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DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial

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Addendum #10
Addendum #11
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Addendum #26
Addendum #27
Addendum #28

Agents	**IND#**	**NSC#**	**Supply**
Ipilimumab	IND# [redacted]	732442	NCI-Supplied
Nivolumab	IND# [redacted]	748726	NCI-Supplied
Dabrafenib	IND# [redacted]	763760	NCI-Supplied
Trametinib	IND# [redacted]	763093	NCI-Supplied

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done through Medidata Rave and the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) system. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program – Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related questions) Contact the Study PI of the lead protocol organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org.		

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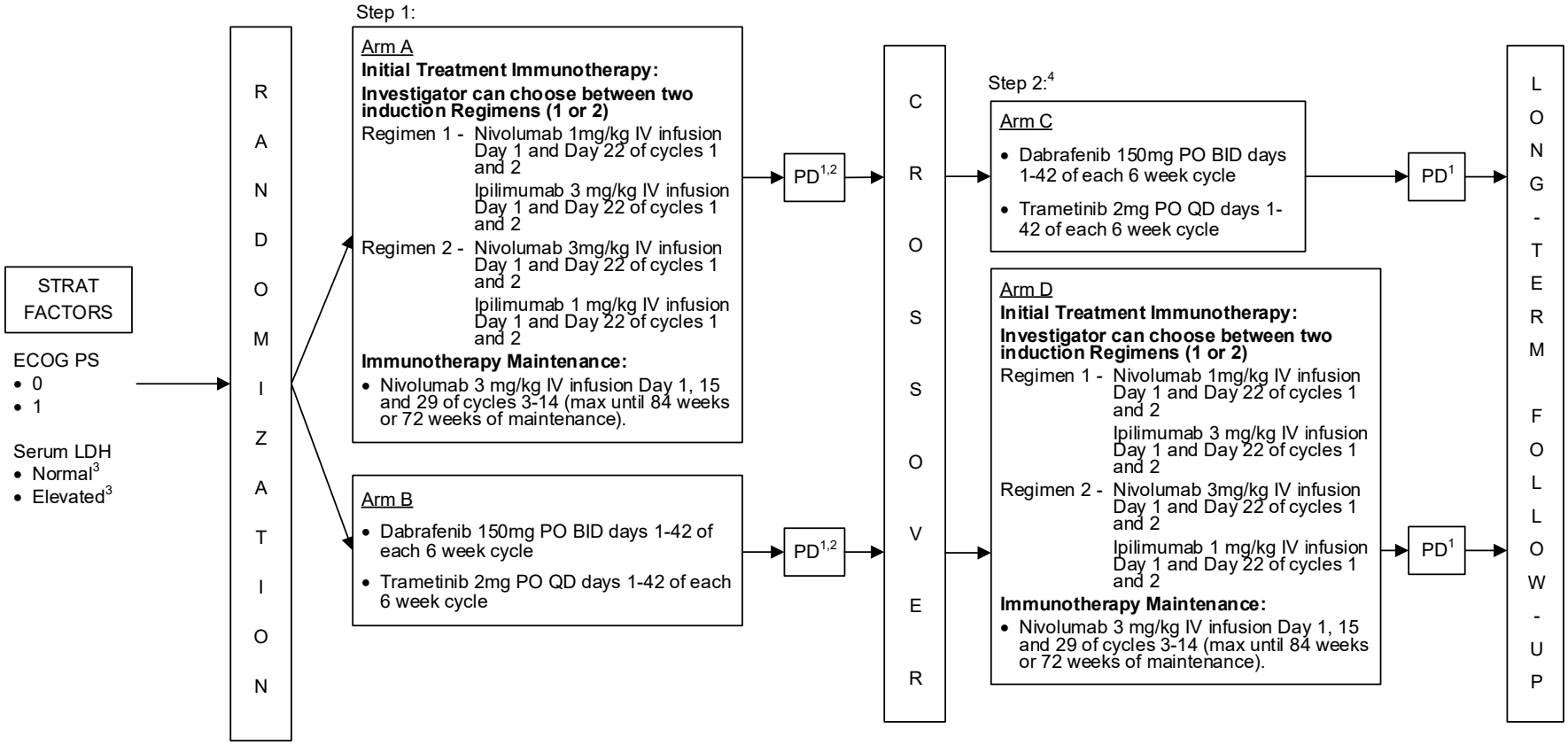
Schema



Cycle = 42 days
Accrual Goal = 300

1. Progressive disease will be determined by RECIST criteria for all arms (See Section 6).
2. Crossover to Step 2 should occur (if possible) no sooner than 1 week following RECIST defined PD (on Arm A or B) or (if possible) no sooner than 1 week following the stoppage of dabrafenib and trametinib for those on Arm B crossing over to Arm D prior to RECIST defined PD.
3. Elevated Serum LDH is defined as above ULN for institution
4. Must meet eligibility criteria in Section 3.2

1. Introduction

1.1 Research Hypothesis

We hypothesize that initial treatment of patients with BRAFV600 mutant melanoma with ipilimumab + nivolumab (+/- followed by dabrafenib + trametinib) will maximize their chance for therapeutic benefit and result in greater 2 year survival and more durable complete responders than initial treatment with dabrafenib + trametinib (+/- followed by ipilimumab + nivolumab).

It is conceivable, however, that this assumption is false and that either the two treatment approaches produce roughly equivalent outcome or that initial therapy with dabrafenib + trametinib results in superior 2-year survival outcome. Therefore, the study is designed with a two-tailed p value.

The results of this study will establish a data driven approach to this treatment decision for patients with BRAFV600 mutant melanoma that maximizes their chance for long-term benefit. Further, information on the relative value of initial treatment with immunotherapy vs molecularly targeted therapy may have implications for treatment choices with other immunotherapies and targeted therapies in melanoma and for other cancer types where both immunotherapy and targeted therapies have shown efficacy (e.g. RCC, NSCLC etc). Measuring the severity, duration, and overall impact of CTCAE compiled and patient-reported toxicities, symptoms and function for each treatment sequence will provide additional guidance for treatment decision-making and complement the primary endpoint of overall survival.

1.2 Disease Background

Melanoma is currently the 5th and 7th most common cancer in American men and women, respectively.[1] Although early stage patients can be treated successfully with surgical resection in the majority, many will develop disseminated disease. The prognosis for patients with metastatic melanoma receiving treatments available prior to 2011 had been dismal, with an overall 5-year mortality rate exceeding 95%.

Recently, treatment options for patients with advanced melanoma have expanded greatly with the FDA approval in 2011-2013 of the CTLA4 blocking antibody, ipilimumab and the highly selective inhibitors of BRAFV600E, vemurafenib and dabrafenib. In addition, the MEK inhibitor, trametinib, also received FDA approval in 2013 for the treatment of patients with BRAFV600E mutant melanoma. Finally, the combination of dabrafenib and trametinib received FDA approval in 2014 based on a randomized Phase II study in which the combination showed superior efficacy relative to dabrafenib alone.

Ipilimumab has been shown to produce two year survival of 24% and prolonged median overall survival in two randomized phase III trials.[2,3] A composite analysis of 12 clinical studies confirmed the potential long-term survival impact of ipilimumab. In this series, 1,257 patients were pretreated and 604 were previously untreated for metastatic disease. The dose of ipilimumab was 3 mg/kg for 965 patients and 10 mg/kg for 706 patients. The median overall survival for the whole patient population was 11.4 months. Most important, the survival curve reached a plateau of 22% at 3 years, which persisted to 10 years, and it was

independent of the dose.[4] Ipilimumab activity has been seen across a broad spectrum of prognostic groups including patients with CNS metastases[5] and does not appear to be influenced by the BRAF mutational status of the patient's tumor.[6,7] Recent data has shown that the combination of ipilimumab and the anti-PD1 antibody nivolumab when administered concurrently shows highly promising antitumor activity with 53% of patients treated at the optimal dose and schedule exhibiting tumor responses, the majority of which were > 80% tumor shrinkage observed within 12 weeks of treatment initiation.[8] While long-term follow-up data remains preliminary, these results suggest that as many as 88% of these patients will be alive at 2 years.[22] The combination of ipilimumab and nivolumab is currently being examined in comparison to ipilimumab or nivolumab alone in a BMS sponsored randomized phase III registration trial.

The BRAF inhibitors vemurafenib and dabrafenib have been shown to produce objective tumor responses in 40-60% of patients with advanced melanoma containing BRAFV600E mutations.[9,10] Median overall survival in the phase II second line trial of vemurafenib was 15.9 months.[9] Twenty-five percent of patients were shown to be alive at 2 years.[30] Furthermore, in a randomized Phase III trial vemurafenib produced significant prolongation in progression free (HR 0.26) and overall survival with HR 0.37 on the initial analysis, and HR 0.76 on the longer follow-up relative to dacarbazine.[11,12] Dabrafenib has shown similar antitumor activity to vemurafenib. In the pivotal phase III trial, in which 250 patients were randomly assigned in a 3:1 ratio to either dabrafenib or dacarbazine, dabrafenib significantly increased PFS compared with dacarbazine (median 5.1 versus 2.7 months, HR 0.33, 95% CI 0.20-0.54). Based upon independent review of the data, the PFS was similarly increased (6.7 versus 2.9 months, HR 0.35, 95% CI 0.20-0.61).[10] Overall survival favored patients treated with dabrafenib (HR 0.76), but was not statistically significant due to extensive (57%) cross-over of patients initially treated with dacarbazine to dabrafenib, likely obscuring the overall benefit produced by the initial dabrafenib therapy. However, despite the major breakthrough provided by BRAF inhibitor therapy, the median PFS for patients with BRAFV600E melanoma treated with vemurafenib or dabrafenib is only 5-7 months.[9-12] Furthermore, few patients experience complete response and most patients exhibit disease progression (in many cases rapid) following discontinuation of therapy.

Several mechanisms of resistance to BRAF inhibitors have been described, and they are generally divided into MEK dependent and MEK independent resistance. Therefore, clinical trials have been conducted with a combination of BRAF and MEK inhibitors in patients with metastatic melanoma who were naïve to BRAF inhibitors as well as in patients who progressed after a BRAF inhibitor. The combination of dabrafenib 150 mg twice daily and trametinib 2 mg once daily in BRAF inhibitor-naive patients showed responses in 41 of 54 (76%) patients compared with 29 of 54 (54%) given dabrafenib monotherapy, and longer median progression-free survival compared with dabrafenib alone (9 *vs* 5 months).[13] These results led to the FDA approval of combination dabrafenib + trametinib as standard therapy for patients with BRAF V600 mutant melanoma in 2014. Recent updates for patients enrolled in the full dose dabrafenib + trametinib cohort showed a median overall survival of 25 months and a 2 year survival of 75% (56%-86%) for patients with a normal LDH compared with 18% (6%-36%) for patients with an elevated LDH.[25] In addition, it appears that the combination treatment was well tolerated. In particular, a significant decrease in the number of

cutaneous squamous cell carcinomas (7% vs 19%) and other skin toxicity was noted relative to dabrafenib alone. A large phase 3 randomized clinical trial of dabrafenib plus trametinib versus dabrafenib plus placebo (Combi-d) confirmed the superior efficacy of dabrafenib and trametinib over dabrafenib alone). PFS for the combination was 9.3 months vs 8.8 months for dabrafenib alone [HR 0.75; 95% CI (0.57-0.99)] and overall response rate 67% for the combination vs 51% for the single agent. On preliminary analysis, overall survival was improved with the combination (HR 0.63, 95% CI 0.42-0.94) although these results were not statistically significant, as they did not cross the predefined boundary for early stopping.[23] These results further support the use of this combination in patients with BRAF mutant melanoma.

