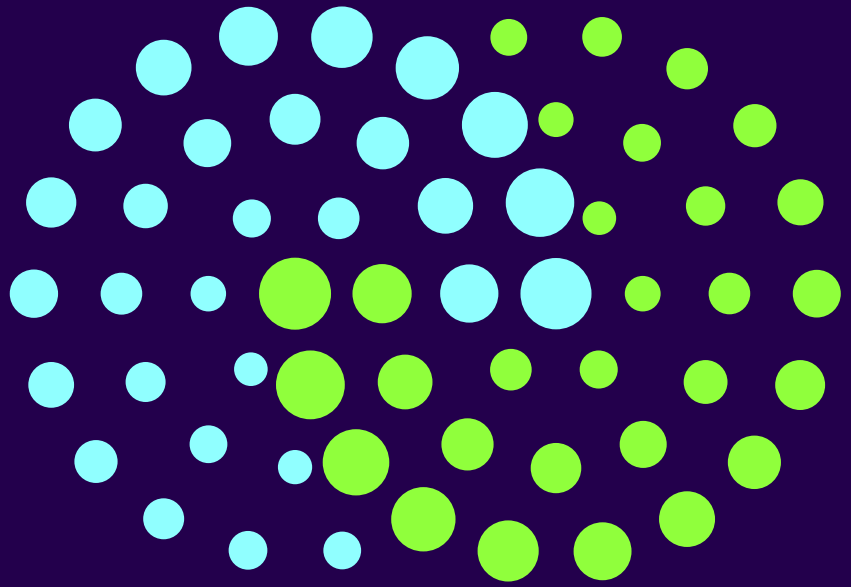

Expanding the chronic GvHD treatment paradigm with novel therapeutics

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Dana-Farber Cancer Institute,

Massachusetts, United States

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Disclaimer

This presentation, organised and funded by Sanofi, is for Great Britain healthcare professionals only.

Rezurock▼ (belumosudil) is indicated for the treatment of patients aged 12 years and older with chronic GvHD who have received at least two prior lines of systemic therapy in Great Britain.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to the Sanofi drug safety department on 0800 0902 314. Alternatively, send via email to UK-drugsafety@sanofi.com.

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Disclosures

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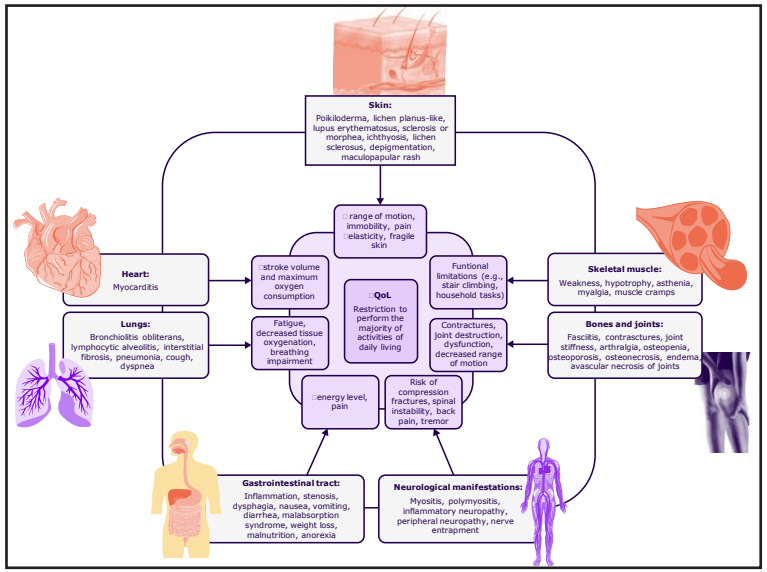
DSMB: Allovir, Angiocrine

Chronic graft-versus-host disease is a complex immune-mediated complication of allo-HSCT



Clinical manifestations of cGvHD and impact on patient QoL[2]

cGvHD occurs in 30–70% of allo-HSCT patients and is characterized by:

- Chronic inflammation and fibrosis
- Increased morbidity and early mortality
- Immune dysregulation

Systemic steroid therapy is the first-line treatment for GvHD although about **50% of patients will become refractory to treatment**

Developing effective treatments with an acceptable safety profile for cGvHD is of utmost importance especially for those whose disease becomes refractory to systemic steroid therapy

There is an unmet need for novel non-steroid or steroid-sparing treatment options to improve cGvHD outcomes

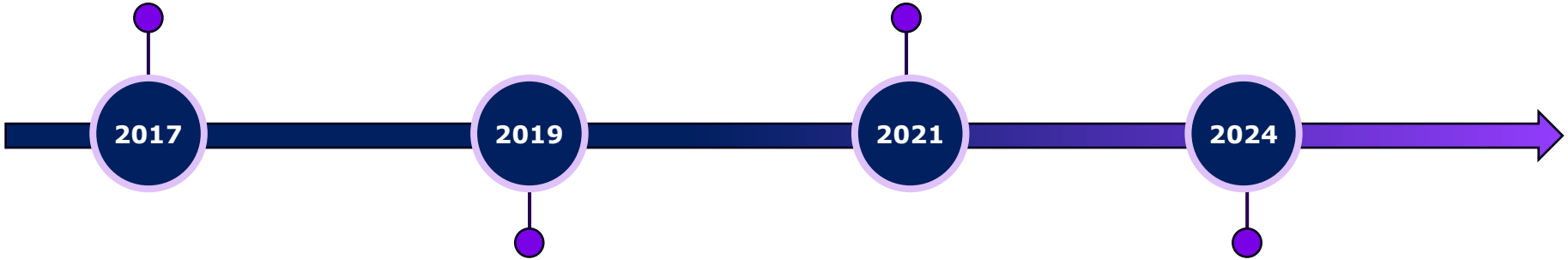
allo, allogenic; cGvHD, chronic graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; qol, quality of life

