REQUEST FOR PROJECT TEAM MEMBER APPLICATION FOR CONDUCTING CLINICAL TRIALS USING MPDL3280A (NSC# 783608)

The Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member Applications (PTMAs) for a project using MPDL3280A, an anti-PD-L1 monoclonal antibody (mAb) being developed by CTEP as an anticancer agent in collaboration with Genentech/Roche. MPDL3280A is a high-affinity human mAb that binds to programmed death-ligand 1 (PD-L1; also called B7-H1 or CD274) and prevents its interaction with programmed cell death 1 (PD-1) and B7-1 (Herbst *et al.*, 2014). MPDL3280A has demonstrated clinical activity in advanced urothelial bladder cancer (UBC) (Powles *et al.*, 2014) and non-small cell lung cancer (NSCLC) (Herbst *et al.*, 2014), among others. On the basis of these results, the Food and Drug Administration (FDA) granted MPDL3280A Breakthrough Therapy Designation in May 2014 for the treatment of bladder cancer (Roche, 2014), and in February 2015 for the treatment of people with PD-L1 positive NSCLC whose disease progressed during or after platinum-based chemotherapy (Roche, 2015).

At the present time, the preliminary CTEP drug development plan is for both single-agent and combination phase 1/2 trials of MPDL3280A, including the following four trials: 1) MPDL3280A in combination with vaccines, 2) MPDL3280A in the setting of adoptive T-cell therapy, 3) MPDL3280A in combination with a poly (ADP-ribose) polymerase (PARP) inhibitor, and 4) MPDL3280A in combination with bevacizumab in gynecological malignancies.

This solicitation is for applications to participate in the Anti-PD-L1 Project Team. The role of the Project Team is to evaluate all available evidence to modify and refine this initial plan. The Project Team will include:

1. **Clinician-scientists** with expertise in early phase studies and with an interest in adoptive T cell transfer therapy, PARP inhibitor drug development, breast and ovarian cancer with homologous recombination defects, and vaccine combination therapy (fill out **Part A** of the attached Application);
2. **Translational scientists** with an interest in biomarker development in immuno-oncology and adoptive T cell transfer therapy (fill out **Part B** of the attached Application); and
3. **Basic scientists** with expertise in immuno-oncology, homologous recombination defects, and basic tumor immunology (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 the research questions regarding MPDL3280A combination trials, including prioritization of biomarker studies. It is anticipated that the clinicians on the Drug Project Team will be tasked with writing the Letters of Intent describing the study design, based upon the team's recommendations, for CTEP approval, and that these clinicians will ultimately lead the clinical studies. It is also anticipated that other extramural members of the Drug Project Team will stay involved in the subsequent design and execution of the proposed trials. It is anticipated that the Project Team will complete its work in two to three months or less.

Background/Rationale

PD-L1 is part of a complex system of receptors and ligands that regulate the balance between T-cell activation and tolerance, and plays an important part in blocking the antitumor immune response by downregulating T-cell activation through its interaction with PD-1 and B7-1 (Butte *et al*., 2007). PD-L1 is expressed on a variety of cells (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), in addition to a number of tumors (Zou and Chen, 2008). Tumor-expressed PD-L1 binds to PD-1 on activated T cells and delivers an inhibitory signal protecting the tumor from immune elimination. PD-L1 expression in a broad range of cancers 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).

Antibodies targeting the PD-1 pathway have demonstrated durable objective responses; for example, the anti-PD-1 inhibitor nivolumab showed 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 NSCLC who had failed prior therapy (Topalian *et al*., 2012). Blocking the PD-1 signaling pathway by targeting PD-L1, instead of PD-1, leaves the PD-1/PD-L2 and PD-1/B7-1 interactions intact, allowing for maintenance of immune homeostasis potentially with less 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), suggesting that preserving these additional pathways may potentially allow for reduced toxicity of treatment.

