

Systematic Review of Comparative Effectiveness Data for Oncology Orphan Drugs

Mindy M. Cheng, MS; Scott D. Ramsey, MD, PhD; Emily Beth Devine, PharmD, MBA, PhD; Louis P. Garrison, PhD; Brian W. Bresnahan, PhD; and David L. Veenstra, PharmD, PhD

Comparative effectiveness research (CER) can be described as the assessment of a medical intervention against alternative interventions with the intent of identifying treatment strategies that are likely to have preferable benefit-risk profiles or are considered cost-effective in real-world clinical settings. The purpose of CER is to assist healthcare providers, payers, patients, and decision makers in making informed healthcare decisions that will improve individual and population health.¹

Definitions of a rare disease differ around the world and the prevalence threshold varies between countries.² In the European Union, a disease is considered rare if it affects fewer than 215,000 individuals, while in the United States, a rare disease is described as a condition with prevalence of less than 200,000 or a disease with distinct subpopulations consisting of fewer than 200,000 individuals nationwide.^{2,3} As of 2010, 362 drugs indicated for rare diseases (orphan drugs) have received US Food and Drug Administration (FDA) market approval, and oncology therapies comprise the largest clinical subcategory.⁴ In general, orphan drugs have relatively higher costs than other drugs because manufacturers must rely on smaller patient populations to recoup development investments. In the United States, 15 orphan drugs were commercialized between 2006 and 2008; 6 of these cost more than \$100,000 per patient per year.⁵

Previous studies have suggested that orphan drugs have less robust bodies of evidence because smaller patient populations and limited knowledge of rare conditions constrain the design, conduct, analysis, and interpretation of clinical trials.^{2,6,7} Due to the rapid rate of oncology orphan drug development and the significant financial burden associated with cancer treatments, there have been increasing pressures on drug manufacturers to demonstrate the value of their products. Less robust bodies of evidence will present particular challenges to CER and will make decision making about orphan drug accessibility difficult. The comparative effectiveness data supporting oncology orphan drugs marketed in the United States have not been well studied. The primary objective of this study was to systematically and critically assess the level and quality of clinical and economic evidence currently available for all oncology orphan drugs marketed in the United States. A secondary

objective was to highlight the challenges and opportunities for evidence development within this pharmaceutical category.

Objectives: To systematically assess clinical and economic evidence for oncology orphan drugs marketed in the United States and to highlight the challenges and opportunities for evidence development within this pharmaceutical category.

Study Design: Systematic review.

Methods: We conducted systematic literature searches of the Medline and Embase databases for clinical and cost-effectiveness studies published before June 2010 for all oncology orphan drugs marketed in the United States. We used the Grading of Recommendations Assessment, Development and Evaluation method and the Quality of Health Economic Studies criteria to assess the quality of the selected studies.

Results: We identified 60 randomized controlled trials and 21 cost-effectiveness analyses to support 47 oncology orphan drugs. A total of 21 drugs had moderate or high-quality bodies of clinical evidence, 11 had low-quality or very low quality clinical evidence, and 15 drugs could not be evaluated because we were unable to identify clinical evidence that met our inclusion criteria. The Spearman rank correlation coefficient for the level of evidence for oncology orphan drugs and disease prevalence was 0.3 (95% confidence interval, 0.0-0.5). The cost-effectiveness analyses received quality scores between 72 and 100 (range 0-100), with a mean score of 85.

Conclusions: The results of our study show that oncology orphan drugs marketed in the United States have varying levels and quality of clinical evidence and a paucity of evidence regarding economic value. Innovative analytic and policy approaches are needed to develop and implement a decision-making framework for this pharmaceutical category that is consistent with evidence-based medicine and comparative effectiveness research.

(Am J Manag Care. 2012;18(1):47-62)

In this article
Take-Away Points / p48
www.ajmc.com
Full text and PDF

**For author information and disclosures,
see end of text.**

Take-Away Points

We conducted a systematic literature review to critically assess the clinical and economic evidence supporting oncology orphan drugs marketed in the United States.

- Oncology orphan drugs marketed in the United States have varying levels and quality of clinical evidence, and a paucity of evidence demonstrating their economic value.
- The current levels of clinical and economic evidence present challenges for decision making about oncology orphan drug availability and accessibility.
- Innovative analytic and policy approaches are necessary to develop and implement a decision-making framework for oncology orphan drugs that is consistent with evidence-based medicine and comparative effectiveness research.

as part of a combination therapy regimen, the trial is designed so that the clinical effect of the orphan drug can be isolated and directly assessed (eg, drugs A, B, and C vs drugs B and C); (4) article is published in the English language; and (5) entire article is available for review. **Figure 1** presents a flow diagram that describes the literature search methods and the restrictions applied to our search.

METHODS

The Cumulative List of Designated Approved Orphan Products (www.fda.gov/orphan/designate/allap.rtf) describes drug products that have received orphan designation and have ever received marketing approval from the FDA.

We used this list, updated May 5, 2009, by the FDA, to identify products indicated to treat rare cancers. Orphan products indicated for diagnosis, palliative care, or treatment of secondary conditions associated with cancer, such as neutropenia, were not included in this study. Any product withdrawn or discontinued from the US market as of June 2010 was also excluded.

For each oncology orphan drug included in this study, we conducted a literature search in the Medline and Embase databases for randomized controlled trials (RCTs) and cost-effectiveness analyses published prior to June 2010, using search terms that included the drug's US brand name, generic name, disease indication, and the terms "randomized," "efficacy," "cost-effectiveness," and "economic." Our priority was to identify RCTs, but we also used the literature search to identify observational studies (prospective or retrospective) or other studies that described the treatment effect of the drug. We also identified published articles through information provided on the FDA Web site for new drug approvals and manual searches of article references. We defined cost-effectiveness analysis using the definition established by the Panel on Cost-Effectiveness in Health and Medicine as "An analytic tool in which costs and effects of a program and at least one alternative are calculated and presented in a ratio of incremental cost to incremental effect."⁸

For each literature search, 1 author (MMC) reviewed all of the titles and abstracts of studies likely to meet the following inclusion criteria: (1) original RCT or cost-effectiveness analysis evaluating the orphan drug used for its approved orphan indication, or observational study or published article describing the treatment effect of the orphan drug used for its approved orphan indication; (2) comparative RCTs in which the orphan drug is compared with placebo or a clinically relevant comparator; (3) if the orphan drug (eg, drug A) is used

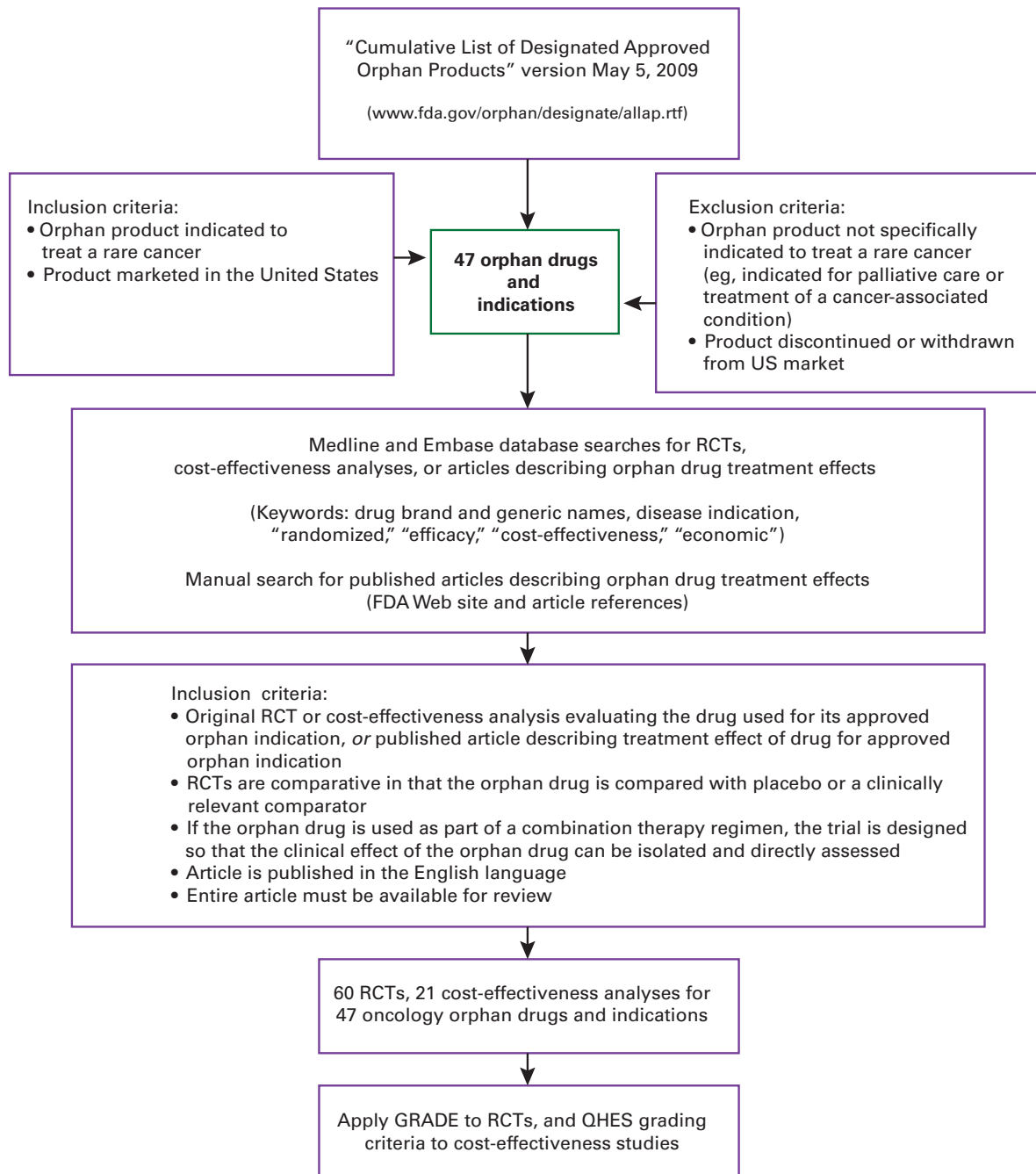
For each clinical study that met the inclusion criteria, we abstracted information about the comparator, patient characteristics, study design and treatment allocation, primary outcome measure, statistical analytic method, reporting of treatment effect with uncertainty, and study sponsor. For each cost-effectiveness analysis that met the inclusion criteria, we abstracted information about the comparator, study perspective, methods, data sources, primary outcome measure, base-case and sensitivity analysis results, and study sponsor (if reported).

