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## **Can nivolumab alone cure patients with relapse or refractory Hodgkin lymphoma? Five-year analysis of the French early access program**

Guillaume Manson<sup>1</sup>, Charles Herbaux<sup>2</sup>, Jean-Marc Schiano<sup>3</sup>, Olivier Casasnovas<sup>4</sup>, Aspasia Stamatoullas<sup>5</sup>, Bénédicte Deau<sup>6</sup>, Anna Schmitt<sup>7</sup>, Caroline Regny<sup>8</sup>, Krime Bouabdallah<sup>9</sup>, Adrien Chauchet<sup>10</sup>, Hervé Ghesquieres<sup>11</sup>, Adrian Tempescul<sup>12</sup>, Remy Dulery<sup>13</sup>, Emmanuelle Nicolas-Virelizier<sup>14</sup>, Alain Delmer<sup>15</sup>, Cecile Borel<sup>16</sup>, Laurent Dercle<sup>17</sup>, Pauline Brice<sup>18</sup> and Roch Houot<sup>1,19</sup>, on behalf of the LYSA

<sup>1</sup> Department of Hematology, University Hospital of Rennes, Rennes, France

<sup>2</sup> Department of Hematology, University Hospital of Lille, Lille, France

<sup>3</sup> Department of Hematology, Paoli-Calmette Institute, Marseille, France

<sup>4</sup> Department of Hematology, University Hospital of Dijon, Dijon, France

<sup>5</sup> Department of Hematology, Centre Henri Becquerel, Rouen, France

<sup>6</sup> Department of Hematology, Cochin Hospital, AP-HP, Paris, France

<sup>7</sup> Department of Hematology, Bergonie Institute, Bordeaux, France

<sup>8</sup> Department of Hematology, University Hospital of Grenoble, Grenoble, France

<sup>9</sup> Department of Hematology, Bordeaux University Hospital, F-3300 Bordeaux, France

<sup>10</sup> Department of Hematology, University Hospital of Besançon, Besançon, France

<sup>11</sup> Department of Hematology, University Hospital of Lyon, Lyon, France

<sup>12</sup> Department of Hematology, University Hospital of Brest, Brest, France

<sup>13</sup> Department of Hematology, Saint-Antoine Hospital, AP-HP, Paris, France

<sup>14</sup> Department of Hematology, Leon Berard Center, Lyon, France

<sup>15</sup> Department of Hematology, University Hospital of Reims, Reims, France

<sup>16</sup> Department of Hematology, Institut universitaire du cancer Toulouse-Onco-pole, Toulouse, France

<sup>17</sup> Department of Radiology, Columbia University Medical Center, New York, New York, USA

<sup>18</sup> Department of Hematology, Saint-Louis Hospital, AP-HP, Paris, France

<sup>19</sup> INSERM, U1236, Rennes, France

### **Corresponding author:**

Dr Guillaume Manson

Department of Hematology, University Hospital of Rennes, INSERM U1236, Rennes, France

2 rue Henri Le Guilloux

35033 Rennes Cedex 9

France

Tel: +33 (0)2 99 28 42 26

Fax: +33 (0)2 99 28 41 61

guillaume.manson@chu-rennes.fr

Checkpoint blockade with anti-PD1 monotherapy have shown great efficacy in patients with relapsed/refractory Hodgkin lymphoma (R/R HL) (Chen *et al*, 2017; Armand *et al*, 2018; Beköz *et al*, 2017; Manson *et al*, 2019). Patients who are unable to achieve a complete response (CR) usually experience limited progression-free survival (PFS) in the absence of consolidation with allogeneic hematopoietic stem cell transplantation (alloHSCT) (Manson *et al*, 2019; Chen *et al*, 2019). Despite its curative potential, alloHSCT cannot be performed in all patients due to its particular toxicity profile after anti-PD1 therapy (Merryman *et al*, 2021, 2017).

On the other hand, patients achieving a CR may experience durable remission without further therapy (Manson *et al*, 2019; Chen *et al*, 2019; Bekoz *et al*, 2020). These prolonged responses may persist even after anti-PD1 discontinuation (Manson *et al*, 2018). It has been suggested that younger patients with an early and deep response had a higher probability of being relapse-free one year after anti-PD1 discontinuation (Manson *et al*, 2020). However, in these studies, the median follow-up remained limited (median 1.5 to 2.8 years) and data are lacking to assess whether some of these patients may be cured with anti-PD1 therapy alone.

Here, we report the 5-year analysis of the ATU-nivo study, a retrospective, nationwide study of patients aged  $\geq 18$  years with R/R HL who were treated with nivolumab in the French early access program (EAP). The study included patients with HL relapsing or refractory after three lines of chemotherapy (including Brentuximab-Vedotin) and autoHSCT, or four lines of chemotherapy if the patient was not eligible for HSCT. All patients who had received at least one dose of nivolumab as part of the French EAP were eligible for the study. Nivolumab was administered at 3 mg/kg every 2 weeks until progression, death of any cause, unacceptable toxicity, consent withdrawal, or treating physician's decision. Treatment efficacy was assessed using [ $^{18}\text{F}$ ]FDG-PET/CT. Patients were allowed to undergo subsequent alloHSCT according to primary physician's decision. The protocol was approved by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé – CCTIRS (Approval n° 16.861). The 3-year analysis of the cohort has been previously published (Manson *et al*, 2019).

