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Letter to the editor

Anti-PD1 Abs demonstrated remarkable efficacy in relapsed/refractory (R/R) Hodgkin lymphoma (HL) patients. In the two largest prospective studies evaluating anti-PD1 Abs in R/R HL, CHECKMATE-205 (nivolumab)[1] and KEYNOTE-087 (pembrolizumab)[2], the overall (ORR) and complete response (CR) rates were around 70% and 20%, respectively. These results led to the approval of nivolumab and pembrolizumab in R/R HL by the FDA and the EMA. Importantly, a significant proportion of HL patients in complete response (CR) seem to experience durable remissions under anti-PD1 treatment[1]. However, it is unclear whether these patients may be cured and how long they need to continue treatment with anti-PD1 Ab. This question is particularly important in HL patients because i) the remission rates are high questioning the need for continuing therapy, ii) most of these patients are young and pursuing anti-PD1 therapy "indefinitely" (or at least for a prolonged period) may expose them to chronic/long lasting toxicities and preclude procreation, and finally iii) such prolonged treatments will induce a high financial cost.

Recently, Robert *et al*[3] reported the outcome of 67 patients with metastatic melanoma who discontinued pembrolizumab after reaching a CR. Interestingly, 89.9% of the patients maintained their CR after 2 years of anti-PD1 discontinuation. Here, we report the outcome of R/R HL who discontinued nivolumab treatment after reaching a CR and were followed without subsequent therapy.

We retrospectively analyzed 78 patients with R/R HL who were treated with nivolumab in the French early access program (EAP) between March and August 2015. Patients who did not respond to nivolumab and/or those who received subsequent therapy immediately after nivolumab discontinuation (e.g. allogenic HSCT) were excluded. Overall, nivolumab was discontinued in 11 patients, either for prolonged remission (N=7) or toxicity (N=4). Decisions were made at the discretion of the physician. All patients were in CR at the time of nivolumab discontinuation. In the entire cohort, 7 out of 28 patients in CR discontinued nivolumab because of prolonged remission after a median duration of treatment of 13.8 [4.8-24.1] months. Four patients discontinued nivolumab because of toxicity, including 3 patients with prior allogenic-HSCT who experienced acute cerebellar syndrome and fatal gastrointestinal (GI) graft-versus-host disease (GVHD), liver GVHD and cutaneous GVHD. Other limiting toxicity consisted in laryngeal oppression. Exposure to nivolumab prior to discontinuation was shorter in patients who discontinued because of toxicity compared to patients who discontinued for remission (0.23 vs 13.8 months). Characteristics of the patients are summarized in Table 1. As expected, most of the patients were young (median age=33 years), with advanced disease (64% of Ann Arbor stage IV) and had been heavily pre-treated (55% of the patients had previously received ≥ 7 lines of systemic therapy). Five patients (46%) had undergone prior allogenic-HSCT. The median duration of nivolumab treatment was 5.7 [0.5-24.2] months and the median number of cycles was 10 [1-51].

Outcome for entire cohort is summarized in Table 1 and Figure 1. The median follow-up was 28.6 [3.2 – 34.2] months from nivolumab initiation and 21.2 [3.2-29.8] months from nivolumab discontinuation. At the time of last follow-up, all patients remained alive, except one (patient 11). This patient had undergone prior allogenic-HSCT 19 months before anti-PD1 initiation. He received only one injection of nivolumab because he developed an acute

GI and liver GVHD which occurred within a few days after anti-PD1 infusion. The 18F-FDG PET/CT performed one month later showed a CR but unfortunately the patient died of multiple organ failure two months later. Among the 10 remaining patients, 8 patients are still in CR (80%) after a median follow-up of 22.4 [4.2 – 29.8] months from nivolumab discontinuation (patients 2 to 8 and 10). Four of them are more than 21 months off-therapy and remain disease-free. Two patients relapsed after nivolumab discontinuation (patient 1 and 9). Patient 1, who had previously undergone allogenic-HSCT, received 5 cycles of nivolumab, reached a CR, and then discontinued anti-PD1 therapy because of the risk of GVHD. He remained in remission for 21 months without any additional treatment. The patient then relapsed and nivolumab was resumed leading to a PR after 1 month. The patient is still on nivolumab therapy at 6 months. Patient 9 had discontinued nivolumab prematurely (after 2 cycles) because of toxicity (grade 3 laryngeal oppression). Nevertheless, he was considered in CR at the time of first evaluation. The patient relapsed 7 months later and then was treated with vinblastine. Because he was refractory to vinblastine, the patient was retreated with nivolumab which lead to a PR assessed by CT-scan without significant toxicity. Anti-PD1 Ab was discontinued after one year and the patient is currently one month off-therapy.

