



**A PHASE 1 DOSE ESCALATION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF PF-06840003 IN PATIENTS WITH MALIGNANT GLIOMAS**

|  |                |
|--|----------------|
| <b>Compound:</b>   | PF-06840003    |
| <b>Compound Name:</b>  | Not applicable |
| <b>United States (US) Investigational New Drug (IND) Number:</b> | CCI [REDACTED] |
| <b>European Clinical Trials Database (EudraCT) Number:</b>       | Not applicable |
| <b>Protocol Number:</b>  | C0591001       |
| <b>Phase:</b>  | Phase 1        |



**Document History**

| Document    | Version Date     | Summary of Changes and Rationale   |
|-------------|------------------|--|
| Amendment 1 | 19 December 2016 | <p>The reasons for Amendment 1 include:</p> <ul style="list-style-type: none"> <li>• Revision to timepoint when Disease Control Rate will be evaluated from Week 26 to Week 25. – Section 2.</li> </ul> <p>Rationale – Based on an imaging frequency of every 8 weeks, Week 25 is the appropriate assessment timepoint.</p> <ul style="list-style-type: none"> <li>• CCI [REDACTED]</li> </ul> <p>Rationale – Administrative correction to ensure consistency across sections of the protocol.</p> <ul style="list-style-type: none"> <li>• Inclusion of the potential for evaluation of twice daily (BID) dosing – Schedule of Activities and Sections 3 and 5.4.</li> </ul> <p>Rationale – Based on emerging PK data from this study, twice a day dosing may be evaluated as part of the dose escalation if the exposure from once per day dosing does not allow for sufficient target coverage.</p> <ul style="list-style-type: none"> <li>• Clarification on overall sample size for Part 1 of the study. – Sections 3.1 and 9.3.</li> </ul> <p>Rationale – With the inclusion of the possibility to explore BID dosing, more than 6 cohorts may be included in the study. Therefore, the total sample size may be more than approximately 72 for Part 1.</p> <ul style="list-style-type: none"> <li>• Inclusion of inpatient evaluation for PK collection on Cycle 1 Day 1 and Cycle 1 Day 15 for patients enrolled in cohorts where doses of 500 mg QD or 500 mg BID or higher will be evaluated – Schedule of Activities and</li> </ul> |

|  |  |   |
|--|--|---|
|  |  | <p>Section 7.2.</p> <p>Rationale – In order to adequately collect urine for the 24 hour pharmacokinetic assessment, patients will need to be kept as inpatients for sample collection.</p> <ul style="list-style-type: none"><li>• F-18-FLT-PET imaging is to be collected in all patients dosed at 500 mg QD or 500 mg BID or higher at sites where the assessment can be performed. – Schedule of Activities and Section 7.4.1.</li></ul> <p>Rationale – Language added to clarify the assessment is not optional for sites who can complete the imaging.</p> <ul style="list-style-type: none"><li>• Blood samples for PF-06840003 pharmacokinetic evaluation and triplicate ECGs are to be obtained on Day 15 of Cycle 3 and beyond. – Schedule of Activities.</li></ul> <p>Rationale – Administrative clarification.</p> <ul style="list-style-type: none"><li>• Urine PK is to be collected in patients enrolled in cohorts where 500 mg QD or 500 mg BID or higher will be evaluated. – Schedule of Activities.</li></ul> <p>Rationale – As the urine collection requires inpatient evaluation, this will be limited to patients enrolled at doses where the most meaningful data will be collected.</p> <ul style="list-style-type: none"><li>• Correction to definition of patients to be enrolled in Part 1 of the study – Section 4.1.</li></ul> <p>Rationale - Administrative corrections to ensure consistency throughout the entry criteria.</p> <ul style="list-style-type: none"><li>• Estimated creatinine clearance is to be calculated using Cockcroft-Gault, a 24-hour urine collection is not required. – Section 4.1.</li></ul> <p>Rationale – Clarification added to ensure consistency in evaluation of this criteria based</p> |
|--|--|---|

|  |  |   |
|--|--|---|
|  |  | <p>on feedback received from the FDA during the initial Investigational New Drug (IND) application review from the ‘Study May Proceed’ letter for IND 129245 of April 25, 2016 (CDER reference ID:3921862).</p> <ul style="list-style-type: none"><li>• Revisions to the inclusion criteria to allow for patients with Grade 3 disease following a third or fourth recurrence or progression to be included – Section 4.1.</li></ul> <p>Rationale – Inclusion of later stage patients will still allow the study to meet its objectives while also allowing more potential patients to be eligible.</p> <ul style="list-style-type: none"><li>• Revisions to exclusion criteria relating to prior VEGF treatment – Section 4.2.</li></ul> <p>Rationale – Criteria revised to allow more patients to be considered as prior VEGF is not considered to be a safety concern for patients.</p> <ul style="list-style-type: none"><li>• Removal of time requirement for stereotactic biopsy – Section 4.2.</li></ul> <p>Rationale – Timing for biopsy removed to allow for possible performance of a screening biopsy as part of the study procedures.</p> <ul style="list-style-type: none"><li>• Details on rater qualification included – Section 4.5.</li></ul> <p>Rationale - Additional details on certifications required prior to administration of certain assessments added.</p> <ul style="list-style-type: none"><li>• Inclusion of reference to 25 mg strength for tablets in case an intermediate dose requiring use of the 25 mg tablets is required. – Section 5.3.1.</li></ul> <p>Rationale – Included to allow for potential inclusion of 25 mg tablets should evaluation of an intermediate dose be required.</p> <ul style="list-style-type: none"><li>• Fasting for dosing defined as no food for two</li></ul> |
|--|--|---|



|                   |               |   |
|-------------------|---------------|---|
|                   |               | <p>hours before or two hours after dosing – Section 5.4.</p> <p>Rationale – Administrative clarification.</p> <ul style="list-style-type: none"> <li>• Clarification on how the C-SSRS is to be administered included – Section 7.7.</li> </ul> <p>Rationale: Correction on how the assessment will be administered has been included.</p> <ul style="list-style-type: none"> <li>• Study assessments added in the Appendices – Appendix 3, 4, 5 and 6.</li> </ul> <p>Rationale – Administrative clarification.</p> <ul style="list-style-type: none"> <li>• Administrative corrections and edits included – Schedule of Activities and Sections 2.1, 3.1, 4.2, 5.1, 7.2.3, 7.3.2, 7.3.5, 7.6.2 and Appendix 1.</li> </ul> <p>Rationale - Administrative changes.</p> |
| Original protocol | 02 March 2016 | Not applicable (N/A)  |

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

## TABLE OF CONTENTS

|  |    |
|--|----|
| LIST OF TABLES .....   | 10 |
| LIST OF FIGURES .....  | 10 |
| APPENDICES .....   | 11 |
| PROTOCOL SUMMARY .....   | 12 |
| SCHEDULE OF ACTIVITIES.....  | 17 |
| 1. INTRODUCTION .....  | 25 |
| 1.1. Mechanism of Action/Indication.....                                     | 25 |
| 1.2. Background and Rationale .....  | 25 |
| 1.3. Malignant Gliomas .....   | 25 |
| 1.3.1. Rationale for Evaluation in Malignant Gliomas.....                    | 26 |
| 1.4. PF-06840003 in Malignant Gliomas .....                                  | 26 |
| 1.4.1. IDO1 in Malignant Gliomas .....                                       | 26 |
| 1.4.2. Mechanisms .....  | 28 |
| 1.4.3. Perspectives .....  | 28 |
| 1.5. Nonclinical Pharmacology and Safety .....                               | 29 |
| 1.5.1. Nonclinical Pharmacokinetics .....                                    | 29 |
| 1.5.2. Nonclinical Safety .....  | 30 |
| 1.6. Starting Dose Rationale.....  | 32 |
| 2. STUDY OBJECTIVES AND ENDPOINTS.....                                       | 32 |
| 2.1. Objectives.....   | 32 |
| 2.2. Endpoints.....  | 33 |
| 3. STUDY DESIGN.....   | 35 |
| 3.1. Study Overview .....  | 35 |
| 3.1.1. Criteria for Dose Escalation.....                                     | 36 |
| 3.2. DLT Definition.....   | 38 |
| 3.3. MTD Definition.....   | 39 |
| 3.4. Late Onset Toxicity and Toxicities Observed in the Expansion Phase..... | 39 |
| 3.5. Recommended Phase 2 Dose (RP2D) Definition .....                        | 40 |
| 4. PATIENT SELECTION .....   | 40 |
| 4.1. Inclusion Criteria.....   | 40 |
| 4.2. Exclusion Criteria.....   | 42 |

|  |    |
|--|----|
| 4.3. Lifestyle Guidelines .....                              | 44 |
| 4.4. Sponsor’s Qualified Medical Personnel .....             | 45 |
| 4.5. Rater Qualifications.....                               | 45 |
| 5. STUDY TREATMENTS.....                                     | 45 |
| 5.1. Allocation to Treatment .....                           | 46 |
| 5.2. Patient Compliance .....                                | 46 |
| 5.3. Investigational Product Supplies.....                   | 46 |
| 5.3.1. Dosage Form(s) and Packaging.....                     | 46 |
| 5.3.2. Preparation and Dispensing.....                       | 46 |
| 5.4. Administration.....                                     | 47 |
| 5.4.1. Recommended Dose Modifications.....                   | 47 |
| 5.4.2. Dosing Interruptions .....                            | 48 |
| 5.4.3. Dose Delays.....                                      | 48 |
| 5.4.4. Dose Reductions .....                                 | 49 |
| 5.5. Investigational Product Storage .....                   | 50 |
| 5.6. Investigational Product Accountability.....             | 51 |
| 5.6.1. Destruction of Investigational Product Supplies ..... | 51 |
| CCI  |    |
|  |    |
|  |    |
|  |    |
|  |    |
|  |    |
| 6. STUDY PROCEDURES .....                                    | 53 |
| 6.1. Screening.....  | 53 |
| 6.2. Study Period .....                                      | 53 |
| 6.3. Follow-up Visit .....                                   | 53 |
| 6.4. Patient Withdrawal.....                                 | 53 |
| 7. ASSESSMENTS.....  | 54 |
| 7.1. Safety Assessment.....                                  | 54 |
| 7.1.1. Pregnancy Testing .....                               | 54 |
| 7.1.2. Adverse Events .....                                  | 55 |
| 7.1.3. Laboratory Safety Assessment .....                    | 55 |

|   |    |
|---|----|
| 7.1.4. Vital Signs and Physical Examination.....  | 56 |
| 7.1.5. (12-Lead) Electrocardiogram.....   | 57 |
| CCI   |    |
|   |    |
|   |    |
|   |    |
| 7.3. Biomarker and Pharmacodynamic Assessments.....                                     | 59 |
| 7.3.1. Target Engagement – Assessment of Kynurenine, Tryptophan and<br>Metabolites..... | 59 |
| CCI   |    |
| 7.3.3. Cytokines and Chemokines .....   | 60 |
| 7.3.4. T Cell Receptor (TCR) Sequencing.....  | 60 |
| 7.3.5. Tumor Biopsies.....  | 61 |
| 7.4. Tumor Response Assessments .....   | 61 |
| 7.4.1. F-18-FLT PET .....   | 64 |
| CCI   |    |
|   |    |
|   |    |
| CCI   |    |
|   |    |
|   |    |
|   |    |
| CCI   |    |
| 8. ADVERSE EVENT REPORTING.....   | 67 |
| 8.1. Adverse Events.....  | 67 |
| 8.2. Reporting Period .....   | 67 |
| 8.3. Definition of an Adverse Event.....  | 67 |
| 8.4. Medication Errors.....   | 68 |
| 8.5. Abnormal Test Findings.....  | 69 |
| 8.6. Serious Adverse Events.....  | 69 |
| 8.6.1. Protocol-Specified Serious Adverse Events .....                                  | 70 |
| 8.6.2. Potential Cases of Drug-Induced Liver Injury.....                                | 70 |

|   |    |
|---|----|
| 8.7. Hospitalization .....  | 71 |
| 8.8. Severity Assessment.....   | 72 |
| 8.9. Causality Assessment.....  | 73 |
| 8.10. Exposure During Pregnancy.....  | 73 |
| 8.11. Occupational Exposure .....   | 74 |
| 8.12. Withdrawal Due to Adverse Events (See also the Section on Patient<br>Withdrawal).....             | 74 |
| 8.13. Eliciting Adverse Event Information .....   | 75 |
| 8.14. Reporting Requirements.....   | 75 |
| 8.14.1. Serious Adverse Event Reporting Requirements .....  | 75 |
| 8.14.2. Non-Serious Adverse Event Reporting Requirements .....  | 75 |
| 8.14.3. Sponsor’s Reporting Requirements to Regulatory Authorities .....                                | 76 |
| 9. DATA ANALYSIS/STATISTICAL METHODS.....   | 76 |
| 9.1. Analysis Sets .....  | 76 |
| 9.2. Statistical Methods and Properties .....   | 77 |
| 9.2.1. Statistical Methods for Dose Escalation/De-Escalation .....                                      | 77 |
| 9.3. Sample Size Determination.....   | 77 |
| 9.4. Efficacy Analysis .....  | 78 |
| 9.5. Analysis of Pharmacokinetics and Pharmacodynamics .....  | 78 |
| 9.5.1. Analysis of Pharmacokinetics.....  | 78 |
| 9.5.1.1. Single-Dose and Steady-State PF-06840002 and PF-<br>06840001 Pharmacokinetic Analysis .....    | 78 |
| 9.5.2. Analysis of Pharmacodynamics.....  | 79 |
| 9.5.2.1. Analysis of Biomarker Endpoints .....  | 79 |
| 9.5.3. Population Pharmacokinetic Analysis or<br>Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling ..... | 79 |
| 9.6. Safety Analysis.....   | 79 |
| 9.6.1. Analysis of the Primary Endpoint.....  | 79 |
| 9.6.2. Analysis of Secondary Safety Endpoints.....  | 79 |
| 9.6.3. Electrocardiogram.....   | 80 |
| 9.8. Data Safety Monitoring Committee .....   | 81 |

CCI

|   |    |
|---|----|
| 10. QUALITY CONTROL AND QUALITY ASSURANCE.....  | 81 |
| 11. DATA HANDLING AND RECORD KEEPING .....  | 82 |
| 11.1. Case Report Forms/Electronic Data Record .....                                      | 82 |
| 11.2. Record Retention.....   | 82 |
| 12. ETHICS.....   | 83 |
| 12.1. Institutional Review Board /Ethics Committee.....                                   | 83 |
| 12.2. Ethical Conduct of the Study .....  | 83 |
| 12.3. Patient Information and Consent.....  | 83 |
| 12.4. Patient Recruitment .....   | 84 |
| 12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH<br>GCP ..... | 84 |
| 13. DEFINITION OF END OF TRIAL.....   | 84 |
| 14. SPONSOR DISCONTINUATION CRITERIA .....  | 84 |
| 15. PUBLICATION OF STUDY RESULTS .....  | 85 |
| 15.1. Communication of Results by Pfizer .....  | 85 |
| 15.2. Publications by Investigators .....   | 85 |
| 16. REFERENCES .....  | 87 |

#### **LIST OF TABLES**

|   |    |
|---|----|
| Table 1. Dose Escalation Potential Dose Levels .....                          | 37 |
| Table 2. Decision Rules.....  | 38 |
| Table 3. Dose Modifications for Investigational Product-Related Toxicity..... | 50 |
| Table 4. Laboratory Assessments .....   | 56 |
| Table 5. Pharmacodynamic Summary.....   | 59 |
| Table 6. Overall Response Criteria.....                                       | 63 |

#### **LIST OF FIGURES**

|   |    |
|---|----|
| Figure 1. IDO1 mRNA and protein expression levels correlated with overall patient<br>survival (Wainwright et al, 2012)..... | 27 |
| Figure 2. Overall Study Design.....   | 36 |

## APPENDICES

|  |     |
|--|-----|
| Appendix 1. Abbreviations .....  | 90  |
| Appendix 2. Karnofsky Performance Scoring (Karnofsky et al, 1948).....               | 93  |
| Appendix 3. Columbia-Suicide Severity Rating Scale (CSSRS) – Baseline.....           | 94  |
| Appendix 4. Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit ..... | 100 |
| Appendix 5. Patient Health Questionnaire (PHQ-8).....                                | 104 |
| Appendix 6. Neurologic Assessment in Neuro-Oncology (NANO) Scale.....                | 105 |

## **PROTOCOL SUMMARY**

### **Background and Rationale:**

Indoleamine 2, 3-dioxygenase (IDO1) is a heme-containing dioxygenase that catalyzes the oxidation of tryptophan to N-formyl kynurenine in the first and rate-limiting step of tryptophan catabolism. N-formyl kynurenine is subsequently converted to kynurenine and other cytotoxic metabolites via the kynurenine pathway. IDO1 acts to inhibit T-cell function both through depletion of tryptophan and production of kynurenine (Munn & Mellor, 2013; van Baren & Ven den Eynde, 2015).<sup>15,24</sup> IDO1 expression is often higher in the tumor microenvironment, typically in response to inflammatory stimuli such as interferon gamma (IFN- $\gamma$ ) (Mellor & Munn, 2004).<sup>12</sup> The enzymatic activity of IDO1 is associated with suppression of T-cell responses (Uyttenhove et al, 2003)<sup>23</sup> and is correlated with poor prognosis in several cancer indications (Okamoto et al, 2005; Brandacher et al, 2006).<sup>18,5</sup> As such, IDO1 is a target of interest for cancer immunotherapy.

IDO1 is expressed in 96% of malignant glioma (Mitsuka et al, 2013).<sup>13</sup> In a study reported by Mitsuka, IDO immunohistochemistry (IHC) expression has been assessed in 75 surgical specimens. Stronger expression in malignant gliomas was found compared with low-grade gliomas. In 6 cases of secondary glioblastoma, IDO expression was stronger than in the initial low-grade glioma. IDO was expressed more strongly in both primary and secondary glioblastoma tissue than low-grade glioma and could affect clinical outcome. Grade IV patients with strong IDO expression had significantly worse overall survival rates (P = .04) than patients with weak IDO expression.

The higher IDO expression in both primary and secondary glioblastoma tissue compared to low-grade glioma has been confirmed by other authors who reported that this may affect clinical outcome. (Wainwright et al, 2012).<sup>25</sup>

IDO1 messenger ribonucleic acid (mRNA) and protein expression levels correlate with overall patient survival. IDO1 is involved in malignant glioma immunosuppression. IDO1 plays a key role in resistance to immune therapy. The selective nature of IDO1 expression in malignant glioma provides a high potential for targeting specificity.

### **Study Objectives and Endpoints:**

#### **Objectives**

##### **Primary Objective – Part 1**

- To evaluate the safety and tolerability of increasing dose levels of daily oral PF-6840003 in patients with malignant gliomas.
- To characterize the dose limiting toxicities (DLTs) of escalated doses of PF-06840003.



- To determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D).

**Primary Objective – Part 2**

- To further evaluate the safety and tolerability of PF-06840003 at the RP2D.
- To evaluate the efficacy of PF-06840003 in patients with glioblastoma.

