Chemotherapy Effectiveness After First-Line Gefitinib Treatment for Advanced Lepidic Predominant Adenocarcinoma (Formerly Advanced Bronchioloalveolar Carcinoma)

Exploratory Analysis of the IFCT-0401 Trial

Michaël Duruisseaux, MD, Laurence Baudrin, MBsc,† Elisabeth Quoix, MD, PhD,‡ Marie Wislez, MD, PhD,*§ Denis Moro-Sibilot, MD, PhD,‖ Daniel Coëtmeur, MD,¶ Isabelle Monnet, MD,# Pierre Mourlanette, MD,** Jean-François Morère, MD, PhD,†† Jean-Charles Soria, MD, PhD,‡‡ Virginie Westeel, MD, PhD,§§ Franck Morin, MBsc,† and Jacques Cadranel, MD, PhD*†§*

Hypothesis: This study explored whether chemotherapy after first-line gefitinib was effective in patients with advanced lepidic predominant adenocarcinoma (LPA), formerly advanced bronchioloalveolar carcinoma, who were enrolled in the Intergroupe Francophone de Cancérologie Thoracique (IFCT)-0401 trial.

Methods: Overall, 88 patients presenting advanced LPA were enrolled in the IFCT-0401 trial, receiving gefitinib as first-line therapy. No predefined second-line treatment was mandatory in the case of progression or limiting toxicity under gefitinib. However, the carboplatin plus paclitaxel regimen was recommended for patients with a performance status (PS) 0 or 1 and gemcitabine monotherapy for those with a PS 2. For these patients, data concerning treatment efficacy was collected from the IFCT-0401 trial database.

Results: In total, 47 patients (53%) received second-line treatment after the failure of gefitinib, with 43 having PS 0 or 1. Regarding treatment, 43 were treated with chemotherapy, with 38 receiving a platinum-doublet regimen (taxane-based, n = 29; gemcitabine-based, n = 9) and five receiving monotherapy (gemcitabine, n = 3; pemetrexed, n = 2). The overall response rate (ORR) to chemotherapy was 21% (95% confidence interval [CI]: 10–36), disease control rate 56% (95% CI: 40–71), and median progression-free survival (PFS) 3.0 months (95% CI: 2.4–4.9). For patients receiving a platinum doublet (n = 38), ORR was 21% (95% CI: 10–37), with disease control rate being 55% (95% CI: 38–71), and median PFS 2.9 months (95% CI: 2.4–4.4). For patients receiving taxane-based regimen (n = 29) and gemcitabine-based regimen (n = 12), ORR was 28% and 0%, respectively, with a median PFS of 3.3 and 2.0 months, respectively, (p = 0.0243). The two patients receiving pemetrexed experienced a prolonged response. Multivariate Cox model analysis revealed that only the use of taxane-based chemotherapy or pemetrexed was related to PFS.

Conclusion: Platinum-doublet chemotherapy showed some effectiveness in treating advanced LPA patients after first-line gefitinib. Our findings also suggest that taxane-based chemotherapy and pemetrexed should be investigated further in future clinical trials.

Key Words: Non–small-cell lung cancer, Lung adenocarcinoma, Bronchioloalveolar carcinoma, Paclitaxel, Pemetrexed.

(*J Thorac Oncol.* 2012;7: 1423–1431)

*ER2 and GRC-04 Theranoscan, Faculté de Médecine Pierre et Marie Curie, Université Paris VI, Paris, France; †Intergroupe Francophone de Cancérologie Thoracique (IFCT), Paris, France; ‡Hôpitaux Universitaires, Université de Strasbourg, Intergroupe Francophone de Cancérologie Thoracique (IFCT), Strasbourg, France; §Service de Pneumologie et Réanimation, AP-HP Hôpital Tenon, Intergroupe Francophone de Cancérologie Thoracique (IFCT), Paris, France; ‖Service de Pneumologie, PMAC and CHU de Grenoble, Intergroupe Francophone de Cancérologie Thoracique (IFCT), Grenoble, France; ¶Service de Pneumologie, Centre Hospitalier Yves Le Foll, Intergroupe Francophone de Cancérologie Thoracique (IFCT), Saint-Brieuc, France; #Service de Pneumologie, Centre Hospitalier Intercommunal de Créteil, Intergroupe Francophone de Cancérologie Thoracique (IFCT), Creteil, France; **Clinique des Cèdres, Intergroupe Francophone de Cancérologie Thoracique (IFCT), Cornebarrieu, France; ††Service d'Oncologie Médicale, AP-HP Hôpital Avicenne, Université Paris XIII, Intergroupe Francophone de Cancérologie Thoracique (IFCT), Bobigny, France; ‡‡Département de Médecine, Institut Gustave Roussy, Faculté de Médecine Paris-Sud, Université Paris XI, Intergroupe Francophone de Cancérologie Thoracique (IFCT), Villejuif, France; §§Centre Hospitalier Universitaire de Besançon, Intergroupe Francophone de Cancérologie Thoracique (IFCT), Besançon, France.

Disclosure: Dr. Quoix received consulting fees or honoraria from Roche, Lilly, and AstraZeneca, in addition to travel grants from Lilly, AstraZeneca, Merck, and Roche. Dr. Westeel received consulting fees or honoraria for Roche and Lilly, in addition to travel grants from Lilly, AstraZeneca, and Roche. Laurence Baudrin received travel grants from Lilly, AstraZeneca, and Roche. Dr. Morin received travel grants from Lilly, AstraZeneca, and Roche. Dr. Cadranel received consulting fees or honoraria from AstraZeneca, Lilly, Roche, and, in addition to travel grants from Roche. All other authors declare no conflict of interest.

