Real-world occurrence of early-onset pulmonary events with brigatinib for advanced *ALK*+ NSCLC

FPN: 88P

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*At the time of study

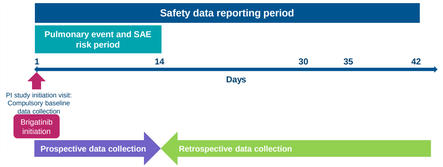
Background

- Interstitial lung disease (ILD) and pneumonitis are known adverse events (AEs) with tyrosine kinase inhibitors (TKIs) used to treat anaplastic lymphoma kinase–rearranged (*ALK*+) non-small cell lung cancer (NSCLC), including brigatinib[1-3]
- In brigatinib clinical trials, pulmonary AEs (eg, ILD, pneumonitis, dyspnea, hypoxia) occurring within 14 days of starting brigatinib were termed early-onset pulmonary events (EOPEs)[4]
- In order to minimize EOPE occurrence observed in early-phase trials, a step-up dosing regimen for brigatinib (180 mg once daily [QD] with a 7-day lead-in at 90 mg QD) was implemented[4-6]
- In patients with advanced NSCLC, symptoms of drug-related pulmonary AEs may be similar to those of the underlying cancer and other lung diseases, making assessment of causality challenging
- This post-authorization safety study evaluated EOPE rates with brigatinib in a real-world setting

Methods

Figure 1: Study design (EUPAS32383)

- **Noninterventional, prospective, observational, single-arm cohort study**
- **Conducted at 29 sites in Europe**
- **Followed adults with advanced *ALK*+ NSCLC during the first 42 days of brigatinib monotherapy**



Electronic case report forms captured:
- **Diagnosis**
- **Description of pulmonary event**
- **Grade of event**
- **Relevant clinical information**
  - **Lab results**
  - **Imaging reports/copies of images**
  - **Histopathology findings**

PI, principal investigator; SAE, serious adverse event

- Primary objective: Assess the occurrence of confirmed EOPEs within 14 days after initiation of brigatinib therapy
- Investigators reported all new or worsening pulmonary AEs and details of treatment exposure
  - Prospectively: Pulmonary AEs occurring within the first 14 days after brigatinib initiation as reported by patients during clinic visits, phone calls, or other contact for Days 1–14
  - Retrospectively: Any pulmonary AEs occurring Days 1–14 reported by patients during their first routine follow-up appointment (4–6 weeks after start of brigatinib as part of routine clinical practice)

Adjudication of EOPEs

- Pulmonary events (eg, dyspnea, hypoxia, pneumonia, pneumonitis/ILD, others) occurring between days 1 to 14 post–brigatinib treatment initiation were considered AEs of special interest (AESIs)
- An independent adjudication committee of 5 physicians with expertise in pulmonary medicine, radiology, and thoracic oncology reviewed all reports of AESIs to determine if they met EOPE criteria
  - Procedures related to the independent adjudication of AESIs were conducted by an IQVIA Clinical Event Validation and Adjudication group
  - Committee members were trained on the predefined EOPE adjudication process outlined in the adjudication charter
  - Adjudication committee members were able to request additional information (eg, imaging) from the clinical site to thoroughly evaluate each event and complete their assessments

EOPE criteria

- Charter-defined criteria for a pulmonary event
  - Presence of a temporal relationship, defined as signs and symptoms beginning within 14 days of starting brigatinib
  - Evidence of a pneumonitis-like process supported by imaging or pathology, such as ground glass opacities on computed tomography/x-ray or diffuse alveolar damage on histopathology
  - Determination that other etiology, such as infection or tumor progression, was unlikely

Statistical analyses

- A total of 120 patients were to be enrolled based on the anticipated number of available patients with advanced *ALK*+ NSCLC starting brigatinib treatment
  - Approximately 8 cases of EOPEs were expected among 120 enrolled patients based on the reported incidence of pulmonary AEs with early onset (6.4%) in the phase 2 ALTA study[6]
- Baseline characteristics, brigatinib exposure and dose patterns, and incidences of pulmonary AESIs and EOPEs were analyzed in the population of all enrolled patients treated with brigatinib
  - For categorical variables, the count and proportions of patients with nonmissing data were determined
  - For continuous variables, median, minimum, and maximum values were summarized for patients with nonmissing values
  - Descriptive statistics were calculated using SAS version 9.4 or higher (SAS Institute, Inc., Cary, NC)

Question

What is the occurrence of EOPEs in patients with *ALK*+ NSCLC treated with brigatinib in real-world practice?