To the best of our knowledge, our study is the first to report the outcome of HL patients after anti-PD1 discontinuation. Although the median follow-up is still limited (21.2 months), almost all patients (91%) remain alive and 80% of them are still in CR after nivolumab discontinuation, some of them beyond 2 years. Interestingly, some of these prolonged remissions occurred in patients who had received only very few cycles of nivolumab, notably in patients with prior allogenic-HSCT. Longer follow-up and larger studies are warranted to confirm these results. Whether some of these patients may be cured remains to be determined. Clinical trials are also needed to prospectively evaluate the optimal duration of anti-PD1 therapy in HL patients and identify patients to whom discontinuation can be safely proposed.

Contribution: G.M. and R.H. designed the research, analyzed data and wrote the paper; C.H., P.B., K.B., A.S., J.-M.S., H.G. and L.D. provided the data. All authors reviewed and approved the final draft.

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Table 1. Patients' characteristics and outcome after nivolumab discontinuation

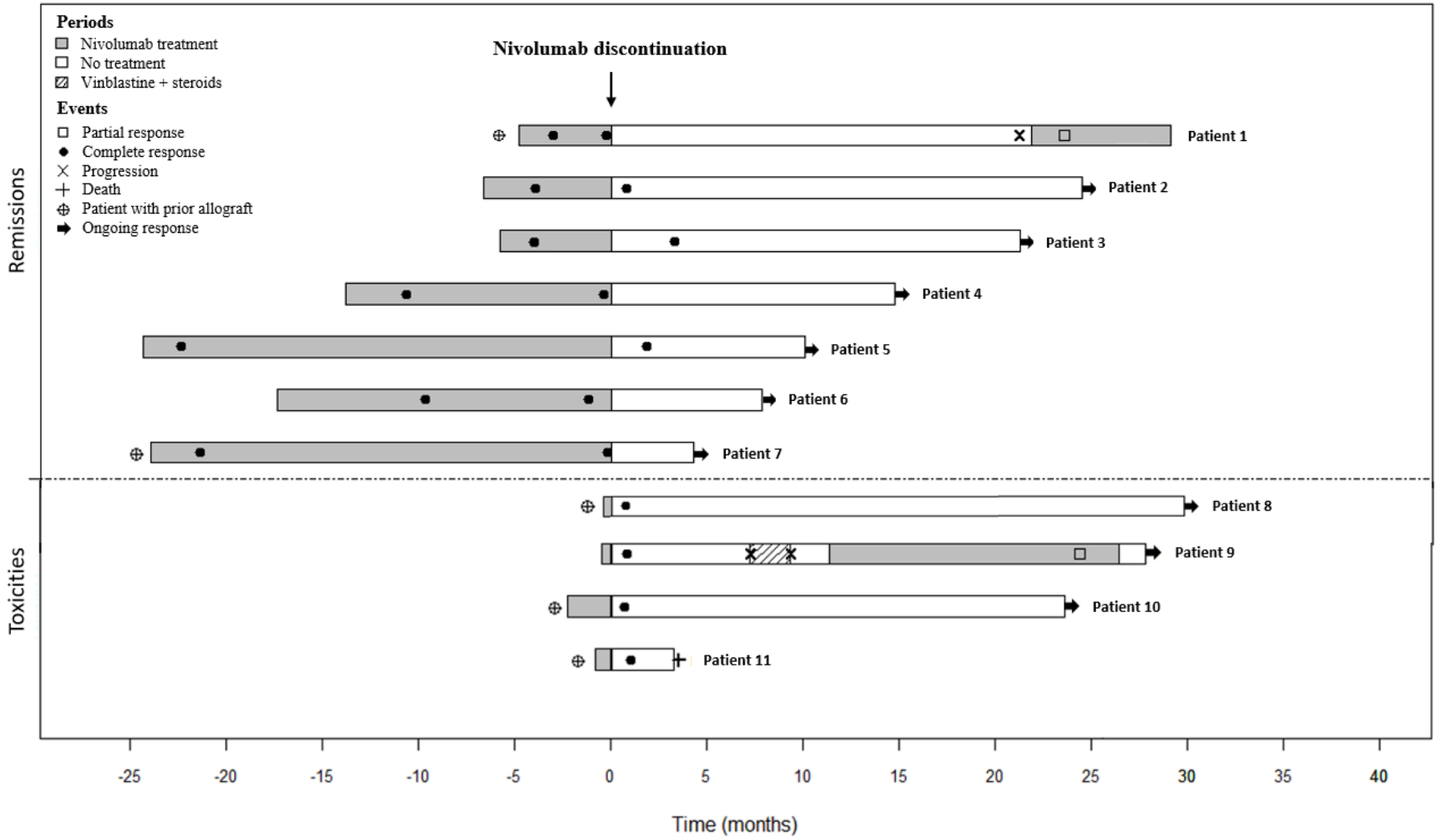
Characteristics at initiation of nivolumab	Remissions (n=7)	Toxicities (n=4)	All (n=11)
Age, years, median [range]	33 [19-66]	35.5 [26-53]	33 [19-66]
Sex, No (%)			
• Male	4 (43%)	3 (75%)	7 (64%)
• Female	3 (57%)	1 (25%)	4 (36%)
Stage disease, No (%)			
• I	1 (14%)	0	1 (9%)
• II	2 (29%)	0	2 (18%)
• IV	4 (57%)	3 (75%)	7 (64%)
• Unknown	0	1 (25%)	1 (9%)
B symptoms, No (%)			
• No	6 (100%)	4 (100%)	10 (100%)
• Missing	1	0	1
Prior lines of systemic therapy, No (%)			