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, an evaluation system created by a diverse group of international guideline developers, to assess the quality of clinical bodies of evidence. The GRADE system assesses the quality of a body of evidence by focusing on 4 main components: study design, quality, consistency of evidence, and directness of comparator, population, and intervention. The method also evaluates limitations, potential biases, and uncertainty to assign 1 of 4 possible grades: high, moderate, low, and very low.^{9,10} We adapted the grading system to our study by including a fifth grade category, "not able to assess," to describe circumstances where we could not identify published studies that met our inclusion criteria. **Table 1** details the GRADE methodology and how it was implemented in this study, and defines each quality grade.

We used the Quality of Health Economic Studies (QHES) grading criteria, a validated quantitative instrument developed by health economists, to assess the quality of cost-effectiveness studies. The QHES grading system consists of 16 criteria that are described in **Table 2**.¹¹ Each criterion is associated with a weighted score that was assigned in its entirety for each criterion perceived by the lead author to be satisfactory. Zero points were assigned to each criterion that was perceived to be unsatisfactory. Certain criteria, such as subgroup analysis, were not applicable for all studies. In these circumstances, we used both a best-case and worst-case scoring method where full points and zero points were assigned to each inapplicable criterion. The weighted scores were summed across all criteria for a total of 100 possible points for each study.

Oncology Orphan Drugs

■ **Figure 1.** Oncology Orphan Drug Identification and Literature Search Methods



FDA indicates US Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; QHES, Quality of Health Economic Studies; RCT, randomized controlled trial.

We graphically explored whether disease prevalence was associated with the level and quality of evidence for oncology orphan drugs and calculated the Spearman rank correlation coefficient to estimate the strength of the relationship. We obtained estimates of disease prevalence from Orphanet,

an electronic reference for rare disease information in Europe (www.orpha.net).¹² This resource was the only one we identified that provided a collection of prevalence estimates for rare diseases. Although the data were derived in Europe, we believe the estimates are of similar magnitude in the

■ **Table 1.** Implementation of GRADE Method and Definition of GRADE Levels^a

1. Assign an initial rating to the body of evidence based on study design. A body of evidence that consists of at least 1 RCT starts HIGH. A body of evidence that consists of no RCT [that meets inclusion criteria], but at least 1 observational study that describes the treatment effect of the drug, starts LOW.

2. Assess study limitations (risk of bias). Subtract 1 to 2 levels based on significance:

Examples of potential limitations:

- Failure to recruit predetermined sample size, failure to adhere to recruitment protocol.
- Loss to follow-up and/or failure to adhere to intention-to-treat principle.
- Selective outcome reporting, or inadequate analysis or reporting of study outcomes.
- Early stoppage of trial or failure to adhere to preestablished stopping rules.

3. Assess inconsistency of results. Subtract 1 level for significant inconsistency:

- Unexplained and widely differing treatment effects of 1 drug between different studies (consider indicated population, dosage, and primary outcome).

4. Assess indirectness of evidence. Subtract 1 to 2 levels based on significance:

- Indirect or irrelevant outcomes, use of surrogate outcomes that may not reflect true clinical benefits or were not explicitly confirmed to be correlated with clinical benefit.

5. Assess imprecision. Subtract 1 level if significant:

- Wide confidence intervals, lack of power, large uncertainty in results.

6. Assess potential reporting bias. Subtract 1 level if significant:

- Evidence of publication bias.
- Evidence of any potential bias that was not explicitly addressed.

7. Assess additional considerations that could raise the quality of a body of evidence. Add 1 or 2 levels depending on magnitude of effect or significance:

- Strong evidence of association and/or effect from observational studies with no plausible confounders or significant threats to validity.

8. Assign final GRADE:

High. Further research is very unlikely to change our confidence in the estimate of effect. (RCTs had no limitations and had consistent, precise, and directly applicable results without evidence of reporting bias. Comparative observational studies had no threats to validity and yielded very large effects.)

Moderate. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. (RCTs had important limitations, inconsistencies, impreciseness, or evidence of reporting bias. Observational studies had no threats to validity and yielded moderate effects or evidence of a dose-response gradient.)

Low. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. (RCTs had very serious limitations, or observational studies had no threats to validity but yielded small effects.)

Very low. Any estimate of effect is very uncertain. (RCTs and observational studies had very serious limitations and inconsistent results with uncertainty about the directness of results.)

Not able to assess. We were unable to identify published RCTs or observational studies that met inclusion criteria for review; body of evidence was too sparse to be evaluated.

GRADE indicates Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial.

^aAdapted from the GRADE Working Group.^{9,10}

United States, assuming similar risk factors for rare cancers. The assessment of correlation excluded 5 drugs: aldesleukin for metastatic melanoma, valrubicin for urinary bladder carcinoma, doxorubicin liposome for metastatic ovarian cancer, and toremifene citrate and exemestane for breast cancer. These cancers are not considered rare. The drugs are indicated for smaller subpopulations of patients with specific disease, physical, or genetic characteristics. Prevalence estimates for patients with these specific characteristics were not reported. We also explored whether the level and quality of evidence for oncology orphan drugs is associated with receipt of FDA accelerated approval.

RESULTS

We initially identified 48 oncology orphan drugs for inclusion in this study from the Cumulative List of Designated Approved Orphan Products. Of these drugs, 3 (Idamycin, Vesanoid, and Mylotarg) have been discontinued or withdrawn from the US market, and 5 drugs (Gleevec, Sprycel, Tasigna, Velcade, and Temodar) were indicated to treat more than 1 orphan indication or patient population; each indication was independently evaluated for these drugs. We did not include expanded or supplemental approvals for nonorphan indications. In total, 47 orphan drugs and indications were included

■ **Table 2. QHES Grading System for Cost-Effectiveness Studies¹¹**

1. Was the study objective presented in a clear, specific, and measurable manner?
2. Were the perspective of the analysis and reasons for its selection stated?
3. Were variable estimates used in the analysis from the best available source (ie, RCT, best; expert opinion, worst)?
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?
5. Was uncertainty handled by (1) statistical analysis to address random events; (2) sensitivity analysis to cover a range of assumptions?
6. Was incremental analysis performed between alternatives for resources and costs?
7. Was the methodology for data abstraction (including value health states and other benefits) stated?
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3%-5%) and justification given for the discount rate?
9. Was the measurement of costs appropriate and was the methodology for the estimation of quantities and unit costs clearly described?
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and were the major short-term, long-term, and negative outcomes included?
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?
12. Were the economic model (including structure), study methods and analysis, and components of the numerator and denominator displayed in a clear, transparent manner?
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?
15. Were the conclusions/recommendations of the study justified and based on the study results?
16. Was there a statement disclosing the source of funding for the study?

QHES indicates Quality of Health Economic Studies; RCT, randomized controlled trial.

in this study and are listed in **Table 3** by their brand and generic names. The majority of oncology orphan drugs are indicated for rare blood cancers (n = 30). Table 3 also describes the date of full and/or accelerated regulatory approval, and lists the number of RCTs identified in the published literature that met the inclusion criteria with citations of all published articles that were used to inform the body of evidence.

We identified a total of 60 RCTs that met our inclusion criteria. The greatest number of RCTs were conducted for interferon alpha-2a indicated for chronic myelogenous leukemia (CML) (n = 7), aldesleukin indicated for metastatic renal cell carcinoma (n = 7), and rituximab indicated for non-Hodgkin B-cell lymphoma (n = 6). The majority of trials we identified comprised the evidence base used for regulatory approval.

Figure 2 summarizes the clinical evidence grades assigned in this study. Twelve drugs had moderate-quality evidence, including cladribine for hairy cell leukemia and arsenic trioxide for acute promyelocytic leukemia. Although we did not identify any RCTs for these drugs that met our inclusion criteria, their clinical bodies of evidence consisted of observational studies that consistently reported similar treatment effects or a dose-response association with little threat to validity. Individual GRADE ratings assigned to each drug and their clinical bodies of evidence are listed in Table 3.

