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Low-dose deferasirox for lower-risk myelodysplastic syndromes after erythropoiesis-stimulating agents (ESA) failure: results of the phase II LODEFI study

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Running Head: Low-dose deferasirox reduces transfusion needs

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Contribution: MMe, SP, VRN, MV and SDT designed the study. MMe, SP, ST, FG, SA, CR, CSal, SM, KL, PE, JD, PF, GF, CSat, SC and SDS contributed to patient enrolment. MMo assessed the deferasirox measurement TL, MRB and ZK assessed the NTBI and Hepcidin measurement. MMe, SP, VRN, MV and SDT analyzed and interpreted the data.

Declaration of interests: MMe served on advisory board with Novartis, BMS, Alexion; speaker: Incyte, GSK. SP reports conflict of interest with Novartis, BMS/Celgene, Takeda, and Pfizer. PF received consultancy fees, research funding, and honoraria from Bristol Myers Squibb/Celgene, a Bristol Myers Squibb Company, and honoraria and research funding from Celgene. The remaining authors declare no competing financial interests.

Lower-risk myelodysplastic syndromes (LR-MDS) are characterized by chronic anemia, with erythropoiesis-stimulating agents (ESAs) remaining the standard first-line treatment (1). However, most patients eventually lose response to ESAs and develop transfusion dependence. Although luspatercept (2) and imetelstat (3) have expanded treatment options after ESA failure, important unmet needs remain, particularly for patients with low transfusion burden who are not eligible for luspatercept due to limitation of access, frail elderly patients for whom myelosuppressive therapies may be inappropriate, or healthcare systems where access to these agents is limited.

Beyond its iron-chelating properties, deferasirox (DFX) exerts biological effects on erythropoiesis. Extend prior observations reporting hematologic improvement under iron chelation (4-7). Our previous in *vitro* dose-response experiments showed that, although a DFX concentration of 20 µM reflects plasma levels achieved with the conventional iron-chelating dose of 20 mg/kg/day, concentrations above 7.5 µM did not further enhance erythroid progenitor proliferation in MDS samples. We therefore selected a lower concentration of 3 µM, corresponding approximately to 5 mg/kg/day, to investigate the erythropoietic effects of DFX independently of conventional iron-chelating doses (8). Based on this biological rationale, we conducted the prospective phase II LODEFI study to evaluate whether plasma concentration-guided low-dose DFX could delay transfusion dependence in patients with LR-MDS and low transfusion burden following ESA failure.

LODEFI was a prospective, multicenter, single-arm phase II trial conducted in 14 French centers of the Groupe Francophone des Myélodysplasies (ClinicalTrials.gov identifier NCT03387475). The study protocol was approved by the local ethics committee. Adult patients with very low-, low-, or intermediate-risk MDS according to IPSS-R who had failed ESA therapy and had received fewer than 4 red blood cell [RBC] units during the previous 16 weeks were eligible. Baseline ferritin was required to range between 200 and 1000 µg/L. Patients received oral deferasirox at a starting dose of approximately 3.5 mg/kg/day, with plasma DFX concentrations measured at months 1 and 6 to adjust dosing toward a target concentration of 3 µM, based on our preclinical data. The primary endpoint was transfusion independence at month 12, defined as the absence of transfusion dependence throughout three consecutive 8-week periods between months 6 and 12. Transfusion dependence corresponded to the administration of at least 2 RBC units per 8-week period. Secondary endpoints included the proportion of patients remaining transfusion independent at 18 months, RBC transfusion burden, hematologic responses according to IWG 2006 and 2018 criteria (9, 10), safety, and iron metabolism parameters. The study was designed according to A'Hern's exact single-stage phase II design, assuming an expected response rate of 50% and a non-interest threshold of 30% (11). Continuous variables were summarized as median and interquartile range (IQR) according to distributions, and categorical variables as frequencies and percentages. Missing data were reported but not imputed. Binary endpoints were described with two-sided 95% confidence intervals. Patients

who discontinued the study before month 12 were conservatively classified as non-responders for primary and secondary efficacy endpoints.

