Methods Research Report

Progression-Free Survival: What Does It Mean for Psychological Well-Being or Quality of Life?

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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10058-I

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AHRQ Publication No. 13-EHC074-EF
April 2013

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Gutman SI, Piper M, Grant MD, Basch E, Oliansky DM, Aronson N. Progression-Free Survival: What Does It Mean for Psychological Well-Being or Quality of Life? Methods Research Report. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC074-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodological issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers, as well as the health care system as a whole, by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Claudia J. Bonnell, M.L.S., B.S.N.; Jennifer Brock, M.P.H.; Lisa Garofalo, B.A.; Lisa Sarsany, M.A.; and Kathleen M. Ziegler, Pharm.D.

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Progression-Free Survival: What Does It Mean for Psychological Well-Being or Quality of Life?

Structured Abstract

Background. Progression-free survival (PFS), defined as the time from random assignment in a clinical trial to disease progression or death from any cause, has recently become an endpoint of considerable interest in the study of new oncology drugs. In comparison to overall survival (OS), the gold standard for cancer drug evaluation, PFS can be evaluated using shorter, smaller and less costly studies. Its use as a primary endpoint, however, can be challenging, as it is subject to a wide range of potential biases, and its use as a surrogate for OS has been demonstrated only for certain disease and treatment scenarios. The objective of this methods project is to address whether PFS is an outcome related to psychological well-being or quality of life (QOL).

Methods. Two Key Questions (KQ) were posed: (1) when PFS is used as a primary clinical endpoint in treating patients with advanced cancer, is there direct evidence that knowing PFS impacts patient anxiety, depression, or psychological well-being, and (2) for agents where PFS is the primary outcome measure being used to establish the performance (efficacy and safety) of a new drug, what evidence exists on the association of PFS with QOL and related outcomes, such as disease symptoms? A Technical Expert Panel (TEP) was convened to refine the KQs, comment on the methodological approach, and identify publications. The literature search for KQ1 sought to identify studies that showed a causal relationship between PFS and improvement on measures of psychological well-being. The search was not limited by tumor type or study design. KQ2, which addressed the association between PFS and QOL, was designed to indirectly answer KQ1, as a low yield of relevant articles was expected from the initial search. The literature search for KQ2 included terms for drugs approved by one or more regulatory agencies on the basis of PFS outcomes for treatment of solid tumor disease between 2005 and 2010, including Avastin®, Ixempra®, Tykerb®, Vectibix®, Doxil®, Gemzar®, Yondelis®, Nexavar®, Votrient®, Sutent®, Tarceva®, and Taxotere®. Both KQ searches were conducted in MEDLINE®, PubMed, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL). From relevant articles, information was abstracted and summarized in data tables on study characteristics, treatment efficacy and safety, patient-reported outcome measure descriptions, and the PFS/QOL association. A quality assessment of the included individual studies was conducted to identify potential biases in the measurement of either PFS and/or QOL.

Results. No studies were identified that addressed KQ1. There was no direct evidence demonstrating that knowing PFS status impacts patient anxiety, depression, or psychological well-being. KQ2 sought to determine an association between PFS and QOL or related outcomes, such as disease symptoms, and four studies were identified that provided such evidence. The four studies demonstrated better QOL or disease symptoms among patients who remained progression-free compared with those who had disease progression. Study design limitations resulted in a poor quality rating for all four studies, and the strength of the evidence was insufficient. Common study limitations included significant data missing not at random, failure to evaluate patient-reported outcomes beyond the window of PFS, and lack of patients and investigator blinding to treatment.

Discussion. The objective of this methods project was to determine whether PFS is an outcome related to psychological well-being or QOL. It focused on the relationship between PFS, an *outcome*, and other *outcomes* of importance to patients. In contrast to a traditional comparison of *interventions*, the variable of interest, PFS, is somewhat problematic, because the presence or absence of progression can only be observed, precluding the ability to design a prospective randomized clinical trial. Defining the relationship between PFS and QOL or other patient-reported outcomes (PRO) involves considering data as if obtained from observational study. A model is provided, including potentially important causal and confounding relationships, for considering further study of the relation between PFS and QOL-related outcomes.

Evidence gaps. There is a need for prospective research to evaluate: (1) any causal relationship between patient knowledge of PFS status with QOL or related PRO; (2) patient impressions of the meaningfulness of PFS as an outcome in the absence of association with OS; and (3) the extent to which improvement in QOL measures associated with progression-free status is related to a common underlying mechanism.

Conclusion. There is insufficient evidence to make any conclusion about the association between PFS and QOL. In cases when measurement of OS is unfeasible, the direct measurement of both PFS and QOL may be a practical and informative alternative strategy.

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Background

Progression-free survival (PFS) is defined as the time from random assignment in a clinical trial to disease progression or death from any cause. PFS as an outcome is of interest to a variety of disciplines, most especially, for purposes of this project, to oncologists, pharmacologists, trialists, social scientists, and other scientists with interest in designing or interpreting clinical trials. This background section addresses how PFS is used, its role as a surrogate for overall survival (OS), the challenges it presents in obtaining accurate and reproducible measurements, and finally its role as a health outcome.

Overall Survival

This section briefly reviews the use of OS as a standard outcome, and the reasons why other survival outcomes, such as PFS, have garnered interest from the clinical research community. OS has long been considered by the Food and Drug Administration (FDA) and the European Medicines Agency as the gold standard for the evaluation of new oncologic therapies.[1] It is defined as the time from random assignment to the date of death due to any cause, or to the date of censoring at the last time the subject was known to be alive in intention-to-treat populations. OS is "an unambiguous endpoint measure because it is evaluated on a continuous time scale, which gives precise accuracy for the time of the event."[2]

However, the use of OS can be challenging. For example, if survival is only incrementally improved by a new treatment, the demonstration of increased OS may require large patient populations, several years of accrual and followup, and higher costs.[3, 4] This is especially true if the natural history of the disease course is lengthy.

The Growing Interest in PFS

Over the past 10 years there has been increasing interest in the use of outcomes other than OS to study new drugs, including PFS. The interest in PFS stems in part from the challenges associated with OS as an endpoint, but it has also been fueled by the fact that many new drugs are targeted toward molecular mechanisms of action that are cytostatic rather than cytotoxic. These drugs are not expected to provide the same objective response rates of earlier drugs, and instead act to prevent progression rather than cause tumors to regress and thereby impact mortality. Interest in PFS has also been sparked by the increasingly common use of treatment paradigms that allow for multiple rounds of drug treatment (first-, second-, third-, and even fourth-stage therapies), each producing incremental changes difficult to capture in the context of a single study using OS as the primary endpoint. In contrast, PFS can be studied in the short-term context of each treatment, without the confounding influence of the next. The FDA has recently published a regulation (21CFR813, subpart H) that allows the use of PFS or other surrogate clinical endpoints other than survival or irreversible morbidity in the accelerated approval of new drugs for serious or life-threatening illnesses.

While this methods project focuses specifically on PFS, it is recognized that there is widespread interest in a number of alternative endpoints, including disease-free survival, relapse-free survival, time to progression, and objective response rate. For informational interest, definitions of these can be found in Appendix A.

Relationship of PFS to OS

The Issue of Surrogacy

The term "clinical endpoint" has been defined by the Biomarkers Definition Working Group as an outcome that measures how a patient feels, functions, or survives.[5] The term "surrogate endpoint" is an outcome measure that has been validated as an adequate substitute for the clinical endpoint. Ideally, identification of a surrogate endpoint in a drug study provides a reliable signal that the clinical endpoint of the study has been met. Surrogate endpoints may be laboratory variables, single measures of disease activity (recurrence, progression, etc.), or composite measures of disease activity. It is important to note that the validation of a surrogate endpoint requires evidence that goes beyond merely showing a statistical association between the surrogate and clinical endpoints. As noted by Shi and Sargent,[6] as a guiding principle, "the treatment effect observed on a valid surrogate endpoint (substitute) should reliably and precisely predict the treatment effect on the clinical endpoint (entity being replaced)." A number of statistical methodologies can be used, including hypothesis testing,[7] estimation and prediction,[8, 9] and meta-analytical approaches.[6]

PFS as a Surrogate for OS

Considerable interest has been focused on the use of PFS as a surrogate endpoint for predicting OS. It is now recognized that the correlation between PFS and OS is both variable and unpredictable and depends on tumor type and tumor stage, as well as the particular drug being investigated.[6] That PFS is not always a reliable surrogate for OS is not entirely surprising, given that the tumor pathways affected by new drugs and the nature of drug and tumor interaction, as well as drug toxicity, are often incompletely known.

Broglio and Berry[10] have recently performed simulation studies partitioning OS into two parts, the first PFS, and the second what they call survival post-progression (SPP). They defined SPP as OS minus PFS. Using preset 6- and 9-month medians for PFS in each arm of a hypothetical two-arm study, they concluded that a statistically significant increase in OS was detected with 90 percent probability if median SPP was 2 months, but less than 20 percent if median SPP was 24 months. They recommended PFS be used as a primary endpoint only when median SPP is short. These conclusions are confirmed by Amir et al.,[11] who evaluated 26 studies of chemotherapy for solid tumors in which a hazard ratio was reported for both OS and PFS (or time to progression, related to PFS, see definition, Appendix A). They also found a higher correlation between OS and PFS when SPP is short than when SPP is long. However, even in instances in which SPP was less than 12 months, they identified only a moderate correlation coefficient of 0.64 between PFS and OS.

PFS as an OS Surrogate for Specific Cancers

Efforts to establish PFS as a surrogate for OS in oncology trials have had variable results depending on the specific cancer. For example, several studies have shown that PFS is a valid surrogate for OS in colorectal cancer,[12-15] and it has been argued that PFS is a reasonable primary endpoint for the disease on its own merit.[16, 17] Similar conclusions have been reached about PFS as a surrogate for OS in first-line therapy for ovarian cancer.[18-20] Expert panelists at two major workshops agreed, however, that the PFS to OS relationship with regard to ovarian cancer may

be different for different patient groups or for first-line compared with second- or third-line therapy.[18, 20]

Contrary to the relative success of PFS as a surrogate endpoint in first-line treatment of colorectal and ovarian cancer, a strong relationship between PFS and OS has not been demonstrated in studies of metastatic breast cancer.[4, 12, 14, 21]

Depending on the toxicity of a new drug that has been found to increase PFS, it is possible to postulate scenarios in which treatment accelerates both psychological and physical morbidity, resulting in decreased patient quality of life (QOL). In the worst case scenario, use of a drug to increase PFS may have the unanticipated downside of actually compromising the balance between tumor and patient resistance to tumor, causing a shorter rather than a longer duration in OS. As witnessed in the recent FDA decision to remove the indication for use of bevacizumab (Avastin®, Genentech/Roche) in breast cancer, there are strong feelings about both the use and interpretation of PFS, as well as differing opinions on the risk-to-benefit value of drug efficacy and toxicity.

Issues in the Measurement and Reporting of PFS

There are several potential sources of measurement bias or variability in studies using PFS as a primary endpoint. Potential for bias should be addressed prospectively in trial designs to ensure the validity of any differences in PFS found between treatment arms.[3, 22-25] This section describes the main sources of potential bias, as well as suggested mechanisms for controlling their impact. In addition to discussing four major sources of bias, including assessment, evaluation, performance, and attrition, the role of detection error is also described. Like bias, this measurement issue can lead to incorrect conclusions about the performance of drugs.

Assessment Bias

The exact date of progression cannot be known, since it is determined based on the types and timing of assessments. At the point in time that progression is identified, it is only known that this event occurred at some point between the last negative evaluation and the one at which this reclassification of disease status occurs. In general, the date of first progression is taken as the date of the evaluation at which progression was first evident, which is likely to be an overestimate of PFS. As Panageas et al.[26] have recently noted, in a trial this overestimation of median PFS can lead to erroneous conclusions about new treatments, suggesting benefits that in fact may not actually exist.

Use of the last date the patient was identified to be progression-free or an intermediate interval, such as the midpoint between the two dates, has been considered as possible alternative or additional mechanisms for reporting PFS. The former may underestimate PFS and the latter, like the date of first identification, likely overestimates PFS. According to Panageas et al.,[26] what is important in capturing an accurate PFS measurement is the timing of the measurement interval in relationship to the true median PFS. They suggested PFS be characterized using interval reporting in which estimates of this event are characterized by the time interval in which they occur. Zhuang et al.,[25] recommended that the assessment interval not exceed the expected improvement in median PFS in the experimental versus control arm.

Freidlin et al.[27] recommended the use of two preselected scan timepoints with strictly chosen schedule limits, instead of multiple regular testing intervals. For optimal evaluation of performance, they suggested the selected timepoints represent the median PFS and twice the

median PFS expected in the control arm of a study, and that a significance test of the difference in PFS rates at the two scan timepoints be assessed on the grouped data.

It is important to note that progression may be detected as a result of the occurrence of symptoms which cause the patient to receive what would otherwise be an unscheduled imaging exam. These unforeseen events clearly must be addressed in the protocol of studies and data should be collected and analyzed in a manner that accounts for them.

Evaluation Bias

Another timing bias has to do with unevenness in the timing of tumor assessment between the two treatment arms. This can result in progression being identified earlier in one arm than the other, even when there is no actual difference in efficacy.[3, 25] Asymmetry can result when assessments are scheduled around the treatment cycle and one arm has more cycle delays than the other, or when there is disparity in unscheduled or missed visits between the two treatment arms. Small treatment-related differences in measurement time (as short as 2 days) have been reported to result in false study conclusions.

For a reliable measurement, patients must be evaluated on a regular and balanced basis across treatment arms. While most well-designed comparative studies address this issue, they should still be monitored for asymmetry. It is important to report and analyze progression events confirmed at preplanned timepoints and at unscheduled visits. One statistical technique for assessing this form of bias is to perform sensitivity analyses to examine the strength of a positive result in a clinical trial relative to the sources of bias.[28]

Performance Bias

The patient's response to treatment or progression status may be influenced by knowledge of the treatment arm.[3, 29, 30] Physicians treating patients in an experimental drug study may believe the drug offers the best treatment outcome, and as a result are inclined to under-diagnosis progression, leaving patients on the experimental drug for a longer period of time. Conversely, physicians may over-diagnose progression in patients receiving control therapy in order to assure an opportunity for cross-over to the experimental drug.

The ideal mechanism for addressing performance bias is to perform a double-blinded study. Unfortunately, because of differences in drug administration or in the toxic profiles of treatments, blinding is not always possible. One mechanism for addressing bias in local evaluations, particularly in studies using standardized radiologic endpoints, is use of blinded independent central review (BICR).[3, 24, 29, 30] Radiological images being evaluated are blindly and independently reviewed by an outside centralized, often expert, group of readers. Conditions for reading are standardized as much as possible (e.g., images are evaluated serially to assure changes from baseline are carefully tracked).

Although recommended in regulatory guidance,[31] BICR has generated some controversy because of its complexity and cost.[24, 29, 32] In addition, depending on the timing of central review, discrepancies in evaluation of progression between local and central reviews can lead to informative censoring (i.e., removal of patients from study who were identified as progressed by local evaluators, but not confirmed by central review), leading to potential bias. Suggestions to address this problem include performing BICR in real time and feeding back results to local study sites or designing studies to allow for continued evaluation of progression for at least one scan after local progression is called.

Tang et al.[33] studied eight trials using PFS as an endpoint comparing results of local evaluations with those of BICR. They concluded that although benefits of treatment could be quite variable (-2 to 2.4 months), there was no evidence of systemic bias. Amit et al.,[34] in a meta-analysis of 27 blinded studies with independent central review of progression performed by the Pharmaceutical Research and Manufacturers Association, reported a strong correlation between local evaluation and BICR. They concluded that when studies are blinded, and/or when large study size effects are anticipated, a BICR might not be warranted. They described a sample-based approach to BICR that defines early and late discrepancy rates between local and central review. Although they did not define a threshold for differential discordance, they suggested this discordance be used in decision-making about whether a full BICR is necessary. Unfortunately, it appears that small, but potentially significant differences (up to 15 percent discordance) are not detected by their approach.[32]

Attrition Bias

When too many patients withdraw from a study or are lost to followup, and when losses are not at random, remaining results may be biased. This is especially problematic when attrition is greater in one arm than the other.[3, 25] PFS data are censored at the time of last available assessment, so the proportion of censored patients should be reported for both treatment arms, along with the reasons for censorship. Short assessment intervals and ongoing physician and patient education regarding the goal of treatment have been found to help minimize patient withdrawal and loss to followup.[25] Sensitivity analysis can be performed to look at various subgroups of patients subject to attrition bias, as well as the effect of attrition bias in total, to assess the impact of this bias on study conclusions.[28]

Detection Error

PFS is most commonly a composite endpoint including radiologic progression, death, and in some cases, nonradiologic criteria, such as symptomatic progression. While death is an absolute endpoint, radiologic progression is a subjective measurement prone to reading errors by the radiologist. Errors in identification of these endpoints are referred to as detection errors.

Dancey et al.,[3] have identified four criteria to establish progression: the appearance of new radiologic lesions; an increase in the size of measurable target lesions; a clear, unequivocal increase in nontarget disease; and/or worsening of nonradiologic signs and symptoms.

There are numerous caveats associated with these criteria. New radiologic lesions, for example, must be unequivocal and significant enough in size to avoid the measurement error in the methodology being used. Oxnard et al.,[35] recently studied 30 patients with non-small cell carcinoma of the lung (1 cm or larger in size), undergoing two computed tomography (CT) scan evaluations within a 15-minute interval. All scans were read side-by-side by three radiologists. Measurement changes were within ± 10 percent for 84 percent of measurements. Changes of 20 percent or more were observed in 3 percent of measurements. They concluded that CT scan measurement of lung lesions has clinically meaningful variability and suggest caution in the interpretation of small changes in lesion size in the care of individual patients and in the interpretation of clinical trial results.