While the combination treatment appears to be more efficacious and similarly well tolerated, as with treatment with a BRAF inhibitor alone, complete responses were infrequent (8% in the phase II study) and continued response off treatment did not occur. Consequently many patients are either unable to stop BRAFi (+/- MEKi) therapy or to receive subsequent treatment. For example, Ackerman et al reported a retrospective analysis of 176 patients who discontinued BRAFi (+/- MEKi) therapy, where the median overall survival was 2.9 months. In the 34 patients who received subsequent ipilimumab no objective responses were observed, and only half of patients were able to receive all 4 doses and median overall survival was 5 months.[14] Additional retrospective data were reported by Ascierto et al.[15] Of 93 patients with BRAFV600 mutation-positive advanced melanoma who received vemurafenib or dabrafenib before (n = 45) or after (n = 48) treatment with ipilimumab 3 mg/kg, the median overall survival from the time of first treatment was 9.9 and 14.5 months, respectively. Among patients treated with a BRAF inhibitor first, median survival from the end of BRAF inhibitor treatment was 1.2 months for those who did not complete 4 doses of ipilimumab treatment. Both of these analyses are likely compromised by biases in the patient populations selected for initial treatment with molecular or immunomodulatory therapy. For example, reports of the phase I trial of the ipilimumab + nivolumab combination included at least one patient who had a dramatic antitumor response following disease progression on BRAF inhibitor therapy. Further, preliminary data from the BMS 037 trial showed that nivolumab administration to patients who had disease progression on both ipilimumab and a BRAFi produced tumor responses in 6 of 26 (23%) patients.[37]

1.3 Ipilimumab

Ipilimumab was studied in a placebo-controlled phase III trial in which 676 patients were randomly assigned in a 3:1:1 ratio to ipilimumab plus gp100 peptide vaccine, ipilimumab alone or gp100 vaccine alone[2]. All patients were HLA-A*0201 positive and had unresectable metastatic melanoma. All patients had received prior systemic treatment for advanced disease with either cytotoxic chemotherapy or IL-2.

Ipilimumab (3 mg/kg) and/or vaccine were given every three weeks for four doses. Patients with confirmed partial or complete response or stable disease for three months or more after completion of the 12-week induction period were allowed to receive reinduction with their original treatment if they subsequently had disease progression. The primary endpoint of the trial was overall survival.

Key results of this trial included the following:

- Overall survival was significantly increased in the two groups that received ipilimumab (median 10.0 and 10.1 versus 6.4 months, in the ipilimumab plus gp100, ipilimumab alone, and gp100 groups, hazard ratios for death 0.68 and 0.66 versus gp100 alone, respectively). Overall survival rates for the three groups were 44, 46, and 25 percent at 12 months and 22, 24, and 14 percent at 24 months, respectively.
- Subset analyses found no evidence that the survival benefit was restricted to any particular patient subsets. Benefits were independent of sex, age (≤ 65 or >65 years), stage at presentation (M0, M1a, and M1b versus M1c), baseline LDH (normal versus elevated), or prior use of interleukin-2.
- The objective response rate was significantly improved in both groups of patients treated with ipilimumab compared to gp100 alone (5.7 and 10.9 versus 1.5 percent, respectively). When objective partial or complete responses were observed, these were maintained for at least two years in 4 of 23 (17 percent) patients treated with ipilimumab plus gp100, 9 of 15 (60 percent) with ipilimumab alone and 0 of 2 with gp100 vaccine only. Responses to ipilimumab, either alone or in combination with gp100, continued to improve more than 24 weeks after initiation of therapy; five patients with stable disease eventually achieved a partial response without additional therapy, and four patients with a partial response went on to achieve a complete response.
- Among 31 patients who initially received ipilimumab either alone or with gp100 and then underwent reinduction therapy with ipilimumab, six (21 percent) had an objective response to retreatment, and 15 (48 percent) had stable disease.

Although this phase III trial limited enrollment to patients who were HLA-A*0201 positive because of the use of the gp100 vaccine, retrospective analysis of 453 patients previously treated with ipilimumab in four phase II trials compared patients who were HLA-A*0201 positive with those who were HLA-A*0201 negative.[16] In this analysis, ipilimumab had similar activity regardless of HLA type. Although patients in this trial did not have tumor profiling for BRAF mutations, limited recently published data suggests that the activity of ipilimumab is independent of BRAF mutational status. Recognizing this data and as a consequence of this study, ipilimumab was approved for the treatment of all patients with advanced melanoma.

Although patients with untreated brain metastases were excluded from the phase III trial, other studies have observed antitumor activity with ipilimumab treatment in patients with brain metastases.[5] Finally, data from phase II trials suggested that a number of patients (up to 10% of those treated) exhibited apparent disease progression after 12 weeks of ipilimumab (with either larger lesions or new lesions), followed by subsequent disease regression. The overall survival outcome of these patients was similar to those exhibiting a tumor response. This led to the establishment of Immune-related Response Criteria that endeavored to capture these patients in the subset of patients achieving treatment benefit.[17]

A second phase III trial involved previously untreated patients.[3] In this study, 502 patients with metastatic melanoma were randomly assigned to ipilimumab plus dacarbazine or to placebo plus dacarbazine. Approximately one-fourth of patients

had received prior adjuvant therapy, but those previously treated for metastatic disease were not eligible. Patients with brain metastases, ocular melanoma, mucosal melanoma, or autoimmune disease were excluded.

All patients received dacarbazine (850 mg/m^2 intravenously) every three weeks for eight cycles in the absence of disease progression or significant toxicity. Patients were randomly assigned to receive either ipilimumab at a dose of 10 mg/kg or placebo on weeks 1, 4, 7, and 10. At week 24, patients with stable disease or an objective response were eligible for maintenance therapy with ipilimumab at 10 mg/kg or placebo given every twelve weeks.

Major results of this trial include the following:

- Overall survival, the primary endpoint of the trial, was significantly increased in patients assigned to ipilimumab plus dacarbazine compared with placebo plus dacarbazine (median 11.2 versus 9.1 months, 1, 2, and 3 year survival rates 47 versus 36, 29 versus 18, and 21 versus 12 percent, respectively).
- The rate of disease control (objective response plus stable disease) did not differ significantly between the two groups (33 versus 30 percent), nor did the best overall response rate (15 versus 10 percent).
- The overall incidence of grade 3 or 4 toxicity was significantly higher with ipilimumab plus dacarbazine compared with dacarbazine alone (56 versus 28 percent). Overall, grade 3 or 4 immune-mediated adverse reactions were significantly more common with the ipilimumab combination (38 versus 4 percent).
- Hepatic toxicity was significantly more common with the combination than with dacarbazine alone (overall incidence of transaminase elevation 29 to 33 versus 6 percent). Furthermore, the incidence of hepatic toxicity was much higher compared with that observed in the phase III trial when ipilimumab was given without dacarbazine or in prior phase II trials ipilimumab administered at this dose and schedule. The increase in hepatic toxicity may be due to its combination with dacarbazine, which is also known to be hepatotoxic.
- The incidence of other immune related toxicities (colitis, rash, hypophysitis) was less than that seen in prior studies with ipilimumab alone, perhaps suggesting that DTIC may have blunted and/or the higher incidence of hepatotoxicity may have pre-empted or altered the immune toxicity profile.
- Whether this blunting of immune toxicity by DTIC might have also blunted the antitumor effect of ipilimumab is a matter of speculation. However, the overall pattern of toxicity and efficacy on this trial do not support the addition of DTIC to ipilimumab nor the use of ipilimumab at the 10 mg/kg dose vs the already approved 3 mg/kg dose.

A composite analysis of 12 clinical studies confirmed the potential long-term survival impact of ipilimumab. In this series, 1,257 patients were pretreated and 604 were previously untreated for metastatic disease. The dose of ipilimumab was 3 mg/kg for 965 patients and 10 mg/kg for 706 patients. The median overall survival for the whole patient population was 11.4 months. Most importantly, the survival curve reached a plateau of 22% at 3 years, which extended to 10 years, and it was independent of the dose.[4]

1.4 Nivolumab

Nivolumab (BMS-936558) is a humanized monoclonal antibody that targets the PD-1 protein. This monoclonal antibody was evaluated in a phase I/II study in 296 patients with a variety of heavily pretreated malignancies, including 107 patients with melanoma.[18]

Efficacy data from this study were updated with one year of additional follow-up for the cohort of 107 patients with advanced melanoma.[19] The overall objective response rate was 31% for the entire melanoma patient cohort and an additional 7% of patients had stable disease. There was no clear-cut dose response relationship, although the 3 mg/kg dose had the highest response rate (41%). The median duration of response was 24 months. Results were updated 14 months after the last patient initiated therapy at the 2014 ASCO meeting. The median overall survival was 17 months, and the one, two and three years survival rates were 63, 48, and 41 percent, respectively.[24]

Grade 3/4 treatment related adverse events were observed in 32 of the 296 patients (14%) enrolled in the entire study.[18] A variety of autoimmune side effects were observed including pneumonitis, vitiligo, hepatitis, hypophysitis and thyroiditis, although autoimmune toxicity was considerably less frequent than observed with ipilimumab.

Three phase III trials have been conducted to evaluate the role of nivolumab in patients with advanced melanoma. In one, patients who have progressed following ipilimumab (and if indicated) BRAF inhibitor therapy were randomly assigned to nivolumab or chemotherapy with either dacarbazine or carboplatin plus paclitaxel. In the second trial, previously untreated patients known to have BRAF wild type tumors were randomly assigned to nivolumab or dacarbazine. Finally, in the third trial previously untreated patients were randomized to receive either ipilimumab, nivolumab or the combination of the two agents. Preliminary data from the first two of these trials have now been reported.

Preliminary results from the first trial was reported at ESMO 2014. The trial accrued 405 patients and results in the preliminary report were based upon 167 patients (120 patients treated with nivolumab, and 47 patients treated with chemotherapy), all of whom had a follow-up of ≥6 months:

- Objective responses by independent review were significantly more common in patients treated with nivolumab compared with chemotherapy (32% vs 10%).
- Median duration of response was longer with nivolumab (median not reached, 36 of 38 still in remission, vs 3.5 months for chemotherapy treated patients).
- Tumor responses were seen with nivolumab in patients with BRAF mutations who had progressed on a prior BRAF inhibitor (6/26= 23%) and appeared to be independent of benefit from prior ipilimumab treatment.
- Grade 3-4 AEs were seen in 9% of patients on nivolumab and 31% of patients on chemotherapy. No nivlumab-related Grade 3-4 AE was reported in more than 2% of patients.
- Based on this data nivolumab received FDA approval for the treatment patients with refractory melanoma on 12/22/2014.

A press release of results from the second trial reported that nivolumab was superior to dacarbazine in the treatment naïve population.

1.5 Nivolumab + Ipilimumab Combination

The combined administration of anti-CTLA-4 immunotherapy with ipilimumab plus anti-PD-1 immunotherapy with nivolumab appears to have a higher level of anti-melanoma activity than either agent alone and a manageable toxicity profile.[8] In a phase I trial in which both drugs were given in successive dose escalation cohorts, 53 patients were treated with concurrent therapy administered every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks through week 24. Subsequent therapy with both drugs was continued once every 12 weeks for a maximum of 8 additional doses. In a separate sequential cohort, nivolumab was given on the same schedule to 33 patients who had received prior ipilimumab. Subsequently, another cohort of 41 patients was treated with the combination of ipilimumab plus nivolumab for four cycles, followed with nivolumab maintenance only given every 2 weeks for up to 84 weeks. [22]

In the 32 patients treated at the top dose levels of ipi 3/nivo 1 or ipi 1/nivo 3 53% of patients had tumor response with > 41% having tumor shrinkage of > 80% all of which was observed at the 12 week tumor evaluation. In the sequenced therapy group 6 of 30 patients had an objective response.

Data was updated at the 2014 ASCO meeting. In the concurrent treatment cohort, the objective response rate was 42% (17% CR and 25% PRs). Responses appeared durable with 18 of 22 responses ongoing at the last follow-up. Overall survival in the original concurrently treated cohort of 53 patients at one and 2 years was 94 and 88%, respectively.

