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ORIGINAL ARTICLE

Risk of relapse after anti-PD1 discontinuation in patients with Hodgkin lymphoma

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Abstract

Introduction Patients with relapsed/refractory Hodgkin lymphoma (R/R HL) experience high response rates upon anti-PD1 therapy. In these patients, the optimal duration of treatment and the risk of relapse after anti-PD1 discontinuation are unknown.

Methods We retrospectively analyzed patients with R/R HL who responded to anti-PD1 monotherapy and discontinued the treatment either because of unacceptable toxicity or prolonged remission. A machine learning algorithm based on 17 candidate variables was trained and validated to predict progression-free survival (PFS) landmarked at the time of discontinuation of anti-PD1 therapy.

Results Forty patients from 14 centers were randomly assigned to training (n = 25) and validation (n = 15) sets. At the time of anti-PD1 discontinuation, patients had received treatment for a median duration of 11.2 (range, 0—time to best response was not statistically significant in discriminating patients with PFS lesser or greater than 12 months). Considering PFS status as a binary variable (alive or dead) at a specific time point (12 months) is convenient, intuitive and allows for comparing the value of potential predicting variables in these two groups of patients. Nonetheless, this approach has two drawbacks: first, it binarizes outcome; second, it excludes patients alive with a time to last follow up lesser 12 months. Therefore, it is less powerful to demonstrate statistically significant association with PFS even if it exists 5 months. Patients discontinued anti-PD1 treatment either because of prolonged remission (N = 27, 67.5%) or unacceptable toxicity (N = 13, 32.5%). Most patients were in CR (N = 35, 87.5%) at the time of anti-PD1 discontinuation. In the training set, the machine learning algorithm identified that the most important variables to predict PFS were patients' age, time to best response, and presence or absence of CR. The performance observed in the training set was validated in the validation set.

Conclusion In this pilot, proof of concept study using a machine learning algorithm, we identified biomarkers capable of predicting the risk of relapse after anti-PD1 discontinuation (age, time to best response, quality of response). Once confirmed, these simple biomarkers will represent useful tools to guide the management of these patients.

Keywords Immunotherapy · Biomarkers · Hodgkin lymphoma · Checkpoint inhibitors

Introduction

Patients with relapsed/refractory Hodgkin lymphoma (R/R HL) experience high response rates upon anti-PD1 therapy [1–4]. Patients 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) [4, 5]. On the other hand, patients in CR might experience durable remission without further therapy [4, 5]. These prolonged responses may persist even after anti-PD1 discontinuation suggesting that some patients might be cured with anti-PD1 alone [6]. Predicting the

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individual risk of relapse after anti-PD1 discontinuation in a given patients would provide important information to physicians for optimal management of HL patients undergoing anti-PD1 therapy. Physicians could identify patients at low risk of relapse in whom anti-PD1 therapy can be safely discontinued and those at high risk of relapse who may require from additional therapies such as consolidation with alloHSCT.

Here, we aimed to identify factors associated with risk of relapse after anti-PD1 discontinuation. We investigated whether a combination of standard of care variables collected before anti-PD1 treatment discontinuation could predict progression free survival (PFS) in R/R HL who responded to anti-PD1 therapy and discontinued the treatment without subsequent therapy.

Methods

Patients

We conducted a retrospective, international study of patients with R/R HL aged ≥ 18 years-old, who reached a partial (PR) or complete response upon anti-PD1 monotherapy (concomitant or ending radiotherapy was permitted) and discontinued the treatment because of unacceptable toxicity or prolonged remission (based on the physician's decision). All patients who received at least one dose of anti-PD1 were included. Patients who discontinued because of relapse/progression or underwent consolidation with alloHSCT were not included.

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 no. 16.861). All patients have been informed and consented before registration.

Prediction of PFS using machine learning

The primary endpoint was to identify the most important variables to predict PFS. PFS was defined by the time from anti-PD1 discontinuation until disease progression or relapse based on medical imaging. PFS was censored at the date of last information and was estimated using the Kaplan-Meier method. Response assessment during treatment and off-therapy was defined by the primary physician using the Cheson criteria [7, 8].

