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Assessment of nivolumab in HIV-Infected patients with advanced non-small cell lung cancer after prior chemotherapy. The IFCT-1602 CHIVA2 phase 2 clinical trial

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1 **Title**

2 **Assessment of Nivolumab in HIV-Infected Patients with Advanced Non-Small Cell**
3 **Lung Cancer after Prior Chemotherapy. The IFCT-1602 CHIVA2 Phase 2 Clinical**
4 **Trial**

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52 *Word count: 1230*

53 **Key Points**

54 *Word count: 99*

55 **Question:** Is nivolumab treatment safe and effective in HIV-infected patients with pretreated
56 advanced non-small cell lung cancer (NSCLC)?

57 **Findings:** In this nonrandomized, open-label, phase 2 study of 16 patients with HIV infection
58 and previously treated advanced NSCLC, nivolumab was well-tolerated and beneficial.

59 Disease control rate was 62.5% at 8 weeks. Most treatment-related adverse events were of
60 grade 1 and 2. One patient had a treatment-related serious adverse event. HIV viral load
61 remained undetectable (or controlled) throughout the study.

62 **Meaning:** Patients with controlled HIV infection can benefit from nivolumab treatment for
63 pretreated advanced NSCLC. Studies in first-line settings are required in this population.

64 **Abstract**

65 *Word count: 299*

66 **Importance:** Therapies targeting immune checkpoints, such as the programmed cell death 1
67 (PD-1) receptor, have become the standard-of-care for patients with non-small cell lung
68 cancer (NSCLC), but people living with HIV (PLWH) were excluded from these studies.

69 Objective: To evaluate the efficacy and tolerability of nivolumab in PLWH with advanced
70 NSCLC.

71 Design: The CHIVA2 study was a nonrandomized, open-label, phase 2 clinical trial in
72 PLWH with previously treated advanced NSCLC.

73 Setting: National multicenter prospective study.

74 Participants: patients had viral load of <200 copies/mL, regardless of their CD4+ T-cell
75 count.

76 Intervention: Nivolumab was administered in second or third line, as monotherapy
77 intravenously at 3 mg/kg every 2 weeks, until disease progression or limiting toxicity.

78 **Main Outcomes and Measures:** The primary endpoint was disease control rate, evaluated
79 using the Response Evaluation Criteria in Solid Tumors, version 1.1. Adverse events were
80 graded using the National Cancer Institute Common Terminology Criteria for Adverse
81 Events, version 4.0.

82 **Results:** Sixteen patients with advanced NSCLC were enrolled: 14 (88%) were men, median
83 age was 58 years (range: 44-71), and all were smokers. The median duration of nivolumab
84 treatment was 3.5 months (range: 0.5-26.5). The median follow-up was 23.6 months. Disease
85 control rate was 62.5% for 15 evaluable patients at 8 weeks (2 with partial response, 8 with
86 stable disease, and 5 with disease progression). Twelve (75%) patients had treatment-related
87 adverse events, which were mild or moderate, except for one patient experiencing severe
88 pruritus, onycholysis, and pemphigoid. There were no opportunistic infections or unexpected
89 immune-related events. HIV viral load was stable during treatment. An increase in
90 proliferating CD8+ and CD4+ T-cells was observed after 3 nivolumab cycles in a subgroup
91 of 9 patients.

92 **Conclusions and Relevance:** Second/third-line nivolumab treatment was well-tolerated and
93 beneficial in PLWH with NSCLC. Future trials should investigate immune checkpoint
94 inhibitors in first-line settings.

95 **Trial Registration:** EudraCT.ema.europa.eu registration number: 2016-003796-22

96 **Abbreviations:** AE: adverse event; C: cycle; (c)ART: (combined) antiretroviral therapy;

97 CI: confidence interval; CTLA-4: cytotoxic T-lymphocyte-associated protein 4;

98 DCR: disease control rate; HIV: human immunodeficiency virus; IC: immune checkpoint;

99 ICIs: immune checkpoint inhibitors; NSCLC: non-small cell lung cancer; OS: overall

100 survival; PD-1: programmed cell death 1 receptor; PD-L1: programmed cell death ligand 1;

101 PFS: progression free survival; PLWH: people living with HIV; TIM-3: T-cell

102 immunoglobulin and mucin domain-containing protein 3; VL: viral load.

