Predictive biomarkers of luspatercept and erythropoiesis-stimulating agent hematological response and overall survival in patients with lower-risk myelodysplastic syndromes in the COMMANDS trial

5613

Guillermo Garcia-Manero,[1] Manuel Ugidos,[2] Maroof Hasan,[2] Matthew E. Stokes,[3] Matteo Giovanni Della Porta,[4] Amer M. Zeidan,[5] Valeria Santini,[6] Uwe Platzbecker,[7] Rami S. Komrokji,[8] Dimana Miteva,[9] Veronika Pozharskaya,[2] Anita K. Gandhi,[2] Daniel L. Menezes,[2] Rajasekhar N.V.S. Suragani[2]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Bristol Myers Squibb, Princeton, NJ, USA; [3]Bristol Myers Squibb, Summit, NJ, USA; [4]Cancer Center IRCCS Humanitas Research Hospital, Milan, Italy; Humanitas University, Milan, Italy; [5]Yale School of Medicine, New Haven, CT, USA; [6]MDS Unit, Hematology, University of Florence, Florence, Italy; [7]University Hospital Leipzig, Leipzig, Germany; [8]Moffitt Cancer Center, Tampa, FL, USA; [9]Bristol Myers Squibb, Boudry, Switzerland

Introduction

- Myelodysplastic syndromes (MDS) are characterized by ineffective hematopoiesis, cytopenias, and clonal expansion, which often progress from lower-risk (LR) to higher-risk MDS or acute myeloid leukemia and lead to death[1]
- Erythropoiesis-stimulating agents (ESAs) improve anemia and reduce transfusion dependency in ~35% of patients with LR-MDS, but resistance typically emerges within 18 to 24 months[2]
  - Baseline erythropoietin (EPO) ≤ 200 U/L and ≤ 2 somatic mutations predict favorable response, whereas driver gene mutations are associated with poorer outcomes[3-5]
- The International Prognostic Scoring System-Molecular (IPSS-M) categorizes patients by progression risk, assessing hematological parameters, bone marrow blasts, cytogenetics, and gene mutations[6]
- Dependency on red blood cell (RBC) transfusions is a prognostic factor in MDS; thus, therapies that reduce this dependency may improve overall survival (OS)
- In the phase 3 COMMANDS study (NCT03682536) in LR-MDS, luspatercept demonstrated a significantly greater rate and durability of RBC-transfusion independence (RBC-TI) versus epoetin alfa as well as a trend for improved OS[7,8]
  - Recently, we have reported that patients treated with luspatercept had more frequent IPSS-M risk downstaging compared with those treated with epoetin alfa due to improved hemoglobin (Hb) levels
  - Luspatercept treatment did not alter gene mutations or variant allele frequency (VAF) changes in a short time frame of 48 weeks,[9] which highlights the need to understand the broader mechanistic attributes that relate to treatment response

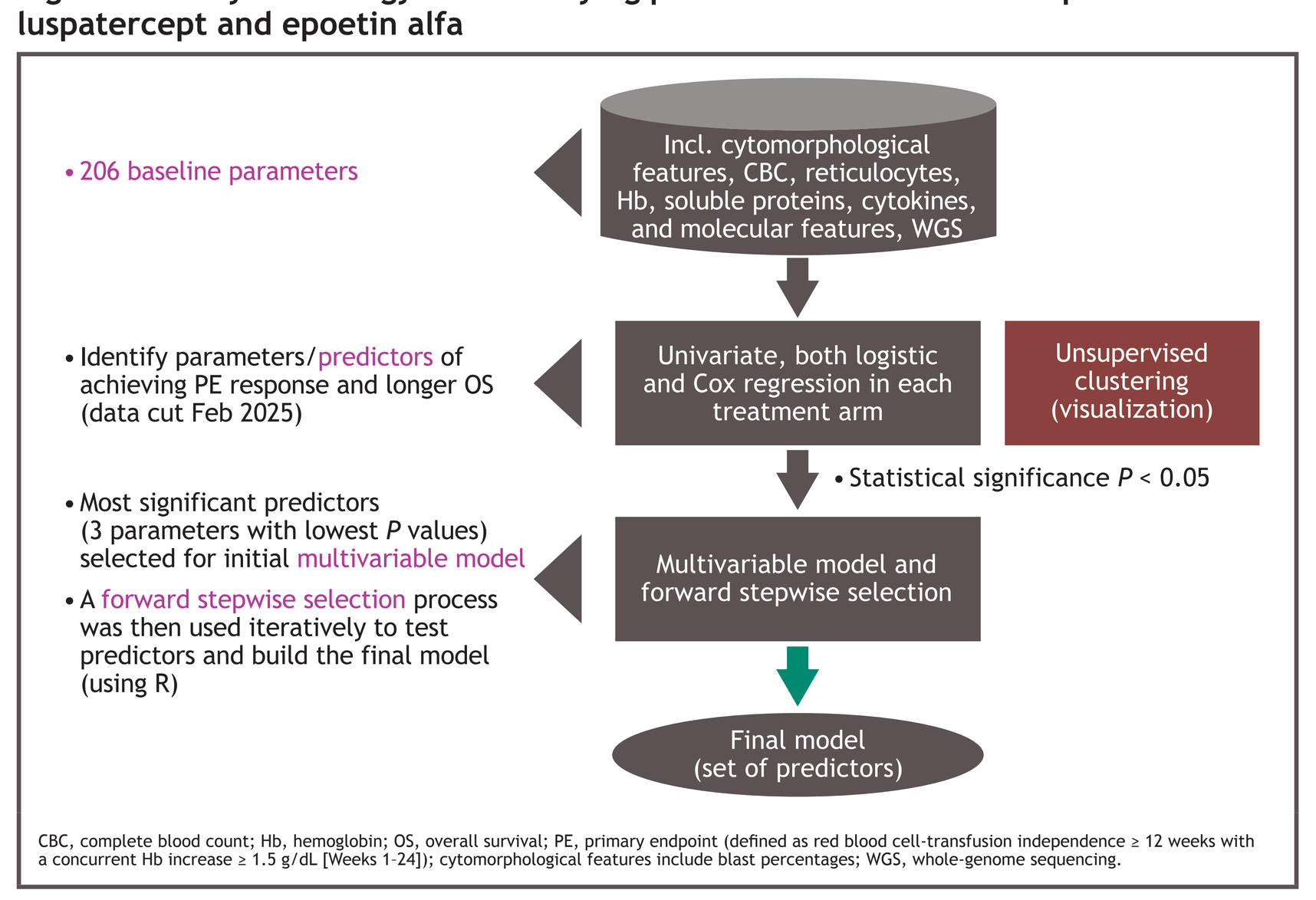
Objective

- To identify exploratory biomarkers associated with hematological response to luspatercept and evaluate its potential association with improved OS compared with epoetin alfa