**Secondary Objectives – Parts 1 and 2**

- To evaluate the overall safety profile.
- To characterize the single and multiple dose plasma pharmacokinetics (PK) of active enantiomer PF-06840002, and inactive enantiomer PF-06840001 after administration of the racemic mixture, PF-06840003.
- To document any anti-tumor activity (Part 1 only).
- To evaluate dose and concentration response relationship for target engagement and pharmacodynamic (PD) biomarkers and to then correlate with PK, safety and efficacy to select dose with full or optimal target engagement.
- To assess the cerebrospinal fluid (CSF) PK exposure of active enantiomer PF-06840002, and inactive enantiomer PF-06840001 after administration of the racemic mixture, PF-06840003.

CCI [REDACTED]

CC  
I [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

C  
C  
I

## Endpoints

### Primary Endpoint – Part 1

- Incidence and grade of treatment-emergent adverse events (TEAE) including DLTs as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

### Primary Endpoints – Part 2

- Adverse Events (AE) as characterized by type, frequency, severity, timing, seriousness, and relationship to study therapy.
- Disease control rate (DCR) at 9 and 25 weeks by magnetic resonance imaging (MRI) using Macdonald criteria (Macdonald et al, 1990).<sup>9</sup>

### Secondary Endpoints

- Laboratory abnormalities as characterized by type, frequency, severity [as graded by National Cancer Institute (NCI) CTCAE v.4.03] and timing;
- Vital Signs;
- PK parameters in the blood of PF-06840002 and PF-06840001 Single Dose (SD) –  $C_{max}$ ,  $T_{max}$ ,  $AUC_{last}$ ,  $AUC_{\tau}$ ,  $CL/F$ , and  $V_z/F$  and  $t_{1/2}$ ,  $AUC_{inf}$  as data permit. Multiple Dose (MD) (assuming steady state is achieved) –  $C_{ss,max}$ ,  $T_{ss,max}$ ,  $AUC_{ss,\tau}$ ,  $t_{1/2}$ ,  $C_{ss,min}$ ,  $C_{ss,av}$ ,  $CL/F$ ,  $V_{ss}/F$ ,  $R_{ac}$  ( $AUC_{ss,\tau}/AUC_{sd,\tau}$ ) and  $R_{ss}$  ( $AUC_{ss,\tau}/AUC_{sd,inf}$ ) as data permit;
- Objective tumor response based on Macdonald criteria;
- Disease Control Rate (DCR) at 9 and 25 weeks by MRI based on Response Assessment for Neuro-Oncology (RANO) criteria;
- On-target activity of PF-06840003 by measurement of kynurenine, tryptophan and kyn/trp (ratio) levels in peripheral blood;
- Steady-state trough level ratio between CSF and plasma samples for PF-06840002 and PF-06840001.

CCI

C  
I

**C**  
**C**  
**I**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### Study Design

This is a Phase 1, open-label, multi-center, multiple-dose, safety, PK and PD study of single agent PF-06840003. This study contains two parts, dose escalation (Part 1) followed by dose expansion (Part 2). In Part 1, sequential cohorts of patients with recurrent malignant gliomas [Glioblastoma Multiforme (GBM) and/or World Health Organization (WHO) grade III anaplastic gliomas] will receive escalating doses of PF-06840003. Part 2 will evaluate safety as well as explore preliminary antitumor activity of the dose selected from Part 1 in additional patients with GBM.

The actual number of patients enrolled in the study will depend on the tolerability of PF-06840003 and the number of dose levels required to identify the MTD or Recommended Phase 2 Dose (RP2D) if the MTD is not reached. The target sample size for each cohort in Part 1 is 2-4 patients, but, the actual number of patients treated at each dose will vary from 2 to 12. It is estimated that the maximum sample size will be approximately 72 patients in Part 1 of the study, although this may be higher if more than 6 dose levels are required to be evaluated. Up to approximately 20 to 25 patients are anticipated to be enrolled in Part 2 of the study.

## Study Treatment

PF-06840003 will be administered daily as an oral dose in 28 day cycles with a starting dose of 125 mg once daily (QD). The pre-specified nominal doses for use in the dose escalation are 125 mg/day, 250 mg/day and 500 mg/day of PF-06840003. If the MTD or the RP2D are not reached within the pre-planned nominal dose range, and the PK and PD data show that the target coverage is not optimal, the sponsor, in conjunction with the investigators, after careful consideration of all available safety, laboratory and PK information may expand the nominal dose range to a higher dosage, up to a maximum dosage of 1000 mg per day. Based on emerging clinical and PK data, twice a day (BID) dosing may be explored. For example, if the exposure over 24 hours does not allow for sufficient target coverage it may be determined that BID dosing is needed. In such a case, BID dosing will be initiated at the QD dose level where no DLTs are observed (ie, starting dose of BID dosing will be 250 mg BID after safety and tolerability profile of 250 mg QD is confirmed). Once a BID dosing regimen is initiated for further escalation towards the maximum tolerated dose (MTD), the escalation with a QD regimen will be suspended. Intermediate doses may also be used if required.

In Part 1 of the study, dose escalation and de-escalation will follow a modified Toxicity Probability Interval (mTPI) method, targeting a DLT rate of 27.5% and an acceptable DLT interval 22.5 to 32.5%.

The dose escalation portion of the study is completed when at least 6 to 12 evaluable patients have been treated at the highest dose associated with DLT rate  $\leq 32.5\%$ .

## SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the [ASSESSMENTS](#) section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

| Protocol Activity                  | Screening<br>(≤28 days<br>prior to<br>registration) | CYCLE 1*<br>(28 day duration)   |       |       |        |        | CYCLE 2<br>(28 day duration) |        | CYCLE ≥3<br>(Each with a<br>28 day duration) |        | End of<br>Treatment | Follow-<br>up <sup>20</sup> |
|------------------------------------|---|---|-------|-------|--------|--------|------------------------------|--------|--|--------|---------------------|-----------------------------|
|                                    |   | Day 1   | Day 4 | Day 8 | Day 15 | Day 22 | Day 1                        | Day 15 | Day 1  | Day 15 |                     |                             |
| <b>Visit Window (days)**</b>       |   |   |       | (±1)  | (±1)   | (±1)   | (±1)                         | (±2)   | (±2)   | (±2)   |                     |                             |
| Informed consent <sup>1</sup>      | X   |   |       |       |        |        |                              |        |  |        |                     |                             |
| Tumor history                      | X   |   |       |       |        |        |                              |        |  |        |                     |                             |
| Medical history                    | X   |   |       |       |        |        |                              |        |  |        |                     |                             |
| Complete physical examination      | X   | X <sup>2</sup>  |       |       |        |        |                              |        |  |        | X                   |                             |
| Abbreviated physical examination   |   |   | X     | X     | X      | X      | X                            | X      | X  | X      |                     | X                           |
| Height                             | X   |   |       |       |        |        |                              |        |  |        |                     |                             |
| Weight                             | X   |   |       |       |        |        | X                            |        | X  |        | X                   |                             |
| Vital signs <sup>3</sup>           | X   | X   | X     | X     | X      | X      | X                            | X      | X  | X      | X                   | X                           |
| Performance status <sup>4</sup>    | X   | X   |       |       |        |        | X                            |        | X  |        | X                   | X                           |
| Contraception check                | X   | X   |       |       |        |        | X                            |        | X  |        | X                   |                             |
| <b>Laboratory</b>                  |   |   |       |       |        |        |                              |        |  |        |                     |                             |
| Unique screening labs <sup>5</sup> | X   |   |       |       |        |        |                              |        |  |        |                     |                             |
| Hematology <sup>6</sup>            | X   | X   | X     | X     | X      | X      | X                            | X      | X  | X      | X                   | X                           |
| Blood Chemistry <sup>7</sup>       | X   | X   | X     | X     | X      | X      | X                            | X      | X  | X      | X                   | X                           |
| Coagulation <sup>8</sup>           | X   | X   | X     | X     | X      | X      | X                            | X      | X  | X      | X                   | X                           |
| Urinalysis <sup>9</sup>            | X   | X   | X     | X     | X      | X      | X                            |        | X  |        | X                   |                             |
| Pregnancy test <sup>10</sup>       | X   | X   |       |       |        |        | X                            |        | X  |        | X                   |                             |
| Single 12 Lead ECG                 | X   |   |       |       |        |        |                              |        |  |        |                     |                             |
| Triplicate(12 lead) ECG            |   | Refer to <a href="#">Schedule of Electrocardiogram, Pharmacokinetic and Pharmacodynamic Assessments</a> |       |       |        |        |                              |        |  |        |                     |                             |

| Protocol Activity                                    | Screening<br>(≤28 days<br>prior to<br>registration) | CYCLE 1*<br>(28 day duration)   |       |               |                |                | CYCLE 2<br>(28 day duration) |                | CYCLE ≥3<br>(Each with a<br>28 day duration) |                | End of<br>Treatment | Follow-<br>up <sup>20</sup> |
|--|---|---|-------|---------------|----------------|----------------|------------------------------|----------------|--|----------------|---------------------|-----------------------------|
|  |   | Day 1   | Day 4 | Day 8<br>(±1) | Day 15<br>(±1) | Day 22<br>(±1) | Day 1<br>(±1)                | Day 15<br>(±2) | Day 1<br>(±2)                                | Day 15<br>(±2) |                     |                             |
| Study Day  |   |   |       |               |                |                |                              |                |  |                |                     |                             |
| Visit Window (days)**                                |   |   |       | (±1)          | (±1)           | (±1)           | (±1)                         | (±2)           | (±2)   | (±2)           |                     |                             |
| ECHO or MUGA   | X   |   | X     |               | X              |                | X                            |                |  |                | X                   |                             |
| <b>Registration and Treatment</b>                    |   |   |       |               |                |                |                              |                |  |                |                     |                             |
| Registration <sup>11</sup>                           |   | X   |       |               |                |                |                              |                |  |                |                     |                             |
| Study treatment <sup>12</sup>                        |   | →   | →     | →             | →              | →              | →                            | →              | →  | →              |                     |                             |
| Inpatient Evaluation for PK collection <sup>13</sup> |   | X   |       |               | X              |                |                              |                |  |                |                     |                             |
| PF-06840003 Dispensing                               |   | X   |       |               |                |                | X                            |                | X  |                |                     |                             |
| PF-06840003 Accountability                           |   |   |       |               |                |                | X                            |                | X  |                | X                   |                             |
| <b>Tumor assessments</b>                             |   |   |       |               |                |                |                              |                |  |                |                     |                             |
| Tumor assessments, including MRI <sup>14</sup>       | X   |   |       |               |                |                |                              |                | X (every 8 weeks)                            |                | X                   |                             |
| F-18-FLT-PET <sup>15</sup>                           | X   |   |       |               |                |                |                              |                | X <sup>15</sup>                              |                | X <sup>15</sup>     |                             |
| <b>Other clinical assessments</b>                    |   |   |       |               |                |                |                              |                |  |                |                     |                             |
| ██████████ CCI                                       | █   |   |       |               |                |                |                              |                | ██████████                                   |                | █                   |                             |
| ██████████ CCI                                       | █   |   |       |               |                |                |                              |                | ██████████                                   |                | █                   |                             |
| CCI ██████████                                       | █   |   |       |               |                |                | █                            |                | █  |                | █                   |                             |
| CCI ██████████                                       | █   |   |       |               |                |                |                              |                | ██████████                                   |                | █                   |                             |
| Adverse events <sup>19</sup>                         |   | X   | X     | X             | X              | X              | X                            | X              | X  | X              | X                   | X                           |
| CCI ██████████                                       | █   | █   | █     | █             | █              | █              | █                            | █              | █  | █              | █                   | █                           |
| <b>Other samplings</b>                               |   |   |       |               |                |                |                              |                |  |                |                     |                             |
| Banked biospecimen                                   |   | X   |       |               |                |                |                              |                |  |                |                     |                             |
| Tumor biopsy   |   | Refer to <a href="#">Schedule of Electrocardiogram, Pharmacokinetic and Pharmacodynamic Assessments</a> |       |               |                |                |                              |                |  |                |                     |                             |
| Pharmacokinetics                                     |   |   |       |               |                |                |                              |                |  |                |                     |                             |
| Pharmacodynamics                                     |   |   |       |               |                |                |                              |                |  |                |                     |                             |

\* A cycle is 28 days in duration

\*\* Visit windows are calculated off the first day of each cycle.

Abbreviations: → = continuous daily dosing; AEs = adverse events; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition scan

1. **Informed Consent:** Must be obtained prior to undergoing any study specific procedures. May be obtained more than 28 days prior to registration.
2. **Complete Physical Examination:** No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment is performed within 7 days of dosing.
3. **Vital signs:** Includes temperature (oral, tympanic, temporal or axillary) and blood pressure (BP) to be recorded in seated position.
4. **Performance Status:** Use Karnofsky performance status scale – (Appendix 2)
5. **Unique Screening Laboratory Tests:** Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody and human immunodeficiency virus (HIV) as well as follicle stimulating hormone (FSH) for post-menopausal women who are amenorrheic for at least 12 consecutive months only. Samples will be analyzed locally.
6. **Hematology:** No need to repeat on Cycle 1 Day 1 if screening assessment is performed within 7 days prior to that date. Complete blood count (CBC) to include hemoglobin, platelets, white blood cells (WBC), absolute neutrophils, lymphocytes, monocytes, eosinophils and basophils. Assessments performed at all subsequent dosing visits should be performed within 48 hours prior to dosing. Samples will be analyzed locally.
7. **Blood Chemistry:** No need to repeat on Cycle 1 Day 1 if screening assessment is performed within 7 days prior to that date. Should include sodium, potassium, chloride, BUN (or urea), uric acid, creatinine, glucose, calcium, magnesium, phosphorus, albumin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase and total bilirubin. Assessments performed at all subsequent dosing visits should be performed within 48 hours prior to dosing. Samples will be analyzed locally.
8. **Coagulation:** No need to repeat on Cycle 1 Day 1 if baseline assessment is performed within 7 days prior to that date. Should include prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). Samples will be analyzed locally.
9. **Urinalysis:** No need to repeat on Cycle 1 Day 1 if baseline assessment is performed within 7 days prior to that date. Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Samples will be analyzed locally.
10. **Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on two occasions prior to starting study treatment – once at the start of screening and once on C1D1 immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment and additional whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board (IRB) or if required by local regulations.
11. **Registration:** Patient number and dose level allocation provided by Pfizer Inc. Registration should occur before any other Day 1 activities are performed and preferably no more than 3 business days before Day 1.
12. **Study Treatment:** Daily oral dosing with PF-06840003 will be initiated on Cycle 1 Day 1 and should continue until end of treatment. Patients assigned to a BID dosing regimen should be instructed to take PF-06840003 every 12 hours ( $\pm$ 1 hour). On days when patients have clinic visits where PK assessments are to be obtained, PF-06840003 should be held (NOT taken) prior to the study visit. The PF-06840003 can be taken after the study procedures required for that visit have been performed.

13. **Inpatient Evaluation for PK Assessment:** For cohorts where 500 mg QD or 500 mg BID or higher will be evaluated, patients will be required to undergo inpatient evaluation for at least 24 hours following receipt of the Cycle 1 Day 1 and Cycle 1 Day 15 dose. The evaluation will be used for collection of samples for evaluation of the PF-06840003 pharmacokinetics.
14. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging should include brain MRI with contrast. Tumor assessments will be made using the Macdonald criteria. On study MRIs are to be collected every 8 weeks ( $\pm 5$  days). Where possible, responses should be confirmed with two assessments at least 4 weeks apart. Tumor assessment should be repeated at the end of treatment visit if more than 4 weeks have passed since the last evaluation. Efficacy evaluations using the Macdonald criteria involve post-contrast MRI findings, non-contrast T1 and T2 fluid attenuated inversion recovery (FLAIR) images, use of corticosteroid dose, and neurological examination. Disease progression will be confirmed with two consecutive timepoints at least 8 weeks apart in the absence of substantial neurological decline if progression is suspected within 6 months of treatment initiation.
15. **F-18-fluorothymidine (FLT) PET:** For locations who are able to perform the assessment, 1 F-18-FLT-PET imaging will be performed in all patients assigned to receive doses of 500 mg/day or higher. Assessment will be performed at screening after all eligibility criteria have been confirmed and at Weeks 9 and 25. Should be performed if the patient discontinues the study prior to Week 9 or between Weeks 9 and Week 25 if more than 4 weeks have passed since the last evaluation.

CCI  
[Redacted text block]

19. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Patients must be followed for AEs for 28 days after the last study treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
20. **Follow-up:** At least 28 days, and no more than 35 days, after discontinuation of treatment, patients will return to undergo the assessments included in the table above which includes a review of concomitant medications and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.



**SCHEDULE OF ELECTROCARDIOGRAM, PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS – FOR COHORTS WHERE INPATIENT EVALUATION IS NOT REQUIRED**

| Protocol Activity  | Screening (≤28 days) | Treatment Period |   |   |   |   |   |       |          |          |          |   |   |   |   |   |         |          |                    |                | End of Treatment |                |   |
|--|----------------------|------------------|---|---|---|---|---|-------|----------|----------|----------|---|---|---|---|---|---------|----------|--------------------|----------------|------------------|----------------|---|
|  |                      | Cycle 1 Only     |   |   |   |   |   |       |          |          |          |   |   |   |   |   | Cycle 2 |          | Cycle 3 and beyond |                |                  |                |   |
| Study Day  |                      | Day 1            |   |   |   |   |   | Day 2 | Day 4    | Day 8    | Day 15   |   |   |   |   |   | Day 16  | Day 1    | Day 15             | Day 1          | Day 15           |                |   |
| Hours Pre-/Post-Dose*  |                      | Pre-dose         | 1 | 2 | 4 | 6 | 8 | 24    | Pre-dose | Pre-dose | Pre-dose | 1 | 2 | 4 | 6 | 8 | 24      | Pre-dose | Pre-dose           | Pre-dose       | Pre-dose         |                |   |
| Triplicate (12 Lead) ECGs <sup>1</sup>                             |                      | X                |   | X |   | X |   | X     | X        |          | X        |   | X |   | X |   | X       | X        | X                  | X <sup>2</sup> | X                | X              |   |
| Blood samples for PF-06840003 PK                                   |                      | X                | X | X | X | X | X | X     | X        | X        | X        | X | X | X | X | X | X       | X        |                    |                | X                | X              | X |
| Cerebrospinal fluid samples for PF-06840003 PK and PD <sup>3</sup> | X                    |                  |   |   |   |   |   |       |          |          | X        |   |   |   |   |   |         |          |                    |                |                  |                |   |
| Kyn and trp  |                      | X                | X | X | X | X | X | X     | X        | X        | X        | X | X | X | X | X | X       |          |                    |                |                  |                | X |
| Cytokine/chemokines  |                      | X                | X |   | X |   | X | X     |          |          | X        | X |   | X |   |   | X       |          |                    |                |                  |                | X |
| CCI  |                      | ■                |   |   |   |   |   | ■     |          | ■        | ■        |   |   |   |   |   |         |          |                    |                |                  |                | ■ |
| TCR sequencing in peripheral blood                                 |                      | X                |   |   |   |   |   |       |          |          |          |   |   |   |   |   |         |          |                    |                |                  | X              | X |
| Tumor biopsies <sup>4</sup>  | X                    |                  |   |   |   |   |   |       |          |          |          |   |   |   |   |   |         |          |                    |                |                  | X <sup>5</sup> |   |

\* All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time from dosing are acceptable.

