INTRODUCTION

Despite most patients affected by classical Hodgkin lymphoma (cHL) can be cured with the first line treatment, there is a subset of patients with relapsed/refractory (R/R) disease that still represents an unmet clinical need. Non-cross resistant salvage chemotherapy followed by autologous stem cell transplantation (ASCT) can save roughly the 50% of R/R...
patients. According to historical data, patients who failed ASCT have an extremely poor prognosis with a median overall survival (OS) of 2 years. In this setting, treatment with anti-CD30 antibody drug-conjugated brentuximab vedotin (BV) has resulted in high objective response rate (ORR), with 35% of patients obtaining a complete response (CR). Despite a small subset of CR patients maintains a durable disease control and seems to be cured with BV as single agent, most patients require additional treatment within 1 year. It is already established that HL is able to escape the immune system likely as a result of the amplification of chromosome band 9p24.1, leading to the upregulation of programmed death ligands and JAK/STAT pathway. The use of anti-Programmed Death-1 (PD1) monoclonal antibodies (check-point inhibitors [CPI], namely nivolumab and pembrolizumab) for HL patients who are R/R to ASCT and/or to BV has shown a good balance between efficacy and toxicity, proving to be a good therapeutic option in a subset of such highly pretreated patients. Nevertheless, almost the 70% of patients treated with CPI reached an objective response, but only one third of them obtained a CR and a large part of the responder patients relapses, with a median progression free survival (PFS) of maximum 12 months. To date, what is the optimal treatment after anti-PD1 failure is still an open question. Retrospective analysis in various tumor types and two multi-centric series in HL showed a potential improvement in response rate to chemotherapy (CHT) after exposure to CPI, suggesting that this kind of treatment could re-sensitize the tumor cells to CHT. Here, we report our monocentric experience in heavily pre-treated and chemo-refractory HL patients treated with salvage chemotherapy after anti-PD1 blockade failure, supporting the hypothesis of a new chemo sensitization after CPI.

2 METHODS

We retrospectively investigated the effectiveness of salvage therapies for unsatisfactory response to anti-PD1 therapy in 25 patients with R/R cHL treated with pembrolizumab or nivolumab from March 2015 to December 2018. Regarding salvage approaches, the choice between multi-agent or single-agent chemotherapy, immunotherapy or transplantation was made mainly on the basis of the therapies performed pre-CPI, avoiding treatments already administered when possible. The choice was based on age, performance status and tolerance of previous treatments. In particular, regarding transplantation, the choice was also based on whether the patient had already received an ASCT or not and whether a related donor was available. The patient list was extracted from the electronic database of our Institute. The study was approved by our institutional board and by our Ethical Committee and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Patients were consecutively enrolled to avoid selection bias, and all patients provided written informed consent to collect retrospectively their data. We obtained a special permission (for scientific purpose) from our Ethical Committee to collect even data of patients who were deceased or lost to follow-up. To be enrolled patients must have received at least two cycles of single agent anti-PD1 and must have unsatisfactory response to CPI (progression disease [PD], partial response [PR] or a CR with a duration less than 3 months). The diagnosis of cHL was established from lymph node biopsies, in accordance with the 2008 World Health Organization classification. PDL1 testing was not performed. Responses were assessed with positron emission tomography (PET) scan and computed tomography (CT) scan every 3 months for the first year and then every 6 months for the second year of treatment. ORR (defined as the sum of complete and partial response rates at the end of treatment) was chosen as primary endpoint, whereas PFS and OS were analyzed as secondary endpoints. OS was defined as the time from initiation of therapy (CHT) to death from any cause and was censored at the date of last available follow up. PFS was measured from initiation of therapy (for both anti-PD1 and subsequent CHT) to progression, relapse, or death from any cause. Responses were classified according to the Lugano criteria. The toxicities were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE version 4.0). No formal sample size estimation and power calculation were made for this observational retrospective study as we enrolled all patients treated at our Institute. Demographics and patients’ characteristics were summarized by descriptive statistics. Survival functions were estimated by using the Kaplan-Meier method and were compared using log-rank test. 95% confidence intervals (CI) were provided. Statistical analyses were performed with Stata 11 (StataCorp LP) and P values for statistical significance were set at .05.