Methods

- The **COMMANDS phase 3 study design** has been previously described[7]
- **The primary endpoint (PE)** was RBC-TI ≥ 12 weeks with a concurrent Hb increase ≥ 1.5 g/dL (Weeks 1–24)
- A total of **206 baseline parameters**, including cytomorphological features, complete blood count, reticulocytes, Hb, platelets, soluble proteins, cytokines, and molecular features (82-panel targeted sequencing [≥ 400 × exon coverage; 3% sensitivity] and whole-genome sequencing [80 ×]), were analyzed; IPSS-M category was determined for each patient[6]
- Univariate, both logistic and Cox regression in each treatment arm were used to identify predictors of achieving PE response and longer OS (February 2025 data cut), respectively (statistically significant variables at $P < 0.05$); for Cox regression, predictors were discretized as high or low based on the median
- Most significant predictors (lowest *P* values) were selected for the initial multivariable model
- A forward stepwise selection process was then used to add predictors and build the final model (using R)
- **Figure 1** shows the analysis strategy for identifying predictors of PE and OS response

Figure 1. Analysis strategy for identifying predictors of PE and OS response with luspatercept and epoetin alfa



CBC, complete blood count; Hb, hemoglobin; OS, overall survival; PE, primary endpoint (defined as red blood cell-transfusion independence ≥ 12 weeks with a concurrent Hb increase ≥ 1.5 g/dL [Weeks 1-24]); cytomorphological features include blast percentages; WGS, whole-genome sequencing.

Results

- Key baseline variables, including IPSS-M score, mutations, soluble proteins (ie, growth differentiation factor 15 [GDF-15], hepcidin, alpha-2 macroglobulin [A2M]), and clinical parameters (Hb, platelet counts, serum iron, white blood cells [WBCs]), were similar between treatment arms (all $P > 0.05$). Other biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and vascular endothelial growth factor (VEGF) levels, showed comparable baseline values. Overall, baseline variables were balanced between treatment arms, supporting unbiased clinical outcome comparisons between cohorts (**Table 1**)
- Univariate analysis identified significant explanatory variables for PE predictors of response (n = 35) and OS (n = 40) across treatment groups (**Table 2**)
  - For **luspatercept**, significant predictors of PE response were lower EPO levels (−0.01; $P = 0.00001$), lower baseline IPSS-M score (−1.17; $P = 0.00002$), and higher A2M (0.79; $P = 0.00120$). Additional significant variables included higher *SF3B1* VAF and hepcidin level and lower *SRSF2* VAF (all $P < 0.01$)
  - For **epoetin alfa**, lower EPO (−0.01; $P = 0.00006$), iron (−0.07; $P = 0.00012$), and GDF-15 (−0.0002; $P = 0.00036$) levels were strongly associated with favorable PE response (all $P < 0.001$). Elevated Hb, myoglobin, unsaturated iron binding capacity (UIBC), transferrin saturation, and stem cell factor (SCF) were also strong notable predictors (all $P < 0.01$). Lower IPSS-M score did not reliably predict PE response to epoetin alfa ($P = 0.05$)

Table 1. Baseline clinical and genomic characteristics of the COMMANDS biomarker cohort

Parameter		Luspatercept (n = 182)	Epoetin alfa (n = 181)	P value[a]
EPO	Median (IQR)	77.3 (142.3)	85.4 (136.7)	0.79
	n	178	179	
Hb	Median (IQR)	7.8 (1.1)	7.8 (1.2)	0.39
	n	182	181	
Iron	Median (IQR)	28.9 (13.8)	27.9 (14.7)	0.53
	n	182	181	
Platelets	Median (IQR)	230 (150)	236 (181)	0.55
	n	180	180	
Transferrin saturation	Median (IQR)	0.53 (0.30)	0.55 (0.28)	0.4
	n	130	132	
WBC	Median (IQR)	4.37 (2.53)	4.38 (2.50)	0.81
	n	182	180	
GDF-15	Median (IQR)	4893.7 (4175.6)	4376.3 (4326.4)	0.44
	n	172	171	
Hepcidin	Median (IQR)	85.0 (102.1)	95.27 (127.0)	0.13
	n	168	163	
A2M	Median (IQR)	2.6 (0.9)	2.7 (1.0)	0.23
	n	176	178	
Myoglobin	Median (IQR)	25 (17)	23 (14)	0.31
	n	175	178	
NT-proBNP	Median (IQR)	1935 (2842)	1945 (2375)	0.93
	n	176	178	
VEGF	Median (IQR)	228.5 (268.8)	261 (289.3)	0.25
	n	176	178	
IPSS-M	Median (IQR)	−0.42 (0.92)	−0.56 (1.00)	0.36
	n	179	173	
SF3B1	Mutated	63% (114)	59% (106)	0.67
	WT	29% (52)	30% (55)	
	Missing	8.8% (16)	11% (20)	
IDH2	Mutated	3.8% (7)	2.8% (5)	0.81
	WT	87% (159)	86% (156)	
	Missing	8.8% (16)	11% (20)	
ASXL1	Mutated	23% (42)	19% (34)	0.44
	WT	68% (124)	70% (127)	
	Missing	8.8% (16)	11% (20)	
CBL	Mutated	2.7% (5)	5% (9)	0.38
	WT	88% (161)	84% (152)	
	Missing	8.8% (16)	11% (20)	
RS status	RS+	73% (133)	72% (130)	0.88
	RS−	27% (49)	28% (51)	
	Missing	0	0	
Mutational burden[b]	High	23% (41)	20% (36)	0.8
	Low	24% (43)	18% (33)	
	Missing	54% (98)	62% (112)	
Bone marrow blasts (%)	Median (IQR)	2 (2.5)	2 (2.88)	0.93
	n	171	170	

[a]*P* value, Wilcoxon-Mann-Whitney test for numeric variables and chi-squared test for categorical variables.
[b]High and low defined by median mutational burden across patients (high > median; low < median).
A2M, alpha-2 macroglobulin; EPO, erythropoietin; GDF-15, growth differentiation factor 15; Hb, hemoglobin; IPSS-M, International Prognostic Scoring System-Molecular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RS, ring sideroblast; VEGF, vascular endothelial growth factor; WBC, white blood cell; WT, wild type.

Table 2. Univariate analysis[a]: significant predictors of PE response for patients treated with (A) luspatercept and (B) epoetin alfa

A.

Variable	Estimate[b]	Lower	Upper	P value	n
EPO	−0.01	−0.01	−0.0044	0.00001	174
IPSS-M	−1.17	−1.73	−0.65	0.00002	175
A2M	0.79	0.33	1.30	0.00120	172
*SF3B1*_VAF	0.03	0.01	0.05	0.00178	114 (162)
Hepcidin	−0.01	−0.01	−0.0022	0.00258	164
SF3B1	0.93	0.26	1.62	0.00685	114 (162)
*SRSF2*_VAF	−0.04	−0.07	−0.01	0.00854	162
Hb	0.47	0.11	0.85	0.01305	178
Lymphocytes	0.69	0.13	1.32	0.02153	174
RS status	0.76	0.10	1.43	0.02515	178
U2AF1	−1.17	−2.30	−0.13	0.03103	16 (162)
SRSF2	−0.96	−1.92	−0.04	0.04306	21 (162)

B.