Among the patients treated with concurrent nivolumab + ipilimumab, treatment related AEs were observed in 93% of cases. The most common events were rash, pruritus, fatigue and diarrhea. Grade 3-4 AEs were reported in 49% of cases, including liver, GI and kidney toxicity (15, 9, and 6% of cases, respectively). Treatment was discontinued due to AEs in 11 cases (21%).

Section 5.3.1 includes a summary of treatment related adverse events on the concurrent cohorts of the ipilimumab + nivolumab combination study.

A randomized phase III registrational trial studying the combination of ipilimumab + nivolumab administered at the above schedule compared with each single agent administered at its optimal schedule (NCT01844505) has completed accrual. Preliminary results from this trial showed that nivolumab alone and the combination of ipillimumab and nivolumab produced longer PFS, greater response rate and greater tumor shrinkage than ipilimumab alone. The combination also appeared to have superior efficacy than nivolumab alone although the trial was not powered to address this endpoint. Also of note, the combination or ipilimumab and nivolumab produced more treatment related side effects than either ipilimumab or nivolumab monotherapy, although there were no treatment related deaths in patients receiving the combination. Critical survival and response duration results are not anticipated until 2016. (Larkin J et N Engl J of Med 2015).

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1.6 Dabrafenib Mesylate (GSK2118436B)

Activating mutations in BRAF are present in approximately 40 to 60 percent of advanced melanomas. In 80 to 90 percent of cases, this activating mutation consists of the substitution of glutamic acid for valine at amino acid 600 (V600E mutation) with most the remainder consisting of an alternate substitution at the V600 locus (V to K).

Dabrafenib is a potent inhibitor of the kinase domain in mutant BRAF. In the pivotal phase III trial, in which 250 patients with unresectable stage III or stage IV melanoma were randomly assigned in a 3:1 ratio to either dabrafenib (150 mg orally twice a day) or dacarbazine (1000 mg/m^2 IV every three weeks).[10] All patients had the V6000E mutation in BRAF. The primary endpoint of the trial was PFS as ascertained by the investigators; the PFS was independently reviewed as a secondary trial endpoint. Patients assigned to dacarbazine were allowed to cross over to dabrafenib upon development of progressive disease. The principal results were as follows:

- Dabrafenib significantly increased PFS compared with dacarbazine (median 5.1 versus 2.7 months, HR 0.33, 95% CI 0.20-0.54). Based upon independent review of the data, the PFS was similarly increased (6.7 versus 2.9 months, HR 0.35, 95% CI 0.20-0.61).
- Objective responses, as assessed by the independent review committee, were seen in 93 of 187 patients treated with dabrafenib (50 percent), including six cases (3 percent) with a complete response. Among those treated with dacarbazine there were four partial responses in 63 cases, for an overall response rate of 6 percent.
- Overall survival was updated at the 2013 ASCO meeting.[20] With a median follow-up of 15 and 13 months for the two groups, overall survival favored patients treated with dabrafenib (HR 0.76, 95% CI 0.48-1.21), but was not statistically significant. However, 26 of 63 patients (57%) originally treated with dacarbazine crossed over to dabrafenib, likely obscuring an overall survival benefit from the initial dabrafenib therapy.
- Treatment with dabrafenib was generally well tolerated. The most frequent grade 2 or greater toxicities were dermatologic. Other grade 2 or greater toxicities observed in between 5 and 15 percent of cases included arthralgia, fatigue, headache, and fever.

Dabrafenib was approved by the US Food and Drug administration in May 2013 for use in patients whose tumors contain the V600 mutation in BRAF.

The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers. This pathway can be constitutively activated by molecular alterations including BRAF activating mutations. Approximately 90% of all identified BRAF mutations in human cancer consist of a T1799 transversion mutation in exon 15, which results in a V600 E/D/K (T1799A) amino acid substitution. This mutation appears to mimic regulatory phosphorylation and increases BRAF activity approximately 10-fold compared to wild type (wt). RAF is a validated target in BRAF V600E-containing melanoma. In August 2011, the FDA approved vemurafenib (PLX4032, Zelboraf®), an ATP-competitive selective RAF inhibitor for the treatment of late-stage BRAFV600E melanoma. In the pivotal phase III trial of vemurafenib vs. dacabazine,[31] vemurafenib demonstrated significant improvement in overall survival (OS) (6-month OS of 84% vs. 64%,

hazard ratio [HR]=0.37; P< 0.001), progression-free survival (PFS) (estimated median PFS of 5.3 months vs. 1.6 months (HR=0.26; P< 0.001]), and overall response rate (ORR) (48% vs. 5%). However, in patients with colorectal cancer (CRC) bearing the BRAF V600E mutation, there was only one partial response (PR) among 20 patients treated (ORR 5%) and four minor responses.[32]

Dabrafenib mesylate (GSK2118436B, Tafinlar®; referred to as dabrafenib hereafter), a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is an ATP-competitive, selective inhibitor of RAF kinase currently in clinical development. On May 29, 2013, the U.S. FDA approved dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test (FDA, 2013). On January 10, 2014, the FDA granted accelerated approval to dabrafenib and MEK inhibitor trametinib for use in combination to treat patients with unresectable or metastatic melanoma with either BRAFV600E or BRAFV600K mutation as detected by an FDA-approved test.[33]

1.6.1 Mechanisms of Action and Preclinical Data with Dabrafenib

Dabrafenib potently inhibits all RAF isoforms, with the strongest potency against the V600 mutant, as compared to its activity against wt BRAF and CRAF (see below). In a panel of more than 270 kinases tested outside RAF isoforms, only 10 kinases were inhibited at a 50% inhibitory concentration (IC50) < 100 nM: LIM domain kinase 1 (LIMK1), activin receptor-like kinase 5 (ALK5)/ transforming growth factor (TGF)-beta receptor type-1 (TGFβ1R), Never In Mitosis Gene A (NIMA)-related kinase 11 (NEK11), salt-inducible kinase 1 (SIK1), salt-inducible kinase 2 (SIK2), polycystin-2 (PKD2), protein tyrosine kinase 6/breast tumor kinase (BRK), pancreatic eukaryotic initiation factor-2 alpha (eIF2α) kinase (PEK)/eIF2α kinase (PERK), endothelium-specific receptor tyrosine kinase 2 (TIE2) (R849W), and yeast casein kinase 1 (CK1) (IB, 2013a).

Inhibitory activity of dabrafenib on RAF

	$BRAF^{V600E}$	$BRAF^{V600K}$	$BRAF^{V600D}$	wt BRAF	CRAF
IC_{50}	0.65 nM	0.50 nM	1.84 nM	3.2 nM	5.0 nM

In a panel of > 110 human tumor cell lines with confirmed BRAF mutational status, dabrafenib potently inhibited proliferation of a majority (73%) of BRAFV600E mutant cell lines with growth IC50 (gIC50) <100 nM (IB, 2013a). In contrast, there was poor or no activity in other BRAF mutants or wt BRAF cell lines.

Dabrafenib given orally (PO) for 14 days at doses ranging from 0.1-300 mg/kg administered once daily (QD), twice daily (BID), or three times daily (TID) inhibited tumor growth in mice bearing BRAFV600E A375P F11s or Colo205 tumor xenografts. The effect was generally dose dependent up to 10 mg/kg/day (A375P F11s) or 30 mg/kg/day (Colo205), yielding 90-120% tumor reduction relative to untreated animals. However, cessation of treatment was associated with regrowth of the tumors. In A375P F11s melanoma xenografts, inhibition of pERK by > 50% in the tumor was seen at doses of ≥3 mg/kg. Based on the single-dose studies, ~100 nM (52 ng/mL)

dabrafenib in blood at 6 h post-dosing was needed for effective pharmacodynamic biomarker inhibition in the tumor. At repeated dosing of 30 mg/kg/day, the tumor pERK levels were reduced by > 50% at 8 h after dosing (69% on Day 1 and 53% on Day 14). Levels of pERK returned to baseline 24 h post-dosing. Similar ↓pERK effects were seen in the ES-2 ovarian xenograft model, but pERK inhibition was weaker in the Colo205 xenograft model. Of note, concentrations of dabrafenib showing pharmacodynamic activity in xenografts did not cause a reduction in pERK/tERK levels in the normal intact brain.

1.7 Trametinib

MEK is a direct target of phosphorylation by BRAF in the MAP kinase pathway and cells with BRAF mutation have an increased level of phosphorylated MEK and are exceptionally sensitive to MEK inhibition in vitro. Trametinib is a potent and highly selective inhibitor of MEK1 and MEK2.

The efficacy of trametinib was demonstrated in the phase III METRIC trial, in which 322 patients with advanced melanoma were randomly assigned in a 2:1 ratio to either trametinib (2 mg/day orally) or chemotherapy (dacarbazine or paclitaxel) [21]. All patients had either the V600E or V600K mutation in their melanoma (87 and 13 percent, respectively). One third of patients had received prior chemotherapy and 30 percent had received prior immunotherapy, but prior BRAF inhibitor therapy was not allowed. Crossover to trametinib was permitted in patients who progressed on chemotherapy.

Key results included the following:

- Progression-free survival, the primary endpoint of the trial, was significantly increased with trametinib compared with chemotherapy (median 4.8 versus 1.5 months, HR 0.47, 95% CI 0.34-0.65).
- Overall survival was significantly improved with trametinib (6 month survival rate 81% vs 67%, HR for death 0.54, 95% CI 0.32-0.92), even though 47% of patients who progressed on chemotherapy received secondary treatment with trametinib.
- The improvements in PFS and overall survival were present in all patient subsets, including those with brain metastases or other visceral metastases (M1c).

Based on this data, trametinib received FDA approval for treatment of patients with BRAFV600 metastatic melanoma in May of 2013.

The RAF-MEK-ERK pathway plays a critical role in multiple cellular functions. Activation of the pathway can result from activation/mutations of the upstream receptor tyrosine kinases (RTKs) and RAS, or upregulation/mutations in RAF and MEK. Upon activation, RAF acts as the MAPK kinase and activates MAPKK (MEK1/2), which in turn catalyze activation of the effectors ERK1/ERK2. Once activated, ERK1/2 translocate into the nucleus and phosphorylate a number of effector proteins and transcriptional factors that regulate cell proliferation, motility, differentiation, and survival.

Trametinib is one of the several MEK inhibitors in clinical development. On May 29, 2013, the U.S. Food and Drug Administration (FDA) approved trametinib for the treatment of patients with unresectable or metastatic melanoma with

BRAFV600E or BRAFV600K mutations as detected by an FDA-approved test.[38] On January 10, 2014, the FDA granted accelerated approval to trametinib and dabrafenib for use in combination to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.[33]

Experience to date indicates that MEK is a valid target. In a phase 3 trial comparing trametinib with dacarbazine or paclitaxel in patients with BRAF V600E or V600K mutant metastatic melanoma, trametinib demonstrated a significantly better response rate, progression-free survival, and overall survival.[13] However, single agent activities are limited.

The most up-to-date preclinical and clinical study information for trametinib can be found in the GSK1120212 (trametinib) Investigator's Brochure (2013).

1.7.1 Mechanisms of Action and Preclinical Data with Trametinib

Trametinib is a dimethyl sulfoxide (DMSO) solvate compound (ratio 1:1) with potent, allosteric and ATP non-competitive inhibition of MEK1/2 (IC50 of 0.7 and 0.9 nM against MEK1 and MEK2, respectively) (Gilmartin et al., 2011). Trametinib inhibited MEK1/2 kinase activity and prevented RAF-dependent MEK phosphorylation (S217 for MEK1), producing prolonged pERK1/2 inhibition. Trametinib showed better potency against unphosphorylated MEK1/2 (u-MEK1/2) when compared with preactivated diphosphorylated MEK (pp-MEK), suggesting that u-MEK affords a higher affinity binding site for trametinib than does pp-MEK.

