Title: An Open-Label Phase II Study of the Combination of GSK2118436 (Dabrafenib) and GSK1120212 (Trametinib) in Patients with Metastatic Melanoma which is Refractory or Resistant to BRAF Inhibitor.

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TABLE OF CONTENTS

ABBREVIATIONS ........................................................................................................................ 5
1. INTRODUCTION ................................................................................................................... 9
  1.1. Background ..................................................................................................................... 9
    1.1.1. MEK1/2 Inhibitor GSK1120212 ............................................................................. 9
      1.1.1.1. Preliminary Safety Data for GSK1120212 from First-in-Human Study .............. 9
    1.1.2. BRAF Inhibitor GSK211843 .................................................................................. 10
      1.1.2.1. Preliminary Clinical Data for GSK2118436 ..................................................... 10
    1.1.3. Drug-Drug Interaction Potential Between GSK1120212 and GSK2118436 ......... 11
  1.2. Rationale ...................................................................................................................... 12
2. OBJECTIVES AND ENDPOINTS .................................................................................. 16
  2.1. Primary Objective ......................................................................................................... 16
  2.2. Secondary Objective .................................................................................................... 16
3. INVESTIGATIONAL PLAN ............................................................................................. 17
  3.1. Discussion of Design .................................................................................................. 17
    3.1.1. Dose Limiting Toxicity Definitions .................................................................... 18
  3.2. Investigational Product Dosage/Administration ....................................................... 18
  3.3. Dose Adjustment/Stopping Criteria ........................................................................... 19
    3.3.1. Continuation on Study ......................................................................................... 19
    3.3.2. Dose Adjustment .................................................................................................. 19
    3.3.3. Stopping Criteria ................................................................................................. 20
      3.3.3.1. Liver Chemistry Stopping Criteria ................................................................. 20
      3.3.3.2. QTc Withdrawal Criteria ............................................................................. 20
      3.3.3.3. Left Ventricular Ejection Fraction (LVEF) Stopping Criteria .................... 20
      3.3.3.4. Visual Changes Stopping Criteria ................................................................. 21
      3.3.3.5. Hypertension Stopping Criteria .................................................................. 22
      3.3.3.6. Pyrexia Stopping Criteria .......................................................................... 24
    3.3.4. Supportive Care ................................................................................................... 26
      3.3.4.1 Supportive Measures for Rash ..................................................................... 26
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3.4.2 Supportive Measures for Diarrhea</td>
<td>27</td>
</tr>
<tr>
<td>3.4. Time and Events Table</td>
<td>28</td>
</tr>
<tr>
<td>4. STUDY POPULATION</td>
<td>30</td>
</tr>
<tr>
<td>4.1. Number of Subjects</td>
<td>30</td>
</tr>
<tr>
<td>4.2. Eligibility Criteria</td>
<td>30</td>
</tr>
<tr>
<td>4.2.1. Inclusion Criteria</td>
<td>30</td>
</tr>
<tr>
<td>4.2.2. Exclusion Criteria</td>
<td>32</td>
</tr>
<tr>
<td>5. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS</td>
<td>33</td>
</tr>
<tr>
<td>5.1. Study Design Considerations</td>
<td>33</td>
</tr>
<tr>
<td>5.1.1. Analysis Populations</td>
<td>36</td>
</tr>
<tr>
<td>5.1.2. Assessment Windows</td>
<td>36</td>
</tr>
<tr>
<td>5.2. Efficacy Analyses</td>
<td>36</td>
</tr>
<tr>
<td>5.3. Biomarker and Pharmacodynamic Analyses</td>
<td>37</td>
</tr>
<tr>
<td>5.4. Resistance Mechanisms Analysis</td>
<td>37</td>
</tr>
<tr>
<td>6. STUDY ASSESSMENTS AND PROCEDURES</td>
<td>37</td>
</tr>
<tr>
<td>6.1. Demographic/Medical History Assessments</td>
<td>37</td>
</tr>
<tr>
<td>6.2. Safety</td>
<td>37</td>
</tr>
<tr>
<td>6.3. Disease Assessments</td>
<td>39</td>
</tr>
<tr>
<td>6.4. Biomarkers, Pharmacodynamics and Resistance Mechanisms Analysis</td>
<td>40</td>
</tr>
<tr>
<td>7. LIFESTYLE AND/OR DIETARY RESTRICTIONS</td>
<td>41</td>
</tr>
<tr>
<td>7.1. Contraception Requirements</td>
<td>41</td>
</tr>
<tr>
<td>7.1.1. Female Subjects</td>
<td>41</td>
</tr>
<tr>
<td>7.1.2. Male Subjects</td>
<td>42</td>
</tr>
<tr>
<td>7.2. Meals and Dietary Restrictions</td>
<td>42</td>
</tr>
<tr>
<td>8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES</td>
<td>42</td>
</tr>
<tr>
<td>8.1. Permitted Medications</td>
<td>42</td>
</tr>
<tr>
<td>8.2. Prohibited Medications</td>
<td>43</td>
</tr>
<tr>
<td>8.3. Cautionary Medications</td>
<td>43</td>
</tr>
<tr>
<td>9. COMPLETION OR EARLY WITHDRAWAL OF SUBJECTS</td>
<td>46</td>
</tr>
<tr>
<td>9.1. Subject Completion</td>
<td>46</td>
</tr>
<tr>
<td>9.2. Subject Withdrawal Criteria</td>
<td>46</td>
</tr>
<tr>
<td>9.3. Subject Withdrawal Procedures</td>
<td>47</td>
</tr>
<tr>
<td>10. INVESTIGATIONAL PRODUCT(S)</td>
<td>47</td>
</tr>
</tbody>
</table>
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase (SGPT)</td>
</tr>
<tr>
<td>AR</td>
<td>Accumulation ratio</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase (SGOT)</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under concentration-time curve</td>
</tr>
<tr>
<td>AUC(0-∞)</td>
<td>Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time</td>
</tr>
<tr>
<td>%AUCex</td>
<td>Percentage of AUC(0-∞) obtained by extrapolation</td>
</tr>
<tr>
<td>AUC(0-x)</td>
<td>Area under the concentration-time curve from zero (pre-dose) to some fixed nominal time x</td>
</tr>
<tr>
<td>AUC(0-t)</td>
<td>Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments</td>
</tr>
<tr>
<td>AUC(0-τ)</td>
<td>Area under the concentration-time curve over the dosing interval</td>
</tr>
<tr>
<td>β-HCG</td>
<td>Beta-Human Chorionic Gonadotropin</td>
</tr>
<tr>
<td>BCRP</td>
<td>Breast cancer resistance protein</td>
</tr>
<tr>
<td>BBB</td>
<td>Bundle Branch Block</td>
</tr>
<tr>
<td>BID</td>
<td>Twice daily</td>
</tr>
<tr>
<td>BLRM</td>
<td>Bayesian logistic regression model</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BPM</td>
<td>Beat Per Minute</td>
</tr>
<tr>
<td>BQL</td>
<td>Below the quantification limit</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood count</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIB</td>
<td>Clinical Investigator’s Brochure</td>
</tr>
<tr>
<td>CLr</td>
<td>Renal clearance</td>
</tr>
<tr>
<td>CL</td>
<td>Systemic clearance of parent drug</td>
</tr>
<tr>
<td>CL/F</td>
<td>Apparent clearance following oral dosing</td>
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<tr>
<td>Cmax</td>
<td>Maximum observed concentration</td>
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<tr>
<td>Cmin</td>
<td>Minimum observed concentration</td>
</tr>
<tr>
<td>Ct</td>
<td>Pre-dose (trough) concentration at the end of the dosing interval</td>
</tr>
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<td>Ct</td>
<td>Last observed quantifiable concentration</td>
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<tr>
<td>CDMP</td>
<td>Clinical Document Management and Publishing</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>CO2</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CPDS</td>
<td>Clinical Pharmacology Data Sciences</td>
</tr>
<tr>
<td>CPK</td>
<td>Creatine phosphokinase</td>
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<td>CPMS</td>
<td>Clinical Pharmacokinetics Modelling &amp; Simulation</td>
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<tr>
<td>CPP</td>
<td>Calcium phosphate product</td>
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<tr>
<td>CPSR</td>
<td>Clinical Pharmacology Study Report</td>
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<td>CP-RAP</td>
<td>Clinical Pharmacology Reporting and Analysis Plan</td>
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<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
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<td>CRU</td>
<td>Clinical Research Unit</td>
</tr>
<tr>
<td>CSR</td>
<td>Central serous retinopathy</td>
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<tr>
<td>CSSO</td>
<td>Clinical Science and Study Operations</td>
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<tr>
<td>CV%</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>DB</td>
<td>Discovery Biometrics</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>DILI</td>
<td>Drug Induced Liver Injury</td>
</tr>
<tr>
<td>DLT</td>
<td>Dose limiting toxicity</td>
</tr>
<tr>
<td>DMPK</td>
<td>Drug Metabolism and Pharmacokinetics</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>ECHO</td>
<td>Echocardiogram</td>
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<td>EDC</td>
<td>Electronic data capture</td>
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<tr>
<td>EISR</td>
<td>Expedited Investigator Safety Report</td>
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<tr>
<td>EWOC</td>
<td>Escalation with overdose control</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FSH</td>
<td>Follicle Stimulating Hormone</td>
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<tr>
<td>FTIH</td>
<td>First time in humans</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GCSP</td>
<td>Global Clinical Safety and Pharmacovigilance</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma glutamyltransferase</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GLS</td>
<td>Geometric Least-Squares</td>
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<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>hCG</td>
<td>Human chorionic gonadotropin</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>h/hr</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IDSML</td>
<td>Integrated Data Standards Library</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
</tr>
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<td>---------</td>
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<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational Product</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>IU</td>
<td>International Unit</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>λz</td>
<td>Terminal phase rate constant</td>
</tr>
<tr>
<td>L</td>
<td>Liter</td>
</tr>
<tr>
<td>LFTs</td>
<td>Liver function tests</td>
</tr>
<tr>
<td>ln</td>
<td>Naperian (natural) logarithm</td>
</tr>
<tr>
<td>LOQ</td>
<td>Limit of quantification</td>
</tr>
<tr>
<td>LLQ</td>
<td>Lower limit of quantification</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>μL</td>
<td>Microliter</td>
</tr>
<tr>
<td>MAT</td>
<td>Mean absorption time</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean corpuscular hemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean corpuscular hemoglobin concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean corpuscular volume</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>Mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>MOA</td>
<td>Mode of action</td>
</tr>
<tr>
<td>MSDS</td>
<td>Material Safety Data Sheet</td>
</tr>
<tr>
<td>msec</td>
<td>Milliseconds</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NQ</td>
<td>Non-quantifiable concentration measured as below LLQ</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>Pgp</td>
<td>p-glycoprotein</td>
</tr>
<tr>
<td>PGx</td>
<td>Pharmacogenetics</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>PSRI</td>
<td>Periodic Safety Reports for Investigators</td>
</tr>
<tr>
<td>QD</td>
<td>Once daily</td>
</tr>
<tr>
<td>QTcB</td>
<td>QT duration corrected for heart rate by Bazett’s formula</td>
</tr>
<tr>
<td>QTcF</td>
<td>QT duration corrected for heart rate by Fridericia’s formula</td>
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<td>RAP</td>
<td>Reporting and Analysis Plan</td>
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<td>RBC</td>
<td>Red blood cells</td>
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<td>RECIST</td>
<td>Response Evaluation Criteria In Solid Tumors</td>
</tr>
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<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RVO</td>
<td>Retinal vein occlusion</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event(s)</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analysis Software</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
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<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum glutamic-oxaloacetic transaminase</td>
</tr>
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<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SPM</td>
<td>Study Procedures Manual</td>
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<tr>
<td>SUSAR</td>
<td>Suspected, Unexpected, Serious Adverse drug Reaction</td>
</tr>
<tr>
<td>T</td>
<td>Infusion duration</td>
</tr>
<tr>
<td>t</td>
<td>Time of last observed quantifiable concentration</td>
</tr>
<tr>
<td>t½</td>
<td>Terminal phase half-life</td>
</tr>
<tr>
<td>t½, eff</td>
<td>Effective half-life</td>
</tr>
<tr>
<td>τ</td>
<td>Dosing interval</td>
</tr>
<tr>
<td>TID</td>
<td>Three times daily</td>
</tr>
<tr>
<td>tlag</td>
<td>Lag time before observation of drug concentrations in sampled matrix</td>
</tr>
<tr>
<td>tlast</td>
<td>Time of last quantifiable concentration</td>
</tr>
<tr>
<td>tmax</td>
<td>Time of occurrence of Cmax</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>Vd/F</td>
<td>Apparent volume of distribution after extravascular (e.g., oral) administration</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cells</td>
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1. INTRODUCTION

The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers. This pathway can be constitutively activated by alterations in specific proteins, including BRAF, which phosphorylates MEK on two regulatory serine residues. Over 45 cancer-associated mutations have been identified in BRAF (1).

