First-line carboplatin plus pemetrexed with pemetrexed maintenance in HIV-positive patients with advanced non-squamous non-small cell lung cancer: the phase II IFCT-1001 CHIVA trial

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In this first clinical trial dedicated to people living with HIV and advanced non-squamous non-small cell lung cancer, first-line 4-cycle carboplatin plus pemetrexed followed by pemetrexed maintenance chemotherapy was effective and reasonably well-tolerated https://bit.ly/2xAqeEl

Cite this article as: Lavole A, Greillier L, Mazières J, *et al*. First-line carboplatin plus pemetrexed with pemetrexed maintenance in HIV-positive patients with advanced non-squamous non-small cell lung cancer: the phase II IFCT-1001 CHIVA trial. *Eur Respir J* 2020; 56: 1902066 [https://doi.org/10.1183/13993003.02066-2019].

ABSTRACT HIV infection is an exclusion criterion in lung cancer trials. This multicentre phase II trial aimed to assess feasibility, efficacy and safety of first-line carboplatin plus pemetrexed (CaP) followed by pemetrexed (P) maintenance in people living with HIV (PLHIV) with advanced non-squamous non-small cell lung cancer (NS-NSCLC).

Four cycles of CaP were followed by P-maintenance therapy in patients with Eastern Cooperative Oncology Group performance status ⩽2. The primary objective was a disease control rate (DCR) ⩾30% after 12 weeks.

Of the 61 PLHIV enrolled, 49 (80%) had a performance status of 0–1, and 19 (31%) had brain metastases. Median CD4 lymphocyte count was 418 cells·μL^{-1} (range 18–1230), median CD4 lymphocyte nadir was 169.5 cells·μL^{-1} (1–822); 48 (80%) patients were virologically controlled. Four-cycle inductions were achieved by 38 (62%) patients, and 31 (51%) started P-maintenance (median of 4.1 cycles (range 1–19)). The 12-week DCR was 50.8% (95% CI 38.3–63.4) and partial response rate 21.3%. Median progression-free survival and overall survival were 3.5 (95% CI 2.7–4.4) and 7.6 months (5.7–12.8), respectively. Patients with a performance status of 0–1 had the longest median progression-free survival (4.3 months, 95% CI 3.1–5.2) and overall survival (11.9 months, 95% CI 6.4–14.3). During induction, CaP doublet was well tolerated apart from grade 3–4 haematological toxicities (neutropenia 53.8%; thrombocytopenia 35.0%; anaemia 30.0%). Two fatal treatment-related sepses were reported. No opportunistic infections were experienced.

In PLHIV with advanced NS-NSCLC, first-line four-cycle CaP induction followed by P-maintenance was effective and reasonably well-tolerated. Further studies should evaluate combination strategies of CaP with immunotherapy in PLHIV.

This article has supplementary material available from erj.ersjournals.com

Received: 22 Oct 2019 | Accepted after revision: 15 April 2020

Introduction

The use of highly active antiretroviral therapy (HAART) in developed countries led to a considerable reduction in AIDS mortality due to opportunistic infections and AIDS-defining cancers [1]. In people living with HIV (PLHIV), non-AIDS-related cancers have become a leading cause of morbidity and mortality, with lung cancer being the first cause of mortality by cancer [2–5]. PLHIV have a greater risk of lung cancer compared with the general population [4, 6, 7], with an estimated 52% (95% CI 43–60) excess in the USA in 2015 [8]. However, the high prevalence of smoking in PLHIV is the primary contributor to lung cancer high incidence [4, 9–11].

Classically, the prognosis of lung cancer is worse in PLHIV [12, 13], but a recent French study showed that lung cancer prognosis in immunologically well-controlled PLHIV was similar to the general population [14].

Different national or expert working group guidelines recommend that PLHIV be treated with the same strategies as in the general population, with close monitoring of interactions between chemotherapy and HAART [15–18]. No trial dedicated to PLHIV with non-squamous non-small cell lung cancer (NS-NSCLC) had been conducted at the time of our study design. Before the era of immunotherapy, first-line chemotherapy with a platinum agent followed by pemetrexed (P)-maintenance therapy represented the standard regimen in the general population with advanced NS-NSCLC in the absence of oncogenic addiction [19–21]. Carboplatin pemetrexed (CaP), with low toxicity in the general population, seemed an ideal candidate in PLHIV with advanced NS-NSCLC, particularly if HAART comprised tenofovir and chemotherapy cisplatin, as both have been incriminated in tubular nephrotoxicity [22]. Moreover, pemetrexed undergoes non-CYP450 metabolism, contrasting with taxanes or vinorelbine, and the CaP doublet is thus unlikely to be altered by HAART [17, 23]. Finally, CaP has shown efficacy in frail NSCLC populations [24–26].

Based on these presumptions, we initiated a phase II, multicentre, non-randomised, open-label clinical trial to evaluate the efficacy and toxicity of CaP as first-line chemotherapy in PLHIV with advanced NS-NSCLC.

