CLINICAL STUDY PROTOCOL

A Two-Part, Phase II, Multi-center Study of the ERK Inhibitor Ulixertinib (BVD-523) for Patients with Advanced Malignancies Harboring MEK or Atypical BRAF Alterations

Protocol Number: BVD-523-ABC

National Clinical Trial (NCT) Identified Number:	NCT04488003
IND Sponsor:	BioMed Valley Discoveries, Inc. 4435 Main Street, Suite 550 Kansas City, MO 64111
Medical Monitor:	Cmed Inc. 4000 Aerial Center Parkway Suite 102 Morrisville, NC 27560
Protocol Version:	1.0
Date:	01 JUN 2020

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: BIOMED VALLEY DISCOVERIES, INC

I have read and understand the contents of Version 1.0 of this clinical protocol for Study No. BVD-523-ABC dated 01 Jun 2020 and I agree to meet all obligations of the sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other investigators of all relevant information that becomes available during the conduct of this study.

Approved By:

Brent L. Kreider, PhD. Chief Operations Officer, BioMed Valley Discoveries, Inc.	Date

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of Version 1.0 of this clinical protocol for Study No. BVD-523-ABC dated 01 Jun 2020 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with current Good Clinical Practices and applicable FDA regulatory requirements:

Principal Investigator:

Name:

Title:

Institution:

Address:

Address:

Phone:

Fax:

Signature **Date**

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1 STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the applicable United States (US) Code of Federal Regulations (CFR). The principal investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and document approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

2 ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
%F	Absolute bioavailability
°F	Degrees Fahrenheit
µg	Microgram
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase (SGPT)
AML	Acute myeloid leukemia
AST	Aspartate transaminase (SGOT)
AUC	Area under the plasma concentration-time curve
BCVA	Best-corrected visual acuity
b.i.d.	Twice daily
BOR	Best overall response
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeter
C_{max}	Maximum concentration
CMC	Carboxymethylcellulose
CMP	Clinical Monitoring Plan
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete remission/complete response
CRC	Colorectal cancer
CRF	Case report form
CRO	Clinical Research Organization
CR_p	Complete remission with incomplete platelet recovery
CSR	Central serous retinopathy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP 1A2	Cytochrome P450 isoform 1A2
CYP 2D6	Cytochrome P450 isoform 2D6
CYP 3A4	Cytochrome P450 isoform 3A4
dL	Deciliter
DLT	Dose limiting toxicity
DOB	Date of birth
DOR	Duration of response
DSPV	Drug Safety and Pharmacovigilance
DUSP	Dual-specificity phosphatase
EC	Ethics Committee

Abbreviation	Definition
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EOS	End-of-study
EOT	End of treatment
ERK	Extracellular signal-regulated kinase
FAS	Full analysis set
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
HCl	Hydrochloride
HDPE	high-density polyethylene
hERG	Human ether-a-go-go related gene
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IST	Investigator sponsored trial
ITT	Intent-to-treat
IxRS	Interactive Voice/Web Response System
kg	Kilogram
LD	Largest diameter
LDH	Lactate dehydrogenase
LS	Least squares
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MDS	Myelodysplastic syndrome
MedDRA®	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase/extracellular signal-related kinase
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NCI	National Cancer Institute

Abbreviation	Definition
ng	Nanogram
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PI	Principal Investigator
PIC	Powder-in-capsule
PK	Pharmacokinetics
PP	Per protocol
PR	Partial response
PT	Prothrombin time
QC	Quality Control
QT	A measure between Q and T waves in heart electrical system
QT_c	Corrected QT interval
QT_cF	Fridericia-corrected QT interval
R2PD	Recommended Phase 2 Dose
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors (Version 1.1)
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 dose
RPPA	Reverse Phase Protein Arrays
RSK	Ribosomal S6 kinase
RTK	Receptor tyrosine kinase
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SD	Standard deviation
SEM	Standard error of the mean
SMC	Safety Monitoring Committee
SoA	Schedule of Activities
SoC	Standard of care
SOP	Standard Operating Procedure
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TFS	Tumor-free survivors
TGD	Tumor growth delay
TGI	Tumor growth inhibition
TTE	Time to endpoint
ULN	Upper limit of normal

Abbreviation	Definition
UV	Ultraviolet
VF	Visual field
WBC	White blood cell
WHO	World Health Organization

3 PROTOCOL SUMMARY

3.1 SYNOPSIS

Sponsor: **BioMed Valley Discoveries, Inc.**	**Investigational Product:** **Ulixertinib (BVD-523)**	**Developmental Phase:** **Phase II**
Protocol Number: BVD-523-ABC		
Title of Study: A two-part, phase II, multi-center study of the ERK inhibitor ulixertinib (BVD-523) for patients with advanced malignancies harboring MEK or atypical BRAF alterations.		
Study Description: BVD-523-ABC is a multi-center, phase II study that will be conducted in two parts. Patients will receive twice daily oral doses of ulixertinib in 28-day treatment cycles until disease progression, unacceptable toxicity, consent is withdrawn, or another withdrawal criterion is met. Treatment cycles will occur consecutively without interruption except when necessary to manage adverse events (AEs). **Part A (tumor histology agnostic)** will be open label and enroll patients to one of six groups based on their tumor alteration: • Group 1: Patients with tumors, other than colorectal cancer (CRC), having a BRAF alteration that results in an amino acid change at positions G469, L485, or L597. • Group 2: Patients with tumors, other than CRC, having a defined Class 2 BRAF alteration (see Appendix 2). • Group 3: Patients with tumors, other than CRC, having an atypical BRAF alteration (non V600) that is not specified in Group 1 or Group 2. • Group 4: Patients with CRC having any atypical BRAF alteration. • Group 5: Patients with tumors, other than CRC, harboring alterations in MEK1/2. • Group 6: Patients with CRC harboring alterations in MEK1/2. **Part B (tumor histology specific)** will randomly enroll patients with one of up to three specified tumor histologies to receive either ulixertinib or the physician's choice of treatment in a 2:1 ratio (physician's choice will be restricted to two approved (not off-label) treatments for each tumor histology (agents targeting BRAF or MEK kinases and experimental agents are not permitted as physician choice)). Tumors must harbor a specified MEK or atypical BRAF alteration. If a patient progresses on physician's choice of treatment, crossover to the ulixertinib arm is permitted. The specific histologies to be included in this part will be selected based on available data and discussion with the clinical investigators, the medical monitor, and the sponsor.		

Sponsor: BioMed Valley Discoveries, Inc.	Investigational Product: Ulixertinib (BVD-523)	Developmental Phase: Phase II

Objectives and Endpoints:

Part A – Tumor histology agnostic

- **Primary:** To assess the clinical benefit of ulixertinib as measured by the overall response rate (ORR) in patients receiving ulixertinib that have advanced malignancies harboring a MEK or atypical BRAF alteration.
  ORR will be defined as the percentage of patients achieving a Best Overall Response (BOR) of confirmed Complete Response (CR) and/or Partial Response (PR), according to RECIST 1.1.
- **Secondary:**
  - To evaluate the safety profile of ulixertinib per CTCAE v5.0, including term, incidence, severity, and duration of AEs.
  - To assess the duration of response (DOR), according to RECIST 1.1.
  - To assess the progression free survival (PFS), according to RECIST 1.1 and overall survival (OS) over 18 months.
  - To measure the blood levels of ulixertinib and selected metabolites: Pharmacokinetic profile of ulixertinib (BVD-523) and selected metabolites.
- **Exploratory:**
  - To evaluate the effects of ulixertinib on pharmacodynamic markers: ctDNA tissue biopsies, and/or blood to assess biomarkers. Assays include, but are not limited to, phosphorylation of RSK from whole blood, Reverse Phase Protein Arrays (RPPA) to assess protein levels, e.g. DUSP 4/6, plus Nanostring and/or RNA-exome to assess mRNA expression in tissue pre- and post-ulixertinib treatment.

Part B – Tumor histology specific

- **Primary:** To assess PFS in patients receiving ulixertinib in defined tumor histologies (up to three histologies to be selected) compared to physician's choice of treatment. Patient's tumors must harbor a specified MEK or atypical BRAF alteration.
  PFS will be defined as the time from first day of trial medication to disease progression according to RECIST 1.1, or death.
- **Secondary:**
  - To evaluate the safety profile of ulixertinib per CTCAE v5.0, including term, incidence, severity, and duration of AEs.
  - To assess OS over 18 months in patients receiving ulixertinib with a defined tumor histology and a MEK or atypical BRAF alteration, compared to physician's choice of treatment.
  - To determine ORR and DOR in patients receiving ulixertinib with a defined tumor histology and a MEK or atypical BRAF alteration, according to RECIST 1.1, compared to physician's choice of treatment.

Study Population - Criteria for Inclusion:

Patients must meet all of the inclusion criteria to be eligible.

1. Patients with a locally advanced or metastatic malignancy, that has progressed following systemic therapy for their disease, if available, or for which the patient is not a candidate or refuses.
2. Tumors harboring a MEK or atypical BRAF alteration.

Sponsor: BioMed Valley Discoveries, Inc.	Investigational Product: Ulixertinib (BVD-523)	Developmental Phase: Phase II

3. Provide signed and dated informed consent prior to initiation of any study-related procedures that are not considered standard of care (SoC).
4. Male or female patients aged ≥18 years.
5. Patients must have measurable disease by RECIST version 1.1.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2.
7. Adequate renal function [creatinine ≤1.5 times ULN (upper limit of normal)] or a glomerular filtration rate (GFR) of ≥50 mL/min (using Cockcroft-Gault).
8. Adequate hepatic function [total bilirubin ≤1.5 times ULN; AST (aspartate transaminase) and ALT (alanine transaminase) ≤3 times ULN or ≤5 times ULN if the elevation is due to liver involvement by tumor].
9. Adequate bone marrow function (hemoglobin ≥9.0 g/dL; platelets ≥100 x 10^9 cells/L; absolute neutrophil count ≥1.5 x 10^9 cells/L).
10. Adequate cardiac function:
    - Left ventricular ejection fraction (LVEF) of >50% as assessed by multi-gated acquisition (MUGA) or ultrasound/echocardiography (ECHO); and
    - A corrected QT interval (QTc) <480ms by the Fridericia method (QTcF).
11. Contraception:
    - For women: Negative pregnancy test for females of child-bearing potential; must be surgically sterile, postmenopausal (no menstrual cycle for at least 12 consecutive months), or compliant with a medically approved contraceptive regimen during and for 3 months after the last administration of study drug. Abstinence is not considered an adequate contraceptive regimen.
    - For men: Must be surgically sterile, or compliant with a medically approved contraceptive regimen during and for 3 months after the last administration of study drug.
12. Willing and able to participate in the trial and comply with all trial requirements.
13. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational agent may be included after consultation with the medical monitor.

Study Population - Criteria for Exclusion:

Patients who fulfill one or more of the following criteria will not be eligible for inclusion in this trial:

1. Gastrointestinal (GI) condition that could impair absorption of study medication (specific cases e.g., remote history of GI surgery, may be enrolled after discussion with the medical monitor) or inability to ingest study medication.
2. Uncontrolled or severe intercurrent medical condition.
3. Known uncontrolled brain metastases. Stable brain metastases either treated or being treated with a stable dose of steroids/anticonvulsants, with no dose change in the previous 4 weeks, can be allowed.
4. Having received any cancer-directed therapy (chemotherapy, hormonal therapy, biologic or immunotherapy, etc.) within 28 days or 5 half-lives (whichever is shorter) prior to the first dose of study drug. Patients previously treated with radiotherapy must have recovered from the acute toxicities associated with such treatment.

Sponsor: BioMed Valley Discoveries, Inc.	Investigational Product: Ulixertinib (BVD-523)	Developmental Phase: Phase II

5. Major surgery within 4 weeks prior to first dose.
6. Any use of an investigational drug within 28 days or 5 half-lives (whichever is shorter) prior to the first dose of study drug. A minimum of 10 days between termination of the prior investigational drug and administration of study drug is required. In addition, any drug-related toxicity except alopecia should have recovered to Grade 1 or less.
7. Prior therapy with any ERK inhibitor (e.g. LY3214996, LTT462).
8. Groups 1-4: Prior therapy with any BRAF and/or MEK inhibitor (e.g. encorafenib, dabrafenib, vemurafenib, binimetinib, trametinib, cobimetinib) is excluded. Prior BRAF and/or MEK inhibitor therapy is permitted for Groups 5 and 6.
9. For Part B, agents targeting BRAF or MEK kinases and experimental agents are not permitted as physician's choice
10. Pregnant or breast-feeding women.
11. Any evidence of serious active infections. Patients are allowed to enroll if they have been fever-free for at least 48 hours and are on an active treatment that is not prohibited in Appendix 1.
12. Any important medical illness or abnormal laboratory finding that would increase the risk of participating in this study (based on the investigator's judgment).
13. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR).
14. Concurrent therapy with any other investigational agent.
15. Concurrent therapy with drugs known to be strong inhibitors or inducers of CYP1A2, CYP2D6, and CYP3A4.

Concomitant Medications:

Necessary supportive care such as antibiotics, blood product transfusions, antiemetics, antidiarrheals, etc., will be allowed. Drugs that are strong inhibitors or inducers of CYP1A2, CYP2D6, and CYP3A4 will not be allowed during the study (see Appendix 1).

Description of Sites/Facilities Enrolling Patients:

The study will take place at sites within the United States. Approximately, up to 25 sites will be utilized, however, because the patient population is relatively rare, clinical sites may need to be added as qualifying patients are found. Clinical trial networks may be utilized.

Description of Study Drug:

Ulixertinib (BVD-523), 600 mg formulated blend, taken orally, with food, twice-daily for each 28-day cycle.

Study Duration:

Approximately 38 months.

Patient Number:

Total enrollment for Part A is targeted at approximately 228 patients with 38 patients per group. Additional patients may be enrolled as appropriate.

Total enrollment for Part B is targeted to approximately 80-100 patients per histology with up to three histologies included; however, additional patients may be enrolled.

Sponsor: BioMed Valley Discoveries, Inc.	Investigational Product: Ulixertinib (BVD-523)	Developmental Phase: Phase II

Patient Duration:

Each patient will continue on study therapy until documented disease progression, intolerable toxicity, study closure, or until other treatment discontinuation criteria is met. Patients who discontinue study therapy prior to disease progression, will continue to be followed for progression. It is estimated that participants will be on study for up to 30 months.

Statistical analysis:

The Full Analysis Set (FAS) will include all patients who received at least one dose of study medication. For Part B, analyses performed on the FAS will allocate patients' treatment group as randomized.

The safety analysis set will include all patients who received at least one dose of study medication. For Part B, analyses performed on the safety population will allocate patients' treatment group as actually received.

The per-protocol (PP) analysis set will include all patients of the FAS who completed the study without any major protocol deviations.

All analyses will be performed separately for Part A and Part B, and by group/tumor histology.

Efficacy analysis:

The efficacy analysis will be performed on the FAS.

ORR is defined as the percentage of patients achieving a BOR of confirmed complete response (CR) and/or partial response (PR) as assessed by the investigator for Part A, and both as assessed by the investigator and as adjudicated by the independent review committee for Part B.

ORR will be calculated with the corresponding 95% confidence interval (CI). For Part B, ORR will be compared between ulixertinib and physician's choice of treatment using a Chi square test.

DOR is defined as the time from first response to disease progression or death. PFS is defined as the time from first day of trial medication to disease progression or death. OS is defined as the time from first day of trial medication to death. Censoring rules will be applied as appropriate.

DOR, PFS, and OS will be analyzed using Kaplan-Meier estimates and curves, median PFS and respective 95% CIs. For Part B, DOR, PFS, and OS will be compared between ulixertinib and physician's choice of treatment using a Log Rank test. These analyses will be performed based on investigator assessment for Part A, and both on adjudicated assessment by the independent review committee and on investigator assessment for Part B.

Sensitivity analyses will be conducted.

