Transfusion independence after lenalidomide discontinuation in patients with del(5q) myelodysplastic neoplasm: a HARMONY Alliance study

Transfusion independence after lenalidomide discontinuation in patients with del(5q) myelodysplastic syndrome: a HARMONY Alliance study

Elena Cris&#x00E0

elena.crisa@ircc.it

Candiolo Cancer Institute, FPO-IRCCS https://orcid.org/0000-0003-1912-0574

María Díez-Campelo

Hospital Universitario y Centro de Investigación del Cáncer

Ulrich Germing

Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University

Cécile Bally

Saint-Louis Hospital, AP-HP, Paris

Mikko Myllymäki

Hematology research unit Helsinki, University of Helsinki

Martin Jädersten

Karolinska University Hospital

Rami Komrokji

H. Lee Moffitt Cancer center https://orcid.org/0000-0002-1876-5269

Anne Sophie Kubasch

University Hospital Leipzig https://orcid.org/0000-0002-0747-4941

Detlef Haase

University Medicine Goettingen

Wolf-Karsten Hofmann

University of Mannheim

Najla Al Ali

Moffitt Cancer Center

Daniela Barraco

ASST Sette Laghi

Joan Bargay

Hospital Son Llatzer

Teresa Bernal

Hospital Universitario Central de Asturias

Félix López-Cadenas
Hospital Universitario de Salamanca
Anna Calvisi
Ospedale San Francesco
Isabella Capodanno
Hematology, AUSL-IRCCS Reggio Emilia
Marco Cerrano
University of Torino https://orcid.org/0000-0003-1666-3100
Rosanna Ciancia
Centro di Riferimento Oncologico di Aviano (CRO) IRCCS
Monica Crugnola
Azienda Ospedaliero-Universitaria di Parma
Andrea Kündgen
Universitätklinikum Düsseldorf
Carlo Finelli
IRCCS - Azienda Ospedaliero-Universitaria di Bologna, Institute of Hematology https://orcid.org/0000-0001-9372-1197
Claudio Fozza
Università di Sassari
Chiara Frairia
Azienda Ospedaliera S. Giovanni Battista
Freja Ebeling
Helsinki University Hospital Comprehensive Cancer Center
Christina Ganster
University Medical Center Göttingen https://orcid.org/0000-0002-7566-5985
Maria Jose Jimenez
Hospital Germans Trias i Pujol https://orcid.org/0000-0002-5469-5237
Roberto LATAGLIATA
Ematologia
Francisca Hernandez-Mohedo
Hospital San Cecilio
Antonieta Molero
Vall d'Hebron Institute of Oncology (VHIO), University Hospital Vall d'Hebron
Elvira Mora
Hospital la Fé
Míriam Vara
Hospital Universitario de Cruces.
Clara aparicio Perez
Hematology Department. Hospital Universitario Reina Sofia,

Giuseppe Pietrantuono
IRCCS-CROB, Referral Cancer Center of Basilicata
Antonella Poloni
Dipartimento di Scienze Cliniche e Molecolari, Clinica di Ematologia, Università Politecnica delle Marche, Ancona https://orcid.org/0000-0002-4221-4125
Helena Pomares
Institut Català d'Oncologia (ICO), Hospital Duran i Reynals
Valle Recasens
Hematology, Hospital Miguel Servet
Axel Rüfer
Luzerner Kantonsspital
Alessio Signori
University of Genova
Eva Hellström-Lindberg
Karolinska Institutet https://orcid.org/0000-0002-7839-3743
Pierre Fenaux
Hopital Saint-Louis, Assistance Publique-Hôpitaux de Paris, Université Paris Diderot, 75475 Paris, France and Universite de Paris, and Inserm U944
Guillermo Sanz
Hospital Universitari i Politècnic La Fe https://orcid.org/0000-0002-2767-8191
Valeria Santini
Universiity of Florence https://orcid.org/0000-0002-5439-2172
Uwe Platzbecker
University Hospital Leipzig https://orcid.org/0000-0003-1863-3239

