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Letter to the Editor: Brentuximab vedotin in the treatment of elderly Hodgkin lymphoma patients at first relapse or with primary refractory disease: a phase 2 study of FIL ONLUS

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Older age represents an adverse prognostic factor in Hodgkin lymphoma (HL). In fact, although in the last decades HL survival has improved also in patients above 60 years of age,[1] lower 5-year overall survival (OS) rates (40-65%) and progression free survival (PFS)/freedom from treatment failure rates (44-60%) have been observed.[2-4] Poor outcomes in older patients are likely due to several factors. First, elderly patients have more comorbidities which can lead to increased toxicity of chemotherapeutic regimens, can compromise dose-intensity or, in some cases, make the use of polychemotherapy impossible.[5,6,] Secondly, HL appears to have a different biology in older patients: in fact, an increased frequency of mixed cellularity subtype and Epstein Barr virus-related disease have been observed. Moreover, older patients often present with "B" symptoms.[2] The treatment of relapsed/refractory (R/R) elderly HL patients is challenging. In a previous retrospective study from German Hodgkin Study Group, responses and survival of patients above 60 years of age affected by R/R HL were analyzed. Best responses were observed with conventional chemo-radiotherapy; in fact, CR rates of 30%, 59% and 12% were registered after treatment with intensified salvage treatments, conventional chemotherapy and/or salvage radiotherapy, and palliative approaches, respectively; OS was 10 months, 41 months and 7 months, respectively.[7]

Recent retrospective studies demonstrated the efficacy of brentuximab vedotin (BV) in older patients affected by R/R HL, although duration of response appeared to be quite short.[8,9]

We present a single-arm, open-label, multicenter, phase 2 clinical trial, aimed at evaluating the antitumor efficacy and safety of BV as first salvage therapy in elderly patients with R/R HL (FIL_BVHD01). Patients aged ≥60 years, who were not suitable for high dose chemotherapy, were eligible if affected by histologically confirmed CD30+ HL at first relapse or with primary refractory disease. The study involved 5 Italian Centers adhering to the Italian Lymphoma Foundation (Fondazione Italiana Linfomi, FIL) and was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of each participating site. Written informed consent was obtained by patients before any study procedure. The trial was registered

at www.clinicaltrials.gov, NCT02227433, and given the EudraCT number 2013-004109-24.

Treatment consisted in 1.8 mg/kg BV administered as a single outpatient intravenous infusion on Day 1 of each 21-day treatment cycle, for a maximum of 16 cycles. The efficacy of single agent BV was measured by overall objective response rate (ORR, sum of complete response [CR] and partial response [PR] rates). Secondary endpoints were CR rate, disease free survival (DFS), 1-year PFS, 1-year OS and safety and tolerability of BV. OS was calculated from start of treatment to the date of death due to any cause and was censored at the last date the patient was known to be alive. DFS was estimated for patients who achieved a CR as time to relapse or death as a result of lymphoma or acute toxicity of treatment from first documentation of response. PFS was calculated as the time from the beginning of treatment until lymphoma progression or death due to any cause. Responses were determined using the Revised Response Criteria for Malignant Lymphoma.[10]

Any adverse event (AE) occurred during treatment was encoded according to NCI Common Terminology Criteria for AEs v. 4.03. Demographics and patients' characteristics were summarized by descriptive statistics and survival functions were estimated by using the Kaplan-Meier method. Statistical analyses were performed with Stata 11 (StataCorp LP, TX).

Twenty patients were enrolled. Eighteen patients were evaluable for safety analysis (2 screening failure) and 17 for efficacy analysis (one patient neither was not primary refractory nor at first relapse). Nine males and 9 females with a median age of 73 years (range 61.2-85.7) underwent BV therapy. Median time from diagnosis to BV treatment was 1 year and median time from last treatment to BV administration was 6 months. All patients' characteristics are summarized in Table 1. Patients underwent a median of 7 cycles of BV monotherapy (range 1-16). Two patients (12%) completed the therapeutic program receiving the 16 scheduled cycles of treatment, 7 patients discontinued treatment early due to lack of response or progression of the disease, 7 for toxicity and 1 patient was lost to follow-up.

Best response was reached at 4th cycle of BV therapy. ORR was 52.9% (9/17 patients) with a CR rate of 23.5% (4/17 patients). With a median follow-up of 24.9 months, median PFS was 8.8 months and median OS was 21.7 months. 1-year PFS and OS were 40% and 68.8%, respectively (Figure 1 and Figure 2). Median time to next treatment was 2 months. Median DFS was 3.9 months: among the four patients who achieved a CR, 3 relapsed (at 2.8, 3.4 and 4.4 months, respectively) while one patient is still in CR 16.4 months after end of treatment.