Safety analysis:

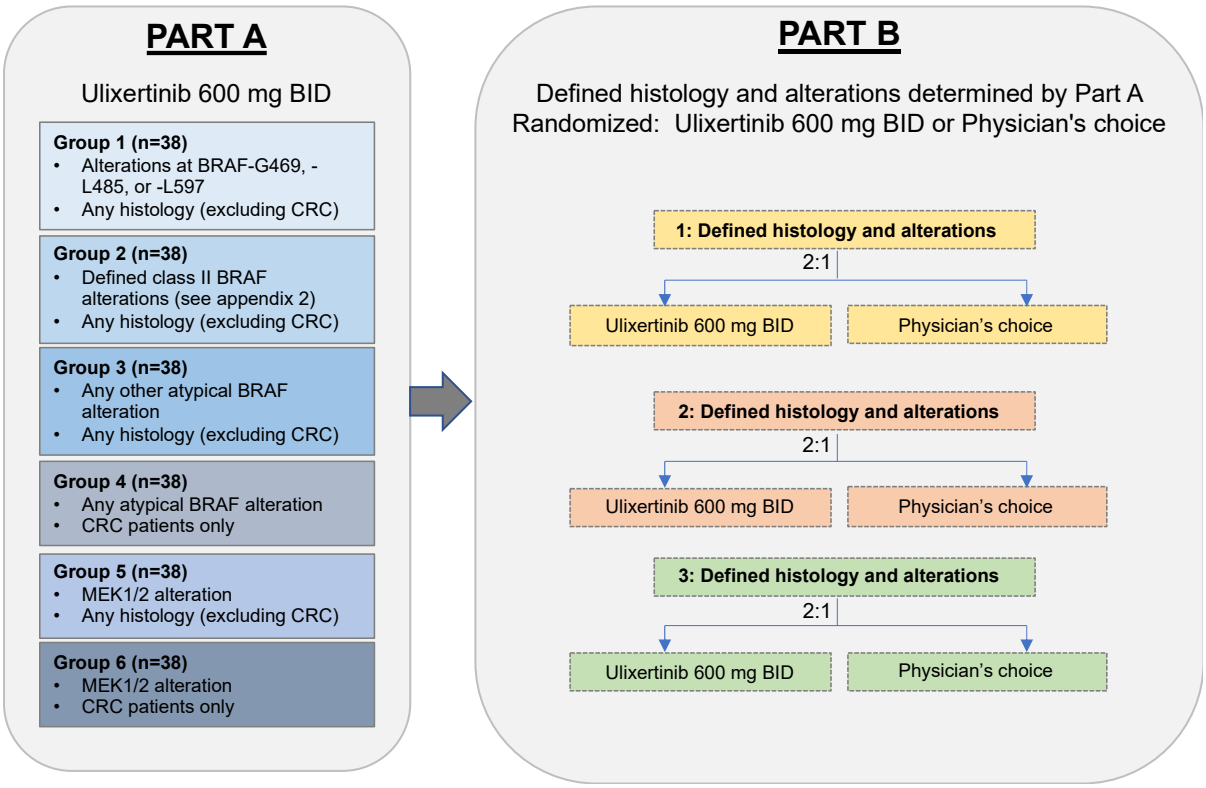
The safety analysis will be performed on the safety analysis set.

AEs, including treatment-emergent adverse event, AEs considered study drug-related, deaths, SAEs, and AEs resulting in study drug discontinuation, will be summarized (number and percentage of patients) by System Organ Class and Preferred Term.

The parameters associated with the clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be summarized with descriptive statistics by visit and for the change from baseline to each planned post-baseline visit. Graded laboratory abnormalities will be defined using the grading scheme based on NCI CTCAE and summarized. Shift tables will also be produced.

Sponsor: BioMed Valley Discoveries, Inc.	Investigational Product: Ulixertinib (BVD-523)	Developmental Phase: Phase II
Changes in the patient's physical examination findings, vital sign parameters, and ECG will be summarized by group/tumor histology and overall, and any abnormal values will be tabulated.		

3.2 SCHEMA



3.3 SCHEDULE OF ACTIVITIES (SOA)

The Schedule of Activities (SoA) table (Table 3.1) provides an overview of the protocol visits and procedures. Refer to Section 10, Study Assessments and Procedures for detailed information on each assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table in order to conduct evaluations or assessments required to protect the wellbeing of the patient. Every effort should be made to follow the SoA for the entire study.

Table 3.1 Part A and B: Schedule of Activities

		Cycle 1 Day 1 through 28			Cycle 2 Day 29 through 56			Cycle 3-X 28-day cycles, visit on 1st day of cycle	Post Treatment Period		
Visit	**1 Screening**	**2 Baseline**	**3 Tx**	**4 Tx**	**5 Tx**	**6 Tx**	**7 Tx**	**8 -X Tx**	**End of Treatment (EOT) Visit**	**Safety Follow-Up[a]**	**Follow-Up[b]**
Visit Day	-28 to -1	1 ± 0	8 ± 3	15 ± 3	29 ± 3	36 ± 3	43 ± 3	57 ± 3	≤14 ± 3 days after last dose	30 ± 3 days after last dose	
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Medical history[c]	X	X	X	X	X	X	X	X	X		
Cancer history[d]	X										X
Concomitant medications	X	X	X	X	X	X	X	X	X		
Measure height	X										
Measure weight	X	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X	X		
Physical examination[e]	X										
ECOG	X	X	X	X	X	X	X	X	X		
Ophthalmology exam[f]	X										
Pregnancy test[g,h]	X	X[g]			X[h]			X[h]	X[h]		
Clinical lab tests[i, j]	X	X[i]	X	X	X	X	X	X[j]	X		
Electrocardiogram (ECG)[k]	X										
ECHO cardiogram or MUGA	X										
Assess current disease status[l]	X				X			X	X		X[m]
Study drug administration[n]		X		X							
Adverse events (AEs)		X	X	X	X	X	X	X	X	X	

Table 3.1 Part A and B: Schedule of Activities

		Cycle 1 Day 1 through 28			Cycle 2 Day 29 through 56			Cycle 3-X 28-day cycles, visit on 1st day of cycle	Post Treatment Period		
Visit	**1 Screening**	**2 Baseline**	**3 Tx**	**4 Tx**	**5 Tx**	**6 Tx**	**7 Tx**	**8 -X Tx**	**End of Treatment (EOT) Visit**	**Safety Follow-Up[a]**	**Follow-Up[b]**
Obtain unused drug			X	X	X	X	X	X	X		
Compliance by pill count			X	X	X	X	X	X	X		
Study drug dispensed		X	X	X	X	X	X	X			
Part A Only											
Tissue biopsy, if indicated[o,p]	X[o]				X				X[p]		
Pharmacodynamic blood samples[q]		X		X							
ctDNA[r]		X		X	X				X		
Pharmacokinetic samples[s]				X[s]							
Part B Only											
Randomization	X										

Table footnotes:

[a] Patients will return to the clinic or will be contacted for a safety follow-up assessment 30 days ± 3 days after the last dose of study drug was taken; or earlier if subsequent therapy for advanced malignancy is initiated prior to 30 days ± 3 days.

[b] Patients or their legally authorized representatives will be contacted every three months (± 7 days) until death, end of the study, or patient withdrawal of consent, whichever comes first. Survival and subsequent treatment status may be collected by public records, medical records, or by contacting the patient or their legally authorized representative by phone.

[c] Full medical history at screening, only review/update of history at subsequent visits.

[d] Oncologic history of the malignancy under study including prior regimens (duration of therapy, best response on therapy, date of discontinuation, and reason for discontinuation), surgery, and radiation therapy.

[e] Physical examinations should be symptom driven after the Screening Visit.

[f] Ophthalmological examinations will be performed by an ophthalmologist at screening, and whenever clinically indicated. In Part B, only patients in the ulixertinib arm need an ophthalmological exam. See section 10.1.5 for a full description of tests.

[g] ONLY if the screening serum pregnancy test was performed more than 1 day previously.

[h] After screening and baseline, if urine pregnancy test is positive, confirm with serum test.

[i] Visit 2 clinical lab samples should be collected pre-dose if not done during Screening Visit within 72 hours of start of treatment.

[j] Chemistry, hematology, and urinalysis. After Cycle 2, clinical labs to be performed prior to starting each new cycle or more frequently when clinically indicated at the investigator's discretion. See section 10.1.6 for a full description of test.

[k] Patients with a normal ECG in Cycle 1 do not need to have repeat ECGs in subsequent cycles. Patients should be supine for 5 minutes prior to the ECG.

[l] Tumor assessments will be made prior to dose initiation, at Visit 5, and then every 2 cycles. Patients who discontinue treatment for reasons other than progression will have assessments at the EOT visit (unless their previous assessment was performed within 28 days). The same imaging modality used for an individual patient (i.e. CT or MRI) at Screening should be maintained throughout the study.

[m] Patients that discontinue study treatment for any reason other than disease progression, must continue to have disease assessments every 8 weeks (± 7 days) until disease progression or the initiation of subsequent anticancer therapy.

[n] Study drug to be taken twice daily. The first dose should be taken in the clinic on days when PD sampling occurs i.e., Cycle 1/Visit 2 (Day 1) and Cycle 1/Visit 4 (Day 15), remaining doses on all other days to be self-administered by patient.

[o] Tissue biopsy for Part A only. If a patient has undergone a biopsy within ≤ 6 months and has not received any anticancer treatment since undergoing the biopsy, archival tissue from this biopsy may be used to fulfill screening tissue requirements.

[p] Tissue biopsy at final study visit/at progression is optional, but strongly encouraged to help elucidate mechanism of resistance.

[q] Collect pre-dose and 4 hour +/- 10 mins post-dose blood samples for PD.

[r] Collect plasma for ctDNA.

[s] Sample for PK should be collected pre-dose trough at steady state (patients who have received at least 5 days, or 10 consecutive doses, of study drug).

4 INTRODUCTION

4.1 STUDY RATIONALE

This BVD-523-ABC study builds on the safety and clinical activity experience of previous studies that have evaluated ulixertinib as a novel targeted cancer treatment in cohorts of patients with specific genetic alterations and tumor histologies that result in aberrant MAPK pathway signaling. Early clinical data have demonstrated anti-tumor activity with ulixertinib treatment and have identified specific groups of patients for whom additional development is warranted.

4.2 BACKGROUND

Ulixertinib (BVD-523) is a small molecule inhibitor of extracellular signal-regulated kinase (ERK) family kinases (ERK1 and ERK2) that is being developed as a novel anti-cancer drug (Germann *et al*, 2017; Sullivan *et al*, 2018). ERK kinases are downstream components of the mitogen-activated protein kinase (MAPK) signaling cascade (RAS-RAF-MEK-ERK). Ulixertinib has demonstrated promising early efficacy for patients with tumors harboring alterations in the MAPK pathway, including atypical (non-V600) BRAF alterations, for which there are currently no approved targeted agents. This clinical protocol expands upon the ulixertinib Phase I signal to evaluate the utility of ulixertinib to treat patients with tumors harboring an atypical BRAF alteration. Furthermore, the potential to treat MEK1/2 mutant cancers will also be explored. This patient population is rare (<1% of cancers), however a strong scientific rationale exists to treat patients harboring putatively activating MEK1/2 alterations with ERK inhibition (Emery *et al*, 2017; Gao *et al,* 2018; Yaeger *et al*, 2019).

The MAPK signaling cascade is among the most frequently mutated pathways in human cancer. Approximately 50% of melanoma patients possess a druggable hotspot V600E/K mutation in the BRAF protein kinase. FDA approvals of both immune system- (ipilimumab, nivolumab, and pembrolizumab) and signal transduction-targeted (dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib) therapies have greatly expanded the armamentarium available for treating BRAF V600 mutation-dependent cancers.

Atypical BRAF alterations (non-V600) are found in many cancers and are more prevalent than V600 mutations in certain tumor types. For example, between 50–80% of BRAF mutations in non-small cell lung cancer (NSCLC) and 22–30% in colorectal cancer (CRC) encode for BRAF non-V600 alterations (Danker *et al*, 2018). As next generation sequencing becomes standard clinical practice, oncologists are frequently identifying non-V600 BRAF alterations in their patients' tumors. Unfortunately, there are no approved therapies targeting these alterations and thus there remains a lack

of viable therapeutic options that could be employed for optimal treatment of these patients.

From recent studies, a new classification system is emerging for BRAF mutations based on biochemical and signaling mechanisms associated with these mutants (Yao *et al*, 2015; Yao *et al*, 2017; Dankner *et al*, 2018; Yaeger *et al*, 2019). Class I BRAF mutations affect amino acid V600 and signal as RAS-independent active monomers. While ulixertinib has demonstrated activity against MAPK pathway activity initiated by Class I BRAF mutations and thus may offer unique possibilities as single-agent or in combinations, these mutations are currently being addressed clinically with FDA approved inhibitors of BRAF plus MEK (dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib).

Class II BRAF alterations function as RAS-independent activated dimers and are not addressed by available approved targeted therapies. Ulixertinib has demonstrated clinical activity against several of these class II BRAF alterations, across multiple tumor types (Sullivan *et al*, 2018).

Class III BRAF alterations exhibit enhanced binding to RAS and wild-type RAF to signal as mutant BRAF-wild-type RAF dimers, thus amplifying the signaling downstream of RAS and thus require upstream activation to drive ERK signaling. For this reason, Class III BRAF alterations commonly co-occur in the context of other drivers of MAPK signaling, e.g. RAS mutation, NF1 loss, RTK activation.

In human tumors the incidence of MEK1/2 mutations is rare (<1%). Similar to BRAF, a mechanism-based classification system has been proposed (Gao *et al*, 2018). Preclinical data has demonstrated activity of ulixertinib in MEK mutant models (Emery *et al*, 2017).

In summary, ulixertinib, is a potent and selective inhibitor of the key MAPK pathway enzymes ERK1 and ERK2, has shown potent anti-tumor effects, including anti-cancer activity using *in vitro* cellular assays and *in vivo* tumor xenograft models. Our initial open-label, first-in-human clinical study (NCT01781429) with oral ulixertinib was conducted to identify the maximum tolerated dose (MTD) and the RP2D. Study aims also included assessment of the PK and pharmacodynamic properties of ulixertinib as well as preliminary efficacy in patients with genetic aberrations in BRAF (both V600 and non-V600 amino acids), NRAS, and MEK. Consistent with current scientific understanding, class II BRAF mutations were demonstrated to be sensitive to single-agent ulixertinib, largely independent of tumor type. In particular, non-V600 BRAF mutations, including G469A/V, L485W, and L597Q, across a variety of solid tumors, were shown to be clinically actionable for the first time, with durable objective responses.

The potential risk profile of ulixertinib is described in further detail in the following sections.

4.2.1 Potential Risk

Preliminary evidence from *in vitro* and *in vivo* toxicological assessments of ulixertinib and data to-date from the experience in humans suggests the molecule has a safety profile supportive of its development as an anti-cancer therapeutic. Additionally, human clinical trials have been conducted using other drugs known to affect the MAPK pathway and findings from these studies may provide information regarding possible safety risks that may be mechanistically attributable to MAPK pathway inhibition.

Thus, the risk profile for ulixertinib may potentially include the following:

Dermatological Lesions

Dermatological lesions have been seen in rodent GLP toxicology studies of ulixertinib. Several of the following findings displayed exposure-dependent increases in incidence and/or severity: non-specific dermal inflammation, pustular dermatitis, epidermal ulceration and acanthosis. These toxicities appeared to be associated with predominantly reversible pharmacodynamics, as the majority of findings were mild and/or of low incidence in animals that underwent dose cessation.

In clinical studies, other drugs that inhibit components of the MAPK pathway exhibit cutaneous toxicity. Multiple investigational inhibitors of MEK1/2 kinases exhibit exposure- dependent, dose-limiting and reversible skin toxicities in a proportion of patients. Specific toxicities include: non-specific rash and pruritus, acneiform dermatitis, epidermal fissure, and paronychia. Additionally, clinical experience with both investigational agents and approved drugs that primarily target BRAF kinase have displayed exposure-dependent and reversible skin toxicities in a proportion of treated patients; relevant lesions here include keratoacanthoma-type squamous cell carcinomas, non-cancerous hyperkeratosis, and actinic keratosis.

A similar pattern of cutaneous toxicity was observed in a subset of the patients treated in studies BVD-523-01 and BVD-523-02, with approximately 81% of patients in study BVD-523-01 and 38% in study BVD-523-02 experiencing TEAEs in the System Organ Class skin and subcutaneous tissue disorders, regardless of attribution. The TEAEs were most frequently rash (coded to various preferred terms), dermatitis acneiform, and pruritus; and one patient with a history of squamous cell carcinoma developed a keratoacanthoma while on treatment with ulixertinib. Rash has been treated with topical and/or oral agents (e.g., steroids), and dose reductions/interruptions as needed. One case of Stevens-Johnson syndrome assessed as possibly related to BVD-523, but confounded by concomitant medications, including an antibiotic, was reported in a 7 y.o. patient who was being treated for astrocytoma. Additionally, this

diagnosis was made clinically, without a biopsy. Discontinuations due to skin disorders have occurred but have been uncommon.

