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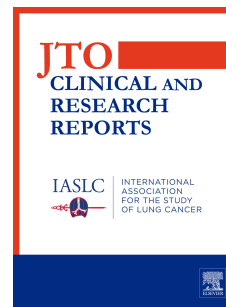
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## **Brief report of Anti-PD1 in HIV setting: relevant and breaking results in first-line Non Small Cell Lung Cancer therapy**

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### **Abstract**

In the recent past, we observed an increased risk of cancer in the HIV population due to the development of antiretroviral therapies that decreased mortality caused by HIV-specific infections. This particularly fragile population is frequently excluded from clinical trials, and up-to-date recommendations for these patients are lacking. Only few cases of HIV patients suffering from cancer and undergoing first-line immunotherapy have been reported so far. Here we report the largest known study of HIV patients with non-small cell lung cancer (NSCLC) (5 patients) undergoing first-line immunotherapy by pembrolizumab, following CANCERVIH group selection. Our results are consistent with previous case reports concerning safety of immunotherapy in HIV patients, showing no severe or fatal toxicity, opportunistic infections, or immune reconstitution inflammatory syndrome (IRIS). Moreover, pembrolizumab did not seem to modify HIV viral parameters. We also assessed effectiveness of immunotherapy in these HIV-immunosuppressed patients: the average survival was 9.8 months, with three patients showing rapid progression and two partial response. However, as well as safety and drug-to-drug interactions, the effectiveness of first-line immunotherapy in people living with HIV (PLWHIV) needs to be supported by larger studies.

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**Conflict of interest:**

Jacques Cadranel received fees from Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Merck Sharp Dohme, Pfizer, Roche and Takeda for participation to boards of experts.

Jean-Philippe Spano declares links of interest with Roche, MSD, Astra Zeneca, Leopharma, Mylan, Biogaran, Novartis, Daiichi Sankyo Oncology, Pfizer, Bristol Myers Squibb, Incyte, Pierre Fabre Oncology, Lilly, Gilead.

Armelle Lavolé reports non-financial support from Bristol Myers Squibb.

Anthony Canellas received fees from Bristol Myers Squibb.

The others authors declare no conflicts of interests.

**Introduction**

The use of highly active antiretroviral therapy (HAART) in developed countries has led to considerable reduction in AIDS mortality caused by opportunistic infections and AIDS-defining cancers. Instead, non-AIDS-related cancers have become a leading cause of morbidity and mortality in people living with HIV (PLWHIV), with non-small cell lung cancer (NSCLC) being the first cause of mortality [1]. Because of a possible drug-to-drug interaction between chemotherapy and HAART, these patients require particular monitoring.

In the last 5 years, immune checkpoint inhibitors (ICIs) – notably programmed cell death 1 (PD-1)/programmed cell death 1 ligand (PD-L1) inhibitors – have become the standard-of-care for advanced NSCLC in the general population, initially as second-line [2], then as first-line treatment in patients with  $\geq 50\%$  tumour PD-L1 expression [3], and finally in combination with chemotherapy in all patients, except those with oncogene-driven NSCLC. Since ICIs act by suppressing immune tolerance and by reactivating an effective immune response, major concerns in PLWHIV were: i) a lack of anti-tumoral response due to HIV-related chronic immune deficiency, and ii) the risk of anti-HIV response modulation and deregulation of immune parameters, potentially leading to immune reconstitution inflammatory syndrome (IRIS).

Until recently, this population was rarely studied: only few cases in phase I and II clinical trials had described the use of ICIs as second or subsequent lines of treatment for PLWHIV with advanced NSCLC [4]. The CHIVA 2 trial has recently addressed the possible use of immunotherapy as second-line treatment of PLWHIV with advanced NSCLC [5]; however, safety and efficacy data on ICIs as first-line therapy are still lacking.

The French CANCEVH network is a multidisciplinary task force supported by the French National Cancer Institute (INCa) whose mission is to optimise management and care of PLWHIV and suffering from cancer. A main objective of CANCEVH is to ensure equal care for PLWHIV, particularly through access to therapeutic innovations including immunotherapy [6]. Here, we report 5 cases taken from the CANCEVH database of PLWHIV with advanced NSCLC and treated with first-line pembrolizumab

## Methods

The CANCEVH working group [7] has recommended that all new cases of PLWHIV with cancer should be included in the CANCEVH database and discussed during the bi-monthly national multidisciplinary board. Moreover, recommendations for immuno-virological monitoring have been published [8].

