TABLE 107-11 FIRST-LINE CHEMOTHERAPY TRIALS FOR METASTATIC NON-SMALL-CELL LUNG CANCER

Trial	Regimen	No. of Patients	RR (%)	Median Survival (months)
ECOG1594	Cisplatin + paclitaxel	288	21	7.8
	Cisplatin + gemcitabine	288	22	8.1
	Cisplatin + docetaxel	289	17	7.4
	Carboplatin + paclitaxel	290	17	8.1
TAX-326	Cisplatin + docetaxel	406	32	11.3
	Cisplatin + vinorelbine	394	25	10.1
	Carboplatin + docetaxel	404	24	9.4
EORTC	Cisplatin + paclitaxel	159	32	8.1
	Cisplatin + gemcitabine	160	37	8.9
	Paclitaxel + gemcitabine	161	28	6.7
ILCP	Cisplatin + gemcitabine	205	30	9.8
	Carboplatin + paclitaxel	204	32	9.9
	Cisplatin + vinorelbine	203	30	9.5
SWOG	Cisplatin + vinorelbine	202	28	8.0
	Carboplatin + paclitaxel	206	25	8.0
FACS	Cisplatin + irinotecan	145	31	13.9
	Carboplatin + paclitaxel	145	32	12.3
	Cisplatin + gemcitabine	146	30	14.0
	Cisplatin + vinorelbine	145	33	11.4
Scagliotti	Cisplatin + gemcitabine	863	28	10.3
	Cisplatin + pemetrexed	862	31	10.3
iPASS[a]	Carboplatin + paclitaxel	608	32	17.3
	Gefitinib	609	43%	18.6

[a]Enrolled selected patients: 18 years of age or older, had histologic or cytologically confirmed stage IIIB or IV non-small-cell lung cancer with histologic features of adenocarcinoma (including bronchioloalveolar carcinoma), were nonsmokers (defined as patients who had smoked <100 cigarettes in their lifetime) or former light smokers (those who had stopped smoking at least 15 years previously and had a total of ≤10 pack-years of smoking), and had had no previous chemotherapy or biologic or immunologic therapy.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; ILCP, Italian Lung Cancer Project; SWOG, Southwest Oncology Group; FACS, Follow-up After Colorectal Surgery; iPASS, Iressa Pan-Asian Study.

one of the targets of pemetrexed, between tumor types. Squamous cancers have a much higher expression of TS compared to adenocarcinomas, accounting for their lower responsiveness to pemetrexed. By contrast, the activity of gemcitabine is not impacted by the levels of TS. Bevacizumab, a monoclonal antibody against VEGF, has been shown to improve response rate, progression-free survival, and overall survival in patients with advanced disease when combined with chemotherapy (see below). However, bevacizumab cannot be given to patients with squamous cell histology NSCLC because of their tendency to experience serious hemorrhagic effects.

Agents That Inhibit Angiogenesis Bevacizumab, a monoclonal antibody directed against VEGF, was the first antiangiogenic agent approved for the treatment of patients with advanced NSCLC in the United States. This drug primarily acts by blocking the growth of new blood vessels, which are required for tumor viability. Two randomized phase III trials of chemotherapy with or without bevacizumab had conflicting results. The first trial, conducted in North America, compared carboplatin plus paclitaxel with or without bevacizumab in patients with recurrent or advanced nonsquamous NSCLC and reported a significant improvement in response rate, progression-free survival, and overall survival in patients treated with chemotherapy plus bevacizumab versus chemotherapy alone. Bevacizumab-treated patients had a significantly higher incidence of toxicities. The second trial, conducted in Europe, compared cisplatin/gemcitabine with or without bevacizumab in patients with recurrent or advanced nonsquamous NSCLC and reported a significant improvement in progression-free survival but no improvement in overall survival for bevacizumab-treated patients. A randomized phase III trial compared carboplatin/pemetrexed and bevacizumab to carboplatin/paclitaxel and bevacizumab as first-line therapy in patients with recurrent or advanced nonsquamous NSCLC and reported no significant difference in progression-free survival or overall survival between treatment groups. Therefore, currently carboplatin/paclitaxel and bevacizumab or carboplatin/pemetrexed and bevacizumab are appropriate regimens for first-line treatment for stage IV nonsquamous NSCLC patients. Of note, there are many small-molecule inhibitors of VEGFR; however, these VEGFR TKIs have not proven to be effective in the treatment of NSCLC.

Maintenance Therapy for Metastatic NSCLC Maintenance chemotherapy in nonprogressing patients (patients with a complete response, partial response, or stable disease) is a controversial topic in the treatment of NSCLC. Conceptually, there are two types of maintenance strategies: (1) switch maintenance therapy, where patients receive four to six cycles of platinum-based chemotherapy and are switched to an entirely different regimen; and (2) continuation maintenance therapy, where patients receive four to six cycles of platinum-based chemotherapy and then the platinum agent is discontinued but the agent it is paired with is continued **(Table 107-12)**. Two studies investigated switch maintenance single-agent chemotherapy with docetaxel or pemetrexed in nonprogressing patients following treatment with first-line platinum-based chemotherapy. Both trials randomized patients to immediate single-agent therapy versus observation and reported improvements in progression-free and overall survival. In both trials, a significant portion of patients in the observation arm did not receive therapy with the agent under investigation upon disease progression; 37% of study patients never received docetaxel in the docetaxel study and 81% of patients never received pemetrexed in the pemetrexed study. In the trial of maintenance docetaxel versus observation, survival was identical to the treatment group in the subset of patients who received docetaxel on progression, indicating this is an active agent in NSCLC. These data are not available for the pemetrexed study. Two additional trials evaluated switch maintenance therapy with erlotinib after platinum-based chemotherapy in patients with advanced

TABLE 107-12 MAINTENANCE THERAPY TRIALS

Group	CT	No. of Patients	Survival OS (months)	Survival PFS (months)
Switch Maintenance				
Fidias	Immediate docetaxel	153	12.3	5.7
	Delayed docetaxel	156	9.7	2.7
Ciuleanu	Pemetrexed	444	13.4	4.3
	BSC	222	10.6	2.6
Paramount	Pemetrexed	472	13.9	4.1
	BSC	297	11.0	2.8
ATLAS	Bev + erlotinib	384	15.9	4.8
	Bev + placebo	384	13.9	3.8
SATURN	Erlotinib	437	12.3	2.9
	Placebo	447	11.1	2.6
Continuation Maintenance				
ECOG4599	Bev 15 mg/kg	444	12.3	6.2
	BSC	434	10.3	4.5
AVAiL	Bev 15 mg/kg	351	13.4	6.5
	Bev 7.5 mg/kg	345	13.6	6.7
	Placebo	347	13.1	6.1
POINTBREAK	Pemetrexed + Bev 15 mg/kg			8.6
	Bev 15 mg/kg			6.9

Abbreviations: Bev, bevacizumab; BSC, best supportive care; CT, chemotherapy; OS, overall survival; PFS, progression-free survival.