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ORIGINAL ARTICLE
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Erlotinib *versus* carboplatin and paclitaxel in advanced lepidic adenocarcinoma: IFCT-0504

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ABSTRACT The IFCT-0504 phase II trial evaluated the efficacy of erlotinib *versus* carboplatin–paclitaxel (CP) as first-line treatment in 130 cases of advanced lepidic-predominant adenocarcinoma (ADC).

The primary objective of the study was treatment efficacy, evaluated based on an end-point of disease control at 16 weeks.

The primary objective was met, with a disease control in 35 (53%) out of 66 patients treated with CP and in 25 (39.1%) out of 64 patients treated with erlotinib. Median progression-free survival (PFS) for the total population was 3.6 months. The disease control rate did not differ between either the therapeutic arms or pathological subtypes, whereas there was a strong interaction between treatment arms and tumour pathological subtypes for PFS (p=0.009). Mucinous tumour patients treated with erlotinib exhibited an increased progression risk (hazard ratio 3.4, 95% CI 1.7–6.5; p≤0.001). The PFS for nonmucinous tumour patients was similar in both arms. Median overall survival was 20.1 months and did not differ between therapeutic arms. These findings were not further elucidated by molecular analyses and the toxicity profiles were as expected.

Our study demonstrated the dominant role of CP alongside erlotinib in the management of advanced lepidic ADC. Based on these findings, erlotinib should not be administered in first-line therapy to patients with lepidic ADC in the absence of an epidermal growth factor receptor mutation.

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Introduction

Bronchioloalveolar carcinoma (BAC) terminology was reviewed in the 2011 guidelines of the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) [1]. Former adenocarcinoma (ADC) with BAC features has been categorised as invasive nonmucinous (NM) lepidic-predominant ADC (L-ADC), along with its mucinous variant.

Advanced L-ADC (formerly ADC-BAC) used to be widely perceived as chemotherapy resistant, with conflicting results reported in older retrospective studies [2, 3], and little was known about the optimal treatment, thus justifying the initiation of a specific trial [2, 3]. Only two nonrandomised phase II trials had previously investigated the efficacy of paclitaxel monotherapy, administered every 3 weeks [4, 5], but the low response rates and unacceptable toxicity reported by the Southwest Oncology Group (SWOG) 9714 trial defined this approach as ill adapted [5]. Pemetrexed monotherapy has recently achieved promising results in the *Intergroupe Francophone de Cancérologie Thoracique* (French Cooperative Thoracic Intergroup (IFCT)) 0401 trial [6] and in one prematurely closed phase II trial [7]. Three phase II trials have evaluated the use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as first- or second-line treatment for advanced ADC-BAC [8–10], demonstrating encouraging efficacy and a favourable toxicity profile. Similar results were also reported using anti-EGFR antibody monotherapy [11].

It appears increasingly crucial to distinguish between NM and mucinous L-ADC [1–3]. In the IFCT-0401 trial, NM patients displayed significantly improved progression-free survival (PFS) under gefitinib, in contrast with mucinous patients, who exhibited early progression under EGFR-TKIs [10]. Overall survival (OS) did not, however, differ between the patient groups until the 22nd month, suggesting that carboplatin–paclitaxel (CP) or pemetrexed, administered after gefitinib, was effective in mucinous patients as "salvage" therapy [6, 10]. We therefore deemed it essential to evaluate the effect of the CP regimen in first-line therapy of advanced L-ADC, CP being one of the four most effective platinum doublets used in non-small cell lung cancer (NSCLC) when the IFCT-0504 trial was designed [12]. Finally, to minimise the toxicity of this chemotherapy and render it more acceptable in terms of tolerance, compared to erlotinib, we chose to administer paclitaxel in a weekly regimen with carboplatin and to maintain paclitaxel alone until progression was observed in patients with controlled disease, as previously suggested by Belani *et al.* [13].

We designed a randomised, phase II, parallel group trial evaluating erlotinib in one arm and carboplatin plus weekly paclitaxel in the second as first-line treatment for advanced L-ADC patients (formerly advanced BAC). A cross-over between the two arms was planned. The impact of pathological subtypes (NM and mucinous) on treatment efficacy was also evaluated, along with an exploratory panel of biomarkers.

Materials and methods

Study design

IFCT-0504 was an open-label, randomised, multicentre, phase II, parallel group trial evaluating first-line erlotinib and CP treatment for advanced L-ADC. The primary objective was treatment efficacy, with an end-point of disease control at 16 weeks. The secondary end-points were PFS and OS. Our secondary objectives were safety and quality of life, the latter featuring as the subject of a future article, as well as the impact of pathological tumour subtypes on efficacy. The exploratory objective comprised a centralised biomarker analysis of *EGFR* and Kirsten Ras (*KRAS*) mutational status, as well as tubulin-β class III (*TUBB3*) protein and MutS protein homologue 2 (*MSH2*) expression in tumour specimens.