BRAF mutations have been identified at a high frequency in specific cancers, including approximately 60% of melanoma (2), 30 to 50% of papillary thyroid, 5 to 20% of colorectal, and approximately 30% of ovarian cancer (1). Approximately 90% of all identified BRAF mutations that occur in human cancer are a T1799I transversion mutation in exon 15, which results in a V600E amino acid Substitution (1, 3). This mutation appears to mimic regulatory phosphorylation and increases BRAF activity approximately 10-fold as compared to wild-type (2). The frequency of this activating mutation and the pathway addiction to which it leads makes mutated BRAF an extremely attractive target.

MEK is an important target for treating human cancer because of its central role in the ERK pathway. Three MEK inhibitors, PD-0325901, CI-1040 and AZD6244 have achieved objective responses in melanoma, pancreatic cancer and non-small cell lung cancer (4-6).

1.1. Background

1.1.1. MEK1/2 Inhibitor GSK1120212 (Trametinib)

GSK1120212 is a potent and highly selective inhibitor of MEK1/2 activation and kinase activity. Inhibition of phospho-MEK1 (P-MEK) by GSK1120212 (Trametinib) is noncompetitive with the binding of adenosine triphosphate (ATP). GSK1120212 (Trametinib) has potent anti-proliferative activity against multiple cell lines, but has minimal effect on normal, non-proliferating cells. In an in vitro assay, GSK1120212 (Trametinib) inhibits both BRAF and C-RAF-dependent MEK activation as well as P-MEK kinase activity. GSK1120212 (Trametinib) is very selective against more than 250 kinases, 23 receptors and 7 enzymes with a pIC50 of less than 5.

1.1.1.1. Preliminary Safety Data for GSK1120212 (Trametinib) from First-in-Human Study

In the first time in human (FTIH) study MEK11054, 162 subjects have been enrolled and administered GSK1120212 (Trametinib) as monotherapy as part of several different regimens. Preliminary pharmacokinetics were available after single and repeat dose administration in subjects with solid tumors. GSK1120212 (Trametinib) is absorbed rapidly with median Tmax
generally occurring within 1-2 hours after administration of GSK1120212 (Trametinib). After repeat dosing (Day 15), the mean area under the curve (AUC0-24) and maximum concentrations (Cmax) increased in an approximately dose proportional way with increased dose. GSK1120212 (Trametinib) accumulates with repeat dose with an effective half-life of approximately 4.4 days.

As of 22 March 2010, 80 (49%) of the 162 subjects remain on the study, and 82 subjects (51%) have withdrawn. The predominant reason for study withdrawal was disease progression (35%); a minority of subjects (5%) withdrew due to adverse events (AEs). Eight subjects had died in the trial as of the cut-off date, all due to disease progression. Across all 162 subjects, the most common AEs experienced by ≥20% subjects were rash, diarrhea, fatigue, nausea, edema peripheral, and vomiting.

Based on the AEs observed in the dose escalation phase of the trial, the maximum tolerated dose was established at 3.0 mg once daily (QD), and the recommended Phase II dose (RP2D) of GSK1120212 (Trametinib) was identified as 2.0 mg QD.

All 46 subjects who received GSK1120212 (Trametinib) at 2.0 mg QD experienced at least one AE. The maximal severity of AEs experienced by 61% of subjects was Grade 1 or 2, whereas 35% of subjects experienced at least one Grade 3 or 4 AE. The most common AEs experienced by ≥20% of subjects were rash, diarrhea, fatigue, nausea, edema peripheral, vomiting, and anemia.

In addition to the common AEs, the potential AEs (based on pre-clinical studies, the ongoing first-time-in-human study, and data from other compounds in the same class) include: ocular toxicity (visual disturbances, blurry vision, retinal vein occlusion [RVO], central serous retinopathy [CSR]), decreased left ventricular ejection fraction with or without associated symptoms.

### 1.1.2. BRAF Inhibitor GSK2118436 (Dabrafenib)

GSK2118436 (Dabrafenib) is a potent and selective inhibitor of BRAF kinase activity with a mode of action (MOA) consistent with ATP-competitive inhibition. Excluding Raf enzymes, GSK2118436 (Dabrafenib) demonstrated IC50 values <100nM against 8 kinases from ~300 protein and lipid kinases tested. GSK2118463 (Dabrafenib) inhibits phosphorylation of MEK and ERK in vitro, inhibits cell proliferation, and achieved tumor regression in xenograft cancer models that encode BRAFV600E.

#### 1.1.2.1. Preliminary Clinical Data for GSK2118436 (Dabrafenib)

Study BRF112680 is an open-label, multiple-dose, dose-escalation study to investigate the safety, pharmacokinetics and pharmacodynamics of GSK2118436 (Dabrafenib), a B-RAF inhibitor, in subjects with solid tumors. Preliminary clinical data are provided based on a clinical data cut-off date of 11 March 2010. As of this date, data were available on 93 subjects.

Following oral administration of GSK2118436 (Dabrafenib) capsules, plasma concentrations of parent drug peaked approximately 2 hrs post-dose and decreased thereafter following a
biexponential decline. Median terminal half-lives ranged from 4.4 to 8.8 hrs. Increases in maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) were generally dose-proportional with single doses up to 150 mg and repeat doses up to 300 mg daily (150 mg BID or 100 mg TID) as assessed on Day 8. Following administration of 150 mg BID, AUC on Day 15 was 32% lower than on Day 8, with an accumulation ratio relative to Day 1 of 0.6. Administration of 200 mg BID resulted in no further increases in AUC relative to 150 mg BID.

GSK2118436 (Dabrafenib) is metabolized via oxidation to an active metabolite, GSK2285403. Plasma concentration of GSK2285403 peaked at about 2 hours post-dose. Exposure of the metabolite is similar to that of parent after single and repeat dosing (median AUC ratio of 0.8-1.1), with a similar half-life. GSK2285403 is further oxidized to GSK2298683, which is 24-fold less active than GSK2118436 (Dabrafenib). GSK2298683 exhibited a long half-life, with an overall median accumulation ratio of 5, and a metabolite to parent ratio of approximately 15. Although less potent than parent, this metabolite may contribute to the activity of GSK2118436 (Dabrafenib) due to its longer half-life and high concentrations relative to parent. GSK2298683 is decarboxylated to GSK2167542, for which concentrations were very low after single dose and accumulated with repeat dosing (25-fold); exposure was lower than parent with a metabolite to parent AUC ratio of 0.6 after repeat dosing. This metabolite is unlikely to contribute to the clinical activity of GSK2118436 (Dabrafenib).

In regard to safety, the most frequent adverse events (≥10%) were: fatigue, headache, skin lesions, nausea, pyrexia, vomiting, rash, decreased appetite, diarrhea, constipation, pain in extremity, hyperkeratosis, myalgia, arthralgia, alopecia, and back pain. The majority of these were grade 1 or 2. Twenty-eight subjects (30%) experienced a grade 3 or greater adverse event. Grade 3 events reported in >1% of subjects included squamous cell carcinoma (SCC) of the skin, hypophosphataemia, and neutropenia. No individual grade 4 or 5 event was reported in more than one subject. As of 11 March 2010, 21 subjects reported 33 SAEs. Of the 33 SAEs, 14 SAEs in 11 subjects were considered possibly related to GSK2118436 (Dabrafenib) by the investigator.

As of 14 April 2010 there were 121 subjects enrolled in BRF112680. Review of the GSK Worldwide Safety Database between the data cut-off and 14 April 2010 identified 5 additional SAEs, all of which were cases of SCC of the skin considered to be possibly related to treatment with GSK2118436 (Dabrafenib).

1.1.3. Drug-Drug Interaction Potential Between GSK1120212 (Trametinib) and GSK2118436 (Dabrafenib)

No drug-drug interaction studies have been conducted with either compound.

Based on in vitro studies, the metabolism of GSK1120212 (Trametinib) occurred by multiple biotransformation pathways. In vitro studies suggest that the metabolism of GSK1120212 (Trametinib) may be mediated by non-cytochrome P450 processes and potentially by CYP3A4. The contribution of the CYP3A4 pathway to the elimination of GSK1120212 (Trametinib) in human in vivo is presently unknown. Drugs that potently inhibit or induce CYP3A4 should be administered with caution as it may increase or decrease exposure to GSK1120212 (Trametinib).
GSK1120212 (Trametinib) is not a substrate of P-glycoprotein (Pgp), and human breast cancer resistant protein (BCRP) transporters. Thus, the likelihood of interaction between GSK1120212 (Trametinib) and transporter inhibitors is low. GSK2118436 metabolism-dependent inhibition of CYP3A4 and produced dose dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels in human hepatocytes. Preliminary results in 6 subjects showed a decrease in midazolam exposure with concomitant GSK2118436 (Dabrafenib) administration, suggesting that GSK2118436 (Dabrafenib) induces CYP3A4-mediated metabolism in vivo.

GSK1120212 (Trametinib) showed inhibitory potential towards CYPs 2C8 (IC50 of 0.34 μM), 2C9 (IC50 of 4.1 μM) and 2C19 (IC50 of 5 μM). Preliminary studies demonstrated that the oxidative metabolism of GSK2118436 (Dabrafenib) was primarily mediated by CYP2C8, CYP3A4 and, to a lesser extent, CYP2C9. Based on these in vitro data, there is potential for a drug-drug interaction between GSK1120212 (Trametinib) and GSK2118436 (Dabrafenib). GSK1120212 (Trametinib) may impact the PK of GSK2118436 (Dabrafenib) via CYP2C8 inhibition, with an increase in GSK2118436 (Dabrafenib) exposure.

1.2. Rationale

The majority of melanomas harbor one or more activating mutations in kinase signaling pathways (7). Point mutations in Braf, which is a serine-threonine kinase in the RAS-RAF-MEK-MAPK signaling pathway, are detected in approximately 50% of cutaneous melanomas, making it the most common somatic mutation in this disease (2, 8). Almost 95% of the detected mutations in Braf affect the V600 residue, with the V600E substitution being the most frequent change (~90%). Preclinical studies demonstrated that the Braf V600E mutation results in hyperactivation of the RAS-RAF-MEK-MAPK signaling pathway, and functional dependence upon this cascade for melanoma growth and survival (9, 10). This suggested that inhibition of BRAF may be an effective therapeutic strategy for melanoma, particularly in tumors with an activating mutation in the BRAF gene.

The therapeutic potential of inhibiting the mutant, hyperactive form of BRAF that is prevalent in melanoma has now been confirmed in two phase I clinical trials. PLX4032/RG7204, a small molecule inhibitor that is highly selective for the V600-mutant form of the BRAF protein, achieved a clinical response rate of 81% in metastatic melanoma patients with the Braf V600E mutation in a Phase I trial (11). GSK2118436 (Dabrafenib), a structurally unrelated mutant-specific BRAF inhibitor, had a 67% response rate in metastatic melanoma patients with Braf V600E mutations in its Phase I trial (12). Both agents were well tolerated, and cutaneous reactions were the dose limiting toxicity (DLT) for both agents. The specificity of the agents for the V600 mutant form of the BRAF protein is supported by the fact that both agents had a clinical response rate of 0% among the patients with a wild-type BRAF gene who were enrolled in the Phase I trials.

