Hypoplasia in PNH : to treat or not to treat?

Andrea Bacigalupo and Hubert Schrezenmeier

Rome *Ulm*

Firenze 4/October/2024

Disclosures

Speakers Bureau for
Sanofi, Pfizer, Therakos, Adienne, MSD, Novartis, Riemser, Eurocept, Takeda, Pierre Fabre, Miltenyi, Jazz

Avisory Board for
Novartis, Jazz, Kiadis, MSD, Clinigen

Hypoplasia in PNH

PNH and AA

AA and PNH

AA/ PNH

MDS/PNH

60 year old lady

Diagnosis of RA in 2016 (with cytopenia ; mainly platelets)
Enrolled in a trial of EPAG in low risk MDS
No response of cytopenia
Activated UD search (2020) – identified MUD 8/8
Patient admitted for transplant-
High LDH prompts search for GPI- cells
Large PNH clone identified
Patient discharged and started on eculizumab
2024 patient AW on eculizumab
PNH misdiagnosed as MDS

How many patients with AA have PNH clones?

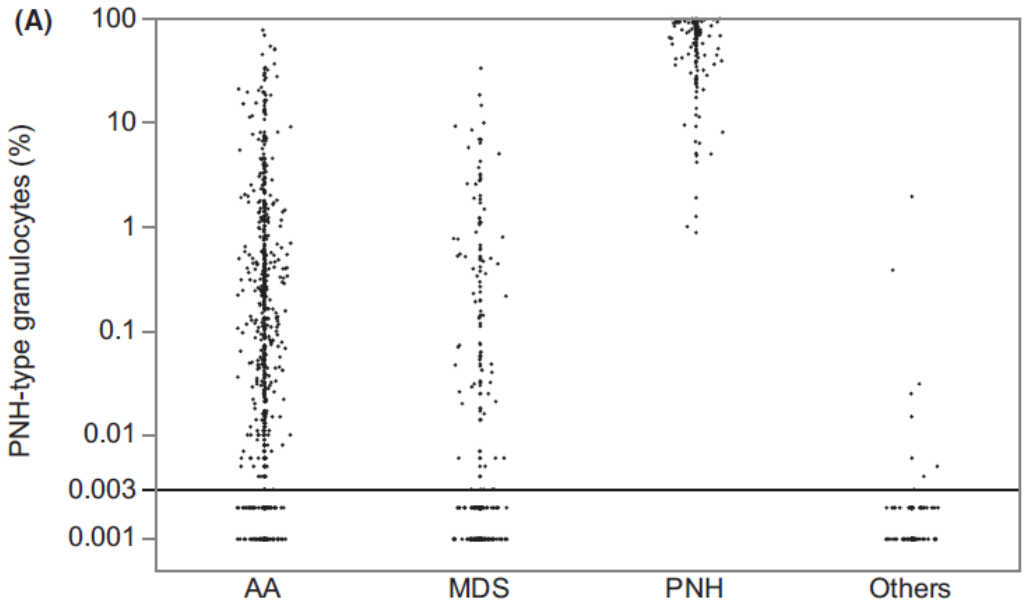
DOI: 10.1111/bjh.19048

ORIGINAL PAPER

Br J Haematol. 2023;203:468–476.

A longitudinal analysis of paroxysmal nocturnal haemoglobinuria-type cells in patients with bone marrow failure: Results of a prospective multi-centre study in Japan

Ken Ishiyama[1,2,3] | Yuji Yonemura[3,4] | Tatsuya Kawaguchi[3,5] | Kohei Hosokawa[1,3] | Chiharu Sugimori[3,6] | Yasutaka Ueda[3,7] | Hiroyuki Takamori[3,7] | Naoshi Obara[3,8] | Hideyoshi Noji[3,9] | Yukari Shirasugi[3,10] | Kiyoshi Ando[3,10] | Tsutomu Shichishima[3,9] | Haruhiko Ninomiya[3,11] | Shigeru Chiba[3,11] | Jun-ichi Nishimura[3,7] | Yuzuru Kanakura[3,7] | Shinii Nakao[1,3]



	AA	MDS	PNH	Others
	1075	900	144	283
PNH+ PMN	52%	13%	100%	3%

Leukemia (2021) 35:3223–3231
https://doi.org/10.1038/s41375-021-01190-9

ARTICLE

Myelodysplastic syndrome

Clinical and prognostic significance of small paroxysmal nocturnal hemoglobinuria clones in myelodysplastic syndrome and aplastic anemia

Bruno Fattizzo[1,2,3] · Robin Ireland[1] · Alan Dunlop[1] · Deborah Yallop[1] · Shireen Kassam[1] · Joanna Large[1] · Shreyans Gandhi[1] · Petra Muus[1] · Charles Manogaran[1] · Katy Sanchez[1] · Dario Consonni[2] · Wilma Barcellini[2] · Ghulam J. Mufti[1,4] · Judith C. W. Marsh[1,4] · Austin G. Kulasekararaj[1,4]

