Futuro en EICRc: Novedades terapéuticas

15th November 2023

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I have had a financial interest/arrangement or affiliation with the organization(s) listed

Affiliation/Financial Relationship

1. Honoraria for lectures:	**Takeda, BMS , Gilead, Sanofi**
2. Honoraria for advisory board activities:	**Merck, Jazz Pharma**
3. Participation in clinical trials (PI):	**Atara, Takeda**
4. Research funding:	**Gilead**

Summary

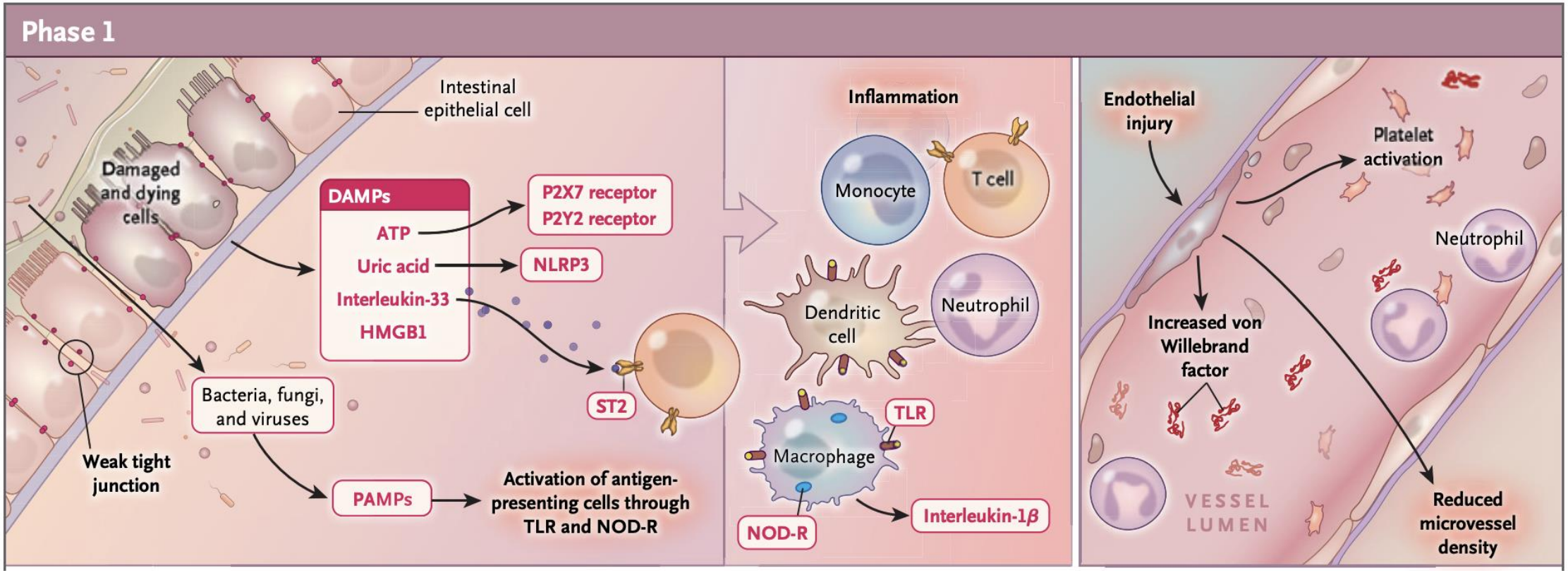
1) Pathogenesis in chronic GVHD

2) Newer approved drugs: ibrutinib, ruxolitinib, belumosudil

3) Early clinical development drugs: axalitimab, abatacept, pirfenidone

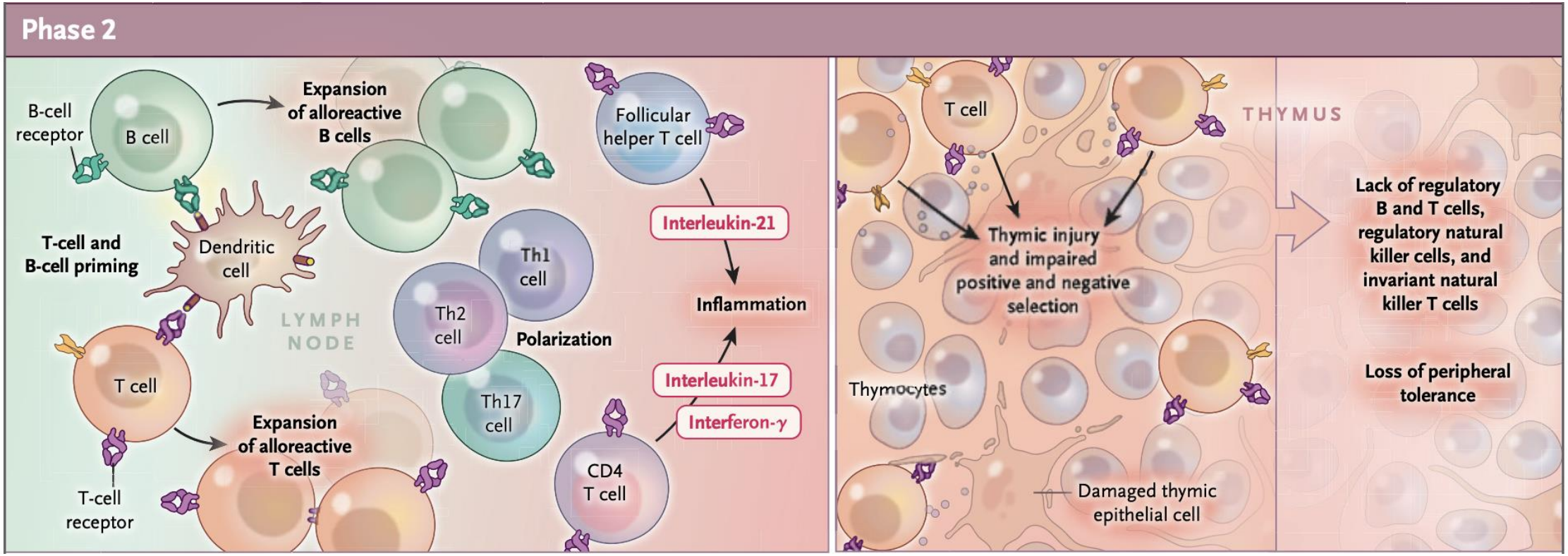
4) Conclusions

Phase 1: tissue damage



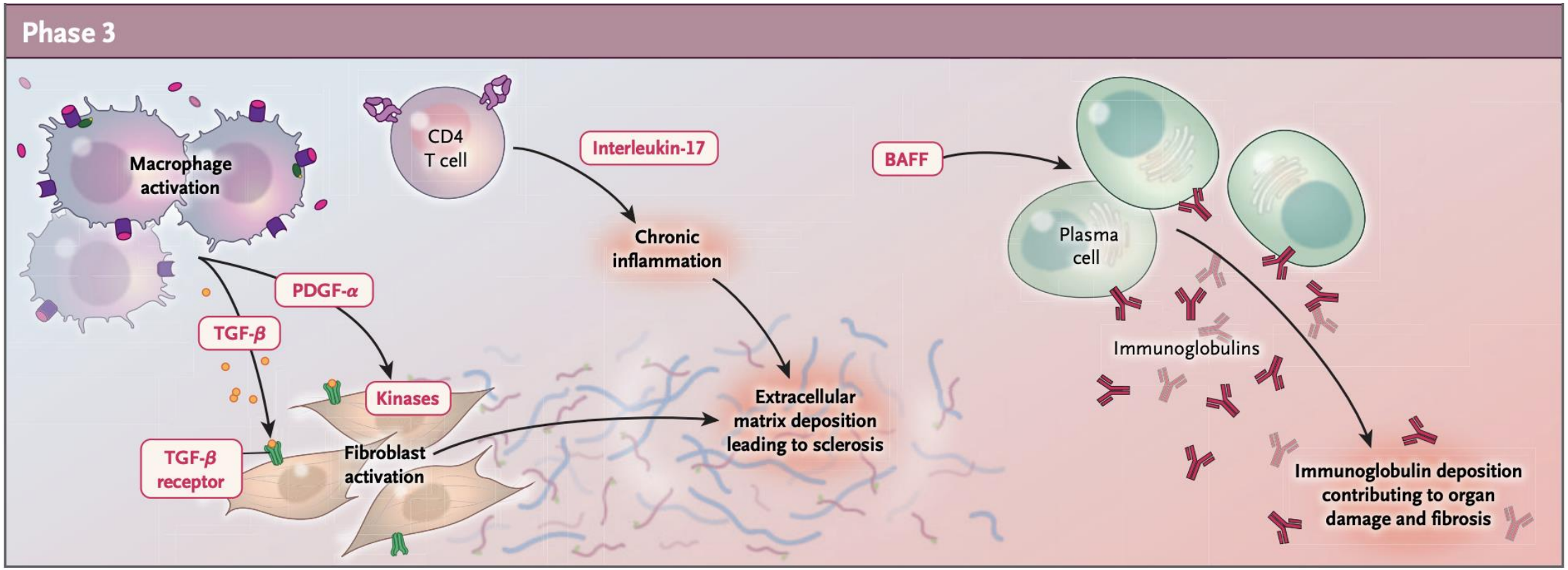
Zeiser R, *N Engl J Med 2017;377:2565-79.*