Between February 2018 and April 2023, 38 patients were enrolled (Figure 1). Median age was 73.5 years (IQR, 69.0–78.0), 57.9% were male, and the median Charlson comorbidity index was 4. Most patients had low-risk disease (81% very low/low IPSS-R), and 86.8% were not transfusion dependent according to IWG 2018 criteria at study entry despite universal ESA failure. Median baseline hemoglobin was 86 g/L and median ferritin concentration was 547 µg/L, indicating moderate iron overload. Baseline characteristics are summarized in Table 1.

The primary endpoint was met. At 12 months of treatment, 18 of 38 patients (47.4%; 95% confidence interval [CI], 31.0–64.2) remained transfusion independent, with a median hemoglobin level of 88 g/L (range, 74–108), thereby meeting the predefined efficacy criterion of the A'Hern design. At 18 months, transfusion independence persisted in 34.2% of patients (95% CI, 19.6–51.4) with a median hemoglobin level of 94 g/L (range, 73–116). Using a more permissive definition of transfusion dependence (>4 RBC units during each 8-week period), at 12 months the response rate increased to 68.4% (95% CI, 51.3–82.5). No difference in efficacy was observed according to the presence of ring sideroblasts. By contrast, conventional IWG 2006 and 2018 erythroid response criteria identified responses in fewer than 10% of patients, illustrating the limited suitability of these criteria in populations with very low baseline transfusion requirements (Supplementary table 1).

Treatment was well tolerated. Nineteen treatment-related adverse events were reported, of which only six were grade ≥3. Gastrointestinal disorders were the most frequent toxicities. No treatment-related deaths occurred, and renal function remained stable throughout treatment, with no clinically meaningful increase in serum creatinine despite the advanced age and comorbidity burden of the study population (Supplementary table 2). Quality-of-life scores assessed by EQ-5D-3L and FACT-An remained unchanged over time, suggesting that prolonged administration of low-dose DFX did not impair patient-reported outcomes. Responders required significantly fewer cumulative RBC transfusions than non-responders (median 6.5 vs. 18 units; P=0.031) and remained on treatment substantially longer (median 16.5 vs. 8.8 months; P<0.001).

Concerning iron metabolism (Supplementary table 3), ferritin concentrations progressively decreased among responders but not among non-responders. At month 12, median ferritin was 357 µg/L in responders compared with 874 µg/L in non-responders (P=0.006), and this difference persisted at month 18.

These findings should be interpreted in the context of the rapidly evolving therapeutic landscape of LR-MDS. Luspatercept and imetelstat have considerably expanded treatment options after ESA failure but have primarily been evaluated in patients with established transfusion dependence and higher transfusion burdens than those enrolled in LODEFI. Nevertheless, ongoing

trials are currently evaluating luspatercept in earlier disease settings, including non-transfusion-dependent patients (ELEMENT-MDS, NCT05949684). By contrast, our study specifically targeted patients at an earlier stage of disease, when transfusion burden remained low but ESA resistance had already occurred. This population is frequently encountered in routine practice yet remains underrepresented in prospective clinical trials. Delaying the transition to sustained transfusion dependence may therefore represent a clinically meaningful therapeutic objective, particularly in older patients with multiple comorbidities. Moreover, our results suggest a higher hematologic response than that reported with conventional doses of DFX. In the GIMEMA MDS0306 trial (4), DFX (10–20 mg/kg/day) achieved transfusion independence in 15.5% of patients, while in the EPIC study (5), DFX (generally 20 mg/kg/day) resulted in an erythroid response in 21.5%. Treatment discontinuation due to adverse events was frequent in both studies. Nevertheless, differences in patient populations, dosing strategies, and response criteria preclude direct comparison with our low-dose DFX study.

The marked discrepancy between high rates of transfusion independence and low rates of IWG-defined erythroid responses highlights a methodological gap in current response assessment for LR-MDS. Nearly 90% of patients were non-transfusion dependent at study entry, making conventional erythroid response criteria poorly suited to detect clinically relevant benefit. IWG 2006 and 2018 criteria were largely designed for patients already requiring regular transfusions, in whom a reduction of at least four units per 8-week interval is a realistic endpoint. In patients with minimal transfusion requirements, such thresholds are rarely met, even when treatment stabilizes hemoglobin levels and prevents escalation of transfusions. Our findings support the development of response criteria specifically adapted to patients with low transfusion burden, in whom maintenance of transfusion independence may better capture clinically meaningful benefit. In LODEFI, the prospectively defined primary endpoint directly addressed this objective and proved sensitive to the observed treatment effect.

