

## REVIEW

# Sufficiency of Single-Arm Studies to Support Registration of Targeted Agents in Molecularly Selected Patients with Cancer: Lessons from the Clinical Development of Crizotinib

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## INTRODUCTION

Clinical development of crizotinib for the treatment of patients with advanced anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) paved the way for approval of molecularly targeted agents by showing that single-arm clinical trials supported by appropriate statistical analyses could be sufficient for regulatory approval in patients with cancer with high unmet medical need and/or rare tumor types, provided the scientific rationale for patient selection is strong and the agent has shown substantial and durable antitumor activity with a favorable safety profile.

A major goal of any clinical development program is to implement the most efficient clinical trials that demonstrate the clinical benefit of a new drug, while limiting the number of patients who may be exposed to a treatment with limited effectiveness and/or tolerability. Traditionally, in oncology drug development, in order to achieve this goal and gain regulatory approval of a new drug, sponsors had to first establish short-term safety and antitumor activity in phase I and II clinical trials that could last up to 5 years. Sponsors then had to demonstrate efficacy benefits vs. an active comparator and further characterize the safety profile in randomized controlled phase III studies of cancer patients who were often phenotype-selected rather than genotype-selected. In order to demonstrate a statistically significant and clinically meaningful benefit of one therapy over another, these trials generally enrolled large numbers of patients and lasted 3–5 years or more. Thus, this standard process typically led to a protracted period of upwards of 10 years or more between drug discovery and regulatory approval.<sup>1,2</sup>

As the dynamics of oncology drug development are changing with increasing demand for reduced time to drug approval and demonstration of greater clinical benefits, while exposing smaller numbers of patients to potentially toxic agents, the traditional drug development paradigm may benefit from adaptation to the modern era. With a transition

from conventional chemotherapy to molecularly targeted agents (MTAs), drugs are now being developed faster for prospectively identified patients whose tumors bear the relevant molecular signatures. Smaller single-arm clinical trials may be sufficient for regulatory approval in the molecularly selected patient population because the treatment effect of an MTA is expected to be much larger than that observed with conventional nonselective agents. In addition, with these new MTAs, there may be situations in which conducting a large randomized phase III clinical trial to gain regulatory approval is impractical or even unnecessary. For example, single-arm clinical trials may be acceptable in situations in which there is a particularly acute medical need (e.g., refractory or resistant patient population) and/or the tumor under treatment is rare. However, clinical trials of MTAs may still be drawn out because a large number of patients may need to be screened to identify and select a small subset of patients with the appropriate molecular signature. Furthermore, the clinical development program may also need to address the requirements for a companion diagnostic test for molecular patient selection in order to secure regulatory approval of the MTA.

The MTA crizotinib (Xalkori, Pfizer, New York, NY) is a potent, selective, small-molecule competitive inhibitor of *ALK*, *MET*, and *ROS1*<sup>3–5</sup> that initially received accelerated approval for the treatment of *ALK*-positive advanced NSCLC from the US Food and Drug Administration (FDA). Full approvals were subsequently achieved in many countries globally on the basis of results obtained from single-arm phase I and II clinical trials. Herein, we present aspects of the regulatory approval process based on outcomes from single-arm studies. We propose that prospective single-arm clinical trial(s) could be sufficient for the future registration of MTA monotherapies for rare tumors, provided that these agents show rapid, durable, and clinically meaningful activity, preferably together with positive health-related quality of life (HRQOL) and favorable (or at least acceptable) tolerability. As illustrated with crizotinib, new MTAs will also need to demonstrate these findings in a prospective clinical trial of a

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**Table 1** Key clinical trials in the development of crizotinib for second-line or later-line treatment of patients with NSCLC

Protocol	ClinicalTrials.gov registration number	Phase	Setting	Trial design	Treatment	Primary end point(s)
Single-arm studies enabling accelerated approval by the FDA and conditional approval in the EU						
PROFILE 1001 <sup>12</sup>	NCT00585195	I	<ul style="list-style-type: none"> <li>Previously treated or untreated</li> <li>Advanced malignancies (except leukemias)</li> <li>ALK-positive NSCLC</li> <li>MET-positive NSCLC</li> <li>ROS1-positive NSCLC</li> <li>Other (ALK-, MET- or ROS1-positive) tumor types</li> </ul>	Single-arm, open-label	Crizotinib	<ul style="list-style-type: none"> <li>Safety</li> <li>Pharmacokinetics</li> <li>ORR</li> </ul>
PROFILE 1005 <sup>13</sup>	NCT00932451	II	<ul style="list-style-type: none"> <li>Second or later line</li> <li>ALK-positive NSCLC</li> </ul>	Single-arm, open-label	Crizotinib	<ul style="list-style-type: none"> <li>ORR</li> <li>Safety</li> </ul>
Randomized-controlled confirmatory study						
PROFILE 1007 <sup>10</sup>	NCT00932893	III	<ul style="list-style-type: none"> <li>Second line</li> <li>ALK-positive NSCLC</li> </ul>	Randomized, open-label	Crizotinib vs. pemetrexed or docetaxel	<ul style="list-style-type: none"> <li>PFS</li> </ul>

ALK, anaplastic lymphoma kinase; EU, European Union; FDA, US Food and Drug Administration; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival.

properly selected patient population based on strong biological rationale, possibly with an appropriate companion diagnostic test.

### CLINICAL DEVELOPMENT OF CRIZOTINIB

Crizotinib, identified in 2005, was originally synthesized as an MET inhibitor<sup>6</sup> and subsequently found to inhibit phosphorylation of NPM-ALK in both Karpas 299 and SU-DHL-1 anaplastic large-cell lymphoma (ALCL) cells.<sup>3</sup> The *EML4-ALK* translocation in NSCLC was discovered in 2007. Commercially available break-apart fluorescence *in situ* hybridization (FISH) probes for detecting *ALK* gene rearrangement in anaplastic large-cell lymphoma were then modified to detect the rearrangement in NSCLC.<sup>7</sup> This assay and the subsequently developed Vysis fluorescence *in situ* hybridization test (Abbott Molecular, Abbott Park, IL) enabled patients with *ALK*-positive NSCLC to be identified for enrollment in crizotinib clinical trials. Modifying an existing assay helped to accelerate development and registration in this specific patient population (**Supplementary Figure S1**).