We randomly assigned patients to training (n = 25) and validation (n = 15) sets. First, we collected 17 candidate variables including patients' characteristics (clinical data: n = 5, previous treatment: n = 5) and data related to anti-PD1 treatment (pattern of response: n = 2; treatment type: n = 4, and toxicity: n = 1). Variables are listed in Supplementary Fig. 1.

Second, a machine learning algorithm previously used by our team and validated [9, 10] was trained (n = 25) to predict PFS using a random forest methodology suitable for censored survival data. The survival analysis was landmarked at the time of discontinuation of anti-PD1 therapy to avoid immortal time bias. We ranked the importance of the 17 candidate variables as potential predictors. Then, the performance of the algorithm was computed using Harrell's concordance index as an error rate for discrimination. We only selected the top three features due to the limited sample size in the training set (n = 25). The signature calculated a prediction (range: 0–1) for each patient via the analysis of a combination of the top three selected features. This prediction quantifies PFS duration.

Third, the signature was validated in the validation set (n = 15). The performance of the algorithm was computed using Harrell's concordance index as an error rate for discrimination.

Fourth, given the limited sample size, we analyzed the association of the three variables identified by the machine learning algorithm with PFS using hazard ratio (HR [95CI]) and Cox regression model.

Description of the characteristics of progression-free patients at 12 months

To further confirm the results of our machine learning algorithm, we compared the distribution of the 17 candidate variables according to patients' PFS status at 12 months. Machine learning is indeed so powerful at handling complex multidimensional data that it can easily learn almost anything from data. Overfitting defines the fact that it has "memorized" that a specific combination of parameters is linked to an individual patient with a specific outcome in a particular set of data. Therefore, to demonstrate further that some variables are associated with PFS, we have evaluated in the overall population the association of the top three variables identified by the machine learning algorithm in the training set with PFS.

Statistical analysis

Analyses were conducted using Microsoft Excel (v2019, Microsoft, USA, 2019) and R (version 3.6.2). A p value less than 0.05 was considered to indicate statistical significance ($\alpha = 0.05$).

Results

Patients' characteristics

Forty patients from 14 centers in France, Italy, Belgium, and Portugal were included. Their characteristics are summarized in Table 1. The median age at anti-PD1 discontinuation was

Table 1 Patients' characteristics

Patients' characteristics	N = 40
Age at anti-PD1 discontinuation, median, years (range)	38.5 (22–84)
Sex, male, no. (%)	25 (62.5)
Prior lines of systemic therapy, median (range)	4 (0–13)
Prior treatment with brentuximab vedotin, no. (%)	37 (92.5)
Prior autologous HSCT, no. (%)	24 (60)
Prior allogenic HSCT, no. (%)	9 (22.5)
Disease stage at anti-PD1 initiation, no. (%)	
I/II	14 (35.9)
III/IV	25 (64.1)
Missing	1
Type of anti-PD1, no. (%)	
Nivolumab	32 (80)
Pembrolizumab	8 (20)
Number of anti-PD1 injections, median (range)	15.5 (1–57)
Duration of anti-PD1 therapy, months, median (range)	11.2 (0–33.5)
Concomitant or ending radiotherapy, no. (%)	8 (20)
Disease status at anti-PD1 discontinuation, no. (%)	
CR	35 (87.5)
PR	5 (12.5)
Time to best response from anti-PD1 initiation, months, median (range)	3.4 (0.1–30.5)
Reason for anti-PD1 discontinuation, no. (%)	
Prolonged response	27 (67.5)
Toxicity	13 (32.5)
Follow-up from anti-PD1 discontinuation, months, median (range)	21.8 (3.2–50.8)
Estimated (Kaplan-Meier) PFS at 24 months, % (CI 95)	57 (42–78)
Estimated (Kaplan-Meier) PFS at 24 months among 35 CR patients, % (CI 95)	63 (47–86)
Relapse/progression, no. (%)	14 (35)
Death, no. (%)	4 (10)

