Caso Clinico

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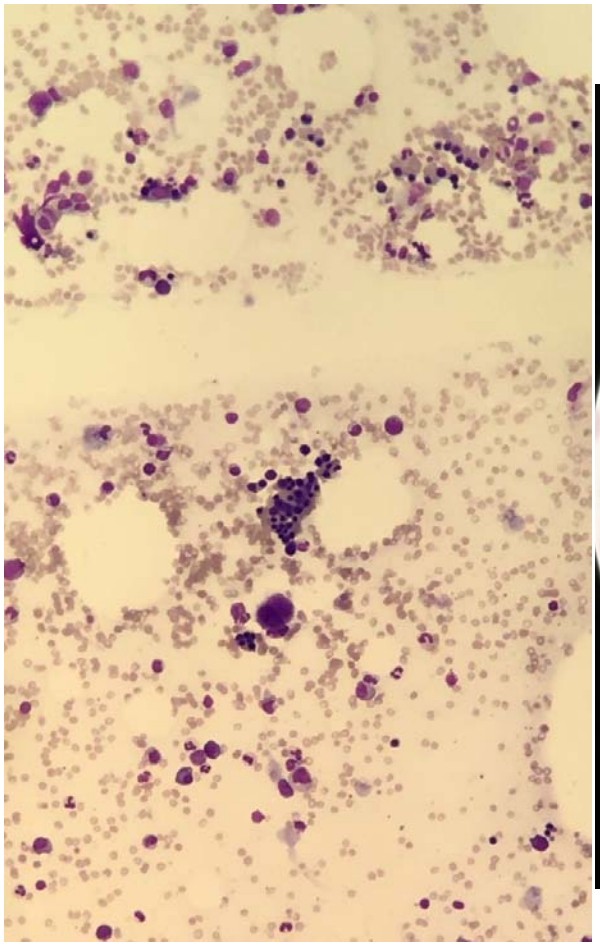
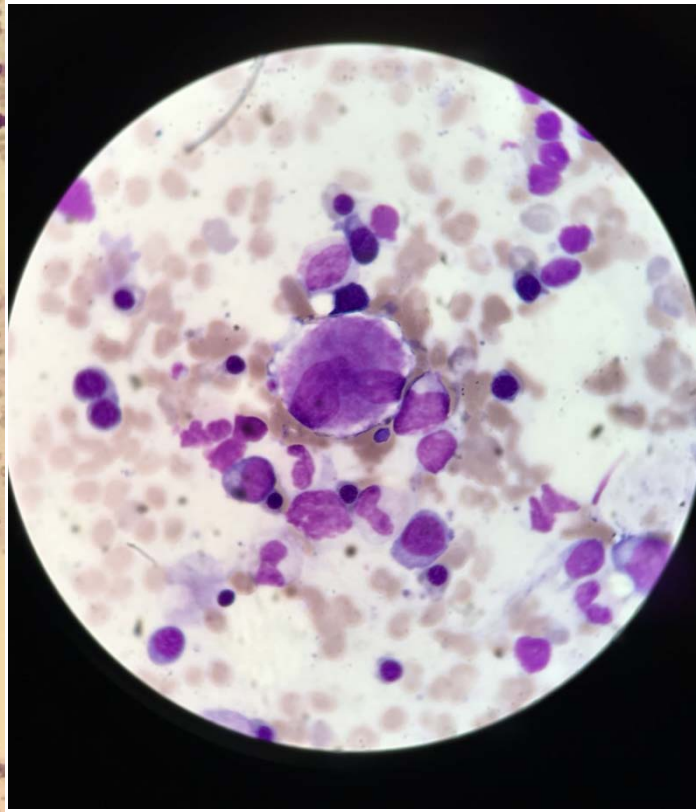
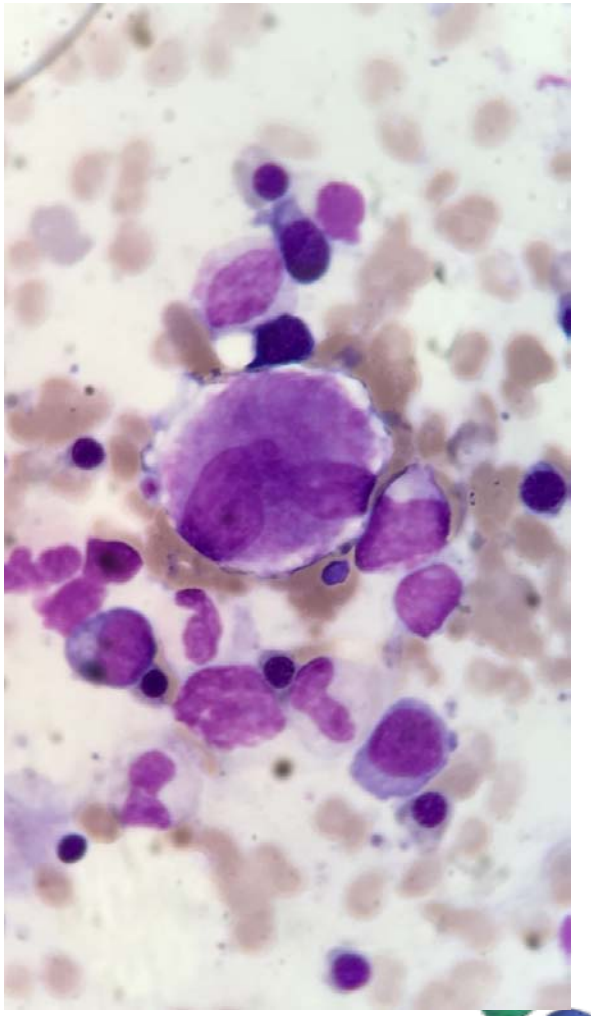
Case report (1)

- 35 year old female patient
- Previous history of autoimmune chronic tyroiditis
- First occurrence of mild, isolated thrombocytopenia 5 years earlier: 70-100 $x10^9$/L, follow up with GP
- She was referred to our Centre on April 2015 for worsening of "chronic thrombocytopenia" 70 -> 34 x 10^9/L , asymptomatic
- Bone marrow aspiration

Bome marrow cytology







Case report (2)

- Routine screening for suspected immune-mediated thrombocytopenia (ITP) with abdominal ultrasound imaging revealed ***mild splenomegaly*** (13 cm) and incomplete **portal vein thrombosis**

- It was not possible to establish the **timing/onset** of the thrombotic event because the patient denied any abdominal symptom in the last months

- Due to thrombocytopenia and hypothetical not acute onset of the thrombosis, **anticoagulant treatment was started with intermediate LMWH dose (nadroparine 0.6 ml/die –** body weight 63 kg**)** until diagnostic tests ongoing would be completed

Case report (3)

- Screening for congenital and acquired thrombophilia (APA syndrome) was negative
- FISH analysis on bone marrow aspiration was negative
- **Cytofluorimetry** was performed: 6 colours method, markers: CD45, CD59, CD235a, CD33, CD15, CD14, CD24, FLAER
- The test was consistent with presence of **a PNH clone** on 85% of neutrophils, 70% of monocytes and 4% of erythrocytes

