

## **Management of anemia with erythropoiesis stimulating agents**

# Disclosures

## **Speakers bureau**

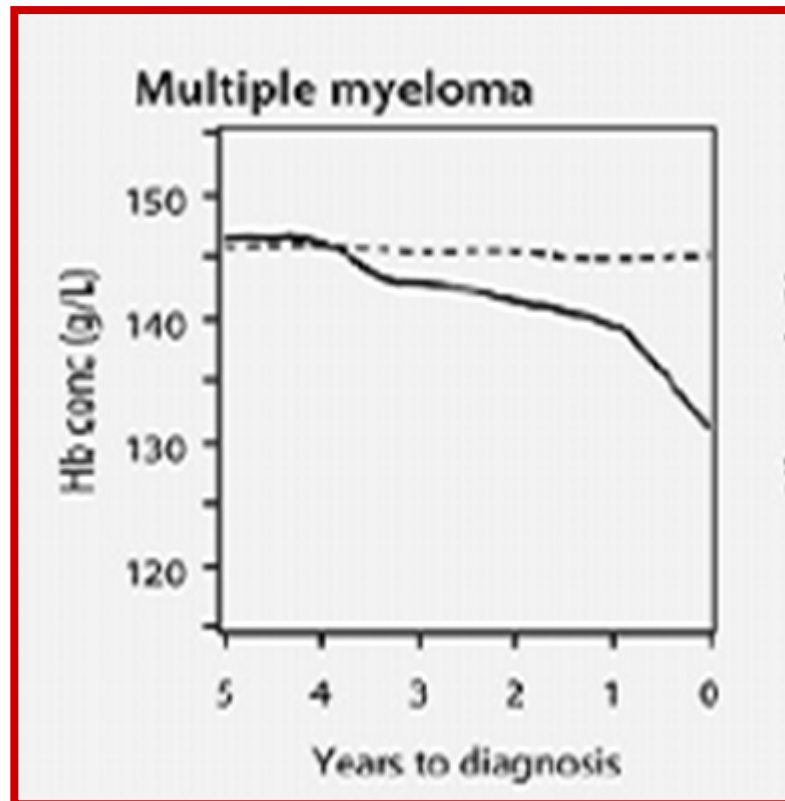
AMGEN, Janssen Cilag, Vifor

## **Advisory boards**

Vifor, Sandoz, Janssen-Cilag, AMGEN

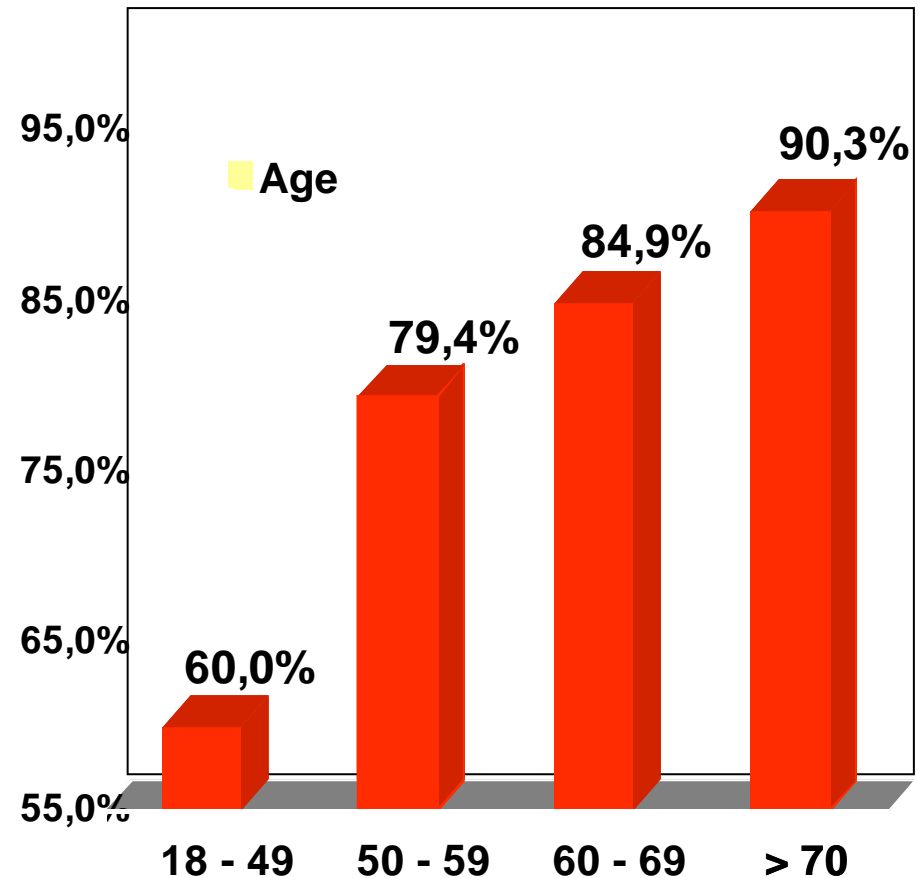
## Anemia – often present before diagnosis Prevalence increases with age