MPDL3280A is a human mAb that specifically binds to PD-L1. To prevent the depletion of activated T cells, MPDL3280A was engineered to replace an aspartic acid with an alanine at position 298 in the CH2 domain of each heavy chain of the crystallizable fragment (Fc). This results in an antibody without *N*-linked oligosaccharides that is incapable of binding to human Fcγ receptors, therefore removing antibody-dependent cellular cytotoxicity (ADCC) at clinically relevant doses. MPDL3280A treatment has been shown to be generally well tolerated, and in NSCLC and UBC especially, yield rapid, durable responses, with higher response rates in patients with greater PD-L1 expression (Herbst *et al.*, 2014; Powles *et al.*, 2014).

Mechanism of Action

MPDL3280A is a high-affinity human monoclonal immunoglobulin G1 (IgG1) antibody that specifically binds to PD-L1 (dissociation constant [K_d] = 0.4 nM) and prevents its interaction with PD-1 and B7.1, while leaving the interaction of PD-1 with its alternative ligand PD-L2 intact (Herbst *et al.*, 2014).

Clinical Studies of MPDL3280A

As of January 2015, there are 18 single and combination Genentech/Roche-sponsored studies using MPDL3280A (ClinicalTrials.gov). These trials are summarized in the tables below:

MPDL3280A Single-Agent Trials

Study ID(s) and NCT #	Phase	Patient population	Planned enrollment
PCD4989g, NCT01375842	1	Advanced or metastatic solid tumors	344
GO29293, NCT02108652	2	Locally advanced or metastatic UBC	330
GO28625, NCT01846416	2	PD-L1$^+$ locally advanced or metastatic NSCLC	128
GO28754, NCT02031458	2	PD-L1$^+$ locally advanced or metastatic NSCLC - "BIRCH"	635
GO28753, NCT01903993	2	Locally advanced or metastatic NSCLC who have failed platinum therapy - "POPLAR"	287
MO29112, NCT02291289	2	Metastatic colorectal cancer	610
GO28915, NCT02008227	3	Patients with locally advanced or metastatic NSCLC who have failed platinum therapy - "OAK"	850
GO29294, NCT02302807	3	Locally advanced or metastatic UBC	767

MPDL3280A Combination Trials

Study ID(s) and NCT #	Phase	Patient population	Combination agents	Planned enrollment
GP28328, NCT01633970	1	Locally advanced or metastatic solid tumors	Bevacizumab (Arm A), bevacizumab plus FOLFOX (Arm B), carboplatin and paclitaxel (Arm C), carboplatin and pemetrexed (Arm D), carboplatin and nab-paclitaxel (Arm E), and nab-paclitaxel (Arm F)	180
WP29158, NCT02013219	1	NSCLC	Tarceva (erlotinib)	32

Study ID(s) and NCT #	Phase	Patient population	Combination agents	Planned enrollment
GP28363, NCT01988896	1	Locally advanced or metastatic solid tumors	Cobimetinib	90
GO29322, NCT02174172	1	Locally advanced or metastatic solid tumors	Ipilimumab in NSCLC (Arm A) and plus interferon alfa-2b in advanced or metastatic RCC and melanoma. (Arm B)	200
GP28384, NCT01656642	1	Previously untreated $BRAF^{V600}$-mutation positive metastatic melanoma	Vemurafenib or vemurafenib plus cobimetinib	44
BP29392, NCT02304393	1	Locally advanced or metastatic solid tumors	RO7009789	160
GO29383, NCT02220842	1	Relapsed/refractory follicular lymphoma and diffuse large B-cell lymphoma	Obinutuzumab	52
BP29428, NCT02323191	1	Locally advanced or metastatic solid tumors	RO5509554	110
BP29435 NCT02350673	1	Locally advanced or metastatic solid tumors	RO6895882	75
WO29074, NCT01984242	2	Untreated advanced RCC	Combination with Avastin (bevacizumab) versus sunitinib	150

Clinical data are derived primarily from two clinical trials (a phase 1 monotherapy [PCD4989g] and a phase 1b combination [GP28328] study) in patients with solid tumors and hematologic malignancies.

