Triple Therapy for SAA

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Disclosures

Advisory boards

Biocryst
Novartis
Pfizer
SOBI
Rockets

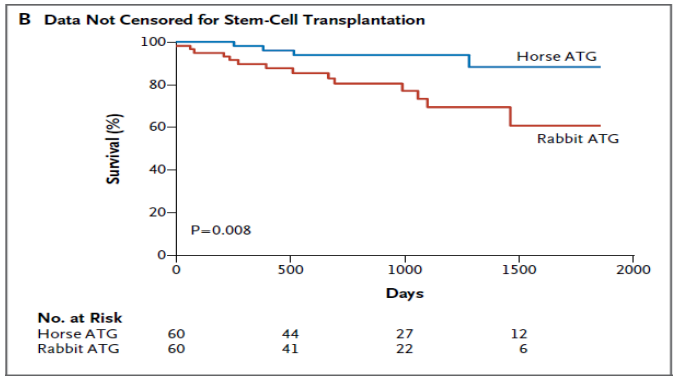
Consulations
Gilead

STORIA della IMMUNOSOPPRESSIONE in SAA

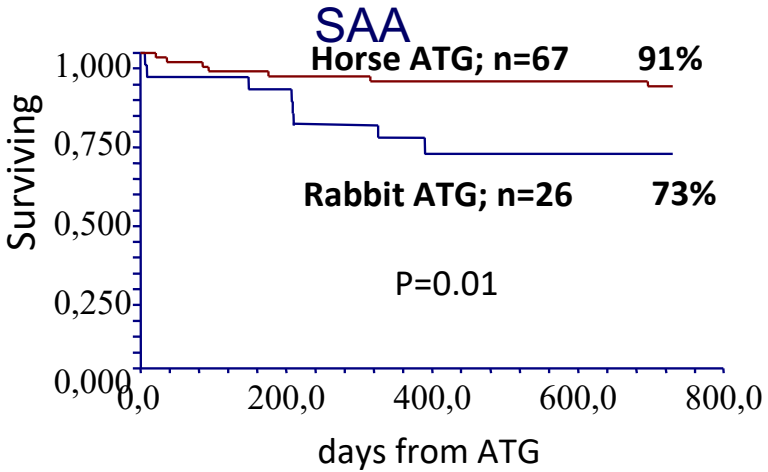
- CsA da sola < 10% risposta long-term
- ATG da solo 30-40% risposta long-term
- ATG+ CsA fino al 77% di risposta

  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

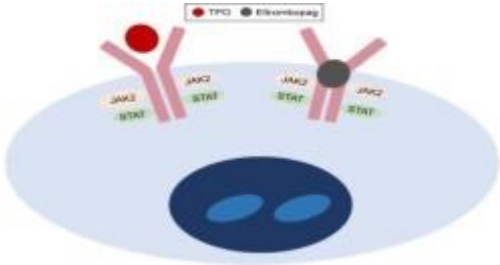
OS ≈ 90 %

OR 60-70%

CR 30-40%

Horse ATG better than Rabbit ATG

ELTROMBOPAG



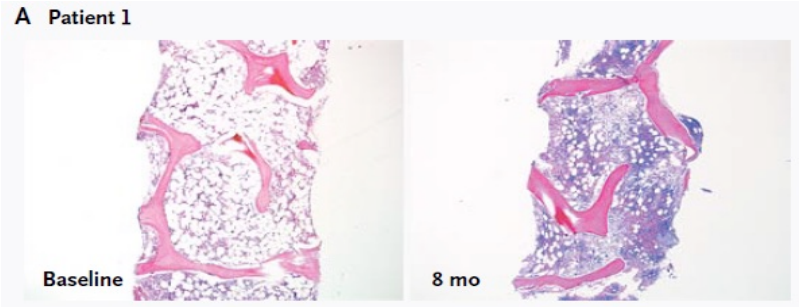
- Activates SC proliferation via JAK2/STAT & MAPK
- Additive effect with TPO
- Long half life 21-32 hrs
- Blocks pro inflammatory cytokines (IFN- **γ**, TNF- α)
  Schiffer A. et al, Semin Hematol 2016, Alvarado LJ, Blood 2017
- Reduces intracellular iron content and related ROS production
  Zhao et al,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

EPAG IMPROVES HEMATOPOIESIS IN REFRACTORY SAA

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

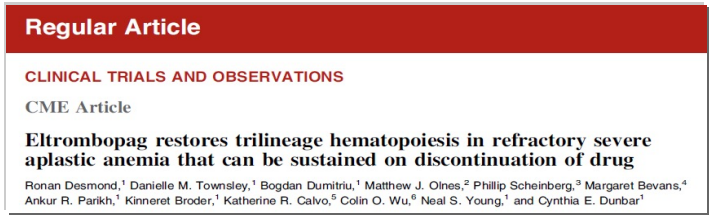
44% hematological response (at least 1 lineage)
- Plt response 36%
- Hb response 24%
- ANC response 36%
- Some bi-lineage

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia

Danielle M. Townsley, M.D., Philip Scheinberg, M.D., Thomas Winkler, M.D., Ronan Desmond, M.D., Bogdan Dumitriu, M.D., Olga Rios, R.N., Barbara Weinstein, B.S.N., Janet Valdez, P.A., Jennifer Lotter, P.A., Xingmin Feng, Ph.D., Marie Desierto, B.S., Harshraj Leuva, M.B., B.S., Margaret Bevans, Ph.D., Colin Wu, Ph.D., Andre Larochelle, M.D., Ph.D., Katherine R. Calvo, M.D., Cynthia E. Dunbar, M.D., and Neal S. Young, M.D.

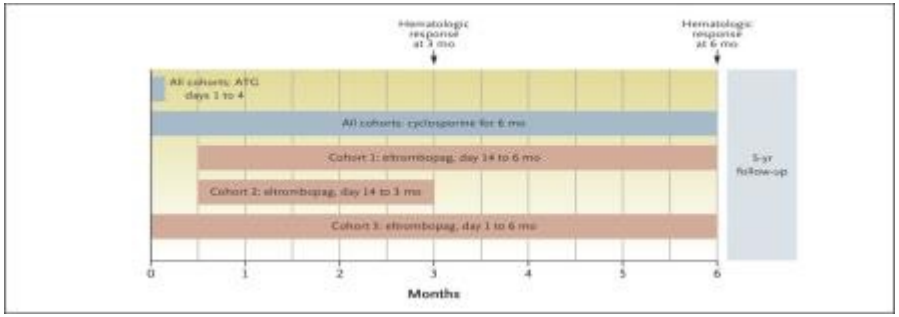
OR at 6 months 87%
CR at 6 months 37%
Relapse 32% at 6 months
Clonal evolution 8 %. All «high grade» MDS.

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; 376:1540-1550

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

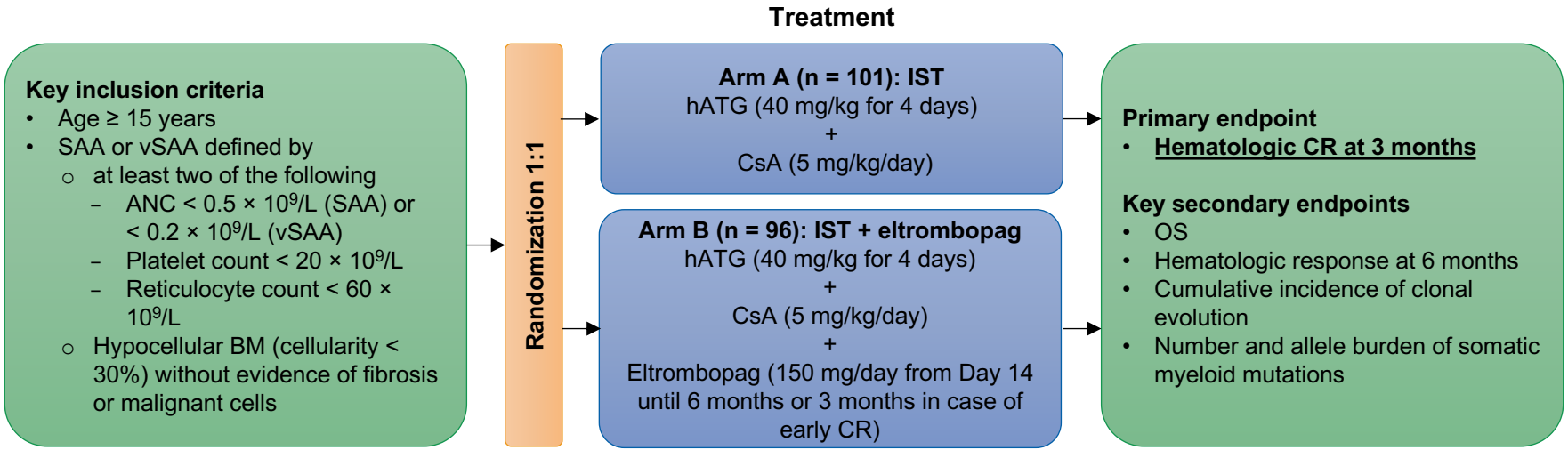
Inclusion july 2015- april 2019

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

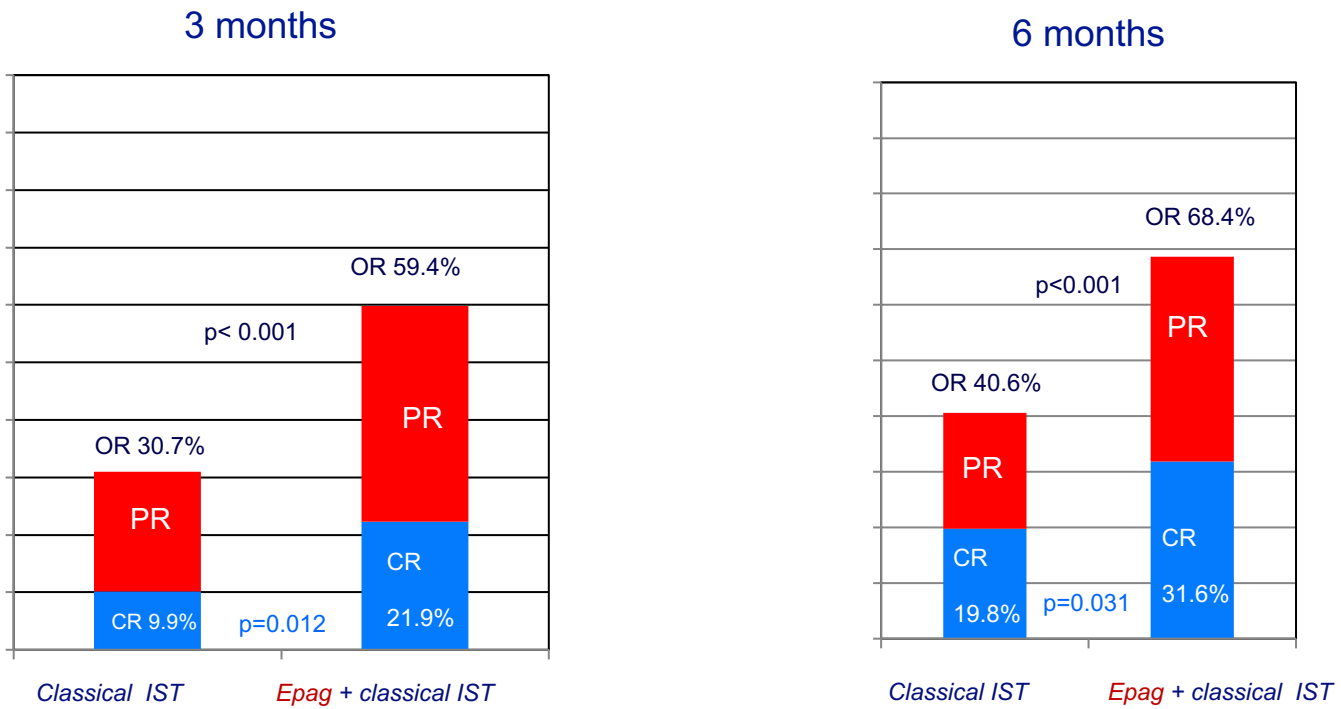


Central laboratory King's college, London

Stratification based on disease severity age and center

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

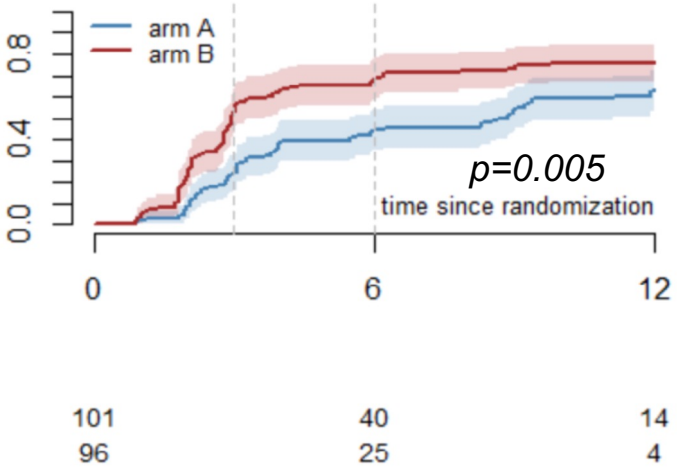
Hematologic Response



Hematological response

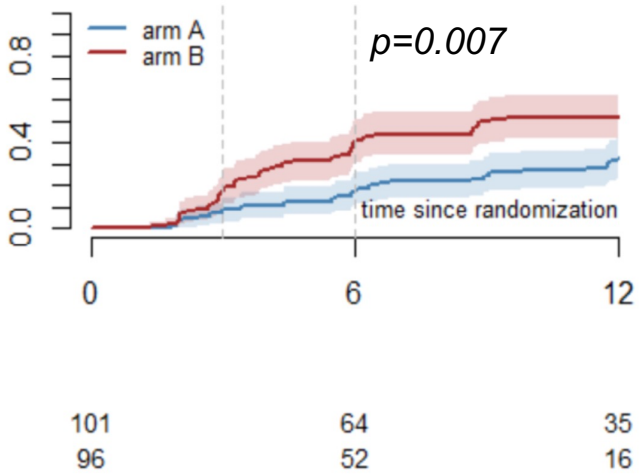
Time to first response*:*

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

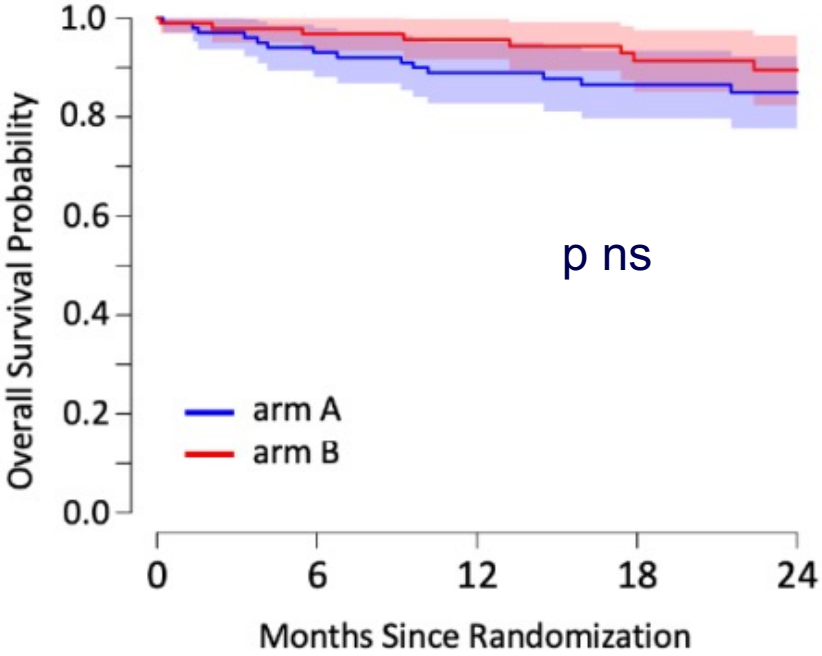


Faster and better quality response in the EPAG Arm

Overall Survival

Median Follow-up

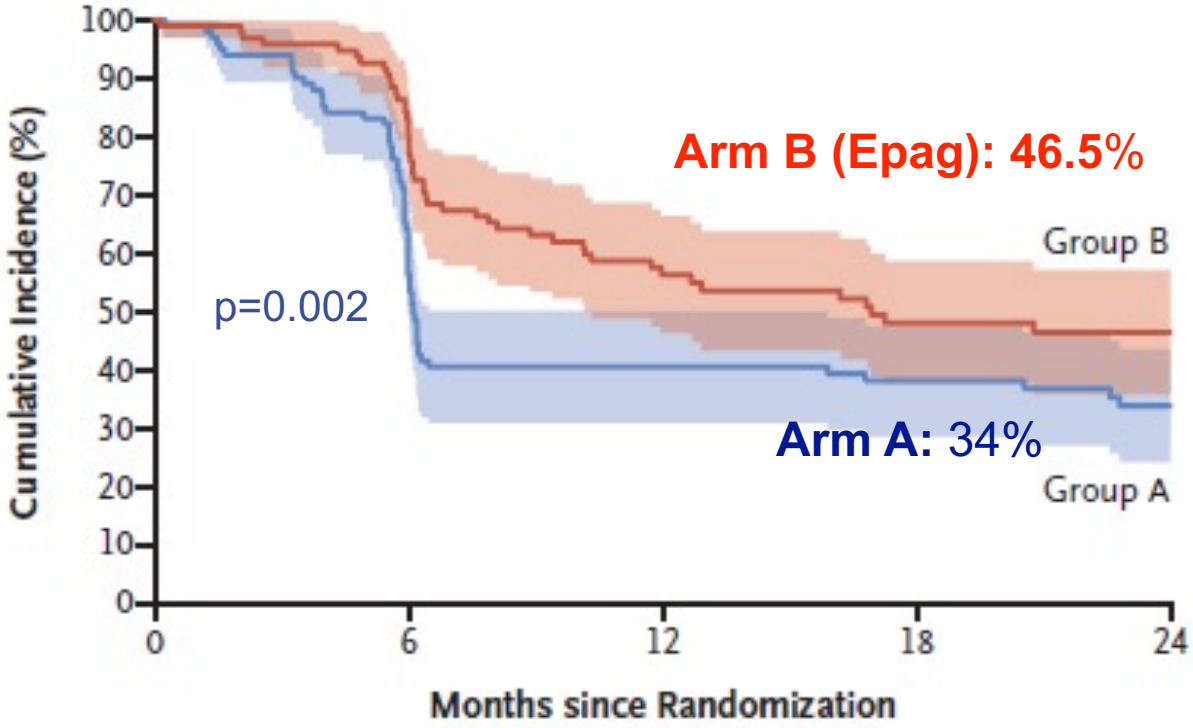
24 months



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

Predictors of Response

- CR at 3 months and OR at 6 months

  - Arm B (EPAG)
  - Age > 40 y
  - SAA

- No correlation with

  -mutations at baseline,
  -PNH clone,
  -lymphocytes & reticulocytes

TL not tested

Karyotypic Abnormalities

- 1 in arm A

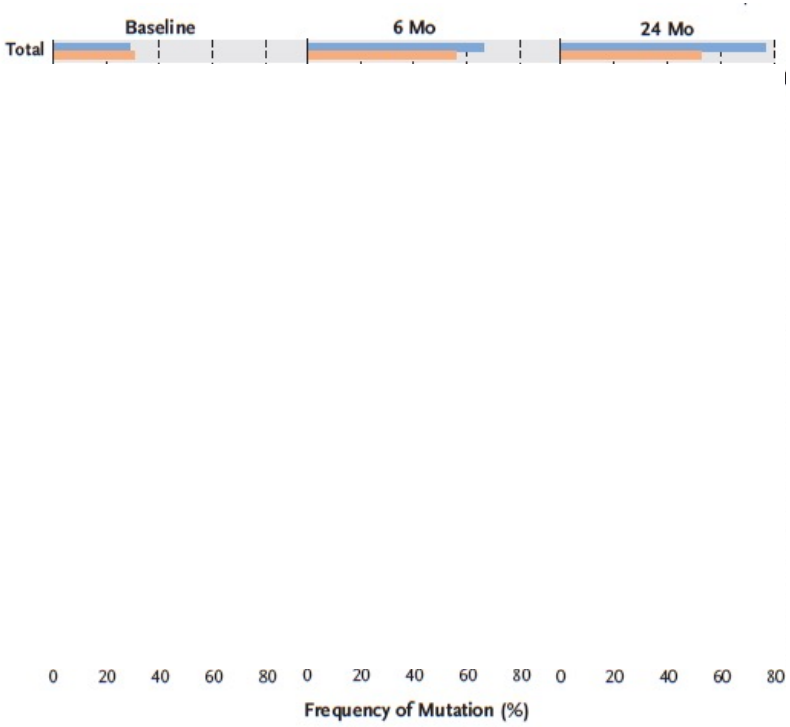
  -1 mono 7, with BCOR, DNMT3 and TET2 mutations,

- 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

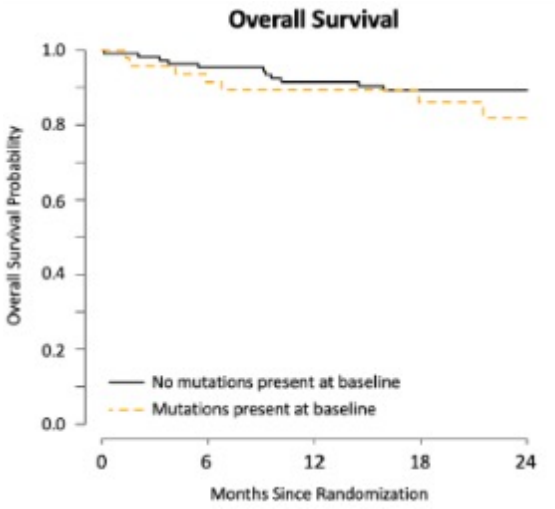
Both total and specific gene mutations

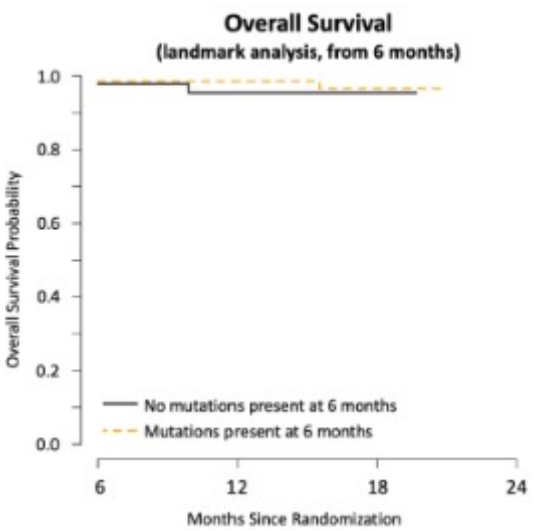
Somatic mutations increased at 6 months, without affecting the hematologic response and 2-year outcome.

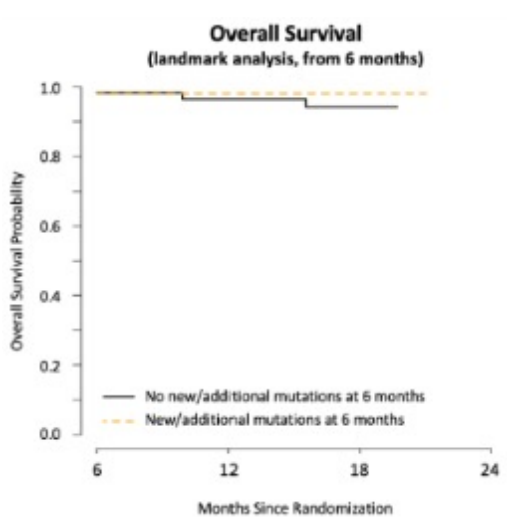
Eltrombopag did not increase high-risk evolution.

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

Impact of somatic mutations on survival







No effect of mutational status at baseline and 6 months;
No effect of new mutations between baseline and 6 months

Impact of somatic mutations on response and additional mutations

- CR at 3 months

  Patients without mutations at baseline 14%
  Patients with mutations at baseline 21%

- OR at 6 months

  Patients without mutations at baseline 49%
  Patients with mutations at baseline 60%

No effect of mutation status and of new/additional mutations acquired at 6 and 24 months on response
But …only 2 years follow up

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%)

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

RACE conclusion - Perspective

- EPAG added to standard IST (hATG and CsA), **significantly increases the rate of CR at 3 months** with **no safety concern** at time of analysis (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

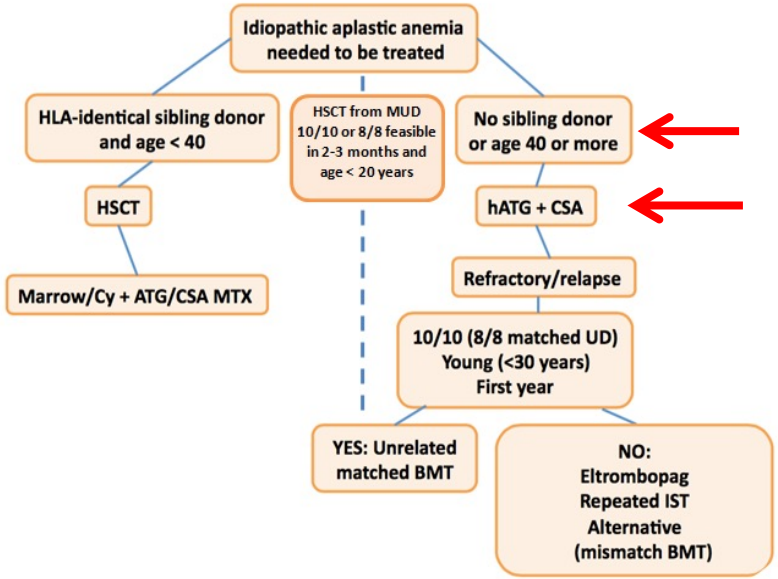
- So far no increased frequency of somatic mutation in eltrombopag arm

  Also, 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

Changes in the algo in adults ?

- Further support
- Displaces MRD



medically fit)?

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

IST + ETPAG *vs* MRD HSCT

99 pts, multicentric

48 MSD HSCT, age 29.5y
51 IST+EPAG, age 46 y

	IST+EPAG	MSD HSCT	p
OS	96.1%	95.8%	0.97
OS VSAA	85.7%	100%	0.04
EFS	71%	89.6%	0.04
CR	15.7%	79.2%	<0.01
ORR	72.6%	97.9&	<0.01

Similar OS
Far higher EFS and Response MSD-HSCT*vs* IST+EPAG

Li-fang Huang et al, Transplantation and Cellular Therapy, vol 28,9, Sept 2022, 596e1-586e7

IST + ETPAG *vs* MRD HSCT

- Prospective, multicenter
- IST+ EPAG age 29y, MRD HSCT 34.4y.

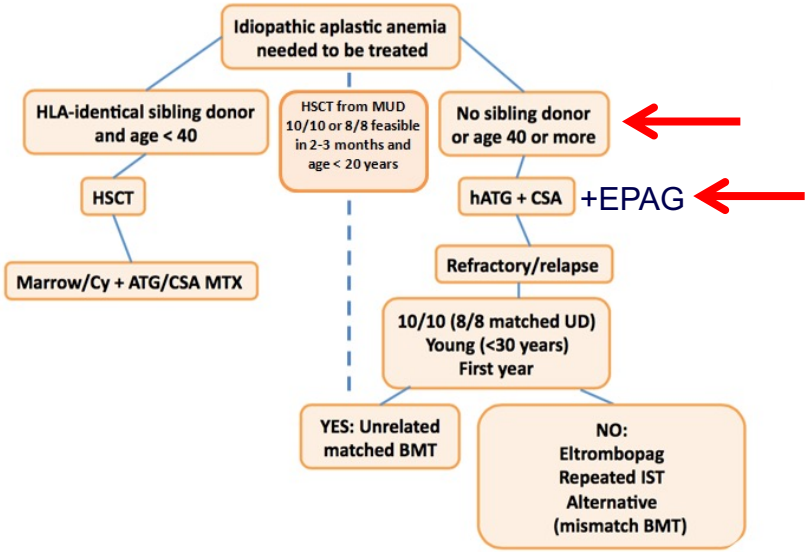
	IST+EPAG (104)	MRD HSCT (108)	p
OS	84.2	89.7	0.164
OS > 40 y	100 %	77.8%	0.036
FFS	59.1 %	81.4 %	0.002
FFS < 40 y	81.0%	63.7 %	0.033
FFS in VSAA	54.9%	86.1%	0.003
CE	13%	9%	0.215

In MV, MRD-HSCT favorably associates with normal blood values at 6-month and FFS ($p < 0.05$).

MRD-HSCT remains the preferred first-line option for SAA patients aged < 40 years or with vSAA even in the era of EPAG.

Limin Liu et al J Hematol Oncol, 2022 Aug 12;15(1):105).

Changes in the Algo in adults



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

Even more so after RACE !

FDA OK
EMA no
National agencies ongoing

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

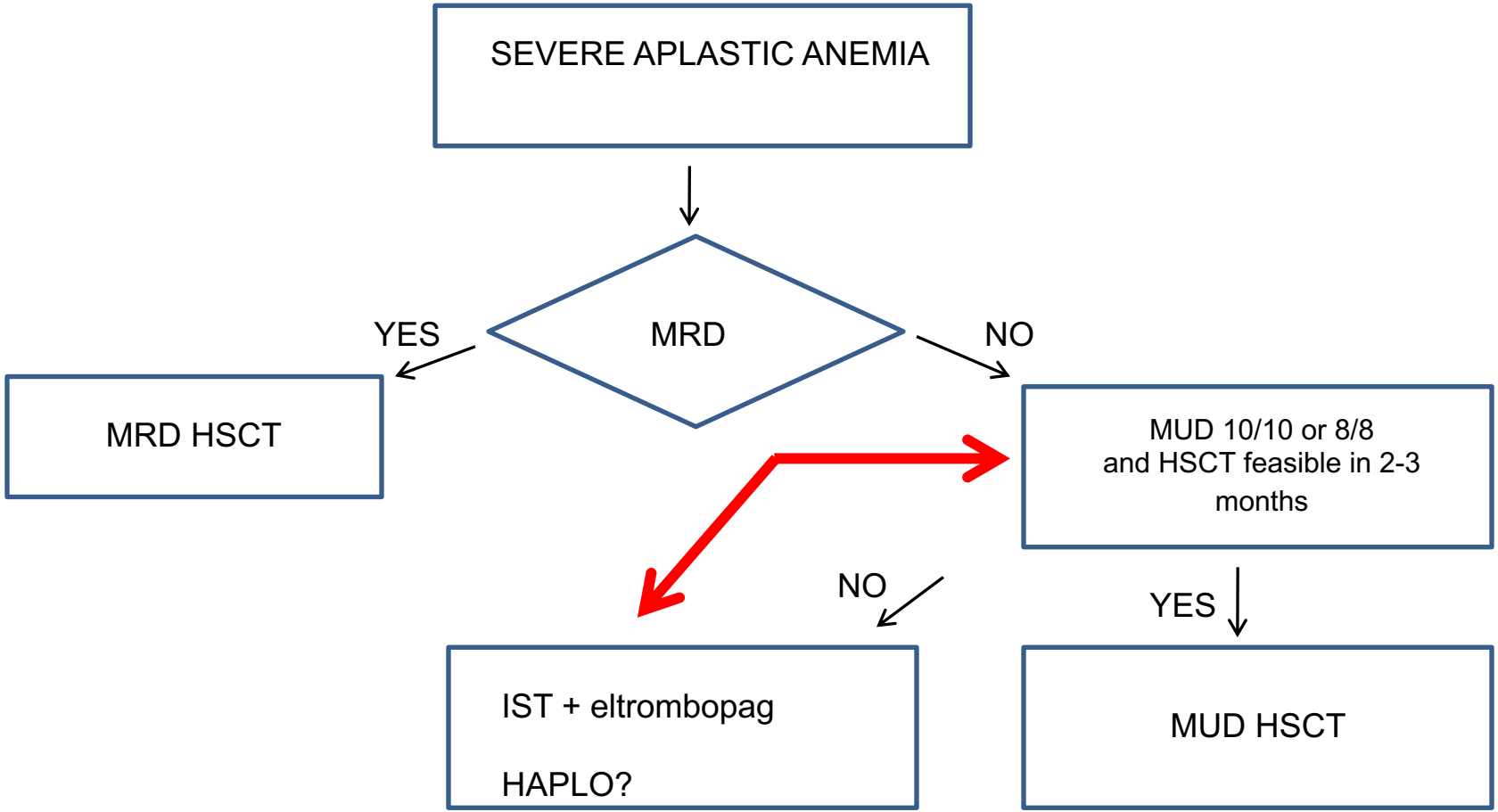
49 pts hATG + CsA+ EPAG (2mg/kg/day, from day 1) age 10.5 yrs

