REQUEST FOR PROJECT TEAM MEMBER APPLICATION FOR CONDUCTING CLINICAL TRIALS USING ANETUMAB RAVTANSINE

The Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member applications for a project using anetumab ravtansine (BAY 94-9343), an anti-mesothelin antibody-drug conjugate (ADC) being developed by CTEP as an anticancer agent in collaboration with Bayer. In results presented at the 2015 World Conference on Lung Cancer, anetumab ravtansine showed encouraging efficacy with durable partial responses (PRs) in patients with advanced mesothelioma (Hassan *et al.*, 2015). Five of 16 (31%) mesothelioma patients treated at the maximum tolerated dose (MTD) had a durable PR (>600 days in 4 patients), and 7 (44%) patients had stable disease (SD). Five PRs occurred in 11 mesothelioma patients who received anetumab ravtansine as second line treatment; a response rate of 45%. The recommended phase 2 dose (RP2D) is anetumab ravtansine 6.5 mg/kg administered intravenously (IV) every 3 weeks (q3w).

At the present time, the preliminary CTEP drug development plan initially will consist of 3-4 trials, including phase 1 combination studies with CTEP IND agents, with at least one trial of anetumab ravtansine in combination with an immune checkpoint inhibitor for the treatment of mesothelioma, ovarian cancer, or non-small cell lung cancer (NSCLC), and a possible phase 2 basket trial for the treatment of rare malignancies with high mesothelin expression. The major emphasis is to investigate strategies to enhance the activity of the ADC in malignancies with high target expression, either through the augmentation of immune response or enhancement of the mechanisms of direct cell killing by the ADC.

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

It is anticipated that CTEP will activate 3-4 different early phase trials with anetumab ravtansine. The Project Team will include:

1. **Clinician-scientists** with expertise in early phase studies and with an interest in tumors with high mesothelin expression (fill out **Part A** of the attached Application);
2. **Translational scientists** with an interest in biomarker development as it relates to mesothelin-directed therapy (fill out **Part B** of the attached Application); and
3. **Basic scientists** with expertise in mesothelin biology (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 anetumab ravtansine in 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 8-12 weeks or less; all participants selected for the Anetumab Ravtansine Project Team are required to attend all teleconferences.

Background/Rationale

Mesothelin is a differentiation antigen that is normally found on the mesothelial cells of the pleura, peritoneum, and pericardium, but is also highly expressed in a number of cancers, including pancreatic and ovarian cancers and mesotheliomas (Chang and Pastan, 1996; Hassan *et al.*, 2004). While the biological function of mesothelin is not clearly defined, it is a known cancer antigen (CA)125 binding protein and may play a role in the metastatic spread of ovarian cancer and in the growth and invasion of pancreatic cancers (Rump *et al.*, 2004; Gubbels *et al*., 2006; Bharadwaj *et al.*, 2011a; Bharadwaj *et al.*, 2011b). The protein encoded by the mesothelin gene is processed to a GPI-anchored, glycosylated precursor that is subsequently cleaved to generate the 40-kDa membrane-bound mesothelin and a 31-kDa shed fragment called megakaryocyte-potentiating factor (MPF) (Hassan *et al.*, 2004). Membrane-bound mesothelin is cleaved by a specific

sheddase, tumor necrosis factor α converting enzyme (TACE/ADAM17) (Zhang *et al.*, 2011). Levels of soluble mesothelin have been found to be elevated in the blood of patients with mesothelioma and ovarian cancer, and may be useful in the diagnosis or follow-up of patients with mesothelin-expressing cancers (Hassan *et al.*, 2004). The restricted expression of mesothelin on normal tissues and high expression in many cancers makes it a good target for cancer therapy, and there are multiple anti-mesothelin drugs in clinical development (*e.g.*, SS1P, amatuximab, CRS-207).

Anetumab ravtansine is a novel ADC consisting of a fully human anti-mesothelin immunoglobulin G1 (IgG1) antibody conjugated to a maytansinoid DM4, a potent anti-tubulin cytotoxic agent. The monoclonal antibody moiety of anetumab ravtansine targets and binds to mesothelin, and upon internalization, the DM4 moiety binds to tubulin and disrupts microtubule assembly/disassembly dynamics, resulting in inhibition of cell division and cell growth.

Nonclinical Studies of Anetumab Ravtansine

Anetumab ravtansine binds to human mesothelin with high affinity (dissociation constant [K_d]=10 nmol/L) and specificity and was demonstrated to be internalized using a human ovarian carcinoma cell line (OVCAR-3) (Golfier *et al.*, 2014). *In vitro*, anetumab ravtansine demonstrated antiproliferative activity in human pancreatic (MIA PaCa-2; half maximal inhibitory concentration [IC_{50}]=1.59×10^{-9} mol/L) and colon carcinoma (HT-29; IC_{50}=7.15×10^{-10} mol/L) cell lines that were transfected with human mesothelin, and in OVCAR-3 (IC_{50}=1.59×10^{-9} mol/L) and mesothelioma (NCI-H226; IC_{50}=5.72×10^{-9} mol/L) cell lines with endogenous mesothelin expression. *In vivo*, anetumab ravtansine localized specifically to mesothelin-positive tumors and inhibited tumor growth in subcutaneous (MIA PaCa-2/meso, HT-29/meso, OVCAR-3, and NCI-H226 cells) and orthotopic (OVCAR-3-s-05 cells) xenograft tumor models. In mice subcutaneously inoculated with different ratios of mesothelin-positive and -negative HT-29 cells, anetumab ravtansine treatment demonstrated mesothelin expression-dependent antitumor efficacy. When compared with standard of care treatments, the antitumor efficacy of anetumab ravtansine was more pronounced than gemcitabine (P<0.01), cisplatin (P<0.01), and cisplatin (P<0.05) and pemetrexed (P<0.001) in pancreatic, ovarian, and mesothelioma patient-derived tumor models, respectively.

