REQUEST FOR PROJECT TEAM MEMBER APPLICATION FOR CONDUCTING CLINICAL TRIALS USING MEDI4736 (NSC# 778709)

The Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member Applications (PTMAs) for a project using MEDI4736, an anti-PD-L1 monoclonal antibody (mAb) being developed by CTEP in collaboration with MedImmune/AstraZeneca. MEDI4736 is a human immunoglobulin G1 kappa (IgG1κ) mAb that binds with high specificity and inhibits human programmed death ligand 1 (PD-LI), without triggering antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) (Lu *et al*., 2014). An initial single-agent study (NCT01693562) has shown promising antitumor activity in multiple tumor types, as early as 6 weeks after initiation of treatment (Lutzky *et al*., 2014; Segal *et al*., 2014).

It is anticipated that CTEP will sponsor three different combination trials with MEDI4736. **This solicitation is for applications to participate as a member of the Anti-PD-L1 Project Team in one of the following roles.**

1. **Clinician-scientists** with expertise in phase 1/2 studies and immunotherapy drug development and preferably experience in one of the areas of high priority for this agent (fill out **Part A** of the attached Application);
2. **Translational scientists** with an interest in biomarker development in immunotherapy and in combinations including other immunologic agents, targeted therapy, and radiation therapy (fill out **Part B** of the attached Application); and
3. **Basic scientists** with expertise in human immunology and immunotherapy (fill out **Part C** of the attached Application).

Prospective Team members may apply for multiple roles using a single application form by completing all the appropriate Parts. The Project Team will be recruited nationally and will prioritize research questions for trials with MEDI4736, including biomarker studies. It is anticipated that the clinicians on the Drug Project Team will be asked to take the lead for writing the Letters of Intent (LOI) submitted to CTEP describing a proposed study design based upon the Team's recommendations. Whenever possible, following approval, these clinicians would lead the clinical studies. It is also anticipated that all other extramural members of the Drug Project Team will be involved in design and conduct of the trials, including proposed correlative studies. It is anticipated that the Project Team will complete its work with the approval of an LOI within two to three months.

Background/Rationale

PD-L1 is part of a complex system of receptors and ligands that modulate the physiologic balance between T-cell activation and "tolerance" through its interaction with PD-1 (CD279) and CD80 (B7-1) (Butte *et al*., 2007). It is expressed on T cells, B cells, dendritic cells (DCs), monocytes/macrophages, natural killer (NK) cells, activated vascular endothelial cells, mesenchymal stem cells, and cultured bone marrow-derived mast cells (Zou and Chen, 2008), and frequently on tumors cells. PD-L1 on tumor or immune cells delivers an inhibitory signal to activated T cells, protecting the tumor from immune elimination (Zou and Chen, 2008). PD-L1 is expressed in a broad range of cancers, and is associated with reduced survival and unfavorable prognosis in lung (Mu *et al*., 2011), renal (Thompson *et al*., 2006), pancreatic (Wang *et al*., 2010), and ovarian cancers (Hamanishi *et al*., 2007). In ovarian cancer, the 5-year survival rate in patients with low levels of PD-L1 was 80.2% versus 52.6% in patients with high levels of PD-LI (Hamanishi *et al*., 2007). Targeting the PD-1 pathway with the anti-PD-1 antibody nivolumab, resulted in an overall response rate (ORR) of 28% in patients with advanced melanoma, 27% in patients with renal cell carcinoma (RCC), and 18% in patients with non-small cell lung cancer (NSCLC) who had failed prior therapy (Topalian *et al*,. 2012). Targeting PD-L1 on the other hand, leaves the PD-1/PD-L2 and PD-1/CD80 (B7-1) interactions intact – maintaining immune homeostasis with potentially less risk of autoimmunity. In a mouse model of asthma, PD-L2 null mice had significantly enhanced severity of airway hyperreactivity and inflammation versus PD-L1 null mice, where the response was not significantly different from wild-type (Akbari *et al*., 2010).

MEDI4736 contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors, which are involved in triggering ADCC or CDC effector function (Lu *et al*., 2014; Oganesyan *et al*., 2008).

Clinical Studies of MEDI4736

As of January 2015, there are 19 single and combination MedImmune/AstraZeneca-sponsored studies using MEDI4736 (ClinicalTrials.gov). These trials are summarized in the tables below:

MEDI4736 Single-Agent Trials

Study NCT	Phase	Disease/Indication	Planned accrual
NCT01938612	1	Advanced solid tumors	118
NCT02117219	1	Myelodysplastic syndrome	70
NCT01693562	1/2	Advanced solid tumors	760
NCT02207530	2	PD-L1^{+} recurrent or metastatic SCCHN	112
NCT02087423	2	NSCLC	282

SCCHN = squamous cell carcinoma of the head and neck; NSCLC = non-small cell lung cancer

