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Original article

Final results of the IFCT-0803 study, a phase II study of cetuximab, pemetrexed, cisplatin, and concurrent radiotherapy in patients with locally advanced, unresectable, stage III, non-squamous, non-small-cell lung cancer

Résultats de l'étude clinique IFCT-0803, de phase II, sur le cétuximab, le pémétrexed, le cisplatine et la radiothérapie concomitante chez des patients atteints d'un cancer du poumon non à petites cellules localement évolué, non résécable, de stade III, non épidermoïde

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ABSTRACT

Purpose. – Roughly 20% of patients with non-small-cell lung cancer exhibit locally advanced, unresectable, stage III disease. Concurrent platinum-based chemoradiotherapy is the backbone treatment, which is followed by maintenance immunotherapy, yet with poor long-term prognosis. This phase II trial (IFCT-0803) sought to evaluate whether adding cetuximab to cisplatin and pemetrexed chemoradiotherapy would improve its efficacy in these patients.

Materials and methods. – Eligible patients received weekly cetuximab (loading dose 400 mg/m^2 day 1; subsequent weekly 250 mg/m^2 doses until two weeks postradiotherapy). Chemotherapy comprised cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2), both delivered on day 1 of a 21-day cycle of maximally four. Irradiation with maximally 66 Gy started on day 22. Disease control rate at week 16 was the primary endpoint.

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Results. – One hundred and six patients were included (99 eligible patients). Compliance exceeded 95% for day 1 of chemotherapy cycles 1 to 4, with 76% patients receiving the 12 planned cetuximab doses. Maximal grade 3 toxicity occurred in 63% patients, and maximal grade 4 in 9.6%. The primary endpoint involving the first 95 eligible patients comprised two (2.1%) complete responses, 57 (60.0%) partial responses, and 27 (28.4%) stable diseases. This 90.5% disease control rate (95% confidence interval [95% CI]: 84.6%–96.4%) was achieved at week 16. After median 63.0-month follow-up, one-year and two-year survival rates were 75.8% and 59.5%. Median overall survival was 35.8 months (95% CI: 23.5–NR), and median progression-free survival 14.4 months (95% CI: 11.2–18.8), with one-year and two-year progression-free survival rates of 57.6% and 34.3%.
Conclusion. – These survival rates compare favourably with published data, thus justifying further development of cetuximab-based induction chemoradiotherapy.

Keywords :
Stage III NSCLC
Concurrent chemoradiotherapy
Cetuximab
Pemetrexed
Cisplatin

RÉSUMÉ

Objectif de l'étude. – Environ 20 % des cancers du poumon non à petites cellules sont de stade III, localement évolués et non résécables. La chimioradiothérapie à base de platine concomitante est le traitement de référence, qui est suivi d'une immunothérapie d'entretien, mais avec un pronostic défavorable à long terme. Cet essai de phase II (IFCT-0803) visait à évaluer si l'ajout de cétuximab au cisplatine et au pémétrexed améliorerait son efficacité chez ces patients.
Matériels et méthodes. – Les patients éligibles ont reçu du cétuximab chaque semaine (dose de charge 400 mg/m^2 au jour 1 ; doses hebdomadaires ultérieures de 250 mg/m^2 jusqu'à deux semaines après la radiothérapie). La chimiothérapie comprenait du cisplatine (75 mg/m^2) et du pémétrexed (500 mg/m^2), tous deux administrés le jour 1 d'un cycle de 21 jours de quatre au maximum. L'irradiation avec un maximum de 66 Gy a commencé le jour 22. Le taux de contrôle de la maladie à la semaine 16 était le critère d'évaluation principal.
Résultats. – Cent six patients ont été inclus (99 patients éligibles). L'observance a dépassé 95 % pour le jour 1 des cycles de chimiothérapie 1 à 4, avec 76 % des patients recevant les 12 doses de cétuximab prévues. Une toxicité maximale de grade 3 est survenue chez 63 % des patients et une toxicité maximale de grade 4 chez 9,6 %. Le critère principal d'évaluation sur les 95 premiers patients éligibles comprenait deux réponses complètes (2,1 %), 57 réponses partielles (60,0 %) et 27 maladies stables (28,4 %). Le taux de contrôle de la maladie à la semaine 16 était de 90,5 % (intervalle de confiance à 95 % [IC95 %] : 84,6 % à 96,4 %). Après un suivi médian de 63 mois, les taux de survie à un an et à deux ans étaient respectivement de 75,8 % et 59,5 %. La médiane de survie globale était de 35,8 mois (IC95 % : 23,5–NR) et la survie médiane sans progression de 14,4 mois (IC95 % : 11,2–18,8), avec des taux de survie sans progression à un an et deux ans respectivement de 57,6 % et 34,3 %.
Conclusion. – Les taux de survie dans l'étude IFCT-0803 se comparent favorablement aux données publiées, justifiant ainsi le développement ultérieur de la chimioradiothérapie d'induction à base de cétuximab.