38.5 years old (range, 22–84) years. The median number of prior lines of treatment was 4 (range, 0–13); 93% of patients had been previously treated with brentuximab vedotin; 60% and 23% of them had undergone prior autologous or alloSCT, respectively. Thirty-two (80%) were treated with nivolumab and 8 (20%) with pembrolizumab. The median duration of exposure to anti-PD1 was 11.2 (range, 0–33.5) months, and the median number of cycles was 15.5 (range, 1–57). Eight (20%) patients were treated with concomitant or ending radiotherapy.

Reasons for anti-PD1 discontinuation were prolonged response and toxicity in 27 (68%) and 13 (33%) patients, respectively. The median follow-up from anti-PD1 discontinuation was 21.8 (range, 3.2–50.8) months.

Prediction of PFS using machine learning

In the training set, the random forest for survival was developed using a forest terminal node size of 3 and an average number of 7 terminal nodes. Five out of seventeen variables were tried at each split. Trees were grown using SWOR resampling method and log-rank as a splitting rule.

Using all 17 variables, the error rate of the machine learning algorithm was 31.6% in the training set (n = 25) demonstrating a good performance for prediction of PFS. The random forest for survival algorithm ranked the importance of the 17 variables recorded before anti-PD1 discontinuation using as a metrics the Z score of variable importance (Fig. 1). The three most important variables identified were as follows: age (Z score = 2.7), time to best response (Z score = 1.5), and presence or absence of CR (Z score = 1.4) (Fig. 1). Using only these three variables, the performance of a 3-feature signature to predict and classify patients' PFS based upon these three variables—observed in the training set (error rate: 28.54%)—outperformed a 17-feature signature which can be understood by the fact that the other features have

