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Favorable tolerability of asciminib *versus* ATP-competitive tyrosine kinase inhibitors in the ASC4FIRST study of newly diagnosed patients with chronic-phase chronic myeloid leukemia

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DATA SHARING STATEMENT

Novartis is committed to sharing access to patient-level data and supporting clinical documents from eligible studies to qualified external researchers. These requests will be reviewed and approved by an independent review panel based on scientific merit. All data provided will be anonymized to respect the privacy of patients who have participated in the trial consistent with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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GCI, RAL, TPH, AH, NT, FB, JW, DDHK, JM, Y-TG, PC, GE, DA, EG, YZ, TM, NA, RJ, AD, IS, and JEC contributed to the data acquisition and interpretation, writing, and reviewing the manuscript, and approving the final manuscript.

CONFLICT OF INTEREST DISCLOSURES

GCI: Celgene: research funding; Kura Oncology: consultancy, research funding; Novartis: consultancy, research funding; Syndax: research funding. **RAL:** Novartis: consultancy and research funding; Bristol Myers Squibb: consultancy and research funding; Takeda: consultancy. **TPH:** Novartis: consultancy, research funding; Bristol Myers Squibb: consultancy, research funding; Ariad: consultancy, research funding. **AH:** Bristol Myers Squibb, Pfizer: institutional research support; Novartis and Incyte: institutional research support, personal honoraria. **MB:** Bristol Myers Squibb, Celgene, Pfizer, Incyte, and Novartis: consultancy and honoraria; AbbVie: consultancy. **NT:** Novartis: research funding, honoraria, speakers bureau, advisory committees; Pfizer: research funding, honoraria, speakers bureau, advisory committees; Otsuka: research funding, honoraria, speakers bureau, advisory committees. **FB:** CML Advocates Network, MPN

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ABSTRACT

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Many patients with chronic myeloid leukemia (CML) treated with adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs) experience persistent adverse events (AEs) that negatively impact daily living and the ability to remain on treatment. Asciminib, an allosteric inhibitor of BCR::ABL1, was designed to enhance efficacy and reduce off-target effects vs ATP-competitive TKIs. The phase 3 randomized ASC4FIRST trial established the overall favorable safety profile of asciminib in patients with newly diagnosed CML in chronic phase (CP). This exploratory post hoc analysis of ASC4FIRST focused specifically on the tolerability of asciminib vs imatinib and asciminib vs second-generation [2G] TKIs. Analyses were conducted within each stratum to account for differences between strata; patients prerandomized to the imatinib stratum were older and had higher cardiovascular risk than those in the 2G stratum. Within both strata, patients receiving asciminib experienced fewer difficult-to-tolerate AEs (such as gastrointestinal toxicity, rash, and pleural effusion) and fewer AEs leading to dose modifications and discontinuations due to nonhematologic and hematologic AEs vs the investigator-selected (IS) TKI comparator, with a shorter median duration of dose modification. Additionally, median onset of AEs leading to dose modification occurred later in patients receiving asciminib vs IS-TKIs. The safety and tolerability of asciminib observed in the ASC4FIRST trial demonstrate asciminib's excellent benefit-risk profile as a frontline therapy for a broad range of patients with newly diagnosed CML-CP.

INTRODUCTION

The pivotal phase 3 ASC4FIRST study compared asciminib with investigator-selected (IS) ATP-competitive tyrosine kinase inhibitors (TKIs), imatinib or second-generation (2G) TKIs (nilotinib, dasatinib, bosutinib), in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP).[1] Prior to randomization, investigators selected a TKI that patients would receive if randomized to the comparator group.[1] Patients were randomized 1:1 to receive asciminib or an IS-TKI, stratified by European Treatment and Outcome Study long-term survival (ELTS) category and TKI selected prior to randomization.[1] Asciminib, which inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein by binding to the ABL myristoyl pocket, was designed to enhance efficacy and reduce off-target effects vs current ATP-competitive TKIs.[2,3] In ASC4FIRST, asciminib demonstrated statistically superior efficacy at week 48 and favorable safety and tolerability in patients with newly diagnosed CML-CP.[1]

Based on the results from ASC4FIRST, asciminib received accelerated approval in the United States[1,4] and several other countries[5] for adult patients with newly diagnosed Philadelphia chromosome–positive (Ph+) CML-CP. Asciminib was initially approved for Ph+ CML-CP[4] after ≥2 TKIs and in patients with the T315I mutation based on data from the phase 3 ASCEMBL[3] and phase 1 dose-escalation studies,[6] respectively, which demonstrated asciminib's favorable long-term safety and tolerability with up to 8 years of exposure.[7,8]

Because CML is now managed as a lifelong, chronic disease,[9-11] treatment goals have evolved from extending survival to include improving quality of life (QoL).[11-13] Many patients receive long-term ATP-competitive TKI therapy and often experience persistent low-grade adverse events (AEs) that can negatively impact QoL[13-15] and may lead to poor adherence,[16,17]

potentially resulting in suboptimal treatment outcomes.[18-22] CML treatment should optimize tolerability, to increase the likelihood that patients remain on therapy and achieve treatment goals.

In ASC4FIRST, at the time of the week 48 data cutoff, asciminib demonstrated a favorable tolerability profile, with less frequent grade ≥3 AEs and AEs leading to discontinuation with asciminib in combined strata (38.0% and 4.5%, respectively) than with imatinib (44.4% and 11.1%) and 2G TKIs (54.9% and 9.8%).[1] Patients in the imatinib stratum were older and had higher risk of cardiovascular disease than those in the 2G TKI stratum,[1] providing a rationale to assess tolerability in each stratum. This exploratory post hoc analysis focuses on the type, number, duration, and onset of safety events leading to dose reductions and interruptions, including grade 1 and 2 nonhematologic AEs, which may directly impact treatment tolerability but are not routinely the focus of safety analyses, as well as on AEs resulting in treatment discontinuations as a readout of patient tolerability. These results offer insights into the differential tolerability profiles of asciminib compared with imatinib and 2G TKIs within each individual stratum.

METHODS

ASC4FIRST Study Design

Study methods were previously described.[1] ASC4FIRST is a phase 3, multicenter, open-label, randomized trial that enrolled adult patients with CML-CP that was newly diagnosed within 3 months prior to enrollment (NCT04971226).[1] Prior to randomization, investigators in consultation with patients selected either imatinib or a 2G TKI (nilotinib, dasatinib, or bosutinib)

each patient would receive if randomly assigned to the comparator arm (prerandomization-selected TKI), taking into consideration treatment goals, disease and patient characteristics, and comorbidities.[1] Patients were randomized 1:1, stratified by prerandomization-selected TKI and ELTS risk category, to receive either asciminib 80 mg once daily (QD) or an IS-TKI at approved doses for patients with newly diagnosed CML.[1] The protocol was approved by the sites' institutional review boards and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent.

Post Hoc Tolerability Analyses

Exploratory tolerability analyses assessed aspects not reported in the primary ASC4FIRST manuscript.[1] These new analyses were conducted within strata (henceforth called asciminib [ASC]^{IMA}, ASC^{2G}, IMA, and 2G TKI) to account for differences in patient demographics between strata. Analyses included determining the frequency, duration, grade, and type of AEs (nonhematologic or hematologic), including those that led to dose reductions and/or interruptions and discontinuations.

Additionally, the time to first nonhematologic and hematologic grade 1/2 AEs, including those leading to dose modification, was determined.

Tolerability analyses were conducted within the safety population, which included patients who received ≥1 dose of study treatment according to the actual treatments received.[1]

Statistical Analyses

Descriptive statistics are presented for this exploratory post hoc analysis. Further details on descriptive statistics are in the supplemental materials. Comparative statistical analyses were not performed and P values are not available; all differences identified are numerical.

Time to first nonhematologic and hematologic grade 1/2 AEs, including those leading to dose modification, were estimated using the Kaplan-Meier method.

Dosing in the ASC4FIRST Trial

For patients receiving asciminib who did not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either required or recommended (**Table S1**). Dose reduction to 40 mg QD was indicated based on the presence and severity of AEs; reduction below 40 mg total daily was not allowed.[1] Re-escalation to 80 mg QD was allowed more than once if the patient's risk-benefit assessment changed at the lower dose level and if each event was significantly different. For patients receiving IS-TKIs, dose modifications were performed at the investigator's discretion per institutional practice and local labels. Further details on dose modifications and discontinuation are in the Supplemental Materials.

ASC4FIRST Study Assessments

AEs were coded using the Medical Dictionary for Regulatory Activities version 26.1 and graded according to the CTCAE version 5.0.[1]

RESULTS

Patients

Patient details were described previously.[1] Briefly, 405 patients were randomized to receive asciminib (ASC^{IMA}, n=101; ASC^{2G}, n=100), imatinib (n=102), or 2G TKIs (n=102; **Figure S1**). Demographics and baseline characteristics were similar in the asciminib and IS-TKI arms. Demographics and baseline characteristics were similar between groups within strata; however, patients in the imatinib stratum were older and had greater risk for cardiovascular disease and

lower ELTS risk scores than did the 2G TKI stratum.[1,23] Within the safety set (n=401; ASC^{IMA}; n=100; ASC^{2G}, n=100; IMA, n=99; 2G TKIs n=102),[1] the median follow-up was 14.3 months with ASC^{IMA}, 13.9 with IMA, 17.4 with ASC^{2G}, and 17.0 with 2G TKIs. At the data cutoff (November 28, 2023),[1] treatment was ongoing in 85 (85.0%) and 62 patients (62.6%) receiving ASC^{IMA} and IMA and 88 (88.0%) and 78 (76.5%) receiving ASC^{2G} and 2G TKIs, respectively. Discontinuation due to AEs occurred in 6 patients (6.0%) receiving ASC^{IMA}, 11 (11.1%) receiving IMA, 5 (5.0%) receiving ASC^{2G}, and 10 (9.8%) receiving 2G TKIs.

Tolerability

Overview of AEs

Odds ratios for AEs reported in ≥10% of patients were calculated to quantify the impact of each treatment on the probability of occurrence of a specific AE within the strata. Patients receiving ASC^{IMA} had lower odds of experiencing muscle spasms, nausea, and diarrhea compared with patients receiving IMA (**Figure S2A**); patients receiving ASC^{2G} had lower odds of experiencing increased aspartate aminotransferase and alanine aminotransferase compared with patients receiving 2G TKIs (**Figure S2B**). No AEs had greater odds of occurring with asciminib than with IMA or 2G TKIs. Rates of low-grade (grades 1/2) and high-grade (grade ≥3) nonhematologic AEs are shown in **Figure 1A and 1B.**

Nonhematologic AEs occurring more frequently, defined as an increase in incidence ≥5%, in patients receiving IMA than ASC^{IMA} were diarrhea, myalgia, nausea, vomiting, muscle spasms, and edema (**Table S2**); constipation and headache were more frequent in patients receiving ASC^{IMA} compared with IMA. Nonhematologic AEs occurring more frequently in patients

receiving 2G TKIs than ASC^{2G} included symptomatic AEs (i.e., diarrhea, nausea, and headache) and nonsymptomatic AEs (i.e., increased alanine aminotransferase, increased aspartate aminotransferase, and increased lipase). No nonhematologic AEs were more frequent in patients receiving ASC^{2G} than 2G TKIs. Some AEs, such as enzyme elevations, occurred in more patients receiving ASC^{IMA} than patients receiving ASC^{2G}. Conversely, more patients receiving ASC^{2G} experienced gastrointestinal symptoms compared with patients receiving ASC^{IMA} (**Figure S2**).

Most hematologic AEs commonly associated with TKI treatment occurred less often in patients with ASC^{IMA} vs imatinib and ASC^{2G} vs 2G TKIs (**Figure S3A, B**; **Table S3**).

By week 48, more patients receiving asciminib had not experienced a nonhematologic AE compared with patients receiving IS-TKIs. The probability of not experiencing a nonhematologic AE at or before week 48 was 12.2% with ASC^{IMA} vs 8.8% with IMA and 13.9% for ASC^{2G} vs 2.1% with 2G TKIs (**Figure 2A, B**). Similar trends were seen with hematologic AEs (**Figure S4A, B**).

Dose modifications (adjustments and/or interruptions)

Overall and within individual strata, patients receiving asciminib generally experienced fewer dose reductions and interruptions for any reason vs IS-TKIs (**Figure S5A, B**). The median number of dose reductions for any reason per patient was 1.0 (range, 1-1) with ASC^{IMA} vs 1.0 (1-6) with IMA and 1.0 (1-2) with ASC^{2G} vs 2.0 (1-16) with 2G TKIs. The median duration of dose reductions due to any cause was 38 (range 1-551) days with ASC^{IMA}, 208 (6-505) days with IMA, 43 (1-455) days with ASC^{2G}, and 84 (1-617) days with 2G TKIs (**Figure 3A, B**). The median number per patient and median duration of dose interruptions for any cause were similar with ASC^{IMA} vs IMA and with ASC^{2G} vs 2G TKIs. Fewer patients experienced ≥1 dose reduction due to

AEs with ASC^{IMA} vs IMA (14.0% vs 19.2%) and with ASC^{2G} vs 2G TKIs (11.0% vs 39.2%; **Figure S6A, B**). Dose interruptions due to AEs also occurred less frequently with ASC^{IMA} than with IMA (28.0% vs 36.4%) and with ASC^{2G} than with 2G TKIs (32.0% vs 44.1%). The median duration of dose interruption due to AEs was 14.5 (range, 2-80) days with ASC^{IMA} and 13.5 (1-71) days with IMA, and 17.5 (4-71) days with ASC^{2G} and 14.0 (1-155) days with 2G TKIs.

All-grade AEs leading to dose modifications (adjustment/interruption) were less frequent with asciminib vs IS-TKIs both overall and within strata, both nonhematologic (all asciminib vs all IS-TKIs, 18.5% vs 26.4.%; ASC^{IMA} vs IMA, 18.0% vs 20.2%; ASC^{2G} vs 2G TKIs, 19.0% vs 32.4%) and hematologic (all asciminib vs all IS-TKIs, 16.0% vs 23.9%; ASC^{IMA} vs IMA, 14.0% vs 22.2%; ASC^{2G} vs 2G TKIs, 18.0% vs 25.5%). Nonhematologic grade 1/2 AEs resulting in dose modifications were less frequent among patients receiving asciminib both overall and within strata (all asciminib vs all IS-TKIs, 10.0% vs 20.9%; ASC^{IMA} vs IMA, 9.0% vs 14.1%; ASC^{2G} vs 2G TKIs, 11.0% vs 27.5%; **Figures 4A, B**). Nonhematologic grade ≥3 AEs leading to dose modifications occurred in 12.0% vs 8.1% of patients with ASC^{IMA} vs IMA and in 10.0% vs 12.7% with ASC^{2G} vs 2G TKIs, respectively. A similar trend was seen with hematologic grade 1/2 AEs (**Figure S7A, B**). Individual nonhematologic and hematologic grade 1/2 and grade ≥3 AEs leading to dose modifications are shown in **Figures 5A**, **B** and **Figures S8A, B**, respectively.

In both strata, grade 1/2 nonhematologic AEs with asciminib less frequently resulted in dose modification by week 48 than did those with IS-TKIs (**Figure 6A, B**). Notably, the probability of not experiencing a grade 1/2 nonhematologic AE resulting in dose modification decreased within the first 6 weeks with imatinib and more noticeably decreased with 2G TKIs, indicating that poorly tolerated nonhematologic grade 1/2 AEs emerged early in treatment. **Figures S9A**

and **S9B** show the Kaplan-Meier curve of time to first grade 1/2 hematologic AEs leading to dose modifications in the imatinib and 2G TKI strata.

Discontinuations

Overall, fewer patients discontinued treatment due to any reason with asciminib vs imatinib and vs 2G TKIs within both strata (**Figure S10A, B**); fewer patients with ASC^{IMA} vs IMA (6.0% vs 11.1%) and with ASC^{2G} vs 2G TKIs (5.0% vs 9.8%) discontinued study treatment due to AEs. Most discontinuations were due to nonhematologic AEs, with lower rates seen with asciminib (**Table S4**; **Figure 7A, B**). Rates of discontinuation were higher with IMA vs ASC^{IMA} (5.1% vs 3.0%) and 2G TKIs vs ASC^{2G} (4.9% vs 0%) due to grade 1/2 nonhematologic AEs. The same trend was seen with grade ≥3 nonhematologic AEs leading to treatment discontinuation, which were higher with IMA vs ASC^{IMA} (3.0% vs 2.0%) and 2G TKIs vs ASC^{2G} (3.9% vs 2.0%). All-grade nonhematologic AEs leading to treatment discontinuation in >1 patient in any treatment group were increased lipase with asciminib (n=3) in the imatinib stratum, diarrhea with imatinib (n=2), and pleural effusion with 2G TKI (n=2; **Table S4**). Few hematologic AEs led to treatment discontinuation; rates of grade 1/2 and grade ≥3 hematologic AEs leading to treatment discontinuation were relatively similar between strata (**Table S4**; **Figure S11A, B)**.

Overview of AEs of interest with asciminib

We reviewed the occurrence of select AEs commonly associated with asciminib treatment and examined whether these events resulted in dose modifications and/or discontinuations, which was not reported in the primary analysis from ASC4FIRST.[1]

Lipase elevation

Of patients receiving ASC^{IMA} and IMA, 9 (19.0%) and 14 (14.1%) experienced increased lipase of any grade, respectively. In the ASC^{IMA} group, increased lipase led to dose modifications in 3 patients (3.0%), all of whom had grade ≥3 events, and discontinuation in 3 (3.0%), with 1.0% of these cases being grade ≥3. In patients receiving IMA, increased lipase led to dose modifications in 1 patient (1.0%), with no grade ≥3 events or discontinuations.

Increased lipase occurred in 4 patients (4.0%) receiving ASC^{2G} and 10 (9.8%) receiving 2G TKIs. Dose modification due to increased lipase occurred in 1 patient (1.0%) receiving ASC^{2G} (grade ≥3) and 2 patients (2.0%) receiving 2G TKIs (1.0% of which was grade ≥3), respectively. No patients discontinued due to increased lipase in the ASC^{2G} or 2G TKI groups.

Pancreatitis

One patient (1.0%) receiving ASC^{IMA} experienced grade ≥3 pancreatitis, resulting in discontinuation. Three patients (3.0%) receiving IMA experienced pancreatitis; 1 (1.0%) who experienced a grade ≥3 event had dose modification, and 1 (1.0%) who experienced a grade 1/2 event discontinued.

One patient (1.0%) receiving ASC^{2G} experienced grade ≥3 pancreatitis, resulting in dose modification; no patient receiving 2G TKIs experienced pancreatitis.

Arterial hypertension

Ten patients (10.0%) receiving ASC^{IMA} and 6 (6.1%) receiving IMA experienced hypertension. Four patients (4.0%) receiving ASC^{2G} and 2 (2.0%) receiving 2G TKIs experienced hypertension.

