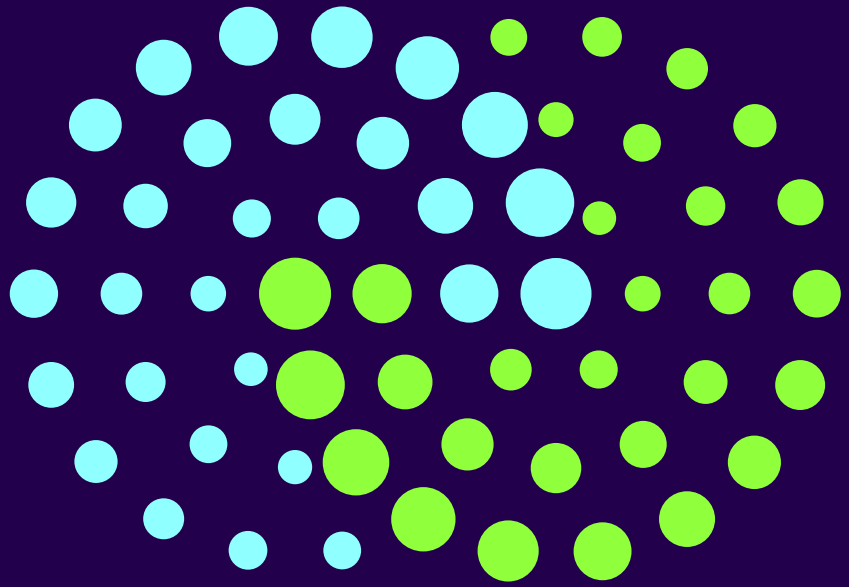

Frontline treatment of chronic GvHD

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GvHD, graft-versus-host disease.

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.

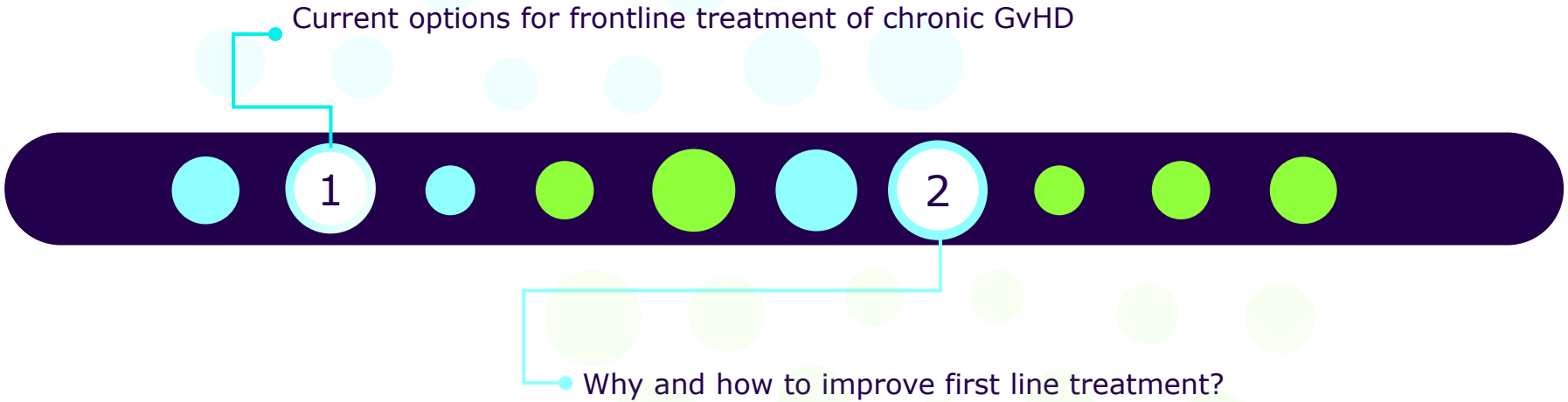
Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to the Sanofi drug safety department on 0800 0902 314. Alternatively, send via email to UK-drugsafety@sanofi.com.

