Clinical Cancer Research

FDA Approval of Palbociclib in Combination with Fulvestrant for the Treatment of Hormone Receptor–Positive, HER2-Negative Metastatic Breast Cancer

Amanda J. Walker, Suparna Wedam, Laleh Amiri-Kordestani, Erik Bloomquist, Shengui Tang, Rajeshwari Sridhara, Wei Chen, Todd R. Palmby, Jeanne Fourie Zirkelbach, Wentao Fu, Qi Liu, Amy Tilley, Geoffrey Kim, Paul G. Kluetz, Amy E. McKee, and Richard Pazdur

Abstract

On February 19, 2016, the FDA approved palbociclib (Ibrance, Pfizer) for use in combination with fulvestrant (Faslodex, AstraZeneca) for the treatment of women with hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer (MBC) with disease progression following endocrine therapy. The approval was based on the results of a randomized, double-blind, placebo-controlled trial conducted in 521 pre- and postmenopausal women with HR-positive, HER2-negative advanced or MBC. Patients were randomized (2:1) to receive palbociclib plus fulvestrant ($n = 347$) or placebo plus fulvestrant ($n = 174$). The primary endpoint was investigator-assessed progression-free survival (PFS). A statistically significant and clinically meaningful improvement in PFS (9.5 months vs. 4.6 months) was observed in patients receiving palbociclib plus fulvestrant [HR 0.46; 95% confidence interval (CI), 0.36–0.59; $P < 0.0001$]. Safety data confirmed the known adverse reaction profile of palbociclib. The most common adverse reactions (>20%) in patients treated with palbociclib were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, headache, diarrhea, and thrombocytopenia. This approval was granted in the context of a prior accelerated approval for palbociclib in combination with letrozole in patients with HR-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy. *Clin Cancer Res; 22(20); 4968–72. ©2016 AACR.*

Introduction

Breast cancer is the second leading cause of cancer-related death among women in the United States (1). The majority of breast cancers are characterized as hormone receptor (HR)-positive/HER2-negative, with endocrine therapy being the mainstay of systemic treatment in this group of patients. Even with early-stage disease and optimal treatment, many patients will develop recurrent or progressive disease and ultimately require treatment with cytotoxic chemotherapeutics (2). Multiple agents have been approved for patients with HR-positive metastatic disease or locally advanced disease not amenable to surgical resection; however, the disease remains fatal due to acquired resistance to available therapies.

In recent years, there has been a search for novel agents to treat recurrent or metastatic HR-positive breast cancer. The cyclin-dependent kinases (CDK) are a family of serine/threonine kinases that play a critical role in the orderly and controlled progression through the cell cycle, and as such, represent an attractive target for new molecularly targeted agents. Palbociclib is an oral, small-molecule kinase inhibitor with activity against CDK 4 and 6, which play a critical role in facilitating the gap 1- (G_1) to synthesis (S)-phase transition (3).

Palbociclib was granted breakthrough therapy designation in April 2013 for the treatment of patients with breast cancer and was granted accelerated approval for the use in combination with letrozole in February 2015. This initial approval was based on the results of the phase II trial, PALOMA-1, and may be contingent upon verification of the description of clinical benefit in the ongoing and fully accrued confirmatory trial, PALOMA-2 (4). The current article summarizes the FDA regulatory process and data in support of regular approval of palbociclib for use in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer (MBC) with disease progression following endocrine therapy.

Study A5381023 (PALOMA-3)

Study design

The FDA approval of this supplemental new drug application (sNDA) for palbociclib was based on the results of PALOMA-3, a placebo-controlled, double-blind, international phase III clinical trial, which randomly allocated (2:1) 521 patients with advanced or metastatic HR-positive, HER2-negative, breast cancer, whose disease progressed after prior endocrine therapy to either fulvestrant (Faslodex) with or without palbociclib. Premenopausal patients were treated with the luteinizing hormone–releasing

Center for Drug Evaluation and Research, U.S. Food and Drug Administration, White Oak, Maryland.

A.J. Walker and S. Wedam share first authorship.