An additional strength of the study is the favorable safety profile of low-dose DFX. Treatment-related adverse events were predominantly grade 1–2, no treatment-related deaths occurred, renal function remained stable throughout follow-up, and quality of life was preserved despite prolonged treatment exposure. These observations are particularly relevant considering the advanced age and comorbidity burden of the study population and suggest that plasma concentration-guided low-dose deferasirox can be administered safely over prolonged periods.

Several limitations should nevertheless be acknowledged. First, LODEFI was a single-arm phase II study with a relatively small sample size, precluding direct comparison with contemporary second-line therapies. Second, the selected population—patients with low transfusion burden and moderate iron overload after ESA failure—limits extrapolation of these findings to more heavily transfused patients. Nevertheless, the prospective design, the prespecified A'Hern single-stage framework, and

the consistent reduction in transfusion burden and ferritin among responders suggest that the observed benefit is unlikely to reflect spontaneous fluctuations in transfusion requirements alone. Given its oral administration, favorable safety profile, limited cost, and biologic rationale, low-dose DFX may represent an attractive early intervention strategy in selected LR-MDS patients after ESA failure, who are not candidates for, or do not have access to, currently approved second-line therapies.

In conclusion, the LODEFI study provides prospective evidence that plasma concentration-guided low-dose deferasirox may delay progression toward transfusion dependence in selected patients with lower-risk MDS after ESA failure. In this under-studied population, preventing escalation of transfusion requirements and maintaining transfusion independence may constitute a clinically meaningful endpoint, not fully captured by current IWG criteria. Low-dose DFX may thus offer a simple, safe, and accessible option for selected patients. These findings warrant confirmation in a randomized controlled trial and support further investigation of low-dose DFX as an early disease-modifying approach in lower-risk MDS.

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Table 1: Baseline characteristics of the study population (n = 38).

	n = 38
Age, med[IIQ]	73.5 [69.0 ; 78.0]
Index de Charlson, med[IIQ]	4.0 [3.0 ; 5.0]
Gender	
Man	22 (57.9%)
Female	16 (42.1%)
Index de Charlson	
med[IIQ]	4.0 [3.0 ; 5.0]
0	1 (2.6%)
2	5 (13.2%)
3	10 (26.3%)
4	9 (23.7%)
5	10 (26.3%)
6	3 (7.9%)
WHO 2006 MDS Classification, n(%)	
RA	7 (18.4%)
RARS	13 (34.2%)
RCMD	10 (26.3%)
CMML	1 (2.6%)
RAEB-1	4 (10.5%)
MDS-U	3 (7.9%)
IPSS-R, n(%)	
very low	6 (16.2%)
low	24 (64.9%)
Intermediate	6 (16.2%)
High	1 (2.7%)
missing data, n	1
Hemoglobin level(g/l), med[IIQ]	86.0 [81.0 ; 97.0]
Platelets count (G/l), med[IIQ]	230.0 [144.5 ; 366.5]
Neutrophiles count (G/l), med[IIQ]	2.3 [1.2 ; 3.7]
Number of red blood cell units, n(%)	
0	21 (55.3%)
1	2 (5.3%)
2	10 (26.3%)
3	1 (2.6%)
4	3 (7.9%)
5	1 (2.6%)
Statut IWG 2018, n(%)	
Non-transfused	33 (86.8%)

Low Transfusion Burden	5 (13.2%)
Prior ESA, n(%)	
Epoetin alpha	10 (26.3%)
Epoetin beta	4 (10.5%)
Darbepoetin	21 (55.3%)
Epoetin Zeta	11 (28.9%)

CMML: Chronic myelomonocytic leukemia, ESA: erythropoietin stimulating agent, MDS-U: Myelodysplastic syndrome unclassifiable, RA: refractory anemia, RAEB1: refractory anemia with excess of bone marrow blasts 1, RARS: refractory anemia with ring sideroblast, RCMD: refractory cytopenia with multilineage dysplasia.

FIGURES LEGENDS

Figure 1: Flow chart LODEFI. A total of 38 patients were enrolled. At month 6, 36 patients were evaluable, with two patients not evaluable due to one death and one withdrawal of consent. At month 12 and 18, 25 and 23 patients remained evaluable respectively. Reasons for non-evaluability included death, withdrawal of consent, progression to transfusion dependence, and other unspecified reasons.