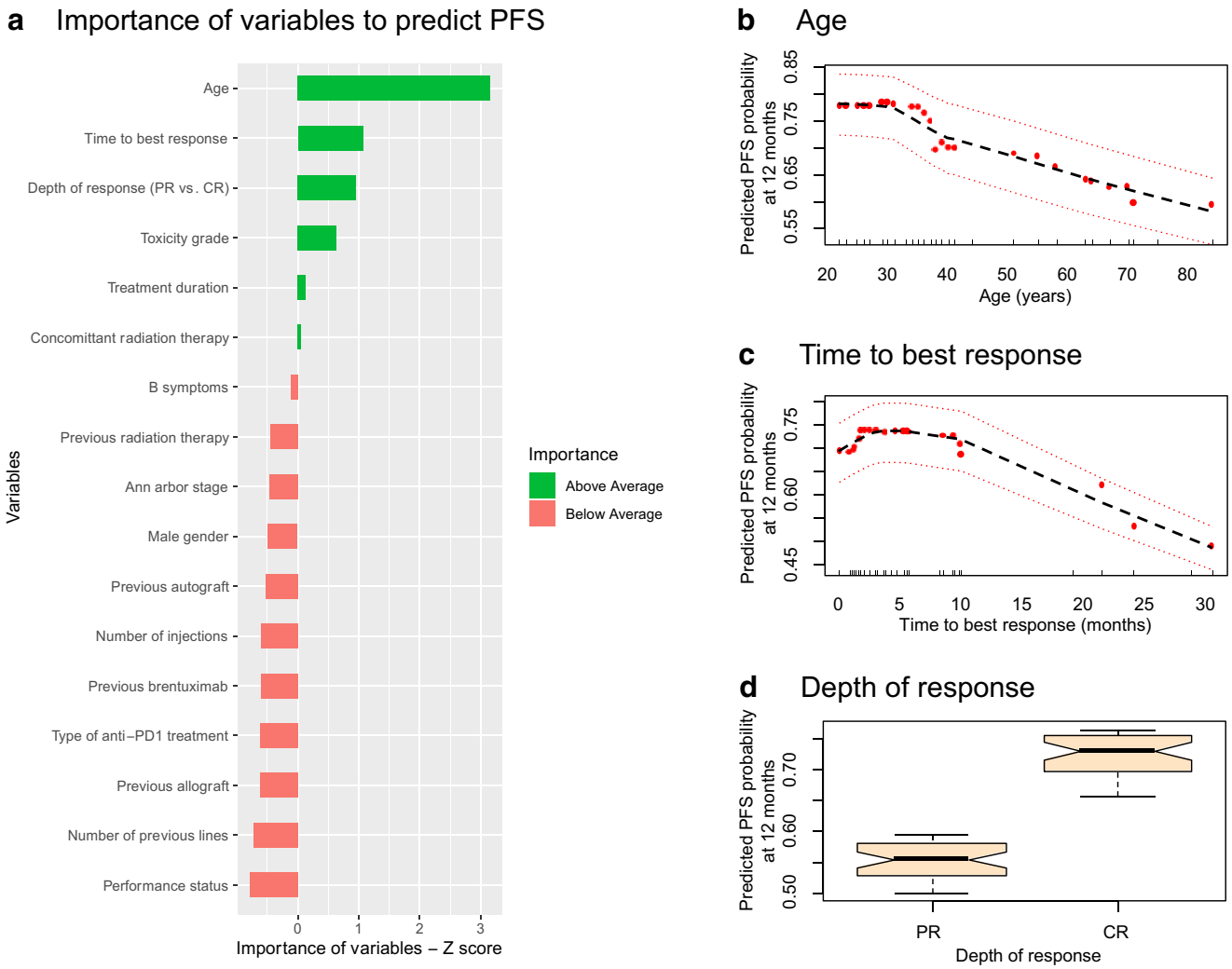

Fig. 1 a A machine learning algorithm was trained (n = 25) to predict PFS using a random forest methodology suitable for censored survival data. The survival analysis was landmarked at the time of discontinuation of anti-PD1 therapy to avoid immortal time bias. We ranked the importance of the 17 candidate variables as potential predictors. Importance of variables in the machine learning algorithm is displayed using as a metrics the Z score of "variable importance." Variables above (green) and below (red) the average variable importance are displayed using a color code. The three most important variables selected were: age (Z score = 2.7), time to nadir (Z score = 1.5), and presence or absence of complete response (Z score = 1.4). b, c, and d The overall PFS probability can be predicted for each patient at any time using machine learning. For instance, the PFS probability at 12 months post landmark was computed as a function of age (a), time to best response (b), and depth of response (c), which were the most important variables included in the signature

limited importance (Fig. 1) and therefore are likely to overfit the model. Consequently, we validated the 3-feature signature in the validation set (error rate: 32.83%). These results confirmed that prolonged PFS was observed in younger patients with faster and deeper responses.

As a sensitivity analysis in the overall population (n = 40), multivariate Cox regression model demonstrated that out of these three features, age per year was significantly and independently associated with PFS (HR: 1.04 [95CI: 1.01–1.07], P = 0.008), meaning that there would be an HR of 1.4 between two patients with a 10-year difference of age, and an HR of 2.8 with a difference of 20 years.

Description of the characteristics of progression-free patients at 12 months

To further confirm the results of our machine learning algorithm, we compared the distribution of the 17 candidate variables according to patients' PFS status at 12 months. The PFS status at 12 months was known in 32/40 patients. Among these patients, twenty-two remained relapse-free (69%) at 12 months.

The characteristics of the patients based on PFS are displayed in Table 2 and Supplementary Fig. 2. These analyses confirmed those found with the machine learning algorithm: these patients were younger (mean age 38 vs. 55 years old, P = 0.03), had more CR (96% vs. 60%, P < 0.01), and

Table 2 Patients' characteristics based on relapse-free survival at 12 months after anti-PD1 discontinuation