Abbreviations: → = continuous sample collection; ECG = electrocardiogram; kyn = kynurenine; PK = pharmacokinetics; TCR = T cell repertoire; trp = tryptophan

1. **Triplicate 12-Lead ECGs:** Triplicate 12-lead ECG: At each timepoint, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged ( $>500$  msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
2. Triplicate ECGs are to be collected pre-dose on Day 1 and Day 15 of each subsequent cycle.
3. **Cerebrospinal fluid sample for PF-06840003 PK and PD:** Cerebrospinal fluid will be collected at screening and prior to dosing on Cycle 1 Day 15 ( $\pm 1$  days) in at least 4 patients in Part 1 and at least 6 patients in Part 2 from select sites. Collection will be optional based on investigator assessment of the safety of the patient. The screening sample should preferably be collected after all other screening assessments have been completed. Samples may also be used for evaluation of pharmacodynamic markers.
4. **Tumor biopsies:** If feasible, optional fresh tumor biopsies will be collected at screening and C2D1 (predose)  $\pm 2$  days for measurement of kynurenine/tryptophan (and metabolites), assessment of tumor-infiltrating lymphocytes, RNA-profiling and TCR sequencing. The screening biopsy should preferably be collected after all other screening assessments have been completed. The screening and C2D1 biopsies should preferably be taken from the same site. Biopsies collected within 30 days of registration will be acceptable.

**SCHEDULE OF ELECTROCARDIOGRAM, PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS – FOR INPATIENT EVALUATION COHORTS**

| Protocol Activity  | Screen (≤28 days) | Treatment Period |   |   |   |   |    |    |    |       |          |          |          |   |   |   |   |         |    |                    |        | End of Treatment |          |                |          |   |   |
|--|-------------------|------------------|---|---|---|---|----|----|----|-------|----------|----------|----------|---|---|---|---|---------|----|--------------------|--------|------------------|----------|----------------|----------|---|---|
|  |                   | Cycle 1 Only     |   |   |   |   |    |    |    |       |          |          |          |   |   |   |   | Cycle 2 |    | Cycle 3 and beyond |        |                  |          |                |          |   |   |
| Study Day  |                   | Day 1            |   |   |   |   |    |    |    | Day 2 | Day 4    | Day 8    | Day 15   |   |   |   |   |         |    |                    | Day 16 | Day 1            | Day 15   | Day 1          | Day 15   |   |   |
| Hours Pre-/Post-Dose*  |                   | Pre-dose         | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24    | Pre-dose | Pre-dose | Pre-dose | 1 | 2 | 4 | 8 | 12      | 16 | 20                 | 24     | Pre-dose         | Pre-dose | Pre-dose       | Pre-dose |   |   |
| Triplicate (12 Lead) ECGs <sup>1</sup>                             |                   | X                |   | X |   | X |    |    |    | X     | X        |          | X        |   | X |   | X |         |    |                    | X      | X                | X        | X <sup>2</sup> | X        | X |   |
| Blood samples for PF-06840003 PK                                   |                   | X                | X | X | X | X | X  | X  | X  | X     | X        | X        | X        | X | X | X | X | X       | X  | X                  | X      | X                |          |                | X        | X | X |
| Urine samples for PF-06840003 PK <sup>3</sup>                      |                   | X                |   |   |   |   |    |    |    |       |          |          | →        | → | → | → | → | →       | →  | →                  | →      |                  |          |                |          |   |   |
| Cerebrospinal fluid samples for PF-06840003 PK and PD <sup>4</sup> | X                 |                  |   |   |   |   |    |    |    |       |          |          | X        |   |   |   |   |         |    |                    |        |                  |          |                |          |   |   |
| Kyn and trp  |                   | X                | X | X | X | X | X  | X  | X  | X     | X        | X        | X        | X | X | X | X | X       | X  | X                  | X      | X                |          |                |          |   | X |
| Cytokine/chemokines  |                   | X                | X |   | X |   | X  |    |    | X     |          |          | X        | X |   | X |   |         |    |                    |        | X                |          |                |          |   | X |
| CCI  |                   | ■                |   |   |   |   |    |    |    | ■     |          | ■        | ■        |   |   |   |   |         |    |                    |        |                  | ■        |                |          |   | ■ |
| TCR sequencing in peripheral blood                                 |                   | X                |   |   |   |   |    |    |    |       |          |          |          |   |   |   |   |         |    |                    |        | X                |          |                |          | X |   |
| Tumor biopsies <sup>5</sup>  | X                 |                  |   |   |   |   |    |    |    |       |          |          |          |   |   |   |   |         |    |                    |        | X <sup>3</sup>   |          |                |          |   |   |

\*All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time from dosing are acceptable.

Abbreviations: → = continuous sample collection; ECG = electrocardiogram; kyn = kynurenine; PK = pharmacokinetics; TCR = T cell repertoire; trp = tryptophan

1. Triplicate 12-Lead ECGs: Triplicate 12-lead ECG: At each timepoint, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged ( $>500$  msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
2. Triplicate ECGs are to be collected pre-dose on Day 1 and Day 15 of each subsequent cycle.
3. Urine sample for PF-06840003 PK: Urine will be collected on Cycle 1 Day 1 and for 24 hours after PF-06840003 dosing on Cycle 1 Day 15 over the following intervals: 0 to 4 hours, 4 to 12 hours, and 12 to 24 hours post-dose.
4. Cerebrospinal fluid sample for PF-06840003 PK and PD: Cerebrospinal fluid will be collected at screening and prior to dosing on Cycle 1 Day 15 ( $\pm 1$  days) in at least 4 patients in Part 1 and at least 6 patients in Part 2 from select sites. Collection will be optional based on investigator assessment of the safety of the patient. The screening sample should preferably be collected after all other screening assessments have been completed. Samples may also be used for evaluation of pharmacodynamic markers.
5. Tumor biopsies: If feasible, optional fresh tumor biopsies will be collected at screening and C2D1 (predose)  $\pm 2$  days for measurement of kynurenine/tryptophan (and metabolites), assessment of tumor-infiltrating lymphocytes, RNA-profiling and TCR sequencing. The screening biopsy should preferably be collected after all other screening assessments have been completed. The screening and C2D1 biopsies should preferably be taken from the same site. Biopsies collected within 30 days of registration will be acceptable.

## 1. INTRODUCTION

### 1.1. Mechanism of Action/Indication

PF-06840003 is an Indoleamine 2,3-Dioxygenase (IDO1) inhibitor that is currently being investigated in patients with malignant gliomas.

### 1.2. Background and Rationale

Indoleamine 2, 3-dioxygenase (IDO1) is a heme-containing dioxygenase that catalyzes the oxidation of tryptophan to N-formyl kynurenine in the first and rate-limiting step of tryptophan catabolism. N-formyl kynurenine is subsequently converted to kynurenine and other cytotoxic metabolites via the kynurenine pathway. IDO1 acts to inhibit T-cell function both through depletion of tryptophan and production of kynurenine (Munn & Mellor, 2013; van Baren & Ven den Eynde, 2015).<sup>15,24</sup> IDO1 expression is often higher in the tumor microenvironment, typically in response to inflammatory stimuli such as interferon gamma (IFN- $\gamma$ ) (Mellor & Munn, 2004).<sup>12</sup> The enzymatic activity of IDO1 is associated with suppression of T-cell responses (Uyttenhove et al, 2003)<sup>23</sup> and is correlated with poor prognosis in several cancer indications (Okamoto et al, 2005; Brandacher et al, 2006).<sup>18,5</sup> As such, IDO1 is a target of interest for cancer immunotherapy.

### 1.3. Malignant Gliomas

In 2010 an estimated 23,000 primary brain and central nervous system neoplasms were diagnosed in the United States, representing approximately 1.5% of all primary malignant cancers (Altekruse et al, 2010).<sup>2</sup> The most common of these in the adult population are malignant intra-parenchymal tumors that arise from glial cells and are termed malignant gliomas. Malignant gliomas are classified as: Grade III (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ependymoma and Grade IV (glioblastoma). Of these tumors, Glioblastoma (GBM) (World Health Organization WHO Grade IV), and Anaplastic Astrocytoma (AA) (WHO Grade III), have the highest incidence, accounting for an estimated 13,000 cases annually in the United States.

Despite representing only 1.5% of all primary malignant cancers, these tumors are responsible for approximately 2.8% of all cancer deaths, indicating both the severity of the disease and that GBMs are responsible for the highest number of “average years of life lost” (approximately 20 years) of all cancers (Burnet et al, 2005).<sup>6</sup> The median survival for patients with primary GBM from first diagnosis who receive best current treatment options is approximately 15 months, with only 5% to 10% of patients surviving longer than 2 years (Furnari et al, 2007).<sup>9</sup> Standard therapy for primary GBM and AA consists of surgical resection with adjuvant chemoradiation followed by post-radiation temozolomide maintenance therapy and systemic steroids to reduce edema in brain tissue. At recurrence a second surgical resection is possible in some patients (approximately 30 – 40%), where they may also receive an intra-operative carmustine-impregnated polymer wafer implantation in the resection site and possible additional systemic therapies. Patients with recurrent disease who are not candidates for a surgical resection may receive additional temozolomide maintenance therapy and bevacizumab (Avastin<sup>®</sup>) (Cohen et al, 2009).<sup>7</sup>

There are very few treatments that have demonstrated clear therapeutic benefit and received regulatory approval for patients diagnosed with GBM or Grade 3 glioma. This may be due to a number of factors, including the highly anaplastic and infiltrative nature of these tumors, reflected in their uncontrolled growth characterized by robust angiogenesis and resistance to apoptosis. In addition, GBM and AA have shown pronounced genetic heterogeneity and instability, which may confer multiple resistance phenotypes and consequent generally poor chemosensitivity (Mellinghoff et al, 2005; Beroukhim et al, 2007).<sup>11,4</sup> There are different subtypes of Grade 3 gliomas including anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma and anaplastic ependymoma. There are several forms of GBM: pure GBM, GBM with oligodendroglial features, MOA4, small cell GBM; Grade 3 astrocytomas display the same heterogeneity: anaplastic astrocytomas, oligoastrocytomas, oligodendrogliomas. Their prognosis and outcomes may be different if they share the same very poor prognosis.

Therefore, treatment of GBM or AA remains a crucial unmet medical need.

### **1.3.1. Rationale for Evaluation in Malignant Gliomas**

There is a very high degree of unmet medical need for improved treatment for recurrent GBM and Grade 3 glioma patients. Upon recurrence, management depends on age, performance status, histology, initial therapy response, time from original diagnosis and whether the occurrence is local or diffuse. In the case of diffuse or multiple tumor recurrences, palliative care is the preferred choice. In patients with localized disease, combination of surgery (20 to 25% of patients), biospecimens-based therapies and radiation (standard re-irradiation or highly conformal) is used with poor results. A response to chemotherapy is unlikely after 2 consecutive agents have failed to produce a response (Stewart, 2002).<sup>22</sup>

Bevacizumab has shown an overall response rate (ORR) of ~20 to 25% and a median response duration of 3.9 to 4.2 months, in two pivotal Phase 2 trials of recurrent high grade glioma patients following prior surgery, radiotherapy, and temozolomide treatment (Cohen et al, 2009).<sup>7</sup> Grade 3-5 adverse events related to bevacizumab included bleeding/hemorrhage, hypertension, proteinuria, thromboembolic events, wound-healing complications and gastrointestinal perforation. An agent with a >20% ORR, durable response and with manageable toxicity in a patient population expressing a specific target for the molecule would be highly relevant within the recurrent GBM clinical landscape.

## **1.4. PF-06840003 in Malignant Gliomas**

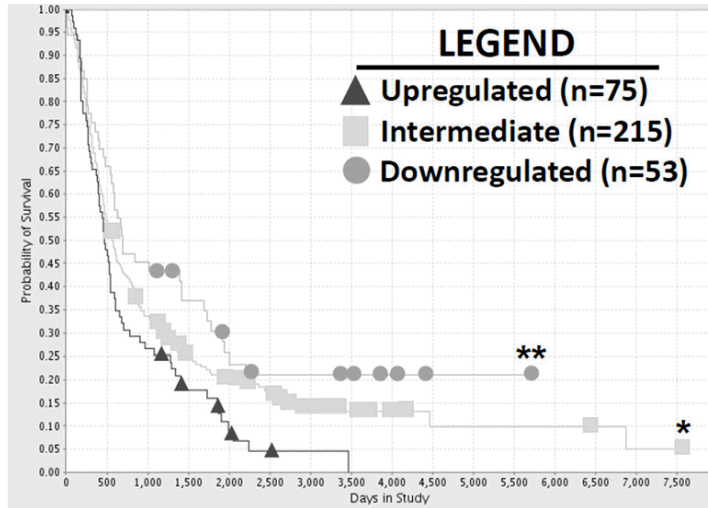
### **1.4.1. IDO1 in Malignant Gliomas**

IDO1 is expressed in 96% of malignant glioma (Mitsuka et al, 2013).<sup>13</sup> In a study reported by Mitsuka, IDO immunohistochemistry (IHC) expression has been assessed in 75 surgical specimens. Stronger expression in malignant gliomas was found compared with low-grade gliomas. In 6 cases of secondary glioblastoma, IDO expression was stronger than in the initial low-grade glioma. IDO was expressed more strongly in both primary and secondary glioblastoma tissue than low-grade glioma and could affect clinical outcome. Grade IV

patients with strong IDO expression had significantly worse overall survival rates ( $P = .04$ ) than patients with weak IDO expression.

The higher IDO expression in both primary and secondary glioblastoma tissue compared to low-grade glioma has been confirmed by other authors who reported that this may affect clinical outcome. (Wainwright et al, 2012).<sup>25</sup>

**Figure 1. IDO1 mRNA and protein expression levels correlated with overall patient survival (Wainwright et al, 2012)**



*The overall survival of patients with upregulated-, intermediate- and down regulated- expression in glioma specimens was  $24.9 \pm 2.76$ ,  $34 \pm 2.71$  and  $44.3 \pm 6.21$  months, respectively. Moreover, glioma upregulated for IDO was significantly correlated to an earlier average time of death (post-diagnosis), when compared to patients with intermediate ( $p < 0.05$ )- and down regulated ( $p < 0.005$ )- expressing glioma. Further analysis correlated the absolute expression level of IDO with survival, age of diagnosis and Karnofsky score, among grade(s) II, III and IV astrocytoma. Upregulated IDO expression in glioma predicted a poor prognosis in patients and this expression level tends to predominate in high grade glioma.*

The immunosuppressive impact of IDO1-mediated tryptophan (Trp) catabolism is well known, as well as active transport of Trp and the IDO1-downstream Trp catabolite, kynurenine (Kyn), across the blood brain barrier. The depletion of Trp and/or accumulation of Kyn has been shown to induce T cell deactivation, apoptosis and/or the induction of immunosuppressive programming via the expression of FoxP3 in malignant gliomas (Zhai et al, 2015).<sup>27</sup>

When comparing individuals without tumors to GBM patients prior to surgical resection, or at the 48 hour (48 h) and  $\geq 10$  week (10w+) postoperative time points, Trp levels in blood were significantly decreased ( $p < 0.0002$ ). Similarly, Kyn levels were decreased in the pre- and 48 h postoperative GBM patients ( $p < 0.0001$ ). Patients with a high Kyn/Trp ratio ( $\geq 9.5$ ) at 10 week postoperative had a mean overall survival (OS) of  $23.6 \pm$  a standard error of 6.8 months, compared to an OS of  $38.7 \pm 4.9$  months for patients with lower Kyn/Trp values. Kyn/Trp index may be a relevant clinical benchmark, providing prognostic value for GBM patients who are enrolled in immunotherapeutic regimens (Zhai et al, 2015).<sup>27</sup>

### 1.4.2. Mechanisms

The lack of response to treatment, immune therapy or chemotherapy in GBM patients may be attributed to the immunosuppressed microenvironment that is characteristic of invasive glioma.

GBMs are actively infiltrated by regulatory T-cells (Tregs) and some authors reported a strong correlation between glioma-induced immunosuppression and Tregs. (Ooi et al, 2014).<sup>19</sup> IDO in brain tumors increases the recruitment of T Regs and negatively impacts survival by promoting tumor invasion, migration, and growth, leading to a poor prognosis in high-grade glioma patients (Wainwright et al, 2014).<sup>26</sup> Induction of Treg activity has been correlated with glioma development in both murine models and patients. Tregs may contribute critically to the evasion of immunosurveillance by malignant gliomas: gliomas induce secretion of immunosuppressive factors such as HIF- $\alpha$  and PGE<sub>2</sub>, which are responsible for Treg recruitment and preferential proliferation and survival within the tumor microenvironment. Increased percentages of Tregs in glioma patients may induce immunosuppressive factors such as IL-10, TGF- $\beta$ , and various other cytokines.

IDO, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and programmed death-ligand 1 (PD-L1) are dominant molecular participants in the suppression of GBM immunity through complementary mechanisms including: IDO-mediated accumulation of Tregs (CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup>) in the tumor microenvironment; interaction of CTLA-4 expressed on tumor infiltrating T-cells with CD80 expressing dendritic cells; and the interaction of PD-L1 expressed by tumor cells and/or macrophages with PD-1 expressed by T-cells.

Individual inhibition of each pathway has been shown to increase survival in the context of experimental GBM. IDO-deficient tumors provide a selectively competitive survival advantage against IDO-competent tumors.

Therapeutic inhibition of IDO, CTLA-4, and PD-L1 in a mouse model of glioma maximally decreases tumor-infiltrating Tregs, coincident with a significant increase in T-cell-mediated long-term survival. 100% of mice bearing intracranial tumors are long-term survivors following triple combination therapy. Expression and/or frequency of T cell expressed CD44, CTLA-4, PD-1, and IFN- $\gamma$  depended on timing after immunotherapeutic administration. Individual inhibition of each pathway has been shown to increase survival in the context of experimental GBM and therapeutic inhibition of IDO, CTLA-4, and PD-L1 in mouse models of glioma maximally decreases tumor-infiltrating Tregs, coincident with a significant long-term survival (Wainwright et al, 2014).<sup>26</sup>

Unlike its competitors, PF-06840003 crosses the blood brain barrier (BBB).

### 1.4.3. Perspectives

IDO1 messenger ribonucleic acid (mRNA) and protein expression levels correlate with overall patient survival. IDO1 is involved in malignant glioma immunosuppression. IDO1 plays a key role in resistance to immune therapy. The selective nature of IDO1 expression in malignant glioma provides a high potential for targeting specificity.



