



## REQUEST FOR PROJECT TEAM MEMBER APPLICATIONS FOR CONDUCTING CLINICAL TRIALS USING BAY 1895344 (NSC# 810486)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member Applications for a project using BAY 1895344 (NSC# 810486), an ATR kinase inhibitor being developed by CTEP as an anticancer agent in collaboration with Bayer Pharmaceuticals. Currently, BAY 1895344 is being tested as a single agent in phase 1 clinical studies sponsored by Bayer.

### Clinical Trials with BAY 1895344 of Interest to CTEP

The BAY 1895344 project team will be responsible for building up CTEP's initial development plan of the agent. CTEP is considering a number of phase 1b combination trial concepts with BAY 1895344:

- A phase 1 trial of BAY 1895344 in combination with a camptothecin because there is preclinical evidence that ATR inhibition will synergize with this class of agents in a relevant clinical context
- A phase 1 trial of BAY 1895344 in combination with temozolomide because there is preclinical evidence that ATR inhibitors will act synergistically with temozolomide and other DNA damaging agents in a relevant clinical context. Studies of BAY 1895344 with temozolomide and ionizing radiation may also be considered.
- A phase 1 trial with escalating doses of BAY 1895344 in combination with standard of care chemotherapy and immunotherapy in a clinical context in which chemotherapy and immunotherapy have an established role. Preclinical data to support this proposal will be discussed with the project team members.
- Phase 1 studies of BAY 1895344 with cisplatin, carboplatin, and gemcitabine individually. Each study might have expansion cohorts of patients with tumors appropriate for the specific chemotherapy and with known high incidence of DNA damage response (DDR) alterations. Once the RP2D of these combinations had been established, further phase 1 development of BAY 1895344 with cisplatin/gemcitabine and with carboplatin/gemcitabine could be considered.

The project team will be expected to review all relevant pre-clinical and clinical data, to prioritize study concepts, and propose study designs that will be reviewed by the Investigational Drug Steering Committee.

The project team for BAY 1895344 will include:

1. **Clinician Scientists** with expertise in phase 1 studies and with an interest in SCLC, glioblastoma, and cancers with known high incidence of DNA repair or other DDR alterations (including bladder, squamous cell carcinoma of the head and neck, squamous lung cancer, ovarian cancer, and prostate cancer) should fill out **Part A** of the attached Application. Clinician Scientists must belong to a qualifying NCI grant funded institution as defined at the end of this letter.
2. **Translational Scientists** with an interest in biomarker development for ATR inhibition, other pathway activation markers of DNA damage, and dose-scheduling effects may fill out **Part B** of the attached Application and see the submission instructions at the end of this letter; and
3. **Basic Scientists** with expertise in DNA repair, DDR and mechanistic understanding of the effects of ATR inhibition should fill out **Part C** of the attached Application and see the submission instructions at the end of this letter.

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 BAY 1895344 in combination with topotecan, temozolomide and cranial radiation therapy, and individual combinations with cisplatin, carboplatin, and gemcitabine. 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 and biomarker studies. It is anticipated that the project team will complete its work in approximately three months.

## **Background and Rationale**

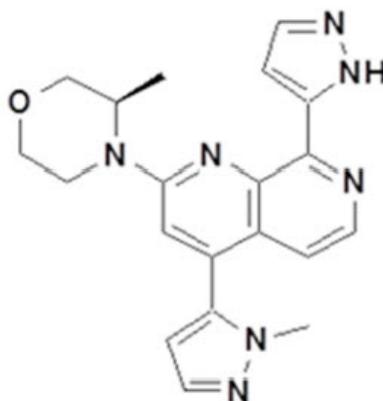
The ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) kinases are two PI3K-like protein kinases responsible for regulation of the DNA damage response (DDR) pathway in human cells (Karnitz and Zou 2015). ATR responds to a broad range of DNA damage or replication stressors, while ATM primarily responds to double-strand DNA breaks. ATR activation results in phosphorylation of CHK1, an effector kinase responsible for activation of the downstream pathway, which will then promote cell cycle arrest, DNA repair, and stabilization of the replication fork. In tumor cells, ATR signaling is upregulated by a variety of factors, including the presence of several oncoproteins that promote replication stress, ATM deficiency, loss of specific DNA repair proteins, hypoxia-induced replication stress, and activation of alternative lengthening of the telomeres pathway (Lecona and Fernandez-Capetillo, 2018). The promise of the ATR inhibitor BAY 1895344, as an anti-cancer agent, is to exploit this increased reliance of tumor cells on the ATR pathway.

Failure to activate the ATR pathway on encountering oncogene-driven replication stress or deficient DNA repair mechanisms would lead to further genomic instability and tumorigenesis (Rundle and Bradbury, 2017). ATR inhibition has been shown to be synthetically lethal with DNA damage inducing therapies or in DDR pathway-deficient cancers (Weber and Ryan, 2015). Therefore, inhibition of ATR kinase is a viable pharmacological target.