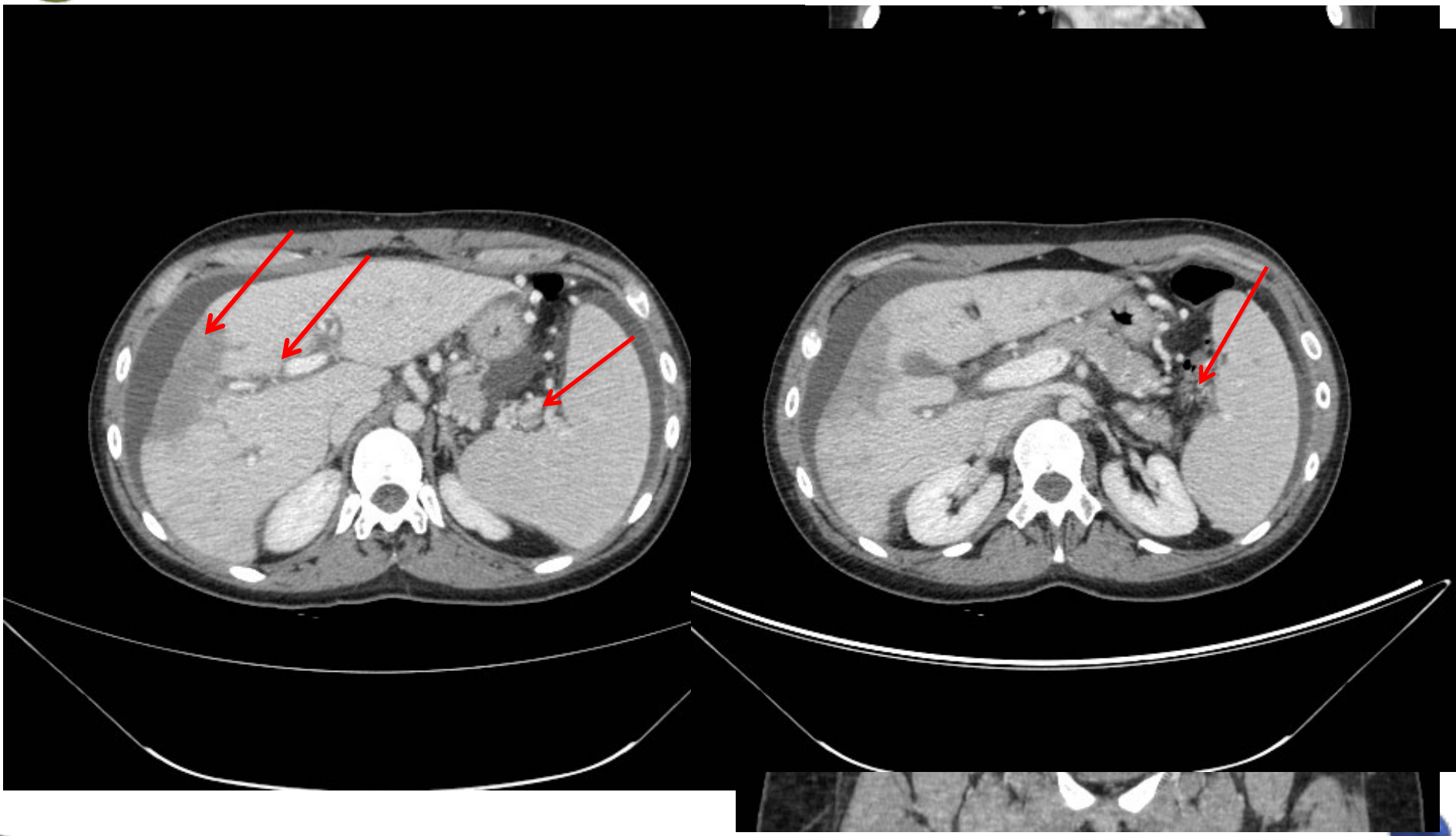
Thrombocytopenia in PNH

Table 1. Patients' demographics and clinical characteristics at enrollment into the International PNH Registry.

Parameter	Patients (n=1610)
Age, years, median (range)	42 (3-99)
Females, n (%)	857 (53.2)
Age at disease start, years, median (range)	32 (3-87)
Disease duration, years, median (range)	4.6 (<1-47)
Lactate dehydrogenase, ×ULN, median (5th, 95th percentile)[a]	1.96 (0.65, 10.32)
Hematologic parameters, median (5th, 95th percentile)	
Hemoglobin, g/L (n=1425)	106 (70, 145)
Platelets, ×10⁹/L (n=1430)	131 (19, 271)
Absolute neutrophils, ×10⁹/L (n=1275)	1.7 (0.00, 5.10)
Absolute reticulocytes, ×10⁹/L (n=971)	113 (27, 400)
Reticulocytes, % (n=1024)	3.6 (0.82, 13.06)

Schrezenmeier H, Haematologica 2014

Case report (4)



Case report (5)

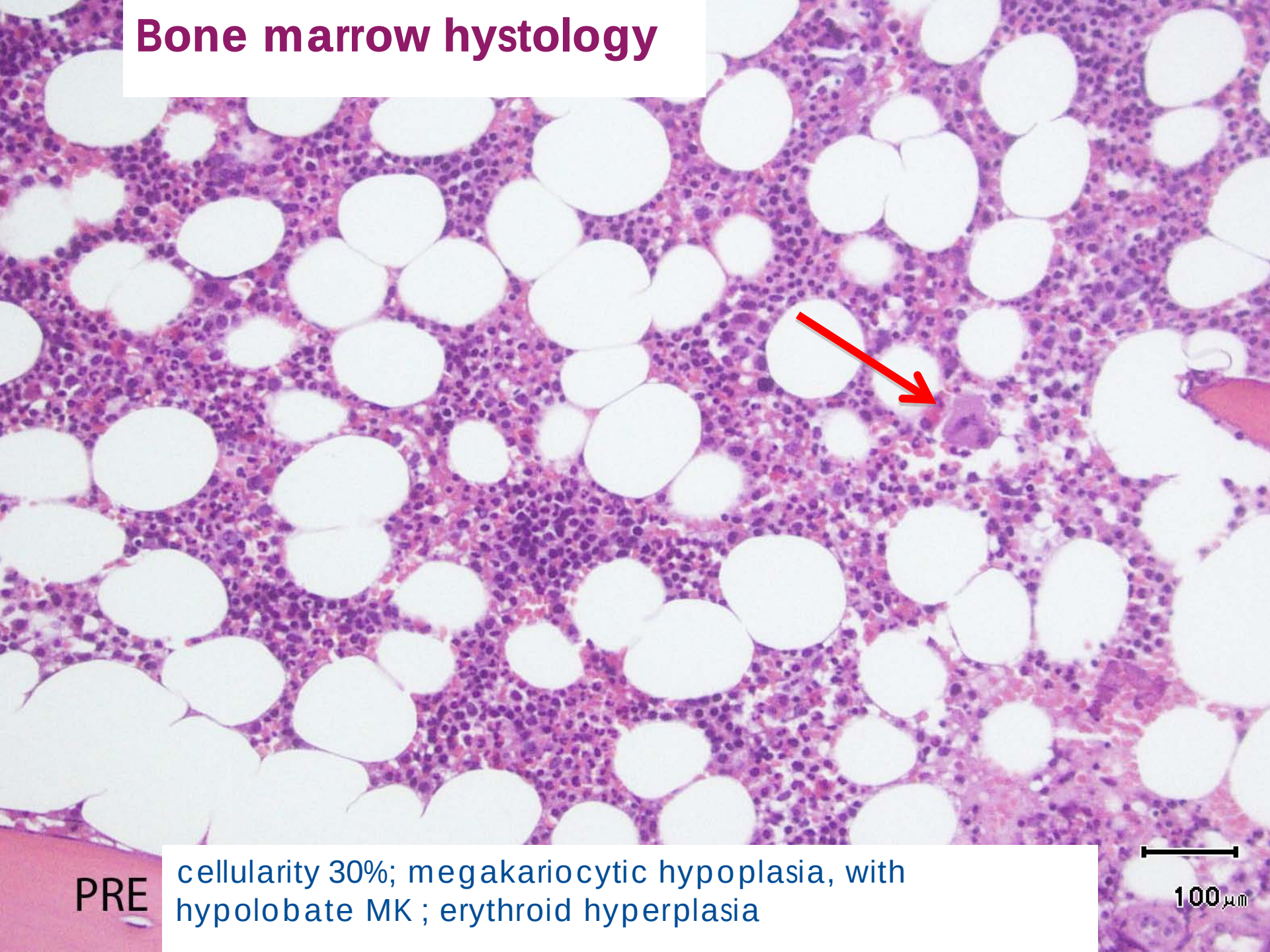
- A CT scan confirmed the previous known portal vein thrombosis and revealed **a thrombotic occlusion of sovra-hepatic and splenic veins**

- A diagnosis of **Budd Chiari** syndrome in PNH was confirmed

Case report: action taken

- LMWH : 100 U/KG x 2/die (even if thrombocytopenic, but stable...) and VKA
- **Eculizumab** (600 mg e.v/weekly for 4 weeks, and 900 mg every 15 days thereafter)
- Recommended vaccination (meningococcal ACWY vaccine,) was administered
- Prednisone 1 mg/kg was started without response on platelet count
- Bone marrow biopsy was taken