Address for Correspondence: Jacques Cadranel, MD, PhD, Service de Pneumologie, Hôpital Tenon, 4 rue de la Chine, F-75970, Paris, France. E-mail: jacques.cadranel@tnn.aphp.fr

ISSN: 1556-0864/12/0709-1423

Bronchioloalveolar carcinoma (BAC) is a rare histological subtype of lung adenocarcinoma (ADC), accounting for 3% to 4% of all non–small-cell lung cancers (NSCLC). The disease is defined in the 2004 revised classification of the World Health Organization (WHO) and International Association for the Study of Lung Cancer (IASLC) as an ADC proliferation arising from acinar and bronchiolar cells with no evidence of stromal, pleural, or vascular invasion.[1] Diagnosis can only be established after pathological tumor analysis excludes evidence of a histological invasion after complete surgical resection. This strict definition was substantiated by the 100% 5-year survival rate of less than 3 cm peripheral ADC, with pure BAC now termed adenocarcinoma in situ.[2] Former ADC with BAC features, being more frequent, has recently been termed invasive nonmucinous (NM) lepidic predominant ADC (LPA) along with its mucinous variant, as it displays several foci of invasion, but with predominant lepidic features.[3] Given the "lepidic" growth pattern and aerogenous propagation of these tumors, ipsilateral, and contralateral pulmonary recurrences, but with uncommon extrapulmonary metastases,[4] are frequently observed. This cancer type shares similar characteristics with adenocarcinoma in situ in terms of epidemiology (no gender bias; nonsmokers or mild smokers), clinical and radiological findings (better performance status [PS], less advanced diagnostic stage, ground-glass or alveolar pattern on computed tomography [CT] scan), and prognosis (more indolent course and better prognosis compared with other ADC subtypes).[5]

Historically, advanced LPA, formerly advanced BAC, was widely perceived as being chemoresistant, with older retrospective studies reporting conflicting results.[6–11] In the prospective Eastern Cooperative Oncology Group (ECOG) 1594 trial comparing four platinum-based chemotherapy regimens as first-line therapy in advanced NSCLC patients, LPA response rates to chemotherapy were lower than other NSCLC pathological subtypes (6% versus 20%).[6] As advanced LPA patients are frequently excluded from NSCLC trials, little is known about optimal treatment, thus justifying the initiation of specific trials.[12] There are only two nonrandomized phase II trials specifically focused on advanced LPA, studying the effectiveness of paclitaxel monotherapy.[13,14] However, the low response rates along with unacceptable toxicity observed in the Southwest Oncology Group (SWOG) 9714 trial using a 96-hour infusion regimen did not support the use of such a chemotherapeutic approach.[13] In addition, three phase II trials evaluated the use of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) as first-line or second-line treatment for patients with advanced LPA. Encouraging results involving control rates of 29% to 58% and overall survival of 13 to 17 months along with a favorable toxicity profile lent support to the EGFR-TKI approach (Table 1).[15–17] Recently, similar results were reported using anti-EGFR antibody monotherapy as first-line or second-line therapy in advanced LPA patients.[18]

Pathological classification distinguishes three histological subtypes: NM, mucinous (M), and mixed. This histological classification appears to be clinically relevant in terms of treatment efficacy, likely due to the distinctive molecular tumor profile.[19,20] NM tumors often exhibit *EGFR* mutations, with M tumors frequently presenting *K-Ras* mutations.[21–23] Importantly, the presence of the *EGFR* mutation is predictive of EGFR-TKI response, whereas the *K-Ras* mutation appears to be associated with EGFR-TKI resistance.[16,24] The Intergroupe Francophone de Cancérologie Thoracique (IFCT)-0401 trial showed that patients with NM tumors displayed significantly improved progression-free survival (PFS) with gefitinib, whereas patients with M tumors did not,[17] which is in line with the differing molecular profiles of these two histological subtypes.[24] Overall survival curves, however, did not diverge until 22 months, suggesting that chemotherapy given after gefitinib was effective in patients with M tumors as "salvage" therapy. Furthermore, radiological response to the 96-hour infusion of paclitaxel in the SWOG 9714 trial was observed in the M tumors (3 of 16) and not in the NM tumors (0 of 13).[13]

The aim of this study was to describe the characteristics of patients with advanced LPA who received a second- or third-line treatment after the failure of gefitinib as part of the IFCT-0401 trial. Furthermore, we explored the effectiveness of the different therapeutic regimens administered, with a special focus on chemotherapy.

TABLE 1. Results of Phase II Trials in Advanced Lepidic Predominant Adenocarcinoma, Formerly Advanced Bronchioloalveolar Carcinoma, in the First-Line and Second-Line Setting

Trial	No.	ORR (%)	DCR (%)	PFS in months (median)	OS in months (median)
EORTC 08956[14]; paclitaxel	19	11*	54	2	9
SWOG 9714[13]; paclitaxel	58	14	—	5	12*
Miller[16]; erlotinib	75	22*	60	4	17
SO126[15]; gefitinib	136	17	49	3.6	13.0*
IFCT-0401[17]; gefitinib	88	13	30*	2.9	13.2
ECOG-1504[18]; cetuximab	68	7*	42	3.3	13.0

*Trial primary endpoints

DCR, disease control rate; PFS, progression-free survival; OS, overall survival; EORTC, European Organisation for Research and Treatment of Cancer; SWOG, Southwest Oncology Group; IFCT, Intergroupe Francophone de Cancérologie Thoracique; ECOG, Eastern Cooperative Oncology Group.

MATERIALS AND METHODS

Summary of the IFCT-0401 Trial

The prospective multicentre phase II IFCT-0401 trial was conducted between April 2004 and July 2005 to evaluate gefitinib 250 mg daily as front-line therapy in treatment-naive patients with nonresectable advanced LPA, formerly advanced BAC.[17] Disease control rate (DCR) was the primary endpoint. Eligibility criteria were the following: histologically or cytologically proven advanced LPA from the outset or after recurrence; PS of 0, 1, 2, or 3; one or more pulmonary lesions evaluable on CT scan; fiberoptic bronchoscopy with macroscopically normal findings. A chest radiograph and CT scan of the chest, brain, and upper abdomen were performed before inclusion. Response rates and disease control were assessed with the same imaging methods employed for the baseline

tumor assessment and using the WHO criteria.[17] In total, 88 patients were enrolled, with none lost to follow-up. Written informed consent was obtained after providing comprehensive information about the investigational nature of the protocol. The protocol was approved by the local ethics committees and regulatory authorities.

Chemotherapy Effectiveness in Advanced LPA

Describing the effect of second-line and third-line chemotherapy was a secondary objective of the IFCT-0401 trial. No predefined second-line chemotherapy was mandatory in the case of progression or limiting toxicity under gefitinib. However, a carboplatin plus paclitaxel regimen was recommended for patients with PS 0 or 1 and gemcitabine monotherapy for those with PS 2.

