Recent Advances in Lung Cancer

Summary of Presentations from the 45th Annual Meeting of the American Society of Clinical Oncology (2009)

Boone Goodgame, MD,† Thomas E. Stinchcombe, MD,‡ George Simon, MD, FACP, FCCP,§ Antoinette Wozniak, MD,‖ and Ramaswamy Govindan, MD*†*

Abstract: Over the past decade, gradual progress has been made in improving the outcomes of patients with lung cancer. This review summarizes the findings from selected studies presented at the recently concluded 45th annual meeting of the American Society of Clinical Oncology. This report will focus only on findings that are of immediate relevance to clinical practice. The topics discussed here range from the long-term safety of adjuvant chemotherapy and a new systemic chemotherapy regimen for locally advanced non-small cell lung cancer to the emerging issue of maintenance chemotherapy and the use of biomarkers in the treatment of patients with metastatic non-small cell lung cancer.

Key Words: NSCLC, Lung cancer, ASCO, Update.

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Lung cancer is a leading cause of cancer-related mortality globally. Over the past decade, a few notable advances have been made in the treatment of non-small cell lung cancer (NSCLC). Adjuvant chemotherapy improves survival in patients with resected stages II and III NSCLC. Inhibitors of epidermal growth factor receptor tyrosine kinase (EGFR TK) such as gefitinib and erlotinib produce striking responses in patients with activating mutations in the EGFR TK domain. Systemic chemotherapy continues to play an important role in the treatment of advanced NSCLC, however. This brief review summarizes the key presentations from the recently concluded 45th annual meeting of the American Society of Clinical Oncology (ASCO). Continued work in these areas presented at this meeting has improved our understanding of the role of EGFR TK inhibitors in the front line therapy for advanced NSCLC, provided reassuring data on the safety of adjuvant chemotherapy and have made us rethink about the current paradigm of administering chemotherapy only for a limited duration in the front line setting for patients with metastatic disease.

*Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; †Alvin J Siteman Cancer Center at Washington University School of Medicine, St Louis, Missouri; ‡Division of Medical Oncology, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina; §Department of Medical Oncology, Thoracic Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania; and ‖Division of Hematology/Oncology, Barbara Ann Karmanos Cancer Center, Detroit, Michigan.

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Address for correspondence: Ramaswamy Govindan, MD, Division of Medical Oncology, Washington University School of Medicine, 660 S. Euclid, Box 8056, St Louis, MO 63110. E-mail: rgovinda@im.wustl.edu

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RESECTABLE NSCLC

Administration of cisplatin-based chemotherapy improves overall survival (OS) in patients with resected stages II and III NSCLC.[1–3] Nevertheless, several questions remain with regard to use of adjuvant chemotherapy in this setting. How best to identify patients who are not likely to relapse, so that they can be spared of the toxicities of adjuvant therapy? Are there any molecular markers of predictors of response to platinum based therapy? Could there be any long-term consequences, especially given the fact that we have begun using adjuvant chemotherapy in NSCLC only recently? Finally, is there still a role for neoadjuvant chemotherapy and how does it fare against adjuvant chemotherapy. Some of these questions were addressed at this meeting.

At the annual meeting of ASCO last year, the investigators from International Adjuvant Lung Trial (IALT) presented a diminishing benefit from adjuvant chemotherapy over time [from a hazard ratio (HR) of 0.86 ($p = 0.03$) at 4.7 years to a HR of 0.91 ($p = 0.10$) at 7.5 years].[4] There was an unexpected increase in the mortality from nonlung cancer deaths in patients treated with chemotherapy in the IALT study. Naturally, these disturbing findings prompted the Canadian investigators to analyze the long-term follow-up data from the adjuvant study, JBR.10. This randomized phase III trial compared vinorelbine and cisplatin with observation in completely resected stages IB and II NSCLC. A total of 482 patients were randomized to chemotherapy or observation, and arms were well balanced for clinical and pathologic characteristics. At the time of the initial report in April 2004, there was an overall benefit with chemotherapy in the intent to treat population (HR = 0.69, $p = 0.009$) at a median

