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A first-in-human Phase 1, multicenter, open-label study of M3554, a novel anti-GD2 antibody-drug conjugate, in patients with advanced solid tumors

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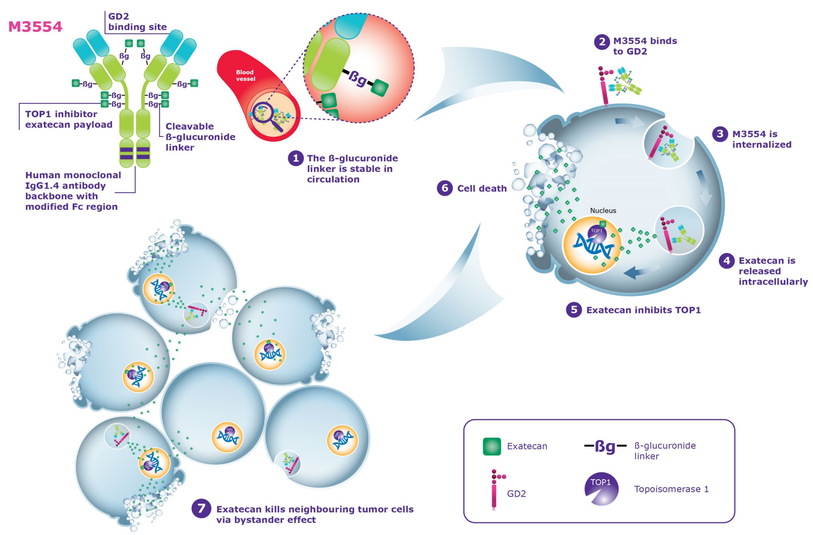
STUDY STATUS

The study is currently recruiting and aims to enroll ≈52 patients in the dose escalation phase and ≈110 patients in the dose expansion phase (STS, n≈80; GBM, n≈30) globally, including in the US, Belgium, France, and Japan

INTRODUCTION

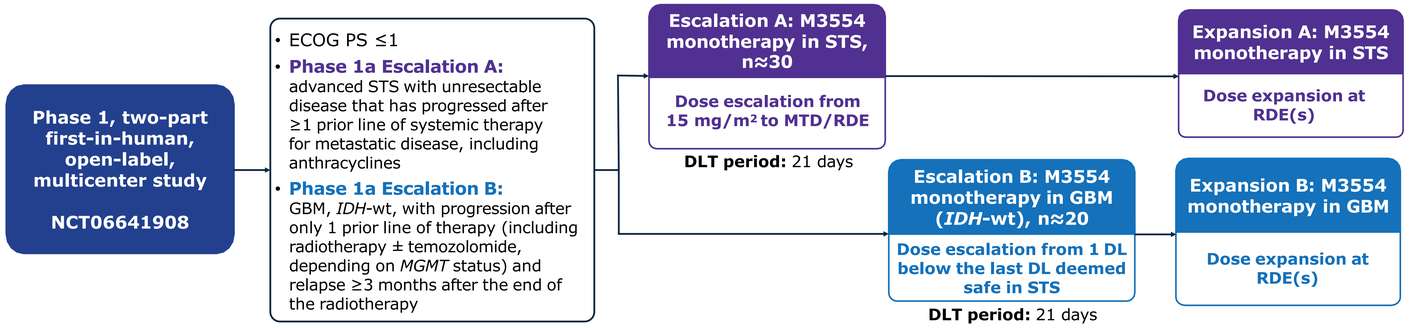
- Disialoganglioside **GD2** shows **high expression** in **STS** and **GBM**, and is a rational, **clinically-validated target** in **NBL**, all of which are indications with a high unmet medical need[1,2]
  - Currently approved anti-GD2 antibodies (e.g., dinutuximab, naxitamab) have been associated with severe pain adverse events hypothesized to be due to Fcγ receptor-mediated immune activation via **antibody-dependent cellular cytotoxicity** and **complement-dependent cytotoxicity**[3]
- **M3554 is a first-in-class anti-GD2 ADC** with a **ß-glucuronide-exatecan linker-payload combination**, which selectively delivers **exatecan**, a potent TOP1 inhibitor, to tumors with GD2 expression[2]
- M3554 uses a **Fc-modified** anti-GD2 antibody to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity effector functions, **potentially reducing incidence and severity of pain** adverse events[2]
- In **preclinical** studies, M3554 showed **strong anti-tumor activity** in patient-derived xenograft models of neuroblastoma, sarcoma, and GBM; and a **favorable PK and safety profile** in animal studies[3]

