Published OnlineFirst March 6, 2020; DOI: 10.1158/1078-0432.CCR-19-3056

Randomized Phase II Trial Evaluating Treatment with EGFR-TKI Associated with Antiestrogen in Women with Nonsquamous Advanced-Stage NSCLC: IFCT-1003 LADIE Trial

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ABSTRACT

Purpose: The incidence of lung cancer has dramatically increased in women. Preclinical data have suggested that combining EGFR–tyrosine kinase inhibitor (TKI) with an antiestrogen may overcome resistance to EGFR-TKI.

Patients and Methods: The IFCT-1003 LADIE trial was a 2 × 2 arms parallel open-label randomized phase II trial. EGFR-TKI–naïve postmenopausal women with advanced lung cancer were treated with gefitinib (G) versus gefitinib + fulvestrant (G+F) in the EGFR-mutated group ($EGFR^+$) or with erlotinib (E) versus erlotinib + fulvestrant (E+F) in the EGFR wild-type group (EGFR-WT). The primary objective was progression-free survival (PFS) at 3 and 9 months for EGFR-WT and $EGFR^+$ patients.

Results: Overall, 204 patients (gefitinib 104 and G+F 100) and 175 patients (erlotinib 87 and E+F 88) were enrolled in the $EGFR^+$ and EGFR-WT cohorts. In the $EGFR^+$ cohort, the primary endpoint was reached, with 58% of the G+F group patients being nonprogressive at 9 months. Adding fulvestrant to gefitinib was not associated with improved PFS (9.9 vs 9.4 months) or overall survival (OS; 22.1 vs 28.6 months). In the EGFR-WT cohort, the primary endpoint was also achieved (33.7% of the patients were nonprogressive at 3 months). Adding fulvestrant to erlotinib was not associated with improved outcome (PFS 1.8 vs 2.0 and OS 10.3 vs 7.3 months). No PFS difference was observed regarding estrogen receptor alpha expression. The tolerance was as expected with no treatment-related death.

Conclusions: Adding fulvestrant to EGFR-TKI is feasible, but not associated with prolonged PFS regardless of EGFR status. The lack of benefits while combining fulvestrant to EGFR-TKI does not support its future development in an unselected population.

Introduction

Lung cancer remains the leading cause of cancer-related mortality, worldwide, with 2.1 million new lung cancer cases and 1.8 million deaths estimated in 2018 (1). Its incidence has been increasing in women, reaching up to 725,000 new cases. During the last decade, lung cancer in women has become the primary cause of cancer-related death in the United States, surpassing breast cancer. It is the secondary cause in Europe. These figures fully justify a specific focus on this major public health problem.

Biology of lung cancer in women is currently considered as being similar to lung cancer in men and, thus, treated in the same way. Nevertheless, numerous studies have highlighted the specific features of lung cancer in women, such as clinical and radiological presentations, pathologic types, oncogenic drivers, response to cancer treatments, as well as patient survival (2, 3).

Several hypotheses have been put forward to account for the specific characteristics of lung cancer affecting women. The most appealing is based on several epidemiologic and biological arguments supporting the relevance of hormonal factors in lung oncogenesis. First, lung cancer shares certain hormonal risk factors with gynecologic cancers (4, 5). Likewise, lung cancer hormone dependence may be further supported by the aggressiveness of lung cancer during pregnancy (3). Links between hormone replacement therapy (HRT) and lung cancer in women have been widely studied. Second, hormone use is associated with worse outcome. Ganti and colleagues reported that there is a link between HRT and lung cancer diagnosis at a younger age and poorer

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ClinicalTrials.gov Identifier: NCT01556191

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Clin Cancer Res 2020;XX:XX–XX

doi: 10.1158/1078-0432.CCR-19-3056

Published OnlineFirst March 6, 2020; DOI: 10.1158/1078-0432.CCR-19-3056

Translational Relevance

Preclinical models suggest that EGFR and estrogen pathways are interdependent. We thus tested the double inhibition of both pathways in a phase II randomized trial. We show that adding an estrogen receptor antagonist, fulvestrant, to an EGFR–tyrosine kinase inhibitor (TKI) is associated with favorable outcomes and acceptable safety. Nonetheless, this combination fails to increase progression-free survival compared with EGFR-TKI alone in both mutated and wild-type EGFR women with non–small cell lung cancer. Subgroup analysis based on estrogen receptor alpha and beta failed to select responders.

survival rates. These two arguments have favored a procarcinogen effect derived from HRT (6). In addition, the Women's Health Initiative study reported that taking estradiol in conjunction with progesterone as replacement therapy correlated with poorer survival rates observed in patients with non–small cell lung cancer (NSCLC; 46% mortality in the arm receiving HRT vs 26% in the placebo arm; ref. 7). Slatore and colleagues evaluated the risk of developing lung cancer based on a cohort of more than 36,000 peri- or postmenopausal patients, with or without HRT. The authors observed an increased risk of developing lung cancer for women having received HRT (8).

Moreover, the presence of estrogen receptors (ER) in lung tumors has been reported by our team and others (9–12), although their prognostic impact remains controversial. It has been clearly shown that ER pathway activation in cell and animal models plays a major role in oncogenesis (10, 13). The ER alternative pathway may interact with other pathways controlled by growth signals. Some preclinical data have suggested that both ER and EGFR pathways can substitute each other. The combination of fulvestrant (F) and EGFR–tyrosine kinase inhibitors (TKI) on a xenograft model in a nude mouse has shown to be superior to EGFR-TKI alone, suggesting the usefulness of a dual inhibition (14). Small phase I and II studies conducted have revealed the feasibility of such combinations, although these trials were not aimed at molecular defined subgroups (15, 16).

We have thus conducted a large phase II trial to investigate the tolerance and efficacy of fulvestrant combined with an EGFR-TKI inhibitor in two distinct cohorts of women with stage IV NSCLC, either EGFR wild-type (WT) or EGFR mutated ($EGFR^+$).

Patients and Methods

Patients

The main inclusion criteria were histologically confirmed inoperable stage III or stage IV nonsquamous NSCLCs, with analyzable tissue for the research of EGFR-activating mutation (exon 19 and 21 mutation and deletion known to be oncogenic). Analysis was to be performed at INCa (French National Institute of Cancer)-certified laboratories according to a validated procedure. Two cohorts were identified: (i) patients with an *EGFR* mutation who were either chemo-naïve or in progression after only one previous chemotherapy line (including maintenance), and (ii) patients without an EGFR mutation who had received one or two chemotherapy lines beforehand.