3085 patients
869 MDS
531 AA

AA 61% PNH+
MDS 20% PNH+

Other malign 9-12%

How many patients with AA have PNH clones: 52%- 61%

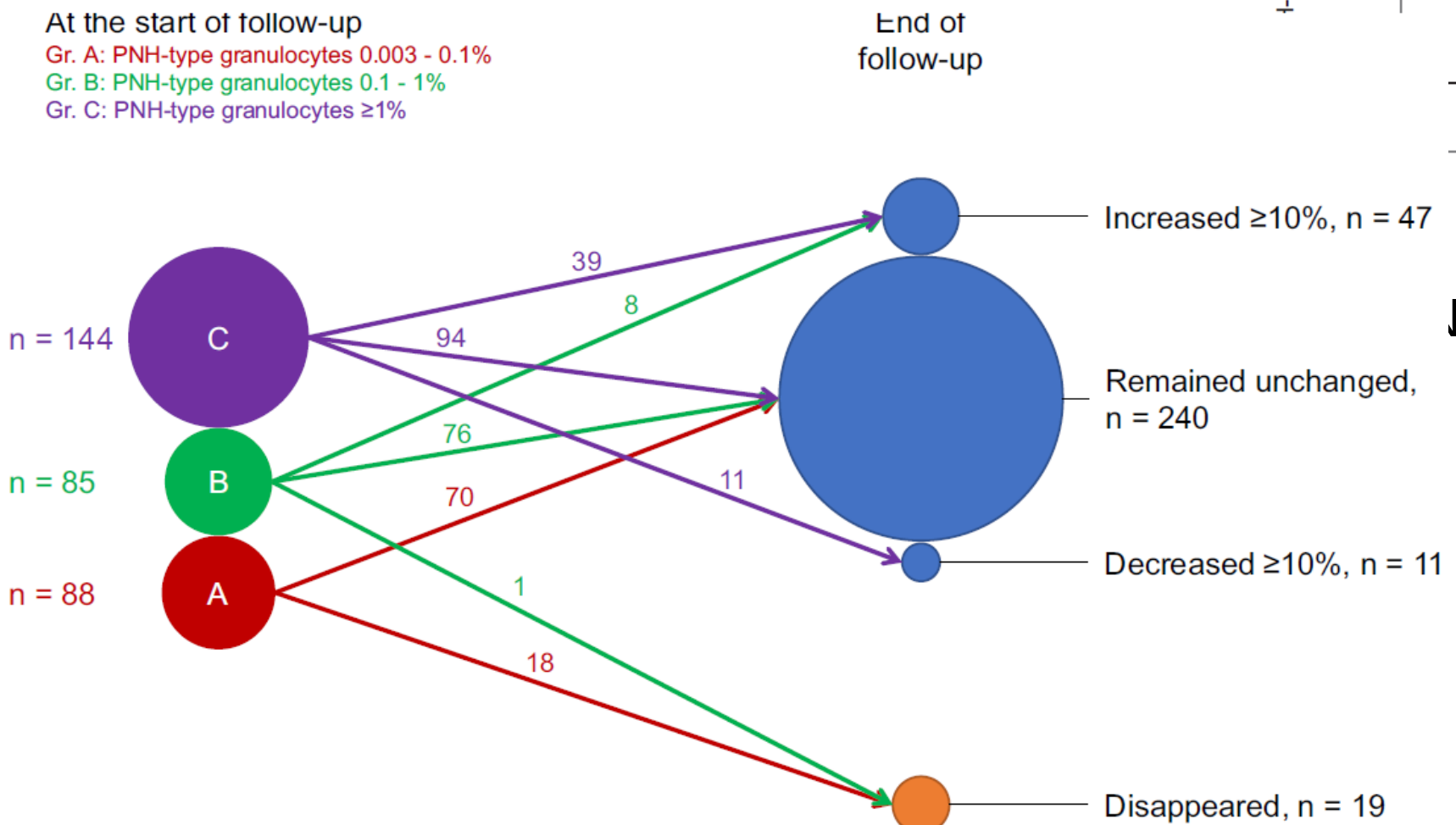
what % of PNH clones are circulating ?