103 **Introduction**

104 Antiretroviral therapy (ART) has significantly extended life expectancy for people living
105 with human immunodeficiency virus (HIV) infection (PLWH). In parallel, mortality due to
106 non-acquired immune deficiency syndrome-defining cancers, particularly lung cancer, has
107 risen¹. In these patients, immunosuppressive cancer therapies such as chemotherapy and
108 radiotherapy can cause an initial decline in CD4⁺ T-cell counts, which is associated with an
109 increased mortality hazard².

110 Cancer therapy targeting immune checkpoint (IC) pathways, including the programmed cell
111 death 1 (PD-1) receptor/programmed cell death ligand (PD-L)1/2 pathway, has become the
112 standard-of-care for non-small cell lung cancer (NSCLC) in the general population, initially
113 as second-line, then as first-line treatment in patients with PD-L1 expression on $\geq 50\%$ of
114 tumor cells, and in combination with chemotherapy in all patients, except those with
115 oncogene-driven NSCLC³. However, PLWH were excluded from these clinical trials due to

116 concerns that T-cell stimulation may reactivate HIV infection or exacerbate immune
117 responses to HIV-related opportunistic infections⁴.
118 *In vitro* studies show that HIV-infected memory CD4⁺ T-cells preferentially express PD-1,
119 suggesting that IC inhibitors (ICIs) could reinvigorate the CD4⁺ T-cell HIV reservoir⁵.
120 PD-1/PD-L1 blockade facilitates latency reversal in cells from ART-treated individuals,
121 leading to increased virus production⁶. It also restores specific CD8⁺ and CD4⁺ T-cell
122 functions i.e. cytokine and cytotoxic molecules' production and cell proliferation^{7,8}.
123 Retrospective studies have shown that ICIs are generally well-tolerated in PLWH with
124 advanced stage NSCLC, with no or transient effects on HIV viral load (VL) observed^{4,9}. At
125 the time of initiating this trial, only case reports and studies in small cohorts were reported,
126 but no phase 2 trial had been conducted in this setting.
127 We conducted a phase 2 prospective study to investigate the tolerability and efficacy of
128 nivolumab, a fully human anti-PD-1 antibody, in PLWH with advanced NSCLC, after prior
129 platinum-based doublet chemotherapy.

130 **Methods**

131 Sixteen patients with combined (c)ART-controlled HIV-1 infection (VL <200 copies/mL),
132 regardless of their CD4⁺ T-cell count, and histologically/cytologically proven NSCLC stage
133 IIIB or IV at diagnosis or after relapse post-surgery were included. Patients had received at
134 least one prior platinum-based doublet chemotherapy regimen. Full inclusion and exclusion
135 criteria are provided in the trial's protocol ([Supplement 1](#)). Nivolumab was administered
136 intravenously over 30 minutes at 3 mg/kg every 2 weeks, until disease progression or limiting
137 toxicity. The protocol was approved by an independent ethics committee and the French
138 health authorities (ANSM). Written informed consent was obtained from each patient.

139 The primary endpoint was disease control rate (DCR) at 8 weeks. Secondary endpoints
140 included progression free survival (PFS) and overall survival (OS). Adverse events (AEs)
141 were graded using the National Cancer Institute Common Terminology Criteria for AEs v4.0.
142 Phenotypes of T-cell activation/proliferation were explored in a subgroup of 9 patients at
143 baseline, at cycle (C) C2, C3, C9, C15, C27, and C51, and at the end of treatment. The
144 complete study objectives, assessments, and statistical analyses are provided in the eMethods
145 ([Supplement 2](#)).

146 **Results**

147 Sixteen patients were enrolled between December 2017 and July 2019 (eFigure 1,
148 [Supplement 3](#)). Baseline characteristics are presented in **Table 1** and eTable 1, [Supplement 3](#).
149 Fourteen (88%) patients were men, median age was 58 years (range: 44-71), and 16 (100%)
150 were smokers. Ten (63%) patients had adenocarcinoma. PD-L1 expression was negative in
151 9/14 (64%) tumors and positive in 5/14 (36%) tumors, with 3 expressing PD-L1 on $\geq 50\%$ of
152 cells. Median CD4⁺ T-cell count was 385 cells/ μ L (range: 187-778) and HIV-VL was
153 25 copies/mL (range: 0-44). Patients received nivolumab as second- (69%) or third-line
154 (31%) treatment for a median duration of 3.5 months (range: 0.5-26.5). The median
155 follow-up was 23.6 months (95% confidence interval [CI95%]: 13.9-30).