Other inclusion criteria were: the presence of at least one lesion that could be measured by a CT scan (RECIST v1.1), postmenopausal female (either >60 years or amenorrhea >12 months), with a World Health Organization performance index of 0, 1, or 2.

The main exclusion criteria were known or suspected cerebral metastases or spinal cord compression, unless asymptomatic without treatment or stable after being treated by surgery, radiotherapy, or both; history of venous thrombosis of less than 3 months; long-term curative anticoagulant treatment; or hemorrhagic disorders.

The research protocol was approved by a national Ethics Committee. The study was conducted according to the Declaration of Helsinki of 1964 and Good Clinical Practice guidelines. All patients provided written informed consent to participate.

Study design

This was a phase II randomized clinical trial evaluating the combination of an EGFR-TKI with an antiestrogen treatment in women with advanced-stage lung cancer (NCT01556191).

The primary objective was to analyze progression-free survival (PFS) at 3 and 9 months for EGFR-WT patients and $EGFR^+$ patients, respectively, who were treated with EGFR-TKI, either combined with fulvestrant or given alone. These endpoints have been chosen to identify the impact of addition of fulvestrant on PFS in an exploratory noncomparative phase II trial.

The secondary objectives were to assess the combined safety of EGFR-TKI and fulvestrant, the overall response rate, and overall survival (OS). The exploratory objectives were aimed to identify prognostic and predictive biomarkers.

Treatment

Patients with *EGFR* mutations were treated with gefitinib (G, 250 mg/day), administered on its own or combined with fulvestrant. Gefitinib was the standard of care at the time of the study for $EGFR^+$ patients. Patients with EGFR-WT were treated with erlotinib (E, 150 mg/day) on its own or combined with fulvestrant. Here also, erlotinib was approved in EGFR-WT patients at the time of the study. Fulvestrant was administered by two slow, intramuscular injections (2×250 mg, 1–2 minutes per injection) with prefilled syringes once a month, with an additional injection at cycle 1 day 15 according to its approval. Syringes were kept refrigerated (2°C–8°C) in their original packaging.

Assessments

We assessed tumors on imaging at baseline and then every 8 weeks. Tumor response was assessed according to RECIST 1.1 based on chest CTs, upper abdomen CTs, and any other abnormal tests with target lesions at screening, and in case of suspicious signs. Tumor assessments were pursued until progression.

Evaluation of safety and tolerability

Adverse event monitoring was performed at day 15 of the first cycle, before each cycle (ie, every 4 weeks until the end of protocol treatment), and for 30 days after drug discontinuation. Adverse events and laboratory abnormalities were graded according to the NCI Common Terminology Criteria for Adverse Events, Version 4.0.

Biomarker analysis

Representative tissue was available for 172 samples. All antibodies were tested on whole sections obtained from formalin-fixed, paraffin-embedded paraffin blocks after morphologic examination by the pathologist.

Three antibodies were tested for immunostaining: Estrogen Receptor alpha (ER clone EP1, Dako Agilent), Progesterone Receptor (PR

Published OnlineFirst March 6, 2020; DOI: 10.1158/1078-0432.CCR-19-3056

clone PgR636, Dako Agilent), and HER2 (HercepTest, Dako Agilent). For ER and PR, sections were deparaffinized, rehydrated, and heated for antigen retrieval, 20 minutes in high pH buffer (Dako). IHC was performed on Dako Link Autostain with Envision Flex revelation system. Positive control slides were used for each series of stains. For HER2: the HercepTest for Automated Link Platforms was performed on Dako Autostainer according to the manufacturer's instructions integrating positive controls. All the slides were incubated in diaminobenzidine and counterstained with hematoxylin, dehydrated, and mounted. For ER and PR, the percentage and intensity of staining were evaluated. For HER2, a scoring was made according to the manufacturer's guidelines

In situ hybridization was also performed for *HER2*. *HER2* IQ probe was used (IQFISH HER2).

Table 1. Biomarkers analysis performed in the trial.

Marker	Procedure	*n*	*n* evaluable	*n* positive
ER	IHC	172	165	34 (>1%)
PR	IHC	172	170	2 (>1%)
HER2	IHC	162	161	39 ++ 2 +++
HER2	FISH	172	116	7

Number of samples tested for each biomarker, numbers of evaluable samples, and positive specimens for each analysis are presented in **Table 1**.

