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**Survival outcomes of patients with primary plasma cell leukemia (pPCL) treated with novel agents**

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# UNIVERSITÀ DEGLI STUDI DI TORINO

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**TITLE:** Survival outcomes of patients with primary plasma cell leukemia (pPCL) treated with novel agents.

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### **Author contributions**

R.M., N.S.J. are responsible for the concept of this manuscript. R.M and D.A. collected, assembled, and analysed the data; R.M. performed the statistical analysis; R.M coordinated the various authors and wrote the first draft; and all authors were given unrestricted access to the data, critically reviewed the manuscript drafts, approved the final version, and made the decision to submit the manuscript for publication.

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**KEYWORDS:** primary plasma cell leukemia (pPCL); novel agents; chemotherapy; autologous stem cell transplantation (ASCT); maintenance.

## ABSTRACT

**Introduction** Primary plasma cell leukemia (pPCL) is an aggressive plasma-cell disorder characterized by circulating plasma cells and poor prognosis. Although pPCL patients benefit from the use of stem-cell transplantation (SCT) and novel agents, their prognosis remains inferior to that of myeloma patients.

**Methods.** We conducted a retrospective analysis on 38 consecutive pPCL patients diagnosed between October 2005 and July 2016, and registered in the Winship Cancer Institute of Emory University database. Baseline characteristics, as well as data about treatment and survival outcomes were collected.

**Results.** The median age at diagnosis was 58 years. All patients received a bortezomib-based induction regimen and 92% of them received both bortezomib and an immunomodulatory drug (thalidomide or lenalidomide); 74% of patients underwent autologous-SCT (ASCT) and 61% received maintenance therapy. Best response to first line therapy was  $\geq$  partial response in 87% of patients, with 45% of  $\geq$ complete responses (CR). The achievement of  $\geq$ CR was a predictor for prolonged progression-free survival (PFS) and overall survival (OS).

Median PFS and OS were 20 and 33 months, respectively. ASCT prolonged PFS as compared to no ASCT (25 vs. 6 months;  $p=0.004$ ) and patients who received maintenance after ASCT had prolonged median PFS (27 vs. 11 months;  $p=0.03$ ) and a trend towards prolonged OS (median, 38 vs. 22 months;  $p=0.06$ ) as compared to no maintenance.

**Conclusions** This data supports the use of regimens combining novel agents in the upfront treatment of pPCL patients, as well as the role of ASCT and maintenance therapy for long-term disease control.

## **CONDENSED ABSTRACT**

This is the first extensive report in pPCL patients to show that treatment with proteasome inhibitors and immunomodulatory drugs, both as induction and maintenance treatment, results into prolonged survival.

pPCL patients undergoing ASCT and continuous treatment have prolonged PFS and OS.

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## INTRODUCTION

Plasma cell leukemia (PCL) is a rare but aggressive variant of multiple myeloma.<sup>1</sup> It may occur “de novo”, referred to as primary PCL (pPCL), or it may present as an end-stage, leukemic evolution of a refractory multiple myeloma (MM), and thus termed secondary PCL (sPCL). pPCL and sPCL constitute approximately 60% and 40% of all PCLs, respectively. Based on Kyle’s criteria, the diagnosis of PCL requires greater than  $2 \times 10^3/\mu\text{L}$  circulating clonal plasma cells in the peripheral blood, accounting for more than 20% of the white cell count.<sup>2</sup> However, recent studies reported that even lower levels of circulating plasma cells are significant and portend poor prognosis, similar to that observed among PCL patients.<sup>3,4</sup> Unlike MM, pPCL usually occurs in younger patients and presents with higher tumour burden. Patients with pPCL exhibit an increased rate of high-risk features associated with poor survival, such as renal failure, advanced international staging system (ISS) disease and complex cytogenetic abnormalities.<sup>1,5</sup>

Before the availability of stem cell transplant (SCT) and novel agents, the overall survival (OS) of patients treated with conventional chemotherapy was less than 12 months.<sup>6,7</sup> Later studies suggested a mild improvement in progression-free survival (PFS) and OS among pPCL patients undergoing autologous SCT (ASCT).<sup>5,8</sup> Subsequent retrospective studies of pPCL patients treated upfront with novel agents, especially bortezomib, reported improved PFS and OS as compared to historical controls, particularly among patients that were able to undergo SCT.<sup>9-11</sup>

