CeReCAI
Centre De Référence
Cytopénies Auto-immunes
de l'Adulte

MaRIH

Actualités thérapeutiques dans le PTI

Journée annuelle du CERECAI

7 octobre 2022

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Ciml IMMUNOLOGY

MARSEILLE IMMUNOPÔLE

"The sponsor (Sanofi) and first author designed the trial in collaboration. The conduct of the trial was overseen by the sponsor. Data were collected by the investigators and analyzed by the sponsor. The first draft of the manuscript was written by the first author, and medical writing assistance was paid for by the sponsor."

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rilzabrutinib, an Oral BTK Inhibitor, in Immune Thrombocytopenia

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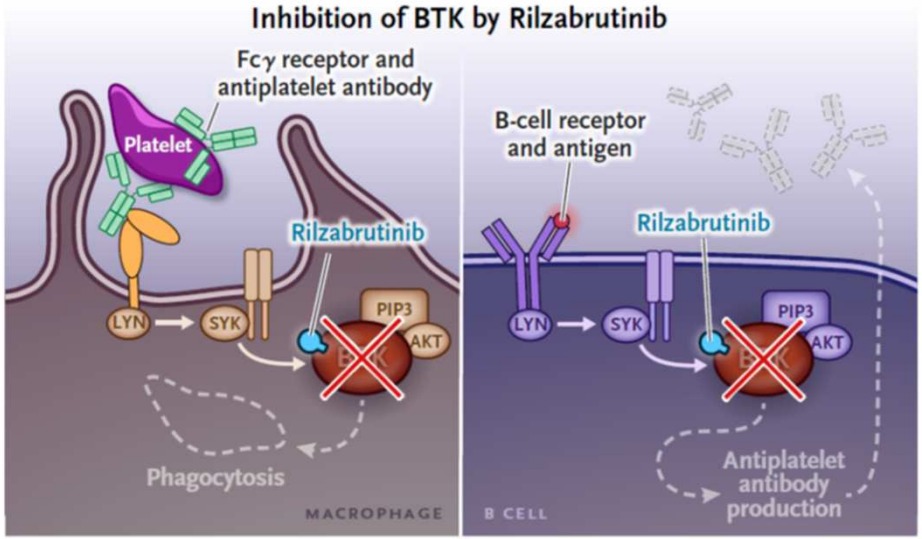
N ENGL J MED 386;15 NEJM.ORG APRIL 14, 2022

Rilzabrutinib au cours du PTI : mécanisme d'action

Rilzabrutinib
(PRN1008)
is an oral, reversible,
potent BTK inhibitor



Covalent binding => long BTK-target engagement and durable inhibition with limited drug exposure is accompanied by rapid systemic clearance, which reduces the potential for off-target toxic effects.

High specificity => **decrease the risk of off-target toxic effects (e.g., atrial fibrillation)** by means of the PI3K–AKT signaling pathway, which is associated with other BTK inhibitors

In contrast to the known effects that have been observed with other BTK inhibitors, rilzabrutinib use **did not alter platelet aggregation** in healthy volunteers or in patients with immune thrombocytopenia

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Phase 1–2 trial to identify a safe and effective rilzabrutinib dose in patients with immune thrombocytopenia to be tested in phase 3 trials.

Critères d'inclusion :

- 18 to 80 years of age (or 18 to 65 years of age in the Czech Republic and Norway)
- **Platelet counts < $30\times10^3/mm^3$** on two occasions ≥ 7 days apart within the 15 days before trial entry
- Response to at least one previous therapy for ITP (including splenectomy)
- but no response to the previous or concomitant therapy maintained at baseline

(Only stable concomitant therapy with a glucocorticoid or TPO-Ra with no more than a 10% change in the dose within the 2 weeks before the initiation of rilzabrutinib was allowed throughout the treatment period)

Eligible patients (≥$50\times10^3/mm^3$ or ≥$30\times10^3/mm^3$ AND x2 of the baseline count for ≥50% of the patient's final 8 weeks of rilzabrutinib therapy): long-term extension study at a dose of 400 mg x2/d

Treatment was discontinued if a dose-limiting toxic effect occurred, rescue medication was used, or concomitant medication for ITP was changed beyond the 10% level as defined above

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Critères d'exclusion :

- pregnant or lactating women,
- treatment with rituximab or splenectomy **≤ 3 months**
- Electrocardiogram QTcF >450 msec (males)/>470 msec (females)
- ongoing need for proton pump inhibitor drugs
- concomitant use of strong-to-moderate CYP3A4 inducers/inhibitors or sensitive substrates
- planned or **concomitant use of anticoagulants or platelet aggregation inhibiting agents**
- Current drug or alcohol abuse
- a history of solid organ transplant
- positive screening for HIV, hepatitis B or hepatitis C virus

