Project Name: Report on the Evidence Regarding Off-Label Indications for Targeted Therapies used in Cancer Treatment

Project ID: CANT1106

Disposition of Comments

Table 2: Public Review Comments

[1] Names are alphabetized by last name. Those who did not disclose name are labeled "Anonymous Reviewer 1," "Anonymous Reviewer 2," etc.

[2] Page and line numbers refer to the draft report.

[3] Page and line numbers refer to the final report.

Reviewer Name[1]	Reviewer Affiliation	Section[2]	Reviewer Comments[2]	Author Response[3]
Anonymous Reviewer 1	American Society of Clinical Oncology (ASCO)	General	These comments are submitted by the American Society of Clinical Oncology (ASCO) in response to a solicitation for public comment on the Agency for Healthcare Research and Quality (AHRQ) report, "Technology Assessment: Report on the Evidence Regarding Off-Label Indications for Targeted Therapies used in Cancer Treatment" released October 26th, 2009. ASCO is the national organization representing physicians who specialize in the treatment of cancer. We are very interested in issues raised by this report and appreciate the opportunity to comment.	Thank you for reviewing and commenting on the draft report.

Anonymous Reviewer 1	ASCO	General	As an organization that routinely undertakes its own systematic reviews to support clinical practice guideline development, ASCO appreciates the scope and quality of review undertaken by AHRQ in preparing this report. We agree with many of the points raised in the Discussion section of this Assessment (Chapter 4), and provide specific comments below. In general, ASCO makes the following comments: • We agree with AHRQ's conclusion that systematic reviews are not always able to answer questions about clinical effectiveness in the off label setting. • The FDA and the NIH are critical partners in assuring a strong, efficient clinical trials system that can provide answers critical to achieving the best care for people with cancer. • There is a need for tools, such as high quality compendia, to guide clinical decision making when clinical evidence is still evolving, but not yet sufficient to support a clinical practice guideline. • Data standards for supplemental indications that build on existing safety information and innovative clinical trial designs are needed to streamline the path to answers and to address the challenges of limited populations. • For very rare tumors and rare patient subpopulations in the context of more common tumors, assembling the study population will be challenging so more limited data is likely to be key to informing patient and physician decision making.	Thank you for these thoughtful comments, which are consistent with findings presented in the report.
Anonymous Reviewer 1	ASCO	General	*Systematic Reviews: Some Limitations* There is increasing recognition among researchers and clinicians that "classic" systematic reviews and technology assessments, by their very nature, may not provide a timely enough response to the rapidly evolving nature of scientific discovery. Development of pre-specified inclusion and exclusion criteria, systematic searches with date boundaries, identification of relevant databases, quality assessment of evidence, data extraction, and other components of systematic reviews take considerable time. Although systematic reviews are considered the "gold standard" in synthesizing and evaluating clinical evidence, the rigor and length of this process is such that, when published, the final product often may already be out of date and of little use to its intended audience.	Thank you for this thoughtful comment, which is consistent with findings presented in the report.

Anonymous Reviewer 1	ASCO	General	*Systematic Reviews: Some Limitations (continued)* In addition to issues around the timeliness of systematic reviews and technology assessments, the existence of high quality data upon which to base conclusions varies widely. Absence of high quality evidence from rigorous studies is a frequent concern for developers of systematic reviews worldwide. Often, specific clinical questions, even for relatively common interventions or treatments, cannot be answered with any degree of confidence because of limited or poor quality data, inconsistent trial primary and secondary endpoints, lack of rigorous statistical analysis plans, and inconsistent conflict of interest disclosures.	Thank you for this thoughtful comment, which is consistent with findings presented in the report.
Anonymous Reviewer 1	ASCO	General	*Systematic Reviews: Some Limitations (continued)* The focus on comparative effectiveness research, regardless of the direction taken by health care reform, is providing the ability to identify and fund projects to address gaps in evidence. The Institute of Medicine and Federal Coordinating Council reports lay the groundwork for identifying areas in need of additional study, but this must be an ongoing assessment to help prioritize questions from the clinical community that are in need of additional research.	Thank you for this suggestion, which is fundamental to current discussions of comparative effectiveness research and learning health care systems.

Anonymous Reviewer 1	ASCO	General	*The Need for a Strong Federal Commitment to Clinical Research* The other critical element is how to facilitate this kind of research. Ongoing availability of federal funding is important because these are areas that industry is not likely to address. Additionally, we need to improve the efficiency with which we conduct clinical trials. ASCO has convened experts in the field to develop consensus recommendations on optimized data collection in an effort to focus resources on the collection of data that serves to inform regulatory and clinical decisions for supplemental indications. It is our hope that these recommendations will be incorporated by regulatory officials in guidance documents for the clinical trial community to enable use of innovative designs, standardize and improve the quality and efficiency of data collection, and ultimately improve our ability to conduct clinical trials. Despite the best efforts of the Duke Evidence Based Practice Center and AHRQ staff to gather all relevant data for this report – including extensive abstract searches and a horizon scan – it was extremely difficult to reach definitive conclusions on the efficacy of specific drugs in the nineteen areas studied. As noted in the draft report, data among (and even within) studies of the same drug varied enormously in quantity and quality. The draft report discusses possible reasons for these deficiencies in the evidence base, many of which are well known to researchers and clinicians: diseases treated by targeted therapies are frequently rare, which limits the numbers of patients available to enroll in trials; the cost of clinical research is outpacing funding; and there is publication bias.	Thank you for nicely summarizing some of the key findings of the report.
Anonymous Reviewer 1	ASCO	General	*Innovative Clinical Trial Design* AHRQ's experience, which mirrors our own, highlights two important areas for continuing discussion: 1) improved clinical trial design in emerging areas of science, and 2) the need to provide timely guidance to clinicians in the face of rapidly changing or developing evidence. ASCO is active on both fronts. Recently, we convened experts in the field to discuss key questions regarding the uses of alternative trial designs. We are using the same process to look at design issues particular to conducting trials where there is a small pool of patients available. Again, we hope that these consensus recommendations will be reflected in guidance to the clinical trial and drug development communities and ultimately help improve use of these designs.	We applaud ASCO's efforts in this area.

Anonymous Reviewer 1	ASCO	General	*Support for Clinicians as Data Emerge* Asking the right clinical questions is important both for designing clinical trials and for developing clinical guidelines. ASCO guidelines pose multiple questions for any given topic which are identified a priori by an expert panel in order to address issues relevant to clinical practice. This process assures that a breadth of question and scenarios of immediate interest to practitioners are addressed by the systematic review(s) and that areas with deficient evidence are identified.	This is an important point that is evidently guiding ASCO's work.
Anonymous Reviewer 1	ASCO	General	*Support for Clinicians as Data Emerge (continued)* Because ASCO is committed to helping its members make sound clinical decisions based on the best available evidence, our clinical practice guidelines program requires a rigorous systematic review for each published guideline. However, we recognize that there are many situations where a systematic review may not be feasible or practicable. In these situations, clinicians still need answers to the questions being posed. For this reason, we recently implemented a program to publish provisional clinical opinions (PCO). PCOs are intended to offer timely clinical direction to the ASCO membership following the publication or presentation of potentially practice-changing information. In 2009, ASCO completed its first PCO on the role of KRAS mutation testing in metastatic colorectal cancer. Another two PCOs are under development. Because PCOs typically address an emerging technology that is being implemented based on relatively few published studies, the processes of conducting the supporting literature search, extracting the relevant evidence, and constructing evidence tables consume much less time and other resources. Other medical professional societies have developed analogous mechanisms to provide more timely responses to emerging evidence.	Thank you for this information.
Anonymous Reviewer 1	ASCO	General	*Support for Clinicians as Data Emerge (continued)* The pace of scientific discovery, the rapidly escalating cost of care, and the national effort to undertake health reform are combining to create unprecedented challenges for the medical community. These tensions are keenly felt across oncology. ASCO looks forward to working with AHRQ and others on identifying potential solutions to these complex issues. Ultimately, we share the same goal: delivering the right care, delivered to the right patient, at the right time.	Thank you.

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	General	I am writing on behalf of Millennium Pharmaceuticals, Inc., (Millennium) to comment on the agency's draft report Evidence Regarding Off-Label Indications for Targeted Therapies Used in Cancer Treatment. Millennium manufactures VELCADE® (bortezomib) for Injection, a novel proteasome inhibitor, indicated for the treatment of patients with multiple myeloma (MM), as well as for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Millennium shares AHRQ's commitment to uncovering, analyzing and disseminating evidence in order to determine the best course of treatment for patients. We appreciate the opportunity to comment on the general findings of the report and also the methodology and specific evaluation of bortezomib and its use in Non-Hodgkin's Lymphoma (NHL).	Thank you.
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	General	As mentioned in the report, due to ongoing investigatory work, the use of certain therapies often evolves quickly and outpaces the Food and Drug Administration (FDA)'s process for approval of drugs for additional indications. Access to cutting edge therapies is particularly important in oncology, where patients desperately need access to a wide spectrum of medications for life saving purposes. Physicians treating cancer routinely rely on "off-label" drugs to treat patients with cancer, a difficult disease to treat that frequently demands extraordinary treatment regimens to improve and prolong the lives of those afflicted. As referenced in the report, Medicare law specifies that coverage decisions should be made with reference to certain Compendia. Recommendations for off-label use of an anti-cancer therapeutic regimen in one of the specified Compendia largely establish Medicare's coverage. For anti-cancer drugs, given the large volume of clinical literature that Medicare's claims processing contractors would otherwise have to evaluate, the Compendia provide a useful tool in determining coverage.	Thank you for this comment, which nicely summarizes the compendia's role.

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	General	The report demonstrates that the task of keeping up with and assessing diverse and quickly changing literature is difficult, and as such, recognizes that the breadth and scope of the task expected of Compendia is a difficult one. The report also notes that the pace of research and the need for timeliness in evidence review are particularly acute challenges in oncology – a challenge which was not met by the AHRQ report given the timelines of the data reviewed. For this reason, we would like to point out that the report does not directly evaluate Medicare-approved drug Compendia in general or in connection with particular therapies. Nor does it address how well the Compendia perform their role of providing reliable guidance for physicians and patients in making clinical decisions. The Compendia system has been in place for many years, and is seen as a viable and necessary option in the evaluation of off-label coverage, yet the report does not have any reference to Compendia and its usefulness to the determination of prescribing behavior and/or drug coverage.	This is a valid comment, but the suggestions made lie outside the scope of our report. The funded study addressed the state of the evidence for targeted therapies; it did not encompass comparison or evaluation of the compendia themselves.
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	General	It is Millennium's opinion that the use of Compendia should play an important role and should continue serving in their vital capacity to evaluate the use of off-label cancer therapies. As discussed above, Compendia fill a very important role, and incorporate not only the most up to date literature, but also the opinions of key physicians who treat patients within each distinct disease state. It is, of course, important that they be judiciously considered within the process of reviews for comparative effectiveness.	Thank you for expressing this perspective.
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	General	We truly appreciate the opportunity to provide our perspective and comments on the report. Millennium recognizes and appreciates the work involved in preparing the Draft Technology Assessment. Our comments fall into two general categories and are presented below.	Thank you.

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Methodology: General Approach	*I. Comments on the methodology used for the Draft Technology Assessment – General Approach* We expected the report to contain an in depth review of evidence types used to achieve Compendia listing. That is, review of relevant evidence attributes such as internal and external validity, credibility of study method, biases, and whether the evidence is likely to approximate the truth. We believe that this evidence review could have included the evidence used within the 19 drug-disease pairs identified but also the comparative evidence used in applications for Compendium listings that were not approved (if the information was available), evidence used for drug-disease pairs which subsequently gained FDA labeling, those that were rejected for labeling and potentially other sub-categories. Further, such an analysis may have identified a quantifiable evidence level that has been used for Compendia listings or guidance as to the evidence level that should be used or other insights into evidence usage in Compendia listings. The decision as to whether to grant Compendia listing is currently binary, listed or not. This is balanced by the non-binary nature of evidence – it was our hope that the Draft Technology Assessment would address this conundrum both by looking at the way Compendia listings are expressed and how the binary decision is made within a continuum of evidence.	Thank you for this comment. In the present report, we do not address the compendia processes for determining inclusion of evidence; that issue was not part of the scope of work delineated for this technology assessment.

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Methodology: Drug-disease pairs	*I. Comments on the methodology used for the Draft Technology Assessment – Comment on Methods of the Technology Assessment of Drug-Disease Pairs* It is our opinion that the Draft Technology Assessment is incomplete as compared to Compendia findings, as the Duke report for many drug-disease pairs comes to no clear conclusion as to whether a listing should have occurred. Indeed as the Duke report only assessed drug-disease pairs that did achieve Compendium listing, the report is unable to comment on any drug-disease pairs that failed to achieve listing (though perhaps should have), or to include comments on the evidence from failed listings. In addition, there is no summary table comparison of the Duke review against Compendium listing on any type of scale. Such a scale would of course be complicated by the unidirectional nature of the assessment as noted above. We are of the opinion that a fair comparative assessment of evidence reviews would have considered the same evidence. The Duke group reviewed published literature from a Medline search, whereas, the Compendia examined more than the published literature, including submitted material from manufacturers and consensus from the expert reviewers (including physicians whom treat patients in the various tumor types) as to best practice.	Again, this approach falls outside the scope of our report. We focused specifically on the state of the evidence, and did not focus on compendia decisions and decisionmaking processes.

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Methodology: Drug-disease pairs *(continued)*	*I. Comments on the methodology used for the Draft Technology Assessment – Comment on Methods of the Technology Assessment of Drug-Disease Pairs (continued)* Finally, we were unable to find any reference to National Institute for Clinical Excellence (NICE) evidence criteria; however, the application of these criteria to this report is mentioned.	Thank you for this comment. The mention in the draft report of "quality assessment criteria from NICE" was misleading. We actually used the quality assessment criteria described in a 2003 British report on imatinib mesylate for unresectable and/or metastatic gastrointestinal stromal tumors (GIST); these criteria were, in turn, drawn from a 2001 methodological publication of the British National Health Service Centre for Reviews and Dissemination. We have clarified this in the revised report (pp. 12-13).

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data	*II. Comments on the accuracy of the bortezomib-specific data used for the Draft Technology Assessment* In order to ensure the accuracy of the review, Millennium would like to provide clarifications on the information reported regarding the approved indications for VELCADE® (bortezomib) for Injection. Additionally, while Millennium does not recommend or promote the use of any medication outside of its FDA label, we have provided clarifications and comments on the studies used in the NHL review of bortezomib for your consideration. Again, we appreciate this opportunity to ensure the accuracy of the review conducted. *Comment 1:* In December of 2006, VELCADE® (bortezomib) for Injection was approved for use in patients with MCL who have received at least one prior therapy. Table 2 on page 15 erroneously lists bortezomib as approved for MM patients who have received at least one prior therapy only and omits the mention of the MCL indication. Thus, listing bortezomib as being used off-label in NHL is not entirely accurate as any use in MCL patients was on-label as of December 2006. If bortezomib was truly considered for off-label use in NHL, then any data from MCL patients should have been omitted. On a related note, the literature search that was last run on September 14th 2007 should have included an article by Fisher et al., published in the Journal of Clinical Oncology (JCO) in October of 2006 ("Multicenter Phase II Study of Bortezomib in Patients With Relapsed or Refractory Mantle Cell Lymphoma"). This article reports data from the pivotal Phase II trial in MCL patients that served as the basis for approval of bortezomib in this patient population.	See responses to specific comments immediately below. We have updated the bortezomib entry in Table 2 (p. 9) by adding relapsed/refractory mantel cell lymphoma (MCL) as an FDA-approved indication. The bortezomib/MCL drug/ disease combination did not fall within the scope of this report because (as noted immediately above) this indication is FDA-approved. Hence the Fisher article, studying bortezomib for MCL, was excluded.
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data *(continued)*	*Comment 2:* NHL is a heterogeneous disease that consists of multiple subtypes based on the cellular origin of each tumor. The subtypes range from indolent to aggressive in their behavior and vary greatly in terms of diagnosis, prevalence and unmet medical need. Thus, data resulting from an overall NHL patient population (i.e. combining data from patients with different subtypes of NHL) is difficult to interpret. Additionally, inclusion of studies in Waldenström's macroglobulinemia (WM) patients further complicates the matter as WM is often viewed separately from both MM and NHL (for example, NCCN lists WM as a separate disease, although the treatment guidelines are published in the same document as the MM treatment guidelines).	Thank you for this comment, which provides a case in point of the difficulties encountered in trying to interpret the diverse data related to targeted therapy indications. This comment is consistent with the findings of our report.

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data *(continued)*	*Comment 3:* We appreciate the principle of using robust evidence only to make treatment choices. However, the definition of "robust" will vary depending on the disease. For example, some of the NHL subtypes are rare and it is not feasible to run large, randomized trials in these disease areas. These rare subtypes are often ones with the highest unmet medical need. Thus, a non-controlled, Phase II trial may be the highest level of evidence one could hope to achieve in that disease setting and should be treated as such. Specifically, methodology used to assess the value of bortezomib in NHL did not consider the context of the disease itself.	This general point is now underscored more clearly in the Discussion section at the end of the main report, where we have adjusted the wording on p. 23 as follows (edits underscored): "In some diseases, despite limited, lower quality, and/or ambiguous data, the use of an off-label indication may be a reasonable clinical decision. For example, given the rarity of dermatofibrosarcoma protuberans (DFSP) tumors, the substantial mortality risk for those tumors that progress into a sarcoma or metastasize, the lack of other systemic therapeutic interventions for DFSP, and the presence of the PDGF receptor as a target in DFSP, treatment with imatinib in DFSP is a sensible strategy even in the setting of few published reports, incomplete exploration in clinical trials, or data coming only from uncontrolled Phase II trials."

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data *(continued)*	*Comment 4:* In the Discussion, page 35, the authors note: "Sometimes referred to as the 'June 5 effect', oncologists start applying new data presented in abstract form at the ASCO conference that takes place at the beginning of June, often with a resulting uptick [sic] in relevant drug utilization". Given this observation, it is puzzling why conference data was omitted from the later literature search (for years 2008 and 2009). Publications in peer-reviewed journals sometimes take more than a year to get published and thus often lag behind the research presented at the major medical meetings. Using data from major conference presentations would clearly add value to the timeliness and practicality of the drug use in the off-label indication in question. Furthermore, comments from an authority like AHRQ on data from conference presentations could provide guidance to physicians who may be considering use of a given drug based on the latest information.	This statement regarding the "June 5 effect" was made to illustrate the need for timely access to the latest data, not to recommend the immediate use of data presented in abstracts. For the purposes of this report, we ran our last search for published reports on September 14, 2007, and held to the same cut-off date for abstracts; hence, the 2008 and 2009 conference proceedings were excluded. (The statement included on p. 22 of the draft report suggesting that we updated the literature search again on June 30, 2009, was in error and has been deleted in the final report.) If we had included the 2008-2009 abstracts, but not published full reports from the same time period, we would have weighted the results of the systematic reviews in favor of abstracts – an inadvisable approach.

