MEDI4736 is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (MAb) directed against human PD-L1.

**Dose expansion phase** open at this time

The primary objectives of the dose-expansion phase are:

- to determine the safety profile of MEDI4736 in subjects with advanced cutaneous melanoma, uveal melanoma, hepatocellular carcinoma (HCC), squamous cell carcinoma of the head and neck (SCCHN), NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, triple negative breast cancer (TNBC), and pancreatic adenocarcinoma
- to evaluate the antitumor activity of MEDI4736 in subjects with non-squamous NSCLC who have received 2 or more prior lines of therapy and subjects with squamous NSCLC who have received 1 prior lines of therapy and 2 or more prior lines of therapy

Inclusion Criteria (partial listing):

Written informed consent and any locally-required authorization (eg, HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations

- In the dose-expansion phase: histologically or cytologically confirmed advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous and nonsquamous, gastroesophageal cancer, TNBC, or pancreatic adenocarcinoma
- HCC subjects must be of Child-Pugh class A (not amenable to or refractory to locoregional therapy). Subjects with HCC associated with hepatitis B virus must be receiving adequate antiviral therapy
- Subjects with histologically or cytologically documented NSCLC must present with Stage IIIB/ Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy) for locally advanced disease
  a. For advanced stage NSCLC, maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy
  b. Prior platinum containing neoadjuvant chemotherapy for operable disease, adjuvant chemotherapy for completely resected disease or definitive chemoradiation therapy given for locally advanced disease is not considered a separate regimen of therapy.
  c. For first-line therapy NSCLC cohorts: Subjects must not have received prior chemotherapy or systemic anti-neoplastic therapy (eg, tyrosine kinase inhibitor [TKI], MAb therapy) for advanced disease. Prior surgery and/or localized irradiation are permitted.
d. For second-line therapy NSCLC cohorts: Subjects without known sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements must have experienced disease progression or recurrence following one prior platinum based doublet chemotherapy for advanced disease. Subjects with sensitizing EGFR mutations or ALK rearrangements must have experienced disease progression or recurrence following either a TKI therapy or prior platinum based doublet chemotherapy for advanced disease.

e. For third-line or greater therapy NSCLC cohorts: Subjects must have experienced disease progression or recurrence after both a platinum-doublet based chemotherapy regimen and at least 1 additional systemic therapy for advanced disease. For subjects with sensitizing EGFR mutations or ALK rearrangements, the additional therapy must include a TKI therapy. Additional therapies are defined as agents that are US FDA- or European Medicine Agency-approved for use after a prior regimen, given as monotherapy or in combination; or vinorelbine- or gemcitabine-containing regimens given as part of locally accepted standard-of-care, for subjects who are not candidates for docetaxel.

- If an approved first-line therapy is available, subjects must have failed, be intolerant to, be ineligible for, or have refused treatment

Schedule: 14-day cycle

MEDI4736 is given IV over 1 hour, Q 2 weeks

Restaging scans at 6 weeks, 12 weeks, 16 weeks and every 8 weeks thereafter

Treatment in the dose-expansion phase will continue on a Q2W schedule for 12 months or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent or other reasons to discontinue treatment occur. In the event of confirmed PD, subjects may continue to receive MEDI4736 in the absence of clinical deterioration and if investigators consider that subjects continue to receive benefit from treatment. Subjects who have achieved and maintained DC (ie, CR, PR, or SD) through to the end of the 12-month treatment period will enter follow-up. Upon evidence of PD during follow-up, subjects will be re-administered MEDI4736 at the highest dose previously received via IV infusion Q2W. Subjects may continue MEDI4736 retreatment for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Only one round of retreatment with MEDI4736 will be allowed. Subjects who have confirmed PD during the 12-month initial treatment or retreatment period and cannot continue to receive MEDI4736 will enter follow-up for 90-day safety assessments and survival follow-up.