

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org



### Guideline

### ASTCT and USCLC Clinical Practice Recommendations for Allogeneic Stem Cell Transplant in Mycosis Fungoides and Sézary Syndrome



Amrita Goyal<sup>1,\*,#</sup>, Daniel O'Leary<sup>2,#</sup>, Bouthaina Dabaja<sup>3</sup>, Wen-Kai Weng<sup>4</sup>, Jasmine Zain<sup>5</sup>, Corey Cutler<sup>6</sup>, Joan Guitart<sup>7</sup>, Youn H. Kim<sup>8</sup>, Larisa J. Geskin<sup>9</sup>, Richard T. Hoppe<sup>10</sup>, Lynn D. Wilson<sup>11</sup>, Anne W. Beaven<sup>12</sup>, Steve Horwitz<sup>13</sup>, Pamela B. Allen<sup>14</sup>, Stefan K. Barta<sup>15</sup>, Kimberly Bohjanen<sup>1</sup>, Jonathan E. Brammer<sup>16</sup>, Joi B. Carter<sup>17</sup>, Nneka Comfere<sup>18</sup>, Jennifer A. DeSimone<sup>19</sup>, Kathryn Dusenbery<sup>20</sup>, Madeleine Duvic<sup>21</sup>, Auris Huen<sup>21</sup>, Deepa Jagadeesh<sup>22</sup>, Chris R. Kelsey<sup>23</sup>, Michael S. Khodadoust<sup>24</sup>, Mary Jo Lechowicz<sup>25</sup>, Neha Mehta-Shah<sup>26</sup>, Alison J. Moskowitz<sup>13</sup>, Elise A. Olsen<sup>27</sup>, Christina Poh<sup>28</sup>, Barbara Pro<sup>29</sup>, Christiane Querfeld<sup>30</sup>, Craig Sauter<sup>22</sup>, Lubomir Sokol<sup>31</sup>, Olayemi Sokumbi<sup>32</sup>, Ryan A. Wilcox<sup>33</sup>, John A. Zic<sup>34</sup>, Mehdi Hamadani<sup>35</sup>, Francine Foss<sup>36</sup>

- <sup>4</sup> Blood and Marrow Transplantation, and Cellular Therapy, Department of Medicine, Stanford University, Stanford, California
- <sup>5</sup> Division of Lymphoma, Department of Hematology & Hematopoietic Cell Transplantation, City of Hope National Medical Center,

### Duarte, California

- <sup>8</sup> Departments of Dermatology and Medicine/Division of Oncology, Stanford University, Stanford, California
- <sup>9</sup> Department of Dermatology, Columbia University, New York, New York
- <sup>10</sup> Department of Radiation Oncology, Stanford University, Stanford, California
- <sup>11</sup> Department of Therapeutic Radiology, Yale School of Medicine, New Haven, Connecticut
- <sup>12</sup> Division of Hematology, University of North Carolina, Chapel Hill, North Carolina
- <sup>13</sup> Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, New York
- <sup>14</sup> Department of Hematology & Medical Oncology, Emory University Winship Cancer Institute, Atlanta, Georgia
- <sup>15</sup> Division of Hematology and Oncology, University of Pennsylvania, Philadelphia, Pennsylvania
- <sup>16</sup> Division of Hematology, Ohio State University James Comprehensive Cancer Center, Columbus, Ohio
- <sup>17</sup> Department of Dermatology, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire
- <sup>18</sup> Departments of Dermatology and Laboratory Medicine & Pathology, Mayo Clinic, Rochester, Minnesota
- <sup>19</sup> Department of Dermatology, University of Virginia Schar Cancer Institute, Fairfax, Virginia
- <sup>20</sup> Department of Radiation Oncology, University of Minnesota, Minneapolis, Minnesota
- <sup>21</sup> Department of Dermatology, University of Texas MD Anderson Cancer Center, Houston, Texas
- <sup>22</sup> Department of Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Center, Cleveland, Ohio

<sup>23</sup> Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina

Financial disclosure: See Acknowledgments on page 1058.

\*Correspondence and reprint requests: Amrita Goyal, MD, Department of Dermatology, University of Minnesota, 420 Delaware St SE, Minneapolis MN 55401.

E-mail address: Goyal046@umn.edu (A. Goyal).

<sup>#</sup> co-first authors.

### https://doi.org/10.1016/j.jtct.2024.08.020

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<sup>&</sup>lt;sup>1</sup> Department of Dermatology, University of Minnesota, Minneapolis, Minnesota

<sup>&</sup>lt;sup>2</sup> Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, Minnesota

<sup>&</sup>lt;sup>3</sup> Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas

<sup>&</sup>lt;sup>6</sup> Division of Transplantation and Cellular Therapy, Dana-Farber Cancer Institute, Boston, Massachusetts

<sup>&</sup>lt;sup>7</sup> Department of Dermatology, Northwestern Feinberg School of Medicine, Evanston, Illinois

<sup>24</sup> Division of Oncology, Department of Medicine, Stanford University, Stanford, California

<sup>25</sup> Department of Hematology and Medical Oncology, Emory University, Atlanta, Georgia

<sup>26</sup> Department of Medicine, Division of Oncology, Washington University School of Medicine in St. Louis, St. Louis, Missouri

<sup>27</sup> Departments of Dermatology and Medicine, Duke University Medical Center, Durham, North Carolina

<sup>28</sup> Division of Hematology and Oncology, University of Washington, Seattle, Washington

<sup>29</sup> Department of Hematology and Oncology, New York Presbyterian - Columbia University Irving Medical Center, New York, New York

<sup>30</sup> Department of Pathology, Division of Dermatology & Beckman Research Institute, City of Hope National Medical Center, Duarte, California