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Abstract

Lenalidomide (LEN) can induce RBC transfusion independence (RBC-TI) in 60–70% of del(5q) myelodysplastic syndrome (MDS) patients. Current recommendation is to continue LEN in responding patients until failure or progression, with likelihood of toxicity and a high cost for healthcare systems. This HARMONY Alliance study investigated the outcome of MDS del(5q) patients who discontinued LEN in RBC-TI. We enrolled 118 patients with an IPSS-R low-intermediate risk. Seventy patients (59%) discontinued LEN for intolerance, 38 (32%) per their physician decision, nine (8%) per their own decision and one (1%) for unknown reasons. After a median follow-up of 49 months from discontinuation, 50/118 patients lost RBC-TI and 22/30 who underwent cytogenetic re-evaluation lost complete cytogenetic response. The median RBC-TI duration was 56 months. In multivariate analysis RBC-TI duration after LEN discontinuation correlated with low transfusion burden before LEN therapy, treatment ≥ 12 LEN cycles, younger age and higher Hb level at LEN withdrawal. Forty-eight patients were re-treated with LEN for loss of response and 28 achieved RBC-TI. These data show that stopping LEN therapy in MDS del(5q) patients in RBC-TI allows prolonged maintenance of TI in a large subset of patients.

Background

Del(5q) is one of the most common cytogenetic abnormalities in *de novo* MDS, occurring in approximately 10–20% of MDS patients (1–3). Treatment with lenalidomide (LEN) can lead to red blood cell-transfusion independence (RBC-TI) in 60 to70% of patients with RBC-transfusion dependent (RBC-TD) MDS with lower-risk and isolated del(5q), and to complete cytogenetic response (CCyR) in 30–40% of them (4–7). Current practice in patients who attain RBC-TI is to continue LEN treatment indefinitely until loss of response or disease progression. However, the optimal duration of LEN treatment has never been formally addressed. Although LEN treatment in MDS with del(5q) does not appear to increase the risk of AML transformation (8–10), other long-term effects of immunomodulation have not been clearly elucidated and a possible intermittent use or discontinuation of LEN may benefit some patients. Moreover, although treatment with LEN is usually well tolerated, serious side effects may occur. Indeed, the most common grade 3/4 adverse events (AEs) reported in del(5q) MDS are cytopenias, which may be a result of direct cytotoxic effects of LEN on the del(5q) clone, and are more frequent and severe during the first cycles of treatment (11). Among extra-hematological toxicities, cutaneous rash and diarrhea are the most common AEs. More rarely thromboembolic events, in particular deep vein thrombosis, and hypothyroidism have also been reported (7, 12, 13). Furthermore, albeit a report by the Moffitt Cancer Center involving a large cohort of MDS patients did not show an increased risk of secondary malignancies in those treated with LEN, some concerns about its long-term cancerogenic potential still exist (14, 15). Besides, despite the reduction in the cost of LEN in recent years, there is still concern about the healthcare resources utilization associated with the monitoring of potential side effects and the appearance or increase in clonal size of *TP53* mutations. Indeed, LEN treatment in patients with *TP53* mutations, present in 12–25% of del(5q) patients, could trigger disease progression, due to the selective expansion of *TP53* mutant clones that are less sensitive to LEN (16–19).

Some retrospective case reports or series involving a small number of patients have shown that most RBC-TI patients who stopped LEN maintained the hematological response. This finding was more evident in patients who had received at least 6–12 months of LEN and who were RBC-TI and had achieved a CCyR (20–22).

This study, the largest to date, aimed to assess the outcome of patients with del(5q) MDS who discontinue LEN while in RBC-TI response based on a large international data set.

Methods

Within the MDS working group of the European Innovative Medicines Initiative HARMONY project, we included cases from centers and registries of seven European countries (Italy, Germany, Spain, France, Finland, Switzerland, and Sweden) and from one US center (Moffitt Cancer Center) with the diagnosis of MDS with isolated del(5q) according to 2016 WHO classification (blasts < 5%, presence of del(5q) alone or with 1 additional abnormality except − 7 or del(7q)), who discontinued therapy after achieving and maintaining RBC-TI, according to IWG criteria 2006 (23–25).

Other inclusion criteria were age > 18 years, RBC-TD before LEN start, bone marrow (BM) blast percentage at diagnosis and at study entry < 5%, IPSS-R very low, low or intermediate risk at LEN treatment start and RBC-TI at LEN discontinuation (26).