Prescribing information is available at the end of this presentation.

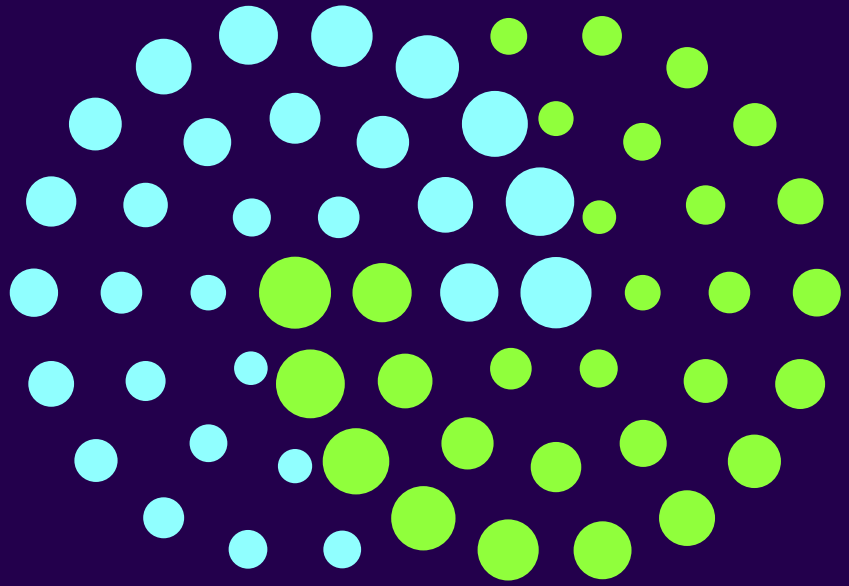
Disclosures

- **Speakers Bureau**: Kite-Gilead, Novartis
- **Advisory board**: Kite-Gilead, Novartis, BMS, Janssen, Jazz pharmaceuticals, Noevii, Sanofi, MSD, Amgen, Pfizer

Objectives



GvHD, graft-versus-host disease.



Background

1. Chronic GvHD requires multiple lines of therapies

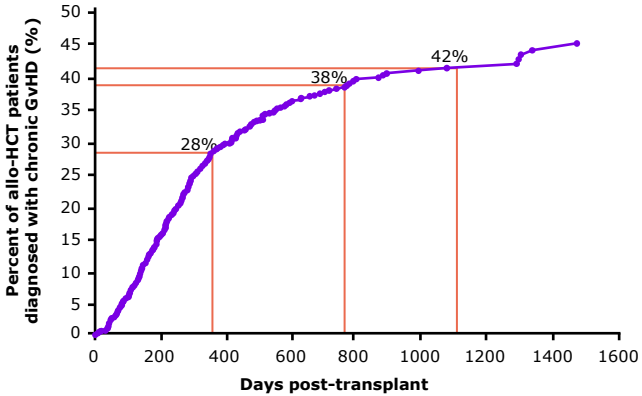


Figure 1.
Chronic GvHD cumulative incidence curve among allogenic HCT patients[1]

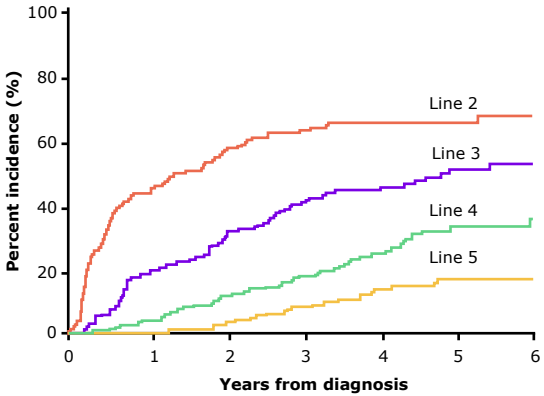


Figure 2.
Cumulative incidence of starting LOTs[2]