Blood donors before diagnosis of MM



Edgren et al. In J Cancer 2010

Frequency of anemia in patients with MM



Birgegard et al Eur J Heamatol 2006

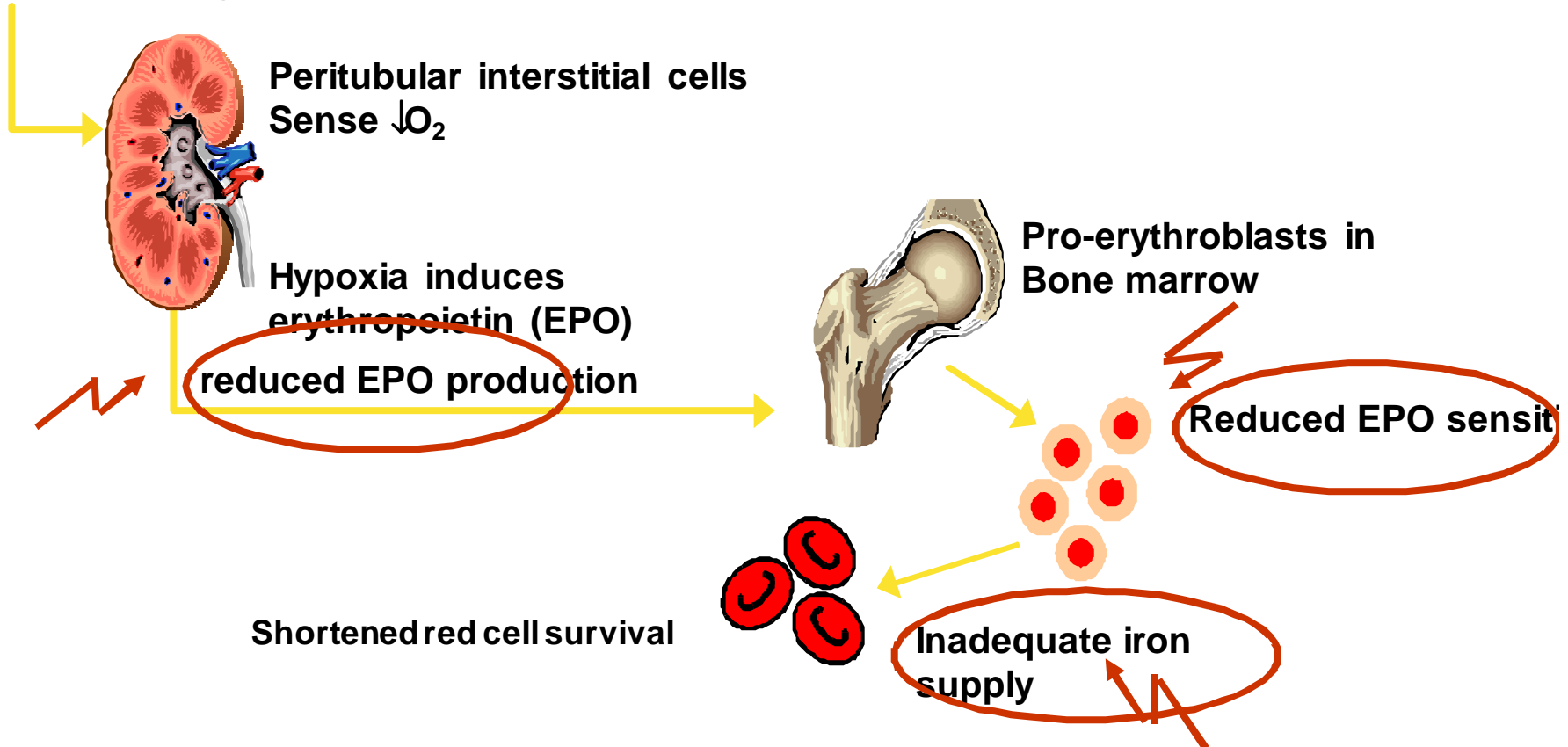
## Investigation of patients with anemia

