Marizomib

Standard treatment for patients with newly diagnosed glioblastoma includes surgery, radiotherapy (RT) and temozolomide (TMZ) chemotherapy (TMZ/RT→TMZ). The proteasome has long been considered a promising therapeutic target because of its role as a central biological hub in tumor cells. Marizomib is a novel pan-proteasome inhibitor that crosses the blood brain barrier.

Methods: EORTC 1709/CCTG CE.8 was a multicenter, randomized, controlled, open label phase 3 superiority trial. Key eligibility criteria included newly diagnosed glioblastoma, age > 18 years and Karnofsky performance status > 70. Patients were randomized in a 1:1 ratio. The primary objective was to compare overall survival (OS) in patients receiving marizomib in addition to TMZ/RT→TMZ with patients receiving only standard treatment in the whole population, and in the subgroup of patients with MGMT promoter-unmethylated tumors.

Results: The trial was opened at 82 institutions in Europe, Canada and the US. A total of 749 patients (99.9% of planned 750) were randomized. OS was not different between the standard and the marizomib arm (median 17 vs 16.5 months; HR=1.04; p=0.64). PFS was not statistically different either (median 6.0 vs. 6.3 months; HR=0.97; p=0.67). In patients with MGMT promoter-unmethylated tumors, OS was also not different between standard therapy and marizomib (median 14.5 vs 15.1 months, HR=1.13; p=0.27). More CTCAE grade 3/4 treatment-emergent adverse events were observed in the marizomib arm than in the standard arm.

Conclusions: Adding marizomib to standard temozolomide-based radiochemotherapy resulted in more toxicity, but did not improve OS or PFS in patients with newly diagnosed glioblastoma [1].

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Roth P, Gorlia T, Reijneveld JC, de Vos F, Idbaih A, Frenel JS, Le Rhun E, Sepulveda JM, Perry J, Masucci GL, Freres P, Hirte H, Seidel C, Walenkamp A, Lukacova S, Meijnders P, Blais A, Ducray F, Verschaeve V, Nicholas G, Balana C, Bota DA, Preusser M, Nuyens S, Dhermain F, van den Bent M, O'Callaghan CJ, Vanlancker M, Mason W, Weller M; EORTC Brain Tumor Group and the Canadian Cancer Trials Group. Marizomib for patients with newly diagnosed glioblastoma: a randomized phase 3 trial. Neuro Oncol. 2024 Mar 19:noae053. doi: 10.1093/neuonc/noae053. Epub ahead of print. PMID: 38502052.