<sup>31</sup> Malignant Hematology, Moffitt Cancer Center, Tampa, Florida

<sup>32</sup> Departments of Dermatology and Laboratory Medicine & Pathology, Mayo Clinic, Jacksonville, Florida

<sup>33</sup> Division of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, Michigan

<sup>34</sup> Department of Dermatology, Vanderbilt University Medical Center, Nashville, Tennessee

<sup>35</sup> Division of Hematology & Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

<sup>36</sup> Department of Hematology/Oncology, Yale University School of Medicine, New Haven, Connecticut

Article history: Received 25 August 2024 Accepted 26 August 2024

### ABSTRACT

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common subtypes of cutaneous T-cell lymphoma (CTCL). While MF generally follows an indolent course, a subset of patients will experience progressive and/or treatment-refractory disease; Sézary syndrome is an aggressive lymphoma associated with high morbidity and mortality. Although allogeneic hematopoietic cell transplant (allo-HCT) is the only currently available potentially curative treatment modality for MF/SS there is no published guidance on referral criteria, transplant timing orallo-HCT approach. To develop consensus clinical practice recommendations, we performed a Delphi survey of 32 specialists in dermatology (n = 9), transplant hematology/oncology (n = 10), non-transplant hematology/ oncology (n = 8), and radiation oncology (n = 5) from across the United States. Consensus required agreement of >75% of participants. Sixteen consensus statements were generated on four topics: (1) criteria for referral for consideration for allo-HCT, (2) allo-HCT preparative regimens and procedures (3) disease status at the time of allo-HCT, and (4) multidisciplinary management in the pre- and post-transplant settings. These clinical practice guidelines provide a framework for decision-making regarding allo-HCT for MF/ SS and highlight areas for future prospective investigation.

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#### **INTRODUCTION**

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common subtypes of cutaneous T-cell lymphoma (CTCL).

While MF generally follows an indolent course, a subset of patients will experience progressive and/or treatment-refractory disease.<sup>1-3</sup> Sézary syndrome is an aggressive CTCL associated with high morbidity and mortality secondary to immune compromise and opportunistic infection.<sup>4</sup>

Allogeneic hematopoietic cell transplantation (allo-HCT) is currently the only available potentially curative treatment modality for MF/SS.<sup>5-7</sup> Although the literature on allo-HCT for MF/SS is limited, a recent systematic review and metaanalysis highlighted the potential benefit of this treatment for patients with aggressive disease.<sup>8</sup> The authors found 1-year and 3+ year progression-free survival (PFS) of 42% (95% Cl 31% to 53%) and 33% (25% to 42%), respectively. The 1-year and 3+ year overall survival (OS) rates were 51% (39% to 64%) and 40% (32% to 9%), respectively. Meta-analysis showed that relapse after allo-HCT occurred in 47% (95% Cl 40% to 53%) of patients, with a median time to relapse of 7.9 months (range 1.6 to 24 months); almost all relapses occurred within 1.5 years of allo-HCT.<sup>8</sup>

Despite the inclusion of allo-HCT in both the National Comprehensive Cancer Network (NCCN) and American Society for Transplantation and Cellular Therapy (ASTCT) guidelines and position statements for MF/SS,<sup>9-11</sup> there is no published guidance regarding referral criteria, timing and allo-HCT approach at the time of transplant.

We performed a Delphi survey of United States physicians in dermatology, hematology/oncology (transplant and non-transplant), and radiation oncology with expertise in MF/SS to generate consensus clinical practice guidelines on the use of allo-HCT in these diseases. Endorsement of this effort was provided by the American Society of Transplantation and Cell Therapy (ASTCT) Committee on Practice Guidelines and the United States Cutaneous Lymphoma Consortium (USCLC).

Here we present Delphi-based consensus clinical practice guidelines on the use of allo-HCT for treatment of MF/SS, regarding four major topics: (1) criteria for referral for consideration for allo-HCT, (2) allo-HCT preparation regimens and procedures (3) disease status at the time of allo-HCT, and (4) multidisciplinary management in the preand post-transplant settings.

#### MATERIALS AND METHODS Panel Composition

A systematic review and meta-analysis of the existing literature on allo-HCT for patients with MF/SS was previously published by members of the Steering Committee (AG [dermatology/dermatopathology], DO [transplant hematology/oncology], FF [transplant hematology/oncology]).<sup>8</sup> The steering committee designed the RAND-modified Delphi protocol (Supplementary Table 1)<sup>12</sup> and recruited members of the expert panel (transplant hematology/oncology, n = 10; non-transplant hematology/ oncology, n = 8; radiation oncology n = 5; dermatology, n = 9), with consideration given to expertise (based on clinical experience and prior research and publications), involvement in the ASTCT, USCLC, and/or NCCN, geographic location, practice setting, and physician demographics. The Steering Committee included a physician in community-based practice (AG).<sup>12</sup>

#### **Consensus Methodology**

An initial baseline demographics and scope (BD&S) survey was administered electronically (Qualtrics LLC, Provo, UT. The Steering Committee). The Steering Committee formulated consensus statements for the First Voting Survey of 32 statements, divided into 4 major topics: indications for referral for consideration for allo-HCT (n = 9), allo-HCT conditioning regimen (n = 5), disease status at the time of allo-HCT (n = 12), and multidisciplinary management of advanced-stage MF/SS<sup>13</sup> (n = 5). Panelists rated each statement on a 5-point Likert scale (strongly agree, somewhat agree, neither agree nor disagree, somewhat disagree, strongly disagree) and provided written comments.<sup>14</sup> A predetermined threshold of  $\geq$ 75% voting "strongly agree" or "somewhat agree" was required for consensus. All panelists voted on statements on referral indications and multidisciplinary management. Hematologist/oncologists (transplant and non-transplant) and radiation oncologists voted on statements on transplant regimen and disease status at the time of transplant; non-transplant hematologist/oncologists and radiation oncologists were asked to comment and vote on the transplant-specific recommendations given the intensely collaborative nature of management of these patients.

The results were analyzed by the Steering Committee, an anonymized summary of the results provided electronically to all panelists, and two virtual discussion sessions held (Zoom, San Jose, CA). Groupings of related statements achieving consensus were reformulated for clarity and concision. Statements failing to achieve consensus were modified or eliminated.

The Second Voting Survey of 16 statements was performed and the results provided to the panelists for additional comments (Supplementary Appendix). Final statements were graded based on the strength and level of supporting evidence in accordance with the Agency of Healthcare Research and Quality (AHRQ) grading. "Good" was defined as data from randomized-controlled trials or high-quality meta-analyses, and "fair" based on observational, retrospective, or registry analyses.<sup>15-17</sup>

### RESULTS

### **Member Participation**

The expert panel consisted of 32 physicians, plus the 3 non-voting Steering Committee members, together representing 23 US institutions (Table 1).

### **First Voting Survey**

Thirty-two participants completed the First Voting Survey (hematology/oncology, n = 18; radiation oncology, n = 5, dermatology, n = 9). Of 32 statements, 26 achieved the consensus (Supplementary Appendix). Seven statements were included in the second voting survey without modification, three eliminated, six consolidated, and three revised.

#### Second Voting Survey

Of the initial 32 participants, 29 (transplant hematology/oncology, n = 8; non-transplant hematology/oncology, n=8; radiation oncology n = 5; dermatology, n = 8) completed the Second Voting Survey of 16 statements. Three respondents (2 hematology/oncology and 1 dermatology) were no longer available. This survey consisted of 16 statements derived from the first voting survey results. All statements achieved consensus (Tables 2-5).

#### DISCUSSION

### Recommendations on Referral for Consideration for Allo-HCT

Three consensus statements were generated to guide referral of patients with MF/SS for consideration for transplant (Table 2). Given the heterogeneity of clinical presentation and disease course in patients with MF/SS, the panel acknowledges that it is impossible to capture every possible clinical scenario in a limited number of consensus statements. The guidelines presented here are meant to offer guidance in making referrals, but ultimately the decision to make a referral for consideration allo-HCT is a subjective clinical judgement based on evaluation of the individual patient. In

Expert Panel and Steering Committee Demographics and Institutional Characteristics (n = 35; Expert Panel, n = 32; Steering Committee, n = 3). Allo-HCT, Allogeneic Hematopoietic Stem Cell Transplant

Panelist Characteristics		
	Response	Number of Participants (n, %)
Practice setting	Academic institution/teaching hospital	33 (94%)
	Community practice	1(3)
	Unspecified	1(3)
Field	Hematology/oncology, including allogeneic transplant	11 (31)
	Hematology/oncology, not including allogeneic transplant	8 (23)
	Radiation Oncology	5(14)
	Dermatology	11 (31)
Years of practice	<5	3 (9)
_	5-9	3 (9)
	10-19	14 (40)
	20-29	10 (29)
	30+	5(14)
Institutional characteristics (by partie	cipants)	
	Response	Number of partici- pants (n, %)
Allo-HCT performed at the	Yes	34 (97)
institution	No	1 (3)
Patients with MF seen annually	<5	2(6)
	5-10	0(0)
	11-25	2(6)
	26-50	3 (9)
	50+	28 (80)
Patients with SS seen annually	<5	2(6)
	5-10	9(26)
	11-25	6(17)
	26-50	11 (31)
	50+	7 (20)
Patients with MF referred for allo-	0	1(3)
HCT evaluation annually	1-5	17 (49)
	6-10	13 (37)
	11-25	3 (9)
	26-50	0(0)
	50+	1 (3)
Patients with SS referred for allo-	0	1 (3)
HCT evaluation annually	1-5	27 (77)
	6-10	5(14)
	11-25	1 (3)
	26-50	0(0)
	50+	1 (3)
Patients with MF undergoing allo-	0	1 (3)
HCT annually	1-5	29 (83)
	6-10	4(11)
	11-25	0(0)
	26-50	0(0)
·	-	

(continued)

**Table 1** (Continued)

Panelist Characteristics			
	Response	Number of Participants (n, %)	
	50+	1 (3)	
Patients with SS undergoing allo- HCT annually	0	1 (3)	
	1-5	33 (94)	
	6-10	0(0)	
	11-25	0(0)	
	26-50	0(0)	
	50+	1 (3)	

general, the transplant physicians involved in the study favored permissive guidelines for referral. Early evaluation allows the delivery of information to patients, can enhance multidisciplinary care by facilitating discussion about plans/timing of future lines of therapy, and permits assessment of the likelihood of finding a suitable donor. Given the comparatively low absolute volume of patients with mycosis fungoides (MF) and Sézary syndrome (SS) in the United States, it was deemed improbable that liberal referral criteria would lead to an overwhelming influx of referrals.

The consensus recommendations regarding patient selection resulting from this Delphi survey are specifically for referral for consideration for allo-HCT, meaning referral for evaluation by an allo-HCT physician to assess the patient's suitability for allo-HCT. The choice of whether to perform allo-HCT is a complex, individualized and collaborative decision, which takes into account patient age and functional status, comorbidities, disease stage, response to therapy, donor availability, patient wishes, the availability of social support among networks. numerous other considerations.<sup>18</sup>

Consultation with a transplant physician to assess allo-HCT eligibility may help guide the selection, sequencing, and timing of further lines of therapy, even if a patient does not ultimately undergo allo-HCT. For example, the decision to use combination chemotherapy as the next treatment line versus maximizing the of use of single agents may be impacted by optimal donor availability and the patient's readiness to move forward with allo-HCT upon attainment of sufficient disease control. Additionally, the administration of some medications in close temporal proximity to allo-HCT (particularly mogamulizumab and checkpoint inhibitors) may be associated with increased risk of graft-versus-host disease (GVHD).

### Statement 1. The role of disease stage and failure of prior lines of therapy in referral for consideration of allo-HCT.

The panel recommended referral for consideration for allo-HCT for patients with stage IIB or higher disease stage and refractory disease, progression, relapse, or short-lived response duration after at least two lines of systemic therapy. We suggest defining "short-lived" as <4 months duration.<sup>19</sup> Staging is as defined by Olsen et al.<sup>13</sup> For the purposes of this survey, lines of "systemic therapy" excluded systemic corticosteroids, retinoids, interferon, methotrexate, and extracorporeal photopheresis (ECP) which have low potential for significant toxicities.

In general, patients with stage IA/IB/IIA are rarely considered for allo-HCT, and the majority of allo-HCT are performed on patients with stage IIB disease or higher.<sup>20-23</sup> The panel noted that there are many circumstances in which referral may be considered before the failure of two lines of therapy. These may include, but are not limited to, patients with rapid disease progression, high burden of disease, atypical immunophenotypes (particularly cytotoxic phenotypes), short duration of response to therapy (<6 months), or young patients with clinically aggressive disease. The recommendation for failure of two lines of therapy is also made with the caveat that some patients may have been on clinical trials with unclear benefit profiles, including durability, underscoring the importance of careful evaluation of each individual case.

Additional risk factors that may correlate with more aggressive disease course and which may be considered in the decision to refer include large cell transformation (LCT), elevated serum lactate dehydrogenase (LDH), N3 nodal involvement, high volume of disease, and tolerance to systemic therapies.<sup>3,24-26</sup> Given that finding a suitable donor may be more challenging for certain ethnic groups,<sup>27</sup> consideration could be given to

Final Clinical Practice Guideline Consensus Statements on Indications for Referral for Consideration for Allogeneic Stem Cell Transplant.

Statement	Grading of Recommendation	Panelists in agreement (%) N = 29*	References
1. The panel recommends referral for consideration for allo-HCT for MF/SS patients with stage IIB or higher AND refractory dis- ease, progression, or relapse after at least TWO lines of systemic therapy.	С	87%	20-23
2. The panel recommends referral for consideration for allo-HCT for MF/SS patients with multifocal/generalized stage IIB or higher disease AND histological large-cell transformation, irre- spective of number of prior lines of therapy.	С	90%	30
3. The panel recommends referral for consideration for allo-HCT for MF/SS patients with N3 nodal disease or visceral involve- ment (M1), irrespective of number of prior lines of therapy.	C	97%	3

\* Participants: Transplant heme/onc, n = 8; Non-transplant heme/onc, n = 8; Radiation oncology, n = 5; Dermatology, n = 8."Systemic therapy" EXCLUDES corticosteroids, retinoids, interferon, methotrexate, and extracorporeal photopheresis (ECP). Stage is as defined by ISCL/EORTC revised classification (Blood, 2007).<sup>13</sup>

Agency of Healthcare Research and Quality (AHRQ) grading of recommendations based on level of evidence:

A: There is good research-based evidence to support the recommendation.

B: There is fair research-based evidence to support the recommendation.

C: The recommendation is based on expert opinion and panel consensus.

X: There is evidence of harm from this intervention.

referring patients of non-European ancestry earlier to facilitate a donor search. The importance of this specific consideration may become less of a factor over time given the increased use of haploidentical donors, as studies have shown equivalent outcomes of allo-HCT using matched unrelated donors versus haploidentical donors in non-Hodgkin lymphoma. <sup>28,29</sup>

### Statement 2. The role of large cell transformation in referral for consideration for allo-HCT.

Large-cell transformation (LCT) has been correlated with a worse prognosis in MF/SS.<sup>30,31</sup> On this basis, the panel recommends referral for patients with multifocal/generalized stage IIB or higher disease AND histological large-cell transformation, irrespective of number of prior lines of therapy. The decision to refer patients with stage IIB and LCT can be challenging as stage IIB disease encompasses a wide spectrum of presentations, ranging from patients with single tumors to those with widespread disease. Those with an isolated tumor may benefit from localized radiation and might not need referral for consideration for allo-HCT, while those with generalized tumors or multiple episodes of LCT would likely benefit from early referral for consideration for allo-HCT.

# Statement 3. The role of nodal or visceral involvement in referral for consideration for allo-HCT.

The panel recommended that patients with N3 or M1 disease should be referred for consultation for allo-HCT, regardless of prior lines of therapy. Both N3 and M1 disease have been identified as adverse prognostic factors,<sup>3</sup> so these patient populations may benefit from expeditious referral. The panel notes that grading of lymph node (N1, N2, N3) involvement may not always be included in all pathology reports, which may make this recommendation challenging to apply in practice; in cases in which lymph nodes are noted to be involved but lymph node grading is not provided, it may be prudent to either request that the pathologist provide a grade or to send lymph node specimens for consultation by a hematopathologist with expertise in hematologic malignancies.<sup>13</sup>

### **Statements Not Achieving Consensus**

The panel did not achieve consensus on a proposed statement recommending referral for consultation of patients with MF/SS and B2 blood disease irrespective of the number of prior lines of therapy (Table 3). It was noted that such a recommendation would effectively mean that all patients with

Final Clinical Practice Guideline Consensus Statements on Allo-HCT Preparation Regimen

Statement	Grading of Recommendation	Panelists in agreement (%) N=21*	References
4. The panel does NOT recommend autologous SCT for treat- ment of MF/SS.	A	90%	33
5. Panel recommends lower-intensity (RIC or NMA) regimens for patients with MF/SS undergoing allo-HCT conditioning.	A	100%	8,20
6. The panel recommends that patients with MF/SS receive total skin electron beam therapy (TSEBT) to achieve a maximal skin response prior to allo-HCT. Doses of 12 to 36 Gy, depend- ing upon clinical circumstances, would be appropriate.	C	100%	35,36
7. The panel recommends caution with recent use of mogamu- lizumab in patients undergoing allo-HCT as there may be a higher risk of GVHD.	В	86%	38-40
8. The panel recommends caution with recent use of Pro- grammed Death-1 (PD-1) inhibitors in patients undergoing allo-HCT as there may be a higher risk of GVHD.	В	86%	41,43

\* Transplant heme/onc, n=8; Non-transplant heme/onc, n=8; Radiation oncology, n=5; Dermatology, n=8

Agency of Healthcare Research and Quality (AHRQ) grading of recommendations based on level of evidence:

A: There is good research-based evidence to support the recommendation.

B: There is fair research-based evidence to support the recommendation.

C: The recommendation is based on expert opinion and panel consensus.

X: There is evidence of harm from this intervention.

Sézary syndrome be referred upon diagnosis without acknowledging that there is variability in prognosis for B2 patients depending on their clinical presentation and degree of blood burden.<sup>32</sup> The availability of therapies that are particularly effective against circulating disease burden (ie, mogamulizumab) has also greatly impacted this decision making. Nonetheless, the panel did encourage early referral for consultation for such patients, particularly if other risk factors are present.

### Recommendations on Allo-HCT Preparation Regimen

Five consensus statements regarding allo-HCT preparation regimen were generated (Table 3).

### Statement 4. Autologous HCT is not recommended for MF/SS.

In accordance with published data, the panel recommends *against* the use of autologous HCT for the treatment of MF/SS outside of the context of a clinical trial.<sup>33,34</sup>

### Statement 5. Lower-intensity (RIC or NMA) conditioning regimens for allo-HCT preparation are recommended.

The members of the panel agreed that reduced intensity/non-myeloablative regimens are preferred. This study did not attempt to achieve consensus on a specific regimen. This is supported by data from a recent systematic review and metaanalysis comparing outcomes of myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) for MF/SS, which demonstrated that overall survival (OS) with RIC (58% [95% CI 47% to 68%]) was superior to that with MAC (30% [95% CI 7% to 42%]) (p < .001).<sup>8</sup> Panel members noted poor outcomes in those patients with high disease burden when selecting a myeloablative conditioning, and suggest alternative therapeutic choices instead. Moreover, registry data for T- and B-cell lymphoma patients undergoing allo-HCT do not suggest any clear benefit of MAC over RIC.<sup>15,31-33</sup> As is discussed below, the panel was unable to achieve consensus on the role of total body

irradiation (TBI) and total lymphoid irradiation (TLI) in conditioning.

### Statement 6. Total skin electron beam therapy in preparation for allo-HCT.

The panel recommended that MF/SS receive total skin electron beam therapy (TSEBT) to achieve a maximal skin response and debulking prior to allo-HCT conditioning. The indication for TSEBT should be made based on the extent of cutaneous disease burden prior to allo-HCT. Of note, due to the heterogeneity of disease, this study did not attempt to consider individual subsets of patients and their management with respect to TSEBT.

Although regimens for TSEBT vary by institution and by patient related variables, such as prior TSEBT, ranges of 12 to 36 Gy are generally recommended.<sup>35,36</sup> The panel suggested doses of 30 to 36 Gy for patients with thicker plaques or tumors, 24 to 30 Gy for those with thinner patches and plaques, and 12 to 24 Gy for those with minimal to no clinical disease. Prior local radiation is generally not considered in determining dosage. Intent to use allo-HCT conditioning regimens that include total body irradiation (TBI) or total lymphoid irradiation (TLI) may impact radiation dosage.

TSEBT is generally delivered using a modified Stanford technique with dual fields and 6 positions, although modified floor, recumbent, and rotational techniques may be considered for patients with mobility restrictions. In general, the total dose per week is 4-6 Gy, given in 1-2 Gy fractions, although other fractionation schemes may be appropriate. Radiation cycles can be delivered at a faster rate if necessary due to time restrictions, but appropriate reduction of the total dose may be necessary to minimize toxicity. Tumors or thick plaques may require additional local boosts with electrons or orthovoltage irradiation, as may "shadowed" areas of the body (top of the scalp, perineum, soles, and inframammary folds).<sup>35-37</sup> Tumors can be supplemented with up to 10 Gy in fractionated doses. Blocking or shielding of specific body areas during treatment is critical to management of side effects, but is very individualized.

It is crucial to monitor for acute skin toxicity and manage appropriately with emollients, oral antihistamines, and aggressive wound care with non-occlusive dressings. If patients develop acute dermatitis or skin breakdown, a 1- to 2-week pause may be appropriate. Antibiotics should be considered for erosions or ulcerations showing signs of possible infection. The panel noted that careful attention must be paid to timing the TSEBT. As a full treatment course may require 3 to 6 weeks, additional time may be required for healing of any skin wounds or treatment of bacterial superinfections prior to the initiation of conditioning.

## Statement 7. Mogamulizumab and timing of allo-HCT.

The panel recommends caution with recent use of the anti-CCR4 monoclonal antibody mogamulizumab in patients undergoing allo-HCT, as recent administration may be associated with higher risk of acute GVHD, as demonstrated in the adult Tcell leukemia/lymphoma (ATLL) literature.<sup>38</sup> Given mogamulizumab's efficacy in achieving the deep response in the blood that is a pre-requisite for allo-HCT (particularly in patients with SS), members of the panel emphasized that this caution should not prevent the use of mogamulizumab as a potential therapy to control disease, but rather encourage spacing between treatment and allo-HCT. Retrospective studies of patients with ATLL have documented an association between administration of mogamulizumab prior to allo-HCT and an increased risk of severe acute GVHD (relative risk 1.80; p < .01), steroid-refractoriness for acute GVHD (relative risk 2.09; p < .01) and poor clinical outcomes.<sup>38</sup> Case series have documented varying rates and severity of GVHD in patients with MF/SS previously treated with mogamulizumab.<sup>39,40</sup> The panel suggested a 2 to 4 month wash-out period from last administration of mogamulizumab to allo-HCT, when clinically appropriate. Members of the panel noted that pre-transplant TSEBT (which can take 3-6+ weeks) could be initiated during a wash-out period. There is lack of data on the potential impact of post-transplant cyclophosphamide GVHD prophylaxis in this setting.

## Statement 8. Checkpoint inhibitors and timing of allo-HCT.

The panel additionally recommends caution with recent use of immune checkpoint inhibitors in patients undergoing allo-HCT, as recent administration may be associated with higher risk of acute and chronic GVHD. A systematic review and meta-analysis of the literature demonstrated higher rates of hyper-acute (7%), acute (56%), and chronic (29%) graft versus host disease (GVHD) in patients receiving checkpoint inhibitors prior to allo-HCT.<sup>41,42</sup> The majority of patients in that study had Hodgkin lymphoma, and the majority received nivolumab, with a minority receiving pembrolizumab or ipilimumab. Based on

literature on use of PD-1 inhibitors for treatment of Hodgkin lymphoma, the panel suggested a 6week wash-out period from last administration of a PD-1 inhibitor to allo-HCT, when clinically feasible.<sup>43</sup> As with mogamulizumab, there is a lack of data about the potential impact of post-transplant cyclophosphamide GVHD prophylaxis in this setting.

### Statements not achieving consensus.

The panel did not achieve consensus regarding the use of reduced-intensity total body irradiation or total lymphoid irradiation in the first voting survey, and this statement was dropped from the second voting survey given heterogeneity of treatment regimens among institutions and lack of published data to support a recommendation (Table 6). Although these techniques are integral components of some published allo-HCT regimens for MF/SS<sup>23</sup> and other malignancies such as non-Hodgkin lymphoma,<sup>44</sup> their use is highly institution-specific. Further research is required to fully assess the role of TBI or TLI in conditioning regimens for allo-HCT for MF/SS.

### **Recommendations on Disease Status at the Time of Allo-HCT**

Three consensus statements regarding disease status at the time of allo-HCT were generated (Table 4).

### Statements 9. Patients in complete remission.

Members of the panel agreed that patients with MF/SS should ideally be in complete remission in all compartments (skin, lymph node, viscera, and blood) at the time of allo-HCT. This is supported by recent data on long-term outcomes of allo-HCT for MF/SS using a non-myeloablative regimen of TSEBT/TLI/ATG. This study showed that patients in CR after treatment with TSEBT had significantly lower rates of progressive disease or relapse (20.8% vs. 70.6%, p = .006). The 5-year OS in this cohort was 37.7% (MF 36.7%, SS 57.1).<sup>45</sup>

However, the panel acknowledges that achievement of CR in MF/SS may be difficult to achieve. In fact, the majority of patients who undergo allo-HCT for MF/SS are *not* in CR in all compartments at the time of allo-HCT.<sup>20,21,23</sup> For example, in the study of a non-myeloablative regimen of TLI-ATG-TSEBT by Weng et al, all 35 patients had active disease, with 100% having active disease in the skin, 34% in the blood, 22% in the lymph nodes, and 5% in the viscera; this regimen produced a 5-year OS of 56%.<sup>23</sup>

### Statement 10. Patients in partial remission.

In panel discussions there was agreement that patients with limited disease in the skin and blood may be considered for allo-HCT, particularly patients with skin involvement who will receive TSEBT. Thus, the panel further agreed that patients should be in *at least* partial remission in

### Table 4

Final Clinical Practice Guideline Consensus Statements on Disease Status at the Time of Allogeneic Stem Cell Transplant

Statement	Grading of Recommendation	Panelists in Agreement (%) N = 21*	References
9. The panel recommends that patients with MF/SS are ideally in complete remission (CR) in all compartments (skin, lymph node, viscera, and blood) at the time of allo-HCT.	С	95%	20,21,23,45
10.The panel recommends that patients with MF/SS are in at least partial remission (PR) in the skin, lymph nodes, and blood at the time of allo-HCT	C	95%	20,21,23,45
11. The panel does NOT recommend allo-HCT for MF/SS patients with progressive disease (PD) in any compartment (skin, lymph node, viscera, blood) the time of allo-HCT.	С	91%	20,21,23,45

\* Transplant heme/onc, n = 8; Non-transplant heme/onc, n = 8; Radiation oncology, n = 5.

Disease response is as defined in Olsen et al (JCO, 2011).<sup>58</sup>

A: There is good research-based evidence to support the recommendation.

B: There is fair research-based evidence to support the recommendation.

Agency of Healthcare Research and Quality (AHRQ) grading of recommendations based on level of evidence:

C: The recommendation is based on expert opinion and panel consensus.

X: There is evidence of harm from this intervention.

Final Clinical Practice Guideline Consensus Statements on Multidisciplinary Management

Statement	Grading of Recommendation	Panelists in Agreement (%) N = 29*	References
12. The panel recommends that, when possible, the care of patients with Sézary syndrome or advanced-stage mycosis fungoides (stage IIB or higher) be carried out as a multidis- ciplinary collaboration between dermatology, hematology/ oncology, radiation oncology, and dermatopathology/ hematopathology.	C	97%	10,46
13. The panel recommends that patients with MF/SS con- tinue to be seen by dermatology for ongoing management of their skin disease, including symptomatic lesions, infec- tion, pruritus, even after referral to hematology/oncology and/or transplant.	C	97%	47–50
14. The panel recommends that in patients with MF/SS, localized radiation therapy continue to be used for treat- ment of appropriate symptomatic skin lesions in the set- tings of ongoing systemic treatment, preparation for allo- HCT, or relapse/progression after allo-HCT.	C	97%	35–37
15. The panel recommends that, when possible, referrals for allo-HCT evaluation be made to transplant centers with experience in allo-HCT for MF/SS.	C	97%	10,46
16. The panel recommends that patients with MF/SS who develop skin rash after allo-HCT undergo skin biopsy with dermatopathology evaluation to distinguish between GVHD, cutaneous relapse of MF/SS, and other dermatitides. When available, T-cell receptor gene rearrangement analy- sis in the tissue should be performed and results compared to prior studies in the blood and/or tissue.	В	97%	54-57

\* Transplant heme/onc, n=8; Non-transplant heme/onc, n=8; Radiation oncology, n=5; Dermatology, n=8 Agency of Healthcare Research and Quality (AHRQ) grading of recommendations based on level of evidence:

A: There is good research-based evidence to support the recommendation.

B: There is fair research-based evidence to support the recommendation.

C: The recommendation is based on expert opinion and panel consensus.

X: There is evidence of harm from this intervention.

the skin, lymph nodes, and blood at the time of allo-HCT. Transplant physicians noted that treatments administered as part of preparation and conditioning for allo-HCT (eg, TSEBT, total lymphoid irradiation, anti-thymocyte globulin) may be able to clear residual disease from these compartments prior to allo-HCT.

### Statement 11. Patients with progressive disease.

Based on their clinical experience, the panel strongly recommended AGAINST use of allo-HCT in patients with progressive disease in any compartment.

### Statements not achieving consensus

The panel was unable to achieve consensus on a statement regarding allo-HCT for patients in PR in the viscera (Table 6). The panel's general experience has been that patients with active disease in the visceral compartments generally have poor outcomes from allo-HCT. However, it was noted that exceptions to this generality may be possible (eg, a patient with a single active focus of disease in a visceral organ that could be treated with targeted radiation). Given the challenge of capturing such clinical nuances in a consensus statement,

Statements Not Achieving Consensus in Survey Round 1 and Dropped Prior to Administration of Survey Round 2

Statement	Grading of Recommendation	Panelists in Agreement
The panel recommends referral for consultation for consideration for allo-HCT for MF/SS patients with high blood burden (B2).	Consensus not achieved, dropped from second voting survey	66%
The panel recommends that patients with MF/SS undergoing allo-HCT receive conditioning regi- mens containing reduced-intensity (non-myeloa- blative) total body irradiation (TBI) or total lymphoid irradiation (TLI), for the purpose of immunosuppression.	Consensus not achieved, dropped from second voting survey	61%
The panel recommends that patients with MF/SS are in at least partial remission (PR) in the viscera at the time of allo-HCT.	Consensus not achieved, dropped from second voting survey	74%

this voting statement was dropped from the second voting survey.

### Recommendations on Multidisciplinary Management of MF/SS

Five consensus statements were generated regarding multidisciplinary management of MF/ SS (Table 5).

### Statement 12. Multidisciplinary collaboration.

These statements highlight the fact that MF and SS are complex and challenging diseases, the treatment of which necessitates collaboration among multiple specialties, including but not limited to dermatology, hematology/oncology, radiation oncology, and dermatopathology.<sup>46</sup> The panel acknowledges that not all patients will have access to a single center or multi-disciplinary clinic with expertise in all of these disciplines. These guidelines seek to highlight the importance of collaboration and communication among all treating providers, regardless of whether they are all housed within a single institution.

### Statement 13. Dermatology in multidisciplinary management.

The panel strongly believes that ongoing collaboration throughout the course of care, particularly in the setting of systemic treatment or allo-HCT, is necessary. Dermatologists may be best positioned to diagnose CTCL and non-CTCL skin findings, manage skin symptoms, recommend therapy, assess response to therapy and recognize adverse events. Dermatologists can play an important role before and after allo-HCT.<sup>47-50</sup>

### Statement 14. Radiation oncology in multidisciplinary management.

In the setting of ongoing systemic treatment, assistance from radiation oncology to administer involved-site localized radiation to individual lesions is critical.<sup>37,51</sup> Members of the panel note that concurrent use of radiation during systemic therapy must be approached carefully and on an individualized basis, as some concurrent systemic therapies may increase toxicities associated with radiation.

### Statement 15. Referral to centers with experience in allo-HCT for MF/SS.

Given the rarity of MF/SS and the nuances of allo-HCT for these diseases, the panel recommended that when possible referrals for allo-HCT evaluation be made specifically to centers with experience in treating these diseases, in accordance with NCCN guidelines.<sup>46</sup> Data suggests that patients with MF/SS undergoing any treatment at centers with higher annual treatment volume (ATV) have higher OS: the OS for MF/SS patients treated at centers in the lowest quintile of ATV  $(\leq 1 \text{ patient annually})$  was 56.7%, compared to 83.8% for those in the highest quintile (>9 annually).<sup>52</sup> The panel acknowledges that this may not be logistically or financially realistic in all cases, but are hopeful that the expansion of telemedicine capabilities may make this recommendation more feasible.<sup>53</sup>

### Statement 16. Biopsy for evaluation of skin rashes after allo-HCT.

Dermatology and dermatopathology evaluation were felt to be particularly important in the posttransplant setting in the event of development of cutaneous lesions. Patients undergoing allo-HCT for MF/SS may develop a variety of skin rashes, including cutaneous GVHD, cutaneous relapses, and drug-associated dermatitides, which can be very challenging to distinguish clinically and histopathologically.<sup>54,55</sup> This recommendation is in accordance with previously published guidelines on the histopathologic assessment for sus-GVHD.<sup>56</sup> Our pected panel particularly encouraged the use of comparative T-cell receptor gene rearrangement studies to help distinguish cutaneous relapse from other etiologies.<sup>57</sup> The panel encourages consultation by dermatopathologists when feasible and appropriate.

### CONCLUSIONS

MF and SS are rare challenging lymphomas that require ongoing multidisciplinary collaboration for optimal patient management. Although numerous therapies exist for these diseases, allo-HCT is the only potentially curative modality currently available. Because of the rarity of MF/SS there are few prospective data available to guide management of patients with refractory or advanced disease. We used the RAND-modified Delphi method to formulate expert recommendations from clinicians specializing in dermatology, hematology/oncology, and radiation oncology to guide clinicians in the use of allo-HCT for patients with MF/SS. This paper provides a framework for patient selection and management, as summarized in Tables 2-5.

The panel recognizes that consensus statements cannot adequately encompass the nuances of every possible clinical scenario, particularly for diseases as heterogeneous as MF and SS. Although we have sought to highlight supporting data when available, many of these recommendations rest largely on the clinical expertise and experience of the panel.

We anticipate that these clinical practice recommendations will provide a valuable tool to help clinicians better assess which patients with MF/SS may benefit from referral for consideration of allo-HCT and help guide all practitioners who are involved in the care and management of patients with advanced stage MF/SS.

### ACKNOWLEDGMENTS

### Financial Disclosure: None.

*Conflict of interest statement:* W. Weng reports: Data Safety and Monitoring Board: Dren Bio. YH Kim reports: Research funding: Kyowa Kirin, Innate Pharma, Corvus Pharmaceuticals, CRISPR Therapeutics, Dren Bio, Pfizer. Advisory board: Kyowa Kirin, Citius, Dren Bio, Innate Pharma. S. Horwitz reports: Honoraria: Takeda, Seagen. Consulting or Advisory Role: Kvowa Hakko Kirin, Ono Pharmaceutical, Secura Bio, Daiichi Sankyo Europe GmbH, DAAN Biotherapeutics, Affimed Therapeutics. Research Funding (institutional): Seagen, Trillium Therapeutics, Daiichi Sankyo, Affimed Therapeutics, Secura Bio, C4 Therapeutics, CRISPR DAAN **Biotherapeutics.** therapeutics, Travel, Accommodations, Expenses: Takeda, SeaGen. S. Barta reports: Advisory Board/Consultation Acrotech, BMS, Daiichi Sankyo, Kyowa Kirin. Non-CME lectures: Acrotech. Data Safety and Monitoring Board: Janssen. C. Querfeld reports: Steering committee/advisory board: Helsinn, Kyowa Kirin; Investigator: Helsinn, Celgene (Bristol Myers Squibb), Kyowa Kirin; Research Grants: Celgene, Helsinn. C. Sauter reports: Paid consultant: Kite/a Gilead Company, Celgene/BMS, Gamida Cell, Karyopharm Therapeutics, Ono Pharmaceuticals, MorphoSys, CSL Behring, Syncopation Life Sciences, CRISPR Therapeutics, Ipsen Biopharmaceuticals and GSK. Research funding: He has received research funds for clinical trials from: Juno Therapeutics, Celgene/BMS, Bristol-Myers, Squibb, Precision Biosciences, Actinium Pharmaceuticals, Sanofi-Genzyme, Cargo Therapeutics, Affimed, and NKARTA, L. Sokol reports: Research funding: Kyowa Kirin, Inc; EUSA Pharma. Advisory board: Kyowa Kirin, Inc; CRISPR Therapeutics; Citius Pharmaceutical, Inc. M. Hamadani reports: Research support/Funding: Takeda Pharmaceutical Company; ADC Therapeutics; Spectrum Pharmaceuticals; Astellas Pharma. Consultancy: ADC Therapeutics, Omeros, CRISPR, BMS, Kite, AbbVie, Caribou, Genmab, Autolus. Speaker's Bureau: ADC Therapeutics, AstraZeneca, Bei Gene, Kite. DMC: Inc, Genentech, Myeloid Therapeutics, CRISPR. A.W. Beaven reports: Research support: Genentech. N Mehta-Shah reports: Consulting or Advisory Role: Kyowa Hakko Kirin, Daiichi Sankyo/UCB Japan, Secura Bio, AstraZeneca, Genentech/Roche, Janssen Oncology, and Institutional Research Funding: Bristol Myers Squibb (Inst), Genentech/Roche, Celgene, Verastem, Innate Pharma, Corvus Pharmaceuticals, AstraZeneca, C4 Therapeutics, Daiichi Sankyo, Yingli Pharma, Dizal Pharma, Secura Bio.

### SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2024.08.020.

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