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Guideline

Clinical Practice Recommendations for Hematopoietic Cell Transplantation and Cellular Therapies in Follicular Lymphoma: A Collaborative Effort on Behalf of the American Society for Transplantation and Cellular Therapy and the European Society for Blood and Marrow Transplantation

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A B S T R A C T
Follicular lymphoma (FL) is the most common indolent B-cell non-Hodgkin lymphoma (NHL), accounting for nearly one-third of all NHL. The therapeutic landscape for patients with FL has significantly expanded over the past decade, but the disease continues to be considered incurable. Hematopoietic cell transplantation (HCT) is potentially curative in some cases. Recently, the emergence of chimeric antigen receptor T-cell therapy (CAR-T) for patients with relapsed/refractory (R/R) FL has yielded impressive response rates and long-term remissions, but definitive statement on the curative potential of CAR-T is currently not possible due to limited patient numbers and relatively short follow up. A consensus on the contemporary role, optimal timing, and sequencing of HCT (autologous or allogeneic) and cellular therapies in FL is needed. As a result, the American Society of Transplantation and Cellular Therapy (ASTCT) Committee on Practice Guidelines endorsed this effort to formulate consensus recommendations to address this unmet need. The RAND-modified Delphi method was used to generate 15 consensus statements/recommendations. These clinical practice recommendations will help guide clinicians managing patients with FL. Of note, the use of bispecific antibodies in R/R FL was not in the scope of this project.

INTRODUCTION

Follicular lymphoma (FL) is the second most common histologic type of non-Hodgkin lymphoma diagnosed worldwide [1,2]. The disease is characterized by an indolent clinical behavior but is not curable by standard chemoimmunotherapy (CIT) or targeted therapies. Marked heterogeneity is also observed in the clinical behavior of patients with FL, with a prognostically unfavorable subset experiencing early disease relapse within 2 years of receiving treatment with front line CIT (POD24).

Several new treatments have been approved over the years for patients with FL, resulting in improved progression-free survival (PFS) and overall survival (OS) in the current era [3,4]. But, except for hematopoietic cell transplantation (HCT), no treatment has been shown to be potentially curative [5-7]. More recently, 2 CD19-directed chimeric antigen receptor T-cell therapies (CAR-T), namely tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel) have been approved for the treatment of relapsed/refractory (R/R) FL [8,9]. The approval of CAR-T extends the armamentarium of effective treatments for patients with R/R FL but also generates uncertainty regarding the optimal timing and sequencing of cellular therapies and autologous (auto) and allogeneic (allo) HCT in FL [10].

Consolidation with auto-HCT in FL as front-line treatment in the pre and post rituximab era did not show any improvement in OS, accordingly, auto-HCT in FL has been mostly considered in the setting of chemosensitive relapsed disease [11-14]. The efficacy of allo-HCT in relapsed FL has also been extensively debated but there is lack of clear consensus on the timing or the role of allo-HCT, especially as new therapies have become available. Studies comparing outcomes between auto-HCT vs. allo-HCT from both the pre-and post-rituximab era report a lower rate of non-relapse mortality (NRM) with auto-HCT, but this benefit is offset by a higher risk of relapse in the auto-HCT group, ultimately resulting in comparable OS [15-19]. Subsequent attempts to limit NRM while harnessing the graft-versus-lymphoma (GVL) effect have led to a greater utilization of reduced intensity (RIC)/non-myeloablative (NMA) conditioning regimens for allo-HCT in FL [5,20-23].

Five-year OS for patients with POD24 has been reported to be 50% vs.90% for those without POD24; the association of POD24 with poor OS has also been validated in a pooled analysis of over 5000 patients [24,25]. Auto-HCT has been shown in retrospective studies to improve outcomes for patients with POD24 in the pre-CAR-T era, especially when used within the first-year

post failure of frontline CIT [26,27]. When comparing outcomes between auto-HCT vs. allo-HCT for patients with POD24; a time varying effect is observed in most studies regarding NRM and disease relapse, where the impact of a higher NRM post allo-HCT is diminished after one year and an advantage for lower relapse rate is observed [16,28].