TABLE 1. Overall Survival Benefit in Adjuvant Chemotherapy Trials by Stage and Duration of Follow-Up

	IALT[4]		CALGB[40]		JBR.10[5]		ANITA[3]
Follow-up (yr)	4.7	7.5	4	6.2	5.2	9.3	6.3
Overall survival benefit by stage							
IB HR			0.62 ($p = 0.03$)	0.83 ($p = 0.12$)	0.94 ($p = 0.79$)	1.03 ($p = 0.87$)	1.14 (p = NS)
II HR	*0.86 ($p = 0.03$)	*0.91 ($p = 0.10$)			0.59 ($p < 0.01$)	0.68 ($p = 0.01$)	0.67 ($p < 0.05$)
IIIA HR							0.60 ($p < 0.05$)

Stage distribution by study: IALT: IA (10%), IB (27%), II (25%), and III (39%); CALGB: IB (100%); JBR.10: IB (45%), II (55%); and ANITA: IB (36%), II (24%), III (39%).
*Stage-specific outcomes not reported in IALT. Pooled results for all stages shown here.
IALT, International Adjuvant Lung Trial; CALGB, Cancer and Leukemia Group B, HR, hazard ratio.

follow-up time of 5.2 years. The survival benefit was seen only in patients with stage II disease (HR = 0.59, p = 0.004).[2] In the updated analysis at this meeting, now with a median follow-up time of 9.3 years, the survival advantage with chemotherapy remained clinically and statistically significant for the entire population (HR 0.78, p = 0.04) and more so in patients with stage II disease (HR = 0.68, p = 0.01).[5] Most importantly, unlike the IALT, there was no increase in nonlung cancer mortality in patients treated with adjuvant chemotherapy. Table 1 summarizes the available data with regard to the efficacy of adjuvant chemotherapy including changes in survival benefit over time. Although there are no clear explanations for the increased nonlung cancer deaths in patients treated with adjuvant therapy in the IALT study, the data from the JBR.10 are quite reassuring. The available data thus support a continued long-term survival benefit from adjuvant cisplatin based therapy at least as of now.

The role of preoperative chemotherapy in patients with resectable NSCLC has not been well defined. A meta-analysis of seven randomized controlled clinical trials of neoadjuvant chemotherapy versus surgery alone showed an improved survival with chemotherapy with a HR of 0.82 [95% confidence interval (CI); 0.69–0.97] somewhat comparable with the efficacy of chemotherapy reported in the adjuvant setting.[6] The Chemotherapy for Early Stages Trial study presented at ASCO 2008 showed a benefit from three cycles of neoadjuvant gemcitabine with cisplatin (HR = 0.63, 95% CI; 0.42–0.93).[7] At ASCO this year, the NATCH trial was presented, which randomized 624 patients with stages IA–IIIA clinically staged disease to surgery alone or three cycles of neoadjuvant or adjuvant carboplatin with paclitaxel.[8] The primary end point was disease-free survival (DFS). Half the patients enrolled in this study had pathologically confirmed stage I NSCLC. Chemotherapy delivery was superior in the neoadjuvant arm with 97% receiving treatment, when compared with only 66% in the adjuvant arm. There were no differences in DFS between the adjuvant and surgery alone arms, although there was a trend toward improvement in DFS in patients treated with neoadjuvant therapy (HR = 0.92, p = 0.176). This trend was stronger in patients with stage II or III disease (HR = 0.81, p = 0.07). Preliminary OS data showed no differences between the arms. The study results are difficult to interpret because of the large proportion of patients with stage I disease who are not known to benefit from systemic chemotherapy. These results, in our opinion, do not change the current practice of offering cisplatin based adjuvant therapy in patients with resected stages II and III NSCLC.

