Real world outcomes of pomalidomide for treatment of relapsed light chain amyloidosis

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Author contributions: FS and AW conceived study, analysed data and wrote the manuscript. RM, SM, SS, PNH, JG, CW and HL all contributed to the manuscript and provided critical input. All authors reviewed the final version of the manuscript.

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Summary:

Pomalidomide is a next-generation immunomodulatory agent with activity in relapsed light chain (AL) amyloidosis, but real world outcomes are lacking. We report the experience from the UK National Amyloidosis Centre.

All patients with AL amyloidosis treated with pomalidomide from 2009-2017 were included. Data was collected on treatment toxicity and clonal response. Survival was calculated by method of Kaplan-Meier and outcomes reported on an intent to treat (ITT) basis.

A total of 29 patients treated with pomalidomide were identified. **Haematologic responses at 3 months were: complete response (CR) nil, very good partial response (VGPR) 10 (35%), partial response (PR) 9 (31%), stable or progressive disease 7 (24%), unevaluable 3 (10%).** On an ITT basis (n=28) at 6 months: CR- nil, VGPR-11 (39%), PR-2 (7%) and the remaining patients were non-responders 15 (53%). Median overall survival (OS) was 27 months (95% CI 15.7-38.1 months). Median progression free survival (PFS) was 15 months (95% CI 6.24-23.77).

In conclusion, pomalidomide has activity in patients with relapsed AL amyloidosis. Responses are rapid and early responses may be predictive of a sustained overall response. Deep responses (VGPR or better) are seen in only a third of all patients and combination therapy needs to be explored.

Key Words: Haemotoxicity, chemotherapy, amyloidosis, pomalidomide, survival

Introduction

Systemic AL amyloidosis is a plasma cell disorder characterised by the deposition of monoclonal immunoglobulin light chains in the form of amyloid fibrils leading to progressive organ dysfunction. Most patients present with advanced organ involvement with a poor overall survival. The survival of patients with systemic light chain (AL) amyloidosis has improved over the last decade, with a 4 year overall survival (OS) of 54% (2010-2014) compared to 31% (2000-2004).(Muchtar and Gertz 2017) This improvement is largely a consequence of the introduction of effective, novel treatment agents.(Merlini, *et al* 2013) More patients are surviving beyond first line treatment reflected by a reduction in six month mortality (37% in 2000-2004, to 24% 2010-2014).(Muchtar and Gertz 2017) The disease course in AL amyloidosis now more closely resembles that of multiple myeloma, characterised by remission and subsequent relapse; hence there is a need for alternative effective lines of therapy at each relapse.

Since AL **amyloidosis** is characterised by significant organ dysfunction, treatment must not only be effective in terms of providing a deep and rapid clonal haematological response, but also be minimally toxic to prevent any worsening of organ function. Most patients are treated with a proteasome inhibitor based treatment in the front line setting, and a recent phase III trial has shown clear superiority of this approach over alkylator based treatment.**(Kastritis, *et al* 2016)** However, there is no standardised pathway for the treatment of relapsed disease. The immunomodulatory drugs (thalidomide, lenalidomide or pomalidomide) have a role in the treatment of patients with AL amyloidosis who relapse after front line treatment. Single agent thalidomide has poor tolerance and has limited efficacy.(Palladini, *et al* 2005) Thalidomide combined with cyclophosphamide or melphalan **h**as reasonable activity but toxicity remains high.**(Jelinek, *et al* 2016)** Lenalidomide has an improved toxicity profile and is better tolerated when used at doses of 15mg per day, with overall haematological response rates ranging from 41-67%, and is widely used as a second line agent in combination with dexamethasone. **(Dispenzieri, *et al* 2007, Sanchorawala, *et al* 2007)**

Pomalidomide is a next generation immunomodulatory agent that is licenced for **the** treatment of myeloma patients **who have** relapsed after treatment with lenalidomide. Pomalidomide has been reported in AL amyloidosis in **three early** phase trials with much better tolerance then lenalidomide and thalidomide.(Dispenzieri, *et al* 2012, **Palladini, *et al* 2017, Sanchorawala, *et al* 2016)** Experience of this drug outside of a trial setting is however limited.