One patient (1.0%) each receiving ASC^{IMA} and ASC^{2G} experienced grade ≥3 hypertension leading to dose modification. No patients discontinued treatment due to hypertension.

Arterial occlusive events (AOEs)

One patient (1.0%) receiving ASC^{IMA}, 1 (1.0%) receiving ASC^{2G}, 2 (2.0%) receiving 2G TKIs, and 0 receiving IMA experienced an AOE. The patient receiving ASC^{IMA} discontinued study treatment due to grade ≥3 cerebrovascular accident; 1 patient receiving dasatinib required temporary study treatment interruption due to grade ≥3 myocardial infarction and grade 1/2 myocardial ischemia.[1] No deaths were reported due to AOEs.[1]

Arrhythmias

Grade 1/2 arrhythmia events experienced by patients receiving ASC^{IMA} included palpitations, ventricular extrasystoles, atrial fibrillation, and sinus tachycardia (n=1 [1.0%] each); none experienced a grade ≥3 arrhythmia event or required dose modification or discontinuation. In patients receiving IMA, 1 patient (1.0%) experienced grade 1/2 palpitations, 1 (1.0%) experienced grade ≥3 atrial fibrillation, and 3 (3.0%) experienced grade 1/2 sinus bradycardia; no dose modifications or discontinuations were required. No patients receiving ASC^{2G} experienced arrhythmia events. Two patients (2.0%) receiving 2G TKIs had grade 1/2 arrhythmia, and 5 (4.9%) had grade 1/2 palpitations; 1 patient (1.0%) each experienced grade 1/2 atrioventricular block, bradycardia, and long QT syndrome. Only 1 patient receiving 2G TKIs who experienced grade 1/2 arrhythmia required dose modification.

Cardiac failure

No patients receiving asciminib in either stratum or imatinib experienced cardiac failure; one patient receiving a 2G TKI experienced grade ≥3 cardiac failure that led to treatment discontinuation.

Thrombocytopenia (including thrombocytopenia and platelet count decreased)

Of patients receiving ASC^{IMA} and IMA, 26 (26.0%) and 28 (28.3%) experienced thrombocytopenia of any grade, with 12.0% and 6.1% of grade ≥3, respectively. In the ASC^{IMA} group, thrombocytopenia led to dose modifications in 12 patients (12.0%; all grade ≥3) and discontinuations in 1 (1.0%; grade ≥3). In patients receiving IMA, thrombocytopenia led to dose modifications in 10 patients (10.0%; 6.1% of grade ≥3) and no discontinuations.

Thrombocytopenia occurred in 30 patients (30.0%; 14.0% of grade ≥3) receiving ASC^{2G} and 35 (34.3%; 13.7% of grade ≥3) receiving 2G TKIs. In patients receiving ASC^{2G}, thrombocytopenia led to dose modifications in 14 patients (14.0%; all grade ≥3) and discontinuations in 1 (1.0%; grade 1/2). In patients receiving 2G TKIs, thrombocytopenia led to dose modifications in 19 patients (18.6%; 13.7% of grade ≥3) and discontinuations in 1 (1.0%; grade ≥3).

DISCUSSION

This post hoc exploratory analysis reporting new results from ASC4FIRST week 48 data cutoff provides greater clarity regarding the tolerability of TKI treatment. In the absence of a uniform definition of tolerability, these analyses focused on nonhematologic AEs leading to dose reductions, interruptions, and treatment discontinuations as a readout of tolerability. In

particular, persistent grade 1/2 AEs may decrease tolerability of treatment but are not routinely the focus of safety readouts.[24] Some nonhematologic AEs are symptomatic and therefore can impact a patient's daily living, making these AEs difficult to tolerate.[25-27] Safety assessments in clinical trials often do not provide specific information on when AEs develop, resolve, or improve with supportive interventions; these are critical measures affecting tolerability.[24]

Demographics and baseline characteristics were similar between groups within each stratum (ASC^{IMA} vs imatinib or ASC^{2G} vs 2G TKI), consistent with the comparisons of this analysis. Differences in tolerability observed between strata (ASC^{IMA} vs ASC^{2G} or imatinib vs 2G TKI) could potentially be attributed to differences in demographics between strata.[1]

Managing and monitoring AEs is critical because treatment intolerance has been associated with decreased adherence and subsequent poor response to TKI therapy[20-22,28-30] and may lead to dose modifications, which can negatively affect rates of molecular response milestone achievement and/or maintenance[31-33]; some patients may require early treatment switch.[34-36] In this analysis, AEs leading to dose modification included grade 1/2 gastrointestinal toxicity, rash, and pleural effusion and were more common in patients receiving imatinib or 2G TKIs than in those receiving asciminib within stratum. Additionally, the longer median duration of AEs leading to dose modification with imatinib and 2G TKIs compared with asciminib suggests easier mitigation of these AEs in asciminib-treated patients. Patients had fewer dose reductions due to any reason with asciminib than with imatinib or 2G TKIs; these data may have been influenced by reduction criteria more strictly requiring dose reduction but also limitations in reduction intensity to only 40 mg QD for patients receiving asciminib.

TKIs are associated with unique and overlapping safety profiles.[11,14,37] Some AEs may be more strongly associated with a specific TKI.[11,14,37] Other AEs, including increased lipase, pancreatitis, hypertension, and thrombocytopenia, are of special interest because they may be class effects of TKIs[14,38]; these AEs are also among those most commonly reported with asciminib.[1,3,6] Lipase elevation was experienced at similar rates by patients receiving asciminib (11.5%) and IS-TKIs (11.9%) and infrequently led to dose modification (in 4 patients [2.0%] receiving asciminib and 3 [1.5%] receiving IS-TKIs) and discontinuation (3 patients [1.5%] receiving asciminib and none receiving IS-TKIs). Pancreatitis was notably uncommon (in 2 [1%] and 3 [1.5%] patients receiving asciminib and IS-TKIs, respectively) but often led to modification (in 1 patient each receiving asciminib and IS-TKIs) and discontinuation (in 1 patient each receiving asciminib and imatinib). Hypertension was somewhat more common with asciminib than with IS-TKIs (in 7.0% and 4.0%, respectively) but rarely led to dose modification (in 2 patients receiving asciminib). The study protocol did not provide required guidance on blood pressure recording methodology–values may be subject to differing methodology, inherent intrapatient variability, and the "white coat effect." Thrombocytopenia, although relatively common, was less frequent among asciminib-treated patients and seldom required dose reductions and discontinuations. Established guidelines such as those from the National Comprehensive Cancer Network have special considerations for specific nonhematologic AEs (such as arterial AEs, pleural effusion, and pancreatitis) that may require interventions to improve tolerability; these guidelines include recommendations for dose modifications, supportive care, and switching TKIs.[39] The choice of TKI treatment depends on the unique tolerability profiles of each TKI; in the absence of a comorbidity that could be exacerbated by a

specific TKI, the selection of more tolerable TKI may be more dependent on class effects, complicating the selection of a most tolerable treatment.[11] Regarding AEs constituting TKI class effects, the tolerability profile of asciminib compared favorably with those of IS-TKIs.

An important class effect of ATP-competitive TKIs is the safety concern of AOEs and other cardiovascular events (e.g., arrhythmia and cardiac failure).[37,40,41] The incidence of AOEs was low with both asciminib and IS-TKIs[1]; however, longer-term follow-up is needed because the incidence of these events may continue increasing over time. Importantly, in the phase 3 ASCEMBL trial, exposure-adjusted rates of AOEs decreased with longer follow-up.[3,42] Additionally, arrhythmias (including palpitations, ventricular extrasystoles, atrial fibrillation, atrioventricular block, bradycardia, sinus bradycardia, sinus tachycardia, and long QT syndrome) were experienced by few patients and infrequently led to dose modification or treatment discontinuation. All TKI-treated patients should be appropriately assessed for baseline risk, actively monitored, and managed as clinically indicated.[41,43]

With a majority of patients receiving TKI treatment for multiple years, the optimization of QOL is an important treatment goal.[11] A global survey of 361 patients with CML and 198 physicians in 11 countries documented patients' frequent dissatisfaction with tolerability and other aspects of treatment that impact QoL.[44,45] Historically, tolerability has been difficult to assess and has not been clearly defined for CML.[11,38,46] The Friends of Cancer Research and several other organizations have defined tolerability as "the degree to which symptomatic and non-symptomatic AEs associated with [a medical] product's administration affect the ability or desire of the patient to adhere to the dose or intensity of therapy. A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and

functioning while on treatment."[47-49] In a double-blinded Delphi panel on TKI intolerance in patients with CML-CP (funded by Novartis Pharmaceuticals Corporation), 13 US experts agreed that the degree to which AEs interfere with a patient's daily activities within the past week determines treatment intolerance and the necessity of treatment modification.[50] To provide patient perspectives in addition to physician-based measure of treatment tolerability, a dedicated analysis of patient-reported outcome results from a later timepoint in ASC4FIRST is planned for a future publication.

To complement the primary publication from ASC4FIRST with an assessment of treatment tolerability beyond safety analyses, the type, number, duration, and onset of AEs leading to dose modifications and treatment discontinuations were analyzed. The results of these analyses demonstrate a favorable tolerability profile for asciminib compared with ATP-competitive TKIs—imatinib and 2G TKIs—in newly diagnosed patients within the respective patient strata that differed in age and comorbidities**.** The safety and tolerability of asciminib observed in the ASC4FIRST trial to date, together with rapid and deep molecular responses reported from previous analyses, demonstrate asciminib's excellent benefit-risk profile as a frontline therapy for a broad range of patients with newly diagnosed CML-CP.

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FIGURE LEGENDS

Figure 1. Grade 1/2 and grade ≥3 nonhematologic AEs in ≥10% of patients in any group[a,b]. (a) Nonhematologic AEs by grade in the imatinib stratum. (b) Nonhematologic AEs by grade in the 2G TKI stratum.

2G, second generation; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; IMA, imatinib; TKI, tyrosine kinase inhibitor; URTI, upper respiratory tract infection.

[a] Rates of COVID-19 and URTI are not shown.

[b] Patients experiencing an AE of varying severity may be counted under both grade 1/2 and grade ≥3.

Figure 2. Time to first nonhematologic AE within the imatinib and 2G TKI strata. (a) Time to first nonhematologic AE within the imatinib stratum. (b) Time to first nonhematologic AE within the 2G TKI stratum.2G, second generation; AE, adverse event; ELTS; EUTOS long-term safety; EUTOS, European Treatment and Outcome Study; KM, Kaplan-Meier; TKI, tyrosine kinase inhibitor.

[a] Median (time to event) and its 95% CI are generated by KM estimation.

[b] Hazard ratio estimated by Cox proportional hazards model and 2-sided p-value based on a log-rank test (adjusted for ELTS score from randomization data).

Figure 3. Median duration of dose reductions and interruptions due to any reason. (a) Median duration of dose reductions and interruptions due to any reason the imatinib stratum. (b) Median duration of dose reductions and interruptions due to any reason in the 2G TKI stratum.

2G, second generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.

Figure 4. Proportion of patients with grade 1/2 and grade ≥3 nonhematologic AEs leading to dose adjustment and/or interruption. (a) Proportion of patients with nonhematologic AEs leading to dose adjustment and/or interruption by grade the imatinib stratum. (b) Proportion of patients with nonhematologic AEs leading to dose adjustment and/or interruption by grade in the 2G TKI stratum.

2G, second generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.

[a] AEs occurring during treatment or within 30 days of the last study medication are summarized.

[b] A patient with multiple severity grades for an AE was counted separately.

Figure 5. Grade 1/2 and grade ≥3 nonhematologic AEs leading to dose adjustment and/or interruption in ≥2% of patients in any group. (a) Nonhematologic AEs leading to dose adjustment and/or interruption by grade in the imatinib stratum. (b) Nonhematologic AEs leading to dose adjustment and/or interruption by grade in the 2G TKI stratum.

2G, second generation; AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, γ-glutamyl transferase; IMA, imatinib; TKI, tyrosine kinase inhibitor.

[a] AEs occurring during treatment or within 30 days of the last study medication are summarized.

[b] Patients experiencing an AE of varying severity may be counted under both grade 1/2 and grade ≥3.

[c] COVID-19 is not shown.

Figure 6. Time to first grade 1/2 nonhematologic AEs leading to dose adjustment and/or interruption. (a) Time to first grade 1/2 nonhematologic AEs leading to dose adjustment and/or interruption in the imatinib stratum. (b) Time to first grade 1/2 nonhematologic AEs leading to dose adjustment and/or interruption in the 2G TKI stratum.2G, second generation; AE, adverse event; ASC, asciminib; ELTS, EUTOS long-term safety; EUTOS, European Treatment and Outcome Study; KM, Kaplan-Meier; IMA, imatinib; NE, not estimable; TKI, tyrosine kinase inhibitor.

[a] Median (time to event) and its 95% CI are generated by KM estimation.

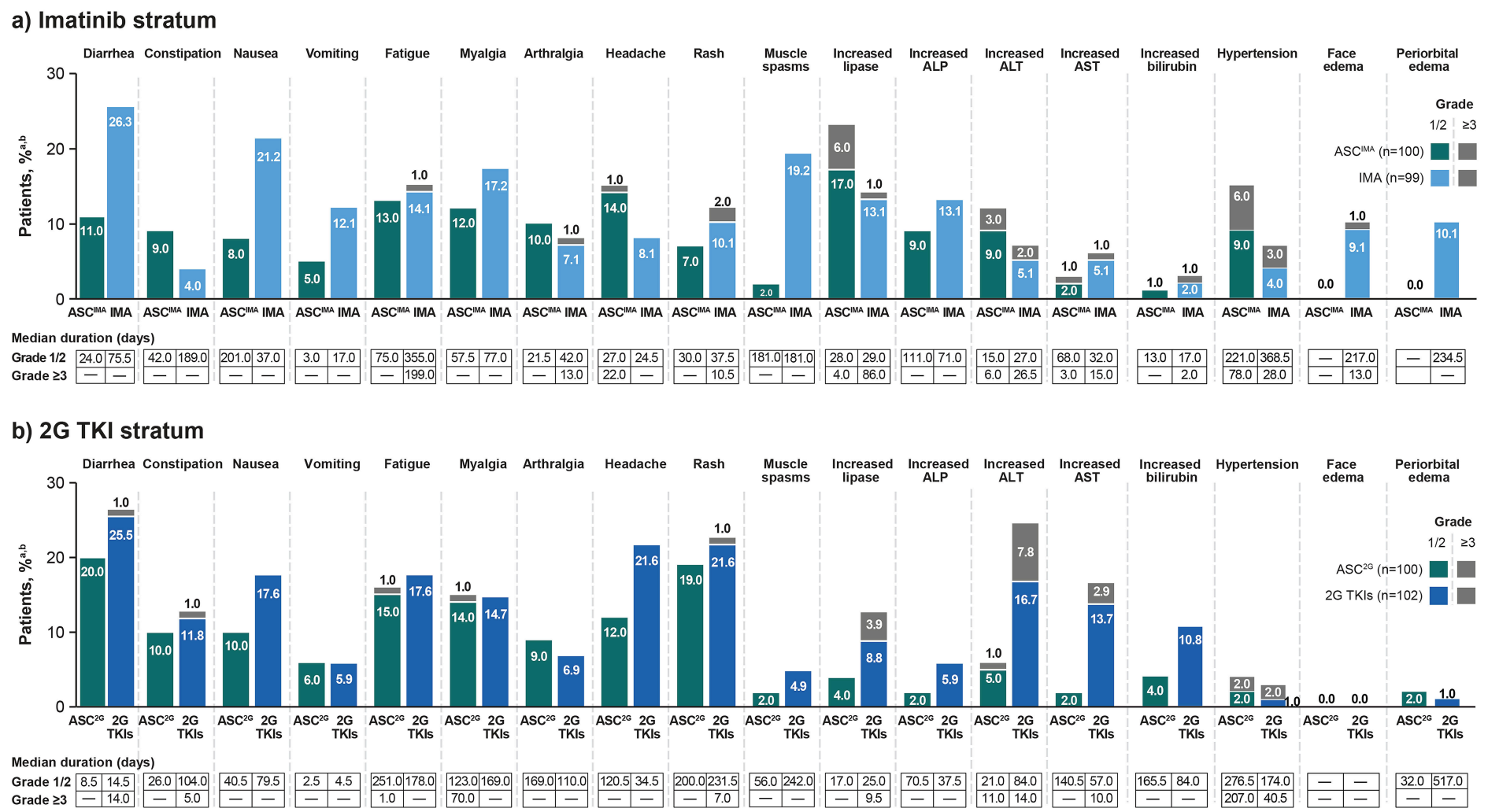
[b] Hazard ratio estimated by Cox proportional hazards model and 2-sided p-value based on a log-rank test (adjusted for ELTS score from randomization data).

Figure 7. Proportion of patients with grade 1/2 and grade ≥3 nonhematologic AEs leading to discontinuation. (a) Proportion of patients with nonhematologic AEs leading to discontinuation by grade in the imatinib stratum. (b) Proportion of patients with nonhematologic AEs leading to discontinuation by grade in the 2G TKI stratum.

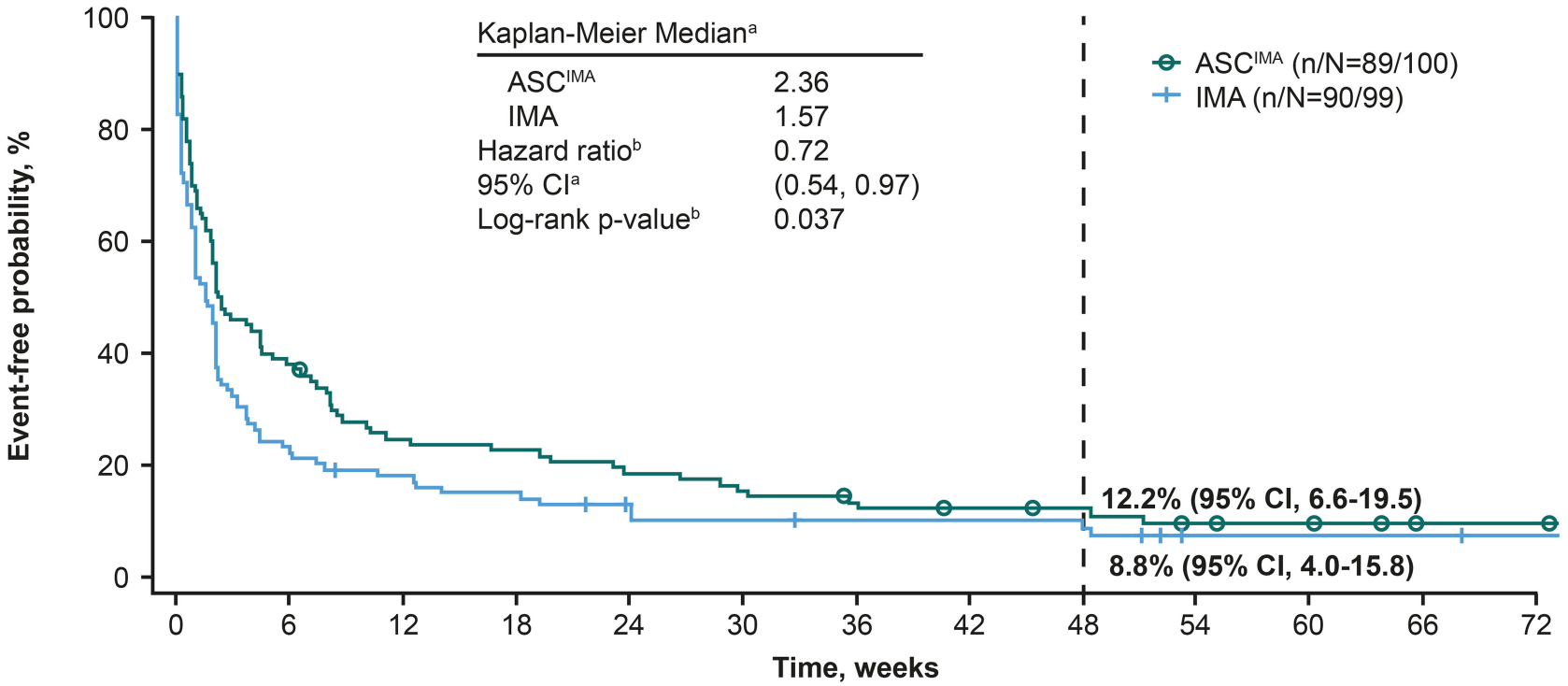
2G, second generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.