Mots clés :
CPNPC de stade III
Chimioradiothérapie concomitante
Cétuximab
Pémétrexed
Cisplatine

1. Introduction

Lung cancer, including non-small-cell lung cancer and small-cell lung cancer, is the leading cause of cancer death worldwide [1]. Non-small-cell lung cancer constitutes approximately 85% of lung cancers, with the adenocarcinoma subtype alone accounting for half. Approximately 20% patients exhibit locally advanced, unresectable stage III disease [2]. For patients with unresectable stage III non-small-cell lung cancer, chemotherapy combined with radiotherapy (chemoradiotherapy) has become the backbone treatment. In multimodal curative-intent protocols, cisplatin-based doublet induction therapy has been adapted to stage III non-small-cell lung cancer [3]. Given these patients' poor long-term prognosis, new therapeutic combinations are urgently needed. In the PACIFIC phase III study, anti-PD-L1 immune checkpoint (durvalumab) therapy, following cisplatin-based concurrent chemoradiotherapy, improved long-term survival by prolonging median progression-free survival and overall survival [4,5]. However, PACIFIC trial patients were only randomized after the first combination therapy was completed. New chemoradiotherapy schemes that increase the percentage of patients amenable to maintenance immunotherapy are thus required.

The epidermal growth factor receptor (EGFR) is a potential target, as EGFR is activated in response to ionizing radiation and contributes to radio-resistance [6]. Cetuximab blocks EGF's binding to EGFR's extracellular domain. Combining cetuximab with chemotherapy regimens in patients with metastatic non-small-cell lung cancer has revealed cetuximab to be effective, with manageable toxicity [7]. Preclinically, cetuximab amplified the chemotherapy response and displayed radiosensitizing properties [8].

According to our hypothesis, adding cetuximab to induction chemoradiotherapy could improve its efficacy, with tolerable safety. The final results of the phase II feasibility study that evaluated adding cetuximab to a cisplatin and pemetrexed chemoradiotherapy in stage III non-squamous non-small-cell lung cancer are presented herein.

2. Patients and methods

2.1. Patient selection

This phase II study recruited patients aged 18 to 70 years old, with pathologically confirmed, inoperable, stage III non-squamous non-small-cell lung cancer, with Eastern Cooperative Oncology

Group performance status (ECOG PS) score ≤ 1, weight loss less than 10% in the previous 3 months, at least one measurable target (RECIST 1.1 criteria), adequate organ function, DLCO/VA ≥ 50% theoretical value, and $PaO_2 \geq 60$ mmHg.

Prestudy evaluations conducted within two weeks before the study were: patient's history and physical examination, performance status, complete blood count, and laboratory profile. Patients had undergone a chest computed tomography (CT), brain CT or magnetic resonance imaging, electrocardiogram, and pulmonary function tests within four weeks prestudy. CT scans were used for all subsequent evaluations and tumour measurements. The initial assessment included a positon-emission tomography (PET)-CT for determining irradiation volumes.

Patients with the following criteria were excluded: disease amenable to potentially curative surgery, previous chemotherapy or radiotherapy, severe/poorly controlled comorbidity, previous malignant disease within 5 years (excepting skin basal cell or in situ cervical carcinomas), squamous or composite histology (since pemetrexed is contraindicated in squamous cell carcinoma), bronchioloalveolar carcinoma, small-cell lung cancer, or cancers complicated by superior vena cava syndrome inaccessible to endovascular stenting. Patients with contralateral hilar or subclavicular adenopathy or Pancoast syndrom were excluded; minimal pleural cytologically-negative effusion was permitted.

2.2. Study design and treatment

Eligible patients received an induction chemotherapy of cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2), delivered on day 1 of a 21-day cycle. All received a 400 mg/m^2 cetuximab loading dose (day 1; week 1), followed by weekly 250 mg/m^2 doses, until two weeks postradiotherapy, for overall 12 intravenous administrations.

