Targeting EphA2 in bladder cancer using a novel antibody-directed nanotherapeutic

Walid Kamoun1, Elden Swendsen1, Christine Pien1, Lia Luan1, Jason Cain1, Irawati Kandela2, Richard Huang3, Suresh Tipparaju1, Dmitri Kortepuin1, Wiam Bahara2, Vasilios Askoxylakis1, Carl Morrison2, and Daryl Drummond1
1 Merrimack Pharmaceuticals, Inc., Cambridge, MA  2 Roswell Park Cancer Institute, Buffalo, NY  3 Developmental Therapeutics Core Facility, Northwestern University, Evanston, IL

Abstract

Eph receptor A2 (EphA2) is a member of the Eph/Eph receptor family that is involved in cell signaling, including proliferation, differentiation, and migration. EphA2 is overexpressed in a broad range of cancers, including bladder cancer, making it a potential therapeutic target. We previously showed promising preclinical activity of a novel EphA2-targeted antibody-drug conjugate (ADC) in bladder cancer xenografts. Here, we studied EphA2 expression and activity in metastatic lesions to determine the potential use of EphA2-directed ADCs in patients with bladder cancer.

EphA2 Prevalence and Prognostic Effect in Bladder Cancer

EphA2 overexpression was seen in 80-100% of tumors and correlated with shorter patient survival (147 bladder cancer samples in tissue microarray (Roswell Park Cancer Institute)).

**Key Points:**
- EphA2 expression correlated with overall survival.
- EphA2 expression was maintained in metastases (10 pairs of primary and metastatic samples from patients with bladder cancer).
- Positive PD-L1 expression in the tumor cells was seen in a majority of EphA2-positive samples.

EphA2 Expression on Tumor Cells and Tumor-associated Blood Vessels

Majority of tumors showing EphA2 expression on tumor cells also show EphA2 on tumor-associated blood vessels (20 urothelial cancer samples)

We examined EphA2 tumor expression in 5 sets of patient samples:

1. Tissue microarray with matched survival data: Observations. EphA2 expression correlated with overall survival.
2. Urothelial carcinoma resections: Observations. EphA2 was expressed in both tumors and tumor-associated vasculature.

We tested the activity of MM-310, an EphA2-targeted nanotherapeutic (encapsulated docetaxel prodrug), in EphA2-expressing bladder PDX models:

- All showed reduction in tumor burden with MM-310 alone, greater activity with MM-310 than with an epodic dose of docetaxel, and potential for effective combination with gemcitabine.

Together, these data present a compelling case for targeting EphA2 with MM-310 in advanced bladder cancer trials.

**Key Points:**
- MM-310: An EphA2-Targeted Nanotherapeutic
- DOXETAXEL NANOLIPOSOME
  - Formulation extended drug circulation time in pre-clinical models with reduction in hematological toxicities compared to docetaxel.
  - Liposome deposition led to sustained release at the tumor site.
- EphA2 TARGETING scFv
  - Targeted EphA2-expressing cancer cells in primary tumors and metastatic lesions
  - Targeted tumor associated blood vessels
  - Led to more pronounced and sustained tumor regression in vivo.

**Impact:**
- EphA2 expression pattern is maintained in metastases (10 pairs of primary and metastatic samples from patients with bladder cancer).

**Summary:**

MM-310 Shows Activity Alone and in Combination with Gemcitabine in Bladder Cancer Patient-Derived Xenograft Models

Mice bearing patient-derived bladder cancer xenografts (implanted s.c. on flank, EphA2+) were dosed with MM-310, docetaxel (DTX), gemcitabine (GEM) or combinations of these agents 4 x q3d, and the tumor sizes were followed for >100 days.

#5771 /16