Bone marrow hystology



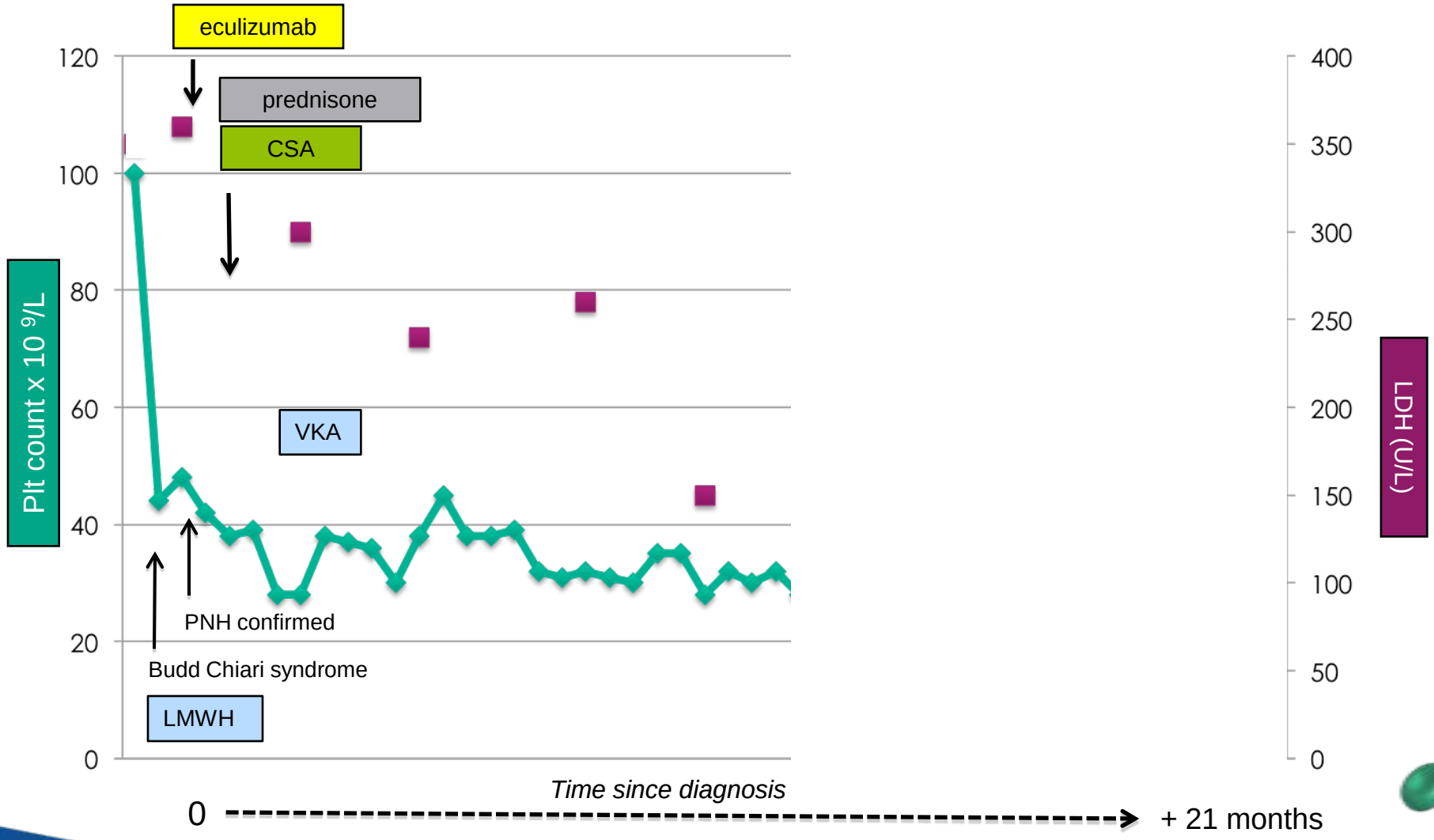
cellularity 30%; megakariocytic hypoplasia, with hypolobate MK ; erythroid hyperplasia

Rationale for combined therapy (1)

- Due to **low cellularity of the bone marrow**, knowing that aplastic anemia is a typical feature of PNH we started also **cyclosporin** (CSA) to enhance platelet count (if we believe that thrombocytopenia is the"aplastic side" of the clinical feature in this specific patient, but CSA is useful also in ITP)

- No response on platelet count was observed in the next 6 months

LDH and platelet count before and after eculizumab, CSA, steroid and VKA



LDH normal value: 135-214 (U/L)

Rationale for combined therapy (2)

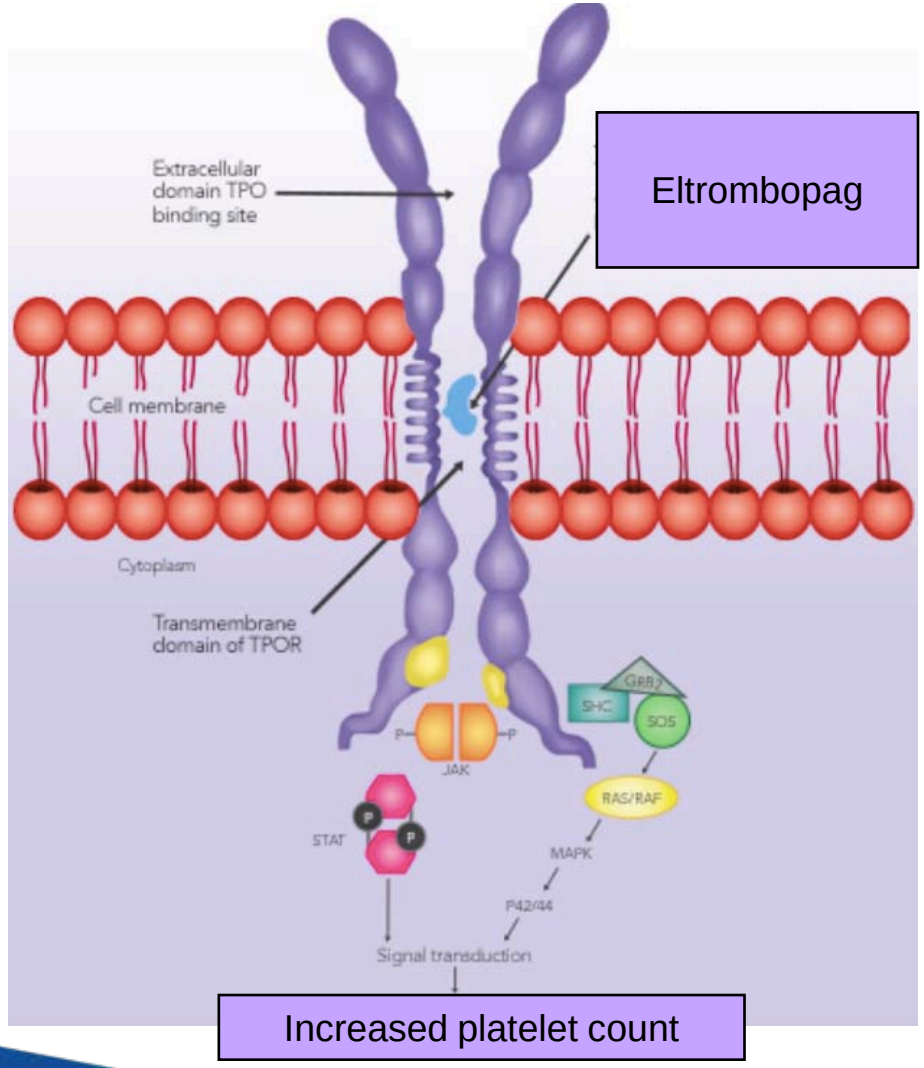
- So far the pathogenesis of thrombocytopenia in this patient is not well ascerteined (pre-existing ITP and PNH subsequently? Or isolated thrombocytopenia as first sign of PNH?)

