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CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE II STUDY OF CONCURRENT DABRAFENIB AND TRAMETINIB WITH STEREOTACTIC RADIATION IN THE MANAGEMENT OF PATIENTS WITH BRAF MUTATION–POSITIVE MALIGNANT MELANOMA AND BRAIN METASTASES

CCTG Protocol Number: **IND.224**

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(For contact information of study personnel see Final Page.)

TABLE OF CONTENTS

STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Novartis.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG and Novartis to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of Novartis and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Novartis and CCTG of any such disclosure.

I understand and acknowledge the following:

i. According to the Participating Centre Agreement between this Participating Centre and CCTG, for trials that involve the use of Study Drug provided by a third party support provider, CCTG endeavours to contractually bind the provider to indemnify each Participating Centre who activates on the trial;

ii. For this study, the support provider would not agree to indemnify the Participating Centres. However, the company does represent and warrant that all Study Drug(s) provided will be in compliance with all applicable requirements and specifications of the Therapeutic Products Directorate of Health Canada;

iii. Furthermore, both study drugs are approved by Health Canada, are commercially available, and are being used within their indication in this study; that is, for patients with advanced BRAF mutation-positive melanoma. The addition of the radiation therapy for their brain metastases is the investigational part of the study. This is an academic trial which was developed by the CCTG Melanoma Disease-Site Committee.

I will provide the above information about the indemnification to the relevant personnel at my Participating Centre.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG or Novartis with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Novartis and CCTG and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Qualified Investigator
(printed name and signature)

Date

Protocol Number: CCTG IND.224

CENTRE: _____

TREATMENT SCHEMA

Eligibility

- Histologically confirmed melanoma metastatic to brain and determined to be BRAF V600 mutated.
- Patients who have received prior systemic anti-cancer treatment (including single agent PD1 or combination immunotherapy) are eligible.
- Patients must have recovered from prior treatment related toxicity related to prior systemic therapy with a window of 4 weeks since previous treatment.
- Prior systemic treatment in the adjuvant setting is allowed.
- Patients may have received prior whole brain radiation with progressive and/or new brain metastases to be treated with radiosurgery such that up to 10 metastases will be treated according to protocol. In total (previously treated in addition to study eligible metastases), there can be no more than 10 metastases in the brain.
- Patients who have had prior surgery and whole brain radiation or cavity radiosurgery for brain metastases are eligible if they are planned for radiosurgery to up to 10 intact metastases and treated per study protocol.
- A minimum of 2 weeks from prior surgery is required before the study protocol can be delivered to eligible metastases.
- In total (previously treated in addition to study eligible metastases), there can be no more than 10 metastases in the brain.
- Age ≥ 18 years.
- Karnofsky Performance Status of 70-100 (Appendix I).
- Patients must have a life expectancy of at least 12 weeks.
- Presence of measurable disease (i.e. present with at least one measurable CNS lesion per RECIST 1.1).
- Presence of 1-10 brain metastases as confirmed on a thin slice axial T1 post-gadolinium MRI sequence. The maximum diameter of a single brain lesion should be ≤ 4 cm, and presence of a measurable lesion ≥ 1 cm based on baseline MRI of brain.
- All CNS metastases amenable to single fraction SRS and or fractionated SRS. Hemorrhagic lesions are allowed if the treating radiation oncologist deems the lesion amenable to focal SRS.
- Able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
- Laboratory requirements (within 14 days prior to registration):
  - ANC ≥ 1.2 x 10^9/L
  - Hemoglobin ≥ 90 g/L
  - Platelet count ≥ 100 x 10^9/L
  - PT/INR & PTT ≤ 1.3 x ULN
  - Total bilirubin ≤ 1.5 x ULN
  - AST and ALT ≤ 2.5 x ULN
  - Serum creatinine or ≤ 1.5 x ULN or
    Creatinine Clearance ≥ 50 ml/min (calculated by Cockcroft and Gault)
  - LVEF ≥ LLN (within 28 days prior to registration)
- No prior treatment with a BRAF inhibitor or a MEK inhibitor.
- No known ocular or primary mucosal melanoma.

- No current use of a prohibited medication as described in Section 7.2.
- No history of malignancy with confirmed activating RAS mutation at any time.
- No history of malignancy other than disease under study within 3 years, of study enrolment, (see 4.2.6 for exceptions).
- No leptomeningeal metastases or metastases causing spinal cord compression that are symptomatic or untreated or not stable for ≥ 3 months (must be documented by imaging). Subjects on a stable dose of corticosteroids > 2 weeks or who have been off of corticosteroids for at least 2 weeks can be enrolled with approval of the CCTG.
- No serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures.
- No history of Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (subjects with laboratory evidence of cleared HBV and/or HCV will be permitted).
- No history or evidence of cardiovascular risk (see 4.2.10 for details).
- No history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) (see 4.2.11 for complete details).
- No known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).
- No pregnant or lactating women.
- No history of interstitial lung disease or active pneumonitis.
- Presence of any one brain metastases > 4 cm in maximal diameter, and/or presence of brain metastases of less than 1 cm.
- No brainstem metastases.
- No contraindications to MRI and/or Gadolinium contrast or stereotactic brain radiation therapy.

<u>Pre-Treatment Evaluations</u>

- History, physical exam (including vital signs - blood pressure, heart rate, temperature, height and weight, Karnofsky Performance Status (Appendix I)), hematology, biochemistry, coagulation, adverse events/baseline symptoms, pregnancy test (if applicable), clinical tumour measurements (if applicable), within 14 days prior to registration.
- Radiology: CT thorax/abdomen/pelvis (contrast enhanced); MRI brain; other scans as necessary, within 28 days of registration (within 35 days if negative).
- ECHO/MUGA (within 28 days prior to registration).

<u>On-Treatment Evaluations</u>

- Physical Exam: weight, Karnofsky Performance Status (Appendix I), clinical tumour measurements (if applicable): day 1 each cycle.
- Vital signs: blood pressure, heart rate, temperature: day 1 each cycle.
- Hematology & Biochemistry: day 1 each cycle.
- PT/INR and PTT: as clinically indicated.
- Radiology (MRI brain and CT chest, abdomen and pelvis): every 8 weeks.
- EKG, ECHO/MUGA, ophthalmology and dermatology exam: as clinically indicated.
- Adverse events: end of each cycle.

Duration of Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 7.0.
- Tumour progression or disease recurrence as defined in Section 8.0.
- Request by the patient.

1.0 OBJECTIVES

1.1 Primary Objective

- To determine the intracranial objective response rate to concurrent dabrafenib and trametinib with stereotactic radiation in patients with BRAF mutation-positive malignant melanoma and brain metastases.

1.2 Secondary Objectives

- Extra-cranial objective response rate and overall ORR.
- Duration of response.
- Intracranial and overall progression free survival.
- Overall Survival.
- To evaluate the safety and tolerability of the regimen using the CTCAE v.4.

2.0 BACKGROUND INFORMATION AND RATIONALE

Brain metastases are common in patients with malignant melanoma. Melanoma is the third most common cancer causing brain metastases, after cancers of the lung and breast *[Johnson 1996]*. Brain metastases are responsible for 20 to 54 percent of deaths in patients with melanoma *[Skibber 1996]*, and among those with documented brain metastases, these lesions contribute to death in up to 95 percent of cases *[Sampson 1998]*. The frequency of clinically significant brain metastases in patients with melanoma will likely increase as systemic therapy improves control of extra-cranial disease and patient survival improves. The primary approaches to the treatment of brain metastases include whole brain radiation therapy (WBRT), surgery, and stereotactic radiosurgery (SRS). WBRT is only marginally effective for radio-resistant tumours such as melanoma and renal cell carcinoma. SRS is as effective for these tumors as it is for radiosensitive tumours such as breast and lung *[Yaeh 2015]*. SRS is thus preferred for melanoma patients with brain metastases if it can be administered.

The goal of managing patients with metastatic melanoma is to control both cranial and extracranial disease maximally. Traditionally, once brain metastases are diagnosed then systemic therapy is either held, or delayed, to complete radiation. Delays and interruptions in systemic therapy are sub-optimal as the aim is to control the overall disease burden. Thus, new agents such as dabrafenib and trametinib that show potential to penetrate the blood-brain-barrier, and have an effect on brain metastases as well as extracranial disease, are attractive. Administration of drugs concurrent and following brain SRS may also be preferred in patients with brain metastases, to maximize inhibition of the MAPK pathway and induce tumour cell death. Clinically, the rationale to treat with brain SRS is to control gross disease in the brain at the outset, which is clinically preferable, while the drugs control sub-clinical disease not visible on MRI and enhance the effect of SRS on the treated lesions.

Activity of Dabrafenib and Trametinib in Melanoma

Dabrafenib, a selective BRAF inhibitor, has shown activity with a manageable safety profile in phase I/II studies in patients with BRAF V600E metastatic melanoma. Recently, the results of the BREAK-3 trial were reported *[Hauschild 2012]*. This was a phase III, randomized open-label trial comparing dabrafenib to dacarbazine in patients with BRAF V600E melanoma. Dabrafenib significantly improved progression-free-survival and objective response rates over dacarbazine. Trametinib is a reversible, selective allosteric inhibitor of both MEK1 and MEK2. The phase III trial randomized patients with BRAF mutation positive advanced melanoma to trametinib or chemotherapy. Trametinib was associated with a significant improvement of progression-free-survival and overall survival.

Recent data of two phase III combination trials involving dabrafenib and trametinib in metastatic melanoma patients have shown an improvement in RR, PFS and OS. In the phase III COMBI-d trial, 423 patients with advanced melanoma with V600E or V600K mutation were randomly assigned to either dabrafenib (150 mg twice per day) plus trametinib (2 mg once per day) or to dabrafenib plus placebo *[Long 2014; Long 2015]*. Progression-free survival, the primary endpoint of the trial, was significantly prolonged with the combination compared with dabrafenib alone (median 11.0 versus 8.8 months, hazard ration [HR] 0.67, 95% CI 0.53-0.84). Overall survival was improved with the combination (median 25.1 versus 18.7 months, HR 0.71, 95% CI 0.55-0.92). The objective response rate (complete plus partial) was significantly improved (69 versus 53 percent) with the combination compared with dabrafenib alone; the complete response rates were 16 versus 13 percent, respectively. In the other phase III trial, 704 patients with previously untreated metastatic melanoma were randomly assigned to either dabrafenib plus trametinib or vemurafenib *[Robert 2015]*. All patients had melanoma containing a BRAF V600 mutation. The trial was stopped for efficacy based upon positive results after a planned interim analysis. Overall survival, the primary endpoint of the trial, was significantly increased with the dabrafenib plus trametinib combination (one-year survival rate 72 versus 65 percent, HR for death 0.69, 95% CI 0.53-0.89). Median progression-free survival was also significantly increased (11.4 versus 7.3 months, 95% CI 0.46-0.69) as was the objective response rate (64 versus 51 percent).

Combination therapy was well tolerated. Cutaneous toxicities were significantly more common in patients treated with dabrafenib plus placebo compared with dabrafenib plus trametinib. Squamous cell carcinoma was observed in 9 percent with dabrafenib plus placebo versus 3 percent with the combination. Toxicities more frequently associated with the combination included diarrhea (18 versus 9 percent), pyrexia (52 versus 25 percent), and chills (28 versus 14 percent).

Chorioretinopathy was rare, seen in less than 1% of patients and a decrease in LVEF was seen in 4% of patients in the COMBI-D trial *[Long 2014]*. Combination therapy with a BRAF plus MEK inhibitor will soon be a standard of care for metastatic melanoma that harbours a BRAF mutation.