Gastrointestinal Toxicity

Preclinical toxicity studies of ulixertinib have provided evidence of exposure-related, reversible gastrointestinal toxicities, and these toxicities, including nausea, vomiting, and diarrhea, have also been observed at high frequency in the clinical program, in some cases occurring in association with dehydration and elevated creatinine/renal insufficiency. Nausea, vomiting, and diarrhea have been managed with ulixertinib dosing interruptions and supportive medications as needed and, in some cases, dose reduction of ulixertinib has been undertaken. Gastrointestinal hemorrhage (both upper and lower) has been reported in the ulixertinib program with the majority of events assessed as unrelated to study drug. The severity and reversibility of these non-clinical and clinical toxicities, while not meriting a specific monitoring or treatment plan, warrant active routine monitoring of patients for this toxicity.

General Disorders

Study drug-related disorders characterized as general disorders, including fatigue, edema, and fever, have been observed in the ulixertinib program. In some patients, fatigue has been assessed as grade 3 in severity, but has not prompted study drug discontinuation. Events in the general disorders' category have been managed variably with supportive medications and/or interruption of study drug administration until improvement or resolution. A Death (NOS) assessed as possibly related to ulixertinib and to metastatic duodenal carcinoma was reported in a 79-year-old patient; no autopsy was performed.

Hepatic and Renal Effects

Study drug-related events of mild, moderate, and severe elevated AST and/or ALT have also been observed in the ulixertinib clinical program and were described as dose limiting toxicities (DLTs) in study BVD-523-01 at a dose of 900mg b.i.d. and in study BVD-523-02 at a dose of 750mg b.i.d. Drug-related events of elevated AST and/or ALT have been managed with interruptions of study drug followed in some instances by dose reduction. Study drug-related events of mild, moderate, and severe increased creatinine have also been observed, sometimes in conjunction with vomiting, diarrhea, and dehydration. Management has consisted of study drug interruption, rehydration, and, in some instances, dose reduction or discontinuation of study drug.

Hematological Effects

Hematological effects observed in a rat repeat-dose study included lowered reticulocyte counts, mean corpuscular volume, platelet counts (in females only), and increased neutrophil, monocyte, basophil and large unstained cell counts. In dogs, the clinical pathology findings were consistent with inflammation (increased white blood cell count, neutrophils, fibrinogen and globulin), and decreased albumin and hemorrhage (decreased red cell mass).

Hematologic effects in the ulixertinib clinical program have included, anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia. One case of possibly related, grade 3, reversible, thrombotic thrombocytopenia purpura was reported in a patient with melanoma while receiving ulixertinib at a dose of 450mg b.i.d. A case of grade 4, life-threatening thrombocytopenia assessed as possibly related to ulixertinib as well as to underlying Noonan Syndrome was reported in a 23-year-old woman.

In order to monitor for potential hematologic toxicity in humans, routine clinical laboratory hematology tests, should be performed and any indication of abnormalities may result in further investigations.

Phototoxicity

Ulixertinib exhibits an absorbance peak in the range of UV-A/UV-B light, specifically at ~320 nm. In clinical studies with ulixertinib to date, 5 TEAEs of photosensitivity reaction in patients on 75mg (1 patient) and 600mg b.i.d. (4 patients) have been reported (all in study BVD-523-01).

Beyond dermatological monitoring (above), potential risks of direct phototoxic reactions induced by ulixertinib should be further minimized by advising patients to minimize sun exposure, use broad-spectrum sunscreens, and wear sunglasses. Patients will be informed that relevant sun exposure may occur even through glass, such as while driving.

Ophthalmological Effects

While the preclinical toxicology studies of ulixertinib have not revealed any exposure-dependent ophthalmological toxicities, based on clinical studies of MEK1/2 inhibitors which highlighted ocular toxicities that may reflect mechanistically attributable risks observable in a proportion of patients, clinical studies of ulixertinib have included close monitoring for ocular toxicities. In the clinical trials to date, the following ocular events have been rarely reported (n=115): visual impairment (7%), vision blurred (4%), photophobia (2%), retinal vein occlusion (<1%, reversible grade 3), vitreous floaters (<1%), chorioretinopathy (<1%), halo vision (<1%), and retinal detachment (<1%). Although it is not definitively understood whether ocular toxicities reflect primary pharmacology associated with global inhibition of the MAPK pathway, specific

management and exclusion criteria will be defined in this study protocol as the toxicities could potentially severely and irreversibly impact patient well-being.

Cardiac Effects

The balance of preclinical evidence suggests ulixertinib has low, but observable, potential to cause QT prolongation. In study BVD-523-01, 105 patients (24 patients in Part 1 and 81 patients in Part 2) were included in an analysis of QT prolongation. Electrocardiograms extracted from 12-lead Holter monitors, along with time matched pharmacokinetic blood samples, were collected over 12 hours on cycle 1, day 1 and cycle 1, day 15 and analyzed by a core ECG laboratory. The estimated mean changes from the baseline in the study-specific QTc interval, at the ulixertinib C_{max}, were – 0.529 msec (90% confidence interval [CI] – 6.621, 5.562) on day 1 and – 9.202 msec (90% CI – 22.505, 4.101) on day 15, well below the 20 msec threshold considered appropriate for oncology agents. Overall, the evaluated ECG data showed that ulixertinib does not prolong the corrected QT interval using the Fridericia formula (QTcF) interval in patients in a concentration-dependent manner; ulixertinib may modestly increase the heart rate to a degree not likely to be of clinical significance for patients without underlying significant cardiovascular conditions (Mendzelevski *et al*, 2018).

TEAEs in the System Organ Class of cardiac disorders have been reported in approximately 14% of the patients treated to date, with preferred terms including tachycardia, atrial fibrillation, and palpitations. One case of cardiac failure was considered at least possibly related to ulixertinib. Patients dosed with ulixertinib undergo assessment of cardiac status (LVEF and ECG) at baseline and subsequently as needed.

Tissue Mineralization

Dose-dependent tissue mineralization in association with an increase in serum phosphorus and a modest decrease in serum calcium was observed in rodent toxicology studies of ulixertinib. Furthermore, tissue mineralization has been reported in rodents with other compounds that target the MAPK pathway and published studies suggest that the MAPK pathway is a negative regulator of matrix mineralization both *in vitro* and *in vivo*.

Routine clinical laboratory tests that may indicate shifts in mineralization of the bone and tissues, including blood chemistry analyses for calcium and inorganic phosphate, are performed in the clinical program and any indication of abnormalities may result in further investigations. TEAEs of hypocalcemia and increased blood phosphorus have been reported; however, tissue mineralization has not been reported.

4.2.2 Pharmacology Studies

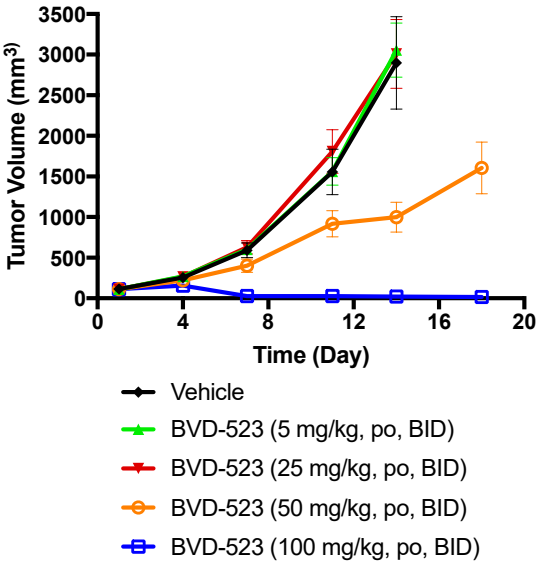
In this section a short summary of preclinical data is provided. Detailed information is presented in the current ulixertinib (BVD-523) Investigator's Brochure and Germann *et al*, 2017.

The observation that ulixertinib's cellular potency is associated with MAPK pathway alterations, which are characterized by ERK activity and dependency, was confirmed and extended with the use of murine xenograft models. Ulixertinib has demonstrated dose-dependent efficacy in human mouse xenograft models, which harbor alterations within the MAPK pathway. This includes BRAF (V600E) cell line xenograft models A375 (melanoma) and colo205 (colon), and KRAS (G12C) mutant model MIAPaca2 (pancreas). In addition, ulixertinib activity has also been demonstrated in a patient derived xenograft melanoma model established from the tumor of an individual relapsing off BRAF targeted therapy with vemurafenib. Furthermore, ulixertinib displayed impressive activity when used in combination with BRAF inhibitor dabrafenib (Germann *et al*, 2017).

4.2.2.1 Single Agent Ulixertinib is Efficacious in a Mouse Xenograft Model of BRAF Mutant Human Melanoma Cell Line (A375)

In A375 cell line xenografts, 5, 25, 50, and 100 mg/kg twice daily doses of ulixertinib were compared following 18 days of treatment. For all doses, no significant body weight changes were observed. Ulixertinib demonstrated significant dose-dependent antitumor activity starting at 50 mg/kg twice daily (Figure 4.1). Doses of 50 and 100 mg/kg twice daily significantly attenuated tumor growth, with tumor growth inhibition (TGI) of 71% ($P = 0.004$) and 99% ($P < 0.001$), respectively. Seven partial responses (PR) were noted in the 100 mg/kg twice daily group; no regression responses were noted in any other group.

Figure 4.1 BVD-523 Displays Dose Dependent Efficacy in the Murine Xenograft Model of Human BRAF-Mutant Melanoma Cell Line A375



4.2.2.2 Ulixertinib Demonstrates Profound Anti-Tumor Activity when Combined with Dabrafenib in Mouse Xenograft Model of BRAF Mutant Human Melanoma Cell Line (A375)

To evaluate the benefit of the combination, efficacy was assessed *in vivo* utilizing xenografts of the BRAF (V600E) mutant human melanoma cell line A375. Because of the response of combined dabrafenib and ulixertinib treatment, dosing in the combination groups was stopped on day 20 to monitor for tumor regrowth and was reinitiated on day 42 (Figure 4.2). Tumors were measured twice weekly until the study was terminated on day 45. The median time to endpoint (TTE) for controls was 9.2 days, and the maximum possible tumor growth delay (TGD) of 35.8 days (end of study) was defined as 100%. Temozolomide treatment resulted in a TGD of 1.3 days (4%) and no regressions. The 50- and 100-mg/kg dabrafenib monotherapies produced TGDs of 6.9 days (19%) and 19.3 days (54%), respectively, a significant survival benefit ($P < 0.001$), and 1 PR in the 100 mg/kg group. The 100-mg/kg ulixertinib monotherapy resulted in a TGD of 9.3 days (26%), a significant survival benefit ($P < 0.001$), and 2 durable complete responses (CRs). The combinations of dabrafenib with ulixertinib each produced the maximum possible 100% TGD with statistically superior OS compared with their corresponding monotherapies ($P < 0.001$). The lowest dose combination produced a noteworthy 7/15 tumor-free survivors (TFS), and the 3 higher dosage combinations produced a total of 43/44 TFS, consistent with curative or near-curative activity observed in the Kaplan-Meyer plot (

Figure 4.3).

Figure 4.2 Mean Tumor Volume Plot; BVD-523 and Dabrafenib Combination Demonstrates Superior Efficacy Compared to Either Single Agent Alone in the A375 BRAF Mutant Melanoma Xenograft Model

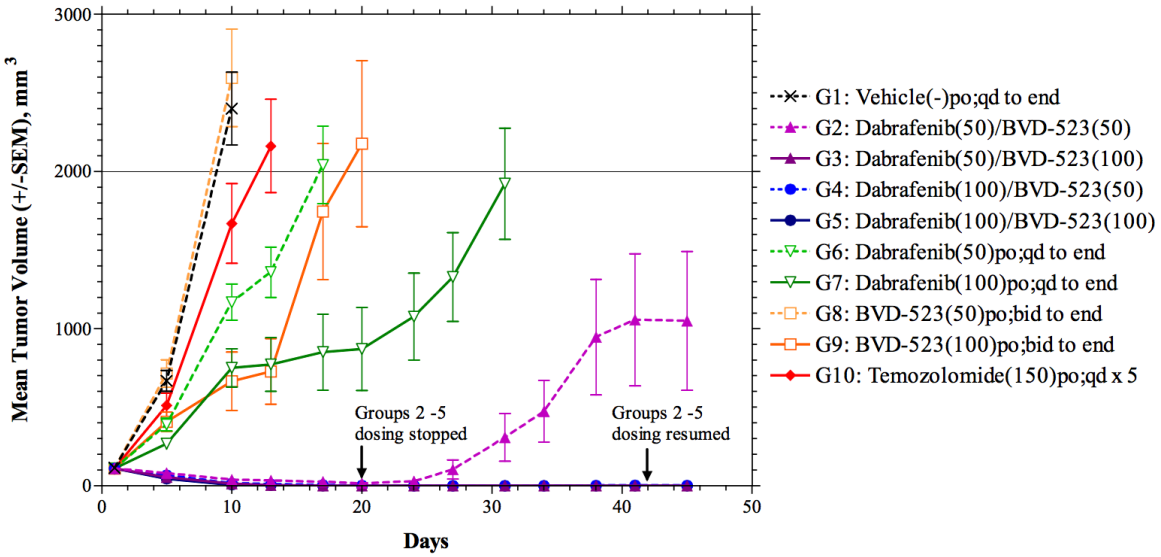
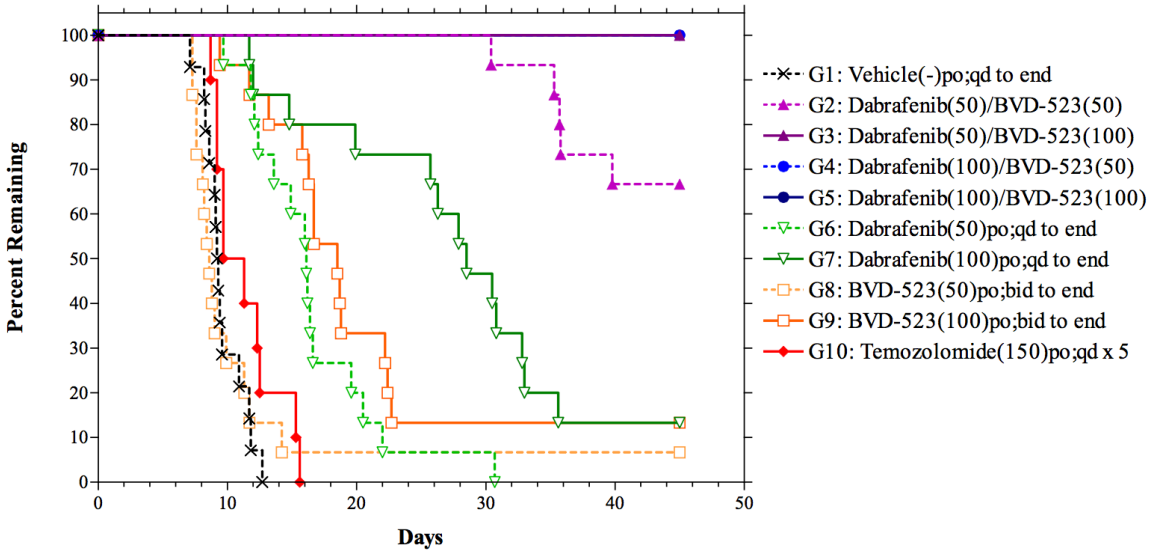


Figure 4.3 Kaplan-Meyer Plot; BVD-523 and Dabrafenib Combination Demonstrates Superior Survival Compared to Either Single Agent Alone in the A375 BRAF Mutant Melanoma Xenograft Model



4.2.3 Toxicity and Safety Studies

When ulixertinib was characterized using *in vitro* screens against 66 receptors and ion channels, no toxicologically significant interactions were identified. Additionally, ulixertinib was negative in bacterial mutation and *in vivo* micronucleus screening assays; therefore, ulixertinib is not considered to have a significant genetic toxicology risk.

