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Prior Radiation in Subjects Who Were Treated With Toca 511 and Toca FC Across 3 Toca 511 Phase 1 Trials

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Purpose/Objective(s): Recurrent high grade gliomas (rHGG) have a dismal prognosis and a high unmet need for effective therapies. Toca 511 (vocimagene amiretrorepvec), an investigational retroviral replicating vector, encodes the transgene cytosine deaminase (CD). Toca 511 selectively infects, persists, and spreads in actively proliferating cancer cells. Subsequent oral administration of the extended-release antifungal drug 5-fluorocytosine (Toca FC) results in production of 5-fluorouracil (5-FU) by the CD enzyme within infected cells. 5-FU kills cancer cells and myeloid derived suppressor cells, leading to robust antitumor immune responses in animal models. This sequence of events is amplified with multiple cycles of 5-fluorocytosine. Clinical data from 2 phase 1 trials in rHGG (NCT01156584, NCT01470794) are consistent with this mechanism of action, and show a favorable safety profile and extended survival compared to historical controls. To begin to assess the tolerability of radiation therapy (RT) with Toca 511/Toca FC, the RT dose delivered and safety are described.

Materials/Methods: Three ongoing dose escalating clinical studies using Toca 511/Toca FC are designed to evaluate the safety and preliminary efficacy of this investigational therapy in patients with rHGG (NCT01156584, NCT01985256, and NCT01470794). Toca 511 is administered by three different routes: intratumorally, into the walls of the resection cavity, and intravenously. In all studies, Toca 511 treatment is followed by repeated courses of Toca FC. The safety evaluable population for Toca 511 (107 subjects) and Toca FC (96 subjects) across multiple dose cohorts were evaluated for adverse events (AEs).

Results: Across the 3 trials, all subjects received RT prior to Toca 511 treatment with a median dose of 60 Gy (range 54 - 64 Gy). Twelve subjects received a second course of radiation with a median dose of 79 Gy and a range from 42.5 to 95.0 Gy. All but one subject received the first Toca 511 treatment at least 12 weeks after the last dose of RT. Toca 511 related AEs of grade 1/2 (23.4%) and grade ≥ 3 (3.7%), and Toca FC related AEs of grade 1/2 (33.3%) and grade ≥ 3 (2.1%) were reported. Adverse events regardless of attribution in this rHGG patient population, the majority of whom had undergone a neurosurgical procedure, were reported with Toca 511 (grade 1/2 40.2% and grade ≥ 3 56.1%), and Toca FC (grade 1/2 46.9% and grade ≥ 3 47.9%). There were no treatment related deaths. Overall, safety was tolerable and adverse events were manageable.

Conclusion: In three Phase I trials in recurrent HGG, all patients received RT prior to Toca 511 and Toca FC and showed a manageable safety profile. Updated data will be provided. Based on the tolerability observed and as a next step in the development plan, concurrent Toca 511 with surgery and chemoradiation with temozolomide will be studied in newly diagnosed HGG patients in the Toca 7 study (NCT02598011). Author

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