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data *(continued)*	*Editorial/fact checking comments on the bortezomib section:* • In addition to the Fisher et al. JCO 2006 article, another full report that should have been identified by the literature search was published by Strauss et al., in the May 2006 issue of JCO: "Bortezomib Therapy in Patients With Relapsed or Refractory Lymphoma: Potential Correlation of In Vitro Sensitivity and Tumor Necrosis Factor Alpha Response With Clinical Activity". • Given that these two significant references (Fisher et al., JCO 2006 and Strauss et al., JCO 2006) were missed during the literature search, one questions the thoroughness of the search and methodology in general • We would also suggest adding duration of response as an important efficacy measure	As with the Fisher article (see response to comment above), the Strauss article was ineligible for inclusion in this report because it did not study one of the 19 drug/disease combinations that were the focus of the technology assessment. On duration of response as an important efficacy measure, there are a number of cancer-related outcome measures we could have chosen, including duration of response. We elected to focus on a standardized set of response measures consistent with those chosen in the 2005 and 2006 AHRQ-funded Technology Assessments of oral cancer drugs. Those reports were previously public- and peer-reviewed. Moreover, we do not think the addition of other measures would have changed the ultimate findings of this report. Finally, while duration of response is useful in some contexts, it is not a standard cancer outcome.
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data *(continued)*	We focused our efforts on data checking of the two full reports used in this analysis: that is, the publications by Goy et al., JCO 2005 and O'Connor et al., JCO 2005. Page 226/lines 21-23: First and last sentence of this paragraph contain the same information.	Thank you for spotting this error. We have deleted the redundant last sentence (p. 167).

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data *(continued)*	Page 227/line 9: Suggest adding "across different NHL subtypes" after "90 percent". Page 227/line 10: Same as above after "7 to 14 percent".	We have made the suggested edit in both places (p. 167).
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data *(continued)*	Page 227/lines 20-21: Missing references; we were not able to verify that the combination of bortezomib with doxorubicin and dexamethasone was tested in patients with NHL (since it is commonly used in MM). It is misleading to mention this combination under "horizon scan" because at the time of the literature search there was already solid Phase II evidence that this combination is effective not only in the laboratory but also in the clinic (Oakervee et al., BJH 2005). An ongoing phase III trial led by Dr. Pieter Sonneveld (HOVON65 GMMG-HD4) is examining this combination in newly diagnosed MM patients eligible for transplantation and comparing it to vincristine-doxorubicin-dexamethasone. The trial started in 2005 and was most recently presented in June 2009 at the European Hematology Association meeting in Berlin.	The reference is to a 2006 case report by Mai et al. (Mai W, Meng H, Jin J, et al. Treatment with bortezomib in a patient with heavily pretreated refractory T-cell lymphoblastic lymphoma. European Journal of Haematology 2006;77[5]:445-7); it is cited in Table A29. The term "horizon scan" is used to refer to the source of data (i.e., abstracts) and is not intended to reflect on the quality or strength of the data, or to indicate early-stage trials only.
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data *(continued)*	Page 229/Table A27 (Goy 2005 entry): • Study design is described on page 669 of the article, under "Statistical Methods" • Median age between two study groups was as follows: o Arm A: 61 (45-78) o Arm B: 60 (38-81) • In the tumor response column, CR data shows both CR and unconfirmed CR (CRu) – suggest revising accordingly	The suggested edits have been made (Table A27, p. 169).
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data *(continued)*	Page 229/Table A27 (O'Connor 2005 entry): • Study design is described on page 678 of the article, under "Study Design" • Stage of disease was reported for follicular lymphoma patients • In the tumor response column, CR data shows both CR and unconfirmed CR (CRu) – suggest revising accordingly	The suggested edits have been made (Table A27, pp. 169-70).

Melody A. Brown	Millennium Pharma-ceuticals, Inc.	Bortezomib data *(continued)*	Pages 240-241/Table A30: • Suggest adding number of patients evaluated for safety for each trial: o Goy, N=59 o O'Connor, N=26 • Thrombocytopenia entry should read 27% instead of 29% for O'Connor study (7/26 patients)	We have now provided information on the number of patients evaluated for safety in the text on p. 167. The data for thrombocytopenia have been corrected as suggested in Table A30 (p. 180).
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	General	In conclusion, we would encourage AHRQ to re-orient the report to focus more on the types and quality of evidence used in achieving Compendia listing rather than forming separate conclusions as to whether each of 19 drug-disease pairs should have been listed or not. It is our opinion that the analysis of the specific 19 drug-disease pairs is inadequate. We understand the limitations for timeliness of evidence review, and we recognize the challenges "cut-off" dates and timelines present.	Thank you for your suggestion. The stated purposes of this study were "to evaluate the state of the evidence supporting the use of targeted therapies outside of their FDA-approved indications; it also evaluates the practicality of traditional systematic review approaches in rapidly evolving therapeutic areas such as targeted therapies for various cancers." We did not, therefore, set out to evaluate the compendia and their processes for determining inclusion.
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	General	Furthermore, we are concerned about the factual inaccuracies in the bortezomib data contained within the report and the failure of the literature search in finding references on the use of bortezomib in refractory mantle cell lymphoma as evidence considered for the brief technology review of bortezomib in NHL.	We have addressed the factual issues as delineated above.
Melody A. Brown	Millennium Pharma-ceuticals, Inc.	General	Once again, we appreciate the opportunity to comment on this important draft Technology Assessment conducted by AHRQ upon the request of CMS and we hope that our comments are useful in ensuring the most accurate and impactful Comparative Effectiveness reviews moving forward. Additionally, we are very interested in continuing the discussion around the specifics related to AHRQ's future review process.	Thank you for your careful review and well-considered comments.

Randy Burkholder and Andrea Douglas	Pharma-ceutical Manufac-turers of America (PhRMA)	General	The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to comment on the draft technology assessment, “Report on the Evidence Regarding Off-Label Indications for Targeted Therapies used in Cancer Treatment” (the “Assessment”), released by the Duke Evidence-based Practice Center under the Technology Assessment Program of the Agency for Healthcare Research and Quality (“AHRQ”). PhRMA is a voluntary, nonprofit association representing the country’s leading researchbased pharmaceutical and biotechnology companies – companies devoted to discovering new medicines that allow patients to lead longer, healthier, and more productive lives. PhRMA's member companies play a leading role in developing new therapies and in advancing the scientific and clinical knowledge essential to the search for new cures. We share AHRQ’s commitment to the generation of evidence to support improvements in health care quality and patient health outcomes. PhRMA believes that health care decisions should be informed by the best available evidence. Empowering patients and physicians by providing them with high quality information on a range of available treatment options will help ensure that our health system delivers the best possible results.	Thank you for this affirming comment.

Randy Burkholder and Andrea Douglas	PhRMA	General	*Summary* PhRMA appreciates the thorough, thoughtful approach taken in this technology assessment. The draft report underscores the important role of targeted therapies in improving treatment of cancer patients, both for approved indications and medically appropriate off-label uses, as well as the rapid evolution of treatment approaches and the evidence base in this field. It also illustrates the value of recognized compendia and peer-reviewed literature as mechanisms to provide Medicare coverage for medically appropriate off-label uses.[1] Finally, the report points to the need for new models for identifying and closing the constantly evolving evidence gaps in the field of oncology. In light of the "challenges in the current methods of evidence review" identified in the assessment, it is important for coverage policy to continue to give physicians flexibility in the care of cancer patients, and avoid policies that impose treatment standards based on a point-in-time assessment of the evidence that do not account for the ways medical care, treatment options, and the evidence base evolve over time. <u>Note:</u> [1] We note that under the Federal Food, Drug, and Cosmetic Act, pharmaceutical manufacturers may not promote medicines for uses that are inconsistent with the FDA-approved labeling. FDA has, however, recognized that "off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading." FDA, Guidance for Industry - Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (2009).	Thank you for this comment, which is consistent with the report's findings.

Randy Burkholder and Andrea Douglas	PhRMA	General	*The Role of New Medicines in the Fight Against Cancer* PhRMA appreciates the Assessment's recognition of the increasingly important role of targeted drug therapies in the treatment of cancer. As the Assessment notes, targeted therapies are designed to attack cancer cells with greater precision, thus providing patients important therapeutic benefits, but with far fewer side effects and with an improved quality of life. They have "been heralded as a promising new approach to cancer treatment." Targeted therapies, along with other advances in diagnosis and treatment, are playing an important role in the gains we are making in the war against cancer. Since 1980 life expectancy for cancer patients has increased about 3 years and 83% of those gains are attributable to new treatments, including medicines.[2] Another study found that medicines specifically account for 50-60% of increases in survival rates since 1975.[3] In addition, the chances that a cancer patient will live at least 5 years has increased across cancers. In 1975-79 the 5-year survival rate was just 50%. By 2000 survival rose to 67%.[4] For many specific types of cancer, survival is increasing dramatically. Between 1975-79 and 1996-2003 5-year survival went up 19% for breast cancer, 43% for prostate cancer, 28% for colon and rectum cancer, and 22% for lung and bronchus cancer.[5] <u>Notes:</u> [2] E. Sun, et al., "The determinants of recent gains in cancer survival: An analysis of the Surveillance, Epidemiology, and End Results (SEER) database." *Journal of Clinical Oncology,* May 2008 Suppl (Abstract 6616). [3] F. Lichtenberg, "The Expanding Pharmaceutical Arsenal in the War on Cancer," NBER Working Paper 10328, February, 2004. [4] Surveillance, Epidemiology, and End Results (SEER), http://seer.cancer.gov/csr/1975_2005/results_single/sect_02_table.06.pdf. [5] National Cancer Institute, "SEER Cancer Statistics Review 1975–2004", 2004.	Thank you for adding this comment to the public record.

Randy Burkholder and Andrea Douglas	PhRMA	General	*The Role of New Medicines in the Fight Against Cancer (continued)* The continued scientific advances noted in the technology assessment hold out the promise of continued progress against cancer. As noted by Rickard L. Schilsky, MD, President of the American Society of Clinical Oncology, "Scientifically, we have never been in a better position to advance cancer treatment. … We now understand many of the cellular pathways that can lead to cancer. We have learned how to develop drugs that block these pathways. And increasingly, we know how to personalize therapy to the unique genetics of the tumor, and the patient."[6] In sum, targeted therapies, as they enter clinical practice, represent an important measure of progress in the fight against cancer. We appreciate AHRQ's attention to this important topic. <u>Note:</u> [6] American Society of Clinical Oncology, "Clinical Cancer Advances 2008: Major Research Advances in Cancer Treatment, Prevention and Screening," *Journal of Clinical Oncology,* 22 December 2008.	We appreciate your response to the report, and your contribution of PhRMA's perspective to the public discourse on the topic of targeted therapies.

Randy Burkholder and Andrea Douglas	PhRMA	General	*Importance of Patient Access to Off-Label Uses of Cancer Therapies* We also appreciate the Assessment's recognition of the importance to patients of access to medically appropriate off-label uses of targeted therapies and other cancer treatments. As the National Cancer Institute has noted, off-label uses often represent the "standard of care" for patients with cancer.[7] We agree that an important outcome of the assessment is its "description of the state of the evidence in a single, quickly evolving, field of biomedical research." The report effectively describes the "rapid evolution" of medical practice and medical literature on off-label uses of targeted cancer medications. For example, the assessment lists the number of identified publications available annually for each of the eight treatments included in the assessment between 2005 and 2008 (with additional figures extrapolated for 2009). For each treatment, an increasing number of new publications were available each year. For alemtuzumab, for example, the number of publications was 238 in 2005; in 2008, 395 additional publications became available. More broadly, the rapid evolution in the literature on targeted therapies is a direct and positive reflection of rapid advances in the medically appropriate uses of the therapies themselves. The fact that the Assessment found substantial increases in the number of publications on targeted therapies suggests a field in which research is advancing and in which physicians and patients are acquiring more therapeutic options for addressing cancer's serious and often deadly effects. The fact that over the course of the Assessment FDA approved several of the previously off-label targeted drug indications further underscores the dynamic cycles through which data are accumulated, learning advanced, and new therapies developed. Note: [7] "Understanding the Approval Process for New Cancer Treatments," National Cancer Institute, http://www.nci.nih.gov/clinicaltrials/learning/approval-process-for-cancer-drugs/page5, accessed November 9, 2009.	Thank you for this considerate comment.

Randy Burkholder and Andrea Douglas	PhRMA	General	*The Need for Flexible Coverage Policy for Medically Appropriate Off-Label Uses* Medicare law and policy recognize the important role of medically appropriate off-label use of medicines in the treatment of cancer patients. As the Assessment notes, a discrete Medicare statutory provision established the basis for coverage of off-label uses of certain anti-cancer drug indications. Enacted in the early 1990s, this provision[8] was intended to address barriers to cancer patients' access to medically appropriate off-label uses. The continuing importance of this purpose is affirmed by rapid advances in targeted therapies and other cancer medications. A key approach underlying the early-1990s statutory change was to recognize listings in authorized drug compendia as a basis for coverage of medically appropriate anti-cancer medicines under Medicare Part B -- a conscious choice by Congress in favor of timely beneficiary access and continued clinical progress. In addition to compendia, the statute recognizes peer-reviewed medical literature as an independent basis of coverage for off-label cancer therapy indications. By describing the rapid evolution in cancer care – both in treatment options and the evidence base – the technology assessment underscores the importance of maintaining a strong Medicare policy for coverage of off-label uses of anti-cancer medicines that relies on recognized compendia and peer reviewed literature. This approach ensures that treatments are available to Medicare beneficiaries for medically appropriate off-label uses based on available medical evidence, while providing the flexibility needed in a rapidly evolving field such as cancer care. The Assessment points out that the soundness of this approach is underscored by the fact that many states and private third-party insurers rely on compendia listings as a means for ensuring appropriate patient access to off-label uses of cancer medications. Note: [8] Social Security Act §1861(t)(2)(B) (42 U.S.C. §1395x(t)(2)(B)).	Thank you for this comment and for offering your perspective on the compendia.

Randy Burkholder and Andrea Douglas	PhRMA	General	*The Need for Flexible Coverage Policy for Medically Appropriate Off-Label Uses (continued)* The assessment further supports the soundness of current Medicare coverage policy for offlabel uses of anticancer medicines by illustrating that, after an initial FDA approval, there is a continued progression to higher levels of evidence and subsequent FDA approvals for additional treatment indications. The assessment notes, for example, that seven of the 19 indications identified as off-label indications at the beginning of the evaluation were approved by FDA as additional onlabel indications before the technology assessment was completed and released. The importance of compendia and medical literature in day-to-day treatment decisions is demonstrated by a 2008 survey of oncologists and oncology practice managers sponsored by the Association of Community Cancer Centers, the Biotechnology Industry Organization and PhRMA. When the survey's 165 respondents were queried about the sources of information they used to make off-label treatment decisions for anti-cancer therapies, two-thirds cited compendia listings as one source and nearly 90 percent cited peer-reviewed medical journals as another.[9] These findings emphasize the importance of maintaining a robust and flexible Medicare framework for covering off-label indications of cancer medicines. For example, PhRMA supports the annual process CMS now uses to determine the need for changes to the list of recognized compendia. For Medicare contractors to implement the program's evidentiary requirements effectively, it is important that CMS maintain open, transparent processes for ensuring that the number of authorized compendia, and the pool of approved medical journals, is consistent with the access needs of beneficiaries. <u>Note:</u> [9] "Impact of Payer Coverage and Reimbursement Policies on Off-Label Use of Anticancer Therapies," Covance Market Access Services (Sept. 24, 2008).	Thank you for this comment regarding the vital role of the compendia and of an up-to-date body of published medical literature.

Randy Burkholder and Andrea Douglas	PhRMA	General	*The Assessment Could Be Strengthened with Further Analysis to Link the Literature Reviewed to the Assessment's Conclusions* It would be useful if the analyses could look across the drug/off-label-indication pairs to synthesize the data in a way that clearly demonstrates the breadth, range, and diversity of studies. For example, the investigators conclude (correctly) that there is variability in study design type and quality. This conclusion is based on their experience of creating the summary and data table(s) for individual pairs. The investigators could quantify this and make the variability clearer to the reader by constructing consolidated tables or graphs that depict the number of studies of each design and/or quality across all the pairs to provide a snapshot of the variability described. This would give the conclusions, which we all agree to be accurate, a more quantitative basis as well as provide a baseline for future assessments.	These are excellent suggestions, but they lie beyond the scope of our project as outlined by AHRQ.

Randy Burkholder and Andrea Douglas	PhRMA	General	*New Approaches to Evidence Generation and Evaluation Should Maintain Physician Flexibility and Patient Access to Medically Appropriate Care* The Assessment makes a comprehensive, and conscientious, attempt to conduct systematic reviews for 19 separate clinical indications in a rapidly evolving field of medicine. Reflecting the inherent challenges the reviewers faced, the assessment notes, "the 'moving target' nature of evidence calls into question the feasibility of a time-bounded, static, evidence review process based on systematic review, in an environment where the evidence pool is continuously expanding." It concludes by asserting that "[a] different model of evidence generation and evaluation is warranted," but then quickly and appropriately asks, "is it possible?" This challenge, while particularly acute in oncology, is not unique to this medical specialty. Continual changes in treatment options and the evidence base are of critical importance to patients. Yet if evidence reviews are poorly designed or policy applications too simplistic, this dynamic is easily overlooked. PhRMA supports the new policy avenues the Assessment identifies – comparative effectiveness research, rapid learning, and the expeditious translation of research and learning into clinical practice. At the same time, it is important to ensure that the application of these tools by policy-makers does not exacerbate the very challenges highlighted in the assessment. As noted by the Institute of Medicine in its December 2008 report, *HHS in the 21st Century: Charting a New Course for a Healthier America,* "Comparative effectiveness research, like any sharp tool, needs to be used carefully…there will rarely be black and white choices that can guide coverage decisions."	Thank you for this comment and the cautionary note.