Variable	Estimate[b]	Lower	Upper	P value	n
EPO	−0.01	−0.01	−0.01	0.00006	175
Iron	−0.07	−0.10	−0.04	0.00012	177
GDF-15	−0.0002	−0.0004	−0.0001	0.00036	167
Hb	0.67	0.28	1.09	0.00119	177
Myoglobin	0.04	0.02	0.07	0.00233	174
UIBC	0.04	0.02	0.07	0.00362	176
Transferrin saturation	−2.91	−5.03	−0.93	0.00510	128
SCF	0.002	0.001	0.004	0.00909	174
Apo(a) Lp(a)	0.002	0.0004	0.003	0.01182	174
Factor VII	0.004	0.0009	0.007	0.01243	174
ASXL1	−1.29	−2.42	−0.35	0.01246	34 (157)
*ASXL1*_VAF	−0.05	−0.09	−0.01	0.01967	34 (157)
TIBC	0.02	0.003	0.036	0.02123	176
MMP-3	0.06	0.01	0.12	0.02125	174
Urinary creatinine	−0.08	−0.16	−0.01	0.03163	172
RBC	0.88	0.10	1.73	0.03231	176
SAP	0.07	0.01	0.14	0.03544	174
IBIL	−0.05	−0.10	−0.01	0.04017	176
TM	0.18	0.01	0.36	0.04391	174
CBL	1.47	0.09	3.06	0.04408	9 (157)

PE was RBC-TI ≥ 12 weeks with a concurrent Hb increase ≥ 1.5 g/dL (Weeks 1-24).
[a]Gene mutation prevalence shown as n of (total patients). Purple indicates the 3 most significant predictors (lowest *P* values) selected for the initial multivariable model.
[b]Change in response probability per unit increase of the predictor variable (ie, positive estimate value indicates higher response rate as the value of the predictor increases, and negative estimate value indicates higher response rate as the value of the predictor decreases). Lower and upper represent the CI of the estimate.
A2M, alpha-2 macroglobulin; apo(a), apolipoprotein(a); EPO, erythropoietin; GDF-15, growth differentiation factor 15; Hb, hemoglobin; IBIL, indirect bilirubin; IPSS-M, International Prognostic Scoring System-Molecular; Lp(a), lipoprotein(a); MMP-3, matrix metalloproteinase-3; PE, primary endpoint; RBC, red blood cell; RBC-TI, red blood cell-transfusion independence; RS, ring sideroblast; SAP, serum amyloid P component; SCF, stem cell factor; TIBC, total iron binding capacity; TM, thrombomodulin; UIBC, unsaturated iron binding capacity; VAF, variant allele frequency.

- Univariate analysis was performed to identify significant predictors of OS in the luspatercept and epoetin alfa treatment arms (**Table 3**)
  - For **luspatercept**, lower IPSS-M score (HR, 0.27) and *SF3B1* mutational status (HR, 0.35) conferred favorable OS benefit ($P < 0.0001$). Additional significant predictors included lower creatinine (HR, 0.32), lower beta-2 microglobulin (B2M) levels (HR, 0.35), and higher lymphocytes (HR, 0.39). Several molecular parameters (eg, *SRSF2*, *STAG2*, *ASXL1*) were adversely linked to differences in OS
  - For **epoetin alfa**, significant features were lower IPSS-M score (HR, 0.34), higher platelet count (HR, 0.3), and *ASXL1* wild-type status (HR, 0.24)

Table 3. Univariate analysis[a]: significant predictors of OS response for patients treated with (A) luspatercept and (B) epoetin alfa

A.

Variable	HR	Lower	Upper	P value	n
IPSS-M	3.75	2.10	6.68	7.44E−06	179
CBL	8.21	3.22	20.89	1.01E−05	5 (166)
SF3B1	0.35	0.21	0.59	9.00E−05	114 (166)
Creatinine	3.11	1.75	5.53	0.00011	182
B2M	2.85	1.63	4.99	0.00025	176
Lymphocytes	0.39	0.23	0.68	0.00077	178
SRSF2	2.72	1.48	4.98	0.00120	21 (166)
STAG2	5.24	1.87	14.66	0.00162	5 (166)
eGFR	0.42	0.24	0.73	0.00214	182
CRP	2.35	1.36	4.05	0.00216	176
*ASXL1*_VAF	2.70	1.42	5.10	0.00237	166
*SRSF2*_VAF	2.97	1.41	6.28	0.00433	166
U2AF1	2.83	1.38	5.80	0.00465	16 (166)
RUNX1	3.29	1.40	7.70	0.00616	7 (166)
VEGF	0.45	0.24	0.81	0.00864	150
WBC	0.50	0.30	0.85	0.00988	182
EOS	0.50	0.28	0.87	0.01349	162
TNFR2	1.95	1.14	3.32	0.01454	176
*RUNX1*_VAF	4.28	1.33	13.77	0.01483	166
BASO	0.50	0.29	0.88	0.01541	162
*IDH2*_VAF	4.26	1.31	13.81	0.01571	166
Erythroferrone	0.51	0.29	0.89	0.01690	162
IDH2	3.03	1.21	7.63	0.01832	7 (166)
ASXL1	1.93	1.11	3.35	0.02047	42 (166)
ALT	0.54	0.32	0.91	0.02163	182