Due to the rarity of the disease, only two prospective trials investigated the role of the proteasome inhibitor (PI) bortezomib and the immunomodulatory drug (IMiD) lenalidomide for the upfront treatment of pPCL patients thus far. Fortunately these studies confirmed a positive survival trend for patients treated with novel agents in comparison with patients

treated with conventional chemotherapy. In the Italian GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) trial, lenalidomide was used both in the induction and maintenance phase and patients were offered SCT when feasible. The median OS for the entire population was 28 months. In the phase II trial presented by the Intergroup Francophone du Myelome (IFM), pPCL, ASCT-eligible patients received a bortezomib-based induction regimen followed by a tandem SCT, bortezomib-lenalidomide-dexamethasone (VRD) consolidation and lenalidomide maintenance. This approach resulted in a median OS of 36 months.<sup>12,13</sup> Despite the impressive improvement in survival outcomes among all patients with MM, especially with increasing utilization of SCT and incorporation of novel agents in the induction and maintenance phase,<sup>14</sup> the survival improvement observed in pPCL patients is still not on par with MM patients.<sup>15</sup> Here we present a single center, retrospective analysis of pPCL patients to validate the role of ASCT and the incorporation of PIs and IMiDs in the induction and maintenance phase.

## **PATIENTS AND METHODS**

### *Data sources*

We conducted a retrospective, IRB approved analysis on patients diagnosed with pPCL and registered in the Winship Cancer Institute database at Emory University. According to the International Myeloma Working Group (IMWG) criteria, primary plasma cell leukemia was defined by the presence of more than 20% circulating clonal plasma cells and/or  $>2 \times 10^3/\mu\text{L}$  absolute number of clonal plasma cells in the peripheral blood.<sup>16</sup> Patients were included in this analysis if they had received at least one PI and/or IMiD as part of the induction treatment.



For each patient we collected baseline data at the time of diagnosis, including age, gender, isotype and quantity of monoclonal protein, chemistry panel, complete blood counts, bone marrow aspirate and core biopsy to evaluate the plasma cell infiltrate, conventional cytogenetics, FISH panel, and radiological evaluation to establish the presence of bone disease. We also collected information about the type and response to first line treatment, including transplantation and maintenance therapies, as well as the date of first relapse, second line of treatment, date of second relapse, date of the last follow-up, and the survival status at the time of the last contact. Response to treatment was evaluated according to the IMWG response criteria.<sup>16</sup>

### *Statistical analysis*

Survival outcomes studied included PFS, second progression-free survival (2nd-PFS) and OS. PFS was defined as time from diagnosis to first relapse or death from any cause, whichever came first. 2nd-PFS was defined as the time from start of a second line of therapy to second relapse or death, whichever came first. OS was defined as the time from diagnosis to death. PFS, 2nd-PFS and OS curves were plotted using the Kaplan-Meier method and comparisons were performed with the log-rank test. All hazard ratios (HRs) were estimated with their 95% confidence intervals (95% CI) and two-sided p-values. The statistical significance boundary was set at 5%. Fisher Exact test was used for discrete variables. Data analysis was done using a cut-off date of March 2018 using R (Version 3.1.1).

## **RESULTS**

### *Patients' characteristics*

Thirty-eight consecutive patients who were diagnosed with pPCL between October 2005 and July 2016, and who had received at least a PI and/or IMiD as part of their induction treatment, were included in the analysis. The median age at diagnosis was 58 years (range 34-80 years). Half of patients presented with IgG pPCL (53%), whereas 24% and 18% presented with free-light chain and IgA pPCL, respectively. At diagnosis, 58% of patients presented with bone disease and 47% with hypercalcemia, while 50% had a serum creatinine value greater than 2 mg/dl. Patients were more likely than those with MM to present with high-risk disease features. Forty-two % of patients had ISS stage 3 disease and among 34 patients with available FISH data, 34% had high risk disease defined by the presence of at least one high-risk cytogenetic abnormality, including t(4;14), t(14;16) and del(17p).

#### *First-line treatment and response to treatment*

Data on induction regimens are listed in table 1. All patient received a bortezomib-based induction and 35/38 patients (92%) received a combination of bortezomib and an IMiD (thalidomide or lenalidomide). The median number of induction cycles was 3 (range, 1-15); the median number of induction cycles for patients treated with novel agents with or without conventional chemotherapy was 2 and 4, respectively. The overall response rate (ORR) after the induction phase was 82%, with 45% of patients achieving at least a very good partial response (VGPR) and 18% a complete response (CR) (table2).

ASCT was performed in 28 patients after induction treatment, with a median time to ASCT of 3 months (range, 2-12 months). Ten patients did not proceed to ASCT: 4 patients due to sub-optimal response or progression after induction, 4 according to their preference, and 2 because of age (over 75 years).