The protocol was approved by the *Comité de Protection des Personnes Ile-de-France X*, the French regional research ethics body, and the trial was authorised by the French National Authority for Health (www.clinicaltrials.gov identifier number NCT00384826), with written informed consent provided by all patients.

Eligibility criteria

For inclusion, all patients had to exhibit histologically or cytologically diagnosed advanced BAC (stage IIIB/IV), with inoperable stage I–IIIA patients also being eligible [14]. Patients with cytological ADC features

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lacking any available histological specimens were eligible if they had a diffuse or pneumonic-type radiological presentation suggestive of BAC [1, 15]. Pathological diagnosis was initially based on local pathology assessment according to the 2004 World Health Organization (WHO) pathological classification [14] with all tumour samples subsequently reviewed by the IFCT pathological panel for this final report, and reclassified as L-ADC and for the corresponding pathological subtypes, using IASLC/ATS/ERS 2011 BAC terminology [1]. Diastase-resistant periodic acid–Schiff staining was performed to more clearly distinguish NM from mucinous tumours [1, 16].

Patients aged ⩾18 years with an Eastern Cooperative Oncology Group performance status (PS) of 0, 1 or 2 were eligible. Patients having undergone prior systemic therapy for lung cancer were excluded from participation.

Treatment

Patients were randomised 1:1 to receive either erlotinib (arm E) or CP (arm CP) using the minimisation method, stratified by sex, PS (0–1 *versus* 2) and smoking status (never-smoker or former smoker with <5 pack-years *versus* former smoker with ⩾5 pack-years or active smoker). Erlotinib (150 mg per day) was administered orally, and CP were administered by intravenous infusion (carboplatin at area under the curve 6 on day 1, and paclitaxel at 90 $mg{\cdot}m^{-2}$ on days 1, 8 and 15) for up to six 28-day cycles, followed by weekly paclitaxel (90 $mg{\cdot}m^{-2}$) maintenance. Patients received treatment until disease progression, intolerable toxicity or death. Further therapy consisted of a crossover of the two treatments in both arms. Third-line therapy was pemetrexed (500 $mg{\cdot}m^{-2}$) on day 1 to be repeated every 21 days.

Assessment

Age, sex, smoking status and respiratory symptom score (RSS) [10] were recorded at inclusion. Within 4 weeks prior to study inclusion, patients were required to display pulmonary lesions on computed tomography (CT) and normal fibreoptic bronchoscopy in order to be included. Extrathoracic work-up consisted of brain CT or magnetic resonance imaging and upper abdominal CT or ultrasonography.

Response was assessed using the WHO criteria [17], with a CT scan performed after 4 weeks, then every 12 weeks. We included an early evaluation at 4 weeks due to early progression observed in a BAC patient subset in the previous IFCT-0401 trial [10]. The WHO criteria were favoured over RECIST (Response Evaluation Criteria In Solid Tumors), given the latter's tendency to delay disease progression diagnosis [18, 19]. An independent review was performed by the IFCT-0504 steering committee, blinded to treatment assignment.

Toxicities were graded using the National Cancer Institute Common Toxicity Criteria (version 3.0).

Biomarker analysis

EGFR (exons 18–21) and *KRAS* mutations were detected centrally as previously described [20] (online supplementary material). Immunostaining of TUBB3 and MSH2 proteins was performed, with the results expressed as previously described [21, 22] (online supplementary material).

Statistical methods

Fleming's two-stage optimal design was used. The hypotheses we tested were whether the control rate at 16 weeks would reach at least 50% (H1) *versus* 30% (H0) within each arm. In the first stage, 30 patients were accrued. If nine or fewer nonprogressive disease cases were observed in these 30 patients, the arm would be stopped for futility. if ⩾14 nonprogressive disease cases were observed, the arm would be stopped and the null hypothesis rejected. Otherwise, 30 additional patients would be accrued to achieve a total of 60 patients in each arm. The null hypothesis would be rejected if ⩾21 nonprogressive disease cases were observed in 60 patients. This design provided a Type I error rate of 10% (one-sided) and power of 95%. Taking account of a possible ineligibility of 10% of patients, as assessed retrospectively by the steering committee, the design would enable 65 patients to be randomised in each arm.

The pairwise interactions between therapeutic arms (E and CP) and pathological subtypes (mucinous and NM) were tested in all analyses. When significant interaction was observed, stratification was performed, and the univariate and multivariate analyses were presented by strata. A logistic regression analysis [23] was conducted in order to explore the demographic and clinical factors associated with disease control and response. Variables with $p<0.2$ on univariate analysis were included in the multivariate logistic regression, then selected by a backward procedure, with a stay significance level of 0.05. OS and PFS were estimated using the Kaplan–Meier method [24] and median survival time using the method described by Brookmeyer and Crowley [25]. For overall survival and PFS, a Cox model [26] was applied to calculate the hazard ratio (HR), with a Wald test used for each variable. The Cox models were applied to identify factors significantly associated with survival. $p<0.05$ was considered statistically significant. All analyses were carried out using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Enrolment occurred from September 2006 to July 2009, with 133 patients registered and 130 eligible (arm E: n=64; arm CP: n=66). Of these, 96 (73.8%) were able to undergo centralised molecular tumour analysis (figure 1 and table 1). All except 12 patients presented as stage IIIB–IV at diagnosis (table 1). Of the 12 stage I–IIIA patients at diagnosis, 11 exhibited recurrence after surgery with advanced disease and one remained stage IB but developed inoperable disease, before inclusion in the trial.

