# Retrospective analysis on molecular characteristics and clinical outcome of pre-CAR chronic Graft-versus-Host Disease after CAR-T19 or CAR-T BCMA treatment for relapse of the hematological disease

Saar Gill and Dietger Niederwieser

## Background

Hematopoietic cell transplantation (HCT) is an established treatment for patients with hematological malignancies including B-cell neoplasia. The principles of HCT reside in killing the malignant cells by a preparative regimen and by an immunological anti-tumor effect. Unfortunately, HCT may be associated with acute and chronic alloimmune reactions against the host (Graft-versus-Host Disease (GvHD)), Chronic graft-versus-host disease (cGvHD) remains the leading cause of long-term morbidity and mortality after HCT and may affect different organs and its more severe form life-threatening. Human and animal studies support the conclusion that the biology of cGvHD is complex and heterogenous, but B-cells, T-cells, macrophages and regulatory cells are described to play a key role in this process (Figure 1) [1]. Interventions targeting these cells and their interactions have been successfully used in the treatment of steroid-resistant cGVHD. Agents with regulatory approval for the treatment of cGVHD include ruxolitinib (JAK1/2 inhibition), ibrutinib (BTK inhibition), belumosidil (ROCK2 inhibition), and axatilimab (CSF1 receptor blockade). Many other agents are used off-label.[2,3]

B-cells have been shown to have an important role in preclinical murine cGvHD studies and in clinical human biomarker studies [4]. Based on these, a single-arm open-label study with ibrutinib gained regulatory approval in 2017. A further B-cell targeting strategy for cGvHD demonstrated clinical responses in steroid-refractory cGvHD using the anti-CD20 monoclonal antibody (mAb) rituximab.

