# Rituximab plus cyclophosphamide and dexamethasone *versus* bortezomib plus cyclophosphamide and dexamethasone in newly diagnosed symptomatic Waldenström macroglobulinemia: a randomized controlled trial

Waldenström macroglobulinemia (WM) is a rare B-cell lymphoma characterized by the production of monoclonal immunoglobulin M (IgM) and infiltration of the bone marrow and other organs by IgM-producing clonal lymphocytes, lymphoplasmacytic cells, and plasma cells.[1] Although there is a general consensus on the diagnosis and treatment of WM, the regimens used for patients remain heterogeneous.[2] Due to the lack of prospective randomized clinical trials, there is no standard first-line therapy.

The clinical manifestations of WM include features of both lymphoma and myeloma, such as lymphadenopathy and secretion of monoclonal IgM proteins. Its biological characteristics are also defined by the dual characteristics of lymphoma and myeloma. For example, the tumor cells express both CD20 and CD38, and abnormalities in the nuclear factor kappa-B (NF-κB) signaling pathway are important for its pathogenesis.[3] Rituximab-based regimens are most frequently used in WM patients.[2,4] Bortezomib, a proteasome inhibitor, can inhibit NF-κB signaling in WM cells, and bortezomib monotherapy has produced a 26% response rate.[5,6]

Rituximab- or bortezomib-based regimens are routinely used for untreated WM patients in China.[7] Prospective clinical trials have shown that a combination of rituximab and bortezomib can achieve a high response rate and long-term responses.[8] However, the combination of these two drugs seemed not improve patients' survival.[9] A comparison between rituximab-based and bortezomib-based regimens is still lacking. We therefore initiated a randomized, controlled phase III trial to compare the activity of rituximab, cyclophosphamide, and dexamethasone (RCD) with that of bortezomib, cyclophosphamide, and dexamethasone (BCD) in newly diagnosed patients with WM. The trial complied with the ethical principles set forth in the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. Patients provided informed consent in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the Institute of Hematology and Blood Disease Hospital review board before implementation (IIT2015005-EC-2) and registered at ClinicalTrials.gov (NCT02844322).

The eligible patients were randomly assigned in a 1:1 ratio to receive six cycles of either RCD (rituximab 375 mg/m$^2$ on day 8; cyclophosphamide 500 mg/m$^2$ on days 1, 8, and 15; and dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23) or BCD (bortezomib 1.6 mg/m$^2$ administered by subcutaneous injection on days 1, 8, and 15 of the 28-day cycle; cyclophosphamide 500 mg/m$^2$ on days 1, 8, and 15; and dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23). Patients with less than a minor response after three cycles of treatment were allowed to cross over to the other treatment group. After crossing to the other group, an additional three cycles were given if a minor response or better was achieved. Otherwise, the patient was withdrawn from the study. The key inclusion and exclusion criteria for patients are presented in *Online Supplementary Table S*1. The primary endpoint was progression-free survival assessed by investigators. The key secondary endpoints were the overall response, complete response, and very good partial response rates.

Between March 1, 2016 and November 29, 2020, 40 patients were randomly assigned to receive RCD or BCD. Two patients did not undergo follow-up after receiving two courses of treatment, so the final analysis was performed on 38 patients. The baseline characteristics of the two groups were well balanced (Table 1). The median age was 62 years (range, 36-73) and 60 years (range, 35-75) in the RCD and BCD groups, respectively. The median baseline IgM was 3,200 mg/dL (range, 210-12,100) and 3,800 mg/dL range, 138-10,400), respectively. Four patients in the RCD group and three patients in the BCD group had undergone plasmapheresis.

One patient (5.3%) in the RCD group and three (15.8%) in the BCD group achieved a complete response. Seven patients (36.8%) in the RCD group had a very good partial response compared with only two patients (10.5%) in the BCD group. Nine patients each in the RCD and BCD groups achieved a partial response. The overall response rate was the same in both groups (89.5% *vs*. 89.5%; *P*=1.000). The major response rate was higher in the RCD group than in the BCD group (89.5% *vs*. 73.7%; *P*=0.209). The proportion of patients who achieved a very good partial response or better was also higher in the RCD group than in the BCD group (42.1% *vs*. 26.3%; *P*=0.305) (Figure 1A). The median times to first and best responses were, respectively, 1 month (range, 1-7) and 4 months (range, 1-9) in the BCD

group and 2 months (range, 1-4) and 5 months (range, 1-9) months in the RCD group.