- VKA therapy was well tolerated and well managed (**TTR* 74%**), without bleeding events until August 2016

- In september 2016, after AIFA approval of **eltrombopag** (Elt) for aplastic anemia, we decide to introduce Elt to improve platelet count

*TTR: time in therapeutic range of INR

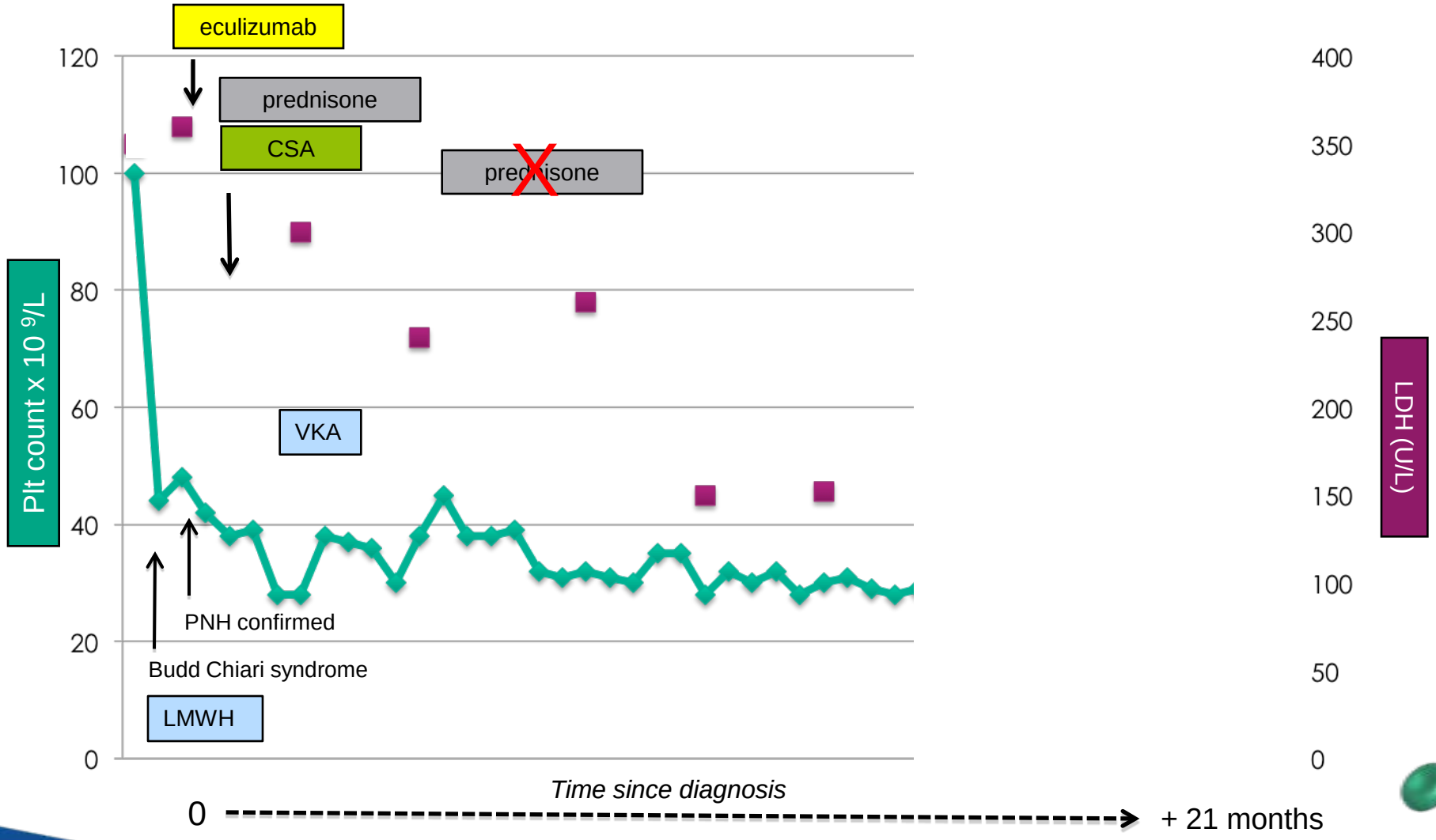
Eltrombopag



AIFA approval:

1)chronic ITP: if no response to at least 1 previous line of therapy
2)acquired aplastic anemia: if no response to immunosupressive therapy

LDH and platelet count before and after eculizumab and eltrombopag



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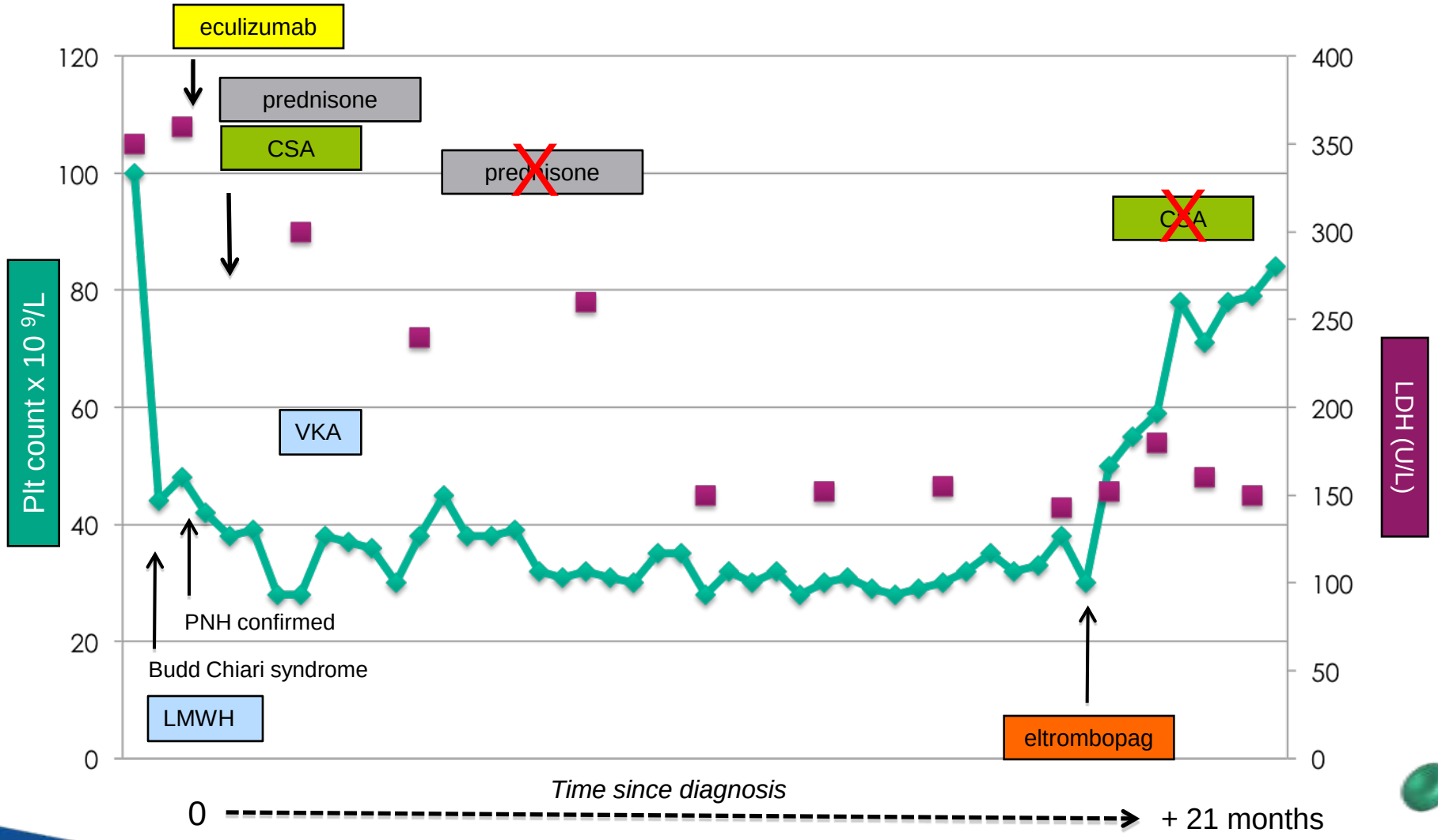