## 1.5. Nonclinical Pharmacology and Safety

The nonclinical pharmacokinetics (PK) and metabolism program was designed to characterize the in vivo and in vitro absorption, distribution, and metabolism properties and the pharmacokinetic/pharmacodynamic (PK/PD) relationship of PF-06840003 to support the nonclinical safety evaluation. The single dose PK of PF-06840002 (active) and PF-06840001 (inactive) following intravenous (IV) and/or oral gavage administration of PF-06840003 was assessed in rats and monkeys as well as in the toxicology species (mice and dogs). Toxicokinetic (TK) data were obtained using a validated liquid chromatography-mass spectrometry (LC-MS)/MS assay following repeated dose administration. In vitro studies were also conducted to assess plasma protein binding as well as blood partitioning of PF-06840002 (active) and PF-06840001 (inactive) in mouse, dog and human matrices. In vitro metabolism was assessed across species as well as the potential for drug-drug interactions using liver enzymes and hepatic and liver transporters. Finally, studies were performed in vivo in tumor- and non-tumor-bearing mice to assess the PK/PD and efficacy relationship of PF-06840003 either as a monotherapy or in combination with PD-L1 blockade. Together, these studies helped to inform the human dose prediction.

General toxicity was evaluated by oral administration in exploratory single-dose and repeat-dose studies in mice and dogs, and pivotal 1-month studies in mice and dogs. The oral route of administration was selected for these studies since it is the intended route of clinical administration. Mice and dogs were selected as the nonclinical species based on the ability of PF-06840003 and its active enantiomer PF-06840002 to inhibit mouse, dog and human IDO1 enzymatic activity in an enzymatic mass spectrometry (MS) assay. In addition, both mice and dogs showed adequate systemic exposure following oral administration. Exploratory genetic toxicology studies included an in vitro micronucleus and a microbial reverse mutation assays.

### 1.5.1. Nonclinical Pharmacokinetics

The PK parameters of the active enantiomer PF-06840002 were characterized after single oral and/or IV administration of the racemic mixture, PF-06840003 in CD-1 mice, Wistar Han rats, beagle dogs, and cynomolgus monkeys. After IV dosing of PF-06840003, PF-06840002 (active) exhibited a low plasma clearance ( $CL_p$ ) in the mouse and rat, and moderate  $CL_p$  in the dog with a low volume of distribution ( $V_{ss}$ ) in these species, resulting in a short apparent terminal half-life ( $t_{1/2}$ ). PF-06840002 (active) was rapidly absorbed in all evaluated preclinical species after oral administration of PF-06840003 with an oral bioavailability (%F) in the mouse, rat, and dog of 59, 94, and 19%, respectively.

Systemic exposure [maximum observed concentration ( $C_{max}$ ) and area under the concentration-time curve from time zero to 24 hours ( $AUC_{24}$ )] of PF-06840002 (active) increased with increasing dose of PF-06840003 and there were no sex-related differences in exposure in the pivotal toxicology studies in mouse and dogs. In vitro studies suggest that PF-06840003 is not likely to be a substrate of P-glycoprotein (P-gp) efflux in humans.

The fraction unbound ( $f_u$ ) of PF-06840002 (active) to plasma proteins in mouse, rat, dog, and human ranged from 0.25 to 0.48, and demonstrated relatively equal distribution into plasma relative to red blood cells. PF-06840002 (active) was detected in the brain and the cerebrospinal fluid (CSF) after oral dosing to rats, suggesting that PF-06840002 (active) could cross central nervous system (CNS) barriers.

Renal excretion of PF-06840002 (active) following dosing of PF-06840003 in rats and dogs and biliary excretion in rats was limited. In vitro studies with PF-06840003 to assess the biliary excretion of PF-06840002 (active) in humans using sandwich-cultured human hepatocytes suggested minimal biliary excretion in humans.

PF-06840003 was primarily metabolized by oxidation and hydrolysis in human hepatocytes. The in vitro metabolic profile observed in humans was similar to that observed in the preclinical species evaluated. Phenotyping studies with PF-06840002 (active) indicated that cytochrome P450 (CYP)-mediated metabolism accounted for approximately 61% of the metabolic fate of this molecule and CYP1A2 was the primary enzyme responsible for oxidation. PF-06840002 (active) also demonstrated chiral inversion in buffer at pH 7.4 and in plasma to its inactive enantiomer (PF-06840001).

The mean  $IC_{50}$  values for inhibition of CYPs 1A2, 2B6, 2C8, 2C9, 2D6, and 3A4/5 were  $>100 \mu\text{M}$ , while the  $IC_{50}$  value for CYP2C19 was  $78 \mu\text{M}$ . In addition, PF-06840003 did not demonstrate metabolism-dependent or time-dependent inhibition of any of the CYP enzymes investigated. Similarly, treatment of human hepatocytes with PF-06840003 did not cause induction of CYP1A2 mRNA however there was induction of CYP3A4 and CYP2B6 mRNA. The concentrations of PF-06840003 to inhibit 50% of substrates of P-gp or breast cancer resistance protein (BCRP) were  $>300 \mu\text{M}$  ( $69600 \text{ ng/mL}$ ) and  $65.4 \mu\text{M}$  ( $15200 \text{ ng/mL}$ ), respectively. Since the dose of PF-06840003 in human will be determined in combination with other agents, drug-drug interaction (DDI) assessments will be made once the clinically effective dose has been ascertained.

In vitro studies in human blood and in vivo PK/PD TGI studies in BALB/c mice suggested that the unbound concentration of PF-06840002 (active) required to achieve maximum tumor growth inhibition (TGI) and PD-modulation was approximately  $5.00$  to  $5.69 \mu\text{M}$  ( $1160$  to  $1320 \text{ ng/mL}$ ) and can be considered to be the pharmacologically active concentration required to achieve 90% inhibition of IDO1. In humans, PF-06840002 (active) is projected to have a  $CL_p$  of  $0.64 \text{ ml/min/kg}$ ,  $V_{ss}$  of  $1.03 \text{ L/kg}$ , and a  $t_{1/2}$  of approximately 18.7 hours. The bioavailability of PF-06840002 (active) after an oral dose of PF-06840003 was projected to be 64%. Using the predicted human PK parameters and a conservative estimate of  $5.69 \mu\text{M}$  ( $1320 \text{ ng/mL}$ ) to achieve 90 % inhibition of IDO1, the pharmacologically active dose of PF-06840003 is projected to be 200 mg twice a day (BID) and 500 mg once daily (QD).

### 1.5.2. Nonclinical Safety

PF-06840003 was assessed in a series of nonclinical studies with the oral route of exposure since this is the intended route of clinical administration. Good Laboratory Practice (GLP) 1-month repeat-dose studies were conducted in mice and dogs.

In the 1-month mouse study, the primary target organs were the CNS, liver, spleen, and adrenals. Four animals (2 main study, 2 toxicokinetic) receiving 2000 (1000 BID) mg/kg/day were euthanized prior to dosing on Day 2 due to PF-06840003 related adverse clinical signs, including decreased activity, partially closed eyes, recumbency, unable to rise, twitching, tremors and convulsions. No PF-06840003 related microscopic findings were observed in these animals, and therefore a cause for the morbidity was not determined. Dosing was discontinued after the second daily dose on Day 1 for this group of animals and resumed at 1200 (600 BID) mg/kg/day on Day 4. PF-06840003-related, non-adverse findings included microscopic findings in the liver (minimal to mild centrilobular hypertrophy associated with higher liver weight, and minimal increases in extra medullary hematopoiesis), spleen (increases in severity [mild and moderate] of extra medullary hematopoiesis associated with higher splenic weight), adrenals (increases in severity [mild] of vacuolated cells in the X zone in female mice only), increased adrenal weight (male mice only), higher cholesterol (female mice only), and higher globulin values with lower associated albumin/globulin ratios (female mice only). Additional PF 06840003-related, non-adverse findings included intermittent observation of discolored urine without associated microscopic changes, and higher body weight and food consumption. All changes showed reversibility at the end of the 1-month recovery phase.

In the 1-month dog study, the primary target organs or systems were the liver, thyroid, and the cardiovascular, hematopoietic, and coagulation systems. PF-06840003 related, adverse microscopic findings were noted in the liver (minimal to mild hepatocellular degeneration with accompanying increases in hepatic enzymes [1.4 19x baseline] and/or serum and urine bilirubin [2-4x baseline]); adverse effects on body weight and food consumption with associated adverse clinical signs were also noted. Additional non-adverse liver effects included decreased glycogen content of hepatocytes considered secondary to decreased food consumption, higher liver weights without microscopic correlates, and deposition of pigmented material (hemosiderin) in Kupffer cells related to the primary finding of mild hepatocellular degeneration and associated hemorrhage. PF-06840003-related, non-adverse effects were observed in the thyroid (minimal follicular cell hypertrophy) and thymus (minimal decrease in lymphoid cellularity, lower thymus weight). The changes noted in the thymus were observed in a single high dose (600 [300 BID] mg/kg/day) male dog showing adverse clinical signs and were considered secondary to stress. PF-06840003-related, non-adverse effects were also observed in clinical pathology parameters (decreased red cell mass parameters and albumin, increased prothrombin time, activated partial thromboplastin time and fibrinogen). Additional PF-06840003-related, non-adverse changes included emesis, abnormal urine color and lower urine pH. All changes showed reversibility at the end of the 1-month recovery phase, except for the deposition of hemosiderin in Kupffer cells and the change in prothrombin time. Reversibility of the effects on prothrombin time could not be evaluated as recovery animals did not demonstrate these changes during the dosing phase, but would be expected to recover based on the normalization of activated partial thromboplastin time during recovery.

## 1.6. Starting Dose Rationale

The selection of the starting dose for this first-in-patient (FIP) study is based on the preclinical toxicology results in accordance with the International Conference on Harmonization (ICH) S9 Guidance entitled “Nonclinical Evaluation for Anticancer Pharmaceuticals”, as well as predicted pharmacologically active dose in humans. Results from preclinical toxicity studies indicate that mouse is the most sensitive species, and STD10 in mouse was determined to be 1200 mg/kg. Based on S9 guidance, the STD10 of 1200 mg/kg in mouse results in Maximum Recommended Starting Dose (MRSD) of approximately 580 mg in human (assuming body weight of 60 kg), which is greater than the projected human pharmacological active dose ranging from 125 to 500 mg derived from IDO1 inhibition. Therefore, the recommended starting dose for this FIP study is 125 mg given as oral administration once daily (QD), and this dose represents approximately 1/47<sup>th</sup> of mouse STD10 (based on human equivalent dose normalized to body surface area). In addition, given the projected human PK parameters, the projected human AUC for PF-06840003 at the proposed starting dose of 125 mg is expected to be approximately 1/18<sup>th</sup> of the observed mouse AUC at STD10.

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the investigator’s brochure.

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Objectives

#### Primary Objective – Part 1

- To evaluate the safety and tolerability of increasing dose levels of daily oral PF-6840003 in patients with malignant gliomas.
- To characterize the dose limiting toxicities (DLTs) of escalated doses of PF-06840003.
- To determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D).

#### Primary Objective – Part 2

- To further evaluate the safety and tolerability of PF-06840003 at the RP2D.
- To evaluate the efficacy of PF-06840003 in patients with glioblastoma.

## Secondary Objectives – Parts 1 and 2

- To evaluate the overall safety profile.
- To characterize the single and multiple dose plasma PK of active enantiomer PF-06840002, and inactive enantiomer PF-06840001 after administration of the racemic mixture, PF-06840003.
- To document any anti-tumor activity (Part 1 only).
- To evaluate dose and concentration response relationship for target engagement and PD biomarkers and to then correlate with PK, safety and efficacy to select dose with full or optimal target engagement.
- To assess the CSF PK exposure of active enantiomer PF-06840002, and inactive enantiomer PF-06840001 after administration of the racemic mixture, PF-06840003.

CCI [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

## 2.2. Endpoints

### Primary Endpoint – Part 1

- Incidence and grade of treatment-emergent adverse events (TEAE) including DLTs as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

## Primary Endpoints – Part 2

- Adverse Events (AE) as characterized by type, frequency, severity, timing, seriousness, and relationship to study therapy.
- Disease control rate (DCR) at 9 and 25 weeks by MRI using Macdonald criteria (Macdonald et al, 1990).<sup>10</sup>

## Secondary Endpoints

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;
- Vital Signs;
- PK parameters in the blood of PF-06840002 and PF-06840001 Single Dose (SD) –  $C_{max}$ ,  $T_{max}$ ,  $AUC_{last}$ ,  $AUC_{\tau}$ ,  $CL/F$ , and  $V_z/F$  and  $t_{1/2}$ ,  $AUC_{inf}$  as data permit. Multiple Dose (MD) (assuming steady state is achieved) –  $C_{ss,max}$ ,  $T_{ss,max}$ ,  $AUC_{ss,\tau}$ ,  $t_{1/2}$ ,  $C_{ss,min}$ ,  $C_{ss,av}$ ,  $CL/F$ ,  $V_{ss}/F$ ,  $R_{ac}$  ( $AUC_{ss,\tau}/AUC_{sd,\tau}$ ) and  $R_{ss}$  ( $AUC_{ss,\tau}/AUC_{sd,inf}$ ) as data permit;
- Objective tumor response based on Macdonald criteria.
- Disease Control Rate at 9 and 25 weeks by MRI based on Response Assessment for Neuro-Oncology (RANO) criteria.
- On-target activity of PF-06840003 by measurement of kynurenine, tryptophan and kyn/trp (ratio) levels in peripheral blood.
- Steady-state trough level ratio between CSF and plasma samples for PF-06840002 and PF-06840001.

CCI [REDACTED]

CC [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

**C**  
**C**  
**I**

[REDACTED]

[REDACTED]

[REDACTED]

### 3. STUDY DESIGN

#### 3.1. Study Overview

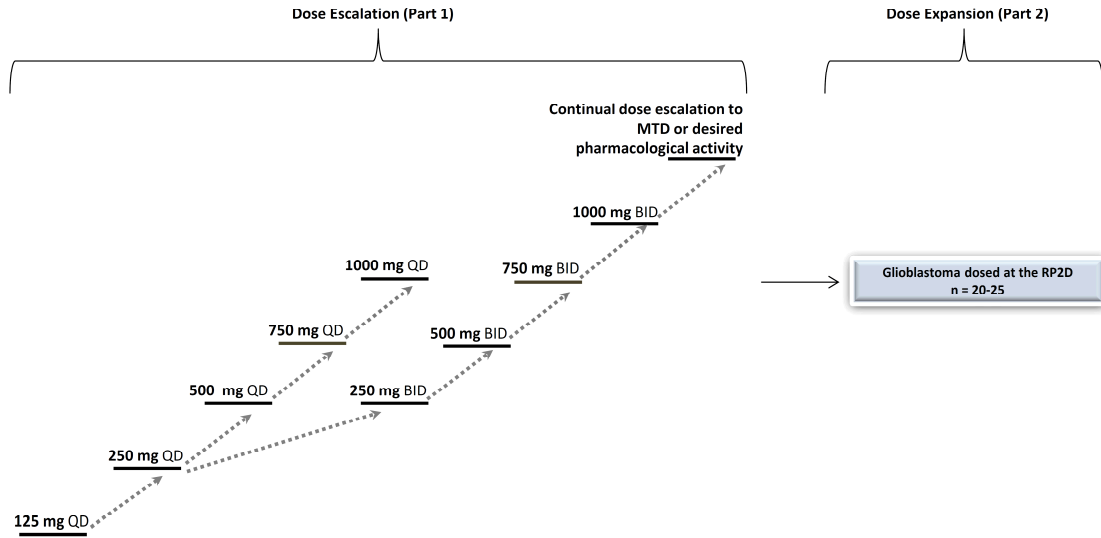
This is a Phase 1, open-label, multi-center, multiple-dose, safety, PK and PD study of single agent PF-06840003. This study contains two parts, dose escalation (Part 1) followed by dose expansion (Part 2). In Part 1, sequential cohorts of patients with recurrent malignant gliomas (GBM and/or WHO grade III anaplastic gliomas) will receive escalating doses of PF-06840003. Part 2 will evaluate safety as well as explore preliminary antitumor activity of the dose selected from Part 1 in additional patients with GBM.

The actual number of patients enrolled in the study will depend on the tolerability of PF-06840003 and the number of dose levels required to identify the MTD or Recommended Phase 2 Dose (RP2D) if the MTD is not reached. The target sample size for each cohort in Part 1 is 2-4 patients, but, the actual number of patients treated at each dose will vary from 2 to 12. It is estimated that the maximum sample size will be approximately 72 patients in Part 1 of the study, although this may be higher if more than 6 dose levels are required to be evaluated. Up to approximately 20 to 25 patients are anticipated to be enrolled in Part 2 of the study.

PF-06840003 will be administered daily as an oral dose in 28 day cycles with a starting dose of 125 mg once daily (QD). The pre-specified nominal doses for use in the dose escalation are 125 mg/day, 250 mg/day and 500 mg/day of PF-06840003. If the MTD or RP2D are not reached within the pre-planned nominal dose range, and the PK and PD data show that the target coverage is not optimal, the sponsor, in conjunction with the investigators, after careful consideration of all available safety, laboratory and PK information may expand the nominal dose range to a higher dosage, up to a maximum dosage of 1000 mg per day. Based on emerging clinical and PK data, twice a day (BID) dosing may be explored. For example, if the exposure over 24 hours does not allow for sufficient target coverage it may be determined that BID dosing is needed. In such a case, BID dosing will be initiated at the QD dose level where no DLTs are observed (ie, starting dose of BID dosing will be 250 mg BID after safety and tolerability profile of 250 mg QD is confirmed). Once a BID dosing regimen is initiated for further escalation towards the MTD, the escalation with a QD regimen will be suspended. Intermediate doses may also be used if required.

The overall study design is depicted in Figure 2. Treatment will continue until either disease progression, patient refusal, or unacceptable toxicity occurs, whichever is earliest, unless the investigator and medical monitor agree to treatment beyond disease progression based on individual benefit/risk assessments.

**Figure 2. Overall Study Design**



The proposed doses, schedule(s) and PK time points may be reconsidered and amended during the study based on the emerging safety and PK data. Intermediate doses may be evaluated.

### 3.1.1. Criteria for Dose Escalation

In Part 1 of the study, dose escalation and de-escalation will follow a modified Toxicity Probability Interval (mTPI) method, targeting a DLT rate of 27.5% and an acceptable DLT interval 22.5 to 32.5%. The dose levels to be evaluated in Part 1 of the study are listed in the following table:



**Table 1. Dose Escalation Potential Dose Levels**

| Potential Dose Level | PF-06840003 (mg QD)*  | PF-06840003 (mg BID)  |
|----------------------|---|---|
| Starting Dose        | 125   | N/A   |
| 2                    | 250   | N/A   |
| 3                    | 500   | 250   |
| 4                    | 750   | 500   |
| 5                    | 1000  | 750   |
| 6                    | To be determined  | 1000  |
| 7                    | Escalation to continue to the MTD or desired pharmacological activity | Escalation to continue to MTD or desired pharmacological activity |

\* While a more frequent dosing regimen is initiated for further escalation towards the MTD, the escalation with a QD regimen will be suspended.

