Il trattamento delle Aplasie acquisite nell'era dei TPO-mimetici

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Disclosures

Advisory boards

Biocryst
Novartis
Pfizer
SOBI
Rockets

Consulations
Gilead

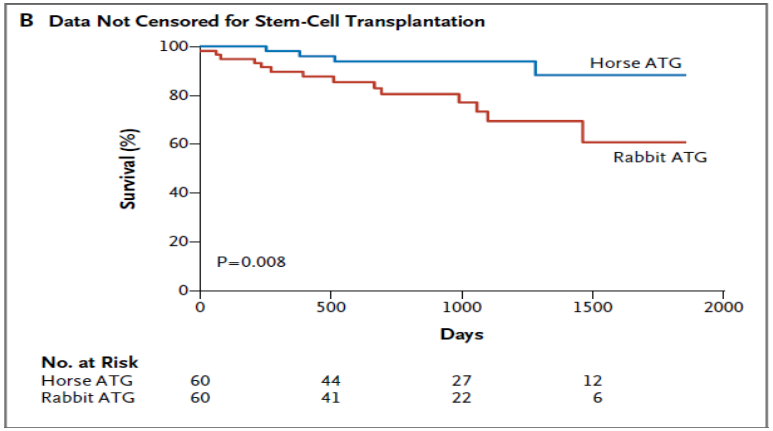
Contenuto

- Storia dell’immunosoppressione in SAA
- Newcomers in IST
- Newcomers in HSCT
- Cambiamenti nell’algoritmo terapeutico

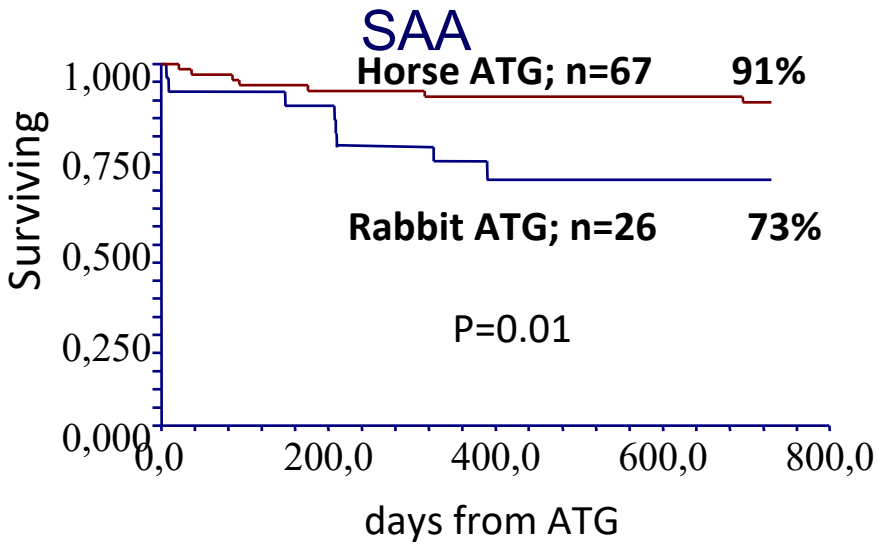
STORIA della IMMUNOSOPPRESSIONE in SAA

- CsA da sola < 10% risposta long-term
- ATG da solo 30-40% risposta long-term
- ATG+ CsA fino al 77% di risposta
  Non responders hanno maggiori probabilità di disturbo clonale EBMT/GITMO Bacigalupo, Blood 2000.
- ATG+CsA fanno significativamente meglio di ATG e CsA da soli SAAWP EBMT, Locasciulli, Haematologica 2007

Horse ATG +CsA



Scheinberg P, NEJM, 2011



Marsh J for SAAWP EBMT, Blood 2012

OS ≈ 90 %
OR 60-70%
CR 30-40%

Horse ATG better than Rabbit ATG

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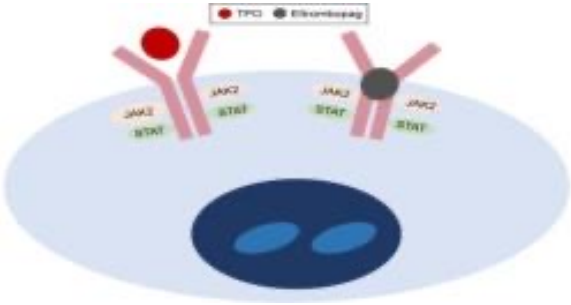
ELTROMBOPAG