Because of the relatively modest benefit with adjuvant chemotherapy, identification of patients likely to respond to adjuvant chemotherapy would be of great benefit. A molecular analysis of a subset of patients enrolled in the IALT suggested that only those patients whose tumors had low expression of ERCC1 (a deoxyribonucleic acid repair enzyme) had a benefit with adjuvant treatment.[9] In the JBR.10 trial, patients whose tumors had K-ras mutations did not benefit from adjuvant chemotherapy.[2] This year, a second subset analysis of the IALT was presented evaluating the expression of another deoxyribonucleic acid repair protein, MutS homolog 2 (MSH2).[10] Of 1867 patients enrolled in the IALT study, 673 had evaluable tumors, of which 257 (38%) were considered MSH2 positive and 416 (62%) were MSH2 negative. There was a long-term survival benefit with chemotherapy in the MSH2 negative group (HR = 0.76, p = 0.03) but not in the MSH2 positive group (HR = 1.12, p = 0.48). MSH2 expression also had prognostic utility in patients assigned to observation only in which MSH2 expression was associated with a survival benefit (HR = 0.66, p = 0.01). The combined expression data for ERCC1 and MSH2 were available in 658 patients. The survival benefit associated with each marker was independent. It is conceivable that we will soon be able to select patients likely to respond to cytotoxic chemotherapy. Prospective validation of the markers such as ERCC1, MSH2, or K-Ras in the adjuvant setting is necessary before being considered for use in routine clinical practice.

LOCALLY ADVANCED NSCLC

The treatment of locally advanced NSCLC is evolving with regard to type and schedule of chemotherapy, integration of molecularly targeted agents, dose and schedule of radiation, and the role of surgery. The CALGB 30407 is a randomized phase II trial of carboplatin (area under the curve 5)and pemetrexed (500 mg/m^2) administered every 3 weeks for four cycles with or without cetuximab (400 mg/m^2 loading and 250 mg/m^2 weekly for 7 weeks) given concurrently with radiotherapy (70 Gy over 7 weeks) for patients with locally advanced NSCLC.[11] Pemetrexed was continued for four cycles after completion of the radiotherapy. All patients

had mandatory pretreatment Fludeoxyglucose-8 positron emission tomography. The primary end point was OS. It was determined that if either arm achieved a median OS of 20.9 months or greater, further exploration would be appropriate. The overall median survival for both arms of the trial was 22 months with a trend for better survival in the patients with nonsquamous histology (22 versus 18 months). Incidences of hematologic toxicity, esophagitis, and pneumonitis were consistent with expected toxicities for concurrent chemoradiation and were not significantly increased with the addition of cetuximab. Tissue was collected for biomarkers, but the results were not reported. It is reasonable to conclude that pemetrexed and carboplatin can be delivered safely in full systemic doses concurrent with radiotherapy with or without cetuximab. The median survival of 22 months is quite promising, though large phase III definitive studies should be done before considering this approach as a standard of care. The PROCLAIM trial is one such large global phase III study that will compare cisplatin and pemetrexed with cisplatin and etoposide given concurrently with thoracic radiotherapy in stage III unresectable disease. The role of cetuximab in the treatment of locally advanced NSCLC is being tested in the ongoing intergroup study led by the Radiation Therapy Oncology Group.

METASTATIC NSCLC

First-Line Therapy

The addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), and the addition of cetuximab, a monoclonal antibody against the EGFR, to standard platinum-based therapy has demonstrated a statistically significant improvement in progression-free survival (PFS) and/or OS in comparison with platinum-based therapy alone.[12–15] The safety of adding both cetuximab and bevacizumab to a platinum-based doublet therapy was investigated in a single arm phase II trial performed by the Southwest Oncology Group (SWOG).[16] The primary end point was defined by the frequency of grade 4 hemorrhagic toxicities, and secondary end points included response rate (RR), PFS, and OS. Patients with previously untreated nonsquamous NSCLC received carboplatin area under the curve of 6, paclitaxel (200 mg/m^2), cetuximab (400 mg/m^2 week 1 and 250 mg/m^2 weekly), and bevacizumab (15 mg/kg) every 3 weeks for up to six cycles, and then received cetuximab weekly and bevacizumab every 3 weeks until disease progression or unacceptable toxicity. Of the 110 patients enrolled, 104 were assessable. The trial met the primary end point with a rate of grade 4 hemorrhage of 2% (95% CI, 0–7%), and there were four treatment-related deaths [pulmonary hemorrhage ($n = 2$), infection ($n = 1$), and unknown ($n = 1$)]. With a median follow-up of 15 months, the PFS was 7 months (95% CI, 6–8), and OS was 14 months (95% CI, 11–20). The RR ($n = 95$) observed was 54% (95% CI, 43–64%). An exploratory analysis of biomarkers revealed that K-ras ($n = 32$) and EGFR mutation ($n = 33$) were not predictive of benefit. This combination should be considered investigational at the present time. A large phase III study is being conducted by SWOG to assess the efficacy of this novel regimen.

