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QuANTUM-First: Safety By Treatment Phase and by Age in Newly Diagnosed Patients with FMS-Like Tyrosine Kinase 3–Internal Tandem Duplication (*FLT3*-ITD) Positive Acute Myeloid Leukemia

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QuANTUM-FIRST STUDY

Background and Methods

BACKGROUND

- Based on the QuANTUM-First (NCT02668653) data[1]:
  - Quizartinib has been approved in the US,[2,3] EU,[4] and in Japan[5] in combination with chemotherapy across induction, consolidation, and as maintenance monotherapy (but not after transplantation in the US) for the treatment of adult patients with newly diagnosed *FLT3*-ITD–positive AML[1]
  - 40% of the QuANTUM-First study population was ≥60 years of age

OBJECTIVES

- Safety by phase (induction, consolidation, continuation) and by age (<60, 60-75 years) is reported here in patients with newly diagnosed AML treated in the QuANTUM-First study

METHODS

- Safety was evaluated in patients treated with ≥1 dose of quizartinib or placebo
  - Treatment-emergent adverse events were coded by MedDRA v24.0, severity by NCI CTCAE v4.03

1. Erba HP, et al. *Lancet*. 2023;401(10388):1571-1583. 2. Daiichi Sankyo Press Release. VANFLYTA® First FLT3 Inhibitor Approved in the U.S. Specifically for Patients with Newly Diagnosed FLT3-ITD Positive AML. Published July 20, 2023. https://www.daiichisankyo.com/files/news/pressrelease/pdf/202307/20230720_E.pdf. Accessed July 31, 2023. 3. VANFLYTA® (quizartinib) package insert. Daiichi Sankyo, Inc. July 2023. 4. Daiichi Sankyo Press Release. VANFLYTA® Approved in the EU as the First FLT3 Inhibitor Specifically for Patients with Newly Diagnosed FLT3-ITD Positive AML. Published November 9, 2023. https://www.daiichisankyo.com/files/news/pressrelease/pdf/202311/20231109_E.pdf. Accessed November 14, 2023. 5. Daiichi Sankyo Press Release. VANFLYTA® First FLT3 Inhibitor Approved in Japan for Patients with Newly Diagnosed FLT3-ITD Positive AML. Published May 25, 2023. https://www.daiichisankyo.com/files/news/pressrelease/pdf/202305/20230525_E.pdf. Accessed June 13, 2023. AML, acute myeloid leukemia; EU, European Union; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; US, United States.

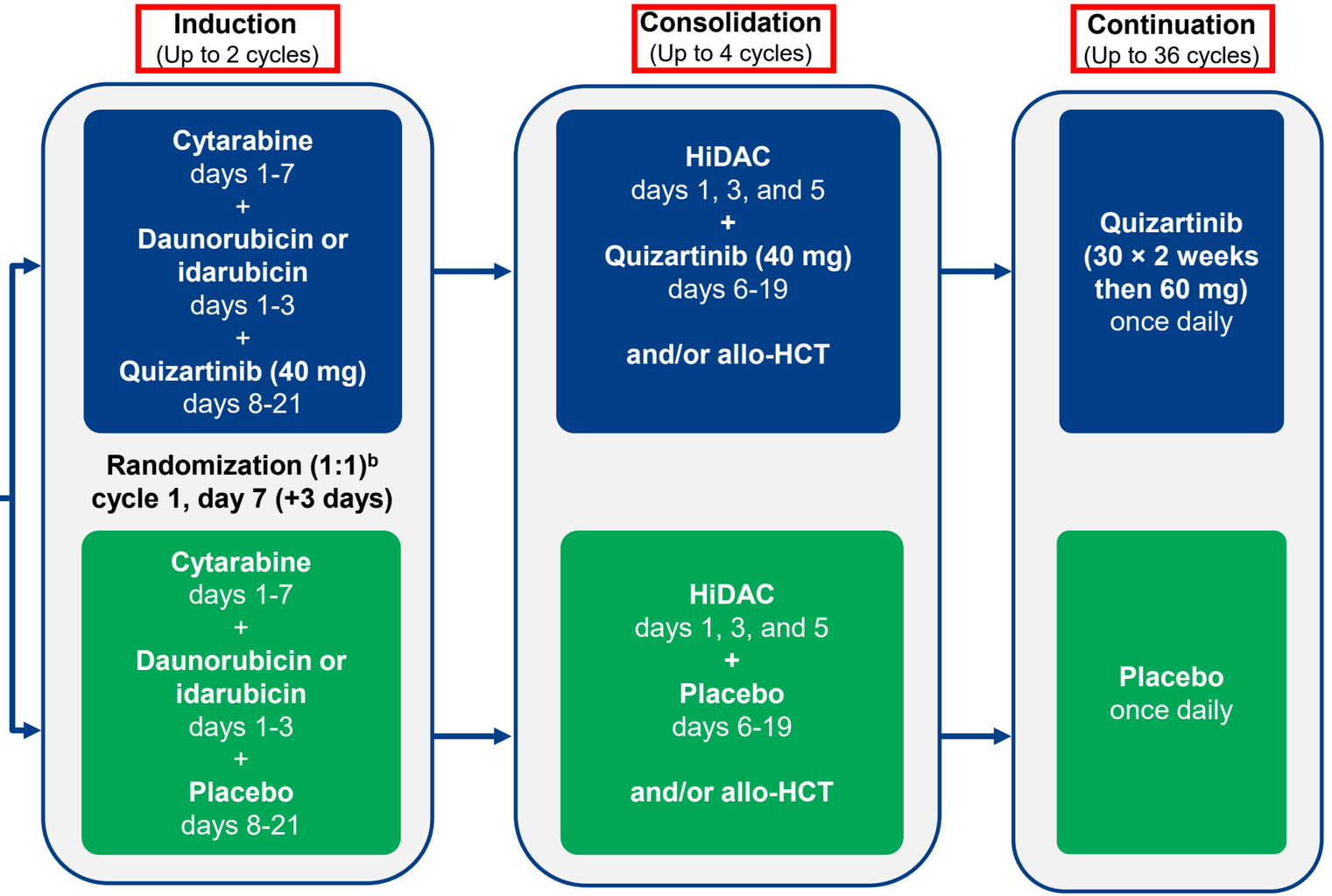
QuANTUM-First Phase 3 Trial: Quizartinib Plus Standard Induction Chemotherapy and Consolidation Followed by Single-Agent Quizartinib

