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Phase I Study to Determine the Safety and Tolerability of the Oral Microtubule Destabilizer BAL101553 in Combination with Standard Radiation in Patients with *MGMT* Promoter Unmethylated Newly Diagnosed Glioblastoma

A Protocol of the Adult Brain Tumor Consortium (ABTC)

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1.0 OBJECTIVES

1.1 Primary Objectives

To determine the maximum tolerated dose of BAL101553 in combination with standard radiation in patients with newly diagnosed *MGMT* promoter unmethylated GBM.

1.2 Secondary Objectives

- To estimate safety and tolerability of BAL101553 in combination with standard radiation in patients with newly diagnosed *MGMT* promoter unmethylated GBM.
- To determine overall and progression-free survival.
- To assess the pharmacokinetics of BAL101553 and BAL27862.
- To explore expression of tissue biomarkers, including BubR1, stathmin and EB1 at baseline (exploratory biomarkers).

2.0 BACKGROUND AND RATIONALE

2.1 Study Disease

Glioblastoma

Glioblastomas (GBM) are the most common primary brain cancers in adults. Despite advances over the past two decades in treating these cancers, virtually all tumors eventually recur and patients die of their disease. New approaches and more effective therapies are urgently needed for the treatment of this devastating disease.

2.2 BAL101553

Microtubule targeting agents in cancer chemotherapy

Microtubule targeting agents (MTAs) are among the most active cytotoxic anticancer drugs currently in use, and have a broad spectrum of activity. Microtubule destabilizers (e.g., Vinca alkaloids) are used in the treatment of several types of hematologic malignancies and solid tumors such as lung cancer; microtubule stabilizers (e.g., taxanes) are used in the treatment of a variety of solid tumors.

Despite a high initial sensitivity of many malignancies to MTAs, resistance can arise through several potential mechanisms, including tumor overexpression of P-glycoprotein (P-gp), elevated levels of β-tubulin subtype III, reduced levels of the cancer susceptibility gene BRCA1, elevated levels of the cell cycle inhibitory protein p21, and acquired mutations in β-tubulin. Accordingly, it is important to identify improved tubulin-inhibiting agents that may overcome these resistance factors and improve the effectiveness of treatment.

BAL101553 as a microtubule targeting agent

BAL101553 is a water-soluble, lysine pro-drug of the synthetic small molecule BAL27862[9]. The active drug BAL27862 (a furazano-benzimidazole derivative), reversibly binds tubulin heterodimers at the colchicine site, inhibiting microtubule formation and disrupting microtubule organization[1].

The active compound BAL27862 (molecular weight = 387.4 g/mol) is lipophilic (LogD = 2.49 at pH 7.4), highly permeable (permeability = 135×10^{-6} cm/s in a Caco-2 model), and demonstrated excellent drug penetration into tissues, including the brain, in an autoradiography study in mice[2].

BAL27862 displays a novel microtubule fragmentation activity, destabilizing the mitotic spindle leading to the formation of tiny microtubule asters[1]. The microtubule phenotype associated with BAL27862 treatment is distinct from that observed with conventional MTAs, including taxanes and Vinca alkaloids[4].

Nonclinical studies with BAL101553

Nonclinical pharmacodynamics and activity

BAL27862 induces apoptosis, and shows marked antiproliferative activity against cancer cell lines and patient-derived tumor cells from several solid tumor histotypes. BAL27862 is also active against temozolomide (TMZ) sensitive and resistant glioblastoma lines[3]. Antiproliferative activity is retained in tumor cells that over-express the drug efflux pump Pgp, as well as diverse tumor models that are refractory to Vinca alkaloids, taxanes, and epothilone B through non-Pgp-related resistance mechanisms[6,10]. Importantly, patient-derived tumor cells exhibiting intrinsic resistance to paclitaxel have been demonstrated to be sensitive to BAL27862 using clonogenic assays[4]. Normal human stem cells and peripheral blood mononucleocytes are relatively insensitive to BAL27862.

BAL101553 exhibits antitumor activity with intravenous (IV) and oral administration in human xenograft mouse models derived from several chemo-sensitive tumor histotypes, where activity is comparable to standard antineoplastic drugs[4]. Immunohistochemical examination of treated tumors indicates profound effects on tumor cell proliferation and viability, together with a potent disruption of the tumor vasculature; supporting *in vitro* analyses indicating a dual mechanism of action on refractory tumor cells and vascular cells. Moreover, a single BAL101553 administration has dose-dependent effects on tumor vascularization, with profound antivascular effects at MTD IV doses and reduced antivascular effects associated with MTD daily oral doses[4,5]. Fractionation of the IV dose does not decrease antitumor activity, indicating that AUC rather than C_{max} is the main factor in antitumor response[6,9]. Moreover, equivalent antitumor responses are observed with both daily and weekly oral BAL101553 dosing in a Pgp-overexpressing colorectal cancer model[6]. Antitumor activity has also been observed with oral and IV BAL101553 in Pgp-overexpressing tumor xenograft models[6,9]. These Pgp models are known to be refractory to standard MTAs, such as paclitaxel and vincristine. Moreover, BAL101553 exhibits antitumor activity in an epothilone- and taxane-resistant non-small cell lung cancer xenograft model associated with mutation of class I β-tubulin[6], as well as in diverse TMZ- and ionizing radiation-sensitive and refractory GBM models.

Co-administration of capecitabine or cisplatin results in a trend towards increased antitumor activity, suggesting a potential for combination with cytotoxic agents[4]. More profound antitumor effects have also been shown in combination with ionizing radiation[6,8], TMZ[8] and trastuzumab[7], further indicating a potential to combine BAL101553 with radiotherapy (RT), alkylating agents and therapeutic antibodies.

Nonclinical pharmacokinetics

The pro-drug BAL101553 is converted *in vitro* and *in vivo* to the active drug BAL27862 in blood, but to a much lesser extent in plasma, suggesting the involvement of a membrane-bound enzyme for the cleavage of the lysine pro-moiety. Metabolism (oxidation, side chain cleavage and conjugation) is complex, but several Cytochrome P450 (CYP) isoenzymes, including CYP3A4, CYP2C9 and CYP2C19, are involved. Metabolite patterns *in vitro* and *in vivo* qualify rat, rabbit and dog as suitable toxicological species. The main *in vivo* metabolites (> 10% of the administered dose) have no anticancer activity. Plasma protein binding is species independent and amounted to ~97%.

Caco-2 cells grown in monolayer are highly permeable to the active drug BAL27862, and the drug is not a substrate of Pgp. The pro-drug is cleaved on the brush border and intracellularly, and the remaining intact pro-drug is moderately permeable through Caco-2 cell monolayers. *In vivo* this translates to good oral bioavailability of the drug administered either as drug or pro-drug.

Intravenous pharmacokinetics

After IV administration of the pro-drug, the conversion into the active BAL27862 amounts to between 35% and 61% in mice, rats, and dogs. Conversion of pro-drug is rapid, with a half-life ranging from 0.1–2 h. In animals BAL27862 has a large volume of distribution, a moderate-to-high metabolic clearance, and half-lives ranging from 2.0–5.3 h in animals. Administration of pro-drug or drug leads to distribution into all tissues, notably tumor and brain; tumor retention is observed to be longer after administration of the pro-drug. Penetration of the active drug in brain was demonstrated in a SW480 mouse xenograft model. In this species, the ratio brain/plasma concentrations is approximately 1. The mass-balance of both IV BAL27862 and BAL101553 is complete, with predominant elimination in the feces. Urinary excretion of both drug and pro-drug as unchanged drug is < 1%.

After repeated IV administration of BAL27862 or BAL101553 to mice, rats and dogs, the exposure is almost dose proportional, without indication of a gender effect, accumulation or induction.

Oral pharmacokinetics

After repeated oral administration of BAL27862 or BAL101553 to rats and dogs, the exposure is almost dose proportional, without indication of accumulation or induction; female rats tend to be more exposed than male rats, however, this gender difference is not observed in dogs. Comparison of the exposures after oral administration of the pro-drug as a solution, with those observed after IV administration of the drug, suggests an oral bioavailability ranging from 30–50% in the rat and 50–100% in the dog. Importantly, the oral bioavailability of BAL27862 in the rat is similar after administration of either the drug or the pro-drug. After oral administration only traces of the pro-drug are detected in plasma,

suggesting a pre-systemic cleavage. These findings are in agreement with experiments in Caco-2 cells which showed that cleavage of BAL101553 to BAL27862 occurs both in the incubation medium and intracellularly, and that BAL27862 is highly permeable.

A dedicated pharmacokinetic (PK) study performed in dogs, using the capsule formulation intended for clinical use, confirmed the excellent oral bioavailability of BAL101553.

Brain and tumor penetration

Quantitative whole-body autoradiography in tumor-bearing nude mice after intravenous bolus administration of ^{14}C-BAL101553 or ^{14}C-BAL27862 indicate a large distribution of radioactivity to all organs, including brain and tumor. This was confirmed by further experiments in nude mice, where brain drug levels were measured following multiple infusions of both BAL101553 and BAL27862. Concentrations of BAL27862 in brain were comparable to those in plasma at most time points analyzed. The brain/plasma ratio and its extent close to 1 was also not dependent on the route or the species as demonstrated in rats after oral administration of BAL101553. A 4-week toxicity study in rats with 5 days a week oral BAL101553 alone, temozolomide alone, and the combination demonstrated that the brain/plasma ratios of BAL27862 and temozolomide were 1 and 0.3 and were unaffected by co-administration of both drugs. However, PK studies in rat suggest that BAL101553 and temozolomide should be sequentially administered, as co-administration decreased the absorption of both drugs in this species.

Nonclinical toxicology

BAL101553 was investigated in 4-week oral toxicity studies in rats and dogs, with once daily administration. The patterns of clinical, functional, laboratory and post-mortem findings were consistent with the expected adverse events (AEs) of anticancer drugs, and were comparable to previous studies with once-weekly IV administration. The main targets of toxicity were the gastrointestinal tract, blood, immune and lymphatic systems, and the testes. With the exception of testicular degeneration, changes were generally reversible after a 4-week recovery period. Considering weekly exposure (AUC), daily oral administration was better tolerated than weekly IV administration. The no-adverse-effect-level after once-daily oral dosing was < 2.5 mg/kg/day in rats and 0.5 mg/kg/day in dogs; the maximum tolerated dose (MTD) was 10 and 5 mg/kg/day in male and female rats, respectively, and 2 mg/kg/day in dogs.

There were no clinical indications of central nervous system or peripheral neurotoxicity, or drug-related effects on the QTc-interval, in IV- or oral-administration animal studies.

In addition, two exploratory studies were conducted to investigate the potential cumulative toxicity of oral BAL101553 when given in combination with temozolomide. No differences in the cumulative toxicity were observed with the combination compared to temozolomide or BAL101553 given alone.

<u>Rationale for use of BAL101553 in GBM patients:</u>

BAL101553 is a novel synthetic oral microtubule destabilizer with promising activity in preclinical models both as a single agent and in combination with radiation (RT). Statistically significant combination effects have been demonstrated, both in combination

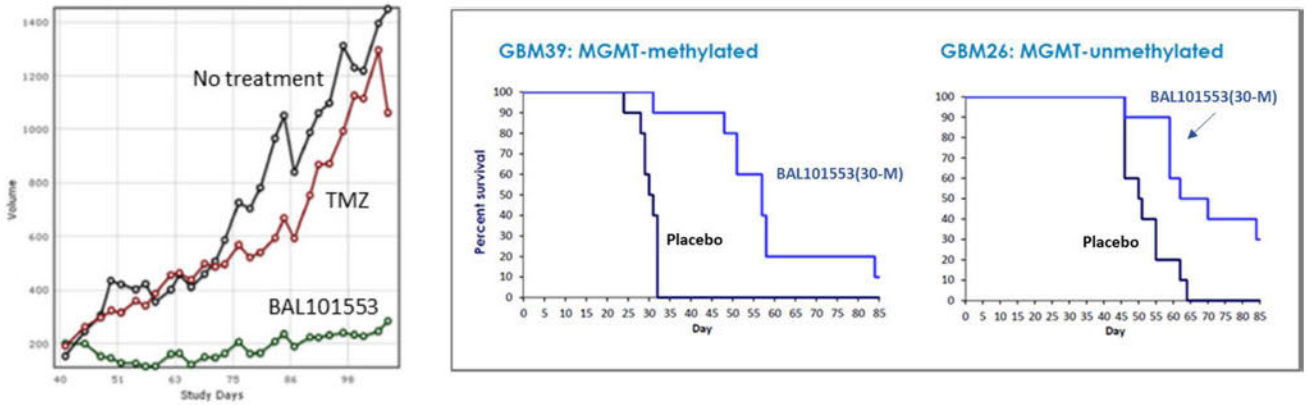
with RT as well as in combination with RT and concomitant TMZ. It is of specific interest for the potential application in high-grade gliomas due to excellent preclinical activity of the drug in GBM models, as it can cross the blood-brain barrier (BBB) and can be given orally with a daily regimen. It is of note that in other solid tumors, such as lung cancer and esophageal cancer, taxanes have been used in combination with RT effectively as part of standard of care. In GBM however, taxanes have failed to show clinical activity when given systemically. This is believed to have been due to poor BBB penetration and long intervals between doses due to systemic toxicity. There is however evidence that if directly administered, taxanes can be highly active in malignant gliomas. As an example, a phase I/II study in patients with recurrent high-grade gliomas who received paclitaxel intratumorally via convection enhanced delivery, the response rate was 73%[2]. We therefore argue that microtubule inhibitors are an active class of drugs for the treatment of GBM and that the reason for their previous failure in the clinical setting was primarily related to failure in drug delivery, i.e. their inability to cross the BBB. These are the reasons why we feel that BAL101553 deserves high priority for clinical testing in patients with GBM.

Single-agent activity of BAL101553 (preclinical data in GBM):

Preclinical data showed broad activity against a panel of drug-sensitive and drug-resistant tumor models, including Pgp- and non-Pgp-related drug-resistant cancers[3-10]. BAL101553 has anticancer activity as a single agent in both *MGMT* methylated and unmethylated (including temozolomide-insensitive) GBM cell lines *in vitro*[3,4] and after oral administration in xenograft models (Figure 1 and Table 1). In a GBM flank model with high resistance to temozolomide (GBM150), BAL101553 treatment induced tumor regressions (Figure 1A). In mice bearing orthotopic GBM tumors, daily oral administration of BAL101553 led to survival advantages in both *MGMT* methylated (e.g. GBM39) and unmethylated (e.g. GBM26) models (Figure 1B and Table 1)[8].

Figure 1 A) Oral BAL101553 in a TMZ-resistant GBM flank model with GBM150 subcutaneous xenografts and B) its single-agent activity in orthotopic GBM models

A. **B.**



A. Treatment: BAL101553 30 mg/kg/day (green), TMZ 50 mg/kg/day (red), no treatment (black).
B. Treatment with BAL101553 30 mg/kg/day p.o. until moribund.

Table 1 Summary oral BAL101553 single-agent activity in orthotopic GBM models.