Figure 3 shows that there are drugs indicated for cancers with lower prevalence that had high-quality evidence and drugs indicated for cancers with higher prevalence that had low-quality evidence or lacked a sufficient body of evidence for review. The Spearman rank correlation coefficient between disease prevalence and the level of evidence for oncology orphan drugs was 0.3 (95% confidence interval [CI], 0.0-0.5). This indicates that there may be a weak correlation between the prevalence of rare cancers and the number of RCTs conducted for drugs indicated to treat rare cancers. A total of 14 drugs in our study received accelerated approval for the orphan indication. Of these, zero had high-quality bodies of evidence and 5 had moderate-quality bodies of evidence. Although our sample size was small, these results provided some indication that the accelerated approval provision does not optimize high-quality evidence generation for oncology orphan drugs.

We identified 21 cost-effectiveness studies that met our inclusion criteria. Of those studies, 10 evaluated the use of either interferon alpha or imatinib mesylate, or compared both for CML. **Table 4** summarizes the cost-effectiveness studies included in this assessment and describes comparators, study perspectives, base-case incremental cost-effectiveness ratios, and results of sensitivity analyses.

■ **Table 3.** Oncology Orphan Drugs and Their Assigned Clinical Evidence Grades

Drug (US Trade Name)	Drug (Generic Name)	Indication	Regular Approval Date	Accelerated Approval Date	No. of RCTs	GRADE
Blood Cancer						
Treanda	Bendamustine HCl	CLL	3/20/2008		1	Low ¹³
Campath	Alemtuzumab	B-cell CLL	9/19/2007	5/7/2001	1	Low ¹⁴
Oforta	Fludarabine phosphate (oral tablets)	B-cell CLL (not responsive to or progressing during or after treatment with at least 1 standard alkylating agent-containing regimen)		12/18/2008	0	Low ¹⁵
Fludara	Fludarabine phosphate (injection)	B-cell CLL (not responsive to or progressing during treatment with at least 1 standard alkylating agent-containing regimen)	4/18/1991		1	Very low ¹⁶
Nipent	Pentostatin	Hairy cell leukemia	10/11/1991		1	Moderate ¹⁷⁻²¹
Leustatin Injection	Cladribine	Hairy cell leukemia	2/26/1993		0	Moderate ^{17-19, 22, 23}
Trisenox	Arsenic trioxide	APL (refractory or relapsed from retinoid and anthracycline chemotherapy and presence of t(15:17) translocation or PML/RAR-alpha gene)	9/25/2000		0	Moderate ²⁴⁻²⁸
Sprycel	Dasatinib	Ph+ ALL (resistant or intolerant to prior therapy)	6/28/2006		0	Not able to assess
Gleevec	Imatinib mesylate	Ph+ ALL (relapsed or refractory)	10/19/2006		0	Low ^{29,30}
Oncaspar	PEG-asparaginase	ALL (patients hypersensitive to native forms of L-asparaginase)	2/1/1994		1	Very low ³¹⁻³³
Arranon	Nelarabine	T-cell ALL or T-cell lymphoblastic leukemia (refractory or relapsed after 2 chemotherapy regimens)	10/31/2005		0	Not able to assess
Clolar	Clofarabine	Pediatric ALL (refractory or relapsed after at least 2 prior regimens)		12/28/2004	0	Very low ³⁴
Sprycel	Dasatinib	CML (resistance or intolerance to prior therapy including imatinib)	5/21/2009	6/28/2006	1	Moderate ³⁵⁻³⁸
Gleevec	Imatinib mesylate	CML (chronic phase, after failure of IFN alpha therapy)	12/5/2003	5/10/2001	1	Moderate ³⁹⁻⁴¹
Roferon A	Interferon alpha-2a	CML	10/19/1995		7	High ⁴²⁻⁵⁰
Tasigna	Nilotinib	Ph+ CML (chronic phase or accelerated phase, resistant or intolerant of imatinib)	10/29/2007		0	Not able to assess ⁵¹
Tasigna	Nilotinib	Newly diagnosed Ph+ CML (chronic phase)	6/17/2010		1	Moderate ⁵²
Gleevec	Imatinib mesylate	Newly diagnosed CML		12/20/2002	0	Not able to assess ⁵²
Gleevec	Imatinib mesylate	Newly diagnosed Ph+ CML (pediatric)		9/27/2006	0	Not able to assess
Gleevec	Imatinib mesylate	Chronic eosinophilic leukemia (CEL)	10/19/2006		0	Not able to assess
Velcade	Bortezomib	Multiple myeloma	3/25/2005	5/13/2003	3	Moderate ⁵³⁻⁵⁷
Alkeran for injection	Melphalan	Multiple myeloma	11/18/1992		0	Not able to assess
Thalomid	Thalidomide	Multiple myeloma (+ dexamethasone)		5/26/2006	2	Low ^{58,59}
Velcade	Bortezomib	Mantle cell lymphoma (patients received 1 prior therapy)	12/8/2006 (supplement)		0	Not able to assess
Vidaza	Azacitidine	MDS	5/19/2004		2	Moderate ⁶⁰⁻⁶³
Dacogen	Decitabine	MDS	5/2/2006		1	Low ⁶⁴
Gleevec	Imatinib mesylate	MDS/MPD associated with PDGFR gene rearrangement	10/19/2006		0	Not able to assess

(Continued)

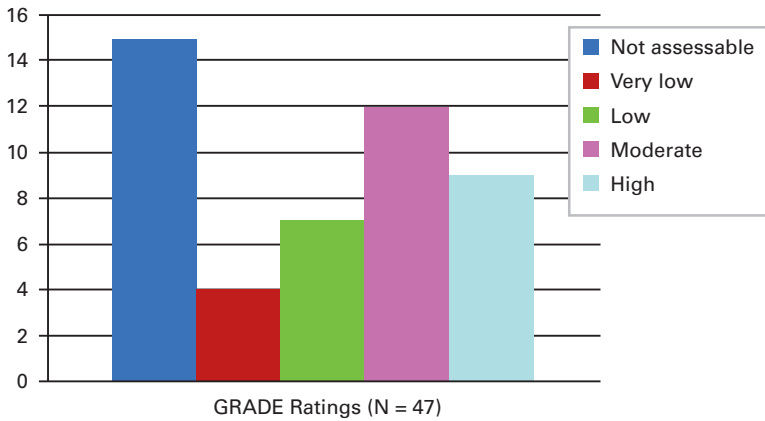
Oncology Orphan Drugs

Table 3. Oncology Orphan Drugs and Their Assigned Clinical Evidence Grades (Continued)

Drug (US Trade Name)	Drug (Generic Name)	Indication	Regular Approval Date	Accelerated Approval Date	No. of RCTs	GRADE
Blood Cancer (Continued)						
Rituxan	Rituximab	Non-Hodgkin B-cell lymphoma (CD20+, low grade or follicular, relapsed or refractory)	11/26/1997		6	Moderate ⁶⁵⁻⁷²
Treanda	Bendamustine HCl	Non-Hodgkin B-cell lymphoma (indolent, progressed within 6 months of rituximab regimen)	10/31/2008		0	Not able to assess
Zevalin	Ibritumomab tiuxetan	Non-Hodgkin B-cell lymphoma (low-grade, follicular, or transformed, relapsed or refractory)	2/19/2002		1	Low ⁷²⁻⁷⁴
Skin Cancer						
Proleukin	Aldesleukin	Metastatic melanoma	1/9/1998		3	High ⁷⁵⁻⁷⁷
Targretin	Bexarotene (capsule)	Cutaneous T-cell lymphoma (refractory to 1 prior systemic therapy)	12/29/1999		0	Not able to assess ⁷⁸
Ontak	Denileukin diftitox	Cutaneous T-cell lymphoma (persistent, recurrent, CD25 component of IL-2 receptor)	10/15/2008	2/5/1999	1	Moderate ⁷⁹
Zolinza	Vorinostat	Cutaneous T-cell lymphoma (progressive, persistent, recurrent disease during or following 2 systemic therapies)	10/6/2006		0	Not able to assess
Gleevec	Imatinib mesylate	Dermatofibrosarcoma protuberans (unresectable, recurrent, and/or metastatic)	10/19/2006		0	Not able to assess
Renal and Bladder Cancer						
Proleukin	Aldesleukin	Metastatic renal cell carcinoma	5/5/1992		7	Moderate ⁸⁰⁻⁸⁷
Nexavar	Sorafenib tosylate	Advanced renal cell carcinoma	12/20/2005		2	High ⁸⁸⁻⁹¹
Torisel	Temsirolimus	Advanced renal cell carcinoma	5/30/2007		1	High ⁹²
Valstar	Valrubicin	Urinary bladder carcinoma (BCG refractory, in situ)	9/25/1998		0	Not able to assess
Ovarian and Breast Cancer						
Doxil	Doxorubicin liposome	Metastatic ovarian cancer (refractory to paclitaxel and platinum-based chemotherapy)	1/28/2005	6/28/1999	4	Moderate ⁹³⁻⁹⁸
Fareston	Toremifene citrate	Metastatic breast cancer (postmenopausal women with estrogen+ or receptor unknown tumors)	5/29/1997		2	High ^{99,100}
Aromasin	Exemestane	Advanced breast cancer (postmenopausal women, disease progression after tamoxifen)	10/21/1999		5	High ¹⁰¹⁻¹⁰⁹
Brain Cancer						
Temodar	Temozolomide	Refractory anaplastic astrocytoma	3/15/2005	8/11/1999	0	Not able to assess
Temodar	Temozolomide	Glioblastoma multiforme (+ radiotherapy)	3/15/2005		1	High ^{110,111}
Gastrointestinal Cancer, Liver Cancer, and Mesothelioma						
Gleevec	Imatinib mesylate	Gastrointestinal stromal tumors (Kit CD117+, unresectable and/or metastatic malignant)	9/29/2008	2/1/2002	0	Very low ¹¹²⁻¹¹⁴
Nexavar	Sorafenib tosylate	Hepatocellular carcinoma (unresectable)	11/16/2007		2	High ¹¹⁵⁻¹¹⁸
Alimta	Pemetrexed disodium (intravenous infusion)	Malignant pleural mesothelioma	2/4/2004		2	High ¹¹⁹⁻¹²¹

