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

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Abstract

Ephrin receptor A2 (EphA2) is a member of the Ephin/Eph receptor cell to cell signaling family of molecules and plays a key role in proliferation, differentiation, and migration. EphA2 is overexpressed in a broad range of cancers, including bladder cancer, and is associated with increased metastasis and poor prognosis. Several potential EphA2-targeted therapies were developed and showed promising preclinical activity but failed to translate clinically due to narrow therapeutic window. we propose using a novel antibody-directed nanotherapeutic (ADN) approach to target EphA2 for the treatment of bladder cancer. This work characterizes the expression of EphA2 in bladder cancer patients, evaluates its prognostic power, and tests an investigational EphA2-targeted ADN, MM-310, in patient-derived xenograft (PDX) models. EphA2 expression in tumors was investigated using a validated immunohistochemistry assay performed in 147 bladder cancer samples, enabling analysis of prevalence and prognostic power. Whole sections of primary and metastatic tumor resections were used to assess EphA2 expression in tumor-associated vessels and tumor cells. Four EphA2+ PDX models were used to evaluate the activity of MM-310 compared to free docetaxel, alone or in combination with gemcitabine.

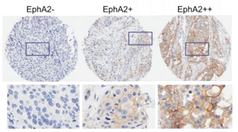
EphA2 was expressed in tumor cells and tumor-associated blood vessels in primary and metastatic lesions. EphA2 overexpression was seen in 80%-100% of tumors and correlated with shorter survival. In the PDX models, MM-310 controlled tumor growth, mediated greater regression, and was more active than free docetaxel at equitoxic dosing (Table). Additionally, the combination of MM-310 and gemcitabine controlled tumor growth better than each drug alone, and outperformed the combination of free docetaxel and gemcitabine in the single PDX model where it was compared.

Thus, in bladder cancer models, a docetaxel-based ADN administered as a monotherapy or in combination with gemcitabine targeted EphA2 and led to significant tumor regression.

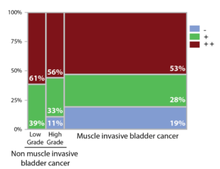
EphA2 Prevalence and Prognostic Effect in Bladder Cancer

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)).
• Positive PD-L1 expression (≥10% PD-L1 expression in tumor cells) was seen in majority of EphA2-positive samples.

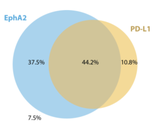
EphA2 IMMUNOHISTOCHEMISTRY EVALUATION



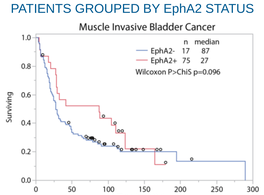
PREVALENCE RELATIVE TO HISTOLOGICAL GRADE



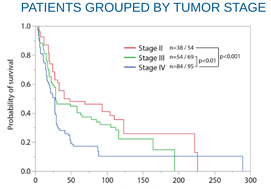
EXTENT of PD-L1 CO-EXPRESSION



OVERALL SURVIVAL: PATIENTS GROUPED BY EphA2 STATUS



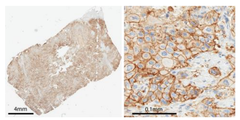
OVERALL SURVIVAL: PATIENTS GROUPED BY TUMOR STAGE



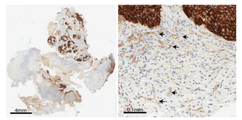
EphA2 Expression on Tumor Cells and Tumor-associated Blood Vessels

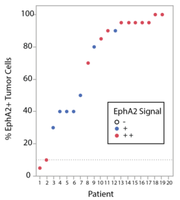
Majority of tumors showing EphA2 expression on tumor cells also show EphA2 on tumor-associated blood vessels (20 urothelial cancer samples)

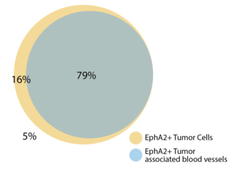
EphA2 ON TUMOR CELLS



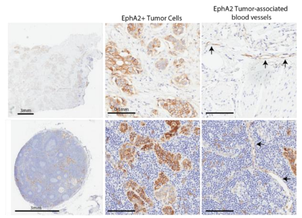
EphA2 ON TUMOR-ASSOCIATED BLOOD VESSELS

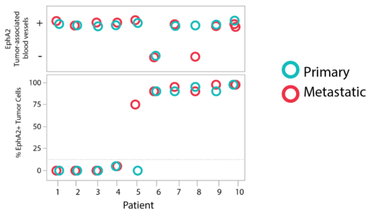




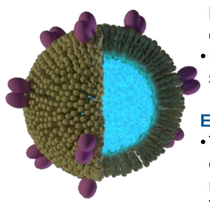


EphA2 expression pattern is maintained in metastases (10 pairs of primary and metastatic samples from patients with bladder cancer)





MM-310: An EphA2-Targeted Nanotherapeutic



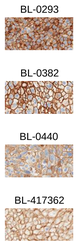
DOCETAXEL NANOLIPOSOME
- Formulation extended drug circulation time in pre-clinical models with reduction in hematological toxicities compared to docetaxel.
- Liposome deposition led to sustained release at the tumor site.

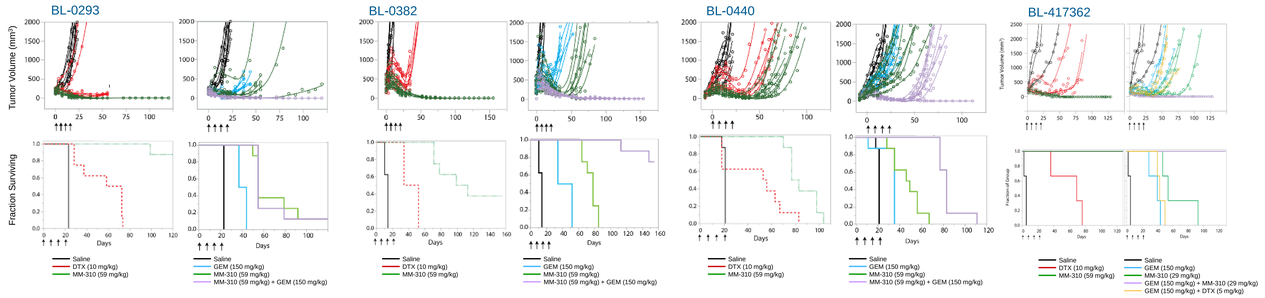
EphA2 TARGETING scFv
- Targeted EphA2-expressing cancer cells in primary tumors and metastatic lesions.
- Targeted tumor associated blood vessels.
- Led to more pronounced and sustained tumor regression *in vivo.*

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

Mice bearing patient-derived bladder cancer xenografts (implated s.c. on flank, EphA2+) were dosed with MM-310, docetaxel (DTX), gemcitabine (GEM) or combinations of these agents 4 x q7d, and the tumor sizes were followed for >100 days.

EphA2 IHC





Summary

We examined EphA2 tumor expression in 3 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.

3) Matched primary and metastatic sections:
Observations: EphA2 expression showed concordance between sample pairs.

We tested the activity of MM-310, an EphA2-targeted nanotherapeutic (encapsulated docetaxel prodrug), in EphA2-expressing bladder PDX models:
All showed reduction of tumor burden with MM-310 alone, greater activity with MM-310 than with an equitoxic 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.

A PASSION FOR OUTTHINKING CANCER

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