Clinical Studies of Anetumab Ravtansine

As of March 15, 2016, there are four ongoing studies of anetumab ravtansine, all sponsored by Bayer (ClinicalTrials.gov). These studies are summarized in the table below.

NCT #	Phase	Agent(s)	Disease/Indication	Planned Accrual
NCT02696642	1	Anetumab ravtansine	Mesothelin-expressing advanced solid cancers and concurrent hepatic or renal impairment	36
NCT02485119	1	Anetumab ravtansine	Advanced malignancies (Japanese patients)	15
NCT02639091	1b	Anetumab ravtansine in combination with pemetrexed and cisplatin	Mesothelin-expressing predominantly epithelial mesothelioma or nonsquamous NSCLC	30
NCT02610140	2	Anetumab ravtansine *vs.* vinorelbine	Advanced or metastatic malignant pleural mesothelioma overexpressing mesothelin and progressed on first line chemotherapy	183

Preliminary results from a phase 1 study of anetumab ravtansine in patients with advanced solid tumors were presented at the 2015 World Conference on Lung Cancer (Hassan *et al*., 2015). Anetumab ravtansine was administered IV q3w in 77 patients: 45 patients in 10 dose escalation cohorts, and 32 patients in two expansion cohorts (12 mesothelioma patients and 20 ovarian cancer patients). The MTD was determined to be anetumab ravtansine 6.5 mg/kg IV q3w; 38 patients were treated at this dose (16 mesothelioma, 21 ovarian, 1 breast). Dose limiting toxicities (DLTs) included keratitis and peripheral neuropathy. Seventeen of 38 (45%) patients had drug-related adverse events (AEs) requiring dose reduction. Liver function test (LFT) increases were the most common drug-related laboratory abnormality (grade 3 LFT events were aspartate aminotransferase increase [n=2] and alkaline phosphatase increase [n=1]). All drug-related AEs were reversible. Fourteen of 38

(37%) patients or 4 of 16 (25%) mesothelioma patients at MTD had keratitis. Anetumab ravtansine 6.5 mg/kg IV q3w showed a PR in 6 (19%) patients and SD in 18 (47%) patients. Five of 16 (31%) mesothelioma patients at the MTD had durable PR (>600 days in 4 patients), and 7 (44%) patients had SD. Five PRs occurred in 11 mesothelioma patients who received anetumab ravtansine as second line treatment; a response rate of 45%.

CTEP's Plans for Anetumab Ravtansine Development

Preliminary CTEP interests include studying anetumab ravtansine in tumors with high expression of mesothelin. Bayer will provide a validated immunohistochemical assay for mesothelin to aid in patient selection.

Studies of anetumab ravtansine of interest to CTEP may include:

- In combination with immune checkpoint inhibitors in mesothelioma, NSCLC, and/or ovarian cancer;
- In combination with other agents that may decrease mesothelin shedding, enhance cellular uptake of the ADC, or augment the cytotoxicity of DM4. For example:
    - ABT263 – shown to be synergistic with T-DM1;
    - Tyrosine kinase inhibitors (TKIs) that inhibit DDR1 (*e.g*. dasatinib) – shown to be synergistic with mesothelin immunotoxin RG7787 (Ali-Rahmani *et al.*, 2016);
- Monotherapy phase 2 basket trial for rare tumors with high mesothelin IHC expression; *e.g.* cholangiocarcinoma, thymic carcinoma, synovial sarcoma, gastric cancer, triple-negative breast cancer (TNBC); and
- In combination studies with other ADCs where target antigens are co-expressed: brentuximab (CD30), glembatumumab (gpNMB).

Correlative Studies of Interest to CTEP

Biomarker studies may include, but are not limited to, examining TACE-mediated mesothelin ectodomain shedding and how membrane attachment and turnover may influence the effectiveness of the anti-mesothelin ADC, mesothelin IHC, and measurement of circulating mesothelin-related peptides such as MPF.

Anetumab Ravtansine Project Team Selection, Composition, and Tasks

The Anetumab Ravtansine 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 early phase studies in tumors with high expression of mesothelin and with experience in mesothelin-directed therapeutic agents; translational scientists with expertise in biomarker development; and basic scientists with expertise in mesothelin biology. 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 of tumors with high expression of mesothelin (such as mesothelioma, ovarian cancer, and NSCLC).

Questions regarding this request for applications may be addressed to Jeff Moscow, M.D., Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6101; FAX: 240-276-7894; e-mail: jeffrey.moscow@nih.gov).

CTEP recognizes the importance of encouraging and supporting young investigators as they embark upon a clinical cancer research career. CTEP highly encourages Career Development Applications (CrDAs) from these investigators and their mentors as Project Team members to develop Career Development Letters of Intent (CrDLs).

Project Team Member Applications (PTMAs) should contain a clear indication of the applicant's desired role on the Anetumab Ravtansine 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), May 3, 2016. 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: CTEPPTMASubmissions@mail.nih.gov

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