We describe the outcome of 29 patients with systemic AL amyloidosis, treated at the UK-National amyloidosis centre (NAC), with a pomalidomide based regime.

Methods

All patients treated with pomalidomide between 2009-2017 were identified from the database of UK-NAC. Six patients were excluded as pomalidomide was initiated prior to assessment at the NAC, or the patients were lost to follow-up, leaving 29 patients eligible for analysis. Diagnosis of amyloidosis was confirmed by demonstration of characteristic birefringence under cross polarized light, with **C**ongo-red staining, on a tissue biopsy and AL typing was confirmed by immunohistochemistry with specific antibodies or by mass spectrometry. All patients had detailed baseline assessment for organ function, imaging and biomarker assessments. The starting dose of pomalidomide was 4mg daily (days 1-21 in a 28 day cycle) with weekly dexamethasone 20-40 mg. Monthly data was collected on treatment, toxicity and clonal response. Organ involvement was defined according to the international amyloidosis consensus criteria.(Gertz, *et al* 2005) Haematological and organ responses were defined according to the international amyloidosis consensus criteria. **(Palladini, *et al* 2012)** Organ responses were assessed from the time of starting pomalidomide to the end of therapy.(Comenzo, *et al* 2012, Gertz, *et al* 2005) The primary outcomes were haematological responses (HR) and overall survival (OS) following pomalidomide treatment. **Overall survival was defined as time in months from start of pomalidomide treatment to death from any cause.** Secondary outcomes included: progression free survival (PFS), calculated from start of pomalidomide therapy to haematological progression, or need for second line treatment, or death. Outcomes are reported on an intent to treat (ITT) basis.

Statistical analysis was performed using SPSS version 21. Approval for analysis and publication was obtained from the institutional review board at the University College London, and written consent was obtained from all patients in accordance with the Declaration of Helsinki. Survival outcomes were analyzed using the Kaplan-Meier method with comparisons done using the log rank test. All p-values were two sided with a significance level of < 0.05.

Results

A total of 29 patients were included in this study. The patient baseline characteristics are listed in table 1. The median number of organs involved was 3 (range 1-6) with renal, cardiac and liver involvement in 65.5%, 69.0% and 20.7% of patients respectively. All patients had relapsed disease. The median number of lines of prior treatment was 4 (range 1-7). Twenty-six (90%) patients had received prior bortezomib and 24 (83%) and 10 (35%) patients had received prior lenalidomide and thalidomide respectively. Seven percent of patients were refractory to bortezomib, 10% were refractory to lenalidomide, and 3% to both therapies. **The standard dose of pomalidomide was 4mg daily, with 20mg of dexamethasone given weekly. In six patients pomalidomide was started at a lower dose, (3 patients - 3mg, 2 patients - 2mg and 1 patient - 1mg). The reasons for dose reduction were: started at a low dose due to frailty and pre-existing cytopenias**. The median number of cycles of pomalidomide was 4 (range 1-24) and median duration on pomalidomide was 5 months (range 1-29). **Median duration of treatment was 7 months (range 2-25) for non-responders (stable or progressive disease), and 4 months (range 3-29) for responders (partial response or better).** The median NT-BNP (N-terminal pro-brain natriuretic peptide) increased in 75% of the patients on pomalidomide (from a median of 7800 ng/L (range 144-77585 ng/L) to 14690 ng/L (range 447-155161 ng/L)) at a median of 4 months of pomalidomide therapy.

Haematological responses were rapid with one patient achieving a CR and eight patients achieving a VGPR by end of one cycle. **By the end of 3 cycles of treatment the haematologic responses were: CR- nil, VGPR 10 (34.5%), PR 9 (31.0%), stable or progressive disease 7(24.1%). Three patients were unevaluable owing to missing light chain measurements. The median time to best response**

was 3 months (range 1-6). The final response assessment was done at end of six months (missing data on one patient). On an ITT basis (n=28) at six months, **no patients were in a CR**, 11 (39%) had achieved a VGPR, 2 (7%) had a partial response and the remaining patients had stable or progressive disease (i.e. non-responders - 53%) (see figure 1). However, of the patients who had achieved a VGPR at 3 months, only 2 patients had progressed by six months. Of the patients not achieving a VGPR or better by 3 months, only one additional patient achieved a VGPR at 6 months. There was no impact of prior bortezomib or lenalidomide exposure on depth of response.