Maintenance was administered to 23 patients (22 after ASCT); 5 patients did not receive maintenance after ASCT due to patients' preference (n=4) or disease progression (n=1). The standard maintenance approach for this high-risk population consisted of a combination of a PI, an IMiD and dexamethasone administered up to 3 years. Thereafter, treatment was switched to single agent maintenance.<sup>17</sup> The majority of patients received VRD maintenance (n=14), whereas in 3 patients, carfilzomib-pomalidomide-dexamethasone was chosen due to sub-optimal response after induction with VRD. Two patients received either ixazomib or carfilzomib instead of bortezomib, and 1 patient received pomalidomide rather than lenalidomide, at the treating physician's discretion.

The best response to first line treatment was at least a partial response (PR) in 87% of patients, with 68% and 45% of them achieving at least a VGPR or CR, respectively. Median time to best response was 5 months (range, 1-24 months). The achievement of at least CR was associated with significantly prolonged median PFS (25 vs. 11 months; HR: 0.4, p=0.02) and OS (63 vs. 28 months; HR:0.4, p=0.04) as compared to those patients achieving a PR or VGPR.

#### Second line treatment

Thirty-one patients progressed after first line therapy, and 4 (13%) of these patients relapsed with central nervous system (CNS) involvement by plasma cells. Twenty-four patients received a second line of treatment. Ten of these patients received a triplet combination based on two novel agents and dexamethasone (RVD, carfilzomib-lenalidomide-dexamethasone, pomalidomide-bortezomib-dexamethasone, elotuzumab-lenalidomide-dexamethasone, daratumumab-pomalidomide-dexamethasone), 10 patients received a combination of at least

one novel agent plus conventional chemotherapy, and four patients underwent ASCT in second remission. The median number of treatment lines was 2 (range, 1-8).

### Survival outcomes

After a median follow-up of 88 months (95% CI 59-NA), 25 patients have died. Only one patient died within the first month from diagnosis, for an early mortality rate of 3%.

In the overall population, median PFS was 20 months (95% CI 11-33), with 28% of patients alive and free from progression at 3 years (Figure 1a). The median 2nd-PFS was 6 months (95% CI 4-28). The median overall survival was 33 months (95% CI 25-53), with 39% of patients being alive at 3 years (Figure 1b).

Median PFS was significantly longer in patients who received ASCT upfront as compared to those who did not (25 vs. 6 months; HR: 0.3,  $p=0.004$ ) (Figure 2a). Furthermore, a trend towards improved OS, though not statistically significant, was observed among patients who underwent ASCT upfront as compared to those who did not (median, 36 vs. 26 months; HR 0.5,  $p=0.08$ ) (Figure 2b).

The administration of maintenance therapy after ASCT significantly prolonged median PFS (27 vs. 11 months; HR: 0.3,  $p=0.03$ ) with a trend towards a longer median OS (38 vs. 22; HR:0.4,  $p=0.06$ ) as compared to no maintenance (Figure 3).

In patients ( $n=17$ ) who received an intensive treatment strategy consisting of a PI plus IMiD induction regimen, consolidation with a single ASCT followed by a three-drug maintenance regimen, median PFS was 33 months (25-NA) and median OS was 63 months (33-NA), with 3-year PFS and OS of 47% and 58%, respectively.

In these patients, no differences in terms of ORR (90% vs. 75%;  $p=0.7$ ), CR rate (20% vs. 17%;  $p=1$ ), median PFS (25 vs. 36 months;  $p=0.3$ ) and OS (38 vs. 43;  $p=1$ ) was observed in

those who received novel agents with or without intensive chemotherapy as part of induction therapy.

## **DISCUSSION**

Before the introduction of ASCT and novel agents, conventional chemotherapy proved to be inadequate for disease control in pPCL patients, offering a median OS less than 12 months.<sup>6,18</sup> Given the rarity of the disease, the first reports on the use of novel agents in this setting were retrospective studies. Bortezomib demonstrated the ability to induce an objective response in up to 78% of patients, thus resulting into a prolonged median OS (range, 18-28 months) as compared to conventional chemotherapy.<sup>9,10,19,20</sup> Similarly, lenalidomide, though in small retrospective reports, showed some degree of activity in pPCL patients.<sup>21,22</sup>

The only two prospective trials published to date evaluating newly diagnosed pPCL patients were conducted by the GIMEMA and the IFM groups. The GIMEMA group evaluated 23 patients with untreated pPCL who received lenalidomide-dexamethasone (Rd) induction, with the option to proceed to SCT if eligible, and subsequently received lenalidomide maintenance.<sup>23</sup> Median PFS and OS for the entire population were 15 and 28 months, respectively. However, the survival advantage was exclusively confined to transplanted patients, while no improvement was seen among patients who did not undergo SCT in terms of median PFS (27 vs. 2 months) and OS (NR vs. 12 months).