MEDI4736 Combination Trials

Study NCT	Phase	Disease/Indication	Combination agent(s)	Planned accrual
NCT02088112	1	NSCLC	Gefitinib	35
NCT02143466	1	EGFR mutation positive NSCLC	AZD9291	240*
NCT02261220	1	Advanced solid tumors	Tremelimumab	210
NCT02262741	1	Recurrent or metastatic SCCHN	Tremelimumab	164
NCT02000947	1	Advanced NSCLC	Tremelimumab	301
NCT02118337	1	Advanced malignancies	MEDI0680	150
NCT02141347	1	Advanced solid malignancies (Japan)	Tremelimumab	22
NCT02027961	1/2	Melanoma	Dabrafenib, Trametinib	69
NCT02340975	1b/2	Gastric or gastroesophageal junction adenocarcinoma	Tremelimumab	174
NCT02205333	1b/2	Advanced solid tumors or aggressive B-cell lymphomas	MEDI6469	212*
NCT02319044	2	Recurrent or metastatic SCCHN	Tremelimumab	240
NCT02179671	2	Locally advanced or metastatic NSCLC (stage IIIB-IV)	Small molecule inhibitors (Gefitinib, AZD9291, Selumetinib +Docetaxel) or Tremelimumab followed by MEDI4736	40
NCT02125461	3	Stage III unresectable NSCLC	Chemoradiation followed by MEDI4736	702
NCT02352948	3	Local advanced or metastatic NSCLC	Tremelimumab	900*

SCCHN = squamous cell carcinoma of the head and neck; NSCLC = non-small cell lung cancer.
* Planned accrual for the entire trial; the MEDI4736 combination is only one arm of the study.

The ongoing phase 1/2 open-label study (NCT01693562) is evaluating safety, pharmacokinetics (PK), and antitumor activity of MEDI4736 (Lutzky *et al*., 2014; Brahmer *et al*., 2014). MEDI4736 was given every 2 weeks (Q2W) or every 3 weeks (Q3W) in a 3+3 dose escalation with a 28-day (Q2W) or 42-day (Q3W) dose-limiting toxicity (DLT) window, followed by expansion cohorts in eight solid tumors. As of January 17, 2014, of the 26 patients accrued (13 NSCLC, 8 melanoma, 5 other) in the dose escalation portion of the study, MEDI4736 demonstrated an acceptable safety profile and durable clinical activity. No DLTs or maximum tolerated dose (MTD) were identified for Q2W or Q3W dosing. Expansion cohorts opened in September 2013 using a 10 mg/kg Q2W MEDI4736 dose, and 151 patients have been dosed (Segal *et al*., 2014). Preliminary data suggest that the agent safety is acceptable. As of May 2014, 155 patients had been accrued in the NSCLC

cohort of NCT01693562 (Brahmer *et al*., 2014). The phase 1 combination study of MEDI4736 and tremelimumab (NCT02000947) is using a 4-week dosing interval in NSCLC patients (Brahmer *et al*., 2014; Pinder *et al*., 2014). This study is evaluating the safety, pharmacodynamics, and preliminary activity of the combination of these two agents and is currently enrolling patients in the dose escalation phase using a 3+3 design. As of April 2014, 12 patients have been treated at four dose levels. Preliminary data from these two studies were presented at the 2014 American Society of Clinical Oncology (ASCO) and Society for Immunotherapy of Cancer (SITC) meetings and are summarized below.

Pharmacokinetics

In the NCT01693562 study, MEDI4736 has shown dose-dependent PK over the dose range used (0.1 – 10 mg/kg Q2W and 15 mg/kg Q3W IV MEDI4736) (Fairman *et al*., 2014). The linear clearance (Cl), volume of distribution (V_d), and concentration at half maximal elimination (K_M) were 240 mL/day, 3.6 L, and 0.4 mcg/mL, respectively. The half-life ($T_{½}$) was approximately 23 days at doses ≥3 mg/kg Q2W MEDI4736. Greater than 99% target saturation (soluble and membrane bound) is expected at ≥40 mcg/mL of MEDI4736. Out of 31 patients, 3 were positive for anti-drug antibody (ADA) with an impact on PK in 1 patient. Based on preclinical/clinical PK, pharmacodynamics, and safety data, a dose of 10 mg/kg Q2W was selected for the expansion phase.