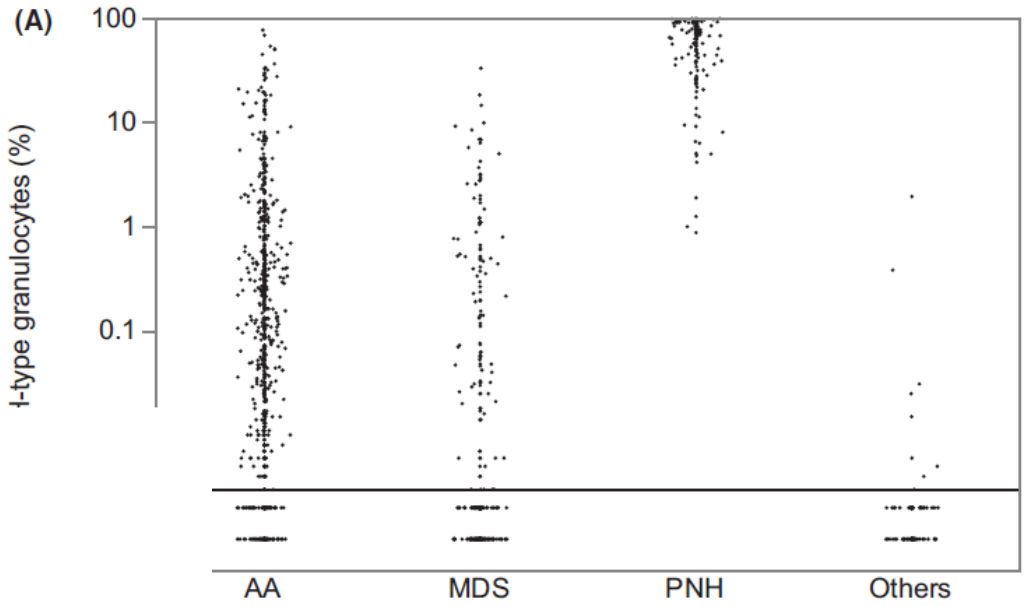
DOI: 10.1111/bjh.19048

ORIGINAL PAPER

Br J Haematol. 2023;203:468–476.

A longitudinal analysis of paroxysmal nocturnal haemoglobinuria-type cells in patients with bone marrow failure: Results of a prospective multi-centre study in Japan





1075 900 144 283

52% 13% 100% 3%

25% 0.003-0.1%
25% 0.1-1%
50% ≥1%

 # How many patients with AA have PNH clones: 52%- 61%

 # what % of PNH clones are circulating : 50% have ≥1%

 # what is AA/PNH ?

AA/PNH definition

any patient with a diagnosis of AA and a PNH clone

- independent of the size of the PNH clone
- independent of peripheral blood counts
- independent of LDH levels
- independent of transfusion requirement
- independent of thrombosis

 # How many patients with AA have PNH clones: 52%- 61%

 # what % of PNH clones are circulating : 50% have ≥1%

 # hypoplastic PNH : any AA with a PNH clone

 # do we treat hypoplastic PNH ?

AA/PNH

	hematology	*PNH clone*	*LDH*	*treat*
A	*cytopenia TD*	*yes*	*low*	*AA*
B	*cytopenia Ti*	*yes*	*low*	*AA??*

65 year old ; PMN 800; Plt 40; Hb 10 LDH 180
gran 2% Mono 3%, RBC 0.5% → options

 # W &W

 # CSA

 # EPAG

 # ATG

 # thrombosis prophylaxis YES NO

45 year old ; PMN 800; Plt 40; Hb 10
gran 20% Mono 3%, RBC 25% ***LDH 1000*** *→ options*

 # eculizumab alone

 # eculizumab + CSA +/- EPAG

 # eculizumab + ATG

 # W&W

 # thrombosis prophylaxis YES NO

AA/PNH

	hematology	*PNH clone*	*LDH*	*treat*
A	*cytopenia TD*	*yes*	*low*	*AA*
B	*cytopenia Ti*	*yes*	*low*	*AA*
C	*PR /CR*	*yes*	*low*	*AA*
D	*PR /CR*	*yes*	***HIGH***	***PNH***

In AA/PNH

How high should the LDH be to use eculizumab (AA/PNH)

X2 normal value

X3 normal value

AA/PNH

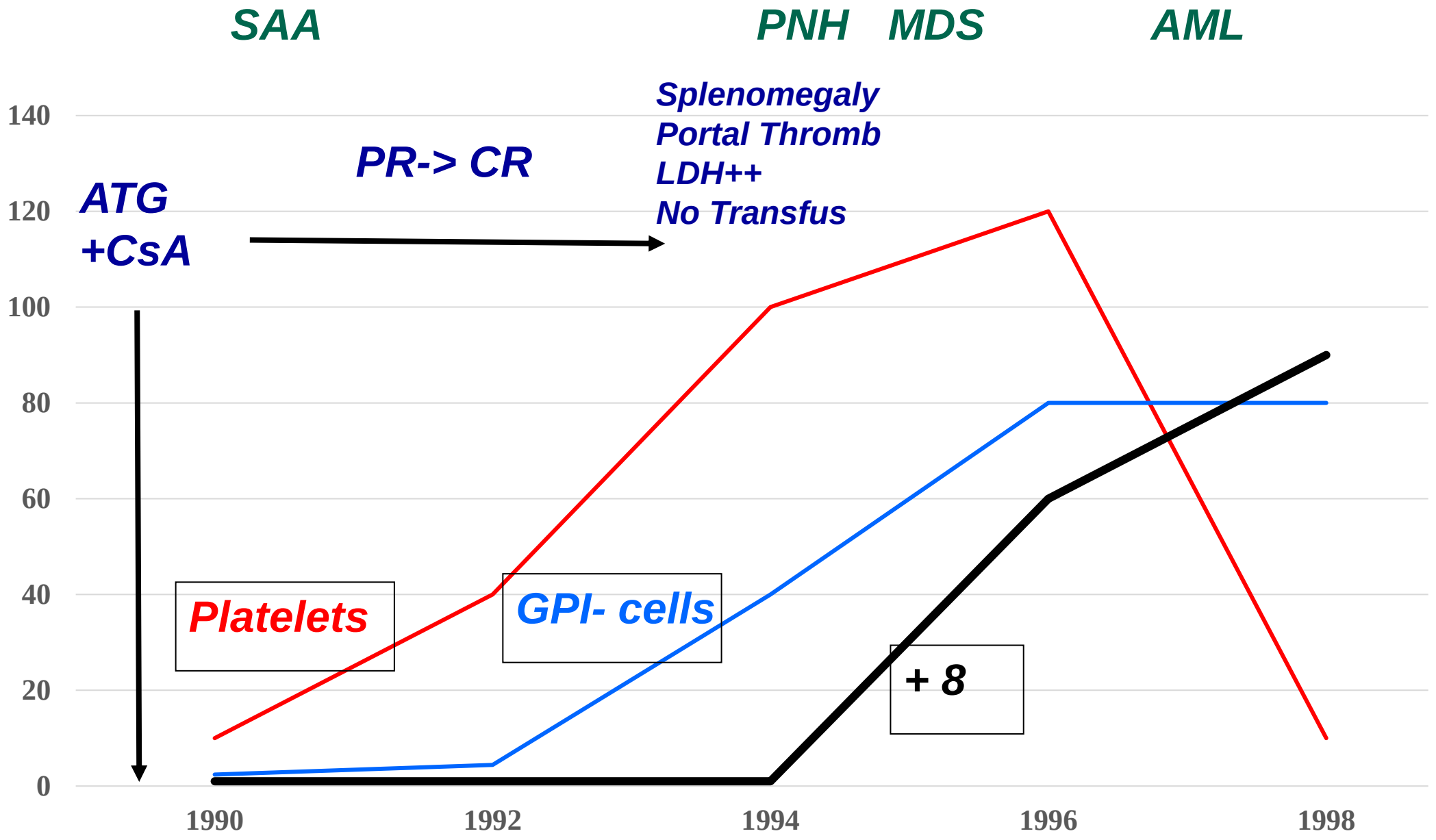
	hematology	*PNH clone*	*LDH*	*treat*
A	*cytopenia TD*	*yes*	*low*	*AA*
C	*cytopenia Ti*	*yes*	*low*	*AA*
D	*PR /CR*	*yes*	*low*	*AA*
E	*PR /CR*	*yes*	***HIGH***	***PNH***