[a] AEs occurring during treatment or within 30 days of the last study medication are summarized.

[b] A patient with multiple severity grades for an AE is counted only under the maximum grade/severity.


a) Imatinib stratum
Diarrhea
Constipation
Nausea
Vomiting
Fatigue
Myalgia
Arthralgia
Headache
Rash
Muscle spasms
Increased lipase
Increased ALP
Increased ALT
Increased AST
Increased bilirubin
Hypertension
Face edema
Periorbital edema
Patients, %a,b
Grade
1/2
≥3
ASCIMA (n=100)
IMA (n=99)
ASCIMA IMA
Median duration (days)
Grade 1/2
24.0 75.5
42.0 189.0
201.0 37.0
3.0 17.0
75.0 355.0
57.5 77.0
21.5 42.0
27.0 24.5
30.0 37.5
181.0 181.0
28.0 29.0
111.0 71.0
15.0 27.0
68.0 32.0
13.0 17.0
221.0 368.5
— 217.0
— 234.5
Grade ≥3
— —
— —
— —
— —
— 199.0
— —
— 13.0
22.0 —
— 10.5
— —
4.0 86.0
— —
6.0 26.5
3.0 15.0
— 2.0
78.0 28.0
— 13.0
b) 2G TKI stratum
Diarrhea
Constipation
Nausea
Vomiting
Fatigue
Myalgia
Arthralgia
Headache
Rash
Muscle spasms
Increased lipase
Increased ALP
Increased ALT
Increased AST
Increased bilirubin
Hypertension
Face edema
Periorbital edema
Patients, %a,b
Grade
1/2
≥3
ASC2G (n=100)
2G TKIs (n=102)
ASC2G 2G TKIs
Median duration (days)
Grade 1/2
8.5 14.5
26.0 104.0
40.5 79.5
2.5 4.5
251.0 178.0
123.0 169.0
169.0 110.0
120.5 34.5
200.0 231.5
56.0 242.0
17.0 25.0
70.5 37.5
21.0 84.0
140.5 57.0
165.5 84.0
276.5 174.0
— —
32.0 517.0
Grade ≥3
— 14.0
— 5.0
— —
— —
1.0 —
70.0 —
— —
— —
— 7.0
— —
— 9.5
— —
11.0 14.0
— 10.0
— —
207.0 40.5
— —
— —

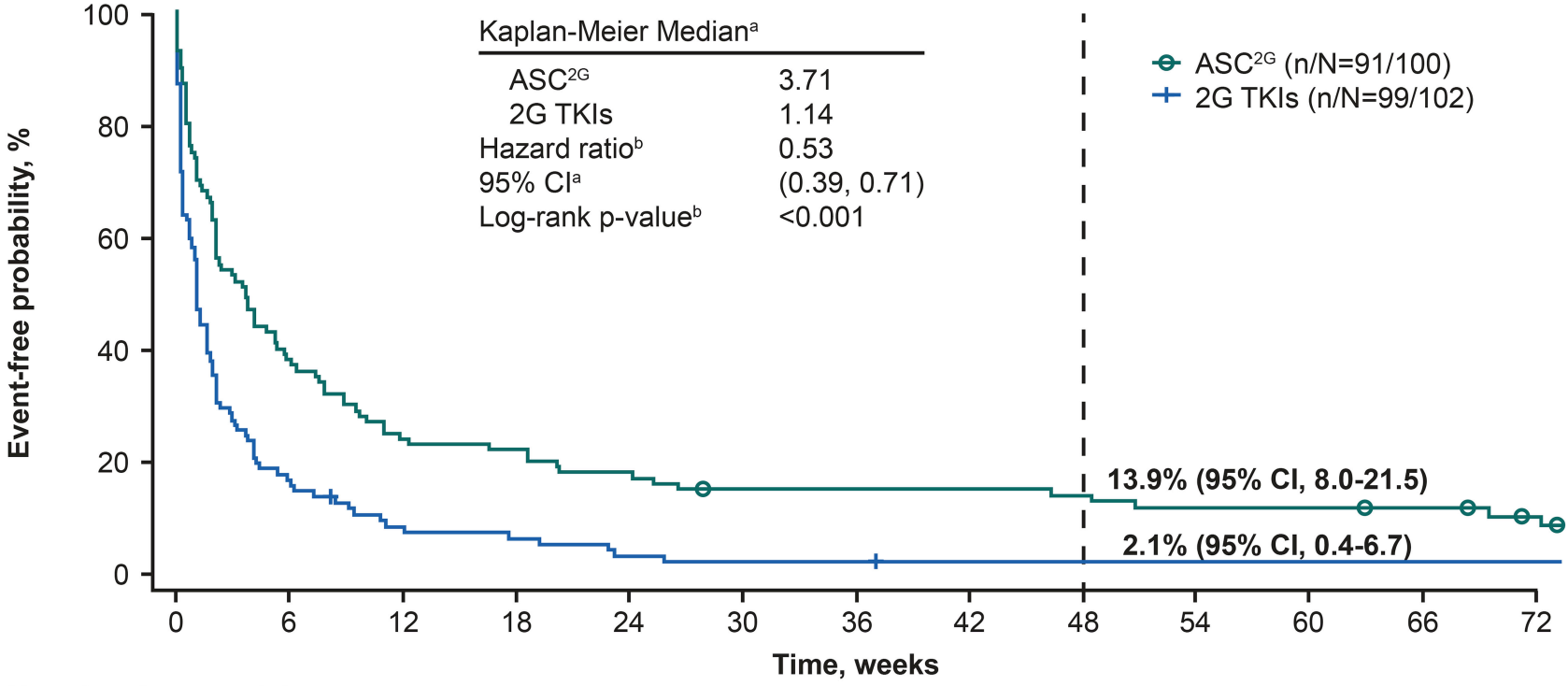
a) Time to first nonhematologic AE within the imatinib stratum



No. of patients at risk

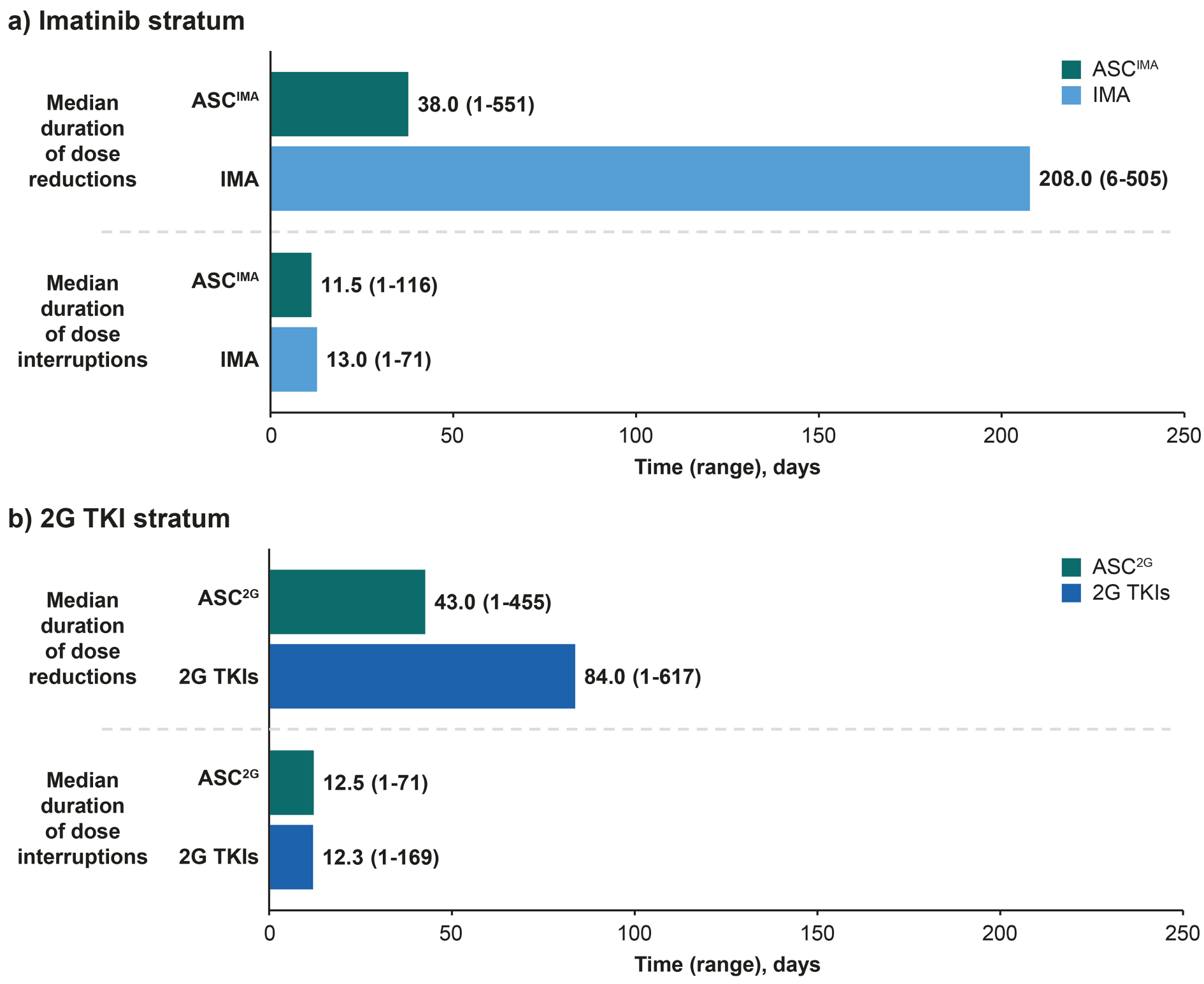
ASC[IMA]	100	38	24	22	18	15	12	10	9	6	5	2	2
IMA	99	22	17	14	10	8	7	7	6	2	2	2	1

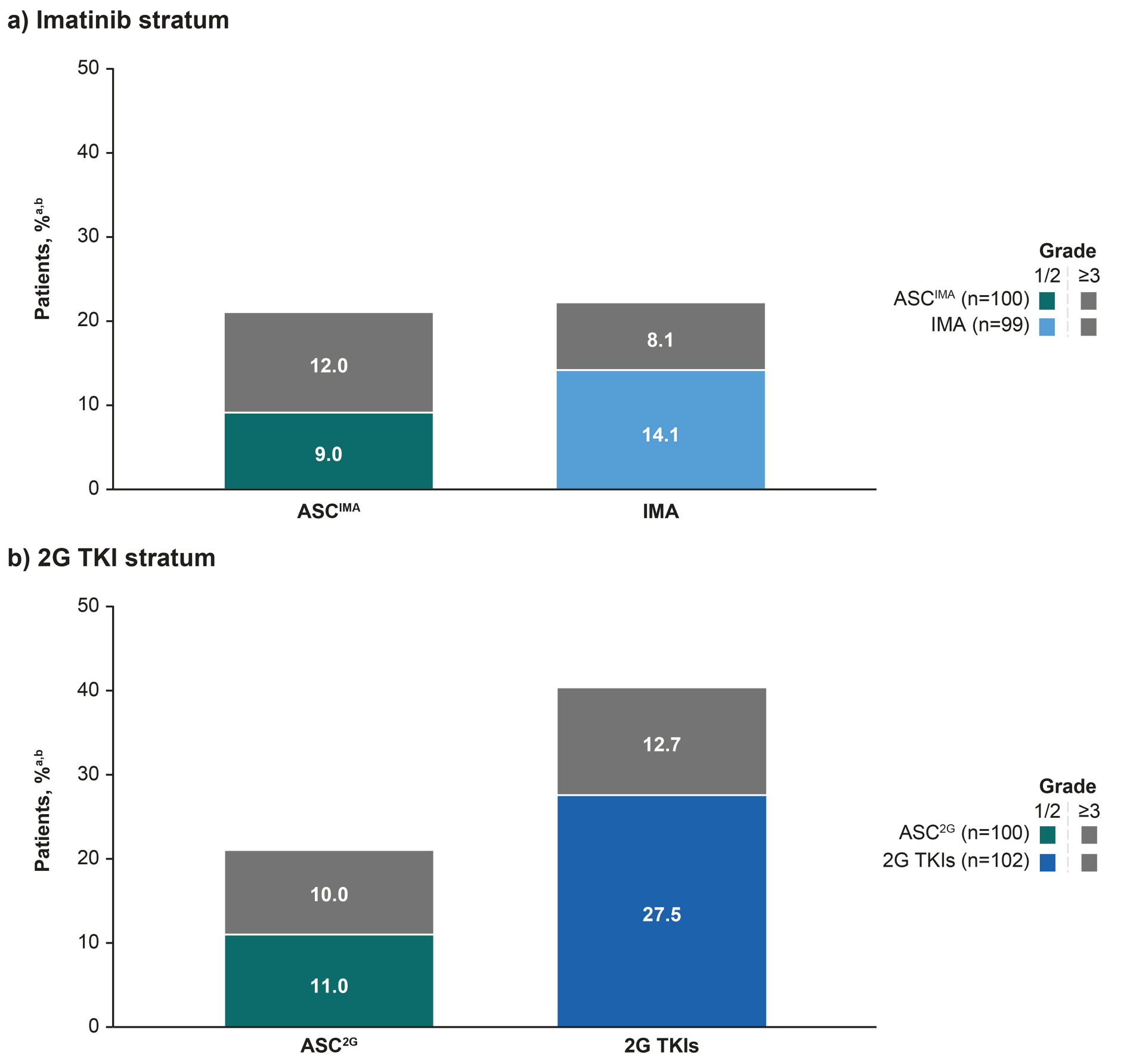
b) Time to first nonhematologic AE within the 2G TKI stratum