Randy Burkholder and Andrea Douglas	PhRMA	General	*New Approaches to Evidence Generation and Evaluation Should Maintain Physician Flexibility and Patient Access to Medically Appropriate Care (continued)* We believe these new assessment methods should be deployed in a way that complements and supplements, but does not disrupt, Medicare's long-held policy framework for ensuring appropriate patient access to off-label indications of anti-cancer therapies. For example, new health information tools that provide clinical decision support at the point of care may increasingly help oncologists access pertinent information on off-label indications of new medicines. Tools like these can speed the distribution of evidence and accelerate the pace of clinical learning, and, as such, can strengthen Medicare's current policy framework. At the same time, if these new HIT tools misuse the evidence to define rigid treatment rules or "best practices," they will fail to capture the constant evolution in medical practice and evidence described in the assessment, and undermine delivery of optimal patient care to the individual.	Thank you for emphasizing the need to develop decision support tools that are able to adapt and evolve in step with the evidence base.
Randy Burkholder and Andrea Douglas	PhRMA	General	*Conclusion* PhRMA appreciates the thorough, thoughtful approach that the reviewers took in this technology assessment. It illustrates how the state of clinical practice and the evidence base in cancer care are continually, rapidly evolving, and describes the importance of medically appropriate offlabel uses of medicines in the care of cancer patients. Further, the Assessment points to the challenges of conducting and applying static, point-in-time assessments in this field, and the need to develop new models of evidence generation and assessment. PhRMA agrees that tools like rapid learning and comparative effectiveness research can help meet this need. As these new tools are developed and deployed, it is important that they support Medicare's existing policy framework for providing Medicare beneficiaries timely coverage and access to medically appropriate off-label uses.	Thank you for your carefully articulated comments.

Megan Gordon Don	Pancreatic Cancer Action Network	General	The Pancreatic Cancer Action Network is a national nonprofit organization dedicated to working together to advance research, support patients, and create hope for those affected by pancreatic cancer and is guided by a pre-eminent Scientific Advisory Board and Medical Advisory Council. We have reviewed the draft report "Technology Assessment: Report on the Evidence Regarding Off-Label Indications for Targeted Therapies used in Cancer Treatment" recently released by the Agency for Healthcare Research and Quality (AHRQ). The draft report covers eight targeted therapies used off-label for different indications, with two relevant to pancreatic cancer: bevacizumab (Avastin®) and cetuximab (Erbitux®). We are writing today to express our concerns about some of the statements on the use of these targeted therapies in pancreatic cancer.	Thank you for this information, and for reviewing and commenting on the draft report.

Megan Gordon Don	Pancreatic Cancer Action Network	General – pancreatic cancer	First, it must be noted that pancreatic cancer is one of the deadliest cancers; in fact, it is the fourth leading cause of cancer-related death and has a five-year survival rate of just 5%. There are no early detection tests and very few effective treatment options for those diagnosed with this disease. Surgery at a high-volume center currently offers the best opportunity for long-term survival, but surgery is generally only performed when the cancer is detected at an early stage. Unfortunately, only 15% of cases are diagnosed early enough for surgery and the majority (80%) of surgery patients have a recurrence of the cancer within five years. As of today, only three drugs have been approved by the Food and Drug Administration (FDA) to treat pancreatic cancer: fluorouracil (5-FU), gemcitabine (Gemzar), and erlotinib (Tarceva), a targeted therapy used in conjunction with gemcitabine. It should be noted that while these treatments can be beneficial in treating some patients, they are not considered curative. In fact, 95% of pancreatic patients die within five years of being diagnosed, 76% within one year. Clinical trials are essential to finding new pancreatic cancer treatments, and many trials are exploring a combination of pharmacologic therapies, sometimes in conjunction with surgery and/or radiation to improve outcomes. Given the limited alternatives, pharmacologic therapies, including off-label targeted therapies, are often the best hope for people with pancreatic cancer. Unfortunately, the nature of pancreatic cancer - which is both a leading cancer killer and a rare cancer - makes it difficult to investigate. Pancreatic cancer research receives limited funding, especially relative to the other leading cancer killers, which adds to the difficulties of research. The limited number of references in the draft technology assessment and the brief summary discussions in the draft report attest to the paucity of research.	The situation for pancreatic cancer patients is particularly dire and requires both expedited research and improved access to new treatments as soon as evidence becomes available. Pancreatic cancer provides a compelling example for the case that a new, more timely, approach to evidence development and review is necessary. Our findings substantiate your picture of limited options and a paucity of research in this area.

Megan Gordon Don	Pancreatic Cancer Action Network	Bevacizumab for pancreatic cancer	As mentioned, the summary discussion on bevacizumab is very short: The findings from the Phase II studies suggest that bevacizumab does little to improve clinical outcomes in the treatment of pancreatic adenocarcinoma. Complete responses ranged from 0 to 1% in these studies. The single Phase III trial, which enrolled 602 patients and compared gemcitabine plus bevacizumab 10 mg/kg to gemcitabine plus placebo, did not demonstrate a survival benefit associated with bevacizumab. These findings are consistent with recently published expert opinion that there is no consensus about second-line therapy after pancreatic cancer progression after gemcitabine failure. The brevity of the summary discussion in and of itself indicates the limited amount research on this treatment option. In fact, there are only 56 results in PubMed.gov for "pancreatic cancer" and "bevacizumab," yet a search for “bevacizumab” alone results in 3245 publications listed in PubMed.gov. We recognize that some of the published studies on the use of this targeted therapy in pancreatic cancer have not been positive or have shown no difference and acknowledge that there is no evidence that bevacizumab is widely beneficial. At the same time, we note that several studies have shown some positive results which suggests potential benefit in certain patients.	We want to emphasize that the short discussion on bevacizumab does not indicate any lack of importance. Rather, we adhered to a brief and somewhat formulaic approach in presenting the evidence in order to prevent the document from growing to an unmanageable size. (Even with our efforts to present information as succinctly as possible, the report is very lengthy.) We concur on this point. Thank you for expressing the importance of exploring all avenues that may offer hope of effective treatment. In this report, however, we must report only what the evidence supports and avoid giving an indication of efficacy where the data are unclear, conflicting, or ambiguous.

Megan Gordon Don	Pancreatic Cancer Action Network	Bevacizumab for pancreatic cancer	The specific concerns of the Pancreatic Cancer Action Network about the summary discussion on bevacizumab are as follows: 1) That there is no consensus on the use of bevacizumab does not mean that there is never any value to its use. 2) Research is still needed to determine whether this therapy may benefit a certain sub-population of pancreatic-cancer patients, e.g., locally advanced pancreatic cancer patients or advanced pancreatic cancer patients or patients with certain genetic biomarkers. 3) Some studies indicate that bevacizumab in combination with other therapies, including other pharmacological therapies or radiation, show promise.	We thank you for this insightful summary, and for pointing out that there may be value for some patients. In this technology assessment, we are constrained to reporting what has been conclusively demonstrated in well-designed studies. "Potential" benefit, or the "promise" of efficacy are not reportable as definitive results – though they do offer hope for the future and, importantly, indicate areas for future research.
Megan Gordon Don	Pancreatic Cancer Action Network	Bevacizumab for pancreatic cancer	It should also be noted that a poster on bevacizumab in combination with two other therapies was presented at the annual meeting of the American Society of Clinical Oncology in June 2009 and thus was not included in the draft assessment report. This poster (A phase II trial of gemcitabine, docetaxel, and bevacizumab (GDB) in metastatic pancreas cancer) found that the combination of gemcitabine, docetaxel, and bevacizumab was overall well tolerated in a small study.[1] Using the primary endpoint of time to progression (TTP) and secondary endpoints such as therapy toxicity and overall survival, the authors reported that the response rates warranted further study. At the time the abstract was submitted, "disease control at 8 wks is 100% (24/24 pts) radiographic RR is 48% (12/25 pts) and tumor marker RR is 95% (18/19 evaluable pts expressed CA19.9, median decline 80%, 5 pts normalized). Of 24 pts evaluable for TTP, 9/18 (50%) initial pts achieved > 9 mo TTP (range 9.2-18.5 mo); the remaining 6 pts continue progression-free on therapy (range 2+-7+ mo). Median OS has not been reached and will be > 8.3 mo." Reference: [1] Picozzi, VJ, Canlas, LA, Sicuro, PL, Malpass, TW. A phase II trial of gemcitabine, docetaxel, and bevacizumab (GDB) in metastatic pancreas cancer. J Clin Oncol 27:15s, 2009 [suppl; abstr 4606]. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=32231	These results are promising and, as the investigators note, warrant further study. You are correct that the ASCO abstracts from the 2009 annual meeting were not included in our search. As explained above, for the purposes of this report, we chose a search cut-off date of September 14, 2007, for both published reports and conference abstracts.

Megan Gordon Don	Pancreatic Cancer Action Network	Bevacizumab for pancreatic cancer	As you develop the final report, we encourage you to consider that additional research is currently underway that may help shed light on these important issues. In addition, several studies have been completed but have yet to publish any results. According to a search of ClinicalTrials.gov in November 2009, nearly thirty studies on the use of bevacizumab in pancreatic cancer treatment are yet to be completed or have yet to publish results. (The majority of these trials look at bevacizumab in combination with at least two other therapies.) The findings from those studies may be necessary to make a more educated judgment about the use of bevacizumab in pancreatic cancer.	We are delighted to hear that you have identified this promising line of research, and sincerely hope to see published positive results in the future.
Megan Gordon Don	Pancreatic Cancer Action Network	Bevacizumab for pancreatic cancer	In summary, we believe that due to the status of ongoing research of bevacizumab in pancreatic cancer, there appears to be some value in continuing to make bevacizumab available for the treatment of some pancreatic cancer patients.	The decision as to whether or not to make specific treatments available to patients is not ours to make; the current report was not intended to provide this sort of specific recommendation.
Megan Gordon Don	Pancreatic Cancer Action Network	Cetuximab for pancreatic cancer	The summary discussion on cetuximab is even shorter than the summary discussion on bevacizumab: Results from the clinical trials published as abstracts demonstrate that the use of cetuximab as an adjunct in the treatment of pancreatic adenocarcinoma is associated with an increase in partial response from 8% to 16%. Only a single subject who received cetuximab had a complete response. Further research is needed to evaluate the efficacy and safety of cetuximab for patients with this cancer.	Yes, the discussion is brief, as noted. Again, this is not intended to indicate any lack of importance.
Megan Gordon Don	Pancreatic Cancer Action Network	Cetuximab for pancreatic cancer	The Pancreatic Cancer Action Network sees promise in the increased partial response cited and agrees on the need for further research, particularly on the role of cetuximab in combination with other therapies, including other drugs or radiation, which show potential. There are only 65 results in PubMed.gov on "pancreatic cancer" and “cetuximab,” a small fraction of the 1699 publications found when conducting a search on “cetuximab” alone. We are pleased that additional research is forthcoming: according to a search of ClinicalTrials.gov in November 2009, 21 studies are yet to be completed or to have results published. (Most of the trials look at cetuximab in combination with at least two other therapies.)	We join you in looking forward to the results of the studies you identified.

Megan Gordon Don	Pancreatic Cancer Action Network	Cetuximab for pancreatic cancer	As is the case with bevacizumab (and in fact any therapy), we believe that it is crucial to investigate whether or not certain sub-populations of pancreatic-cancer patients can benefit from cetuximab, e.g., locally advanced pancreatic cancer patients or advanced pancreatic cancer patients or patients with certain genetic biomarkers.	These are, indeed, valid research questions.
Megan Gordon Don	Pancreatic Cancer Action Network	Cetuximab for pancreatic cancer	In summary, we believe that the statements on cetuximab in the summary discussion are appropriate; more research is warranted.	Thank you; we agree.
Megan Gordon Don	Pancreatic Cancer Action Network	General	The Pancreatic Cancer Action Network believes in using health care resources wisely but cannot ignore the limited treatment options available to people with pancreatic cancer and the benefits to these targeted therapies found in some clinical studies. The Pancreatic Cancer Action Network believes that both of these targeted therapies [bevacizumab and cetuximab] should be available while they continue to be studied in clinical trials. Thank you for your consideration of these comments submitted on behalf of the thousands of people seeking an effective treatment for their pancreatic cancer.	Thank you for expressing these views in the public arena. Thank you again for reviewing and commenting on the draft report.
Martine George	Pfizer, Inc.	General	Pfizer is pleased to submit comments to the Agency for Healthcare Research and Quality (AHRQ) on the draft technology assessment (TA), "Report on the Evidence Regarding Off-Label Indications for Targeted Therapies used in Cancer Treatment," conducted by the Duke Evidence-based Practice Center at the request of the Centers for Medicare and Medicaid Services (CMS). Pfizer is a global leader in life sciences and a research-based company with extensive clinical expertise in oncology. We applaud the efforts of AHRQ and its research partners to develop evidence reports and technology assessments that assist physicians and patients in better decision making. We thank AHRQ for recognizing that the evidence base supporting the off-label use of cancer therapies is an area that deserves attention, and the authors for their effort to provide an extensive evaluation of the state of the evidence. We believe this report is a necessary first step in developing a clear understanding of the evidence base on this topic, and we respectfully submit comments on possible areas for refinement before the draft report is finalized.	Thank you.

Martine George	Pfizer, Inc.	General	*General Findings* We commend AHRQ for conducting this technology assessment, and we recognize the magnitude of effort required for the undertaking. As an organization committed to oncology research, we share AHRQ's commitment to ensuring that patients and providers have the best available evidence to make informed decisions about what cancer treatment is most appropriate. The growing list of potential uses for targeted therapies, beyond their initial FDA-approved indications, is an important issue. According to a 2005 survey by the National Comprehensive Cancer Network, off-label prescribing in oncology increased from one-half of anticancer medication prescribing in 1991 to three-quarters by 2005.[1] Such widespread off-label use, highlights the critical need for research evaluating the evidence base on the health outcomes associated with off-label uses of cancer therapies, and underscores the value of AHRQ's work in tackling this important and difficult topic. We agree that given the rapid evolution of literature on this topic, it is challenging for clinicians and compendia to keep up with the most current evidence on the off-label use of cancer therapies. Targeted cancer therapies play an important role in improving the treatment of cancer patients, both for approved indications and medically appropriate off-label uses. More specifically, we appreciate the authors' following statement: "The clinician's judgment of best treatment choice for an individual patient must take into account whatever evidence is available, and base the decision on that data, albeit limited."[2] We generally agree with the investigators' findings that the quality and quantity of evidence varies across pairs (drugs/off-label indication) and that the variation in quality raises the issue of what constitutes good evidence for off-label indications. It is recognized that clinicians are faced with reliance on low quality evidence when nothing else exists. <u>References:</u> [1] Soares M. Off-label indications for oncology drug use and drug compendia: history and current status. J Oncol Practice 2005; 1:102-105. [2] P. 34, lines 13-15.	Thank you.

Martine George	Pfizer, Inc.	Methodology	*Review Methodology and Analysis* Pfizer recognizes the difficult nature of the task with which the investigators were charged. The rapidly growing body of literature for cancer treatments makes it difficult to capture evidence at any one point in time; a static reflection of all evidence on even a targeted cancer therapy is an arduous endeavor and could result in questionable conclusions. We acknowledge the tremendous volume of evidence that was captured and evaluated to create this horizon scan, and we generally agree with the search strategy and methodology the authors used in the literature review to gather the sources. While we support the search strategy employed in the Medline search, a more rigorous systematic review would incorporate searches of multiple literature databases, similar to the research model followed by the Cochrane collaboration. Further, increased clarity around how AHRQ defines "horizon scan" and the objectives and level of methodological rigor that it associates with the process would be beneficial in better aligning the goals of the study with the expectations of the report's users.	The authors have extensive experience with Cochrane reviews and understand the differences between the methods of Cochrane systematic reviews and the 19 reviews performed under the umbrella of this technology assessment. While we agree that there are other valid approaches, we used the same method as in our two previous peer-reviewed reports in order to gather all of the information we could find that might be of relevance to clinicians in decisionmaking positions with respect to the treatments of interest. Please note that the traditional Cochrane approaches would not capture this range of information. Additionally, in our report we attempted to reflect the data that the compendia use and therefore were more generous in the evidence types selected than would be allowed in a Cochrane review. Although other databases are available, including EMBASE and CDSR, review of these was outside the agreed scope of our work with AHRQ. We have no reason to believe that our primary conclusion – that this approach is not a feasible way to review the existing evidence – would be different if we had used additional databases.

Martine George	Pfizer, Inc.	Methodology	*Review Methodology and Analysis (continued)* We appreciate the need to systematically assess the quality of each study for comparison across a body of evidence; however, the reference provide for the National Institute for Clinical and Economic Excellence (NICE) criteria does not represent a specific set of criteria, but rather a specific NICE technology appraisal. Therefore, we are not sure of the derivation for the 5 questions employed for the quality assessment. In terms of the evidence appraisal that was conducted, the scores derived from this analysis are not systematically presented, and it is unclear to readers how they impacted the evidence appraisal and inform the findings and conclusions. We recommend that the authors clearly cite the study quality appraisal scale and provide a summary table of the scores across studies.	See similar comment above (from Melody Brown of Millennium Pharmaceuticals). As indicated there, the mention in the draft report of "quality assessment criteria from NICE" was misleading. We have corrected this in the revised report (pp. 12-13). The questions used for quality assessment, along with the answers for each study ("Yes," "No," or "Unknown") are listed in the far right column of the appendix tables summarizing full reports (e.g., Tables A1, A5, A9, and so on).

Martine George	Pfizer, Inc.	Methodology	*Review Methodology and Analysis (continued)* With regard to study findings, we noted that the TA provides per drug/indication-pair narrative descriptions of the evidence with per-pair associated tables. The report does not evaluate and adjudicate the literature that exists across the pairs of therapies and their associated off-label indications. Given the complexity of the data and the volume of the findings, it would be valuable to provide summary tables to clearly demonstrate the breadth of and range in research quality for each drug/indication pair from which the conclusions are derived. While we acknowledge that the data for all drug/off-label pairs may not be sufficiently robust, it may prove insightful to select those targeted therapies and their associated off-label uses to show which pairs have a more conclusive body of evidence. As an example, the attached graph (will be provided in hard copy) could be a helpful format to present the quantity and quality of clinical evidence that exists for each pair. According to the graph, the evaluated drug/off-label indication pairs populate the x-axis, with the quantity and quality of studies information associated with each pair captured within the individual bars. Using a hierarchy of study designs, emphasis would be placed on studies that utilized randomization, appropriate concealment, and blinding. While we understand that, based on the sheer volume of pairs the report evaluates, the substantial body of literature associated with each, and the heterogeneity of outcome measurements that exist, rigorous meta-analyses would be very difficult. However, Pfizer encourages the authors to amplify the depth of scientific analysis for a few of the drug/off-label indication pairs where there is enough evidence to do so. At minimum, it would be useful if the authors indicated which pairs might form the basis for worthwhile meta-analysis and the rationale for the selections.	The proposed additional work may yield very interesting information, especially graphically presented (as you suggest). It is, however, beyond the scope of the present project.
Martine George	Pfizer, Inc.	General	*Conclusion* In conclusion, we would like to commend the researchers on a valuable review of the literature and look forward to seeing these comments and recommendations incorporated in the final report. As Pfizer's efforts in this therapeutic area continue, we look forward to further collaboration with the Agency on improving the body of clinical evidence for therapies used in cancer treatment.	Thank you for your comments.

