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Efficacy of anti-PD1 re-treatment in patients with Hodgkin lymphoma who relapsed after anti-PD1 discontinuation

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Patients with relapsed/refractory Hodgkin lymphoma (R/R HL) experience high response rates upon anti-PD1 therapy. In these patients, there is limited data about the optimal duration of treatment and the risk of relapse after anti-PD1 discontinuation. We have previously reported the outcome of 11 patients with R/R HL who discontinued anti-PD1 therapy after achieving a complete response (CR) upon nivolumab¹. These patients experienced favorable outcome as only 2 of them had relapsed after a median follow-up of 21.2 months from discontinuation. Despite the low relapse rate observed in that study, physicians may be worried about the possibility to further rescue these heavily pre-treated patients in case of relapse after anti-PD1 discontinuation. Notably, it is still unknown whether these patients will remain sensitive to a 2nd course of anti-PD1.

Here, we investigated the efficacy of anti-PD1 re-treatment in patients who have been initially sensitive to anti-PD1 therapy but who relapsed after anti-PD1 discontinuation.

We retrospectively analyzed patients with R/R HL who experienced a partial (PR) or complete (CR) response upon anti-PD1 monotherapy and discontinued the treatment either because of unacceptable toxicity or prolonged remission, based on physician's decision. Patients who discontinued anti-PD1 therapy because of relapse/progression or underwent consolidation with allogenic stem cell transplantation (alloSCT) were not included. Patients meeting the eligibility criteria were identified through the French lymphoma network (LYSA).

We identified 7 patients who met the inclusion criteria. Their characteristics are summarized in Table 1. At anti-PD1 initiation, most patients presented with advanced disease (5 of them had Ann Arbor stage III/IV) and had been heavily pre-treated (median number of prior systemic lines = 6, 7 had received prior brentuximab vedotin, 5 prior autologous stem cell transplantation (SCT) and 2 prior allogenic SCT). Overall, anti-PD1 was discontinued after a

median duration of 11.4 (range, 0 – 26.7) months and a median of 23 (range, 1 – 51) infusions. Anti-PD1 was discontinued because of prolonged remission (n=5) or toxicity (n=2, patient 5 had experienced grade 4 acute liver graft-host-disease [aGVHD] and patient 7 grade 3 laryngeal tightness). Disease status at anti-PD1 discontinuation was CR for 6 patients and PR for 1 patient. The median time to relapse after anti-PD1 discontinuation was 12.1 (range, 5.3 – 26.7) months. All patients were re-treated with the same anti-PD1 antibody as initially (6 with nivolumab and 1 with pembrolizumab).

All patients responded to anti-PD1 re-treatment (Figure 1). Best response was CR for 4 patients and PR for 3 patients. At the time of analysis (median follow-up = 19.2 months from anti-PD1 re-treatment), 4 out of 7 patients have ongoing responses upon anti-PD1 monotherapy, 3 of them beyond 12 months. Interestingly, 3 patients discontinued anti-PD1 treatment after achieving a second objective response upon anti-PD1 re-treatment (patients 3, 5 and 7). Patient 3 discontinued anti-PD1 treatment a second time because of hyper-eosinophilia and then relapsed 2 months later. Patient 7 tolerated well the second course of nivolumab (notably, there was no recurrence of laryngeal tightness), achieved a PR and discontinued the treatment after 12 months. Unfortunately, he relapsed 5 months later. The patient then received a third course of nivolumab and achieved another PR which is still ongoing at 18 months.

Patient 5 had undergone alloSCT before anti-PD1 therapy. He discontinued nivolumab after a single infusion because of grade 4 liver acute GVHD. Nevertheless, he achieved a CR which lasted for 9 months. At relapse, he received a salvage therapy with GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) followed by ibrutinib without efficacy. At progression, he received a reduced dose of nivolumab (total dose of 30 mg) which induced a GVHD flare. The patient further experienced 2 disease progressions which were treated with

2 additional infusions of low dose nivolumab (10 mg) which resulted again in GVHD flares. These sequential treatments induced transient lymphoma regression, with PR as best response. The GVHD flares observed in this patient are not unexpected. Indeed, prior studies have reported that anti-PD1 therapy may induce GVHD reactivation in patients who have previously undergone alloSCT^{2,3}. Anti-PD1 re-treatment did not induce other significant toxicities in the other patients.

