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Virginia Laspidea, Iker Ausejo-Mauleon, Daniel de la Nava, Sara Nuin, Reyes Hernandez-Osuna, Javier Marco-Sanz, Daniel Palacios-Alonso, Candelaria Gomez-Manzano, Juan Fueyo, Marta Alonso
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Virginia Laspidea, Iker Ausejo-Mauleon, Daniel de la Nava, Sara Nuin, Reyso Hernandez-Osuna, Javier Marco-Sanz, Daniel Palacios-Alonso, Candelaria Gomez-Manzano, Juan Fuyo, Marta Alonso; 1Department of Pediatrics, Clinic University of Navarra, Pamplona, Spain. 2Department of Neuro-Oncology, MD Anderson Cancer Center, Houston, USA

Diffuse Midline Gliomas (DMG) are very aggressive brain tumors that arise in the brainstem of children. The prognosis of these patients is still dismal, with an overall survival of less than one year. DMG tumors are poorly infiltrated by the immune system, and therefore in this project, we propose the use of the oncolytic adenovirus Delta-24-RGDOX to enhance the antitumor immune response. Delta-24-RGDOX is based on the Delta-24-RGD platform and incorporates the OX40 ligand (OX40L). The binding of OX40 to OX40L leads to the co-stimulation of CD4 and CD8 cells, generating effector and memory T cells. Therefore, the aim of this
project is to improve the antitumor effect of the virus, providing a greater co-stimulation in the tumor. In vitro, Delta-24-RGDOX was able to efficiently infect and express viral proteins in human and murine DMG cell lines, and to cause cell death in a dose-dependent manner. Moreover, the virus expressed OX40L on the membrane of infected cells, which was functional and capable of activating CD8 T cells. Once we confirmed that the viral administration into DMG in vivo models was safe, we evaluated the therapeutic effect of the virus. We observed a significant survival increase after Delta-24-RGDOX treatment of a DMG model at early tumor stage (P=0.0033, median OS PBS 9 vs 12 days for virus treated mice) and in already established tumors (P=0.018, median OS PBS 9 vs 12.5 days for virus treated mice). Importantly, tumors from treated mice (7 days after treatment) displayed a significant increase of immune infiltration compared to controls. Moreover, splenocytes from Delta-24-RGDOX treated mice were also more activated. These data demonstrated that Delta-24-RGDOX expresses OX40L on infected cells, promoting the modulation of the tumor microenvironment and leading to an improved survival outcome in DMG models.