Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients with little or no radiological evidence of honeycombing: secondary analysis of a randomised, controlled trial


Summary

Background Present guidelines for the diagnosis of idiopathic pulmonary fibrosis require histological confirmation of surgical lung biopsy samples when high-resolution CT images are not definitive for usual interstitial pneumonia. We aimed to assess the predictive value of high-resolution CT in a cohort of patients with suspected idiopathic pulmonary fibrosis from a previous randomised trial.

Methods ARTEMIS-IPF was a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial of ambrisentan for adults aged 40–80 years with well-defined idiopathic pulmonary fibrosis and 5% or less honeycombing on high-resolution CT. In December, 2010, an interim analysis showed lack of efficacy and the trial was stopped. In the present follow-on analysis, we assessed patients who were screened for ARTEMIS-IPF who underwent high-resolution CT as part of screening and surgical lung biopsy as part of standard clinical care. A radiologist and a pathologist from a central panel independently assessed anonymised CT scans and biopsy samples. We calculated the positive and negative predictive value of high-resolution CT (classified as usual interstitial pneumonia, possible usual interstitial pneumonia, and inconsistent with usual interstitial pneumonia) for confirmation of histological patterns of usual interstitial pneumonia. This study is registered with ClinicalTrials.gov, number NCT00768300.

Findings 315 (29%) of 1087 consecutively screened patients in ARTEMIS-IPF had both high-resolution CT and surgical lung biopsy samples. 108 of 111 patients who met high-resolution CT criteria for usual interstitial pneumonia had histologically confirmed usual interstitial pneumonia (positive predictive value 97.3%, 95% CI 92.3–99.4), as did 79 of 84 patients who met high-resolution CT criteria for possible usual interstitial pneumonia (94.0%, 86.7–98.0%). 22 of 120 patients had an inconsistent high-resolution CT pattern for usual interstitial pneumonia that was histologically confirmed as not or possible usual interstitial pneumonia (negative predictive value 18.3%, 95% CI 11.9–26.4).

Interpretation In the appropriate clinical setting, for patients with possible usual interstitial pneumonia pattern on high-resolution CT, surgical lung biopsy sampling might not be necessary to reach a diagnosis of idiopathic pulmonary fibrosis if high-resolution CT scans are assessed by experts at regional sites familiar with patterns of usual interstitial pneumonia and management of idiopathic interstitial pneumonia.

Funding Gilead Sciences.

Introduction

Idiopathic pulmonary fibrosis is characterised by worsening respiratory symptoms and pulmonary function and usually leads to death from respiratory failure within 5 years of diagnosis.1 Accurate diagnosis of the disease is essential to provide clinical guidance for treatment decisions, stratify enrolment into clinical trials, and establish prognosis and priority for lung allograft allocation. Diagnosis is made with the highest degree of confidence when clinical, radiological, and pathological data are reviewed by a multidisciplinary discussion team, consisting of a clinician, a radiologist, and a pathologist who all have expertise in the diagnosis of interstitial lung diseases.2,3 Assessment of surgical lung biopsy samples in patients with idiopathic pulmonary fibrosis will show a pattern classified as usual interstitial pneumonia with increased diagnostic accuracy if specimens are obtained from more than one lobe.1 With the advent of high-resolution CT, characteristic patterns of abnormalities have been identified in patients with idiopathic pulmonary fibrosis.4 Evidence-based guidelines provide specific criteria for the radiological pattern of usual interstitial pneumonia and, in the appropriate clinical setting, histological confirmation is not needed when a confident diagnosis is made with high-resolution CT.5 The usual interstitial pneumonia pattern on high-resolution CT has a high positive predictive value for the presence of a histological pattern of usual interstitial pneumonia. The appropriate clinical setting is defined as, typically, a male patient older than 60 years with unexplained dyspnoea on
exertion and pulmonary fibrosis of unknown cause, including absence of collagen vascular disease and absence of identifiable cause or environmental factor attributable to the manifested pulmonary fibrosis.1 To classify a high-resolution CT as showing usual interstitial pneumonia, honeycombing and reticular abnormalities in a predominantly basilar and subpleural distribution need to be present. In addition, the high-resolution CT should not show any atypical features for usual interstitial pneumonia, including prominent ground glass abnormalities, nodules, air trapping, and peribronchovascular or upper lung predominant patterns of distribution. If such atypical features are prominent, the high-resolution CT pattern is designated as inconsistent with usual interstitial pneumonia1 and procurement of a surgical lung biopsy should be considered. The guidelines recognise a third potential radiological diagnosis: possible usual interstitial pneumonia pattern, which is characterised by the presence of bilateral lower lobe subpleural reticular abnormalities without honeycombing and without atypical features. In patients with this pattern, the guidelines1 require surgical lung biopsy evidence of usual interstitial pneumonia to confirm the diagnosis of idiopathic pulmonary fibrosis.