Methods

Eligibility criteria

To be eligible, PLHIV were diagnosed with histological or cytological confirmed NS-NSCLC [27], tumour–node–metastasis (TNM) stage III–IV, and had no previous administration of chemotherapy [28]. Cytopathological diagnosis and molecular testing were performed in each clinical centre. Molecular testing included: 1) immunohistochemistry (IHC) for *ALK,* confirmed by fluorescence *in situ* hybridisation in case of IHC positivity; and 2) EGFR (exon 18–21), KRAS (exon 2 and 13) and BRAF V600 mutation testing using the Sanger sequencing method or a more sensitive, validated, allele-specific technique. Other eligibility criteria were an age between 18 and 75 years, an Eastern Cooperative Oncology Group performance status (ECOG-PS) 0–2, a weight loss >10% of total body weight within the previous month and normal organ functions. Finally, patients with symptomatic or asymptomatic brain metastases could be included without prior treatment. This clinical trial (ClinicalTrials.gov, number NCT01296113) was approved by an Ethic Committee, and complied with French legislation, Good Clinical Practices, and the principles outlined in the latest version of Declaration of Helsinki. All patients gave their written informed study-specific consent.

Chemotherapy regimen

Patients received first-line intravenous chemotherapy with pemetrexed, 500 $mg{\cdot}m^{-2}$, bolus infused in 10 min, every 3 weeks, combined with carboplatin bolus infusion, with a target area under the curve value

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of 5 mg·mL^{-1}·min^{-1} [29], on day 1 for a maximum of four cycles. After the four-cycle induction, patients achieving disease control (partial responses or stable diseases) and ECOG-PS ⩽2 were continued on pemetrexed. Folic acid and vitamin B12 supplementation were mandatory, and prednisone 20 mg twice daily for 3 days was routinely administered.

Concomitant therapy

No other anticancer therapies, immunotherapies, hormonal cancer therapies, therapeutic radiotherapy (palliative radiotherapy being authorised) or experimental medications were permitted while patients were on study trial. Chemoprophylaxis against *Pneumocystis* pneumonia (PCP) and toxoplasmosis with trimethoprim-sulfamethoxazole (TMP–SMX), or alternative agents (pentamidine, atovaquone) in case of allergy or intolerance, was left to the investigator's appreciation but recommended if CD4 count was or fell below 200 cells·μL^{-1} during follow up.

Study objectives

The primary objective was a disease control rate (DCR) of at least 30% at week 12. Secondary objectives were progression-free survival (PFS), overall survival; overall survival and PFS according to performance status in class (0–1 and 2), quality of life (QoL) and overall toxicity. As we hypothesised that PLHIV with lung cancer were more at risk of infectious complications under chemotherapy than persons without HIV [30], safety objectives included characterising chemotherapy doublet toxicities, HIV viral load and CD4 lymphocyte count changes as well as opportunistic infections.

Study end points

12-week DCR was defined as the aggregated rates of complete or partial responses and stable diseases. PFS was defined as the time between patient's inclusion and disease progression, relapse or death of any cause, and overall survival as the time between inclusion and death from any cause.

Response to treatment was classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria v1.1 [31]. Tumour assessments were made by physical examination and total body computed tomodensitometry scan, which included brain evaluation, every two cycles. Primary criterion was DCR evaluated within the 4 weeks following completion of the 4-cycle induction phase.

Toxicity was scored every 3 weeks during induction period and according to usual practice scheduled during maintenance period, using the National Cancer Institute Common Adverse Events Criteria (CTCAE), version 3.0 [32]. QoL was evaluated using the Lung Cancer Symptom Scale (LCSS) at each cycle [33].

Statistical considerations

All patients were included in an intention-to-treat analyses for efficacy. The safety population comprised all patients who received at least one cycle of study chemotherapy.

Using the Fleming one-step method, and assuming that 12-week DCR of 30% or less (null hypothesis) was of no therapeutic interest and that a target DCR of at least 50% (alternative hypothesis) defined the doublet clinically efficient, 62 eligible patients were required (with 95% power and one-sided α error of 0.05). A triangular test [34] was used to analyse non-haematological grade 3–4 toxicities occurring with first-line chemotherapy (cycle 1–4) [35, 36]. Thirty percent (p_0) or less of patients with non-haematological grade 3–4 toxicities (except for nausea and vomiting) was considered reasonable in this population, and 50% (p_1) or more considered unacceptable. Two safety runs (with one-sided α error of 0.05 and a power of 95%) were planned after 10 and 31 treated patients to stop the trial for non-haematological toxicity if more than eight or 15 patients with cases of grade ⩾3 non-haematological toxicity (excluding nausea and vomiting) occurred between cycles 1 and 4 of chemotherapy respectively. PFS and overall survival were estimated using Kaplan–Meier method with a censure of the follow-up on June 30, 2017. Hazard ratios and 95% confidence intervals for overall survival and PFS were estimated using a Cox model to select the most promising prognostic variables. The variables to be tested in the multivariable model were selected based on univariate analysis results ($p<0.20$). In the multivariable model, a $p<0.05$ was considered statistically significant. The QoL was described by the sum of the score of all domains of LCSS questionnaire, at the end of each first-line chemotherapy cycle compared to the baseline value [37].