ALL indicates acute lymphocytic leukemia; APL, acute promyelocytic leukemia; BCG, bacillus Calmette-Guerin; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IFN, interferon; IL-2, interleukin 2; MDS, myelodysplastic syndrome; MPD, myeloproliferative disease; PDGFR, platelet-derived growth factor receptor; Ph+, Philadelphia chromosome; RCT, randomized controlled trial.

■ **Figure 2.** GRADE Ratings for FDA-Approved Oncology Orphan Drugs



FDA indicates US Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

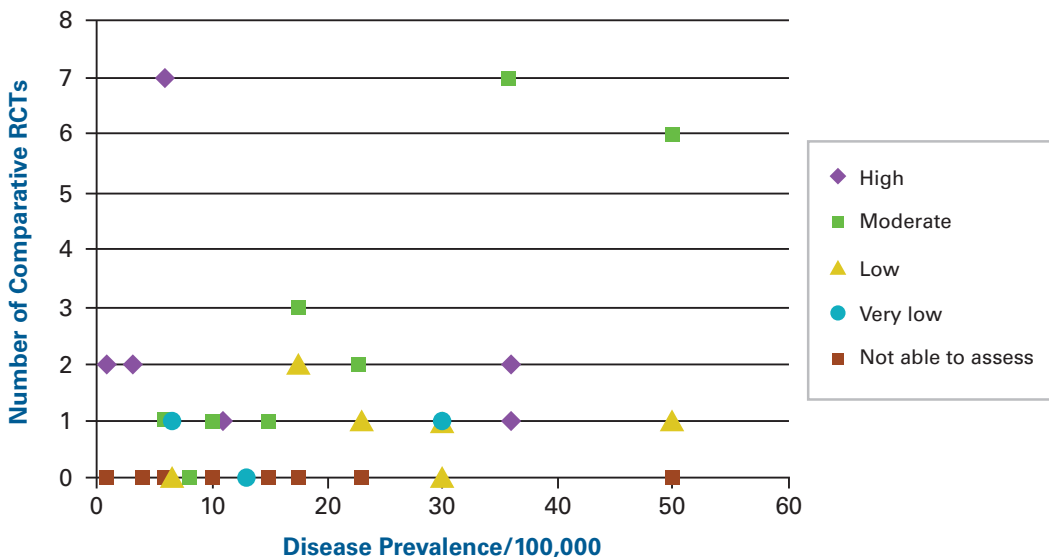
The cost-effectiveness analyses received QHES scores ranging from 72 to 100, with a mean score of 85. The clinical data used to inform the studies were largely obtained from either randomized trials or patient medical records. The majority of studies implemented modeling techniques to project longer-term health outcomes that could not be obtained from limited clinical data. Cost inputs were obtained from administrative databases and the published literature. The most common shortcomings were as follows: 11 studies used data inputs from sources that might potentially incorporate bias and did

not provide explicit discussion about the direction and magnitude of potential biases; 6 studies did not specify the source of funding for the study, which is recommended to add transparency; and 5 studies either failed to specify the time horizon for analysis, conducted analysis using a short time horizon that is not expected to fully capture clinically significant costs and effects, or did not implement adequate discounting for both future costs and outcomes. Table 4 reports the quality scores assigned to each cost-effectiveness study using the best-case scoring method where full points were assigned to inapplicable criteria. Scores assigned using the worst-case approach, where zero points were assigned to inapplicable criteria, are reported in parentheses.

DISCUSSION

We conducted a systematic literature review to identify and assess clinical and economic evidence for 47 oncology orphan drugs marketed in the United States and applied 2 independent grading frameworks to the selected studies to critically assess the quality of each body of evidence. The supporting bodies of evidence available for marketed oncology orphan drugs vary in quality, with limited evidence demonstrating their economic value.

■ **Figure 3.** Disease Prevalence Versus Level and Quality of Evidence



RCT indicates randomized controlled trial.

Oncology Orphan Drugs

Table 4. Summary of Cost-Effectiveness Studies and QHES Evidence Grades

First Author and Year	Comparators	Disease Indication	Study Perspective	Base-Case Results (Range)	QHES
Blood Cancer					
Kattan 1996 ¹²²	IFN alpha vs hydroxyurea	CML (chronic phase)	Not specified	IFN alpha: \$34,800/QALY (range not provided)	73 (65)
Liberato 1997 ¹²³	IFN alpha vs hydroxyurea	CML (chronic phase)	Social	IFN alpha for patients with hematologic response: \$89,500/QALY (\$16,000-\$198,700/QALY) IFN alpha for patients with cytogenetic remission in 2-year period: \$63,500/QALY (\$9500-\$218,400/QALY)	89 (81)
Messori 1998 ¹²⁴	IFN alpha vs busulphan or hydroxyurea	CML (chronic phase)	Social	IFN alpha: \$93,461-\$226,545/LYG (varies based on different international clinical trial data used for analysis) (\$56,022-\$204,680/LYG)	89 (81)
Beck 2001 ¹²⁵	IFN alpha vs IFN alpha + cytarabine vs hydroxyurea	CML (chronic phase)	Not specified	IFN alpha vs IFN alpha + cytarabine: \$16,900/QALY (\$7000-\$35,000/QALY) IFN alpha vs hydroxyurea: \$23,700/QALY	76 (68)
Gordois 2003 ¹²⁶	Imatinib mesylate vs conventional chemotherapy and palliative care	CML (accelerated and blast crisis phases)	UK National Health Service	Imatinib (accelerated phase): £29,344/QALY (£9132-£60,991/QALY) Imatinib (blast crisis phase): £42,239/QALY (£11,556-£122,016/QALY)	92 (92)
Warren 2004 ¹²⁷	Imatinib mesylate vs hydroxyurea	CML (chronic phase)	UK National Health Service	Imatinib: £38,468/QALY (£14,195-£62,745/QALY)	92 (91)
Dalziel 2005 ¹²⁸	Imatinib mesylate vs IFN alpha vs hydroxyurea	CML	UK National Health Service	Imatinib vs IFN alpha: £26,180/QALY (£19,449-£51,870/QALY) Imatinib vs hydroxyurea: £86,934/QALY (£69,701-£147,095/QALY)	100 (99)
Skrepnek 2005 ¹²⁹	Imatinib mesylate vs allogeneic bone marrow transplantation	CML	US third-party payer	Imatinib: dominant	97 (89)
Reed 2004 ¹³⁰	Imatinib vs IFN alpha + low dose cytarabine	CML (chronic phase)	US healthcare system	Imatinib (using AWP drug cost): \$57,103/QALY (\$51,800-\$57,500/QALY) Imatinib (using WAC drug cost): \$46,082/QALY (\$42,000-\$46,200/QALY)	100 (99)
Chen 2009 ¹³¹	Imatinib mesylate vs IFN alpha	CML (chronic phase)	Chinese public healthcare system	Imatinib: RMB 73,674/QALY (RMB 67,712-RMB 79,637/QALY)	83 (82)
Guest 2009 ¹³²	Pentostatin vs cladribine	Hairy cell leukemia	UK National Health Service	Pentostatin: <£5000/QALY (≤£6500/QALY)	84 (76)
Scott 2007 ¹³³	Alemtuzumab vs fludarabine + cyclophosphamide + rituximab (FCR)	CLL (third line)	New Zealand Pharmaceutical Management Agency (PHARMAC)	Alemtuzumab: NZ\$46,016/QALY (range not provided)	73 (65)
Mehta 2004 ¹³⁴	Bortezomib vs thalidomide vs best supportive care	Multiple myeloma (relapsed, refractory)	US third-party payer	Bortezomib vs best supportive care: \$45,356/LYG Bortezomib with previous thalidomide use vs best supportive care: \$49,797/LYG Bortezomib without previous thalidomide use vs thalidomide: \$21,483/LYG (\$18,000-\$52,705/LYG)	77 (70)

(Continued)

■ **Table 4.** Summary of Cost-Effectiveness Studies and QHES Evidence Grades (*Continued*)