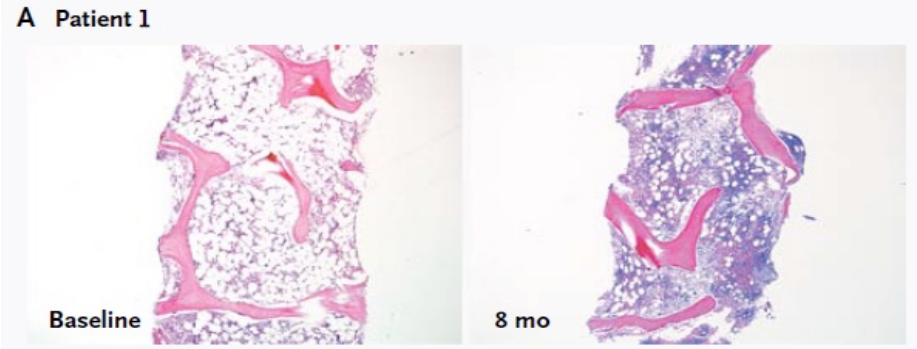
- Activates SC proliferation via JAK2/STAT & MAPK
- Additive effect with TPO
- Long half life 21-32 hrs
- Blocks pro inflammatory cytokines (IFN- **γ**, TNF- α)
  Schiffer A. et al, Semin Hematol 2016, Alvarado LJ, Blood 2017
- Reduces intracellular iron content and related ROS production
  Zhao et al, Blood 2018
- Increases T-Regs

EPAG IMPROVES HEMATOPOIESIS IN REFRACTORY SAA

Phase II study
25 pts
Eltrombopag 50-150 mg, orally, for 12 weeks

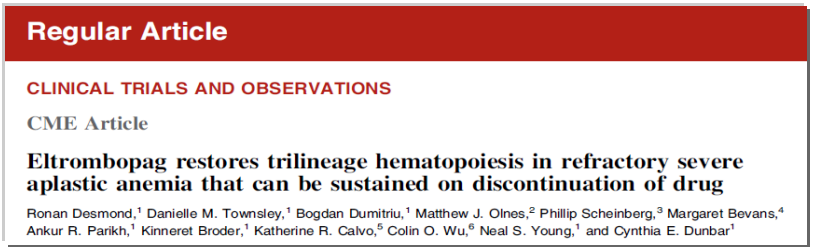
44% hematological response (at least 1 lineage)
- Plt response 36%
- Hb response 24%
- ANC response 36%
- Some bi-lineage

Increased marrow cellularity (resp.)
Minimal toxicity (transaminitis), no fibrosis



Olnes MJ et al, N Engl J Med. 2012 Jul 5;367(1):11-9. doi:

EPAG RESTORES TRILINEAGE HEMATOPOIESIS IN REFRACTORY SAA


Regular Article

CLINICAL TRIALS AND OBSERVATIONS

CME Article

Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug

Ronan Desmond,[1] Danielle M. Townsley,[1] Bogdan Dumitriu,[1] Matthew J. Olnes,[2] Phillip Scheinberg,[3] Margaret Bevans,[4] Ankur R. Parikh,[1] Kinneret Broder,[1] Katherine R. Calvo,[5] Colin O. Wu,[6] Neal S. Young,[1] and Cynthia E. Dunbar[1]

Additional 18 patients (total 43)

OR 17/43 = 40%

Long-term follow up

Eltrombopag discontinued in 5 robust VGPR, with sustained response.

Clonal evolution in 8/43 =18%, mostly in non-responders (6/8);

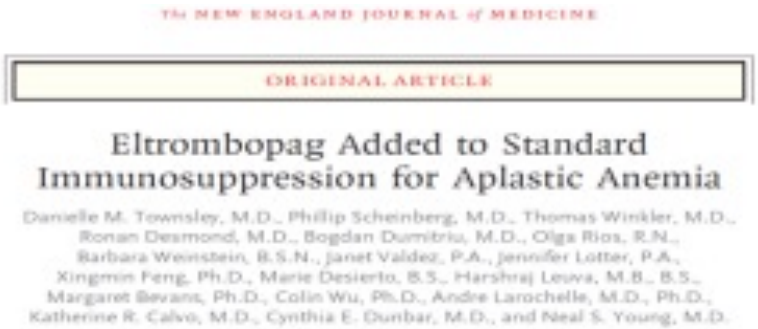
NR 7-/del(7) [n=5], +8 [n=1]