Safety

As of January 17, 2014, in the dose-escalation cohort of the NCT01693562 study, treatment-related adverse events (AEs) occurred in 34% of all patients, all were grade 1-2, and none led to discontinuation of the study drug (Lutzky *et al*., 2014). The most frequent were diarrhea, fatigue, rash, and vomiting (12% each). There were no events of colitis, pneumonitis, or hyperglycemia. In the expansion cohort, treatment-related AEs occurred in 33% of all patients, with related ≥grade 3 AEs in 7% of patients (Segal *et al*., 2014). The most frequently observed treatment-related AEs were fatigue (13%), nausea (8%), rash (6%), vomiting (5%), and pyrexia (5%). One patient developed grade 2 pneumonitis that resolved with drug interruption and steroids; there were no reports of colitis or hyperglycemia. As of May 2014, in the NSCLC cohort, treatment-related AEs occurred in 29% of patients, all were grade ≥3, and none led to the discontinuation of the study drug (Brahmer *et al*., 2014). The most frequent AEs were fatigue (7%), nausea (5%), and vomiting (5%). Of the four patients treated with the MEDI4736 and tremelimumab combination (NCT02000947), treatment-related AEs ≥grade 3 were experienced in 3 patients (Brahmer *et al*., 2014). One patient had elevated aspartate transaminase (AST) / alanine transaminase (ALT; grade 3) and grade 5 myasthenia; a second patient suffered grade 3 diarrhea/colitis; and the third had elevated amylase (grade 4). Drug treatment was discontinued in the patients that experienced the grade 5 myasthenia and grade 3 colitis. No DLTs were observed in any cohort.

Efficacy

In the dose-escalation cohort of the NCT01693562 study, tumor shrinkage was observed as early as 6 weeks at all dose levels (Lutzky *et al*., 2014). Out of 26 patients, 4 showed partial responses (PRs; 3 NSCLC, 1 melanoma), and 5 additional patients showed tumor shrinkage not meeting PR. Disease control rate (PR + SD [stable disease] ≥12 weeks) was 46%. In the expansion cohorts, with a median follow-up time of 6 weeks, tumor shrinkage was already being detected in multiple tumor types (melanoma, head and neck, gastroesophageal, and pancreatic) (Segal *et al*., 2014). As of May 2014, out of 58 patients in the NSCLC cohort, 16% had PRs; the duration of response ranged between 5 - 54+ weeks, and the disease control rate was 35% (Brahmer *et al*., 2014).

CTEP's Plans for MEDI4736 Development

CTEP is interested in developing MEDI4736 in combination with other therapies. Combinations of interest include, but are not limited to:

- MEDI4736 in combination with a Wee1 inhibitor;
- MEDI4736 in combination with radiation therapy;
- MEDI4736 in combination with other targeted agents.

*Note: MEDI4736-based combination regimens in the proposed trials may be developed further to include tremelimumab, where appropriate. Tremelimumab is a human IgG2 mAb against human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), and is also under development in collaboration with MedImmune/AstraZeneca.

Correlative studies of interest to CTEP include, but are not limited to:
Immunohistochemistry (IHC) analysis at baseline, post-treatment, and progression:

- PD-LI expression on tumor-infiltrating immune cells, as well as tumor cells;
- "Immune-score"-like analysis of cellular infiltrates;
- Exploratory biomarkers: indoleamine-2,3-dioxygenase (IDO), CC chemokine receptor 4 (CCR4), lymphocyte activation gene 3 (LAG3), T-cell immunoglobulin and mucin domain 3 (TIM3), and CD27; and

Genomics:

- Sequencing for immunogenic neo-antigens;
- Germline single-nucleotide polymorphisms (SNPs), including CTLA4 variants;
- Inflammatory signatures; and
- TCR monitoring.

We anticipate that the Project Team will have the opportunity to develop biomarker assays as a collaborative effort among the NCI, the CRADA partner, and participating investigators.

The role of the Project Team will be to evaluate all available evidence to modify and to refine this initial plan.

Anti-PD-L1 Project Team Selection, Composition and Tasks

The Anti-PD-L1 Drug Project Team will meet regularly by WebEx to review available evidence and determine promising strategies, identify biomarkers to evaluate these strategies, and evaluate clinical trial designs to test these strategies. The Project Team will be composed of intramural and extramural members. The extramural members will include clinician-scientists with experience in phase 1/2 studies in immunotherapy drug development; translational scientists with expertise in biomarker development; and basic scientists with expertise in immune-oncology. Since the clinician-scientists selected for the Project Team will be expected to lead the clinical trials that come out of this process, the evaluation criteria for the clinician-scientists will include not only clinical trial expertise, but also their documented record of accrual to early phase studies.

Questions regarding this request for applications may be addressed to Howard Streicher, M.D., Senior Clinical Investigator, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: streicherh@ctep.nci.nih.gov). All applicants must have an active CTEP Identity and Access Management (IAM) account before the submission deadline. To create a CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam/index.jsp and click the "Request New Account" link at the right. For questions about CTEP-IAM account creation, please contact the CTEP Registration Help Desk: ctepreghelp@ctep.nci.nih.gov.

Project Team Member Applications should contain a clear indication of the applicant's desired role on the Anti-PD-L1 Project Team (clinician-scientist, translational scientist, or basic scientist). The PTMA should also be accompanied by an NIH Biosketch containing a personal statement customized to this project. The PTMAs should be sent to the Protocol and Information Office (PIO) at the address below by **5:00 PM Eastern Time (ET), April 28, 2015**. The most recent version of the PTMA form, available on the CTEP Website (http://ctep.cancer.gov), must be used. PTMAs should be submitted electronically to:

PIO, CTEP/DCTD/NCI
E-mail: pio@ctep.nci.nih.gov

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