NM tumours were detected in 67 and mucinous tumours in 53. In total, 12 patients were not evaluable for pathological subtype (cytological diagnosis), with the last remaining patient not being eligible as they lacked a L-ADC diagnosis. Except for the exclusion of patients with a cytological L-ADC diagnosis, the clinical and pathological characteristics did not differ, either between therapeutic arms (table 1) or between overall trial and molecular populations (online supplementary table S1).

Disease control and response

Overall, 109 patients were assessed for response at 16 weeks: 52 in arm E arm and 57 in arm CP. In total, 21 patients could not be evaluated due to death (n=15), early withdrawal due to toxicity (n=3), loss to follow-up (n=1), refusal of treatment change (n=1) or other causes (n=1). Early therapeutic crossover was applied in 42 (32.3%) due to disease progression at the 4-week evaluation (24 and 18 in arms E and CP, respectively).

The primary end-point was met, with disease control achieved in 25 patients treated with erlotinib (disease control rate (DCR) 39.1%, 95% CI 27.1–51.0%) and in 35 treated by CP (DCR 53.0%, 95% CI 42.0–65.0%), according to the two-stage Fleming's design (see the methods section). Furthermore, disease control was achieved in 60 patients at 16 weeks, for the total population (DCR 46.2%, 95% CI 37.6–54.7%),

