UK and US patient preferences for tyrosine kinase inhibitors in ALK+ advanced non-small cell lung cancer in the first-line setting

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Introduction

- Anaplastic lymphoma kinase (ALK)-targeting tyrosine kinase inhibitors (TKIs) have transformed the treatment of ALK+ advanced non-small cell lung cancer (aNSCLC) in the first-line setting.
- The first-generation ALK TKI crizotinib has been shown to have a limited effect on brain metastases due to its poor blood brain barrier (BBB) penetration, while second generation (ceritinib, alectinib, brigatinib) and third generation (lorlatinib) ALK TKIs are designed to cross the BBB to control and prevent the development of brain metastases.
- While these newer generation ALK TKIs have demonstrated superior efficacy as compared to crizotinib,[1-3] they have not been compared in head-to-head clinical trials in the first-line setting.
- Available data from ALEX, ALTA-1L, and CROWN clinical trials indicate that newer generation ALK TKIs differ in their systemic and intracranial efficacy and safety profiles as first-line treatments for ALK+ aNSCLC.[1-3]
- Median progression-free survival (PFS) was 34.8 months for alectinib and 30.8 months for brigatinib after approximately 3 years of follow-up,[1, 2] whereas median PFS for lorlatinib was not reached after 5 years of follow-up, with a 5-year PFS rate of 60%.[3]
- Lorlatinib has been approved as first-line treatment for ALK+ aNSCLC in the US, Asia, and European Union, but not in the UK.
- As patients may stay on first-line treatment longer than later-line treatments, understanding patient preferences for first-line treatments is crucial to improve satisfaction and outcomes and may reveal novel insights into how geographic and regulatory differences influence treatment decisions.

Objective

- To understand which treatment attributes influence decision-making, we explored patient experiences, expected treatment benefits, and treatment-related risks associated with ALK+ TKIs in the first-line setting for patients in the UK and US.

Methods

- Thirty semi-structured, qualitative interviews were conducted via web-assisted telephone with 20 US and 10 UK patients with a self-reported diagnosis of ALK+ aNSCLC and who were receiving an ALK+ TKI.
- US patients were recruited from independent panels, databases, and patient advocacy groups between April and May 2023, and UK patients were recruited by ALK Positive, Inc., a registered charity, in February 2024.
- A semi-structured interview guide was developed based on a literature review and updated through iterative discussions with the research team and steering committee, which consisted of clinical experts and patient advocacy groups.
- The study protocol was approved by an external institutional review board (Salus: 23056) and written informed consent was obtained from all participants prior to interviews.
- Participants were asked open-ended questions about their treatment experiences and expectations.
- A coding framework was developed based on an interview guide and iteratively updated based on initial interviews to accommodate additional concepts that emerged.
- Descriptive sociodemographic and clinical data were collected by using an online questionnaire taken by participants during screening and following the interview.
- Qualitative data were analyzed using an inductive thematic approach to identify key themes that described important concepts raised by participants.[4]
- An inductive thematic approach involves identifying recurring themes or patterns directly from the data without predefined categories, making it ideal for exploring complex issues.

Results

Patient characteristics

- US and UK patient demographics were similar in terms of sex and race; however, US patients were on average older than UK patients (**Table 1**).
- Fewer US patients had received their diagnosis in the past two years than UK patients (US: 15%, UK 60%).
- US patients also had more experience with multiple TKIs in their treatment sequence than UK patients (US: 70%, UK: 30%).
- Fewer US patients than UK patients reported they were on their first-line treatment (US: 25%, UK: 70%).
- Most US and UK patients had been on their current treatment line for over one year (US: 75%, UK: 70%) and had self-reported stable disease (US:85%, UK: 90%).
- Although US and UK patients had similar rates of distant metastatic disease (US:85%, UK: 70%), US patients had a higher incidence of brain metastases than UK patients (US: 60%, UK: 40%).
- Most US patients reported being restricted in strenuous activity (65%), whereas most UK patients reported being fully active (70%).

Table 1. US and UK Patient Characteristics

Characteristics	US patients (N=20)	UK Patient (N=10)
Age, mean years (range)	52 (38–69)	48 (31–62)
Female sex, n (%)	12 (60)	6 (60)
Race, n (%)		
White or Caucasian	16 (80)	10 (100)
Black/African American	2 (10)	0 (0)
Asian/Asian American	1 (5)	0 (0)
American Indian/Alaska Native	1 (5)	0 (0)
Years since diagnosis, n (%)		
<1 year	0 (0)	2 (20)
1-2 years	3 (15)	4 (40)
3-5 years	8 (40)	3 (30)
6 years or more	9 (45)	1 (10)
Disease Status, n (%)		
Stable	17 (85)	9 (90)
In remission	3 (15)	1 (10)
Current disease progression, n (%)		
Local metastasis	3 (15)	3 (30)
Distant metastasis	17 (85)	7 (70)
Brain metastasis, n (%)		
Yes	12 (60)	4 (40)
No	8 (40)	6 (60)
Time on current treatment, n (%)		
<1 year	5 (25)	3 (30)
≥1 year	15 (75)	7 (70)
Line of treatment, n (%)		
First line	5 (25)	7 (70)
Second line	8 (40)	1 (10)
Third line	7 (35)	2 (20)
Previous TKI experience, n (%)		
Yes	14 (60)	3 (30)
No	6 (30)	7 (70)
Current functioning level, n (%)		
Fully active	7 (35)	7 (70)
Restricted activity	13 (65)	3 (30)

Treatment benefits

- Both US and UK patients reported that treatment efficacy, preventing or controlling the spread of disease, and quality of life were important factors in their treatment decision-making (**Figure 1**).
- Most US and UK patients ranked OS (US: 90%, UK: 70%) and PFS (US: 85%, UK: 70%) as the most important treatment benefits (**Figure 2**).
- Preventing brain metastases (US: 55%, UK: 50%) and controlling existing brain metastases (US: 40%, UK: 40%) were also ranked as important treatment benefits in both populations.
- Quality of life improvements were primarily described as coming from cancer control.
- Patients without brain metastasis were concerned about its development, particularly those from the UK, as this may significantly impact their independence and their activities of daily living, such as driving.

Figure 1. Key quotes related to treatment benefits

Survival: *"The number one meaningful benefit has been length of life or overall survival rate." [US P019]*

Prevent spread: *"I'm petrified every time I go for an MRI. Every time I get a headache, I don't know if it's spread…I can't live my life worrying where it spread…I can only pray that the medication that I'm on is doing its job." [US P012]*

Control spread: *"I have [brain metastases], but every time I have a scan, they say they're stable…[It] would be good if they didn't develop at all, and you never had them." [US P015]*

Improve symptoms: *"I can deal with symptoms if I get them, as long as I know it's working" [US P015]*

Improve quality of life: *"Preventing the spread of the cancer will kind of relate to the improved symptoms and improved quality of life" [US P010]*

Survival: *"I want to live as long as possible. [UK 13]"*

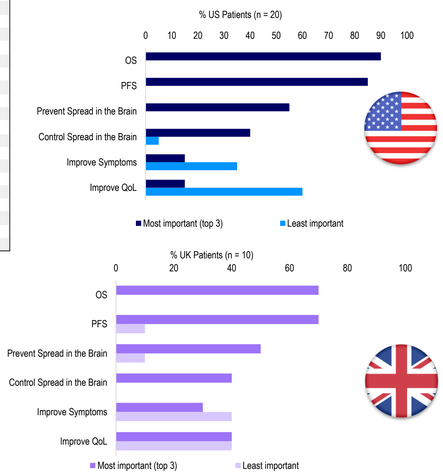
Prevent spread: *"I think [brain metastases] occurring for the first time is the worrying thing for me because once you've got them, you've got them. And then it's obviously losing my driving license…." [UK 05]*

Control spread: *"I've got brain mets…So, for me, that's really important that…something can control that and the primary cancer." [UK 02]*

Improve symptoms: *"…the reduction in the physical symptoms that I was experiencing. So, I was struggling to breathe, I couldn't move very far because of my lung capacity being significantly reduced because of the tumors" [UK 01]*

Improve quality of life: *"The most important thing for me is to live a reasonably good life as long as I can. I wouldn't want to live a long [time] and not be able to get out of bed…but I wouldn't want to live in absolutely perfect health for just 3 months." [UK 08]*

Figure 2. US and UK Patient Ranking of Benefits



Abbreviations: OS, overall survival; PFS, progression-free survival; QoL, quality of life.

Results (cont.)

Treatment burden

- The most frequently mentioned treatment burdens reported by patients were adverse events (US: 70%, UK: 50%) followed by mode of administration (US: 15%, UK:30%).
- The most common adverse events experienced by patients included fatigue (US: 85%, UK: 60%) and weight gain (US: 65%, UK: 60%), constipation (US: 60%, UK: 60%), and cognitive effects (US:55%, UK: 50%) (**Figure 3**).
- There were slight variations in adverse event experiences between US and UK patients, including peripheral neuropathy (US: 45%, UK: 50%), muscle pain (US: 65%, UK: 30%), and mood effects (US: 25%, UK: 50%).
- Both US and UK patients were most concerned about cognitive effects (US: 50%, UK: 50%), weight gain (US: 35%, UK: 40%), liver enzyme elevation (US: 35%, UK: 30%), and fatigue (US: 30%, UK: 30%) (**Figure 4**).
- US patients were more concerned about hyperlipidemia (US: 35%, UK: 10%) and less concerned about ocular toxicity (US: 5%, UK: 20%) than UK patients.
- Many patients were willing to tolerate treatment-related adverse events because of the efficacy treatments provided, with one patient reporting that "my life is more important than the side effects" [US 001-016].
- Patients in both countries indicated a preference for a regimen that was infrequent (e.g., once a day) and without dietary restrictions, but few individuals (n=7) conveyed dissatisfaction with their treatment due to administration requirements (**Figure 3**).

Figure 3. Key quotes related to treatment burden

Adverse events: *"We have talked about if the edema were to get worse, doing a reduced dose…but we don't want to do that because it's working." [US P016]*

"I don't mind fatigue. If I get super tired, I can just take a nap, that's just how I handle it, but I don't do that often." [US P015]

"This new TKI that I'm on, that one has fatigue, which when I just started it, it was very problematic. I mean, I've found ways to cope. So, for the most part, I think, it's been doing its job and it's been okay." [US P010]

Administration requirements: *"[I would rather not have to take medications, but yeah [the number of pills is] fine." [US P010]*

Adverse events: *"So, for me, the first drug, I couldn't cope with the side effects and had to do a reduction because I couldn't get out of bed; I had headaches, I was tired, I had pains in my legs, I couldn't walk. But with the second drug, as I said, there was definitely more side effects, but I coped with them…there was a lot of times I thought about [reducing it], but I persevered with it because…after I reduced my first one, I had progression quite quickly afterwards. So, I think I just basically learned to put up with the side effects more." [UK 05]*

"I haven't experienced [fatigue], but I am concerned about it. It was one of the key symptoms of cancer and it had such a massive impact on life." [UK 09]

"[ocular toxicity is] a concern because obviously if my eyesight gets worse, then I might not be able to drive." [UK04]

Administration requirements: *"[The main challenge is] remembering to take it every day." [UK09]*

Treatment decision-making

- Patients from both countries reported that treatment selection and change of treatment decision were discussed with their doctors (**Figure 5**).
- Previous experience with TKI beyond current treatment was more common among US than UK patients (US: 14; UK = 3).
- Of those patients, nearly all reported discussing the change in treatment with their oncologist (US: 12, UK: 3), and only 2 patients reported that the decision to change treatment was not a shared decision (US: 1, UK: 1).
- The shared decision-making process was described as evolving over time, with patients initially relying solely on their oncologists' advice and later gaining confidence in conducting independent research to be *"very involved in all the decisions" [US P017].*

Figure 4. Top adverse events that US and UK patients want to avoid

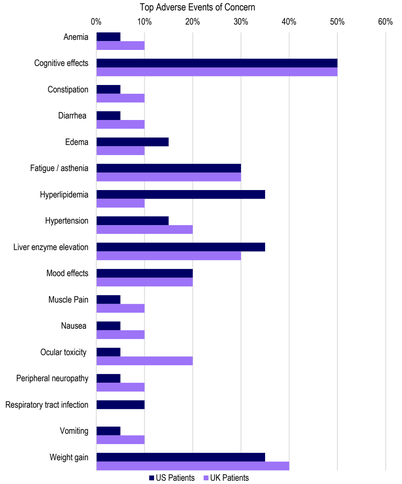


Figure 5: Key quotes related to treatment decision-making

"…we had always had this discussion that we were pretty much riding out the first one until any signs of progression, which we figured would be in the brain because that's the only area that the medication did not protect against. So, as soon as we saw the mets, we were just like, 'Okay, all right. So, it's time to switch.'" [US-010]

"[The doctor] knows what she's talking about, but I do a lot of research in my free time…so I will share my ideas to her and she will investigate it and she will decide if this is the right path to go or not." [US P020]

"It's very easy for me when they make a recommendation. We've already talked about the possibilities. At the same time, my husband and I both do a little bit of research and reading just to make sure that we're on the same page they are…The team is very open and very honest in their discussions along the way, and before we get to the point where they write the prescription." [US P016]

"Yes, so the first line of treatment, they did give me the option to wait and see and just have another scan and see how it was going. But I was coughing quite violently at that point, so I made the decision to move on to the second treatment." [UK 05]

"[The doctor] discussed what I would be moving on to, which I already knew 'cause I know quite a lot from different forums and stuff. I moved on to that at that point in time, after I had got a tissue biopsy, and I also got a blood test done as well at that point, when I had progressed." [UK06]

"Well, there aren't any options. There's… with NICE guidance in the UK, there is a linear progression through the TKIs, so there wasn't any option." [UK 13]

Conclusions

- This multi-method interview study demonstrates that patients with ALK+ aNSCLC in both countries prioritized overall survival, progression-free survival, intracranial efficacy as the most important treatment benefits, and were willing to tolerate treatment-related adverse events (or define TRAE in result section as use abbreviation) to maximize those possible treatment benefits.
- Although the priorities of US and UK patients were similar, small differences were observed in preferences for symptom and quality-of-life improvements and risks of ocular toxicity and hyperlipidemia.
- These differences could be attributed to the fact that UK patients were slightly younger and had less experience with ALK TKIs (70% in first-line treatment) than US patients.
- Since ALK+ patients are more likely receiving treatments longer than other types of aNSCLC, it is important to consider patient preferences in shared decision making to enhance patients' quality of life.
- This study highlights the importance of improving first-line treatment access for patients with ALK+ aNSCLC in the UK, accounting for patients' preferences to maximize treatment benefits and survival.
- To validate these qualitative findings, a quantitative preference elicitation survey is being developed to assess treatment choices in the first-line setting of ALK+ aNSCLC.
- By understanding the differences and similarities in patient perspectives regarding ALK TKI treatments across different regions, policymakers and healthcare professionals can develop targeted recommendations that cater to the diverse needs and preferences of different populations.
- Further research with a larger sample size across different countries is needed to better understand the underlying factors influencing patients' perspectives, and to inform the development of patient-centric guidelines in ALK+ aNSCLC.

Limitations

- This study represented a geographically restricted sample from the US and UK, which may affect generalizability of the findings.
- This study also faced potential selection bias due to participants' self-selection based on the recruitment materials they received.

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Disclosures

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