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A Multicenter, Retrospective Study Comparing Immunosuppressive Therapy Combined with Eltrombopag to Immunosuppressive Therapy Alone as Front-Line Treatment for Pediatric Severe Aplastic Anemia

Atay D. et al.: EPAG Combined with IST in Pediatric SAA Patients

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Abstract
Objective: Eltrombopag (EPAG) added to standard immunosuppressive therapy (IST) was associated with higher overall (OR) and complete response (CR) rates in patients with treatment-naïve severe aplastic anemia (SAA) in adults, but the clinical evidence on the efficacy of EPAG in children with acquired aplastic anemia is limited and controversial.
Material and Metods: We compared the efficacy and safety of EPAG combined with IST (n=38) versus IST alone (n=57) as a front-line treatment for pediatric patients with SAA.
Results: The EPAG+IST group had higher CR and OR rates at 3 and 6 months, although 1-year OR, CR, and partial response (PR) rates showed no significant difference between two groups. Older age at diagnosis (>8.95

years) was associated in the EPAG+IST group with higher OR rates at 6 months and 1-year (p=0.007, p=0.005, respectively). The addition of EPAG to IST did not demonstrate superiority over IST alone in terms of overall survival (OS) and event-free survival (EFS) in this study; with 1-year EFS of 81.1% for EPAG+IST and 71.3% for IST, and with 1-year OS of 89.2% vs. 80.4%.
Conclusion: Eltrombopag induced a faster response compared to those receiving IST alone without increasing toxic effects, but EPAG does not confer additional benefits regarding OS or relapse rates in children. Notably, older age at diagnosis in the EPAG+IST group was significantly associated with improved response rates.
Keywords: Eltrombopag · Immunosuppression · Treatment · Severe aplastic anemia

Özet
Amaç: Standart immünosüpresif tedaviye (IST) eklenen eltrombopag (EPAG), yetişkinlerde tedavi görmemiş şiddetli aplastik anemisi (SAA) olan hastalarda daha yüksek genel (OR) ve tam yanıt (CR) oranları ile ilişkilendirilmiştir, ancak edinilmiş aplastik anemisi olan çocuklarda EPAG' in etkinliğine ilişkin klinik kanıtlar sınırlı ve tartışmalıdır.
Gereç ve Yöntem: Çalışmada SAA' li pediatrik hastalarda ilk basamak tedavi olarak IST ile kombine EPAG' in (n=38) etkinliği ve güvenliği tek başına IST (n=57) alan hasta grubu ile karşılaştırıldı.
Bulgular: EPAG+IST grubu 3 ve 6. aylarda daha yüksek CR ve OR oranlarına sahipti, ancak 1 yıllık OR, CR ve parsiyel yanıt (PR) oranları iki grup arasında anlamlı bir fark göstermedi. EPAG+IST grubunda tanı anında daha büyük yaşta olmak (>8.95 yaş), 6 ay ve 1 yılda daha yüksek OR oranları ile ilişkiliydi (sırasıyla p=0.007, p=0.005). Bu çalışmada EPAG' in IST' ye eklenmesi, genel sağkalım (OS) ve olaysız sağkalım (EFS) açısından tek başına IST' ye göre üstünlük göstermedi (1 yıllık EFS EPAG+IST için %81.1 ve IST için %71.3 ve 1 yıllık OS %89.2'ye karşı %80.4).
Sonuç: Eltrombopag toksik etkileri artırmadan tek başına IST alanlara kıyasla daha hızlı yanıt almayı sağladı. Ancak IST' ya EPAG eklenmesi çocuklarda OS veya relaps oranları açısından tek başına IST' ye göre ek fayda sağlamadı. Tanı sırasında daha büyük yaşta olan çocuklarda özellikle IST' ye EPAG eklenmesi daha iyi yanıt oranları ile önemli ölçüde ilişkiliydi.
Anahtar sözcükler: Eltrombopag · immünsupresyon · tedavi · ağır aplastik anemi

