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An academia-driven compassionate use program for patients with recurrent H3K27-altered diffuse midline glioma: a new way to access innovation when clinical trials are lacking.

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Diffuse midline gliomas H3K27-altered have a very poor prognosis both in adults and children (1). The current therapeutic strategy is based on radiotherapy, that can only slow down the progression of the disease (2). In this context, it is a priority to find new agents to be tested in clinical trials. In the last years, a new drug developed by OncoceuticsTM and then ChimerixTM, ONC201 / dordaviprone, has emerged as a promising agent in a phase II clinical trial in the USA (3). The drug was well tolerated with just grade 1 or 2 toxicities like nausea, vomiting, and fatigue (3)(4). As the drug was only available in the clinical trial setting and compassionate use programs in the USA and Japan, In Germany, a biosimilar GsONC201 was produced by a private pharmacist and purchased by families (5). In this setting, considering the possible efficacy of the agent in this disease with no other therapeutic options, a compassionate use program for patients with confirmed H3K27-altered DMG at progression after radiotherapy was launched under the supervision of the French Competent Authority (Agence Nationale de Sécurité des Médicaments, ANSM) with the support of the Gustave Roussy Foundation. This pharmaceutical preparation, identical to the drug ONC201 developed in the US, was compounded at Gustave Roussy pharmacy from the raw material to the finished product. The product pharmaceutical quality was validated by an independent ANSM Quality Control Laboratory. Each potentially eligible patient was presented at a national molecular tumor board to define the most appropriate therapeutic recommendation, based on patient's previous treatment and tumor molecular alterations identified by sequencing. Suggestions for treatment, including ONC201, were made and ranked. The process is summarized in Figure 1. 152 patients with progressive disease from 47 centers in France and other countries have had access to ONC201 in this academia-driven compassionate use program from November 2021 to May 2023. Patients were closely followed-up in the SACHA study (NCT04477681) which is monitoring safety and efficacy of off-label and compassionate anticancer treatments in pediatrics and adults. Twenty of them (11 children and 9 adults) experienced sustained response or stable disease with a median duration of treatment of 111 days (range 36-198). Eleven patients out of 20 received a second course of radiotherapy. No severe adverse effects were reported.