Luana R. Lamkin, RN, MPH	Association of Community Cancer Centers (ACCC)	General	On behalf of the Association of Community Cancer Centers (ACCC), we appreciate this opportunity to comment on the Agency for Healthcare Research and Quality's (AHRQ) draft Technology Assessment: Report on the Evidence Regarding Off-Label Indications for Targeted Therapies Used in Cancer Treatment (the "Draft Report"). ACCC is a membership organization whose members include hospitals, physicians, nurses, social workers, and oncology team members who care for millions of patients and families fighting cancer. ACCC's more than 900 member institutions and organizations treat 60 percent of all U.S. cancer patients when combined with our physician membership. ACCC is committed to ensuring that cancer patients have access to the entire continuum of quality cancer care, including access to the most appropriate cancer therapies. Cancer is a deadly disease, and patients often require treatment with the most innovative and cutting-edge therapies to win their battles against it. Although some advances in cancer care are made by developing new drugs, many involve the discovery of new uses for drugs already approved for other indications by the Food and Drug Administration (FDA). This "off-label" use of cancer drugs is a common medical practice that is a critical component of many treatment regimens and is integral to the discovery of new cures.	Thank you for this information, and for reviewing and commenting on the draft report.

Luana R. Lamkin, RN, MPH	ACCC	General	The Centers for Medicare & Medicaid Services (CMS) requested this technology assessment of the efficacy and safety of selected targeted therapies when prescribed for off-label indications, with the secondary purpose of conducting a "horizon scan of early-stage trials (Phase I or prominent preclinical studies) of these agents" [p. 12]. [See p. 6, where "targeted therapies" are defined as agents "designed not to kill cells but, more precisely, to attack growth factors, cell surface receptors, and intracellular proteins that mediate a malignancy's ability to proliferate, grow, or evade cell death." Examples of targeted therapies include small molecule inhibitors, monoclonal antibodies, and conjugated agents (p. 6)]. The Draft Report says, "CMS will consider this information as background to its further discussion of coverage for and policies regarding targeted therapies" [p. 6]. This technology assessment evaluates the strength of the evidence for 19 different drug/disease combinations using targeted therapies [p. 13]. The reviewers searched four compendia to identify off-label indications for these drugs [p. 13], and conducted MEDLINE searches and searches of conference abstracts for evidence on the uses of these drugs for these indications [pp. 17-19]. The Draft Report makes several important observations that support the importance of the Medicare law and policy covering off-label uses of anti-cancer chemotherapeutic drugs supported by entries in certain compendia or by published research in certain journals [Social Security Act § 1861(t)(2); Medicare Benefit Policy Manual, ch. 15, § 50.4.5].	Thank you for this summarizing comment.
Luana R. Lamkin, RN, MPH	ACCC	General	First, the Draft Report confirms "the pervasive sense among clinicians that the drug landscape in oncology is frequently changing" [p. 31]. ACCC agrees that cancer care continually is evolving. In this challenging landscape, it is essential that Medicare and other payers maintain flexible coverage policies that provide access to anti-cancer drugs based on up-to-date clinical research. Medicare currently uses just such a flexible approach by covering uses supported in any of four compendia or by research published in any of 26 publications.	Thank you for this perspective.

Luana R. Lamkin, RN, MPH	ACCC	General	Second, the Draft Report recognizes the important and challenging role the compendia play in clinical decision-making and coverage policy. The Draft Report notes that the compendia function as a "stepping stone" between drug development and research and FDA approval [p. 31]. ACCC agrees with this observation. The compendia perform a critical service to patients, physicians, and policy-makers by collecting, analyzing, and disseminating the constantly-growing body of clinical research on cancer therapies. As the Draft Report recognizes, this is an enormous task, requiring the compendia to "continuously perfor[m] and updat[e] systematic reviews on the comprehensive list of FDA-approved drugs and biologics" [p. 31] Because this task is so substantial, it must be shared by a group of publications. Given the rapid changes in cancer care and supporting research, it is highly unlikely that any one publication could describe all of the medically accepted treatment options for every variety of cancer at any given point in time. Each publication applies a slightly different standard for inclusion and a different method of indicating whether a use is supported by clinical evidence and the weight of that evidence. For these reasons, ACCC supports Medicare's recognition of multiple compendia, and we believe that any technology assessment of off-label uses of cancer therapies should examine all of the compendia currently used by Medicare.	Thank you for this clearly outlined response.
Luana R. Lamkin, RN, MPH	ACCC	General	Third, the Draft Report observes that a different standard may apply to evidence for cancer treatment than to treatments in other disciplines [p. 36]. As the Draft Report notes, "in some diseases, despite limited and/or ambiguous data, the use of an off-label indication may be a reasonable clinical decision" [p. 34]. In addition, "many cancers are potentially life-limiting diseases, for which there are few if any effective treatment options," and "[o]ncologists and patients find themselves in a situation characterized by urgency, fear, and a desperate desire to take action in hopes of a response" [p. 36]. ACCC agrees with these observations, and we ask AHRQ to include them in the final report. As CMS considers the evidence on off-label uses of FDA-approved therapies, it must recognize that patients and physicians must make treatment decisions under extremely difficult circumstances, and applying unduly strict standards to the clinical evidence will deny patients access to potentially lifesaving care.	Thank you for this comment.

Luana R. Lamkin, RN, MPH	ACCC	General	Finally, the Draft Report notes that “a different model of evidence generation and evaluation is warranted,” but asks, “is it possible?” [p. 36]. The Draft Report identifies “rapid learning healthcare” that “develops research insights as a natural byproduct of the care process” and comparative effectiveness research as “logical next area[s] of exploration in the effort to understand and improve upon the state of the evidence available to support medical care” [p. 37]. ACCC strongly supports efforts to improve the quality of clinical evidence available to support treatment and policy decisions. We also acknowledge that treatment decisions must be made today with the information available now. Until any new research models are developed and implemented, CMS and other payers must continue to cover off-label treatments supported by the compendia or other published peer-reviewed research.	Through this mechanism, AHRQ and CMS will receive and consider your injunction.

J. Leonard Lichtenfeld and Daniel Smith	American Cancer Society (ACS) and American Cancer Society Action Network (ACS CAN)	General	The American Cancer Society (the Society) and the Society's nonprofit, nonpartisan advocacy affiliate, the American Cancer Society Cancer Action Network (ACS CAN), appreciate the opportunity to comment on the referenced technology assessment to highlight the importance of off-label drug use in cancer and respectfully urge caution in making any resulting Medicare off-label policy changes that may restrict coverage for quality cancer care. Use of drugs off-label is an important element of providing quality cancer treatment and care. Oncologists consistently have confirmed the importance of having a range of anticancer therapies available for use in treating their patients, including availability of medications used for off-label indications. Because of the complexity of cancer and its rapidly changing treatment landscape, the most technologically advanced, cutting-edge cancer therapies are often available only through off-label use. This is particularly true with respect to new cancer therapies and targeted therapies. In fact, as the National Cancer Institute website emphasizes, "[f]requently the standard of care for a particular type or stage of cancer involves the off-label use of one or more drugs." For example, Gleevec had initially received accelerated FDA approval for treatment of chronic myeloid leukemia, with a market of about 50,000 patients a year. Now Gleevec is FDA-approved effective for ten cancers, and is used by 200,000 patients worldwide. Because of Gleevec's accelerated approval, and physicians' willingness to prescribe a promising new drug off-label, thousands of cancer patients have benefited. Numerous studies over decades have consistently confirmed the importance of off-label therapies as an essential element of quality cancer care. As a result, the federal government and many states have adopted policies that ensure coverage for off-label uses of cancer chemotherapeutic agents under various health plans, most notably Medicare and state-regulated private health insurance policies.	Thank you for this well-articulated background comment.

J. Leonard Lichtenfeld and Daniel Smith	ACS/ACS CAN	General	Effective treatment and management of cancer requires physicians to consider the type of cancer, the unique presentation and history and symptoms of the patient, the stage of the cancer, as well as the available and accessible therapeutic alternatives. Patients who present with advanced stages of cancer, difficult-to-treat cancers, or rare cancers often require off-label use of a drug as part of their treatment. It is therefore critical that physicians have access to the best evidence available for their clinical decision making. As such, oncologists rely on a wide range of evidence sources to support medically appropriate off-label uses, including drug compendia, peer-reviewed literature, manufacturer hotlines, and case reports. Of these various sources, drug compendia remain the most reliable guide available today that oncologists can consult in evaluating the evidence available for medically appropriate off-label drug uses. The compendia process serves as a meaningful and effective mechanism for undertaking systematic reviews of off-label drug uses, particularly in oncology, given the frequently changing oncology drug landscape. In fact, the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) has confirmed its confidence that physicians can rely on the available compendia to determine appropriate off-label uses for anticancer drugs and biologicals. Similarly, Congress recognized the importance of compendia in off-label drug use in the Medicare Improvements for Patients and Providers Act of 2008 (MIPPA) by codifying the process for identifying appropriate compendia, and requiring that all compendia have a "publicly transparent process for evaluating therapies and for identifying potential conflicts of interest," accomplished through the current Physician Fee Schedule for Calendar Year 2010.	Thank you for this comment affirming the valuable role that the compendia play in providing information to prescribing clinicians.

J. Leonard Lichtenfeld and Daniel Smith	ACS/ACS CAN	General	Cancer treatment is always evolving as new evidence becomes available, a fact that the authors of the TA acknowledge. In fact, of the nineteen off-label indications examined in the report, seven of these indications were FDA-approved by the time the report was published. Clinicians need to have ready access to reliable, evidence-based information so they can incorporate new information into their clinical judgments about the best treatment approaches for each individual cancer patient. The Society is concerned that this report, for which there was a limited time to review and comment, could influence the use of compendia in clinical decision making. We fear that limitations on the range of evidence sources available for clinical decision making about the use of specific cancer therapies, or changes to Medicare's coverage of off-label drugs, could have a detrimental impact on the cancer care that patients receive. The Society and ACS CAN stand ready to work with AHRQ and CMS and others to ensure that a balanced approach is taken in applying the findings of this report to protect patient access to these life-saving therapies.	Thank you for clearly expressing this point. It is useful to consider that some might view this report as indicating that the role of the compendia should be limited. We have not espoused this view in the document and agree that, under the current system, the compendia do play a vital role as a source of information for clinicians. The report calls into questions the quality, validity, and reliability of the evidence that compendia have to work with and illustrates the difficult task managed by the compendia in trying to stay abreast of current evidence as it emerges, but it does not suggest that the compendia themselves are at fault or should be curtailed in their role.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	General	Genentech, a member of the Roche Group, is pleased to submit comments to the Agency for Healthcare Research and Quality (AHRQ) regarding the draft technology assessment related to off-label indications for targeted therapies in cancer, conducted by the Duke Evidence-based Practice Center (EPC).[1] The draft report is one of a series of technology assessments conducted for AHRQ's Technology Assessment Program's joint work with the Centers for Medicare & Medicaid Services' (CMS') Coverage & Analysis Group (CAG), in support of national coverage analyses, Medicare Coverage Advisory Committees, and for other policy and planning considerations. Genentech is a leading biotechnology company, headquartered in South San Francisco, California. Genentech markets five products indicated for the treatment of various cancers, including three targeted therapies that were included in the draft report: bevacizumab (Avastin®),[2] erlotinib (Tarceva®),[3] and rituximab (Rituxan®).[4] Genentech supports AHRQ's mission to improve the quality, safety, efficiency, and effectiveness of health care for all Americans, and to help patients and providers make more informed health care decisions. Genentech is also pleased that the draft assessment on off-label uses of targeted cancer therapies acknowledges the importance of compendia and the work that compendia perform in reviewing off-label indications and listing those that are supported by medical evidence. *(Comment continued next row.)* <u>References:</u> [1] Technology Assessment: Report on the Evidence Regarding Off-Label Indications for Targeted Therapies used in Cancer Treatment, available at http://www.ahrq.gov/clinic/ta/targthrps/. Posted October 26, 2009. [2] Full prescribing information available at http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf. [3] Full prescribing information available at http://www.gene.com/gene/products/information/pdf/tarceva-prescribing.pdf. [4] Full prescribing information available at http://www.gene.com/gene/products/information/pdf/rituxan-prescribing.pdf.	Thank you for this information, and for reviewing and commenting on the draft report.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	General	As a leader in the development of target therapies for cancer, Genentech is well aware of the time and resources required to perform the extensive reviews done by the Duke EPC. In the future, we hope that AHRQ and the EPCs with whom it contracts to perform these evidence based reviews, will reach out to companies like Genentech for assistance in identifying and reviewing the extensive literature on the products that they manufacture. To that end, we provide the following comments related to the draft assessment and request that these comments be included in the final report in order to improve the report's accuracy: I. Additional detail is needed that outlines the exact scope, purpose, and intentions of the draft report; II. Specific recommendations are needed to acknowledge the role compendia have in providing current information on anti-cancer products; III. Additional citations should be added to provide a more complete list of the available evidence referenced in the draft report; IV. Corrections are needed to address inaccuracies and factual errors in the presentation of data from individual trials involving Genentech's products; and V. Statements included in the draft report related to comparative effectiveness that go beyond the scope of the draft report should be deleted.	Responses to each of the categories of comment are provided below, where Genentech provides feedback in greater detail.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Scope, purpose, and intent of draft report	Of great concern to Genentech is that the authors of the draft report do not explain in any detail exactly why CMS requested this technology assessment. In the report, the authors indicate the purpose of this report as: "This technology assessment has been conducted to evaluate the state of the evidence supporting the use of targeted therapies outside of their FDA-approved indications; it also evaluates the practicality of traditional systematic review approaches in rapidly evolving therapeutic areas such as targeted therapies for various cancers."[5] "…CMS requested a technology assessment of the efficacy and safety of selected targeted therapies when prescribed for off-label indications…CMS will consider this information as background to its further discussion of coverage for and policies regarding targeted therapies."[6] *(Comment continued next row)* References: [5] Draft report, page 7. [6] Draft report, page 12.	This report is the result of work performed under contract with AHRQ, sponsored by CMS. We will pass the comment along to CMS, which defined the scope of the project; it is not our role to articulate the rationale for conducting the study.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Scope, purpose, and intent of draft report *(continued)*	*(Continuation of previous comment)* Medicare is required by law to provide coverage for cancer therapies that are approved by the Food & Drug Administration (FDA) when such cancer therapies are used as directed by FDA. Medicare is also required under the Omnibus Reconciliation Act of 1993 (OBRA) to consider coverage for anti-cancer therapies when they are used for off-label uses that are supported by listings in one or more drug and biological compendia.[7] Specifically, CMS has delegated to its Part A/B Medicare Administrative Contractors[8] and contracted Part D plan sponsors the responsibility of reviewing compendia listings and covering off-label use of anti-cancer therapies based on these listings.[9] Thus, it is unclear why CMS national office is in need of a separate evaluation of the state of the evidence for such therapies if compendia already conduct such analyses. <u>References:</u> [7] Omnibus Reconciliation Act of 1993, Public Law 103-66, enacted August 10, 1993. [8] Medicare Benefit Policy Manual, Chapter 15, section 50.4.5. Last revised October 24, 2008. This revision officially incorporated American Hospital Formulary System's Drug Information (AHFS-DI), Clinical Pharmacology's Gold Standard, Thomson MicroMedex□s DRUGDEX, and the National Comprehensive Cancer Network□s (NCCN) Drugs and Biologics Compendium as sources for medically accepted indications, along with CMS guidance for interpreting each compendium's rating system. [9] Medicare Part D Benefit Manual, Chapter 6, section 10.6. Last revised July 18, 2008.	See response immediately above.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Scope, purpose, and intent of draft report *(continued)*	*(Continuation of previous comment)* As stated by the authors in the draft report, and as provided by law in OBRA 1993, compendia serve as a "stepping stone" between new clinical evidence and physician use of novel oncologic treatments.[10] Genentech agrees with the authors and Congress and supports the use of compendia in helping to ensure patient access to medically necessary anti-cancer therapies based on their compendia listings. We find the language outlining the scope of the draft report cited above troubling because it seems to imply that CMS is contemplating a revision to its use of the compendia in allowing coverage of anti-cancer therapies. We ask that AHRQ clarify and state with more certainty what it knows about how CMS will use this information. We also ask that AHRQ recommend, given the legal coverage requirements, that if CMS decides to revise any of its policies regarding unapproved uses of certain cancer therapies included in compendia, it do so using a transparent process that solicits the input of all stakeholders. Reference: [10] Draft report, page 31.	This comment is most appropriately directed to CMS, as sponsor of the study, and not to the authors of the draft report. We will pass the comment along accordingly.
Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Role of compendia for access to anti-cancer therapies	Genentech is pleased that the draft report acknowledges the size, scope, and difficulty of the task compendia have with respect to reviewing the literature on off-label use of targeted anti-cancer therapies. Importantly, the draft report indicates that although compendia must continuously perform and update their reviews of off-label use of these agents, they do a commendable job of reviewing the available medical evidence in a timely and efficient manner. The examples cited in the draft report demonstrate that the compendia added and withdrew citations for certain unapproved indications in accordance with the published medical evidence while the draft report was being researched and written. Furthermore, no example of an inappropriate citation by the compendia is given in the report.	Thank you for this comment. Our purpose was not to evaluate the compendia; thus, conclusions drawn about the compendia's performance are those of the reviewer rather than the authors.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Role of compendia for access to anti-cancer therapies *(continued)*	Compendia have played a critical role in providing Medicare coverage for many anti-cancer products by regularly reviewing and re-evaluating emerging evidence and determining whether the evidence supports a particular off-label use. The following examples [see additional rows, below] outlined in the draft report illustrate the value of compendia for anti-cancer therapies:[11] Reference: [11] The following examples involve unapproved FDA uses of Genentech products at the time period mentioned in the draft report. These examples are provided for illustrative purposes only; Genentech does not promote our products for unapproved FDA uses as required by law and regulation.	See responses to specific examples below.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Role of compendia for access to anti-cancer therapies *(continued)*	*[Beginning of bulleted list of examples mentioned in previous comment]* • In 2007, the data available to support the use of rituximab to treat chronic lymphocytic leukemia (CLL) included numerous Phase II studies and case-series, and was favorable enough to be listed in certain compendia.[12] Primarily due to the "Accepted" rating in a compendium recognized by CMS at the time (U.S. Pharmacopeia's Drug Information, or USP-DI), payers generally covered rituximab for use in CLL. As the authors make clear in the draft report, the evidence available for rituximab when used in CLL grew over time as additional studies were conducted.[13] In 2009, Genentech filed a supplemental biologics license application (sBLA) with FDA for use of rituximab in CLL based on the strength of two positive superiority Phase III trials, whose results were not available at the time the compendia published a favorable rating for rituximab's use in CLL.[14] References: [12] In 2007, rituximab for the treatment of CLL was supported in several compendia. However, only two were recognized by CMS at that time – American Hospital Formulary System□s Drug Information (AHFS DI) and USP DI. Those supportive compendia included USP DI, Clinical Pharmacology's Gold Standard, Thomson MicroMedex's DRUGDEX, and the National Comprehensive Cancer Network's Drugs and Biologics Compendium. [13] Because these two Phase III trials were still enrolling patients in 2007, they are not included in AHRQ's literature search in the draft report. For more information on these trials, please see the following two citations: 1) Fludarabine and Cyclophosphamide With or Without Rituximab in Patients With Previously Untreated Chronic B-Cell Lymphocytic Leukemia (CLL-8). Available at http://clinicaltrials.gov/ct2/show/NCT00281918?term=CLL-8&rank=1. Last accessed November 2, 2009; and 2) FCR Versus FC Alone in the Treatment of Chronic Lymphocytic Leukemia (CLL). Available at http://clinicaltrials.gov/ct2/show/NCT00090051?cond=chronic+lymphocytic&intr=rituximab&spons=biogen&phase=2&rank=2. Last accessed November 2, 2009. [14] Genentech filed the sBLA with FDA on May 17, 2009. FDA granted the submission priority review, and confirmed November 17, 2009 as its Prescription Drug User Fee Act (PDUFA) date.	Thank you for contributing to the public record this example of compendia responsiveness.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Role of compendia for access to anti-cancer therapies *(continued)*	• As of January 2007, bevacizumab for the treatment of pancreatic adenocarcinoma was listed in compendia as an appropriate use.[15] However, data emerged from both Genentech-funded research and community and academic research that demonstrated a lack of efficacy in this indication. Therefore, Genentech decided not to pursue FDA approval for this indication and, on the weight of the emerging evidence, bevacizumab is no longer recommended for pancreatic cancer in any compendia. Reference: [15] National Comprehensive Cancer Network's *Drugs and Biologics Compendium*, 2007.	Thank you for this example of evidence development and compendia response.
Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Role of compendia for access to anti-cancer therapies *(continued)*	• In the case of rare diseases such as Waldenström's macroglobulinemia, when it is not feasible to perform large Phase III trials, compendia play an important role in establishing patient access to effective therapies. Specifically, rituximab is a well-accepted therapeutic option for Waldenström's,[16] and even though Genentech is unlikely to obtain FDA approval for this indication (the limited population suffering from this rare condition makes a Phase III program impractical), compendia listings allow medically appropriate patients to receive rituximab when it is medically necessary. Reference: [16] In 2007, USP DI supported rituximab use for Waldenström's macroglobulinemia. Currently this use is supported by AHFS DI, DRUGDEX, and NCCN.	The current report did not focus on the role of the compendia in enabling patients with rare diseases to gain access to potentially life-saving therapies.
Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Role of compendia for access to anti-cancer therapies *(continued)*	Based on the value of information outlined in the various compendia, we request that AHRQ states in the final report that the compendia do a commendable job of reviewing newly published evidence in a timely and efficient manner, and act rapidly to update their listings, when appropriate, based on new evidence.	This report was not designed in order to, or conducted in such a way as to, review and evaluate compendia performance.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Additional citations	Genentech is concerned about the exclusion of abstracts from the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), and other key oncology conferences from Duke EPC's literature review. Clinical information provided in abstracts can be useful in understanding the use of a particular treatment and can also be a format for which groundbreaking information is initially presented to the medical community. For example, the Eastern Cooperative Oncology Group (ECOG) unveiled the results of a pivotal Phase III trial (E2100) of Avastin in metastatic breast cancer (mBC) in an abstract presented at the San Antonio Breast Cancer Symposium in December 2007.[17] The abstract is not listed in the horizon scan in the draft report, but the trial formed the basis of Genentech's filing and FDA's granting of accelerated approval for Avastin in mBC.[18] References: [17] Miller KD, Wang M, Gralow J, et al. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the ECOG (E2100). Breast Cancer Res Treat 2005;94:S6. SABCS Abstract #3. Note: this citation is listed also in Appendix Table G-4. [18] FDA granted accelerated approval to bevacizumab for metastatic breast cancer on February 22, 2008. ECOG's E2100 Phase III trial was also discussed at great length at FDA□s Oncologic Drugs Advisory Committee, held December 5, 2007.	By design of this technology assessment, abstracts were considered as part of the horizon scan, but were not the primary focus of the evidence search, which was on published peer-reviewed literature. While we recognize that abstracts are often the first presentation of vital research evidence, it is also true that many abstracts never make it to full publication; that abstracts have not yet been peer-reviewed and therefore may contain methodological shortcomings; and that a comprehensive search of abstracts for each of the drug/indication combinations would be nearly infeasible due to the many venues for abstract presentation and high volume of abstracts.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Additional citations needed	The authors indicate that abstracts from ASCO and ASH conferences in 2006 and 2007 were only "minimally instructive"[19] to the draft report and therefore they did not include information from these abstracts in the report's literature review. The authors then use this as a reason why they also do not include abstracts from 2008 and 2009 in the horizon scan section in the draft report. Genentech is concerned that this approach by Duke's EPC is not comprehensive. ASCO and ASH are not the only meetings where the rapidly expanding evidence in oncology clinical studies is disseminated. Genentech believes that 2006 and 2007 abstracts from the following clinical conferences listed below should have been included in the draft report as they provide useful clinical information and allow for a more robust body of evidence: • American Association for Cancer Research (AACR), • ASCO Gastrointestinal Cancers Symposium (ASCO GI), • Annual Conference of the American Society for Therapeutic Radiology and Oncology (ASTRO), • European Breast Cancer Conference (EBCC), • European Society for Medical Oncology (ESMO), • International Working Group on Chronic Lymphocytic Leukemia (iwCLL), • Lugano International Conference on Malignant Lymphoma, • San Antonio Breast Cancer Symposium (SABCS), and • Society of Gynecological Oncologists (SGO). Reference: [19] Draft report page 19.	Please see the immediately preceding response. Given the scope of this technology assessment, boundaries for inclusion were a necessity. We therefore decided against attempting a full and comprehensive search for abstracts across multiple conferences and symposia. One of the most striking findings of this report was that, methodologically, it is nearly impossible to access, include, and assess all evidence in this rapidly evolving area. This challenge is exacerbated when trying to include abstracts, given the volume and frequency with which they can be presented, as well as the inability to fully assess a study's methodology or findings on the basis of the short abstract text.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Additional citations needed	While Duke EPC found the 2006 and 2007 ASCO and ASH abstracts only minimally instructive, and may draw the same conclusion on the additional conferences suggested above, we request that the final report discuss in much greater detail why the abstracts were not predictive of the emergence of future supportive evidence. As written, this appears to be an unsupported conclusion in the draft report. We also believe that the Duke EPC should include ASCO, ASH, and other clinical conference abstracts from 2008 and 2009 in its final report as well.	Please see our responses to related comments immediately above. With respect to conference abstracts from 2008 and 2009, as indicated above, we ran our last search for published reports on September 14, 2007, and held to the same cut-off date for abstracts. We excluded all evidence emerging after that date. Inclusion of only abstracts, but not publications, from 2008-2009, would have weighted our findings in favor of abstracts over publications; we did not pursue that strategy.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Inaccuracies and factual errors for Genentech products	Genentech acknowledges that the undertaking of 19 independent systematic reviews is a monumental task and commends the Duke EPC for taking it on in the draft report. However, upon our preliminary review of the clinical data cited in the draft report, in addition to finding several missing citations for each of our products and indications, we also found errors in the presentation of the data. We have listed these omissions and errors in Tables G-1, G-2, G-3, and G-4.[20] For the final report, we request that Duke EPC incorporate the citations we provide in Tables G-1 and G-2, correct the errors listed in Table G-3, and consider including the abstracts from other major clinical conferences listed in Table G-4. *[Note from report authors: Genentech tables cited above are reproduced at the end of this comments-and-responses table.]* Reference: [20] Genentech is able to provide the information in Tables G-1 through G-4 because we have an internal database that includes publications referencing our products. We maintain this internal database to respond to unsolicited request for medical information as allowed by regulatory guidelines. Please note that given the time constraints with the short public comment period for this report, we did not attempt to reproduce the exact search methodology documented by Duke EPC as listed on pages 16-19 of the draft report.	In response to the suggestions regarding references which were "missed" or should have been included, we examined all 146 references suggested in these Public Comments. Of these 146, 112 fell outside of the date range for inclusion in the report (last searches conducted on September 14, 2007) or were abstracts from conferences other than the ones we indentified for inclusion; 1 was a "working paper" that fell outside our search scope; 1 had been identified in our search, but was excluded at the title/abstract screening stage; 2 had been identified in our search, but were excluded at the full-text screening stage; and 7 were included in the draft report. This left 23 potentially relevant references. Of these, 18 were excluded either because they evaluated an ineligible drug-disease combination or because they did not meet study design inclusion criteria. Of the 5 remaining reports, 2 were published full reports, and 3 were ASCO 2007 abstracts. We reviewed all 5 references and determined that including them in the revised report would not alter our conclusions and would add little or no informative evidence to the report. *(Response continued next page)*

