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Biosimilar Rituximab (Redditux) Added to CHOP Chemotherapy for De-novo Diffuse Large B-cell Lymphoma Patients: Real-life Single Center Experience
Biyobenzer Rituksimab (Redditux) ile CHOP Kemoterapisinin Yeni Tanı Diffüz Büyük B-hücreli Lenfoma Hastalarında Kullanımı: Gerçek Yaşam Tek Merkez Deneyimi

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ABSTRACT

Objective: Redditux®(RED), the biosimilar rituximab, was approved in Turkey for all indications of the original Mabthera®(MAB) in March 2018. The aim of our study was to evaluate the efficacy and safety of RED in de-novo DLBCL.

Materials and Methods: Fifty-one patients received RED combined with CHOP regimen. The median follow-up was 31 months. The historical control group included 219 patients treated with MAB-CHOP regimen and the median follow-up time was 38 months. We compared the response rates and survival outcomes of the RED- and MAB-CHOP treated cohorts.

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Results: In the RED cohort, the overall response rate (ORR) at the end of the treatment protocol was 86%, with 37 CR (72.5%) and 7 PR (13.5%). In the historical MAB cohort, the overall response rate was 84%, with a CR and PR rate of 82% and 2%, respectively.
The 24-month PFS rates were 73.76% (95%CI 0.59-0.84) and 85.2 (95%CI:0.79-0.90) for RED and MAB cohorts, respectively (p=0.0106). The 24-month OS rates were 78.4% (95%CI:0.64-0.87) and 81.4% (95%CI:0.75-0.86) for RED and MAB cohorts, respectively (p=0.7461). For pts with high R-IPI score; the 24-month PFS was 45.5% (95%CI:0.17-0.71) and 63% (95%CI:0.37-0.80) for RED and MAB cohorts, respectively (p=0.0711).
In the RED cohort, CNS relapse was significantly increased compared to MAB cohort (10% vs 1.83%, p=0.004). Among our RED cohort, bone involvement at the time of diagnosis was a risk factor for CNS relapse (p=0.028). Thirteen pts died in the follow-up. There was not any serious adverse event causing the cessation of the drug.
Conclusion: RED has similar ORR to MAB. However, PFS rates were worse in the RED cohort. Additionally, CNS relapse ratio was a major concern for our RED cohort. Large prospective controlled studies and real-life data with longer follow-up are needed to document the non-inferiority of RED compared to MAB.
Keywords: Rituximab, biosimilar, Redditux, diffuse large B cell lymphoma, non-Hodgkin lymphoma

