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Poster# **CO56**

Comparative efficacy of Asciminib versus second generation TKIs in newly diagnosed Ph+CML using unanchored matching-adjusted indirect comparisons

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KEY FINDINGS & CONCLUSIONS

- Asciminib demonstrated significant improvements in MMR by 96 weeks versus dasatinib and bosutinib, with favourable trends versus nilotinib.
- Asciminib showed a significant benefit in DMR by 96 weeks versus dasatinib, with favourable trends versus bosutinib and nilotinib.
- Asciminib demonstrated significant lower rates of TTDAE by 96 weeks versus bosutinib, and favourable trends versus nilotinib and dasatinib.
- These findings support the use of asciminib as a first-line therapy in newly diagnosed Ph+ CML.

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INTRODUCTION

Asciminib is an inhibitor specifically targeting the ABL myristoyl pocket and has demonstrated superior efficacy and safety versus ATP-competitive tyrosine kinase inhibitors (TKIs) in newly diagnosed patients with Philadelphia chromosome-positive chronic myeloid leukemia in Chronic Phase (Ph+ CML-CP).

- In the Phase III **ASC4FIRST** trial (NCT04971226), asciminib 80 mg once daily showed superior efficacy and favourable safety compared with investigator-selected tyrosine kinase inhibitor (IS-TKI) in newly diagnosed adults with CML-CP. ASC4FIRST trial has a unique design which allowed a randomization by considering modern best available practice that includes several investigator selected (IS-)TKIs depending on patients' profile. ASC4FIRST control arm hence reflects the distribution of standard of care (SoC) TKIs in real-world medical practice. The ASC4FIRST trial was not designed to show superiority over individual 2G TKIs, highlighting the need for indirect comparisons, however a numerical benefit in efficacy along with a favorable safety profile and tolerability vs 2G TKIs was demonstrated.
- **Objective: To evaluate the indirect comparative efficacy and safety of asciminib as first line therapy versus relevant 2G-TKIs, including nilotinib, dasatinib, and bosutinib in newly diagnosed CML-CP patients.**

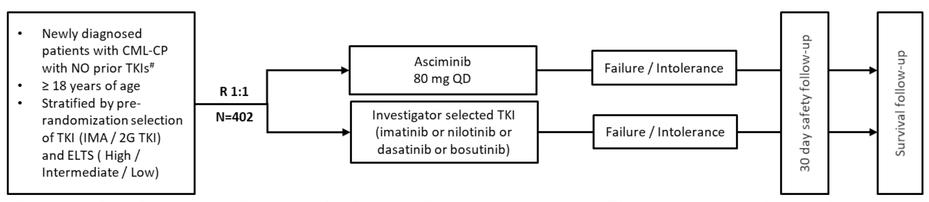
METHODS

An unanchored matching-adjusted indirect comparison (MAIC) was conducted to address the absence of a common comparator and inter-trial heterogeneity, focusing on molecular outcomes including major molecular response (MMR), deep molecular response (DMR = MR4.5) as well as rates of discontinuation due to adverse event (TTDAE) by week 96.

Feasibility assessment of the ITC

- A systematic literature review (SLR) conducted in October 2023 identified 12 randomized control trials (RCTs) evaluating six interventions in patients with CML-CP. A feasibility assessment was conducted based on these SLR findings to assess the best methodology for the ITC and the following key comparator trials were selected: ENESTnd (nilotinib 300mg BID, NIL)[6], DASISION (dasatinib 100mg QD, DAS) [7], and BFORE (bosutinib 400mg QD, BOS) [8].
- ASC4FIRST (NCT04971226) is a Phase III study evaluating asciminib versus (vs) an approved, investigator-selected tyrosine kinase inhibitor (IS-TKI). Patients were randomized 1:1 to the asciminib and IS-TKI arms (FAS). All patients were additionally split into two strata: patients assigned to receive imatinib (imatinib stratum) and second generation (2G TKI stratum, including nilotinib, dasatinib, or bosutinib, Figure 1). **For the purposes of the ITC, the 2G-TKI randomization stratum was considered the most relevant for the analysis of efficacy outcomes (MMR and DMR), as these patients are the most likely to receive nilotinib, dasatinib, or bosutinib in real-world.** For the analysis of safety outcome, the IS-TKI (FAS) of asciminib from ASC4FIRST was used to capture all adverse events reported in the trial.
- The stratified design of ASC4FIRST prevented the use of an anchor arm (imatinib) for the ITC. Consequently, an **unanchored MAIC** was identified as the most appropriate method for this analysis.

Figure 1. ASC4FIRST trial randomization design



#: either imatinib, or nilotinib, or dasatinib or bosutinib for ≤ 2 weeks is allowed. No other treatment with TKIs prior to randomization is permitted.