	PFS status at 12 months is unknown (censored)	PFS < 12 months	PFS > 12 months	P test
n	8	10	22	
Age (mean (SD))	46.12 (18.17)	55.00 (16.97)	37.77 (15.19)	0.027
Male Gender (%)	6 (75.0)	4 (40.0)	15 (68.2)	0.224
Ann Arbor stage (%)				0.484
I	1 (12.5)	0 (0.0)	3 (13.6)	
II	2 (25.0)	1 (10.0)	8 (36.4)	
III	0 (0.0)	1 (10.0)	1 (4.5)	
IV	5 (62.5)	8 (80.0)	10 (45.5)	
Performance status (%)				0.304
0	4 (50.0)	2 (20.0)	13 (59.1)	
1	2 (25.0)	5 (50.0)	8 (36.4)	
2	1 (12.5)	2 (20.0)	1 (4.5)	
3	1 (12.5)	1 (10.0)	0 (0.0)	
Number of prior lines (mean (SD))	3.12 (0.99)	5.90 (3.54)	5.00 (2.54)	0.091
Prior radiation therapy (%)	3 (37.5)	4 (40.0)	11 (50.0)	0.777
Prior autograft (%)	4 (50.0)	6 (60.0)	14 (63.6)	0.737
Prior allograft (%)	1 (12.5)	3 (30.0)	5 (22.7)	0.676
Prior brentuximab (%)	8 (100.0)	9 (90.0)	20 (90.9)	0.664
Treatment with nivolumab (%)	5 (62.5)	9 (90.0)	18 (81.8)	0.333
Treatment duration (mean (SD))	15.46 (11.83)	10.87 (12.57)	12.30 (7.80)	0.617
Number of injections (mean (SD))	28.75 (22.90)	15.40 (17.81)	23.27 (16.52)	0.298
Time to best response in months (mean (SD))	4.34 (3.29)	11.33 (12.69)	4.98 (4.68)	0.062
CR as BOR (%)	8 (100.0)	6 (60.0)	21 (95.5)	0.009
Concomitant radiation Therapy (%)	1 (12.5)	0 (0.0)	7 (31.8)	0.095

BOR best overall response, CR complete response, SD standard deviation

Patients with PFS beyond 12 months had younger mean age (38 vs. 55 years old, P = 0.03), higher rate of complete response (96% vs. 60%, P < 0.01), and a shorter mean time to nadir (5.0 months vs. 11.3 months, P = 0.06). P test < 0.05 are in italics

tended to have a shorter time to best response (mean 5.0 months vs. 11.3 months, P = 0.06).

PFS in the overall population

In the overall population, fifteen events occurred and the median PFS was not reached (95CI: 15.7-NA months). Kaplan-Meier analysis demonstrated that patients in CR had longer PFS than patients in PR (log-rank, P = 0.002) (Fig. 2).

Among the 35 patients who were in CR at the time of anti-PD1 discontinuation, the estimated PFS was 63% (CI 95, 47–86) at 24 months (Fig. 2). Strikingly, five patients who had received only a short course of anti-PD1 (< 6 months) remained in CR more than 3 years after anti-PD1 discontinuation. One of them received a single dose of nivolumab for a relapse post-alloSCT and remains disease-free 47.6 months later. Ten (29%) patients in CR at discontinuation relapsed after a median of 10.4 (range, 5.6–26.7) months.

Four out of 5 patients in PR at discontinuation relapsed after a median of 5.1 (range, 1–7.4) months. One patient was in PR at discontinuation and has not relapsed 21 months after discontinuation. In this patient, a few FDG avid lesions consistent with Hodgkin lymphoma remained stable. These lesions were not biopsied because the patient declined the procedure.

Overall, 4 patients died: three from disease progression and one from severe graft-versus-host disease (GVHD) while in CR.

Discussion

Using standard of care variables collected at the time of anti-PD1 treatment discontinuation, we were able to predict PFS in R/R HL who discontinued the treatment without subsequent therapy. The most important variables associated with PFS were age, time to best response, and the quality of response (PR vs. CR). Patients who remained relapse-free beyond 12 months after anti-PD1 discontinuation were typically young (median age 38 years old), in CR at the time of discontinuation (96%), and had responded rapidly to anti-PD1 therapy (mean time to best response 5.0 months).