Maintenance Therapy ("Early Second Line Therapy")

Several trials presented at this meeting investigated the treatment paradigm of initiating an approved second-line agent immediately after completion of a defined number of cycles of first-line platinum-based therapy before disease progression.[17–19] Three studies individually explored the role of pemetrexed, erlotinib in patients treated with platinum-based doublet therapy and addition of erlotinib to bevacizumab in patients initially treated with a regimen containing bevacizumab.

The preliminary results of a phase III trial of pemetrexed plus best supportive care versus placebo plus best supportive care were presented last year,[20] and the final results were presented this year.[17] Patients were initially treated with four cycles of platinum-based therapy, and those without evidence of disease progression and a performance status (PS) of 0 or 1 were randomized to pemetrexed (500 mg/m^2) ($n = 441$) or placebo ($n = 222$) every 3 weeks until they have disease progression or unacceptable toxicities. The primary end point was PFS, and OS was a secondary end point. The final results in the overall study population revealed an improvement in PFS and OS with immediate pemetrexed in comparison with placebo (Table 2). Based on a previously observed interaction between pemetrexed and nonsquamous histology,[21,22] a subset analysis was performed for patients with nonsquamous ($n = 482$) and squamous histology ($n = 181$). Patients whose tumors had nonsquamous histology experienced a significantly superior PFS (HR = 0.47, 95% CI, 0.37–0.6, $p < 0.00001$; median PFS of 4.4 and 1.8 months, respectively) and OS (HR = 0.70, 95% CI, 0.56–0.88, $p = 0.002$; median OS of 15.5 and 10.3 months, respectively). In contrast, patients with squamous-type NSCLC did not experience an improvement in PFS (HR = 1.03, 95% CI, 0.77–1.5, $p = 0.896$, median PFS of 2.4 and 2.5 months, respectively) or OS (HR = 1.07, 95% CI, 0.49–0.73, $p = 0.678$, median OS of 9.9 and 10.8 months, respectively). The treatment-related grade 3/4 toxicities observed at statistically significant higher rate on the pemetrexed treatment arm were fatigue (5% versus 0.5%) and neutropenia (2.9% versus 0%). Nearly two thirds of patients assigned to placebo received subsequent therapy on disease progression (67%). Preliminary quality of life (QoL) data using the Lung Cancer Symptom Scale to estimate the time to worsening of symptoms was presented at the ASCO 2008 meeting, and HR for time to worsening of symptoms showed no significant difference but favored the pemetrexed treatment arm.[23] Based on the improvement in OS in this study, pemetrexed was approved on July 2, 2009, by the U.S. Food and Drug Administration for maintenance treatment of patients with locally advanced or metastatic nonsquamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.[24]