Cisplatin and cetuximab were administered at full antitumour dose (radiosensitization was not the desired mode).

The first chemotherapy course was followed by chemoradiotherapy from day 22, with chemotherapy administered at the same schedules for maximally three cycles, with maximally four administered. Irradiation started at day 22 in daily 2 Gy fractions for five/seven days, up to maximally 66 Gy.

Systematic vitamin supplementation was administered to all patients, including daily oral 400 μg folic acid intake and 1 mg vitamin B12 intramuscularly injected. At first follow-up, clinical and radiological assessments were performed at week 3, prior to radiotherapy, then repeated at weeks 16 and 24, then three-monthly after year 2, and six-monthly at years 3–5. Cardiac and pulmonary toxicity, both acute and delayed, were particularly monitored.

2.3. Radiation therapy

After the first induction cycle, chemoradiotherapy combination could only be initiated for patients with response or disease stabilization, without any residual grade 2 or above toxicity (according to National Cancer Institute Common Criteria [NCI-CTC] 3.0), and the patient still in good general condition (PS < 2).

Thoracic ≤ 6MV (yet ≤ 16MV) photon beam irradiation began at week 4, with standard fractionated, three-dimensional, conformal or intensity-modulated radiation therapy. Radiation doses were prescribed to the planning target volume, with motion management required. Using PET-CT, CT, and four-dimensional CT for radiation therapy planning was encouraged. Elective nodal irradiation was not permitted. Dose volume histograms were generated for planning target volume, normal lung, spinal cord, heart, and esophagus for all patients. Radiation therapy plans were centrally reviewed. Dose constraints and specifications were defined according to international standards, with a maximally accepted spinal cord dose ≤ 46 Gy. The volumetric whole lung percentage receiving a radiation dose ≥ 20 Gy (V20) had to be less than 35%, with the average dose for both lungs 20 Gy or less. The mean oesophagus admitted dose was less than 34 Gy, and mean heart dose less than 10 Gy.

2.4. Treatment modifications

Toxicity was scored according to NCI-CTC v3.0-.

Cetuximab was discontinued for maximally two weeks for grade 3 or 4 allergies, hypersensitivity, or cytokine release reactions, with possibly reintroducing cetuximab in cases with toxicity score 2 or less. For new scores grade 3 or above, cetuximab could be stopped for two consecutive weeks, with cetuximab treatment then resumed at reduced dosage. Following cetuximab reintroduction, dosage could no longer be increased.

Chemotherapy administration required compatible haematological functions ([Hb] ≥ 10 g/dL, neutrophils > 1500/mm^3, platelets > 100,000/mm^3) and renal functions (creatinine clearance > 45 mL/min).

For grade 3 chemoradiotherapy-related oesophagitis, chemotherapy was suspended, yet irradiation maintained. For grade 4 oesophagitis, full treatment was stopped, with chemoradiotherapy possibly resumed with a 50%-reduced pemetrexed dose after grade 2 toxicity had been retrieved.

For grade 3 radiation pneumonitis or pulmonary infiltrates, chemoradiotherapy was stopped, and corticosteroid therapy initiated.

2.5. Endpoints and assessment

The primary endpoint was disease control rate, as the patient number with best overall complete response, partial response, or stable disease at week 16.

Secondary endpoints were disease control rate at week 24 inclusion; complete response, partial response, and stable disease rates at weeks 16 and 24, progression-free survival, overall survival, overall tolerance up to week 24, with specific cetuximab-related tolerance.

The disease response duration was defined as the time between first measured response (partial or complete) and progression or any-cause death, progression-free survival as the time between study inclusion and progression or death dates, overall survival as the time between inclusion and death.

Participating centres pertained to the French cooperative thoracic intergroup (Intergroupe francophone de cancérologie thoracique, IFCT). Patients provided optional archived tumour tissue samples to test whether treatment effects were modulated by EGFR, PI3K, B-Raf, or K-Ras tumour mutation status. EGFR immunohistochemistry was retrospectively assessed using the anti-EGFR human antibody (Eurobio, France). Tumours were scored for membrane staining intensity and cell fraction stained at each intensity (0%–100%). An EGFR immunohistochemistry score on a continuous scale of 0–300 was generated [9].