Statistical analyses were performed using SAS software version 9.4; all p-values and confidence intervals were two sided.

Results

Patients' characteristics

Between May 2011 and July 2015, 61 patients were enrolled (figure 1). Their baseline characteristics are summarised in table 1. The HIV viral load was undetectable (<50 copies·mL^{-1}) in 48 of the 60

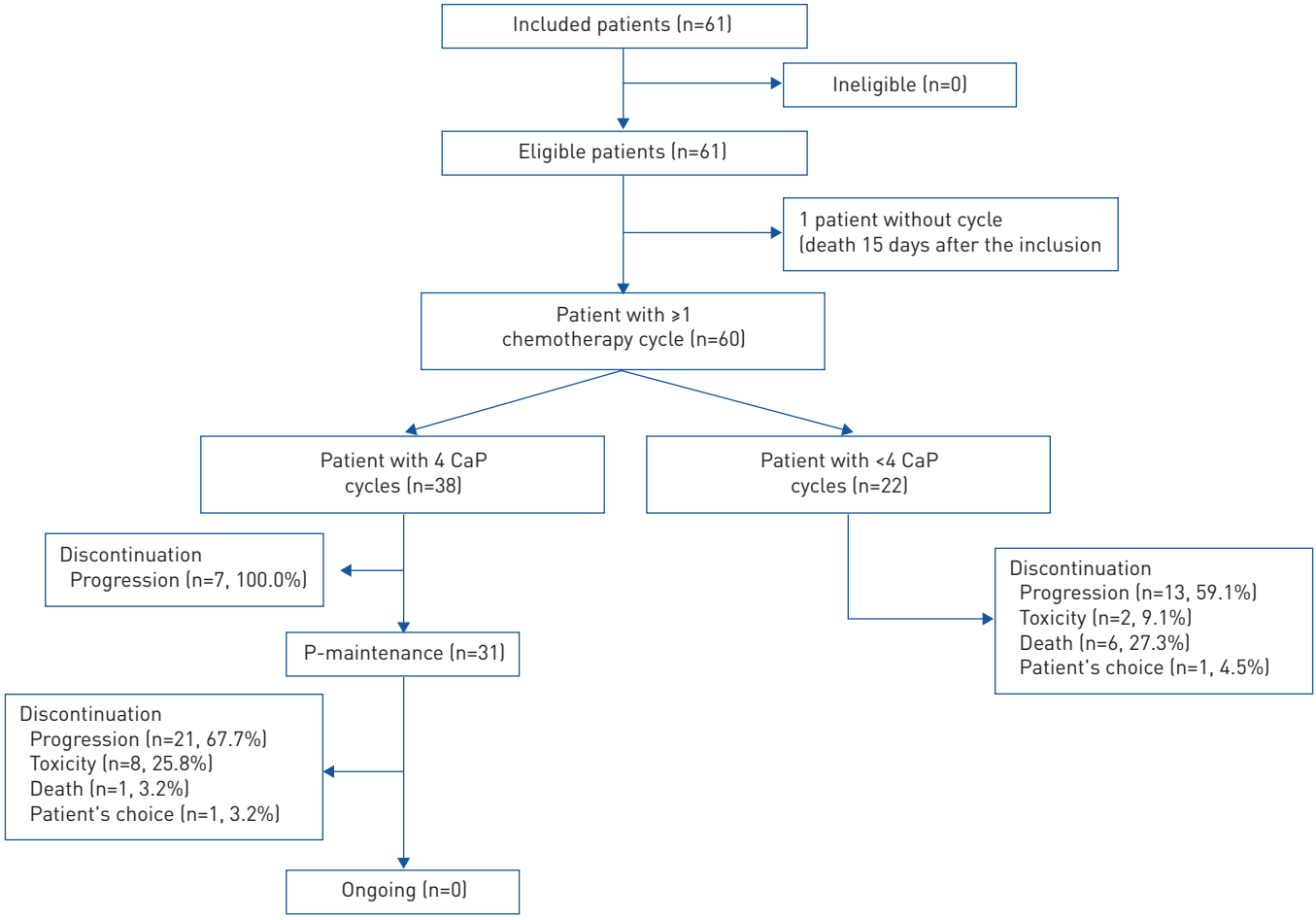

FIGURE 1 CONSORT flow chart. CaP: carboplatin plus pemetrexed

documented patients (80.0%), and median CD4 count was 418 cells·μL^{-1} (range 18–1230). At inclusion, 58 patients (95.1%) were treated (detailed in supplementary table A1), 12 (19.6%) were ECOG-PS2 and 19 (31.1%) presented with brain metastases, of whom nine were symptomatic.