The specificity of trametinib was confirmed against a panel of 183 kinases, including MEK5 (the closet kinase homolog to MEK1/2), CRAF, BRAF, ERK1, and ERK2 (Yamaguchi et al., 2011). Trametinib demonstrated equal potency against activated MEK1- and MEK2-mediated phosphorylation of ERK (sequence identity of 85% across the whole protein and 100% in the active site for humans). Trametinib demonstrated preferential inhibition of RAF-mediated MEK1 activation (IC50 = 0.60 nM) over pMEK1 kinase activity (IC50 = 13 nM) (Investigator’s Brochure, 2012a).

BRAF-mutant Colo205, A375P F11s, and HT-29 human tumor xenograft mouse models showed the most significant mean tumor growth inhibition (TGI) (80% to 87%) at 3.0 mg/kg trametinib, with multiple complete and partial tumor regressions. In the Colo205 model, tumor regression was observed even at a dose of 0.3 mg/kg (Yamaguchi et al., 2011). Two KRAS-mutant xenograft models, HCT-116 and A549, also showed significant TGI (83% and 75%) but without significant tumor regressions (Gilmartin et al., 2011). As predicted by cell proliferation assays, tumor xenograft lines with wild-type (wt) RAF/RAS (PC3, BxPC3, and BT474) were much less sensitive, showing only modest TGI (44-46%) with no tumor regressions.

Pharmacodynamic studies were performed in mice treated with trametinib for 14 days (Gilmartin et al., 2011). In the A375P F11s xenograft model, the first dose of trametinib (3 mg/kg) significantly

reduced pERK for more than 8 hours on Day 1. pERK inhibition was more sustained (over 24 hours) after the Day 7 dose, probably due to an increase in the steady-state levels of trametinib after repeated doses. The average Cmax in blood was 1,410 nM on Day 7, with an estimated half-life (t1/2) of 33 hours. In addition, immunohistochemistry (IHC) also confirmed inhibition of cell proliferation (reduced Ki67) and G1 cell cycle arrest (elevated p27Kip1/CDKN1B) following 4 days of treatment.

1.8 Dabrafenib and Trametinib Combination

Trametinib has been combined with dabrafenib in an effort to delay the development of resistance to dabrafenib and potentially reduce toxicity associated with BRAF inhibitor induction of paradoxical activation of the MAP kinase pathway in cells lacking a BRAF mutation.

A phase I/II study demonstrated the feasibility of combining full doses of dabrafenib (150 mg twice daily) and trametinib (2 mg daily). In the phase II component of the trial, 162 patients whose tumor contained a V600 mutation were randomly assigned to one of 3 regimens: dabrafenib (150 mg twice daily) as monotherapy, dabrafenib plus trametinib (150 mg twice daily and 1 mg once daily, respectively), or dabrafenib plus trametinib (150 mg twice daily and 2 mg once daily, respectively). In the analysis of this randomized component of the trial, treatment with the combination regimen using full doses of dabrafenib and trametinib (2 mg daily dose) significantly prolonged PFS compared to dabrafenib monotherapy (median 9.4 vs 5.8 months, HR 0.39, 95% CI 0.25-0.62) and significantly increased the proportion of patients alive and progression-free at one year (41% vs 9%).[13] Recent updates for patients enrolled in the full dose dabrafenib + trametinib cohort showed a median overall survival of 25 months and a 2 year survival of 75% (56%-86%) for patients with a normal LDH compared with 18% (6%-36%) for patients with an elevated LDH.[25] Dermatologic toxicity, manifested by squamous cell carcinoma (including keratoacanthoma) was decreased in both the combination arms relative to dabrafenib alone (5% vs 19%), although the incidence of pyrexia was increased (71% vs 26%).

Two phase III trials have been initiated in which patients with advanced melanoma containing either a V600E or K mutation are randomly assigned to the combination of dabrafenib and trametinib or to either dabrafenib plus placebo (Combi-d) or vemurafenib (Combi-v). These trials have completed accrual. The Combi-d enrolled 423 patients and reported preliminary results in a press release in January 2014. This trial confirmed the superior efficacy of dabrafenib and trametinib over dabrafenib alone. PFS for the combination was 9.3 months vs 8.8 months for dabrafenib alone [HR 0.75; 95% CI (0.57-0.99)] and overall response rate 67% for the combination vs 51% for the single agent. These results supported to randomized Phase II which were the basis of FDA approval of combination dabrafenib + trametinib as standard therapy for patients with BRAF V600 mutant melanoma in early 2014.

Results were formally presented at the 2014 American Society of Clinical Oncology (ASCO) meeting[23] Additional information included:

- Many more patients (18 vs 6) on the dabrafenib + placebo arm were censored early prior to formal imaging perhaps contributing to agreater than anticipated median PFS on the dabrafenib + placebo arm.

- Overall survival was potentially better with the combination (HR 0.63, 95% CI 0.42-094). However, as these results were preliminary and did not cross the threshold for significance, additional follow-up for overall survival is required.
- There were substantial differences in toxicity. Toxicities decreased with the combination of dabrafenib plus trametinib included the incidence of cutaneous squamous cell carcinoma and keratoacanthoma (2 versus 9 percent), hyperkeratosis (3 versus 32 percent), skin papilloma (2 versus 21 percent), hand-foot syndrome (5 versus 21 percent), and alopecia (7 versus 26 percent). Toxicities more frequently associated with the combination included diarrhea (24 versus 14 percent) and hypertension (22 versus 14 percent).
- Dose interruptions were significantly more frequent with the combination. This was due to enhanced pyrexia and chills associated with the combination relative to dabrafenib alone.

Table 2 includes a summary of frequently occurring treatment related adverse events on the dabrafenib + trametinib combination.[23]

Table 2

	Dabrafenib + Trametinib* N=209 n (%)		
	All Grades	**Grade 3**	**Grade 4**
All Events	199(95)	66(32)	7(3)
Pyrexia	107(51)	12(6)	0
Fatigue	74(35)	4(2)	0
Headache	63(30)	1 (<1)	0
Nausea	63 (30)	0	0
Chills	62(30)	0	0
Arthralgia	51(24)	1 (<1)	0
Diarrhea	51(24)	2 (<1)	0
Rash	48(23)	0	0
Hypertension	46(22)	8(4)	0
Vomiting	42(20)	2(<1)	0
Alopecia	15(7)	0	0
Hyperkeratosis	7(3)	0	0
Skin papilloma	3(1)	0	0

*4 fatal SAEs, not treatment related: 3 intracranial hemorrhage, 1 pneumonia

1.9 Study rationale

Given these new treatment approaches for patients with BRAFV600 mutant melanoma, patients and physicians now (and in the future) have to make a choice regarding initial treatment and the sequence of these modalities. There is currently little information to guide this choice. While BRAFi therapy appears to

be equally active in patients whose disease has progressed following immunotherapy[14] and those who are immunotherapy-naive there is no formal data on its activity following resistance to ipilimumab + nivolumab. Similarly, there is no formal prospective data on the activity of ipilimumab (or even the feasibility of stopping BRAFi therapy and administering ipilimumab) following disease progression on BRAF (+/- MEK) inhibitor therapy. While some anecdotal data suggests that response to either nivolumab or the ipilimumab + nivolumab combination can be seen in patients whose disease has become resistant to BRAFi, there is no formal data to assess the activity, tolerability or feasibility of this promising immunotherapy combination in that setting. It is conceivable that patients treated initially with immunotherapy may get the benefit of durable response in a subset of patients (up to 40%-50%) without compromising the benefit of subsequent BRAF inhibitor therapy for those patients who exhibit disease progression, while those started on BRAF/MEK inhibitor therapy may not be able to benefit as much from subsequent immunotherapy at time of progression as they would in the treatment naïve setting. It is also possible that the high response rate and prolonged PFS associated with dabrafenib + trametinib combination relative to ipilimumab + nivolumab may overwhelm any benefit that might be achieved with initial immunotherapy. Further, it is possible that subsets of patients, defined by clinical and/or tumor characteristics (Performance Status, disease stage, serum LDH level, PTEN loss, immune infiltration, PDL1 expression, germ line polymorphisms, etc.), might do better with one initial therapy or sequence than with the other. Finally, the sequence of treatments may be influenced by Quality of Life factors that are largely unknown for either treatment approach as described below.

Patient-Reported Outcomes (PROs), which include patient-reported symptoms, physical, mental, social function, and toxicities, have become increasingly important in cancer clinical trials to provide information on the range and severity of treatment effects on a patient's health and well-being. PROs are used to assess symptom relief from improved disease control, differences in treatment-related toxicities, functional declines or improvement, and reasons for treatment non-adherence. Furthermore, PROs are an important complement to survival outcomes since PROs may provide crucial information for guiding treatment decision making when there are no (or minimal) survival difference between treatment arms. In addition, independent of survival outcomes, PROs can provide patients, their caregivers, and clinicians a more complete understanding of what to expect from treatment as part of managing expectations and planning for palliative care.

Based on clinical experience and previous toxicity reports, the type and severity of treatment-related adverse events are different for ipilimumab-nivolumab vs. dabrafenib-trametinib. For ipilimumab-nivlumab the most common toxicities include severe rash, vomiting and diarrhea; while dabrafenib-trametinib toxicities are more commonly muscle pain, fatigue, and severe chills. Research examining PROs on these treatments are limited, mainly evaluating short-term effects. Individuals at 12-weeks on ipilimumab report moderate problems with fatigue, sleep disturbance, appetite loss and role-functioning.[34] Dabrafenib and trametinib have reported minimal symptoms except diarrhea at 12-weeks.[35, 36] To date, no research has examined the long-term functional treatment impact or differences due to therapy sequence, which could help inform treatment decisions.

Therefore, we propose to collect longitudinal information on PROs which we categorize under the following 3 sub-domains: patient toxicities, symptoms and, function. Our primary objective will be to compare quality-adjusted time without symptoms of disease progression or toxicity of treatment by initial treatment assignment over 2 years. Our secondary objectives will be to examine changes in function and symptoms during and after initial treatment, explore differences in function and symptoms due to treatment sequence, and describe differences in patient-reported treatment toxicities for each treatment. Our design will provide novel longitudinal information on PROs based on treatment sequence and crossover in patients with advanced melanoma.

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1.10 Rationale for Tobacco Use Assessment

NOTE: Please refer to Appendix XIII for EAQ16T references

A significant proportion of cancer patients are current smokers at the time of cancer diagnosis,[1–5] and there are known risks associated with continued smoking following cancer diagnosis. These include decreased survival time; increased complications from surgery, radiation, and chemotherapy; and increased risk of second primary tumors.[6–11] As such, the National Comprehensive Cancer Network (NCCN), the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) have identified persistent smoking as a modifiable risk factor and recommend cessation counseling for cancer patients who smoke. Although evidence-based guidelines for treating tobacco dependence exist,[12] they have not yet been well-integrated into cancer care settings. Moreover, knowledge regarding the scope and patterns of tobacco use among cancer patients is limited.

Tobacco use following a cancer diagnosis compromises treatment outcomes but is not well understood. About 10% to 30% of cancer patients are smoking at the time of diagnosis,[1–4,14,15] and the majority of cancer patients who smoke at diagnosis continue to smoke following diagnosis.[3,16] Quitting smoking upon cancer diagnosis may improve cancer treatment effectiveness, reduce risk of recurrence and of developing new primary tumors,[9–11,17–21] and improve chances of survival.[1,22–24] Conversely, continuing to smoke may result in diminished QOL,[1,25,26] treatment delays and increased treatment complications.[2,6–8,22,27–34]

Tobacco use following a cancer diagnosis may compromise patient reported outcomes. It is hypothesized that smoking may be used as a means of reducing symptom burden among cancer patients, which may be a barrier to smoking cessation. Relatedly, research has shown that cancer patients who are smoking experience more difficulty with physical and psychological symptom control, compared to nonsmokers.[35–38] Research is needed to examine how symptom levels differ, by tobacco use and exposure and how tobacco use changes may affect reported symptom burden.

National initiatives emphasize the importance of identifying tobacco use in cancer care settings. Smoking status was designated as a core objective in the 2010 federal government “Meaningful Use” electronic health record documentation.[39,40] In 2013, the American Association for Cancer Research (AACR) released guidelines emphasizing the provision of tobacco cessation services to cancer patients.[41] The American Society of Clinical Oncology (ASCO) recommends cessation counseling to all smokers by their second oncology visit as a core

quality indicator.[42] The National Comprehensive Cancer Network (NCCN) published Smoking Cessation guidelines to formalize these initiatives.[43]

Integrated, evidence-based services are needed during cancer care. The USPHS Practice Guidelines recommend that evidence-based tobacco treatment be delivered to all smokers in health care settings, yet little progress has been made to integrate these guidelines into cancer care.[44] This is unfortunate, as cessation closer to the time of diagnosis results in a higher likelihood for continued abstinence,[1,45–48] effective interventions exist,[1,45–48] and many cancer patients who smoke want to quit smoking.[45,46,49,50] Little work has been done to explore the delivery and effectiveness of tobacco treatment among racial/ethnic minority cancer patients who are at elevated risk of continued smoking.[51–53]

Tobacco use is often not being assessed or intervened upon during cancer care. Recent surveys of oncologists and of clinical practices at comprehensive cancer centers and community oncology settings demonstrate that assessment of tobacco dependence is lacking.[54–57] During treatment, most cancer patients do not get assistance with smoking cessation support.[58–60] Tobacco use assessments and cessation support have not been incorporated in most cooperative group clinical trials.[61] No one has assessed cancer patients' reports of their oncology providers' assistance behaviors.

The NCI-AACR Cancer Patient Tobacco Use Asssessment Task Force developed the Cancer Patient Tobacco Use [1–4,13,14] Questionnaire (C-TUQ). We propose that administering selected C-TUQ items to participants enrolling in 8 Phase II and Phase III ECOG ACRIN (EA) therapeutic trials will add value to parent trial research questions by advancing the field. Specifically, among patients with varied cancers (tobacco-related and non tobacco-related) and cancer treatments, we will administer C-TUQ questions at EA trial enrollment and 3 and 6 month follow-up.

We have the following aims:

1. **Treatment toxicity:** To determine the effects of tobacco, operationalized as combustible tobacco (1a), other forms of tobacco (1b), and environmental tobacco exposure (ETS) (1c) on provider-reported cancer-treatment toxicity (adverse events (both clinical and hematologic) and dose modifications).
2. **Symptom burden:** To determine the effects of tobacco on patient-reported physical symptoms and psychological symptoms.
3. **Cessation patterns and treatment:** To examine quitting behaviors and behavioral counseling/support and cessation medication utilization.
4. **Trial outcomes:** To explore the effect of tobacco use and exposure on treatment duration and relative dose intensity, and on therapeutic benefit, of 8 selected EA trials.

The findings will advance the nascent field of tobacco use in the context of cancer care by: 1) longitudinal assessment of cigarette smoking, other forms of tobacco use and secondhand smoke exposure at trial enrollment and at 3 and 6 month follow-up; 2) increase knowledge about the effects of tobacco use and exposure on treatment toxicity, physical and psychological symptoms and 3) oncology provider delivery, and 4) patient's perceptions of stigma and utilization of behavioral and pharmacological treatment of tobacco dependence. Finally, the use of this assessment would provide a unique additional value to the hypothesis

of this trial, by allowing investigation of previously unanswered questions about the effects of tobacco use and exposure on trial adherence and outcomes among patients with smoking-related and non-smoking related cancers.

2. Objectives

2.1 Primary Objective

To determine whether initial treatment with either combination ipilimumab + nivolumab (with subsequent dabrafenib in combination with trametinib) or dabrafenib in combination with trametinib (with subsequent ipilimumab + nivolumab) significantly improves 2 year overall survival (OS) in patients with unresectable stage III or stage IV BRAFV600 mutant melanoma.

2.2 Secondary Clinical Objectives

2.2.1 To evaluate the impact of initial treatment on median OS and Hazard Ratio for death.

2.2.2 To determine whether initial treatment choice significantly improves 3 year OS.

2.2.3 To evaluate the anti-tumor activities (RECIST-defined response rate, median PFS) and safety profiles of ipilimumab + nivolumab and dabrafenib-trametinib in a Cooperative Group trial of patients with V600 mutant melanoma.

2.2.4 To evaluate the activity (RECIST-defined response rate, median PFS) and safety of dabrafenib + trametinib in patients who have had disease progression on ipilimumab + nivolumab and in comparison to its activity and safety in ipilimumab + nivolumab naïve patients.

2.2.5 To evaluate the activity of ipilimumab + nivolumab (RECIST-defined response rate, median PFS) and safety in patients who have had disease progression on dabrafenib + trametinib and in comparison to its activity and safety in dabrafenib + trametinib naïve patients.

2.2.6 To assess the feasibility of crossover to the alternative treatment strategy (percentage of patients who are able to cross-over from one arm to the other and complete at least an initial course (12 weeks) of treatment after crossover without intervening symptomatic disease progression or treatment limiting toxicity).

2.3 Secondary Laboratory Objectives

2.3.1 Association of inherited variation with immune mediated adverse events and response to ipilimumab + nivolumab

2.3.1.1 To determine the association of inherited genetic variation and immune-associated adverse events in patients with metastatic melanoma treated with ipilimumab containing regimens by completing candidate-based gene and pathway analyses of genes involved in lymphocyte activation, cytokines, cytokine receptors and within the MHC region and an agnostic genome-wide SNP-based approach.

2.3.1.2 To investigate the association between inherited genetics and survival in patients with metastatic melanoma treated

with ipilimumab containing regimens by completing candidate-based gene and pathway analyses of genes involved in lymphocyte activation, cytokines profile, cytokine receptors and within the MHC region and an agnostic genome-wide SNP-based approach.

2.3.1.3 To replicate genomic markers identified in the above aims in an independent sample set of patients treated with ipilimumab containing regimens and preliminarily characterize their potential functional role by completing replication of variation as associated with irAEs and survival and bio-informatic assessment of genomic markers.

2.3.2 To determine the utility of circulating BRAF levels in determining the response and resistance to either BRAF/MEK directed and/or combination immunotherapy in patients with BRAF mutant melanoma.

2.3.2.1 To determine if changes in blood BRAF levels utilizing peripheral blood $BRAF^{V600}$ mutational testing in patients with Stage IV BRAF mutant melanoma correlate with response and resistance to combination BRAF/MEK directed therapy.

2.3.2.2 To determine if changes in blood BRAF levels utilizing peripheral blood $BRAF^{V600}$ mutational testing in patients with Stage IV BRAF mutant melanoma correlate with response and resistance to combination immunotherapy.

2.3.2.3 To compare the kinetics of peripheral blood $BRAF^{V600}$ levels during response and resistance in groups of patients receiving BRAF targeted therapy or combination immunotherapy as initial therapy.

2.3.2.4 To compare the kinetics of peripheral blood $BRAF^{V600}$ levels during response and resistance to combination BRAF targeted therapy or combination immunotherapy in individual patients (initial treatment vs crossover treatment).

2.4 Secondary Patient Reported Outcomes Objectives

2.4.1 To evaluate differences in overall health between initial treatment arms (dabrafenib + trametinib vs. ipilimumab + nivolumab immunotherapy) at 2 years, accounting for toxicities and overall survival. (Primary)

2.4.2 To assess differences in overall function over 2 years between initial treatment with dabrafenib + trametinib vs. ipilimumab + nivolumab. (Secondary)

2.4.3 To document the effects of treatment crossover and treatment administration sequence on symptom burden and overall function. (Secondary)

2.4.3.1 To compare differences in function and symptoms by treatment sequence for ipilimumab + nivolumab (arm A vs. D), and dabrafenib + trametinib, (arm B vs. C) at baseline, 6 weeks, 12 weeks, and 6 months after the initiation of each treatment.

2.4.3.2 To describe the frequency and severity of treatment toxicities at baseline, 6 weeks, 12 weeks, and 6 months after initiation of each treatment.

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2.5 Exploratory Tobacco Use Objectives

2.5.1 To determine the effects of tobacco, operationalized as combustible tobacco (1a), other forms of tobacco (1b), and environmental tobacco exposure (ETS) (1c) on provider-reported cancer-treatment toxicity (adverse events (both clinical and hematologic) and dose modifications).

2.5.2 To determine the effects of tobacco on patient-reported physical symptoms and psychological symptoms.

2.5.3 To examine quitting behaviors and behavioral counseling/support and cessation medication utilization.

2.5.4 To explore the effect of tobacco use and exposure on treatment duration, relative dose intensity, and therapeutic benefit.

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NOTE: Tobacco Use objectives described above are ancillary for the Tobacco Use Assessment project approved by NCI. A combined analysis of the data from the selected ECOG-ACRIN trials is planned. Data collected from the tobacco use assessment in each parent study will not be analyzed and reported in the clinical study report.

Rev. Add21

2.6 Exploratory Correlative Objective

2.6.1 To assess serum based biomarkers of efficacy and adverse events due to treatment with immune checkpoint inhibitors.

2.6.2 To monitor tumor response by comparing changes in circulating cell-free mutant tumor DNA (**ctDNA**) as a readout of tumor burden (**a**) at week 12 relative to baseline before treatment in responders and non-responders; (**b**) before and during immunosuppressive treatment to control irAEs.

2.6.3 To monitor organ-specific adverse events (irAEs) using circulating cell-free, tissue-specific methylated DNA (**cmeDNA**) as a readout of tissue-specific toxicity (**a**) at the time of grade 3-4 irAE relative to baseline and control patients without irAEs; (**b**) during immunosuppressive treatment for irAEs.

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: All questions regarding eligibility should be directed to the study chair or study chair liaison.

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

3.1 Eligibility Criteria Step 1:

_____ 3.1.1 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of dabrafenib or dabrafenib + trametinib or nivolumab or nivolumab + ipilimumab therapy in patients < 18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

_____ 3.1.2 ECOG Performance status: 0 or 1

_____ 3.1.3 Women must not be pregnant or breast-feeding, as the effects of ipilimumab + nivolumab or dabrafenib + trametinib on the developing human fetus are unknown.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

A female of childbearing potential is anyone, regardless of whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

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Female of childbearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

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_____ 3.1.4 The effects of dabrafenib and trametinib or ipilimumab and nivolumab on the developing human fetus are unknown. Furthermore, dabrafenib has been reported to interfere with the effect of hormone based oral contraceptives. For this reason and because other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing

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potential and sexually active males must agree to use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for the duration of their participation in the study, and for at least 4 weeks after treatment with dabrafenib or for 4 months after dabrafenib in combination with trametinib. Women of child-bearing potential must use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for at least 5 months after the last dose of nivolumab and/or ipilimumab. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

_____ 3.1.5 Patients must have unresectable stage III or stage IV disease.

_____ 3.1.6 Patients must have measurable disease as defined in Section 6.1. All sites of disease must be evaluated within 4 weeks prior to randomization.

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_____ 3.1.7 Patients must have histological or cytological confirmation of melanoma that is metastatic or unresectable and clearly progressive.

NOTE: Any patient with BRAFV600 mutant melanoma (whether cutaneous, acral or mucosal primary) who meets the eligibility criteria is eligible for participation in this trial. Patients with uveal melanoma are not eligibile for this trial.

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_____ 3.1.8 Patients must have BRAFV600 mutation, identified by an FDA-approved test at a CLIA-certified lab. If test at CLIA-certified lab used a non-FDA approved method, information about the assay must be provided. (FDA approved tests for BRAF V600 mutations in melanoma include: THxID BRAF Detection Kit and Cobas 4800 BRAF V600 Mutation Test, Foundation Medicine. Prompt information on tumor BRAF mutation status can also be obtained via Novartis "knowNow" Program. See link for details. https://www.knownowbraf.com/melanoma-testing).

_____ 3.1.9 Patients may have had prior systemic therapy in the adjuvant setting; however this adjuvant treatment must not have included a CTLA4 or PD1 pathway blocking antibody or a BRAF/MEK inhibitor. Also, patients may not have had any prior systemic treatment for advanced (measurable metastatic) disease.

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_____ 3.1.10 Patients must have discontinued chemotherapy, immunotherapy or other investigational agents used in the adjuvant setting ≥ 4 weeks prior to entering the study and recovered from adverse events due to those agents. Mitomycin and nitrosoureas must have been discontinued at least 6 weeks prior to entering the study. Patients must have discontinued radiation therapy ≥ 1 week prior to entering the study and recovered from any adverse events associated with treatment. Prior surgery must be ≥ 2 weeks from registration and patients must be fully recovered from post surgical complications.

_____ 3.1.11 Patients must not receive any other investigational agents while on study or within four weeks prior to registration.

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_____ 3.1.12 Patients are ineligible if they have any currently known active and definitive CNS metastases. Patients who have treated brain metastases (with either surgical resection or stereotactic radiosurgery (SRS)) could be eligible. Patients must not have taken any steroids ≤ 10 days prior to randomization for the purpose of managing their brain metastases. Repeat imaging after SRS or surgical resection is not required so long as baseline MRI is within 4 weeks of registration. Patients with multiple brain metastases treated with SRS (w or w/o WBRT), are not an exclusion. Patients with definitive CNS metastases treated with only WBRT are ineligible. Patients with potential CNS metastases that are too small for treatment with either SRS or surgery (e.g. 1-2 mm) and/or are of uncertain etiology are potentially eligible, but need to be discussed with and approved by the Study PI.

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_____ 3.1.13 Patients must not have other current malignancies, other than basal cell skin cancer, squamous cell skin cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast. Patients with other malignancies are eligible if they have been continuously disease-free for > 2 years prior to the time of registration.

_____ 3.1.14 Patients must have the following values for initial laboratory tests obtained within 4 weeks prior to randomization (ULN: institutional upper limit of normal):

_____ 3.1.14.1 White Blood Count ≥ 3,000/uL

_____ 3.1.14.2 ANC ≥ 1,500/uL

_____ 3.1.14.3 Platelet Count ≥ 100,000/uL

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_____ 3.1.14.4 Hemoglobin > 8 g/dL

_____ 3.1.14.5 Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or serum creatinine clearance (CrCl) ≥ 40ml/min. (CrCl= Wt (kg) x (140-age)*/72 x Cr. level, *female x 0.85)

_____ 3.1.14.6 AST and ALT ≤ 3 x ULN (≤ 5 x ULN for patients with documented liver metastases)

_____ 3.1.14.7 Alkaline Phosphatase ≤ 2 x ULN (≤ 5x ULN for patients with known liver involvement and ≤ 7x ULN for patients with known bone involvement)

_____ 3.1.14.8 Total Bilirubin ≤ 1.5 x ULN except subjects with normal direct bilirubin or those with known Gilbert's syndrome

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3.1.15 Patients must not have any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), including but not limited to, ongoing or active infection requiring parenteral antibiotics on day 1, or psychiatric illness/social situations that would limit compliance with study requirements, interfere with subject's safety, or obtaining informed consent. Therapeutic level dosing of warfarin can be used with close monitoring of PT/INR by the site. Exposure may be decreased due to enzyme induction when on treatment, thus warfarin dosing may need to be adjusted based upon PT/INR. Consequently, when discontinuing dabrafenib, warfarin

exposure may be increased and thus close monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate. Prophylactic low dose warfarin may be given to maintain central catheter patency.

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_____ 3.1.16 Patients must not have a history of or evidence of cardiovascular risks including any of the following:

- QT interval corrected for heart rate using the Bazett's formula QTcB ≥ 480 msec.at baseline.

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- History of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within the past 24 weeks prior to registration.
- History prior to registration or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) functional classification system. (See Appendix IX)
- LVEF ≤ 45% on cardiac echo or MUGA.
- Intra-cardiac defibrillator.

_____ 3.1.17 Individuals who are known to be HIV infected are ineligible (Note: HIV testing is not required for entry into the study).

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_____ 3.1.18 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), should be evaluated for the presence of target organ involvement and potential need for systemic treatment. If no systemic immune suppression is deemed necessary they can be eligible.

_____ 3.1.19 The following medications or non-drug thrapies are also prohibited while on treatment in this study:

- Other anti-cancer therapies
- Other investigational drugs

Patients taking any medications or substances that are strong inhibitors or inducers of CYP3A or CYP2C8 are ineligible (see Appendix XI).

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_____ 3.1.20 Patients must not have history of retinal vein occlusion (RVO).

_____ 3.1.21 Patients must not have evidence of interstitial lung disease or pneumonitis.

_____ 3.1.22 Patients must not have malabsorption, swallowing difficulty, or other conditions that would interfere with the ingestion or absorption of dabrafenib or trametinib.

_____ 3.2 Eligibility Criteria Step 2 (Crossover arms):

_____ 3.2.1 The patient must have met all eligibility criteria in Section 3.1 (except as detailed below) at the time of crossover.

3.2.1.1 (3.1.6) – RECIST defined measurable disease is not required (see 0).

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3.2.1.2 (3.1.9) - Only prior systemic therapy as part of Step 1 is allowed. Patients who received allowed systemic therapy in the adjuvant setting prior to Step 1 (see Section 3.1.9) and were eligible for Step 1 are not excluded from proceeding to Step 2 if they meet other eligibility criteria.

3.2.1.3 (3.1.22 and 3.1.21) malabsorption, swallowing difficulty, or other conditions that would interfere with the ingestion or absorption of dabrafenib or trametinib, or history of retinal vein occlusion are acceptable for patients crossing over to Arm D (ipilimumab + nivolumab) treatment.

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3.2.1.4 (3.1.19, 3.1.22) history of autoimmune disease, excluding interstitial lung disease or pneumonitis, is allowed in patients crossing over to Arm C (dabrafenib/trametinib) therapy (see 3.2.4).

3.2.1.5 (3.1.10, 3.1.12) Patients crossing over from Arm A (nivolumab/ipilimumab) to Arm C (dabrafenib/trametinib) who underwent surgery or SRS to CNS metastases need not be off of steroids to start treatment (see 3.2.6).

3.2.1.6 (3.1.14) There is no restriction on serum LDH at crossover.

3.2.1.7 (3.1.16) Patients with a history of cardiovascular risks that developed during Step 1 of therapy should be discussed with study PI at time of crossover.

_____ 3.2.2 Patients randomized to Arm A on Step 1 must have melanoma that is metastatic and clearly progressive on Step 1 therapy prior to crossing over to Arm C.

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NOTE: Patients should (if possible) be at least 1 week from documented PD on Step 1 of current study. All sites of disease must be evaluated within 4 weeks prior to registration.

3.2.3 Patients randomized to Arm B on Step 1 may cross over to Arm D at or prior to disease progression

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NOTE: If possible, patients should wait to cross over until after the cycle with the next protocol-required imaging assessment is completed. All sites of disease must be evaluated within 4 weeks prior to Step 2 registration.

NOTE: Patients should start Arm D treatment at least 1 week after stopping dabrafenib and trametinib, unless otherwise clinically indicated.

NOTE: Baseline labs and QOL assessments should be completed, and patients should follow the Arm D schedule as described in Section 5.1.4.

_____ 3.2.4 Patients must have recovered from adverse events (toxicities resolved to grade 1 or less) of prior therapy. Patients with immune related toxicities from ipilimumab + nivolumab may continue onto Step 2 even if still on steroids to control side effects, so long as toxicity has resolved to grade 1 or less.

_____ 3.2.5 Patients must have discontinued radiation therapy prior to registering to Step 2 of the study and recovered from any adverse events associated with treatment. Prior surgery must be ≥ 2 weeks from registration to Step 2 and patients must be fully recovered from post-surgical complications.

_____ 3.2.6 Patients are ineligible if they have any currently active and definitive CNS metastases. Patients who have treated brain metastases (with either surgical resection or stereotactic radiosurgery (SRS)) could be eligible to proceed. Patients crossing over from Arm B (dabrafenib/trametinib) to Arm D (nivo/ipi) must not have taken any steroids ≤ 10 days prior to Step 2 registration for the purpose of managing their brain metastases. Patients with only Whole Brain irradiation for treatment of CNS metastases are ineligible. Patients with definitive CNS metastases treated with only WBRT are ineligible. Patients with potential CNS metastases that are too small for treatment with either SRS or surgery (e.g. 1-2 mm) and/or are of uncertain etiology are potentially eligible, but need to be discussed with and approved by the Study PI.

Rev. Add13 _____ 3.2.7 Patients must not have other current malignancies.

Rev. Add13 _____ 3.2.8 Women must not be pregnant or breast-feeding, as the effects of ipilimumab + nivolumab or dabrafenib + trametinib on the developing human fetus are unknown. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to Step 2 crossover to rule out pregnancy.

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A female of childbearing potential is anyone , regardless of whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months.

Female of child bearing potential? _____ (Yes or No)

Date of blood test or urine study_____

_____ 3.2.9 The effects of dabrafenib and trametinib or ipilimumab and nivolumab on the developing human fetus are unknown. Furthermore, dabrafenib has been reported to interfere with the effect of hormone based oral contraceptives. For this reason and because other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and sexually active males must agree to continue to use the same contraception requirements as on Step 1 of this study (ie: use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for the duration of their participation in the study, and for at least 4 weeks after treatment with dabrafenib or for 4 months after dabrafenib in combination with trametinib. Women of child-bearing potential must use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for at least 5 months after the last dose of nivolumab and/or ipilimumab.Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

_____ _____

Physician Signature Date

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

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4. Registration and Randomization 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).

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

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).

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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. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. 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:

Site registration forms may be downloaded from the **EA6134** protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- 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
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol EA6134
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

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Requirements for EA6134 (DREAMseq) Trial Site Registration:

- EA Ipilimumab Investigator Training (please see Section 4.3.5)

Submitting Regulatory Documents

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Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

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

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

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2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: **The above submissions must include the following details:**

   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

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 at the top of your screen;
- Click on the Site Registration tab;
- 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 Step 1 randomization.

Treatment should start within seven working days after Step 1 randomization.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

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;
- To perform enrollments or request slot reservations: 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).

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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.

The following information will be requested:

4.1 Randomization (Step 1)

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient demographics
  - Sex
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - ZIP code
  - Method of payment
  - Country of residence

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4.1.4 Eligibility Verification

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

4.1.5 Stratification Factors

- ECOG PS: 0 or 1
- Serum LDH: Normal or elevated, defined as above ULN for institution.

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4.2 Randomization (Step 2)

Patients on Arm A or Arm B will re-register and crossover to Step 2. Arm A patients will re-register and crossover to Arm C in Step 2. Arm B patients will re-register and crossover to Arm D in Step 2.

NOTE: Before crossover to Arm C, Arm A patients must have melanoma that is metastatic and clearly progressive on Step 1 therapy. Confirmation of PD with second imaging scan after 4 weeks is not needed in patients with symptoms or laboratory data (rising LDH) supporting disease progression.

NOTE: In response to the Data and Safety Monitoring Committee (DSMC) recommendations, Arm B patients may cross over to Arm D either prior to or at disease progression.

Treatment must start within 7 working days of registration to Step 2.

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4.2.1 Protocol Number

Investigator Identification

- Institution and affiliate name
- Investigator's name

4.2.2 Patient Identification

- Patient's initials (first and last)
- Patient demographics
  - Sex
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - ZIP code
  - Method of payment
  - Country of residence

4.2.3 Eligibility Verification

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Patients must meet all of the eligibility requirements listed in Section 3.2.

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.

4.3.2 Pathological samples are required to be submitted for central diagnostic review (mandatory) and for defined laboratory research studies (per patient consent) as indicated in Section 10.

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4.3.3 Biological samples are to be submitted for defined laboratory research studies per patient consent as outlined in Section 10.

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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.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and

- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent 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 listed 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 accounts 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.

Rev. Add21

4.3.4 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.

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4.3.5 Additional Registration Training Requirement

Mandatory Investigator Training Course:

ECOG-ACRIN has developed a training course to provide additional information to enrolling investigators on the toxicity profile of the ipilimumab and nivolumab combination. Each investigator is required to take the training course entitled: **ECOG-ACRIN EA6134 Protocol Training**, prior to their first patient enrollment.

Investigators and site staff are able to self-enroll in the course by accessing the training URL:
http://coccg.mindflash.com/PublicCoursePage.aspx?c=1232832108.

Patient enrollments will be blocked via the OPEN system if the enrolling investigator has not completed the required training. All site research staff participating in EA6134 are also encouraged to take the training course.

Upon completion of the training course, continue through to the end of the module until you are directed to the electronic copy of your completion certificate. You will also receive an email notification at the email address registered with Mindflash that the training has been completed. Download and save the certificate, as you will need to upload this to the CTSU Regulatory Submission Portal, following the process listed below. Please note that only investigators need to submit the training completion certificate to the CTSU. Once submitted, the training record will be stored in the regulatory database as a person attribute and the corresponding site regulatory requirement will be updated.

If you have questions regarding training, please contact the CTSU Regulatory Office at 1-866-651-2878 or the ECOG-ACRIN Clinical Education and Awareness Team at EAClinEd@ecog-acrin.org. Additional information can be accessed on the CTSU: Search EA6143 → Supplemental Documents → 12Dec2019 post date

Training Requirement Approval Process:

1. Complete the required protocol training, using the link provided in the protocol
2. Save a copy of the training completion certificate
3. Submit certificate to the CTSU Regulatory Office:
   3.1. Regulatory Submission Portal: https://www.ctsu.org

3.2. Log in to the Members' area using your CTEP-IAM username and password

3.3. Select the Regulatory Tab → Regulatory Submission → Add New Submission

3.4. Under the "Documents being submitted are for:" drop-down menu, select "Specific Person(s) Only"

3.5. In the "Pick Person(s)" field either select the applicable name(s) using the drop-down menu, or type the applicable name(s) into the search field to narrow down the choices in the drop-down menu

3.6. Select "Add to Cart"

3.7. Select "Next"

3.8. Upload and submit a copy of your training certificate

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4.3.6 ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) System:

When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to EASEE-PRO, and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how

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to activate their account for self-directed web entry of surveys. After their account is activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

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 and EASEE-PRO according to the schedule in the EA6134 Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

In Step 1, patients will be randomized to either Arm A (Induction Immunotherapy with Nivolumab 1mg/kg IV infusion + Ipilimumab 3mg/kg followed by Immunotherapy Maintenance with Nivolumab 3mg/kg alone) or Arm B (Dabrafenib 150 mg + Trametinib 2 mg).

Treatment must be started within 7 working days of randomization to Step 1.

Patients progressing on either Arm A or Arm B will re-register and crossover to Step 2. Arm A patients will re-register and crossover to Arm C in Step 2. Arm B patients will re-register and crossover to Arm D in Step 2.

NOTE: In response to the Data and Safety Monitoring Committee (DSMC) recommendations, patients on Arm B may crossover to Arm D prior to progression.

Treatment must start within 7 working days of registration to Step 2.

Doses are based on actual body weight. Recalculate dosing at each cycle only if there is a 10% change in weight (See Section 8.1.5 for dosing specifics for Ipilimumab. See Section 8.2.8 for dosing specifics for Nivolumab.)

For all arms, 1 cycle is 42 days (6 weeks) long.

5.1.1 ARM A

5.1.1.1 Initial Treatment

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Immunotherapy Induction: 1 cycle is 42 days (6 weeks) long.

Investigators can choose between two induction regimens (Regimen 1 or Regimen 2 below) of nivo/ipi which appear to have equivalent efficacy. (Lebbe C et al ESMO 2018)

Regimen 1: Nivolumab 1 mg/kg IV infusion Day 1 and 22 of Cycles 1 and 2.

Nivolumab is to be administered as a 30-60-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron low-protein binding in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 1 mg/mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

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Ipilimumab 3 mg/kg IV infusion Day 1 and 22 of Cycles 1 and 2.

Ipilimumab is to be administered as a 30-90-minute IV infusion (dependent on institutional standard/policy), using a volumetric pump with a 0.2 to 1.2 micron low-protein

binding in-line filter. Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 2 mg/mL.

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Regimen 2: Nivolumab 3 mg/kg IV infusion Day 1 and 22 of Cycles 1 and 2.

Nivolumab is to be administered as a 30-60 minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron low-protein binding in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 1 mg/mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

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Ipilimumab 1 mg/kg IV infusion Day 1 and 22 of Cycles 1 and 2.

Ipilimumab is to be administered as a 30-90-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron low-protein binding in-line filter. Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 2 mg/mL.

When infusions of ipilimumab and nivolumab are given on the same day, the preferred treatment is to give nivolumab followed by ipilimumab. Separate infusion bags and filters must be used for each infusion. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

Toxicity management for the combined agents follows the same template guidelines and algorithms for single agent nivolumab.

5.1.1.2 **Immunotherapy Maintenance: 1 cycle is 42 days (6 weeks) long.**

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Nivolumab 3 mg/kg IV infusion Day 1, 15 and 29 of cycles 3-14 (max until 84 weeks or 72 weeks of maintenance).

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At disease progression, crossover to Arm C.

5.1.2 ARM C

Dabrafenib 150 mg po twice daily days 1-42 of each 6 week cycle

Trametinib 2 mg po daily days 1-42 of each 6 week cycle

Treatment will continue for as long as patient is responding and tolerating therapy.

5.1.3 ARM B

Initial Treatment

Dabrafenib 150 mg po twice daily days 1-42 of each 6 week cycle

Trametinib 2 mg po daily days 1-42 of each 6 week cycle

Treatment will continue for as long as patient is responding and tolerating therapy.

At (or prior to) disease progression, crossover to Arm D.

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5.1.4 ARM D

Immunotherapy Induction (See Section 5.1.1.1 for treatment administration details).

Investigators can choose between two induction regimens (Regimen 1 or Regimen 2 below) of nivo/ipi which appear to have equivalent efficacy. (Lebbe C et al ESMO 2018)

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Regimen 1: Nivolumab 1 mg/kg IV infusion Day 1 and 22 of Cycles 1 and 2 (Should be administered ahead of ipilimumab on days when both to be administered)

Nivolumab is to be administered as a 30-60-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron low-protein binding in-line filter at the protocol-specified dose. The drug can be diluted with 0.9%

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normal saline for delivery but the total drug concentration of the solution cannot be below 1 mg/mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Ipilimumab 3 mg/kg IV infusion Day 1 and 22 of Cycles 1 and 2

Ipilimumab is to be administered as a 30-90-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron low-protein binding in-line filter. Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 2 mg/mL.

OR

Regimen 2: Nivolumab 3 mg/kg IV infusion Day 1 and 22 of Cycles 1 and 2 (Should be administered ahead of ipilimumab on days when both to be administered)

Nivolumab is to be administered as a 30-60 minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron low-protein binding in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 1 mg/mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Ipilimumab 1 mg/kg IV infusion Day 1 and 22 of Cycles 1 and 2.

Ipilimumab is to be administered as a 30-90-minute IV infusion (dependent on institutional standard/policy), using a volumetric pump with a 0.2 to 1.2 micron low-protein binding in-line filter. Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 2 mg/mL.

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Immunotherapy Maintenance

Nivolumab 3 mg/kg IV infusion Day 1,15 and 29 of cycles 3-14 (max 84 or 72 weeks of maintenance)

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5.1.5 Progressive disease will be determined by RECIST criteria for all arms. Crossover should occur at a minimum of 1 week after defined PD on either arm. Patients on either arm with “equivocal” progression, defined as PD by RECIST in the absence of disease related symptoms and in the setting of evidence of potential ongoing treatment benefit (e.g. falling LDH, shrinkage of the majority of lesions) can delay cessation of initial treatment and crossover until PD is confirmed with a repeat scan performed 4 weeks (+/- 1 week) after the initial scan. If RECIST PD is confirmed then treatment discontinuation must happen at that time. The initial PD scan will be designated the time of PD. For patients on Step 1, a washout period of 1 week is still required from either the last dose of dabrafenib/trametinib or the first missed dose of nivo +/- ipi due to documentation of PD prior to crossover. Potential exceptions to this 1 week washout must be discussed with study PI and approved. Crossover should happen within 12 weeks of initial date of RECIST defined PD. Exceptions to this timeframe must be discussed with the study PI. If PD is not confirmed, (e.g. new lesions no longer present or are getting smaller, or overall disease is smaller and no longer meets criteria for RECIST defined PD) patient may continue on therapy with scans performed at the time dictated by the protocol e.g. subsequent scans should continue at the 12 week interval defined from the time of treatment initiation for that step of therapy. The same rules will apply to discontinuation of study treatment after crossover to the alternative treatment regimen.

Patients taken off treatment for any reason other than progression per RECIST criteria will undergo tumor imaging at protocol defined times and cannot proceed to Step 2 until RECIST defined disease progression is documented (more frequent scanning is allowed in this situation). Patients taken off treatment on Arm B can proceed to Arm D without the need for documented progression.

Patients must meet Step 2 eligibility criteria at the time of crossover registration with improvement of treatment related toxicity to grade 1 or less. Some notable exceptions are below. Please see Section 3.2 for more details.

1. Patients on Arm A may be on a stable (for at least 1 week) or tapering dose of steroids at time of crossover to dabrafenib and

trametinib. Patients on Arm B must be off of steroids for at least 2 weeks at time of crossover.

2. There is no LDH cutoff at time of crossover.

Patients may undergo local therapy (e.g. RT or surgery) for treatment of local disease progression, but still must meet eligibility criteria regarding treatment interval before initiating crossover therapy.

Patients who are more than 4 weeks from previous staging CT scan at time of crossover should have a repeat staging prior to initiating crossover therapy.

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5.2 Adverse Event Reporting Requirements

Effective April 1, 2018 expedited adverse event reporting done via CTEP-AERS will use CTCAE version 5.0 terminology and grading. Routine adverse event reporting and dose modifications guidelines will continue to be based on CTCAE version 4.0 terminology and grading.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 and 5.0. A copy of both versions of the CTCAE can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as 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.

5.2.2 Routine Reporting of Adverse Events (Medidata Rave)

Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave 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 E1912 forms packet for instructions on where, when and what adverse events are to be reported routinely on this protocol.

5.2.3 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 the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). Sections 5.2.5-5.2.10 outline the procedure for expedited reporting of adverse events on this protocol.

5.2.4 Terminology

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

laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories. For patients developing AEs attributable to protocol treatment following crossover, attribution should be designated to the appropriate treatment regimen (e.g. Ipilimumab+Nivolumab or Dabrafenib+Trametinib) to the extent possible.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to protocol treatment.
Unlikely	The AE is *doubtfully related* to protocol treatment.
Possible	The AE *may be related* to protocol treatment.
Probable	The AE is *likely related* to protocol treatment.
Definite	The AE is *clearly related* to protocol treatment.

- **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. 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 patient at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** 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 a serious when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported in CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event. Since this protocol uses multiple investigational agents, if an AE is listed on multiple SPEERS, use the lower of the grades to determine if expedited reporting is required.

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5.2.5 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 https://ctepcore.nci.nih.gov/ctepaers. Use the protocol number and the protocol-specific patient ID assigned during registration on the CTEP-AERS reports and all supporting or follow up data.

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)
- the NCI (301-897-7497)

Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS by the original reporter.

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. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-7404) and in the same timeframe. All supporting and follow up documentation must include the protocol number, patient ID number, and CTEP-AERS ticket number on each page.

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NCI 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 EA6134 and outline the specific expedited adverse event reporting requirements for study EA6134.