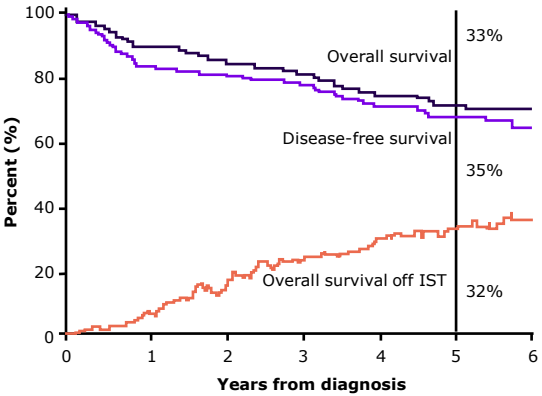


Figure 3.
Prevalence of OS, DFS and OS without IST[2]

allo, allogenic; DFS, disease-free survival; GvHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; IST, immunosupressive therapy; LOT, lines of therapy; OS, overall survival.

1. Bachier CR, et al. Transp Cell Ther 2021;27:504.e1–504.e6; 2. Lee SJ, et al. Biol Blood Marrow Transplant 2018;24:555–62.

2. Chronic GvHD is associated with lower relapse[1]

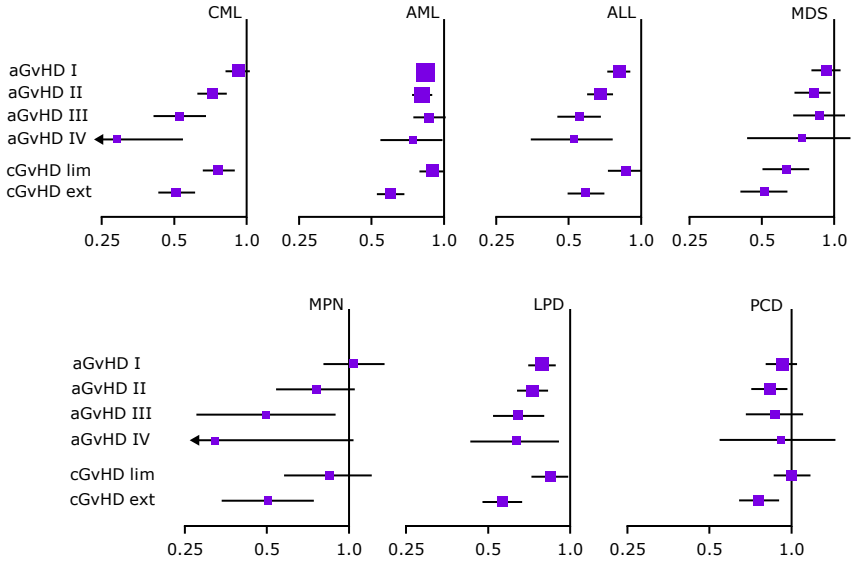


Figure 1. HRs for disease relapse/progression in patients developing aGvHD and/or cGvHD grouped disease[1] Positions of boxes represent HRs; size of box represents fraction of patients experiencing GvHD of this grade and horizontal lines represents 95% CIs. HRs for aGvHD and cGvHD were derived from separate Cox models, each adjusted for disease stage, graft source, intensity of conditioning regimen, type of donor, T-cell depletion of the graft and year of transplant.