2.6. Statistical analysis

The last patient was recruited on January 29, 2014. Survival rates and survival curves were analysed using Kaplan–Meier methodology. The number of required subjects was based on the Simon two-stage approach [10] and disease control rate at 16 weeks, with a null hypothesis (H0) set as p ≤ p0 = 60%, and an alternative hypothesis (H1) set as p ≥ p1 = 75%.

In a first step, disease control rate was analysed after accruing 34 evaluable patients. In case of disease control rate 21 or less, the trial had to be stopped. Conversely, if disease control rate was greater than 21, the trial could be continued, with an additional 61

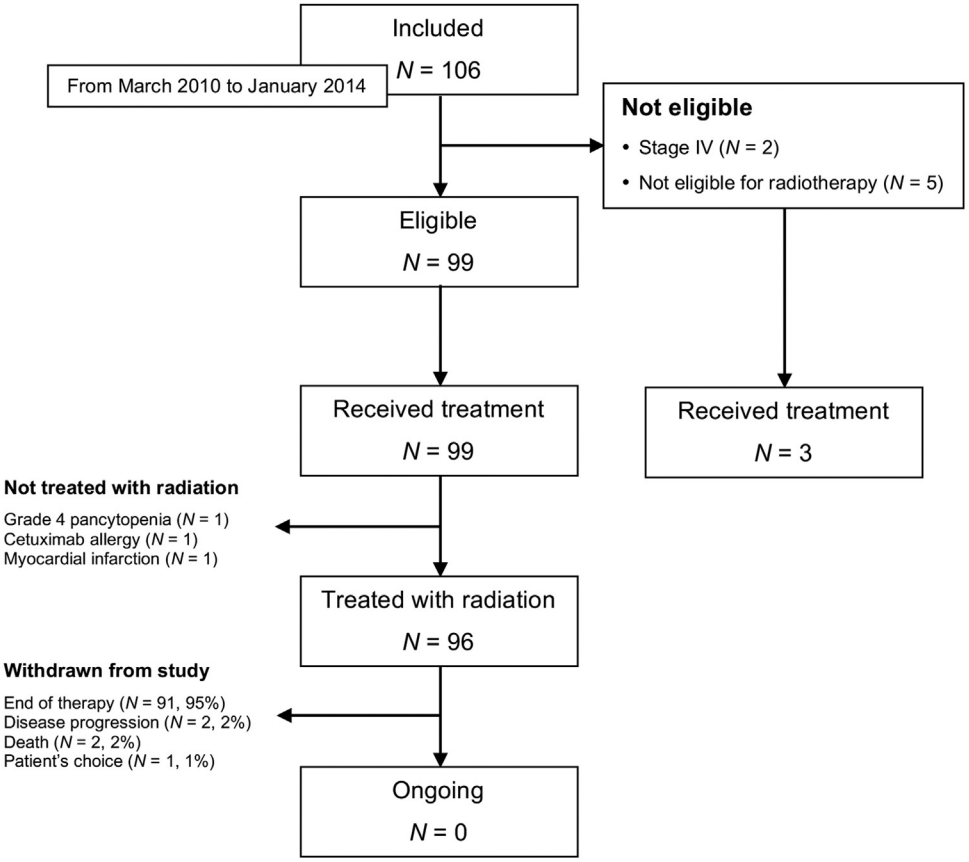

Fig. 1. Trial profile of the IFCT-0803 study, a phase II study of cetuximab, pemetrexed, cisplatin, and concurrent radiotherapy in patients with locally advanced, unresectable, stage III, non-squamous, non-small-cell lung cancer.

patients to be included. Considering a 10%-ineligible patient rate, 106 patients had to be included to result in 95 eligible patients.

The primary study endpoint had to be assessed on the first 95 eligible patients, with secondary endpoints assessed on all eligible patients.

3. Results

3.1. Patient characteristics

Between March 2010 and January 2014, 106 patients at 25 IFCT centres were enrolled. Of these, seven were deemed ineligible (five for technical irradiation impossibility; two for occult metastatic disease), resulting in 99 eligible patients (Fig. 1).

The patient characteristics are listed in Table 1. All patients underwent diagnostic PET-CT.

3.2. Treatment delivery and compliance

Of the 99 eligible patients, 96 patients received radiation therapy. Three patients did not receive radiation therapy due respectively to grade 4 pancytopenia, cetuximab allergy, or myocardial infarction-related death before radiotherapy. Among patients receiving radiotherapy, 91 patients (95%) completed treatment, discontinuations being due to disease progression ($n = 2$), death ($n = 2$), or patient preference ($n = 1$).

