ASTCT
American Society for
Transplantation and Cellular Therapy

SUBMITTED ELECTRONICALLY

November 28, 2023

Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Lauren K. Roth
Associate Commissioner for Policy
Division of Hematological Malignancies
Center for Drug Evaluation and Research
Rockville, MD

Re: *Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment - Guidance for Industry* [Docket No. FDA-2023-D-3900]

Dear Commission Califf,

On behalf of the American Society for Transplantation and Cellular Therapy (ASTCT) we write to comment on the recently promulgated FDA Draft Guidance, entitled, *Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment -Guidance for Industry* [Docket No. FDA-2023-D-3900].

The ASTCT is a professional membership association of more than 3,000 physicians, scientists, pharmacists, and other health care professionals promoting blood and marrow transplantation and cellular therapy through research, education, scholarly publication, and clinical standards. Our Society's clinical teams have been instrumental in developing and implementing clinical care standards and advancing transplantation science, including leading and participating in the trials that led to current FDA approvals for the drugs currently used in the prevention and treatment of acute and chronic graft-vs.-host disease (GVHD).

ASTCT would like to applaud the FDA for assembling this guidance for the development of additional agents in the GVHD space. We respectfully provide this commentary for your consideration. For any additional questions, please contact our Director of Government Relations, Alycia Maloney, at amaloney@astct.org.

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Drug Combinations (line 283)
"In general, in the absence of a scientific rationale, drugs that failed as prior treatment of aGVHD or cGVHD should be discontinued, and the patients should be receiving the fewest number of immunosuppressive therapies concurrently."

ASTCT Comment: While complete responses to therapeutics in acute GVHD may occur more frequently, complete responses in advanced chronic GVHD are uncommon, and partial responses often require additional therapy. The abrupt discontinuation of one agent to facilitate participation in another clinical trial might pose a risk to the patient, and disease progression that occurs following the institution of a new agent may be incorrectly ascribed to inactivity of the novel agent, rather than to the abrupt discontinuation of the prior agent. Given that many newer agents are in fact immunomodulatory rather than being strictly immunosuppressive, and that these agents are unlikely to be active in the same biological pathway, we recommend that subjects may be permitted to stay on prior immunosuppressive agents, as long as predefined measures of drug dosing stability are ensured. This strategy might be useful to define activity with combinatorial therapy in patient subgroups without performing dedicated clinical trials.

Organ Specific Systemic Therapies (line 301)
"…even when an organ-specific claim is being sought, the assessment of any organ-specific benefit should be in addition to a GVHD-free survival (GFS), rather than in lieu of it... Whether demonstration of an organ-specific effect in the absence of impact on the overall GVHD outcome would be sufficient to support a marketing application will be a review issue."

ASTCT Comment: We note that aside from high-morbidity organ involvement (i.e., lung), the majority of cGVHD is not associated with mortality. Additionally, organ-specific therapeutics, even when administered systemically, may not result in systemic responses. As such, we suggest that organ specific responses be considered sufficient for regulatory approval. We note that significant clinical benefit can be afforded by responses in individual organs (i.e., the eye), even while systemic cGVHD progression might be occurring.

GVHD Prophylaxis – Efficacy Endpoints (line 339)
"Moderate-to-severe cGVHD GFS: From date of HSCT to first occurrence of moderate-to-severe cGVHD with follow-up through 24 months post HSCT or death"

ASTCT Comment: We note that moderate-severe cGVHD represent a heterogeneous group of patient outcomes, that range from moderate single-organ oral or ocular cGVHD to severe multiorgan cGVHD with functional and severe quality of life consequences. As such, we recommend consideration of the inclusion of systemic corticosteroid-requiring or systemic immunosuppressant-requiring in the endpoint definition. In doing so, the systemic severity of cGVHD beyond NIH stage can be captured. In randomized trials, bias should not be introduced with this modification.

In addition, we note that the preferred use of composite endpoints necessarily equates very disparate endpoints, such as single-organ, NIH grade 2 cGVHD ("Moderate cGVHD") and more important and severe outcomes, such as non-relapse mortality. Composite endpoints are only useful when the endpoints are weighted equally.

GVHD Prophylaxis - Pivotal Trials Considerations (line 472)
"GVHD prophylaxis for HLA-identical related donor HSCT and for matched unrelated donor or other alternative donor HSCT are considered separate indications. Marketing applications seeking both indications should include a trial designed to generate data sufficient to test efficacy in each indication individually or separate trials for each indication."

ASTCT Comment: ASTCT agrees that alternative donor HSCT (i.e. haploidentical and ≤7/8 HLA-matched donors) should be considered distinct indications from HLA-matched donor HSCT. However, there is ample evidence to suggest that outcomes following 8/8 HLA-matched, related transplantation and 8/8 HLA-matched unrelated donor transplantation are nearly identical. As such, we believe that trials in fully HLA-matched donor HSCT should include both related and unrelated donors without distinction.

Chronic GVHD – Efficacy Endpoints (line 869)
"Duration of response (DOR) is defined as the time from the date of first response to the date of progression, new systemic therapy for cGVHD,or death from any cause, whichever occurs first."

ASTCT Comment: In clinical practice, the FDA has defined the duration of response as being from the date of best response to the date of any organ progression, even if this progression is not beyond the baseline measurement for the patient in that individual organ. This measurement is different from the duration of response measurement used in clinical settings, and as defined in prior clinical trials, where the duration of response is measured from the time of response to progression beyond initial organ-specific staging. As an example, we note the discrepant reporting of DOR times in the pivotal ROCKStar trial as reported by investigators (54 months) in comparison with the listed DOR in the package label (1.9 months). This discrepancy can lead to confusion among patients and investigators. We suggest that the DOR as measured from the time of maximal response to the time of disease progression beyond initial organ-specific staging be used. Patients who attain a response (even a complete response) and regress slightly are still considered partial responders.

Pivotal Trial Considerations (line 1000)
"FDA considers the following criteria to be acceptable to define cGVHD that failed steroids:

- *Manifestations progress despite the use of >1 mg/kg/day PE for at least 1 week,*
- *Manifestations persist without improvement despite treatment with >0.5 mg/kg/day or 1 mg/kg every other day for at least 4 weeks,*
- *Recurrence after a CR, or*
- *Progression after a PR"*

ASTCT Comment: We wish to note that patients with partial but incomplete responses to corticosteroids should be considered eligible for trials of steroid-refractory cGVHD. These patients represent a significant subset of patients that require novel therapeutics. We agree that subjects with steroid intolerance alone, as well as those who are steroid-dependent represent a unique subset of patients and should not be assessed with true steroid refractory patient cohorts, however, these patients do require novel therapeutics, and ASTCT is concerned that a pathway for use of these

novel compounds in these patient populations is not evident, as clinical trials are not likely to be performed in these specific patient populations.

Pivotal Trial Design (line 1077)
"In second or later lines of therapy when a highly effective SOC therapy is available, a randomized trial should be used to support the marketing application."

ASTCT Comment: Given the number of agents that are currently and expected to be approved in the near future in the cGVHD space, ASTCT encourages head-to-head clinical trials. A direct comparison of agents will help define an algorithmic approach to the selection of therapeutics, particularly when a number of agents will have similar labeled indications. This is particularly important since at this time, there are no biologic or phenotypic patient characteristics that inform the selection of therapeutic agents. However, we feel strongly that even when not noted to be superior in direct comparative trials, novel agents still could gain FDA approval for use when substantial clinical activity and safety is demonstrated, since most agents used clinically in advanced cGVHD therapy have median failure-free survival times of approximately 12 months, and the majority of patients with advanced disease require multiple sequential agents that might have similar approval indications. Non-inferiority trials may be impractical due to sample size inflation and the costs of conducting these trials, so active clinical activity in a head-to-head trial should be evaluated independently of the comparand strategy.

General Comment

ASTCT would like to suggest that guidelines for trials designed with a biological endpoint or that study biologically-defined patient groups be included in this document. As patient groups begin to be separated by defined phenotypes and pathobiological processes and pathways, guidance from the Agency becomes far more important. We suggest that principles from the Chronic GVHD Consensus Conference Biology Task Force (Buxbaum et al, Blood Adv 2023) be followed in this regard.