Corresponding Authors: Amanda J. Walker, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Building 22, Room 2103, Silver Spring, MD 20993-0004. Phone: 301-796-1377; Fax: 301-796-9845; E-mail: amanda.walker@fda.hhs.gov; and Suparna Wedam, suparna.wedam@fda.hhs.gov

doi: 10.1158/1078-0432.CCR-16-0493

AACR

hormone agonist goserelin. Refer to section 14 (clinical studies) of the palbociclib United States package insert for further details regarding the PALOMA-3 trial design (5).

Study endpoints

The primary efficacy endpoint of PALOMA-3 was investigator-assessed progression-free survival (PFS), defined as the time from the date of randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. Prespecified secondary endpoints included overall survival (OS), objective response rate (ORR), clinical benefit response, and patient reported outcome (PRO) measures obtained using three specific instruments: The European Organization for Research and Treatment of Cancer Quality of Life Instrument (EORTC QLQ-30), European Organization for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ-BR23), and the EuroQol (EQ-5D; refs. 6, 7).

Statistical plan

The study was designed to detect a 3.4-month difference in median PFS (6.0 months vs 9.4 months) with a HR of 0.64, while using a one-sided α of 0.025. The study planned to enroll 417 subjects and have the final PFS analysis when 238 events had occurred in both arms. The study was designed to have one interim analysis (IA) after 143 events (60% of the final planned events) had occurred to allow for early stopping of the study due to efficacy. The Haybittle–Peto efficacy boundary was to be used at the IA with an α allocation of 0.00135. The intent-to-treat (ITT) population of all randomized patients, regardless of the actual treatment received, was used for all efficacy analyses. A random blinded independent central review (BICR) audit of 40% of the total sample was planned to assess whether bias existed in assessment of effect with respect to the primary investigator PFS endpoint. The safety population consisted of all patients who received at least one dose of study drug or placebo.

Patient baseline characteristics

Patients enrolled in this study had a median age of 57 years (range 29–88). The majority of patients on study were White (74%), all patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and 80% were postmenopausal. All patients had received prior systemic therapy and 75% of patients had received a previous chemotherapy regimen. Twenty-five percent of patients had progressed while on or within 12 months of adjuvant endocrine therapy and had not received prior therapy in the metastatic setting, 60% had visceral metastases, 23% had bone only disease, and 60% had received more than one prior hormonal regimen for the primary diagnosis. The two arms appeared to be well balanced on demographic and baseline characteristics.

Efficacy results

The trial was stopped at the interim analysis based on the recommendation of the independent DMC. At the time of the IA, 193 investigator assessed PFS events had occurred. The median PFS was 9.2 months in the palbociclib plus fulvestrant arm (95% CI, 7.5, NR) and 3.8 months (95% CI, 3.5–5.5) in the placebo plus fulvestrant arm (HR = 0.42; 95% CI, 0.32–0.56; $P < 0.0001$). A final PFS analysis was performed after an additional 3 months of follow-up and 64 more progression events (Table 1 and Fig. 1).

Table 1. Efficacy results—PALOMA-3 (IA, ITT population)

	Palbociclib plus fulvestrant ($n = 347$)	Placebo plus fulvestrant ($n = 174$)
Median PFS (months)	9.5	4.6
95% CI	9.2–11.0	3.5–5.6
Number of PFS events (%)	145 (41.8%)	114 (65.5%)
HR	0.46	
95% CI	0.36–0.59	
P	<0.0001	
ORR	24.6%	10.9%
DOR (months)	9.3	7.6
Clinical benefit response	66.6%	39.7%

Abbreviations: Clinical benefit response, complete response or partial response or stable disease ≥24 weeks per RECIST version 1.1; DOR, duration of response; ORR, overall response rate.

Consistent results were observed across stratification subgroups of disease site, sensitivity to prior hormonal therapy, and menopausal status. Results of a BICR audit, subgroup analysis, and sensitivity analyses all supported the primary efficacy endpoint results.

