67yrs old gentleman

- Family history : negative for hematological neoplasms
- Moderate smoker: 15 sigarettes/day
- Type II diabetes in treatment with insulin; no other known comorbidity
- March 2012: macrocytic anemia Hb 11.9 g/dL, MCV 107 fL, WBC and PLT normal, total bilirubin 2.59 mg/dL
  October 2013: worsening of anemia Hb **9.7** g/dL, MCV **108** fL, WBC 5.2 x10^9/L, ANC 3.08 x10^9/L, eosinophils 0.43 x10^9/L , PLT 293 x10^9/L, bilirubin **1.61** mg/dL, folate and vitB12 normal;

  LDH **451** UI/L (normal <214 UI/L); haptoglobin <0.30 mg/dL; TSH, Ft3, Ft4 in normal range
- Peripheral blood: anisopoichylocytosis, NRBC 3/100 WBC, neutrophil with hyposegmented nuclei and hypogranular cytoplasm.
- Bone marrow aspirate: hypercellular, well represented , maturing granulocyte precursors, abundant terminally mature elements with 20% dysplasia, stimulation of erythropoiesis (56% of cellularity) with 60% dysplasia and ring sideroblasts >15%, megacaryocytes normally expressed with 40% dysplasia, blasts 1%
- Karyotype: 47,XY,+8
- BM Biopsy: hypercellular bone marrow , stimulated erythroid and myeloid lineages , blasts < 5%, absence of fibrosis (MF0)
- Microbiology : negative for active infections
- Ultrasound abdomen: negative; spleen size (12.5 cm)

What do you think is missing in the diagnostic procedures for this patient?

December 2013: diagnosis and management in a community hospital

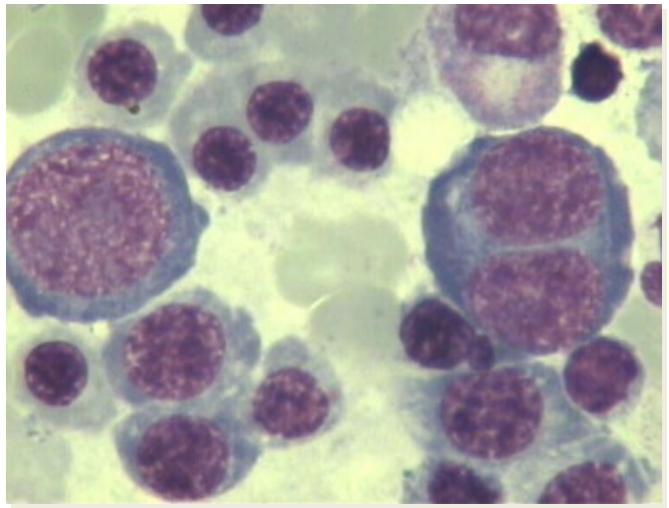
Refractory cytopenia with ring sideroblasts (WHO 2008 RCMD)
IPSS 0.5, INT-1

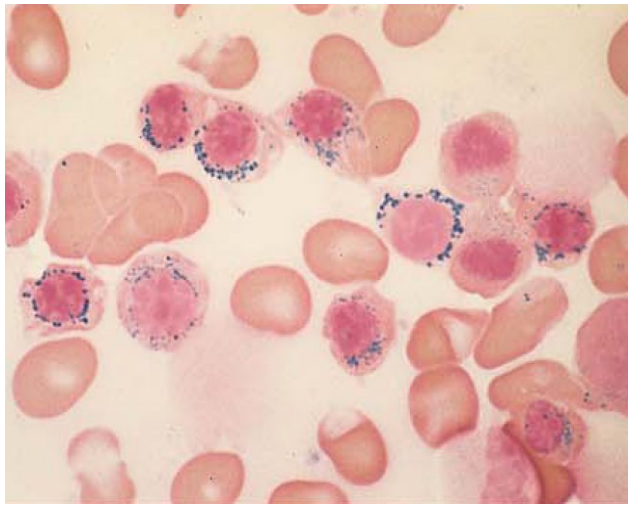
- Therapy with Erythropoietin alfa 40000 UI/week plus VitB12 and folic acid
- Progressive but slow increase in Hb values→ April 2015: Hb 11.9 g/dL, MCV 110 fL, WBC 3.4 $x10^{12}$/L

January 2016 → increase in dose of Erythopoietin alfa to 40000 UI/twice a week
July 2016 → stop EPO therapy for complete loss of response
September 2016 → transfusion dependence: 2 RBC/4 weeks