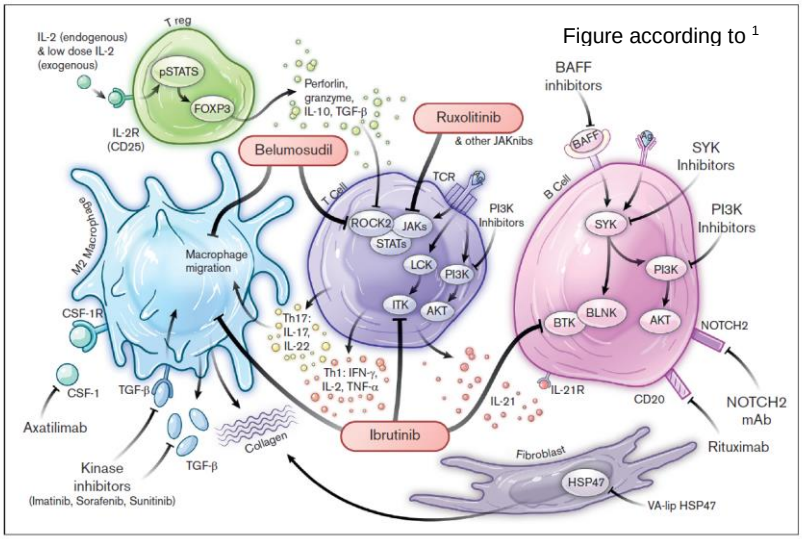


**Figure 1. Pathophysiological networks and targeted approaches for prevention and treatment of cGvHD.** FDA-approved drugs are highlighted within red bubbles. Ag, antigen; AKT, Ak strain transforming; BAFF, B-cell activating factor; BAFF R, BAFF receptor; BCR, B-cell receptor; BLNK, B-cell linker; BTK, Bruton's Tyrosine Kinase; BTK/ITK, Bruton's Tyrosine Kinase /IL-2 Inducible T-cell Kinase; CD, cluster of differentiation; FOXP3, forkhead box P3; HSP47, heat shock protein 47; INF-γ, interferon gamma; ITK, IL-2-inducible T-cell kinase; Jakinibs, Janus kinase inhibitors; JAKs, Janus kinases; LCK, lymphocyte-specific protein tyrosine kinase; NOTCH2, Neurogenic locus notch homolog protein 2; NOTCH2 mAb, neurogenic locus notch homolog protein 2 mAb; PI3K, phosphoinositide 3-kinase; pSTAT5, phosphorylated signal transducer and activator of transcription 5; ROCK2, Rho associated coiled-coil containing protein kinase 2; STATs, signal transducers and activators of transcription; SYK, spleen associated tyrosine kinase; TCR, T-cell receptor; TGF-β, transforming growth factor beta; Th, T helper; TNF-α, tumor necrosis factor alpha; Treg, T regulatory cell; VA-lip HSP47, vitamin A coupled liposomal containing small interfering RNA (siRNA) against heat shock protein 47.

The overall responses to ruxolitinib[2], belumosidil[5], ibru-tinib[4]and axatilimab[6,7] in the pivotal studies were 50%, 69% 67% and 70% respectively. Complete responses were infrequent. Thus, there is still a high unmet medical need for more effective and specific treatment options for steroid-refractory cGvHD.

Despite infrequent, relapses of the underlying disease occur during cGvHD and are treated either with a second HCT or in B-cell malignancies with Chimeric Antigen Receptor (CAR-T) 19 or in multiple myeloma by CAR-T BCMA. These CAR-T cell therapies have transformed treatment of B-cell malignancies and are used successfully in second line therapies of Non-Hodgkin Lymphomas, ALL and CLL in adult and pediatric patients. These ex-vivo cell therapies have shown remarkable responses to patients with advanced and refractory cancers even after relapses following HCT. Recently CAR-T cell therapy has shown great promise in the treatment of patients with B-cell mediated autoimmune disease[8].

The observations described above provide a solid rationale for testing CAR-T19 cells for the treatment of cGvHD through killing of B-cells that are involved in initiation and perpetuation of cGvHD. Successful treatment of autoimmune disease with similar pathophysiology and clinical appearance of cGvHD represent a further rationale. In a first step we will collect retrospective information on patients with chronic GvHD relapsing after HCT treated either with CAR-T19 (ALL, CLL, NHL) or CAR-T BCMA (multiple Myeloma) for relapse. In case of positive results a prospective study is planned.

Hypothesis

CAR-T19 cell and CAR-T BCMA treatment will induce CR and resolution of their cGVHD in pediatric and adult patients with relapse of their B-cell malignancy (including Multiple myeloma) and chronic GvHD.

Previous observation

An unpublished clinical observation reported a resolution of extensive cGvHD in a patient treated with CAR-T19 for relapse of his B-cell malignancy after HCT (….).

Aim of the study

1. Role of CAR-T19 and CAR-T BCMA treatment on pre-CAR cGvHD in patients relapsing of their B-malignancies (ALL, NHL, CLL).
2. peripheral blood mononuclear cells that were obtained and viably cryopreserved at pre- and post-CART timepoints, if available, would be analyzed using single cell RNA sequencing to uncover underlying biology of response or resistance.

Study type

Retrospective observational multicenter study

Inclusion criteria

Retrospective collection of worldwide information on adult and pediatric patients relapsing after allogeneic HCT with chronic GvHD and treated with CAR-T19 or CAR-TBCMA cells from the following registries: EBMT, cIBMTR, APBMT, LABMT, EMBMT and singular institutions

Endpoints

Primary: Change in cGvHD by 24 weeks after CAR-T19 infusion using established response criteria according to NIH consensus

Secondary: Overall survival after CAR-T infusion, failure-free survival (FFS), duration of response (DOR), nonrelapse mortality (NRM), and malignancy relapse/recurrence, % full donor chimerism, Overall response rate (ORR; complete response or partial response by National Institutes of Health response criteria), Dosing of Immunosuppressive therapy

Study size:

We expect to include at least 10 patients and have biological material on at least 5 patients.