The most common AEs were hematological: 5 cases (27%) of neutropenia (1 grade 1, 2 grade 2, 2 grade 3) and one grade 3 thrombocytopenia (5%) were observed. The most frequent extra-hematological toxicity was neuropathy, which occurred in 6 patients (33%) starting from cycle 2 (2 grade 1, 3 grade 2, 1 grade 3). Three patients (16%) experienced hepatic toxicity (2 grade 2, 1 grade 3), while skin rash occurred in 4 patients (22%) and gastric symptoms in 3 patients (16%). Overall, 7 serious adverse events (SAE) and 2 suspected unexpected serious adverse reactions (SUSAR) were observed in 9 patients (50%), 6 of them judged related to BV. SAEs included 3 infectious complications, 3 cases of polyneuropathy, and 1 case of nausea/vomiting; SUSARs included 1 amylase and lipase elevation and 1 stroke. All the SAEs lead to treatment discontinuation.

Currently, no standard second-line treatment is available in this setting of elderly R/R HL. In some selected cases, high-dose chemotherapy followed by ASCT can represent a curative option. Nevertheless, most of elderly patients are not eligible to high dose chemotherapy due to comorbidities or poor performance status. In such patients, a non-chemotherapeutic approach could represent the best treatment option.

Efficacy and safety of BV have been demonstrated also in older patients as first-line treatment approach: despite high ORR and CR rate (92% and 73%, respectively), responses were not durable: in fact, median PFS was 10.5 months.[11]

A recent retrospective study evaluated the effectiveness and tolerability of BV in R/R HL patients: an ORR of 74%, median PFS of 15.1 months and

median OS of 17.8 months were observed. The most common AEs included leukopenia, anemia, and diarrhea. The documented incidence of peripheral neuropathy during BV treatment was only 9.6%.[9]

In our study, we observed a lower ORR (52.9%) and PFS (8.8 months); these inferior outcomes could be due to the significantly higher median age of our patient population (73 vs 66.7 years), with all the limitations to compare efficacy with effectiveness. We also observed a higher incidence of peripheral neuropathy (33.3%), which is indeed in line with data from the phase II pivotal trial (42%);[12] this discrepancy could be explained by the retrospective nature of Bröckelmann and colleagues' study: it is possible that such AEs were underreported.[9] Of note, we observed a high rate of AEs which led to hospitalization, which suggests that this subset of frail patients should be carefully monitored during treatment with BV.

To our knowledge, our study is the first trial evaluating efficacy and safety of BV in elderly patients affected by HL in first relapse or refractory to first line treatment. The main limitations of the study are represented by the lack of a control group and the lack of frailty and geriatric assessment. However, one inclusion criteria was ECOG performance status ≤1 to guarantee patient capacity to perform activities of daily living.

We observed a low rate of durable responses in a population of patients who were not heavily pretreated. Moreover, only two patients (12%) were able to complete the 16 scheduled cycles of treatment; this could suggest that the optimal number of cycles for older patients should be lower. As regarding toxicity, results were unexpected on the basis of previous reports:[11,12] earlier dose reductions of BV to improve tolerability should be considered. With a median age of 73, combination chemotherapy could still be considered in this population, or appealing strategies could include checkpoint inhibition alone or in combination with BV.[13] However, the small sample size could have biased study results. Therefore, further studies are needed to identify the subset of patients who could more benefit from treatment with BV, and case-control studies are needed to compare BV with other therapeutic regimens in this specific population. Altogether, multicenter collaborations that integrate novel

agents and incorporate formal assessments of functional status to tailor therapy on a patient-specific basis will be critical to the successful study of and improved outcomes for older patients with HL.

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Authors' Contribution: P.L.Z., M.M., L.A. and V.S conceived the study; P.L.Z., M.M., V.S. and L.A. designed the study, collected and, and wrote the manuscript; L.A. analyzed data; A.R., A.L., M.B., A.P., N.B., and C.P. provided advice and assisted with data collection and interpretation; all the authors approved the final manuscript.

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Table 1. Patients' characteristics (n = 18).