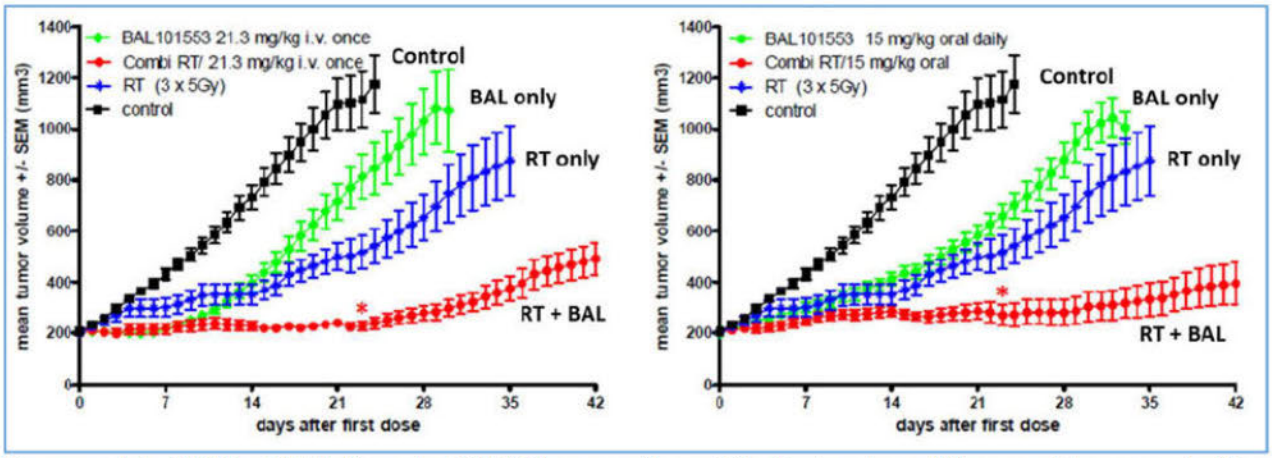
Line	MGMT promoter status	Placebo median	BAL median	Placebo mean±SD	BAL mean±SD	P value	Percent change
G6	unmethylated	48	60	47 ± 4	58 ± 10	<0.01	24%
G8	methylated	47	64	48 ± 5	64 ± 7	<0.01	36%
G10	unmethylated	35	38	35 ± 2	38 ± 5	0.04	10%
G12	methylated	23	31	22 ± 2	32 ± 3	<0.01	35%
G15	methylated	71	87	110 ± 120	89 ± 21	0.41	22%
G22TMZ	methylated	27	26	26 ± 5	27 ± 4	0.55	-4%
G26	unmethylated	51	66	52 ± 7	71 ± 17	<0.01	31%
G39	methylated	31	57	30 ± 3	55 ± 14	<0.01	87%
G59	methylated	45	56	52 ± 28	68 ± 36	0.02	23%
G84	methylated	56	73	58 ± 8	68 ± 8	<0.01	29%
G108	unmethylated	39	43	41 ± 5	49 ± 16	0.11	12%
G115	unmethylated	139	183	146 ± 40	199 ± 60	0.07	31%
G116	methylated	61	64	118 ± 117	66 ± 12	0.45	5%
G117	methylated	65	81	77 ± 22	86 ± 23	0.30	26%
G122	unmethylated	80	84	83 ± 11	90 ± 15	0.28	5%
G150	unmethylated	52	69	52 ± 6	84 ± 40	<0.01	32%

Treatment: BAL101553 (BAL) 30 mg/kg/day p.o. until moribund. Yellow indicates significant single agent activity at $p<0.01$ (Log rank test). Survival medians are expressed as days.

Combination of BAL101553 and RT as well as RT/TMZ in preclinical models

Preclinical data using treatment-refractory lung and colorectal cancer xenograft models showed more profound anticancer effects when BAL101553 was combined with radiation as compared to single agent treatment. BAL101553 could be administered intravenously or orally[4, 6] (Figure 2).

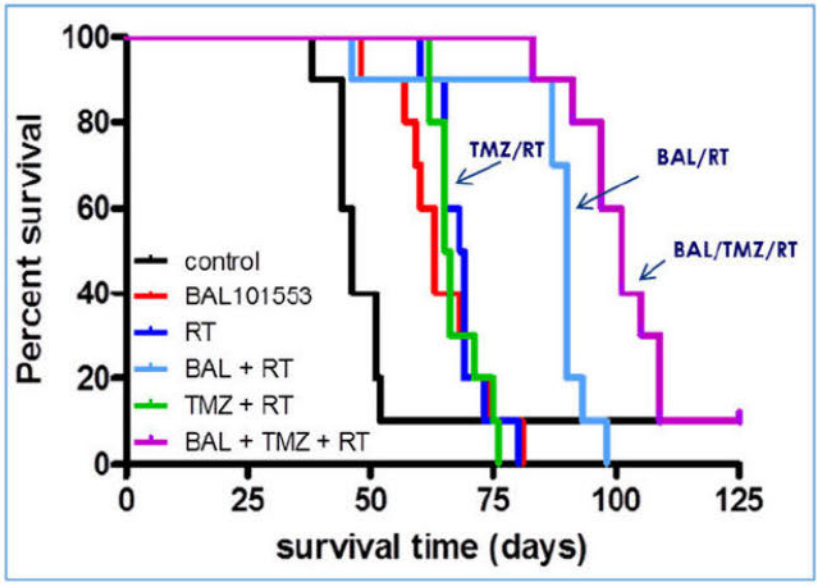
Figure 2 Treatment of non-small cell lung cancer xenografts with A) IV or B) oral BAL101553.



Tumor model: A549Epo40 tubulin mutant NSCLC xenografts; model refractory to epothilones and taxanes and with reduced radiation sensitivity. Treatment: Radiation (5 Gy) given on days 1, 2, 3. BAL101553 given either IV at 21.3 mg/kg on day 0 only (A) or oral BAL101553 given as 15 mg/kg/day for 3 weeks (5× weekly) (B).

In an orthotopic GBM model (GBM6) with reduced TMZ and RT sensitivity, more profound survival effects were observed when oral BAL101553 was combined with RT (2-week RT treatment regimen) or RT/TMZ (Figure 3), as compared to the single agents or to RT and TMZ combined[8], with BAL101553/RT demonstrating a statistically significant improvement over TMZ/RT ($p<0.001$).

Figure 3 Activity of oral BAL101553 alone and in combination with RT, with or without TMZ, in a xenograft model of GBM

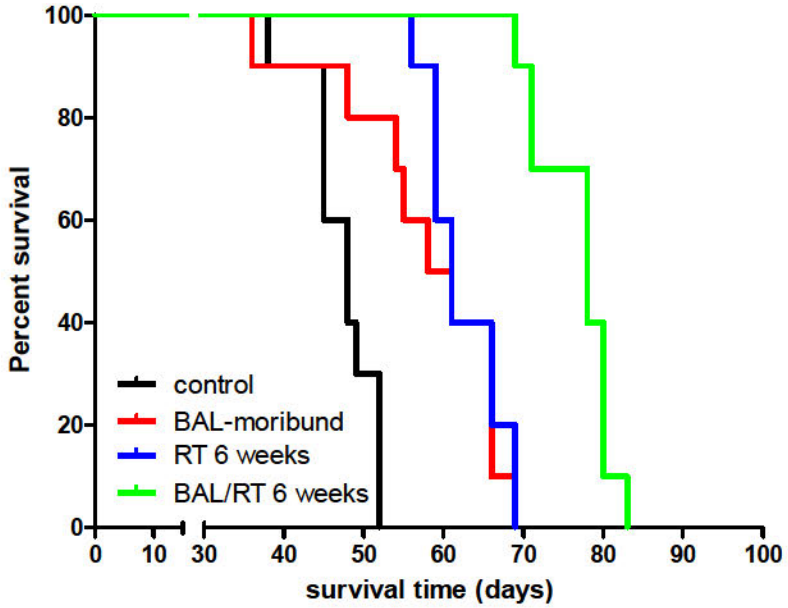


The combination of oral BAL101553 and RT results in enhanced activity compared to either treatment alone (BAL101553+RT vs BAL101553 or RT; both $p<0.001$) and is superior to TMZ in combination with RT (BAL+RT

vs TMZ+RT; p<0.001). Combined BAL101553/RT/TMZ treatment is superior to RT with either compound alone (BAL+TMZ+RT vs TMZ+RT [p<0.001] or BAL+RT [p=0.0012]). Tumor model: GBM6 *MGMT* unmethylated orthotopic GBM xenografts with reduced TMZ and RT sensitivity. Treatment schedule: BAL101553 30 mg/kg/day p.o. until moribund; RT 2 Gy/day for 2 weeks; MTZ 20 mg/kg/day (oral) for 2 weeks. (Data provided by J. Sarkaria, Mayo Clinic.)

In the experiment described in Figure 3 above, BAL101553 treatment was continued until moribund for both the single-agent and combination groups. However, a similar statistically-significant positive interaction between BAL101553 and RT was also observed for a 6-week treatment regimen of RT with concurrent BAL101553 (Figure 4)[8]. These data support the potential of BAL101553 as an oral therapy for GBM patients in combination with RT or RT and TMZ.

Figure 4 Activity of oral BAL101553 alone and in combination with RT in a xenograft model of GBM



The combination of oral BAL101553 and RT results in enhanced activity compared to either treatment alone (BAL/RT 6 weeks vs BAL-moribund or RT 6 weeks; both p<0.001). Tumor model: GBM6 *MGMT* unmethylated orthotopic GBM xenografts with reduced TMZ and RT sensitivity. Treatment schedule: Single-agent BAL101553 30 mg/kg/day p.o. until moribund; RT 2 Gy M/W/F for 6 weeks; concomitant BAL101553/RT was for 6 weeks only. (Data provided by J. Sarkaria, Mayo Clinic.)

Prior and ongoing clinical trials with BAL101553

One clinical study with BAL101553 has been completed (study CDI-CS-001 using a 2-hour intravenous infusion), and two studies are ongoing: CDI-CS-002 (daily oral dosing) and CDI-CS-003 (48-hour infusions on Days 1, 8 and 25 of 28-day treatment cycles).

Study CDI-CS-001

This was a single-agent, open-label first-in-human Phase I/IIa IV study, carried out in patients with advanced solid tumors. A total of 73 patients were dosed with IV

BAL101553, administered on Days 1, 8 and 15 of each 28-day cycle. In the Phase I portion of the study, 24 patients received IV BAL101553 at dose levels of 15 mg/m^2 (n=1), 30 mg/m^2 (n=3), 45 mg/m^2 (n=3), 60 mg/m^2 (n=10), and 80 mg/m^2 (n=7). The MTD was determined at 60 mg/m^2. Grade 2 to Grade 3 gait disturbance was dose limiting at 80 mg/m^2 and occurred together with Grade 2 peripheral neuropathy.

In the subsequent Phase IIa portion of study CDI-CS-001, patients were randomized to receive BAL101553 at 60 mg/m^2, or at a lower dose level of 30 mg/m^2, to define whether the MTD or a sub-MTD dose is more appropriate for further clinical development. Dose-limiting toxicities (DLTs) in this part of the study (detailed below), included Grade 3 troponin increases and ECG changes.

The overall safety profile of IV BAL101553 administered as a 2-hour infusion was characterized by dose-related patterns of nausea/vomiting, transient arterial hypertension, reversible or partially reversible peripheral sensory neuropathy, reversible gait disturbance, myocardial injury and pain at the tumor site.

Dose-related blood pressure (BP) increases > 170 mmHg (systolic) were observed at dose levels ≥ 45 mg/m^2, consistent with the vascular-disrupting effect observed in animal BAL101553 infusion, coinciding with the T_{max} of the active drug BAL27862 and were generally resolved within 24 hours following the IV dose.

Due to the observation of asymptomatic troponin elevations in the Phase IIa portion of the study, at dose levels of 60 mg/m^2 (2 patients) and 45 mg/m^2 (1 patient), the RP2D for a 2-hour infusion of BAL101553 was determined to be 30 mg/m^2.

Of the 73 patients dosed in study CDI-CS-001, 59 were evaluable for efficacy. One partial response was observed in a 61 year old female patient with metastatic ampullary adenocarcinoma, who received BAL101553 treatment for more than 2 years and who discontinued the study due to the development of a BAL101553-related allergy.

An additional 14 patients had stable disease as best response in the Phase I (n=5) and Phase IIa (n=9) portions of the study (N=72 total), with six patients presenting with stable disease for four or more treatment cycles.

Based on non-clinical data, exposure (AUC) is considered to be the driver of BAL101553's antiproliferative activity. Considering that the tolerability profile of a 2-hour intravenous infusion of BAL101553 was characterized by vascular toxicity which was clearly linked to the C_{max} of BAL27862, it was rationalized that further clinical studies should aim to minimize C_{max}, to enable higher total exposures and a broader therapeutic window. Accordingly, two additional studies have been initiated in patients with advanced solid tumors and are currently ongoing: study CDI-CS-002 with daily-oral dosing, and study CDI-CS-003 with 48-hour IV infusions administered on Days 1, 8 and 15 of each 28-day cycle.

Study CDI-CS-002

This daily oral dosing study is currently ongoing in the Phase I dose escalation phase.

Solid tumor arm

Seven dose cohorts have been completed in the solid tumor arm, with 26 patients having received daily-oral BAL101553 at doses of 2 mg per day (Cohort 1), 4 mg per day (Cohort 2), 8 mg per day (Cohort 3), 16 mg per day (Cohorts 4 and 6), 20 mg per day (Cohort 7), and 30 mg per day (Cohort 5). BAL101553 was well tolerated up to and including the dose level of 16 mg per day, with no observations of DLTs or severe drug-related AEs. There were no signals with respect to blood-pressure elevations or vascular toxicity. Dose levels of 8 mg per day (3 patients) and 16 mg per day (7 patients) were shown to be safe and well tolerated. Grade1/Grade 2 drug-related side effects at these dose levels included anorexia, constipation, diarrhea, fatigue/lethargy, hyponatremia, nausea, oral mucosa dryness, rhinorrhea clear and transparent, and stomatitis. One Grade 3 AE of hypertension (at 8 mg/day) was observed in a patient with variable pre-dose blood pressure levels; however, there was no clear impact on the overall blood pressure profile in this patient or in other patients treated at doses between 2 mg per day and 16 mg per day. There was also no impact on blood pressure at the maximum administered dose of 30 mg per day.

In Cohort 5, at 30 mg per day oral BAL101553, DLTs were observed in two of the three patients treated and included Grade 3 hyponatremia and hypokalemia and reversible Grade 2 hallucinations. Based on these observations, the dose level of 30 mg per day was defined as the maximum administered dose (MAD) for oral BAL101553. In Cohort 7 (7 patients), at 20 mg oral BAL101553 per day, two DLTs of reversible Grade 4 hyponatremia were observed. The MTD was declared at 16 mg.

Glioblastoma arm

In addition, patients with histologically-confirmed GBM or high-grade glioma, with progressive or recurrent disease after prior radiotherapy (with or without chemotherapy) are being treated with daily oral BAL101553 in a separate study arm within study CDI-CS-002 to assess the MTD of BAL101553 in patients with recurrent GBM using BAL101553 as a monotherapy (the GBM arm). Safety data is available from four patients treated at the starting dose of 8 mg/day, from three patients treated at 15 mg/day and from six patients treated at 20 mg/day. Drug-related side effects that occurred in more than one patient included Grade 1/2 fatigue (n=2), Grade 1/2 hepatic enzyme elevations (n=2) and Grade 1 seizures (n=2). One DLT of Grade 2 depression and fatigue was observed at 20 mg. As of 18 January 2018, a cohort for treatment at 25 mg/day has been open for enrollment in the GBM arm.