Since cardiac response was assessed **by NT-proBNP values, to minimise the impact of the increase in NT-proBNP with pomalidomide treatment, we evaluated organ responses at six months and also at the end of pomalidomide treatment. Of the 20 patients with cardiac involvement, 13 patient were evaluable at six months (the remaining 4 patients with NT-proBNP <650 ng/L and 3 others with missing NT-proBNP values). Of these patients, 38% (5/13) had a cardiac response, 46% (6/13) cardiac progression, and 15% (2/12) were non-responders. At the end of pomalidomide treatment 14 patients were evaluable: 43% (6/14) with a cardiac response, 29% (4/14) with cardiac progression and 29% patients (4/14) were non-responders. Only one additional patient therefore achieved a cardiac response after stopping pomalidomide and so there was only a small actual bias introduced by the increase in NT-proBNP on response assessment. The median time to reach a cardiac response was 7 months (3-9 months).**

Of the 19 patients with renal involvement, four patients were established on dialysis prior to pomalidomide and one patient died before repeat creatinine readings were taken leaving 14 patients eligible for analysis. Seven patients had an increase of 25% of their creatinine during pomalidomide therapy, but only one patient went on to require renal replacement therapy. For the remaining six patients, two patients renal function has continued to deteriorate after stopping pomalidomide therapy (but they remain dialysis independent), one patient's renal function has improved, one two patients have not had repeat creatinine readings (one due to death and the second due to no follow-up since stopping pomalidomide). Seven patients' creatinine readings remained stable on pomalidomide treatment, and no patients' creatinine readings improved.

Renal response was assessed at 6 months. Renal progression was seen in 33% (3/9) and a renal response was seen in 44% (4/9) and no response in 22% (2/9) patients. All three patients with renal progression were non-responders, i.e had stable or progressive disease. This suggests that these were true renal amyloid progression events, rather than pomalidomide induced.

With a median follow-up of 13 months (2-37 months), there were 12 deaths. The median overall survival from start of pomalidomide was 27 months (95% CI 20.1-33.9 months) (Figure 2). The overall survival for patients achieving response at six months was: very good partial response (VGPR) or better 37 months, partial response (PR) 27 months, non-responders 15 months, progressive disease 19 months (see figure 3). The median progression free survival was 15 months, (95%CI 6.2-23.8 months) (Figure 2).

The most common adverse events were: non-neutropenic infection (56%), lethargy (56%), sensory neuropathy (44%), neutropenia (33%), pain (33%), constipation (22%), diarrhoea (22%), fluid overload (22%), hypotension (11%), mucositis (11%), peripheral motor neuropathy (11%), rash (11%), somnolence (11%) and renal impairment (11%). The highest CTCAE grade was 3 and the adverse events with this grade were: non-neutropenic infection (33%), neutropenia (22%), sensory neuropathy (22%), fatigue (11%), and fluid overload (11%). Nineteen patients have stopped **pomalidomide** treatment, 1 has died and 9 patients remain on ongoing therapy. The reason for discontinuing therapy was available in 17/19 (89%) of patients. Six patients (35.2%) stopped pomalidomide due to a planned clinical decision, since the patient had reached an adequate haematologic response. Seven (41.1%) patients discontinued due to adverse events – one patient each due to: fatigue, worsening peripheral sensory neuropathy, renal impairment, worsening orthostatic hypotension and frailty, respectively, and in two cases due to patient preference. Four patients (23.5%) discontinued pomalidomide due to stable or progressive disease and only two patients went on to receive a further line of therapy after pomalidomide, one with carfilzomib and the other with thalidomide based therapy.

Discussion

This data demonstrates that pomalidomide has activity in patients with AL amyloid**osis** at relapse with patients achieving a relatively rapid response by 3 months. Some patients, even in this heavily pre-treated patient population, achieve deep clonal response**s** of VGPR or better, however this real-world data suggests that despite encouraging early responses longer term benefits appear much less. A significant proportion of patients die or discontinue therapy, and there is a lack of persisting response with 52% having no response, died or progressed by 6 months.