Comparative studies of transplant and novel cellular therapies such as CAR-T in FL (FL grade 1, 2 and 3a) are not available and are difficult to conduct [10]. Clinical practice recommendations addressing areas of clinical ambiguity can aid not only the transplant and cellular therapy physicians but can also inform the practice of lymphoma experts and community hematologists who refer these patients to transplant and cell therapy programs [29,30]. Therefore, American Society for Transplantation and Cellular Therapy (ASTCT) undertook this project as a collaborative effort on behalf of ASTCT and the European Society for Blood and Marrow Transplantation (EBMT) to formulate consensus recommendations to inform on the contemporary role, timing and sequencing of transplant and cellular therapies in patients with FL. The use of bispecific antibodies in R/R FL was not in the scope of this project.

METHODS

Panel Composition

The development of practice recommendations was undertaken as a collaborative effort on behalf of ASTCT and EBMT. As an initial step, a steering committee was formed comprising of seven members including 2 project leaders, 4 subject matter experts and an independent methodologist with expertise in systematic reviews, meta-analysis, and the RAND-modified Delphi method. The steering committee was responsible for drafting the protocol, developing the initial draft of consensus statements based on clinical expertise, clinical practice considerations, and setting up the expert panel [31].

The goal was to assemble an expert panel with balanced distribution of “FL” and “cellular therapy and transplant” experts to have a broad expertise and to cover a wide spectrum of views, while keeping administrative efforts manageable, as previously recommended [32,33]. The panel of experts comprised of physicians with diverse geographical representation and expertise in the field, as demonstrated by their track record of peer-reviewed publications, leadership on clinical trials relevant to the consensus project, and by their involvement in national and international lymphoma or HCT organizations. Additionally, a physician representing a community-based practice was included in the panel, as previously recommended (A.S.K) [31]. The final consensus panel comprised 27 physicians including the 7 steering committee members. Of note, the (non-clinical) independent methodologist (A.K.), did not vote.

Consensus Methodology

The RAND-modified Delphi method [31,32] was utilized to generate consensus statements addressing the sequencing, timing, and role of HCT and novel cellular therapies in patients with newly diagnosed and R/R FL. In the Delphi method, participants rate the statements anonymously in 2 rounds of voting. In the modified version of the method, a face-to-face meeting with presentation of the results precedes the second round of voting (if needed) [31,32,34]. Details regarding the systematic step-by-step approach used in this project are illustrated in Table 1.

After the panel selection, the steering committee formulated demographic and practice related questions for the expert panel (Table 2) and consensus statements regarding clinical management for the first round of voting (Tables 3, 4, and 5).

The *First Voting Survey* included 9 demographic and practice related questions and 15 consensus statements. Panel members rated each statement electronically. The steering committee methodologist analyzed and summarized the results while keeping the individual ratings anonymous. A specific statement was defined as having achieved formal consensus, if $\geq$70% of the panel members voted to agree with the proposed statement.

All surveys were conducted online using www.Qualtrics.com (Qualtrics LLC, Provo, UT) and results were reviewed and collated independently by the methodological expert. At each step of the process, the electronic survey also allowed the participating members to provide written feedback and comments about each statement.

RESULTS

Member Participation

The results of demographic and the practice related questions of the consensus panel members are summarized in Table 2. Included were transplant and cell-therapy physicians (>75% of practice time in HCT), non-cell therapy academic physicians, mixed practitioners, and a community-based practitioner. A mixed practice was defined as practitioners devoting approximately 50% of clinical time to HCT and non-cell therapy related lymphoma, each. Panelist participation

Table 1
Steps Involved in the RAND-Modified Delphi Methodology.

Step	Representation*	Description	Method
Concept development and approval	Steering Committee	Approved and endorsed by ASTCT CoPG, July 2022	Teleconference
Protocol development	Steering Committee	Protocol development according to the modified Delphi method Identify and invite potential members of Consensus Panel including academic experts plus a community practice representative	Email & electronic communication
First Voting Survey	Consensus Panel	(i) Obtain demographic and practice setting details of the participants and (ii) Rate clinical practice recommendation statements on a Likert score, April 2023	Online survey (100% panel response rate)
Review of results of First Voting Survey	Steering Committee	(i) Results complied and reviewed by the Steering Committee	Email
Second Voting Survey†	NA	NA	NA
Final evaluation of consensus and manuscript	Steering Committee/ Consensus Panel	Ratings are accepted if consensus is reached based on predefined threshold. If no consensus reached, statements were noted as "consensus could not be reached." Results compiled as manuscript and 1st draft written by steering committee and shared with Consensus Panel for review and editing	Email

Abbreviations: ASTCT CoPG - American Society of Transplantation and Cellular Therapy Committee on Practice Guidelines; allo – allogeneic; HCT – hematopoietic cell transplantation; NA – not applicable

* Steering committee comprised of 7 members including 2 project leaders, 1 statistical expert (independent non-voting member), and 4 experts. Consensus Panel (n = 27) comprised of the 7 Steering Committee members (except the statistical expert) plus 17 academic experts and 1 community representative.

† All statements achieved consensus (≥70% agreement), hence, a *Second Voting Survey* was not conducted

and response rates were excellent. During the voting process, 100% (n = 27) panel member participation was noted for the *First Voting* surveys.

First Voting Survey

The *First Voting survey* consisted of 15 statements specific to the role of auto-HCT, CAR T-cell therapy, and allo-HCT in eligible newly diagnosed FL patients (2 statements), in first relapse (5 statements) and late first relapse, second relapse and beyond (8 statements). All statements achieved consensus by predefined criteria (Tables 3, 4, and 5). The results of the *First Voting Survey* were electronically shared with all panel members. Key recommendations are as noted below.

- Autologous-HCT is recommended as an option for consolidation therapy in patients with POD24 after receiving front line CIT and who do not have evidence of histological transformation and achieve a CR or PR to salvage second line therapy (Table 4 #1).
- CAR-T should be considered as a treatment option for patients who did not achieve CR or PR after the second or subsequent lines of therapy (Table 4 #5, Table 5 #2).
- Allogeneic-HCT is considered as consolidative treatment in relapsed FL patients who have received 3 or more lines of systemic therapy and are in specific scenarios (Table 5 #6).

Second Voting Survey

As all statements achieved consensus (≥70 % agreement), a *Second Voting Survey* was not required.

Recommendations

Front-line setting

1) The panel does not recommend auto-HCT or allo-HCT as consolidation therapy in FL patients who achieve complete (CR) or partial remission (PR) after first line therapies (Table 3, #1).
2) The panel does not recommend CAR-T in FL patients who achieve CR or PR after first line therapies, unless in the setting of a clinical trial (Table 3, #2).

Table 2
Demographic Information of Members of Consensus Panel

Member Demographics		N = 27* (%)
Age group (years)	30-35	0
	36-45	7 (26)
	46-55	11 (41)
	56-65	8 (30)
	>65	1 (4)
Gender	Male	16 (59)
	Female	11 (41)
	Transgender	0
	Non-binary/non-conforming	0
	Prefer not to answer	0
Years of clinical experience in lymphoma and/or HCT practice	<5	1 (4)
	5-10	4 (15)
	11-15	7 (26)
	16-20	3 (11)
	>20	12 (44)
Description of clinical practice	Non-transplant/non-cellular therapy lymphoma practice	1 (4)
	Primarily HCT and/or cell therapy practice	4 (15)
	Combined lymphoma and HCT/cell therapy practice	22 (82)
Setting of practice	University/Teaching hospital	26 (96)
	Non-teaching hospital	1 (4)
Region of practice	USA	20 (74)
	Canada	1 (4)
	Europe	6 (22)
Estimated number of follicular lymphoma patients seen at your center annually	≤ 25	3 (11)
	26-50	3 (11)
	51-75	7 (26)
	>75	14 (52)
Estimated number of autologous-HCT performed at your center annually	<50	2 (7)
	51-100	8 (30)
	101-200	8 (30)
	>200	9 (33)
Estimated number of allogeneic-HCT performed at your center annually	<50	1 (4)
	51-100	11 (41)
	101-200	9 (33)
	>200	6 (22)
Estimated number of CAR T-cell therapies performed at your center annually	≤ 20	4 (15)
	20-50	9 (33)
	>50	14 (52)

Abbreviations: HCT– hematopoietic cell transplantation, CAR– chimeric antigen receptor.
* Statistical expert Dr. Ambuj Kumar did not participate in the voting process.

Early first relapse/progression (on or within 24 months from receiving front line CIT [POD24])

3) The panel recommends auto-HCT as an option for consolidation therapy in patients with POD24 who do not have evidence of histological transformation and achieve a CR or a PR to salvage second line therapies (Table 4, #1).

4) The panel does not recommend auto-HCT as consolidation therapy in relapsed FL patients with POD24 who do not achieve CR or PR after

Table 3
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T-Cell Therapy Following First Line Chemoimmunotherapy in Follicular Lymphoma.

Question	Response* (N = 27)		Consensus Achieved†
	Agree N (%)	Disagree N (%)	
1. The panel **DOES NOT** recommend autologous or allogeneic transplantation as consolidation therapy in eligible FL patients in complete or partial remission after first line therapies.	27 (100)	0	Yes
2. The panel **DOES NOT** recommend consolidation with CAR T-cell therapy in eligible FL patients in complete or partial remission after first line therapies, outside the setting of a clinical trial.	26 (96)	1(4)	Yes

Abbreviations: FL-follicular lymphoma, CAR-chimeric antigen receptor.
* Statistical expert Dr. Ambuj Kumar did not participate in the voting process.
† A specific statement was defined as having achieved formal consensus, if >70% of the panel members voted to agree with the proposed statement

Table 4
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T-Cell Therapy in Relapsed FL *(First Relapse Occurred Within Less Than 24 Months From Receiving Front Line Chemoimmunotherapy [POD24] and Without Evidence of Histological Transformation)*

Question	Response* (N = 27)		Consensus Achieved†
	Agree N (%)	Disagree N (%)	
1. The panel **recommends** autologous transplant as an option for consolidation therapy in eligible, relapsed POD24 FL patients who have achieved complete or partial remission after second line therapies.	19 (70)	8 (30)	Yes
2. The panel **DOES NOT** recommend autologous transplant as consolidation therapy in eligible, relapsed FL patients who do not achieve complete or partial remission after second or subsequent line therapies.	26 (96)	1 (4)	Yes
3. The panel **DOES NOT** recommend allogeneic transplant as consolidation therapy in eligible, relapsed POD24 FL patients who have achieved complete or partial remission after second line therapies.	24 (89)	3 (11)	Yes
4. The panel **DOES NOT** recommend commercially available CAR T-cell therapy in eligible, relapsed FL patients who have achieved complete or partial remission after second line therapies.	21 (78)	6 (22)	Yes
5. The panel **considers** CAR T-cell therapy as a treatment option for patients who did not achieve complete or partial remission after second or subsequent line therapies.	26 (96)	1 (4)	Yes

Abbreviations: FL-follicular lymphoma, CAR-chimeric antigen receptor
* Statistical expert Dr. Ambuj Kumar did not participate in the voting process.
† A specific statement was defined as having achieved formal consensus, if >70% of the panel members voted to agree with the proposed statement

second or subsequent line therapies (Table 4 #2).

5) The panel does not recommend allo-HCT as consolidation in patients with POD24 who have achieved CR or PR to salvage second line therapies (Table 4 #3).
6) The panel does not recommend commercially available CAR-T in relapsed FL patients with POD24 who have achieved a CR or PR after second line therapies (Table 4 #4).
7) The panel considers CAR-T as a treatment option for patients with POD24 who did not achieve CR or PR after second or subsequent line therapies (Table 4 #5).

Late first relapse, second relapse and beyond setting

8) The panel does not recommend auto-HCT as consolidation in relapsed FL patients who did not achieve CR or PR after second or subsequent line therapies (Table 5 #1).
9) The panel recommends considering CAR-T in relapsed FL patients who did not achieve CR or PR after second line of therapy (Table 5 #2).

Table 5
Final clinical practice guidelines consensus statements for transplantation and CAR T-cell treatments for late first relapse, second relapse and beyond FL

Question	Response* (N = 27)		Consensus Achieved†
	Agree N (%)	Disagree N (%)	
1. The panel **DOES NOT** recommend autologous transplant as consolidation therapy in eligible, relapsed FL patients who did not achieve complete or partial remission after second or subsequent line therapies.	26 (96)	1 (4)	Yes
2. The panel **recommends** considering CAR T-cell therapy in relapsed FL patients who did not achieve complete or partial remission after second line of therapy.	24 (89)	3 (11)	Yes
3. The panel **recommends** considering CAR T-cell therapy in relapsed FL patients who did not achieve complete or partial remission after third or subsequent lines of therapies.	25 (93)	2 (7)	Yes
4. The panel **recommends** considering CAR T-cell therapy in eligible, relapsed FL patients who have relapsed after an autologous transplant and did not achieve complete or partial remission to most recent anti-lymphoma treatment.	25 (93)	2 (7)	Yes
5. The panel **DOES NOT** recommend autologous transplant as consolidation therapy in eligible, relapsed FL patients who have relapsed after CAR T-cell therapy and did not achieve complete or partial remission to most recent anti-lymphoma treatment.	26 (96)	4 (1)	Yes
6. The panel **recommends** considering allogeneic transplant as consolidation therapy in eligible, relapsed FL patients who have received 3 or more lines of systemic therapy and are in one of the following clinical scenarios: i. Develop disease relapse early post autologous transplant and do not have access to CAR T-cell therapy ii. Develop disease relapse post CAR T-cell therapy iii. Develop therapy related myeloid neoplasm or bone marrow failure syndrome.	22 (81)	5 (19)	Yes
	24 (89)	3 (11)	Yes
	25 (93)	2 (7)	Yes
7. The panel **recommends** that allogeneic transplant be considered as a salvage/consolidation therapy only in patients who have achieved complete or partial remission to the most recent anti-lymphoma treatment. Candidacy for allogeneic transplant is dependent on good performance status and adequate organ function.	21 (78)	6 (22)	Yes
8. The panel **recommends** CAR T-cell therapy in eligible, relapsed FL patients who have relapsed after allogeneic transplant and are untreated or did not achieve complete or partial remission to most recent anti-lymphoma treatment.	25 (93)	2 (7)	Yes

Abbreviations: FL-follicular lymphoma, CAR-chimeric antigen receptor.
* Statistical expert Dr. Ambuj Kumar did not participate in the voting process.

10) The panel recommends considering CAR-T in relapsed FL patients who did not achieve CR or PR after third or subsequent lines of therapies (Table 5 #3).
11) The panel recommends considering CAR-T in eligible, relapsed FL patients who have relapsed after an auto-HCT and did not achieve CR or PR to most recent anti-lymphoma treatment (Table 5 #4).
12) The panel does not recommend auto-HCT as consolidation in FL patients who have relapsed post CAR-T and did not achieve CR or PR to most recent anti-lymphoma treatment (Table 5 #5).
13) The panel recommends considering allo-HCT as consolidation in relapsed FL patients who have received 3 or more lines of systemic therapy and are in one the 3 clinical scenarios: a)

develop disease relapse early post auto-HCT and do not have access to CAR-T; b) develop disease relapse post CAR-T; c) develop therapy related myeloid neoplasms or bone marrow failure syndromes (Table 5 #6).

14) The panel recommends that allo-HCT should be considered as a salvage/consolidation therapy only in patients who have achieved CR or PR to the most recent anti-lymphoma treatment and maintain adequate performance status and organ function (Table 5 #7).

15) The panel recommends CAR-T in relapsed FL patients who have relapsed after allo-HCT and are untreated or did not achieve CR or PR to most recent anti-lymphoma treatment (Table 5 #8).

DISCUSSION

In this project, an ASTCT endorsed panel broadly representing experts in lymphoma, transplant, and cellular therapy with diverse practice experience and geographical representation was formed to provide 15 consensus recommendations on the roles of auto-HCT, allo-HCT and CAR T-cell therapy for newly diagnosed and R/R FL. This project was conceived to offer rational clinical guidance in 2024 on treatment sequencing to inform the choice between auto-HCT, allo-HCT and CAR-T in those with newly diagnosed FL and R/R FL.

Auto-HCT or allo-HCT is not recommended as consolidation therapy in FL patients who achieve CR or PR after first line therapy **(**Table 3, **#1)**. This recommendation is based on prospective randomized data from the GELF-94 trial conducted in the pre-rituximab era and the GITMO/IIL trial from the post rituximab era where no improvement in OS was observed with auto-HCT for FL patients in first remission [11,12]. Although improved event-free survival with auto-HCT was observed in the GITMO/IIL trial, the use of auto-HCT as salvage after failure of front-line CIT was also associated with comparable good outcomes [12].

Nearly 20% of patients experience POD24 after treatment with front line CIT and outcomes for these patients have been shown to be markedly inferior compared to those who do not experience POD24 [24,25]. The use of auto-HCT has been shown to be associated with improved outcomes, especially when used within the first year of failure of front-line CIT [26]. Non-CIT based regimens such as rituximab and revlimid (R2) have also shown similar outcomes to CIT based regimens in newly diagnosed FL but there is lack of data regarding application of auto-HCT in such patients upon experiencing POD24 [35]. Auto-HCT is recommended as an appropriate option for consolidation therapy in patients with POD24 after receiving front line CIT and who do not have evidence of histological transformation and achieve a CR or a PR to salvage second line therapy **(**Table 4, **#1)**. The role of auto-HCT is also best established for patients who achieve objective response to salvage CIT, the use of auto-HCT after salvage with immunotherapy-based regimens such as R2 is to be determined [36]. The panel recognizes the lack of prospective and randomized data for auto-HCT in POD24.

Two autologous anti-CD19 directed CAR-T (tisacel and axi-cel) are currently approved by the United States Food and Drug Administration for patients with R/R FL after at least 2 lines of therapy. Results from the 2 single arm phase 2 CAR-T trials, ELARA and ZUMA-5, establishing the safety and efficacy of CAR-T in multiply relapsed FL are summarized in Table S1 [9,8]. In these trials, most patients were heavily pre-treated with over half of the patients having POD24 and median number of prior lines >2 [8,9]. Importantly, long term outcomes were noted to be similar in patients with POD24 and those without POD24 [8,9]. Although follow up is still limited, CAR-T is considered as a standard care treatment option for patients with POD24 who do not achieve CR or PR after second or subsequent line therapy **(**Table 4 **#5)**.

CAR-T is recommended to be considered also for patients who experience late relapse and do not achieve CR or PR after second or subsequent line of therapy **(**Table 5 **#2, #3)**. CAR-T is also recommended to be considered in patients who have relapsed after an auto-HCT and did not achieve CR or PR to most recent anti-lymphoma treatment **(**Table 5 **#4)**. Tisa-cel and axi-cel have both demonstrated high overall response and CR rates; 3-year long-term follow-up data is now available, demonstrating durable remissions with median PFS of around 40 months and median OS not reached [37,38]. In a propensity score matched comparative analysis of ZUMA-5 (the pivotal trial evaluating axi-cel) with SCHOLAR-5, an international real world retrospective study of patients with R/R FL who had received third or later line of therapy, CAR-T was shown to have substantial improvement in all clinical outcomes when compared to other treatment options [39]. However, to date it remains unclear whether CAR-T can provide cure in patients with untransformed FL.

Mosunetuzumab, CD20xCD3 T-cell–engaging bispecific antibody, is currently approved for

patients with R/R FL who have failed at least 2 lines of systemic therapy [40]. As discussed earlier, CAR-T is also approved in the 3rd line of therapy, but it is currently unknown as to what is the best sequence of treatments between CAR-T and bispecific antibody. CD19 is being developed as a target in bispecific antibody (ies) also and whether CD-19 directed CAR-T will be effective after exposure to CD19 directed bispecific antibody is unknown [41]. Enrollment in novel clinical trials of CAR-T, targeting antigens other than CD19 will be a potential consideration in such clinical setting. Each treatment however has its own pros and cons; CAR-T is a one-time treatment but has logistical challenges associated with requirement for apheresis, short term relocation to a tertiary medical center and potential long term risks of infection and secondary cancers [42,43]; bispecific antibody (ies) require long term treatment but are available off the shelf and allow for outpatient administration [40].

Allo-HCT is associated with notable non-relapse mortality, limiting its applicability. Allo-HCT is not recommended as consolidation in patients with POD24 who have achieved CR or PR to salvage second line therapy **(**Table 4 **#3)**. Several retrospective analyses as well as prospective clinicals trials have reported on the efficacy and safety of allo-HCT in patients with relapsed FL [5,20,15]. Durable remissions and cure have been demonstrated even in heavily pretreated patients especially when transplanted in CR [5,20]. The main limitation of allo-HCT however is NRM, which can be significantly reduced with the use of NMA conditioning regimens. The use of RIC/NMA regimens has allowed for limited toxicity, whilst exploiting the GVL effect of allo-HCT [5,22,44]. Thus, in a very selected and preferably young patient with POD24, a discussion of the pros and cons of allo-HCT may be considered, especially since similar long term follow up data is currently not available for other emerging novel therapies. Allo-HCT is considered as consolidation in relapsed FL patients who have received 3 or more lines of systemic therapy and are in specific clinical settings: post CAR-T failure, lack of access to CAR-T and therapy related myeloid neoplasms. Only patients who have achieved complete or partial remission to the most recent anti-lymphoma treatment should be offered allo-HCT **(**Table 5 **#6)**.

Formal consensus recommendations can be an invaluable resource to inform clinical decision making in scenarios where data from prospective studies are either scarce or unavailable, and in situations where patient populations included in trials are less relevant to contemporary clinical practice [45]. The recently approved therapeutic options such as bispecific antibody and earlier evaluation of CAR-T (ZUMA-22) and bispecific antibodies alone or in combinations will likely further alter the therapeutic landscape of R/R FL and treatment algorithms will continue to evolve. Meanwhile, we hope the clinical practice recommendations in this article will serve as a tool to guide clinicians managing patients with newly diagnosed and R/R FL.

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SUPPLEMENTARY MATERIALS

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