The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in the current dose level to determine one of the following dose-finding decisions: the subsequent dose should be escalated, maintained at the current dose, or de-escalated in the next cohort of 2 to 4 patients, or the trial should be terminated.

As an example, if the total number of patients treated at the current dose level is 4, the following dosing rules are applied:

- 0 DLT -> escalate
- 1 DLT -> remain at the same dose
- 2 DLTs -> de-escalate
- 3-4 DLTs -> de-escalate and consider current dose as intolerable

The general approach to dose-finding, using the mTPI method, involves the following:

- The target cohort size is 2 to 4, depending on the number of potential patients identified at participating sites;
- The next cohort can be enrolled when all patients at the current dose cohort have been evaluated for 28 days of the first treatment cycle, or experience a dose-limiting toxicity (DLT), whichever comes first;
- If a patient withdraws from the study before receiving  $\geq 80\%$  of the planned first-cycle dose for reasons other than investigational product-related toxicity, another patient will be enrolled to replace that patient at the current dose combination;
- In the situation in which the safety of the starting dose does not allow for escalation to the next dose level, a lower dose will be considered.

The dose escalation portion of the study is completed when at least 6 to 12 evaluable patients have been treated at the highest dose associated with DLT rate  $\leq 32.5\%$ .

**Table 2. Decision Rules**

| Number of Patients having DLT | Number of Patients Treated at a Dose Level |     |     |     |     |     |     |     |      |      |      |
|-------------------------------|--|-----|-----|-----|-----|-----|-----|-----|------|------|------|
|                               | n=2  | n=3 | n=4 | n=5 | n=6 | n=7 | n=8 | n=9 | n=10 | n=11 | n=12 |
| 0                             | E  | E   | E   | E   | E   | E   | E   | E   | E    | E    | E    |
| 1                             | S  | S   | S   | E   | E   | E   | E   | E   | E    | E    | E    |
| 2                             | U  | D   | S   | S   | S   | S   | S   | S   | S    | E    | E    |
| 3                             |  | U   | U   | D   | D   | S   | S   | S   | S    | S    | S    |
| 4                             |  |     | U   | U   | U   | U   | D   | D   | D    | S    | S    |
| 5                             |  |     |     | U   | U   | U   | U   | U   | D    | D    | D    |
| 6                             |  |     |     |     | U   | U   | U   | U   | U    | U    | U    |
| 7                             |  |     |     |     |     | U   | U   | U   | U    | U    | U    |

Actions to be taken:

D = De-escalate the dose; E: Escalate the dose; S: Stay at the dose.

U = Unacceptable toxicity.

### 3.2. DLT Definition

Severity of AEs will be graded according to CTCAE version 4.03. For the purpose of dose escalation, any of the following adverse events occurring in the first cycle of treatment (28 days) will be classified as DLTs, unless there is a clear alternative explanation (eg, related to underlying disease/progression, change in concurrent medication or co-morbid event):

#### Hematologic:

- Grade 4 neutropenia lasting  $\geq 5$  days;
- Febrile neutropenia [defined as absolute neutrophils count (ANC)  $< 1,000/\text{mm}^3$  with a single temperature of  $> 38.3^\circ\text{C}$  ( $101^\circ\text{F}$ ) or a sustained temperature of  $\geq 38^\circ\text{C}$  ( $100.4^\circ\text{F}$ ) for more than one hour];
- Grade  $\geq 3$  neutropenia with infection;
- Grade  $\geq 3$  thrombocytopenia with bleeding;

- Grade 4 thrombocytopenia.

**Non-hematologic:**

- Any toxicity attributable to PF-06840003 that results in administration of less than 80% of the planned doses during Cycle 1.
- Grade 4 non hematologic AE.
- Grade 3 AE lasting >7 days despite optimal supportive care.
- Grade 3 CNS AE regardless of duration. CNS AEs are those events listed within the nervous system disorders category in the NCI CTCAE version 4.03.
- Grade 3 QTc prolongation (QTc >500 msec) will be considered a DLT only if persisting after correction of any reversible causes.
- Concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x upper limit of normal (ULN) and total bilirubin >2 x ULN.

The following AEs will not be considered as DLTs:

- Isolated Grade 3 or 4 laboratory abnormalities that are not associated with clinical sequelae or are corrected to Grade  $\leq$ 1 with supplementation/appropriate management within 72 hours of their onset.

**3.3. MTD Definition**

The estimated MTD is the dose level associated with approximately 27.5% of DLT-evaluable patients experiencing a DLT. The target interval for the DLT rate is (22.5%, 32.5%) Due to the discreteness of the dose levels and in the interest of the safety of the patients, the estimated MTD is the highest tested dose level with DLT rate  $\leq$ 32.5% (see [Table 2](#)).

**3.4. Late Onset Toxicity and Toxicities Observed in the Expansion Phase**

Adverse events that meet the same grading criteria as the DLT criteria listed above occurring after the DLT observation period will lead Pfizer to immediately schedule a meeting with the investigators to review the details of the potential late onset toxicity and determine if the enrollment has to be held for this dose level or if a dose reduction should be implemented for all ongoing patients. Late onset toxicities meeting the definition of a DLT will be used in the evaluation of the MTD.

In addition, adverse events that meet the same grading criteria as the DLT criteria listed above occurring in the expansion phase (Part 2) will prompt Pfizer to immediately schedule a meeting with the investigators to review the details of the toxicity and determine the necessary action to be implemented for all patients.

### **3.5. Recommended Phase 2 Dose (RP2D) Definition**

The RP2D is the dose chosen for further study based on Phase 1 study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

## **4. PATIENT SELECTION**

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

### **4.1. Inclusion Criteria**

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Pathologically documented and definitively diagnosed recurrent WHO Grade IV GBM.
2. Pathologically documented and definitively diagnosed recurrent WHO Grade III anaplastic gliomas (including anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma and mixed gliomas) – Part 1 only.
3. Access to archived formalin fixed paraffin embedded material from the initial diagnosis or subsequent relapse of Grade IV GBM or Grade III anaplastic glioma that is of diagnostic quality and representative of their diagnosed malignancy available for submission to the sponsor. If archival tissue is not available, the patient must consent to surgical intervention to acquire tumor tissue at screening.
4. For patients with Grade IV GBM, recurrent disease (confirmed by MRI and evaluable by Macdonald criteria) at the time of first or second recurrence or progression following prior definitive therapy(s) such as surgery with adjuvant radiation therapy and/or chemotherapy. For patients with Grade III anaplastic glioma, recurrent disease (confirmed by MRI and evaluable by Macdonald criteria) at the time of at least a first recurrence but no more than a fourth recurrence or progression following prior definitive therapy(s).
5. Must have recovered to Grade 0 or 1 or pre-treatment baseline from clinically significant toxic effects of prior therapy (including but not limited to exceptions of alopecia, laboratory values listed per inclusion criteria, and lymphopenia which is common after therapy with temozolomide).

6. Must have stable dosing of corticosteroid treatment for at least 7 days prior to registration and are neurologically stable.
7. Must have recovered from the acute effects of radiation therapy or surgery or systemic treatment prior to study entry.
8. Age  $\geq 18$  years.
9. Karnofsky performance score  $\geq 70\%$ .
10. Have received no more than two prior lines of therapy.
11. Adequate Hematologic Function, including:
  - a. Absolute Neutrophil Count (ANC)  $\geq 1,500/\text{mm}^3$  or  $\geq 1.5 \times 10^9/\text{L}$ ;
  - b. Platelets  $\geq 100,000/\text{mm}^3$  or  $\geq 100 \times 10^9/\text{L}$ ;
  - c. Hemoglobin  $\geq 9$  g/dL.
  - d. Prothrombin time (PT) or partial thromboplastin time (PTT)  $< 1.5$  x upper limit of normal (ULN).
12. Adequate Renal Function, including:
  - a. Estimated creatinine clearance  $\geq 60$  mL/min as calculated using the Cockcroft-Gault calculator. A 24-hour urine collection is not required but should be used to confirm estimated creatinine clearance if a urine collection is obtained as part of standard of care.
13. Adequate Liver Function, including:
  - a. Total serum bilirubin  $\leq 1.0$  x ULN unless the patient has documented Gilbert syndrome or extrahepatic source by increased indirect bilirubin function;
  - b. Aspartate and Alanine transaminase (AST and ALT)  $\leq 1.5$  x ULN ( $\leq 3$  x ULN for patients on chronic anticonvulsive therapies known to increase transaminases)
  - c. Alkaline phosphatase  $\leq 1.5$  x ULN; ( $\leq 3$  x ULN for patients on chronic anticonvulsive therapies known to increase transaminases)
14. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.
15. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
  - Have medically confirmed ovarian failure; or
  - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.
16. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.
17. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

#### **4.2. Exclusion Criteria**

Patients with any of the following characteristics/conditions will not be included in the study:

1. History of CNS bleeding as defined by stroke or intraocular bleed (including embolic stroke) within 6 months before registration.
2. Evidence of acute intracranial / intratumoral hemorrhage, except for patients with stable Grade 1 hemorrhage.
3. Peripheral sensory neuropathy  $\geq$  Grade 2.
4. Requires treatment with high dose systemic corticosteroids defined as dexamethasone (or equivalent)  $>2$  mg/day or bioequivalent for at least 3 consecutive days within 2 weeks of registration.
5. Previous high-dose chemotherapy requiring stem cell rescue.
6. Previous anti-angiogenic or anti-vascular endothelial growth factor (VEGF) targeted agents (eg, bevacizumab, cediranib, aflibercept, vandetanib, XL-184, sunitinib, etc.) within 12 months of registration. In addition, patients who experienced significant bleeding during bevacizumab treatment will also be excluded.
7. Surgical resection within 4 weeks of registration.
8. Completion of radiation therapy within 12 weeks of registration unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field or there is unequivocal histologic confirmation of tumor progression.

9. Cytotoxic therapy within 4 weeks (except 6 weeks for nitrosoureas), investigational agent within 5 half-lives, antibody within 6 weeks or any other anti-tumor therapies within 4 weeks (or 5 half-lives, whichever is shorter) of registration.
10. History of suicidal ideation within 12 months of registration. Patients who have a history of suicidal ideation within 12 months of registration can be included if a risk assessment by a qualified mental healthcare professional determines the patient is deemed acceptable for inclusion.
11. Life expectancy of less than 3 months in the opinion of the investigator.
12. Prior treatment with a compound of the same mechanism.
13. Active and clinically significant bacterial, fungal, or viral infection, including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.
14. Any of the following in the previous 6 months: myocardial infarction, symptomatic congestive heart failure (New York Heart Association > class II), unstable angina, or uncontrolled hypertension (defined as systolic >160 mmHg or diastolic >100 mmHg).
15. History of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer, or other solid tumors curatively treated with no evidence of disease for  $\geq 2$  years.
16. Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease or previous gastric resection or lap-band. Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed.
17. Current use or anticipated need for food or drugs that are known strong CYP1A2 inhibitors, including their administration within 10 days prior to the first PF-06840003 dose (such as, but not limited to: Strong CYP1A2 Inhibitors: fluvoxamine, ciprofloxacin, clinafloxacin, enoxacin, oltipraz, propranolol, rofecoxib, thiabendazole, and zafirlukast).
18. Current use or anticipated need for food or drugs that are known strong CYP1A2 inducers, including their administration within 10 days prior to the first PF-06840003 dose (ie, Strong CYP1A2 Inducers: tobacco (including cigarettes and products containing tobacco)).
19. Patients with known malabsorption syndrome or other condition that may impair absorption of study medication.
20. Severe acute or chronic medical or psychiatric condition, including recent laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

21. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

22. Pregnant female patients; breastfeeding female patients.

### **4.3. Lifestyle Guidelines**

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive PF-06840003, a compound for which the teratogenic risk is currently unknown. Two (2) methods of highly effective contraception must be used throughout the study and continued for at least 28 days after the last dose. The investigator or his or her designee, in consultation with the patient, will confirm the patient has selected two appropriate methods of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below) and will confirm the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of at least 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected in the patient or the patient's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the post vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).



6. Female partner who meets the criteria for non-childbearing potential, defined as:
- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
  - Have medically confirmed ovarian failure; or
  - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

#### **4.4. Sponsor's Qualified Medical Personnel**

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

#### **4.5. Rater Qualifications**

Site staff (eg, physicians, nurses, psychologists, social workers, coordinators and research assistants) must be trained on the administration of the C-SSRS form prior to completing the first assessment. Completion of the necessary training will be documented in a training certificate.

Prior to implementation of the cognitive assessments in Part 2, site staff must also be trained on the administration of the COWA and HVLT-R. Completion of the necessary training will be documented in a training certificate.

### **5. STUDY TREATMENTS**

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different

from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

### **5.1. Allocation to Treatment**

Dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary screening assessments. Registration should occur before any other Day 1 activities are performed and preferably no more than 3 business days before Day 1. The site staff will email a complete Patient Enrollment Form to the designated sponsor study team member. The sponsor will assign a patient enrollment number and this email to the site.

No patient shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- confirmation of the patient's enrollment;
- specification of the dose level for that patient and
- permission to proceed with dosing the patient;

### **5.2. Patient Compliance**

Patients will be required to return all unused study treatment at the beginning of each cycle. The number of tablets returned by the patient at the end of the cycle will be counted, documented, and recorded for drug accountability. Treatment compliance (reported as a percent) will be defined as the number of tablets taken during the study divided by the expected number of tablets multiplied by 100%. Tablets that are not returned will be considered to have been taken unless reported otherwise by the patient. Drug diary records will be provided to the patients as an aid for the recording of study treatment compliance. Patients with a less than 75% compliance with the study requirements, for reasons other than toxicity, may be withdrawn from the study.

### **5.3. Investigational Product Supplies**

#### **5.3.1. Dosage Form(s) and Packaging**

PF-06840003 will be provided as tablets for oral administration. The 125 mg or 25 mg tablets will be supplied in high-density polyethylene (HDPE) bottles and labeled according to local regulatory requirements.

#### **5.3.2. Preparation and Dispensing**

The study treatment should be dispensed at each visit per the [schedule of activities](#). A qualified staff member will dispense the investigational product in the bottles provided, in quantities appropriate for the study visit schedule. The patient should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit where accountability is to be performed.

See the Investigational Product manual for instructions on investigational product dispensation for administration. Investigational product should be dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

#### **5.4. Administration**

On days when patients have clinic visits where PK assessments are to be obtained, PF-06840003 should not be taken prior to the study visit. Daily oral dosing with PF-06840003 will be initiated on Cycle 1 Day 1 and should continue until end of treatment. The PF-06840003 can be taken after the study procedures required for that visit have been performed. Patients will be instructed to swallow the investigational product whole, and to not manipulate or chew the investigational product prior to swallowing.

PF-06840003 will be administered orally on an empty stomach (ie, no food or beverages other than water for two hours before or two hours after dosing) without adjustment for body size. Tablets should be administered with approximately 240 mL of ambient temperature water. Patients should be instructed to take their medication at approximately the same time each day and to not take more than the prescribed dose at any time. Patients who are assigned to a BID dosing regimen should be instructed to take their PF-06840003 every 12 hours  $\pm$  1 hour.

If a patient assigned to take PF-06840003 one time per day misses a day of treatment, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed.

If a patient assigned to take PF-06840003 two times per day misses a dose by more than 4 hours of when they should have taken it, he/she must be instructed not to "make it up" but to resume subsequent doses at the next scheduled dosing time as prescribed.

If a patient vomits any time after taking a dose, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of PF-06840003.

##### **5.4.1. Recommended Dose Modifications**

Every effort should be made to administer investigational product on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in the current and/or subsequent cycle based on toxicity experienced in the current/previous cycle.

#### **5.4.2. Dosing Interruptions**

Patients experiencing the following adverse events should have their treatment interrupted:

- Grade 3 or 4 potentially treatment related toxicity;
- Intolerable Grade 2 toxicity despite supportive care.

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in [Section 5.4.3 Dose Delays](#).

Doses may be held as needed until toxicity resolution. Depending on when the AE resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the AE that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in section [Dose Reductions](#), unless expressly agreed otherwise following discussion between the investigator and the sponsor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >4 weeks, treatment resumption will be decided in consultation with the sponsor.

#### **5.4.3. Dose Delays**

Re-treatment following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- ANC  $\geq 1,000/\text{mm}^3$ .
- Platelet count  $\geq 50,000/\text{mm}^3$ .
- Non-hematologic toxicities have returned to baseline or Grade  $\leq 1$  severity (or, at the investigator discretion, Grade  $\leq 2$  if not considered a safety risk for the patient).

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If these conditions are met within 2 weeks of treatment interruption or cycle delay, PF-06840003 dosing may be resumed. Refer to Section Dose Reductions for AEs requiring dose reduction at the time of treatment resumption.

If these conditions are not met, treatment resumption must be delayed up to a maximum of 2 weeks. If these parameters have not been met after 2 weeks of dosing interruption, or 2 weeks of new cycle delay, permanent discontinuation of treatment with PF-06840003 should be considered. Treatment resumption for patients recovering from treatment-related toxicity after >2 weeks of treatment interruption or cycle delay may be considered only if the patient is deemed to be deriving obvious clinical benefit per the investigator's best medical judgment and needs to be agreed between the investigator and the sponsor.

If a treatment interruption continues beyond Day 28 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

#### **5.4.4. Dose Reductions**

Following dosing interruption or cycle delay due to toxicity, the PF-06840003 dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade  $\leq 1$  or baseline is achieved.

Dose reductions of PF-06840003 are not allowed for patients receiving the starting dose of 125 mg. Dose reduction of PF-06840003 by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. However, dose reductions below 125 mg daily are never allowed. Patients requiring more than 2 dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the patient's source notes and case report form (CRF).

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

Patients experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved. Dose reductions for patients experiencing a late onset toxicity or toxicity in the expansion phase will be discussed in consultation with the sponsor.

**Table 3. Dose Modifications for Investigational Product-Related Toxicity**

| Toxicity        | Grade 1                          | Grade 2                          | Grade 3  | Grade 4   |
|-----------------|----------------------------------|----------------------------------|--|---|
| Non-hematologic | Continue at the same dose level. | Continue at the same dose level. | Withhold dose until toxicity is Grade $\leq 1$ , or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator*. | Withhold dose until toxicity is Grade $\leq 1$ , or has returned to baseline within 14 days, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator*. |
| Hematologic     | Continue at the same dose level. | Continue at the same dose level. | Withhold dose until toxicity is Grade $\leq 1$ , or has returned to baseline, then resume treatment at the same dose level**.  | Withhold dose until toxicity is Grade $\leq 1$ , or has returned to baseline, then reduce the dose by 1 level and resume treatment or discontinue at the discretion of the investigator**.                |

\* Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification.

\*\* Cycle will not be extended to cover for the missing doses.

### 5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label.

Storage conditions stated in the single reference safety document (SRSD) (eg, Investigator Brochure) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be documented. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct patients on the proper storage requirements for take home study treatment.

## **5.6. Investigational Product Accountability**

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. Patients will be required to return all unused study treatment at the beginning of each cycle.