Identification of new lesions should unequivocally demonstrate a metastatic deposit. In order to be certain this is the case, baseline anatomic scanning is required to detect the presence of disease in all areas likely to be the site of metastases based on what is known about the tumor being evaluated.

Most problematic is establishing progression in disease that is detectable, but not measurable. Assessing a worsening of disease burden, such as disease-related symptoms, from a nonmeasurable baseline, is a largely subjective determination. Efforts should be directed at creating an operational definition of progression of nonmeasurable disease. Commonly, these will be imaging studies at lesion sites difficult to quantify and/or evidence of adverse events related to disease. The additional data elements identified should be relevant to the disease setting, clearly understood, collected in case report forms, and appropriately included in the analysis plan. Optimally, these elements would lend themselves to independent verification.

If changes indicating disease progression are equivocal, Dancey et al.,[3] recommend, when medically possible, that the patient remain on study until progression is unequivocal. At that time, a decision would need to be made as to whether the progression date is backdated to the first equivocal finding or recorded as the date of the unequivocal determination. Of note, measurement variability will generally not lead to study bias since it occurs in all treatment arms of the study. It is, however, likely to lead to failure to identify changes in disease status that result from use of a new drug.

PFS as a Health Outcome

Many advocates for the use of PFS as an endpoint contend that delaying tumor progression independently confers clinical benefit, since being progression-free is considered an indication of disease control and stabilization. A direct result should be stability, and perhaps even reduction, in disease symptoms, thus improving QOL for patients. While in PFS patients are spared the symptoms of progressive disease, from undergoing further treatment with additional therapies and their attendant toxicities, and from the psychological burden and uncertainty associated with disease progression.[36] In this scenario, the main impact of PFS is expected to be in QOL, which may or may not represent a causal relationship. Of interest in exploring this relationship is the question of how knowledge about PFS can impact perception of patient symptoms and other more global measures of QOL.

As noted by Fallowfield and Fleissig in their abstract, "New treatments that increase PFS may not be of sufficient value to patients with advanced-stage cancer unless accompanied by tangible quantity or QOL advantages. Any symptom relief that patients gain from treatment resulting in tumor shrinkage or stabilization must be balanced against the toxic effects that drug therapy itself creates."[37] A task force—Assessing the Symptoms of Cancer Using Patient-Reported Outcomes (ASCPRO) Multisymptom Task Force—has recently proposed that the measurement of symptomatic change, as a subset of QOL, may be a sufficient outcome in clinical trials to allow health providers, patients and regulators confidence in the use of new treatments.[38] Of note, the FDA has explicitly included a symptom benefit as an option for the pharmaceutical industry for both anticancer and supportive-care agents in its 2007 "Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics."[39]

Recent studies have used conjoint analysis to try to understand and quantify the value of PFS to patients versus avoidance of risk of toxicities. Mohamed et al.,[40] evaluated the benefit-risk preferences of patients with renal cell carcinoma, using a series of 12 tradeoff questions to determine what magnitude of PFS improvement was worth significant treatment-related risks. Patients were willing to accept significant treatment-related risks of 2 to 3 percent for liver failure and blood clot to increase PFS by 11 months.

Bridges et al.,[41] in a conjoint analysis of patients with advanced non–small-cell lung cancer, examined the tradeoffs patients were willing to make between increased PFS and the risk of

experiencing disease symptoms, such as fatigue, diarrhea, nausea and vomiting, fever, infection, and rash. They concluded the value patients attribute to an increase in PFS was conditional upon the severity of disease symptoms experienced. These studies suggest that QOL, in relation to PFS, is important to patients. As Hartzband and Groopman[42] have recently noted "basing decisions on the outcome of death ignores vital dimensions of life that are not easily quantified. …There is more to life than death."

Because PFS itself is an outcome, it is not possible to study it in the same manner applied to a drug treatment. Normally, randomization of patients to either intervention or control arms in a clinical trial ensures the equal distribution of confounding variables. However, because PFS is an outcome, it cannot be predicted in advance, and patients cannot be randomized according to its improvement or lack thereof. Thus, an important aspect to the investigation of PFS, and its impact on other outcomes of importance to patients, is an examination of how the relationship is studied and whether it is feasible to clearly define the relationship exclusive of other factors.

The objective of this methods project was to determine whether PFS is an outcome related to psychological well-being or QOL.

Methods

The Methods chapter describes the purpose and composition of the Technical Expert Panel (TEP), the Key Question (KQ) development and rationale, eligibility criteria, the search strategies used for published and gray literature, and the processes for article screening and selection, data abstraction, quality assessment, and data synthesis.

Technical Expert Panel

The TEP, a group of six individuals with particular expertise in a variety of areas directly pertinent to this methods paper, was assembled to provide input regarding the scope and execution of the project. This group included representatives of the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid, an academic oncologist, a professional advocate for cancer treatment and research (representing the American Cancer Society), a patient advocate, a social scientist, and a Task Order Officer from the Agency for Healthcare Research and Quality (AHRQ). The Blue Cross Blue Shield Technology Evaluation Center Evidence-Based Practice Center (EPC) held teleconferences with the TEP, which provided input on the scope and Key Questions of this project and helped to define parameters for the methodology of the critical appraisal performed.

Key Questions

After discussion with the TEP, two KQs were developed in an effort to evaluate evidence demonstrating progression-free survival (PFS) to be an outcome of importance to patients, or showing an association between PFS and other outcomes of importance to patients.

KQ1: PFS as an Outcome of Importance to Patients

KQ1: When PFS is used as a primary clinical endpoint in treating patients with advanced cancers, is there direct evidence that knowing PFS impacts patient anxiety, depression, or psychological well-being?

- If yes, does the manner of communicating PFS affect patient anxiety, depression, or psychological well-being?

KQ1 is focused on the direct causal relationship between knowledge of PFS status and the psychological impact on patients. This is an important question because PFS, when measured using imaging techniques, may occur as an asymptomatic event and may or may not be associated with changes in overall survival (OS). In these cases, PFS can be a stand-alone finding, and its greatest impact may be in promoting patient psychological well-being, depending on the information provided and a patient's understanding of that information.

KQ2: Associations of PFS with Quality of Life Outcomes

KQ2: For agents where PFS is the primary outcome measure being used to establish the performance (efficacy and safety) of a new drug, what evidence exists regarding the association of PFS with QOL or related outcomes, such as disease symptoms?

KQ2 is focused on the statistical association between PFS and QOL-related outcomes of importance to patients that might be observed as part of the results of a drug treatment trial. To answer KQ2 we identified a targeted sample of drugs. First, we chose the category of drugs used for treating patients with locally advanced or metastatic solid epithelial tumors (breast, ovary, colon, kidney, lung and head/neck). These high profile tumors represent an attractive study set because they exhibit variable speeds of progression, variable effect sizes, and differences in manifestations of symptoms. We identified drugs approved between 2005 and 2010, by one or more regulatory agencies, on the basis of trials using PFS as the primary endpoint for treatment of solid epithelial tumors. This timeframe was selected because it represented a unique period in time in which a relatively large number of drugs for treatment of advanced epithelial tumors were approved for use in the United States, Europe and/or Canada based on studies using PFS as an endpoint. The change in endpoints from an emphasis on objective response rate in the 1990s toward increased use of overall and progression-free survival in the 2000s is described in a series of publications by scientists at the FDA.[2, 43, 44]

The drugs identified from the selected time window included Avastin®, Ixempra®, Tykerb®, Vectibix®, Doxil®, Gemzar®, Yondelis®, Nexavar®, Votrient®, Sutent®, Tarceva®, and Taxotere® (Appendix B). We chose these drugs that received regulatory approval based on PFS because we wanted to ensure authoritative vetting of the reliability of PFS measures used in the studies. For our purposes, regulatory approval was a proxy for the reliability of the PFS measure. Thus in the reports included in this review we were able to focus on whether studies demonstrated a causal relationship or statistical association between PFS and QOL or other patient-reported outcomes (PROs). The applicability of our findings regarding PFS and its association with QOL or other PROs may perhaps be restricted to this select group of drugs and the patients who received them. However, because this sample represents almost all drugs within our category of interest, bias was expected to be minimal. It is unlikely that drugs approved using PFS either before or subsequent to the time period studies would be likely to differ substantially.

To date, the FDA has rarely used PRO data as a factor in drug approvals or labeling for patients with advanced solid epithelial cancers; however, the agency has created clear guidance on requirements for studies of PRO.[45] Measurement of meaningful differences in QOL in patients with advanced solid epithelial cancers may be a challenging task. In this population blinding is difficult, particularly if treatment is identifiable by unique toxicities.

Patients generally want to know the status of their disease and may report surprisingly good QOL even in the face of drug toxicity if there is an expectation that the drug has potential to change other outcomes for the better. For the purposes of understanding how knowledge of PFS might affect patients, we concluded measurement of global QOL is preferable to reports of specific symptoms. Our analysis did allow for PRO tools that included disease specific symptoms, these were identified in several reports studied, but the emphasis in this report was on broader measurements of patient well-being.

Eligibility Criteria

Study inclusion/exclusion criteria for KQ1 and KQ2 are outlined in Table 1 and Table 2, respectively. This methods project focuses on the causal relationship (KQ1) or association (KQ2) between PFS and QOL or other PRO.

As noted in the Background chapter, in contrast to a traditional comparison of interventions, PFS is an outcome, and as such it cannot be preselected or randomized as part of a prospective study. Thus, a new parameter appears in the inclusion/exclusion criteria; that is, "comparator outcomes," which is a modification of the traditional population, intervention, comparator, timing, and setting (PICOTS) framework. The comparator outcomes of interest are those of importance to patients, such as QOL and psychological well-being.

Table 1. Inclusion/exclusion criteria for KQ1

Category	Inclusion/Exclusion Criteria
Population	Inclusion: Patients with cancer
Interventions	Inclusion: Chemotherapy
Primary outcomes	Inclusion: PFS Exclusion: Studies without PFS as an endpoint
Comparator outcomes	Inclusion: Outcomes of importance to patients, including psychological well-being (or anxiety, depression) and quality of life
Time period	From 1999 to 2012
Setting	Oncology care settings for patients with neoplasms
Publication language	English or English language translations when available
Study designs	Clinical studies
Follow-up duration	All
Sample size	Studies of any size

PFS = progression-free survival

Table 2. Inclusion/exclusion criteria for KQ2

Category	Inclusion/Exclusion Criteria
Population	Inclusion: Patients with advanced solid epithelial cancers studied as part of a randomized clinical trial for the following targeted drugs: Avastin, Ixempra, Tykerb, Vectibix, Doxil, Gemzar, Yondelis, Nexavar, Votrient, Sutent, Tarceva, Taxotere) (see Appendix B)
Interventions	Inclusion: Chemotherapy using a drug approved for use by a U.S. Canadian, or European regulatory body based on PFS outcomes
Primary outcomes	Inclusion: PFS Exclusion: Studies not including PFS Note: Studies in which a drug also improves OS will not be excluded
Comparator outcomes	Inclusion: Outcomes of importance to patients, including psychological well-being (or anxiety, depression) and quality of life
Time period	2004 to 2012
Setting	Oncology care settings for patients with advanced solid epithelial tumors
Publication language	English or English language translations when available
Study designs	Prospective randomized clinical trials
Follow-up duration	All
Sample size	Studies of any size

PFS = progression-free survival; OS = overall survival

Literature Search

Published Literature

Literature searches were conducted in the following databases:

- MEDLINE® (via PubMed)
- Embase®
- Cochrane Central Register of Controlled Trials (CENTRAL)

The research librarian, in collaboration with the project team, developed and implemented search strategies designed to identify evidence relevant to each key question. Appendix B provides the actual terms employed in the search strategy.

To address KQ1, a comprehensive search was developed that would find any article looking for a causal relationship between knowing PFS status and outcomes of importance to patients, in particular those that affected psychological states (see KQ1, PFS as an Outcome of Importance to Patients). Databases were queried using search terms such as PFS and psychological, anxiety, and depression, in combination with terms for cancer. Accepted study designs included randomized controlled trials, observational studies, case studies, or other clinical studies. The timeframe (1999 to 2012) was selected because it represents a transition period in drug approvals, in which the FDA moved away from use of response rate or time to progression toward an increased use of OS or PFS.[2,43] Because input from the TEP suggested there would be few, if any, publications addressing KQ1, the search criteria were deliberately broad and include all tumors and most types of published studies for use as evidence, including randomized prospective clinical trials, observational studies, and case series. Editorials, commentaries, and reviews were not included as evidence, but may have contributed additional references or to the background information.

For KQ2, a targeted search strategy included the identified drugs of interest—drugs approved for treatment of advanced solid epithelial tumors based on PFS as a primary endpoint (see KQ2, Associations of PFS with Outcomes of Importance to Patients) and QOL. The search encompassed the years 2004 to 2012 and as noted above was aimed at identifying studies that included drugs approved between 2005 and 2010 (Appendix C), a period of time in which a number of drugs were approved using PFS as the primary endpoint in the newly formed Office of Oncology Drug Products at the FDA and/or by European and Canadian regulators.

The literature searches for KQs 1 and 2 were restricted to the study of humans in the English language, with the exception of published articles in other languages for which English translations were available. Previous studies have shown that excluding non–English-language studies has little impact on conclusions relative to the resources required for translation.[46, 47] The literature search was updated on July 3, 2012.

Gray Literature

The gray literature was searched for relevant studies that met the inclusion/exclusion criteria. For the purposes of this methods project, the gray literature comprises information that is not controlled by commercial publishing, including abstracts presented at major oncology meetings (e.g., the National Comprehensive Cancer Network Outcomes Database Abstracts, the Annual Congress or the American Society of Clinical Oncology Annual Meeting); U.S. regulatory documents (e.g., guidance documents on cancer endpoints and PROs, public summaries of FDA meetings on cancer endpoints or FDA new drug approval briefings packages), meeting

transcripts and materials, appeals, and clinical reviews; clinical trial registries (ClinicalTrials.gov), and documents developed and posted by European and Canadian drug regulating agencies. Because unpublished literature was not used as evidence in this project, the gray literature was used to identify potential publications in progress and for background information.

Citation Screening

Articles obtained from the searches were uploaded to an EndNote® (Thomson Reuters Corporation, New York, United States) reference manager database and then transferred to DistillerSR® (Evidence Partners Inc., Ottawa, Canada) software for study eligibility screening. Using six preset questions that reflected the inclusion criteria, two reviewers independently screened titles and abstracts, marking each of the questions as: (1) yes (eligible for full-text screening); (2) no (ineligible for inclusion); or (3) uncertain (include in full-text screening to resolve eligibility). DistillerSR® provided a report on reviewer discrepancies, which were resolved by discussion and consensus opinion; a third reviewer was consulted as needed.

Using a second set of three selection questions, two reviewers independently screened full-text articles using the same approach as above to determine eligibility for data abstraction. The title/abstract and full-text screening questions are presented in Appendix D. Although the title/abstract screening and full-text screening questions used "PRO or QOL" as the pivotal selection terms, for KQ1, reviewers included articles with reference to changes in any psychological state, such as anxiety, mood, or depression, as outcomes of importance to compare to PFS. The logic for considering QOL and, in particular, psychological outcomes is described above (see Background, PFS as a Health Outcome). For KQ2, reviewers included articles with any reference to changes in the above psychological states, plus QOL, disease symptoms, or any similar type of outcome of importance to patients.

Data Extraction

Articles were distributed among the team members for abstraction. A Microsoft Excel® spreadsheet was created and used for abstracting information from the eligible studies. Each article was abstracted by a single reviewer, with 100 percent fact-checking being completed by a second reviewer. Discrepancies were resolved by discussion and, if necessary, a third opinion was sought. The abstraction form items are presented in Appendix E.

Data Synthesis

The analysis of study data is qualitative only. No effort was made to pool results, and no quantitative assessment was performed. The unique features of the included studies were captured in separate tables describing study characteristics, treatment safety and efficacy, description of the QOL measurement, the extent of missing data and how the issue was addressed, the statistical analysis, and the description of the association between PFS and QOL or other PRO, such as disease symptoms.

A causal model, represented as a directed acyclic graph, was posited based on the associations expressed as plausible or likely by the TEP and also informed by the literature reviewed. This model is based on techniques described in Supplement 2 of a recently published draft AHRQ report.[48]

Quality Assessment of Individual Studies

To prepare for the quality assessment of included studies, existing quality assessment tools were reviewed for their applicability to the association being evaluated. In this methods project, the relationship of interest was not a comparison of treatment effects, but instead, compared two outcomes: PFS (considered the primary outcome) and other outcomes of interest to patients (considered the comparator outcomes). Owing to the nature of this focus, none of the existing quality assessment tools was judged entirely appropriate to capture the potential biases associated with this type of comparison. Accordingly, a more general approach developed and applied by Turner et al.,[49] was adopted for evaluation of internal bias (i.e., study quality). This approach entails "envisioning" an "idealized version" of a study that would be free of bias, and then compares the included study to the idealized one to identify potential sources of bias. This approach allows considering any unique aspects of questions and studies, and includes well-established sources of potential bias, including selection, performance, attrition, detection, and other sources.[50-52] Taking this approach was further justified based on its applicability to observational studies.[49] Using this approach, and with consensus among the study investigators, four additional items that specifically addressed the potential for bias in studies evaluating an association between PFS and QOL were added to the quality assessment criteria (see Appendix F).