Phase 2: thymic injury, B/T cell dysregulation



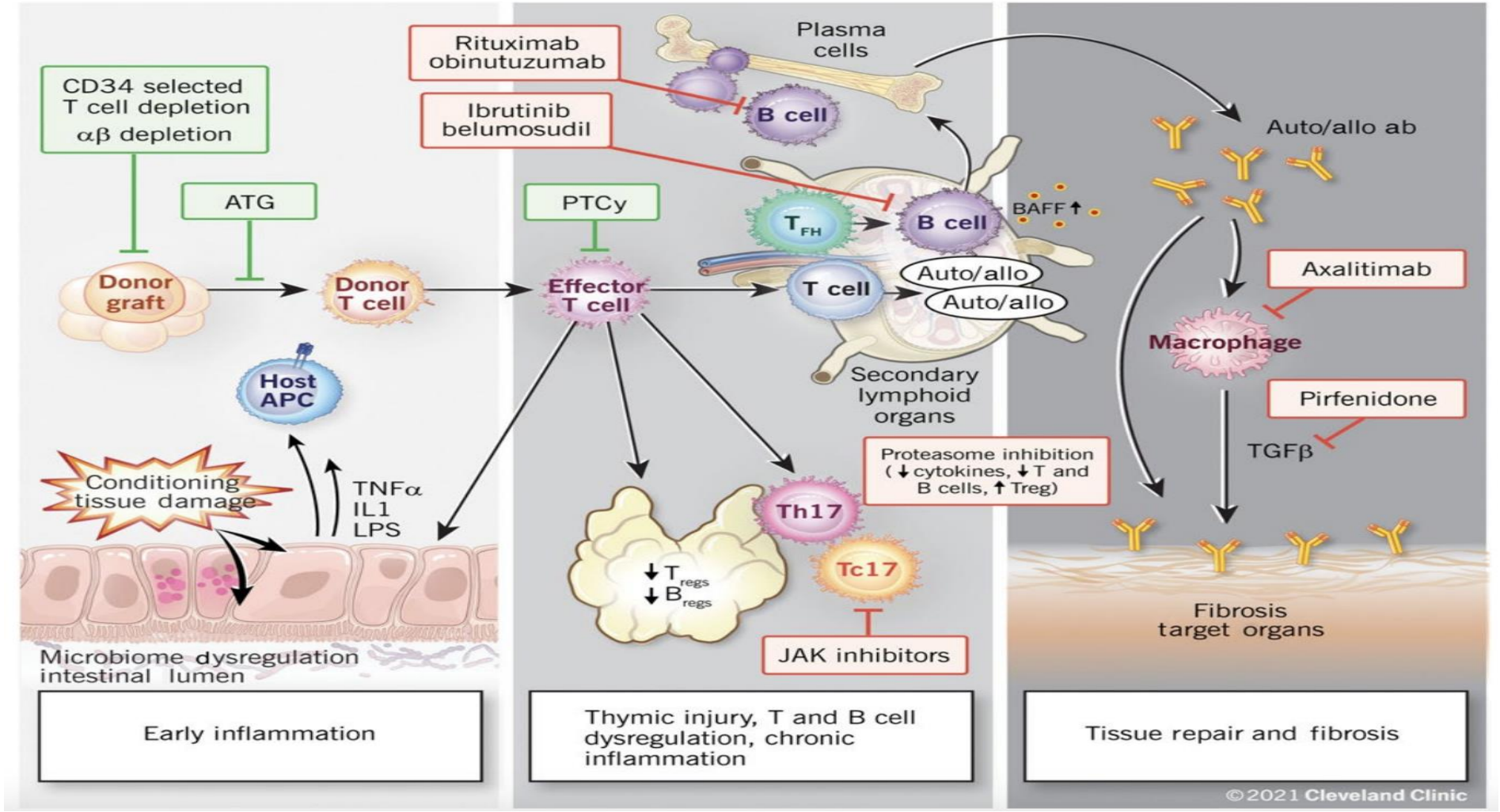
Zeiser R, *N Engl J Med 2017;377:2565-79.*

Phase 3: tissue repair and fibrosis



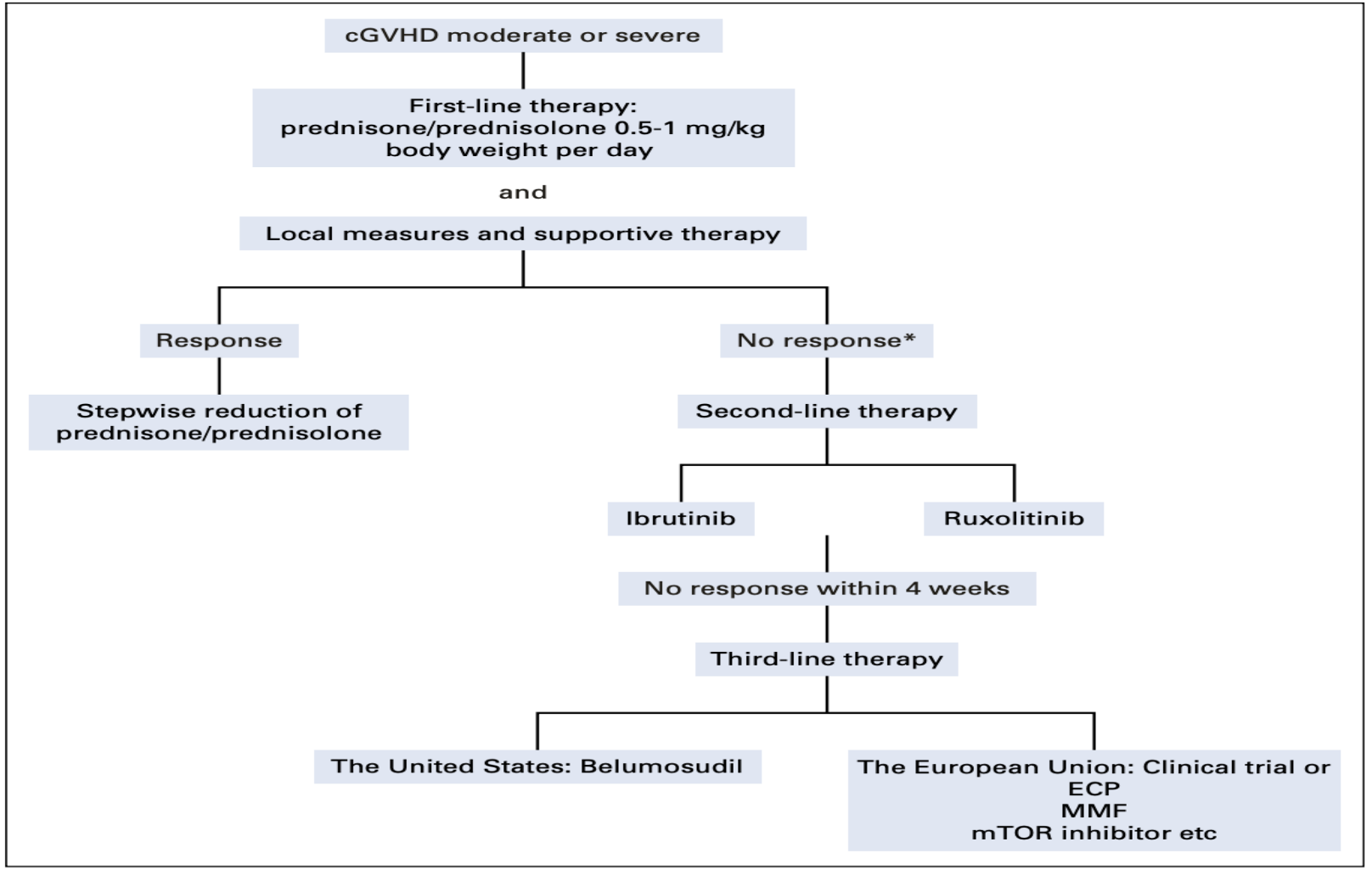
Zeiser R, *N Engl J Med 2017;377:2565-79.*

New therapeutic targets



Hamilton BK, Hematology Am Soc Hematol Educ Program. 2021 Dec 10;2021(1):648-654

Therapeutic approach USA 2023



Zeiser R, Journal of Clinical Oncology 41, no. 10 (April 01, 2023) 1820-1824

Ibrutinib* (BTK inhibitor)

Phase 1b/2 study (#NCT02195869)
Number of patients = 42
Inclusion criteria: cGVHD refractory to 1-3 previous lines of therapy
Ibrutinib dose = 420 mg/day