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Inaccuracies and factual errors for Genentech products *(continued)*	*(See immediately preceding comment – response continued at right)*	On the corrections requested in the reviewers' Table G-3 (included at the end of this comments and responses table), we have checked all of these and, except in one case noted in Table G-3, have made the requested corrections. Finally, based on considerations of study scope and funding, we respectfully decline to follow through on the recommendation that we summarize abstracts from the non-ASH and non-ASCO conferences listed in Table G-4.
Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	General	As the authors of the draft report note, review of each trial and article included in this draft report is very time and labor intensive. The brief period for public comments has not afforded us time to carefully review all of the citations listed in great detail. In fact, we were able to review only a fraction of the studies cited in the draft report. We believe other manufacturers may have also discovered errors in the presentation of the data and may be in the same situation as we are. Therefore, we request that AHRQ extend the comment period to allow all manufacturers to identify all potential errors in this draft report and bring any errors to the attention of AHRQ for the purpose of correcting these items in the final report. If AHRQ declines to extend the comment period, we request that it establish a process that would enable manufacturers to identify and submit a summary of all errors in the draft report to AHRQ for inclusion in the final report. If AHRQ decides that an error identified by a manufacturer was not, in fact, an error, then it should include in the final report the error as reported and its response as to why the reported error was not, in fact, an error.	We will pass this comment and request along to AHRQ. Note that the unwieldiness of reviewing this quantity of data, especially within a short timeframe, is precisely the issue highlighted by the draft report.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Additional citations and inaccuracies	Table G-0 *[reproduced at the end of this comments-and-responses table]* provides a summary of the technical corrections related to Genentech products and indications. As mentioned above, a comprehensive listing of the technical corrections summarized in Table G-0 are provided in greater detail in Tables G-1 through G-4. • Table G-1: Clinical reports missing from the core assessment for literature published prior to September 2007. • Table G-2: Citations missing from the horizon scan, including fully published reports and ASCO and ASH conference abstracts. • Table G-3: Errors found in reporting of existing data. • Table G-4: Citations publicly available from other major clinical conferences that should have been included in the draft report given the stated scope.	Addressed above (see response to comment on “Inaccuracies and factual errors for Genentech products”).

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Pages 36-37	Genentech agrees with the discussion in the draft report regarding the quality of the available medical evidence on off-label indications, the difficulty clinicians have in translating that evidence into good medical practice, and the potential need for a new model of evidence generation and evaluation. We also agree that any such model must be designed to enable clinicians to rapidly translate an evolving literature into making sound clinical decisions. However, Genentech is confused by the references to comparative effectiveness research (CER) in the draft report, which, as the authors themselves state, appear to go beyond the scope of the report and are not supported by the data evaluated in the report. More specifically, the draft report refers to a "Developing consensus…that the new system…must include evaluation of the comparative effectiveness of available treatments…."[21] The report also states that: "Two clear foci of this technology assessment that highlight the need for comparative effectiveness research…. are (1) the nature of adverse event data….and (2) the lack of comparative effectiveness data, where the volume of Phase II studies…serves only to suggest potential benefit but not to describe how each new therapy may compare to other available treatments…"[22] *(Comment continued next row)* References: [21] Draft report pages 36-37. [22] Draft report page 37.	Thank you for this comment. We have added to the Discussion at the end of the main report the following statement: "As yet, there is no articulated consensus on the role of comparative effectiveness research [CER] in evaluation of cancer treatments, but national discussion is striving to define the parameters of, and the appropriate context for, CER" (p. 25). Later in the same paragraph (p. 25) we have added the following statement: "It remains unclear, however, whether CER is more appropriate than other types of clinical trial for establishing the efficacy and role of targeted therapies in treating specific cancers, and thus whether and how CER should be integrated into drug discovery trials." Having expressed these caveats in the Discussion, we have elected to retain references to CER in the individual systematic review appendices.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	Pages 36-37 *(continued)*	*(Continuation of immediately preceding comment)* Genentech agrees that CER will, and should, play a role in the evaluation of targeted therapies. However, Genentech is not aware of a consensus as to exactly what that role should be, especially for evaluating off-label indications and for use of treatments in rare forms of cancer where performance of any clinical trials, let alone comparative effectiveness trials, is extremely challenging. Therefore we request that these references to CER in the discussion section, and references in other sections of the draft report (for example, the reference to the need for comparative effectiveness trials for Rituxan in chronic lymphocytic leukemia and the references to the need for CER in the appendices and presentation of the data) be removed from the final report. If the authors wish to include these statements then we request that the final report include statements that make it clear that there currently is no consensus as to the proper role of CER is in evaluating new treatments for cancer, including off-label indications for such treatments and the use of such treatments in rare forms of cancer. In addition, Genentech requests that the authors include a statement in the final report that it is also unclear how or if CER should be integrated into drug development programs because it remains to be determined whether CER is more appropriate than other types of clinical trials in establishing the “proper role” of any targeted therapy for any form of cancer. Genentech actively supports an environment of continuous learning and rapid translation of the best available evidence into clinical practice, but the role of CER in that process is currently evolving and is well beyond the scope of this report.	See response immediately above.

Evan Morris, Timothy Dube, and Sarah Pitluck	Genentech, Inc.	General (concluding comments)	In summary, Genentech requests that the Duke EPC and AHRQ incorporate the following changes into the final report: • Provide additional detail that better explains the exact scope, purpose, and intent of the technology assessment; • Explicitly acknowledge the appropriateness of the role compendia in providing current and accurate clinical information related to drugs and biologics, particularly anti-cancer therapies; • Evaluate and include additional citations, abstracts and select articles, that were overlooked in the draft report; • Correct inaccuracies and factual errors in the presentation of data from individual trials involving Genentech's products as outlined in our comments above; and • Remove statements related to comparative effectiveness that go beyond the scope of the draft report.	These general comments are responded to above. Specifically, questions about the intent of the report are appropriately directed to CMS. We note your comment on the important role of the compendia in providing a source of information for clinicians, while acknowledging the difficulty of their task. We have addressed the cited data inaccuracies (see comments above). We have explained our evaluation of additional citations in responses to specific comments, above. With respect to statements regarding comparative effectiveness, these general statements are part of the discussion but are not the topic of the report nor a focus. See our more detailed response on this, above.
Lauren Neff	Bio-technology Industry Organiza-tion (BIO)	General	The Biotechnology Industry Organization (BIO) appreciates this opportunity to comment on the Agency for Healthcare Research and Quality's (AHRQ) "Report on the Evidence Regarding Off-Label Indications for Targeted Therapies used in Cancer Treatment" (the "Draft Report"). As an association whose members are dedicated to discovering new therapies using science and evidence-based medicine, BIO appreciates AHRQ's contributions in this area. We also urge AHRQ and other policymakers to avoid setting evidentiary standards that unduly interfere with the practice of medicine, however, or harm access to breakthrough treatments for patients that need them the most.	Thank you for expressing this widespread view.

Lauren Neff	BIO	General	*BIO's Membership and Evidence Development* BIO is the largest trade organization to serve and represent the biotechnology industry in the United States and around the globe. BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers, and related organizations in the United States. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. As the representative of an industry committed to discovering new therapies and ensuring patient access to them, BIO appreciates the analysis that AHRQ has provided regarding the use of targeted therapies for off-label indications. BIO's members are strongly committed to increasing the body of evidence available regarding diseases and their treatments. Our members invest millions of dollars each year on clinical studies, both before and after Food and Drug Administration (FDA) approval of their therapies, to produce high-quality clinical evidence to support FDA approval as well as medical decision-making. We also support the dissemination of this evidence to further clinical knowledge and enhance and improve the clinical decision making process. The commitment of our member companies to developing evidence extends far beyond studies of a particular therapy. We support a rigorous evidence development process that encompasses all aspects of a disease from examining how it affects the body to studying the costs and benefits of therapies. Our members' research initiatives advance the understanding of disease pathology, diagnostic and therapeutic mechanisms of action, clinical effectiveness in naturalistic settings, health-related quality of life, and health economic impacts of therapies in addition to clinical safety and efficacy. The development and evaluation of therapies are part of this broader process and must be considered in context.	Thank you for this detailed description of your organization and its membership.

Lauren Neff	BIO	General	*BIO's Membership and Evidence Development (continued)* Our members' evidence development processes combined with Medicare's current coverage policies, especially the use of compendia, allows beneficiaries timely access to new therapies and encourages innovation. The Medicare statute and manuals give local contractors the flexibility and freedom to make timely coverage decisions, ensuring Medicare beneficiaries' access to the latest drugs and biologicals for medically accepted uses. These policies also encourage innovation and continued research by giving patients a choice of new therapies, recognizing new uses of therapies, and promoting a relatively stable and predictable reimbursement environment that is critical for many of our smaller member companies who depend on private sector investment. BIO requests that AHRQ specify in the Final Report that Medicare's current processes should continue so as to ensure patient access to care with needed oncology treatments.	Thank you for this perspective on the current system. Although we will be sure that AHRQ and CMS receive your comment, it is not in the scope of this report to make recommendations to CMS regarding Medicare policies.