First Author and Year	Comparators	Disease Indication	Study Perspective	Base-Case Results (Range)	QHES
Renal Cancer					
Hoyle 2010 ¹³⁵	Sorafenib vs best supportive care	Advanced renal cell carcinoma (second line)	UK National Health Service	Sorafenib: £75,398/QALY (£47,440-£82,821/QALY)	84 (83)
Breast Cancer					
Hillner 2001 ¹³⁶	Exemestane vs megestrol	Advanced breast cancer	US societal	Exemestane: \$10,600/LYG (\$6200-\$209,000/LYG)	84 (76)
Lindgren 2002 ¹³⁷	Exemestane vs megestrol	Advanced breast cancer	Payer perspective in Australia, Belgium, France, Germany, Italy, The Netherlands, Spain, UK	Exemestane for 1080 days: Australia: €11,169/LYG (€7528-€9878/LYG) Belgium: €6911/LYG (€3822-€4552/LYG) France: €6966/LYG (€4769-€5827/LYG) Germany: €1353/LYG (€1899-€3104/LYG) Italy: €10,638/LYG (€9844-€11,147/LYG) The Netherlands: €13,016/LYG (€6571-€11,801/LYG) Spain: €7806/LYG (€7867-€8415/LYG) UK: €11,733/LYG (€10,390-€13,106/LYG)	78 (70)
Lundkvist 2007 ¹³⁸	Exemestane vs tamoxifen	Early-stage breast cancer (adjuvant treatment after 2-3 years treatment with tamoxifen)	Swedish health-care system	Exemestane: €31,000/QALY (€13,000-€46,000/QALY)	100 (92)
Gastrointestinal Cancer and Mesothelioma					
Huse 2007 ¹³⁹	Imatinib mesylate vs no imatinib (palliative or supportive care)	Gastrointestinal stromal tumors	US societal	Imatinib: \$38,723/QALY (\$4267-\$61,673/QALY)	77 (76)
Contreras-Hernandez 2008 ¹⁴⁰	Imatinib vs sunitinib vs palliative care	Gastrointestinal stromal tumors (second line)	Mexican Insurance System (Instituto Mexicano del Seguro Social)	Sunitinib vs palliative care: \$46,109/LYG Sunitinib vs imatinib: dominant (ranges not specified)	72 (64)
Mabasa 2008 ¹⁴¹	Imatinib vs no imatinib (supportive care)	Gastrointestinal stromal tumors	British Columbia Cancer Agency	Imatinib: Can\$16,911/LYG (median) (Can\$0-Can\$50,806/LYG)	82 (74)
Cordony 2008 ¹⁴²	Pemetrexed + cisplatin vs cisplatin	Malignant pleural mesothelioma	UK National Health Service	Pemetrexed + cisplatin vs MVP: £21,731/QALY Pemetrexed + cisplatin vs vinorelbine + platinum: £26,437/QALY Pemetrexed + cisplatin vs active symptom control: £32,066/QALY (£20,475-£68,598/QALY)	78 (77)

Summary of QHES scores: range, 72-100 (64-99); mean, 85 (80); median, 84 (77).

AWP indicates average wholesale price; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; IFN, interferon; LYG, life-year gained; MVP, mitomycin-C + vinblastine + cisplatin; QALY, quality-adjusted life-year; QHES, Quality of Health Economic Studies; UK, United Kingdom; WAC, wholesale acquisition cost.

Although the GRADE methodology is relatively explicit, reviewer judgment is required. In particular, we found that it was necessary to grade certain criteria subjectively in order to better accommodate oncology orphan drug characteristics. For example, the majority of RCTs for oncology orphan drugs

had relatively small sample sizes that could lead to substantial imprecision (eg, lack of power, wide confidence intervals). We assigned lower ratings for studies that did not meet predetermined enrollment criteria or appeared underpowered to detect differences in their primary end point, but we did

not consider a smaller sample size in itself to be a limitation. We critically assessed each study and lowered ratings when we identified instances of bias that were not explicitly addressed. We also lowered ratings when studies were poorly reported, or when bodies of evidence consisted of studies that reported inconsistent treatment effects.

The number of RCTs identified in our study is comparable to the number in a study conducted by Tsimberidou and colleagues that evaluated the long-term marketing outcome of oncology drugs approved by the FDA without a randomized trial.¹⁴³ In their study, 68 approved oncology drugs were identified and almost half ($n = 31$) were approved without an RCT. Kesselheim and colleagues recently evaluated pivotal trial characteristics of orphan and nonorphan drugs approved between 2004 and 2010 to treat cancer and concluded that pivotal trials for approved oncology orphan drugs were more likely to be smaller, nonrandomized, and unblinded, and to use surrogate end points to assess efficacy.⁴ The study is limited in that it only evaluated pivotal trials and did not account for other available clinical information. Also, the study was restricted to recently approved oncology orphan drugs and did not review the entire pharmaceutical category. We observed the same characteristics in the clinical trials that were included in our study. We also observed that there is a lack of published postmarketing studies and information about longer-term safety and efficacy.

We hypothesized that the level of evidence available for oncology orphan drugs would have a strong correlation with disease prevalence in that larger patient populations enable better evidence generation. However, our results suggested a potentially weak correlation between the prevalence of rare cancers and the level of evidence available for drugs indicated to treat rare cancers. A weak relationship suggests that evidence development for oncology orphan drugs may not depend as much on the size of a particular patient population. Instead, evidence development in this pharmaceutical category may depend more on other factors, possibly regulatory requirements or reimbursement considerations.

The overall dearth of cost-effectiveness studies in this pharmaceutical category, and in oncology as a whole, may reflect evidence limitations or publication bias, where studies of drugs with higher costs, greater benefit-risk uncertainty, or lower effectiveness are not published. In assessing the economic challenges of orphan drugs, Drummond and colleagues stated: "In short, if standard health technology assessment (HTA) procedures were to be applied to orphan drugs, virtually none of them would be 'cost-effective'."¹⁷ This conclusion was largely based on 2 factors: (1) high incremental cost per quality-adjusted life-year and (2) insufficient breadth and quality of clinical evidence for orphan drugs compared with drugs for more

common diseases.⁷ Our results demonstrated that, contrary to these prior suggestions, it is feasible for some oncology orphan drugs to be considered cost-effective in specific healthcare settings using standard methods of health technology assessment. The clinical and economic value of each orphan drug should be assessed individually, on a case-by-case basis. We observed that all of the drugs considered cost-effective in their respective studies had moderate-quality to high-quality bodies of clinical evidence. This finding suggests there may be a relationship between the level and quality of clinical evidence and the likelihood that an oncology orphan drug has published estimates of cost-effectiveness.

Evidence development is costly and challenging for all healthcare interventions, but particularly for orphan drugs, due to smaller patient populations and limited clinical knowledge of rare conditions. The trade-offs to generating more robust bodies of evidence may include delayed product accessibility, higher costs, or reduced availability of therapies. For conditions that have therapeutic alternatives, these trade-offs may be acceptable. However, for life-threatening conditions with limited therapy options, these trade-offs may not be considered acceptable. For rare diseases with only a single treatment option, one may question whether economic analysis should apply. Cost-effectiveness analysis is useful in that it provides information about the value of a health intervention compared with an alternative, which may be best supportive care or no therapy. From an equity perspective, McCabe and colleagues argue that there is no sustainable reason why the cost-effectiveness of orphan drugs should be evaluated differently from other drugs.² However, healthcare systems may wish to consider additional factors when making decisions about orphan drugs, such as budget impact, disease severity, availability of alternative therapies, or societal preferences toward patients with rare diseases.

Our study highlights 3 important policy questions. First, what types of study designs, incentives, or methods can be used to encourage better evidence development for oncology orphan drugs? Second, how much evidence is necessary or considered sufficient to healthcare decision makers, and what types of evidence should be generated prior to and after marketing approval? Finally, what are the process and decision-making criteria for evaluating comparative effectiveness data for oncology orphan drugs? Emerging private and public initiatives are attempting to address these questions to some extent with evolving methods such as coverage with evidence development^{144,145} or value of information analysis,^{146,147} but additional innovative analytic methods and policy approaches are necessary.

We recognize several limitations to this study. The most important limitation is that the GRADE assessment framework provides information about the amount of confidence that can be associated with a body of evidence and does not

relay any information about the magnitude of clinical benefit or safety of a drug. Certain oncology orphan drugs with low-grade published evidence may yield significant clinical benefits, and conversely, certain drugs with high-grade evidence may yield very little benefit. Currently, there is no established framework for quantifying the magnitude of benefits or risks from health interventions. Garrison and colleagues suggest pairing CER and benefit-risk analysis into 1 framework and describe how cost-effectiveness analysis models could be adapted to conduct quantitative benefit-risk assessments.^{148,149} It is important for manufacturers to engage in continuous evidence generation, even after a product is commercialized, so that the effectiveness and safety of their products can be accurately assessed. Comparative effectiveness research methods that capture and incorporate nonpublished clinician or patient experiences could also be useful to help better identify the real-world value of marketed oncology orphan drugs.

Given the large number of drugs included in this review and the numerous keywords we could have used to search for potential clinical and economic studies, this review may not have captured all relevant drugs or studies. We used broad search terms in 2 major databases and also conducted manual searches of reference citations; this methodology allowed us to screen as many studies as possible. Only 1 author (MMC) reviewed potential studies, abstracted information, critically assessed articles, and assigned quality ratings. Although attempts were made to be accurate and consistent, it is possible that unintentional errors and inconsistencies could have reduced or improved the quality rating for a body of evidence. The QHES is limited in its ability to identify poorly analyzed studies and does not have a benchmark for total scores, which limits its ability to quantitatively categorize and distinguish high-quality studies from low-quality studies.