The IFM conducted a phase II trial enrolling 40 untreated pPCL patients eligible for SCT. After bortezomib-based induction, patients could proceed to either a double ASCT followed by 1-year of RVD maintenance or a tandem ASCT/allogeneic-SCT. The median PFS and OS for the entire population were 15 and 36 months, respectively.<sup>12</sup>

Here, we present the results of a single center, retrospective analysis on pPCL patients treated at the Winship Cancer Institute of Emory University. To our knowledge, this is the first extensive report on the combined use of PIs and IMiDs as initial treatment of pPCL patients: 92% and 53% of patients analysed received induction and maintenance regimens combining a PI (bortezomib, carfilzomib or ixazomib) with an IMiD (thalidomide, lenalidomide or pomalidomide).

The ORR and the at least VGPR rate (87% and 68%, respectively) in our study compare favorably to those reported in prospective studies with either lenalidomide (74% and 39%, respectively) or bortezomib (69% and 59%, respectively).<sup>12,23</sup> Katodritou et al reported a significant survival advantage in patients who achieved at least a VGPR as best response during first-line therapy. In our study, patients achieving at least CR as best response had a significantly longer PFS (median, 25 vs. 11 months) and OS (median, 63 vs. 28 months) as compared to those who achieved a PR or VGPR only, thus highlighting the benefit of profound cytoreduction in obtaining long-term disease control.<sup>10</sup>

The efficacy displayed by the incorporation of PIs and IMiDs in the induction phase of pPCL treatment is also reflected by the lower early mortality rate (within the first month) observed among our patients (3%) as compared to the early mortality rates reported in the SEER analysis (15% among patients treated after 2006) and in the retrospective analysis conducted by Katodritou et al (6%).<sup>15</sup> Interestingly, the addition of intensive chemotherapy to novel agents as induction therapy did not translate into significant differences in terms of ORR, median PFS, and OS, as compared to intensive chemotherapy-sparing regimens. However, given the retrospective nature of this study and the lack of a randomization, these results need to be cautiously interpreted and should be validated in a prospective trial.

In our study, both median PFS (20 months) and OS (33 months) for the entire population compare favorably to those reported with lenalidomide (15 and 28 months, respectively) and bortezomib-based regimens (12 and 18 months).<sup>13,23</sup> Although cross-trial comparisons are difficult to perform, in this study, combining bortezomib and IMiDs seems to improve the ORR (82% vs. 69%) and the CR rate (44% vs. 33%) obtained after the induction phase, reducing the rate of primary refractory patients (5% vs. 26%,) as compared to the bortezomib-based induction adopted in the IFM trial. This, along with a longer duration of maintenance (3 vs. 1 year) might account for the better PFS observed in our trial.

As previously described, we confirmed that the greatest survival benefit, in terms of both PFS (25 vs. 6 months) and OS (36 vs. 26 months), was observed among patients undergoing ASCT, thus validating the role of ASCT as a standard consolidation approach after initial cytoreduction.<sup>13,23</sup> In this light, the promising 6-month OS (92%) observed in the overall population supports the benefit of combining bortezomib with IMiDs upfront to obtain rapid disease control and enable transplant eligible patients to proceed to ASCT.

Allogeneic-SCT has been regarded as a potentially curative approach for PCL. However, in large retrospective analyses comparing autologous to allogeneic-SCT, patients in the allogeneic-SCT group, despite having a better disease control, also displayed a significantly higher treatment-related mortality, ultimately resulting in the lack of a survival benefit.<sup>8,24</sup> Indeed, the adoption of reduced-intensity conditioning regimens and the availability of new drugs as post-transplant consolidation/maintenance, might redefine the role of allogeneic-SCT. The currently ongoing BMT CTN 1302 study (NCT02440464), will provide further insight into the role of allogeneic-SCT and the use of ixazomib maintenance for pPCL patients. While maintenance treatment has been proven to prolong both PFS and OS of MM patients, thus becoming a standard of care, little evidence is available about the role of continuous treatment in pPCL.<sup>25</sup> In our cohort, 22 patients received maintenance therapy after ASCT in

first remission and, notably, 19/22 received a 3-drug regimen consisting of 2 novel agents and dexamethasone. Patients who received maintenance treatment after ASCT had a significantly prolonged PFS (27 vs. 11 months) and OS (38 vs. 22 months) as compared to patients who did not receive maintenance. As it has already been shown among high-risk MM patients,<sup>17</sup> this evidence endorses the use of a three drug maintenance strategy combining PIs and IMiDs to obtain long-term disease control in pPCL patients.