BICR audit results

A third party, not affiliated with the applicant, randomly selected 40% of the total patients ($n = 211$) to be reviewed for a BICR audit. To help assess randomness of the audit sample, Fisher exact test was used on demographic variables to test whether the 40% audit sample appeared to be a random sample. For all demographic variables tested, the nominal *P* value was above 0.05. The number of subjects with progressive disease on the control arm differed between the audit sample and the ITT population, although this difference is likely due to chance. Using the audit sample, three methods were utilized to assess how well the BICR audit results support the primary PFS results. The PhRMA method estimated the early discrepancy rate (EDR) and late discrepancy rate (LDR) difference (control – treatment; ref. 8). For EDR, the rate difference was 21.4% with an EDR of 42.9% in the palbociclib arm and 21.4% in the placebo arm. For LDR, the rate difference was −39.7% with an LDR of 25.0% in the palbociclib arm and 64.7% in the placebo arm. In a situation with bias, it is expected that the EDR rate difference will be negative and the LDR rate difference will be positive. Two additional methods were used to assess bias. Both methods estimate the BICR HR as if a full BICR review was completed. The first method, the NCI method estimated a HR equal to 0.24 with a one-sided upper confidence limit equal to 0.34 (9). The second method, a multiple imputation-based method developed internally by the reviewer, estimated a HR equal to 0.24 with a 95% CI of 0.16–0.37. A forthcoming manuscript will provide more details on this methodology.

Safety results

The safety database included 345 patients from the PALOMA-3 trial who received palbociclib at an oral daily dose starting at 125 mg daily as well as safety data from approximately 1,015 patients participating in Industry-sponsored completed or ongoing clinical trials with palbociclib. The most common adverse events (AEs) were neutropenia (83%), leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), and stomatitis (28%). The most common (≥5%) grade ≥3 AEs in the palbociclib plus fulvestrant arm were neutropenia (56% grade 3, 11% grade 4), and