Data taken from patients receiving second-and third-line treatment after the failure of gefitinib was collected from the IFCT-0401 trial database. The following data were collected for each line of treatment: PS at treatment initiation, date of first infusion, drugs used according to eight categories (cisplatin, carboplatin, paclitaxel, docetaxel, gemcitabine, vinorelbine, pemetrexed, and other), number of cycles, best response according to five categories (complete response, partial response, stable disease, progression, and nonevaluable), grade 3 and 4 treatment toxicity, and date and reason for treatment failure (progression, toxicity, death, and other).

Patients were followed up using clinical and CT evaluations every 3 months until death. Response was evaluated by CT scan and assessed by investigators according to the WHO criteria, as defined in the original IFCT-0401 protocol.[17] Disease control was defined as no radiological or clinical progression at the time of best response after a minimum of 6 weeks of treatment.

EGFR and *K-Ras* Mutation Analysis

Overall, 62 formalin-fixed and paraffin-embedded tumor samples were collected from the 88 patients enrolled in the IFCT-0401 trial, with 34 obtained by surgical exeresis and 28 either by CT-directed core needle biopsy or transbronchial biopsy. Briefly, for each sample, a 3-μm tissue section was stained with hematoxylin and eosin and examined by light microscopy to determine the presence of tumor cells. After DNA isolation (QIAamp DNA mini kit; Qiagen, Courtaboeuf, France) from three 20-μm tissue sections, *EGFR* 18–21 and *K-Ras* 2 exons were amplified and sequenced in both directions and analyzed using the SeqScape software, as previously described.[24]

Statistical Analysis

All eligible patients from the IFCT-0401 trial were enrolled. Characteristics of patients who did or did not receive second-line therapy were compared using the χ^2 or Fisher's exact test. Comparisons were also performed according to therapeutic regimens for patients receiving chemotherapy.

An analysis of efficacy was performed on the overall study population. Overall response rates (ORR) and DCR were given with their 95% exact confidence intervals (CI) and compared using Fisher's exact test. PFS was defined as the time from treatment initiation to disease progression diagnosed by CT scan or to all-cause death, and was assessed using the Kaplan–Meier method. Cox univariate analysis was undertaken to identify the covariables associated with the risk of progression or death in the second-line setting. The following variables were analyzed: sex (men versus women), age (≤70 years versus >70 years), PS (0–1 versus 2–3), smoking status (smoker versus nonsmoker), stage at diagnosis (I–IIIA versus IIIB–IV), respiratory symptoms score (<9 versus ≥9), DCR at 3 months using gefitinib (control versus noncontrol), *EGFR* and *K-Ras* mutational status (mutated versus wild type), and second-line treatment (pemetrexed versus taxane-based versus gemcitabine-based chemotherapy). Variables with p value less than 0.2 were included in a multivariate Cox's regression model and selected using a backward procedure. Two-sided p values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Characteristics of Patients Receiving Second-Line Treatment

In total, 47 of the 88 (53%) patients enrolled in the IFCT-0401 trial received second-line treatment after gefitinib failure. Table 2 compares the clinical and molecular characteristics of patients who did (n = 47) and did not receive second-line therapy (n = 41). Patients eligible for second-line treatment had a lower DCR at 3 months with the initial gefitinib therapy ($p = 0.005$). They were also younger ($p = 0.007$) and had a better PS ($p = 0.01$) at the IFCT-0401 trial inclusion. The frequency of *EGFR* and *K-Ras* mutations did not differ between the two groups.

Description of Treatment and Related Toxicity

Details of the drugs administrated as second- and third-line treatment and related toxicities are provided in Table 3. Dose and schedule regimens are presented in the Supplementary Tables (Supplemental Digital Content 1 and 2, http://links.lww.com/JTO/A315 and http://links.lww.com/JTO/A316). Regarding treatment, 43 patients were treated with chemotherapy as second-line treatment, with 38 receiving a platinum-doublet regimen (taxane-based, n = 29; gemcitabine-based, n = 9) and five receiving monotherapy (gemcitabine, n = 3; pemetrexed, n = 2). The clinical characteristics and *EGFR* and *K-Ras* mutational status of patients receiving taxane-based or gemcitabine-based chemotherapy were not different (Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/JTO/A315). The remaining four patients received a targeted therapy (bortezomib, n = 3; erlotinib, n = 1). Three cases of grade 3 or 4 toxicity resulted in treatment discontinuation. Two patients experienced a grade 3 sensory neuropathy under a taxane-based regimen, while one patient had a grade 4 febrile neutropenia under a gemcitabine-based regimen. In addition, 11 patients received pemetrexed monotherapy as second- line treatment (n = 2) or third-line treatment (n = 9), without any grade 3 or 4 limiting toxicity.

TABLE 2. Clinical and Biological Characteristics of Patients Who Did and Did Not Receive Second-Line Treatment After the Failure of Gefitinib

	No. of 2nd line treatments	2nd line treatment	
	n = 41	n = 47	
Characteristics	**n (%)**	**n (%)**	***p***
Sex			
Female	22 (54)	26 (55)	0.876
Male	19 (46)	21 (45)	
Age			
≤70 years	20 (49)	36 (77)	0.0068
>70 years	21 (51)	11 (23)	
Performance status			
0–1	29 (71)	43 (91)	0.0118
2–3	12 (29)	4 (8)	
Smoking			
Smoker	24 (59)	26 (55)	0.7612
Nonsmoker	17 (41)	21 (45)	
Stage at diagnosis			
Stage I–IIIA	5 (12)	10 (21)	0.2584
Stage IIIB–IV	36 (88)	37 (79)	
Histological subtype			
Nonmucinous	10 (24)	11 (23)	0.9732
Mucinous	18 (44)	20 (43)	
Unspecified	13 (32)	16 (34)	
RSS			
≤9	25 (61)	23 (49)	0.1913
>9	14 (33)	23 (49)	
MD	2 (6)	1 (2)	
EGFR status			
Mutated	4 (10)	3 (6)	0.6228
Wild type	22 (54)	27 (57)	
NA	3 (7)	3 (6)	
MD	12 (29)	14 (31)	
K-Ras status			
Mutated	5 (12)	4 (8)	0.4815
Wild type	17 (41)	24 (50)	
NA	7 (17)	5 (11)	
MD	12 (30)	14 (31)	
DCR at 3 mo with gefitinib			
No	21 (51)	39 (83)	0.0053
Yes	17 (42)	8 (17)	
MD	3 (7)	0 (0)	

p value investigated using χ^2 test or Fisher's exact test.RSS, respiratory symptoms score; MD, missing data; *EGFR*, epidermal growth factor receptor; NA, nonamplifiable; DCR, disease control rate.