How high?

expert consensus in Japan : 3 fold normal value

(Shinji Nakao)

52 year old lady with cytopenia



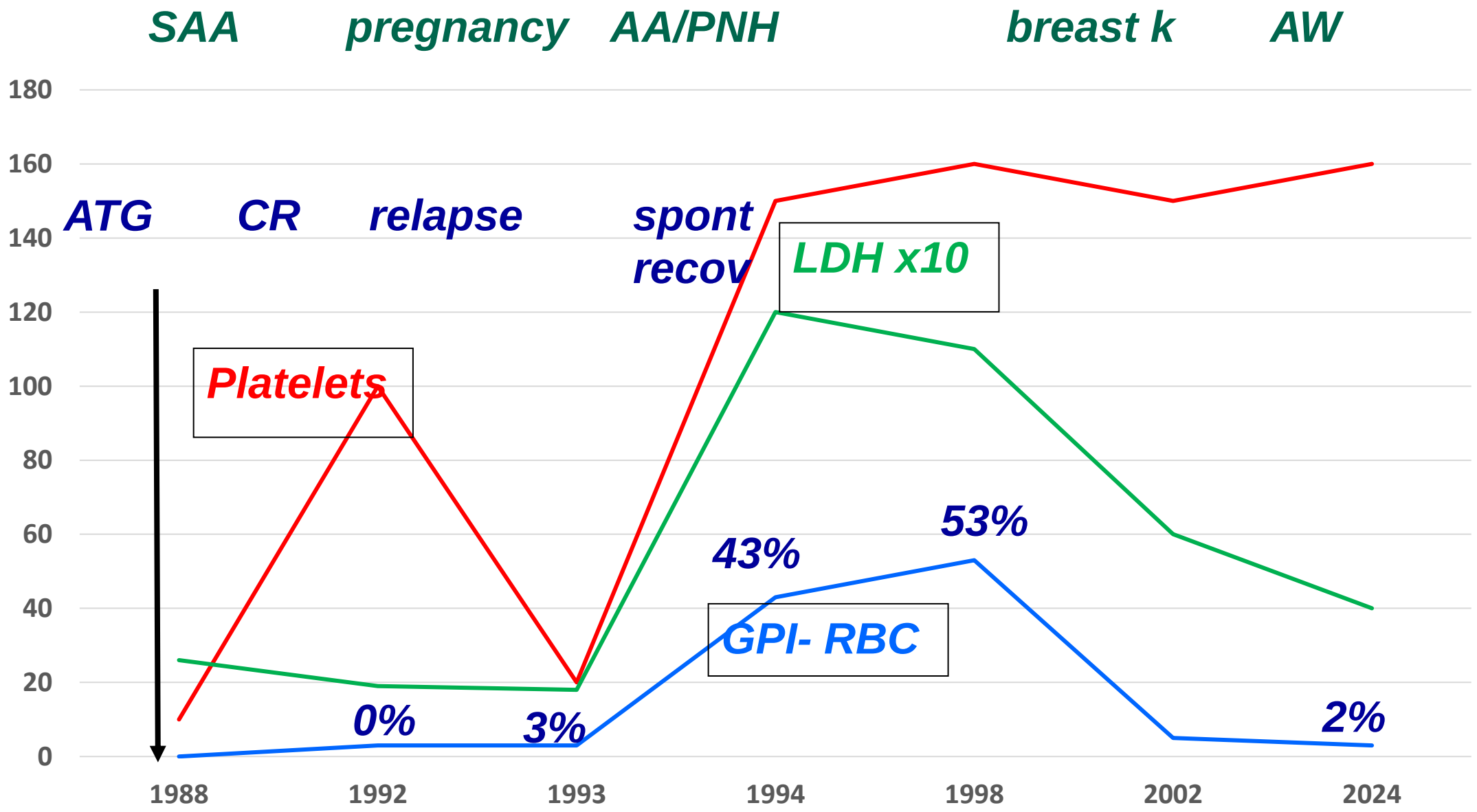
Patient 1

 # would have been eligible for anti-C treatment

 # not available in 1994

 # ??would not have prevented MDS-AML (+8 present in G-SCF mobilized PB cells collected at diagnosis)

25 year old pt with cytopenia



Treatment of AA/PNH

Depends on

 # degree of cytopenia (AA)

 # level of PNH clone and LDH (PNH)

- SAA WP
- Regis Peffault de la Toutr and Antonio Risitano
- Carlo Dufour, Ajstin Kulasekararaji, Anna Locasciulli, Franco Locatelli, Christina Peters, Rosi Oneto, Jacob Passweg,
- Maria Teresa Van Lint, Gérard Socié, Andre Tichelli , Judith Marsh, Hubert Schrezenmeier, Carlos Vallejo

- N Young, P Scheinberg, J Deeg, S Nakao , S Kojima ,
- Xiaofan Zhu, Xiaojuan Chen, Surapol Issaragrisil, Suporn Chuncharunee , Dae Chul Jeong , Yizhou Zheng

Excellence in science
EBMT
European Group for Blood and Marrow Transplantation

50% of Aplastic Anemia patients have a PNH clone; these GPI- cells may be spared by the immune attack

GPI- cells should be monitored with time : increased ***GPI- cells*** *and/or* ***LDH*** *and/or* ***spleen*** *and/or* ***thrombosis*** *should alert on the evolution towards PNH*

