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# Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma

by Jeffrey Barnes, Eric Jacobsen, Yang Feng, Arnold Freedman, Ephraim Hochberg, Ann LaCasce, Philippe Armand, Robin Joyce, Aliyah Sohani, Scott Rodig, Donna Neuberg, David Fisher, and Jeremy Abramson

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# Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma

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*ABSTRACT*

**Background**

Diffuse large B cell lymphoma is an aggressive non-Hodgkin lymphoma with out a standard therapy for patients who relapse after or are not eligible for salvage autologous stem cell transplant. In vitro analysis of lymphoma cell lines has shown ability of everolimus to inhibit cell cycle progression in vitro and inhibitors of the mammalian target of rapamycin (mTOR) have already demonstrated single-agent activity in relapsed non-Hodgkin lymphoma including diffuse large B cell lymphoma , validating mTOR as a viable therapeutic target. We performed an open label phase II study of everolimus, an inhibitor of mTOR, in combination with rituximab to examine efficacy and tolerability in patients with relapsed/refractory diffuse large B cell lymphoma.

**Design and Methods**

Eligible patients were treated with everolimus 10mg by mouth once daily on days 1-28 of a 28 day cycle with rituximab administered weekly during cycle one and then on day one of subsequent cycles. Patients were treated for a total of 12 cycles or until disease progression. The primary end point was objective response rate, with secondary end points of toxicity, progression free survival, duration of response, and overall survival.

**Results**

Twenty six (24 evaluable) were enrolled with an overall response rate was 38% (90% CI [21%-56%]) with 3 complete responses and 6 partial responses among 24 patients. The median duration of response among responders was 8.1 months. At median follow up of 12 months, the overall survival rate was 37% (90% CI [20%, 54%]. The most common grade 3 to 4 toxicities were neutropenia, anemia, and thrombocytopenia.

**Conclusion**

Everolimus in combination with rituximab is well tolerated and demonstrates activity in relapsed diffuse large B cell lymphoma. Further studies of this combination are warranted.

*clinicaltrials.gov identifier: NCT00869999*

Key words: Diffuse large B cell lymphoma, everolimus, mTOR, rituximab, non-Hodgkin lymphoma.

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## *INTRODUCTION*

Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults, accounting for approximately 25,000 new cases each year in the United States. High-dose chemotherapy with autologous stem cell transplantation cures a minority of patients with relapsed or refractory disease, [1] but relapsed DLBCL remains an unmet medical need in patients who relapse after or are ineligible for high-dose chemotherapy due to chemotherapy insensitivity, advanced age, or comorbid disease.

Constitutive activation of the PI3K/AKT pathway and mTOR signaling has been noted to be a critical event in lymphoma pathogenesis.[2] Everolimus (RAD001) is an orally bioavailable inhibitor of mTOR. In vitro analysis of DLBCL cell lines has shown ability of everolimus to inhibit cell cycle progression in vitro by inducing G1 arrest and an associated decrease in the phosphorylation targets of mTOR, p70 s6 kinase and 4-EBP-1, as well as retinoblastoma protein, cyclin D3 and cyclin A.[3] mTOR inhibitors have already demonstrated single-agent activity in relapsed non-Hodgkin lymphoma including DLBCL, validating mTOR as a viable therapeutic target.[4, 5] These agents work primarily through cell cycle arrest, so we hypothesized that combining their cytostatic activity with a cytotoxic agent rituximab may yield increased clinical responses. In vitro studies show that everolimus and rituximab synergistically induce apoptosis in DLBCL cell lines.[3]

We report the results of a phase II study of everolimus 10mg daily in combination with rituximab. Included in this cohort are patients relapsed after or ineligible for autologous stem cell transplant for which the standard of care is undefined.

## *DESIGN AND METHODS*

### Patient Eligibility

Patients were eligible if they had previously received therapy and had refractory or relapsed disease. There was no limit on the number of prior therapies. Patients were required to have failed or not been eligible for autologous stem cell transplantation. Patients were ≥18 years old with histologically confirmed DLBCL, measurable disease, ECOG performance status ≤ 2, absolute neutrophil count ≥1,000/mcL, platelets ≥75,000/mcL, creatinine ≤ 2.0 X upper limit of normal (ULN), and AST(SGOT)/ALT(SGPT) ≤ 2.5 X ULN. Given known toxicities of everolimus, patients were required to have a fasting serum cholesterol ≤300 mg/dL and fasting triglycerides ≤ 2.5 x ULN. Patients with known leptomeningeal or brain metastases, HIV infection, severely impaired lung function defined as DLCO of < 50%, chronic active hepatitis, or prior treatment with an mTOR inhibitor were excluded. This study was conducted in accordance with the Declaration of Helsinki, approved by the institutional review board of participating centers, and registered with clinicaltrials.gov (NTC00869999).