Effectiveness of Second-Line and Third-Line Treatment

In the second-line setting, ORR with chemotherapy was 21% (9 of 43) (95% CI: 10–36), DCR 56% (95% CI: 40–71), and median PFS 3 months (95% CI: 2.4–4.9). For patients receiving a platinum doublet (n = 38), ORR was 21% (95% CI: 10–37), DCR 55% (95% CI: 38–71), and PFS 2.9 months (95% CI: 2.4-4.4). Data for the ORR, DCR, and PFS after second- line therapy and third-line therapy with taxane-based chemotherapy and gemcitabine-based chemotherapy or pemetrexed monotherapy is provided in Table 4.

TABLE 3. Description of Drugs Used as Second-Line and Third-Line Therapy After the Failure of Gefitinib and Related Grade 3 or 4 Toxicities

	Second-Line		Third-Line	
Drugs Used	**n (%)**	**Grade 3/4 Toxicity**	**n (%)**	**Grade 3/4 Toxicity**
Taxane-based chemotherapy	29 (62%)	2 (7%)	6 (19%)	2 (33%)
Carboplatin-paclitaxel	*24*	*2*	*2*	*0*
Carboplatin-docetaxel	*4*	*0*	*1*	*0*
Cisplatin-docetaxel	*1*	*0*	*0*	
Paclitaxel	*0*		*2*	*2*
Docetaxel	*0*		*1*	*0*
Gemcitabine-based chemotherapy	12 (26%)	1 (8%)	8 (26%)	3 (43%)
Carboplatin-gemcitabine	*3*	*1*	*2*	*1*
Cisplatin-gemcitabine	*6*	*0*	*2*	*1*
Gemcitabine	*3*	*0*	*4*	*1*
Pemetrexed	2 (4%)	0	9 (29%)	0
Others	4 (7%)	0	8 (26%)	0
Bortezomib	*3*	*0*	*0*	
Erlotinib	*1*	*0*	*7*	*0*
RAD 001	*0*		*1*	*0*

Univariate analysis revealed that achieving higher DCR at 3 months with gefitinib ($p = 0.04$) and using taxane-based chemotherapy ($p = 0.02$) or pemetrexed ($p = 0.02$) as second-line treatment were favorable prognostic factors for PFS (Table 5). Multivariate analysis confirmed that the type of second-line treatment was an independent prognostic factor. Kaplan–Meier curves for PFS according to the use of taxane- and gemcitabine-based chemotherapy are illustrated in Figure 1. A waterfall plot of PFS for each patient according to the third-generation drugs used for second- and third-line treatments is shown in Figure 2*A, B*, respectively. A waterfall plot of individual PFS values for each patient according to NM or M histological subtypes is illustrated in Figure 3. *EGFR* and *K-Ras* mutation status did not impact these results.

DISCUSSION

Little data is available concerning chemotherapy effectiveness in patients with advanced LPA. Only two noncontrolled phase II trials have examined this issue, with disappointing results obtained with the two different schedules of paclitaxel monotherapy. In the European Organisation for Research and Treatment of Cancer (EORTC) 08956 trial,[14] 200 mg/m^2 of paclitaxel administered every 3 weeks was shown to be well tolerated, but with an ORR of 11%, leading to trial discontinuation. In the SWOG 9714 trial, the observed 14% ORR and 5-month median PFS appeared encouraging,[13] but the 96-hour infusion schedules of paclitaxel were highly toxic, resulting in six treatment-related deaths. Consequently, this treatment

TABLE 4. Progression-Free Survival, Overall Response Rate, and Disease Response Rate of Second-Line and Third-Line Therapies After Gefitinib Treatment According to the Chemotherapy Regimen

Line	Taxane-Based Chemotherapy	Gemcitabine-Based Chemotherapy	Pemetrexed	Total	*p*
Second-Line	n = 29	n = 12	n = 2	n = 43	
PFS, mo, (95% CI)	3.3 (2.6–5.7)	2.0 (1.4–2.7)	10 and 32	3.0 (2.4–4.9)	0.0072
ORR, n, % (95% CI)	8, 28% (13–47)	0	1 (NA)	9, 21% (10–36)	0.0734
DCR, n, % (95% CI)	18, 62% (44–80)	4, 33% (10–65)	2 (NA)	24, 56% (40–71)	0.1265
Third-line	n = 6	n = 8	n = 9	n = 22	
PFS, mo, (95% CI)	3.4 (NA)	2.2 (NA)	5.7 (NA)	2.9 (2.4–4.9)	<0.0001
ORR, n, % (95% CI)	2 (NA)	1 (NA)	4 (NA)	7, 30% (13–53)	0.4490
DCR, n, % (95% CI)	4 (NA)	3 (NA)	7 (NA)	14, 61% (39–80)	0.2749

PFS, progression-free survival; DCR, disease control rate; CI, confidence interval; NA, non applicable.

TABLE 5. Univariate and Multivariate Analyses of Progression-Free Survival When Using Second-Line Chemotherapy

Variable	No. of Patients	Univariate Hazard Ratio (95% CI)	*p*	Multivariate Hazard Ratio (95% CI)	*p*
Sex					
Male	18	0.52 (0.27–1.01)	0.0549		
Female	25	1			
Age					
>70 yr	11	0.60 (0.29–1.23)	0.1662		
≤70 yr	32	1			
RSS					
<9	19	0.69 (0.37–1.29)	0.2440		
≥9	23	1			
Stage at diagnosis					
I–IIIA	7	1.00 (0.44–2.29)	0.9968		
IIIB–IV	36				
DCR at 3 mo with gefitinib					
Yes	6	0.37 (0.14–0.95)	0.0382		
No	37	1			
EGFR status					
Mutated	3	0.58 (0.17–1.98)	0.3879		
Wild type	24	1			
K-Ras status					
Mutated	22	0.47 (0.13–1.67)	0.2409		
Wild Type	3	1			
Performance status					
2	4	0.66 (0.23–1.86)	0.4267		
0–1	39	1			
Treatment used in second line					
Pemetrexed	2	0.08 (0.01–0.63)	0.0165	0.08 (0.01–0.63)	0.0165
Taxan-based chemotherapy	29	0.44 (0.21–0.90)	0.0249	0.44 (0.21–0.90)	0.0249
Gemcitabine-based chemotherapy	12	1			

option should not be considered for routine use. There is no available data regarding the efficacy of platinum-based or other chemotherapeutic regimens in patients with advanced LPA after first-line EGFR TKI.

