Phase 1/2 study of Mocetinostat and Durvalumab (MEDI4736) in patients with advanced solid tumors and non-small cell lung cancer (NSCLC)

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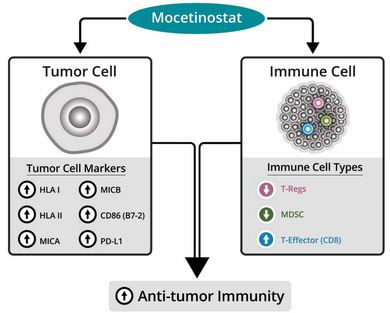
BACKGROUND

- Immune checkpoint inhibitors produce durable clinical responses in a subset of patients, however strategies are needed to improve clinical efficacy of these agents and overcome innate or acquired resistance to therapy
- Growing evidence suggests that tumors evade immune detection through modulation of intrinsic immunogenicity and inhibition of both innate and adaptive anti-tumor immune responses
- Mocetinostat, a class I histone deacetylase inhibitor, has multiple potential immunomodulatory features including[1-6]:
  - Induction of tumor associated antigens and human leukocyte antigen (HLA) Class I and Class II expression on tumor cells
  - Enhancement of tumor antigen cross-presentation by antigen presenting cells
  - Enhancement of T effector cell function
  - Reduction in number and function of immunosuppressive cell subsets including regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs)
- Given these pleiotropic immune activating effects, combination therapy of moce-tinostat and a PD-L1 blocking mAb, durvalumab, is a rational approach to restoring or enhancing the clinical activity of immune checkpoint blockade in patients with NSCLC

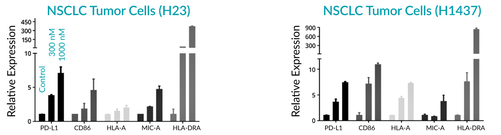
Mocetinostat may enhance the efficacy of immune checkpoint inhibitors by increasing intrinsic tumor immunogenicity and activating anti-tumor immunity



Tumor cell markers and immune cell types associated with increased tumor cell immunogeneticity

Mocetinostat demonstrates dose-dependent induction of markers of antigen presentation and innate immunity

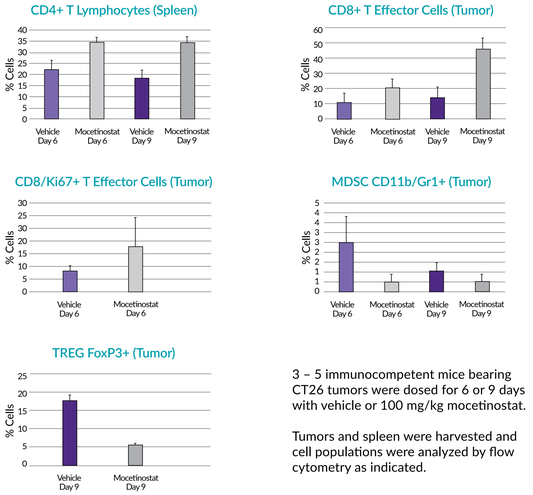
PRECLINICAL DATA



NSCLC cell lines H23 (left) and H1437 (right) were treated with DMSO or mocetinostat at 300 or 1000 nM for 48 hrs. Gene expression was analyzed by qRT-PCR and normalized to housekeeping genes and DMSO controls.

Mocetinostat demonstrates induction of T effector cells and depletion of immunosuppressive cells in preclinical models

PRECLINICAL DATA



3 – 5 immunocompetent mice bearing CT26 tumors were dosed for 6 or 9 days with vehicle or 100 mg/kg mocetinostat.

Tumors and spleen were harvested and cell populations were analyzed by flow cytometry as indicated.

STUDY OBJECTIVES

PRIMARY OBJECTIVE:

- Determine the recommended Phase 2 dose of mocetinostat in combination with full dose durvalumab
- Evaluate efficacy of combination therapy in patients with NSCLC having differing tumor expression of PD-L1 or prior treatment with checkpoint inhibitors

SECONDARY OBJECTIVES:

- To evaluate safety and tolerability
- To evaluate secondary efficacy endpoints
- To evaluate pharmacokinetics (PK) for mocetinostat and durvalumab
- To evaluate incidence of anti-drug antibodies to durvalumab
- To evaluate mocetinostat effect on tumor cell PD-L1 expression during lead-in

EXPLORATORY OBJECTIVES:

- To assess effectiveness of mocetinostat monotherapy during lead-in period on circulating PD-L1, tumor infiltrating and circulating immune cell populations, and circulating cytokines
- To assess effectiveness of mocetinostat and durvalumab treatment on circulating PD-L1, immune cell populations, and cytokines
- To assess effectiveness of mocetinostat and durvalumab treatment on tumor cell PD-L1 expression and tumor infiltrating immune cell populations

METHODS

- This open-label Phase 1/2 study is evaluating the tolerability and clinical activity of mocetinostat in combination with durvalumab
- Phase 1 explores increasing doses of mocetinostat administered orally (50, 70, 90 mg three times weekly [TIW]) in combination with durvalumab in patients with advanced solid tumors
- The regimen begins with a 7-day lead-in period of mocetinostat single agent TIW followed by the combination regimen with durvalumab (1500 mg intravenously every 28 days)

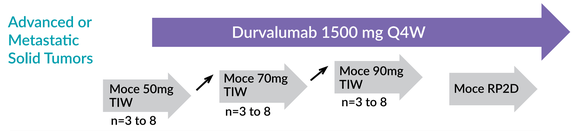
PHASE 1:

- Modified Toxicity Probability Interval (mTPI) method for dose escalation decisions
- The assumptions to be applied in establishing the mTPI methodology are:
  - Each specific regimen exploration will include up to 30 patients;
  - The MTD is defined to have 0.25 probability of toxicity; and
  - The acceptable variance around the MTD is ± 0.05 (i.e., the region of the MTD is 20% to 30% incidence of dose limiting toxicity)

PHASE 2:

- Two-stage Simon optimal design
- Four population cohorts are included:
  1) immunotherapy naïve, no/low PD-L1 expression
  2) immunotherapy naïve, high PD-L1 expression
  3) prior clinical benefit with PD-L1 or PD-1 inhibitor treatment followed by progression
  4) prior treatment with PD-L1 or PD-1 inhibitor with progression within 16 weeks of initiation of treatment

Study Design



			Stage 1	Expand if ≥ X Responses	Stage 2
Any histology NSCLC Receipt of previous platinum doublet for advanced disease	Naive to Immunotherapy	No/Low PD-L1 Expression	n=9	≥ 1	n=8
		High PD-L1 Expression	n=17	≥ 6	n=27
	Refractory to anti-PD-1 or anti-PD-L1	Prior Responder	n=9	≥ 1	n=8
		Prior Non-Responder	n=9	≥ 1	n=8

KEY INCLUSION CRITERIA:

- Phase 1: Solid tumor malignancy with metastatic or unresectable, locally advanced disease; Phase 2: NSCLC with metastatic or unresectable, locally advanced disease
- Phase 1: Not amenable to curative treatment; Phase 2: Receipt of at least one platinum-based doublet; Cohorts 3 and 4 most recent treatment must have included a checkpoint inhibitor
- Phase 2: Cohorts 1 and 2 require biopsy to determine PD-L1 expression status
- ECOG performance status of 0 or 1
- Adequate bone marrow and organ function

KEY EXCLUSION CRITERIA:

- Prior therapies:
  - HDAC inhibitor
  - Immunotherapies not previously specified including anti-CTLA-4, anti-OX40, and anti-CD137
  - Phase 2 Cohorts 1 and 2-prior treatment with anti-PD-1 or anti-PD-L1; Phase 2 Cohorts 3 and 4- receipt of systemic cancer treatments since progression of disease during or following checkpoint inhibitor therapy
- Previous treatment-related, severe (≥ Grade 3) AE or any neurologic or ocular AE of any grade while receiving checkpoint inhibitors
- Active or prior documented autoimmune disease within 2 years
- Brain metastases or spinal cord compression unless asymptomatic, treated and stable
- Impaired cardiac function

DOSING REGIMEN AND ASSESSMENTS:

- Patients receive oral mocetinostat TIW in combination with durvalumab 1500 mg intravenously every 4 weeks, as continuous 28 day cycles
- Routine safety assessments performed throughout the study
- Disease assessments using RECIST version 1.1
- Other assessments include safety, tolerability, PK and changes in circulating and tumor cell PD-L1 expression, circulating and tumor infiltrating immune cell populations, and cytokines

SUMMARY

- Immune checkpoint inhibitors produce durable clinical responses in a subset of patients, however strategies are needed to improve clinical efficacy of these agents and overcome innate or acquired resistance to immunotherapy
- Given the pleiotropic immune activating effects of mocetinostat, combination therapy with the PD-L1 blocking mAb, durvalumab, is a rational approach to enhancing or restoring the clinical activity of immune checkpoint blockade in patients with NSCLC
- Enrollment into the study opened in June 2016 and is ongoing in the United States. Clinical Trial Information: NCT02805660

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Study Trial Information: **www.mirati.com**