Collaboration agreement

A collaboration agreement will be signed between WBMT and society/centers

Publication policy

Results will be published according to the number of patients in one (combined) or two (clinical and laboratory) manuscripts. Every center entering a patient will have one author/patient in alphabetical order between the second and last author. For the clinical part we suggest Niederwieser first and Gill last (or opposite). For the laboratory work to be determined otherwise result included in the main paper.

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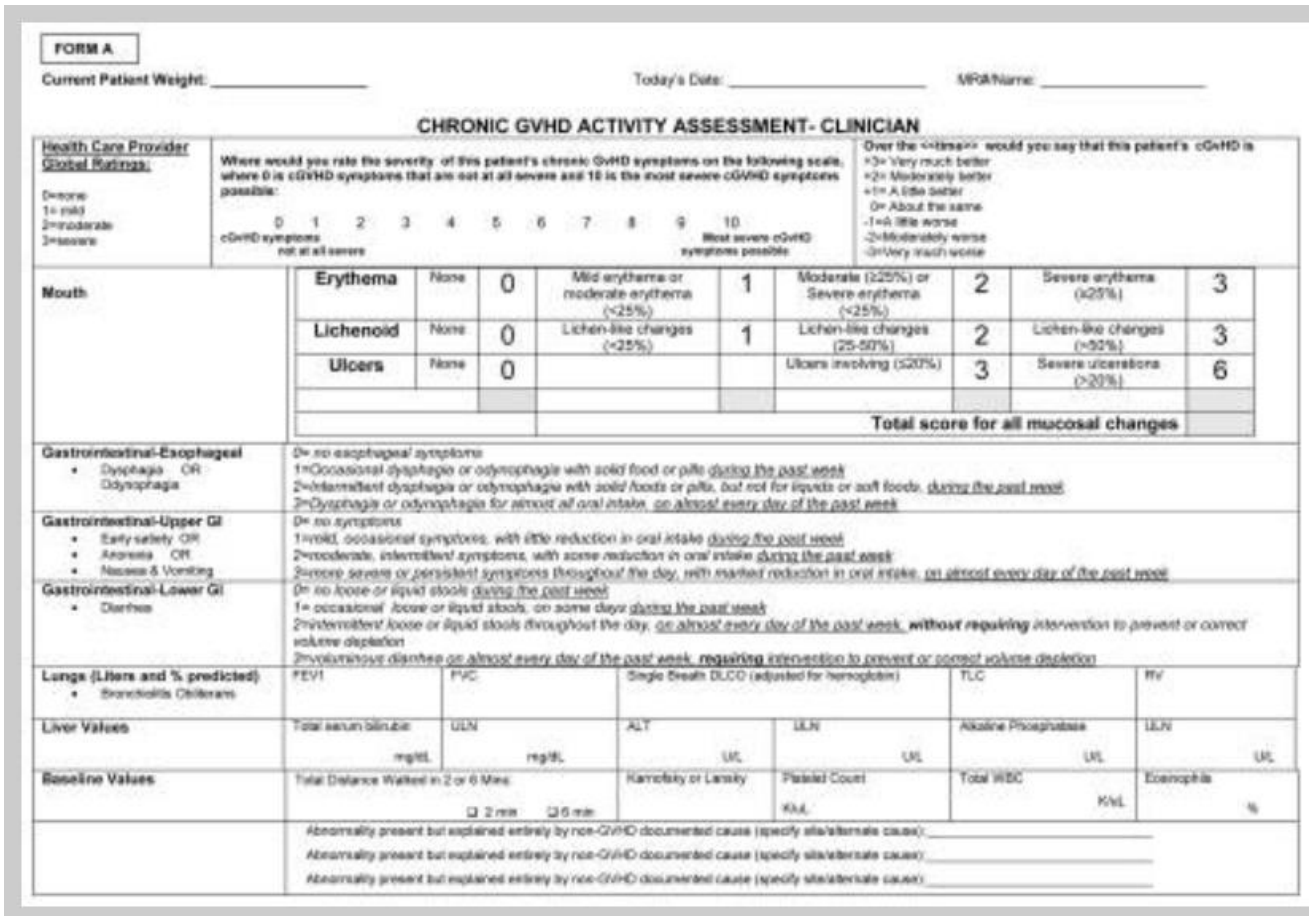
Appendix A: Response criteria for cGvHD will be collected according to the NIH consensus[9]
Appendix B: Crf