Study design

- **Noninterventional, observational study in real-world practice**
- **(n=98)**
- **Adults with advanced *ALK*+ NSCLC**
- **Initiating treatment with brigatinib monotherapy**
- **Brigatinib administered according to routine local practice and followed up for ≤42 days**
- **Pulmonary AEs occurring within 14 days after first brigatinib dose reviewed by independent adjudication committee for EOPE confirmation**

Results

Independent adjudication committee

EOPE adjudication

Adjudication process
Criteria
• Signs/symptoms within 14 days of brigatinib initiation
• Evidence of pneumonitis-like process
• Other etiology unlikely
Adjudication committee: Pulmonologist, radiologist, thoracic oncologist
Suspected EOPE report sent to 2 members who adjudicated independently
• Agreement: Adjudication complete
• Disagreement: Adjudicated by third member; if no agreement with 1 other member, full committee discussed until consensus reached

Results

EOPEs and pulmonary AESIs within 14 days after brigatinib initiation

Adverse event	Brigatinib n=98
Confirmed EOPE, n	0
Pulmonary AESI, no. of pts (%) [no. of events]	10 (10) [11]
Cough	4 (4) [4]
Dyspnea	2 (2) [2]
Atypical pneumonia	1 (1) [1]
Pneumonia	1 (1) [1]
Pneumonitis	1 (1) [1]
Productive cough	1 (1) [1]
NSCLC	1 (1) [1]

Key takeaway

The independent adjudication committee found that no confirmed EOPEs occurred during the study

Results

Patients

- Of 100 screened patients, 98 met eligibility and were enrolled from January 15, 2021, to February 15, 2024 (**Table 1**)
- 29% of patients had received prior anticancer therapy, most often chemotherapy (19%)
- Brigatinib was the first line of ALK-TKI therapy for 90% of patients
  - Among the 10 patients previously treated with an ALK TKI, all received prior alectinib, 4 received prior crizotinib (3 before and 1 after alectinib), and 2 received prior lorlatinib (both after alectinib)

Results continued

Table 1: Demographic and baseline characteristics

Characteristic	Brigatinib n=98
Median age, y (range)	59.5 (26–88)
≥65 y, n (%)	38 (39)
Female, n (%)	49 (50)
Smoking status, n (%)	(n=93)[a]
Never, Former, Current	49 (53), 38 (41), 6 (6)
≥20 pack/year (former and current smokers)	38/44 (86)
BMI, n (%)	(n=81)[a]
<18.5 kg/m², ≥18.5 to <24 kg/m², ≥24 kg/m²	9 (11), 34 (42), 38 (47)
Any prior anticancer therapy, n (%)	28 (29)
1 prior line, ≥2 prior lines	19 (68), 9 (32)
Any prior TKI therapy, n (%)	10 (10)
Alectinib, Crizotinib, Lorlatinib	10 (10), 4 (4), 2 (2)
Median time from diagnosis of advanced disease to brigatinib first dose, mo (range)	(n=90)[a] 1.0 (0–69)
Disease stage at study entry, n (%)	(n=90)[a]
IIIA or IIIB, IV	10 (11), 80 (89)
History of ILD or pneumonitis, n (%)	3 (3)
Pulmonary condition or disease other than ILD or pneumonitis within 180 days before brigatinib initiation, n (%)	10 (10)
Pulmonary embolism, Asthma, COPD, Dyspnea, Other[b]	2 (2), 1 (1), 1 (1), 1 (1), 7 (7)

[a]Number of patients with nonmissing data; [b]Other pulmonary conditions or disease occurring within 180 days before brigatinib initiation were hyperresponsive bronchial system (n=1), cough and hoarseness (n=1), asthma-COPD overlap (n=1), relapse (n=1), shortness of breath on exertion and when speaking fast (n=1), cough (n=1), respiratory desaturation and febrile cough (n=1)
BMI, body mass index; COPD, chronic obstructive pulmonary disease

Treatment patterns

- Most patients (79%) started brigatinib at 90 mg QD and transitioned to 180 mg QD (**Table 2**)
  - In the first 7 days, 92% of patients received a 90 mg daily dose
  - After Day 7, 49% received only brigatinib 180 mg daily
  - Brigatinib dosing was adjusted due to AEs in 7 patients and due to lack of efficacy in 3 patients
  - Four patients discontinued the study due to death (n=2), AEs (n=1), and lack of efficacy (n=1)
- Median brigatinib dose intensity was 162.5 mg/day (range: 64.3–171.4), and the median relative dose intensity was 99.4% (range: 39.0%–103.9%)
- Medical duration of brigatinib exposure was 42.0 days (range: 6.0–43.0)

Table 2. Real-world brigatinib treatment patterns

Dose pattern	Brigatinib n=98
Within the first 7 days, n (%)	
90 mg daily	90 (92)
90 mg daily → 180 mg daily	3 (3)
90 mg daily → 0 mg daily	2 (2)
Other[a]	3 (3)
During the entire study period, n (%)	
90 mg daily → 180 mg daily	77 (79)
90 mg daily	4 (4)
90 mg daily → 180 mg daily → 0 mg daily → 90 mg daily	3 (3)
90 mg daily → 0 mg daily → 90 mg daily → 180 mg daily	2 (2)
90 mg daily → 180 mg daily → 120 mg daily	2 (2)
Other[b]	8 (8)
Dose modifications during the entire study, n (%)[c]	
Dose increased	93 (95)
Dose reduced	4 (4)
Dose interrupted	12 (12)
Physician intervention	11 (92)
Patient decision/action	1 (8)
Drug withdrawn	11 (11)
Switch to new therapy	7 (64)[d]
Reason for dose adjustment, n (%)[c]	
Adverse event	7 (7)
Lack of efficacy	3 (3)
Other	94 (96)
Standard of care[e]	92 (98)
PI decision	1 (1)
Planned dose increase	1 (1)

[a]Other dose patterns during the first 7 days of treatment were: 90 mg daily → 0 mg daily → 90 mg daily (n=1); 60 mg daily → 0 mg daily (n=1); and 30 mg daily (n=1); [b]Other dose patterns during the entire study period were: 30 mg daily → 60 mg daily → 90 mg daily (n=1); 60 mg daily → 0 mg daily → 90 mg daily → 120 mg daily (n=1); 90 mg daily → 0 mg daily → 90 mg daily → 90 mg daily → 0 mg daily → 180 mg daily (n=1); 90 mg daily → 180 mg daily → 0 mg daily → 90 mg daily → 0 mg daily → 90 mg daily (n=1); 90 mg daily → 180 mg daily → 0 mg daily → 90 mg daily → 180 mg daily (n=1); 90 mg daily → 180 mg daily → 90 mg daily (n=1); and 90 mg daily → 60 mg daily (n=1); [c]There could be more than one dose modification and reason for dose adjustment per patient; [d]Calculated as a percentage of patients with drug withdrawn (n=11); [e]The recommended brigatinib dose regimen is 90 mg QD for the first 7 days and 180 mg QD thereafter. Dosing interruption and/or dose reduction may be required based on individual safety and tolerability.[7]

Pulmonary AESIs

- Ten patients experienced a total of 11 pulmonary AESIs during the first 14 days of brigatinib treatment
  - Three AESIs in 3 patients were serious AEs
    - Pneumonia requiring or prolonging hospitalization
    - Dyspnea requiring or prolonging hospitalization
    - NSCLC disease progression
- An additional 2 serious AEs were reported
  - Pleural effusion requiring or prolonging hospitalization (patient who had AESI of dyspnea)
  - Death due to unknown cause
- None of the serious AEs were considered related to treatment
- All pulmonary AESIs were reviewed by the independent adjudication committee, and none were adjudicated as confirmed EOPEs

Conclusions

- In this real-world study, most patients (79%) received brigatinib at doses consistent with recommended step-up dosing
- There were no confirmed EOPEs after review by the independent adjudication committee
- With the inclusion of an independent adjudication committee, this study may provide a more accurate representation of EOPE incidence than previous studies

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Acknowledgments

- The authors thank all the patients and their families and the investigators and staff at all clinical sites for their participation in the study. This study is sponsored by Takeda Development Center Americas, Inc. Medical writing support for the development of this poster, under the direction of the authors, was provided by Lauren Gallagher, RPh, PhD, of Peloton Advantage, LLC, an OPEN Health company, and funded by Takeda Development Center Americas, Inc., Cambridge, MA, and complied with the Good Publication Practice (GPP) guidelines (DeTora LM, et al. Ann Intern Med 2022;175:1298–304).

Disclosures

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Presented at the European Lung Cancer Congress (ELCC), March 26–29, 2025, Paris, France