Between January 2014 and December 2019, 105 PLWHIV suffering from lung cancer at various stages were presented. Among them, five with advanced NSCLC were eligible for first-line pembrolizumab monotherapy, having an Eastern Cooperative Oncology Group (ECOG) Performance Status  $\leq 1$ ; PD-L1 tumour expression  $\geq 50\%$ , and patient agreement.

All patients received a fixed dose of 200 mg pembrolizumab every 3 weeks until disease progression or unacceptable toxicity. The outcome of this treatment is reported here (**Table 1**). The data for this analysis were collected from CANCEVH database which one has received an approval from the French IRB (n°15-009), the CCTIR (n°16-391) and from the “Commission Nationale de l’Informatique et des Libertés (CNIL n°916500)” and as a retrospective analysis no consent is required.

## Results

The median age was 57.4 years (range 50-69) and 4 patients were men. Apart from 1 patient (Case 3), all were current or former smokers. The prevalent histology was squamous and undifferentiated carcinoma; only 1 patient had adenocarcinoma. Tumour cell PD-L1 expression was 80% in 2 cases (Cases 1 and 3). No epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) aberrations were found. All patients had undetectable plasma HIV load and were stable under antiretroviral treatment, except Case 4, who had concomitant advanced NSCLC and HIV diagnostics (HIV load: 44 500 copies/mL). Median CD4<sup>+</sup> lymphocyte count was 595/mm<sup>3</sup> (range 76-1024). No opportunistic infection was reported.

At the cut-off date of data analysis (March 2020), median overall survival was 9.8 months (range 1-25) and patients received a median of 9 pembrolizumab infusions (range 1-28) (**Table 1**). According RECIST, best tumour response was partial response in 2 patients (40%) and disease progression in 3 (60%).

Two patients reported immune-related adverse events: grade 1 hyperthyroidism (Case 2) and grade 3 immunological thrombocytopenic purpura (Case 4). None of the patients experienced IRIS, not even Case 4, who received pembrolizumab concomitantly with HIV treatment by HAART.

HIV load remained or became (Case 4) undetectable at cut-off and blood CD4<sup>+</sup> lymphocyte counts remained stable in all patients.

## Discussion

Here we report 5 cases of PLWHIV with advanced NSCLC treated with first-line pembrolizumab immunotherapy. No severe or fatal toxicity, opportunistic infections, or IRIS were reported during follow-up. Our safety results are consistent with retrospective series reported in the systematic review by *COOK et al.* (13 articles plus 4 reports from meetings including various types of cancers in PLWHIV receiving ipilimumab, pembrolizumab, nivolumab, or atezolizumab) [4] and the observational study by *SPANO et al.* (2019) [9], which included 23 PLWHIV suffering from various malignancies (NSCLC [not including our cases], melanoma, head and neck cancers) and receiving pembrolizumab (first-, second- or subsequent lines) or nivolumab ( $\geq$ second line). This study reported only 1 case of grade 3 immune-related interstitial lung disease after pembrolizumab.

We also assessed the effectiveness of ICI in these HIV-immunosuppressed patients and found an average survival of 9.8 months. Due to the small sample size, we cannot compare these data to larger studies in the general population [3]. Three patients had rapid progression occurring only after 1-5 treatment cycles, despite the high PD-L1 tumour expression (>50%). In contrast, of 2 patients with partial response, one (Case 2) had 2 additional cycles after data collection (9 in total), then progressed and started chemotherapy (overall survival of 24 months); and the other had a longer-term response (Case 4, 28 treatment cycles).

However, high PD-L1 expression is only one prognostic factor of response to anti-PD-L1 immunotherapy and other potential markers are unknown. For example, one of our non-responders (Case 3) had 80% tumour PD-L1 expression, but was also a non-smoker, a condition which is unrelated to tumour immune response – even with high PD-L1 expression

[10] – but rather relates to the activation of molecular pathways of addiction. Even if no EGFR or ALK mutations were seen in this patient, many others were not assessed. Alternatively, immunotherapy may be combined with chemotherapy in these patients, with a potential synergistic effect and improved response. Besides addiction pathways, another factor to be considered in PLWHIV is HIV-induced immune cell qualitative abnormality, which could potentiate cancer cell-mediated immunosuppression via PD-L1.

As for anti-HIV response, despite high expectations of anti-PD-1/anti-PD-L1 immunotherapy that followed *in vitro* studies showing the reestablishment of anti-HIV immune response, recent *in vivo* observations did not support these results. Indeed, ICIs did not seem to modify viral parameters in stable PLWHIV or impact the response to HAART in newly discovered PLWHIV (Case 4) [4,9].