Measuring therapeutic responses in cGvHD[9]



FORM A

Current Patient Weight: _____ Today's Date: _____ MRN/Name: _____

**CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN**

| Health Care Provider Global Ratings: | Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible: | Over the <<time>> would you say that this patient's cGvHD is |
|---|---|---|
| 0=none<br>1= mild<br>2=moderate<br>3=severe | 0 1 2 3 4 5 6 7 8 9 10<br>cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible | +3= Very much better<br>+2= Moderately better<br>+1= A little better<br>0= About the same<br>-1=A little worse<br>-2=Moderately worse<br>-3=Very much worse |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Mouth** | **Erythema** | None | 0 | Mild erythema or moderate erythema (<25%) | 1 | Moderate (≥25%) or Severe erythema (<25%) | 2 | Severe erythema (≥25%) | 3 |
| | **Lichenoid** | None | 0 | Lichen-like changes (<25%) | 1 | Lichen-like changes (25-50%) | 2 | Lichen-like changes (>50%) | 3 |
| | **Ulcers** | None | 0 | | | Ulcers involving (≤20%) | 3 | Severe ulcerations (>20%) | 6 |
| | | | | | | | | | |
| | | | | | | **Total score for all mucosal changes** | | | |

| | |
|---|---|
| **Gastrointestinal-Esophageal**<br>• Dysphagia OR Odynophagia | 0= no esophageal symptoms<br>1=Occasional dysphagia or odynophagia with solid food or pills during the past week<br>2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week<br>3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week |
| **Gastrointestinal-Upper GI**<br>• Early satiety OR<br>• Anorexia OR<br>• Nausea & Vomiting | 0= no symptoms<br>1=mild, occasional symptoms, with little reduction in oral intake during the past week<br>2=moderate, intermittent symptoms, with some reduction in oral intake during the past week<br>3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week |
| **Gastrointestinal-Lower GI**<br>• Diarrhea | 0= no loose or liquid stools during the past week<br>1= occasional loose or liquid stools, on some days during the past week<br>2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion<br>3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion |

| | | | | | |
|---|---|---|---|---|---|
| **Lungs (Liters and % predicted)**<br>• Bronchiolitis Obliterans | FEV1 | FVC | Single Breath DLCO (adjusted for hemoglobin) | TLC | RV |
| **Liver Values** | Total serum bilirubin mg/dL | ULN mg/dL | ALT U/L | ULN U/L | Alkaline Phosphatase U/L | ULN U/L |
| **Baseline Values** | Total Distance Walked in 2 or 6 Mins ☐ 2 min ☐ 6 min | Karnofsky or Lansky | Platelet Count K/uL | Total WBC K/uL | Eosinophils % |

Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____

Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____

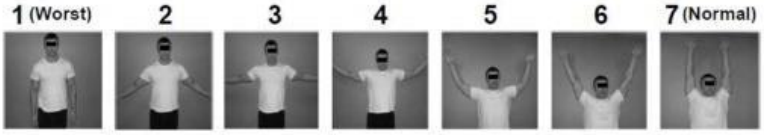
Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____

## CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **SKIN**<br><br>*GVHD features to be scored by BSA:*<br>**Check all that apply:**<br>Maculopapular rash / erythema<br>Lichen planus-like features<br>Sclerotic features<br>Papulosquamous lesions or ichthyosis<br>Keratosis pilaris-like | No BSA involved | 1-18% BSA | 19-50% BSA | >50% BSA |
| Abnormality present but explained entirely by non-GVHD documented cause (specify):_____ | | | | |
| **SKIN FEATURES SCORE:** | No sclerotic features | | Superficial sclerotic features "not hidebound" (able to pinch) | **Check all that apply:**<br>Deep sclerotic features<br>"Hidebound" (unable to pinch)<br>Impaired mobility<br>Ulceration |
| If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____<br><br>How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible:<br><br>0 1 2 3 4 5 6 7 8 9 10<br>Symptoms not at all severe … Most severe symptoms possible | | | | |
| **EYES** | No symptoms symptoms | Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day) | Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS | Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS |
| Abnormality present but explained entirely by non-GVHD documented cause (specify):_____ | | | | |
| **LUNGS** | No symptoms | Mild symptoms (shortness of breath after climbing one flight of steps) | Moderate symptoms (shortness of breath after walking on flat ground) | Severe symptoms (shortness of breath at rest; requiring $0_2$) |
| Abnormality present but explained entirely by non-GVHD documented cause (specify):_____ | | | | |

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **JOINTS AND FASCIA** | No symptoms | Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL | Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL | Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.) |
| Abnormality present but explained entirely by non-GVHD documented cause (specify):_____ | | | | |

**Shoulder**

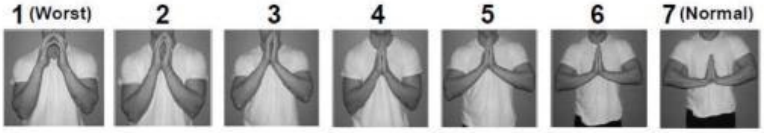



❑ Not done

**Elbow**

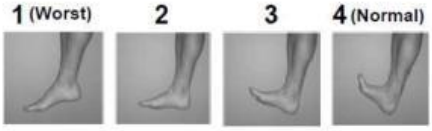

❑ Not done

**Wrist/finger**




❑ Not done

**Ankle**




❑ Not done

Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

**FORM B**

Today's Date: _____ MR#/Name: _____

## CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

| **Symptoms**<br>**Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.** | **Not Present** 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | **As Bad As You Can Imagine** 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Your **skin itching** at its WORST? | O | O | O | O | O | O | O | O | O | O | O |
| Your **skin and/or joint tightening** at their WORST? | O | O | O | O | O | O | O | O | O | O | O |
| Your **mouth sensitivity** at its WORST? | O | O | O | O | O | O | O | O | O | O | O |
| Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis) | O | O | O | O | O | O | O | O | O | O | O |

| | | |
|---|---|---|
| Eyes | What is your main complaint with regard to your eyes? | |
| | Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe): | 0 1 2 3 4 5 6 7 8 9 10 |

**Patient Global Ratings:**

**1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?**
1= mild
2=moderate
3=severe

**2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.**

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

**3. Compared to a month ago, overall would you say that your cGvHD symptoms are:**

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Appendix B
Summary of Crf

| Patient and HCT characteristics | | | | | | | | | | cGvHD | | | | | chimerism (possibly T) | Relapse post allo | | cGvHD after CAR-appearance or resoltuion | | | | Outcome of malig-nancy | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Identification | center | Respons to EMail | responsible physician | email | disease | Stage | Age at HCT | HCT date if possible | conditioning | donor | cGvHD date or day after HCT | cGvHD stage at diagnosis | Max stage | Before CAR-T 19/BCMA | Treatment line | % before CAR-T | Yes/no | Relapse date or day after HCT | CAR-T infusion or day after HCT | Max cGvHD response or appearance after CAR-T or BCMA | Immune suppression after CART infusion | Response day day 28 | remission | Date or days after CAR-T | alive | Non relapse mortality |
| Example | | | | | CLL | richter transformation | 44 a | 02/24/2021 | MAC | sibling | 07/22/2023 | | | | PD—> RT—> Ibrutinib | 99% | CART19 | 8/20/2024 | 10/31/2024 | GvHD score | No CyA, no steroids | GvHD score | yes | 30/6/2025 | yes | no |