GSK2118436 (Dabrafenib) has also demonstrated significant clinical activity in metastatic melanoma patients with brain metastases. In the BREAK-MB phase II clinical trial, GSK2118436 (Dabrafenib) treatment achieved an intracranial clinical response rate of 39% of patients with a BRAF V600E and previously untreated brain metastases and 31% in patients with previously treated brain metastases [Long, Lancet Oncology 2012].
While the response rates that have been observed with the selective BRAF inhibitors PLX4032/RG7204 and GSK2118436 (Dabrafenib) in metastatic melanoma patients with a BRAF mutation are virtually unprecedented, unfortunately many of the clinical responses have been relatively short in duration. For example, in the phase I trial of PLX4032, in which the clinical response rate was 80%, the median duration of response among those patients was estimated to be approximately 7 months (13). The response duration data for GSK2118436 (Dabrafenib) is still being collected, but investigators at our site and others have observed relapses after impressive initial responses with this agent as well (12). Thus, while the response rates with PLX4032 and GSK2118436 (Dabrafenib) are very promising, there is still a need to develop approaches that will prevent and/or overcome drug resistance, to improve the duration of disease control.

A number of studies have examined the molecular mechanisms that cause resistance to selective BRAF inhibitors (14-17). In contrast to other targeted therapies, to date there have not been any secondary mutations in the target gene, BRAF, detected in cells lines or tumors that have developed secondary resistance. However, frequently the resistant melanoma cells demonstrate continued activation despite the presence of doses of the selective BRAF inhibitors that potently inhibited the pathway initially. At this time the mechanism that causes this is poorly understood, as the multiple studies that have identified this basic phenotype have shown different, non-overlapping molecular etiologies. Causes include concurrent mutation of the NRAS gene, utilization of ARAF and CRAF to activate MEK, and increased expression of the COT1 serine-threonine kinase. In each case, cell lines with such changes remained dependent upon activation of the RAS-RAF-MEK-ERK signaling pathway, which can still be inhibited by treatment with a MEK inhibitor. Combined treatment with a MEK inhibitor and a selective BRAF inhibitor induced growth arrest and/or cell death in cells that had become resistant to the BRAF inhibitor alone. An additional study demonstrated that initial combination treatment with a MEK inhibitor and a BRAF inhibitor prevented the outgrowth of cells with secondary resistance, as compared to treatment with a BRAF inhibitor alone (18).

These recent findings about mechanisms that cause resistance to BRAF inhibitors provide a strong theoretical rationale to test the efficacy of combined treatment with the BRAF inhibitor GSK2118436 (Dabrafenib) and the MEK inhibitor GSK1120212 in patients with BRAF-mutant melanoma who have failed treatment with a selective BRAF inhibitor. Preclinical testing with these two compounds has provided further direct support for this strategy (GlaxoSmithKline, unpublished data). The BRAF-mutant cell line A375PF11s cells were gradually exposed to increasing concentrations of the BRAF inhibitor GSK2118436 (Dabrafenib). This yielded several cell lines (12R5, 12R8, 16R5, 16R6) that were 100- to 1000-fold less sensitive to GSK2118436 (Dabrafenib) compared to the parent cell, thus modeling secondary resistance to selective BRAF inhibitors. All of the cell lines retained the same BRAF V600E mutation as the parental cell line. All of the cell lines were still sensitive to the MEK inhibitor GSK1120212 (Trametinib), although to a slightly lesser degree than the parental cell line (12 to 60-fold). However, the combination of GSK2118436 (Dabrafenib) and GSK1120212 resulted in a synergistic inhibition of growth and survival in the resistant cell lines in vitro and in vivo. This data is similar to the results published with other selective BRAF-inhibitor resistant cell lines treated with these agents, as well as with PLX4032 combined with other MEK inhibitors (14-17).
Approximately 20% of patients treated with BRAF inhibitors develop brain metastases as their initial site of disease progression [Kim et al. ASCO 2011]. Previous studies have found that anti-cancer agents often achieve lesser penetration of the CNS compartment and tumors compared to exposure in non-CNS metastases [Chen, Biochem Pharmacol 2012; 83:305-314]. As comparison of the degree of target inhibition in tumor cells correlated with the degree of tumor shrinkage achieved in the patients enrolled in the phase I study of vemurafenib [Bollag, Nature 2010], it is possible that the combination of GSK2118436 (Dabrafenib) and GSK1120212 (Trametinib) may have clinical benefit in progressing brain metastases due to increased inhibition of the MAPK pathway in the presence of both drugs. Thus, there is an additional rationale to assess the activity of this regimen in patients with progressing brain metastases.

In addition to increased efficacy, it is possible that the combination of a BRAF inhibitor and a MEK inhibitor may alleviate the cutaneous toxicity that is the predominant toxicity of the selective BRAF inhibitors. Preclinical studies have demonstrated that treatment of human cell lines with a wild-type BRAF gene generally results in increased growth in vitro and in vivo (19-21). This is due to the selective BRAF inhibitors inducing heterodimer formation between the wild-type BRAF proteins and wild-type CRAF proteins. The formation of these heterodimers, which are not normally present in melanoma cells with activating BRAF mutations, hyperactivates the catalytic activity of the CRAF protein, which subsequently phosphorylates and activates MEK and then ERK. There is evidence in several of the models that this hyperactivation of signaling by MEK and ERK in response to the selective BRAF inhibitors critically depends on the presence of an activated RAS molecule (19-21). It is hypothesized that the skin toxicity that has been observed with both of the selective BRAF inhibitors in patients is due to frequent activation of RAS molecules in the cells of the skin. As treatment with MEK inhibitors blocked the hyperproliferative response induced by the selective BRAF inhibitors in cells with a wild-type BRAF gene in preclinical models, including those with a hyperactive RAS (19-21), it is possible that this combination treatment may reduce cutaneous toxicity in patients.

While there is a strong rationale to determine the efficacy and safety of the combination of GSK21184356 (Dabrafenib) and GSK1120212 (Trametinib) in patients with BRAF-mutant melanomas that have developed resistance to, or were unable to tolerate, single-agent treatment with a selective BRAF inhibitor, it is possible that other resistance mechanisms may exist that will not respond to this regimen. Recently, researchers have identified activating MEK mutations in clinical specimens following the development of resistance to a selective BRAF inhibitor (22). This same mutation has previously been demonstrated to also cause resistance to MEK inhibitors (18), and thus tumors with this mutation would be highly unlikely to benefit from treatment with the regimen of combined BRAF and MEK inhibitors. In addition, studies of cell lines and tumors with secondary resistance to selective BRAF inhibitors have occasionally demonstrated molecular changes that may activate other pathways. For example, loss of the tumor suppressor PTEN, which is a critical negative regulator of the oncogenic PI3K-AKT pathway, has been reported in 10-30% of melanomas (23, 24). Loss of PTEN function is mutually exclusive with NRAS mutations in tumors and cell lines, but they frequently occur in melanomas that have an activating BRAF mutation (25, 26). Loss of PTEN correlates with reduced sensitivity to tumor cell killing by both MEK and selective BRAF inhibitors in preclinical models (27, 28). Loss of PTEN has also been detected in tumor biopsy at the time of
In addition to its role in promoting melanoma cell proliferation, recent evidence from a number of groups has demonstrated that BRAF V600E expression in melanoma cells can induce immune suppression within the tumor microenvironment. Specifically, V600E expression has been associated with production of the immunomodulatory cytokines interleukin (IL)-6, IL-8, and vascular endothelial growth factor (VEGF) (29-31). Our research group has also identified immune markers IL-1α, IL-1β, COX-2, and programmed cell death (PD)-1 ligands B7-H1 and B7-DC as being induced by V600E expression (unpublished results). Collectively, these molecules form part of a ‘wound healing’ inflammatory immune signature that has been described in several other cancer types to suppress CD8+ T cell-mediated anti-tumor immune responses (32). Furthermore, chemokines induced by V600E in the tumor microenvironment may promote infiltration of CD14+CD68+ monocytes or myeloid suppressor cells, which are highly prevalent in many types of cancer, including melanoma (33-35). Since melanoma is known to be one of the most responsive cancers to immunotherapeutic interventions, modulation of immune suppression through BRAF(V600E) inhibition may enhance the efficacy of these therapies.

The central hypothesis of this study is that the combination of GSK2118436 (Dabrafenib) and GSK1120212 (Trametinib) will be an effective and safe therapy in patients with metastatic melanoma whose melanoma lesions are either refractory or resistant to treatment with a selective BRAF inhibitor, such as RO5185426 (PLX4032; RG7204) or GSK2118436 (Dabrafenib). In order to test this hypothesis we will conduct a 30-patients phase II study with this combination in patients with extracranial metastases only with disease progression on prior BRAF inhibitor therapy (“Cohort A”). We will similarly use this combination in a separate cohort of 15 patients with new and/or progressing CNS metastases on prior BRAF inhibitor therapy (“Cohort B”). These cohorts will be evaluated separately due to the differences in outcomes in patients with versus without CNS metastases historically, and the potential for differences in drug exposure in intracranial and extracranial metastases that may impact treatment efficacy. The primary objective of the study is to determine the overall response rate of combined treatment with GSK2118436 (Dabrafenib) and GSK1120212 (Trametinib) in these populations. The secondary objectives include an evaluation of the safety and tolerability, the pharmacodynamic effects, and the identification of biomarkers that predict and/or correlate with primary and secondary resistance to this regimen.

In a Phase I study of the combination of GSK2118436 (Dabrafenib) and GSK1120212 (Trametinib) in patients with advanced solid tumors harboring a BRAF mutation, 121 patients were enrolled (36). No dose-limiting toxicities (DLTs) were found at the at the first 3 dose levels, and only one patient had a DLT (recurrent grade 2 neutrophilic panniculitis) among 53 patients at the highest dose level (150 mg BID of GSK2118436 (Dabrafenib) + 2 mg QD of GSK1120212 (Trametinib)); therefore, this dosing schedule was selected as a recommended dose for a Phase II study. Interestingly, squamous cell carcinoma (SCC) of the skin occurred in 2% of...
the patients in this Phase I study while 9\% of patients receiving GSK2118436 (Dabrafenib) alone had SCC of the skin (37). At the dose level recommended for a Phase II study, among 19 patients who had not received a BRAF inhibitor, 14 (74\%) patients had a clinical response (36), and among 26 patients who were previously treated with a BRAF inhibitor, 5 (20\%) had a (unconfirmed) partial response (38). These preliminary results indicate that this combination regimen is safe and the clinical efficacy is very promising."

2. OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

- To evaluate the response rates of the combination of GSK2118436 (Dabrafenib) and GSK1120212 (Trametinib) in patients with metastatic melanoma which is refractory or resistant to a selective BRAF inhibitor.
  - Cohort A: Patients with no active CNS metastases
  - Cohort B: Patients with new and/or progressing CNS metastases

2.2. Secondary Objective

- To evaluate the progression-free survival of the combination of GSK2118436 (Dabrafenib) and GSK1120212 (Trametinib) in patients with metastatic melanoma which is refractory or resistant to a selective BRAF inhibitor.
- To evaluate the overall survival
- To evaluate the safety/toxicity of the study drugs
- To identify pre-treatment and/or pharmacodynamic markers that predict resistance to the combination
- To evaluate tumor samples at the time of disease progression to identify mechanisms of resistance to the combination
- To evaluate the safety of the combination of GSK2118436 (Dabrafenib) and GSK1120212 (Trametinib) in patients with active CNS metastasis

3. INVESTIGATIONAL PLAN

3.1. Discussion of Design

There will be 2 cohorts of patients in this study:
- Cohort A – Patients without active brain/CNS metastasis (or <10 mm CNS lesion[s]);
- Cohort B – patients with active brain/CNS metastasis (≥10 mm CNS lesion[s])

Cohort A:
After subjects sign informed consent for this study, they will be required to undergo tumor biopsy of a safely accessible extracranial metastasis to assess the p-MEK expression. Within 10 business days of the biopsy, treatment will be started for eligible patients. The first treatment will begin on Day 1 of Cycle 1, and each cycle is 28 days of treatment. Dosing will be continuous daily dosing.