ÖZ
Amaç: Rituksimab biyobenzeri olan Redditux®(RED), ülkemizde Mart 2018'de original Mabthera®(MAB) molekülünün tüm endikasyonlarında kullanılmak üzere onaylandı. Çalışmamızda, yeni tanı DBBHL hastalarında RED'in etkinliğini ve güvenirliğini değerlendirmeyi amaçladık.
Yöntem ve Gereçler: Elli bir hasta RED ile birlikte CHOP tedavisi aldı. Ortanca takip süresi 31 aydı. Tarihsel control grubunda, MAB-CHOP ile tedavi edilmiş 219 hasta mevcuttu ve ortanca takip süresi 38 aydı. RED ve MAB-CHOP ile tedavi edilmiş grupların tedavi sonuçlarını karşılaştırdık.
Bulgular: RED grubunda genel yanıt oranı (GYO) %86 iken, 37 hastada TY (%72,5) ve 7 hastada KY (%13,5) elde edildi. Tarihi MAB grubunda ise GYO %84 iken TY ve KY oranları sırasıyla %82 ve %2 idi. 24-aylık progresyonsuz sağkalım (PSK), RED ve MAB grupları için sırasıyla %73,76(95%CI 0.59-0.84) ve %85,2(95%CI:0.79-0.90) olarak saptandı (p=0.0106). 24-aylık genel sağkalım (GSK) oranları ise RED ve MAB grupları için sırasıyla %78,4 (95%CI:0.64-0.87) ve %81,4 (95%CI:0.75-0.86) idi (p=0.7461). Yüksek R-IPI skoru olan hastalarda 24-aylık PSK, RED ve MAB kohortları için sırasıyla %45,5(95%CI:0.17-0.71) ve %63 (95%CI:0.37-0.80) bulundu (p=0.0711).
RED grubunda MSS nüksü riski MAB grubuna göre anlamlı derecede artmış bulundu (%10'a karşı %1.83; p=0.004). RED kohortunda, tanı sırasında kemik tutulumu olması, MSS nüksü için risk faktörü olarak tespit edildi (p=0.028). Takipte 13 hasta vefat etti. İlacın sonlanmasına neden olacak ciddi yan etki gözlenmedi.
Sonuç: RED, orijinal MAB molekülüne benzer GYO gösterdi. Ancak RED grubunda, MAB grubuna göre PSK oranları daha kötüydü. Ayrıca RED kohortumuzda MSS nüksü önemli bir sorundu. RED'in MAB'a eşdeğer etkinliğini ve güvenirliğini doğrulamak için yüksek katılımlı prospektif kontrollü çalışmalar, uzun takipli gerçek yaşam verilerine ihtiyaç vardır.
Anahtar kelimeler: Rituksimab, biyobenzer, Redditux, diffüz büyük B hücreli lenfoma, non-Hodgkin lenfoma

INTRODUCTION

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Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphomas (NHL). Introduction of the biological product rituximab, a chimeric anti-CD20 human immunoglobulin G1 monoclonal antibody, to the B-cell NHL treatment significantly improved the response rates in DLBCL [1]. Biosimilars are highly similar to a reference biological products from the point of view of purity, potency and safety [2]. Although they are identical to reference product on an amino acid sequence level, biosimilars have some differences on a protein level [3].

Redditux® (RED), the biosimilar rituximab first approved in India in 2007 [4], was approved in Turkey for all indications of the reference molecule Mabthera® (MAB) in March 2018. There are scarce clinical trials and real-life experiences in hematological malignancies, including diffuse large B cell lymphoma (DLBCL). Since 2019, our hospital administration decided to use more affordable biosimilar RED in virtue of its cost advantage after approval from ministry of health and being reimbursed.

Here we present data on real-life experience with the biosimilar rituximab RED in de-novo DLBCL. We previously published our preliminary results [5]. The aim of current analysis is to document the efficacy and safety of RED in de-novo DLBCL by comparing with historical DLBCL cohort [6] treated with MAB-based regimen.

METHOD

All of the patients were diagnosed with de novo DLBCL using World Health Organization criteria [7].Cell of origin was determined according to the Hans' protocol [8]. Bone marrow biopsy was applied to all patients at the time of diagnosis. Staging and response assessment was made by using PET/CT imaging. Ann Arbor classification was used to stage the disease [9]. Tumor mass size greater than 10 cm in diameter was defined as 'bulky disease'[10]. Patients with CNS involvement were not included in the study. Complete response (CR), partial response (PR), progression, refractory disease and relapse were defined according to ECOG criteria in the MAB cohort [11] and according to Lugano classification in the RED cohort [12]. All the patients were treated at the same institution with R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) given as three-weekly and Redditux was used as rituximab (RED-CHOP). Treatment algorithm was designed according to ESMO guidelines [13]. CNS prophylaxis was with intrathecal methotrexate (IT-MTX) given in patients having a high CNS-IPI score for equal or greater than 4 [14].

