Immune-response and adverse reactions:

PRCA case example

Nicole Casadevall

Recombinant human erythropoietin (rhUEPO)

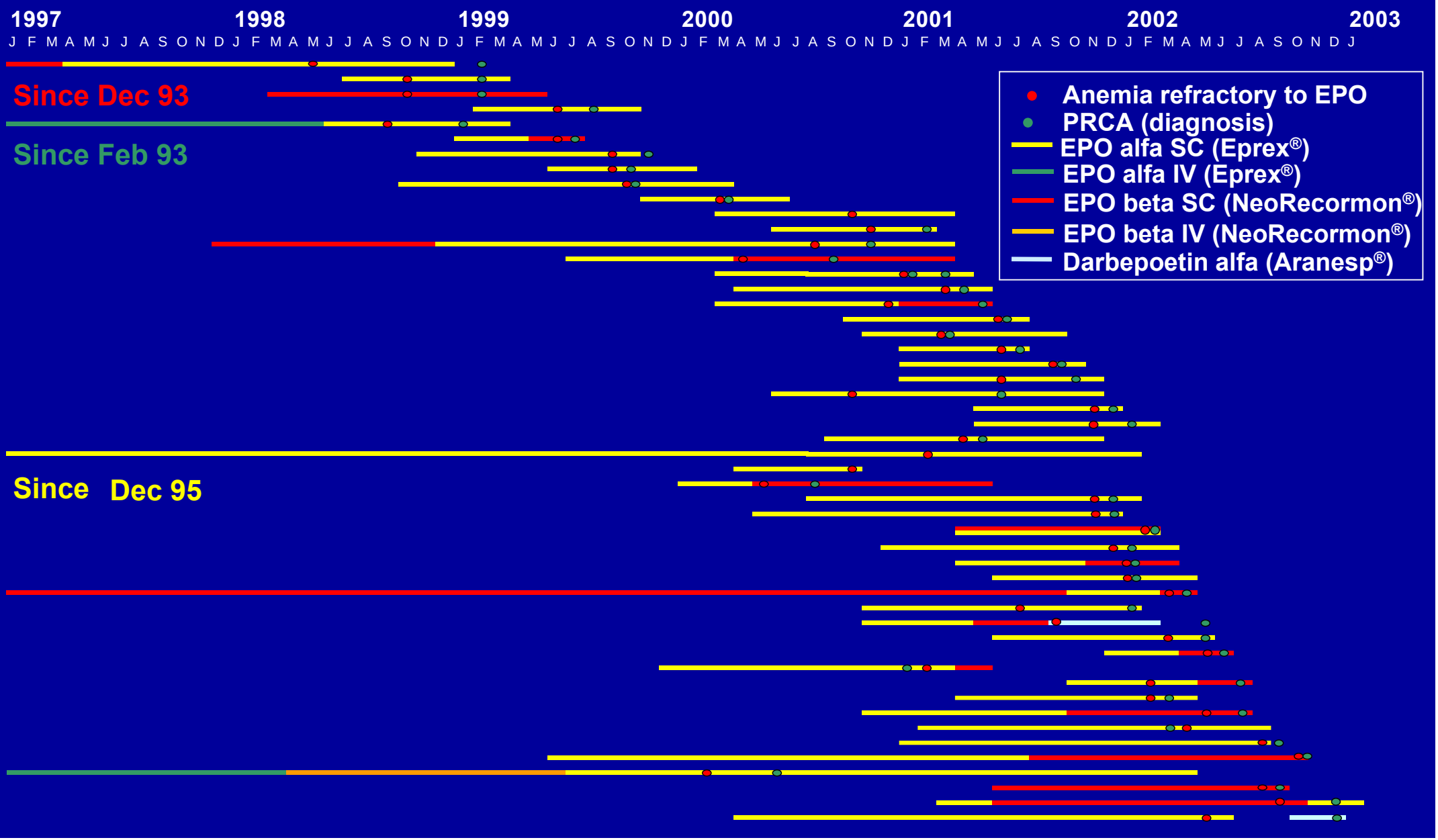
- 1985: EPO gene cloned
- 1986: first clinical trials in CKD
- 1988: rhEPO is licensed for hemodialysed chronic kidney disease (CKD) patients
- Further licenses
  - CKD patients non dialysed
  - peri-surgery – autotransfusion programs
  - anaemia of prematurity
  - patients with anaemia of cancer
  - patients with lymphoproliferative syndromes