We aimed to assess the value of high-resolution CT showing a possible usual interstitial pneumonia pattern for prediction of a histological pattern consistent with usual interstitial pneumonia in a subgroup of participants who were screened for inclusion in a multicentre trial6 of ambrisentan.

Methods

Study design and participants

ARTEMIS-IPF was a randomised, double-blind, placebo-controlled, multicentre, event-driven phase 3 trial6 to assess whether the selective endothelin receptor antagonist ambrisentan was effective for reduction of the rate of progression of idiopathic pulmonary fibrosis. All participants provided written, informed consent, and the study was approved by local ethics committees. After 1087 patients had been screened between Jan 21, 2009, and Dec 21, 2010, and 494 patients randomly allocated to study drugs, the sponsor terminated the study prematurely after an interim analysis showed lack of efficacy.3

ARTEMIS-IPF was started before publication of the 2011 ATS-ERS-JRS-ALAT evidence-based guidelines for the diagnosis and management on idiopathic pulmonary fibrosis.1 The criteria used for diagnostic classification by the radiology charter for the study were equivalent to those of current practice guidelines, however the terminology used was slightly different. To minimise potential confusion and to ensure consistency of this report with the conventions likely to be adopted by future publications on this topic, we amended our charter terms to match those in recently published guidelines. The ARTEMIS-IPF charter term “definite idiopathic pulmonary fibrosis” was therefore changed to “usual interstitial pneumonia”, the term “consistent with idiopathic pulmonary fibrosis” was changed to “possible usual interstitial pneumonia”, and the term “inconsistent with idiopathic pulmonary fibrosis” was changed to “inconsistent with usual interstitial pneumonia”. The histopathological nomenclature was the same in both the ARTEMIS-IPF charter and in the 2011 published guidelines, although the ARTEMIS-IPF charter did not include a category of unclassifiable fibrosis.

Eligible participants were aged 40–80 years, and had clinically well-defined idiopathic pulmonary fibrosis for at least 3 months. Participants had undergone assessment at community and academic clinical centres for their clinical manifestation of pulmonary fibrosis and had been diagnosed as idiopathic pulmonary fibrosis, and were thus referred for consideration of participation in the clinical trial.1 The study was done at 136 sites in North America, South America, western Europe, and Australia. High-resolution CT was a required study procedure but surgical lung biopsy samples were obtained as part of standard care. As a part of screening to assess eligibility for participation in the clinical trial, all of the high-resolution CT images were reviewed by one expert chest radiologist (DL) from a centralised panel of radiologists (DL, JDG, RW) and the surgical lung biopsy slides were reviewed by one expert pathologist (TVC) from a central panel of pathologists (TVC, KOL). The expert chest radiologist and the expert pathologist independently interpreted the radiological and histological features from all 315 patients with both high resolution CT and surgical lung biopsy data who were screened for enrolment. We used precise prespecified criteria in case report forms to interpret the patterns of usual interstitial pneumonia and each investigator was masked to the results of the corollary interpretation. The decision of one expert from the panel was regarded as final in all cases.

On the basis of a previous study,7 patients with 5% or less honeycombing on high-resolution CT images of the lung were postulated to respond to endothelin-receptor blockade and thus patients with more than 5% honeycombing on the high-resolution CT were excluded. Other key exclusion criteria were congestive heart failure, history of collagen vascular disease, evidence of occupational lung disease, evidence of coexisting obstructive airflow defect or prominent emphysema on high-resolution CT (defined as emphysema more prominent than reticular abnormality), recent hospital admission or respiratory infection within 60 days, chronic treatment for pulmonary hypertension, and chronic treatment with immunosuppressive therapy. Of 1087 participants screened for ARTEMIS-IPF, 315 had both high-resolution CT images and surgical lung biopsies submitted for assessment by central reviewers, and data from that cohort were analysed in this study (appendix). Therefore the cohort for the primary analysis in our present study included both a subset of participants eligible for ARTEMIS-IPF and some individuals.
who were screened but were ineligible for ARTEMIS-IPF. Analysed participants classified as possible usual interstitial pneumonia by high-resolution CT had, by definition, no honeycombing on high-resolution CT. Although participants in the usual interstitial pneumonia and inconsistent high-resolution CT categories, who were eligible for ARTEMIS-IPF had less than 5% honeycombing, these categories also included ineligible participants with more than 5% honeycombing.