Results regarding efficacy and safety were compared with a cohort in which the patient's received rituximab as Mabthera (MAB)-CHOP. These data were collected electronically by permission of Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Hematology team. Continuous variables were presented as medians and the number of categorical variables were presented. Differences between groups were analyzed with the $\chi 2$ test. Both the OS and PFS were censored at the last date for which information was available. The median duration of response, PFS, and OS rates along with their two-sided 95% confidence intervals (CIs) were estimated using the Kaplan– Meier method. Survival functions were compared using log- rank test. We also performed nearest neighborhood matching analysis to match our RED and MAB cases.

Our study was approved by Istanbul Medical Faculty ethical committee (2019/1454) and conducted in accordance with the rules of Good Clinical Practice and Helsinki Declaration. Statistical analyses were done with STATA MP-17.

RESULTS

General Characteristics

Between February 2019 and September 2019, a total of 51 DLBCL patients received RED-CHOP regimen at Istanbul Medical Faculty. The median age was 60 years (range: 17-79) and 57% of the cohort was male. Half of the cases had germinal center B cell subgroup. Twenty-eight patients (55%) had advanced stage (III-IV) disease. Bone marrow involvement was

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observed in nine cases (17.7%). R-IPI score was low in 8 patients whereas it was intermediate and high in 22 and 18 patients, respectively (Table 1).

The historical control group included 219 patients treated with MAB-CHOP regimen. Almost half of the patients were male. One third of the cases had disease of GCB origin and another third of non-GCB origin. The ratio of patients with unknown cell of origin was higher compared to the actual cohort. Fifty-two percent of cases had advanced stage disease and 16.6% of the historical cohort had bone marrow involvement at the initial presentation. R-IPI score was high in 33.3% of the patients (Table 1).

Response Rates

Median 6 cycles of biosimilar (range:4-8) were administered. Four pts' CNS-IPI score was high and received intrathecal methotrexate injections as planned. Thirteen pts having bulky disease at diagnosis received involved field radiotherapy additional to medical therapy [13]. In the RED cohort, the overall response rate (ORR) at the end of the treatment protocol was 86%, with 37 CR (72.5%) and 7 PR (13.5%). Seven patients had primary refractory disease. In the historical MAB cohort, the overall response rate was 84%, with a CR and PR rate of 82% and 2%, respectively. Around 14% of cases were refractory in RED cohort, whereas this ratio was 15.6% in MAB cohort. The overall response rates in patients with high R-IPI score were 72.2% and 68.5% in RED and MAB cohorts, respectively. The response rates of the RED and historical MAB cohorts are summarized in Table 2.

Survival Rates

The follow-up period was median 31 (range:8-39), and 38 months (range: 1-106) in RED and Mab cohort, respectively.

In our RED cohort, apart from 7 cases with primary refractory disease, 10 cases had progressive disease in the follow-up. Median time to progression was 14.5 months for these 10 cases (range:7-29 months).

The 24-month PFS rates were 73.76% (95% CI: 0.59-0.84) and 85.2 (95% CI: 0.79-0.90) for the entire RED and MAB cohorts, respectively. The log-rank test for equality of survivor functions favored MAB for PFS analysis (p=0.0106) (Figure 1A).

The 24-month OS rates were 78.4% (95% CI: 0.64-0.87) and 81.4% (95% CI: 0.75-0.86) for RED and MAB cohorts, respectively (p=0.7461) (Figure 1B). Thirteen patients died in the RED cohort.

Among subgroup analysis regarding patients with high R-IPI score the 24-month PFS was 45.5% (95% CI: 0.17-0.71) and 63% (95% CI: 0.37-0.80) for RED and MAB cohorts, respectively (p=0.0711) (Figure 2A). The 24-month OS rates for the same group was 46% (95% CI: 0.17-0.71) and 53% (95% CI: 0.34-0.69) for RED and MAB patients, respectively (p=0.7461) (Figure 2B).