Dabrafenib alone was also tested in a phase II cohort study in patients with brain metastases and showed an OIRR of 31 to 39% with a median duration of IORR of 20.1 and 28.1 weeks in those with previously treated brain metastases *[Long 2012]*. This median duration is not significantly different than what is observed historically with SRS or WBRT alone and hence a combined approach may be needed to improve duration of response.

Radiation Therapy for the Management of Brain Metastases

In the past, all patients with brain metastases were treated with WBRT. Although WBRT is effective in reducing the risk of new brain metastases, typically from 50% if omitted to 30% if delivered *[Slotman 2007;Chang 2009; Sun 2011; Sahgal 2015]*, local progression rates following WBRT are sub-optimal. A recent study, in the era of MRI screening and follow-up, reported a median PFS of 5.9 months and a crude risk of progression of 60% following WBRT. Beyond the poor long-term local control rates, WBRT is associated with significant side effects which can include a reduction in appetite, increased fatigue, and reductions in quality of life and neurocognitive assessment *[Slotman 2007;Chang 2009; Sun 2011]*. Moreover, these side effects can result in delays and hamper tolerability to further systemic therapy.

With the emergence of focal radiation in the form of SRS *[Sahgal 2009]*, patients now have an alternative to WBRT with a better side effect profile and efficacy with respect to local control. We typically observe 1 year local control rates of ~70%. The drawback to SRS alone lies in distant brain control, as the risk of new distant brain metastases is typically ~50% which is reduced to ~30% with adjuvant WBRT. This implies that patients require close follow-up, and treatment with salvage radiation (further SRS or WBRT) more often with SRS alone. There have now been three randomized trials comparing SRS alone to SRS plus adjuvant WBRT *[Gondi 2014]*. Patients with good performance status (KPS at least 70) and up to 4 tumours were included. The results show no difference in overall survival when WBRT is omitted. More recently, an individual patient data meta-analysis reports a survival advantage with SRS alone in younger patients *[Sahgal 2015]*. These survival results in general, from the individual trials and meta-analyses, show no advantage to WBRT. However, gains in local control and distant brain control are consistently observed with adjuvant WBRT. It is hypothesized that the toxicities of WBRT may negate the beneficial impact with respect to these endpoints and explains the survival outcomes *[Sun 2011; Tsao 2012; Aoyama 2006; Sahgal 2015]*.

Based on the current evidence, SRS alone is considered a standard of care treatment option for patients at least with up to 4 lesions *[Sahgal 2015]*. It is increasingly being recognized and advocated for by professional societies (for example, the NCCN), that the number of lesions is not as important as compared to the suitability of SRS treatment as the sole treatment modality. In fact, the American Society of Radiation Oncology now recommends, in their Choosing Wisely campaign, withholding adjuvant WBRT if a patient is treated with SRS alone. The evidence is emerging to support SRS alone for patients with multiple metastases, and the highest level of evidence comes from Japan. Yamamoto et al. reported a Phase 2 study of SRS alone for patients with up to 10 lesions *[Yamamoto 2014]*. The data suggest that patients with 5 to 10 tumours fare similarly with respect to survival, local control and distant brain control as compared to those with 2 to 4. Therefore, for patients with up to 10 lesions, the use of SRS alone is reasonable and now evidence-based. As a result of the most current evidence and standards of care, our study proposes to treat with SRS alone and include two cohorts consisting of 1) patients with 1-4 metastases to be treated with SRS concurrent with dabrafenib with trametinib, and 2) patients with 5-10 metastases to be treated with SRS concurrent with dabrafenib with trametinib. WBRT will be withheld and may be used as a salvage therapy as needed *[http://www.choosingwisely.org/astro-releases-second-list/]*.

Traditionally, SRS has been limited by tumour size/volume. Dose reductions are required for larger tumours to minimize the risk of radiation necrosis (typically ~5-10%), and the resulting control rates worse for tumours greater than 2-3 cm. The recommended maximal tumour linear dimension for SRS has been 4 cm for these reasons. However, with modern SRS technology there are now alternative focal radiation strategies to treat large lesions in the form of fractionated SRS. The practice of 2 to 5 fraction SRS allows larger tumours to be treated effectively and the limited data suggest superior efficacy for larger metastases *[Feuvret 2014; Kim 2011]*. As a result of the practice shift, we will allow fractionated SRS as directed by the treating radiation oncologist. With respect to salvage therapy, if limited progression is observed such that further SRS can be delivered then this will be recommended; however, if the pattern of relapse is such that SRS is not indicated then salvage WBRT will be allowed.

We expect, for patients with BRAF mutation–positive malignant melanoma and metastases to the brain, we will observe a longer time to progression intracranially, higher objective response rate and a longer duration of response with respect to overall brain control with our strategy of SRS plus dabrafenib and trametinib. Ultimately, this strategy will translate to an increase in overall survival. We propose a phase 2 study of concurrent SRS plus dabrafenib with trametinib followed by continued drug therapy in two cohorts (patients with 1-4 metastases and 5-10 metastases).

BRAF inhibitor therapy can have a radiosensitizing effect on cancerous and healthy tissue *[Zahnreich 2016]*. Radiation skin injury has been reported with concurrent use of BRAF inhibitors such as vemurafenib and dabrafenib and radiation including whole brain radiation for brain metastases. However, SRS limits dose to skin by using multiple beams from various angles, and only in a few fractions, we believe that this will not be a limiting toxicity. A recent study by Hecht et al. reported safety with SRS concurrent with a BRAF inhibitor such that no increase in skin toxicity or severe adverse events was observed *[Hecht 2015]*. No similar data exists for concurrent dabrafenib with trametinib. A recent report from the Eastern Cooperative Oncology Group (ECOG) acknowledged the lack of data with respect to SRS and concurrent BRAF inhibitors, and did not conclude any additional risk of radiation necrosis and hemorrhage from brain metastases when treated with a BRAF inhibitor and radiation. They suggested, based on limited literature and practice patterns, that the BRAF inhibitor be withheld 1 day prior to and after SRS, and 3 days prior to and after fractionated radiation; however, acknowledged that concurrent use should be evaluated on trial *[Anker 2016]*. Therefore, we will have an interim safety assessment after 5 patients in each cohort. If radiation dermatitis occurs, the study treatment will be modified so that dabrafenib and trametinib will be started two days after SRS is completed. These recommendations can be modified based on the physician's assessment of the risk of radiation skin injury.

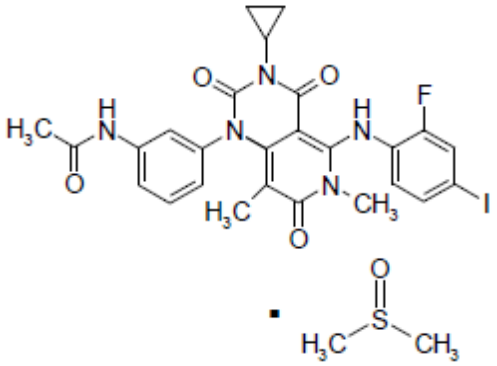
3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Trametinib

3.1.1 *Name and Chemical Information trametinib, SYNONYM(S)m: MEKINIST, GSK1120212*

COMMON TRADE NAME(S): Mekinist®
Common name: trametinib dimethyl sulfoxide
Chemical name: equimolecular combination of N-(3-{3-cyclopropyl-5-[(2- fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo- 3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl}phenyl)acetamide with (methylsulfinyl)methane
Molecular formula: C26H23FIN5O4.C2H6OS
Molecular mass: 693.53 (DMSO solvate of parent) 615.39 (non-solvated parent)

3.1.2 *Chemical Structure*



3.1.3 *Mechanism of Action*

Trametinib is small molecule inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2). MEK1 and MEK2 are components of the mitogen-activated protein kinase (MAPK) pathway. The RAS effector pathway RAF-MEK-ERK, is an essential, shared element of mitogenic signaling involving tyrosine kinase receptors, leading to a wide range of cellular responses, including growth, differentiation, inflammation, and apoptosis. Mutant BRAF and RAS proteins subsequently signal through MEK1 and MEK2 leading to consecutive activation of the MAPK pathway and stimulation of cell growth. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50% of melanoma.

3.1.4 *Experimental Antitumour Activity*

Trametinib is a reversible, and selective allosteric inhibitor of MEK1 and MEK2 activation and kinase activity. The IC_{50} values for the unphosphorylated form of MEK1 and MEK2 are 0.7 nM and 0.9 nM, respectively. The IC_{50} values for the phosphorylated form of MEK1 and MEK2 are 13.2 nM and 10.7 nM, respectively. Trametinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma xenograft models.

3.1.5 *Animal Toxicology*

The nonclinical toxicology findings associated with trametinib administration to mice, rats and dogs are consistent with pharmacologically mediated changes as a result of MEK1/MEK2 inhibition and disruption of mitogen-activated protein kinase (MAPK) signaling pathways. Trametinib caused adverse effects in a variety of tissues and systems (skin, gastrointestinal tract, phosphate homeostasis, liver, ovary, bone and hematological tissues) mainly at doses ≥ 0.03 mg/kg/day. The majority of findings in mice and dogs appeared to be related to effects within the gastrointestinal tract, where in mice, effects were observed at or above clinical exposures and primarily consisted of perforation of the colon with secondary peritonitis and degeneration/necrosis of the glandular mucosa of the stomach, and in dogs presented clinically as decreased bodyweight, decreased food consumption and/or fecal abnormalities and occurred at subclinical exposures. In conclusion, the toxic potential of trametinib has been characterized in a comprehensive battery of nonclinical studies. The effects observed in nonclinical studies were generally, either directly or indirectly, associated with the pharmacologic inhibition of MEK1/MEK2 by trametinib and generally consistent with adverse effects observed in cancer patients.

Carcinogenicity:	Unknown. Studies have not been conducted.
Pregnancy and Lactation:	Genotoxicity: No Embryotoxicity: Yes Fetotoxicity: Yes Trametinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for 4 months after the last dose.
Abortifacient effects:	Yes
Excretion into breast milk:	Do not breastfeed when taking trametinib.
Fertility effects:	Probable

3.1.6 *Phase III Trials*

The efficacy and safety of trametinib monotherapy were evaluated in a phase III randomized, multi-centre, international, open label study comparing trametinib to chemotherapy in patients with unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. The efficacy and safety of trametinib in combination with dabrafenib in the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma has been evaluated in one phase III multi-centre, international clinical study MEK115306. MEK115306 is a phase III double blind, randomized study of 423 patients with BRAF V600E or BRAF V600K mutation.

Screening for both studies included central laboratory testing of BRAF mutation (V600E or V600K) using a BRAF mutation assay conducted on the most recent tumour sample available from either a primary tumour or a tumour from a metastatic site.

In the primary efficacy population, trametinib demonstrated a statistically significant improvement in investigator-assessed PFS (HR = 0.44; [95% CI: 0.31, 0.64], N=273, P<0.0001) which represents a 56% reduction in the risk of tumour progression or death for patients treated with trametinib compared with those treated with chemotherapy. Comparable PFS results were observed in the ITT population (HR = 0.45; [95% CI: 0.33, 0.63], N=322, P<0.0001). Similar PFS results were seen based on an Independent Review Committee evaluation. At the time of the primary analysis, the median follow-up were 4.9 months for patients treated with trametinib and 4.8 months for those treated with chemotherapy.

At the time of primary analysis, OS data were not mature with 20% events reported in the ITT population and 51 (47%) patients in the chemotherapy arm had crossed over to receive trametinib after a confirmed disease progression. An updated analysis was conducted with 63% events.