156 DCR was 62.5% (CI95%: 39-86%) for 15 evaluable patients at 8 weeks, including 2 patients
157 with partial response, 8 with stable disease, and 5 with progressive disease. Median PFS and
158 OS were 3.4 months (CI95%: 1.8-5.6, n=14) and 10.9 months (CI95%: 2.2-not reached,
159 n=10), respectively (eFigure 2, [Supplement 3](#)). Among 9 PD-L1-negative patients, 1 had a
160 partial response, 3 were stable, 4 progressed, and 1 was not determined. Among
161 5 PD-L1-positive patients, 1 had a partial response and 4 were stable.

162 Twelve (75%) patients had treatment-related AEs, mostly of grade 1 and 2, except for one
163 patient experiencing grade 3 pruritus, onycholysis, and pemphigoid (**Table 2**). The AE of
164 pemphigoid (grade 2) was also reported as serious. No opportunistic infections or unexpected
165 immune-related events were observed. There were no significant changes in CD4⁺ and CD8⁺
166 T-cell counts, and HIV-VL was globally stable during nivolumab treatment (**Figure 1**).

167 In the 9 patients selected for exploratory studies, there was a significant increase in the
168 proportion of CD8⁺Ki67⁺ T-cells at C3 compared to C1 (p=0.047) and in the proportion of
169 CD4⁺Ki67⁺ T-celles at C3 compared to C1 (p=0.0313) (eFigure 3, [Supplement 3](#)). These
170 changes were not associated with better tumor response, since among 4 patients with the
171 highest proportion of CD8⁺Ki67⁺ T-cells, tumor progression occurred in 2 cases.
172 PD-1 was almost undetectable on CD4⁺ and CD8⁺ T-cells from C2 onwards, suggesting high
173 receptor occupancy, whereas T-cell immunoglobulin and mucin domain-containing protein 3
174 (TIM-3) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression significantly
175 increased at C3 on CD4⁺ (p=0.031) and CD8⁺ (p=0.015) T-cells, respectively (eFigure 3,
176 [Supplement 3](#)). Notably, most of the patients with TIM-3 or CTLA-4 upregulation at C3 were
177 progressing (3/4 and 3/3 patients, respectively).

178 **Discussion**

179 In this phase 2 prospective study, the only one focusing on NSCLC, nivolumab was not
180 associated with HIV-VL rebound, replication blip, or unexpected treatment-emergent safety
181 signals, in agreement with two other prospective studies in ART-controlled PLWH with solid
182 tumors^{10,11}. Efficacy findings (62.5% DCR at 8 weeks, 3.4 months PFS, and 10.9 months OS)
183 are consistent with phase 3 studies in the general population³ and better than in real-life
184 settings in the same regional population of NSCLC¹². Patients with PD-L1-positive tumors

185 seemed to respond better, although this should be confirmed in a larger cohort. Most
186 treatment-related AEs were mild or moderate.

187 As previously observed^{7,8}, PD-1 blockade rapidly induced peripheral CD8⁺/CD4⁺ T-cell
188 activation, which may reflect a boost in T-cell immunity against the tumor and/or the HIV
189 infection (tissue biopsies were unavailable at this stage to confirm this). However, only
190 2/4 patients with increased peripheral T-cell counts were responders, supporting preliminary
191 data that suggest independent immune responses elicited by viral infections and within the
192 tumor microenvironment, and imply that antitumor and antiviral treatments may be safely
193 combined¹³.

194 TIM-3 and CTLA-4 were significantly upregulated on CD4⁺ and CD8⁺ T-cells, respectively,
195 at C3. This seemed to be associated with tumor progression, suggesting a compensatory
196 mechanism whereby alternative ICs are upregulated following PD-1/PD-L1 blockade, thus
197 inhibiting antitumoral T-cell responses. Upregulation of alternative ICs has been observed *in*
198 *vitro* on activated CD4⁺ T-cells and regulatory T-cells in the presence of cancer cells in the
199 context of ICIs¹⁴.

