



Nouvelles approches thérapeutiques dans la GVH chronique

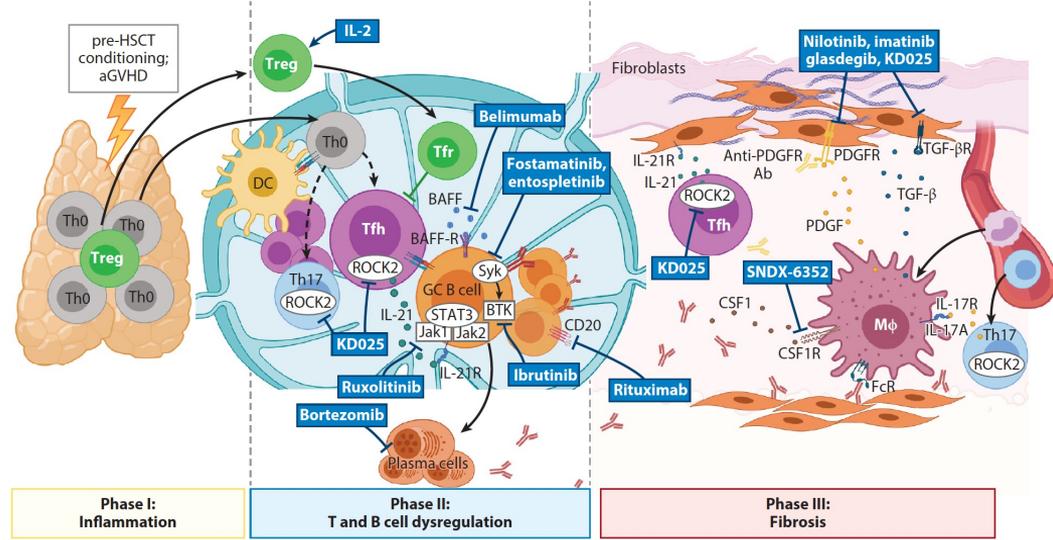
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19ème congrès de la Société Française d'Hémaphérèse, Lyon, 2026

Etat des lieux : évolution du paysage thérapeutique de la GVH chronique en 10 ans

Treatment	Study type	No. of patients	Overall response (%)	Overall survival
Therapies reported during the 2 years review period				
ECP	Phase II	23	70	78%
	Retrospective	43	65	70%/1 year
	Retrospective	9	67	
Rituximab	Phase II	37	86	72%/1 year
	Meta-analysis	111	66	
Imatinib	Phase I/II	19	79	84%/1.5 year
	Phase I/II	9	22	78%/1.5 year
	Retrospective	14	50	75%/1.5 year
Pentostatin	Phase II	51	53	60%/3 year
	Retrospective	18	56	34%/1 year
MSC infusions	Phase I/II	19	74	78%/2 year
	Phase I/II	8	50	
Mycophenolate mofetil	Retrospective	23	26 ^a	96%/1 year
	Retrospective	11	64	67%/1 year
	Retrospective	34	76	72%/3 year
mTOR inhibitor				
Other therapies summarized in recent reviews				
Calcineurin inhibitor				
High-dose methylprednisolone				
Methotrexate				
Thalidomide				
Hydroxychloroquine				
Clofazimine				
Thoracoabdominal irradiation				
Alefacept				
Infliximab				

20–82% overall response rates reported



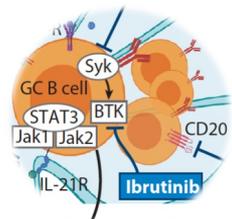
Inamoto et Flowers, Curr. Op. Hematol, 2011

Hill et al., Ann Rev Immunol, 2021

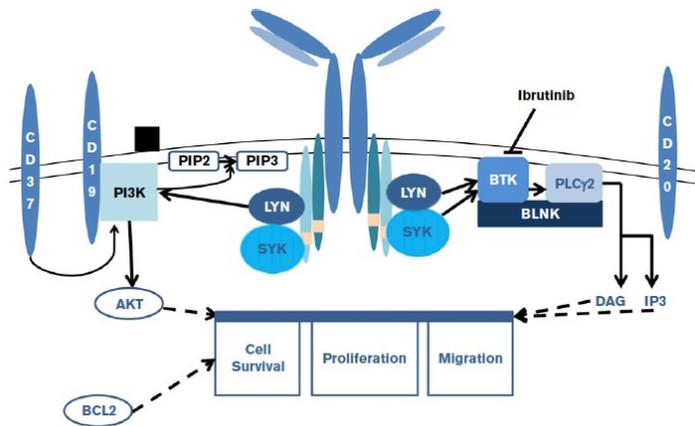
Peut-on faire mieux que le standard de la corticothérapie à 1 mg/kg en première ligne ?

- Diminuer le recours à une deuxième ligne
- Accélérer la décroissance de la corticothérapie
- Prévenir et réduire l'apparition de la fibrose
- Éviter la corticothérapie ?

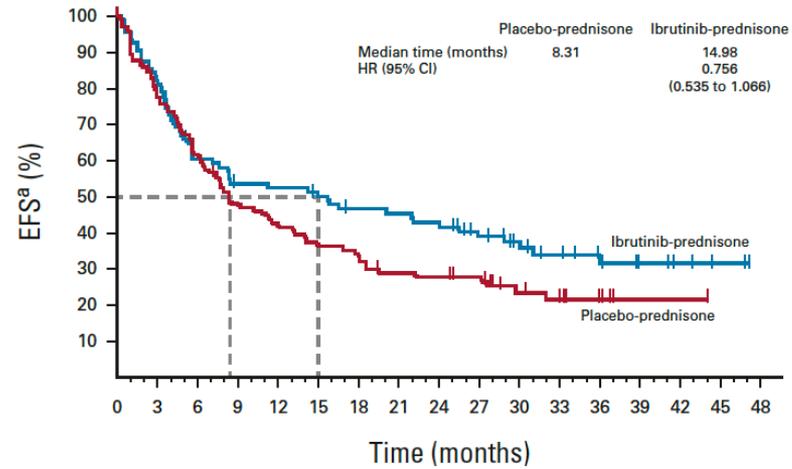
Les combinaisons thérapeutiques en première ligne : l'échec de l'ibrutinib



Ibrutinib for First-Line Treatment of Chronic Graft-Versus-Host Disease: Results From the Randomized Phase III iINTEGRATE Study