R del(13) [n=2]

no RAEB/AML

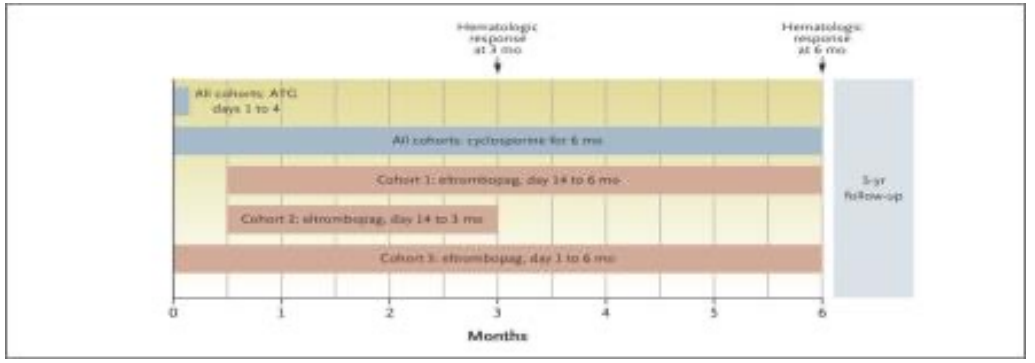
Desmond R et al, Blood 20, March, 2014,123, 12

IST + EPAG



OR at 6 months 87%
CR at 6 months 37%
Relapse 32% at 6 months
Clonal evolution 8 %. All «high grade» MDS.

Neutrophils >500 d+ 48.
Ts independence 32 dd platelets; 39 dd Red Cells.
Childfren not different from adults



Cohort 3 (32 patients) ETPAG from d +1

OR at 6 months 94%
CR a 6 months 58% .
Neutrophils > 500 d + 35

NOT a RCT

Townsley D et al for NIH, N Engl J Med 2017; 376:1540-155

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 6, 2022 VOL. 386 NO. 1

Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia

R. Peffault de Latour, A. Kulasekararaj, S. Iacobelli, S.R. Terwel, R. Cook, M. Griffin, C.J.M. Halkes, C. Recher, F. Barraco, E. Forcade, J.-C. Vallejo, B. Drexler, J.-B. Mear, A.E. Smith, E. Angelucci, R.A.P. Raymakers, M.R. de Groot, E. Daguindau, E. Nur, W. Barcellini, N.H. Russell, L. Terriou, A.-P. Iori, U. La Rocca, A. Sureda, I. Sánchez-Ortega, B. Xicoy, I. Jarque, J. Cavenagh, F. Sicre de Fontbrune, S. Marotta, T. Munir, J.M.L. Tjon, S. Tavitian, A. Praire, L. Clement, F. Rabian, L. Marano, A. Hill, E. Palmisani, P. Muus, F. Cacace, C. Frieri, M.-T. van Lint, J.R. Passweg, J.C.W. Marsh, G. Socié, G.J. Mufti, C. Dufour, and A.M. Risitano, for the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation*

RCT

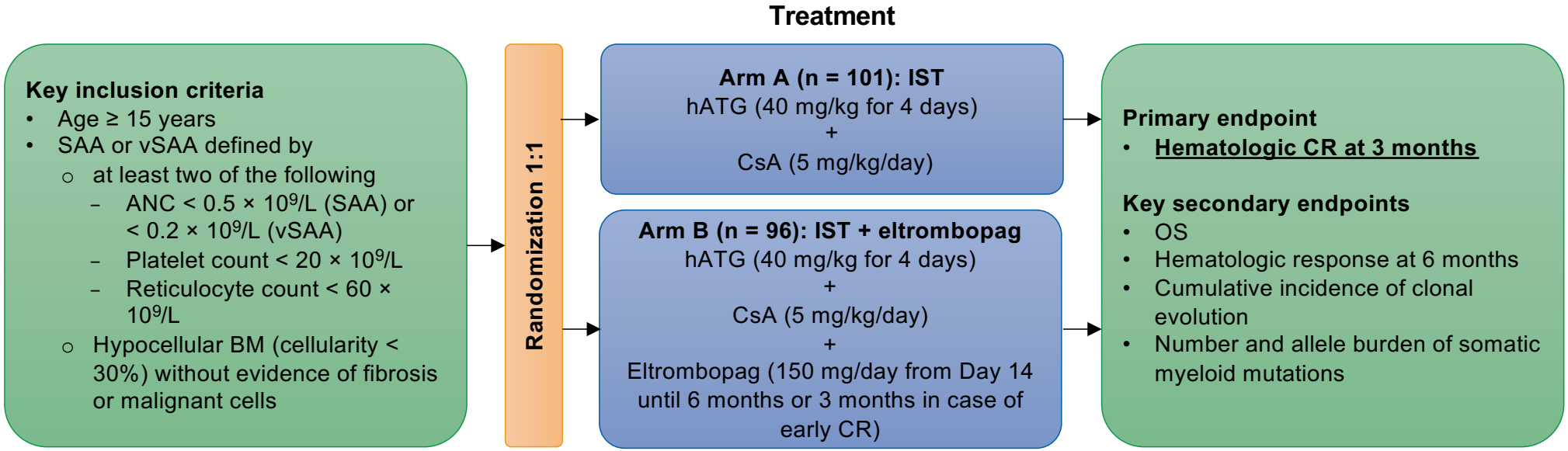
Inclusion july 2015- april 2019

205 treatmet naïve patients

6 nations, 26 centres

RACE TRIAL DESIGN

Investigator-driven, open-label, phase 3, randomized trial comparing the combination of hATG, CsA, and eltrombopag with IST alone in patients with SAA



