J Neurooncol. 2023 Nov 28. doi: 10.1007/s11060-023-04514-0. Online ahead of print.

A multi-site phase I trial of Veliparib with standard radiation and temozolomide in patients with newly diagnosed glioblastoma multiforme (GBM)

Lawrence Kleinberg [1 2 3], Xiaobu Ye [4 5], Jeff Supko [6], Glen H J Stevens [7], Hui-Kuo Shu [8], Tom Mikkelsen [9], Frank Lieberman [10], Glenn J Lesser [11], Emerson Lee [12], Stuart A Grossman [12]

Affiliations

PMID: 38015376 DOI: 10.1007/s11060-023-04514-0

Abstract

Purpose: A multi-site Phase I trial was conducted to determine the safety, maximum tolerated dose, and pharmacokinetics (PK) of Veliparib, a Poly (ADP-ribose) polymerase [PARP] enzyme inhibitor, when administered with temozolomide (TMZ) alone and then with temozolomide and radiation (RT) in patients with newly diagnosed glioblastoma.

Methods: Given the potential for myelosuppression when a PARP inhibitor is combined with chemotherapy, the first 6 patients accrued were given Veliparib 10 mg bid and TMZ 75 mg/m2/d daily for six weeks. If this was well tolerated, the same doses of Veliparib and TMZ would be tested along with standard radiation with plans to dose escalate the Veliparib in subsequent patient cohorts. Once a maximal tolerated dose was determined, a 78 patient phase II study was planned. Peripheral blood pharmacokinetics were assessed.

Results: Twenty-four patients were enrolled. In the first 6 patients who received 6 weeks of TMZ with Veliparib only one dose limiting toxicity (DLT) occurred. The next 12 patients received 6 weeks of RT + TMZ + veliparib and 4/12 (33%) had dose limiting hematologic toxicities. As a result, Veliparib was reduced by 50% to 10 mg BID every other week, but again 3/3 patients had dose limiting hematologic toxicities. The trial was then terminated. The mean clearance (± SD) CL/F of Veliparib for the initial dose (27.0 ± 9.0 L/h, n = 16) and at steady-state for 10 mg BID (23.5 ± 10.4 L/h, n = 18) were similar. Accumulation for BID dosing was 56% (± 33%).

Conclusions: Although Veliparib 10 mg BID administered with TMZ 75 mg/m2 for six weeks was well tolerated, when this regimen was combined with standard partial brain irradiation it was severely myelosuppressive even when the dose was reduced by 50%. This study again highlights the potential of localized cranial radiotherapy to significantly increase hematologic toxicity of marginally myelosuppressive systemic therapies.

Keywords: Glioblastoma; Myellosuppression; PARP inhibitor; Radiotherap; Temozolomide; Toxicity.