Dear Editor,

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of hematopoietic cell transplantation (HCT) conditioning or non-transplant-associated chemotherapy. The three established symptoms of VOD/SOS are elevated bilirubin (although ~20% of patients have anicteric VOD/SOS), sudden weight gain (ascites), and hepatomegaly/liver tenderness. Severe, untreated VOD/SOS has been reported to have a mortality rate >80%, and can result in multi-organ dysfunction (MOD), typically renal and/or pulmonary dysfunction.

VOD/SOS is associated with endothelial cell (EC) damage from chemotherapy and high-dose HCT-conditioning regimens. During HCT, ECs are activated and damaged by cytokines produced by injured tissues and toxic chemotherapy metabolites. EC dysfunction leads to loss of cytoskeletal structure, inflammatory responses resulting in sinusoidal narrowing, and a shift to a procoagulant and hypofibrinolytic state. These effects reduce hepatic venous outflow and induce post-sinusoidal hypertension, potentially leading to MOD.

The incidence of VOD/SOS in adults ranges from 8% to 14%; it can be influenced by multiple factors, including age, primary disease, diagnostic criteria, conditioning regimen, and type of HCT, which may explain variations in the reported incidence among published studies.

**Risk factors**

Multiple factors are known to increase the risk of developing VOD/SOS. Age, leukemia diagnosis, Karntovsky index <90%, glutathione S-transferase Mu 1 null genotype, platelet refractoriness, sepsis pre-HCT, and pre-existing hepatic or pulmonary dysfunction are all patient-related factors associated with a higher VOD/SOS risk. Prior treatments shown to increase VOD/SOS risk include abdominal radiation, HCT (particularly allogeneic and unrelated/human leukocyte antigen mismatch HCT), high-intensity conditioning regimens, and certain regimens for graft-versus-host disease prophylaxis. Prior treatment with the antibody–drug conjugates gemtuzumab ozogamicin (GO) or inotuzumab ozogamicin (InO) has also been shown to increase the risk of VOD/SOS. The reported odds ratio for developing VOD/SOS following GO exposure is 19.8; based on data from Kantarjian et al., the odds ratio for VOD/SOS following InO treatment is calculated to be 22.0.

**GO background**

GO is a humanized anti-CD33 monoclonal antibody conjugated to calicheamicin, a cytotoxic agent. In 2000, GO was granted accelerated approval by the United States (US) Food and Drug Administration (FDA) for relapsed acute myeloid leukemia (AML) in patients aged >60 years or ineligible for intensive induction chemotherapy. In the first year after approval, a black box warning was added regarding severe or fatal VOD/SOS. In 2010, GO was withdrawn from the US and European markets after a phase 3 study; SWOG S0106 failed to show improved efficacy versus standard of care. Later, the phase 3 ALFA-0701 study demonstrated that a lower, fractionated dose allowed
for safer delivery of higher cumulative GO doses (VOD/SOS reported in 6/131 [5%] patients) and led to improved outcomes in patients. Based on these results, GO was reapproved in 2017 by the FDA for the treatment of newly diagnosed and relapsed/refractory CD33-positive AML. In 2018, the European Medicines Agency approved GO combined with daunorubicin/cytarabine for the treatment of patients aged >15 years with de novo CD33-positive AML, except acute promyelocytic leukemia.

The current black box warning for GO lists the risk of hepatotoxicity and VOD/SOS in adult patients who receive higher doses of GO monotherapy, in patients with moderate or severe hepatic impairment prior to receiving GO, and patients treated with GO before or after HCT. InO also uses calicheamicin as its cytotoxic moiety; it targets CD22 and has been associated with a similar increase in risk of hepatotoxicity and VOD/SOS.

Defibrotide background
Defibrotide is approved for the treatment of VOD/SOS with renal or pulmonary dysfunction post-HCT in the US and Canada, and severe hepatic VOD/SOS post-HCT in patients aged >1 month in the European Union. In vivo evidence suggests defibrotide protects ECs and restores the thrombo-fibrinolytic balance. Data on the response to defibrotide in patients who developed VOD/SOS following treatment with GO are limited. We conducted a literature analysis to evaluate outcomes in patients treated with defibrotide after prior GO exposure.

Literature analysis
In May 2019, PubMed was searched for studies and case reports to date that included “gemtuzumab ozogamicin” and “defibrotide”. The search included reports on outcomes of defibrotide prophylaxis or treatment for VOD/SOS that developed following GO treatment. Duplicate studies, reviews, or guidelines were excluded.

Overall, 11 publications were identified (Supplementary Fig. 1); 3 were guideline publications or review articles and were excluded from the analysis. The remaining publications were included and comprised four clinical studies, three case reports, and one retrospective study.

The definition of “successful treatment” varied among the identified studies; therefore, the descriptors used for successful treatment (e.g., survival and/or response) were according to each study design.

Results
Summary of selected studies
Across the studies, 18 patients received defibrotide prophylaxis following GO exposure (Table 1). One patient who received defibrotide prophylaxis and later received defibrotide for treatment of VOD/SOS was also included in the treatment group.

A total of 248 patients in the identified studies had been treated with GO, with 36 (15%) patients developing VOD/SOS (Table 1). Of the patients who developed VOD/SOS following GO exposure, 27 were treated with defibrotide.

Additionally, a congress report was analyzed separately from the results of the PubMed search. In that report, a total of 11 patients received defibrotide prophylaxis following GO exposure.

Defibrotide prophylaxis following GO exposure
Of the 18 patients who received defibrotide for VOD/SOS prophylaxis following GO exposure, 2 (11%) subsequently developed VOD/SOS (Fig. 1a).

In the congress report (analyzed separately), 2 of 11 (18%) patients who received defibrotide prophylaxis for VOD/SOS subsequently developed VOD/SOS (Fig. 1a). Comparatively, 2 of 5 (40%) control patients who did not receive defibrotide prophylaxis also developed VOD/SOS.

Defibrotide treatment of VOD/SOS following GO exposure
A total of 27 of 248 (11%) patients across the identified studies developed VOD/SOS following GO exposure and were treated with defibrotide. Treatment was successful (survival and/or response) in 17 of 27 (63%) patients (Fig. 1b). One patient responded to defibrotide but died due to disease progression after failing to respond to GO.

Of the 27 patients in the overall analysis, 20 were from a phase 2, dose-finding study investigating defibrotide in VOD/SOS patients with MOD post-HCT who had prior GO exposure (Fig. 1b). Ten (50%) of these patients survived to Day 100 post-HCT and 11 of 19 (58%) evaluable patients achieved a complete response (CR). For comparison, patients in the phase 2 study who received defibrotide for VOD/SOS with MOD but had not received previous GO treatment had an overall Day 100 survival rate of 40% (n = 52/129) and a CR rate of 44% (n = 54/122; Fig. 1b). In the entire study population, the overall Day 100 survival rate was 42% (n = 62/149) and the CR rate was 46% (n = 65/141; Fig. 1b). As another point of comparison, in a phase 3 study in which only 1 patient in the defibrotide arm had previous exposure to GO, the observed Day 100 survival rate post-HCT in patients treated with defibrotide (n = 102) was 38% (95% CI: 29%-48%); in the historical control group (n = 32), the observed Day 100 survival rate was 25% (95% CI: 10%-40%).

Across the studies selected for this analysis, there were no new safety signals identified with defibrotide treatment.

Discussion
Several studies and analyses have noted the development of VOD/SOS, both post-HCT and without HCT, in patients with prior GO exposure. Although the data in the literature are limited, this analysis suggests the efficacy...
| Reference                     | Patient population receiving GO | DF as prophylaxis | Outcome of VOD/SOS with DF treatment |
|------------------------------|---------------------------------|-------------------|--------------------------------------|
| PubMed search                |                                 |                   |                                      |
| Battipaglia et al. 2017      | Retrospective; HCT in 146 adults | 4 patients        | 2 developed VOD/SOS                  |
| Richardson et al. 2010       | 20 adult and pediatric patients with VOD/SOS and MOD | —                 | —                                    |
| Zwaan et al. 2010            | 30 pediatric patients treated for AML relapse | 8 patients        | No cases of VOD/SOS                  |
| Bornhäuser et al. 2008       | 31 patients with refractory AML  | —                 | —                                    |
| Lannoy et al. 2006           | 1 patient treated for relapsed AML | —                 | —                                    |
| Reinhardt et al. 2004        | 12 pediatric patients treated for relapsed AML | —                 | —                                    |
| Versluys et al. 2004         | 7 patients treated for relapsed AML prior to HCT | 6 patients        | No cases of VOD/SOS                  |
| Saviola et al. 2003          | 1 adult with refractory AML      | —                 | —                                    |
| Congress report identified separately from PubMed search |                                 |                   |                                      |
| Corbacioglu et al. 2015      | 16 pediatric patients at high risk of VOD/SOS prior to HCT | 11 patients       | 2 developed VOD/SOS                  |

*This ASH abstract reporting a study of 356 patients was not included in the analysis, which focused on published manuscripts in PubMed.*

GO gemtuzumab ozogamicin, DF defibrotide, VOD/SOS veno-occlusive disease/sinusoidal obstruction syndrome, HCT hematopoietic cell transplantation, MOD multi-organ dysfunction, CR complete response, AML acute myeloid leukemia.
of defibrotide in patients with VOD/SOS post-HCT with prior GO exposure was similar to that observed in VOD/SOS patients without prior GO exposure. Of note, the observed Day 100 post-HCT survival rate of 50% in defibrotide-treated VOD/SOS patients with previous GO exposure compares favorably to the survival rates observed in the overall populations of phase 2 and 3 studies of defibrotide (42% and 38%, respectively).

No new safety signals were identified by this analysis. The safety of defibrotide following GO treatment was comparable to the safety profile reported in previous defibrotide studies.

Similar to GO, patients receiving InO are at a higher risk of developing VOD/SOS. A PubMed search for patients who received defibrotide for the treatment of VOD/SOS following exposure to InO identified three
studies\textsuperscript{3,24,25}. In these studies, a total of 25 patients who developed VOD/SOS following InO treatment received defibrotide. Resolution of VOD/SOS was not reported in 4 (16\%) of these patients as VOD/SOS was ongoing at the time of publication. Among the 21 patients for whom resolution of VOD/SOS was reported, VOD/SOS was resolved in 10 (48\%) patients. These observations suggest that, similar to its effect in patients treated with GO, defibrotide may benefit patients with prior InO exposure who develop VOD/SOS post-HCT.

The GO analysis was limited by the small number of studies that reported on outcomes in defibrotide-treated patients with prior GO exposure and the limited number of patients who received defibrotide following GO treatment within those studies. The interpretation of these results is also restricted by a lack of controls, differences in response assessment between studies, the time between results is also restricted by a lack of controls, differences in the nature of this analysis.

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Conflict of interest
P.G.R. has served on advisory committees and received research funding from Jazz Pharmaceuticals. S.C. has served as a consultant to and received honoraria from Gentium/Jazz Pharmaceuticals.

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References
1. Coppel, J. A. et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant. 16, 157–168 (2010).
2. Dalle, J. H. & Giralt, S. A. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. Biol Blood Marrow Transplant. 22, 400–409 (2016).
3. Kantarjian, H. M. et al. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukemia: results from the open-label, randomised, phase 3 INO-VATE study. Lancet Haematol. 4, e387–e398 (2017).
4. Mylotarg\textsuperscript{TM} (gemtuzumab ozogamicin) [packet insert] (Wyeth Pharmaceuticals Inc., Philadelphia, 2018).
5. Magwood-Golston, J. S., Kessler, S. & Bennett, C. L. Evaluation of gemtuzumab ozogamicin associated sinusoidal obstructive syndrome: findings from an academic pharmacovigilance program review and a pharmaceutical sponsored registry. Leuk. Res. 44, 61–64 (2016).
6. Amadori, S. et al. Gemtuzumab ozogamicin versus best supportive care in older patients with newly diagnosed acute myeloid leukaemia unsuitable for intensive chemotherapy: results of the randomized phase II EORTC-GIMEMA ANL-19 trial. J. Clin. Oncol. 34, 972–979 (2016).
7. Mylotarg\textsuperscript{TM} [summary of product characteristics]. (Pfizer Ireland Pharmaceuticals, Ireland, 2018).
8. Defitelio (defibrotide sodium) injection [packet insert] (Jazz Pharmaceuticals Inc., 2016).
9. Defitelio. Summary of Product Characteristics. (Gentium SpA, Villa Guardia, Italy, 2013).
10. Defitelio Product Monograph. (Jazz Pharmaceuticals Ireland, Limited, Dublin, Ireland, 2017).
11. Dignan, F. L. et al. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. Br J Haematol. 163, 444–457 (2013).
12. Godwin, C. D., McDonald, G. B. & Walter, R. B. Sinusoidal obstruction syndrome following CD33-targeted therapy in acute myeloid leukaemia. Blood 129, 2330–2332 (2017).
13. Fan, C. Q. & Crawford, J. M. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). J Clin Exp Haematol. 4, 332–346 (2014).
14. Battipaglia, G. et al. Risk of sinusoidal obstruction syndrome in allogeneic stem cell transplantation after prior gemtuzumab ozogamicin treatment: a retrospective study from the Acute Leukemia Working Party of the EBMT. Bone Marrow Transplant. 52, 592–599 (2017).
15. Richardson, P. G. et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. Biol Blood Marrow Transplant. 16, 1005–1017 (2010).
16. Zwaan, C. M. et al. Salvage treatment for children with refractory first or second relapse of acute myeloid leukaemia with gemtuzumab ozogamicin: results of a phase II study. Br J Haematol. 148, 768–776 (2010).
17. Bornhauser, M. et al. Gemtuzumab ozogamicin as part of reduced-intensity conditioning for allogeneic hematopoietic cell transplantation in patients with relapsed acute myeloid leukemia. Clin Cancer Res. 14, 5585–5593 (2008).
18. Lainoy, D. et al. Gemtuzumab ozogamicin-induced sinusoidal obstructive syndrome treated with defibrotide: a case report. J Clin Pharm Ther. 31, 389–392 (2006).
19. Reinhardt, D. et al. Gemtuzumab ozogamicin (Mylotarg) in children with refractory or relapsed acute myeloid leukaemia. Onkologie 27, 269–272 (2004).
20. Venlyks, B. et al. Prophylaxis with defibrotide prevents veno-occlusive disease in stem cell transplantation after gemtuzumab ozogamicin exposure. Blood 103, 1998 (2004).
21. Savola, A. et al. Late occurrence of hepatic veno-occlusive disease following gemtuzumab ozogamicin: successful treatment with defibrotide. Br J Haematol. 123, 752–753 (2003).
22. Corbacioglu, S. et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in pediatric hematopoietic stem cell transplantation: subanalysis data from an open-label, phase II, randomized trial. Blood 126, 4310 (2015).
23. Richardson, P. G. et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood 127, 1666–1665 (2016).
24. Kantarjian, H. M. et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med. 375, 740–753 (2016).
25. DeAngelo, D. J. et al. Inotuzumab ozogamicin in adults with relapsed or refractory CD22-positive acute lymphoblastic leukemia: a phase 1/2 study. Blood Adv. 1, 1167–1180 (2017).