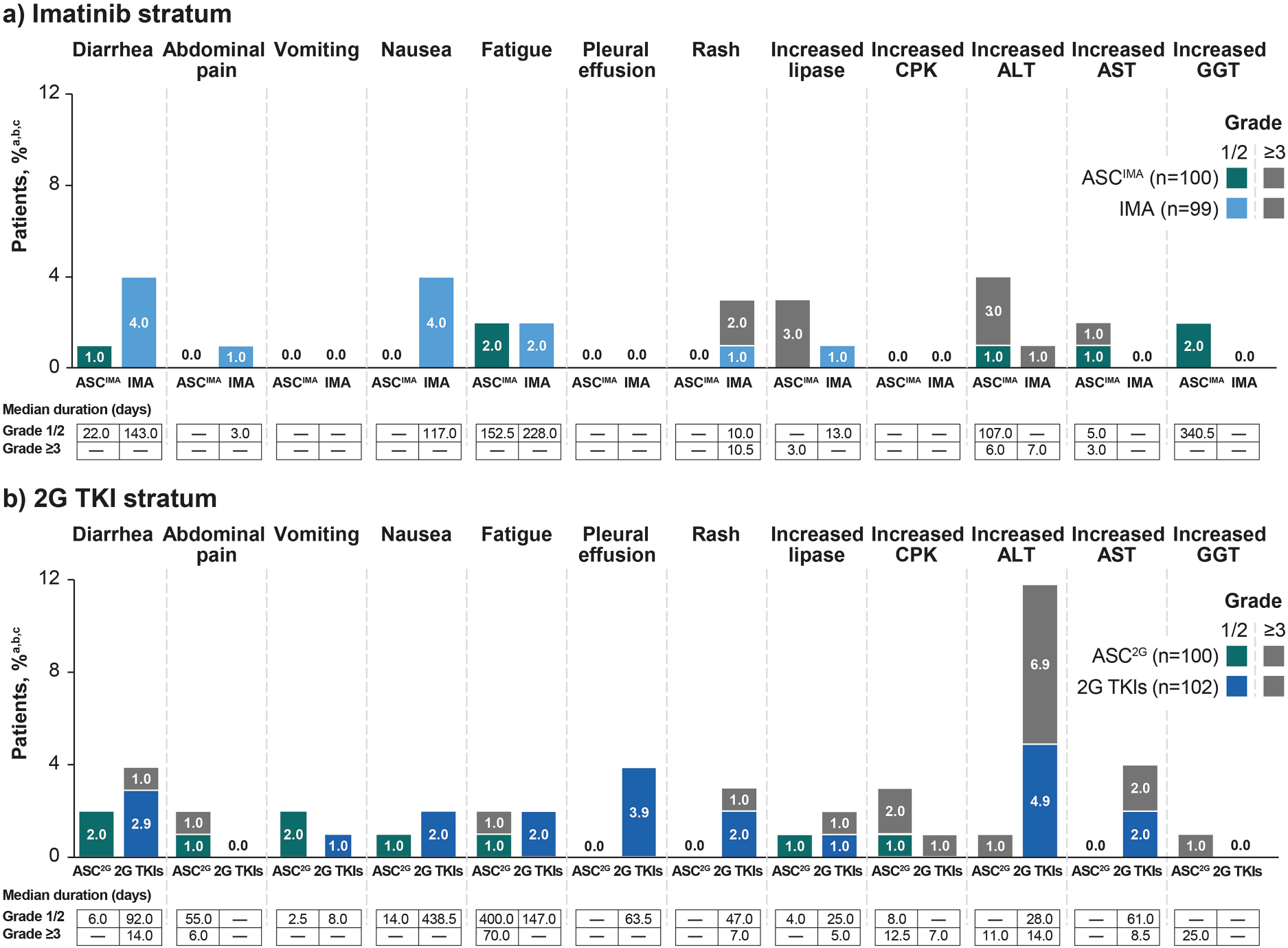


No. of patients at risk

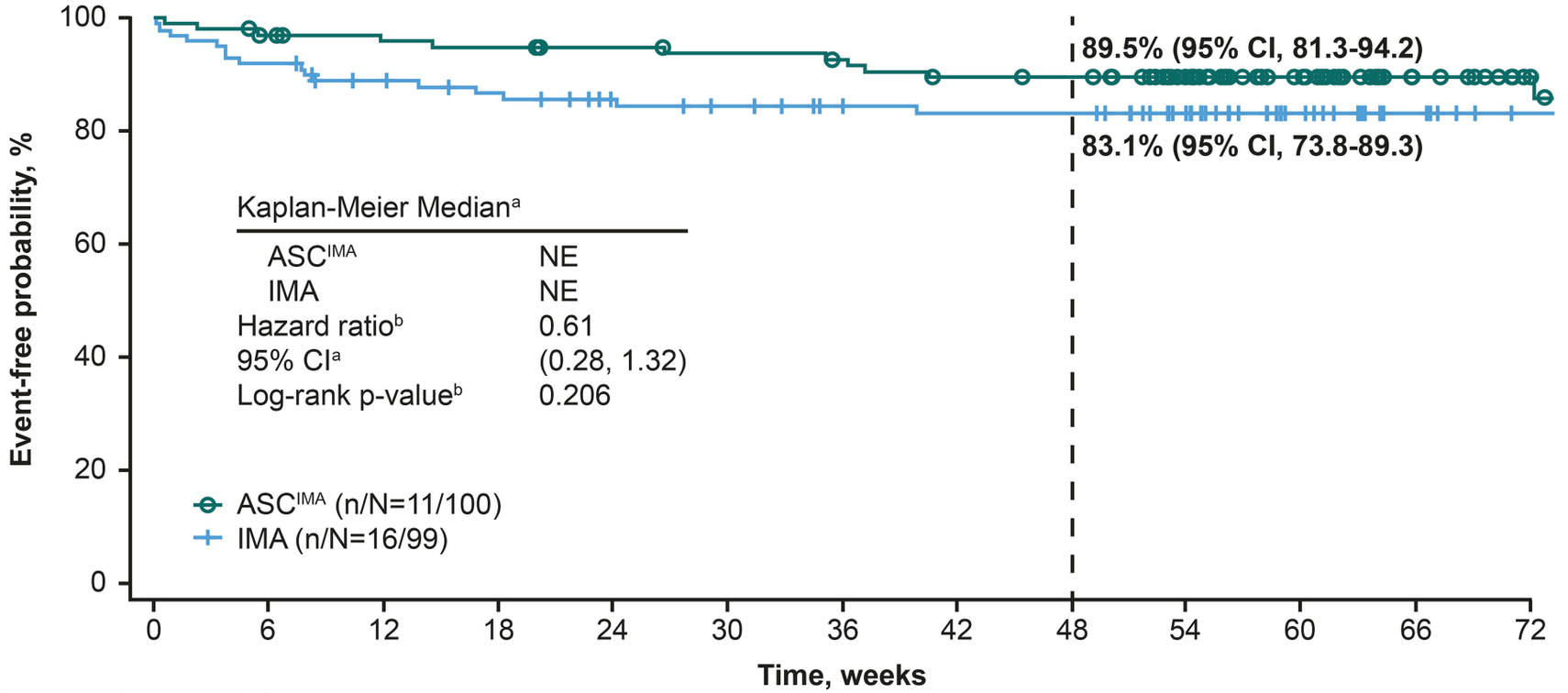
ASC[2G]	100	38	24	22	18	14	14	14	13	11	11	10	6
2G TKIs	102	17	8	6	3	2	2	1	1	1	1	1	1


a) Imatinib stratum
Median duration of dose reductions
ASCIMA
IMA
38.0 (1-551)
208.0 (6-505)
Median duration of dose interruptions
ASCIMA
IMA
11.5 (1-116)
13.0 (1-71)
0
50
100
150
200
250
Time (range), days
b) 2G TKI stratum
Median duration of dose reductions
ASC2G
2G TKIs
43.0 (1-455)
84.0 (1-617)
Median duration of dose interruptions
ASC2G
2G TKIs
12.5 (1-71)
12.3 (1-169)
0
50
100
150
200
250
Time (range), days


a) Imatinib stratum
Patients, %a,b
50
40
30
20
10
0
12.0
9.0
8.1
14.1
ASCIMA
IMA
Grade
1/2
≥3
ASCIMA (n=100)
IMA (n=99)
b) 2G TKI stratum
Patients, %a,b
50
40
30
20
10
0
10.0
11.0
12.7
27.5
ASC2G
2G TKIs
Grade
1/2
≥3
ASC2G (n=100)
2G TKIs (n=102)


a) Imatinib stratum
Diarrhea
Abdominal pain
Vomiting
Nausea
Fatigue
Pleural effusion
Rash
Increased lipase
Increased CPK
Increased ALT
Increased AST
Increased GGT
Patients, %a,b,c
12
8
4
0
Grade
1/2
≥3
ASCIMA (n=100)
IMA (n=99)
1.0 4.0
0.0 1.0
0.0 0.0
0.0 4.0
2.0 2.0
0.0 0.0
0.0 2.0 1.0
3.0 1.0
0.0 0.0
3.0 1.0 1.0
1.0 1.0 0.0
2.0 0.0
ASCIMA IMA
Median duration (days)
Grade 1/2
Grade ≥3
22.0 143.0
— —
— 3.0
— —
— —
— —
— 117.0
— —
152.5 228.0
— —
— —
— —
— 10.0
— 10.5
— 13.0
3.0 —
— —
— —
107.0 —
6.0 7.0
5.0 —
3.0 —
340.5 —
— —
b) 2G TKI stratum
Diarrhea
Abdominal pain
Vomiting
Nausea
Fatigue
Pleural effusion
Rash
Increased lipase
Increased CPK
Increased ALT
Increased AST
Increased GGT
Patients, %a,b,c
12
8
4
0
Grade
1/2
≥3
ASC2G (n=100)
2G TKIs (n=102)
2.0 1.0 2.9
1.0 1.0 0.0
2.0 1.0
1.0 2.0
1.0 1.0 2.0
0.0 3.9
0.0 1.0 2.0
1.0 1.0
2.0 1.0 1.0
1.0 6.9 4.9
0.0 2.0 2.0
1.0 0.0
ASC2G 2G TKIs
Median duration (days)
Grade 1/2
Grade ≥3
6.0 92.0
— 14.0
55.0 —
6.0 —
2.5 8.0
— —
14.0 438.5
— —
400.0 147.0
70.0 —
— 63.5
— —
— 47.0
— 7.0
4.0 25.0
— 5.0
8.0 —
12.5 7.0
— 28.0
11.0 14.0
— 61.0
— 8.5
— —
25.0 —

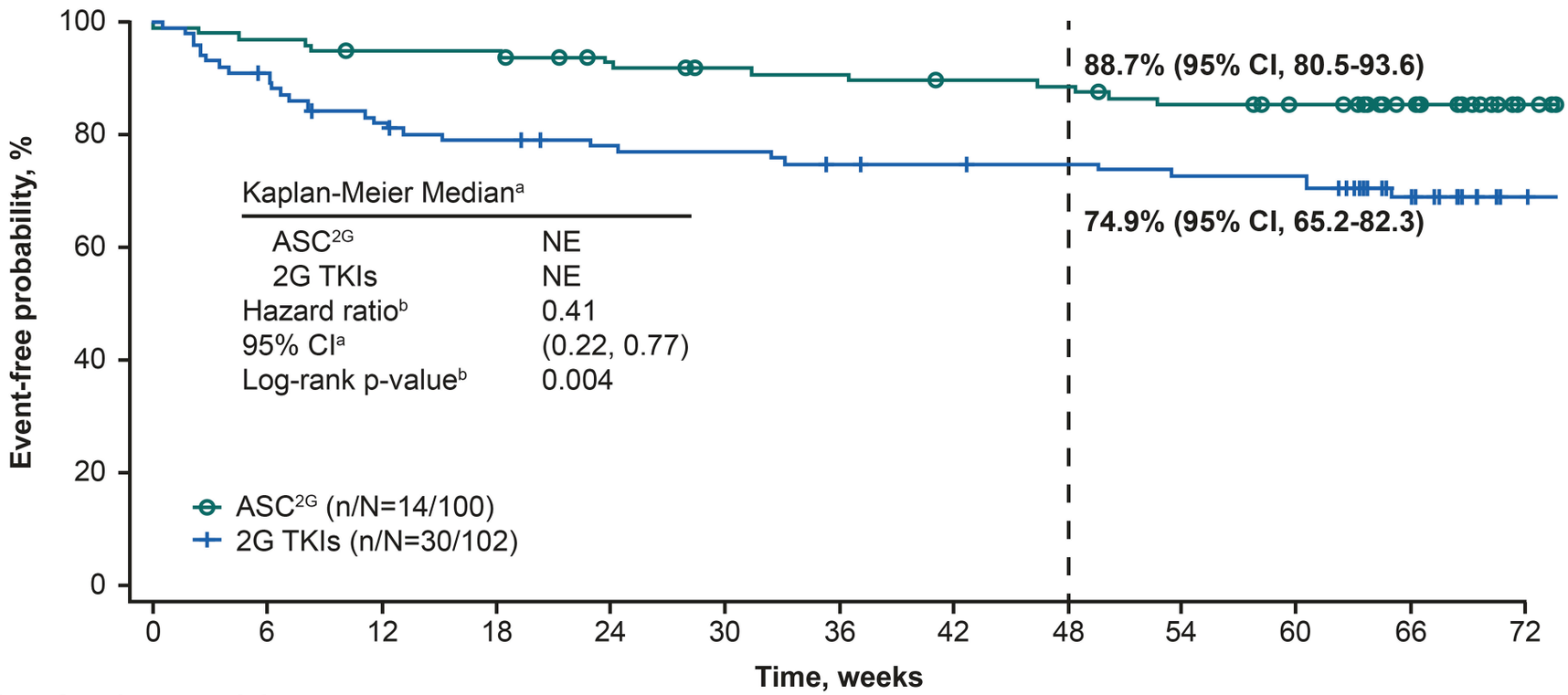
a) Time to first grade 1/2 nonhematologic AEs leading to dose adjustment and/or interruption within the imatinib stratum



No. of patients at risk

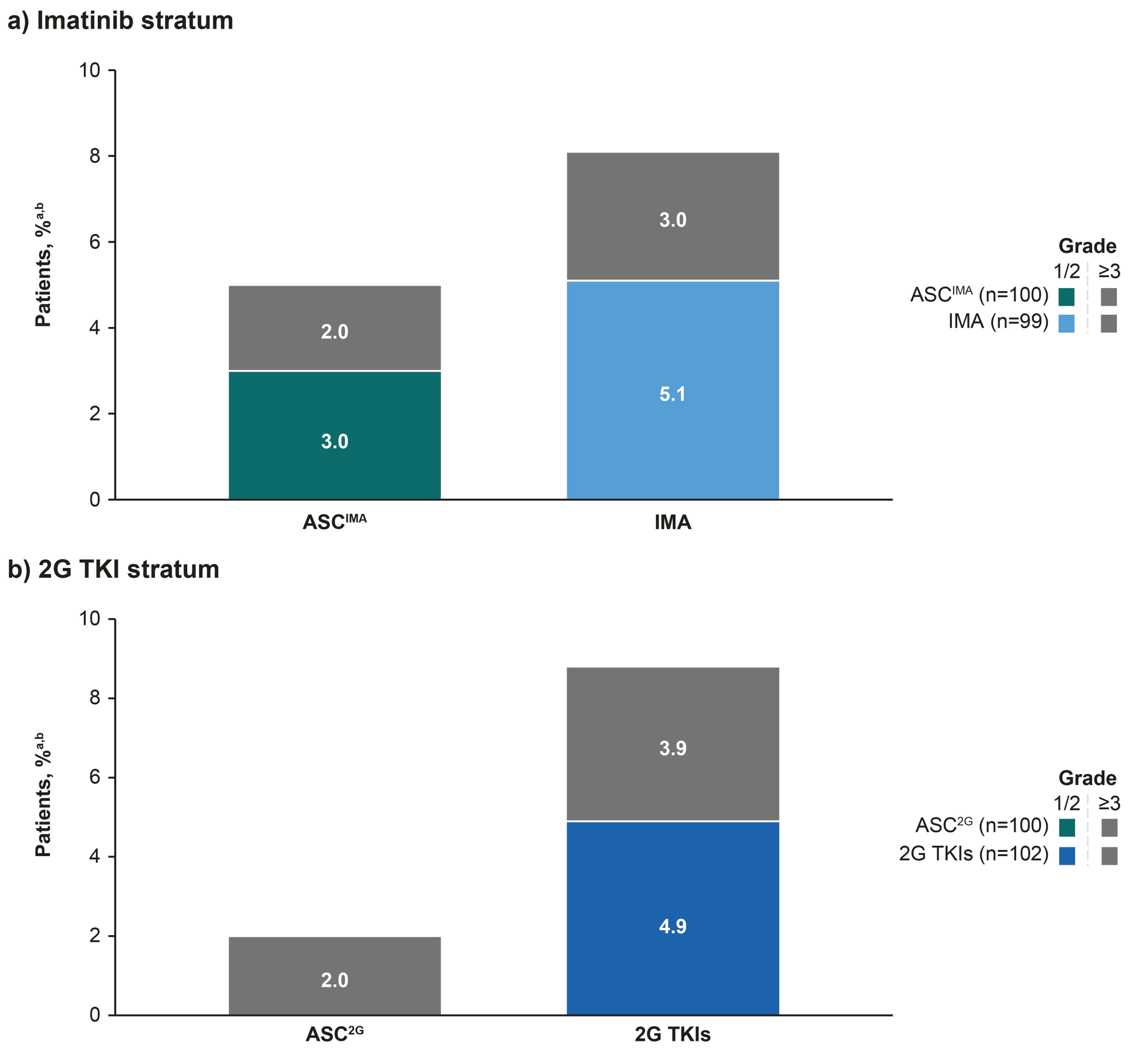
ASC[IMA]	100	95	92	91	89	87	85	81	80	68	53	35	26
IMA	99	91	84	80	72	69	63	62	62	52	35	26	19

b) Time to first grade 1/2 nonhematologic AEs leading to dose adjustment and/or interruption within the 2G TKI stratum



No. of patients at risk

ASC[2G]	100	97	94	94	88	86	85	83	82	78	75	63	48
2G TKIs	102	92	81	77	74	73	70	69	68	66	66	50	38


a) Imatinib stratum
Patients, %a,b
10
8
6
4
2
0
2.0
3.0
3.0
5.1
ASCIMA
IMA
Grade
1/2
≥3
ASCIMA (n=100)
IMA (n=99)
b) 2G TKI stratum
Patients, %a,b
10
8
6
4
2
0
3.9
2.0
4.9
ASC2G
2G TKIs
Grade
1/2
≥3
ASC2G (n=100)
2G TKIs (n=102)

Supplemental Appendix

Supplemental methods

Study design

Of the patients in the prerandomization-selected imatinib stratum, approximately half were randomized to receive asciminib (ASC^{IMA}) or the tyrosine kinase inhibitor (TKI) imatinib selected by investigator (IMA). Of the patients in the prerandomization-selected second-generation (2G) TKI stratum, approximately half were randomized to receive asciminib (ASC^{2G}) or 2G TKIs selected by investigator (2G).[1]

Dosing In the ASC4FIRST Trial

Patients receiving asciminib were not permitted to receive asciminib >80 mg QD.[1] Dose escalation was allowed for imatinib, dasatinib, and bosutinib in patients who did not experience grade 3 toxicity and met the criteria for suboptimal response per European LeukemiaNet 2020 recommendations.[2]

Patients receiving imatinib were allowed dose escalations from a starting dose of 400 mg once daily (QD) to 600 mg QD; for dasatinib, 100 mg QD to 140 mg QD; for bosutinib, ≤2 sequential dose escalations were allowed in increments of 100 mg QD from a starting dose of 400 mg QD to a maximum dose of 600 mg QD; for nilotinib, dose escalation beyond 300 mg twice daily (BID) was not permitted. For patients with hepatic and renal impairment, dose recommendations on local labels were followed.[1]

Dose reductions designated as recommendations were provided to assist investigators in case a patient experienced toxicity with asciminib; however, strict adherence was required for

dose interruptions and/or reductions designated as mandatory. Dose reduction was indicated based on the presence and severity of adverse events (AEs). Dose reduction to 40 mg QD was permitted from a starting dose of 80 mg QD (<40 mg total daily was not allowed).[1] Briefly, the protocol required dose modifications and/or treatment discontinuation for grade ≥3 AEs, with requirements for specific AEs.[1] Originally, re-escalation to asciminib 80 mg QD was allowed only once per patient if the patient's risk-benefit assessment changed at the lower dose level; following a protocol amendment on May 15, 2023, patients were allowed more than one re-escalation in the case the event was considered to be significantly different than the one(s) experienced previously. After study treatment was resumed at a lower dose level, if the toxicity recurred with the same or worse severity (except in the case of recurring cytopenias), asciminib was discontinued. For a nonhematologic toxicity, study treatment was discontinued if a dose interruption lasted >28 days; for a hematologic toxicity (grade 3/4 cytopenias), study treatment was discontinued if a dose interruption lasted >42 days without recovery to grade ≤2.[1]

Dose modifications for IS-TKIs were done per institutional practice and local labels at the investigator's discretion. No protocol-specified dose adjustments or interruptions occurred. Patients who required dose interruption for >28 days due to a nonhematologic toxicity were discontinued from the study. If a hematologic toxicity (grade 3/4 cytopenias) lasted for >42 days without recovery to grade ≤2 despite study treatment interruption and adequate management (including hematopoietic growth factors), the patient was discontinued from the study.[1]

Study treatment could be permanently stopped for any reason by the patient or the investigator. The investigator was required to discontinue study treatment for the patient if the investigator believed continuation would negatively impact the patient's well-being.[1]

Supplemental Tables

Supplemental Table S1. Criteria for dose reductions/interruption and re-initiation of asciminib treatment for AEs.[a,b]