In the IFCT-0401 trial, 53% of patients were eligible for second-line therapy. Our results suggest that platinum-based doublet regimens were well tolerated and effective after front-line gefitinib therapy in advanced LPA. In the second-line setting, platinum-based doublets were administrated to 38 out of 47 patients (81%) and had a good safety profile, with only three cases of treatment discontinuation observed due to grade 3 or 4 toxicity (Table 3). Platinum-based doublets exhibited favorable efficacy results, with an ORR of 21%, DCR of 55 %, and median PFS of 2.9 months (range, 0.7–17.1 months).

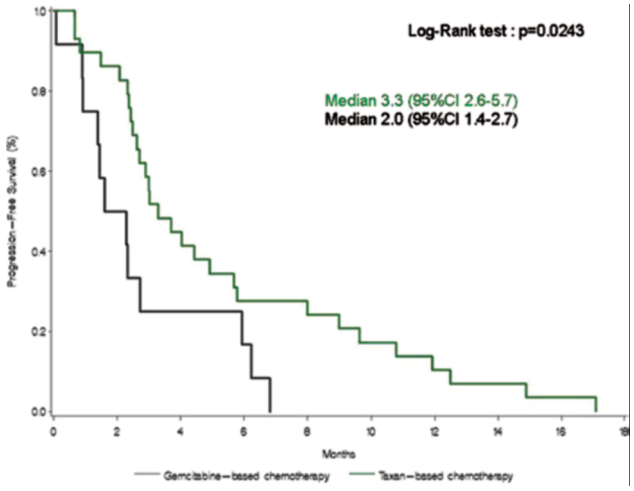

FIGURE 1. Curve for progression-free survival using gemcitabine-based chemotherapy (black line) or taxane-based chemotherapy (green line) as second-line treatment. CI, confidence interval.

Taxane-based (paclitaxel n = 24 and docetaxel n = 5) and gemcitabine-based (n = 12) chemotherapy were the most common regimens used in the second-line setting. However, treatment efficacy appeared to be associated with the type of platinum-based doublet or monotherapy used. The ORR, DCR, and PFS were in favor of taxane- rather than gemcitabine-based chemotherapy (ORR 28% versus 0%, $p = 0.04$; DCR 62% versus 33%, $p = 0.09$; PFS 3.3 versus 2.0 months, $p = 0.02$) (Table 4; Figs. 1 and 2). Second-line pemetrexed monotherapy was administered to two patients, demonstrating notable prolonged responses of 10 and 32 months. In multivariate analyses, the use of taxane-based chemotherapy (n = 29) or pemetrexed (n = 2) was associated with a better PFS in the second-line setting. However, caution is needed when interpreting PFS, ORR, and DCR because of our retrospective study design and the absence of a central review of radiological responses. In addition, given the small number of patients, our study lacked statistical power.

The molecular rationale behind the lack of gemcitabine efficacy in advanced LPA patients is still unclear. Gemcitabine acts by blocking DNA strand elongation through inhibition of the intracellular ribonucleoside-diphosphate reductase large subunit target encoded by the RRM1 gene. High levels of RRM1 expression were proposed to be predictors of low response rates to gemcitabine in several NSCLC clinical studies.[25,26] However, differential RRM1 expression types in various histological NSCLC subsets, especially in LPA, were never demonstrated. In contrast, in the IFCT-0401 population, second-line taxane-based chemotherapy was associated with promising ORR (28%) contrary to the ORR observed with first-line paclitaxel monotherapy in the EORTC 08956[14] and SWOG 9714[13] trials (11% and 14%, respectively). High levels of βIII-tubulin isoform expression, which is targeted by tubulin-binding agents, such as taxanes, may be predictive of poor responses to taxane- and platinum-based agents in advanced NSCLC.[26,27] As the βIII-tubulin isoform expression is unknown with regards to LPA, LPA sensitivity to taxane-based regimens need to be further explored.

The efficacy profile of the multitargeted antifolate pemetrexed may be accounted for by the following rationale. Firstly, its efficacy profile tends to be better than that achieved with gemcitabine-based chemotherapy (Table 5; Fig. 2). Furthermore, pemetrexed efficacy appeared to be preserved when given as third-line therapy (Table 5; Fig. 2) or even fourth-line therapy (data not shown) in patients previously treated with EGFR-TKI and gemcitabine-based or taxane-based regimens. As previously reported,[28] two patients experienced successive responses after resuming pemetrexed therapy. This observation suggests that a subset of tumors were highly sensitive to pemetrexed without developing secondary resistance after exposure to pemetrexed. However, the molecular determinants of its efficacy are still unknown.[29] In a large phase III trial comparing cisplatin/pemetrexed with cisplatin/gemcitabine combinations as front-line treatment of advanced NSCLC, a significant survival difference was shown in the histological ADC subgroup when using the cisplatin/pemetrexed regimen.[30] A lower expression of thymidilate synthase (TS) in ADC versus squamous cell carcinoma may explain this survival difference.[31,32] Nevertheless, no data is available regarding TS expression in advanced LPA patients. In a preclinical trial, an overexpression of FR-α, a folate receptor with high affinity for pemetrexed, was suggested to be present in LPA tumors as compared with mesothelioma and non-LPA lung ADC.[33] In a recent case report, Garfield et al. described a dramatic response to pemetrexed after the rapid failure of the carboplatin and paclitaxel regimen in a patient with a M histological subtype presenting FR-α overexpression (approximately 30% of tumor cells with 3+ intensity).[34]

In our study, NM and M histological subtypes were not found to be strong predictors of PFS (Fig. 3), response, or DCR after chemotherapy (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JTO/A316). When considering second- and third-line therapy, an objective response was observed in six of 14 NM tumors (43%) and eight of 29 M tumors (27%). The ORR was 31% (5 of 16) and DCR 56% (9 of 16) in patients with M tumors being treated with taxane-based regimens. As suggested in the SWOG 9714 trial, taxanes proved effective in the M subtype. Finally, *EGFR* and *K-Ras* mutation status did not impact on chemotherapy efficacy.