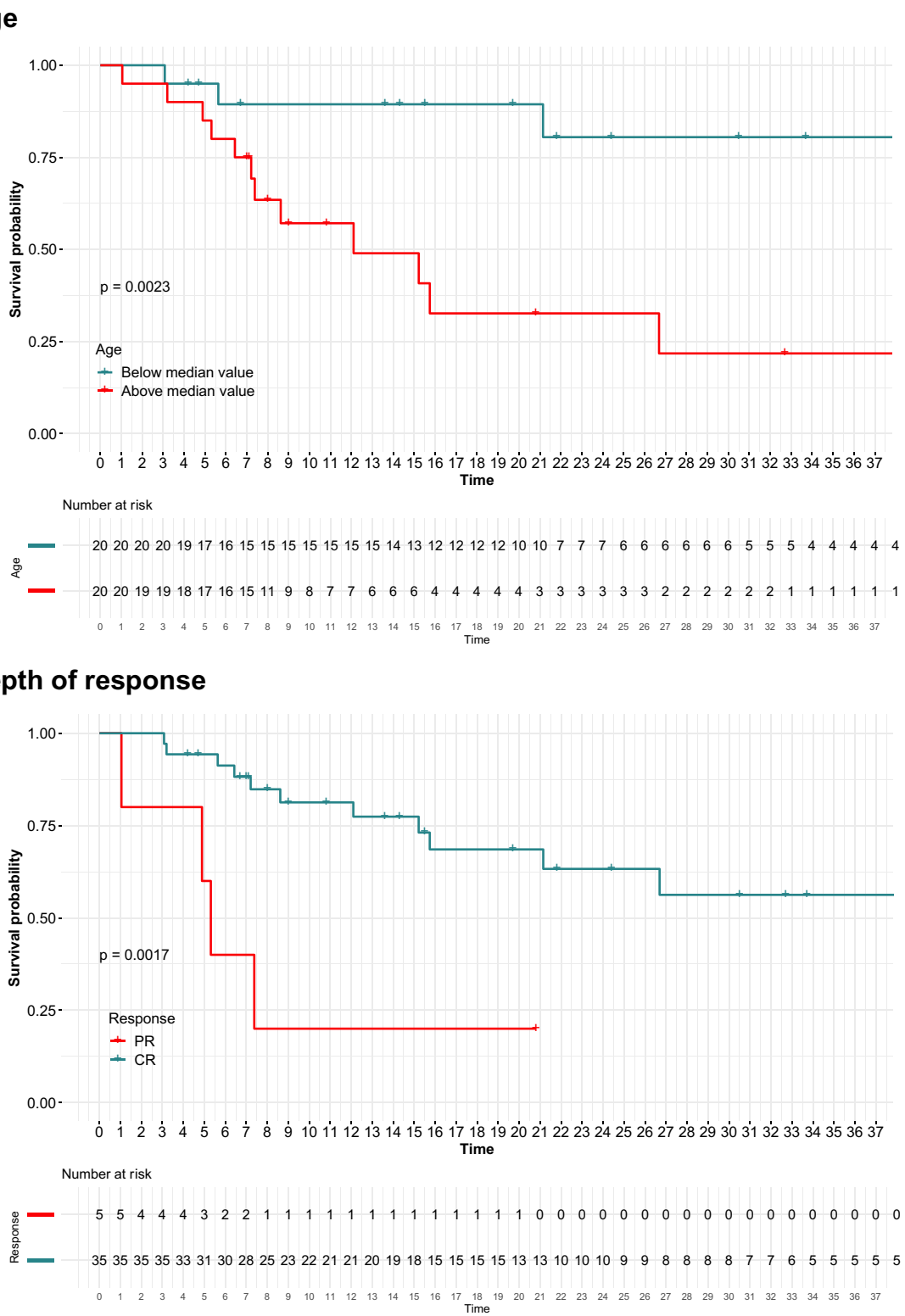

Fig. 2 In the overall population, fifteen events occurred and the median PFS was not reached (95CI: 15.7-NA months). a Median (interquartile range) age was 38.5 years (30–58). Kaplan-Meier analysis demonstrated that younger patients with age below median (38.5 years) had longer PFS than otherwise (log-rank, P = 0.002). b Kaplan-Meier analysis demonstrated that patients in CR had longer PFS than patients in PR (log-rank, P = 0.002)