We included 76 patients in the efficacy analysis. After a median follow-up of 5.7 years, the estimated 5-year PFS and overall survival (OS) were 27% and 53%, respectively. Thirty (39.5%) patients experienced a CR as best response, of whom 11 received a consolidation therapy: 9 with an alloHSCT, one with an auto-HSCT, and one with chemotherapy. As previously reported (Manson *et al*, 2020), patients in CR had a significantly better outcome than non-CR patients (**supplementary figure 1**).

To assess whether some patients might be cured with nivolumab alone as systemic treatment, we analyzed the 19 patients who achieved a CR and did not receive a consolidation (concomitant radiotherapy was performed in 5 patients). Their characteristics are summarized in **table 1**. These patients were young (median age = 39.4 years, range 19 – 77 years) and heavily pre-treated with a median number of 6 prior systemic lines of treatment, including brentuximab-vedotin (100%),

autoHSCT (57.9%) and alloHSCT (36.8%). They received a median of 20 cycles of nivolumab. The median time to CR was 2.1 months (range 1 – 5).

All patients had discontinued nivolumab therapy at the time of analysis, mostly because of prolonged remission (52.6%) or adverse event (21%, 2 acute graft-versus-host diseases, 1 laryngeal oppression and 1 cerebellar syndrome). Three (15.8%) patients discontinued because of disease recurrence and 2 (11.1%) because of non-hematological malignancies.

After a median follow-up of 5.6 years (4.0 years from nivolumab discontinuation), 9/19 (47.4%) patients remained alive and disease-free. The median PFS was 41.9 months and the median OS was not-reached (**figure 1**). The 5-year estimated PFS was 42.3%.

Nine patients have relapsed, of whom 6 received a salvage therapy: 3 received a second course of anti-PD1, 3 received radiotherapy and/or chemotherapy. Half of the patients achieved a CR upon salvage therapy. Most relapses occurred within the first two years of treatment (N=7). Two patients experienced late relapses, 40 and 60 months after nivolumab initiation, respectively.

In total, 2 patients died: one due to metastatic colorectal cancer (6 months after nivolumab initiation), and one from COVID-19. There was no late adverse event reported.

In the entire cohort (n = 76), the estimated 5-year PFS was 27% after a median follow-up of 5.7 years, which is to the best of our knowledge, the longest follow-up ever reported in this setting. All patients who remain in remission had either achieved a CR or had been consolidated with an alloHSCT after a PR. Although most relapses seem to occur during the first 3 years, some patients may experience late relapses, sometimes beyond 5 years, and no clear plateau can yet be seen (**supplementary figure 1**). Among CR patients who have not been consolidated (n = 19), the estimated 5-years PFS was 42.3%. Although late relapses (> 3 years) may occur (N=2), some patients experienced a very long remission (> 5 years) with anti-PD1 alone (N=6 in our cohort), suggesting that a subset of patients may be cured. In conclusion, our study confirms that, with a long follow-up, nivolumab is an effective strategy in this very heavily pre-treated population. Furthermore, a subset of patients (10 – 15 %) may be cured with anti-PD1 therapy alone.

**Table 1. Patients achieving a CR upon nivolumab alone and who did not receive a consolidation**

<b>Characteristics at nivolumab initiation</b>	<b>N = 19</b>
<b>Age, years, median [range]</b>	39.4 [19 – 77]
<b>Sex, No (%)</b>	
• Male	12 (63.2%)
• Female	7 (36.8%)
<b>Stage disease, No (%)</b>	
• I/II	6 (35.3%)
• III/IV	11 (64.7%)
• Unknown	2
<b>Prior lines of systemic therapy, median [range]</b>	6 [2 – 13]
<b>Prior radiation therapy, No (%)</b>	10 (52.6%)
<b>Prior treatment with Brentuximab Vedotin, No (%)</b>	19 (100%)
<b>Prior autologous HSCT, No (%)</b>	11 (57.9%)
<b>Prior allogenic HSCT, No (%)</b>	7 (36.8%)
<b>Nivolumab treatment and response</b>	
<b>Number of nivolumab injections, median [range]</b>	20 [1 – 105]
<b>Duration of anti-PD1 therapy, months, median [range]</b>	14.8 [0 – 66]
<b>Time to CR from Nivolumab initiation, months, median [range]</b>	2.1 [1 – 5.8]
<b>Permanent treatment discontinuation</b>	19 (100%)
<b>Reason for treatment discontinuation</b>	
• Decision of the physician (prolonged remission)	10 (52.6%)
• Adverse events	4 (21%)
• Disease progression	3 (15.8%)
• Second primary malignancy	2 (11.1%)
<b>Concomitant radiotherapy, No (%)</b>	5 (26.3%)
<b>Follow-up from nivolumab initiation, months, median [range]</b>	67 [1 – 73.3]
<b>Follow-up from nivolumab discontinuation, months, median [range]</b>	47.6 [17.9 – 67.1]
<b>PFS from nivolumab initiation, median (95% CI)</b>	41.9 (17.9 - NA)
<b>OS from nivolumab initiation, median (95% CI)</b>	Not reached
<b>Relapse</b>	9 (47.4%)
<b>If relapse, salvage therapy</b>	6 (66.7%)
• Second course of anti-PD1	3 (50%)
• Radiotherapy +/- chemotherapy	3 (50%)
<b>Response after salvage therapy</b>	
• CR	3 (50%)
• PD	2 (33.3%)
• Non-evaluated/missing	1 (16.7%)
<b>Deaths</b>	2 (10.5%)
• COVID19	1 (5.3%)
• Other malignancy	1 (5.3%)

CR, complete response; HSCT, hematopoietic stem cell transplantation; PD, progressive disease; PD-1, programmed-death 1; PFS, progression-free survival; OS, overall survival

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GM and RH performed the research, analyzed the data and wrote the manuscript. All remaining authors reviewed and approved the final manuscript.

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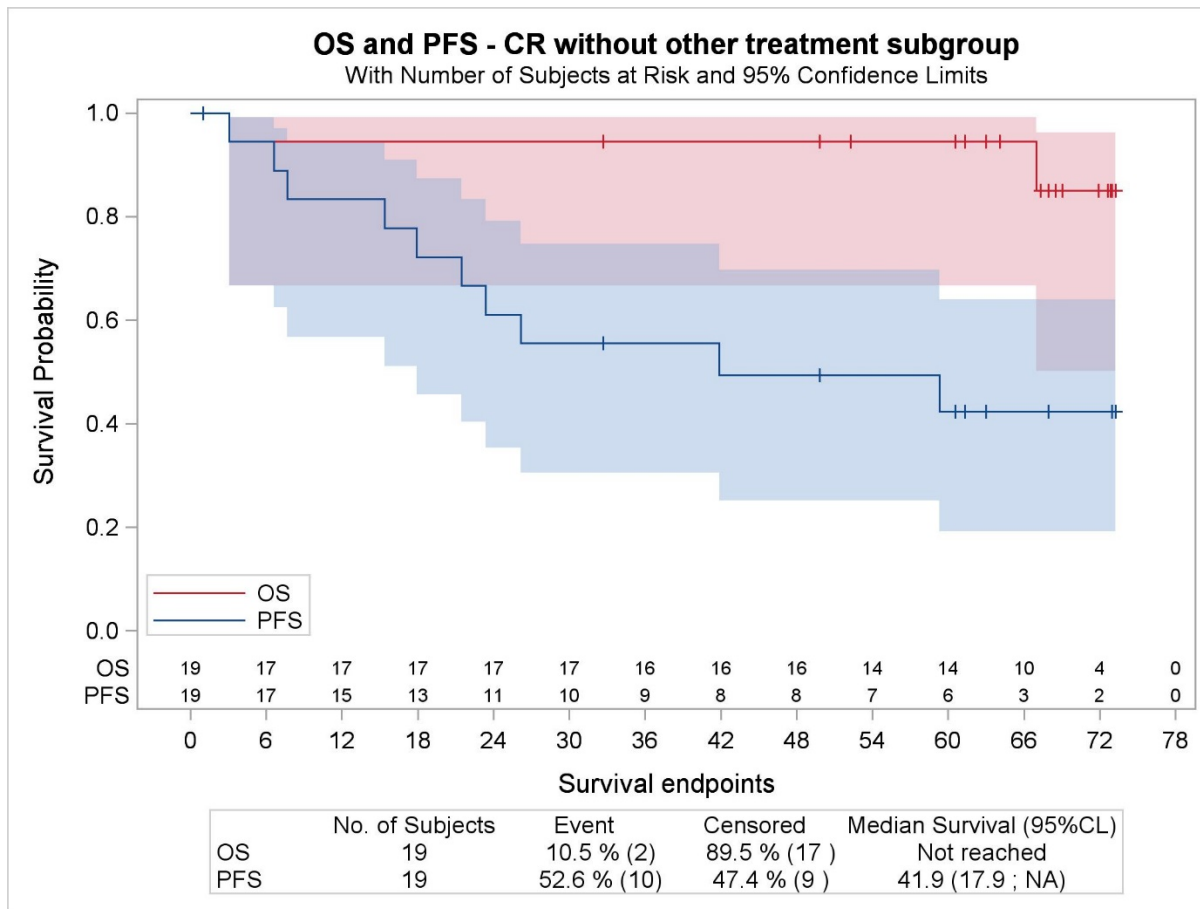


**Figure legend:**

**Figure 1:** PFS (blue) and OS (red) of patients in CR with nivolumab monotherapy without concomitant/consolidative treatment (radiotherapy permitted)

**Supplementary figure 1:** PFS (A and C) and OS (B and D) of the entire cohort (A and B) and according to best response upon nivolumab monotherapy (C and D). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival.

figure 1 – PFS and OS from nivolumab initiation



# Supplementary figure 1