The investigator-assessed best confirmed overall response rate (ORR) was 22% in the trametinib arm compared to 8% in the chemotherapy arm. However, in the trametinib treatment arm, the confirmed overall response rate was 10% in patients with BRAF V600K mutation compared to 24% in those with BRAF V600E mutation.

Treatment effect with trametinib was observed across all subgroups. However, in patients with BRAF V600K mutation, the investigator-assessed best confirmed overall response rate was 10% in the trametinib arm (n=29) compared to 18% in the chemotherapy arm (n=11).

3.1.7 *Pharmacokinetic Studies*

Trametinib pharmacokinetics were determined after single- and repeat-dose oral administration of trametinib tablets in subjects with solid tumors. Trametinib is absorbed rapidly with median time to maximum plasma concentration (tmax) generally occurring 1.50 hours after single oral administration of trametinib under fasting conditions. The absolute oral bioavailability of a single trametinib 2.0 mg tablet is moderate to high (72%) relative to a co-administered intravenous (IV) microdose. Single-dose administration of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in Cmax, a 24% decrease in area under the concentration-time curve from time zero (predose) to last time point (AUC[0-t]) and a 10% decrease in AUC extrapolated to infinity (AUC[0-∞]) compared to fasted conditions.

Following repeat-dosing the mean area under the curve from 0 hours to the time of next dosing (AUC[0-τ]) and Cmax increased in an approximately dose proportional manner. Trametinib accumulates with repeat dosing with a mean accumulation ratio at the recommended dose of 2 mg once daily of 5.97 and a terminal half-life of 5.3 days determined after single dose administration. Steady state appears to be achieved by Day 15, with little difference in pre-dose (trough) concentration at the end of the dosing interval (C_τ), Cmax and area under the concentration-time curve from time zero (pre-dose) to 24 hrs (AUC[0-24]) between Days 15 and 21.

Trametinib is a low extraction ratio drug based on plasma IV clearance of 3.21 L/hr, which represents approximately 1% of liver blood flow. Trametinib has a high volume of distribution (Vd) of 1060 L determined following an IV microdose.

Following a single dose of [^{14}C]-trametinib, approximately 50% of circulating radioactivity is represented as the parent compound. The fecal route was the major excretion pathway of radioactivity after a single [^{14}C]trametinib oral dose, accounting for >80% of excreted radioactivity recovered up to 10 days post-dose (or 39.2% and 35.0% of the radioactive dose in 2 subjects) while urinary excretion accounted for up to 19% of excreted radioactivity recovered (up to 9% of the radioactive dose). In vitro and in vivo data suggest that trametinib is unlikely to affect the PK of other drugs and that the PK of trametinib is unlikely to be affected by other drugs. Trametinib is eliminated predominantly via deacetylation which is mediated by CES1b, CES1c, CES2 and possibly other hydrolases. There is little evidence from clinical studies for drug interactions mediated by carboxylesterases.

3.1.8 *Pharmaceutical Data*

Supplied: Trametinib 0.5 mg tablets are yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face. Available in bottles of 30 tablets. Bottles contain a silica gel desiccant.

Trametinib 2.0 mg tablets are pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face. Available in bottles of 30 tablets. Bottles contain a silica gel desiccant.

Trametinib tablets contain 0.5, 1.0*, or 2.0 mg of trametinib and the following nonmedicinal ingredients: croscarmellose sodium, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide (colloidal), and sodium lauryl sulphate. The tablet coating contains: hypromellose polyethylene glycol, and titanium dioxide. In addition, the 0.5 mg tablets contain iron oxide yellow and the 2.0 mg tablets contain iron oxide red and polysorbate 80.

* *Trametinib 1 mg tablets not available in Canada.*

Stability: Refer to current IB.

Storage: Store refrigerated, 2-8°C. Protect from light and moisture. Do not remove desiccant. Dispense in original bottle.

Route of Administration: Oral. The recommended dose of trametinib is 2 mg given orally once daily with a full glass of water. Trametinib should be taken without food, at least one hour before or two hours after a meal.

Missed Dose: If a dose is missed, trametinib should not be taken if it is less than 12 hours until the next dose.

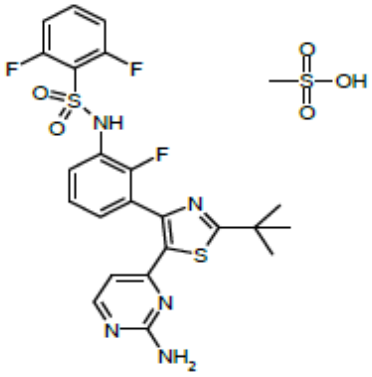
3.2 Dabrafenib

3.2.1 *Name and Chemical Information*

COMMON TRADE NAME(S): PrTAFINLAR®

Common name: Dabrafenib mesylate
Chemical name: N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)- 1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt
Molecular formula: $C_{23}H_{20}F_3N_5O_2S_2 . CH_4O_3S$
Molecular mass: 519.57 g/mol (dabrafenib free base)
615.6 g/mol (dabrafenib mesylate)

3.2.2 *Chemical Structure*



3.2.3 *Mechanism of Action*

Dabrafenib is an orally bioavailable, small molecule inhibitor of RAF kinases, including BRAF. Oncogenic mutations in BRAF lead to constitutive activation of the mitogen-activated protein kinase (MAPK) pathway (including RAS/RAF/MEK/ERK) and may promote tumour cell growth. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50 % of melanomas. The most commonly observed BRAF mutation, V600E, and the next most common, V600K, account for approximately 95 % of BRAF mutations found in patients with melanoma. A number of less common substitutions include V600D, V600G and V600R.

3.2.4 *Experimental Antitumour Activity*

Dabrafenib is a potent, selective, ATP-competitive inhibitor of RAF kinases requiring low concentrations to inhibit 50% of enzyme activity (IC50) in *in vitro* kinase. The inhibitory activity of dabrafenib has not been determined for BRAF variants V600R, V600G and V600M. The results from the in vitro kinase assays were consistent with the inhibition of proliferation of melanoma cell lines. Melanoma cell lines harbouring V600E, V600K or V600D mutations were sensitive to cell growth inhibition by dabrafenib (IC50 < 1 M) compared to melanoma cell lines expressing wild-type BRAF. Dabrafenib demonstrated suppression of phosphorylated ERK (pERK) in tumour cell lines and achieved biomarker suppression and tumour regression in BRAF V600E human melanoma mouse xenografts. Suppression of pERK and tumour regression in BRAF V600K human melanoma mouse xenografts by dabrafenib has not been evaluated.

3.2.5 *Animal Toxicology*

Dabrafenib inhibited hERG repolarization with an estimated IC25 of 11.7 μM (6.1 μg/mL); however, its 3 active metabolites did not inhibit hERG (IC50 > 30 μM). In an ex-vivo rabbit left ventricular wedge assay, dabrafenib caused QT interval shortening (29.7% at 30 μM) with no significant changes in QRS interval and no torsadogenic potential. In rats, a single oral dose of dabrafenib of ≥ 5 mg/kg caused a dose-dependent, mild to moderate increase in heart rate (9 to 48 beats/minute or up to 18%). In dogs, a single oral dose of 50 mg/kg dabrafenib produced a mild increase in heart rate (28%) along with a mild decrease in PR interval (7%) that reversed by 24 hours post dose.

Adverse cardiovascular effects, including coronary arterial degeneration/necrosis and/or hemorrhage, cardiac atrioventricular valve hypertrophy/hemorrhage and atrial fibrovascular proliferation were seen in dogs (≥ 2 times human clinical exposure based on AUC). Focal arterial/perivascular inflammation in various tissues was observed in mice and an increased incidence of hepatic arterial degeneration and spontaneous cardiomyocyte degeneration with inflammation (spontaneous cardiomyopathy) was observed in rats (≥ 0.5 and 0.6 times human clinical exposure for rats and mice respectively). Hepatic effects, including hepatocellular necrosis and inflammation were observed in mice (≥ 0.6 times clinical exposure). Bronchoalveolar inflammation of the lungs was observed in several dogs at ≥ 20 mg/kg/day (≥ 9 times human clinical exposure based on AUC) and was associated with shallow and/or laboured breathing.

Reversible hematological effects have been observed in dogs and rats given dabrafenib. In studies of up to 13 weeks, decreases in reticulocyte counts and/or red cell mass were observed in dogs and rats (≥ 10 and 1.4 times clinical exposure, respectively).

Reproductive and Developmental Toxicity

Dabrafenib is embryofetal toxic and teratogenic in animals at doses similar to human clinical exposures. In combined female fertility, early embryonic and embryofetal development studies in rats, a reduction in fertility was observed at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC). There was also delayed skeletal development and reduced fetal body weight at doses ≥ 20 mg/kg/day (≥ 0.5 times human clinical exposure based on AUC). The numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day. Developmental toxicity including embryo-lethality and ventricular septal defects were also seen at 300 mg/kg/day.

Male fertility studies with dabrafenib have not been conducted. However, in repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥ 0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period.

Carcinogenesis and Mutagenesis

Carcinogenicity studies with dabrafenib have not been conducted. Dabrafenib was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

3.2.6 *Phase III Trials*

The efficacy and safety of dabrafenib mesylate monotherapy in the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma has been evaluated in three multi-centre, international clinical studies. The efficacy and safety of dabrafenib in combination with trametinib in the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma has been evaluated in one phase III multi-centre, international clinical study MEK115306. MEK115306 is a phase III double blind, randomized study of 423 patients with BRAF V600E or BRAF V600K mutation.

Screening for eligibility required central testing for BRAF V600 mutation using a BRAF mutation assay conducted on the most recent tumour sample available from either a primary tumour or a tumour from a metastatic site. The assay used in clinical studies differentiates between V600E and V600K mutations.

The efficacy and safety of dabrafenib in previously treated patients with BRAF V600E mutation positive advanced (Stage III unresectable) or metastatic (Stage IV) cutaneous melanoma were evaluated in study BRF113683 comparing dabrafenib to dacarbazine (DTIC).

Patients were permitted to have prior IL-2 treatment, surgery and radiotherapy. The primary objective was to evaluate the efficacy of dabrafenib compared to DTIC with respect to progression-free survival (PFS) per investigator assessment. Secondary efficacy endpoints included comparison of overall survival (OS), overall response rate (ORR), duration of response and health-related quality of life (HRQoL) status.

Patients were randomized (3:1) to receive either dabrafenib 150 mg twice daily or intravenous DTIC 1000 mg/m^2 every 3 weeks. Randomization was stratified according to disease stage. Patients on the DTIC arm were permitted to cross over to dabrafenib after initial progression.

Treatment with dabrafenib monotherapy was associated with a statistically significant improvement on the primary endpoint, investigator-assessed PFS, compared to treatment with DTIC (HR 0.30, 95% CI: 0.18, 0.51; $p<0.0001$). This represents a relative reduction of 70% in the risk of disease progression or death compared with DTIC. Across subgroups, a consistent PFS benefit of the same magnitude as the overall study population was seen. Independent reviewer-assessed PFS results were consistent with investigator-assessed results.

The secondary endpoint of investigator assessed best confirmed ORR favoured dabrafenib over DTIC. Overall survival data were not mature at the time of the study's primary analysis.

3.2.7 *Pharmacokinetic Studies*

The pharmacoketics of dabrafenib were determined in patients with BRAF mutation-positive metastatic melanoma after single dose and after repeat dosing at 150 mg twice daily with dosing approximately 12 hours apart.

Absorption: Dabrafenib is absorbed orally with a mean absolute bioavailability of 95% (with a lower 90% CI of 81%) and with a median time to achieve peak plasma concentration of 2 hours post-dose in the fasted state.