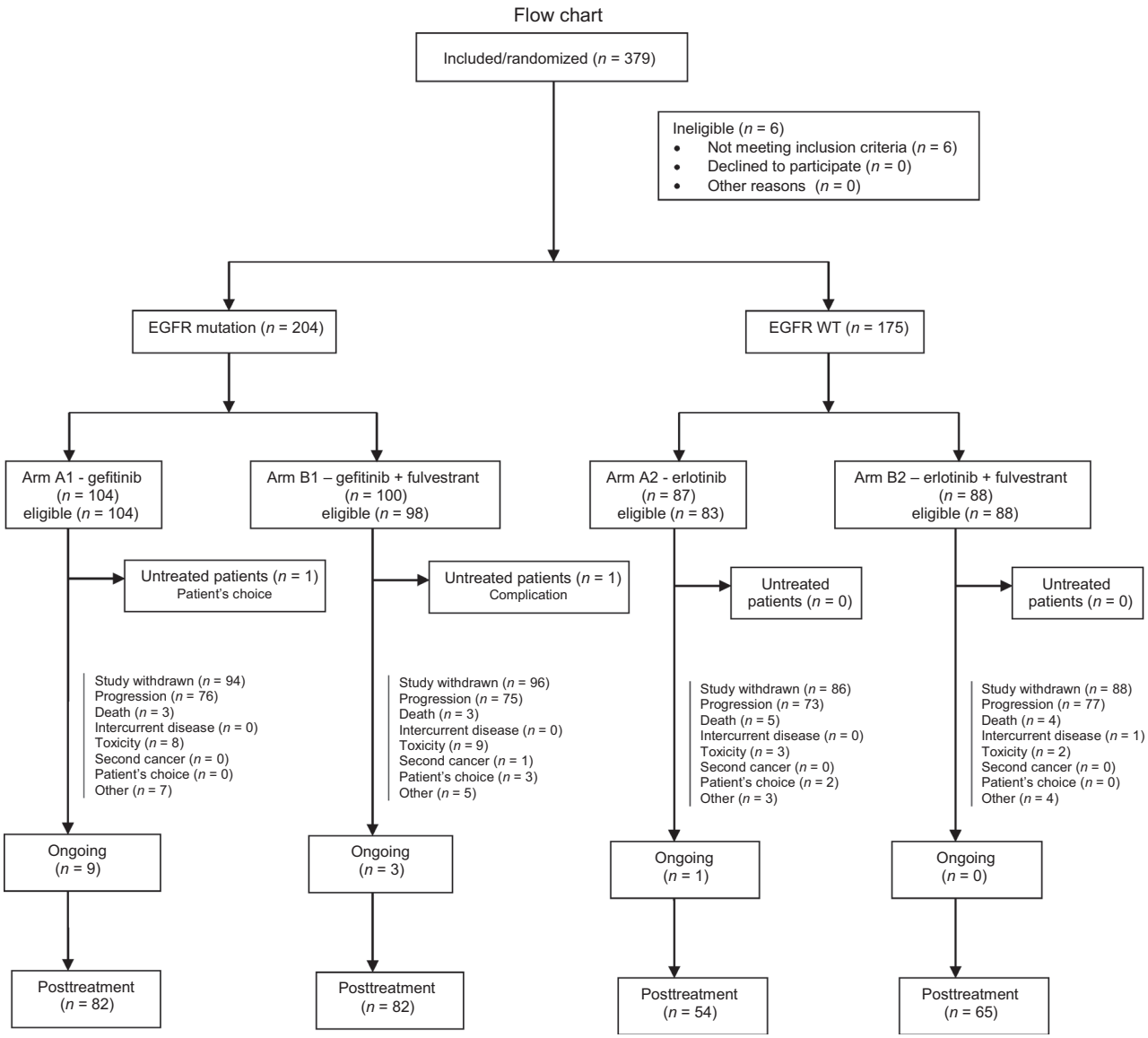

Figure 1.
Consort diagram.

Published OnlineFirst March 6, 2020; DOI: 10.1158/1078-0432.CCR-19-3056

Statistical design and analyses

Only the experimental group was considered for the effectiveness evaluation during this phase II trial. The reference arms were used as comparator with literature data to validate the study population and rule out the existence of possible selection biases.

The calculation for the number of patients was based on a Fleming one-stage method, with a 5% unilateral alpha risk and 90% power in each of the four arms.

This calculation was based on PFS at 3 months in EGFR-WT patients with H0: $P0 \leq 30\%$ and H1: $P1 \geq 45\%$. On the basis of these hypotheses, 95 patients were required for each arm, thus 190 in total. PFS at 9 months was chosen in EGFR$^+$ patients with H0: $P0 \leq 45\%$ and H1: $P1 \geq 60\%$. On the basis of these hypotheses, 102 patients were required in each arm, thus 204 in total. We randomly assigned patients enrolled by investigators (1:1) to the two treatment groups. Randomization was centrally performed by computer. We used a minimization method (random factor of 0.8) and stratified patients by center, performance status (PS, 0–1 vs 2), age (<70 vs ≥70), and treatment line (1 vs 2).

Efficacy (PFS, OS, response at 2 months, and best response) was assessed in eligible patients, whereas description was employed in the intention-to-treat population. Safety was assessed in the safety population defined as all patients who had received at least one cycle of their assigned study treatment.

SAS software (Version 9.4) was used.

Analysis of PFS at 3 and 9 months was estimated using the Kaplan–Meier method. Likewise, median PFS and OS were estimated using the Kaplan–Meier method with follow-up censored on May 1, 2018.

Results

Patient characteristics

Between May 2012 and March 2017, for the EGFR$^+$ and EGFR-WT cohorts, 204 (gefitinib 104; G+F 100) patients and 175 (erlotinib 87; E+F 88) patients were enrolled, respectively. The CONSORT diagram (see **Fig. 1**) illustrates the repartition of the patients within the two cohorts/four arms. In the EGFR$^+$ cohorts, the median age was 68 years, with mainly nonsmokers, PS 0 or 1, and adenocarcinoma. They were either chemo-naïve or had previously received one line of systemic treatment. The clinical characteristics were well balanced between the two groups, with or without fulvestrant. In the EGFR-WT cohorts, the median age was 63 years, with mainly smokers (75%); PS of 0 (39%), 1 (45%), or 2 (16%); and adenocarcinoma (94%). Patients were previously treated with either one (69%) or two (31%) treatment lines (see **Table 2**). Here, again, no difference was observed between both groups.

Efficacy

The median follow-up was 67.8 months [95% confidence interval (CI), 65.3–NR]. In the EGFR$^+$ cohort, on the 93 first eligible patients (as defined in the protocol), 54 patients in the G+F group were nonprogressive at 9 months giving a 58.1% (48.0–68.1) 9-month PFS rate, comprised in the preset H0–H1 interval. Nevertheless, adding fulvestrant to gefitinib was not associated with significantly improved median PFS [9.9 months (7.7–11.2) vs 9.4 months (8.0–12.7)] or median OS [22.1 months (18.6–25.7) vs 29.9 (23.2–43.8) months]. In the EGFR-WT cohort treated with E+F, 3-month PFS was 33.7% (23.7–43.7) while H0 set at 30%. Here, again, adding fulvestrant to erlotinib was not associated with improved outcome [PFS 1.8 months (1.7–2.1) vs 2.0 (1.8–2.6); OS 10.0 months (6.6–14.6) vs 7.3 months (5.4–9.3); see **Figs. 2** and **3**, **Table 5**]. The complete and partial responses at 2 months were not statistically different either between gefitinib (54.8%) and G+F (52.0%) or between erlotinib (3.4%) and E+F (2.3%). Best response was also assessed and was not significantly different between gefitinib (69.3%) and G+F (64%) or between erlotinib (3.4%) and E+F (3.4%). Disease control rates were also comparable in each subgroup (see **Table 3**).