The main exclusion criteria were concomitant treatments for MDS in addition to LEN (excluding the use of growth factors), lack of response to LEN, disease progression, or death before LEN discontinuation.

Clinical data were collected retrospectively and prospectively from January 2019 to June 2023. In some cases, molecular analysis by next generation sequencing (NGS) panel and isolated Sanger for *TP53* mutation, were performed at diagnosis, at LEN start, at LEN discontinuation and in case of disease progression.

The study complied with the declaration of Helsinki and all the patients signed an informed consent form before being included in the study.

The primary endpoint of the study was RBC-TI duration after LEN discontinuation. Secondary end points were event-free survival (EFS) (events included for this endpoint were loss of transfusion independence, re-challenge with LEN therapy, disease progression, acute myeloid leukemia (AML) evolution or death), overall survival (OS), progression-free survival (PFS), time to AML transformation, response rate to LEN re-challenge, and identification of clinical or biological predictors of response duration after LEN discontinuation.

Statistical methods

The median value and range were used for reporting continuous variables and the absolute and relative frequency were reported for categorical variables.

RBC-TI duration, EFS, PFS and OS survival curves were calculated using the Kaplan-Meier method.

The comparison among groups for EFS, RBC-TI duration, PFS and OS curves was performed by the log-rank test. Cox proportional hazards regression models were performed to estimate hazard ratios (HR) with 95% confidence intervals (95% CI). All characteristics with a p-value < 0.10 at univariable analyses were selected to be considered in the multivariable model. Only those characteristics with a p-value < 0.1 in the multivariable model were retained.

Cumulative incidence of RBC-TI loss was calculated considering death and lenalidomide retreatment as competing events.

All statistical tests were two-tailed, and the significance level was set to 0.05. Stata software (v.16; StataCorp) was used for all statistical analyses.

Results

Patient population

One hundred-eighteen patients (80% females) fulfilled the study criteria and were included in the analysis. LEN treatment had been started between December 2003 and September 2022 and this treatment had been discontinued between July 2004 and January 2023.

At LEN treatment start patients were receiving a median of 4 RBC units per month. Of note, 21 (18%) patients were receiving less than 4 RBC units in the 8 weeks before starting treatment and could not be strictly defined as RBC-TD by 2006 IWG criteria. According to IPSS-R categories, 26 patients (22%), 68 (58%) and 24 (20%) were very low, low, and intermediate risk respectively.

As per protocol eligibility criteria, all patients had achieved RBC-TI during LEN therapy. Cytogenetic analysis on bone marrow aspirate was evaluated after treatment in 95 patients and 15 (16%) had achieved partial CyR while 48 (51%) CCyR.

The median number of LEN cycles received before discontinuation was 12 (range 1–72, median treatment duration 12 months) and 85 patients (71%) had experienced hematological or non-hematological treatment-related AEs during treatment. Seventy-nine (67%) AEs were grade1-2 and 59 (50%) grade 3–4, respectively. In 42 patients (35%) LEN dose had to be reduced due to toxicity.

Median age at LEN discontinuation was 77 years (range, 33–93 years). The reason for stopping treatment was intolerance in 70 patients (59%), physician decision due to optimal response in 38 (32%), patient’s decision in nine (8%) and unknown in one patient (1%).

Among the 70 patients who discontinued treatment for intolerance, 48 had a non-hematological toxicity (31/48 of grade 3/4).

Patient characteristics at lenalidomide start/stop are summarized in Table 1.

Table 1
Patients main characteristics at lenalidomide start, over treatment and at lenalidomide discontinuation.