From a PK perspective, exposure with oral BAL101553 was dose-proportional, with weekly AUCs of ~8,700 ng*h/mL at 16 mg per day and of ~20,000 ng*h/mL at 30 mg per day. The weekly exposure at 8 mg/day and 15 mg/day was in the same range in the solid tumor and GBM arms, although with a somewhat lower exposure observed in the GBM arm. The weekly exposure at 30 mg per day was more than 2-fold higher than that achieved with a weekly 2-hour infusion of BAL101553 at the MAD of 80 mg/m^2 in study CDI-CS-

001 (mean AUC of ~ 8,600 ng*h/mL). In contrast, C_{max} levels with daily-oral dosing at up to 30 mg per day were at or below 210 ng/mL, compared to an average of ~ 600 mg/mL with a 2-hour IV infusion at 80 mg/m^2. Therefore, daily-oral dosing was successful at achieving significantly higher exposures at reduced C_{max} levels compared to those with a 2-hour infusion regimen, with no vascular toxicities.

The study drug to be used for this ABTC trial is the same oral formulation of BAL101553 currently used in study CDI-CS-002, which is ongoing in Europe.

Study CDI-CS-003

This study, in which BAL101553 is administered as 48-hour infusions on Days 1, 8 and 15 of each 28-day cycle, is currently ongoing. Phase I enrollment was completed with 20 patients (7M/13F; median age 60 years; median three prior chemotherapies) receiving IV BAL101553 at doses of 30, 45, 70 or 90 mg/m^2. Dose-limiting toxicities included transient Grade 3 hypotension at 70 mg/m^2 and reversible Grade 3 hyponatremia, Grade 3 neutropenia, Grade 2 hallucinations and ataxia at 90 mg/m^2. In Phase 2a, patients will be treated at the MTD of 70 mg/m^2.

Blood-brain barrier permeability considerations

BAL27862 is a small molecule (MW=387) with a high permeability *in vitro* using the Caco-2 model system and it is not a Pgp drug-efflux pump substrate[4,10]. Moreover, quantitative whole-body autoradiography in tumor-bearing nude mice after IV BAL101553 administration indicated a large distribution of ^{14}C-labelled BAL27862 to all organs, including brain and tumor[3,4]. The brain/blood ratio was approximately 1, indicating good penetration into brain tissue. This was confirmed in further experiments in nude mice, where brain drug levels were measured following multiple infusions of either BAL101553 or BAL27862. Concentrations of BAL27862 in brain were comparable to those in plasma at most time points analyzed. Furthermore, exposure (AUC) to BAL27862 after BAL101553 infusion was almost as high in brain tissue as in plasma[3,4].

The brain/plasma ratio of close to 1 was also not dependent on the route or the species, as demonstrated in rats after oral administration of BAL101553. These findings indicate that plasma levels are to some extent predictive of those in brain. The physicochemical properties of BAL27862 and the preclinical evidence of its efficient penetration into brain suggest that this drug will efficiently penetrate the BBB and brain tumors in patients.

2.3 Rationale

More effective treatments are urgently needed for treatment of patients with GBM. BAL101553 is a novel microtubule inhibitor that shows promising activity in GBM in preclinical studies, including in *MGMT* unmethylated models. In addition to preclinical evidence of single-agent activity of the drug, there are data showing significant synergy of BAL101553 when combined with RT and in combination with RT and TMZ. Oral BAL101553 can be given daily, and there is preclinical evidence to suggest that it has the ability to cross the BBB.

This Phase I study will define the MTD and assess the safety of oral BAL101553 when administered once daily in combination with standard RT in patients with *MGMT*

unmethylated newly diagnosed GBM. The results of this study will be the stepping stone for further development of oral BAL101553 in newly-diagnosed GBM.

After completion of this study, the planned next step will be to determine drug delivery into the tumor by performing a PK study in patients with recurrent high-grade glioma, using the MTD as defined by this study (ABTC 1601). Brain penetration of BAL27862 was demonstrated in animal models, with a brain/plasma ratio of approximately 1.

If drug delivery can be demonstrated in humans, the plan is to initiate efficacy trials testing BAL101553 in combination with RT and RT+TMZ in newly-diagnosed GBM in a clinical trial program conducted subsequent to study ABTC # 1601.

Rationale for omitting concomitant TMZ from the RT treatment regimen for patients newly diagnosed with *MGMT* promoter unmethylated GBM in this trial

This Phase I study is designed specifically to determine the safety of combining BAL101553 with standard RT. There is increasing consensus in the field that *MGMT* promoter unmethylated GBM patients benefit minimally, if at all, from the addition of TMZ. It has been reported that patients with *MGMT* unmethylated GBM who have benefited from TMZ are likely to have actually had *MGMT* promoter methylation, but were misclassified[14]. Studies in this patient population are being increasingly conducted without TMZ, thereby eliminating the added toxicity of the treatment and allowing full doses of the respective investigational agent to be used. Therefore, in this study, BAL101553 will be studied in combination with RT alone, without TMZ.

2.4 Correlatives Studies Background

Based on detailed analyses of the mechanism of action of BAL27862, a panel of potential patient-stratification biomarkers is available and is currently being evaluated in ongoing BAL101553 studies. Of particular interest is the observation that an intact microtubule spindle assembly complex (SAC) is essential for the anti-proliferative activity of BAL27862[4,15]. Consequently, the key SAC component BubR1 has been identified as a potential correlative biomarker for BAL101553 sensitivity[4,15,16]. Human tumor epidemiology experiments have shown that BubR1 is expressed in both primary and recurrent GBM, with high levels associated with elevated proliferation indices[17]. Furthermore, the microtubule-interacting protein EB1 (end-binding 1-protein) has also been shown to be involved in the activity of BAL101553 in GBM models *in vitro* and in orthotopic xenografts[18]. Specifically, sub-cytotoxic drug concentrations strongly inhibited GBM stem-like cell proliferation and invasion, resulting in a differentiated phenotype; a phenomenon found to be dependent on EB1 expression. As EB1 is overexpressed in GBM tumors and is a factor of bad prognosis[19], this protein could be a potential predictive biomarker for GBM response.

3.0 PATIENT SELECTION

3.1 Patient Population

Sample Size:

Dose Finding: cohorts of 3–5 patients, up to 5 dose levels.

Accrual Rate:

2–3 patients per month.

Gender:

Male and female.

Age:

Patients must be at least 18 years of age.

Race:

Minorities will be actively recruited. No exclusion to this study will be based on race or ethnicity.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	1	2	1	1	**5**
White	7	10	1	2	**20**
More Than One Race	1	1	0	1	**3**
Total	**10**	**14**	**2**	**4**	**30**

3.2 Eligibility Criteria

1. Patients must have histologically-proven GBM.
2. Patients must have recovered from the immediate post-operative period.
3. Patients must have tumor *MGMT* methylation status of unmethylated as determined by local pathologist using a CLIA-approved diagnostic test. Results of routinely-used methods for *MGMT* methylation testing (e.g. MS-PCR or quantitative PCR) are acceptable.
4. Patients must be able to undergo MRI of the brain with gadolinium.
5. Patients must not have received prior RT, chemotherapy, immunotherapy or therapy with a biologic agent (including immunotoxins, immunoconjugates, antisense, peptide receptor antagonists, interferons, interleukins, tumor-infiltrating lymphocytes, lymphokine-activated killer cells, or gene therapy), or hormonal therapy for their brain tumor. Corticosteroid therapy is allowed.

6. Patients must be 18 years of age or older.
7. Patients must have a tumor tissue form indicating availability of archived tissue from initial resection at diagnosis of GBM, completed and signed by a pathologist (see Section 9.5.2)
8. Patients must have a Karnofsky Performance Status ≥ 60% (i.e. the patient must be able to care for himself/herself with occasional help from others).
9. Patients must have the following organ and marrow functions:

Absolute neutrophil count	≥1,500/μL
Platelets	≥100,000/μL
Hemoglobin	≥ 9 g/dL
Total bilirubin	≤ 1.5 × institutional upper limit of normal (ULN), (except for patients with known Gilbert's syndrome who must have normal direct bilirubin)
AST (SGOT)/ALT (SGPT)	≤ 2.5 × ULN
Creatinine	≤ 1.5 × ULN
	OR
Creatinine clearance	≥ 60 mL/min/1.73m^2
APTT/PTT	≤ 1.5 × ULN
Sodium	≥ the institutional lower limit of normal

10. Patients must be able to provide written informed consent.
11. Patients must have baseline MRI performed within the 21 days prior to starting treatment.
12. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to the first dose of BAL101553. Women of childbearing potential must agree to use highly-effective contraceptive methods for the duration of study participation and for an additional 90 days after the last dose of study drug. Highly-effective contraceptive methods include male or female sterilization (bilateral tubal occlusion or vasectomy); intrauterine device (IUD); combined (estrogen- and progesterone-containing) hormonal contraception (oral, vaginal ring or transdermal patch) with an ethinylestradiol dose of at least 30 μg, plus use of male condoms (preferably with spermicides), female condoms, a female diaphragm or a cervical cap; or total sexual abstinence. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Male patients must agree not to donate sperm from the first dose of study drug until 90 days after the last dose of study drug. Male patients, without a vasectomy and with a partner of childbearing potential, must agree to use condoms during the study and for at least 90 days after the last dose of study drug. The patient should be instructed that their female partner should use another form of contraception for the duration of the study and continue this use for at least 90 days after the last dose of study drug.

13. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, breast, or bladder. Patients with prior malignancies must be disease-free for ≥ 5 years.
14. Patients must be maintained on a stable corticosteroid regimen (no increase for 5 days) prior to the baseline MRI.
15. Patients must be able to swallow whole capsules.

3.3 Exclusion Criteria

1. Patients receiving any other investigational agents are ineligible.
2. Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to BAL101553 are ineligible. The BAL101553 Investigator Brochure can be referenced for more information.
3. Patients on **drugs that are strong inhibitors and/or inducers of CYP2C9, CYP2C19 or CYP3A4 (including** enzyme-inducing anti-epileptic drugs [EIAEDs]; see Appendix IV), are not eligible for treatment under this protocol. Patients taking non-EIAEDs are permitted to take part in the study. Patients previously treated with **any of the prohibited concomitant medications listed above** may be enrolled if they have been off of the **medication** for ≥ 10 days prior to the first dose of BAL101553.
4. Patients may not be on coumarin anti-coagulants (warfarin, etc.). Heparin, low-molecular weight heparin (LMWH), or other antithrombotic medications are permitted. See Section 4.6.
5. Patients with gastrointestinal disease, or those who have had a procedure that is expected to interfere with the oral absorption or tolerance of BAL101553 (e.g., functionally-relevant gastrointestinal obstruction, or frequent vomiting unresolved upon anti-emetic supportive care), are ineligible.
6. Patients with peripheral neuropathy ≥ Common Terminology Criteria for Adverse Events (CTCAE) grade 2 are ineligible.
7. Patients with ataxia ≥ CTCAE grade 2 are ineligible.
8. Patients with known acute or chronic hepatitis B or hepatitis C infection are ineligible.

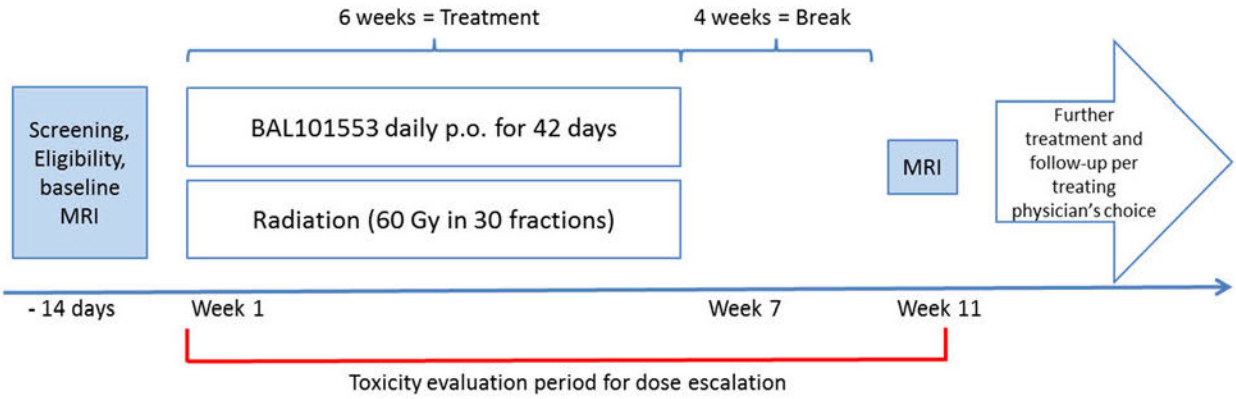
9. Patients with systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg at the Screening visit are ineligible. Patients with an initial clinic blood pressure (BP) ≥ 140/90 mmHg may be included if SBP < 140 mmHg and DBP < 90 mmHg is confirmed in two subsequent BP measurements on the same day.
10. Patients with BP combination treatment with more than two antihypertensive medications are ineligible.
11. Significant cardiac disease or abnormality, including any one of the following:
    - Left ventricular ejection fraction < 50% at Screening (assessed by echocardiography, cardiac MRI or MUGA).
    - QTcF > 470 ms on Screening electrocardiogram (ECG), or a clinically-relevant ECG abnormality.
    - Congenital long QT syndrome.
    - History of sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes.
    - Presence of atrial fibrillation with tachyarrhythmia (ventricular response rate > 100 bpm).
    - Bradycardia (heart rate < 50 bpm).
    - Complete left bundle branch block.
    - Bifascicular block (complete right bundle branch block and anterior or posterior left hemiblock).
    - Myocardial infarction, acute coronary syndrome (including unstable angina), coronary revascularization procedures, or coronary arterial bypass grafting within the 6 months prior to starting study drug.
    - Cardiac troponin (either troponin T or troponin I) > ULN.
    - Congestive heart failure of New York Heart Association class III or IV.
    - Unstable angina pectoris.
12. Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements, are ineligible.
13. Pregnant women are excluded from this study because BAL101553 has potential for teratogenic or abortifacients effects. As there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with BAL101553, breastfeeding should be discontinued if the mother is treated with BAL101553.
14. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with BAL101553. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive/immune-suppressive therapy.

4.0 TREATMENT PLAN

This is a Phase I, open-label, multicenter, dose-finding study of BAL101553 when given in combination with RT in patients with newly diagnosed *MGMT* promoter unmethylated GBM. All subjects must have had histological confirmation of glioblastoma (GBM), either by biopsy or by resection.

4.1 Study Design

Figure 5 Schema



This study will define the MTD of daily oral BAL101553 when given in combination with standard RT (60 Gy in 30 daily fractions, M-F) in patients with newly diagnosed *MGMT* promoter unmethylated GBM.

Following tumor resection, patients will begin an assigned BAL101553 dose in combination with the standard 6 weeks of radiation. The starting dose of BAL101553 will be 4 mg per day, i.e. approximately 25% of the MTD of oral BAL101553 in the solid tumor arm of Phase I clinical study CDI-CS-002 in patients with solid (non-brain) cancers, which is ongoing in Europe. 8 mg/day was the starting dose in the ongoing GBM arm of study CDI-CS-002.