Figure 1. M3554 mechanism of action



STUDY DESIGN

Figure 2. Study design



METHODS

- Phase 1a consists of two separate dose escalation cohorts (staggered enrollment, starting with the STS cohort) to determine RDE(s) and MTD (**Figure 2; Table 1; Table 2**)
- Phase 1b consists of two expansion cohorts to inform selection of the recommended Phase 2 dose

Table 1. Study endpoints of Phase 1a

Endpoints
Primary endpoints
• Occurrence of dose-limiting toxicities • Occurrence of adverse events
Secondary endpoints
• Pharmacokinetic parameters of M3554 related analytes (total antibody, conjugated antibody, unconjugated payload) such as: ◦ Area under the concentration-time curve over a dosing interval ◦ Area under the concentration-time curve from time zero to last time point ◦ Maximum concentration (C_{max}) ◦ Trough concentration (C_{trough}) ◦ Clearance ◦ Volume of distribution ◦ Half-life ($t_{1/2}$)
• Objective response[a] • Duration of response[a] (time from first documentation of objective response to progressive disease or death) • Progression-free survival[a] (time from date of first study intervention to progressive disease or death)
• Change from baseline QTc (ΔQTc) at predefined timepoints based on triplicate ECG measurements

[a]According to RECIST v1.1 (STS) or RANO v2.0 criteria (GBM).

Table 2. Key eligibility criteria

Key inclusion criteria	
• ≥18 years of age • ECOG PS ≤1 • Adequate hematological, hepatic, and renal function	
STS	**GBM**
Escalation A: • Archival formalin-fixed, paraffin-embedded tissue[a] + formalin-fixed tumor tissue[b] are required. If unavailable, a baseline biopsy is required	**Escalation B:** • Archival tumor tissue is not required for eligibility but is highly recommended to be provided, if available
Key exclusion criteria	
• AEs related to previous therapies that have not recovered to grade ≤1 per NCI-CTCAE v5.0 • History of grade ≥3 neurotoxicity secondary to previous treatments • Ongoing grade 1 neurotoxicity from previous anticancer therapies • STS only: History of brain metastasis, leptomeningeal metastasis, or spinal cord compression • Other common Phase 1 exclusion criteria	

[a]For centralized pathological confirmation of the STS subtype. [b]For GD2 evaluation for correlation with efficacy.

STUDY CONTACT

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- For further information, please visit https://clinicaltrials.gov/ct2/show/NCT06641908.

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; DL, dose level; DLT, dose-limiting toxicity; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; GBM, glioblastoma; *IDH*-wt, isocitrate dehydrogenase wild type; *MGMT*, O6-methylguanine-DNA methyltransferase; MTD, maximum tolerated dose; NBL, neuroblastoma; NCI-CTCAE v5.0, National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0; PK, pharmacokinetics; QTc, corrected QT interval; RANO v2.0, Response Assessment in Neuro-Oncology version 2.0; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RDE, recommended dose for expansion; STS, soft tissue sarcoma; TOP1, topoisomerase 1; US, United States.

References 1. Nazha B, et al. *Front Oncol*. 2020;10:1000. 2. Philippova J, et al. *Front Immunol*. 2024;15:1371345. 3. Amendt C, et al. *Cancer Res*. 2024;84:ND08.

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