# Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

# eAppendix. PhALLCON Investigators, PhALLCON Steering Committee, and Supplemental Methods

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**Supplemental Methods**

**Dose Reduction Guidelines**
Ponatinib dose reduction guidelines for adverse events deemed drug-related by the investigator and dose modification guidelines for arterial occlusive and venous thromboembolic events are summarized in eTable 2 and eTable 3. Dose reduction below 10 mg once daily was not permitted. Patients were discontinued from ponatinib for myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic attack, or revascularization procedures. After dose reductions for toxicity, the dose of ponatinib or imatinib could be re-escalated to the previously administered level if all grade 2 or worse nonhematologic toxicities had recovered to grade 1 or less for at least 1 month or if all grade 3 or worse hematologic and nonhematologic toxicities had recovered to grade 2 or less and were manageable with supportive therapy.

## eTable 1. Key Eligibility Criteria

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Men or women aged ≥ 18 y | History or current diagnosis of chronic-phase, accelerated-phase, or blast-phase chronic myeloid leukemia |
| Newly diagnosed Ph+ ALL, as defined by 2017 National Comprehensive Cancer Network guidelines | Prior/current systemic anticancer therapy and/or radiotherapy for ALL, except for an optional prephase therapy or chemotherapy induction (no more than one cycle) |
| Eastern Cooperative Oncology Group performance status ≤ 2 | Treatment with investigational products ≤ 30 days before randomization or six half-lives of the agent, whichever is longer |
| Clinical laboratory values ≤ 30 days before randomization:<br>• Total serum bilirubin ≤ 1.5x the upper limit of normal<br>• Alanine aminotransferase or aspartate aminotransferase ≤ 2.5x the upper limit of normal<br>• Serum creatinine ≤ 1.5x the upper limit of normal and estimated creatinine clearance ≥ 30 mL/min[a]<br>• Serum lipase and amylase ≤ 1.5x the upper limit of normal | Taking drugs with a known risk of causing prolonged QT corrected interval or torsades de pointes |
| Normal QT interval corrected per Fridericia method on screening electrocardiogram, defined as ≤ 450 ms (males) or ≤ 470 ms (females) | Taking medications or herbal supplements known to be strong inhibitors or strong inducers of cytochrome P450 3A4 ≤ 14 days before first dose of study drug |
| Female patients:<br>• Postmenopausal for ≥ 1 y before screening, OR<br>• Surgically sterile, OR<br>• If of childbearing potential, agree to practice one highly effective method of contraception and one additional effective (barrier) method at the same time from informed consent through 1 month after last dose of study drug or a longer period per any local regulation, OR<br>• Agree to practice true abstinence, when in line with preferred and usual lifestyle | History of acute pancreatitis in ≤ 1 y of screening or history of chronic pancreatitis |
| Male patients, even if surgically sterilized:<br>• Agree to practice effective barrier contraception during entire study treatment period and through 120 days after the last dose of study drug, OR<br>• Agree to practice true abstinence, when in line with preferred and usual lifestyle | Uncontrolled hypertriglyceridemia (triglycerides > 450 mg/dL) |
| | History/presence of clinically relevant CNS pathology |
| | Clinical manifestations of CNS or extramedullary involvement with ALL other than lymphadenopathy or hepatosplenomegaly |
| | Poorly controlled diabetes |
| | Clinically significant, uncontrolled, or active cardiovascular, cerebrovascular, or peripheral vascular disease, or history of or active VTE disease, including, but not limited to:<br>• Complete left bundle branch block<br>• Right bundle branch block plus left anterior hemiblock, or bifascicular block<br>• History of or presence of clinically significant ventricular or atrial tachyarrhythmias<br>• Clinically significant resting bradycardia (<50 beats per minute)<br>• Uncontrolled HTN; systolic BP ≥150 mmHg and/or diastolic BP≥90 mmHg). Patients with Stage 2 HTN (systolic BP ≥140 mmHg and/or diastolic BP ≥90 |

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| | mmHg should be under treatment at study entry per the current American Heart Association guidelines to ensure BP control. Patients requiring 3 or more antihypertensive medications should have controlled HTN for the past 6 months. Isolated elevation(s) of systolic and/or diastolic BP during screening are not exclusionary<br>• Any history of myocardial infarction, unstable angina, coronary artery disease, cerebrovascular accident, ischemic stroke, or transient ischemic attack. Note: Patients with any history of these events, whether considered clinically significant or not, are excluded<br>• History of congestive heart failure (New York Heart Association class III or IV) or left ventricular ejection fraction <40%, within 6 months before randomization<br>• Symptomatic peripheral vascular disease or history of infarction, including visceral infarction<br>• History of any revascularization procedure, including the placement of a stent<br>• Patients with documented significant pleural or pericardial effusions unless thought to be secondary to leukemia<br>• Any history of venous thromboembolism, including, but not limited to, DVT or pulmonary embolism within 6 months before randomization; patients with catheter-associated DVTs or superficial vein thrombosis, which are considered to be resolved/controlled, may be included after discussion with the sponsor's medical monitor/designee |
| | Female patients:<br>• Lactating, breastfeeding, or positive serum pregnancy test during screening or<br>• positive urine pregnancy test on Day 1 before administration of study drug |

[a]Cockcroft-Gault formula.

Abbreviations: ALL, acute lymphoblastic leukemia; BP, blood pressure; CNS, central nervous system; DVT, deep venous thrombosis; HTN, hypertension; Ph+, Philadelphia chromosome–positive; VTE, venous thromboembolic event.

## eTable 2. Ponatinib Dose Modification Guidelines for Drug-Related Adverse Events

| Toxicity | Modification[a] |
|---|---|
| **Nonhematologic** | |
| **General** | |
| Grade 1 or transient grade 2 | No intervention |
| Grade 2 lasting ≥ 7 days with optimal care | First occurrence: hold until grade ≤ 1 or return to baseline; resume at current dose level |
| | Recurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Recurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| Grade 3 or 4 | Occurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Occurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| **Pancreatitis and Elevation of Lipase** | |
| Asymptomatic grade 1 or 2 elevation of serum lipase | Consider interruption or dose reduction |
| Asymptomatic grade 3 elevation of lipase (> 5x the upper limit of normal), symptomatic grade 3 elevation of lipase (> 2x the upper limit of normal), or asymptomatic radiologic pancreatitis (grade 2 pancreatitis) | Occurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Occurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| Symptomatic grade 3 pancreatitis or grade 4 elevation of lipase (> 5x the upper limit of normal) | Occurrence at 30 mg: hold until complete symptom resolution and after lipase elevation recovery to grade ≤ 1; resume at 15 mg |
| | Occurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| Grade 4 pancreatitis | Discontinue ponatinib |
| **Hepatic Toxicity** | |
| Transaminase elevation > 3x the upper limit of normal | Occurrence at 30 mg: hold and monitor hepatic function until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Occurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| Elevation of aspartate aminotransferase or alanine aminotransferase > 3x the upper limit of normal concurrent with elevation of bilirubin > 2x the upper limit of normal and alkaline phosphatase < 2x the upper limit of normal | Discontinue ponatinib |
| **Left Ventricular Ejection Fraction/Congestive Heart Failure** | |
| Grade 1 | No dose adjustment |
| Grade 2 | Monitor by echocardiogram |
| | First occurrence: hold until grade ≤ 1 or return to baseline; resume at current dose level |
| | Recurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Recurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| Grade 3 | Monitor by echocardiogram |
| | Occurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |

| Toxicity | Modification[a] |
|---|---|
| | Occurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| Grade 4 | Discontinue ponatinib |
| **Skin Rash** | |
| Grade 1 | No intervention |
| Grade 2 or 3, persistent despite optimal symptomatic therapy | First occurrence at any dose level: hold until grade ≤ 1 or return to baseline; resume at current dose level |
| | Recurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Recurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| Grade 4 | Discontinue ponatinib |
| **Hematologic** | |
| **Absolute Neutrophil Count/Platelets** | |
| Grade 1 or 2 | No dose adjustment |
| Grade 3 or 4 | First occurrence at any dose level: hold until grade ≤ 1 or return to baseline; resume at current dose level |
| | Recurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Recurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |

[a]Discontinue ponatinib 10 mg for occurrence/recurrence of any toxicity.

## eTable 3. Ponatinib Dose Modification Guidelines for Arterial Occlusive Events and Venous Thromboembolic Events

| Toxicity | Modification[a] |
|---|---|
| **Arterial Occlusive Events** | |
| **Arterial Occlusion: Other Cardiovascular and Cerebrovascular Events** | |
| Grade 1 | Consider interruption or dose reduction of ponatinib until the event resolves |
| Grade 2 | First occurrence at any dose level: hold until grade ≤ 1 or return to baseline; resume at current dose level |
| | Recurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Recurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| Grade 3 and 4 | Discontinue ponatinib |
| **Other Arterial Occlusions, Including Peripheral Vascular Events** | |
| Grade 1 | Consider interruption or dose reduction of ponatinib until the event resolves |
| Grade 2 | First occurrence at any dose level: hold until grade ≤ 1 or return to baseline; resume at current dose level |
| | Recurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Recurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| Grade 3 | Occurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Occurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| | Recurrence (any dose): discontinue ponatinib |
| Grade 4 | Discontinue ponatinib |
| **Venous Thromboembolic Events** | |
| Grade 1 | Consider interruption or dose reduction of ponatinib until the event resolves |
| Grade 2 | First occurrence at any dose level: hold until grade ≤ 1 or return to baseline; resume at current dose level |
| | Recurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Recurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| | Recurrence at 10 mg: discontinue ponatinib |
| Grade 3 | Occurrence at 30 mg: hold until grade ≤ 1 or return to baseline; resume at 15 mg |
| | Occurrence at 15 mg: hold until grade ≤ 1 or return to baseline; resume at 10 mg |
| | Occurrence at 10 mg: discontinue ponatinib |
| Grade 4 | Discontinue ponatinib |

[a]Discontinue ponatinib 10 mg for occurrence/recurrence of any toxicity.

## eTable 4. Endpoint Definitions and Response Criteria

| Endpoint | Definition/Criteria |
|---|---|
| **Primary** | |
| MRD-negative CR at end of induction | *BCR::ABL1*/*ABL1* ratio ≤ 0.01% or undetectable *BCR::ABL1* transcripts in cDNA with ≥ 10,000 *ABL1* transcripts (ie, MR4) and meeting criteria for CR |
| **Key Secondary** | |
| Event-free survival | Date of randomization until:<br>• Death due to any cause<br>• Failure to achieve CR by end of induction<br>• Relapse from CR |
| **Other Secondary** | |
| CR and CRi rates at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier) | CR: meeting all of the following for ≥ 4 weeks (ie, no recurrence):<br>• No circulating blasts and < 5% blasts in the BM<br>• Normal maturation of all cellular components in the BM<br>• No extramedullary disease (CNS involvement, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass)<br>• ANC > 1000/μL (or > 1.0 x $10^9$/L)<br>• Platelets > 100,000/μL (or > 100 x $10^9$/L)<br><br>CRi: Hematologic complete remission with incomplete hematologic recovery. Meets all criteria for CR except platelet count and/or ANC |
| Molecular response rates (MR3, MRD negativity [MR4], and MR4.5) at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier) | MR3: ≤ 0.1% *BCR::ABL1* or undetectable *BCR::ABL1* transcripts in cDNA with ≥ 1000 *ABL1* transcripts<br><br>MR4: ≤ 0.01% *BCR::ABL1* or undetectable BCR::ABL1 transcripts in cDNA with ≥ 10,000 *ABL1* transcripts<br><br>MR4.5: ≤ 0.0032% *BCR::ABL1* or undetectable *BCR::ABL1* transcripts in cDNA with ≥ 32,000 *ABL1* transcripts |
| Rates of PIF and ORR at the end of induction | PIF: Patients who received treatment for ALL but never achieved CR or CRi by the end of induction. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have never been in CR or CRi<br><br>ORR: CR + CRi |
| Rates of MRD-negative CR at multiple intervals after the end of induction | *BCR::ABL1*/*ABL1* ratio ≤ 0.01% or undetectable *BCR::ABL1* transcripts in cDNA with ≥ 10,000 *ABL1* transcripts (ie, MR4) and meeting criteria for CR |
| Duration of MRD-negative CR | The interval between the first assessment at which the criteria for MRD-negative CR are met until the earliest date at which loss of MRD negativity or relapse from CR occurs |
| Duration of CR | The interval between the first assessment at which the criteria for CR are met until the time at which relapse from CR occurs |
| Time to treatment failure | Time to end of study-randomized treatment (except for HSCT without loss of MRD-negative CR) due to safety and/or efficacy reasons |
| Duration of MR4.5 in patients who achieved MR4.5 | Interval between first assessment at which criteria for MR4.5 are met until earliest date at which loss of MR4.5 occurs |
| OS and rate of relapse from CR for on-study patients with and without HSCT | OS: The interval between randomization and death due to any cause<br>Relapse from CR: Reappearance of blasts in the blood or BM (> 5%) or in any extramedullary site after a CR |
| OS | The interval between randomization and death due to any cause |

| Endpoint | Definition/Criteria |
|---|---|
| **Other endpoints** | |
| PFS | • Death due to any cause<br>• Failure to achieve CR by the end of induction<br>• Relapse from CR<br>• Failure to achieve MRD negativity by the end of treatment<br>• Loss of MRD negativity |
| Time to subsequent anti-neoplastic treatment | Time from randomization to the date of first documentation of subsequent antineoplastic therapy or the last contact date for patients who never received subsequent antineoplastic therapy |

Abbreviations: ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; BM, bone marrow; cDNA, complementary DNA; CNS, central nervous system; CR, complete remission; CRi, incomplete remission; HSCT, hematopoietic stem cell transplantation; MR3, molecular response 3-log reduction; MR4, molecular response 4-log reduction; MR4.5, molecular response 4.5-log reduction; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PIF, primary induction failure.

## eTable 5. Additional Patient Demographics and Baseline Disease Characteristics

| Characteristic | Ponatinib group (N = 164) | Imatinib group (N = 81) |
|---|---|---|
| Race, No. (%)[a] | | |
| American Indian or Alaska Native | 2 (1) | 2 (2) |
| Asian | 20 (12) | 11 (14) |
| Black or African American | 9 (5) | 4 (5) |
| White | 104 (63) | 62 (77) |
| Other[b] | 29 (18) | 2 (2) |
| Geographic region, No. (%) | | |
| Europe | 71 (43) | 33 (41) |
| North America | 50 (30) | 26 (32) |
| South America | 21 (13) | 10 (12) |
| Asia | 18 (11) | 10 (12) |
| Australia | 4 (2) | 2 (2) |
| Median leukocyte count x $10^9$/L (range) | 4.4 (0.4 to 197.3) | 3.2 (0.2 to 81.2) |
| Median leukemic blasts (%) (range) | 80 (0 to 100) | 75 (0 to 100) |

[a]Race was selected from a list of predefined categories in an electronic data capture form.
[b]Other includes multiple races reported (one patient in ponatinib group) and race not reported (28 patients in the ponatinib group and two patients in the imatinib group).

## eTable 6. Patient Disposition

| No. (%) | Ponatinib group (N = 164) | Imatinib group (N = 81) |
|---|---|---|
| Intention-to-treat population | 164 (100) | 81 (100) |
| Intention-to-treat population with p190/p210 per central laboratory | 154 (94) | 78 (96) |
| Safety evaluable population[a] | 163 (99) | 81 (100) |
| Randomized and treated | 163 (99) | 81 (100) |
| Ongoing on study | 135 (82) | 63 (78) |
| Ongoing on-study treatment | 68 (41) | 10 (12) |
| Ongoing in follow-up | 61 (37) | 44 (54) |
| Discontinued from study treatment | 95 (58) | 70 (86) |
| Primary reason for discontinuation | | |
| Hematopoietic stem cell transplant | 50 (30) | 30 (37) |
| Lack of efficacy | 12 (7) | 21 (26) |
| Adverse event | 20 (12) | 10 (12) |
| Progressive disease[b] | 7 (4) | 5 (6) |
| Other | 6 (4) | 4 (5) |
| Received hematopoietic stem cell transplant at any time | 56 (34) | 39 (48) |

[a]One patient was randomized to the ponatinib group and died before receiving treatment.
[b]Defined as an increase of ≥ 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease.

## eTable 7. Subsequent Anticancer Therapy

| Treatment, No. (%) | Ponatinib group (n = 163) | Imatinib group (n = 81) |
|---|---|---|
| Any subsequent anticancer therapy | 57 (35) | 46 (57) |
| Any BCR::ABL1 TKI or immunotherapy | 48 (29) | 37 (46) |
| First-generation BCR::ABL1 TKI | 17 (10) | 7 (9) |
| Second-/third-generation BCR::ABL1 TKI and/or immunotherapy | 31 (19) | 30 (37) |
| Ponatinib-based | 13 (8) | 13 (16) |

Abbreviation: TKI, tyrosine kinase inhibitor.

## eTable 8. Treatment-Emergent Adverse Events

| Event, No. (%) | Ponatinib group (n = 163) | | Imatinib group (n = 81) | |
|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| Any[a] | 162 (99) | 147 (90) | 80 (99) | 75 (93) |
| **Hematologic** | | | | |
| Anemia[b] | 118 (72) | 50 (31) | 54 (67) | 29 (36) |
| Platelet count decreased[b] | 111 (68) | 103 (63) | 56 (69) | 47 (58) |
| White blood cell count decreased[b] | 111 (68) | 87 (53) | 52 (64) | 40 (49) |
| Neutrophil count decreased[b] | 98 (60) | 80 (49) | 43 (53) | 37 (46) |
| Lymphocyte count decreased[b] | 93 (57) | 62 (38) | 47 (58) | 38 (47) |
| Febrile neutropenia | 41 (25) | 38 (23) | 17 (21) | 15 (19) |
| **Nonhematologic** | | | | |
| Headache | 70 (43) | 3 (2) | 35 (43) | 1 (1) |
| Alanine aminotransferase increased | 68 (42) | 31 (19) | 27 (33) | 7 (9) |
| Constipation | 62 (38) | 1 (1) | 17 (21) | 1 (1) |
| Pyrexia | 61 (37) | 4 (2) | 21 (26) | 2 (2) |
| Nausea | 57 (35) | 5 (3) | 41 (51) | 6 (7) |
| Hypertension | 52 (32) | 20 (12) | 11 (14) | 5 (6) |
| Peripheral neuropathy | 51 (31) | 1 (1) | 19 (23) | 1 (1) |
| Lipase increased | 44 (27) | 21 (13) | 29 (36) | 15 (19) |
| Fatigue | 43 (26) | 3 (2) | 18 (22) | 1 (1) |
| Hypokalemia | 40 (25) | 10 (6) | 31 (38) | 15 (19) |
| Vomiting | 36 (22) | 2 (1) | 31 (38) | 2 (2) |
| Diarrhea | 28 (17) | 0 | 27 (33) | 2 (2) |
| Peripheral edema | 17 (10) | 0 | 26 (32) | 1 (1) |

[a]Adverse events that occurred in ≥ 25% of patients in either treatment group are shown.
[b]Based on laboratory values.

## eTable 9. Serious Treatment-Emergent Adverse Events Reported in More Than Two Patients

| Event, No. (%) | Ponatinib group (N = 163) | Imatinib group (N = 81) |
|---|---|---|
| Any | 97 (60) | 45 (56) |
| Febrile neutropenia | 27 (17) | 12 (15) |
| Pyrexia | 6 (4) | 3 (4) |
| Septic shock | 6 (4) | 3 (4) |
| Thrombocytopenia | 6 (4) | 2 (2) |
| COVID-19 | 7 (4) | 1 (1) |
| Sepsis | 6 (4) | 2 (2) |
| Pneumonia | 4 (2) | 3 (4) |
| Neutropenia | 4 (2) | 1 (1) |
| Anemia | 4 (2) | 0 |
| Pancreatitis | 4 (2) | 0 |
| COVID-19 pneumonia | 3 (2) | 2 (2) |
| Cellulitis | 2 (1) | 1 (1) |
| Acute kidney injury | 3 (2) | 0 |
| Device-related infection | 3 (2) | 0 |
| Headache | 3 (2) | 0 |
| Urinary tract infection | 3 (2) | 0 |
| Dyspnea | 2 (1) | 2 (2) |
| Platelet count decreased | 2 (1) | 2 (2) |
| Intracranial hemorrhage | 2 (1) | 1 (1) |
| Muscular weakness | 1 (1) | 2 (2) |
| Neutrophil count decreased | 1 (1) | 2 (2) |
| Stomatitis | 1 (1) | 2 (2) |

Abbreviation: COVID, coronavirus disease 2019.

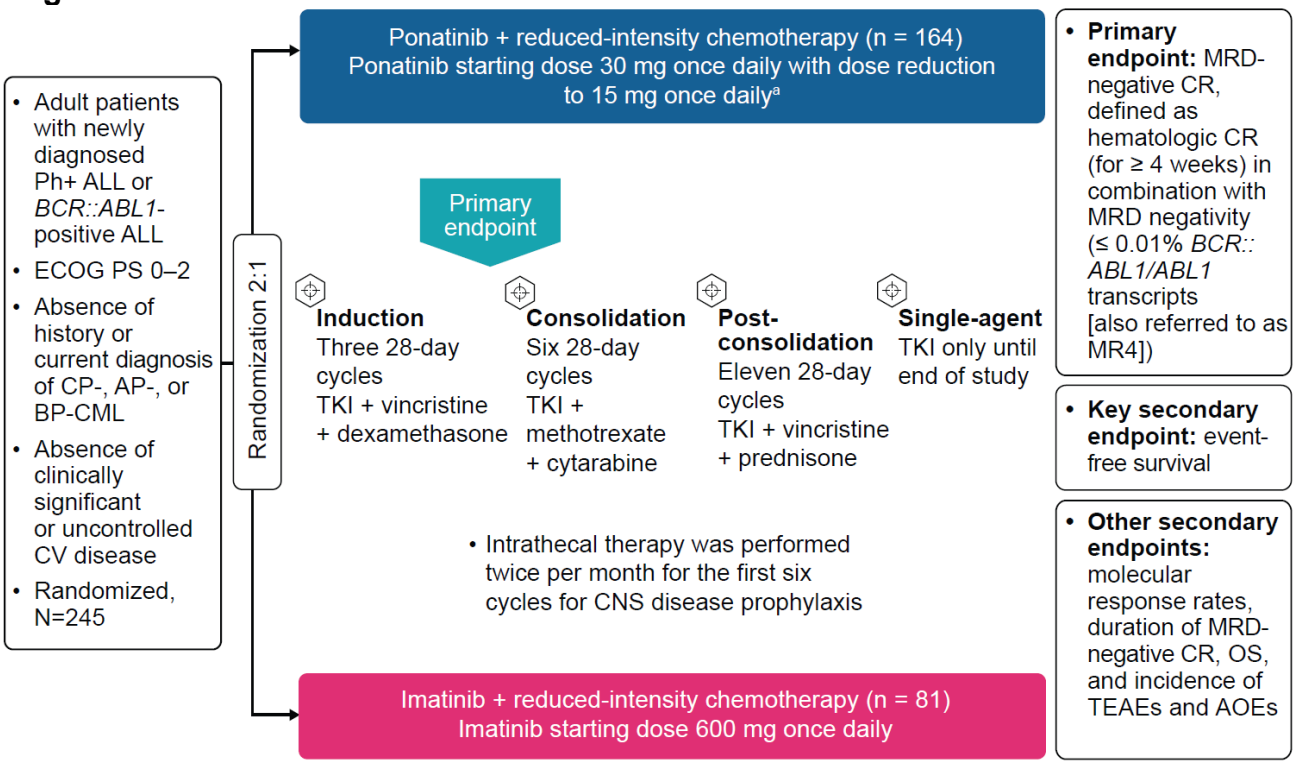
## eTable 10. Dose Modification for Treatment-Emergent Adverse Events

| Treatment modification, No. (%) | Ponatinib group (n = 163) | Imatinib group (n = 81) |
|---|---|---|
| Discontinuation | 17 (10) | 7 (9) |
| Reduction | 33 (20) | 18 (22) |
| Interruption | 111 (68) | 32 (40) |

## eTable 11. Treatment-Emergent Adverse Events Leading to Death

| Characteristic, No. (%) | Ponatinib group (n = 163) | Imatinib group (n = 81) |
|---|---|---|
| **Deaths attributed to treatment-emergent adverse events** | **8 (5)** | **4 (5)** |
| **Infections and infestations** | **6 (4)** | **3 (4)** |
| Septic shock | 4 (2) | 1 (1) |
| Abdominal sepsis | 1 (1) | 0 |
| Pseudomembranous colitis | 0 | 1 (1) |
| Pulmonary sepsis | 0 | 1 (1) |
| Sepsis | 1 (1) | 0 |
| **Respiratory, thoracic, and mediastinal disorders** | **2 (1)** | **0** |
| Pneumonitis | 1 (1) | 0 |
| Respiratory failure | 1 (1) | 0 |
| **Nervous system disorders** | **0** | **1 (1)** |
| Depressed level of consciousness | 0 | 1 (1) |

## eFigure 1. PhALLCON Study Design and Reduced-Intensity Chemotherapy Regimens

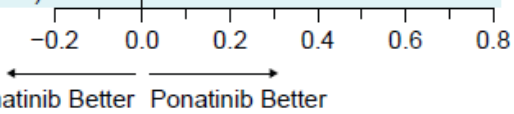



| Phase | Regimen[b] |
|---|---|
| Induction (Three 28-day cycles) | Vincristine: 1.4 mg/m$^2$ intravenous (maximum 2 mg), Days 1 and 14 |
| | Dexamethasone: 40 mg (age < 60 y) or 20 mg (age ≥ 60 y) oral, Days 1 to 4 and 11 to 14 |
| Consolidation (Six 28-day cycles) | Methotrexate: 1000 mg/m$^2$ (age < 60 y) or 250 mg/m$^2$ (age ≥ 60 y) intravenous, Day 1, 24-h infusion, folinic acid rescue, study Cycles 4, 6, and 8 |
| | Cytarabine: 1000 mg/m$^2$ every 12 h (age < 60 y) or 250 mg/m$^2$ every 12 h (age ≥ 60 y) intravenous, Days 1, 3, and 5, 2-h infusion, study Cycles 5, 7, and 9 |
| Maintenance (Eleven 28-day cycles) | Vincristine: 1.4 mg/m$^2$ (maximum 2 mg) intravenous, injected over 1 minute, Day 1 |
| | Prednisone: 200 mg/d (age < 60 y), 100 mg/d (age ≥ 60 to 69 y), or 50 mg (age ≥ 70 y) oral, Days 1 to 5 |
| Single-agent Maintenance | Post Cycle 20 continue with single-agent ponatinib or imatinib |

Abbreviations: ALL, acute lymphoblastic leukemia; AOE, arterial occlusive event; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukemia; CP, chronic phase; CR, complete remission; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; MRD, minimal residual disease; OS, overall survival; PD, progressive disease; Ph+, Philadelphia chromosome–positive; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.
[a]Dose reductions to 15 mg once daily were implemented in patients who achieved MRD-negative CR after completion of the induction phase.
[b]Intrathecal methotrexate, cytarabine, and corticosteroid therapy were administered on Days 1 and 14 of the first six cycles as central nervous system prophylaxis.

## eFigure 2. MRD-Negative CR Rate at End of Induction by Patient Subgroup

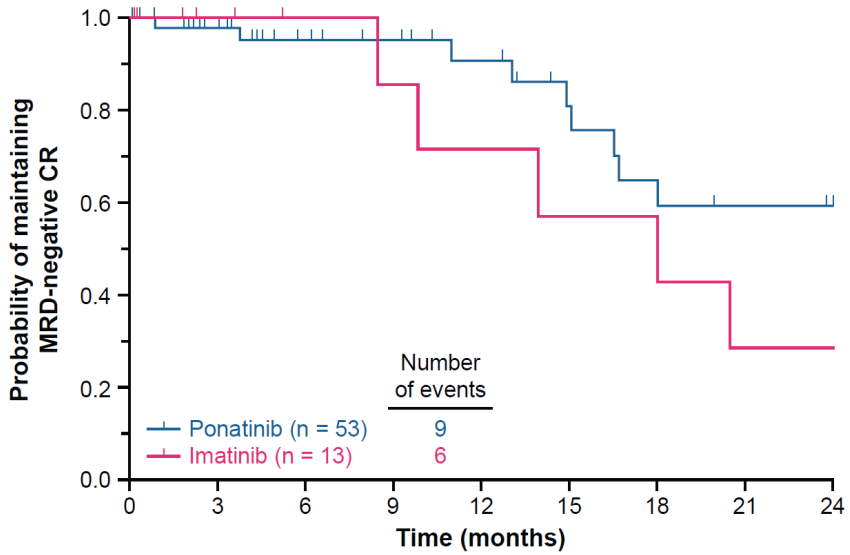
| Subgroup | Ponatinib | Imatinib | Risk Difference (95% CI) |
|---|---|---|---|
| | No. of Patients | | Ponatinib vs Imatinib |
| Overall | 154 | 78 | 0.18 (0.06 to 0.29) |
| Age, years | | | |
| 18 to < 45 | 50 | 27 | 0.09 (−0.10 to 0.29) |
| 45 to < 60 | 44 | 22 | 0.11 (−0.11 to 0.34) |
| ≥ 60 | 60 | 29 | 0.30 (0.13 to 0.46) |
| < 60 | 94 | 49 | 0.10 (−0.04 to 0.25) |
| Sex | | | |
| Female | 85 | 40 | 0.17 (0.02 to 0.32) |
| Male | 69 | 38 | 0.19 (0.02 to 0.36) |
| Race | | | |
| Non-White | 57 | 18 | 0.28 (0.12 to 0.44) |
| White | 97 | 60 | 0.15 (0.01 to 0.29) |
| Region | | | |
| Asia-Pacific | 22 | 12 | 0.23 (−0.01 to 0.48) |
| Europe | 68 | 31 | 0.11 (−0.05 to 0.26) |
| North America | 47 | 25 | 0.15 (−0.08 to 0.37) |
| South America | 17 | 10 | 0.49 (0.19 to 0.79) |
| *BCR::ABL1* Variant | | | |
| p190 | 114 | 53 | 0.22 (0.08 to 0.35) |
| p210 | 40 | 25 | 0.07 (−0.13 to 0.26) |
| ECOG Performance Status | | | |
| 0 | 67 | 32 | 0.14 (−0.01 to 0.30) |
| 1 | 80 | 42 | 0.21 (0.05 to 0.38) |
| 2 | 7 | 4 | 0.14 (−0.12 to 0.40) |
| White Blood Cell Count | | | |
| < 30 x $10^9$/L | 131 | 70 | 0.17 (0.05 to 0.30) |
| ≥ 30 x $10^9$/L | 16 | 4 | 0.19 (0.00 to 0.38) |
| Prephase Therapy | | | |
| Yes | 69 | 40 | 0.21 (0.06 to 0.36) |
| No | 85 | 38 | 0.14 (−0.02 to 0.31) |




Abbreviations: CI, confidence interval; CR, complete remission; ECOG, Eastern Cooperative Oncology Group; MRD, minimal residual disease.

## eFigure 3. Duration of MRD-Negative CR[a]

Median duration of MRD negative CR was NE (95% CI: 16.6–NE) in the ponatinib group and 18.0 (95% CI: 8.4–27.8) months in the imatinib group.

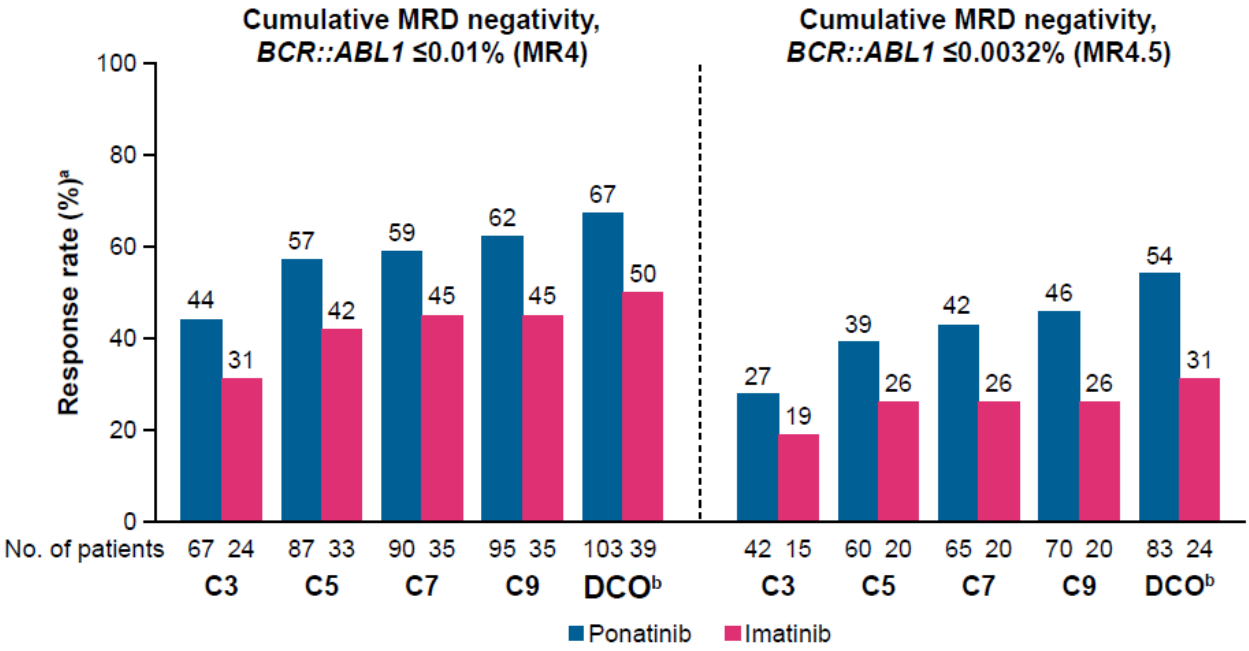



| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ponatinib | 53 | 39 | 28 | 25 | 21 | 15 | 12 | 9 | 8 |
| Imatinib | 13 | 9 | 7 | 6 | 5 | 4 | 4 | 2 | 2 |

Abbreviations: CI, confidence interval; CR, complete remission; IQR, interquartile range; MRD, minimal residual disease; NE, not estimable.

[a]MRD-negative CR was defined as achievement of central laboratory–reported MRD negativity (defined as ≤ 0.01% *BCR::ABL1*$^{IS}$ [MR4]) and investigator-reported CR (bone marrow blast response with hematologic recovery as measured by absolute neutrophil and platelet counts) for ≥ 4 weeks at end of induction.

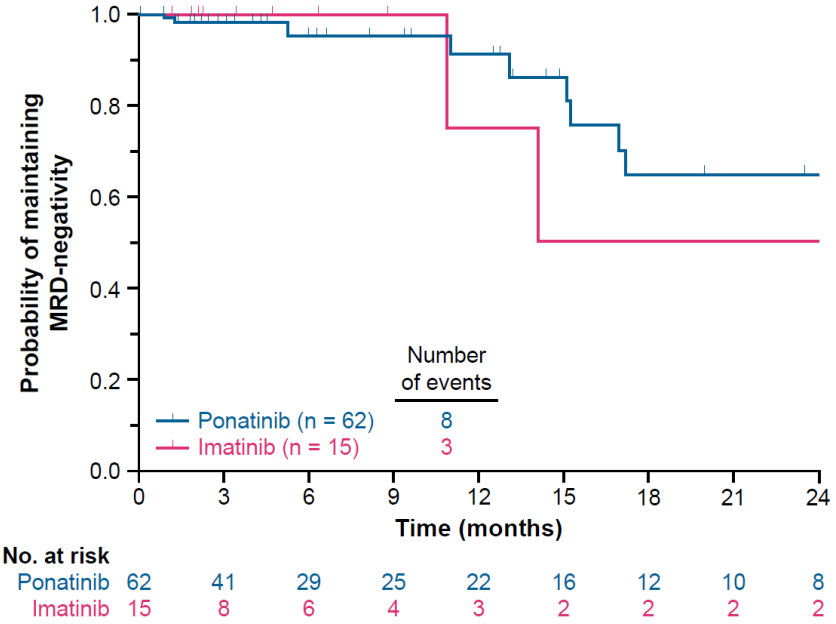
## eFigure 4. Cumulative Molecular Response Rates by Treatment Cycle




Abbreviations: C, Cycle; DCO, data cutoff; MRD, minimal residual disease.
[a]Denominator is 154 for ponatinib and 78 for imatinib.
[b]Patients who achieved MR4 and MR4.5 by August 12, 2022, DCO.

## eFigure 5. Duration of MRD Negativity

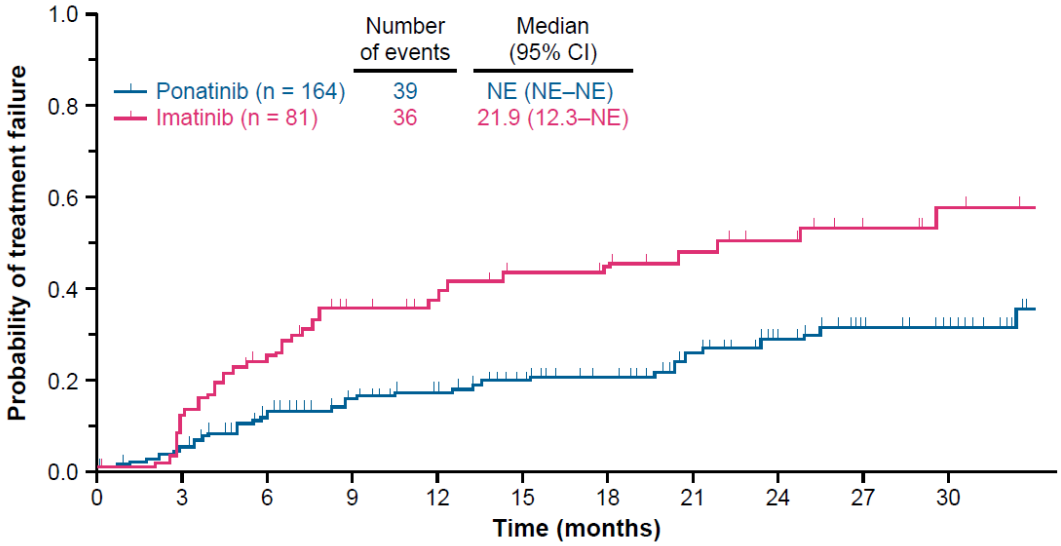
Median duration of MRD negativity was NE (95% CI: 17.0 months–NE) in the ponatinib arm and 20.9 (95% CI: 10.9–NE) in the imatinib arm.




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ponatinib | 62 | 41 | 29 | 25 | 22 | 16 | 12 | 10 | 8 |
| Imatinib | 15 | 8 | 6 | 4 | 3 | 2 | 2 | 2 | 2 |

Abbreviations: CI, confidence interval; MRD, minimal residual disease; NE, not estimable.

## eFigure 6. Time to Treatment Failure

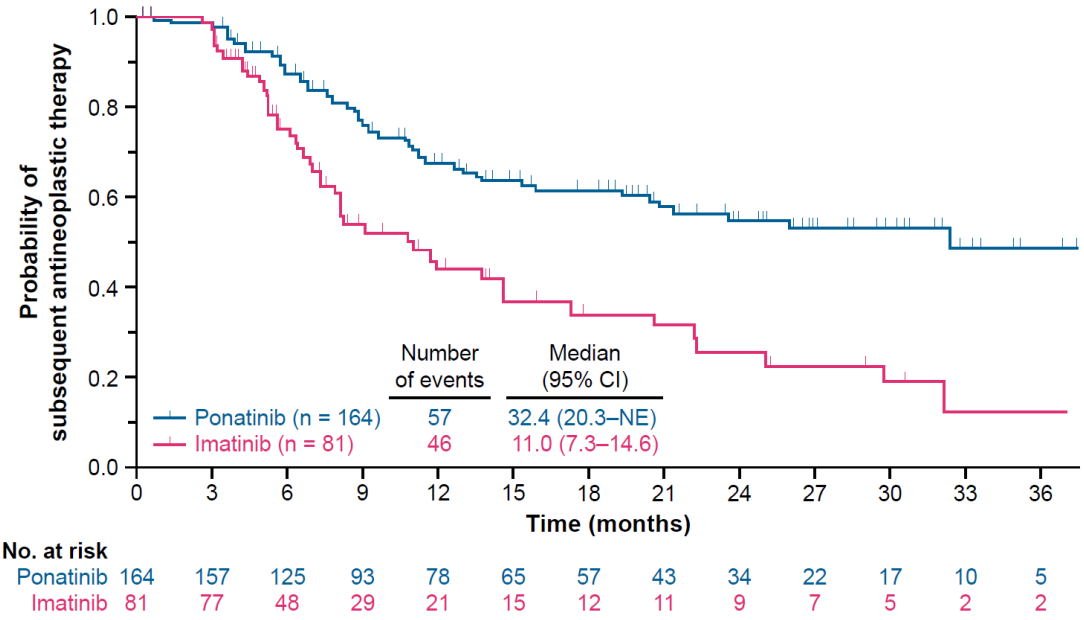



**No. at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ponatinib | 164 | 155 | 131 | 109 | 99 | 85 | 75 | 60 | 48 | 33 | 26 |
| Imatinib | 81 | 77 | 54 | 39 | 33 | 28 | 26 | 22 | 18 | 13 | 10 |

Abbreviations: CI, confidence interval; NE, not estimable.

## eFigure 7. Time to Subsequent Antineoplastic Treatment



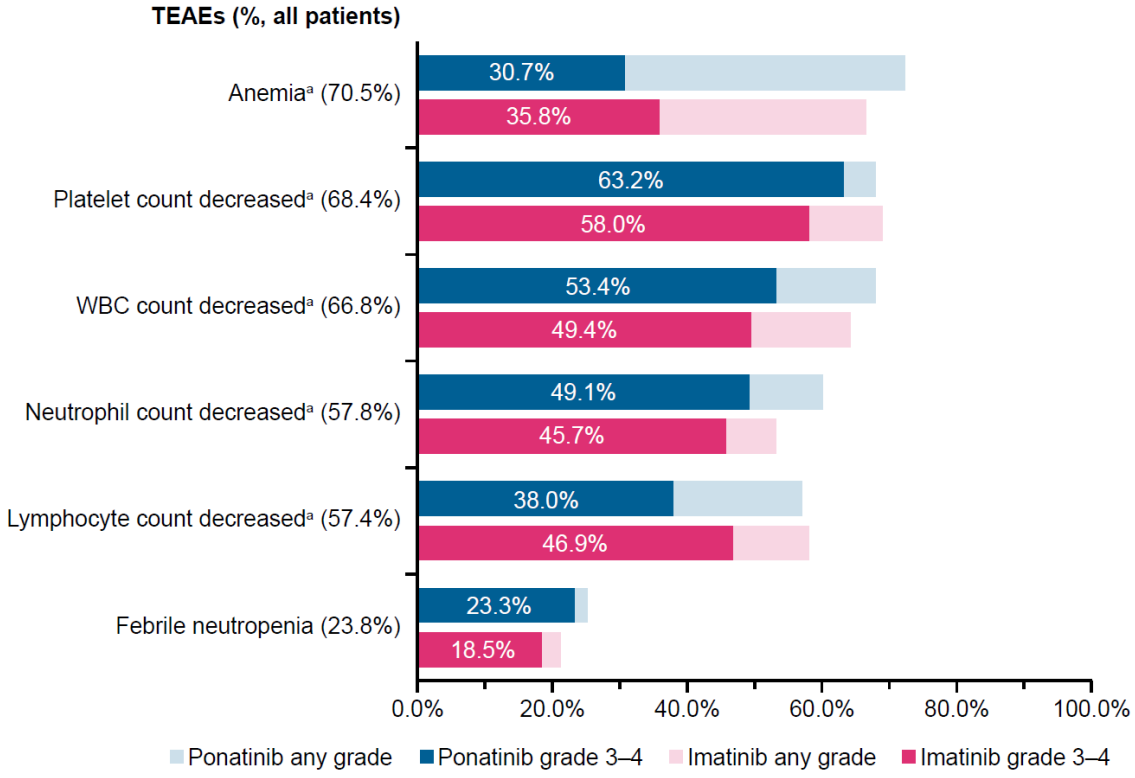

| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ponatinib | 164 | 157 | 125 | 93 | 78 | 65 | 57 | 43 | 34 | 22 | 17 | 10 | 5 |
| Imatinib | 81 | 77 | 48 | 29 | 21 | 15 | 12 | 11 | 9 | 7 | 5 | 2 | 2 |

Abbreviations: CI, confidence interval; NE, not estimable.

## eFigure 8. Treatment-Emergent Adverse Events

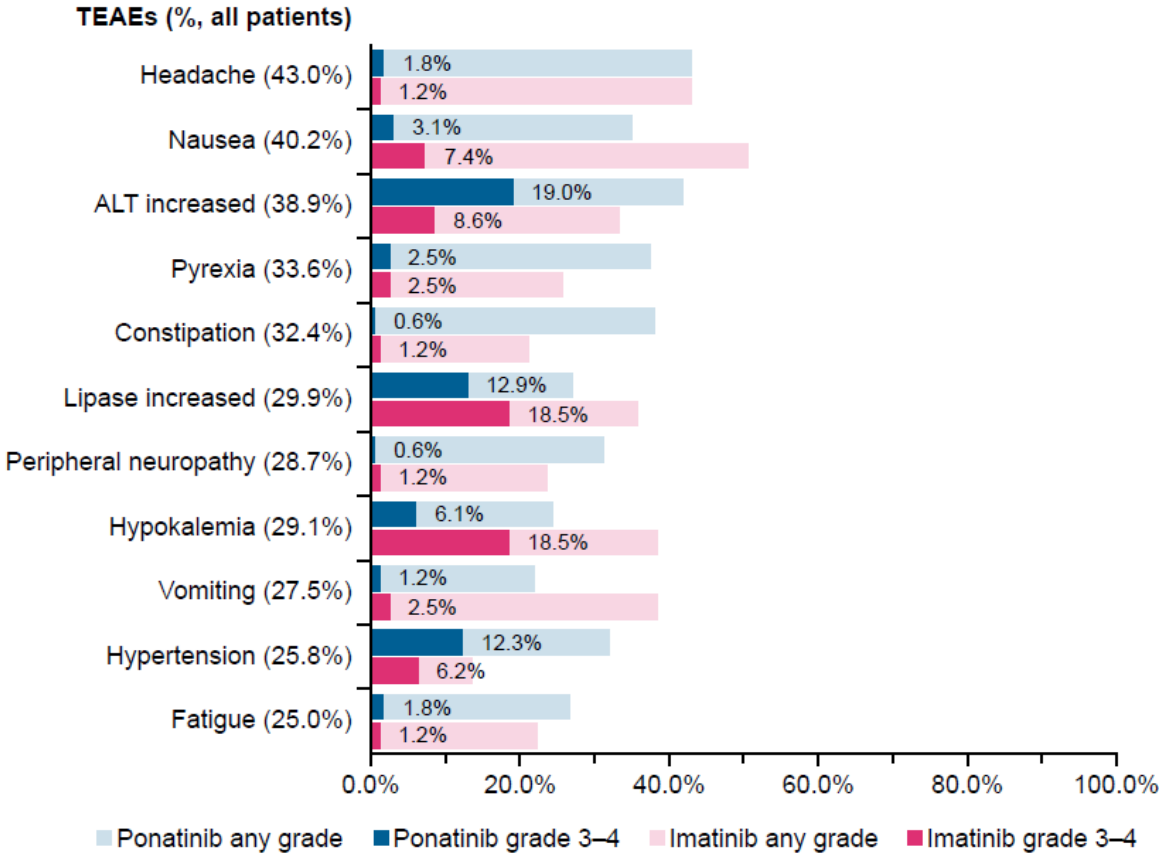
(A) Hematologic TEAEs (≥ 10% of all patients). (B) Nonhematologic TEAEs (≥ 25% of all patients). Percentages shown within bars indicate rates of grade 3–4 TEAEs.

### A. Hematologic TEAEs (≥ 10% of All Patients)




Abbreviations: ALT, alanine aminotransferase; TEAE, treatment-emergent adverse event; WBC, white blood cell.
[a]Based on laboratory values.

## B. Nonhematologic TEAEs (≥ 25% of All Patients)




Abbreviations: ALT, alanine aminotransferase; TEAE, treatment-emergent adverse event; WBC, white blood cell.