3 RESULTS

3.1 Patients

Thirteen females and 12 males with a median age at diagnosis of 32.4 years (range 17.8-67.1) were enrolled. According to Ann-Arbor classification, 56% of patients (n = 14) had stage II and 44% (n = 11) had stage III/IV; B symptoms and bulky disease were counted in 14 and 7 patients, respectively. The study population was highly pretreated with a median of four prior therapies (1-10), including ASCT (44%) and BV (92%). None of the 25 patients received allogeneic stem cell transplantation (alloSCT) before PD1 blockade. Twenty patients (80%) were refractory to the first line of treatment.
(for all patients ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine). There was a high heterogeneity in the treatment given immediately before CPI, with the most common being BV as single agent (eight patients, 32%) or in combination with bendamustine (three patients, 12%), and ASCT (four patients, 16%). Twenty-three patients (92%) were refractory to the last therapy before CPI (Table 1). At the start of anti-PD1 therapy, the median age was 33.6 years (range 19.6-72.0), 16 patients had Ann-Arbor III/IV stage and 6 had B symptoms. Patients had anti-PD1 therapy in the context of clinical trials (n = 21) or in the named patient program (n = 4): 15 out of 25 received pembrolizumab (3 patients at the dose of 10 mg/kg and 12 at the flat dose of 200 mg every 3 weeks) and the remaining underwent nivolumab (3 mg/kg every 2 weeks). A median of 14 cycles (range 3-52) of anti-PD1 therapy were infused (Table 1).

Patient evaluation after start of CHT was done after a median of 3 months with PET and CT scan. The best response obtained with CPI was CR in 3 patients, PR in 16 patients, PD in 5 patients and stable disease (SD) in 1 patient. At the last PET and CT scan performed under treatment, 68% of patients did not respond to anti-PD1 therapy (15 PD and 2 SD), whereas six had a PR and only two patients achieved a CR, with an ORR of 32%. Twenty-three out of 25 patients discontinued the anti-PD1 treatment due to unsatisfactory response (21 patients, 15 in PD, 2 in SD and 4 in PR) or serious AEs (SAEs) (2 patients). In details, SAEs were a bronchiolitis obliterans with organizing pneumonia and an eosinophilic pneumonia, both resolved with steroids combined with CPI discontinuation.

### 3.2 | Salvage therapy after PD-1 blockade

After a median time of 1.5 months from the response assessment to anti-PD1, 15 patients received a single agent CHT, whereas 10 had a multi-agent treatment (Table 2). Overall, after a median of three cycles (range 1-10), eight patients obtained a CR and seven a PR, with an ORR of 60%. Among the 15 patients who received a single agent CHT the ORR was 33% (1 CR and 4 PR), whereas, all the 10 patients treated with a multi-agent regimen obtained a response with 7 CR and 3 PR (ORR 100%). In our series only three patients were re-exposed to the same CHT agents that they have received before the CPI treatment, all of them were refractory at the first exposure and became responsive after anti-PD1 therapy.

Sixteen out of 25 patients (64%) discontinued the salvage treatment: seven due to unsatisfactory response at the first evaluation (five PD and two SD), eight due to a consolidation with stem cell transplantation and only one patient due to a grade 3-4 toxicity (febrile neutropenia with pneumonia).

Four patients (one in CR and three in PR) received ASCT and four had alloSCT (three patients were in CR and one in