Available clinical and nonclinical pharmacokinetic data support single-agent activity of BAY 1895344 *in vitro* and *in vivo* with tumor models containing a range of DDR defects. BAY 1895344 demonstrates some potential advantage in selectivity and cellular potency over other ATR inhibitors in clinical development, and the oral availability and CNS penetration of BAY 1895344 may be important in some clinical applications. BAY 1895344 demonstrates strong synergistic potential with immune checkpoint inhibitors, PARP inhibitors, radiation treatment, and PI3K inhibitors. Some of these preclinical findings are informing the initial development plan for BAY 1895344 by Bayer Pharmaceuticals and may not be performed by the project team. The ongoing first-in-human single agent BAY 1895344 trial includes patients with different tumor types and a range of possible DNA repair defects with promising preliminary response results.

### Mechanism of Action

BAY 1895344 (Figure 1), a naphthyridine derivative, is a highly selective oral ATR inhibitor ( $IC_{50} = 7$  nM) (Luecking *et al.*, 2017). In cellular assays using hydroxyurea-induced dNTP deprivation as a replication stressor, BAY 1895344 inhibited  $\gamma$ H2AX phosphorylation demonstrating the anticipated mode of action.



**Figure 1: Structure of BAY 1895344**

### Nonclinical Studies of BAY 1895344

*In vitro*, BAY 1895344 inhibited proliferation in several human cancer cell lines with low- to sub- micromolar IC<sub>50</sub> values (Luecking *et al.*, 2017). *In vivo* activity of BAY 1895344 along with Radium-223 has been observed in a bone metastatic castration-resistant prostate cancer (mCRCP) model as well as a mouse intratibial human LNCaP mCRPC xenograft model (Wengner *et al.*, 2017). In the mCRCP model, BAY 1895344 had the highest anti-tumor efficacy with 20 mg/kg BAY 1895344 administered once daily for 2 days on/ 5 days off, or with a 40 mg/kg dose administered once daily for 1 day on/ 6 days off starting 24 hours after the first Radium-223 dose and given in continued weekly cycles. BAY 1895344 was assessed in combination with external beam radiation therapy (EBRT), poly-ADP-ribose polymerase (PARP) inhibition or anti-androgen (AA) therapy (Wengner *et al.*, 2018). In these studies, synergistic activity of BAY 1895344 was observed in cellular anti-proliferation assays as well as in tumor xenografts.

### Clinical Studies of BAY 1895344

BAY 1895344 has been under investigation for the treatment of patients with advanced solid tumors and lymphomas in an ongoing phase 1 trial (NCT03188965) designed to evaluate the safety, tolerability, maximum tolerated dose (MTD) for cancer patients, and the response of the cancer to the treatment. This phase 1 study has an initial arm as a single-agent dose-escalation of BAY 1895344 to determine the MTD and the recommended phase 2 dose (R2PD). In accordance with the preclinical studies, the starting dose of BAY 1895344 will be 5 mg twice daily for 3 days, then off for 4 days in a weekly schedule for a 21-day cycle, with no breaks in between cycles. A second arm will confirm the MTD (or RP2D) dose in Japanese patients. Once the MTD has been defined, a third arm will be a dose expansion cohort to determine safety, pharmacokinetic profiles, pharmacodynamics of target engagement, and preliminary efficacy.

Table 1: BAY 1895344 clinical trial listing on ClinicalTrials.gov							
NCT	Phase	Agent(s)	Disease/ Indication	Study Start-End	Status/ Sponsor	Planned Accrual	Publications/ Abstracts
NCT03188965	1	BAY1895344	Advanced solid tumors Lymphomas	06/2017 - 12/2019	Recruiting/Bayer	219	

### **Correlative Studies with BAY 1895344 of Interest to CTEP**

Translational researchers on the BAY 1895344 team could consider studies examining the optimal timing of BAY 1895344 in cancer models during or after treatment with DNA damaging chemotherapeutics. It has been shown that ATR inhibition is most effective when administered after cytotoxic chemotherapy, after allowing stalled replication forks to develop. The optimal timing with ATR-inhibitor M6620 varied between platinum-based therapy, gemcitabine, PARP inhibitors, and topoisomerase 1 inhibitors, suggesting that a treatment plan with BAY 1895344 might show similar variation. The induction of  $\gamma$ H2AX could be a primary readout and the

studies would be important to determine the optimal sequence and timing of BAY 1895344 with DNA-damaging chemotherapy. If preclinical data was considered critical to the development of CTEP-sponsored trials with BAY 1895344, funding for such studies through the UM1 funding sources or from NCI supplement funding could be considered.

While BAY 1895344 has CNS penetration in animals, making it potentially attractive for brain tumor trials, there is a lack of specific preclinical data with BAY 1895344 in combination with external beam radiation therapy (EBRT) or BAY 1895344 in combination with temozolomide in glioblastoma models. ATR inhibitors have been reported to be radiation sensitizers and to have synergistic interactions with temozolomide (Aasland and Gotzinger, 2019). The examination of BAY 1895344 in combination with ionizing radiation, or temozolomide, or with the triplet in glioblastoma models would be useful in justifying these combinations for a clinical trial and might be considered by translational researchers on the project team.