Accelerated approval by the FDA was achieved in 2011 for the treatment of patients with locally advanced or metastatic *ALK*-positive NSCLC<sup>9</sup> – approximately 4 years after the initial discovery of *ALK* gene rearrangements in NSCLC and 6 years after the initial discovery of crizotinib. This was based on data from ongoing phase I (PROFILE 1001; NCT00585195) and phase II (PROFILE 1005; NCT00932451) clinical trials in patients with *ALK*-positive NSCLC. These studies indicated that crizotinib was associated with high objective response rates (ORRs), rapid and durable responses, and a generally tolerable safety profile. At the time of the accelerated approval, two randomized phase III trials were ongoing. Full approval was granted in 2013 by the FDA after the availability of efficacy and safety results from one of these trials (PROFILE 1007; NCT00932893), comparing crizotinib to standard-of-care second-line chemotherapy.<sup>9–11</sup> In addition to the United States, crizotinib received conditional approval in the Euro-

pean Union for the treatment of adults with previously treated advanced *ALK*-positive NSCLC in late 2012 and has since received regulatory approvals in more than 80 other countries.

The FDA accelerated approval of crizotinib occurred at the same time as the approval of the companion diagnostic test for *ALK* gene rearrangement in NSCLC. In all markets, commercial availability of a locally registered *ALK* assay was required before approval of crizotinib.

### PROFILE 1001: PHASE I STUDY IN ALK-POSITIVE NSCLC

PROFILE 1001 is a first-in-human, single-arm, phase I clinical trial of crizotinib (**Table 1**) that originally had two parts<sup>7,12,14</sup>. Part one recruited patients with a variety of advanced solid tumors refractory to standard therapy in order to establish the maximum tolerated dose (MTD) of crizotinib; and part two evaluated the safety and antitumor activity of the maximum tolerated dose, initially among patients screened for tumors that harbored *MET* amplifications<sup>6</sup> and, after discovery of *ALK* gene rearrangements in NSCLC in 2007, among patients with *ALK*-positive NSCLC.

Emerging data suggested that *ALK* gene rearrangements were relatively rare (~3–5% of patients with NSCLC),<sup>15,16</sup> and patients with this genetic event had clinicopathologic characteristics distinct from unselected patients with NSCLC,<sup>17</sup> being generally younger never-smokers with tumors having a histology of adenocarcinoma.<sup>6,18</sup> Facilitated by the availability of an *ALK* test and initial evidence of crizotinib activity in patients with *ALK*-rearranged NSCLC in part two of PROFILE 1001, an intensive effort began among the clinical sites to screen for this genomic rearrangement. A separate cohort of patients with *ALK*-positive NSCLC across all lines of standard therapy was consequently added to PROFILE 1001 in 2008.<sup>7</sup>

In this clinical trial, patients' baseline demographic and disease characteristics were reflective of the distinct clinicopathologic features that were previously described

**Table 2** Baseline demographics and disease characteristics of patients with *ALK*-positive NSCLC in crizotinib clinical trials

Characteristics	PROFILE 1001 <sup>12,a</sup> (phase I)	PROFILE 1005 <sup>13,b</sup> (phase II)	PROFILE 1007 <sup>10,c</sup> (phase III)	
	Crizotinib (n = 149)	Crizotinib (n = 261)	Crizotinib (n = 173) <sup>d</sup>	Chemotherapy (n = 174)
Males, no. (%)	73 (49)	119 (46)	75 (43)	78 (45)
Median age, y (range)	52 (21–86)	52 (24–82)	51 (22–81)	49 (24–85)
Race, no. (%)				
White	95 (64)	154 (59)	90 (52)	91 (52)
Asian	41 (28)	94 (36)	79 (46)	78 (45)
Other	13 (9)	13 (5)	4 (2)	5 (3)
Smoking status, no. (%)				
Never	106 (71)	176 (67)	108 (62)	111 (64)
Former	42 (28)	73 (28)	59 (34)	54 (31)
Current	1 (<1)	12 (5)	5 (3)	9 (5)
Histology, no. (%)				
Adenocarcinoma	144 (97)	245 (94)	164 (95)	164 (94)
ECOG performance status, no. (%)				
0	56 (38)	68 (26)	72 (42)	65 (37)
1	75 (50)	148 (57)	84 (49)	95 (55)
≥2 <sup>e</sup>	18 (12)	45 (17)	16 (9)	14 (8)
No. of previous regimens for advanced or metastatic disease, no. (%)				
0	24 (16)	0	2 (1)	5 (3)
1	47 (32)	32 (12)	155 (90)	150 (86)
2	31 (21)	91 (35)	14 (8)	19 (11)
≥3	47 (32)	138 (53)	1 (<1)	0

*ALK*, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

<sup>a</sup>As of June 2011.

<sup>b</sup>As of January 2012.

<sup>c</sup>As of March 2012.

<sup>d</sup>Smoking status, ECOG performance status, and previous regimen data missing for 1 patient each.

<sup>e</sup>ECOG performance status 2 for PROFILE 1007.

(**Table 2**). For the heavily pretreated patients with *ALK*-positive advanced NSCLC in this trial (median two to three prior systemic therapies), antitumor activity for crizotinib (250 mg twice daily continuously) was found to be consistent as the number of patients enrolled increased: ORR was nearly 60% from the first report based on 19 patients in 2009.<sup>14</sup> At the first analysis of progression-free survival (PFS;  $n = 82$ ), the median had not been reached<sup>7</sup>; at a later analysis ( $n = 149$ ), the median PFS was approximately 10 months (95% confidence interval [CI] = 8–13)<sup>12</sup> (**Table 3**). Crizotinib was also well tolerated, and most treatment-related adverse events were grade 1 or 2 in severity. The most common adverse events were vision disorder, nausea, diarrhea, constipation, vomiting, and peripheral edema.<sup>12</sup>

### PROFILE 1005: PHASE II STUDY IN *ALK*-POSITIVE NSCLC

Based on early results of PROFILE 1001, a single-arm phase II study was initiated in 2010 (PROFILE 1005; **Table 1**).<sup>13</sup> This study evaluated the antitumor activity and

safety of crizotinib (250 mg twice daily continuously) in patients with *ALK*-positive advanced NSCLC whose disease progressed after one or more chemotherapy regimens for locally advanced/metastatic disease.