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**Treatment Plan**

Everolimus was administered orally once daily at 5mg on days 1 through 14 of cycle 1. If tolerated, the dose was then increased to 10 mg for days 15 through 28 of cycle 1. For cycle 2 and beyond, patients continued to receive everolimus at 10mg daily continuously. Rituximab at 375 mg/m2 was administered intravenously weekly for four doses during cycle 1, and then on day 1 of cycles 2 through 6. After cycle 6, patients could receive an additional 6 months of everolimus monotherapy in the absence of disease progression or unacceptable toxicity.

Response was assessed every 2 cycles by PET/CT during cycles 1 through 6 and every 3 months during the monotherapy phase and interpreted according to the International Harmonization Project criteria.[6] Toxicity was assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). For patients who were unable to tolerate the protocol-specified dosing schedule, dose adjustments were permitted. For patients with hematologic toxicity (neutropenia defined as an ANC $\leq 1$ x$10^9$/L or thrombocytopenia defined as platelets $\leq 50$ x$10^9$/L) treatment was held until recovery to $\leq$ grade 2 and resumed at the initial dose with growth factor support for neutropenia. If cytopenias recurred, treatment again was held until recovery $\leq$ grade 2 and everolimus and rituximab were resumed with everolimus dose reduced by 50%. For patients with grade 3 non-hematologic toxicity, treatment was held until recovery to grade $\leq$1 then reintroduced with everolimus reduced to 5mg. Additional dose reductions to 5mg every third day were allowed. No more than 2 dose reductions were allowed. There were no rituximab dose reductions. Patients with grade 4 non-hematologic toxicity were removed from study.

mTOR activity was assessed by immunohistochemical analysis of formalin-fixed, paraffin-embedded tissue samples, where available, using phospo-70 s6 kinase antibodies (1:50) (Cell Signaling Technology, Danvers, MA). The intensity and proportion of tumor cell staining was assessed independently using standard light microscopy by two hematopathologists (ARS and SJR) who were blinded to treatment response. A case was considered positive for a given antibody if at least 30% of tumor cells were positive. Cell of origin was determined by immunophenotype with stains for CD10, BCL6, and Mum1 using the Hans algorithm as previously reported. [7]

**Study Design**

We employed a Simon's two-stage design. The primary endpoint was overall response rate (ORR). Twenty-five patients were required to distinguish between an unacceptable response rate of 10% compared to a response rate of 30% which would be considered promising for further study. Sixteen patients were enrolled in stage one, which required at least two responses to proceed to stage two. We then accrued an additional nine patients on stage two to complete accrual. Five or more out of the 25 were needed to respond in order to consider this regimen worthy of further study. The study had 90% power and 10% type 1 error rate.

Overall survival (OS), progression free survival (PFS) and duration of response (DOR) were secondary end points. OS was defined as the time from registration to death, or last

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known date of survival. PFS was defined to be the time from registration to progression or death. DOR was defined among responders only as the time interval between the date of first confirmed response and the date of disease progression or death. OS, PFS, and DOR curves were calculated using the Kaplan-Meier method with 90% confidence intervals calculated using Greenwood's formula.

## *RESULTS*

### Patient Characteristics

Between July 2009 and June 2010, 26 patients were enrolled. Twenty-five patients initiated treatment, and 24 are included in the efficacy analysis. One patient was removed due to progressive disease prior to receiving any study treatment. The other patient was treated, but the only site of measurable disease was subsequently resected 9 months after study entry and found to be infectious (atypical mycobacterium); this subject is included only in the toxicity analysis. Patient characteristics at the time of study entry are listed in table 1. The median age was 65 years (range 33-87). The median number of prior therapies was 4 (range 1-7)with 5 (21%) patients having undergone prior autologous stem cell transplant. Thirteen patients (54%) were refractory to initial therapy and 18 (75%) were refractory to rituximab, defined as progressive disease during or within 6 months of rituximab therapy. All patients had previously received rituximab plus CHOP or a CHOP-like regimen. Fourteen patients (58%) had a germinal center immunophenotype, 6 (25%) a non-germinal center immunophenotype, and information was not available for 4 patients (17%).