Safety

The tolerance was correct, with grade 1–2 toxicity in 72.7% of the G+F group versus 72.8% of the gefitinib group, and in 70.5% of the E+F group versus 75.9% of the erlotinib group. Grade 3–4 toxicity was observed in 24.2% of the G+F group versus 21.4% of the gefitinib group, and 15.9% of the E+F group versus 13.8% of the erlotinib group.

Table 2. Baseline patient characteristics.

			A1 - gefitinib ($N = 104$)	B1 - gefitinib and fulvestrant ($N = 100$)	A2 - erlotinib ($N = 87$)	B2 - erlotinib and fulvestrant ($N = 88$)
Age (years)		Median	67.71	68.30	64.56	61.03
		Range	(49.5–89.1)	(50.1–90.9)	(43.6–85.4)	(43.7–80.5)
Smoking status	Smoker	*N* (%)	24 (23.1)	31 (31.0)	62 (71.3)	70 (79.5)
Pack-years		Median	12.00	11.50	37.50	35.00
		Range	(1.0–54.0)	(1.0–50.0)	(1.0–92.0)	(1.0–120.0)
ECOG performance status	0	*N* (%)	42 (40.4)	42 (42.0)	27 (31.0)	41 (46.6)
	1	*N* (%)	53 (51.0)	49 (49.0)	46 (52.9)	33 (37.5)
	2	*N* (%)	9 (8.7)	9 (9.0)	14 (16.1)	14 (15.9)
Histological subtype	Adenocarcinoma	*N* (%)	99 (95.2)	95 (95.0)	82 (94.3)	82 (93.2)
	Nonadenocarcinoma	*N* (%)	5 (4.8)	5 (5.0)	5 (5.7)	6 (6.8)
EGFR mutation	Yes	*N* (%)	104 (100.0)	100 (100.0)	0	0
Number of previous lines of treatment	1 (second-line patients)	*N* (%)	104 (100.0)	100 (100.0)	61 (70.1)	59 (67.0)
	≥2 (third-line patients or more)	*N* (%)	0	0	26 (29.9)	29 (33.0)
Postmenopausal patient	Yes	*N* (%)	104 (100.0)	100 (100.0)	87 (100.0)	88 (100.0)
ERα	Negative	*N* (%)	34 (77.3)	41 (82.0)	26 (78.8)	25 (75.8)
	Positive	*N* (%)	10 (22.7)	9 (18.0)	7 (21.2)	8 (24.2)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Published OnlineFirst March 6, 2020; DOI: 10.1158/1078-0432.CCR-19-3056

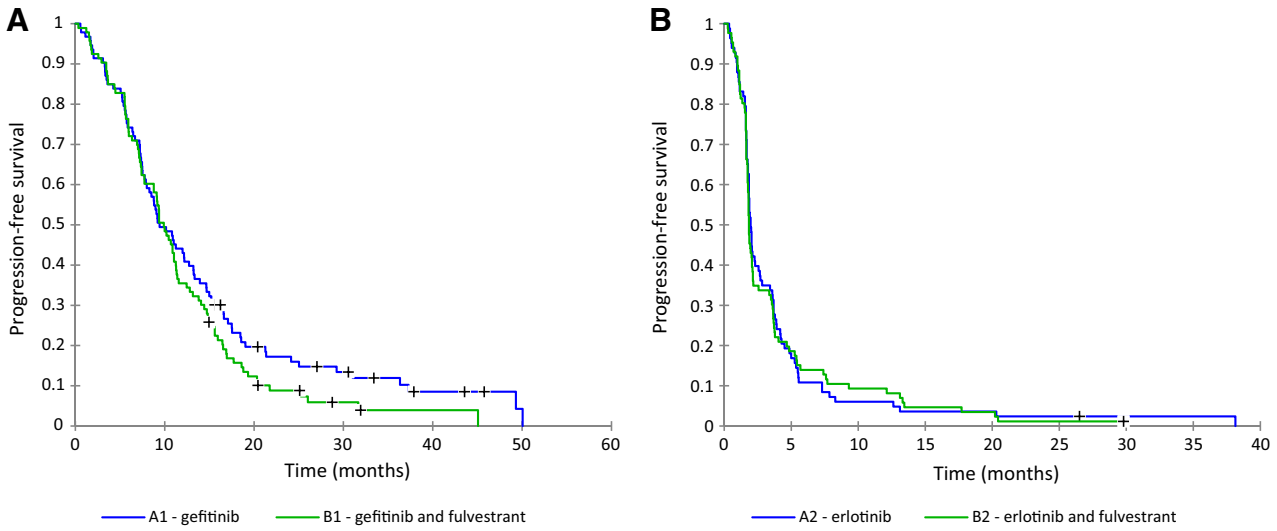

Figure 2.
PFS. **A,** PFS of EGFR$^+$ patients. **B,** PFS of EGFR-WT patients. Crosses represent censored patients.

No treatment-related death was reported. The main toxicity occurred in the EGFR-TKI inhibitor class, consisting of gastrointestinal disorders and skin toxicity. A specific focus was put on a potential increase in vascular undesirable effects like phlebitis. We observed a higher incidence of grade 1–2 vascular disorders in patients receiving the combination (20.2 vs 6.8 for G+F vs G; 11.4 vs 4.6 for E+F vs E). Only two grade 3–4 toxicities were observed in the E+F arm, with no unexpected toxicity (see **Table 4**).

Biomarkers

As fulvestrant is restricted to women with breast cancer and positivity for ER, we sought to analyze the outcome in terms of ER, PR, and HER2 expression. PFS was slightly better in the subgroup with ERα-positive expression versus patients with no expression (14.7 vs 8.3 months for the gefitinib group, 11.3 vs 9.4 months for the G+F group). ERα expression was also associated with better OS (not reached vs 22.2 months for the gefitinib group and 29.8 vs 23.1 months for the G+P group), yet irrespective of the addition of fulvestrant (see **Fig. 4** and **Table 5**). This suggests that ERα is more a prognostic marker than a predictive marker. No differences according to the expression of PR or HER2 were observed (data not shown).