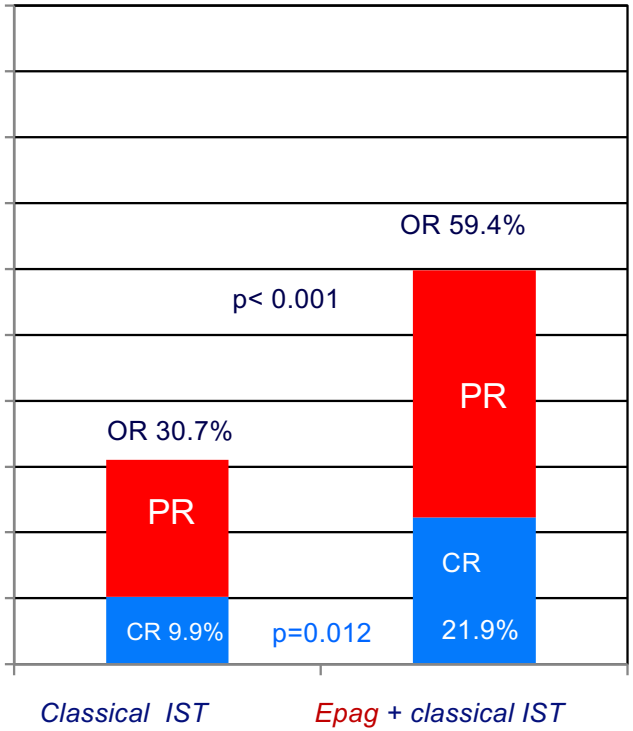
Central laboratory King's college, London

Stratification based on disease severity age and center

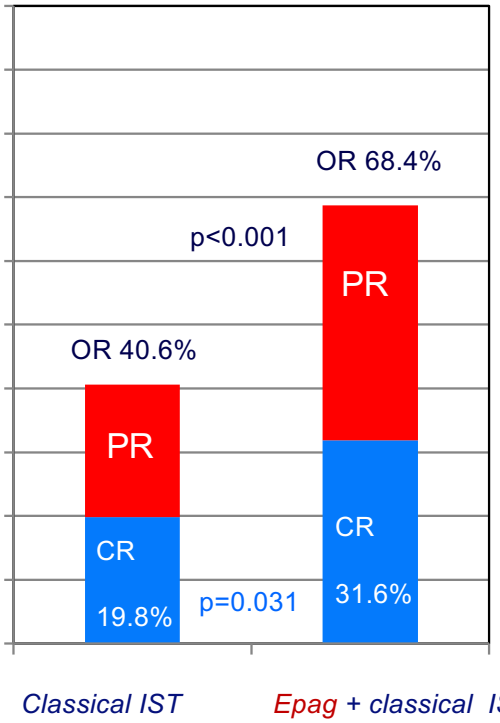
ANC, absolute neuthrophil count; vSAA, very severe aplastic anemia.