### Table 1 Patient characteristics

| Parameter                                      | N = 25 |
|------------------------------------------------|--------|
| Sex, n (%)                                     |        |
| Male                                           | 12 (48) |
| Female                                         | 13 (52) |
| Median age at diagnosis, years (range)         |        |
| 32.4 (17.8-67.1)                                |        |
| Histologic subtypes, n (%)                     |        |
| Nodular sclerosis                              | 19 (76) |
| Mixed cellularity                              | 2 (8)  |
| Lymphocyte rich                                | 1 (4)  |
| Unknown                                        | 3 (12) |
| Ann Arbor stage at diagnosis, n (%)            |        |
| I                                              | 0 (0)  |
| II                                             | 14 (56) |
| III                                            | 2 (8)  |
| IV                                             | 9 (36) |
| B symptoms, n (%)                              |        |
| Yes                                            | 14 (56) |
| No                                             | 11 (44) |
| Bulky disease, n (%)                           |        |
| Yes                                            | 7 (28)  |
| No                                             | 18 (72) |
| Prior therapies to PD-1 inhibitor, median (range)|        |
| ASCT, n (%)                                    | 11 (44) |
| BV, n (%)                                      | 23 (92) |
| Radiotherapy, n (%)                            | 9 (36)  |
| Allogeneic SCT, n (%)                          | 0 (0)   |
| Final response to the front-line therapy (ABVD), n (%) |        |
| Relapse                                        | 5 (20)  |
| Refractory                                     | 20 (80) |
| Final response to the last therapy prior to PD-1 inhibitor, n (%) |        |
| Relapse                                        | 2 (8)   |
| Refractory                                     | 23 (92) |
| PD-1 inhibitor received, n (%)                 |        |
| Pembrolizumab                                  | 15 (60) |
| Nivolumab                                      | 10 (40) |
| Number of cycles of PD1-inhibitor, median (range)|        |
| 14 (3-52)                                      |        |
| Best response to PD1-inhibitor, n (%)          |        |
| CR                                             | 3 (12)  |
| PR                                             | 16 (64) |
| SD                                             | 5 (20)  |
| PD                                             | 1 (4)   |
| Reason for CHT after anti-PD-1, n (%)          |        |
| PD                                             | 16 (64) |
| Sub-optimal response (PR or SD)                | 7 (28)  |
| Relapse                                        | 2 (8)   |

**Abbreviations:** ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; CHT, chemotherapy; CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease.
| Pts | CHT before anti-PD1 | Response | Anti-PD1 | Response to anti-PD1 | First line CHT after anti-PD1 | N of cycles | Response | Re-exposure to the same CHT | SCT | Response to SCT | Status at last follow-up | Alive |
|-----|---------------------|----------|----------|----------------------|-------------------------------|-------------|----------|----------------------------|-----|----------------|------------------------|-------|
| 1   | BV                  | PD       | Pembro   | PD                   | BeGeV                         | 4           | CR       | Benda; IGeV                |     |                |                        | yes   |
| 2   | BV + Benda          | PD       | Pembro   | PD                   | BEACOPP                        | 3           | PR       | Bleomycin, Adrymicin       | ASCT| PR             | CR                     | No    |
| 3   | BV                  | PD       | Pembro   | PD                   | Benda                          | 3           | PD       | No                         |     |                | SD                     | Yes   |
| 4   | BV                  | PD       | Nivo     | PD                   | Benda                          | 6           | PD       | No                         |     |                | CR                     | Yes   |
| 5   | BV + Benda          | PD       | Nivo     | PD                   | EDO101                         | 3           | PD       | No                         |     |                | PD                     | No    |
| 6   | IGeV                | PD       | Nivo     | PR                   | PegDox                         | 3           | PD       | No                         |     |                | SD                     | No    |
| 7   | BV                  | PD       | Nivo     | PD                   | DHAP                           | 3           | PR       | No                         | alloSCT| CR             | CR                     | No    |
| 8   | DHAP                | PD       | Nivo     | PD                   | Daunorubicine                   | 2           | PR       | No                         |     |                | CR                     | Yes   |
| 9   | BEAM + ASCT         | PD       | Nivo     | CR                   | PegDox                         | 3           | PD       | No                         |     |                | PD                     | Yes   |
| 10  | Melphalan + ASCT    | PD       | Nivo     | CR                   | Benda                          | 6           | PR       | No                         |     |                | CR                     | Yes   |
| 11  | Lena + Benda        | SD       | Pembro   | PD                   | PegDox                         | 3           | SD       | No                         |     |                | CR                     | Yes   |
| 12  | BV + Benda          | PD       | Pembro   | PD                   | PegDox                         | 5           | PR       | No                         | ASCT| CR             | CR                     | Yes   |
| 13  | DHAP                | CR       | Pembro   | PD                   | EDO101                         | 10          | PR       | No                         |     |                | PD                     | Yes   |
| 14  | BV                  | PD       | Pembro   | PR                   | EDO101                         | 5           | SD       | No                         |     |                | unk                   | Yes   |
| 15  | Gemcitabine         | PD       | Pembro   | PR                   | EDO101                         | 6           | SD       | No                         |     |                | PD                     | Yes   |
| 16  | Benda               | CR       | Pembro   | PD                   | PegDox                         | 4           | CR       | No                         | alloSCT| CR             | CR                     | Yes   |
| 17  | ABVD                | PD       | Pembro   | PR                   | BeGeV                          | 2           | CR       | No                         | ASCT| CR             | CR                     | Yes   |
| 18  | Vinblastine         | PD       | Nivo     | PD                   | PegDox                         | 2           | PD       | No                         |     |                | PD                     | No    |
| 19  | DHAP                | PR       | Pembro   | PD                   | ICE                            | 2           | PR       | Ifosfamide                 | ASCT| PR             | PD                     | No    |
| 20  | BEAM + ASCT         | PD       | Nivo     | PD                   | IGeV                           | 3           | CR       | No                         | alloSCT| CR             | CR                     | Yes   |
| 21  | BV                  | PD       | Pembro   | PD                   | BEAM + ASCT                     | 1           | CR       | No                         |     |                | CR                     | Yes   |
| 22  | BV                  | PD       | Pembro   | PR                   | BEAM + ASCT                     | 1           | CR       | No                         |     |                | CR                     | Yes   |
| 23  | Radiotherapy        | PD       | Pembro   | SD                   | PegDox                         | 3           | SD       | No                         |     |                | unk                   | Yes   |
| 24  | BV                  | PD       | Pembro   | PR                   | BEAM + ASCT                     | 1           | CR       | No                         |     |                | CR                     | Yes   |
| 25  | FEAM + ASCT         | PD       | Nivo     | PD                   | BeGeV                          | 3           | CR       | No                         | alloSCT| CR             | CR                     | Yes   |