The doses of the study drugs are as follows:

- GSK2118436 (Dabrafenib): 150 mg PO BID
- GSK1120212 (Trametinib): 2 mg PO daily

Dose interruptions should not alter the assessment schedule for any subsequent treatment period.

Patients will be evaluated for toxicity on day 8 and 15 of cycle 1 by research staff during the first cycle, and then on day 1 of every cycle. Clinical responses will be evaluated using RECIST 1.1 criteria after every 2 cycles (8 weeks). The response evaluation may be performed earlier if clinically indicated (for example, if patient has symptomatic deterioration suggesting rapid disease progression or to confirm clinical response at 4 weeks after achieving response).

For patients with easily accessible tumors, tumor biopsy will be performed between day 4 to 10 of cycle 1 for assessment of pharmacodynamic effects of the combination. If subjects have disease progression, they will undergo tumor biopsy within 14 days of disease progression to provide tumor tissue for assessing the mechanism of resistance.

Study treatment will continue until protocol-defined treatment withdrawal criteria are met (Section 9.2). While on study treatment, subjects will be closely monitored for safety and, in the first four weeks of treatment, dose-limiting toxicities (Section 3.1.1). Procedures to minimize or monitor potential risks, dose modification guidance and supportive care recommendations are provided in Section 3.3.

In this cohort, at least 15 patients must have mandatory tumor biopsy at baseline, on day 4-10 and at the time of disease progression

**Cohort B:**
The treatment plan will be same as Cohort A. However, all tumor biopsy procedures (including the baseline biopsy) will be optional. For this cohort, MRI scan of the brain at the end of cycle 1 will be performed as clinically indicated.

**3.1.1. Dose Limiting Toxicity Definitions**

An event will be considered a dose limiting toxicity (DLT) if it occurs within the first 4 weeks of treatment and meets at least one of the following criteria:

- Grade 3 or 4 non-hematologic toxicity (excluding alopecia, including rash, nausea, vomiting and diarrhea and laboratory abnormalities only if uncontrolled with supportive therapy.
- Rash ≥ Grade 3 that requires dose reduction despite supportive care
- Grade 4 or greater hematologic toxicity.
- Treatment delay of greater than 21 consecutive days due to unresolved toxicity.

### 3.2. Investigational Product Dosage/Administration

<table>
<thead>
<tr>
<th>Investigational Product</th>
<th>GSK2118436 (Dabrafenib)</th>
<th>GSK1120212 (Trametinib)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation Description:</strong></td>
<td>Each capsule contains 50mg or 75mg of GSK2118436 (Dabrafenib) as free base (present as the mesylate salt). The inactive ingredients include microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, gelatin, FDA red iron oxide and titanium dioxide.</td>
<td>The drug substance is blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon oxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate), and compressed into tablets. The tablets are then coated with either a white or pink opaque film* (*Opadry White and Pink, a titanium oxide-based and iron oxide formulation)</td>
</tr>
<tr>
<td><strong>Dosage form:</strong></td>
<td>Capsule</td>
<td>Tablet</td>
</tr>
<tr>
<td><strong>Unit dose strength(s)/Dosage level(s):</strong></td>
<td>50mg, 75mg</td>
<td>0.5mg, 1mg, 2mg</td>
</tr>
<tr>
<td><strong>Route/Regimen</strong></td>
<td>Oral/ The initial dosing regimen will be twice daily continuous oral daily dosing. This regimen may be adjusted based on emerging data. Subjects should be encouraged to take study medication at approximately the same time(s) of the day each day. Subjects should be encouraged to take their doses at 12 hour intervals and at similar times every day. GSK2118436 (Dabrafenib) will be dosed with approximately 200 ml of water, twice daily.</td>
<td>Oral/ The initial dosing regimen will be once daily continuous oral daily dosing. This regimen may be adjusted based on emerging data. Subjects should be encouraged to take study medication at approximately the same time(s) of the day each day. Subjects should be encouraged to take their doses at similar times every day. GSK1120212 (Trametinib) will be dosed with approximately 200 ml of water, daily.</td>
</tr>
<tr>
<td><strong>Physical description:</strong></td>
<td>50mg: Size 2, Swedish orange opaque capsule 75mg: Size 2 capsule</td>
<td>0.5mg: White modified oval biconvex film-coated tablets, 4.8mm x 8.9mm 1mg: White to off-white round biconvex film-coated tablets, 7mm in diameter.</td>
</tr>
</tbody>
</table>
3.3. Dose Adjustment/Stopping Criteria

3.3.1. Continuation on Study

In the absence of unacceptable toxicity, disease progression, or subject withdrawal, subjects may continue on treatment with GSK2118436 (Dabrafenib) and/or GSK1120212 (Trametinib) (see Section 9.2).

3.3.2. Dose Adjustment

In the event of a DLT or other clinically significant AE, treatment may be withheld and supportive therapy administered as clinically indicated. If the toxicity or event resolves to baseline or Grade 1 in less than or equal to 21 days of stopping therapy, treatment may be restarted. Dose reduction should be considered as clinically indicated. Any dose adjustment or interruption will be recorded.

If the toxicity does not resolve to at least Grade 1 in less than or equal to 21 days, withdrawal from the trial is recommended. However, if the investigator agrees that further treatment will benefit the subject, treatment can continue with a reduction of one or both study drugs. Suggested dose reduction of each drug is as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK2118436 (Dabrafenib)</td>
<td></td>
</tr>
<tr>
<td>Starting dose</td>
<td>150 mg BID</td>
</tr>
<tr>
<td>1st dose reduction</td>
<td>100 mg BID</td>
</tr>
<tr>
<td>2nd dose reduction</td>
<td>50 mg BID</td>
</tr>
<tr>
<td>GSK1120212 (Trametinib)</td>
<td></td>
</tr>
<tr>
<td>Starting dose</td>
<td>2 mg daily</td>
</tr>
<tr>
<td>1st dose reduction</td>
<td>1.5 mg daily</td>
</tr>
<tr>
<td>2nd dose reduction</td>
<td>1 mg daily</td>
</tr>
</tbody>
</table>

3.3.3. Dose Modification / Stopping Criteria
3.3.3.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of GSK2118436 (Dabrafenib) and the follow-up period. GSK2118436 (Dabrafenib) and/or GSK1120212 (Trametinib) will be stopped if any of the following liver chemistry stopping criteria are met:

- ALT >8xULN
- ALT >5xULN for more than 2 weeks
- ALT or AST >3xULN and bilirubin >2xULN without evidence of biliary obstruction
- ALT >3xULN with the appearance or worsening of eosinophilia

Refer to Section 12, Liver Chemistry Testing Procedures, for details of the assessments required if a subject meets any of the above criteria in the absence of disease progression.

3.3.3.2. QTc Withdrawal Criteria

A subject that meets the criteria QTc\(^1\) below will have study drug withheld:

- QTc > 500 msec, or uncorrected QT > 600 msec
- If subject has Bundle Branch Block (BBB), then follow the criteria listed below:

<table>
<thead>
<tr>
<th>BASELINE QTc WITH BBB</th>
<th>DISCONTINUATION QTc WITH BBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 450 MSEC</td>
<td>&gt; 500 MSEC</td>
</tr>
<tr>
<td>450 MSEC ≤ BASELINE &lt; 480 MSEC</td>
<td>≥ 530 MSEC</td>
</tr>
</tbody>
</table>

1. based on average QTc value of triplicate ECGs

If the QTc prolongation resolves to grade 1 or baseline, the subject may be re-started on the study drug if the investigator agrees that the subject will benefit from further treatment.

3.3.3.3. Left Ventricular Ejection Fraction (LVEF) Stopping Criteria

Subjects who have an asymptomatic, absolute decrease of > 10% in LVEF compared to baseline and the ejection fraction is below the institution’s lower limit of normal (LLN) should temporarily discontinue GSK1120212 (Trametinib) and/or GSK2118436 (Dabrafenib) and have a repeat evaluation of LVEF within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until LVEF recovery to above institutional lower limit of normal and within 10% of baseline.

- If the LVEF recovers (defined as ≥ LLN and absolute decrease ≤ 10% compared to baseline) at any time during the next 4 weeks, the subject may be restarted on
GSK2118436 (Dabrafenib) at the current dose and/or GSK1120212 (Trametinib) at a reduced dose(s). For such subjects, monitoring of LVEF will then be performed 4 weeks after rechallenge.

- If repeat LVEF does not recover within 4 weeks, then the subject should permanently discontinue GSK1120212 (Trametinib) and GSK2118436 (Dabrafenib). Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution, whichever occurs first.

- Subjects with a Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue GSK1120212 (Trametinib) and GSK2118436 (Dabrafenib). Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution, whichever occurs first. If recovery occurs (LVEF to above institutional LLN and symptom resolution) within 4 weeks, the subject may restart GSK2118436 (Dabrafenib) at the current dose and GSK1120212 (Trametinib) at a reduced dose.

ECHO must be performed at baseline, and on day 1 of cycle 2 and then every 12 weeks and as clinically indicated during the course of the study.

3.3.3.4. Visual Changes Stopping Criteria

For Grade 1 visual changes, including asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

For Grade 2 visual changes, including moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate ADL; or for Grade 3 visual changes, including severe or medically significant but not immediately sightthreatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL:

- immediately withhold GSK1120212 (Trametinib) and refer patient to a retinal specialist for evaluation with an ophthalmic exam.
  - if RVO is diagnosed, permanently discontinue GSK1120212 (Trametinib).
  - if CSR is diagnosed, temporarily withhold GSK1120212 (Trametinib) until signs and symptoms have resolved. Consider resuming GSK1120212 (Trametinib) with ≥ 0.5mg dose reduction.
  - if there is no evidence of RVO or CSR, withhold GSK1120212 (Trametinib) until signs and symptoms have returned to Grade 1 or resolved. Consider resuming GSK1120212 (Trametinib) with ≥ 0.5mg dose reduction.

For Grade 4 visual changes, including sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye: permanently discontinue treatment with GSK1120212 (Trametinib).

3.3.3.5. Hypertension Stopping Criteria
In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final blood pressure measurement. The averaged value should be recorded. Persistent hypertension is defined as an increase of systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg in three consecutive visits with blood pressure assessments from two readings collected as described above. Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in Section 3.4.

Asymptomatic hypertension is defined as an increase of SBP >140 mm Hg and/or DBP >90 mm Hg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension that resolve after the blood pressure is controlled within the normal range.

For subjects experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described below:
Management and Dose Modification Guidelines for Hypertension

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Action and Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Scenario A)</strong></td>
<td></td>
</tr>
<tr>
<td>• Asymptomatic and persistent(^{a}) SBP of ≥140 and &lt;160 mmHg, or DBP ≥90 and &lt;100 mmHg, or • Clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).</td>
<td>• Continue study treatment at the current dose • Adjust current or initiate new antihypertensive medication • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled(^{b}) BP • If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).</td>
</tr>
<tr>
<td><strong>(Scenario B)</strong></td>
<td></td>
</tr>
<tr>
<td>• Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or • Failure to achieve well-controlled BP within 2 weeks in Scenario A</td>
<td>• Interrupt study treatment if clinically indicated • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP • Once BP is well controlled(^{b}), restart study treatment <strong>reduced by one dose level</strong></td>
</tr>
<tr>
<td>• Symptomatic(^{c}) hypertension or • Persistent(^{d}) SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment</td>
<td>• Interrupt study treatment • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication during the next 2 weeks as indicated to achieve well-controlled BP • Referral to a specialist for further evaluation and follow-up is recommended • Once BP is well controlled, restart study treatment <strong>reduced by one dose level</strong></td>
</tr>
<tr>
<td>• Refractory hypertension unresponsive to above interventions or hypertensive crisis.</td>
<td>• Permanently discontinue study treatment • Continue follow-up per protocol.</td>
</tr>
</tbody>
</table>

Abbreviations:  BP = blood pressure; DBP = diastolic blood pressure; mmHg = millimetres mercury; SBP = systolic blood pressure;
\(^{a}\) Hypertension detected in two separate readings during up to three consecutive visits
\(^{b}\) Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits.
c. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.

d. Persistent hypertension is defined as asymptomatic hypertension after initially successful anti-hypertensive intervention.

3.3.3.6. Pyrexia Stopping Criteria

In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness. Pyrexia accompanied by hypotension, dehydration requiring IV fluids, or severe rigors/chills should be reported as an SAE. Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take non-steroidal anti-pyretics as appropriate to control fever. In subjects experiencing pyrexia associated with rigors, severe chills, dehydration, hypotension, etc., renal function should be monitored carefully. Guidelines regarding management and dose reduction for pyrexia considered to be related to study treatment are provided below.
# Management and Dose Modification Guidelines for Pyrexia

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Adverse Event Management</th>
<th>Action and Dose Modification</th>
</tr>
</thead>
</table>
| Pyrexia\(^a\) | **1\(^{st}\) Event\(^b\):**  
- Clinical evaluation for infection and hypersensitivity\(^c\)  
- Laboratory work-up\(^c\)  
- Hydration as required\(^d\)  
- Blood sample for cytokine analysis\(^e\)  
- Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment\(^f\)  

**2\(^{nd}\) Event\(^g\):**  
- Clinical evaluation for infection and hypersensitivity\(^c\)  
- Laboratory work-up\(^c\)  
- Hydration as required\(^d\)  
- Blood sample for cytokine analysis\(^e\)  
- Within 3 days of onset of pyrexia:  
  - Optimize anti-pyretic therapy  
  - Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated\(^d\)  

**Subsequent Events:**  
- Clinical evaluation for infection and hypersensitivity\(^c\)  
- Laboratory work-up\(^c\)  
- Hydration as required\(^d\)  
- Blood sample for cytokine analysis\(^e\)  
- within 3 days of onset of pyrexia:  
  - Optimize oral corticosteroid dose as clinically indicated for recalcitrant  

**1\(^{st}\) Event:**  
- Interrupt dabrafenib  
- Continue trametinib or placebo  
- Once pyrexia resolves to baseline, restart dabrafenib at the same dose level  
  - If fever was associated with dehydration or hypotension, reduce dabrafenib by one dose level  

**2\(^{nd}\) Event:**  
- Interrupt dabrafenib  
- Continue trametinib or placebo  
- Once pyrexia resolves to baseline, restart dabrafenib at the same dose level  
  - If fever was associated with dehydration or hypotension, reduce dabrafenib by one dose level  

**Subsequent Events:**  
- Interrupt dabrafenib  
- Continue trametinib or placebo  
- Once pyrexia resolves to baseline, restart dabrafenib reduced by one dose level\(^h\)  
  - If dabrafenib must be reduced to <75 mg BID, permanently discontinue both study
pyrexia

- If corticosteroids have been tapered and pyrexia recurs, restart steroids
- If corticosteroids cannot be tapered consult medical monitor

a. Pyrexia is defined as a body temperature equal to or above 38.5 Celsius or 101.3°F Fahrenheit.
b. For subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended.
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, BUN, CRP, liver-function tests, blood culture, and urine culture.
d. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.
e. If febrile episode is > 48 hours blood sample for cytokine analysis (Serum IL-1β, IL-6, IL-8, IFN-α, VEGF, COX-2, CD3, CD4, CD8, B cells, mDC, monocytes) must be drawn and sent to the central laboratory.
f. Anti-pyretic treatment may include acetaminophen, ibuprofen, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia.
g. In subject experiencing pyrexia complicated by rigors, severe chills, etc., which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started at the 2nd event and doses should be gradually increased for subsequent events.
h. Dabrafenib should be reduced by one dose level after three episodes of pyrexia complicated by rigors, severe chills, etc., which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

3.3.4. Supportive Care

3.3.4.1. Supportive Measures for Rash

**Prophylaxis**

Subjects should be encouraged to avoid exposure to sunlight. Prophylactic treatment may be considered as clinically indicated. The exact prophylactic regimen should be based on the investigator’s experience; however, the following regimen is recommended:

1. Broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with an SPF ≥15;
2. Skin moisturizer; and,
3. Topical steroid (1% hydrocortisone cream), applied on a daily basis starting on Day 1, and more often as needed.

**Reactive Management**
It is strongly recommended that subjects who develop dermatological reactions receive evaluations for management on the specific side effect.

A variety of agents can be used to manage skin reactions. These include:

- Mild-to-moderate strength steroid creams (fluticasone propionate 0.5%)
- Topical or systemic antibiotics, topical or systemic antihistamines and hypoallergenic moisturizers
- Emollients for dry skin (5-10% urea in cetomacrogel cream or soft paraffin)

The need for oral or topical antibiotics (minocycline, doxycycline, fluclaciocline or metronidazole cream) and higher strength topical steroids is a clinical decision of the investigator and, if indicated, a dermatology consultation.

- For pruritic lesions, the use of cool compresses and oral antihistamine agents may be helpful.
- For fissuring, the use of Monsel’s solution, silver nitrate, or zinc oxide cream is advised.
- For desquamation, thick emollients and mild soap are recommended.
- For paronychia, antiseptic bath and local potent corticosteroids in addition to tetracycline therapy are recommended and, if no improvement is seen, a dermatology or surgery consultation is recommended.
- For infected lesions, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.

Oral retinoids, topical retinoids, and oral steroids are not recommended.

For subjects with an extensive or symptomatic Grade 3 or 4 dermatologic events, or for subjects with chronic, persistent or recurring lower grade skin events, a dermatology consultation is encouraged.

### 3.3.4.2. Supportive Measures for Diarrhea

For **uncomplicated Grade 1 to 2 diarrhea** (i.e., mild to moderate and defined as CTCAE v4.0 Grade 1-2 with no complicating signs or symptoms):

- Dietary modifications: stop all lactose containing products and eat small meals.
- Hydration: drink 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth)
- Administer standard dose of loperamide:
  - Initial dose of 4 mg followed by 2 mg every four hours or after every unformed stool
Continuation of loperamide is suggested until diarrhea free for 12 hours

- Consider a temporary GSK2118436 (Dabrafenib) and/or GSK1120212 (Trametinib) dose interruption until symptoms have resolved to baseline or Grade 1. Re-treatment with GSK1120212 (Trametinib) and GSK2118436 (Dabrafenib) may then be resumed at 100% of current dose level. Please refer to Table 6 and Table 7 for additional guidance.

- If mild to moderate diarrhea persists for more than 24 hours, administer loperamide 2 mg every two hours. Consider adding oral antibiotics.

- If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, start second-line agents (otreotide, budesonide or tincture of opium). Consider adding oral antibiotics.

For **Grade 3 to 4 diarrhea or complicated Grade 1 to 2 diarrhea** (i.e., cramping, nausea/vomiting ≥Grade 2, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration):

- The subject must call the investigator immediately for any complicated severe diarrhea event.
- Discontinue GSK1120212 (Trametinib) and GSK2118436 (Dabrafenib) treatment and hold until symptoms resolve to ≤Grade 1 or baseline. Consider re-starting therapy at a reduced dose level.
- If loperamide has not been initiated, initiate loperamide immediately. Initial dose 4 mg followed by 2 mg every two hours or after every unformed stool.
- For dehydration, use intravenous fluids as appropriate; if severe dehydration, administer octreotide.
- Administer antibiotics as needed (e.g., fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3 to 4 neutropenia.
- Intervention should be continued until the subject is diarrhea-free for at least 24 hours.
- Intervention may require hospitalization for subjects most at risk for lifethreatening complications.

### 3.4. Time and Events Table

Baseline screening evaluations are to be conducted within 4 week prior to start of protocol therapy. Scans and x-rays must be done ≤ 4 weeks prior to the start of therapy. Since one cycle is 4 weeks of treatment, the day 1 of cycle 2 and beyond starts on day 29 of the previous cycles. However, +/-3 business days are allowed for the day 1 of 2+ cycles. The week numbers in the Study Calendar below may be adjusted to accommodate this flexibility.

<table>
<thead>
<tr>
<th>Screening</th>
<th>Cycle 1</th>
<th>Cycle 2 and beyond</th>
<th>Off-study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 8</td>
<td>Day 15</td>
<td>Day 1</td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td>X^f</td>
<td></td>
</tr>
<tr>
<td>Concurrent meds</td>
<td>X</td>
<td>X^o</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>X</td>
<td>X^o</td>
<td>X</td>
</tr>
<tr>
<td>Serum pregnancy test^a</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination^b</td>
<td>X</td>
<td>X^f</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs^c &amp; weight</td>
<td>X</td>
<td>X^o</td>
<td>X</td>
</tr>
<tr>
<td>ECOG Performance status</td>
<td>X</td>
<td>X^o</td>
<td>X</td>
</tr>
<tr>
<td>12-lead ECG</td>
<td>X</td>
<td>X</td>
<td>X^l</td>
</tr>
<tr>
<td>CBC w/diff, plts</td>
<td>X</td>
<td>X^f</td>
<td>X</td>
</tr>
<tr>
<td>Serum chemistry^d</td>
<td>X</td>
<td>X^f</td>
<td>X</td>
</tr>
<tr>
<td>ECHO</td>
<td>X</td>
<td>X^f</td>
<td>X</td>
</tr>
<tr>
<td>Coagulation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD blood collection^e</td>
<td>X</td>
<td>X^g</td>
<td>X</td>
</tr>
</tbody>
</table>

**Study Drug Dosing**

<table>
<thead>
<tr>
<th>Disease assessment</th>
<th>X</th>
<th>Every 8 weeks^kp</th>
<th>X^hk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor tissue biopsy^l</td>
<td>X</td>
<td>X^h</td>
<td>X^i</td>
</tr>
<tr>
<td>Ophthalmology exam</td>
<td>X^m</td>
<td>X^m</td>
<td>X^m</td>
</tr>
<tr>
<td>Dermatology exam</td>
<td>X</td>
<td>X^n</td>
<td></td>
</tr>
</tbody>
</table>

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- ^a: serum β-hCG - For women of childbearing potential only
- ^b: Must include complete skin examination
- ^c: Include systolic and diastolic blood pressure, pulse rate, and temperature
- ^d: Albumin, alkaline phosphatase, total bilirubin, bicular, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, AST, ALT, sodium
- ^e: Must be collected prior to tumor biopsy if performed on a same day.
- ^f: May not need to be performed if they were performed within 8 days prior to day 1 of cycle 1.
- ^g: Must be performed on day 1 of cycle 1 only if it was not performed during the screening period. PD blood collection must be done before treatment begins.
- ^h: Follow-up disease assessment results for subjects who discontinue study medication for any other reason than progression or death
- ^i: Subjects who have been shown to have progressive disease will be allowed to continue receiving GSK2118436 (Dabrafenib) and GSK1120212 (Trametinib) up to 48 hours until a final tumor biopsy is taken
- ^j: On day 1 of cycle 2 and 4 only
- ^k: At screening, An MRI or CT of the head is required at screening and on all future disease assessments if clinically indicated. For Cohort B only, MRI (not CT) scans of the brain is mandatory.
- ^l: every 12 weeks up to 24 weeks only and then as clinically indicated
- ^m: As clinically indicated including grade 1 visual changes. Ophthalmologic examinations must be performed within 1 week of any reported ophthalmologic AE. Screening ophthalmology exam will be done if clinically indicated, and not required for all patients

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n. Every other cycles (8 weeks) starting on day 1 of cycle 3 while on study and for one time 6 months after treatment discontinuation.
o. May not need to be repeated if performed within 72 hours prior to cycle 1 day 1.
p. For cohort B only, MRI scan of the brain at the end of cycle 1 will be performed as clinically indicated.
q. For Cohort A, at least 15 patients must have mandatory tumor biopsy at baseline, on days 4-10 and at the time of disease progression. For Cohort B, all tumor biopsy procedures are optional.