TABLE 2. Trials of Maintenance Therapy in Advanced NSCLC Presented at ASCO 2009

First Author	Comparison (*n*)	Hazard Ratio	
		PFS (95% CI)	OS (95% CI)
Belani et al.	Pemetrexed (441) and placebo (222)	0.60 (0.49–0.73), $p < 0.00001$	0.79 (0.65–0.95), $p = 0.012$
Subset	Nonsquamous (481)	0.47 (0.37–0.6), $p < 0.00001$	0.70 (0.56–0.88), $p = 0.002$
	Squamous (182)	1.03 (0.77–1.5), $p = 0.896$	1.07 (0.49–0.73), $p = 0.678$
Cappuzzo et al.	Erlotinib (438) and placebo (451)	0.71 (0.62–0.82), $p < 0.0001$	Not available
Subsets	Adenocarcinoma (401)	0.60 (0.48–0.75, $p < 0.0001$	Not available
	Squamous (359)	0.76 (0.60–0.95), $p = 0.0148$	Not available
	EGFR, wild type (388)	0.78 (0.63 to 0.96), $p = 0.0185$	Not available
	EGFR, mutation (49)	0.10 (0.04 to 0.25), $p < 0.0001$	Not available
	EGFR IHC (+) (681)	0.69 (0.58 to 0.82), $p < 0.0001$	Not available
Miller et al.	Bevacizumab + placebo (373) and bevacizumab + erlotinib (370)	0.722 (0.592 to 0.881), $p = 0.0012$	Not available

NSCLC, non-small cell lung cancer; CI, confidence interval; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry.

The trial by Cappuzzo et al.[19] investigated the impact of erlotinib in comparison with placebo in patients who had not experienced disease progression after four cycles of first-line platinum-based therapy. Patients were enrolled at the time of initiating chemotherapy ($n = 1949$), and 889 patients were randomized to erlotinib 150 mg daily ($n = 438$) or placebo ($n = 451$) until disease progression or unacceptable toxicity. The primary end point was PFS, and coprimary end point was PFS in patients whose tumors demonstrate increased EGFR expression using IHC. Patients were assessed for disease progression every 6 weeks from time of randomization. The PFS was significantly prolonged among patients who received erlotinib in comparison with patients who received placebo according to investigator assessment and confirmed by independent radiologic review (HR = 0.71, 95% CI, 0.62–0.82; $p < 0.0001$; median PFS of 12.3 and 11.1 weeks) and among patients with EGFR expression by IHC (HR = 0.69, 95% CI, 0.58–0.82; $p < 0.0001$). Patients with both adenocarcinoma and squamous carcinoma histology and whose tumors were EGFR wild type and with activating EGFR mutations experienced a significantly longer PFS in comparison with placebo. The rate of all grades adverse events were higher on the erlotinib arm in comparison with placebo including rash (60% versus 9%), and diarrhea (20% versus 2%), and the rate of grade 3/4 rash and diarrhea on the erlotinib arm was 9% and 2%, respectively. No deterioration of QoL as assessed by the Functional Assessment of Cancer Therapy-Lung was observed on the erlotinib or placebo arms.

The trial by Miller et al.[18] investigated the impact of the addition of erlotinib to bevacizumab in comparison with bevacizumab alone after initial treatment with platinum-based therapy in combination with bevacizumab. Patient with treated brain metastases were eligible, and patients were initially were required to have nonsquamous histology, but after the trial was initiated, it was amended to include patients with extrathoracic and peripheral squamous cell cancers. The primary end point was PFS, and this trial was closed after the data monitoring committee determined that the trial had met the primary end point after a planned interim efficacy analysis. The median follow-up is 8.3 months from randomization (range, 0–24.4 months). Patients who received bevacizumab and erlotinib experienced a superior PFS in comparison with patients who received bevacizumab alone (HR = 0.722, 95% CI, 0.592–0.881; $p = 0.0012$; median PFS 3.75 and 4.76 months, respectively) according to investigator assessment. The subset of patients with squamous histology ($n = 17$) is too small to make any assessment of the efficacy and safety of bevacizumab alone or in combination with erlotinib. The rate of grade 3/4 adverse events was higher of the bevacizumab and erlotinib arm in comparison with bevacizumab alone (44.1% versus 30.4%); the rate of grade 3/4 rash (10.4% versus 0.5%) and diarrhea (9.3% versus 0.8%) were higher on the erlotinib containing treatment arm. The percentage of patients who received subsequent therapy was similar among patients on the bevacizumab and placebo arm and bevacizumab and erlotinib arms, 55.5% and 50.3%, respectively. Approximately 40% of patients received erlotinib as subsequent therapy on both arms. Independent radiologic review is being conducted, and OS is expected to be available later in 2009.

