Bevacizumab plus hypofractionated radiotherapy versus radiotherapy alone in elderly patients with glioblastoma: the randomized, open-label, phase II ARTE trial


Background
The addition of bevacizumab to temozolomide-based chemoradiotherapy (TMZ/RT TMZ) did not prolong overall survival (OS) in patients with newly diagnosed glioblastoma in phase III trials. Elderly and frail patients are underrepresented in clinical trials, but early reports suggested preferential benefit in this population.

Patients and methods
ARTE was a 2 : 1 randomized, multi-center, open-label, non-comparative phase II trial of hypofractionated RT (40 Gy in 15 fractions) with bevacizumab (10 mg/kg×14 days) (arm A, N = 50) or without bevacizumab (arm B, N = 25) in patients with newly diagnosed glioblastoma aged ≥65 years. The primary objective was to obtain evidence for prolongation of median OS by the addition of bevacizumab to RT. Response was assessed by RANO criteria. Quality of life (QoL) was monitored by the EORTC QLQ-C30/BN20 modules. Exploratory studies included molecular subtyping by 450k whole methylome and gene expression analyses.

Results
Median PFS was longer in arm A than in arm B (7.6 and 4.8 months, P = 0.003), but OS was similar (12.1 and 12.2 months, P = 0.77). Clinical deterioration was delayed and more patients came off steroids in arm A. Prolonged PFS in arm A was confined to tumors with the receptor tyrosine kinase (RTK) I methylation subtype (HR 0.25, P = 0.014) and proneural gene expression (HR 0.29, P = 0.025). In a Cox model of OS controlling for established prognostic factors, associations with more favorable outcome were identified for age <70 years (HR 0.52, P = 0.018) and Karnofsky performance score 90%-100% (HR 0.51, P = 0.026). Including molecular subtypes into that model identified an association of the RTK II gene methylation subtype with inferior OS (HR 1.73, P = 0.076).
Conclusion
Efficacy outcomes and exploratory analyses of ARTE do not support the hypothesis that the addition of bevacizumab to RT generally prolongs survival in elderly glioblastoma patients. Molecular biomarkers may identify patients with preferential benefit from bevacizumab.

Clinical trial registration number
NCT01443676.