4. STUDY POPULATION

4.1. Number of Subjects

Subjects with BRAF mutant metastatic melanoma will be enrolled. A total of 45 patients (30 patients in Cohort A, and 15 patients in Cohort B) will be enrolled and treated. If a patient is not treated with the study drugs after enrollment, he/she will be replaced to reach a total of 45 (30 treated patients for Cohort A, 15 for cohort B).

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
2. Patients must have histologically or cytologically confirmed Stage IV or recurrent or unresectable Stage III melanoma.
3. BRAF mutation-positive melanoma (i.e., V600E, V600K or V600D)
4. For Cohort A, patients must have easily accessible tumor for a mandatory biopsy. This is not required for patients enrolled on Cohort B.
5. Patients must have measurable disease, defined by RECIST 1.1.
6. Patients must have tumor lesions which is refractory or resistant to a selective BRAF inhibitor (RO5185426 or GSK2118436 (Dabrafenib)).
7. Age ≥ 16 years.
8. ECOG performance status 0–2
9. Patients must have organ and marrow function as defined below:
   • absolute neutrophil count ≥1,500/mcL
   • platelets ≥ 75,000/mcL
   • total bilirubin ≤1.5 × institutional upper limit of normal: no restriction to serum bilirubin level if Gilbert’s syndrome is diagnosed or suspected
   • AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal (≤3x upper limit of normal for AST and ALT for those subjects with liver metastasis)
10. Ability to understand and the willingness to sign a written informed consent document.

11. For Cohort B, patients must have at least 1 measurable parenchymal brain metastasis of at least 10 mm in the greatest diameter and no greater than 40 mm diameter. There must be at least one parenchymal brain metastasis that has not received any previous locally-directed treatment (i.e. surgery or radiation), or that has progressed after prior treatment for the brain metastases (i.e. surgery or radiation).

12. Male subjects must agree to use one of the contraception methods listed in Section 7.1.2. This criterion must be followed from the time of the first dose of study medication until 4 weeks after the last dose of study medication. However, it is advised that contraception be used for a total of 16 weeks following the last dose (based on the lifecycle of sperm).

13. A female subject is eligible to participate if she is of:

- Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MIU/mL and estradiol < 40 pg/mL (<140 pmol/L) is confirmatory]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods in Section 7.1.1 if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

- Child-bearing potential and agrees to use one of the contraception methods listed in Section 7.1.1 for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until 4 weeks after the last dose of study medication, and must have a negative serum pregnancy test within 14 days prior to the start of dosing.

   Note: Oral contraceptives are not reliable due to potential drug-drug interaction.

4.2.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

- creatinine ≤1.3 \times \text{institutional upper limit of normal} \ OR
- creatinine clearance ≥60 \text{mL/min/1.73 m}^2\ for\ patients\ with\ creatinine\ levels\ above\ 1.3 \times \text{institutional upper limit of normal}
1. Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy, or biologic therapy) except a selective RAF inhibitor.

2. Patients must not have previously received a selective BRAF inhibitor (RO5185426, GSK2118436 (Dabrafenib)) and a selective MEK inhibitor (AZD6244, GSK1120212 (Trametinib)) concurrently.

3. Received an investigational anti-cancer drug within four weeks or five half-lives (whichever is shorter) of study drug administration, at least 14 days must have passed between the last dose of the prior investigational anti-cancer drug and the first dose of study drug. However, there is no required washout period for any BRAF inhibitors at least until the baseline biopsy is performed.

4. Current use of a prohibited medication or requires any of these medications during treatment with study drug.

5. Any major surgery, within the last 3 weeks. Radiotherapy, or immunotherapy within the last 2 weeks.

6. Unresolved toxicity greater than NCI-CTCAE v4 Grade 1 from previous anti-cancer therapy except alopecia and peripheral neuropathy, for which ≤ grade 2 toxicity is allowed to participate.

7. Presence of rheumatoid arthritis.

8. History of RVO or CSR, or predisposing factors to RVO or CSR (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes).

9. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of drugs.

10. Brain Metastases
   a. For cohort A, patients will be excluded if they have brain metastases, unless they have been previously treated brain metastases with surgery or stereotactic radiosurgery and the disease has been confirmed stable (i.e., no increase in lesion size) for at least 4 weeks with MRI scans using contrast prior to Day 1. Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs and/or steroids to control symptoms/signs of brain metastases. Patients previously treated with whole brain radiation therapy must have confirmed stable disease for at least 12 weeks prior to starting treatment. However, untreated asymptomatic brain metastasis less than 10 mm will be allowed if no steroid and anti-epileptic drugs are used.
   b. For cohort B, patients may not have any evidence of leptomeningeal disease. Use of corticosteroids is permitted as long as the dose of steroids required for symptom control has been stable or decreasing for at least 3 weeks prior to the first dose of study treatment.

11. History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within the past 6 months.

12. QTc interval ≥ 480 msec (≥ 500 msec for subjects with Bundle Branch Block).
13. Uncontrolled arrhythmias.
   - Subjects with controlled atrial fibrillation for >1 month prior to study Day 1 are eligible.

14. Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.

15. Abnormal cardiac valve morphology (subjects with minimal abnormalities can be entered on study if deemed not clinically significant).

16. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drugs, or excipients. NOTE: To date there are no known FDA approved drugs chemically related to GSK2118436 (Dabrafenib) or GSK1120212 (Trametinib).

17. Pregnant or lactating female.

18. Unwillingness or inability to follow the procedures required in the protocol.

19. Uncontrolled diabetes, hypertension or other medical conditions that may interfere with assessment of toxicity.

20. Subjects with known glucose 6 phosphate dehydrogenase (G6PD) deficiency.

5. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

5.1. Study Design Considerations

A maximum of 45 patients will be enrolled (30 patients in Cohort A; 15 patients in Cohort B) and we estimate an accrual rate of 3-4 patients per month. It is expected that the accrual into the trial can be completed within 12 months.

The primary objective of the study is to estimate the response rate (CR or PR) in this patient population. Response will be evaluated every 2 cycles, and the primary outcome of response rate will be evaluated at the end of 6 treatment cycles. We desire that the response rate be at least 25%. We will monitor for toxicity during the first cycle and we desire that the dose-limiting toxicity (as defined in Section 3.1.1.) rate be no higher than 33%. If there is a low probability that the response rate is greater than 25%, or if there is a high probability that the dose-limiting toxicity rate is greater than 33% we will terminate the trial early. The method of Thall, Simon, and Estey (36) will be employed to perform interim efficacy and safety monitoring. To monitor both response rate and toxicity, each a binary outcome, there are four possible elementary outcomes. These are 1 = [toxicity, response], 2 = [toxicity, no response], 3 = [no toxicity, response], 4 = [no toxicity, no response]. We denote the corresponding standard outcome probability vector by qS, and the probability vector with the experimental treatment by qE. We assume a Dirichlet (82.5, 247.5, 167.5, 502.5) prior on qS, which in particular has mean response rate of 25% and a mean toxicity rate of 33%. We assume a Dirichlet (0.33, 0.99, 0.67, 2.01) prior on qE, which has the same prior rates but carries very little prior information.
The maximum sample size for Cohort A will be 30, which will ensure that if, for example 8/30 (27%) responses are observed, then the posterior 95% credible interval for the probability of response, based on the marginal beta (1, 3) prior assumed, will run from 12% to 41%. For Cohort B, the maximum sample size will be 15, and the posterior 95% credible interval around a 27% response rate (4/15) will be (8%, 46%).

Safety Monitoring
The following decision criteria will be applied after each cohort of 5 patients has been evaluated, up to the 30th patient for Cohort A and up to the 15th patient for Cohort B.

For Cohort A:
Targeting a 25% response rate and allowing 33% toxicity rate as a trade-off, the trial will be stopped early according to the following two monitoring rules.

1) Response rate
Pr[qS(CR+PR) < qE (CR+PR) | data] < .02

That is, if at any time during the trial we determine that we have less than 2% chance of showing that the average response rate in the experimental treatment group is higher than what would be expected on the standard of care (i.e. 25%) we will stop this cohort. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

(# of patients with response) / (# patients evaluated) ≤
0/10, 1/20, or 2/25

We will not suspend accrual while waiting to assess patient outcomes.

Or 2) Toxicity rate
Pr[qS(Tox) < qE (Tox) | data] > 0.98

That is, if at any time during the study we determine that there is more than a 98% chance that the toxicity rate by the end of first two cycles in the experimental treatment group is more than would be expected on the standard of care (i.e. 33%) we will stop this cohort. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

(# of patients with toxicity) / (# patients evaluated) ≥
5/5, 7/10, 10/15, 12/20, 14/25, or 16/30.

The operating characteristics of these rules are shown in the table below.

<table>
<thead>
<tr>
<th>True Pr(Tox)</th>
<th>True Pr(Response)</th>
<th>Pr (Stop Early)</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>25th Percentile</td>
</tr>
<tr>
<td>33%</td>
<td>25%</td>
<td>0.11</td>
<td>30</td>
</tr>
<tr>
<td>40%</td>
<td>25%</td>
<td>0.19</td>
<td>30</td>
</tr>
<tr>
<td>50%</td>
<td>25%</td>
<td>0.46</td>
<td>15</td>
</tr>
<tr>
<td>33%</td>
<td>40%</td>
<td>0.04</td>
<td>30</td>
</tr>
</tbody>
</table>
For Cohort B:
We will target the same response rate (25%) and toxicity rates (33%) as in cohort A. This cohort will stop early according to the following two monitoring rules:

1) Response rate: \( \Pr[qS(CR+PR) < qE (CR+PR) | \text{data}] < 0.05 \)

That is, if at any time during the trial we determine that we have less than 5% chance of showing that the average response rate in the experimental treatment group is higher than what would be expected on the standard of care (i.e., 25%) we will stop this cohort. Stopping boundaries corresponding to this probability criterion are to terminate the cohort if

\[
\frac{\text{(# of patients with response)}}{\text{(# patients evaluated)}} \leq \frac{0}{10}
\]

2) Toxicity rate: \( \Pr[qS(Tox) < qE (Tox) | \text{data}] > 0.95 \)

That is, if at any time during the study we determine that there is more than a 95% chance that the toxicity rate by the end of first two cycles in the experimental treatment group is more than would be expected on the standard of care (i.e., 33%) we will stop this cohort. Stopping boundaries corresponding to this probability criterion are to terminate the cohort if

\[
\frac{\text{(# of patients with toxicity)}}{\text{(# patients evaluated)}} \geq \frac{4}{5} \text{ or } \frac{7}{10}.
\]

The operating characteristics of these rules are shown in the table below.

<table>
<thead>
<tr>
<th>True Pr(Tox)</th>
<th>True Pr(Response)</th>
<th>Pr (Stop Early)</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>25th Percentile</td>
</tr>
<tr>
<td>33%</td>
<td>25%</td>
<td>0.11</td>
<td>15</td>
</tr>
<tr>
<td>40%</td>
<td>25%</td>
<td>0.16</td>
<td>15</td>
</tr>
<tr>
<td>50%</td>
<td>25%</td>
<td>0.30</td>
<td>10</td>
</tr>
<tr>
<td>33%</td>
<td>40%</td>
<td>0.06</td>
<td>15</td>
</tr>
<tr>
<td>33%</td>
<td>50%</td>
<td>0.05</td>
<td>15</td>
</tr>
<tr>
<td>33%</td>
<td>15%</td>
<td>0.24</td>
<td>15</td>
</tr>
<tr>
<td>33%</td>
<td>20%</td>
<td>0.11</td>
<td>15</td>
</tr>
<tr>
<td>20%</td>
<td>40%</td>
<td>0.01</td>
<td>15</td>
</tr>
</tbody>
</table>

5.1.1. Analysis Populations

The Intent-to-Treat (ITT) population will comprise all enrolled subjects regardless of whether or not treatment was administered. This population will be the primary population for the analysis of efficacy data.
The All Subjects Population will consist of all subjects that received at least one dose of investigational product. Safety data will be evaluated based on this population.

5.1.2. Assessment Windows

Safety assessments that occur prior to the administration of study drug will be considered screening assessments. Safety assessments that occur after dosing has begun will be considered as having occurred while on treatment.

Disease assessments will be distinguished as belonging to either screening, continued therapy or post-study phases of the study.

5.2. Efficacy Analyses

Efficacy will be evaluated based on clinical evidence and the RECIST 1.1 criteria for solid tumors (Appendix 3) (37). The overall response rate and duration of response will be summarized.

The overall response rate is defined as the percentage of subjects with a confirmed complete response (CR) or a PR at any time as per RECIST 1.1 criteria (Appendix 3). Subjects with unknown or missing response will be treated as non-responders, i.e., these subjects will be included in the denominator when calculating the percentage. At the end of the trial, the overall response rate will be reported with a 95% credible interval.

The duration of response is defined for the subject or subjects with a confirmed CR or PR, as the time from the first documented evidence of a CR or PR until the first documented disease progression or death due to any cause.

Progression free survival (PFS) will be estimated and summarized using the method of Kaplan and Meier. Additionally, Cox proportional hazards regression analysis will be used to analyze the association between PFS and demographic and disease covariates of interest.

5.3. Biomarker and Pharmacodynamic Analysis

Biomarker analysis will be performed on pre-treatment biopsies to identify markers that correlate with a lack of response to the combination of GSK2118436 (Dabrafenib) and GSK21120212 (Trametinib). The planned analysis will include an assessment of mutations that have been reported in oncogenic signaling pathways. The expression and activation of proteins in signaling pathways implicated in response and resistance to MAPK pathway inhibitors will also be assessed. Additional exploratory analyses will be performed to determine the genetic status and expression of additional molecules and/or pathways that may correlate with sensitivity to the inhibitors.

Optional tumor biopsies obtained on days 4 – 10 of cycle 1 will be assessed for the expression and activation of proteins in signaling pathways implicated in response and resistance to MAPK...
pathway inhibitors, and will be compared to expression in the pre-treatment biopsies to
determine the pharmacodynamic effects of the treatment regimen. Additional exploratory
analyses will be performed to determine the expression of additional molecules and/or pathways
that may correlate with sensitivity to the inhibitors.

5.4. Resistance Mechanisms Analysis
Biomarker analysis will be performed on biopsies obtained at the time of disease progression to
investigate possible mechanisms of resistance to the combination of GSK2118436 (Dabrafenib)
and GSK21120212 (Trametinib). The planned analysis will include an assessment of mutations
that have been reported in oncogenic signaling pathways, and specifically in resistance to BRAF
and/or MEK inhibitors. The expression and activation of proteins in signaling pathways
implicated in response and resistance to MAPK pathway inhibitors will also be assessed.
Additional exploratory analyses will be performed to determine the genetic status and expression
of additional molecules and/or pathways that may correlate with sensitivity to the inhibitors.

6. STUDY ASSESSMENTS AND PROCEDURES
This section lists the parameters of each planned study assessment. The exact timing of each
assessment is listed in the Time and Events Tables in Section 3.4.

6.1. Demographic/Medical History Assessments
The following demographic parameters will be captured: date of birth, gender, race and ethnicity.
Medical history will be assessed as related to the eligibility criteria.

6.2. Safety
Planned timepoints for all safety assessments are listed in the Time and Events Tables
(Section 3.4).

Physical Exams/ Dermatological Exams
A complete physical examination will be performed by a qualified physician or a midlevel
provider (physician’s assistant, nurse practitioner, etc.).

Baseline skin exam must be performed. Skin photography of new skin lesions or lesions that
change during therapy recommended at each reassessment while the subject is on therapy.

Vital Signs
Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, and
temperature. On days where vital signs are measured multiple times, temperature does
not need to be repeated.
Ophthalmic Exam

Patients will have a standard ophthalmic exam performed by an ophthalmologist as clinically warranted (refer to Visual Changes Stopping Criteria, Section 3.3.3.4). The exam will include indirect fundoscopic examination, visual acuity, visual field examination, tonometry, and direct fundoscopy, with special attention to retinal abnormalities that are predisposing factors for RVO or CSR.

Assessment of Skin Changes

Biopsy of skin lesions related to treatment may be performed as clinically indicated. Exploratory analysis of markers (DNA, RNA, or protein) related to the activity of GSK1120212 (Trametinib) and/or GSK2118436 (Dabrafenib) may be performed. Any genetic analysis will be limited to genetic alterations seen in human tumors. Analysis may also include HPV or other viral testing of skin lesions.

Electrocardiogram (ECG)

12-lead ECGs will be obtained as indicated in the Times and Events Tables in Section 3.4. At each assessment a 12-lead ECG will be performed after the subject has rested at least five minutes in a semi-recumbent or supine position.

Those QTc values greater than 480msec as calculated by the machine must be confirmed manually using Bazette’s formula given below:

\[
\text{QTc (Bazett)} = \frac{QT}{\sqrt{RR}}
\]

If there are any clinically significant abnormalities including but not limited to a QTcB > 500msec, confirm with two additional ECGs taken at least 5 minutes apart.

ECHO

ECHO will be performed to assess cardiac ejection fraction and cardiac valve abnormalities as indicated in the Times and Events Tables in Section 3.4. Echocardiography should include an evaluation for left ventricular ejection fraction and both right- and left sided valvular lesions. For each subject, the same procedure should be performed at the screening and as clinically warranted during the course of the study.

Clinical Laboratory Assessments

Hematology, clinical chemistry, and additional parameters to be tested are listed below:

**Hematology**

<table>
<thead>
<tr>
<th>Platelet Counts</th>
<th>Automated WBC Differential:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC Count</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>WBC Count (absolute)</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Monocytes</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Eosinophils</td>
</tr>
<tr>
<td></td>
<td>Basophils</td>
</tr>
</tbody>
</table>

**Clinical Chemistry**

<table>
<thead>
<tr>
<th>Albumin</th>
<th>Sodium</th>
<th>AST (SGOT)</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>Potassium</td>
<td>ALT (SGPT)</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Chloride</td>
<td>Alkaline phosphatase</td>
<td>Inorganic phosphorus</td>
</tr>
<tr>
<td>Glucose, fasting</td>
<td>Total CO₂</td>
<td>Total bilirubin</td>
<td>Total Protein</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Performance Status**

The performance status assessment is based on the ECOG scale:

0 – Fully active, able to carry on all pre-disease performance without restriction.

1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).

2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 – Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

**6.3. Disease Assessments**

Disease assessment will include imaging (e.g., computed tomography, magnetic resonance imaging, bone scan, plain radiograph), and physical examination (as indicated for palpable/superficial lesions). At screening, an MRI or CT of the head is required for subjects with melanoma. For cohort B only, MRI scan (not CT) of the brain will be required for all the evaluation timepoints.

Disease assessment will be completed within 28 days prior to the first dose of study drug, then as indicated in the Time and Events Tables (Section 3.4). It is not necessary to repeat radiologic assessments at the final study visit if the subject was withdrawn due to disease progression. More frequent disease assessments may be performed at the discretion of the investigator. To ensure comparability between baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

Disease response will be recorded as complete response (CR), partial response (PR), stable disease, or progressive disease according to RECIST 1.1 criteria (Appendix 2) (37).

Subjects who discontinue study medication for any other reason than progression or death should have disease assessment at follow-up.
6.4. Biomarkers, Pharmacodynamics and Resistance Mechanisms Analysis

Tumor sample collection:

After signing informed consent, each patient will undergo a mandatory baseline tumor biopsy (punch biopsy, core-needle biopsy with or without ultrasound guidance, or excisional biopsy) within 10 business days. A second mandatory biopsy will also be performed on day 4 to 10 of cycle 1. A third mandatory tumor biopsy/excision will be performed within 14 days of disease progression.

Tumor tissue collection will be performed in as many of the following formats as possible, but will be done so in this order of priority:

- Frozen Tissue: Two thirds of the tumor tissue will be embedded in OCT compound and frozen in liquid nitrogen. If a fresh tumor specimen is available but OCT compound is not available, the specimen should be snap frozen in foil.
- Formalin Fixed, Paraffin Embedded Tissue: One third of the tissue will be placed in formalin and within 48 hours will be embedded in paraffin.

Biomarker Evaluation:

Every collected tumor tissue will be both snap frozen in OCT and formalin fixed paraffin embedded.

- DNA-based: DNA will be screened for mutations in *BRAF*, *NRAS*, *MEK1/2*, *AKT1/2/3*, and *PIK3CA*.
- RNA-Based: RT-PCR for *COT1* expression.
- Protein-Based: Expression of growth factor receptors (PDGFR-beta, EGFR, c-MET, c-KIT, and IGF1R); Expression of activation specific markers in the MAPK (i.e. Phospho-MEK, -ERK) and the PI3K-AKT (i.e. PTEN, Phospho-AKT, -PRAS40, -S6) pathways. Analyses will be performed by IHC and/or reverse phase protein arrays (RPPA), depending on the available reagents for each marker.
- Immunomodulation assays: CD8, IFN-γ, PD-1, CD14, CD68, VEGF, COX-2, B7-H1, B7-DC, IL-1α, IL-1β, IL-6, and IL-8 in tumor and immune cells
- Additional exploratory studies may include:
  1) DNA-based: whole genome or whole exome sequencing; whole genome copy number analysis (i.e. MIP arrays);
  2) RNA-based: whole-genome mRNA expression profiling; miRNA profiling;
  3) Protein-Based: expanded RPPA analysis; mass-spectroscopy based proteomic analysis.

Blood sample collection:

Blood samples (including serum 10 ml in 1 red top tube and Peripheral blood mononuclear cells [PBMC] 50 ml in 5 green top tubes) will be taken for the pharmacodynamic studies and for
cytokine collection in the event of febrile episodes at the following time point: pretreatment, on
days 8 and 15 of cycle 1, day 1 of cycle 2 and 4 and at the time of disease progression.

The following analysis will be performed:

- Serum IL-1α, IL-1β, IL-6, IL-8, IFN-γ, VEGF, COX-2.
- Blood leukocyte counts: CD3, CD4, CD8, B cells, mDC, monocytes.

7. LIFESTYLE AND/OR DIETARY RESTRICTIONS

7.1. Contraception Requirements

7.1.1. Female Subjects

Female subjects of childbearing potential must not become pregnant and so must be sexually
inactive by abstinence or use contraceptive methods with a failure rate of < 1%.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the
subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods)
and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of < 1%

- Abstinence
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as
  stated in the product label
- Male partner sterilization prior to the female subject's entry into the study, and this male
  is the sole partner for that subject.
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps)
  plus spermicidal agent (foam/gel/film/cream/suppository)

These allowed methods of contraception are only effective when used consistently, correctly and
in accordance with the product label. The investigator is responsible for ensuring subjects
understand how to properly use these methods of contraception.

7.1.2. Male Subjects

To prevent pregnancy in a female partner or to prevent exposure of any partner to the
investigational product from a male subject’s semen, male subjects must use one of the following
contraceptive methods:
• Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

• Condom (during non-vaginal intercourse with any partner - male or female) OR

• Condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository) (during sexual intercourse with a female)

7.2. Meals and Dietary Restrictions

Subjects should be fasted for at least one hour prior to dosing through at least two hours after dosing due to a potential food effect on GSK1120212 (Trametinib) and GSK2118436 (Dabrafenib) absorption. GSK1120212 (Trametinib) and GSK2118436 (Dabrafenib) are oral agents and should be taken at the same time.

In addition, subjects shall abstain from ingestion of Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids, pomegranate juice or fruit juices for 2 hours prior and 2 hour after each dose of the study drug(s).

8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

8.1. Permitted Medications

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded. Additionally, a complete list of all prior cancer therapies will be recorded.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate.

8.2. Prohibited Medications

The use of certain medications, and illicit drugs within 7 days (if the drug is a potential enzyme inducer) prior to the first dose of study drug and for the duration of the trial will not be allowed.

The following medications or non-drug therapies are prohibited:

• Other anti-cancer therapy while on treatment in this study

• Use of other investigational drugs within 14 days preceding the first dose of GSK2118436 (Dabrafenib)

• Antiretroviral drugs (subjects with known HIV are ineligible for study participation)

• Drugs that are strong inhibitors or inducers of CYP3A or CYP2C8, p-glycoprotein (Pgp) or Bcrp transporter because they may alter GSK2118436 (Dabrafenib) concentrations.
The list may be modified based on emerging data. These include but are not limited to those listed below, consider therapeutic substitutions for these medications.