Discussion

Preclinical and epidemiologic data strongly suggest that lung cancer in women can be associated, at least to some extent, with hormonal

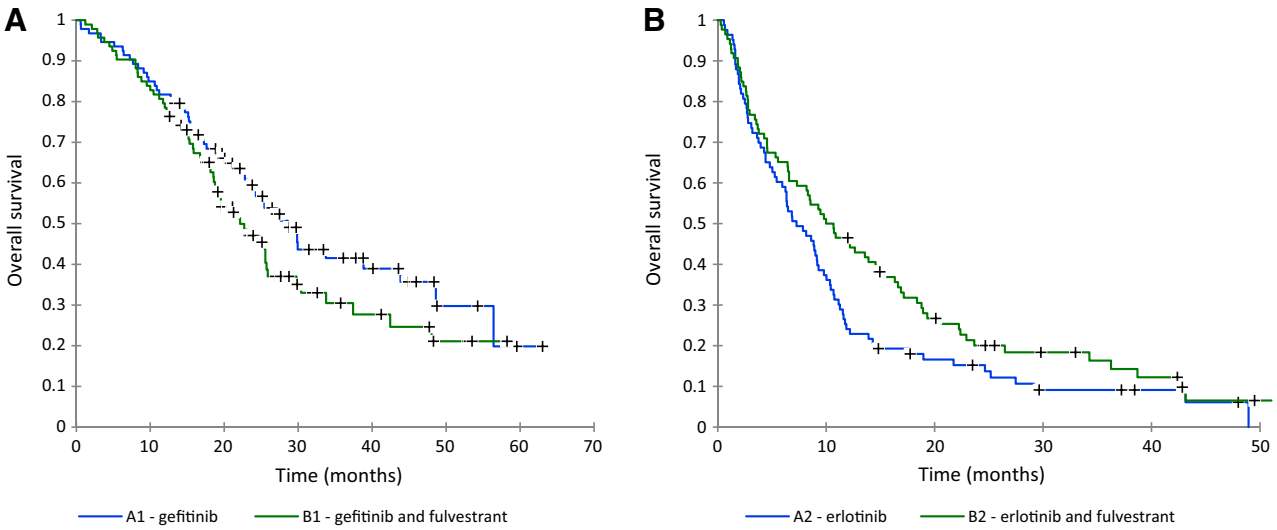

Figure 3.
OS. **A,** OS of EGFR$^+$ patients. **B,** OS of EGFR-WT patients. Crosses represent censored patients.

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Table 3. Response at 2 months and best response at eligible population.

			A1 - gefitinib (*N* = 104)	B1 - gefitinib and fulvestrant (*N* = 98)	A2 - erlotinib (*N* = 83)	B2 - erlotinib and fulvestrant (*N* = 88)
Response at 2 months	Complete response	*N* (%) (CI 95%)	1 (1.0) (0.0–2.8)	0	0	0
	Partial response	*N* (%) (CI 95%)	56 (53.8) (44.3–63.4)	52 (52.0) (42.2–61.8)	3 (3.4) (0.0–7.3)	2 (2.3) (0.0–5.4)
	Stable disease	*N* (%) (CI 95%)	35 (33.7) (24.6–42.7)	34 (34.0) (24.7–43.3)	25 (28.7) (19.2–38.2)	24 (27.3) (18.0–36.6)
	Disease control rate	*N* (%) (CI 95%)	92 (88.5) (82.3–94.6)	86 (86.0) (79.2–92.8)	28 (32.2) (22.4–42.0)	26 (29.5) (20.0–39.1)
	Disease progression	*N* (%) (CI 95%)	12 (11.5) (5.4–17.7)	14 (14.0) (7.2–20.8)	59 (67.8) (58.0–77.6)	62 (70.5) (60.9–80.0)
Best response	Complete response	*N* (%) (CI 95%)	1 (1.0) (0.0–2.8)	2 (2.0) (0.0–4.7)	1 (1.1) (0.0–3.4)	0
	Partial response	*N* (%) (CI 95%)	71 (68.3) (59.3–77.2)	62 (62.0) (52.5–71.5)	3 (3.4) (0.0–7.3)	3 (3.4) (0.0–7.2)
	Stable disease	*N* (%) (CI 95%)	23 (22.1) (14.1–30.1)	23 (23.0) (14.8–31.2)	26 (29.9) (20.3–39.5)	24 (27.3) (18.0–36.6)
	Disease control rate	*N* (%) (CI 95%)	95 (91.3) (85.9–96.7)	87 (87.0) (80.4–93.6)	30 (34.5) (24.5–44.5)	27 (30.7) (21.0–40.3)
	Disease progression	*N* (%) (CI 95%)	9 (8.7) (3.3–14.1)	13 (13.0) (6.4–19.6)	57 (65.5) (55.5–75.5)	61 (69.3) (59.7–79.0)

factors. Therefore, testing pharmaceutical modulators of the estrogen pathway in this setting appeared to be an appealing strategy. Several trials to address this hypothesis (15, 16) had previously been conducted in unselected patient populations. We, herein, addressed the potential usefulness of combining an EGFR-TKI with an ER inhibitor in both EGFR-WT and $EGFR^+$ patients. Both combinations, for each patient subgroups, $EGFR^+$ or EGFR-WT, led to acceptable 9-month and 3-month PFS, respectively, above the preset lower boundary for H0. However, median PFS or OS were not substantially different with or without fulvestrant in each group and we failed to demonstrate that the ER inhibitor fulvestrant was able to delay recurrence and increase survival.

In patient subgroups based on ERα expression, no significant differences were found. The link between ER expression and lung oncogenesis remains unclear. The lungs are particularly rich in hormone receptors (17), and different studies have reported ER expression involving the two types, namely alpha (α) and beta (β; ref. 18). The ER expression in lung tumors is controversial, but ERβ is seemingly expressed in most NSCLCs, regardless of gender (10, 12, 19–21). However, studies have revealed contradicting results in terms of ERα expression. While several studies have reported a high rate of lung tumors expressing ERα, others have found only little or no expression (11, 12, 21–23). Finally, Stabile and colleagues and Hershberger and colleagues (10, 13) have clearly demonstrated ER pathway activation in cell and animal models, suggesting the ER pathway to be not only present in the lungs, but also playing a major role in oncogenesis.

In a pilot study conducted on 22 patients, Traynor and colleagues showed that the combination therapy of gefitinib with fulvestrant was well tolerated, while demonstrating activity on the disease (15).

Table 4. Treatment-related adverse events.