Hematologic Response

3 months

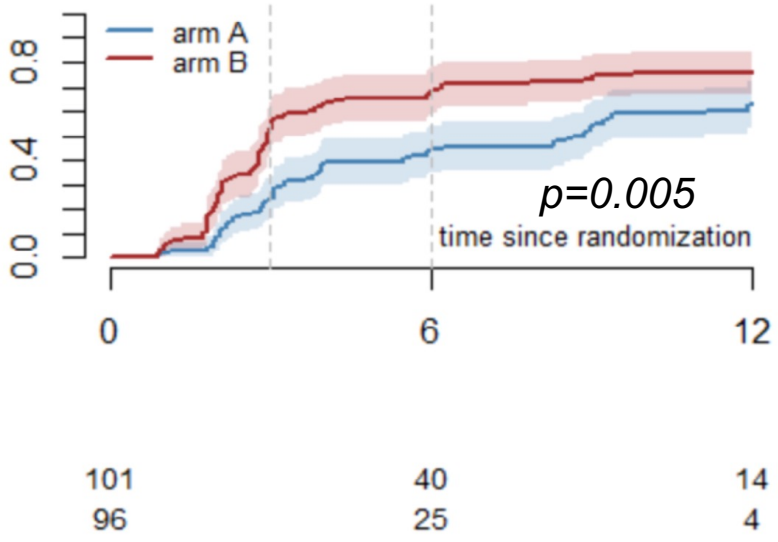


6 months

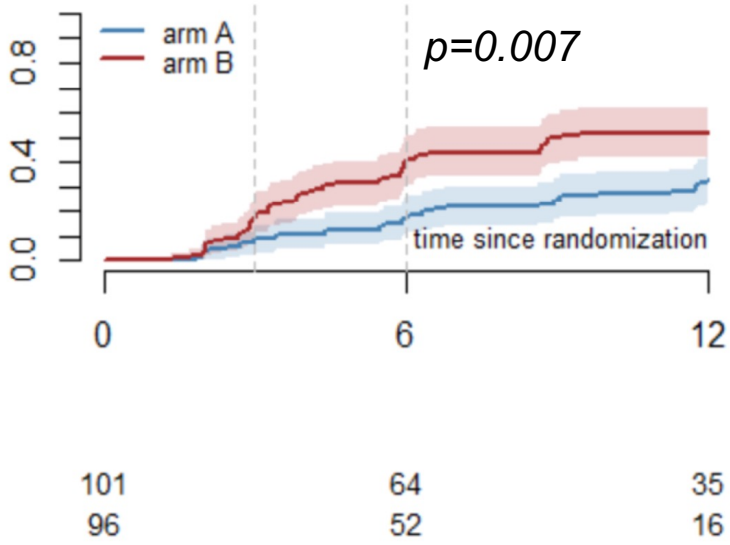


Hematological response

Time to first response*:*
3 months in EPAG arm vs 8.8 months in NON EPAG arm



Time to complete response*:*
9.1 months in EPAG arm vs not reached in NON EPAG arm

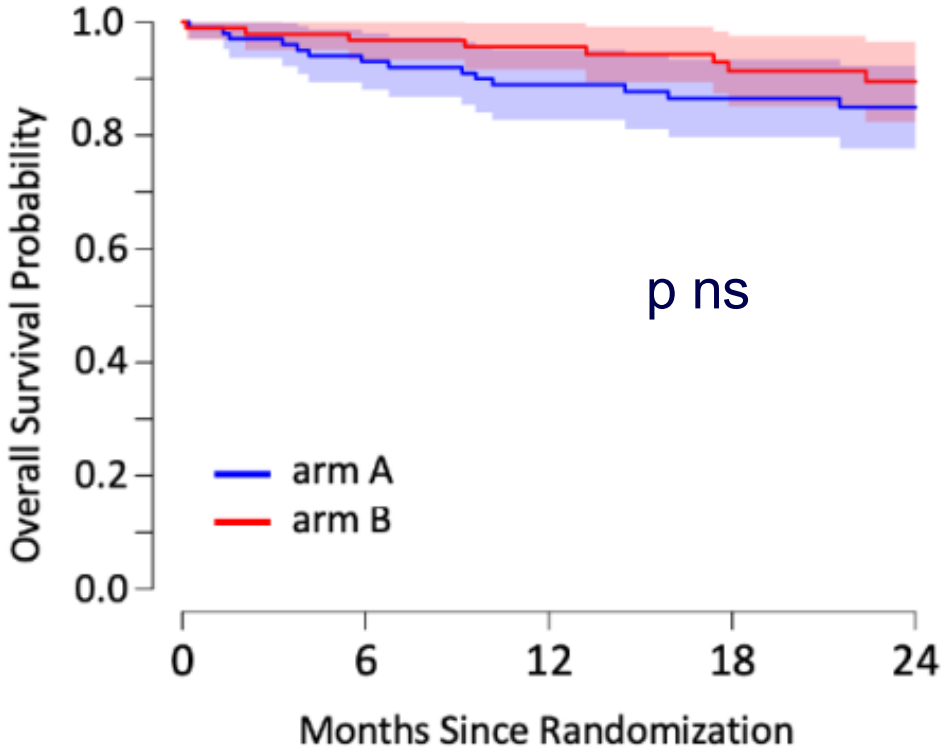


Faster and better quality response in the EPAG Arm

Overall Survival

Median Follow-up

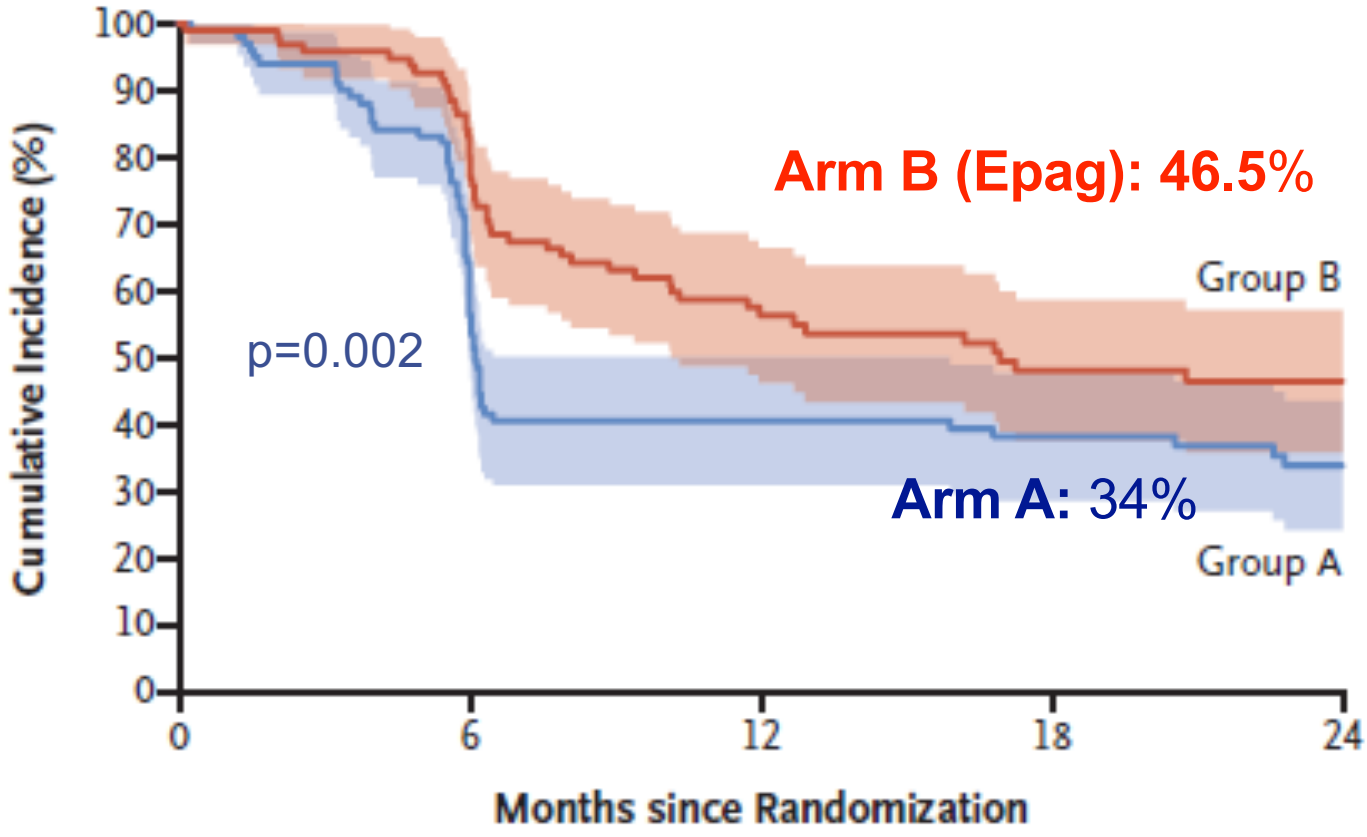
24 months



Number of Patients at Risk

arm A	101	93	80	64	26
arm B	96	92	74	58	25

2yrs -EFS



No. at Risk					
Group B	96	76	45	31	15
Group A	101	60	38	30	10

Karyotypic Abnormalities

- 1 in arm A

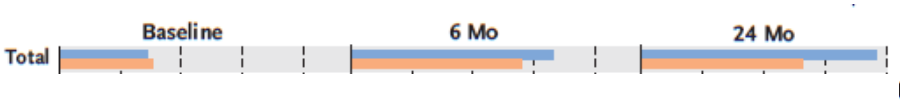
  -1 mono 7, with BCOR, DNMT3 and TET2 mutations,

- 2 in arm B

  -1 del 13q, with PIGA mutation
  -1 del 13q, with no mutations

No morphologic evidence of MDS in all

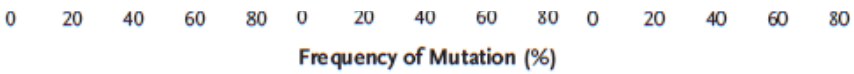
Somatic mutations



No increase of somatic mutations in EPAG over NO EPAG arm

Both total and specific gene mutations

Somatic mutations increased but did not affect the hematologic response and 2-year outcome.



Eltrombopag did not increase high-risk evolution.

Groarke EM et al.; Leukemia. 2022 Jul 27. doi: 10.1038/s41375-022-01636-8

Safety

	Arm A	Arm B	Total
Serious Adverse Events*	135	145	280
Fatal cases (most infections)	14	8	22
Drop off patients requiring second line HSCT	13	11	24
Pregnancy	3	1	4

*Events are classified per SOC (system organ class) according to the CTCAE (Common Terminology Criteria for Adverse Events (US National Cancer Institute of the National Institutes of Health).

Long-term outcomes

- Need for HSCT during study follow-up
  - Arm A: n=12
  - Arm B: n=11

- Relapse (CI at 18 months)
  - Arm A: 11.3% (95% CI, 2.2% to 20.4%)
  - Arm B: 19.1% (95% CI, 9.2% to 28.9%) Epag dependence?

- Ciclosporine independence (at 2 years)
  - Arm A: 18.8%
  - Arm B: 27.6%

RACE conclusion - Perspective

- EPAG + standard IST (hATG and CsA), **significantly increases the rate of CR at 3 months** with **no safety concern** (18 months median follow-up).

- At 24 months, clonal evolution is very rare (2-3%) with no difference between arms.

  But a far longer follow up (10-15 years after diagnosis) is needed for appropriate assessment

- So far no increased frequency of somatic mutation in eltrombopag arm

  No impact of somatic mutations on any outcome, but follow- up still short

- **Long Term Follow-Up study (RACE-2)** is ongoing to answer these questions in the future

IST + ETPAG in CHILDREN

- 40 evaluable pts. IBMF excluded by germ-line testing
- Median age 13 years.
- hATG + CsA + EPAG

	IST+EPAG	Only IST	p
OS	94%	84%	0.092
EFS	57%	69%	0.049
ORR	70%	72%	0.78
CR	30%	23%	0.42
Relapse	43%	27	0.66
CE	13%	9%	0.215

Groarke EM et al Br J Haematol. 2021 Feb;192(3):605-614

RCT

49 pt hATG + CsA age 8.7 yrs

49 pts hATG + CsA+ EPAG (2mg/kg/day, from day 1) age 10.5 yrs

	IST	IST+EPAG	p
ORR at 4 mos	53%	65%	0.218
PR	40.8%	34.7%	ns
CR	12.2%	30.6%	0.027
ORR SAA	57%	89%	0.028
ORR VSAA	50%	52%	0.902
3y OS	91%	89%	0.673
3y EFS	41%	53%	0.326
Time to CR	371 d	384 d	ns
Time to PR	123 d	78 d	0.096

- No unexpected toxicity related to Epag (transaminitis)
- Second course of IST+Epag resulted in a high ORI in initial ELTR (-)
- Second course of IST+Epag limited efficacy in who received ELTR upfront

Goronkowa O et al. Blood Advances apr 2022

Addition of EPAG in children not as beneficial as in adults

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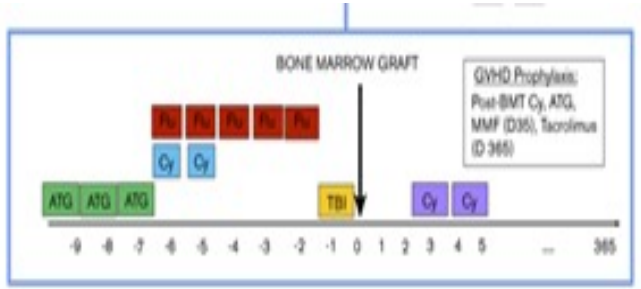
Haplo PTCY

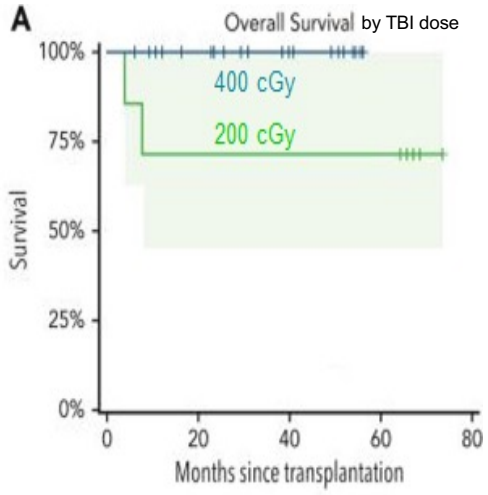
27 treatment naive pts
Median age 25 y, but 11 > 40y, 9 >50y
Diagn- transpl 78 d