Compliance with systemic treatment (chemotherapy and cetuximab) was high (100% for all cycles), as was radiation therapy compliance (Table 2). The protocol non-compliance rate with radiation therapy was 9%. Median time between baseline PET-CT and the start of radiotherapy was 43 days.

Table 1
Results of the IFCT-0803 study, a phase II study of cetuximab, pemetrexed, cisplatin, and concurrent radiotherapy in patients with locally advanced, unresectable, stage III, non-squamous, non-small-cell lung cancer: Pretreatment patient characteristics ($n = 99$).

Median age	57.1 years [30.6–71.0 years][a]
Gender (n)	
Male	61 (61.6%)
Female	38 (38.4%)
Smoking status[b] (n)	
Yes	93 (93.9%)
No	6 (6.1%)
Stage (n)	
IIIA	51 (51.5%)
IIIB	48 (48.5%)
ECOG performance status (n)	
0	61 (61.6%)
1	38 (38.4%)
Median weight	69 kg[c]
Histology (n)	
Adenocarcinoma	75 (75.8%)
Other (non-squamous)	24 (24.2%)

ECOG: Eastern Cooperative Oncology Group.
[a] Age > 70: deviation.
[b] Smokers or ex-smokers (median pack-year: 40.0).
[c] 77% having lost < 5% ideal weight.

3.3. Safety

Of the 106 patients, 102 were evaluable for safety, with four not receiving any treatment (Table 3). Two toxic deaths occurred, one due to traumatic subdural haematoma (grade 4 thrombocytopenia) and the other due to grade 4 radiation pneumonitis and cancer

Table 2
Results of the IFCT-0803 study, a phase II study of cetuximab, pemetrexed, cisplatin, and concurrent radiotherapy in patients with locally advanced, unresectable, stage III, non-squamous, non-small-cell lung cancer: compliance to radiotherapy.

n = 96	Median or %	Range
Radiotherapy duration (days)	48	8–66
Delay day 1 cycle 1 and start of radiotherapy (days)	21	14–31
Total dose (Gy)	66[a]	16–68
Number of fractions	33	8–34
Dose by fraction (Gy)	2.00	2.0–2.1
PET-CT of fusion	49 (51.6%)	
Gross tumoral volume (cm^3)	91	3–805
Lung V30 (%)	19.00	0.0–60.3
Lung V20 (%)	26.11	0.0–39.0
Lung V5 (%)	49.90	18.0–85.0
Mean pulmonary dose (Gy)	14.2	3.4–21.0
Heart volume receiving more than 35 Gy (%)	6.00	0.0–46.0
Mean dose to oesophagus (Gy)	27.00	0.0–55.0
Volume of esophagus receiving more than 50 Gy (%)	30	0–71

PET-CT: positron emission tomography-computed tomography.
[a] Nine patients did not receive the prescribed or per-protocol radiotherapy dose: 68 Gy (*n* = 1), 64 Gy (*n* = 2), 60 Gy (*n* = 4), 56 Gy (*n* = 1), 16 Gy (due to toxicity).

progression. There was no significant immediate pulmonary toxicity. Yet, six patients exhibited grade 1 or 2 dyspnoea (5.9%), and five grade 3 oesophageal toxicity (4.9%). Late toxicity is outlined in Table 4.

3.4. Efficacy

Efficacy endpoints were assessed after chemotherapy. Two complete responses (2.1%), 57 partial responses (60.0%), and 27 stable diseases (28.4%) were achieved at week 16, 86 patients exhibiting a disease control rate of 90.5% (95% confidence interval [95% CI]: 84.6%–96.4%). Disease progression was noted in three patients, whereas six were non-evaluable.

After a median follow-up of 63.0 months (95% CI: 57.4–65.4 months), one-year and two-year survival rates were respectively 74.7% and 59.5%. The median overall survival was 35.8 months (95% CI: 23.5–NR) (Fig. 2).