CONCLUSIONS

The results of our study show that oncology orphan drugs marketed in the United States have varying levels and quality of clinical evidence and a shortage of evidence demonstrating economic value. It is uncertain whether the current evidence levels for oncology orphan drugs marketed in the United States are sufficient to support decision-making practices consistent with principles of evidence-based medicine and CER. This issue remains an open policy question that requires additional evaluation.

Acknowledgments

The authors would like to thank their anonymous reviewers for their helpful suggestions.

Author Affiliations: From Pharmaceutical Outcomes Research and Policy Program, University of Washington (MMC, SDR, EBD, LPG, BWB, DLV), Seattle, WA; Fred Hutchinson Cancer Research Center (SDR), Seattle, WA.

Funding Source: Mindy Cheng was supported by a Pharmaceutical Research and Manufacturers of America Foundation pre-doctoral fellowship.

Author Disclosures: Dr Veenstra reports receiving paid consultancies from Genentech and Novartis. He also reports receiving lecture fees from Vertex. The other authors (MMC, SDR, EBD, LPG, BWB) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (MMC, LPG, BWB, DLV); acquisition of data (MMC); analysis and interpretation of data (MMC, SDR, EBD, LPG, BWB, DLV); drafting of the manuscript (MMC, LPG, BWB, DLV); critical revision of the manuscript for important intellectual content (MMC, SDR, EBD, LPG, BWB, DLV); statistical analysis (MMC); obtaining funding (MMC); and supervision (SDR, EBD, LPG, DLV).

Address correspondence to: David L. Veenstra, PharmD, PhD, University of Washington Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy, Box 357630, Seattle, WA 98195-7630. E-mail: veenstra@u.washington.edu.

REFERENCES

1. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med.* 2009;151(3):203-205.
2. McCabe C, Claxton K, Tsuchiya A. Orphan drugs and the NHS: should we value rarity? *BMJ.* 2005;331(7523):1016-1019.
3. National Institutes of Health, Genetic and Rare Diseases Information Center (GARD). Fact sheet. <http://report.nih.gov/NIHfactsheets/View-FactSheet.aspx?csid=80>. Accessed December 16, 2011.
4. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *JAMA.* 2011;305(22):2320-2326.
5. IMS. Orphan drugs: rarity no guarantee of access. *Pricing & Market Access Review.* <http://www.imshealth.com/web/end/0,3150,64576068,63872702,81912725,00.html>. Published 2006. Accessed May 28, 2008.
6. Drummond M, Evans B, LeLorier J, et al. Evidence and values: requirements for public reimbursement of drugs for rare diseases—a case study in oncology. *Can J Clin Pharmacol.* 2009;16(2):e273-e281.
7. Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. *Int J Technol Assess Health Care.* 2007;23(1):36-42.
8. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-effectiveness in Health and Medicine.* New York, NY: Oxford University Press; 1996.
9. Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ.* 2004;328(7454):1490.
10. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926.
11. Chiou CF, Hay JW, Wallace JF, et al. Development and validation of a grading system for the quality of cost-effectiveness studies [published correction appears in *Med Care.* 2003;41(3):446]. *Med Care.* 2003;41(1):32-44.
12. Orphanet. *Prevalence of Rare Diseases: Bibliographic Data.* Orphanet Report Series, Rare Diseases Collection. May 2011. Number 1. http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf. Accessed June 22, 2011.
13. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol.* 2009;27(26):4378-4384.
14. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol.* 2007;25(35):5616-5623.
15. Boogaerts MA, Van Hoof A, Catovsky D, et al. Activity of oral fludarabine phosphate in previously treated chronic lymphocytic leukemia. *J Clin Oncol.* 2001;19(22):4252-4258.
16. Johnson S, Smith AG, Löffler H, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic

- lymphocytic leukaemia: the French Cooperative Group on CLL. *Lancet*. 1996;347(9013):1432-1438.
17. Dearden CE, Matutes E, Hilditch BL, Swansbury GJ, Catovsky D. Long-term follow-up of patients with hairy cell leukaemia after treatment with pentostatin or cladribine. *Br J Haematol*. 1999;106(2):515-519.
18. Else M, Ruchlemer R, Osuji N, et al. Long remissions in hairy cell leukemia with purine analogs: a report of 219 patients with a median follow-up of 12.5 years. *Cancer*. 2005;104(11):2442-2448.
19. Else M, Dearden CE, Matutes E, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. *Br J Haematol*. 2009;145(6):733-740.
20. Grever M, Kopecky K, Foucar MK, et al. Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: an intergroup study. *J Clin Oncol*. 1995;13(4):974-982.
21. Flinn IW, Kopecky KJ, Foucar MK, et al. Long-term follow-up of remission duration, mortality, and second malignancies in hairy cell leukemia patients treated with pentostatin. *Blood*. 2000;96(9):2981-2986.
22. Saven A, Burian C, Koziol JA, Piro LD. Long-term follow-up of patients with hairy cell leukemia after cladribine treatment. *Blood*. 1998;92(6):1918-1926.
23. von Rohr A, Schmitz SFH, Tichelli A, et al; Swiss Group for Clinical Cancer Research (SAKK), Bem, Switzerland. Treatment of hairy cell leukemia with cladribine (2-chlorodeoxyadenosine) by subcutaneous bolus injection: a phase II study. *Ann Oncol*. 2002;13(10):1641-1649.
24. Soignet SL, Maslak P, Wang ZG, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. *N Engl J Med*. 1998;339(19):1341-1348.
25. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol*. 2001;19(18):3852-3860.
26. Niu C, Yan H, Yu T, et al. Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. *Blood*. 1999;94(10):3315-3324.
27. Lazo G, Kantarjian H, Estey E, Thomas D, O'Brien S, Cortes J. Use of arsenic trioxide (As₂O₃) in the treatment of patients with acute promyelocytic leukemia: the M.D. Anderson experience. *Cancer*. 2003;97(9):2218-2224.
28. Shen Y, Shen ZX, Yan H, et al. Studies on the clinical efficacy and pharmacokinetics of low-dose arsenic trioxide in the treatment of relapsed acute promyelocytic leukemia: a comparison with conventional dosage. *Leukemia*. 2001;15(5):735-741.
29. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome [published correction appears in *N Engl J Med*. 2001;345(3):232]. *N Engl J Med*. 2001;344(14):1038-1042.
30. Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood*. 2002;100(6):1965-1971.
31. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood*. 2002;99(6):1986-1994.
32. Graham ML. Pegaspargase: a review of clinical studies. *Adv Drug Deliver Rev*. 2003;55(10):1293-302.
33. Dinndorf PA, Gootenberg J, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: pegaspargase (Oncaspar) for the first-line treatment of children with acute lymphoblastic leukemia (ALL). *Oncologist*. 2007;12(8):991-998.
34. Jeha S, Razzouk B, Rytting M, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute myeloid leukemia. *J Clin Oncol*. 2009;27(26):4392-4397.
35. Kantarjian H, Pasquini R, Hamerschlak N, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: a randomized phase 2 trial. *Blood*. 2007;109(12):5143-5150.
36. Apperley JF, Cortes JE, Kim DW, et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START A trial. *J Clin Oncol*. 2009;27(21):3472-3479.
37. Kantarjian H, Pasquini R, Lévy V, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R). *Cancer*. 2009;115(18):4136-4147.
38. Kantarjian H, Cortes J, Kim D-W, et al. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. *Blood*. 2009;113(25):6322-6329.
39. Guilhot F, Druker B, Larson RA, et al. High rates of durable response are achieved with imatinib after treatment with interferon alpha plus cytarabine: results from the International Randomized Study of Interferon and ST1571 (IRIS) trial. *Haematologica*. 2009;94(12):1669-1675.
40. Druker BJ, Guilhot F, O'Brien SG, et al; IRIS Investigators. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006;355(23):2408-2417.
41. Cohen MH, Johnson JR, Pazdur R. US Food and Drug Administration Drug Approval Summary: conversion of imatinib mesylate (ST1571; Gleevec) tablets from accelerated approval to full approval. *Clin Cancer Res*. 2005;11(1):12-19.
42. Hehlmann R, Heimpel H, Hasford J, et al. Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. *Blood*. 1994;84(12):4064-4077.
43. Allan NC, Richards SM, Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukaemia: improved survival irrespective of cytogenetic response: the UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukaemia. *Lancet*. 1995;345(8962):1392-1397.
44. Baccarani M, Rosti G, de Vivo A, et al; Italian Cooperative Study Group on Myeloid Leukemia. A randomized study of interferon-alpha versus interferon-alpha and low-dose arabinosyl cytosine in chronic myeloid leukemia. *Blood*. 2002;99(5):1527-1535.
45. Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia: the Italian Cooperative Study Group on Chronic Myeloid Leukemia. *N Engl J Med*. 1994;330(12):820-825.
46. Ohnishi K, Ohno R, Tomonaga M, et al. A randomized trial comparing interferon-alpha with busulfan for newly diagnosed chronic myelogenous leukemia in chronic phase. *Blood*. 1995;86(3):906-916.
47. Ohnishi K, Tomonaga M, Kamada N, et al. A long term follow-up of a randomized trial comparing interferon-alpha with busulfan for chronic myelogenous leukemia: the Kouseisho Leukemia Study Group. *Leukemia Res*. 1998;22(9):779-786.
48. Lipton JH, Khoroshko N, Golenkov A, et al; Pegasys CML Study Group. Phase II, randomized, multicenter, comparative study of peginterferon-alpha-2a (40 kD) (Pegasys) versus interferon alpha-2a (Roferon-A) in patients with treatment-naïve, chronic-phase chronic myelogenous leukemia. *Leuk Lymphoma*. 2007;48(3):497-505.
49. Berger U, Engelich G, Maywald O, et al; German CML-Study Group. Chronic myeloid leukemia in the elderly: long-term results from randomized trials with interferon alpha. *Leukemia*. 2003;17(9):1820-1886.
50. Kloke O, Wandl U, Opalka B, et al. A prospective randomized comparison of single-agent interferon (IFN)-alpha with the combination of IFN-alpha and low-dose IFN-gamma in chronic myelogenous leukaemia. *Eur J Haematol*. 1992;48(2):93-98.
51. Jabbour E, Cortes J, Kantarjian H. Nilotinib for the treatment of chronic myeloid leukemia: an evidence-based review. *Core Evid*. 2010;4:207-213.
52. Saglio G, Kim DW, Issaragrisil S, et al; ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2251-2259.
53. Richardson PG, Sonneveld P, Schuster MW, et al; Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2005;352(24):2487-2498.
54. Orłowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol*. 2007;25(25):3892-3901.
55. San Miguel JF, Schlag R, Khuageva NK, et al; VISTA Trial Investigators. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med*. 2008;359(9):906-917.
56. Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol*. 2010;28(13):2259-2266.

57. Kane RC, Farrell AT, Sridhara R, Pazdur R. United States Food and Drug Administration approval summary: bortezomib for the treatment of progressive multiple myeloma after one prior therapy. *Clin Cancer Res.* 2006;12(10):2955-2960.
58. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR; Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2006;24(3):431-436.
59. Rajkumar SV, Rosiñol L, Hussein M, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. *J Clin Oncol.* 2008;26(13):2171-2177.
60. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol.* 2002;20(10):2429-2440.
61. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al; International Vidaza High-Risk MDS Survival Study Group. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. *Lancet Oncol.* 2009;10(3):223-232.
62. Fenaux P, Gattermann N, Seymour JF, et al. Prolonged survival with improved tolerability in higher-risk myelodysplastic syndromes: azacitidine compared with low dose ara-C [published correction appears in *Br J Haematol.* 2010;149(6):919]. *Br J Haematol.* 2010;149(2):244-249.
63. Kaminski E, Farrell AT, Wang Y-C, Sridhara R, Pazdur R. FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. *Oncologist.* 2005;10(3):176-182.
64. Kantarjian H, Issa JPJ, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer.* 2006;106(8):1794-1803.
65. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346(4):235-242.
66. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol.* 2006;24(19):3121-3127.
67. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood.* 2005;106(12):3725-3732.
68. Forstpointner R, Dreyling M, Repp R, et al; German Low-Grade Lymphoma Study Group. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood.* 2004;104(10):3064-3071.
69. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood.* 2005;105(4):1417-1423.
70. Pfreundschuh M, Trümper L, Osterborg A, et al; MabThera International Trial Group. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomized controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2006;7(5):379-391.
71. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *J Clin Oncol.* 2005;23(9):1984-1992.
72. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol.* 2002;20(10):2453-2463.
73. Gordon LI, Witzig T, Molina A, et al. Yttrium 90-labeled ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with previously treated B-cell lymphoma. *Clin Lymphoma.* 2004;5(2):98-101.
74. Witzig TE, Molina A, Gordon LI, et al. Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan. *Cancer.* 2007;109(9):1804-1810.
75. Keilholz U, Punt CJA, Gore M, et al. Dacarbazine, cisplatin, and interferon- α -2b with or without interleukin-2 in metastatic melanoma: a randomized phase III trial (18951) of the European Organisation for Research and Treatment of Cancer Melanoma Group. *J Clin Oncol.* 2005;23(27):6747-6755.
76. Hauschild A, Garbe C, Stolz W, et al. Dacarbazine and interferon alpha with or without interleukin 2 in metastatic melanoma: a randomized phase III multicentre trial of the Dermatologic Cooperative Oncology Group (DeCOG). *Br J Cancer.* 2001;84(8):1036-1042.
77. Agarwala SS, Glaspy J, O'Day SJ, et al. Results from a randomized phase III study comparing combined treatment with histamine dihydrochloride plus interleukin-2 versus interleukin-2 alone in patients with metastatic melanoma. *J Clin Oncol.* 2002;20(1):125-133.
78. Wong SF. Oral bexarotene in the treatment of cutaneous T-cell lymphoma. *Ann Pharmacother.* 2001;35(9):1056-1065.
79. Prince HM, Duvic M, Martin A, et al. Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. *J Clin Oncol.* 2010;28(11):1870-1877.
80. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon α -2a, or both in metastatic renal-cell carcinoma. *N Engl J Med.* 1998;338(18):1272-1278.
81. McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2005;23(1):133-141.
82. Negrier S, Perol D, Ravaud A, et al; for The French Immunotherapy Intergroup. Medroxyprogesterone, interferon α -2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis, results of a randomized controlled trial. *Cancer.* 2007;110(11):2468-2477.
83. Jayson GC, Middleton M, Lee SM, Ashcroft L, Thatcher N. A randomized phase II trial of interleukin 2 and interleukin 2-interferon α in advanced renal cancer. *Br J Cancer.* 1998;78(3):366-369.
84. Atkins MB, Sparano J, Fisher RI, et al. Randomized phase II trial of high-dose interleukin-2 either alone or in combination with interferon α -2b in advanced renal cell carcinoma. *J Clin Oncol.* 1993;11(4):661-670.
85. Donskov F, Middleton M, Fode K, et al. Two randomised phase II trials of subcutaneous interleukin-2 and histamine dihydrochloride in patients with metastatic renal cell carcinoma. *Br J Cancer.* 2005;93(7):757-762.
86. Reeves DJ, Liu CY. Treatment of metastatic renal cell carcinoma. *Cancer Chemother Pharmacol.* 2009;64(1):11-25.
87. Dutcher JP, Atkins M, Fisher R, et al. Interleukin-2-based therapy for metastatic renal cell cancer: the Cytokine Working Group experience, 1989-1997. *Cancer J Sci Am.* 1997;3(suppl 1):S73-S78.
88. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon α -2a in patients with metastatic renal cell carcinoma [published correction appears in *J Clin Oncol.* 2009;27(13):230]. *J Clin Oncol.* 2009;27(8):1280-1289.
89. Escudier B, Eisen T, Stadler WM, et al; TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma [published correction appears in *N Engl J Med.* 2007;357(2):203]. *N Engl J Med.* 2007;356(2):125-134.
90. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol.* 2009;27(20):3312-3318.
91. Kane RC, Farrell AT, Saber H, et al. Sorafenib for the treatment of advanced renal cell carcinoma. *Clin Cancer Res.* 2006;12(24):7271-7278.
92. Hudes G, Carducci M, Tomczak P, et al; Global ARCC Trial. Temsirolimus, interferon α , or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007;356(22):2271-2281.
93. Ferrandina G, Ludovigli M, Lorusso D, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. *J Clin Oncol.* 2008;26(6):890-896.
94. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol.* 2001;19(14):3312-3322.
95. Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in