The median follow-up time was 55 months (range, 12-76). Five patients in the RCD group and 13 in the BCD group progressed. One patient in the RCD group and six in the BCD group died. The treatments after progression and the causes of death are shown in *Online Supplementary Table S2*. One patient in the BCD group experienced a histological transformation to diffuse large B-cell lymphoma 10 months after treatment. The estimated 5-year progression-free survival rate in the RCD group was 69.4% (95% confidence interval [95% CI]: 35%-88%), which was significantly higher than the rate of 35.5% (95% CI: 15%-57%) observed in the BCD group (*P*=0.009). The median progression-free survival in the BCD group was 33.0 months (95% CI: 15.7-50.3), which was shorter than in the RCD group (not reached, hazard ratio [HR]=0.324, 95% CI: 0.121-0.774, *P*=0.009) (Figure 1B). Seventeen patients in each group achieved at least a minor response. The median duration of response in the RCD group was not reached, and was longer than the 32.0 months (95% CI: 15.6-48.4) observed in the BCD group (HR= 0.2117, 95% CI: 0.069-0.649; *P*=0.007) (Figure 1C). At the end of follow-up, 73.7% of the patients in the RCD group were still in remission as compared to 31.6% of the patients in the BCD group.

The estimated 5-year overall survival rate was 88.9% (95% CI: 43%-98%) in the RCD group and 71.3% (95% CI: 44%-87%) in the BCD group (*P*=0.034). The median overall survival was not reached and was 70 months in the RCD and BCD groups, respectively. The hazard ratio for death was 0.154 (95% CI: 0.050-0.964) (Figure 1D).

Minimal residual disease (MRD) and cellular components

**Table 1.** Characteristics of the patients in the two groups at the time of starting treatment.

| Characteristics | RCD N=19 | BCD N=19 | Total N=38 |
|---|---|---|---|
| Age | | | |
| Median (range), years | 62 (36-73) | 60 (35-75) | 62 (35-75) |
| ≥65 years old, N (%) | 7 (36.8) | 4 (21.1) | 11 (28.9) |
| Gender, N (%) | | | |
| Male | 13 (68.4) | 10 (52.6) | 23 (60.5) |
| Female | 6 (31.6) | 9 (47.4) | 15 (39.5) |
| ISSWM, N (%) | | | |
| Low | 3 (15.8) | 3 (15.8) | 6 (15.8) |
| Intermediate | 8 (42.1) | 9 (47.4) | 17 (44.7) |
| High | 8 (42.1) | 7 (36.8) | 15 (39.5) |
| IgM level | | | |
| Median (range), mg/dL | 3,200 (210-12,100) | 3,800 (138-10,400) | 3,655 (138-12,100) |
| ≥4,000 mg/dL, N (%) | 7 (36.8) | 9 (47.4) | 16 (42.1) |
| Cytopenia at baseline | | | |
| Hemoglobin ≤11 g/dL, N (%) | 17 (89.5) | 17 (89.5) | 34 (89.5) |
| Platelet count ≤100x$10^9$/L, N (%) | 6 (31.6) | 6 (31.6) | 12 (31.6) |
| ANC ≤1.5x$10^9$/L, N (%) | 2 (10.5) | 2 (10.5) | 4 (10.5) |
| Median hemoglobin (range), g/dL | 8 (4.9-13.4) | 7.9 (4.5-12.5) | 7.9 (4.5-13.4) |
| Bone marrow infiltration | | | |
| Median cellularity (range), % | 60.5 (7.5-86.5) | 48 (27.5-86.0) | 57 (7.5-86.5) |
| Median cellularity detected by flow cytometry (range), % | 13.5 (0.2-80.6) | 15.8 (1.1-74.4) | 14.8 (0.2-80.6) |
| $\beta_2$ microglobulin level | | | |
| Median (range), mg/L | 3.2 (1.9-7.5) | 3.7 (2.5-8.0) | 3.6 (1.9-8.0) |
| Elevated, N (%) | 15 (78.9) | 17 (89.5) | 32 (84.2) |
| Lactate dehydrogenase level | | | |
| Median (range), U/L | 149 (69-470) | 164 (94-569) | 154 (69-569) |
| Elevated, N (%) | 2 (10.5) | 4 (22.2) | 6 (15.8) |
| Extramedullary disease, N (%) | | | |
| Splenomegaly | 8 (42.1) | 9 (47.4) | 17 (44.7) |
| Hepatomegaly | 4 (21.1) | 6 (31.6) | 10 (26.3) |
| Adenopathy | 7 (36.8) | 9 (47.4) | 16 (42.1) |
| B symptoms, N (%) | 6 (31.6) | 8 (42.1) | 14 (36.8) |

RCD: rituximab, cyclophosphamide, dexamethasone; BCD: bortezomib, cyclophosphamide, dexamethasone; IgM: immunoglobulin M; ISSWM: International Staging System for Waldenström Macroglobulinemia; ANC: absolute neutrophil count.

were assessed by multiparameter flow cytometry. MRD negativity was defined as a clonal malignant cell count of $<10^{-4}$ (0.01%). After treatment, six patients in the RCD group and four in the BCD group were MRD-negative. All patients who achieved a complete response were MRD-negative. The residual cellular components of bone marrow were analyzed in patients who achieved a partial or very good partial response. Before treatment, all patients who achieved a partial or very good partial response had both monotypic plasmacytosis and monotypic B cells. Eleven patients in the RCD group who achieved a partial or very good partial response were MRD-positive. Among these patients, six (54.5%) patients only retained abnormal plasma cells and no abnormal B lymphocytes, and one patient had only abnormal B lymphocytes and no plasma cells. In comparison, in the BCD group, ten patients who achieved a partial or very good partial response were MRD-positive. However, only one patient had abnormal plasma cells and absent abnormal B lymphocytes (10%). Nine patients had both abnormal plasma cells and B lymphocytes (*Online Supplementary Figure S1A*). Comparisons of the percentages of abnormal B lymphocytes and plasma cells before and after treatment in the RCD and BCD groups are illustrated in *Online Supplementary Figure S1B, C.*

As shown in Table 2, the most common adverse event of any grade in both groups was hematologic toxicity. The grades of both hematologic and non-hematologic adverse events were similar between the two groups. Serious hematologic adverse events (≥grade 3) were experienced by 15.8% and 21.2% of patients in the RCD and BCD groups, respectively. Common non-hematologic adverse events in the RCD group included non-infectious fever (26.3%),