Age	
Median (range), years	73 (61.2-85.7)
Sex, N	
Male	9
Female	9
Stage (Ann Arbor), N	
At diagnosis:	
I	2
II	0
III	7
IV	9
At time of BV treatment:	
I	1
II	2
III	8
IV	7
Performance status at BV treatment (ECOG), N	
0	11
1	7
Time I diagnosis-BV, median (range)	1 year [2 mos-21 yrs]
Time last treatment-BV, **median (range)**	6 mos [1 mo-20 yrs]
Last treatment, N	
ABVD/MBVD	13 (2 plus RT)
VBM	2
COPP	2

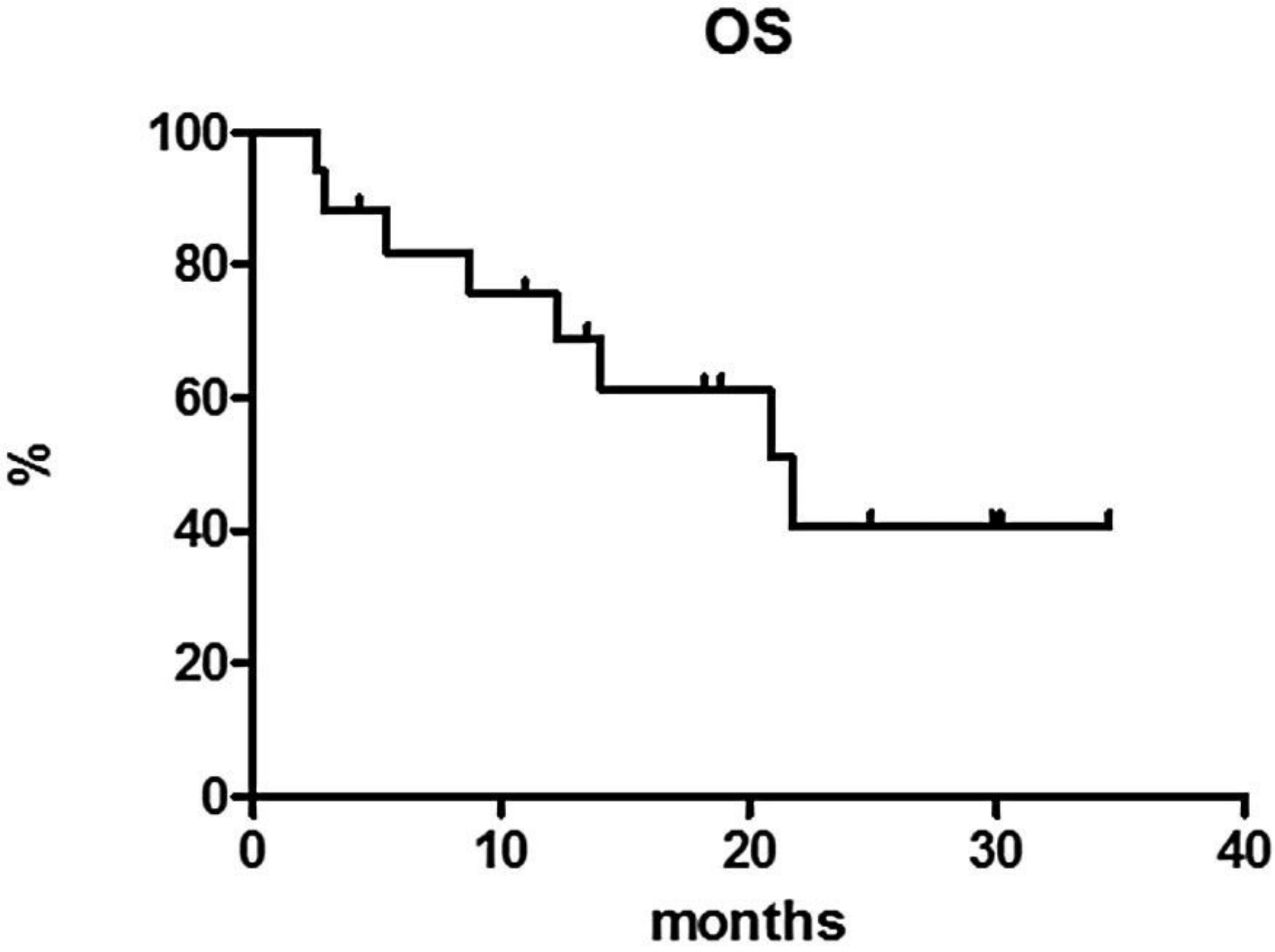
gemcitabine	1
Response to last treatment, N	
Refractory	6
Relapsed	12

ECOG: Eastern Cooperative Oncology Group, ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine, MBVD: liposomal doxorubicin, bleomycin, vinblastine, dacarbazine, VBM: vinblastine, bleomycin, methotrexate, COPP: cyclophosphamide, vincristine, procarbazine and prednisone, RT: radiotherapy.