There is a decrease in exposure observed with repeat dosing, due to induction of its own metabolism. The steady-state AUC(0-τ) and Cmax to single dose values were 0.73 and 1.0, respectively. Interpatient variability (CV%) in steady-state Cmax and AUC for 14 patients in the phase III study was determined to be 37.1% and 37.7%, respectively.

Administration of dabrafenib capsules with food reduced the bioavailability (Cmax and AUC decreased by 51 % and 31 %, respectively) and delayed absorption of dabrafenib when compared to the fasted state.

Distribution: Dabrafenib and its metabolites hydroxy-, carboxy-, and desmethyl-dabrafenib, are highly bound to plasma proteins with percent bound of 99.7, 96.3, 99.5, and 99.9%, respectively. The apparent volume of distribution of dabrafenib (Vc/F) is 70.3 L.

Metabolism: The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib. Hydroxy-dabrafenib terminal half-life parallels that of parent with a half-life of 10 hours while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21-22 hours).

Elimination: Dabrafenib terminal half-life is 8 hours after oral administration. Apparent clearance was estimated to be 34.6 L/h using the recommended 150 mg BID dosing regimen. Fecal excretion is the major route of elimination after oral dosing, accounting for 71 % of a radioactive dose while urinary excretion accounted for 23 % of radioactivity.

3.2.8 *Pharmaceutical Data*

Supplied: Dabrafenib 50 mg capsules are opaque, dark red capsules, monogrammed with 'GS TEW' and '50 mg'. Bottles contain 120 capsules, and a silica gel desiccant.

Dabrafenib 75 mg capsules are opaque, dark pink capsules, monogrammed with 'GS LHF' and '75 mg'. Bottles contain 120 capsules, and a silica gel desiccant.

Dabrafenib capsules contain dabrafenib as dabrafenib mesylate, and the following non-medicinal ingredients: magnesium stearate, colloidal silicon dioxide, and microcrystalline cellulose. Capsule shells contain hypromellose, red iron oxide (E172), and titanium dioxide (E171). Monogramming ink contains black iron oxide, shellac, and propylene glycol.

Stability: Refer to current IB.

Storage: Store between 15-30°C.

Route of Administration: Oral

Missed Dose: If the missed dose is less than 6 hours late, dose should be taken as soon as patient remembers. If the missed dose is more than 6 hours late, dabrafenib should not be taken until next dose is due to be taken.

3.3 Adverse Events of the Trametinib and Dabrafenib Combination

The most common adverse reactions (≥ 20%) for trametinib in combination with dabrafenib include pyrexia, fatigue, nausea, headache, chills, diarrhea, rash, arthralgia, hypertension, vomiting and cough. For details of the adverse events for trametinib, dabrafenib and the combination, please refer to the product monographs and investigator brochures.

3.4 Stereotactic Radiosurgery (SRS)

Stereotactic radiosurgery utilizes immobilization, detailed imaging methods and computerized 3 dimensional treatment planning systems to deliver high doses of focal radiation in a highly precise manner in a single fraction or up to 5 fractions. Three general methods are used - Gamma Knife, Cyberknife and Linear Accelerator (Linac) based systems.

The Gamma Knife is based on multiple cobalt sources arranged in a semi-circular arrangement. Each Cobalt source emits gamma ray irradiation, and the average beam energy is 1.25 MeV. A sophisticated collimation system allows for the convergence of multiple beams of irradiation to a focus (isocenter) within the treatment volume, effectively delivering a highly focused "shot" of radiation. Several shorts of radiation directed to the entire target volume results in the delivery of the prescribed treatment dose. Gamma Knife technology has been based on using an invasive head frame for immobilization; however, the Gamma Knife now has a dedicated frameless system that allows for frameless SRS delivery.

Linac-based systems are the most common technology delivering SRS. Essentially, a high energy beam is shaped using different sized circular cones or multileaf collimators to conform around the target volume and delivery with high precision to the entire target volume. Linac-based SRS was historically based on using an invasive stereotactic head frame, however, non-invasive frameless head immobilizations systems are now available and in use to deliver frameless SRS.

The Cyberknife consists of a miniaturized linac mounted onto a robotic arm. There is an integrated image-guidance system. The robot moves the linac around the patient and the 6MV beam is collimated using different sized circular collimators or even an MLC system specific to Cyberknife technology. The system allows for the prescribed dose to be delivered to the target volume with high precision and an established SRS technology. Due to the integrated image-guidance system and near-real time feedback of the patient's cranium position, this system allows for frameless SRS.

Regardless of the delivery system, standards for SRS have to be followed according to AAPM guidelines. Commissioning of any SRS delivery system is well defined in accordance with AAPM guidelines. The biological effect is the same regardless of the technology such that radiation induces DNA damage leading to cell kill. SRS, whether single fraction or multi-fractions (up to 5 fractions), is a standard radiotherapeutic application for brain metastases. Acute side effects consist of radiation-induced edema that may require use of dexamethasone and manifests typically as headache, nausea, vomiting. Rarely are more serious side effects observed which can consist of obstructive hydrocephalus (<1%). The most significant late side effect consists of radiation necrosis and asymptomatic radiographic necrosis can occur in 10-20% of patients with symptomatic radiation necrosis in <10% of patients. Radiation necrosis represents an inflammatory reaction of the radiated tissue and can mimic tumour progression. Typically is the patient experiences headache, nausea and vomiting then dexamethasone is the primary treatment, rarely if neurologic deficit the surgery may be required. Typically radiation necrosis resolves with use of dexamethasone and confirmatory MRI scans are required to show stability or regression as opposed to progression. With well-defined normal tissue guidelines for dose limits, damage to other sensitive tissues in the brain such as the optic structures and brainstem is extremely rare. Precise pre-treatment planning is necessary to avoid damage to these organs at risk, and the dose limits proposed in this trial represents well defined standards for safe practice.

4.0 STUDY POPULATION

Patients with BRAF mutation positive melanoma with brain metastases with no contraindications to dabrafenib, trametinib and SRS will be eligible for this study.

This study is designed to include women and minorities as appropriate, but is not designed to measure differences in intervention effects.

4.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of registration. Questions about eligibility criteria should be addressed prior to calling for registration.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfil all of the following criteria to be eligible for admission to the study:

4.1.1 Histologically confirmed melanoma metastatic to brain and determined to be BRAF V600 mutated.

4.1.2 *Previous Therapy*

Systemic Therapy:

Patients who have received prior systemic anti-cancer treatment (including single agent PD1 or combination immunotherapy) are eligible.

Patients must have recovered from prior treatment related toxicity related to prior systemic therapy with a window of 4 weeks since previous treatment.

Prior systemic treatment in the adjuvant setting is allowed.

Radiation and Surgery:

Patients may have received prior whole brain radiation with progressive and/or new brain metastases to be treated with radiosurgery such that up to 10 metastases will be treated according to protocol. In total (previously treated in addition to study eligible metastases), there can be no more than 10 metastases in the brain.

Patients who have had prior surgery and whole brain radiation or cavity radiosurgery for brain metastases are eligible if they are planned for radiosurgery to up to 10 intact metastases and treated per study protocol. A minimum of 2 weeks from prior surgery is required before the study protocol can be delivered to eligible metastases. In total (previously treated in addition to study eligible metastases), there can be no more than 10 metastases in the brain.

4.1.3 Age ≥ 18 years.

4.1.4 Karnofsky Performance Status of 70-100 (Appendix I).

4.1.5 Patients must have a life expectancy of at least 12 weeks.

4.1.6 Presence of measurable disease (i.e. present with at least one measurable CNS lesion per RECIST 1.1).

4.1.7 Presence of 1-10 brain metastases as confirmed on a thin slice axial T1 post-gadolinium MRI sequence. The maximum diameter of a single brain lesion should be $\leq$ 4 cm, and presence of a measurable lesion $\geq$ 1 cm based on baseline MRI of brain.

4.1.8 All CNS metastases amenable to single fraction SRS and or fractionated SRS. Hemorrhagic lesions are allowed if the treating radiation oncologist deems the lesion amenable to focal SRS.

4.1.9 Able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

4.1.10 Laboratory Requirements
(must be done within 14 days prior to registration)

Hematology	Absolute neutrophil counts (ANC)	$\geq$ 1.2 x 10^9/L
	Hemoglobin	≥ 90 g/L
	Platelets	$\geq$ 100 x 10^9/L
Coagulation	PT/INR[a] and PTT	≤ 1.3 x upper normal limit (UNL)
Chemistry	Serum creatinine[b] *or:* creatinine clearance	≤ 1.5 x UNL $\geq$ 50ml/min
	Total bilirubin[c]	$\leq$ 1.5 x UNL
	Alanine aminotransferase (AST) and aspartate aminotransferase (ALT)	$\leq$ 2.5 x UNL
Cardiac *(within 28 days of registration)*	Left Ventricular Ejection fraction (LVEF)[d]	≥ LLN

a. Subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to randomization.
b. If serum creatinine is > 1.5 UNL, calculate creatinine clearance using standard Cockcroft-Gault formula (below). Creatinine clearance must be ≥ 50 mL/min to be eligible.
c. Direct if patient known to have Gilbert's syndrome.
d. Either ECHO or MUGA scan but same modality must be used throughout the study

Creatinine clearance as calculated by Cockcroft-Gault formula:

Females: $GFR = \frac{1.04 \times (140 - age) \times weight\ in\ kg}{serum\ creatinine\ in\ \mu mol/L}$

Males: $GFR = \frac{1.23 \times (140 - age) \times weight\ in\ kg}{serum\ creatinine\ in\ \mu mol/L}$

4.1.10 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to registration and prior to tests which are considered to be study specific (see Section 5).

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

4.1.12 Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits (for example: 1 ½ hour's driving distance) placed on patients being considered for this trial. (Call the CCTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

4.1.13 In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient registration.

4.1.14 Women/men of childbearing potential must have agreed to use a highly effective contraceptive method. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Section 5.0); this may include an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin is high and partner is vasectomized, it may be associated with tumour production of hCG, as seen with some cancers. Patients will be considered eligible if an ultrasound is negative for pregnancy.

4.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

4.2.1 Prior treatment with a BRAF inhibitor or a MEK inhibitor.

4.2.2 Known ocular or primary mucosal melanoma.

4.2.3 Current use of a prohibited medication as described in Section 7.2.

4.2.4 History of malignancy with confirmed activating RAS mutation at any time. *Note*: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility.

4.2.5 History of malignancy other than disease under study within 3 years of study enrolment, except for patients with a history of completely resected non-melanoma skin cancer, or indolent malignancies such as chronic lymphocytic leukemia are eligible. (*Please call CCTG if any questions about the interpretation of this criterion*).

4.2.6 Leptomeningeal metastases or metastases causing spinal cord compression that are symptomatic or untreated or not stable for ≥ 3 months (must be documented by imaging). Subjects on a stable dose of corticosteroids > 2 weeks or who have been off of corticosteroids for at least 2 weeks can be enrolled with approval of the CCTG.

4.2.7 Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures.

4.2.8 A history of Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (subjects with laboratory evidence of cleared HBV and/or HCV will be permitted).

4.2.9 A history or evidence of cardiovascular risk including any of the following:

- A QT interval corrected for heart rate using the Bazett's formula (QTcB) ≥ 480 msec;
- A history or evidence of current clinically significant uncontrolled arrhythmias (*Exception: subjects with atrial fibrillation controlled for > 30 days prior to dosing are eligible)*.
- A history of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within 6 months prior to registration.
- A history or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines;
- Patients with intra-cardiac defibrillators;
- Abnormal cardiac valve morphology (≥ grade 2) documented by echocardiogram (subjects with grade 1 abnormalities [i.e. mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.
- Treatment refractory hypertension defined as a blood pressure of systolic > 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy.