**Procedures**

Centralised interpretation and obtaining of radiological images was supported by a clinical trial service provider (Perceptive Informatics, Billerica, MA, USA). We acquired three sets of axial spaced high-resolution CT images for all patients (supine inspiration, supine expiration, and prone inspiration), anatomically extending from lung apices to costophrenic recess (appendix).

We used prespecified criteria for categorisation of high-resolution CT images into usual interstitial pneumonia, possible usual interstitial pneumonia, and inconsistent with usual interstitial pneumonia (panel 1). Radiologists were also asked to determine if two other exclusion criteria were met: an extent of honeycombing involving more than 5% of the lung area and presence of prominent emphysema, defined as emphysema affecting an area of more than the area affected by the reticular pattern.

High-resolution CT images were anonymised by a third-party vendor (Perceptive Informatics) and films were shown to one of the three radiologists at the time of screening for study enrolment. The radiology reader interpreted the images with a standardised scoring sheet.

Radiologists were provided high-resolution CT scans for assessment of patterns and distribution to gauge eligibility status for participation in ARTEMIS-IPF study, but did not have access to other clinical or histological data. The radiologists had a face-to-face training session before study start to agree on the scoring criteria and jointly reviewed non-study standard cases. However, once the study was started, no discussion was undertaken of the eligibility of individual study participants between radiologists or with the study site or sponsor.

For histopathological analysis, four categories were used to interpret the microscopic features in the surgical lung biopsy (usual interstitial pneumonia, probable usual interstitial pneumonia, possible usual interstitial pneumonia, and not usual interstitial pneumonia).1 In the first draft of the protocol, patients classified with possible usual interstitial pneumonia were eligible for inclusion, but after consultation with regulatory authorities, participants with possible findings were regarded as ineligible to ensure recruitment of a well-defined study population. For analysis in the present study, we consolidated surgical lung biopsy results into two categories: definite and probable findings were grouped as usual interstitial pneumonia whereas possible and not usual findings were grouped as not usual interstitial pneumonia. Slides were anonymised before review by the pathologists (TVC or KOL). Pathologists were provided slides from the surgical lung biopsy for interpretation of the histopathological patterns to gauge eligibility status for participation in the ARTEMIS-IPF study, but did not have access to other clinical or radiological data.

**Statistical analysis**

We calculated positive predictive values for patterns consistent with usual interstitial pneumonia and possible usual interstitial pneumonia on high-resolution CT for a histological diagnosis of usual interstitial pneumonia and probable usual interstitial pneumonia. We also calculated the negative predictive value of an inconsistent with usual interstitial pneumonia finding on high-resolution CT for a histological diagnosis of possible usual interstitial pneumonia or not usual interstitial pneumonia. We used the Clopper-Pearson method to calculate 95% CIs. We did not calculate sensitivity and specificity of high-resolution CT because the study population was enriched for patients with possible usual interstitial pneumonia and thus the true prevalence of disease in patients with high-resolution CT patterns not of this type was not known. We used SAS version 9.2 for analyses.

This study is registered with ClinicalTrials.gov, number NCT00768300.

### Panel 1: High-resolution CT diagnostic criteria

**Usual interstitial pneumonia pattern (all of the following four features)**
- Subpleural, basal predominance
- Reticular abnormality
- Honeycombing (<5% of lung area)
- No features listed as inconsistent with usual interstitial pneumonia pattern

**Possible usual interstitial pneumonia pattern (all of the following four features)**
- Subpleural, basal predominance
- Reticular abnormality
- No honeycombing
- No features listed as inconsistent with usual interstitial pneumonia pattern

**Inconsistent with usual interstitial pneumonia (any of the following seven features)**
- Upper of mid-zone predominance
- Peribronchovascular predominance
- Extensive ground glass abnormality (ie, greater in extent than reticular abnormalities)
- Prominent micronodules
- Discrete cysts (multiple, bilateral away from area of honeycombing)
- Diffuse mosaic attenuation or air trapping
- Consolidation of bronchopulmonary segments
Role of the funding source
Gilead Sciences funded both the original ARTEMIS-IPF trial and this study. TGO’R is an employee of Gilead Sciences and cowrote the first draft of the manuscript with GR. LS and HZ are employees of the funding source and were responsible for statistical analysis. LS, HZ, TGO’R, and PSP had full access to raw data. TGO’R and GR had the final responsibility for the decision to submit to publication.