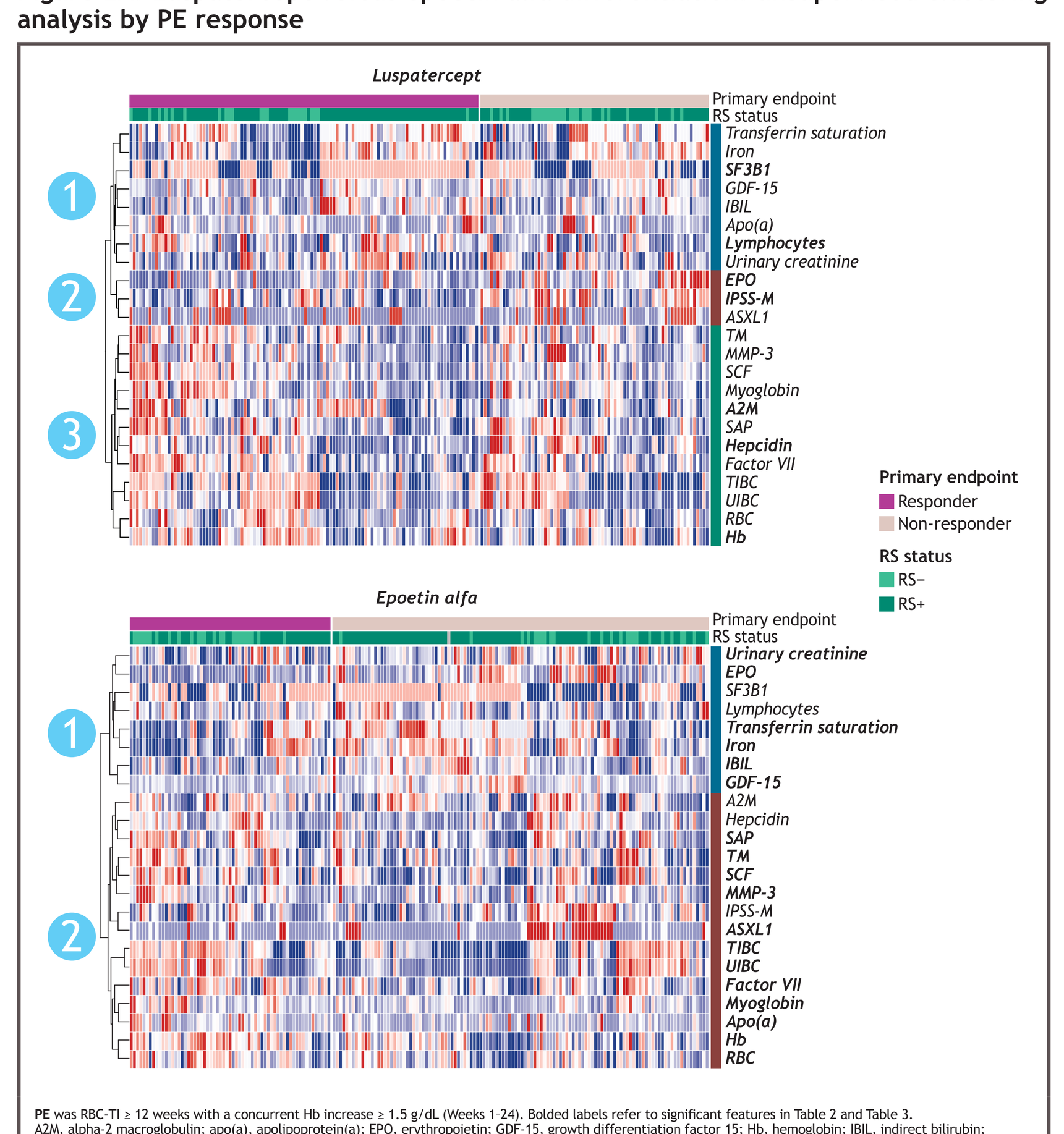
B.

Variable	HR	Lower	Upper	P value	n
ASXL1	4.18	2.44	7.14	0.00000	34 (161)
Platelets	0.30	0.18	0.51	0.00001	180
IPSS-M	2.90	1.73	4.86	0.00005	173
U2AF1	3.18	1.74	5.82	0.00017	22 (161)
BDNF	0.40	0.24	0.67	0.00041	177
SF3B1	0.44	0.27	0.73	0.00128	106 (161)
*ASXL1*_VAF	2.73	1.41	5.30	0.00299	161
Hepcidin	2.07	1.24	3.48	0.00573	163
EOS%	0.49	0.28	0.83	0.00772	157
Creatinine clearance	0.52	0.32	0.85	0.00868	177
IDH2	4.97	1.49	16.58	0.00903	5 (161)
NT-proBNP	1.91	1.17	3.10	0.00955	178
BASO%	0.50	0.30	0.85	0.01081	157
IL-18	1.87	1.15	3.03	0.01166	178
BASO	0.54	0.32	0.91	0.02104	157
GDF-8	0.57	0.35	0.94	0.02853	170
EOS	0.58	0.34	0.97	0.03765	157

Lower and upper represent the CI of the estimate.
[a]Gene mutation prevalence shown as n of (total patients). Purple indicates the 3 most significant predictors (lowest *P* values) selected for the initial multivariable model.
ALT, alanine aminotransferase; B2M, beta-2 microglobulin; BASO, basophil; BASO%, basophil percentage in leukocyte differential; BDNF, brain-derived neurotropic factor; CRP, C-reactive protein; eGFR, glomerular filteration rate based on serum creatinine; EOS, eosinophil; EOS%, eosinophil percentage in leukocyte differential; GDF-8, growth differentiation factor 8; IL-18, interleukin-18; IPSS-M, International Prognostic Scoring System-Molecular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OS, overall survival; TNFR2, tumor necrosis factor receptor 2; VAF, variant allele frequency; VEGF, vascular endothelial growth factor; WBC, white blood cell.