Oral BAL101553 will be given once daily (7 days per week) for 6 weeks, concurrent with standard RT. This will be followed by a 4-week no-treatment period. The duration of study treatment will be defined as these 6 weeks of treatment plus the 4 weeks of rest. The safety evaluation period is the 10 weeks from start of treatment.

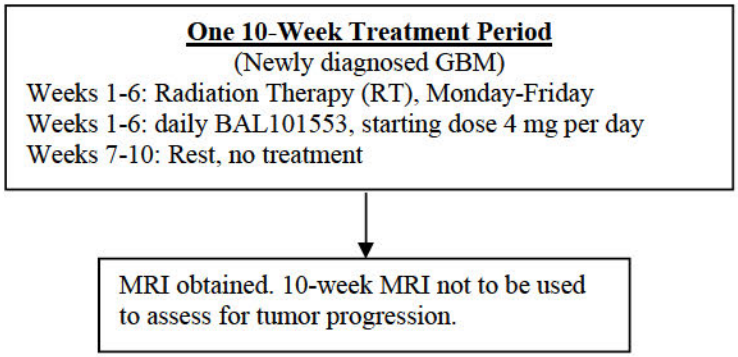
There is approximately a 20% progression rate during the first 10 weeks from initial diagnosis among patients with newly diagnosed GBM (Hegi 2005[20]; and unpublished data). Patients or treating physicians may request early withdrawal from the trial prior to the patient completing the 10 weeks of treatment or the evaluation period, due to disease progression or reasons other than toxicity. Therefore, to prevent unreasonable delay in completing each cohort, five patients will be enrolled onto a dose cohort to ensure 3 evaluable patients at the end of the 10-week treatment period. The standard 3+3 design will be used for dose-finding. Dose escalation will be done in a stepwise fashion. As a precautionary measure, subsequent patients at each new dose level may only be dosed after

confirmation of safety in the first patient over the first 3 weeks of treatment. The target DLT rate is 33%.

After the 4-week rest period following the 6 weeks of treatment, patients will be off study treatment and should continue standard-of-care treatment with adjuvant TMZ and appropriate follow-up.

4.2 Treatment Plan

Figure 6 Dose escalation of BAL101553, administered concurrently with RT, given for the first 6 weeks of a 10-week treatment period



Treatment with BAL101553 should begin on the same day as RT.

Patients will receive 6 weeks of concurrent standard RT and BAL101553 treatment. The starting dose of BAL101553 is 4 mg, given orally every day during the 6 weeks of RT. BAL101553 administration and RT must both commence on the same day; this will constitute the first day of the treatment cycle. This period of treatment will be followed by 4 weeks of rest (i.e., no treatment); these 10 weeks will comprise the study treatment.

Patients will be followed by routine blood work, general and neurological examination, Mini-Mental State Examination (MMSE®)[21], and MRI, and will be monitored for AEs throughout the treatment period. See Section 9.1 for schedule.

An MRI will be performed at the end of the 10-week treatment period, after which patients will be off study treatment. All patients will be followed for survival.

4.2.1 Survival Follow-up

Patients will be followed until death. Patients will only be off study at the time of death. Patients will be followed every two months for progression, for up to one year from the off-treatment date. All patients will be followed for survival every 2 months for the first 2 years; after 2 years, patients will be followed every 6 months until death.

4.2.2 Dose Finding

Up to five pre-specified doses levels of BAL101553 will be tested. If an MTD is not reached at the highest dose being tested (15 mg daily during RT), the ABTC central office and the Study Chair will review the safety and pharmacokinetic data and determine whether further exploration of higher dose levels is justified. The exploration of additional dose

levels would be implemented via a substantial protocol amendment. The MTD is defined as the dose of BAL101553 in combination with standard RT that yields a DLT rate of ≤ 33% in 6 patients.

Dose-escalation schedule

Table 2 BAL101553 concurrent with RT (6 weeks treatment + 4 weeks rest)

Dose Level	BAL101553
-1	2 mg daily during RT
1 (starting dose)	4 mg daily during RT
2	6 mg daily during RT
3	8 mg daily during RT
4	12 mg daily during RT
5	15 mg daily during RT

Five patients will be enrolled at each dose level to ensure 3 evaluable patients at the end of the toxicity evaluation period. Accrual to the next dosing level will not start until a minimum of 10 weeks after the final patient is accrued to the lower dosing level. Dose escalation rules follow a 3+3 design in principle; see Section 11.1 for further detail.

- If none of the initial three patients in a cohort experience DLT, then a new cohort of three patients will be treated at the next higher dose level.
- If one of the three patients in a cohort experiences DLT, then three additional patients will be treated at the same dose level.
- If 2-3/3 or ≥3 /6 in a cohort experience DLT, then the MTD will have been exceeded, and no further dose escalation will occur. The previous dose level will be considered as the MTD.
- If only three evaluable patients were treated at a dose level under consideration as the MTD, then three additional patients will be accrued. If no more than two of the six patients at that dose level experience a DLT, then that dose level will be confirmed as the MTD. If three or more patients in that cohort experience DLT, then the previous dose level will be studied in the same fashion. If three or more patients at 15 mg experience a DLT, then 10 mg will be studied.

Table 3 Dose-escalation criteria

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 additional patients at the **next higher** dose level.
1 out of 3	Enter 3 additional patients at the **same** dose level.
2-3 out of 3, or ≥3 out of 6	MTD exceeded, previous dose level is MTD
≤2 out of 6	MTD achieved

Dose-limiting toxicity is defined in Section 5.1. No intra-patient dose escalation is allowed.

Patients will be evaluable for the cohort if they have completed ≥80% of their expected dose of BAL101553 for the 6 weeks of combined treatment and 4 weeks of rest (10 weeks total). Patients who experience a DLT will be evaluable for the cohort if they have received at least one dose of BAL101553. The toxicity evaluation period is the entire 10-week study period.

The target DLT rate is 33%. If ≥ 2 patients in a cohort are unable to complete ≥ 75% of RT due to toxicity related to the combined use of RT and BAL101553, the study will be stopped.

If an MTD is not reached at the highest dose being tested (15mg daily during RT), the ABTC central office and the Study Chair will review the safety and pharmacokinetic data and determine whether further exploration of higher dose levels is justified. The exploration of additional dose levels would be implemented via a substantial protocol amendment.

MRIs will be performed at baseline and at 10 weeks.

4.3 Treatment Requirements

All eligible patients who consent to this study must have a baseline (post-operative, if surgery is applicable) pre-treatment MRI. This baseline scan must be done within 21 days prior to the initiation of treatment. A second MRI will be performed at the end of the 10-week treatment period.

Patients will receive BAL101553 according to their assigned dose level in Table 2 in Section 4.2 above and will receive concomitant radiotherapy as described in Section 4.5.

4.4 Drug Administration

To ensure accurate dose level and administration, all participating pharmacies must confirm dose levels with the ABTC Central Office. Please call [redacted] to confirm the current dose level before preparing drug for administration.

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients will be provided with medication diaries and instructed in their use. Study drug will be dispensed weekly (see Section 4.4.24.2.24.2.24.2.2). Patients will be instructed to bring all unused capsules and their medication diaries to each study visit for assessment of compliance.

4.4.1 BAL101553 Administration

Oral BAL101553 should be taken on an empty stomach, after a period of fasting of at least 4 h. Patients should refrain from food intake for at least 1 h after drug administration. Intake of water is permitted at any time.

Patients should take their BAL101553 dose at approximately the same time each day. BAL101553 should be taken about 1 hour before each weekday session of RT.

If the duration of RT exceeds 6 weeks, then treatment with BAL101553 should be stopped after 49 days.

If a dose of BAL101553 is missed due to reasons other than toxicity, the missed dose can be taken later in the same day, as long as the patient is able to observe the fasting requirements. If the patient cannot follow the fasting guidelines, or cannot take the dose for reasons other than toxicity, the dose will not be replaced (i.e., patients should not take more than one day's dose on any given calendar day). Should a patient miss a scheduled dose due to vomiting, the patient should not re-take the dose and should wait until their next scheduled dose.

Starting Dose

BAL101553 will be administered on an outpatient basis, once daily as an oral dose of 4 mg, for 6 continuous weeks during RT.

4.4.2 Drug dispensing to patients

New study drug will be dispensed to patients at study visits at weekly intervals. All safety parameters (including laboratory safety parameters and MMSE®) applicable for assessing the ability for a patient to continue receiving study medication must be reviewed at any study visit prior to dispensing new study medication.

4.5 Cranial Irradiation

Only conformal techniques (3DCRT or IMRT) will be allowed in this study. Two dimensional techniques not employing volumetric target volume definition and three-dimensional (3D) assessments of radiation dose are not allowed. All centers participating in the protocol are expected to complete 3DCRT/IMRT accreditation according to the procedures outlined in the ABTC Radiation Oncology QA Plan, located on the ABTC website, www.abtconsortium.org (on home page, in ABTC Member Area click on "Web Community Area" and log in; under "Workspaces, go to "General ABTC" and click on

"Radiation" bullet; under "Document area", click on "Document Area-Radiation, click on "Topic: Radiation" to locate document).

4.5.1 Equipment

Modality

All patients must be treated with a linear accelerator with nominal photon energy between 6 to 18 MV. Co-60 is not allowed on this study. Electrons and protons may not be used.

Calibration

The calibration of therapy machines used in this protocol shall be verified by the Radiological Physics Center (RPC).

4.5.2 Treatment Volumes

The goal of the treatment-planning process is to deliver a uniform dose to a planning target volume (PTV), which includes all known tumor plus a specified margin. The volume of normal brain outside the PTV receiving > 95% of the prescription dose should be minimized. For treatment planning, the PTV is defined below.

Gross Tumor Volumes (GTV)

GTV1

The GTV1 is the T1 enhancing and non-enhancing tumor volume (T2 or FLAIR) as visualized on the postoperative day 0/1 MRI scan. In cases when another MRI is performed for protocol eligibility or for clinical reasons and the second MRI indicates progression, the more recent MRI should be utilized for treatment planning.

GTV2

The GTV2 is the T1 enhancing tumor volume as visualized on the postoperative day 0/1 MRI scan. This would include the resection cavity in patients undergoing resection. In cases when another MRI is performed for protocol eligibility or for clinical reasons and the second MRI indicates progression, the more recent MRI should be utilized for treatment planning.

Clinical Target Volume (CTV)

The CTV is the GTV plus a margin of 5 mm in all directions. However, the CTV must not extend outside the brain, and care must be taken when extending it inferiorly, to minimize the amount of normal cervical cord included. In uncommon cases where an MRI cannot be utilized for treatment planning due pacemaker or other factor, an additional 1 cm margin should be added to define the CTV1 and CTV2 to the MRI-based definitions below. Margin may be reduced at true anatomic boundaries (e.g. bone, nonviolated tentorium, ventricle).

CTV1

CTV1 is the GTV1 plus a margin of 5 mm in all directions

CTV2

CTV2 is the GTV2 plus a margin of 5 mm in all directions

Planning Target Volume (PTV)

The PTV is the CTV plus a margin in all directions to account for daily setup variation and patient movement, but not beam penumbra or build-up. The margin should not exceed 5 mm and will commonly be 3–5 mm depending upon immobilization device and frequency of image guidance. Individual institutions are encouraged to perform studies defining the appropriate PTV margin based upon institutional immobilization and localization procedures. As the PTV is not structure limited, it may extend into and below the skull.

PTV1

PTV1 is the CTV1 plus a margin all directions to account for daily setup variation and patient movement (typically 3–5 mm).

PTV2

PTV2 is the CTV2 plus a margin all directions to account for daily setup variation and patient movement (typically 3–5 mm).

4.5.3 Target Radiotherapy Dose

Prescription Point

For 3D treatment planning, the prescription point is at or near the isocenter. The goal of the treatment plan is to encompass at least 99% of the PTV within the 95% isodose surface. IMRT plans may be prescribed to an isodose line provided that dose uniformity guidelines are met.

Dose Definition

The absorbed dose is specified as cGy to muscle.

Tissue Heterogeneity

Calculations shall take into account the effect of tissue heterogeneities.

Total Dose

The total dose to the prescription point will be 6000 cGy in 30 daily fractions of 200 cGy each. PTV1 will receive 4600 cGy in 23 fractions. PTV2 will receive an additional 1400 cGy in 7 fractions (total 6000 cGy in 30 fractions).

Dose Uniformity

For conformal planning techniques (3D conformal and IMRT), the 99% PTV shall be encompassed within the 95% isodose surface and no more than 10% of the PTV should receive more than 110% of the prescription dose, as evaluated by dose volume histogram.

4.5.4 Radiotherapy Time and Dose Considerations

Fractionation

Patients will receive one RT treatment per day, 5 days per week. All fields will be treated each day. At least 2 fractions must be given during the first week of treatment.

4.5.5 Treatment Technique

Any 3D treatment technique which delivers the appropriate dose to the PTV is permitted. Coplanar and noncoplanar techniques are both allowed. A treatment planning

computerized-tomography (CT) scan is required. The MRI defined volumes should be superimposed onto the treatment planning CT.

Simulation

Simulation will be performed using a CT simulator.

Patient Position and Immobilization

Reproducible setups are critical and the use of immobilization devices such as thermoplast mask, bite-block, etc. should be used for all patients.

Field Shaping

Field shaping can be done with blocks or multi-leaf collimation

Isocenter verification

The equivalent of orthogonal (AP and lateral) digitally reconstructed radiographs (DRRs) and corresponding orthogonal weekly portal images (film or electronic) are required. Alternatively, image guidance with KV imaging and setup digital reconstructed radiographs or cone beam CT is acceptable.

4.5.6 Organs at Risk

Dosimetry constraints for organs at risk will be judged on the composite plan. When possible to do so without shielding gross tumor, attempts should be made to limit dose to the following structures:

Table 4 Dosimetry constraints for organs at risk

Organ	Dose limitation
Brainstem inferior to thalamus	1% or less receiving 54 Gy
Optic chiasm	1% or less receiving 54 Gy
Optic nerve	1% or less receiving 54 Gy
Globe or retina	1% or less receiving 50 Gy
Normal brain outside PTV1	Minimize volume receiving 5700 cGy

4.5.7 Radiotherapy Dose Calculation and Reporting

Isodose Distributions and Dose Volume Histograms

Selected 3DCRT cases and all IMRT cases will be electronically submitted for review according to details in the ABTC Radiation Oncology QA plan (www.abtconsortium.org). Hard copy plans will not need to be submitted. This electronic system will allow review of isodose lines and dose volume histograms.

IMRT Plan Verification

If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry. Treatment may proceed if the calculated dosimetric error is estimated to be 5% or less.

Digital Submission

Submission of treatment plans in digital format (either Dicom RT or RTOG format) is required for selected cases of 3DCRT and all cases of IMRT according to the ABTC Radiation Oncology QA plan (www.abtconsortium.org). The MRI (T1 post-contrast and T2/FLAIR), treatment planning CT, and DICOM-RT objectives utilized to generate the treatments will need to be digitally submitted including separate plans for PTV1, PTV2, and composite (sum) plan. Plans should be submitted within 14 days of the completion of radiation therapy.

Questions

Questions regarding the RT section of this protocol should be directed to:

[redacted]

4.5.8 Definitions of Deviations in Protocol Performance

The QA assessment of PTV coverage will be based upon the individual plans for PTV1 and PTV2. Normal tissue tolerance will be assessed based upon the composite (sum) plan.