### **5.6.1. Destruction of Investigational Product Supplies**

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI



### **5.7.1. Other Anti-tumor/Anti-cancer or Experimental Drugs**

No additional anti-tumor treatment will be permitted while patients are receiving study treatment. Additionally, the concurrent use of select vitamins or herbal supplements is not permitted.

### **5.7.2. Supportive Care**

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

### **5.7.3. Anti-inflammatory Therapy**

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the [Concomitant Treatment\(s\)](#) section.

Due to the immunologic nature of PF-06840003 administration, cerebral edema could theoretically result as a consequence of PF-06840003 administration due to immune infiltration of the brain. Symptoms related to cerebral edema may include headache or neurologic deficit that is either new or worsened. Patients with any signs or symptoms of cerebral edema should be treated as clinically appropriate including initiation or increased systemic corticosteroid dosing, treatment with an osmotic diuretic or surgical decompression. Subsequent PF-06840003 dosing should be immediately interrupted if significant clinical symptoms attributable to cerebral edema develop. Treatment with additional PF-06840003 doses may only be re-initiated if clinically significant symptoms attributable to cerebral edema have resolved to grade  $\leq 1$  or pre-treatment baseline. Patients who develop CTCAE 4.0 grade 4 cerebral edema attributable to PF-06840003 administration should not receive further PF-06840003 doses and should discontinue study therapy.

### **5.7.4. Surgery**

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06840003 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06840003 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate



PF-06840003 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

## **6. STUDY PROCEDURES**

### **6.1. Screening**

For screening procedures see Schedule of Activities and [ASSESSMENTS](#) section.

### **6.2. Study Period**

For treatment period procedures, see Schedule of Activities and [ASSESSMENTS](#) section.

### **6.3. Follow-up Visit**

For follow-up procedures see Schedule of Activities and [ASSESSMENTS](#) section.

### **6.4. Patient Withdrawal**

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression according to the iRANO criteria. Disease progression is to be confirmed with two consecutive timepoints at least 8 weeks apart in the absence of substantial neurological decline if progression is suspected within 6 months of treatment initiation.
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Investigator discretion;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product, request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

If the patient refuses further visits, no further study specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

## **7. ASSESSMENTS**

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 preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

### **7.1. Safety Assessment**

Safety assessments will include collection of AEs, serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (ECG) [12-lead], laboratory assessments, including pregnancy tests and verification of concomitant treatments.

#### **7.1.1. Pregnancy Testing**

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment – once at the start of screening and once at Cycle 1 Day 1 immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a

further negative pregnancy result will then be required at the Cycle 1 Day 1 visit: within 5 days after the first day of the menstrual period counting the first day as Day 1 > before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive human chorionic gonadotropin (hCG) test, the patient will be withdrawn from treatment and from the study. Additional pregnancy tests may also be undertaken if requested by institutional review board (IRB)/ ethics committees (ECs) or if required by local regulations.

### **7.1.2. Adverse Events**

Assessment of AEs will include the type, incidence, severity (graded by the NCI CTCAE version 4.03) timing, seriousness, and relatedness. Patients must be followed for AEs for 28 days after the last study treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anti-cancer therapy in the meantime.

Adverse events that occur during the study, will be recorded on the AE CRF page.

### **7.1.3. Laboratory Safety Assessment**

Haematology, blood chemistry, coagulation and urinalysis will be drawn at the time points described in the [Schedule of Activities](#) and analyzed at local laboratories. Cycle 1 Day 1 hematology, blood chemistry, coagulation and urinalysis assessments do not need to be repeated if the screening assessment is performed within 7 days prior to that date. Assessments collected on dosing days should be obtained within 48 hours prior to dosing.

**Table 4. Laboratory Assessments**

| Hematology           | Chemistry                | Coagulation | Urinalysis  | Pregnancy Test  | Unique Screening Labs   |
|----------------------|--------------------------|-------------|---|---|---|
| Hemoglobin           | ALT                      | PT or INR   | Urine dipstick for urine protein:<br>If positive collect 24-hr and microscopic (Reflex Testing) | For female patients of childbearing potential, serum or urine (to be specified in the protocol) | Hepatitis B surface antigen<br>Hepatitis B core antibody<br>Hepatitis C antibody<br>HIV |
| Platelets            | AST                      | PTT         |   |   |   |
| WBC                  | Alk Phos                 |             | Urine dipstick for urine blood:<br>If positive collect a microscopic (Reflex Testing)           |   | FSH – for post-menopausal women   |
| Absolute Neutrophils | Sodium                   |             |   |   |   |
| Absolute Lymphocytes | Potassium                |             |   |   |   |
| Absolute Monocytes   | Magnesium                |             |   |   |   |
| Absolute Eosinophils | Chloride                 |             |   |   |   |
| Absolute Basophils   | Total Calcium            |             |   |   |   |
|                      | Total Bilirubin***       |             |   |   |   |
|                      | BUN or Urea              |             |   |   |   |
|                      | Creatinine               |             |   |   |   |
|                      | Uric Acid                |             |   |   |   |
|                      | Glucose (non-fasted)     |             |   |   |   |
|                      | Albumin                  |             |   |   |   |
|                      | Phosphorous or Phosphate |             |   |   |   |

\*\*\* For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase.

**7.1.4. Vital Signs and Physical Examination**

Patients will have a physical examination (PE) to include weight, vital signs, assessment of Karnofsky performance status and height; height will be measured at screening only.

A complete PE will be performed at Screening, Cycle 1 Day 1 and at the End of Treatment visit for each patient and will include an assessment of all body systems (including neurological examination, genitourinary examination is optional). The Cycle 1 Day 1 assessment does not need to be repeated if the screening assessment is performed within 7 days of dosing. Findings of all physical examinations should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an AE in the CRF.

Abbreviated PEs should be performed as appropriate per the Schedule of Activities, and on an as needed basis for assessment of AEs. Abbreviated exams should include a neurological exam as well as be targeted to specific symptoms or complaints and be consistent with local standard of care.

Vital signs will include measurements of blood pressure and temperature (oral, tympanic, temporal or axillary). On dosing days, vital signs should be measured prior to administration of any of the study treatments. Sitting blood pressure (BP) will be measured with the patient's arm supported at the level of the heart and recorded to the nearest mmHg. The same arm (preferably the dominant arm) should preferably be used throughout the trial. A BP cuff, which has been properly sized and calibrated, should be used to measure BP. The use of automated devices for measuring BP is acceptable.

#### **7.1.5. (12-Lead) Electrocardiogram**

Electrocardiogram (ECG): Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs, except the screening assessment. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the [Schedule of Activities](#)), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged ( $>500$  msec, ie, CTCAE Grade  $\geq 3$ ), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of  $>500$  msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If QTcF interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be held until the QTcF interval decreases to 500 msec. Patients will then restart the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to  $<500$  msec after 2-weeks, or if at any time a patient has a QTcF interval  $>515$  msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

### 7.3. Biomarker and Pharmacodynamic Assessments

One of the key elements of this study is the possibility to evaluate potential molecular targets that could be modified in vivo by PF-06840003 used in this study. The biomarker studies will be used to help understand the in vivo mechanism of action of the agent(s) studied as well as potential mechanisms of resistance. The studies may help in the future development of this drug as a single agent, or in combination with other compounds.

Table 5 summarizes representative assays to be used and the source of the samples. Refer to the Schedule of Activities for details pertaining to specific days of sample collection and to the study manual for details of sample preparation.

**Table 5. Pharmacodynamic Summary**

| <i>Assay</i>  | <i>Source</i>                       |
|---|-------------------------------------|
| Measurement of kynurenine, tryptophan, and metabolites by mass spectrometry | Peripheral blood, Tumor Tissue, CSF |
| CCI [REDACTED]  | CCI [REDACTED]                      |
| Assessment of serum cytokines and chemokines                                | Peripheral Blood Serum              |
| CCI [REDACTED]  | CCI [REDACTED]                      |
| mRNA profiling (Part 2 only)  | Tumor Tissue                        |
| TCR sequencing (Part 2 only)  | Tumor Tissue                        |

#### 7.3.1. Target Engagement – Assessment of Kynurenine, Tryptophan and Metabolites

Blood samples (approximately 4 mL of whole blood) will be collected for the evaluation of pharmacodynamic markers; kyn, trp, and metabolites for patients as outlined in the [Schedule of Activities](#). Details regarding the collection, processing, storage and shipping of these samples will be provided in the study manual.

The levels of kyn, trp, and metabolites in whole blood samples will be determined using a qualified analytical method in compliance with Pfizer standard operating procedures.

An assay specific for the detection of kyn, trp, and metabolites will be developed. This assay will provide proof of mechanism (target engagement) as IDO1 is a protein that catalyzes the first step in trp catabolism to N-formyl-kynurenine, and trp degradation by IDO1 yields a series of kynurenes.

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

### 7.3.3. Cytokines and Chemokines

Blood samples (approximately 4 mL) to provide approximately 1 mL serum for analysis of serum cytokine and chemokines will be collected at times specified in the [SOA](#).

Instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

Samples collected for this purpose will be retained in accordance with local regulations and if not used within this timeframe, will be destroyed.

### 7.3.4. T Cell Receptor (TCR) Sequencing

Whole blood samples (approximately 10 mL) for evaluation of T cell receptor usage, clonality, and frequency will be collected at the times specified in the [SOA](#).

Instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.



### **7.3.5. Tumor Biopsies**

Patients enrolled into the trial must have access to their archival formalin-fixed paraffin embedded material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy. A fresh pre-treatment biopsy is acceptable if archival tumor is not available. If required, the screening biopsy should preferably be obtained after all eligibility criteria have been verified. Tissue blocks are preferred, but freshly-cut paraffin sections are acceptable and must comprise 10-15 paraffin sections, 4-microns in thickness, cut within 1 week of submission, and placed individually on unstained, unbaked charged glass microscope slides.

Additionally, fresh pre-treatment and on-treatment biopsies are optional. On-treatment biopsy samples are to be collected on Cycle 2 Day 1 and should preferably be taken from the same lesion and from a lesion that has not been previously irradiated. Biopsies collected within 30 days of registration will be acceptable.

Biomarker evaluation will be performed on the biopsies. Analyses will be conducted at an IHC reference lab and include IHC assessment of IDO1 in addition to lymphocyte markers such as CD4, CD8, CD3 and exploratory biomarkers. RNA profiling will be conducted to explore immune-modulatory (immune effector and tolerance-associated) and checkpoint, cytokine, chemokine transcripts, IO and non-IO gene signatures in Part 2 only. Additionally, evaluation of TCR usage, clonality, and frequency via TCR sequencing may be performed.

Instructions for sample collection, processing, storage and shipment will be provided in the study manual. Samples may be retained in accordance with local regulations and if not used within this timeframe, will be destroyed.

### **7.4. Tumor Response Assessments**

Tumor assessments will include all known or suspected disease sites. A standard contrast-enhanced cranial MRI will be performed at screening/baseline and every 8 weeks ( $\pm 5$  days). Non-contrast cranial MRI may only be used to document disease in those patients who are allergic to contrast. Tumor assessments should be repeated at the end of treatment visit if more than 4 weeks have passed since the last evaluation.

The same imaging technique used to characterize each identified and reported lesion at screening will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at screening, during treatment as specified in the Schedule of Activity, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks). All patients' files and radiologic images must be available for source verification and for potential peer review.

Assessment of response will be made using the Macdonald criteria, RANO and iRANO. Disease progression will be confirmed with two consecutive timepoints at least 8 weeks apart in the absence of substantial neurological decline if progressive disease is suspected within 6 months of treatment initiation. Responses should be confirmed with two assessments at

least 4 weeks apart. Efficacy evaluations using the Macdonald criteria involve post-contrast MRI findings, non-contrast T1 and T2 fluid attenuated inversion recovery (FLAIR) images, use of corticosteroid dose, and neurological examination as defined below:

**Complete Response (CR) – ALL of the following:**

- Complete disappearance of all enhancing measurable and non-measurable disease sustained for  $\geq 4$  weeks.
- No new lesions.
- Stable or improved non-enhancing (T2/FLAIR) lesions.
- Off-steroids.
- Neurological condition stable or improved.

**Partial Response (PR) – ALL of the following:**

- Greater than or equal to 50% decrease compared to baseline in the sum of the perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks.
- No progression of non-measurable disease.
- No new lesions.
- Stable or improved non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared with baseline scan.
- The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at the time of the baseline scan.
- Neurological condition stable or improved.

**Progressive Disease (PD) – ANY of the following:**

- Greater than or equal to 25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing dose of corticosteroids\*.
- Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing dose of corticosteroids compared with baseline scan or best response following initiation of therapy\*, not due to co-morbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).

- Any new lesion.
- Clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose.
- Failure to return for evaluation due to death or deteriorating condition.
- Clear progression of non-measurable disease.

\*Stable doses of corticosteroids includes patients not on corticosteroids.

**Stable Disease (SD):**

- Does not qualify for CR, PR, or PD.
- Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
- Stable clinically.

**Table 6. Overall Response Criteria**

|                         | <b>CR</b>   | <b>PR</b>   | <b>SD</b>    | <b>PD<sup>1</sup></b> |
|-------------------------|-------------|-------------|--------------|-----------------------|
| T1-Gd                   | None        | ≥50%↓       | <25%↑- <50%↓ | ≥25%↑*                |
| T2/FLAIR                | Stable or ↓ | Stable or ↓ | Stable or ↓  | ↑*                    |
| New Lesion              | None        | None        | None         | Present*              |
| Corticosteroids         | None        | Stable or ↓ | Stable or ↓  | NA                    |
| Clinical Status         | Stable or ↑ | Stable or ↑ | Stable or ↑  | ↓*                    |
| Requirement of response | All         | All         | All          | Any*                  |

1. Progression occurs when any of the criteria with \* are present; NA: increase in corticosteroid dose alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; ↓=decrease; ↑=increase

#### 7.4.1. F-18-FLT PET

For locations that are able to perform the tumor evaluation by F-18-FLT-PET, assessment will be performed in all patients assigned to receive doses of 500 mg QD or 500 mg BID or higher. Assessment will be performed at screening after all other eligibility criteria has been confirmed and again at Week 9 and Week 25 (Zhao et al, 2014; Corroyer-Dulmont et al, 2013).<sup>28,8</sup> F-18-FLT-PET should be performed at the end of treatment visit if the patient discontinues the study prior to Week 9 or between Weeks 9 and 25 if more than 4 weeks have passed since the last evaluation.

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

I [Redacted]

I [Redacted]

[Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

| [REDACTED]

| [REDACTED]

| [REDACTED]

| [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **8. ADVERSE EVENT REPORTING**

### **8.1. Adverse Events**

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

### **8.2. Reporting Period**

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through the patient's last visit.

- If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

### **8.3. Definition of an Adverse Event**

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;

- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

#### **8.4. Medication Errors**

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;



- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

### **8.5. Abnormal Test Findings**

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

### **8.6. Serious Adverse Events**

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE) grade 5 (see the section on [Severity Assessment](#)).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

### **8.6.1. Protocol-Specified Serious Adverse Events**

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the section on [Serious Adverse Event Reporting Requirements](#)).

### **8.6.2. Potential Cases of Drug-Induced Liver Injury**

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values  $\geq 3$  times the upper limit of normal ( $\times$  ULN) concurrent with a total bilirubin value  $\geq 2 \times$  ULN with no evidence of hemolysis and an alkaline phosphatase value  $\leq 2 \times$  ULN or not available;
- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
- For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value  $\geq 2$  times the baseline values and  $\geq 3 \times$  ULN, or  $\geq 8 \times$  ULN (whichever is smaller);

Concurrent with

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least  $1 \times$  ULN **or** if the value reaches  $\geq 3 \times$  ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

### **8.7. Hospitalization**

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute an hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

### 8.8. Severity Assessment

| GRADE | Clinical Description of Severity   |
|-------|--|
| 0     | No Change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.) |
| 1     | MILD adverse event   |
| 2     | MODERATE adverse event   |
| 3     | SEVERE adverse event   |
| 4     | LIFE-THREATENING consequences; urgent intervention indicated   |
| 5     | DEATH RELATED TO adverse event   |

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

## 8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on [Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

## 8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant women (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

### **8.11. Occupational Exposure**

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

### **8.12. Withdrawal Due to Adverse Events (See also the Section on [Patient Withdrawal](#))**

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

### **8.13. Eliciting Adverse Event Information**

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

### **8.14. Reporting Requirements**

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

#### **8.14.1. Serious Adverse Event Reporting Requirements**

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

#### **8.14.2. Non-Serious Adverse Event Reporting Requirements**

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

### **8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities**

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

## **9. DATA ANALYSIS/STATISTICAL METHODS**

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

### **9.1. Analysis Sets**

#### 1. Safety analysis set.

The safety analysis set includes all enrolled patients who receive at least one dose of study treatment.

#### 2. Full analysis set.

The full analysis set includes all enrolled patients.

#### 3. Per-protocol analysis set (evaluable for MTD).

The per-protocol analysis set includes all enrolled patients who receive at least one dose of study treatment and who do not have major treatment deviations during the 28-day observation period. Patients with major treatment deviations in this cycle are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation. Major treatment deviations include:

- Administration of less than 50% of the planned dose of PF-06840003, provided that it is not due to toxicity attributable to PF-06840003
- Administration of more than 150% of the planned dose of PF-06840003

#### 4. PK analysis sets

The PK parameter analysis population is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest.

The PK concentration population is defined as all enrolled patients who are treated and have at least 1 analyte concentration.

#### 5. Biomarker analysis set(s)

The biomarker analysis set includes all enrolled patients with at least one of the PD/biomarker parameters evaluated at pre- and/or post-dose.



## **9.2. Statistical Methods and Properties**

### **9.2.1. Statistical Methods for Dose Escalation/De-Escalation**

Part 1, the dose escalation phase of this study, employs an mTPI design to estimate the MTD. The mTPI design employs a simple beta binomial model with a conjugated prior beta (0.5, 0.5). Decision rules are based on calculating the unit probability mass (UPM) of 3 intervals corresponding to underdosing, proper dosing, and overdosing in terms of dose limiting toxicity. A proper dosing interval is centered at the target toxicity rate (pT) of 27.5% with 5% uncertainty ( $0.225 < pT < 0.325$ ). The under dosing interval is (0, 0.225), and the overdosing interval is (0.325, 1). The 3 dosing intervals are associated with 3 different dose escalation decisions. The underdosing interval corresponds to a dose escalation I, overdosing corresponds to a dose de-escalation, and proper dosing corresponds to staying at the same current dose. Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM implies the corresponding dose finding decision. That decision provides the dose level to be used for future patients. For example, if the underdosing interval has the largest UPM, decision E (to escalate) will be executed, and the next cohort of patients will be treated at the next higher dose level. Under the mTPI design, a trial is terminated when either the lowest dose is above the MTD or a pre-specified maximum sample size is reached. Doses with an incidence of DLT >33% (eg, 4 out of 10) will not be declared as MTD even though it is allowed by the mTPI method.