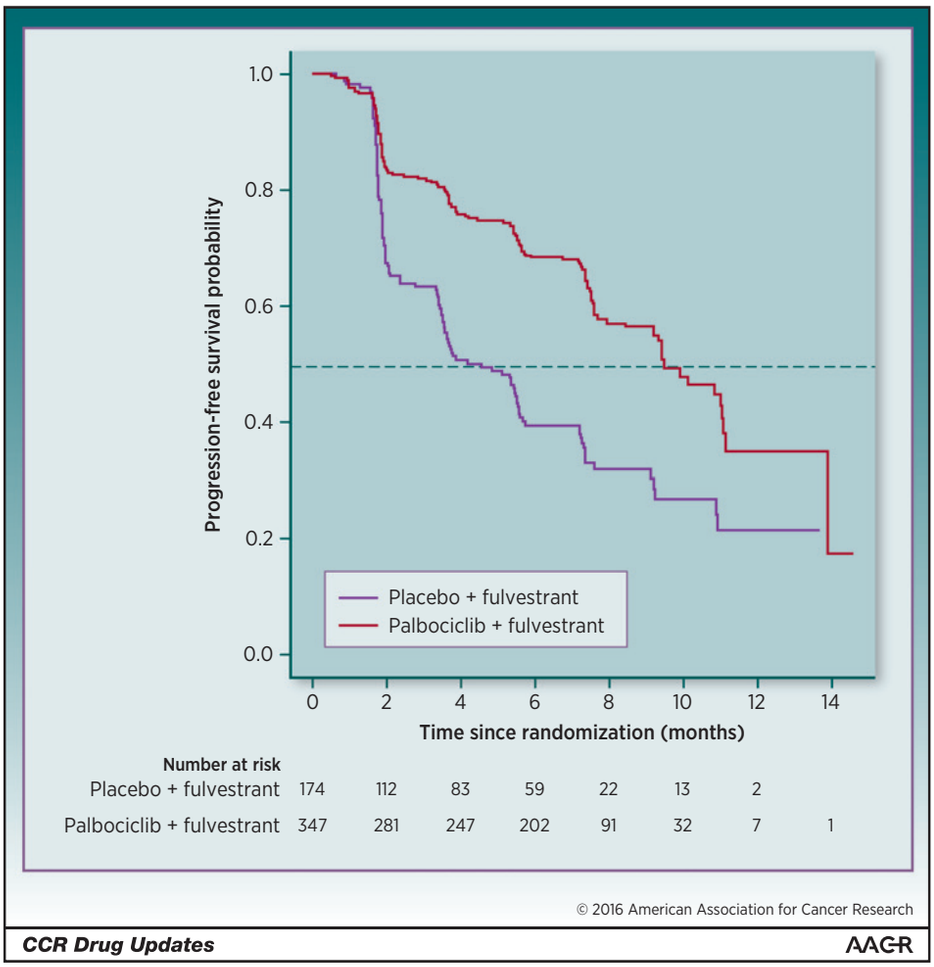

Figure 1.
Kaplan–Meier plot of PFS (IA, ITT population).

leukopenia (30% grade 3, 1% grade 4). See palbociclib drug label for further details regarding safety results (5).

Patient-reported outcome results

In PALOMA-3, patients completed the EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D on day 1 of cycles 1 to 4, then on day 1 of every other cycle starting with cycle 6, and at the end-of-treatment. EORTC QLQ-C30 assessed five function scales, 3 symptom scales, a global QOL scale, and 6 single item measures. The breast cancer module, EORTC QLQ-BR23, incorporates five multi-item scales assessing treatment side effects, arm symptoms, breast symptoms, body image, and sexual functioning. All PRO measures were scored according to their perspective user manuals. The time to deterioration (TTD) of pain was prespecified as a study endpoint defined as the time between baseline and first occurrence of increase of $\geq$10 in the EORTC QLQ-C30 pain scale score.

PRO data were collected rigorously with noncompletion rates between 5% and 10%. Using a repeated-measures mixed model, the global QOL scale from the EORTC QLQ-C30 instrument had −0.9 overall change from baseline (95% CI, −2.5–0.7) in the palbociclib arm and −4.0 change from baseline (95% CI, −6.3 to 1.7) in the placebo arm. These results favored the palbociclib arm. From the five functional scales in EORTC QLQ-C30, only the emotional functioning scale differed slightly, also favoring the palbociclib arm. In the EORTC QLQ-BR23 instrument, there was a difference in scores for the question "Were you upset by the loss of your hair?" favoring the placebo arm. There was an improvement in the median TTD in pain from 3.5 months in the placebo arm (95% CI, 2.5–5.4) to 7.2 months in the palbociclib arm (95% CI, 5.6, NE) with a HR of 0.66 (95% CI, 0.51–0.88). There were no notable differences between treatment arms on any of the other scales.

Discussion

The recent supplemental approval of palbociclib is based on results from PALOMA-3, a well-designed and conducted trial in a more refractory patient population. In its decision, the Agency considered the clinically significant improvement in median PFS improvement, the consistency of findings across subgroups, and the overall acceptable safety profile of the agent.

This is the first application in which the Agency reviewed a BICR audit rather than a full BICR review to evaluate the potential for bias within the primary investigator-assessed PFS results. Three methods were utilized to assess how well the BICR audit results supported the primary PFS results. The EDR and LDR results using the PhRMA method suggested that there was little bias in the primary investigator PFS results. Using this method, the EDR rate difference was positive and LDR rate difference was negative. In a

situation with bias, we would expect the EDR rate difference to be negative and the LDR rate difference to be positive. Results from the two additional methods, NCI and MI, also supported that minimal bias was present. Thus, using results from all three methods in combination provided strong evidence that the BICR audit supports the conclusions of the primary PFS results. This was also in the setting of consistent results across subgroups and sensitivity analyses all favoring the palbociclib plus fulvestrant treatment arm. A BICR audit may not be suitable for all applications; however, in certain situations, for example, solid tumors, it may be used as an alternate to a full BICR review.