1. Martini et al. Oncol 2022;27:685–693

cGvHD drugs: timeline of FDA approval[1,2]

Ibrutinib[3]
- FDA approved
- Adults with cGvHD
- 420 mg once daily

Belumosudil[5] ▼
- FDA and MHRA approved
- Adults and children ≥12 years old
- 200 mg once daily



Ruxolitinib[4]
- FDA and EMA approved
- Adults and children ≥12 years old
- 10 mg twice daily

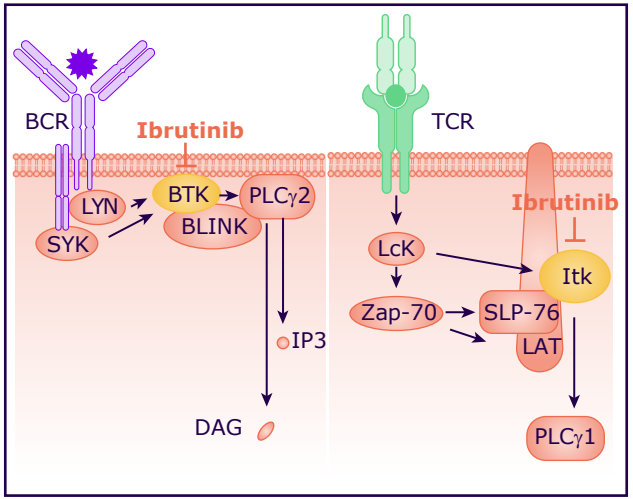
Axatilimab (investigational)
Ongoing trials investigating prevention of cGvHD*

The products mentioned on this slide may not be approved in your country for the indications discussed. Sanofi does not recommend the use of its products in any manner inconsistent with that described in the label available in your country. Please refer to your local product labeling information before prescribing. *FDA approved for prevention of acute GvHD.
cGvHD, chronic graft-versus-host disease; EMA, European Medicines Agency; FDA, Food and Drug Administration; MHRA, medicines healthcare regulatory authority.
Zeiser R, et al. Front Immunol 2023;14:1241069; Ngwube A, et al. Ther Adv Hematol 2023;14:1–13; 3. Prescribing information: Imbruvica https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/217003s000lbl.pdf (Last accessed June 2024); 4. Prescribing information: Jakafi https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202192s023lbl.pdf (Last accessed June 2024); 5. Prescribing information: Rezurock: Prescribing information is available at the end of this presentation

Ibrutinib is an FDA-approved BTK and IL-2 ITK inhibitor

Ibrutinib is an FDA-approved BTK inhibitor used as a second-line treatment for adult patients with chronic GvHD after failure of 2 systemic LOTs[1,3]

Mode of action of ibrutinib[2]



Treatment effects in cGvHD[2]

- ↓ Cell survival
- ↓ Cell proliferation
- ↓ Autoantibody production
- ↓ Cytokine production (IL-9, IL-17A, IL-2)

ITK inhibition favors the formation of Th-1 immune responses

Ibrutinib may not be approved in your country for the indications discussed. Sanofi does not recommend the use of its products in any manner inconsistent with that described in the label available in your country. Please refer to your local product labeling information before prescribing.

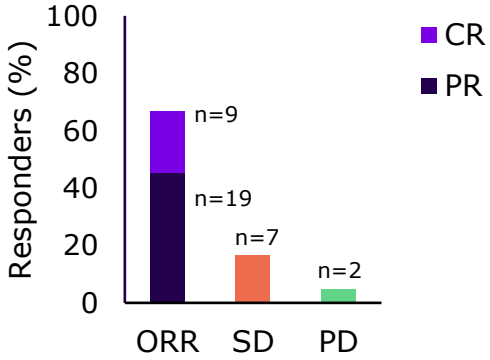
BTK, bruton tyrosine kinase; cGvHD, chronic graft-versus-host disease; IL, interleukin; ITK, inducible t-cell kinase; LOTs, lines of therapy; Th, T-helper.

1. Miklos et al. Blood 2023 130:2243–2250; 2. Zeiser and Lee. Blood 2022; 139(11); 3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/217003s000lbl.pdf (last accessed June 2024).

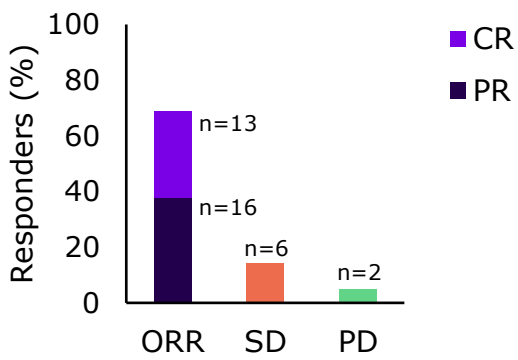
Miklos, et al: Responses are durable with ibrutinib in SR or SD cGvHD

Patients were enrolled if they were aged ≥18 years, had steroid-dependent or -refractory cGVHD after hematopoietic stem cell transplant, and had received ≤3 prior regimens for cGVHD. Active cGVHD was required, and patients were to have either >25% body surface area erythematous rash or a National Institutes of Health (NIH) mouth score >4

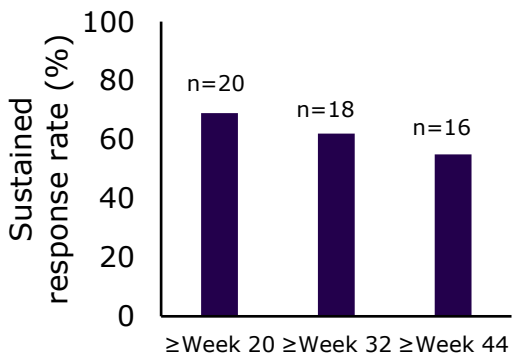
Median follow-up 13.9 months[1]