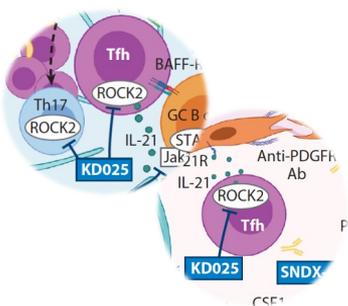
ORR 41% versus 37%, p=0.5



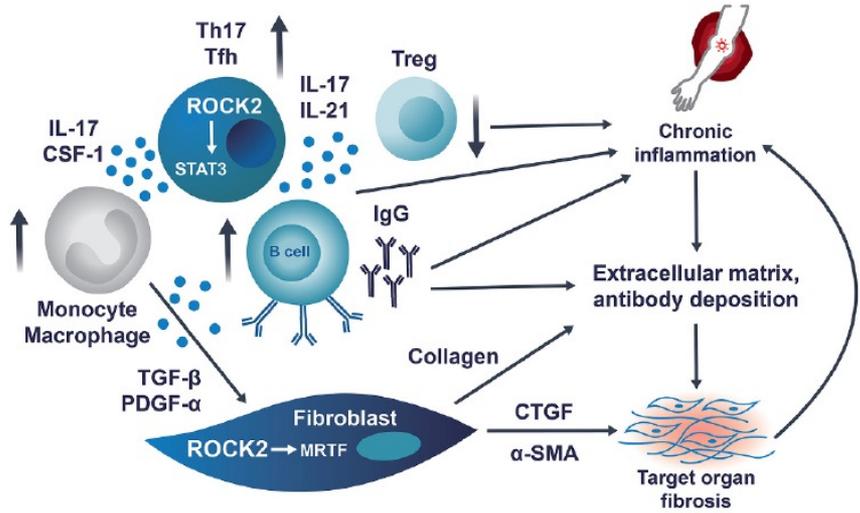
No. at risk:

Ibrutinib-prednisone	95	76	54	46	45	42	38	37	35	28	22	17	13	8	5	3
Placebo-prednisone	98	75	59	45	39	34	31	26	25	23	13	9	4	1	1	

Les combinaisons thérapeutiques en première ligne : le bélumosudil



ROCKnrol-1 : A Study to Test an Oral Medicine, Belumosudil, in Combination With Corticosteroids in Participants at Least 12 Years of Age With Newly Diagnosed Chronic Graft Versus Host Disease.

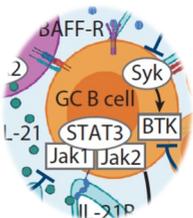


Double hit : cibler l'inflammation et la fibrose par l'inhibition de la voie ROCK1/2

260 inclusions prévues
Essai multicentrique international, randomisé et en double aveugle

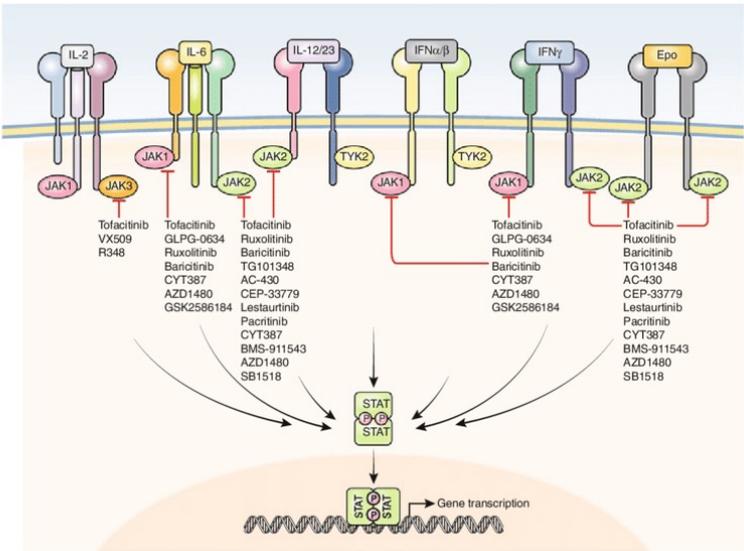
Arrêt précoce de l'essai en 2025

Les combinaisons thérapeutiques en première ligne : l'itacitinib



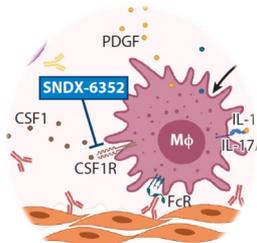
GRAVITAS-309: A Phase 2/3 Study of Itacitinib and Corticosteroids as Initial Treatment for Chronic Graft-Versus-Host Disease

Itacitinib (INCB039110) and Extracorporeal Photopheresis (ECP) for First-Line Treatment in Chronic GVHD (FLIGHT)



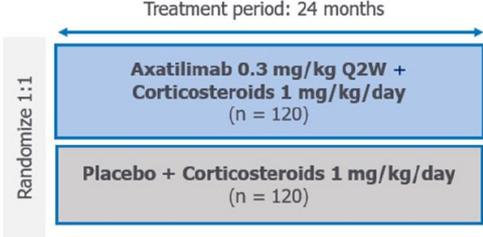
- Inhibition de JAK1 en combinaison avec les corticoïdes en première ligne ou en combinaison avec la PCE
- Essai multicentrique international, randomisé et en double aveugle
- Arrêt précoce pour futilité

Les combinaisons thérapeutiques en première ligne : les essais anti CSF-1



INCA34176-357 : A phase 3, randomized, double-blind, placebo-controlled study of axatilimab and corticosteroids as initial treatment for chronic graft-versus-host disease

- ≥ 12 years of age
- 1 allo-HSCT, any donor source/type
- Moderate to severe cGVHD
- No prior systemic therapy for cGVHD
- ≤ 7 days of systemic corticosteroids for cGVHD



Stratification factors

- cGVHD severity (moderate/severe)
- Ongoing treatment with a CNI or mTOR (yes/no)

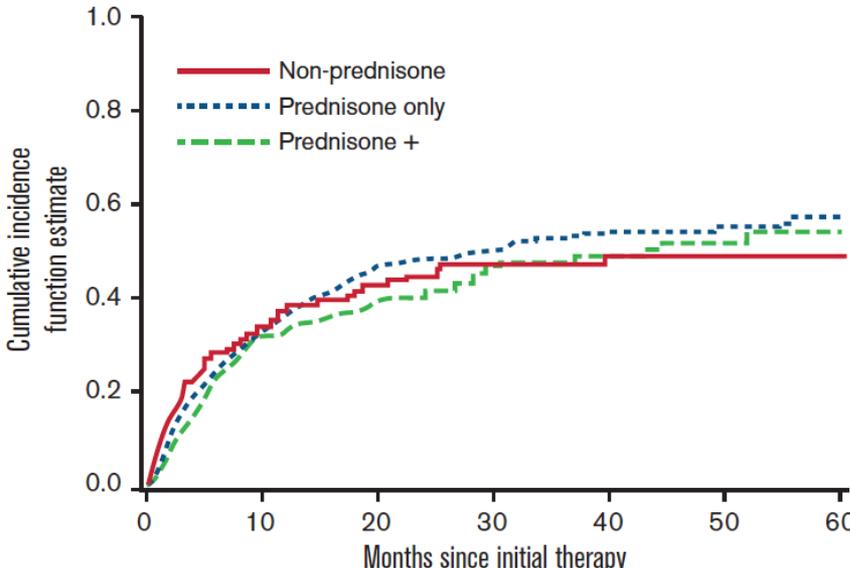
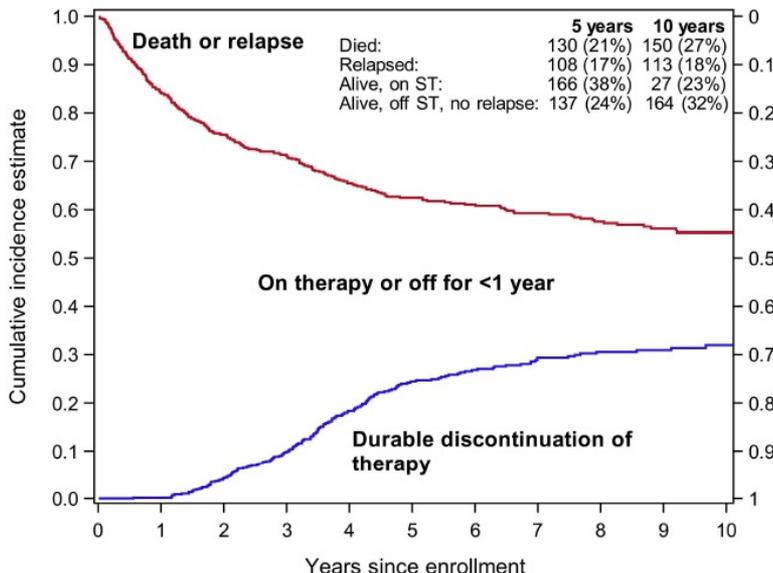
INCA34176-254: A Phase 2, Open-Label, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Axatilimab in Combination With Ruxolitinib in Participants With Newly Diagnosed Chronic Graft-Versus-Host Disease

Evaluer une stratégie de première ligne sans corticoïdes :
ruxo versus ruxo + axatilimab versus corticoïde 1mg/kg

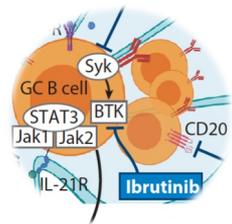
La problématique de la deuxième ligne et des GVHc cortico-résistantes

Comment définir la cortico-résistance dans la GVH chronique ?

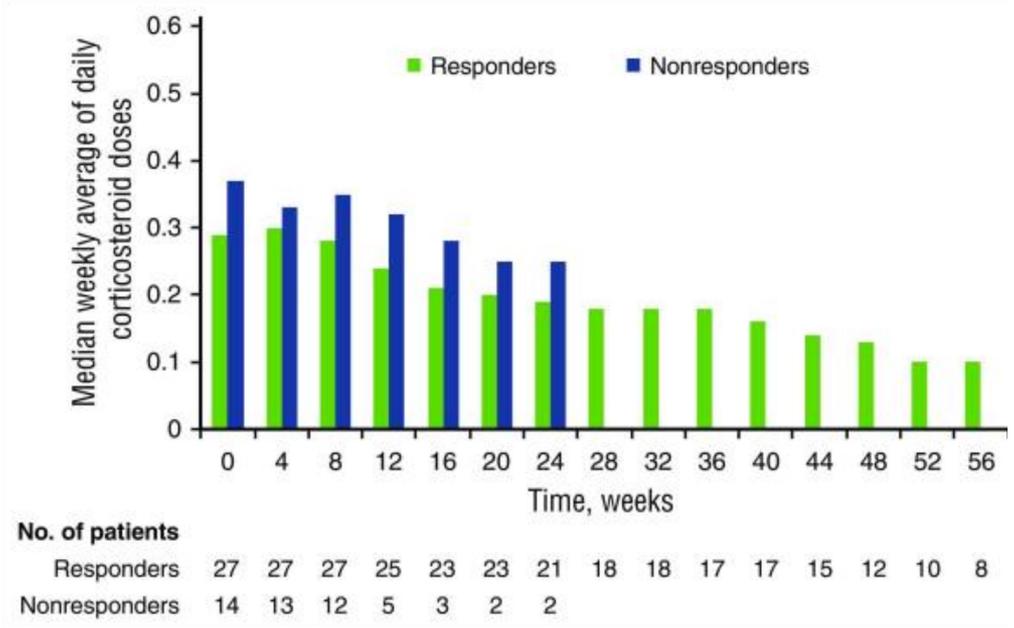
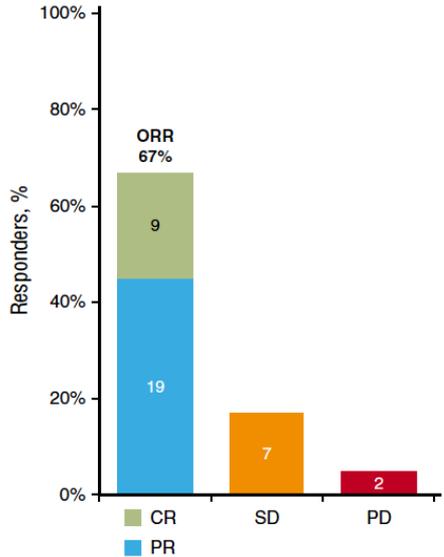
- Progression à 2 semaines sous corticoïdes 1mg/kg
- Stabilité de la maladie pendant 4 à 8 semaines sous au moins 0,5mg/kg/j
- Impossibilité de réduire les corticoïdes < 0,5mg/kg/j



La deuxième ligne dans les GVH chroniques cortico-résistantes : l'ibrutinib



Essai de phase 2, n=47 après échec de plus de 1 ligne de traitement dans la GVH chronique, ORR = 67% (FDA approved)

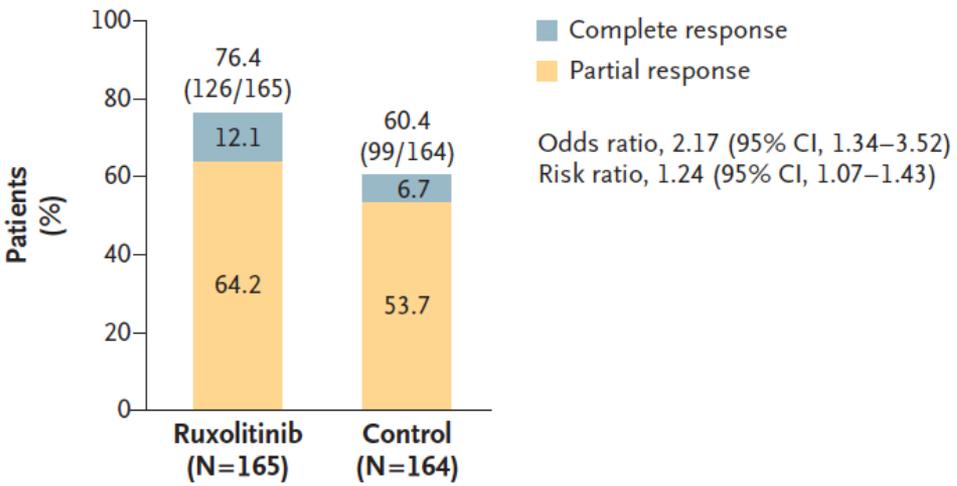


La deuxième ligne dans la GVH chronique cortico-résistante : le ruxolitinib

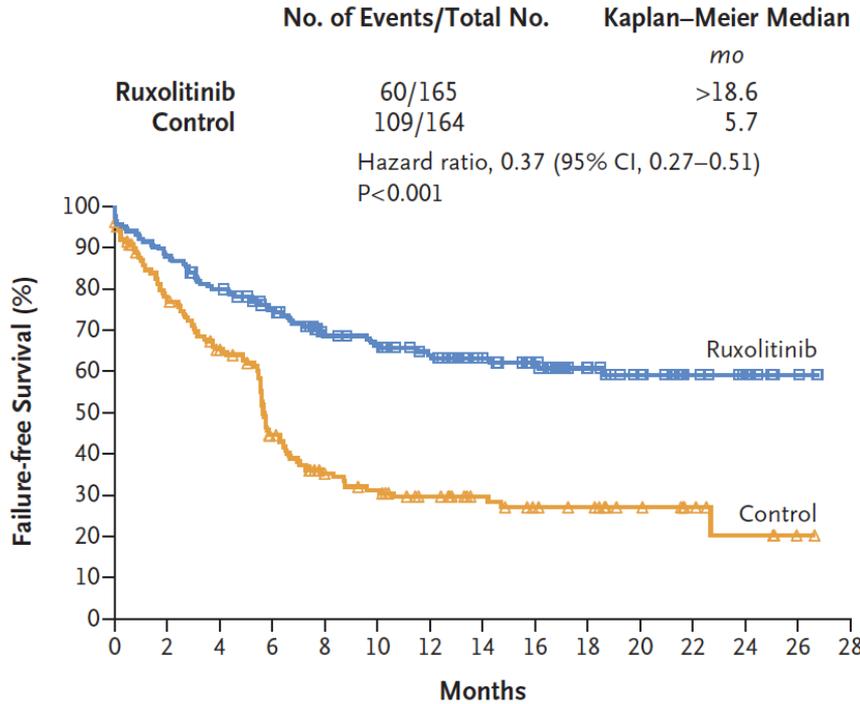
Reach3 et le positionnement du ruxolitinib

- Best ORR ruxo versus BAT : 76,4% versus 60,4%

Best Overall Response

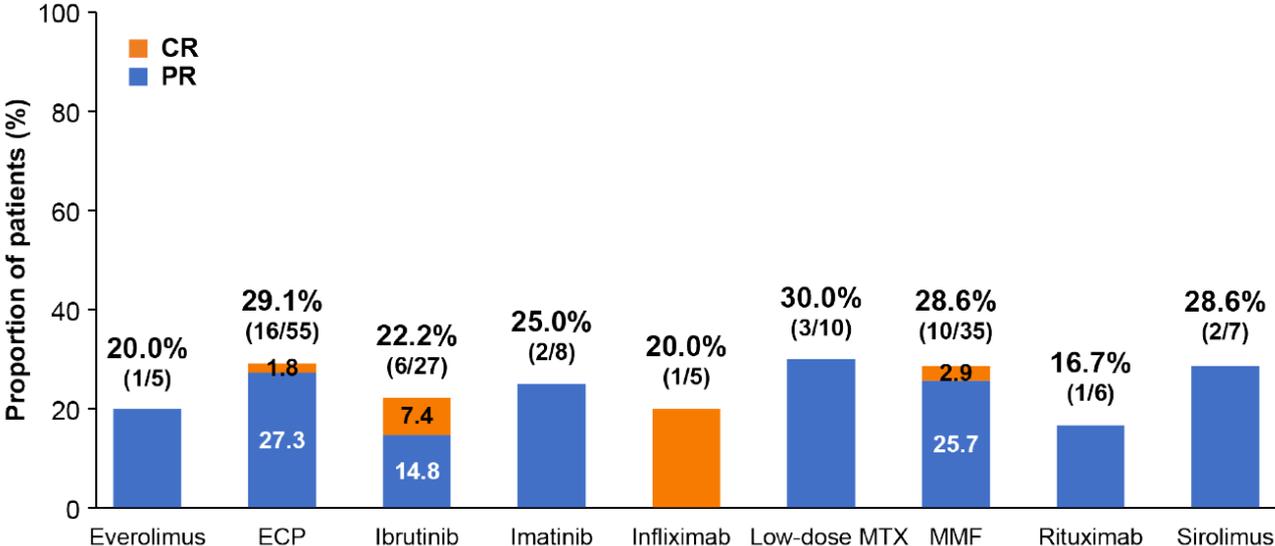


Failure-free Survival



La deuxième ligne dans la GVH chronique cortico-résistante

Résultat du BAT inférieur aux données des études rétrospectives ou de phase 2



Données antérieures issues des phases 1/2 ou rétrospectives:

76% 65-70% 67% 22-79% 26-64% 66-86% 76%

Les alternatives au ruxolitinib : les autres inhibiteurs de Jak

Drug/Therapy	Target(s)	Indication	Mechanism	Key Trial/Study	FDA Approval	Phase	Route	Clinical Efficacy	Toxicity Profile
Ruxolitinib	JAK1/2 Inhibitor	Steroid-refractory aGVHD and cGVHD	Blocks JAK1/2, reduces IFN- γ , IL-6	REACH2, REACH3	Yes (2019/2021)	Approved	Oral	High ORR in both aGVHD and cGVHD; durable responses	Cytopenias (anemia, thrombocytopenia), infections
Baricitinib	JAK1/2 Inhibitor (JAK3 sparing)	Investigational GVHD therapy	Effective Treg preservation and Th1/Th17 suppression; promotes epithelial healing	Preclinical, early-phase	No	Preclinical	Oral	Effective in preclinical models; improved Treg:Teff ratio	Thrombotic risk, lipid alterations (preclinical)
Itacitinib	JAK1-selective Inhibitor	Frontline aGVHD (modest effect)	Selective JAK1 blockade	GRAVITAS-301	No	Phase III	Oral	Modest ORR; failed to meet primary endpoint	Less cytopenia; GI toxicity, infections
Pacritinib	JAK2/FLT3 Inhibitor	Investigational GVHD therapy	Suppresses STAT3 ⁺ CD4 ⁺ T cells; preserves GvL effect	Preclinical + Phase I	No	Phase I	Oral	Promising preclinical efficacy; early clinical data emerging	GI upset, cytopenias, potential QTc prolongation

Pas de données disponibles sur les autres inhibiteurs comme l'itacitinib (JAK1), le baricitinib (JAK1/2) ou le pacritinib (JAK2/FLT3)

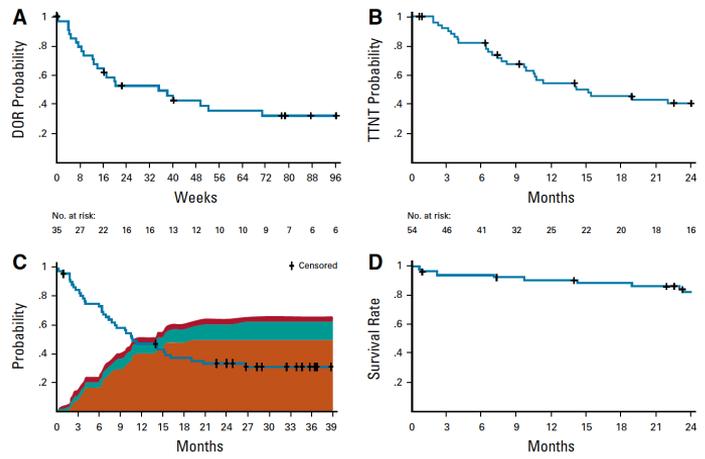
- A Pilot Study of INCB039110 (Itacitinib) for the Treatment of Steroid Refractory Chronic Graft-Versus-Host Disease : arrêt précoce
- A Phase 1/2 Study of Baricitinib, a JAK1/2 Inhibitor, in Chronic Graft-Versus-Host Disease (cGVHD) After Allogeneic Hematopoietic Stem Cell Transplantation (SCT) : inclusion terminée en attente des résultats

L'incertitude de la 3^{ème} ligne et au delà : le belumosudil

ROCK2 Inhibition With Belumosudil (KDO25) for the Treatment of Chronic Graft-Versus-Host Disease

Journal of Clinical Oncology*

N=54 after 1 to 3 LOT in moderate to severe cGVHD
 200mg/d vs 200mgx2/d vs 400mg/d
ORR = 65% (51-77)
 Failure Free Survival : 76% at 6 months and 47% at 12 months

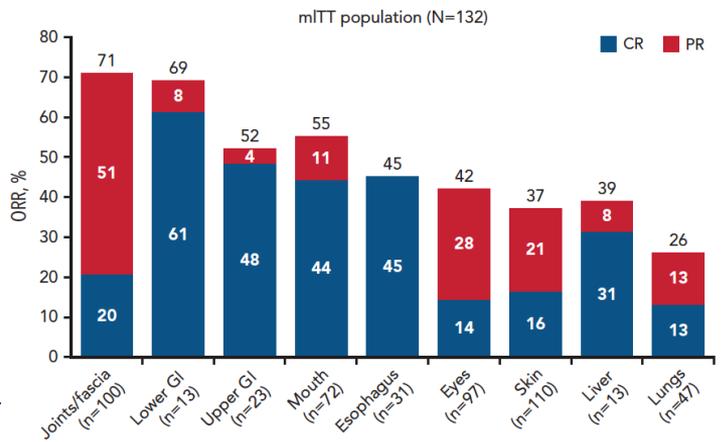


TRANSPLANTATION

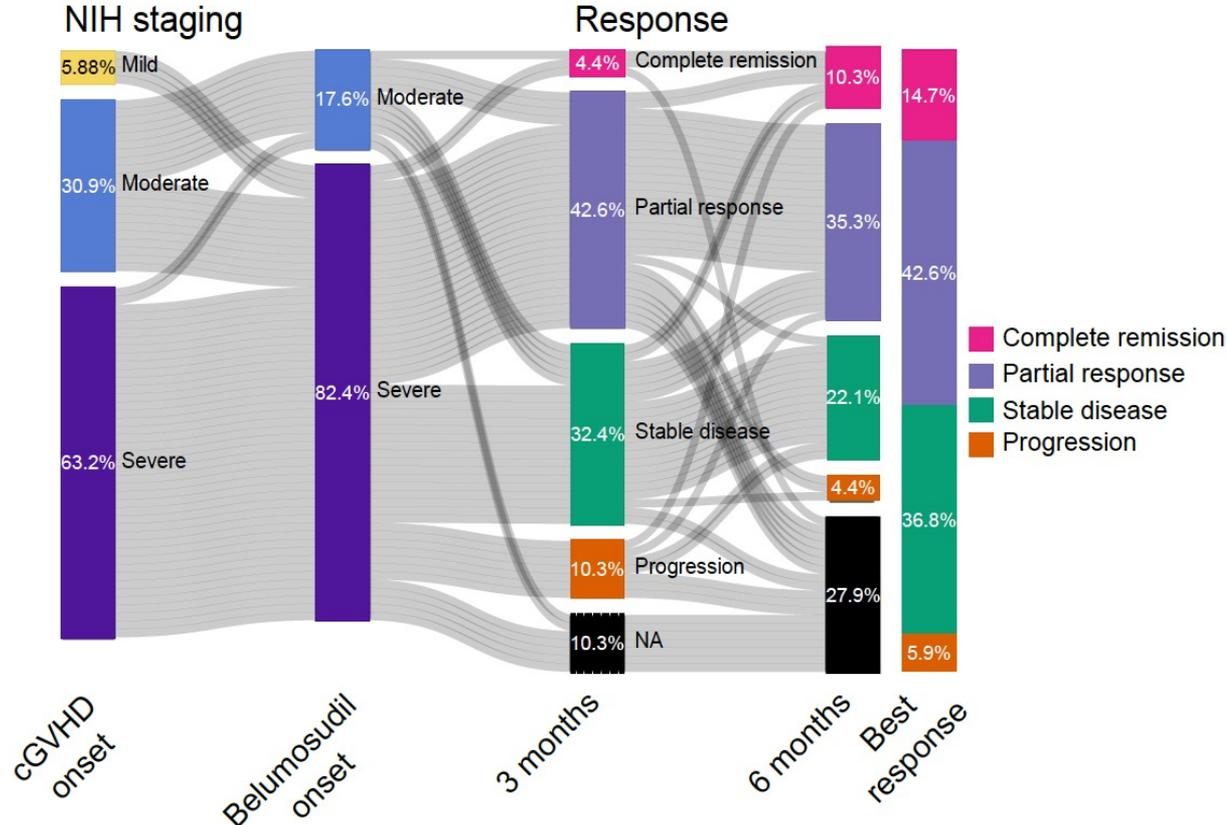
Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study

blood* 2 DECEMBER 2021 | VOLUME 138, NUMBER 22

N=132 after 2 to 5 LOT in moderate to severe cGVHD
 200mg/d vs 200mgx2/d
ORR = 76% (68-83)
 Failure Free Survival : 75% at 6 months, 56% at 12 months



L'incertitude de la 3^{ème} ligne et au delà : le belumosudil, données françaises

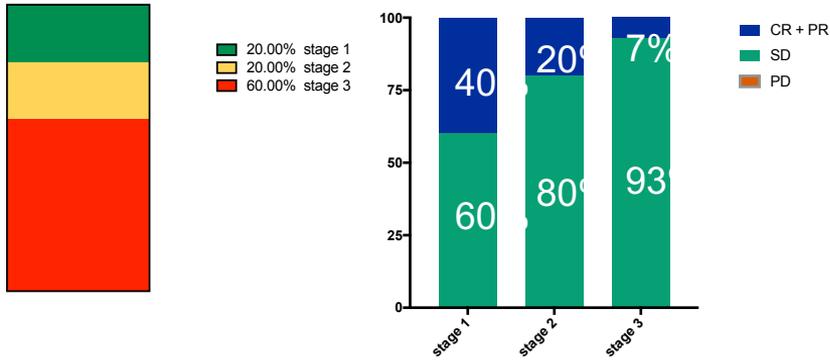
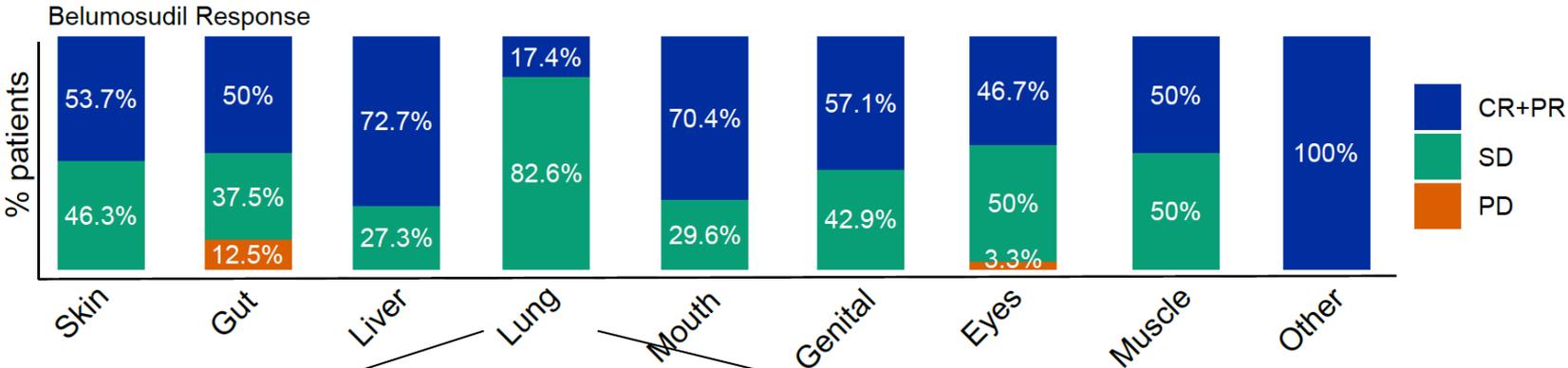


N=68 patients
ORR at 6 months : 45.6%
Best ORR : 57.3%
Mean delay of best response : 183 days (14-560)

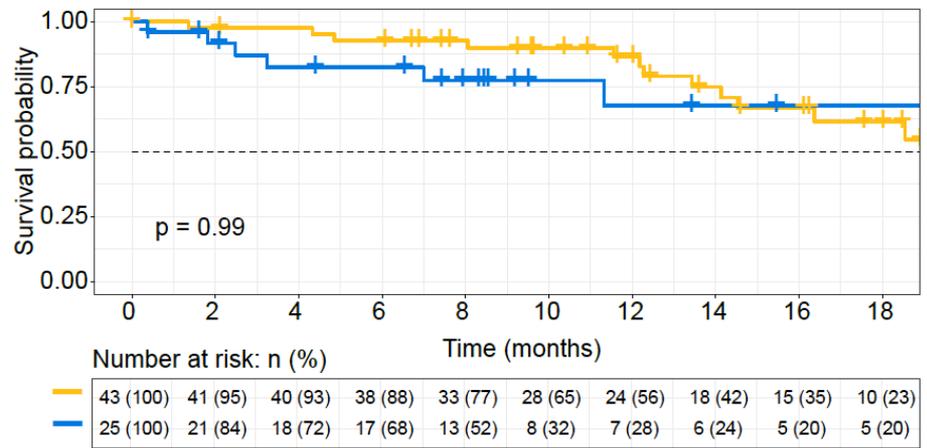
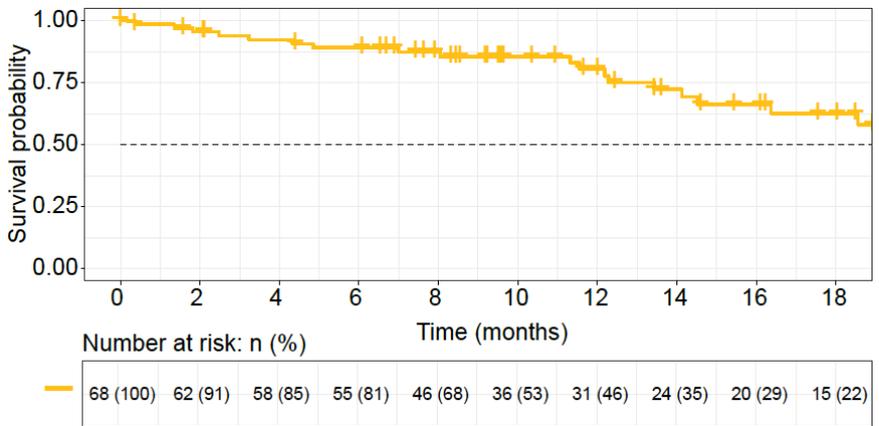
Posology:
200mg, n=23 (34%)
200mg BID, n=45 (66%)

Drug association :
PPI, n=46 (67%)
Posaconazole, n=9 (13%)
Isavuconazole, n=12 (17.6%)

L'incertitude de la 3^{ème} ligne et au delà : le belumosudil, données françaises



L'incertitude de la 3^{ème} ligne et au delà : le belumosudil, données françaises



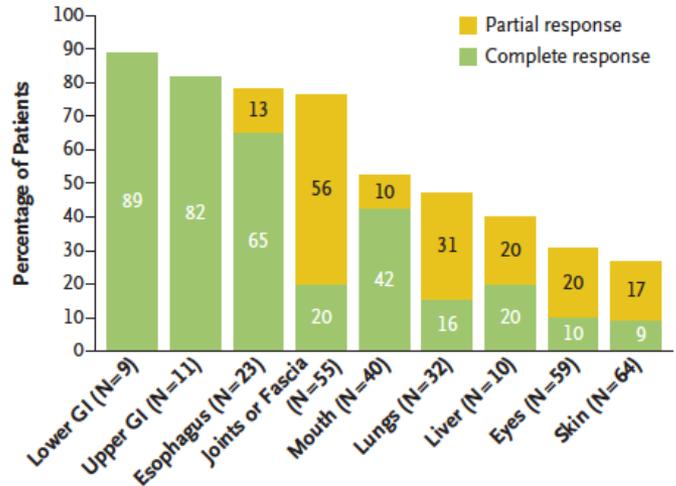
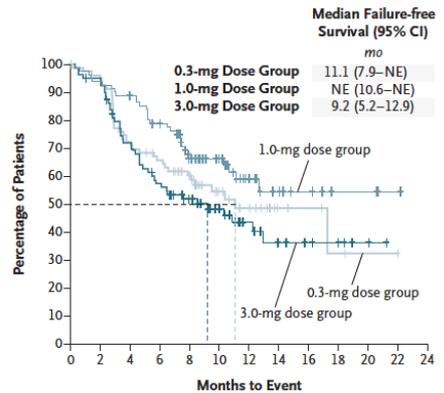
Failure-free survival:
 89% at 6 months
 80% at 12 months

- + Belumosudil in > 3rd line treatment
- + Belumosudil in 3rd line treatment

L'incertitude de la 3^{ème} ligne et au delà : l'axatilimab

AGAVE-201 : essai de phase 2 avec randomisation de 3 doses, n=241 patients avec cGVHD en échec de deux lignes de traitement.

ORR : 0.3mg : 74%, 1mg : 67%, 3mg : 50%



No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24
0.3-mg dose group	80	75	57	50	38	20	14	6	4	2	1	1	0
1.0-mg dose group	81	76	71	61	43	31	17	10	7	3	3	1	0
3.0-mg dose group	80	75	55	43	32	22	13	8	6	5	2	0	0

Wolff et al., NEJM, 2024

A Phase 3, Randomized, Open-Label Study of Axatilimab Versus Best Available Therapy in Participants With Chronic Graft Versus Host Disease After at Least 2 Prior Lines of Systemic Therapy : inclusion suspendue

Les innovations dans la GVH chronique : la double inhibition JAK/ROCK

JAK/Rock Inhibitor Rovadicitinib for Glucocorticoid-Refractory or -Dependent Chronic Graft-Versus-Host Disease: Updated Results of Multicenter, Phase 1b/2a Trial

ASH 2024

Rovadicitinib (inhibiteur JAK1/2 +ROCK1/2) : essai de phase 1b/2, n=44 avec deux doses : 10mg BID ou 15mg BID

- cGVHD modérée (36.4%) ou sévère (63.6%) en échec d'au moins une première ligne
- Best ORR : 10mg (96.6%) et 15mg (80%)
- ORR 24 semaines : 10mg (75.9%) et 15mg (46.7%)
- profil de tolérance à évaluer (Serious TEAE = 20%) : infections viral et pulmonaire, neutropénie

Les innovations dans la GVH chronique : les inhibiteurs oraux de CSF-R1

A Phase II Study to Evaluate the Efficacy and Safety of Pimicotinib (ABSK021) in Chronic Graft Versus Host Disease (cGvHD) after 1 or More Lines of Systemic Treatment

ASH 2024

Pimicotinib : essai de phase 2 ouvert avec un inhibiteur oral du CSF1R avec escalade de dose (5,10,20 et 25mg), n=28 patients avec cGVHD en échec d'au moins une première ligne

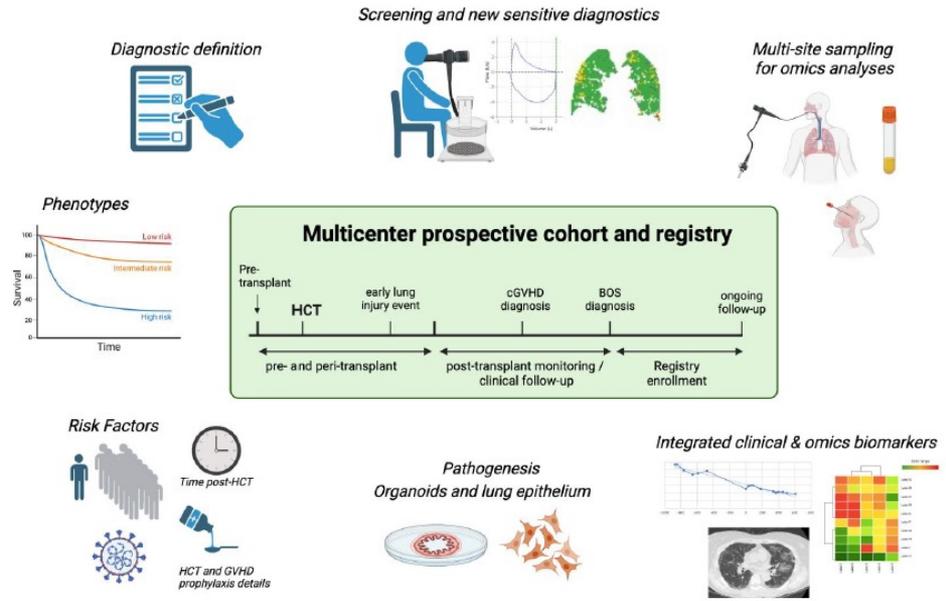
- 64.3% de cGVHD sévère
- ORR : 5mg (100%), 10mg (66.7%), 20mg (57.9%) et 25mg (33.3%)
- profil de tolérance à évaluer (Serious TEAE = 21.4%)

