The Impact of Patient Profiles on Hematologist-Oncologists' Preferences for Treating Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL) using Tyrosine Kinase Inhibitors (TKIs) in Combination with Chemotherapy: A Discrete Choice Experiment

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Question: How do patient characteristics influence physicians' preferences for treating newly diagnosed Ph+ ALL?

Background

- The treatment landscape for newly diagnosed Ph+ ALL is evolving, with the US FDA granting its first approval of a frontline TKI + chemotherapy treatment for Ph+ ALL to ponatinib in 2024.[1,2]
- Recently approved (ponatinib)[1,2] and off-label TKI-based frontline therapies have distinct benefit-risk profiles[2-4] and acceptable benefit-risk trade-offs may vary according to patients' and physicians' preferences and patient clinical characteristics.
- Patient preferences for frontline TKI-based treatment of Ph+ ALL have been explored in a prior discrete choice experiment (DCE).[5] Patients generally prioritized efficacy over avoiding risks.[5]
- Given that physicians are critical contributors to shared decision-making, it is important to understand how they weigh the benefits and risks of potential treatments and whether they adapt their recommendations based on a patient's clinical characteristics.

Methods

- US-based hematologist-oncologists completed an online DCE with 12 tasks. In each task, they were shown two hypothetical TKI + reduced-intensity chemotherapy (chemo) treatment profiles and chose their preferred frontline treatment (Figure 1).
  - Treatment profiles depicted likelihoods of minimal residual disease-negative complete remission (MRD-neg CR) and three treatment-related risks (Table 1). The likelihoods shown in each task varied within ranges informed by the Phase 3 PhALLCON trial (NCT03589326) of frontline ponatinib + reduced-intensity chemo vs. imatinib + reduced-intensity chemo, the only randomized trial comparing TKIs in Ph+ ALL.[6,7]
  - Participants chose their preferred treatment first for a "less complex" (baseline) patient profile and then for four patient profiles with different clinical characteristics (Table 2; Figure 1).
- Participants' choices were analyzed using mixed multinomial logit models. Analyses were conducted on 1) choices made for each individual patient profile (separately) and 2) choices made across the five patient profiles (pooled together). Outputs generated included:
  - Clinically-relevant relative attribute importance (cRAI) scores. cRAI scores sum to 100% and capture the relative influence of each treatment attribute on participants' choices, considering improvements in attributes from their worst to best level across the clinically-relevant range. Clinically-relevant ranges were informed by PhALLCON data[6,7] (Table 1).
  - Predicted choice probabilities (PCPs). PCPs reflect the estimated likelihood that participants would recommend a particular treatment to a patient. PCPs for ponatinib + reduced-intensity chemo or imatinib + reduced-intensity chemo were calculated using both preference results and PhALLCON data[6,7] (Table 1).

Table 1: Treatment Characteristics and Levels

Characteristics	Levels used in the DCE	Data from PhALLCON[6,7]		Clinically-relevant Range
		Ponatinib + Chemo	Imatinib + Chemo	
Chance of being in MRD-neg CR at the end of induction	15%; 25%; 35%	34.4%[7]	16.7%[7]	16.7%–34.4%
Risk of an arterial occlusive event	1%; 2%; 3%	2.5%[6]	1.2%[6]	2.5%–1.2%
Risk of grade 3–4 hepatotoxicity	10%; 15%; 20%; 25%	21.5% (data on file)	12.3% (data on file)	21.5%–12.3%
Risk of grade 3–4 hematotoxicity	65%; 75%; 85%	73.6% (data on file)	75.3% (data on file)	75.3%–73.6%

Abbreviations: chemo, reduced-intensity chemotherapy; DCE, discrete choice experiment; MRD-neg CR, minimal residual disease-negative complete remission.

Table 2: Patient Profiles

	Profile Name	Profile Description
	"Less complex" (baseline) *(name not seen by participants)*	45 years old; ECOG score of 0 (fully active); no comorbidities
	Age ≥65 years	Patient aged 65 years or older
	Hypertension	Patient who has hypertension
	Diabetes	Patient who has diabetes
	ECOG score 3	Patient with an ECOG score of 3 (limited self-care; confined to bed/chair >50% of waking hours)

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

Figure 1: 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-neg CR at the end of induction**	15 out of 100 (15%) people will be in **MRD-neg 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	☐	☐
Has diabetes	☐	☐
Has hypertension	☐	☐

Abbreviations: DCE, discrete choice experiment; ECOG, Eastern Cooperative Oncology Group; MRD-neg CR, minimal residual disease-negative complete remission; Ph+ ALL, Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia; TKI, tyrosine kinase inhibitor.

Results

121 US-based hematologist-oncologists participated in the DCE

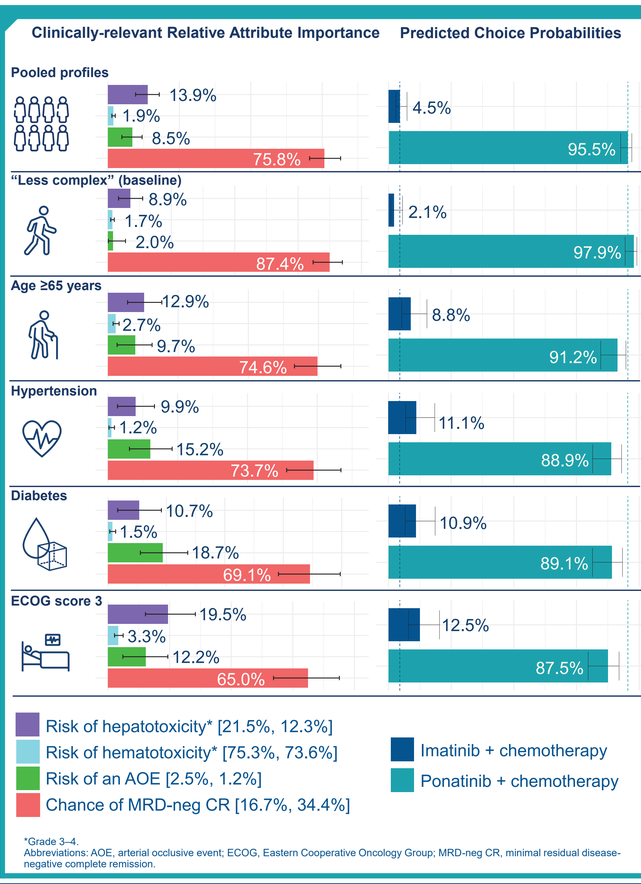
- **Male sex:** 79% | **Mean age:** 47 years | **Race:** 52% White, 29% Asian, 14% not disclosed
- **Years practicing medicine:** 16 (mean) | **Ph+ ALL patients treated in last year:** 47 (mean)
- **Practice setting:** 44% academic hospital, 38% community hospital, 16% hybrid
- **Practice area:** 54% urban, 42% suburban, 4% rural

Relative importance of treatment attributes across clinically-relevant levels

- Pooled across patient profiles, increasing the chance of MRD-neg CR had the largest impact on physicians' preferences (cRAI, 75.8%); hepatotoxicity was the most concerning risk (cRAI, 13.9%), followed by the risk of an arterial occlusive event (cRAI, 8.5%). Hematotoxicity was least important (cRAI, 1.9%).
- MRD-neg CR was the most important driver of physicians' decision-making for each patient profile, though physicians weighed benefits and risks differently across patient profiles.
  - The relative importance of MRD-neg CR to physicians varied from 65.0% when considering patients with an ECOG score of 3 to 87.4% when considering "less complex" patients.
  - Arterial occlusive event risk was more important when physicians considered patients with diabetes ($p<0.001$) or hypertension ($p<0.01$) than when they considered "less complex" patients.
  - Hematotoxicity ($p<0.05$) and hepatotoxicity ($p<0.05$) risks had a larger impact on physicians' recommendations for patients with an ECOG score of 3 than for vs. "less complex" patients.

Predicted probabilities of recommending ponatinib vs. imatinib

- Pooled across patient profiles, physicians were predicted to prefer the benefit-risk profile of ponatinib + chemo (PCP, 95.5%) vs. that of imatinib + chemo (PCP, 4.5%).
- The probability of recommending ponatinib vs. imatinib varied across patient profiles.
  - Physicians were most likely to prefer ponatinib for the "less complex" patients (PCP, 97.9%). Ponatinib was also preferred for patients aged ≥65 years (PCP, 91.2%), with diabetes (PCP, 89.1%), with hypertension (PCP, 88.9%), and with an ECOG score of 3 (PCP, 87.5%).



*Grade 3–4.
Abbreviations: AOE, arterial occlusive event; ECOG, Eastern Cooperative Oncology Group; MRD-neg CR, minimal residual disease-negative complete remission.

Conclusions

- **Across patient profiles, physicians' decision-making was primarily driven by increasing the chance of MRD-neg CR. The relative importance of MRD-neg CR and treatment risks varied by patient profile, with physicians more willing to tolerate risks for "less complex" patients.**
- **Predicted treatment choice probabilities – calculated from physicians' preference data and PhALLCON data[6,7] – suggest that physicians would recommend ponatinib over imatinib for each considered patient profile, given the higher MRD-neg CR offered with ponatinib. The likelihood of preferring ponatinib ranged from 87% to 98% across patient profiles and varied in line with the relative importance of MRD-neg CR for that profile.**
- **Physicians considered patient characteristics when recommending frontline treatment but were likely to choose the profile of ponatinib across patient profiles due to its comparatively higher efficacy than imatinib in the PhALLCON trial.**

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