

Translation of DNX-2401 from the bench to the clinic for pediatric high-grade gliomas including diffuse intrinsic pontine gliomas

Naiara Martinez-Vélez, Marc Garcia-Moure, Virginia Laspidea, Oren Becher, Juan Fueyo, Cande Gomez-Manzano, Ana Patiño, Ricardo Díez-Valle, Sonia Tejada-Solís and Marta M. Alonso.

Despite our increased understanding of the genetic make-up and new derived therapies for pediatric high grade glioma (pHGG) and Diffuse Intrinsic Pontine Glioma (DIPG) the outcome remains grim. Delta-24-RGD (DNX-2401 in the clinic) has been tested for adult glioblastoma presenting a safe profile and promising efficacy. The objective of this study was to evaluate the suitability of DNX-2401 as treatment for pHGG/DIPGs. Our results showed that DNX-2401 exerts a potent antitumor effect in pHGG (n=5) and DIPG (n=6) human cell lines in vitro and in vivo. Our clinical trial experience with DNX-2401 in adult glioblastoma underscored the importance of the immune system in durable responses observed in patients. . DNX-2401 administration was safe and without toxicity in two DIPG immunocompetent models. DNX-2401 prolonged the overall survival, leading 20% to 80% of long-term survivors. Histologic examination showed that DNX-2401 stimulated T-cell infiltration (CD3+, CD4+ and CD8+; $p < 0.001$) within the tumor. In addition, splenocytes from DNX-2401 treated-mice co-cultured with tumor cells significantly increase the IFN γ production ($p < 0.0001$). In conclusion, the therapeutic benefit observed is mediated by the immune response triggered against DIPG tumor by DNX-2401. These outstanding preclinical results allowed us to open a phase I clinical trial for newly diagnosed DIPGs (NCT03178032) where the patients received an intratumoral viral injection followed by standard radiotherapy. Up to date 7 patients have been treated within the trial (3×10^{10} viral particles in 1mL). The procedure was well tolerated and safe. Patients were home 3-4 days after the procedure. All the patients displayed a reduced tumor volume after combined treatment. In the next weeks, we will have information regarding the median survival. We are currently conducting molecular and functional studies to assess the response of the patients to the virus. Information acquired within this clinical study would aid to understand the response of DIPGs to viral therapies therefore to better tailor this strategy to improve the survival and the quality of life of pediatric brain tumor patients.