Initial FDA approval of crizotinib in 2011 was primarily based on an ORR of 51%, a median duration of response of 41.9 weeks, and a generally tolerable safety profile from the first 136 patients enrolled in PROFILE 1005 as of February 2011,<sup>19</sup> together with favorable efficacy and safety data from PROFILE 1001. Efficacy results from PROFILE 1005 (e.g., ORR; **Table 3**) were also found to be consistent at different reporting times.<sup>13,19</sup> In this study, treatment-related adverse events were similar to those observed in PROFILE 1001: They were mostly grade 1 or 2 in severity and included gastrointestinal (nausea, vomiting, and diarrhea) and ophthalmologic (visual impairment, photopsia, blurred vision, and vitreous floaters) events. Clinically meaningful improvements were also observed in key lung cancer symptoms, such as cough, pain in chest, and dyspnea, and in global HRQOL.<sup>13</sup>

### SUFFICIENCY OF PROFILE 1001 AND PROFILE 1005 OUTCOMES FOR REGULATORY APPROVAL

PROFILE 1001 and PROFILE 1005 represented the first studies of any MTA in patients with NSCLC prospectively selected for a specific genetic event – in this case, *ALK* gene rearrangement. Although clinical trials of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib had taken place before PROFILE 1001 and PROFILE 1005, these studies were prospectively conducted in unselected patients with NSCLC, with retrospective analyses of patients with *EGFR* mutation-positive NSCLC.<sup>20–24</sup>

PROFILE 1001 and PROFILE 1005 were also notable because of the large clinical benefits observed, further supported by retrospective analyses described below, led to approval of crizotinib before the availability of randomized phase III study data. Consistently robust data from two global single-arm clinical trials were important for regulatory agencies at the time when making their benefit–risk assessments.

Although the rapid clinical development and approval of crizotinib was successful, the development of this MTA was associated with unique challenges – not the least of which was the rarity of *ALK*-positive NSCLC. Additionally, historical data on typical end points (ORR, PFS, or overall survival [OS]) for other cancer therapies in this specific patient population were lacking. Data were also lacking on the natural history of *ALK*-positive NSCLC. As such, several questions arose regarding interpretation of the results, including in the absence of a comparator arm, how did the crizotinib data from these single-arm studies in *ALK*-positive NSCLC patients compare with data from standard therapies, and was the *ALK* gene rearrangement a predictor of clinical outcome with standard chemotherapies or TKI therapy? We addressed each of these questions using retrospective efficacy data analyses performed at different times during the drug development process, as described below.

**Table 3** Summary of previously published efficacy results for patients with *ALK*-positive NSCLC in crizotinib clinical trials

	PROFILE 1001 <sup>12,a</sup> (phase I)	PROFILE 1005 <sup>13,b</sup> (phase II)	PROFILE 1007 <sup>10,c</sup> (phase III)	
	Crizotinib (n = 149)	Crizotinib (n = 261)	Crizotinib (n = 173)	Chemotherapy (n = 174)
Response <sup>d</sup>				
ORR, % (95% CI) <sup>e</sup>	60.8 (52.3–68.9)	59.8 (53.6–65.9)	65.3 (57.7–72.4)	19.5 (13.9–26.2)
Median duration of response, <sup>f</sup> wk (95% CI)	49.1 (39.3–75.4) <sup>g</sup>	45.6 (35.3–53.6) <sup>g</sup>	32.1 (range, 2.1–72.4)	24.4 (range, 3.0–43.6)
Median time to response, wk (range) <sup>h</sup>	7.9 (2.1–39.6)	6.1 (4.9–49.1)	6.3 (4.4–48.4)	12.6 (5.0–37.1)
PFS				
Median, <sup>f</sup> mo (95% CI)	9.7 (7.7–12.8)	8.1 (6.8–9.7)	7.7 (6.0–8.8)	3.0 (2.6–4.3)
HR (95% CI)	NA	0.37 (0.19–0.74) <sup>j</sup> 0.59 (0.41–0.85) <sup>k</sup>	0.49 (0.37–0.64) <sup>j</sup>	

All data are observed data.

*ALK*, anaplastic lymphoma kinase; CI, confidence interval; HR, hazard ratio; NA, not applicable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival.

<sup>a</sup>As of June 2011.

<sup>b</sup>As of January 2012, for first 261 patients with *ALK*-positive NSCLC enrolled into study.

<sup>c</sup>As of March 2012.

<sup>d</sup>Confirmation of response was required in PROFILE 1001 (which utilized Response Evaluation Criteria In Solid Tumors [RECIST] version 1.0. 143 patients evaluable for response) and PROFILE 1005 (which utilized RECIST v1.1. 259 patients evaluable for response), but not in PROFILE 1007 (which utilized RECIST version 1.1).

<sup>e</sup>Exact method using the F distribution.

<sup>f</sup>Kaplan–Meier method.

<sup>g</sup>Brookmeyer and Crowley method.

<sup>h</sup>Tumor assessments were to be done at 8-week intervals in PROFILE 1001 and 6-week intervals in PROFILE 1005 and PROFILE 1007.

<sup>i</sup>As of June 2011 (439 crizotinib-treated patients with *ALK*-positive NSCLC), between-patient analysis: Crizotinib (n = 62) vs. pemetrexed/docetaxel (n = 117).

<sup>j</sup>Crizotinib vs. chemotherapy.

<sup>k</sup>As of June 2011 (439 crizotinib-treated patients with *ALK*-positive NSCLC), within-patient analysis: Crizotinib (n = 117) vs. pemetrexed/docetaxel (n = 117).