Chemotherapy administration

60 patients received at least one first-line CaP cycle. A dose reduction was reported for carboplatin and for pemetrexed in 17 patients (27.9%). The relative dose-intensities were 95.9% for pemetrexed and 86.1% for carboplatin. The full planned induction regimen (four cycles) was completed in 38 patients (62.3%). The remaining 22 patients (36.1%) withdrew because of disease progression (n=13), death (n=6), adverse events (n=2) or patient's choice (n=1). Among the 38 four-cycle completers, 31 patients (50.8% of efficacy population) started pemetrexed-maintenance (figure 1) and received a median of four maintenance cycles (range: 1–19) with a relative dose-intensity of 95.1%.

Disease response

The primary objective of 12-week DCR ⩾30% was reached as 31 patients (50.8% (95% CI 38.3–63.4)) of the efficacy population had disease control while a minimum of 26 patients were hypothesised for treatment success (table 2). Objective response and stabilisation rates were 21.3 and 29.5%, respectively. Considering the patients with ECOG-PS 0–1, 57.1% of them reached disease control (*versus* 50.8% in overall population), reflecting an increase in the rate of stable disease (34.7% in ECOG-PS 0–1 *versus* 29.5% in the overall population).

PFS and overall survival

The median follow-up duration of patients was 45.5 months (range 23.9–73.2). The median PFS was 3.5 months (95% CI 2.7–4.4) (figure 2a), and the median overall survival 7.6 months (95% CI 5.7–12.8)

TABLE 1 Patients' characteristics at baseline

Patients n	61
Age years	52.9 (36.6–67.5)
HIV-associated factors	
CD4 count cells·μL^{-1}	418.0 (18–1230)
Nadir CD4 count (range) cells·μL^{-1}	169.5 (1–822)
Undetectable HIV viral load[#] (n=60)	48 (80.0)
ART at study entry[¶]	
Yes	58 (95.1)
No	3 (4.9)
Median known duration of HIV infection (range) years	20.7 (0.1–29)
History of cancer	9 (14.7)
AIDS related[+]	3 (4.9)
Non-AIDS related[§]	6 (9.8)
History of infection	44 (72.1)
AIDS-related infections[f]	18 (29.5)
Hepatitis C	24 (39.3)
Hepatitis B	7 (11.5)
Others	10 (16.4)
Demographics	
Sex	
Male	46 (75.4)
Female	15 (24.6)
ECOG-PS	
0	17 (27.9)
1	32 (52.5)
2	12 (19.6)
Smoking status	
Current	54 (88.5)
Former	3 (4.9)
Pack-years	36 (6–120)
Never	4 (6.6)
Comorbidities	30 (49.2)
Arterial hypertension	10
Dyslipidaemia	7
Diabetes	3
Cardiopathy	8
Others	16
Disease characteristics	
Histology	
Adenocarcinoma	56 (91.8)
Sarcomatoïd	1 (1.6)
Non-squamous cell predominant NSCLC	4 (4.6)
Disease stage	
III/IV	6 (9.8)/55 (90.2)
Brain metastases	19 (31.1)
Symptomatic	9
Asymptomatic	10
Genetic status (n=56)	
Wild type	44
KRAS mutation	7
ALK mutation	2
BRAF V600 mutation	2
EGFR mutation L858R exon 21	1

Data are presented as n or median (range), unless otherwise stated. ART: antiretroviral therapy; ECOG-PS: Eastern Cooperative Oncology Group performance status; NSCLC: non-small-cell lung cancer. [#]: Undetectable viral load: <50 copies·mL^{-1}; [¶]: ART taken at study entry are detailed in supplementary table A1; [+]: non-Hodgkin lymphoma n=2, Kaposi sarcoma n=1; [§]: Hodgkin lymphoma n=2, other cancers n=4; [f]: toxoplasmosis n=5, *Pneumocystis jiroveci* pneumonia n=8, tuberculosis n=5.

TABLE 2 Best overall response during the 4-cycle first-line chemotherapy

	Efficacy population		Patients with ECOG-PS 0–1	
	n	%	n	%
Patients n	61		49	
Disease control (PR+SD)	31	50.8	28	57.1
Partial response	13	21.3	11	22.4
Stable disease	18	29.5	17	34.7
Progressive disease	30	49.2	21	42.9

ECOG-PS: Eastern Cooperative Oncology Group performance status; PR: partial response; SD: stable disease.

(figure 2b). After treatment discontinuation, 37 (60.7%) received second-line chemotherapy (supplementary table A2). 55 patients (90.2%) died, mostly due to NSCLC progression (47 out of 55 patients (85.5%)).

