CORRELATIVE STUDY GUIDANCE DOCUMENT

This section should be developed in close collaboration with the Translational Research and Pharmacology Core (TRPC) personnel at an early stage in protocol development.

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OR
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- The TRPC staff assists in the correlative study design and logistics, feasibility, scientific merit, and experimental details of the study. In addition, they can formulate the budget for correlative studies, assist in responses to PRMC or IRB, and will develop specimen logs. Biospecimens can be acquired, processed, stored, shipped, delivered or analyzed in the TRPC.

- The investigator must consider if there is funding available to cover the costs of these acquiring, processing and analyzing specimens, including the draw (example: DCRU) and courier, (paid for by study, etc). Acquiring, logging, processing to stability and storage in the TRPC can provide a reasonable low-cost mechanism for retaining specimens for later analyses, when additional funds become available.

- Please briefly describe all planned correlative studies. Explicit instructions for handling, preserving and shipping the specimens should be provided. Information on endpoint validation including additional background (as needed), description of the assay(s) used, materials and methods, and assay validation should be provided. A plan for statistical analysis of the results of the correlative study(s) should be provided in Section Analysis of Secondary Endpoints.

- A suggested format for presentation of the required information is shown below and may be used to design studies or modified as required.

Use a separate section for each correlative study.

Name of Correlative Study #1
Example: Pharmacodynamic Analysis of IGF-1 Signaling in PBMCs

Describe the correlative study endpoint
The purpose of this correlative study is to provide a biological correlate of the pharmacokinetics of OSI-906, whereby the drug onboard will be measured in peripheral blood by assaying IGF-1 stimulated signaling in normal T cells.

Background
Provide background describing the scientific basis for the correlative endpoint and its relevance to the objectives of the study.

Rationale for Analysis
Describe how the analytical data will be analyzed and advance the objectives of the study. Consultation with Biostatistics is recommended for this section.

Collection of Specimens
Include the number of specimens to be acquired from each subject, timepoints (cycles, day) and at what time. This information should also be included in the Study Calendar. Consultation with Biostatistics is recommended for this section, unless these are designed to be pilot, feasibility or descriptive studies.

Example: Blood samples will be drawn into one 8 ml heparinized (green top) tube at the following 3 time points:

1. Cycle 1, Day 1: pre treatment

2. Cycle 1, Day 1: 1 hour after ingestion of OSI-906

3. Cycle 1, Day 1: 2 hours after ingestion of OSI-906

Handling of Specimens

Example: TRC personnel will acquire the specimen from _____, log the specimen information into the OnCore database, de-identify the specimen using a code specific for this trial and transport the specimen to the Case Comprehensive Cancer Center Cytometry Core Facility Laboratory within 1 hour of acquisition. Include time constraint only if applicable. Include if the specimen has temperature specifications, dry ice, etc.

OR

Example: All specimens are to be shipped to the TRC at the address below. TRC Personnel will log the specimen information into the OnCore database, de-identify the specimen using a code specific for this trial and transport the specimen to the Case Comprehensive Cancer Center Cytometry Core Facility Laboratory within 1 hour of acquisition. Include time constraint only if applicable. Include if the specimen has temperature specifications, dry ice, etc.

For UHCMC:
Translational Research & Pharmacology Core
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For CC:
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E-mail: pharmlab@ccf.org

Analytical Laboratory
Will the specimens be analyzed at a clinical laboratory, a central reference laboratory, other collaborating laboratory, a Case Comprehensive Cancer Center Core Laboratory, or the Principal Investigator's laboratory? Please provide all contact information including the responsible party.

Example: The specimens will be analyzed in the Case Comprehensive Cancer Center Cytometry Core Facility, under the direction of Dr. James Jacobberger. Dr. Jacobberger will provide overall guidance on experimental design and interpretation of results. Personnel in the Cytometry Core Facility will perform all staining, cytometry and analysis.

Case Comprehensive Cancer Center Cytometry Core Facility
2103 Cornell Rd, WRB-3517
Cleveland, OH 44106
Contact: R. Michael Sramkoski
Telephone: (216)368-1021
Email: rms19@case.edu

Correlative Methods
Describe the methods used to measure the endpoint. Provide references or general information on the assay. Please state if a clinically validated assay (CLIA approved) will be used.

Example: Correlative study Calendar

Phase I Biospecimen Submissions

The collection and submission of pharmacokinetic blood samples is MANDATORY. Guidelines for sample submissions are outlined in Section 11.

All samples must be logged and tracked via the ECOG-ACRIN Sample Tracking System (STS). All times are relative to time of administration of AZD1775.