PRCA with antibodies to EPO

1988 → 1998

- Only three cases of allo-antibodies published
  - Bergrem H et al 1993
  - Peces R et al 1996
  - Prabhakar SS et al 1997

Time Course of PRCA Cases



Epo antibody mediated PRCA

Diagnosis

- Unexplained loss of effect (LOE)
- Anaemia (Hb decreases by about 0.1 g/dl/day)
- Low reticulocyte count (< 10 000/µl)
- Platelets. White blood cells : normal

- Bone marrow (strongly recommended)
  - Normal cellularity
  - Erythroblasts very rare (< 5 %)
- Positive Epo antibody test

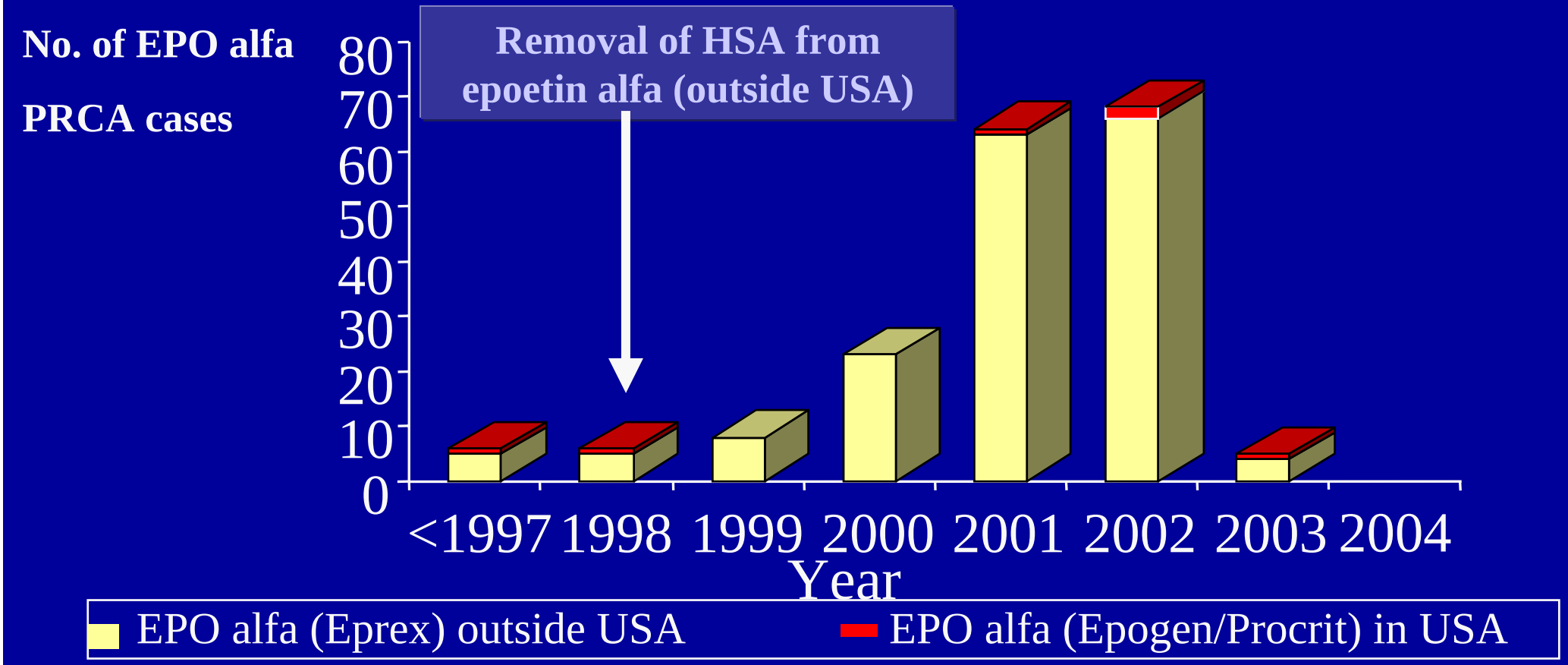
PRCA and epoetin treatment

- Virtually all cases observed in renal patients (2 cases in MDS patients)
- No cases in cancer patients
- High correlation with SC exposure to Eprex®
- No cases with exclusive IV exposure
- Median time from first exposure to anaemia: 11 months (range: 3–90 months)