Median follow-up 26 months[2]



Sustained response at 26 Week follow-up[2]



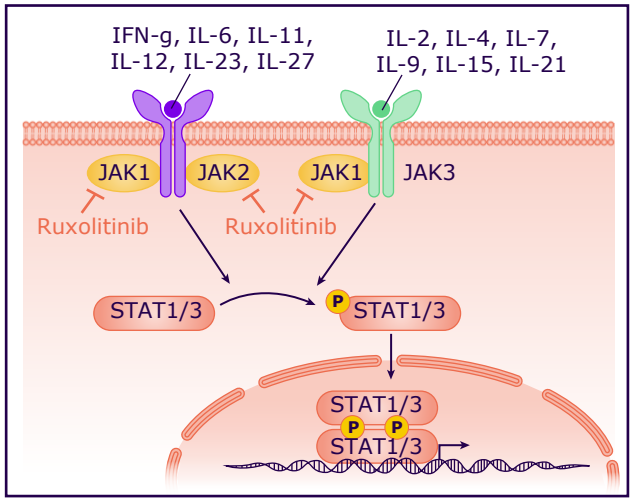
- Ibrutinib demonstrated an **acceptable safety profile**; **most treatment-related AEs were grade 1–2** and included fatigue (n = 24, 57%), diarrhea (n = 37, 37%), and muscle spasms (n = 12, 28%)
- Owing to specifity of patient population, anticoagulatory capacity was not assessed as part of the study.
- There were 6 serious AEs listed as pneumonia. The 1 fatal pneumonia was bacterial (*Enterococcus*). The remaining 5 nonfatal pneumonias included 1 each of bacterial, fungal *(Aspergillus*), and multiagent (bacterial, fungal, and viral) origin and 2 of unknown etiology

PCYC-1129 was an open-label, multicenter, Phase Ib/II study (July 14, 2014 to September 18, 2017) investigating the safety and efficacy of ibrutinib in patients with cGVHD that failed to respond to at least 1 systemic corticosteroid-based therapy and who needed additional treatment (n=42). Treatment was initiated at an ibrutinib dose of 420 mg with 6 to 27 patients being evaluated in phase Ib depending on the frequency of dose limiting toxicities (DLTs) and need for dose reductions. If unacceptably high DLTs were seen, the ibrutinib dose could be sequentially reduced to 280 mg and then 140 mg. Patients in phase Ib who did not experience a DLT were permitted to continue treatment and follow-up in phase II at their phase I dose. The primary end point for phase Ib was safety and tolerability, which included the number of DLTs occurring within the first 28 days on ibrutinib. The primary efficacy endpoint for phase II was the best overall cGVHD response rate, which was defined as the proportion of all patients who achieved a complete or partial response. AEs, adverse events; cGvHD, chronic graft-versus-host disease; LOTs, lines of therapy; SD, steroid-dependant; SR, steroid-refractory.

1. Miklos D et al. Blood 2017;130:2243–2250; 2. Waller EK et al. BBMt 2019; 25:2002–2007.

Ruxolitinib leads to the disruption of cytokine and growth factor signaling pathways

Mode of action of ruxolitinib[1]



Treatment effects in cGvHD[1]

- ↓ Cytokine production
- ↓ Proliferation
- ↓ Th17 cells
- ↓ Extracellular matrix production
- ↑ Treg cells

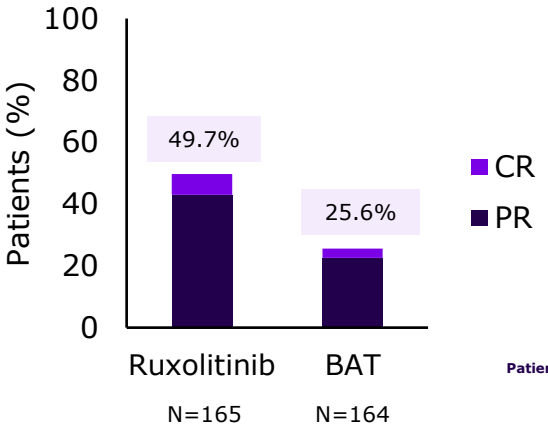
Ruxolitinib is an FDA and EMA approved TKI indicated for the treatment of aGvHD and cGvHD in certain adults and children ≥ 12 years of age*[2–4]

*Prior to prescribing, please consult your local label for the approved indication of ruxolitinib in your country.
aGvHD, acute graft-versus-host disease; cGvHD, chronic graft-versus-host disease; IL, interleukin; ITK, inducible t-cell kinase; JAK, janus kinase; Th, T-helper; TKI, tyrosine kinase inhibitor; LOTs, lines of therapy.

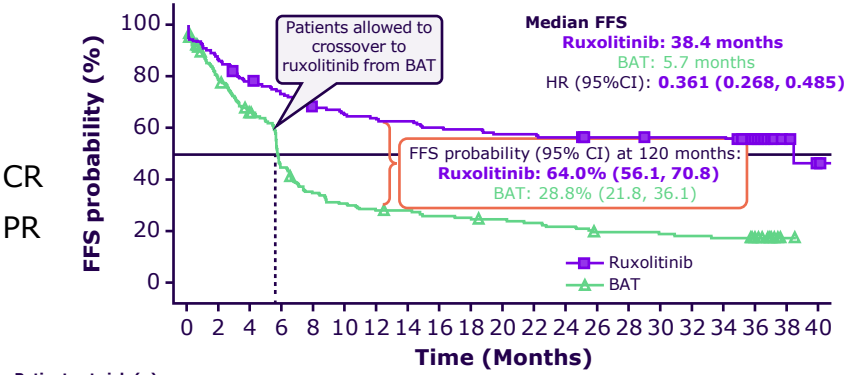
1. Zeiser R and Lee SJ. Blood 2022;139:1642–5; 2. https://www.jakavi.com/en/graft-versus-host-disease/efficacy (last accessed June 2024); 3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202192lbl.pdf (last accessed June 2024); 4. https://www.ema.europa.eu/en/documents/product-information/jakavi-epar-product-information_en.pdf (last accessed June 2024).