Prescription Dose

Minor Deviation

The dose to the prescription point differs from that in the protocol by between 6% and 10%.

Major Deviation

The dose to the prescription point differs from that in the protocol by more than 10%.

Dose Uniformity

Minor Deviation

99% of the PTV receives less than 95% of the prescription dose, or more than 10% of the PTV receives more than 110% of the prescription dose

Major Deviation

80% of the PTV receives less than 95% of the prescription dose.

Dose and volumes deviations will not be scored if the normal tissue dosimetry in the Dose Calculation and Reporting section is the reason for the dose deviation.

Volume

Minor Deviation

Margins less than specified or fields excessively large as deemed by the study.

Major Deviation

Transection of tumor (GTV) or potentially tumor bearing area (CTV).

4.6 General Concomitant Medication and Supportive Care Guidelines

Patients may receive other medications that the Investigator deems to be medically necessary, with the specific exception of non-protocol-specified chemotherapy, RT, anti-neoplastic biological therapy, or other investigational agents. Patients who require the use of any of the aforementioned treatments for clinical management should be removed from the study.

4.6.1 Prohibited Concomitant Medication during Study

There must be a period of at least 10 days from discontinuation of prohibited drugs and initiation of therapy unless otherwise specified in the protocol. Requests for specific exceptions to the required wait time can be submitted to the ABTC Central Office by providing a pharmacological rationale that the washout period for a particular drug should be less than 10 days (or as specified in the protocol); this must be approved by the ABTC Central Office.

Patients on drugs that are strong inhibitors and/or inducers of CYP2C9, CYP2C19 or CYP3A4 (including EIAEDs; see Appendix IV), are not eligible for enrollment or treatment under this protocol. Patients taking non-EIAEDs (see below) are permitted to take part in the study. Patients previously treated with EIAEDs, or any of the prohibited concomitant medications listed in Appendix IV, may be enrolled if they have been off the medication for ≥ 10 days prior to the first dose of BAL101553.

Concomitant use of BAL101553 with P-gp substrates should be avoided if possible. In cases where the concomitant use of BAL101553 with P-gp substrates cannot be avoided, patients should be carefully monitored for clinical signs of toxicity (see Appendix IV for additional recommendations).

Coumarin derivates (including warfarin potassium, phenprocoumon or acenocoumarol) **are not permitted**. Other anticoagulant treatments (including heparin, low-molecular weight heparin, direct thrombin/factor Xa inhibitors, aspirin, or other oral platelet inhibitors such as clopidogrel) are allowed.

Enzyme-Inducing Anti-Epileptic Drugs (EIAED)

For this study, patients may not be on EIAEDs, such as phenytoin; patients who require anti-epileptic drugs (AED) may be on non-EIAEDs (NEIAEDs). If a patient on this study protocol needs to have an AED started or needs to have a second AED added then only NEIAED should be used. There must be a ≥ 10 day period from discontinuation of an EIAED and initiation of therapy. In the event that an EIAED must be used for a patient on study, the patient will be removed from the protocol.

Drugs that are strong inhibitors and/or inducers of CYP2C9, CYP2C19 and CYP3A4

In vitro studies suggested a potential for interactions in drug metabolism between BAL27862, the active component of BAL101553, and concomitant use of drugs interfering with CYP2C9 (and to a lesser extent with CYP3A4 and CYP2C19). Patients using concomitant medications known to be strong inhibitors and/or inducers of CYP2C9,

CYP2C19 and CYP3A4 (see Appendix IV) will be excluded from participating in the study.

Herbal and Non-Traditional Medications

No data exist regarding the interaction of BAL101553 with commonly-used herbal or non-traditional medications. Patients should be instructed not to use such medications while receiving BAL101553 therapy. The intake of St. John's Wort is prohibited under this protocol (see Appendix IV).

4.6.2 Permitted use of Prophylactic/Supportive Concomitant Treatments

Antiemetics

Prophylactic antiemetic treatment is not primarily recommended. However, once a patient has experienced ≥ CTCAE grade 1 nausea or vomiting this patient may then receive prophylactic antiemetic therapy at the discretion of the Investigator. Patients taking antiemetic treatment prior to the study may continue their treatment at the discretion of the Investigator.

Antidiarrheal treatment

The use of antidiarrheal treatment should be commenced at the first sign of abdominal cramping, loose stools or overt diarrhea. Diagnosis and appropriate management of diarrhea is mandatory.

Bisphosphonates

Bisphosphonates may be continued or initiated at the discretion of the Investigator. A dental examination and appropriate preventive dental care should be available or should be performed, and renal function should be carefully monitored.

Corticosteroids

Postoperatively, corticosteroids should be tapered to a stable dose as determined by the clinical status of the patient. The lowest required steroid dose should be maintained throughout the duration of the study in order to eliminate steroid effects as a confounding variable in the interpretation of serial brain-imaging studies. Corticosteroid doses can be tapered as clinically indicated if the patient appears to be responding to therapy, as judged by serial scans. Corticosteroid dose may, of course, be increased in the event of clinical deterioration or at the discretion of the attending physician. In the event of suspected clinical deterioration, repeat brain imaging is recommended.

Blood pressure elevations

Prophylactic antihypertensive treatment is not primarily recommended. If transient BP elevations are observed following administration of oral BAL101553, the administration of short-acting antihypertensive drugs (such as labetalol or captopril) should be considered. See Table 5 below for details.

Patients may also receive chronic antihypertensive treatment (e.g., long-acting calcium channel blockers, ACE-inhibitors, angiotensin receptor blockers, thiazide diuretics or beta blockers). Additional short-acting antihypertensive medication may be given as add-on therapy (on an "as needed" basis).

Patients who experience symptomatic BP elevations (e.g., symptoms consistent with hypertensive encephalopathy, suspected intracerebral hemorrhage, stroke or transient ischemic attack, acute myocardial infarction, acute left ventricular or dissecting aortic aneurysm) should be managed and treated according to institutional standards of care.

Table 5 Blood Pressure Requirement for Initiation and Continuation of BAL101553 Dosing

Systolic BP	**Diastolic BP**	
< 140 mmHg	< 90 mmHg	Required for patient eligibility at Screening
< 160 mmHg	< 100 mmHg	Required on study to continue long-term study treatment
< 180 mmHg	< 110 mmHg	Required to continue dosing
Recommended Interventions Related to Blood Pressure		
BP	**Time point**	**Recommended Intervention**
SBP ≥ 140 mmHg or DBP ≥ 90 mmHg	Screening	Patient ineligible unless repeat BP measurements are SBP < 140 mmHg AND DBP < 90 mmHg.
SBP ≥ 160 mmHg or DBP ≥ 100 mmHg (confirmed upon repeated measurements)	Any post-Screening study visit day	Initiate antihypertensive treatment or modify existing treatment to achieve SBP < 160 mmHg AND DBP < 100 mmHg within 1 week.
SBP ≥ 180 mmHg or DBP ≥ 110 mmHg (confirmed upon repeated measurements)	Any post-Screening study visit day	Withhold dose until SBP < 160 mmHg AND DBP < 100 mmHg.
Any recording of SBP > 220 mmHg or DBP > 110 mmHg	Any post-Screening study visit day	DLT: withhold dose until SBP < 160 mmHg AND DBP < 100 mmHg; then reduce dose by one level.
SBP ≥ 160 mmHg or DBP ≥ 100 mmHg that persists for > 1 week despite antihypertensive treatment	Any post-Screening study visit day	DLT: withhold dose until SBP < 160 mmHg AND DBP < 100 mmHg; then reduce dose by one level.
Grade 4 hypertension	Any post-Screening study visit day	DLT: discontinue patient from study.

5.0 DOSE MODIFICATION FOR TOXICITY

5.1 Dose Limiting Toxicity

A DLT is defined as a clinically-significant AE or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and meets any of the criteria below. Any DLT must be a toxicity considered at least possibly related to BAL101553 or the combination of BAL101553 and radiation.

Treatment-related DLTs are defined below. Dose limiting toxicities must have an attribution of possible, probable, or definite to BAL101553 or the combination of BAL101553 and radiation. For patients experiencing a DLT, BAL101553 will be interrupted. If the patient recovers (≤ grade 1 [or tolerable grade 2 for non-hematologic toxicity] or ≤ baseline), a BAL101553 dose reduction (1 dose level reduction) is required for subsequent doses. Skipped BAL101553 doses will not be made up. If there is any question or clarification required concerning a potential DLT, the treating site should contact the ABTC Central Office to determine patient's DLT status. The ABTC Central Office, with the Study Chair, will make the final decision.

- **Hematological toxicities** will be considered dose limiting if any of the following occur and complete blood counts and differentials were obtained according to the mandated schedule (CBC, differential, and platelets drawn twice a week until the ANC ≥ 1500/mm^3 and platelets ≥100,000/mm^3):
  - ANC of < 500/mm^3.
  - Platelets < 25,000/mm^3.
  - Febrile neutropenia
  - Any hematological toxicity that prevents administration of ≥ 80% of the planned BAL101553 dose

  Grade 3 or 4 lymphopenia will <u>not</u> be considered a DLT.

- **Central nervous system toxicities**
  - **≥ Grade 2** central nervous system (CNS) ischemia will be considered a DLT
  - **≥ Grade 2** neurological toxicities that interfere with activities of daily living and do not resolve spontaneously or with steroids, anticonvulsants, or electrolyte correction within 2 weeks will be considered a DLT
  - Symptomatic CNS hemorrhage of any grade will be considered a DLT.
- **Grade 3 and 4 non-hematological, non-CNS toxicities** will be considered dose limiting with the following exceptions:
  - Grade 3 nausea, vomiting, or diarrhea without sufficient prophylaxis with a duration < 3 days;
  - Alopecia;
  - Grade 3 fatigue;
  - Grade 3 hyperglycemia that is reversible and without clinical symptoms;
  - Grade 3 electrolyte disturbances that are asymptomatic and reversible within 3 days, and do not re-occur upon continuing or re-initiation at the same dose;
  - Grade 3 or 4 hypophosphatemia, unless considered clinically relevant;
  - Grade 3 or 4 elevations in alkaline phosphatase;
  - Grade 3 hypertension that resolved to ≤Grade 2 hypertension within 1 week either spontaneously or upon implementation of antihypertensive therapy

- A subject's first episode of deep venous thrombosis (DVT) or pulmonary embolism will not require dose modification.

➢ **Any adverse event that leads to missing > 6 doses of BAL101553** will be considered dose limiting.

➢ **Any recording of SBP > 220 mmHg or DBP > 110 mmHg or any Grade 4 hypertension** will be considered dose limiting.

ANY DLT (AS DEFINED ABOVE) CAUSING DELAY IN TREATMENT OF OVER 7 DAYS WITHOUT RECOVERY TO A ≤ GRADE 1 OR BASELINE STATUS WOULD RESULT IN TAKING THE PATIENT OFF TREATMENT.

5.2 Dose Delay and Dose Reduction

If multiple toxicities occur, dose-modification decisions should be based on the most severe toxicity.

The dose levels and the general approach to BAL101553 dose modification on this trial are shown below. Adverse events should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented on the case report form.

Dose reductions are required for any DLT (as defined in Section 5.1). Dosing will stop until the DLT has resolved to ≤ grade 1 [or tolerable grade 2 for non-hematologic toxicity] or ≤ baseline. The maximum length of time that BAL101553 can be held is 7 days. After resolution, the dose of BAL101553 will be reduced by 1 dose level as stipulated below, with a maximum of 2 dose reductions. Patients who require more than 2 dose reductions will be discontinued from the study. A patient must be discontinued from the study if, after treatment is resumed at a lower dose, the same toxicity recurs with the same or worse severity. If there are any questions, the ABTC Central Office and the Study Chair should be contacted.

Table 6 BAL101553 Dose Reduction Schedule

Dose Level	BAL101553
5	15* mg daily × 6 weeks
4	12 mg daily × 6 weeks
3	8 mg daily × 6 weeks
2	6 mg daily × 6 weeks
1 (starting dose)	4 mg daily × 6 weeks
-1	2 mg daily × 6 weeks

* Dose reduction levels: 10 mg, 5 mg.

If the dose must be reduced below dose level -1, the patient will be taken off treatment.

5.2.1 Adverse Events Requiring Permanent Discontinuation of Study Drug

Patients meeting any of the following criteria will be required to permanently discontinue study drug and will be withdrawn from the study:

- Grade 4 anemia
- ≥ Grade 3 serum creatinine (S-Cr > 3.0 × ULN)
- Grade 4 total bilirubin (TB > 10 × ULN)

- Grade 4 diarrhea
- Recurrent QTcF > 500 ms or > 60 ms change vs baseline
- Grade 4 hypertension
- Grade 4 neurological events that do not respond within two weeks to steroids, anticonvulsants, or electrolyte correction
- Any DLT causing a delay in treatment of over 7 days without recovery to ≤ Grade 1 or baseline status. This includes ≥ Grade 3 electrolyte disturbances (except for hypophosphatemia if not clinically relevant) that are symptomatic or not reversible within 3 days, or that re-occur upon continuing or re-initiation at the same dose (see Section 5.1).
- Any non-treatment-related Grade 3 or Grade 4 hematologic or non-hematologic adverse event which requires a delay of treatment and which is not resolved (≤ Grade 1 or ≤ baseline) within 8 days (see Section 5.3).

5.2.2 Management of Decline in Mini-Mental State Examination Score

MMSE® Score[21]	**Management**
Score ≥ 26 OR Decline from baseline ≤3	No actions
Score < 26 AND Decline from baseline >3	Perform Neuro Exam within 1 calendar day. Withhold dose and study-drug dispensing until Neuro Exam is performed. If Neuro Exam indicates a DLT (see Section 5.1), withhold dosing and dispensing of study drug until resolution of DLT and follow procedures in Section 5.2. Otherwise, continue patient dosing and drug dispensation and follow general study procedures. A scheduled MMSE® can be replaced by a Neuro Exam.

5.3 Major Events

Major events are non-treatment-related grade 3 or 4 hematologic and non-hematologic adverse events. Treatment should be delayed for major events if BAL101553 may further complicate the non-treatment-related event. If a major event requires a delay of treatment, treatment must be delayed until the event is resolved (≤ grade 1 or ≤ baseline). If the event is not resolved in ≤ 8 days, the patient will be removed from treatment. The ABTC Central Office should be consulted if you are not clear on whether to continue or delay treatment.

5.4 Use of Hematologic Growth Factors

No growth factors (G-CSF or GM-CSF) are to be used prophylactically in this protocol. Clinicians caring for patients on this protocol are permitted to use these growth factors to

provide optimal care for patients with severe neutropenia in accordance with the ASCO guidelines, (JCO, 12, 1994: pp2471-2508). If these growth factors are used in the acute setting of neutropenia and infection (documented or suspected), they will not be utilized prophylactically in subsequent cycles and they will not subsequently be used *in lieu* of dose reduction of BAL101553.

5.5 Toxicity Criteria

All toxicities will be described and graded according to the NCI CTCAE version 4.0 until March 31, 2018; CTCAE version 5.0 will be utilized beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). See also Section 9.2.1, Recording of Adverse Events.