Sixty-eight patients were diagnosed with progression, distantly from the primary tumour (*n* = 47, 69%; brain being the first relapse site), while 21 exhibited a local relapse (31%). The median

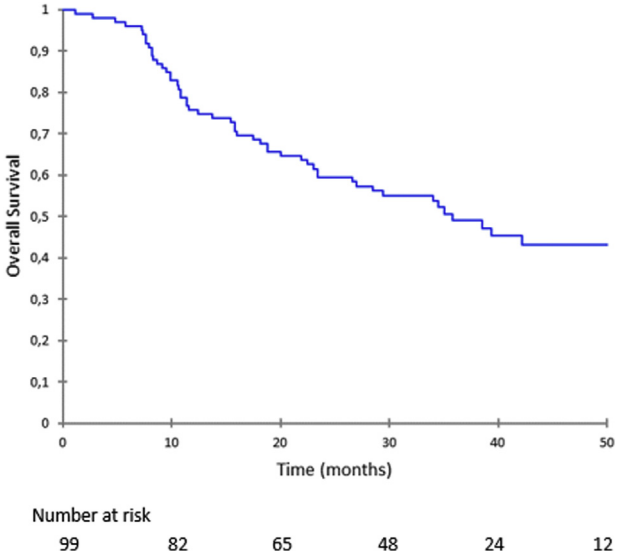

Fig. 2. Results of the IFCT-0803 study, a phase II study of cetuximab, pemetrexed, cisplatin, and concurrent radiotherapy in patients with locally advanced, unresectable, stage III, non-squamous, non-small-cell lung cancer: overall survival rate.
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progression-free survival was 14.4 months (95% CI: 11.2–18.8), with one-year and two-year progression-free survival rates respectively of 57.6% and 34.3% (Fig. 3).

Differences in performance status, disease stage (IIIA vs. IIIB), and histology (adenocarcinoma vs. other) did not significantly influence survival rates (*P* = 0.10, 0.47, and 0.52, respectively).

When considering the time from beginning to treatment end, the median overall survival was 33.4 months, and progression-free survival 12.2 months.

4. Discussion

Six phase II trials have tested cetuximab combined with radiation therapy, with or without chemotherapy, for stage III non-small-cell lung cancer [11]. The median overall survival ranged

Table 3
Results of the IFCT-0803 study, a phase II study of cetuximab, pemetrexed, cisplatin, and concurrent radiotherapy in patients with locally advanced, unresectable, stage III, non-squamous, non-small-cell lung cancer: toxicity occurring during treatment and within 3 months after treatment end.

	Total (*n* = 102)			
	Any grade	Grade 1 or 2	Grade 3	Grade 4
Any treatment-related adverse events	83 (81.4%)	61 (59.8%)	19 (18.6%)	3 (2.9%)
Skin toxicity	64 (62.7%)	62 (60.8%)	2 (2.0%)	0 (0%)
Oesophageal toxicity	43 (42.2%)	38 (37.3%)	5 (4.9%)	0 (0%)
General toxicity	42 (41.2%)	36 (35.3%)	6 (5.9%)	0 (0%)
Nausea–vomiting	28 (27.5%)	25 (24.5%)	3 (2.9%)	0 (0%)
Respiratory toxicity	6 (5.9%)	6 (5.9%)	0 (0%)	0 (0%)
Renal toxicity	4 (3.9%)	3 (2.9%)	1 (1.0%)	0 (0%)
Neurological toxicity	3 (2.9%)	3 (2.9%)	0 (0%)	0 (0%)
Hypersensitivity	1 (1.0%)	1 (1.0%)	0 (0%)	0 (0%)

Table 4
Results of the IFCT-0803 study, a phase II study of cetuximab, pemetrexed, cisplatin, and concurrent radiotherapy in patients with locally advanced, unresectable, stage III, non-squamous, non-small-cell lung cancer: late toxicity (occurring at least 3 months after treatment end) for all patients who had received at least one treatment dose.

	Total (*n* = 102)			
	Any Grade	Grade 1 or 2	Grade 3	Grade 4
Any treatment-related adverse event	3 (2.9%)	2 (2.0%)	1 (1.0%)	0 (0%)
Dysphagia	1 (1.0%)	0 (0%)	1 (1.0%)	0 (0%)
Neuropathy	1 (1.0%)	1 (1.0%)	0 (0%)	0 (0%)
Pneumopathy	1 (1.0%)	1 (1.0%)	0 (0%)	0 (0%)