200 **Limitations**

201 Our study is limited by the small sample size, which was due to difficulties in recruiting
202 patients with the rare HIV-NSCLC combination, the study independent data monitoring
203 committee recommended that patient inclusion be stopped in January 2020. The use of ICIs as
204 first-line standard-of-care also rapidly evolved during this trial and led to the premature
205 discontinuation of the study.

206 **Conclusions**

207 In summary, nivolumab treatment after prior chemotherapy was well-tolerated and beneficial
208 in PLWH with advanced NSCLC. Future studies should investigate first-line immunotherapy,

209 as monotherapy or in combination with chemotherapy or a second ICI. Since the strength of
210 our conclusions was limited by the small sample size, we endorse recent recommendations to
211 extend inclusion criteria to patients with controlled HIV infection in future trials¹⁵.

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Figure Legends

Figure 1. Peripheral CD4⁺ and CD8⁺ T-cell Count and HIV Viral Load.

A, B) Overall, peripheral CD4⁺ T-cells (A) and CD8⁺ T-cells (B) (counts/mm³) did not change significantly from baseline (BS) to the end of treatment (EoT). **C)** Peripheral viral load remained stable during the study. Data are depicted for n=16 patients. BS: baseline; C: cycle; EoT: End of Treatment.

Tables

Table 1. Baseline Characteristics of the Patients

Characteristic	No. (%) ^a (n = 16)
Age, median (range), years	58 (44-71)
Sex	
Male	14 (88)
Female	2 (13)
Smoking	
Yes	16 (100)
No	0 (0)
Pack per year, median (range)	40 (13-90)
ECOG performance status	
0-1	12 (75)
2	4 (25)
No. of prior cancer therapies	
1	11 (69)
≥2	5 (31)
Histology	
Adenocarcinoma	10 (63)
Unspecified NSCLC	1 (6)
Squamous cell carcinoma	5 (31)
Stage	
IIIB	1 (6)
IVA	4 (25)
IVB	11 (69)
PD-L1 ^b	
<1%	9 (64)
1-49%	2 (14)
≥50%	3 (21)
Duration of HIV infection, median (range), years	24 (3-39)
CD4 ⁺ T-cell count, median (range), cells/mm ³	385 (187-778)
Nadir CD4 ⁺ T-cell count, median (range), cells/mm ³	274 (32-778) ^c
HIV viral load, median (range), copies/mL	25 (0-44)
History of cancer	6 (38)
AIDS-related	1 (6)
Non-AIDS-related	5 (31)
History of infection	11 (69)
AIDS-related infections	3 (19)
Hepatitis B	2 (13)
Hepatitis C	3 (19)
Others	8 (50)
Comorbidities ^c	
Yes	8 (53)
No	7 (47)

Abbreviations: AIDS, acquired immune deficiency syndrome; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1.

^a Percentages are rounded off.

^b Data were available for n=14 patients (biopsies were not collected for 2 patients).

^c Data were available for n=15 patients (one patient missing/unknown).

Table 2. Adverse Events Related to Treatment

Type of adverse event	No. (%) ^a (n = 16)					
	Grade					
	Any	1	2	3	4	5
Any	12 (75)	4 (25)	7 (44)	1 (6)	0 (0)	0 (0)
Serious ^b	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	7 (44)	4 (25)	3 (19)	0 (0)	0 (0)	0 (0)
Diarrhea	3 (19)	3 (19)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	3 (19)	1 (6)	2 (13)	0 (0)	0 (0)	0 (0)
Aphthous ulcer	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Constipation	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Dry mouth	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Stomatitis	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Vomiting	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Endocrine disorders	4 (25)	3 (19)	1 (6)	0 (0)	0 (0)	0 (0)
Hyperthyroidism	2 (13)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)
Hypothyroidism	2 (13)	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	3 (19)	0 (0)	3 (19)	0 (0)	0 (0)	0 (0)
Asthenia	3 (19)	0 (0)	3 (19)	0 (0)	0 (0)	0 (0)
General physical health deterioration	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Xerosis	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	3 (19)	1 (6)	2 (13)	0 (0)	0 (0)	0 (0)
Arthralgia	3 (19)	1 (6)	2 (13)	0 (0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	3 (19)	2 (13)	0 (0)	1 (6)	0 (0)	0 (0)
Pruritus	3 (19)	2 (13)	0 (0)	1 (6)	0 (0)	0 (0)
Alopecia	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Alopecia areata	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Madarosis	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Onycholysis	1 (6)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)
Pemphigoid	1 (6)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)
Rash	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Blood and lymphatic system disorders	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Anemia	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Investigations	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Weight decreased	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Hyperkalemia	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Tremor	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)