4.2.10 A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including:

a. Presence of predisposing factors to RVO or CSR (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes); or
b. Visible retinal pathology as assessed by ophthalmic examination that is considered a risk factor for RVO or CSR such as:
    i. Evidence of new optic disc cupping;
    ii. Evidence of new visual field defects on automated perimetry;
    iii. Intraocular pressure >21 mmHg as measured by tonography.

4.2.11 Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).

4.2.12 Pregnant or lactating women. Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to registration. Men and women of childbearing potential who do not agree to use adequate contraception (intrauterine device, double barrier method of birth control; abstinence) prior to study entry, for the duration of the study participation and 4 months after last dose of study treatment. (Should a woman become pregnant or suspect she is pregnant, or should a man father a child, while participating in this study, she/he should inform the treating physician immediately.) *Note*: Hormonal-based methods (e.g. oral contraceptives) are not permitted as contraception due to potential drug-drug interactions with dabrafenib.

4.2.13 History of interstitial lung disease or active pneumonitis.

4.2.14 Any one brain metastases > 4 cm in maximal diameter , and/or presence of brain metastases of less than 1 cm.

4.2.15 Brainstem metastases.

4.2.16 Contraindications to MRI and/or Gadolinium contrast or stereotactic brain radiation therapy.

5.0 PATIENT EVALUATION FLOWSHEET: PRE-TREATMENT, ON STUDY, AND AFTER TREATMENT

All patients entered on study must be evaluated according to the schedule outlined below with documentation submitted according to the schedule in Appendix III.

Required Investigations	Pre-study (≤ 14 days prior to registration)	Within 28 days prior to registration	Day 1 each cycle, and as clinically indicated	Every 8 weeks from date of registration	4 weeks after completion of protocol therapy	3 month follow-up (only required for pts without confirmed PD and ongoing toxicities[1])
History and Physical Exam						
including: height, weight, Karnofsky Performance Status, clinical tumour measurements (if applicable)	X		X[2]		X	
Blood pressure, heart rate, temperature (assessed by medical personnel)	X		X[2]		X	X
Hematology*						
CBC, differential, platelets	X		X[2]		X[3]	X
Coagulation*						
PT/INR and PTT	X[4]					
Biochemistry*						
Sodium, potassium, chloride, bicarbonate, magnesium, calcium, albumin, alkaline phosphatase, ALT, AST, total bilirubin, blood glucose (random, unless abnormal then fasting required), creatinine and creatinine clearance[5], LDH, total protein	X		X[2]		X[3]	X
Radiology[6]						
CT thorax/abdomen/pelvis (contrast enhanced) and other scans as required to document all sites of disease		X[7]		X[8]	X[9,10]	X[9]
MRI of brain (required)		X[7]		X[8]	X[9,10]	X[9]
Other Investigations						
Pregnancy Test[11]	X					
EKG			as clinically indicated			
ECHO/MUGA[6]		X[4]				
Ophthalmologic exam			as clinically indicated			
Dermatology exam			as clinically indicated			
Adverse events[12]	X[13]	continuously				X[1]

footnotes on next page

*	Pre-treatment blood draws and physical exams may be done up to two working days prior to treatment if necessary (e.g. Friday for treatment on Monday, or to accommodate holidays). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.
1.	Every three months thereafter to follow adverse events felt related until resolved to ≤ grade 2.
2.	Labs do NOT need to be repeated C1D1 but vital signs should be done on day 1 of each cycle, including cycle 1.
3.	At 4 weeks then every 3 months thereafter to follow abnormal results felt related until resolved to ≤ grade 2.
4.	Then as clinically indicated.
5.	Creatinine clearance required if serum creatinine ≥ 1.5 ULN. To be measured directly by 24 hour urine sampling or calculated by Cockcroft Formula (see protocol Section 4.1.11).
6.	To ensure comparability, baseline X-rays/scans/LVEF evaluation must be performed using identical techniques.
7.	35 days if negative.
8.	+/- 14 day window to aid in scheduling.
9.	To be done additionally every 3 months thereafter until relapse or progression for patients with CR, PR, or SD response.
10.	Patients with a CR or PR should have scans repeated after 4 weeks to confirm response.
11.	For women of childbearing potential only. Required within 14 days prior to registration.
12.	Adverse Events to be evaluated using the NCI Common Terminology Criteria for Adverse Events (see Appendix IV).
13.	Within 7 days prior to registration; again within 24 hours prior to first treatment.

5.1 Follow-up for Ineligible Patients

The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the Baseline Report. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

6.0 ENTRY/REGISTRATION PROCEDURES

6.1 Entry Procedures

All registrations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the IND.224 trial specific web-site. If sites experience difficulties accessing the system and/or registering patients please contact the help desk (link in EDC) or the IND.224 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

The following information will be required:

- trial code (CCTG IND.224)
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- confirmation of the requirements listed in Section 4.0, including dates of essential tests and actual laboratory values
- height and weight

6.2 Registration

Registration will be provided electronically.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting registration/randomization.

All registered patients are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the Baseline Report. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

7.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient registration.

Patients should begin taking dabrafenib and trametinib a minimum of 7 days and a maximum of 14 days prior to commencement of SRS.

There will be 2 cohorts of patients. Each cohort is based on the number of brain metastases at presentation on T1-post gadolinium volumetric axial MRI.

Cohort 1: minimum 20 to 25 patients

Patients with 1-4 metastases will receive focal SRS to all lesions and dabrafenib + trametinib. Agents will begin a minimum of 7 days and a maximum of 14 days prior to SRS and continue post-SRS until progression or unacceptable toxicity.

Cohort 2: minimum 20 to 25 patients

Patients with 5-10 metastases will receive focal SRS to all lesions and dabrafenib + trametinib. Agents will begin a minimum of 7 days and a maximum of 14 days prior to SRS and continue post-SRS until progression or unacceptable toxicity.

7.1 Chemotherapy Treatment Plan

7.1.1 *Drug Administration*

Cohort	Agent(s)	Route	Dose	Frequency	Schedule
1 & 2	Dabrafenib	PO	150 mg	BID	Continuously*
	Trametinib	PO	2 mg	OD	
* A treatment cycle (reporting period) is defined as 28 days. There will be no breaks between cycles.					

7.1.2 *Premedication*

Not required. Prophylactic corticosteroids are not required but may be used prior to SRS based on institutional standards and investigator discretion. The following is an example regimen:

- Prophylactic dexamethasone at 10 mg IV 1 hour prior to start of SRS.
- Prophylactic dexamethasone at 4 mg po in am per day of fractionated SRS is permitted according to institutional practice.

7.1.3 *Dose Modifications*

For New Primary Cutaneous Malignancies:
No dose modifications are required.

For New Primary Non-Cutaneous Malignancies:
No dose modifications are required for trametinib. If used in combination with dabrafenib, permanently discontinue dabrafenib in patients who develop RAS mutation-positive non-cutaneous malignancies.

Doses will be reduced for adverse reactions as described in Table 2.

Dose Level	Dabrafenib	Trametinib
-1	100 mg orally twice daily	1.5 mg orally once daily
-2	75 mg orally twice daily	1 mg orally once daily
-3	50 mg orally twice daily	Permanently discontinue
-4	Permanently discontinue	

Table 2: Recommended Dose Modifications for Trametinib and Dabrafenib Administered in Combination

Severity of Adverse Reaction*	**Trametinib**	**Dabrafenib**
Febrile drug reaction		
• Fever of 38.5-40°C without complications	• Trametinib may be continued at the same dose.	• Withhold dabrafenib until fever resolves. Then resume at same or lower dose level.
• Fever higher than 40°C • Fever complicated by rigors, hypotension, dehydration, or renal failure	• Withhold trametinib until fever resolves. Then resume trametinib at same or lower dose level.	• Withhold dabrafenib until fever resolves. Then resume at a lower dose level. Or • Permanently discontinue dabrafenib.
Cutaneous		
• Grade 2 rash (tolerable)	• Reduce dose of trametinib by 0.5 mg or discontinue in patients taking 1 mg daily	• Dabrafenib may be continued at the same dose. Monitor as clinically indicated.
• Intolerable Grade 2 rash or ≥ Grade 3 rash	• Withhold trametinib for up to 3 weeks. If improved within 3 weeks, resume at a lower dose (reduced by 0.5 mg) or discontinue in patients taking 1 mg daily	• Withhold until adverse reaction resolves or improves to Grade 1 and reduce by one dose level when resuming therapy
• Intolerable Grade 2 or ≥ Grade 3 rash that does not improve within 3 weeks despite interruption of dosing	• Permanently discontinue trametinib	• Permanently discontinue treatment with dabrafenib

table continues on next page …

Severity of Adverse Reaction*	Trametinib	Dabrafenib
Cardiac		
• Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pre-treatment value	• Withhold trametinib for up to 4 weeks.	• Dabrafenib may be continued at the same dose. Monitor as clinical indicated.
• Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below LLN that improves to normal LVEF value within 4 weeks following interruption of trametinib	• Resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue in patients taking 1 mg daily	• Dabrafenib may be continued at the same dose. Monitor as clinically indicated.
• Absolute decrease in LVEF of 10% or greater from baseline and is below LLN that does not improve to normal LVEF value within 4 weeks following interruption of trametinib	• Permanently discontinue trametinib	• Dabrafenib may be continued at the same dose. Monitor as clinically indicated.
• Symptomatic congestive heart failure • Absolute decrease in LVEF of greater than 20% from baseline that is below LLN	• Permanently discontinue trametinib	• Withhold dabrafenib until adverse reaction resolves and resume dabrafenib at the same dose or at a reduced dose level.
Ocular Toxicities		
• Grade 2-3 retinal pigment epithelial detachments (RPED)	• Withhold trametinib for up to 3 weeks.	• Dabrafenib may be continued at the same dose. Monitor as clinically indicated.
• Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	• If improved within 3 weeks, resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue in patients taking 1 mg daily	• Dabrafenib may be continued at the same dose. Monitor as clinically indicated.
• Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks OR recurrence of RPED (any Grade) after dose interruption or reduction	• Permanently discontinue trametinib	• Dabrafenib may be continued at the same dose. Monitor as clinically indicated
• Retinal vein occlusion	• Permanently discontinue trametinib.	• Dabrafenib may be continued at the same dose. Monitor as clinically indicated.
• Uveitis that responds to local ocular therapy	• Trametinib may be continued at the same dose	Dabrafenib may be continued at the same dose. Monitor as clinically indicated.
• Uveitis that does not improve despite ocular therapy	• Withhold trametinib until adverse reaction resolves and resume at the same or a reduced dose	• Withhold dabrafenib until adverse reaction resolves and reduce by one dose level when resuming therapy
Pulmonary		
• Interstitial lung disease/pneumonitis	• Permanently discontinue trametinib.	• Dabrafenib may be continued at the same dose. Monitor as clinically indicated.

table continues on next page …

Severity of Adverse Reaction*	Trametinib	Dabrafenib
Other		
• Grade 1 or Grade 2 (tolerable)	Trametinib may be continued at the same dose. Monitor as clinically indicated.	• Dabrafenib may be continued at the same dose. Monitor as clinically indicated.
• Grade 2 (intolerable) OR Grade 3 adverse reaction	• Withhold trametinib. If adverse reaction resolves or improves to Grade 1, reduce by one dose level when resuming therapy.	• Withhold dabrafenib until adverse reaction resolves or improves to grade 1 and reduce by one dose level when resuming therapy.
• Grade 4 adverse reaction OR Grade 3 adverse reaction that does not improve to Grade 0-1	• Permanently discontinue trametinib.	• Permanently discontinue dabrafenib OR withhold therapy until adverse reaction resolves or improves to Grade 1 and reduce by one dose level when resuming therapy.
* Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix V).		