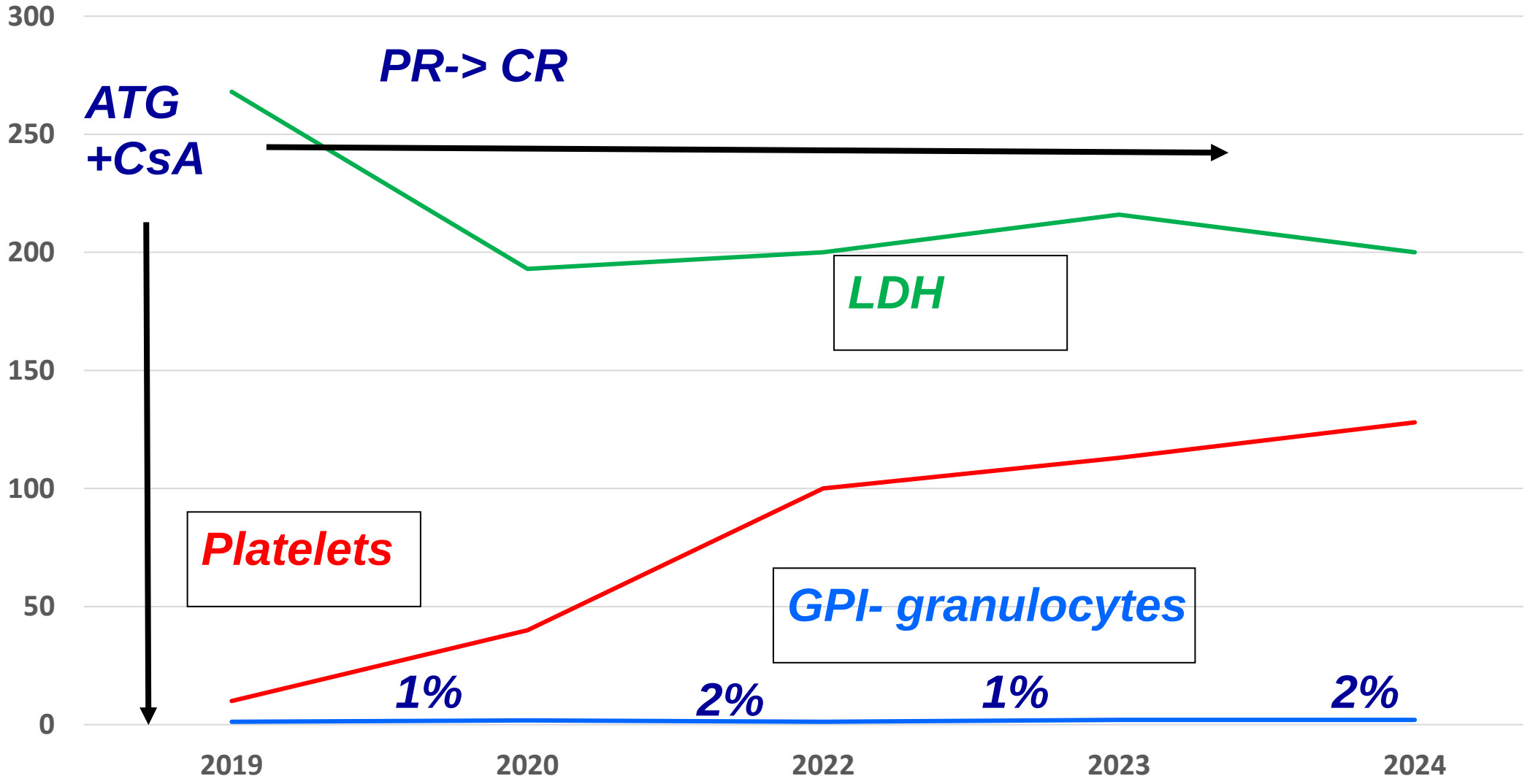
Patient 1

 # would have been eligible for anti-C treatment

 # not available in 1994

 # would not have prevented MDS-AML (+8 present in G-SCF mobilized PB cells collected