Second opinion at MDS Unit – AOU Careggi Firenze. BM re-evaluation

- MDS-RS-MLD with >90% di RS (WHO 2016)
- Karyotype 47XY,+8
- Somatic mutations NGS: mutSF3B1 and mutDNMT3A
- IPSS-R score 4 : intermediate risk
- Total bilirubin 3 mg/dL → test for mutation gene UGT1A1 → diagnosis of Gilbert syndrome

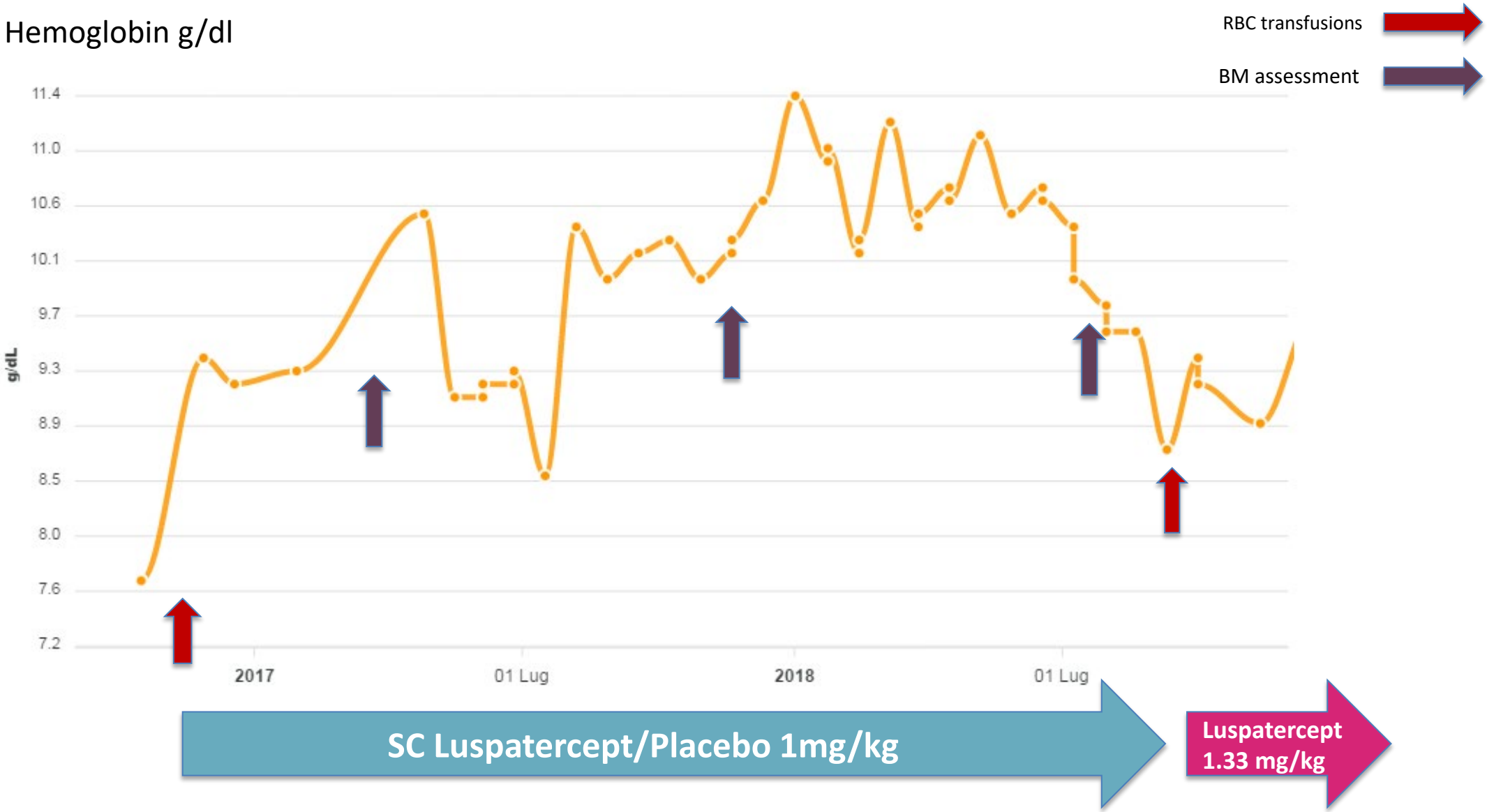




We propose to the patient the inclusion in protocol

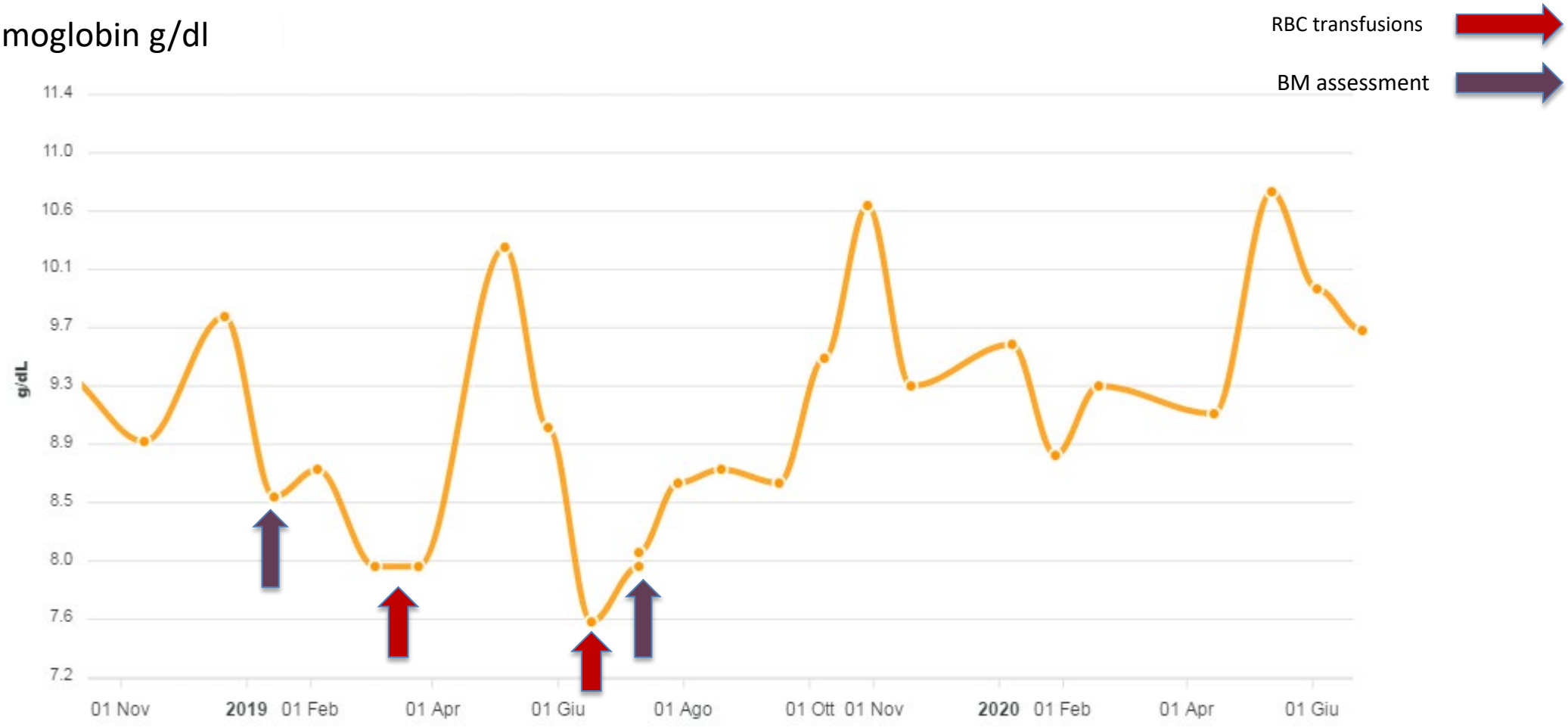
ACE536MDS001(Medalist) Luspatercept vs PBO

Patient case : Erythroid response



Patient case: Erythroid response

Hemoglobin g/dl



Luspatercept 1.33 mg/kg

Luspatercept 1.75 mg/kg

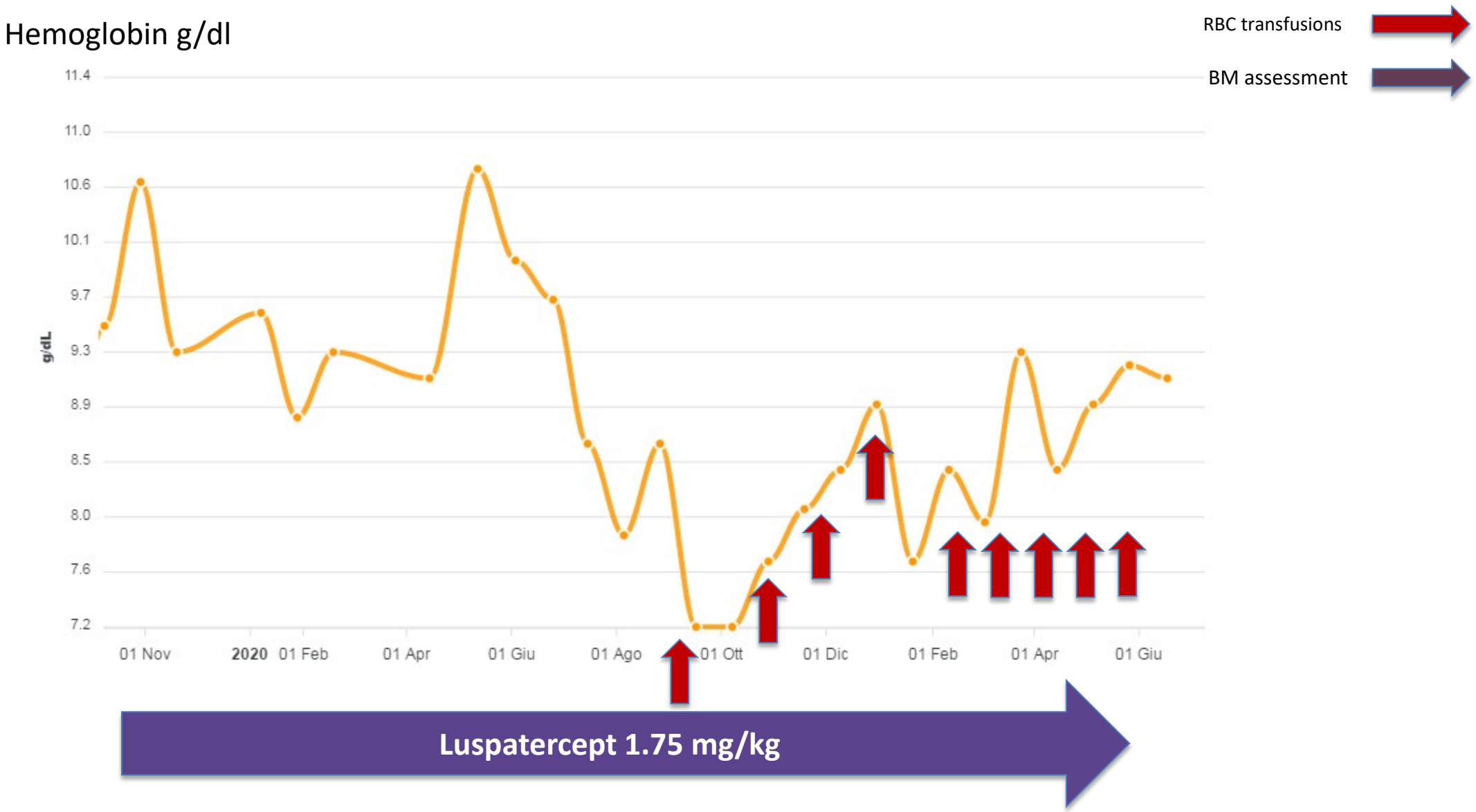
Disease re-evaluation post C39D1 (10/7/19)

- WBC 5.290/µL, Hb 9,6 g/dL; MCV 100 fL; Plt 174.000/µL
- ferritin 2264 ng/mL; LDH 302 U/L; total bilirubin 2,2 mg/dL;
- At cytofluorimetric analysis: 0,058% mastocytes with aberrant expression of CD25
- Bone marrow aspirate : mastocytes 2%. Other lineages stable
- MDS-RS-MLD with 80% RS
- BOM: Hypercellular marrow (95%), eythroid hyperplasia, blasts CD34+<5%, mastocytes CD117+ CD25+ 1%
- Karyotype 47XY,+8
- Somatic mutations NGS: JAK2 (VAF 51%), TET2 (VAF 27%), SF3B1 (VAF 44%), DNMT3A (VAF 31%)
- Triptase: 166 mg/L
- Mutation KIT D816V: negative

How would you modify the treatment approach, given the occurence of mastocytosis ?

What is your diagnosis?

Patient : Erythroid response



- Since 16/9/2020 transfusion need→ 1GRC/4 weeks

- Stable but increased ferritin (2121 ng/ml) → iron chelation therapy with deferasirox
- June 2021: transfusion need increased to 4 GRC/4 weeks → stop luspatercept
- Patient at present has the same transfusion burden

- This patient responded to luspatercept from September 2016 to September 2020 for a total of 207 weeks→ 4 years.
- At present only receiving supportive care with iron chelation, no further increase of mastocytes, but general condition worsened for neurological and cognitive impairment.

UNIVERSITÀ DEGLI STUDI FIRENZE

DIPARTIMENTO DI MEDICINA SPERIMENTALE E CLINICA

Azienda Ospedaliero Universitaria Careggi

FISiM FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

MDS UNIT

EMSCO MYELODYSPLASTIC SYNDROMES

AIRC