Abbreviations: ABVD, adrimycin, belomycin, vinblastine, dacarbazine; alloSCT, allogenic stem cell transplantation; ASCT, autologous stem cell transplantation; BEACOPP, bleomycin, etoposide, adrimycin, cyclophosphamide, vincristine, procarbazine, prednisone; BEAM, carmustine, etoposide, cytarabine, melphalan; benda, bendamustine; CHT, chemotherapy; CR, complete response; DHAP, dexamethasone, high dose cytarabine, cisplatin; EDO101, first-in-class fusion molecule of an alkylator, bendamustine and the histone-deaceetylase inhibitor vorinostat; FEAM, fotemustine, etoposide, cytarabine, melphalan; ICE, ifosfamide, carboptarin, etoposide; IGeV, ifosfamide, gemcitabine, vinorelbine; Lena, lenalidomide; Nivo, nivolumab; PD, progression disease; PegDox, pegylated liposomal doxorubicin hydrochloride; Pembro, pembrolizumab; PR, partial response; Pts, patients; SCT, stem cell transplantation; SD, stable disease.
PR) as consolidation strategy. Among patients who underwent alloSCT: one patient received haploidentical transplant while the others received matched unrelated donor (MUD) transplantation with a reduced intensity conditioning regimen. The patient, who had haploidentical transplant, experienced a cutaneous grade 1-2 acute graft vs. host disease (GVHD) treated and resolved with high-dose steroids. Among the patients who received a MUD transplant, only one had a GVHD: she experienced cutaneous and intestinal grade 3 and liver grade 2 acute GVHD, resolved with high-dose steroids and ruxolitinib. The transplant strategy allowed two patients to convert their PR into CR. Overall, 16 (64%) of the 25 patients who failed treatment with CPis achieved a CR, with a median of two lines of salvage CHT (range 1-4). Seventeen patients (68%) experienced hematological toxicities: nine patients had neutropenia grade 3-4, seven patients had thrombocytopenia (3 grade 1-2 and 4 grade 3-4, respectively), one patient had grade 1-2 anemia. Six patients (24%) had extra-hematological toxicities: two patients experienced grade 1-2 fatigue, two patients had grade 1-2 cutaneous rash, one patient had grade 1 diarrhea and one patient had a grade 3-4 febrile neutropenia with pneumonia which resulted in treatment discontinuation.

### 3.3 | Outcomes

Median PFS with salvage treatment was reached at 19.1 months (Figure 1). PFS estimated from start of the salvage therapy was 41.2% at 3.8 years (95% CI 38.1-44.3) and it was statistically higher in patients who underwent a multi-agent regimen (59.3% [95% CI 57.2-61.4] vs. 28.6% [95% CI 26.1-31.1], respectively; \( P = .0252 \), Figure 2). After a median follow-up of 32.4 months, 6 patients died (four due to a PD, one in CR due to secondary acute myeloid leukemia and the other also in CR due to pneumonia) and 13 patients are still alive and in CR. Eight out of these 13 patients are in continuous CR (CCR) after the first salvage treatment post PD1 blockade. The estimated OS from the start of the CHT was 56.5% at 3.8 years (median not reached, 95% CI 54.0-59.0).