Results
Of 1087 consecutive participants screened for enrolment in ARTEMIS-IPF study (figure 1), 315 patients had both a high-resolution chest CT (a required study procedure) and a surgical lung biopsy sampling (not a required study procedure but obtained as part of standard clinical care before enrolment) that was interpreted by the local radiologists and pathologists. Figure 2 shows representative examples of high-resolution CT images. Six screened participants had surgical lung biopsy data but not high-resolution CT data; one of these biopsy samples showed definite usual interstitial pneumonia, one showed possible usual interstitial pneumonia with features of hypersensitivity pneumonia, three had other diagnoses (one showed hypersensitivity pneumonia and two non-specific intestinal pneumonia), and one was a non-diagnostic transbronchial lung biopsy submitted in error.

30 (10%) of 315 surgical lung biopsy samples were interpreted as not usual interstitial pneumonia or possible usual interstitial pneumonia (table 1). Of the 30 surgical lung biopsy samples that did not confirm usual interstitial pneumonia, suggested alternative diagnoses included hypersensitivity pneumonia (11 patients), non-specific intestinal pneumonia (seven patients), desquamative interstitial pneumonia (one patient), cryptogenic organising pneumonia (two patients), non-specific airway disease (three patients), adenocarcinoma (one patient), or inadequate sampling to suggest a diagnosis (five patients).

Demographics and baseline lung function did not differ between groups based on high-resolution CT diagnosis or availability of surgical lung biopsy samples (table 2). Despite the inclusion requirement of less than 5% honeycombing on high-resolution CT, we noted a wide range of impairment of lung function in all groups. Overall mean forced vital capacity was 69.8% (SD 15.6) and diffusion capacity was 42.6% (17.3) of predicted.
suggesting that many of the screened patients had strikingly impaired lung function.

Table 1 shows the positive predictive value of a radiological diagnosis of usual interstitial pneumonia or possible usual interstitial pneumonia and the negative predictive value of radiological diagnosis of inconsistent with usual interstitial pneumonia. Table 1 also shows data for the four subcategories of histological diagnosis. The histological pattern of usual interstitial pneumonia was 3–4 times more common than was the pattern of probable usual interstitial pneumonia in this cohort of patients.

In a post-hoc analysis of the 120 participants with a high-resolution CT diagnosis of findings inconsistent with usual interstitial pneumonia, we assessed differences in baseline characteristics between 98 patients with histologically confirmed or probable usual interstitial pneumonia and 22 patients with histological findings of possible or not usual interstitial pneumonia. Groups did not differ at baseline in terms of mean percentage predicted forced vital capacity, haemoglobin-adjusted diffusion capacity, or sex, although patients who were subsequently histologically diagnosed with possible or not usual interstitial pneumonia had a mean age of 58·2 years (SD 10·6) compared with 63·2 years (7·6) for patients histologically diagnosed with confirmed or probable usual interstitial pneumonia (p=0·0525; appendix).

Discussion

For assessment of patients with interstitial lung disease, presence of unambiguous honeycombing on a high-resolution CT has a valuable positive predictive value for usual interstitial pneumonia.1,3–7,10–12 When honeycombing is not present or minimal, diagnosis of idiopathic pulmonary fibrosis is challenging. Present guidelines recommend that patients suspected to have idiopathic pulmonary fibrosis with possible usual interstitial pneumonia pattern on high resolution CT also have a surgical lung biopsy taken to confirm diagnosis from

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**Table 1: Diagnostic value of high-resolution CT**

<table>
<thead>
<tr>
<th>Usual interstitial pneumonia on high-resolution CT</th>
<th>Possible usual interstitial pneumonia on high-resolution CT</th>
<th>Inconsistent with usual interstitial pneumonia on high-resolution CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>With SLB (n=111)</td>
<td>Without SLB (n=388)</td>
<td>With SLB (n=84)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>64·2 (8·0)</td>
<td>68·0 (6·9)</td>
</tr>
<tr>
<td>Median (IQR, range)</td>
<td>66 (60–70, 35–79)</td>
<td>69 (63–73, 48–87)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>86/111 (77%)</td>
<td>278/387 (72%)</td>
</tr>
<tr>
<td>Female</td>
<td>25/111 (23%)</td>
<td>109/387 (28%)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or ex-smoker</td>
<td>60/93 (65%)</td>
<td>185/270 (69%)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>33/93 (35%)</td>
<td>85/270 (31%)</td>
</tr>
<tr>
<td><strong>Predicted forced vital capacity (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients assessed</td>
<td>105</td>
<td>331</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>69·6% (14·7)</td>
<td>70·2% (15·2)</td>
</tr>
<tr>
<td>Median (IQR, range)</td>
<td>68·9% (59–79, 240–105·4)</td>
<td>70·3% (59–78, 240–100·5)</td>
</tr>
<tr>
<td><strong>Predicted haemoglobin-adjusted DLCO (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients assessed</td>
<td>103</td>
<td>309</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>43·7% (14·9)</td>
<td>42·4% (18·8)</td>
</tr>
<tr>
<td>Median (IQR, range)</td>
<td>42·0% (33·9–51·1, 13·1–101·7)</td>
<td>41·5% (35·1–54·4, 0·0–242·4)</td>
</tr>
</tbody>
</table>