## CRIZOTINIB DATA FROM PROFILE 1001 AND PROFILE 1005 GREATLY SURPASSED SIMULATED OUTCOMES WITH STANDARD THERAPIES

### Covariate-Matched and Covariate-Adjusted Analyses: Background

In the absence of comparative data, it was unclear whether the distinct clinicopathologic characteristics of patients with *ALK*-positive NSCLC noted above might be contributing to the observed antitumor activity of crizotinib. To put the efficacy results from PROFILE 1001 and PROFILE 1005 into perspective, covariate-matched and covariate-adjusted modeling analyses<sup>25,26</sup> were retrospectively performed to simulate outcomes of randomized controlled studies of crizotinib vs. standard advanced NSCLC treatment (Pfizer, data on file).<sup>27</sup> These analyses utilized data from the control arms of three Pfizer-sponsored phase III studies evaluating first-line paclitaxel – carboplatin or gemcitabine – cisplatin and second-line or later-line erlotinib regimens in patients with advanced unselected NSCLC.<sup>28–30</sup>

In the covariate-matched analyses (Pfizer, data on file),<sup>27</sup> the efficacy outcomes of patients with *ALK*-positive advanced NSCLC in PROFILE 1001 and PROFILE 1005 were compared with those from patients with similar baseline characteristics in the control arms of the three aforementioned phase III studies.<sup>28–30</sup> Baseline characteristics for matching, based on the known clinicopathologic characteristics of patients with *ALK*-positive disease and potential predictors of outcome, included histology, race, smoking classification, and age.

The covariate-adjusted modeling analyses (Pfizer, data on file)<sup>27</sup> were performed to retrospectively “predict” the antitumor efficacy of patients with advanced *ALK*-positive NSCLC in PROFILE 1001 and PROFILE 1005 as if they had received one of the treatment regimens from the control arms of the

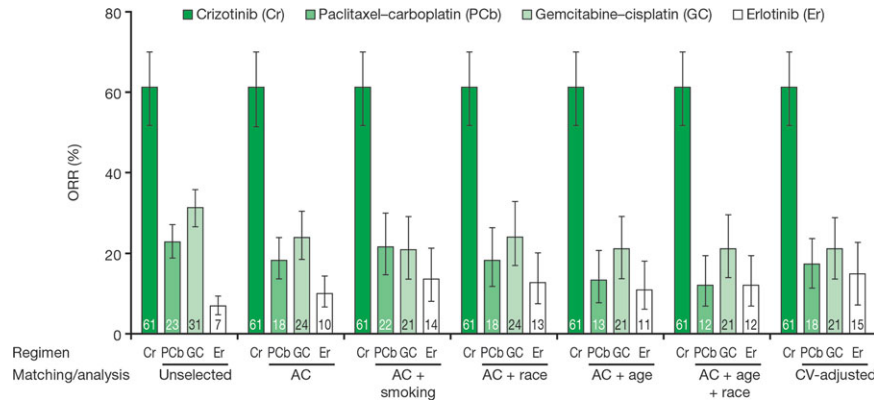
phase III studies described above,<sup>28–30</sup> and then compare them with the efficacy outcomes of patients in PROFILE 1001 and PROFILE 1005. A logistic regression model was used to predict ORR. The Cox proportional hazard model was used to predict PFS and OS. Baseline characteristics for this analysis, in addition to those used in the covariate-matched analysis, included gender, disease stage, Eastern Cooperative Oncology Group (ECOG) performance status, and weight.

### Findings from the Covariate-Matched and Covariate-Adjusted Analyses of PROFILE 1001 and PROFILE 1005

In PROFILE 1001, the observed ORR in 119 patients treated with crizotinib (61%; 95% CI = 52–70) far exceeded the ORRs from control patients in the covariate-matched analyses (ORRs of 12–24% for patients receiving paclitaxel – carboplatin or gemcitabine – cisplatin, and 10–14% for patients receiving erlotinib; **Figure 1** and **Table 4**).<sup>27</sup> Similarly, in the covariate-adjusted analyses, predicted ORRs for the control treatment regimens described above were significantly lower than that observed with crizotinib in PROFILE 1001 as evidenced by nonoverlapping CIs around ORR estimates.

The median PFS for patients in PROFILE 1001 was 10.0 months (95% CI = 8.2–14.7) across all lines of treatment. In contrast, covariate-matched and adjusted median PFS for historical first-line treatment regimen controls ranged between 4.6 and 5.9 months for paclitaxel – carboplatin or gemcitabine – cisplatin, and 1.9 and 3.1 months for second-/third-line erlotinib (**Table 4**). In addition, PFS hazard ratios (HRs) for crizotinib vs. any of the three control regimens in the covariate-matched or covariate-adjusted analyses ranged from 0.24 to 0.43 (**Table 4**).

Although OS for crizotinib-treated patients was still immature and the median was not reached at the time



**Figure 1** Objective response rates (ORRs) by treatment (crizotinib or chemotherapy regimen) and baseline patient/disease characteristics in covariate (CV)-matched and CV-adjusted analyses (PROFILE 1001 and three Pfizer-sponsored trials).<sup>27</sup> Bars for crizotinib represent ORRs in patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). In all analyses except the CV-adjusted analysis, bars for the other regimens represent ORRs among patients matched for the indicated characteristics. In the CV-adjusted analysis, bars for the other regimens represent ORRs that PROFILE 1001 patients would have achieved had they been treated with these agents. Error bars represent 95% exact confidence intervals (CIs) for the unselected and adenocarcinoma (AC) analyses; averages of 95% exact CIs from bootstrap samples for the AC + smoking, AC + race, AC + age, and AC + age + race analyses; and 95% CIs estimated based on the delta method in the CV-adjusted modeling analysis.

of PROFILE 1001 analysis, the HRs for crizotinib compared with any of the three standard-of-care regimens were similar for the covariate-adjusted and covariate-matched analyses and ranged between 0.25 and 0.47 (Table 4).

Similar findings for ORR, PFS, and OS were observed with PROFILE 1005 data (Figure 2 and Table 4; Pfizer, data on file).

#### Retrospective Efficacy Analyses of PROFILE 1005 Indicated Longer PFS for Crizotinib Compared with Pemetrexed or Docetaxel in ALK-Positive NSCLC

Limited populations of patients with rare tumors – such as ALK-positive NSCLC – can present difficulties in terms of conducting adequately sized clinical trials. European Medicines Agency guidelines state that, in such cases, it is appropriate to conduct a within-patient time to tumor progression (TTP)/PFS analysis, in which TTP on the last prior therapy is compared with TTP on experimental therapy,<sup>31</sup> and superiority should be demonstrated. Both between-patient and within-patient PFS analyses were performed in patients with ALK-positive NSCLC in PROFILE 1005 (Pfizer, data on file).