Lauren Neff	BIO	General	*The Role of Compendia in Protecting Access to Innovative Therapies* It is imperative that coverage policies keep up with the pace of innovation and clinical discovery to allow beneficiaries timely access to the most appropriate treatment options in their battles against deadly diseases. This is precisely why the Medicare statute requires contractors to cover "drugs and biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication," defined as a use approved by the FDA or a use of an FDA-approved drug supported by citations in certain compendia or by peer-reviewed medical literature. BIO supports these standards for identifying medically accepted indications because they help to protect beneficiary access to the most appropriate and promising treatment options. The Draft Report notes that the drug landscape in oncology is frequently changing. BIO understands that the practice of medicine constantly evolves through the incorporation of new clinical evidence into the standard of care, and that the ability of clinicians to make patient-centered decisions based on the scientific evidence is particularly important in oncology. The standard of care in oncology can change rapidly as clinical researchers discover more effective, safer, or more tolerable treatment regimens. These new treatment options often involve the use of drugs and biologicals for indications not yet approved by the FDA and offer patients and physicians renewed hope and greater choice in fighting illness. These advances can be particularly important for patients with advanced stages of cancer. As scientific advances are publicized through peer-reviewed publications, drug and biological compendia often incorporate this information before manufacturers can file compelling data with FDA and receive updates to a product's FDA-approved labeling. Further, not all indications actually achieve FDA approval for a variety of reasons. In such cases, coverage based on compendia listings may be the only option for providing patient access. Thus, compendia are an important resource for physicians when determining the most appropriate treatment regimen for their patients who are Medicare beneficiaries and for payers in determining which uses to cover. Although all of the compendia are evidence-based, the content of the compendia may vary due to differences in publication schedules, priorities, review processes, local practices and methods of describing the evidence for each listing. Compendia protect beneficiary access to advanced cancer therapies by providing physicians and policymakers with a wider body of evidence to use in making treatment and coverage decisions.	Thank you for this cogent argument for maintaining the current role of the compendia.

Lauren Neff	BIO	General	*Issues to Consider Concerning Comparative Effectiveness Research* The Draft Report notes the potential need to identify "a different model of evidence generation and evaluation" and specifically highlights comparative effectiveness research as one method to better inform evidence development. BIO supports efforts to increase the availability of accurate, scientific evidence to inform clinical decision-making. BIO believes that individual patients and their doctors should be armed with the best available information to help assess the relative clinical benefits and risks of various treatment alternatives. Comparative effectiveness information is a valuable tool that, together with a variety of other types of medical evidence, can contribute to improving health care delivery. However, BIO is concerned that comparative effectiveness information may be used strictly as a means to contain costs, rather than to deliver health care value by improving patient health outcomes. Because the Draft Report was requested by the Coverage and Analysis Group at the Center for Medicare and Medicaid Services (CMS), it is important to clarify that comparative effectiveness research should not be used to make coverage and reimbursement decisions. As mentioned earlier, the Draft Report references the rapidly evolving nature of evidence development in oncology. The inappropriate use of comparative effectiveness research in coverage or reimbursement could have a stifling effect on this medical progress. *(Comment continued next row)*	We register your concern that CER results may be used for cost-containment purposes rather than to evaluate effectiveness of treatments. If anything, this report suggests that CER evidence cannot be used to make decisions regarding cost and reimbursement. Observations made in this report that may be relevant to Medicare policies covering off-label uses of anti-cancer chemotherapeutic drugs, which are supported by entries in certain compendia or by published research in certain journals, include: (1) that there is a pervasive sense among clinicians that the drug landscape in oncology is frequently changing; (2) that the compendia play an important and challenging in clinical decision-making and coverage policy; (3) that a different standard may apply to evidence for cancer treatment than to treatments in other disciplines; (4) that a different model of evidence generation and evaluation is warranted, but a feasible model is as yet hard to envision. We also acknowledge that treatment decisions must be made today with the information available now. This report is not intended to influence reimbursement decisions.

Lauren Neff	BIO	General	*(Continued from previous row)* Further, BIO believes that the application of comparative effectiveness research should advance the goals of personalized medicine and encourage the development of targeted therapies rather than create one-size-fits-all policies. Advancements in the development of innovative and targeted therapies are grounded in the ability of researchers to focus on the mechanisms of action that allow particular therapies to work in specific patient populations. A reimbursement environment that allows the right drug or biological in the right form to reach the right patient in a timely manner is a critical corollary to these advances. Promoting innovation in personalized medicine requires clinicians to have the ability to make patient centered treatment choices without being required to conform to inflexible standards or practice guidelines. CMS and AHRQ must continue to be mindful of this delicate balance. In fact, NIH Director Dr. Francis Collins recently warned, "There is a potential collision" between personalized medicine and comparative effectiveness research. He went on to say, "We need to be mindful of the goal of comparative effectiveness research and not lose all that we have gained in understanding how individuals differ and how that could be factored into better diagnostics and preventive strategies." BIO believes comparative effectiveness research should move personalized medicine forward and not backwards.	See response immediately above.
Lauren Neff	BIO	General	*Comparative Effectiveness Issues Specific to Targeted Medicines* The Draft Report notes that the quantity and quality of data varied widely across the indications included in the analysis, and that targeted therapies are used to treat diseases that are "frequently rare". While targeted therapies are not exclusively for rare diseases, due to the small size, heterogeneity, and other characteristics of certain patient populations, any therapies targeting rare or "orphan" diseases, as well as severe, rapidly progressive, or life-threatening diseases, are not conducive to comparative effectiveness studies. Government policies addressing comparative effectiveness need to acknowledge the limitations of current methodologies and ensure that they do not lead to conclusions and decisions that discourage or impede medical advancements and breakthroughs that can address unmet medical needs. With the FDA working to increase its ability to advance targeted therapies, accompanying research as well as coverage and reimbursement policies should not hinder such advancement through broad, non-targeted (non-personalized) reports, decisions, or policies.	Thank you for making the point that CER is not appropriate for evaluation of treatments in certain cases (e.g., in rare diseases where the population affected is small). The view that government should consider a variety of study designs and sources of information, in light of the diversity of disease/treatment scenarios, is consistent with the report.

Lauren Neff	BIO	General	*Conclusion* BIO greatly appreciates the opportunity to comment on the important issues raised by the draft report regarding off-label indications for targeted therapies. We look forward to continuing to work with AHRQ to ensure patient access to critical drug and biological therapies.	Thank you.
Lawrence A. Solberg and Carol Schwartz	American Society of Hema-tology (ASH)	General	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.	Thank you for this suggestion regarding time allotted for review, which we will pass along to AHRQ.

Lawrence A. Solberg and Carol Schwartz	ASH	General framework of report	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 lymphocytepredominant 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.	Thank you for this thoughtful comment.

Lawrence A. Solberg and Carol Schwartz	ASH	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.”	You have nicely described the issues related to lack of a clear mathematical methodology to conduct systematic reviews with varied data. Thank you.

Lawrence A. Solberg and Carol Schwartz	ASH	Methodology *(continued)*	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.	This comment highlights the problems, underscored by this technology assessment, with static representation of the evidence in current literature review methods. New dynamic approaches, ones that entail frequent update and evolution, are needed.
Lawrence A. Solberg and Carol Schwartz	ASH	Methodology *(continued)*	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.	This is a very cogent argument for inclusion of the gray literature, with a well-considered suggested approach. Thank you.

Lawrence A. Solberg and Carol Schwartz	ASH	Alemtuzumab for cutaneous T-cell lymphoma	Please note a recent publication of alemtuzumab use in relapsed and refractory erythrodermic cutaneous T-cell lymphoma [given below]. 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.	Thank you for this suggestion, but the article you have cited does not fit within the time period for study inclusion (last search September 14, 2007).
Lawrence A. Solberg and Carol Schwartz	ASH	Imatinib mesylate for myelo-dysplastic 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 plateletderived growth factor receptor beta (PDFFRB) 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.	We have added the following parenthetical note on p. 256: “note that CMML is now classified by the World Health Organization as a myeloproliferative neoplasm (MPN) rather than as MDS.” The suggested references are not eligible for inclusion in this study because they either not clinical studies (# 2 and 3) or not one of the included drug/disease combinations (#4 and 5).
Lawrence A. Solberg and Carol Schwartz	ASH	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.	Thank you for this comment. Table 2 (p. 9) now lists relapsed/refractory mantle cell lymphoma as an FDA-approved indication; for this reason, we did not include bortezomib/MCL as a drug/disease combination in this technology assessment of off-label indications.

Lawrence A. Solberg and Carol Schwartz	ASH	Rituximab for Walden-ström's Macro-globulinemia (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.	We appreciate this comment. WM was previously considered a different clinical entity. Its classification changed after we began this project. We have updated Table 1 (p. 8) and the body of the report on p. 324 to reflect the FDA's recent approval of rituximab for relapsed or refractory WM.
Lawrence A. Solberg and Carol Schwartz	ASH	General	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.	Thank you very much for your comments and for this offer of participation.
Cara Tenen-baum	Ovarian Cancer National Alliance	General	According to the American Cancer Society, 21,000 American women in 2009 will be diagnosed with ovarian cancer, and approximately 15,000 will lose their lives to this terrible disease. Ovarian cancer is the deadliest gynecologic cancer and the fifth leading cause of cancer death among women in America. Currently, more than half of the women diagnosed with ovarian cancer will die within five years. The Ovarian Cancer National Alliance is a survivor-led national umbrella organization with state and local groups, representing grassroots activists, women's health advocates and health care professionals. The Ovarian Cancer National Alliance submits this testimony as a patient advocacy group dedicated to conquering ovarian cancer. The Technology Assessment released in October, 2009, included a section on the use of Bevacizumab for Epithelial Ovarian Cancer, which concluded that the use of the drug is not yet rooted in the science. As an organization committed to evidence based medicine, the Ovarian Cancer National Alliance has four points regarding this conclusion.	Thank you for responding.

Cara Tenen-baum	Ovarian Cancer National Alliance	Bevacizumab for epithelial ovarian cancer *(continued)*	*1. The conclusion is premature* A Phase III trial on the use of Bevacizumab for Epithelial Ovarian Cancer, GOG-218 (NCT00262847), was activated in late 2005. GOG-218 is a randomized, double-blind phase III trial studying carboplatin/paclitaxel and Bevacizumab or placebo in Stage III or IV ovarian epithelial, primary peritoneal cancer, or fallopian tube cancer. It is expected that results from this trial will be available in the first half of 2010. To make any statements about the use of the drug when results are expected soon are premature, and will inhibit the availability of the drug in the case that positive results are shown, and that there is a lag between the results and FDA approval.	The trial mentioned in this comment is not yet complete and hence was not included in our systematic review. A primary conclusion of the report is that it is nearly impossible to assert definitive conclusions about these agents at present, because evidence continues to emerge (as well as for reasons of poor study quality, difficulties in comparing data across studies, etc.). The study mentioned is an example of forthcoming evidence that will inevitably be excluded in its current form from any systematic review because of the need to establish a cut-off point for inclusion under current evidence review procedures.

Cara Tenen-baum	Ovarian Cancer National Alliance	Bevacizumab for epithelial ovarian cancer *(continued)*	*2. The conclusion is not based on all data* There are numerous peer-reviewed studies not included in this Technology Assessment that have shown positive results for Bevacizumab for Epithelial Ovarian Cancer. These include: • Robert A. Burger, Michael W. Sill, Bradley J. Monk, Benjamin E. Greer, Joel I. Sorosky, Phase II Trial of Bevacizumab in Persistent or Recurrent Epithelial Ovarian Cancer or Primary Peritoneal Cancer: A Gynecologic Oncology Group Study, Journal of Clinical Oncology, Vol 25, No 33 (November 20), 2007: pp. 5165-5171. • Stephen A. Cannistra, Ursula A. Matulonis, Richard T. Penson, Julie Hambleton, Jakob Dupont, Howard Mackey, Jeffrey Douglas, Robert A. Burger, Deborah Armstrong, Robert Wenham,and William McGuire, Phase II Study of Bevacizumab in Patients With Platinum-Resistant Ovarian Cancer or Peritoneal Serous Cancer, Journal of Clinical Oncology, Vol 25, No 33 (November 20), 2007: pp. 5180-5186. • Agustin A. Garcia, Hal Hirte, Gini Fleming, Dongyun Yang, Denice D. Tsao-Wei, Lynda Roman, Susan Groshen, Steve Swenson, Frank Markland, David Gandara, Sidney Scudder, Robert Morgan, Helen Chen, Heinz-Josef Lenz, Amit M. Oza, Phase II Clinical Trial of Bevacizumab and Low-Dose Metronomic Oral Cyclophosphamide in Recurrent Ovarian Cancer: A Trial of the California, Chicago, and Princess Margaret Hospital Phase II Consortia, Journal of Clinical Oncology, Vol 26, No 1 (January 1), 2008: pp. 76-82. These studies show that Bevacizumab is an active agent against Epithelial Ovarian Cancer.	All three studies cited were published after the date of our last search (September 14, 2007) and so were not included in the review.
Cara Tenen-baum	Ovarian Cancer National Alliance	Bevacizumab for epithelial ovarian cancer *(continued)*	*3. Clinical Practice Should Be Guided By Evidence* Gynecologic oncologists and medical oncologists adhere to practice guidelines because they are evidence based. However, drugs and procedures may be judiciously used based on expert opinion, rather than guidelines. Doctors and patients must have the flexibility to try cutting edge therapies that work for the patient.	Thank you for expressing this perspective.

Cara Tenen-baum	Ovarian Cancer National Alliance	Bevacizumab for epithelial ovarian cancer *(continued)*	*4. Ovarian Cancer Does Have Symptoms* Further, the Technology Assessment states that "[B]ecause early-stage EOC is usually asymptomatic, fewer than 20 percent of all ovarian cancers are detected prior to metastatic spread." Citing Cannistra SA. Cancer of the ovary. N Engl J Med 2004;351(24):2519-29. In fact, more recent data show that even early stage ovarian cancer may have symptoms (See: Goff BA, Mandel LS, Melancon CH, Muntz HG. JAMA. 2004 Jun; 291: 2705-2712).	Thank you for this comment. We have changed the sentence in question to read, "However, because early-stage EOC is often not associated with clinical symptoms, fewer than 20 percent of all ovarian cancers are detected prior to metastatic spread" (p. 139).
Cara Tenen-baum	Ovarian Cancer National Alliance	Bevacizumab for epithelial ovarian cancer *(continued)*	*Recommendation* The Ovarian Cancer National Alliance recommends that decisions regarding the efficacy or Bevacizumab in Epithelial Ovarian Cancer be suspended pending Phase III data.	This report is not intended to provide the basis for making decisions regarding the efficacy of any of the included drugs. Rather, it summarizes existing evidence as of September 14, 2007.

Additional tables submitted by Evan Morris, Timothy Dube, and Sarah Pitluck of Genentech, Inc. (cited in comments table, above)

Table G-0. Summary of Technical Corrections Needed for Genentech Products and Indications

Product	Indication	Missed Citations Prior to September 2007 (Table G-1)	Citations Available Since September 2007 (Table G-2)	Errors or Inconsistencies in Summarized Evidence (Table G-3)	Citations from Other Major Clinical Conferences (Table G-4)
Bevacizumab (Avastin)	Breast Cancer	8 ASCO abstracts (2004-2007)	2 full publications (2007, 2008) and 8 ASCO abstracts (2007-2009)	Errors found	9 SABCS abstracts (2002-2009) and 1 EBCC abstract (2008)
Bevacizumab (Avastin)	Ovarian Cancer	4 full publications (2007) and 7 ASCO abstracts (2005-2007)	6 full publications (2008-2009) and 3 ASCO abstracts (2009)	Minor inconsistencies found	5 SGO abstracts (2008-2009) and 1 AACR abstract (2009)
Bevacizumab (Avastin)	Pancreatic Adenocarcinoma	3 ASCO abstracts (2006-2007)	1 full publication (2009) and 2 ASCO abstracts (2008-2009)	Errors found	4 ASCO GI abstracts (2007-2009) and 1 ASTRO abstract (2006)
Bevacizumab (Avastin)	Renal Cancer	1 full publication and 2 ASCO abstracts (2006-2007)	4 full publications (2008-2009) and 4 ASCO abstracts (2008-2009)	Errors found	3 ASCO GI abstracts (2008-2009)
Erlotinib (Tarceva)	Head and Neck Cancer	2 ASCO abstracts (2004-2006)	1 full publication (2009) and 1 ASCO abstract (2009)	*Abstracted data not reviewed for factual accuracy due to time constraint in comment period*	1 ASTRO abstract (2008)
Rituximab (Rituxan)	Chronic Lymphocytic Leukemia	1 full publication (2003) and 1 ASH abstract (2007)	5 full publications (2008-2009) and 8 ASH abstracts (2008)		1 other abstract (2008)
Rituximab (Rituxan)	Hodgkin's Disease	1 ASH abstract (2003)	2 full publications (2008)		None
Rituximab (Rituxan)	Waldenström's Macroglobulinemia	4 full publications (2000, 2003, 2004, 2006)	7 full publications (2007-2009) and 2 ASH abstracts (2007-2008)		None

Abbreviations: AACR=American Association for Cancer Research, ASH=American Society of Hematology, ASCO=American Society of Clinical Oncology, ASCO GI=ASCO Gastrointestinal Cancers Symposium, ASTRO=American Society for Thoracic Radiology and Oncology, EBCC=European Breast Cancer Conference, SABCS=San Antonio (TX) Breast Cancer Symposium, SGO=Society for Gynecological Oncologists.