	A1 - gefitinib (*N* = 103)		B1 - gefitinib and fulvestrant (*N* = 99)		A2 - erlotinib (*N* = 87)		B2 - erlotinib and fulvestrant (*N* = 88)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Any adverse event	75 (72.8%)	22 (21.4%)	72 (72.7%)	24 (24.2%)	66 (75.9%)	12 (13.8%)	62 (70.5%)	14 (15.9%)
Serious adverse event	1 (1%)	3 (2.9%)	1 (1%)	3 (3%)	2 (2.3%)	3 (3.4%)	1 (1.1%)	4 (4.5%)
Led to discontinuation	1 (1%)	7 (6.8%)	3 (3%)	5 (5.1%)	1 (1.1%)	2 (2.3%)	1 (1.1%)	1 (1.1%)
Led to death	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	81 (78.6%)	3 (2.9%)	68 (68.7%)	6 (6.1%)	50 (57.5%)	2 (2.3%)	51 (58%)	1 (1.1%)
Gastrointestinal disorders	73 (70.9%)	4 (3.9%)	69 (69.7%)	5 (5.1%)	47 (54%)	6 (6.9%)	42 (47.7%)	3 (3.4%)
General disorders and administration site conditions	38 (36.9%)	3 (2.9%)	48 (48.5%)	3 (3%)	25 (28.7%)	4 (4.6%)	23 (26.1%)	1 (1.1%)
Investigations	36 (35%)	9 (8.7%)	34 (34.3%)	8 (8.1%)	17 (19.5%)	0	14 (15.9%)	4 (4.5%)
Infections and infestations	31 (30.1%)	1 (1%)	28 (28.3%)	4 (4%)	16 (18.4%)	0	13 (14.8%)	0
Blood and lymphatic system disorders	19 (18.4%)	1 (1%)	18 (18.2%)	1 (1%)	19 (21.8%)	1 (1.1%)	21 (23.9%)	2 (2.3%)
Metabolism and nutrition disorders	17 (16.5%)	1 (1%)	15 (15.2%)	0	16 (18.4%)	1 (1.1%)	20 (22.7%)	1 (1.1%)
Vascular disorders	7 (6.8%)	0	20 (20.2%)	0	4 (4.6%)	0	10 (11.4%)	2 (2.3%)
Eye disorders	15 (14.6%)	0	9 (9.1%)	0	11 (12.6%)	1 (1.1%)	3 (3.4%)	0
Musculoskeletal and connective tissue disorders	9 (8.7%)	0	11 (11.1%)	0	3 (3.4%)	0	7 (8%)	0
Nervous system disorders	10 (9.7%)	0	12 (12.1%)	0	2 (2.3%)	0	3 (3.4%)	0
Renal and urinary disorders	11 (10.7%)	0	4 (4%)	0	1 (1.1%)	2 (2.3%)	4 (4.5%)	0
Respiratory, thoracic, and mediastinal disorders	7 (6.8%)	1 (1%)	6 (6.1%)	0	2 (2.3%)	1 (1.1%)	4 (4.5%)	0
Reproductive system and breast disorders	3 (2.9%)	0	7 (7.1%)	0	0	0	1 (1.1%)	0
Hepatobiliary disorders	4 (3.9%)	0	5 (5.1%)	0	0	0	1 (1.1%)	0

Note: Data are *n* (%). Only events occurring in at least 5% of the population of any group are included.

Published OnlineFirst March 6, 2020; DOI: 10.1158/1078-0432.CCR-19-3056

Table 5. Patient outcomes.

	A1–gefitinib	B1–gefitinib and fulvestrant		A2–erlotinib	B2–erlotinib and fulvestrant
N patients	93	93	Eligible patients	83	86
Disease progression	84	88	Disease progression	82	85
Censored needed at 9 months for trial to be positive (number of patients)		≥**51**	Censored needed at 3 months for trial to be positive		≥**34**
Censored at 9 months	50	54	Censored at 3 months	29	29
PFS (months), median (95% CI)	9.4 (8.0–12.7)	9.9 (7.7–11.2)	PFS (months), median (95% CI)	2.0 (1.8–2.6)	1.8 (1.7–2.1)
9-month PFS	53.8% (43.6–63.9)	58.1% (48.0–68.1)	3-month PFS	34.9% (24.7–45.2)	33.7% (23.7–43.7)
Death	51	58	Death	76	73
N patients	104	98	*N* patients	83	88
OS (months), median (95% CI)	29.9 (23.2–43.8)	22.1 (18.6–25.7)	OS (months), median (95% CI)	7.3 (5.4–9.3)	10.0 (6.6–14.6)

Note: Data are *n* unless otherwise stated.

Later on, the same team initiated a phase II trial combining gefitinib and fulvestrant in postmenopausal women with advanced NSCLC, although the trial was suspended as gefitinib was no longer available in the United States. Thereafter, the trial was amended using erlotinib instead. An open-label, randomized, phase II study aimed to evaluate erlotinib plus fulvestrant versus erlotinib alone was then conducted. Although there was no improvement in PFS or OS observed with erlotinib plus fulvestrant when considering all of the

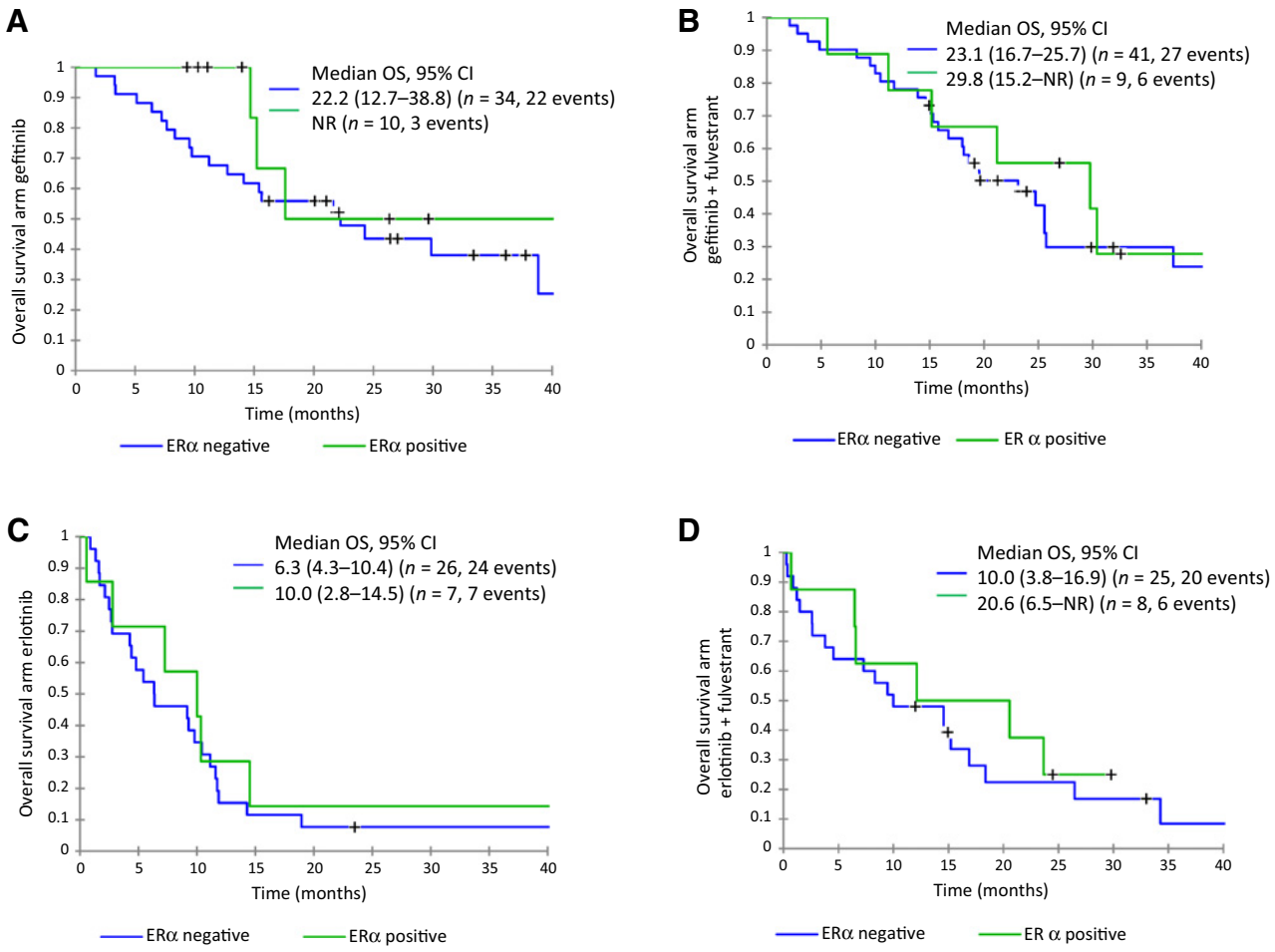

Figure 4.

Outcomes in terms of ERα status. **A,** OS of patients in gefitinib arm. **B,** OS of patients in gefitinib and fulvestrant arm. **C,** OS of patients in erlotinib arm. **D,** OS of patients in erlotinib and fulvestrant arm. (*Continued on the following page.*)

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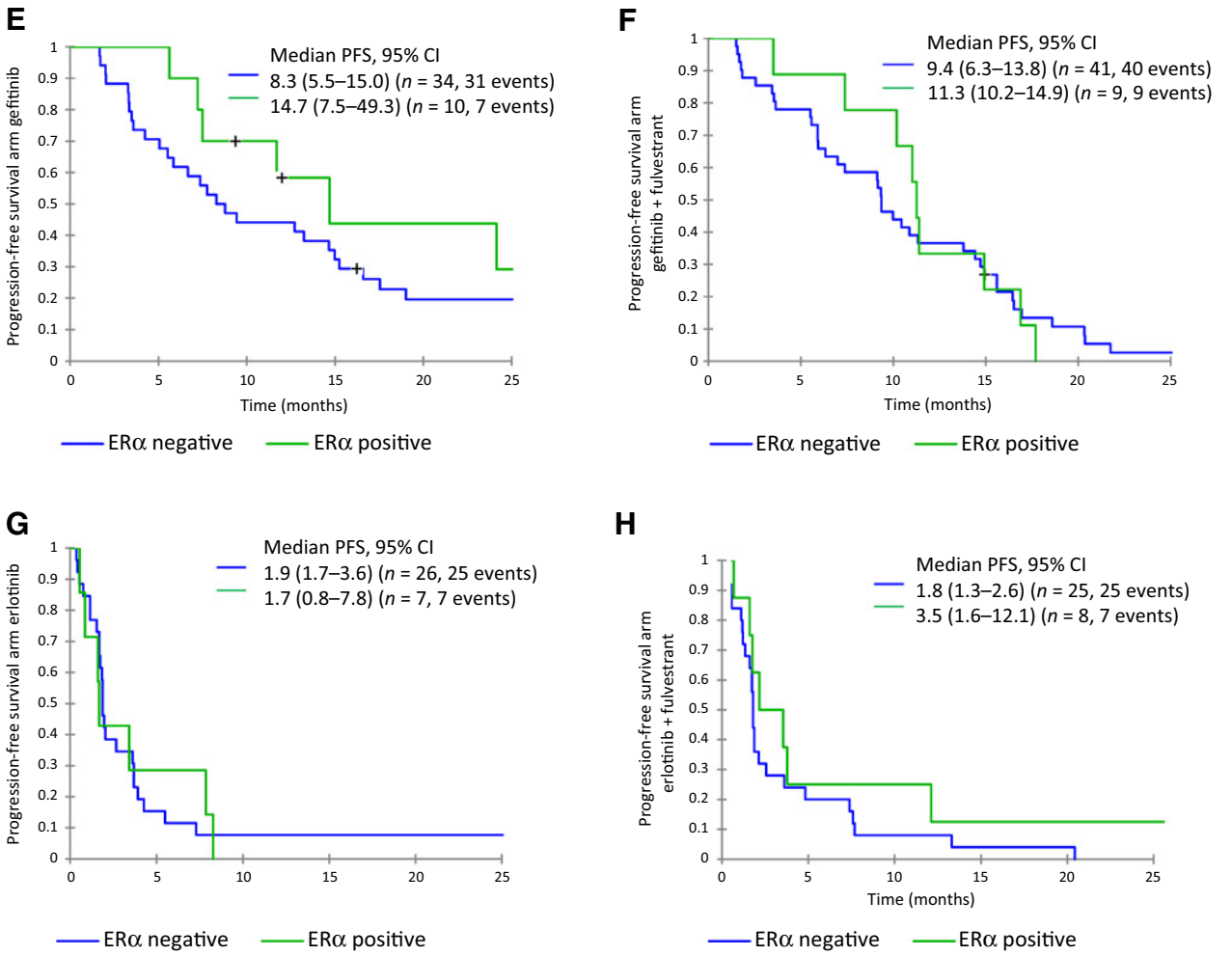

Figure 4.