There have been three previous phase 2 trials conducted with pomalidomide in the setting of AL amyloid. Table 2 summarises the previous trials and outcomes. The overall survival of patient**s** treated with pomalidomide is remarkably similar in all previous studies, (OS of 26-28 months), and the outcomes of th**is** current cohort are comparable with an OS of 27 months. Likewise, a PFS of 15 months in th**is** current cohort is comparable to the previously reported PFS of 14-17.8 months. In our current cohort, the overall response rate was similar to the Italian cohort at 3 months (66%). The Italian group however report best response at 7 cycles, which is very different from our cohort **where median time to best response was 3 months**. In our cohort, only one patient who had not achieved a VGPR by 3 months improved depth of response and, indeed, two patients with VGPR at 3 months had progressed by 6 months. This suggests that early response predicts the longer-term response and that prior therapy may affect the durability of haematologic responses. Interestingly, this is similar to our previous data using CTDa, where we found very few responses beyond three months and this resulted in a change in clinical practice at our centre, reviewing therapy at 3 months to add/switch to an alternative agent.(Wechalekar, *et al* 2007) It appears intriguing that Pomalidomide, which has structural similarity to thalidomide (and lenalidomide), appears to show a similar pattern.

Two **factors may be limiting the duration of response in** our cohort compared to the previous studies: the majority of our patients had prior IMiD based treatment **and** the standard practice in UK is for patients to receive a fixed duration of treatment. A quarter of patients in the current series had planned discontinuation of treatment after achieving a haematologic response. Since almost all studies with

pomalidomide in AL and in myeloma have used continuous therapy, there is limited data on progression after stopping pomalidomide. Based on data from previous AL studies with other regimes, (Wechalekar, *et al* 2007) we know that patients can remain in a stable haematologic **response** even after discontinuing therapy – indeed in the current cohort of the 6 patients who stopped therapy in a planned manner – 2 relapsed and 4 are still in remission. This suggests that in some patients after achieving a deep response, where tolerance may be a problem, discontinuation of pomalidomide could considered.

The toxicity profile of pomalidomide when used in myeloma is favourable, in a recent pooled analysis of 1088 myeloma patients only 9.7% of patients had to discontinue pomalidomide therapy, with myelosupression most commonly reported.(Jelinek, *et al* 2016) In AL amyloidosis, this is remarkably different with discontinuation rates of 60-93% in the previous studies. In our cohort, 38.9% were unable to tolerate therapy with side effects ranging from fatigue to worsening of neuropathy and orthostatic hypotension – consistent with previously reported data. A limiting feature of this series is the limitation of a retrospective series in capturing true adverse event data– the reported number is likely to be an under-representation of the true toxicity of pomalidomide.

In conclusion, pomalidomide combined with dexamethasone is a useful treatment option for patients with AL amyloidosis with relapsed refractory clonal disease. A significant proportion of patients achieve good haematologic responses, however responses are not as deep nor as durable in the real world setting. Responses are rapid and early responses appear to define longer-term outcomes. Pomalidomide is not as well tolerated in AL amyloidosis as myeloma and careful dose titration of pomalidomide may allow more patients to remain in therapy. Combination studies of pomalidomide with other agents like proteasome inhibitors or Venetoclax may offer additional and deeper responses and needs future prospective studies.

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Figure Legends

Figure 1: Percent Change in the difference in free light chains (dFLC) at 6 months: CR-nil, VGPR-11 (37.9%), PR-2 (6.9%), NR-8 (27.6%), PD- 7 (24.1%), missing-1 (3.4%)

Figure 2: Overall Survival (OS) of 27 months (blue curve) and progression free survival (PFS), of 15 months (green curve).

Figure 3: Overall survival difference between haematological responders, defined as partial response or better, (blue curve) versus non-responders, defined as stable or progressive disease, (green curve)

Table 1: Baseline patient characteristics.