Table G-1. Clinical reports missing from the core assessment for literature published prior to September 2007

Product	Indication	Citations Not Included
Bevacizumab (Avastin)	Breast Cancer	• Chan D, Allen H, Hu E, et al. Phase 2 study of docetaxel (D) plus bevacizumab (B) in Her/2 negative metastatic breast carcinoma (MBC). J Clin Oncol 2006;24. ASCO Abstract #13047. • Conlin AK, Seidman AD, Moynahan ME, et al. Randomized phase II trial of three dosing schedules of nanoparticle albumin-bound paclitaxel with bevacizumab as first-line therapy for HER2-negative metastatic breast cancer: An initial interim safety report. J Clin Oncol 2007;25. ASCO Abstract #1104. • Dickler M, Rugo H, Caravelli J, et al. Phase II trial of erlotinib (OSI-774), an epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor, and bevacizumab, a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF), in patients (pts) with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 2004;22:127. ASCO Abstract #2001. • Rugo HS, Dickler MN, Scott JH, et al. Change in circulating endothelial cells (CEC) and tumor cells (CTC) in patients (pts) receiving bevacizumab and erlotinib for metastatic breast cancer (MBC) predicts stable disease at first evaluation. Proc Am Soc Clin Oncol 2005;23:10s. ASCO Abstract #525. • Traina TA, Rugo H, Caravelli J, et al. Letrozole (L) with bevacizumab (B) is feasible in patients (pts) with hormone receptor-positive metastatic breast cancer (MBC). J Clin Oncol 2006;24. Abstract #3050. • Link JS, Waisman JR, Nguyen B, et al. Bevacizumab and albumin-bound paclitaxel treatment in metastatic breast cancer. J Clin Oncol 2007;25. ASCO Abstract #1101. • Lobo CF, Lopes G, Silva O, et al. Nanoparticle albumin-bound (Nab) paclitaxel (P) in combination with bevacizumab (B) with and without gemcitabine (G): Early experience at the Braman Family Breast Cancer Institute. J Clin Oncol 2006;24. ASCO Abstract #10748. • Ordonez J, Gomez Martin C, Cortes-Funes H. Trastuzumab in combination with bevacizumab in advanced breast cancer patient resistant to chemotherapy. J Clin Oncol 2006;24. ASCO Abstract #10762.
Bevacizumab (Avastin)	Ovarian Cancer	• Micha JP, Goldstein BH, Rettenmaier MA, et al. A phase II study of outpatient first-line paclitaxel, carboplatin, and bevacizumab for advanced-stage epithelial ovarian, peritoneal, and fallopian tube cancer. Int J Gynecol Cancer 2007;17:771-776. • Chura JC, Van Iseghem K, Downs Jr LS, et al. Bevacizumab plus cyclophosphamide in heavily pretreated patients with recurrent ovarian cancer. Gynecol Oncol 2007;107:326-330. • Wright JD, Secord AA, Numnum TM, et al. A multi-institutional evaluation of factors predictive of toxicity and efficacy of bevacizumab for recurrent ovarian cancer. Int J Gynecol Cancer. E-pub Date: 2007. DOI #10.1111/j.1525-1438-2007.01027.x. • Simpkins F, Belinson JL, Rose PG. Avoiding bevacizumab related gastrointestinal toxicity for recurrent ovarian cancer by careful patient screening. Gynecol Oncol. E-pub Date: April 2007. DOI # 10.1016/j.ygyno.2007.06.004. • Konner JA, Fallon K, Pezzuli S, et al. A phase II study of intravenous (IV) and intraperitoneal (IP) paclitaxel (Tax), IP cisplatin (Cis), and IV bevacizumab (Bev) as first-line chemotherapy for optimal stage II or III ovarian, primary peritoneal, and fallopian tube cancer. J Clin Oncol 2007;25. ASCO Abstract #5523. • Herzog TJ, Spirtos NM, Hines JF, et al. Preliminary safety and efficacy results of a phase II study of oxaliplatin, docetaxel, and bevacizumab as first-line therapy of advanced cancer of the ovary, peritoneum, and fallopian tube. J Clin Oncol 2007;25. ASCO Abstract #5518. • Friberg G, Oza AM, Morgan RJ, et al. Bevacizumab (B) plus erlotinib (E) for patients (pts) with recurrent ovarian (OC) and fallopian tube (FT) cancer: preliminary results of a multi-center phase II trial. J Clin Oncol 2006;24. ASCO Abstract #5018.

		(List continued next page)
Bevacizumab (Avastin)	Ovarian Cancer *(continued)*	*(Continuation of list on previous page)* • Cannistra SA, Matulonis U, Penson R, et al. Bevacizumab in patients with advanced platinum-resistant ovarian cancer. J Clin Oncol 2006;24. ASCO Abstract #5006. • Azad NS, Posadas EM, Kwitkowski KE, et al. Increased efficacy and toxicity with combination anti-VEGF therapy using sorafenib and bevacizumab. J Clin Oncol 2006;24. ASCO Abstract #3004. • Garcia AA, Oza AM, Hirte H, et al. Interim report of a phase II clinical trial of bevacizumab (Bev) and low dose metronomic oral cyclophosphamide (mCTX) in recurrent ovarian (OC) and primary peritoneal carcinoma: a California Cancer Consortium Trial. Proc Am Soc Clin Oncol 2005;23:455s. ASCO Abstract #5000. • Burger RA, Sill M, Monk BJ, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer (EOC) or primary peritoneal cancer (PPC): a Gynecologic Oncology Group (GOG) study. Proc Am Soc Clin Oncol 2005;23:457s. ASCO Abstract #5009.
Bevacizumab (Avastin)	Pancreatic Adenocarcinoma	• Kindler HL, Bylow KA, Hochster HS, et al. A randomized phase II study of bevacizumab (B) and gemcitabine (G) plus cetuximab (C) or erlotinib (E) in patients (pts) with advance pancreatic cancer (PC): A preliminary analysis. J Clin Oncol 2006;24. ASCO Abstract #4040. • Javle MM, Iyer RV, Yu J, et al. Phase II study of gemcitabine, capecitabine and bevacizumab for advanced pancreatic cancer (APC) with ECOG PS 0-1. J Clin Oncol 2006;24. ASCO Abstract #4117. • Ko AH, Dito E, Schillinger B, et al. A phase II study of gemcitabine (GEM) given at fixed-dose rate (FDR) infusion, low-dose cisplatin (CDDP), and bevacizumab (BEV) for metastatic adenocarcinoma of the pancreas (PanCa): Update with completion of study accrual. J Clin Oncol 2007;25. ASCO Abstract #4548.
Bevacizumab (Avastin)	Renal Cell Carcinoma	• Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 2009;27:2231-2237. • Picozzi VJ, Canlas LA, Sicuro PL, et al. A phase II trial of gemcitabine, docetaxel, and bevacizumab (GDB) in metastatic pancreas cancer. J Clin Oncol 2009;27. ASCO Abstract #4606. • Blaszkowsky LS, Zhu AX, Abrams TA, et al. A phase II study of gemcitabine (G), bevacizumab (B), and erlotinib (E) in locally advanced (LAPC) and metastatic adenocarcinoma (MPC) of the pancreas. J Clin Oncol 2008;26. ASCO Abstract #15515.
Erlotinib (Tarceva)	Head and Neck Cancer	• Rhoades C, Kraut E, Schuller D, et al. Phase I and phase II study of OSI-774 with docetaxel in squamous cell carcinoma of the head and neck (SCCHN). Presented at the 40th Annual Meeting of the American Society of Clinical Oncology in New Orleans, Louisiana; July 5-8, 2004. ASCO Poster #5441. • Savvides P, Agarwala SS, Greskovich J, et al. Phase I study of the EGFR tyrosine kinase inhibitor erlotinib in combination with docetaxel and radiation in locally advanced squamous cell cancer of the head and neck (SCCHN). J Clin Oncol 2006;24. ASCO Abstract #5545.
Rituximab (Rituxan)	Chronic Lymphocytic Leukemia	• Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood 2003;101:3413-3415. • Lin TS, Donohue KA, Lucas MS, et al. Consolidation therapy with subcutaneous (SC) alemtuzumab results in severe infectious toxicity in previously untreated CLL patients who achieve a complete response (CR) after fludarabine and rituximab (FR) induction therapy: interim safety analysis of the CALGB Study 10101. Blood 2007;110. ASH Abstract #755.
Rituximab (Rituxan)	Hodgkin's Disease	• Canales MA, Sanjurjo MJ, Bustos JG, et al. Rituximab in lymphocyte-predominant Hodgkin's disease. Blood 2003;102:303b. ASH Abstract #4934.
Rituximab (Rituxan)	Waldenström's Macroglobulinemia	• Foran JM, Rohatiner AZ, Cunningham D, et al. European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell

		lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. J Clin Oncol 2000;18:317-324. *(List continued next page)*
Rituximab (Rituxan)	Waldenström's Macroglobulinemia *(continued)*	*(Continuation of list on previous page)* • Emmanouilides C, Territo M, Menco H, et al. Mitoxantrone-cyclophosphamide-rituximab: an effective and safe combination for indolent NHL. Hematol Oncol 2003;21:99-108. • Poole JA, Harbeck R, Kirkpatrick C. Common variable immune deficiency after therapy with rituximab, a monoclonal anti-CD20 antibody. Ann Allergy Asthma Immunol 2004;92:109. • Noronha V, Fynan TM, Duffy T. Flare in neuropathy following rituximab therapy for Waldenstrom's macroglobulinemia. J Clin Oncol 2006;24:e3.

Table G-2. Citations missing from the horizon scan, including fully published reports and ASCO and ASH conference abstracts

Product	Indication	Citations Not Included
Bevacizumab (Avastin)	Breast Cancer	• Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357:2666-2676. • Dellapasqua S, Bertolini F, Bagnardi V, et al. Metronomic cyclophosphamide and capecitabine combined with bevacizumab in advanced breast cancer. J Clin Oncol. E-pub Date: September 22 2008. DOI #10.1200/JCO.2008.17.4789. • Klencke BJ, Bhattacharya S, Samant MK, et al. Independent review of E2100 progression-free survival (PFS) with the addition of bevacizumab (B) to paclitaxel (P) as initial chemotherapy for metastatic breast cancer (MBC). J Clin Oncol 2008;26. ASCO Abstract #1036. • Miles D, Chan A, Romieu G, et al. Randomised, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. J Clin Oncol 2008;26. ASCO Abstract #LBA1011. • Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). J Clin Oncol 2009;27. ASCO Abstract #1005. • Conlin AK, Hudis CA, Bach A, et al. Randomized phase II trial of nanoparticle albumin-bound paclitaxel in three dosing schedules with bevacizumab as first-line therapy for HER-2-negative metastatic breast cancer (MBC). J Clin Oncol 2009;27. ASCO Abstract #1006. • Danso MA, Blum JL, Robert NJ, et al. Phase II trial of weekly nab-paclitaxel in combination with bevacizumab as first-line treatment in metastatic breast cancer. J Clin Oncol 2008;26. ASCO Abstract #1075. • Brufsky AM, Hoelzer KL, Keaton MR, et al. A phase II study of paclitaxel and bevacizumab ± gemcitabine as first-line treatment for metastatic breast cancer (MBC): Interim safety results. J Clin Oncol 2008;26. ASCO Abstract #1095. • Glück S, Lobo C, Reis I, et al. Phase II study of nab-paclitaxel, bevacizumab, and gemcitabine for first-line therapy of patients with HER2-negative metastatic breast cancer (MBC). J Clin Oncol 2008;26. ASCO Abstract #1089. • Traina TA, Theodoulou M, Dugan U, et al. A novel capecitabine dosing schedule combined with bevacizumab is safe and active in patients with metastatic breast cancer: A phase II study. J Clin Oncol 2008;26. ASCO Abstract #1101.
Bevacizumab (Avastin)	Ovarian Cancer	• Garcia AA, Hirte H, Fleming G, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. J Clin Oncol 2008;26:76-82. • Jurado Garcia JM, Sanchez A, Pajares B, et al. Combined oral cyclophosphamide and bevacizumab in heavily pre-treated ovarian cancer. Clin Transl Oncol 2008;10:583-586. • Sanchez-Munoz A, Jurado JM, Perez-Ruiz E, et al. Second complete remission induced by cyclophosphamide plus bevacizumab in two patients with heavily pre-treated ovarian cancer. Clin Transl Oncol 2009;11:329-331. • Richardson DL, Backes FJ, Seamon LG, et al. Combination gemcitabine, platinum, and bevacizumab for the treatment of recurrent ovarian cancer. Gynecol Oncol 2008;111:461-466. • Nimeiri HS, Oza AM, Morgan RJ, et al. Efficacy and safety of bevacizumab plus erlotinib for patients with recurrent ovarian, primary peritoneal, and fallopian tube cancer: a trial of the Chicago, PMH, and California Phase II consortia. Gynecol Oncol 2008;110:49-55. *(List continued next page)*

Bevacizumab (Avastin)	Ovarian Cancer *(continued)*	*(Continuation of list on previous page)* • Azad NS, Annunziata CM, Steinberg SM, et al. Lack of reliability of CA125 response criteria with anti-VEGF molecularly targeted therapy. Cancer. E-pub Date: February 2008. DOI # 10.1002/cncr.23374. • Carducci MA, Armstrong DK, Collins C, et al. Phase I study of enzastaurin (ENZ) and bevacizumab (BV) in patients with advanced cancer: safety, pharmacokinetics (PK), and response assessment. J Clin Oncol 2009;27. ASCO Abstract #3517. • Kikuchi Y, Kouta H, Kikuchi R, et al. Effects of weekly bevacizumab and pegylated liposomal doxorubicin in heavily pretreated patients with recurrent or progressed ovarian cancer. J Clin Oncol 2009;27. ASCO Abstract #5547. • Muggia FM, Boyd L, Liebes L, et al. Pegylated liposomal doxorubicin (PLD) with bevacizumab (B) in second-line treatment of ovarian cancer (OC): pharmacokinetics (PK), safety, and preliminary outcome results. J Clin Oncol 2009;27. ASCO Abstract #5548.
Bevacizumab (Avastin)	Pancreatic Adenocarcinoma	• Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 2009;27:2231-2237. • Picozzi VJ, Canlas LA, Sicuro PL, et al. A phase II trial of gemcitabine, docetaxel, and bevacizumab (GDB) in metastatic pancreas cancer. J Clin Oncol 2009;27. ASCO Abstract #4606. • Blaszkowsky LS, Zhu AX, Abrams TA, et al. A phase II study of gemcitabine (G), bevacizumab (B), and erlotinib (E) in locally advanced (LAPC) and metastatic adenocarcinoma (MPC) of the pancreas. J Clin Oncol 2008;26. ASCO Abstract #15515.
Bevacizumab (Avastin)	Renal Cell Carcinoma	• Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 2008;26:5422-5428. • Melichar B, Koralewski P, Ravaud A, et al. First-line bevacizumab combined with reduced dose interferon- 2a is active in patients with metastatic renal cell carcinoma. Ann Oncol. E-pub Date: April 11 2008. DOI #10.1093/annonc/mdn161. • Medioni J, Banu E, Helley D, et al. Salvage therapy with bevacizumab-sunitinib combination after failure of sunitinib alone for metastatic renal cell carcinoma: a case series. Eur Urol 2009;56:207-211. • Azad NS, Posadas EM, Kwitkowski VE, et al. Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and antitumor activity. J Clin Oncol 2008;26:3709-3714. • Chung EK, Posadas EM, Kasza K, et al. A phase II trial of gemcitabine(G), capecitabine (C), and bevacizumab (B) in patients (pts) with metastatic renal cell carcinoma (RCC). J Clin Oncol 2009;27. ASCO Abstract #e16072. • Miller L, Lal LS, Tannir NM, et al. Treatment of poor-risk metastatic renal carcinoma patients with combination gemcitabine, capecitabine, and bevacizumab at a tertiary cancer center. J Clin Oncol 2009;27. ASCO Abstract #e16112. • Whorf RC, Hainsworth JD, Spigel DR, et al. Phase II study of bevacizumab and everolimus (RAD001) in the treatment of advanced renal cell carcinoma (RCC). J Clin Oncol 2008;26. ASCO Abstract #5010. • Cooney MM, Garcia JA, Elson P, et al. Sunitinib and bevacizumab in advanced solid tumors: a phase I trial. J Clin Oncol 2008;26. ASCO Abstract #3530.
Erlotinib (Tarceva)	Head and Neck Cancer	• Cohen EEW, Davis DW, Karrison TG, et al. Erlotinib and bevacizumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck: a phase I/II study. Lancet Oncol. E-pub Date: February 2009. DOI # 10.1016/S1470-2045(09)70002-6. • Meluch AA, Spigel D, Burris HA, et al. Combined modality therapy with radiation therapy (RT), chemotherapy, bevacizumab, and erlotinib in the treatment of patients (pts) with locally advanced squamous carcinoma of the head and neck. J Clin Oncol 2009;27. ASCO Abstract #6012.

Rituximab (Rituxan)	Chronic Lymphocytic Leukemia	• Del Poeta G, Del Principe MI, Buccisano F, et al. Consolidation and maintenance immunotherapy with rituximab improve clinical outcome in patients with B-cell chronic lymphocytic leukemia. Cancer 2008;112:119-128. • Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008;112:975-980. • Foon KA, Boyiadzis M, Land SR, et al. Chemoimmunotherapy with low-dose fludarabine and cyclophosphamide and high dose rituximab in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27(4):498-503. • Hainsworth JD, Vazquez ER, Spigel DR, et al. Combination therapy with fludarabine and rituximab followed by alemtuzumab in the first-line treatment of patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase 2 trial of the Minnie Pearl Cancer Research Network. Cancer 2008;112:1288-1295. • Zent CS, Call TG, Shanafelt TD, et al. Early treatment of high-risk chronic lymphocytic leukemia with alemtuzumab and rituximab. Cancer 2008;113:2110-2118. • Hallek M, Fingerle-Rowson G, Fink A-M, et al. Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL). Blood 2008b;112. ASH Abstract #325. • Reynolds C, Di Bella N, Lyons RM, et al. Phase III trial of fludarabine, cyclophosphamide, and rituximab vs. pentostatin, cyclophosphamide, and rituximab in B-cell chronic lymphocytic leukemia. Blood 2008;112. ASH Abstract #327. • Robak T, Moiseev SI, Dmoszynska A, et al. Rituximab, fludarabine, and cyclophosphamide (R-FC) prolongs progression free survival in relapsed or refractory chronic lymphocytic leukemia (CLL) compared with FC alone: final results from the international randomized phase III REACH trial. Blood 2008b;112. ASH Abstract #15742. • Fischer K, Stilgenbauer S, Schweighofer CD, et al. Bendamustine in combination with rituximab (BR) for patients with relapsed chronic lymphocytic leukemia (CLL): a multicentre phase II trial of the German CLL Study Group (GCLLSG). Blood 2008;112. ASH Abstract #330. • James DF, Castro JE, Sandoval-Sus JD, et al. Rituximab and high-dose methylprednisolone for the initial treatment of chronic lymphocytic leukemia is associated with promising clinical activity and minimal hematologic toxicity. Blood 2008;112. ASH Abstract #47 • Kay NE, Kim HT, Kempin S, et al. Predictors of clinical outcome to pentostatin, cyclophosphamide and rituximab (PCR) followed by Campath for relapsed/refractory CLL - a study of the Eastern Cooperative Oncology Group, E2903. Blood 2008;112. ASH Abstract #1057. • Tam CS, Shanafelt TD, Wierda WG, et al. De novo deletion 17p13.1 chronic lymphocytic leukemia shows significant clinical heterogeneity: the MD Anderson / Mayo Clinic experience. Blood 2008;112. ASH Abstract #1056. • Wierda WG, O'Brien SM, Faderl SH, et al. CFAR, an active frontline regimen for high-risk patients with CLL, including those with del 17p. Blood 2008;112. ASH Abstract #2095.
Rituximab (Rituxan)	Hodgkin's Disease	• Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trials by the German Hodgkin Lymphoma Study Group (GHSG). Blood 2008;111:109-111. • Azim HA, Jr., Pruneri G, Cocorocchio E, et al. Rituximab in lymphocyte-predominant Hodgkin disease. Oncology 2009;76:26-29.