In our analysis, despite access to second generation novel agents, the median 2<sup>nd</sup>-PFS was 6 months only, a result similar to that reported by Katodritou et al. (median, 6.5 months),<sup>13</sup> without significant differences among patients who received maintenance as compared to those who did not (median, 3 vs. 7 months, p=0.4). Moreover, 13% of relapse presented with CNS involvement. The aggressiveness of the disease at first relapse and its refractoriness to second line therapies, as proven by the shortness of 2<sup>nd</sup>-PFS and the pattern of relapse, suggest that the overall survival of pPCL greatly depends upon the first line treatment, thus supporting the role of an intensive treatment strategy upfront.

A small cohort of patients in our dataset (18%) achieved long-term survival, being alive at 5 years. In this subgroup, only one patient had high-risk features by FISH, while three patients were positive for t(11;14). All but one patient underwent ASCT and received RVD maintenance; five of these seven were in at least VGPR after induction, and subsequently obtained a CR. Despite the limited number of patients, this data suggests that the absence of high-risk cytogenetics and an early and deep response to induction treatment, might characterize a subset of patients in whom long-term survival can be achieved, particularly with the use of intensive and prolonged treatment.

In conclusion, we present the results of the first large cohort of pPCL patients treated with a combination of PIs and IMiDs during the induction and maintenance phase. We validated the role of ASCT as a consolidation strategy to obtain durable remissions and prolonged survival



and showed that maintenance treatment is associated with a better survival. However, despite the encouraging results, the prognosis of patients with pPCL remains largely unsatisfactory when compared to that of MM patients. Newer compounds, such as second and third generation PIs and IMiDs, as well as monoclonal antibodies, along with intensive treatment strategies may continue to improve survival of pPCL patients moving forward.

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## Tables and figures: titles and legends

Table 1. First line treatment.

Table 1 – Legend. VTD-PACE bortezomib, thalidomide, dexamethasone, cisplatinum, adriamycin, cyclophosphamide, etoposide; RVD lenalidomide, bortezomib, dexamethasone; VD-CEP bortezomib, dexamethasone, cyclophosphamide, etoposide, cisplatinum; VTD bortezomib, thalidomide, dexamethasone; RVDPACE lenalidomide, bortezomib, dexamethasone, cisplatinum, adriamycin, cyclophosphamide, etoposide; VTD-C bortezomib, thalidomide, dexamethasone, cyclophosphamide; VD bortezomib, dexamethasone; VAD vincristine, adriamycin, dexamethasone; ASCT autologous stem-cell transplantation; KPd carfilzomib, pomalidomide, dexamethasone; KRd carfilzomib, lenalidomide, dexamethasone; PVd pomalidomide, bortezomib, dexamethasone; IRd ixazomib, lenalidomide, dexamethasone; Rd: lenalidomide, dexamethasone.

Table 2. Best response to first-line treatment.

Table 2 – Legend. sCR stringent complete response; CR complete response; VGPR very good partial response; PR partial response; SD stable disease; PD progressive disease; ORR: overall response rate.

Figure 1a. Progression-free survival in the studied population

Figure 1b. Overall survival in the studied population

Figure 2a. ASCT versus no ASCT - PFS

Figure 2b. ASCT versus no ASCT - OS

Figure 2 – Legend. Fig. 2a Progression free-survival (PFS) and Fig. 2b overall survival (OS) in patients who received autologous stem cell transplantation (ASCT; blue curve) and in patients who did not receive ASCT (red curve)

Figure 3a. Maintenance versus no Maintenance - PFS

Figure 3b. Maintenance versus no Maintenance - OS

Figure 3 – Legend. Fig. 3a Progression free-survival (PFS) and Fig. 3b overall survival (OS) in patients who received maintenance treatment (blue curve) and in patients who did not receive maintenance treatment (red curve)

Table 1. First line treatment.

Regimen	N° of patients (%)
<b>Induction</b> <b>(n=38)</b>	
VTD-PACE	16 (42)
RVD	15 (40)
VD-CEP	2 (5)
VTD	2 (5)
RVD-PACE	1 (2)
VTD-C	1 (2)
VD	1 (2)
<b>Consolidation</b>	
ASCT	28 (74)
<b>Maintenance</b> <b>(n=23)</b>	
RVD	14 (37)
KPd	3 (8)
KRd	1 (2)
PVd	1 (2)
IRd	1 (2)
Rd	1 (2)
Lenalidomide	1 (2)
Thalidomide	1 (2)