Among the 3 predictive factors identified in our study, 2 of them are not unexpected: time to best response and the quality of response. Two retrospective studies assessed the prognostic value of early PET/CT response during nivolumab therapy in HL patients [11, 12]. These studies found that early CR (i.e., 2 months after initiation) was associated with better PFS and overall survival. Our results suggest that this observation holds true (at least for PFS) even after anti-PD1 discontinuation. More surprisingly, we found that age was the strongest factor associated with the risk of relapse. The underlying biology to explain this observation remains unclear. Age is known to be a prognostic factor in HL, independent of the type of therapy [13, 14]. This may be due to the intrinsic biology of HL tumors in elderly patients. The higher rate of relapse in this population may also relate to the host and may be due to a reduced capacity to mount long-lasting responses to immunotherapy because of immunosenescence. However, in solid tumors, most retrospective studies and meta-analysis found no impact of age on the efficacy of checkpoint inhibitors [15–17], yet this question has not been addressed in patients with Hodgkin lymphoma.

This predictive score may provide important information to physicians for the management of HL patients undergoing anti-PD1 therapy. Indeed, HL patients who respond to anti-PD1 therapy may classically be offered 3 different options: (1) continue treatment until disease progression, (2) consolidate with alloSCT, and (3) discontinue treatment without further anticancer therapy. The first option raises the question of the financial and potentially toxic cost without evidence of utility. Consolidation with alloSCT exposes patients to a 10–15% risk of treatment-related mortality and a high morbidity rate, although it is likely to lower the risk of relapse [2, 4, 18]. The third option is the one with the lower cost and toxicity but should be restricted to patients with a low risk of relapse. Prior studies suggested that a subset of patients may be cured with anti-PD1 monotherapy as some of them remain disease-free more than 3 years after anti-PD1 discontinuation [6]. Our predictive score allows identification HL patients with a low risk of relapse in whom anti-PD1 therapy can be safely discontinued without further treatment.

In this pilot, proof of concept study, we implemented several strategies to limit the risk of false-positive findings. First, the machine learning algorithm was different from most studies in the literature using conventional random forest algorithm (RF) for binary classification. In this study, we used a RF for survival algorithm, which was trained to predict PFS as a spectrum and as a continuous, censored value. The output was a signature value on a continuous scale from 0 to 1 (most to least favorable PFS). This point is critical because the error rate of an RF for survival classification does not mean that the prediction is inherently erroneous; it means that sometimes, the algorithm could not perfectly classify patients when it ranked them on a continuous scale from the most to least favorable PFS. Second, we created a low-dimensional model. Of note, we screened 17 candidate variables, but we observed that several were highly correlated and, therefore, redundant or did not provide any valuable prognostic information. Nonetheless, the unsupervised RF algorithm demonstrated in the training set that only three variables were necessary: two continuous variables and one binary variable (CR vs. PR). Using more than three variables did not significantly improve the performance of the model in our training set. In practice, this means that the number of dimensions in this signature (3) is limited and that the signature is likely underfitted (larger datasets would allow for developing more complex models achieving higher performance). Third, this low dimensional signature was tested on a validation set that was not used for training and reached similar performance as the training set, hence validating it as a prognostic tool. Fourth, the machine learning was not a black box and we can see on Fig. 1 that there is a clear association between the observed PFS and the value of the two continuous biomarkers selected by the signature. The model predicted PFS with an error estimated around 33% in the validation set (a perfect model would reach an error rate for classification of 0% and the error rate ranges between 0% and 100%). This error rate was derived from Harrell's concordance index. Therefore, it means that the signature prediction was able to correctly rank-order the actual observed PFS times of two random individuals in 67.2% of cases in the validation set. This is an enticing result since this machine learning algorithm is a mathematical model built to perform this specific task without using explicit instructions. Consequently, larger datasets are expected to harness higher performance by deciphering more precisely complex interactions between the three inputted variables and the outputted PFS.

