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 immunotherapy.
• Growing evidence suggests that tumors evade immune detection through modulation of intrinsic immunogenicity and induction of both innate and adaptive tumor-immune responses.
• Mocetinostat, a class I histone deacetylase inhibitor, has multiple potential immunomodulatory effects including:
  - 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
  - Induction of tumor associated antigens and human leukocyte antigen (HLA)
  - Reduction in number and function of immunosuppressive cell subsets including regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs)

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

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 end point efficacy
- To evaluate pharmacokinetics (PK) for mocetinostat and durvalumab
- To evaluate incidence of anti-drug antibodies to durvalumab
- To evaluate mocetinostat effect on tumor PD-L1 expression during lead-in

EXPLORATORY OBJECTIVE:

- To determine the impact of mocetinostat monotherapy in 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

STUDY DESIGN

Advanced or Metastatic Solid Tumors

Any histology NSCLC

Not to be treated

Any histology NSCLC

Recruiting previous platinum doublet for advanced disease

Refusals to anti-PD-1 or anti-PD-L1

Any histology NSCLC

Delays to PD-1/PD-L1 immunotherapy

Refusals to anti-PD-1 or anti-PD-L1

Any histology NSCLC

Delays to PD-1/PD-L1 immunotherapy

Refusals to anti-PD-1 or anti-PD-L1

KEY EXCLUSION CRITERIA:

- Phase 1: Patients with metastatic or unresectable disease
- Phase 2: NSCLC with metastatic or unresectable, locally advanced disease

KEY INCLUSION CRITERIA:

- Phase 1: Patients with metastatic or locally advanced disease
- Phase 2: NSCLC with metastatic or unresectable, locally advanced disease

REFERENCES


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, combination therapy of mocetinostat and durvalumab is a rational approach in enhancing or restoring the clinical activity of immune checkpoint blockade in patients with NSCLC.

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Study Trial Information: www.mirati.com

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