### 4 | DISCUSSION

Immune CPis are transforming the standard of care across different tumor types leading to an improvement in the outcome and long-term survival of a large subset of hematological patients. In particular, the inhibitors of PD1/PD-L1 signaling has shown a good efficacy and a favorable toxicity profile in heavily pre-treated HL and non-Hodgkin lymphoma patients, with almost 70% of patients affected by Hodgkin disease reaching a response, including those who already underwent to ASCT and/or BV treatment. Despite these good results, a large part of the responder patients’ relapses, with a median PFS of maximum 12 months. Therefore, the attention is now focusing on how improving the response and on overcoming the resistance to CPis. Based on a rationale that DNA damaging agents are able to promote immunogenicity of cancer cells trough increasing neo-antigen repertoire, inducing immunogenic cell death and changing the cytokine milieu into the tumor microenvironment, with a consequence redistribution and increase expression of PDL-1 on tumor cells, good results are being achieved combining PD1 inhibitors with chemotherapy, both in solid tumors and in lymphomas setting. On the other side, patients who already failed anti-PD1 therapy, seems to benefit from a re-treatment with conventional CHT, leading to the idea that PD1 inhibitors can re-sensitize tumor cells to conventional treatment, previously failed. Rossi et al showed an overall response in 16 (67%) out of 30 R/R HL patients treated with conventional CHT after anti-PD1 treatment (CR: 46%), regardless of whether patients had been
re-exposed to an agent to which they were previously resistant. A trend to a better response was seen in those patients in which CHT was combined to anti-PD1 in comparison to those in which CHT was administered after stopping PD1 inhibitors, underlining again a potential synergy between these two approaches.\(^{13}\) In a retrospective analysis from seventeen centers across US and Canada, 77 R/R HL patients received different type of salvage treatment after CPi failure. The ORR was 52% (17 CR and 9 PR) with a median PFS of 10.7 months. The authors pointed out that a response to salvage treatment appears to correlate with response to CPi itself, although a PD following anti-PD1 therapy did not preclude a response to subsequent CHT.\(^{13}\) In our analysis, all the 25 R/R HL patients underwent conventional CHT only after quitting anti-PD1 treatment and 15 patients (60%) achieved a response (eight CR and seven PR) to the first salvage treatment. Among the responder patients, eight underwent SCT, consolidating their response. We observed a better improvement of ORR (100% vs 33%) and a statistically higher PFS at 3.4 years (59.3% vs. 28.6%, respectively; \(P = .0252\)) in patients treated with a multi-agent regimen compared to those treated with single agent. No differences in term of response to salvage treatment were seen between those who relapsed after or were refractory to CPi. After a median follow-up of 32.4 months, 13 patients are still alive and in CR, with 8 patients still in CCR after first salvage treatment post CPi. To note, in this heavily pre-treated population the median OS was not reached.

Our results are in line with what previously observed, supporting the hypothesis of a new chemo-sensitization due to anti-PD1 treatment in HL patients with highly pre-treated and chemo-refractory disease. This approach gave also a chance for some patients to receive consolidation with SCT (both allogeneic and autologous), increasing the likelihood of being cured. Further studies are needed to better understand the biological rationale of the new chemo-sensitization after CPi and to establish the most appropriate chemotherapy regimen and the best timing of CHT and anti-PD1 administration in the R/R cHL therapeutic algorithm.

**CONFLICT OF INTEREST**

Authors declare no conflict of interest.

**AUTHOR CONTRIBUTIONS**

BC, LA, AM, MC, and PLZ contributed to conception and design. LA contributed to data Analysis. BC, LA, and PLZ contributed to interpretation of the data. BC, LA, and PLZ contributed to drafting of the article. BC, LA, MC, and PLZ contributed to critical revision for important intellectual content. BC, AM, GL, AB, CP, LN, VS, MC, and PLZ contributed to provision of study materials or patients. BC, LA, AM, GL, AB, CP, LN, VS, PEC, and M.C contributed to collection and assembly of data. All authors participated in writing and/or critically reviewing the manuscript and approved this version for submission.

**DATA AVAILABILITY STATEMENT**

The datasets used and analyzed during the current study are available from the corresponding authors on reasonable request.

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