While ulixertinib modestly inhibits the human ether-a-go-go related gene (hERG) current (IC_{50} 3.4 µM), no significant effects were seen in action potentials recorded from dog Purkinje fibers exposed to up to 10 µg/mL and no significant cardiovascular findings were observed upon acute oral dosing of the compound at dose levels up to 50 mg/kg in dogs (C_{max} = 17.3 µM). Thus, ulixertinib is considered to have a low potential to cause QT prolongation in patients, but, as stated, patients dosed with ulixertinib in the first-in-human study, BVD-523-01, were monitored for potential QTc prolongation and related cardiotoxicities via Holter monitoring. No clinically significant cardiac abnormalities have been seen in the ulixertinib clinical program to date.

In vitro studies suggest that the compound is metabolized primarily via oxidation by multiple CYPs including 3A4, 2D6, and 1A2. No significant CYP induction was observed after up to 14 days drug treatment in rats. *In vitro* human liver microsome studies do demonstrate ulixertinib to induce CYP1A2, CYP2B6, and CYP3A4 mRNA expression, whist also directly inhibiting CYP2C8 and CYP3A4/5. These data suggest a limited potential for drug-drug interactions.

Ulixertinib HCl salt is orally available in multiple species (absolute bioavailability %F = 23% in dog to 100 % in monkey) when formulated as a simple suspension in 1% carboxymethyl-cellulose (CMC) and has a half-life of 2-4 hours across all species.

Ulixertinib was administered to male and female Sprague-Dawley rats in several toxicology studies: (1) a GLP study for up to 28 days at dose levels up to 50 mg/kg/day twice daily; (2) for up to 14 days at dose levels up to 100 mg/kg twice daily; and (3) for up to 5 days at dose levels up to 150 mg/kg/dose once daily. The incidence and severity of mineralization seen in these studies was dose-dependent and effects were observed in one or more tissues at toxic doses. In animals in which mineralization occurred after treatment with ulixertinib, significantly increased serum phosphorus and modestly decreased serum calcium were seen. These effects were not observed in animals in which there was no mineralization. Therefore, the risk of tissue mineralization can be assessed by serum phosphorus and calcium monitoring. A clinical monitoring strategy similar to this was previously employed for related drugs that target the MAPK pathway because those compounds likewise elicited mineralization in rodents.

When ulixertinib was administered to male and female Sprague-Dawley rats for up to 28 days at a dose level of 25 or 50 mg/kg twice daily, ulixertinib was poorly tolerated. Although most clinical signs and clinical pathology findings reversed following 4 weeks of recovery, skin lesions and histopathology findings persisted in many tissues at both dose levels after the recovery. Based on these findings, 25 and 50 mg/kg twice daily dose levels were considered severely toxic. Administration of 12.5 mg/kg twice daily for 28 days was generally well-tolerated by rats of both sexes; however, this dose level was associated with test article-related findings that included (1) swelling in the neck, (2) decreased forelimb strength, (3) multiple clinical pathology findings, and (4) enlarged lymph nodes, spleen, and mammary gland. Based on these observations, the severely toxic dose in 10% of the animals (STD_{10}) for ulixertinib when administered for up to 28 days in Sprague-Dawley rats is 12.5 mg/kg given twice daily (25 mg/kg/day). On Day 28 of the dosing phase, this dose level corresponded with a C_{max} of 28700 and 15323 ng/mL and AUC_{0-12} of 264868 and 124341 hr.ng/mL for males and females, respectively.

Ulixertinib was administered to male and female beagle dogs for up to 28 days at dose levels of 15, 5, or 2 mg/kg twice daily. Initial analysis of the toxicity profile observed shows that ulixertinib was well tolerated in dogs. The rat was designated the most sensitive species and rat data were used to calculate the starting dose in man.

Based on the data accumulated to date, ulixertinib possesses a toxicology profile which presents no impediment to its development as an anti-cancer agent.

4.2.4 Previous Human Experience

Ulixertinib has been administered to humans in 5 commercially sponsored clinical studies, 4 investigator sponsored trials (IST), and 3 NCI sponsored trials to date:

Table 4.1 Previous Human Experience with Ulixertinib

Study Type	Study Identifiers	Status/Results
Commercial sponsored	NCT01781429 BVD-523-01 Phase 1 Dose-Escalation, Safety, Pharmacokinetic and Pharmacodynamic Study of BVD-523 in Patients with Advanced Malignancies.	In the first in human, phase I study of ulixertinib a total of 135 patients were enrolled in the dose escalation and dose expansion phases of the study. Twenty-seven patients were enrolled in the dose escalation phase (10-900 mg b.i.d.). The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) was determined to be 600 mg twice daily given continuously. Dose-limiting toxicities (DLT) included rash, diarrhea, elevated AST, and elevated creatinine. Drug exposure was dose proportional up to the RP2D, which provided near-complete inhibition of ERK activity in whole blood. In the expansion cohort (108 patients), there were no drug related deaths; however, 32% of patients required a dose reduction. The most common AEs at RP2D, regardless of attribution, were diarrhea (50%), fatigue (50%), nausea (45%), decreased appetite (31%), and dermatitis acneiform (31%). In addition to 3 patients with partial responses during escalation (11%), an additional 11 of 81 (14%) evaluable patients at expansion had a partial response: 1 $BRAF^{V600E}$ mutant melanoma patient refractory to prior BRAF/MEK inhibitor treatment, 3 NRAS mutant melanoma patients, 3 patients with BRAF mutant lung cancers including response in brain metastases, 1 with $BRAF^{V600E}$ mutant glioblastoma multiforme, 1 with $BRAF^{G469A}$ head & neck cancer, 1 with $BRAF^{G469A}$ small-bowel cancer, and 1 with $BRAF^{L485W}$ gallbladder cancer. The duration of response ranged from 2 to 24+ months (82, 98). A total of 28 evaluable patients whose BRAF mutations were not at amino acid V600 were included in the BVD-523-01 solid tumor study of ulixertinib. Figure 4.4 and 4.5 provide the percent target lesion change and study duration for patients with atypical BRAF alterations, respectively.

Study Type	Study Identifiers	Status/Results
Commercial sponsored	NCT02296242 BVD-523-02 Phase 1/2 Dose-Escalation, Safety, Clinical Activity, Pharmacokinetic and Pharmacodynamic Study of the ERK 1/2 Inhibitor BVD-523 in Patients with Acute Myelogenous Leukemia or Myelodysplastic Syndromes	An open-label, multi-center Phase I/II study to determine the safety, tolerability, and pharmacokinetic profile of ulixertinib in patients with AML or MDS, as well as to assess clinical response, PFS, and duration of response in those patients. The study consisted of 2 parts: Part 1 was a dose-escalation phase to investigate safety and determine the MTD and the RP2D, and Part 2 was a cohort-expansion phase using the RP2D to examine safety, and to identify early indications of clinical effects. Patients received continuous twice-daily oral dosing with ulixertinib in 21-day cycles. A total of 18 patients received at least one dose of ulixertinib in the dose-escalation phase (300-750mg b.i.d.). In Part 1, the MTD and RP2D were determined to be 600 mg b.i.d., and this is the dose that was tested in the cohort-expansion phase (Part 2) of the study. A total of 35 patients received at least one dose of ulixertinib in the cohort-expansion phase of the study. Of the 35 patients in Part 2, 14 patients (40%) were RAS mutant positive and 21 patients (60%) were RAS mutant negative. The most frequently reported study drug-related events at RP2D were diarrhea (31%), nausea (20%), increased creatinine (17%), vomiting (9%), and rash (5%). All bone marrow biopsies in Part 1 showed less than partial response. In Part 2, one patient with RAS (+) AML, had CRp at two sequential visits. A second patient with RAS (-) AML, had a CR on Cycle 2, Day 1. All other evaluations in Part 2 AML patients showed less than PR. A third patient with RAS (+) MDS had a PR on Cycle 2, Day 1. All other bone marrow evaluations in Part 2 MDS patients showed less than PR.
Commercial sponsored	NCT02994732 BVD-523HV001: A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [^{14}C]BVD-523 Following Single Oral Dose Administration in Healthy Male Subjects	The purpose of study BVD-523HV001 was to evaluate the absorption and excretion characteristics as well as relevant pharmacokinetic properties of ulixertinib; and to characterize and, where possible, identify the metabolites present in plasma, urine, and feces in healthy male subjects following a single dose of 600mg (approximately 200 µCi) of [14C]-ulixertinib. The secondary objective of this study was to evaluate the safety and tolerability of a single oral dose of [14C]-labeled ulixertinib in healthy male subjects. A total of 6 subjects were enrolled. The absorption of ulixertinib (BVD-523) was moderate and after reaching C_{max}, concentrations of ulixertinib (BVD-523) in plasma appeared to decline in a generally biphasic manner. Ulixertinib (BVD-523) undergoes moderate metabolism to produce 13 identified/characterized metabolites in plasma and excreta. The metabolites BVD-502+BVD503 and BVD-513 were formed moderately rapidly and their plasma concentration-time profiles generally mirrored that of parent drug, suggesting formation rate limited elimination. The metabolite BVD-506 was found to be present and disproportionate levels compared to levels measured in pre-clinical in vivo studies. The primary route of elimination was through fecal excretion. No clinically significant findings with respect to clinical laboratory, vital signs, ECG, or physical examinations. Fatigue and diarrhea were reported for 2 subjects (33%) and were possibly related to study drug. All TEAEs were of mild severity and there were no moderate or severe events reported.

Study Type	Study Identifiers	Status/Results
Commercial sponsored	BVD-523A-FE A Randomized, Open-Label, Single-Dose, 2-Way Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics, Safety and Tolerability of Orally Administered BVD-523 in Healthy Volunteers	A Phase I, randomized, open-label, single-dose, 2-way crossover study to assess the safety and PK in 14 healthy male and female subjects. Subjects received a single oral dose of BVD-523A (an investigational formulated blend of ulixertinib) in 2 different treatment periods; once after an overnight fast of at least 10 hours and once after consumption of a FDA-defined high-fat breakfast. There was a washout period of 5 days between dosing in one period and dosing in the next period. Subjects were randomized equally to receive 1 of 2 treatments sequences (fasted/fed or fed/fasted), with 7 subjects assigned to each sequence. Each subject received both treatments. PK concentrations achieved in the fed group were considerably higher than observed in the fasted group. However, fasting and fed conditions were extreme. Collective experience in patients and healthy volunteers shows that best exposure and variability is achieved when ulixertinib is taken with food. There were no clinically significant findings with respect to clinical laboratory, vital signs, ECG, or physical examination. Headache in 2 subjects (14%) under fed conditions and diarrhea in 1 subject (7%) under fasted conditions were considered by the investigators to be possibly related to the study drug. All TEAEs were of mild severity, and there were no moderate or severe events reported.
Commercial sponsored	BVD-523-FC A Randomized, Open-Label, Single-Dose, 2-Way Crossover Study Evaluating the Pharmacokinetics, Safety, and Tolerability of two oral formulations of Ulixertinib (BVD-523) in Healthy Volunteers	A Phase I, randomized, open-label, single-dose, 2-way crossover study to assess the effect of two oral formulations of ulixertinib on the PK, safety, and tolerability of a single oral dose of 600mg ulixertinib in 14 healthy male and female subjects. The oral formulations included a single dose of 600mg powder in capsule (PIC) formulation and a single oral dose of 600mg formulated blend formulation of ulixertinib. Subjects were randomized equally to receive 1 of the 2 treatment sequences with 7 subjects assigned to each sequence and a washout period of 5 days separated the treatments. The formulated blend formulation produced peak and total systemic exposures which were slightly lower than PIC formulation. Additionally, the AUC_{last} and AUC_{inf} of the formulated blend formulation were approximately 25% lower than compared to PIC formulation. No clinically significant findings with respect to clinical laboratory, vital signs, ECGs, or physical examinations. Headaches were reported in 4 subjects (29%) and were possibly related to study drug. All other possibly related TEAEs were only reported by 1 subject (7%). All events were of mild severity, except for 1 event of urticaria, which was of moderate severity.
Investigator sponsored	NCT02608229 Phase Ib Study of BVD-523 Plus Nab-Paclitaxel and Gemcitabine in Patients with Metastatic Pancreatic Cancer	Study was stopped after part 1 (dose escalation) due to tolerability issues experienced from the triple combination treatment.

Study Type	Study Identifiers	Status/Results
Investigator sponsored	NCT03454035 A Phase I Trial of Ulixertinib (BVD-523) in Combination with Palbociclib in Patients with Advanced Solid Tumors with Expansion Cohort in Previously Treated Metastatic Pancreatic Cancer	Ongoing
Investigator sponsored	NCT04145297 Phase 1 study of ulixertinib and hydroxychloroquine in patients with advanced MAPK-mutated gastrointestinal adenocarcinomas	Ongoing
Investigator sponsored	NCT03417739 A Phase II Study of BVD-523 in Metastatic Uveal Melanoma	In interim analysis of 13 patients, four patients had best response of SD (31%), seven had best response of progressive disease (54%), and two were unevaluable for response (15%). According to the Simon design, the trial stopped recruitment at this point due to lack of responders in the first stage.
NCI sponsored	NCT03155620 Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients with Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders (The Pediatric MATCH Screening Trial)	Ongoing
NCI sponsored	NCT02465060 Targeted Therapy Directed by Genetic Testing in Treating Patients with Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial)	Ongoing

Study Type	Study Identifiers	Status/Results
NCI sponsored	NCT03698994 Ulixertinib in Treating Patients with Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With MAPK Pathway Mutations (A Pediatric MATCH Treatment Trial)	Ongoing

Figure 4.4 Percent Target Lesion Change in Patients from BVD-523-01 with BRAF non-V600 mutations

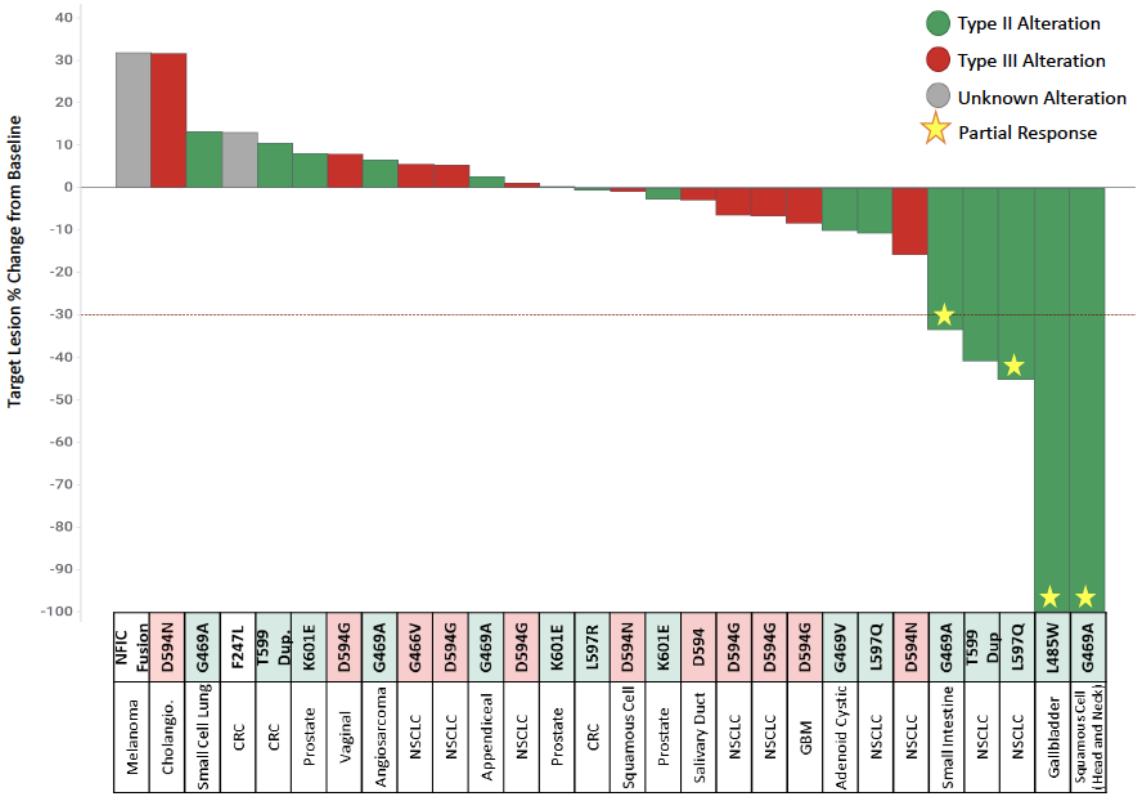
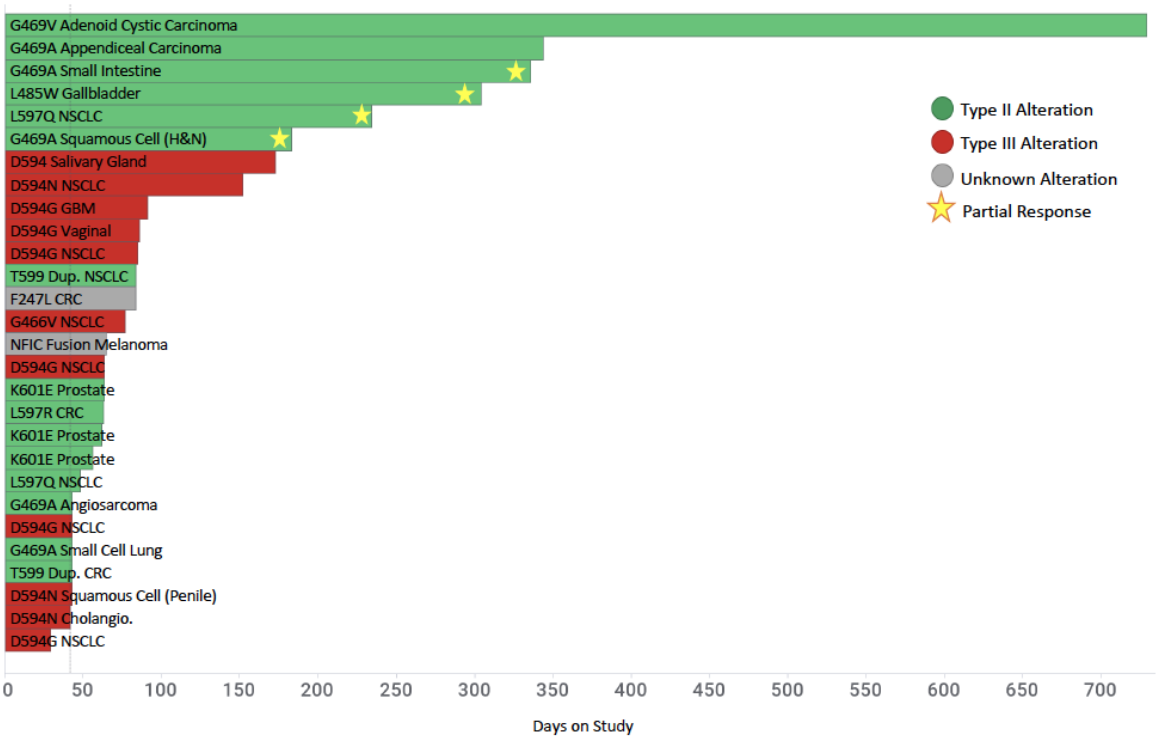