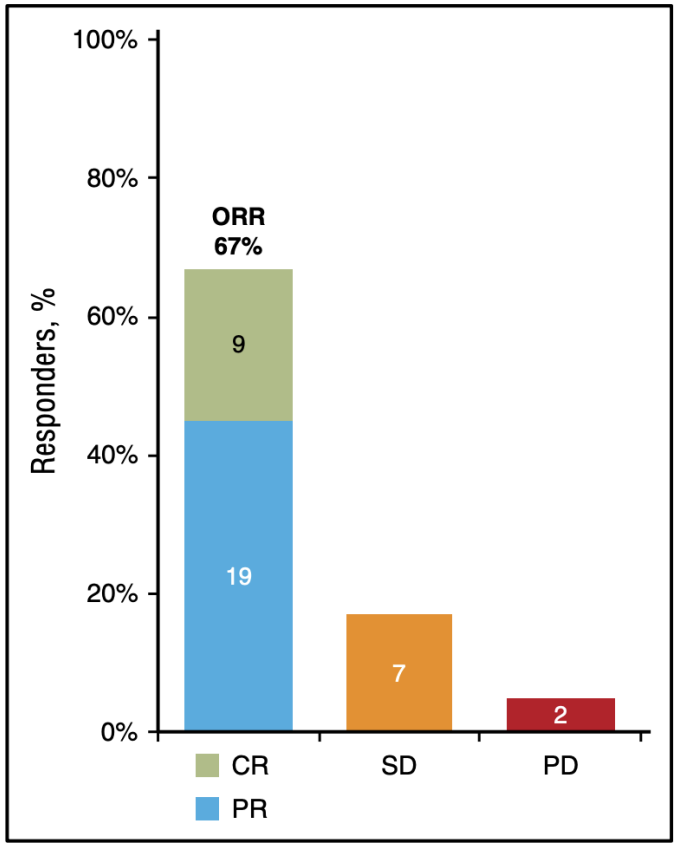
Steroid dependence of cGVHD	
Steroid-dependent cGVHD	28 (67)
Steroid-refractory cGVHD	6 (14)
Both	8 (19)
Number of involved organs	
1	6 (14)
2	24 (57)
3	9 (21)
≥4	3 (7)
Involved organ	
Mouth	36 (86)
Skin	34 (81)
Gastrointestinal system	15 (36)
Liver	3 (7)
Lungs	2 (5)

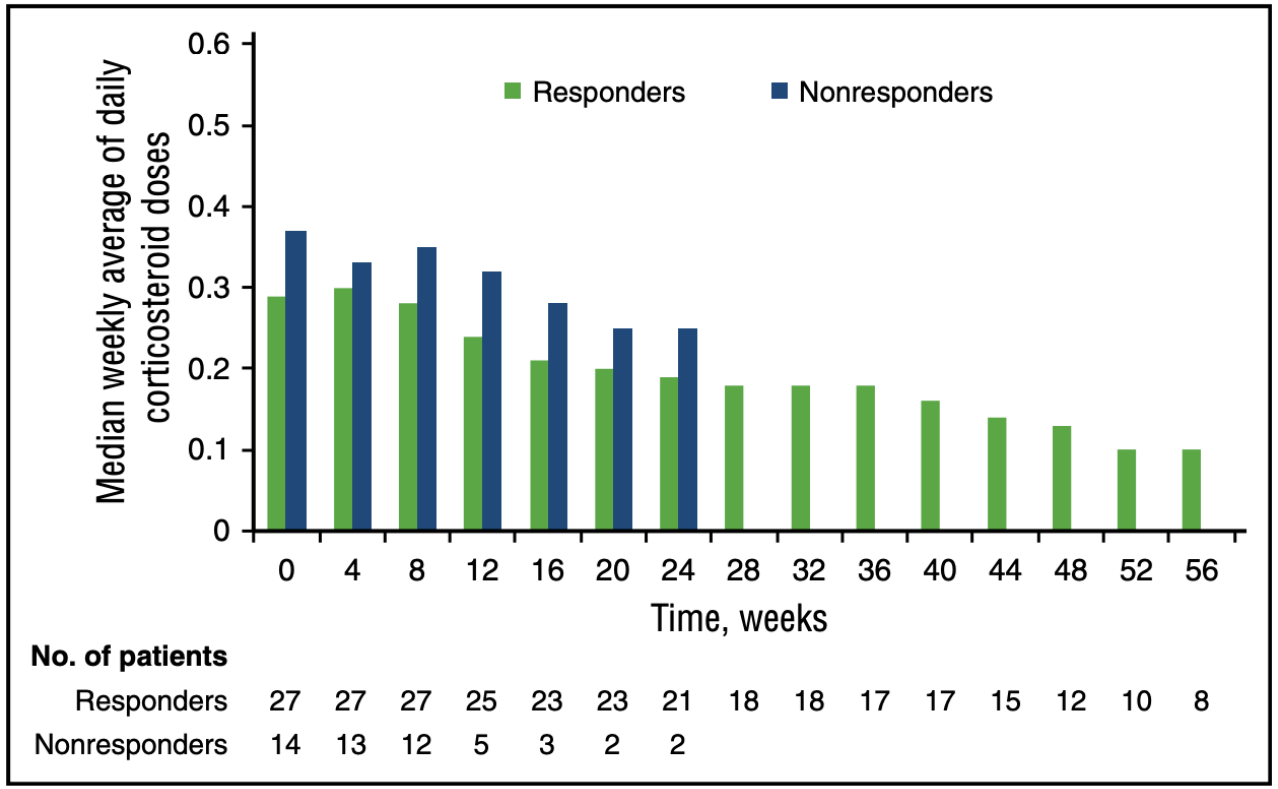
Median prior lines of treatment of cGVHD (range)	2 (1-3)
Mean prednisone dose at enrollment (range), mg/kg per day	0.31 (0.1-1.3)
Prior therapies for cGVHD	
Corticosteroids	42 (100)
Tacrolimus	21 (50)
Extracorporeal photopheresis/PUVA photochemotherapy	11 (26)
Rituximab	11 (26)
Mycophenolate mofetil	10 (24)
Cyclosporine	8 (19)
Sirolimus	7 (17)
Other immunosuppressants	2 (5)

Miklos D, Blood. 2017 Nov 23;130(21):2243-2250

*Producto no comercializado en la UE para tratamiento de la EICRc

Ibrutinib* (BTK inhibitor)





Miklos D, Blood. 2017 Nov 23;130(21):2243-2250

*Producto no comercializado en la UE para tratamiento de la EICRc

Real-life ibrutinib*

Retrospective monocentric study
53 patients with cGVHD treated with ibrutinib outside clinical trials

2-year Failure-free survival = 9%

Median Failure-free survival = 4.5 months.

ORR: CR/PR 12%; SD 64%; POD 25%

NO steroid reduction

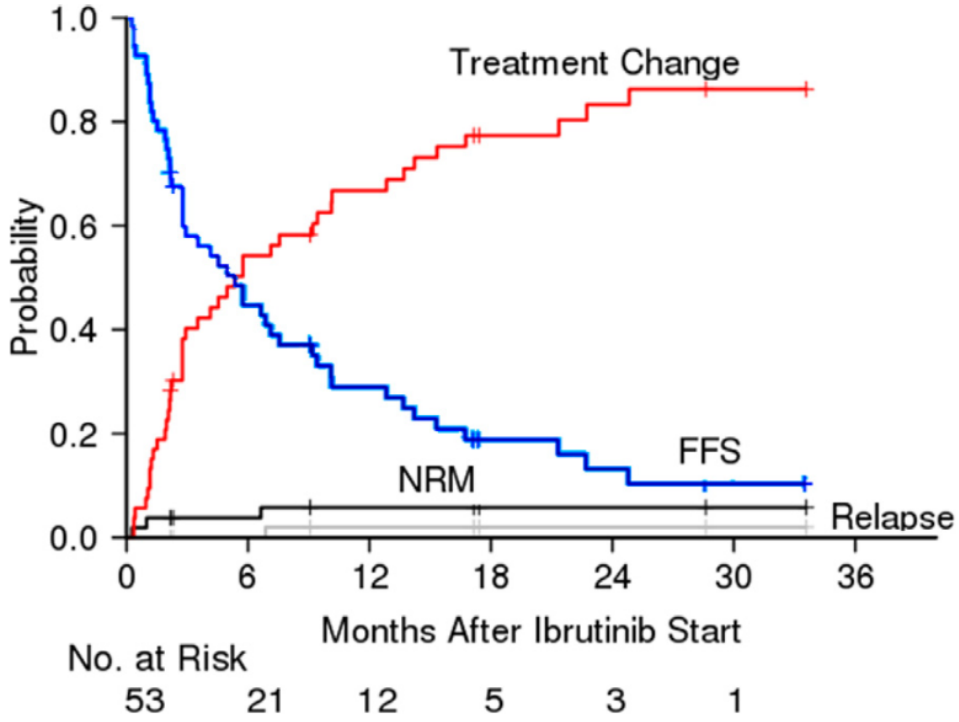


Figure 2. FFS events.