Nearest Neighborhood Matching Analysis

We evaluated our results also with nearest neighborhood matching analysis to match RED and MAB cases for age (<60 vs ≥60), gender, DLBCL cell type, disease stage (high vs low), LDH level (normal vs high), performance score (ECOG 0-1-2 vs 3-4) and number of extranodal sites (<2 vs ≥2). The 24-month PFS rates for matched cases in RED and MAB cohort were 75.33% (95%CI: 0.58-0.86) and 88.99% (95%CI: 0.81-0.94), respectively (p=0.0074). The CNS relapse risk is also increased in RED cohort among matched cases (p=0.001).

CNS relapse

In the RED cohort, five cases (10%) experienced CNS relapse. Two of them had CNS-IPI score were 1 and 3 at diagnosis, did not receive prophylactic IT-MTX and had CNS involvement developed during PD.

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The remaining three cases had achieved CR (n=2) or PR (n=1) at the end of first line treatment. The patients with CR had initial CNS-IPI scores of 0 and 2. Only one patient who had PR had high CNS-IPI score of 5 at the diagnosis and had received IT-MTX as four times.

Of these 5 cases, 3 had bone involvement, defined as increased FDG uptake pointing to lymphoma involvement in the bone tissue excluding the bone marrow at the time of diagnosis. When we evaluated total cohort from the point of view of risk factors for CNS disease, we detected those three of eleven cases with bone involvement experienced CNS disease, which was the only risk factor reflecting a statistical significance (p=0.028).

Among the historical cohort MAB-CHOP received group, the CNS relapse rate as being 1.83% was significantly low compared to in RED cohort (p=0.004). Among 25 cases who had bone involvement, only one had CNS relapse (p=0.389).

Adverse Events and Deaths

RED-CHOP protocol related AEs were reported in 51% (n=26) of patients (Table 3). We should state that these AEs does not only include RED related, but also CHOP related AEs. Dose modification was not needed in any patient in RED cohort. Most common AE was neutropenia seen in 39% of cases (n=20). Grade 2 infusion reactions (shivering, nausea, fever) requiring medical intervention in 20% of pts, accompanied with rash in half of them. Grade 3&4 AEs were leucopenia (n=2; 4%), neutropenia (n=20; 39%) febrile in 2 cases, anemia (n=6; 12%), thrombocytopenia (n=3; 6%). There was not any serious adverse event ending in the cessation of the drug. The safety results could not be compared to historical MAB cohort due to missing data.

Thirteen pts died in the follow-up. Causes of death were PD (n=8, two cases with CNS involvement), infection during allogeneic stem cell transplantation conditioning (n=1), post-COVID herpes zoster infection (n=1), COVID related pulmonary disease (n=1), renal failure (n=1) and unknown (n=1).

Discussion

Comparing to the reference molecules, biosimilars have minor differences on a protein level [3]. With the introduction of biosimilars, the physicians had more choice in prescription [15]. Roy et al compared RED, which is licensed in India since 2007, with MAB in de-novo DLBCL patients [4]. In a total of 223 patients, 101 received MAB and 72 patients received RED accompanied CHOP regimen. The ORR was 89% and 95% for original molecule and biosimilar, respectively. Although the ORR was shown to be better in the RED group, the number of patients with advanced stage disease (44% vs 56%), ECOG score >1 (14% vs 19%), bulky disease (24% vs 31%), high revised-IPI score (15% vs 23%) were less compared to the MAB cohort. The 5-year PFS and OS rates were 81% vs 72% and 76% vs 66% for RED vs MAB groups, respectively. There was not a statistically significant difference in survival rates [4]. In the study published by Bankar et al, the risk factors were more equilibrated between RED and MAB cohorts [16]. The ORR was 82.6% and 88.3% for RED and MAB, respectively. The 5 year PFS and OS rates were also similar [16]. DRL-rituximab, an FDA approved rituximab biosimilar, was reported to have comparable ORR rates (82%; 95% CI 0.70-0.90) to MAB (84.8%; 95% CI 0.73-0.92) in a cohort of 151 DLBCL patients[17]. There were not any statistically significant differences in event free survival, relapse or progression and OS rates. The grade 3 or 4 AE rates were 72.3% and 84% in the DRL-rituximab and MAB groups, respectively. Among thirteen patients who discontinued study drug, eight of them were in the DRL-rituximab cohort and five of them were in the MAB cohort. Authors concluded that the DRL-rituximab and MAB had comparable safety, efficacy, immunogenicity and progression rates [17]. In the Dutch population-based study, Brinx et al included 3553 and 876 patients receiving R-originator and R-biosimilar patients, respectively [18]. The authors reported similar ORR rates, being 85% versus 84% for R-originator versus R-biosimilar groups, respectively (p=0.326). Three-year OS rates in cases treated with original MAB compared to rituximab

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biosimilars (73% vs 73%, respectively). PFS rates were not reposted in this study [18]. Other biosimilars, RTXM83 [19], HLX01 [20], Truxima [21] and IBI301 [22] had similar ORR and safety profiles compared to MAB.

The ORR for RED receiving patients was 86.3% in our cohort, with 37 CR (72.5%) and 7 PR (13.5%). One patient had SD whereas 6 patients had PD. Regarding the patients who had stage 2 to 4 diseases; the ORR was similar (85.3%). The 24-month estimated PFS was 73.76% and OS was 78.4%. Compared to the historical trial [1], our CR rates in stage 2-4 patients seem to be slightly lower (69% vs 75%), although the ORRs are quite similar (86% vs 82%).

Comparing with our historical control cohort, the 24-month PFS rates were 73.76% (95% CI: 0.59-0.84) and 85.2 (95% CI: 0.79-0.90) for RED and MAB cohorts, respectively. The log-rank test for equality of survivor functions favored MAB for PFS analysis (p=0.0106). For pts with high R-IPI score; the 24-month PFS was 45.5% (95% CI: 0.17-0.71) and 63% (95% CI: 0.37-0.80) for RED and MAB cohorts, respectively (p=0.0711).

The characteristics of the RED and MAB cohorts were similar, and the only difference was the ratio of low performance patients, being higher in RED cohort. However, R-IPI score distribution were similar, and we think that the higher percentage of low performance cases cannot be responsible of this significant difference in PFS rates. There were more cases in the GCB subgroup in RED cohort. This may be due to relatively higher rate of cases with undetermined cell of origin in the MAB cohort. The PET/CT was widely used in response evaluation in the RED cohort, which may have contributed to the difference in PFS rates between the RED and the historical MAB cohorts. It may be speculated that COVID-19 related deaths may have contributed to this difference, however postulating these two cases were alive did not affect the statistical significance of the difference between PFS rates. The population pharmacokinetics revealed that the volume of central compartment was 0.95 L for redditux whereas it varied between 1.8 and 3.9 L for Mabthera [23]. Tout et al commented that this means an estimated central volume of distribution 68-76% lower compared to Mabthera [24]. Additionally, they calculated the elimination half-life of Redditux as 11.2 days, which varies between 20.2 and 100.5 days for Mabthera [24]. These pharmacokinetic differences may be the cause of PFS differences between our RED and MAB cohorts.

Compared to the CNS relapse rates ranging between 2-4% reported in the literature [25,26,27], our result was unexpectedly high in our cohort (10%). We applied IT-MTX in high-risk patients and recent data showed that the CNS relapse risk is similar in patients receiving IT-MTX or high dose methotrexate [28]. Among 5 cases who had CNS disease, only one had high CNS-IPI score. Additionally, three of these five cases had initial bone involvement. From the point of view of bone involvement, three of eleven cases who had initial bone involvement had CNS relapse and this reached statistical significance (p=0.028). CNS-IPI approach is relatively new and patient selection for CNS prophylaxis was not uniform in the historical MAB cohort. Similar to RED cohort, IT MTX was used for cases with high risk of CNS relapse according to physician's decision in the MAB cohort. Nevertheless, the CNS relapse ratio was 1.83% in the historical MAB cohort, leading to a statistical significance (p=0.004).

Biosimilar rituximab was reported to affect the outcome of DLBCL patients in low socioeconomic group who could not afford original molecule in the study cohort, constituting an important financial advantage [29]. The main medicine cost of R-CHOP regimen was shown to be due to rituximab in Europe and authors stated that cost saving could be realized with the usage of biosimilar medications [30].

Retrospective evaluation and low number of patients were the limitations of our study. We could not compare the AEs between RED and MAB cohorts as the data was incomplete in the historical MAB cohort. To be licensed by the major European and US authorities assures physicians globally to be more comfortable with the drug, which RED has not yet.

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According to our results, the biosimilar RED has similar overall survival rates. However, comparing to the historical MAB cohort, PFS rates were found to be worse in the RED group, especially in the high R-IPI scored patients. Additionally, CNS relapse ratio was a major concern for our cohort, and we could not analyze its relationship with the type of rituximab molecule. Head-to-head comparison of RED and MAB pharmacokinetics, large prospective controlled studies and, more real-life data with longer follow-up are needed to document the non-inferiority and safety of RED compared to MAB.

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. The study was approved by I.U. Istanbul Medical Faculty ethical committee (2019/1454).

Conflict of interest: The authors declare that they have no conflict of interest.

Author Contribution

SKB and MÖ designed the study. MÖ, MGM, ÖÖ, TOT, SE, EPÖ, TE, İYH, AEE, MCA, MNY, TS, MN and BF collected the data. MÖ and SKB wrote the manuscript. All authors read and accepted the current for of the manuscript. SKB served as the principal investigator.

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Table 1: Patient characteristics

	Redditux® group (n=51)	**MabThera® group (n=219)**	***p* value**
Median follow-up, months (range)	31 (8-39)	38 (1-106)	***0.002***
Median age, years (range)	60 (17-79)	55 (19-83)	0.498
Sex n, (%)			
Male	29 (57)	113 (52)	0.498
Female	22 (43)	106 (48)	
Subgroup n, (%)			
GCB	25 (49)	73 (33)	0.097
Non-GCB	13 (25)	71 (32)	
TCRBCL	3 (6)	0	
NA	10 (20)	75 (35)	
Advanced stage n, (%)	28 (55)	114 (52)	0.714
Elevated LDH n, (%)	23 (48)	110 (50.5)	0.750
Extranodal site>1 n, (%)	14 (27.5)	63 (28.8)	0.851
Age>60 years n, (%)	26 (51)	84 (38.4)	0.098
ECOG>1 n, (%)	15 (29.4)	30 (13.7)	***0.007***
Bulky>10cm n, (%)	8 (16)	NA	
Primary extranodal n, (%)	12 (23.5)	56 (25.6)	0.762
Bone involvement n, (%)	11 (21.6)	NA	
Bone marrow involvement n, (%)	9 (17.7)	36 (16.6)	0.856
Liver involvement n, (%)	4 (7.8)	20 (9.2)	0.764
Stage n, (%)			

I	10 (19.6)	61 (27.9)	0.369
II	13 (25.5)	44 (20)	
III	11 (21.6)	59 (27)	
IV	17 (33.3)	55 (25.1)	
R-IPI score* n, (%)			
Low (0)	8 (16.7)	46 (21)	0.753
Intermediate (1-2)	22 (45.8)	100 (45.7)	
High (3-5)	18 (37.5)	73 (33.3)	
*Available in 48 patients in redditux cohort			

Table 2: Treatment responses.