at diagnosis)

52 year old lady with cytopenia



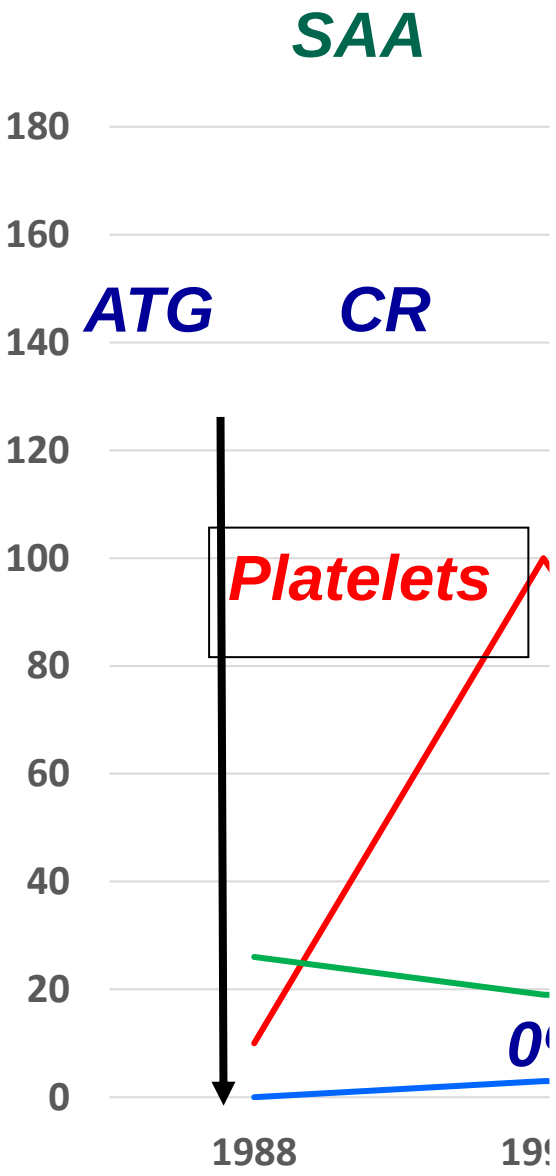
Patient 2

 # AA in CR after ATG CSA

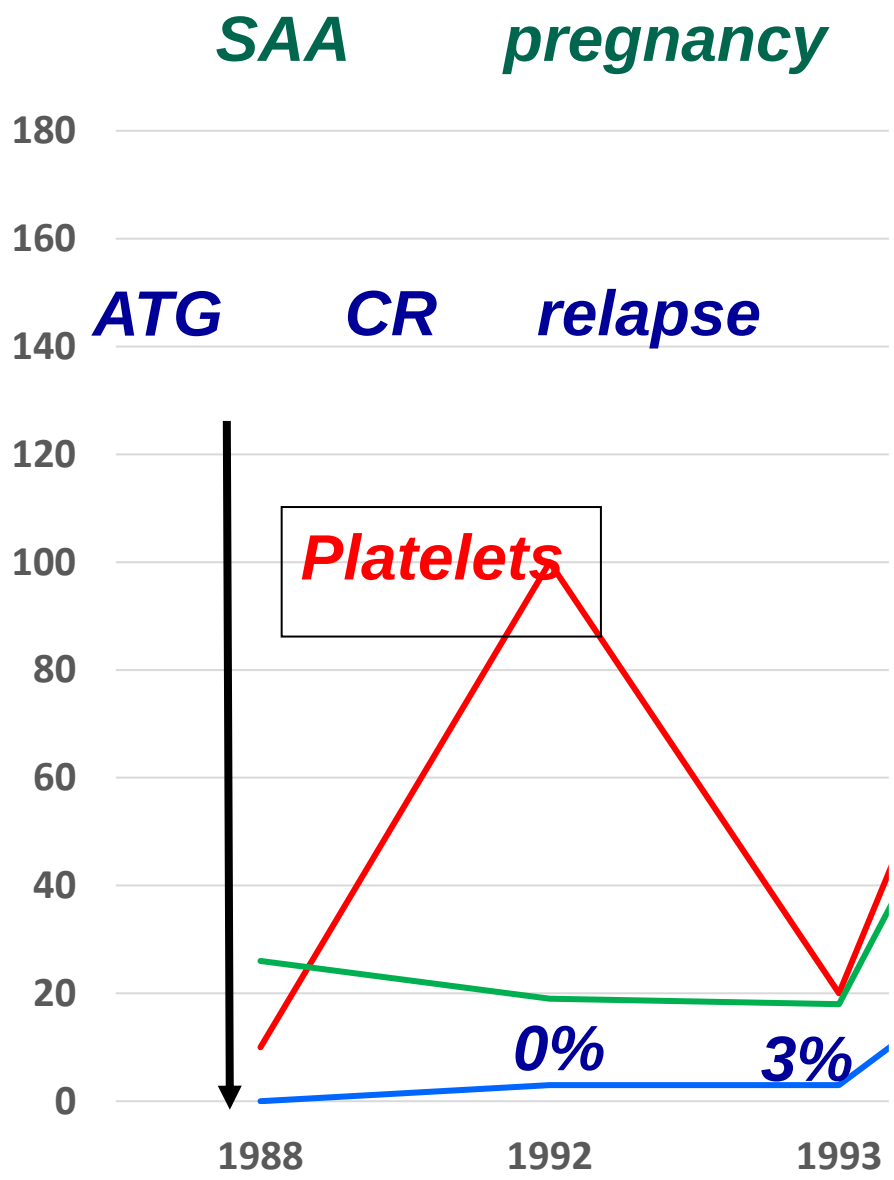
 # PNH clone stable over years / normal LDH