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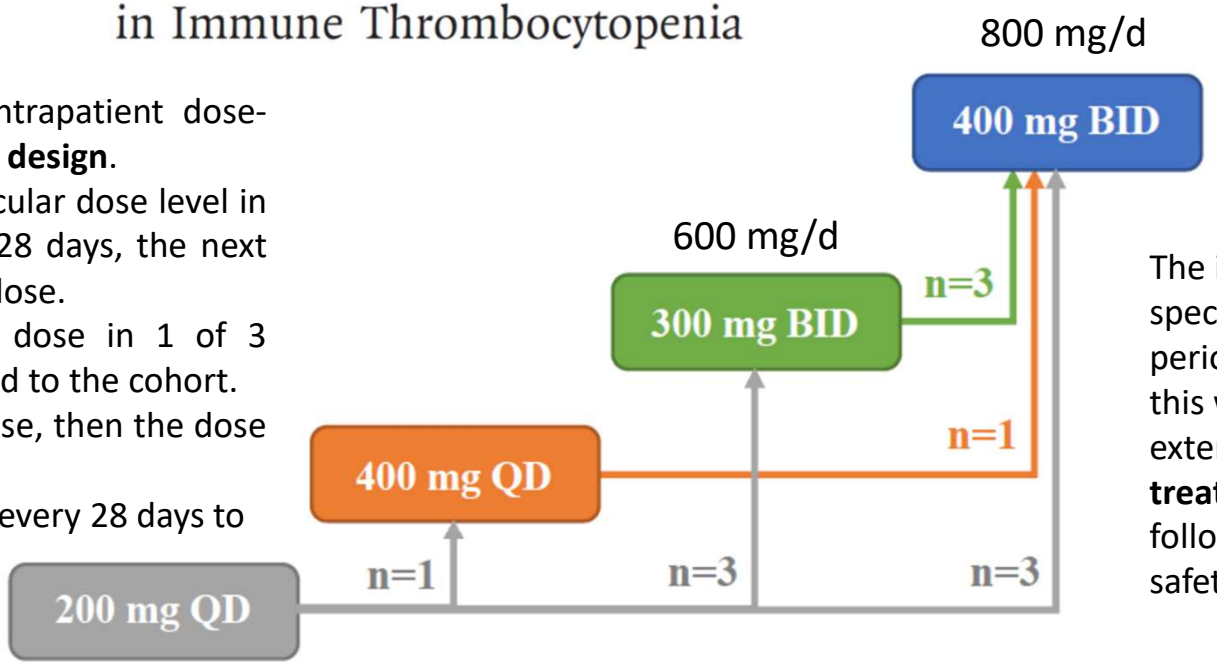
Rilzabrutinib was administered as an intrapatient dose-escalation treatment utilizing a **3+3 study design**.
If no responses were observed at a particular dose level in 3 patients from the sentinel cohort for 28 days, the next higher dose was considered the starting dose.
If response was observed at the low dose in 1 of 3 patients, then 3 more patients were added to the cohort.
If a patient experienced a platelet response, then the dose was held constant at the next cycle.
Intrapatient dose escalation was allowed every 28 days to improve responses up to the maximum allowed 400 mg bid dose.



The initial trial protocol specified a treatment period of 12 weeks; this was subsequently extended to a **24-week treatment period** followed by a 4-week safety follow-up period.

Starting Dose	n=9	n=1	n=5	n=45
Maintained Dose	n=2	n=0	n=2	n=45
Dose-escalated	n=7	n=1	n=3	N/A

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The **primary end points** were **safety** and **platelet response**.
Safety: graded according to the **C**ommon **T**erminology **C**riteria for **A**dverse **E**vents, version 4.0, of the NCI
Platelet response: at least 2 consecutive platelet counts (separated by ≥5 days) of **at least $50\times10^3/mm^3$** and an **increase from baseline of at least $20\times10^3/mm^3$** without the use of rescue medication for ITP in the 4 weeks before the latest elevated platelet count

Post hoc subgroup analyses of the primary efficacy end point to evaluate the potential effect of patient and ITP characteristics at baseline.

Secondary efficacy end points:
- % of weeks with a platelet count ≥$50\times10^3/mm^3$
- % of patients who had a platelet count ≥$50x10^3/mm^3$ at four or more of the final eight platelet count
- the change from baseline to the mean of the post–day 1 platelet counts among patients who had received more than 4 weeks of treatment
- the number of weeks with a platelet count ≥$50\times10^3/mm^3$
- the number of weeks with a platelet count ≥$30\times10^3/mm^3$
- the time to the first platelet count ≥$50\times10^3/mm^3$

Post hoc analyses of secondary efficacy end points were conducted in patients with a response

Secondary safety end points:
- rescue medication use
- % of patients with a bleeding event of grade 2 or higher
- bleeding scale scores (according to an ITP–specific bleeding assessment tool) at the end of the treatment period

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Overall, 40 patients received concomitant medication (not including rescue medication) (aRTPO n=24 and glucocorticoids n=23)

