Patient and oncologist preferences for ALK+ advanced non-small cell lung cancer tyrosine kinase inhibitor treatments

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Introduction

- Anaplastic lymphoma kinase (ALK)-targeting tyrosine kinase inhibitors (TKIs) have transformed the therapeutic approach to ALK-positive advanced non-small cell lung cancer (NSCLC) in the first-line setting.
- Next generation ALK TKIs are designed to cross the blood brain barrier, providing a strategy for controlling or preventing brain metastases, and have demonstrated superior efficacy when compared with the first-generation ALK inhibitor crizotinib.[1]
- While head-to-head clinical trials comparing alectinib, brigatinib, and lorlatinib are lacking, available data from ALEX, ALTA-1L, and CROWN indicate that these treatments differ in their systemic and intracranial efficacy and safety profiles.[2-4]
- Recent advancements in ALK TKIs highlight the need to evaluate the preferences of patients and oncologists for key treatment attributes in ALK-positive advanced NSCLC, as no prior studies have focused exclusively on the next-generation ALK TKIs.[5-7]
- Quantifying the risk-benefit trade-offs for newer ALK TKI treatment attributes can facilitate shared decision-making, enabling oncologists and patients to develop treatment plans that effectively meet patient medical needs and preferences.

Objective

- To understand the preferences of patients and oncologists in the US for key attributes associated with ALK TKIs including the first-line setting and their willingness to trade-off between benefits and risks.

Methods

Discrete Choice Experiment

- Patients with ALK-positive advanced NSCLC who were currently on ALK TKIs and board-certified oncologists who were treating at least one new patient with ALK-positive advanced NSCLC per year were recruited.
- An online stated preference survey was developed to elicit participant preferences for ALK TKIs, which included a best-worst scaling discrete choice experiment (DCE), multidimensional thresholding tool, and a clinical and sociodemographic questionnaire.
- The DCE design, attributes and levels were informed by a targeted evidence review, an attribute selection workshop with multiple stakeholders, 30 qualitative and cognitive pilot interviews, and consultations with a steering committee of two members, including an oncologist and a patient advocate.
- Eight treatment attributes (three benefit and five risk attributes) were selected for inclusion in the DCE (**Figure 1**), and attribute levels were informed by the major randomized clinical trials of ALK TKIs in the first-line setting (i.e., ALEX, ALTA-1, and CROWN).[2,3,8-11]
- Each participant completed one practice DCE task and 12 randomly ordered experimental design tasks, selecting their first and second best options in each.
- The DCE responses were analyzed using a mixed logit model.[12] Relative attribute importance (RAI) scores, minimum acceptable benefit (MAB) and maximum acceptable risk (MAR) were calculated.

Figure 1. Example of a DCE Choice Task (Patient Version)

	Treatment A	Treatment B	Treatment C
Muscle and bone pain	Moderate muscle and bone pain	No muscle or bone pain	No muscle or bone pain
Fatigue	Moderate fatigue	Moderate fatigue	No fatigue
Mood, cognitive or psychotic effects	No known risk	7 out of 100 (7%)	35 out of 100 (35%)
Metabolic events	Abnormal tests that over time may require dose reduction or treatment pause	No abnormal tests	No abnormal tests
Weight gain	10% of body weight gain ↑10%	10% of body weight gain ↑20%	20% of body weight gain ↑20%
Stopping brain metastases from developing	99 out of 100 (99%)	75 out of 100 (75%)	50 out of 100 (50%)
Stopping brain metastases from getting worse	75 out of 100 (75%)	75 out of 100 (75%)	30 out of 100 (30%)
Lung cancer control	40 out of 100 (40%)	55 out of 100 (55%)	65 out of 100 (65%)

Results

Participant characteristics

- A total of 151 patients and 150 oncologists participated in the study (**Table 1**).
- Approximately half of patients were restricted in physical functioning (50%) and were in their first line of treatment (50%). Approximately one-quarter (23%) currently had BM.
- Most oncologists had treated more than two patients with ALK-positive advanced NSCLC per month on average in the past 12 months (73%).
- Oncologists practiced in a variety of settings, including academic medical centers (43%), and community hospitals (21%).