	Patients n(%)/median(range)
Median age, years	65 (41-85)
Organ involvement	3 (1-6)
Cardiac	20 (69.0)
Renal	19 (65.5)
Liver	6 (20.7)
PNS	7 (24.1)
ANS	4 (13.8)
Soft tissue	9 (31.0)
Other	10 (34.5)
Median baseline:	
Creatinine (µmol/L)	100 µmol/L
NT-pro-BNP	786 ng/L
Albumin	36 g/L
Mayo Stage at Presentation,	
I	7 (31.8)
II	9(40.9)
IIIa	6 (27.3)
IIIb	0
Missing values	7 (24.1)
Prior treatment, median no. lines (range) and included:	4 (1-7)
Lenalidomide, n (%)	24(82.8)
Bortezomib	26 (89.7)
Melphalan	12 (41.1)
Thalidomide	10 (34.5)
Other	7 (24.1)
Refractory to: n(%)	
Velcade	2(6.9)
Lenalidomide	3(10.3)
Both	1(3.4)
Duration of pomalidomide	
Months	5.0 (1-29)
Median no. of cycles	4 (1-24)

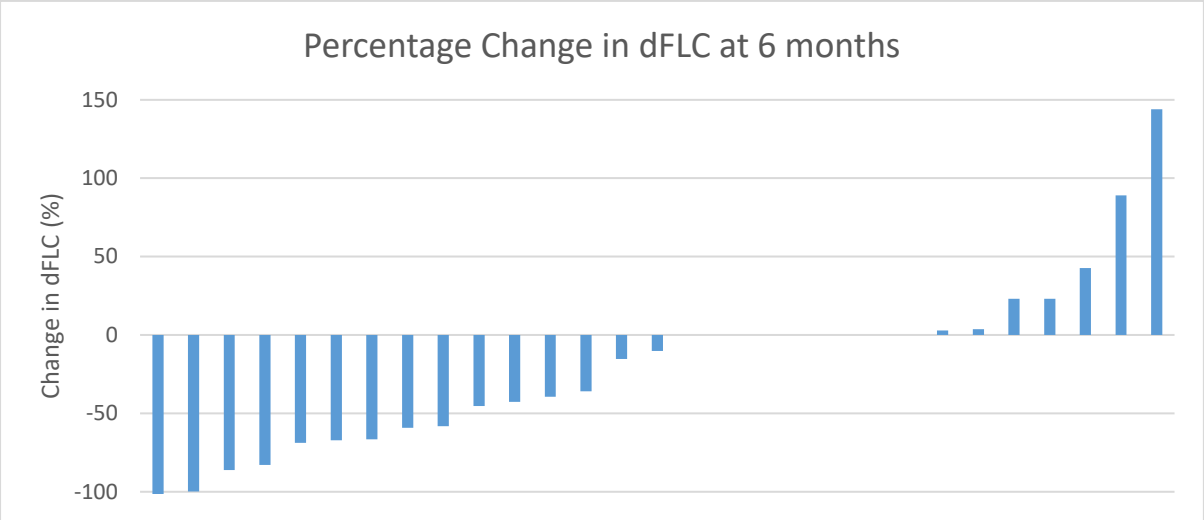
PNS= peripheral nervous system ; ANS= autonomic nervous system ; NT-pro-BNP= N-terminal pro-brain natriuretic peptide.

Table 2: A comparison of the three previous phase 2 trials of pomalidomide in AL amyloidosis, the Mayo group (Dispenzieri, *et al* 2012) the Boston group (Sanchorawala, *et al* 2016) the Italian group (Palladini, *et al* 2017) and the data presented here from the NAC (National Amyloidosis Centre).

	Mayo (2012) n(%)	**Boston (2016) n(%)**	**Italian (2017) n(%)**	**NAC (2018) n(%)**
Patient no.	33	27	28	29
Prior regimens				
Alkylator	30 (91)	/	21 (75) melphalan, 19 (88)cyclophosphamide	12 (41.1)
IMIDs	7(21)	13 (48)	11 (39)	26 (89.7)
PI	14 (42)	21 (78)	27 (96)	27 (90)
ASCT	16 (48)	16 (59)	6(21)	5(17)
Organs involved				
Heart	27 (82)	18 (67)	22 (79)	20 (69)
Kidney	12 (36)	14 (52)	11 (39)	19 (66)
Liver	1 (3)	/	1 (4)	6 (21)
Time from diagnosis to enrolment (months)	37	27	16	
Treatment				
Pomalidomide dose (mg)	2	2(d1-28), 3(d1-21) MTD 4mg	MTD 4mg	
Dexamethasone dose (mg)	40 weekly	20 weekly	20 weekly	
Duration of treatment (median no. of cycles)		6 (0-18)	6(1-30)	
Overall haematological response (6 months)	16(48)	12 (50)	17(61)	13(46)
VGPR/CR	6(18)		7(25)	
Organ response rates				
Cardiac	4(15)	/	/	
Renal	2(17)	1(7)	2(17)	
Overall Survival (months)	27.9	Not reached	26	27
Progression free survival (months)	14.1	17.8	16	15
Severe myelosuppression	15 (45)	7 (25.9)	2(7.1)	1 (3)
Treatment discontinued	27(82)	24(89)	26(93)	19 (66)
Due to AEs or patient refusal	11 (33)	5(29)	11 (39)	7 (39)
Due to PD or death	15 (45)	11 (41)	14 (50)	4 (24)