For the quality assessment, the general qualitative principles described in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" chapter, "Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions" were applied.[53] Narrative descriptions were developed to correspond to the quality assessment of excellent, fair, and poor quality studies (Table 3). The most critical sources of potential bias were deemed to be failure to blind, significant patient drop out, and failure to provide follow-through observations after progression of disease.[54-56]

Table 3. Definitions of overall study quality ratings

Study Quality	Quality Attributes
Excellent	Adequate blinding, minimal patient attrition (20% or less), no censoring at progression, and conformance with 12 or more additional positive quality factors (Table 9)
Fair	Adequate blinding, minimal patient attrition (20% or less), no censoring at progression, and conformance with 6 or more additional positive quality factors (Table 9)
Poor	No blinding and/or more than minimal patient attrition (more than 20%) and censoring at progression

Strength of Evidence

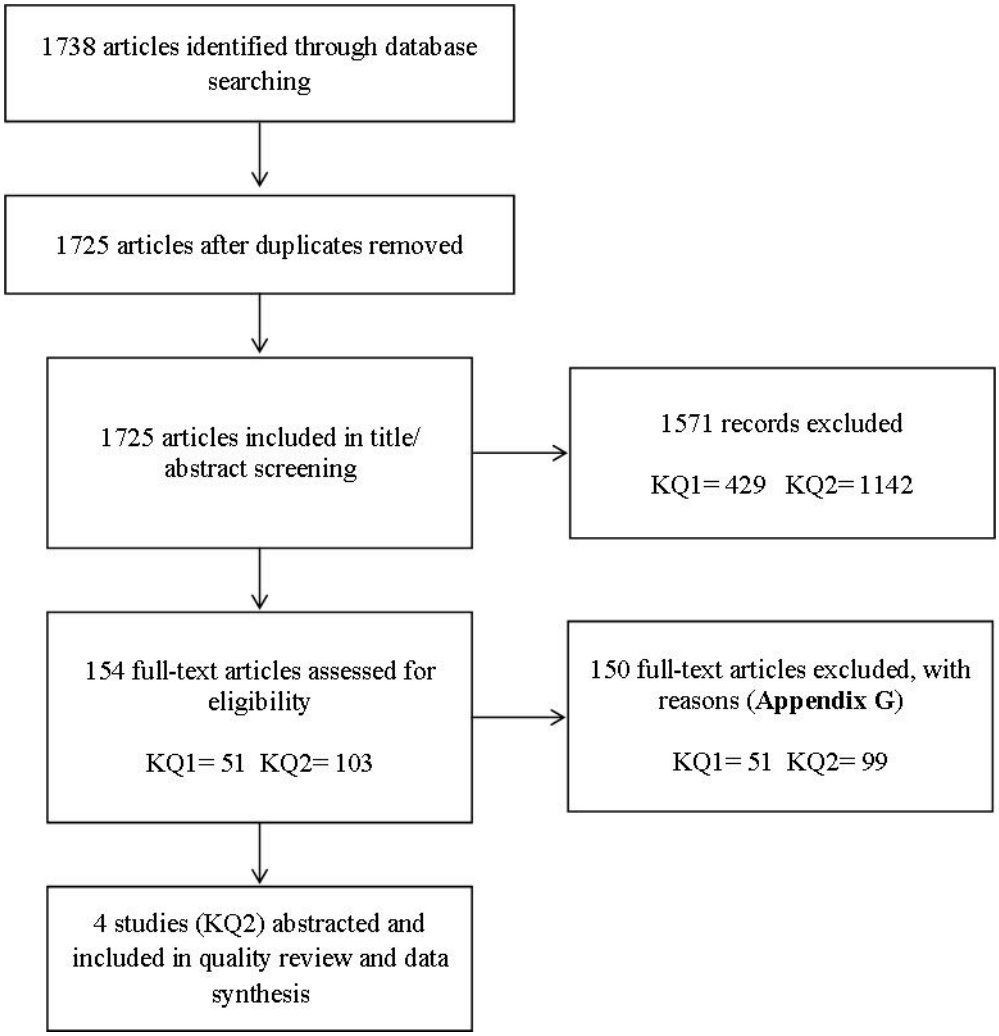
The system published by Owens et al.[57] for grading the strength of evidence was used to systematically describe the evidence in this methods project. The system considers four standard domains: risk of bias, consistency, directness, and precision. These allow for four possible grades: high, moderate, low, or insufficient.

Results

Searches of Published Literature

The initial and updated searches for published literature conducted in Medline, PubMed, Embase, and Cochrane Database of Systematic Reviews identified 1,738 citations. Figure 1 presents a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process. During title and abstract screening, 1,571 articles were excluded, and the remaining 154 articles were retrieved and evaluated at the full-text screening level. Of these, no articles were identified which addressed KQ1, and only four articles addressed KQ2. The four articles were eligible for abstraction, because they included at least one of the targeted disease/drug combinations, assessed QOL, and reported an association between PFS and QOL. Appendix G provides a list, by reason, of the 150 articles excluded during the full-text screening. After abstraction, all four studies remained eligible for quality review and data synthesis.

Figure 1. PRISMA flow diagram of study selection



KQ = Key Question

Searches of Gray Literature

The gray literature search yielded the following results:

- Regulatory Information: The search yielded a Food and Drug Administration (FDA) guidance document[39] which provided background information on cancer endpoints, including detailed information on the use of PFS, but did not specifically elucidate relationships between PFS and other endpoints of interest to patients with cancer. Similar guidelines were identified in publications by the European Medicines Agency[58] and Health Canada.[59] In addition, four FDA new drug application briefing documents, two meeting transcripts, one approval package, one clinical review, an appeals document with review response, and 13 public presentations at workshops on endpoints were reviewed. Finally, nine European regulatory scientific summaries and seven Health Canada drug Summary Basis of Decisions were reviewed. None of these specifically addressed the relationship between PFS and other outcomes of importance to patients, therefore these documents provided only background information.
- Clinical trial registries: ClinicalTrials.gov was searched using combined search terms: "progression-free survival" AND "primary endpoint" AND "quality of life" and by combined search terms: "progression-free survival" AND "cancer" AND either "anxiety," "depression" or "psychological." Thirty-seven trials were identified, but review of the study descriptions revealed none that were relevant.
- The National Comprehensive Cancer Network (NCCN) oncology outcomes database and the ASCO (American Society of Clinical Oncology) annual meeting abstract database (past 3 years) were searched using the same terms as in the literature searches. Only one[60] of 35 identified ASCO abstracts was relevant (an update of Zhou[61]), but no full-text article has been published. No relevant NCCN abstracts were identified.

Key Questions

KQ 1: When PFS is used as a primary clinical endpoint in treating patients with advanced cancers, is there direct evidence that knowing PFS impacts patient anxiety, depression, or psychological well-being? If yes, does the manner of communicating PFS affect patient anxiety, depression, or psychological well-being?

Based on the search criteria established for KQ1, we identified no studies that directly addressed the question. No information was obtained on patients' psychological response to knowing their PFS status, or whether the manner of communicating PFS results affects patient anxiety or psychological well-being.

KQ 2: For agents where PFS is the primary outcome measure being used to establish the performance (efficacy and safety) of a new drug, what evidence exists regarding the association of PFS with QOL or related outcomes, such as disease symptoms?

Four studies[61-64] were identified that statistically evaluated the association between PFS and a QOL-related measure, with each study a post hoc analysis following a published primary study of drug efficacy and safety (see Study Design, Table 4). This pattern is the norm for QOL

assessments, which are rarely reported at the time of the publication on primary treatment effect. Due to the post hoc analyses, these studies are at best viewed as exploratory, of use only in generating hypotheses for further study. Another concern given the delay in publishing QOL results is that there may be a time-lag bias occurring because of earlier publication of favorable results.[65] These are important issues since high quality information on QOL is of great interest to patients who may wish to know whether they will observe a disease response while maintaining or improving daily function.

The study characteristics are presented in Table 4. Sample sizes ranged from 219 to 463. Overall, 1,515 patients were enrolled in these studies. The types of cancers and (treatment drug) included breast (Tykerb/lapatinib),[61,63] colorectal (Vectibix/panitumumab),[64] and renal cell (Votrient/pazopanib).[62]

The four drug studies all demonstrated statistically significant improvement in median PFS for the treatment arm compared with the control arm (Table 5). However, not surprisingly given the very different nature of the diseases and treatments studied, the range of times observed for PFS in the four reports varied markedly. In response to therapy, PFS showed increases in median duration from as low as 0.7 weeks (8 vs. 7.3 weeks;[64] patients with end stage renal cancer being followed until death) to 5 months (9.2 vs. 4.2 months;[63] patients with metastatic breast cancer who are expected to live an extended length of time even with disease recurrence.) These differences made it possible in the latter case to assess both the immediate and chronic toxicities associated with treatment, but this same evaluation was obviously not possible in the former. Because the nature of both disease and treatment vary greatly in the four examples studied, drawing conclusions from pooled outcomes is not feasible.

The four studies all used validated assessment tools to collect QOL information (Table 6). They included at least one or more global QOL measures, such as the European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire C-30, the functional assessment of cancer therapy: general, or the EuroQOL 5 dimensions index. Three of the studies also included disease-specific scales (the Functional Assessment of Cancer Therapy Colorectal Cancer symptom index)[64] or subscales (the breast cancer subscale of the Functional Assessment of Cancer Therapy Breast)[61,63] that addressed disease symptoms and/or general QOL measurement. All four studies established a minimally important difference threshold before analysis, but none provided detailed information on administration of the QOL measure (e.g., whether the QOL measure was administered in a standardized, reproducible manner each time, the conditions of administration, whether patients were informed of their PFS status prior to administration, etc.). QOL testing intervals ranged from 2- to 12-week intervals.

A problem common to all four studies was significant patient dropout (Table 7). In two studies,[63,64] the minimum requirement for inclusion in the analyses was QOL assessment at baseline and at least one followup. Even using this relatively liberal inclusion threshold, overall dropout rates ranged from 66 percent to 73 percent in experimental arms and from 77 percent to 96 percent in control arms. Disease progression was the major cause of dropout. All four studies addressed data missing not at random in the statistical plan.[61-64] The most common technique used by these studies for addressing data missing not at random was last observation carried forward (LOCF).[61,63,64] Of note, LOCF is not a recommended imputation method.[66] The opportunity to follow patients for QOL or other PROs obviously varies depending on the course of patients with advanced disease. In patients with longer term survival (i.e., breast compared with renal cell cancer) it may be easier to collect data than in patients who are likely to progress and become symptomatic more quickly and to have shorter times until death. Regardless of the

differences, missing data are always a challenge in the study of PROs, and this needs to be addressed in the research design.

The most important finding relating to this methods project was the relationship between PFS and QOL or other PRO, such as disease symptoms, found in all four studies (Table 8). More specifically, being progression-free had a statistically significant positive association with better QOL and/or decreased disease symptoms. All four studies demonstrated better QOL or disease symptoms among patients who remained progression-free compared with those who had progressed. Statistical methods to analyze the association between PFS and the QOL ranged from correlational techniques to more robust analysis of covariance (ANCOVA) and regression analyses. All four of the studies adjusted for QOL baseline scores in their analyses.

In the four included studies, there was better QOL or disease symptoms among patients who remained progression-free; however, the ability to draw conclusions from this important finding was compromised by the significant problems observed in the quality of these studies. As shown in Table 9, each of the four included studies met approximately 50 percent of identified quality items. However, all four failed to address the four items specifically developed to address the potential for bias in studies evaluating an association between PFS and QOL (items in italics). In addition, in all four studies there was substantial data missing not at random, and in two studies,[55, 58] investigators and patients were not blinded to treatment. Missing data, censoring at progression, and overall lack of conformance with quality items were much more problematic than blinding in this methods paper. Based on the assessment of risk of bias and the overall study quality criteria (Table 3), all four studies received a poor quality rating.

The strength of evidence assessment goes beyond looking at study design alone, and takes into account other facets of the evidence, including the presence or absence of bias, directness, consistency, and precision.[57] This allows clinicians, policy-makers, and patients to make well-informed decisions based on a more comprehensive evaluation of the evidence. Based on the poor quality of the four included articles, risk of bias was considered high. All four studies produced evidence of a positive association between PFS and QOL or disease symptoms, so although the body of evidence was small, it exhibited high consistency. However, this observation was tempered by the fact that the studies were of different designs, used different measurement tools, and assessed different outcomes. Consequently, it was not possible to measure the range of effect sizes. A quantitative analysis of pooled performance could not be performed, so no estimate of precision was possible. Based on the small body of literature identified and the factors discussed above, the strength of evidence is insufficient to demonstrate an association between PFS and QOL. Moreover, this association is only supportive of, but does not directly address KQ1, whether knowing PFS status impacts patient anxiety, depression, or psychological well-being, for which no direct evidence was found at all. Thus, the overall body of evidence is judged insufficient.

Table 4. Study characteristics

Author, Year	Cancer Type	Cancer Stage	Experimental Drug vs. Control	Study Design	1° / 2° Outcomes	Total N (n Exp/Control)	Age, Mean (SD); Median (range)
Cella, 2012[62]	Renal cell	Advanced, Stage IV, untreated or cytokine pretreated	pazopanib (Votrient) vs. placebo	Post hoc HRQL analysis of Sternberg 2010, phase III, randomized, double-blind, placebo-controlled, multicenter	PFS / OS, ORR, QOL, safety	434 (289/145) ITT	pazopanib 59 (28-85); placebo 60 (25-81)
Sherrill, 2010[63]	Breast	Metastatic, receptor-pos HER-2+, Stage IIIB/IIIC or IV, untreated	letrozole + lapatinib (Tykerb) vs. letrozole + placebo	Post hoc subset analysis (HER-2+ pts) of Johnston 2009, phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter	PFS / OS, ORR, QOL, clinical benefit rate	HER-2+ subset: 219 (111/108)	NR
Siena, 2007[64]	Colorectal	Metastatic, progressed on prior Tx	panitumumab (Vectibix) + BSC vs. BSC alone	PFS-QOL association analysis of Van Cutsem 2007, phase III, randomized-controlled, open-label, multicenter	PFS / OS, ORR, QOL, safety	463 (231/232) ITT	pan + BSC 62 (27-82); BSC alone 63 (27-83)
Zhou, 2009[61]	Breast	Advanced, metastatic, HER2+, progressed on prior treatment	lapatinib (Tykerb) + capecitabine vs. capecitabine alone	HRQL analysis of Cameron 2008, phase III, randomized, open-label, multicenter	TTP / PFS, OS, ORR, QOL, clinical benefit rate, safety	399 (198/201) ITT	lap+ cap 54 (26-80); cap alone 51 (28-83)

BSC = best supportive care; HER2 = human epidermal growth factor receptor type 2; HRQL = health-related quality of life; ITT = intention-to-treat; NSCLC = non–small-cell lung cancer; ORR = object response rate; OS = overall survival; PFS = progression-free survival; QOL = quality of life; TTP = time to progression

Table 5. Treatment efficacy and safety

Author, Year	Experimental Drug vs. Control	Median PFS (Experimental vs. Control)	PFS, Experimental vs. Control HR (95% CI)	Median OS (Experimental vs. Control)	OS, Experimental vs. Control HR (95% CI)	ORR, Experimental vs. Control % (95% CI)	Any Grade 3/4 Adverse Events in Experimental Group N (%)	Any Grade 3/4 Adverse Events in Control Group N (%)
Cella, 2012[62]	pazopanib vs. placebo	9.2 vs. 4.2 mos	0.46 (0.34-0.62), p< 0.0001	NR	NR (data not mature)	30 vs. 3, p< 0.001	40%	20%
Sherrill, 2010[63]	letrozole + lapatinib vs. letrozole + placebo	8.2 vs. 3 mos	0.71 (0.53-0.96), p= 0.019	33.3 vs. 32.3 mos	0.74 (0.5-1.1), p= 0.113	28 vs. 15, p= 0.021	diarrhea 10%; rash 1%	diarrhea 1%; rash 0%
Siena, 2007[64]	panitumumab + BSC vs. BSC alone	8 wks vs. 7.3 (mean 13.8 wks vs. 8.5)	0.54 (0.44-0.66), p<0.0001	NR	1.0 (82-1.22), p= 0.81	10 vs. 0 (at 1 yr)	of 229, 79 (35)	of 234, 45 (20)
Zhou, 2009[61]	lapatinib + capecitabine vs. capecitabine alone	NR	0.55 (0.4-0.74), p< 0.001	15.6 vs. 15.3 mos	0.78 (0.55-1.12), p= 0.177	24 vs. 14, p= 0.017	35%	33%

BSC = best supportive care; CI = confidence interval; HR = hazard ratio; Mo(s) = months; NR = not reported; ORR = objective response rate; P = probability; PFS = progression-free survival; OS = overall survival; Wks = weeks

Table 6. QOL measurement description

Author, Year	QOL Measure	Significant Change Threshold	QOL Measure Administration	QOL Testing Intervals & Discontinuation Criteria	Timing of Drug Treatment	Variables Measured or Compared (Experimental vs. Control)
Cella, 2012[62]	EORTC QLQ-C30, EQ-5D Index, EQ-5D VAS	QLQ-C30 5 to 10 pts; EQ-5D 0.08 pts; EQ-5D VAS 7 pts	blinded patient self-report	baseline, 6, 12, 18, 24, 48 weeks	daily until disease progression, unacceptable toxicity, death, or withdrawn consent	baseline scores; time to HRQL deterioration; correlation between response and HRQL
Sherrill, 2010[63]	FACT-B total score, FACT-G, TOI	FACT-B 7-8 pts; BCS 2-3 pts; FACT-G / TOI 5-6 pts	self-administered	Day 1 (baseline), every 12 weeks, at study withdrawal	daily until disease progression or withdrawal from study due to toxicity or other reasons	baseline scores; change scores; correlation between QOL and tumor response
Siena, 2007[64]	FACT-FCSI, EQ-5D Index, EQ-5D VAS, QLQ-C30 GHS	FCSI - 4-pt; EQ-5D - 0.08-pt.; EQ-5D VAS - 5.48-pt; GHS - 7.07-pt.	NR	baseline, every 2 weeks (FCSI) or monthly (all others) during treatment, at 30-day safety followup visit	2-week cycles	association between mean changes in HRQL/disease symptoms and PFS
Zhou, 2009[61]	FACT-B total score, FACT-G, TOI	FACT-B 7-8 pts; BCS 2-3 pts; FACT-G / TOI 5-6 pts	self-administered	at screening (baseline) visit, every 6 wks for 24 wks, every 12 wks, study discontinuation, until disease progression or withdrawal due to toxicity or other reasons	21-day cycles until PD or withdrawal because of toxicity or other reasons	Baseline scores; change scores; QOL changes from baseline based on tumor response

BCM20 = Brain Cancer Module20; BSC = best supportive care; EORTC-QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-B = Functional Assessment of Cancer Therapy-Breast; FACT-G = FACT-general; FCSI = FACT Colorectal Symptom Index; GHS = Global Health Status; HRQL = health-related quality of life; PD = progressive disease; PF = physical functioning; PFS = progression-free survival; QOL = quality of life; TOI = Trial Outcome Index; VAS = Visual Analog Scale

Table 7. QOL Measurement—missing data

Author, Year	QOL Analysis-Requirement for Inclusion	Baseline Completion Rate N (%) (Exp/Ctrl)	Experimental Group Dropout N (%)	Control Group Dropout N (%)	Primary Reasons for Dropout	Statistical Method for Missing Data
Cella, 2012[62]	All available HRQL assessments during periods of best response for each pt were used	QLQ-C30: 288 (99.7)/142 (97.9) EQ-5D: 287 (99.3)/143 (98.6) EQ-5D VAS: 283 (97.9)/141 (97)	wk 48, QLQ-C30 194 (67), EQ-5D 192 (67), EQ-5D VAS 188 (66)	wk 48, QLQ-C30 121 (85), EQ-5D 121 (85), EQ-5D VAS 118 (84)	disease progression	sensitivity analyses of HRQL deterioration using a composite end-point, where PD and HRQL deterioration were considered as an event
Sherrill, 2010[63]	Baseline & at least one followup QOL assessment	110 (100)/101 (98)	wk 48, 79 (72)	wk 48, 78 (77)	disease progression or withdrawal from Tx	LOCF - missing scores imputed from the last nonmissing score at a previous visit
Siena, 2007[64]	Baseline & at least one followup QOL assessment	207 (90)/184 (79)	wk 16, 145 (70)	wk 16, 177 (96)	disease progression	two methods, last value carried forward and slope method, used to impute missing values
Zhou, 2009[61]	All data collected up to close of study enrollment (no data after crossover or alt tx)	171 (86)/168 (84)	wk 24, 124 (73)	wk 24, 138 (82)	disease progression or withdrawal for other reasons	LOCF; exploratory random pattern effects model to deal with missing data showed QOL comparable bet Tx arms (data not shown)

BSC = best supportive care; HRQL = health-related quality of life; LOCF = last observation carried forward; NR = not reported; PD = progressive disease; PF = physical functioning; QOL = quality of life; QLQ = Quality of Life Questionnaire; VAS = Visual Analog Scale; Tx = treatment; Wk = week

Table 8. PFS - QOL association

Author, Year	Cancer Type	Exp Drug vs. Control	PFS-QOL Association	PFS-QOL Statistical Method
Cella, 2012[62]	Renal cell carcinoma	pazopanib vs. placebo	Progression-free (CR/PR) patients experienced significantly less HRQL deterioration than patients with SD and PD for GHS, EQ-5D utility index, EQ-5D VAS	Univariate and multivariate regression models, adjusted for baseline HRQL scores, were developed to determine the association between changes in HRQL and tumor response
Sherrill, 2010[63]	Breast	letrozole + lapatinib vs. letrozole + placebo	At wks 24 and 36, average FACT-B change scores from baseline were statistically and clinically significantly improved for patients with no PD versus those with PD	Least squared means from an ANCOVA, adjusted for baseline value, was used to compared QOL score changes from baseline between progressors and nonprogressors
Siena, 2007[64]	Colorectal	panitumumab + BSC vs. BSC alone	At week 8, being progression-free was associated with significantly and clinically meaningful lower CRC symptomatology for both treatment arms and higher HRQL for panitumumab patients only	T-tests and least-squares estimates were calculated for differences in QOL measures at weeks 4, 8, 12, 16 controlling for baseline score by progression status as of wk 8 (PD vs. no PD) within each treatment arm
Zhou, 2009[61]	Breast	lapatinib + capecitabine vs. capecitabine alone	At 12 wks, patients with SD had significantly positive changes from baseline, whereas patients with PD had negative changes in FACT-B, FACT-G, TOI, EQ-5D utility index, EQ-5D VAS scores	ANCOVA examined the relationship between tumor response status (SD vs. PD) adjusted for baseline scores (treatment arms pooled for this analysis)

ANCOVA = analysis of covariance; BSC = best supportive care; CR = complete response; FACT-B = Functional Assessment of Cancer Therapy-Breast; FACT-G = Functional Assessment of Cancer Therapy-General; GHS = Global Health Status; HRQL = health-related quality of life; PD = progressive disease; PF = physical functioning; PR = partial response; QOL = quality of life; SD = stable disease; SF = social functioning; VAS = Visual Analog Scale

Table 9. Summary of individual article quality assessments

Bias	Quality Criteria	Cella, 2012[62]	Sherrill, 2010[63]	Siena, 2007[64]	Zhou, 2009[61]	# of Studies Meeting Criterion
Selection Bias	Subjects in different groups recruited from same population	Yes	Yes	Yes	Yes	4
	Subjects in different groups recruited over same time period	Yes	Yes	Yes	Yes	4
	Inclusion/exclusion criteria clearly stated	Yes	Yes	Yes	Yes	4
	Randomization used	Yes	Yes	Yes	Yes	4
	Comparable baseline characteristics between groups	Yes	Yes	Yes	Yes	4
	Apart from treatment under investigation, groups treated equally	Yes	Yes	Yes	Yes	4
	*Similarity between groups in potentially important confounders (e.g., those with and without PFS) or adequate adjustment for confounding**	No	No	No	No	0
	*Patients not censored at progression**	No	No	No	No	0
Performance Bias	PFS assessed in valid and reliable manner (central radiology review, RECIST criteria used, inter- and intra-observer variability reported)	Yes	Yes	Yes	Yes	4
	Subjects and investigators blind to treatment group	Yes	Yes	No	No	2
	*Subjects awareness of PFS status is described**	No	No	No	No	0
Attrition Bias	Missing data addressed by description and analysis	Yes	Yes	Yes	Yes	4
	Results unlikely to be affected by losses to followup	No	No	No	No	0
	Missing data likely to be at random	No	No	No	No	0
Detection Bias	Outcome (progression) assessors blind to treatment group	Yes	No	Yes	Yes	3
	PFS and other endpoints defined	Yes	Yes	Yes	Yes	4
	QOL administration process was described	No	No	No	No	0
	*A priori hypothesis regarding the relationship between PFS and QOL**	No	No	No	No	0
# Yes (of 18 items)		**12**	**11**	**11**	**11**	
Quality Assessment Rating (definitions in Table 3)		**Poor**	**Poor**	**Poor**	**Poor**	

PFS =progression-free survival; QOL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors
*Italicized criteria are those that are uniquely important to trials comparing PFS and QOL (see Appendix F)

Discussion

The objective of this methods project was to address whether PFS is an outcome related to psychological well-being or QOL. As described in the Background, using PFS as an outcome can be challenging, especially in terms of potential bias (assessment, evaluation, performance, attrition), detection error, and its utility as a surrogate for other outcomes. There is a growing literature describing the best practices to address sources of bias, including careful prospective definition of progression,[39] blinding of patients and physicians to treatment,[3, 29] use of blinded external radiological review,[3, 24, 29, 30] and attention to patient attrition and data censoring.[3, 25, 28] However, accurate measurement of PFS can still be problematic. In addition, the implications of PFS are dependent on the context defined by specific disease, disease stage, the types of drugs and their toxicities, and patient response to the risks and benefits of treatment.[6] Regardless of these issues, PFS has been an attractive endpoint because, compared with OS, studies may be conducted more quickly using fewer subjects and at lower costs.

There has been growing evidence that PRO measures can provide important information for assessing the burden of cancer and effectiveness of treatments.[67] A variety of relevant outcomes have been identified, including symptom status, functional status, measures of overall well-being, satisfaction with care, treatment adherence, and measures of QOL.

Symptom status has recently been of particular interest as a PRO measurement with potential value in the study of cancer treatments. The ASCPRO Multisystem Task Force has recently proposed that the measurement of symptomatic changes, as a subset of QOL, may be a sufficient outcome in clinical trials to make decisions about whether to introduce a new treatment.[38] Evaluation of symptoms is complicated by the fact that they often occur in clusters and can be modified by comorbid conditions or the effects of supportive care, previous treatments, and other factors.[38] A number of trial scenarios assessing the impact of symptoms are plausible, including treatment leading to a reduction in disease-related symptoms, treatment leading to a delay in the onset of disease-related symptoms, treatment itself producing symptoms, or two therapies resulting in equally effective results, but with differing toxicity profiles. Unfortunately, as Cleeland[38] has noted, while it is well understood that symptoms in a patient can be produced by disease, treatment, or both or neither, attempts at symptom attribution are notoriously unreliable.

It has been noted that approaches for assessing specific symptoms by patient report in clinical trials have been lacking.[68] A simple patient report on the presence or absence of a symptom, such as nausea or pain, can provide information about how the patient feels. However, this information is subjective and conveys little or no information about the impact of symptoms on functioning or other aspects of well-being. The benefit of adding a QOL measurement to the assessment of symptoms is the ability to determine symptom impact on functional status and/or global well-being.[67] In measuring QOL there are a number of options, including the use of: (a) unidimensional domains or multidimensional domains (tools with one definable aspect or domain versus tools with many); (b) psychometric or preference-based measurements (tools measuring response along a subjective scale of well-being versus anchored scales where absolute conditions of well-being are designated); and (c) generic (tools applicable to a range of diseases) versus general cancer or site- or problem-specific cancer measurements.

We focused specifically on the association between an *outcome*, PFS, and other *outcomes* of importance to patients, such as QOL or disease symptoms. In contrast to a traditional comparison of *interventions*, ascertaining causal associations between PFS and other outcomes can be problematic, because progression can only be observed and not manipulated. This has implications for study design, interpreting results, quality evaluation, and even the feasibility of

designing a study that might address the issues posed here. The study of PFS and how it relates to other outcomes of importance to patients must be addressed from the vantage of observational data and their inherent potential for bias.

We first performed a broad-based review of the literature to identify studies examining the direct impact of PFS status on patient anxiety, depression, or psychological well-being. The search revealed no studies that addressed this question. This is a notable gap in the evidence, because one can speculate that knowing they are progression-free might make patients feel relief,[23] while news about disease progression might make them feel worried, but this has not been systematically studied. There is literature on the delivery of bad news to patients, including reports specifically addressing the direct psychological impact of telling patients they have been diagnosed with cancer.[69-71] How applicable this is to the setting of PFS remains unexamined. The psychological response to information on PFS may depend on the way it is delivered by a physician and on the patient's understanding of what PFS actually means. It is not known whether patients would view PFS differently if news of measurable progression or lack thereof was delivered with an explanation that PFS may not predict OS.

The lack of studies addressing KQ1 is not surprising given the difficulty in obtaining reliable and objective measurements of both PFS and psychological well-being/QOL in a coordinated manner that extends data collection of QOL into the period beyond progression. More research is clearly needed on how patients view the risks and benefits of even small potential changes in treatment outcomes, on how knowledge about PFS status might affect psychological well-being/QOL, and on how this information might be used to inform treatment decisions.

We also conducted a focused review of trials administering drugs recently approved by one or more regulatory authorities, for which PFS was the primary endpoint. In this way we explored the available evidence regarding the association of PFS with QOL, disease symptoms, or other QOL-related outcomes. Four studies[61-64] were identified, each of which reported better QOL or disease symptoms among patients who remained progression-free compared with those who had progressed. However, interpretation of this association is compromised by the poor quality of all four studies.

Evidence for a causal relationship in these studies remains unclear. It could be that a common underlying mechanism improves both PFS and QOL. For example: tumor shrinkage leads to improved pain that is detected via a QOL questionnaire and also is seen as disease regression on imaging. Alternatively, it could be that patient knowledge of progression status itself affects subjective impressions of overall QOL (or affects a specific symptom that impacts overall QOL measure scores, such as anxiety). The issue of causality is important in terms of considering future use of the PFS endpoint in clinical research, particularly when PFS is not serving as a surrogate for OS, but rather as a marker of QOL. If the underlying mechanism affecting PFS and QOL are the same, then the clinically meaningful endpoint is actually QOL, with PFS as an intermediate or surrogate outcome. In this case, a logical approach would be to design studies making QOL the primary focus.

Several sources of potential bias associated with PFS ascertainment were identified and discussed in the Methods section; all four sources of bias were evident in the included studies, weakening confidence in the reported PFS/QOL association. All four studies were limited by a failure to develop an a priori hypothesis regarding the association of PFS and QOL, by censoring at the time of progression, and by substantial rates of missing data not at random. While all four studies did describe analytical approaches to address missing data not at random, the ability to

account for the large dropout observed is doubtful. In addition, two[61, 64] of the four studies failed to provide patient-investigator blinding to treatment.

All four of the studies adjusted for QOL baseline scores in their analyses. This is particularly important because patients with better baseline scores might have longer PFS. Although the use of QOL as a prognostic factor for PFS is not the focus of this methods project, there is evidence that QOL itself is a prognostic indicator of survival.[72-75] The basic mechanism involved appears unrelated to the association of PFS with QOL; however, if QOL is prognostic for survival, there is the potential to confound studies evaluating the impact of PFS on QOL.

Duration of PFS and OS was relatively short in these studies (i.e., weeks to months). If treatments are making only small improvements in survival outcomes, it becomes that much more important to develop reliable estimates of the impact on disease symptoms and QOL, so that patients and physicians can make informed choices. It is expected that patients' interpretations of what might be meaningful changes in outcomes may differ from those of other stakeholders; in particular, best-case scenarios regarding their own outcomes may drive patient decisions. Studies determining how delivery of news may impact a patient's understanding, QOL, and use of information are needed.

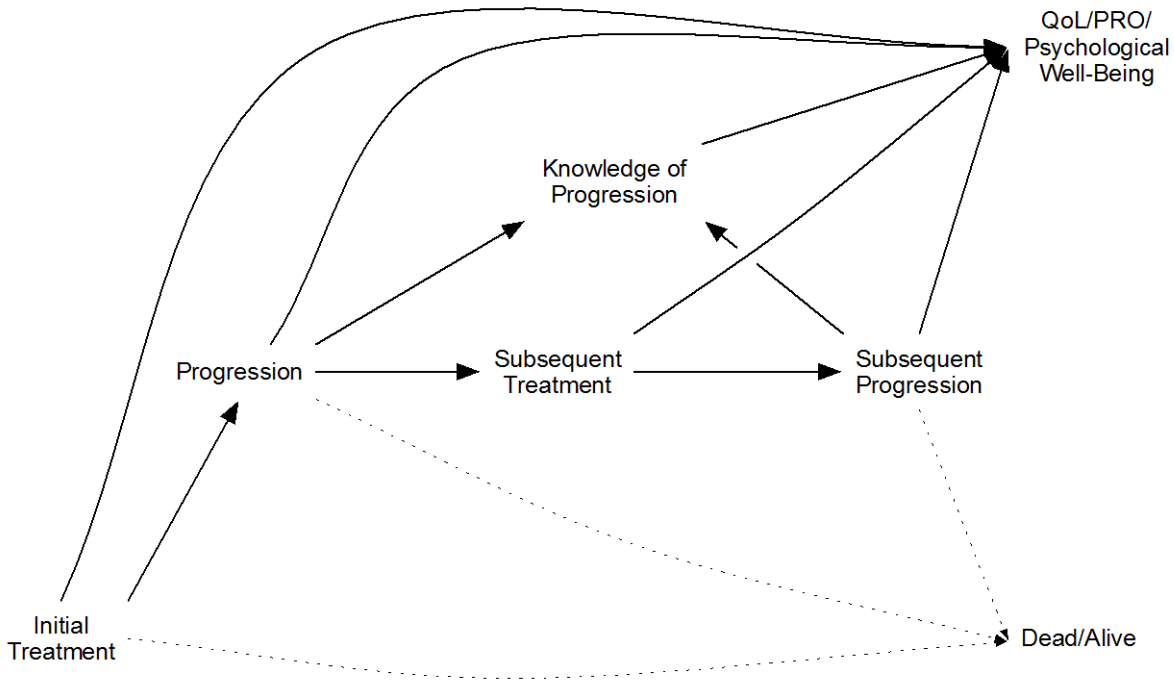
Heterogeneous patient populations make interpreting the included studies challenging. More studies with a clear description of sub-populations of interest are needed to help address these issues. Future studies using patient level data and analysis would also be useful.

The studies identified here were accompanied by important sources of bias. For that reason they provided limited evidence to address the questions posed. Ideally, studies would be free from bias. Describing a study design eliminating all biases[76] facilitates understanding the challenges ascertaining how treatment, disease progression (and knowledge of it), and other outcomes are associated. The purpose of such an exercise is to better understand issues that need to be addressed in future studies, not to outline a perfect study. In order to address known sources of bias an ideal study would include the following:

- Two treatments accompanied by similar overall survival rates and toxicities (QOL outcomes are not confounded by differential toxicities).
- Patients failing either treatment due to disease progression do not receive further therapy (eliminates time-dependent confounding).
- One treatment results in longer PFS so that the two study arms are similar in all respects except PFS.
  (Under these conditions, an unbiased comparison of other clinically important outcomes and their association with disease progression could be assessed.)
- A second randomization to being informed about or blinded to PFS status would determine if knowledge about PFS impacts QOL outcomes. Patients would also be informed that PFS may not be associated with overall survival.

These characteristics could not accompany any real study, and it is difficult to consider blinding patients to knowledge of progression. Accordingly, the biases present in studies examining the questions posed here must be addressed. At a minimum, disease progression must be sufficiently measurable; no design or analysis can obviate large measurement error. Second, a therapeutic failure evidenced by disease progression would be typically followed by subsequent treatment (we assume avoiding second therapy is a potential benefit). Finally, because one is observing, not manipulating PFS, it is useful to posit a basic causal model to place these abstract notions in context (Figure 2).

Figure 2. Basic causal model for treatments, progression, and outcomes



PRO = patient-reported outcomes; QoL = quality of life

The graph depicts relationships among the variables of interest, both causal and confounding. Beginning on the left lower corner, initial treatment may impact disease progression and influence survival either through progression or other mechanisms (arrow from treatment to dead/alive). Treatment can influence QOL or other PROs through toxicities. A second treatment requires considering time-dependent confounding. The remainder of the graph can be interpreted in a likewise manner.

The association of primary interest here is between progression (and subsequent progression) and QOL (PROs or psychological well-being). To define that association, confounding must somehow be accounted for—a potentially difficult task. It is necessary to take into account initial and subsequent treatments, whether patients are aware of progression, treatment efficacy, and toxicities. Even if the many shortcomings identified in the studies reviewed here were absent, the data would be limited to inform the relevant associations.

In summary, there is evidence that PFS provides information on the direct effect of treatment on tumor burden,[23, 77] although there is a lack of consensus regarding its use. This is not surprising given the fact that there is a significant gap in information on the direct and indirect relationship between PFS and QOL or other related outcomes. Our assessment of the state of the evidence on PFS and QOL or related outcomes led to some important observations not appreciated a priori: PFS is observed, not randomized; studies examining the associations of interest are generally of poor quality; standard quality assessment tools have shortcomings in this setting requiring novel quality measures; and positing a causal model facilitates understanding the limitations of current evidence and can inform future research.

Given these underpinnings, we suggest future research adopt the following approach to assess the relationship between PFS and QOL. While it is not possible to randomize PFS status, it may be informative to identify patients with or without progression and to observe whether the

state of progression can be linked to QOL or other PRO. In a best case scenario, it might be possible to consider PFS a surrogate for QOL using statistical techniques described in the PFS/OS setting (hypothesis testing, estimation, prediction).[6] It is unlikely blinding would be feasible, but alternative designs could be explored. For example, PFS information could be conveyed to one group of randomized patients using standard techniques (most commonly verbal interaction between an oncologist and patient). The second randomized group would receive information through the use of decisional aides that are constructed to clearly and correctly communicate the meaning of PFS as an outcome. A comparison could then be performed between the two groups to determine how delivery of information affects QOL outcomes. Whether PFS might be an indirect method of predicting QOL, or whether direct measurement of QOL in parallel with PFS represents a more practical approach, remains an open issue.

Evidence Gaps

There is a need for prospective research to evaluate: 1) the causal relationship between patient knowledge of progression status and other outcomes of importance to patients, including specific symptoms and overall QOL; 2) patient impressions of the meaningfulness of progression as a health outcome in the absence of association with overall survival; and 3) the extent to which improvement in patient-reported outcomes associated with improvement in PFS is related to a common underlying mechanism, such as tumor shrinkage positively impacting symptomatology and therefore QOL. Because PFS is a variable which cannot be manipulated, but only observed, there is also a significant need to explore what models are available to better understand this endpoint. In general, better tools are needed to measure QOL, and more robust studies of QOL with clear a priori hypotheses and endpoints are needed.

Pending further study of the association between PFS and outcomes of importance to patients, there is insufficient evidence to support the use of PFS alone to demonstrate QOL or related outcomes. It is acknowledged that in some situations, measurement of OS is impractical or unfeasible.[10] In such cases, the direct measurement of PFS and PROs, such as QOL or patient-reported symptoms, may be a practical alternative. Further study of these drugs and confirmation and expansion of the findings reported here would advance our understanding of these complex relationships. In particular, future studies should address and remedy the biases and quality issues described in this report.

Limitations

In this methods project, what was being studied was not a comparison of treatment interventions, but rather the relationship between two outcomes of treatment; therefore the standard approaches used for randomized clinical trials were not applicable. We posited a causal model for addressing this issue, but recognize that this is a hypothetical construct that requires further study and validation.

Existing validated quality assessment tools were not entirely applicable for our purposes. This resulted in the adaptation of the quality assessment tool to include items addressing potential biases unique to the study of the association between PFS and QOL. However, the modified quality assessment is unvalidated.

It would be interesting to know whether improvements in PFS in advanced disease would be predictive of a survival benefit from the use of the same treatment in the adjuvant setting. However, we did not address this issue as part of our key questions or data inquiry and are unable to address whether such a relationship exists.

Finally, in order to provide a focused review commensurate with the resources available to this methods project, the search for articles on outcomes of interest to patients used terms for psychological outcomes (depression, depressive disorder, anxiety, psychological), the term Quality of Life, and the term PRO. Had this search been broadened by use of separate search terms for symptoms or toxicities, additional articles may have been identified, but this was beyond the scope of the project. In selecting articles, we chose only reports that included a direct quantitative comparison of PFS status to the QOL-related outcomes of interest. It is unlikely that an expanded review of studies would have overcome the challenge of addressing the issues of heterogeneity and quality that prevented pooling of data in our analysis.

Conclusion

The objective of this methods project was to address whether PFS is an outcome related to psychological well-being or QOL. There were no studies that directly addressed the question of a causal relationship between knowing PFS status and patient anxiety, depression, or psychological well-being. Due to limitations in their design, the four studies demonstrating an association between PFS and better QOL or disease symptoms were all of poor quality. Hence, there is insufficient evidence to make any conclusions about the association between PFS and QOL or related outcomes. The direct measurement of both PFS and QOL may be a practical and informative alternative when measurement of OS is unfeasible.

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Appendix A. Definitions of Additional Oncology Drug Endpoints

Disease-free survival (DFS): The time from random assignment to cancer recurrence or death from any cause.

Relapse-free survival (RFS): The time from treatment of disease to any event, irrespective of cause, except for any second primary cancers

Time to progression (TTP): The time from random assignment to disease progression. TTP does not include deaths, and these events are censored, either at the time of death or at an earlier visit.

Objective response rate (ORR): The proportion of subjects with a predefined amount of reduction in tumor burden as assessed on the basis of specific criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST). Generally, ORR has been defined as the sum of partial responses plus complete responses (divided by total patients) and is considered a direct measure of drug antitumor activity.

Appendix B. Search Strategy

MEDLINE® (via PubMed) 1/10/12

Key Question 1:

"Disease-Free Survival"[Mesh] OR "progression free survival" OR "progression-free survival" OR "time to progression"
AND
(("Quality of Life"[Mesh]) OR ("Depression"[Mesh] OR "Depressive Disorder"[Mesh])) OR "Anxiety"[Mesh] OR “clinical benefit” OR “clinical benefits” OR “quality of life” OR “patient-reported outcomes” OR depression OR anxiety OR “psychological”
AND
"Neoplasms"[Mesh] OR cancer OR neoplasms OR carcinoma
AND
("progression-free" OR "progression free") Field: Title/Abstract
AND
Limits: Humans, English, Publication Date from 1999 to 2012
We made 2 sets – one with publication types letter, editorial, comment, OR review – the second was the rest of the articles in the set.

Key Question 2 includes the above search AND

Additional drug specific searches -
("bevacizumab" [Supplementary Concept] OR Bevacizumab OR avastin) AND ("Breast Neoplasms"[Mesh] OR (breast AND (cancer OR cancers OR neoplasms OR carcinoma*)) AND ("progression-free survival" OR "time to progression")

("ixabepilone" [Supplementary Concept] OR ixabepilone OR ixempra) AND ("Breast Neoplasms"[Mesh] OR (breast AND (cancer OR cancers OR neoplasms OR carcinoma*)) AND ("progression-free survival" OR "time to progression")

("lapatinib" [Supplementary Concept] OR lapatinib OR Tykerb) AND ("Breast Neoplasms"[Mesh] OR (breast AND (cancer OR cancers OR neoplasms OR carcinoma*)) AND ("progression-free survival" OR "time to progression")

("bevacizumab" [Supplementary Concept] OR Bevacizumab OR avastin) AND ("Colorectal Neoplasms"[Mesh] OR ((colon OR colorectal) AND (cancer OR cancers OR neoplasms OR carcinoma*))) AND ("progression-free survival" OR "time to progression")

("panitumumab" [Supplementary Concept] OR panitumumab OR vectibix) AND ("Colorectal Neoplasms"[Mesh] OR ((colon OR colorectal) AND (cancer OR cancers OR neoplasms OR carcinoma*))) AND ("progression-free survival" OR "time to progression")

("Doxorubicin"[Mesh] OR doxorubicin OR doxil) AND ("Ovarian Neoplasms"[Mesh] OR ((ovary OR ovarian) AND (cancer OR cancers OR neoplasms OR carcinoma*))) AND ("progression-free survival" OR "time to progression")

("gemcitabine" [Supplementary Concept] OR gemcitabine OR gemzar) AND ("Ovarian Neoplasms"[Mesh] OR ((ovary OR ovarian) AND (cancer OR cancers OR neoplasms OR carcinoma*))) AND ("progression-free survival" OR "time to progression")

("trabectedin" [Supplementary Concept] OR trabectedin OR yondelis) AND ("Ovarian Neoplasms"[Mesh] OR ((ovary OR ovarian) AND (cancer OR cancers OR neoplasms OR carcinoma*))) AND ("progression-free survival" OR "time to progression")

("sorafenib" [Supplementary Concept] OR sorafenib OR nexavar) AND ("Carcinoma, Renal Cell"[Mesh] OR "renal cell carcinoma") AND ("progression-free survival" OR "time to progression")

("pazopanib" [Supplementary Concept] OR pazopanib OR votrient) AND ("Carcinoma, Renal Cell"[Mesh] OR "renal cell carcinoma") AND ("progression-free survival" OR "time to progression")

("sunitinib" [Supplementary Concept] OR sunitinib OR sutent) AND ("Carcinoma, Renal Cell"[Mesh] OR "renal cell carcinoma") AND ("progression-free survival" OR "time to progression")

("erlotinib" [Supplementary Concept] OR erlotinib OR tarceva) AND ("Carcinoma, Non-Small-Cell Lung"[Mesh] OR ("non-small cell lung" AND (cancer OR cancers OR neoplasms OR carcinoma))) AND ("progression-free survival" OR "time to progression")

("docetaxel"[Mesh] OR doxetaxel OR taxotere) AND ("Head and Neck Neoplasms"[Mesh] OR (("head and neck") AND (cancer OR cancers OR carcinoma* OR neoplasms))) AND ("progression-free survival" OR "time to progression")

The EMBASE search was
'progression-free survival'/exp OR 'time to progression' in abstract or title
AND
'clinical benefit' OR 'clinical benefits' OR 'quality of life'/exp OR 'patient-reported outcomes' OR 'depression'/exp OR 'anxiety'/exp OR 'psychological'
AND
'cancer'/exp OR 'neoplasms'/exp OR 'carcinoma'/exp
AND
Human/English/1999-2012
NOT MEDLINE

MEDLINE 12/26/2011 = 293
For KQ1: ‘progression-free survival’/OR ‘PFS’
AND

‘clinical benefit’ OR ‘quality of life’ OR ‘patient-reported outcomes’ OR ‘depression’ OR ‘anxiety’ OR ‘psychological’
AND ‘cancer’
For KQ2: above AND each of the convenience drugs added individually
Limited to human/English/post 1999 (KQ1) or 2004 (KQ2)
above search limited to ‘randomized’ = 82

Sets – N=1505
From Medline = 82
KQ1_EMBASE = 426
KQ1_PubMed_EditComm=232 (these are the editorials, comments, letters and reviews from PubMed)
KQ1_PubMed_nonindexed=105 (these are the PubMed nonindexed that search obtained but that fell out when the English, Human and 1999-2012 limits were added)
KQ1_PubMed=655 (these are the PubMed results for the search strategy that we discussed minus the editorials, comments, letters and reviews above)
KQ2_PubMed=5 (these are the drug specific search results that were not already in the database – there were no drug specific search unique records in EMBASE).

Appendix C. List of Drugs Approved Using Studies With a Primary Endpoint of PFS

Oncology drugs for advanced solid epithelial cancers approved by regulatory authorities using PFS as the primary endpoint (2005 to 2010)

Targeted Cancer	Drug	Approved (jurisdictions)	Stage	Type of Trial	Increase in OS
Breast cancer	Avastin (bevacizumab)	US, Europe, Canada	Metastatic	III	No
Breast cancer	Ixempra (Ixabepilone)	US, Canada	Metastatic or locally advanced	III	No
Breast cancer	Tykerb (Lapatinib ditosylalte)	US, Europe, Canada	Metastatic or locally advanced	III	No
Colorectal cancer	Avastin (bevacizumab)	US, Europe, Canada	Metastatic	III	No
Colorectal cancer	Vectibix (panitumumab)	US, Europe, Canada	Metastatic	III	No
Ovarian cancer	Doxil (Doxorubicin)	Europe, Canada	Metastatic	III	No
Ovarian cancer	Gemzar (gemcitabine)	US, Europe, Canada	Advanced	III	No
Ovarian Cancer	Yondelis (trabectedin)	Europe, Canada	Relapsed	III	No
Renal Cell Cancer	Nexavar (sorafenib)	US, Europe, Canada	Advanced	III	No
Renal Cell Cancer	Votrient (pazopanib)	US, Europe, Canada	Advanced, metastatic	III	No
Renal Cell Cancer	Sutent (sunitinib)	US, Europe, Canada	Advanced, metastic	III	No
NSCLC	Tarceva (erlotinib)	US, Europe, Canada	Metastatic, locally advanced	III	Yes
Squamous Cell Cancer of Head and Neck	Taxotere (docetaxel)	US, Europe, Canada	Inoperable, locally advanced	III	Yes

Appendix D. Screening Questions

Title/Abstract Screening Questions

1.**Is this article published in English?**

- ☐ Yes
- ☐ No-EXCLUDE

2.**Is this a human study?**

- ☐ Yes
- ☐ No-EXCLUDE

3.**Is PFS an outcome measure?**

- ☐ Yes
- ☐ No-EXCLUDE

4. **Is this study**
A) a phase III (RCT) trial *AND*
B) does it address one of the combinations below:

Ixabepilone (Ixempra) - Breast cancer
Bevacizumab (Avastin) – breast cancer and colorectal cancer
lapatinib (Tykerb) - Breast cancer
panitumumab (Vectibix) - Colorectal cancer
doxorubicin (Doxil) - Ovarian cancer
gemcitabine (Gemzar) - Ovarian cancer
trabectedin (Yondelis) - Ovarian cancer
sorafenib (Nexavar) - RCC
pazopanib (Votrient) - RCC
sunitinib (Sutent) - RCC
erlotinib (Tarceva) - NSCLC
docetaxel (Taxotere) - Squamous cell ca of head and neck

- ☐ Yes BOTH A and B---KQ2
- ☐ No

5. Is there a PRO/QoL outcome? (This include outcomes that address psychological state, mood, . depression, anxiety, hope)

- ☐ Yes
- ☐ No-EXCLUDE

6. **Do the authors of the article appear to be trying to establish a direct link between PFS and a PRO or Qol measure?**

- ☐ Yes or Uncertain---KQ1
- ☐ No-EXCLUDE

Full-Text Screening Questions

Click if applies:

- ☐ EXCLUDE - ABSTRACT ONLY, FULL-TEXT NOT AVAILABLE
- ☐ EXCLUDE – REVIEW
- ☐ EXCLUDE - CONFERENCE PRESENTATION

1. Does this study utilize one or more validated PRO/QoL tools to measure the PRO/QoL outcome(s) reported?

- ☐ Yes
- ◉ No-EXCLUDE

2. Does this article address one of the combinations below?:

Ixabepilone (Ixempra) - Breast cancer
Bevacizumab (Avastin) – breast cancer and colorectal cancer
lapatinib (Tykerb) - Breast cancer
panitumumab (Vectibix) - Colorectal cancer
doxorubicin (Doxil) - Ovarian cancer
gemcitabine (Gemzar) - Ovarian cancer
trabectedin (Yondelis) - Ovarian cancer
sorafenib (Nexavar) - RCC
pazopanib (Votrient) - RCC
sunitinib (Sutent) - RCC
erlotinib (Tarceva) - NSCLC
docetaxel (Taxotere) - Squamous cell ca of head and neck

- ☐ Yes-INCLUDE KQ2
- ☐ No

3. Does this study report a direct association between PFS and a PRO/QoL outcome? This study can be prospective or retrospective, observational and/or survey based.

- ☐ Yes-Include KQ1
- ☐ No-EXCLUDE

Appendix E. Abstraction Form Items

Study Characteristics

Refid
Author, Year
Key Question
Abstractor
Cancer type
Cancer Stage
Exp Drug v Control
Study Design
N Exp/Control
Age, Mean (SD); Median (range)

Treatment Efficacy and Safety

Primary Endpoint (Defined)
PFS, Experimental v Control, HR (95% CI)
OS, Experimental v Control, HR (95% CI)
ORR, Experimental v Control, % (95% CI)
Total Grade 3/4 AEs -- N (%) of pts on Experimental tx
Total Grade 3/4 AEs-- N (%) of pts in Control

QoL Description and PFS-QoL Association

QoL Tool Used
Threshold used for significant changes
Information on how the QoL was administered
Testing intervals for QoL, discontinuation criteria
QoL Timing for Drug treatment
QoL test (last administration) drop-out -- Experimental (N and % of total tx)
QoL test (last administration) drop-out -- Control (N and % of total tx)
Primary reasons for drop-out
Was Missing Data statistically addressed
PFS-QoL association descriptive results
PFS-QoL statistical method used

Appendix F. Relevance of Quality Assessment Items

Quality Criteria	Important to Drug Treatment Trials	Important in Studies Relating PFS to QoL	Unique to Trials Comparing PFS and QoL
Selection bias			
Subjects in different groups recruited from same population	X	X	
Subjects in different groups recruited over same time period	X	X	
Inclusion/exclusion criteria clearly stated	X	X	
Randomization used	X		
Comparable baseline characteristics between groups	X		
Apart from treatment under investigation, groups treated equally	X		
Similarity between groups in potentially important confounders (e.g., those with and without PFS) or adequate adjustment for confounding			X
Patients are not censored at progression			X
Performance bias			
PFS assessed in valid and reliable manner (central radiology review, RECIST criteria used, inter- and intra-observer variability reported)	X	X	
Subjects and investigators blind to treatment group	X	X	
Subjects awareness of PFS status is described			X
Attrition bias			
Missing data addressed through description and analysis	X	X	
Results unlikely to be affected by losses to follow-up	X	X	
Missing data likely to be at random	X	X	
Detection bias			
Outcome (progression) assessors blind to treatment group	X	X	
PFS and other endpoints defined	X	X	
QOL administration process was described	X	X	
A priori hypothesis regarding the relationship between PFS and QOL			X

APPENDIX G. Articles Excluded at Full-Text Screening by Reason

Level 2, Form Full-Text Screening, -> EXCLUDE - ABSTRACT ONLY, FULL-TEXT NOT AVAILABLE...

Refid: 103, Estimating quality of life in advanced melanoma; A comparison of standard gamble, SF-36 mapped, and eortc QLQ-c30 mapped utilities
A. J. Batty, D. Fisher, B. Winn, Q. Wang, K. Tolley and D. Rowen
Level: 2, State: Excluded

Refid: 162, Patient preferences for non-small cell lung cancer (NSCLC) treatments
J. F. Bridges, A. Mohamed, H. W. Finnern, A. Woehl and A. B. Hauber
Level: 2, State: Excluded

Refid: 202, Time to deterioration (TTD) in patient-reported outcomes in phase 3 axis trial of axitinib vs sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC)
D. Cella, B. Escudier, B. Rini, C. Chen, H. Bhattacharyya, J. Tarazi, B. Rosbrook, S. Kim and R. Motzer
Level: 2, State: Excluded

Refid: 232, Health-related quality of life (HRQOL) in 1st line non-squamous non-small cell lung cancer (NSCLC) patients in a real life setting: Bevacizumab-based versus non-bevacizumab based therapy in a european pilot study
C. Chouaid, H. G. Bischoff, A. Vergnenegre, D. F. Heigener, G. Taylor-Stokes, A. Roughley and S. Walzer
Level: 2, State: Excluded

Refid: 310, Asthenia and fatigue as potential biomarkers of sunitinib efficacy in metastatic renal cell carcinoma
M. P. Davis, R. A. Figlin, T. E. Hutson, D. Goldstein, S. Li, J. Perkins and R. J. Motzer
Level: 2, State: Excluded

Refid: 326, Patient preference-based utility weights from the functional assessment of cancer therapy-general (FACT-G) in women with hormone receptor positive metastatic breast cancer receiving letrozole plus lapatinib or letrozole alone
T. E. Delea, O. Sofrygin and M. Amonkar
Level: 2, State: Excluded

Refid: 396, Unresectable colorectal liver metastases treated by intraoperative radiofrequency ablation with or without resection: the ARF2003 study
S. Evrard, M. Rivoire, J. P. Arnaud, E. Lermite, C. Bellera, S. Mathoulin-Pelissier, M. Fonck, R. Brunet, Y. Becouarn and C. Lalet
Level: 2, State: Excluded

Refid: 496, Analysis of toxicity profile, Dose reduction and efficacy of sunitinib in metastatic renal cancer
C. Gonzalez-Perez, B. I. Pajares-Hachero, B. Muros-de Fuentes, J. Gonzalez-Contreras, A. I. Gomez-Sanchez and B. Solano-Hernandez
Level: 2, State: Excluded

Refid: 563, How much do patients with renal cell carcinoma (RCC) value progression free survival in medical decision making?-results from a benefit-risk conjoint study
A. B. Hauber, A. F. Mohamed, F. R. Johnson and M. P. Neary
Level: 2, State: Excluded

Refid: 679, Erlotinib maintenance therapy for non-small cell lung cancer preserves quality of life
E. Juhasz, J. H. Kim, L. Stelmakh, S. Cicenas and G. Klingelschmitt
Level: 2, State: Excluded

Refid: 772, Efficacy of Biological Agents (BA) in metastatic Triple Negative Breast Cancer (TNBC): A systematic review
N. M. La Verde, A. Bramati, P. Sburlati, E. Galfrascoli, A. Moretti, A. Bianchi, S. Girelli, S. Piva, M. C. Garassino and G. Farina
Level: 2, State: Excluded

Refid: 807, Sofrafenib versus sunitinib in metastatic renal cell carcinoma: Indirect comparison analysis
H. W. Leung and A. L. Chan
Level: 2, State: Excluded

Refid: 1007, Ariadna study - Evaluation of symptoms on daily life and health-related quality of life (HRQOL) of patients with advanced non-small cell lung cancer (NSCLC)
J. Oramas, M. Cobo, A. Paredes, E. Arriola, M. Sala, A. Artal, R. Girones, M. J. Martinez, S. Figueroa and M. Domine
Level: 2, State: Excluded

Refid: 1144, An interim analysis of health-related quality of life (HRQOL) in patients with non-squamous non-small-cell lung cancer (NSNSCLC) receiving bevacizumab vs bevacizumab + pemetrexed for maintenance therapy in avaperl 1
A. Rittmeyer, C. Chouaid, J. H. Kim, M. J. Ahn, V. Gorbunova, A. Scherpereel, J. Oramas, S. Walzer and F. Barlesi
Level: 2, State: Excluded

Refid: 1350, Utility elicitation study in the UK general public for late stage chronic lymphocytic leukemia
K. Tolley, C. Goad, Y. Yi, P. A. Maroudas and G. Thompson
Level: 2, State: Excluded

Refid: 1370, Bevacizumab in combination with chemotherapy for the first-line treatment of metastatic colorectal cancer
R. Ubago, M. A. Castillo, S. Flores and C. Beltran
Level: 2, State: Excluded

Refid: 1434, A Q-twist analysis comparing panitumumab plus best supportive care (BSC) with bsc alone in patients with wild-type kras metastatic colorectal cancer
J. Wang, Z. Zhao, B. Sherrill, M. Peeters, J. Wiezorek and B. Barber
Level: 2, State: Excluded

Refid: 1469, Tumour response, skin rash and health-related quality of life (HRQOL) - Post-HOC data from the IPASS study
Y. Wu, M. Fukuoka, T. S. K. Mok, N. Saijo, S. Thongprasert, J. C. H. Yang, D. T. Chu, J. J. Yang and Y. Rukazenkov
Level: 2, State: Excluded

Refid: 1530, Improved progression-free survival does not translate into better quality of life in chronic lymphocytic leukaemia -results of the randomised EBMT-Intergroup study on the value of autologous transplantation
L. C. De Wreede, M. Watson, M. Van Os, D. Milligan, M. Van Gelder, M. Michallet, P. Dreger, C. E. Dearden, C. Cordonnier, M. Leporrier, V. Koza, J. Homewood, B. Corront, G. M. Baerlocher, W. Herr, D. W. Niederwieser, L. Sutton, T. M. De Witte and J. Schetelig
Level: 2, State: Excluded

Refid: 1588, Independent radiologic review of OCEANS, a phase III trial of carboplatin, gemcitabine, and bevacizumab or placebo for the treatment of platinum-sensitive, recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer
C. Aghajanian, S. Makhija, T. Rutherford, S. Sharma, L. Nycum, M. Sovak, H. Nguyen, J. Yi and A. Husain
Level: 2, State: Excluded

Level 2, Form Full-Text Screening, -> EXCLUDE - REVIEW

Refid: 110, Sunitinib in Advanced Renal Cell Carcinoma: Clinical Evidence
J. Bellmunt
Level: 2, State: Excluded

Refid: 231, Disparities at presentation, diagnosis, treatment, and survival in African American men, affected by prostate cancer
G. Chornokur, K. Dalton, M. E. Borysova and N. B. Kumar
Level: 2, State: Excluded

Refid: 275, Targeted therapy for advanced renal cell carcinoma
C. Coppin, L. Le, F. Porzsolt and T. Wilt
Level: 2, State: Excluded

Refid: 308, Temozolomide: A review of its use in the treatment of malignant gliomas, malignant melanoma and other advanced cancers
M. J. M. Darkes, G. L. Plosker and B. Jarvis
Level: 2, State: Excluded

Refid: 347, Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer after previous platinum-containing chemotherapy: A NICE single technology appraisal
R. Dickson, A. Bagust, A. Boland, M. Blundell, H. Davis, Y. Dundar, J. Hockenhull, C. Martin Saborido, J. Oyee and V. S. Ramani
Level: 2, State: Excluded

Refid: 984, The European Medicines Agency review of pazopanib for the treatment of advanced renal cell carcinoma: Summary of the scientific assessment of the Committee for Medicinal Products for Human Use
M. Nieto, J. Borregaard, J. Ersboll, G. J. A. Ten Bosch, B. Van Zwieten-Boot, E. Abadie, J. H. M. Schellens and F. Pignatti
Level: 2, State: Excluded

Refid: 1043, Panitumumab in Combination With Cytotoxic Chemotherapy for the Treatment of Metastatic Colorectal Carcinoma
M. Peeters, A. Cohn, C. H. Kohne and J. Y. Douillard
Level: 2, State: Excluded

Refid: 1145, Cetuximab in metastatic or recurrent head and neck cancer: the EXTREME trial
F. Rivera, A. Garcia-Castano, N. Vega, M. E. Vega-Villegas and L. Gutierrez-Sanz
Level: 2, State: Excluded

Refid: 1437, Panitumumab: in metastatic colorectal cancer with wild-type KRAS
J. Weber and P. L. McCormack
Level: 2, State: Excluded

Refid: 1449, Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer
S. Whyte, A. Pandor, M. Stevenson and A. Rees
Level: 2, State: Excluded

Level 2, Form Full-Text Screening, -> EXCLUDE - CONFERENCE PRESENTATION

Refid: 1208, Do hope, optimism and other psychological factors predict survival in patients with metastatic colorectal cancer?
P. Schofield, M. Stockler, D. Zannino, N. Wong, D. Ransom, E. Moylan, J. Simes, T. Price, N. Tebbutt and M. Jefford
Level: 2, State: Excluded

Level 2, Form Full-Text Screening, Does this study utilize one or more validated PRO/QoL tools to measure the PRO/QoL outcome(s) reported?... -> No-EXCLUDE

Refid: 24, 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)
D. S. Alberts, P. Y. Liu, S. P. Wilczynski, M. C. Clouser, A. M. Lopez, D. P. Michelin, V. J. Lanzotti and M. Markman
Level: 2, State: Excluded

Refid: 35, Lapatinib and HER2 status: results of a meta-analysis of randomized phase III trials in metastatic breast cancer
E. Amir, A. Ocana, B. Seruga, O. Freedman and M. Clemons
Level: 2, State: Excluded

Refid: 131, Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer
K. L. Blackwell, H. J. Burstein, A. M. Storniolo, H. Rugo, G. Sledge, M. Koehler, C. Ellis, M. Casey, S. Vukelja, J. Bischoff, J. Baselga and J. O'Shaughnessy
Level: 2, State: Excluded

Refid: 252, Quality-of-life-adjusted survival comparison of sustained-release cytosine arabinoside versus intrathecal methotrexate for treatment of solid tumor neoplastic meningitis
B. F. Cole, M. J. Glantz, K. A. Jaeckle, M. C. Chamberlain and J. I. Mackowiak
Level: 2, State: Excluded

Refid: 384, Predictors of response to sequential sunitinib and the impact of prior VEGF-targeted drug washout in patients with metastatic clear-cell renal cell carcinoma
A. A. Elfiky, D. C. Cho, D. F. McDermott, J. E. Rosenberg, B. Fortner, L. Antras, K. Chen, M. Sheng Duh, S. S. Jayawant, W. K. Oh, M. B. Atkins and T. K. Choueiri
Level: 2, State: Excluded

Refid: 453, Bevacizumab in combination with metronomic chemotherapy in patients with anthracycline- and taxane-refractory breast cancer
J. A. Garcia-Saenz, M. Martin, A. Calles, C. Bueno, L. Rodriguez, J. Bobokova, A. Custodio, A. Casado and E. Diaz-Rubio
Level: 2, State: Excluded

Refid: 484, U.S. Food and Drug Administration approval: panitumumab for epidermal growth factor receptor-expressing metastatic colorectal carcinoma with progression following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens
R. M. Giusti, K. Shastri, A. M. Pilaro, C. Fuchs, R. Cordoba-Rodriguez, K. Koti, M. Rothmann, A. Y. Men, H. Zhao, M. Hughes, P. Keegan, K. D. Weiss and R. Pazdur
Level: 2, State: Excluded

Refid: 485, FDA drug approval summary: panitumumab (Vectibix)
R. M. Giusti, K. A. Shastri, M. H. Cohen, P. Keegan and R. Pazdur
Level: 2, State: Excluded

Refid: 529, Efficacy and safety of bevacizumab plus chemotherapy in Chinese patients with metastatic colorectal cancer: a randomized phase III ARTIST trial
Z. Z. Guan, J. M. Xu, R. C. Luo, F. Y. Feng, L. W. Wang, L. Shen, S. Y. Yu, Y. Ba, J. Liang, D. Wang, S. K. Qin, J. J. Wang, J. He, C. Qi and R. H. Xu
Level: 2, State: Excluded

Refid: 571, A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer
J. R. Hecht, E. Mitchell, T. Chidiac, C. Scroggin, C. Hagenstad, D. Spigel, J. Marshall, A. Cohn, D. McCollum, P. Stella, R. Deeter, S. Shahin and R. G. Amado
Level: 2, State: Excluded

Refid: 575, Second-line erlotinib in patients with advanced non-small-cell lung cancer: Subgroup analyses from the TRUST study
D. F. Heigener, Y. L. Wu, N. van Zandwijk, P. Mali, K. Horwood and M. Reck
Level: 2, State: Excluded

Refid: 629, Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer
H. Hurwitz, L. Fehrenbacher, W. Novotny, T. Cartwright, J. Hainsworth, W. Heim, J. Berlin, A. Baron, S. Griffing, E. Holmgren, N. Ferrara, G. Fyfe, B. Rogers, R. Ross and F. Kabbinavar
Level: 2, State: Excluded

Refid: 630, The clinical benefit of bevacizumab in metastatic colorectal cancer is independent of K-ras mutation status: analysis of a phase III study of bevacizumab with chemotherapy in previously untreated metastatic colorectal cancer
H. I. Hurwitz, J. Yi, W. Ince, W. F. Novotny and O. Rosen
Level: 2, State: Excluded

Refid: 637, Clinical outcome of panitumumab for metastatic colorectal cancer with wild-type KRAS status: a meta-analysis of randomized clinical trials
E. M. Ibrahim and K. M. Abouelkhair
Level: 2, State: Excluded

Refid: 643, Quality-adjusted survival in a crossover trial of letrozole versus tamoxifen in postmenopausal women with advanced breast cancer
W. Irish, B. Sherrill, B. Cole, C. Gard, G. A. Glendenning and H. Mouridsen
Level: 2, State: Excluded

Refid: 666, Approval summary for erlotinib for treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen
J. R. Johnson, M. Cohen, R. Sridhara, Y. F. Chen, G. M. Williams, J. Duan, J. Gobburu, B. Booth, K. Benson, J. Leighton, L. S. Hsieh, N. Chidambaram, P. Zimmerman and R. Pazdur
Level: 2, State: Excluded

Refid: 667, Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer
S. Johnston, J. Pippen, Jr., X. Pivot, M. Lichinitser, S. Sadeghi, V. Dieras, H. L. Gomez, G. Romieu, A. Manikhas, M. J. Kennedy, M. F. Press, J. Maltzman, A. Florance, L. O'Rourke, C. Oliva, S. Stein and M. Pegram
Level: 2, State: Excluded

Refid: 680, Addition of Bevacizumab to Fluorouracil-Based First-Line Treatment of Metastatic Colorectal Cancer: Pooled Analysis of Cohorts of Older Patients From Two Randomized Clinical Trials
F. F. Kabbinavar, H. I. Hurwitz, J. Yi, S. Sarkar and O. Rosen
Level: 2, State: Excluded

Refid: 808, Multikinase inhibitors in metastatic renal cell carcinoma: indirect comparison meta-analysis
H. W. C. Leung and A. L. F. Chan
Level: 2, State: Excluded

Refid: 823, VEGF pathway-targeted therapy for advanced renal cell carcinoma: A meta-analysis of randomized controlled trials
F. Liu, X. Chen, E. Peng, W. Guan, Y. Li, Z. Hu, Z. Ye and Q. Zhuang
Level: 2, State: Excluded

Refid: 870, Single agent carboplatin versus carboplatin plus pegylated liposomal doxorubicin in recurrent ovarian cancer: Final survival results of a SWOG (S0200) phase 3 randomized trial
M. Markman, J. Moon, S. Wilczynski, A. M. Lopez, K. M. Rowland Jr, D. P. Michelin, V. J. Lanzotti, G. L. Anderson and D. S. Alberts
Level: 2, State: Excluded

Refid: 883, SABRE-B: an evaluation of paclitaxel and bevacizumab with or without sunitinib as first-line treatment of metastatic breast cancer
E. L. Mayer, S. Dhakil, T. Patel, S. Sundaram, C. Fabian, M. Kozloff, R. Qamar, F. Volterra, H. Parmar, M. Samant and H. J. Burstein
Level: 2, State: Excluded

Refid: 914, Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer
D. W. Miles, A. Chan, L. Y. Dirix, J. Cortes, X. Pivot, P. Tomczak, T. Delozier, J. H. Sohn, L. Provencher, F. Puglisi, N. Harbeck, G. G. Steger, A. Schneeweiss, A. M. Wardley, A. Chlistalla and G. Romieu
Level: 2, State: Excluded

Refid: 933, Early adjuvant radiotherapy toward long-term survival and better quality of life for craniopharyngiomas--a study in single institute
S. H. Moon, I. H. Kim, S. W. Park, I. Kim, S. Hong, C. I. Park, K. C. Wang and B. K. Cho
Level: 2, State: Excluded

Refid: 971, Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET
S. Negrier, E. Jager, C. Porta, D. McDermott, M. Moore, J. Bellmunt, S. Anderson, F. Cihon, J. Lewis, B. Escudier and R. Bukowski
Level: 2, State: Excluded

Refid: 981, Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy
Q. N. Nguyen, A. S. Shiu, L. D. Rhines, H. Wang, P. K. Allen, X. S. Wang and E. L. Chang
Level: 2, State: Excluded

Refid: 1055, Erlotinib as maintenance therapy in patients with advanced non-small cell lung cancer: A pooled analysis of three randomized trials
F. Petrelli, K. Borgonovo, M. Cabiddu and S. Barni
Level: 2, State: Excluded

Refid: 1068, Capecitabine and celecoxib as second-line treatment of advanced pancreatic and biliary tract cancers
M. S. Pino, M. Milella, A. Gelibter, I. Sperduti, S. De Marco, C. Nuzzo, E. Bria, L. Carpanese, E. M. Ruggeri, P. Carlini and F. Cognetti
Level: 2, State: Excluded

Refid: 1089, Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse
E. Pujade-Lauraine, U. Wagner, E. Aavall-Lundqvist, V. Gebski, M. Heywood, P. A. Vasey, B. Volgger, I. Vergote, S. Pignata, A. Ferrero, J. Sehouli, A. Lortholary, G. Kristensen, C. Jackisch, F. Joly, C. Brown, N. Le Fur and A. du Bois
Level: 2, State: Excluded

Refid: 1142, Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomised phase 3 trial
B. I. Rini, B. Escudier, P. Tomczak, A. Kaprin, C. Szczylik, T. E. Hutson, M. D. Michaelson, V. A. Gorbunova, M. E. Gore, I. G. Rusakov, S. Negrier, Y. C. Ou, D. Castellano, H. Y. Lim, H. Uemura, J. Tarazi, D. Cella, C. Chen, B. Rosbrook, S. Kim and R. J. Motzer
Level: 2, State: Excluded

Refid: 1151, RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer
N. J. Robert, V. Dieras, J. Glaspy, A. M. Brufsky, I. Bondarenko, O. N. Lipatov, E. A. Perez, D. A. Yardley, S. Y. T. Chan, X. Zhou, S.-C. Phan and J. O'Shaughnessy
Level: 2, State: Excluded

Refid: 1184, Balancing risk and benefit for first-line treatment of metastatic colorectal cancer: a graphic communication tool for patients and physicians
M. S. Sanatani and M. D. Vincent
Level: 2, State: Excluded

Refid: 1201, Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial
W. Scheithauer, B. Schull, H. Ulrich-Pur, K. Schmid, M. Raderer, K. Haider, W. Kwasny, D. Depisch, B. Schneeweiss, F. Lang and G. V. Kornek
Level: 2, State: Excluded

Refid: 1217, Lapatinib plus letrozole as first-line therapy for HER-2+ hormone receptor-positive metastatic breast cancer.[Erratum appears in Oncologist. 2010;15(3):327 Note: Schwarzberg, Lee S [corrected to Schwartzberg, Lee S]]
L. S. Schwartzberg, S. X. Franco, A. Florance, L. O'Rourke, J. Maltzman and S. Johnston
Level: 2, State: Excluded

Refid: 1241, Erlotinib in previously treated non-small-cell lung cancer
F. A. Shepherd, J. Rodrigues Pereira, T. Ciuleanu, E. H. Tan, V. Hirsh, S. Thongprasert, D. Campos, S. Maoleekoonpiroj, M. Smylie, R. Martins, M. van Kooten, M. Dediu, B. Findlay, D. Tu, D. Johnston, A. Bezjak, G. Clark, P. Santabarbara and L. Seymour
Level: 2, State: Excluded

Refid: 1322, A nonradiation-containing, intermediate-dose methotrexate regimen for elderly patients with primary central nervous system lymphoma
K. Taoka, Y. Okoshi, N. Sakamoto, S. Takano, A. Matsumura, Y. Hasegawa and S. Chiba
Level: 2, State: Excluded

Refid: 1360, 1. Sorafenib in advanced clear-cell renal-cell carcinoma. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM, TARGET Study Group, Department of Medicine, Institut Gustave Roussy, Villejuif, France
D. L. Trump
Level: 2, State: Excluded

Refid: 1378, Magnitude of benefit of the addition of bevacizumab (BEVA) to first-line chemotherapy (CT) for advanced/metastatic colorectal cancer (MCRC): Meta-analysis of randomized clinical trials
V. Vaccaro, F. Cuppone, F. Loupakis, M. Milella, P. Carlini, C. Nistico, A. Falcone, E. Terzoli, F. Cognetti and E. Bria
Level: 2, State: Excluded

Refid: 1424, Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies
B. Wacker, T. Nagrani, J. Weinberg, K. Witt, G. Clark and P. J. Cagnoni
Level: 2, State: Excluded

Refid: 1433, A Q-TWiST analysis comparing panitumumab plus best supportive care (BSC) with BSC alone in patients with wild-type KRAS metastatic colorectal cancer
J. Wang, Z. Zhao, B. Barber, B. Sherrill, M. Peeters and J. Wiezorek
Level: 2, State: Excluded

Refid: 1488, Survival benefits from lapatinib therapy in women with HER2-overexpressing breast cancer: a systematic review
A. Y. Yip, L. A. Tse, E. Y. Ong and L. W. Chow
Level: 2, State: Excluded

Refid: 1507, Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment
E. S. Thomas, H. L. Gomez, R. K. Li, H. C. Chung, L. E. Fein, V. F. Chan, J. Jassem, X. B. Pivot, J. V. Klimovsky, F. H. de Mendoza, B. Xu, M. Campone, G. L. Lerzo, R. A. Peck, P. Mukhopadhyay, L. T. Vahdat and H. H. Roche
Level: 2, State: Excluded

Refid: 1509, beta-Tubulin-II expression strongly predicts outcome in patients receiving induction chemotherapy for locally advanced squamous carcinoma of the head and neck: a companion analysis of the TAX 324 trial
K. J. Cullen, L. Schumaker, N. Nikitakis, O. Goloubeva, M. Tan, N. J. Sarlis, R. I. Haddad and M. R. Posner
Level: 2, State: Excluded

Refid: 1514, Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial
J. H. Lorch, O. Goloubeva, R. I. Haddad, K. Cullen, N. Sarlis, R. Tishler, M. Tan, J. Fasciano, D. E. Sammartino and M. R. Posner
Level: 2, State: Excluded

Refid: 1516, Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324: survival, surgery, and organ preservation
M. R. Posner, C. M. Norris, L. J. Wirth, D. M. Shin, K. J. Cullen, E. W. Winquist, C. R. Blajman, E. A. Mickiewicz, G. P. Frenette, L. F. Plinar, R. B. Cohen, L. M. Steinbrenner, J. M. Freue, V. A. Gorbunova, S. A. Tjulandin, L. E. Raez, D. R. Adkins, R. B. Tishler, M. R. Roessner and R. I. Haddad
Level: 2, State: Excluded

Refid: 1518, Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer
J. B. Vermorken, E. Remenar, C. van Herpen, T. Gorlia, R. Mesia, M. Degardin, J. S. Stewart, S. Jelic, J. Betka, J. H. Preiss, D. van den Weyngaert, A. Awada, D. Cupissol, H. R. Kienzer, A. Rey, I. Desaunois, J. Bernier and J. L. Lefebvre
Level: 2, State: Excluded

Refid: 1596, Ixabepilone plus capecitabine in advanced breast cancer patients with early relapse after adjuvant anthracyclines and taxanes: A pooled subset analysis of two phase III studies
J. Jassem, L. Fein, M. Karwal, M. Campone, R. Peck, V. Poulart and L. Vahdat
Level: 2, State: Excluded

Refid: 1600, Phase II escalation study of sorafenib in patients with metastatic renal cell carcinoma who have been previously treated with anti-angiogenic treatment
A. Mancuso, E. D. Di Paola, A. Leone, A. Catalano, F. Calabro, L. Cerbone, A. Zivi, C. Messina, S. Alonso, L. Vigna, R. Caristo and C. N. Sternberg
Level: 2, State: Excluded

Refid: 1615, OCEANS: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Chemotherapy With or Without Bevacizumab in Patients With Platinum-Sensitive Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
C. Aghajanian, S. V. Blank, B. A. Goff, P. L. Judson, M. G. Teneriello, A. Husain, M. A. Sovak, J. Yi and L. R. Nycum
Level: 2, State: Excluded

Refid: 1616, CA-125 can be part of the tumour evaluation criteria in ovarian cancer trials: experience of the GCIG CALYPSO trial
J. Alexandre, C. Brown, D. Coeffic, N. Raban, J. Pfisterer, J. Maenpaa, H. Chalchal, B. Fitzharris, B. Volgger, I. Vergote, C. Pisano, A. Ferrero and E. Pujade-Lauraine
Level: 2, State: Excluded

Refid: 1618, Bevacizumab based chemotherapy in first line treatment of HER2 negative metastatic breast cancer: results of a Moroccan observational institutional study
L. Boulaamane, S. Boutayeb and H. Errihani
Level: 2, State: Excluded

Refid: 1620, Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial
A. Brufsky, V. Valero, B. Tiangco, S. Dakhil, A. Brize, H. S. Rugo, R. Rivera, A. Duenne, N. Bousfoul and D. A. Yardley
Level: 2, State: Excluded

Refid: 1621, Sunitinib followed by sorafenib or vice versa for metastatic renal cell carcinoma--data from the Czech registry
T. Buchler, R. Klapka, B. Melichar, P. Brabec, L. Dusek, R. Vyzula and J. Abrahamova
Level: 2, State: Excluded

Refid: 1624, First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study
E. Diaz-Rubio, A. Gomez-Espana, B. Massuti, J. Sastre, A. Abad, M. Valladares, F. Rivera, M. J. Safont, P. Martinez de Prado, M. Gallen, E. Gonzalez, E. Marcuello, M. Benavides, C. Fernandez-Martos, F. Losa, P. Escudero, A. Arrivi, A. Cervantes, R. Duenas, A. Lopez-Ladron, A. Lacasta, M. Llanos, J. M. Tabernero, A. Anton and E. Aranda
Level: 2, State: Excluded

Refid: 1628, Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitive ovarian cancer patients: results from a subset analysis of the CALYPSO phase III trial
L. Gladieff, A. Ferrero, G. De Rauglaudre, C. Brown, P. Vasey, A. Reinthaller, E. Pujade-Lauraine, N. Reed, D. Lorusso, S. Siena, H. Helland, L. Elit and S. Mahner
Level: 2, State: Excluded

Refid: 1630, A Randomized, Phase II Trial of Standard Triweekly Compared with Dose-Dense Biweekly Capecitabine Plus Oxaliplatin Plus Bevacizumab as First-Line Treatment for Metastatic Colorectal Cancer: XELOX-A-DVS (Dense Versus Standard)
H. Hurwitz, E. P. Mitchell, T. Cartwright, A. Kwok, S. Hu, E. McKenna and Y. Z. Patt
Level: 2, State: Excluded

Refid: 1633, Gastrointestinal perforation associated with bevacizumab use in metastatic colorectal cancer: results from a large treatment observational cohort study
F. F. Kabbinavar, P. J. Flynn, M. Kozloff, M. A. Ashby, A. Sing, C. E. Barr and A. Grothey
Level: 2, State: Excluded

Refid: 1635, Randomized phase 2b study of pralatrexate versus erlotinib in patients with stage IIIB/IV non-small-cell lung cancer (NSCLC) after failure of prior platinum-based therapy
K. Kelly, C. G. Azzoli, P. Zatloukal, I. Albert, P. Y. Jiang, D. Bodkin, J. R. Pereira, E. Juhasz, N. O. Iannotti, G. Weems, T. Koutsoukos and J. D. Patel
Level: 2, State: Excluded

Refid: 1636, Pharmacogenetic analysis of BR.21, a placebo-controlled randomized phase III clinical trial of erlotinib in advanced non-small cell lung cancer
G. Liu, D. Cheng, K. Ding, A. Le Maitre, N. Liu, D. Patel, Z. Chen, L. Seymour, F. A. Shepherd and M. S. Tsao
Level: 2, State: Excluded

Refid: 1637, Phase II study of NGR-hTNF in combination with doxorubicin in relapsed ovarian cancer patients
D. Lorusso, G. Scambia, G. Amadio, A. di Legge, A. Pietragalla, R. De Vincenzo, V. Masciullo, M. Di Stefano, G. Mangili, G. Citterio, M. Mantori, A. Lambiase and C. Bordignon
Level: 2, State: Excluded

Refid: 1644, Trabectedin plus pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer: Overall survival analysis
B. J. Monk, T. J. Herzog, S. B. Kaye, C. N. Krasner, J. B. Vermorken, F. M. Muggia, E. Pujade-Lauraine, Y. C. Park, T. V. Parekh and A. M. Poveda
Level: 2, State: Excluded

Refid: 1650, Bevacizumab is equally effective and no more toxic in elderly patients with advanced colorectal cancer: a subgroup analysis from the AGITG MAX trial: an international randomised controlled trial of Capecitabine, Bevacizumab and Mitomycin C
T. J. Price, D. Zannino, K. Wilson, R. J. Simes, J. Cassidy, G. A. Van Hazel, B. A. Robinson, A. Broad, V. Ganju, S. P. Ackland and N. C. Tebbutt
Level: 2, State: Excluded

Refid: 1653, Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial
R. Rosell, E. Carcereny, R. Gervais, A. Vergnenegre, B. Massuti, E. Felip, R. Palmero, R. Garcia-Gomez, C. Pallares, J. M. Sanchez, R. Porta, M. Cobo, P. Garrido, F. Longo, T. Moran, A. Insa, F. De Marinis, R. Corre, I. Bover, A. Illiano, E. Dansin, J. de Castro, M. Milella, N. Reguart, G. Altavilla, U. Jimenez, M. Provencio, M. A. Moreno, J. Terrasa, J. Munoz-Langa, J. Valdivia, D. Isla, M. Domine, O. Molinier, J. Mazieres, N. Baize, R. Garcia-Campelo, G. Robinet, D. Rodriguez-Abreu, G. Lopez-Vivanco, V. Gebbia, L. Ferrera-Delgado, P. Bombaron, R. Bernabe, A. Bearz, A. Artal, E. Cortesi, C. Rolfo, M. Sanchez-Ronco, A. Drozdowskyj, C. Queralt, I. de Aguirre, J. L. Ramirez, J. J. Sanchez, M. A. Molina, M. Taron and L. Paz-Ares
Level: 2, State: Excluded

Refid: 1654, Phase III trial of cetuximab, bevacizumab, and 5-fluorouracil/leucovorin vs. FOLFOX-bevacizumab in colorectal cancer
L. Saltz, S. Badarinath, S. Dakhil, B. Bienvenu, W. G. Harker, G. Birchfield, L. K. Tokaz, D. Barrera, P. R. Conkling, M. A. O'Rourke, D. A. Richards, D. Reidy, D. Solit, E. Vakiani, M. Capanu, A. Scales, F. Zhan, K. A. Boehm, L. Asmar and A. Cohn
Level: 2, State: Excluded

Refid: 1655, Sunitinib Plus Erlotinib Versus Placebo Plus Erlotinib in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer: A Phase III Trial
G. V. Scagliotti, M. Krzakowski, A. Szczesna, J. Strausz, A. Makhson, M. Reck, R. F. Wierzbicki, I. Albert, M. Thomas, J. E. Miziara, Z. S. Papai, N. Karaseva, S. Thongprasert, E. D. Portulas, J. von Pawel, K. Zhang, P. Selaru, L. Tye, R. C. Chao and R. Govindan
Level: 2, State: Excluded

Refid: 1657, Randomised phase-II trial of CAPIRI (capecitabine, irinotecan) plus bevacizumab vs FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) plus bevacizumab as first-line treatment of patients with unresectable/metastatic colorectal cancer (mCRC)
J. Souglakos, N. Ziras, S. Kakolyris, I. Boukovinas, N. Kentepozidis, P. Makrantonakis, S. Xynogalos, C. Christophyllakis, C. Kouroussis, L. Vamvakas, V. Georgoulias and A. Polyzos
Level: 2, State: Excluded

Refid: 1659, Maintenance of Clinical Efficacy After Dose Reduction of Ixabepilone Plus Capecitabine in Patients With Anthracycline- and Taxane-Resistant Metastatic Breast Cancer: A Retrospective Analysis of Pooled Data from 2 Phase III Randomized Clinical Trials
V. Valero, E. Vrdoljak, B. Xu, E. Thomas, H. Gomez, A. Manikhas, C. Medina, R. K. Li, J. Ro, L. Bosserman, L. Vahdat, P. Mukhopadhyay, D. Opatt and J. A. Sparano
Level: 2, State: Excluded

Refid: 1689, Overall Survival Benefit With Lapatinib in Combination With Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer: Final Results From the EGF104900 Study
K. L. Blackwell, H. J. Burstein, A. M. Storniolo, H. S. Rugo, G. Sledge, G. Aktan, C. Ellis, A. Florance, S. Vukelja, J. Bischoff, J. Baselga and J. O'Shaughnessy
Level: 2, State: Excluded

Refid: 1722, Q-TWiST analysis to estimate overall benefit for patients with metastatic renal cell carcinoma treated in a phase III trial of sunitinib vs interferon-alpha
S. Patil, R. A. Figlin, T. E. Hutson, M. D. Michaelson, S. Negrier, S. T. Kim, X. Huang and R. J. Motzer
Level: 2, State: Excluded

Refid: 1739, Efficacy and safety of sorafenib in advanced renal cell carcinoma patients: Results from a long-term study
L. Yang, L. Shi, Q. Fu, H. Xiong, M. Zhang and S. Yu
Level: 2, State: Excluded

Level 2, Form Full-Text Screening, Does this study report a direct association between PFS and a PRO/QOL outcome? -> No-EXCLUDE

Refid: 73, Health-related quality of life in patients with advanced colorectal cancer treated with cetuximab: overall and KRAS-specific results of the NCIC CTG and AGITG CO.17 Trial
H. J. Au, C. S. Karapetis, C. J. O'Callaghan, D. Tu, M. J. Moore, J. R. Zalcberg, H. Kennecke, J. D. Shapiro, S. Koski, N. Pavlakis, D. Charpentier, D. Wyld, M. Jefford, G. J. Knight, N. M. Magoski, M. D. Brundage and D. J. Jonker
Level: 2, State: Excluded

Refid: 87, Biweekly carboplatin/gemcitabine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: report of efficacy, quality of life and geriatric assessment
A. Bamias, G. Lainakis, E. Kastritis, N. Antoniou, G. Alivizatos, A. Koureas, M. Chrisofos, A. Skolarikos, E. Karayiotis and M. A. Dimopoulos
Level: 2, State: Excluded

Refid: 108, Patient-reported outcomes in a phase iii study of everolimus versus placebo in patients with metastatic carcinoma of the kidney that has progressed on vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy
J. L. Beaumont, Z. Butt, J. Baladi, R. J. Motzer, T. Haas, N. Hollaender, A. Kay and D. Cella
Level: 2, State: Excluded

Refid: 114, Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment
L. Bennett, Z. Zhao, B. Barber, X. Zhou, M. Peeters, J. Zhang, F. Xu, J. Wiezorek and J. Y. Douillard
Level: 2, State: Excluded

Refid: 152, Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse
M. Brada, K. Hoang-Xuan, R. Rampling, P. Y. Dietrich, L. Y. Dirix, D. Macdonald, J. J. Heimans, B. A. Zonnenberg, J. M. Bravo-Marques, R. Henriksson, R. Stupp, N. Yue, J. Bruner, M. Dugan, S. Rao and S. Zaknoen
Level: 2, State: Excluded

Refid: 167, Effects of sorafenib on symptoms and quality of life: results from a large randomized placebo-controlled study in renal cancer
R. Bukowski, D. Cella, K. Gondek, B. Escudier and T. C. T. G. Sorafenib
Level: 2, State: Excluded

Refid: 189, The prognostic effects of performance status and quality of life scores on progression-free survival and overall survival in advanced ovarian cancer
M. S. Carey, M. Bacon, D. Tu, L. Butler, A. Bezjak and G. C. Stuart
Level: 2, State: Excluded

Refid: 200, Baseline quality of life as a prognostic survival tool in patients receiving sunitinib for metastatic renal cell carcinoma
D. Cella, A. G. Bushmakin, J. C. Cappelleri, C. Charbonneau, M. D. Michaelson and R. J. Motzer
Level: 2, State: Excluded

Refid: 201, Quality of Life Predicts Progression-Free Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib Versus Interferon Alfa
D. Cella, J. C. Cappelleri, A. Bushmakin, C. Charbonneau, J. Z. Li, S. T. Kim, I. Chen, M. D. Michaelson and R. J. Motzer
Level: 2, State: Excluded

Refid: 204, Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon alfa: results from a phase III randomized trial
D. Cella, J. Z. Li, J. C. Cappelleri, A. Bushmakin, C. Charbonneau, S. T. Kim, I. Chen and R. J. Motzer
Level: 2, State: Excluded

Refid: 260, Baseline physical functioning status of metastatic colorectal cancer patients predicts the overall survival but not the activity of a front-line oxaliplatin-fluoropyrimidine doublet
P. Comella, R. Casaretti, R. Manzo, C. Sandomenico, M. Licenziato, A. Avallone and L. Franco
Level: 2, State: Excluded

Refid: 285, Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy
B. Coudert, T. Ciuleanu, K. Park, Y. L. Wu, G. Giaccone, W. Brugger, P. Gopalakrishna and F. Cappuzzo
Level: 2, State: Excluded

Refid: 313, Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer
A. de Gramont, A. Figer, M. Seymour, M. Homerin, A. Hmissi, J. Cassidy, C. Boni, H. Cortes-Funes, A. Cervantes, G. Freyer, D. Papamichael, N. Le Bail, C. Louvet, D. Hendler, F. de Braud, C. Wilson, F. Morvan and A. Bonetti
Level: 2, State: Excluded

Refid: 315, Lung Cancer Symptom Scale outcomes in relation to standard efficacy measures: an analysis of the phase III study of pemetrexed versus docetaxel in advanced non-small cell lung cancer
F. de Marinis, J. R. Pereira, F. Fossella, M. C. Perry, M. Reck, M. Salzberg, J. Jassem, P. Peterson, A. M. Liepa, P. Moore and R. J. Gralla
Level: 2, State: Excluded

Refid: 365, Phase III trial of carboplatin plus paclitaxel with or without gemcitabine in first-line treatment of epithelial ovarian cancer
A. du Bois, J. Herrstedt, A. C. Hardy-Bessard, H. H. Muller, P. Harter, G. Kristensen, F. Joly, J. Huober, E. Avall-Lundqvist, B. Weber, C. Kurzeder, S. Jelic, E. Pujade-Lauraine, A. Burges, J. Pfisterer, M. Gropp, A. Staehle, P. Wimberger, C. Jackisch and J. Sehouli
Level: 2, State: Excluded

Refid: 412, Phase II trial of vinorelbine and oxaliplatin as first-line therapy in malignant pleural mesothelioma
D. A. Fennell, C. S. JP, J. Shamash, M. T. Sheaff, M. T. Evans, T. I. Goonewardene, M. L. Nystrom, N. H. Gower and R. M. Rudd
Level: 2, State: Excluded

Refid: 416, Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer
P. M. Fidias, S. R. Dakhil, A. P. Lyss, D. M. Loesch, D. M. Waterhouse, J. L. Bromund, R. Chen, M. Hristova-Kazmierski, J. Treat, C. K. Obasaju, M. Marciniak, J. Gill and J. H. Schiller
Level: 2, State: Excluded

Refid: 449, Temozolomide in elderly patients with newly diagnosed glioblastoma and poor performance status: an ANOCEF phase II trial
J. Gallego Perez-Larraya, F. Ducray, O. Chinot, I. Catry-Thomas, L. Taillandier, J. S. Guillamo, C. Campello, A. Monjour, S. Cartalat-Carel, M. Barrie, A. Huchet, P. Beauchesne, M. Matta, K. Mokhtari, M. L. Tanguy, J. Honnorat and J. Y. Delattre
Level: 2, State: Excluded

Refid: 660, Phase II study of induction chemotherapy with TPF followed by radioimmunotherapy with Cetuximab and intensity-modulated radiotherapy (IMRT) in combination with a carbon ion boost for locally advanced tumours of the oro-, hypopharynx and larynx--TPF-C-HIT
A. D. Jensen, J. Krauss, K. Potthoff, A. Desta, G. Habl, A. Mavtratzas, C. Windemuth-Kiesselbach, J. Debus and M. W. Munter
Level: 2, State: Excluded

Refid: 682, Health-related quality of life impact of bevacizumab when combined with irinotecan, 5-fluorouracil, and leucovorin or 5-fluorouracil and leucovorin for metastatic colorectal cancer
F. F. Kabbinavar, J. F. Wallace, E. Holmgren, J. Yi, D. Cella, K. J. Yost and H. I. Hurwitz
Level: 2, State: Excluded

Refid: 915, Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer
K. Miller, M. Wang, J. Gralow, M. Dickler, M. Cobleigh, E. A. Perez, T. Shenkier, D. Cella and N. E. Davidson
Level: 2, State: Excluded

Refid: 916, Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer
K. D. Miller, L. I. Chap, F. A. Holmes, M. A. Cobleigh, P. K. Marcom, L. Fehrenbacher, M. Dickler, B. A. Overmoyer, J. D. Reimann, A. P. Sing, V. Langmuir and H. S. Rugo
Level: 2, State: Excluded

Refid: 947, Sunitinib versus interferon alfa in metastatic renal-cell carcinoma
R. J. Motzer, T. E. Hutson, P. Tomczak, M. D. Michaelson, R. M. Bukowski, O. Rixe, S. Oudard, S. Negrier, C. Szczylik, S. T. Kim, I. Chen, P. W. Bycott, C. M. Baum and R. A. Figlin
Level: 2, State: Excluded

Refid: 957, Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer
D. G. Mutch, M. Orlando, T. Goss, M. G. Teneriello, A. N. Gordon, S. D. McMeekin, Y. Wang, D. R. Scribner, Jr., M. Marciniack, R. W. Naumann and A. A. Secord
Level: 2, State: Excluded

Refid: 996, Health-related quality of life and colorectal cancer-specific symptoms in patients with chemotherapy-refractory metastatic disease treated with panitumumab
D. Odom, B. Barber, L. Bennett, M. Peeters, Z. Zhao, J. Kaye, M. Wolf and J. Wiezorek
Level: 2, State: Excluded

Refid: 1044, Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and KRAS status in patients receiving panitumumab monotherapy
M. Peeters, S. Siena, E. Van Cutsem, A. Sobrero, A. Hendlisz, S. Cascinu, H. Kalofonos, G. Devercelli, M. Wolf and R. G. Amado
Level: 2, State: Excluded

Refid: 1046, Experience of external beam radiotherapy given adjuvantly or at relapse following surgery for craniopharyngioma
L. S. Pemberton, M. Dougal, B. Magee and H. R. Gattamaneni
Level: 2, State: Excluded

Refid: 1060, Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG
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J. Pfisterer, M. Plante, I. Vergote, A. du Bois, H. Hirte, A. J. Lacave, U. Wagner, A. Stahle, G. Stuart, R. Kimmig, S. Olbricht, T. Le, J. Emerich, W. Kuhn, J. Bentley, C. Jackisch, H. J. Luck, J. Rochon, A. H. Zimmermann and E. Eisenhauer
Level: 2, State: Excluded

Refid: 1061, Combination therapy with gemcitabine and carboplatin in recurrent ovarian cancer
J. Pfisterer, I. Vergote, A. Du Bois and E. Eisenhauer
Level: 2, State: Excluded

Refid: 1066, Carboplatin Plus Paclitaxel Versus Carboplatin Plus Pegylated Liposomal Doxorubicin As First-Line Treatment for Patients With Ovarian Cancer: The MITO-2 Randomized Phase III Trial
S. Pignata, G. Scambia, G. Ferrandina, A. Savarese, R. Sorio, E. Breda, V. Gebbia, P. Musso, L. Frigerio, P. Del Medico, A. V. Lombardi, A. Febbraro, P. Scollo, A. Ferro, S. Tamberi, A. Brandes, A. Ravaioli, M. R. Valerio, E. Aitini, D. Natale, L. Scaltriti, S. Greggi, C. Pisano, D. Lorusso, V. Salutari, F. Legge, M. Di Maio, A. Morabito, C. Gallo and F. Perrone
Level: 2, State: Excluded

Refid: 1073, Health-related quality of life outcomes of docetaxel/carboplatin combination therapy vs. sequential therapy with docetaxel then carboplatin in patients with relapsed, platinum-sensitive ovarian cancer: results from a randomized clinical trial
R. Pokrzywinski, A. A. Secord, L. J. Havrilesky, L. E. Puls, R. W. Holloway, G. S. Lewandowski, R. V. Higgins, L. R. Nycum, M. F. Kohler and D. A. Revicki
Level: 2, State: Excluded

Refid: 1129, Raltitrexed-eloxatin salvage chemotherapy in gemcitabine-resistant metastatic pancreatic cancer
M. Reni, L. Pasetto, G. Aprile, S. Cordio, E. Bonetto, S. Dell'Oro, P. Passoni, L. Piemonti, C. Fugazza, G. Luppi, C. Milandri, R. Nicoletti, A. Zerbi, G. Balzano, V. Di Carlo and A. A. Brandes
Level: 2, State: Excluded

Refid: 1198, Interferon-alpha as maintenance therapy in patients with multiple myeloma
C. G. Schaar, H. C. Kluin-Nelemans, C. Te Marvelde, S. le Cessie, W. P. Breed, W. E. Fibbe, W. A. van Deijk, M. M. Fickers, K. J. Roozendaal and P. W. Wijermans
Level: 2, State: Excluded

Refid: 1204, Outpatient taxol and carboplatin chemotherapy for suboptimally debulked epithelial carcinoma of the ovary results in improved quality of life: an Eastern Cooperative Oncology Group Phase II Study (E2E93)
J. C. Schink, E. Weller, L. S. Harris, D. Cella, J. Gerstner, C. Falkson and S. Wadler
Level: 2, State: Excluded

Refid: 1288, Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial
C. N. Sternberg, I. D. Davis, J. Mardiak, C. Szczylik, E. Lee, J. Wagstaff, C. H. Barrios, P. Salman, O. A. Gladkov, A. Kavina, J. J. Zarba, M. Chen, L. McCann, L. Pandite, D. F. Roychowdhury and R. E. Hawkins
Level: 2, State: Excluded

Refid: 1307, Health-related quality of life as prognostic factor for response, progression-free survival, and survival in women with metastatic breast cancer
H. Svensson, T. Hatschek, H. Johansson, Z. Einbeigi and Y. Brandberg
Level: 2, State: Excluded

Refid: 1334, Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study
N. C. Tebbutt, K. Wilson, V. J. Gebski, M. M. Cummins, D. Zannino, G. A. van Hazel, B. Robinson, A. Broad, V. Ganju, S. P. Ackland, G. Forgeson, D. Cunningham, M. P. Saunders, M. R. Stockler, Y. Chua, J. R. Zalcberg, R. J. Simes and T. J. Price
Level: 2, State: Excluded

Refid: 1340, High-dose chronomodulated infusion of 5-fluorouracil (5-FU) and folinic acid (FA) (FF5-16) in advanced colorectal cancer patients
E. Terzoli, C. Garufi, A. R. Zappala, B. Vanni, P. Pugliese, G. A. Cappellini, A. M. Aschelter, M. Perrone and D. Giannarelli
Level: 2, State: Excluded

Refid: 1349, Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer
J. Tol, M. Koopman, A. Cats, C. J. Rodenburg, G. J. M. Creemers, J. G. Schrama, F. L. G. Erdkamp, A. H. Vos, C. J. van Groeningen, H. A. M. Sinnige, D. J. Richel, E. E. Voest, J. R. Dijkstra, M. E. Vink-Borger, N. F. Antonini, L. Mol, J. H. J. M. van Krieken, O. Dalesio and C. J. A. Punt
Level: 2, State: Excluded

Refid: 1383, Irinotecan versus infusional 5-fluorouracil: a phase III study in metastatic colorectal cancer following failure on first-line 5-fluorouracil. V302 Study Group
E. Van Cutsem and G. H. Blijham
Level: 2, State: Excluded

Refid: 1440, Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer
J. T. Wei, R. L. Dunn, H. M. Sandler, P. W. McLaughlin, J. E. Montie, M. S. Litwin, L. Nyquist and M. G. Sanda
Level: 2, State: Excluded

Refid: 1445, Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study
L. B. Wenzel, H. Q. Huang, D. K. Armstrong, J. L. Walker and D. Cella
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Refid: 1447, Erlotinib for advanced non-small-cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21
P. Wheatley-Price, K. Ding, L. Seymour, G. M. Clark and F. A. Shepherd
Level: 2, State: Excluded

Refid: 1468, Impact of lapatinib plus trastuzumab versus single-agent lapatinib on quality of life of patients with trastuzumab-refractory HER2+ metastatic breast cancer
Y. Wu, M. M. Amonkar, B. H. Sherrill, J. O'Shaughnessy, C. Ellis, J. Baselga, K. L. Blackwell and H. J. Burstein
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Refid: 1495, A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse
W. K. Yung, R. E. Albright, J. Olson, R. Fredericks, K. Fink, M. D. Prados, M. Brada, A. Spence, R. J. Hohl, W. Shapiro, M. Glantz, H. Greenberg, R. G. Selker, N. A. Vick, R. Rampling, H. Friedman, P. Phillips, J. Bruner, N. Yue, D. Osoba, S. Zaknoen and V. A. Levin
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Refid: 1496, Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group
W. K. Yung, M. D. Prados, R. Yaya-Tur, S. S. Rosenfeld, M. Brada, H. S. Friedman, R. Albright, J. Olson, S. M. Chang, A. M. O'Neill, A. H. Friedman, J. Bruner, N. Yue, M. Dugan, S. Zaknoen and V. A. Levin
Level: 2, State: Excluded

Refid: 1508, Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21
A. Bezjak, D. Tu, L. Seymour, G. Clark, A. Trajkovic, M. Zukin, J. Ayoub, S. Lago, R. de Albuquerque Ribeiro, A. Gerogianni, A. Cyjon, J. Noble, F. Laberge, R. T. Chan, D. Fenton, J. von Pawel, M. Reck and F. A. Shepherd
Level: 2, State: Excluded

Refid: 1688, Efficacy, safety and quality-of-life associated with lenalidomide plus dexamethasone for the treatment of relapsed or refractory multiple myeloma: the Spanish experience
A. Alegre, A. Oriol-Rocafiguera, J. Garcia-Larana, M. V. Mateos, A. Sureda, C. M. Chamorro, M. T. Cibeira, B. Aguado, R. Knight and B. Rosettani
Level: 2, State: Excluded

Refid: 1738, Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: A subanalysis of the phase III, randomized SATURN study
Y. L. Wu, J. H. Kim, K. Park, A. Zaatar, G. Klingelschmitt and C. Ng
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