Enrollment dates: Sep 2016 to Aug 2019
Data cutoff: Aug 13, 2021

Key endpoints[a]
- **Primary endpoint**: OS
- **Secondary endpoints**: EFS, CR, CRc, CR/CRc with MRD− end of induction, safety
- **Exploratory endpoints**: RFS, DoCR

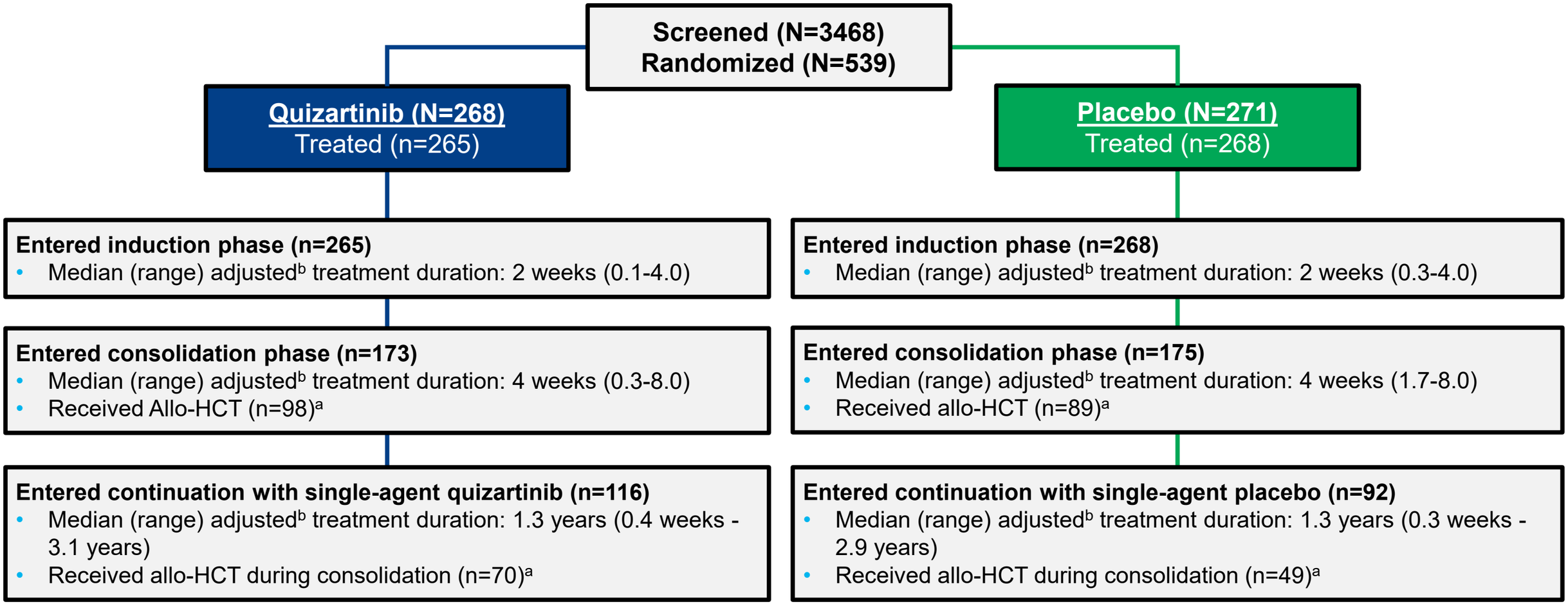
- Newly diagnosed *FLT3*-ITD+ AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allelic frequency
- Patients begin 7+3 chemotherapy during screening

Safety assessments
- Safety was evaluated in patients treated with ≥1 dose of quizartinib or placebo
- TEAEs coded using MedDRA v24.0 and graded for severity by NCI CTCAE v4.03



[a]A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR, CRc, CR with *FLT3*-ITD MRD negativity, and CRc with *FLT3*-ITD MRD negativity. [b]Stratification factors at randomization: region (NA, EU, and Asia/other regions), patient age (<60 years, ≥60 years), and WBC ($<40\times10^9$/L, $\geq40\times10^9$/L). NCT02668653. Allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; DoCR, duration of complete remission; EFS, event-free survival; EU, European Union; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HiDAC, high-dose cytarabine; MedDRA, Medical Dictionary for Regulatory Activities; MRD, measurable residual disease; NA, North America; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, overall survival; RFS, relapse-free survival; TEAE, treatment-emergent adverse event; WBC, white blood cell.