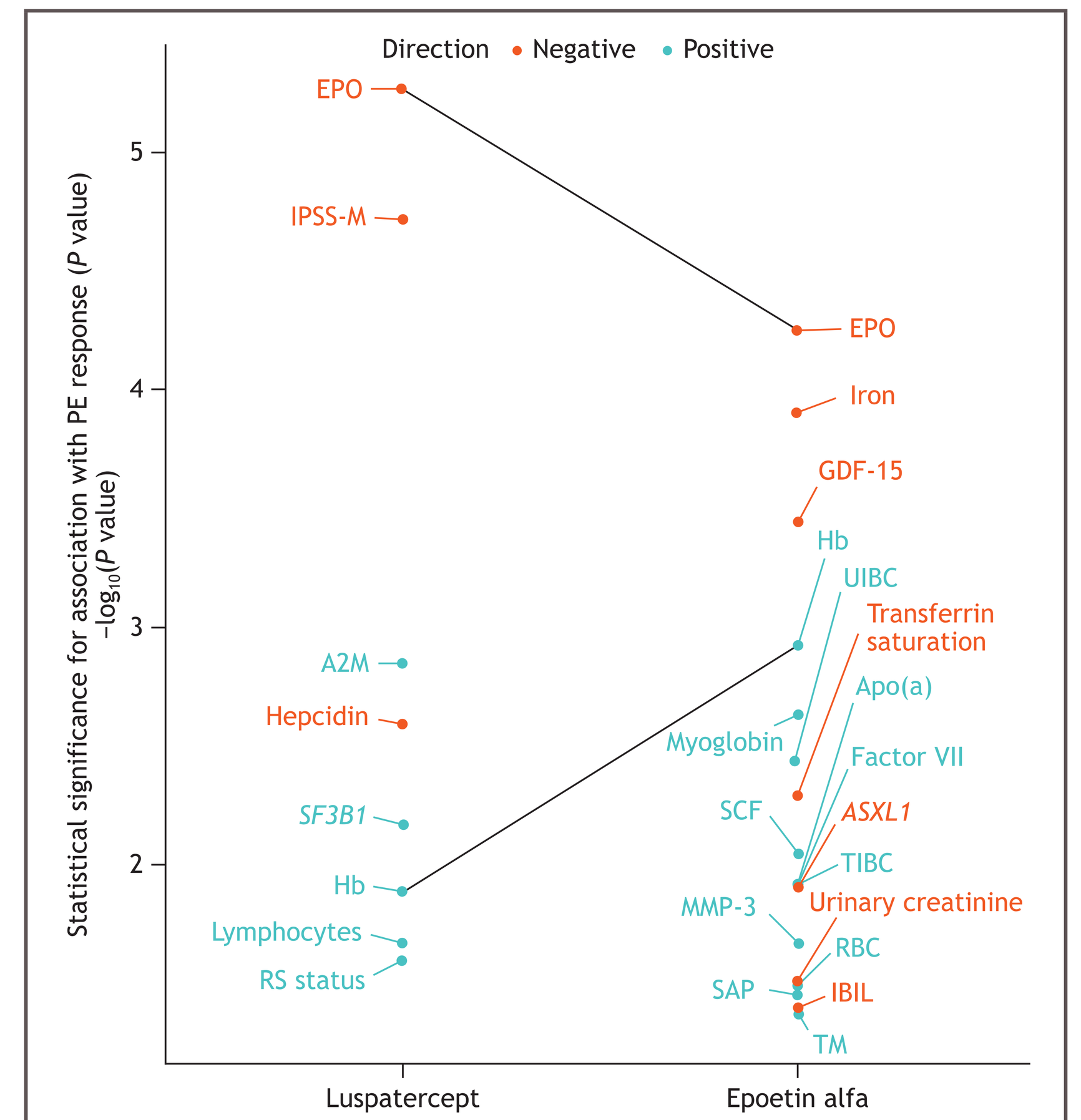
- Unsupervised clustering analysis was conducted to differentiate patterns of patient responses between treatments for PE and OS response, respectively (**Figures 2** and **3**)
- Different clusters emerged for each treatment arm, indicating unique biomarker patterns of better response within patient subgroups (**Figure 2A**)
  - For **luspatercept**, the response clusters were characterized by the enrichment of (1) iron erythropoiesis and hepatorenal axis: *SF3B1*^{mut}, lymphocytes^{hi}; (2) lower disease risk with EPO^{lo}, *ASXL1*^{wt}, IPSS-M^{lo}; and (3) red cell mass and protein synthesis/coagulation: Hb^{hi}, hepcidin^{lo}, A2M^{hi}
  - **Epoetin alfa** highlighted response clusters enriched in (1) erythropoiesis and hepatorenal axis bilirubin levels: indirect bilirubin^{lo}, GDF-15^{lo}, iron^{lo}, EPO^{lo}, *SF3B1*^{mut}, creatinine^{lo}, transferrin saturation^{lo}; and (2) reduced iron overload and cardiorenal-endothelial stress: serum amyloid P component^{hi}, thrombomodulin^{hi}, SCF^{hi}, matrix metalloproteinase-3^{hi}, Factor VII^{hi}, myoglobin^{hi}, apolipoprotein(a)^{hi}, Hb^{hi}, RBC^{hi}
- **Figure 2B** depicts the comparative predictors of PE response in patients treated with luspatercept versus epoetin alfa
  - For **luspatercept**, higher levels of A2M, lymphocytes, Hb, *SF3B1* mutation, and ring sideroblast–positive status were positively and strongly associated with response, while higher hepcidin and EPO levels were negatively associated with response
  - For **epoetin alfa**, parameters such as higher myoglobin, Hb, apo(a), UIBC/total iron binding capacity, and Factor VII exhibited strong positive predictor correlations, whereas higher EPO, iron, and transferrin saturation were strongly negative predictors

Figure 2A. Luspatercept versus epoetin alfa differentiation: unsupervised clustering analysis by PE response



PE was RBC-TI ≥ 12 weeks with a concurrent Hb increase ≥ 1.5 g/dL (Weeks 1-24). Bolded labels refer to significant features in Table 2 and Table 3.
A2M, alpha-2 macroglobulin; apo(a), apolipoprotein(a); EPO, erythropoietin; GDF-15, growth differentiation factor 15; Hb, hemoglobin; IBIL, indirect bilirubin; IPSS-M, International Prognostic Scoring System-Molecular; MMP-3, matrix metalloproteinase-3; PE, primary endpoint; RBC, red blood cell; RBC-TI, red blood cell-transfusion independence; RS, ring sideroblast; SAP, serum amyloid P component; SCF, stem cell factor; TIBC, total iron binding capacity; TM, thrombomodulin; UIBC, unsaturated iron binding capacity.

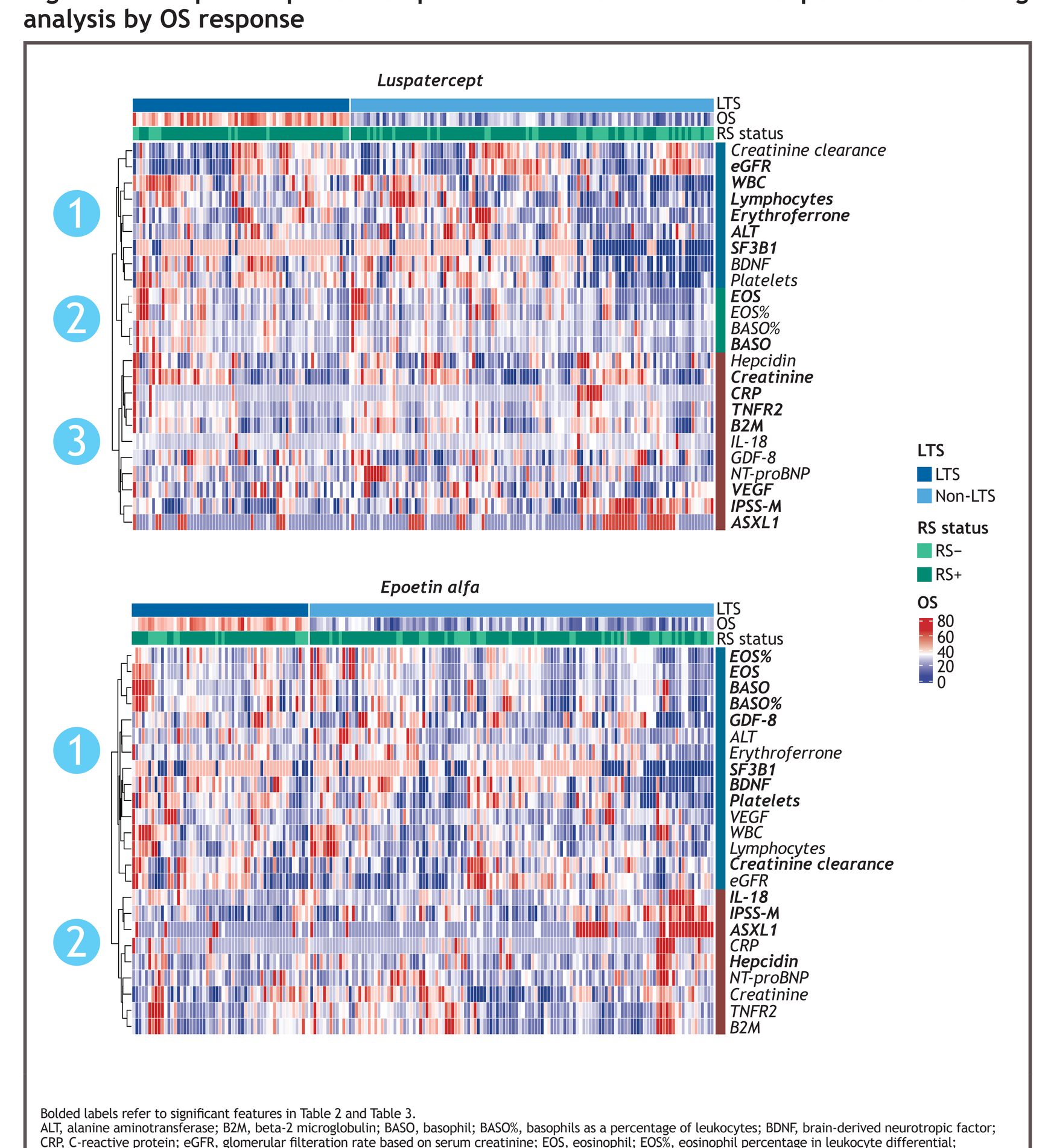
Figure 2B. Comparative analysis of parameters that influence PE response between treatment arms



BLUE = positively associated; RED = negatively associated; DARK GRAY line connects the same parameter between arms.
A2M, alpha-2 macroglobulin; apo(a), apolipoprotein(a); EPO, erythropoietin; GDF-15, growth differentiation factor 15; Hb, hemoglobin; IBIL, indirect bilirubin; IPSS-M, International Prognostic Scoring System-Molecular; MMP-3, matrix metalloproteinase-3; PE, primary endpoint; RBC, red blood cell; RS, ring sideroblast; SAP, serum amyloid P component; SCF, stem cell factor; TIBC, total iron binding capacity; TM, thrombomodulin; UIBC, unsaturated iron binding capacity.

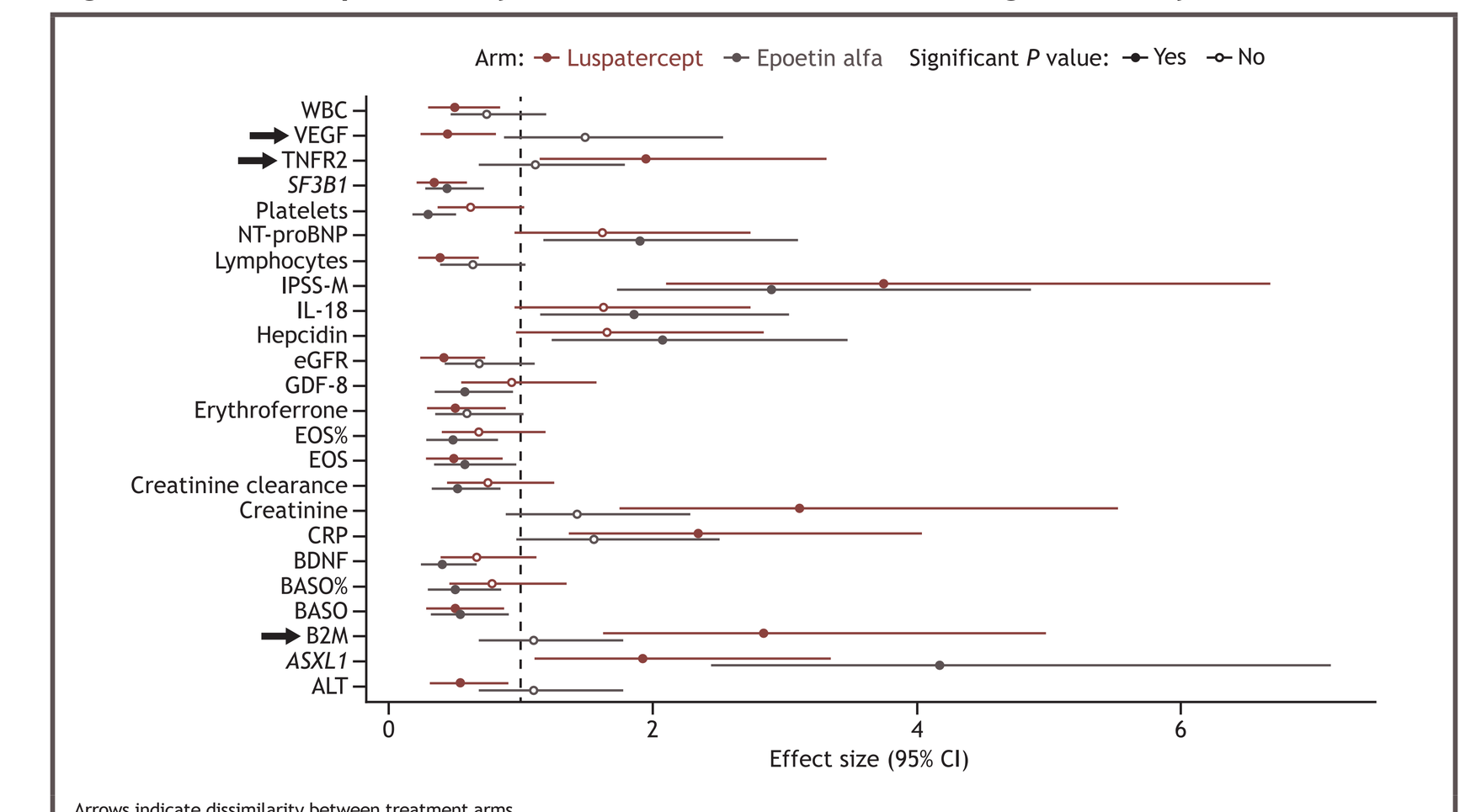
- Similarly, unsupervised clustering analysis was conducted to compare luspatercept and epoetin alfa based on OS response (**Figure 3A**). Two/three clusters emerged that correlated with enriched OS response
  - **Luspatercept:** BLUE cluster (glomerular filtration rate based on serum creatinine [eGFR]^{hi}, erythroferrone^{hi}, alanine aminotransferase^{lo}), GREEN cluster (WBC^{hi}, lymphocytes^{hi}, *SF3B1*^{mut}, eosinophil [EOS]^{hi}, basophil [BASO]^{hi}), and RED cluster (creatinine^{lo}, C-reactive protein^{lo}, tumor necrosis factor receptor 2 [TNFR2]^{lo}, B2M^{lo}, VEGF^{lo}, IPSS-M^{lo}, *ASXL1*^{wt})
  - **Epoetin alfa:** BLUE cluster (EOS^{hi}, BASO^{hi}, growth differentiation factor 8^{hi}, *SF3B1*^{mut}, brain-derived neurotropic factor [BDNF]^{hi}, platelets^{hi}, creatinine clearance^{lo}) and RED cluster (interleukin-18^{lo}, IPSS-M^{lo}, *ASXL1*^{wt}, hepcidin^{lo})
- The effect of key baseline biomarkers on OS response for the luspatercept and epoetin alfa treatment arms is shown in **Figure 3B**. Significant predictors differ in prevalence and magnitude between the luspatercept and epoetin alfa cohorts. IPSS-M score and *ASXL1* had substantial impact on OS with both treatments ($P < 0.05$). In contrast, specific biomarkers, such as VEGF, TNFR2, and B2M, demonstrated treatment-specific relevance
- A comparative plot of significant predictors of OS response between treatment arms in shown in **Figure 3C**
  - **Luspatercept:** *SF3B1*, WBC, eGFR, and lymphocytes were strongly positively associated with response, while IPSS-M score and B2M levels were negatively associated with response
  - **Epoetin alfa:** Creatinine clearance, *SF3B1*, platelets, BDNF, and hepcidin presented as strong positive predictors, whereas *ASXL1* and IPSS-M score were negative predictors