Data are n/n with available data. Data for 976 patients who had high-resolution CT data submitted during ARTEMIS-IPF screening. DLCO = diffusion capacity.

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**Table 2: Baseline characteristics stratified by availability of surgical lung biopsy (SLB)**
than 60 years and often have comorbidities, and thus an accurate diagnosis of idiopathic pulmonary fibrosis without the need for surgical lung biopsy is desirable. Our study suggests that, if the following two key conditions are met, radiological diagnosis of possible usual interstitial pneumonia is sufficient for diagnosis of idiopathic pulmonary fibrosis to be made without surgical lung biopsy. The first condition is that the clinical presentation and demographics are typical of idiopathic pulmonary fibrosis and were ascertained by an expert in interstitial lung disease. Patients should have a thorough history taken for possible exposure to overt and occult factors in the patient’s environment and lack clinical and serological features of collagen vascular diseases. The second condition is that high-resolution CT images, assessed by a radiologist with expertise in interstitial lung disease, show a subpleural basal predominant reticular abnormality with the absence of atypical features for usual interstitial pneumonia pattern (panel 1). With these conditions, absence of honeycombing in the high-resolution CT images of the chest should not always, in isolation, mandate a lung biopsy to establish a diagnosis of idiopathic pulmonary fibrosis.

The term possible usual interstitial pneumonia has a precise radiological criteria and pattern. In an earlier classification, the term possible usual interstitial pneumonia specifically applied to patients with high-resolution CT that showed both an absence of honeycombing and atypical findings. Studies assessing the predictive value of high-resolution CT images in patients with idiopathic interstitial lung disease have tended to group patients whose CT images are otherwise consistent with usual interstitial pneumonia (apart from absent honeycombing) with those who have atypical features. To our knowledge, no previous studies have assessed large numbers of patients with suspected idiopathic pulmonary fibrosis after expert clinical assessment by an interstitial lung disease clinician and multidisciplinary discussion, high-resolution CT images that are consistent with a possible usual interstitial pneumonia pattern, no atypical findings on high-resolution CT, and alternative diagnoses to usual interstitial pneumonia made on histological analyses of surgical lung biopsy samples. Nevertheless, the results of our retrospective analyses of data gathered prospectively from patients screened for the ARTEMIS-IPF study complement those of a recent retrospective single-centre study of 135 patients who had surgical lung biopsy samples obtained for diagnosis of idiopathic interstitial lung disease (panel 2). Use of a semiquantitative scoring system for fibrosis accurately diagnosed usual interstitial pneumonia in the absence of honeycombing in patients aged 55 years and older, without prespecification of atypical radiological findings as an exclusion criteria. The investigators suggested that older age was a key factor predictive of usual interstitial pneumonia and the mean age in our analysis supports these findings. In another recent study, retrospective diagnosis of idiopathic pulmonary fibrosis could be made in 21 patients on the basis of high-resolution CT criteria in the absence of honeycombing in 44 cases of biopsy-proven usual interstitial pneumonia in the appropriate clinical setting.

The focus of our study was on patients with possible usual interstitial pneumonia on high-resolution CT rather than on patients with CT findings that were inconsistent with usual interstitial pneumonia (who, by definition, have atypical findings on high-resolution CT. Any such patients who had an alternative diagnosis established by surgical lung biopsy would not have been referred to this study). Our findings in patients with possible usual interstitial pneumonia on high resolution CT are pertinent and clinically relevant because the diagnostic criteria for possible usual interstitial pneumonia are much narrower than they are for the inconsistent pattern and patients in this group are more likely than those with inconsistent findings to undergo surgical lung biopsy in clinical practice to clarify or confirm the diagnosis of idiopathic pulmonary fibrosis because they had little or no honeycombing on high-resolution CT. The 2011 guidelines for diagnosis of idiopathic pulmonary fibrosis emphasise the exclusion of known causes or conditions associated with pulmonary fibrosis, the need for multidisciplinary discussions, and recommend referrals to regional centres with expertise in interstitial lung disease for patients similar to the cohorts enrolled in our study.