3. Chronic GvHD severity impacts survival and NRM but not relapse[2]

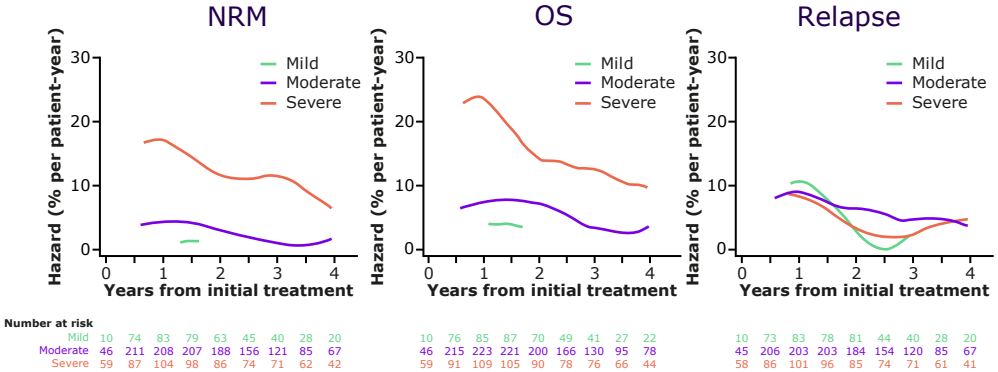
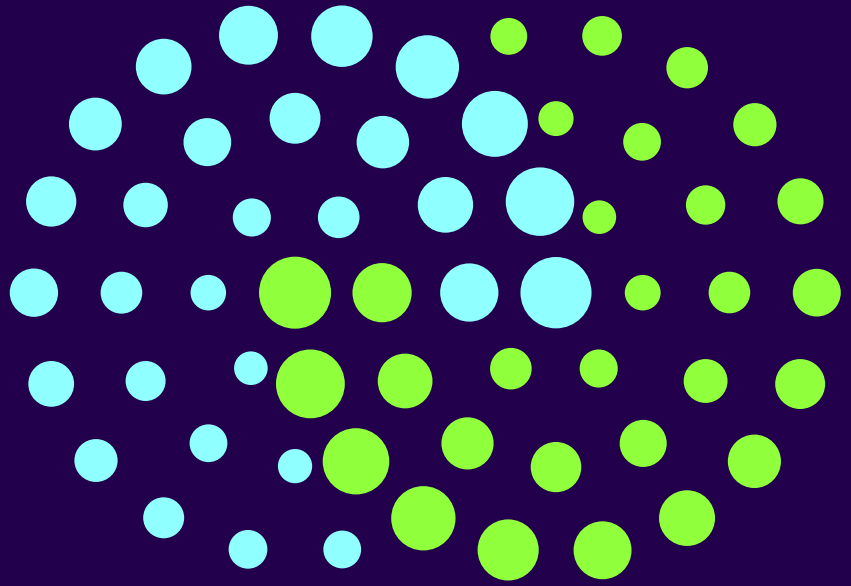


Figure 2. Smoothed hazard rates over time according to NIH global score. Plots are not illustrated for the first 6 months or for time intervals with small numbers of events[2]

aGvHD, acute graft-verus-host disaese; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; cGvHD, chronic graft-versus-host disease; CI, confidence interval; CML, chronic myelogenous leukemia; GvHD, graft-versus-host disease; HR, hazard ratio; LPD, lymphoproliferative disorder; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NRM, non-relapse mortality; OS, overall survival; PCD, plasma cell disorder.

1. Stern M, et al. Leukemia 2014;28:2235–40; 2. Inamoto Y, et al. Hematol 2014;99:1618-23.



Current treatments

Chronic GvHD treatment: Standard first-line

- Decision to start: symptom type, NIH severity grading: moderate and severe
- First-line treatment of newly diagnosed chronic GvHD is steroids (NCCN 2A)
  - 0.5–1.0 mg/day prednisone 2–4 weeks
- No benefit of the addition of other (OLD) agents (azathioprine, cyclosporine A, thalidomide, mycophenolate mofetil, or hydroxychloroquine….) to prednisone

- If the patient is already on streoid treatment, the dose of steroids can be increased (if lower than 1 mg per kg) and an alternative strategy is usually applied, such as CNI, ECP (NCCN 2C)
- If already receiving full dose steroid and cyclosporine A, no standard treatment is available. These patients should be treated in clinical trials, if possible (NCCN 2C)

CNI, calcineurin inhibitor; GvHD, graft-versus-host disease; ECP, extracorporeal photopheresis; NCCN, national compehensive cancer network; NIH, National Institute of Health.
Penack O et al. Lancet Hematol 2024;S2352-3026:00342-3; Flowers M and Martin P. Blood 2015;125:606–15.