A between-patient analysis compared the outcomes of 117 patients who received second-line single-agent pemetrexed or docetaxel (standard single-agent regimens for second-line treatment of NSCLC) before entry into PROFILE 1005 with those of 62 patients who received second-line crizotinib in that study. A within-patient analysis<sup>32</sup> compared the outcomes of the same 117 patients who received second-line single-agent pemetrexed or docetaxel before enrollment in PROFILE 1005 with their outcomes to subsequent (third-line or later-line) treatment with single-agent crizotinib in this study.

In both analyses, the median TTP with pemetrexed/docetaxel therapy was 3.5 months (95% CI = 2.8–5.3). The median PFS with crizotinib therapy was not

reached (95% CI = 9.7–not reached) in the between-patient analysis and was 5.7 months (95% CI = 5.3–12.0) in the within-patient analysis. HRs for crizotinib vs. pemetrexed/docetaxel, adjusted for baseline factors, were 0.37 (95% CI = 0.19–0.74) and 0.59 (95% CI = 0.41–0.85), respectively (Table 3).

Consequently, these retrospective analyses in the ALK-positive NSCLC population suggested that treatment with crizotinib in the second-line treatment setting would lead to longer PFS times compared with standard second-line single-agent treatments (docetaxel or pemetrexed), a finding that was later confirmed in a randomized phase III trial, as presented below.

#### ALK Gene Rearrangement was Not a Predictor of Clinical Outcome with Standard Chemotherapies or TKIs

At the time that PROFILE 1001 and PROFILE 1005 were initiated, there were no data on the potential clinical benefit of standard therapy regimens for patients with ALK-positive NSCLC. In the absence of comparative clinical trials, ORRs on prior systemic therapies for patients with advanced ALK-positive NSCLC subsequently treated in PROFILE 1001 or PROFILE 1005 were indirectly compared with ORRs from historical data in unselected patients with advanced NSCLC (Table 5).<sup>33–40</sup> The findings that ORRs on standard chemotherapy and EGFR TKIs in patients with ALK-positive NSCLC were comparable to those reported in patients with unselected NSCLC (Table 5) suggested that ALK-positive status is not a response predictor for standard chemotherapy regimens or TKI therapy. Likewise, Shaw et al.<sup>41</sup> found that ALK gene rearrangement did not seem to be a prognostic indicator of clinical outcome because OS was similar between crizotinib-naïve patients with ALK-positive tumors and patients with tumors that were wild-type for ALK and EGFR. Other retrospective reports

**Table 4** Efficacy of crizotinib in retrospective comparisons with standard-of-care regimens from three Pfizer-sponsored clinical trials in patients with advanced NSCLC

	Crizotinib	Paclitaxel–carboplatin	Gemcitabine–cisplatin	Erlotinib
PROFILE 1001 <sup>27,a</sup>				
ORR, %	61.2 (51.7–70.1)			
Covariate-matched analyses <sup>b</sup>		12.0–21.5	20.7–24.1	10.0–13.8
Covariate-adjusted analyses		17.5 (11.3–23.6)	21.4 (13.8–28.9)	15.0 (7.2–22.8)
Median PFS, mo	10.0 (8.2–14.7)			
Covariate-matched analyses <sup>b</sup>		4.6–5.9	5.0–5.3	1.9–3.1
Covariate-adjusted analyses		4.9	5.5	2.0
HR, crizotinib vs. control				
Covariate-matched analyses <sup>b</sup>		0.30–0.36	0.30–0.34	0.28–0.38
Covariate-adjusted analyses		0.37 (0.25–0.54)	0.43 (0.28–0.63)	0.24 (0.16–0.34)
Median OS, mo	NR			
Covariate-matched analyses <sup>b</sup>		10.6–14.6	12.0–15.9	9.3–12.1
Covariate-adjusted analyses		13.1	14.7	8.5
HR, crizotinib vs. control				
Covariate-matched analyses <sup>b</sup>		0.30–0.46	0.36–0.47	0.27–0.35
Covariate-adjusted analyses		0.39 (0.24–0.67)	0.42 (0.26–0.72)	0.25 (0.15–0.43)
PROFILE 1005 <sup>c</sup>				
ORR, %	53.3 (47.0–59.6)			
Covariate-matched analyses <sup>b</sup>		14.9–21.2	20.2–24.0	10.0–14.5
Covariate-adjusted analyses		21.1 (13.8–28.4)	20.9 (14.7–27.2)	14.2 (7.3–21.1)
Median PFS, mo	8.5 (6.2–9.9)			
Covariate-matched analyses <sup>b</sup>		4.7–5.9	5.0–5.3	2.1–3.4
Covariate-adjusted analyses		4.9	5.2	3.1
HR, crizotinib vs. control				
Covariate-matched analyses <sup>b</sup>		0.45–0.55	0.47–0.54	0.37–0.45
Covariate-adjusted analyses		0.57 (0.43–0.73)	0.62 (0.47–0.80)	0.43 (0.33–0.57)
Median OS, mo	NR			
Covariate-matched analyses <sup>b</sup>		10.6–14.2	11.0–15.0	9.9–12.6
Covariate-adjusted analyses		12.0	13.5	9.8
HR, crizotinib vs. control				
Covariate-matched analyses <sup>b</sup>		0.49–0.77	0.55–0.75	0.43–0.55
Covariate-adjusted analyses		0.55 (0.39–0.70)	0.58 (0.41–0.73)	0.38 (0.27–0.49)

All crizotinib data are observed; data for the three standard-of-care regimens were simulated using the analyses shown. Values in parentheses are 95% confidence intervals.

ALK, anaplastic lymphoma kinase; HR, hazard ratio; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

<sup>a</sup>As of October 2010, 119 patients with ALK-positive NSCLC had received crizotinib, and 116 of these patients were evaluable for response.<sup>27</sup>

<sup>b</sup>Ranges are presented for the various combinations of matching variables.