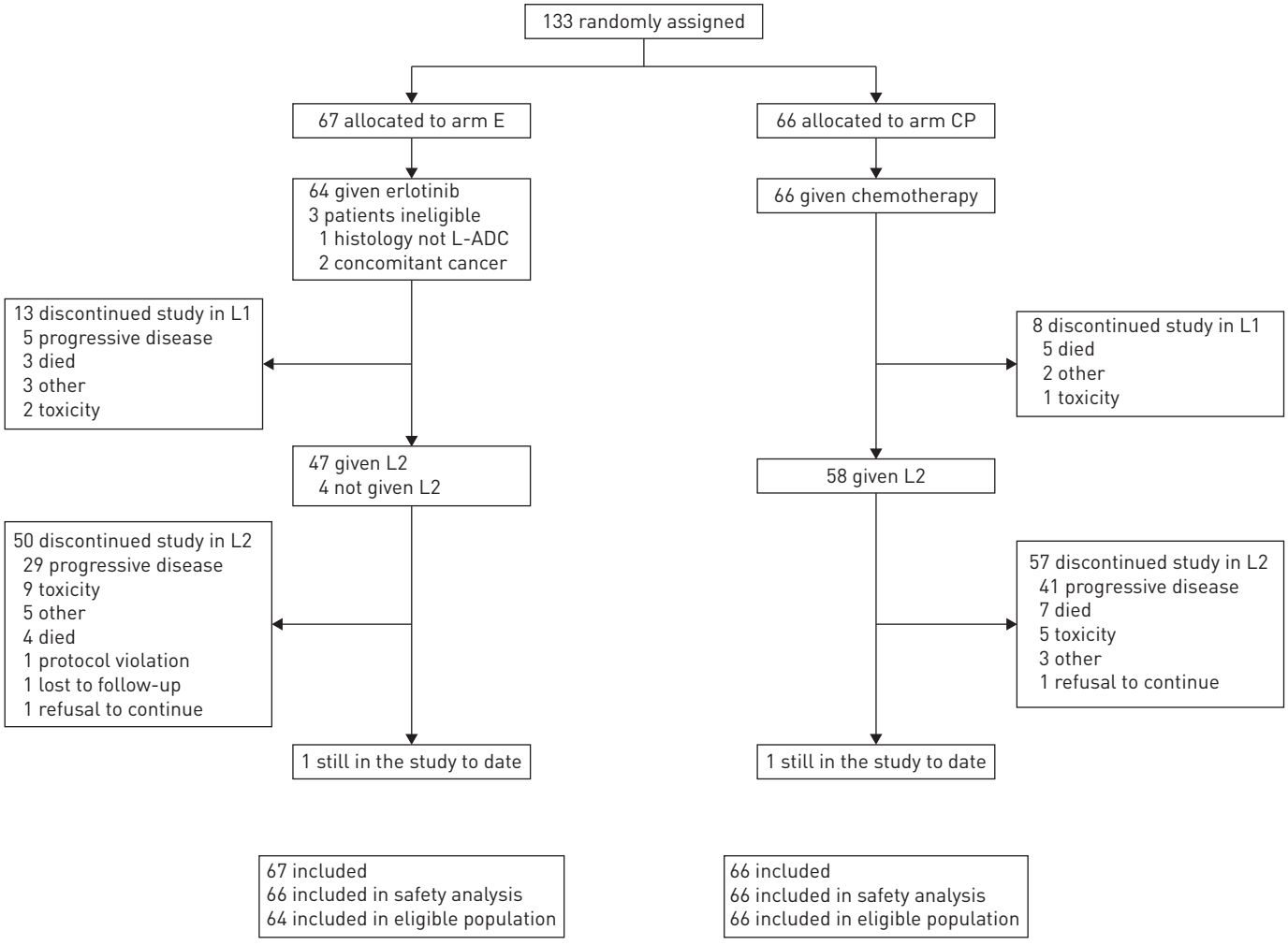

FIGURE 1 Study profile. E: erlotinib; CP: carboplatin–paclitaxel; L-ADC: lepidic-predominant adenocarcinoma; L1: first line; L2: second line.

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TABLE 1 Baseline patient characteristics in both arms

Characteristics	Erlotinib	CP	All patients	p-value
Patients n	67	66	133	
Sex				0.94
Male	41 (61.2)	40 (60.6)	81 (60.9)	
Female	26 (38.8)	26 (39.4)	52 (39.1)	
Age years	67.4 (19.6–81.6)	68.2 (43.3–82.5)	67.8 (19.6–82.5)	0.71
Smoking status				0.89
Never-smoker	19 (28.4)	18 (27.3)	37 (27.8)	
Former/active smoker	48 (71.6)	48 (72.7)	96 (72.2)	
Stage at diagnosis				0.54
I–IIIA[#]	5 (7.6)	7 (10.6)	12 (9.0)	
IIIB–IV	61 (92.4)	59 (89.4)	120 (90.2)	
Missing data	1	0	1	
PS				0.59
0	31 (46.3)	25 (37.9)	56 (42.1)	
1	27 (40.3)	32 (48.5)	59 (44.4)	
2	9 (13.4)	9 (13.6)	18 (13.5)	
RSS	8 (0–20)	7 (0–19)	7 (0–20)	0.71
Pathological subtype				0.35
Mucinous	25 (37.3)	28 (42.4)	53 (39.8)	
Nonmucinous	33 (49.3)	34 (51.5)	67 (50.4)	
Not evaluable[¶]	8 (11.9)	4 (6.1)	12 (9.0)	
Not applicable[+]	1 (1.5)	0	1 (0.8)	

Data are presented as n (%) or median (range), unless otherwise stated. CP: carboplatin–paclitaxel; RSS: respiratory symptom score. [#]: of the 12 stage I–IIIA patients at diagnosis, 11 relapsed with advanced disease after surgery before inclusion in the trial, and one remained as stage IB but with inoperable disease; [¶]: diagnostic of lepidic-predominant adenocarcinoma based on cytological specimens; [+]: one patient did not have lepidic adenocarcinoma after centralised pathological review.

with two (1.5%) exhibiting complete response, 24 (18.5%) partial response and 34 (26.2%) stable disease. In an exploratory analysis, DCR did not differ statistically between the arms (39.1% and 53% in arms E and CP, respectively; p=0.11) or pathological subtypes (table 2).

No interactions were found between the treatment effect on DCR and pathological characteristics. Patients with low RSS, female sex or age >70 years exhibited significantly increased DCR at 16 weeks (online supplementary table S2).

Therapeutic compliance and toxicity

Therapeutic compliance was equally good in both arms. The median number of 28-day cycles administered was three in both arms (interquartile range: arm E, 1–6.5; arm CP, 1–9). The median dose intensity of drugs administered during the first six cycles was 100% (range 52.6–100%) and 81.3% (range 0–103%) for erlotinib and paclitaxel, respectively, and 99.7% (range 0–135%) for carboplatin.

There were no unexpected adverse events (table 3). Therapy was discontinued due to treatment-related adverse events in three (4.5%) patients in the arm E and in 16 (24.2%) in arm CP (p=0.001).

Overall, 105 (80.8%) patients received second-line treatment (CP after erlotinib: n=47; erlotinib after CP: n=58) and 77 (59.2%) third-line treatment (pemetrexed in 87.0%). There were 112 deaths, one potentially attributed to treatment toxicity in arm E.

PFS and OS

The median follow-up duration was 69.4 months (range 53.0–87.4 months), with one patient lost to follow-up after 3 months. Median PFS and OS were 3.6 months and 20.1 months, respectively (figure 2). The 1-, 2- and 3-year OS rates were 63.9% (95% CI 55.7–72.1%), 43.6% (95% CI 35.2–52.0%) and 30.8% (95% CI 23.0–38.7%), respectively.