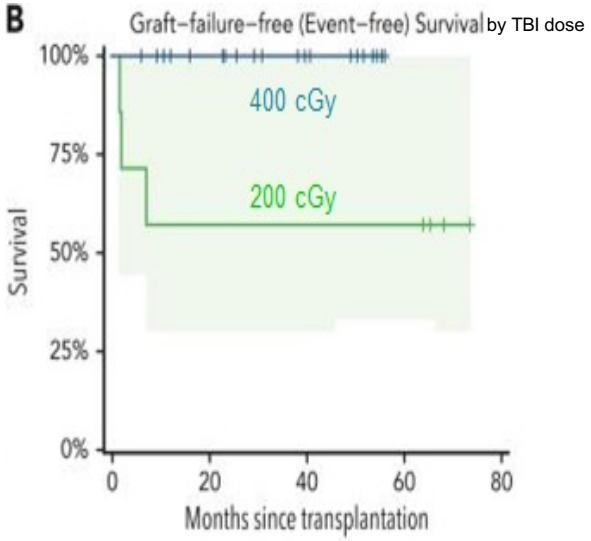


Recovery: ANC day 17
Red cells day 25.5
Platelets day 25.5

OS 92% at 1, 2, and 3 years

Two deaths (6%) all in 200 cGy cohort due to viral infection in graft failure

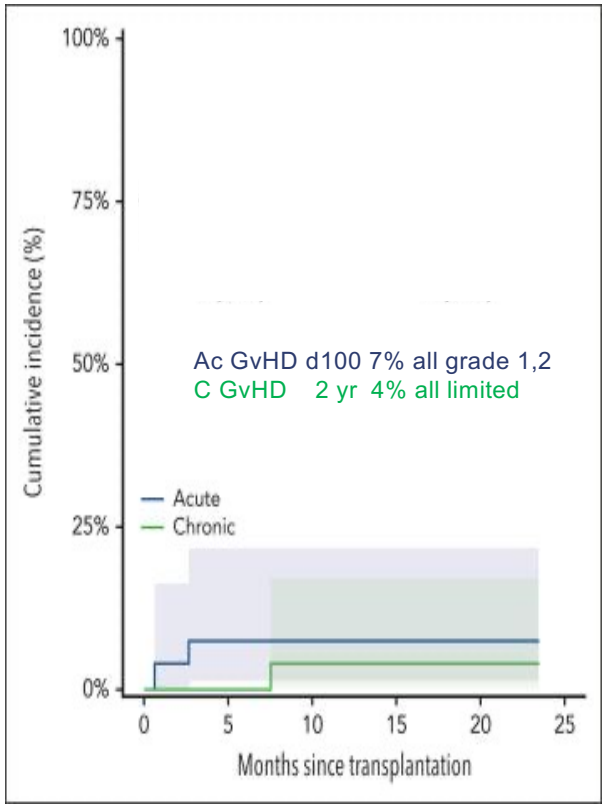




Some concern on 400cGY for late effects in young pts

De Zern AE et al. Blood. 2023 Jun 22;141(25):3031-3038.

Haplo PTCY



Infection episodes	39
Grade 2	37
Grade 5	2

Type	n. of patients
Bacterial	11
Viral	20
Fungal	4
CMV infection	11
CMV infection requiring therapy	6
EBV infection	2
EBV infection requiring therapy	1
PTLD	1

De Zern AE et al. Blood. 2023 Jun 22;141(25):3031-3038.

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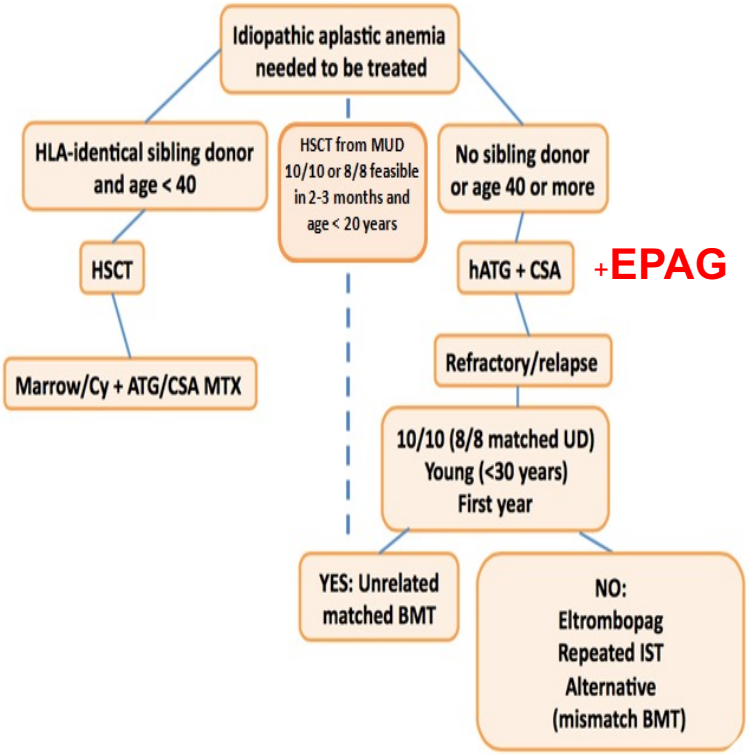
Changes in the algo in adults



+**EPAG** or Haplo in specifc situations??

FDA ok
EMA no
National agencies ongoing

R. Peffault de Latour, A. Risitano, C Dufour, EBMT textbook 2019

NCT02833805 ongoing study comparing Haplo with MUD HSCT for newly diagnosed SAA
Recruitment completed