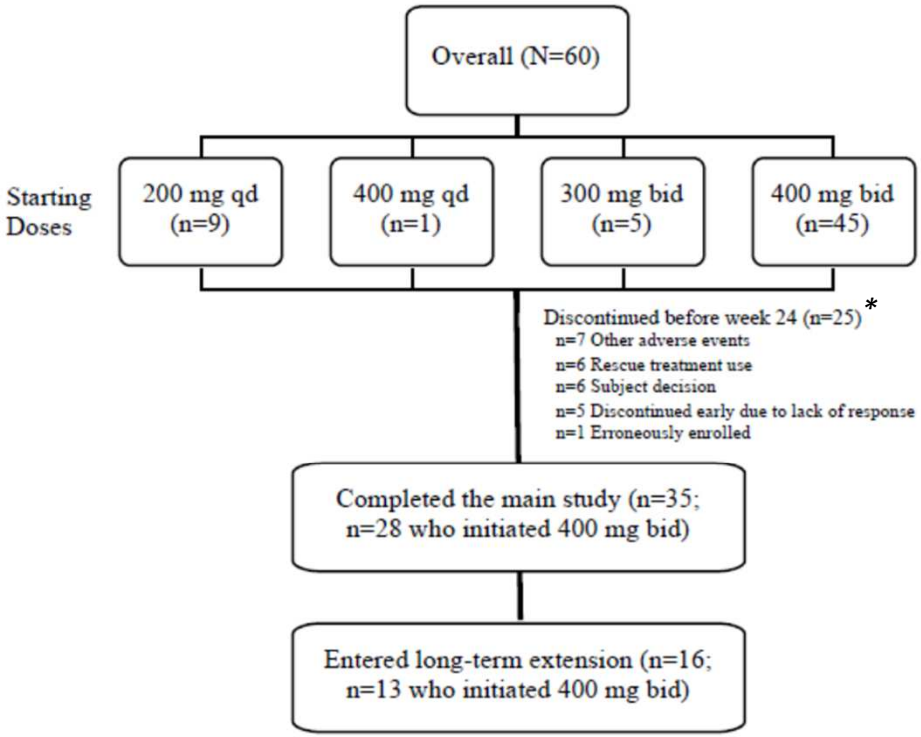

Table 1. Characteristics of the Patients at Baseline (Safety Population).*

Characteristic	All Patients (N=60)	Patients with Starting Rilzabrutinib Dose of 400 mg Twice Daily (N=45)
Median age (range) — yr	50 (19–74)	49 (19–74)
Sex — no. (%)		
Male	26 (43)	18 (40)
Female	34 (57)	27 (60)
Median baseline platelet count (range) — $\times 10^{-3}/mm^3$	15 (2–33)	15 (2–33)
Median duration of ITP (range) — yr†	6.3 (0.4–52.5)	6.1 (0.4–52.5)
Median no. of different previous ITP therapies (range)‡	4 (1–17)	4 (1–17)
Previous splenectomy — no. (%)‡	15 (25)	11 (24)
Most common previous ITP therapies — no. (%)‡		
Glucocorticoid	55 (92)	42 (93)
Thrombopoietin-receptor agonist§	35 (58)	24 (53)
Intravenous immune globulin	26 (43)	21 (47)
Rituximab	24 (40)	22 (49)
Fostamatinib	8 (13)	7 (16)

**All 45 patients who started rilzabrutinib treatment at the highest dose (400 mg twice daily) continued at that dose with no dose reductions or interruptions due to adverse events and no dose-limiting toxic effects*

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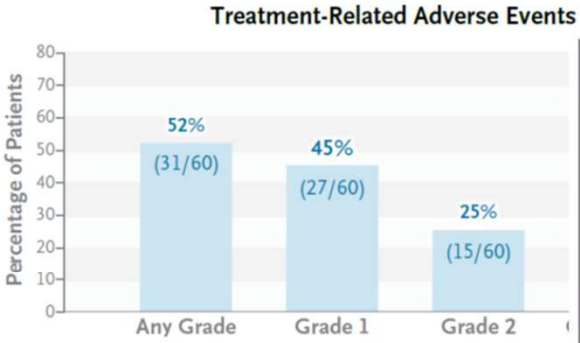


« No other signs or symptoms of adverse events that have been typically associated with BTK inhibitors (i.e., neutropenia, treatment-related infection, bleeding, thrombotic events, fungal infection, or atrial fibrillation) »

Table 2. Adverse Events According to Grade in All 60 Patients.