	Worst toxicity (grade per CTCAE version 5.0)	**Recommended and mandatory dose modification or discontinuation**
Investigations (hematologic[c])	**Neutropenia (ANC)**	
	Grade 3 (ANC <1.0 to 0.5×10^9/L) Grade 4 (ANC <0.5×10^9/L)	**Mandatory:** Omit dose until grade ≤2. If resolved in ≤14 days, maintain dose level. If resolved in >14 days, reduce by 1 dose level.
	Febrile neutropenia (ANC < 1.0×10^9/L, fever ≥38.5°C)	**Mandatory:** Omit dose until resolved, then reduce by 1 dose level.
	Thrombocytopenia	
	Grade 3 (PLT <50 to 25×10^9/L) Grade 4 (PLT <25×10^9/L)	**Mandatory:** Omit dose until grade ≤2. If resolved in ≤14 days, maintain dose level. If resolved in >14 days, reduce by 1 dose level.
	Recurrence of all cytopenias	**Recommended:** Omit dose until resolved to grade ≤2, then maintain current dose level.
	Grade 2	**Recommended:** Omit dose until resolved to grade ≤1, then maintain dose level.
	Grade 3	**Mandatory:** Omit dose until grade ≤1, then reduce by 1 dose level.
	Grade 4	**Mandatory:** Permanently discontinue.
Investigations (renal)	**Serum creatinine**	
	Grade 2 (>1.5× to 3.0× baseline; >1.5× to 3.0× ULN)	**Recommended:** Omit dose until resolved to ≤1.5×ULN or baseline, then maintain dose level.
	Grade 3 (>3.0× baseline; >3.0 to 6.0× ULN)	Permanently discontinue

	Grade 4 (>6.0× ULN)	
Investigations (hepatic)	**Isolated TBL elevation**	
	Grade 2 (>1.5 to 3.0× ULN [normal or abnormal baseline])	**Recommended:** Omit dose until resolved to ≤1.5× ULN or baseline. If resolved in ≥14 days, maintain dose level. If resolved in >14 days, then reduce by 1 dose level.
	Grade 3 (>3.0-10.0xULN [normal baseline]; >3.0-10.0x baseline [abnormal baseline[c]])	**Mandatory:** Omit dose. If resolved to ≤1.5× ULN or baseline in ≤14 days, then reduce by 1 dose level. If resolved in >14 days, discontinue.
	Grade 4 (>10.0× ULN [normal baseline]; >10.0× baseline [abnormal baseline[d]])	**Mandatory:** Permanently discontinue.
	Isolated AST or ALT elevation	
	>5.0× to 10.0× ULN (normal baseline); >5.0× to 10.0× baseline (abnormal baseline)	**Mandatory:** Omit dose until resolved to ≤3.0× ULN if baseline was normal or to 1.5× to 3.0× baseline if baseline was abnormal. If resolved in ≤14 days, maintain dose level. If resolved in >14 days, reduce by 1 dose level.
	>10.0× to 20.0× ULN (normal baseline); >10.0× to 20.0× baseline (abnormal baseline)	**Mandatory:** Omit dose until resolved to ≤3.0× ULN if baseline was normal or to 1.5× to 3.0× baseline if baseline was abnormal. Then reduce by 1 dose level.
	Grade 4 (>20.0× ULN [normal baseline]; >20.0× baseline [abnormal baseline])	**Mandatory:** Omit dose. Once resolved to ≤3× ULN (or ≤5× ULN in patients with baseline value >3.0× to 5.0× ULN), resume treatment at the next lowest dose level. Only 1 dose reduction is allowed; if reoccurs at >5× ULN, discontinue.
	Combined[e] elevations of AST or ALT and TBL	
	For patients with normal baseline ALT and AST and TBL value: AST or ALT >3.0× ULN combined with TBL >2.0× ULN without evidence of cholestasis[f]	**Mandatory:** Interrupt treatment. If causality assessment indicates DILI is probable, permanently discontinue. If not DILI, once resolved, reduce by 1 dose level if treatment related.

	For patients with elevated baseline AST or ALT or TBL value AST or ALT >3× baseline OR [>8.0× ULN], whichever is lower, combined with TBL >2× baseline AND >2.0× ULN[g]	
Investigation (metabolic)	**Asymptomatic amylase and/or lipase elevation**	
	Grade 3 (>5.0× ULN)	**Mandatory:** Omit dose until resolved to ≤1.5× ULN or baseline. If resolved in <7 days, reduce dose. If resolved in >7 days, discontinue treatment.
	Grade 4 (>5.0× ULN with signs/symptoms)	**Mandatory:** Permanently discontinue.
Vascular disorders	**Hypertension**	
	Grade 3 (systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg)	**Mandatory:** Omit dose until resolved grade ≤1 or baseline, then reduce by 1 dose level.
	Grade 4 (life-threatening consequences)	**Mandatory:** Permanently discontinue.
Gastrointestinal	**Pancreatitis**	
	Grade 2 (enzyme elevations with radiologic findings)	**Mandatory:** If radiologic findings, hold treatment until resolved to grade ≤1 or baseline. If treatment delay is ≤21 days, then reduce by 1 dose level. If treatment delay >21 days, discontinue treatment.[h]
	Grade ≥3	**Mandatory:** Permanently discontinue.
	Diarrhea	
	Grade 2	**Recommended:** Omit dose until resolved to grade ≥1, then maintain dose level. If returns as grade ≥2, omit dose until resolved to grade ≥1, then reduce by 1 dose level.
	Grade 3	**Recommended:** Omit dose and discontinue.
	Grade 4	**Mandatory:** Permanently discontinue.

	Nausea/vomiting	
	Grade 2	**Recommended:** Omit dose until resolved to grade ≤1, then maintain dose level. If returns as grade ≥2, omit dose until resolved to grade ≤1, then reduce by 1 dose level.
	Grade 3	**Mandatory:** Omit dose until resolved to grade ≤1, then reduce by 1 dose level.
	Grade 4	**Mandatory:** Permanently discontinue.
Skin and subcutaneous tissue disorders	**Rash/photosensitivity**	
	Grade 3 despite skin toxicity therapy	**Recommended:** Omit dose until resolved to grade ≤1. If resolved in ≤7 days, then reduce by 1 dose level. If resolved in >7 days, then discontinue.
	Grade 4 despite skin toxicity therapy	**Mandatory:** Permanently discontinue.

AE, adverse event; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BP, blood pressure; CT, computed tomography; CTCAE, Common Toxicity Criteria for Adverse Events; DILI; drug-induced liver injury; L, liter; mm, millimeter; PLT, platelet; TBL, total bilirubin; ULN, upper limit of normal.

[a] All dose modifications should be based on the worst preceding toxicity.

[b] A patient requiring a dose interruption of >28 days for a nonhematologic toxicity must be discontinued from study treatment.

[c] A patient with a hematologic toxicity (cytopenia grade 3 or 4) lasting for >42 days without recovery to grade ≤2, with study treatment interruption and adequate management (including hematopoietic growth factors), must be discontinued from study treatment.

[d] If TBL >3.0× ULN is due to the indirect (nonconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduce by 1 dose level and continue treatment at the investigator's discretion.

[e] "Combined" is defined as TBL increase to the defined threshold concurrently with ALT/AST increase to the defined threshold.

[f] "Cholestasis" is defined as ALP elevation (>2.0× ULN and R value <2) in patients without bone metastasis or elevation of ALP liver fraction in patients with bone metastasis.

[g] For patients with Gilbert syndrome, ≥2-fold increase in direct bilirubin.

[h] A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any grade ≥3 of amylase and/or lipase. If asymptomatic grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued from study treatment.

Table S2. All-grade nonhematologic AEs in ≥2 patients in any group with highlighted frequencies differing by ≥5% or duration ≥2 times longer between treatment groups within stratum[a]

	Imatinib stratum				2G TKI stratum			
	ASC^{IMA} (n=100)		IMA (n=99)		ASC^{2G} (n=100)		2G TKIs (n=102)	
	%[b]	Median duration (days)[c]	%[b]	Median duration (days)[c]	%[b]	Median duration (days)[c]	%[b]	Median duration (days)[c]
Diarrhea	11.0	24.0	26.3	75.5	20.0	8.5	25.5	14.5
Rash	7.0	30.0	10.1	41.5	19.0	200.0	21.6	235.0
Lipase increased	19.0	28.0	14.1	30.0	4.0	17.0	9.8	21.5
Headache	15.0	25.0	8.1	24.5	12.0	120.5	21.6	34.5
Fatigue	13.0	75.0	14.1	360.0	15.0	251.0	17.6	178.0
Myalgia	12.0	57.5	17.2	77.0	14.0	123.0	14.7	169.0
Nausea	8.0	201.0	21.2	37.0	10.0	40.5	17.6	79.5
Constipation	9.0	42.0	4.0	189.0	10.0	26.0	12.7	85.0
Arthralgia	10.0	21.5	8.1	42.0	9.0	169.0	6.9	110.0
Hypertension	10.0	232.0	6.1	343.0	4.0	213.5	2.0	127.5
ALT increased	9.0	15.0	6.1	28.5	5.0	21.0	18.6	56.0
Blood alkaline phosphatase increased	9.0	111.0	13.1	71.0	2.0	70.5	5.9	37.5
Abdominal pain	8.0	28.0	3.0	3.0	9.0	22.0	8.8	34.0

Amylase increased	9.0	37.0	4.0	71.5	1.0	316.0	4.9	167.0
URTI	8.0	6.5	10.1	9.5	6.0	13.0	7.8	12.0
Cough	3.0	24.0	6.1	92.0	8.0	29.5	9.8	28.0
Nasopharyngitis	8.0	11.0	6.1	6.5	4.0	7.0	4.9	13.0
Pyrexia	3.0	4.0	6.1	3.5	8.0	2.5	2.9	5.0
Dry eye	3.0	378.0	4.0	179.0	8.0	212.0	3.9	123.5
Gamma-glutamyltransferase increased	6.0	91.5	4.0	120.0	7.0	92.0	8.8	237.0
Abdominal pain upper	1.0	23.0	4.0	279.5	7.0	15.0	2.9	51.0
Pruritus	7.0	147.0	4.0	33.5	6.0	84.5	2.9	432.0
Vomiting	5.0	3.0	12.1	17.0	6.0	2.5	5.9	4.5
Dry skin	6.0	119.0	0	0	6.0	441.0	6.9	252.0
Hyperuricemia	3.0	119.0	3.0	91.0	6.0	34.5	4.9	170.0
Back pain	5.0	346.0	9.1	36.0	5.0	28.0	8.8	148.0
Asthenia	5.0	59.0	8.1	263.0	3.0	207.0	2.9	406.0
Blood creatine phosphokinase increased	5.0	25.0	4.0	165.0	5.0	23.0	6.9	29.0
Hypercholesterolemia	5.0	225.0	2.0	15.5	4.0	445.5	4.9	99.0
Hypertriglyceridemia	3.0	162.0	2.0	118.0	5.0	173.0	1.0	15.0
Blood bilirubin increased	1.0	13.0	2.0	18.0	4.0	165.5	10.8	84.0

Pain in extremity	4.0	73.5	6.1	183.5	2.0	116.5	3.9	42.0
Dizziness	4.0	15.5	2.0	176.0	4.0	44.5	5.9	35.5
Dyspepsia	2.0	21.5	5.1	104.0	4.0	40.0	4.9	61.0
Hyperlipidemia	4.0	282.0	1.0	322.0	3.0	113.0	4.9	225.0
Urticaria	4.0	198.0	0	0	1.0	11.0	4.9	73.0
Insomnia	4.0	86.0	4.0	189.5	3.0	477.0	3.9	372.5
Bronchitis	3.0	7.0	3.0	10.0	4.0	33.0	1.0	3.0
Oropharyngeal pain	1.0	4.0	2.0	105.5	4.0	4.5	2.0	7.5
Vitamin D deficiency	0	0	1.0	457.0	4.0	329.5	1.0	75.0
Hypocalcemia	3.0	16.0	7.1	197.0	2.0	28.5	2.9	116.0
Decreased appetite	2.0	246.0	4.0	155.5	3.0	23.0	5.9	78.5
Pain	3.0	20.0	3.0	2.0	1.0	10.0	2.9	43.0
Blood cholesterol increased	3.0	128.0	1.0	214.0	3.0	84.0	2.0	445.0
Gastroesophageal reflux disease	1.0	296.0	1.0	22.0	3.0	257.0	2.0	189.0
Depression	3.0	151.0	0	0	1.0	583.0	2.0	182.0
Hyperglycemia	2.0	59.5	1.0	27.0	3.0	79.0	1.0	141.0
Low density lipoprotein increased	0	0	1.0	16.0	3.0	102.0	0	0
Axillary pain	0	0	0	0	3.0	8.0	0	0

Dry mouth	3.0	321.0	0	0	2.0	31.0	0	0
Muscle spasms	2.0	181.0	19.2	181.0	2.0	56.0	4.9	242.0
AST increased	2.0	69.5	6.1	31.0	2.0	140.5	14.7	30.0
Periorbital edema	0	0	10.1	234.5	2.0	32.0	1.0	517.0
Alopecia	2.0	478.0	4.0	220.5	2.0	306.5	8.8	168.0
Peripheral edema	1.0	123.0	7.1	149.0	2.0	244.0	5.9	23.5
Edema peripheral	1.0	123.0	7.1	149.0	2.0	244.0	5.9	23.5
Herpes zoster	1.0	5.0	6.1	17.0	2.0	9.0	0	0
Blood creatinine increased	1.0	85.0	5.1	52.0	2.0	19.5	3.9	75.5
Chest pain	0	0	2.0	15.5	2.0	103.5	4.9	13.0
Eczema	2.0	78.0	3.0	127.0	2.0	259.0	4.9	52.0
Edema	2.0	56.5	4.0	83.5	0	0	0	0
Neck pain	1.0	12.0	0	0	2.0	190.0	3.9	150.0
Rhinorrhea	2.0	28.0	1.0	414.0	1.0	5.0	3.9	13.0
Weight decreased	2.0	115.0	1.0	105.0	1.0	430.0	3.9	246.5
Influenza	2.0	18.5	3.0	7.0	2.0	8.5	2.0	9.0
Weight increased	1.0	189.0	3.0	34.0	2.0	389.5	1.0	22.0
Contusion	2.0	83.5	0	0	2.0	66.0	2.9	59.0
Dermatitis allergic	2.0	272.0	0	0	0	0	2.9	456.0

Folliculitis	1.0	259.0	0	0	2.0	257.0	2.9	121.0
Night sweats	1.0	331.0	1.0	399.0	2.0	56.0	2.9	71.0
Rash maculo-papular	1.0	8.0	0	0	2.0	179.5	2.9	429.0
Stomatitis	0	0	1.0	18.0	2.0	9.5	2.9	27.0
Urinary tract infection	2.0	11.5	1.0	9.0	1.0	5.0	2.9	5.0
Anxiety	2.0	274.5	1.0	89.0	2.0	155.0	2.0	301.0
Arthritis	2.0	263.0	2.0	142.5	0	0	0	0
Bone pain	2.0	167.0	1.0	3.0	2.0	276.5	2.0	236.5
Conjunctivitis	2.0	28.0	2.0	166.5	2.0	159.5	1.0	5.0
Fall	2.0	151.5	1.0	1.0	1.0	1.0	2.0	16.5
Gastritis	0	0	1.0	158.0	2.0	311.0	2.0	36.5
Heavy menstrual bleeding	0	0	0	0	2.0	12.0	2.0	273.0
Hyperbilirubinemia	0	0	0	0	2.0	368.0	2.0	89.0
Hyperhidrosis	0	0	2.0	90.5	2.0	356.5	1.0	36.0
Vision blurred	0	0	2.0	60.0	2.0	176.5	2.0	127.0
Gout	2.0	18.5	0	0	1.0	23.0	2.0	36.0
Blood triglycerides increased	2.0	410.0	1.0	15.0	1.0	523.0	0	0
Breast mass	1.0	200.0	0	0	2.0	450.0	1.0	228.0
Flatulence	1.0	155.0	0	0	2.0	66.5	1.0	18.0

Hyperphosphatemia	0	0	1.0	13.0	2.0	77.5	1.0	83.0
Hypothyroidism	1.0	523.0	1.0	79.0	2.0	240.5	0	0
Peripheral sensory neuropathy	0	0	0	0	2.0	235.5	1.0	99.0
Pharyngitis	0	0	1.0	2.0	2.0	101.5	0	0
Photosensitivity reaction	0	0	0	0	2.0	594.0	1.0	184.0
Respiratory tract infection	0	0	0	0	2.0	95.0	1.0	27.0
Syncope	0	0	0	0	2.0	1.0	1.0	2.0
Hematoma	2.0	16.0	1.0	13.0	0	0	1.0	9.0
Sinusitis	2.0	38.5	1.0	44.0	0	0	1.0	4.0
Autoimmune thyroiditis	0	0	0	0	2.0	532.0	0	0
Blood albumin increased	0	0	0	0	2.0	45.0	0	0
Blood bilirubin unconjugated increased	0	0	0	0	2.0	159.0	0	0
Flank pain	2.0	20.5	0	0	0	0	0	0
Nasal congestion	0	0	0	0	2.0	4.5	0	0
Non-cardiac chest pain	1.0	2.0	0	0	2.0	335.0	0	0
Pulmonary mass	0	0	0	0	2.0	200.5	0	0
Tremor	1.0	50.0	0	0	2.0	88.0	0	0
Vitreous floaters	0	0	0	0	2.0	116.5	0	0

White coat hypertension	0	0	0	0	2.0	179.0	0	0
Limb discomfort	2.0	119.0	0	0	0	0	0	0
Productive cough	2.0	19.0	0	0	0	0	0	0
Vaginal hemorrhage	2.0	7.0	0	0	0	0	0	0
Hypophosphatemia	1.0	324.0	6.1	97.0	0	0	2.0	312.0
Vertigo	1.0	326.0	5.1	4.0	0	0	3.9	93.0
Abdominal distension	0	0	0	0	1.0	20.0	4.9	82.0
Acne	1.0	15.0	0	0	1.0	127.0	4.9	163.0
Influenza like illness	1.0	14.0	0	0	1.0	5.0	4.9	6.0
Palpitations	1.0	4.0	1.0	9.0	0	0	4.9	36.0
Pneumonia	1.0	71.0	1.0	39.0	0	0	4.9	12.0
Hypokalemia	1.0	10.0	4.0	18.5	0	0	1.0	8.0
Dyspnea	0	0	2.0	375.0	1.0	21.0	3.9	89.5
Hemorrhoids	1.0	262.0	0	0	0	0	3.9	74.0
Iron deficiency	0	0	1.0	105.0	1.0	57.0	3.9	341.0
Muscular weakness	1.0	71.0	1.0	29.0	0	0	3.9	79.0
Dermatitis acneiform	1.0	298.0	1.0	12.0	1.0	274.0	2.9	242.0
Erythema	0	0	1.0	176.0	1.0	191.0	2.9	7.0
Pollakiuria	1.0	151.0	0	0	0	0	2.9	89.0