## References


1 Buxbaum NP, Socié G, Hill GR, MacDonald KPA, Tkachev V, Teshima T *et al.* Chronic GvHD NIH Consensus Project Biology Task Force: evolving path to personalized treatment of chronic GvHD. *Blood Adv* 2023; **7:** 4886–902; doi:10.1182/bloodadvances.2022007611

2 Zeiser R, Russo D, Ram R, Hashmi SK, Chakraverty R, Middeke JM *et al.* Ruxolitinib in Patients With Corticosteroid-Refractory or Corticosteroid-Dependent Chronic Graft-Versus-Host Disease: 3-Year Final Analysis of the Phase III REACH3 Study. *J Clin Oncol* 2025: JCO2402477; e-pub ahead of print 25 June 2025; doi:10.1200/JCO-24-02477

3 Forcade E, Paz K, Flynn R, Griesenauer B, Amet T, Li W *et al.* An activated Th17-prone T cell subset involved in chronic graft-versus-host disease sensitive to pharmacological inhibition. *JCI Insight* 2017; **2; e-pub ahead of print** 15 June 2017; doi:10.1172/jci.insight.92111

4 Miklos DB, Kim H, Miller KH, Guo L, Zorn E, Lee SJ *et al.* Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. *Blood* 2005.

5 Jagasia M, Arora M, Flowers MED, Chao NJ, McCarthy PL, Cutler CS *et al.* Risk factors for acute GVHD and survival after hematopoietic cell transplantation. *Blood* 2012; **119:** 296–307; doi:10.1182/blood-2011-06-364265

6 Le RQ, Godder K, Wang J, Collazo JS, Konicki R, Choe M *et al.* FDA Approval Summary: Axatilimab for Adult and Pediatric Patients Weighing at Least 40 Kilograms with Chronic GVHD after Two Prior Lines of Systemic Therapy. *Clin Cancer Res* 2025; e-pub ahead of print 27 June 2025; doi:10.1158/1078-0432.CCR-25-0896

7 Wolff D, Cutler C, Lee SJ, Pusic I, Bittencourt H, White J *et al.* Axatilimab in Recurrent or Refractory Chronic Graft-versus-Host Disease. *N Engl J Med* 2024; **391:** 1002–14; doi:10.1056/NEJMoa2401537

8 Schett G, Mackensen A, Mougiakakos D. CAR T-cell therapy in autoimmune diseases. *Lancet* 2023; **402:** 2034–44; e-pub ahead of print 22 September 2023; doi:10.1016/S0140-6736(23)01126-1

9 Lee SJ, Wolff D, Kitko C, Koreth J, Inamoto Y, Jagasia M *et al.* Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. *Biol Blood Marrow Transplant* 2015; **21:** 984–99; doi:10.1016/j.bbmt.2015.02.025

worldwide network
for blood and marrow transplantation
NGO in official relations with the World Health Organization (WHO)

WBMT, c/o Blutspende SRK Schweiz AG, Waldeggstrasse 51, CH-3097 Liebefeld, Switzerland

# TO WHOM IT MAY CONCERN

January, 2026

**Re: "Clinical outcome of chronic Graft-versus-Host Disease after CAR-T19 or CAR-T BCMA for hematological relapse" by Saar Gill and Dietger Niederwieser**

This is to confirm that the WBMT is conducting a retrospective study on clinical outcome of chronic Graft-versus-Host Disease following CAR-T19 or CAR-TBCMA treatment for hematological relapse. The PI of the retrospective analysis are Gill Saar and Dietger Niederwieser. Information on patients treated on different sites worldwide will be collected in anonymized form and analyzed by the PI. The sites can only see their one and the aggregated data.

Sincerely

Damiano Rondelli
President WBMT

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