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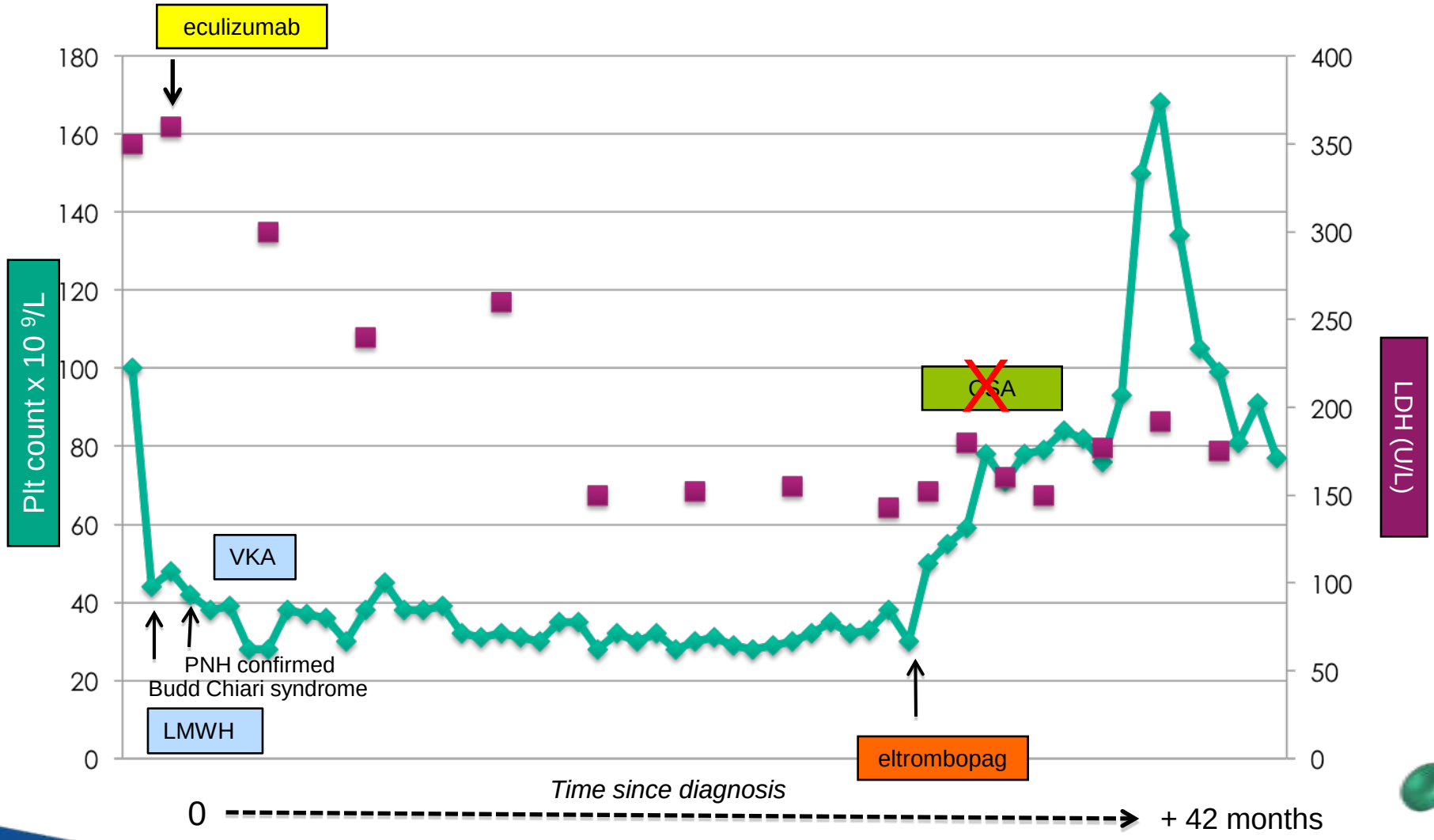
LDH and platelet count before and after eculizumab and eltrombopag



LDH normal value: 135-214 (U/L)

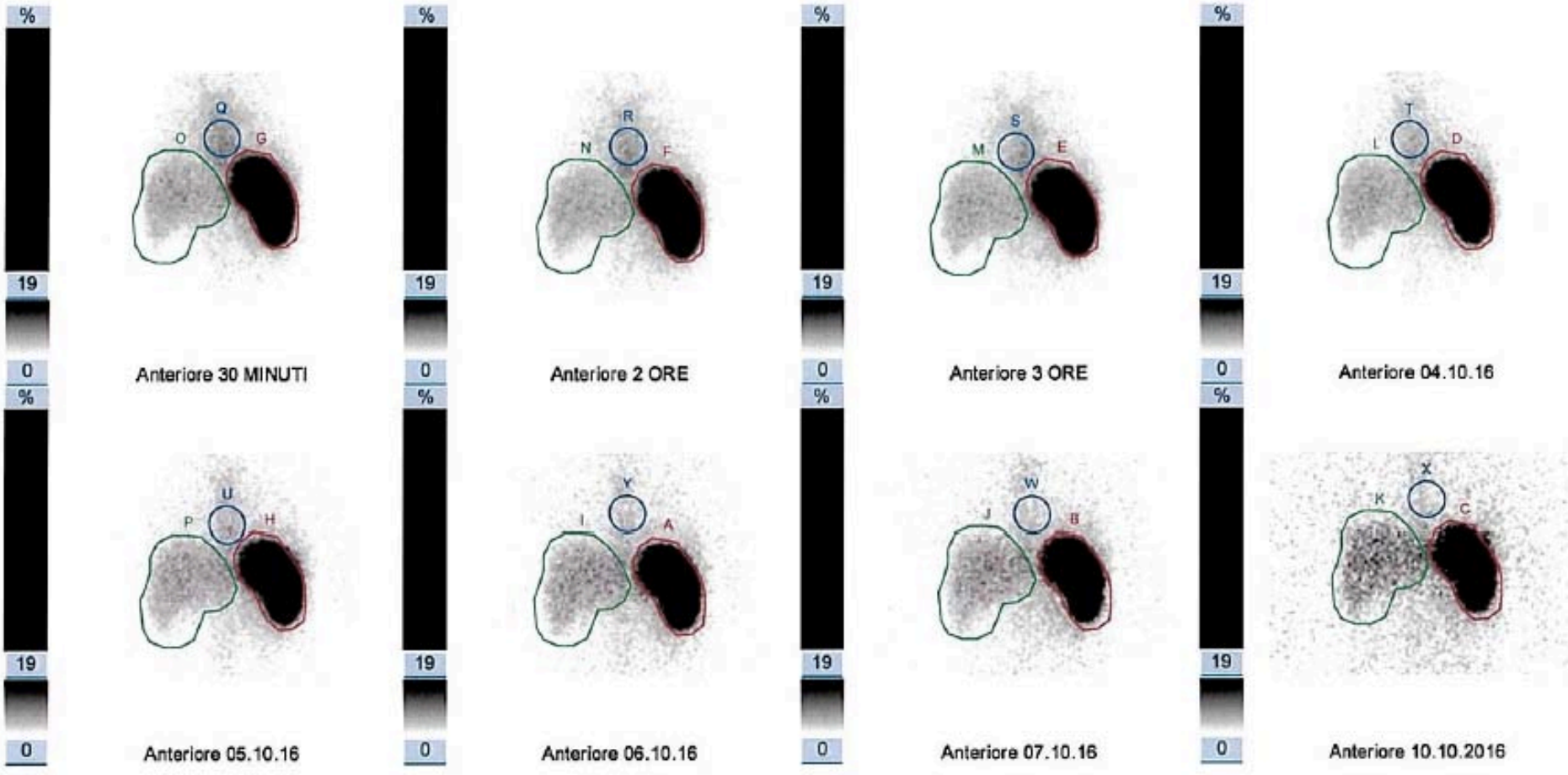
Other diagnostic tools

- Ab anti platelet were tested: negative

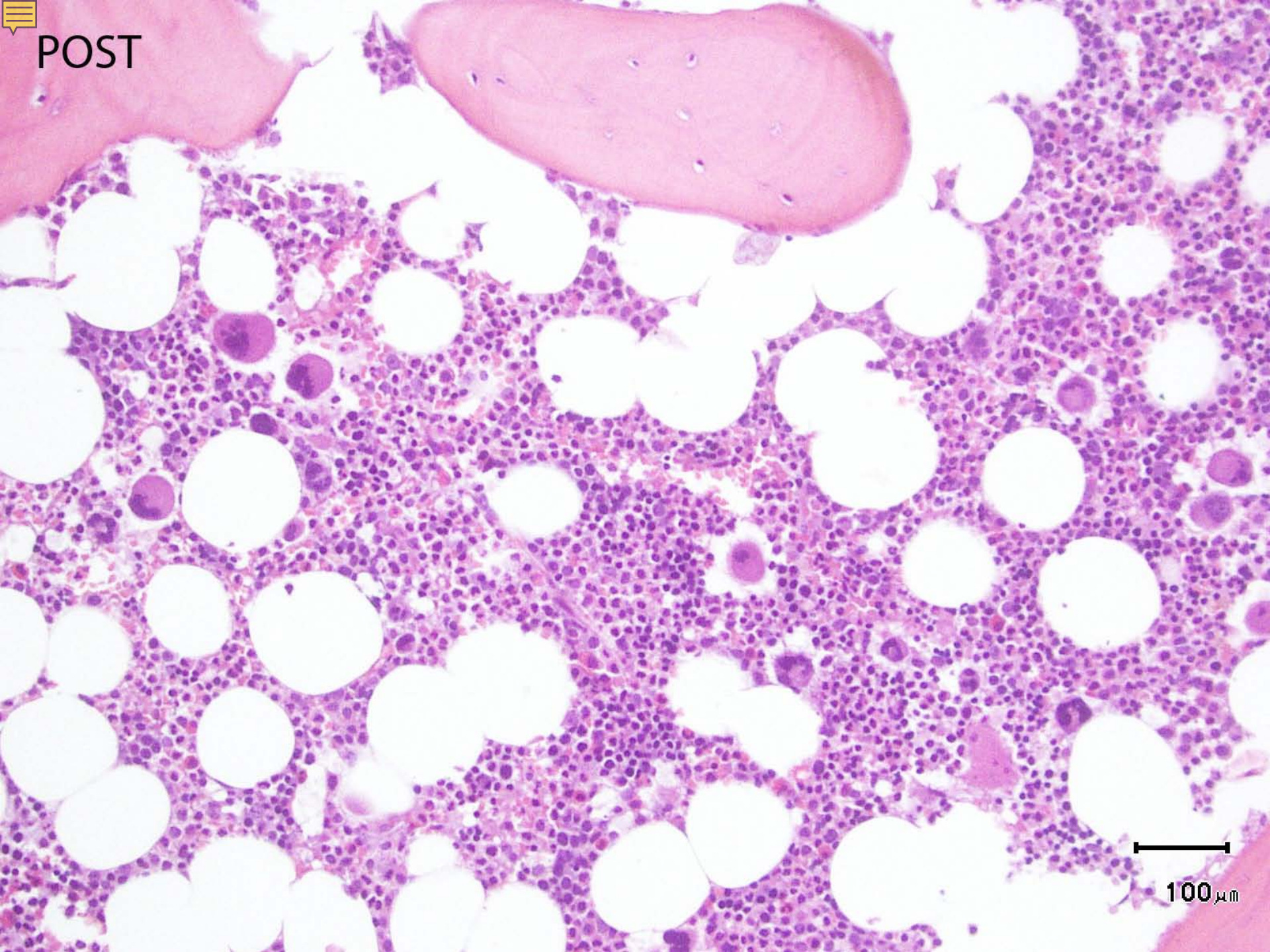
- Platelet survival studies (PSSs) to estimate the site of clearance was performed

Platelet survival studies

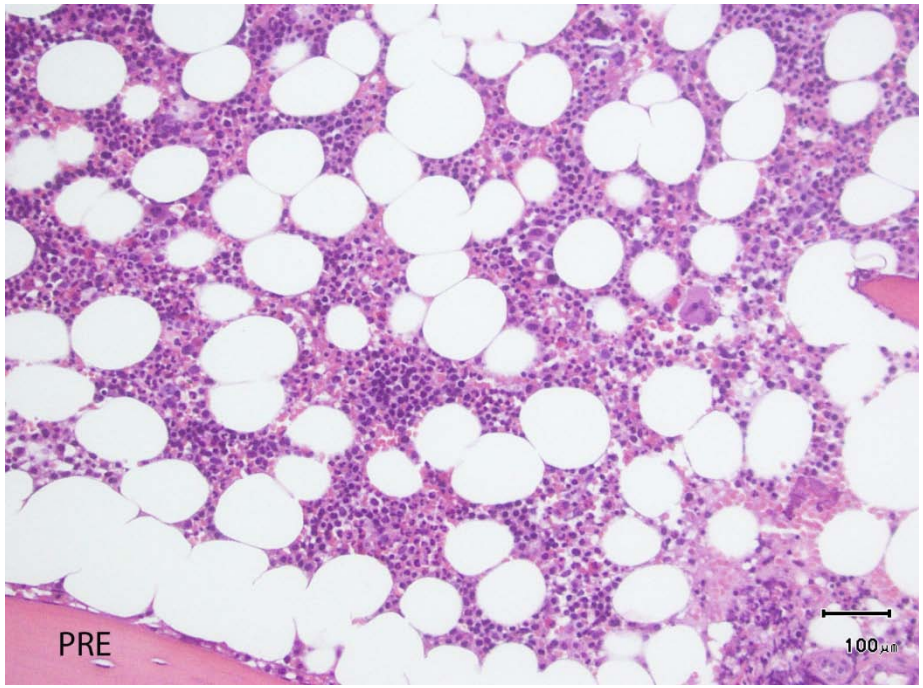
[redacted] DOB: 20-Sep-79 ID: 90317947 SEX: F
STUDY DATE: 03-Oct-16 ACCESSION #: 103094689
Patient Name: [redacted] Patient ID: 90317947 DOB: 20-Sep-79
Study Name: Study Date: 03-Oct-16

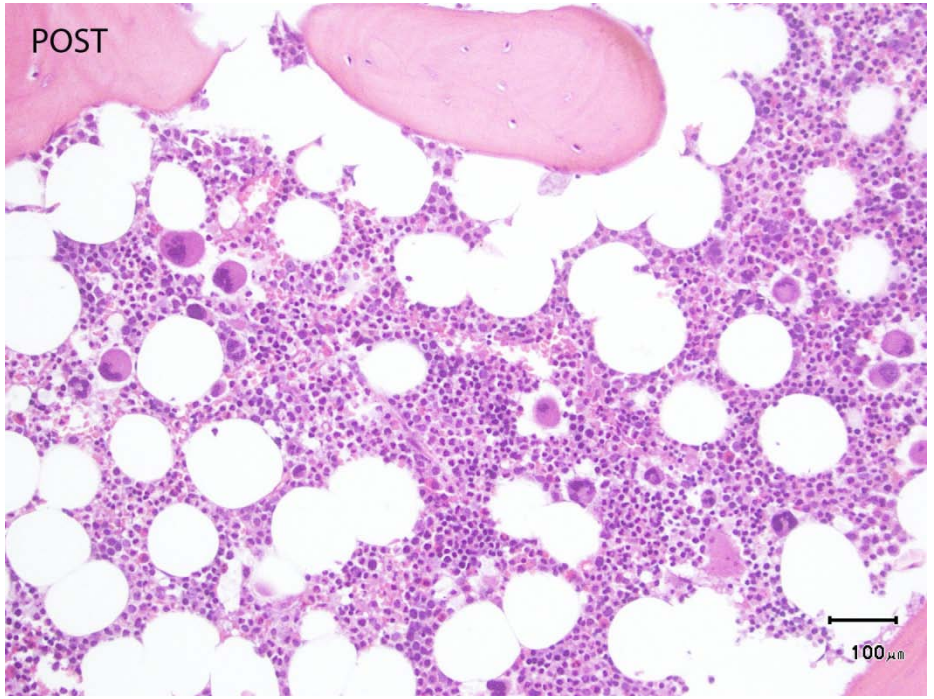


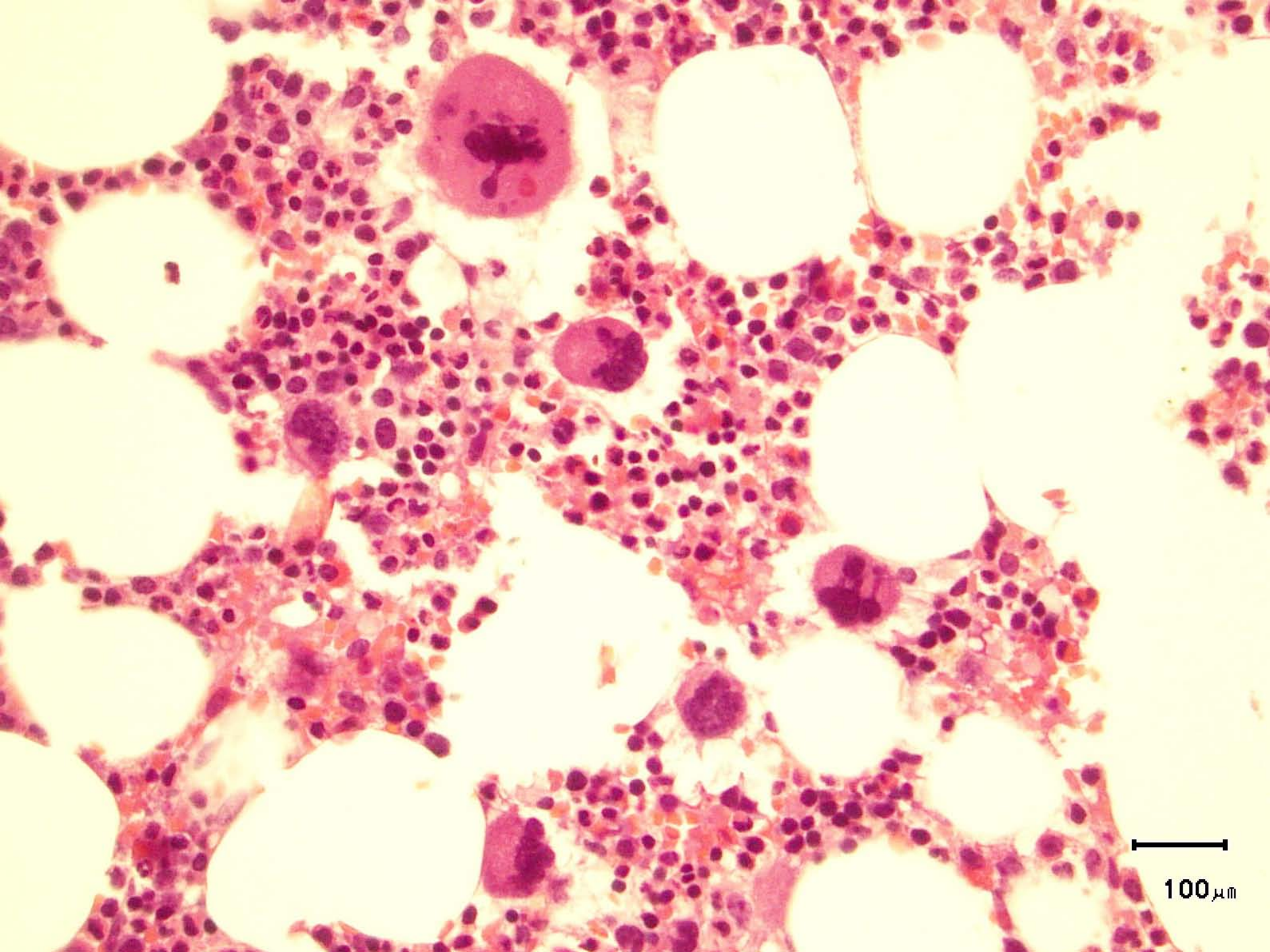
Tempo medio di sopravvivenza inferiore alla norma: il 10% dell'attività circolante si raggiunge tra il 6° e 7° giorno (v.n 7-10 gg)


POST
100 μm

Bone marrow hystology pre and during eltrombopag treatment



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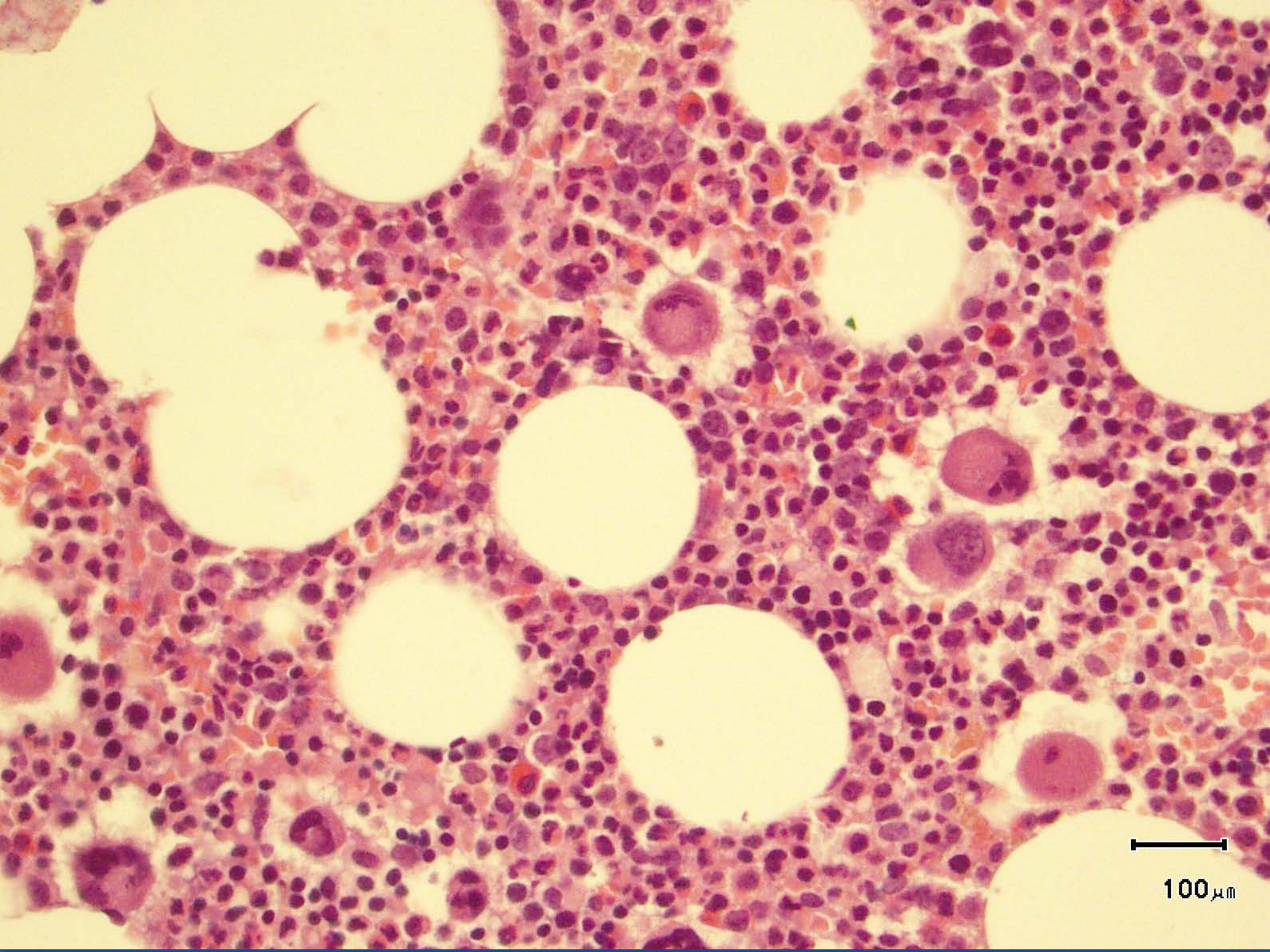
100 μm

Last follow up: 3 rd December 2018

- Asymptomatic, good performance status and quality of life
- Hb 12.4, Plt 84 x 10^9/L, WBC 3200 (ANC 1800)
- LDH normal
- No more thrombotic events
- Eculizumab, eltrombopag and warfarin ongoing
- PNH clone stable (80% neutrophils, 72% of monocytes and 5% of erythrocytes

Open questions

- VKA forever? Or should we stop it? (sooner or later..?)
- Switch VKA→ DOAC?
- Splenectomy or splenic artery embolization? (to improve platelet count and withold eltrombopag)
- If not, eltrombopag tapering? Timing?

- **ANSWERS ARE WELCOME!!**

Quando l’ematologo deve mantenere un equilibrio difficile..

Grazie per l’attenzione

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M.P.B,
nata 1/7/1945

- Maggio 2009: esordio di aplasia midollare “non severe”(Plt 2000/mmc, ANC 650/mmc, Hb 8.9 g/dL).
- Esami di funzionalità epatica e renale normali, LDH nomale
- AAM e BOM non suggestivi di patologia oncologica, cellularità 20%
- TC total body negativa
- Ricerca clone EPN negativo
- Trattata con ATG e CSA con stabilizzazione del quadro ematologico e mantenuta in supporto trasfusionale nei primi 4 mesi dall’esordio, poi progressivamente non più necessario fino a giugno 2013 (normalizzata Hb e Plt, solo lieve leucopenia)

M.P.B,
nata 1/7/1945

- In giugno 2013 repentino peggioramento della crasi ematica con anemia e piastrinopenia (Hb 8 g/dL, Plt 80000/mmc, GB 2000 con ANC 1080)
- Malessere generale, non disturbi specifici
- Indici di emolisi alterati: aptoglobina < 0.1 mg/dL, LDH elevato (892 U/l), bilirubina normale

- Ripete BOM: quadro di ipocellularità, non atipie
- **Ricerca clone EPN: positivo** (granulociti 85%, monociti 85%, eritrociti 16%)

30 giugno 2013

- Nel frattempo peggioramento della crasi ematica, riprende supporto trasfusionale

To do list….