- patients with platinum-resistant ovarian cancer. *J Clin Oncol*. 2007;25(19):2811-2818.
- 96. Alberts DS, Liu PY, Wilczynski SP, et al; Southwest Oncology Group.** Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group protocol S0200). *Gynecol Oncol*. 2008;108(1):90-94.
- 97. Markman M, Moon J, Wilczynski S, et al.** Single agent carboplatin versus carboplatin plus pegylated liposomal doxorubicin in recurrent ovarian cancer: final survival results of a SWOG (S0200) phase 3 randomized trial. *Gynecol Oncol*. 2010;116(3):323-325.
- 98. Thigpen JT, Aghajanian CA, Alberts DS, et al.** Role of pegylated liposomal doxorubicin in ovarian cancer. *Gynecol Oncol*. 2005;96(1):10-18.
- 99. Holli K, Valavaara R, Blanco G, et al.** Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer: Finnish Breast Cancer Group. *J Clin Oncol*. 2000;18(20):3487-3894.
- 100. Pyrhönen S, Valavaara R, Modig H, et al.** Comparison of toremifene and tamoxifen in post-menopausal patients with advanced breast cancer: a randomized double-blind, the 'nordic' phase III study. *Br J Cancer*. 1997;76(2):270-277.
- 101. Kaufmann M, Bajetta E, Dirix LY, et al.** Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. *J Clin Oncol*. 2000;18(7):1399-1411.
- 102. Paridaens R, Dirix L, Lohrisch C, et al; European Organization for the Research and Treatment of Cancer (EORTC)-Investigational Drug Branch for Breast Cancer (IDBBC).** Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. *Ann Oncol*. 2003;14(9):1391-1398.
- 103. Paridaens RJ, Dirix LY, Beex LV, et al.** Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol*. 2008;26(30):4883-4890.
- 104. Ranganathan A, Moore Z, O'Shaughnessy JA.** Phase III trial comparing fulvestrant with exemestane in patients with advanced breast cancer in whom previous nonsteroidal aromatase inhibitor therapy has failed. *Clin Breast Cancer*. 2007;7:446-447.
- 105. Chia S, Gradishar W, Mauriac L, et al.** Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol*. 2008;26(10):1664-1670.
- 106. Mauriac L, Romieu G, Bines J.** Activity of fulvestrant versus exemestane in advanced breast cancer patients with or without visceral metastases: data from the EFECT trial. *Breast Cancer Res Treat*. 2009;117(1):69-75.
- 107. Coombes RC, Hall E, Gibson LJ, et al; Intergroup Exemestane Study.** A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med*. 2004;350(11):1081-1092.
- 108. Campos SM, Guastalla JP, Subar M, Abreu P, Winer EP, Cameron DA.** A comparative study of exemestane versus anastrozole in patients with postmenopausal breast cancer with visceral metastases. *Clin Breast Cancer*. 2009;9(1):39-44.
- 109. Lønning PE, Geisler J.** Experience with exemestane in the treatment of early and advanced breast cancer. *Expert Opin Drug Metab Toxicol*. 2008;4(7):987-997.
- 110. Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group.** Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996.
- 111. Mirimanoff RO, Gorlia T, Mason W, et al.** Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. *J Clin Oncol*. 2006;24(16):2563-2569.
- 112. Blanke CD, Rankin C, Demetri GD, et al.** Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the Kit receptor tyrosine kinase: S0033. *J Clin Oncol*. 2008;26(4):626-632.
- 113. Demetri GD, von Mehren M, Blanke CD, et al.** Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002;347(7):472-480.
- 114. Cohen MH, Farrell A, Justice R, Pazdur R.** Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Oncologist*. 2009;14(2):174-180.
- 115. Cheng AL, Kang YK, Chen Z, et al.** Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10(1):25-34.
- 116. Llovet JM, Ricci S, Mazzaferro V, et al; SHARP Investigators Study Group.** Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378-390.
- 117. Rimassa L, Santoro A.** Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. *Expert Rev Anticancer Ther*. 2009;9(6):739-745.
- 118. Keating GM, Santoro A.** Sorafenib, a review of its use in advanced hepatocellular carcinoma. *Drugs*. 2009;69(2):223-240.
- 119. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al.** Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 2003;21(14):2636-2644.
- 120. Jassem J, Ramlau R, Santoro A, et al.** Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol*. 2008;26(10):1698-1704.
- 121. Haziara M, White RM Jr, Booth BP, et al.** Pemetrexed in malignant pleural mesothelioma. *Clin Cancer Res*. 2005;11(3):982-992.
- 122. Kattan MW, Inoue Y, Giles FJ, et al.** Cost-effectiveness of interferon-alpha and conventional chemotherapy in chronic myelogenous leukemia. *Ann Intern Med*. 1996;125(7):541-548.
- 123. Liberato NL, Quaglini S, Barosi G.** Cost-effectiveness of interferon alfa in chronic myelogenous leukemia. *J Clin Oncol*. 1997;15(7):2673-2682.
- 124. Messori A.** Cost-effectiveness of interferon in chronic myeloid leukaemia: analysis of four clinical studies. *Ann Oncol*. 1998;9(4):389-396.
- 125. Beck JR, Guilhot J, Giles FJ, Aoki N, Wirt DP, Guilhot F.** Cytarabine added to interferon improves the cost-effectiveness of initial therapy for patients with early chronic phase chronic myelogenous leukemia. *Leuk Lymphoma*. 2001;41(1-2):117-124.
- 126. Gordois A, Scuffham P, Warren E, Ward S.** Cost-utility analysis of imatinib mesilate for the treatment of advanced stage chronic myeloid leukaemia. *Br J Cancer*. 2003;89(4):634-640.
- 127. Warren E, Ward S, Gordois A, Scuffham P.** Cost-utility analysis of imatinib mesylate for the treatment of chronic myelogenous leukemia in the chronic phase. *Clin Ther*. 2004;26(11):1924-1933.
- 128. Dalziel K, Round A, Garside R, Stein K.** Cost effectiveness of imatinib compared with interferon-alpha or hydroxycarbamide for first-line treatment of chronic myeloid leukaemia. *Pharmacoeconomics*. 2005;23(5):515-526.
- 129. Skrepnek GH, Ballard EE.** Cost-efficacy of imatinib versus allogeneic bone marrow transplantation with a matched unrelated donor in the treatment of chronic myelogenous leukemia: a decision-analytic approach. *Pharmacotherapy*. 2005;25(3):325-334.
- 130. Reed SD, Anstrom AJ, Ludmer JA, Glendenning GA, Schulman KA.** Cost-effectiveness of imatinib versus interferon-alpha plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia. *Cancer*. 2004;101(11):2574-2583.
- 131. Chen Z, Wang C, Xu X, Feng W.** Cost-effectiveness study comparing imatinib with interferon-alpha for patients with newly diagnosed chronic-phase (CP) chronic myeloid leukemia (CML) from the Chinese public health-care system perspective (CPHSP). *Value Health*. 2009;12(suppl 3):S85-S88.
- 132. Guest JF, Smith H, Sladkevicius E, Jackson G.** Cost-effectiveness of pentostatin compared with cladribine in the management of hairy cell leukemia in the United Kingdom. *Clin Ther*. 2009;31(pt 2):2398-2415.
- 133. Scott WG, Scott HM.** Economic evaluation of third-line treatment with alemtuzumab for chronic lymphocytic leukaemia. *Clin Drug Invest*. 2007;27(11):755-764.
- 134. Mehta J, Duff SB, Gupta S.** Cost effectiveness of bortezomib in the treatment of advanced multiple myeloma. *Manag Care Interface*. 2004;17(9):52-61.
- 135. Hoyle M, Green C, Thompson-Coon J, et al.** Cost-effectiveness of sorafenib for second-line treatment of advanced renal cell carcinoma. *Value Health*. 2010;13(1):55-60.

- 136. Hillner BE, Radice D.** Cost-effectiveness analysis of exemestane compared with megestrol in patients with advanced breast carcinoma. *Cancer*. 2001;91(3):484-489.
- 137. Lindgren P, Jönsson B, Redaelli A, Radice D.** Cost-effectiveness analysis of exemestane compared with megestrol in advanced breast cancer. *Pharmacoeconomics*. 2002;20(2):101-108.
- 138. Lundkvist J, Wilking N, Holmberg S, Jönsson L.** Cost-effectiveness of exemestane versus tamoxifen as adjuvant therapy for early-stage breast cancer after 2-3 years treatment with tamoxifen in Sweden. *Breast Cancer Res Treat*. 2007;102(3):289-299.
- 139. Huse DM, von Mehren M, Lenhart H, et al.** Cost effectiveness of imatinib mesylate in the treatment of advanced gastrointestinal stromal tumours. *Clin Drug Investig*. 2007;27(2):85-93.
- 140. Contreras-Hernández I, Mould-Quevedo JF, Silva A, et al.** A pharmaco-economic analysis of second-line treatment with imatinib or sunitinib in patients with advanced gastrointestinal stromal tumours. *Br J Cancer*. 2008;98(11):1762-1768.
- 141. Mabasa VH, Taylor SCM, Chu CCY, et al.** Verification of imatinib cost-effectiveness in advanced gastrointestinal stromal tumor in British Columbia (VINCE-BC study). *J Oncol Pharm Pract*. 2008;14(3):105-112.
- 142. Cordony A, Le Reun C, Smala A, Symanowski JT, Watkins J.** Cost-effectiveness of pemetrexed plus cisplatin: malignant pleural mesothelioma treatment in UK clinical practice. *Value Health*. 2008;11(1):4-12.
- 143. Tsimberidou AP, Braiteh F, Stewart DJ, Kurzrock R.** Ultimate fate of oncology drugs approved by the US Food and Drug Administration without a randomized trial. *J Clin Oncol*. 2009;27(36):6243-6250.
- 144. Miller FG, Pearson SD.** Coverage with evidence development: ethical issues and policy implications. *Med Care*. 2008;46(7):746-751.
- 145. Carlson JJ, Sullivan SD, Garrison LP, Neumann PJ, Veenstra DL.** Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy*. 2010;96(3):179-190.
- 146. Claxton K, Neumann PJ, Araki S, Weinstein MC.** Bayesian value-of-information analysis: an application to a policy model of Alzheimer's disease. *Int J Technol Assess*. 2001;17(1):38-55.
- 147. Claxton K, Cohen JT, Neumann PJ.** When is evidence sufficient? *Health Aff (Millwood)*. 2005;24(1):93-101.
- 148. Garrison LP.** Regulatory benefit-risk assessment and comparative effectiveness research: strangers, bedfellows or strange bedfellows? *Pharmacoeconomics*. 2010;28(10):855-865.
- 149. Garrison LP, Towse A, Bresnahan BW.** Assessing a structured, quantitative health outcomes approach to drug risk-benefit analysis. *Health Aff (Millwood)*. 2007;26(3):684-695. ■