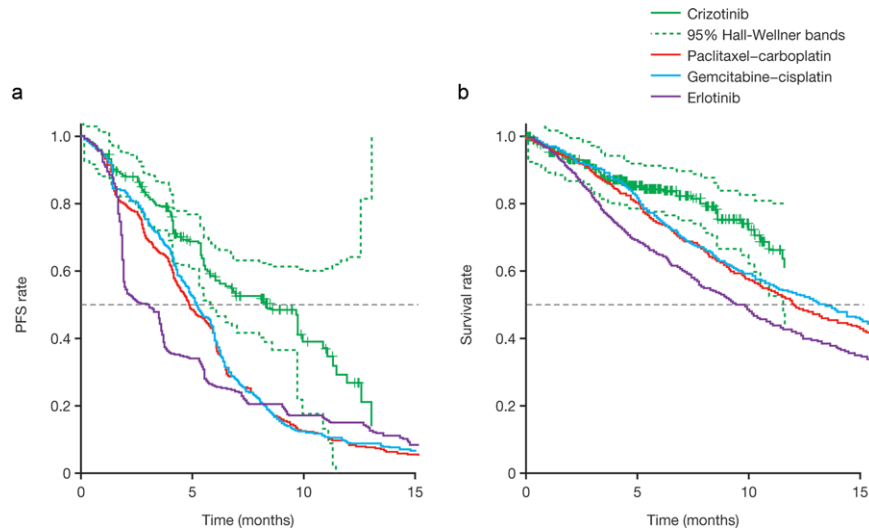
<sup>c</sup>As of June 2011, ORR based on 255 patients with ALK-positive NSCLC evaluable for response from first 261 patients enrolled into study (Pfizer, data on file); PFS/OS based on 439 crizotinib-treated patients with ALK-positive NSCLC.

involving very small patient cohorts (8–19 patients) suggested that pemetrexed may be more effective either as a single agent or in combination with chemotherapy in patients with advanced ALK-positive NSCLC.<sup>42–44</sup> Contrary to these findings, large retrospective analyses (141–711 patients) that evaluated ORR and TTP with pemetrexed chemotherapy in patients with ALK-positive NSCLC before receiving crizotinib in PROFILE 1005 showed much smaller effects that were consistent with those reported for patients with unselected NSCLC (**Figure 3**). This finding further supported the concept that ALK-positive status was not likely to be a predictor of clinical outcome for pemetrexed that was later confirmed in the randomized phase III trial presented below, although the ORR for patients treated with pemetrexed was higher than expected in this study.

### Findings from Single-Arm Clinical Trials of Crizotinib Confirmed in a Randomized Controlled Clinical Trial

Findings from the retrospective analyses mentioned above from PROFILE 1001 and PROFILE 1005 were subsequently corroborated by the results of randomized phase III clinical trial PROFILE 1007 (**Table 1**) comparing crizotinib with chemotherapy (pemetrexed or docetaxel) in the second-line treatment of patients with advanced ALK-positive NSCLC,<sup>10</sup> which:

- Demonstrated that crizotinib is significantly more effective than standard-of-care chemotherapy, with efficacy results consistent with those of the single-arm studies and retrospective analyses, in this selected population of patients with NSCLC (**Table 3**);



**Figure 2** Observed and expected progression-free survival (PFS) (a) and overall survival (OS) (b) in patients with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC;  $n = 439$ ) in PROFILE 1005 (Pfizer, data on file). Observed results are presented for crizotinib along with 95% Hall-Wellner bands that represent simultaneous confidence intervals for the survival function; expected results for the chemotherapy regimens from three Pfizer-sponsored clinical trials were obtained using direct covariate-adjusted modeling.

**Table 5** ORR with standard therapy in patients with unselected or ALK-positive NSCLC – historical and crizotinib study data

Systemic treatment	Unselected NSCLC		ALK-positive NSCLC			
	Historical <sup>a</sup>	ORR, %	PROFILE 1001 <sup>b</sup>		PROFILE 1005 <sup>c</sup>	
			No. of patients <sup>d</sup>	ORR, %	No. of patients <sup>d</sup>	ORR, %
First-line chemotherapy	15–35		89	16	115	18
Second-line chemotherapy	9–12		43	7	91	16
Single-agent EGFR TKI	9		43	7	59	4

ALK, anaplastic lymphoma kinase; EGFR, endothelial growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

<sup>a</sup>Refs. 33–40.

<sup>b</sup>Pre-study ORRs as of November 2010 (Pfizer, data on file).

<sup>c</sup>Pre-study ORRs as of February 2011 (Pfizer, data on file).

<sup>d</sup>Number of patients within each category of prior treatment.