### Efficacy

Twenty-four patients were evaluable for response. The median number of cycles was 2 (range 1-12) and 3 (13%) subjects received more than 6 cycles. The ORR was 38% (90% CI [21%-56%]) (Table 3). There were 3 complete responses (CR) and 6 partial responses (PR). Eight of nine responders had their best response after 2 cycles of therapy with one patient with a PR after 2 cycles converting to a CR after 4 cycles. Six of the 9 responders had progressed on their prior chemotherapy, 2 had relapse within 3 months of autologous transplant, and 1 was more than 2 years from RCHOP but not eligble for transplant due to advanced age. The median DOR was 8.1 months (Figure 2A). The median PFS was 2.9 months (90% CI [1.8, 3.8]) (Figure.1A). At a median follow up of 12 months, the PFS is 22% (90% CI [8%-37%]. Fifteen subjects have died at last follow-up. The median OS was 8.6 months (90% CI [4.9-16.3]). At a median follow up of 12 months, the OS is 37% (90% CI [20%, 54%] (Figure.1B).

All three patients with a CR are alive and free of disease (Figure 2B). One patient was removed from study after 5 cycles and consolidated with an allogeneic stem cell transplant. One patient with progressive disease after salvage chemotherapy who then under went allogeneic transplant with out a response began everolimus on day 174 post allo and had a complete response to study treatment after 2 cycles. This patient then went on to have consolidation with 3 donor lymphocyte infusions (the first DLI occurring 118 days after starting everolimus) and remains disease free. One patient completed 12 cycles of everolimus and is disease free 12 months after completion of therapy. Of the six

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patients with a partial response, 3 are alive. Three patients received additional therapy after progression including two with allogeneic transplants and remain alive. One patient in a partial response after two cycles died in a motor vehicle accident. Two patients died of progressive lymphoma.

Cell of origin immunophenotype was available for 20 of 25 patients with no clear pattern of response among GCB and non-GCB subtypes (Table 4A). There was also no correlation with IPI score at relapse and with response. The phospho-70 s6 kinase immunophenotypic marker of mTOR pathway activation was available for 13 patients (Table 4B), 11 from the pretreatment specimen and 2 at the time of relapse. One patient had biopsies available both at pre-treatment and relapse time points which showed no mTor activation at either time point. All patients with a CR had evidence of mTOR activation, but 6 of 8 non-responders also had evidence of mTOR activation with no difference seen between the two groups.

**Safety and Tolerability**

The most common grade 3 to 4 toxicities were neutropenia, anemia and thrombocytopenia (Table 2). Eleven patients had treatment held for toxicity (6 for neutropenia, 3 for thrombocytopenia, and 2 for nausea). Only 1 patient was not escalated from 5mg to 10mg of everolimus during cycle 1 due to thrombocytopenia. Four patients required dose reduction to 5mg daily (2 due to neutropenia, 1 due to thrombocytopenia, and 1 due to fatigue and nausea). Disease progression was the most common cause for discontinuation of therapy, with 18 (72%) patients stopping therapy due to progression. One patient stopped therapy after 8 cycles due to toxicity (pneumonitis), 1 stopped due to investigator decision, and 1 patient died in an automobile accident while in partial remission. One patient completed a full year of everolimus therapy. One patient died of hepatitis B reactivation after removal from study for disease progression. This patient was hepatitis surface antibody positive, surface antigen negative, and viral DNA undetectable prior to study entry. This patient had hepatitis B reactivation 3 months after their final study treatment and after additional rituximab containing salvage therapy.

## *DISCUSSION*

Relapsed and refractory DLBCL remains an unmet medical need given the low rate of cure in patients relapsing after R-CHOP chemotherapy.[1] The rationale for everolimus in DLBCL is based on preclinical data showing dependence on the mTOR/PI3kinase pathway. [2] In a phase II study of everolimus monotherapy in 77 patients with relapsed NHL, 47 had DLBCL, among whom the ORR was 30%, with no complete responses [4]. The median PFS and DOR for the entire cohort were 3.0 and 5.7 months, respectively. In our study of the combination of everolimus and rituximab, we report an encouraging ORR of 38%. While the value of the addition of rituximab to everolimus cannot be ascertained from the current study, the combination included 3 complete responses, and 2 patients used protocol therapy as a bridge to allogeneic stem cell transplantation, both of whom are alive and free of disease at a median of 19 months (range 17-24) (Figure 2). Among patients who did not go on to stem cell transplantation, two patients achieved long-term disease control following everolimus/rituximab treatment (one completing 12

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months of therapy in a CR and one stopping after 9 months due to pneumonitis in a PR with progression 5 months later).