Although the focus of our study was on the predictive value of a radiological diagnosis of possible usual interstitial pneumonia, 98 (82%) of 120 patients with an inconsistent with usual interstitial pneumonia radiological pattern had either usual interstitial pneumonia, 98 (82%) of 120 patients with an inconsistent with usual interstitial pneumonia radiological pattern had either usual interstitial pneumonia or probable usual interstitial pneumonia on surgical lung biopsy. The study design restricts extrapolation to a wider population and warrants further investigations in future studies. Our findings complement results from a previous single centre prospective study, which noted a high specificity of a radiological diagnosis of idiopathic pulmonary fibrosis (90%) but a fairly low sensitivity (78-5%).

If an inconsistent with usual interstitial pneumonia radiological pattern is noted in patients after thorough assessment of other causes of interstitial lung disease, the possibility of the diagnosis of idiopathic pulmonary fibrosis still exists and under these circumstances surgical lung biopsy evidence of usual interstitial pneumonia is needed to ascertain the diagnosis. Such a procedure is in keeping with the 2011 published guidelines because the combination of the histopathological evidence of usual interstitial pneumonia in the patient showing radiological diagnosis of inconsistent pattern for usual interstitial pneumonia allows the diagnosis of idiopathic pulmonary
fibrosis in the appropriate clinical setting. Assessment is warranted of whether any of the seven components characterising the inconsistent pattern (panel 1) have a high or unique negative predictive value for histopathological features of usual interstitial pneumonia in this population. For example, some criteria such as ground glass attenuation have been well characterised in previous studies but others such as mosaic attenuation in exhalation images might be worthy of further exploration. Similarly, whereas the distinction between usual interstitial pneumonia, idiopathic pulmonary fibrosis, and non-specific interstitial pneumonia has been well studied, differentiation between a diagnosis of chronic hypersensitivity pneumonia and idiopathic pulmonary fibrosis continues to pose a challenge to expert clinicians. In a recent prospective study, diagnosis of chronic hypersensitivity pneumonia was ascertained when patients were re-evaluated in more than 40% of patients presenting with features of idiopathic pulmonary fibrosis. This finding is in keeping with the 2011 guidelines that emphasise the need to exclude environmental and other causes associated with pulmonary fibrosis and for multidisciplinary discussions among expert clinicians, radiologists and pathologists familiar with interstitial lung disease to confirm a diagnosis of idiopathic pulmonary fibrosis. The need for such discussions is further emphasised when there are discordances between the radiological and histopathological criteria.

Our study had limitations. Patients were referred to have a surgical lung biopsy procedure only on the basis of the clinical judgment of the primary physician and the decision was made before screening and independent from the study. Patients with definite usual interstitial pneumonia on high-resolution CT were eligible to enter ARTEMIS-IPF without undergoing a surgical lung biopsy procedure and were therefore not included in our analysis. ARTEMIS-IPF’s inclusion criteria of less than 5% honeycombing also enriched the population with a radiological diagnosis of possible usual interstitial pneumonia, the true sensitivity and specificity of high-resolution CT images for a histological diagnosis of usual interstitial pneumonia in the general population with features of idiopathic pulmonary fibrosis and idiopathic interstitial pneumonias cannot be calculated from our dataset.

If patients with a high-resolution CT pattern of possible usual interstitial pneumonia had an alternative histological diagnosis, they would not have been referred for participation in this study. 102 patients who were referred with possible usual interstitial pneumonia on high-resolution CT were not eligible to participate in the trial because they had not had a biopsy sample taken. Whether alternative diagnoses would have been made for some of these patients is not known. However, only five of 84 patients with possible usual interstitial pneumonia on high-resolution CT did not have a histological diagnosis of usual interstitial pneumonia (one had features suggestive of non-specific interstitial pneumonia, one had features of hypersensitivity pneumonitis, one had non-specific airway disease, and two had inadequate sampling).