IMID= immunomodulatory drug (includes thalidomide, lenalidomide); PI= proteasome inhibitor; ASCT= autologous stem cell transplant; AE= adverse event; PD= progressive disease, MDT= maximum tolerated dose; VGPR= very good partial response; CR= complete response; NAC= National Amyloidosis Centre.

Figure 1



dFLC= difference in serum free light chain;

Figure 2

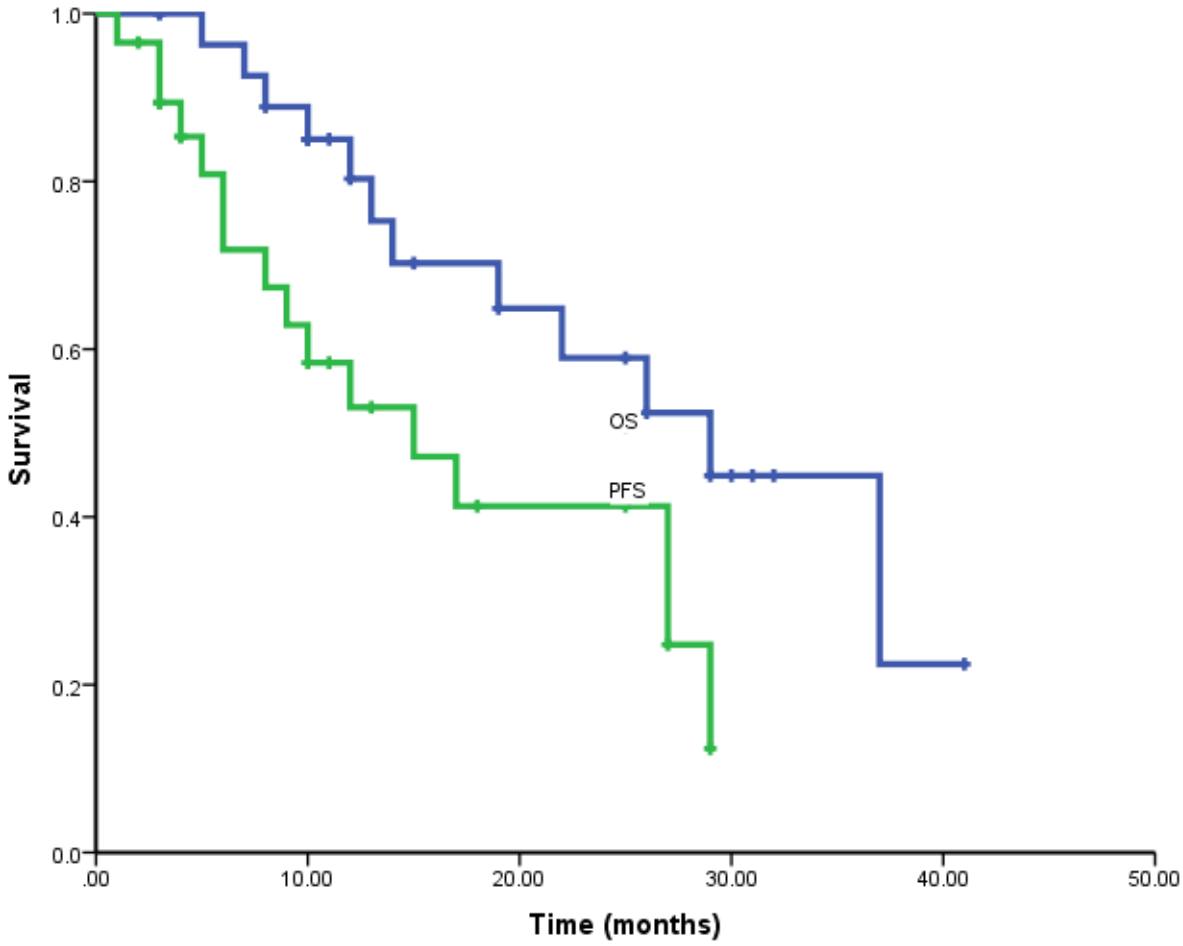
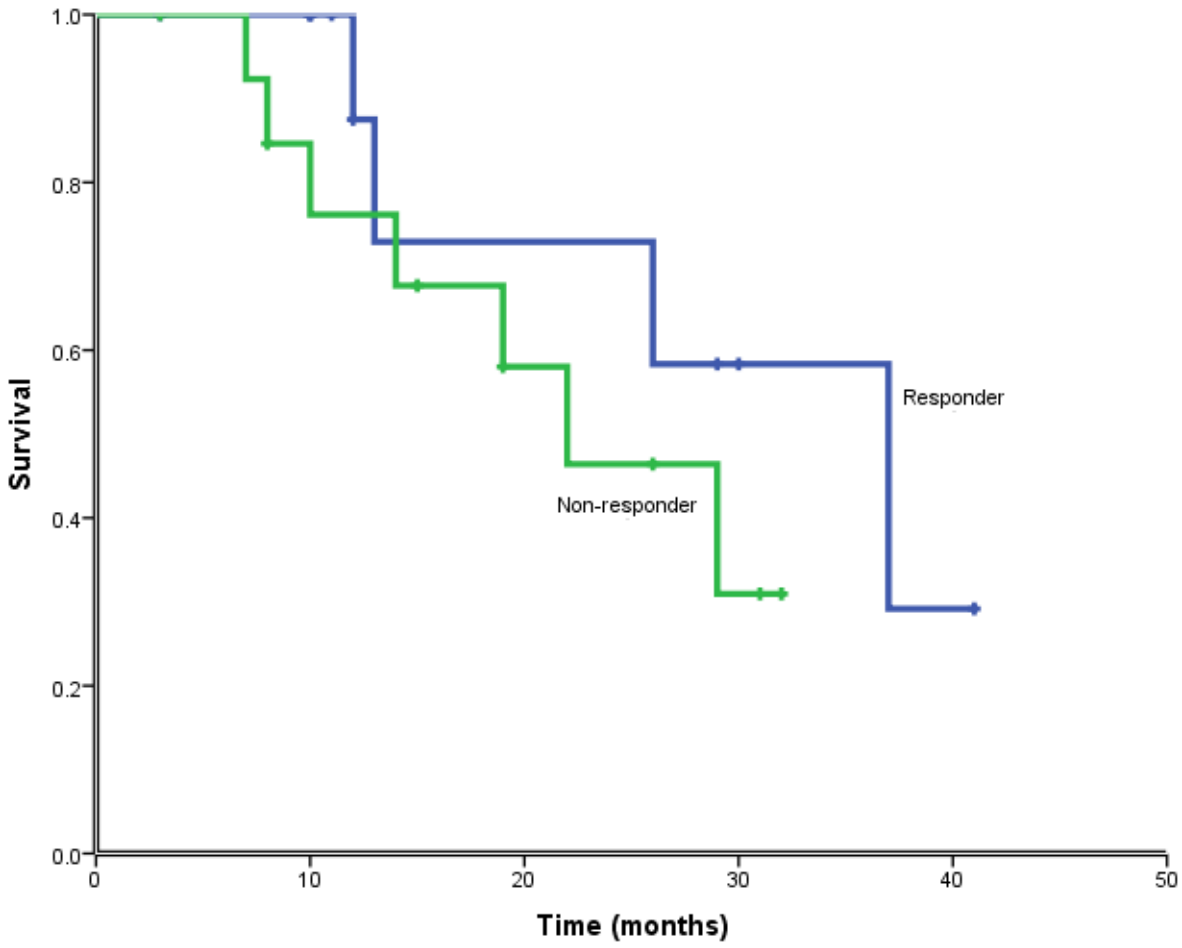


Figure 3


Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Time (months)
Responder
Non-responder