For the proposed clinical trials with BAY 1895344, expansion cohorts with pre-treatment biopsies or pre- and post-treatment biopsies for pharmacodynamic studies may be considered. The readout from these studies could involve activation of the ATR/CHK1 pathway, or markers of DNA damage and apoptosis. The use of large multiplex immuno-multiple reaction monitoring (MRM) mass spectrometry assays, which quantitate DDR proteins, may also be considered in tumor models or with tumor specimens from the BAY 1895344 program. Clinical trials developed through the BAY 1895344 project team and obtaining tumor biopsy samples before and after drug treatment, could investigate the possibility of having these samples analyzed in collaboration with investigators in the pharmacodynamics laboratories of the Division of Cancer Treatment and Diagnosis, NCI.

Other novel studies of preclinical activity of BAY 1895344 in tumor models with high prevalence of DDR network aberrations or enhanced replication stress may be considered to provide rationale for subsequent clinical trials. These preclinical studies might include tumors such as mantle cell lymphoma (MCL) or small cell lung cancer (SCLC) characterized by overexpression of oncogenes conferring increased replicative stress, translational studies of ATR inhibition in tumor models with ATM loss or other defects in DDR gene signaling, or other tumor models with genetic or epigenetic changes which have been associated with hypersensitivity to ATR inhibition.

The project team will review data of all potentially relevant genetic or pharmacodynamic biomarkers and will attempt to develop a shared biomarker platform for all project team studies.

### **BAY 1895344 Project Team Selection, Composition, and Tasks**

The BAY 1895344 drug project team will meet regularly by WebEx to review available evidence, determine promising strategies, examine clinical trial designs to test those strategies, and to identify biomarkers to evaluate those strategies. The project team will be composed of intramural and extramural members. The extramural members will include clinician scientists with experience in phase 1 studies and with an interest in SCLC, NSCLC, glioblastoma, and cancers with known high incidence of DDR genomic alterations: translational scientists with expertise in biomarker development for ATR inhibition, DDR pathway signaling, and assessment of DNA damage; and basic scientists with expertise in DNA repair and mechanistic understanding of the effects in cancer of DDR pathway alteration and ATR inhibition. 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 clinical studies in the relevant indications, as represented in the NIH Biosketch.

Questions regarding this request for applications may be addressed to L. Austin Doyle, M.D., Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: doylela@mail.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 to participate as Project Team members and to develop Career Development Letters of Intent (CrDLs) after conclusion of Project Team activities.

Project Team Member Applications (PTMAs) should contain a clear indication of the applicant's desired role on the BAY 1895344 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), March 26, 2019**. The most recent version of the PTMA form, which has been distributed with this communication, must be used. PTMAs should be submitted electronically to:

PIO, CTEP/DCTD/NCI

E-mail: [CTEPPTMASubmissions@mail.nih.gov](mailto:CTEPPTMASubmissions@mail.nih.gov)

**Please note that Clinician Scientists may only participate through association with the ETCTN, an NCTN Group, or a consortium (see below), and will need to submit the PTMA through their ETCTN LAO's Coordinating Center or the Group/Consortium Operations office, as applicable.** That organization will then need to submit the Clinician's application to PIO on your behalf to confirm that they are in support of the proposal. All submissions funded by NCTN organizations should include a Letter of Support from the Group Chair. Please allow sufficient time for your organization's review. Qualifying clinical institutions include:

- ETCTN Participating Institution (under UM1 grant)
- NCTN Group member institution (under U10 grant; Alliance, COG, ECOG-ACRIN, NRG Oncology, or SWOG)
- Institutional affiliation with the Pediatric Brain Tumor Consortium (PBTC), Adult Brain Tumor Consortium (ABTC), or Cancer Immunotherapy Trials Network (CITN)

**Basic and Translational Scientists** who belong to a participating ETCTN institution (Lead Academic Organization [LAO] or Affiliated Organization [AO]) **must** submit applications through your LAO's Coordinating Center. Please allow sufficient time for your organization's review. Basic and Translational Scientists from non-ETCTN-affiliated institutions may submit their applications directly to PIO.

## **Bibliography**

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Wengner, A.M., G. Seimeister, U. Luecking, et al. (2017). ATR inhibitor BAY 1895344 shows potent anti-tumor efficacy in monotherapy and strong combination potential with the targeted alpha therapy Radium-223 dichloride in preclinical tumor models. *Cancer Res.* 77(13 Suppl):Abstract nr 836.

Wengner, A.M., G. Seimeister, U. Luecking, et al. (2018). Synergistic *in vivo* activity of the ATR inhibitor BAY 1895344 in combination with the targeted alpha therapy radium-223 dichloride in a preclinical tumor models. *Cancer Res.* 78(13 Suppl):Abstract nr 321.