Increase in PRCA coincides with changes in EPREX® formulation in 1998

- Human serum albumin (HSA) removed to comply with new European regulations
- Replaced with Polysorbate 80 (Tween 80)

EPO alfa PRCA cases



- **Epoetin α formulation in US still contains HSA**
  - **No increase in EPO-associated PRCA in USA**

Change in formulation

- Clinical pharmacokinetic/pharmacodynamic study in healthy volunteers
- Physico - chemical characterization studies
- Stability – purity studies

(Comparison new/old formulation)

- No clinical studies required

Increase in PRCA Mechanisms ?

- New formulation may be
  - less stable ?
  - more immunogenic ?
- Several hypotheses

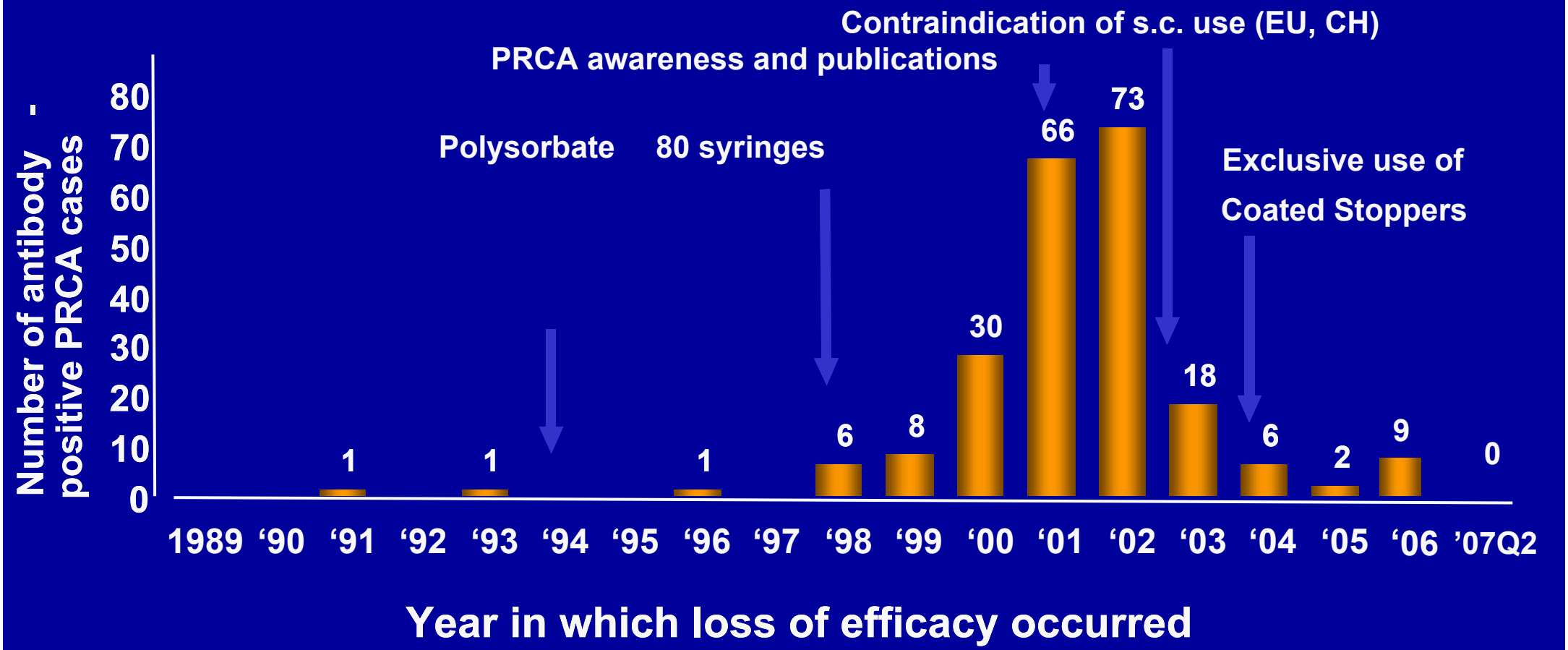
  (micelles ? leachates ?)