The observation and hypothesis that taxane-based regimens and pemetrexed allowed for disease control in cases of rapid EGFR-TKI failure were specifically addressed in the IFCT-0504 trial.[35] In this trial, advanced LPA patients were randomly assigned to receive either erlotinib or carboplatin and weekly paclitaxel as front-line therapy, with a crossover treatment being administered at 1 month in the case of disease progression and pemetrexed being given as third-line treatment after crossover treatment failure. Essential information is likely to arise from ongoing trials regarding the predictive role of NM or M histological subtypes, *EGFR* and *K-Ras* mutational statuses, and biological factors, such as PAS-diastase resistance staining, βIII-tubulin, expression of mutator gene homologue 2, and TS by immunohistochemistry.

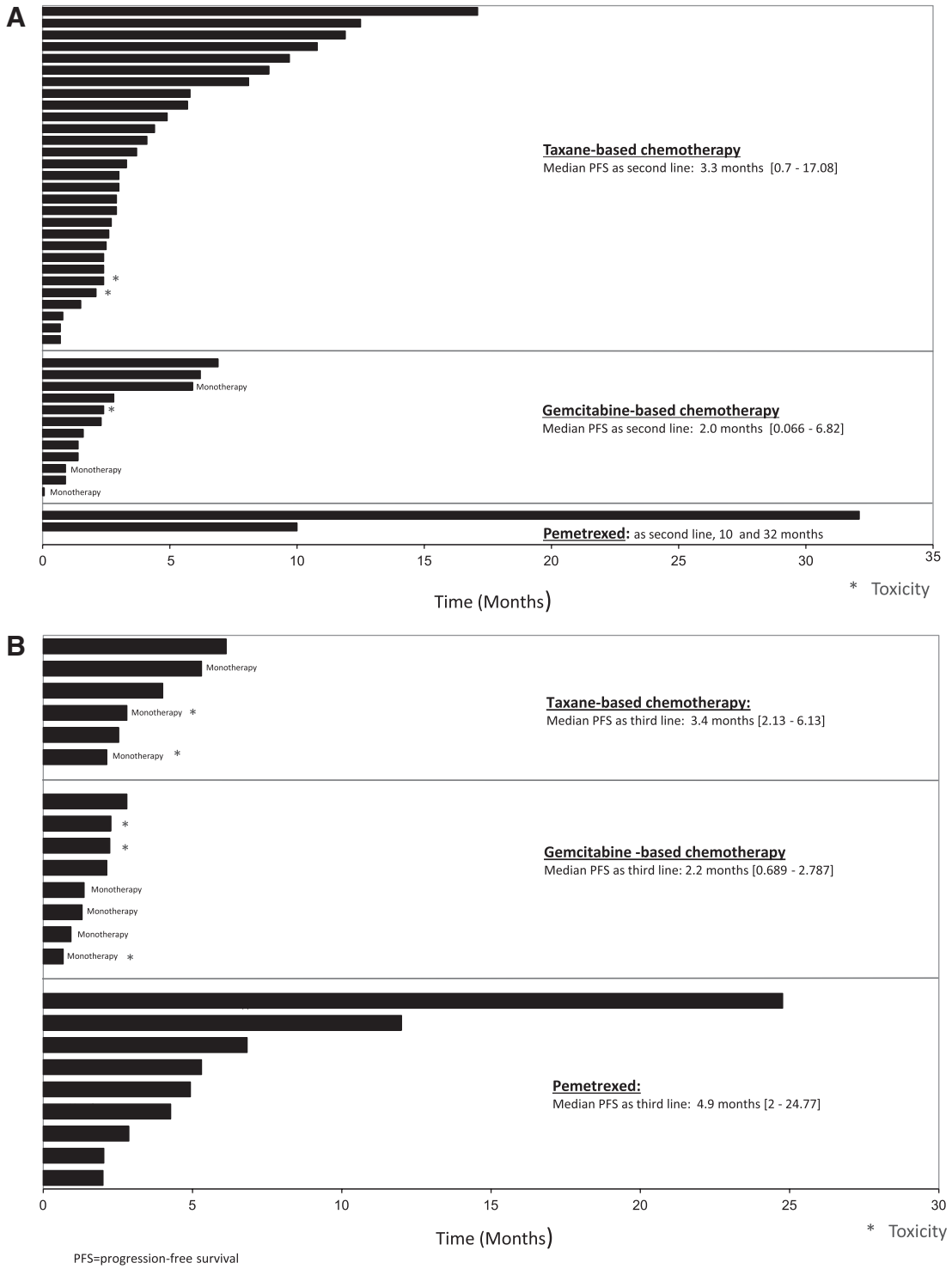

FIGURE 2. Waterfall plot of progression-free survival in second-line therapy (A) and third-line therapy (B) for each patient according to the third-generation chemotherapy regimens used. Median progression-free survival in months and its extent according to each third-generation chemotherapy regimen is shown in the insert box. Patients who discontinued treatment because of toxicity are marked with an asterisk. PFS, progression-free survival.

SWOG 0526[36] was the first phase II trial to investigate pemetrexed efficacy when given as first- or second-line therapy in advanced LPA patients, with an analysis of folate markers (TS, FR-α) and *EGFR* and *K-Ras* mutational status in both tumor specimens and blood samples. The results are still pending.