7.2 Concomitant Medications and Non-Drug Therapies

7.2.1 *Permitted Medications and Non-Drug Therapies*

The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of study treatment. Any concomitant medication(s), including dietary supplements, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior surgical procedures will be recorded in the eCRF.

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, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted provided that INR is monitored in accordance with local institutional practice.

7.2.2 *Prohibited Medications and Non-Drug Therapies*

The use of certain medications and illicit drugs within 28 days or 5 half lives, whichever is shorter, prior to registration and for the duration of the study will not be allowed.

The following medications or non-drug therapies are also prohibited while on treatment in this study:

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs (Note: Subjects with known HIV are ineligible for study participation);
- Herbal remedies (e.g. St. John's Wort);

- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibition, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in Table 3) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the CCTG Senior Investigator is required in these situations. The list may be modified based on emerging data. Refer to the SPM for the most current list.

Table 3: Prohibited Medications

PROHIBITED – strong inducers of CYP3A or CYP2C8, since concentrations of dabrafenib may be decreased	
Class/Therapeutic Area	Drugs/Agents
Antibiotics	Rifamycin class agents (e.g., rifampin, rifabutin, rifapentine),
Anticonvulsant	Carbamazepine, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan, St. John's wort
PROHIBITED – Strong inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	Drugs/Agents
Antibiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Hyperlipidemia	Gemfibrozil
Antiretroviral	ritonavir, saquinavir, atazanavir
Miscellaneous	Conivaptan

7.2.3 *Medications to be Used With Caution*

The following medications should be used with caution as their concentrations may be altered by dabrafenib or they may alter dabrafenib concentrations:

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases. Transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) and transporters 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. A partial list of these medications is provided in the SPM.

- Therapeutic level dosing of warfarin can be used with close monitoring of PT/INR by the site. Exposure decreased by 37% due to enzyme induction when on treatment, thus warfarin dosing may need to be adjusted based upon PT/INR. Consequently, when discontinuing dabrafenib, warfarin exposure may be increased and thus close monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate. Prophylactic low dose warfarin may be given to maintain central catheter patency.
- Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib pharmacokinetics. In an ad-hoc analysis, no differences in Cmax and AUC were noted between subjects who reported taking pH-elevating products relative to other subjects. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these medicinal products that increase gastric pH should be used with caution when administered with dabrafenib.

7.3 Radiation Treatment Plan

7.3.1 *Pre-Treatment Guidelines*

Patients must be suitable candidates for serial MRI imaging on study. If claustrophobic, then sedatives may be given as per institutional standards for the MRI and SRS procedure.

Patients may be given 10 mg of intravenous decadron at the time of SRS at the discretion of the treating physician, and for 5 fractions SRS then daily oral decadron may be given at the discretion of the treating physician (typically 4 mg orally per day is practiced to start day 1 of fractionated SRS and discontinued with no taper once complete).

7.3.2 *Equipment and Treatment Delivery*

7.3.2.1 *Equipment*

Single fraction SRS must be delivered using a commissioned delivery apparatus and treatment planning system for brain SRS. The technology may be a Gamma Knife, Cyberknife or linac-based system equipped with isocentric circular collimators or a multi-leaf collimator with a leaf width of no more than 5 mm.

For 5 fraction SRS, a linac system equipped with a multi-leaf collimator and leaf width of no more than 5 mm may be used. In this situation, the beam energy must be 6 MV and image guidance applied with cone-beam CT or a stereoscopic X-ray imaging system. With respect to treatment planning, either fixed field intensity modulated radiotherapy or volumetric modulated arc therapy may be used. Gamma Knife and Cyberknife technology may also be used to deliver 5 fraction SRS.

7.3.2.2 *Treatment Delivery*

Treatment delivery will be based on the apparatus used. Cyberknife systems and Gamma Knife systems are dedicated SRS systems with their own treatment planning software and procedures. For linac-based SRS, either cone based or MLC based single fraction SRS may be delivered. Cone based SRS is usually delivered using multiple non-coplanar arcs. For MLC based SRS, varying treatment delivery methods can be used such as fixed field intensity modulated radiotherapy or volumetric modulated arc therapy.

7.3.3 *Positioning, Immobilization and Localization/Simulation*

7.3.3.1 *Positioning*

Patients are supine with their arms by their side.

7.3.3.2 *Immobilization*

Single fraction SRS must be delivered with the head immobilized using an invasive stereotactic head frame or non-invasive relocatable head frame specifically approved by Health Canada for brain SRS. For 5 fraction SRS, either a relocatable non-invasive head frame or a thermoplastic head mask may be used as per department policy and procedures.

7.3.3.3 *Localization Imaging/Simulation*

Patients will have a CT simulation (3-D treatment planning volumetric imaging) with the patient supine and head immobilized using immobilization systems as described in 7.3.3.2. Typical practice is to use 1 mm CT slice thickness (no more than 2 mm slice thickness permitted). IV contrast may be administered for simulation at the discretion of the treating radiation oncologist as per departmental policy and procedures, but not necessary. The treatment planning MRI will be fused to the treatment planning CT for contouring and treatment planning. The MRI may be done by the diagnostic imaging department, and the patient does not have to be in treatment position with the immobilization device in place. For Gamma Knife technology, MRI only simulation and planning is often performed. Institutional practice will be respected and must comply with known standards per the relevant AAPM reports (in particular TG report 54 and 135).

If image artifacts, for example as a result of dental fillings, are present and will affect the dose calculation, the method in which they are accounted for must be stated. Specifically, describe the regions of artifacts that were contoured and state the density used to override the regions.

7.3.4 *Volume Definitions*

7.3.4.1 *Gross Tumour Volume (GTV)*

The GTV will be defined as the contrast enhanced tumor on the post-gadolinium T1-MRI. If contrast is used on the treatment planning CT this may aid delineation of the target but the final target will be based on the MRI imaging.

7.3.4.2 *Planning Target Volume (PTV)*

A margin may be applied as a three dimensional expansion beyond the GTV as per institutional practice for single fraction SRS to create a PTV, and can range from 0 to 2 mm. For 5 fraction SRS, a PTV expansion margin beyond the GTV should be applied, and may range from 0 to 3 mm.

7.3.4.3 *Organs at Risk (OAR)*

Each lens will be contoured in their entirety as per MRI.

Each globe will be contoured in their entirety as per MRI.

Each optic nerve will be contoured as per MRI from its insertion on the globe to the point where it forms the optic chiasm.

The optic chiasm will be contoured as per MRI.

The entire brainstem will be contoured with the cranial extent defined by the junction with the thalamus and caudally to the level of the foramen magnum.

Each cochlea will be contoured in their entirety as per MRI.

The entire normal brain will be contoured as per MRI.

7.3.4.4 *Planning Organ at Risk Volume (PRV)*

PRV is not required.

7.3.4.5 *Unspecified Tissue*

For IMRT (which also includes VMAT) plans, a volume known as unspecified tissue must be identified. This volume is defined as tissue contained within the skin but which is not included in any other contoured structure including the PTVs. This is relevant to fractionated SRS as opposed to single fraction SRS.

7.3.4.6 Nomenclature

Each GTV will be numbered according to 1 to 10 as per GTV1, GTV2, GTV3, GTV4, GTV5, GTV6, GTV7, GTV8, GTV9, GTV10. If PTV is applied, then the corresponding number should be applied such that the PTV for GTV1 would be named PTV1, for GTV2 the corresponding PTV would be named PTV2 and so forth up to 10.

Naming according to dose is not feasible as each target may be treated with the same dose.

For the OAR that are bilateral then preceding the name should be R or L for right and left, for example, R cochlea.

7.3.5 *Dose Specification*

7.3.5.1 *Targets*

Each target will have a total dose prescribed to an isodose surface which encompasses the margin of the contoured target (GTV or PTV). Typically the dose is prescribed to the highest isodose line covering the GTV and/or PTV, and the range of acceptable isodose surfaces to prescribe is 45% to 95%. If the treatment planning system is such that the prescribed dose is to a point, or to the mean or median dose to the PTV or CTV, that is acceptable and needs to be recorded.

Dose is to be specified in Gray (Gy).

The prescribed dose is determined according to the maximal diameter of the GTV and/or PTV according to the following table.

Maximum SRS dose based on lesion maximum diameter per baseline treatment planning MRI	
GTV and/or PTV less than 2.0 cm in widest diameter	20 Gy
GTV and/or PTV= 2.0 - < 3.0 cm in widest diameter	18 Gy
GTV and/or PTV= ≥ 3.0 - ≤ 4.0 cm in widest diameter	15 Gy or 25-35 Gy in 5 fractions fractionated radiosurgery

7.3.5.2 *Organs at Risk*

The critical organs at risk, which include the lens, globes, optic nerves, optic chiasm, brainstem, cochlea and normal brain, will be contoured. For single fraction SRS, the maximum point dose to each lens should not exceed 5 Gy, each globe should not exceed 8 Gy, optic chiasm should not exceed 10 Gy, each optic nerve should not exceed 10 Gy, brainstem should not exceed 15 Gy, and for each cochlea should not exceed 8 Gy.

For 5 fractions radiosurgery, the maximum point dose to each lens should not exceed 5 Gy, each globe should not exceed 20 Gy, optic chiasm should not exceed 25 Gy, each optic nerve should not exceed 25 Gy, brainstem should not exceed 25 Gy, and for each cochlea (recommended but not mandated) should not exceed 15 Gy.

7.3.5.3 *Unspecified Normal Tissue Dose Limits*

The unspecified normal tissue volume receiving prescription should be minimized as per department protocol.

7.3.5.4 *Fractionation*

Single fraction SRS to a target GTV or PTV is delivered in one treatment over one day. In cases of multiple metastases where the department wants to deliver single fraction SRS over several days, all lesions must be treated a minimum of 7 days and a maximum of 14 days of treatment planning.

For multiple fraction SRS (5 fraction), treatment typically is delivered in 5 consecutive days, Monday to Friday, however may span over a weekend or be interrupted by a machine service day such that the intended treatment should be completed within 16 days from treatment planning.

Combinations of single fraction and fractionated are permitted based on the radiation oncologist practice. The above guidelines must be adhered to with respect to treatment completion of the single fraction and multiple fraction SRS.

7.3.5.5 *Corrections for Interruptions*

None.

7.3.6 *Treatment Planning*

7.3.6.1 *Beam Energy*

Gamma Knife technology is based on the Cobalt sources and Cyberknife is based on 6 MV photons. For linac delivery a beam energy of 6 MV is desirable. However, flattening-filter-free (FFF) beams of other energies is allowed with some additional explanation from the participating centre on why this energy is being used.

7.3.6.2 *Beam Arrangement*

Gamma Knife treatments are based on multiple cobalt beams converging at the isocenter to deliver a shot of radiation and multiple shots used to deliver the dose to the intended target. Cyberknife treatments are based on cone or MLC based delivery. Linac-based SRS treatments can be based on arc delivery using cones, or MLC based IMRT or VMAT.

7.3.6.3 *Beam Modifiers*

No physical wedges are permitted.

7.3.6.4 *Planning Priorities*

The protocol priorities are: 1) critical OAR, 2) PTV coverage, 3) non-critical OAR, 4) unspecified normal tissue.