Figure 4.5 Study Durations of Patients from BVD-523-01 with BRAF non-V600 mutations



Based on these data it was concluded that ulixertinib at 600mg twice a day has an acceptable safety profile and has produced durable responses in patients with NRAS mutant melanoma, BRAF V600 and non-V600 mutant solid tumors including melanoma, glioblastoma multiforme, gallbladder, head and neck cancers, and lung cancers and exhibits clear CNS activity. Ulixertinib also resulted in durable responses in patients who progressed on prior BRAF +/- MEK inhibitor treatment or who were treatment naïve.

5 OBJECTIVES AND ENDPOINTS

5.1 PART A – TUMOR HISTOLOGY AGNOSTIC

5.1.1 Primary Objective

To assess the clinical benefit of ulixertinib as measured by the ORR in patients receiving ulixertinib that have advanced malignancies harboring a MEK or atypical BRAF alteration.

Primary Endpoint(s): ORR will be defined as the percentage of patients achieving a Best Overall Response (BOR) of confirmed Complete Response (CR) and/or Partial Response (PR), according to RECIST 1.1.

5.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate the safety profile of ulixertinib
- To assess the DOR
- To assess the PFS and OS over 18 months
- To measure the blood levels of ulixertinib and selected metabolites

Secondary Endpoint(s):

- Safety profile, including term, incidence, severity, and duration of AEs, as per CTCAE v5.0
- DOR according to RECIST 1.1
- PFS time according to RECIST 1.1
- OS time
- Pharmacokinetic profile of ulixertinib (BVD-523) and selected metabolites

5.1.3 Exploratory Objectives

To evaluate the effects of ulixertinib on pharmacodynamic markers.

Exploratory Endpoint(s):

- ctDNA, tissue biopsies, and/or blood to access biomarkers. Assays include, but are not limited to, phosphorylation of RSK from whole blood, RPPA to assess protein levels, e.g. DUSP 4/6, plus Nanostring and/or RNA-exome to asses mRNA expression in tissue pre- and post-ulixertinib treatment.

5.2 PART B – TUMOR HISTOLOGY SPECIFIC

5.2.1 Primary Objective

To assess PFS in patients receiving ulixertinib in defined tumor histologies (up to three histologies to be selected) compared to physician's choice of treatment. Patient's tumors must harbor a specified MEK or atypical BRAF alteration.

Primary Endpoint(s): PFS will be defined as the time from first day of trial medication to disease progression according to RECIST 1.1, or death.

5.2.2 Secondary Objectives

The secondary objectives are:

- To evaluate the safety profile of ulixertinib
- To assess OS over 18 months in patients receiving ulixertinib with a defined tumor histology and specified MEK or atypical BRAF alteration, compared to physician's choice of treatment
- To determine the ORR and DOR in patients receiving ulixertinib with a defined tumor histology and a MEK or atypical BRAF alteration, according to RECIST 1.1, compared to physician's choice of treatment

Secondary Endpoint(s):

- Safety profile, including term, incidence, severity, and duration of AEs, as per CTCAE v5.0
- OS time
- ORR and DOR according to RECIST 1.1

6 STUDY DESIGN

6.1 OVERALL DESIGN

BVD-523-ABC is a two-part, phase II, multicenter study of the ERK inhibitor ulixertinib (BVD-523) with an open-label, tumor histology agnostic part (Part A) and a tumor histology specific part (Part B).

6.1.1 Part A: Tumor Histology Agnostic

Part A will include six groups of patients with advanced malignancies. Group 1 will include patients with advanced malignancies, other than CRC, having a BRAF alteration that results in an amino acid change at position G469, L485, or L597. Group 2 will include patients with advanced malignancies, other than CRC, having a specified Class 2 BRAF alteration (see Appendix 2). Group 3 will include patients with advanced malignancies, other than CRC, having any atypical BRAF alteration that is not specified in Group 1 or 2. Group 4 will include patients with CRC having any activating atypical BRAF alteration. Group 5 will include patients with tumors, other than CRC, harboring alterations in MEK1/2. Group 6 will include patients with CRC harboring alterations in MEK1/2.

Ongoing data from Part A will be used, in part, to prioritize one or more tumor histologies that warrant study in Part B.

6.1.2 Part B: Tumor Histology Specific

Part B will randomly enroll patients with one of up to three specified tumor histologies to receive either ulixertinib or the physician's choice of treatment in a 2:1 ratio. Physician's choice will be restricted to two approved (not off-label) treatments for each tumor histology (agents targeting BRAF or MEK kinases and experimental agents are not permitted as physician's choice). Tumors must harbor either a MEK or atypical BRAF alteration. The specific histology/histologies and alterations to be included in this part will be selected based on available data from Part A and discussion with the clinical investigators, the medical monitor, and the sponsor.

The randomization information can be found in Section 8.3. In Part B, if a patient progresses on the physician's choice of treatment, then they may crossover to the ulixertinib arm.

6.2 JUSTIFICATION FOR DOSE

Based on the experience of the studies BVD-523-01 and BVD-523-02, 600 mg b.i.d. taken orally will be the starting dose for all patients initiating therapy with ulixertinib as a single agent.

6.3 NUMBER OF PATIENTS

Total enrollment for Part A is targeted at approximately 228 patients with 38 patients per group. Additional patients may be enrolled as appropriate.

Total enrollment for Part B is targeted to approximately 80-100 patients per histology with up to three histologies included, however, additional patients may be enrolled.

6.4 NUMBER OF STUDY SITES

The study will take place at sites within the United States. Approximately, up to 25 sites will be utilized, however, because the patient population is relatively rare, clinical sites may need to be added as qualifying patients are found. Clinical trial networks may be utilized. Each study site may enroll as many eligible patients as possible due to the relatively rare patient population.

6.5 STUDY DURATION AND END OF STUDY DEFINITION

The estimated duration of accrual is 21 months. The total duration of the study will be approximately 38 months.

A patient is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

7 STUDY POPULATION

7.1 INCLUSION CRITERIA

Patients must meet all of the inclusion criteria to be eligible:

1. Patients with a locally advanced or metastatic malignancy, that has progressed following systemic therapy for their disease, if available, or for which the patient is not a candidate or refuses.

2. Tumor harboring a MEK or atypical BRAF alteration.

3. Provided signed and dated informed consent prior to initiation of any study-related procedures that are not considered standard of care (SoC).

4. Male or female patients aged ≥18 years.

5. Patients must have measurable disease by RECIST version 1.1.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2.

7. Adequate renal function (using Cockcroft-Gault) [creatinine ≤1.5 times ULN (upper limit of normal)] or a glomerular filtration rate (GFR) of ≥50 mL/min.

8. Adequate hepatic function [total bilirubin ≤1.5 times ULN; AST (aspartate transaminase) and ALT (alanine transaminase) ≤3 times ULN or ≤5 times ULN if due to liver involvement by tumor].

9. Adequate bone marrow function (hemoglobin ≥9.0 g/dL; platelets ≥100 x 10^9 cells/L; absolute neutrophil count ≥1.5 x 10^9 cells/L).

10. Adequate cardiac function:

    - Left ventricular ejection fraction (LVEF) of >50% as assessed by multi-gated acquisition (MUGA) or ultrasound/echocardiography (ECHO); and
    - A corrected QT interval (QTc) <480ms by the Fridericia method (QTcF).

11. Contraception:

    a. For women: Negative pregnancy test for females of child-bearing potential; must be surgically sterile, postmenopausal (no menstrual cycle for at least 12 consecutive months), or compliant with a medically approved contraceptive regimen during and for 3 months after the treatment period. Abstinence is not considered an adequate contraceptive regimen.

    b. For men: Must be surgically sterile, or compliant with a medically approved contraceptive regimen during and for 3 months after the treatment period.

12. Willing and able to participate in the trial and comply with all trial requirements.

13. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational agent may be included after consultation with the medical monitor.

7.2 EXCLUSION CRITERIA

Patients who fulfill one or more of the following criteria will not be eligible for inclusion in this trial:

1. Gastrointestinal (GI) condition that could impair absorption of study medication (specific cases e.g., remote history of GI surgery, may be enrolled after discussion with the medical monitor) or inability to ingest study medication.

2. Uncontrolled or severe intercurrent medical condition.

3. Known uncontrolled brain metastases. Stable brain metastases either treated or being treated with a stable dose of steroids/anticonvulsants, with no dose change in the previous 4 weeks, can be allowed.

4. Having received any cancer-directed therapy (chemotherapy, hormonal therapy, biologic or immunotherapy, etc.) within 28 days or 5 half-lives (whichever is shorter) prior to the first dose of study drug. Patients previously treated with radiotherapy must have recovered from the acute toxicities associated with such treatment.

5. Major surgery within 4 weeks prior to first dose.

6. Any use of an investigational drug within 28 days or 5 half-lives (whichever is shorter) prior to the first dose of study drug. A minimum of 10 days between termination of the investigational drug and administration of study drug is required. In addition, any drug-related toxicity except alopecia should have recovered to Grade 1 or less.

7. Prior therapy with any ERK inhibitor (e.g. LY3214996, LTT462).

8. Groups 1-4: Prior therapy with any BRAF and/or MEK inhibitor (e.g. encorafenib, dabrafenib, vemurafenib, binimetinib, trametinib, cobimetinib) is excluded. Prior BRAF and/or MEK inhibitor therapy is permitted for Groups 5 and 6.

9. For Part B, agents targeting BRAF or MEK kinases and experimental agents are not permitted as physician choice.

10. Pregnant or breast-feeding women.

11. Any evidence of serious active infections. Patients are allowed to enroll if they have been fever-free for at least 48 hours and are on an active treatment that is not prohibited in Appendix 1.

12. Any important medical illness or abnormal laboratory finding that would increase the risk of participating in this study (based on the investigator's judgment).

13. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR).

14. Concurrent therapy with any other investigational agent.

15. Concurrent therapy with drugs known to be strong inhibitors or inducers of CYP1A2, CYP2D6, and CYP3A4.

7.3 SCREEN FAILURES

Screen failures are defined as patients who consent to participate in the clinical trial but who do not meet one or more criteria required for participation in the trial during the screening procedures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened (up to a maximum of 1 time for the same individual). Rescreened patients will be assigned a new subject identification number. Labs can be retested within the screening window and not count as a rescreen.

7.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential patients will be identified by investigators in the setting of their clinics. Potential patients may also be identified by Strata Oncology through their Strata Precision Oncology Network.

8 STUDY DRUG

8.1 STUDY DRUG(S) ADMINISTRATION

8.1.1 Study Drug Description

Ulixertinib (BVD-523) is a novel, reversible, ATP-competitive small molecule that potently inhibits both ERK1 and ERK2 protein kinases in the sub-nanomolar range, while not significantly inhibiting any of an array of kinases even at 1000-fold greater concentrations (Germann *et al*, 2017).

More information is available in the Investigator's Brochure for ulixertinib.

8.1.2 Dosing and Administration

Patients will initially receive 600 mg oral doses of the formulated blend formulation of ulixertinib. Ulixertinib is to be taken twice daily (b.i.d.) orally with at least 8 ounces of water for 28 days (a "Cycle"), at 12-hour ± 2 hour intervals. The study drug should be taken at approximately the same time each day with food. A patient that is observed to vomit an intact capsule after dosing in the clinic during the PK measurements may receive a substitute dose of drug. However, patients should be instructed NOT to take a substitute capsule if vomiting occurs after self-dosing at home. Missed doses should be skipped and not taken as a double dose at the next dosing timepoint.

Patients will be provided enough ulixertinib for a full cycle to self-administer at home.

8.1.3 Dose Interruptions and Adjustments

Patients experiencing unacceptable toxicity will have their treatment interrupted until the toxicity returns to ≤ Grade 1 or pre-treatment baseline (whichever is more severe). Resumption of ulixertinib may occur at a lower dose level, aligning with capsule dose availability. Such dose adjustments will be done in consultation with the investigators and medical monitor of the study.

If a non-treatment related AE or toxicity-related dose delay lasts for > 21 days, treatment will be discontinued permanently, and the patient should be removed from study treatment.

8.2 ACCOUNTABILITY/APPEARANCE/STORAGE

8.2.1 Acquisition and Accountability

Dispensing instruction will be provided in the Pharmacy Manual.

The investigator or study staff will verify the integrity of the clinical trial supplies (storage conditions, correct amount received, condition of shipment, kit numbers, etc.) according to their Standard Operating Procedures (SOP).

The following data will be tracked on the drug accountability log provided by the sponsor, and recorded in the eCRF:

- Date received
- Lot number
- Date dispensed
- Patient number

Records of study medication (used, lost, destroyed, and returned containers, individual capsules) should be made at each patient visit in the eCRF. Drug accountability and reconciliation will be checked by the site study monitor during site visits and at completion of study treatment.

Unless prohibited by investigational site's SOP, used study medication is to be retained until the monitor has verified drug accountability. Once the site monitor has verified drug accountability at the site, any drug remaining in opened dispensing containers will be destroyed. Unused and unopened study medication will be returned to the sponsor.

8.2.2 Formulation, Appearance, Packaging, and Labeling

Ulixertinib drug substance is manufactured according to cGMP as a mono-hydrochloride salt and is supplied as a formulated powder blend comprised of standard excipients to support the manufacturing processes that is encapsulated in a hard gelatin capsule. Capsules (white) contain 150 mg of ulixertinib calculated on free base content and are packaged in white high-density polyethylene (HDPE) bottles.

8.2.3 Product Storage and Stability

Information will be provided in the study manual.

8.3 RANDOMIZATION

Part A is designed as an open-label study. All patients in Part A will receive treatment with orally administered ulixertinib. Patients in Part B will receive either treatment with orally administered ulixertinib or the physician's choice of treatment in a 2:1 ratio. In Part B, if a patient progresses on the physician's choice of treatment then they may crossover to the ulixertinib arm.