### Exclude/diagnose

- **Vitamin B12 and folate deficiency**
  - **Iron deficiency**
  - **Severe infection**
  - **Hemolysis**
  - **Blood loss**
  - **Bone marrow insufficiency**
  - **DIC**
  - **Congenital anemia**
- 
- **Distinguish between anemia of myeloma and chemotherapy associated anemia.**
  - **Consider that MDS may occur concomitantly with myeloma**

# 'Anemia of myeloma' – usually multifactorial in pathogenesis

Decreased oxygen delivery to the kidneys



## Important causes of anemia in multiple myeloma

- **↑ Inflammatory cytokines (e.g. IL-1, TNF, IFN- $\gamma$ ) and hepcidin induction – impaired iron utilisation**
- **↓Erythropoeitin production**
- **↓Number of erythroid precursors**
- **↓Sensitivity of erythroid precursors towards erythropoietin**
- **Fas-L and TRAIL induced apoptosis of erythroid precursors**
- **Decreased osteoblast-induced stimulation of hematopoiesis**
- **Others**
  - Renal insufficiency
  - Infection
  - Chemotherapy
  - Hypervolemia
  - Bone marrow infiltration
  - Hemolysis

## Indications for use erythropoietins and for RBC transfusions

### Consider ESAs

- chemotherapy induced anemia
- ,chronic' anemia of myeloma
- symptoms from anemia (Hb <11g/dl) or if Hb <10g/dl)

### Consider RBC transfusions

- symptomatic patients with Hb <8g/dl
- in case rapid symptom improvement important
- refractory to ESAs