Figure Legends

Figure 1. Overall Survival (OS).

Figure 2. Progression Free Survival (PFS).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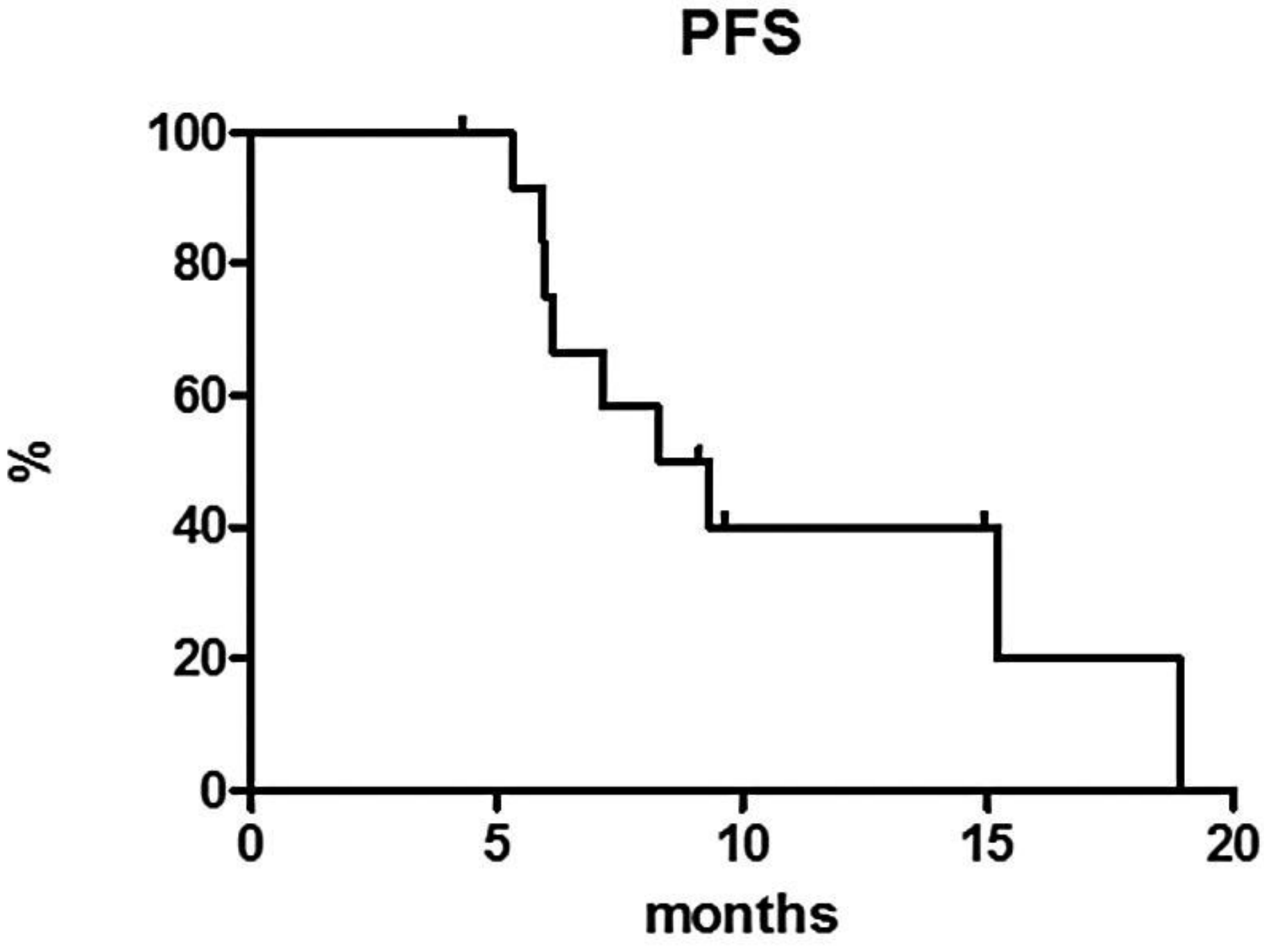
PFS
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