Table 1. Characteristics of Patients and Oncologists

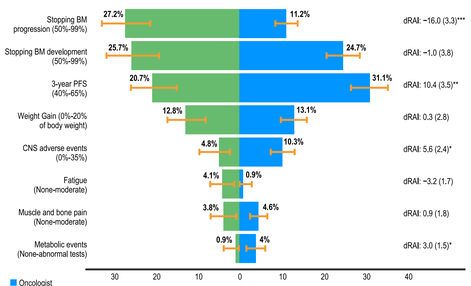
Patient characteristics	N=151	Oncologist characteristics	N=150
Age, mean years (range)	58.5 (39–78)		
Female sex	53 (35%)	**Female sex**	25 (17%)
Race		**Race**	
White or Caucasian	71 (47%)	White or Caucasian	91 (61%)
Black/African American	40 (27%)	Black/African American	2 (1%)
Hispanic/Latino	33 (22%)	Hispanic/Latino	5 (3%)
Asian/Asian American	9 (6.0%)	Asian/Asian American	31 (21%)
Middle Eastern/North African	1 (<1%)	Middle Eastern/North African	4 (3%)
Years since diagnosis		Prefer not to say	19 (13%)
<1 year	79 (52%)	**Practice location**	
1–2 years	33 (22%)	Major city, >500,000	59 (39%)
3-5 years	34 (23%)	Urban area, 100,000–500,000	45 (30%)
≥6 years	4 (3%)	Suburb, >100,000	39 (26%)
Disease status, n (%)		Small city, 30,000–100,000	7 (5%)
Stable	129 (85%)	Rural/small town, <30,000	4 (3%)
In remission	22 (15%)	**Practice US region**	
Current progression		Northeast	38 (25%)
Local progression	87 (58%)	South	52 (35%)
Metastatic	64 (42%)	Midwest	31 (21%)
Brain metastasis		West	
Yes	35 (23%)	**Time as board-certified oncologist**	
No/Not sure	116 (77%)	< 1 year	3 (2%)
Time on current treatment line		1–2 years	5 (3%)
0-6 months	91 (60%)	3–5 years	9 (6%)
7-11 months	37 (25%)	>5 years	133 (89%)
≥1 year	23 (15%)	**Practice Setting***	
Treatment line for ALK+ NSCLC	5 (25)	Academic/University Hospital	64 (43%)
First	76 (50%)	Group Practice, Single-specialty	33 (22%)
Second	32 (21%)	Community Hospital	31 (21%)
Third	43 (29%)	Group Practice, Multi-specialty	28 (19%)
Current functioning level		**New ALK+ NSCLC patients in last 12 months**	
Fully active	36 (24%)	>1 in last 12 months	16 (11%)
Restricted activity	76 (50%)	1 per month	24 (16%)
Unable to work or worse	32 (26%)	2 to 5 per month	54 (36%)
		>5 per month	56 (37%)

Multiple responses allowed. Abbreviations: ALK+ = anaplastic lymphoma kinase-positive; NSCLC = non-small cell lung cancer

Treatment attribute preference estimates

- Overall, improvements in treatment benefits were more important than risks for patients and oncologists, contributing to 74% of patient choices and 67% of oncologist choices (**Figure 2**).
- The most important attribute driving patient treatment choice was probability of preventing BM from getting worse from 30% to 75% (RAI = 27%; p<0.001); for oncologists this was fourth most important (RAI = 11%).
- The most important driver of oncologist treatment choice was improving 3-year PFS from 45% to 65% (RAI = 31%; p<0.01), which was third most important for patients (RAI = 21%).
- Patients and oncologists assigned similar importance to weight gain and muscle/bone pain.
- Oncologists placed twice as much importance on CNS adverse events (RAI = 10% vs. 5%; difference of RAI p<0.05) and four times as much importance on metabolic events (RAI = 4% vs. 1%%; difference of RAI p<0.05) than patients in their first-line treatment decisions.
- Patients placed more importance on fatigue than oncologists (RAI = 4% vs. 1%; difference of RAI p<0.05).

Figure 2: RAI Scores for Patients and Oncologists

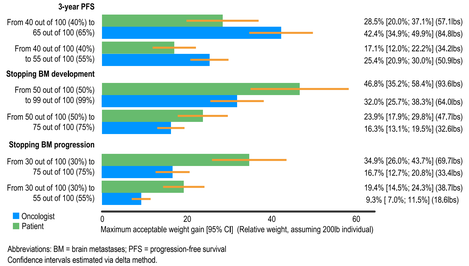


P values: *** <0.001, ** <0.01%, * <0.05%. Abbreviations: BM = bone metastases; CNS = central nervous system; dRAI = difference of relative attribute importance; PFS = progression-free survival; RAI = relative attribute importance. Difference of RAI presented as: dRAI: X.X (standard error); dRAI standard errors estimated via bootstrapping

