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Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukaemia: an open-label, multicentre, single-arm, phase 2 trial

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Résumé en anglais

BACKGROUND: Old age and FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutations in patients with acute myeloid leukaemia are associated with early relapse and poor survival. Quizartinib is an oral, highly potent, and selective next-generation FLT3 inhibitor with clinical antileukaemic activity in relapsed or refractory acute myeloid leukaemia. We aimed to assess the efficacy and safety of single-agent quizartinib in patients with relapsed or refractory acute myeloid leukaemia.

METHODS: We did an open-label, multicentre, single-arm, phase 2 trial at 76 hospitals and cancer centres in the USA, Europe, and Canada. We enrolled patients with morphologically documented primary acute myeloid leukaemia or acute myeloid leukaemia secondary to myelodysplastic syndromes and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 into two predefined, independent cohorts: patients who were aged 60 years or older with relapsed or refractory acute myeloid leukaemia within 1 year after first-line therapy (cohort 1), and those who were 18 years or older with relapsed or refractory disease following salvage chemotherapy or haemopoietic stem cell transplantation (cohort 2). Patients with an FLT3-ITD allelic frequency of more than 10% were considered as FLT3-ITD positive, whereas all other patients were considered as FLT3-ITD negative. Patients received quizartinib once daily as an oral solution; the initial 17 patients received 200 mg per day but the QTcF interval was prolonged for more than 60 ms above baseline in some of these patients. Subsequently, doses were amended for all patients to 135 mg per day for men and 90 mg per day for women. The co-primary endpoints were the proportion of patients who achieved a composite complete remission (defined as complete remission + complete remission with incomplete platelet recovery + complete remission with incomplete haematological recovery) and the proportion of patients who achieved a complete remission. Efficacy and safety analyses included all patients who received at least one dose of quizartinib (ie, the intention-to-treat population). Patients with a locally assessed post-treatment bone marrow aspirate or biopsy were included in efficacy analyses by response; all other patients were considered to have an unknown response. This study is registered with ClinicalTrials.gov, number NCT00989261, and with the European Clinical Trials Database, EudraCT 2009-013093-41, and is completed.

FINDINGS: Between Nov 19, 2009, and Oct 31, 2011, a total of 333 patients were enrolled (157 in cohort 1 and 176 in cohort 2). In cohort 1, 63 (56%) of 112 FLT3-ITD-positive patients and 16 (36%) of 44 FLT3-ITD-negative patients achieved composite complete remission, with three (3%) FLT3-ITD-positive patients and two (5%) FLT3-ITD-negative patients achieving complete remission. In cohort 2, 62 (46%) of 136 FLT3-ITD-positive patients achieved composite complete remission with five (4%) achieving complete remission, whereas 12 (30%) of 40 FLT3-ITD-negative patients achieved composite complete remission with one (3%) achieving complete remission. Across both cohorts (ie, the intention-to-treat population of 333 patients), grade 3 or worse treatment-related treatment-emergent adverse events in 5% or more of patients were febrile neutropenia (76 [23%] of 333), anaemia (75 [23%]), thrombocytopenia (39 [12%]), QT interval corrected using Fridericia's formula (QTcF) prolongation (33 [10%]), neutropenia (31 [9%]), leucopenia (22 [7%]), decreased platelet count (20 [6%]), and pneumonia (17 [5%]). Serious adverse events occurring in 5% or more of patients were febrile neutropenia (126 [38%] of 333; 76 treatment related), acute myeloid leukaemia progression (73 [22%]), pneumonia (40 [12%]; 14 treatment related), QTcF prolongation (33 [10%]; 32 treatment related), sepsis (25 [8%]; eight treatment related), and pyrexia (18 [5%]; nine treatment related). Notable serious adverse events occurring in less than 5% of patients were torsades de pointes (one [<1%]) and hepatic failure (two [1%]). In total, 125 (38%) of 333 patients died within the study treatment period, including the 30-day follow-up. 18 (5%) patients died because of an adverse event considered by the investigator to be treatment related (ten [6%] of 157 patients in cohort 1 and eight [5%] of 176 in cohort 2.

INTERPRETATION: Single-agent quizartinib was shown to be highly active and generally well tolerated in patients with relapsed or refractory acute myeloid leukaemia, particularly those with FLT3-ITD mutations. These findings confirm that targeting the FLT3-ITD driver mutation with a highly potent and selective FLT3 inhibitor is a promising clinical strategy to help improve clinical outcomes in patients with very few options. Phase 3 studies (NCT02039726; NCT02668653) will examine quizartinib at lower starting doses.

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