### Prohibited Medications

<table>
<thead>
<tr>
<th>Strong CYP2C8/3A/Pgp/Bcrp Inhibitor/Inducer</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>clarithromycin, telithromycin, rifamycin class agents (e.g. rifampin, rifabutin, rifapentine), troleandomycin</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>itraconazole, ketoconazole, posaconazole, voriconazole</td>
<td>Antifungals</td>
</tr>
<tr>
<td>nefazodone</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>gemfibrozil</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>carbamazepine, phenobarbital, amiodarone, , phenytoin, s-mephenytoin, bosentan, mibefrani, conivaptan</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Immunosuppressive agents</td>
</tr>
</tbody>
</table>

### Cautionary Medications

The following medications should be used with caution:

- Drugs that are substrates of CYP2C8, CYP2C9, and CYP2C19 that are highly sensitive to inhibitors or that have a low therapeutic index because concentrations of these substrates may be altered by GSK2118436 (Dabrafenib).

- Drugs that are mild/moderate inhibitors or inducers of CYP3A, CYP2C8, or Pgp or Bcrp transporter because they may alter GSK2118436 (Dabrafenib) concentrations.

- Additionally, GSK2118436 (Dabrafenib) may induce CYP3A4 and CYP2B6. Other enzymes such as CYP2C8, CYP2C9, and CYP2C19 may be affected as well. Coadministration of GSK2118436 (Dabrafenib) and medications which are affected by the induction of these enzymes may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications. The list may be modified based on emerging data.

These include but are not limited to those listed below.

### Cautionary Medications
**USE WITH CAUTION** – Concentrations of these drugs may be altered (increased or decreased) by GSK2118436.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>cerivastatin</td>
<td>HMG-CoA Reductase Inhibitors</td>
</tr>
<tr>
<td>tolbutamide, nateglinide, repaglinide</td>
<td>Antidiabetics</td>
</tr>
<tr>
<td>amitriptyline, clomipramine, imipramine</td>
<td>Antidepressants</td>
</tr>
</tbody>
</table>

**USE WITH CAUTION** – Potential for inhibitors of CYP3A, CYP2C8, Pgp and Bcrp since concentrations of GSK2118436 may be increased

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>erythromycin</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>fluconazole</td>
<td>Antifungal</td>
</tr>
<tr>
<td>diltiazem, verapamil</td>
<td>Antiarrhythmics</td>
</tr>
<tr>
<td>aprepitant, cimetidine, montelukast</td>
<td>Miscellaneous</td>
</tr>
</tbody>
</table>

**USE WITH CAUTION** – Monitor for loss of efficacy or substitute another medication

<table>
<thead>
<tr>
<th>Substrates of CYP3A4/CYP2B6/CYP2C8/CYP2C9/CYP2C19 that may be affected by induction</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloramphenicol, doxycycline, erythromycin, moxifloxacin</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>caspofungin, fluconazole, terbinafine</td>
<td>Antifungals</td>
</tr>
<tr>
<td>amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil</td>
<td>Antihypertensives</td>
</tr>
</tbody>
</table>
9. COMPLETION OR EARLY WITHDRAWAL OF SUBJECTS

9.1. Subject Completion

A completed subject is one who has completed at least 4 weeks of treatment including the follow-up visit.

The end of the study is defined as the last subject’s last visit.

Duration of Follow Up: After patients stop study drug, they will be followed approximately every 3 months (either clinic visit or contact by phone or letter) for 5 years or until death. If you are called, the call will last about 5 minutes.

9.2. Subject Withdrawal Criteria
Study treatment should continue until protocol-defined treatment withdrawal criteria are met (Section 3.3).

Each subject may continue on treatment until one of the following occurs:

- Disease progression. Subjects who have been shown to have progressive disease will be allowed to continue receiving GSK2118436 (Dabrafenib) and/or GSK1120212 (Trametinib) up to 48 hours until an optional final tumor biopsy is taken. For subjects in whom there is, in the investigator’s opinion, a definite clinical benefit despite meeting the criteria for disease progression per RECIST 1.1, the treatment can continue until which time there is no more clinical benefit.
- Female subject becomes pregnant;
- Adverse event that is considered by the Investigator to warrant permanent discontinuation of the study drug;
- A clinically significant AE leading to an interruption of treatment for greater than 21 consecutive days. If the investigator concludes that continued treatment will benefit a subject who has had a > 21 day treatment delay, then the subject may continue therapy.
- Subject withdraws consent for further treatment or data collection:
  - If the subject withdraws consent for further treatment, post treatment visits should continue.
  - If the subject withdraws consent for further treatment and data collection, then no additional study visits or data collection should occur.
- Subject is withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons.

A subject may withdraw from investigational product at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons.

### 9.3. Subject Withdrawal Procedures

Following permanent discontinuation of study treatment, every effort should be made for subjects to complete the follow-up visit as described in the Time and Events Table (Section 3.4). The follow-up visit should occur approximately 14 days from last dose of study drugs (±7 days), and prior to initiating further anti-cancer therapy or dosing of a different investigational agent. The reason for discontinuing treatment with study drug will be clearly documented in the subject’s medical record. If the subject withdraws from treatment due to toxicity, ‘Adverse Event’ will be recorded as the primary reason for withdrawal.

### 10. INVESTIGATIONAL PRODUCT(S)

Investigational product dosage and administration details are listed in Section 3.2.
10.1. Blinding

This will be an open-label study.

10.2. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

10.3. Preparation/Handling/Storage/Accountability

No special preparation of investigational product is required.

Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product. Only authorized site staff may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff. Investigational products (GSK2118436 (Dabrafenib) and GSK1120212 (Trametinib)) are to be stored up to 15 to 25 °C in an opaque bottle.

11. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

AEs will be collected from the start of Investigational Product and until the follow-up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g. investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

For this protocol PDMS (Protocol Document Management System) will be used as the electronic case report form (eCRF) and adverse events and protocol specific data will be entered into PDMS and CORe respectively.
11.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject’s condition.

• The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.

• Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.

• Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.2 Serious Adverse Event Reporting

If an event is not an AE per Section 11.1, then it can not be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

• Death
  • A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
  • Inpatient hospitalization or prolongation of existing hospitalization
  • A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  • A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

• Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
11.2.1. Disease-Related Events or Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) should not be reported as a SAE. Progression of the subject’s neoplasia will be recorded in the clinical assessments. Death due to disease progression is to be recorded but not as a SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the Investigator considers that there was a causal relationship between treatment with GSK1120212 (Trametinib), GSK2118436 (Dabrafenib) or protocol design/procedures and the disease progression, then it must be reported as a SAE. Any new primary cancer must be reported as a SAE.

11.2.2. Lack of Anti-cancer Activity

Lack of anti-cancer activity (i.e., progressive disease) per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of anti-cancer activity will be reported if they fulfill the AE or SAE definition (including clarifications).

11.2.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., ECGs or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject’s condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

11.3. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

11.4. Recording of AEs and SAEs
When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

11.5. Evaluating AEs and SAEs

11.5.1. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. When applicable, AE and SAE should be assessed and graded based upon the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.

11.5.2. Assessment of Causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

11.6. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

11.7. Regulatory Reporting Requirements for SAEs

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
• Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
• Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
• Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:
• Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.
• It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor’s guidelines, and Institutional Review Board policy.

12. LIVER CHEMISTRY TESTING PROCEDURES

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 3.3.3.1. They do not apply if subjects develop liver chemistry abnormalities as a result of progressive disease:

• Immediately withdraw the subject from investigational product
• Make every reasonable attempt to have subjects repeat within 24 to 72 hours for repeat liver chemistries, additional testing.
• Monitor subjects at least weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) improve to ≤ grade 1 AE, stabilize or return to within baseline values.
• Obtain viral hepatitis serology testing including:
  o Hepatitis A IgM antibody.
  o Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
  o Hepatitis C RNA.
  o Cytomegalovirus IgM antibody.
  o Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  o Hepatitis E IgM antibody (if subject resides outside the USA or Canada, or has traveled outside USA or Canada in past 3 months).
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin ≥2x ULN.
• Assess eosinophilia

13. STUDY CONDUCT CONSIDERATIONS

13.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrollment of subjects begins.

13.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, including an U.S. Investigational New Drug (IND) Application.

The study will also be conducted in accordance with "good clinical practice" (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

• IRB review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents

• Written informed consent (and any amendments) to be obtained for each subject before participation in the study

• Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB)

14. REFERENCES


Appendices

Appendix 1: Cockcroft-Gault
The Cockcroft-Gault formula is a commonly-used surrogate marker for actual creatinine clearance and employs creatinine measurements and a patient’s weight (kg) to predict the clearance [Cockcroft, 1976].

\[
CrCl (\text{mL/min}) = \frac{\text{Q} \times (140 - \text{age [years]}) \times \text{actual body weight (kg)}^a}{72 \times \text{serum creatinine (mg/dL)}}
\]

| Q=0.85 for females | Q=1.0 for males |

OR

\[
CrCl (\text{mL/min}) = \frac{\text{K} \times (140 - \text{age [years]}) \times \text{actual body weight (kg)}}{\text{serum creatinine (\mu mol/L)}}
\]

| K=0.85 for females | K=1.0 for males |

If the subject is obese (> 30% over ideal body weight), use ideal body weight in calculation of estimate CrCl.

**a. Calculation of Ideal Body Weight Using the Devine Formula** [Devine, 1974]

| Male subjects: | 50.0 kg + (2.3 kg x each inch over 5 feet) |
| | or |
| | 50.0 kg + (0.906 kg x each cm over 152.4 cm) |

| Female subjects: | 45.5 kg + (2.3 kg x each inch over 5 feet) |
| | or |
| | 45.5 kg + (0.906 kg x each cm over 152.4 cm) |

For example:

For a male subject with actual body weight = 90.0 kg, and height = 68 inches, the calculation would be as follows:

Ideal body weight = 50.0 + (2.3) (68-60) = 68.4 kg

*This subject’s actual body weight is >30% over ideal body weight. In this case, the subject’s ideal body weight of 68.4 kg should be used in calculating estimated creatinine clearance.*

**References**


Devine BJ. Case Number 25 Gentamicin Therapy; Clinical Pharmacy Case Studies. Drug Intelligence and Clinical Pharmacy. 1974; 8:650-655.

**Appendix 2: RECIST 1.1 Criteria (37)**

**Measurability of tumor lesions at baseline**
Measurable lesion:

A non nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- $\geq 10$ mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be $\geq 20$ mm).
- $\geq 10$ mm calliper/ruler measurement by clinical exam or medical photography.
- $\geq 20$ mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if

- $\geq 15$mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter $<10$ mm or pathological lymph nodes with $\geq 10$ mm and $<15$ mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions.

Specifications by methods of measurements

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows
interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.

- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

**Clinical Examination:** Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/calipers to measure the size of the lesion, is required. [Eisenhauer, 2009]

**CT and MRI:** *Contrast enhanced CT with 5mm contiguous slices is recommended.* Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used. [Eisenhauer, 2009].

**X-ray:** Should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer, 2009].

**Evaluation of target lesions**

Definitions for assessment of response for target lesion(s) are as follows:

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- **Not Applicable (NA):** No target lesions at baseline.
- **Not Evaluable (NE):** Cannot be classified by one of the five preceding definitions.

**Note:**
• If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for nonnodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.

• If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.

• All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.

• If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

• Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).

• Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.

• Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

• Not Applicable (NA): No non-target lesions at baseline.

• Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

• In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

• In the presence of non-measurable only disease consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
• Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

Frequency of tumor re-evaluation

Target and non-target lesions will be re-evaluated every 8 weeks.

Confirmation of response

To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

Overall response criteria

Table 7 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 7 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR or NA</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD or NE</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD or NA or NE</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD or NA or NE</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>NE</td>
<td>Non-PD or NA or NE</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
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<td>PD</td>
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<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Note:

• Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

• In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.