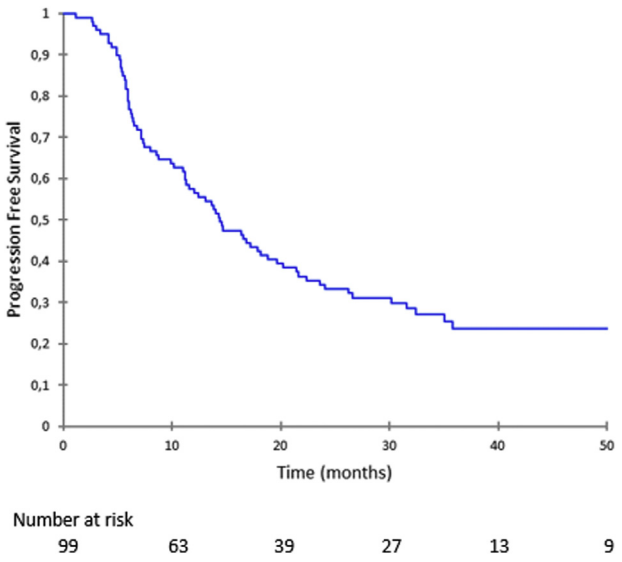

Fig. 3. Results of the IFCT-0803 study, a phase II study of cetuximab, pemetrexed, cisplatin, and concurrent radiotherapy in patients with locally advanced, unresectable, stage III, non-squamous, non-small-cell lung cancer: progression-free survival rate.

from 15.1 to 25.2 months [12,13]. In this final IFCT 0803 phase II trial analysis, with a median 4.4-year observation, we report a meaningfully high disease control rate at 16 weeks (90.5%), median progression-free survival of 14.4 months, and median overall survival of 35.8 months. Although the primary endpoint was quickly met, we chose to wait to have sufficiently robust survival data to present the results of the study. No relationship was observed between biological assessments and efficacy or toxicity, but patient number assessable for EGFR tumour content was low.

Despite lower patient numbers, these results compare favourably with those of Radiation Therapy Oncology Group (RTOG) 0617, a two-by-two factorial phase 3 study published during our current trial. RTOG 0617 enrolled 465 patients undergoing chemoradiotherapy (carboplatin and paclitaxel combination), comparing overall survival after a standard versus high-dose conformal radiotherapy (60 vs. 74 Gy), with or without cetuximab. The authors failed to demonstrate any survival advantage for either regimen. Cetuximab conferred no survival benefit: median overall survival with or without cetuximab was two years for each ($P = 0.97$), at the expense of increased cetuximab toxicity [14]. Median progression-free survival and overall survival were 1.0 year and 28.7 months in the standard-dose arm, respectively [15].

The phase III PROCLAIM study evaluated overall survival for concurrent pemetrexed–cisplatin and thoracic radiation therapy followed by consolidation pemetrexed, versus etoposide–cisplatin and thoracic radiation therapy followed by non-pemetrexed doublet consolidation therapy [16]. With overall survival as primary criterion, pemetrexed–cisplatin combined with thoracic radiation therapy and followed by pemetrexed consolidation was not superior to standard chemoradiotherapy for stage III unresectable non-squamous non-small-cell lung cancer (26.8 vs. 25.0 months, respectively; $P = 0.831$). Progression-free survival did not significantly differ between both arms (11.4 vs. 9.8 months; $P = 0.13$).

Our results compare favourably with the PACIFIC trial data, demonstrating a significant benefit of adding durvalumab to concurrent chemoradiotherapy [4,5]. In this trial, 713 patients were randomized, with 473 patients receiving durvalumab. In the placebo group, after a median 25.2-month follow-up, the median overall survival was 28.7 months, and median progression-free survival 5.6 months. In our trial, when overall survival and progression-free survival are plotted from the last treatment day, the median overall survival was 33.4 months, and median progression-free survival 12.2 months, with a 60% 24-month survival rate, which aligns with the 66% 24-month overall survival observed in the PACIFIC trial.

To the best of our knowledge, the survival results observed with the cetuximab-chemoradiotherapy combination (median overall survival: 35.8 months; median progression-free survival: 14.4 months) are the best data ever obtained in this setting (Table 5). Cetuximab has become key in managing advanced colorectal, and head and neck cancers [17,18]. Yet, despite phase III trials showing a marginal but statistically significant benefit, cetuximab has not yet any place in non-small-cell lung cancer management, beyond research settings [19,20].

