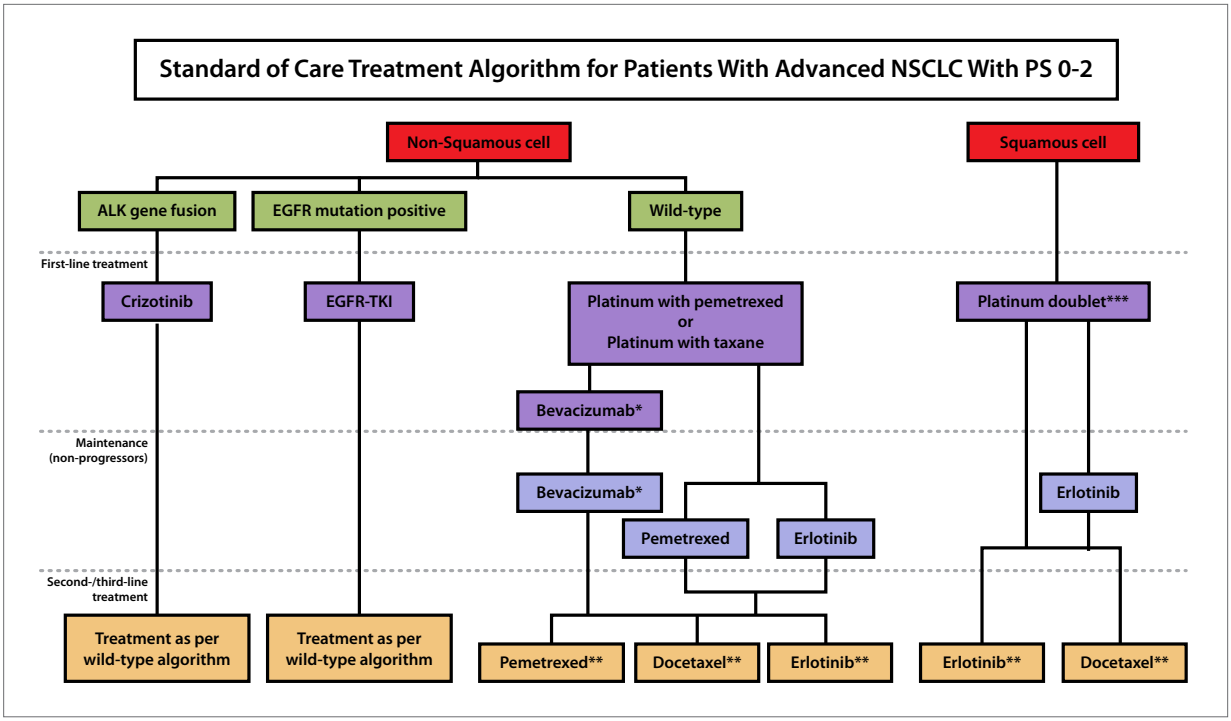

Figure. Proposed treatment algorithm for patients with advanced non–small-cell lung cancer who have a performance status score of 0 to 2.

*Bevacizumab is not recommended in patients with untreated brain metastases, clinically significant hemoptysis, or tumor cavitation.

**Treatment agent based on prior treatments, side effect profile, and patient preference.

***Common platinum partners include paclitaxel, docetaxel, nab-paclitaxel (Abraxane, Celgene), gemcitabine, or vinorelbine.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

tumors, the PARAMOUNT (Phase III Study of Maintenance Pemetrexed [Pem] Plus Best Supportive Care [BSC] Versus Placebo Plus BSC Immediately Following Induction Treatment With Pem Plus Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer [NSCLC]) trial evaluated maintenance pemetrexed vs placebo after pemetrexed/cisplatin. A highly significant survival advantage was demonstrated for pemetrexed maintenance over placebo, with a median PFS of 4.1 months vs 2.8 months (HR, 0.62; *P*<.0001) and a median OS of 13.9 months vs 11 months (HR, 0.78; *P*=.02), respectively.[38,39]