Using a multivariable Cox's model, the only patient and disease characteristics at baseline significantly related to PFS and overall survival was the ECOG-PS (supplementary tables A3 and A4). PS 2 *versus* PS 0–1 patients had shorter PFS and overall survival (HR 2.67 (95% CI 1.31–5.43) and 4.44 (95% CI 1.93–10.22), respectively; data not shown). Exploratory analyses showed that patients with PS 0–1 had much longer median PFS and overall survival than PS-2 patients (figure 3). Patients without brain metastases status had longer median overall survival, with no difference in PFS (supplementary figure A1). Patients entering the pemetrexed-maintenance period had increased survival rates (PFS 5.6 months (95% CI 4.8–7.0); overall survival 16.9 months (95% CI 11.8–23.1) (supplementary figure A2).

Safety

Chemotherapy-related toxicity

During the 12-week induction period, grade 3 to 4 treatment-related adverse events occurring in at least 10% of patients were neutropenia (53.3%) thrombocytopenia (35.0%), anaemia, (30.0%) and asthenia (16.7%) (table 3). In the 58 patients treated with ART at inclusion, AIDS history was the only risk factor of grade 3–4 haematological toxicity (p=0.05; table 4). The safety runs on non-haematological grade 3–4 toxicities (except nausea and vomiting) did not lead to study discontinuation. No grade 3–4 renal toxicity was reported and, among the 4 grade 1–2 renal toxicity, one patient was treated with tenofovir. Two chemotherapy-related death were reported due to sepsis (two out of 61 (3%)). In the 31 patients treated during the pemetrexed-maintenance period, no treatment-related deaths were reported.

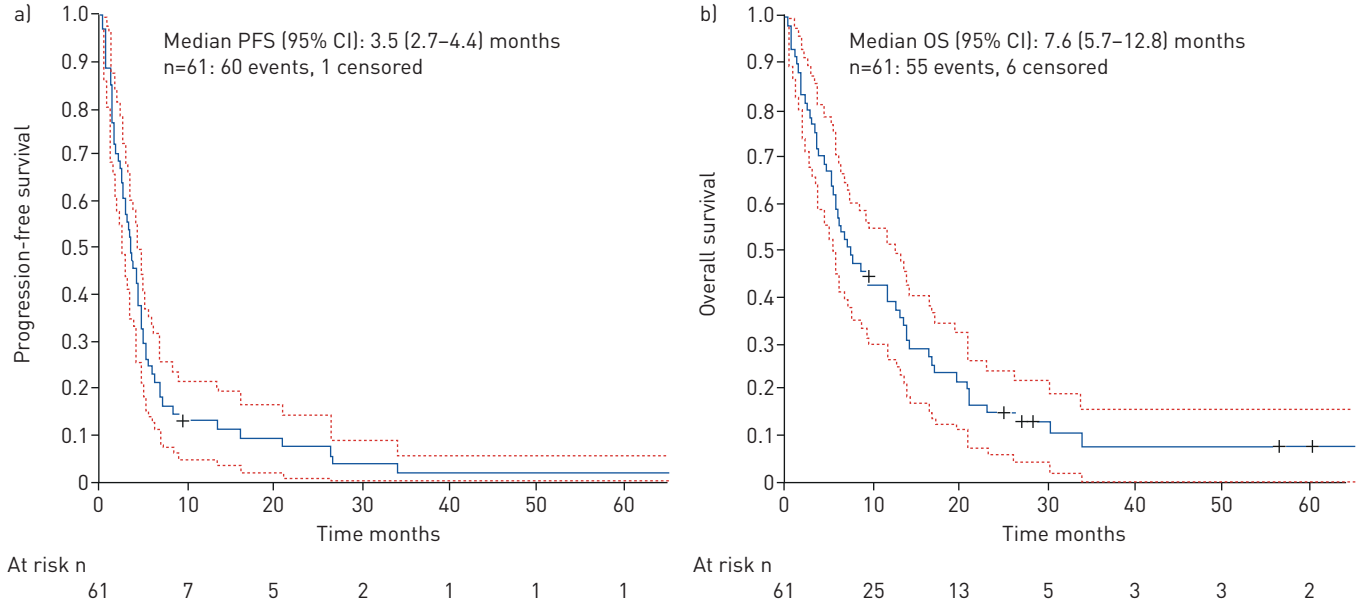

FIGURE 2 Progression-free survival and overall survival (from inclusion): Kaplan Meier curves. a) progression-free survival. b) overall survival. OS: overall survival; PFS: progression-free survival.

