chemotherapy-refractory CLL. That conclusion is based on response data from single-arm studies that report a PR in approximately one third of patients (recognizing that CR are uncommon). From the perspective of drug or multi-agent regimen development, these data are extremely promising and warrant further testing of alemtuzumab.

In their deliberations, the DSG cited these factors as leading to the current recommendation on alemtuzumab:

- Lack of data from properly designed RCTS
- A paucity of data suggesting improved response duration, quality of life, or improved overall survival when alemtuzumab is compared with alternative treatment approaches
- Significant potential toxicity, particularly infection-related morbidity and mortality

Given the anticipated toxicity, data from RCTS demonstrating improvement in clinically meaningful outcome measures—for example, time to progression, quality of life, or overall survival—are required before recommendations permitting the routine use of alemtuzumab in this patient population can be made.

The practice guidelines published by ESMO [29] and the U.K. CLL Forum [30] made recommendations regarding the use of alemtuzumab in previously treated patients. The ESMO guideline recommends alemtuzumab as an option for patients with refractory disease following first-line therapy, based on the lowest-level evidence (ASCO level V: small case-series). In addition, the U.K. CLL Forum guideline recommends alemtuzumab for use in patients without bulky lymphadenopathy (<5 cm) who have been previously treated with alkylating agents and who are refractory to fludarabine. The evidence informing the U.K. CLL Forum recommendation was similar to the evidence contained in the present report and comprised data from a smaller selection of single-arm studies.

The German CLL Study Group determined that definitive recommendations could not be made regarding alemtuzumab use and indicated that further testing in clinical trials would be preferred [31].

Keating *et al.* [26] did not make explicit recommendations regarding the appropriateness of alemtuzumab use in CLL patients, but implied that alemtuzumab is appropriate in fludarabine-refractory patients. Those authors also stated that advanced age should not be a contraindication to alemtuzumab use.

The Hematology DSG considered the above recommendations to be based on low levels of evidence and, initially, DSG members were not convinced that these recommendations could inform best clinical practice. Instead, the DSG initially concluded that potential benefits (response rates in a minority of patients; uncertain benefit in terms of response duration, overall survival, and quality of life) were offset by the potential for significant toxicity. Therefore, an initial recommendation was developed to indicate that the data were insufficient to support the routine use of alemtuzumab in patients with CLL. The DSG acknowledged the potential controversy that could result from issuing a "non-permissive" recommendation regarding alemtuzumab use and the potential implications that such a recommendation might have for drug availability. The DSG was aware that its recommendations differed from those of other existing practice recommendations, including those published by ESMO and the U.K. CLL Forum.

The DSG was also aware that, within the response data described in the literature reviewed, responses reached a magnitude that reporting authors—and members of the DSG—considered to be clinically important. Although the precise frequency of the responses was uncertain (and the best estimate was that they would be infrequent), the DSG acknowledged that an opportunity for such a response, even with substantial risks of toxicity, may be highly desired by some patients. The DSG attempted to reflect this sentiment by indicating that, after balancing the benefits and risks of treatment, certain patients may wish to consider a trial of therapy.

The DSG members had concerns with issuing an unclear and potentially conflicting set of recommendations, but they initially considered this option to represent the best available alternative, and they therefore offered this guidance: For patients with CLL, the evidence is insufficient to recommend the use of alemtuzumab outside of clinical trials. The DSG recognizes that, in highly selected cases, after thorough consideration of the risks and benefits, a trial of alemtuzumab might be considered.

Section 6 details the subsequent practitioner feedback, and it notes that responding clinicians were generally in agreement with the synthesis and interpretation of the available literature and the resulting recommendations. However, a small number of respondents commented on the lack of clarity associated with the recommendations. As a result, the DSG members continued the consensus process in an effort to develop a clearer statement, and the DSG subsequently issued a new set of recommendations. The redeveloped recommendations state that "treatment with alemtuzumab is a reasonable option for patients with progressive and symptomatic CLL that is refractory to both alkylator-based and fludarabine-based regimens." To account for the continued concern about the level of evidence supporting this recommendation and the potential risk–benefit profile of the therapy, a detailed set of qualifying statements was also developed.

6. EXTERNAL REVIEW

The systematic review and practice guideline recommendations were distributed to practitioners in On-