Introduction
Acquired aplastic anemia (AA) is an immune-mediated bone marrow (BM) failure where marrow disruption is driven by a cytotoxic T-cell–mediated autoimmune attack against hematopoietic stem cells. The current treatment approach for severe aplastic anemia (SAA) consists of immunosuppressive treatment (IST) or hematopoietic stem cell transplantation (HSCT) [1,2]. The standard IST protocol involves the use of anti-thymocyte globulin (ATG) and cyclosporine A (CSA), with studies indicating that horse ATG is superior to rabbit ATG in terms of both short-term response and long-term survival [3-7].
Studies have found that all patients with SAA have significantly decreased levels of early progenitor cells and hematopoietic stem cells [8,9]. It has been reported that thrombopoietin (TPO) can stimulate the hematopoietic capacity of primitive HSCs in the bone marrow [9,10]. As an agonist of the TPO receptor, eltrombopag (EPAG) has been found to significantly restore trilineage hematopoiesis in patients with refractory aplastic anemia, which can be sustained even on discontinuation of the drug [8,11,12]. Numerous studies demonstrated its efficacy in patients with SAA refractory to immunosuppression [13-15]. However, the effects of EPAG on pediatric patients with SAA remain controversial and limited. Data from adults showed that adding EPAG resulted in considerable increases in response rates to >80%, nevertheless, the same outcome did not occur in children [16,17]. Therefore, we conducted a retrospective study to determine the efficacy and safety of EPAG combined with IST in pediatric patients with SAA in comparison with standard IST group.

Methods
This was a multicenter, retrospective study that assessed the safety and efficacy of EPAG combined with immunosuppressive therapy for pediatric patients with SAA in comparison with standard IST group. Sixteen pediatric hematology centers participated in the study. Group 1 comprised patients who received EPAG+IST therapy as a front-line treatment for pediatric patients with severe aplastic anemia. A historical pediatric treatment group using standard IST as frontline therapy was used as group 2. We also conducted a subgroup analysis based on the median age of 8.95 years in our study to assess the impact of age.
This study was approved by the Ethical Committee of the Acibadem University School of Medicine (No. 2024-5/166). Informed consents were obtained from all patients and/or their legal guardians according to the Declaration of Helsinki.

Definitions
SAA was defined as BM cellularity <25% and at least 2 of the following: absolute neutrophil count (ANC) $<0.5\times10^9$/L, platelet count $<20\times10^9$/L, or reticulocyte count $<20\times10^9$/L (or corrected reticulocyte count < 1%), according to the Camitta criteria [18]. Very SAA (vSAA) was defined using the same criteria as were used for SAA with the following modification: neutrophils $<0.2\times10^9$/L.

Overall response (OR) was defined as no longer meeting the criteria for SAA in the absence of recent transfusions and without the administration of granulocyte colony-stimulating factor. Complete response (CR) required all ANC $\geq 1.0\times10^9$/L, hemoglobin level ≥10 g/dL and platelet count $\geq 100\times10^9$/L. A partial response (PR) was defined as an overall outcome where the patient did not meet the criteria for a complete response but still achieved transfusion independence, with an ANC of at least 0.5×10^9/L, a hemoglobin level of at least 8 g/dL, and a platelet count of at least 20×10^9/L. Patients who did not complete 6 months of initial IST due to death, HSCT or who underwent a second course of IST or failed to achieve a response by 6 months were considered to have had no response.

Treatment protocol

Patients with previously untreated SAA without matched sibling donors were eligible. History, clinical and laboratory tests were used for screening for classical inherited BM failure syndromes. The diepoxybutane test was applied to rule out Fanconi anemia. PNH clones were assessed by flow cytometry. Standard cytogenetic and FISH for monosomy 7 were used to exclude clonal abnormalities. In the standard IST group, the patients received 40 mg/kg per day hATG (ATGAM®, Pfizer) for 4 days and 3-5 mg/kg/day oral CSA (Sandimmun neoral®, Novartis) daily starting at day 1 to maintain whole blood trough concentrations of 150 to 300 ng/mL. In addition, 1 mg/kg per day of methylprednisolone was iv-administered for days 1 to 4, followed by administration of 1 mg/kg per day of oral prednisolone for 10 days without tapering. CSA was continued for ≥18 months after hematological response plateau achievement, followed by tapering by 5% to 10% of the daily dose per month. In the EPAG+IST group, the patients additionally received EPAG (Revolade®, Novartis) at an initial dose of 150 mg daily for patients aged ≥12 years, 75 mg for those aged 6–11 years and 2.5 mg/kg for those aged 2–5 years per day starting on day 1 of hATG, which was subsequently adjusted according to the results of complete blood counts. The duration of EPAG treatment was ≥120 days: in the absence of at least a PR at 3 months, EPAG was discontinued, and the patients received second line treatment.