Impact of therapeutic arms and pathological subtypes on PFS

While PFS did not differ between therapeutic arms (table 2 and figure 2), there was a strong interaction between treatment effect (arm E *versus* CP) on PFS and mucinous and NM subtypes (p=0.009) (figure 3). The analyses were therefore stratified by pathological subtype.

TABLE 2 Results in overall and molecular populations

	Patients n (%)	DCR % (95% CI)	p-value[#]	PFS months median (95% CI)	p-value[¶]	OS months median (95% CI)	p-value[¶]
Overall population	130	46.2 (37.6–54.8)		3.6 (2.6–5.5)		20.1 (15.2–28)	
Arm			0.11		0.27		0.99
E	64 (49.2)	39.1 (27.1–51.0)		3.4 (1.3–3.7)		21.2 (15.4–32.2)	
CP	66 (50.8)	53.0 (42.0–65.0)		5.7 (2.6–8.7)		17.6 (11.3–28.8)	
Molecular population	96	50 (40.0–60.0)		3.6 (1.9–6.5)		23.0 (15.2–30.0)	
Pathological subtypes			0.54		0.01		0.09
Nonmucinous	53 (55.2)	52.8 (39.4–66.2)		5.8 (1.9–8.7)		28.0 (13.0–32.9)	
Mucinous	43 (46.2)	46.5 (31.6–61.4)		3.5 (1.1–5.5)		18.9 (10.3–28.9)	
EGFR			0.02				
Mutated	5 (5.6)	100		18.5 (9.1–35.8)		Not reached	
Wild type	84 (94.4)	46.4 (35.7–57.1)		3.5 (1.7–6.3)		23.4 (15.4–30.0)	
KRAS							
Mutated	24 (27.3)	41.7 (22.0–61.4)	0.34	3.7 (1.4–8.1)	0.94	20.8 (4.2–28.9)	0.10
Wild type	64 (72.7)	53.1 (40.9–65.3)		3.7 (1.6–7.3)		27.9 (18.5–35.9)	
MSH2			0.86		0.69		0.12
⩽100	50 (59.5)	48 (34.1–61.8)		3.8 (1.6–7.2)		22.8 (10.3–28.8)	
>100	34 (40.5)	50 (33.2–66.8)		3.6 (1.1–8.7)		34.1 (16.9–43.9)	
Tubulin-β class III			0.87		0.95		0.96
0	27 (32.5)	51.9 (33.0–70.7)		3.8 (1.1–10.3)		24.8 (7.9–38.4)	
>0	56 (67.5)	50 (36.9–63.1)		3.7 (1.7–7.2)		22.8 (15.4–30.0)	

DCR: disease control rate; PFS: progression-free survival; OS: overall survival; E: erlotinib; CP: carboplatin–paclitaxel; EGFR: epidermal growth factor receptor; KRAS: Kirsten Ras; MSH2: MutS protein homologue 2. [#]: by Chi-squared test; [¶]: by log-rank test (calculated if number of events >15).

In mucinous L-ADC patients, only the treatment arm correlated with improved PFS on univariate and multivariate analyses (online supplementary table S3). Taking arm CP as a reference, there was a significantly increased risk of progression or death in mucinous patients treated with erlotinib (HR 3.4, 95% CI 1.70–6.50; p<0.001). The median PFS for mucinous patients treated with erlotinib was only 1.4 months (95% CI 0.9–3.6 months) compared to 6.0 months for those treated with CP (95% CI 2.2–11.3 months) (figure 3). Patients with NM L-ADC who were >70 years of age and non-smokers exhibited improved PFS on multivariate analysis. Patients who presented with stage I–IIIA at diagnosis yet relapsed after surgery

TABLE 3 Treatment-related adverse events

	Any grade		Grade 3		Grade 4	
	Arm E	Arm CP	Arm E	Arm CP	Arm E	Arm CP
Total patients n	66	66	66	66	66	66
Patients concerned	62 (93.9)	65 (98.5)	9 (13.6)	35 (53.0)	1 (1.5)	13 (19.7)
Haematological toxicity						
Decreased neutrophil count	1 (1.5)	45 (68.2)	0 (0)	14 (21.2)	0 (0)	11 (16.7)
Febrile neutropenia+febrile aplasia	0 (0)	5 (7.6)	0 (0)	5 (7.6)		
Decreased platelet count	0 (0)	25 (37.9)	0 (0)	3 (4.6)	0 (0)	1 (1.5)
Decreased haemoglobin	7 (10.6)	41 (62.1)	0 (0)	3 (4.6)	0 (0)	1 (1.5)
Nonhaematological toxicity						
General	7 (10.6)	37 (56.1)	0 (0)	13 (19.7)	0 (0)	1 (1.5)
Skin	59 (89.4)	35 (53.0)	6 (9.1)	1 (1.5)		
Gastrointestinal	41 (62.1)	37 (56.1)	1 (1.5)	2 (3.0)		
Liver and pancreatic	5 (7.6)	3 (4.6)	2 (3.0)	1 (1.5)		
Neurological	1 (1.5)	28 (42.4)	0 (0)	7 (10.6)		
Eye	5 (7.6)	0 (0)				
Renal	0 (0)	3 (4.6)				
Respiratory	1 (1.5)	2 (3.0)			1 (1.5)[#]	1 (1.5)
Other	12 (18.2)	25 (37.9)	2 (3.0)	4 (6.1)		

Data are presented as n (%) unless otherwise stated. n=132. E: erlotinib; CP: carboplatin–paclitaxel. [#]: patient died from interstitial pneumonitis.

