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Safety of idroxioleic acid in combination with standard of care (temozolomide and/or radiation therapy) in newly diagnosed glioblastoma patients: A phase Ib trial

C. Balaña[1], S. del Barco Berrón[2], A. Stradella[3], R. Villanueva Vazquez[4], A. Cuesta[5], J.V. Torres[6], J. Roma[7], R. Taylor[8], P.V. Escriba[9], E. Llobet[6], A.G. McNicholl[9]

[1] Medical Oncology Department, Catalan Institute of Oncology (ICO) Badalona, Barcelona, Spain, [2] Medical Oncology Department, Hospital Universitari Dr. Josep Trueta. ICO Girona, Girona, Spain, [3] Oncology, Catalan Institute of Oncology, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain, [4] Department Medical Oncology, ICO - Institut Català d'Oncologia l'Hospitalet (Hospital Duran i Reynals), Hospitalet De Llobregat, Spain, [5] Medical Department, Laminar Pharma, S.A., Palma De Mallorca, Spain, [6] Corporate, Optimapharm Inc, Palma De Mallorca, Spain, [7] Consultant Freelance, Barcelona, Spain, [8] MEdical Affairs, TMRP, London, UK[9] Clinical Operations, Laminar Pharma, S.A., Palma De Mallorca, Spain

Background

Glioblastoma multiforme (GBM) is the most frequent primary malignant brain tumour in adults (>60%), with very poor prognosis. First-line standard of care (SoC) treatment for patients involves surgery/surgical resection along with radiation therapy (RT) and concomitant adjuvant temozolomide (TMZ). Idroxioleic acid (2-hydroxyoleic acid sodium salt; 2-OHOA), a new class of orally bioavailable fatty acid that modulates the lipid composition and structure of the membranes, has shown specific effects against cancer due to a dual-mode molecular mechanism of action (cell cycle arrest and programmed cell death by non-protective autophagy in glioma). The aim of this study was to determine the safety, tolerability and maximum tolerated dose of 2-OHOA added to first-line SoC for newly diagnosed GBM patients.

Methods

A phase 1B, open-label, dose-finding study, 3+3 de-escalating design (starting at 12 g/day). The trial (NCT03867123) recruited newly diagnosed GBM patients with a partial or complete surgical resection of the grade 4 astrocytic tumour in two independent arms: arm 1 (6-week concurrent phase of RT + TMZ + 2-OHOA) and arm 2 (8-week maintenance phase of TMZ + 2-OHOA). Both arms were to be followed by a 4-week safety follow-up.

Results

Nineteen patients were recruited, 10 patients in Arm 1 and 9 in Arm 2. As no DLTs were found, all received 12 g/day of 2-OHOA. All patients from both arms presented at least one AE. The AEs presented in >40% of the patients were diarrhoea (8/10), headache (5/10), nausea (5/10), asthenia (4/10), constipation (4/10) and vomiting (4/10) in Arm 1, and nausea (6/8), diarrhoea (5/8) and vomiting (5/8) in Arm 2. None of the patients suffered any grade 4 or 5 AEs by CTCAE grade in any arm. The only attributed SAE in the study –embolism CTAE 3 in one patient in Cohort 1 (1/10)– was not related to 2-OHOA.

Conclusions

Addition of 12 g daily of 2-OHOA to standard of care (RT/TMZ) in newly diagnosed GBM patients was generally well tolerated, offered a favourable safety profile (no 2-OHOA-related serious or high-grade AEs), and it is the recommended dose of 2-OHOA for phase III trials.

Clinical trial identification

NCT03867123.

Legal entity responsible for the study

Laminar Pharmaceuticals S.A.

Funding

Laminar Pharmaceuticals S.A.

Disclosure

C. Balaña: Financial Interests, Institutional, Advisory Board: Laminar Pharmaceutical. A. Cuesta: Financial Interests, Personal, Full or part-time Employment: Laminar Pharmaceutical. J.V. Torres: Financial Interests, Institutional, Project Lead: Laminar Pharmaceutical. J. Roma: Financial Interests, Personal, Advisory Role: Laminar Pharmaceutical. R. Taylor: Financial Interests,

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