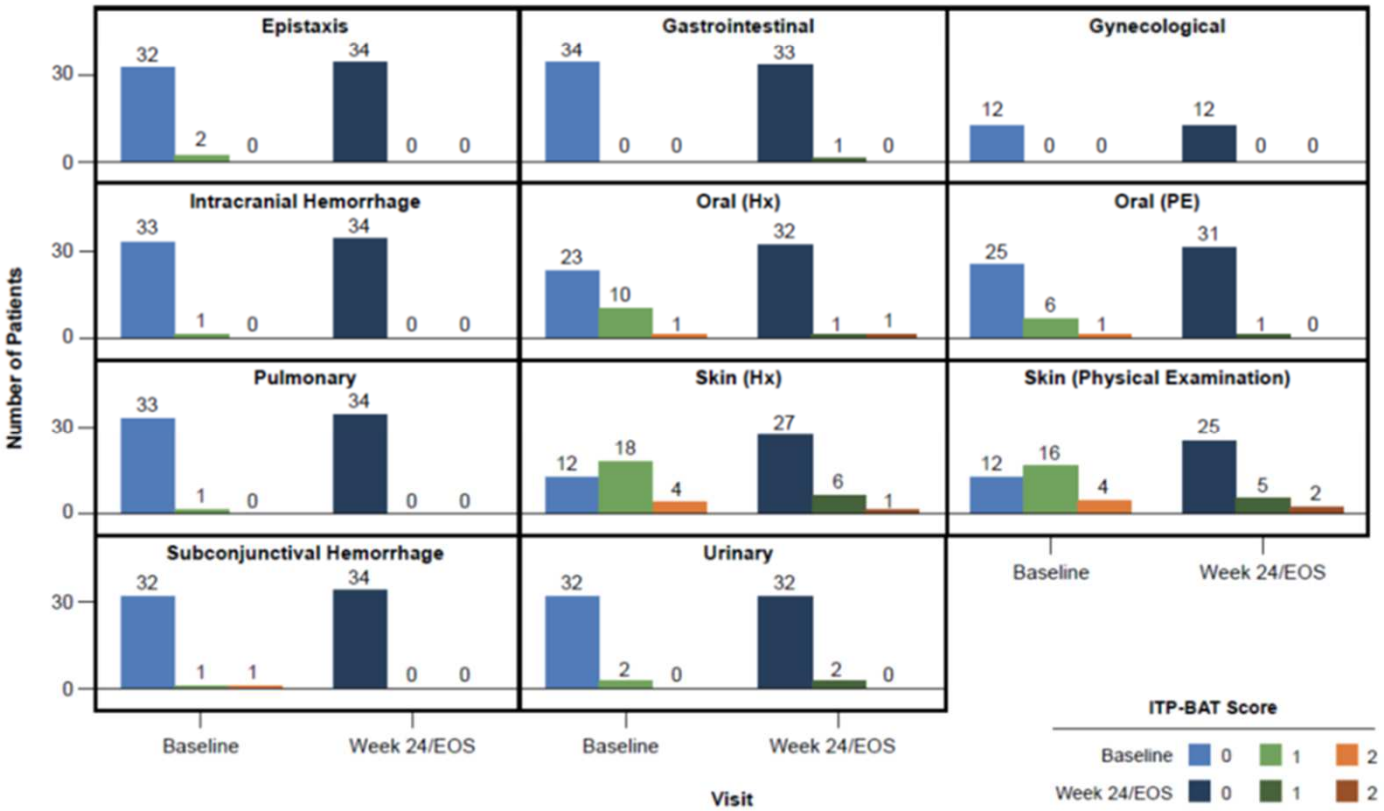
Event	Adverse Events Due to Any Cause				Treatment-Related Adverse Events*			
	Any Grade	Grade 1	Grade 2	Grade 3 or 4	Any Grade	Grade 1	Grade 2	Grade 3 or 4
	number of patients (percent)							
Any adverse event	48 (80)	43 (72)	30 (50)	8 (13)†	31 (52)	27 (45)	15 (25)	0
Diarrhea	22 (37)	19 (32)	3 (5)	0	19 (32)	16 (27)	3 (5)	0
Nausea	21 (35)	18 (30)	3 (5)	0	18 (30)	16 (27)	2 (3)	0
Fatigue	12 (20)	10 (17)	2 (3)	0	6 (10)	5 (8)	1 (2)	0
Abdominal distention	6 (10)	6 (10)	0	0	4 (7)	4 (7)	0	0
Vomiting	4 (7)	3 (5)	1 (2)	0	3 (5)	2 (3)	1 (2)	0

* Adverse events were reported after the first dose of rilzabrutinib. Relatedness of the adverse event to treatment was determined by the investigators. The treatment-related adverse events listed here are those that occurred in at least 5% of the patients.

† Eight patients had an adverse event of grade 3 or 4 that was due to any cause and that was considered by the investigators to be unrelated to rilzabrutinib treatment. Multiple events may have occurred in a single patient. These events included grade 3 anemia (in two patients); grade 3 abnormal alanine aminotransferase level, contusion, gastrointestinal hemorrhage, hematoma, ITP, myelofibrosis, and thrombocytopenia (in one patient each); and grade 4 Evans syndrome and thrombocytopenia (in one patient each).

1 décès, non lié au ttt d'après l'investigateur : arrêt du rilzabrutinib (400 mg twice daily) à J8
"exacerbation" d'un Sd d'Evans pré-existant (PTI + AHAI + neutropénie A-I) avec décès à M4 après sortie de l'étude

Figure S3. ITP-BAT Bleeding Scale Scores at Baseline (Cycle 1, Day 1) and Week 24/End of Study for Patients Who Completed 24 Weeks of Rilzabrutinib (n=34). Bleeding symptoms were grouped by site of bleeding and scored based on grade from lowest (0) to highest (3-4; grade 5 for fatal bleeding), as defined and standardized by the ITP International Working Group. There were no grade 3, 4, or 5 bleeding events at baseline or week 24/EOS; therefore, bars are not shown for these grades. Hx, history; ITP-BAT, ITP-specific bleeding assessment tool; PE, physical examination.



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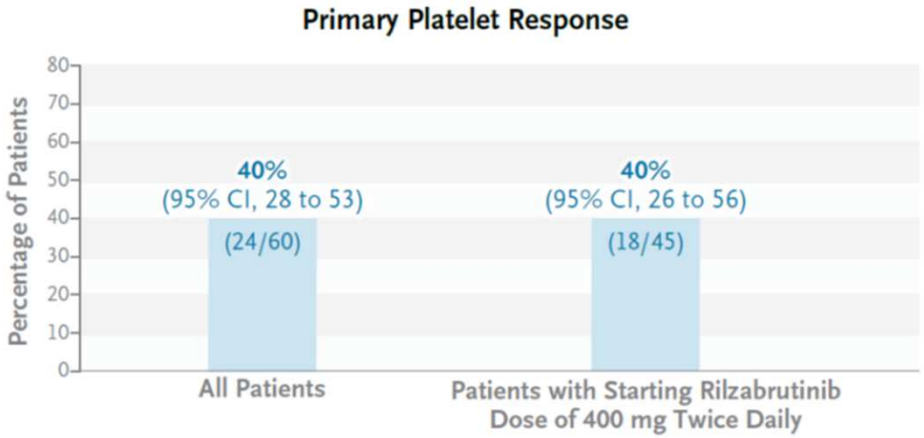

1 of 9 patients (11%) met the primary end point at a dose of 200 mg/d
2 of 8 (25%) at a dose of 400 mg/d
4 of 12 (33%) at a dose of 300 mg x2/d
and 20 of 52 (38%) at a dose of 400 mg x2/d (the highest dose)

Aucun patient avec plaquettes >400 x10^3/mm^3

Table 3. Efficacy End Points.*

End Point	All Patients (N=60)	Patients with Starting Rilzabrutinib Dose of 400 mg Twice Daily (N=45)
Primary end point		
No. of patients with primary platelet response	24†	18
Percent of patients (95% CI)	40 (28–53)	40 (26–56)
Secondary efficacy end points		
Percent of weeks with platelet count of ≥50×10^3/mm^3		
All patients	29±35	28±36
Patients with primary platelet response‡	65±25	67±26
Platelet count of ≥50×10^3/mm^3 at ≥4 of the final 8 platelet counts		
All patients		
No. of patients who met the end point	17	14
Percent of patients (95% CI)	28 (17–41)	31 (18–47)
Patients with primary platelet response‡		
No. of patients who met the end point/total no.	17/24	14/18
Percent of patients (95% CI)	71 (49–87)	78 (52–94)
Change from baseline to the mean of post–day 1 platelet counts among patients who received >4 wk of treatment — ×10^{-3}/mm^3§		
All patients	29±40	31±43
Patients with primary platelet response‡	58±43	64±48
Median no. of weeks with platelet count of ≥50×10^3/mm^3 (range)		
All patients	1 (0–26)	0 (0–24)
Patients with primary platelet response‡	16 (2–26)	14 (3–24)
Median no. of weeks with platelet count of ≥30×10^3/mm^3 (range)		
All patients	5 (0–32)	5 (0–24)
Patients with primary platelet response‡	21 (3–32)	21 (7–24)
Median no. of days to first platelet count of ≥50×10^3/mm^3 (range)¶		
All patients	11.5 (7–142)	12.5 (8–142)
Patients with primary platelet response‡	10.5 (7–71)	11.5 (8–71)

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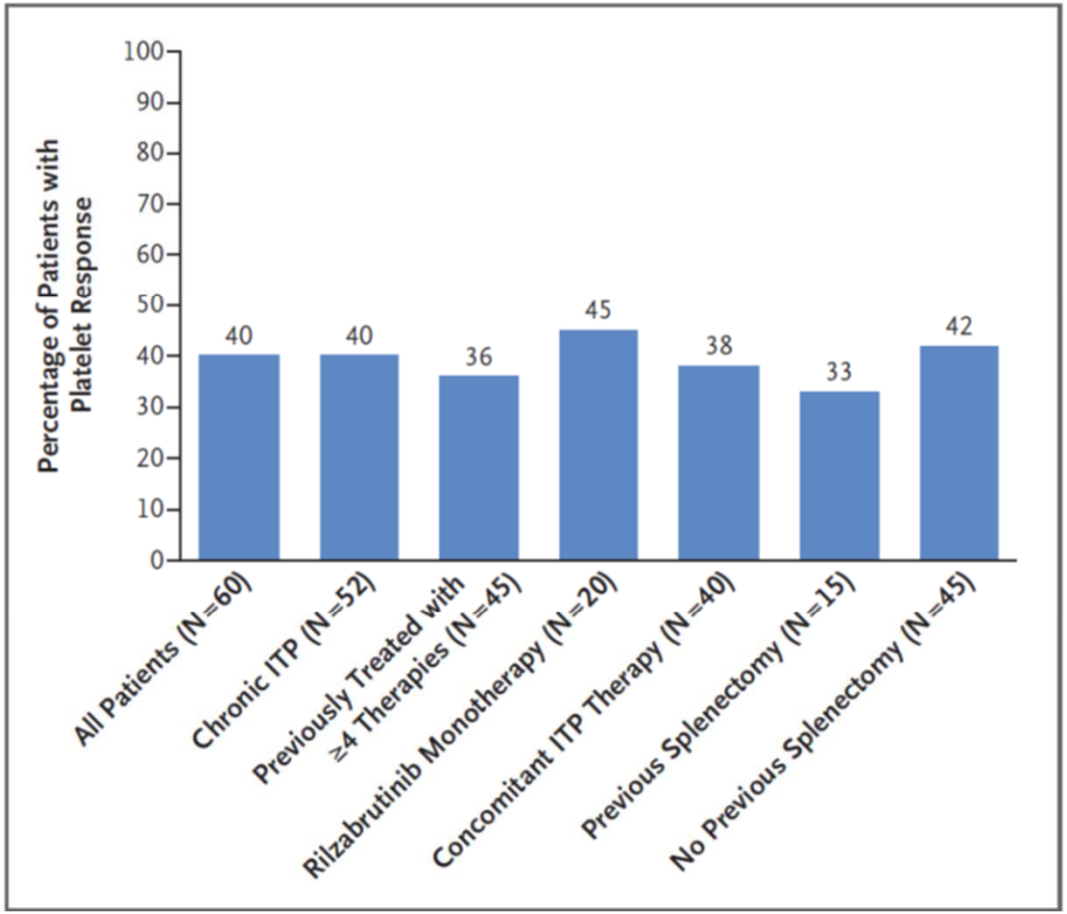
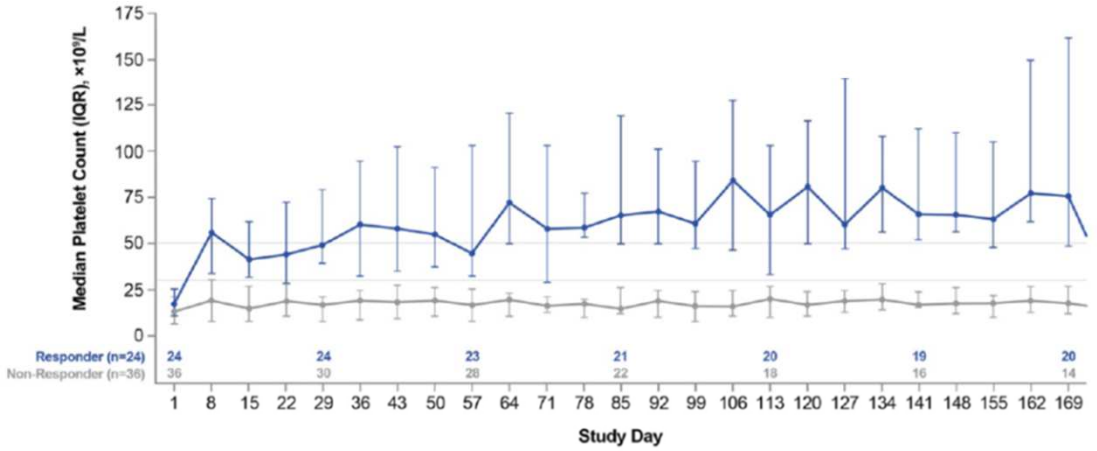
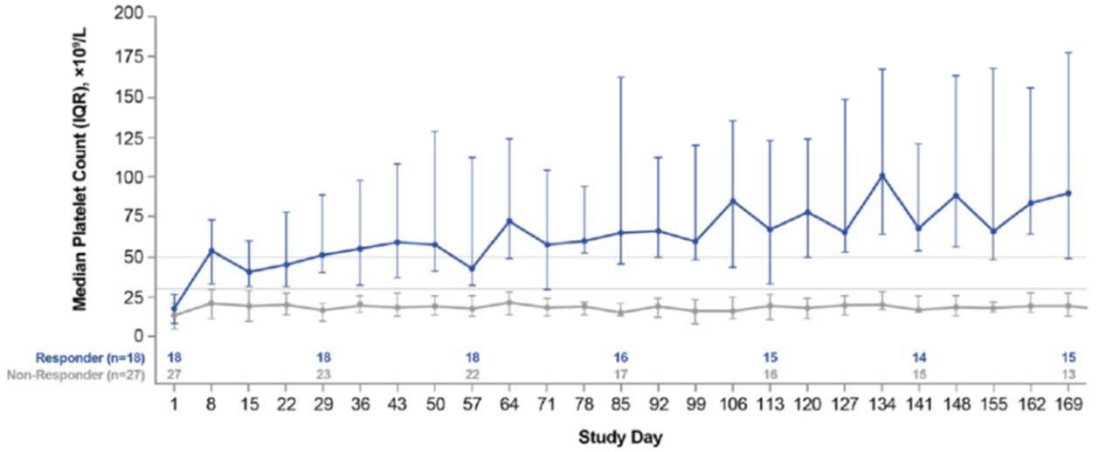


A. All patients (N=60)



B. Patients who initiated 400 mg bid (n=45)



Conclusion / Discussion

LIMITATIONS

- The duration of follow-up was short.
- This early-stage trial lacked a placebo control group.
- The sample size in the trial was small.

- Nouveau médicament ciblant différents mécanismes physiopathologiques impliqués dans le PTI

- Toxicité “faible”/low grade aux doses évaluées, en accord avec les données cliniques précoces (sujets sains et étude préclinique)

- Absence d’infection, d’évènements thrombotiques, d’arythmies cardiaques ++, d’intolerance hépatique, ou de saignements comme associés avec d’autres inhibiteurs de BTK ou sous aRTPO (mais effectif et suivi limités ++…)

- Réponse plaquettaire “cliniquement significative” ($\geq 50\times10^3/mm^3$) chez 40% des patients

- Chez des patients atteints de PTI multitraités

- Temps de R médiane (1ère NFS $\geq 50\times10^3/mm^3$) 11,5 jours ;

- Niveau de réponse maintenu 65% du temps chez les répondeurs pendant les 24 semaines de l’étude

- Taux de réponse ≈ similaires entre sous-groupes de patients / baseline characteristics

=> randomized, double-blind, phase 3 trial comparing rilzabrutinib with placebo in adults and adolescents (≥12 years of age) with persistent or chronic immune thrombocytopenia (LUNA3; ClinicalTrials.gov number, NCT04562766) is ongoing to assess the magnitude and durability of clinical benefit with rilzabrutinib treatment

Ttt de 2nde ligne du PTI : quel rapport coût-efficacité ?

Received: 4 February 2022 | Accepted: 7 February 2022
DOI: 10.1002/ajh.26497

RESEARCH ARTICLE

Cost-effectiveness of second-line therapies in adults with chronic immune thrombocytopenia

George Goshua[1,2] | Pranay Sinha[2,3] | Natalia Kunst[4] | Lauren Pischel[5,6] | Alfred Ian Lee[1] | Adam Cuker[7]

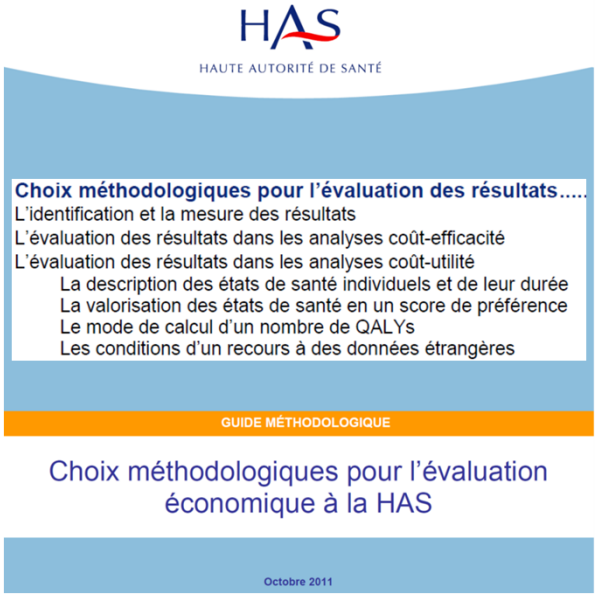


TABLE 2 Baseline cost-effectiveness analysis and probabilistic sensitivity analysis

#	Treatment strategy	Aligns with guidelines?	Cost ($ USD)	QALYs	ICER ($ USD per QALY)	Net monetary benefit ($ USD)	95% Credible interval (net monetary benefit)
5	Splenectomy –> R –> TRA	No	376 350	12.08	–	1 983 417	[1 831 036–2 061 149]
4	R –> splenectomy –> TRA	Yes	387 305	12.10	529 291	1 976 504	[1 829 135–2 053 408]
1	Splenectomy –> TRA –> R	Yes	472 118	12.13	3.0 million	1 897 261	[1 726 838–1 992 321]
3	R –> TRA –> splenectomy	Yes	794 637	12.14	Dominated	1 576 466	[1 388 454–1 696 599]
6	TRA –> splenectomy –> R	No	1 061 539	12.30	3.5 million	1 340 559	[1 111 919–1 487 970]
2	TRA –> R –> splenectomy	Yes	1 063 416	12.28	Dominated	1 334 003	[1 108 413–1 696 599]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; R, rituximab; TRA, thrombopoietin receptor agonist (romiplostim or eltrombopag); USD, United States Dollar.