7.3.6.5 *Inhomogeneity Corrections*

Correction for inhomogeneity is not mandatory and procedures based on department policies should be adhered to.

7.3.6.6 *Acceptable Dose Heterogeneity*

Dose heterogeneity is generally accepted in very small volumes especially with Gamma Knife and Cyberknife delivery within the GTV and/or PTV.

Dose heterogeneity will vary with different SRS delivery methods, with different target sizes and with number of targets.

For single fraction SRS treatments delivered with treatment modalities other than Gamma Knife and when there is no overlap with OARs, the point dose variation within the GTV or PTV can range from 90% to 160% of the prescribed dose. If there is overlap with OARs, the point dose variation within the PTV can range from 85% to 160% of the prescribed dose. For Gamma Knife treatments, if the dose prescription criterion is met (i.e. dose is prescribed to the 45-95% isodose line) the dose heterogeneity is considered acceptable.

For fractionated delivery with treatment modalities other than Gamma Knife and when there is no overlap with OARs, the point dose variation within the GTV and/or PTV can range from 90% to 130% of the prescribed dose. If there is overlap with OARs, the point dose variation within the PTV can range from 85% to 130% of the prescribed dose. For Gamma Knife treatments, if the dose prescription criterion is met (i.e. dose is prescribed to the 45-95% isodose line) the dose heterogeneity is considered acceptable.

7.3.6.7 *Planning technique*

Both the inverse and forward planning is permitted and the dose calculation grid should be less than 0.25 cm.

7.3.6.8 *Treatment Delivery Constraints*

Due to the different techniques used, no specific treatment time and segment size constraints will be listed here.

7.3.7 Verification

7.3.7.1 *Position Verification/Correction*

The method and frequency of verification/correction imaging must be documented, and adhered to according to departmental protocol. For example: state the imaging method (i.e. cone-beam CT), positional tolerance, method of positional correction (for example, couch with 6 degrees of freedom) and frequency of imaging method for fractionated SRS.

7.3.7.2 *Dose Verification*

The dose must be independently verified when feasible. For all SRS cases, follow departmental protocol where an independent monitor unit check and/or pre-treatment verification measurement using films/chambers/diodes/arrays may be conducted.

7.3.8 *Concurrent Therapy*

7.3.8.1 Dabrafenib and trametinib will start a minimum of 7 days and a maximum of 14 days prior to radiation therapy and continue through the days that radiation is given.

7.3.8.2 Scheduling: dabrafenib and trametinib dose should be given at least 1 hour prior to radiation treatment.

7.3.9 *Patient Specific Documentation Requirements*

7.3.9.1 *Volumes*

The volume of all GTV, PTV, OAR as well as any overlapping PTV-OAR volume are to be documented. All GTVs to be displayed on the planning CT. Orthogonal images through the isocenter of all GTVs are to be documented.

7.3.9.2 *Dose Summary Statistics*

Treatment time: the monitor units or time required to deliver the prescribed dose will be calculated and reported.

Dose Uniformity: the maximum and minimum dose for each target (GTV and/or PTV) will be calculated and reported.

The PITV is defined as the ratio of the prescription isodose volume to the target volume. These will be calculated and reported.

Prescription isodose line: The total dose delivered to the prescription isodose line shall be calculated and reported.

Normal tissue and critical OAR dose points: Documentation of the point maximum dose (highest point dose) within the critical OAR are to be calculated and reported.

7.3.9.3 *Dose Distributions*

The isodose distribution for each target must be submitted. Isodose distributions should be displayed on three orthogonal planes, or if not possible, on multiple axial through each target volume.

7.3.9.4 Dose Volume Histogram (DVHs)

DVH for each GTV and/or PTV and OAR must be documented. DVHs must be in absolute dose (Gy). For fractionated SRS IMRT or VMAT treatment plans, DVH data should also include unspecified tissue.

7.3.9.4.1 Specification of DVH Calculation - Differential or cumulative (if relevant)

Cumulative.

7.3.9.4.2 Dose Bin Size (if relevant)

Less than 0.25cm x 0.25cm x 0.25cm.

7.3.9.4.3 Graphical or Tabular (if relevant)

Both are relevant to be calculated and submitted. Tabular data should be submitted with bin-size set to < 10 cGy.

7.3.10 *Quality Assurance Review Criteria*

Treatment related deviations outside protocol recommendations for dosimetry will be reported as minor or major protocol deviations. Such deviations could include failure to identify and treat appropriate targets and excessive treatment of non-target tissues (see Radiotherapy Quality Assurance Manual).

7.3.11 *Credentialing Requirements*

All centres participating in the study will require credentialing for the delivery of SRS (single and fractionated) prior to local activation. This credentialing will consist of a Facility Questionnaire and demonstration of the ability to comply with protocol specifications for treatment planning and delivery using anonymized archival data (dry runs).

Credentialing will be mandated at the investigator level and the site must receive approval from the central QA Reviewer before local activation.

All required credentialing documents must be uploaded to a secure website created specifically to facilitate radiotherapy QA review for this trial.

Please review the Radiotherapy Quality Assurance Manual for more details about documents to be submitted, the Facility Questionnaire, timing of the reviews and procedures for documentation uploading.

7.3.12 *Centre Based Pre-Treatment Review*

The treatment plans will be reviewed for every patient registered on the study. This review will be performed prior to the commencement of radiotherapy by another physician designated for this purpose and identified as study participant, i.e. "local QA reviewer". The following will be reviewed: contoured volumes, dose summary statistics, dose distributions, and DVHs. Specifications for the review are included in the Radiotherapy Quality Assurance Manual. There will be no external real-time review for this study.

7.3.13 *External Post-Treatment Review*

A final review will be completed for all patients after all radiotherapy has been completed and the required documents submitted (see Radiotherapy Quality Assurance Manual).

7.3.14 *Criteria for Retreatment with SRS for New Lesions*

In the event on follow-up that distant brain failure arises (new lesion) then further SRS alone is encouraged as long as the radiation oncologist deems it suitable. Typically, if up to 10 new metastases occur then every effort should be made to treat with SRS alone. In the case of leptomeningeal disease then WBRT is advocated, otherwise the intent is to spare the patient from WBRT at relapse if suitable for SRS.

7.3.15 *Management of Patients with Possible Radiation Necrosis*

If the treated lesion changes in such a way that radiation necrosis is suspected then follow-up scans are required. If no further growth or regression is observed then the response assessment should be stable disease rather than progressive disease. If a patient has surgery and pathology indicates radiation necrosis then this should be noted in the response assessment.

7.3.16 *Glossary*

AAPM - The American Association of Physicists in Medicine

ASTRO - American Society for Radiation Oncology

CT - Computed Tomography

CTV - Clinical Target Volume

DVH - Dose Volume Histogram

GTV - Gross Tumour Volume

IMRT - Intensity Modulated Radiation Therapy

MLC - Multi-leaf Collimators

MRI - Magnetic Resonance Imaging

OAR - Organs at Risk

QA - Quality Assurance

PTV - Planning Target Volume

SRS - Stereotactic Radiosurgery

VMAT - Volumetric Modulated Arc Therapy

7.4 Duration of Protocol Treatment

Treatment will continue until the criteria for removal from protocol treatment have been met (see section 10.0).

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

Response Assessments: The following algorithms will be used to support primary and secondary efficacy endpoints in the present trial.

CNS Assessments: For efficacy assessment in the CNS to support the primary endpoint of intracranial response, a protocol defined RECIST 1.1-based approach will be utilized with modifications that reflect the approach of the RANO-BM Working Group. RECIST 1.1, uni-dimensional longest diameter (LD) measurements will be used with a lower limit of size for defining a measurable lesion, > 1 cm based on the baseline MRI of brain. CNS lesions < 1 cm are non-target lesions. Best overall CNS response represents a composite of radiographic CNS target and non-target response (see definitions below), corticosteroid use, and clinical status.

Extracranial Disease Assessments: Assessment of response of extracranial disease will use RECIST 1.1.

Overall Response Assessments: Overall response assessment will be assessed using RECIST 1.1. Overall response will be measured as the sum of the LD of CNS + extracranial index lesions. The size cut-off of a measurable lesion in the extracranial compartment will follow the RECIST 1.1 definition of 1.0 cm.

8.1.1 Evaluable for adverse events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

8.1.2 Evaluable for response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below *[Eisenhauer 2009]*.

8.2 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee with modifications proposed by RANO to reflect intracranial, extracranial and overall objective response rate.

8.2.1 *Measurable Disease*. Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

8.2.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

8.2.3 *Target Lesions*. When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

8.2.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

8.2.5 *Response*.

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target* lesions. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases [ref RECIST 1.1]) before CR can be accepted. Confirmation of response is required in non-randomized studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is required in non-randomized studies.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

A single CNS lesion must increase by an absolute value of ≥ 5 mm to be considered progression.

Radiation Necrosis versus Progressive Disease: Progression is not unequivocal if change in imaging is possibly due to radiation necrosis. If the treated lesion changes in such a way that radiation necrosis is suspected then follow-up scans are required. If no further growth or regression is observed then the response assessment should be stable disease rather than progressive disease. If a patient has surgery and pathology indicates radiation necrosis then this should be noted in the response assessment. For SRS treated lesions, an advanced imaging modality such as perfusion MR imaging, MR spectroscopy, or 18FLT or 18FDG positron emission tomography (PET) may be used as additional evidence of tumor progression or treatment effect/radionecrosis.

Corticosteroid Use and Clinical Deterioration:

a. An increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumour, will not be used as a sole determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumour do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumour becomes apparent, they will be considered to have progression.

b. The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 points from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose.

Table 1: Integration of Target, non-Target and New Lesions into Response Assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	tumour nodes <10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	tumour nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

For non-randomized trials, where confirmation of response is required, best overall response can be interpreted as follows:

Response: First Time Point	Subsequent Time Point	BEST Overall Response	Also Requires
CR	CR	CR	tumour nodes < 10mm
CR	PR	SD, PD or PR (see comment*)	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	

* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.

Because CNS progression of disease may be masked by corticosteroids or manifest by neurological deterioration without radiological progression, the following ADDITIONAL parameters will be used:

Response Criteria for CNS Metastases

Criterion	CR	PR	SD	PD
Target lesions	None	≥ 30% decrease in sum LD relative to baseline	< 30% decrease relative to baseline but < 20% increase in sum LD relative to nadir	≥ 20% increase in sum LD relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal PD*
New lesion(s)**	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA+
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any+

* Progression occurs when this criterion is met.

** New lesion = new lesion not present on prior scans and visible in at least 2 projections. If a new lesion is equivocal, for example because of its small size, continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression (See "Guidance in the case of new lesion(s) while on immunotherapy").

+ Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

8.3 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

8.4 Stable Disease Duration

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

8.5 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

8.5.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

8.5.2 *Chest X-ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

8.5.3 *CT, MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment in the body while MRI is best modality for the CNS. This guideline has defined measurability of lesions on CT or MRI scan based on the assumption that slice thickness is 5 mm or less. When scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Other specialized imaging or other techniques may also be appropriate for individual case [ref RECIST 1.1]. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

8.5.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

8.5.5 *Endoscopy, Laparoscopy*. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

8.5.6 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

9.0 SERIOUS ADVERSE EVENT REPORTING

This protocol does not contain investigational agent(s), and adverse events occurring as a result of this commercially available treatment should be reported to CCTG in the manner described below. In addition, your local Research Ethics Board (REB) should be notified.

