Aplasie de l’enfant: premières lignes immunosuppresseurs

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1. Comparaison PNDS et groupes d’experts autres pays
2. rATG (rabbit) versus hATG (horse)
3. Eltrombopag (ELTR)

	Adults Children *PNDS 2023*	Children *Blood cells mol and dis 2024*	Adults *Bjh 2024*	Children *PBC 2024*
CsA trough level	200-300 ng/ml	100-250 ng/ml	150-200 ng/ml*	200-350 ng/ml

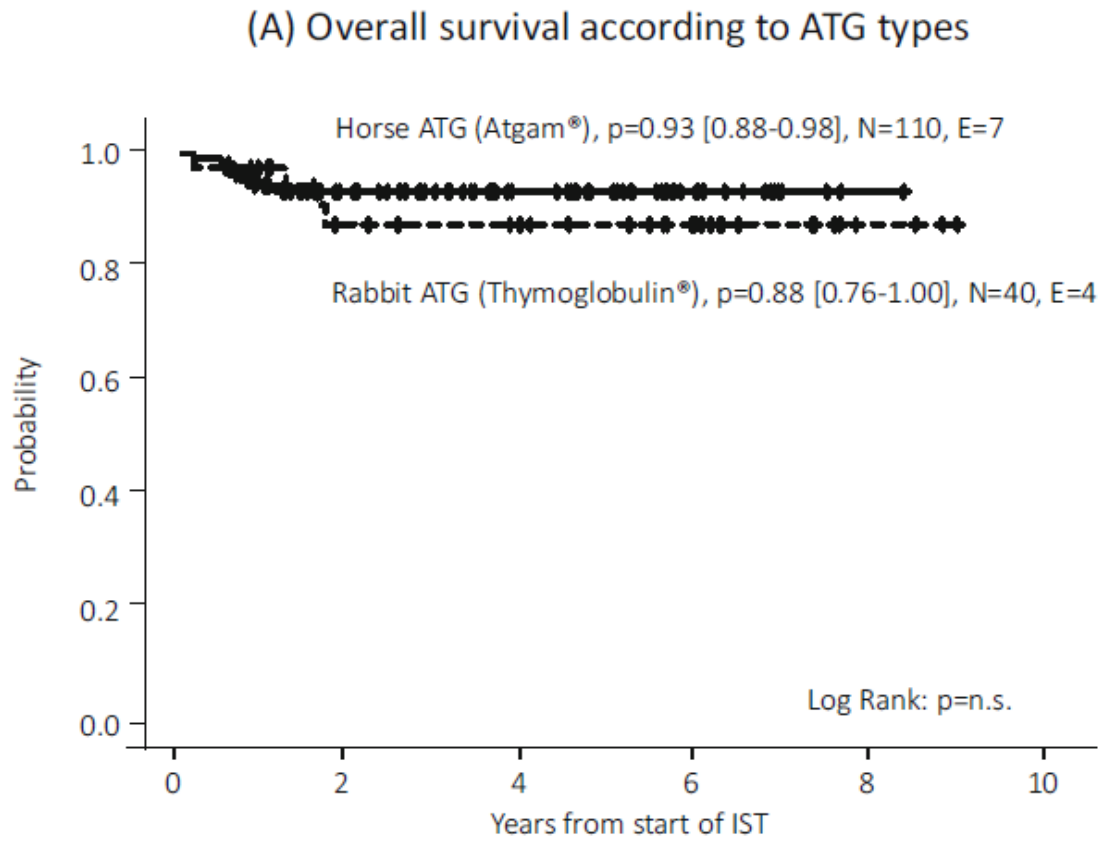
CsA trough level: Although the practice in the UK is to keep levels between 150 and 200 µg/L, higher therapeutic levels between 200 and 400 µg/L are used in many countries, but renal toxicity should be carefully monitored

Continuous use of G-CSF is recommended in SAA treated with IST, but it is not possible to define the duration. When continuous GCSF is not used or not available, on-demand use is recommended in case of febrile neutropenia during IST

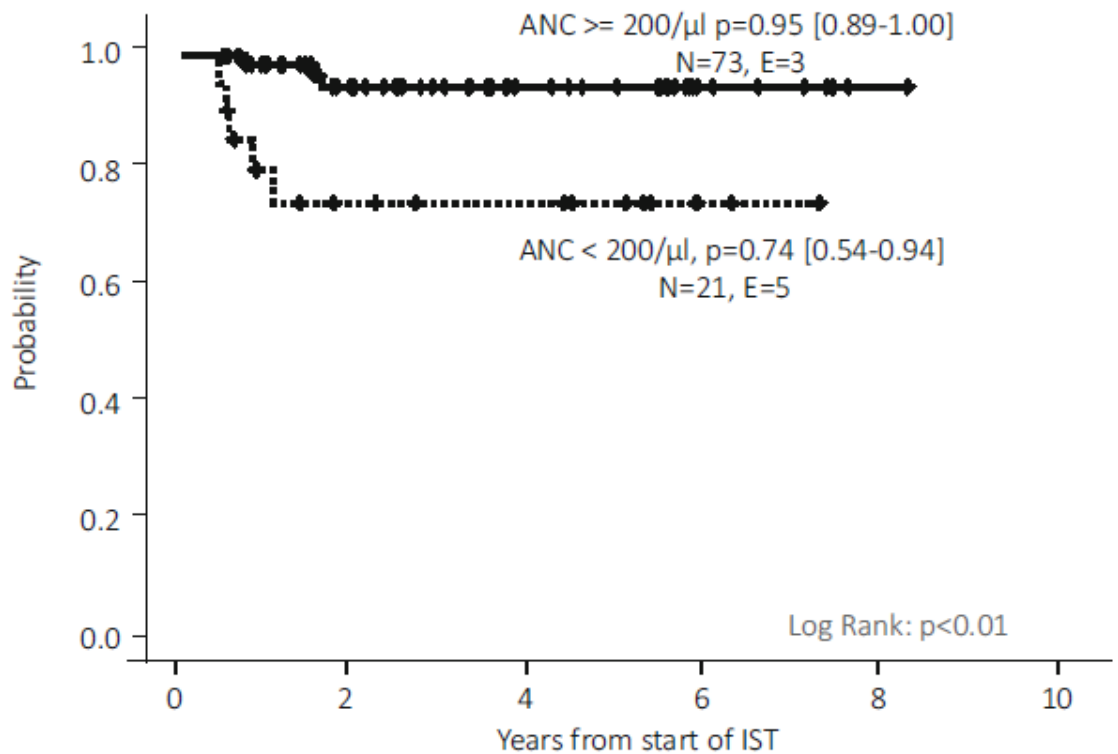
	Adults Children *PNDS 2023*	Children *Blood cells mol and dis 2024*	Adults *Bjh 2024*	Children *PBC 2024*
CsA trough level	200-300 ng/ml	100-250 ng/ml	150-200 ng/ml*	200-350 ng/ml
Duration at full dose	1 year from the last transfusion	1 year from the maximum response	1 year	after 6 months of ttt and CR with stable counts for 3−6 m
Tapering dose	10−20% per 3 month	5−10% per month	25 mg per 2-3 month	5−15% per month
Total duration	2 years minimum from the last transfusion	2 years minimum from the maximum response		
ELTR	75 then 150 mg on day J10		150 mg on day 14	
G-CSF		Recommended*	Ineffective	Not recommended (maybe for vSAA or infection)
Deferasirox		ferritin > 1000 ng/ml	with caution in combination with CsA	

Comparison of outcomes of is with rATG versus hATG and CsA in children with SAA; *Amjh 2024*

- N= 150: hATG(n = 110) vs r-ATG (n=40) from 2011-2020 (prospective)
- G-CSF in the first 28 days (if <0.5 G/L neutrophils) and discontinued by day 60
- Median time from diagnosis to IST: 36 days
- ORR at 6 months: hATG 42% vs rATG 22% (p = 0.03)
- A lower neutrophil count prior to IST and r-ATG were associated with an inferior response to IST at 6 months
- No difference in ORR and OS at time of last follow up


(A) Overall survival according to ATG types
Horse ATG (Atgam®), p=0.93 [0.88-0.98], N=110, E=7
Rabbit ATG (Thymoglobulin®), p=0.88 [0.76-1.00], N=40, E=4
Log Rank: p=n.s.
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Years from start of IST

(C) Overall survival according to ANC



ELTROMBOPAG (ELTR): Addition of ELTR to immunosuppression in frontline treatment of SAA in children

- hATG+ CsA (n = 101) vs idem + ELTR (n = 96)
- Primary endpoint : ORR and CR at 6 months
- ELTR-IST group
  - Higher ORR : 68% vs 41%
  - Higher CR: 32% vs 20%

NEJM 2022

ELTR added to IS for children with treatment-naïve SAA – Phase 1-2; *bjh 2021 E. Groarke*

- A paediatric subgroup analysis : IST+ELTR (n = 40) compared to a historical cohort (n = 87) IST alone
- ELTR 2,5 mg/kg/ 75 mg / 150 mg on day 1, for 3 or 6 months
- No difference in either the ORR or CR rate at 6 months (ORR 70%).
  Adults (n=131 vs 286): ORR 82% (IST-ELTR) vs 58% (P < 0·001)
- Younger children (n=16 <12y) lower response / adolescents with ELTR

NEJM 2022
ORR : 70 vs 40%
CR: 30 vs 20%

Haematological response at 6 months in younger children versus adolescent

	IST	IST-ELTR	
	N=87	N=40	p
< 12 y	N=45	N=16*	
ORR	78%	63%	P=0.29
CR	24%	6%	P=0.049
> 12 y	N=42	N=24	
ORR	67%	75%	P=0.48
CR	21%	46%	P=0.052

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  Adults (n=131 vs 286): ORR 82% (IST-ELTR) vs 58% (P < 0·001)
- Younger children (n=16 <12y) lower response / adolescents with ELTR
- **Addition of ELTR added to standard IST did not improve outcomes in children, this study do not support the addition of ELTR, although it has been FDA approved.**

Efficacy of combined IS with or without ELTR in children with newly diagnosed SAA; *Blood advance 2023 (O. Goronkova)*

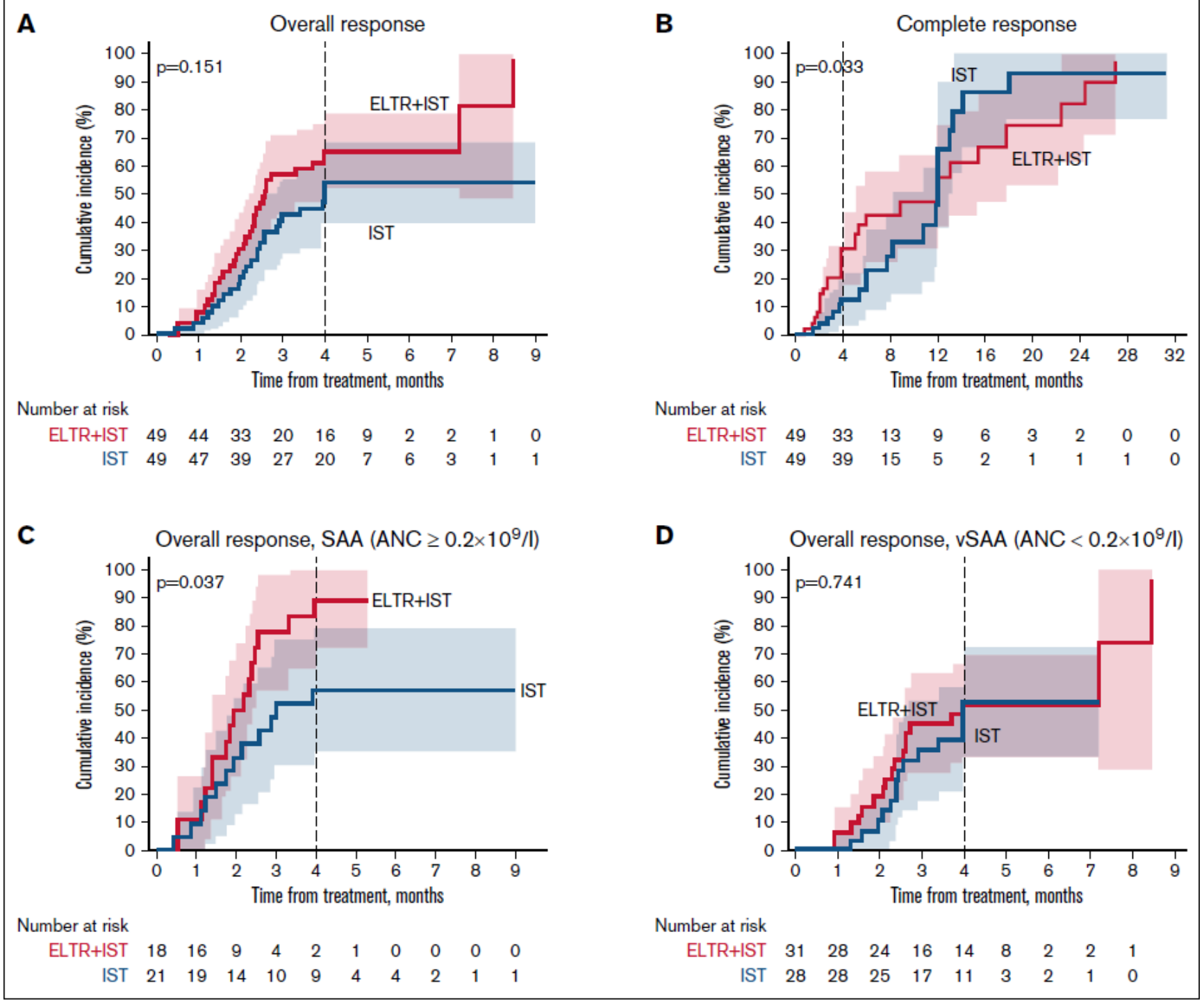
- hATG+ CsA (n = 49) vs idem + ELTR (n=49) - randomization
- ELTR 2 mg/kg/d for ≥ 4 mois
- Primary endpoint : ORR at 4 months. <u>After 4 months, crossover of nonresponders</u>
- ELTR-IST group
  - Similar ORR : 65% vs 53%; P = 0.22
  - Higher CR: 31% vs 12%; P = 0.027
  - Higher ORR non vSAA: 89% vs 57%(P = 0.028) (vSAA : 50%)
- At 6 months after the crossover, 61% of initial IST patients achieved a response compared with 17% of initial IST-ELTR (p = 0.016)

NEJM 2022
ORR : 70 vs 40%
CR: 30 vs 20%

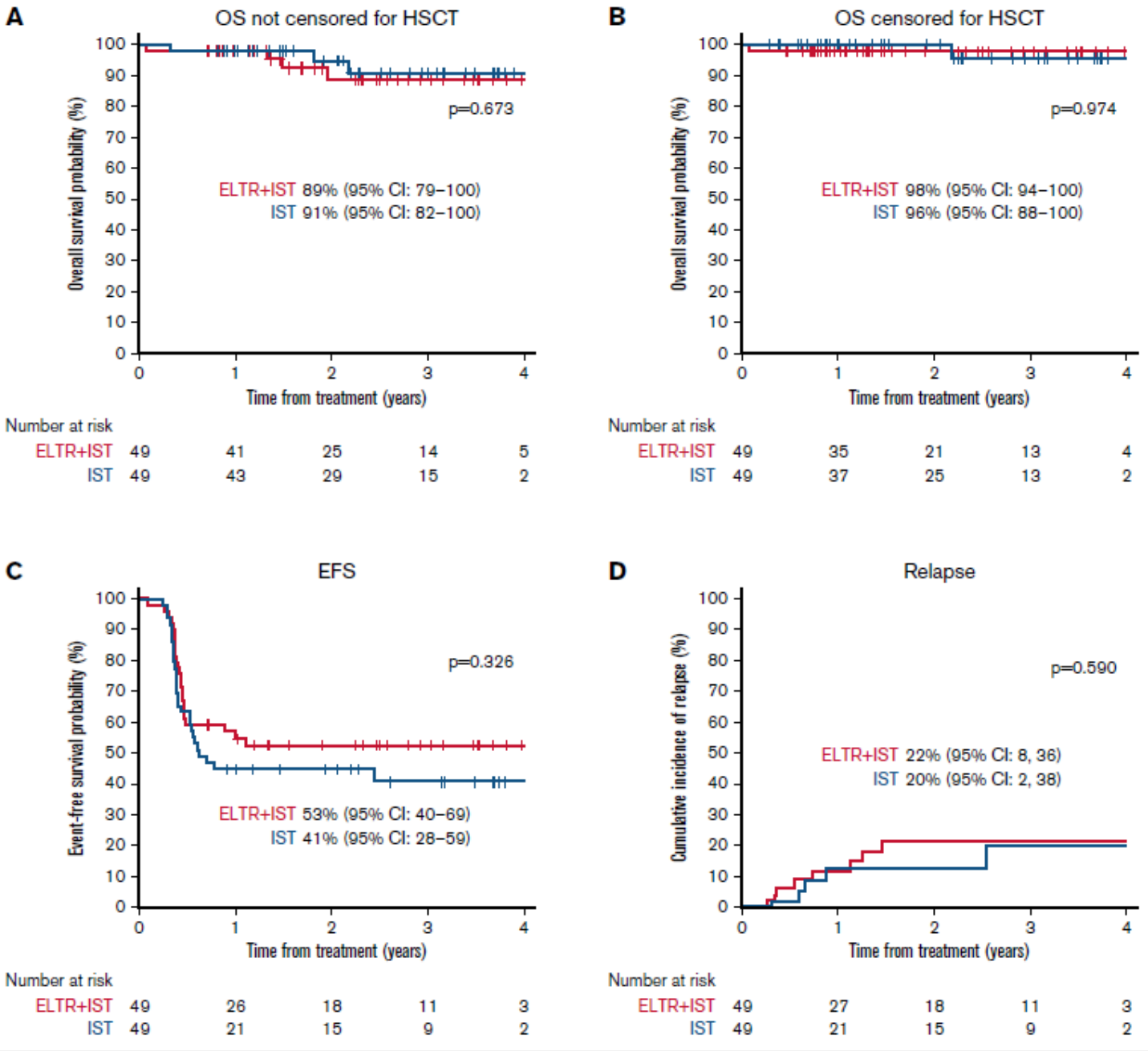
Similar ORR

Higher CR

Higher ORR
In non vSAA



Similar 3-years OS and EFS



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- At 6 months after the crossover, 61% of initial IST patients achieved a response compared with 17% of initial IST-ELTR (p = 0.016)
- **Adding ELTR to IST was well tolerated and increased the CR rate. The greatest benefit was observed in patients with SAA but not in those with vSAA. The second course of IST resulted in a high ORR in initial ELTR(–) patients who added ELTR and had limited efficacy among patients who received ELTR upfront.**

Addition of ELTR to IST in frontline treatment of SAA

- BJH 2021: 40 vs historical cohort. Similar ORR and CR at 6 m (higher ORR for ado). No advantage. “Should not automatically be considered standard of care”

- Blood adv 2024: 40 vs 40, crossover at 4 m. Higher ORR non vSAA, higher CR. “Support the addition of ELTR”
- Despite significant results in adults, the benefit in children is less clear
- FDA approved in 2018 for > 2 years old

- While not generating relevant adverse effect, does not appear to produce clear advantage. Therefore, it can be considered an available option

- Is not recommended

Pour conclure,

- G-CSF, chelation, ciclosporinémie
- Eltr:
- Majoritairement non recommandé plutôt par manque de données que de risque de toxicité
- Utilisé dans le PTI de l’enfant
- On est très tenté de l’utiliser (per os, peu d’effets secondaires, données de l’adulte)
- On peut probablement élargir au adolescents dans un premier temps
- Études en cours