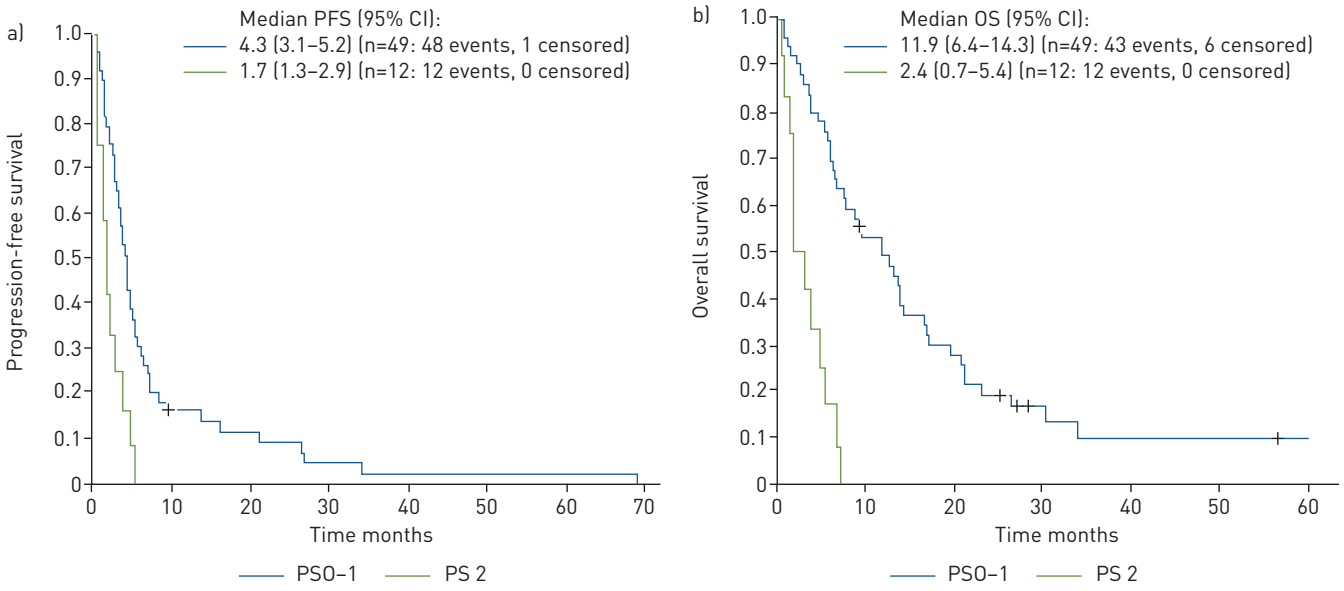

FIGURE 3 Progression-free survival and overall survival (from inclusion) according to Eastern Cooperative Oncology Group performance status (ECOG-PS) class at baseline: Kaplan Meier curves. a) Progression-free survival. b) Overall survival. OS: overall survival; PFS: progression-free survival.

Immunodeficiency-related adverse events

No opportunistic infections were reported. Nine patients (nine out of 12 (75%)) with TCD4 lymphocytes <200 cell·μL^{-1} received cotrimoxazole prophylaxis. 23 infectious events were experienced, including 13 respiratory infections, five infections of the implantable venous access device or pleural drain, and five infections in other sites.

Changes in CD4 lymphocyte count and HIV viral load

In the intention to treat population, the absolute CD4 counts significantly diminished between baseline and the end of the four-cycle first-line chemotherapy (median (range) from 418 cells·μL^{-1} (18–1230) to 292 cells·μL^{-1} (50–1607); p=0.04). The last median CD4 count was 319.5 cells·μL^{-1} (72–816). After four chemotherapy doublet cycles, only two patients (treated with HAART at study enrolment) had detectable viral load (from 397 at baseline to 4916 copies·mL^{-1} and from <50 to 1638 copies·mL^{-1}). Of the 23

TABLE 3 Grade 1 to 5 toxicity of the carboplatin-pemetrexed doublet

Type of toxicities	Any grade (n=60)	Grade 1–2 (n=60)	Grade 3 (n=60)	Grade 4 (n=60)	Grade 5 (n=60)
All	59 (98.3)	21 (35.0)	21 (35.0)	15 (25.0)	2 (3.3)
Haematologic	57 (95.0)	21 (35.0)	19 (31.7)	17 (28.3)	0 (0)
Anaemia	52 (86.7)	34 (56.7)	14 (23.3)	4 (6.7)	0 (0)
Neutropenia	47 (78.3)	15 (25)	17 (28.3)	15 (25.0)	0 (0)
Thrombocytopenia	42 (70)	21 (35)	11 (18.3)	10 (16.7)	0 (0)
Febrile neutropenia	4 (6.7)	0 (0)	1 (1.7)	3 (5)	0 (0)
Non-haematologic#	51 (85.0)	46 (76.7)	12 (20.0)	1 (1.7)	2 (3.3)
Asthenia	40 (66.7)	30 (50.0)	10 (16.7)	0 (0)	0 (0)
Nausea	28 (46.7)	25 (41.7)	3 (5.0)	0 (0)	0 (0)
Vomiting	15 (25.0)	12 (20.0)	3 (5.0)	0 (0)	0 (0)
Anorexia	19 (31.7)	17 (28.3)	2 (3.3)	0 (0)	0 (0)
Weight loss	9 (15.0)	9 (15.0)	0 (0)	0 (0)	0 (0)
Diarrhoea	7 (11.7)	6 (10.0)	0 (0)	1 (1.7)	0 (0)
Renal failure	4 (6.7)	4 (6.7)	0 (0)	0 (0)	0 (0)
Sepsis	3 (5.0)	0 (0)	1 (1.7)	0 (0)	2 (3.3)
Peripheral neuropathy	3 (5.0)	3 (5.0)	0 (0)	0 (0)	0 (0)
Alopecia	3 (5.0)	3 (5.0)	0 (0)	0 (0)	0 (0)

Data are presented as n (%). #: main presented.