Chronic GvHD treatment: Standard first-line

The time needed to preliminarily assess the efficacy of first-line treatment of chronic GvHD is at least one month (NCCN 2C)

Steroid refractory chronic GvHD:

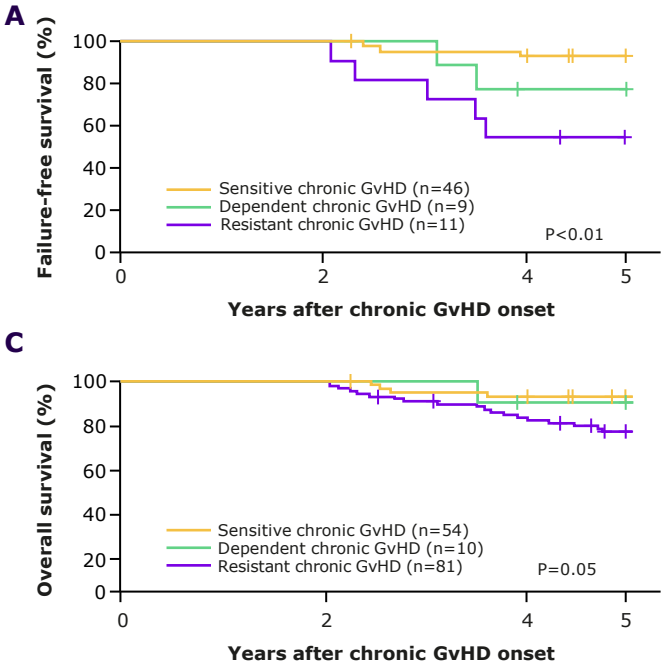
Progression while on prednisone ≥1 mg/kg/d for 1–2 weeks or stability while on prednisone at 0.5 mg/kg/d for 1–2 months

Steroid dependent chronic GvHD:

Prednisone >0.25 mg/kg/d needed to prevent recurrence or progression by at least two individual unsuccessful attempts to taper to a lower dose, separated at least by 8 weeks

Limitations

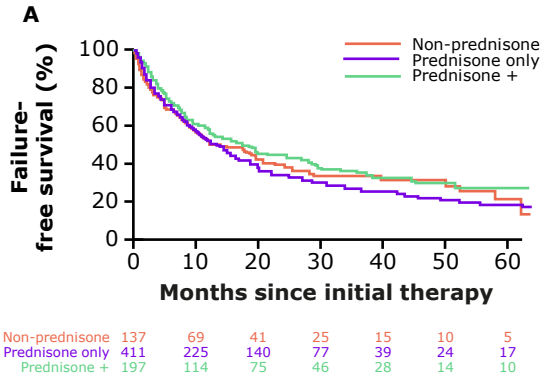
- Usually much more prolonged, 1 year
- Overall responses 50% over 2–3 years
- Most requiring further lines
- Toxicity and disability

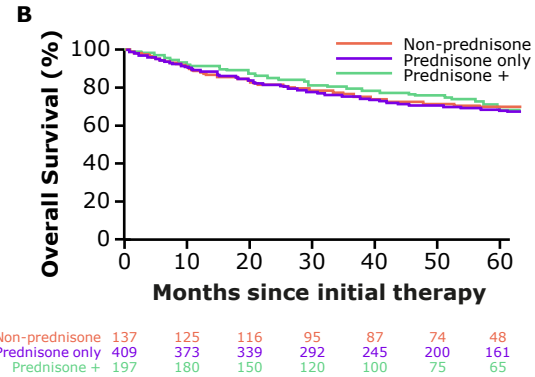


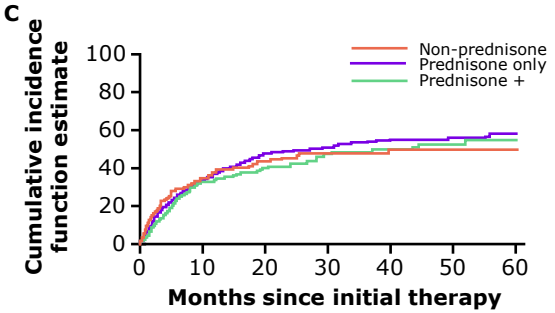
d, day; GvHD; graft-versus-host disease; NCCN, national compehensive cancer network.

