Phase 1 Study of MEDI4736, an Anti-PD-L1 Antibody, in Combination with Dabrafenib and Trametinib or Trametinib Alone in Patients with Unresectable or Metastatic Melanoma

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Background

- Metastatic or unresectable melanoma is the leading cause of skin cancer-related deaths[1]
- In the last decade, a better understanding of the genetics of melanoma has led to the development of targeted treatments resulting in significantly improved patient outcomes
  - The mitogen activated protein kinase (MAPK) pathway has an important role in melanoma development, with activating mutations of BRAF kinase detected in up to 50% of all melanoma cases[2]
  - These mutations result in constitutive activation of the downstream kinases MEK1 and MEK2, leading to abnormal proliferation and uncontrolled growth[3]
  - Complete inhibition of the MAPK pathway via combined BRAF and MEK inhibition has shown clinical activity in the *BRAF* mutation-positive melanoma population[4]
  - The combination of dabrafenib, a V600E BRAF inhibitor, and trametinib, a MEK inhibitor, was recently approved by the US Food and Drug Administration (FDA) for *BRAF* (*V600E/K*) mutation-positive melanoma
  - In clinical trials, trametinib was shown to provide partial responses in 10% of patients with *BRAF* (*V600*) wild-type (WT) melanoma[5]
- Despite recent progress in the treatment of melanoma, prognosis remains poor, highlighting a significant need for novel therapeutic approaches able to generate more durable responses

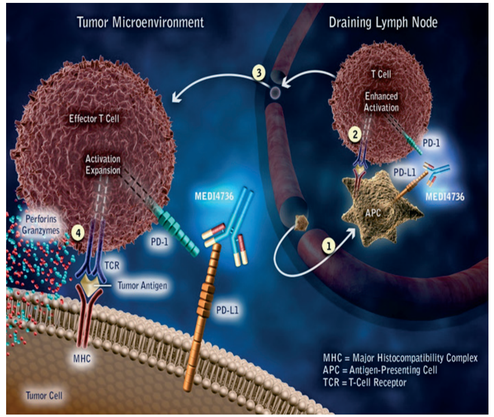
MEDI4736

- Programmed cell death ligand-1 (PD-L1) is widely expressed on antigen presenting cells (APC) and other immune cells
- PD-L1 is up-regulated on tumour cells from a broad range of human cancers, and has been associated with inhibition of antitumour T-cell responses[6–9]
- PD-L1 binds two important receptors on T-cells: programmed cell death-1 (PD-1) and CD80/B7.1[10,11]
  - Binding to PD-1 delivers an inhibitory signal, reducing cytokine production and T-cell proliferation[10,11]
  - Binding to CD80/B7.1 blocks activation of T-cells through CD28 binding[10,11]
- There may be advantages to selectively inhibiting PD-L1 (and not PD-L2)[10]
  - PD-L2 plays a role in controlling inflammation in normal lung tissue (with expression in lung macrophages and APC),[12] and exacerbation of immune-related toxicity in susceptible animal models[13,14]; although its role in modulating tumour immunity has not been identified[15]
- MEDI4736, which targets PD-L1, represents a robust strategy to boost antitumour immune responses, while minimising potential for immune-related toxicity
  - MEDI4736 inhibits PD-L1 interaction with PD-1 (IC_{50} 0.1 nM) and CD80/B7.1 (IC_{50} 0.04 nM) allowing T-cells to recognise and kill tumour cells (Figure 1)[16]
  - Other key attributes are:
    - Does not bind to PD-L2[16]
    - No immunogenicity impacting pharmacokinetics/pharmacodynamics at Phase 3 dose (10 mg/kg) to date[17]
    - Sustained exposure throughout dosing interval (>1 year)[18]
    - Uniquely engineered human IgG1κ monoclonal antibody (mAb); triple mutation in Fc domain removes antibody-dependent cell-mediated cytotoxicity activity[19]
- MEDI4736 has demonstrated promising clinical activity and an encouraging safety profile across multiple tumour types[20]
  - No treatment-related colitis of any grade, and no Grade 3/4 pneumonitis has been reported in a Phase 1 study of MEDI4736 monotherapy[20]
  - Clinical activity observed in multiple tumour types, including melanoma, with early and durable responses reported[20]
    - Initial observations indicate that activity correlates with PD-L1 expression with higher objective response and disease control rates observed in PD-L1 positive patients[20]
  - The latest data from this study will be presented at this ESMO meeting[21–23]
- Here we describe a study evaluating MEDI4736 in combination with dabrafenib and trametinib or trametinib alone in patients *BRAF* WT and mutation-positive metastatic or unresectable melanoma

Rationale for Combining BRAF/MEK Inhibitors with MEDI4736

- Despite high objective response rates with BRAF inhibitors alone or in combination with a MEK inhibitor, the majority of patients with BRAF mutation-positive melanoma develop resistance and progress in <12 months
  - The addition of MEDI4736 may further improve outcomes in this population
- Treatment with a BRAF inhibitor or the combination of a BRAF and a MEK inhibitor is associated with increased melanoma antigen expression, increased T-cell infiltration, and increased PD-L1 expression[24]
  - This suggests that antitumour immune responses may be limited due to expression of immunosuppressive markers, including PD-L1
  - Adding MEDI4736 could therefore relieve this inhibition and enhance antitumour response
- The role of MEK inhibitors in modulating the tumour microenvironment is still being investigated[25]
  - Evidence has shown that treatment with MEK inhibitors results in decreased expression of PD-L1 in melanoma,[25] warranting the evaluation of different schedules of the combination of trametinib and MEDI4736

Figure 1. MEDI4736: Mechanism of Action



Numbers 1–4 indicate stages of antitumour response; the PD-L1 antibody blocks PD-L1 interaction with the negative regulatory signaling molecule PD-1.

Study Design

- This is a Phase 1b, international, multicentre, open-label, dose-escalation (3+3 design) study followed by an expansion phase
- The study consists of three cohorts each receiving a different treatment combination (Figure 2)
- Approximately 20 patients will be evaluated in each cohort at the maximum tolerated dose (MTD)/highest dose of MEDI4736 selected in the escalation phase
- All patients will be followed for survival

Figure 2. Study Design

Patients with metastatic or unresectable melanoma

Cohort A	Cohort B Schedule 1	Cohort C Schedule 2
BRAF mutation-positive	*BRAF* WT	*BRAF* WT
Combination Dabrafenib Trametinib MEDI4736	**Combination** Trametinib MEDI4736	**Combination** Trametinib MEDI4736

Key inclusion criteria	Key exclusion criteria
Age ≥18 years at the time of screening	Prior treatment with a BRAF or MEK inhibitor
Histologically confirmed *BRAF V600E* or *V600K* mutation-positive (Cohort A) or WT (Cohorts B and C) cutaneous melanoma that is either • Stage 3C (unresectable) or • Stage 4 (metastatic)	Any prior irAE Grade ≥3 while receiving immunotherapy or any unresolved irAE at time of study entry
ECOG performance status of 0–1	Active or prior documented autoimmune disease (including inflammatory bowel disease, coeliac disease, irritable bowel syndrome; Wegener, Hashimoto) within the past 2 years
At least one measurable lesion by RECIST v1.1	Current pneumonitis or interstitial lung disease

ECOG, Eastern Cooperative Oncology Group; irAE, immune-related adverse event; RECIST, Response Evaluation Criteria In Solid Tumours.

Current Status

- Recruitment was initiated in November 2013; as of 8 September, 2014, 27 patients have been treated in this study
- Further information can be found at: www.clinicaltrials.gov (identifier: NCT02027961)

Study Objectives

Primary

- Safety and tolerability of MEDI4736 in combination with dabrafenib/trametinib or trametinib alone
  - MTD, adverse events (AEs), serious AEs, vital signs, laboratory evaluations, physical examination

Secondary

- Antitumour activity
  - Objective response (based on RECIST v1.1)
  - Disease control
  - Duration of response
  - Progression-free survival
  - Overall survival
- Pharmacokinetics
  - Maximum concentration (C_{max})
  - Area under the curve (AUC)
- Immunogenicity
  - Number of patients developing anti-drug antibodies

Exploratory

- PD-L1 expression and localisation in tumours and association with treatment response

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Disclaimer

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