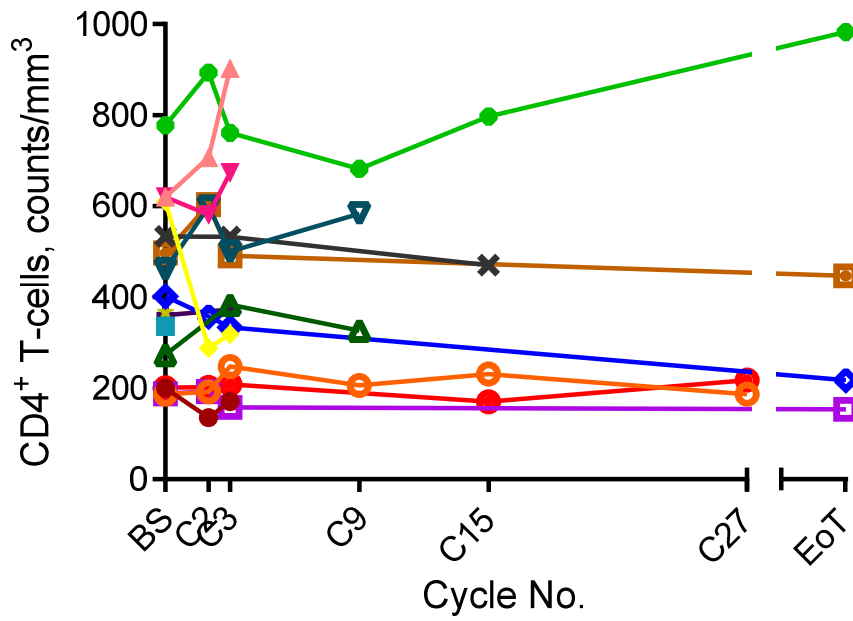
Abbreviations: AE, adverse event; SAE, serious adverse event.

^a Percentages are rounded off and may not sum up to the total exactly.

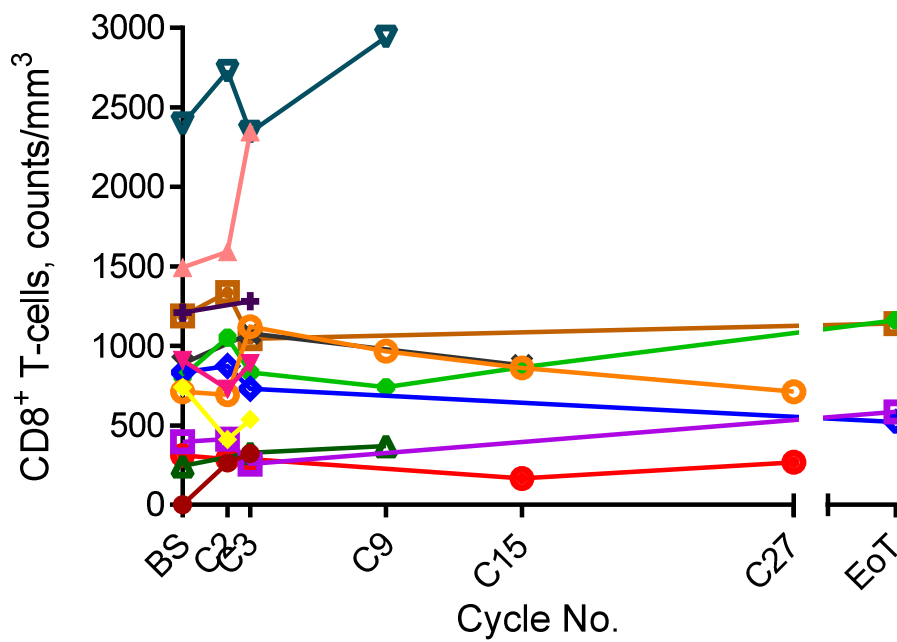
^b SAE's grades are presented as assessed when the event was declared as serious. Grades for the AE's preferred term represent the worst grade for each event.

Figure 1. Peripheral CD4⁺ and CD8⁺ T-cell Count and HIV Viral Load.

A) CD4⁺ T-cells



B) CD8⁺ T-cells



C) Viral load