In summary, these trials demonstrate that the earlier initiation of a second-line agent can improve the PFS, which was the primary end point for all three trials, and more patients will receive second-line therapy when initiated early. The trial by Belani et al. demonstrated an improvement in OS in the overall study population, but consistent with previous other studies, the benefit of pemetrexed was limited to the nonsquamous patient population. The OS is not available for the trials reported by Drs. Miller and Cappuzzo. The QoL assessment was equivalent on the two treatment arms in the trial reported by Dr. Cappuzzo, and updated QoL data is currently not available for the trial reported by Dr. Belani. The strategy of initiating second-line therapy before disease progression should be considered as a treatment option, but the decision to use these treatment strategies should be made on an individual patient basis depending on variety of clinical factors (i.e., PS, histology, tolerance of first-line therapy, and severity of disease-related symptoms) and patient's prefer-

ences. The cost implications for pursuing this approach (for all its modest benefits) have not been evaluated.

Second Line

Vandetanib is an oral agent that is a dual inhibitor of the VEGF and EGFR pathways. A randomized phase II trial in previously treated patients with NSCLC comparing docetaxel with vandetanib plus docetaxel showed an improvement in PFS favoring the combination.[25] These results prompted the ZODIAC trial, which is a double-blind phase III trial that randomized 1391 patients to receive docetaxel (75 mg/m^2 every 3 weeks) plus vandetanib (100 mg daily orally) or docetaxel and placebo for the second-line treatment of advanced NSCLC.[26] The primary end point was a 25% improvement in PFS for vandetanib and docetaxel. The RR and PFS were both statistically significant in favor of the vandetanib study arm. There was no difference in OS between the two arms. The toxicities were similar between the study arms except for rash, which was more prevalent among the vandetanib treated patients. Of note, there was no increase in the toxicities typically associated with anti-VEGF treatment (i.e., hemoptysis and thrombosis). A QoL analysis using the Functional Assessment of Cancer Therapy-Lung assessment tool indicated prolongation of the time to deterioration of symptoms for patients treated with vandetanib and docetaxel (HZ 0.77, $p < 0.001$). Another phase III trial of similar design, ZEAL, was also reported at this meeting.[27] Five hundred thirty-four patients were randomized to receive pemetrexed (500 mg/m^2 every 3 weeks) and vandetanib (100 mg daily orally) or placebo. The survival outcomes were very similar to those in the ZODIAC trial but were not statistically significant probably secondary to the smaller patient sample size on the ZEAL trial (Table 3). Biomarkers were done on tissue samples collected in the ZODIAC trial. Unfortunately, tissue was available on only 25% of the study population, and numbers were too small to make any definitive conclusions regarding the potential ability of these markers to predict benefit from treatment. Considering that both these trials show a very modest benefit in an unselected group of patients, it would be difficult to recommend routine use of vandetanib in combination with docetaxel or pemetrexed based on these data. It is of utmost importance to establish reliable, predictive biomarkers that will refine treatment selection for patients, so that the maximum therapeutic benefit with this agent can be realized. At the present time, vandetanib is not available commercially.