6.0 PHARMACEUTICAL INFORMATION

BAL101553 (NSC# 789724)

BAL101553 is a water-soluble, lysine pro-drug of the synthetic small molecule BAL27862 (a furazano-benzimidazole derivative).

Chemical Name

(2*S*)-2,6-diamino-*N*-{4-[2-(2-{4-[(2-cyanoethyl)amino]-furazan-3-yl}-1*H*-benzoimidazol -1-yl)acetyl]phenyl}hexanamide dihydrochloride.

Molecular Formula

$C_{26}H_{29}N_9O_3 \cdot 2HCl$

Molecular Mass

588.49 g/mol

How Supplied

BAL101553 for oral administration is presented as hard capsules, each containing 1 mg or 5 mg study drug. The capsules also contain mannitol and magnesium stearate as excipients. The white/opaque capsule shell is made of HPMC.

Storage

BAL101553 1 mg capsules should be stored at temperatures between 2-8 °C.

BAL101553 5 mg capsules should be stored at temperatures between 2-25 °C.

Stability

Stability studies are ongoing, please refer to study medication label for expiration date.

Route of Administration

Oral administration. Patients must fast for a minimum of 4 hours prior to, and 1 hour after, dosing. Capsules must be taken with (at least) 250 mL of water. No other intake of food is permitted for 1 hour after taking the dose.

Known Potential Drug Interactions

Drugs that are metabolized by CYP2C9, CYP2C19, and CYP3A4

Contraindications

Patients receiving coumarin anticoagulants, phenytoin

6.1 Potential Risks

Based on the safety experience from 73 patients administered BAL101553 as 2-hour IV infusions at dose levels from 15–80 mg/m^2 in the Phase I and Phase IIa portions of study CDI-CS-001, dose-related patterns were reported for systemic adverse drug reactions (ADRs) of nausea/vomiting, transient arterial hypertension, reversible or partially reversible peripheral sensory neuropathy, reversible gait disturbance, myocardial injury and pain at the tumor site.

Dose-related blood pressure (BP) increases > 170 mmHg (systolic) were observed at dose levels ≥ 45 mg/m^2, consistent with the vascular-disrupting effect observed in animal models. The maximum BP elevations occurred ~1 hour after conclusion of the BAL101553 infusion, coinciding with the T_{max} of the active drug BAL27862 and were generally resolved within 24 hours following the IV dose.

At dose levels of 60 mg/m^2 and 80 mg/m^2, some patients presented with reproducible transient grade 2–3 abdominal pain, possibly reflecting tumor pain, which occurred during dosing and disappeared within a few hours of the end of study-drug administration.

Additional systemic side effects considered to be characteristic for BAL101553, but which did not show a clear dose relationship, included anorexia, diarrhea, fatigue and pyrexia.

Based on the safety experience from 35 patients with solid tumors or glioblastoma / high-grade glioma treated with daily-oral BAL101553 in study CDI-CS-002, clinically-relevant drug-related side effects were reversible hallucinations (Grade 2) and reversible hyponatremia (Grade 3 or Grade 4) at a dose level of ≥20 mg per day.

Dose levels of 8 mg per day (7 patients, including 4 patients in the GBM arm) and 15 mg or 16 mg per day (7 patients with solid tumors, 3 patients in the GBM arm) were shown to be well tolerated. Drug-related side effects at dose levels up to 16 mg per day included Grade 1/Grade 2 anemia, anorexia, arthralgia, constipation, diarrhea, fatigue, lethargy, hepatic enzyme elevations, hypokalemia, hyponatremia, nausea, nose bleed, oral candidiasis, oral mucosa dryness, paresthesia, pruritus, rash, rhinorrhea, seizure, stomatitis, xerodermia, and xerostomia; and Grade 3 hypertension (at 8 mg/day in a solid tumor patient). One solid tumor patient at 16 mg/day developed a systolic blood pressure elevation >160 mmHg which was not drug-related; however, this patient had variable pre-dose blood pressure levels and there was no clear impact on the overall blood pressure profile in this patient or in other patients treated at doses between 2 mg per day and 16 mg per day. There was also no impact on blood pressure at the maximum administered dose of 30 mg per day.

Two solid tumor patients developed a symptomatic Grade 4 hyponatremia at a daily oral dose of 20 mg per day of BAL101553, one with associated symptoms of insomnia,

dysarthria and impairment of concentration, and one with insomnia and hallucinations. One GBM patient developed Grade 2 depression and fatigue at a daily oral dose of 20 mg.

One GBM patient at a daily oral dose of 8 mg combined with radiotherapy developed Grade 2 fever and Grade 3 encephalopathy.

6.2 Agent Ordering

The Investigator, or those named as sub-investigators on the Statement of Investigator Form 1572, agree to supply study drugs only to those subjects enrolled in the study. The Investigator or designee will keep a current and accurate inventory of all clinical drug supplies provided by Basilea. The study site will maintain a dispensing log.

Once a site has submitted all required regulatory documents to ABTC and Basilea (Form 1572, curriculum vitae, licenses, IRB approval of protocol and consent), an initial supply of drug can be ordered. An ABTC drug order form, which can be found on the ABTC website (ABTConsortium.org), should be emailed to the ABTC Central Office to initiate sending of the drug. The ABTC Central Office will forward the drug order form to Basilea. Please allow 7 days from the receipt of the drug order form at Basilea for drug shipment.

6.3 Agent Accountability

Each institutional Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received from Basilea, using the NCI Investigational Drug Accountability Record Form.

Upon termination of the study, the Investigator or designee must complete a final inventory of supplies.

7.0 PROCEDURES FOR PATIENT ENTRY ON STUDY

This study is supported by the NCI Cancer Trials Support Unit (CTSU) Regulatory Office and uses the Oncology Patient Enrollment Network (OPEN).

7.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) and ABTC policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

For questions about Investigator Registration, please contact the ***CTEP Investigator Registration Help Desk*** by email [redacted].

7.2 Site Registration Requirements – Institutional Review Board Approval

Each Investigator or group of Investigators at a clinical site must obtain Institutional Review Board (IRB) approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org and clicking on the RSS tab.

Site registration documents and a CTSU Transmittal Sheet (on CTSU website) must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
[redacted]

7.3 Patient Registration

Patient enrollment will be facilitated using OPEN. All site staff will use OPEN. OPEN is a web-based registration system available for ABTC studies from 9 a.m. to 4:30 p.m. Eastern Time. The system can be accessed by entering credentials at https://www.ctsu.org and clicking on the OPEN tab, or by entering credentials at the OPEN portal URL https://open.ctsu.org.

Since this a Phase I study, patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the registration system on OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot- reservation confirmation is obtained, site staff may then proceed to enroll patients to this study.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for credentialing in the CTSU members' web site.

- To perform registrations, the site user must have been assigned the 'Registrar' role (or equivalent) on the relevant Group or CTSU roster.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Upon completion of the registration process in OPEN, sites must contact the ABTC Central Office to obtain confirmation of the patient's registration and dose assignment. The local investigational pharmacy should call the ABTC Central Office to confirm the actual dose prior to dispensing the first dose of the first cycle. **No patient may begin treatment until registration AND dose have been confirmed by the ABTC Central Office.**

Further instructional information is provided on the CTSU members' web site [redacted]

8.0 SAFETY AND QUALITY ASSURANCE

8.1 Safety assessments

Safety assessments will consist of monitoring and recording all AEs and serious AEs, the regular monitoring of hematology, blood chemistry, troponin, pregnancy testing (in women of childbearing potential) and urine values, regular measurement of vital signs, and the performance of physical/neurological examinations, MMSE®s, and ECGs.

8.2 Quality Assurance

8.2.1 Neuropathology

The neuropathologic diagnosis of GBM will be made at the respective institution. If any question arises regarding the accuracy of the neuropathologic diagnosis, slides (and pathological blocks, if necessary) will be reviewed by the central review pathologist. For protocols with "response" as an outcome, all patients with a documented complete response or partial response will have representative pathology slides undergo central review.

8.2.2 Neuroradiology

MRI scans of patients showing tumor response will be centrally reviewed by a neuroradiologist who will independently assess tumor size and compute percent tumor regression.

8.2.3 Neuro-oncology

The local Investigator at the participating institution will communicate to the ABTC Central Office any unexpected neurological effects such as change in seizure frequency, alteration in neuromuscular function, alteration in cognitive function, or fluctuations in serum anticonvulsant drug levels.

8.2.4 Adherence to protocol therapy

As a quality assurance measure for the treatment delivered on this protocol, primary patient records may be reviewed. The records to be examined will be selected retrospectively and at random; complete records must therefore be maintained on each patient treated on the protocol. These records should include primary documentation (e.g., laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.), which confirm that:

- The patient met each eligibility criterion.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given; any reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (MRI scan, lab reports, dated notes on measurements and clinical assessment, as appropriate).
- NCI Drug Accountability Records were maintained for this protocol.

9.0 MONITORING OF PATIENTS

9.1 Table of Required Observations

Table 7 Required observations

	Baseline	Day 1	Weeks 1-6	Weekly	Day 22	Off Treatment (within 7 days)	30 Day Follow-Up
BAL101553			6				
Corticosteroid Dose Evaluation	1					8	
Prior and Concomitant Medications	1,16			3		8	
AE Evaluation	1			3		8	5,12
Brain MRI	1					8	
H&P/Neuro Exam	1				7	8	
KPS	1				7	8	
Mini-Mental State Examination (MMSE®)		20		3, 20			
Vital Signs	1,4			3,4,14		4,8	
CBC, Diff, Platelets	1			2,3		2,8	
Serum Chemistry	1,10			3,10,13,15		8,10	
Cardiac troponin	1			3,15		8	
Echocardiography, cardiac MRI or MUGA	1						
APTT or PTT and INR	1						
Serum Pregnancy Test	9						
ECG	1			17		(8, 17)	
Archived Tumor Tissue	11						
Blood Samples for PK Analyses		18			18		
Study drug dispensing		19		3, 19			

1. All baseline measurements must be done after obtaining written informed consent and must be performed within 14 calendar days prior to first treatment administration except for the baseline MRI, which may be obtained within 21 days prior to first study drug administration, and the corticosteroid dose evaluation, which should be obtained within 5 days prior to the baseline MRI.
2. If ANC < 1500 or platelets < 100,000, CBCs/differentials will be repeated twice a week until counts are recovered (ANC ≥ 1500 or platelets ≥ 100,000) per protocol. If counts are recovered (ANC ≥ 1500 or platelets ≥ 100,000) on day of scheduled drawing, do not repeat until next scheduled protocol study visit.
3. ±1day
4. Including blood pressure, respiratory rate, heart rate, temperature, weight, height. Weight and height are required at baseline only.

5. Adverse events must be followed for at least 30 days from last dose of BAL101553.
6. BAL101553 is administered orally every day during radiation therapy (see Section 4.4.1). Patients are required to keep a capsule diary (see Appendix I).
7. ±3 days
8. Evaluations are to be performed within the 7 days following the off-treatment date, unless indicated. Evaluations that do not need to be repeated include: MRI if performed within the 14 days prior to the off-treatment date; H&P/neuro, KPS, or labs if performed within the 5 days prior to the off-treatment date.
9. For women of child-bearing potential. Pregnancy testing must be performed within 72 hours prior to first study drug administration.
10. Including albumin, alkaline phosphatase, total bilirubin, calcium, creatinine, magnesium, phosphorus, potassium, SGOT, SGPT, sodium.
11. Unstained slides or tumor blocks from initial resection at diagnosis of glioblastoma, dependent on availability (Section 9.5.2).
12. Within +14 days. May be performed at the off-treatment visit if at least 30 days from last dose of BAL101553.
13. A serum sodium level of < 130 mmol/L (CTCAE Grade 3) that is symptomatic or not reversible within 3 days, or that re-occurs upon study drug continuation or re-initiation at the same dose, is a DLT. Under these circumstances, study treatment must be discontinued temporarily or permanently, depending on the improvement/normalization of sodium levels (see Section 5.1). Serum sodium testing must be repeated twice a week until recovered to ≥ 130 mmol/L.
14. If SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, initiate intervention, Section 4.6.2. Patients with SBP ≥ 160 mmHg or DBP ≥ 100 mmHg must take BP daily until < 160 mmHg AND DBP < 100 mmHg. Patients should record BP readings in the pill diary (Appendix I)
15. Perform weekly during RT+BAL101553 treatment (Days 8, 15, 22, 29, 36, 43); after RT is complete, perform every other week (Day 57 and off treatment).
16. Record all medications taken within 14 days prior to baseline (screening) visit.
17. ECG assessments to be done pre-dose and 2 h (± 30 mins) post-BAL101553 administration on Days 1, 8, 15, 22, 29 and 36 (±1day from Day 8 onwards). A final ECG will be taken within 7 days after the final dose of BAL101553. Patients with any abnormal ECG readings during the study will have an additional ECG performed at the end of the 10-week study period.
18. PK samples will be collected on Days 1 and 22: pre-dose and 0.5 h, 1 h, 2 h (up to 3 h), 4 h, 6 h and 24 h post-dose (see Section 9.5.1).
19. New study drug will be dispensed to patients at study visits at weekly intervals. All safety parameters (including laboratory safety parameters and MMSE®) applicable for assessing the ability for a patient to continue receiving study medication must be reviewed at any study visit prior to dispensing new study medication (see Section 5.2).
20. The MMSE®,[21] will be performed predose on Day 1 (=baseline) and weekly during RT+BAL101553 treatment when no Neuro Exam is planned (Days 8, 15, 29, 36, 43). Based on the MMSE® Score, a Neuro Exam will be scheduled within 1 calendar day if both of the following conditions apply: score < 26 and decline against baseline > 3; see Section 5.2.2.

IMPORTANT: *The guidance below is subject to applicable local Institutional Policy on telemedicine. In the event that local Institutional Policy regarding telemedicine differs from this guidance, then please follow local Institutional Policy.*

Telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate, and where determined by the investigator not to increase the participant's risks. Prior to initiating telemedicine for study visits, the study team will explain to the study participant, what a telemedicine visit entails, and confirm that the participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with your institution's guidance for use of telemedicine research. In the event that telemedicine is not deemed to be feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA- compliant methods approved by the Health System and within licensing restrictions.

Informed consent may be obtained in person, or if deemed necessary, via telemedicine.

9.2 Adverse Events

Patients will be evaluated for safety if they have received at least one dose of BAL101553.

The timely reporting of AEs (including deaths) is required by the U.S. Food and Drug Administration. The reporting of toxicities is part of the data reporting for this study. Adverse events will be collected for at least 30 days following the last dose of study drug. Beyond this time point only newly occurring adverse events that are serious and drug-related will be recorded.

Adverse events must be reported to the ABTC Central Office and the NCI by the investigative site in the manner described and per the requirements of the clinical site's IRB.

Adverse events will be entered into CTEP's iMedidata Rave database by the investigative site in a timely manner. See Section 12.4 – Data Collection/Reporting.