granulocytes	2%
monocytes	1.4%
erythrocytes	0.2%

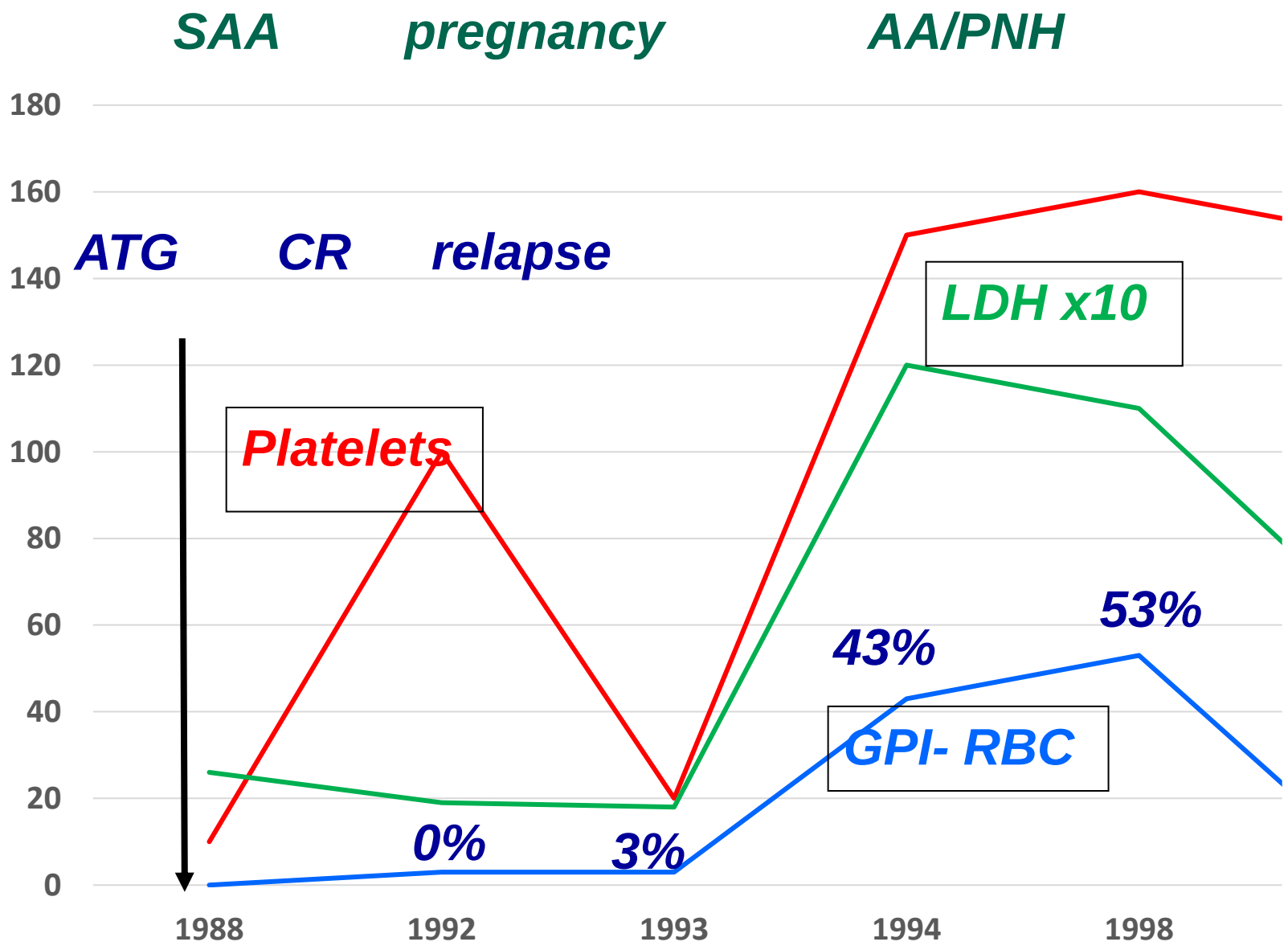
25 year old pt with cy



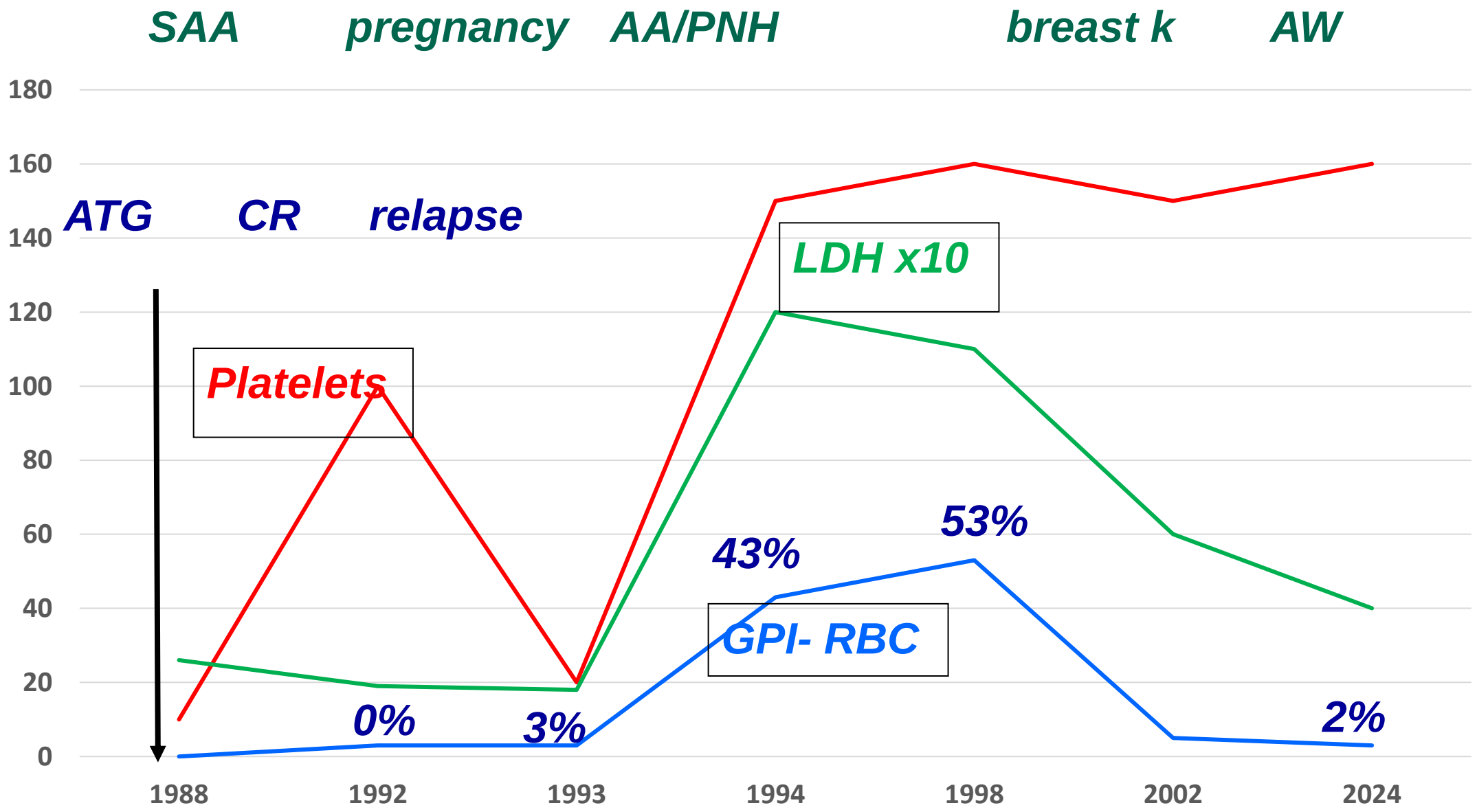
25 year old pt with cytopenia



25 year old pt with cytopenia



25 year old pt with cytopenia



Patient 3

 # AA in CR after ATG

 # AA/ PNH developed after 6 years- untreated

 # the PNH clone underwent spontaneous reduction over several years

Leukemia (2021) 35:3223–3231
https://doi.org/10.1038/s41375-021-01190-9

ARTICLE

Myelodysplastic syndrome

Clinical and prognostic significance of small paroxysmal nocturnal hemoglobinuria clones in myelodysplastic syndrome and aplastic anemia

Bruno Fattizzo[1,2,3] · Robin Ireland[1] · Alan Dunlo
Shreyans Gandhi[1] · Petra Muus[1] · Charles Manoga
Ghulam J. Mufti[1,4] · Judith C. W. Marsh[1,4] · Austin

AA 61% PNH+
MDS 20% PNH+

Other malign 9-12%

3085 patients
869 MDS
531 AA