# Treatment Options for Anemia

## Blood Transfusions



## Erythropoietins

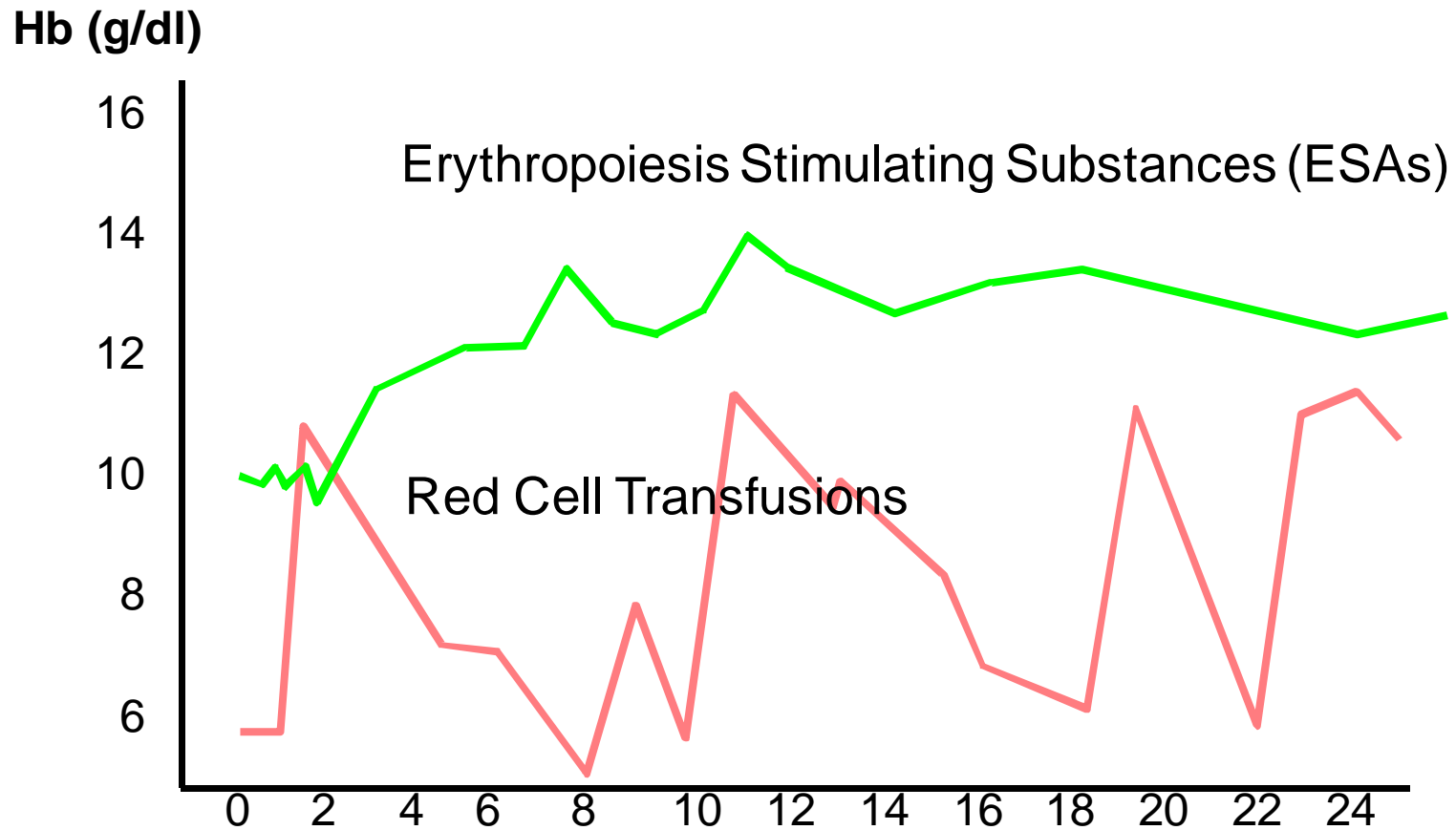


Different indications, benefits and risks

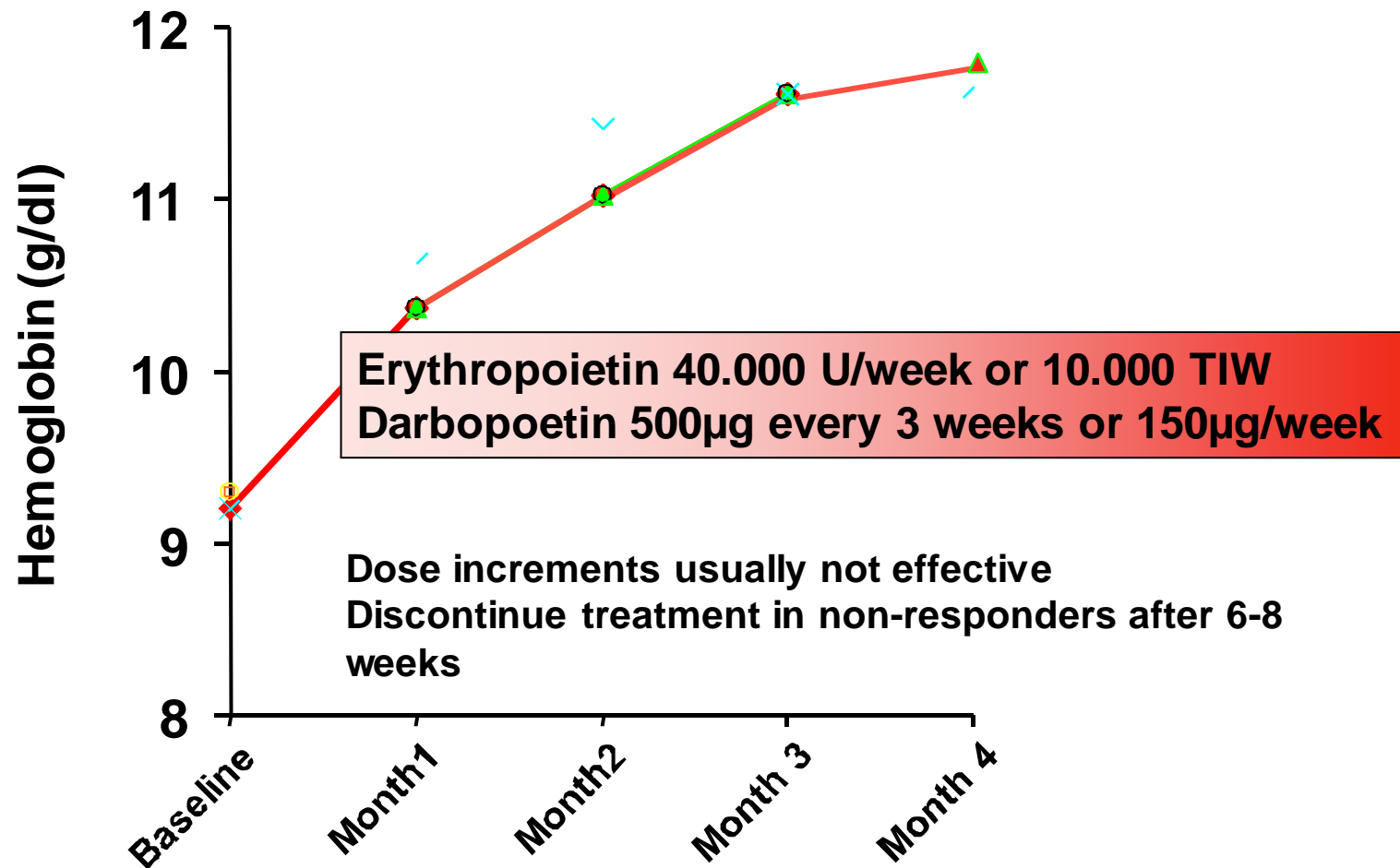
Hb <8g/dl		Hb <11g/dl or <10g/dl
Immediate increase in Hb		Slow increase in Hb
Short effect		Long term effect
Several risks including VTE, infections, induction of lymphomas, and increased mortality		↑ risk for thromboembolic complications ↑ risk for mortality in non-approved indications



# Treatment Options



## Dose and duration of ESA therapy



## Recommendations for ESA therapy

Recommendation	FDA	EMA	ASH/ASCO	NCCN	EORTC
Initiation of ESA therapy	< 10g/dl	≤10g/dl	<10g/d	≤1g/dl or 2g below baseline	≤1g/dl
Target Hb level	Treat to a level to avoid RBC transfusions	<12g/dl	Lowest concentration to avoid RBC transfusions, reduce ESA dose when Hb exceeds 1g/dl in any 2 week period	Not stated	12-13g/dl
Supplementary therapy	Not stated	Not stated	Iron repletion when indicated	Consider iv. iron* when TSAT <20% and ferritin ≤ 800µg/l	Address functional iron deficiency with iv iron