MAIC methodology

- Unanchored MAICs were performed using individual patient data (IPD) from the Phase III ASC4FIRST trial for asciminib[9] and aggregate data from the historical trials using a 96-week cutoff.
- Key prognostic factors (PFs) and treatment effect modifiers (TEMs) were retrieved from the SLR and compared across trials[10,11], including age, sex, race, European Cooperative Oncology Group (ECOG) performance status, white blood cells (WBC) and platelet counts. Variables not reported in a given trial were excluded from the matching.
- Risk score adjustment was not feasible due to differing systems across trials (European Treatment and Outcome Study long-term survival (ELTS) versus Sokal or Hasford). Weights were generated using logistic regression via the method of moments, rebalancing the ASC4FIRST population to match baseline characteristics of each historical comparator.
- Effective sample sizes (ESS) for efficacy outcomes indicated good preservation of the original asciminib population (n=100): asciminib vs nilotinib (ESS = 72.6), dasatinib (84.8), and bosutinib (61.6), supporting the robustness of the weighted estimates (Table 1). The ESS for safety analyses indicated a good coverage of the original sample size (147.8 vs nilotinib, 159.2 for dasatinib and 146.54 vs bosutinib, Table 1).
- Data relative to molecular efficacy outcomes and safety by 96 weeks was collected. A total of nine MAICs were performed to include the three comparators of interest (nilotinib, dasatinib, bosutinib) and three outcomes (MMR, DMR and TTDAE by 96 weeks).
- Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated for all outcomes and interpreted within the context of each reweighted comparator population.

RESULTS

Comparison of population characteristics

- Reweighted baseline characteristics of asciminib were closely aligned with those of the comparator trials ENESTnd, DASISION and BFORE (Table 1). The proportion of high-risk ELTS patients increased in asciminib 2G-TKI population after reweighting in the efficacy analyses (e.g., asciminib vs bosutinib/nilotinib: 20%/17% vs 14% pre-adjustment, Table 1). Previous papers highlighted the association between high-risk profile patients and lower chances to reach molecular response.[13,14] Hence the non-adjustment on risk score is suspected to attenuate the relative effect of asciminib and explain non-significant trends in some comparisons.

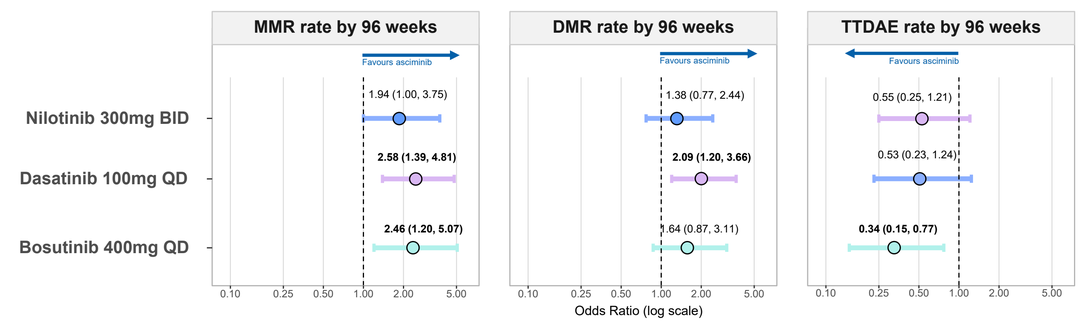
Table 1. Pre- and post-matching populations characteristics

Variables	Asciminib 80mg								Historical trials		
	2GTKI stratum (efficacy)				IS-TKI (FAS, safety)						
	Raw	Weighted			Raw	Weighted					
		NIL	DAS	BOS		NIL	DAS	BOS	NIL	DAS	BOS
N/ESS	100	72.56	84.82	61.57	200	147.8	159.2	146.54	282	259	268
ELTS risk score, n (%)											
Low	60 (60.0)	62.9	63.8	56.8	122 (60.7)	66.08	66.87	59.59	-	-	-
Intermediate	26 (26.0)	20.3	21.4	23.1	56 (27.9)	22.64	22.01	27.06	-	-	-
High	14 (14.0)	**16.8**	**14.8**	**20.1**	23 (11.4)	11.29	11.13	**13.36**	-	-	-
Sex, n(%)											
Male	69 (69.0)	56	55.6	58.2	131 (65.5)	56.0	55.6	58.2	158 (56.0)	144 (55.6)	144 (55.6)
Age											
Mean (sd)	45.6 (15.4)	-	46.40 (14.60)	-	50.8 (15.38)	48.85 (15.21)	46.40 (14.60)	52.79 (14.79)	-	46.4 (14.6)	-
Median (min, max)	43 (18, 76)	-	-	-	52 (18, 79)	-	-	-	47 (18, 85)	-	53 (18, 84)
Age ≤ median, n (%)	-	(50.0)†	-	(50.0)†	-	(50.0)†	-	(50.0)†	(50.0)‡	-	(50.0)‡
Race, n (%)											
White	45 (45.0)	70	56.2	78.7	107 (53.5)	70.9	56.7	78.7	170 (60.3)	132 (51.0)	211 (78.7)
Black or African American	1 (1.0)	1.2	0.9	0.3	2 (1.0)	1.5	1.1	0.4	12 (4.3)	2 (0.8)	10 (3.7)
Asian	53 (53.0)	26.9	41.7	20.6	90 (45.0)	26.9	41.7	20.7	76 (26.9)	108 (42.0)	34 (12.7)
Other	1 (1.0)	1.8	1.2	0.4	1 (0.5)	0.6	0.5	0.2	24 (8.5)	17 (6.6)	14 (5.2)
WBC count in 10^{-9}/L											
Median (min, max)	28 (2.4, 202.60)	-	-	-	25 (1.70, 233)	-	-	-	23 (2 , 247)	25.1 (2.5 , 493)	-
WBC count ≤median, n (%)	-	(50.0)†	(50.0)†	-	-	(50.0)†	(50.0)†	-	(50.0)‡	(50.0)‡	-
Platelet count in 10^{-9}/L											
Median (min, max)	397 (83, 1688)	-		-	391 (16, 1987)	-	-	-	424 (90, 3880)	448 (58, 1880)	-
Platelet count ≤median, n (%)	-	(50.0)†	(50.0)†	-	-	(50.0)†	(50.0)†	-	(50.0)‡	(50.0)‡	-
ECOG PS, n (%)											
0	85 (85.0)	-	82	72.8	170 (85.0)	84.09	82.0	(72.8)	-	213 (82.2)	195 (72.8)
1	15 (15.0)	-	18	27.2	30 (15.0)	15.91	18.0	(27.2)	-	46 (17.8)	73 (27.2)

†Matching was conducted using dichotomous categorization based on the median value of the comparator trial; ‡value was assumed based on the median value; cells coloured in yellow correspond to the variables used in the matching.

MAIC results

Figure 2. MAIC results on MMR, DMR and TTDAE rates by 96 weeks



Abbreviations: 1G or 2G-TKI: first or second-generation, BID: twice a day, BOS: bosutinib 400mg QD, CI: confidence interval, CML: chronic myeloid leukemia, DAS: dasatinib 100mg QD, DMR=MR4.5: deep molecular response, ECOG: European Cooperative Oncology Group, ELTS: European Treatment and Outcome Study long-term survival, ESS: effective sample size, FAS: full analysis set, IPD: individual patient data, IS: investigator selected, IS-TKI: investigator selected TKI, ITC: indirect treatment comparison, MAIC: matching-adjusted indirect comparison, MMR: major molecular response, NIL: nilotinib 300mg BID, OR: odds ratio, Ph+ CML-CP: Philadelphia chromosome-positive chronic myeloid leukemia in chronic-Phase, PF: prognostic factor, QD: once daily, RCT: randomized controlled trial, SLR: systemic literature review, SoC: standard of care, TTDAE: treatment discontinuation due to adverse event, TEM: treatment effect modifier, TKI: tyrosine kinase inhibitors, WBC: white blood cells

- Asciminib demonstrated significant improvements in MMR by 96 weeks versus dasatinib (OR 2.58, 95% CI 1.39–4.81) and bosutinib (2.46, 1.20–5.07), with favourable trends versus nilotinib (1.94, 1.00–3.75).
- Asciminib showed a significant benefit in DMR by 96 weeks versus dasatinib (2.09, 1.20–3.64), with favourable trends versus bosutinib (1.64, 0.87–3.11) and nilotinib (1.38, 0.77–2.44) .
- Asciminib demonstrated significant lower rates of TTDAE by 96 weeks versus bosutinib (0.34, 0.16-0.77), and favourable trends versus nilotinib (0.55, 0.25-1.21) and dasatinib (0.53, 0.23-1.24).

Discussion

In the absence of a head-to-head comparison, this MAIC provides scientific information to further support clinical and reimbursement decision making. Results are subject to potential residual confounding due to the inability to adjust for all relevant prognostic factors and treatment effect modifiers, particularly those not consistently reported across trials. The inability to adjust for CML risk scores, due to differing scoring systems across trials, lead to higher weights for patients with high-risk profile in asciminib and is suspected to attenuate the relative effect of asciminib. It was not possible to calculate the Sokal score[12] for asciminib patients, as some variables for the computation were not retrievable. Despite this constraint, the consistency of results indicates a potential efficacy advantage of asciminib over established 2G-TKIs in the first-line setting.

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Disclosures
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