	Time pt abbreviation	Time point of draw 3 mL EDTA vacutainer Process and submit **PLASMA**
1	C1D1-0h	Cycle 1, Day 1, Prior to AZD1775 administration
2	C1D1-1h	Cycle 1, Day 1, 1 hour
3	C1D1-2h	Cycle 1, Day 1, 2 hours
4	C1D1-4h	Cycle 1, Day 1, 4 hours
5	C1D1-6h	Cycle 1, Day 1, 6 hours
6	C1D1-8h	Cycle 1, Day 1, 8 hours
7	C1D1-24h	Cycle 1, Day 2, 24 hours after Day 1 AZD1775 administration (prior to day 2 administration of AZD1775)
8	C1D16-0h	Cycle 1, Day 16, Prior to AZD1775 administration
9	C1D16-1h	Cycle 1, Day 16, 1 hour
10	C1D16-2h	Cycle 1, Day 16, 2 hours
11	C1D16-4h	Cycle 1, Day 16, 4 hours
12	C1D16-6h	Cycle 1, Day 16, 6 hours
13	C1D16-8h	Cycle 1, Day 16, 8 hours
14	C1D16-24h	Cycle 1, Day 17 (24 hours after Day 16 AZD1775 administration) – strongly encouraged but not required

Example: Correlative Study Calendar

Specimen Collection Schedule

Blood will be collected on Day 1 and Day 15 of Cycle 1 according to the following

schedule: before drug administration and at the following times after administering the oral dose: 0.5, 1, 2, 3, 4, 6, 10 and 24 hours. Additional samples will be collected before the first dose in each subsequent cycle. Thus, 18 samples will be collected in Cycle 1 and 1 sample will be collected in each subsequent cycle.

Given that dabrafenib protein binding levels are > 90%, attempts will be made to determine the unbound fraction of GSK2118436 and its metabolites. Additional blood samples will be collected on Day 15 before the dabrafenib dose and 2 hours after the dabrafenib dose.

Sample Number*	Day of Collection	Planned Collection Time (hr) +/-10%
1	1	Pretreatment
2	1	0.5 (+/-3 min)
3	1	1.0 (+/-6 min)
4	1	2.0 (+/-12 min)
5	1	3.0 (+/-18 min)
6	1	4.0 (+/-24 min)
7	1	6.0 (+/-36 min)
8	1	10 (+/-1 hour)
9	2	24 (+/-2.4 hours)
10	15	Pretreatment
11	15	0.5 (+/-3 min)
12	15	1.0 (+/-6 min)
13	15	2.0 (+/-12 min)
14	15	3.0 (+/-18 min)
15	15	4.0 (+/-24 min)
16	15	6.0 (+/-36 min)
17	15	10 (+/-1 hour)
18	16	24 (+/-2.4 hours)
19+	1st Day of each subsequent cycle	Pretreatment

* 3 mL of blood should be collected in order to generate 1.5 mL of plasma (split into 3 aliquots; 2 aliquots for PK and one for plasma protein binding (PPB).

Example: Cohort Correlative Study Calendar

Cohorts A1, A2[1]

	Day	Timing of Blood collection (time allowance)
Week 1	Day 1	Before administration of panitumumab 30 minutes (± 5 min) after the completion of panitumumab infusion 8 hr (± 20 min) after the completion of panitumumab infusion
	Day 2	24 hr (± 2 hr) after the completion of panitumumab infusion
	Day 3	2 days (± 1 day) after the completion of panitumumab infusion
	Day 5	4 days (± 1 day) after the completion of panitumumab infusion
Week 2	Day 8	Before administration of panitumumab 30 minutes (± 5 min) after the completion of panitumumab infusion
Week 3	Day 15	Before administration of panitumumab 30 minutes (± 5 min) after the completion of panitumumab infusion 8 hr (± 20 min) after the completion of panitumumab infusion
	Day 16	24 hr (± 2 hr) after the completion of panitumumab infusion
	Day 17	2 days (± 1 day) after the completion of panitumumab infusion
	Day 19	4 days (± 1 day) after the completion of panitumumab infusion
Week 4	Day 22	Before administration of panitumumab 30 minutes (± 5 min) after the completion of panitumumab infusion
Every 8 weeks		Before administration of panitumumab 30 minutes (± 5 min) after the completion of panitumumab infusion

[1] Also Cohorts D1 and D2, as applicable

Cohorts B1, B2

	Day	Timing of Blood collection (time allowance)
Week 1	Day 1	Before administration of panitumumab 30 minutes (± 5 min) after the completion of panitumumab infusion
	Day 2	24 hr (± 2 hr) after the completion of panitumumab infusion
	Day 5	4 days (± 1 day) after the completion of panitumumab infusion
Week 2	Day 8	7 days (± 1 day) after the completion of panitumumab infusion
	Day 11	10 days (± 1 day) after the completion of panitumumab infusion
Week 3	Day 15	Before administration of panitumumab 30 minutes (± 5 min) after the completion of panitumumab infusion
Week 5	Day 29	Before administration of panitumumab 30 minutes (± 5 min) after the completion of panitumumab infusion
	Day 30	24 hr (± 2 hr) after the completion of panitumumab infusion
	Day 33	4 days (± 1 day) after the completion of panitumumab infusion
Week 6	Day 36	7 days (± 1 day) after the completion of panitumumab infusion
	Day 39	10 days (± 1 day) after the completion of panitumumab infusion
Week 7	Day 43	Before administration of panitumumab 30 minutes (± 5 min) after the completion of panitumumab infusion
Every 8 weeks		Before administration of panitumumab 30 minutes (± 5 min) after the completion of panitumumab infusion