• 3	1 (14%)	0	1 (9%)
• 4	2 (29%)	0	2 (18%)
• 5	0	1 (25%)	1 (9%)
• 6	1 (14%)	0	1 (9%)
• ≥7	3 (43%)	3 (75%)	6 (55%)
Prior radiation therapy, No (%)	4 (57%)	2 (50%)	6 (55%)
Prior treatment with Brentuximab Vedotin, No (%)	7 (100%)	4 (100%)	11 (100%)
Prior autologous SCT, No (%)	4 (57%)	3 (75%)	7 (64%)
Prior allogenic SCT, No (%)	2 (29%)	3 (75%)	5 (46%)
Anti-PD1 treatment, discontinuation and outcome			
Number of nivolumab injections, median [range]	28 [5 – 51]	1.5 [1 – 5]	10 [1 – 51]
Duration of anti-PD1 therapy, months, median [range]	13.8 [4.8 – 24.1]	0.2 [0 – 1.8]	5.7 [0 – 24.1]
Concomitant radiotherapy, No (%)	2 (29%)	0	2 (18%)
Reason for nivolumab discontinuation			
• Prolonged remission	7 (100%)	-	7 (64%)
• Toxicity	-	4 (100%)	4 (36%)
○ Acute GVHD	-	2	2
○ Cerebellar syndrome	-	1	1
○ Laryngeal oppression	-	1	1
Disease status at anti-PD1 discontinuation, No (%)			
• CR (Cheson 2007)	7 (100%)	4 (100%)	11 (100%)
Duration between first CR upon nivolumab and anti-PD1 discontinuation, months, median [range]	9.7 [3 – 22.4]	-	9.7 [3 – 22.4]
Follow-up from anti-PD1 discontinuation, median, months [range]	14.7 [4.2 – 29]	25.6 [3.2 – 29.3]	21.2 [3.2 – 29.3]
Patients alive at last follow-up, No (%)	7 (100%)	3 (75%)	10 (91%)
Patients in CR at last follow-up among patients alive, No (%)	6 (86%)	2 (67%)	8 (80%)
Retreatment with anti-PD1 monotherapy among relapsed patients	1/1	1/1	2/2
Response to retreatment with anti-PD1 in relapsed patients			
• CR	0	0	0

• PR	1	1*	2

GVHD, Graft-Versus-Host Disease; SCT, Stem Cells Transplantation

**Cheson 1999*

Figure 1. Outcome of patients after nivolumab discontinuation



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