REACH 3[1,2]

Overall response rate at Week 24[1]



Failure-free survival at 3-year follow-up[1]



Patients at risk (n):

Ruxolitinib	165	143	129	120	110	106	103	102	98	97	94	94	92	90	90	89	89	89	64	8	4
BAT	164	125	102	69	53	47	43	42	39	37	36	34	32	28	28	27	26	25	16	1	0

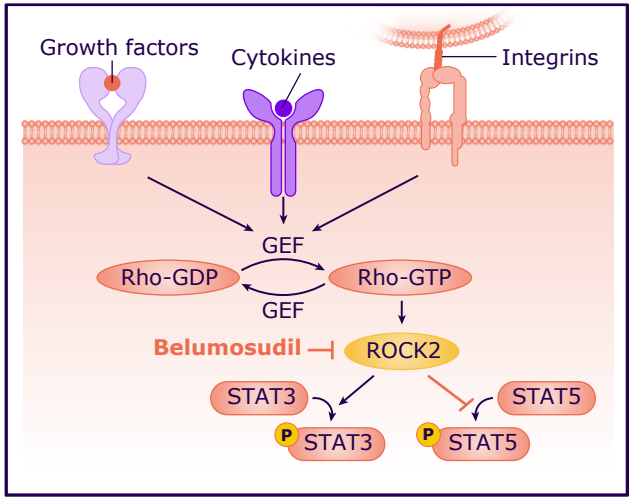
- Participants receiving ruxolitinib had a **higher modified LSS response** rate (24.2% vs 11.0%) compared to the BAT group[2]
- Frequently reported AEs were anemia (33.9%), pneumonia (17.6%) and neutropenia (15.2%)[1]

Results from a Reach 3, a Phase III, open-label, randomized, multicenter clinical trial of ruxolitinib compared with BAT in CS-refractory or CS-dependent patients aged ≥12 years with moderate or severe cGvHD. The primary endpoint was overall response (complete or partial response) at week 24; key secondary endpoints were failure-free survival and improved score on the mLSS at week 24. Between July 11, 2017 and November 18, 2019, a total of 329 patients were randomly assigned to receive ruxolitinib (165 patients) or a control therapy (164 patients). Patients were randomly assigned in a 1:1 ratio to receive ruxolitinib at a dose of 10mg twice daily or therapy. BAT was selected by the investigator on a patient-by-patient basis and included extracorporeal photopheresis (ECP), low dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), infliximab, rituximab, pentostatin, imatinib, or ibrutinib.

AEs, adverse events; BAT, best available therapy; cGvHD, chronic graft-versus-host disease; FFS, failure-free survival; LSS, lee symptom scale; ORR, overall response rate.

1. Zeiser R, et al. Oral presentation at ASH 2023 #654; 2. Zeiser R and Lee SJ. Blood 2022;139:1642–5.

Belumosudil affects both the inflammatory and fibrotic processes related to cGvHD



Mode of action of belumosudil[1]

Treatment effects in cGvHD[1]

- ↓ Cytokine production
- ↓ Proliferation
- ↓ Th17 cells
- ↓ Extracellular matrix production
- ↑ Treg cells

Belumosudil is a once-daily FDA and NICE approved treatment option for the management of cGvHD in adults and children ≥12 years after failure of ≥2 systemic LOTs[2,3]

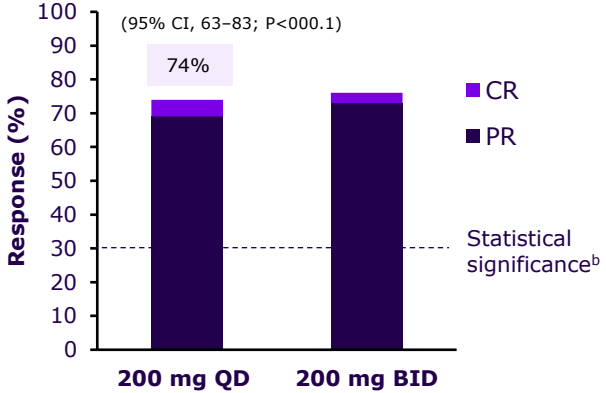
cGvHD, chronic graft-versus-host disease; IL, interleukin; ITK, inducible t-cell kinase; TKI, tyrosine kinase inhibitor; LOTs, lines of therapy.

1. Zeiser R and Lee SJ. Blood 2022;139:1642–5; 2. Rezurock (Belumosudil) PI is available at the end of this presentation; 3. https://www.nice.org.uk/guidance/ta949/resources/belumosudil-for-treating-chronic-graftversushost-disease-after-2-or-more-systemic-treatments-in-people-12-years-and-over-pdf-82615676934085 (last accessed June 2024).

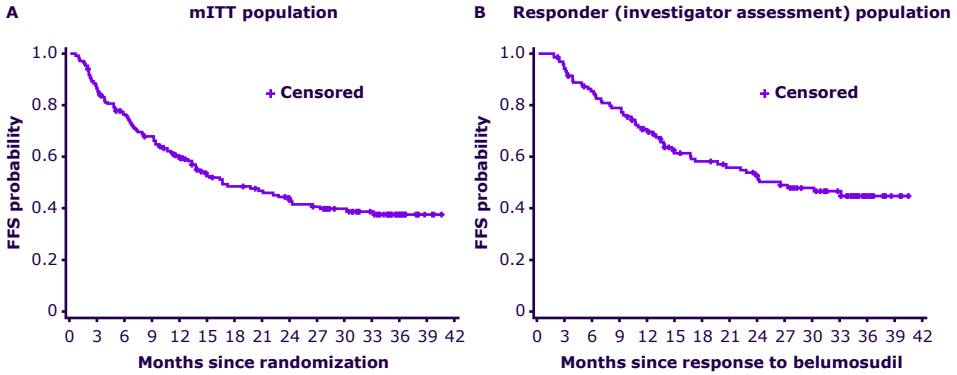
ROCKstar: 3-year follow-up data

ROCKstar was a Phase II randomized multicenter study (October 2018 to 19 August 2020) evaluating belumosudil 200 mg od (n=66) and 200 mg bd (n=66) in subjects with cGVHD who had received **2–5 prior lines of therapy;** the primary endpoint was best ORR[1]

3-year ORR[1]



3-year FFS in mITT (A) and responder (B) population[1]



The 3-year follow up of the ROCKstar study demonstrated consistent efficacy and tolerability of belumosudil[b]

200 mg BID dosing is recommended for patients who are co administered strong CYP3A inducers and/or proton pump inhibitors

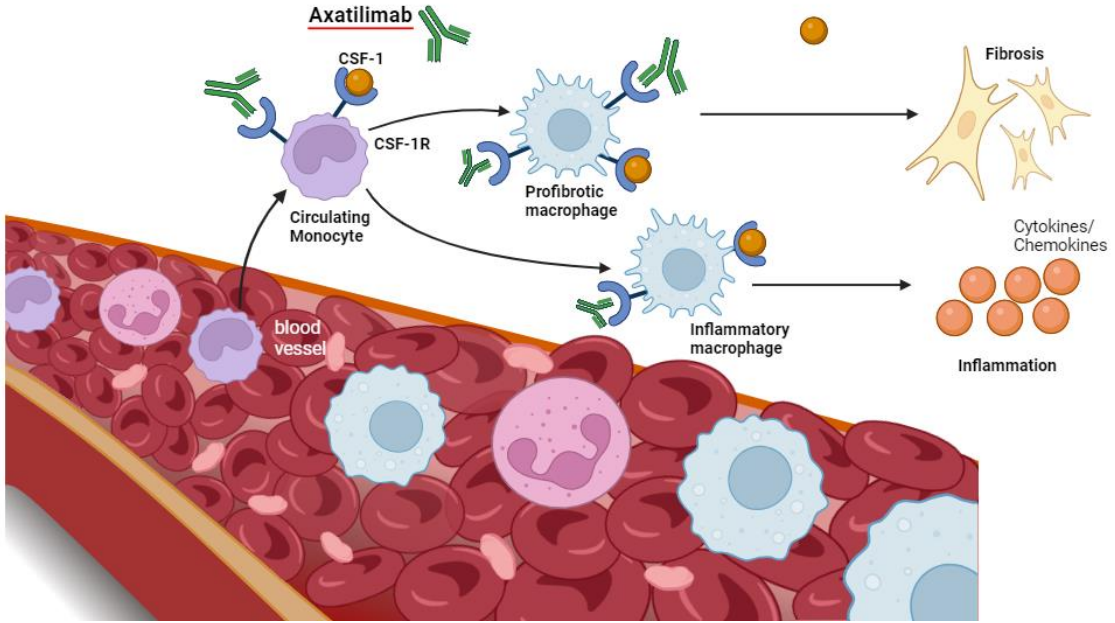
[a]Statistical significance was achieved if the lower bound of the 95% CI of ORR exceeded 30%. [b]The most common adverse reactions (≥5%) were asthenia (21.0%), nausea (12.4%), liver function test abnormalities of elevation of AST (7.5%), elevation of ALT (7.0%) and elevation of GGT (4.8%), headache (8.6%), diarrhoea (7.0%) and musculoskeletal pain (5.9%). The most common Grade 3 or 4 adverse reaction (≥ 2%) was asthenia (2.7%). Serious adverse reactions were pneumonia (1.1%), cellulitis, infectious colitis, staphylococcal bacteraemia, diarrhoea, nausea, vomiting, microangiopathic haemolytic anaemia, multiple organ dysfunction syndrome and cGVHD (0.5% each). The most common adverse reactions leading to discontinuation were nausea (2.4%) and headache (2.4%). Adverse reactions leading to dose interruption occurred in 9.6% of patients and were mainly investigations (3.6%), including ALT increased, GGT increased and blood creatine phosphokinase increased (1.2% each), and infections (2.4%).[2]

AE, adverse events; BD, twice daily; cGvHD, chronic graft-versus-host disease; CI, confidence interval; CR, complete response; LOTs, lines of therapy; mitt, modified intent-to-treat; QD, once daily; ORR, overall response rate; PR, partial response.

1. Lee SJ, et al. Transplant Cell Ther 2024; Poster #346; 2. Rezurock (Belumosudil) PI is available at the end of this presentation.

Axatilimab is an investigational monoclonal antibody that targets key cGvHD pathology mediators

- Axatilimab is an investigational monoclonal antibody that targets CSF-1R on monocytes and macrophages[1]
- CSF-1R–dependent monocytes and macrophages mediate inflammation and fibrosis[1,2]
- Axatilimab **has shown favorable safety and promising efficacy** in recurrent/refractory cGVHD, with an ORR of 67% in the first 6 cycles[2]



cGvHD, chronic graft-versus-host disease; ORR, overall response rate.

1. Wolff D, et al. American Society of Hematology. ASH plenary session. 2023; 2. Kitko CL, et al. J Clin Oncol. 2023;41:1864–1875.

AGAVE 201: Study design

AGAVE 201 was a phase II, open-label, multicenter trial designed to evaluate the safety and efficacy of axatilimab (0.3, 1.0 and 3 mg/kg) in patients with recurrent or refractory cGVHD with ≥2 prior lines of systemic therapy[1]

Key inclusion criteria[1]

- Age ≥2 years with ≥2 prior lines of systemic therapy
- Active cGVHD defined per 2014 NIH Consensus Criteria
- Concomitant use of corticosteroids (65%), calcineurin inhibitors (28%), or mTOR inhibitors (12%) was allowed, but not required
- No additional systemic cGVHD therapy was allowed

Primary endpoint[1]

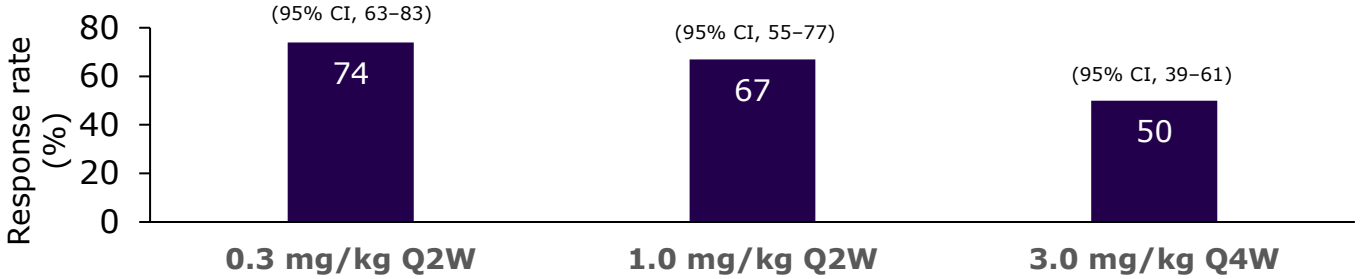
- ORR in the first 6 cycles as defined by NIH 2014 Consensus criteria*

Secondary and exploratory endpoints[1]

- Clinically meaningful improvement in mLSS (≥7 points)
- Organ-specific response rates, DOR, FFS, OS
- Safety

*Endpoint was met if lower bound of 95% CI >30%.
cGvHD, chronic graft-versus-host disease; DOR, duration of response; FFS, failure-free survival; mLSS, modified Lee Symptom Scale; mTOR, mammalian target of rapamycin; NIH, National Institutes of Health; OS, overall survival.
1. Wolff D, et al. American Society of Hematology. ASH plenary session. 2023.

AGAVE 201: Axatilimab conferred clinically meaningful and durable responses at three dose levels among cGvHD patients



	n=80	n=81	n=80
Time to response, median months (range)	1.7 (0.9–8.1)	1.9 (0.9–8.6)	1.4 (0.9–5.6)
Response maintained for ≥12 months, % (95% CI)	60 (43–74)	60 (43–74)	53 (30–71)

Axatilimab at 0.3 mg/kg Q2W demonstrates high efficacy among recurrent/refractory cGvHD patients and acceptable tolerability[1]

Axatilimab has not been approved by any regulatory authority, This information is provided for educational purposes only.
AGAVE-201 was a multicenter trial that evaluated the safety and efficacy of 3 doses of axatilimab in patients with relapsed or refractory cGvHD. Participants (214) were randomised in a 1:1:1 ratio to IV axatilimab at doses of 0.3mg/kg Q2W, 1mg/kg Q2W or 3mg/kg Q4W. The primary efficacy endpoint was the overall response rate during the first 6 cycles (24 weeks). Secondary endpoints included safety and a reduction in symptoms using the mLSS score.
cGvHD, chronic graft-versus-host disease; ORR, overall response rate; Q2W, every 2 weeks; Q4W, every 4 weeks.
1. Wolff D, et al. American Society of Hematology. ASH plenary session. 2023.

Novel therapies hold significant promise for helping address the unmet needs of cGvHD patients

- Ibrutinib trials have demonstrated significant and durable responses with ibrutinib in SR or SD cGvHD
- In REACH 3, ruxolitinib led to significantly greater ORR, FFS and symptom response rates versus the BAT group. Ruxolitinib also led to significant improvements in skin and mucosal manifestations of cGVHD, as well as reductions in corticosteroid doses
- After a 3-year follow-up in the ROCKstar study, belumosudil continued to demonstrate clinically meaningful ORRs
- Investigational drugs, such as axatilimab (0.3 mg/kg Q2W), have been shown to be highly effective in patients with recurrent/refractory cGvHD by reducing symptom burden in 85% of patients, offering a potential therapeutic option for patients who do not respond adequately to conventional therapies

BAT, best available therapy; cGvHD, chronic graft-versus-host disease; FFS, failure-free survival; ORR, overall response rate; Q2W, every two weeks; SR, steroid-refractory; SD, steroid-dependent.

The ROCKstar Study: Safety and Tolerability[1]

ROCKstar was a Phase II randomized multicenter study (October 2018 to 19 August 2020) evaluating belumosudil 200 mg od (n=66) and 200 mg bd (n=66) in subjects with cGVHD who had received **2–5 prior lines of therapy;** the primary endpoint was best ORR[1]

AEs were overall consistent with those expected in patients with cGVHD receiving corticosteroids and other immunosuppressants.

- There was 1 reported case of Epstein-Barr virus and 1 reported case of CMV reactivation.
- Data up to 19 August 2020 included [1].

Commonly reported AEs, n (%)	REZUROCK 200 mg QD (n=66)	REZUROCK 200 mg BID (n=66)	Overall (N=132)
All grades in ≥20% of patients			
Fatigue	**30 (46)**	20 (30)	50 (38)
Diarrhea	**23 (35)**	21 (32)	44 (33)
Nausea	**23 (35)**	18 (27)	41 (31)
Cough	**20 (30)**	17 (26)	37 (28)
Upper respiratory tract infection	**17 (26)**	18 (27)	35 (27)
Dyspnea	**21 (32)**	12 (18)	33 (25)
Headache	**13 (20)**	18 (27)	31 (24)
Peripheral edema	**17 (26)**	13 (20)	30 (23)
Vomiting	**18 (27)**	10 (15)	28 (21)
Muscle spasms	**13 (20)**	13 (20)	26 (20)
Grade ≥3 in ≥5% of patients			
Pneumonia	**6 (9)**	4 (6)	10 (8)
Hypertension	**4 (6)**	4 (6)	8 (6)
Hyperglycemia	**3 (5)**	3 (5)	6 (5)

Safety overview	REZUROCK 200 mg QD (n=66)	REZUROCK 200 mg BID (n=66)	Overall (N=132)
Median duration of treatment, mo	**9.4**	11.8	10.4
Any AE, n (%)	**65 (99)**	66 (100)	131 (99)
Grade ≥3 AEs, n (%)	**37 (56)**	34 (52)	71 (54)
SAEs, n (%)	**27 (41)**	23 (35)	50 (38)
Drug-related AEs, n (%)			
Any related AE	**49 (74)**	40 (61)	89 (67)
Related SAEs	**5 (8)**	2 (3)	7 (5)
Deaths[a], n (%)	**8 (12)**	6 (9)	14 (11)

[a]Six subjects died during long-term follow-up (>28 days after the last dose).

According to the Summary of Product Characteristics, the dosage of Rezurock should be increased to 200 mg twice daily when co-administered with strong CYP3A inducers or proton pump inhibitors (PPIs). Consider switching to a drug less sensitive to OATP1B1 and BCRP inhibition when possible. If used together the dose of rosuvastatin should not exceed 5mg once daily.

AE, adverse event; BCRP, Breast Cancer Resistance Protein; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; OATP1B1, organic anion transporting polypeptides (OATP) 1B1; SAE, serious adverse event.

1. Cutler C, Lee SJ, Arai 3, et al; on behalf of the ROCKstar Study Investigators. Belumosudil for chronic graft- versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study. Blood. 2021;138 (22):2278-2289. doi:10.1182/blood.2021012021.

Prescribing Information: REZUROCK (belumosudil) ▼ 200mg film-coated tablets (Licence valid in GB only)

Therapy should be initiated and supervised by physicians experienced in the management of chronic GVHD.
Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each film-coated tablet contains belumosudil mesilate, equivalent to 200mg belumosudil.
Indication: Rezurock is indicated for the treatment of patients aged 12 years and older with chronic graft-versus- host disease (chronic GVHD) who have received at least two prior lines of systemic therapy.
Dosage and Administration: The recommended dose of Rezurock is 200mg administered orally once daily at approximately the same time with a meal. The film-coated tablet should not be broken, crushed or chewed. Treatment should continue until disease progression or unacceptable toxicity. A complete blood cell count and liver function test must be performed before initiating therapy with Rezurock. Perform liver function tests at least monthly throughout treatment. Dose modification due to hepatotoxicity and other adverse reactions: For Grade 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (>5 – 20 × upper limit of normal (ULN)) or Grade 2 bilirubin (>1.5 – 3 × ULN) or other Grade 3 adverse reactions, hold Rezurock until recovery to ≤Grade 1, then resume Rezurock at the recommended dose at physician's discretion. For Grade 4 ALT or AST (>20 × ULN) or Grade ≥3 bilirubin (>3 × ULN) or other Grade 4 adverse reactions, permanently discontinue Rezurock. Dose modification due to drug interactions: *Strong CYP3A Inducers:* Increase the dosage of Rezurock to 200mg twice daily when co-administered with strong CYP3A inducers. Co-administration of belumosudil with drugs transported by OATP1B1 and BCRP substrates can lead to an increase in exposure of these concomitant drugs (e.g. rosuvastatin). *Proton Pump Inhibitors:* Increase the dosage of Rezurock to 200mg twice daily when co- administered with proton pump inhibitors. *OATP1B1/BCRP substrates:* Consider switching to a drug less sensitive to OATP1B1 and BCRP inhibition when possible. If used together the dose of rosuvastatin should not exceed 5 mg once daily. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 and BCRP. Delayed or missed dose: If a dose is missed or delayed for <12 hours after the scheduled dose, the dose should be taken as soon as possible on the same day with a return to the normal schedule the following day. If a dose is missed or delayed for >12 hours after the scheduled dose, the dose should be taken at the usual time the following day. If a patient vomits following the intake of a dose, the next dose should be taken at the usual time the following day. Patients should not take extra doses to make up the missed dose.
Special Populations: Hepatic impairment: Dose modification is not recommended when administering belumosudil to patients with mild or moderate hepatic impairment (Child-Pugh A and B). Belumosudil is not recommended in patients with severe hepatic impairment. The safety and efficacy of belumosudil in severe (Child-Pugh C) hepatic impairment has not been evaluated. For patients with pre-existing severe hepatic impairment (Child-Pugh C), consider the risks and potential benefits before initiating treatment with belumosudil. Monitor patients frequently for adverse reactions.
Renal impairment: No dose modification of Rezurock is required in patients with mild or moderate renal impairment (creatinine clearance ≥30 mL/min). No data are available for patients with severe renal impairment (creatinine clearance <30 mL/min) or for patients with end-stage renal disease on dialysis. Use with caution. Elderly patients (≥65 years): No additional dose adjustments are recommended for elderly patients. Paediatric population: The posology is the same in adults and adolescents aged 12 – 18 years. The safety and efficacy of Rezurock in children and adolescents aged below 12 years of age have not been established. No data are available.
Contraindications: Pregnancy. Hypersensitivity to the active substance or to any of the excipients.
Precautions and Warnings: Female patients of childbearing potential and male patients with female partners of childbearing potential: Women of childbearing potential (WOCBP) should be advised to avoid becoming pregnant while they or their male partner are taking belumosudil and of the potential risk to a fetus. WOCBP should be advised to have a pregnancy test prior to starting treatment with belumosudil. WOCBP and male patients with female partners of childbearing potential must use a highly effective method of contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil. Hepatotoxicity: Increases in liver function tests were observed in clinical studies with belumosudil and generally occurred early during treatment with the incidence decreasing thereafter. Liver function tests should be performed prior to the initiation of treatment with belumosudil and monitored at least monthly during treatment with belumosudil and the dose should be adjusted for ≥Grade 2 toxicities. Sodium: This product is essentially sodium free. **Interactions:** Effect of CYP3A inhibitors on belumosudil: The co-administration of multiple doses of itraconazole did not alter exposure to belumosudil to any clinically relevant extent. Effect of CYP3A inducers on belumosudil: The co-administration of multiple doses of rifampin decreased belumosudil C_{max} by 59% and AUC by 72%. The co-administration of strong CYP3A4 inducers with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200mg twice daily. The co-administration of moderate CYP3A4 inducers e.g., efavirenz is predicted to have a reduced effect on belumosudil as compared to strong CYP3A4 inducers. The co-administration of moderate CYP3A4 inducers with belumosudil may decrease Belumosudil exposure. No dose adjustment is recommended. Effect of proton pump inhibitors on belumosudil: The co-administration of multiple doses of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80%. The co-administration of multiple doses of omeprazole decreased belumosudil C_{max} by 68% and AUC by 47%. The co-administration of proton pump inhibitors with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200mg twice daily. Effect of other gastric acid reducing agents on belumosudil: The co- administration of belumosudil with gastric acid reducing agents other than proton pump inhibitors may decrease belumosudil exposure. No dose adjustment is recommended, however belumosudil and the gastric acid reducing agent should be taken 12 hours apart. In vitro studies: *Effect of belumosudil on CYP3A substrates:* The co- administration of belumosudil is predicted to increase midazolam C_{max} and AUC approximately 1.3- and 1.5-fold, respectively. No dose adjustment is recommended.

