INBRX-109 in Ewing Sarcoma: Preclinical Rationale for Initiation of a Phase 1 Chemotherapy Combination Expansion Cohort

INBH-109 Mechanism of Action

- INBH-109 (Figure 1) is a tetravalent, agonistic antibody targeting death receptor 5 (DR5), a proapoptotic receptor for the trimeric tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).

- TRAIL selectively induces programmed cell death in cancer cells, with minimal impact on normal tissues, and therefore plays an important role in tumor and viral immune surveillance.

INBH-109 was previously shown to overcome the limitations of earlier-generation DR5 agonists, resulting in optimal agonism and safety.

INBH-109 in Ewing Sarcoma

- Ewing sarcoma is a rare tumor that occurs in children and young adults; recurrence or relapse is common.

- Chemotherapy, including irinotecan (IRI) and temozolomide (TMZ), is widely used to treat patients with relapsed/refractory or metastatic tumors, but survival remains poor.

- Studies have reported overall survival of 12.0 to 14.1 months and progression-free survival of 3.8 to 8.3 months in patients treated with IRI + TMZ.

- In preclinical analyses, INBH-109 demonstrated potent anticancer activity in Ewing sarcoma cell lines in vitro and in a Ewing sarcoma patient-derived xenograft model.

- Additionally, INBH-109 demonstrated activity in combination with SN-38, the active metabolite of oxycodone, across multiple Ewing sarcoma model cell lines.

- These findings suggest that DR5 agonism (INBH-109) combined with inhibition of DNA-replication and transcription (IRI) confers an added benefit in Ewing sarcoma, with INBH-109-mediated DR5 cross-linking providing key proapoptotic signaling in in vitro models of Ewing sarcoma.

OBJECTIVE

- Based on these preclinical data, we further evaluated INBH-109 + IRI combination therapy in an animal model of Ewing sarcoma.

- Furthermore, a Ewing sarcoma expansion cohort to explore INBH-109 in combination with IRI and TMZ was initiated in September 2021 as part of an ongoing phase 1 dose-escalation study (NCT03719533).

- Previous studies showed that INBH-109 induces DR5 expression and downregulates antiapoptotic proteins, suggesting that INBH-109 + IRI + TMZ may improve Ewing sarcoma model cell lines.

- We present preclinical in vivo data for INBH-109 combination therapy and preliminary clinical findings from the INBH-109 Ewing sarcoma expansion cohort.

METHODS

Preclinical

- Female BALB/c nude mice were inoculated subcutaneously with A673 tumor cells and randomized to vehicle (0 mg/kg intravenous [IV]), 10 mg/kg, or 20 mg/kg of INBH-109 (1 mg/kg IV, 10 μg/100 g, or 30 μg/100 g IRI IV, 300 μg/mg body weight [BW], or 100 μg/mg BW) on days 1, 8, 15, and 22.

- Tumor volumes were measured twice per week using Student director software (Systmatics).

- The impact of valency on cell viability of treated 3D human liver microtissues was determined by measuring intracellular adenosine triphosphate (ATP) content (CellTiter-Glo) (Promega) and extracellular lactate dehydrogenase (LDH) release (bioluminescent LDH assay kit [Promega]) after 7 days of treatment with INBH-109 or a hexavalent compound.

Clinical

- A 3-part, phase 1 study (NCT03719533) evaluating the safety and efficacy of INBH-109 in patients with advanced/metastatic solid tumors was initiated in November 2018 (Figure 2).

- Part 1 (single-agent dose escalation) was completed in 2019.

- Significant toxicities were observed; a maximum tolerated dose was not reached, and a dose of 3 mg/kg was chosen for further investigation.

- Part 2 (single-agent expansion) and part 3 (combination therapy expansion) will evaluate efficacy as a primary endpoint; pharmacokinetics and immunogenicity as secondary endpoints, and efficacy as an exploratory endpoint.

- A chemotherapy combination cohort in Ewing sarcoma opened in September 2021 and will enroll 20 patients with locally advanced or metastatic unresectable disease.

RESULTS

In Vivo Antitumor Activity

- Consistent with previous in vitro observations, INBH-109 and IRI coadministration significantly increased antitumor efficacy compared with single-agent treatment in a Ewing sarcoma xenograft animal model (Figure 3).

- Initial tumor regression followed by outgrowth was observed in mice treated with IRI only (Figure 3A), while complete tumor regression was observed in all mice treated with combination therapy (Figure 3A and 3B).

- INBH-109 and IRI coadministration significantly increased adenosine triphosphate (ATP) and lactate dehydrogenase (LDH) release (Figure 3).

- The most common adverse event (AE) was diarrhea, which is consistent with the known safety profile of the chemotherapeutic agents (IRI/TMZ) in the combination treatment (Table 2).

CONCLUSIONS

- INBH-109, a tetravalent, agonistic antibody targeting DR5, demonstrated preclinical antitumor activity in Ewing sarcoma.

- In an animal model of Ewing sarcoma, INBH-109 and IRI coadministration significantly increased antitumor efficacy compared with single-agent treatment.

- Complete tumor regression was observed in all treated mice.

- Treatment with up to 10 mg INBH-109 did not induce cell death in a 3D human liver toxicity model, demonstrating minimal to no hepatotoxicity in vitro.

- INBH-109 + IRI/TMZ is being explored clinically in an ongoing phase 1 study in patients with Ewing sarcoma.

- As of the data cutoff (November 30, 2021), 6 patients had received INBH-109 + IRI/TMZ combination therapy (Table 1).

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REFERENCES


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