Patients characteristics			
At lenalidomide start			
		N°	**%**
Patients		118	
Gender	Male	24	20%
	Female	94	80%
Age (years)	median (range)	77 (42–93)	
Therapy related	no	112	95%
	yes	6	5%
IPSS	low	59	56%
	intermediate I	46	44%
IPSS-r	very low	26	22%
	low	68	58%
	Intermediate I	24	20%
Bone marrow blasts %	median (range)	2 (0–5)	
RBC-transfusion burden > 4 units in 8 weeks	no	21	17%
	yes	97	82%
Best response to lenalidomide	RBC-TI	55	47%
	RBC-TI + CCy	48	40%
	RBC-TI + PCy	15	13%
Hematological toxicity	Grade 1–2	36	30.5%
	Grade 3–4	27	23%
Extra-hematological toxicity	Grade 1–2	43	36%
	Grade 3–4	32	27%
Dose reduction		42	36%

Abbreviations: RBC red blood cells; IPSS International Prognostic Scoring System ; IPSS-R International Prognostic Scoring System revised: CCyR Complete Cytogenetic Response; PCyR Partial Cytogenetic Response

Patients characteristics			
At lenalidomide start			
		N°	**%**
N of lenalidomide cycles	median (range)	12 (17–72	
At lenalidomide discontinuation			
Age (years)	median (range)	77 (33–97)	
Absolute Neutrophils Count x10^9/µl	median (range)	1.51 (0.19–5.1)	
Hemoglobin g/l	median (range)	12 (7.8–15,5)	
Platelets x10^9/µl	median (range)	150 (3-386)	
Bone marrow blasts %	median (range)	1(0–5)	
RBC transfusion-dependence		0	0%
Cytogenetic response	CCyR (95 evaluable patients)	45	47%
	PCyR (92 evaluable patients)	57	62%
Reason for lenalidomide discontinuation	intolerance	70	59%
	optimal response according to physician	38	32%
	patient decision	9	8%
	unknown	1	1%

Abbreviations: RBC red blood cells; IPSS International Prognostic Scoring System ; IPSS-R International Prognostic Scoring System revised: CCyR Complete Cytogenetic Response; PCyR Partial Cytogenetic Response

Follow-up after lenalidomide discontinuation

Median observation time from diagnosis was 82 months (range 5-302) and median follow-up after LEN discontinuation was 49 months. Overall, 50 (42%) patients lost RBC-TI. Median duration of RBC-TI was 56.2 months (range 1-120, Fig. 1A). When considering death or LEN restart as competing events for loss of RBC-TI, cumulative incidence of RBC-TI loss was 45% at 60 months. (Fig. 1 supplementary material)

RBC-TI duration was longer for patients who had received > 12 LEN cycles (median, 85.8 vs 31 months; $p = 0.001$; Fig. 1B) and for those who had received < 2 RBC units per month before LEN start (median 56.2 vs 44.1 $p = 0.024$, Fig. 1C). LEN dose reduction did not impact on RBC-TI after LEN discontinuation.

At multivariable analysis other prognostic factors for RBC-TI length were age ($p = 0.024$) and hemoglobin level ($p = 0.092$) at the time of LEN discontinuation (Table 2).

Table 2
Prognostic factors for Red Blood Cell Transfusion Independence loss on multivariate analysis.

Variables	HR	95,0% CI		
		Lower	Upper	p value
Age *	1.04	1.00	1.07	0.024
RBC unit/8 weeks > 4 at lenalidomide start	3.34	1.18	9.47	0.024
Lenalidomide cycles ≥ 12	0.34	0.18	0.65	0.001
Hemoglobin level at lenalidomide stop*	0.86	0.71	1.03	0.092
*(continuous variable)				
Abbreviations:				
RBC red blood cells				

During study follow-up 23 patients (19%) progressed to higher-risk MDS (high or very high IPSS-R) or AML and 47 (39%) died.

Median EFS was 40.8 months (range 1-130, Fig. 2A) and at multivariate analysis it was affected by age ($p = 0.019$), transfusion burden (packed RBC units per month, $p = 0.013$), hemoglobin level ($p = 0.028$), IPSS-R risk category at LEN start ($p = 0.004$), as well as treatment duration (> or ≤ 12 cycles; $p = 0.031$), (Results shown in Table 3).