Our response rate of 38% in the context of a heavily pre-treated DLBCL population is particularly encouraging given that greater than half of patients were refractory to initial treatment with R-CHOP or R-CHOP-like regimens, and 75% were considered rituximab-refractory at the time of enrollment. Limited data exist on rituximab monotherapy in relapsed/refractory patients. A Japanese phase II trial reported a 35% ORR to rituximab monotherapy, but all patients were rituximab-naive and the majority had received only 1-2 prior regimens, while the majority of our patients were rituximab-refractory with a median of 4 prior regimens. [8] Accordingly, we expect the response rate to rituximab monotherapy in our population to be quite low.

The combination of everolimus and rituximab was well tolerated. Adverse events were similar to and not increased compared to those seen in studies of everolimus monotherapy. Unlike previous trials of everolimus, clinically significant hyperglycemia and hyperlipidemia were uncommon in our study, and only a minority of patients required dose reductions for toxicity.

DLBCL constitutes a heterogeneous group of diseases with diverse biology and outcomes with modern therapy. Given the heterogeneity, investigation of novel agents must also seek prospective biomarkers predictive of response. In addition to predicting response to initial anthracycline and rituximab-based therapy, cell of origin may also be predictive of response in relapsed/refractory DLBCL. For instance, lenalidomide was shown to have a higher response rate in relapsed/refractory DLBCL of non-germinal center origin as assessed by the Hans immunohistochemical algorithm.[9] As noted in table 4, we found that cell of origin did not predict response in this small sample.

Level of phosphorylation of the 70 S6 kinase has been shown to predict response to the mTOR inhibitor temsirolimus in renal cell carcinoma, [10] but we found no correlation with level of activation of the mTOR/PI3Kinase pathway in our exploratory analysis. This analysis was performed on original diagnostic biopsy tissue, where available, and therefore the time of fixation was not controlled. Since most excisional biopsies of lymphoma sit outside of formalin for several minutes while the tissue is triaged for lymphoma work-up it is possibly this is a pre-analytic variable known to affect phosphorylation markers resulted in false negatives and may have affected our results.

In summary, we report that everolimus plus rituximab induces responses in heavily pre-treated patients with DLBCL and may serve as a bridge to allogeneic stem cell transplantation. Studies examining the role of mTOR partners' raptor and rictor in predicting responders are planned for future studies.[11] Clinical studies are also underway evaluating mTOR directed therapy earlier in the course of this disease and in combination with additional agents to overcome resistance thought to occur through escape via the AKT pathway. These studies are likely to identify responders to this therapy and to improve outcomes for patients with resistant DLBCL.

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## AUTHORSHIP CONTRIBUTION

| | |
|---|---|
| *Jeffrey Barnes* | *Designed study, recruited patients, manuscript writing, final approval* |
| *Eric Jacobsen* | *Recruited patients, manuscript writing, final approval* |
| *Yang Feng* | *Data collection and analysis, manuscript writing, final approval* |
| *Arnold Freedman* | *Recruited patients, manuscript writing, final approval* |
| *Ephraim Hochberg* | *Recruited patients, manuscript writing, final approval* |
| *Ann LaCasce* | *Recruited patients, manuscript writing, final approval* |
| *Philippe Armand* | *Recruited patients, manuscript writing, final approval* |
| *Robin Joyce* | *Recruited patients, manuscript writing, final approval* |
| *Aliyah Sohani* | *Pathology review, manuscript writing, final approval* |
| *Scott Rodig* | *Pathology review, manuscript writing, final approval* |
| *Donna Neuberg* | *Data collection and analysis, manuscript writing, final approval* |
| *David Fisher* | *Recruited patients, manuscript writing, final approval* |
| *Jeremy Abramson* | *Designed study, recruited patients, manuscript writing, final approval* |

## AUTHORSHIP DISCLOSURES

| | |
|---|---|
| *Jeffrey Barnes* | *None relevant to the publication* |
| *Eric Jacobsen* | *None relevant to the publication* |
| *Yang Feng* | *None relevant to the publication* |
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| *Ephraim Hochberg* | *None relevant to the publication. Has received consulting fees from Seattle Genetics, Sigma Tau, Genentech, Millenium, Biogen, Amgen, and Proventys.* |
| *Ann LaCasce* | *None relevant to the publication* |
| *Philippe Armand* | *None relevant to the publication* |
| *Robin Joyce* | *None relevant to the publication* |
| *Aliyah Sohani* | *None relevant to the publication* |
| *Scott Rodig* | *None relevant to the publication* |
| *Donna Neuberg* | *None relevant to the publication* |
| *David Fisher* | *Received consulting fees from Genentech* |
| *Jeremy Abramson* | *Has received consulting fees from Novartis and Genentech relevant to the publication.* |