(*Continued.*) **E,** PFS of patients in gefitinib arm. **F,** PFS of patients in gefitinib and fulvestrant arm. **G,** PFS of patients in erlotinib arm. **H,** PFS of patients in erlotinib and fulvestrant arm. Crosses represent censored patients.

patients, a subgroup analysis among EGFR-WT patients revealed that erlotinib plus fulvestrant was associated with an improvement in median PFS. Other approaches are currently testing aromatase inhibitors, such as exemestane given either alone (NCT02666105) or in combination with chemotherapy (carboplatin and pemetrexed; NCT01664754). In many countries, osimertinib is now a new standard of care in first-line and is associated with longer PFS. However, to date, no preclinical or clinical data support the use of estrogen inhibitors in combination with osimertinib in $EGFR^{+}$ patients.

In nonmutated patients, PFS with EGFR-TKI is approximately 3 months, and the majority of patients do not benefit from administered treatments. Since our study began patient recruitment, the benefits of EGFR-TKIs in terms of PFS and OS in managing EGFR-WT NSCLCs has been questioned, leading to the recent withdrawal of approval from the American and European agencies. Clearly, as shown by our data, adding fulvestrant does not improve the PFS. Nevertheless, we observed a numerical gain of 3 months in term of OS that might be explained by an imbalance in second-line treatment or by a delayed effect of fulvestrant. Noteworthy, since this study has been initiated, immune checkpoint inhibitors have become the standard of care in this setting. The possibility that the combination of hormonal therapies with immunotherapy could exert a synergistic effect should be further investigated (24). Nevertheless, the potential role of EGFR inhibitors following first-line immunotherapy and chemotherapy combination deserves further investigation.

In mutated patients, whereas PFS has been significantly improved from approximately 9 to 12 months, a certain number of patients are resistant to EGFR-TKI from the outset, while all the patients treated with EGFR-TKIs develop a secondary resistance. The interplay between the ER and EGFR pathways suggested that ER blockade may help control or delay recurrence. Nonetheless, we were not able to confirm any improvement in our study. Currently, we are moving toward third-generation EGFR-TKIs employed in the first-line setting, and fulvestrant is unlikely to lead to better results when administered in combination with osimertinib. As our study has been conducted in France from 2012 to 2017, it is also unlikely that many patients have been treated with subsequent osimertinib.

In conclusion, adding fulvestrant to EGFR-TKI is feasible and associated with good PFS in the EGFR$^+$ group. Nevertheless, in spite of the preclinical rationale, fulvestrant does not result in improved patient outcomes. The lack of benefits when combining fulvestrant to EGFR-TKI does not support its further development into a phase III trial in female patients suffering from NSCLC.

Disclosure of Potential Conflicts of Interest

J. Mazieres reports receiving commercial research grants from AstraZeneca and Roche. F. Barlesi reports receiving speakers bureau honoraria from and is an advisory board member/unpaid consultant for Roche Genentech. I. Rouquette is an advisory board member/unpaid consultant for AstraZeneca, MSD, and BMS. B. Besse reports receiving commercial research grants from Abbvie, Amgen, AstraZeneca, BeiGene, Blueprint Medicines, BMS, Boehringer Ingelheim, Celgene, Cristal Therapeutics, Daiichi-Sankyo, Eli Lilly, GSK, Ignyta, IPSEN, Inivata, Janssen, Merck KGaA, MSD, Nektar, Onxeo, OSE immunotherapeutics, Pfizer, Pharma Mar, Roche-Genentech, Sanofi, Servier, Spectrum Pharmaceuticals, Takeda, Tiziana Pharma, and Tolero Pharmaceuticals. C. Audigier-Valette is an employee/paid consultant for Roche, MSD, BMS, AstraZeneca, and Takeda. A.-C. Toffart is an employee/paid consultant for Roche, Boehringer Ingelheim, AstraZeneca, AbbVie, BMS, and MSD, and reports receiving commercial research grants from AbbVie, Roche, and Pfizer. V. Westeel is an employee/paid consultant for Bristol-Myers Squibb, Roche, MSD, AstraZeneca, Takeda, and Boehringer Ingelheim, and reports receiving speakers bureau honoraria from Roche, MSD, AstraZeneca, BMS, and Lilly. E. Pichon is an advisory board member/unpaid consultant for AstraZeneca, Takeda, and Bristol-Myers Squibb. A.B. Cortot is an employee/paid consultant for AstraZeneca, Roche, Pfizer, Novartis, and Takeda, and reports receiving other commercial research support from Boehringer Ingelheim, MSD, and BMS. G. Zalcman reports receiving speakers bureau honoraria from Roche, AstraZeneca, and BMS. D. Moro-Sibilot is an employee/paid consultant for Roche, AstraZeneca, Pfizer, and Boehringer Ingelheim. P.-J. Souquet reports receiving commercial research grants from and reports receiving speakers bureau honoraria from Roche and AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

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Study supervision: J. Mazieres, E. Amour, F. Morin, D. Moro-Sibilot

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Other (administrative contribution as president of the sponsor group IFCT during the conception and launching of the LADIE trial): G. Zalcman

Acknowledgments

This work was supported by IFCT, AstraZeneca, and Roche.

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Received October 21, 2019; revised December 16, 2019; accepted March 2, 2020; published first March 6, 2020.

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Published OnlineFirst March 6, 2020; DOI: 10.1158/1078-0432.CCR-19-3056

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Randomized Phase II Trial Evaluating Treatment with EGFR-TKI Associated with Antiestrogen in Women with Nonsquamous Advanced-Stage NSCLC: IFCT-1003 LADIE Trial

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Clin Cancer Res Published OnlineFirst March 6, 2020.