Hematologist-Oncologist Preferences for Treating Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia (Ph+ ALL) Using Tyrosine Kinase Inhibitors in Combination With Chemotherapy: A Discrete Choice Experiment

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Background

- Ph+ ALL is an aggressive, life-threatening cancer that affects the lymph nodes and leads to an overproduction of immature white blood cells.[1,2,3]
- Several tyrosine kinase inhibitors (TKIs) are routinely used in combination with chemotherapy as frontline treatment for Ph+ ALL.[4,5] These treatments have different benefit-risk profiles,[5] which may impact shared decision-making due to competing desires to maximize efficacy and minimize risks.
- In a prior discrete choice experiment (DCE), adults with Ph+ ALL generally prioritized efficacy over avoiding risks when selecting a frontline treatment.[6] However, preferences differed among patients.[6] It is important to understand the preferences of physicians treating Ph+ ALL because they are critical contributors to shared decision-making.

Methods

- An online DCE was conducted to elicit preferences of US-based hematologist-oncologists for frontline treatments of Ph+ ALL.
- Treatment attributes and levels were informed by the Phase 3 PhALLCON trial[7] and feedback from key opinion leader hematologist-oncologists.
- The PhALLCON trial compared two TKI combination therapies head-to-head as frontline treatment for Ph+ ALL.[7] PhALLCON data provide clinically relevant information on levels of risks and rates of minimum residual disease-negative complete remission (MRD−ve CR) [7,8] – a prognostic indicator of long-term survival.[9]
- The DCE was refined based on input from a cognitive pilot interview study with 10 hematologist-oncologists and a quantitative soft launch with 30 hematologist-oncologists.
- In each of 12 DCE choice tasks, participants chose between two hypothetical treatment profiles – each a combination of a TKI and reduced-intensity chemotherapy. Attribute levels varied within each task according to an experimental design.
  - Participants made choices for a "less complex"* baseline patient (Part 1) and then for four other patient profiles (Part 2). Parts 1 and 2 were repeated in each of the 12 tasks.
- Choice data were analyzed using mixed multinomial logit models.
  - Clinically relevant relative attribute importance (cRAI) quantified how participants prioritized efficacy and several risks of treatment and was calculated based on observed efficacy and risk levels from the PhALLCON trial.
  - Willingness to trade off quantified how participants traded off between efficacy and various risks (i.e., if the likelihood of hepatotoxicity increased by 1%-point, how much would the likelihood of MRD−ve CR need to increase to offset the increase in risk?).

Example DCE Task

Part 1: Which frontline treatment would you recommend to your patient who has Ph+ ALL? The patient has an ECOG performance status score of 0, does not have any comorbidities, and is 45 years old.

Reduced-Intensity Chemotherapy + TKI A	Reduced-Intensity Chemotherapy + TKI B
25 out of 100 (25%) people will be in **MRD−ve CR at the end of induction**	15 out of 100 (15%) people will be in **MRD−ve CR at the end of induction**
65 out of 100 (65%) people experience **grade 3-4 hematotoxicity**	75 out of 100 (75%) people experience **grade 3-4 hematotoxicity**
3 out of 100 (3%) people experience **an arterial occlusive event**	1 out of 100 (1%) people experience an **arterial occlusive event**
15 out of 100 (15%) people experience **grade 3-4 hepatotoxicity**	20 out of 100 (20%) people experience **grade 3-4 hepatotoxicity**
❑	❑

Part 2. If the patient profile differed based on the following characteristics, which treatment option would you recommend?

Patient Characteristics to Consider	Reduced-Intensity Chemotherapy + TKI A	Reduced-Intensity Chemotherapy + TKI B
Aged 65 years or older	❑	❑
Has an ECOG score of 3 [a]	❑	❑
Has diabetes	❑	❑
Has hypertension	❑	❑

[a] Capable of only limited self-care; confined to bed or chair >50% of waking hours. Abbreviations: ECOG, Eastern Cooperative Oncology Group; MRD−ve CR, minimal residual disease-negative complete remission; Ph+ ALL, Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia; TKI, tyrosine kinase inhibitor.
* "Less complex" baseline patient profile: age 45 years; ECOG score 0 (fully active); no comorbidities.

Treatment attributes and levels

Attribute	Levels Used in the DCE	Levels From the PhALLCON trial[7,8] Used to Calculate cRAI		
		Clinically Relevant Range	Ponatinib + Chemo	Imatinib + Chemo
Chance of being in MRD−ve CR at the end of induction	15%, 25%, 35%	16.7% – 34.4%	34.4%	16.7%
Risk of an arterial occlusive event	1%, 2%, 3%	2.5% – 1.2%	2.5%	1.2%
Risk of grade 3–4 hematotoxicity	65%, 75%, 85%	75.3% – 73.6%	73.6%	75.3%
Risk of grade 3–4 hepatotoxicity	10%, 15%, 20%, 25%	21.5% – 12.3%	21.5%	12.3%

Abbreviations: chemo, reduced-intensity chemotherapy; cRAI, clinically relevant relative attribute importance; DCE, discrete choice experiment; MRD−ve CR, minimal residual disease-negative complete remission.

Question

When hematologist-oncologists decide between frontline treatments for Ph+ ALL, what benefit-risk trade-offs are they willing to make? How do these trade-offs vary based on the clinical characteristics of a patient?

Study design

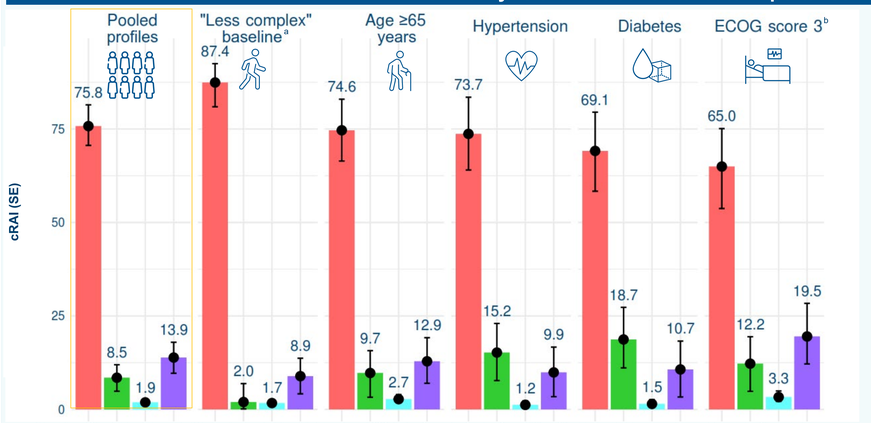
Results

Participants

121 US-based hematologist-oncologists

- Sex at birth: 79% male
- Mean age: 46 years
- Race: 52% White; 29% Asian; 14% Prefer not to say
- Mean experience: 16 years
- Mean Ph+ ALL patients treated in the last year: 47
- Practice setting: 44% academic hospital; 38% community hospital; 16% hybrid
- Practice area: 54% urban; 42% suburban; 4% rural

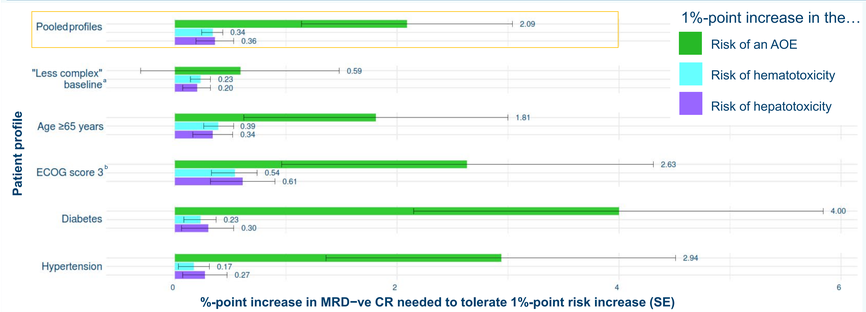
Clinically relevant relative attribute importance



Abbreviations: AOE, arterial occlusive event; cRAI, clinically relevant relative attribute importance; ECOG, Eastern Cooperative Oncology Group; MRD−ve CR, minimal residual disease negative complete remission; SE, standard error.
[a] "Less complex" patient profile: age 45 years; ECOG score 0 (fully active); no comorbidities. | [b] Capable of only limited selfcare; confined to bed or chair >50% of waking hours.

- For each patient profile, increasing the chance of MRD−ve CR from 16.7% to 34.4% had the largest impact on treatment preferences (cRAI=65.0%–87.4%).
- Pooled across patient profiles,
  - Increasing MRD−ve CR was at least 5x more important than reducing any individual risk.
  - Hepatotoxicity was the most important risk (cRAI=13.9%), followed by the risk of an arterial occlusive event (cRAI=8.5%). Hematotoxicity was least important (cRAI=1.9%).

Willingness to trade off: Increases in efficacy attribute needed to tolerate 1%-point increases in risk



Abbreviations: AOE, arterial occlusive event; ECOG, Eastern Cooperative Oncology Group; MRD-ve CR, minimal residual disease negative complete remission; SE, standard error.
[a] "Less complex" patient profile: age 45 years; ECOG score 0 (fully active); no comorbidities. | [b] Capable of only limited selfcare; confined to bed or chair >50% of waking hours.

- Pooled across patient profiles, accepting a 1%-point increase in the risk of an arterial occlusive event required a greater increase in MRD−ve CR (2.1%-point) than did 1%-point increases in the risks of hematotoxicity (0.3%-point) or hepatotoxicity (0.4%-point).
- Participants' willingness to trade off varied across the five patient profiles.
  - Out of all 1%-point increases in risk, participants were least willing to tolerate a 1%-point increase in the risk of an arterial occlusive event for patients with diabetes, requiring a 4.0%-point increase in MRD−ve CR.
  - Participants were more willing to tolerate a 1%-point increase in the risk of an arterial occlusive event in "less complex" baseline patients than in patients with diabetes (p<0.01).

Conclusions

- When choosing a frontline TKI treatment for Ph+ ALL, hematologist-oncologists in this study prioritized increasing the chance of achieving MRD−ve CR over avoiding risks.
  - This aligns with patients' preferences for increasing efficacy over avoiding risks, as determined in an earlier DCE involving patients with Ph+ ALL.[6]
- Hematologist-oncologists weighed treatment benefits and risks differently across patient profiles.
  - Although efficacy was prioritized for all patient profiles, hematologist-oncologists were more willing to tolerate risks for the "less complex" patient profile.
- The treatment priorities generated in this study – based on clinically relevant ranges of treatment performance – can help to better understand the perspectives of hematologist-oncologists during shared decision-making.

Key takeaway

Increasing MRD−ve CR was more important to hematologist-oncologists than decreasing risks of an arterial occlusive event, hematotoxicity, or hepatotoxicity, regardless of patient profile.

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