TABLE 4 Risks factors of grade 3 to 4 haematologic toxicity of the carboplatin-pemetrexed doublet in patients treated with antiretroviral therapy at study enrolment (n=58)

	Grade 3 to 4 toxicity of the CaP doublet		
Risk factors	**Yes (n=33)**	**No (n=25)**	**p-value**
ECOG-PS			
0–1	81.8	88.0	0.72
2	18.2	12.0	
CD4 count			
⩽200 cells·μL^{-1}	24.2	12.0	0.32
>200 cells·μL^{-1}	75.8	88.0	
HIV viral load			
<50 copies·mL^{-1}	78.1	84.0	0.74
⩾50 copies·mL^{-1}	21.9	16.0	
History of AIDS			
No	60.6	84.0	0.05
Yes	39.4	16.0	
History of cancer			
No	78.8	92.0	0.27
Yes	21.2	8.0	
TMP–SMX prophylaxis			
No	78.8	92.0	0.27
Yes	21.2	8.0	

Date are presented as %, unless otherwise stated. CaP: carboplatin plus pemetrexed; ECOG-PS: Eastern Cooperative Oncology Group performance status; TMP–SMX: trimethoprim–sulfamethoxazole.

patients with undetectable baseline viral load and with values available after inclusion, 22 remained undetectable (95.6%).

Quality of life

LCSS Questionnaire scores improved from baseline with an increase of score in 25–29% of patients after the first cycle of chemotherapy, but 9–21% of patients experienced a decline in their QoL (supplementary figure A3).

Discussion

Whereas PLHIV are traditionally excluded from lung cancer trials, we report the results of the first trial on first-line chemotherapy in PLHIV with NS-NSCLC. Half of the patients achieved disease control at the end of the four-cycle first-line CaP doublet treatment reaching the primary study objective of at least 30% of DCR. Patients were relatively young (median age 52.9 years), nearly all smokers, mainly ECOG-PS 0–1 (80%), and with controlled HIV disease. These features are relatively consistent with a previous French cohort and with most PLHIV under HAART in France [23]. The study DCR was 51% which is close to that of NS-NSCLC patients of the general population treated with pemetrexed-based doublet in the PARAMOUNT trial (57%) [20]. Overall survival was 7.6 months in our study while overall survival in PLHIV with advanced NSCLC still remained poor ranging from 3 to 7 months in previous retrospective cohorts [23–26, 33].

Despite being virologically well controlled, survival of PLHIV in our study seemed shorter than previously observed in NS-NSCLC patients of the general population, treated with platinum-based doublet followed by pemetrexed maintenance [20, 21]. However, in these studies, patients were ECOG-PS 0–1 at baseline whereas in our study, PLHIV were ECOG-PS 0–2 at baseline. Furthermore, our ECOG-PS 0–1 subgroup almost reached similar median overall survival [20, 21]. As observed in the general population, and in PLHIV [24, 25] ECOG-PS was significantly related to PFS and overall survival.

Patients entering pemetrexed-maintenance received a median of four cycles (range 1–19), consistent with reports in the general population (PARAMOUNT study: four cycles (range 1–19); JMEN trial: five cycles (range 1–55)] [20, 21]. These patients reached similar or sometimes longer survival rates than in the general population treated with platinum-based doublet [20, 21]. During both study periods, relative dose-intensities remained stable in a vast majority of patients, underlying good tolerability of the regimen and its compatibility with antiretroviral therapies. Likewise during induction, the QoL after each CaP cycle

remained stable for most of the studied patients, and even improved for more than 25% of them after their first induction cycle.

No unexpected toxicity was observed, reflecting the absence or a low level of interactions with HAART [17, 23]. Only one renal toxicity grade 1–2 was reported under tenofovir. Two treatment-related deaths (3%) were noted, lower than a study with 6 out of 13 (46%) haematological deaths when HAART was associated with cytotoxic chemotherapy metabolised by the CYP450 [23]. The haematological toxicities of this carboplatin doublet were relatively high compared with other studies in the general population [27, 29], but similar to another study with elderly people [28]. AIDS was the only risk factor found to be associated with the haematological toxicity. PLHIV may be facing decreased haematopoiesis, particularly in those with a history of advanced HIV disease, which may persist despite HAART [38], justifying in some cancers in PLHIV systematic administration of growth factors such as granulocyte-colony stimulating factor [16, 18, 39, 40].

The CD4 count and viral load remained stable during chemotherapy. No toxoplasmosis or PCP cases were experienced. Prophylaxis was recommended only for patients with CD4 count <200 cells·μL^{-1}, thus for a minority of persons. Our study argues against systematic prophylaxis independent of CD4 lymphocyte count in PLHIV with lung cancer, in contrast with the recommendations of the French expert panel and European AIDS Clinical Society (EACS) recommendations [40, 41], but in accordance with the British HIV Association and the NCCN guidelines [16, 18]. However, further studies with more PLHIV are necessary to confirm these findings.

The trial suffers from a bias related to the potential heterogeneity of the PLHIV population; however, the option of a restricted population of patients without PS 2 and without symptomatic brain metastases could have affected the recruitment of this first trial dedicated PLHIV with NS-NSCLC. Patients with oncogenic-driven NSCLC were not excluded and three patients would have received tyrosine kinase inhibitors as first-line treatments in the present era. Moreover, Anti-programmed death (PD)1 and anti-PD ligand (PDL)1 treatment regimens (immuno-oncology) are now the standard of care for non-oncogenic driven advanced NSCLC but at the time of the trial accrual (2011–2015) no data existed concerning the immuno-oncology therapeutic strategy and, therefore, the knowledge of programmed death ligand 1 (PD-L1) tumour was not mandatory. The treatment landscape of NSCLC has changed since the advent of immuno-oncology and trials are in progress in PLHIV with lung cancer (NTC03354936, NCT03304093). Real-life safety and efficacy data of immuno-oncology following chemotherapy in PLHIV with lung cancer and other cancers have been reported [43–45].

Recent guidelines recommend for patients with high (PD-L1) expression (tumour proportion score (TPS) ⩾50%) and NS-NSCLC a single-agent pembrolizumab and for patients with either negative (0%) or low positive (1% to 49%) PD-L1 a pembrolizumab/platin/pemetrexed combination, although PLHIV were excluded from all these studies [42]. Our study will be a reference when assessing the potential impact on toxicities of a platin doublet in combination with immuno-oncology as first-line treatment for PLHIV with NS-NCLC.

In conclusion, this study conducted in PLHIV with NS-NSCLC showed the effectiveness of the induction doublet carboplatin/pemetrexed. Despite its relative haematological toxicity, it was well tolerated, without severe renal toxicity nor treatment-related unexpected deaths. This doublet is thus a relevant first-line chemotherapy in PLHIV with NS-NSCLC, leading to relatively long survivals, particularly in those entering pemetrexed maintenance. There is a crucial need for additional data on responses and tolerance in PLHIV of lung cancer therapies developed in the general population, such as immunotherapies [46].

Acknowledgements: We thank the participating patients and their families as well as the study teams involved in the trial, the clinical research assistants, study coordinators and IFCT operations staff, as well as G. Cremer at Cremer Consulting (Strasbourg, France) for medical writing support. We thank also the French National Cancer Institute (INCa) and the French League against Cancer. Prior presentation: Presented at the 2016 annual ASCO meeting, Chicago, IL, USA, June 4, 2016.

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J. Cadranel; financial support: F. Morin; administrative support: F. Morin; provision of study material or patients: A. Lavolé, L. Greiller, J. Mazières, I. Monnet, L. Kiakouama-Maleka, X. Quantin, J.P. Spano, H. Lena, P. Fraisse, H. Janicot, C. Audigier-Valette and J. Cadranel; collection and assembly of data: A. Lavolé, A. Langlais, F. Morin, A. Makinson and J. Cadranel; data analysis and interpretation: A. Lavolé, J. Mazières, A. Langlais, F. Morin, A. Makinson and J. Cadranel; manuscript writing: all authors; final approval of manuscript: all authors; accountable for all aspects of the work: all authors.

Conflict of interest: A. Lavole has nothing to disclose. L. Greillier reports personal fees from AstraZeneca, Boehringer Ingelheim, Roche, Bristol-Myers Squibb, MSD, Takeda, Abbvie and Novartis, outside the submitted work; travel and accommodation expenses from MSD and Pfizer. J. Mazières has nothing to disclose. I. Monnet has nothing to disclose. L. Kiakouama-Maleka has nothing to disclose. X. Quantin has nothing to disclose. J.P. Spano reports personal fees for consultancy from MSD, Roche and Biogaran, personal fees for advisory board work from Lilly, Mylan and Novartis, personal fees for advisory board work and lectures from Pfizer and Leopharma, personal fees for lectures from Pierre Fabre Oncology, AstraZeneca and Gilead, grants from BMS and MSD Avenir, outside the submitted work. H. Lena has nothing to disclose. P. Fraisse has nothing to disclose. H. Janicot has nothing to disclose. C. Audigier-Valette has nothing to disclose. A. Langlais has nothing to disclose. F. Morin has nothing to disclose. A. Makinson has nothing to disclose. J. Cadranel reports grants from AstraZeneca, Novartis and Pfizer, outside the submitted work.

Support statement: Lilly (France) supplied pemetrexed and a research grant to Intergroupe Francophone de Cancérologie Thoracique (IFCT) for the IFCT-1001 CHIVA Trial. Funding information for this article has been deposited with the Crossref Funder Registry.

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