9.2.1 Adverse Event Characteristics

Definition - An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment (BAL101553 combined with concurrent radiotherapy) or procedure, regardless of whether it is considered to be related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Recording of Adverse Events - ABTC AE Form

- The Investigator will monitor each patient closely for the development of AEs from the time of the first dose of BAL101553 and record all such events on the ABTC AE Case Report Form. Each single sign or symptom must be reported separately.
- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI CTCAE version 4.0 will be utilized for AE reporting until March 31, 2018. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). **You must use one of the CTCAE criteria to define your event.**

  Adverse events not included in the CTCAE should be reported under "Other" within the appropriate category and graded 1 to 5 according to the general grade definitions - mild, moderate, severe, life-threatening, fatal or disabling - as provided in the CTCAE or the CTCAE Manual. New AEs may be submitted to the CTEP Help Desk at [redacted] for annual evaluation by the CTCAE Change Management Committee.
- All AEs should be followed up in accordance with good medical practice. Abnormalities of laboratory events which, in the opinion of the Investigator, constitute AEs (even if not serious) should be followed.
- **Attribution of the AE:** The Investigator will be asked to document his/her opinion of the relationship of the event to study medication as follows:
  - *Unrelated* - The AE is clearly not related to the investigational agent(s).
  - *Unlikely* - The AE is doubtfully related to the investigational agent(s).
  - *Possible* - The AE may be related to the investigational agent(s).

- *Probable* - The AE is most likely related to the investigational agent(s).
- *Definite* - The AE is clearly related to the investigational agent(s).

9.3 Serious Adverse Events and Expedited Adverse Event Reporting

9.3.1 Definition – Serious Adverse Event (SAE)

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect
6) Important Medical Events (IMEs) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3.2 Expedited Adverse Event Reporting

➢ **Use CTEP-AERS Web Application and Document on ABTC AE Form**

- All SAEs that occur from the time of the first administration of study drug until 30 days after the last study treatment must be documented on both the ABTC AE form and using the CTEP-AERS Web Application within 24 hours of learning of the event. SAEs beyond 30 days after last study treatment must be documented on both the ABTC AE form and using the CTEP-AERS Web Application within 24 hours of learning of the event if these events are considered to be causally related to study treatment.
- Expedited AE reporting for this study will use CTEP-AERS (CTEP AE Reporting System), accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers).

  In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to the ABTC Central Office by telephone at [redacted] Once Internet connectivity is restored, the 24-hour notification must be entered electronically into CTEP-AERS by the original submitter at the site.
- All SAEs reported through the Web Application are automatically sent to the ABTC Central Office. The pharmaceutical Sponsor, Basilea, will be notified by ABTC Central Office when an SAE is reported through CTEP-AERS (within 24 hours). All SAEs will be documented and tracked by Basilea as well as through the ABTC Central Office. Queries and follow up required for completing all SAEs will be conducted through Basilea and the ABTC Central Office in a timely fashion. When an expedited report is required (7/15 days), a speedy resolution of queries will be expected in order to allow for on-time reporting to the FDA. Basilea is responsible for reporting all applicable SAEs to the FDA.

- All SAEs (related or unknown relationship to study drug) will be followed until satisfactory resolution or until the Investigator deems the event to be chronic or the subject to be stable. Withdrawal from the study and all therapeutic measures will be at the discretion of the Investigator.

9.3.3 SAE Reporting

Any SAE, as described in Section 9.3.1, including death due to any cause, which occurs during this study must be **reported immediately (within 24 hours)** to the ABTC Central Office.

A phone call must be made to:

[redacted] ABTC Manager: [redacted]

Basilea will be responsible for reporting of any SAE to the FDA as required by legislation. Basilea will notify the FDA of any unexpected, fatal or life-threatening experience (expedited report) associated with the use of study drug as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within 15 calendar days. For other unexpected serious events (i.e. that are not fatal or life-threatening) associated with the use of study drug, Basilea will notify the FDA as soon as possible, but no later than 15 days, of the initial receipt of information.

These events also must be reported by the Investigator to the appropriate IRB.

Patients who are removed from study due to AEs should be followed until the AE has resolved or stabilized. Copies of relevant documentation, such as laboratory reports, should be kept with the patient's study records.

9.4 Routine Adverse Event Reporting

All AEs **must** be reported in routine study data submissions. **Adverse events reported expeditiously through CTEP-AERS must also be reported in routine study data submissions (Section 12.4).**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

9.4.1 Second Malignancy and Secondary Malignancy

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic treatment [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in Section 9.4.

9.5 Correlative Studies

9.5.1 Pharmacokinetic Analyses

Blood samples will be collected to assess the dose proportionality and the single- and multiple-dose PK of BAL27862 after oral administration of BAL101553.

Serial samples will be collected on Day 1 and Day 22: pre-dose and 0.5, 1, 2, 4, 6 and 24 hours post-BAL101553 administration. The collection window for the samples scheduled for 0.5, 1, 4 and 6 hours post-dose is ± 15 minutes. The 2-hour sample may be collected up to 3-hours post-dose in the event that the timing conflicts with the scheduled RT. If the 2-hour sample cannot be collected within this timeframe, the sample can be omitted and collection should resume with the 4-hour sample. The collection window for the 24-hour sample is ± 1 hour.

Details for the collection, processing, and shipment of samples are provided in a separate PK Manual provided by Basilea.

Shipment and analysis of PK samples will be organized by Basilea.

9.5.2 Archival Tumor Tissue

Archival FFPE tumor blocks or unstained slides will be collected from all patients when available. Blocks which have been appropriately prepared and conserved from the time of GBM diagnosis will be used for the analysis of exploratory biomarkers potentially predictive of tumor response.

Based on the preclinical mechanism of action, tumor-expression epidemiology studies and technical feasibility, archival pre-treatment tumor tissue will be stained for baseline expression of protein biomarkers that are potentially predictive of response to BAL101553. These will include BubR1 and EB1 (potential markers of sensitivity to BAL101553) and stathmin (potential marker of resistance to BAL101553) and potentially additional biomarkers of interest. Moreover, markers of tumor cell proliferation (e.g., Ki67) and tumor vascularization (e.g., CD34 and CD31) will also be analyzed.

Ten uncovered, unstained slides will be prepared from archival FFPE tumor blocks on Superfrost plus positively charged slides. Tissue slices should ideally be 2-3 µm thick and

should be dried at 37°C overnight. Slides should be forwarded within 1 month of preparation to Basilea, at room temperature, using the slide transport boxes provided by the Sponsor (pre-labelled with the shipment details). Processing for immunohistochemical (IHC) staining will be performed by [redacted]

Send slides to:

[redacted]

10.0 OFF-TREATMENT/OFF-STUDY CRITERIA

Each subject has the right to withdraw from the study at any time without prejudice. The Investigator may discontinue any subject's participation for any reason, including AEs or failure to comply with the protocol (as judged by the Investigator, such as compliance below 80%, failure to maintain appointments, etc.).

Should a subject withdraw from the study, the reason(s) must be stated on the case report form and a final evaluation of the subject should be performed.

Patients who go off treatment must be followed for AEs for at least 30 days from the last dose of BAL101553.

10.1 Off-Treatment Criteria

1. Progression of Disease: remove patient from protocol therapy at the time progressive disease is documented.

   Disease progression is defined as: progressive neurologic abnormalities not explained by causes unrelated to tumor progression (e.g. anticonvulsant or corticosteroid toxicity, electrolyte abnormalities, hyperglycemia, etc.) or a greater than 25% increase in the measurement of the tumor by MRI scan. If neurologic status deteriorates, on a stable or increasing dose of steroids, or if new lesions appear on serial MRI, further study treatment will be discontinued.
2. Intercurrent illness that prevents further administration of treatment.
3. Extraordinary Medical Circumstance: if at any time the treating physician feels constraints of this protocol are detrimental to the patient's health remove the patient from protocol therapy.
4. Patient's refusal to continue treatment: in this event, document the reason(s) for withdrawal.
5. Failure to comply with protocol (as judged by the Investigator, such as compliance below 80%, failure to maintain appointments, etc.).

6. Patients who experience unacceptable toxicity. Patients removed from study for unacceptable AEs will be followed until resolution or stabilization of the AE, see Section 5.2.1.
7. Patients who experience a DLT causing a delay in treatment > 7 days without recovery to a ≤ Grade 1 or baseline status (including ≥ Grade 3 electrolyte disturbances [except for hypophosphatemia if not clinically relevant] that are symptomatic or not reversible within 3 days, or that re-occur upon continuing or re-initiation at the same dose) (see Section 5.2.1).
8. Delay in protocol-defined treatment > 8 days for major events (see Section 5.3) or other non-treatment related delays.
9. Patients who require more than two dose reductions will be discontinued from the study.
10. Completion of treatment.

10.2 Off-Study Criteria

Patients will only be off study at the time of death. Patients will be followed every two months for progression, for up to one year from the off-treatment date. All patients will be followed for survival every 2 months for the first 2 years from the off-treatment date; after 2 years, patients will be followed every 6 months until death. Survival status may be obtained by phone call, clinic visit, or medical records (e.g. physician notes/laboratory results of clinic or hospital visit).

10.3 Premature Termination of the Study

This study will be terminated if ≥2 patients within a dose level are unable to complete ≥75% of their radiation dose due to toxicity considered by the investigator to be related to the combined BAL101553 and radiotherapy treatment.

The Sponsor reserves the right to terminate the study at any time. An Investigator has the right to terminate his or her participation to the study at any time. Should this be necessary, the Investigator, ABTC and Basilea will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor, ABTC and Investigator must ensure that adequate consideration is given to the protection of the patients' rights.

11.0 STATISTICAL CONSIDERATIONS

This is a multicenter, open-label dose-finding trial to determine the MTD of BAL101553 when given in combination with radiation therapy (RT) in patients with newly diagnosed *MGMT* promoter unmethylated GBM.

11.1 Primary Objective/Dose Finding (MTD)

Five pre-specified dose levels of BAL101553 will be tested. If an MTD is not reached at the highest dose being tested (15 mg daily during RT), the ABTC central office and the Study Chair will review the safety and pharmacokinetic data and determine whether further exploration of higher dose levels is justified. The exploration of additional dose levels

would be implemented via a substantial protocol amendment. BAL101553 will be given daily for 6 weeks continuously and concurrently with RT. The safety evaluation period is the initial 10 weeks from treatment start. Due to the nature of the disease on early progression within 10 weeks of diagnosis, 5 patients will be enrolled per dose cohort to ensure three evaluable patients/progression-free at end of the 10-week evaluation period. The standard 3+3 design will be used for dose finding in principle. Dose escalation will take a stepwise fashion with a minimum of 6 patients being treated at the putative MTD. The targeted dose limiting toxicity (DLT) rate is 33% (see section 4.2.2 for details).

The MTD is defined as the dose of BAL101553 in combination with standard RT that yields a dose limiting toxicity rate of less than or equal to 33%.

The table below shows the possible outcomes (number of patients with a DLT / number of evaluable patients) for a dose cohort with 5 subjects enrolled.

0/3 **1/3** 2/3 3/3
0/4 1/4 2/4 3/4 4/4
0/5 1/5 2/5 3/5 4/5 5/5

The DLT rates for dose escalation are 0/3, 0/4, 0/5, 0/6, 1/4, and 1/5,
The DLT rates for dose de-escalation are 2/3, 2/4, 2/5, 3/3, 3/4, 3/5, 4/4, 4/5, and 5/5,
The DLT rate for dose expansion is 1/3.

If ≥ 2 patients in a cohort are unable to complete $\geq 75\%$ of RT due to toxicity related to the combined use of RT and BAL101553, the study will be stopped.

The overall sample size for the trial is not fixed. It will depend on the number of dose levels being tested.

The anticipated accrual rate is 2-3 patients per month.

11.2 Secondary Objectives:

1. Safety/Toxicity: NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for scoring toxicity and adverse events until March 31, 2018; CTCAE version 5.0 will be utilized beginning April 1, 2018
2. Overall survival (death)
3. Progression-free survival (progression)
4. Expression of BubR1, also stathmin and EB1 at baseline
5. Pharmacokinetics of BAL101553 and BAL27862 (including maximum plasma concentration and time of maximum plasma concentration, area under the concentration-time curve and where possible, half-life, clearance and volume of distribution). The pharmacokinetic dose proportionality will also be assessed.

11.3 Statistical Analysis Plan:

Safety/Toxicity

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for scoring toxicity and adverse events until March 31, 2018; CTCAE version 5.0 will be utilized beginning April 1, 2018. Type, severity, and frequency of toxicity will be tabulated by the tested dose or doses using descriptive statistics. Per type of toxicity, a

proportion of subjects who experienced grade 3 or above toxicity will be estimated along with 95% confidence interval.

Overall Survival
To estimate overall survival – Endpoint is death. Survival time is defined as the time from initial diagnosis to the date of death/ or censored at the time of last known alive. Median time of survival along with 95% confidence interval will be estimated using the Kaplan-Meier method. An overall event rate (hazards rate) will be estimated with 95% confidence interval.

Progression-free Survival
To estimate progression-free survival – Endpoint is progression. Progression-free survival time is defined as the time from initial diagnosis to the date progression is defined. Median time of progression-free survival along with 95% confidence interval will be estimated using Kaplan-Meier method.

Expression of BubR1, also stathmin and EB1 at baseline
The markers expression level at baseline will be summarized using descriptive statistics.

Pharmacokinetics
Individual subject plasma concentration-time curves will be analyzed by non-compartmental methods. PK parameters will be presented as listings and descriptive summary statistics by dose groups and PK days. Dose proportionality will be evaluated using the power model.

There is no planned interim analysis.

12.0 STUDY ADMINISTRATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

12.1 Investigator's Study File

The Investigator's Study File must contain all essential documents as required by ICH E6, including IRB and governmental approvals with correspondence, informed consent forms, patient enrollment and identification logs, drug accountability records, staff *curriculum vitae*, authorization forms and other appropriate documents/correspondence etc.

12.2 Source Data/Documents

Patient source documents used to record key efficacy/safety parameters, independent of the CRFs, may include for example, patient hospital/clinic records, original laboratory reports, ECG read-outs, MRI reports, pathology and special assessment reports, etc.

Source documents are part of the study documents and must be maintained and direct access to source documents made available upon request for monitoring visits, IRB review, audits or inspections.

12.3 Document Retention and Archiving

The Investigator must keep all study documents on file for at least 5 years after

completion or discontinuation of the study. Subsequently, the Sponsor will inform the Investigator when the study documents can be destroyed, subject to local regulations.

These files must be made available for inspection, upon reasonable request, to authorized representatives of Sponsor or regulatory authorities.

Should the Investigator wish to assign the study records to another party, or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the investigational site for any or all of the documents, arrangements must be made between the Investigator and the Sponsor for appropriate storage.

12.4 Data Collection/Reporting

Data collection for this study will be done exclusively through CTEP's Medidata Rave.

Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in the Regulatory Support System (RSS). To access iMedidata/Rave the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of the ABTC must have the Rave CRA role in RSS at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive an invitation from iMedidata to activate their account. If you have any questions please contact the CTSU Help Desk [redacted].

- All data are due within 14 days of evaluation time point. Please see Section 9.1 for evaluation time points. Note: Source documentation to verify each CRF must be uploaded into Rave.
- Serious Adverse Events, PHONE IMMEDIATELY, SEE SECTION 9.3.

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. The ABTC Central Office is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

Cumulative protocol- and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means by FTP burst of data. Reports are due January 31, April 30, July 31 and October 31.

12.5 Study Monitoring

The CRA must visit the Investigator and the study facilities on a regular basis throughout the study to verify the adherence to Good Clinical Practice (GCP), the protocol and the

completeness, consistency and accuracy of the data being entered into the CRFs. The CRA will also ensure that the study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator shall ensure that the CRA has direct access to all required study data (source documents) during the regular monitoring visits. This includes all patient records needed to verify the entries in the CRFs.