Treatment attribute trade-offs

- The MAB values show the benefit required to accept an increase in treatment risks (**Figure 3**).
  - Oncologists were willing to accept a 0% to 35% increase in probability of CNS adverse events in exchange for 7.6% improvement in probability of 3-year PFS, 23.2% improvement in probability of stopping BM development, or 39.2% improvement in probability of stopping BM progression.
  - Patients and oncologists were willing to accept worsening in muscle/bone pain, fatigue, and metabolic events in exchange for different treatment benefits.
  - Patients and oncologists were willing to accept the risk of 20% body weight gain but required the largest improvements in treatment benefits as compared with other risks.
- The MAR values show the risk that patients and oncologists were willing to tolerate in exchange for increases in treatment benefits (**Figure 4**)
  - Patients and oncologists were willing to accept increases weight gain for improvements in treatment benefits
  - For every 1% increase in 3-year PFS, preventing BM development, and stopping BM progression, patients were willing to accept a 1.14%, 0.95%, and 0.77% increase in their body weight, respectively, while oncologists were willing to accept a 1.7%, 0.65%, and 0.37% increase in patient body weight, respectively.

Figure 4: Maximum Acceptable Weight Gain Patients and Oncologists Would Accept for Treatment Benefits



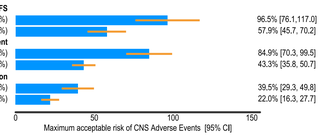
Abbreviations: BM = brain metastases; PFS = progression-free survival
Confidence intervals estimated via delta method.

Figure 3: MAB for Patients and Oncologists to Accept a Worsening in Treatment Risk*

*Results for patient and oncologist MAB of 3-year PFS, stopping BM from developing, and stopping BM from progressing for the five treatment risks. Percentages can be interpreted as the increase in probability of experiencing each treatment benefit that would be required to accept the treatment risk; 0% indicates MAB findings that were not significantly different from zero.
Abbreviations: BM = brain metastasis; CNS = central nervous system; PFS = progression-free survival

- Oncologists were willing to tolerate increases in CNS adverse events for BM efficacy improvements (**Figure 5**).
- For every 1% increase in probability of 3-year PFS, stopping BM developing, or stopping BM progression, oncologists were willing to accept a 3.86%, 1.73%, or 0.88% increase in the risk of CNS adverse events, respectively.
- The MAR for patients was not significantly estimated since changes in the risk of CNS adverse events did not significantly impact patient treatment choice.

Figure 5: MAR of CNS Adverse Events Oncologists Would Accept for Treatment Benefits*



*Results for oncologists MAR of CNS adverse events were estimated using an alternate model specification where CNS adverse events was linearly coded. Some of the MARs estimated were outside of the range of CNS AE probability presented in the study, it was assumed the MAR was constant beyond the range presented in the study. Preference estimates were not significant for patients, indicating that changes in risk of experiencing CNS adverse events did not impact their treatment decision-making process.
Abbreviations: BM = brain metastases; CNS = central nervous system; PFS = progression-free survival.
Confidence intervals estimated via delta method.

Subgroup analysis

- No significant differences were observed across patients according to BM status.
- Patients with previous TKI experience placed more importance on preventing BM progression (RAI = 44%) than patients without previous TKI experience (RAI = 20%, p<0.001).
- Younger patients (<50 years) placed more importance on stopping BM from developing (RAI = 45%) compared with older patients (RAI = 21%, p<0.01).
- Patients on second-line treatment or higher placed more importance on stopping BM from developing (RAI = 33%) compared with those on first-line treatment (RAI = 21%, p<0.05).
- Oncologists treating more than five patients/month placed greater importance on risk of CNS adverse events (RAI = 15%) compared with those treating fewer than five patients/month (RAI = 12%; p <0.01).
- No significant differences were observed across oncologists practicing in academic vs. non-academic settings.

Limitations

- Participants may not represent the larger population and were recruited in line with soft-quotas of interest, which limits the generalizability of findings.
- Participants selected their preferred treatments from hypothetical scenarios, which may not reflect their actual choices in the real-world situations.

Conclusions

- This quantitative preference elicitation survey was the first to assess treatment choices in the first line setting relevant to ALK+ advanced NSCLC among 151 patients, and 150 oncologists in the US.
- Patients assigned greater relative importance to preventing BM, while oncologists assigned greater importance to improving 3-year PFS.
- Patients and oncologists ranked efficacy higher than treatment-related risks and were willing to trade-off some risks for improvements in 3-year PFS, preventing-BM development, or stopping BM progression.
- By understanding the trade-offs in treatment attributes that inform treatment choices, oncologists and patients can better engage in shared decision making discussions and select the most suitable ALK TKIs for the personalized treatment of ALK+ advanced NSCLC in the first-line setting.

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