Rituximab (Rituxan)	Waldenström's Macroglobulinemia	• Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenstrom macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. J Clin Oncol 2009;27:3830-3835. • Dimopoulos MA, Anagnostopoulos A, Kyrtsonis M-C, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol 2007;25:3344-3349. • Mauermann ML, Ryan ML, Moon J-S, et al. Case of mononeuritis multiplex onset with rituximab therapy for Waldenström's macroglobulinemia. J Neurol Sci. E-pub Date: April 2007. DOI # 10.1016/j.jns.2007.04.009. • Lazarevic VL, Liljeholm M, Forsberg K, et al. Fludarabine, cyclophosphamide and rituximab (FCR) induced pulmonary hypertension in Waldenström macroglobulinemia. Leuk Lymphoma 2008;49:1209-1211. • Treon SP, Branagan AR, Ioakimidis L, et al. Long-term outcomes to fludarabine and rituximab in Waldenstrom macroglobulinemia. Blood 2009;113:3673-3678. • Buske C, Hoster E, Dreyling M, et al. The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). Leukemia 2009;23:153- 161. • Ioakimidis L, Patterson CJ, Hunter ZR, et al. Comparative outcomes following CP-R, CVP-R, and CHOP-R in Waldenström's macroglobulinemia. Clin Lymphoma Myeloma 2009;9:62-66. • Tedeschi A, Benevolo G, Varettoni M, et al. Results of a phase II multicenter study of immunochemotherapy with fludarabine, cyclophosphamide and rituximab (FCR) for symptomatic Waldenstrom's macroglobulinemia. Blood 2008;112. ASH Abstract #3692. • Hamarshi M, Harindhanavudhi T, Kishk MA, et al. Lymphoplasmacytic lymphoma with IgA gammopathy, case report and review of literature. Blood 2007;110. ASH Abstract #4409.

Table G-3. Errors found in reporting of existing data*

Product	Indication	Citations Not Included
Bevacizumab (Avastin)	Background sections – all four indications	In all four Avastin background sections, the authors fail to list glioblastoma as an FDA-approved indication. FDA granted accelerated approval for this indication on May 5, 2009.
Bevacizumab (Avastin)	Breast Cancer	Cobleigh 2003: • Tumor Response: Age 48.1 (29-78) range left out; OR: 7pts [9.3%] (confirmed 5pts [6.7%]); CR: 1 (1.3%); PR: 6 (8%) (2[2.6%] unconfirmed); Stable Disease: 12 [16]; At 154 days… 12 of 75 (16%) • Other: 47(63%) HER2- Miller 2005: • Survival: Survival Overall (from start of treatment) Median Survival: 14.5 mo (Arm A) v 15.1 mo (Arm B); Survival (disease-free): IRF: 4.17 mo (Arm A) v 4.8 mo (Arm B) [0.98 HR], INV: Data not included but stated also no improvement Ramaswamy 2006: • Design: For consistency with other abstracted studies, the study is "Prospective, cohort" • Age: For consistency with other abstracted studies, the age range is (39-68) • Previous treatment: should state "No – 21 (78%)". Majority of patients didn't receive treatment in metastatic setting per table. • Median duration of response, the current range is incorrect, should state (4.6-6.5) • Median survival (disease-free): the current range is incorrect, should state (6.2-8.3) • Adverse events: Table A16.2 is missing "Nail Changes (0%)" as a column since it was cited in the study Wedam 2006 • Design: For consistency with other abstracted studies, the study is "Prospective, cohort" • Eligibility criteria: missing Age ≥18 yr • Age: For consistency with other abstracted studies, the age range is (35-73) • Drug dose/day: consider writing out Cycle 1 and Cycle 2-7 since C1 and C2-7 is not common abbreviation. If use abbreviation, need to define in the caption below. • Drug dose/day: for bevacizumab dosing after surgery, consider stating "q 3 wk" after the dosing of 15 mg/kg for clarity • Tumor response: PR section missing confidence interval (CI: 43%-85%) • Comments: For accuracy, it should state, "16 completed all 7 neo-adjuvant therapy cycles prior to surgery". • Confusing the way it is currently written since it states regimens for 7 cycles. • ADVERSE EVENTS: Current evidence table tells you to see Table A16, however, no safety information on this study is presented in the table currently. Did it accidently get dropped off? Dickler 2007 • Drug dose/day: the regimen is inaccurate, should state: " Dose dense AC q2 wk x4; then……" *(List continued next page)*

* All errors cited have been corrected in the final report, except where indicated under Saif 2007 (see "Response from authors," next page).

Bevacizumab (Avastin)	Breast Cancer *(continued)*	*(Continuation of list on previous page)* Ferrero-Torres 2007 • Eligibility criteria: strike ECOG score 0 as criteria since not explicitly stated in eligibility section. Just happened the 12 patients were ECOG PS 0. • Stage of disease: Stage II/III, neoadjuvant study (stated in results section) • Median survival and median survival (disease-free): leave blank (currently states Not reached which is inaccurate). Mayer 2007: • Age: clarify that it is "Median 50" • N: 40 (was blank) Rocca 2007 • Previous treatments: endocrine/chemo/trastuzumab 13/21/1 patients • Stage of disease: advanced disease Sledge 2007 • Eligibility criteria: add HER2-negative, ECOG PS 1, no prior anti-angiogenic or oral fluoropyrimidine therapy • N: note that 91 patients were used to assess tumor response Swain 2007: • Design: Open label • Stage of Disease: Before surgery with inflammatory or locally advanced breast cancer • PR: 14(67%)
Bevacizumab (Avastin)	Ovarian Cancer	Campos 2007: • Design: Open label • Eligibility criteria: ECOG status ≤ 2
Bevacizumab (Avastin)	Pancreatic Adenocarcinoma	Kindler 2005: • Outcome sought: ORR; Tumor Response (N): 52 Saif 2007: • Unsure why included Saif references and Kindler within safety tables and listed twice since they are the same study. Used ASCO-GI abstract though ASCO Annual abstract was available leading to differing results. Even if ASCO-GI reference was used, errors within table for PR: 12.4% vs. 7.5 for (G+B/G) and OS: 5.2 (G+B) vs. 5.8 mo (G). ***Response from authors:*** Not changed. When discrepancies were noted between fully published reports and abstracts, or between 2 fully published reports with overlapping data, we used figures reported in the first fully published report listed in the evidence table (in this case, Saif 2007). The reports by Saif and by Kindler et al. are combined in Table A19 because of overlapping data. Adverse events data, however, are reported separately in Table A22.2 because we felt that it was informative to report the different AE rates reported in these two overlapping but not identical studies. *(List continued next page)*

Bevacizumab (Avastin)	Pancreatic Adenocarcinoma *(continued)*	*(Continuation of list on previous page)* Astsaturov 2007: • Median OS is flipped for Group A (43 days) and Group B (45 days). Comments about the reason why study was discontinued is inaccurate. Study was terminated due to lack of PFS benefit in both arms not due to any safety reasons. Gomez-Martin 2007: • Under AE, correct “neuropenia" to “neutropenia,” and correct “Grade 2 asthenia” to “Grade 3 asthenia.” Kim 2007: • Missing ECOG PS 0-2 under the eligibility criteria; Median survival at 1 year should be NR (confusing and inconsistent the way it is written currently) Small 2007: • Stage of disease should say non-metastatic (not NR); under AE, should state “No Grade 4 or 5 toxicity” Grade 3 should be listed prior to cytopenia and DVT for clarity. Crane 2006: • Drug dose per day should be for Avastin and should state “dose escalation from 2.5 – 10 mg/kg every 2 weeks with capecitabine and radiotherapy. Comments for this study does not represent summary. Suggest the following within this section, “Nine of 46 assessable patients (20%) had confirmed partial responses for median of 6.2 months. Median overall survival was 11.6 months. Three patients developed Grade 4 neutropenia and five patients developed Grade 3 or worse ulceration with bleeding or perforation.” • Safety tables: See above comment for Saif 2007.
Bevacizumab (Avastin)	Renal Cell Carcinoma	Elaraj 2004: • Phase: This study should actually be considered a Phase II not Phase I as written. Hainsworth 2005: • Study design: should state XRT >8 weeks prior. As it reads now only patients who received XRT exactly 8 weeks prior were eligible • Previous treatment: should state 68% None; 26% IFN +/- IL2; 6% IL-2. • Drug dose/day: Bevacizumab was given 10 mg/kg q 2weeks, not daily as currently written. • Stable disease: major typo which should state 36 patients, not 6 patients. • Safety table on page 223: Inaccurate as currently listed. In the study, “nausea and diarrhea” was considered one category. As written, it looks as if nausea occurred in 10% and diarrhea occurred also in 10%. *(List continued next page)*

Bevacizumab (Avastin)	Renal Cell Carcinoma *(continued)*	*(Continuation of list on previous page)* Yang 2003: • Drug dose/day: Placebo group did not receive the loading dose. Should be written as "Placebo or PK modeled loading dose followed by 3 mg/kg or 10 mg/kg…." • •Outcomes sought: Should also state toxicity as an endpoint • Survival (disease-free): Numbers provided are incorrect. Should state, "PFS: 4.8 mo vs. 3.0 mo vs. 2.5 mo (high-dose vs. low-dose vs. placebo). • Safety table on page 223: Grade ¾ Proteinuria occurred in 7% of patients, not 13%. Ernstoff 2007: • Eligibility criteria: missing "no coagulopathy or thrombotic event" • Drug dose/day: IL-2 dosing inaccurate, should state "IL-2 600K unites q 8 hrs x 5 days x 2 as part of an 84-day cycle for up to 28 doses. Escudier 2007: • Selection/randomization: should state, "Randomized and stratified by country and Motzer score" • Age: median age was 61 years and the range is (18-82) • Adverse events and tolerability: epistaxis was very rare. Would suggest the following instead "Grade 3 or 4 proteinuria, fatigue, and asthenia were ≥3% more common in bevacizumab arm." Feldman 2007: • Drug dose/day: Typo "snf" should be "and" Garcia 2007: • Eligibility criteria: should also include "normal organ function" • Drug dose/day: Bevacizumab was not given for only 8 weeks in the study. The 8-weeks apply only to IL-2. Bevacizumab was given until disease progression. • Outcomes sought: missing "Response" as an endpoint.
Erlotinib (Tarceva)	Head and Neck Cancer	*Abstracted data not reviewed for factual accuracy due to time constraint*
Rituximab (Rituxan)	All Indications	In all three rituximab background sections, authors state that rituximab was first approved by FDA in 2006. In fact, FDA first granted approval to rituximab for relapsed or refractory non-Hodgkins lymphoma in November 1997.
Rituximab (Rituxan)	Chronic Lymphocytic Leukemia	*Abstracted data not reviewed for factual accuracy due to time constraint*
Rituximab (Rituxan)	Hodgkin's Disease	*Abstracted data not reviewed for factual accuracy due to time constraint*
Rituximab (Rituxan)	Waldenström's Macroglobulinemia	*Abstracted data not reviewed for factual accuracy due to time constraint*

Table G-4. Citations publicly available from other major clinical conferences that should have been included in the draft report given the stated scope

Product	Indication	Citations Not Included
Bevacizumab (Avastin)	Breast Cancer	• Miller KD, Wang M, Gralow J, et al. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100). Breast Cancer Res Treat 2005;94:S6. SABCS Abstract #3. • Perez EA, Hillman DW, Kugler JW, et al. North Central cancer treatment group (NCCTG) N0432: phase II trial of docetaxel with capecitabine and bevacizumab as first line chemotherapy for patients with metastatic breast cancer. Breast Cancer Res Treat 2006;100. SABCS Abstract #2069. • Pegram M, Chan D, Dichmann RA, et al. Phase II combined biological therapy targeting the HER2 protooncogene and the vascular endothelial growth factor using trastuzumab (T) and bevacizumab (B) as first line treatment of HER2-amplified breast cancer. Breast Cancer Res Treat 2006;100. SABCS Abstract #301. • Burstein HJ, Parker LM, Savoie J, et al. Phase II trial of the anti-VEGF antibody bevacizumab in combination with vinorelbine for refractory advanced breast cancer. Breast Cancer Res Treat 2002;76:115. SABCS Abstract #446. • Burstein HJ, Spigel D, Kindsvogel K, et al. Metronomic chemotherapy with and without bevacizumab for advanced breast cancer: a randomized phase II study. Breast Cancer Res Treat 2005;94:S6. SABCS Abstract #4. • Mayer E, Kozloff M, Qamar R, et al. SABRE-B: A randomized phase II trial evaluating the safety and efficacy of combining sunitinib with paclitaxel + bevacizumab as first-line treatment for HER2-negative metastatic breast cancer (MBC): final results. 2008. SABCS Abstract #3126. • Smith IE, Biganzoli L, Cortes-Funes H, et al. Primary analysis of study M019391, an open-label safety study of bevacizumab (B) plus taxane-based therapy as 1st-line treatment of patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC). Cancer Res 2009;69. SABCS Abstract #4118. • Ardavanis A, Doufexis D, Kountourakis P, et al. Bevacizumab (BEV) and paclitaxel (PAC) every two weeks as first-line treatment for advanced breast cancer (ABC). preliminary results. Cancer Res 2009;69. SABCS Abstract #4121. • Dickler M, Franco S, Stopeck A, et al. Final results from a phase II evaluation of lapatinib (L) and bevacizumab (B) in HER2-overexpressing metastatic breast cancer (MBC). Cancer Res 2009;69. SABCS Abstract #3133. • Hurvitz S, Allen HJ, Moroose RL, et al. Final results of a phase II study of bevacizumab plus docetaxel for the first-line treatment of metastatic breast cancer (TORIBO1). Eur J Cancer Suppl 2008;6:217. EBCC-6 Abstract #567.
Bevacizumab (Avastin)	Ovarian Cancer	• McGonigle KF, Muntz HG, Vuky J, et al. Phase II prospective study of weekly topotecan and bevacizumab in platinum-resistant ovarian, fallopian tube or primary peritoneal cancer. Gynecol Oncol 2009;112:S145. SGO Abstract #286. • Seamon LG, Richardson DL, Hurt JD, et al. Bevacizumab and weekly topotecan as salvage chemotherapy for ovarian cancer. Gynecol Oncol 2009;112:S57. SGO Abstract #112. • Hurt JD, Richardson DL, Seamon LG, et al. Sustained progression-free survival with weekly paclitaxel and bevacizumab in recurrent ovarian cancer. Gynecol Oncol 2009;112:S154. SGO Abstract #305. • Bevis KS, Numnum TM, Shipman KA, et al. The efficacy and toxicity of bevacizumab plus gemcitabine in patients with recurrent ovarian cancer. Gynecol Oncol 2008;108:S119. • Azad N, Annunziata CM, Greenberg L, et al. Combination therapy with sorafenib and bevacizumab is active in epithelial ovarian cancer. Gynecol Oncol 2008;108:S23-S23. • Chambers SK, Clouser MC, Roe DJ, et al. Phase II trial of bevacizumab and erlotinib in women with refractory ovarian cancer. Presented at the 100th Annual Meeting of the American Association for Cancer Research in Denver, CO; April 18-22, 2009. AACR Abstract #3582.

Bevacizumab (Avastin)	Pancreatic Adenocarcinoma	• Jafari M, Varadhachary GR, Xiong H, et al. Bi-institutional phase II trial of gemcitabine, oxaliplatin, and bevacizumab in patients with advanced pancreatic cancer. Presented at the Gastrointestinal Cancers Symposium in Orlando, Florida; January 19-21, 2007. ASCO GI Abstract #141. • Ko AH, Dito E, Schillinger B, et al. A phase II study of bevacizumab (BEV) and erlotinib (ERL) in patients with gemcitabine (GEM)-refractory metastatic adenocarcinoma of the pancreas (PanCa). Presented at the Gastrointestinal Cancers Symposium in Orlando, Florida; January 19-21, 2007. ASCO GI Abstract #187. • Crane CH, Krishnan S, Rana V, et al. Does the addition of bevacizumab to chemoradiation prolong median survival in locally advanced pancreatic cancer patients? Int J Radiat Oncol Biol Phys 2006;66:S173. ASTRO Abstract #1076. • Ko AH, Dicke K, Gurtler J, et al. Phase II, randomized, open-label study of cetuximab and bevacizumab alone or in combination with fixed-dose rate (FDR) gemcitabine as first-line therapy for patients with metastatic adenocarcinoma of the pancreas (MPC). Presented at the 2009 Gastrointestinal Cancers Symposium in San Francisco, California; January 15-17, 2009. ASCO GI Abstract #183. • Starling N, Watkins D, Chau I, et al. A phase I study of chemotherapy doublet (gemcitabine plus capecitabine [GemCap]), combined with a biologic doublet (bevacizumab plus erlotinib) in patients with advanced pancreatic adenocarcinoma (PC): the TARGET trial. Presented at the 2008 Gastrointestinal Cancers Symposium in Orlando, Florida; January 25-27, 2008. ASCO GI Abstract #141.
Bevacizumab (Avastin)	Renal Cell Carcinoma	• Ko AH, Dicke K, Gurtler J, et al. Phase II, randomized, open-label study of cetuximab and bevacizumab alone or in combination with fixed-dose rate (FDR) gemcitabine as first-line therapy for patients with metastatic adenocarcinoma of the pancreas (MPC). Presented at the 2009 Gastrointestinal Cancers Symposium in San Francisco, California; January 15-17, 2009. ASCO GI Abstract #183. • Starling N, Watkins D, Chau I, et al. A phase I study of chemotherapy doublet (gemcitabine plus capecitabine [GemCap]), combined with a biologic doublet (bevacizumab plus erlotinib) in patients with advanced pancreatic adenocarcinoma (PC): the TARGET trial. Presented at the 2008 Gastrointestinal Cancers Symposium in Orlando, Florida; January 25-27, 2008. ASCO GI Abstract #141. • Tamaskar IR, Rini B, Mekhail T, et al. A phase II trial of low-dose interleukin-2 (IL-2) and bevacizumab for patients (pts) with metastatic renal cell carcinoma (mRCC). 2008 Gastrointestinal Cancers Symposium 2008. ASCO GI Abstract #363.
Erlotinib (Tarceva)	Head and Neck Cancer	• Arias de la Vega F, Herruzo I, de la Torre A, et al. Erlotinib and chemoradiation in patients with surgically resected locally advanced squamous head and neck cancer (HNSCC): A gicor phase I study. Int J Radiat Oncol Biol Phys 2008;72:S377. ASTRO Abstract #2464.
Rituximab (Rituxan)	Chronic Lymphocytic Leukemia	• Zagoskina TP, Malykh OV, Kudryavtseva AV, et al. Supporting rituximab therapy in chronic lymphocytic leukemia Kirov scientific research institute of hematology and blood transfusion of rosmedtechnologies, Kirov. Haematologica 2008;93:527. Abstract #1380.
Rituximab (Rituxan)	Hodgkin's Disease	• No citations missing
Rituximab (Rituxan)	Waldenström's Macroglobulinemia	• No citations missing