SMALL CELL LUNG CANCER

Little progress has been made in chemotherapy for small cell lung cancer (SCLC) over the past 20 years. Based on superior outcomes in the JCOG 9511 trial, irinotecan and cisplatin (IC) is now the standard of care in Japan.[28] Nevertheless, SWOG 0124, a study that compared the same regimen (PE versus IC) in the U.S. population found no differences in outcomes.[29] To explain these contrasting outcomes, the SWOG and the Japanese investigators directly compared the two studies at ASCO this year. The JCOG study contained fewer women (14% versus 43%) and fewer PS 0 patients (12% versus 32%) than the SWOG study. The JCOG study had more severe neutropenia and anemia in each arm compared with the SWOG study ($p < 0.001$). Response rates were also higher for each arm in Japanese when compared with U.S. patients ($p = 0.01$). OS was similar in the PE arms for both population but Japanese patients had significant improvements with IC, when compared with U.S. patients (12.8 versus 9.9 months; $p < 0.001$).[30] These findings suggest the possibility of significant inherited differences in the metabolism of irinotecan accounting for differing outcomes between the Japanese and SWOG study with irinotecan. A randomized study comparing carboplatin-etoposide with carboplatin-irinotecan in European patients with extensive stage SCLC presented at this meeting showed no differences in outcomes, though more hematologic toxicities with etoposide and more nonhematologic toxicities with irinotecan.[31]

For second-line treatment of SCLC, topotecan is approved in the United States, and amrubicin is standard of care in Japan. A randomized phase II study of these two agents in the U.S. population was presented, which showed significant improvements in RR with amrubicin (44% versus 11.5%, $p = 0.005$) compared with topotecan.[32] The PFS and OS were slightly improved with amrubicin, 9.3 versus 7.7 months and 4.6 versus 3.3 months, respectively, but these were not statistically significant. Amrubicin may have a role for second-line treatment of SCLC in Western population and is currently being evaluated in a phase III study.

MALIGNANT PLEURAL MESOTHELIOMA

Malignant pleural mesothelioma (MPM) remains largely an incurable disease. The role of resection for patients with localized disease remains controversial. A SEER study of the incidence and outcomes of surgically treated MPM presented at this meeting reported that of the 3300 new cases

TABLE 3. Results of ZODIAC and ZEAL Trials

TRIAL	ZODIAC		ZEAL	
Treatment	Docetaxel + Vandetanib (694)	Docetaxel + Placebo (697)	Pemetrexed + Vandetanib (256)	Pemetrexed + Placebo (278)
RR (%)	17[a]	10	19[a]	8
DC at 6 wk (%)	60	55	57[a]	46
PFS (mo)	4.0 (HR 0.79)[a]	3.2	4.0 (HR 0.86)	2.8
OS median (mo)	10.6 (HR 0.91)	10.0	10.5 (HR 0.86)	9.2
OS at 1-yr (%)	44.7	41.2	NR	NR

[a] $p < 0.05$.
RR, response rate; DC, disease control; PFS, progression free survival; OS, overall survival; HR, hazard ratio; ZODIAC and ZEAL trials; Refs 25 and 26.

each year in the United States only 11% of patients receive any type of definitive surgical resection.[33] The median OS of patients treated with surgery was only 13 months, with 5-year survival of 12%, when compared with 3% in patients treated nonoperatively. Surgery seems to only marginally improve the outcomes in patients with malignant mesothelioma. A second study was presented, which evaluated the feasibility of induction cisplatin-pemetrexed, given the efficacy of this regimen in the metastatic setting. Patients were treated with chemotherapy, extrapleural pneumonectomy, and postoperative radiotherapy. Of the 49 patients enrolled, seven (14%) had treatment-related mortality with an OS of 18.4 months.[34] The benefit associated with neoadjuvant therapy seems to be modest at best in mesothelioma.[35,36]

Tumors with elevated thymidylate synthase (TS) have been shown to be relatively resistant to pemetrexed in other malignancies. A study of TS levels in 50 patients with epithelial MPM was presented and showed that low-TS protein expression was associated with a longer progression free and OS (40 versus 16 months, $p = 0.01$) when treated with pemetrexed, but these findings need to be validated in large prospective studies.[37]