Bilirubin conjugated increased	0	0	0	0	1.0	118.0	2.0	218.0
Eye pain	0	0	0	0	1.0	5.0	2.0	68.0
Eye swelling	0	0	2.0	119.5	1.0	3.0	0	0
Gastroenteritis	1.0	2.0	2.0	21.0	0	0	2.0	3.0
Hematochezia	1.0	2.0	0	0	0	0	2.0	85.0
Joint swelling	0	0	2.0	291.5	1.0	622.0	0	0
Liver injury	0	0	0	0	1.0	233.0	2.0	253.5
Malaise	0	0	2.0	68.0	1.0	1.0	0	0
Musculoskeletal pain	1.0	15.0	2.0	318.5	1.0	2.0	1.0	59.0
Pancreatitis	0	0	2.0	22.5	1.0	6.0	0	0
Paresthesia	0	0	0	0	1.0	6.0	2.0	88.5
QT prolongation	1.0	443.0	0	0	0	0	2.0	41.0
Rash pruritic	1.0	454.0	2.0	241.5	0	0	0	0
Skin infection	0	0	2.0	10.0	1.0	174.0	0	0
Toothache	0	0	2.0	20.5	1.0	3.0	1.0	4.0
Atrial fibrillation	1.0	246.0	1.0	5.0	0	0	0	0
Face edema	0	0	10.1	155.5	0	0	0	0
Eyelid edema	0	0	8.1	267.5	0	0	0	0

Pleural effusion	0	0	0	0	0	0	6.9	84.0
Conjunctival hemorrhage	0	0	3.0	8.0	0	0	0	0
Sinus bradycardia	0	0	3.0	78.0	0	0	0	0
Swelling of eyelid	0	0	3.0	378.0	0	0	1.0	8.0
Cystitis	0	0	1.0	12.0	0	0	2.9	100.0
Disturbance in attention	0	0	0	0	0	0	2.9	143.0
Skin irritation	0	0	0	0	0	0	2.9	9.0
Arrhythmia	0	0	0	0	0	0	2.0	19.5
Blood bicarbonate decreased	0	0	0	0	0	0	2.0	13.5
Blood glucose increased	0	0	2.0	87.5	0	0	2.0	275.5
Blood lactate dehydrogenase increased	0	0	2.0	18.0	0	0	2.0	10.5
Blood urea increased	0	0	0	0	0	0	2.0	159.5
Catarrh	0	0	0	0	0	0	2.0	31.0
Groin pain	0	0	2.0	34.5	0	0	0.0	0.0
Helicobacter infection	0	0	0	0	0	0	2.0	148.5
Hepatic enzyme increased	0	0	0	0	0	0	2.0	274.0
Hypersensitivity	0	0	1.0	422.0	0	0	2.0	9.5
Hyponatremia	0	0	2.0	18.0	0	0	1.0	5.0

Joint dislocation	0	0	2.0	79.5	0	0	0	0
Neuropathy peripheral	0	0	2.0	213.5	0	0	1.0	313.0
Pericardial effusion	0	0	0	0	0	0	2.0	28.5
Rhinovirus infection	0	0	0	0	0	0	2.0	16.0
Skin papilloma	0	0	0	0	0	0	2.0	387.5
Testicular pain	0	0	0	0	0	0	2.0	15.5
Tinnitus	0	0	0	0	0	0	2.0	198.0

2G, 2nd generation; AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; IMA, imatinib; TKI, tyrosine kinase inhibitor; URTI, upper respiratory tract infection.

[a] Rates of COVID-19 are not shown.

[b] AE with rates occurring at a difference of ≥5% between treatment groups within stratum are highlighted in red.

[c] AEs with median duration ≥2 times longer between treatment groups within stratum are highlighted in yellow.

Supplemental Table S3. Frequency and duration of all-grade hematologic AEs in ≥2 patients in any group with highlighted frequencies differing by ≥5% or duration ≥2 times longer between treatment groups within stratum

	Imatinib stratum				2G TKI stratum			
	Asciminib (n=100)		Imatinib (n=99)		Asciminib (n=100)		2G TKIs (n=102)	
Event, %	%[a]	Median duration (days)[b]	%[a]	Median duration (days)[b]	%[a]	Median duration (days)[b]	%[a]	Median duration (days)[b]
Thrombocytopenia[c]	26.0	27.5	28.3	40.0	30.0	31.5	34.3	42.0
Neutropenia[c]	24.0	26.5	31.3	64.0	26.0	28.5	34.3	46.0
Leukopenia[c]	17.0	29.0	29.3	84.0	21.0	29.0	19.6	70.0
Anemia	10.0	56.0	26.3	127.5	13.0	30.0	22.5	169.0
Lymphopenia[c]	8.0	182.5	16.2	51.5	4.0	32.5	6.9	170.0
Monocyte count decreased	2.0	110.5	3.0	27.0	3.0	17.0	2.0	156.0
Leukocytosis	1.0	92.0	0	0	3.0	36.0	1.0	11.0
Iron deficiency anemia	0	0	0	0	0	0	2.9	365.0
WBC count increased	0	0	0	0	2.0	44.0	0	0

2G, second generation; AE, adverse event; TKI, tyrosine kinase inhibitor; WBC, white blood cell.

[a] AE with rates occurring at a difference of ≥5% between treatment groups within stratum are highlighted in red.

[b] AEs with median duration ≥2 times longer between treatment groups within stratum are highlighted in yellow.

[c] Leukopenia includes leukopenia and decreased white blood cell count; lymphopenia includes lymphopenia and decreased lymphocyte count; neutropenia included neutropenia and decreased neutrophil count; thrombocytopenia includes thrombocytopenia and decreased platelet count.

Supplemental Table S4. Nonhematologic and hematologic AEs leading to treatment discontinuation. (a) Nonhematologic and hematologic AEs leading to treatment discontinuation in the imatinib stratum. (b) Nonhematologic and hematologic AEs leading to treatment discontinuation in the 2G TKI stratum.

(a) Imatinib stratum

Nonhematologic AEs leading to discontinuation				
	Patients, %[a,b]		All grades	Grade ≥3
ASC (n=100)	**Patients with ≥1 event**		**5.0**	**2.0**
	Pancreatic[c,d]	Pancreatitis	1.0	1.0
		Increased lipase	3.0	1.0
	Psychiatric	Delirium	1.0	0
	Nervous system	Cerebrovascular accident	1.0	1.0
IMA (n=99)	**Patients with ≥1 event**		**8.1**	**3.0**
	GI/metabolism	Diarrhea	2.0	0.0
		Nausea	1.0	0.0
		Decreased appetite	1.0	0.0
	Pancreatic	Pancreatitis	1.0	0.0
	Constitutional	Face edema	1.0	1.0
		Asthenia	1.0	0.0
		Pyrexia	1.0	0.0
		Myalgia	1.0	0.0
	Liver[c]	Hepatotoxicity	1.0	0.0
		Increased ALT	1.0	1.0
		Increased AST	1.0	1.0
	Neoplasms	Metastatic gastric cancer	1.0	1.0
		Prostate cancer	1.0	0.0

Hematologic AEs leading to discontinuation			
	Patients, %[a,b]	All grades	Grade ≥3
ASC[IMA] (n=100)	**Patients with ≥1 event**	**1.0**	**1.0**
	Thrombocytopenia[e]	1.0	1.0
IMA (n=99)	**Patients with ≥1 event**	**3.0**	**3.0**
	Lymphopenia	2.0	2.0
	Neutropenia[e]	1.0	1.0

(b) 2G TKI stratum

Nonhematologic AEs leading to discontinuation				
	Patients, %[a,b]		All grades	Grade ≥3
ASC (n=100)	**Patients with ≥1 event**		**2.0**	**2.0**
	Liver	Hepatotoxicity	1.0	1.0
	Nervous system	Neuralgia	1.0	1.0
2G TKIs (n=102)	**Patients with ≥1 event**		**8.8**	**3.9**
	Cardiac	Cardiac failure	1.0	1.0
	GI	Colitis	1.0	1.0
	Investigations	Electrocardiogram QT prolonged	1.0	0.0
	Constitutional	Generalized edema	1.0	1.0
		Hypersensitivity	1.0	0.0
		Muscular weakness	1.0	1.0
	Respiratory	Pleural effusion	2.0	1.0
	Skin/ subcutaneous	Rash	1.0	0.0
		Rash maculopapular	1.0	0.0

Hematologic AEs leading to discontinuation			
	Patients, % [a,b]	All grade	Grade ≥3
ASC[2G] (n=100)	**Patients with ≥1 event**	**1.0**	**1.0**
	Thrombocytopenia[e]	1.0	0.0
	Neutropenia	1.0	1.0
2G TKIs (n=102)	**Patients with ≥1 event**	**1.0**	**1.0**
	Thrombocytopenia[e]	1.0	1.0

2G, second generation; AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; GI, gastrointestinal; IMA, imatinib; TKI, tyrosine kinase inhibitor.

[a] AEs occurring during treatment or within 30 days of the last study medication are summarized.

[b] A patient with multiple severity grades for an AE is counted only under the maximum grade/severity.

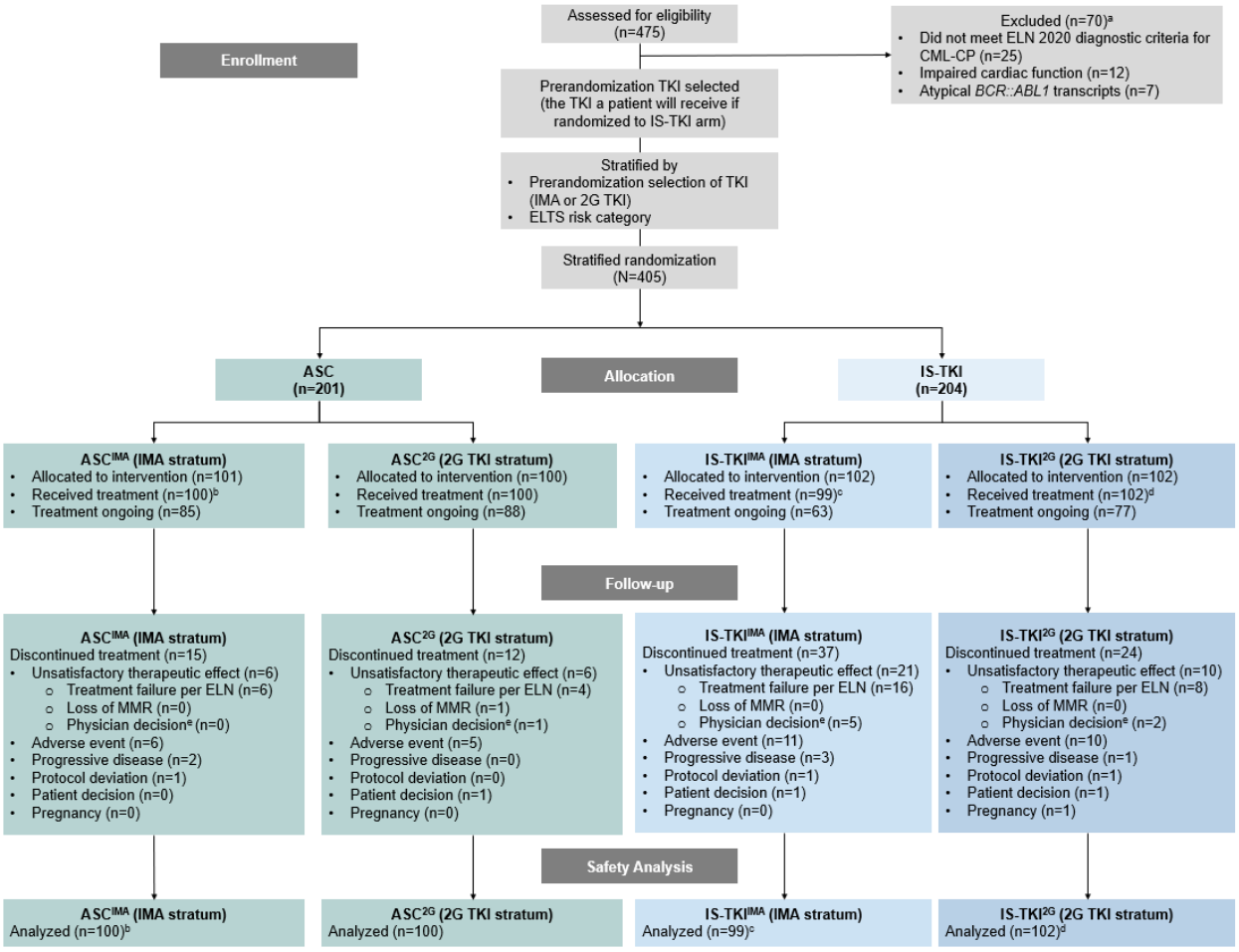
[c] Includes enzyme elevations.

[d] Includes both pancreatitis and acute pancreatitis.

[e] Thrombocytopenia includes thrombocytopenia and platelet count decreased; neutropenia includes neutropenia and neutrophil count decreased; lymphopenia includes lymphopenia and lymphocyte count decreased.

Supplemental Figures

Supplemental Figure S1. CONSORT diagram



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2G, second generation; ASC, asciminib; ELN, European LeukemiaNet; ELTS, EUTOS long-term survival; EUTOS, European Treatment and Outcome Study; IMA, imatinib; IS-TKI, investigator-selected tyrosine kinase inhibitor; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); TKI, tyrosine kinase inhibitor.

[a] The most common reasons for screen failure are listed.

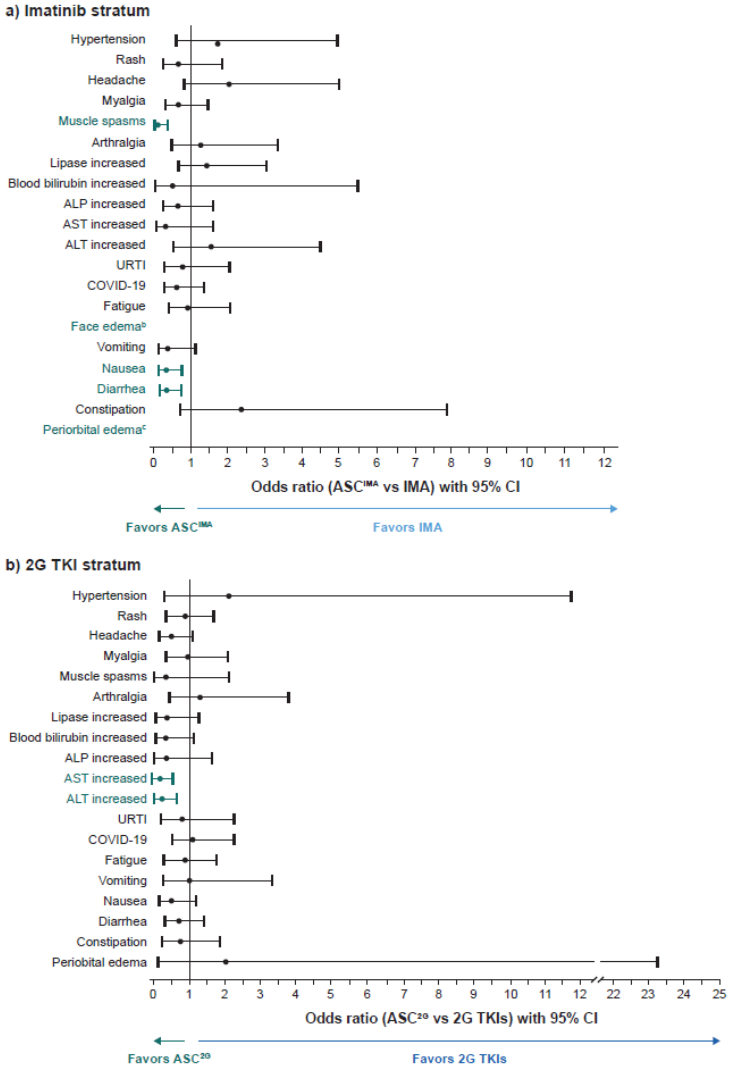
[b] One patient randomized to receive asciminib decided to discontinue before treatment started.

[c] Three patients randomized to receive imatinib did not receive imatinib: one patient recorded as receiving imatinib received a 2G TKI instead.

[d] The patient recorded as receiving imatinib received a 2G TKI instead; additionally, one patient randomized to receive a 2G TKI decided to discontinue before treatment started.

[e] Individual reasons for discontinuation due to physician decision were no achievement of MMR (ASC), lack of efficacy (IMA), no hematologic response (IMA), no optimal response (2× IMA , 1× 2G TKI), *BCR::ABL1* level increased (IMA), and no MMR after 60 weeks of treatment (2G TKI).

Figure S2. AEs reported in ≥10% of patients.[a] (a) AEs reported in ≥10% of patients in the imatinib stratum. (b) AEs reported in ≥10% of patients in the 2G TKI stratum.



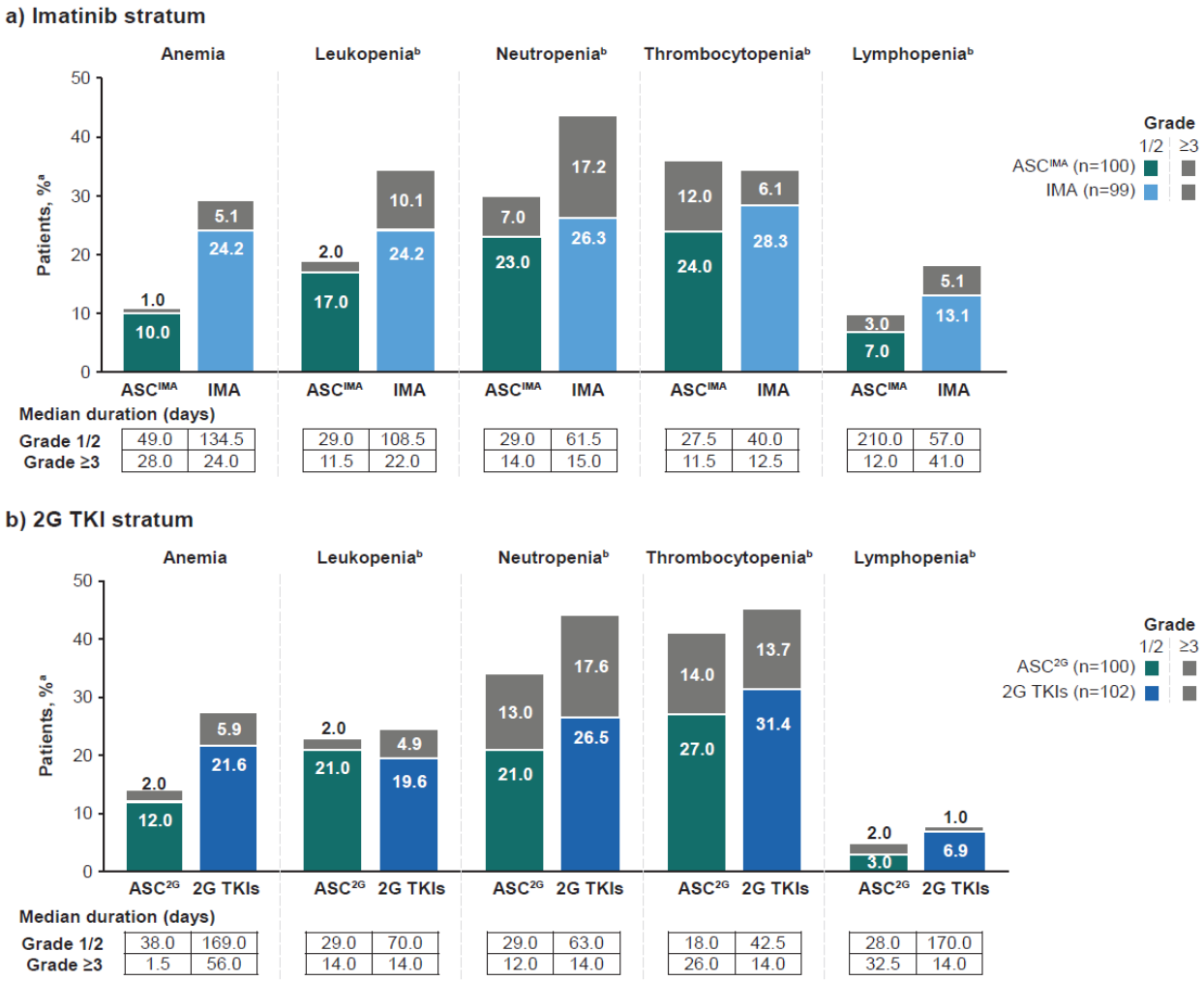
2G, second generation; AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; IMA, imatinib; TKI, tyrosine kinase inhibitor; URTI, upper respiratory tract infection.

[a] Odd ratios with 95% CIs are shown for AEs that occurred in ≥10% of patients. Green favors asciminib, blue favors (a) imatinib and (b) 2G TKIs.

[b] No patients receiving ASC^{IMA} experienced face edema compared with 10.1% of patients receiving IMA.

[c] No patients receiving ASC^{IMA} experienced periorbital edema compared with 10.1% of patients receiving IMA.

Supplemental Figure S3. Grade 1/2 and grade ≥3 hematologic AEs in ≥5% of patients in any group. (a) Grade 1/2 and grade ≥3 hematologic AEs in ≥5% of patients in the imatinib stratum. (b) Grade 1/2 and grade ≥3 hematologic AEs in ≥5% of patients in the 2G TKI stratum



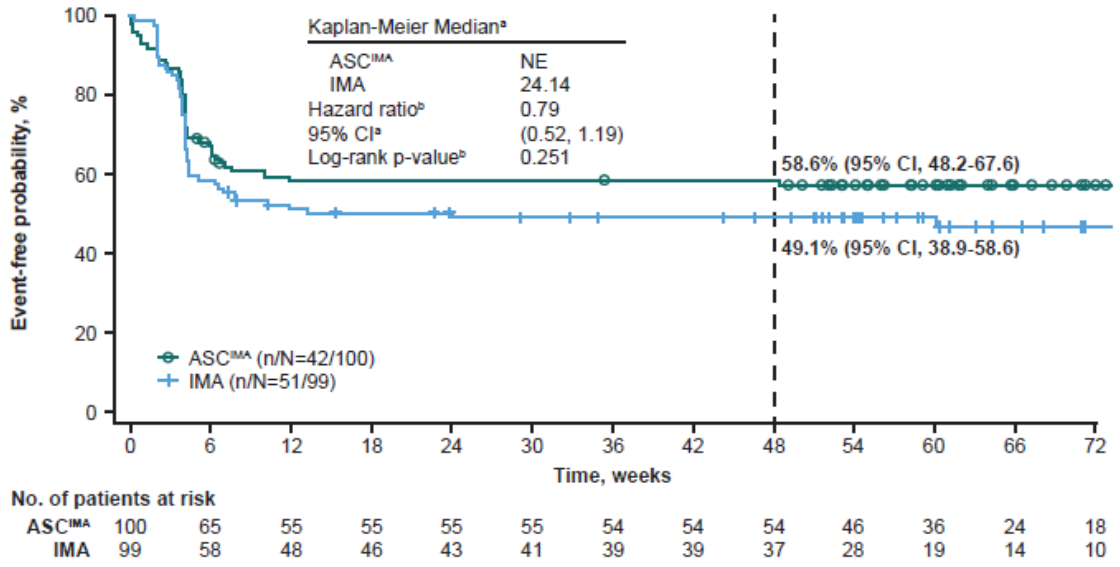
2G, second generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor; WBC, white blood cell.

[a] Patients experiencing an AE of varying severity may be counted under both grade 1/2 and grade ≥3.

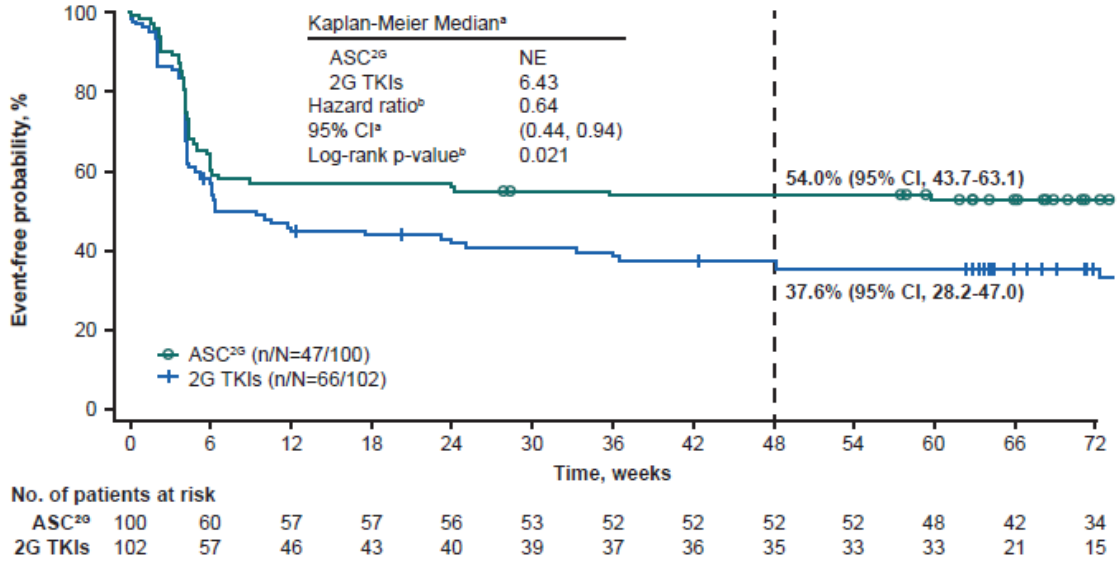
[b] Leukopenia includes leukopenia and decreased WBC count; neutropenia includes neutropenia and decreased neutrophil count; thrombocytopenia includes thrombocytopenia and decreased platelet count; lymphopenia includes lymphopenia and decreased lymphocyte count.

Supplemental Figure S4. Time to first hematologic AE. (a) Time to first hematologic AE in the imatinib stratum. (b) Time to first hematologic AE in 2G TKI stratum.

a) Imatinib stratum



b) 2G TKI stratum

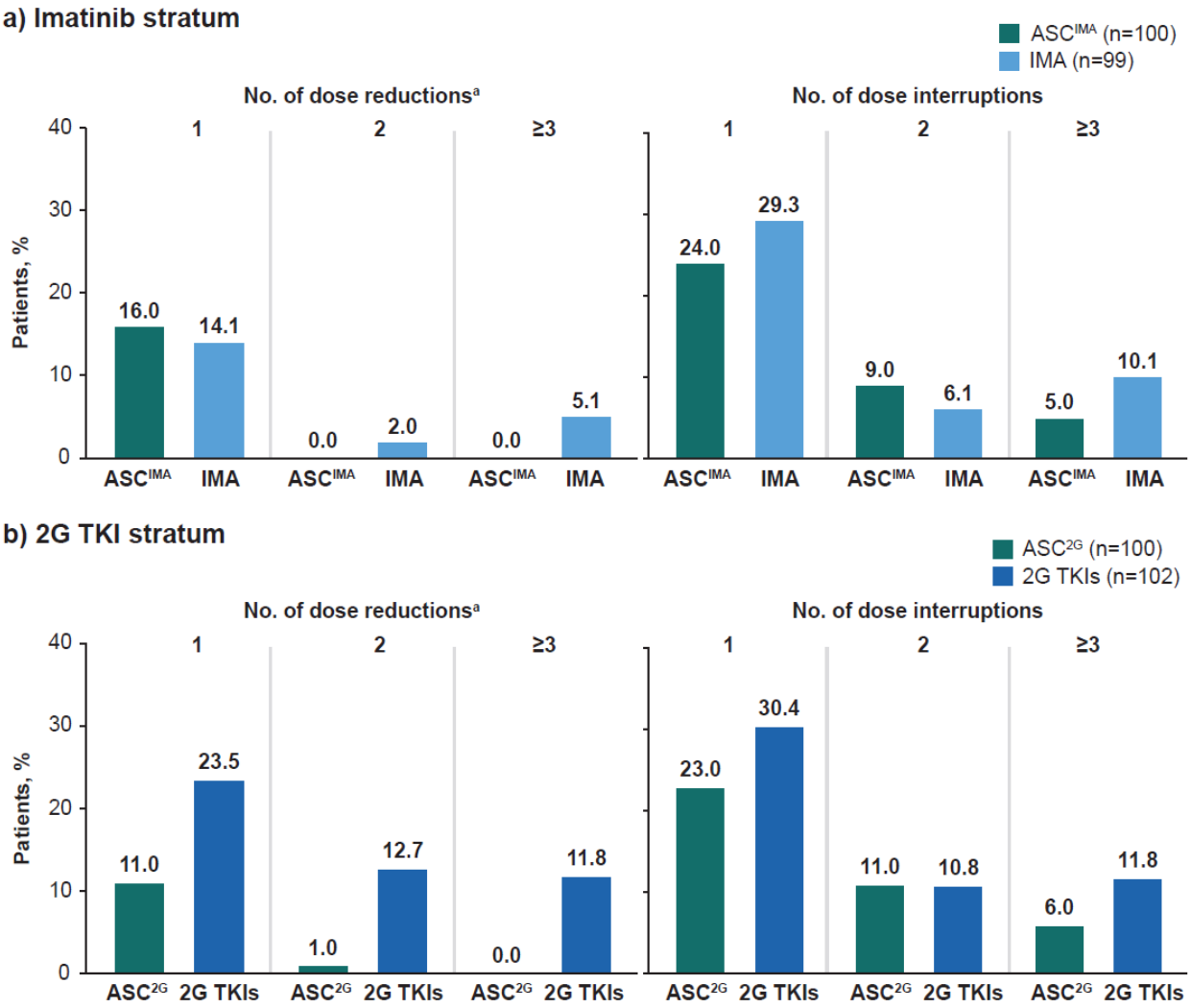


2G, second generation; AE, adverse event; ELTS; EUTOS long-term safety; EUTOS, European Treatment and Outcome Study; KM, Kaplan-Meier; TKI, tyrosine kinase inhibitor.

[a] Median (time to event) and its 95% CI are generated by KM estimation.

[b] Hazard ratio estimated by Cox proportional hazards model and 2-sided p-value based on a log-rank test (adjusted for ELTS score from randomization data).

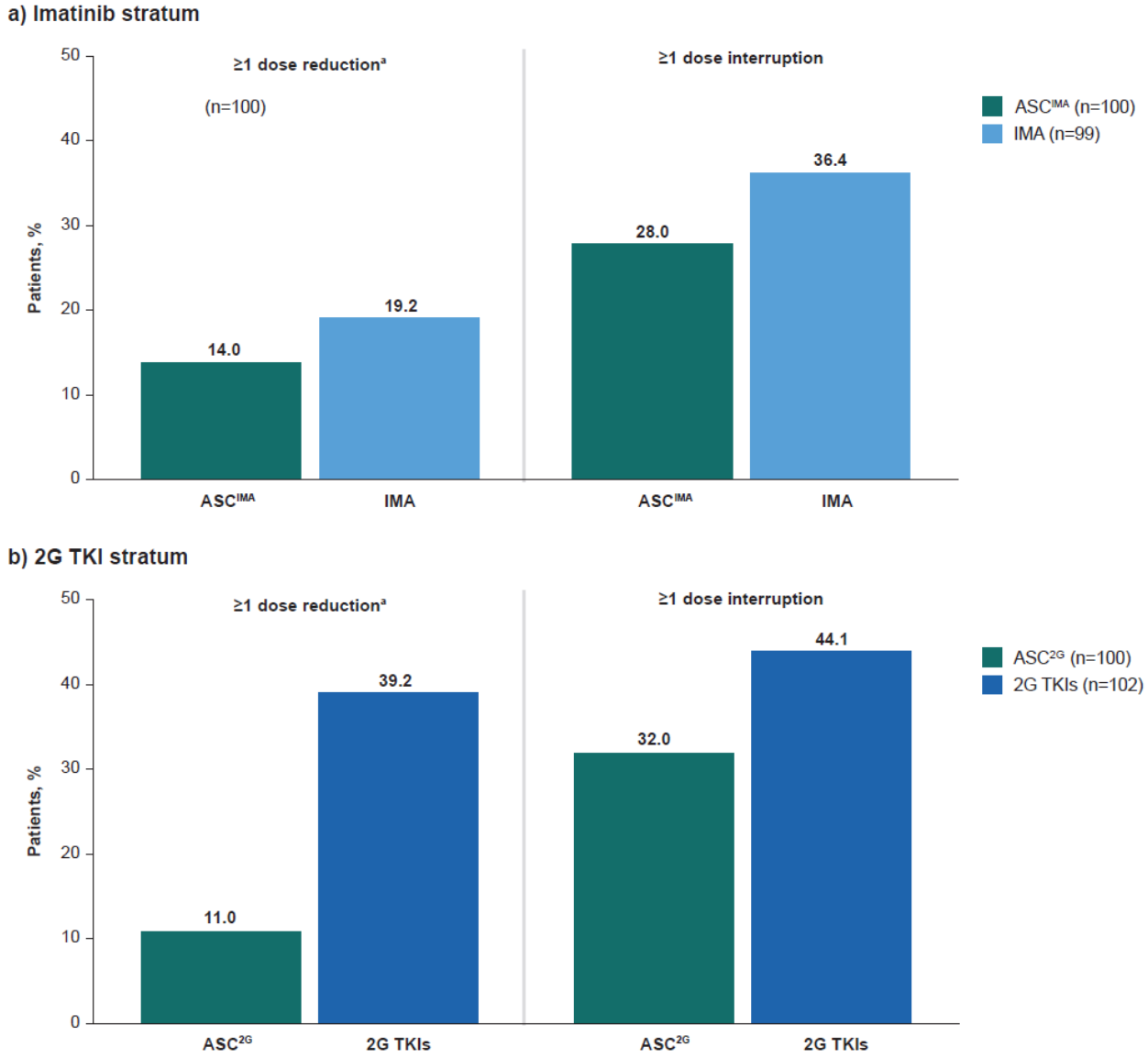
Supplemental Figure S5. Proportion of patients requiring dose reductions and interruptions for any reason. (a) Proportion of patients requiring dose reductions and interruptions for any reason in the imatinib stratum. (b) Proportion of patients requiring dose reductions and interruptions for any reason in the 2G TKI stratum.



2G, second generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.

[a] Per protocol, asciminib dose reduction below a total daily dose of 40 mg was not permitted; re-escalation to 80 mg QD was permitted but allowed only once for any specific event.[1]

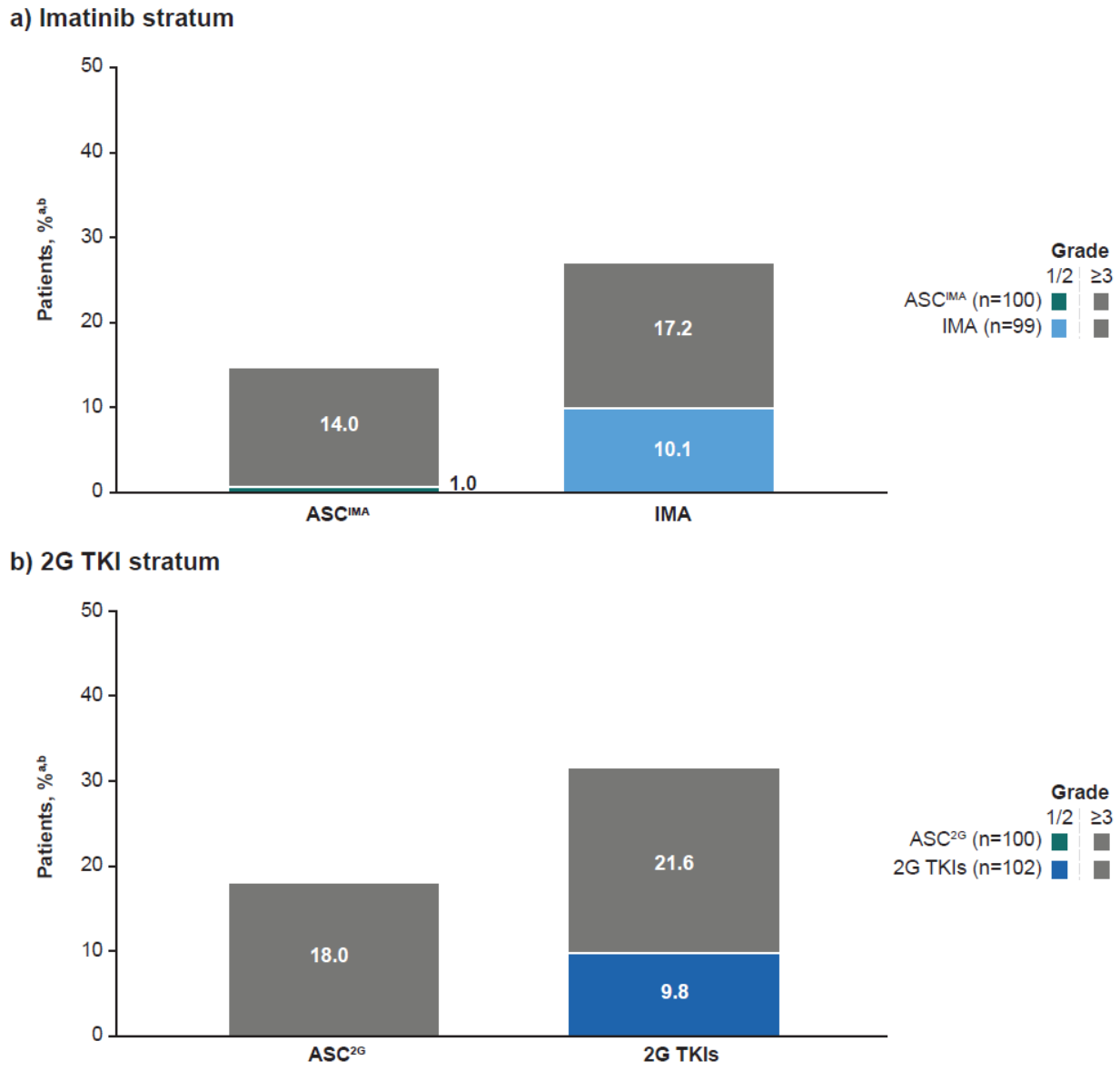
Supplemental Figure S6. Proportion of patients requiring dose reductions and interruptions due to AEs. (a) Proportion of patients requiring dose reductions and interruptions due to AEs in the imatinib stratum. (b) Proportion of patients requiring dose reductions and interruptions due to AEs in the 2G TKI stratum.