Notably, ARTEMIS-IPF was started before the publication of the 2011 guidelines. These guidelines state that if a patient in the appropriate clinical setting has a high-resolution CT pattern consistent with a pattern of possible usual interstitial pneumonia, a diagnosis of idiopathic pulmonary fibrosis can be confidently established if the histopathology features in the surgical lung biopsy show patterns of usual or probable usual interstitial pneumonia; a diagnosis of idiopathic pulmonary fibrosis is probable if the histopathology features in the surgical lung biopsy show pattern of possible usual interstitial pneumonia following a multidisciplinary discussion; and a diagnosis of idiopathic pulmonary fibrosis is not made if the histopathology features in the surgical lung biopsy show a pattern of not usual interstitial pneumonia. By grouping patients with histological features of possible or not usual interstitial pneumonia as not usual interstitial pneumonia (for the purposes of the study), we were conservative in the approach used for this analysis and the positive predictive value of possible findings on high-resolution CT would otherwise have been higher than the 94% reported in the results if we had applied the 2011 criteria. Even with expert histological assessment, distinguishing usual interstitial pneumonia from non-specific interstitial pneumonia and other interstitial disease is challenging because patients with usual interstitial pneumonia have substantial geographical heterogeneity in the histological findings. The probable explanation for the low prevalence of alternative histological diagnoses to usual interstitial pneumonia in our series is that the patients considered for enrolment were selected to meet the criteria of ARTEMIS-IPF.
inclusion criteria for the study purposes. Alternatively, in the appropriate clinical presentation, patients with concomitant possible usual interstitial pneumonia on high-resolution CT and not usual interstitial pneumonia on surgical lung biopsy might be uncommon.

On review of free-text comments of the expert pathology reviewers, we also noted that for possible usual interstitial pneumonia and not usual interstitial pneumonia categories, reviewers frequently inserted comments that suggested either suspicion of other disorders or concerns about adequacy of sampling. By contrast, we noted few comments about alternative diagnoses for slides classified as usual interstitial pneumonia and probable usual interstitial pneumonia. Therefore, we therefore felt that grouping possible usual interstitial pneumonia and not usual interstitial pneumonia was appropriate for the purpose of this analysis.

Radiological diagnoses of possible usual interstitial pneumonia in our study were made on the basis of analysis of clinical data by an expert clinician familiar with interstitial lung diseases. Although the reliance on a single expert radiologist to assess each individual case could be regarded as a limitation, the positive predictive value of the radiological diagnosis of possible usual interstitial pneumonia was sufficiently high (94%) that addition of a second reader could not have significantly improved the positive predictive value. Finally, the observations from our study should not be extrapolated to the setting of inconsistent patterns on high-resolution CT.

Absence of definitive honeycombing on high-resolution CT should prompt increased scrutiny for detection of atypical clinical presentation (including consideration of underlying environmental and collagen vascular disease) and radiological findings. However, our study suggests that high-resolution CT is appropriate for diagnosis of idiopathic pulmonary fibrosis in patients with a possible pattern of usual interstitial pneumonia in the appropriate clinical setting. If such patients are assessed by experienced experts, histological confirmation might not be essential to obtain this diagnosis.

Contributors
GR was ARTEMIS Steering Committee Chair, overlooked the study design, interpreted data, reviewed the results with TGO’R (ARTEMIS Medical Monitor), wrote the first draft with TGO’R, and incorporated feedback from co-authors with TGO’R. DL, JDG, RW, and RS interpreted the high-resolution CT images and revised the report. TVC and KOL interpreted the histopathological features of the surgical lung biopsy and revised the report. JB, KKB, JJE, KRF, FJM, and AUW were ARTEMIS Steering Committee Members and revised the report. LS and HZ did the data analysis. PSP designed the clinical trial. ABM designed the clinical trial and revised the report.

Declaration of interests
GR, DL, JDG, RW, TVC, KOL, JB, KKB, JJE, KRF, FJM, and AUW are paid consultants for the sponsor, Gilead Sciences. LS, HZ, PSP, and TGO’R are employees of the sponsor and own Gilead stock. RS is an employee of Perceptive Informatics, which is a vendor under contract with Gilead Sciences. ABM owns Gilead stock.

Acknowledgements
We thank the patients and site coordinators for their contributions and the members of the Steering Committee of the ARTEMIS IPF trial who are the authors of this paper, and Steven Kawut for reviewing this report.

