A phase 1 study evaluating the safety, pharmacology and preliminary activity of MM-310 in patients with solid tumors

Abstract TPS2604

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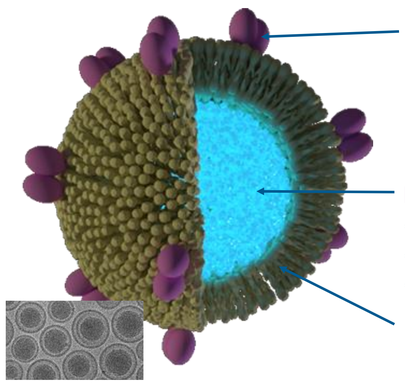
Background

Ephrin receptor A2 (EphA2) is expressed in cancer and stroma cells in a wide range of solid tumors. MM-310 is an EphA2-targeting liposomal form of a docetaxel prodrug. Preclinical investigation revealed a high correlation between EphA2 expression on cancer cells and MM-310 uptake. *In vivo* studies in multiple xenograft models demonstrated superior antitumor activity compared with standard of care agents and toxicology analysis in rodents and non-rodent animal models revealed a favorable toxicity profile. The overexpression of EphA2 in a wide range of tumors, the high tumor specificity of MM-310 through the enhanced permeability and retention effect, and the EphA2 targeting support the investigation of MM-310 for potential clinical utility.

MM-310: An EphA2-Targeting Liposomal Form of a Docetaxel Prodrug



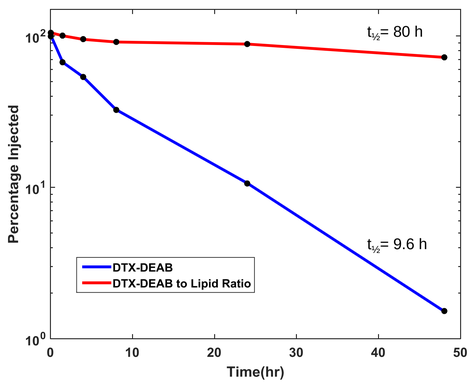
EphA2 Targeting Antibody
- 15 scFv per liposome
- High prevalence in tumors
- Limited accessibility in healthy organs
- Expressed in tumor and stromal cells

Docetaxel Prodrug
- Approximately 30,000 per Ls
- Broad spectrum activity
- Improved stabilization and release

Lipid Matrix
- Provides encapsulation and stability

High Tumor Specificity
- EphA2 targeting
- Enhanced permeability and retention (EPR) effect

Wide Therapeutic Window
- Slow prodrug release
- Conversion to docetaxel



Modeling of MM-310 pharmacokinetics
DTX-DEAB = MM-310

Presented at AACR 2016

EphA2 Prevalence

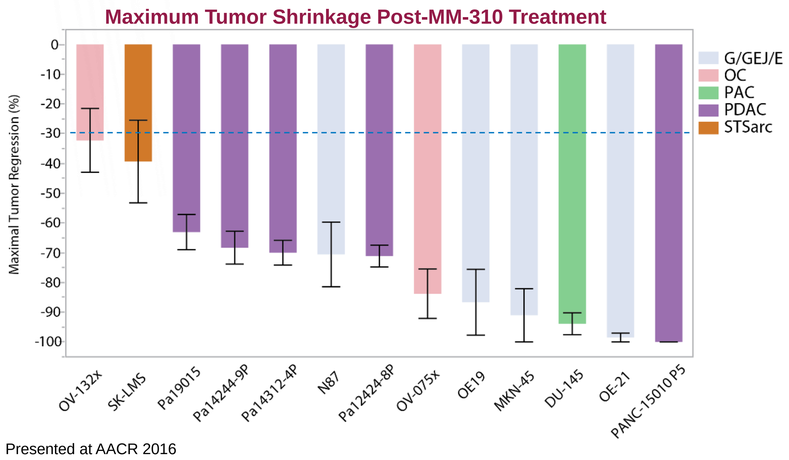
EphA2 is an attractive target due to its high prevalence in a wide range of solid tumors and its expression in both cancer cells and stromal components of tumors, such as tumor associated blood vessels.

Type of Cancer	Cancer Cells	Tumor-associated Blood Vessels	EphA2 Overall Score
UC (n=19)	95%	79%	95%
G/GEJ/E (n=20)	90%	85%	100%
SCCHN (n=18)	83%	42%	100%
Ovarian (n=18)	56%	95%	95%
PDAC (n=19)	79%	58%	89%
NSCLC (n=37)	45%	65%	76%
Prostate (n=45)	46%	62%	72%
TNBC (n=78)	8%	44%	49%

EPhA2 prevalence using 10% cutoff of positive cancer cells or 2 positive high power fields of view in the case of tumor associated blood vessels. EphA2 overall score reflects patients that show EphA2 positivity in any of the two compartments.

Preclinical Activity

MM-310 preclinical activity was tested in a set of patient-derived (PDx) and cell-derived (CDx) models covering 5 indications. Tumor-bearing animals were treated with weekly doses of MM-310 at 59 mg/kg (at around 50% preclinical MTD).



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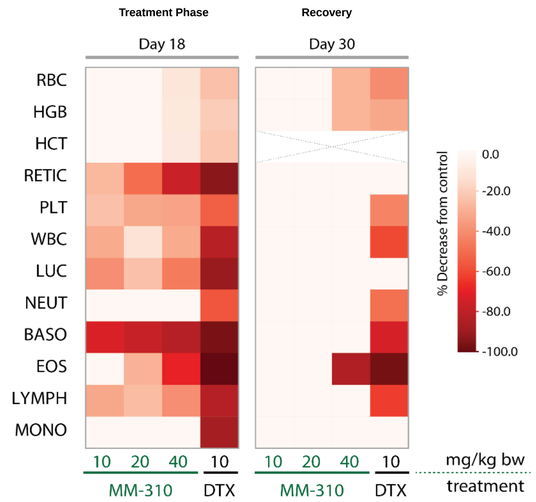
Preclinical Toxicity

MM-310 demonstrated an improved hematologic toxicity profile in rats when compared with docetaxel.

In a chronic toxicology study, rats were dosed with MM-310 or docetaxel on days 0, 7, 14 and 21. Controls were injected with saline.

Hematology parameters assessed on days 18 and 30 show significantly less toxicity MM-310 than with docetaxel.



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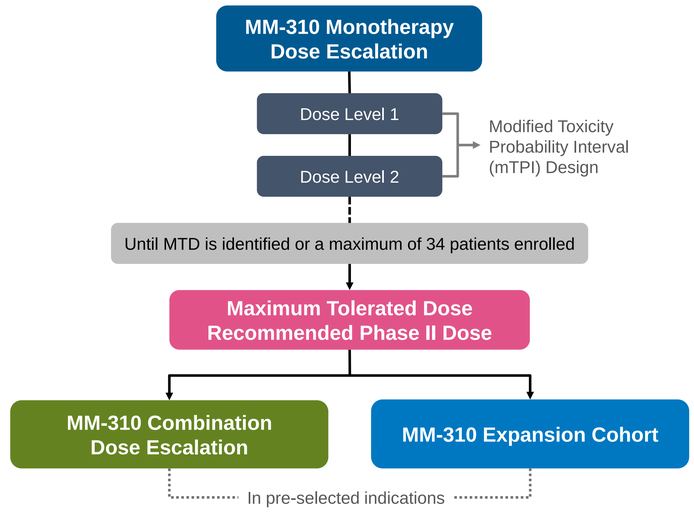
Study Objectives

PRIMARY
- Determine the maximum tolerated dose (MTD) and describe the dose-limiting toxicities (DLT) of MM-310 administered once every 3 weeks, in patients with metastatic solid tumors

SECONDARY
- Determine the pharmacokinetic parameters
- Characterize the adverse event profile
- Determine the immunogenicity parameters
- Describe any objective response based on RECIST v1.1 or other disease-relevant criteria
- Assess disease control rate (RECIST response of SD, PR and CR for > 3 months)
- Assess progression-free survival (PFS) based on RECIST v1.1 or other disease-relevant criteria

EXPLORATORY
- Assess correlation of safety, efficacy, pharmacokinetics, pharmacodynamics, with EphA2 expression and other predictive biomarkers

Study Design



Key Eligibility Criteria

INCLUSION
- One of the following cancers:
  - Urothelial carcinoma (UC)
  - Gastric/ gastroesophageal junction/ esophageal carcinoma (G/GEJ/E)
  - Squamous cell carcinoma of the head and neck (SCCHN)
  - Ovarian cancer
  - Pancreatic ductal adenocarcinoma (PDAC)
  - Prostate adenocarcinoma (PAC)
  - Non-small cell lung cancer (NSCLC)
  - Small cell lung cancer (SCLC)
  - Triple negative breast cancer (TNBC)
  - Endometrial carcinoma
  - Soft tissue sarcoma subtypes except GIST, desmoid tumors and pleiomorphic rhabdomyosarcoma
- ≥ 18 years of age
- ECOG performance status 0 or 1
- Adequate hematologic parameters, hepatic and renal function
- Adequate coagulation function (PT, APTT, and INR within normal limits)
- Availability of a cancerous lesion amenable to biopsy and willingness to undergo biopsy

EXCLUSION
- Prior treatment with docetaxel within 6 months of study enrollment
- Treatment with systemic anticoagulation
- Received prior treatment known to have anti-VEGF/VEGFR activity within 5 half-lives of study enrollment
- Any evidence of hematemesis, melena, hematochezia, severe hemoptysis, or gross hematuria
- Any hereditary bleeding disorders
- Peripheral neuropathy
- Known CNS metastasis

Summary

- MM-310 demonstrated promising activity and an improved toxicity profile in preclinical models
- This first-in-human study is evaluating the safety and tolerability of MM-310 in patients with certain relapsed or refractory solid tumors
- Five participating sites across the United States are open for enrollment
- First patient was enrolled in March 2017; dose escalation is ongoing
- Clinical trial information: NCT03076372

Please contact lzalutskaya@merrimack.com with questions or comments

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