Finally, our results are consistent with previous observations by *OSTIOS-GARCIA et al.* (2018) on 3 PLWHIV with advanced NSCLC receiving first-line pembrolizumab [11]. Since this study, 3 more clinical trials [5,12,13] in PLWHIV have been published (**Table 1**). PLWHIV were also included in 2 additional phase III therapeutic trials, evaluating cemiplimab monotherapy as first-line treatment for advanced NSCLC with PD-L1 >50% [14] and nivolumab in combination with low-dose ipilimumab versus platinum doublet chemotherapy [15]. However, results for this group of patients have not been reported yet.

Indeed, we have to consider HIV patients with uncontrolled infections separately, because all previous studies included patients with controlled immune response at baseline. Prior antiretroviral therapy is recommended in HIV patients who have uncontrolled infections (as evidenced by high viral load and low CD4<sup>+</sup> cell counts), since the effectiveness of immunotherapy in these patients is unknown.

## Conclusion

We report 5 PLWHIV with NSCLC treated with first-line pembrolizumab immunotherapy. As well as safety and drug-to-drug interactions, the effectiveness of first-line immunotherapy in PLWHIV needs to be supported by large studies.

Inclusion of specific populations such as PLWHIV in clinical trials remains marginal, leading to considerable delays in drafting recommendations for these particularly at-risk patients.

**Table 1. Outcome of immune checkpoint inhibitor therapy in PLWHIV with advanced stage cancers.**

Source	Case #	PS	Histology (NSCLC)	Baseline CD4 <sup>+</sup> cells/mm <sup>3</sup>	Baseline VL (copies/mL)	Tumour PD-L1 (%)	ICI start date <sup>1</sup> (infusions)	Best tumour response	CD4 <sup>+</sup> cells/m <sup>3</sup> at cut-off <sup>2</sup>	VL at cut-off <sup>2</sup> (copies/mL)	Survival (months)	Status at cut-off <sup>2</sup>
CANCERVIH	1	2	Adenocarcinoma	413	<30	80	29 Aug 2018 (5)	Progression	319	<30	9	Death (May 2019)
CANCERVIH	2	0	Undifferentiated carcinoma	1000	<30	60	08 Aug 2019 (7)	Partial response	342	<30	8	Alive (death in Sept 2020)
CANCERVIH	3	0	Squamous carcinoma	463	<30	80	01 Apr 2019 (1)	Progression	N/A	<30	3	Death (July 2019)
CANCERVIH	4	0	Squamous carcinoma	76	44500	≥50	13 Feb 2018 (28)	Partial response	N/A	<30	25	Alive
CANCERVIH	5	1	Undifferentiated carcinoma	1024	<30	≥50	23 Jan 2019 (4)	Progression	1230	<30	4	Death (May 2019)
Source	N <sup>3</sup>	PS	Tumour type	Baseline CD4 <sup>+</sup> cell count	Baseline VL (copies/mL)	Tumour PD-L1 (%)	ICI therapy (treatment line)	Best tumour response	CD4 <sup>+</sup> cells/m <sup>3</sup> at cut-off	VL at cut-off	Overall survival (months)	Adverse events
<i>ULDRICK et al. (2019)[12]</i>	30	0-1	Various advanced cancers (1 NSCLC)	285 (132-966)	<200	N/A	pembrolizumab (Second-line)	1 Complete Response (NSCLC)	Stable	Detectable (<400) in 7 patients; Stable in others	N/A	80% grade 1-2: hypothyroidism (6/30 patients), pneumonitis (3/30), rash (1/30)
<i>GONZALEZ-CAO et al. (2020)[13]</i>	20	0-1	Various advanced cancers (14 NSCLC)	397 (294-513)	Undetectable	<1: n=11 1-49: n=1 ≥50: n=3	durvalumab (All lines)	25% Partial response; 31% stable disease	Stable	Stable	9.2	Only grade 1-2 in 10/20 patients (diarrhoea, asthenia, arthromyalgia)
<i>LAVOLE et al. (2021) [5]</i>	16	0-2	Stage III-IV NSCLC	385 (187-778)	25 (0-44)	<1 or unknown: n=11 1-49: n=2 ≥50: n=3	nivolumab (≥Second-line)	12.5% Partial response; 50% stable disease	Stable	Stable	10.9	69% grade 1-2; 1 patient with grade 3 pemphigoid

ICI: immune checkpoint inhibitor; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death 1 ligand; PLWHIV: people living with HIV; PS: performance status; VL: viral load.  
\*determined through investigator-assessed RECIST

<sup>1</sup>pembrolizumab start date.

<sup>2</sup>Cut-off date was March 2020.

<sup>3</sup>Number of included patients.



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