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**Table 1.** Patient characteristics at enrollment for eligible and treated patients.

| | N=24 |
|---|---|
| Mean Age (range) | 65 (33,88) |
| Age >60 | 14(58%) |
| Sex, Female | 10 (42%) |
| Stage III or IV at relapse | 17 (71%) |
| Elevated LDH | 16 (67%) |
| >1 extra nodal site | 10 (42%) |
| ECOG PS 0-1 | 21 (88%) |
| IPI 3-5 | 14 (58%) |
| Median # prior therapies (range) | 4 (1,7) |
| Median months from diagnosis (range) | 14 (4, 261) |
| Refractory to initial therapy | 13 (54%) |
| Refractory to rituximab | 18 (75%) |
| Prior autologous stem cell transplant | 5 (21%) |
| GCB/Non-GCB/N/A | 14(58%)/ 6(25%)/ 4(17%) |

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**Table 2.** Toxicities (adverse events considered at least possibly related to study treatment).

| | Treatment-related toxicities by grade | | | | |
|---|---|---|---|---|---|
| Adverse Event | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Grade 3-4 (%) |
| **General** | | | | | |
| Fatigue | 6 | 2 | 0 | 0 | 8 |
| Anorexia | 3 | 0 | 0 | 0 | 0 |
| Dry mouth | 1 | 0 | 0 | 0 | 0 |
| Mucositis | 1 | 0 | 0 | 0 | 0 |
| Rash | 3 | 0 | 0 | 0 | 0 |
| **Hematologic** | | | | | |
| Neutropenia | 3 | 3 | 3 | 0 | 24 |
| Anemia | 8 | 2 | 0 | 0 | 40 |
| Thrombocytopenia | 8 | 3 | 0 | 0 | 12 |
| Leukocytosis | 6 | 1 | 1 | 0 | 8 |
| **Gastrointestinal** | | | | | |
| Constipation | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 1 | 0 | 0 | 0 | 0 |
| Dysphagia | 1 | 0 | 0 | 0 | 0 |
| Viral Hepatitis | 0 | 0 | 0 | 1 | 4 |
| **Metabolic** | | | | | |
| Hyperglycemia | 6 | 0 | 0 | 0 | 0 |
| Hypokalemia | | 1 | 0 | 0 | 4 |
| Hyposphophatemia | | 0 | 0 | 0 | 0 |
| Hypertriglyceridemia | 4 | 2 | 0 | 0 | 8 |
| Hyperuricemia | 0 | 0 | 1 | 0 | 4 |
| **Infection** | | | | | |
| Infection With grade ¾ ANC | 0 | 1 | 0 | 0 | 4 |
| Infection with <grade 3 ANC | 0 | 4 | 0 | 0 | 0 |
| **Pulmonary** | | | | | |
| Dyspnea | 2 | 0 | 0 | 0 | 0 |
| Pneumonitis | 0 | 1 | 0 | 0 | 4 |

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**Table 3.** Efficacy.

| BEST RESPONSE | N=24 (%) |
|---|---|
| Overall Response | 9 (38%) (90% CI [21,56]) |
| Complete Response | 3 (13%) |
| Partial Response | 6 (25%) |
| Stable Disease | 2 (8%) |
| Progressive Disease | 13(54%) |

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**Table 4.** Response assessment by cell of origin and activation of the mTOR pathway.

A) Response by cell of origin

| | Responders | Non-Responders |
|---|---|---|
| GCB | 6 | 8 |
| Non-GCB | 2 | 4 |
| COO N/A | 1 | 4 |

B) Response by activation of mTOR pathway

| | Responders | Non-Responders |
|---|---|---|
| pS6 + | 4 | 6 |
| pS6- | 1 | 2 |
| N/A | 4 | 8 |

GCB – Germinal center B cell; COO – cell of origin; pS6 – phsophoS6 kinase; N/A – tissue not available

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## FIGURE LEGENDS

**Figure 1.** Progression free (panel A) and overall survival (panel B) for the 24 evaluable patients.

**Figure 2. A –** Kaplan-Meier curve of the duration of response for the 9 responding patients. B . Outomes of the 9 responders. Blue bars denote response duration on therapy to day 0 the first day off treatment. Yellow bars then demonstrate progression free survival post treatment. The three patients with ongoing remissions at last follow up are indicated with a (►) symbol. The 3 patients with a compete response to everolimus are indicated with a (+) symbol. One patient received an allogeneic stem cell transplant, indicated by a (*) symbol, prior to starting everolimus also received one donor lymphocyte infusion (#) during everolimus treatment and two additional DLIs after completing everolimus.