Response evaluation

1. The primary endpoints were responses, including complete responses and partial responses, at the following timepoints: 3, 6, and 12 months, as well as at the end of treatment. Secondary indexes included times of transfusion independence for G-CSF, RBC, and platelets.
2. The secondary endpoints were the safety parameters including tolerability and toxicities of EPAG, relapse, OS and EFS.

Statistical analysis

The statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). For data that were not normally distributed, measurements were presented as medians with ranges. The Kaplan–Meier method was used to analyze the overall survival and duration of the responses. The Mann-Whitney U and Pearson χ^2 tests were used to compare continuous and categorical variables with a level of statistical significance of $p<0.05$. Variables with a p-value of less than 0.2 in the univariate analysis were included in the multivariate analysis. Multivariable Cox proportional hazard regression models were used to analyze the factors influencing both OS and EFS.

Results

Patient characteristics

A total of 95 pediatric patients aged between 1.2-18 years (median 8.95 years) were enrolled in the study. The duration of EPAG treatment was a median 28 (4-106) weeks. The median follow-up was 41.73 (1.10-88.77) months in the EPAG+IST group and 69 (1.03-344.13) months in the IST group.

Hematological response

Patients in group EPAG+IST had a higher probability of a CR and an OR at 3 months and 6 months (Table 2, p=0.02). CR rate was 15.6% at 3 months and 48.1% at 6 months in the EPAG+IST group compared to the IST group at 1.8% and 13.3% respectively (p=0.01 and p=0.002). Additionally, the number of nonresponder patients was higher in group 2 at 3 months (66.1%) and at 6 months (48.9%). However, response rates at the end of therapy and at 1 year were not statistically significantly different between the two groups in terms of OR, CR, PR, or NR.

Relapse and clonal evolution

Of a total of 17 complete responders in group 1 patients, 11.7% relapsed compared to 11.1% in group 2 patients. The time to relapse was 4 and 18 months following the cessation of eltrombopag therapy in group 1 patients, and 30 and 48 months after stopping immunosuppressive therapy in group 2 patients. The cumulative incidence of relapse did not differ significantly between two groups.

The most frequent clonal evolution was the development of PNH clone. Ten patients developed PNH during follow-up, while progression to MDS or AML was observed in 5 patients. In group 1, clonality was observed in 4 patients (3 with PNH and 1 with MDS). The PNH clone appeared in 3 patients at 4, 11, and 12 months after therapy, while MDS was detected 3 months after therapy. In group 2, clonality was observed in 11 patients (7 with PNH, 3 with MDS, and 1 with AML). The PNH clone appeared in 7 patients between 8 and 84 months after therapy. MDS was detected in 3 patients at 4, 12, and 22 months after therapy, and AML was detected in 1

patient 9 months after therapy. No PNH-related clinical manifestations were detected. HSCT was performed in all patients who developed MDS or AML. Clonal evolution was not significantly different between two groups.

OS and EFS

Twenty-three patients died during the study; 6 patients in group 1 and 17 patients in group 2. Three patients in group 1 and 4 patients in group 2, who were also nonresponders, passed away due to post-HSCT complications (GVHD and infection). Three patients in group 1 and 13 patients in group 2, died due to cytopenia related infection or bleeding complications. The event-free survival rate was similar between group 1 and group 2 patients (p=0.142, Table 2, Figure 1) and no difference was found in the OS rate of the groups (p=0.26, Table 2, Figure 1).

Subgroup analysis

The subgroup analysis showed that the OR rates at 6 months and 1-year were significantly better in subgroup 2 (children >8.95 years), respectively (p=0.008, p=0.009, Table 3). This observed significance was found to be applicable only to patients in the EPAG+IST group. However, the response rate at 6 months and 1 year was significantly higher in the EPAG+IST group compared to subgroup 1 patients (p=0.007, p=0.005, respectively). While there was no difference in OS between the two subgroups, EFS was statistically significantly better in subgroup 1 patients compared to those in subgroup 2 (p=0.01, Figure 2). This significance was only observed in the patients receiving IST therapy (p=0.006).

We observed that clonality occurred statistically more frequently in children older than 8.95 years (25.5% vs. 6.4%; p=0.01). A higher occurrence of clonality was observed in subgroup 2 patients who received IST alone. Detailed treatment responses and survival analysis results are summarized in Table 3.