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix V). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

9.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 9.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the investigator brochure or product monograph.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect
- Any new primary cancers and treatment emergent malignancies (including squamous cell carcinoma and new primary melanoma) with the exception of basal cell carcinoma (BCC). BCC should be reported as an AE or SAE based on the discretion of the investigator.
- Symptomatic LVEF decrease that meets stopping criteria or asymptomatic LVEF decrease that does not recover, as outlined as LVEF guidance (Section 7.1.3 Table 2)
- Retinal pigment epithelial detachment (RPED) or retinal vein occlusion (RVO)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

9.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the IND.224 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours: Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.

Within 7 days: Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

IND.224 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2411

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the IND.224 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

9.3 Other Protocol Reportable Events – Exposure Reporting, and Pregnancy Reporting

9.3.1 *Pregnancy Prevention*

Women of childbearing potential (WOCBP) and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criteria 4.2.13. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

9.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in female participants, and female partners of male participants. Pregnancies occurring up to 4 months after the completion of study treatment must also be reported.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

If the pregnancy results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

9.3.3 *Exposure Reporting (Non-study Participants)*

The investigator is required to report to CCTG any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non- study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant swallowing study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure in a timely manner, within 24 hours of learning of the exposure, using the CCTG Exposure Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further exposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual. All follow-up reports must be submitted to CCTG in a timely manner. A copy of the signed exposure follow-up consent signature page must also be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

If the exposure results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

9.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

The CCTG will provide expedited reports of SAEs to Health Canada for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

9.5 CCTG Reporting Responsibility to Novartis

Novartis will be notified of all protocol reportable serious adverse events within 1 working day.

9.6 Novartis Reporting Responsibilities

Novartis will report all regulatory reportable serious adverse events from non-CCTG trials (Safety Updates) to Health Canada and also provide to CCTG within the timelines outlined in the contract. CCTG will review these events to determine which meet the criteria (serious, unexpected, drug related) for IND.224 investigator distribution.

9.7 Reporting Safety Reports to Investigators

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial IND.224 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial IND.224 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 7.0.
- Tumour progression or disease recurrence as defined in Section 8.0.
- Request by the patient.
- Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Therapy After Protocol Treatment is Stopped

At the discretion of the investigator.

Note, patients with CNS progression that can be managed with additional SRS or whole brain radiotherapy can continue on dabrafeinib and trametinib if there is no evidence of progression outside of the CNS and it is felt that continuation of systemic treatment may benefit the patient.

10.3 Follow-up Off Protocol Treatment

All patients will be seen at 4 weeks after completion of protocol therapy. Thereafter, continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to $\leq$ grade 2) and late toxicities (including second malignancies). For patients who go off protocol treatment with CR, PR, or SD ongoing, follow-up will be required every 3 months until relapse. Final report (Death Report) will be required on all patients. Due within 2 weeks of knowledge of death (see Appendix III - Documentation for Study).

11.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

11.1 Central Radiology Review

At the conclusion of the trial, a central review of x-rays and/or scans will be carried out if any responses have been claimed. For purposes of reporting, the results of both local and central radiology reviews will be included.

11.2 Central Pathology Review

There will be no central pathology review for this study.

12.0 STATISTICAL CONSIDERATIONS

12.1 Objectives and Design

The primary objective is to determine the intracranial objective response rate to concurrent dabrafenib and trametinib with stereotactic radiation in patients with BRAF mutation-positive malignant melanoma and brain metastases. There will be two cohorts based on the numbers of CNS metastases. Secondary endpoints include:

- Extra-cranial objective response rate and overall ORR.
- Duration of response.
- Intracranial and overall progression free survival.
- Overall survival.
- To evaluate the safety and tolerability of the regimen using the CTCAE v.4.

12.2 Primary Endpoints and Analysis

The primary endpoint is objective response rate in the brain. Based on the literature objective response rate is not influenced by the numbers of metastases that are treated by SRS *[Follwell 2012]*. However, toxicity may be different based on numbers of metastases treated. For this reason, patients will be evaluated for ORR; however, toxicity will be evaluated for two cohorts: those with 1-4 lesions and those with 5-10 lesions. Response will be assessed using RECIST v1.1. Results between cohorts will only be compared descriptively with one another and with previously published data. There will be an interim safety analysis for both radiation cohorts after 5 patients in each cohort have completed SRS with 4 weeks of follow-up time.

12.3 Sample Size and Duration of Study

We propose to target a 20% increase in intracranial ORR based on a baseline of 40% for SRS or dabrafenib alone *[Follwell 2012; Liew 2011; Neal 2014; Sueng 1998]* versus 60% ORR with the combination *[Long 2016]* difference with alpha and beta = 0.10. With a Simon two stage design there would be > 7 responses/18 patients in the first stage and 22/46 in the second stage. Assuming 10% inevaluable patients or dropouts, we propose a maximum of 50 patients.

We propose to evaluate secondary endpoints of safety and intracranial PFS in the two previously defined cohorts 1-4 and greater than 5-10 and to having at least 20-25 patients/cohort for these endpoints.

With accrual of 4-5 patients/month the accrual duration will take an estimated 12-18 months with an additional 6 months of follow-up to assess objective responses.

12.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported bi-annually at investigators' meetings.

12.5 Interim Analysis

An interim assessment for safety of the first 5 patients treated within each cohort is planned. Results will be reviewed by the trial study team to determine if toxicity is acceptable to proceed.

13.0 PUBLICATION POLICY

13.1 Authorship of Papers, Meeting Abstracts, Etc.

13.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group and Novartis, may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.

13.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

13.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following study closure the manuscript has not been submitted, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results

CCTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG website: http://www.ctg.queensu.ca.

13.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by Novartis, the CCTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

14.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

14.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

14.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

14.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in an CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

14.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner, exposed individual) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the main consent form adequately addresses the collection of information regarding the outcome of a pregnancy of a trial participant, a "Pregnancy Follow-up consent form will not be required by CCTG.

Trial-specific consent forms for "Pregnancy Follow-up" and "Exposure Follow-up" can be found on the trial webpage. The appropriate consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner or exposed individual).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to pregnancy/exposure. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

Obtaining Consent for Research on Children

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/guardian.

For reporting an exposure, the parent/guardian is required to sign an "Exposure Follow-up" consent form (even if they are a participant in the main study) prior to collecting information about the child.

14.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

14.5 Retention of Patient Records and Study Files

All essential documents must be maintained in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

14.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI). Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

14.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

The drug company, Novartis, has reserved the right to audit participating centres. Audits may only be conducted after consultation with CCTG.

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APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Drug Distribution

Commercial supplies of Dabrafenib and Trametinib will be supplied by Novartis to the distributor, Bay Area Research Logistics (BARL), and distributed by BARL to participating centres.

Drug Labelling

Drug supplies for this study contain all information required under the drug labelling regulations.

Initial Drug Supply

Once a centre is locally activated (following receipt and review of all required documentation), the CCTG will authorize a start-up supply of dabrafenib and trametinib to be shipped directly to the centre. Drug will be shipped to the centre within 5 working days of local activation.

Drug accountability and drug re-order forms for each agent will be included on the IND.224 trial website.

Drug Ordering (Re-Supply)

Subsequent requests for more drug should be made by authorized personnel at each centre. A copy of the Request for Drug Shipment form (available on the IND.224 trial website) should be faxed to the distributor. Please allow sufficient time for shipment of drug. Note: shipment will not be made on Fridays and weekends.

Drug Accountability

The investigational products are to be prescribed only by the investigator and co-investigators on the participants list. Under no circumstances will the investigator allow the drug to be used other than as directed by the protocol. Accurate records must be maintained accounting for the receipt of the investigational product and for the disposition of the product (Drug Accountability Log).

Drug Destruction or Return:

Details to be supplied at the time of study closure.

PLEASE NOTE

DRUG FROM THIS SUPPLY IS TO BE USED ONLY

FOR PATIENTS REGISTERED ON THIS STUDY

Study drug shipped to participating centres may be transferred from the main hospital pharmacy to a satellite pharmacy, provided separate drug accountability records are maintained in each pharmacy. Investigational agent may NOT however, be transferred to pharmacies or physicians outside the participating centre.

APPENDIX III - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of registration and will apply to all eligible and ineligible patients. This trial will use a web-based Electronic Data Capture (EDC) system for all data collection including SAE reporting (see Section 9.0 for details regarding SAE reporting). For details about accessing the EDC system and completing the on-line Case Report Forms, please refer to the Data Management Guidebook posted on the IND 224 area of the CCTG web-site (www.ctg.queensu.ca).

Electronic Case Report Form	To be Completed/Submitted Electronically	Supporting Documentation to be sent using Supporting Document Upload Tool*
PATIENT ENROLLMENT FOLDER	Must be completed at time of registration to confirm eligibility.	
BASELINE REPORT	Due within 2 weeks of patient registration.	Copies of signature pages of main consent forms; relevant pathology & radiology reports; LVEF report
TREATMENT REPORT	To be completed every 4 weeks (i.e. after each cycle/reporting period). Due within 2 weeks of end of cycle/reporting period. This form documents treatment, adverse events, investigations and response assessment for each cycle/reporting period.	Relevant radiology reports; LVEF report (if applicable)
END OF TREATMENT REPORT	To be completed when patient permanently discontinues protocol treatment. Due within 2 weeks of end of protocol treatment.	
4 WEEK POST TREATMENT REPORT	To be completed once on all patients, 4 weeks after the end of the last cycle. Due within 2 weeks after contact with patient.	
FOLLOW-UP REPORT	Continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to ≤ grade 2) and late toxicities (including second malignancies). For patients who go off protocol treatment with response or stable disease ongoing, Follow-Up form to be completed every 3 months until relapse/progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.
RELAPSE/PROGRESSION REPORT	To be completed at the time of disease relapse or progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.
DEATH REPORT **	Death Report will be required on all patients. Due within 2 weeks of knowledge of death.	Autopsy report, if done.
SERIOUS ADVERSE EVENT REPORT FORM	All reportable serious adverse events must be reported as described in Section 9.0. Preliminary CCTG Serious Adverse Event Report due within 24 hours. Updated CCTG Serious Adverse Event Report due within 7 days.	All relevant test reports, admission, discharge summaries/notes.

* Supporting documents should be uploaded immediately after the report they refer to has been submitted electronically.
** NB It is the investigator's responsibility to investigate and report the date/cause of death of any patient who dies during this period. Any death that occurs during this protocol therapy or within 30 days after last dose must also be reported as a Serious Adverse Event as described in section 9.

APPENDIX IV - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

APPENDIX V - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 7th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org). These staging criteria should be used for new trials.

LIST OF CONTACTS

PATIENT REGISTRATION

All patients must be registered with CCTG before any treatment is given.

	Contact	Tel. #	Fax #
STUDY SUPPLIES Electronic Case Report Forms, Protocols, Data Management Guidebook, Safety Information	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*	613-533-6430	613-533-2411
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Linda Hagerman Study Coordinator, CCTG Email: lhagerman@ctg.queensu.ca or: Dr. Janet Dancey Senior Investigator, CCTG Email: janet.dancy@oicr.on.ca		
STUDY CO-CHAIRS	Dr. Teresa Petrella Study Co-Chair Email: teresa.petrella@sunnybrook.ca	416-480-5248	416-480-7802
	or: Dr. Arjun Sahgal Study Co-Chair Email: arjun.sahgal@sunnybrook.ca	416-480-4834	416-480-0456
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Janet Dancey Senior Investigator, CCTG *or* Linda Hagerman Study Coordinator, CCTG	613-533-6430	613-533-2411
DRUG ORDERING	See Appendix II for full details		