Penack O et al. Lancet Hematol 2024; S2352-3026(23)00342-3; Schoemans HM, et al. Bone Marrow Transplant 2018;53:1401–1415; El Jurdi, N et al. Transplant Cell Ther 2024; https://doi.org/10.1016/j.jtct.2024.03.011; Wolff D, et al. Bone Marrow Transplant 2021;56:2079–2087.

Chronic GvHD treatment: Standard first-line





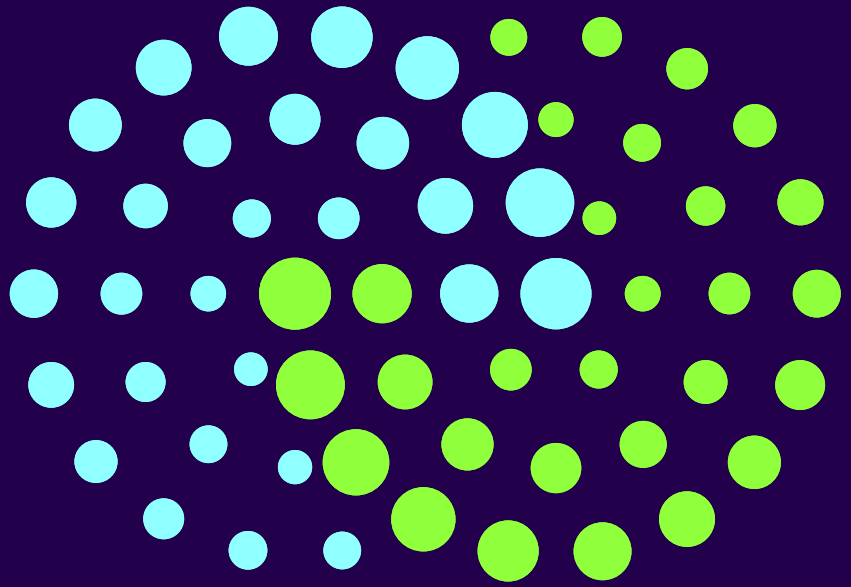


No differences according to initial therapy

No differences according to steroids doses

GvHD, graft-versus-host disease

Pidala J, et al. Blood Adv 2021;5(22):4549-4559.



Why and how to improve first line treatment

Why and how to improve first-line treatment

WHY

- Reduce chronic GvHD progression
- Reduce steroid AEs
- Reduce chronic GvHD sequelae and mortality
- Improve ORR in poor-R, difficult to treat organs

HOW

- Association of new drugs with steroids
- Using new drugs shortening the duration and dose of steroids up to steroid-free options

AE, adverse event; GvHD, graft-versus-host disease; ORR, overall response rate; R, response.
Pidala J, et al. Blood Adv 2021;5:4549–59. (Clinical insights provided by Professor Bonifazi)

Latest (and ongoing) studies for first-line treatment of chronic GvHD

With steroid association

Phase	Treatment	Drug mechanism	Enrollment (estimated)	Key primary endpoint	NCT number
Phase 1/2	Ofatumumab+ prednisone	Anti-CD20	44	ORR 6 months	NCT01680965
Phase 2	Arsenic Trioxide+prednisone	Glutatione depletion	21	ORR 6 months	NCT02966301
Phase 2	Bortezomib+ prednisone	Proteasome inhibitor	22	ORR 15 weeks	NCT00815919
Phase 2	Everolimus+ prednisone	mTOR inhibitor	38	ORR 6 months	NCT01862965
Phase 2	Ruxolitinib+ prednisone in BOS	JAK1/2 inhibitor	50	FEV_1 increase ≥10% 3 months	NCT05413356
Phase 1	SHR0302+ prednisone	JAK1 inhibitor	73	Safety	NCT04146207
Phase 2	Ibrutinib + itraconazole + prednisone	BTK inhibitor	13	Safety	NCT05348096
Phase 3	Ibrutinib+ prednisone	BTK inhibitor	193	ORR 48 weeks	NCT02959944
Phase 3	Hydroxychloroquine+ prednisone	APC inhibition	82	PFS (length of study)	NCT00031824

