Immunomodulatory effects of an EphA2-targeted Docetaxel antibody-directed nanotherapeutic and synergistic combination with PD-1 inhibitor

Andrew J. Sawyer, Anne-Sophie Dugast, Lia Luus, Suresh Tipparaju, Zhaohua Richard Huang, Dmitri Kirpotin, Daryl C. Drummond, and Walid S. Kamoun

Merrimack Pharmaceuticals Inc., Cambridge, MA

Abstract # 4711

Abstract

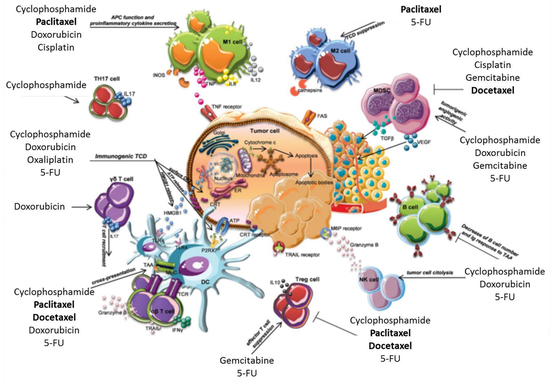
Certain chemotherapeutic agents including taxanes and anthracyclines can increase immunogenicity, resulting in therapeutic synergy with immune checkpoint inhibitors. Treatment with a taxane has been shown to increase the recruitment of CTLs and decrease immunosuppressive cells such as MDSCs and Tregs. Additionally, the immune-modulatory activity of paclitaxel has been shown to increase with prolonged exposure of the taxane at the tumor level, which can be achieved through metronomic dosing. MM-310 is an Ephrin Receptor A2 (EphA2)-targeted antibody-directed nanotherapeutic (ADN) that encapsulates a docetaxel prodrug. Preclinically, MM-310 leads to prolonged exposure of docetaxel at the tumor level, while lowering systemic exposure to bioavailable docetaxel. Compared to equitoxic doses of free docetaxel, MM-310 produces less dose-limiting neutropenia and less killing of circulating lymphocytes potentially critical to anti-PD-1/PD-L1 activity. Based on these data, we hypothesize that MM-310 can synergistically combine with anti-PD-1 therapy.

We evaluated the potential combination of MM-310 and a murine anti-PD-1 Ab in the treatment of several syngeneic mouse tumor models. The mouse syngeneic tumor lines EMT-6, CT-26, and LLC were selected to provide a range of sensitivity to each of docetaxel and anti-PD-1. *In vivo* activity studies and immune-phenotype studies were performed comparing MM-310+anti-PD-1 combination to the monotherapies. MM-310 administration was initiated two days prior to anti-PD-1 therapy and consisted of four weekly doses, while anti-PD-1 was dosed twice weekly for four weeks.

The response to MM-310 or anti-PD-1 as monotherapies varied among the models: LLC was unresponsive to anti-PD-1 and poorly responsive to MM-310, CT-26 was poorly responsive to both anti-PD-1 and MM-310, while EMT-6 responded moderately to anti-PD-1 with tumor stasis and well to MM-310, achieving tumor regression. In all models, MM-310 given in combination with anti-PD-1 outperformed controls and both monotherapy arms as measured by growth inhibition and tumor regression rate. In the EMT-6 model, combination treatment resulted in durable complete regressions in 6/10 mice when compared to 2/10 and 0/10 for MM-310 and anti-PD-1 monotherapies respectively. In both groups, re-challenge of mice with the same tumor cells, at 10 weeks post treatment interruption, did not lead to tumor growth, suggesting that treatment with anti-PD1+MM-310 promotes the development of a memory response against the tumor antigen.

In conclusion, the novel combination of MM-310, an EphA2-targeted docetaxel ADN with an anti-PD-1 antibody, is highly active in syngeneic tumor models, and represents a promising strategy for the treatment of cancer.

Immunomodulatory effects of taxanes

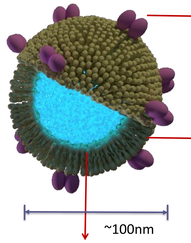


Potential benefits of taxane combination therapy

- Increase PD-1, MHC1, and antigen expression
- Increase TILS
- Increase CD8+ T cells and ifnγ+ CD8+ T cells
- Increase CTL mediated cell killing
- Increase NK cells
- Decrease MDSCs and Tregs
- Shift macrophages towards M1 phenotype

Bracci, Cell death and differentiation 2014

MM-310: An EphA2-targeted, docetaxel ADN



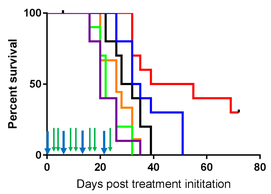
EphA2 scFv
15 scFv / liposome
- High prevalence
- Good specificity
- Restricted accessibility in healthy tissues
- Expression on stromal cells

Lipid matrix:
Egg-SM/Chol/PEG-lipid
- Chemical stability
- Improved pegylation strategy

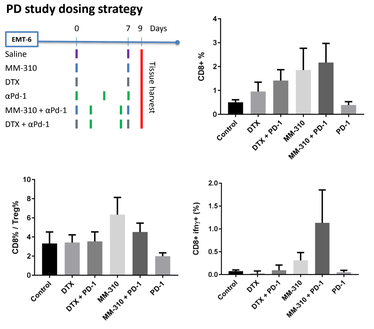
Docetaxel prodrug/SOS gel
Approximately 30,000 prodrug per liposome
- Broad spectrum activity (prostate, bladder, gastric, NSCLC, ovarian, pancreatic)
- Improved prodrug strategy (stabilization and release)
- Dose limiting toxicities that can be improved upon

MM-310 shows improved activity and increase in CD8+ T cells in comparison to docetaxel

EMT-6 flank tumor in Balb/c mouse

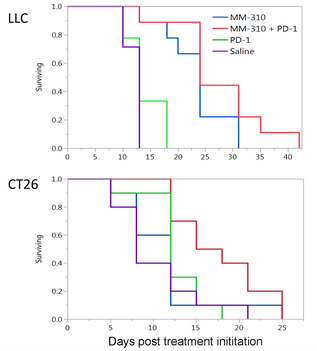


PD study dosing strategy



In a paired activity and PD study MM-310 was compared to DTX alone and in combination with αPD-1. MM-310 showed improved activity relative to DTX in both dosing strategies. After two dose cycles, FACS was used to compare the immunomodulatory capacity of both drugs. MM-310 increased CD8+ T cells and the ratio of CD8+ T cells to Tregs, indicating the creation of an antitumor immune response

MM-310 improves activity in combination with αPD-1 in multiple syngeneic models

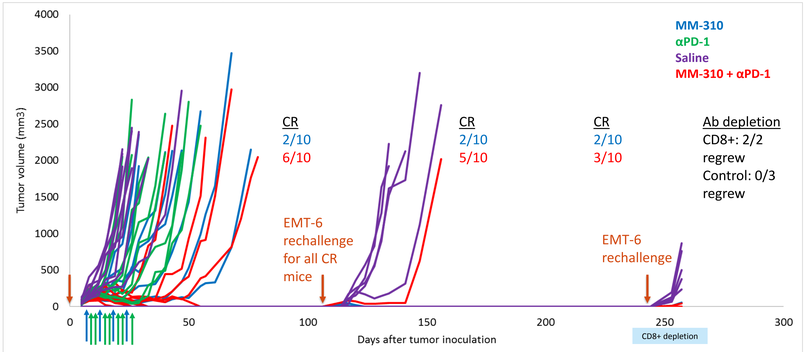


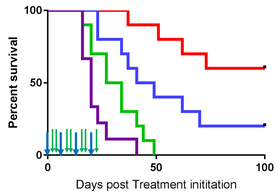
LLC	Dosing	TGI (%)
Saline	0, q1wx4	0 ± 13
PD-1	10 mg/kg, q3d x4	-23 ± 20
MM-310	50 mg/kg, q1w x4	31 ± 8
MM-310 +PD-1	50 + 10 mg/kg	45 ± 10

CT26	Dosing	TGI (%)
Saline	0, q1wx4	0 ± 13
PD-1	10 mg/kg, q3d x4	42 ± 11
MM-310	50 mg/kg, q1w x4	12 ±14
MM-310 +PD-1	50 + 10 mg/kg	50 ±7

MM-310 in combination with PD-1 inhibition improves survival in vivo.

EMT-6 flank tumor in Balb/c mouse

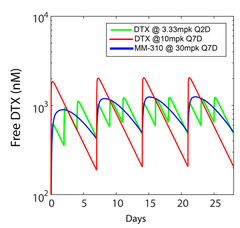




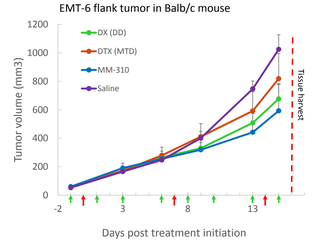
	Dosage	(CR, PR, NR) %	TGI (%)
Saline	0	0, 0, 100	0 ± 17
αPD-1	10 mg/kg	0, 20, 80	54 ± 16
MM-310	50 mg/kg	20, 30, 50	81 ± 6
MM-310 + αPD-1	50 + 10 mg/kg	60, 30, 10	93 ± 1.8

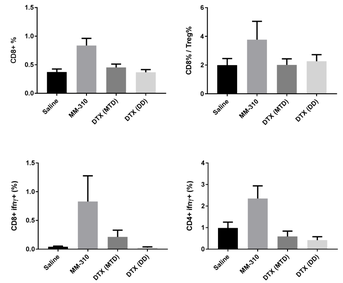
- MM-310 in combination with PD-1 inhibition improved survival and growth inhibition in EMT-6 flank tumors
- Combination therapy resulted in durable, tumor-free survivors with resistance to rechallenge

Dose-dense delivery of docetaxel improves tumor growth inhibition, but does not have the immunomodulatory capacity of MM-310



EMT-6 flank tumor in Balb/c mouse





FACS was used to compare the immunomodulatory capabilities of DTX given weekly at MTD levels or spread over three doses. A dose-dense regime was able to approach the growth inhibition of MM-310, but did not induce a similar shift in tumor T cell populations.

Summary

(1) The immunomodulatory effects of taxanes makes them potentially favorable combination partners for IO agents.

(2) MM-310 in combination with αPD-1 improves activity and survival in multiple murine syngeneic tumor models, including the EMT-6 model where the combination produced a 60% complete response rate.

(3) MM-310 + αPD-1 complete response mice were resistant to rechallenge, showing antitumor immunity.

(4) MM-310 treatment increased intratumoral CD8+ T cells and the ratio of CD8+ T cells to Tregs, indicating the creation of an anti-tumor immune response.

(5) MM-310 + αPD-1 is superior to DTX + αPD-1 , and while dose-dense dosing can improve the growth inhibition of DTX, it does not appear to yield the shift in T cell populations observed after treatment with MM-310.