Part B randomization will be performed as total enrollment rather than on a site basis. Randomization/enrollment in both parts will be performed by using Interactive Voice/Web Response System (IxRS). Once written consent has been given by the patient, all inclusion/exclusion criteria must be checked by the investigator in order to confirm eligibility prior to IxRS randomization/enrollment procedures. In Part B, the IxRS will randomly assign the patient to one of the two treatment arms (ulixertinib or

the physician's choice of treatment). In both parts, the IxRS will assign the patient a unique patient identification number. This patient identification number will then be reported on all eCRF pages and in any study documents.

8.4 STUDY DRUG COMPLIANCE

The investigator will dispense the study drug only for use by patients enrolled in the study as described in this protocol. The study drug is not to be used for reasons other than those described in this protocol.

The investigator or other study staff will supervise study drug treatment given in the clinic and instruct the patient on study drug self-administration. Patients will be asked to bring their study drug container with them at each visit and compliance with protocol-defined study drug intake will be checked by pill count. In case of non-compliance, the patients will be instructed again.

8.5 CONCOMITANT THERAPY AND RESCUE MEDICATION

A detailed history of medications, including prior anti-cancer therapies, and procedures will be documented for each patient. Concomitant medications (especially changes in medication, including any anti-cancer therapies) will be documented for each patient at each scheduled visit.

Necessary supportive care such as anti-emetics and anti-diarrheals, etc., will be allowed. Medications that are known to be strong inhibitors or inducers of CYP3A4, CYP2D6, and CYP1A2 are not permitted during the study (for list of non-permitted drugs, see Appendix 1).

If deemed necessary by the treating investigator and reviewed by the medical monitor, palliative radiation therapy for a single site of bone or brain metastasis is allowed provided that it is the only site of disease progression. The radiation field must not affect any of the target lesions designated for disease assessment. Protocol treatment will be held during radiation therapy and will be re-started after any acute toxicities have resolved.

All medications administered from 30 days prior to the commencement of study treatment (Day 1) through the end of the treatment period will be recorded on the eCRF. Any changes of dosages of medication will also be noted.

9 STUDY DRUG DISCONTINUATION AND PATIENT DISCONTINUATION/WITHDRAWAL

9.1 DISCONTINUATION OF STUDY DRUG

Discontinuation from the study drug does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in patient management is needed. Any new clinically relevant finding will be reported as an AE.

9.2 PATIENT DISCONTINUATION CRITERIA

Treatment is to be discontinued for any of the following reasons:

- Disease progression (at the discretion of the investigator). If brain or bone metastases develop while on study, patients may be permitted to continue on study, after discussion with the medical monitor, if the overall risk/benefit is still favorable.
- Unacceptable toxicity.
- Changes in the patient's condition which render the patient unacceptable for further treatment (at the discretion of the investigator).
- Investigator’s judgement.

Patients who have been discontinued from treatment should still be followed for survival.

9.3 PATIENT WITHDRAWAL FROM THE STUDY

Patients must be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent.
- Patient non-compliance (at the discretion of the investigator).
- Patient becomes pregnant (withdrawal is required).
- Patient is lost to follow-up.

Patients will also to be withdrawn at any time if the investigator concludes that it would be in the patient’s best interest for any reason. Protocol violations will not lead to patient withdrawal unless they constitute a significant risk to the patient’s safety.

Patients can voluntarily withdraw from the trial for any reason at any time. They are to be considered withdrawn if they state an intention to withdraw, fail to return for visits, became lost to follow up for any reason, or if any of the following occurs:

- Discovery of patient ineligibility.

- Missed / unscheduled / off-schedule / incomplete / incorrect assessments that result in patients being put at risk.

Patients who withdraw at any time preceding the last visit of Cycle 2 (Day 43) will constitute an early discontinuation, will not be replaced, and will be evaluated in the efficacy analysis. If patients withdraw due to progressive disease or AEs, replacement of such patients potentially introduces bias into the study. If a patient withdraws for other reasons, replacement of the patient will be decided by the Safety Monitoring Committee.

The investigator must determine the primary reason for a patient's withdrawal from the study and record this information on the eCRF.

9.4 LONG TERM FOLLOW UP

Upon discontinuation of study drug, patients will be followed for survival and the initiation of subsequent anticancer therapy for 18 months from the date of study therapy initiation. Patients that discontinue study treatment for any reason other than disease progression, must continue to have disease assessments every 8 weeks (± 7 days) until disease progression or the initiation of subsequent anticancer therapy.

Patients or their legally authorized representatives will be contacted every three months (± 7 days) until death, end of the study, or patient withdrawal of consent, whichever comes first. Survival and subsequent treatment status may be collected by public records, medical records, or by contacting the patient or their legally authorized representative by phone. All efforts should be made to contact the patient at these time points. Refer to Section 9.5 for Lost to Follow-Up guidelines.

9.5 LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if they fail to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions will be taken if a patient fails to return to the clinic for a required study visit:

- The site will attempt to contact the patient and reschedule the missed visit and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address). These contact attempts should be documented in the patient's medical record or study file.

- Should the patient continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10 STUDY ASSESSMENTS AND PROCEDURES

10.1 METHODS OF ASSESSMENT AND CRITERIA FOR EVALUATION

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventative actions that were taken to ensure that normal processes are adhered to as soon as possible.

All trial data will be recorded on the electronic case report forms (eCRFs). Blood and tissue biopsy specimens will be sent to a third-party laboratory vendor for analysis.

10.1.1 Demographic Data

Include date of birth (DOB), age, gender, race, and ethnicity.

10.1.2 Medical and Cancer History

A complete medical history will be obtained from each patient including the specifics of their advanced malignancy and molecular alterations. For female patients of child-bearing potential, the date of the last menstrual period will be noted. Smoking history and prior cancer therapy will be recorded. Data will be reviewed and updated at each visit.

10.1.3 Prior and Concomitant Medications

See Section 8.5.

10.1.4 Vital Signs and Physical Examination

Height should be recorded at screening only. Body weight should be recorded at each visit.

Vital sign records should include body temperature, systolic/diastolic blood pressure (BP), and pulse rate. BP should be assessed on the same arm during the study.

Full physical examination evaluations at screening should include general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations. Subsequent targeted physical exams should include body systems as appropriate.

Performance status (ECOG) should be assessed within 72 hours before start of study treatment and at each study visit (see Appendix 3).

10.1.5 Ophthalmology Examination

A full ophthalmic examination will be performed at the time points described in the SoA or when clinically indicated. They will include best-corrected visual acuity (BCVA), visual field examination (VF), intraocular pressure, external eye examination, and dilated fundoscopy. For additional details refer to study manual.

Any patient experiencing vision changes must stop taking ulixertinib and have an ophthalmic evaluation. Ulixertinib may be re-started when symptoms resolve.

10.1.6 Laboratory Assessments

The following clinical laboratory tests will be performed:

- **Hematology** (blood sample: EDTA) – hemoglobin, hematocrit, white blood cells (WBC) count with differential, red blood cells (RBC) count, and platelet count.
- **Blood Chemistry** (blood sample: serum) – albumin, alkaline phosphatase (ALP), total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, blood urea nitrogen (BUN), uric acid, lactic dehydrogenase (LDH), cholesterol, and triglycerides.
- If the total bilirubin concentration is increased above 1.5 times the upper normal limit, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
- **Urinalysis** – specific gravity, pH; semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood and a microscopic examination including RBC, WBC, and casts will be performed if the dipstick is abnormal.
- **Pregnancy** – Beta-hCG Qualitative Urine or Serum

After Cycle 2, clinical chemistry (to include calcium and inorganic phosphorus), hematology, and urinalysis may be performed once per cycle or more frequently at the investigator's discretion.

Blood chemistry will be analyzed at each trial center by a certified laboratory and a report of the laboratory values will be sent to the investigator. The investigator or designee will review the laboratory report after receipt of the results and assess the clinical significance of all abnormal values. Results must be reviewed prior to dosing and appropriate action taken for any clinically significant abnormal values. Values will be documented on the laboratory report until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study medication) or baseline.

Any laboratory value that remains abnormal at the end-of-study (EOS) and that is considered clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline.

10.1.7 Electrocardiogram (ECG)

All patients require a single 12-lead ECG measurement. The parameters to be recorded are QT, QTc, QTC F, PR, and QRS. A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. Patients should be supine for 5 minutes prior to the ECG.

Patients with a normal ECG in screening do not need to have repeat ECGs in subsequent cycles unless clinically indicated.

10.1.8 Echocardiogram (ECHO) or Multi-Gated Acquisition (MUGA)

LVEF will be assessed by ECHO or MUGA performed at screening and as clinically indicated.

10.1.9 Disease Status

The decision for body areas to be scanned will depend on the extent of disease. Disease assessments must include all known or suspected disease sites. Imaging will be performed on the abdomen, chest, pelvis, and the site of the primary tumor if elsewhere.

Tumor measurements based on physical examination will occur at baseline and on the first day of each treatment cycle. Tumor assessments will be made by CT/MRI/Physical Exam prior to dose initiation, at the 1st protocol-specified tumor measurement evaluation at the beginning of Cycle 2 and then every 2 cycles, and at End of Treatment. Patients that discontinue study treatment for any reason other than disease progression, must continue to have disease assessments every 8 weeks (± 7 days) until disease progression or the initiation of subsequent anticancer therapy. The schedule of tumor assessments should be fixed according to the calendar, starting with cycle one day one, regardless of treatment delays or interruptions due to toxicity. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

10.1.10 Tissue Biopsy

Tumor biopsy during the screening period and during Visit 5 (Day 28) of treatment in Part A is required. If a patient has undergone a biopsy within ≤ 6 months and has not received any anticancer treatment since undergoing the biopsy, archival tissue from this biopsy may be used to fulfill screening tissue requirements. Assays to investigate pharmacodynamic markers of ERK inhibition in addition to exploratory analysis to

evaluate adaptive response in pathways in addition to MAPK will be deployed. These may include, but are not limited to, RPPA, Nanostring, and RNA-exome. An optional tumor biopsy is requested at end of treatment; this is not a mandatory collection but strongly encouraged in patients relapsing following robust response to ulixertinib. Broad molecular profiling will be applied to end of treatment/at relapse tumor samples to aid scientific understanding of mechanisms of resistance to ERK inhibition.

10.1.11 Blood Samples for Pharmacokinetic (PK) Analysis

In Part A only, plasma samples will be collected for PK analysis at Visit 4, pre-dose. Patients need to be at steady state for this collection, which means 10 consecutive doses, or 5 consecutive days.

10.1.12 Blood Samples for Pharmacodynamic (PD) and ctDNA Analysis

In Part A only, blood samples will be collected for PD and ctDNA analysis at Baseline and Visit 4. Samples for ctDNA will also be collected at Visit 5 and End of Treatment.

Blood samples for pharmacodynamic analyses will be taken from all patients in Part A until the sponsor determines sampling may be discontinued based on accumulated patient experience.

10.1.13 Adverse Events

Toxicity/severity of AEs will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grading System, Version 5.0, as detailed on web page: http://ctep.cancer.gov.

Also see Section 10.6.

10.2 CRITERIA FOR EVALUATION

10.2.1 Efficacy

Overall response rate (ORR), duration of response (DOR), and progression free survival (PFS) are primary or secondary objectives and will be evaluated by standard RECIST v1.1 criterion per local investigator's assessment and, for Part B only, independent, third-party review.

The response criteria for target lesions are defined as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for Progressive Disease, taking as reference the smallest sum diameters while on study.

10.2.2 Pharmacokinetics (PK)

- Blood samples will be collected to measure ulixertinib (BVD-523) and selected metabolite pharmacokinetic parameters.
- If a patient changes doses, an additional blood sample will be collected at steady state (for each dose level a patient experiences).

10.2.3 Circulating Tumor DNA

- Blood samples will be collected to measure circulating tumor DNA, including, but not limited to, BRAF and MEK alterations.

10.2.4 Pharmacodynamics (PD)

- Evaluation of tissue biopsies, and/or blood to assess biomarkers such as dual-specificity phosphatase (DUSP), RSK, and c-Myc.
- Additional biomarkers may be identified and measured as appropriate.

10.3 DESCRIPTION OF STUDY VISITS FOR PATIENTS RECEIVING ULIXERTINIB

10.3.1 Description of Study Visits for Cycle 1

Procedures performed in the first cycle are specified in the Schedule of Activities (SoA). Patients receiving multiple cycles of treatment will not have blood drawn for PK and PD measurements after Cycle 1 unless additional PK and PD data are deemed necessary after initial analysis or the patient changes dose.

10.3.1.1 Visit 1 (Day -28 to -1); Screening

The following procedures will be performed at Visit 1 (Screening):

- Obtain written informed consent (before start of any study-related procedures that are not considered Standard of Care) including optional consents (Note: informed consent may be obtained up to -28 days to allow flexibility in scheduling of the screening procedures).

- Evaluate all inclusion and exclusion criteria to ensure that patients meet all inclusion criteria and none of the exclusion criteria.
- Record demographic data including date of birth (DOB), age, gender, race, and ethnicity. Where full DOB is collected, initials will not be used.
- Review medical history including all previous cancer treatments, best response to those cancer treatments, and reason for stopping them.
- Record prior and concomitant medications including start/stop dates, indication, dose, toxicities, and frequency taken within 30 days of Cycle 1, Day 1.
- Measure and record height and weight.
- Record vital signs. Measure body temperature, systolic / diastolic BP, and pulse rate.
- Perform and record physical examination.
- Assess and record performance status (ECOG) within 72 hours before start of treatment.
- Perform and record ophthalmology examination (ulixertinib patients only).
- Collect blood for a serum pregnancy test for female patients who are not postmenopausal or surgically sterile. If positive, repeat and confirm results prior to Visit 2. A second positive test will result in exclusion of the patient from the study.
- Collect blood samples for blood chemistries, hematology, and calculated creatinine clearance (using Cockcroft-Gault) within 72 hours before start of treatment. Analyze, review, and report any clinically significant abnormalities to the medical monitor before dosing.
- Collect urine samples for urinalysis within 72 hours before start of treatment.
- Obtain a 12-lead electrocardiogram (ECG), and echocardiogram (ECHO) or multi-gated acquisition (MUGA) for left ventricular ejection fraction (LVEF).
- Assess and record current disease status within 28 days. Tumor assessments will be made by CT/MRI/Physical Exam.
- PART A only: Tissue biopsy within -28 days of Visit 1 (required unless investigator and medical monitor deems collection inadvisable). If a patient has undergone a biopsy within ≤ 6 months and has not received any anticancer treatment since undergoing the biopsy, archival tissue from this biopsy may be used to fulfill screening tissue requirements.
- Complete Screening/Enrollment Form and submit to medical monitor for review prior to treatment of patient.
- For Part B only, prior to Visit 2, obtain a randomization code as outlined in Section 8.3.

10.3.1.2 Visit 2 (Day 1 ± 0); Baseline/Drug Dispensing/Initiation of Treatment

The following procedures will be performed at Visit 2 (Baseline):

- Review Screening/Enrollment Form to confirm consent to enroll was obtained from medical monitor or sponsor.
- Review all inclusion and exclusion criteria to ensure that patients meet all inclusion criteria and none of the exclusion criteria.
- Review medical history for any changes since Screening Visit.
- Record medications including start/stop dates, indication, dose, toxicities, and frequency for any changes since Screening Visit.
- Measure and record weight.
- Record vital signs. Measure body temperature, systolic / diastolic BP, and pulse rate.
- Assess and record performance status (ECOG), if not done during Screening Visit, within 72 hours of start of treatment.
- ONLY if the screening pregnancy test was performed more than 1 day previously, collect blood for a repeat serum pregnancy test for female patients who are not postmenopausal or surgically sterile.
- Collect pre-dose blood samples for blood chemistries, hematology and creatinine clearance if not done during Screening Visit within 72 hours of start of treatment.
- Collect pre-dose urine samples for urinalysis.
- PART A only: Collect pre-dose blood samples for pharmacodynamic (PD) and ctDNA analyses.
- Administer first dose of ulixertinib.
- PART A only: Collect 4-hour (± 10 minutes) post-dose blood samples for pharmacodynamic analyses.
- Assess and record AEs.
- Dispense study drug and instruct patients how to take study drug, daily every 12 hours ± 2 hours with at least 8 ounces of water and food.
- Inform patients of the potential photosensitizing effects of ulixertinib and instruct them to avoid sunlight and wear protective clothes, sunglasses, and apply sunblock when outside, including when driving a car.