Table 3
Prognostic factors for event-free survival on multivariate analysis

Variables	HR	95,0% CI		
		Lower	Upper	p value
Age at diagnosis*	1.04	1.01	1.07	0.005
RBC unit/8 weeks > 4 at lenalidomide start	1.28	1.05	1.56	0.013
IPSS-R very low vs low/intermediate	0.33	0.16	0.70	0.004
Lenalidomide cycles ≥ 12	0.55	0.32	0.95	0.031
Hemoglobin level at lenalidomide stop*	0.82	0.69	0.98	0.028
*(continuous variable)				
Abbreviations: RBC red blood cells;IPSS International Prognostic Scoring System; IPSS-R IPSS revised				

In particular, median EFS of patients who were treated with LEN for > 12 cycles was 58.0 months as compared with 18.8 months for patients who received ≤ 12 cycles (Fig. 2B)

Patients who were in CCyR at LEN discontinuation had a longer EFS and RBC-TI at univariable analysis (median ,53.3 vs 31.0; $p = 0.031$ and 85.8 vs 50.4; $p = 0.011$, respectively), however these data were not confirmed in multivariable analysis.

Moreover, patients who discontinued LEN for physician choice or for their own decision had a better outcome in terms of EFS and RBC-TI duration compared with patients who stopped treatment for toxicity (median EFS, 54.3 and 26.4 months, respectively, p = 0.006 and median RBC-TI, 85.8, and 59 months, respectively, $p = 0.004$, Fig. 2 Supplementary material). Of note, MDS del(5q) patients who discontinued LEN for toxicity in 39% had experienced of cases an adverse event grade 3/4, had received less LEN cycles (median 8 vs 16, $p < 0.001$), and did not achieve CCyR in most cases (30% vs 75% for the other patients, $p < 0.001$).

After LEN discontinuation cytogenetic re-evaluation was performed in 30 patients, among these, 22 lost CCyR (73%). Twenty-three of 118 patients (19%) progressed to higher risk MDS (n = 15) or AML (n = 8) after a median time of 102 months (range 28–151) from diagnosis and of 29 months (range 1-125) from LEN discontinuation. Median PFS after LEN discontinuation was not reached and 5 years PFS rate was 83%. Twenty/23 patients progressed after having lost RBC-TI, of whom 4 progressed notwithstanding their response to LEN re-treatment; 3/23 patients underwent disease progression without losing TI, after 20, 28, and 40 months from LEN discontinuation.

Median OS after LEN discontinuation was 78.4 months (range 2-186) and was affected by age, transfusion burden at LEN start, and number of LEN cycles. Moreover, patients who lost RBC-TI had a

shorter survival (median 71.3 vs 102.1 months, $p = 0.003$) as 70% of them subsequently progressed as compared with 30% of patients maintaining RBC-TI ($p = 0.003$).

Finally, 48 patients were re-treated with LEN because of loss of response. Forty-two patients were evaluable for response and 28 of them (67%) achieved RBC-TI again. Cytogenetic analysis in these cases was rarely available. However, 3 and 2 patients attained CCyR and partial CyR, respectively. The efficacy of LEN re-challenge correlated with the length of RBC-TI after LEN suspension (median RBC-TI after LEN stop 52 months in patients responding to LEN rechallenge vs 12 months in non-responsive patients, $p = 0.008$).

Molecular data

Molecular data for a large number of somatic mutations by NGS were available for 30 patients whereas *TP53* mutations by NGS or Sanger were available in 82 cases. Before LEN discontinuation, somatic mutations other than *TP53* were detected by NGS in 20/30 (67%) patients (5/30 *SF3B1*, 4/30 *TET2*, 3/30 *DNMT3A*, *ASXL1* and *JAK2*, 1/30 *BCOR*, *IKZF* and *SETBP1*). *TP53* mutations were present in 13 of 82 screened patients. A patient who presented a *TP53* mutation with a variable allele frequency (VAF) of 7% at LEN discontinuation, experienced loss of RBC-TI after 4 months. This was accompanied by an increase to 26% in the *TP53* mutation VAF and an acquisition of a new cytogenetic abnormality (del(20q)). This patient progressed to MDS with excess blasts after 22 months from LEN withdrawal.

The presence of *TP53* mutations did not impact on OS or AML transformation.

Discussion

In this study we present the largest series in our knowledge of MDS del(5q) cases who had discontinued LEN treatment while transfusion independent, with a long follow up (49 months). In large randomized prospective studies RBC-TI duration upon continued LEN therapy was around 2 years (4–7). In our cohort median duration of RBC-TI from LEN discontinuation was 56 months. In particular, 70% of the patients treated for > 12 LEN cycles were still RBC-TI at 5 years.

Since its serendipitous demonstration of an exceptional efficacy in MDS with del(5q) almost 20 years ago, LEN has been largely and successfully employed in the clinics with erythroid and cytogenetic response, leading to prolongation of OS (27). With its activity in promoting erythropoiesis in MDS del(5q), LEN has demonstrated an acceptable profile of tolerability, but it is not completely devoid of toxicity. Although myelotoxicity induced in the first cycles of therapy is known to herald good response, still in rare cases is not self-resolving and may appear after several months of therapy, requiring use of growth factors or LEN dose reduction, facilitating infections or bleeding. Beside hematological toxicity, that may be acceptable in the majority of cases in the balance with benefits (transfusion independence), some patients experience extra-hematological toxicity as hypothyroidism or more frequently skin rash, renal insufficiency of various grade, as well as gastrointestinal symptoms like diarrhea, not always responding to symptomatic medications (5–7). LEN treatment is recommended to be continued until loss of

response, therefore, the above-mentioned side effects can be an obstacle and impair quality of life of patients.

LEN acts in MDS with del5q with a specific mechanism of action by inducing the proteasomal degradation of casein kinase 1, and it preferentially affects del(5q) cells because they express this gene at haplo-insufficient levels (28). This specific modulation of ubiquitin ligase function leads to elimination/reduction of the neoplastic clone (29). In this sense, one may envisage an interruption of treatment once the burden of disease is significantly diminished, in analogy to what has been demonstrated for imatinib therapy in chronic myeloid leukemia (30).

In our study patients who were treated with LEN for at least 12 months showed the longest duration of RBC-TI after interruption, consistent with the hypothesis that reduction of the clone allowed achievement of stable response, as supported by the evidence that CCyR prolonged EFS at univariable analysis. Longitudinal cytogenetic analysis were available only in a minority of cases, reflecting clinical practice of avoiding repeated bone marrow evaluations in responding patients. However, 73% of the patients for whom CCyR was documented, lost it. On the other hand, 67% of the patients who were retreated with LEN at TI loss achieved it again. This data may suggest a potential strategy of intermittent administration of LEN, with possibly long period of time of interruption. Sequential cytogenetic data during follow up could help to better understand whether residual del(5q) clone size after LEN discontinuation is determinant for the duration of RBC-TI.

In the past, it has been postulated that LEN treatment could select resistant clones and drive disease progression, particularly in case of *TP53* mutation (16–19). More recently it has been shown that LEN treatment provides a selective advantage to *TP53*-mutant hematopoietic stem and progenitor cells in vitro and in vivo (31). On the other hand, it has been shown that the presence of biallelic *TP53* mutations has a negative impact on OS and response to LEN, therefore the evaluation of this molecular alteration needs to be interpreted carefully.

In our cohort only 19% of patients progressed to higher risk MDS or AML, and mainly after a long disease history. This progression rate is comparable to what reported in patients responding to LEN and was not related to *TP53* mutation (4). Establishing the optimal duration of lenalidomide treatment as well as its early inception to avoid clone expansion (Sintra-REV trial (32), could anyhow be relevant to define the risk of disease progression. Indeed, in our study patients who started LEN with a low transfusion burden, that could suggest lower burden of disease, had better outcome after LEN discontinuation.

In conclusion, this is the largest series to date exploring the outcome of MDS del(5q) patients who discontinued LEN while in RBC-TI response. The main limitations of our study are the heterogeneity of the population (time from diagnosis and length of lenalidomide treatment differ profoundly among cases), the absence of sequential cytogenetic/molecular evaluations and the possible bias due to the lack of a matched cohort of patients continuing LEN until progression or loss of response. Our data suggest that stopping LEN in RBC-TI patients, particularly after more than one year of treatment,

constitutes a possible option and may spare toxicities, likely improving patients' quality of life, as well as reduce the economic impact on National Healthcare Systems.

Some open issues remain, as whether CCyR achievement is a mandatory criterion to allow response maintenance after LEN discontinuation, although in our cohort patients who attained CCyR before treatment suspension seemed to have a more favorable outcome.

This retrospective study may provide the needed background for building a prospective study assessing the optimal duration of LEN treatment, also exploring clone size variations and presence/acquisition of somatic mutations during LEN treatment and after its discontinuation.

The possibility to discontinue LEN treatment in a substantial percentage of MDS del5q patients could be an innovative and cost-effective way to optimize available therapies.

Declarations

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Authors' Contributions

EC designed the study, collected and analyzed data, performed statistical analysis and wrote the paper; VS designed the study and wrote the paper; AS performed statistical analysis and wrote statistical methods of the paper; all the authors treated the patients, collected data, reviewed and approved the manuscript.

Competing Interests

U.P. declares research support and Honoraria from Geron, BMS and Janssen.

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None of the other Authors has competing interest related to this study.

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Figures

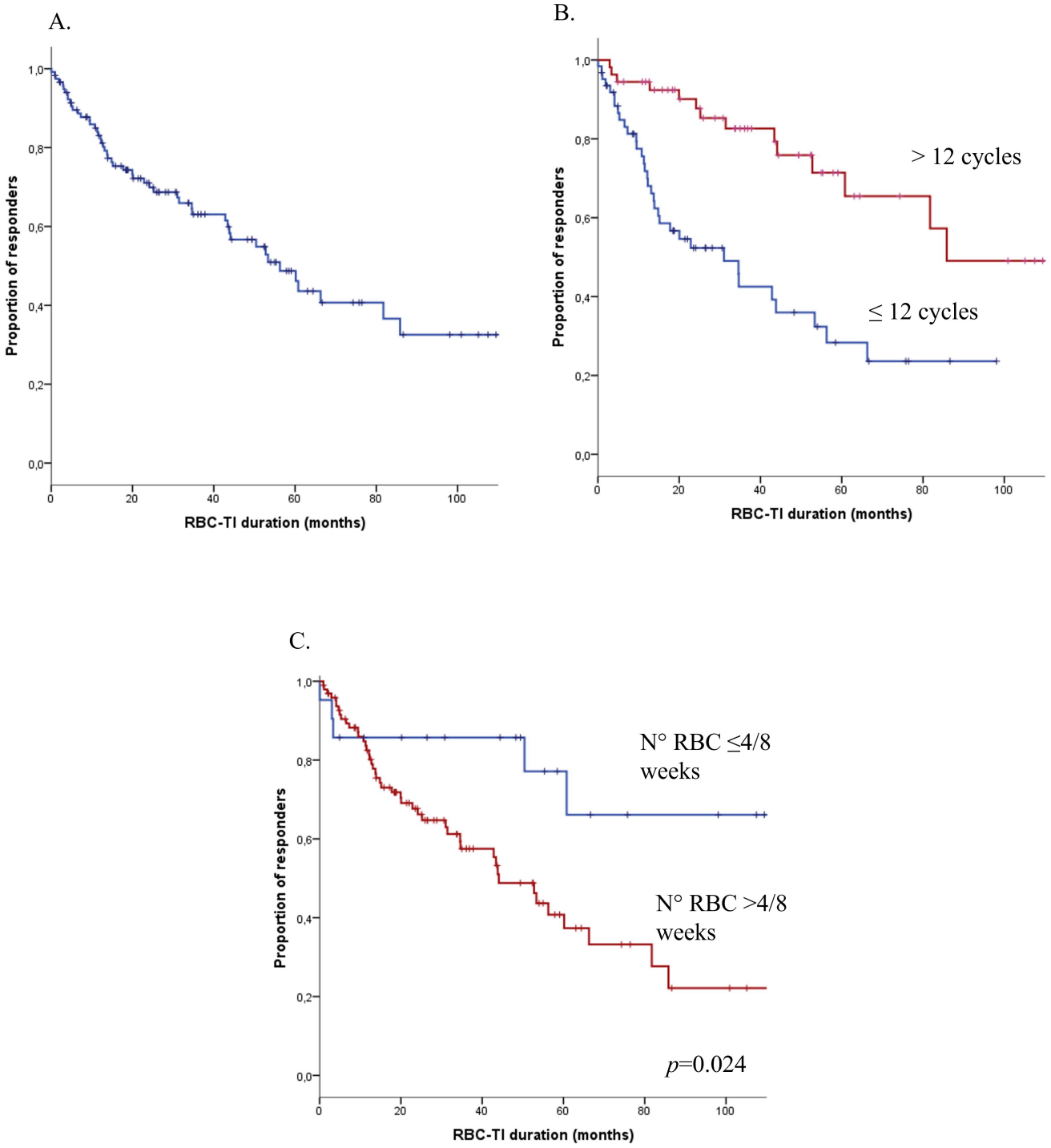

Figure 1

Red blood cell transfusion independence duration after lenalidomide discontinuation. A Overall. B. By N° of lenalidomide cycles. C. By transfusion burden before lenalidomide start