Our prospective trial confirms that cetuximab combined with induction chemotherapy followed by chemoradiotherapy is feasible and clinically active for patients with good performance status and locally advanced, non-squamous non-small-cell lung cancer. In the induction phase, immediate cetuximab introduction concurrently with the cisplatin–pemetrexed doublet showed efficacy with tolerability. During the chemoradiotherapy phase, the triplet drug displayed excellent compliance. The treatment was well tolerated. Grades 3 and 4 toxicity were predominantly haematological, whereas grade 3 oesophagitis incidence was low, without any grade 3 pneumonitis.

While these encouraging results are probably not exclusively due to adding cetuximab to chemoradiotherapy, we strongly believe that they can be explained by several factors:

- selection of a younger-patient cohort (57 vs. 64 years in the RTOG and PACIFIC trials, and 59.5 years in the PROCLAIM study);
- selection of a non-squamous histological type (43% and 45.7% had a squamous cell tumour in the RTOG and PACIFIC trials, respectively, with all PROCLAIM study patients exhibiting unresectable non-squamous non-small-cell lung cancer);
- patients receiving optimized treatment, proven by its particularly good tolerance, compared with the RTOG trial cetuximab arm;
- low doses received by at-risk organs, much lower than in the RTOG trial.

Table 5
Comparison of the survival results of the IFCT-0803 study, a phase II study of cetuximab, pemetrexed, cisplatin, and concurrent radiotherapy in patients with locally advanced, unresectable, stage III, non-squamous, non-small-cell lung cancer, with that of other chemoradiotherapy trials.

Clinical trial	Sample size	Median OS (months)	Median PFS (months)	1-yr OS rate (%)	2-yr OS rate (%)	1-yr PFS rate (%)	2-yr PFS rate (%)
PROCLAIM (pemetrexed–cisplatin arm)	301	26.8	11.4	76	52	–	–
RTOG 0617 (SD arm)	166	28.7	12.0	–	59.6	–	30.7
PACIFIC (placebo arm)	237	28.7	5.6	75.3	55.6	34.4	–
PACIFIC (durvalumab arm)	476	NR	17.2	83.1	66.3	55.7	–
IFCT 0803	99	35.8	14.4	74.7	59.5	57.6	34.3
IFCT 0803, (from the end of treatment)	99	33.4	12.2	73.7	60	50.5	–

OS: overall survival; PFS: progression-free survival; yr: year; NR: not reached.

One of our study strengths is that we included approximately 100 patients who were suitable for such a combined regimen.

5. Conclusion

These final IFCT-0803 results warrant further evaluation of combining cetuximab with a concurrent chemoradiotherapy regimen for managing patients with stage III, non-resectable, non-squamous non-small-cell lung cancer. The interaction between therapeutic antibodies targeting tumour cells and checkpoint inhibitors provides a rational basis [21]. Following the PACIFIC study results, a new approach could integrate cetuximab into induction patients' treatment to increase its initial efficacy and render adjuvant immunotherapy available to a greater patient proportion [4,5].

Clinical practice points

The results (disease-control rate, progression-free survival, overall survival) of this IFCT-0803 trial justify further development of cetuximab-based induction chemoradiotherapy.

Patient informed consent and study compliance.

All patients provided written informed consent. The study protocol and amendments were approved by the ethics committee of the Comité de protection des personnes de l'Île-de-France, and the study performed in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and Helsinki Declaration.

Disclosure of interest

Jean Trédaniel, Delphine Lerouge, Éric Pichon, Sylvestre Le Moulec, Lionel Moreau, Lidia Petit, Olivier Carré, Francois Guichard, Olivier Raffy, Julie Villa, Alain Prevost, Alexandra Langlais, Franck Morin and Philippe Giraud declare that they have no competing interest.

Fabrice Barlési reports personal fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer and Takeda, non-financial support from Abbvie, ACEA, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eisai, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo, Novartis, Medimmune, Merck, MSD, Pierre Fabre, Pfizer, Sanofi-Aventis and Takeda.

Cecile Le Péchoux reports financial relationships with Amgen, Lilly and Medscape due to participation to educational meetings, financial relationships with AstraZeneca, Nanobiotix and Roche due to participation to advisory board and personal fees from PrimeOncology.

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Author contribution

IFCT collected and interpreted the data. The investigators were responsible for data collection. All authors and investigators had full study data access.

Clinical trial registration

The protocol was registered with ClinicalTrials.gov (number NCT01102231).

Appendix A. Supplementary data

Supplementary data (radiation therapy parameters and molecular and biological data) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.canrad.2021.12.005.

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