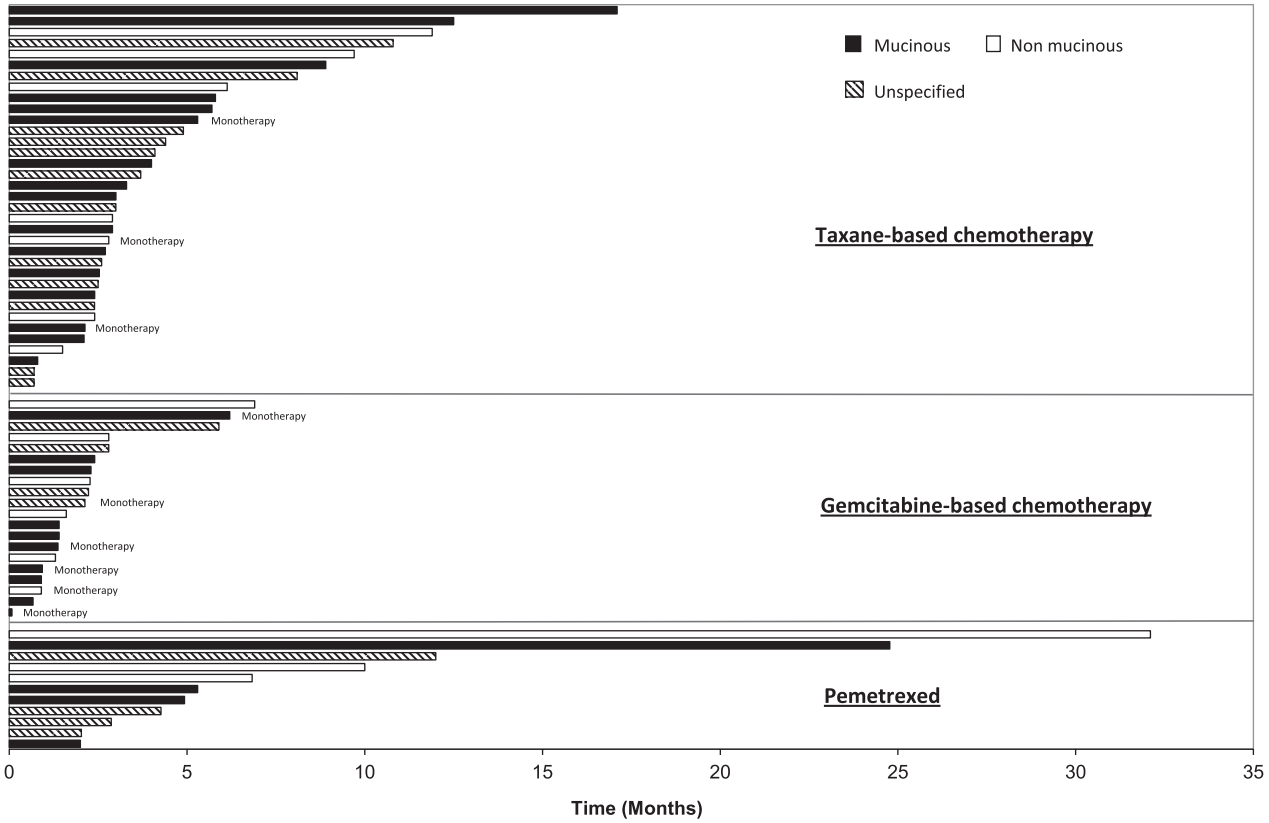

FIGURE 3. Waterfall plot of progression-free survival using second-line or third-line therapies for each patient according to histological subtypes.

In conclusion, our study results suggest that patients with advanced LPA, formerly advanced BAC, may benefit from platinum-based doublet chemotherapy after EGFR-TKI failure. In addition, platinum-taxane doublets or pemetrexed monotherapy as opposed to platinum-gemcitabine regimens appeared to be more promising candidates to be investigated in future trials. Lastly, the results of the phase II SWOG 0526 and IFCT-0504 trials are likely to be instrumental in improving our understanding of the clinical and biological predictors for paclitaxel-carboplatin doublet and pemetrexed activities in advanced LPA, thus facilitating the design of future clinical trials.

ACKNOWLEDGMENTS

Supported by Ligue Nationale Contre le Cancer (LNCC – French league against cancer). The authors thank the patients, their families, and caregivers who made this study possible.

Investigators (by contribution): Elisabeth Quoix (Hôpitaux Universitaires de Strasbourg, Strasbourg), Marie Wislez (AP-HP, Hôpital Tenon, Paris), Denis Moro-Sibilot (CHU, Grenoble), Daniel Coëtmeur (CH, Saint Brieuc), Isabelle Monnet (CHI, Créteil), Pierre Mourlanette (Clinique des Cèdres, Cornebarrieu), Jean-François Morère (AP-HP, Hôpital Avicenne, Bobigny), Jean-Charles Soria (Institut Gustave Roussy, Villejuif), Virginie Westeel (CHU, Besançon), Jean-Louis Bizec (CH Bretagne Atlantique, Vannes), Suzanne Bota (CHU, Rouen), Stéphane Chouabe (CH, Charlesville-Mézières), Eric Dansin (Centre Oscar Lambert, Lille), Gislaine Fraboulet (CH, Pontoise), Radj Gervais (Centre François Baclesse, Caen), Henri Janicot (CHU, Clermont Ferrand), Jacques Le Treut (CH, Aix-en-Provence), Gérard Oliviero (CH, Longjumeau), Eric Pichon (CHU, Tours), Gilles Robinet (CHU, Brest), Pierre-Jean Souquet (Hospices Civiles de Lyon, Lyon-Sud), and Alain Vergnenègre (Hôpital du Cluzeau, Limoges).

REFERENCES

1. Travis WD, Brambilla E, Muller-Hermelink HK, et al. Pathology and genetics of tumors of the lung, pleura, thymus and heart. In *World Health Organisation Classification of Tumours.* Lyon, France. IARC Press 2004.
2. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 1995;75:2844–2852.
3. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244–285.
4. Wislez M, Massiani MA, Milleron B, et al. Clinical characteristics of pneumonic-type adenocarcinoma of the lung. *Chest* 2003;123:1868–1877.
5. Garfield DH, Cadranel JL, Wislez M, Franklin WA, Hirsch FR. The bronchioloalveolar carcinoma and peripheral adenocarcinoma spectrum of diseases. *J Thorac Oncol* 2006;1:344–359.
6. Kris MG, Giaccone G, Davies A, et al. Systemic therapy of bronchioloalveolar carcinoma: results of the first IASLC/ASCO consensus conference on bronchioloalveolar carcinoma. *J Thorac Oncol* 2006;1(9 Suppl): S32–S36.