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**Figure 1**

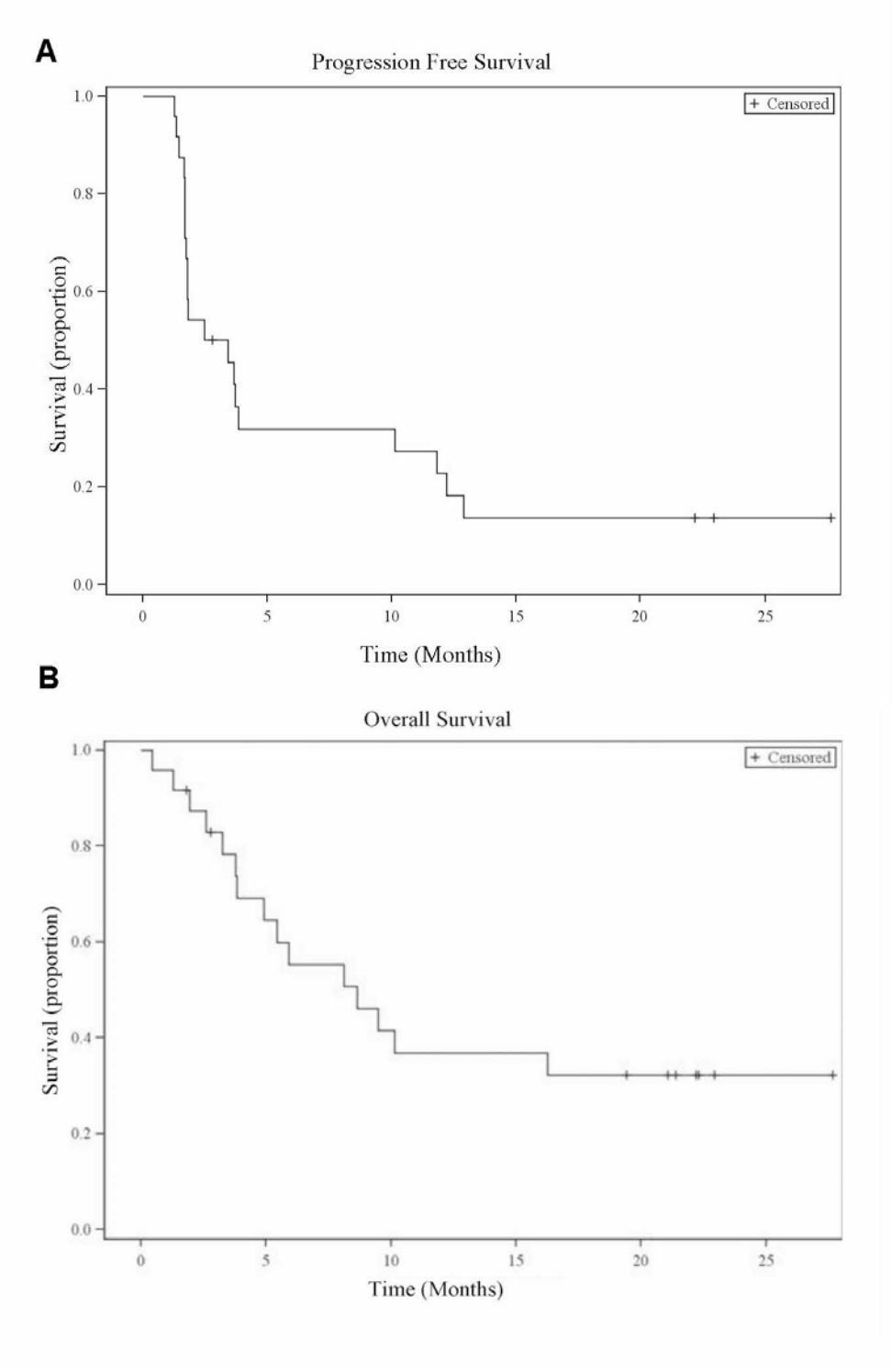

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**Figure 2**