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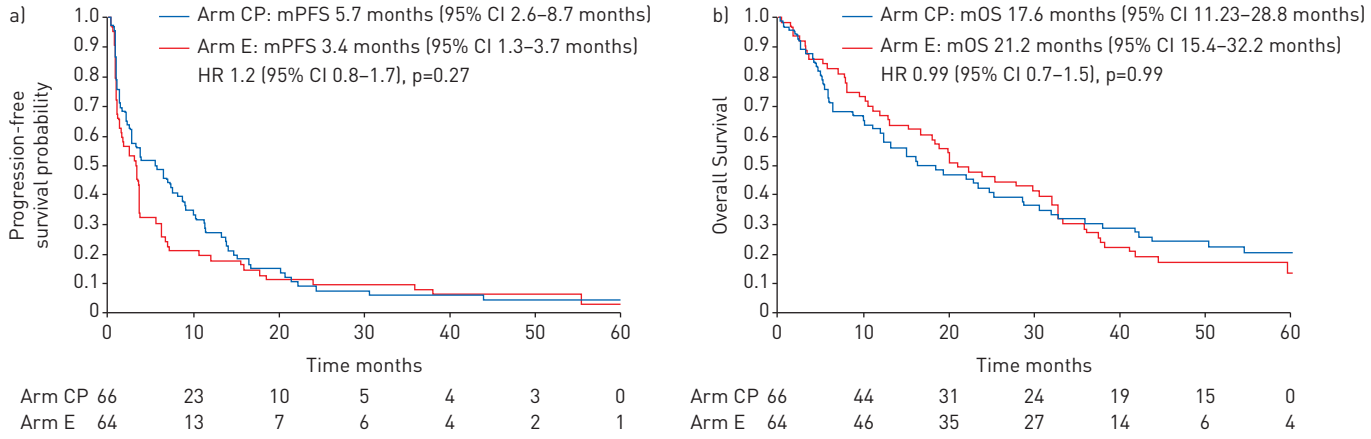

FIGURE 2 a) Progression-free and b) overall survival by treatment arm in the overall population. Arm CP (carboplatin–paclitaxel) was used as the reference when calculating hazard ratios (HRs). E: erlotinib; mPFS: median progression-free survival; mOS: median overall survival.

were associated with worse PFS (online supplementary table S4). The median PFS for NM patients was similar in the two arms (E: 3.6 months, 95% CI 1.3–11.7 months; CP: 4.8 months, 95% CI 1.3–8.7 months) (figure 3).

Impact of therapeutic arms and pathological subtypes on OS

OS did not differ between the therapeutic arms, with medians of 21.2 months in arm E (95% CI 15.4–32.2 months) and 17.6 months in arm CP (95% CI 11.3–28.8 months) (figure 2 and table 2). No interaction was found between the treatment effect on OS and pathological characteristics. Patients who were female, exhibited low RSS at diagnosis and had a PS of 0–1 demonstrated improved OS on multivariate analysis (online supplementarytable S5).

Exploratory analysis in the molecular population

In the molecular population, DCR was 50.0% (95% CI 40.0–60.0%), with median PFS and OS being 3.6 months (95% CI 1.9–6.5 months) and 23.0 months (95% CI 15.2–30.0 months), respectively (table 2).

Results of biomarker analysis

Overall, 76 (79.2%) out of 96 tumour specimens underwent all four biomarker analyses (table 2). *EGFR* mutations (exon 19: n=3; exon 21; n=2) were observed in five (5.6%) cases, all of which featured NM tumours (100%) (p=0.03 between mucinous and NM tumours). *KRAS* mutations were observed in 24 (27.3%) cases, 19 of which were mucinous tumours (44.2%) and five NM (9.4%) (p=0.0003).