Predictors of Response

Details of the multivariable analyses are provided in Table 4. In the multivariable analysis, randomization groups, patient age at diagnosis, and initial platelet counts were the only three factors associated with a response. Patients in EPAG+IST group had a higher probability of an ORR at 3 months and at 6 months. Higher initial platelet count was significantly related to a higher ORR at 3 months. Younger age at diagnosis was associated with lower ORRs at 6 months and 1-year.

The multivariate analyses for OS in terms of randomization groups, age at diagnosis, Hb/ANC/Plt counts at diagnosis, 3-months/6-months/1-year responses and not receiving G-CSF therapy showed that none of these factors significantly affected the OS, but being a nonresponder was significantly correlated with worse OS (p=0.004).

For EFS, being a nonresponder, not receiving G-CSF therapy and older age at diagnosis were confirmed as risk factors (p=0.017, p=0.048 and p=0.008; Table 4).

Safety data

Eltrombopag was well tolerated, with no serious adverse events observed related to the therapy. In all, 4 patients had reversible liver function abnormalities possibly attributable to EPAG. The most common adverse events were indirect bilirubin elevation. Fifteen patients in the EPAG group (44.7%) had indirect hyperbilirubinemia, which was temporary and controllable in 9 patients with dose reduction. Seven patients, who were also nonresponders or partial responders, discontinued medication due to grade 2 indirect hyperbilirubinemia.

Discussion

Severe aplastic anemia is mainly immune-mediated, acute onset, rapidly progressive disease. There are studies, particularly in adults, that show the addition of eltrombopag to standard IST improves the rate, rapidity, and strength of hematologic response in previously untreated patients with severe aplastic anemia, without adding extra toxic effects. The EBMT phase III study comparing first-line ATG and CSA with or without eltrombopag for SAA (RACE trial) showed a significant increase in CR with eltrombopag [14]. The addition of eltrombopag increased the CR at 3 months, the OR at 6 months and the shorter median time to response as compared to standard IST. 2-year OS was similar between the two arms. Efficacy of frontline concomitant IST with eltrombopag in pediatric group is still conflicting. Groarke et al. (n=40) showed no improvement at 6 months in terms of ORR and CR compared with historical IST cohort in children [16]. Goronkova et al. conducted a randomized prospective study to compare the efficacy and safety IST with (n=49) or without (n=49) EPAG in children with SAA and showed no significant difference in OR at 4 months between IST with or without EPAG, although the CR rate at 4 months was higher in the IST+EPAG group[19]. No difference in survival was observed between the two groups. Our study showed that patients in the EPAG+IST group had higher CR and ORRs at 3 and 6 months compared to those treated with IST alone. More nonresponders were found in the IST group than the EPAG+IST group at 3 months and 6 months. Long-term response rates showed no significant difference between groups, but the addition of EPAG to IST therapy provided the patient with the opportunity to respond at an earlier period. Prolonging treatment beyond 3-6 months for patients with a partial response did not lead to a complete response. While long-term CR rates were higher in the EPAG+IST group than the IST group (64% vs 43.8%), it wasn't statistically significant.

Previous pediatric studies have also reported the impact of age on treatment outcomes, suggesting that younger children may not experience the same benefits from EPAG. Groarke et al. found that younger children (<12

years) had lower response rates than adolescents when treated with EPAG, with OR and CR rates of 63% vs. 78% and 6% vs. 46%, respectively [16]. Similarly, Zhao et al.'s study indicated that younger children (<14 years) had lower response rates compared to adolescents, with OR rates of 50.0% vs. 85.7% and CR rates of 12.5% vs. 85.7% [17]. Our subgroup analysis by median age showed higher OR rates in older children (>8.95 years) at 6 months (50% vs. 79.4%) and 1 year (64.3% vs. 93.1%). The significance was only noted in older patients treated with EPAG+IST (p=0.007, p=0.005). Due to the small sample size, these conclusions require further verification, and it is essential to investigate the potential mechanisms underlying the differences in responses between younger children and adolescents.

The addition of EPAG to IST did not demonstrate superiority over IST alone in terms of OS and EFS in this study. But EFS was statistically significantly better in younger patients receiving IST therapy. Further analysis of the factors influencing EFS revealed a higher incidence of clonality in children older than 8.95 years (25.5% vs. 6.4%). While age did not affect clonality development in patients treated with EPAG+IST, a higher occurrence of clonality was noted in older patients who received only IST. Future studies involving a larger patient population will clarify this matter. In our cohort, at a median follow-up of 44.5 months, adding EPAG to IST treatment did not reduce relapse frequency consistent with findings from other pediatric studies.

The ability to identify patients who have a higher probability of hematologic response is important. None of the previously reported baseline hematologic characteristics were associated with the overall response rate in our study [20-21]. Our findings indicate that the addition of EPAG to IST therapy, older age at diagnosis, and higher initial platelet counts were the only three factors significantly associated with a hematological response in the multivariate analyses. Also being a nonresponder was significantly correlated with worse OS.

In conclusion, EPAG induced a faster response compared to those receiving immunosuppressive therapy alone without increasing toxic effects. However, the determination of which SAA patients benefit most from the addition of eltrombopag therapy remains unresolved. The retrospective nature of this study limited its power. Due to the varying results in different pediatric groups, it remains uncertain whether concomitant IST with eltrombopag is superior to historical IST. Therefore, these outcomes should be further validated in large, prospective, and multicenter studies in the future.

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Abbreviations

Eltrombopag (EPAG); immunosuppressive therapy (IST); overall response (OR); complete response (CR); severe aplastic anemia (SAA); partial response (PR); overall survival (OS); event-free survival (EFS); hematopoietic stem cell transplantation (HSCT); anti-thymocyte globulin (ATG); cyclosporine A (CSA); thrombopoietin (TPO); absolute neutrophil count (ANC); granulocyte-stimulating factor (G-CSF)

Keywords Eltrombopag · Immunosuppression · Treatment · Severe aplastic anemia

Ethics Statement

This study was approved by the Ethical Committee of the Acibadem University School of Medicine (No. 2024-5/166). Informed consents were obtained from all patients and/or their legal guardians according to the Declaration of Helsinki.

All authors contributed to the writing of the manuscript, interpreted the results, and gave final approval. All authors are responsible for the accuracy and integrity of the work. All authors read and approved the final manuscript.

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References

1. “Consensus for the Treatment of Severe Aplastic Anaemia in Children and Adolescents.” EWOG-SAA, March 21, 2023. https://ewog-mds-saa.org/fileadmin/mediapool/10_andere/ewog-mds/pdf/protocoldocs/Concensus_for_treatment_of_SAA_v1.7.pdf.

2. Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol. 2016;172(2):187–207. doi:10.1111/bjh.13853.

3. Babushok DV, DeZern AE, de Castro CM, et al. Modified Delphi panel consensus recommendations for management of severe aplastic anemia. Blood Adv. 2024 Aug 13;8(15):3946-3960.

4. Marsh JC, Bacigalupo A, Schrezenmeier H, et al. Prospective study of rabbit antithymocyte globulin and cyclosporine for aplastic anemia from the EBMT severe aplastic anaemia working party. Blood. 2012;119(23):5391–5396. doi:10.1182/blood-2012-02-407684.

5. Scheinberg P, Nunez O, Weinstein B, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N Engl J Med. 2011;365(5):430–438.

6. Takahashi Y, Muramatsu H, Sakata N, et al. Rabbit antithymocyte globulin and cyclosporine as first-line therapy for children with acquired aplastic anemia. Blood. 2013;121(5):862–863.
7. Jeong DC, Chung NG, Cho B, et al. Long-term outcome after immunosuppressive therapy with horse or rabbit antithymocyte globulin and cyclosporine for severe aplastic anemia in children. Haematologica. 2014;99(4):664–671.
8. Townsley DM, Scheinberg P, Winkler T, et al. Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia. N Engl J Med. 2017 Apr 20;376(16):1540-1550.
9. Alexander WS, Roberts AW, Nicola NA, et al. Deficiencies in progenitor cells of multiple hematopoietic lineages and defective megakaryocytopoiesis in mice lacking the thrombopoietic receptor c-Mpl. Blood. 1996;87(6):2162–2170.
10. Qian H, Buza-Vidas N, Hyland CD, et al. Critical role of thrombopoietin in maintaining adult quiescent hematopoietic stem cells. Cell Stem Cell. 2007;1(6):671–684.
11. Desmond R, Townsley DM, Dumitriu B, et al. Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. Blood. 2014;123(12):1818–1825.
12. Olnes MJ, Scheinberg P, Calvo KR, et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. N Engl J Med. 2012;367(1):11–19.
13. Assi R, Garcia-Manero G, Ravandi F, et al. Addition of eltrombopag to immunosuppressive therapy in patients with newly diagnosed aplastic anemia. Cancer. 2018;124(21):4192-4201.
14. Peffault de Latour R, Kulasekararaj A, Iacobelli S, et al. Eltrombopag added to immunosuppression in severe aplastic anemia. N Engl J Med. 2022; 386(1):11-23.
15. Li X, Shangguan X, Wang H, et al. Comparison of efficacy of eltrombopag combined with immunosuppression in the treatment of severe aplastic anemia and very severe aplastic anemia: real-world data and evidence. Ann Hematol. 2024 Sep;103(9):3483-3491.
16. Groarke EM, Patel BA, Gutierrez-Rodrigues F, et al. Eltrombopag added to immunosuppression for children with treatment-naïve severe aplastic anaemia. Br J Haematol. 2021 Feb;192(3):605-614. Erratum in: Br J Haematol. 2022 Jun;197(5):640-641.
17. Zhao Y, Yang W, Zhao X, et al. Efficacy of eltrombopag with immunosuppressive therapy for children with acquired aplastic anemia. Front Pediatr. 2023 Jan 10;10:1095143.
18. Camitta BM, Rappeport JM, Parkman R, Nathan DG. Selection of patients for bone marrow transplantation in severe aplastic anemia. Blood. (1975) 45:355–63.
19. Goronkova O, Novichkova G, Salimova T, et al. Efficacy of combined immunosuppression with or without eltrombopag in children with newly diagnosed aplastic anemia. Blood Adv. 2022.
20. Zaimoku Y, Patel BA, Shalhoub R, et al. Predicting response of severe aplastic anemia to immunosuppression combined with eltrombopag. Haematologica. 2022;107(1):126.
21. Eguchi K, Ishimura M, Ohga S, et al; Japan Childhood Aplastic Anemia Study Group. Adjunctive effects of eltrombopag on immunosuppressive therapy for childhood aplastic anemia. Int J Hematol. 2024 Dec 27.

Table 1. Patients' characteristics			
	EPAG+IST (group 1) (n=38)	**IST (group 2) (n=57)**	**p**
Age at diagnosis, years, median (range)	10.42 (1.42–17.50)	8.75 (1.2–18)	0.65
Laboratory values, median(range)			
Haemoglobin, g/dL	7.1(3.2-12.3)	6.9(1.5-11.5)	0.06
Absolute neutrophil count, x 10^9/l	0.13(0-3.2)	0.1(0-1.8)	0.27
Platelet count, x 10^9/l	6 (1-68)	10 (1-76)	**0.02**
Median duration of follow-up, months	41.73 (1.1-88.77)	69 (1.03-344.13)	0.11
EPAG, eltrombopag; IST, immunosuppressive therapy			

Table 2. Hematological responses in EPAG+IST group versus IST group.			
	EPAG+IST (group 1) (n=38)	**IST (group 2) (n=57)**	**p**
3-months response, n (%)			
Overall response	19 (59.4)	19 (33.9)	**0.02**
CR	5 (15.6)	1 (1.8)	**0.01**
PR	14 (43.8)	18 (32.1)	
NR	13 (40.6)	37 (66.1)	
Off Study*	6	1	
6-months response, n (%)			
Overall response	22 (81.5)	23 (54.8)	**0.02**
CR	13 (48.1)	6 (13.3)	**0.002**
PR	9 (33.3)	17 (37.8)	
NR	5 (18.5)	22 (48.9)	
Off Study	11	12	
1-year response, n (%)			
Overall response	20 (80)	25 (78.1)	0.86
CR	16 (64)	14 (43.8)	0.23
PR	4 (16)	11 (34.4)	
NR	5 (20)	7 (21.9)	
Off Study	13	25	
End of therapy response, n (%)			
Overall response	23 (60.5)	27 (47.41)	0.20
CR	17 (39.5)	18 (31.6)	0.38
PR	6 (15.8)	9 (15.8)	
NR	15 (39.5)	30 (52.6)	
Relapse, n/responder	2/23	2/27	0.83
Clonality, n (%)	4 (10.52)	11 (19.30)	0.27
Time to platelet transfusion independence; days, median (range)	60 (14-171)	64.5 (3-550)	0.38
Time to RBC transfusion independence; days, median (range)	49 (14-171)	77 (28-751)	0.05

OS 1-year OS, (%) 2-year OS, (%) 5-year OS, (%)	 89.2 86.5 82.6	 80.4 74.7 72.2	 0.26
EFS 1-year EFS, (%) 2-year EFS, (%) 5-year EFS, (%)	 81.1 78.4 74.3	 71.3 65.4 53.5	 0.14
*Off-study: Patients who were off study at 3 months, 6 months and 1 year were for many different reasons including: EPAG stopped due to toxicity, alternate treatment such as repeat IST or HSCT, death, or were lost to follow-up. Patients who were deemed non-responders at 3 or 6 months were not routinely monitored for late response beyond this timepoint as they were taken off study. CR, complete response; PR, partial response; NR, no response; OS, overall survival; EFS, event-free survival.			

Table 3. Hematological responses between subgroups according to age at diagnosis.

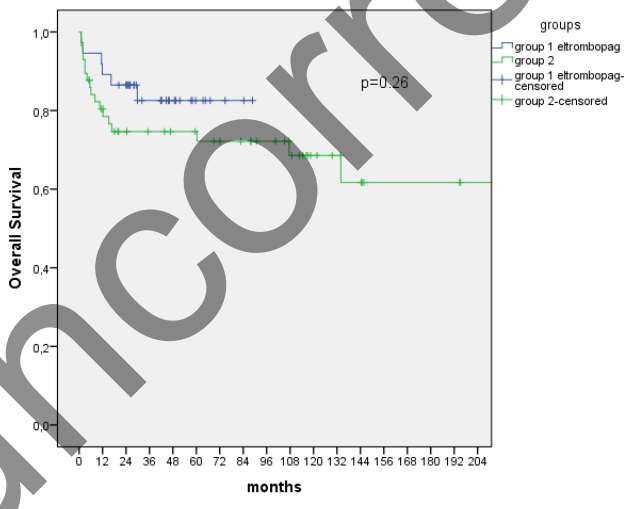
	subgroup 1 (age <8.95 y; n=47)	**subgroup 2 (age >8.95 y; n=48)**	**p**
3-month response, n (%)			
Overall response	16 (37.2)	22 (47.7)	0.27
CR	2 (4.7)	4 (9.1)	0.48
PR	14 (32.6)	18 (40.9)	
NR	27 (62.8)	22 (50)	
Off Study	4	4	
6-month response, n (%)			
Overall response	17 (50)	27 (79.4)	**0.009**
CR	7 (20.6)	11 (30.6)	**0.02**
PR	9 (26.5)	17 (47.2)	
NR	18 (52.9)	8 (22.2)	
Off Study	13	12	
1-year response, n (%)			
Overall response	18 (64.3)	27 (93.1)	**0.008**
CR	14 (56)	16 (55.2)	**0.013**
PR	4 (16)	11 (37.9)	
NR	7 (28)	2 (6.9)	
Off Study	22	19	
End of therapy response, n (%)			
Overall response	21 (44.7)	28 (60.4)	0.12
CR	14 (29.8)	21 (43.8)	0.28
PR	7 (14.9)	8 (16.7)	
NR	26 (55.3)	19 (39.6)	
Relapse, n/responders	1/21	3/28	0.42
Clonality, n (%)	3 (6.4)	12 (25.5)	**0.01**
Time to platelet transfusion independence; days, median (range)	109.5 (14-730)	70.5 (3-875)	0.07
Time to RBC transfusion independence; days, median (range)	120 (14-730)	79 (20-852)	0.10

OS			
1-year OS, (%)	84.8	82.8	
2-year OS, (%)	80.3	78.5	0.74
5-year OS, (%)	76	75.7	
EFS			
1-year EFS, (%)	82.7	67.6	
2-year EFS, (%)	78.1	63.1	**0.01**
5-year EFS, (%)	69.7	49.2	

Table 4. Multivariate analysis of factors associated with favorable outcomes

Outcomes	**Odds ratio (95% CI)**	***P***
Overall response 3-months after treatment		
Group (EPAG+IST vs. IST)	0.136 (0.035–0.531)	**0.004**
Platelet count at diagnosis	1.000 (1.000–1.000)	**0.030**
Overall response 6-months after treatment		
Patient age at diagnosis	1.147 (1.026–1.283)	**0.016**
Group (EPAG+IST vs. IST)	0.274 (0.081–0.927)	**0.037**
Overall response 1-year after treatment		
Patient age at diagnosis	1.321 (1.096–1.592)	**0.003**
Outcomes	**Hazard ratio (95% CI)**	***P***
Overall survival		
Overall response after treatment	0.122 (0.029–0.516)	**0.004**
Event-free survival		
Patient age at diagnosis	1.167 (1,041–1,308)	**0.008**
Overall response after treatment (no vs. yes)	0. 255 (0.083–0.786)	**0. 017**
G CSF treatment (no vs. yes)	0. 341 (0.118–0.990)	**0. 048**

CI, confidence interval; vs., versus; IST, immunosuppressive therapy; EPAG, eltrombopag.



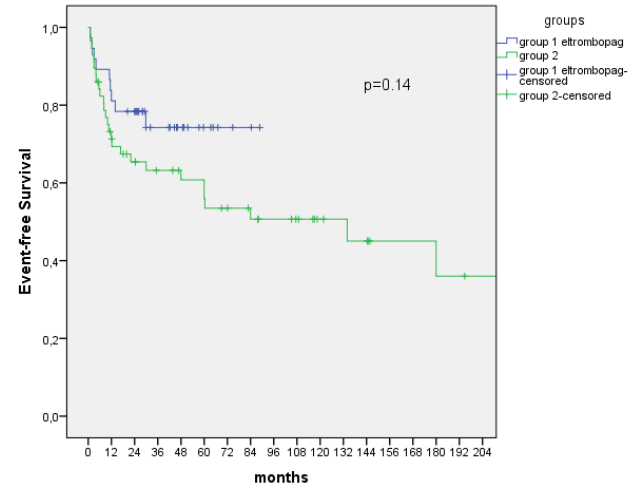
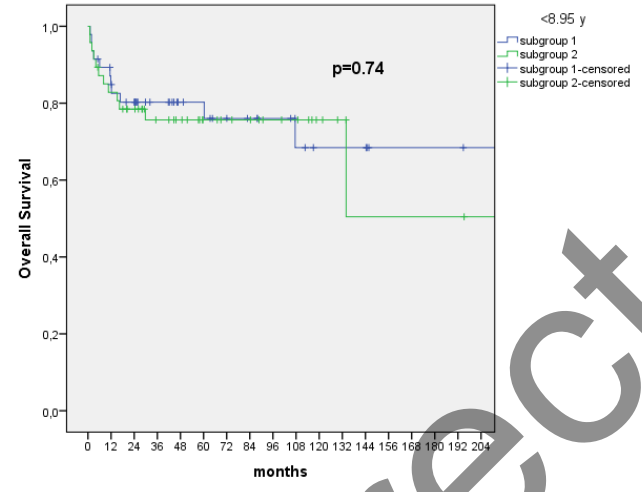


Figure 1. Comparison of overall survival and event-free survival between treatment groups.



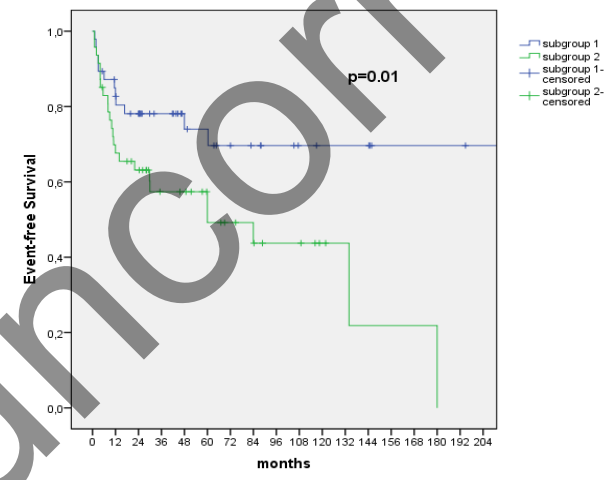


Figure 2. Comparison of overall survival and event-free survival between subgroups according to median age (subgroup 1, age <8.95 y; subgroup 2, age >8.95).