Our study has several limitations including its retrospective nature, the limited number of patients, and the relatively short follow-up. Moreover, the assessment of response was local review and not central review. Of note, PET scan interpretation can be challenging in the immunotherapy setting [19], and therefore, there is a risk of discordance between institutions. Nonetheless, the local assessment was the tumor board assessment. Therefore, it is a robust assessment that involved a consensus between hematologists, radiologists, and nuclear medicine physicians. Additionally, the vast majority of our cohort of patients had CR which is a straightforward diagnosis in patients with HL since there are clear guidelines defining what is a CR on PET CT [7, 8]. Our algorithm has been trained with this dataset using well-defined response criteria. Of note, theoretically, results could have been different if we had used another criterion. However, based upon our previous publications in the field [4, 12, 19–21], there is no evidence suggesting that using another criteria for the definition of CR/PR (e.g., with 5PS score) would have changed our results.

Time to best response was not statistically significant in discriminating patients with PFS lesser or greater than 12 months (Table 2). Considering PFS status as a binary variable (alive or dead) at a specific time point (12 months) is convenient, intuitive and allows for comparing the value of potential predicting variables in these two groups of patients. Nonetheless, this approach has two drawbacks: first, it binarizes outcome; second, it excludes patients alive with a time to last follow up lesser 12 months. Therefore, it is less powerful to demonstrate statistically significant association with PFS even if it exists.

We included patients who underwent concomitant/ending radiotherapy (n = 8, 20%). This was performed to increase statistical power as well as recruiting all patients treated with anti-PD1 in France for this indication. Of note, patients who underwent concomitant RT tend to have different characteristics. Therefore, it could have constituted a selection bias if it had been selected as among the predictors of PFS by the RF analysis. Nonetheless, the RF analysis has not ranked concomitant/ending radiotherapy among the best predictors of PFS. Further studies should prospectively validate these findings.

In conclusion, our machine learning algorithm was able to identify simple biomarkers (age, time to best response, and quality of response) applicable in routine practice to evaluate the individual risk of relapse after anti-PD1 discontinuation. This predictive score represents a useful tool for physicians to identify patients in whom anti-PD1 therapy can be safely discontinued. These hypotheses generating results and signature should be leveraged in larger cohorts and ideally confirmed in prospective studies.

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Authors' contributions G.M., L.D., and R.H. designed the research, analyzed data, and wrote the paper. P.B., C.H., M.G.S., K.B., B.D-F, J.B., J-M.S., E.N-V., M.M., H.G., A.S., C.A., C.C-S., M.D.R., and F.P. provided the data, and all authors reviewed and approved the final draft. This study was supported in part by Grant No. 20575 (to C.C-S) from the Italian Association for Cancer Research, Milan, Italy.

Compliance with ethical standards

Conflict of interest G.M. and P.B. have received consulting fees and/or honoraria from Bristol-Myers Squibb. M.G.S received research grant form Gilead Sciences, and was consultant for Abbvie, Gilead Sciences, Janssen Cilag, Roche. E.N-V. received consulting fees from Sanofi. A.S. has received consulting fees from Takeda and Celgene. C.C.-S. received honoraria for speaker engagements from Bristol Myers Squibb, Merck Sharp & Dohme, Amgen, Janssen Oncology, Astra-Zeneca; provided consultancy to Boehringer Ingelheim, Sanofi, ADC Therapeutics; and received scientific advisory fee from Servier, Novartis, Roche, ADC Therapeutics; and received research funding from Rhizen Pharmaceuticals. RH received honoraria from Bristol-Myers Squibb, MSD, Gilead, Kite, Roche, Novartis, Janssen, and Celgene. All other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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