Study PCD4989g (NCT01375842) is an open-label, phase 1 study of MPDL3280A designed to assess the safety, tolerability, and pharmacokinetics (PK) in patients with locally advanced or metastatic solid tumors, or hematologic malignancies (ClinicalTrials.gov). As of April 2013, 277 patients were treated with MPDL3280A (Herbst *et al.*, 2014). The efficacy analysis included 175 patients who received ≥1 mg/kg MPDL3280A by October 1, 2012. Patients in the UBC cohort were dosed at 15 mg/kg every 3 weeks (Q3W) (Powles *et al.*, 2014). Enrollment in the expansion phase is ongoing.

Study GP28328 (NCT01633970) is an ongoing phase 1b study evaluating the safety and pharmacology of MPDL3280A administered with bevacizumab alone or MPDL3280A administered with bevacizumab plus chemotherapy in patients with advanced solid tumors (ClinicalTrials.gov). As of January 21, 2014, 33 patients in Arm A (MPDL3280A with bevacizumab alone) and 29 patients in Arm B (MPDL3280A with bevacizumab plus FOLFOX) were dosed with MPDL3280A (Lieu *et al.*, 2014).

Pharmacokinetics

In the phase 1 monotherapy study PCD4989g, 277 patients with advanced cancer were treated with 0.03 mg/kg – 20 mg/kg intravenous (IV) MPDL3280A Q3W (Herbst *et al.*, 2014). Mean single-dose MPDL3280A PK were consistent with a typical IgG1 at doses ≥1 mg/kg with a mean terminal serum half-life ($T_{1/2}$) of approximately 3 weeks.

Safety

Treatment was well tolerated up to the maximum administered dose of 20 mg/kg MPDL3280A Q3W in the 277 patients in study PCD4989g (Herbst *et al.*, 2014). Treatment-related adverse events (AEs) were reported in 70% of patients; fatigue (67%), decreased appetite (33%), nausea and pyrexia (32% each), and diarrhea and rash (29% each) were the most frequent. Fatigue and pyrexia were most common during the first cycle of treatment. Additionally, an approximately two-fold increase in activated proliferating $CD8^+$ T cells, and a trend of increasing interferon (IFN)-γ, was observed during the end of the first cycle. Treatment-related grade 3-4 AEs were reported in 35 (13%) patients; fatigue (5 patients), increased alanine aminotransferase (ALT),

increased aspartate aminotransferase (AST), and hypoxia (3 patients each) were the most frequent. Immune-related grade 3-4 AEs were observed in 3 patients (1%). No cases of grades 3-5 pneumonitis were observed.

As of January 1, 2014, 68 patients with UBC enrolled in an expansion cohort of study PCD4989g were evaluable for safety (Powles *et al.*, 2014). Treatment-related AEs were reported in 57% of patients, mostly grade 1 or 2. Decreased appetite, fatigue, and nausea (11.8% each) were the most frequent. Treatment-related grade 3-4 AEs were reported in 3 (4%) patients.

In preliminary data presented at the European Society for Medical Oncology (ESMO) 2014 Congress for study GP28328, MPDL3280A administered in combination with bevacizumab ± FOLFOX was well tolerated and there were no unexpected AEs (Lieu *et al.*, 2014). Grade 3-4 AEs, regardless of attribution, occurred in 42% of Arm A patients, including abdominal pain, hyperbilirubinemia, pneumonia and tumor pain (6% each), and in 52% of Arm B patients, including neutropenia (31%) and diarrhea (14%). No MPDL3280A-related infusion reactions occurred. Serious AEs (SAEs) occurred in 30% and 17% of patients in Arms A and B, respectively.

Efficacy

In study PCD4989g, confirmed responses (complete responses [CRs] + partial responses [PRs]) were observed in 32 of 175 (18%) patients with all tumor types, 11 of 53 (21%) NSCLC patients, 11 of 43 (26%) melanoma patients, 7 of 56 (13%) RCC patients, and 3 of 23 (13%) patients with other tumors (including colorectal cancer, gastric cancer, and head and neck squamous cell carcinoma) (Herbst *et al.*, 2014). Four additional patients had unconfirmed responses. Responses following MPDL3280A administration could also be rapid and durable; some responders were reported to have shrinking or resolving palpable lesions within days. Nearly all responders, especially those with NSCLC, continued to respond and remained in the study. The median progression-free survival (PFS) was 18 weeks. Additionally, PD-L1 expression on tumor-infiltrating immune cells, but not tumor cells, was significantly associated with response in NSCLC (P=0.015) and all tumors (P=0.007). For example, in NSCLC patients with a PD-L1 immunohistochemistry (IHC) score of 3 (on a scale of 0-3) there was an 83% ORR with only 17% developing progressive disease (PD), while 43% of IHC 2 (tumor-infiltrating immune cell) NSCLC patients achieved stable disease (SD). These data suggest that status of this biomarker may be predictive of treatment efficacy.