There is only limited data regarding the efficacy of re-challenge with anti-PD1 antibodies in cancer patients. Only a few cases have been reported in patients with solid tumors, namely in non-small cell lung cancer⁴ and melanoma⁵. However, most of these patients had failed initial anti-PD1 therapy and received chemotherapy before anti-PD1 re-treatment. This is contrast with our study in which all patients were sensitive to initial anti-PD1 therapy and in response (CR or PR) at the time of discontinuation.

At the ISHL11 meeting, Ansell *et al.* reported in abstract form the efficacy of anti-PD1 re-treatment in 5 patients who achieved remission upon nivolumab but relapsed after treatment discontinuation⁴. All patients responded to nivolumab re-treatment (1 CR and 4 PR).⁶ Recently, Chen *et al.* reported an update of the KEYNOTE-087 study after 2 years of follow-up⁷. This study evaluated pembrolizumab in R/R HL. In a subset analysis, Chen *et al.* reported the outcome of 10 patients who received a second course of pembrolizumab after anti-PD1 discontinuation. Eight patients were evaluable and 6 of them (75%) experienced an objective response upon re-treatment with pembrolizumab (4 CR and 2 PR). The study did not report on the efficacy of the first course of anti-PD1, the reasons for anti-PD1 discontinuation nor the tumor status at anti-PD1 discontinuation in these patients. Nevertheless, the study shows that most patients responded to anti-PD1 re-treatment.

Our study, along with the one recently published by Ansell *et al.*⁶ and Chen *et al.*⁷, are the first to report on the efficacy of anti-PD1 re-treatment in anti-PD1 sensitive, R/R HL patients who relapsed/progressed after anti-PD1 discontinuation. These two studies show high response rates (75-100%) after anti-PD1 re-treatment suggesting that these patients usually remain “anti-PD1 sensitive” at relapse. These observations suggest that anti-PD1 is an effective salvage therapy for HL patients who relapse after anti-PD1 discontinuation. Larger studies are warranted to confirm these results.

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Table 1. Patients' characteristics at anti-PD1 initiation

Patients characteristics	N = 7
Age, median, years (range)	47 (34 – 71)
Sex, male, No (%)	2 (28.6)
cHL subtype, No (%)	
- Nodular sclerosis HL	6 (85.7)
- Unclassifiable	1 (14.3)
Performance status (ECOG), No (%)	
- 0 – 1	5 (71.4)
- ≥ 2	2 (28.6)
Stage disease, No (%)	
- I/II	2 (28.6)
- III/IV	5 (71.4)
Prior lines of systemic therapy, median (range)	6 (4 – 11)
Prior radiation therapy, No (%)	4 (57.1)
Prior treatment with Brentuximab Vedotin, No (%)	7 (100)
Prior autologous HSCT, No (%)	5 (71.4)
Prior allogenic HSCT, No (%)	2 (28.6)
Anti-PD1, No (%)	
- Nivolumab	6 (85.7)
- Pembrolizumab	1 (14.3)
Number of anti-PD1 infusions during 1st course, median (range)	23 (1 – 51)
Duration of 1st course of anti-PD1 therapy (months), median (range)	11.4 (0 – 26.7)
Best Overall Response to 1st course of anti-PD1, No (%)	
- CR	6 (85.7)
- PR	1 (14.3)
Reason for anti-PD1 discontinuation, No (%)	
- Prolonged response	5 (71.4)
- Toxicity*	2 (28.6)
Disease status at anti-PD1 discontinuation, No (%)	
- CR	6 (85.7)
- PR	1 (14.3)
Time between discontinuation and relapse (months), median (range)	12.1 (5.3 – 26.7)
Follow-up from anti-PD1 re-treatment (months), median (range)	19.2 (4.8 – 39.9)
Best response to 2nd course of anti-PD1	
- CR	4 (57.1)
- PR	3 (42.9)

* One grade IV acute liver graft-versus-host-disease, and one grade III laryngeal oppression

Legend:

Figure 1. Efficacy of anti-PD1 re-treatment

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