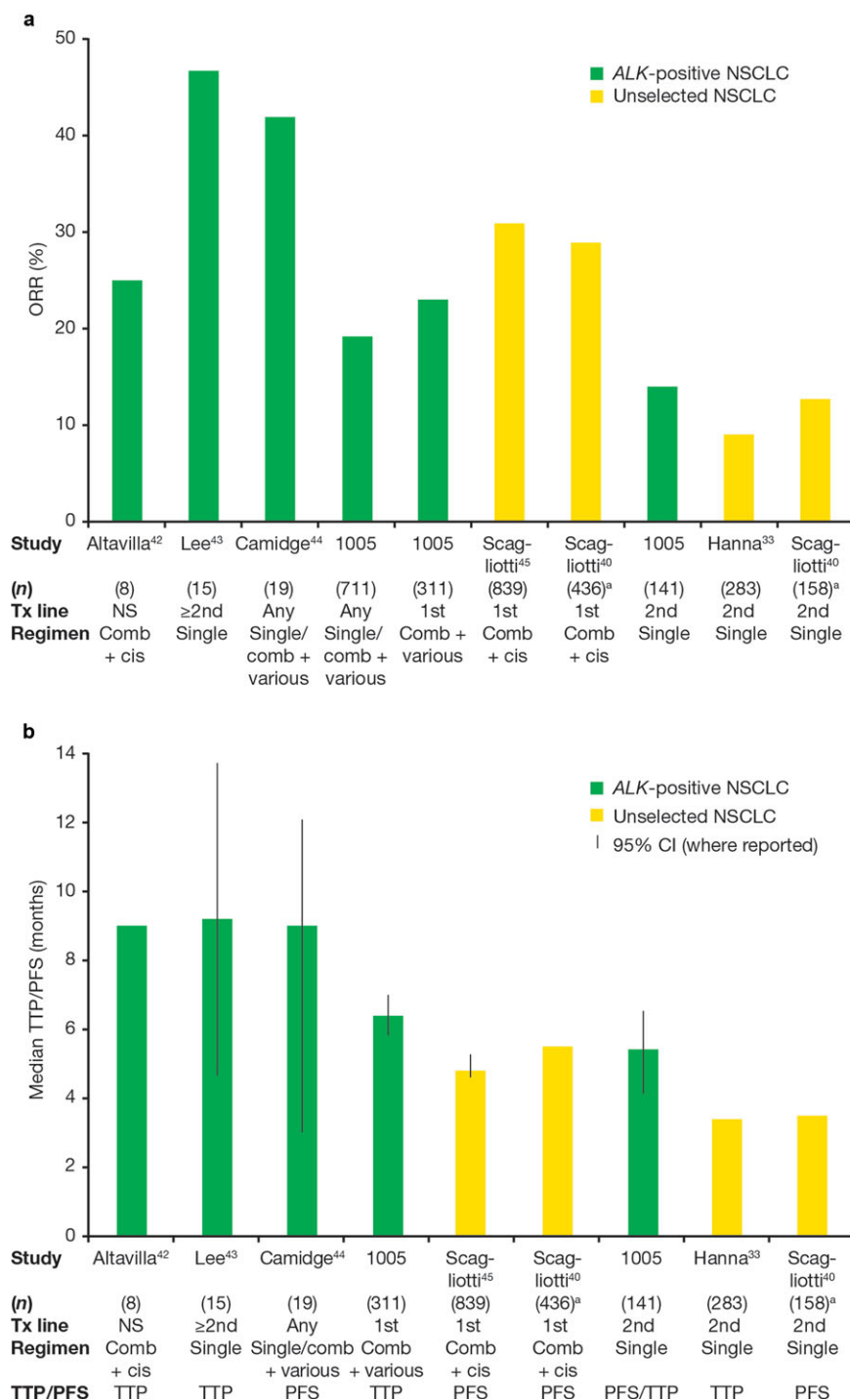
- Indicated that results from the single-arm clinical trials were not driven by the distinct clinicopathologic characteristics of patients with ALK-positive NSCLC;
- Suggested that ALK positivity is predictive of outcome for crizotinib but not for either pemetrexed or docetaxel;
- Supported retrospective findings that the clinical benefit of pemetrexed was less than that originally suggested in the retrospective studies described above in patients with ALK-positive NSCLC, although the ORR on pemetrexed was slightly higher than expected vs. the unselected population of patients with NSCLC who had previously been treated with chemotherapy;
- Confirmed that crizotinib was generally well-tolerated; and
- Demonstrated that crizotinib is associated with greater reductions in symptoms of lung cancer and greater improvements in global HRQOL compared with chemotherapy, in line with preliminary HRQOL data from PROFILE 1005.<sup>10</sup>

Results of PROFILE 1007 also confirmed that the interpretation of results from the single-arm phase I and II studies plus

associated retrospective efficacy analyses results was valid. Taken together, outcomes of PROFILE 1007 supported the decision made by regulators to grant approval of crizotinib based on the earlier data from single-arm clinical trials. These results from PROFILE 1007 ultimately supported the conversion of accelerated approval of crizotinib to full approval in the United States.

## DISCUSSION

Based on our experience, we conclude that consistent evidence of dramatic and durable antitumor activity with a favorable safety profile from prospective single-arm clinical trial(s) could be sufficient for approval of monotherapy MTAs for rare tumors, for tumors that express the therapeutic target in the large majority of patients, or for prospectively molecularly selected patients with common advanced tumors provided there is high unmet medical need. Such an approval process would enable accelerated patient access to new treatment options. Single-arm studies provide a number of benefits, including a requirement for smaller numbers of patients and generally shorter study duration than



**Figure 3** Objective response rates (ORRs) (a) and median time to tumor progression (TTP)/progression-free survival (PFS) (b) with pemetrexed in patients with advanced anaplastic lymphoma kinase (ALK)-positive or unselected non-small cell lung cancer (NSCLC) in PRO-FILE 1005 and historical data.<sup>33,40,42-45</sup> Adapted from Ref. 46 with permission from the author. CI, confidence interval; cis, cisplatin; comb, combination; NS, not specified; single, single-agent; Tx, treatment. <sup>a</sup>Adenocarcinoma only.

randomized clinical trials, whereas still enabling a reliable assessment of clinical benefit. In the case of crizotinib, the time from the discovery of ALK-positive NSCLC to initial regulatory approvals was approximately 4 years. Patients with ALK-positive NSCLC were therefore able to gain access

to this MTA much earlier than would have been the case had a traditional drug development approach been taken.

Accelerated (and conditional) approval of crizotinib in the United States (and the European Union), and full approval in other countries, was granted based on the rapid and durable



responses and clinically meaningful ORRs seen in prospective single-arm phase I and II clinical trials in prospectively selected patients with *ALK*-positive NSCLC. These approvals of crizotinib were also based on the evidence that the observed results were a direct antitumor effect of crizotinib based on strong scientific rationale and observed target modulation. Additionally, for an MTA monotherapy to be approved based on single-arm clinical trials, the drug must show at least an acceptable safety profile, preferably with positive effects on quality of life as well. In the case of crizotinib, the generally favorable safety profile that emerged early in development was confirmed by later studies and after longer durations of exposure.<sup>10,12,13</sup> A safety database of 255 patients (119 from PROFILE 1001 and 136 from PROFILE 1005) was considered sufficient for crizotinib in the approved indication, although this could vary for other agents depending on various factors, such as the rarity of the disease or condition and the magnitude of the treatment effect. Crizotinib also showed positive effects on HRQOL in PROFILE 1005,<sup>13</sup> which were later confirmed against an active control in PROFILE 1007.<sup>10</sup> Although HRQOL data are not needed for approval based on single-arm clinical trials, they can provide valuable supplemental data to support efficacy and safety assessments.