	Redditux® group (n=51)	**MabThera® group (n=219)**
Distribution of treatment responses (entire cohort) (%)		
CR	37 (72.6)	178 (81.7)
PR	7 (13.7)	5 (2.3)
SD	0	1 (0.5)
PD	7 (13.7)	34 (15.5)
Distribution of treatment responses in patients with high R-IPI score (score 3-5) (%)	**n=18**	**n=73**
CR	8 (44.4)	46 (63)
PR	5 (27.8)	4 (5.5)
SD	1 (5.6)	0
PD	4 (22.2)	23 (31.5)
Survival rates		
24-month PFS	73.76% (95% CI: 0.59-0.84)	85.2 (95% CI: 0.79-0.90)
24-month OS	78.4% (95% CI: 0.64-0.87)	81.4% (95% CI: 0.75-0.86)

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Table 3: Adverse events in the Redditux cohort				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neutropenia			9	11
Infusion reactions requiring medical intervention		10		
Leucopenia				2
Anemia		1	4	2
Thrombocytopenia	1	1	2	
Peripheral neuropathy	3			
Fatigue		2	1	
Neutropenic fever	2			
Pneumonia		2		
Urinary tract infection		2		
Loss of apetite		1		
Constipation		1		
Nausea		1		
Diarrhea		1		
Anal fissure	1			
Elevated transaminanses		1		
Myalgia		1		
Bone pain		1		

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Figure 1: Survival curves according to treatment cohort

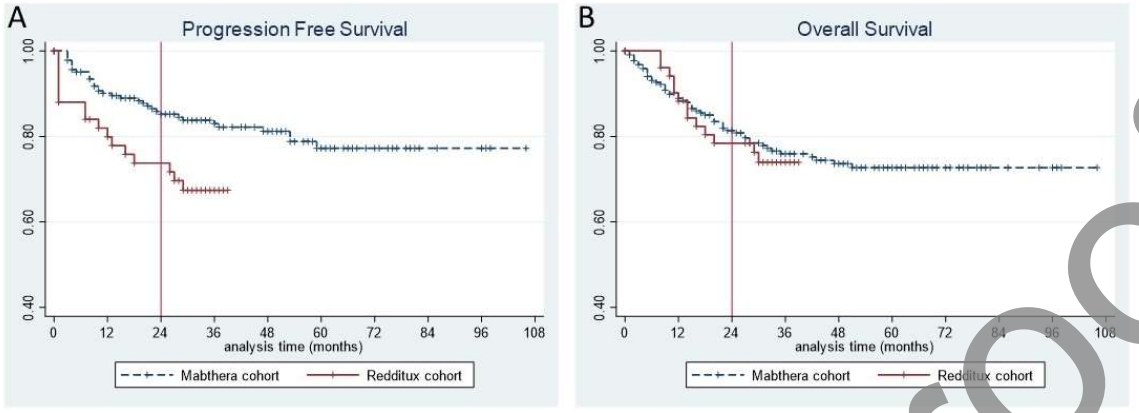
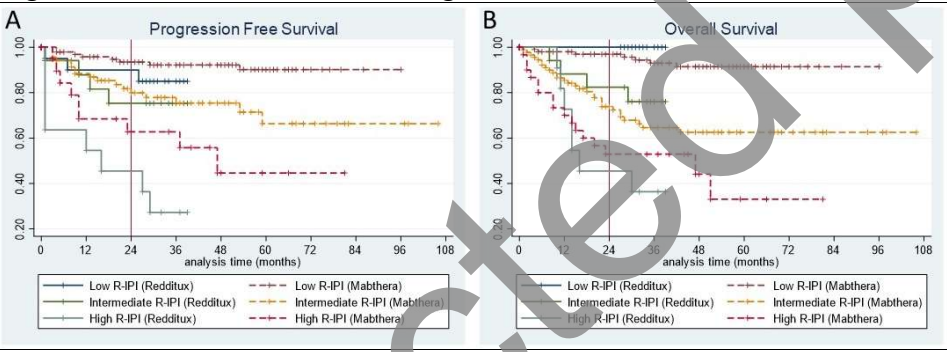


Figure 2: Survival curves according to treatment cohort and R-IPI scores



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