Official Study Title

A Prospective Study Assessing Neurological Function and Its Clinical Implications in Patients With Locally Advanced or Metastatic Urothelial Carcinoma Receiving Enfortumab Vedotin-Based Therapy

ClinicalTrials.gov Identifier (NCT Number): Pending Assignment

Document Date: June 27, 2025

Confidentiality Notice:

This document is intended for use in the ClinicalTrials.gov registration and results reporting process only. It does not contain any personal identifiers of study participants.

1. Official Study Title

A Prospective Study Assessing Neurological Function and Its Clinical Implications in Patients With Locally Advanced or Metastatic Urothelial Carcinoma Receiving Enfortumab Vedotin-Based Therapy

2. Background and Rationale

Locally advanced or metastatic urothelial carcinoma (la/mUC) remains a highly lethal disease despite advances in systemic therapy. While platinum-based chemotherapy (Plt-ChT) has long been the mainstay of first-line treatment, its survival benefit is limited by significant toxicity and a lack of durable response. Enfortumab vedotin (EV) is a NECTIN-4-directed antibody-drug conjugate (ADC) that has demonstrated robust antitumor activity in patients with la/mUC. In the phase III EV-301 study, EV significantly improved overall survival in patients who progressed following Plt-ChT and ICIs. More recently, the phase III EV-302 trial established EV in combination with pembrolizumab as a superior first-line therapy compared to Plt-ChT, regardless of cisplatin eligibility. Based on these data, EV has been approved in both first-line (in combination) and third-line (monotherapy) settings and is considered a standard of care in la/mUC.

However, peripheral neuropathy (PN), a known adverse event associated with the payload monomethyl auristatin E (MMAE), remains a major dose-limiting toxicity of EV. PN occurs in 40–50% of patients, can be irreversible, and significantly impairs patients' quality of life. Although the underlying mechanisms are not fully elucidated, they may include both on-target and off-target effects, such as MMAE-induced microtubule disruption, premature drug release, and neuroinflammatory processes. Notably, the lack of objective tools for early identification and quantitative monitoring of EV-induced PN poses a clinical challenge.

This study aims to prospectively assess neurological function in patients receiving EV-based therapy for la/mUC. By correlating objective neurological assessments with patient-reported outcomes, we seek to improve the understanding of EV-related PN, identify high-risk individuals, and lay the groundwork

for future preventive or mitigating strategies. The findings may ultimately contribute to optimizing EV-based treatment by balancing efficacy with tolerability.

3. Objectives

3-1. Primary Objective

(1) To investigate the correlation between neurological function and subjective symptoms of PN during EV-based therapy.

3-2. Secondary Objectives

(1) To evaluate the relationship between patient characteristics/neurological function changes and patient-reported PN in order to identify high risk patients for developing PN during EV-based therapy.

(2) To investigate the correlation between neurological function changes and oncological outcomes of EV-based therapy, including objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

4. Study Design

4-1. **Study Type**: Observational

4-2. **Study Design**: Prospective cohort study

4-3. **Study Center**: Single-center (National Taiwan University Hospital, NTUH); may expand to multi-center in the future

4-4. **Enrollment Method**: Consecutive enrollment of eligible patients

4-5. **Study Period**: July, 2025 to December 31, 2031

4-6. **Estimated Sample Size**: 100 patients receiving EV-based therapy

5. Study Population

5-1. Inclusion Criteria

(1) Age ≥ 20 y/o

(2) Histologically confirmed urothelial carcinoma

(3) Radiologically documented locally advanced or metastatic disease

(4) Prepare for receiving EV (as monotherapy or in combination with immune checkpoint inhibitors)

(5) Complete and identifiable medical records

5-2. Exclusion Criteria

(1) Do not agree to receive regular neurological examinations

(2) Do not agree to provide complete medical records during treatment

5-3. Sampling Method

(1) Consecutive enrollment of eligible patients meeting the inclusion criteria

6. Study Groups/Cohorts

6-1. Group 1: EV-based Therapy Cohort

(1) Population: Patients with locally advanced or metastatic urothelial carcinoma receiving EV-based therapy

(2) Diagnostic test: Neurological evaluations including neurological examination (NE), nerve conduction study (NCS), quantitative sensory testing (QST), autonomic function testing (AFT), and the Toronto Clinical Neuropathy Score (TCNS) questionnaire. Assessments will be conducted at baseline and every three months until six months after completion of EV treatment.

7. Endpoints / Outcome Measures

7-1. Primary Outcome Measure

(1) Correlation between neurological function and subjective PN symptoms:

Correlation between objective neurological assessments (including NE, QST, AFS, and TCNS) and patient-reported PN symptoms.

Time Frame: Baseline to 6 months post-treatment.

7-2. Secondary Outcome Measure

(1) Correlation between neurological function changes and oncological outcomes: To evaluate whether the degree or pattern of neurological function changes (e.g., worsening in NCS, QST) correlates with clinical efficacy measures such as ORR, PFS, and OS.

Time Frame: From date of EV initiation to the date of death from any cause, assessed up to 36 months

8. Methods / Assessments

8-1. Neurological assessment

(1) NE

(2) NCS

(3) QST

(4) AFT

(5) TCNS

All of these neurological function assessment will be evaluated as baseline , every three month during treatment, up to 6 months after completion of treatment.

8-2. Data Collection

Demographic, clinical, and treatment-related data will be recorded, including age, sex, comorbidities, ECOG performance status, prior treatments, EV regimen details, and cumulative dose. Patient-reported outcomes (PN symptoms) and oncological outcomes (ORR, PFS, OS) will also be collected.

8-3. Statistical Analysis

(1) Descriptive statistics will be used to summarize patient characteristics.

(2) Survival analysis:

- Kaplan–Meier method for estimating PFS and OS
- Log-rank test for between-group comparisons

(4) Multivariable analysis:

- Cox proportional hazards model to assess the independent association of neurological function factors with survival outcomes
- Logistic regression for associations with objective response

9. Ethics / Regulatory Compliance

9-1. The study protocol has been reviewed and approved by the Research Ethics Committee B of National Taiwan University Hospital.

IRB Approval Number:202502005RINB

Approval Date: 2025-03-13

9-2. This study will be conducted in accordance with the principles of the Declaration of Helsinki, ICH Good Clinical Practice (GCP) guidelines, and applicable local regulatory requirements.

9-3. Informed consent will be obtained from all participants before enrollment. The consent process will include information on study purpose, procedures, risks, benefits, data confidentiality, and the voluntary nature of participation.

9-4. Confidentiality and data protection:

(1) All personal identifying information will be coded and stored securely in password-protected databases.

(2) Only authorized study personnel will have access to identifiable data.

(3) Data will be reported in aggregate to prevent the identification of individual participants.

10. Study Timeline

10-1. Planned Study Start Date: Jul, 2025

10-2. **Planned Study End Date (Final Data Collection):** December 31, 2031

10-3. **Primary Completion Date:** December 31, 2030

10-4. **Study Completion Date:** December 31, 2031