The SATURN (Sequential Tarceva in Unresectable NSCLC) trial evaluated maintenance therapy with erlotinib vs placebo after a first-line doublet regimen in patients with any non–small-cell histology. Erlotinib met its primary endpoint of prolonging PFS, with a median of 12.3 weeks vs 11.1 weeks for placebo (HR, 0.71; *P*<.0001); OS was significantly different between the arms at 12 months vs 11 months, respectively (HR, 0.81; *P*=.0088; Table 1).[40] In a subset of patients with an EGFR-mutated tumor, maintenance erlotinib showed a PFS HR of 0.10 (*P*<.001). These data supported the approval of erlotinib as a maintenance therapy. Erlotinib maintenance was added to bevacizumab in the ATLAS (A Study Comparing Bevacizumab Therapy With or Without Erlotinib for First-Line Treatment of Non-Small Cell Lung Cancer) trial. In this large phase 3 study, all patients received a platinum doublet plus bevacizumab. Non-progressing patients were then randomized to bevacizumab with erlotinib or placebo. The PFS (Table 1) was 4.8 months for erlotinib and 3.7 months for placebo (HR, 0.722; *P*=.0012).[41] A non-significant improvement in OS was observed for the erlotinib arm (15.9 months).[42]

In one study, French investigators evaluated both switch maintenance (gemcitabine plus cisplatin followed by erlotinib or observation) and continuation maintenance (gemcitabine plus cisplatin followed by gemcitabine or observation). Both maintenance therapies met the primary goal of prolonging PFS, as shown in Table 1.[43] The gemcitabine maintenance arm reported a median PFS of 3.8 months vs 1.9 months for the observation arm (HR, 0.56; *P*<.001), and the erlotinib maintenance arm recorded a median PFS of 2.9 months vs 1.9 months for the observation arm (HR, 0.69; *P*=.003). OS was longer in the maintenance arms, but this was not statistically significant.

Since both pemetrexed and bevacizumab are beneficial in the maintenance setting for patients with non-

Table 2. Known Mutations in Adenocarcinoma and Squamous Cell Carcinoma

Oncogenic Driver	Prevalence	Oncogenic Driver	Prevalence
Adenocarcinoma (N=733)		***Squamous Cell Carcinoma (N=178)***	
KRAS mutation	25%	CDKN2A deletion/mutation/methylation	72%
EGFR (sensitizing mutation)	15%	PIK3CA mutation	16%
ALK gene rearrangement	8%	PTEN mutation/deletion	15%
HER2 mutation	2%	FGFR1 amplification	15%
BRAF mutation	2%	PDGFRA amplification/mutation	9%
PIK3CA mutation	1%	CCND1 amplification	8%
MET amplification	1%	DDR2 mutation	4%
NRAS mutation	1%	BRAF mutation	4%
MEK mutation	<1%	ERBB2 amplification	4%
		FGFR2 mutation	3%

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PDGFRA, platelet-derived growth factor receptor alpha.

squamous histology, the AVAPERL (A Study of Avastin [Bevacizumab] With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous Non-Small Cell Lung Cancer) trial set out to evaluate the combination of bevacizumab plus pemetrexed maintenance. All patients received pemetrexed, cisplatin, and bevacizumab. Non-progressing patients were randomized to the doublet therapy or to bevacizumab alone. The study met its primary PFS endpoint, demonstrating superiority of the combination with a median PFS of 3.7 months for bevacizumab and 7.4 months for bevacizumab plus pemetrexed (HR, 0.48; *P*<.001). The median OS for the combination has not been reached and was 12.8 months for bevacizumab alone (HR, 0.75; *P*=.219; Table 1).[44] Importantly, there were no new safety signals with the combination. A similar observation was seen in the POINTBREAK study, in which patients who received the maintenance combination had a longer PFS and OS.[36] To definitively determine the role for maintenance pemetrexed plus bevacizumab, the ECOG 5508 trial is evaluating switch maintenance therapy with either bevacizumab or pemetrexed monotherapy with bevacizumab/pemetrexed in NSCLC patients after completion of 4 cycles of carboplatin/paclitaxel/bevacizumab.

In summary, there is convincing evidence for the routine use of maintenance therapy. However, the physician, together with the patient, should determine whether this is the most appropriate treatment. For some patients, a drug holiday is a reasonable option.

Second- and Third-Line Therapies

All patients will ultimately progress on or after first-line therapy and many patients will be eligible to receive additional treatment. In the United States, docetaxel and pemetrexed have been approved for second-line treatment and erlotinib is approved for second- or third-line treatment. As illustrated in Table 1, 2 phase 3 trials demonstrated a survival benefit with docetaxel in patients with ECOG performance status (PS) scores of 0 to 2 who had disease recurrence following first-line treatment. The first trial compared docetaxel with best supportive care (BSC). Docetaxel produced a median survival of 7 months, whereas BSC resulted in a median survival of 4.6 months (*P*=.047).[45] When docetaxel was compared with ifosfamide or vinorelbine, the PFS at 26 weeks was 17% with docetaxel vs 8% for ifosfamide or vinorelbine (*P*=.031). The 1-year survival rate was 32% vs 19%, respectively (*P*=.025).[46]

Pemetrexed was compared with docetaxel in patients with good PS (0-2) in a non-superiority trial design. Pemetrexed and docetaxel demonstrated no significant difference in OS, (8.3 months vs 7.9 months [HR, 0.99; *P*=.226]), respectively. The PFS and ORR were also equivalent between the 2 treatment arms. However, docetaxel was associated with more grade 3 and 4 toxicities.[47] A reanalysis of this trial revealed that patients with non-squamous histology responded better to pemetrexed than those with squamous histology. The OS was 9.3 months vs 8 months with pemetrexed and docetaxel, respectively (HR, 0.78; *P*=.048; Table 1).[32] Thus, pemetrexed is a second-line treatment option for recurrent, advanced NSCLC in patients with non-squamous histology.

The benefit of erlotinib in relapsed/refractory disease was shown in an unselected patient population in the BR21 trial by the National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG), which eventually led to the FDA approval of erlotinib in the third-line

treatment setting. This phase 3, double-blind, placebo-controlled trial sought to determine whether erlotinib would prolong OS over placebo. As described in Table 1, patients with a PS of 0 to 3 who were treated with erlotinib in the second- or third-line setting had an OS of 6.7 months compared with 4.7 months in the placebo arm (HR, 0.70; *P*<.001).[48] The RR and PFS were also statistically superior in the erlotinib group.

Most recently, the TAILOR (Erlotinib Versus Docetaxel as Second-Line Treatment of Patients With Advanced Non-Small-Cell Lung Cancer and Wild-Type EGFR Tumours) trial was conducted to determine whether docetaxel was superior to erlotinib in an EGFR wild-type patient population. Patients who received docetaxel had a significantly better median PFS (3.4 months vs 2.4 months; HR, 0.69; *P*=.014), RR (13.9% vs 2.2%; *P*=.004), and disease control rate (41.5% vs 22.8%; *P*=.007) compared with patients who received erlotinib (Table 1).[49] OS has not been reported. The DELTA (Docetaxel and Erlotinib Lung Cancer Trial) phase 3 study from Japan had a similar trial design but was looking for superiority of erlotinib over docetaxel. Surprisingly, the docetaxel arm showed a more favorable outcome. In patients with wild-type EGFR tumors, the median PFS was 2.9 months for docetaxel and 1.3 months for erlotinib (HR, 1.452; *P*=.010; Table 1).[50] OS was 10.1 months with docetaxel and 9 months with erlotinib, but the difference was not statistically different.

Among the agents approved for second-line treatment of advanced NSCLC, there appears to be no significant difference in OS; however, there are differences in toxicities.

Treatment Algorithm

With the multiple advances in the treatment of advanced-stage NSCLC, the following treatment algorithm (Figure) was devised to assist colleagues in selecting an appropriate therapy for a patient who is not eligible to participate in a clinical trial. Three important points to remember are: 1) All patients must have their tumor histologically subclassified. A diagnosis of NSCLC not otherwise specified is not acceptable today. 2) All patients with adenocarcinoma, regardless of their smoking status, should have their tumor tested for EGFR and ALK alterations. 3) Only patients with non-squamous cell histology are eligible to receive pemetrexed and/or bevacizumab.

Therapies: Future Directions

The unprecedented efficacy of EGFR-TKIs and crizotinib has firmly established a new treatment paradigm for lung cancer that is based on current understanding of the molecular biology of this disease. As a consequence, numerous promising drugs are being developed. These agents can be divided into 3 categories: 1) agents that target driver mutations, 2) agents that target crucial biological pathways, and 3) agents that target the tumor environment.

Given that the most successful drug development strategy targets driver mutations, an exhaustive search for additional druggable drivers is ongoing. Table 2 lists the known mutations for adenocarcinoma and for squamous cell carcinoma.[51,52] The Lung Cancer Mutational Consortium assayed 733 adenocarcinomas for 10 mutations that are targetable or potentially targetable using Clinical Laboratory Improvement Amendments-certified laboratories.[51] Of the tumors tested for all 10 genes, an oncogenic driver was detected in 64%. The ROS1 gene rearrangement was not evaluated in this panel, but it was reported to have a mutation prevalence of 1.4% in another study.[53] In squamous cell lung cancer, The Cancer Genome Atlas conducted a comprehensive genomic analysis of 178 tumors.[52,54] Sixty-four percent of the tumors had an alteration that was potentially targetable. Many agents developed to inhibit these specific targets are in early phases of clinical evaluation with promising results. For example, crizotinib is active in patients with tumors harboring a ROS1 gene rearrangement, with 8 of 14 patients (57%) demonstrating an ORR. Another phase 2 trial evaluating dabrafenib (a BRAF inhibitor) in 20 lung cancer patients with a BRAF V600E mutation showed a partial remission (PR) rate of 54%.[55,56]

Although EGFR-TKIs and crizotinib have revolutionized the treatment of lung cancer, all patients will develop resistance to these agents. Hence, strategies to understand the mechanisms of resistance that can be exploited for drug development are vigorously being pursued. Multiple mechanisms of resistance have been identified for both EGFR-TKIs and crizotinib.[57,58] One mechanism is the development of additional mutations. The T790M resistance mutation occurs in over 50% of tumors in patients who have progressed on EGFR-TKIs.[57] Several resistance mutations have also been reported in crizotinib failures.[58] As a consequence, second-generation TKIs have been developed to overcome and/or prevent resistance. Afatinib, in combination with cetuximab, has demonstrated impressive results in erlotinib failures. In a phase 1 trial involving 96 patients with resistance to EGFR-TKIs, 30% of patients achieved an ORR and 75% had disease control.[59] Patients with and without T790M tumors responded to treatment. Two confirmatory phase 3 trials are planned. One trial will evaluate the combination in the second-line setting to determine its role in overcoming EGFR-TKI resistance and the other trial will be conducted in the upfront setting to determine if the combination can prevent resistance. Second-generation

ALK inhibitors are showing similar efficacy. A potent ALK inhibitor, LDK378, produced a 73% PR rate in 64 crizotinib-resistant patients.[60] Thus, we can expect to see several second-generation TKIs developed with the goal of overcoming and preventing drug resistance.

Agents that target MET amplification and/or overexpression are in phase 3 testing. Research has shown that MET may be a driver of malignancy in a subset of wild-type EGFR tumors that overexpress MET. Support for this hypothesis stems from the favorable results evaluating MET inhibitors in erlotinib-naive patients. Treatment with erlotinib plus onartuzumab (MetMAb), a monoclonal antibody that binds to the extracellular domain of the MET receptor and prevents receptor activation, was compared with treatment with erlotinib and a placebo. In the combination arm, MET-positive patients had a clinically significant improvement in PFS (median, 3.0 months vs 1.5 months; HR, 0.47; *P*=.01) and OS (median, 12.6 months vs 4.6 months; HR, 0.37; *P*=.002).[61] A phase 3 trial of onartuzumab plus erlotinib vs placebo plus erlotinib in MET-expressing patients recently completed enrollment. A clinical benefit was seen for erlotinib plus the small molecule MET inhibitor tivantinib when compared with erlotinib alone in a phase 2 study, but the confirmatory phase 3 trial was discontinued owing to futility.[62] Of note, patients in these studies were not selected for MET expression. MET amplification has also been shown to be a resistance mechanism for EGFR-TKI therapy in patients with mutated tumors.[57] Thus, studies evaluating MET inhibitors alone and in combination with EGFR-TKIs as a strategy to overcome and prevent EGFR resistance have been implemented.

Enthusiasm has emerged for MEK inhibitors as a pathway approach to targeting tumors with KRAS mutations, the most frequently identified mutation in lung cancer. Many attempts to inhibit activated KRAS have been unsuccessful, leaving us searching for alternative strategies. MEK proteins are downstream of KRAS in the mitogen-activated protein kinase (MAPK) proliferation pathway. By blocking MEK, tumors that rely on this pathway—such as KRAS-mutated tumors—could potentially be shut down. A randomized phase 2 trial of selumetinib in combination with docetaxel vs single-agent docetaxel in 83 patients with KRAS-mutated tumors showed a PFS of 5.3 months vs 2.1 months, respectively (HR, 0.58; *P*=.0138). The ORR was impressive for the combination at 37% vs 0% for single-agent docetaxel (*P*<.0001). This combination is undergoing phase 3 evaluation to confirm its efficacy.[63]

A broader molecular approach to the treatment of NSCLC is also being explored. Heat-shock proteins protect numerous client oncoproteins from degradation. Inhibitors such as ganetespib prevent the binding of heat-shock proteins to their clients, which leads to client degradation. Recently, encouraging efficacy results for the combination of docetaxel plus ganetespib vs single-agent docetaxel in patients with adenocarcinoma histology were reported.[64] Prolonged PFS was observed in a large subset of patients diagnosed more than 6 months prior to enrollment with a median PFS of 5.4 months in the ganetespib combination arm vs 3.4 months (HR, 0.61; *P*=.041) for docetaxel alone. A randomized phase 3 trial in this subset of patients has been initiated.

A new treatment approach that targets the immune system has generated much excitement. Program death-1 (PD-1) protein is a co-T-cell regulatory receptor that mediates immunosuppression by binding to the PD-L1 ligand found on tumor cells and stromal cells. Preclinical data have demonstrated that inhibition of this receptor-ligand interaction leads to an enhanced T-cell response and increased tumor killing. In a phase 1 trial of nivolumab (a PD-1–blocking antibody) in heavily pretreated NSCLC patients, a 17% ORR was observed and the median OS was 9.6 months.[65,66] Similar efficacy has been noted with PD-L1 antibodies.[67] Randomized phase 3 trials are planned.

Conclusion

Lung cancer is a heterogeneous and genetically complex disease. Nonetheless, we have made significant treatment advances with the introduction of molecularly-targeted agents in selected patients, the optimization of chemotherapy based on histology, and the routine use of maintenance therapy. We are optimistic that a biologically-based approach to drug development will lead to more efficacious agents that, alone or in combination with established therapy, will result in more durable and prolonged survival times for patients.

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