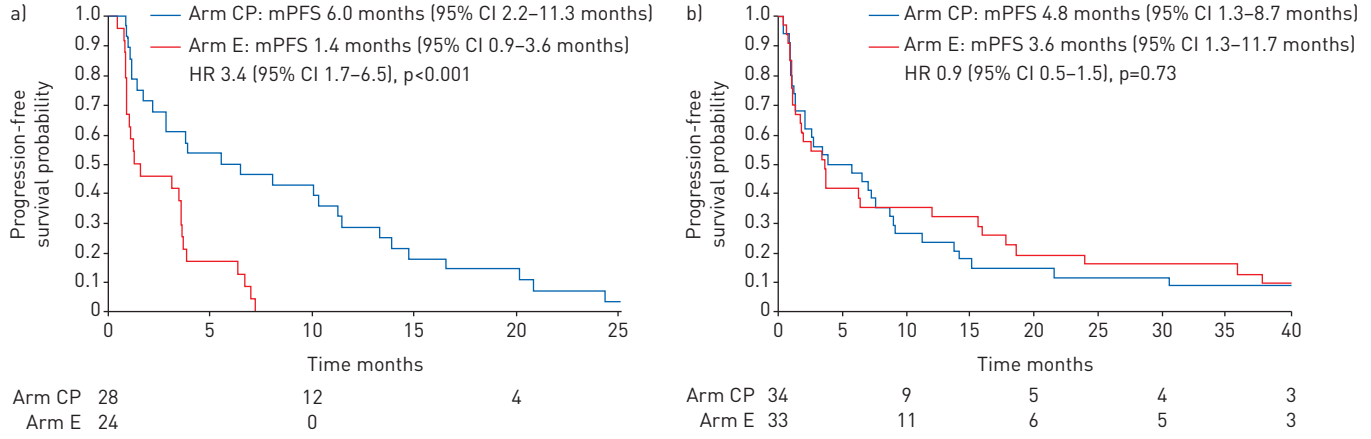

FIGURE 3 Progression-free survival by treatment arm and pathological subtype in the overall population. a) Progression-free survival in mucinous tumours in the carboplatin–paclitaxel (CP) and erlotinib (E) arms. b) Progression-free survival in nonmucinous tumours in arms CP and E. Arm CP (carboplatin–paclitaxel) was used as the reference when calculating hazard ratios (HRs). p-value for interaction: p=0.009. mPFS: median progression-free survival.

EGFR mutational status, and MSH2 and TUBB3 expression were well-balanced between the two arms. *KRAS* mutations were less frequent in arm E compared with CP (17.1% *versus* 36.2%, p=0.04) (online supplementary table S6) and only seven of the 24 tumours harbouring *KRAS* mutations were found in arm E. MSH2 and TUBB3 expression did not differ between mucinous and NM patients (data not shown).

Impact of biomarker analysis on DCR, PFS and OS

No interactions were found between treatment arm effect on DCR and pathological characteristics in the molecular population. The presence of L-ADC harbouring *EGFR* mutation (OR 10.3, 95% CI 1.3–undetermined; p=0.025) and age >70 years (OR 3.5, 95% CI 1.3–9.9; p=0.01) were associated with significantly increased DCR at 16 weeks on multivariate analysis (data not shown).

A significant interaction between the therapeutic arms and tumour pathological subtypes (p=0.04) was found for PFS in the molecular population (online supplementary figure S1). The analyses were thus stratified by pathological subtype. No molecular test, however, was able to provide additional predictive efficacy information for mucinous and NM patients.

As in the general population, only the treatment arm was associated with improved PFS for mucinous L-ADC patients on multivariate analysis. Taking the CP arm as a reference, there was a significantly increased risk of progression or death in the mucinous patients treated with erlotinib (HR 4.1, 95% CI 1.9–9.0; p<0.001) (online supplementarytable S7). In NM L-ADC patients, nonsmoker status was associated with improved PFS on multivariate analysis, whereas stage I–IIIA at diagnosis was associated with worse PFS. The PFS for NM patients was similar in the two arms (online supplementarytable S8).

Biomarker data were found to have no impact on OS on multivariate analysis, although patients with NM L-ADC (p=0.09) or *EGFR* mutations (p=0.05) tended to exhibit improved survival (table 2).

Discussion

The IFCT-0504 trial was the first to assess the management of advanced L-ADC since the publication of the 2011 IASLC/ATS/ERS guidelines and achieved its primary objective, with DCR at 16 weeks exceeding 30% in both arms. The findings originating from its secondary objectives were also of interest. There was a strong interaction between erlotinib and CP efficacy and L-ADC pathological subtypes. However, this finding was not elucidated by molecular analysis. Finally, OS did not differ according to first-line therapy choice (erlotinib *versus* CP).

Our study population was similar to that of previous trials assessing advanced BAC, especially in terms of the relative proportion of NM (51%) and mucinous (42%) tumours [5, 7, 8, 9, 10, 11]. In line with previous reports, *EGFR* and *KRAS* mutations were detected in 5.6% (6–22%) [9, 10, 11] and 27% (10–30%) [2, 3] of cases, respectively. *EGFR* mutations were exclusively found in NM tumours, whereas *KRAS* mutations were associated with mucinous tumours or smoking patients with NM tumours. Our results were similar to those recorded in lung ADC cases that were not otherwise specified for positive TUBB3 expression (67.5%) [27, 28] and high MSH2 expression (40.5%) [29], although no clear correlation between protein expression and clinical characteristics or L-ADC pathological subtypes was found.