The Investigator agrees to cooperate with the CRA and ABTC to ensure that any deviations or issues detected in the course of monitoring visits are resolved.

12.6 Audits and Inspections

The study may be audited at any time, with appropriate notification, by qualified personnel from the Sponsor or its designees, to assess compliance with the protocol, GCP and regulatory requirements. These audits may also be conducted for quality assurance to ensure that complete and accurate data are submitted and that adverse events, complications and/or adverse reactions are being identified and reported.

The study may also be inspected by health authority inspectors, after appropriate notification. In the event of an audit or an inspection, the Investigator must ensure that direct access to all study documentation, including source documents, is granted to the auditors or inspectors.

13.0 REFERENCES

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14.0 ETHICAL AND LEGAL CONSIDERATIONS

This study will be conducted in accordance with the Declaration of Helsinki and in compliance with all applicable laws and regulations of the locale where the study is conducted.

It is the responsibility of the Investigator that the patient is made aware and consent is given that personal information may be scrutinized during audits by competent authorities and properly authorized persons, but that personal information will be treated as strictly

confidential and not be publicly available. The Investigator is responsible for the retention of the patient log and patient records.

15.0 INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

Protocol	ABTC#1601/CDI-CS-004	Basilea Product No:	BAL101553
Protocol Title:	Phase I Study to Determine the Safety and Tolerability of the Oral Microtubule Destabilizer BAL101553 in Combination with Standard Radiation in Patients with MGMT Promoter Unmethylated Newly Diagnosed Glioblastoma		

Coordinating Center: ABTC Central Operations Office

Sponsor: Basilea Pharmaceutica International Ltd

Study Chair: Matthias Holdhoff, MD, PhD

Sponsor's Contact: Thomas Kaindl, MD

Protocol Version Date:

Name of Principal Investigator:

Study Center:

I agree to the conditions relating to this study as set out in the above named Protocol and Study Procedures. I fully understand that any changes instituted by the Investigator(s) without previous discussion with the Study Chair, Sponsor's Project Clinician, and Biostatistician (only if required) would constitute a violation of the protocol, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the well-being of the patients).

I agree to follow International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), including the FDA Code of Federal Regulations (CFR) Title 21-Chapter I-Subchapter A-Part 50, and specifically, obtain approval from the Institutional Review Board prior to study start, allow direct access to source documents and agree to inspection by auditors from Basilea and regulatory authorities, as required by ICH GCP. I will ensure that the investigational product(s) supplied by the Sponsor will be used only as described in the above named protocol; if *any* other use is desired, *written permission* must be obtained from the Sponsor.

I acknowledge that I have read the protocol for this study, and I agree to carry out all of its terms in accordance with applicable laws and regulations.

To be signed by Principal Investigator (at a minimum):

Please print name, qualifications, and date next to the signature

Signature	**Name**	**Date**
	Principal Investigator	

APPENDIX I – PATIENT MEDICATION DIARY

BAL101553 Diary – ***page 1***

Patient Name_____ *(initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **BAL101553 _____ mg on Days 1- 7 every week during Radiation Therapy**. Take the capsules on an empty stomach, 1 hour before a meal or 4 hours after, about 1 hour prior to radiation therapy. You can drink water at any time.
   Dose: take ___ 5 mg capsules.
2. Record the date, the time you took the capsules, and the number of capsules of each strength that you took. Record missed or skipped dose(s).
3. Bring this form and your bottles of BAL101553 capsules when you return for each appointment.

Week	Day	Date	Time of dose	# of 5 mg capsules	BP measurement (if applicable)	Comments
1	1					
	2					
	3					
	4					
	5					
	6					
	7					
2	1					
	2					
	3					
	4					
	5					
	6					
	7					
3	1					
	2					
	3					
	4					
	5					
	6					
	7					

Number of capsules returned: _____

Patient's Signature_____ **Date** _____

Research Staff Signature_____ **Date**_____

BAL101553 Diary – ***page 2***

Patient Name_____ (*initials acceptable*) **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **BAL101553 _____ mg on Days 1- 7 every week during Radiation Therapy**.
   Take the capsules on an empty stomach, 1 hour before a meal or 4 hours after, about 1 hour prior to radiation therapy.
   You can drink water at any time.
   Dose: take ___ 5 mg capsules.
2. Record the date, the time you took the capsules, and the number of capsules of each strength that you took.
   Record missed or skipped dose(s).
3. Bring this form and your bottles of BAL101553 capsules when you return for each appointment.

Week	Day	Date	Time of dose	# of 5 mg capsules	BP measurement (if applicable)	Comments
4	1					
	2					
	3					
	4					
	5					
	6					
	7					
5	1					
	2					
	3					
	4					
	5					
	6					
	7					
6	1					
	2					
	3					
	4					
	5					
	6					
	7					

Number of capsules returned:_____

Patient's Signature _____ **Date** _____

Research Staff Signature_____ **Date**_____

APPENDIX II – PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, ***BAL101553***, with the title *'Phase I Study to Determine the Safety and Tolerability of the Oral Microtubule Destabilizer BAL101553 in Combination with Standard Radiation in Patients with MGMT Promoter Unmethylated Newly Diagnosed Glioblastoma.'* This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Patients are NOT permitted to take coumarin derivatives (e.g. warfarin, or acenocoumarol) or the anti-seizure medication phenytoin (Dilantin) during this trial.

Also, patients on drugs that are strong inhibitors and/or inducers of CYP2C9, CYP2C19 or CYP3A4, including enzyme-inducing anti-epileptic drugs (EIAEDs), are not eligible for enrollment or treatment in this clinical trial.

Furthermore, concomitant use of BAL101553 and drugs that are substrates for P-gp should be avoided, as BAL27862 (the active principle of BAL101553) is a potent inhibitor of this transporter. In cases where the concomitant use of BAL101553 with P-gp substrates cannot be avoided, patients should be carefully monitored for clinical signs of toxicity and blood level testing should be performed in case of concomitant use of BAL101553 with digoxin, everolimus or sirolimus and aPTT and/or ECT testing should be performed for concomitant use of BAL101553 with dabigatran.

Please let the patient's Study Doctor know if you are prescribing any new medications for this patient.

- In an ongoing Phase 1 study with oral BAL101553, the main side effects observed have been dose-limiting side effects of reversible hyponatremia, hypokalemia and hallucinations that were first observed at a dose of 30 mg per day.
- Based on a recently completed Phase 1/2a study with an IV formulation of BAL101553, the possible-side effects may include nausea, vomiting, diarrhea, peripheral sensory neuropathy, gait disturbance, fatigue, anorexia, pyrexia, hypertension, troponin elevations and ECG changes, and tumor pain.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

BAL101553 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy). It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:
Medications for supportive cancer care or over-the-counter medications are permitted, but please inform your Study Doctor about any new treatment as soon as possible.

BAL101553 must be used very carefully with other medicines as patients in a Phase 1 trial may be at increased risk of side-effects compared to patients receiving licensed medication.

BAL101553 may interact with certain specific enzyme(s) in your liver, and certain transport proteins that help move drugs out of cells.

- The enzymes in question are CYP2C9, CYP2C19 and CYP3A4. If drugs that inhibit or stimulate these enzymes are taken with *BAL101553,* these drugs may increase or decrease the levels of *BAL101553* and may alter the side-effect profile or potential effects on the tumor.
- The protein transporter in question is P-glycoprotein (P-gp). If drugs that are pumped out of cells by this transporter are taken with *BAL101553,* these drugs may increase or decrease and this may alter the side-effect profile or the effects of these drugs.

Before you enroll onto the clinical trial, your Study Doctor will work with your regular health care providers to review any medicines and herbal supplements that are not permitted during the trial.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- You should NOT be given coumarin derivatives (e.g. warfarin, or acenocoumarol).
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your Study Doctor's name is

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a Phase 1 clinical trial using the experimental anticancer drug BAL101553. This clinical trial is sponsored by the NCI. BAL101553 may interact with certain medications, you should talk to your doctor before taking any new medications. You should NOT take coumarin derivatives (e.g. warfarin, or acenocoumarol) or St John's Wort.

It is very important to:

- Check with your Study Doctor before you stop taking any medicines or start taking any new medicines, unless these medications are required for emergency treatment.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.

Additional Information on Reverse

- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- In case of hospitalization, new medications given, or for additional information, please contact the research team:

  Mon to Fri, 9am to 5pm: *add phone numbers(s)*

  Other hours: *add phone number(s)*

- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX III–RESPONSE ASSESSMENT IN NEURO-ONCOLOGY (RANO) CRITERIA

Measurable disease. Bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are too many measurable lesions to measure at each evaluation, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measureable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

Complete Response (requires all of the following):

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b) No new lesions.
c) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
d) Subjects must be off corticosteroids (or on physiologic replacement doses only).
e) Stable or improved non-enhancing (T2/FLAIR) lesions.
f) Stable or improved clinically.

Note: Subjects with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial Response (requires all of the following):

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b) No progression of non-measurable disease.
c) No new lesions.
d) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e) The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
g) Stable or improved clinically.

Note: Subjects with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Stable Disease (requires all of the following):

a) Does not qualify for CR, PR, or progression.
b) The designation of stable disease requires a minimum of 4-week duration.
c) All measurable and non-measurable sites must be assessed using the same techniques as baseline.
d) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
e) Stable clinically.

Progressive Disease (defined by any of the following):

a) ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.*
1. b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy,* not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).
c) Any new lesion.
d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose. The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decrease in 20% of KPS or from any baseline to 50% or less be considered, unless attributable to comorbid events.
e) Failure to return for evaluation due to death or deteriorating condition.
f) Clear progression of non-measurable disease.

* Stable doses of corticosteroids include patients not on corticosteroids.

APPENDIX IV–PROHIBITED MEDICATIONS AT SCREENING (PRIOR 10 DAYS OF STARTING STUDY MEDICATION WITH BAL101553) AND DURING THE STUDY

Patients on drugs that are strong inhibitors and/or inducers of CYP2C9, CYP2C19 or CYP3A4, including enzyme-inducing anti-epileptic drugs (EIAEDs), are not eligible for enrollment or treatment under this protocol (see Section 4.6.1). Patients taking non-EIAEDs are permitted to take part in the study. Patients previously treated with EIAEDs, or any of the prohibited concomitant medications listed in Table A1, may be enrolled if they have been off the medication for ≥ 10 days prior to the first dose of BAL101553.

Medications that are prohibited or should be avoided while taking BAL101553 are summarized in Table A1 and , below.

The lists of drugs in these tables are not exhaustive. For more information, investigators should also refer to reliable sources such as:

- The FDA website (Drug development and drug interactions): https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm
- Micromedex
- University of Indiana website when evaluating potential drug-interactions: http://medicine.iupui.edu/clinpharm/ddis/main-table/
- Or other reliable sources that describe drug interactions

Table A1 Overview strong inhibitors and/or inducers of CYP2C9, CYP2C19 and CYP3A4

Compound	DDI potential re. strong CYP2C9, 2C19 or 3A4 inhibition/induction	Indication/drug class	Source for classification
Fluconazole	CYP2C9-inhibitor	Antifungal (azole)	FLO, FDA, EMA
Itraconazole	CYP3A4-inhibitor		FLO, EMA
Ketoconazole			FLO, FDA, EMA
Posaconazole			FDA
Voriconazole	CYP2C9-inhibitor		FLO
	CYP3A4-inhibitor		FDA
Boceprevir	CYP3A4-inhibitor	HCV treatment, PI	FDA
Telaprevir			
Cobicistat	CYP3A4-inhibitor	HIV treatment CYP3A inhibitor	FDA
Indinavir		HIV treatment, PI	FLO
Nelfinavir			FLO
Danoprevir + ritonavir			FDA
Elvitegravir + ritonavir			FDA
Indinavir +ritonavir			FDA
Lopinavir + ritonavir			FDA
Paritaprevir + ritonavir +(ombitasvir ±dasabuvir)			FDA
Saquinavir + ritonavir,			FDA
Tipranavir + ritonavir,			FDA
Ritonavir	CYP3A4-inhibitor		FLO, EMA
	CYP2C19 inducer		FDA
Clarithromycin	CYP3A4-inhibitor	AB, Macrolide	FLO, EMA
Rifampin	CYP3A4-inducer CYP2C19-inducer	AB, Polyketide	FDA
Isoniazid	CYP2C9-inhibitor	TB treatment	FLO
Metronidazole		AB, Nitroimidazole	FLO
Sulfamethoxazole		AB, Sulfonamide	FLO
Carbamazepine	CYP3A4-inducer	Anticonvulsant Benzodiazepine	FDA
Phenobarbital (or other long-acting barbituates)		Anticonvulsant Barbiturate	FLO
Phenytoin		Anticonvulsant Hydantoine	FDA
Paroxetine	CYP2C9-inhibitor	Antidepressant, SSRI	FLO
Fluoxetine			FDA
Fluvoxamine			FDA
St. John's wort	CYP3A4-inducer	Antidepressant, Herbal	FDA
Enzalutamide	CYP3A4-inducer	Prostate cancer, ARA	FDA
Mitotane	CYP3A4-inducer	ACC, Steroid metabolism modifier	FDA

Compound	DDI potential re. strong CYP2C9, 2C19 or 3A4 inhibition/induction	Indication/drug class	Source for classification
Conivaptan	CYP3A4-inhibitor	Hyponatremia treatment, AVP-R-A	FDA
Grapefruit juice		Food	FDA
Ticlopidine	CYP2C9-inhibitor	Antiplatelet drug Thienopyridine	FDA

AB: Antibacterial; AF: atrial fibrillation; ARA: Androgen-receptor antagonist; AVP-R-A: arginine vasopressin receptor antagonist; CHF: congestive heart failure; HCV: Hepatitis C Virus; PI: protease-inhibitor; SSRI: selective serotonin reuptake inhibitor; TB: tuberculosis.

FDA: FDA Guidance for Industry Drug Interaction Studies Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations DRAFT GUIDANCE, February 2012, plus web table accessed on 05 May 2017 at: https://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm #table3-1

FLO: Flockhart Chart (Clinical): Accessed on 05 May 2017 at: http://medicine.iupui.edu/CLINPHARM/ddis/clinical-table

EMA: Guideline on the investigation of drug interactions" (CHMP/EWP/560/95/Rev.1 Corr2), 21 June 2012

Note: the following not approved/marketed drugs were not included: talinolol, troleandromycin, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP).

Table A2 Overview P-gp substrates

Compound	Primary recommendation re. concomitant use with BAL101553	Recommended actions when of concomitant administration of P-gp substrate with BAL101553 cannot be avoided
Imatinib Lapatinib Maraviroc Nilotinib Topotecan	Concomitant use contraindicated as per protocol Sections 3.3 and 4.6	Patient should be excluded from the study
Digoxin Everolimus Sirolimus	Concomitant use should be avoided	Monitor for clinical toxicity and perform blood drug-level testing
Dabigatran		Monitor for clinical toxicity and perform aPTT and/or ECT testing
Aliskiren Ambrisentan Colchicine Fexofenadine Loperamide Posaconazole Quinidine Ranolazine Saxagliptin Sitagliptin Tolvaptan	Concomitant use should be avoided	Monitor for clinical toxicity