



November 16, 2009

Dear Targeted Therapies Project Team,

The American Society of Hematology (ASH) appreciates the opportunity to comment on the October 7, 2009 draft of the Agency for Healthcare Research & Quality (AHRQ) technology assessment: Report on the Evidence Regarding Off-Label Indications for Targeted Therapies used in Cancer Treatment. ASH represents over 16,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases such as leukemia, lymphoma, sickle cell disease, anemia and hemophilia. ASH solicited input on the technology assessment from hematology experts throughout the organization. ASH notes that 21 days were given for independent analysis and feedback on this 428 page report and recommends additional time be provided in the future to ensure thorough analysis. The Society's comments fall into three areas: framework, methodology, and specific feedback on selected areas addressed in the AHRQ technology assessment.

Framework

This report was requested by the Coverage and Analysis Groups at the Centers for Medicare and Medicaid Services (CMS) and was assigned by AHRQ to the Duke Evidence-based Practice Center. The policy context of this report relates to the role of compendia listings of non-FDA approved indications for cancer drugs. The report is thorough, thoughtful, and highlights the shortcomings of current methodology.

Two facts should be considered as part of the national discourse on the use of targeted therapies for off label drug use. The first is that current research is weak and the second is that, nevertheless, patients present daily to hematologists seeking treatment for these uncommon disorders. ASH notes that both have been addressed in this report. The Society agrees that one challenge is that randomized controlled trials or comparative effectiveness research (CER) of sufficient rigor may be difficult to accomplish for the diseases discussed in this review because of their rarity. The sensitivity of the authors to this is appreciated, e.g. in the statement "In some diseases, despite limited and/or ambiguous data, the use of an off-label indication may be a reasonable clinical decision." Specifically, the authors mention the issues of imatinib for dermatofibrosarcoma protuberans (DFSP) tumors and rituximab for nodular lymphocyte-predominant Hodgkin disease.

Ideally, in the future every clinical encounter will be addressed by solid CER, so the most effective pathway will be clear. Coverage determinations aligned with such evidence will also serve patients and clinicians. As mentioned in the report "The exercise of performing 19 systematic reviews of off-label indications in oncology pointed to clear challenges in the current methods of evidence review; these challenges are likely heightened in areas of medicine where research is advancing rapidly and scientific productivity is high".

ASH cautions that there must be a pathway from the current system towards the future. Moving away from compendia based coverage may well better serve patients and clinicians, but only if a truly better system is in place. Until methodologies exist for integrating published literature with the high-velocity dynamic reality of medical literature now occurring, premature intervention in this area may simply create more complexity for physicians and patients struggling to deal with the specific circumstance of an individual patient, the evidence, and the coverage availability.

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ASH comments on methodology

As stated in the report, systematic reviews for this set of disorders were difficult due to the widely varying quality of evidence, the rapidity with which the field is evolving and the necessity to review data from various sources including abstracts from major meetings such as ASH and the American Society of Clinical Oncology. Given the potential use of these reviews by CMS to formulate policy about coverage for off-label indications for targeted therapies, ASH would like to present some comments about methodological issues.

Meta-analysis was designed to combine the results of randomized clinical trials producing larger "relative" sample sizes than are available from any of the individual, contributing studies. When used, meta-analysis tools should be employed with trepidation and a clear understanding of underlying statistical assumptions that may be violated. As mentioned earlier, randomized controlled trials and CER of sufficient rigor may remain unattainable for the diseases discussed in this report because of their rarity and/or because of the clear effectiveness of an agent in the setting of no alternative makes the conduct of randomized control trials challenging. As a result, comprehensive systematic reviews such as those outlined in this report must incorporate data derived from less robust sources such as cohort studies, case control studies, case series and conference abstracts.

Unfortunately, appropriate mathematical tools to combine the results of such disparate literature do not exist and, as a result, such combinatorial analysis is problematic. Real clinical situations reflect the need for all available data to be presented in a comprehensive manner with the least possible amount of bias to clinicians and patients. **ASH supports developing different models for evidence generation and evaluation as well as new systems that allow “rapid learning and expedient translation of research results into clinical practice improvements.”**

ASH also believes that this specific review is a static interpretation of a dynamic field even as the authors have recognized the challenge of the velocity of data generation in this area and have started to address this. Static interpretations will miss novel data in a rapidly evolving field. **ASH suggests that if evaluations like this become part of the data base used for coverage determinations, they be subject to regular and rigorous updates. An online repository might be developed into which published literature could be placed by experts to facilitate ongoing review of the subject area.** As noted in the report, over a period of time between the initial literature search and the final literature search the data set on some subjects more than doubled. Clearly, any static representation of this data set will be severely challenged and may be out of date long before it is published. This potentially endangers patients as new indications for better evidence for all indications may be unavailable to a static interpretation.

Finally, ASH would like to take the opportunity to address the issue of "gray literature". Abstracts from major scientific congresses represent a very “low form of methodological life” because they have been neither subject to peer review nor is their complete data set available for

assessment. However, within highly dynamic fields of literature failure to include data from abstracts may result in significant "voids" in the assessment of the evidence. **ASH supports that data derived from the abstract literature be included, but suggests that such evidence be sequestered in separate sections, subject to updating as the original data becomes available in the form of a full publication. To increase the likelihood of complete data acquisition, ASH also suggests that these systematic reviews include up-to-date reviews of clinical trials registries in order that future revisions properly accommodate to current and planned research. Abstracts not followed by peer reviewed publication might sunset after a defined time such as 48 months.** This would reduce the bias associated with the use of "grey literature" while ensuring that authors are pressured to publish in full and that the bias associated with the inclusion of abstracts would be minimized.

Specific Feedback

Alemtuzumab for Cutaneous T-Cell Lymphoma

Please note a recent publication of alemtuzumab use in relapsed and refractory erythrodermic cutaneous T-cell lymphoma. It would be reasonable to include this article as this represents a unique patient population. It is also the largest population of erythrodermic CTCL that has been published so far.

1. Querfeld, C. et al. Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. *Leukemia & Lymphoma*. 2009; Early Online, 1–8.

Imatinib mesylate for Myelodysplastic syndrome.

Chronic myelomonocytic leukemia) is now classified by the World Health Organization (WHO) as a myeloproliferative neoplasm (MPN) rather than MDS. The following references should be reviewed:

2. Baxter EJ, Kulkarni S, Vizmanos JL et al. Novel translocations that disrupt the platelet-derived growth factor receptor beta (PDGFRB) gene in BCR-ABL-negative chronic myeloproliferative disorders. *Br J Haematol*. 2003; 120: 251.
3. Steer EJ. 5q31-25. Role of the platelet-derived growth factor receptor. *Beta Acta Haematol*. 2002; 107-113.
4. Manusson MK, et al. Activity of STI571 in chronic myelomonocytic leukemia with a platelet-derived growth factor beta receptor fusion oncogene. *Blood*. 2002; 100: 1088-1091.

5. Apperley JF, et al. Response to Imatinib Mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. *New Engl J Med.* 2002; 347:481.

Bortezomib for Non-Hodgkin Lymphoma (NHL)

With regard to NHL, Bortezomib is in fact approved by the FDA for the treatment of relapsed/refractory mantle cell lymphoma following the publication of the article noted below:

6. Fisher et al, Multicenter phase II study of Bortezomib in patients with relapsed or refractory mantle cell lymphoma. *JCO.* 2006, 24. 4867-4874.


Rituximab for Waldenström's Macroglobulinemia (WM)

With regard to rituximab in WM, it is in error to say that it is used off label since with approval of rituximab in the relapsed/refractory setting, the FDA had included all indolent relapsed/refractory NHL including WM (based on WHO/REAL) criteria.

ASH appreciates the challenge to CMS and AHRQ in developing coverage determinations that reflect good evidence in a highly dynamic arena of clinical investigation dealing often with uncommon disorders. This report contributes to this important area of public policy. ASH would like to serve as a partner in trying to arrive at the best approaches to evidence-based coverage determinations for off-label uses of targeted therapies.

Please feel free to contact Carol Schwartz, Senior Manager of Policy & Practice at (202)292-0298 or cschwartz@hematology.org for additional discussion on this document or other relevant AHRQ endeavors.

Sincerely,



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Chair

ASH Committee on Practice