Our DCR and PFS results were similar to those previously reported in an advanced BAC population [4, 5, 7–11]. DCR did not differ between therapeutic arms or pathological subtypes, although there was a strong interaction between treatment effect (arm E *versus* CP) on PFS and mucinous and NM subtypes (p=0.009) (figure 3), as previous studies have suggested [10]. Taking the CP arm as reference, there was a significantly increased risk of disease progression or death in the mucinous patients treated with erlotinib (HR 3.4, 95% CI 1.7–6.5; p≤0.001), with the median PFS for erlotinib-treated mucinous patients being four times inferior to that of CP-treated mucinous patients. However, the choice of therapeutic arm did not affect PFS in NM L-ADC patients.

These findings were confirmed in the molecular population. *EGFR* mutations were associated with both improved DCR (100% *versus* 46.2% for *EGFR* mutant and wild type, respectively; p=0.02) and PFS (18.5 *versus* 3.5 months, p=0.08) (table 2) [9–11]. However, the low *EGFR* mutation rate (n=5, 5.6%) indicates that this molecular alteration only minimally impacts the treatment efficacy, even in arm E. DCR and PFS were not affected by tumour *KRAS* mutation status (table 2). Given that *KRAS* mutations were observed in only seven of the 41 tumours in arm E patients, this finding cannot account for erlotinib's low efficacy in mucinous patients [30]. TUBB3 and MSH2 are markers that have previously been revealed to demonstrate positive expression in adenocarcinoma [21, 22]. Previous reports also suggested that TUBB3 [27, 28] and MSH2 [29] protein levels, assessed by immunohistochemistry, are predictive of cisplatin and taxane responses in NSCLC. However, MSH2 and TUBB3 tumour expression did not impact on either DCR or PFS (table 2), even in the CP arm, in contrast to a recently published meta-analysis on NSCLC patients undergoing taxane/vinorelbine-based chemotherapy [31].

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Our results suggest that, for advanced L-ADC patients, the choice of first-line treatment appears more dependent on pathological subtype than on putative predictive biomarkers, except in a few NM L-ADC patients harbouring *EGFR* mutations. We did not, however, explore other biomarkers associated with EGFR-TKI resistance in wild-type *EGFR* NSCLC [32]. Other molecular abnormalities in the EGFR signalling pathway (*AKT*, *ERK* (extracellular signal-regulated kinase) and *PTEN* (a phosphatase and tension homologue) loss) were observed in advanced BAC [33, 34]. HER2 (human EGFR2) [33, 35] or hepatocyte growth factor/c-met overexpression/amplification was reported to be more frequently observed in mucinous BAC [36], possibly related to EGFR-TKI resistance. Mucinous tumours have recently been found to overexpress insulin-like growth factor-1 receptor (IGF1R) and amphiregulin compared with NM tumours [33, 34], with higher IGF1R expression associated with disease progression under gefitinib [37, 38].

Although improved OS has been reported in mucinous patients treated with paclitaxel monotherapy [5] and in NM patients treated with EGFR-TKIs [8, 10], these observations were not supported by our data. We found that the strong correlation between pathological subtypes and treatment effect in the overall population had no impact on OS, which was also unexpected, especially in the mucinous subtype. Finally, neither *EGFR* and *KRAS* mutational status nor MSH2 and TUBB3 expression were clearly associated with long-term survival, which may be a result of our trial design. Given our trial's lack of power for such subset analyses, the IFCT-0504 trial design could explain these findings. Firstly, erlotinib may have been more effective than gefinitib in this mostly non-*EGFR*-mutated population, as previously suggested [39]. Secondly, we applied paclitaxel as a platinum-based doublet in a weekly schedule, which has now been shown to improve OS compared with monotherapy in ADC in general [40]. Thirdly, our crossover treatment phase was designed to expose all patients to the two best therapeutic regimens currently evaluated in advanced BAC (EGFR-TKI and paclitaxel-based chemotherapy) [2, 3]. Our predefined third-line pemetrexed regimen was based on prior data from the IFCT-0401 trial indicating gemcitabine to be less effective [6], whereas pemetrexed monotherapy has recently been proven to offer excellent activity in advanced BAC [7]. Finally, we included an early evaluation (4 weeks) to detect the risk of early progression in patients with wild-type *EGFR* L-ADC receiving EGFR-TKIs as first-line therapy [41, 42].

The role of conventional chemotherapy including platinum salts, paclitaxel and pemetrexed in managing advanced L-ADC has thus been corroborated by our study. Our findings also urge physicians not to administer TKIs as first-line therapy to patients with an *EGFR* wild-type tumour. With pathological findings proving more valuable than nonaddictive molecular biomarkers (*KRAS*, MSH2 and TUBB3) for choosing the optimal treatment, our data confirmed that chemotherapy should be preferred over EGFR-TKIs for patients with mucinous L-ADC. However, several novel somatic gene fusions could represent a therapeutic opportunity for advanced mucinous L-ADC, a tumour for which no effective treatment exists, except chemotherapy, and which frequently presents with multifocal unresectable disease [43, 44].

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