Figure 3A. Luspatercept versus epoetin alfa differentiation: unsupervised clustering analysis by OS response



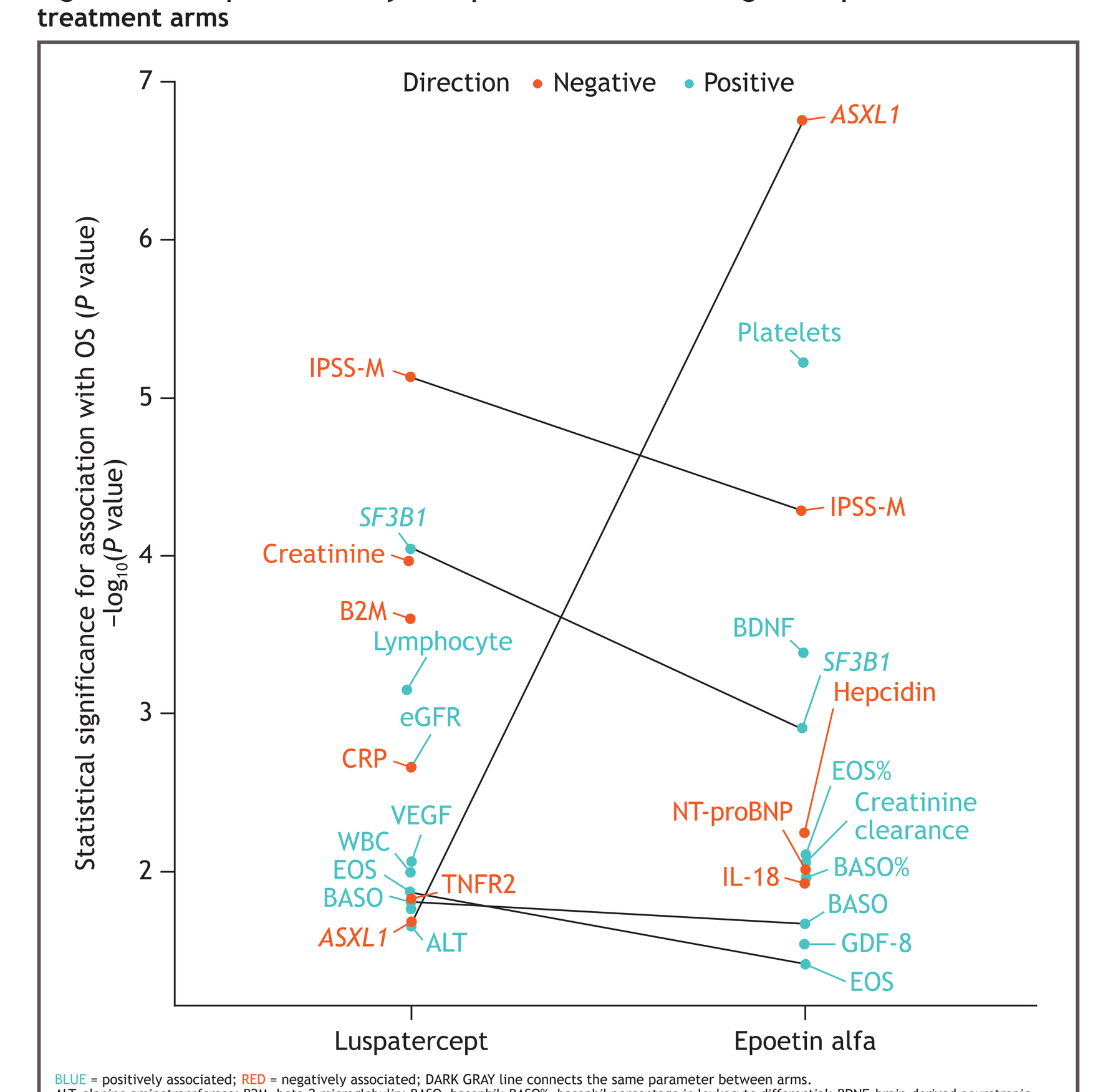
Bolded labels refer to significant features in Table 2 and Table 3.
ALT, alanine aminotransferase; B2M, beta-2 microglobulin; BASO, basophil; BASO%, basophils as a percentage of leukocytes; BDNF, brain-derived neurotropic factor; CRP, C-reactive protein; eGFR, glomerular filteration rate based on serum creatinine; EOS, eosinophil; EOS%, eosinophil percentage in leukocyte differential; GDF-8, growth differentiation factor 8; IL-18, interleukin-18; IPSS-M, International Prognostic Scoring System-Molecular; LTS, long-term survivors based on an OS > 36 months; February 2025 data cut; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OS, overall survival; RS, ring sideroblast; TNFR2, tumor necrosis factor receptor 2; VEGF, vascular endothelial growth factor; WBC, white blood cell.

Figure 3B. Forest plot of key baseline biomarkers on OS segmented by treatment arm



Arrows indicate dissimilarity between treatment arms.
ALT, alanine aminotransferase; B2M, beta-2 microglobulin; BASO, basophil; BASO%, basophil percentage in leukocyte differential; BDNF, brain-derived neurotropic factor; CRP, C-reactive protein; eGFR, glomerular filtration rate based on serum creatinine; EOS, eosinophil; EOS%, eosinophil percentage in leukocyte differential; GDF-8, growth differentiation factor 8; IL-18, interleukin-18; IPSS-M, International Prognostic Scoring System-Molecular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OS, overall survival; TNFR2, tumor necrosis factor receptor 2; VEGF, vascular endothelial growth factor; WBC, white blood cell.