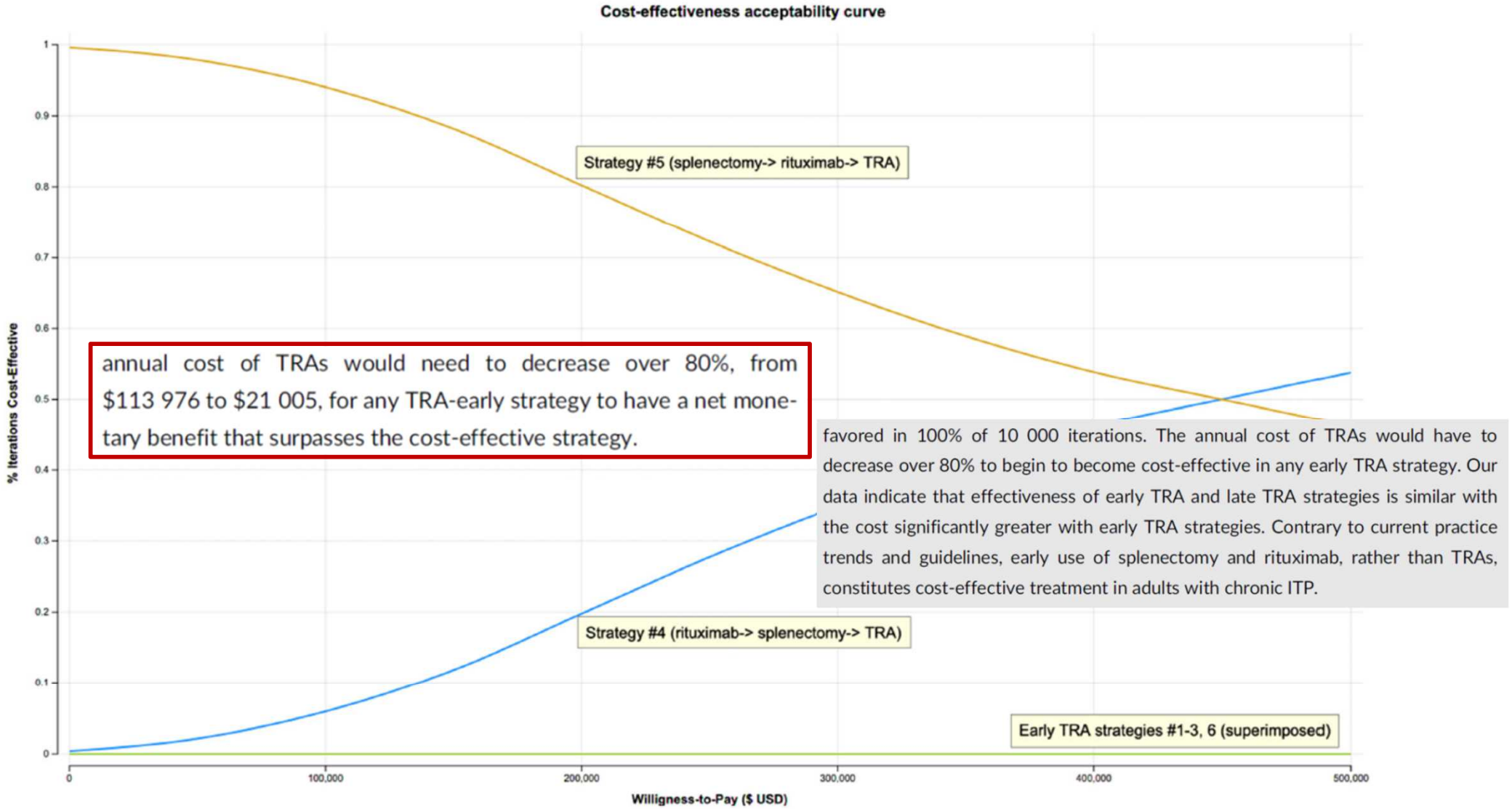


FIGURE 2 Cost-effectiveness acceptability curve. At a willingness-to-pay of $195 300, strategy #5 is favored in 81% and strategy #4 in 19% of 10 000 iterations. Early TRA therapy strategies (#1–3, 6) are favored in 0% of 10 000 iterations. TRA, thrombopoetin receptor agonist

Ttt de 2nde ligne du PTI : quel rapport coût-efficacité ?

Annexe 6.
Critères pouvant être pris en compte pour le choix du traitement de seconde ligne au cours du PTI de l'adulte

Facteurs pouvant être pris en compte dans le choix du traitement de seconde ligne	Traitements de seconde ligne			
	Splénectomie	Rituximab	Agonistes du récepteur de la TPO	Dapsone ou Danazol
Avis et préférence du patient	OUI	OUI	OUI	OUI
PTI ayant une durée d'évolution ≤ 1 an	NON			
Co-morbidité(s) sévère(s)	NON		OUI	
Patient très âgé	NON			
Troubles cognitifs si patient âgé			Préférer le romiplostim à l'eltrombopag	
Espérance de vie limitée	NON		OUI	
Antécédents d'infection sévère, hypogammaglobulinémie, exposition antérieure à une corticothérapie prolongée ou des immunosuppresseurs	À EVITER	À EVITER	OUI	
Antécédents ou facteurs de risque de thromboses veineuses et/ou artérielles	À EVITER	OUI	À EVITER	À EVITER pour le danazol
Site de séquestration splénique ou hépato-splénique aux épreuves isotopiques si elles sont réalisées	OUI			
Coût ?