\*with erythropoetic therapy

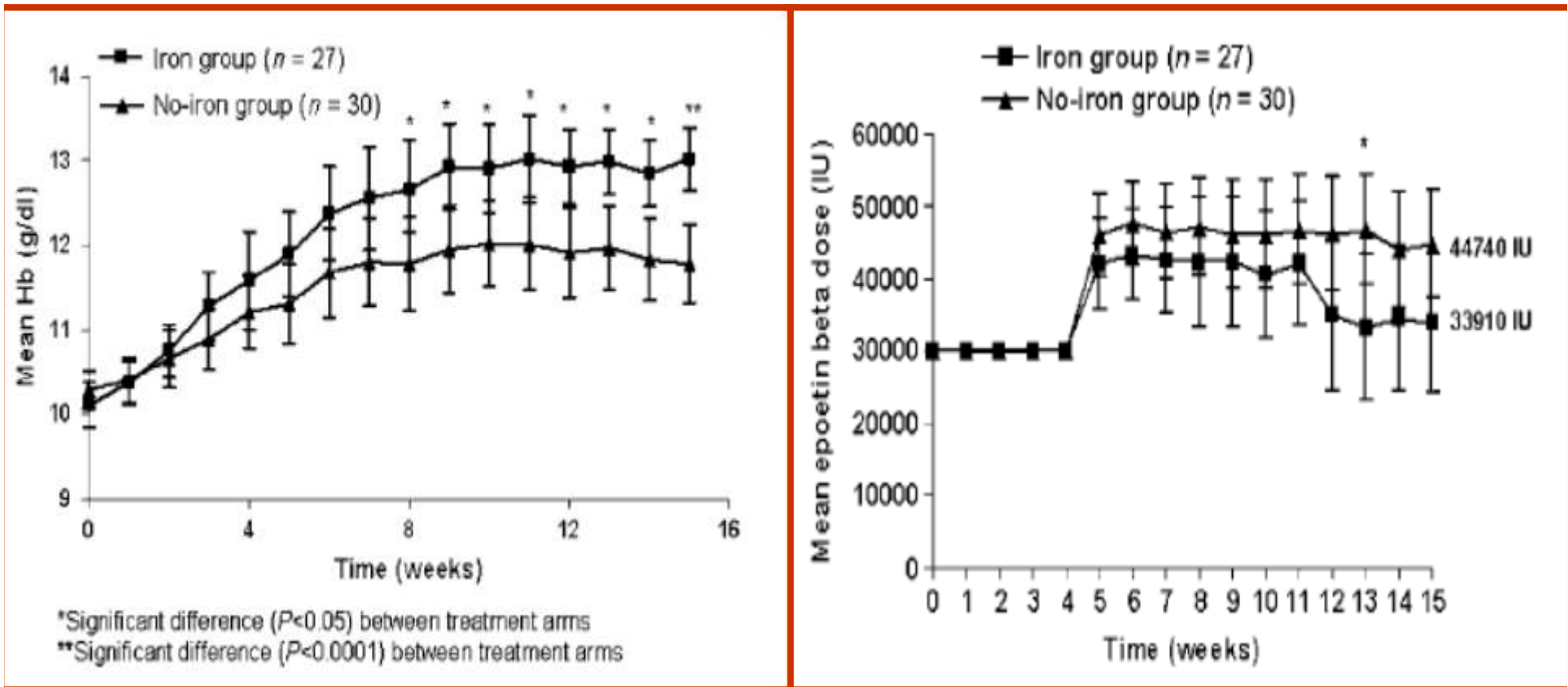
## Iron deficiency by ISS stage in multiple myeloma

ISS Stage	AID TSAT <20%, Ferritin <30µg/l	FID TSAT <20%, Ferritin >30µg/l	No ID	Total
I	2 (4.8%)	10 (24.3%)	29 (70.7%)	41
II + III	7 (6.7%)	37 (35.6%)	60 (57.6%)	104
Total	9 (6.2%)	47 (32.4%)	89 (61.3%)	145

**AID: Absolute iron deficiency**  
**FID: Functional iron deficiency**

## Epoetin beta and Intravenous Iron Sucrose vs. Epoetin beta (30.000 U once Weekly) only

65 Patients with MM, NHL, CLL iron sucrose (Venofer®) 100mg/week x6, followed by 100mg biweekly (until week 14)



## Intravenous iron

**iv. iron may be considered with erythropoietins  
in patients with anemia and functional iron  
deficiency:**

**TSAT <20%, Ferritin <800µg/l**

## Benefits of ESA therapy

- **60-70% of patients will respond**
  - **good risk patients more likely to respond**
  - **in aggressive disease response rate may be as low as 35%**
- **Reduction in transfusion need by ~> 70%**
- **Improved QoL in responders**
- **Response rate can be increased with iv. iron**