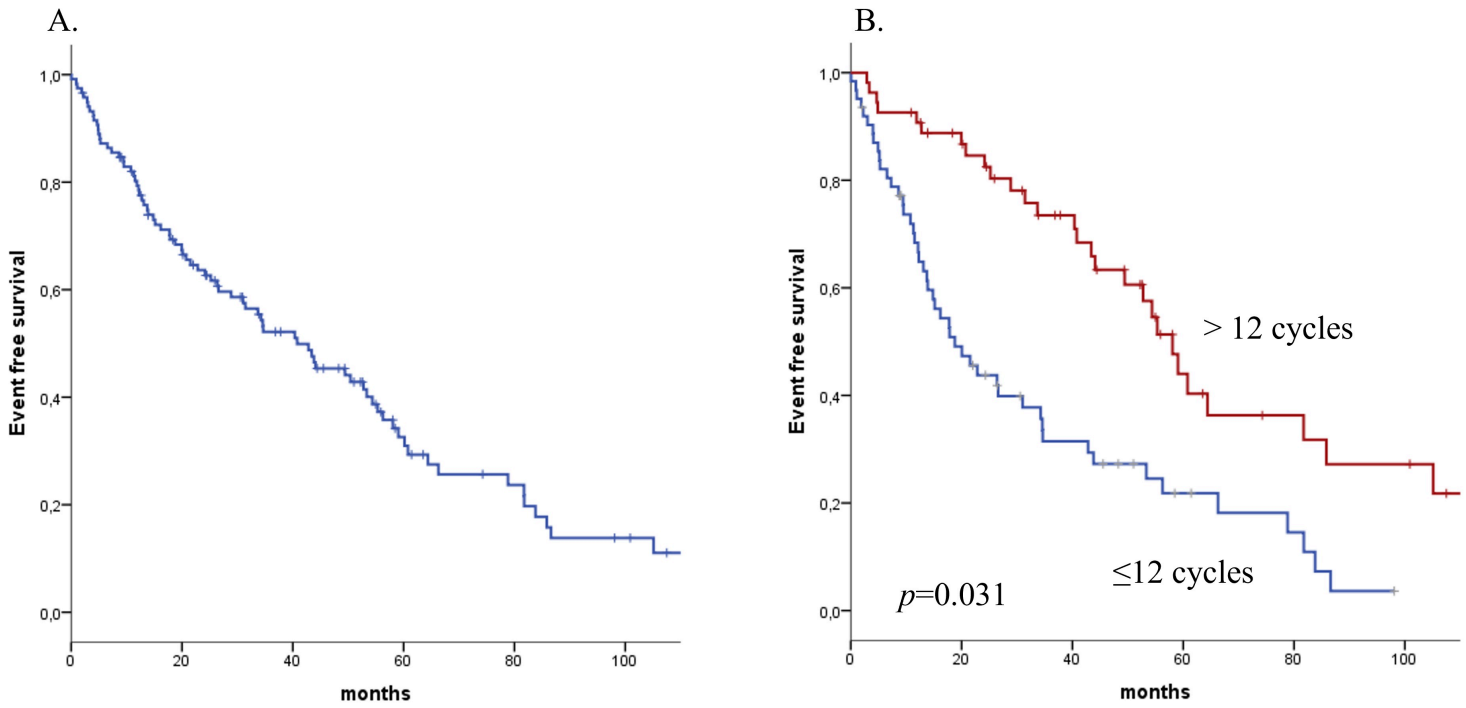

Figure 2

Event free survival (EFS) after lenalidomide discontinuation. A Overall. B. By N° of lenalidomide cycles

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