APC, antigen presenting cell; BOS, bronchiolitis obliterans syndrome; BTK, Bruton's tyrosine kinase; FEV_1, forced expiratory volume in 1 second; GvHD, graft-versus-host disease; mTOR, mechanistic target of rapamycin; JAK, janus kinase; ORR, overall response rate; PFS, progression-free survival.
Table adapted from Hamilton BK. Hematololgy Am Soc Hematol Educ Program 2021:648–54; www.clinicaltrials.gov (last accessed April 2024).

Latest (and ongoing) studies for first-line treatment of cGVHD

Phase	Treatment	Drug mechanism	Enrollment (estimated)	Key primary endpoint	NCT number
Phase 2/3	Itacitinib + prednisone	JAK1 inhibitor	155	Safety/ORR 6 months	NCT03584516
Phase 2	Belumosudil + prednisone (BEBOP trial) newly or early stage BOS	ROCK2 inhibitor	45	ORR 24 weeks	NCT05922761
Phase 3	Belumosudil+ prednisone	ROCK2 inhibitor	240	EFS	NCT06143891
Without steroid association					
Phase 1	Fostamatinib	SYK inhibitor	19	Maximum tolerated dose	NCT02611063
Phase 1	Extracorporeal photopheresis with methoxalen + standard of care	Treg stimulation	60	ORR 28 weeks	NCT01380535
Phase 2	Belumosudil - Pre-emptive	ROCK2 inhibitor	82	Time to next IS treatment	NCT05996627
Phase 2	Itacitinib + Extracorporeal photopheresis	JAK1 inhibitor/ Treg stimulation	3	ORR 24 weeks	NCT04446182
Phase 2	Ibrutinib	BTK inhibitor	40	ORR 6 months	NCT04294641
Phase 2	Ibrutinib + Rituximab	BTK inhibitor /anti-CD20	19	Remaining off IS therapy at 8 weeks	NCT04235036

BTK Bruton's tyrosine kinase; cGvHD, chronic graft-versus-host disease; EFS, event-free survival; JAK, janus kinase; IS, immunosuppresive; SYK spleen tyrosine kinase; Treg, T-regulatory cell; ORR, overall response rate.
Table adapted from Hamilton BK. Hematololgy Am Soc Hematol Educ Program 2021:648–54; www.clinicaltrials.gov (last accessed April 2024).

Despite notable therapeutic advancements for chronic GvHD, lung specific responses are challenging

	Cases (%)	ORR	ORR-Lung	PR-Lung	CR-Lung
Ruxolitinib (Zeiser 2021)	70/165 (42)	49.7%	6/70 (9%)	NR	NR
Belumosudil* (Cutler 2021)	47/132 (36)	75%	12/47(26%)	6/47 (13%)	6/47(13%)
Belumosudil* (Jagasia 2021)	17/54 (31)	65%	12/17 (70%)	12/17 (70%)	0/12 (0%)
Belumosudil* (Defilipp 2022)	59/59 (100)	NR	19/59 (32%)	10/59 (17%)	9/59 (15%)
Ibrutinib (Miklos 2017)	2/42 (5)	67%	NR	NR	NR
Ibrutinib (Miklos 2023)	18/95 (19)	41%	NR	NR	NR
Ibrutinib (Chin 2021)	18/53 (34)	11%	NR	NR	NR
Axatilimab (Kitko 2023)	16/40 (40)	82%	5/16 (31%)	3/16 (19%)	2/16 (12%)