Figure 3C. Comparative analysis of parameters influencing OS response between treatment arms



BLUE = positively associated; RED = negatively associated; DARK GRAY line connects the same parameter between arms.
ALT, alanine aminotransferase; B2M, beta-2 microglobulin; BASO, basophil; BASO%, basophil percentage in leukocyte differential; BDNF, brain-derived neurotropic factor; CRP, C-reactive protein; eGFR, glomerular filtration rate based on serum creatinine; EOS, eosinophil; EOS%, eosinophil percentage in leukocyte differential; GDF-8, growth differentiation factor 8; IL-18, interleukin-18; IPSS-M, International Prognostic Scoring System-Molecular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OS, overall survival; TNFR2, tumor necrosis factor receptor 2; VEGF, vascular endothelial growth factor; WBC, white blood cell.

- A forward stepwise regression analysis was then conducted to identify the combined significant predictors of PE and OS response in patients treated with either luspatercept or epoetin alfa. The resulting multivariable models were as follows:
- For PE (**Table 4A**)
  - **Luspatercept:** improved PE response was explained by higher A2M ($P = 0.007$), lower plasma iron ($P = 0.01$), lower hepcidin ($P = 0.03$), and higher transferrin saturation ($P = 0.04$)
  - **Epoetin alfa:** significant PE response predictors included lower iron ($P = 0.01$) and elevated Hb ($P = 0.02$) and myoglobin ($P = 0.04$)
- For OS (**Table 4B**)
  - **Luspatercept:** improved OS was linked to lower NT-proBNP ($P < 0.001$), higher WBC count ($P < 0.001$), and higher VEGF ($P = 0.01$)
  - **Epoetin alfa:** lower NT-proBNP ($P < 0.001$) and *ASXL1* wild type ($P < 0.001$) significantly predicted improved OS. Higher platelet count (HR, 0.54; $P = 0.01$) and lower hepcidin ($P = 0.01$) were also favorable for patients treated with epoetin alfa

Table 4A. Significant predictors of PE response after forward stepwise regression process[a]

Luspatercept			Epoetin alfa		
Variable	Coefficient	P value	Variable	Coefficient	P value
IPSS-M	−0.55	0.21520			
EPO	0.00	0.07474	EPO	−0.003	0.23639
A2M	0.78	0.00682			
Hepcidin	−0.01	0.02663			
Iron	−0.11	0.01050	Iron	−0.07	0.01152
Transferrin saturation	3.94	0.04488			
*SF3B1*_VAF	0.02	0.14762			
			GDF-15	−0.0002	0.06440
			Myoglobin	0.04	0.04367
			Hb	0.33	0.01759

[a]Purple parameters indicate the 3 most significant predictors (lowest *P* values) from the univariate analysis that were selected for the initial multivariable model; coefficient represents change in response probability per unit increase of the predictor variable (ie, positive estimate value indicates higher response rate as the value of the predictor increases, and vice versa); significant *P* values are highlighted in red.
A2M, alpha-2 macroglobulin; EPO, erythropoietin; GDF-15, growth differentiation factor 15; Hb, hemoglobin; IPSS-M, International Prognostic Scoring System-Molecular; PE, primary endpoint; VAF, variant allele frequency.

Table 4B. Significant predictors of OS response after forward stepwise regression process[a]

Luspatercept			Epoetin alfa		
Variable	HR	P value	Variable	HR	P value
IPSS-M	1.21	0.323	IPSS-M	0.61	0.06
SF3B1 mut	0.66	0.374			
NT-proBNP	2.64	< 0.001	NT-proBNP	2.14	< 0.001
WBC	0.39	< 0.001			
VEGF	0.59	0.01	VEGF	1.39	0.07
*IDH2*_VAF	0.68	0.084			
Hepcidin	1.62	0.041	Hepcidin	1.7	0.01
			ASXL1 mut	5.56	< 0.001
			Platelets	0.54	0.01

[a]The set of variables of the initial model are highlighted in purple; significant *P* values are highlighted in red.
IPSS-M, International Prognostic Scoring System-Molecular; mut, mutation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OS, overall survival; VAF, variant allele frequency; VEGF, vascular endothelial growth factor; WBC, white blood cell.

Conclusions

- **Our COMMANDS subanalyses suggest that PE response and OS benefit with luspatercept and ESA treatment are influenced by distinct baseline clinical, soluble biomarkers and molecular features**
- **Clustering stratifies responders**
  - Unsupervised analyses identified biomarker-defined subgroups for PE and OS response, revealing treatment-specific patterns that correlated with differential outcomes
- **Convergent multivariable models**
  - **Luspatercept:** PE response was predicted by high A2M, low iron and hepcidin, and high transferrin saturation; and OS response by low NT-proBNP, high WBC count, and high VEGF
  - **Epoetin alfa:** PE response was predicted by high Hb and myoglobin and low iron; and OS response by low NT-proBNP, *ASXL1* wild type, high platelets, and low hepcidin
- **Potential implications**
  - **Luspatercept:** PE response correlates with effective late-stage erythroid maturation due to higher iron availability; improved OS response is linked to lower NT-proBNP and higher WBC and VEGF, suggesting the role of favorable baseline immune and cardiac function
  - **Epoetin alfa:** PE response was associated with higher baseline Hb/myoglobin and low iron, indicating a relationship with less severe anemia and less severe iron overload; OS response was linked to low NT-proBNP, *ASXL1* wild type, high platelets, and low hepcidin (less aggressive disease; preserved megakaryopoiesis)
- Additional longitudinal analyses are warranted to further refine these predictive biomarkers

References

1. Della Porta MG et al. *Lancet Haematol*. 2024;11:e646–e658.
2. Platzbecker U. *Blood*. 2019;133:1096–1107.
3. Papaemmanuil E et al. *Blood*. 2013;122:3616–3627.
4. Bersanelli M et al. *J Clin Oncol*. 2021;39:1223–1233.
5. Nazha A et al. *J Clin Oncol*. 2021;39:3737–3746.
6. Bernard E et al. *NEJM Evid*. 2022;1:EVIDoa2200008.
7. Platzbecker U et al. *Lancet*. 2023;402:373–385.
8. Garcia-Manero G et al. *J Clin Oncol*. 2025;43:6512.
9. Komrokji R et al. *HemaSphere*. 2025;9(suppl 1). Abstract PS1610.

Acknowledgments

- The study was supported by Celgene, a Bristol Myers Squibb Company, in collaboration with Acceleron Pharma Inc., a wholly owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA
- All authors contributed to and approved the poster
- Writing and editorial assistance were provided by Alex Dimitri, PhD, of Lumanity Communications Inc., and were funded by Bristol Myers Squibb

Presented at the 67th American Society of Hematology (ASH) Annual Meeting and Exposition; December 6–9, 2025; Orlando, FL, USA