Les innovations dans la GVH chronique : l'enjeu majeur de la BOS

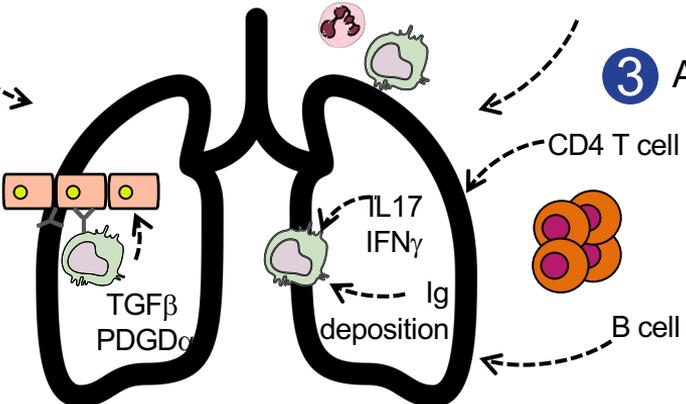
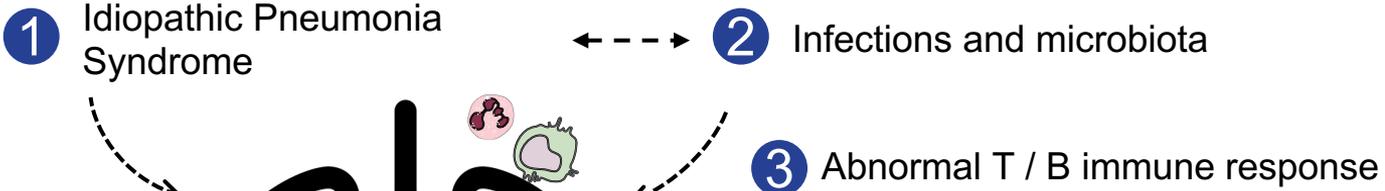
Addressing Knowledge Gaps in the Early Detection of Bronchiolitis Obliterans Syndrome after Hematopoietic Cell Transplantation

An Official American Thoracic Society Research Statement

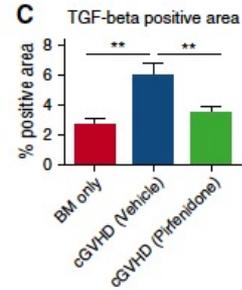
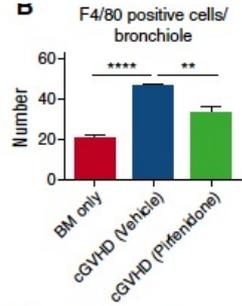
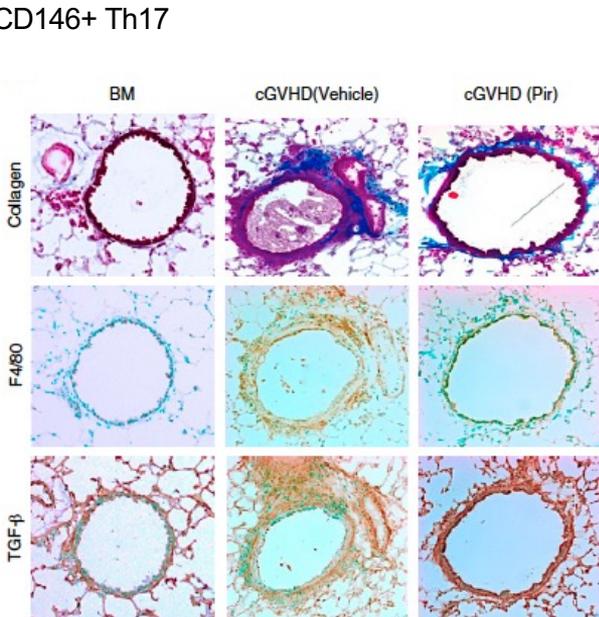
Guang-Shing Cheng, Ajay Sheshadri, Jane Turner, Kirsten M. Williams, Joe L. Hsu, Thomas Agoritsas, M. Haider Ali, Louise Bondeelle, Guy Bouguet, Pascal Chanez, Kenneth R. Cooke, Craig J. Galban, Samuel Goldfarb, Teal S. Hallstrand, Sarah Johnson, David C. L. Lam, David Michonneau, David N. O'Dwyer, Sophie Paczesny, Husham Sharifi, Jamie L. Todd, Daniel Wolff, Hemang Yadav, Gregory A. Yanik, and Anne Bergeron; on behalf of the American Thoracic Society Assembly on Clinical Problems



Les innovations dans la GVH chronique : l'enjeu majeur de la BOS



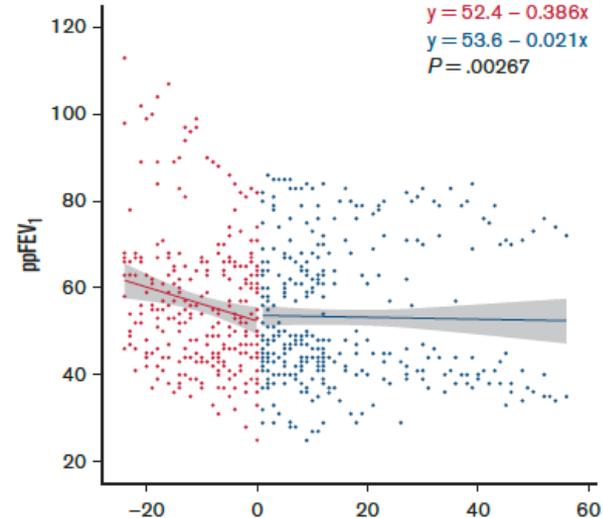
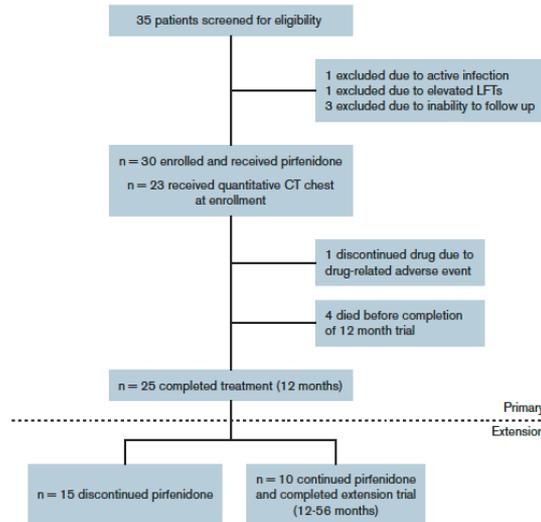
- Pirfenidone reduces macrophage infiltration and TGFβ production
- Pirfenidone is associated with reduced Ig deposition and fibrosis, and improvement of pulmonary function test



Les innovations dans la GVH chronique : l'enjeu majeur de la BOS

Pirfenidone for the treatment of bronchiolitis obliterans syndrome related to chronic graft-versus-host disease

Husham Sharifi,^{1,2} Carson Tyler Moss,² Zayan Musa,³ Alexander Bell,⁴ Christian O'Donnell,² Carlos Hernandez Borges,^{1,2} Efthymia Iliana Matthaïou,⁵ Laura Johnston,⁶ Craig J. Galban,⁴ Ajay Sheshadri,⁷ Gregory Yanik,⁸ Guang-Shing Cheng,^{9,10} and Joe L. Hsu^{1,2}



Merci pour votre attention



Questions : david.michonneau@aphp.fr