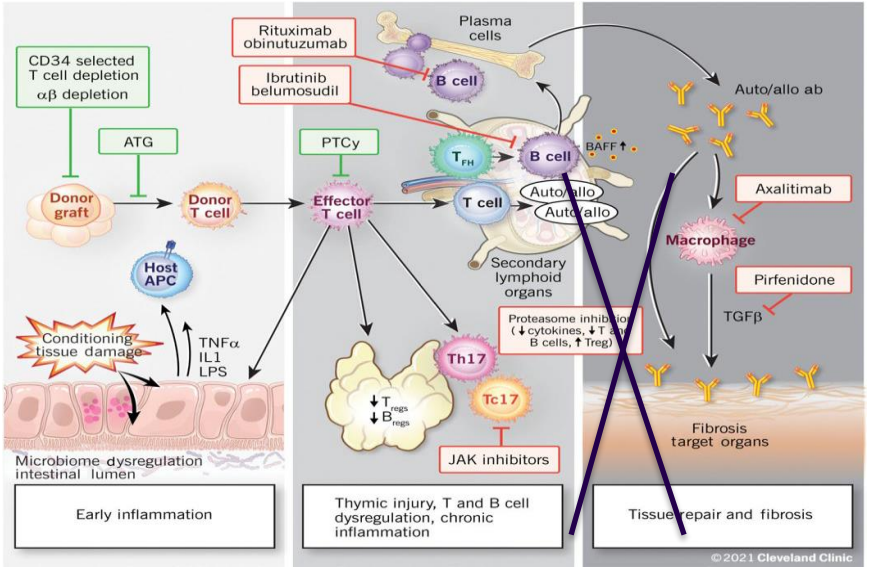
***belumosudil was administered in the 3rd line setting in line with the product label.**
This table includes data from various trials. Direct comparisons should not be made as no head-to-head study was performed and as various factors, such as patient populations, may vary between trials. This information is provided for educational purposes only.

CR, complete response; GvHD, graft-versus-host disease; NR, not reported; ORR, overall response rate; PR, partial response.

Zeiser R, et al. N Engl J Med 2021;385:228-38; Cutler C, et al. Blood, 2021;138:2278–89; Jagasia M, et al. J Clin Oncol, 2021;39:1888–98; DeFilipp Z, et al. Blood Adv, 2022;6:6263–70; Miklos D, et al. Blood, 2017;130:2243-50; Miklos D et al. J Clin Oncol 2023;41:1876–87; Chin KK, et al. Transplant Cell Ther 2021;27:990.e1–990.e7; Kitko CL et al., J Clin Oncol. 2023;41:1864-75.

Conclusions

- Chronic GvHD still impacts late mortality, quality of life and disability
- The current standard approach with steroids could be hopefully overcome by new target-drugs
- Earlier interventions, in particular for ***difficult-to-treat organs***, are deemed to prevent progression, reduce severity and long-term sequelae, and improve long-term patient outcomes (before fibrosis appearance)



GvHD, graft-versus-host disease.
Hamilton BK, Haematology Am Soc Hematol Educ Program. 2021;648-54.

Acknowledgements

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Patients

Nurses & Transplant coordinators

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Transplant unit

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Francesco De Felice
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Michele Dicataldo
Marcello Roberto

Rita Bertoni
Enrica Tomassini

Research immunobiology lab

Gianluca Storci
Serena De Matteis
Noemi Laprovitera
Nicola Salvatore Bertuccio
Daria Messelodi
Francesca Vaglio
Lucrezia Rossini
Maria Naddeo

Massimiliano Bonafe'
Manuela Ferracin
Paolo Garagnani

Labs of immunology And processing

Pierluigi Tazzari
Francesca Ricci
Elena Campanini
Elisa Dan
Barbara Sinigaglia
Luca Zazzeroni

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.
uk-medicalinformation@sanofi.com

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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.
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