The safety data within this application demonstrated that palbociclib was generally tolerable with adverse reactions manageable through the use of dose reduction, temporary treatment discontinuation, and/or standard medical care. Although more than half of the patients who received palbociclib experienced grade 3 or higher neutropenia, it is reassuring that there were very few cases of febrile neutropenia or neutropenic sepsis ($\leq$1% each). There was an increase in infections reported in patients receiving palbociclib plus fulvestrant compared with placebo plus fulvestrant (47% vs. 31%, respectively); however, the rates of grade 3 and 4 infections were comparable between the two treatment arms (4% vs. 3%, respectively). The safety results seen with palbociclib are novel in that the neutropenia is relatively self-limited and does not appear to be associated with a higher incidence of neutropenia-related adverse events such as febrile neutropenia and severe or life-threatening infections. The observed effect is consistent with the *in vitro* studies performed by the applicant (5). The treatment of bone marrow progenitor cells with palbociclib caused a G_1 cycle arrest that was characterized by a fully reversible, concentration-dependent inhibition of proliferation without apoptosis, cellular senescence, or DNA damage. It has been postulated that palbociclib-associated neutropenia likely reflects a cytostatic rather than cytotoxic effect of the drug on bone marrow progenitor cells as compared to the traditional cytotoxic chemotherapeutics (10). Although the incidence of febrile neutropenia was low and the rate of grade 3 or 4 infections were comparable between the two treatment arms in PALOMA-3, providers must remain diligent in monitoring patients for signs of infection and other complications related to myelosuppression while receiving palbociclib.

PRO measures provide information regarding disease- and treatment-related symptoms and health-related quality of life from a patient perspective and can add value to the assessment of the risks and benefits of a therapeutic intervention (11). The PRO data submitted with this application were carefully analyzed by the Agency during the review process. Although the global QOL scale and the TTD in pain results were supportive, favoring palbociclib combination with fulvestrant in PALOMA-3, there were several limitations that prevented the inclusion of PRO data in the product label, including lack of adjustment for multiplicity testing and uncertainty regarding whether observed differences were clinically meaningful.

It was noted that the timing of the questionnaires in relation to the treatment schedule was not ideal. The questionnaires were given in clinic on day 1 of each 28-day cycle. Palbociclib is administered daily on days 1 to 21 followed by 7 days off treatment. Many questions on the EORTC QLQ-C30 and EORTC QLQ-BR23 asked the patient how they felt within the last week. For patients on PALOMA-3, this would cover the week that they were not receiving palbociclib/placebo. By querying symptoms over the off-treatment week, the impact of the side effects of palbociclib and fulvestrant on quality of life may be attenuated. The timing of the questionnaires is critical for assessing treatment-related symptoms. It is acknowledged that optimal timing and assessment frequency of PRO measures must be feasible and will vary on the goals of the PRO strategy.

The analyses performed by the Applicant and Agency regarding TTD in pain favored the palbociclib plus fulvestrant arm, and these results were supportive in reviewing the benefit-risk analysis for this application. Although TTD for pain was a prespecified analysis, it was not included in the endpoint hierarchy with alpha allocation. There was uncertainty whether the prespecified definition for deterioration of pain ($\geq$10 point change) would be considered clinically meaningful as there was no clear evidence to support this definition from available data or literature. In addition, information regarding analgesic use was not incorporated into the TTD for pain analyses.

The Agency is committed to working with Sponsors to identify opportunities to generate important patient-centered data in cancer clinical trials (12–14). Although all PRO data are carefully reviewed to inform safety and efficacy, inclusion of PRO data in the product label depends on the adequacy of submitted data, the strengths and limitations of the instrument within the given context of use, and the design and conduct of the trial. Claims of superiority in PRO measures must be statistically tested and controlled for type I error. PRO data without a prospectively specified statistical analysis plan are considered exploratory and descriptive.

Although the added clinical benefit from the combination of palbociclib plus fulvestrant was demonstrated in PALOMA-3, there are still some uncertainties regarding the benefit of palbociclib in combination with letrozole as initial endocrine therapy. We await the results of the postmarketing required study (PALOMA-2) to confirm the benefit of palbociclib in combination with letrozole as initial endocrine therapy. In addition, although biomarkers are currently being explored as agreed upon in a postmarketing commitment by the applicant after the accelerated approval of palbociclib in 2015, there have been no identified novel biomarkers to predict resistance or response to palbociclib.