Chin K, Transplantation and Cellular Therapy 27 (2021) 990.e1990.e7

*Producto no comercializado en la UE para tratamiento de la EICRc

Ruxolitinib (JAK2 inhibitor)

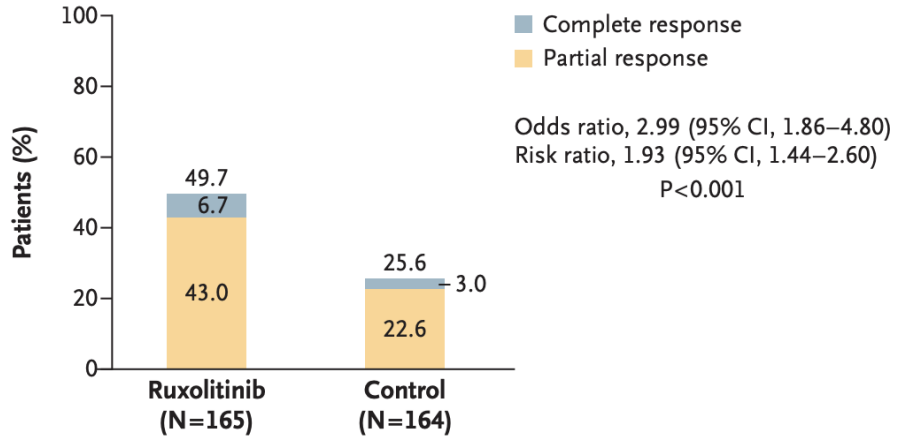
Phase 3 study (#NCT03112603, REACH 3 study)
Number of patients = 329
Inclusion criteria: cGVHD steroid-dependent or steroid-refractory
Ruxolitinb 10mg/day *versus* Best Available Treatment

Previous acute GVHD — no. (%)	92 (55.8)	88 (53.7)
Chronic GVHD severity — no. (%)†		
Mild	1 (0.6)	1 (0.6)
Moderate	67 (40.6)	74 (45.1)
Severe	97 (58.8)	89 (54.3)
Donor type — no. (%)‡		
Related	91 (54.5)	87 (52.1)
Unrelated	76 (45.5)	80 (47.9)
Previous systemic therapy for chronic GVHD or glucocorticoid-refractory or -dependent chronic GVHD — no. (%)§		
Glucocorticoid only	70 (42.4)	81 (49.4)
Glucocorticoid + calcineurin inhibitors	68 (41.2)	69 (42.1)
Glucocorticoid + calcineurin inhibitors + other systemic therapy	10 (6.1)	4 (2.4)
Glucocorticoid + other systemic therapy	14 (8.5)	9 (5.5)
Missing data	3 (1.8)	1 (0.6)

Zeiser R, N Engl J Med 2021;385:228-38

Ruxolitinib (JAK2 inhibitor)

A Overall Response at Week 24

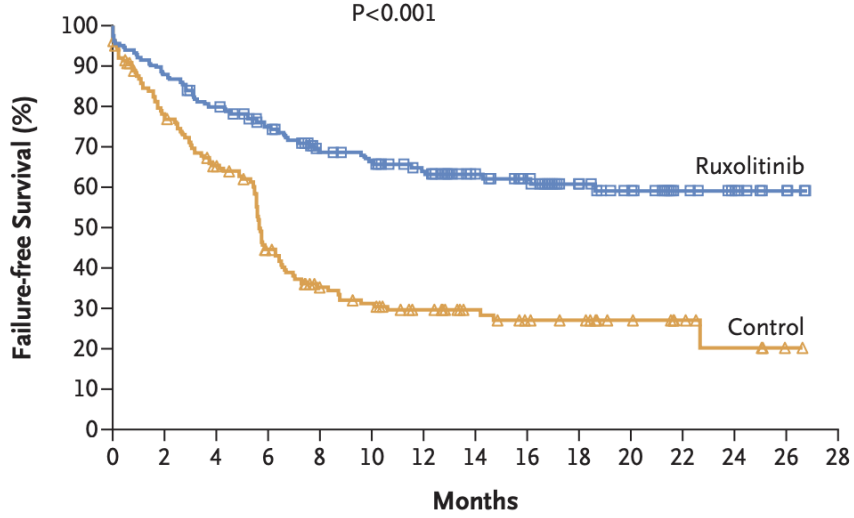


Odds ratio, 2.99 (95% CI, 1.86–4.80)
Risk ratio, 1.93 (95% CI, 1.44–2.60)
P<0.001

B Failure-free Survival

	No. of Events/Total No.	Kaplan–Meier Median (*mo*)
Ruxolitinib	60/165	>18.6
Control	109/164	5.7

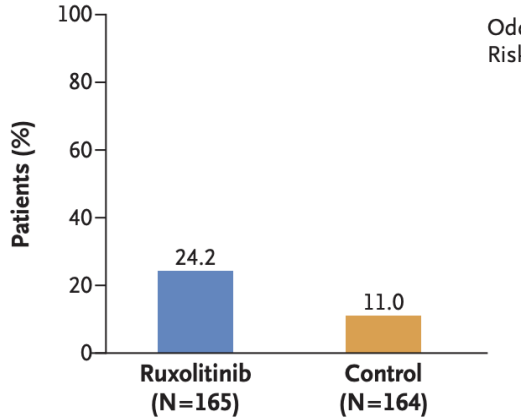
Hazard ratio, 0.37 (95% CI, 0.27–0.51)
P<0.001



No. at Risk

Ruxolitinib	165	145	130	115	92	87	76	58	49	37	27	15	9	4	0
Control	164	123	100	64	45	39	31	23	17	15	9	6	3	1	0

C Response on Modified Lee Symptom Scale at Week 24



Odds ratio, 2.62 (95% CI, 1.42–4.82)
Risk ratio, 2.19 (95% CI, 1.31–3.65)
P=0.001

Zeiser R, N Engl J Med 2021;385:228-38

Belumosudil** (ROCK2 inhibitor)

Phase 2 multicenter ra ndomized study (#NCT03640481, ROCKstar study)

Number of patients = 132

Inclusion criteria: cGVHD after ≥ 2 prior lines of therapy

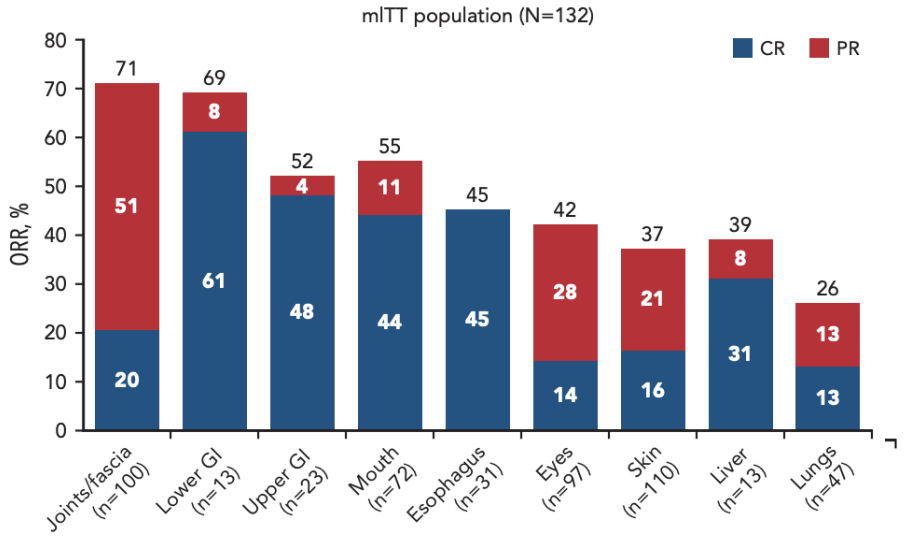
Belumosudil dose: 200mg/day vs 200mg/12h

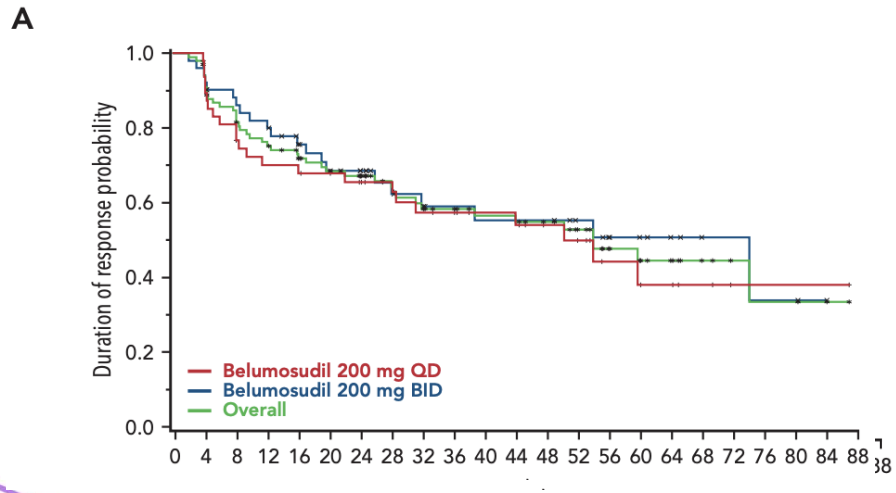
Characteristic	Belumosudil, 200 mg daily (n = 66)	Belumosudil, 200 mg twice daily (n = 66)	Total (N = 132)
NIH cGVHD severity*			
Severe	46 (70)	43 (65)	89 (67)
Moderate	18 (27)	23 (35)	41 (31)
Mild	2 (3)	0	2 (2)
Prior systemic cGVHD therapy type			
CS (prednisone)	65 (99)	65 (99)	130 (99)
Tacrolimus	40 (61)	42 (64)	82 (62)
ECP	31 (47)	32 (49)	63 (48)
Sirolimus	29 (44)	33 (50)	62 (47)
Ibrutinib	22 (33)	23 (35)	45 (34)
Ruxolitinib	20 (30)	18 (27)	38 (29)
MMF	18 (27)	15 (23)	33 (25)
Rituximab	15 (23)	13 (20)	28 (21)
MTX	3 (5)	3 (5)	6 (5)
Cyclosporine	4 (6)	1 (2)	5 (4)
Imatinib	3 (5)	1 (2)	4 (3)
Ixazomib	0	1 (2)	1 (1)
Ofatumumab	0	1 (2)	1 (1)

Cutler C. Blood (2021) 138 (22): 2278–2289.

**Producto no comercializado en la UE

Belumosudil** (ROCK2 inhibitor)



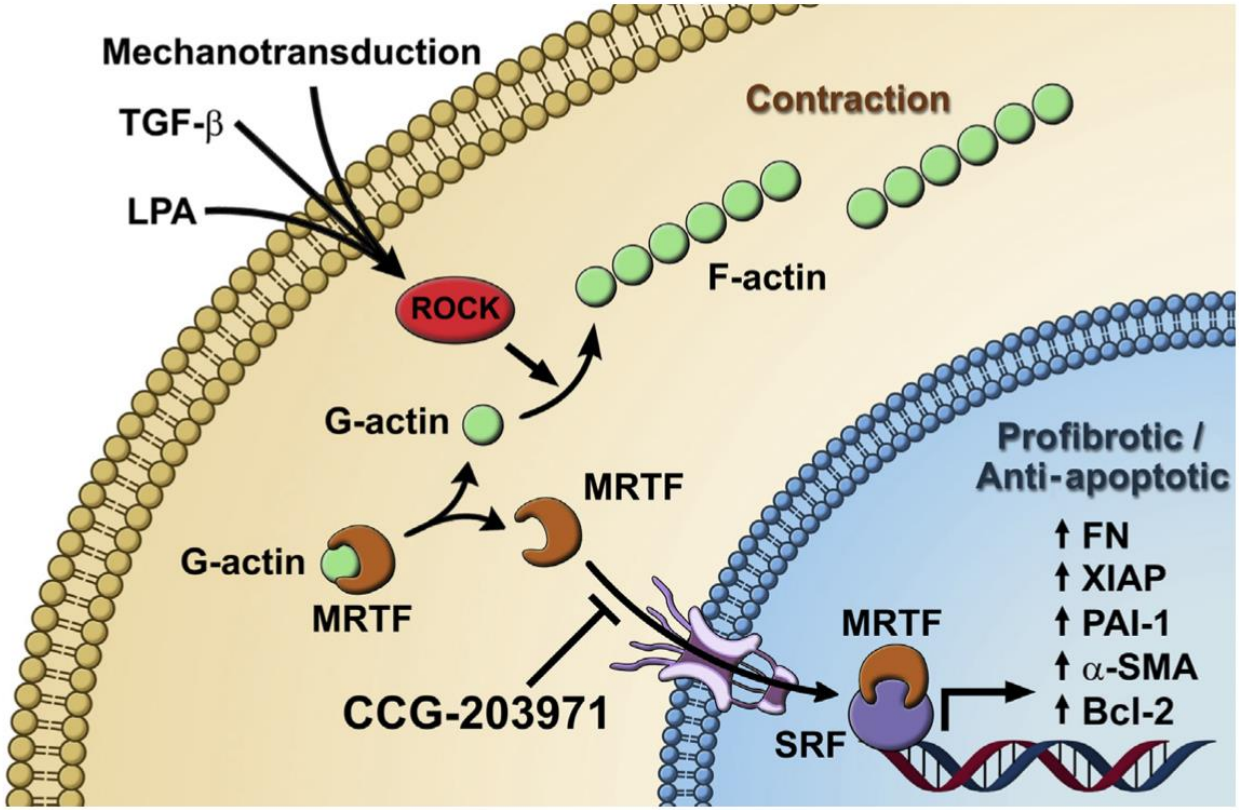


All grades in ≥20% of subjects (overall)	
Fatigue	50 (38)
Diarrhea	44 (33)
Nausea	41 (31)
Cough	37 (28)
Upper respiratory tract infection	35 (27)
Dyspnea	33 (25)
Headache	31 (24)
Peripheral edema	30 (23)
Vomiting	28 (21)
Muscle spasms	26 (20)
Grade ≥3 in ≥5% of subjects in either arm	
Pneumonia	10 (8)
Hypertension	8 (6)
Hyperglycemia	6 (5)

Cutler C. Blood (2021) 138 (22): 2278–2289.

**Producto no comercializado en la UE

ROCK inhibition for pulmonary fibrosis



Riches DWH, American Journal of Pathology 2015, 185(4): 909-912

Belumosudil** for BOS

BOS patients treated with belumosudil on 2 prospective clinical trials
Number of patients = 59

NIH lung score at diagnosis: score = 1 (59%); score = 2 (39%); score = 3 (10%)

ORR lung cGVHD: PR 32% , CR 15%

Response rates were inversely proportional to baseline NIH GVHD lung score at enrollment (lung score 1: ORR 50%; lung score 2: ORR 17%, lung score 3: ORR 0%) (P = .006)

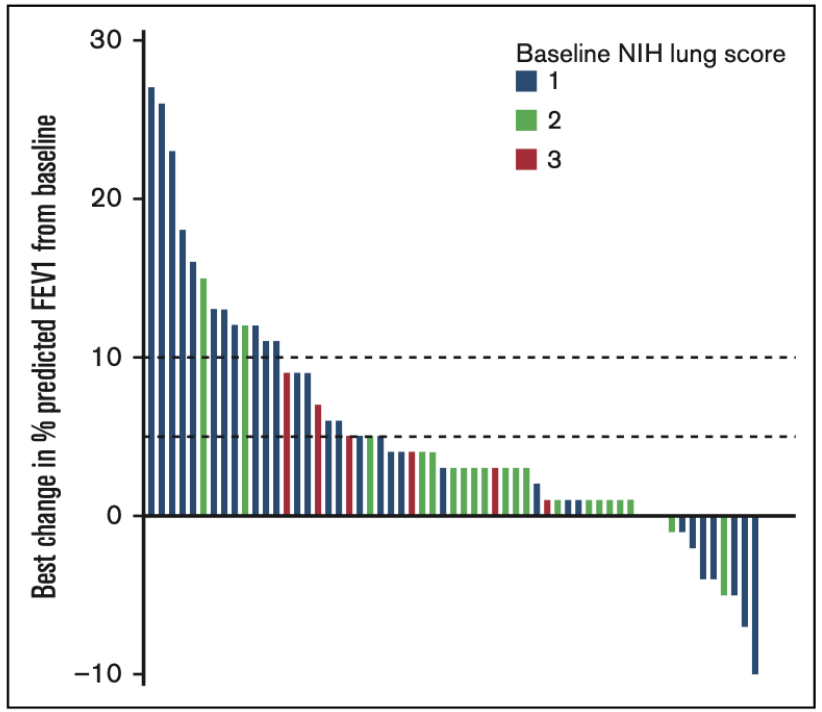


Table 2. Lung-specific NIH response according to lung score at baseline

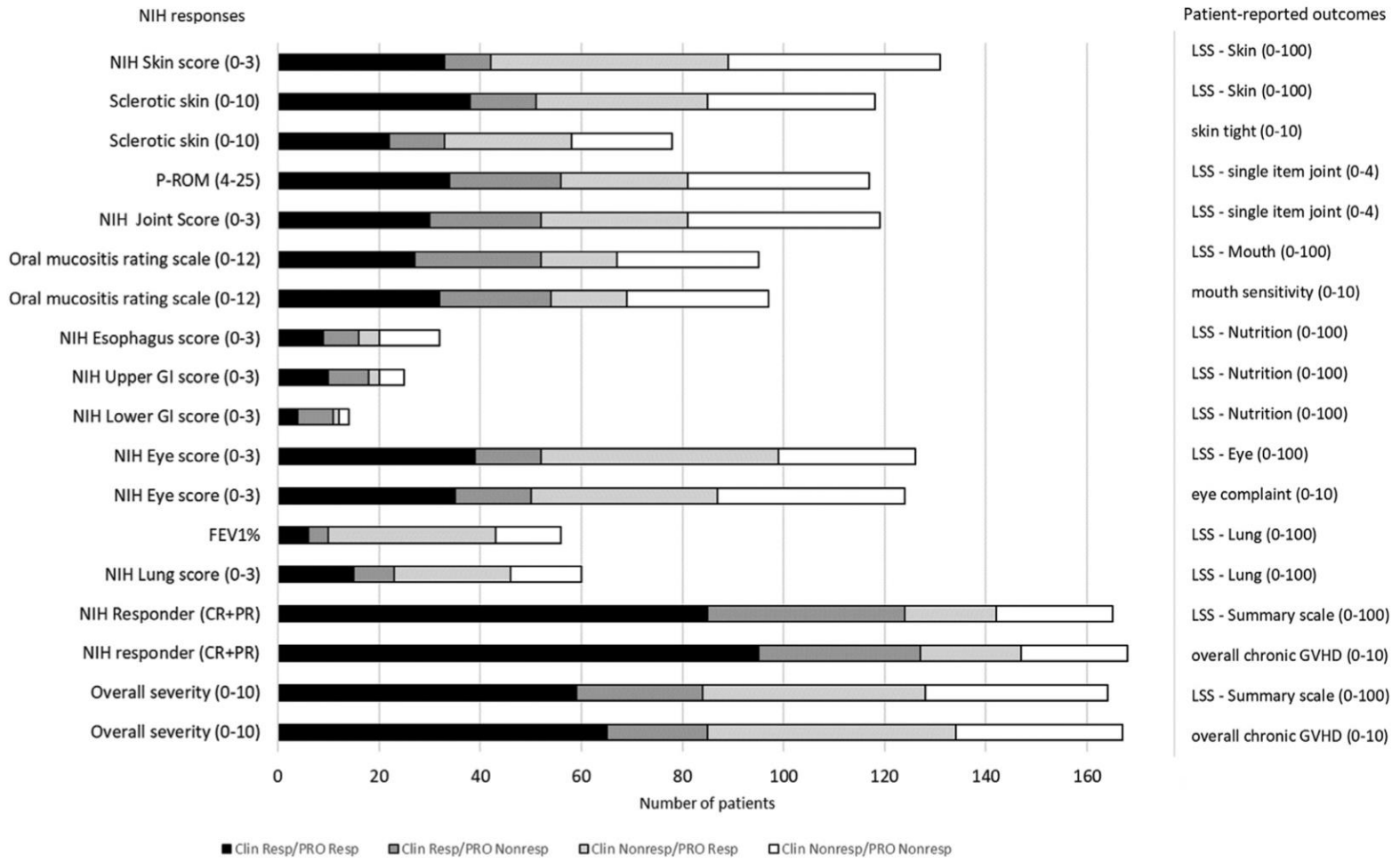
NIH lung score at baseline	Number of subjects	PR rate	CR rate	Best ORR
1	30	23% (7/30)	27% (8/30)	50% (15/30)
2	23	13% (3/23)	4% (1/23)	17% (4/23)
3	6	0% (0/6)	0% (0/6)	0% (0/6)
Total		17% (10/59)	15% (9/59)	32% (19/59)

DeFilipp Z, Blood Advances 2022 6(24):6263-6270

**Producto no comercializado en la UE

Belumosudil** and Patient-reported outcomes (PROs)

- BOS patients treated with belumosudil on 2 prospective clinical trials
- Number of patients = 170 (NCT02841995, n = 54; NCT03640481, n = 132)
- At least: 1 baseline PRO; 1 follow-up PRO; 1 disease response



**Producto no comercializado en la UE.

DeFilipp Z, Blood Advances 2022 6(24):6263-6270

Axalitimab^ (anti CSF-1 receptor)

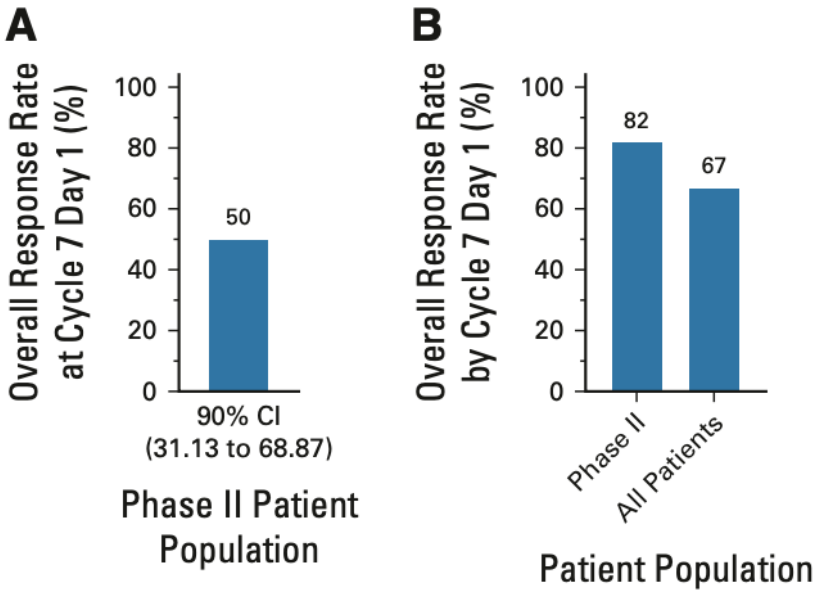
Phase 1/2 study (#NCT03604692)
Number of patients = 40
Inclusion criteria: cGVHD after ≥ 2 previous lines of therapy
Axalitimab 3 mg/kg every 2 weeks (dose escalation trial)

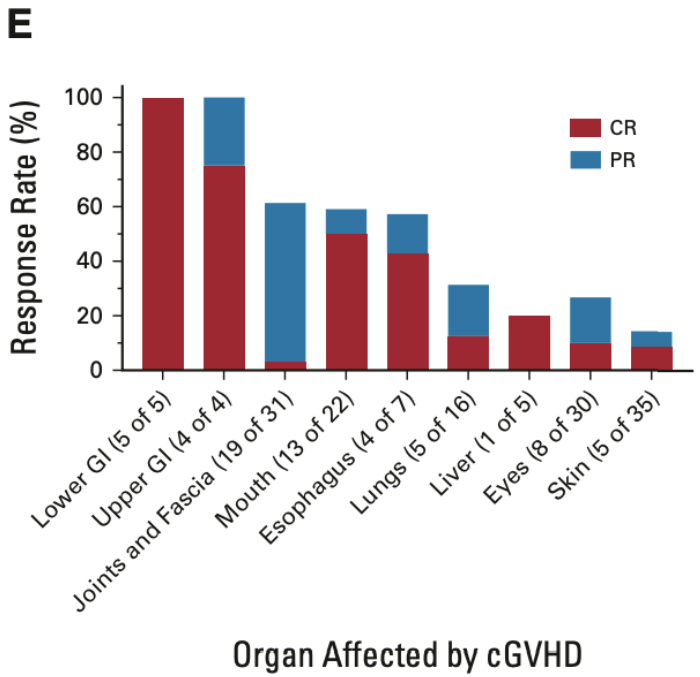
Characteristic	Phase I (n = 17)	Phase II (n = 23)	Total (N = 40)
NIH cGVHD severity, No. (%)			
Moderate	1 (5.9)	5 (21.7)	6 (15.0)
Severe	16 (94.1)	18 (78.3)	34 (85.0)
No. of prior therapies, median No. (range)	4 (1-9)	3 (2-11)	4 (1-11)
1-3, No. (%)	4 (23.6)	13 (56.5)	17 (42.5)
≥ 4, No. (%)	13 (76.4)	10 (43.5)	23 (57.5)
Prior systemic therapy, No. (%)			
Corticosteroids	17 (100.0)	23 (100.0)	40 (100.0)
Ibrutinib	13 (76.5)	13 (56.5)	26 (65.0)
Ruxolitinib	10 (58.8)	11 (47.8)	21 (52.5)
Extracorporeal photopheresis	10 (58.8)	9 (39.1)	19 (47.5)
Sirolimus	6 (35.3)	11 (47.8)	17 (42.5)
Rituximab	7 (41.2)	6 (26.1)	13 (32.5)
Tacrolimus	3 (17.6)	9 (39.1)	12 (30.0)
Belumosudil	6 (35.3)	2 (8.7)	8 (20.0)

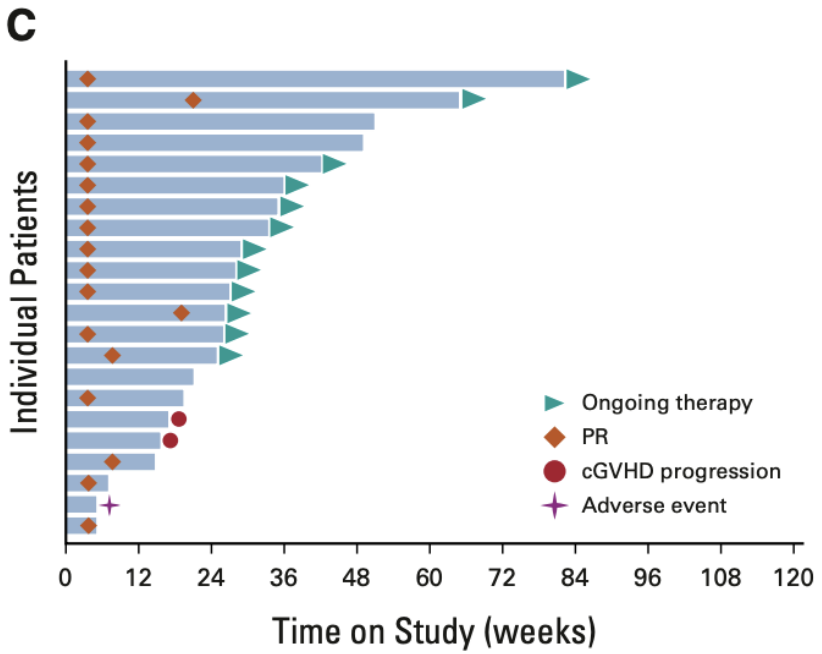
Kitko c, J Clin Oncol 2022 (41):1864-1875

^Contiene información de un producto en investigación. Este producto no ha sido evaluado por ninguna autoridad reguladora.

Axalitimab^ (anti CSF-1 receptor)







Kitko C, J Clin Oncol 2022 (41):1864-1875

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Abatacept***(CTLA-4 agonist)

Phase 1/2 study (#NCT01954979)
Number of patients = 39
Inclusion criteria: cGVHD after 1 previous line of therapy
Abatacept 10 mg/kg every 2 weeks doses 1-3 and then every 4 weeks doses 4-6

Characteristic	Number of patients, n = 39 (%)
Prior systemic therapy for cGVHD	
Prior lines of therapy, median (range)	3 (1-8)
Corticosteroid (prednisone, methylprednisolone)	39 (100)
Tacrolimus	24 (61.5)
Mycophenolate mofetil	15 (38.5)
Sirolimus	11 (28.2)
Cyclosporine	2 (5.1)
Rituximab	10 (25.6)
Ruxolitinib	7 (17.9)
Ibrutinib	4 (10.3)
Aldesleukin	7 (17.9)

Baseline NIH cGVHD severity score	
Mild	0 (0)
Moderate	18 (46.2)
Severe	21 (53.8)
Organs involved	
Number of organs involved, median (range)	3 (2-7)
≥4 organs involved	19 (48.7)
Skin	33 (84.6)
Mouth	17 (43.5)
Eyes	28 (71.7)
GI	6 (15.3)
Liver	9 (23.1)
Lung	22 (56.4)
Joints	32 (82.1)

Koshy AG, Blood (2023) 141 (24): 2932–2943

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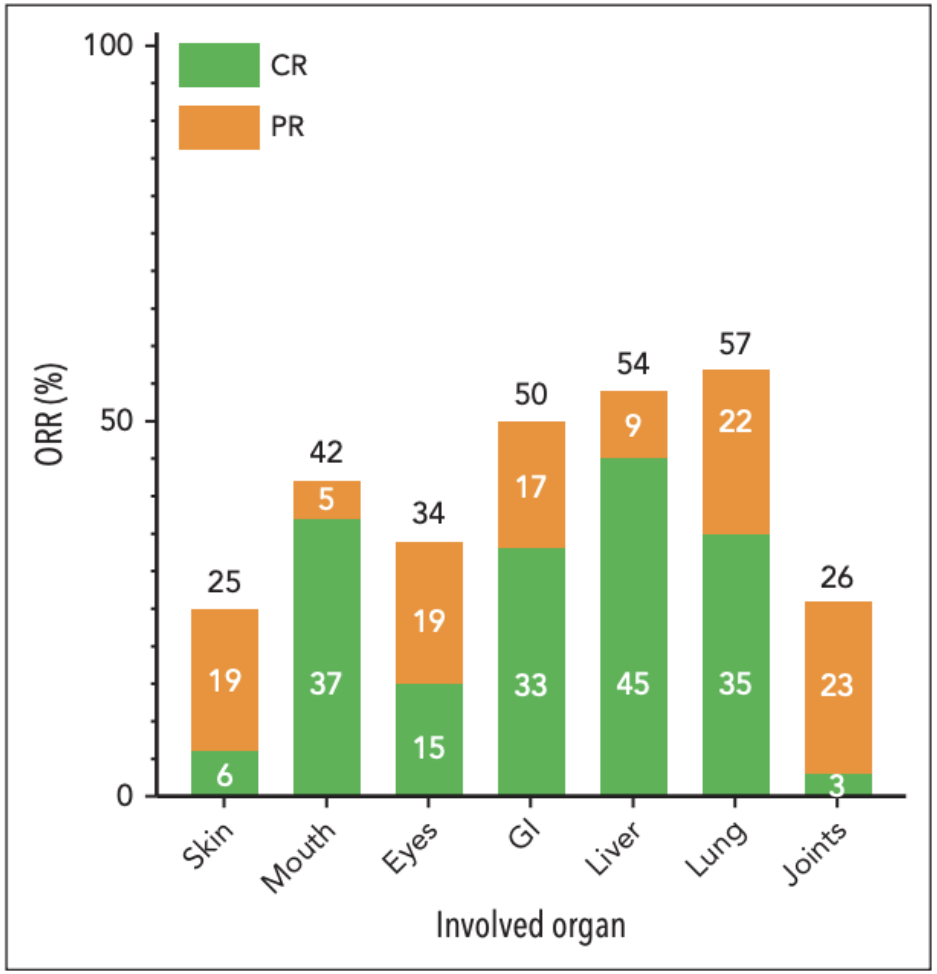
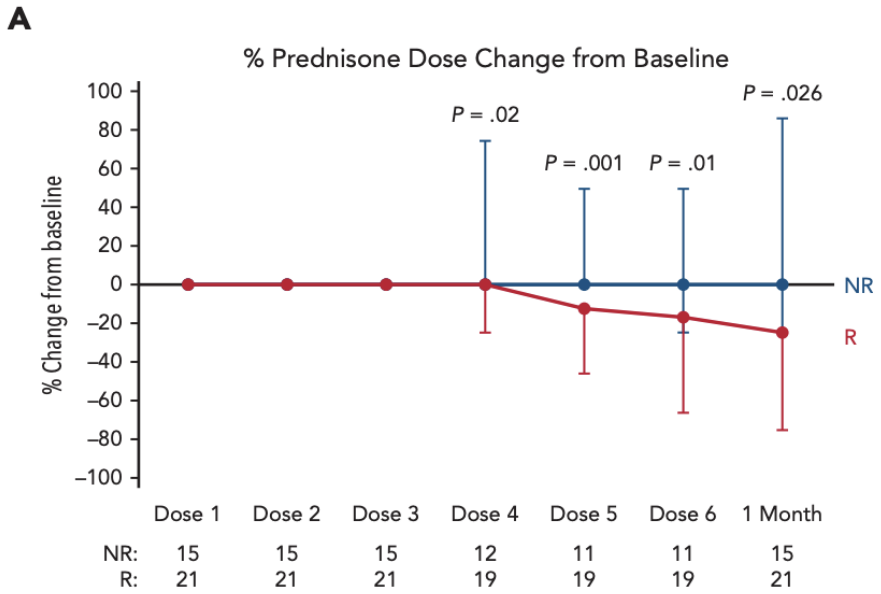
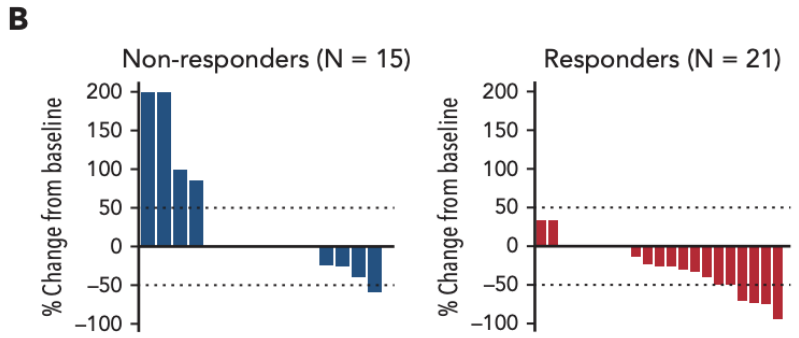
Abatacept***(CTLA-4 agonist)