CONSORT Diagram



[a]Includes protocol-specified allo-HCT. [b]Adjusted treatment duration for each phase is the treatment duration minus the planned off drug days in each phase.
Allo-HCT, allogeneic hematopoietic cell transplantation.

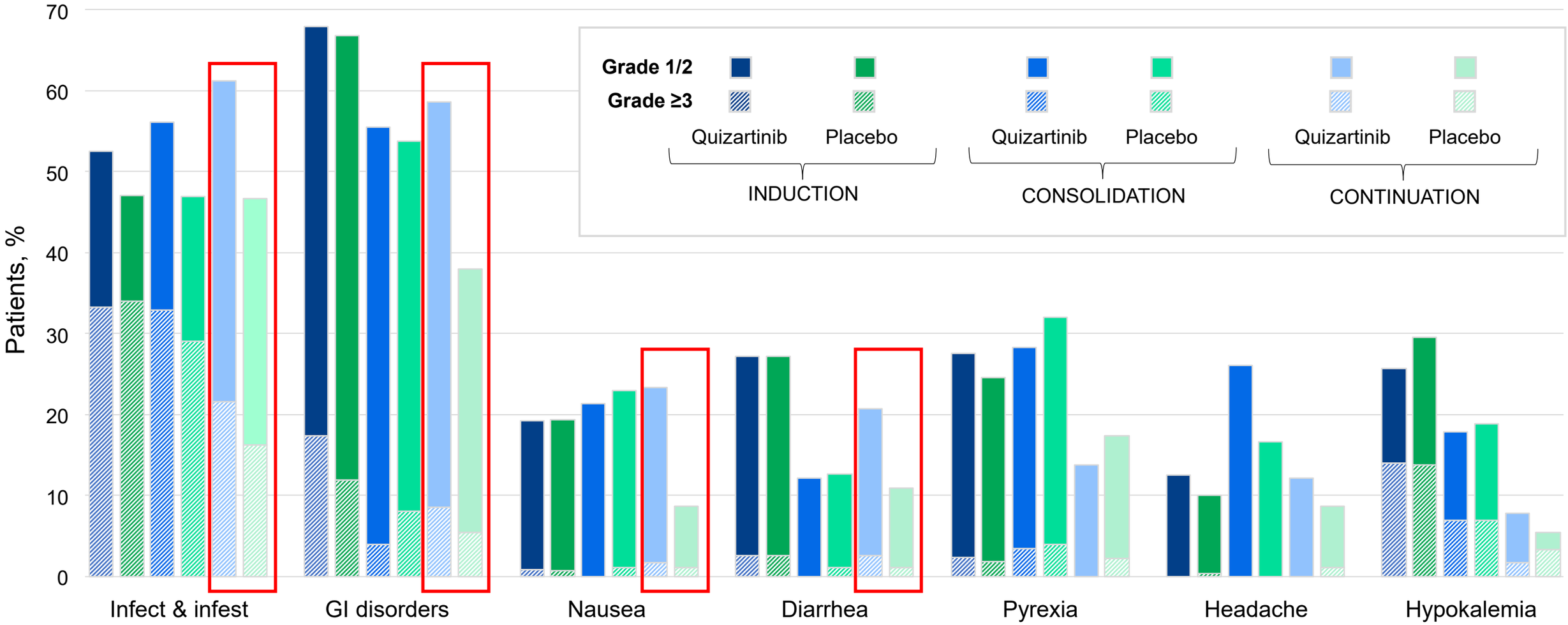
Summary of Overall Safety of QuANTUM-First by Treatment Phase

	Induction phase		Consolidation phase		Continuation phase	
	Quizartinib (n=265)	Placebo (n=268)	Quizartinib (n=173)	Placebo (n=175)	Quizartinib (n=116)	Placebo (n=92)
AEs, %						
Any TEAEs	98.1	97.4	92.5	91.4	94.0	91.3
Grade ≥3 TEAEs (including grade 5)	70.6	74.6	69.4	69.1	78.4	57.6
Serious TEAEs	28.3	24.6	34.1	30.9	33.6	37.0
AEs associated with fatal outcome	7.2	4.9	4.6	2.9	2.6	7.6
Dose modifications due to TEAEs, %						
Treatment discontinuation	9.8	4.1	5.8	2.9	15.5	7.6
Dose interruption	9.1	11.2	8.1	7.4	56.0	23.9
Dose reduction	2.6	1.1	2.3	0	36.2	15.2
Dose reductions due to QT prolongation	1.1	0	1.2	0	5.2	1.1
QTcF interval, %						
>450 ms	23.0	11.9	22.5	7.4	26.7	15.2
>480 ms	3.8	1.5	4.0	1.7	6.9	0
>500 ms	0.8	0.7	2.3	0	0	0

	Induction phase	
Early deaths, %	Quizartinib (n=265)	Placebo (n=268)
Deaths within 30 days of first dose	5.7	3.4
Deaths within 60 days of first dose	7.5[a]	4.9