Increase in PRCA
Mechanisms ? Multifactorial ++++

- New formulation
- Cold chain respect (handling – storage)
- Route of administration (SC/IV)
- Patient (CKD – Cancer)
- Concomitant medications
- Lenght of treatment
- Other factors ?

Chronology of EPREX Ab-mediated PRCA

(All Spontaneous CKD Reports Received by 30 June 2007)



Reinstatement of EPREX sc in CKD

- Exclusive use of coated stopper seringes since March 2004 : 3 cases in the world (excluding Thailand) with the new formulation
- Strict control of handling (cold chain)
- New FluroTec coated stopper product for sc use approved in:
  - All major markets
    - European Union
    - Switzerland
    - Australia
    - Canada
  - Others (…Thailand)

Antibody-positive PRCA cases

- ≥ 237 cases in CKD patients treated with ESA
  - 189 treated with HSA-free epoetin alfa (Eprex®, Erypo®) only
  - 10 treated with epoetin alfa (Epogen®, Procrit®) only
  - 12 treated with epoetin beta (Neorecormon®) only
  - 2 treated with HSA-free darbepoetin alfa (Aranesp®) only
  - ≥ 24 mixed cases
- 4 cases in non-CKD patients treated with ESA
  - 2 MDS patient treated
  - 2 patients with hepatitis C (+ Interferon and Ribaverin)
- (2 cases in CKD patients treated with biosimilars)

Incidence of EPO Ab-mediated PRCA

- Only reported using erythropoiesis stimulating agents (ESA) subcutaneous

- Very rare

• ARANESP® and Epogen	< 1 case/ 100.000 PY
• NEORECORMON	1-2 cases/100.000 PY
• EPREX - in the world except Thailand	3/120.000 PY
- in Thailand	9/6.500 PY

PRCA in Thailand

- Epo Ab-mediated PRCA is more common than in other countries

- Most cases reported with Eprex (9 cases) but also with :
  - Recormon®
  - Hemax® (local biosimilar)

PRCA in Thailand

- Storage and cold chain not guaranteed at out-of-hospital pharmacies
- No tracability – substitution is frequent
- 7 marketed biosimilars
- Thai FDA announced that products are illegaly imported
- Counterfeit products

A Thai « loss of effect » registry is set-up run by hematology, nephrology and hospital pharmacy associations

Antibody-mediated PRCA - Summary

- Development of antibodies cannot be anticipated
  (very rare cutaneous reactions/hypereosinophilia)

- When antibodies are detected « it is too late »

- Diagnosis of ESA-induced Ab-mediated PRCA requires a reliable test for detection of anti-EPO Ab
  (sensitive – specific – reproductible – standardized)

Antibody mediated PRCA - Summary

- Is usually very rare
  - Background incidence 1-3/100.000 PY
- Has been reported with all ESAs – injected subcutaneously
- Immunogenicity cannot be detected in pre-approval clinical studies (number of patients)
- Only robust post-marketing risk management programs will be able to capture these very rare events

Ab mediated PRCA - Summary

- Minor modifications of biological products can alter their characteristics and immunogenicity
- It cannot be assumed that all products (biosimilars) have the same immunogenicity profile
- Improper handling and storage can alter the safety profile of ESA
- Substitution will be unavoidable… but should be as infrequent as possible
- Traceability of all ESA given to a patient is essential
- If the same INN is given to different biosimilars, traceability will be almost impossible
- Ideally… serum sample should be stored before any switch is made … but this seems to be very difficult in clinical practice
- IV route of administration should be promoted in hemodialysis patients, for safety reasons