10.3.1.3 Visit 3 (Day 8 ± 3)

The following procedures will be performed at Visit 3:

- Review medical history.
- Record concomitant medications including start/stop dates, indication, dose, toxicities, and frequency taken after Visit 2.

- Measure and record weight.
- Record vital signs. Measure body temperature, systolic / diastolic BP, and pulse rate.
- Assess and record performance status (ECOG).
- Collect blood samples for blood chemistries, hematology, and creatinine clearance.
- Collect urine samples for urinalysis.
- Assess and record AEs.
- Obtain all unused study drug from patient.
- Assess study drug compliance by pill count.
- Dispense drug supply for self-dosing and remind patients of dosing instructions.

10.3.1.4 Visit 4 (Day 15 ± 3)

The following procedures will be performed at Visit 4:

- Review medical history.
- Record concomitant medications including start/stop dates, indication, dose, toxicities, and frequency taken after Visit 3.
- Measure and record weight.
- Record vital signs. Measure body temperature, systolic / diastolic BP, and pulse rate.
- Assess and record performance status (ECOG).
- Collect blood samples for blood chemistries, hematology, and creatinine clearance.
- PART A only: Collect pre-dose trough blood samples for pharmacokinetic (PK), pharmacodynamic (PD), and ctDNA analyses. These assessments should be collected when the patient reaches steady state. Steady state refers to patients who have received at least 5 days, or 10 consecutive doses, of investigational product. If patients are not at steady state, these assessments will be rescheduled and completed at the next visit in which steady state is achieved.
- Administer first daily dose of ulixertinib.
- PART A only: Collect 4-hour (± 10 minutes) post-dose blood samples for pharmacodynamic analyses.
- Collect urine samples for urinalysis.
- Assess and record AEs.
- Obtain all unused study drug from patient.
- Assess study drug compliance by pill count.
- Dispense study drug supply for self-dosing.

10.3.2 Description of Study Visits for Cycle 2

10.3.2.1 Visit 5 (Day 29 ± 3, first day of Cycle 2)

The following procedures will be performed at Visit 5:

- Review medical history.
- Record concomitant medications including start/stop dates, indication, dose, toxicities, and frequency taken after Visit 4.
- Measure and record weight.
- Record vital signs. Measure body temperature, systolic / diastolic BP, and pulse rate.
- Assess and record performance status (ECOG).
- PART A only: Tissue biopsy (required unless investigator and medical monitor deems collection inadvisable).
- PART A only: Collect blood samples for ctDNA.
- Collect blood samples for blood chemistries, hematology, and creatinine clearance.
- Collect urine samples for urinalysis.
- Perform urine pregnancy test for female patients who are not postmenopausal or surgically sterile. If urine test is positive, collect blood for a serum pregnancy test. If serum pregnancy test is positive, withdraw patient from study and contact the medical monitor.
- Assess and record AEs.
- Obtain all unused study drug from patient.
- Assess study drug compliance by reviewing pill count.
- Assess and record disease status (every 2 cycles).
- Dispense study drug supply for self-dosing. Extra doses may be dispensed at the investigator's discretion to ensure continuous dosing.

10.3.2.2 Visit 6 and 7

Cycle 2 visits 6 and 7 procedures are similar to Cycle 1 visit 3, although no pharmacokinetic or pharmacodynamic measurements will be made unless specifically requested by investigator or the patient changes dose level.

10.3.3 Cycle 3 and Subsequent Cycles Visit (Day 1 ± 3 of each cycle)

Cycle 3 and subsequent cycles have one scheduled visit per cycle. No pharmacokinetic or pharmacodynamic measurements will be made unless specifically requested by the investigator or the patient changes dose level.

The following procedures will be performed at the Cycle 3 and Subsequent Cycles Visit:

- Review medical history.
- Record concomitant medications including start/stop dates, indication, dose, toxicities, and frequency taken since previous visit.
- Measure weight.
- Record vital signs. Measure body temperature, systolic / diastolic BP, and pulse rate.
- Assess and record performance status (ECOG).
- Collect blood samples for blood chemistries, hematology, and creatinine clearance.
- Collect urine samples for urinalysis.
- Perform urine pregnancy test for female patients who are not postmenopausal or surgically sterile. If urine test positive, test, collect blood for a serum pregnancy test.
- Assess and record disease status (every 2 cycles).
- Assess and record AEs.
- Obtain all unused study drug from patient.
- Assess study drug compliance by reviewing pill count.
- Dispense study drug supply for self-dosing. Extra doses may be dispensed at the investigator's discretion to ensure continuous dosing.

10.3.4 Description of Study Visits for Patients Enrolled in Part B and Receiving Physician's Choice of Treatment

Study procedures for patients enrolled in Part B and randomized to physician's choice of treatment will be the similar to those for patients receiving ulixertinib; however, no pharmacokinetic or pharmacodynamic samples will be collected in Part B, and an ophthalmology examination will be performed only for patients receiving ulixertinib. Appropriate SoC monitoring can be completed at the discretion of the investigator. If clinical experience gained in Part A requires significant deviations in Part B from the procedures in Part A, these changes will be addressed in a protocol amendment.

10.3.5 End of Treatment Visit

At the time of study drug discontinuation, the End of Treatment (EOT) Visit should be completed for all patients within 14 ± 3 days after the last dose of study drug, and every effort should be made to perform the procedures required. The following procedures will be performed at EOT Visit:

- Review medical history.
- Record concomitant medications including start/stop dates, indication, dose, toxicities, and frequency taken since previous visit.
- Measure and record weight.

- Record vital signs. Measure body temperature, systolic / diastolic BP, and pulse rate.
- Assess and performance status (ECOG).
- PART A only: Collect blood samples for ctDNA.
- PART A only: Tissue biopsy, optional, but strongly encouraged.
- Collect blood samples for blood chemistries, hematology and creatinine clearance.
- Collect urine samples for urinalysis.
- Perform urine pregnancy test for female patients who are not postmenopausal or surgically sterile. If urine test is positive, collect blood for a serum pregnancy test.
- Assess and record disease status.
- Assess and record AEs.
- Obtain all unused study drug from patient.
- Assess study drug compliance by reviewing pill count.
- Complete end of treatment form.

10.3.6 Safety Follow-Up Assessment

Patients will return to the clinic or will be contacted for a safety follow-up assessment 30 days ± 3 days after the last dose of study drug was taken; or earlier if subsequent therapy for advanced malignancy is initiated prior to 30 days ± 3 days. Only information about AEs and SAEs will be collected at this visit.

10.3.7 Follow Up

Patients will be followed for survival and the initiation of subsequent anticancer therapy for 18 months from the date of study therapy initiation, as outlined in Section 9.4.

Patients that discontinue study treatment for any reason other than disease progression, must continue to have disease assessments every 8 weeks (± 7 days) until disease progression or the initiation of subsequent anticancer therapy.

10.3.8 Unscheduled Visits

Additional visits can be performed as appropriate and at the discretion of the investigator. All unscheduled study visits, procedures, examinations, clinical laboratory evaluations etc., will be noted in the patient's medical record and the eCRF including:

- Reason for visit/procedure.
- Follow-up.

- Recording of AEs and use of concomitant measures.

10.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

10.4.1 Definition of Adverse Events (AE)

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening, need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AE information will be elicited by asking the patient a non-leading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?”. AEs should be reported on the appropriate page of the eCRF.

10.4.2 Definition of Serious Adverse Events (SAE)

A Serious Adverse Event (SAE) is any untoward medical occurrence that occurs at any dose (including after the ICF is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent AE are not considered SAEs.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period (see below). If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event should be reported using the term “disease progression” with a CTCAE severity of Grade 5.

10.4.3 Classification of an Adverse Event

10.4.3.1 Severity of an Event

The severity of the AE will be graded according to the NCI CTCAE Grading Scale Version 5.0 (see the NCI CTCAE web page at http://ctep.cancer.gov for details). For AEs not covered by NCI CTCAE, the severity will be characterized according to the following definitions:

- Mild events are usually transient and do not interfere with the patient’s daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient’s usual daily activities.
- Life-threatening events require urgent intervention.
- Fatal events result in the patient’s death.

10.4.3.2 Relationship to Study Drug

The investigator will make a judgment regarding whether or not the AE was related to study drug, as outlined below, and in accordance with FDA guidance of 2012.

Unrelated	The AE is unlikely to have been caused by study drug.
Possibly related	It is unclear whether the AE may have been caused by study drug, but there is at least a reasonable possibility of a relationship, or a relationship cannot be ruled out.
Related	The AE is likely to have been caused by study drug.

10.4.3.3 Expectedness

The CRO DSPV group and CRO medical monitor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study drug, as documented within the most recent version of the Investigator’s Brochure.

10.4.4 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care, or upon review by a study monitor. At each study visit, the investigator or their designee will inquire about the occurrence of AE/SAEs since the last visit.

Any medical condition that is present at the time that the patient is screened will be considered as baseline and not reported as an AE. However, if the study patient's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All reportable events will be recorded with start dates occurring any time after informed consent is obtained through and including 30 calendar days after the last administration of ulixertinib. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the study product is suspected. If the patient begins a new anti-cancer therapy, the safety reporting period ends at the time the new treatment is started, however, death must always be reported when it occurs during the 30-day reporting period irrespective of intervening treatment.

All events will be followed for outcome information in accordance with good medical practice until they are resolved, stabilize, or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related (possibly related, related) must be followed until resolution or until stabilization.

10.4.4.1 Post-Study Adverse Events and Serious Adverse Events

All unresolved AEs will be followed by the investigator until the events are resolved (see Section 10.4.4), the patient is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to participation in this study. Prior to the conclusion of the study at the site, the investigator should notify the designated CRO safety team (see Section 10.4.6) of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. After study conclusion the investigator should notify BioMed Valley Discoveries, Inc., or their CRO designee, of any death or AE they are aware of occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. BioMed Valley Discoveries, Inc., should also be notified if the investigator should become aware of the development of cancer or of a

congenital anomaly in a subsequently conceived offspring of a person that has participated in this study.

10.4.5 Adverse Event Reporting

All AEs, including local and systemic reactions, not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, investigator's assessment of severity, seriousness, relationship to the study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single diagnosis. The action taken and the outcome must also be recorded. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

10.4.6 Serious Adverse Event Reporting

All SAEs must be entered into the eCRF within 24 hours of first knowledge of the event by study personnel. It is important that the investigator provide their assessment of relationship to study drug at the time of the initial report. Follow-up information must also be reported within 24 hours of first knowledge. Entry of an SAE (or updated SAE information) into the eCRF will trigger an automatic alert to the designated CRO safety team. Timely notification of an event supersedes the requirement to have all information at the time of the initial report.

If the EDC system is **not available**, the investigator must send a completed paper SAE Report Form to the CRO safety team via email or fax as follows, within 24 hours. If no acknowledgement is received within one working day, the report should be re-submitted.

Safety Report Email Address: sae@cmedresearch.com

Safety Report Fax No.: 866.240.8830 (US) or +44 1403 330459 (international)

The SAE data must be entered into the eCRF as soon as it becomes available.

The following information must be reported on the eCRF SAE report form:

- Protocol number
- Site and/or Investigator number
- Patient number
- Demographic data
- Brief description of the event

- Onset date and time
- Resolution date and time, if the event resolved
- Current status, if event not yet resolved
- Any concomitant treatment and medication
- Investigator's assessment of whether the SAE was related to investigative product or not
- Outcome of the event if available

The CRO safety team will contact the site for clarification of data entered onto the eCRF, or to obtain missing information. In the event of questions regarding SAE reporting, the site may contact Cmed Drug Safety and Pharmacovigilance via email sae@cmedresearch.com.

Unexpected serious suspected adverse reactions are subject to expedited reporting to FDA. The CRO safety team is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the FDA and to investigators participating in ongoing clinical studies with the study medication, according to 21 CFR 312.32 and the applicable guidance documents. All investigators participating in ongoing clinical studies with the study medication are responsible for prompt submission of these reports to their Institutional Review Board (IRB) or Ethics Committee (EC).

10.4.7 Overdose

No information on treatment of overdose of ulixertinib is currently available. In the event of an overdose, within 24 hours of awareness, the overdose should be reported as an AE and the medical monitor should be notified. All overdose cases will be discussed by the sponsor and medical monitor on a case-by-case basis.

10.4.8 Reporting of Pregnancy

Each pregnancy in a patient or partner of a patient on ulixertinib must be reported to the designated CRO safety team within 24 hours of learning of its occurrence, on a Pregnancy Notification Form and via the contact details noted in Section 10.4.6. If a patient becomes pregnant, study drug administration must be discontinued immediately. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Follow-up and documentation must occur even if the patient withdraws from the study or the study is completed.

Pregnancy per se is not considered an AE unless there is cause to believe that the study drug may have interfered with the effectiveness of a contraceptive medication.

Hospitalization for normal delivery of a healthy newborn should not be considered a SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported as such.

The avoidance of pregnancy or fathering a child is suggested for 3 months following the discontinuation of ulixertinib therapy. No information is currently available regarding the effects of ulixertinib on fertility, gestation or subsequent child development.

Any pregnancy within 3 months after the last study drug administration should be reported to the study investigator and to the CRO.

11 STATISTICAL CONSIDERATIONS

11.1 STATISTICAL ANALYSIS PLAN

A formal detailed statistical analysis plan (SAP), covering statistical analyses planned for Part A and Part B, will be developed and finalized prior to the main analysis of Part A data. This section is a summary of the planned statistical analyses at the time of protocol development.

A separate analysis plan will be developed specifically for the safety reviews to be conducted by the SMC.

11.2 SAMPLE SIZE DETERMINATION

11.2.1 Part A

Approximately 38 patients will be recruited into each group in Part A.

With 34 patients in a group and assuming the true ORR is 40%, there is approximately 80% power to reject the null hypothesis that the true ORR is ≤ 20% in that group, with a 1-sided alpha of 5%. Assuming a 10% drop out rate, up to 38 patients will be recruited in each group.

11.2.2 Part B

It is not possible to accurately calculate the required sample size until the histologies of interest have been confirmed. Once the histologies of interest have been confirmed these calculations will be repeated and the final sample size confirmed.

Approximately 80-100 patients will be randomized, using a 2:1 ratio, for each histology group in Part B.

Using a 2-sided, log-rank test with a 5% alpha, and assuming a median PFS of 1.7 to 8.5 months (depending on histology) in the physician's choice arm and twice as long on the ulixertinib arm, approximately 80 to 100 patients will be required in each group to achieve 80% power to show a statistically significant difference between the arms. This also assumes that each group will take approximately 24 months to accrue and the analysis is expected to be performed 18 months following the last patient accrued. The anticipated loss to follow-up is estimated to be 10%.

11.3 RANDOMIZATION

Part A of this study is open-label, and all patients enrolled in Part A will be treated with ulixertinib.

Part B of this study is open-label, patients will be randomly assigned to receive either ulixertinib or the physician's choice of treatment in a 2:1 ratio. Also see Section 8.3.

11.4 ANALYSIS SETS

11.4.1 Full Analysis Set

The full analysis set (FAS) will consist of all patients who received at least one dose of study medication. This analysis set will be used for all efficacy analyses.

For Part B, analyses performed on the FAS will allocate patients' treatment group as randomized.

11.4.2 Safety Analysis Set

The safety analysis set will consist of all patients who received at least one dose of study medication. This analysis set will be used for all safety analyses.

For Part B, analyses performed on the safety population will allocate patients' treatment group as actually received.

11.4.3 Per Protocol Analysis Set

The per-protocol (PP) analysis set will consist of all patients of the FAS who completed the study without any major protocol deviations.

11.5 DATA PRESENTATION

Descriptive statistics for continuous variables will include the number of patients, mean, standard deviation, median, minimum, maximum; frequencies and percentages will be displayed for categorical data.

Summary data will be provided separately for Part A and Part B, and by group/tumor histology.

Data will be analyzed using the SAS system software version 9.4 (or later).

11.5.1 Demographic

Demographic characteristics of patients will be summarized in appropriate tables and with descriptive statistics.

The following characteristics will be summarized in the FAS, PP, and safety analysis sets:

- Age
- Gender
- Race
- Ethnicity
- Advanced malignancy information including relapsed or refractory status
- MEK or Atypical BRAF alteration

11.5.2 Baseline Characteristics

Baseline characteristics will be summarized in appropriate tables and with descriptive statistics.