For conditions in which patient selection is warranted (i.e., a large proportion of patients do not exhibit the genetic event of interest), the development of a reliable companion diagnostic test is key to successfully identifying patients most likely to respond. In the case of crizotinib, the early availability of a companion diagnostic test enabled patients to be more precisely and potentially more rapidly selected for enrollment in the clinical trial program, thereby reducing the development timelines for this MTA.

Appropriate additional analyses may be important to augment standard analyses of data from single-arm studies. For example, with crizotinib, there were unique challenges in the interpretation of findings from the early clinical trials, including the lack of comparative historical data for other therapies specifically in the population of patients with *ALK*-positive NSCLC. However, not all of the analyses presented for crizotinib may be needed for future approval of MTAs. One could consider prospectively examining prior treatments of patients enrolled in the single-arm clinical trials or comparing data from single-arm clinical trials with those from historical studies. However, it is important to show that having the molecular signature of interest is not predictive of clinical outcome with standard therapy and not a prognostic biomarker. Additionally, although not necessarily on the critical path to regulatory approval, activity of new MTAs in patients with marker-negative disease should ultimately be evaluated. In the case of crizotinib, evaluation of patients with prospectively identified *ALK*-negative NSCLC is currently underway.

The randomized phase III clinical trial PROFILE 1007 confirmed the efficacy and safety of crizotinib,<sup>10</sup> consistent with findings from the earlier single-arm phase I and II studies in patients with *ALK*-positive NSCLC, including consistency with the various retrospective efficacy analyses summarized herein. Therefore, although retrospective exploratory statistical analyses successfully projected the efficacy outcomes of PROFILE 1007, this study, in turn, also validated the ret-

rospective exploratory statistical analyses, thus supporting the conclusion that results from single-arm clinical trials may be sufficient for the regulatory approval of MTA monotherapies. In PROFILE 1001, patients with *ALK*-positive NSCLC were enrolled in the study independent of treatment line. In PROFILE 1005, patients with second-line or later-line NSCLC were enrolled. Although there were only a small number of untreated patients with NSCLC enrolled in PROFILE 1001, it was reasonable to conclude that the consistency of the ORR results independent of treatment line may well have been sufficient for crizotinib to gain a broad indication across treatment lines. Indeed, the broader indication was supported by the results of the second ongoing randomized phase III study PROFILE 1014 (NCT01154140) that demonstrated significant improvement in PFS for crizotinib vs. standard-of-care chemotherapy in the first-line treatment of patients with locally advanced or metastatic *ALK*-positive NSCLC.<sup>47</sup>

Traditionally, the preferred end point in any cancer clinical development program has been OS.<sup>31,48</sup> As described above, the approval of crizotinib (accelerated/conditional approval in some countries, full approval in others) was based on objective response and duration of response, rather than on OS. However, it should be noted that responses with crizotinib were rapid and durable, ORRs were clinically meaningful, and the outcomes were backed by the biological rationale for the MTA and rationally selected patient population. Furthermore, consistent with the ORR data, crizotinib also showed meaningful improvements in PFS. Support for the potential sufficiency of ORR as a primary end point for single-arm clinical trials of MTAs was provided in a recent review of 14 studies of advanced NSCLC treatments submitted to the FDA since 2003 (3 of which involved MTAs in molecularly selected patient populations). In this review, a strong association was found between ORR and PFS, although no associations between ORR and OS or PFS and OS were found, potentially because of crossover and longer survival after disease progression in the studies of MTAs in molecularly selected patient populations.<sup>49</sup>

The era of regulatory approvals based on single-arm studies began in 2001 when imatinib received FDA approval based on the results of four single-arm studies.<sup>50,51</sup> A decade later, the high response rate observed with crizotinib in PROFILE 1001 led to the suggestion that one single-arm clinical trial could be sufficient for early approval of MTAs,<sup>52</sup> paving the way for even shorter times to approval of other MTAs. This recently came to pass with the next-generation *ALK* inhibitor, ceritinib, which received accelerated approval in the United States 3 years after initiation of one single-arm study in patients with crizotinib-resistant or -intolerant *ALK*-positive metastatic NSCLC.<sup>53,54</sup> Likewise, the next-generation *ALK* inhibitor, alectinib, was approved in Japan just less than 4 years after initiation of one single-arm study in *ALK* inhibitor-naïve patients with advanced *ALK*-rearranged NSCLC.<sup>55,56</sup>

A risk of an accelerated approach, however, is that approval may come without a complete understanding of the toxicity of an agent, as seen in the case of ponatinib, which was originally approved in 2012 based on results of a single-arm study.<sup>57</sup> Longer-term monitoring in this and another single-arm clinical trial, however, revealed high rates of thrombotic events, leading first to withdrawal of pona-

tinib in 2013, followed by its reintroduction with a narrower indication in 2014.<sup>57</sup> So far, however, this seems to be an isolated case. Of 24 accelerated approvals of cancer drugs by the FDA between 2011 and early 2015, 13 were based on single-arm clinical trials (9 involving targeted or molecularly selected patient populations and 4 involving unselected patient populations).<sup>58</sup> Of these 24 conditional approvals, delivery of postmarketing requirements and conversion to full approval has as of yet only been achieved for crizotinib.

The advent of the highly effective MTAs for the treatment of patients with cancer described above has led representatives of the FDA, the pharmaceutical industry, cancer research foundations, and cancer research and treatment centers to propose a set of standards for determining whether a single-arm study is robust enough to support traditional approval.<sup>59</sup> These criteria include the agent's mechanism of action being supported by a strong scientific rationale; the treatment being specified for a well-defined patient population; the demonstration of substantial durable tumor responses clearly exceeding those of available therapies; and a favorable benefit–risk assessment. Limitations of relying on single-agent clinical trial data were also noted. Examples included the use of ORR as a surrogate for long-term clinical benefit, which must be validated in randomized trials, and the need to identify a comparative data set for use as a historical control. Additionally, a determination of whether treatment-emergent adverse events are due to the MTA, taking into account the disease, aging, or other characteristics, will be necessary. The single-agent studies and retrospective statistical analyses that supported accelerated approval of crizotinib, as described herein, conformed to these standards and addressed the limitations raised, representing a successful case study of their application. Moreover, they reaffirm the sufficiency of prospective single-arm studies for approval of MTAs, eliminating the need for randomized controlled trials under these circumstances.

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