2G, second generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.

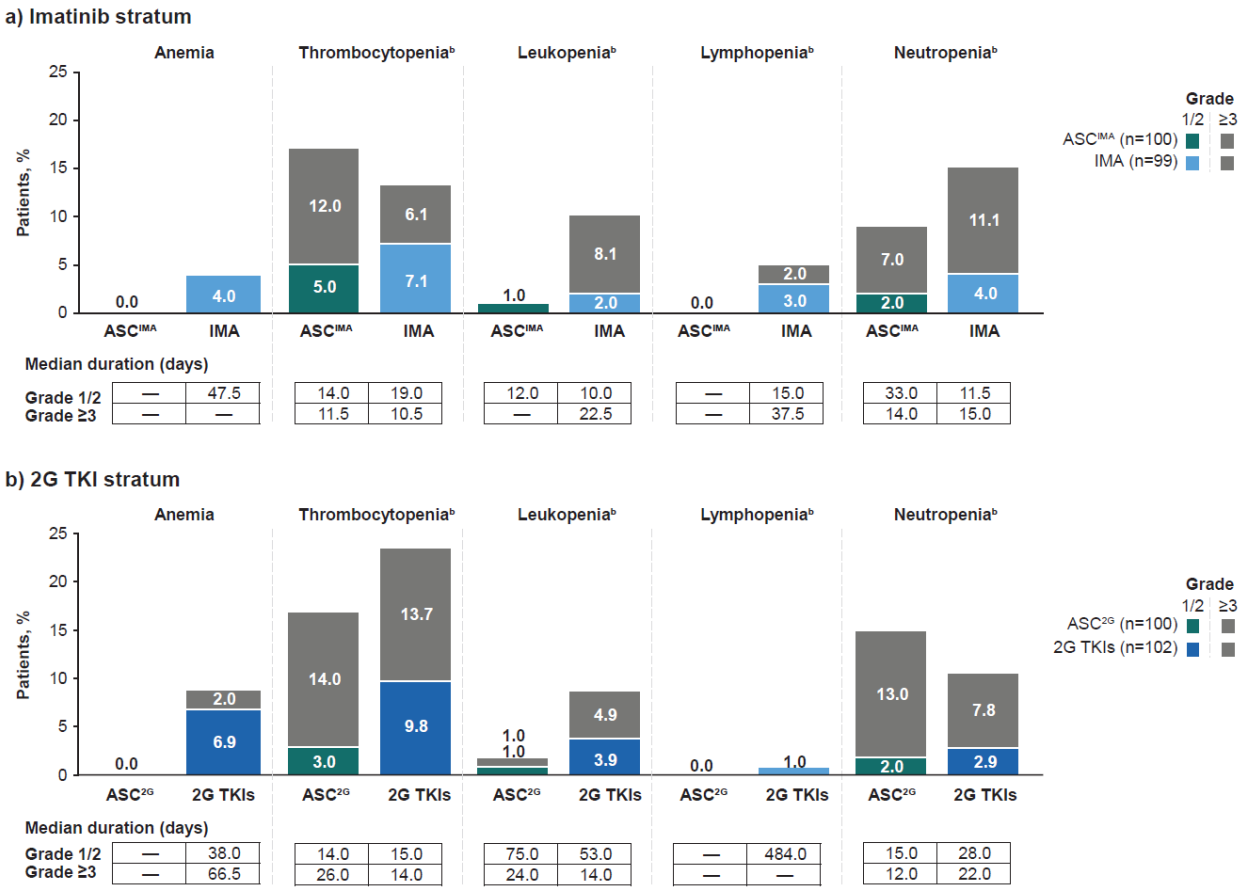
[a] Per protocol, asciminib dose reduction below a total daily dose of 40 mg was not permitted; re-escalation to 80 mg QD was permitted but allowed only once for any specific event.[1]

Supplemental Figure S7. Proportion of patients with grade 1/2 and grade ≥3 hematologic AEs leading to dose adjustment and/or interruption in (a) Proportion of patients with hematologic AEs leading to dose adjustment and/or interruption by grade in the imatinib stratum and (b) Proportion of patients with hematologic AEs leading to dose adjustment and/or interruption by grade in the 2G TKI stratum.



2G, second generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.
[a] AEs occurring during treatment or within 30 days of the last study medication are summarized.
[b] A patient with multiple severity grades for an AE was counted separately.

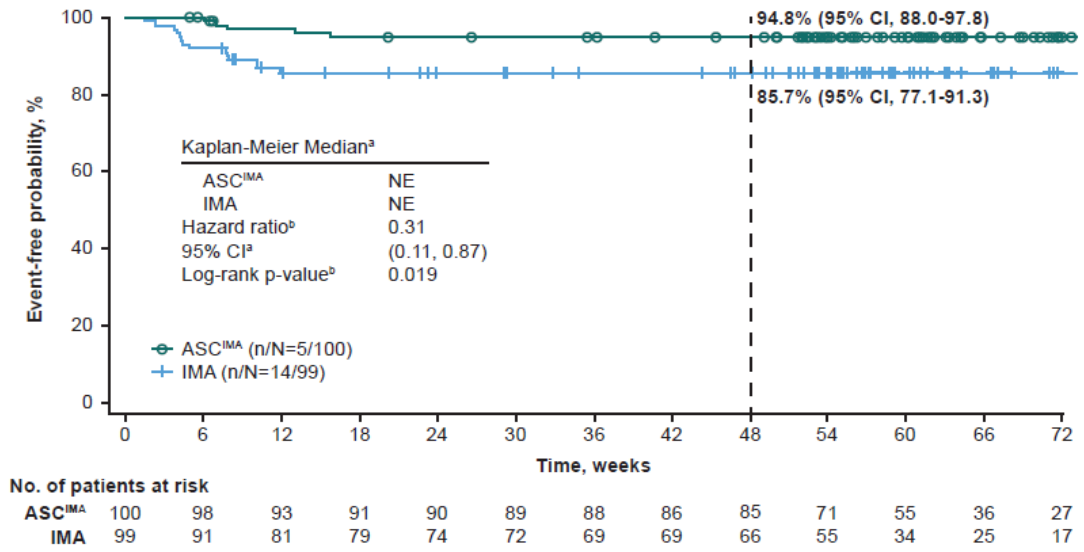
Supplemental Figure S8. Grade 1/2 and grade ≥3 hematologic AEs leading to dose adjustment and/or interruption in ≥2% of patients in any group. (a) Hematologic AEs leading to dose adjustment and/or interruption in ≥2% of patients by grade in the imatinib stratum and (b) Hematologic AEs leading to dose adjustment and/or interruption in ≥2% of patients by grade in the 2G TKI stratum



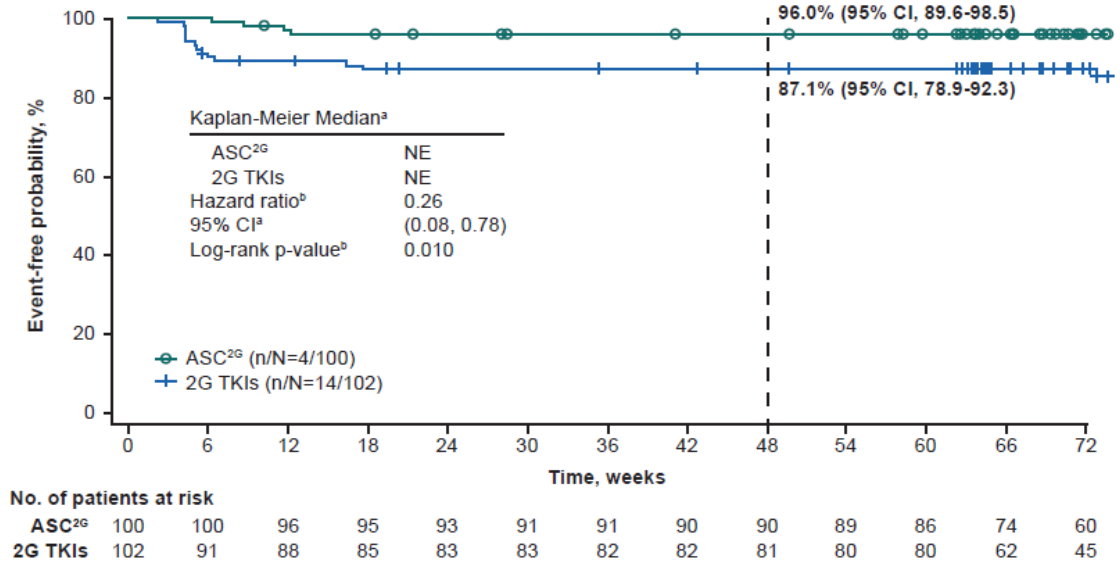
2G; second generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.
[a] Patients experiencing an AE of varying severity may be counted under both grade 1/2 and grade ≥3.
[b] Thrombocytopenia includes thrombocytopenia and platelet count decreased; leukopenia includes leukopenia and white blood cell count decreased; lymphopenia includes lymphopenia and lymphocyte count decreased; neutropenia includes neutropenia and neutrophil count decreased.

Supplemental Figure S9. Time to first grade 1/2 hematologic AEs leading to dose adjustment and/or interruption. (a) Time to first grade 1/2 hematologic AEs leading to dose adjustment and/or interruption in the imatinib stratum. (b) Time to first grade 1/2 hematologic AEs leading to dose adjustment and/or interruption in the 2G TKI stratum.

a) Imatinib stratum



b) 2G TKI stratum

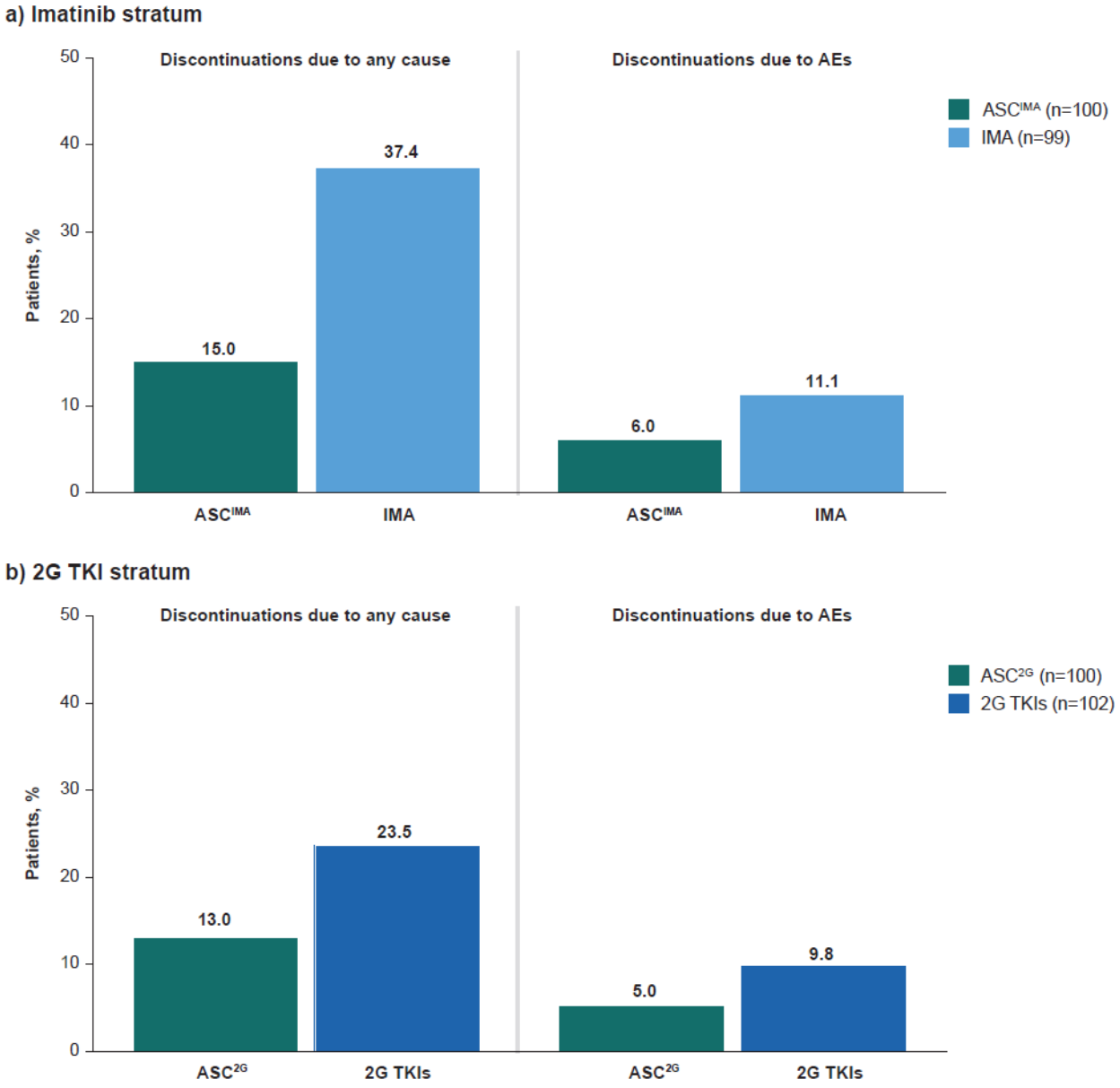


2G, second generation; AE, adverse event; ELTS; EUTOS long-term safety; EUTOS, European Treatment and Outcome Study; KM, Kaplan-Meier; TKI, tyrosine kinase inhibitor.

[a] Median (time to event) and its 95% CI are generated by KM estimation.

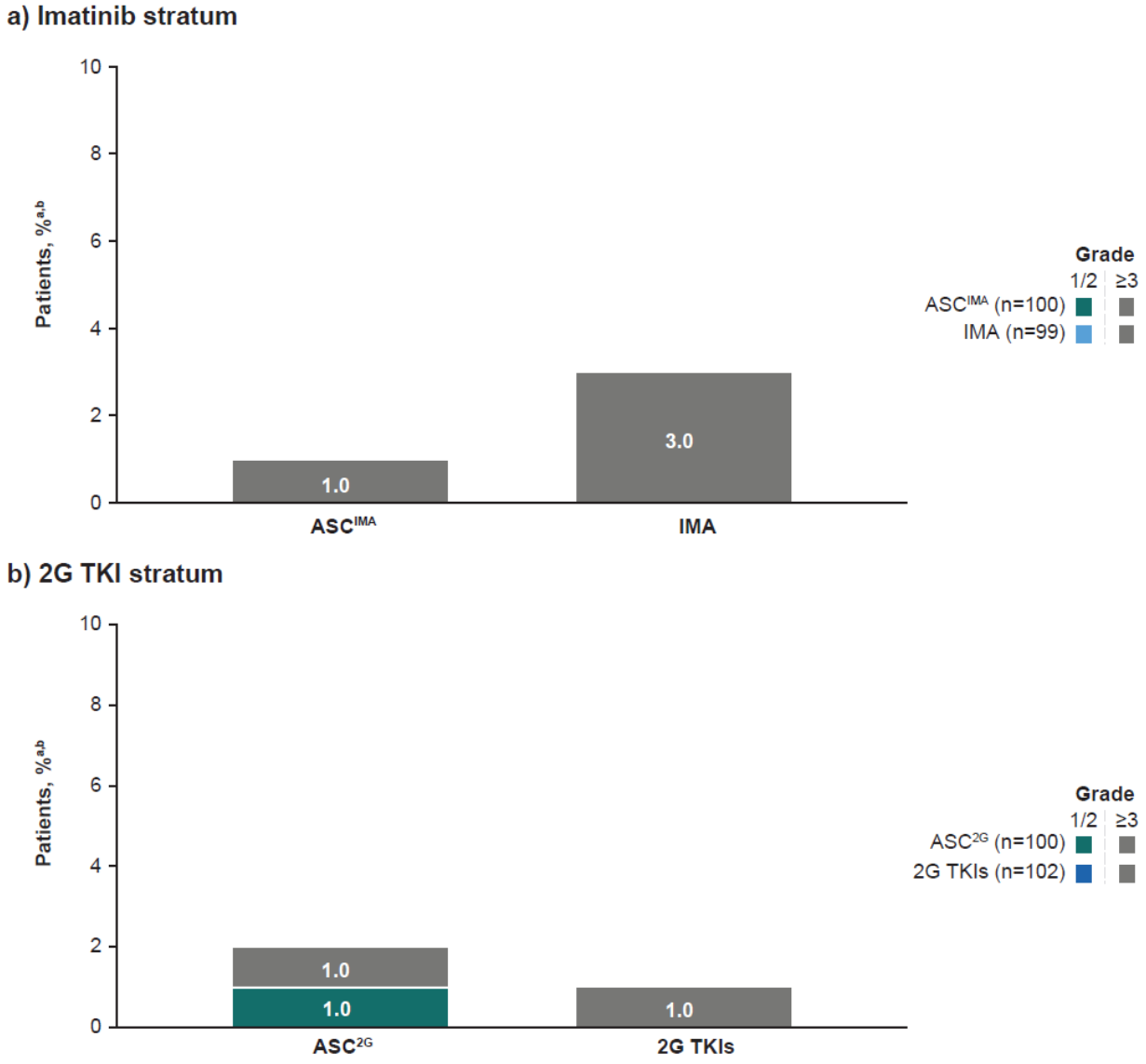
[b] Hazard ratio estimated by Cox proportional hazards model and 2-sided p-value based on a log-rank test (adjusted for ELTS score from IRT).

Supplemental Figure S10. Proportion of patients requiring discontinuations for any reason and due to AEs. (a) Proportion of patients requiring discontinuations for any reason and due to AEs in the imatinib stratum. (b) Proportion of patients requiring discontinuations for any reason and due to AEs in the 2G TKI stratum.



2G, second generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.

Supplemental Figure S11. Proportion of patients with grade 1/2 and grade ≥3 hematologic AEs leading to discontinuation. (a) Proportion of patients with hematologic AEs leading to discontinuation by grade in the imatinib stratum. (b) Proportion of patients with hematologic AEs leading to discontinuation by grade in the 2G TKI stratum.



2G, second generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.

[a] AEs occurring during treatment or within 30 days of the last study medication are summarized.

[b] A patient with multiple severity grades for an AE is counted only under the maximum grade/severity.

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1. Hochhaus A, Wang J, Kim DW, et al. Asciminib in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2024;391(10):885-898.
2. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-984.