VTD-PACE bortezomib, thalidomide, dexamethasone, cisplatinun, adriamycin, cyclophosphamide, etoposide; RVD lenalidomide, bortezomib, dexamethasone; VD-CEP bortezomib, dexamethasone, cyclophosphamide, etoposide, cisplatinum; VTD borteozomib, thalidomide, dexamethasone; RVDPACE lenalidomide, bortezomib, dexamethasone, cisplatinum, adriamycin, cyclophosphamide, etoposide; VTD-C bortezomib, thalidomide, dexamethasone, cyclophosphamide; VD bortezomib, dexamethasone; VAD vincristine, adriamycin, dexamethasone; ASCT autologous stem-cell transplantation; KPd carfilzomib, pomalidomide, dexamethasone; KRd carfilzomib, lenalidomide, dexamethasone; PVd pomalidomide, bortezomib, dexamethasone; IRd ixazomib, lenalidomide, dexamethasone; Rd: lenalidomide, dexamethasone.

Table 2. Best response to first-line treatment.

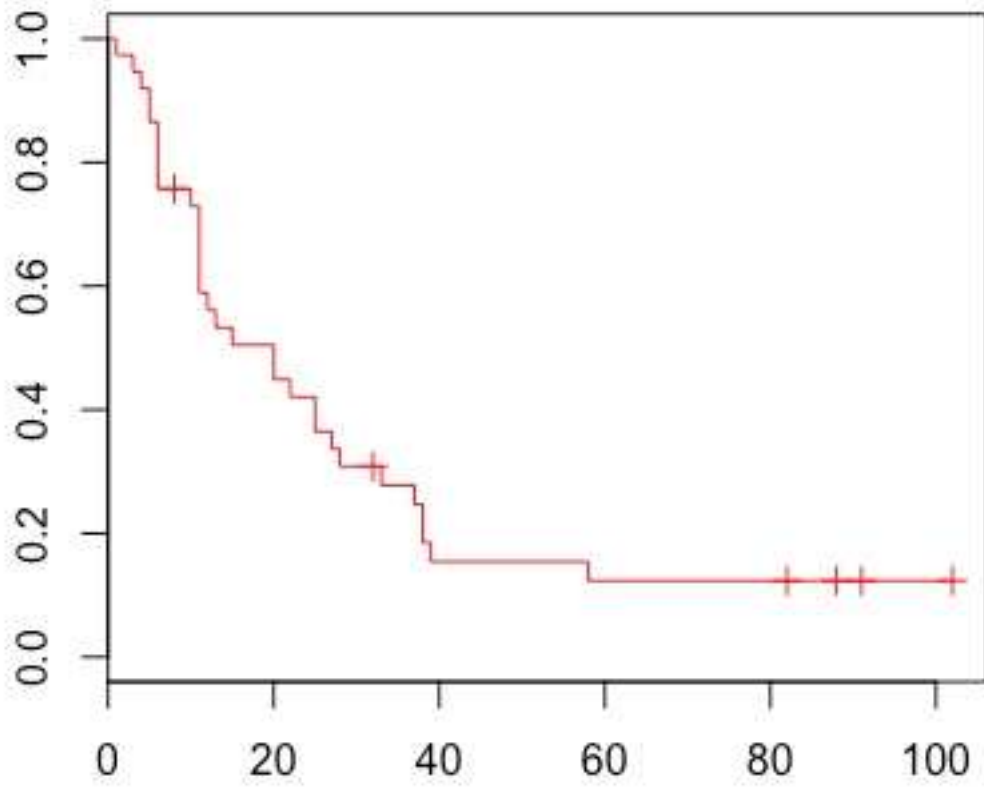
<b>Response rate</b>				
<b>(n=38)</b>				
	<b>After induction</b>		<b>Best response</b>	
	n	%	n	%
<b>sCR</b>	-	-	7	(18%)
<b>CR</b>	7	(18%)	10	(26%)
<b>VGPR</b>	10	(26%)	9	(24%)
<b>PR</b>	14	(37%)	7	(18%)
<b>SD</b>	4	(10%)	2	(5%)
<b>PD</b>	2	(5%)	2	(5%)
<b>NA</b>	1	(2%)	1	(2%)
<b>ORR</b>	31	(82%)	33	(87%)
<b>≥VGPR</b>	15	(45%)	26	(68%)

sCR stringent complete response; CR complete response; VGPR very good partial response;

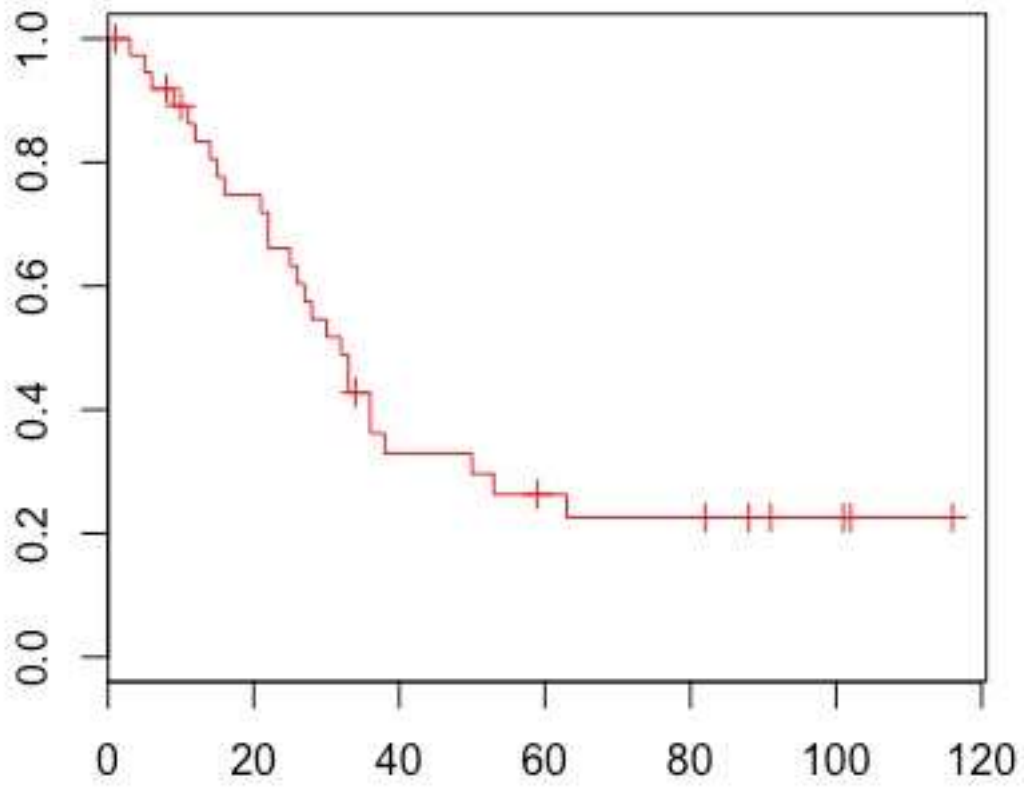
PR partial response; SD stable disease; PD progressive disease; ORR: overall response rate.



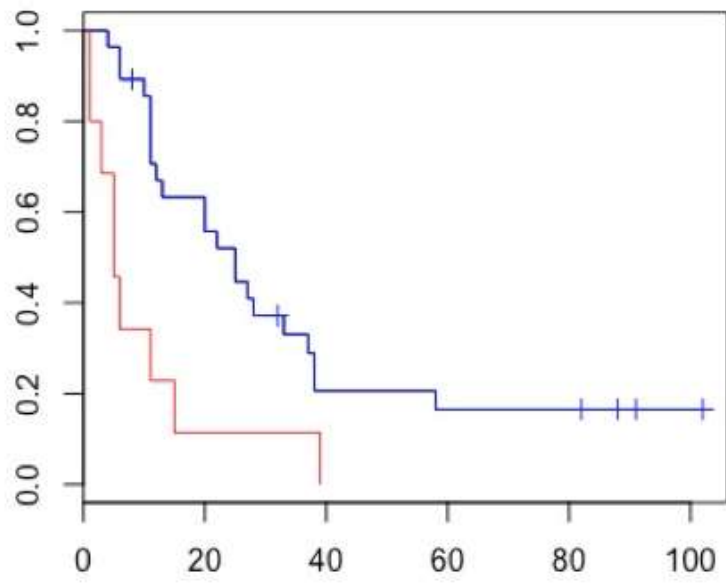
1a



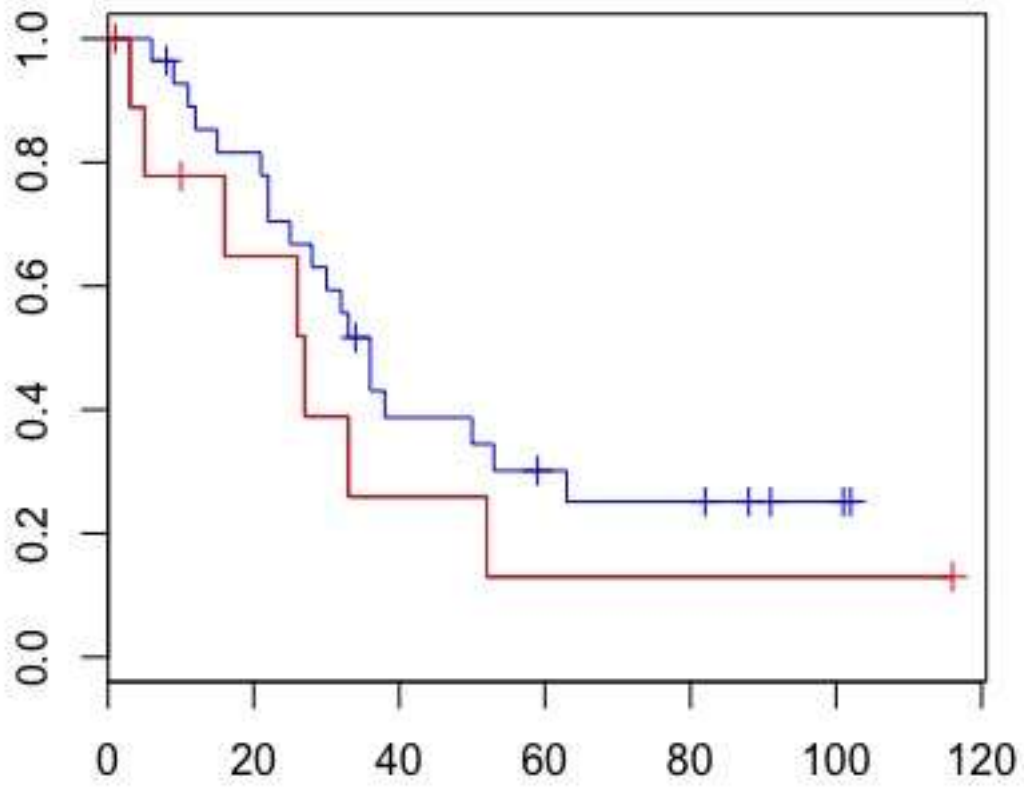
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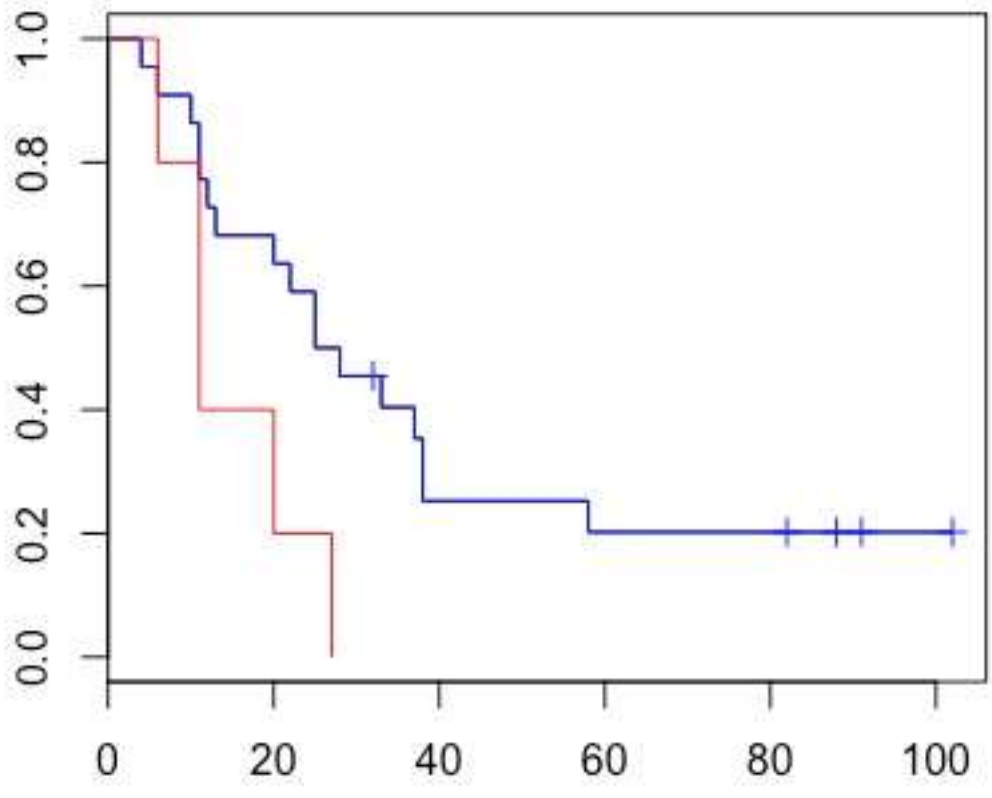
2a



2b



3a



3b