7. Breathnach OS, Ishibe N, Williams J, Linnoila RI, Caporaso N, Johnson BE. Clinical features of patients with stage IIIB and IV bronchioloalveolar carcinoma of the lung. *Cancer* 1999;86:1165–1173.
8. Feldman ER, Eagan RT, Schaid DJ. Metastatic bronchioloalveolar carcinoma and metastatic adenocarcinoma of the lung: comparison of clinical manifestations, chemotherapeutic responses, and prognosis. *Mayo Clin Proc* 1992;67:27–32.
9. Heikkilä L. Results of surgical treatment in bronchioloalveolar carcinoma. *Ann Chir Gynaecol* 1986;75:183–191.
10. Sørensen JB, Hirsch FR, Olsen J. The prognostic implication of histopathologic subtyping of pulmonary adenocarcinoma according to the classification of the World Health Organization. An analysis of 259 consecutive patients with advanced disease. *Cancer* 1988;62:361–367.
11. Harpole DH Jr, Herndon JE 2nd, Young WG Jr, Wolfe WG, Sabiston DC Jr. Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. *Cancer* 1995;76:787–796.
12. Travis WD, Garg K, Franklin WA, et al. Bronchioloalveolar carcinoma and lung adenocarcinoma: the clinical importance and research relevance of the 2004 World Health Organization pathologic criteria. *J Thorac Oncol* 2006;1(9 Suppl):S13–S19.
13. West HL, Crowley JJ, Vance RB, et al. Southwest Oncology Group. Advanced bronchioloalveolar carcinoma: a phase II trial of paclitaxel by 96-hour infusion (SWOG 9714): a Southwest Oncology Group study. *Ann Oncol* 2005;16:1076–1080.
14. Scagliotti GV, Smit E, Bosquee L, et al. European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group (LCG). A phase II study of paclitaxel in advanced bronchioloalveolar carcinoma (EORTC trial 08956). *Lung Cancer* 2005;50:91–96.
15. West HL, Franklin WA, McCoy J, et al. Gefitinib therapy in advanced bronchioloalveolar carcinoma: Southwest Oncology Group Study S0126. *J Clin Oncol* 2006;24:1807–1813.
16. Miller VA, Riely GJ, Zakowski MF, et al. Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. *J Clin Oncol* 2008;26:1472–1478.
17. Cadranel J, Quoix E, Baudrin L, et al. IFCT-0401 Trial Group. IFCT-0401 Trial: a phase II study of gefitinib administered as first-line treatment in advanced adenocarcinoma with bronchioloalveolar carcinoma subtype. *J Thorac Oncol* 2009;4:1126–1135.
18. Ramalingam SS, Lee JW, Belani CP, et al. Cetuximab for the treatment of advanced bronchioloalveolar carcinoma (BAC): an Eastern Cooperative Oncology Group phase II study (ECOG 1504). *J Clin Oncol* 2011;29:1709–1714.
19. Garfield DH, Cadranel J, West HL. Bronchioloalveolar carcinoma: the case for two diseases. *Clin Lung Cancer* 2008;9:24–29.
20. West HL,Garfield DH. Bronchioloalveolar carcinoma: not as easy as "BAC". *J Thorac Oncol* 2009;4:1047–1048.
21. Sakuma Y, Matsukuma S, Yoshihara M, et al. Distinctive evaluation of nonmucinous and mucinous subtypes of bronchioloalveolar carcinomas in EGFR and K-ras gene-mutation analyses for Japanese lung adenocarcinomas: confirmation of the correlations with histologic subtypes and gene mutations. *Am J Clin Pathol* 2007;128:100–108.
22. Finberg KE, Sequist LV, Joshi VA, et al. Mucinous differentiation correlates with absence of EGFR mutation and presence of KRAS mutation in lung adenocarcinomas with bronchioloalveolar features. *J Mol Diagn* 2007;9:320–326.
23. Hata A, Katakami N, Fujita S, et al. Frequency of EGFR and KRAS mutations in Japanese patients with lung adenocarcinoma with features of the mucinous subtype of bronchioloalveolar carcinoma. *J Thorac Oncol* 2010;5:1197–1200.
24. Wislez M, Antoine M, Baudrin L, et al. Non-mucinous and mucinous subtypes of adenocarcinoma with bronchioloalveolar carcinoma features differ by biomarker expression and in the response to gefitinib. *Lung Cancer* 2010;68:185–191.
25. Boukovinas I, Papadaki C, Mendez P, et al. Tumor BRCA1, RRM1 and RRM2 mRNA expression levels and clinical response to first-line gemcitabine plus docetaxel in non-small-cell lung cancer patients. *PLoS ONE* 2008;3:e3695.
26. Chang A. Chemotherapy, chemoresistance and the changing treatment landscape for NSCLC. *Lung Cancer* 2011;71:3–10.
27. Gan PP, Pasquier E, Kavallaris M. Class III beta-tubulin mediates sensitivity to chemotherapeutic drugs in non small cell lung cancer. *Cancer Res* 2007;67:9356–9363.
28. Duruisseaux M, Cadranel J, Biron E, Pérol M, Guérin JC, Arpin D. Major and prolonged response to pemetrexed in two cases of lung adenocarcinoma with bronchioloalveolar carcinoma features. *Lung Cancer* 2009;65:385–387.
29. Duruisseaux M, Cadranel J, Pérol M, Arpin D. The role of pemetrexed in lung adenocarcinoma, mixed subtype with bronchioloalveolar carcinoma features. *Curr Drug Targets* 2010;11:74–77.
30. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–3551.
31. Ceppi P, Volante M, Saviozzi S, et al. Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase. *Cancer* 2006;107: 1589–1596.
32. Sun JM, Han J, Ahn JS, Park K, Ahn MJ. Significance of thymidylate synthase and thyroid transcription factor 1 expression in patients with nonsquamous non-small cell lung cancer treated with pemetrexed-based chemotherapy. *J Thorac Oncol* 2011;6:1392–1399.
33. TracyS, JohnsonEB, Jänne AP. In-vitro effects of pemetrexed on bronchioloalveolar and adenocarcinoma of the lung. *Proc Amer Assoc Cancer Res* Meeting 2005; abstract #5864.
34. Garfield DH,Franklin W. Dramatic response to pemetrexed in a patient with pneumonic-type mucinous bronchioloalveolar carcinoma. *J Thorac Oncol* 2011;6:397–398.
35. Cadranel J. Therapeutic strategy in advanced bronchioloalveolar carcinoma. Available at: http://clinicaltrials.gov/show/NCT00384826. Accessed September 26, 2008.
36. Ho C, Ross H, Davies A. Phase II trial of premetrexed in patients with selected stage IIIB/IV bronchioloalveolar carcinoma. *Clin Lung Cancer* 2006;8:220–222.