PREDICTIVE VALUE OF BIOMARKERS

The biomarker data from the recently reported iPASS trial were particularly instructive.[38] The iPASS study is a phase III randomized trial, conducted in Asia, which compared gefitinib with carboplatin and paclitaxel in patients with advanced NSCLC of the adenocarcinoma subtype who are never smokers or light smokers. The presence of an activating mutation in the EGFR TK inhibitor domain was the best predictor of response with 71.2% of mutation positive patients responding to gefitinib in comparison with 58.8% of the EGFR-FISH-positive patients and 51.5% of IHC-positive patients. In sharp contrast, only 1.1% of mutation negative patients responded to gefitinib. Mutation-positive patients treated with gefitinib also had improved PFS compared with mutation positive patients treated with chemotherapy (9.5 versus 6.3 months: HR = 0.48; $p < 0.0001$), whereas the reverse was true for mutation negative patients (1.5 versus 5.5 months; HR = 2.85; $p < 0.0001$). The PFS was also substantially better with gefitinib in mutation positive versus mutation negative patients (9.5 versus 1.5 months). There was also significant overlap among the three markers with 40.1% of patients being positive for all three biomarkers and 60, 62, and 74% of patients being positive for EGFR mutation, FISH and IHC, respectively. Of the patients who were FISH positive, 83.3% of the patients were also mutation positive. In FISH-positive patients, the HRs for PFS favored gefitinib if they were also mutation positive (0.48) and favored chemotherapy if they were mutation negative (3.85). This suggests that FISH-positive patients derive benefit from gefitinib only if they are also mutation positive, and therefore the mutation status emerges as the best predictor of improved response and PFS with gefitinib. Even though the OS favored gefitinib in mutation-positive patients (HR = 0.78; 95% CI 0.50–1.20) and favored chemotherapy in the mutation-negative patients (HR = 1.38; 95% CI 0.92–2.09), in both instances the HR crossed unity. This could be explained by the fact that there was significant cross over in both arms and with 39% of patients in each arm crossing over and receiving gefitinib if originally assigned to chemotherapy and vice versa.

The biomarker data from the FLEX trial were less definitive.[39] This was a phase III randomized trial that added cetuximab to cisplatin and vinorelbine in patients with advanced NSCLC who were also EGFR positive by IHC. There was a statistically significant improvement in OS in the cetuximab arm (11.3 versus 10.1 months; HR = 0.87, $p = 0.04$). K-ras mutational status and EGFR-FISH status were the biomarkers examined in this trial. Nineteen percent of the patients were K-ras positive, whereas 37% of the patients were EGFR-FISH positive. This contrasts with 62% of patients being EGFR-FISH positive in the select iPASS population of patients. The FISH status did not predict for improved response, PFS, or OS for treatment with cetuximab. Interestingly and contrary to the colon cancer experience, the presence of K-ras mutations was not a negative predictor for clinical benefit for cetuximab. Nevertheless, the number of patients with K-ras mutations who received cetuximab is small, and additional studies are needed before definitive conclusions can be derived. Corroborating previous observations, rash during the first cycle was a good predictor of response to cetuximab. For the 56% of the patients in the cetuximab arm who had any grade rash, the median OS was 15 months versus 10.3 months if there was no rash (HR = 0.631, $p < 0.001$). Therefore, it seems that rash may be the best predictor of clinical benefit with cetuximab rather than a molecularly based marker.

The biomarker data from ASCO 2009 strengthen the rationale for using EGFR TK mutation analyses to select patients likely to benefit from front line therapy with gefitinib (and presumably erlotinib). Clinical characteristics (including smoking status) alone are insufficient to guide therapy in the frontline setting. Unlike the experience with colon cancer, K-ras mutation status in lung cancer does not reliably identify patients likely to benefit from cetuximab.

SUMMARY

The issue of maintenance (or early second line) chemotherapy in advanced stage NSCLC has become a major topic for discussion and debate. It seems that the field is moving toward using EGFR TK mutation to identify patients who are likely to benefit from frontline gefitinib (or erlotinib) therapy. Pemetrexed-based chemotherapy regimen in combination with thoracic radiation seems feasible and is being studied in a large global phase III study. Finally, we are poised to use biomarkers to guide adjuvant therapy. Although there were no major breakthroughs in the treatment of lung cancer reported at this ASCO meeting, these studies collectively represent small steps of progress in the right direction.

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