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Ponatinib vs. Imatinib as Frontline Treatment for Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia: A Matching-adjusted Indirect Comparison

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Introduction

- The Philadelphia chromosome (Ph) is a common cytogenetic abnormality associated with acute lymphoblastic leukemia (ALL)[1-3]
  - Ph is formed due to a reciprocal translocation that causes the fusion of the ABL1 tyrosine kinase gene (chromosome 9) with the BCR gene (chromosome 22) and results in the formation of the *BCR::ABL1* oncogene
- Tyrosine kinase inhibitors (TKIs) are used to treat Ph+ ALL and have contributed to improved outcomes for patients. Current treatment strategies based on TKIs for newly-diagnosed adult patients with Ph+ ALL mostly consist of imatinib combined with chemotherapy
- Ponatinib is the only pan-BCR::ABL TKI currently indicated for patients who are resistant to dasatinib; patients who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; and patients who have the BCR::ABL T315I mutation
  - Head-to-head comparisons of ponatinib and imatinib-based regimens are not available. Therefore, an indirect treatment comparison is required to establish the relative efficacy of ponatinib vs. imatinib
- Matching-adjusted indirect comparison (MAIC) is an approach that enables treatments in different trials to be compared by adjusting for between-trial differences in baseline characteristics[4]

Objective

- The objective of this study was to evaluate, through an MAIC, the relative efficacy of:
  - Ponatinib + hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) compared to imatinib + hyper-CVAD as a first-line treatment for patients with Ph+ ALL
  - Ponatinib + steroids compared to an imatinib-based regimen as a first-line treatment for patients with Ph+ ALL not eligible for high-dose therapy

Methods

Ponatinib studies

- MDACC (NCT01424982)
  - Phase II, single-center, single-arm study of ponatinib plus hyper-CVAD in adults with Ph+ ALL **(high-dose eligible population) (Table 1)**
  - The treatment strategy in this patient group was to reduce the severity of disease to allow for stem cell transplantation (SCT) and provide a cure
- GIMEMA LAL1811 (NCT01641107)
  - Phase II, multicenter, single-arm study of ponatinib monotherapy in adults with Ph+ ALL aged >60 years or unfit for intensive chemotherapy and SCT **(high-dose ineligible population)**
  - The treatment strategy in this patient group was to prolong life and improve quality of life

Imatinib-based studies, identified via a systematic literature review (SLR)

- Systematic searches were conducted in
  - Electronic databases (articles published in 2000–2021)
  - Conference proceedings (abstracts published in 2015–2021)
  - ClinicalTrials.gov
- Studies included in the SLR included ≥15 patients receiving imatinib or ponatinib therapy and were published in English:
  - Randomized, controlled, single-arm or non-randomized trials (phase II–IV)
  - Observational/real-world studies
  - **Excluded:** Studies evaluating (1) other interventions or imatinib/ponatinib in combination with other targeted therapies; (2) pediatric patients; (3) patients with Ph- ALL and other leukemia types
- Clinical experts were consulted to determine which of the imatinib studies identified in the SLR reflected current real-world clinical practice
- Imatinib studies were selected for the MAIC based on the following criteria:
  - High-dose eligible population: imatinib given in combination with hyper-CVAD or as part of a protocol investigated by the German multicenter study group for adult ALL (GMALL)
  - High-dose ineligible population: imatinib started at the beginning of the induction therapy AND given continuously throughout the study

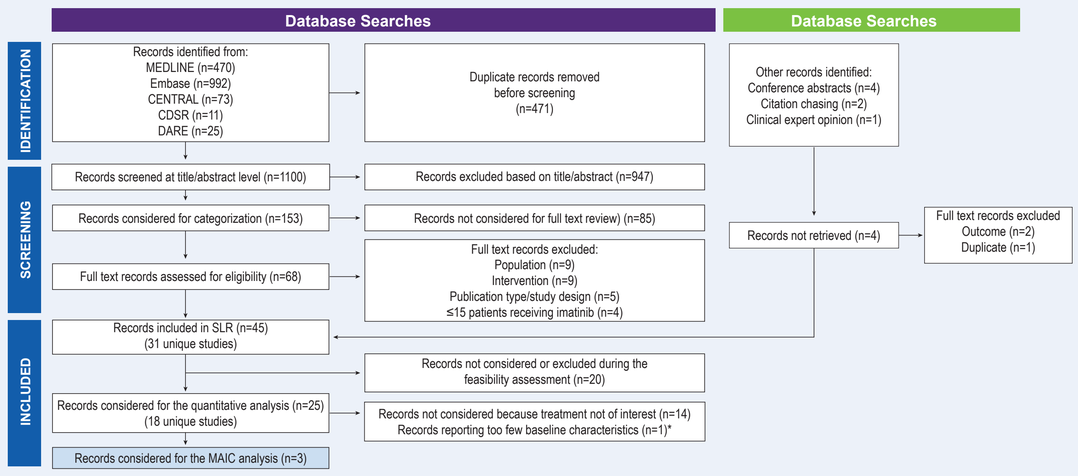
MAIC methodology

- The MAIC was conducted using the methods described by Signorovitch and colleagues[4] and NICE guidelines[5]
  - Clinical experts were consulted to identify key prognostic factors and effect modifiers to be included in the MAIC
    - Studies that reported too few characteristics to allow a meaningful population adjustment were excluded from the MAIC
    - Age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), white blood cell count at baseline, and type of BCR::ABL transcript were included in the adjustment
  - The MAIC adjusted for imbalances in as many prognostic factors and effect modifiers as possible whilst maximising the effective sample size (ESS). The ESS corresponded to the number of independent unweighted patients that would give the same level of precision in the estimates as that obtained in the weighted cohorts
  - Only matching scenarios that would achieve an ESS of at least 15 were further considered in the analyses
- Ponatinib and imatinib were compared on overall survival (OS) and the complete molecular response (CMR) rate
  - For OS, hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. Reconstructed individual patient level data were generated for the comparators using the Guyot et al. algorithm.[6] Robust estimators of variance were used
  - For CMR, odds ratios (ORs) with 95% CIs were estimated. Robust estimators of variance were used

Results

- The literature search for the SLR was conducted on 15 March 2021. 18 imatinib studies were identified, of which 3 were included in the MAIC analyses (**Figure 1**)

Figure 1. PRISMA diagram



Abbreviations: CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; DARE = Database of Abstracts of Reviews of Effectiveness; SLR = systematic literature review

*Study only reported the median age of patients

- Two studies on high-dose therapy eligible patients and one study on high-dose therapy ineligible patients were selected for MAIC analysis (**Table 1**)

Table 1. Characteristics of Ponatinib and Imatinib studies

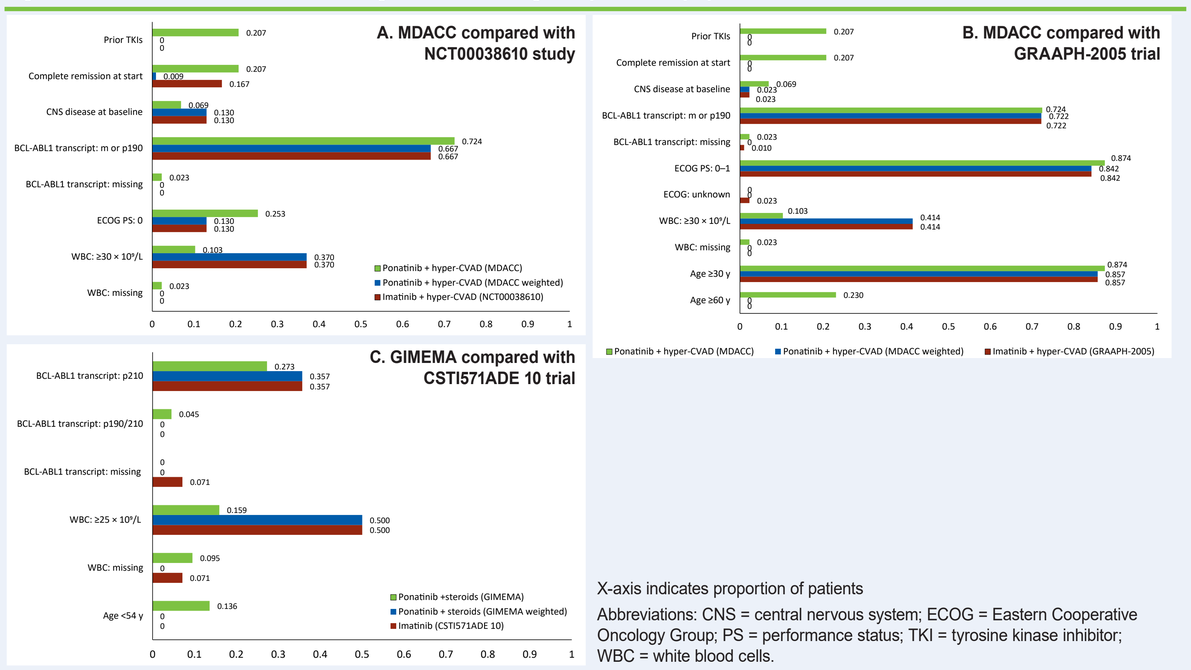
Characteristics	MDACC[7]	GIMEMA LAL1811[8]	GRAAPH-2005[9]	NCT00038610[10]	CSTI571ADE 10[11]
Study design	Single-center, single-arm, phase 2	Multicenter, single-arm, phase 2	Multicenter, randomized, open label, phase 3	Single-center, open-label, phase 2	Multicenter, randomized, open-label, phase 2
Median follow-up duration	45.1 months	34.9 months	57.6 months	130 months among patients still alive	11.2 months
Intervention	Ponatinib + hyper-CVAD 8 cycles of 21 days of oral ponatinib (45 mg/day) continuously (only for the first 14 days in cycle 1) alternating with hyper-CVAD and high-dose methotrexate and cytarabine. Patients in complete remission received maintenance with ponatinib 45 mg/day with monthly vincristine and prednisone for 2 years followed by ponatinib indefinitely.	Ponatinib + steroids 8 cycles of 6 weeks of oral ponatinib (45 mg/day) with prednisone (60 mg/m^2/day) from days 1 to 21 then tapered and stopped at day 29.	Imatinib + hyper-CVAD Induction with imatinib + reduced-intensity chemotherapy vs. induction with hyper-CVAD. Induction followed by an imatinib + methotrexate + cytarabine cycle to bridge to SCT. Up to 8 cycles of treatment alternating imatinib + hyper-CVAD with imatinib + methotrexate + cytarabine for patients not receiving transplant.	Imatinib + hyper-CVAD 8 induction-consolidation courses of imatinib + hyper-CVAD alternated with imatinib + methotrexate + cytarabine.	Imatinib induction followed by imatinib + age-adapted / intrathecal consolidation chemotherapy. After pre-phase chemotherapy, patients were randomly assigned to imatinib (at a dose of 600 mg/day) or multiagent induction chemotherapy in a 4-week cycle. After completing remission therapy, patients randomized to either treatment arm (imatinib vs chemotherapy) received imatinib at a dose of 600 mg/day imatinib + successive cycles of consolidation and reinduction chemotherapy.
Eligible for HDT-SCT	Yes	No	Yes	Yes	No

Abbreviations: CVAD = cyclophosphamide, vincristine, doxorubicin, and dexamethasone; SCT = stem cell transplant; TKI = tyrosine kinase inhibitor.

- Following MAIC, baseline characteristics were balanced for the factors included in the population adjustment (**Figure 2**)
- Across populations and studies, ponatinib significantly prolonged OS (**Figure 3 and Table 2**), and patients treated with ponatinib were significantly more likely to achieve a CMR (**Table 2**) compared to patients treated with imatinib-based regimens

Results (cont'd)

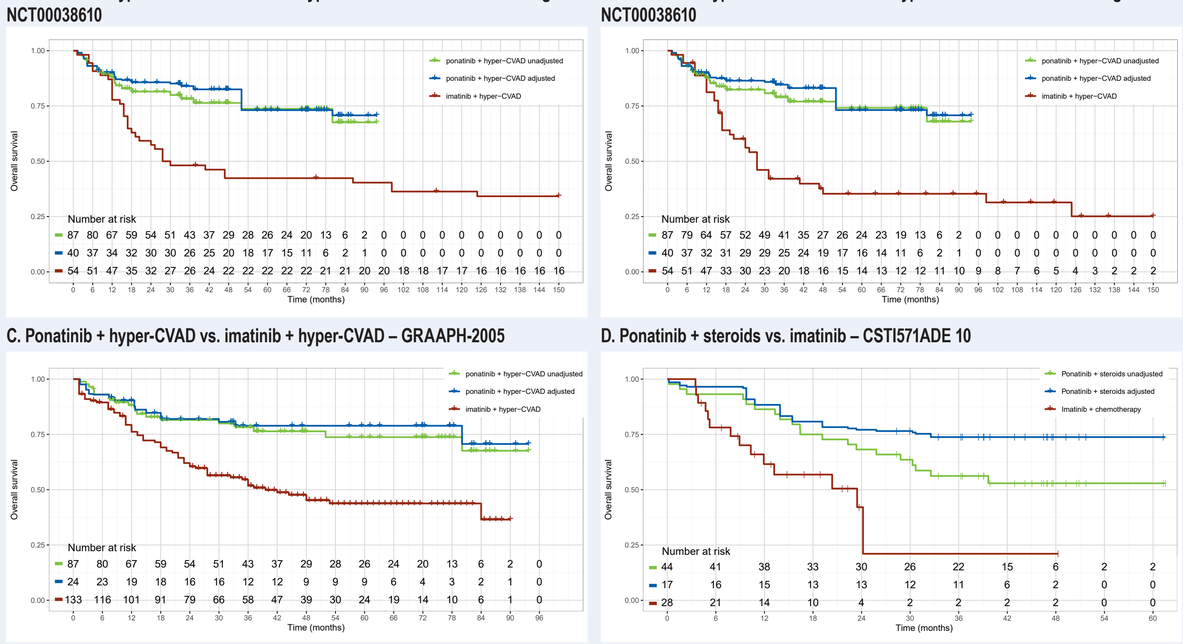
Figure 2. Baseline characteristics of weighted and unweighted ponatinib populations



X-axis indicates proportion of patients

Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; PS = performance status; TKI = tyrosine kinase inhibitor; WBC = white blood cells.

Figure 3. Unadjusted and adjusted Kaplan-Meier estimates of OS



Abbreviations: CVAD = cyclophosphamide, vincristine, doxorubicin, and dexamethasone; OS = overall survival; SCT = stem cell transplant.

Table 2. Relative efficacy results for observed and weighted ponatinib populations vs imatinib

	Ponatinib + hyper-CVAD vs. imatinib + hyper-CVAD (GRAAPH-2005) (95% CI) [p-value]	Ponatinib + hyper-CVAD vs. imatinib + hyper-CVAD (NCT00038610) (95% CI) [p-value]	Ponatinib + steroids vs. imatinib (CSTI571ADE 10) (95% CI) [p-value]
Effective sample size	40	24	17
OS – Unadjusted comparison	HR: 0.41 (0.25, 0.68) [<0.001]	HR: 0.42 (0.24, 0.73) [0.002] with no censoring on SCT HR: 0.36 (0.20, 0.63) [<0.001] with censoring on SCT	HR: 0.40 (0.20, 0.81) [0.011]
OS – Population-adjusted comparison	HR: 0.35 (0.17, 0.74) [0.006]	HR: 0.35 (0.18, 0.70) [0.003] with no censoring on SCT HR: 0.30 (0.15, 0.59) [0.001] with censoring on SCT	HR: 0.24 (0.09, 0.64) [0.004]
CMR – Unadjusted comparison	OR: 12.34 (5.77, 26.41) [<0.001]	OR: 4.93 (2.13, 11.39) [<0.001]	OR: 7.65 (2.48, 23.64) [<0.001]
CMR – Population-adjusted comparison	OR: 12.11 (3.77, 38.87) [<0.001]	OR: 5.65 (2.02, 15.76) [<0.001]	OR: 6.20 (1.60, 24.00) [0.008]

Abbreviations: CI = confidence interval; CMR = complete molecular response; CVAD = cyclophosphamide, vincristine, doxorubicin, and dexamethasone; HR = hazard ratio; OR = odds-ratio; OS = overall survival; SCT = stem cell transplant.

Limitations

- The ponatinib and imatinib populations may have been imbalanced with respect to unobserved confounders that could not be included in the population adjustment
- Heterogeneity was noted in the ORs for CMR in the high-dose therapy eligible populations
  - This could be explained by the different monitoring of patients for response in the GRAAPH-2005 trial (response assessed only during the initial 2 cycles of treatment)
- The outcomes estimated from the comparison of ponatinib vs. imatinib in high-dose ineligible patients were subject to uncertainty because of the low ESS and the few baseline characteristics available for adjustment. Notably, baseline ECOG PS was not available in CSTI57ADE 10
- The OS data was immature in the ponatinib studies: point estimates of relative efficacy for OS might change with more follow-up in the ponatinib studies

Conclusions

- **High-dose therapy eligible and ineligible patients treated with ponatinib had prolonged OS and were significantly more likely to achieve a CMR compared to patients treated with imatinib-based regimens**
- **Unanchored MAICs are observational in nature and have limitations that should be considered when interpreting these results**
- **This study is, to our knowledge, the most objective comparative analysis of ponatinib versus imatinib-based regimens in patients with newly-diagnosed Ph+ ALL**

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