### **9.3. Sample Size Determination**

Due to the dynamic nature of the Bayesian allocation procedure, the sample size using the mTPI approach cannot be determined in advance in the dose escalation phase of the study. The target sample size for each cohort is 2 to 4, the actual number of patients treated at each dose will vary from 2 to 12. It is estimated no more than approximately 72 DLT evaluable patients will be enrolled in the dose escalation stage in order to have a reliable and accurate estimate of the MTD, although this may be higher if more than 6 dose levels are required to be evaluated. Up to approximately 20 to 25 patients are anticipated to be enrolled in Part 2 of the study.

In Part 2, the expansion phase of the study, multiple efficacy endpoints will be investigated, namely: 1) disease control rate (DCR) at Week 9; 2) DCR at Week 25; 3) objective response rate (ORR) by MRI by or at Week 9; 4) ORR by F-18-FLT-PET scan by or at Week 9 (if collected). The sample size is driven by DCR at Week 9 and ORR by MRI.

The expansion phase of the study will be a single arm study, the recommended dose from Part 1 will be used in this phase. With 20 patients, the study will have an approximately 75% power to detect a 25% improvement in Disease Control Rate (DCR), aiming for a 65% DCR, from the null hypothesis of 40% DCR. The study will have an approximately 78% power to detect a 15% improvement in ORR, aiming for a 20% ORR, from the null hypothesis of 5% ORR. These sample size calculations use an one-sample test for a single proportion with an one-sided alpha level of 0.05. The statistical power will be slightly higher than stated above if this phase of the study enrolls more than 20-25 patients.

As data accumulates, a Bayesian approach with a non-informative Jeffery's prior beta (0.5,0.5) will be used to calculate the posterior probability of observing certain DCR and ORR. For example, if 2 responders were observed in the first 10 patients enrolled, the posterior probability of observing 20% ORR is about 53.3%; if 2 responders were observed in the first 12 patients enrolled, the posterior probability of observing 20% ORR is about 41.5%; if only 1 responder was observed in the first 15 patients enrolled, the posterior probability of observing 20% ORR is about 8.7%. If a posterior probability is less than 15% for both of the 2 efficacy endpoints, the study team may choose to stop the expansion phase for futility. The safety data will also be reviewed in that decision-making process.

#### **9.4. Efficacy Analysis**

There is no efficacy analysis in the dose escalation phase of the study (Part 1).

In the expansion phase (Part 2), anti-tumor activity is one of the two primary objectives.

Tumor assessment in the study will be based on the Macdonald criteria. DCR, ORR, duration of response (DOR), and Progression-Free Survival (PFS) will be calculated and presented. For binary variable (eg, ORR, DCR), descriptive statistics will be used; for time-to-event variables (eg, DOR, PFS), Kaplan-Meier analysis may be performed. The detailed analyses will be described in the statistical analysis plan.

#### **9.5. Analysis of Pharmacokinetics and Pharmacodynamics**

##### **9.5.1. Analysis of Pharmacokinetics**

##### **9.5.1.1. Single-Dose and Steady-State PF-06840002 and PF-06840001 Pharmacokinetic Analysis**

Plasma PK parameters including the maximum plasma concentration ( $C_{max}$ ), time to maximum plasma concentration ( $T_{max}$ ), and area under the plasma concentration versus time curve ( $AUC_{last}$ ,  $AUC_{\tau}$ ) for PF-06840002 and PF-06840001 will be estimated using non-compartmental analysis. If data permit or if considered appropriate, area under the plasma concentration versus time curve to infinity ( $AUC_{inf}$ ), terminal elimination half-life ( $t_{1/2}$ ), oral plasma clearance ( $CL/F$ ), apparent volume of distribution ( $V_z/F$ ), accumulation ratio ( $R_{ac}$ ) and linearity ratio ( $R_{ss}$ ) will be also estimated. The single-dose and steady-state PK parameters will be summarized descriptively by dose, cycle and day.

Urine concentration data will be analyzed to estimate the fraction of drug excreted unchanged in urine ( $Ae\%$ ) and renal clearance ( $CL_r$ ) for PF-6840002 and PF-06840001. CSF concentration data will be analyzed to estimate steady-state trough level ratio between CSF and plasma samples.

Drug concentrations will be summarized descriptively (n, mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day and nominal time. Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle and day (single dose and steady state) using nominal times. Individual and median profiles will be presented on both linear-linear and log-linear scales.

## **9.5.2. Analysis of Pharmacodynamics.**

### **9.5.2.1. Analysis of Biomarker Endpoints**

For biomarker samples, summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined at baseline and post-treatment. For each pair of specimens, the percent change from baseline of these same parameters will also be calculated.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance (ANOVA). The statistical approach will examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

### **9.5.3. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling**

Pharmacokinetic and PD data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF-06840002 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

## **9.6. Safety Analysis**

Summaries and analyses of safety parameters will include all patients in the Safety Analysis Set.

### **9.6.1. Analysis of the Primary Endpoint**

Dose-Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in the [STUDY DESIGN](#) section. Adverse Events constituting DLTs will be listed per dose level. DLT summary table by dose level may be generated, if deemed necessary, for data interpretation or for estimating the MTD purposes

### **9.6.2. Analysis of Secondary Safety Endpoints**

#### **Adverse Events**

Adverse Events will be graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on TEAEs, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, TEAE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle.

## **Laboratory Test Abnormalities**

The number and percentage of patients who experience laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle. Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

Other safety endpoints, including physical examination, vital signs, ECHO/MUGA, and concomitant medications may be summarized by dose and visit, if deemed necessary. Detailed analyses will be described in the statistical analysis plan.

### **9.6.3. Electrocardiogram**

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as the latest assessment prior to receipt of the first dose (ie, Cycle 1 Day 1).

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Fridericia's). Data will be summarized and listed for QT, HR, response rate (RR), PR, QRS, QTcF, and dose. Individual QT (all evaluated corrections) intervals will be listed by time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT using maximum CTCAE Grade. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment (yes, no, not done: (n, %)). Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration-corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

CCI

CCI

CCI

### **9.8. Data Safety Monitoring Committee**

An external Data Safety Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures include:

- Surveillance for serious adverse events (SAEs) according to regulatory guidelines;
- Discussions between the investigators and the sponsor of AEs and laboratory tests alterations seen at each dose level in an on-going manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment is appropriate.

### **10. QUALITY CONTROL AND QUALITY ASSURANCE**

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## **11. DATA HANDLING AND RECORD KEEPING**

### **11.1. Case Report Forms/Electronic Data Record**

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

### **11.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## **12. ETHICS**

### **12.1. Institutional Review Board /Ethics Committee**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

### **12.2. Ethical Conduct of the Study**

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

### **12.3. Patient Information and Consent**

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

#### **12.4. Patient Recruitment**

Advertisements approved by IRBs/Ecs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

#### **12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP**

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

### **13. DEFINITION OF END OF TRIAL**

End of trial in all participating countries is defined as the last subject last visit (LSLV).

### **14. SPONSOR DISCONTINUATION CRITERIA**

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06840003 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a time period set by Pfizer. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.



## **15. PUBLICATION OF STUDY RESULTS**

### **15.1. Communication of Results by Pfizer**

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or [www.pfizer.com](http://www.pfizer.com), and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Pfizer posts clinical trial US Basic Results on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

[EudraCT](#)

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

[www.pfizer.com](http://www.pfizer.com)

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on [www.pfizer.com](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **15.2. Publications by Investigators**

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II – “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

## 16. REFERENCES

1. “Metabolism and Transport, Drug Interaction Database”, Department of Pharmaceutics, University of Washington. [www.druginteractioninfo.org](http://www.druginteractioninfo.org) . Accessed May 2009.
2. Altekruse SF, Kosary CL, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2007/](http://seer.cancer.gov/csr/1975_2007/), based on November 2009 SEER data submission, posted to the SEER web site, 2010.
3. Benedict RHB, et al. Hopkins Verbal Learning Test–Revised: Normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist*. 1998;12:43–55.
4. Beroukhim R, Getz G, Nghiemphu L, et al. Assessing the significance of chromosomal aberrations in cancer: methodology and application to glioma. *Proc Natl Acad Sci U S A*. 2007 Dec 11;104(50):20007-12.
5. Brandacher G, Perathoner A, Ladurner R, et al. Prognostic value of indoleamine 2,3-dioxygenase expression in colorectal cancer: effect on tumor-infiltrating T cells. *Clin Cancer Res* 2006; 12(4):1144-51.
6. Burnet NG, Jefferies SJ, Benson RJ, et al. Years of life lost (YLL) from cancer is an important measure of population burden—and should be considered when allocating research funds. *Br J Cancer*. 2005 Jan 31;92(2)241:5.
7. Cohen MH, Shen YL, Keegan P, et al. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. *Oncologist*. 2009 Nov;14(11):1131-8.
8. Corroyer-Dulmont A, Peres EA, Petit E, et al. Noninvasive assessment of hypoxia with 3-[18F]-fluoro-1-(2-nitro-1-imidaxolyl)-2-propanol ([18F]-FMISO): a PET study in two experimental models of human glioma. *Biol Chem*. 2013 Apr;394(4):529-39.
9. Furnari FB, Fenton T, Bachoo RM, et al. Malignant astrocytic glioma: genetics, biology, and paths to treatment. *Genes Dev*. 2007 Nov 1;21(21):2683-710.
10. Macdonald DR, Cascino TL, Schold SC, et. al. Response criteria for Phase II studies of supratentorial malignant glioma. *J. Clin. Oncol*. 1990;8 (7): 1277-80.
11. Mellinghoff IK, Wang MY, Vivanco I, et al. Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. *N Engl J Med*. 2005 Nov 10;353(19):2012-24.
12. Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. *Nat Rev Immunol* 2004; 4(10):762-74.

13. Mitsuka K, Kawataki T, Satoh E, et al. Expression of indoleamine 2,3-dioxygenase and correlation with pathological malignancy in gliomas. *Neurosurgery*. 2013 Jun;72(6):1031-8.
14. Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. *Nat Rev Immunol*. 2004 Oct;4(20):762-74. Review.
15. Munn DH, Mellor AL. Indoleamine 2,3 dioxygenase and metabolic control of immune responses. *Trends Immunol* 2013; 34(3):137-43.
16. Nayak L, DeAngelis L, Wen P. et al. The Neurologic Assessment in Neuro-Oncology (NANO) Scale: A Tool to Assess Neurologic Function for Integreation in the Radiologic Assessment in Neuro-Oncology (RANO) Criteria. *Neurology* April 8, 2014 vol. 82 no. 10 Supplement S22.005
17. Okada H, Weller M, Huang R, et al. Immunotherapy response assessment in nuero-oncology: a report of the RANO working group. *Lancet Oncol*. 2015 Nov;16(15):e534-42.
18. Okamoto A, Nikaido T, Ochiai K, et al. Indoleamine 2,3-dioxygenase serves as a marker of poor prognosis in gene expression profiles of serous ovarian cancer cells. *Clin Cancer Res* 2005; 11(16):6030-9.
19. Ooi YC, Tran P, Ung N, et al. The role of regulatory T-cells in glioma immunology. *Clin Neurol Neurosurg*. 2014 Apr;119:125-32.
20. Reitan RM. Trail Making Test: Manual for administration and scoring. Tucson, AZ: Reitan Neuropsychology Laboratory; 1958. 1992.
21. Ruff RM, et al. Benton Controlled Oral Word Association Test: reliability and updated norms. *Arch Clin Neuropsychol*. 1996;11:329–338.
22. Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and metaanalysis of individual patient data from 12 randomised trials 2002 *Lancet* 359: 1011-1018.
23. Uyttenhove C, Pilotte L, Theate I, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. *Nat Med* 2003; 9(10):1269-74.
24. Van Baren N, Van den Eynde BJ. Tumoral immune resistance mediated by enzymes that degrade tryptophan. *Cancer Immunol Res* 2015; 3(9):978-85.
25. Wainwright DA, Balyasnikova IV, Chang AL, et al. IDO expression in brain tumors increases the recruitment of regulatory T cells and negatively impacts survival. *Clin Cancer Res*. 2012 Nov 15;18(22):6110-21.

26. Wainwright DA, Chang AL, Dey M, et al. Durable therapeutic efficacy utilizing combinatorial blockade against IDO, CTLA-4, and PD-L1 in mice with brain tumors. *Clin Cancer Res.* 2014 Oct 15;20(20):5290-301.
27. Zhai L, Lauing KL, Chang AL, et al. The role of IDO in brain tumor immunotherapy. *J Neurooncol.* 2015 Jul ;123(3) :395-403.
28. Zhao F, Cui Y, Li M, et al. Prognostic value of 3'-deoxy-3'-18F-fluorothymidine ([<sup>18</sup>F] FLT PET) in patients with recurrent malignant gliomas. *Nucl Med Biol.* 2014 Sep;41(8):710-5.

## Appendix 1. Abbreviations

| Abbreviation | Term   |
|--------------|--|
| AA           | Anaplastic astrocytoma                         |
| AE           | Adverse Event                                  |
| AIDS         | Acquired immune deficiency                     |
| ALT          | Alanine aminotransferase                       |
| ANC          | Absolute Neutrophil Count                      |
| ASCO         | American Society of Clinical Oncology          |
| AST          | Aspartate aminotransferase                     |
| AUC          | Area under the curve                           |
| BBB          | Blood brain barrier                            |
| BCRP         | Breast cancer resistance protein               |
| BID          | Twice a day                                    |
| BP           | Blood pressure                                 |
| C1D1         | Cycle 1 Day 1                                  |
| CD           | Cluster of differentiation                     |
| CLp          | Plasma clearance                               |
| Cmax         | Maximum observed                               |
| CNS          | Central nervous system                         |
| CCI          | CCI  |
| CR           | Complete response                              |
| CRF          | Case Report Form                               |
| CSA          | Clinical supply agreement                      |
| CSF          | Cerebrospinal fluid                            |
| CCI          | CCI  |
| CT           | Computerized tomography                        |
| CTCAE        | Common Terminology Criteria for Adverse Events |
| CYP          | Cytochrome                                     |
| DCR          | Disease control rate                           |
| DDI          | Drug-drug interaction                          |
| DLT          | Dose limiting toxicity                         |
| DNA          | Deoxyribonucleic acid                          |
| EC           | Ethics committee                               |
| ECG          | Electrocardiogram                              |
| EDP          | Exposure during pregnancy                      |
| CCI          | CCI  |
| FIP          | First in patient                               |
| FLAIR        | Fluid-attenuated inversion recovery            |
| FSH          | Follicle stimulating hormone                   |
| GBM          | Glioblastoma Multiforme                        |
| GCP          | Good Clinical Practice                         |
| GLP          | Good Laboratory Practice                       |
| h            | hour   |

|      |   |
|------|---|
| HBV  | Hepatitis B Virus                         |
| HCV  | Hepatitis C Virus                         |
| HDPE | High-density polyethylene                 |
| HIV  | Human Immunodeficiency Virus              |
| CCI  | CCI                                       |
| ID   | Identification                            |
| ICH  | International Conference on Harmonisation |
| IDO1 | Indoleamine 2,3-Dioxygenase               |
| IHC  | Immunohistochemistry                      |
| IND  | Investigational new drug                  |
| C    | CCI                                       |
| IRB  | Institutional review board                |
| IUD  | Interuterine device                       |
| IV   | Intravenous                               |
| kg   | kilogram                                  |
| LFT  | Liver function test                       |
| LSLV | Last subject last visit                   |
| MAO  | Monoamine oxidase inhibitor               |
| MDRD | Modified Diet in Renal Disease            |
| mg   | milogram                                  |
| CCI  | CCI                                       |
| mL   | milliliter                                |
| MRI  | Magnetic resonance imaging                |
| MRSD | Maximum Recommended Starting Dose         |
| mRNA | Messenger ribonucleic acid                |
| MTD  | Maximum tolerated dose                    |
| mTPI | Modified toxicity probability interval    |
| N/A  | Not applicable                            |
| CCI  | CCI                                       |
| NCI  | National Cancer Institute                 |
| ORR  | Overall response rate                     |
| OS   | Overall survival                          |
| PD   | Progressive disease                       |
| PE   | Physical examination                      |
| PET  | Positron emission tomography              |
| CCI  | CCI                                       |
| PR   | Partial response                          |
| PT   | Prothrombin time                          |
| PTT  | Partial thromboplastin time               |
| QD   | Once daily                                |
| RNA  | Ribonucleic acid                          |
| CCI  | CCI                                       |
| RP2D | Recommended Phase 2 Dose                  |
| SAE  | Serious adverse event                     |

|       |   |
|-------|---|
| SD    | Stable disease                              |
| CCI   | CCI   |
| SNRI  | Serotonin-norepinephrine reuptake inhibitor |
| SOA   | Schedule of activities                      |
| SRSD  | Single reference safety document            |
| SSRI  | Selective serotonin reuptake inhibitor      |
| t1/2  | Terminal half-life                          |
| TCR   | T-cell repertoire                           |
| TEAE  | Treatment emergent adverse event            |
| TK    | Toxicokinetic                               |
| CCI   | CCI   |
| Trp   | Tryptophan                                  |
| ULN   | Upper limit of normal                       |
| UPM   | Unit probability mass                       |
| US    | United States                               |
| VEG-F | Vascular endothelial growth factor          |
| Vss   | Volume of distribution                      |
| WHO   | World Health Organization                   |



## **Appendix 2. Karnofsky Performance Scoring (Karnofsky et al, 1948)**

- 100 - Normal; no complaints; no evidence of disease.
- 90 - Able to carry on normal activity; minor signs or symptoms of disease.
- 80 - Normal activity with effort; some signs or symptoms of disease.
- 70 - Cares for self; unable to carry on normal activity or to do active work.
- 60 - Requires occasional assistance, but is able to care for most of their personal needs.
- 50 - Requires considerable assistance and frequent medical care.
- 40 - Disabled; requires special care and assistance.
- 30 - Severely disabled; hospital admission is indicated although death not imminent.
- 20 - Very sick; hospital admission necessary; active supportive treatment necessary.
- 10 - Moribund; fatal processes progressing rapidly.
- 0 – Dead.