The co- administration of belumosudil may increase exposure of sensitive CYP3A4 substrates with a narrow therapeutic index such as ciclosporin and tacrolimus. No dose adjustment is recommended. *Effect of belumosudil on CYP2C9 substrates*: The co-administration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin). *Effect of belumosudil on CYP2C8 substrates*: The co-administration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C8 substrates that are not an OATP1B1 substrate. *Effect of belumosudil on UGT1A1 substrates*: Belumosudil is a weak inhibitor of UGT1A1, the clinical consequences are not known. *Transporters*: Belumosudil is a substrate of P-gp. Belumosudil inhibits BCRP, P-gp, and OATP1B1. The co-administration of oral BCRP, P-gp and OATP1B1 substrates with belumosudil may increase the concentrations of the substrate drugs (such as digoxin and docetaxel). The co-administration of belumosudil with drugs transported by OATP1B1 and BCRP can lead to an increase in exposure of these concomitant drugs (e.g. rosuvastatin) which may increase the risk of these substrate-related toxicities. Co-administration of belumosudil increases rosuvastatin C_{max} and AUC by 3.6 and 4.6-fold, respectively.

Pregnancy: There are no data on the use of belumosudil in pregnant women. Belumosudil can cause fetal harm based on findings from animal studies and its mechanism of action. As a precautionary measure, belumosudil is contraindicated in pregnancy. **Breast- feeding:** It is unknown whether belumosudil or its metabolites are excreted in human milk. No data are available regarding the presence of belumosudil or its metabolites in animal or human milk or its effects on the breast-fed child, or on milk production. A risk to the infant cannot be excluded. Because of the potential for serious adverse reactions in a breast-fed child, breast-feeding should be discontinued during treatment with belumosudil and for at least one week after the last dose. **Fertility:** There are no human data on the effect of belumosudil on fertility. Based on findings from animal studies, belumosudil may impair male and female fertility at dose levels above the recommended clinical dose. The effects on fertility are reversible.

Adverse Reactions: Very common: Nausea, asthenia. Common: upper and lower respiratory tract infections, anaemia, leukopenia, platelet count decreased, decreased appetite, hyperglycaemia, headache, neuropathy peripheral, dizziness, hypertension, dyspnoea, cough, diarrhoea, vomiting, abdominal pain, constipation, AST and ALT increased, gamma-glutamyltransferase increased, pruritus, musculoskeletal pain, muscle spasms, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine increased, oedema, pyrexia, weight decreased. *Prescribers should consult the SmPC in relation to other adverse reactions.*

Legal Category: POM

GB List Price and Marketing Authorisation Number:
200mg x 30 tablets (PLGB 04425/0902): £6708.

Marketing Authorisation Holder: Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.

Further information is available from: Medical Information, Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.
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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to the Sanofi drug safety department on Tel: 0800 0902 314. Alternatively, send via email to UK-drugsafety@sanofi.com