PCM-13. THE HYPOXIA-ACTIVATED PRODRUG EVOFOSFAMIDE (TH-302) IS EFFICACIOUS IN PEDIATRIC HIGH GRADE GLIOMA CELL LINES AS A MONOTHERAPY AND IN COMBINATION WITH CHEMOTHERAPIES

Pierre Leblond1,4, Pauline Navarin1,4, Mélanie Arcicasa1,4, Christine Bal-Mahieu1,4, Nicole Lemahieu1,4, Pamela Voëlkel2,4, Eric Lartigau1,3, Pierre-Olivier Angrand2,4, and Samuel Meignan1,4; 1Centre Oscar Lambret, Lille, France; 2Lille 1 University, Villeneuve d’Ascq, France; 3Lille 2 University, Lille, France; 4INSERM U908, Villeneuve d’Ascq, France

The prognosis of children with pediatric high grade glioma (pHGG) remains poor despite aggressive multidisciplinary therapeutic approaches. Evofosfamide (Evo, previously known as TH-302) is a 2-nitroimidazole hypoxia-activated prodrug of the cytotoxic bromo-isophosphoramide mustard. Evo has been shown to exhibit preclinical activity against solid tumors. We present here the first data with Evo in pHGG cell lines.

MATERIALS AND METHODS: Evo was evaluated in 3 well-characterized pHGG cell lines (SF188, UW479, KNS42), cultivated under normoxic or hypoxic conditions (1% O2). The cytotoxicity of Evo, used as a single drug or in association with SN38, doxorubicin and etoposide, was evaluated in vitro using a MTS assay. The synergism was analyzed by the Chou and Talalay method. Radio-sensitizing effects were investigated in vitro using clonogenic assays.

RESULTS: Growth of all cell lines was inhibited by Evo single agent, and as expected, the cytotoxicity of Evo was higher under hypoxic conditions (IC50 were 2-8 fold higher in normoxic vs hypoxic conditions). As previously reported, we found a strong synergism between Evo and doxorubicin, and we also demonstrated a significant synergistic effect with SN38 and etoposide (CI ≤ 0.5 in every case). Radio-sensitizing effects and in vivo evaluations are currently ongoing.

CONCLUSION: Hypoxia is a well-known phenomenon leading to glioma cell resistance to cytotoxic drugs. We report here the first preclinical data about a novel hypoxia-activated prodrug Evo in pediatric high grade glioma. Interestingly, Evo appears effective in hypoxic glioma cells and the synergistic effects observed with SN38, doxorubicin and etoposide are of interest for pediatric oncology.