Figure 2: Red blood cell transfusion burden and hemoglobin over time. A) Swimmer plot depicting red blood cells transfusion burden from inclusion to Month 18. At 12 months, 18 of 38 patients (47.4%) remained transfusion independent after 12 months of treatment. **B)** Temporal evolution of hemoglobin.
RBC: red blood cells unit, Study and DFX D/C = Study and DFX discontinuation, Study D/C and DFX C = Study discontinuation and DFX continuation, TD: Transfusion dependence, TI: transfusion independence.

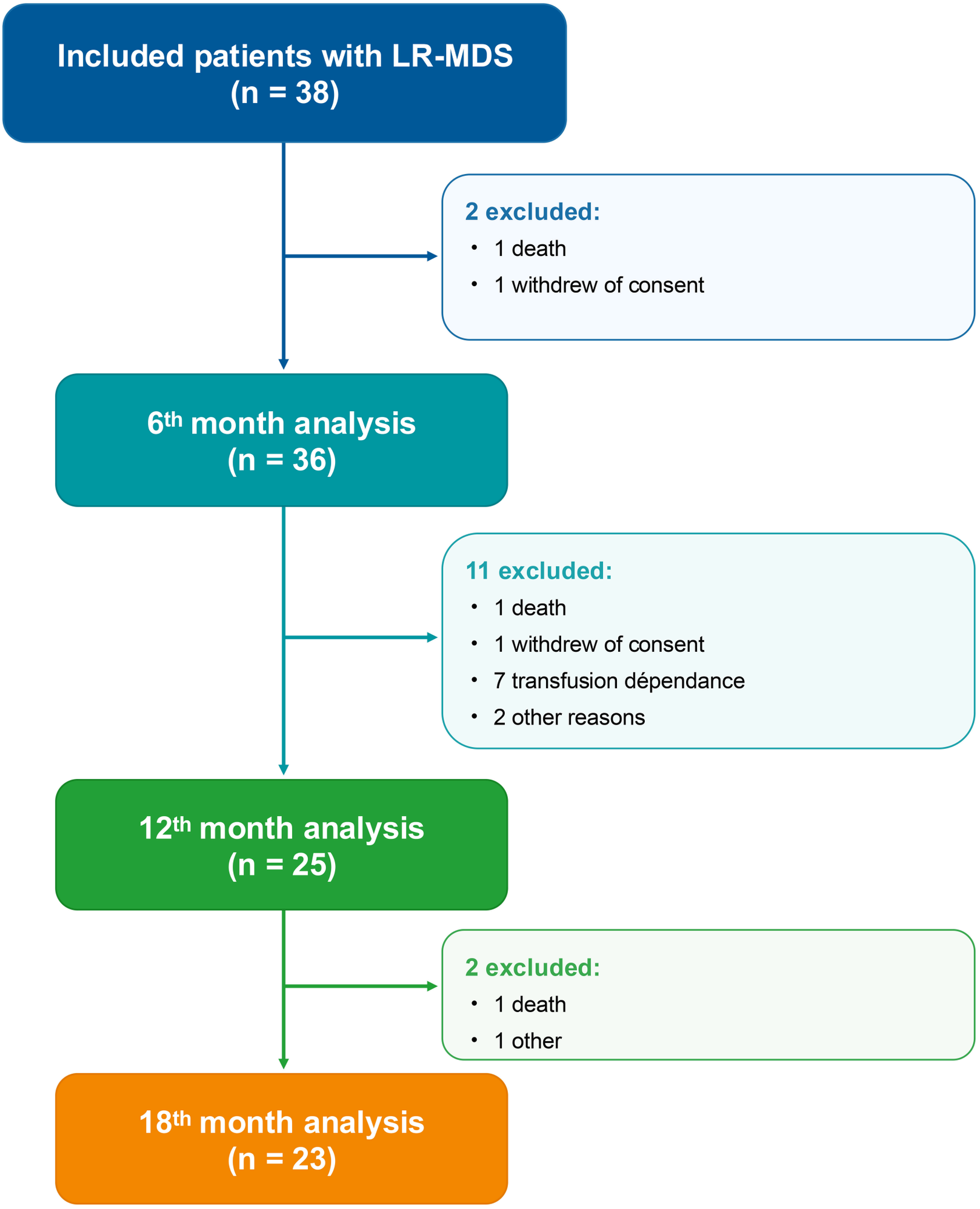
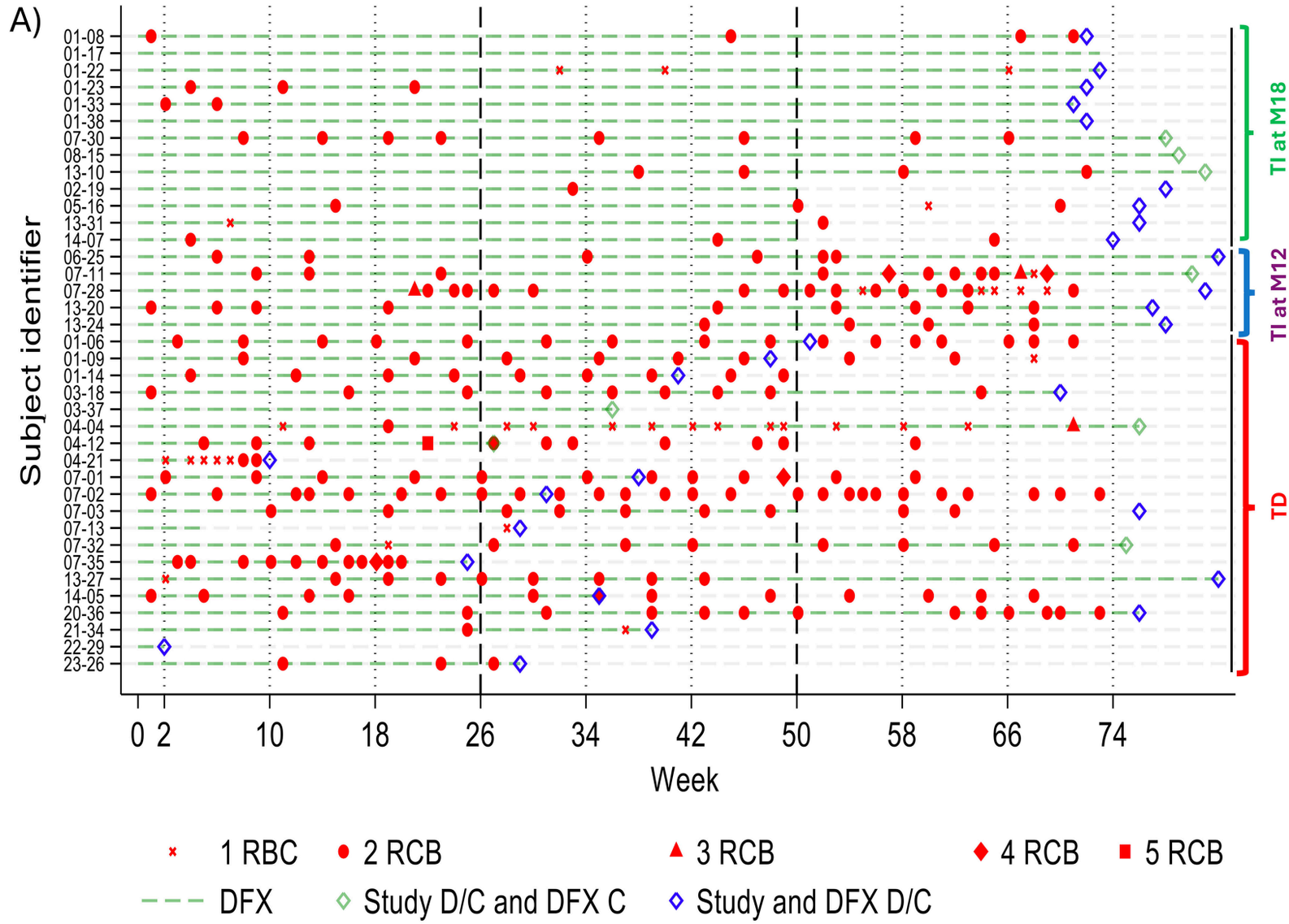

Included patients with LR-MDS
(n = 38)
2 excluded:
• 1 death
• 1 withdrew of consent
6th month analysis
(n = 36)
11 excluded:
• 1 death
• 1 withdrew of consent
• 7 transfusion dépendance
• 2 other reasons
12th month analysis
(n = 25)
2 excluded:
• 1 death
• 1 other
18th month analysis
(n = 23)