	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


SEVERE APLASTIC ANEMIA
MRD
YES
NO
MRD HSCT
MUD 10/10 or 8/8
and HSCT feasible in 2-3
months
NO
YES
IST + eltrombopag
HAPLO?
MUD HSCT

AIEOP 2021

What's around in Triple Therapy for SAA

- Romiplostim + rATG+ CsA, front line
  Pilot, single arm, adults
  Hematological response at 6 mos 76.5%, CR 35.3%
  S. Nakao group Poster 827 at EHA Congress 2022

- Avatrombopag + rATG+ CsA, front line
  Pilot, single arm
  OR 46.9% and CR 15.6% at 3 mos
  Xin Zhao, China, Poster at ASH Congress 2022

- Avatrombopag + rATG+ CsA, front line, Diamond Study
  RCT, Australia, Ongoing. S.Thieng is the PI

- Hetrombopag+ pATG +CsA, front line
  Controlled, adults
  CR at 6 mos 34.4% vs 14.6 % in pATG+CsA alone
  OR at 6 mos 68.7% vs 50% in pATG+CsA alone
  Yang W et al, Experimental Hematology-Oncology 2023, 12, 16

- Epag + hATG+CsA, frontline and refractory/relapsed,
  Single arm, children
  Encouraging results in refractory/relapsed
  Shimamura A et al, Oral at ASH Congress 2022

RACE is a team: THANKS!!!

And of course:

- all principal investigators and sites
- all patients!

Thanks

My mentor
Lucio Luzzatto

EBMT SAAWP
Regis Peffault de Latour
Antonio Risitano
Andrea Bacigalupo

NIH
Neal Young

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Phil Scheinberg
Rodrigo Calado
Juan Bueren
Julian Sevilla
Jordi Surrales
Jean Soullier
Alan Warren

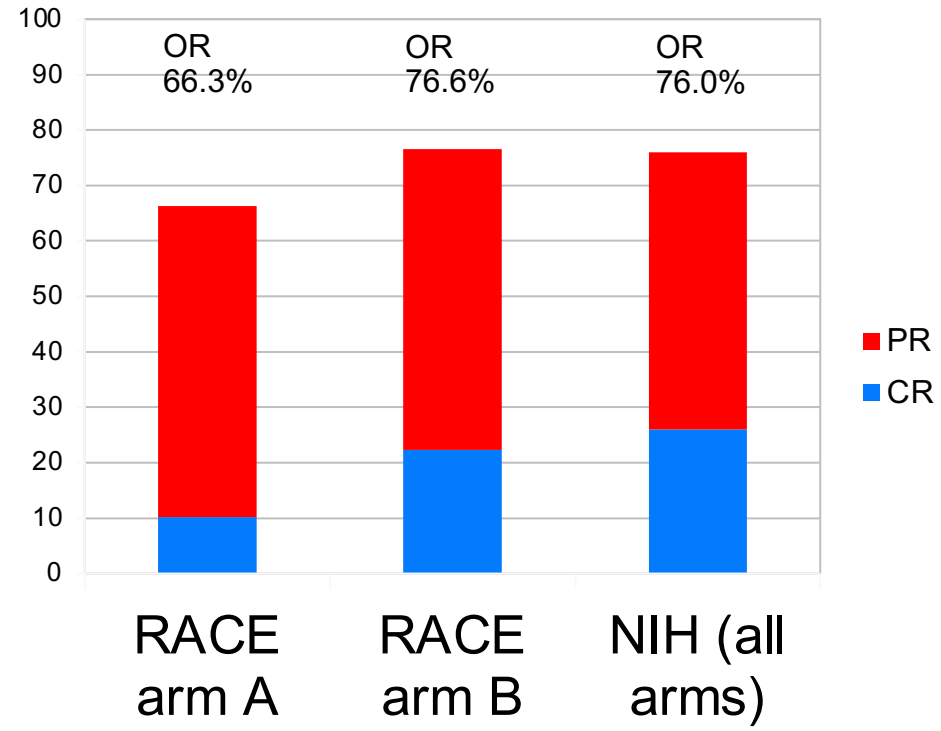
Hematology Unit, Gaslini
F Fioredda,
M Miano
F.Pierri
E Ricci
E Cappelli

Patients and their families

Hematological response

NIH criteria

3 months



6 months