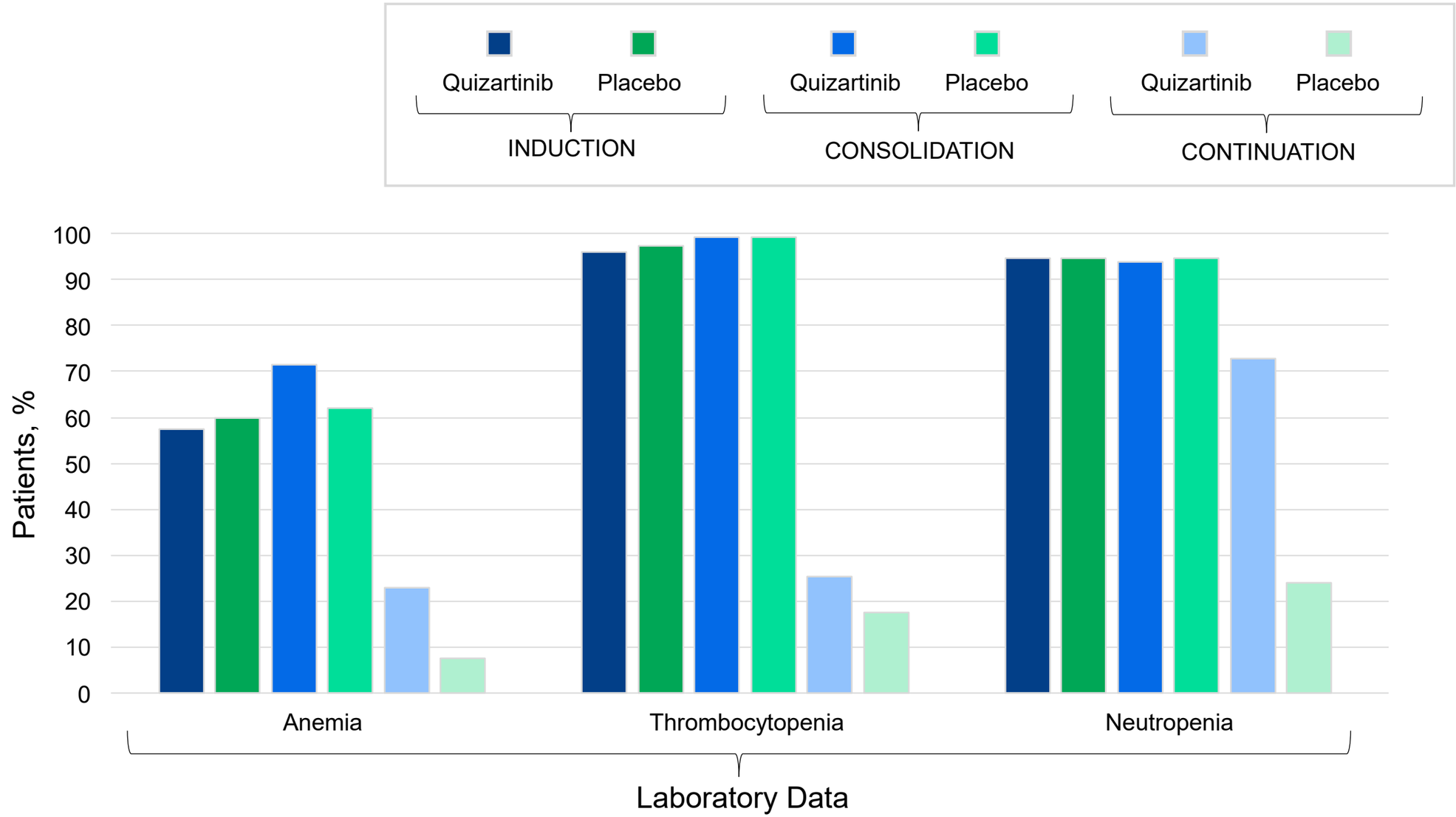
[a]One death occurred in consolidation. AE, adverse event; ms, milliseconds; QTcF, QT interval corrected using Fridericia's formula; TEAE, treatment-emergent adverse event.

Nonhematologic TEAEs Occurring in ≥20% of Patients by Treatment Phase



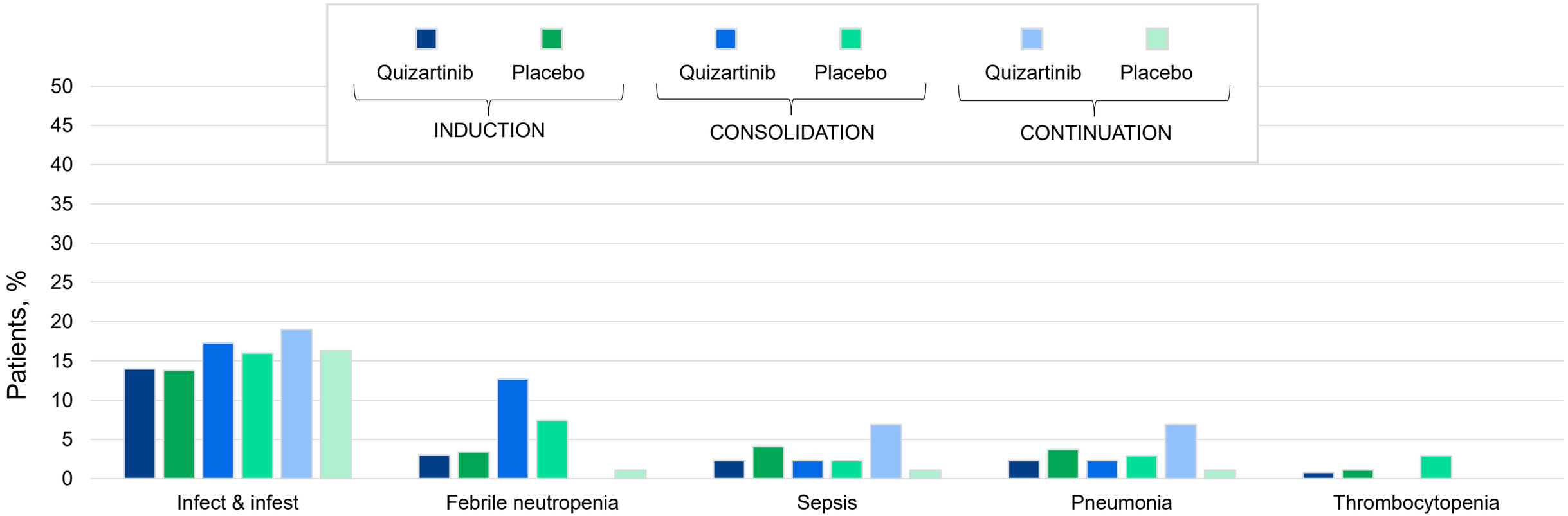
GI, gastrointestinal; TEAE, treatment-emergent adverse event.

Patients Experiencing Grade 3/4 Myelosuppression by Treatment Phase



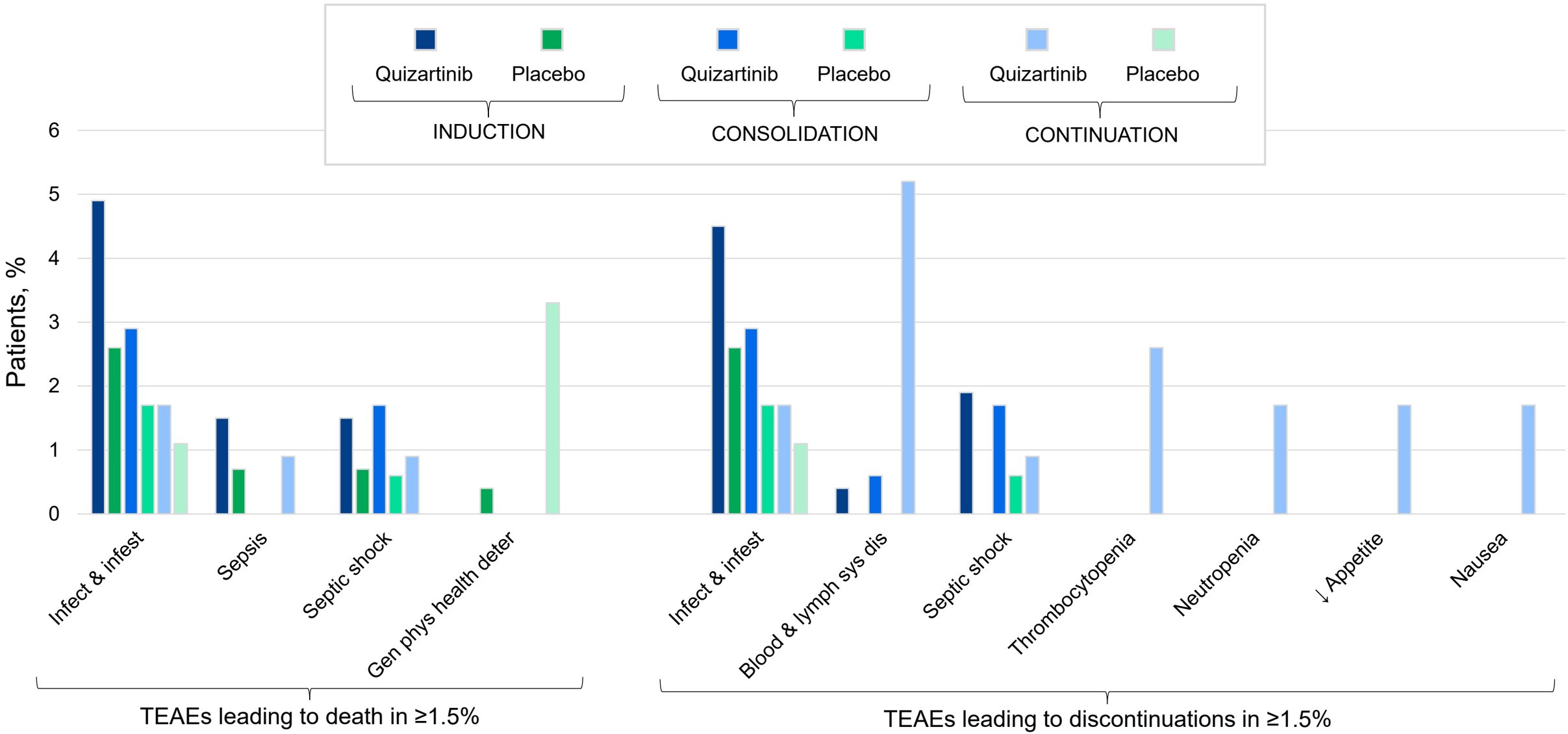
[a]Febrile neutropenia of grade ≥3.

Serious TEAEs Occurring in ≥4% of Patients by Treatment Phase



TEAE, treatment-emergent adverse event.

TEAEs Leading to Death or Discontinuations by Treatment Phase



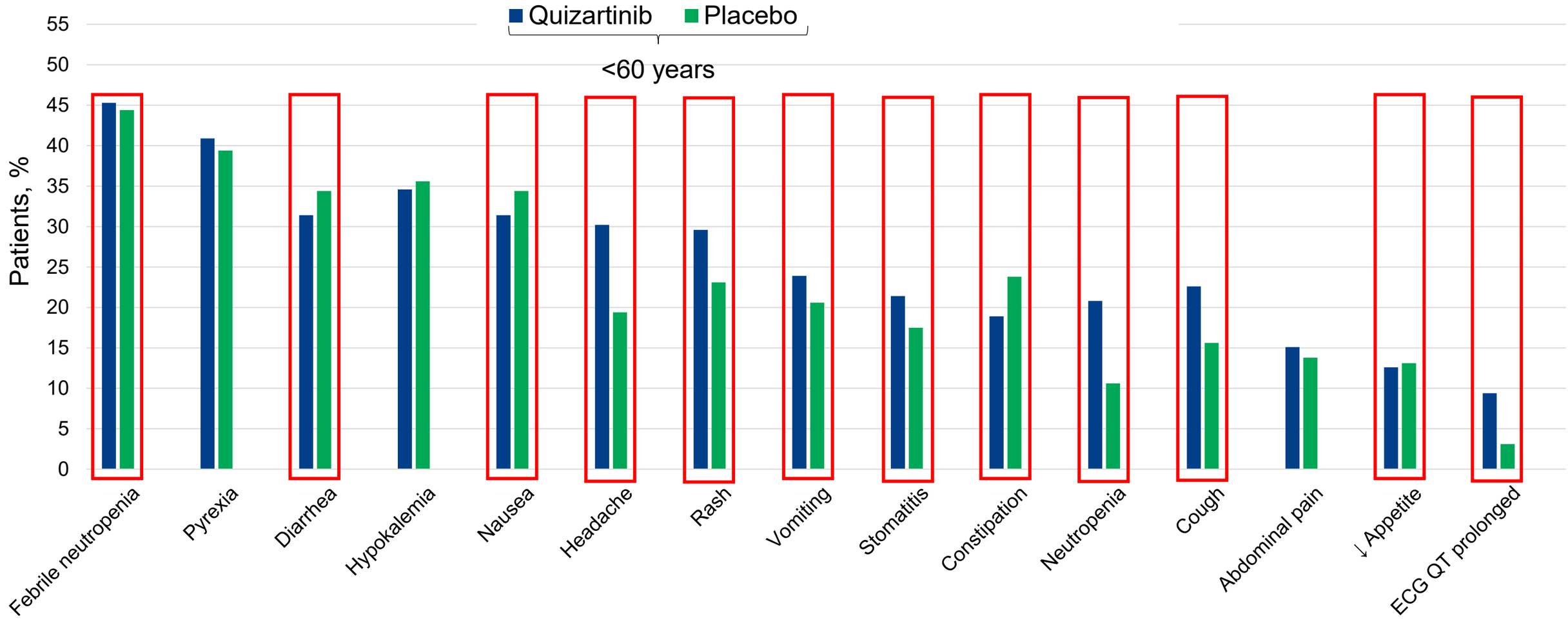
TEAE, treatment-emergent adverse event.

Summary of Overall Safety of QuANTUM-First by Age

	<60 years (N=319)		60-75 years (N=214)	
	Quizartinib (n=159)	Placebo (n=160)	Quizartinib (n=106)	Placebo (n=108)
AEs, %				
Any TEAEs	100.0	99.4	99.1	98.1
Grade ≥3 TEAEs	91.2	88.8	93.4	90.7
TESAEs	52.8	40.0	55.7	54.6
AEs associated with fatal outcome	8.8	7.5	15.1	13.0
Dose modifications due to TEAEs, %				
Treatment discontinuation	16.4	6.9	26.4	11.1
Dose interruption	34.6	16.3	33.0	25.9
Dose reduction	21.4	6.3	15.1	6.5
QTcF interval, %				
>450 ms	34.6	13.1	34.0	25.0
>480 ms	6.9	0.6	8.5	4.6
>500 ms	0.6	0	4.7	1.9

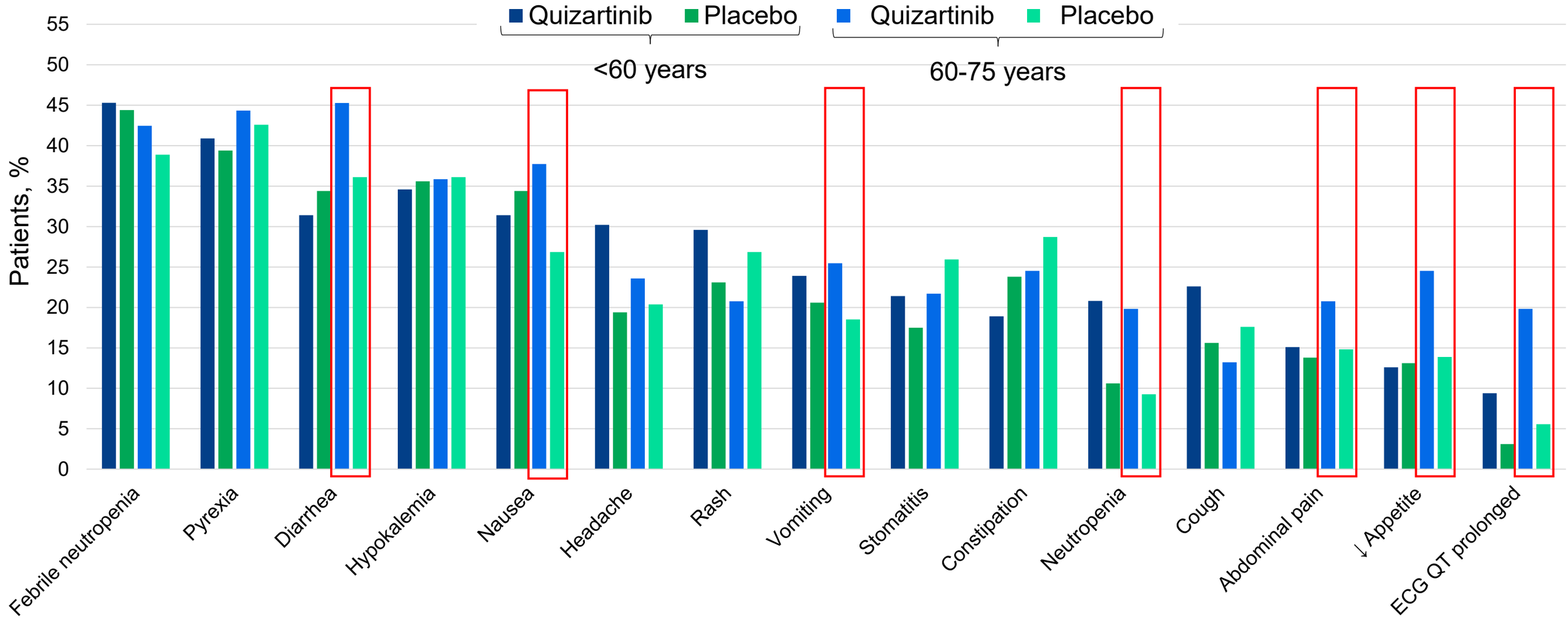
AE, adverse event; ms, milliseconds; QTcF, QT interval corrected using Fridericia's formula; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

TEAEs of All Grades Occurring in ≥20% of Patients by Age



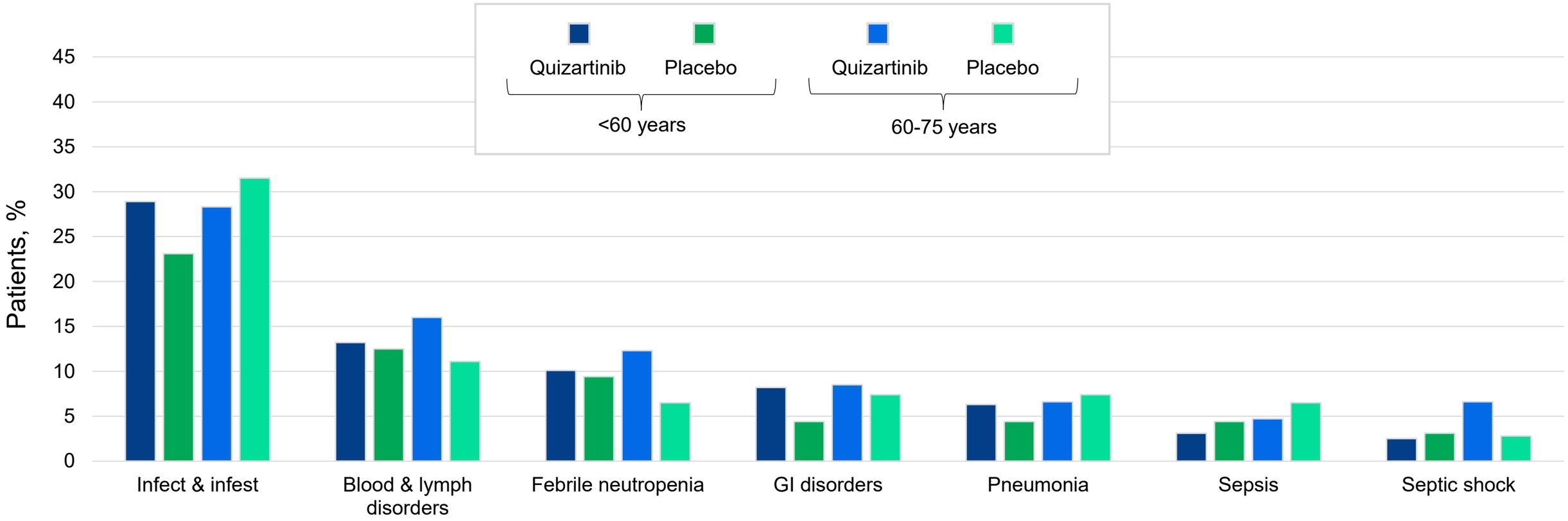
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; TEAE, treatment-emergent adverse event.

TEAEs of All Grades Occurring in ≥20% of Patients by Age



ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; TEAE, treatment-emergent adverse event.

Serious TEAEs reported in ≥5% of patients



AE, adverse event; GI, gastrointestinal; TEAE, treatment-emergent adverse event.

Early Deaths and AEs Associated With Fatal Outcomes by Age

AE, adverse event; GI, gastrointestinal; TEAE, treatment-emergent adverse event.

Conclusions

Safety by phase

- In QuANTUM-First, infections and cytopenias associated with quizartinib were observed across all phases
- Fatal infections were more common with quizartinib in induction and consolidation, but not in continuation
- Rates of prolonged QTcF >500 ms were low overall and only seen in induction & consolidation
- The safety data from the QuANTUM first study supports the use of quizartinib for up to 144 weeks of continuation therapy

Safety by age

- The rate of TEAEs leading to death (including early death) was higher in patients aged ≥60 years in each treatment arm, and rates were numerically higher in the quizartinib group mainly due to infections
- Selection of the optimal treatment for the individual older patient with FLT3 ITD AML remains challenging and is an area of continued clinical investigation

ms, milliseconds; QTcF, QT interval corrected using Fridericia's formula; TEAE, treatment-emergent adverse event.

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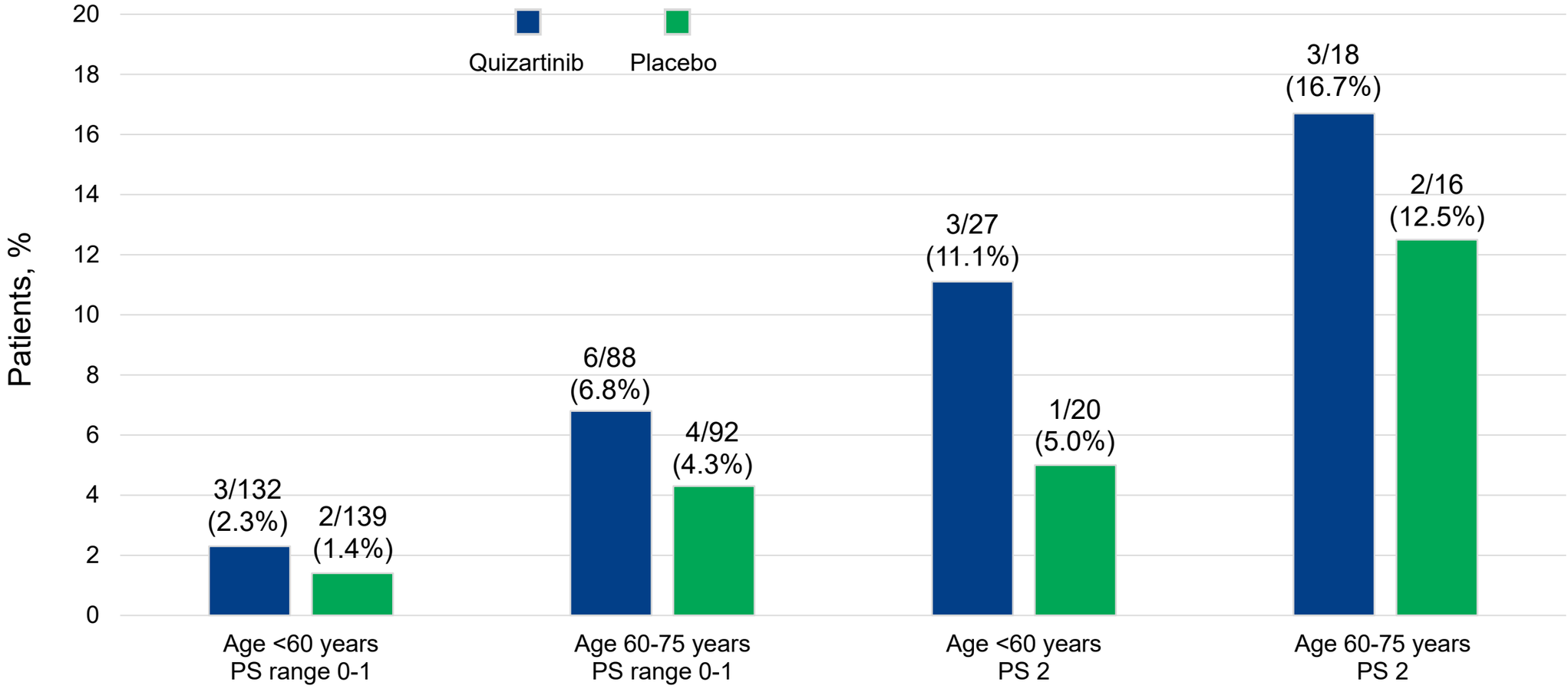
BACKUP SLIDES

Rates of Early Deaths Within 30 Days by Age (<60 years vs 60-75 years) and Performance Status (0-1 vs 2)



Percentage of patients calculated as follows: number of patients with early deaths/number of patients with the specified age/PS.
PS, performance status.