**Appendix 3. Columbia-Suicide Severity Rating Scale (CSSRS) – Baseline**

Protocol ID: \_\_\_\_\_

|        |  |  |  |            |  |  |  |  |  |  |  |  |  |
|--------|--|--|--|------------|--|--|--|--|--|--|--|--|--|
| CENTER |  |  |  | SUBJECT ID |  |  |  |  |  |  |  |  |  |
|        |  |  |  |            |  |  |  |  |  |  |  |  |  |

DATE OF VISIT

|    |  |   |     |  |  |  |  |      |  |  |
|----|--|---|-----|--|--|--|--|------|--|--|
|    |  | - |     |  |  |  |  |      |  |  |
| dd |  |   | MMM |  |  |  |  | yyyy |  |  |

Visit: \_\_\_\_\_

**COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) - BASELINE - Page 1 of 6**

(1) NOT DONE      Language administered:  (44) English for USA

| <b>SUICIDAL IDEATION</b>   |   |   |
|--|---|---|
| <i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i>   |   | Lifetime:<br>Time He/She<br>Felt Most<br>Suicidal |
| <b>1. Wish to be Dead</b><br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br><i>Have you wished you were dead or wished you could go to sleep and not wake up?</i><br>If yes, describe:   | Yes No<br><input type="checkbox"/> <input type="checkbox"/> |   |
| <b>2. Non-Specific Active Suicidal Thoughts</b><br>General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan.<br><i>Have you actually had any thoughts of killing yourself?</i><br>If yes, describe:   | Yes No<br><input type="checkbox"/> <input type="checkbox"/> |   |
| <b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b><br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."<br><i>Have you been thinking about how you might do this?</i><br>If yes, describe: | Yes No<br><input type="checkbox"/> <input type="checkbox"/> |   |
| <b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b><br>Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them."<br><i>Have you had these thoughts and had some intention of acting on them?</i><br>If yes, describe:  | Yes No<br><input type="checkbox"/> <input type="checkbox"/> |   |
| <b>5. Active Suicidal Ideation with Specific Plan and Intent</b><br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br><i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i><br>If yes, describe:   | Yes No<br><input type="checkbox"/> <input type="checkbox"/> |   |

Protocol ID: \_\_\_\_\_

|        |  |  |  |            |  |  |  |  |  |  |  |  |  |
|--------|--|--|--|------------|--|--|--|--|--|--|--|--|--|
| CENTER |  |  |  | SUBJECT ID |  |  |  |  |  |  |  |  |  |
|        |  |  |  |            |  |  |  |  |  |  |  |  |  |

DATE OF VISIT

|    |  |   |     |  |  |  |  |      |  |
|----|--|---|-----|--|--|--|--|------|--|
|    |  | - |     |  |  |  |  |      |  |
| dd |  |   | MMM |  |  |  |  | yyyy |  |

Visit: \_\_\_\_\_

**COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) - BASELINE - Page 2 of 6**

| <b>INTENSITY OF IDEATION</b>   |  |             |
|--|--|-------------|
| <p><i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.</i></p> <p><b>Most Severe Ideation:</b> _____</p> <p style="text-align: center;"><i>Type # (1-5)                      Description of Ideation</i></p>  |  | Most Severe |
| <p><b>Frequency</b><br/> <i>How many times have you had these thoughts?</i></p> <p>(1) Less than once a week<br/>           (2) Once a week<br/>           (3) 2-5 times in week<br/>           (4) Daily or almost daily<br/>           (5) Many times each day</p>   |  | —           |
| <p><b>Duration</b><br/> <i>When you have the thoughts, how long do they last?</i></p> <p>(1) Fleeting - few seconds or minutes<br/>           (2) Less than 1 hour/some of the time<br/>           (3) 1-4 hours/a lot of time<br/>           (4) 4-8 hours/most of day<br/>           (5) More than 8 hours/persistent or continuous</p>  |  | —           |
| <p><b>Controllability</b><br/> <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i></p> <p>(1) Easily able to control thoughts<br/>           (2) Can control thoughts with little difficulty<br/>           (3) Can control thoughts with some difficulty<br/>           (4) Can control thoughts with a lot of difficulty<br/>           (5) Unable to control thoughts<br/>           (0) Does not attempt to control thoughts</p>   |  | —           |
| <p><b>Deterrents</b><br/> <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i></p> <p>(1) Deterrents definitely stopped you from attempting suicide<br/>           (2) Deterrents probably stopped you<br/>           (3) Uncertain that deterrents stopped you<br/>           (4) Deterrents most likely did not stop you<br/>           (5) Deterrents definitely did not stop you<br/>           (0) Does not apply</p> |  | —           |

Protocol ID: \_\_\_\_\_

CENTER: [ ][ ][ ][ ][ ][ ]      SUBJECT ID: [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

DATE OF VISIT: [ ][ ] - [ ][ ][ ] - [ ][ ][ ][ ][ ]

dd                      MMM                      yyyy

Visit: \_\_\_\_\_

**COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) - BASELINE - Page 3 of 6**

| <b>INTENSITY OF IDEATION</b>  |                                |             |
|---|--------------------------------|-------------|
| <i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.</i>  |                                |             |
| <b>Most Severe Ideation:</b> _____  |                                | Most Severe |
| <b>Type # (1-5)</b>   | <b>Description of Ideation</b> |             |
| <b>Reasons for Ideation</b><br><i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i>  |                                |             |
| (1) Completely to get attention, revenge or a reaction from others<br>(2) Mostly to get attention, revenge or a reaction from others<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.<br>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(0) Does not apply |                                | —           |

Protocol ID: \_\_\_\_\_

CENTER

SUBJECT ID

DATE OF VISIT  
  -     -        
 dd                      MMM                      yyyy

Visit: \_\_\_\_\_

**COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) - BASELINE - Page 4 of 6**

| <b>SUICIDAL BEHAVIOR</b><br><i>(Check all that apply, so long as these are separate events; must ask about all types)</i>  | <b>Lifetime</b>   |
|--|---|
| <p><b>Actual Attempt:</b><br/>           A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <b>any</b> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <b>There does not have to be any injury or harm</b>, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br/>           Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.</p> <p><b>Have you made a suicide attempt?</b><br/> <b>Have you done anything to harm yourself?</b><br/> <b>Have you done anything dangerous where you could have died?</b><br/> <i>What did you do?</i><br/> <i>Did you _____ as a way to end your life?</i><br/> <i>Did you want to die (even a little) when you _____?</i><br/> <i>Were you trying to end your life when you _____?</i><br/> <i>Or did you think it was possible you could have died from _____?</i></p> <p><b>Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?</b> (Self-Injurious Behavior without suicidal intent)<br/>           If yes, describe:</p> | <p>Yes    No</p> <p><input type="checkbox"/>   <input type="checkbox"/></p> <p>Total # of Attempts</p> <p>_____</p> <p>Yes    No</p> <p><input type="checkbox"/>   <input type="checkbox"/></p> |
| <p><b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b></p>   |   |
| <p><b>Interrupted Attempt:</b><br/>           When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>).<br/>           Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.<br/>           Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt.<br/>           Jumping: Person is poised to jump, is grabbed and taken down from ledge.<br/>           Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.</p> <p><b>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</b><br/>           If yes, describe:</p>  | <p>Yes    No</p> <p><input type="checkbox"/>   <input type="checkbox"/></p> <p>Total # of interrupted</p> <p>_____</p>  |

Protocol ID: \_\_\_\_\_

CENTER                      SUBJECT ID

DATE OF VISIT  
  -    -

dd                      MMM                      yyyy

Visit: \_\_\_\_\_

**COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) - BASELINE - Page 5 of 6**

| <b>SUICIDAL BEHAVIOR</b><br><i>(Check all that apply, so long as these are separate events; must ask about all types)</i>   | Lifetime                            |   |
|---|-------------------------------------|---|
| <b>Aborted Attempt:</b><br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br><b><i>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</i></b><br>If yes, describe:   | Yes<br><br><input type="checkbox"/> | No<br><br><input type="checkbox"/><br><br>Total # of aborted<br><br>_____ |
| <b>Preparatory Acts or Behavior:</b><br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br><b><i>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</i></b><br>If yes, describe: | Yes<br><br><input type="checkbox"/> | No<br><br><input type="checkbox"/>  |
| <b>Suicidal Behavior:</b><br>Suicidal behavior was present during the assessment period?  | Yes<br><br><input type="checkbox"/> | No<br><br><input type="checkbox"/>  |

Protocol ID: \_\_\_\_\_

CENTER

SUBJECT ID

DATE OF VISIT

-    -

dd                      MMM                      yyyy

Visit: \_\_\_\_\_

**COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) - BASELINE - Page 6 of 6**

| <i>Answer for Actual Attempts Only</i>  | Most Recent Attempt Date: | Most Lethal Attempt Date: | Initial/First Attempt Date: |
|---|---------------------------|---------------------------|-----------------------------|
| <b>Actual Lethality/Medical Damage:</b><br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | <i>Enter Code</i>         | <i>Enter Code</i>         | <i>Enter Code</i>           |
| <b>Potential Lethality: Only Answer if Actual Lethality=0</b><br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br><br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care  | <i>Enter Code</i>         | <i>Enter Code</i>         | <i>Enter Code</i>           |

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD, and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)

**Appendix 4. Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit**

Protocol ID: \_\_\_\_\_

|        |  |  |  |            |  |  |  |  |  |  |  |  |  |
|--------|--|--|--|------------|--|--|--|--|--|--|--|--|--|
| CENTER |  |  |  | SUBJECT ID |  |  |  |  |  |  |  |  |  |
|        |  |  |  |            |  |  |  |  |  |  |  |  |  |

DATE OF VISIT

|    |  |   |     |  |  |   |      |  |  |  |
|----|--|---|-----|--|--|---|------|--|--|--|
|    |  | - |     |  |  | - |      |  |  |  |
| dd |  |   | MMM |  |  |   | yyyy |  |  |  |

Visit: \_\_\_\_\_

**COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) - SINCE LAST VISIT - Page 1 of 6**

(1) NOT DONE      Language administered:     (44) English for USA

| <b>SUICIDAL IDEATION</b>  |  | Since Last Visit |
|---|--|------------------|
| <p><i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i></p>   |  |                  |
| <p><b>1. Wish to be Dead</b><br/>           Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br/> <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i><br/>           If yes, describe:</p>   | <p><b>Yes</b>    <b>No</b></p> <p><input type="checkbox"/>    <input type="checkbox"/></p> |                  |
| <p><b>2. Non-Specific Active Suicidal Thoughts</b><br/>           General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br/> <i>Have you actually had any thoughts of killing yourself?</i><br/>           If yes, describe:</p>  | <p><b>Yes</b>    <b>No</b></p> <p><input type="checkbox"/>    <input type="checkbox"/></p> |                  |
| <p><b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b><br/>           Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."<br/> <i>Have you been thinking about how you might do this?</i><br/>           If yes, describe:</p> | <p><b>Yes</b>    <b>No</b></p> <p><input type="checkbox"/>    <input type="checkbox"/></p> |                  |
| <p><b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b><br/>           Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to "I have the thoughts but I definitely will not do anything about them."<br/> <i>Have you had these thoughts and had some intention of acting on them?</i><br/>           If yes, describe:</p>   | <p><b>Yes</b>    <b>No</b></p> <p><input type="checkbox"/>    <input type="checkbox"/></p> |                  |
| <p><b>5. Active Suicidal Ideation with Specific Plan and Intent</b><br/>           Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br/> <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i><br/>           If yes, describe:</p>   | <p><b>Yes</b>    <b>No</b></p> <p><input type="checkbox"/>    <input type="checkbox"/></p> |                  |



Protocol ID: \_\_\_\_\_

CENTER

SUBJECT ID

DATE OF VISIT   -     -

dd                      MMM                      yyyy

Visit: \_\_\_\_\_

**COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) - SINCE LAST VISIT - Page 2 of 6**

| <b>INTENSITY OF IDEATION</b>  |                                |             |
|---|--------------------------------|-------------|
| <i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).</i>   |                                |             |
| <b>Most Severe Ideation:</b> _____  |                                | Most Severe |
| <b>Type # (1-5)</b>   | <b>Description of Ideation</b> |             |
| <b>Frequency</b><br><b>How many times have you had these thoughts?</b><br>(1) Less than once a week<br>(2) Once a week<br>(3) 2-5 times in week<br>(4) Daily or almost daily<br>(5) Many times each day   |                                | —           |
| <b>Duration</b><br><b>When you have the thoughts, how long do they last?</b><br>(1) Fleeting - few seconds or minutes<br>(2) Less than 1 hour/some of the time<br>(3) 1-4 hours/a lot of time<br>(4) 4-8 hours/most of day<br>(5) More than 8 hours/persistent or continuous  |                                | —           |
| <b>Controllability</b><br><b>Could/can you stop thinking about killing yourself or wanting to die if you want to?</b><br>(1) Easily able to control thoughts<br>(2) Can control thoughts with little difficulty<br>(3) Can control thoughts with some difficulty<br>(4) Can control thoughts with a lot of difficulty<br>(5) Unable to control thoughts<br>(0) Does not attempt to control thoughts   |                                | —           |
| <b>Deterrents</b><br><b>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</b><br>(1) Deterrents definitely stopped you from attempting suicide<br>(2) Deterrents probably stopped you<br>(3) Uncertain that deterrents stopped you<br>(4) Deterrents most likely did not stop you<br>(5) Deterrents definitely did not stop you<br>(0) Does not apply |                                | —           |

Protocol ID: \_\_\_\_\_

CENTER

SUBJECT ID

DATE OF VISIT   -     -

dd                      MMM                      yyyy

Visit: \_\_\_\_\_

**COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) - SINCE LAST VISIT - Page 3 of 6**

| <b>INTENSITY OF IDEATION</b>  |                                |             |
|---|--------------------------------|-------------|
| <i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).</i>   |                                |             |
| <b>Most Severe Ideation:</b> _____  |                                | Most Severe |
| <b>Type # (1-5)</b>   | <b>Description of Ideation</b> |             |
| <b>Reasons for Ideation</b><br><i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i>  |                                |             |
| (1) Completely to get attention, revenge or a reaction from others<br>(2) Mostly to get attention, revenge or a reaction from others<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.<br>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(0) Does not apply |                                | —           |

Protocol ID: \_\_\_\_\_

|        |  |  |  |            |  |  |  |  |  |  |  |  |  |
|--------|--|--|--|------------|--|--|--|--|--|--|--|--|--|
| CENTER |  |  |  | SUBJECT ID |  |  |  |  |  |  |  |  |  |
|        |  |  |  |            |  |  |  |  |  |  |  |  |  |

DATE OF VISIT

|    |  |   |     |  |  |   |      |  |  |  |  |
|----|--|---|-----|--|--|---|------|--|--|--|--|
|    |  | - |     |  |  | - |      |  |  |  |  |
| dd |  |   | MMM |  |  |   | yyyy |  |  |  |  |

Visit: \_\_\_\_\_

**COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) - SINCE LAST VISIT - Page 6 of 6**

| <i>Answer for Actual Attempts Only</i>  |  | Most Lethal Attempt Date: |
|---|--|---------------------------|
| <b>Actual Lethality/Medical Damage:</b><br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death |  | Enter Code<br><br>_____   |
| <b>Potential Lethality: Only Answer if Actual Lethality=0</b><br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br><br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care  |  | Enter Code<br><br>_____   |

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD, and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)

## Appendix 5. Patient Health Questionnaire (PHQ-8)

Protocol ID: \_\_\_\_\_

CENTER:

SUBJECT ID:

DATE OF VISIT:   -    -

dd                      MMM                      yyyy

Visit: \_\_\_\_\_

### PATIENT HEALTH QUESTIONNAIRE (PHQ-8)

(1) NOT DONE      Language administered:  (44) English for USA

| Over the <b>last 2 weeks</b> , how often have you been bothered by the following problems?   | Not at all<br>(0)        | Several days<br>(1)      | More than half the days<br>(2) | Nearly every day<br>(3)  |
|--|--------------------------|--------------------------|--------------------------------|--------------------------|
| 1. Little interest or pleasure in doing things?  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>       | <input type="checkbox"/> |
| 2. Feeling down, depressed, or hopeless?   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>       | <input type="checkbox"/> |
| 3. Trouble falling or staying asleep, or sleeping too much?  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>       | <input type="checkbox"/> |
| 4. Feeling tired or having little energy?  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>       | <input type="checkbox"/> |
| 5. Poor appetite or overeating?  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>       | <input type="checkbox"/> |
| 6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down?  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>       | <input type="checkbox"/> |
| 7. Trouble concentrating on things, such as reading the newspaper or watching television?  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>       | <input type="checkbox"/> |
| 8. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>       | <input type="checkbox"/> |

If you are experiencing any of the problems on this form, how difficult have these problems made it for you to do your work, take care of things at home or get along with other people?

|                                |                              |                          |                               |
|--------------------------------|------------------------------|--------------------------|-------------------------------|
| Not difficult<br>at all<br>(1) | Somewhat<br>difficult<br>(2) | Very<br>difficult<br>(3) | Extremely<br>difficult<br>(4) |
| <input type="checkbox"/>       | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/>      |

PHQ-8 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr Kroenke at [kkroenke@regenstrief.org](mailto:kkroenke@regenstrief.org). Use of the PHQ-8 may only be made in accordance with the Terms of Use available of <http://www.pfizer.com>. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.

## Appendix 6. Neurologic Assessment in Neuro-Oncology (NANO) Scale

Figure 1. Neurologic Assessment in Neuro-Oncology (NANO) Scale

**Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check “Not assessed” if testing for that domain is not done. Please check “Not evaluable” if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.**

Date Assessment Performed (day/month/year): \_\_\_\_\_

Study time point (i.e. baseline, cycle 1, day 1, etc): \_\_\_\_\_

Assessment performed by (please print name): \_\_\_\_\_

### Domains

### Key Considerations

#### Gait

- 0  Normal
- 1  Abnormal but walks without assistance
- 2  Abnormal and requires assistance (companion, cane, walker, etc.)
- 3  Unable to walk
  - Not assessed
  - Not evaluable

- Walking is ideally assessed by at least 10 steps

#### Strength

- 0  Normal
- 1  Movement present but decreased against resistance
- 2  Movement present but none against resistance
- 3  No movement
  - Not assessed
  - Not evaluable

- Test each limb separately
- Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups
- Score should reflect worst performing area
- Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb

#### Ataxia (upper extremity)

- 0  Able to finger to nose touch without difficulty
- 1  Able to finger to nose touch but difficult
- 2  Unable to finger to nose touch
  - Not assessed
  - Not evaluable

- Non-evaluable if strength is compromised
- Trunk/lower extremities assessed by gait domain
- Particularly important for patients with brainstem and cerebellar tumors
- Score based on best response of at least 3 attempts

#### Sensation

- 0  Normal
- 1  Decreased but aware of sensory modality
- 2  Unaware of sensory modality
  - Not assessed
  - Not evaluable

- Recommend evaluating major body areas separately (face, limbs and trunk)
- Score should reflect worst performing area
- Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception
- Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

Visual Fields

- 0  Normal
- 1  Inconsistent or equivocal partial hemianopsia (≥quadrantopsia)
- 2  Consistent or unequivocal partial hemianopsia (≥quadrantopsia)
- 3  Complete hemianopsia
  - Not assessed
  - Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength

- 0  Normal
- 1  Mild/moderate weakness
- 2  Severe facial weakness
  - Not assessed
  - Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating eyebrows

Language

- 0  Normal
- 1  Abnormal but easily conveys meaning to examiner
- 2  Abnormal and difficulty conveying meaning to examiner
- 3  Abnormal. If verbal, unable to convey meaning to examiner. OR non-verbal (mute/global aphasia)
  - Not assessed
  - Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included.
- **Level 1:** Includes word finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2:** Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but “empty” speech.

Level of Consciousness

- 0  Normal
- 1  Drowsy (easily arousable)
- 2  Somnolent (difficult to arouse)
- 3  Unarousable/coma
  - Not assessed
  - Not evaluable

- None

Behavior

- 0  Normal
- 1  Mild/moderate alteration
- 2  Severe alteration
  - Not assessed
  - Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition and confusion
- Consider subclinical seizures for significant alteration