As of January 1 2014, 67 patients in the UBC expansion cohort of PCD4989g were evaluable for efficacy (Powles *et al.*, 2014). Response to MPDL3280A in UBC was also associated with the tumor-infiltrating immune cell IHC scores (P=0.026). For patients with ≥6 weeks of follow-up, ORRs were 43% (13 of 30; 95% confidence interval [CI]: 26–63%, 2 CRs, 11 PRs) for patients with IHC 2/3 tumors and 11% (4 of 35; 95% CI: 4–26%) for patients with IHC 0/1 tumors. Among patients with IHC 2/3 tumors and ≥12 weeks of follow-up, an ORR of 52% (13 of 25; 95% CI: 32–70%) was achieved. Sixteen of the 17 responders had ongoing responses, all 17 responders continued on treatment with MPDL3280A at the data cutoff, and the median duration of response had not been reached.

Preliminary efficacy data from the ESMO 2014 Congress showed a 40% ORR in 1L RCC following treatment with the combination of MPDL3280A and bevacizumab (Lieu *et al.*, 2014). Additionally, in pretreated metastatic RCC treated with MPDL3280A monotherapy, patients with PD-L1 IHC 1/2/3 were more likely to respond than patients with no detectable PD-L1 (IHC 0); 20% *vs.* 10%, respectively (McDermott *et al.*, 2014).

Biomarkers

In addition to the correlation between PD-L1 status and response to MPDL3280A, the presence of markers of T-cell activation (Th1-related CD8 biology and cytotoxic T-lymphocyte-associated protein 4 [CTLA4]), and the absence of baseline fractalkine in the tumor microenvironment correlated with response (Kowanetz *et al.*, 2014; Herbst *et al.*, 2014). Elevated baseline expression of IFN-γ and IFN-γ inducible genes (*e.g.*, indoleamine-pyrrole 2,3-dioxygenase [*IDO1*] and *CXCL9*) was associated with response in melanoma, but not NSCLC or RCC (Herbst *et al.*, 2014). Serial biopsies investigating immunological events associated with tumor response included an increased infiltration of Th1-dominant immune cells and adaptive tumor PD-L1 enhancement with treatment.

CTEP's Proposed Plans for MPDL3280A Development

CTEP is interested in developing MPDL3280A in combination with other therapies, including:

- MPDL3280A in combination with vaccines, particularly those with documented and proven efficacy or biological activity;
- MPDL3280A in combination with bevacizumab in gynecological cancer;
- MPDL3280A in conjunction with adoptive T-cell transfer therapy, including neo-antigen-specific approaches;
- MPDL3280A in combination with a PARP inhibitor in BRCA mutant malignancies; and
- Combinations of MPDL3280A with other CTEP-held IND agents may also be considered.

Correlative studies of interest to CTEP include, but are not limited to:

IHC analysis at baseline, post-treatment, and progression:

- PD-LI expression on tumor-infiltrating immune cells, as well as tumor cells (assays for PD-L1 will be performed in collaboration with Genentech to establish consistency across studies);
- "Immune-score"-like analysis of cellular infiltrates;
- Exploratory biomarkers: 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
- T-cell repertoire.

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

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 members will include clinician-scientists with experience in early phase studies in immuno-oncology, adoptive T cell transfer therapy/neo-antigen specific approaches and PARP inhibitor therapy; translational scientists with expertise in biomarker development; and basic scientists with expertise basic tumor immunology. 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 Elad Sharon, M.D., M.P.H., Senior Clinical Investigator, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: sharone@mail.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.

PTMAs 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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