References
Understanding CT patterns in idiopathic pulmonary fibrosis

No gold standard test exists for diagnosis of idiopathic pulmonary fibrosis, but the presence on a thoracic high resolution CT scan of honeycomb change, defined as dilatations of small airways giving the appearance of clumps of small cysts 3–10 mm in diameter (ie, mature and irreversible fibrosis), has a high predictive value for a pathological diagnosis of usual interstitial pneumonia. Together with a typical history of progressive breathlessness in an older person without significant environmental exposures, drug toxicities, or evidence of a connective tissue disease, presence of usual interstitial pneumonia signifies a diagnosis of idiopathic pulmonary fibrosis. A confident diagnosis of idiopathic pneumonia signifies a diagnosis of idiopathic connective tissue disease, presence of usual interstitial nodules, and consolidation). In the 2011 international guidelines for diagnosis and management of idiopathic pulmonary fibrosis, honeycombing is specified as a requirement for usual interstitial pneumonia pattern on high-resolution CT, with lung biopsy sampling required when honeycombing is absent. However, lung biopsy sampling in this population of older people has substantial risks, and in practice many patients with possible usual interstitial pneumonia pattern on high-resolution CT will not undergo this invasive procedure. These patients are therefore neglected because, according to the guidelines, a confident diagnosis of idiopathic pulmonary fibrosis cannot be made without a biopsy and treatment recommendations do not apply.

In The Lancet Respiratory Medicine, Ganesh Raghu and colleagues go some way towards addressing this problem. In a retrospective study of 315 patients previously screened for a randomised trial in idiopathic pulmonary fibrosis, 79 (94%) of 84 patients (mean age 64.4 years, range 47–78 years) who had a high resolution CT pattern of possible usual interstitial pneumonia (without honeycombing) had histopathological usual interstitial pneumonia after analysis of lung biopsy samples. Consideration should be given to potential selection bias, because the pathology of 102 patients who did not undergo biopsy sampling was not known, although their demographics and lung function were much the same as people who had the procedure. Furthermore, some participants might have had biopsy findings inconsistent with idiopathic pulmonary fibrosis and not been referred for consideration in the trial. Previously, Fell and colleagues showed, in a retrospective study of 135 participants with interstitial lung disease, that in the absence of honeycombing, age and the presence of reticulation on high-resolution CT were able to confidently predict idiopathic pulmonary fibrosis. Age 70 years or older had a positive predictive value of at least 95%, and the presence of more widespread reticulation on high-resolution CT allowed prediction of idiopathic pulmonary fibrosis in younger patients. Although further prospective studies could provide confirmation, patients who have suspected idiopathic pulmonary fibrosis without honeycombing on high-resolution CT could in future be spared the risks of lung biopsy sampling and be given a confident diagnosis of idiopathic pulmonary fibrosis on the basis of clinical and radiological findings alone.

Raghu and colleagues’ findings will probably persuade clinicians to make more inclusive and confident diagnoses of idiopathic pulmonary fibrosis than are advocated by the 2011 guidelines. The results will also help to provide clarity about treatment options for a greater number of patients and increase the pool of patients suitable for inclusion in clinical trials of new therapies. This new inclusivity might be regarded as a throwback to a time when the umbrella term cryptogenic fibrosing alveolitis was preferred in the UK. Arguments for abandoning this terminology included concerns that it encompassed fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis with differing outcomes. Cryptogenic fibrosing alveolitis also encompassed the entity of fibrotic non-specific interstitial pneumonia with a better prognosis compared with typical idiopathic pulmonary fibrosis, although its pathological similarity to usual interstitial pneumonia and coexistence of both pathologies in
individual patients\(^5\) suggest a common pathogenesis. Raghu and colleagues also present tantalising data that patients with suspected idiopathic pulmonary fibrosis and a high-resolution CT scan deemed inconsistent with usual interstitial pneumonia had histopathologically confirmed usual interstitial pneumonia in 81.7% of biopsied cases. Which criteria were met for scans deemed inconsistent (eg, ground glass change, air trapping, atypical distribution) would be interesting to know. A strong argument will be made for a change of terminology if such an appearance is not inconsistent with usual interstitial pneumonia at all.

Interpretation of high-resolution CT patterns should continue to be made together with a typical clinical history, and careful clinical assessment is mandatory to identify those patients who might have immunologically driven disease in which inflammation precedes fibrosis, supported by adjunctive tests such as bronchoalveolar lavage.\(^9\) In the modern era with optimal high-resolution CT imaging and thoracic radiologists familiar with interpretation of interstitial lung disease patterns through participation in multidisciplinary meetings,\(^11\) the role of lung biopsy assessment might diminish further. In future, combination of high-resolution CT with new non-invasive biomarkers and functional imaging could be used to better define phenotypes of fibrotic interstitial lung disease.

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I declare that I have no conflicts of interest.