In summary, the approval of the palbociclib sNDA expanded the licensing indication to include the fulvestrant combination with the first CDK 4/6 inhibitor for treatment of breast cancer in the United States, which represents a significant advance in the treatment of metastatic HR-positive breast cancer. Although progress has been made, breast cancer remains the second leading cause of cancer-related deaths among women. Expediting the development of effective therapies for these patients remains an FDA priority.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A.J. Walker, L. Amiri-Kordestani, R. Pazdur

Development of methodology: A.J. Walker, L. Amiri-Kordestani, R. Sridhara, R. Pazdur

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.J. Walker, S. Wedam

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.J. Walker, S. Wedam, L. Amiri-Kordestani,

E. Bloomquist, S. Tang, R. Sridhara, J. Fourie Zirkelbach, W. Fu, Q. Liu, G. Kim, P.G. Kluetz, R. Pazdur

Writing, review, and/or revision of the manuscript: A.J. Walker, S. Wedam, L. Amiri-Kordestani, S. Tang, R. Sridhara, W. Chen, T.R. Palmby, J. Fourie Zirkelbach, W. Fu, Q. Liu, G. Kim, P.G. Kluetz, A.E. McKee, R. Pazdur

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.J. Walker, A. Tilley, G. Kim, R. Pazdur

Other (project manager): A. Tilley

Received April 20, 2016; revised June 1, 2016; accepted June 7, 2016; published OnlineFirst July 12, 2016.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
2. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687–717.
3. van den Heuvel S, Harlow E. Distinct roles for cyclin-dependent kinases in cell cycle control. Science 1993;262:2050–4.
4. Beaver JA, Amiri-Kordestani L, Charlab R, Chen W, Palmby T, Tilley A, et al. FDA approval: palbociclib for the treatment of postmenopausal patients with estrogen receptor-positive, HER2-negative metastatic breast cancer. Clin Cancer Res 2015;21:4760–6.
5. Palbociclib package insert [PDF on the Internet]; 2015[cited 2016 Apr 14]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207103s002lbl.pdf.
6. Fayers P, Bottomley A, EORTC Quality of Life Group; Quality of Life Unit. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur J Cancer 2002;38Suppl 4:S125–33.
7. EuroQol G. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.
8. Amit O, Mannino F, Stone AM, Bushnell W, Denne J, Helterbrand J, et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. Eur J Cancer 2011;47:1772–8.
9. Dodd LE, Korn EL, Freidlin B, Gray R, Bhattacharya S. An audit strategy for progression-free survival. Biometrics 2011;67:1092–9.
10. Finn R, Crown J, Ettl J, Pinter T, Schmidt M, Huang-Bartlett C, et al. Clinical patterns of palbociclib associated neutropenia in the PALOMA-1/TRIO-18 trial [abstract]. In: Proceedings of the ESMO 2014 Congress; 2014 Sep 26–30; Madrid, Spain. Lugano, Switzerland: European Society for Medical Oncology; 2014. Abstract nr 368P.
11. Basch E, Snyder C, McNiff K, Brown R, Maddux S, Smith ML, et al. Patient-reported outcome performance measures in oncology. J Oncol Pract 2014;10:209–11.
12. Kluetz PG, Slagle A, Papadopoulos E, Johnson LL, Donoghue M, Kwitkowski VE, et al. Focusing on core patient-reported outcomes in cancer clinical trials: symptomatic adverse events, physical function, and disease-related symptoms. Clin Cancer Res 2016;22:1553–8.
13. Basch E, Geoghegan C, Coons SJ, Gnanasakthy A, Slagle AF, Papadopoulos EJ, et al. Patient-reported outcomes in cancer drug development and US regulatory review: perspectives from industry, the food and drug administration, and the patient. JAMA Oncol 2015;1:375–9.
14. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims [PDF on the internet]. Silver Spring, MD: U.S. Food and Drug Administration; 2009[cited 2016 Apr 14]. Available from: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf.