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EA6183

A Phase II Neoadjuvant Study of Encorafenib With Binimetinib in Patients With Resectable Locoregional Metastases From Cutaneous or Unknown Primary Melanoma (Stages III N1B/C/D)

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Addendum #1
Addendum #2
Addendum #3

NCTN STUDY CHAMPION:
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Agents	IND#	NSC#	Supply
Encorafenib	147279	807064	Pfizer
Binimetinib	147279	788187	Pfizer
^{18}F-FLT	147279	743144	Supplied by sites qualified by ECOG-ACRIN NCI Cancer Imaging Program

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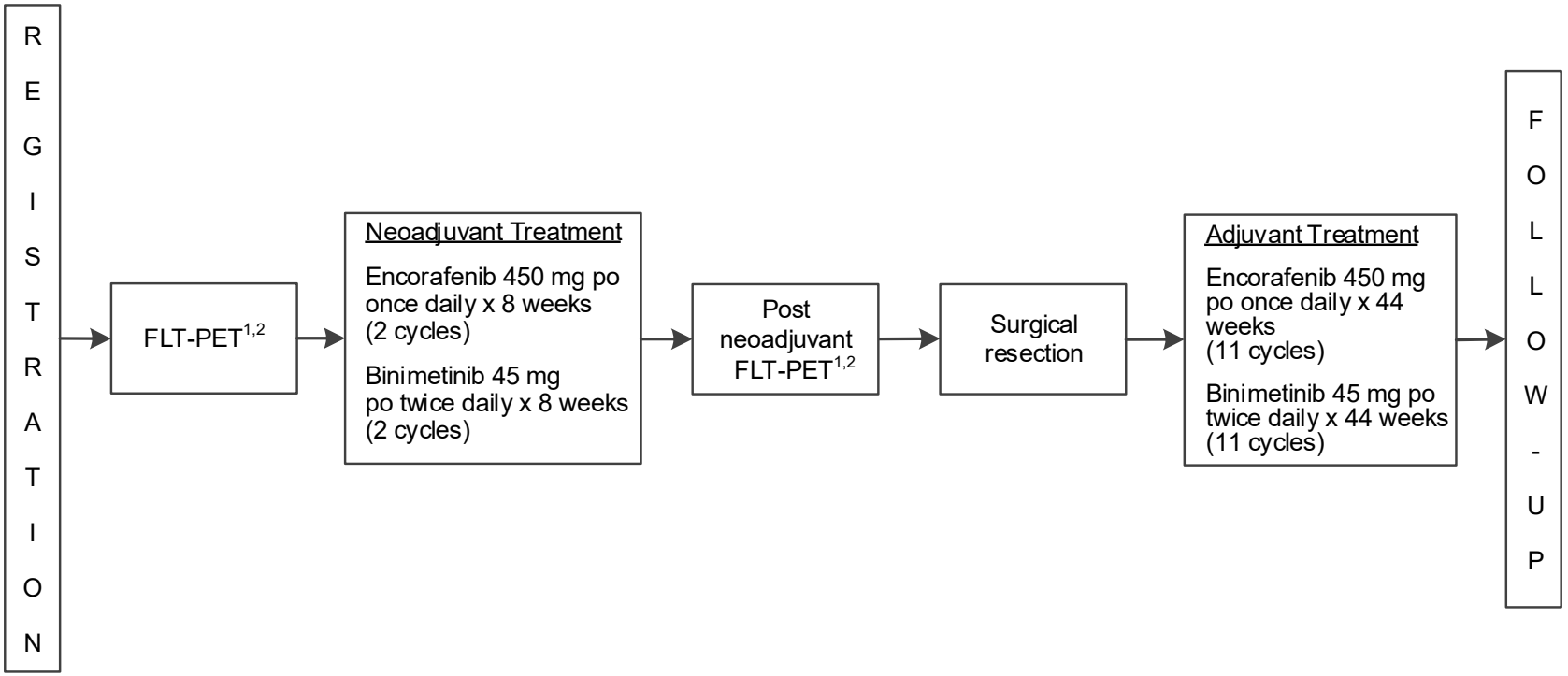
Schema



Cycle length = 28 days

1. FLT-PET: The first FLT-PET is to be done at baseline prior to initiation of neoadjuvant treatment. The second FLT-PET is to be done after the 8 weeks of neoadjuvant treatment is completed and prior to surgery. (See Section 5.3)
2. Tumor biopsies: From consenting patients, tumor biopsies are requested to be performed at baseline (if inadequate material is available from prior procedure) and after 2 weeks of neoadjuvant treatment is completed. If baseline biopsy is performed after study registration, the baseline FLT-PET scan should be completed prior to the biopsy (can be done same day).

1. Introduction

1.1 Importance

Melanoma, despite multiple recent advances and improvements in overall survival, remains a lethal disease for many patients. The incidence of melanoma continues to rise, with an estimated 96,480 new cases in 2019 and 7,230 deaths in the United States [Siegel, 2019]. Five-year melanoma specific survival rates for stage III patients vary widely from 93% to 32% [Gershenwald, 2017] where patients with clinically evident nodal disease, including stage IIIB, IIIC, and IIID melanoma have higher risk of relapse despite complete surgical resections. The dramatic improvements in overall survival in advanced unresectable melanoma has come about due to checkpoint inhibitor therapy and mitogen activated protein kinase (MAPK) pathway inhibitors. These agents are now moving into the adjuvant setting and neoadjuvant setting.

1.2 MAPK pathway inhibitor therapy

Somatic mutations in BRAF are present in approximately 40% of all melanomas [Davies, 2002]. BRAF inhibitors (BRAFi) either with or without MEK inhibitors (MEKi) offer high response rates in patients with metastatic melanoma whose tumors have BRAF mutations. However, typically resistance evolves. Single agent BRAF inhibitor therapy with vemurafenib [Genentech-Roche, South San Francisco, CA] and dabrafenib [Novartis, Basel, Switzerland] initially demonstrated significant overall survival (OS) and progression free survival (PFS) benefits compared with dacarbazine (DTIC) in the treatment of BRAF V600mutant advanced melanoma patients in randomized phase III studies. [Chapman, NEJM 2011; Hauschild, Lancet, 2012] The addition of MEKi to BRAFi in the treatment of advanced melanoma improved response rates, duration of response, overall survival as well as mitigating some of the toxicity of this therapy. [Long, NEJM 2014, Larkin, NEJM 2014, Robert, NEJM 2015] There are extensive safety data in support of the combination BRAFi +MEKi therapy in the metastatic disease setting. The most common adverse events for patients receiving BRAFi are skin rash, hyperkeratosis, dry skin, photosensitivity, headache, pyrexia, arthralgia, myalgias, skin papillomas and skin cancers and fatigue. [Chapman, NEJM 2011, Hauschild, Lancet, 2012] The most frequent and notable adverse events with MEKi are skin rash, diarrhea, nausea, vomiting, edema, hypertension, fatigue, chorioretinopathy, elevated creatinine phosphokinase (CPK), and left ventricular dysfunction.[Flaherty, NEJM, 2012] Combinations of BRAFi and MEKi have resulted in decreased skin toxicity including decrease in the incidence of nonmelanoma skin cancers. [Long, NEJM 2014, Larkin, NEJM 2014, Robert, NEJM 2015]

A third selective BRAF inhibitor, Encorafenib (LGX818) [Pfizer, Boulder, CO], has shown a favorable safety profile and efficacy in a phase I study as a single agent, as well as in phase 1B/2 combination study with binimetinib [Pfizer, Boulder, CO], a MEKi. [Dummer, JCO, 2013, Sullivan, JCO, 2015] The preliminary results of the phase I study identified 450mg daily as the RP2D with 7 patients experiencing a DLT: hand-foot skin reaction, foot pain, fatigue, diarrhea/rash/headache, insomnia/asthenia, facial paresis/confusion, pain/neuralgia- all of which were reversible. [Dummer, JCO, 2013] A total of 54 patients, including 26 BRAFi naïve were treated and the most common AEs

included: rash, dry skin, hand foot palmar plantar dysesthesia, pruritis, alopecia, nausea, decreased appetite, fatigue and arthralgias. Fever was seen in only 5.6% and squamous cell carcinoma in 3.7% (n=2) and keratoacanthoma in 3.7% (n=2). Single-agent encorafenib demonstrated a confirmed RR of 58% in BRAFi naïve patients, without any CRs. The median PFS was 217 days in this cohort and median duration of response was estimated to be 45.3 weeks. Treatment-related grade 3 toxicities were present in 33.3% and all reversible. The Phase 1B/2 study of encorafenib + binimetinib treated 55 BRAFi naïve patients with no MTD declared. [Sullivan, JCO, 2015] Encorafenib at a variety of doses was combined with binimetinib 45mg bid and showed an ORR of 74.5%. For encorafenib 400/450mg with binimetinib 45mg bid, the ORR was 77.8% (n=9). The median PFS was 11.3 months for the entire trial. Grade 3/4 AEs were 55.5%(5/9) for encorafenib 400/450mg + binimetinib 45mg bid cohort; most common AEs included nausea, diarrhea, AST/ALT elevation, fatigue. Only 1/9 had pyrexia, and 1/9 had CPK elevation, 1/9 with retinal pigment epithelium detachment, 1/9 with EF decreased, 1/9 with a neoplasm of the skin. Toxicities for encorafenib 600mg daily were greater. The Columbus study, a three arm 1:1:1 randomized study of vemurafenib 960mg bid vs encorafenib 300mg daily vs the combination of encorafenib 450mg daily and binimetinib 45mg bid in untreated patients with BRAF mutant advanced melanoma enrolled 577 patients.[Dummer, Lancet Oncol, 2018] The primary endpoint was PFS for the combination therapy vs vemurafenib, and the secondary endpoint was PFS for combination therapy vs encorafenib alone. Preliminary results of this study were presented demonstrating PFS [per central review] of 14.9 mos for the combination vs 7.3 mos for vemurafenib alone[p<0.001]; 14.9mos for combination vs 9.6mos [p=0.051] for encorafenib alone.[Flaherty, SMR, 2016] The ORR (central review) was 63% for the combination therapy vs 51% and 40% for Encorafenib 300mg daily and vemurafenib, respectively. The CR rate for combination therapy was 8%. This led to approval by the FDA of this combination therapy for the treatment of metastatic melanoma. Safety was acceptable with 58% grade 3/4 AEs in the combination arm, versus 66% and 63% in the other arms respectively. The incidence of secondary non-melanoma skin neoplasms was 4% [n= 192] for combination therapy vs 9% [n=192] for encorafenib alone vs 18% [n=192] for vemurafenib.[Flaherty, SMR, 2016]. The incidence in the combination arm of elevated CPK was 23%, pyrexia 18%, which is similar or less frequent compared with other combinations of BRAFi/MEKi. [Long, NEJM 2014, Larkin, NEJM 2014, Robert, NEJM 2015] Additionally, this pair of agents had fewer AEs leading to dose interruption or requiring dose reduction compared with single agent BRAFi in the Columbus study. Median overall survival for the combination arm of 33.6 mos versus 16.9 mos for vemurafenib was presented in 2018.[Dummer, JCO, 2018] Updated grade 3/4 toxicity incidence for combination arm was 64%, compared with 67% for encorafenib alone and 66% for vemurafenib alone.

1.3 Adjuvant Therapy

Adjuvant therapy in the management of advanced stage II and stage III melanoma remains controversial. Interferon alfa 2b [Merck, Kenilworth, NJ] has been tested in various doses and schedules over the years and has consistently shown an effect on relapse free survival but inconsistently shown an impact on overall survival. [Mocellin, 2010]. Ipilimumab [Bristol Myers Squibb, New York, NY] 10mg/kg IV over 3 years was approved by the Food and Drug Association

for the treatment of stage III melanoma after showing improved overall survival and relapse free survival compared with placebo. However, the grade 3-4 toxicity rate of approximately 45% with a 1% rate of deaths due to toxicities has impacted its utility.[Eggermont NEJM, 2016] More recently, preliminary data from Checkmate 238 was published and led the FDA to approval of nivolumab [Bristol Myers Squibb, New York, NY] for one year in the adjuvant treatment of stage III melanoma.[Weber, NEJM, 2017] This trial randomized subjects with resected stage IIIB/C/IVM1a/b (AJCC 7th edition) to nivolumab 3mg/kg IV every 2 weeks for one year or Ipilimumab 10mg/kg IV every 3 weeks for 4 doses, then every 3 months for up to one year. Nivolumab demonstrated a superior 12 month RFS of 70.5% (95% CI, 66.1-74.5] compared with 60.8% (95% CI, 56.0-65.2] for ipilimumab with a minimum follow up of 18 months; hazard ratio for disease recurrence/death was 0.65 [97.56% CI, 0.51-0.83]. Updated results showed a 24 month RFS improvement favoring nivolumab (63% v 50% with a hazard ratio for disease recurrence/death of 0.66 [95% CI, 0.54, 0.81]. [Weber, 2018, ASCO] The four year update upheld the RFS improvement for nivolumab compared with ipilimumab [51.7 (95% CI46.8-56.3) vs 41.2% (36.4-45.9)] but there was no difference in overall survival [77.9% (95% CI 73.7-81.5) vs 76.6% (72.2-80.3)].Ascierto, 2020, Lancet Oncol]. Similar preliminary results were reported for pembrolizumab [Merck, Kenilworth, NJ], compared with placebo, in the adjuvant setting. [Eggermont, NEJM 2018] This double blind phase III study randomized 1019 subjects with resected stage IIIA/B/C (7th edition; for IIIA –at least one SLN deposit >1mm required and no in transit metastases) melanoma to pembrolizumab 200mg IV every 3 weeks x 18 doses or placebo. After a median follow up of 15 months, the 1 year RFS for pembro versus placebo was 75.4% [95% CI, 71.3-78.9] vs 61% [95% CI, 56.5-65.1] with a HR for recurrence/death of 0.57 [98.4% CI, 0.43-0.74, p<0.001]. Grade 3-5 AEs for both PD-1 inhibitors were approximately 14%. The RFS at 3 years was greater for pembrolizumab compared with placebo (63.7% vs 44.1%). [Eggermont, 2020, J Clin Oncol]. Overall survival data remains immature for this study.

MAPK inhibitors in the adjuvant setting has also been investigated and reported. The combination of dabrafenib with trametinib [Novartis, Basel, Switzerland] was compared to matched placebos in 870 subjects with resected stage IIIA-IIIC (AJCC 7th edition) who had had a completion lymph node dissection in a double-blind, randomized phase III study. [Long, NEJM, 2017] Patients with stage IIIA melanoma were required to have at least a 1mm SLN metastatic focus. The estimated 3 years RFS was 58% vs 39% favoring dabrafenib with trametinib [HR for relapse/death 0.47, 95% CI 0.39-0.58; p <0.001] at a median follow up of 2.8 years. The 3-year OS was 86% vs 77%, again favoring Dabrafenib with Trametinib [HR 0.57; 95% CI 0.42-0.79; p=0.0006] but did not cross the prespecified interim analysis boundary of p=0.000019. A five-year analysis reported 52% RFS for patients treated with dabrafenib and trametinib compared with 36% for placebo [HR 0.51; 95% CI 0.42-0.61]. [Dummer, 2020, NEJM]. The most common AEs for combination dabrafenib with trametinib were similar to other trials with pyrexia, fatigue, and nausea being most common. In the combination therapy group, 38% had an AE that led to dose reduction and 26% had an AE that led to permanent discontinuation. Similar incidence of melanomas and nonmelanoma skin cancers were reported for both groups. Single agent vemurafenib was evaluated in a double-blinded randomized phase III study in 498 subjects with resected stage IIC/IIIA/IIIB and IIIC assessed in two cohorts (AJCC 7th edition). [Maio, Lancet Oncol 2018] at median follow ups of

33.5 months for stage IIIC subjects, the median disease free survival (DFS) was 23.1 months for vemurafenib vs 15.4 months for placebo [HR 0.80, 95% CI 0.54-1.18; log rank p=0.26]. For subjects with stage IIC/IIIA/IIIB, the median DFS was not reached in the group treated with vemurafenib but was 36.9 months for the placebo group at median follow up of 30.8 months [HR 0.54 [95% CI 0.37-0.78; log rank p =0.0010]. However, as cohort 2 did not meet its primary endpoint, the results of the other cohort were interpreted as exploratory.

1.4 Rationale for Neoadjuvant Therapy

Traditionally, therapeutic agents have not evidenced response rates great enough to explore in a neoadjuvant approach in melanoma. Given the described successes, a neoadjuvant treatment paradigm is being considered in melanoma with BRAF/MEK inhibitors as well as with other agents. Several small prospective studies are completed or ongoing, including three which have been reported, that evaluated Dabrafenib and Trametinib in patients with bulky stage IIIB/C or IV melanoma. Amaria et al published a single institution study of patients with resectable stage IIIB/C or IV melanoma that randomized subjects 2:1 to dabrafenib with trametinib for 8 weeks then complete resection followed by 44 weeks of treatment vs upfront surgery [standard of care]. [Amaria, Lancet Oncol 2018] This was designed to evaluate 12 mos EFS (event free survival) and showed a significant improvement in EFS for systemic therapy (19.7 mo) vs surgery (2.9 mo) [HR 0.016] for the first 21 enrolled patients and thus, the trial was halted early. Of note, 7/12 pts in the neoadjuvant arm achieved a pathologic CR [58%], with 2 pPR [16%]. There was no correlation between RECIST responses and pathologic responses in this study. Therapy was temporarily stopped in 92% (12/13) of patients during the neoadjuvant phase for fevers with 38% requiring at least one dose reduction. There were no surgical delays or unexpected surgical complications. Of the 11 patients who accepted adjuvant therapy, 4 discontinued treatment due to toxicities. A single institution phase II single arm study of neoadjuvant dabrafenib with trametinib was also carried out at the Melanoma Institute Australia [Menzies, Ann Oncol, 2017] Thirty-five patients were treated with dabrafenib and trametinib for 12 weeks, then proceeded to resection, followed by additional D+T for 40 weeks. All patients had bulky stage IIIB/C disease, and pCR was the primary endpoint. The pathologic CR rate was 52% (17/33). RECIST and pathologic responses were discordant. At a median follow up of 12.9 months after resection, 12 (36%) recurred including 6 with prior pCR and 4 while on D+T. Toxicities were as expected, with 79% of patients experiencing drug fever. An initial report stated that 12/14 (86%) of patients had treatment interruption in the first 12 weeks for a median of 7 days. [Saw, JCO, 2016] Published results reported a pCR rate of 17/35 (49% for this study with a median follow up of 27 months. [Long, Lancet Oncol, 2019] Eighty-six percent of patients achieved a RECIST response; 57% (20/35) experienced recurrence: 8 during the first year: 4 on treatment and 4 off treatment (stopped for toxicities), and 12 after 52 weeks. One year RFS was 77.1% [64.4 to 92.4], two year RFS was 43.4% [28.6 to 65.7] with median RFS of 23.3 months [95% CI 17.7 to not reached]. Another neoadjuvant study was presented at ECCO and was designed to assess the ability to convert unresectable stage III/IV patients to resectability with 8 weeks of dabrafenib and trametinib followed by surgery. [Haanen, ECCO 2017]. Twenty one patients were enrolled and treated, 2 progressed and 19 proceeded to surgery, with 17 achieving an R0 resection (tumor free margins) and one patient had an R1 resection while one patient was

deemed unresectable due to vessel encasement.[Blankenstein, Ann Surg, 2021]. Six patients required treatment interruption for toxicities but all completed neoadjuvant treatment. The pathologic responses included: pathologic CR in 28.6% (6/18), near pCR in 14.3% (3/18), pPR in 19% (4/18) and pNR in 23.8% (5/18). Radiologic response on CT or PET did not predict pathologic response. Surgical complications occurred in 80%, mainly seromas, wound infections, and lymphedema. Of these 18 patients who had surgery, 9 patients have recurred, including 6 with distant metastases. Five of the 6 patients with a pCR have not had a recurrence.

Of the 35 patients treated with Dabrafenib with Trametinib neoadjuvantly for 12 weeks in Long et al: 0/35 with clinical or radiologic PD before surgery (16 with CR, 14 with PR); all proceeded to surgery, Surgical complications (including infection requiring antibiotics, seroma, bleeding, lymphedema, thrombus) of any grade occurred in 63% (22) with 26% (9) being grade 3. Two patients stopped treatment before 12 weeks due to treatment related adverse events. Of the 14 patients treated with neoadjuvant Dabrafenib and Trametinib for 8 weeks in Amaria et al: 1 withdrew consent before starting treatment, one withdrew consent for surgery given partial response to oral treatment and 12 patients received surgery. No patients evidenced radiologic or clinical progression prior to surgery: 2 CR, 9 PR and 2 SD. In the 12 who had surgery, 7 had a pCR and 2 had a pPR, while 3 had a pathologic non-response (>50% viable tumor in surgical specimen). They reported no unexpected peri-operative or post-operative treatment-related toxicities, nor were there any treatment related delays in surgery.

Neoadjuvant trials with immunotherapies continue as well. Initial studies evaluated high dose (HD) interferon in patients with palpable stage IIIB/C melanoma which yielded a pCR rate of 15%(3/20), [Moschos JCO 2006] HD Interferon was also evaluated in combination with ipilimumab in palpable stage IIIB/C/IV which yielded a pCR rate of 32% (9/28) but with significant toxicities. [Tarhini JCO 2016] Pembrolizumab was also evaluated in combination with HD interferon in a similar group of patients (n=20) and demonstrated a pCR rate of 35%, [Tarhini JCO 2018] A recent presentation at the American Association for Cancer Research reported on 27 patients enrolled in a single institution trial of neoadjuvant pembrolizumab in patients with resected stage IIIB/C/IV melanoma. [Huang, AACR, 2018] Patients were treated with one dose of pembrolizumab 200mg prior to planned surgery with no delays in planned surgery. The 1 year RFS was 55%, with 8/27 achieving a near pCR or pCR (5/27 with pCR) after one dose and all 8 who have remained relapse free. These data were recently published and updates included a one year DFS rate of 63%, all major or pCR responders remain disease free at 24 months. In paired pre- and post-treatment specimens (n=20), there was a significant decrease in viable tumor cells where ≤10% viable tumor at resection correlated with low risk of recurrence regardless of stage. [Huang, Nat Med, 2019]. There was a greater number of samples post treatment samples with brisk TILs and brisk TIL s was associated with major or pCR and improved DFS. In a subset of 6 patients with 3 week on treatment FDG-PET scans, while tumor size decrease directly correlated with histologic percentage of viable tumor, the change in FDG avidity did not correlate with response. Three additional studies evaluated combination immunotherapy in resectable stage III melanoma. One trial [OpACIN] randomized 20 patients to either neoadjuvant ipilimumab in combination with nivolumab for two cycles followed by surgery and then two additional cycles, while the other arm received surgery followed by 4 cycles of adjuvant combination therapy. [Blank, Nat Med,

2018]. In the 10 patients treated with neoadjuvant therapy, a pCR rate of 33% was achieved with significant toxicities. Another small trial randomized 23 patients to either combination ipilimumab with nivolumab or nivolumab pre and post surgery which achieved pCR rates of 45% and 25%, respectively. [Amaria, Nat Med, 2018] Lastly, another larger study [OpACIN-neo] randomized 86 patients to ipilimumab 3mg/kg with nivolumab 1mg/kg for two cycles versus to ipilimumab 1mg/kg with nivolumab 3mg/kg for two cycles versus to ipilimumab 3mg/kg for 2 cycles followed by nivolumab 3mg/kg for two cycles and then surgical resection. [Rozeman, ESMO, 2018] The pathologic response rates were 47%, 57% and 23% respectively. The last arm was closed early due to toxicities.

An update after 4 years of follow up for OpACIN, there were no relapses in the 7 patients who achieved a pathologic response and the 4 year EFS and OS rates were 80% and 90%, respectively, in the neoadjuvant arm and 60% and 70% in the adjuvant arm. [Rozeman, Nature Med, 2021] In the OpACIN-neo study, the estimated 2yr RFS was 90%, 78%, and 83%, respectively, for the above treatment arms. This included two patients who progressed during neoadjuvant treatment and 12 who progressed after surgery. Outcomes correlated with pathologic response in both studies and baseline interferon-gamma gene signature expression was associated with lower risk of relapse.

Given evolving data, limited patient numbers and multiple variables in studies to date, the neoadjuvant therapeutic paradigm, as well as the endpoint of pathologic CR remain investigational in melanoma. Most of the past and current neoadjuvant trials are designed as single arm studies due to the limited patient numbers and limitations of randomizing to surgery, the current standard of care: NCT01972347, NCT01972347, NCT02036086, NCT02303951, NCT02306850. The Amaria study has been redesigned based on preliminary information to a single arm study. While the above data is intriguing, the optimal agents, schedule, response assessments (radiographic and pathologic) have yet to be determined. Toxicities of all agents, including those of dabrafenib and trametinib, while expected, did impact treatment. A pooled analysis of 6 neoadjuvant studies of immunotherapy and targeted therapies reported an overall pCR rate of 40%: 47% for targeted therapies and 33% for immunotherapy. [Menzies, Nature, 2021] In this analysis of 192 patients, 189 patients proceeded to surgery. pCR correlated with improved RFS and OS. No patients treated with targeted therapy progressed before surgery while 5% treated with immunotherapy did so.

Recurrences were reported in 32% of patients. The authors reported a 1 and 2 year RFS for the entire group of 77% and 65%. In a cross trial comparison, the authors report lower 1 and 2 year RFS for targeted therapy, 75% and 47%,than for immunotherapy treated patients: 78% and 75%.

Table 1. Baseline pCR Estimation from published/presented Data

pCR	n	Regimen	Reference
15%	20	HDI	Moschos JCO 2006
32%	28	HDI+Ipi	Tarhini JCO 2016
35%	20	Pembro+HDI	Tarhini JCO 2018
18.5%	27	Pembro	Huang Nat Med 2019
33%	10	Ipi+Nivo	Blank Nat Med 2019

45%	11 of 23	Ipi+Nivo	Amaria Nat Med 2018
25%	12 of 23	Nivo	
47%	30 of 86	Ipi3+Nivo1	Rozeman LancetOncol 2019
57%	30 of 86	Ipi1+Nivo3	
23%	26 of 86	Ipi3->Nivo3	

1.5 FLT-PET

Response rates for metastatic melanoma patients treated with selective BRAF inhibitors are high, and early evaluation (day 15) with FDG-PET/CT show fairly uniform decreases in FDG activity regardless of duration or depth of benefit [McArthur, JCO, 2012]. Thus, predictive biomarkers of long-term response are needed. Specifically, there was no correlation between time to RECIST response and metabolic response, or between metabolic response at Day 15 and duration of RECIST response, progression free survival (PFS) or overall survival (OS). Potentially, this could be related to change in glucose uptake due to alterations in GLUT1 expression rather than true response to therapy [Ma, JCO, 2009; Parmenter, Ca Discovery 2014]. PET imaging using ^{18}F-fluorothymidine (FLT), a tracer that measures cellular proliferation in an S-phase-dependent manner, has been explored in several malignancies within the first several weeks of treatment in an effort to predict early response or resistance. This is based on the hypothesis that FLT will be more specific for true tumor response, but has yielded variable results [Kenny, EJNMMI, 2007; Sohn, Clin Ca Res, 2008; Bollineni, Eur J Canc, 2016]. Under the auspices of ACRIN, ACRIN 6688 investigated whether early change in FLT-PET SUV could predict pCR in patients with breast cancer receiving neoadjuvant chemotherapy [Kostakoglu, J Nucl Med, 2015]. FLT-PET was performed at baseline (FLT1), 5-10 days after cycle 1 of treatment (FLT2), and after completion of neoadjuvant therapy within 3 weeks of surgery (FLT3). While the predictive value of %change in SUV between FLT1 and FLT2 to predict pCR was minimal, the change between FLT1 and FLT3 was a strong indicator of pCR. Additionally, post therapy FLT uptake significantly correlated with post therapy Ki-67 in the surgical specimens.

In vivo data investigating a role for FLT-PET in melanoma, or with MEK or BRAF inhibitor therapy, are sparse [Solit, Cancer Res, 2007; Leyton, Molec Canc Thera, 2008; McKinley, J Nuc Med, 2013, Geven CMMI, 2015]. There is currently a study underway in patients with advanced unresectable melanoma being treated with vemurafenib and cobimetinib, another BRAF/MEK doublet in which FDG-PET are performed at baseline, at C1D15 and C2D21 (where a cycle is 28 days), and at progression; in addition, FLT-PET are performed at baseline, at C1D14, and at progression [van der Hiel, BMC Cancer, 2017]. The primary aim is to determine if change in either of the PET studies can predict early response compared with standard RECIST response or predict PFS in advanced unresectable melanoma. A pilot study of 5 patients recently reported that decreased tumor volume and tumor proliferation on a 6-week FLT-PET scan compared with baseline after treatment with pembrolizumab correlated with response per RECIST on 12-week CT scans. Specifically, better objective responses were seen in patients with a greater decrease in FLT uptake [delta-PTV(proliferative tumor volume), delta-SUVmax, and delta TLP (total lesion proliferation) and a trend toward higher OS in patients FLT-PET response.[Yeh, Clin Nuc Med, 2020].

1.6 Ki67 and CD8+ T Cell Infiltration

CD8+ T cell infiltration:

There are data to suggest that CD8+ T cell tumor infiltration correlates with clinical response to BRAFi and BRAFi + MEKi.[Wilmott, CCR, 2012; Frederick, CCR, 2013; Wargo, JCO, 201; Long, Lancet Oncol, 2019] A small retrospective analysis did not show any significant change in serum immunologic profiles after treatment with dabrafenib in metastatic melanoma. [Hong, 2012] We hypothesize that CD8+ T cell infiltration, and the change in this in response to treatment, in the tumor or tumor bed directly correlates with pCR, DFS and OS. Early on treatment biopsies have demonstrated unique and informative information regarding response. [Amaria, Nat Med, Chen, Cancer Discov]. We hypothesize that CD8+ T cell infiltration at baseline, and/or the change in CD8+ tumor infiltrating lymphocytes (TIL) with treatment early (on treatment biopsy) and late (at resection), in the tumor or tumor bed directly correlates with pCR, disease free survival (DFS) and overall survival (OS).

Ki67 and proliferation:

Low baseline Ki67 and early large change in Ki67 correlate with OS in melanoma patients treated with BRAFi [Long, et al, PCMR, 2013]. Ki-67 tumor cell IHC will be evaluated in all specimens and correlated with FLT-PET. It is hypothesized that change in FLT-PET uptake will correlate with Ki-67 changes. Correlation of Ki67 in tumor cells may provide evidence that FLT-PET is a true imaging measure of proliferation.

1.7 Trial Rationale

This trial is a single arm phase 2 study to investigate encorafenib, a selective BRAF inhibitor, in combination with binimetinib, a MEK inhibitor, in the neoadjuvant treatment of resectable clinically or radiographically-detected stage IIIB/C/D melanoma. The treatment period planned will be a total of one year, with 8 weeks of therapy prior to planned surgery followed by 44 weeks of combination treatment postoperatively. Responses to combination BRAFi/MEKi usually occur within 2 months, hence an 8-week treatment period was chosen to evaluate response as well as not to delay definitive surgical resection. The Columbus trial of encorafenib with binimetinib yielded favorable response and safety data in advanced metastatic melanoma. [Dummer, Lancet Oncol, 2018] The planned clinical primary end-point is pathologic complete response (pCR) as determined by local assessment of surgical pathologic specimens and radiology studies. Central pathology review of the pre-study biopsy and post-neoadjuvant treatment surgical specimens will also be accomplished retrospectively, as has been customary for ECOG-ACRIN Melanoma Committee studies. This trial will evaluate the benefit of these agents, the role of pathologic CR (pCR) as an endpoint, and the toxicity profile of encorafenib with binimetinib in this setting and population. It is possible that the toxicity profile may be distinct from that seen with other BRAF/MEKi doublets.

Additional hypotheses center upon translational components, which are seeking markers of clinical response and/or early indicators of response (or resistance). In all cases, the relationships of these components to each other will also be explored, e.g., whether changes in measures of melanoma immunity correlate with changes in imaging. This trial will include a radiologic key secondary endpoint with a molecular imaging marker FLT PET, designed to test an early

response indicator that could be used to guide BRAF/MEK targeted therapy. FLT-PET scans will be evaluated at two time points (baseline and eight weeks after therapy initiation) and correlated with pCR. The decrease in FLT-PET uptake, based on the maximum standard uptake value (SUVmax), from baseline to eight weeks will be assessed. Measures of proliferation obtained from FLT-PET will be compared to the tissue reference standard for proliferation, Ki-67. Additional secondary endpoints will explore CD8+T cell infiltration as possible early indicators of clinical response (or resistance) in melanoma patients treated in the neoadjuvant setting with these agents. This trial will collect tumor tissue and blood at multiple time points in the treatment process for correlative studies. Material will be banked for future studies involving resistance mechanisms and more extensive immunologic testing.

1.8 Hypotheses

1.8.1 Primary

1.8.1.1 Neoadjuvant treatment with a combination of binimetinib and encorafenib in Stage IIIB/C/D clinically evident nodal resectable melanoma will yield a pathologic complete response (pCR) rate of at least 57%.

1.8.1.2 Summarizing current pCR data (Table1), a weighted average pCR rate for immunotherapy neoadjuvant trials with ranges from 15%-57%, would be 33%. The two small studies of neoadjuvant BRAF + MEK inhibitors have shown response rates of 52% and 58%. It is hypothesized that encorafenib and binimetinib will have a similar response rate as the other BRAF/MEK inhibitors, and greater than that seen with immunotherapies.

1.8.2 Secondary

1.8.2.1 Patients achieving pCR based on neoadjuvant treatment with a combination of binimetinib and encorafenib will demonstrate a greater decrease in FLT-PET uptake (from baseline to 8 weeks post neoadjuvant treatment initiation) compared to non-pCR patients.

1.8.2.2 Lower post-therapy FLT-PET SUVmax is associated with higher likelihood of pCR.

1.8.2.3 Change in FLT-PET uptake will correlate with Ki-67 changes in tumor cells. In particular, the change in FLT-PET uptake (from baseline to 8 weeks post neoadjuvant treatment initiation) will directly correlate with the change in early (from baseline to 2 weeks) and post therapy (from baseline to 8 weeks after neoadjuvant treatment initiation) specimen Ki-67 assays.

1.8.2.4 Immune effects of treatment with BRAFi + MEKi. CD8+ T cell infiltration at baseline, and/or the change in CD8+ tumor infiltrating lymphocytes (TIL) with treatment early (on treatment biopsy) and late (at resection), in the tumor or tumor bed directly correlates with pCR, disease free survival (DFS) and overall survival (OS).

2. Objectives

2.1 Primary Clinical Objective

2.1.1 To evaluate the pathologic complete response (pCR) rate of neoadjuvant treatment with encorafenib and binimetinib.

2.2 Secondary Clinical Objectives

2.2.1 To determine RR (RECIST), DFS and OS.

2.2.2 To describe correlation of pCR with RR, DFS and OS.

2.2.3 To assess safety and toxicity.

2.3 Correlative Science Objectives

2.3.1 To evaluate CD8+ T cell infiltration and Ki-67 status in tumor or tumor bed pre, during, and post neoadjuvant treatment and the change in CD8+ TIL with neoadjuvant treatment and correlate with clinical response.

2.3.2 To compare local review for pathologic response with central pathology review.

2.4 Imaging Objectives

2.4.1 To compare the change in ^{18}F-FLT PET/CT uptake (from baseline to post-neoadjuvant therapy) among patients with and without pathologic complete response.

2.4.2 To compare post-neoadjuvant ^{18}F-FLT PET/CT uptake among patients with and without pathologic complete response.

2.4.3 To estimate an optimal threshold for prediction of pathologic complete response using i) change in ^{18}F-FLT PET/CT uptake, and ii) post-neoadjuvant ^{18}F-FLT PET/CT uptake.

2.4.4 To assess the correlation between change in ^{18}F-FLT PET/CT uptake and change in Ki-67.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patient must have histologically proven melanoma that is clinically evident (macroscopic LAD) stage III B/C/D, (AJCC 8th Edition) of cutaneous origin or unknown primary. Patient must have at least one clinically evident lymph node metastasis (N1c patients are not eligible). Patients with stage IV melanoma are not eligible.

_____ 3.1.2.1 This may be an initial presentation with primary tumor and nodal metastases or locoregional nodal relapse with history of resected primary melanoma.

3.1.2.2 Stage IIIB

T0- 3a N1b M0 Yes _____ No _____

T1a-3a N2b M0 Yes _____ No _____

3.1.2.3 Stage IIIC

T0 or T3b-4b N2b M0 Yes _____ No _____

T3b-4b N1b M0 Yes _____ No _____

Any T N2c M0 (at least 1 clinically evident node)
Yes _____ No _____

T0-4a N3b M0
Yes _____ No _____

3.1.2.4 Stage IIID

T4b N3b/c M0 (if 3c: at least 1 clinically evident node)
Yes _____ No _____

_____ 3.1.3 Patient must have measurable disease on baseline imaging scans, obtained within 4 weeks prior to registration as defined by RECIST in Section 6.1.3 and by the following criteria.

_____ 3.1.3.1 All melanoma tumors must be completely resectable as determined by a surgical oncologist or experienced melanoma surgeon prior to registration.

_____ 3.1.3.1.1 Extensive satellitosis or extensive in transit metastases are not considered completely resectable.

_____ 3.1.4 Patient must have BRAF V600 mutation positive based on report from CLIA certified laboratory.

_____ 3.1.5 Patient must be medically fit to undergo surgery.

_____ 3.1.6 Patient must have adequate bone marrow, organ function and laboratory parameters (labs must be obtained ≤ 14 days prior to registration) as defined below:

_____ 3.1.6.1 ANC ≥ 1.5 × 10^9/L
ANC:_____ Date of Test:_____

_____ 3.1.6.2 Hemoglobin ≥ 8 g/dL without transfusion
Hemoglobin:_____ Date of Test:_____

_____ 3.1.6.3 Platelets ≥ 100 × 10^9/L without transfusion
Platelets:_____ Date of Test:_____

_____ 3.1.6.4 AST and ALT ≤ 2.0 × Institutional ULN;
AST:_____ Institutional ULN:_____

Date of Test:_____

ALT:_____ Institutional ULN:_____

Date of Test:_____

_____ 3.1.6.5 Total bilirubin ≤ 1.5 × Institutional ULN and < 2 mg/dL; OR total bilirubin >1.5 × Institutional ULN with indirect bilirubin < 1.5 × Institutional ULN
Total Bilirubin:_____ Institutional ULN:_____

Indirect Bilirubin:_____ Institutional ULN:_____

Date of Test:_____

_____ 3.1.6.6 Serum creatinine ≤ 1.5 × Institutional ULN, or calculated creatinine clearance > 50 mL/min by Cockroft-Gault formula
Creatinine:_____ Institutional ULN:_____

Date of Test:_____

Creatinine Clearance:_____ Date of Test:_____

_____ 3.1.6.7 PT, INR, and PTT ≤ 1.5 × Institutional ULN

PT:_____ Institutional ULN:_____

Date of Test:_____

INR:_____Institutional ULN:_____

Date of Test:_____

PTT:_____Institutional ULN:____

Date of Test:_____

_____ 3.1.7 Patient must have an ECOG Performance status 0-1.

_____ 3.1.8 Patient must not have any prior treatment with BRAFi or MEKi.

_____ 3.1.9 Patient must not have any evidence of distant metastases.

_____ 3.1.10 Patient must be able to take oral medications.

_____ 3.1.11 Patient must not have any prior adjuvant therapy at this disease presentation; prior immune therapy (such as adjuvant interferon or checkpoint inhibitors) is permitted if date of registration is ≥ 6 months from last treatment

_____ 3.1.12 Patient must not have any prior radiation to the site of evaluable disease.

_____ 3.1.13 Patient must not have active infection requiring treatment with parenteral antibiotics.

_____ 3.1.14 Patient must be able to lie still during the ^{18}F-FLT PET/CT scan for the duration of the imaging study (up to 1.5 hours), have no previous indication of allergic reaction to the radiotracer, and meet the size limits of the qualified PET/CT scanner.

_____ 3.1.15 Patient must be participating in this study at an institution which has completed the ECOG-ACRIN defined PET/CT scanner qualification procedures and received ECOG-ACRIN PET Scanner approval as outlined in Section 4.

_____ 3.1.16 Patient must not have active Hepatitis B, and/or active Hepatitis C infection given concerns for drug interactions or increased toxicities. Testing is not required.

_____ 3.1.17 Patients known to be HIV positive are eligible if they have undetectable HIV viral load and stable and adequate CD4 counts (≥ 500mm^3) on screening labs provided they meet all other protocol criteria for participation and that there is no high risk drug interactions. See Appendix X.

_____ 3.1.18 Patient must not have other significant medical, surgical, or psychiatric conditions that in the opinion of the investigator may interfere with compliance, or make the administration of study medications hazardous.

_____ 3.1.19 Patient must not have had previous or concurrent other malignancy with the following exceptions:

_____ 3.1.19.1 Adequately treated basal cell or squamous cell carcinoma of the skin, in situ carcinoma of the cervix.

_____ 3.1.19.2 Other solid tumor: if treated and without evidence of recurrence for at least 2 years prior to date of registration.

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_____ 3.1.20 Patient must not be pregnant or breast-feeding due to potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the systemic antineoplastic medications, as well as surgery and radiation being used.

All patients of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy.

A patient of childbearing potential is defined as anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of childbearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

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_____ 3.1.21 Patients must not expect to conceive or father children by using accepted and effective method(s) of contraception (please refer to Appendix VI) or to abstain from sexual intercourse from the time of registration, while on study treatment and for at least 30 days after the last dose of protocol treatment for female patients, and for at least 90 days after the last dose of protocol treatment for male patients. In addition, patients must not donate ova from the time of registration until 30 days after the last dose of study treatment or donate sperm from the time of registration until 90 days after the last dose of protocol treatment.

_____ 3.1.22 Patient must not have known hypersensitivity or contraindication to any component of binimetinib or encorafenib or their excipients.

_____ 3.1.23 Patient must not have impaired cardiovascular function or clinically significant cardiovascular disease including, but not limited to, any of the following:

_____ 3.1.23.1 History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting) < 6 months prior to registration:

_____ 3.1.23.2 Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2).

_____ 3.1.23.3 Left ventricular ejection fraction (LVEF) < 50% as determined by MUGA or ECHO.

_____ 3.1.23.4 Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite current therapy.

_____ 3.1.23.5 History or presence of clinically significant cardiac arrhythmias (including resting bradycardia, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia).

_____ 3.1.23.6 Baseline QTc interval ≥ 480 ms.

_____ 3.1.24 Patient must not have impairment of gastrointestinal function or disease which may significantly alter the absorption of study drug (e.g., active ulcerative disease, uncontrolled vomiting or diarrhea, malabsorption syndrome, small bowel resection with decreased intestinal absorption), or recent (≤ 3 months) history of a partial or complete bowel obstruction, or other conditions that will interfere significantly with the absorption of oral drugs.

_____ 3.1.25 Patient must not have any known history of acute or chronic pancreatitis.

_____ 3.1.26 Patient must not have any concurrent neuromuscular disorder that is associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

_____ 3.1.27 Patient must not have any known history or current evidence of Retinal Vein Occlusion (RVO) or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity, factor V Leiden or activated protein C resistance); history of retinal degenerative disease.

_____ 3.1.28 Patient must not use any medication (including herbal medications, supplements, or foods), as described in Section 8.1.14 and Section 8.2.15, or use of a prohibited medication ≤ 1 week prior to registration. See Appendix X.

_____ 3.1.29 Patient may be on anticoagulation at prophylactic or therapeutic levels. Patients must not be using specific anticoagulants at therapeutic levels that may interfere with encorafenib and binimetinib. See Appendix X.

_____ 3.1.30 Patient must not have a history of thromboembolic or cerebrovascular events ≤ 12 weeks prior to registration. Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (i.e. massive or sub-massive) deep vein thrombosis or pulmonary emboli.

NOTE: Patients with thromboembolic events related to indwelling catheters or other procedures may be registered.

NOTE: Patients with either deep vein thrombosis or pulmonary emboli that does not result in hemodynamic instability are

allowed to register as long as they are on a stable dose of anticoagulants for at least 4 weeks.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Registration Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a

participating organization (i.e., Alliance). Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
- Enter the protocol number in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select ECOG-ACRIN, and protocol number EA6183;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided.

NOTE: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.

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Requirements For EA6183 Site Registration

- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. A primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link on the CTSU website.
- To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory Support System (RSS) to comply the protocol specific requirement. IROC will continue to copy the provider and/or enrolling site on modality approvals.
- Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.
- **Imaging Requirements:** Sites will be required to meet PET/CT Scanner Qualification requirements and approval. Please refer to the EA6183 Site Imaging Manual for guidance on the PET/CT Scanner Qualification process. The EA6183 Site Imaging Manual is available for download on the CTSU members' website. **For FLT PET/CT related questions, please contact Diana Ewen at dewen@acr.org. See study specific training outlined in Sections 4.3.3 and 4.3.4.**

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU Website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Log on to the CTSU members' website;
- Click on the Regulatory tab
- Click on the Site Registration tab at the top of your screen
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Study treatment must start within 14 days after registration.

The baseline FLT scan must be completed within 2 weeks prior to initiating neo-adjuvant treatment. The post neoadjuvant scan, must be completed after 2 cycles of study treatment are completed (ideally 8 weeks after starting neoadjuvant treatment, but the scan can be completed up to 9 weeks after starting neoadjuvant treatment). If patient comes off treatment early, the post neoadjuvant scan should not be completed any sooner than 4 weeks after starting treatment. Scan must be completed when patients have completed neoadjuvant therapy and before surgery.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;

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- To perform enrollments: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Registration Information

The following information is to be provided at the time of registration:

4.1.1 Protocol Number

4.1.2 Site/Investigator Identification

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.3 Additional Requirements

4.3.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

NOTE: Participation in the optional biopsy and additional specimen collections, as outlined in the patient consent, must be offered to all patients.

4.3.2 Bio-specimens are to be submitted as outlined in Section 10.

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4.3.3 Study Specific Training:

Each site must ensure all relevant site personnel responsible for handling ^{18}F-FLT in any manner have reviewed and completed the training on handling and use of FLT. A review of the FLT Investigator Brochure and completion of ECOG-ACRIN generated training related to tracer administration will be required and documented via a training log. This training will be completed as a site initiation webinar prior to activation of the site. Any change in staff will require training of appropriate designated staff and this can be done through a self-study module with slides available on CTSU.

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4.3.4 The Primary Investigator Authorized User

The ordering of ^{18}F-FLT should be done with a written order from the responsible authorized user, and administration of ^{18}F-FLT should be performed by the authorized user or a qualified staff member under the authorized user's supervision (e.g. nuclear medicine technologist). Institutions should follow institutional practice for the injection of investigational radiopharmaceuticals.

Sites must be a qualified user and/or manufacturer of ^{18}F-FLT prior or have access to obtaining ^{18}F-FLT to site activation. A list can be found on the CTSU website, on the EA6183 protocol page under the “Miscellaneous” tab.

4.3.5 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata, site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required. To the hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of

the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

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4.3.6 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

NOTE: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

4.3.7 Image Data Submission Using TRIAD

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM formatted image data, RT data and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site staff that will be submitting images via TRIAD will need to register with CTEP and have a valid and active

CTEP-IAM account. Must be registered as an Associate, Associate Plus, Non-Physician Investigator, or Investigator registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in Registration and Credential Repository (RCR).

- To submit images, site staff must hold the TRIAD Site User role on an NCTN or ETCTN roster. Individuals requiring a TRIAD Site User role should contact the person holding a primary role at the site for their affiliated NCTN or ETCTN roster.
- All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installations:

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org or 1-703-390-9858.

Required Submission of Images for EA6183 via TRIAD

- Baseline ^{18}F-FLT Whole Body PET/CT
- Week 8 ^{18}F-FLT Whole Body PET/CT scan. Scan should take place after all neo-adjuvant treatment is completed and before surgery.
- All Standard of care ^{18}F-FDG PET/CT imaging acquired

4.4 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA6183 Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

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5.1.1 Neoadjuvant Treatment (pre-surgery)

Patients will receive the following:

- Encorafenib 450 mg po once daily x 8 weeks (2 cycles) with or without food. Capsules should be swallowed whole and should not be chewed. Do not make up the dose if vomiting occurs after encorafenib administration.
- Binimetinib 45 mg po twice daily (approximately 12 hours apart) with or without food x 8 weeks (2 cycles). Tablets should be swallowed whole. Do not make up the dose if vomiting occurs after binimetinib administration.

Cycle length = 28 days

- Patients must begin treatment with encorafenib and binimetinib within 14 working days of registration (timeframe to allow for baseline testing).
- Missed doses will not be made up prior to surgery.
- Less than 8 weeks of treatment may be permitted in the event of progressive disease requiring surgery or due to toxicity.
- If medication(s) are being held for a toxicity and overlap with the surgical window and the toxicity resolves according to the dose modification section, and the investigator feels that further treatment will benefit the patient, treatment can resume in the adjuvant setting with the appropriate dose adjustments

5.1.2 Surgical resection

The patient will proceed to surgical resection after neoadjuvant treatment

- Surgery should be performed as soon as possible after completing 8 weeks of therapy; it must be performed within 2 weeks of completing the 8 weeks of neoadjuvant therapy, assuming the patient has adequately recovered from protocol therapy and no other new sites of distant disease are evident and histologically confirmed as specified on post-treatment imaging.
- Resectability, as determined by a surgical oncologist or experienced melanoma surgeon, is necessary prior to registration.
- Surgery date should be arranged in advance.
- Neoadjuvant treatment duration (8 weeks) cannot be extended to accommodate surgery scheduling.

- Encorafenib and binimetinib will be stopped within 48 hours of planned surgery or at 8 weeks, whichever is sooner.
- If there are any reversible issues precluding surgery such as treatment related toxicities or unrelated medical issues, surgery may be delayed by an additional 2 weeks as needed.

- Encorafenib and binimetinib treatment time would not be extended beyond 8 weeks.
- Patients must be surgically managed with complete removal of all target site(s) of metastatic melanoma, i.e. complete lymph node dissection, as feasible by the treating surgeon at the time of surgery.
- If initial presentation with a primary melanoma with nodal metastases, wide local excision of the primary should be carried out per standard of care.
- If the residual target tumor is not visible on post-treatment imaging, surgical exploration and formal lymphadenectomy with excision of primary/ in transit lesions, if applicable, as per standard recommendations is required.
- The treating surgeon should attempt to mark the target lesion with a suture at the time of surgery to facilitate pathologic analysis.

5.1.3 Adjuvant Treatment (post-surgery)

- After surgery, treatment with encorafenib and binimetinib resumes for an additional 44 weeks (11 cycles) of adjuvant treatment at the same doses that were tolerated during the initial 8 weeks (2 cycles) of neoadjuvant treatment.
- Treatment will resume within 2-7 days after surgery, as possible, depending on oral intake, post-operative issues.
- If in the opinion of the investigator, there are medical issues post-operatively that preclude resuming treatment, this must be discussed with the study chair.
- The total planned course of systemic therapy with encorafenib with binimetinib is: 8 (neoadjuvant) + 44 weeks (adjuvant) = 52 weeks.
- Adjuvant treatment will not be extended past 44 weeks.
- Radiation therapy is not permitted after surgery.

5.2 Imaging Schedule

See Section 5.3 for Imaging Protocol details.

- **Baseline FLT-PET/CT**: If the baseline biopsy is done on-study and after registration, then the baseline FLT-PET/CT scan must be performed prior to the baseline biopsy (same day acceptable). The FLT scan needs to be completed within 2 weeks prior to the start of the study-mandated neoadjuvant therapy. If the baseline biopsy of nodal/ in transit melanoma was done prior to study enrollment (can be up to 2 months prior), then the

baseline FLT-PET/CT scan must be performed within 2 weeks prior to the start of the study-mandated neoadjuvant therapy.

- **Post Neo-adjuvant FLT-PET/CT**: A FLT-PET/CT scan will be completed after 8 weeks (or up to 9 weeks) of neoadjuvant therapy and before surgery. The scan must be completed after all neoadjuvant treatment is complete, but prior to surgery. If a patient comes off treatment early, this FLT-PET/CT should not be completed any sooner than 4 weeks after starting neoadjuvant therapy.

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NOTE: Institutions getting FLT from outside suppliers should allow time for arranging delivery of FLT.

5.2.1 AE monitoring period for F-18 (^{18}F-FLT) PET:

The AE monitoring period for ^{18}F-FLT, an ^{18}F based radioisotope imaging agent with a half-life (t ½ of 110 minutes and a 10 half-life equivalent of 18.33 hours) is 24 hours after administration of the imaging agent ^{18}F-FLT.

During the 24 hour period (the "Monitoring period") after administration (including the infusion of the ^{18}F-FLT), the patient will be evaluated for Adverse events (AEs) at each imaging session, during any follow up (in person, by phone or by email), and at the end of the monitoring period (can be done by phone call or email).

AEs for imaging agents are defined as any signs of illness or symptoms that have <u>appeared or worsened</u> since the infusion of the imaging agent. Patients will be queried for potential AEs at multiple time points. These may include:

- At the time of injection;
- Before leaving the PET suite;
- If they call the site as instructed for any concerns at any time during the monitoring period;
- At the end of the monitoring period

5.2.2 Adverse Events to Monitor following the ^{18}F-FLT dose

Certain adverse events that will specifically be monitored during and after the administration include, but are not limited to:

- localized discomfort at the intravenous (IV) injection site
- pain
- respiratory difficulties
- blood pressure instability
- flushing
- dizziness
- pruritus/hives
- any other symptoms that could be related to an allergic or anaphylactic-type reaction
- any previously unreported AE which occurring after the administration should be reported via Medidata Rave

When any AE is reported, concomitant medication taken by the participant in the 2 weeks prior to the event and/or during the time of the AE need to be collected and documented in the patient record and within Medidata Rave (for routine reporting) and CTEP-AERS (for expedited reporting) so that the patient's record may be updated in the CDUS.

5.3 ^{18}F-FLT Whole Body Imaging Protocol

5.3.1 FLT PET Imaging Studies

NOTE: Institutions getting FLT from outside suppliers should allow time for arranging delivery of FLT.

5.3.2 ^{18}F-FLT and ^{18}F-FDG PET Imaging Studies

The required PET/CT data to be submitted for EA6183 are listed below:

- Baseline ^{18}F-FLT Whole Body PET/CT scan
- Week 8 ^{18}F-FLT Whole Body PET/CT scan
- All Standard of care ^{18}F-FDG PET/CT scans acquired

Instructions for image submission is provided in Section 4.3.6

5.3.3 ^{18}F-FLT Administration

^{18}F-FLT will be synthesized according to the standard operating procedures provided by the NCI. A summary of the synthesis procedure and associated quality control can be found in the investigator's brochure.

The injectable activity of ^{18}F-FLT will be ≤ 0.07 mCi/kg of Flourine-18, **not to exceed 5mCi** with a specific activity greater than 200 Ci/mmol at the time of injection. The amount of injected drug is ≤ 6.1 µg (≤ 25 nmol per dose) of FLT. FLT is administered to subjects by intravenous injection of ≤ 10 mL. The drug solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial and has an expiration time of 8 hours. There is no evidence that nonradioactive and radioactive FLT molecules display different biochemical behavior.

^{18}F-FLT will be administered in the PET imaging suite under physician supervision.

An appropriately licensed individual will administer the ^{18}F-FLT by intravenous infusion over one minute, followed by a saline flush.

A fully equipped emergency cart and ACLS certified personnel will be available. The infusion and imaging procedure will be terminated in any patient who exhibits anaphylaxis, chest pain, dyspnea, or grand mal seizure.

5.3.4 Timing of FLT PET/CT Studies

Two ^{18}F-FLT Whole Body PET/CT imaging sessions, a baseline and post-neoadjuvant treatment will be performed (see Study Parameters Table).

5.3.4.1 Baseline FLT-PET/CT:

If the baseline biopsy is done on-study and after registration, then the baseline FLT-PET/CT scan must be performed prior to the baseline biopsy (same day acceptable). The FLT scan needs to be completed within 2 weeks prior to the start of the study-mandated neoadjuvant therapy. If the baseline biopsy of nodal/ in transit melanoma was done prior to study enrollment (can be up to 2 months prior), then the baseline FLT-PET/CT scan must be performed within 2 weeks prior to the start of the study-mandated neoadjuvant therapy.

5.3.4.2 **Post Neo-adjuvant Imaging:**

A FLT-PET/CT scan will be completed after 8 weeks (up to 9 weeks) of neoadjuvant therapy and before surgery. The scan must be completed after all neoadjuvant treatment is complete, but prior to surgery.

All patients who received at least one dose of neoadjuvant therapy are expected to complete post FLT PET/CT regardless of radiologic, clinical or pathologic response. If a patient comes off treatment early the second 18F-FLT PET/CT scan should not be completed any sooner than four weeks after starting neoadjuvant therapy.

Both ^{18}F-FLT imaging time points must be scanned on the same qualified PET/CT scanner with imaging technique and parameters to be as close as possible to that of the baseline scan.

NOTE: Institutions getting FLT from outside suppliers (academic or commercial) should allow time for arranging delivery of FLT.

5.3.5 Imaging Quality Assurance (QA)/Quality Control (QC) Procedure

Participant must be scanned on PET/CT scanners that have been qualified by the ACR Imaging Core Laboratory per the protocol-specific instructions made available to participating sites in the EA6183 Site Imaging Manual The Site Imaging Manual is available on the CTSU website, under the protocol specific page, “Site Registration” Tab.

Qualification Utility for the Imaging Core Laboratory (QUIC); https://quic.acr.org) is the web-based tool for managing the PET/CT scanner qualification process and communicating with the reviewing physicist and core lab staff

A hybrid PET/CT scanner is mandatory. The ability to calculate standardized uptake values (SUVs) is also mandatory.

All sequential imaging sessions are to be performed on the same qualified PET/CT scanner. ACR Core lab QA/QC procedures will

include review of DICOM files against study FLT imaging protocol specifications and EA6183 Site Imaging Manual parameters.

The PET/CT scanner must be kept calibrated in accordance with the manufacturer's recommendations.

The scanner should routinely be assessed for quantitative integrity and stability by being tested using various imaging protocols on a standard phantom.

For SUV measurements, this assessment should include a comparison against a dose calibrator to ensure accuracy; that is, a comparison of the absolute activity measured versus the measured activity injected, should be performed.

A daily QC check must be performed at the beginning of the day, including PET/CT scanner and dose calibrator, in accordance with the manufacturer recommendations.

If any of the QC results are outside of the manufacturer's guidelines, the study must be rescheduled and the problem rectified before scanning any patients.

NOTE: Further details and procedures related to the PET/CT Scanner Qualification process and scanner Quality Control procedures can be found in the EA6183 Site Imaging Manual located on the CTSU Protocol Page under under "Site Registration" tab.

5.3.6 ^{18}F-FLT Imaging Sessions

The participant will report to the PET suite and undergo ^{18}F-FLT injection.

Approximately 60 minutes (± 10 min) after injection, a static whole body PET/CT scan will be acquired.

The whole body scan (top of the head [vertex] to toes) will be obtained.

Upon completion of image acquisition, the PET/CT data will be reconstructed/corrected per scanner manufacturer recommendations including, but not limited to, random coincidences, system dead time, scatter correction and attenuation algorithms.

Both ^{18}F-FLT imaging time points must be scanned on the same qualified PET/CT scanner with imaging technique and reconstruction parameters as close as possible to that of the baseline scan.

Specific information related to the ^{18}F-FLT Whole Body PET/CT acquisition component of this study are found in the EA6183 Site Imaging Manual. The Site Imaging Manual serves as a supplement to the EA6183 clinical protocol and is best suited for technical guidance with regard to PET/CT Scanner Qualification, Quality Control Procedures, ^{18}F-FLT preparation,^{18}F-FLT administration, Whole Body PET/CT procedures, PET/CT image acquisition and reconstruction procedures and image submission via TRIAD to the ACR Core Laboratory for analysis.

5.3.7 Supportive Care Guidelines

Any adverse effects, related or non-related to the injection of ^{18}F-FLT, will be treated as clinically indicated with no study-related restrictions.

5.3.8 Dosing Delays/Dose Modifications

^{18}F-FLT Dose

The dose of ^{18}F-FLT is based on the radiation dosimetry estimates. Due to the potential of a poor radiosynthetic yield or unavoidable time delays, a lesser amount of radioactivity may be administered at the discretion of the site PI, based on whether clinically acceptable images can be acquired with the dose administered. Any such modifications of the agent infusion will be recorded.

5.4 Adverse Event Reporting Requirements

All adverse event grades described throughout this protocol and all reportable adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.4.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.4.2 Routine Reporting of Adverse Events (Medidata Rave)

Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave, the electronic clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA6183 forms packet for instructions on where, when and what is to be reported routinely on this protocol for both therapeutic agent and imaging agent related adverse events.

5.4.3 Expedited Reporting of Adverse Events (CTEP-AERS)

In addition to routine reporting, certain adverse events must be also reported in an expedited manner for timelier monitoring of patient safety and care using CTEP-AERS (CTEP's Adverse Event Reporting System). The remainder of this section provides information and instructions regarding expedited adverse event reporting.

5.4.4 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a therapeutic agent or imaging agent in humans, whether or not considered therapeutic agent or imaging agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an

abnormal laboratory finding), symptom, or disease that worsens or is emergent after the use of a therapeutic agent or imaging agent, whether or not considered related to the therapeutic agent or imaging agent.

- **Attribution:** An assessment of the relationship between the adverse event and any protocol agent (therapeutic or imaging), using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to any protocol agents (therapeutic or imaging)
Unlikely	The AE is *doubtfully related* to any protocol agents (therapeutic or imaging).
Possible	The AE *may be related* to any protocol agents (therapeutic or imaging).
Probable	The AE is *likely related* to any protocol agents (therapeutic or imaging).
Definite	The AE is *clearly related* to any protocol agents (therapeutic or imaging).

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND (an agent whose use is being investigated). Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** SAEs are events as outlined in FDA guidance (21 CRF Part 312.32) Any adverse event occurring at any dose that results in **ANY** of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours)
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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5.4.5 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov, so that ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900) for all events

For this study, an electronic CTEP-AERS report MUST be submitted via CTEP-AERS immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

Many factors determine the requirements for expedited reporting of adverse events on each individual protocol. The instructions and tables in the following sections have been customized for protocol EA6183 and outline the specific expedited adverse event reporting requirements for study EA6183.

5.4.6 Steps to determine if an adverse event is to be reported in an expedited manner – (Treatment Arm Code (TAC) = Arm A in CTEP-AERS)

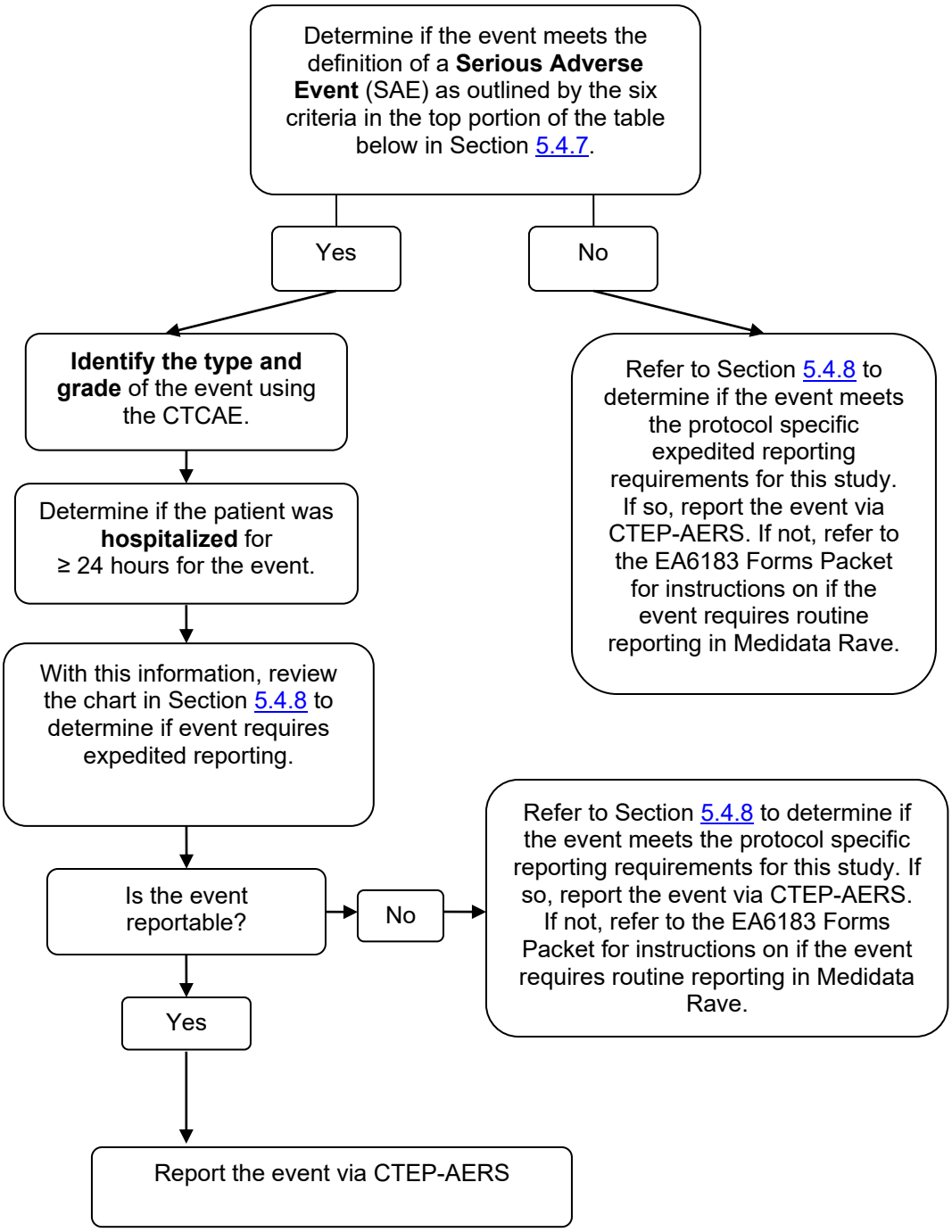
5.4.6.1 Guidelines for adverse events occurring while on protocol treatment and **within 24 hours after the administration of the imaging agent ^{18}f-flt and within 30 days of the last administration of the therapeutic agents encorafenib and binimetinib.**

NOTE: Patients should be queried for potential AEs at multiple time points in the 24 hours following administration of the ^{18}F-FLT:

- At the time of injection;

- Before leaving the PET suite;
- If they call the site as instructed for any concerns at any times during the monitoring period (24 hours)
- At the end of the monitoring period by phone or in person (24 hours post infusion administration).

See Section 5.2.2 for specific adverse events to monitor following the ^{18}F-FLT dose


Determine if the event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.4.7.
Yes
No
Identify the type and grade of the event using the CTCAE.
Refer to Section 5.4.8 to determine if the event meets the protocol specific expedited reporting requirements for this study. If so, report the event via CTEP-AERS. If not, refer to the EA6183 Forms Packet for instructions on if the event requires routine reporting in Medidata Rave.
Determine if the patient was **hospitalized** for ≥ 24 hours for the event.
With this information, review the chart in Section 5.4.8 to determine if event requires expedited reporting.
Is the event reportable?
No
Refer to Section 5.4.8 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event via CTEP-AERS. If not, refer to the EA6183 Forms Packet for instructions on if the event requires routine reporting in Medidata Rave.
Yes
Report the event via CTEP-AERS

5.4.6.2 Guidelines for adverse events occurring **greater than 24 hours after the administration of the imaging agent ^{18}f-flt or greater than 30 days of the last administration of the investigational therapeutic agents encorafenib and binimetinib.**

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.4.7, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4 and Grade 5 AEs

NOTE: Any death occurring greater than 24 hours and up to 30 days after the administration of the imaging agent ^{18}F-FLT must be reported expeditiously via CTEP-AERS even if the patient is off study.

NOTE: Any death occurring greater than 30 days after the last dose of the therapeutic agents Encorafenib and Binimetinib or the imaging agent ^{18}F-FLT with an attribution of possible, probable or definite must be reported expeditiously via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

5.4.7 Expedited Reporting Requirements on protocol EA6183

Investigational Agents: Encorafenib, Binimetinib, and ^{18}F-FLT

Commercial Agents: None

Phase 1 and Early Phase 2 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported via CTEP-AERS Rave within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

5.4.8 Additional instructions, requirements and exceptions for protocol EA6183

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Reporting a death on study:

A death occurring while on study treatment or within 30 days of the last dose of any protocol agent (therapeutic or imaging) requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

EA6183 specific expedited reporting requirements:

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on Encorafenib, Binimetinib or ^{18}F-FLT , or within 28 days the female patient's last dose of Encorafenib, Binimetinib or ^{18}F-FLT , are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix V for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies

EA6183 specific expedited reporting exceptions:

- There are no exceptions to expedited adverse event reporting on this study

5.4.9 Other recipients of adverse event reports and supplemental data

ECOG-ACRIN, the IND sponsor, will forward CTEP-AERS reports to all appropriate regulatory agencies and pharmaceutical company, if applicable.

A drug supporter representative may call a site for additional or supplemental information regarding a serious adverse event. Any

additional written AE information requested by the drug supporter MUST be submitted to BOTH ECOG-ACRIN and the drug supporter.

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.4.10 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported as follows:

- **A <u>second malignancy</u> is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Report the diagnosis on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

   NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).

3. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov.
4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.

5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted in CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.5 Comprehensive Adverse Events and Potential Risks list (CAEPR)

5.5.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Binimetinib (NSC 788187)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. *Frequency is provided based on 662 patients.* Below is the CAEPR for Binimetinib.

Version 2.1, September 11, 2019[1]

Adverse Events with Possible Relationship to Binimetinib (CTCAE 5.0 Term) [n= 1374]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
		Cardiac disorders - Other (bradycardia)
		Heart failure
EYE DISORDERS		
	Blurred vision	
		Eye disorders - Other (ocular hypertension)
		Eye disorders - Other (retinal vascular occlusion)
Eye disorders - Other (visual disorder)[2]		
		Periorbital edema
	Retinopathy[3]	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
Diarrhea		
	Mucositis oral	
Nausea		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema face	
Edema limbs		
Fatigue		
	Fever	
HEPATOBILIARY DISORDERS		
		Hepatic failure
INFECTIONS AND INFESTATIONS		
	Skin infection	

Adverse Events with Possible Relationship to Binimetinib (CTCAE 5.0 Term) [n= 1374]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	CPK increased[4]	
	Ejection fraction decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (myopathy)	
	Myalgia	
		Rhabdomyolysis
NERVOUS SYSTEM DISORDERS		
	Dizziness	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Dyspnea	
		Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Dry skin	
	Pruritus	
Rash acneiform		
Rash[5]		
	Skin and subcutaneous tissue disorders - Other (nail disorders)	
		Skin and subcutaneous tissue disorders - Other (severe cutaneous reaction)[6]
	Skin and subcutaneous tissue disorders - Other (skin fissures)	
VASCULAR DISORDERS		
	Hypertension	
	Thromboembolic event	
	Vascular disorders - Other (hemorrhage)[7]	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Visual disorders may include visual disturbance, blurred vision, visual acuity reduced, flashing light, and floaters.

[3] Retinopathy may include chorioretinopathy, chorioretinitis, and retinal detachment.

[4] CPK increased may be associated with muscle pain and muscle weakness.

[5] Rash may include rash maculo-papular and erythematous rash.

[6] Severe cutaneous reactions may include bullous dermatitis, exfoliative dermatitis, erythema multiforme, and toxic skin eruptions.

[7] The majority of hemorrhage events were mild, although serious bleeding events in the eyes, GI tracts or lungs have rarely been reported.

Adverse events reported on binimetinib trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that binimetinib caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (atrioventricular block); Cardiac disorders - Other (irregular heart rate); Cardiac disorders - Other (tachyarrhythmia); Cardiac disorders - Other (tachycardia); Myocardial infarction; Palpitations; Supraventricular tachycardia

ENDOCRINE DISORDERS - Hypothyroidism

EYE DISORDERS - Dry eye; Eye disorders - Other (eye edema); Eye disorders - Other (visual field defect); Glaucoma

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Cheilitis; Colitis; Colonic obstruction; Dry mouth; Duodenal perforation; Dyspepsia; Dysphagia; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (anorectal discomfort); Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Hemorrhoids; Ileus; Pancreatitis; Small intestinal obstruction; Small intestinal perforation

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema trunk; Flu like symptoms; General disorders and administration site conditions - Other (axillary pain); General disorders and administration site conditions - Other (ulcer hemorrhage); Malaise; Multi-organ failure

HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (biliary colic); Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatic function abnormal)

INFECTIONS AND INFESTATIONS - Bacteremia; Bronchial infection; Kidney infection; Lung infection; Paronychia; Peritoneal infection; Sepsis; Shingles; Soft tissue infection; Upper respiratory infection; Urinary tract infection; Viremia

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Blood lactate dehydrogenase increased; Cardiac troponin I increased; Cardiac troponin T increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Investigations - Other (C-reactive protein increased); Investigations - Other (electrocardiogram change); Investigations - Other (haptoglobin increased); Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia;

Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (diabetes mellitus); Metabolism and nutrition disorders - Other (hypoproteinemia); Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE disorders - Arthritis; Flank pain; Muscle cramp; Neck pain; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain

NERVOUS SYSTEM DISORDERS - Akathisia; Dysgeusia; Headache; Nervous system disorders - Other (dropped head syndrome); Nervous system disorders - Other (myasthenic syndrome); Paresthesia; Presyncope; Somnolence; Spinal cord compression; Syncope; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Confusion; Hallucinations; Insomnia; Psychiatric disorders - Other (abnormal behavior); Suicide attempt

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Atelectasis; Cough; Hypoxia; Oropharyngeal pain; Pharyngolaryngeal pain; Pleural effusion; Pneumothorax; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (asthma); Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Erythroderma; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Skin and subcutaneous tissue disorders - Other (excoriation); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin and subcutaneous tissue disorders - Other (rosacea); Skin and subcutaneous tissue disorders - Other (skin burning sensation); Urticaria

VASCULAR DISORDERS - Hypotension; Lymphedema; Superficial thrombophlebitis; Vascular disorders - Other (aortic dilatation)

NOTE: Binimetinib in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.6 Dose Modifications

Doses of encorafenib and/or binimetinib should be adjusted for AEs (based on assessment per the CTCAE) throughout the study (see Table 3 Recommended Dose Modifications). In general, doses should not be reduced or interrupted for Grade 1 AEs unless the AE is a specific ocular AE referred to in the Recommended Dose Modifications Table but treatment to control symptoms should be provided as appropriate, if applicable.

An individual patient may have their dose of encorafenib and/or binimetinib reduced to the dose levels in Table 2 below:

Table 2. Recommended Dose Levels

	Encorafenib (mg QD)	Binimetinib (mg BID)
Starting Dose	450 (6 capsules)	45 (3 tablets)
Dose Level -1	300 (4 capsules)	30 (2 tablets)
Dose Level -2	225 (3 capsules)	15 (1 tablet)

Dose reductions below the lowest dose levels for each agent are not allowed.

Doses may not be re-escalated.

Missed Doses

- Doses of Binimetinib that are omitted for AEs or missed for any other reason should not be taken within 6 hours of the next scheduled dose.
- Doses of Encorafenib that are omitted for AEs or missed for any other reason should not be taken within 12 hours prior to the next scheduled dose.
- If vomiting occurs after taking either medication, the dose should not be repeated.

Lowest Doses

The lowest recommended dose level of encorafenib is 225 mg QD and the lowest recommended dose level of binimetinib is 15 mg BID. Dose may not be re-escalated.

- In most circumstances, both encorafenib and binimetinib will both be held for toxicities with exceptions listed below:
  - If binimetinib is withheld, encorafenib must be reduced to a maximum dose of 300 mg daily until binimetinib is resumed.
  - If binimetinib is permanently discontinued, treatment with encorafenib alone is permitted but only to a maximum dose of 300 mg once daily.
  - If encorafenib is permanently discontinued, treatment with binimetinib alone is permitted
- If a drug is held for greater than 42 consecutive days, the drug will be permanently discontinued.
  - If both drugs are held for greater than 42 consecutive days, they will both be permanently discontinued and the patient will come off study treatment.

Please refer to Dose Modification Table 3 below for recommended dose modifications for encorafenib and/or binimetinib, if applicable, based on the occurrence of treatment-related AEs.

Follow-up for Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up (by phone or in person) at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts such as an ophthalmologist, cardiologist or dermatologist should be consulted as deemed necessary.

Table 3: Recommended Encorafenib and Binimetinib Dose Modifications

Adverse Event and Grade/Severity		Dose Modifications
New Primary Malignancies		
Non-cutaneous *RAS* mutation-positive malignancies		Permanently discontinue encorafenib.
Cutaneous malignancies (SCC, BCC, additional primary melanoma) – surgical removal as per institutional practice		No interruption or modification indicated
Eye Toxicities		
Uveitis	Grade 1-2	Interrupt dosing of encorafenib and binimetinib for visual complaints and obtain ophthalmology evaluation within 7 days and initiate treatment as recommended. If Grade 1 or 2 does not respond to specific ocular therapy, withhold encorafenib and binimetinib for up to 6 weeks. • If improved, resume both encorafenib and binimetinib at same or reduced dose at the investigator's discretion. • If not improved, permanently discontinue both agents.
	Grade 3	Withhold encorafenib and binimetinib for up to 6 weeks: • If improved within 6 weeks, resume both encorafenib and binimetinib at same or reduced dose, at the Investigator's discretion. • If not improved within 6 weeks, permanently discontinue both drugs.
	Grade 4	Permanently discontinue both encorafenib and binimetinib.
Serous Retinopathy	Symptomatic serous retinopathy/ Retinal pigment epithelial detachments	Withhold binimetinib for up to 10 days. • If improves and becomes asymptomatic, resume binimetinib at the same dose. • If not improved, resume at a lower dose level

Adverse Event and Grade/Severity		Dose Modifications
		or permanently discontinue binimetinib at the investigator's discretion.
Retinal Vein Occlusion (RVO)	Any grade	Permanently discontinue binimetinib and follow-up with ophthalmic monitoring until stabilization or resolution.
Other Eye Disorders	Grade 1	Maintain dose level of encorafenib and binimetinib and monitor symptoms
	Grade 2	Interrupt dosing of encorafenib and binimetinib and obtain ophthalmology evaluation within 7 days and institute treatment as recommended. • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and follow-up with ophthalmic monitoring until stabilization or resolution.
	Grade 3	Interrupt dosing of encorafenib and binimetinib and refer patient to ophthalmologist within 7 days. • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and follow-up with ophthalmic monitoring until stabilization or resolution.
	Grade 4	Permanently discontinue encorafenib and binimetinib and immediately follow-up with ophthalmic monitoring until stabilization or resolution.
Cardiac Toxicities		
QTc Prolongation	QTc ≥ 500 ms and ≤ 60 ms increase from baseline	1st occurrence: • Temporarily interrupt dosing of encorafenib until QTc < 500 ms. Then resume treatment at 1 reduced dose level of encorafenib. 2nd occurrence: • Temporarily interrupt dosing of encorafenib until QTc< 500 ms. Then resume treatment at 1 reduced dose level of encorafenib. 3rd occurrence: Permanently discontinue encorafenib.
	QTcF ≥500 ms and > 60 ms increase from baseline	Permanently discontinue encorafenib.
Cardiomyopathy	Asymptomatic, absolute decrease in LVEF of > 10% from baseline that is also below the LLN	Withhold binimetinib for up to 4 weeks, evaluate LVEF every 4 weeks. Resume binimetinib at a reduced dose if the following are present:

Adverse Event and Grade/Severity		Dose Modifications
		• LVEF is at or above the LLN and • Absolute decrease from baseline is 10% or less and • Patient is asymptomatic. If LVEF does not recover within 4 weeks permanently discontinue binimetinib.
	Grade 3-4 (Symptomatic congestive heart failure or absolute decrease in LVEF of ≥ 20% from baseline that is also below LLN)	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks.
Venous Thromboembolism	Uncomplicated DVT or PE	Withhold binimetinib. • If controlled on anticoagulation, resume at reduced dose. • If not controlled on anticoagulation, permanently discontinue binimetinib.
	Life threatening PE	Permanently discontinue binimetinib
Hepatic Toxicities		
Elevated AST/ALT	Grade 2	• Maintain Encorafenib and Binimetinib doses • If no improvement within 2 weeks and assessed as related to binimetinib, withhold binimetinib (for up to 4 weeks). • If no improvement within 2 weeks, and assessed as related to encorafenib, withhold encorafenib (for up to 4 weeks). • Both drugs may be held if assessed as related to both. • Resume drug(s) at the same dose(s) if improved to Grade 0-1 or to pretreatment/baseline levels.
	Recurrent Grade 2 or first occurrence of any Grade 3	• Withhold encorafenib and/or binimetinib for up to 4 weeks, based on Investigator's assessment of causality. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose(s). • If no improvement, permanently discontinue encorafenib and binimetinib.
	Recurrent Grade 3	Consider permanently discontinuing both study agents
	First occurrence of Grade 4	Withhold encorafenib and/or binimetinib for up to 4 weeks, based on Investigator's assessment of causality. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose.

Adverse Event and Grade/Severity		Dose Modifications
		• If no improvement, permanently discontinue encorafenib and binimetinib.
	Recurrent Grade 4	Permanently discontinue both study agents.
Dermatologic Toxicity		
Dermatologic (Except Hand-foot Skin Reactions)	First occurrence of Grade 2	Systemic management • If no improvement within 2 weeks, withhold encorafenib and/or binimetinib for up to 4 weeks (based on Investigator's assessment of causality), until Grade 0-1. The resume at same dose(s).
	First occurrence of Grade 3	Symptomatic management and withhold encorafenib and/or binimetinib for up to 4 weeks (based on Investigator's assessment of causality), until Grade 0-1. Then resume at same dose(s). • Consider referral to dermatology
	Recurrent Grade 2-3	Symptomatic management and withhold encorafenib and/or binimetinib for up to 4 weeks (based on Investigator's assessment of causality), until Grade 0-1. The resume at reduced dose(s). • Consider referral to dermatology
	Grade 4	Permanently discontinue encorafenib and/or binimetinib. • Consider referral to dermatology
Hand-foot Skin Reaction (HFSR)/ Palmar-plantar Erythodysesthisa Syndrome (dose adjustment for Encorafenib ONLY)	Grade 1	Maintain dose of encorafenib and HFSR should be closely monitored. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modification.
	Grade 2	1st occurrence: • Maintain dose of encorafenib and closely monitor. Promptly institute supporting measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modification. • If no improvement, ≤ 14 days, withhold encorafenib for up to 4 weeks until resolved to Grade ≤ 1. Resume treatment with encorafenib at same dose level. Continue supportive measures.
	Recurrent Grade 2	Treatment with encorafenib may be maintained or interrupted at the Investigator's discretion. If interrupted dosing of encorafenib per Investigator's judgment, interrupt until resolved to Grade ≤ 1. Resume treatment with encorafenib at the same dose level or 1 reduced dose level based upon the Investigator's discretion. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on

Adverse Event and Grade/Severity		Dose Modifications
		lifestyle modifications.
	Grade 3	1st or 2nd occurrence: • Interrupt dosing of encorafenib. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Reassess the patient weekly. If resolved to grade 0-1, then resume encorafenib at one reduced dose level. • Consider referral to dermatologist and manage HFSR per dermatologist's recommendation. ≥ 3nd occurrence: • Interrupt dosing of encorafenib • If resolved to Grade ≤ 1, resume treatment with encorafenib at reduced dose or permanently discontinue encorafenib should be based upon the Investigator's discretion
Gastrointestinal Toxicity		
Nausea/Vomiting	Grade 1-2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.
	Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Promptly institute antiemetic measure. Resume treatment at 1 reduced dose level of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level if considered related.
	Grade 4	Permanently discontinue encorafenib and binimetinib.
Pulmonary		
Interstitial Lung Disease	Grade 2	Withhold binimetinib for up to 4 weeks. • If improved to Grade 0-1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue binimetinib.
	Grade 3 or Grade 4	Permanently discontinue binimetinib.
Rhabdomyolysis or Creatine Phosphokinase (CPK) elevations		
	Grade 4 asymptomatic CPK elevation or Any Grade CPK elevation with symptoms or with renal impairment	Withhold binimetinib dose for up to 4 weeks. • If improved to Grade 0-1 resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue binimetinib.

Adverse Event and Grade/Severity		Dose Modifications
Other Adverse Reactions (Including renal and hemorrhage)		
	Recurrent Grade 2 or First occurrence of any Grade 3	Withhold encorafenib and/or binimetinib (based on Investigator's assessment of causality), for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume held drug(s) at reduced dose. • If no improvement, permanently discontinue encorafenib and/or biniteminb.
	Recurrent Grade 3	Consider permanent discontinuation of encorafenib and/or binimetinib, based on Investigator's assessment of causality.
	First occurrence of any Grade 4	Withhold encorafenib and/or binimetinib (based on Investigator's assessment of causality) for up to 4 weeks. Investigator may elect to permanently discontinue drug(s). • If improves to Grade 0-1 or to pretreatment/baseline levels, resume both agents at a reduced dose(s). • If no improvement, permanently discontinue both agents.
	Recurrent Grade 4	Permanently discontinue both agents.

5.7 Supportive Care

5.7.1 All supportive measures consistent with optimal patient care will be given throughout the study per investigator discretion or institutional guidelines.

- Skin: Encourage good skin care
  - Regular use of topical emollients
  - Avoid unnecessary exposure to sunlight, apply broad spectrum sunscreen and/or sun protective clothing
  - Topical steroids or topical antibiotics may be applied to affected areas as needed (mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (e.g. clindamycin) or oral antibiotics
- Gastrointestinal:
  - Antiemetic and anti-diarrheal agents may be prescribed per investigator or institutional guidelines.

5.8 Duration of Therapy

Neoadjuvant Phase: 8 weeks (2 cycles)

Adjuvant Phase: 44 weeks (11 cycles)

Patients will receive protocol therapy unless:

- New progressive lesions are seen on post neoadjuvant treatment CT, MRI and/or PET scans and confirmed as distant metastatic disease.

- If a new/progressive lesion is noted on imaging after neoadjuvant therapy, histologic evaluation with a biopsy is required to confirm disease progression, unless the lesion is not accessible or a biopsy would cause undue risk to the patient.
- If the progressive disease is still considered eligible for a complete surgical resection, the patient may proceed on to surgery per investigator discretion and a biopsy is not required before surgery.

- If pathology review of surgical specimen confirms progressive disease, these patients will then come off study treatment and not receive the adjuvant phase of therapy, and will be followed for survival.
- If pathology review of surgical specimen shows treatment effect, these patients will continue on study and receive adjuvant phase of therapy.
  - If the progressive disease is not considered resectable based on post treatment scans, biopsy, and surgical consultation/opinion, surgical resection will not be carried out and the patient will be off study treatment and followed for survival.

NOTE: All patients who received at least one dose of neoadjuvant therapy are expected to complete post FLT PET/CT regardless of radiologic, clinical or pathologic response and prior to coming off study treatment. **If a patient comes off treatment early the second ^{18}F-FLT PET/CT scan should not be completed any sooner than four weeks after starting neoadjuvant therapy.**

NOTE: Date of neoadjuvant progression will be the earliest date of confirmed progression before surgery.

Additional Reasons for Treatment Discontinuation

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued per investigator discretion. In this event submit forms according to the instructions in the EA6183 Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Progression of disease per RECIST 1.1 before surgery that renders the patient ineligible for surgery.
- Relapse of disease after surgery.
- Treatment delay/hold of greater than > 42 consecutive days for any reason.

NOTE: All reasons for treatment discontinuation must be documented on the case report forms in Medidata Rave.

Rev Add2

5.9 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration. Patients will

be followed every 3 months for the planned year of treatment and for 1 additional year, then every 6 months for 3 years. All patients must also be followed through completion of all protocol therapy.

- For patients who have confirmed progression per RECIST 1.1 prior to surgery and do not undergo surgery, the patient will come off study treatment and be followed for survival.
- For patients who have confirmed progression per RECIST 1.1 prior to surgery, but are still deemed eligible for surgical resection – they will be followed for progression and survival.
- For patients who come off study treatment for intolerable toxicities at any time, they will be followed for progression and survival. If a patient comes off treatment early for anything other than progression of disease, follow up for the planned year of treatment with scans and H/P will continue at every 3 months.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

6.1.1 Neoadjuvant Effect – Solid Tumors

- Pathologic response: will be assessed once at approximately 10-12 weeks: following surgery and 8 weeks of systemic therapy as assessed on local review. Central review will be performed retrospectively. The following definitions will be employed: [Tetzlaff, Annal Oncol, 2018]
- Pathologic Complete Response (pCR)
  - Complete absence of viable tumor in the treated tumor bed
- Major PR
  - ≤10% of viable tumor in the treated tumor bed
- Partial Pathologic Response (pPR)
  - Less than or equal to 50% of the treated tumor bed is occupied by viable tumor cells
- Pathologic Non-Response (pNR)
  - Great than 50% of the treated tumor bed is occupied by viable tumor cells
  - Radiologic Response: For the purposes of this study, patients should be evaluated for radiologic/clinical response after 8 weeks of therapy but prior to surgery, and then every 12 weeks (+2 weeks) (20 weeks, 32 weeks and 44 weeks and 56 weeks (end of treatment) for one year, then every 12 weeks (+4 weeks) x 1 year, then every 24 weeks (+4 weeks) x 3 (until year 5).

Post-neoadjuvant treatment CT (or MRI) scan of chest, abdomen, pelvis and/or any other involved sites with contrast (unless contraindicated) will be performed and the response to systemic treatment assessed in addition to clinical assessment. Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST. If a new/progressive lesion is noted on imaging after neoadjuvant therapy, histologic evaluation with a biopsy is required unless the lesion is not accessible or a biopsy would cause undue risk to the patient. If the progressive disease is still considered eligible for a complete surgical resection, the patient may proceed onto surgery per investigator discretion and a biopsy is not required before surgery. Pathologic evaluation would then confirm if true disease progression versus treatment effect. If the progressive disease is not considered resectable based on post treatment scans, biopsy, and surgical

consultation/opinion, surgical resection will not be carried out and the patient will be off treatment and followed for survival.

The following general principles must be followed:

2. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
3. Measurable disease is defined by the presence of at least one measurable lesion.
4. All measurements should be recorded in metric notation by use of a ruler or calipers.
5. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.2 Definitions

Evaluable for Response

Evaluable patients are defined as eligible patients (per Section 3) who receive at least one dose of neoadjuvant therapy with encorafenib and binimetinib and are resectable at enrollment.

- Patients who do receive treatment but demonstrate progression of disease per RECIST and do not proceed to surgery will be classified as pathologic non response (pNR).
- Patients who receive at least one dose of treatment but do not receive surgery for other reasons will be evaluated for radiographic/clinical response.

6.1.3 Disease Parameters: evaluation of radiographic response

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be

≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and 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. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.4 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before registration.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray

Lesions on chest x-ray are not acceptable as measurable lesions.

Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. FDG-PET/CT will not be mandated for the study. However, patients who undergo FDG-PET/CT for clinical indications, and had the FDG scan performed on the qualified scanner, will have FDG-PET/CT scans collected for an exploratory comparison to outcomes and to FLT-PET results.

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

6.1.5 Response Criteria

6.1.5.1 Pathologic Response Rate (pCR)

Pathologic complete response (pCR) is defined as the absence of residual melanoma in resected tissue as assessed on local pathology review. These will have central review retrospectively.

- **Pathologic complete response (pCR)**
  - Complete absence of viable tumor in the treated tumor bed
- **Major PR**
  - *≤10% of viable tumor in the treated tumor bed*
- **Partial pathologic response (pPR)**
  - Less than or equal to 50% of the treated tumor bed is occupied by viable tumor cells
- **Pathologic non-response (pNR)**
  - Greater than 50% of the treated tumor bed is occupied by viable tumor cells

Pathologic Response		Remarks
pCR	Complete absence of viable tumor in the treated tumor bed	
Major PR	≤ 10% of viable tumor in the treated tumor bed	
pPR	Less than or equal to 50% of the treated tumor bed is occupied by viable tumor cells	
pNR	Great than 50% of the treated tumor bed is occupied by viable tumor cells	Patients that demonstrate objective RECIST progression, they will be classified at pathologic NR

6.1.5.2 RECIST Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to
< 10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression, See Section 6.1.5.4.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

NOTE: A change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once.

6.1.5.3 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD

Persistence of one or more non-target lesion(s).

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the

basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.1.5.4 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or

b) there is new pathological confirmation that it is disease (regardless of size).

c) new effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

6.1.5.5 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the neoadjuvant treatment until surgery or disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Best response will be collected at one time point:

- After 8 weeks of neoadjuvant therapy (best response to oral treatment)

RECIST response with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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."* Every effort should be made to document the objective progression even after discontinuation of treatment.

6.1.5.6 Duration of disease control

Duration of Overall Response

The duration of disease control is measured from the time of enrollment to the first date of any of the following events: progression prior to surgery such that surgery is not recommended/performed; at time of surgery if resection does not eradicate all disease, progression after surgery, death. If none of the events occur, the date of last contact.

6.2 Progression before surgery

Progression of disease per RECIST 1.1 before surgery that renders the patient ineligible for complete surgical resection per protocol should be classified as local/ regional or distant.

6.3 Local, Regional Recurrence

The development of a local or regional recurrence of melanoma after surgery

6.4 Distant Recurrence

The development of a distant recurrence of melanoma after surgery

6.5 Disease-Free Survival

Date of surgical resection to the date of first treatment failure (recurrence or death before recurrence)

6.6 Survival

Date of registration to date of death

6.7 Recurrence

Recurrence must be documented by radiologic exams and with biopsy in all cases except for brain metastases (biopsy not required). Abnormal blood studies alone (e.g., elevated transaminases or alkaline phosphatase) are not sufficient evidence of relapse. Whenever possible, histologic proof of recurrence should be obtained unless the lesion is not accessible or a biopsy would cause undue risk to the patient.

Documentation of recurrence must specify all involved sites to establish the pattern of recurrence.

A new primary melanoma is not considered recurrence.

7. Study Parameters

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7.1 Therapeutic Parameters

1. Screening and baseline assessments must occur within 4 weeks of registration, unless otherwise specified.
2. Patients must have been seen and evaluated by a melanoma-experienced surgeon prior to enrollment and deemed surgically resectable.
3. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within 4 weeks prior to registration.
4. Prestudy laboratory assessments must be completed < 14 days prior to registration.

		Neo-Adjuvant				Surgery	Adjuvant											
	Screening/ baseline	**Week 0 D1**	**Week 2[10]**	**Week 4**	**Week 8**		**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**EOT**
Informed Consent	X																	
History/ Physical Exam/ ECOG	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Weight/ Vital signs	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[8]	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
CT c/a/p + additional sites as indicated	X				X				X			X			X			X
MRI brain (up to 4 weeks prior to registration)	X																	
Chemistry Labs[1]	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Hematology Labs[1]	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Test[2]	X	X[2]					X											
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pill Count/Diary[3]		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X

		Neo-Adjuvant				Surgery	Adjuvant											
	Screening/ baseline	**Week 0 D1**	**Week 2[10]**	**Week 4**	**Week 8**		**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**EOT**
Echocardiogram/ MUGA[7]	X			X				X			X			X			X	
EKG[7]	X																	
Ophthalmology Exam[4]	X																	
CK[5]	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Surgical Resection[9]						X												
FLT-PET[6]	X				X[9]													
Biological Sample Submissions		See Section 7.2																

1 CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle. PT, PTT, INR will be collected at screening. Additional labs and frequency as clinically indicated per investigator discretion. Screening labs will be obtained within the one-week period prior to administration of FLT. Chemistry labs include; Sodium, chloride, CO2 or bicarbonate, potassium, creatinine, BUN, glucose, calcium, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase, LDH. If patient data is available from clinical records in the appropriate time window, they need not be repeated for the scans.

2 All patients of childbearing potential must have a negative [blood test or urine test] within 14 days prior to study registration to rule out pregnancy. If the pregnancy test done at baseline is greater than 14 days prior to Day 1 of treatment, it should be repeated prior to initiating treatment. A pregnancy test must also be done prior to starting adjuvant treatment.

3 Patients will record medication use of Encorafenib and Binimetinib per scheduled visits. See Appendix III.

4 A full ophthalmic examination will be performed by an ophthalmologist at baseline and include best corrected visual acuity, slit lamp examination, intraocular pressure, dilated fundoscopy. Ocular Coherence Tomography (OCT) will only be performed if clinically indicated at the discretion of the ophthalmologist. Examination of the retina is required, especially to identify findings associated with serous retinopathy and RVO. After baseline, patients should be assessed at every physical examination for visual complaints. Symptomatic patients should be referred for a full ophthalmic consultation. For patients with clinical suspicion of retinal abnormalities of any grade (e.g., serous retinopathy, RVO, photopsia, metamorphopsia, impairment of visual acuity), these additional assessments should be mandatory. Full ophthalmologic exam will be pursued as needed throughout the study as clinically indicated.

5 CK will be performed at the same time points as the hematology collections. Troponin may be drawn as clinically indicated for abnormal CK. Follow up for total creatine kinase (CK) ≥3 X ULN will include weekly assessment of isoenzymes and myoglobin in blood/or urine, and troponin as applicable.

6 The baseline FLT scan must be done within two weeks prior to starting neoadjuvant treatment and the post-treatment FLT scan should be completed after 2 cycles (8 weeks or up to 9 weeks) of treatment and prior to surgery. All study related neoadjuvant treatment should be

completed prior to post-treatment scan. Refer to Section 5.3.4 for more details on scan timing. Specific image acquisition and reconstruction protocols will be provided in a Site Imaging Manual to participating institutions. Patient should be monitored for AE's to the FLT after the imaging is complete and 24 hours after completion of scan, this can be done by phone or email.

7 EKG should be performed at baseline. Additional EKGs are to be performed as clinically indicated. ECHO/MUGA scans are to be performed at screening, on Cycle 2 Day 1 and Cycle 5 Day 1, then every 12 weeks and EOT to determine cardiac ejection fraction. If scheduled ECHO/MUGA was performed and within normal limits within 4 weeks of the end of treatment timeframe, a second ECHO/MUGA does not need to be performed. Whichever modality was used at baseline should be continued throughout the study.

8 See Section 8.1.13 and Section 8.2.14.

9 Surgery should not be delayed if the FLT PET scan cannot be done prior to planned surgery.

10 Week 2 visit can be done by phone if patient does not consent for week 2 biopsy.

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7.2 Biological Sample Submissions

1. Specimens are to be submitted as outlined in Section 10.
2. All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

Biological Materials	Baseline	After Two [2] Weeks of Treament[4]	After Eight [8] Weeks of Treatment	Week 20[6]	Week 32[6]	Week 44[6]	End of Treatment
Mandatory for Central Diagnostic Review							
FFPE Tumor Tissue[7]	X[1]		X[5]				
Collect and submit from patients who answer *"Yes"* to *"I agree to have one or two research biopsies to collect tissue for known laboratory research studies."*							
Tumor Tissue Biopsy[7]	X[3]	X					
Collect and submit from patients who answer "*Yes*" to *"I agree to have my tissue samples collected from procedures performed as part of my standard of care and I agree that my tissue samples and related health information may be used for the laboratory research studies described above."*[8]							
FFPE Tumor Tissue	X[1]		X[5]				
Collect and submit from patients who answer *"Yes"* to "*I agree to provide additional blood samples for future health research*."[8]							
Peripheral Blood (ten 10mL green top heparin tubes)[2]	X	X	X	X	X	X	X
Peripheral Blood (two 10mL SST red top tubes)[2]	X	X	X	X	X	X	X
Peripheral Blood (one 10mL Streck Cell-Free DNA tube)[2]	X	X	X	X	X	X	X

1 Tumor tissue collected within two (2) months prior to performance of imaging and from the surgical resection with the related pathology reports must be submitted for central diagnostic review within one (1) month following registration and the procedure respectively. Failure to submit the required materials may render the case unevaluable. Additional materials are requested for laboratory research studies from patients who consent "Yes" to *"I agree to have my tissue samples collected from procedures performed as part of my standard of care and I agree that my tissue samples and related health information may be used for the laboratory research studies described above."*

2 Kits are being provided for the collection and shipment of the peripheral blood specimens. See Appendix VII for instructions. Kit orders will on average be delivered within three (3) business days from the time the order is placed.

3 If baseline biopsy is performed after study registration, the baseline FLT-PET/ CT scan should be completed prior to biopsy (can be done same day).

4 +/- 1 week.

5 Surgical resection specimen.

6 At every scan evaluation while on treatment.

7 Biopsies are to be performed, if considered at or less than minimal risk (no more than 2% risk of serious complication requiring hospitalization).

8 As outlined in the Informed Consent patient participation in tumor tissue and peripheral blood submissions is optional. Sites must offer participation in these optional studies to all patients.

8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Pfizer is supplying **Encorafenib and Binimetinib** free of charge and will be distributed by McKesson Specialty Pharmacy, LP. Under no circumstances can commercially supplied **Encorafenib and Binimetinib** be used or substituted for the patient specific **Encorafenib and Binimetinib** supplied by Pfizer.

Encorafenib:

Encorafenib is manufactured by Pfizer and is supplied as hard gelatin capsules in a dosage strength of 75 mg. Encorafenib capsules consist of encorafenib drug substance, copovidone, poloxamer 188, succinic acid, microcrystalline cellulose, colloid silicon dioxide, crospovidone, and magnesium stearate of vegetable origin. The capsule shell is commercially available and contains gelatin and titanium dioxide as well as iron oxide red, yellow or black depending on the particular strength.

Encorafenib capsules should be stored at room temperature, not above 25°C and protected from moisture. Capsules are packaged in square, high-density polyethylene bottles that are induction sealed and closed with a polypropylene, child-resistant screw cap. Encorafenib bottles will be labelled, at a minimum, with the lot number, contents (number of tablets), dosage strength, and storage conditions. Encorafenib should be dispensed to patients in the bottles provided by Pfizer and should not be repackaged at the site or pharmacy.

Binimetinib:

Binimetinib is manufactured by Pfizer and is supplied as film-coated tablets in a dosage strength of 15 mg. The film-coated tablets consist of binimetinib drug substance, colloidal silicon dioxide/silica colloidal anhydrous, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose/cellulose, microcrystalline, and a commercial film coating. The tablet is ovaloid biconvex (capsule shaped), yellow to dark yellow in color.

Binimetinib film-coated tablets should be stored at room temperature, not above 25°C and protected from light. Tablets are packaged in square, high-density polyethylene bottles that are induction sealed and closed with a polypropylene, child-resistant screw cap. Binimetinib bottles will be labelled, at a minimum, with the lot number, contents (number of tablets), dosage strength, and storage conditions. Binimetinib should be dispensed to patients in the bottles provided by Pfizer and should not be repackaged at the site or pharmacy.

8.1 Binimetinib (NSC 788187)

Please refer to the package insert or institutional preparation guidelines for additional information.

8.1.1 Chemical Name or Amino Acid Sequence

5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1Hbenzimidazole-6-carboxamide

8.1.2 Other Names

MEK162, ARRY-438162, Mektovi®

8.1.3 Classification

MEK 1/2 inhibitor

8.1.4 CAS Registry Number

606143-89-9

8.1.5 Molecular Formula

C17H15BrF2N4O3 **M.W.:** 441.23

8.1.6 Approximate Solubility

Binimetinib's solubility is pH dependent. At pH 1 solubility is 0.993 mg/mL. At pH 7.4 solubility is 0.012 mg/mL.

8.1.7 Mode of Action

Binimetinib is a potent, selective, allosteric small-molecule inhibitor of mitogen-activated protein (MAP) kinase kinase (MEK 1 and MEK 2) that is uncompetitive with adenosine triphosphate (ATP).

8.1.8 Availability

Binimetinib is provided free of charge by Pfizer and distributed by McKesson Specialty Pharmacy, LP.

Initial Drug Orders for Each Patient

Once a patient has been registered on this study, a supply of Binimetinib may be ordered. Investigators must email a completed EA6183 Binimetinib Study Drug Request Form to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org. A copy of the EA6183 Binimetinib Study Drug Request Form is available for download from the CTSU website (www.ctsu.org).

Please refer to Appendix VII for the EA6183 Binimetinib Study Drug Request Form download instructions.

Binimetinib will be shipped to a responsible person (e.g., a pharmacist) at the investigator's institution. **Sites should order enough drug for 2 cycles of treatment.**

Institutions should allow up to 4 business days to receive drug onsite. McKesson Specialty Pharmacy, LP will ship and arrange drug deliveries to sites on business days only; there will be no weekend or holiday delivery of drugs.

IMPORTANT REORDER INSTRUCTIONS

Once it is determined that the patient will continue treatment, please reorder 2 cycles of study drug immediately by emailing a completed EA6183 Binimetinib Study Drug Request Form to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org.

Institutions should allow up to 4 business days to receive drug onsite. McKesson Specialty Pharmacy, LP will ship and arrange drug deliveries to sites on business days only; there will be no weekend or holiday delivery of drugs.

Drug Destruction and Return

At the completion of each patient's treatment at your institution, all unused drugs, partially used, or empty containers must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.9 Storage

Store below 25°C, protect from light

All deviations from the required storage condition of IMP provided by Pfizer, whether the deviation occur in-transit or on-site, need to be reported to Pfizer for evaluation of the impact the event may have to the usability of the IMP.

Please report temperature deviation events to the Pfizer Clinical Supply team using the following email address:

GCSTempExcursionSupport@pfizer.com

8.1.10 Stability

Stability studies are ongoing. Tablets should be dispensed in the original packaging.

8.1.11 Route and Method of Administration

Orally with or without food. Tablets should be swallowed whole.

8.1.12 Potential Drug Interactions

In vitro, binimetinib is metabolized primarily by glucuronidation mainly via UGT1A1 but also UGT1A3 and 1A9. Binimetinib is a substrate of CYP1A1, 1A2, 2C19, 3A4 in vitro but the potential for a clinical drug interaction is expected to be minimal. Binimetinib is also a substrate of P-gp and BCRP. Inhibitors or inducers of UGT1A1, P-gp, and BCRP should be co-administered with caution.

In vitro, binimetinib showed relatively potent inhibitory effect on CYP2B6 and weak inhibition of CYP1A2 and 2C9. Avoid co-administration with agents that are substrates of CYP2B6. It has little or no inhibition of CYP2A6, 2C8, 2C19, 2D6, 2E1, and 3A4/5. Binimetinib is a weak inhibitor of UGT1A-mediated SN-38 conjugation in vitro. Binimetinib was not found to be an in vitro inhibitor of BCRP, P-gp, or OCT1 but is a weak inhibitor of OCT2. There is a low potential for binimetinib to cause a clinical drug interaction with substrates mainly cleared by OATP and OCT2.

Binimetinib is an in vitro inducer of CYP3A4 but this was not confirmed clinically. Slight induction of CYP2C9 mRNA was also found but did not translate into induction of activity.

Binimetinib is highly protein bound (97.2%). Use caution in patients who are receiving concomitant medications that are also highly protein-bound.

Drugs with a conditional, possible, or known risk to induce Torsades de Pointes or QT prolongation should be co-administered with caution. Patients that take these medications should be monitored frequently or according to protocol.

8.1.13 Side Effects

See Section 5.5.1 for the Comprehensive Adverse Event and Potential Risks (CAEPR) list.

Refer to Section 5.6 for dose modification instructions.

8.1.14 Concomitant Medications

Concomitant strong systemic CYP3A4 inhibitors and moderate/strong CYP3A4 inducers are likely to significantly increase or decrease encorafenib exposure, respectively, and thus, they are not allowed during this study (see Appendix X).

In vitro, binimetinib has been identified to be primarily metabolized by glucuronidation through UGT1A1. Binimetinib has also been shown to be a substrate of P-gp and BCRP. It is advised that inhibitors and inducers of UGT1A1, P-gp or BCRP transporters should be taken with caution when co-administered with binimetinib.

For a listing of examples of substrates, inhibitors and inducers to be used with caution, please consult with the FDA website: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Note that this list is not exhaustive.

Investigators should use caution when administering encorafenib or binimetinib with concomitant medications with a known, conditional or possible risk to prolong the QT interval and/or induce TdP. Subjects receiving such medications must be carefully monitored for potentiation of toxicity due to any individual concomitant medication, and may require dose titration of the concomitant medication. See the CredibleMeds® website for examples: Combined List of Drugs That Prolong QT and/or cause Torsades de Pointes (TDP). Note that this list is not exhaustive.

8.1.15 Nursing/ Patient Care Implications

There is some data that suggest binimetinib exposure may be associated with reproductive toxicity. Binimetinib must not be used in pregnant or nursing women. Educate the patient that diarrhea, nausea, and vomiting has been reported in patients taking binimetinib. Recommend anti-diarrheal medications appropriate anti-emetics, and dietary modifications.

8.1.16 Lifestyle Considerations

Meals and Dietary Restriction

Patients must avoid consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study drugs, due to potential CYP3A4 interaction with encorafenib. Orange juice is allowed.

Activity

Strenuous physical activities, such as competitive sports, can result in significant increases in CK levels while on binimetinib treatment. Patients should be cautioned not to start a new strenuous exercise regimen after first dose of study treatment.

8.2 Encorafenib (LGX818)

Please refer to the package insert or institutional preparation guidelines for additional information.

8.2.1 Chemical Name or Amino Acid Sequence

Methyl N-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3(methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl} pyrimidin-2-yl)amino]propan-2-yl}carbamate

8.2.2 Other Names

LGX818 or ONO-7702

8.2.3 Classification

BRAF Inhibitor

8.2.4 CAS Registry Number

1269440-17-6

8.2.5 Molecular Formula

C22H27ClFN7O4S **M.W.:** 540.01

8.2.6 Approximate Solubility

8.2.7 Mode of Action

Encorafenib is a highly selective ATP-competitive small-molecule RAF kinase inhibitor which suppresses the RAF/MEK/ERK pathway in tumor cells expressing BRAF V600-mutant kinase.

8.2.8 Availability

Encorafenib is provided free of charge by Pfizer and distributed by McKesson Specialty Pharmacy, LP.

Initial Drug Orders for Each Patient

Once a patient has been registered on this study, a supply of Encorafenib may be ordered. Investigators must email a completed EA6183 Encorafenib Study Drug Request Form to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org. A copy of the EA6183

Encorafenib Study Drug Request Forms available for download from the CTSU website (www.ctsu.org).

Please refer to Appendix VII for the EA6183 Encorafenib Study Drug Request Form download instructions.

Encorafenib will be shipped to a responsible person (e.g., a pharmacist) at the investigator's institution. **Sites should order enough study drug for 2 cycles of treatment.**

Institutions should allow up to 4 business days to receive drug onsite. McKesson Specialty Pharmacy, LP will ship and arrange drug deliveries to sites on business days only; there will be no weekend or holiday delivery of drugs.

IMPORTANT REORDER INSTRUCTIONS

Once it is determined that the patient will continue treatment, please reorder 2 cycles of study drug immediately by emailing a completed EA6183 Encorafenib Study Drug Request Form to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org.

Institutions should allow up to 4 business days to receive drug onsite. McKesson Specialty Pharmacy, LP will ship and arrange drug deliveries to sites on business days only; there will be no weekend or holiday delivery of drugs.

Drug Destruction and Return

At the completion of each patient's treatment at your institution, all unused drugs, partially used, or empty containers must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

Drug Inventory Records

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

8.2.9 Storage

Encorafenib capsules should be stored according to the conditions specified on the drug product package labels.

All deviations from the required storage condition of IMP provided by Pfizer, whether the deviation occur in-transit or on-site, need to be reported to Pfizer for evaluation of the impact the event may have to the usability of the IMP.

Please report temperature deviation events to the Pfizer Clinical Supply team using the following email address: GCSTempExcursionSupport@pfizer.com

8.2.10 Route and Method of Administration

Encorafenib capsules are intended for oral administration with water; capsules should be swallowed whole and should not be chewed.

Encorafenib may be taken without regard to food. The administration of encorafenib without regard to food is supported by a formal food-effect study.

8.2.11 Formulation and Presentation

The encorafenib drug product is supplied as a capsule formulation in dosage strengths of 75 mg. The dosage forms for each strength have identical formulations which are packaged in different colored capsules:

75 mg capsule (FMI): Size #00 hard gelatin capsules; flesh opaque cap and white opaque body, with the markings “NVR” or stylized “A” on the cap and “LGX 75mg” on body.

Encorafenib drug substance and the following excipients: copovidone, poloxamer 188, succinic acid, microcrystalline cellulose, colloid silicon dioxide, crospovidone, and magnesium stearate of vegetable origin. The capsule shell is commercially available and contains gelatin, titanium dioxide and iron oxide red, yellow and black depending on particular strength.

8.2.12 Potential Drug Interactions

Formal PD drug interaction studies in nonclinical cancer models have not been performed.

Clinical Study ARRAY-162-105 investigated the PK of encorafenib in the presence of the proton-pump inhibitor rabeprazole in 15 healthy subjects. Co-administration of 4 consecutive days of rabeprazole 20 mg QD resulted in no effect on the total exposure (i.e., AUCinf) of single-dose encorafenib 100 mg due to higher gastric pH, indicating that no dose adjustments are required for patients being treated with gastric pH modifying agents or for patients with achlorhydria. Furthermore, the results indicate that encorafenib can be taken without regard to co-administration of proton pump inhibitors, antacids or H2 antagonists.

Clinical Study ARRAY-818-105 investigated the effect of both CYP3A and P-gp transporter inhibitors on encorafenib exposure in 32 healthy subjects as encorafenib is a substrate of both CYP3A and P-gp. Administration of posaconazole 400 mg (a strong CYP3A inhibitor) with encorafenib 50 mg increased overall encorafenib exposure (i.e., AUC) by approximately 3fold. Administration of diltiazem 240 mg (a moderate CYP3A inhibitor and P-gp transporter inhibitor) with encorafenib 50 mg increased overall encorafenib exposure by approximately 2-fold. The Tmax values were similar for both treatments in each part of the study, suggesting the observed DDIs were not due to differences in absorption rates, but were mechanistically due to inhibition of CYP3A metabolism. Although the contribution of P-gp transporter inhibition by posaconazole and diltiazem is difficult to assess with the results of this study, the intent

was to investigate dual inhibition of CYP3A and P-gp transporter inhibition.

8.2.13 Side Effects

Reasonably foreseeable side effects and risks of the study

8.2.13.1 Side Effects of Encorafenib:

Encorafenib is an investigational drug and not all of the side effects are known. Serious side effects, including death, are a possibility. The long-term effects of encorafenib are also unknown.

Side effects in cancer patients treated with encorafenib may include those described below.

Most likely side effects (greater than 20%):

- Dry skin
- Feeling tired
- Hair loss
- Itching
- Muscle pain or joint pain
- Nausea
- Reddening, swelling, numbness and peeling on palms and soles (hand foot skin reaction)
- Skin rash including redness, itching, hives and raised areas of skin
- Thickening of external part of the skin
- Tingling, numbness or abnormal sensitivity to pain or touch and nerve pain

Less likely side effects (greater than 10% up to 20%):

- Decreased appetite
- Difficulty sleeping
- Increase in blood test results that check how well the liver is working
- Pain including pain in the arms and legs and back pain
- Skin tags, new moles on the skin or changes in existing moles
- Small, rough bumps on the skin
- Vomiting
- Weakness

Side effects that occurred at a lower rate (1% up to 10%):

- Abdominal pain
- Change in how food tastes or change in ability to taste
- Constipation
- Feeling that you are dizzily turning around

- Fever
- High blood sugar
- Inflammation of the eye causing eye discomfort, redness and sensitivity to light
- Increase in a blood test result that checks how well your kidneys are working
- Low red blood cell count
- Muscle weakness and spasms
- New skin growths, including skin cancer
- Weakness of facial muscles or loss of facial movement

Rare but important serious side effects seen in patients receiving encorafenib (less than 1%):

- Inflammation (swelling) of the pancreas causing pain in the stomach that may also be felt in the back, and may be associated with nausea or vomiting. The symptoms can be mild and may go away without treatment, but in some cases can be more severe, needing treatment.
- In addition, there may be a rare side effect of changes in the electrical activity of your heart called QT prolongation. QT prolongation can cause irregular heartbeats that can be life-threatening. Associated symptoms might include shortness of breath, fast or slow heartbeat and lightheadedness or fainting.

8.2.13.2 Side Effects of Encorafenib When Used in Combination with Binimetinib:

Side effects in cancer patients treated with encorafenib in combination with binimetinib may also include those described below.

Most likely side effects (greater than 20%):

- Alteration of the light sensing part of the back of the eye that may affect your vision.
- Increase in a lab test result for creatine phosphokinase (an enzyme found in the blood) that may indicate muscle inflammation or damage.

Less likely side effects (greater than 10% up to 20%):

- Swelling of or damage to the light sensing part of the eye or impaired vision.

Side effects that occurred at a lower rate (1% up to 10%):

- Decrease in a test of the heart’s ability to pump blood (decreased ejection fraction or left ventricular dysfunction)
- Dizziness
- High blood pressure

- Inflammation in the intestine that may cause pain, spasms, diarrhea or bleeding
- Reduction in the kidney's ability to filter wastes

Rare but important serious side effects seen in patients receiving encorafenib when used in combination with binimetinib (less than 1%):

- Bleeding in the stomach, intestines or rectum
- Blood clots in the lungs

Refer to Section 5.6 for dose modification instructions.

8.2.14 Nursing/ Patient Care Implications

Encorafenib capsules should be swallowed whole with water and should not be chewed. Encorafenib capsules may also be opened and the powder mixed with sweetened applesauce. The soft food preparation should be administered orally with water. Encorafenib may be taken without regard to food.

Patients receiving encorafenib should be monitored for skin toxicities include hand food syndrome/palmar plantar erythrodysethesia. Educate the patient on lifestyle modifications to prevent and manage PPE such as avoiding hot water and sources of heat, applying cool compresses to hands and feet, and avoiding activities that may cause friction. Topical remedies may also be recommended.

Monitor patient for anemia:

The majority of toxicities are generally reversible and manageable by appropriate supportive medical care and/or dose modifications or discontinuation. Educate the patient to promptly report side effects so that early supportive care interventions may be initiated.

8.2.15 Concomitant Medications

Encorafenib is a reversible inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP3A4 and UGT1A1. It is also a time-dependent inhibitor of CYP3A4, and induced CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP1A2, CYP2B6, CYP2C9, CYP2C9, CYP3A4, and UGT1A1 or those substrates that have a narrow therapeutic index.

There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least 1 form of non-hormonal contraception is required for females of childbearing potential during participation in this study. Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib.

Encorafenib has been identified in vitro to be metabolized by CYP3A4 and to a lesser extent by CYP2C19. The use of strong inhibitors of CYP3A4 is prohibited. Concomitant use of moderate CYP3A4

inhibitors while on study should be avoided. If use of moderate CYP3A4 inhibitors is unavoidable and no alternatives are available, short-term use (≤ 30 days) is permitted with accompanying dose reduction to one-half of the encorafenib dose prior to use of moderate CYP3A4 inhibitors (or as close as can be achieved without exceeding the target dose). The encorafenib dose that was taken prior to initiating the CYP3A4 inhibitor may be resumed after the inhibitor has been discontinued for 3 to 5 elimination half-lives. Strong inhibitors of CYP2C19 should be used with caution when co-administered with encorafenib. Use of moderate and strong inducers of CYP3A4 is prohibited.

In vitro data showed that encorafenib is a substrate of the transporter P-gp. Thus, drugs that are known to inhibit or induce P-gp should be used with caution. Encorafenib is also a potent inhibitor of the renal transporters, OAT1, OAT3 and OCT2, and the hepatic transporters OATP1B1 and OATP1B3. The co-administration of drugs that are known to be sensitive or narrow therapeutic index substrates of OAT1, OAT3, OCT2, OATP1B1 or OATP1B3 should be used with caution.

Prohibited Concomitant Therapy

Concomitant strong systemic CYP3A4 inhibitors and strong or moderate systemic CYP3A4 inducers are likely to significantly increase or decrease encorafenib exposure, respectively, and thus should not be used during this study.

See Appendix X

8.2.16 Patient Care Implications

- Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation.
- Dermatologic evaluations should be performed by the investigator predose and every 8 weeks on protocol and for up to 6 months following discontinuation of encorafenib treatment, to monitor for the possible development of keratoacanthoma (KA) and/or squamous cell carcinoma (SCC), as these have been reported to occur with selective BRAF inhibitor treatment. In case of occurrence of KA or SCC, patients will undergo complete surgical excision of the skin lesion following institutional standards. Dermatologic evaluations should be performed by a dermatologist as clinically indicated.

8.2.17 Lifestyle Considerations

Meals and Dietary Restriction

Patients must avoid consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study

drugs, due to potential CYP3A4 interaction with encorafenib. Orange juice is allowed.

Activity

Strenuous physical activities, such as competitive sports, can result in significant increases in CK levels while on binimetinib.

8.3 ^{18}F-FLT

For complete information, please refer to the Investigator's Brochure:

"3'-deoxy-3'-F [18] fluorothymidine: [F-18]FLT, An Investigational Positron Emission Tomography (PET) Radiopharmaceutical for Injection intended for use as an *in vivo* diagnostic for imaging active cellular proliferation of malignant tumors", Edition Number 9, Edition date August 27, 2014.

8.3.1 Other Names

3'-deoxy-3'- ^{18}F fluorothymidine, ^{18}F-FLT, FLT

8.3.2 Classification

Investigational new drug: Radiopharmaceutical/radiotracer

8.3.3 Mode of Action

The pharmacology of FLT as a therapeutic agent is based on its action as an inhibitor of DNA synthesis. As a diagnostic imaging agent, phosphorylation by thymidine kinase leads to tracer retention in proliferating tissue.

8.3.4 Storage and Stability

In accordance with regulations, the radioisotope vendor conducts several quality control tests on the FLT product prior to release for human administration. Once delivered to the participating institution, doses will be stored in the appropriate storage area in the nuclear medicine facility until they are administered to the patient.

The drug solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial and has an expiration time of 8 hours.

Rev Add2

All manufacturing sites that are delivering to other sites must have in place the minimum requirements outlined in Appendix XII before shipping ^{18}F-FLT to another site. Receiving sites must also abide to what is outlined in Appendix XII.

8.3.5 Dose Specifics

The administered activity will be 0.07 mCi/kg with a maximum of 5 mCi. The amount of injected drug is ≤ 6.1 µg (≤ 25 nmol per dose) of FLT.

8.3.6 Preparation

The injectable activity of FLT for most studies will be ≤ 0.07 mCi/kg of fluorine-18, not to exceed 5 mCi with a specific activity greater than 200 Ci/mmol at the time of injection. In the dose of FLT, only a small fraction of the FLT molecules are radioactive.

8.3.7 Route of Administration

FLT is administered to subjects by intravenous injection. There is no evidence that nonradioactive and radioactive FLT molecules display different biochemical behavior.

8.3.8 Incompatibilities

N/A

8.3.9 Availability

Rev Add2

8.3.9.1 Drug Ordering

^{18}F-FLT will be supplied by approved manufacturing sites under the ECOG-ACRIN IND. The manufacturing site (supplier) and receiving site including site personnel must meet all requirements and training qualifications as outlined in Sections 4.3.3 & 4.3.4. A list of approved manufacturing sites can be found on the CTSU website, on the EA6183 protocol page under the “Miscellaneous” tab.

For those sites designated as on-site manufacturing, [F-18] FLT chemistry manufacturing and control procedures must be filed with and approved by ECOG-ACRIN IND. For additional information about on-site manufacturing, contact Diana Ewen at dewen@acr.org.

The ordering of ^{18}F-FLT should be done with a written order from the responsible authorized user, and administration of ^{18}F-FLT should be performed by the authorized user or a qualified staff member under the authorized user's supervision (e.g. nuclear medicine technologist). Institutions should follow institutional practice for the injection of investigational radiopharmaceuticals.

All approved manufacturing sites may only deliver to another site if delivery of tracer is completed within the stability time limit. Manufacturing sites may release the ^{18}F-FLT to a commercial radiopharmacy shipper once it passes all quality control testing (excluding sterility).

8.3.9.2 Drug Returns

If for any reason the study imaging is unable to be completed, sites will allow the radioactivity of the FLT solution to decay and then discard it appropriately per site’s policies and procedures. A copy of the policy should be available upon request.

8.3.9.3 Drug Accountability

The investigator or the investigator-designee must maintain a detailed record of receipt, disposition, and destruction dates of FLT solution, using the Drug Accountability Record form available through CTSU.

In accordance with regulations, the radioisotope vendor conducts several quality control tests on the FLT product

prior to release for human administration. Once delivered to the participating institution, doses will be stored in the appropriate storage area in the nuclear medicine facility until they are administered to the patient.

https://ctep.cancer.gov/forms/docs/agent_accountability.pdf

8.3.10 Side Effects

There is a chance of a rare but serious allergic reaction to the FLT.

8.3.11 Nursing/Patient Implications

Standard safety precautions required when handling radioactive materials, predominantly during the injection and uptake period should be followed. FLT requirements are similar to those used for other PET tracers, such as FDG.

9. Statistical Considerations

9.1 Study Design and Objectives

In this phase II study, patients with resectable locoregional metastases from cutaneous or unknown primary melanoma (Stages III N1B/C/D) will be enrolled. The primary objective is to evaluate the pCR rate for the neoadjuvant combination of encorafenib and binimetinib. It is hypothesized that this combination of treatment will yield at least 57% pCR rate. Simon's two-stage design will be used, enrolling with up to 42 patients (for 39 evaluable).

Evaluable patients are defined as eligible patients (per Section 3) who receive at least one dose of neoadjuvant therapy with encorafenib and binimetinib and are resectable at enrollment. The likelihood of progression, delay in resection or failure to proceed to surgery during the neoadjuvant period is expected to be very low. Therefore, we expect at least 39 out of 42 patients will be evaluable.

All patients who receive at least one dose of neoadjuvant therapy will be included in the 15 patient-cohort that will trigger the interim analysis.

Secondary clinical endpoints include: i) to evaluate clinical response rate (RR), DFS, OS, ii) to assess correlation of pCR with RR, DFS, OS, iii) to assess safety and toxicity iv) to evaluate CD8+ T cell infiltration in tumor or tumor bed pre, during and post neoadjuvant treatment and the change in CD8+ TIL with neoadjuvant treatment and correlate with clinical response, and v) to compare local review for pathologic response with central pathology review. Secondary imaging endpoints are addressed in Section 9.7.

9.2 Study Endpoints

Of the 42 patients accrued, we expect at least 39 patients will be evaluable. The main analysis for clinical endpoints will be based on 39 evaluable patients. Based on prior studies, it is not expected that there will be significant issues with disease progression or severe toxicities that interfere with planned surgical resection.

A pCR will be defined as the absence of residual viable melanoma in the resected metastasis site as assessed on local pathology review.

Overall Survival (OS) will be defined as the time from enrollment to death from any cause. Patients who have not died will be censored at the date last known to be alive. Disease-Free Survival (DFS) will be defined as the time from complete surgical resection to disease progression or death (whichever occurs first). Patients who are not eligible for resection will not be included in this analysis. Cases who have not had an event will be censored at the date of last disease assessment documenting the patient was free of progression. Progression will be evaluated based on international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) as described in Section 6. Response will be defined by the RECIST guidelines (version 1.1) as described in Section 6. Toxicity will be defined using the CTCAE.

Ki-67 IHC in tumor cells will be graded as a percentage of total number of tumor cells with nuclear staining (to the nearest 10%) over 10 high powered fields (at 20X magnification).

9.3 Sample Size Considerations and Monitoring Plan

A Simon's optimal two-stage design will be used to allow for an interim analysis for futility. Accrual will be held during the interim analysis. Fifteen (for 14 evaluable) subjects will be enrolled and pCR will be assessed. If 5 or fewer subjects achieve a pCR, the trial will be stopped for futility. If greater than 5 subjects achieve a pCR, then the trial will enroll an additional 27 (for 25 evaluable) patients. If 18 or more subjects out of 39 total evaluable subjects achieve a pCR the study will be considered 'positive'. The study was designed to evaluate the pCR rate improving from 33% to 57%. This design provides 87% power with approximately one-sided type I error rate of 0.05 for the primary endpoint.

The hypothesis states that encorafenib with binimetinib will yield a pCR rate of 57%. The baseline pCR rate of 33% was estimated from published values as summarized in Table 1 in Section 1 and is thus the null pCR rate.

We anticipate an average accrual of 1-3 patients per month. The first stage analysis will occur when the first 15 patients have a pCR assessed. Under the null pCR rate of 33%, there is 70% chance of stopping the study after the first stage evaluation. Adverse events will be closely monitored during the study.

Interim safety analyses based on the first 15 patients will evaluate:

- Proportion of patients who develop progressive disease per RECIST 1.1 before surgery but proceed with surgical resection
- Proportion of patients who develop progressive disease per RECIST 1.1 before surgery and are unresectable
- Proportion of patients who develop toxicities that delay or prohibit surgery
- Surgical complications as defined by the operating surgeon as being related to surgery or oral therapy, at any point during follow up

We anticipate that the proportion of patients who experience any of the event listed in i) -iv) will be less than 15%. If at least one patient (out of 15 patients) experiences any of the event listed in i) - iv), the proposed treatment will be considered unsafe and the result will be discussed with the ECOG-ACRIN DSMC. The probability of observing at least one patient with the event in i) ii), iii) or iv) is 0.794 if the true event rate is 10% and is 0.913 if the true event rate is 15%.

9.4 Secondary Lab Endpoints

CD8+ T cell infiltration:

Given the expected 57% pCR rates, there will be at least 13 responders and 10 non - responders among cases with samples. If the standardized change ((mean value for post-treatment samples – mean value for pre-treatment samples)/sd) is at least 1.1 for responders vs. non-responders, there will be at least 81% power for this comparison. If the post-treatment samples are not available, during-treatment samples will be used. This is based on the two-sample t-test using two-sided type I error rate of 0.1. If normality assumption is not appropriate, Wilcoxon rank sum test will be used during the analysis. Using the median change value, cases will be divided to high and low change groups.

9.5 Statistical Analysis Plan

Efficacy endpoints will be analyzed in evaluable patients (as defined in Section 9.1. The primary endpoint of pCR rate will be estimated and 90% CI adjusting for the first stage analysis will be provided. OS and DFS distributions will be estimated using the Kaplan-Meier method. Median OS and DFS will be described with 95% confidence intervals. Clinical response rate (RR) (per RECIST 1.1) will be estimated with 95% confidence interval. Clinical data from unevaluable patients will be summarized separately.

Safety analyses will be conducted on all patients who received at least one dose of trial therapy (i.e., treated patients). Adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All treatment-emergent and baseline adverse events and hematological/biochemical toxicities based on laboratory measurements, as well as drug related AEs, will be summarized by NCI CTCAE v. 5.0 worst grade. The incidence of deaths and treatment-emergent serious adverse events (defined as number of patients experiencing the AE divided by all treated patients) will be summarized. Also, the incidence of adverse events leading to discontinuation of investigational product and/or withdrawal from the study will be summarized and listed. Changes in the CD8 T cell infiltration in tumor or tumor bed pre-, during and post- neoadjuvant treatment will be assessed and summarized using the descriptive statistics. The change in CD8+ TIL between pre-and post-treatment will be compared among patients achieving a pCR vs. no pCR using the Wilcoxon rank sum test. The concordance of pCR assessed based on local review vs. central pathology review will be evaluated. Kendall's Tau test will be used for this comparison.

In the event of missing data, it will be assumed that the data will be missing at random and no imputation will be performed.

9.6 Gender and Ethnicity

Based on previous data from E1609, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	0	0
Not Hispanic or Latino	15	27	42
Ethnic Category: Total of all subjects	**15**	**27**	**42**

Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	15	27	42
Racial Category: Total of all subjects	**15**	**27**	**42**

9.7 Imaging Statistical Considerations

9.7.1 3'deoxy-3'-(18)F-fluorothymidine (^{18}F-FLT) PET/CT

^{18}F-FLT is a tracer used in PET imaging that measures cellular proliferation in an S-phase-dependent manner. ^{18}F-FLT PET/CT has been explored in several malignancies, within the first several weeks of treatment, in an effort to predict early response or resistance to therapy. However, in vivo data investigating a role for ^{18}F-FLT PET/CT in either melanoma, or more generally with MEK or BRAF inhibitor therapy, are sparse. We propose to study the utility of ^{18}F-FLT PET/CT as an imaging biomarker to guide BRAF/MEK targeted neoadjuvant therapy in melanoma. Demonstrating a significant difference in change in ^{18}F-FLT PET/CT uptake between patients with and without a pathologic complete response after neoadjuvant therapy, as well as providing data on the diagnostic performance of ^{18}F-FLT PET/CT uptake in predicting pCR, would yield valuable data toward this end. In addition, demonstrating correlation between the change in ^{18}F-FLT PET/CT and the change in Ki-67 immunostaining in tumor cells may provide evidence that ^{18}F-FLT PET/CT is a true imaging measure of proliferation.

9.7.2 Imaging Schedule

All registered subjects are expected to undergo ^{18}F-FLT PET/CT at the following time points:

- **Baseline FLT-PET/CT:** If the baseline biopsy is done on-study and after registration, then the baseline FLT-PET/CT scan must be performed prior to the baseline biopsy (same day acceptable). The FLT scan needs to be completed within 2 weeks prior to the start of the study-mandated neoadjuvant therapy. If the baseline biopsy of nodal/in transit melanoma was done prior to study enrollment (can be up to 2 months prior), then the baseline FLT-PET/CT scan must be performed within 2 weeks prior to the start of the study-mandated neoadjuvant therapy.
    - **Post Neo-adjuvant Imaging:** A FLT-PET/CT scan will be completed after 8 weeks of neoadjuvant therapy and before surgery. **Note**: All neoadjuvant study treatment should be completed prior to post-treatment imaging. **Refer to section 5.3.4 for more details on scan timing.**

Both ^{18}F-FLT imaging time points must be scanned on the same qualified PET/CT scanner with imaging technique and parameters to be as close as possible to that of the baseline scan.

NOTE: Institutions getting FLT from outside suppliers should allow time for arranging delivery of FLT.

All ^{18}F-FLT PET/CT images are to be submitted centrally to ECOG-ACRIN via TRIAD as outlined in Section 4.3.6.

It is not expected that the required needle biopsies will have a significant effect upon the ^{18}F-FLT PET/CT scans. However, the baseline ^{18}F-FLT PET/CT will be scanned prior to the baseline biopsy,

even if on the same day, to avoid any confounding. The next scheduled biopsy is 2 weeks after initiation of neoadjuvant treatment. The post-neoadjuvant ^{18}F-FLT PET/CT will take place 5-7 weeks after this interim biopsy, and thus is unlikely to be impacted.

9.7.3 Imaging Aims and Statistics

There are four imaging aims, which are secondary to the main trial. All imaging aims will be based on data derived from central review of the acquired ^{18}F-FLT PET/CT scans, and are distinguished into primary and secondary.

9.7.3.1 Primary imaging aim

To compare the change in ^{18}F-FLT PET/CT uptake (from baseline to post-neoadjuvant therapy) among patients with and without pathologic complete response.

The primary imaging aim consists of evaluating whether the anticipated decrease in ^{18}F-FLT PET/CT uptake from the baseline scan to the post-neoadjuvant scan will be greater in pCR versus non-pCR subsets, among patients with clinically resectable or radiographically-detected stage IIIB/C/D melanoma being treated with the neoadjuvant combination of encorafenib (a selective BRAF inhibitor) and binimetinib (a MEK inhibitor).

Distributional summaries of the continuous percent change in ^{18}F-FLT PET/CT SUVmax will be reported, where percent change is defined as (baseline SUVmax – post-neoadjuvant SUVmax)/(baseline SUVmax)*100%. The comparison of percent change in SUVmax between pCR and non-pCR patients will be performed using a one-sided nonparametric Wilcoxon rank sum test with an alpha level of 0.05.

Of the 42 accrued patients, we assume that 34 (81%) will have interpretable ^{18}F-FLT PET/CT scans at both time points. The mean percentage decrease in SUVmax for non-pCR versus pCR is assumed to be 30% and 50%, respectively, and the standard deviation is assumed to be 20% for both groups. Given that melanoma is expected, on average, to be more proliferative than the breast cancers studied in ACRIN 6688, positing an expected 20% difference in mean percentage decrease in uptake seems justified (55). With a pCR rate of 57%, a sample size of 34 analyzable cases will yield 86% power with a one-sided type I error rate of 0.05 based on the Mann-Whitney Wilcoxon test using Monte Carlo simulation (n=100,000) from appropriate null and alternative normal distributions (PASS 2019); however, the power of this comparison varies depending on the pCR rate. For example, it is 84% with a pCR rate as low as 35%, and 83% with a pCR rate as high as 65%.

For the sake of completeness, we will also report distributional summaries and comparisons for percent change in ^{18}F-FLT PET/CT SUVpeak; however, the prespecified primary comparison will be based on ^{18}F-FLT PET/CT SUVmax.

9.7.3.2 Secondary imaging aims

Secondary imaging aim #1: To compare post-neoadjuvant ^{18}F-FLT PET/CT uptake among patients with and without pathologic complete response.

This secondary imaging aim will be analyzed in a similar manner to the primary imaging aim, but using post-neoadjuvant ^{18}F-FLT PET/CT SUVmax, as opposed to percent change ^{18}F-FLT PET/CT SUVmax.

Again, for completeness, we will also report distributional summaries and comparisons for post-neoadjuvant ^{18}F-FLT PET/CT SUVpeak.

Secondary imaging aim #2: To estimate an optimal threshold for prediction of pathologic complete response using i. change in ^{18}F-FLT PET/CT uptake, and ii. post-neoadjuvant ^{18}F-FLT PET/CT uptake.

This secondary imaging aim consists of evaluating the diagnostic performance of ^{18}F-FLT PET/CT uptake as a marker of pathologic complete response (pCR), and of estimating the optimal threshold (binary cutpoint) and associated sensitivity/specificity.

Diagnostic performance of percent change in ^{18}F-FLT PET/CT SUVmax (from the baseline scan to the post-neoadjuvant scan) as a marker for pCR status will be assessed using receiver operating characteristic curve (ROC) analysis. In particular, the empirical area under the receiver operating characteristic curve (ROC AUC) will be reported, along with corresponding 95% confidence interval. In addition, we will formally test if the ROC AUC exceeds 0.5 using a one-sided test as suggested by DeLong et al (56) with an alpha level of 0.05. Finally, the optimal threshold (binary cutpoint) of continuous percent change in SUVmax will be estimated by means of the Youden index (57). In order to properly reflect sampling variability, a 95% confidence interval for the optimal threshold will be estimated using the bootstrap technique (58).

The corresponding performance of the optimal threshold (measured via sensitivity and specificity) will be estimated using cross-validation. In particular, we will randomly divide the cohort into 5 folds. Using 4 folds, the ROC curve will be fit and optimal threshold (Youden index) obtained. This threshold derived from the 4 folds will then be applied to the subjects in the remaining holdout fold, in order to

define each holdout subject as test positive (> threshold) vs. test negative (≤ threshold). This step will be repeated until every subject has been a holdout and has test result (positive/negative) defined. Sensitivity and specificity will then be calculated and reported, using the test result for each subject defined during holdout.

The proposed sample size of 42 patients (34 analyzable), assuming a pCR rate of 57%, yields a minimum of 81% power to reject the null hypothesis of an uninformative marker (ROC AUC=0.5) based on a one-sided test with type I error rate of 0.05, assuming the true ROC AUC is 0.74 or higher (PASS 2019).

In addition, estimates of diagnostic performance will be reported for percent change in ^{18}F-FLT PET/CT SUVpeak.

This analysis will be repeated separately for post-neoadjuvant ^{18}F-FLT PET/CT uptake.

Secondary imaging aim #3: To assess the correlation between change in ^{18}F-FLT PET/CT uptake and change in Ki-67.

This secondary imaging aim consists of assessing the correlation between the anticipated decrease in ^{18}F-FLT PET/CT (from the baseline scan to the post-neoadjuvant scan) and the change in tumor cell Ki-67 (from baseline to post-neoadjuvant therapy).

The correlation between percent change in continuous SUVmax and percent change in the continuous Ki67 score will be estimated using the Spearman correlation coefficient. A one-sided correlation test with null hypothesis of zero correlation will be conducted at alpha level of 0.05. The corresponding confidence interval for the estimated Spearman correlation coefficient will also be reported.

The proposed sample size of 42 patients (34 analyzable) yields a minimum of 83% power to detect a nonzero correlation, assuming that the true correlation is 0.5 or higher. A two-sided Spearman correlation test with a type I error rate of 0.05 was used for this computation based Monte Carlo simulation (n=100,000) from a bivariate normal distribution (PASS 2019).

Correlation between change in ^{18}F-FLT PET/CT and the early change in tumor cell Ki-67 (from baseline to the week 2 interim biopsy) will also be separately estimated; however, as the week 2 interim biopsy is not mandatory, we expect small numbers of subjects, and thus this analysis will be exploratory. The corresponding correlation with percent change in ^{18}F-FLT PET/CT SUVpeak will also be reported.

10. Specimen Submissions

Representative tumor tissue from the involved lymph node (not a primary melanoma) (block preferred) and related pathology reports from a procedure performed within two (2) months prior to the performance of imaging and from the surgical resection after eight (8) weeks of treatment must be submitted for central diagnostic review. Additional tumor tissue and peripheral blood specimens are to be collected and submitted per patient consent.

- Additional tumor tissue from the archived pre-trial biopsy and surgical biopsy
- Tumor tissue from research biopsies performed prior to start of treatment, if performed, and after two (2) weeks (+/- 1 week) off treatment
- Peripheral blood specimens for potential future research studies

All specimens must be clearly labeled with the ECOG-ACRIN protocol number [EA6183], the patient's initials and ECOG-ACRIN patient sequence number, the collection date, and specimen type. For pathology materials, it is strongly recommended that full patient names be provided.

It is required that all specimens submitted on this trial be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS) (Section 10.4). An STS shipping manifest form is to be included with every submission.

If you have any questions concerning tumor tissue and peripheral blood submissions or need information regarding potential alternative submission requirements, please contact the ECOG-ACRIN CBPF at (844) 744-2420 or eacbpf@mdanderson.org.

10.1 Submissions to ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

The submission of baseline diagnostic and surgical tumor tissue is required for central diagnostic review and pathologic response assessment. Additional tumor tissue from these procedures and from biopsies performed for research from patients who agree to participate in the laboratory research studies are also requested. Tumor tissue is to be submitted within one month of registration or collection.

The tumor tissue specimens are to be labeled with the institution's assigned pathology ID# as well as the information above. If only slides are submitted, slides are to be adequately labeled and numbered in the order sectioned from the block.

Submitting pathologist and clinical research associate may refer to Appendix I which outlines the Pathology Submission Guidelines.

10.1.1 Form Submission Requirements

The following **forms** must be submitted with all pathology submissions.

- STS generated shipping manifest form
- Copy of the institutional diagnostic and surgical pathology reports
- Immunological study reports, if available

10.1.2 MANDATORY Tumor Tissue Submissions

Representative formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks:

A. Baseline Diagnostic Tumor Tissue

Submit the following:

- all available tumor tissue blocks, OR
- two (2) representative unstained FFPE slides per block, OR
- one (1) representative H&E slide and one (1) representative unstained slide per block.

NOTE: If the patient has consented to undergo a research biopsy to obtain tumor tissue for laboratory research studies, material captured prior to start of treatment may be submitted as outlined below in leiu of archived FFPE. If a research biopsy from consenting patients is submitted for the mandatory baseline diagnostic submission, an FFPE block must be submitted.

B. Post Neo-adjuvant Surgical Resection Tumor Tissue

Submit the following from the surgically resected specimen:

- all available tumor tissue blocks, OR
- two (2) representative unstained FFPE slides per block, OR
- one (1) representative H&E slide and one (1) representative unstained slide per block.

NOTE: A three-dimensional macroscopic measurement of the largest grossly positive identified lymph node should be provided in the gross description accompanying the specimen. If the largest grossly positive lymph node measures < 5 cm in greatest dimension, then each grossly positive lymph node should be submitted entirely at 2 mm serially sectioned intervals. For any grossly positive lymph node measuring > 5 cm in greatest dimension, representative sections of the largest lymph nodes may be utilized to avoid oversampling. Following serial sectioning of each lymph node, for those nodes > 5 cm, sections representing a complete cross section of the entire surface area should be submitted per 1 cm of each grossly positive lymph node. Sections submitted should include grossly obvious tumor. All grossly positive lymph nodes < 5 cm in specimens (where the largest node(s) exceeds 5 cm) should be submitted entirely.

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10.1.3 Tumor Tissue Submissions per Patient Consent

10.1.3.1 Additional Baseline Archive and Surgical FFPE Tumor Tissue

If only slides are submitted for the mandatory central diagnostic review, additional tumor tissue is requested to be submitted for laboratory research studies from patients who answer "Yes" to "*My leftover tissue samples and related information may be kept in a Biobank for use in future health research" or "I agree to have my tissue samples collected from procedures performed as part of my standard of care and I agree that my tissue samples and related health information may be used for the laboratory research studies described above."*

- Twenty (20) 5 µm and five (5) 4 µm unstained, positively charged, air-dried plus slides from the thickest part of the tumor
- Also requested: One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420. Adequately label every slide and core submitted, with slides numbered sequentially in the order cut.

10.1.3.2 Research Biopsies

From patients who consent "Yes" to "*I agree to have one or two research biopsies to collect tissue for known laboratory research studies."*

Tumor tissue **blocks** from biopsies performed to obtain research specimens are to be submitted within one (1) month of the procedure. Biopsies are done only if they can be performed at minimal risk (no more than 2% risk of serious complication requiring hospitalization) and are requested at:

- Baseline, following step 1 registration prior to treatment. If a baseline biopsy is performed after study registration, the baseline FLT-PET/ CT scan should be completed prior to biopsy (can be done same day). This biopsy is requested only if there is no material available from a prior procedure performed within two (2) months of imaging.
- Two (2) weeks (+/- 1 week) post treatment.

Tumor tissue specimens will be obtained from the target lymph node metastasis, with or without image guidance. Types of biopsies are to include: 3-4 (1-2 cm in length), 14-16 or 18-gauge core biopsies, or small incisional biopsies (tumor biopsy at least 4-5 mm in diameter) such that the smallest dimension of the residual tumor after initial biopsy

would be at least 1cm. It is suggested that core biopsies be submitted separately into individual tissue blocks.

NOTE: Reimbursement guidelines for research biopsies are outlined in Appendix XI.

10.1.4 Shipping Procedures

Tumor tissue specimens are to be shipped overnight at ambient temperature within one (1) month following registration or collection. During warm months, it is strongly recommended that tumor tissue specimens be shipped with a cool pack to prevent the paraffin from melting.

Ship using the CBPF's FedEx account using the FedEx on-line ship manager.

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
1515 Holcombe Boulevard
Houston, TX 77030
Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

Access to the FedEx shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org.

An STS Shipping Manifest Form must be generated and shipped with all specimen submissions.

10.2 Peripheral Blood Submissions:

10.2.1 Submissions to the MD Anderson Cancer Center CBPF Life Science Plaza

Submit from patients who answer 'Yes' to *'I agree to provide additional blood samples for future health research.*'

Kits for the collection and shipment of the peripheral blood specimens are ordered online from Cenetron Central Laboratories. Instructions are provided in Appendix VIII. Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000. Kits must be ordered after the patient has been registered to the trial and will generally arrive within three (3) business days from when the order was placed.

10.2.2 Collection Schedule

Peripheral blood specimens are to be collected at the following time points:

- Prior to Start of Treatment
- After Two Weeks of Therapy
- After Eight Weeks of Therapy
- Weeks: 20, 32, 44, and End of Treatment

10.2.3 Sample Preparation Guidelines

Package and ship at ambient temperature. SST Red Top and Streck tubes may be packaged with cool packs during the hot season, but the Green Top Heparin tubes are to be shipped ambient only. If a cool pack is used, specimens must be packaged to protect them from freezing, otherwise just ship ambient.

1. Red Top SST Tubes
   - Draw two (2) 10mL red top SST tubes of whole blood at each time point.
2. Green Top Heparin Tubes
   - Draw ten (10) 10mL green top heparin tubes of whole blood at each time point.
3. Streck Cell-Free DNA Tubes
   - Draw one (1) 10mL Streck Cell-Free DNA BCT tube of whole blood at each time point. Fill each tube completely.
   - Ensure at least 10mL of blood is drawn in each tube. Avoid low volume to minimize agitation during shipping.
   - Immediately after collection, gently invert tube 180 degrees and back 10 times to ensure adequate mixing.
   - Maintain blood at room temperature (6ºC to 37ºC) until shipping. **Do Not** place tube in refrigerator.

10.2.4 Shipping Procedures

Peripheral blood specimens in SST Red Top and Streck tubes are to be shipped at ambient temperature day of collection Monday through Thursday via overnight courier.

The green top heparin tubes must be shipped the same day they are drawn because they must be processed the day after collection.

The laboratory is open Monday through Friday to receive specimens. Do not ship on Fridays or Saturdays, or the day before legal holidays. **Friday shipments are ill advised, similarly shipping before holidays is often problematic. The laboratory is closed Saturday, Sunday, and holidays.**

Ship using the CBPF's FedEx account using the FedEx on-line ship manager.

MD Anderson Cancer Center CBPF
Mike Balco

Life Science Plaza - Suite 910
2130 West Holcombe Boulevard, LSP9.4227
Houston, TX 77030

Access to the FedEx shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

An STS Shipping Manifest Form must be generated and shipped with all specimen submissions.

10.3 Central Laboratory: Processing and Routing

Pathology materials will be distributed to investigators for central pathology review and defined laboratory research studies described in Section 11.

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA.