Figure 2.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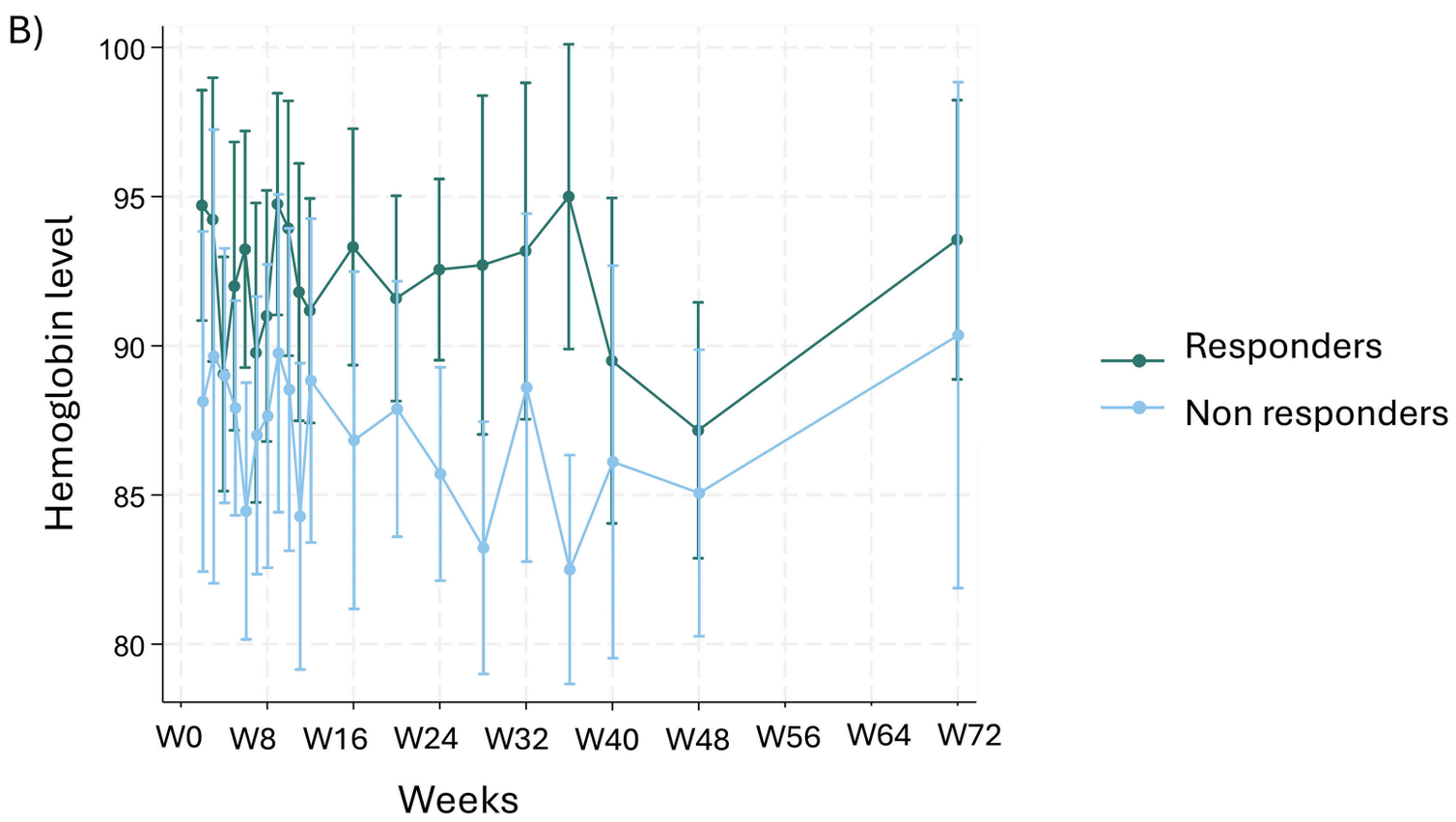
B)
Hemoglobin level
100
95
90
85
80
W0
W8
W16
W24
W32
W40
W48
W56
W64
W72
Weeks
Responders
Non responders