Can nivolumab alone cure patients with relapse or refractory Hodgkin lymphoma? A 5-year analysis of the French early access program (EPA)

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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 allogenic 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 ≥ 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}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

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

G.M. and P.B. have received consulting fees and/or honoraria from Bristol-Myers Squibb. E.N-V. received consulting fees from Sanofi. A.S. has received consulting fees from Takeda and Celgene. RH received honoraria from Bristol-Myers Squibb, MSD, Gilead, Kite, Roche, Novartis, Janssen, and Celgene. The remaining authors declare no competing financial interests.

References:

Armand, P., Engert, A., Younes, A., Fanale, M., Santoro, A., Zinzani, P.L., Timmerman, J.M., Collins, G.P., Ramchandren, R., Cohen, J.B., De Boer, J.P., Kuruvilla, J., Savage, K.J., Trneny, M., Shipp, M.A., Kato, K., Sumbul, A., Farsaci, B. & Ansell, S.M. (2018) Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, **36,** 1428–1439 Available at: http://ascopubs.org/doi/10.1200/JCO.2017.76.0793.

Beköz, H., Karadurmuş, N., Paydaş, S., Türker, A., Toptaş, T., Fıratlı Tuğlular, T., Sönmez, M., Gülbaş, Z., Tekgündüz, E., Kaya, A.H., Özbalak, M., Taştemir, N., Kaynar, L., Yıldırım, R., Karadoğan, İ., Arat, M., Pepedil Tanrıkulu, F., Özkocaman, V., Abalı, H., Turgut, M., et al (2017) Nivolumab for relapsed or refractory Hodgkin lymphoma: real-life experience. *Annals of Oncology*, **28,** 2496–2502 Available at: http://academic.oup.com/annonc/article/doi/10.1093/annonc/mdx341/3903080/Nivolumab-for-relapsed-or-refractory-Hodgkin.

Bekoz, H., Ozbalak, M., Karadurmus, N., Paydas, S., Turker, A., Toptas, T., Tuglular, T.F., Altuntas, F., Cakar, M.K., Sonmez, M., Gulbas, Z., Demir, N., Kaynar, L., Yildirim, R., Karadogan, I., Arat, M., Kapucu, I., Aslan, N.A., Ozkocaman, V., Turgut, M., et al (2020) Nivolumab for relapsed or refractory Hodgkin lymphoma: real-life experience. *Annals of hematology*, **99,** 2565–2576 Available at: http://www.ncbi.nlm.nih.gov/pubmed/32507911.

Chen, R., Zinzani, P.L., Fanale, M.A., Armand, P., Johnson, N.A., Brice, P., Radford, J., Ribrag, V., Molin, D., Vassilakopoulos, T.P., Tomita, A., von Tresckow, B., Shipp, M.A., Zhang, Y., Ricart, A.D., Balakumaran, A., Moskowitz, C.H. & KEYNOTE-087 (2017) Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, **35,** 2125–2132 Available at: http://ascopubs.org/doi/10.1200/JCO.2016.72.1316 [Accessed May 19, 2017].

Chen, R., Zinzani, P.L., Lee, H.J., Armand, P., Johnson, N.A., Brice, P., Radford, J., Ribrag, V., Molin, D., Vassilakopoulos, T.P., Tomita, A., von Tresckow, B., Shipp, M.A., Lin, J., Kim, E., Nahar, A., Balakumaran, A. & Moskowitz, C.H. (2019) Pembrolizumab in relapsed or refractory Hodgkin lymphoma: Two-year follow-up of KEYNOTE-087. *Blood,* blood.2019000324 Available at: http://www.bloodjournal.org/lookup/doi/10.1182/blood.2019000324.

Manson, G., Brice, P., Herbaux, C., Silva, M.G., Bouabdallah, K., Deau, B., Bouteloup, J., Schiano, J.M., Nicolas-Virelizier, E., Maerevoet, M., Ghesquieres, H., Stamatoullas, A., Antier, C., Carlo-Stella, C., de Charette, M., Poizeau, F., Dercle, L. & Houot, R. (2020) Risk of relapse after anti-PD1 discontinuation in patients with Hodgkin lymphoma. *European Journal of Nuclear Medicine and Molecular Imaging*.

Manson, G., Herbaux, C., Brice, P., Bouabdallah, K., Stamatoullas, A., Schiano, J.-M., Ghesquieres, H., Dercle, L. & Houot, R. (2018) Prolonged remissions after anti-PD-1 discontinuation in patients with Hodgkin lymphoma. *Blood*, **131,** 2856–2859 Available at: http://www.bloodjournal.org/lookup/doi/10.1182/blood-2018-03-841262.

Manson, G., Mear, J., Herbaux, C., Schiano, J.-M., Casasnovas, O., Stamatoullas, A., Deau, B., Schmitt, A., Garnier, G., Regny, C., Bouabdallah, K., Moles-Moreau, M.-P., Ghesquieres, H., Tempescul, A., Dulery, R., Nicolas-Virelizier, E., Delmer, A., Borel, C., Chauchet, A., Damotte, D., et al (2019) Long-term efficacy of anti-PD1 therapy in Hodgkin lymphoma with and without allogenic stem cell transplantation. *European Journal of Cancer*, **115,** 47–56 Available at: https://linkinghub.elsevier.com/retrieve/pii/S0959804919302394.

Merryman, R.W., Castagna, L., Giordano, L., Ho, V.T., Corradini, P., Guidetti, A., Casadei, B., Bond, D.A., Jaglowski, S., Spinner, M.A., Arai, S., Lowsky, R., Shah, G.L., Perales, M.-A., De Colella,

J.M.S., Blaise, D., Herrera, A.F., Shouse, G., Spilleboudt, C., Ansell, S.M., et al (2021) Allogeneic transplantation after PD-1 blockade for classic Hodgkin lymphoma. *Leukemia*, **35,** 2672–2683 Available at: http://dx.doi.org/10.1038/s41375-021-01193-6.

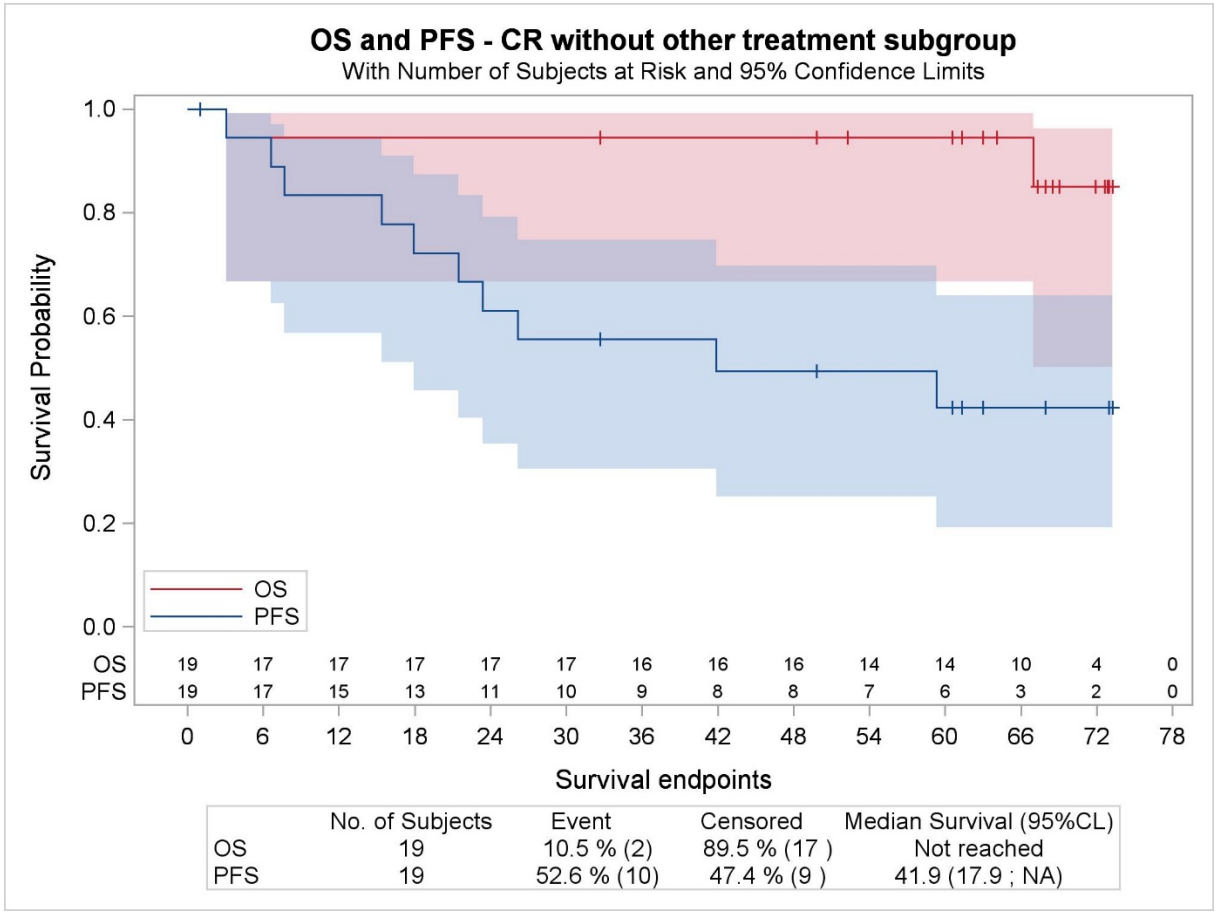
Merryman, R.W., Kim, H.T., Zinzani, P.L., Carlo-Stella, C., Ansell, S.M., Perales, M.-A., Avigdor, A., Halwani, A.S., Houot, R., Marchand, T., Dhedin, N., Lescaut, W., Thiebaut-Bertrand, A., François, S., Stamatoullas-Bastard, A., Rohrlich, P.-S., Labussière Wallet, H., Castagna, L., Santoro, A., Bachanova, V., et al (2017) Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. *Blood*, **129,** 1380–1388 Available at: http://www.ncbi.nlm.nih.gov/pubmed/28073785 [Accessed March 4, 2017].

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