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the currently defined research studies, will be retained in an ECOG-ACRIN designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility. Specimens will be de–identified prior to distribution for any approved research projects.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

10.4 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). As of June 2007, the software will allow the use of either 1) an ECOG-ACRIN username and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated Shipping Manifest must be generated and shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Study Specific Notes

Generic Specimen Submission Form (#2981v3) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

Retroactively enter all specimen collection and shipping information when STS is available.

10.5 Sample Inventory Submission Guidelines

Inventories of all specimens submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Specimen Analyses: Diagnostic Review and Research Studies

11.1 Central Diagnostic Review

The baseline diagnostic and surgical resection tumor tissue is required for central diagnostic review to determine patient evaluability for the trial and for central pathologic response assessments.

11.2 Ki67 and CD8+ infiltration

CD8 and Ki67 assays including staining, digital imaging and image analysis will be performed at MD Anderson Cancer Center and final result analysis will be performed under the direction of Dr. Ari Karunamurthy.

CD8 will be quantified as an H score as proposed and will include cytoplasmic and membranous staining. Focus will be placed on the tumor and peritumoral areas if needed and these areas of interest will be designated by the pathologist.

Ki67 nuclear staining is considered positive and not graded by staining intensity. The positively stained cells will be enumerated and the score will be generated by assessing both the total number and density of positive cells per square millimeter within the tumor/tumor bed area.

Ki-67 IHC in tumor cells will be graded as a percentage of total number of tumor cells with nuclear staining (to the nearest 10%) over 10 high powered fields (at 20X magnification).

Ki-67 alone can highlight any proliferating cell so this may overestimate the percent of proliferating cells. Focus will be placed on the on tumor cell rich areas as designated by pathologist.

Ki-67 IHC

Immunohistochemical studies will be performed on a Leica Bond autostainer, using the following antibodies: 3,3'-diaminobenzidine chromogen anti-Ki-67 (clone MIB-1; Dako, Carpinteria, CA; dilution 1:100).

CD8 IHC

Immunohistochemical studies will be performed on a Leica Bond autostainer, using the following antibodies 3,3'-diaminobenzidine chromogen anti-CD8 (Life Sciences Technologies MS457s; 1:25).

Image Analysis

Slides will be scanned at 20x magnification (Aperio Scanscope AT Turbo; Leica Biosystems). Image analysis software (Aperio ImageScope) measures the number of positive cells within designated areas. A Nuclear v9 algorithm is applied to determine Ki67 positivity. Also, given the relatively small size of immune cells, a modified version of the Nuclear v9 algorithm will be applied as a basis for CD8 immune marker positivity, with the intensity thresholds adjusted manually to remove background artifacts and to account for variable differences in cell size.

For each region of interest designated, the numbers of positive cells will be tabulated, and the total number of positive cells will be divided by the total area (mm^2) in which cells will be counted. The result will be reported as number of IHC+ cells/mm^2.

Specimens will be examined with a minimum of 4 quadrant sections of viable tumor to be submitted for pathological examination. The whole specimen will be evaluated and each slide divided into 4 quadrants. At 20x, intratumoral, peritumoral and perivascular mononuclear cell infiltrates will be enumerated, per published protocols [Tarhini,et al, PLOS One 9(2):1-8.

11.3 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the Investigator.

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12. Electronic Data Capture

Please refer to the EA6183 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

NOTE: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

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Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials
   (instructional sheet for Clinical Research Associates [CRAs])
2. List of Required Materials for EA6183
3. ECOG-ACRIN Generic Specimen Submission Form (#2981v3)

Guidelines for Submission of Pathology Materials

The following pathology materials are to be submitted within one (1) month of registration or collection. If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.

Adequate patient identifying information must be included with every submission to retain chain of custody. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, and will expedite any required communications with the institution (including site pathologists).

Pathology Submissions:

Mandatory:

- Representative formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks from the baseline diagnostic biopsy

  Submit the following:

  - all available tumor tissue blocks, OR
  - two (2) representative unstained FFPE slides per block, OR
  - one (1) representative H&E slide and one (1) representative unstained slide per block.

  NOTE: If the patient has consented to undergo a research biopsy to obtain tumor tissue for laboratory research studies, material captured prior to start of treatment may be submitted as outlined below in leiu of archived FFPE. If a research biopsy from consenting patients is submitted for the mandatory baseline diagnostic submission, an FFPE block must be submitted.

- Representative formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks from the surgical resection biopsy

  Submit the following:

  - all available tumor tissue blocks, OR
  - two (2) representative unstained FFPE slides per block, OR
  - one (1) representative H&E slide and one (1) representative unstained slide per block.

  NOTE: A three-dimensional macroscopic measurement of the largest grossly positive identified lymph node should be provided in the gross description accompanying the specimen. If the largest grossly positive lymph node measures < 5 cm in greatest dimension, then each grossly positive lymph node should be submitted entirely at 2 mm serially sectioned intervals. For any grossly positive lymph node measuring > 5 cm in greatest dimension, representative sections of the largest lymph nodes may be utilized to avoid oversampling. Following serial sectioning of each lymph node, for those nodes > 5 cm, sections representing a complete cross section of the entire surface area should be submitted per 1 cm of each grossly positive lymph node. Sections submitted should include grossly obvious tumor. All grossly positive lymph nodes < 5 cm in specimens (where the largest node(s) exceeds 5 cm) should be submitted entirely.

From Consenting Patients:

Research Biopsies

- Representative formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks from baseline following step 1 registration (prior to treatment) and two weeks post treatment biopsy.

NOTE: This baseline research biopsy is requested only if there is no material available from a prior procedure performed within two (2) months of imaging.

Biopsies to obtain specimens for research must be determined to be minimal risk prior to performance. Tumor tissue specimens are to be obtained from the target lymph node metastases, with or without image guidance. Types of biopsies are to include: 3-4 (1-2 cm in length), 14-16 or 18-gauge core biopsies, or small incisional biopsies (tumor biopsy at least 4-5 mm in diameter) such that the smallest dimension of the residual tumor after initial biopsy would be at least 1 cm [minimal size of single tumor is at least 2 cm in smallest dimension]. It is suggested that core biopsies be submitted separately into individual tissue blocks.

NOTE: Reimbursement guidelines for research biopsies are outlined in Appendix XI.

Forms and Reports:

The following items are to be included with the pathology materials:

- Institutional Diagnostic and Surgical Pathology Report
- ECOG-ACRIN Generic Specimen Submission Form (#2981v3) [if STS is unavailable]
- Sample Tracking System (STS) Shipping Manifest Form
- Immunological study reports, if available

Mail pathology materials to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
1515 Holcombe Boulevard
Houston, TX 77030
Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions, contact the pathology coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone: (844) 744-2420 or email: eacbpf@mdanderson.org

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: **Submission of Pathology Materials for EA6183**: A Phase II Neoadjuvant Study of Encorafenib with Binimetinib in Patients with Resectable Locoregional Metastases from Cutaneous or Unknown Primary Melanoma (Stages III N1B/C/D)

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for central pathology review and defined laboratory research studies.

Please return the diagnostic and surgical pathology reports, the slides and/or blocks and any other required materials to the Clinical Research Associate (CRA). The CRA will forward all required pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and/or slides submitted for this study will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility for undefined future research studies. Paraffin blocks will be returned upon written request for purposes of patient management.

NOTE: Since blocks are being used for laboratory research studies, in some cases the material may be depleted and, therefore, the block may not be returned.

If you have any questions regarding this request, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility at (844) 744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

A Phase II Neoadjuvant Study of Encorafenib With Binimetinib in Patients With Resectable Locoregional Metastases From Cutaneous or Unknown Primary Melanoma (Stages III N1B/C/D)

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Phase II Neoadjuvant Study of Encorafenib With Binimetinib in Patients With Resectable Locoregional Metastases From Cutaneous or Unknown Primary Melanoma (Stages III N1B/C/D)

Appendix III

Patient Pill Calendar

NOTE TO SITES: Local study teams may use a different calendar format as long as all drug/ dates/ doses are recorded for study reporting/ data completion. These should be shared with the Site Principal Investigator and approved by local IRBs per local guidelines, prior to use.

Pill Calendar Directions

1. Take your scheduled dose of each pill.
2. If you forget, the missed pills will not be taken later.
3. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.

Rev Add2

Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets you take each day for Encorafenib and Binimetinib. You should take your scheduled dose of each pill. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

Instructions:

Encorafenib: Take by mouth once daily

Pills should be swallowed whole and may be taken with or without food.

Dose of each pill: 75 mg

Number of pills to take at each dose: _____ capsules

Total dose to take each day: ____mg

Binimetinib: Take by mouth twice daily

Pills should be swallowed whole and may be taken with or without food.

Dose of each pill: 15 mg

Number of pills to take at each dose: ____ tablets

Total dose to take at each dose: ____mg

- Doses of Binimetinib that are missed should not be taken within 6 hours prior to the next scheduled dose.
- Doses of Encorafenib that are missed should not be taken within 12 hours prior to the next scheduled dose.
- If vomiting occurs after taking either medication, the dose should not be repeated

CYCLE DAY	**Date** (Month/ Day/ Year)			**Encorafenib** # Capsules	Time taken	**Binimetinib** # Tablets	Time Taken AM	Time Taken PM	**Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)**
1									
2									
3									
4									
5									
6									
7									
8									

CYCLE DAY	**Date** (Month/ Day/ Year)			**Encorafenib** # Capsules	**Encorafenib** Time taken	**Binimetinib** # Tablets	**Binimetinib** Time Taken AM	**Binimetinib** Time Taken PM	**Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)**
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
21									
22									
23									
24									
25									
26									
27									
28									
Signature of staff (End of cycle)									
Date									

A Phase II Neoadjuvant Study of Encorafenib With Binimetinib in Patients With Resectable Locoregional Metastases From Cutaneous or Unknown Primary Melanoma (Stages III N1B/C/D)

Appendix IV

ECOG Performance Status

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

A Phase II Neoadjuvant Study of Encorafenib With Binimetinib in Patients With Resectable Locoregional Metastases From Cutaneous or Unknown Primary Melanoma (Stages III N1B/C/D)

Appendix V

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on encorafenib and binimetinib or ^{18}F-FLT within 28 days of the female patient's last dose of encorafenib, binimetinib or ^{18}F-FLT must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy (including a positive or inconclusive pregnancy test) must be reported via CTEP's Adverse Event Reporting System (CTEP-AERs).
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERs report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERs report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERs report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.
- *It is recommended the female patient be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERs report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* and separate CTEP-AERs report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as "*A death in utero.*"

It must be reported via CTEP-AERS as a Grade 4 "*Pregnancy Loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A pregnancy loss should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A death occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to encorafenib, binimetinib or ^{18}F-FLT must also be reported via CTEP-AERS. It must be reported via CTEP-AERS as a Grade 4 "*Death neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

Additional Required Forms:

When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-897-7404). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

A Phase II Neoadjuvant Study of Encorafenib With Binimetinib in Patients With Resectable Locoregional Metastases From Cutaneous or Unknown Primary Melanoma (Stages III N1B/C/D)

Appendix VI

Contraception Guidance

Patients of Childbearing Potential

A patient is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Patients in the following categories are **not** considered of child-bearing potential

1. Premenarchal
2. Premenopausal patient with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

    NOTE: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal patient
    - A postmenopausal state is defined as no menses for 24 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in patients not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 24 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Patients on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

NOTE: There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least 1 form of non-hormonal contraception is required for patients of childbearing potential during participation in this study.

The contraception guidelines outlined below are adapted from the recommendations related to contraception and pregnancy testing in clinical trials guidance document (Clinical Trials Facilitation Group Guidelines 2014). Patients must agree to use highly effective methods of

contraception if it is mandated locally or when, in the judgment of the Investigator, compliance with acceptable methods is likely to be suboptimal.

The following methods have been classified as being highly effective (i.e., failure rate < 1% per year when used consistently and correctly) in preventing a pregnancy:

- Complete abstinence from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner (considered highly effective provided the vasectomized partner has received medical assessment of surgical success and that the partner is a female participant's sole sexual partner)

Acceptable birth control methods characterized as having a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

A Phase II Neoadjuvant Study of Encorafenib With Binimetinib in Patients With Resectable Locoregional Metastases From Cutaneous or Unknown Primary Melanoma (Stages III N1B/C/D)

Appendix VII

EA6183 Binimetinib and Encorafenib Study Drug Request Form Download Instructions

Downloading the EA6183 Binimetinib and Encorafenib Study Drug Request Form: The form is available for download from the EA6183 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the ECOG-ACRIN link to expand, then select trial protocol EA6183
- Click on Documents tab, select the Pharmacy tab, and download and complete the forms provided.

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Appendix VIII

EA6183 Collection and Shipping Kit Order Instructions

Specimen Collection/Shipping Kits are being provided by CENETRON CENTRAL LABORATORIES and are to be ordered ONLINE.

Starter kits are not available. Kit requests are to be made after patient registration.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000.

Ordering Process:

- Following registration of the patient to the trial, go to the website www.cenetron.com and click on the 'Order Kits' button at the top right. It is recommended that kits be ordered same day as patient registration.
- The order form is not study specific and can be used for any study. Complete the online form as follows:
  - Sponsor (REQUIRED): ECOG-ACRIN
  - Contact Name (REQUIRED): Name of the institution kit contact.
  - Protocol Number (REQUIRED): EA6183
  - Phone Number (REQUIRED): Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller
  - FAX Number: Fax number of the kit contact
  - Investigator: Last name of the kit contact is adequate
  - Email (REQUIRED): Email of the institution kit contact. Must be entered twice to confirm
  - Date Supplies Needed (REQUIRED): Add three (3) business days or more to order date. (Reminder that weekends and holidays must also be considered in this timeline)
  - KIT NAME (REQUIRED): Type in the kit type needed
    - EA6183 Collection Kit
  - Quantity: 1
  - Comments: Provide EA6183 Patient Case ID# and full shipping address
    - Patient Case ID =' #####
    - *'Ship Kit to'* name of the individual to whom the kit is being shipped. (May be different than the kit contact provided above)
    - Full street address, town, state and zip code
- Answer the security question

Please complete this form correctly, including the valid ECOG-ACRIN patient case number and complete shipping address. If information is missing the kit processing will be delayed.

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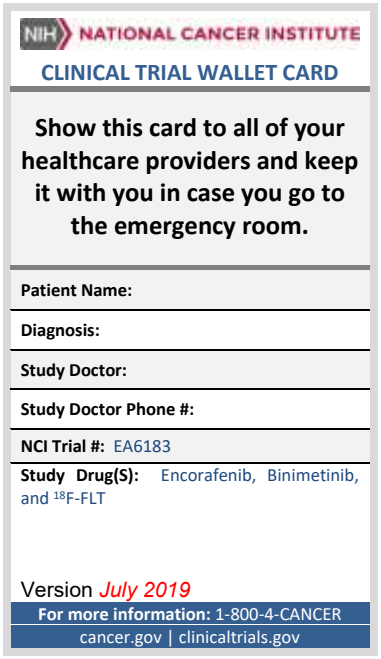
Appendix IX

Clinical Trial Wallet Card

Patients will be given a clinical trial wallet card. The wallet card is to inform other healthcare providers that the patient is participating in a clinical trial. The card also contains the investigator contact information and the investigational drug names. The sites are to complete the wallet card information before providing the Clinical Trial Wallet Card to study patient.



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: EA6183

Study Drug(S): Encorafenib, Binimetinib, and ^{18}F-FLT

Version *July 2019*

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

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Appendix X

CYP3A4 Inducers and Inhibitors

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as Facts and Comparisons or Lexicomp; medical reference texts such as the Physicians' Desk Reference may also provide this information. The Principal Investigator should be alerted if the subject is taking any agent on these lists.

List of moderate/ strong CYP3A4 Inducing Agents:

Carbamazepine
Dexamethasone
Ethosuximide
Glucocorticoids
Griseofulvin
Modafinil
Naficillin
Nelfinavir
Nevirapine
Oxcarbazepine
Phenobarbitol
Phenylbutazone
Enzalutamide
Mitotane
Bosentan
Phenytoin
Primidone
Progesterone
Rifabutin
Rifampin
Rifapentine
Rofecoxib
St. John's Wort
Sulfadimidine
Sulfinpyrazone
Tipranavir
Troglitazone
Etravirine
Efavirenz

List of strong CYP3A4 Inhibitors:

Amiodarone
Cimetidine
Ciprofloxacin
Clarithromycin
Delavirdine
Diethyl-dithiocarbamate
Diltiazem
Erythromycin
Fluconazole
Fluvoxamine
Gestodene
Grapefruit or Grapefruit juice
Indanvir
Itraconazole
Ketoconazole
Mibefradil
Boceprevir
Posaconazole
Cobicistat
Conivaptan
Mifepristone
Nefazodone
Nelfinavir
Norfloxacin
Norfluoxetine
Ritonavir (any ritonavir containing regimen)
Roxithromycin
Saquinavir
Troleandomycin
Voriconazole
Warfarin
Amprenavir
Atazanavir
Miconazole
Telithromycin
Verapamil
Idealisib
Telaprevir

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Appendix XI

Tumor Tissue Biopsy Reimbursement Instructions

Biopsies performed to obtain research specimens from patients who answer "Yes" to "*I agree to have one or two research biopsies to collect tissue for known laboratory research studies.*" at baseline and/or two (2) weeks after treatment are reimbursable at the following research rates per biopsy:

- Lymph Node Biopsy with CT Guidance = $1,743.42
- Lymph Node Biopsy with US Guidance = $1,550.20
- Skin Lesion Biopsy with US Guidance = $494.44

Biopsies that are performed as part of the patient's standard of care are not eligible for reimbursement.

All sites are eligible for the reimbursement for applicable biopsies regardless of cooperative group.

Prior to performing the research biopsies, the following conditions must be met:

a. The research rates outlined above are deemed acceptable by the institution's central research office. Costs above these reimbursement rates are not to be billed to the patient or patient's insurance.

b. The research rate is reported to the institution's financial office and an account established under the designated Investigator's name.

   Reminder that the site must set up the mechanism for the 'billing' of these research biopsies. ECOG-ACRIN recommends billing the cooperative group Principal Investigator (PI) of the site. Contact your coordinating group's operations office and ask to whom this account should be named

Expenses for biopsies will be paid only to participating institutions, not to any other persons or entities, at the above stated research rates.

Distribution of the reimbursements requires:

- Submission and receipt of the biopsies via the ECOG-ACRIN Sample Tracking System (STS)
- Completion and submission of the EA6183 Biopsy Reimbursement Form (Appendix XI, page 2) to the ECOG-ACRIN Operations Office - Boston.
- Supporting documentation, if requested.

EA6183 Biopsy Reimbursement Form

This form is to be used to request reimbursements for the performance and submission of the tumor tissue biopsies at baseline and two weeks post therapy as outlined in Section 12. Reimbursements are NOT applicable for biopsies performed as part of standard of care, and thus billed to patients or their insurance.

If you have questions about the reimbursement process, please contact the EA funding team at ea.fundingsheet@jimmy.harvard.edu.

Please fax the completed form to the ECOG-ACRIN Translational Science Team (TST), FAX: (617) 589-0914

Institution CTEP ID: _____

Name of Investigator: _____

NCI Investigator ID #: _____

Payee Address

Payee/W-9 Name: _____

Payee Tax ID #: _____

Attention To: _____

Street Address: _____

City, State, Zip: _____

Any Requested Reference on Payment (i.e. Invoice #): _____

	ECOG-ACRIN Case ID	Date of Service	Time point	Indicate Service Performed		Amount Requested
#1			Baseline		Lymph Node CT Guidance	$1743.42
					Lymph Node US Guidance	$1550.20
					Skin Lesion US Guidance	$494.44
#2			Week Two		Lymph Node CT Guidance	$1743.42
					Lymph Node US Guidance	$1550.20
					Skin Lesion US Guidance	$494.44

I confirm that these patients are registered to the protocol referenced above, the patient numbers and procedure dates are correct, and the biopsies were performed for the purposes of the trial only, following registration of the patient to the lowest step of the trial, and that the biopsy was NOT standard of care and was NOT billed to insurance or the patient

Signature: _____ **Date:** _____

If there are problems with this invoice, please contact:			
Name	**Phone**	**Fax**	**Email**
_____	_____	_____	_____

ECOG-Operations Office Use Only: TST Reviewer: _____ Date: _____		
Patient	**#1**	**#2**
Date of Registration to Step 1		
Registering Institution		
Data in STS indicates "Not billed to insurance"	☐	☐
Performed after patient registered to the trial and time point is consistent with protocol.	☐	☐
Sample indicated as received by the receiving laboratory in STS	☐	☐
Approved	☐	☐

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Appendix XII

Guidelines for Radiopharmaceutical Production Facilities Shipping ^{18}F-FLT to Sites

1. An existing agreement is required between the Radiopharmaceutical Production Facility (RPF) and receiving site. This agreement shall include, at minimum, the RFP's agreement to comply with all existing and applicable Federal, State and local regulations for radiopharmaceuticals.
2. PET drug products leaving the manufacturing site to be shipped to another site, will meet all Federal, State and local regulations including but not limited to DOT certified radioactive materials shipment regulations.
3. Passing results for all quality control tests (excluding sterility) and final release acceptance criteria will be obtained at the production/shipping site and provided to receiving site prior to injection of the radiopharmaceutical.
4. The receiving site will notify the production/shipping site upon receipt of drug. Expiration time will be listed on the drug in compliance with FDA regulations - injection will take place prior to expiry. Expiration is specific to each production/shipping site as validated in stability testing provided to FDA for review in site specific IND.
5. In the event that the QC testing and release are performed when the shipment is in route, a release form must be received by the study site before the injection can take place. In the event that a release form cannot be obtained, either by test failure or other factors, the injection must not take place. The radioactive material should be disposed following the institutional regulation.