- Per iniziare il trattamento con Eculizumab:

✓Vaccinazione anti meningococcica (tetravalente coniugato)

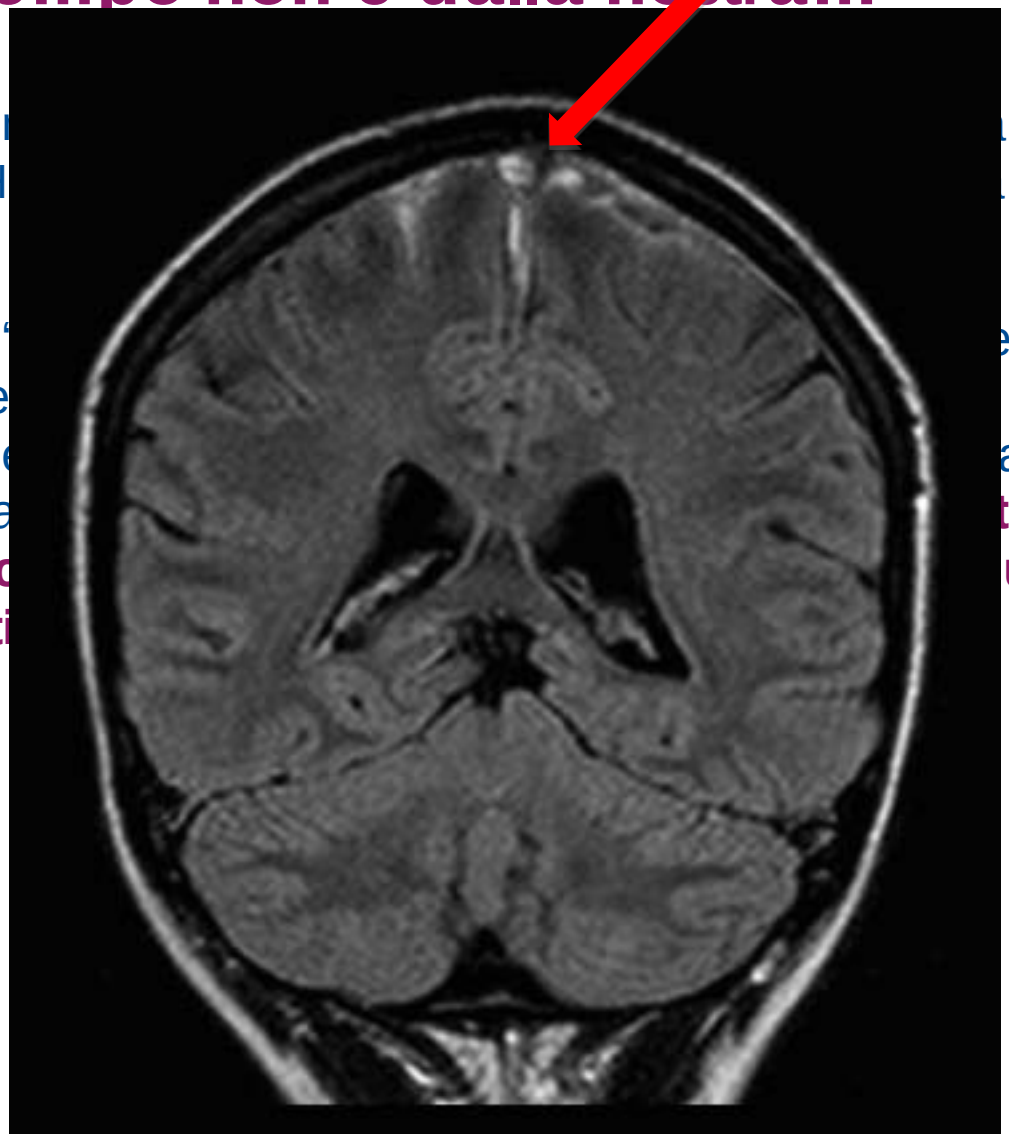
✓Compilazione modulo AIFA

✓Inoltro richiesta alla Direzione Sanitaria e farmacia….

…il tempo non è dalla nostra…

- 6 luglio : crisi co … strinopenia (43000/mmc), H … GT

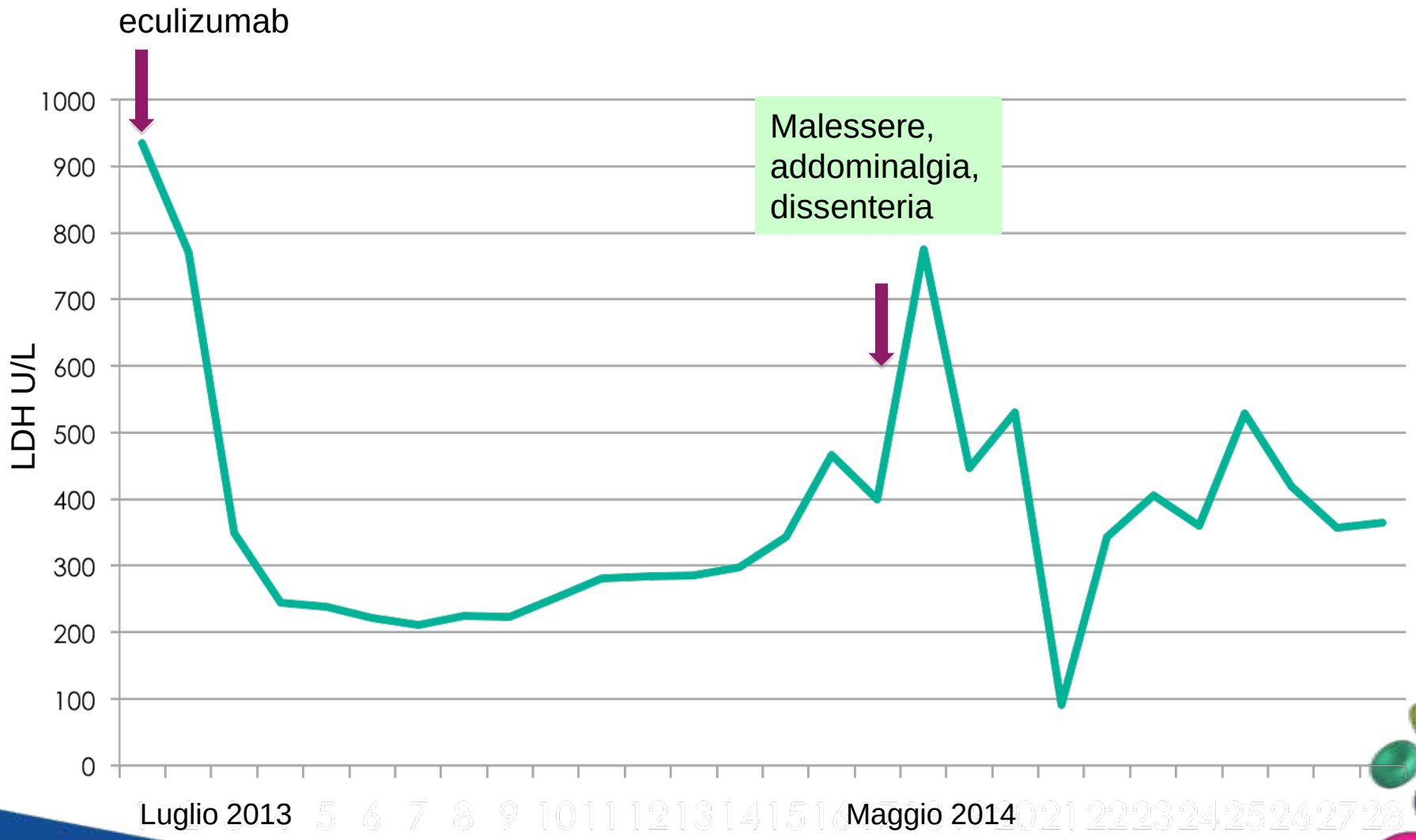
- RMN encefalo: " … e a livello del giro precentrale … corticale" con alcune pete … a della sostanza bianca … **tibile con area di infarto venosc … una vena corticale al verti**



..il seguito del nostro caso clinico…

- Inizia trattamento anticomiziale
- Inizia eparina --→ warfarin
- Prosegue supporto trasfusionale
- Inizia Eculizumab

M.P.B:
LDH dopo introduzione di eculizumab



Problemi aperti

- Breakthrough emolisi saltuaria
- Proseguire Coumadin o “provare” switch a DOAC?
- Proseguire terapia anticoagulante sine die?