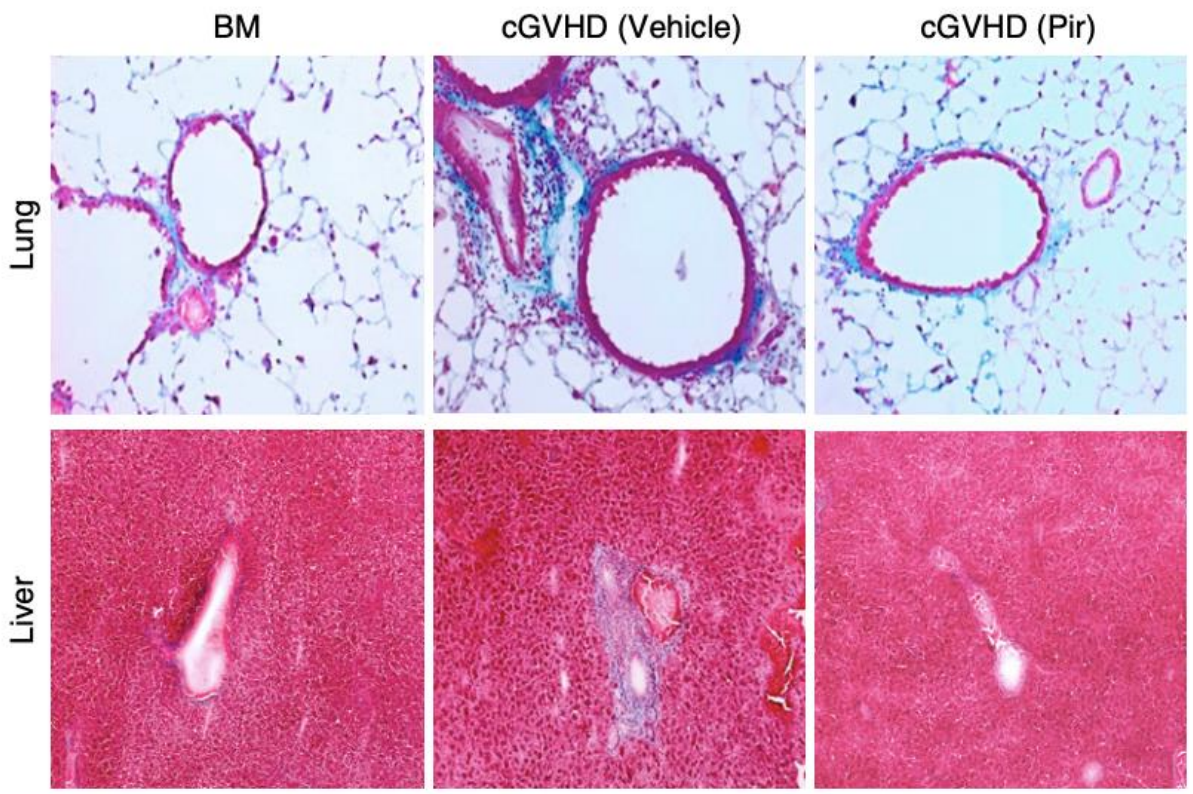


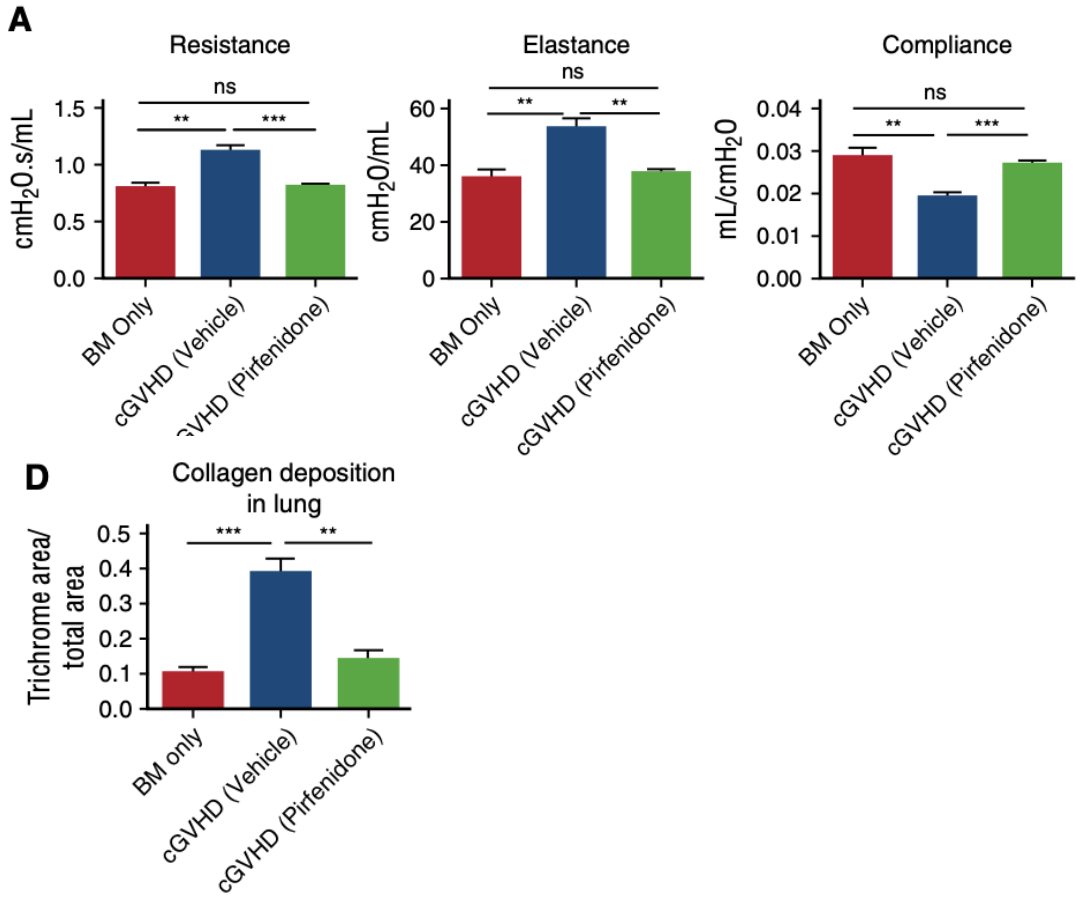
Koshy AG, Blood (2023) 141 (24): 2932–2943

***Contiene información de un producto en investigación. Este producto no ha sido evaluado por ninguna autoridad reguladora para el tratamiento de la EICRc.

Pirfenidone^^(fibrosis inhibitor)

Inhibitor of PDGF-R, TGF-beta, fibroblasts growth factor, IL-13 and other antifibrotic effects
FDA approved for idiopathic pulmonary fibrosis
Tested on Bronchiolitis obliterans mouse models



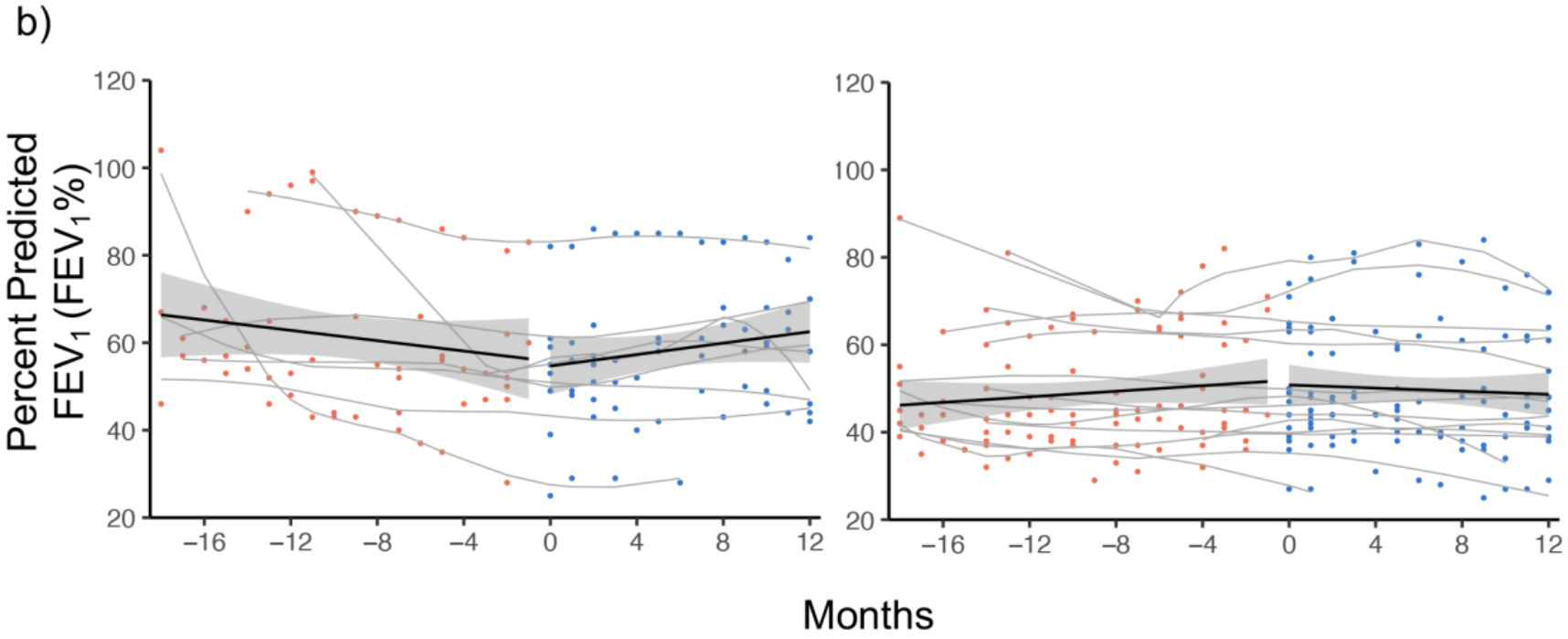


Du J, Blood (2017) 129 (18): 2570–2580

^Contiene información de un producto en investigación. Este producto no ha sido evaluado por ninguna autoridad reguladora para el tratamiento de la BOS

Pirfenidone^^(fibrosis inhibitor)

Phase 1 study (#NCT03315741)
Number of patients = 22
Inclusion criteria: BOS after alloHCT
Pirfenidone 2403 mg/day



Matthaiou EI, Bone Marrow Transplant. 2022 August ; 57(8): 1319–1326

^^Contiene información de un producto en investigación. Este producto no ha sido evaluado por ninguna autoridad reguladora para el tratamiento de la BOS

Conclusions

1) Chronic GVHD pathogenesis has been better clarified in recent years

2) Ibrutinib, ruxolitinib and belumosudil have been approved based on their specific anti-cGVHD mechanism

3) To enable personalized cGvHD treatment, additional diagnostic tools are needed to categorize and diagnose cGvHD by severity and biological subtypes, thus, enabling to choose the most appropriate therapy for each case

Aknowledgements

HEMATOPOIETIC CELL TRANSPLANT AND CELLULAR THERAPY
Marta Peña Domingo
Annalisa Paviglianiti
Abel Santos Carreira
Anna Sureda

HCT NURSES COORDINATORS
Lidia Hurtado Ortega
Raquel Lopez Gil

DATA MANAGER/JACIE
Meriem Kara
Maria del Mar Orea Gomez

IMMUNO-ONCOLOGY LAB
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Ramon Alemany
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