## Risks of ESA therapy

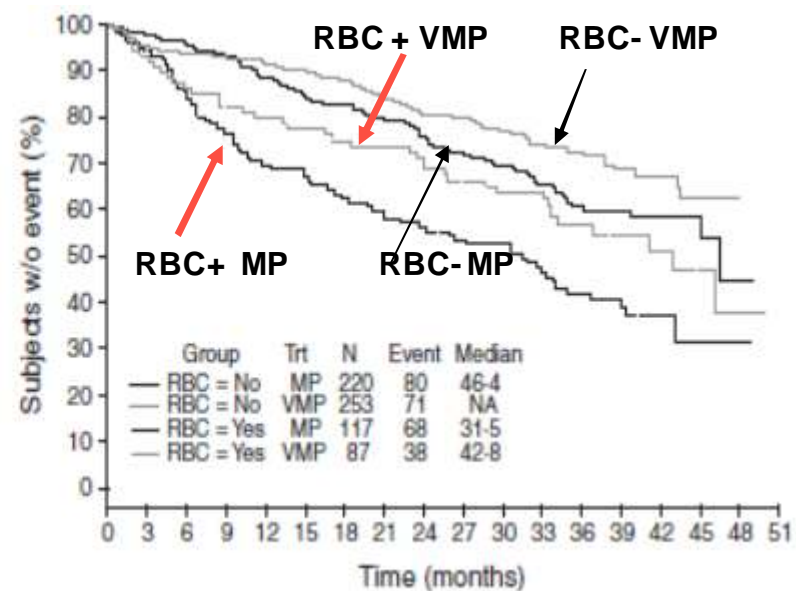
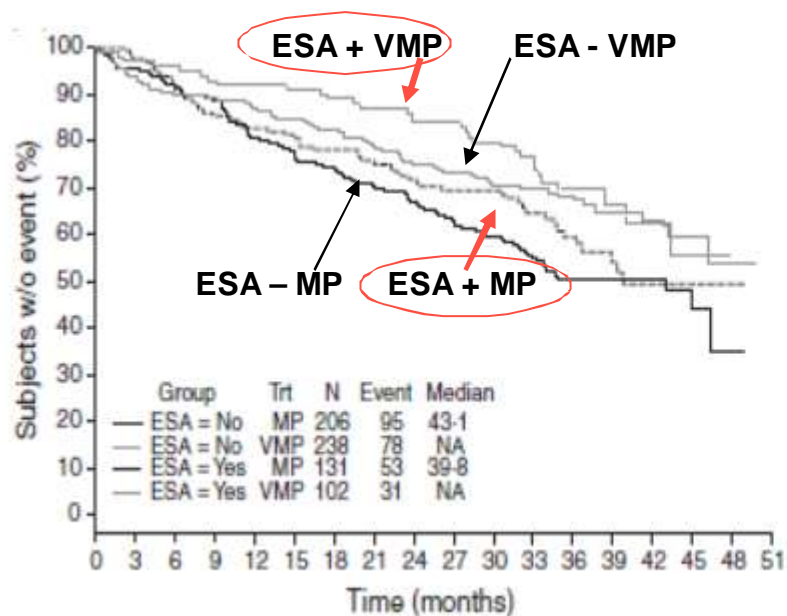
- **Increased TVT/PE rate (HR: 1.65) in cancer patients**
  - **Risk higher in patients**
    - **treated with IMiDs**
    - **on high dose dexamethasone**
    - **with additional risk factors for TVT/PE**
    - **receiving RBC transfusions**
  - **No increased risk in some studies (VISTA, Lonial, Katodritou)**
- **Stimulation of malignant growth?**



## ESAs and survival

Author	Nature of study	Impact on OS
Österborg et al. 2006	Prospective, randomized, unplanned analysis	None
Baz et al., 2006	Retrospective	↑ OS
Kadotitrou et al., 2008	Retrospective	↓ OS
Richardson et al., 2011	Retrospective	None

# ESA treatment did not impair OS, RBC transfusions were associated with shortened OS (retrospective analysis)



## Retrospective analysis of the VISTA study

# Management of anemia with erythropoietins

Chemotherapy associated anemia  
Chronic anemia of myeloma

Hb  $\leq$ 10g/dl

Start ESAs

symptomatic from anemia  
Hb <11g/dl

Start ESAs

Hb >10 g/dl, without symptoms

no therapy

Erythropoietin 40.000 once weekly or 10.000 TIW  
Darbopoetin 500 $\mu$ g, q 3 weeks, or 150 $\mu$ g once weekly

Improvement of symptoms  
RBC transfusions avoided  
Hb between 11-12 g/dl

Halt therapy, restart when symptoms reccur or Hb <11g/dl

- Dose escalation not recommended
- If no response after 6-8 weeks – stopp therapy
- In patients with functional iron deficiency (TSAT <20%, ferritin<800 $\mu$ g/l) consider iv. iron