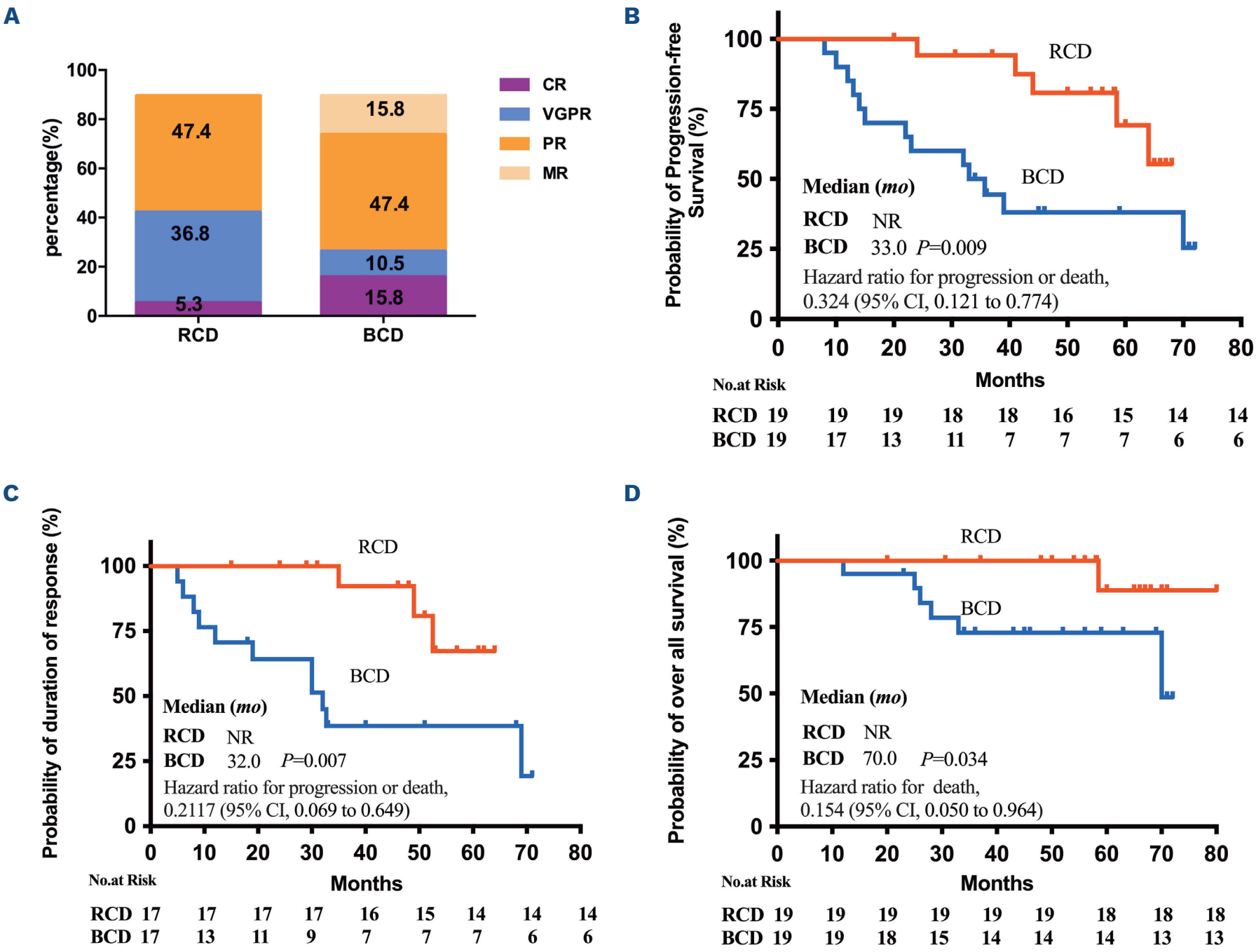


**Figure 1. The response rate and Kaplan-Meier analysis of progression-free survival, duration of response and overall survival.** (A) The best response rates in the two treatment groups. (B) Kaplan-Meier analysis of progression-free survival. (C) Kaplan-Meier analysis of duration of response. (D) Kaplan-Meier analysis of overall survival. The tick marks indicate censoring of data. RCD: rituximab, cyclophosphamide, dexamethasone; BCD: bortezomib, cyclophosphamide, dexamethasone; CR: complete response; VGPR: very good partial response; PR: partial response; MR: minor response: mo: months; NR: not reached; 95% CI: 95% confidence interval.

**Table 2.** Overview of treatment-emergent adverse events in the two groups.

| Events, N (%) of patients | RCD, N=19 | | BCD, N=19 | |
|---|---|---|---|---|
| | All grades | Grade ≥3 | All grades | Grade ≥3 |
| Hematologic adverse events | 18 (94.7) | 3 (15.8) | 18 (94.7) | 4 (21.2) |
| Neutropenia | 17 (89.5) | 2 (10.5) | 15 (78.9) | 3 (15.8) |
| Thrombocytopenia | 3 (15.8) | 1 (5.8) | 10 (52.6) | 2 (10.5) |
| Non-hematologic adverse events | 12 (63.2) | 1 (5.3) | 14 (73.7) | 1 (5.3) |
| Pneumonia | 4 (21.1) | - | 4 (21.1) | - |
| Infectious fever | 3 (15.8) | 0 | 3 (15.8) | 0 |
| Upper respiratory infection | 1 (5.3) | 0 | 3 (15.8) | 0 |
| Non-infectious fever | 5 (26.3) | - | 0 | 0 |
| Hyperglycemia | 3 (15.8) | 1 (5.3) | 2 (10.5) | 1 (5.3) |
| Hypertension | 1 (5.3) | 0 | 2 (10.5) | 0 |
| Peripheral neuritis | 0 | 0 | 5 (26.3) | 0 |
| Rash | 1 (5.3) | 0 | 1 (5.3) | 0 |
| Herpes zoster | 0 | 0 | 2 (10.5) | 0 |
| Flatulence | 1 (5.3) | 0 | 2 (10.5) | 0 |
| Diarrhea | 1 (5.3) | 0 | 2 (10.5) | 0 |
| Edema | 1 (5.3) | 0 | 1 (5.3) | 0 |
| Nausea and vomiting | 0 | 0 | 1 (5.3) | 0 |
| Epistaxis | 0 | 0 | 1 (5.3) | 0 |

RCD: rituximab, cyclophosphamide, dexamethasone; BCD: bortezomib, cyclophosphamide, dexamethasone.

pneumonia (21.1%), and hyperglycemia (15.8%). Common non-hematologic adverse events in the BCD group included peripheral neuropathy (26.3%), pneumonia (21.2%), herpes zoster (10.5%), and flatulence (10.5%). Only one patient in each group experienced grade 3 or higher non-hematologic adverse events.

There are very few randomized trials and limited data comparing different treatment regimens for WM. Here, for the first time, we demonstrated that the rituximab-based regimen, RCD, was superior to the bortezomib-based regimen in terms of both progression-free survival and overall survival . RCD is an active and safe choice for the first-line treatment of WM. In our study, the complete and overall response rates were 5.3% and 89.5%, respectively, in the RCD group, which was similar to the findings of Dimopoulos *et al*.[4] BCD is a recommended treatment for multiple myeloma but is rarely used for WM. Small cohort studies (15 patients and 34 patients) showed that the major response rate was 53%[10] and 74%,[11] with the median progression-free survival being 18.6 months. These results are consistent with those of our study. The longer progression-free survival of patients treated with RCD compared to those treated with BCD may contribute to the strong MRD elimination achieved by rituximab. In the RCD group, six out of 11 patients had eliminated the monoclonal B-cell components after treatment. However, only one of the ten patients in the BCD group had eliminated the monoclonal B-cell components. This was consistent with the findings of a previous study showing that a rituximab-based regimen eliminated monotypic B cells in ten of 41 patients.[12] This study does have some limitations. The small sample size limited further analysis of patients and might have led to biased observations. The overall survival benefit found in the RCD group might also be the result of biased observations, given the small sample size. The results need to be confirmed by further expanding the sample size. However, this study is important for low-resource settings, in which the cost of combining rituximab and bortezomib would be prohibitive, and could impact practice in low-resource countries. It demonstrated that anti-plasma cell therapy alone may not be sufficient to remove tumor cells adequately in WM. In conclusion, this randomized comparison demonstrated that rituximab-based RCD is superior to bortezomib-based BCD for newly diagnosed WM.

## Authors

Wenjie Xiong,[1,2*] Rui Lyu,[1,2*] Ying Yu,[1,2] Tingyu Wang,[1,2] Yuting Yan,[1,2] Yi Wang,[1,2] Wei Liu,[1,2] Gang An,[1,2] Shuhui Deng,[1,2] Yan Xu,[1,2] Weiwei Sui,[1,2] Wenyang Huang,[1,2] Dehui Zou,[1,2] Jianxiang Wang,[1,2] Lugui Qiu[1,2#] and Shuhua Yi[1,2#]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Peking and [2]Tianjin Institutes of Health Science, Tianjin, China

**WX and RL contributed equally as first authors.*

*#SY and LQ contributed equally as senior authors.*

Correspondence:

L. QIU - qiulg@ihcams.ac.cn

S. YI - yishuhua@ihcams.ac.cn

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**Disclosures**

No conflicts of interest to disclose.

**Contributions**

SY and LQ designed the study. WX and RL analyzed the data, performed statistical analyses, and wrote the manuscript. YY, TW, YY, and YW collected data. WL, GA, SD, YX, WS, WH, and DZ acquired data and managed patients. JW and LQ suggested revisions. LQ and SY revised the manuscript critically and approved the final version.

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**Data-sharing statement**

The datasets generated and analyzed during the current study are not publicly available because of applicable privacy laws but are available from the corresponding author upon reasonable request.

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