The following characteristics will be summarized in the FAS, PP, and safety analysis sets:

- Body weight
- Height
- ECOG performance status
- Previous cancer therapies

11.5.3 Medical History and Physical Examination

Medical history and physical examination assessments will be summarized in appropriate tables and with descriptive statistics, in the FAS, PP, and safety analysis sets.

11.5.4 Concomitant Medications or Treatments

The number and percentage of patients taking prior and concomitant medications will be summarized by therapeutic class and preferred term using descriptive statistics. All data will be recorded as follows:

- Prior medication: ended before first day of study drug.
- Concomitant medication: ongoing at first day of study drug or started after first day of study drug.

11.5.5 Efficacy Analysis

All efficacy analyses will be performed using the FAS.

11.5.5.1 Part A

The primary endpoint for Part A is the overall response rate (ORR) within a group. It will be defined as the percentage of patients achieving a BOR of confirmed CR and/or PR as assessed by the investigator. The ORR will be presented with its 95% confidence intervals (CIs).

All response assessments will be presented using swimmer plots and will be listed by patient.

Sensitivity analyses of the primary analysis will include similar analyses using PP analysis set.

Analyses of secondary efficacy endpoints will include Kaplan-Meier estimates and curves, median DoR and respective 95% CIs for analysis of:

- Duration of response (DoR): time from first response to disease progression or death. Patients with no event will be censored at the last available tumor assessment. This analysis will be based on investigator assessment.
- Progression-free survival over 18 months (PFS): time from first day of trial medication to disease progression or death. Patients with no event will be censored at the last available tumor assessment. This analysis will be based on investigator assessment.
- Overall survival over 18 months (OS): time from first day of trial medication to death. Patients with no event will be censored at the last date the patient is known to be alive.

11.5.5.2 Part B

The primary endpoint for Part B is the Progression-Free Survival over 18 months (PFS), defined as time from first day of trial medication to disease progression as adjudicated by the independent review committee or death. Patients with no event will be censored at the last available tumor assessment. PFS will be analyzed using Kaplan-Meier estimates and curves, median PFS and respective 95% CIs.

For each histology, PFS curves will be compared between ulixertinib and physician's choice of treatment using Log Rank Test. The hazard ratio including 95% CI will be calculated by Cox's Proportional Hazards model.

Sensitivity analyses of the primary analysis will include similar analyses based on investigator response assessment and using PP analysis set.

Analyses of secondary efficacy endpoints will include analyses similar to PFS analysis for:

- Overall survival over 18 months (OS): time from first day of trial medication to death. Patients with no event will be censored at the last date the patient is known to be alive.
- Duration of response (DoR): time from first response to disease progression or death. Patients with no event will be censored at the last available tumor assessment. This analysis will be based on assessment as adjudicated by the independent review committee and replicated on investigator assessment.
- Overall response rate (ORR), defined as the percentage of patients achieving a BOR of confirmed CR and/or PR, will be presented with its 95% CIs and compared between ulixertinib and physician's choice of treatment using a Chi-square test. This analysis will be based on assessment as adjudicated by the independent review committee and replicated on investigator assessment.

11.5.6 Pharmacokinetic (PK) / Pharmacodynamic (PD) Data

Pharmacokinetic parameters of ulixertinib (BVD-523) and selected metabolites will be measured on Visit 4 (Day 15) in Part A only, this will be a single time-point collection prior to taking study drug on this day (trough at steady state).

Pharmacokinetic values will be presented in by-patient listings, sorted by site, patient identifier, and dose.

In Part A only, the effects of ulixertinib on pharmacodynamic markers will be evaluated. Collections will include ctDNA, tissue biopsies and/or blood to assess biomarkers. Assays include, but are not limited to, phosphorylation of RSK from whole blood, Reverse Phase Protein Arrays (RPPA) to assess protein levels, e.g. DUSP 4/6, plus Nanostring and/or RNA-exome to assess mRNA expression in tissue pre- and post-ulixertinib treatment. Biomarkers will be explored and listed as appropriate.

11.5.7 Safety Analysis

All safety summaries will be provided for the safety analysis set.

11.5.7.1 Adverse Events (AE)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class, High-Level Group Term, High Level Term, Preferred Term, and Lower-Level Term will be attached to the clinical database.

AEs will be summarized based on the date of onset for the event. Summaries (number and percentage of patients) of treatment-emergent AEs will be provided by System Organ Class and Preferred Term, by group/tumor histology and overall.

Treatment-emergent adverse event (TEAE) is defined as any AE that emerges during treatment having been absent pre-treatment or worsens relative to the pre-treatment state.

Events that are considered study drug-related, deaths, SAEs, and AEs resulting in study drug discontinuation will also be tabulated by System Organ Class and Preferred Term.

A tabulation will also be provided that summarizes treatment-emergent AEs by maximum severity (i.e., CTCAE grade).

All AEs, including treatment-emergent and non-treatment-emergent AEs, will be listed in patient data listings.

11.5.7.2 Laboratory Evaluations

The parameters associated with the clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be summarized with descriptive statistics by visit and

for the change from baseline to each planned post-baseline visit, by group/tumor histology and overall. Listings of all laboratory results and reference ranges will be provided.

Graded laboratory abnormalities will be defined using the grading scheme based on NCI CTCAE (v5.0) and summarized by group/tumor histology and overall. Shift tables will also be produced for gradable parameters based on the baseline CTCAE grade and the maximum CTCAE grade.

11.5.7.3 Other Safety Evaluations

Changes in the patient's ECOG status and vital sign parameters will be summarized by group/tumor histology and overall, and any abnormal values will be tabulated.

Listings of all data related to the patient's ECOG status, physical examination findings, vital signs and ECG will be provided.

11.6 INTERIM ANALYSIS

No formal interim analyses are planned.

The data from Part A will be analyzed at the end of Part A, and the data from Part B will be analyzed at the end of Part B.

11.7 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, the IRB/EC, and the Health Authorities.

Changes to the statistical analyses will be documented in a SAP change log and in the clinical study report.

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

12.1.1 Informed Consent Process

12.1.1.1 Consent and Other Informational Documents Provided to Patients

Consent forms describing in detail the study drug, study procedures, and risks are given to the patient and written documentation of informed consent is required prior to performing any study-related assessment which isn't standard of care. Consent forms will be reviewed and approved by the appropriate IRB/EC prior to being given to potential participants.

12.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the patient agreeing to participate in the study and continues throughout the patient's study participation. Consent forms will be approved by an Institutional Review Board (IRB) and the patient will be asked to read and review the document. The investigator or designee will explain the research study to the patient and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient's comprehension of the purposes, procedures, and potential risks of the study and of their rights as a research participant. The patient will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patient should have the opportunity to discuss the study with their family or surrogates and think about it prior to agreeing to participate. The patient will sign the informed consent document prior to any procedures being done specifically for the study. The patient must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the patient for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the patient undergoes any study-specific procedures. The rights and welfare of the patient will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

12.1.2 Study Discontinuation and Closure

It is agreed that for reasonable cause, either the investigator or the sponsor may temporarily suspend or prematurely terminate this study or the investigator's participation in this study, provided a written notice is submitted at a reasonable time

in advance of intended suspension or termination. If discontinuation is by the investigator, notice is to be submitted to BioMed Valley Discoveries, Inc. If discontinuation is by the sponsor, notice will be provided to each investigator. If the study is suspended or prematurely terminated, the investigator will promptly inform the study patients, IRB, and the sponsor will provide the reason(s) for the suspension or termination. Study patients will be contacted, as applicable, and be informed of changes to the study visit schedule.

If a severe local reaction or drug-related SAE occurs at any time during the study, the Safety Monitoring Committee will review the case immediately.

If one or more patients at any dose level develop any of the following adverse events deemed to be possibly, probably or definitely related to ulixertinib by the investigator and/or medical monitor, based upon close temporal relationship or other factors, the study will be immediately suspended and no additional ulixertinib doses will be administered pending review and discussion of all appropriate study data by the SMC:

- Death
- Anaphylaxis (angioedema, hypotension, shock, bronchospasm, hypoxia, or respiratory distress)

The study will not be restarted until all parties have agreed to the course of action to be taken and the Institutional Review Boards/Ethic Committees (IRBs/ECs) have been notified.

12.1.3 Confidentiality and Privacy

Patient confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to patients. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

The study patient’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be

kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Patient's data collected on eCRFs during the trial will be documented in a deidentified fashion and the patient will only be identified by the patient number, and/or by the patient's initials, if also required. The study data entry and study management systems used will be secured and password protected. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, all parties are bound to keep this information confidential.

The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the trial patients. All parties involved in the study will maintain strict confidentiality to assure that neither the person nor the family privacy of a patient participating in the trial is violated. Likewise, the appropriate measures shall be taken to prevent access of non-authorized persons to the trial data.

12.1.4 Future Use of Stored Specimens and Data

With the patient's approval and as approved by local IRBs, de-identified biological samples will be stored for future analysis as warranted by the rapidly-advancing understanding in this field. During the conduct of the study, an individual patient can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biological specimens' storage may not be possible after the study is completed.

Collected samples may be transferred for analysis to the sponsor, or to other laboratories working for the sponsor.

Biological samples will be stored for the time established by regulatory requirements or destroyed after the final clinical study report has been finalized if storage is not required. There might be a new request for these samples to be used for purposes related to the quality assurance of the laboratory tests described in this protocol, in which case they will be used for this purpose. This may include the assessment of the quality of current tests, the maintenance or improvement of these tests, the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.

If study results suggest that further investigations using stored biological samples are warranted, these tests might be carried out on an exploratory basis. In addition, biological samples may be used by the sponsor or their research partners for further research that is not related to the disease or the product under study. This testing will be done on anonymized samples (meaning that any identification linking the patient to the sample is destroyed). Patients will be asked to sign an additional, separate

consent form for this optional testing and refusal of consent will not affect their possibility of participating in the study.

12.1.5 Key Roles and Study Governance

12.1.5.1 Safety Oversight

An internal Safety Monitoring Committee (SMC) will be set up to review the safety of ulixertinib as the study progresses. The SMC will consist of clinical investigators, the CRO medical monitor, and sponsor representatives. The SMC will review any AEs and SAEs that occur during the study and will examine the safety of ulixertinib, including toleration of the starting dose, dose interruptions, dose reductions, and toxicities that may occur in later cycles of treatment.

The safety review will be performed at regular intervals, at least semi-annually to access safety and efficacy data.

The entire study or treatment of individual patients may be stopped under defined circumstances as outlined in Section 9.

12.1.5.2 Independent Imaging Review

In Part B only, a central imaging vendor selected by the sponsor will review radiological findings and determine response assessments (in accordance with RECIST 1.1).

12.1.5.3 Clinical Monitoring

Site monitoring is conducted to ensure that the rights and well-being of trial patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirements.

Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

A clinical monitoring plan (CMP) will be developed by the sponsor's CRO.

During the course of the study, a site monitor will conduct routine site visits to review protocol compliance, compare eCRF entries with individual patient's original source documents (accessed by the investigator), assess product accountability and ensure the study is conducted according to applicable regulatory requirements. The review of

the patient's original medical records shall be performed in a manner which ensures patient confidentiality is maintained.

The investigator shall permit the site monitor to review study data as frequently as deemed necessary to ensure that data are recorded in an adequate manner and that protocol adherence is satisfactory.

The investigator may not enroll patients into the study until such time that an initiation visit, or with the agreement of the sponsor, attendance at the investigator meeting, has been performed by the site monitor to conduct a detailed training of the protocol and eCRF.

12.1.5.4 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted, data are generated, biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/sponsor's designee, and inspection by local and regulatory authorities. Key trial personnel must be available to assist monitors during visits.

12.1.6 Auditing Procedure

In addition to the routine monitoring procedures, the sponsor or the regulatory authority can conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of GCP.

The investigator agrees that representatives of the sponsor and regulatory authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

12.1.7 Data Handling and Record Keeping

12.1.7.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each patient enrolled in the study. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents. All information on eCRFs must be traceable to source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the eCRFs, which will be documented as being the source data. All data requested on the eCRF must be entered and all missing data must be accounted for.

Clinical data and clinical laboratory data will be entered into a 21 CFR Part 11 compliant electronic data capture system. The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.1.7.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

Study documents include:

- IRB/EC approvals for the study protocol and all amendments
- All source documents and laboratory records
- CRF copies (electronic copies on a CD-ROM)
- Patients' informed consent forms (with study number and title of trial)
- FDA form 1572
- Any other pertinent study document

12.1.8 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or study manual requirements. The noncompliance may be either on the part of the patient, investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents. Protocol deviations must be sent to the reviewing IRB per their policies. The investigator is responsible for knowing and adhering to the review IRB requirements. Further details about the handling of protocol deviations will be included in the study manual.

12.1.9 Publication and Data Sharing Policy

An ICH-compliant integrated clinical and statistical report will be prepared upon completion of the study and data analysis. The results of the study may be published in a relevant peer-reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions, and the sponsor.

All information provided to the investigator by BioMed Valley Discoveries, Inc., or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the investigator.

No information about this study or its progress will be provided to anyone not involved in the study other than by BioMed Valley Discoveries, Inc., or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

12.1.10 Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of person who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, person who have a perceived conflict of interest will be required to have such conflicts managed in such a way that is appropriate to their participation in the design and conduct of this trial.

12.1.11 Insurance

The sponsor has established an insurance policy for the total anticipated duration of the study, covering the patients with respect to the risks involved in taking part in this study in accordance with this protocol. In the case of injury or disability deriving from

participation in the study, patients are requested to inform the investigator or their staff responsible for the study at the institution without delay.

12.2 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

13 REFERENCES

1. **Dahlman *et al*, 2012**. BRAF^{L597} Mutations in Melanoma Are Associated with Sensitivity to MEK Inhibitors. Cancer Discov September 1 2012 (2) (9) 791-797; DOI: 10.1158/2159-8290.CD-12-0097.
2. **Dankner *et al*, 2018**. Classifying BRAF alterations in cancer: new rational therapeutic strategies for actionable mutations. Oncogene 37, 3183–3199; DOI: 10.1038/s41388-018-0171-x.
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4. **Davies *et al*, 2002**. Mutations of the BRAF gene in human cancer. Nature, Jun 27;417(6892):949-54. Epub 2002 Jun 9. DOI: 10.1038/nature00766.
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10. **Jones *et al*, 2017**. Non-V600BRAF Mutations Define a Clinically Distinct Molecular Subtype of Metastatic Colorectal Cancer. JCO 35, no. 23 (August 10, 2017) 2624-2630. DOI: 10.1200/JCO.2016.71.4394
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Appendix 1 Non-Permitted Concomitant Medications

INHIBITORS CYP1A2
ciprofloxacin
enoxacin
fluvoxamine

INHIBITORS CYP2D6
bupropion
fluoxetine
paroxetine
quinidine
terbinafine

INHIBITORS CYP3A
boceprevir
clarithromycin
cobicistat
danoprevir/ritonavir[1]
elvitegravir/ritonavir[1]
grapefruit juice
idelalisib
indinavir/ritonavir[1]
itraconazole
ketoconazole
lopinavir/ritonavir[1]
nefazodone
nelfinavir
paritaprevir/ritonavir[1]
posaconazole
ritonavir
saquinavir/ritonavir[1]
telaprevir
telithromycin
tipranavir/ritonavir[1]
troleandomycin
voriconazole

INDUCERS CYP3A
apalutamide
carbamazepine
enzalutamide
mitotane
phenytoin
rifampin
St. John's Wort

[1]Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

Strong inhibitors: ≥ 5-fold increase in AUC

Strong inducers: ≥ 80% decrease in AUC

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers; Table 3.2 (inhibitors) and Table 3.3 (inducers), dated 12.03.19; Accessed 02.24.20

Appendix 2 List of Accepted Atypical BRAF Type II Alterations for Group 2

BRAF Alteration	Evidence of Pathway Activation (Reference Number)
P367L/S	17
R462I	2, 9, 16
I463S	2, 8, 15
G464V/E/R	2, 3, 4, 8, 9, 10, 16, 17, 18, 19
F468C	9
N486_A489delinsK	17
N486_P490del	17
E586K	2, 3, 4, 16, 17
A598V	2, 10, 13
T599I/K/dup	2, 15, 16, 17
K601_S602delinsNT	17
K601E/N/T	1, 2, 3, 10, 12, 16, 17, 18, 19
A728V	2, 16
BRAF kinase duplication	17
BRAF fusions	2, 3, 12, 17, 18, 19

Appendix 3 ECOG Performance Status

ECOG Performance Status	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead