Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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TABLE OF CONTENTS

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Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to provide recommendations to applicants on endpoints for non-small cell lung cancer (NSCLC) clinical trials of drugs that are submitted to the Food and Drug Administration (FDA) to support effectiveness claims in new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications.[2] This guidance is a companion to the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*.[3]

This guidance addresses the FDA's current thinking regarding efficacy endpoints in trials to evaluate drugs to treat lung cancer and takes into account discussions held at a public workshop (April 15, 2003) and at a meeting of the FDA's Oncologic Drugs Advisory Committee (ODAC) (December 16, 2003).[4] This guidance does not address efficacy endpoints for drugs intended to prevent or decrease the incidence of lung cancer.

[1] This guidance has been prepared by the Division of Oncology Products 2 in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[4] Transcripts are available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm117709.htm#lung and http://www.fda.gov/ohrms/dockets/ac/03/transcripts/4009T1.pdf.

This guidance also does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*. This guidance focuses on specific drug development and trial design issues that are unique to the study of lung cancer drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

According to American Cancer Society estimates, during 2013 there would be nearly 228,190 new cases of lung cancer. Lung cancer accounts for approximately 14 percent of all new cancers and it is the leading cause of cancer deaths, accounting for about 27 percent of all cancer deaths. Evaluation of new drugs for the treatment of lung cancer is based on well-conducted and controlled trials assessing appropriate endpoints to establish clinical benefit and support approval.[5]

A. Endpoints Supporting Past Approvals

For regular approval of an NDA or BLA, the applicant must show direct evidence of clinical benefit or improvement in an established, validated surrogate for clinical benefit. FDA's accelerated approval pathway,[6] allows for the use of two additional types of endpoints to support approval of drugs or biological products that are intended to treat serious or life-threatening diseases and that provide a meaningful therapeutic benefit over existing treatments (e.g., demonstrate an improvement over available therapy or provide therapy where none exists).[7] Specifically, accelerated approval may be based on: (1) an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit; or (2) an effect on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.[8,9]

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[5] See the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* for information regarding regulatory requirements for effectiveness.

[6] See section 506(c) of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 314, subpart H, and part 601, subpart E.

[7] See Johnson, JR, G Williams, R Pazdur, 2003, Endpoints and United States Food and Drug Administration Approval of Oncology Drugs, J Clin Oncol, 21:1404-1411; and Dagher, R, J Johnson, G Williams, P Keegan, R Pazdur, 2004, Accelerated Approval of Oncology Products: A Decade of Experience, JNCI, 96:1500-1509.

[8] See the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* for a detailed discussion on general endpoint and respective trial design considerations.

[9] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics.*

In the past, three commonly used efficacy endpoints in trials assessing treatments of lung cancer were overall survival (OS), time to progression (TTP) or progression-free survival (PFS), and objective tumor response rates (ORR) (see Table 1). Reduction in patients' tumor-related symptoms has also been used as an efficacy endpoint (see Table 1). The majority of drug approvals for NSCLC have been based on a significant improvement in OS, as the median survival was relatively short (less than a year) and thus rarely increased the duration of the trial over use of PFS or ORR as a primary outcome measure. Additionally, OS is an optimal endpoint because the measurement is accurate, is observed on a daily basis, and provides direct evidence of clinical benefit to the patient. Regular approval was granted on the basis of a significant improvement in OS. Similarly, reduction in patients' tumor-related symptoms can also provide direct evidence of clinical benefit and can support regular approval.

When the observed differences in TTP or PFS are of a substantial magnitude, then TTP or PFS may provide evidence of clinical benefit sufficient to support approval. The magnitude of the treatment effect is viewed in the context of the toxicity of the drug, the relatively short survival for NSCLC, especially in those with recurrent or treatment-refractory disease, available therapy for the stage, histologic or genetic subtype of NSCLC, and extent of prior treatment. Because of the significance of these individual factors, a fixed magnitude of effect that generally will support approval cannot be specified.

Treatment effects on ORR have not been demonstrated to reliably predict corresponding effects on survival in NSCLC. We consider demonstration of ORR alone to be a surrogate endpoint reasonably likely to predict clinical benefit only when the treatment effect size is large and the responses are durable. In these circumstances, ORR has been used as the basis only for accelerated approval for NSCLC. In other circumstances, such as when clinical trials have shown that ORR correlated with well-documented improvements in patient tumor-related symptoms (e.g., photodynamic therapy for treatment of obstructing endobronchial therapy), ORR has supported regular approval.

The criteria for disease progression and tumor response are based on subjective interpretation of radiographic images and clinical evaluation. These subjective interpretations have potential to introduce bias, particularly when evaluated in open-label trials. Specifically, primary lung tumors and regional nodal disease frequently have ill-defined borders that can be difficult to accurately and reproducibly measure radiographically. Therefore, confidence in tumor measurement-based outcomes depends on the frequency of assessments as well as clear, objective criteria for defining disease progression and tumor response. Substantial numbers of missing tumor assessments can potentially overestimate or underestimate treatment differences.

Patient-reported outcome (PRO) measures of tumor-related symptoms and functioning can provide direct evidence of treatment benefit if demonstrated to be well-defined and reliable assessments of a clinically meaningful concept or set of concepts, and if evaluated in well-conducted, placebo-controlled or double-blinded, randomized trials.[10] Well-defined and reliable

[10] See the transcripts of the Oncologic Drugs Advisory Committee Endpoints in Clinical Cancer Trials and Endpoints in Lung Cancer Clinical Trials, December 16, 2003, pp 188-368 (http://www.fda.gov/ohrms/dockets/ac/03/transcripts/4009T1.pdf).

assessments include those that have documented evidence of content validity, construct validity, reliability, and ability to detect change, in addition to established methods for interpreting trial results.[11] Well-conducted clinical trials include protocols with defined schedules for PRO assessment at frequencies that correspond to the intended claims, plans to minimize unintentional unblinding, and prespecified statistical strategies for handling missing data, particularly at or near the time of disease progression.

[11] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

Table 1. Regulatory Experience With New Drug Approvals for the Treatment of NSCLC

Drug	Trial Design	Approval Endpoints/Year Approved
First-Line Inoperable/Metastatic NSCLC		
Vinorelbine monotherapy	Open-label, randomized, active-controlled trial vs. 5-FU/leucovorin	OS, ORR/1994
Vinorelbine in combination with cisplatin	Open-label, randomized, active-controlled trial vs. cisplatin	OS, ORR/1994
Docetaxel in combination with cisplatin	Open-label, randomized, active-controlled trial, docetaxel/cisplatin vs. vinorelbine/cisplatin	OS, TTP, ORR/1999
Gemcitabine in combination with cisplatin	(1) Open-label, randomized, active-controlled trial vs. cisplatin (2) Open-label, randomized, active-controlled trial, gemcitabine + cisplatin vs. etoposide + cisplatin	OS/1998 TTP, ORR
Bevacizumab in combination with paclitaxel/carboplatin[1]	Open-label, randomized, active-controlled trial vs. paclitaxel/carboplatin	OS/2006
Paclitaxel in combination with cisplatin	Open-label, active-controlled, dose-ranging, randomized, three-arm trial, paclitaxel (135 mg/m^2)/cisplatin vs. paclitaxel (250 mg/m^2)/cisplatin vs. etoposide/cisplatin	TTP, ORR, OS/1998
Pemetrexed in combination with cisplatin[1,2,3]	Open-label, active-controlled, randomized trial; pemetrexed/cisplatin vs. gemcitabine/cisplatin	OS measured in a subset of patients/2008
Anaplastic Lymphoma Kinase Positive Locally Advanced or Metastatic NSCLC		
Crizotinib monotherapy[2]	Single-arm trial	Durable ORR/2011
First-Line Metastatic NSCLC Whose Tumors Have Epidermal Growth Factor Receptor Exon 19 Deletions or Exon 21 (L858R) Substitution Mutations		
Erlotinib monotherapy	Open-label, randomized, active-controlled trial vs. platinum-based doublet chemotherapy	PFS/2013
Maintenance Therapy		
Pemetrexed in patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy[1]	Randomized, double-blind, placebo-controlled trial	OS/2009
Erlotinib in patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy	Randomized, double-blind, placebo-controlled trial	OS/2010
Second-Line NSCLC		
Docetaxel	Randomized, placebo-controlled trial, docetaxel vs. best supportive care	OS, TTP, ORR/1999

continued

Table 1, continued

Drug	**Trial Design**	**Approval Endpoints/Year Approved**
Erlotinib	Randomized, placebo-controlled trial, erlotinib vs. best supportive care	OS, TTP, ORR/2004
Pemetrexed[1,2]	Randomized, open-label trial vs. docetaxel	Durable ORR, ↓ Toxicity/2004
Third-Line NSCLC		
Erlotinib	Randomized, placebo-controlled trial erlotinib vs. best supportive care	OS, TTP, ORR/2004
Gefitinib[2,4]	Single-arm trial	Durable ORR/2003
Partially or Completely Obstructing Endobronchial Tumor NSCLC and Microinvasive Endobronchial NSCLC in Nonsurgical Candidates		
Porfimer sodium and photodynamic therapy	Randomized, open-label, active-controlled trial vs. YAG laser	Improvement in disease-related symptoms/1998

[1] Limited to non-squamous, non-small cell lung cancer.
[2] Accelerated approval.
[3] Because the approval was based on a subgroup of patients, confirmatory evidence in the subgroup came from an on-going study as required under the accelerated approval.
[4] Subsequent studies did not confirm clinical benefit; indication withdrawn in September 2011.

B. Summary of Workshop and Advisory Committee Discussions

The American Society of Clinical Oncology (ASCO) and the FDA held a public workshop on lung cancer endpoints on April 15, 2003, with participants that included representatives from the FDA, ASCO, the National Cancer Institute, academia, advocacy groups, and industry.[12] The workshop primarily addressed advanced and metastatic NSCLC, and participants discussed the pros and cons of using OS, tumor assessment-based endpoints, and PRO measures in evaluating drugs for marketing approval. These discussions recognized that although ORR is a commonly used endpoint, it does not predict effects on OS. The clinical significance of small differences in TTP may be unclear, especially when evaluating toxic therapy. TTP is subject to ascertainment bias in open-label trials, and bias can occur if follow-up schedules are asymmetric among trial arms.

Speakers at the workshop noted that assessment of disease progression at frequent intervals is labor intensive and can be expensive. PRO measures can constitute important clinical benefit endpoints, particularly in a predominantly symptomatic disease such as NSCLC. However, adequate evaluation of treatment effect based on PRO measures involves blinded, randomized trials using instruments that reliably and validly measure concepts that define treatment benefit in the targeted clinical trial population, with response options and a recall period that have been demonstrated to be appropriate and interpretable in the subset of patients studied. Analytical challenges, including sensitive but uninterpretable instruments or large amounts of missing data, pose additional difficulties in evaluating an experimental therapy based on PRO data. OS is considered the most appropriate endpoint that is definitive and easy to determine. An observed OS benefit in a well-conducted, randomized trial can be directly attributed to the experimental therapy.

Subsequent to the above-mentioned public workshop, an ODAC meeting was held on December 16, 2003, in which the workshop discussions regarding lung cancer endpoints were presented to the committee.

(1) The committee voted 17 to 2 that since no drug was approved for the adjuvant treatment of NSCLC, hypothetically disease-free survival can be a reasonable endpoint to evaluate new therapy in an adjuvant setting.

(2) As of the date of the meeting, approval for the treatment of metastatic NSCLC generally had been based on demonstration of improvement in OS. The committee considered whether studies incorporating a tumor-based time-to-event endpoint such as PFS or TTP as a primary endpoint could support regular approval, or only accelerated approval. The committee recommended that the tumor-based endpoint of PFS be considered to be preferable to TTP, since PFS includes deaths particularly when there are missing assessments. The uncertainties in measuring PFS were recognized (e.g., measure provides indirect evidence of clinical benefit, unclear clinical meaning of small differences in PFS, the noise and variability in the assessments caused by imaging or

[12] See the workshop summary: American Society of Clinical Oncology/FDA Lung Cancer Endpoints Workshop, April 15, 2003 at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm117709.htm#lung.

timing of assessments, missing and unevaluable data). The committee voted 11 to 8 that PFS may be used as an endpoint to evaluate drug effect in metastatic disease for consideration of regular approval.

(3) Regarding the evaluation of drug effect in inoperable or locally advanced disease, the committee voted 15 to 3 that an effect on PFS should not be considered sufficient to support regular approval and that new drugs should be evaluated based on OS. To consider differences in PFS as the basis for accelerated approval, the committee was of the opinion that the treatment differences based on PFS had to be substantial (e.g., 3 months or more). It was also recognized that PRO endpoints, such as delay in symptom progression, are important and that better tools are needed to minimize bias and to define what constitutes a benefit.

(4) The committee also discussed the challenges in using noninferiority trial designs with OS and PFS endpoints. A trial with a noninferiority hypothesis should be considered only if the active control has established efficacy, the active control effect size can be estimated for patients with the indication under consideration, and the percent of active control effect size to be retained can be prespecified.[13] The effect size of the active control on the primary endpoint of interest should be established based on meta-analysis of historical, randomized trials. It is not possible to prespecify the percent of active control effect size to be retained when the active control effect size is not well established. When considering trials with a noninferiority hypothesis, an assumption that should be assessed is the constancy of the treatment effect over time attributed to the active comparator. Because medical practice, clinical trial conduct, the timing of tumor progression assessments, the radiological modalities used, and the criteria and definition for assessing progression that have evolved over time vary between trials, especially when trials are conducted in different geographic regions, it is difficult to verify the constancy assumption with PFS as primary endpoint.

Based on these recommendations from the 2003 advisory committee meeting, we have continued to recommend OS as the primary endpoint for NSCLC clinical trials. However, a clinical trial demonstrating a large improvement in PFS, with acceptable toxicity, could potentially lead to regular approval, particularly in an unmet medical need population.

III. RECOMMENDATIONS

We consider OS to be the standard clinical benefit endpoint that should be used to establish efficacy of a treatment in patients with locally advanced or metastatic NSCLC. However, other endpoints can be considered for regulatory decision-making based on the population and risk-benefit profile of a drug. We also recognize that it may not always be feasible to conduct separate trials in patients with locally advanced and metastatic NSCLC.

[13] See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

PFS may be appropriate as the primary endpoint to establish efficacy for drug approval if the trial is designed to demonstrate a large magnitude for the treatment effect as measured by both the hazard ratio and absolute difference in median PFS and an acceptable risk-benefit profile of the drug is demonstrated. Sponsors should justify use of PFS as the primary efficacy endpoint and the magnitude of PFS effect considered likely to predict OS or to represent clinical benefit *versus* the risk of the drug in the context of the lung cancer stage and results of treatment with alternative therapy. Because of the subjectivity in the measurement of PFS assessments and the fact that the assessments depend on frequency, accuracy, reproducibility, and completeness, the observed magnitude of effect should be substantial and statistically robust. If investigator-assessed PFS is considered the primary endpoint for establishing efficacy, then evidence of lack of bias should be provided, for example, by verification of investigator assessment in a random sample audit conducted by an independent review committee.

Planned interim efficacy analyses based on OS may be appropriate. However, interim efficacy analyses of PFS before completion of patient accrual are discouraged. Early interim efficacy analyses of PFS that cross a stopping boundary often overstate the magnitude of the effect. An interim PFS efficacy analysis is unlikely to provide an accurate or reproducible estimate of the treatment effect size because of inadequate follow-up, missing assessments, inconsistent readings between radiological reviewers, and/or lack of concordance between investigators and independent assessors. Stopping a trial based on interim PFS efficacy results that may not be verifiable after adjudication can render the trial results uninterpretable. In addition, a statistically significant difference in PFS that is small in magnitude may not be deemed clinically meaningful. Interim analyses to detect harmful effects or futility for PFS or OS endpoints may be appropriate.

We encourage the development of well-defined and reliable PRO instruments that capture the essential treatment benefit concepts in the targeted population. To interpret PRO data, it is generally useful to gather a complete record of all doses of the concomitant medications, such as analgesics, antidepressants, antiemetics, and antidiarrheals, that may confound interpretation of the PRO of interest and limit the ability to differentiate anticancer treatment effects from the effects of concomitant medication. Recording of concomitant medications can be accomplished using PRO instruments (i.e., event logs) or other assessment tools. We will review the adequacy of all PRO measures based on the principles outlined in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

Regardless of which efficacy endpoints are chosen, NSCLC is a heterogeneous disease with varying response to treatment across different molecular and histopathologic subgroups (e.g., pemetrexed, erlotinib). We recommend that clinical trials be prospectively designed to evaluate such differences in treatment effect.[14]

Although general principles outlined in this guidance should help applicants select endpoints for marketing applications, we recommend that applicants meet with the FDA before submitting protocols intended to support NDA or BLA marketing applications. These meetings will include

[14] See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic.

a multidisciplinary FDA team of oncologists, statisticians, clinical pharmacologists, measurement experts, and often external expert consultants. Applicants can also submit a request for special protocol assessment to obtain confirmation of the appropriateness of endpoint measures and protocol design for individual trials, considered within the context of the overall development program, intended to support drug marketing applications.[15] Marketing approval depends not only on the design of clinical trials, but on FDA review of the results and data from all trials in the marketing application. Applicants who plan to prospectively evaluate treatment effects in a defined subgroup of NSCLC (e.g., a molecularly defined subgroup) should identify such a development program early and refer to guidance on co-development of drugs and devices in the guidance for industry and Food and Drug Administration staff *In Vitro Companion Diagnostic Devices*.

[15] See the guidance for industry *Special Protocol Assessment*.

APPENDIX A: TUMOR MEASUREMENT DATA COLLECTION[16]

The following are important considerations for tumor measurement data. We recommend that:

- The case report form (CRF) and electronic data document the target lesions identified during the baseline visit before treatment. The possibility of bias cannot be eliminated when retrospective identification of lesions is made for local site evaluations of tumor-based endpoints.

- Tumor lesions be assigned a unique identifying letter or number. This assignment differentiates among multiple tumors occurring at one anatomic site and matches tumors measured at baseline with tumors measured during follow-up.

- A mechanism be in place that ensures complete data collection at critical times during follow-up. The CRF should ensure that all target lesions are assessed at baseline and that the same imaging or measuring method is used for all tests required at baseline and follow-up.

- The CRF contains data fields that indicate whether scans were performed at each visit.

- A zero be recorded when a lesion has completely resolved. Otherwise, disappearance of a lesion cannot be differentiated from a missing value.

- Follow-up tests provide for timely detection of new lesions both at initial and at new sites of disease. The occurrence and location of new lesions should be recorded in the CRF and in the submitted electronic data for both protocol-specified evaluations and those identified on *unscheduled* visits.

[16] For the purposes of this appendix, *tumor data* refers to data in SAS transport files, not images. Generally, images are not submitted to the NDA or BLA but can be audited by the FDA during the review process.

APPENDIX B: ISSUES TO CONSIDER IN PFS ANALYSIS

The protocol and statistical analysis plan (SAP) should detail the primary analysis of PFS. This analysis should include a detailed description of the endpoint, appropriate modalities for evaluating tumors, and procedures for minimizing bias. One or two secondary analyses should be specified to evaluate anticipated problems in trial conduct and to assess whether results are robust. The following important factors should be considered.

- **Definition of progression date.** In survival analyses, the exact death date is known. In PFS analyses, the exact progression date is unknown. The following two methods can be used for defining the *recorded progression date (PDate)* used for PFS analysis.

    1. PDate assigned to the first time at which progression can be declared.

        – For progression based on a new lesion, the PDate is the date of the first observation that the new lesion was detected.

        – If multiple assessments based on the sum of target lesion measurements are done at different times, the PDate is the date of the first observation or radiological assessment of target lesions that shows a predefined increase in the sum of the target lesion measurements.

    2. PDate as the date of the protocol-scheduled clinic visit immediately after all radiological assessments (which collectively document progression) have been done. Generally, this is recommended for sensitivity analysis.

- **Definition of censoring date.** Censoring dates are defined in patients with no documented progression before data cutoff or dropout. In these patients, the censoring date is often defined as the last date on which progression status was adequately assessed. One acceptable approach uses the date of the last assessment performed. However, multiple radiological tests can be evaluated in the determination of progression. A second acceptable approach uses the date of the clinic visit corresponding to these radiological assessments.

- **Definition of an adequate PFS evaluation.** In patients with no evidence of progression, censoring for PFS often relies on the date of the last *adequate tumor assessment.* A careful definition of what constitutes an adequate tumor assessment includes adequacy of target lesion assessments and adequacy of radiological tests both to evaluate nontarget lesions and to search for new lesions.

- **Analysis of partially missing tumor data.** Analysis plans should describe the method for calculating progression status when data are partially missing from *adequate tumor assessment* visits.

- **Completely missing tumor data.** Assessment visits where no data are collected are sometimes followed by death or by assessment visits showing progression. In other cases, the subsequent assessment shows no progression. In the latter case, it may seem appropriate

to continue the treatment and continue monitoring for progression. However, this approach treats missing data differently depending upon subsequent events and can represent informative censoring when progression or death is recorded subsequently. Another possible approach is to include data from subsequent PFS assessments. This can be appropriate when evaluations are frequent and when only a single follow-up visit is missed. Censoring at the last adequate tumor assessment can be more appropriate when there are two or more missed visits.

The SAP should detail primary and secondary PFS analyses to evaluate the potential effect of missing data. Reasons for dropouts should be incorporated into procedures for determining censoring and progression status. For instance, for the primary analysis, patients going off-study for undocumented clinical progression, change of cancer treatment, or decreasing performance status can be censored at the last adequate tumor assessment. The secondary sensitivity analysis would include these dropouts as progression events. Although missed visits for progression can be problematic, all efforts should be made to keep following patients for disease progression irrespective of the number of visits missed. Another analysis could ignore these missing assessments and consider the date that progression or death is recorded in a subsequent assessment as the time to event.

- **Progression of nonmeasurable disease.** When appropriate, progression criteria should be described for each assessment modality (e.g., CT scan, bone scan).

- **Suspicious lesions.** An algorithm should be provided for evaluating and following indeterminate lesions for assignment of progression status at the time of analysis.

APPENDIX C: EXAMPLE TABLES FOR PRIMARY PFS ANALYSIS

Examples of prespecified censoring scheme that can be used are provided in the following tables.

Table C1. Example 1 for censoring scheme for PFS

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of last progression with no documented progression	*Censored*
New anticancer treatment started	Date of last progression assessment with documented nonprogression before start of new treatment	*Censored*
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last progression assessment with documented nonprogression	*Censored*

Table C2. Example 2 for censoring scheme for PFS

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of documented progression with protocol specified continued follow-up in all treatment arms	*Progressed*
New anticancer treatment started	Date of documented progression with protocol specified continued follow-up in all treatment arms	*Progressed*
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of documented progression	*Progressed*

APPENDIX D: EXAMPLE TABLES FOR PFS SUPPORTIVE ANALYSIS

Sensitivity analyses can be helpful in determining whether the PFS analysis is robust. However, these sensitivity analyses are exploratory and supportive of the results of the primary analysis, and efficacy may not be claimed based on sensitivity analysis alone. Different sensitivity analyses can be described in tables that specify how dates of progression events and dates for censoring of progression data can be assigned. The following three tables describe examples of three different sensitivity analyses.

The sensitivity analysis in Table D1 corrects for potential bias in follow-up schedules for tumor assessment by assigning the dates for censoring and events only at scheduled visit dates. However, this approach can introduce bias if the progression occurred closer to the last visit.

Table D1. PFS 1 (uniform progression and assessment dates)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Date of next scheduled visit	Progressed
No progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for undocumented progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censored
New anticancer treatment started	Date of last visit with adequate assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last visit with adequate assessment	Censored

The sensitivity analysis in Table D2 uses a conservative approach by assigning the dates of discontinuation, change of treatment, or missed visit as an event date.

Table D2. PFS 2 (any change considered as progression event)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of discontinuation	Progressed

continued

Table D2, continued

Situation	Date of Progression or Censoring	Outcome
Treatment discontinuation for toxicity or other reason	Date of discontinuation	Progressed
New anticancer treatment started	Date of start of new anticancer treatment	Progressed
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of first missed visit	Progressed

The sensitivity analysis in Table D3 evaluates PFS according to the investigator's assessment. However, this approach can introduce bias if the progression occurred closer to the last visit.

Table D3. PFS 3 (includes clinical progression)

Situation	Date of Progression or Censoring	Outcome
No baseline assessment	Randomization	Censored
Progression documented between scheduled visits	Next scheduled visit	Progressed
No progression	Date of last visit with adequate disease progression assessment	Censored
Investigator claim of clinical progression	Scheduled visit (or next scheduled visit if between visits)	Progressed
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate disease progression assessment	Censored
New anticancer treatment started with no claim of progression	Date of last visit with adequate disease progression assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits or after patient misses one assessment visit	Date of death	Progressed
Death after an extended lost-to-follow-up time (two or more missed assessments)	Date of last visit with adequate disease progression assessment	Censored