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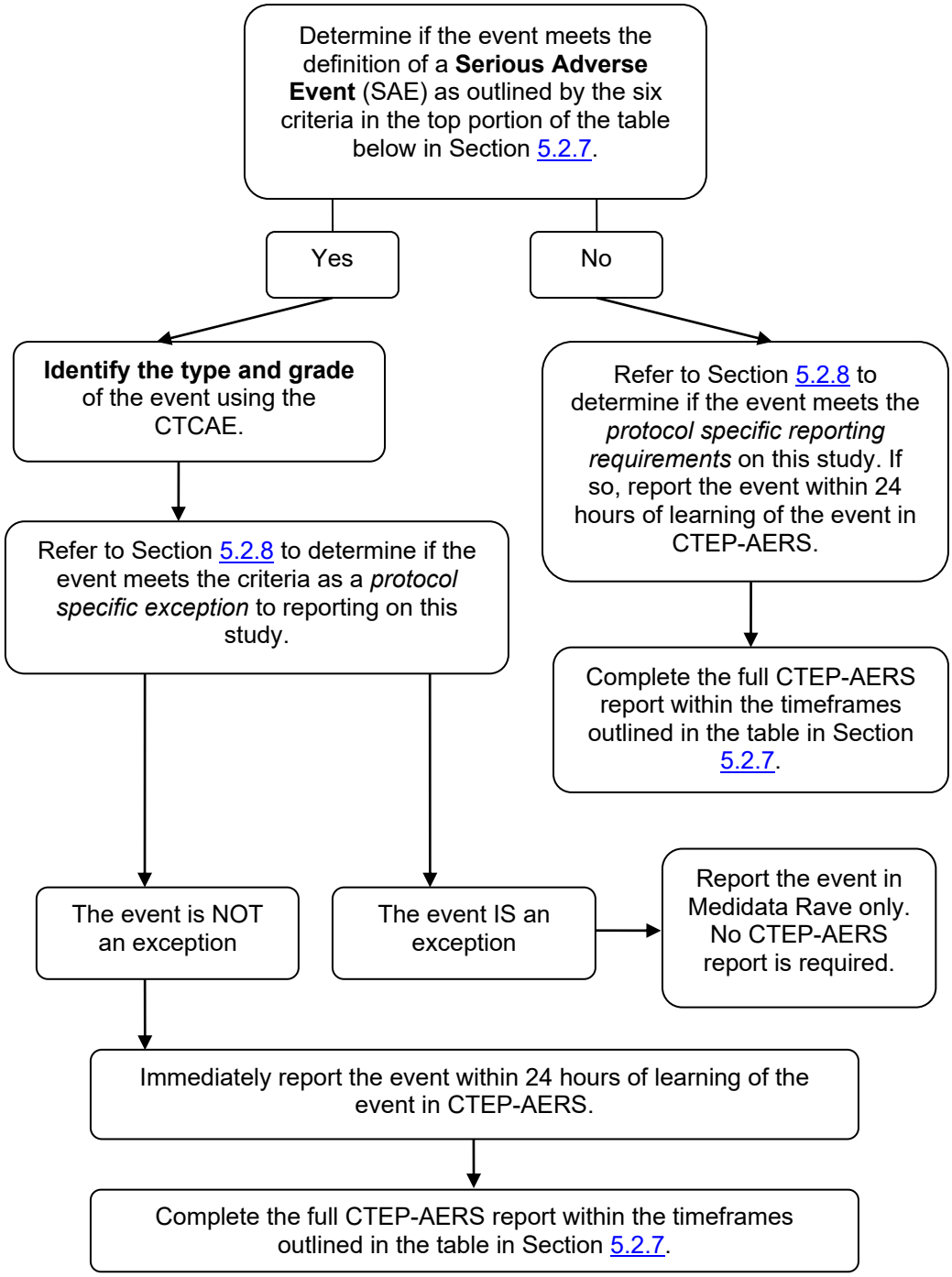
5.2.6 Steps to determine if an adverse event is to be reported in an expedited manner – Arms A, B, C, and D

5.2.6.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.2.6.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

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 5.2.7 OR the protocol specific requirements in Section **Error! Reference source not found.**, 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 4-5 SAEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported within 24 hours of learning of the events in CTEP-AERS even if the patient is off study.

Expedited 24-hour notification followed by complete report within 10 calendar days for:

- All Grade 1-3 SAEs

5.2.7 Expedited Reporting Requirements for Arm A, B, C, and D on protocol EA6134

Investigational Agents: Ipilimumab, Nivolumab, Dabrafenib, Trametinib

Late Phase 2 and Phase 3 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(s).*[1]

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

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

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

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

1. Death
2. A life-threatening AE
3. An AE 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 SAEs that meet the above criteria **MUST** be immediately reported in CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported in CTEP-AERs within 24 hours of learning of the event. The full CTEP-AERS report must be completed within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported in CTEP-AERs within 24 hours of learning of the event. The full CTEP-AERS report must be completed within 5 calendar days of the initial 24-hour report.

[1]SAEs 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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

Effective Date: August 30, 2024

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Rev. Add14

5.2.8 Additional instructions, requirements and exceptions for protocol EA6134

Additional Instructions

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events , 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 study treatment 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.

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EA6134 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 patient is onprotocol treatment, or within 90 days of the patient’s last dose of protocol treatment are considered immediately reportable events . The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported immediately (within 24 hours of learning of the event) in CTEP-AERS.Complete the full CTEP-AERS report within 5 calendar days. . Please refer to Appendix VI for detailed instructions and timeframes on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.
- **Immune Related Adverse Events (IRAEs)**: Any grade 3 or higher immune related adverse events (see Section 5.4.3 for definitions) must be reported immediately (within 24 hours of learning of the event) in CTEP-AERS. Complete the full CTEP-AERS report within the timeframes outlined in the SAE table in Section 5.2.7. If available, please submit any supporting data as well (e.g.: autoimmune serology tests or biopsy reports). Any questions regarding if an event qualifies as an IRAE can be directed to the study chair. Of note, delayed IRAEs may still occur in patients on Arm C as a consequence of delayed toxicity from prior ipilimumab/nivolumab with or without potential exacerbation by dabrafenib/trametinib. Examples include but are

not limited to interstitial nephritis and renal failure, severe potentially immune related hepatitis or skin rash.

NOTE: In order for ECOG-ACRIN to appropriately report these events to regulatory agencies, please be sure to state that the event being reported is an IRAE in the 'Description of Event' section of the CTEP-AERS report.

For Arms B and C only:

- **LVEF Changes:** If any of the following circumstances occur, the event(s) must be reported immediately (within 24 hours of learning of the event) in CTEP-AERS. Complete the full CTEP-AERS report within the timeframes outlined in the AE table in Section 5.2.7.
  - Asymptomatic: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN and LVEF **does not recover** within 4 weeks
  - Symptomatic: Grade 3-4 LVEF

Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for LVEF Decrease

- **Visual Changes:** If RPED (retinal pigment epithelial detachments) or RVO (retinal vein occlusion) are diagnosed, the event(s) must be reported immedieately (within 24 hours of learning of the event) in CTEP-AERS. Complete the full CTEP-AERS report within the outlined in the SAE table in Section 5.2.7. Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for Visual Changes.
- **Liver Chemistry Changes:** If any of the following circumstances occur, the event(s) must be reported immediately (within 24 hours of learning of the event) in CTEP-AERS Complete the full CTEP-AERS report within the outlined in the SAE table in Section 5.2.7.
  - ALT ≥ 3xULN **and** bilirubin ≥ 2x ULN or > 35% direct bilirubin
  - ALT ≥ 3xULN **and** INR >1.5, if INR measured (INR threshold does not apply if subject is on anticoagulant)

Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for Liver Chemistry Changes

For Arms A and D only:

- **Infusion Reactions:** Any grade 3 or higher Nivolumab related infusion reaction that meets the definition of SAE in Section 5.2.7 must be reported immediately (within 24 hours of learning of the event) in CTEP-AERS. Complete the full CTEP-AERS report within the timeframes outlined in the SAE table in Section 5.2.7.

EA6134 specific expedited reporting exceptions:

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For study arms A, B, C and D the adverse events listed below **do not** require expedited reporting in CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event. Since this protocol uses multiple investigational agents, if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

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NOTE: Any reporting requirement outlined in the EA6134 specific expedited reporting requirements section above supercedes any exception listed in the SPEER.

5.2.9 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Supporting and follow up data must be forwarded to ECOG-ACRIN, and the NCI as outlined in Section 5.2.5.

Adverse events determined to be reportable via CTEP-AERS 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.

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5.2.10 Second Primary Cancer Reporting Requirements

All cases of second (second malignancy is a cancer that is unrelated to any prior anti-cancer treatment, including the treatment on this protocol) **and** secondary malignancies (secondary malignancy is a cancer caused by any prior anti-cancer treatment, including the treatment on this protocol), including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and RAS-mutation positive malignancies, regardless of attribution, that occur following treatment on NCI-sponsored trials must be reported as follows:

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Report the diagnosis in the CTEP-AERS application, regardless of attribution, at https://ctepcore.nci.nih.gov/ctepaers

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   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy, d.) Neoplasms Other, malignant (grade 3 or 4)
3. Upload a copy of the pathology report to ECOG-ACRIN in Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.

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

NOTE: **All new malignant tumors must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment.** All new malignancies should be reported including solid tumors (including non-melanoma skin malignancies), hematologic malignancies, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML), and *in situ* tumors.

Whenever possible, the CTEP-AERS report should include the following:

- tumor pathology
- history of prior tumors
- prior treatment/current treatment including duration
- any associated risk factors or evidence regarding how long the tumor may have been present
- when and how the tumor was detected

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- molecular characterization or cytogenetics, including RAS-mutation status, of the original tumor (if available) and of any new tumor
- tumor treatment and outcome (if available).

NOTE: The 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 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 via CTEP-AERS or by the Second Primary Form.

5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR)

5.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab (MDX-010, NSCs 732442 and 720801)

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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER. Since this protocol uses multiple investigational agents if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

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Rev. Add12
Rev. Add17

Version 2.10, March 29, 2019[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis[2] (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
		General disorders and administration site conditions - Other (Systemic inflammatory response syndrome [SIRS])	
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder[2]		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders - Other (immune-mediated encephalitis)[2]	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[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]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia

CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy

EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)

GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatic failure[2]

IMMUNE SYSTEM DISORDERS - Allergic reaction

INFECTIONS AND INFESTATIONS - Infection[7]

INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia

RENAL AND URINARY DISORDERS - Proteinuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation

VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

NOTE: Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) 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.

5.3.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for BMS-936558 (Nivolumab, MDX-1106, NSC 748726)

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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2069 patients. Below is the CAEPR for Nivolumab.

Rev. 12/15
Rev. Add22

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER. Since this protocol uses multiple investigational agents, if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

Rev. 3/16, 2/17

Rev. Add12

Version 2.6, May 14, 2025[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (lymphatic dysfunction)	
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hyperthyroidism[3]		
	Hypophysitis[3] Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)[3]	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-related hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoid granuloma, sarcoidosis)[3]	
		Immune system disorders - Other (solid organ transplant rejection)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocytes decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (eruptive keratoacanthoma)	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (immune-related nephritis)	
		Renal and urinary disorders - Other (renal dysfunction)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		(bronchiolitis obliterans with organizing pneumonia (BOOP))[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3] Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[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]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Nivolumab, being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia and systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving nivolumab. These complications may occur despite intervening therapy between receiving nivolumab and allo-SCT.

[7]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia

EAR AND LABYRINTH DISORDERS - Vestibular disorder

EYE DISORDERS - Eye disorders - Other (iridocyclitis)

GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Malaise; Pain

HEPATOBILIARY DISORDERS - Bile duct stenosis

IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (complications of allogeneic HSCT); Immune system disorders - Other (limbic encephalitis)

INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection

INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Lymphocyte count increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis)

NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage

PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (rosacea)

VASCULAR DISORDERS - Hypertension; Hypotension; Vasculitis

NOTE: Nivolumab 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.

Rev. 1/17

5.3.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Trametinib dimethyl sulfoxide (GSK1120212B, NSC 763093)

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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol

specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1111 patients.* Below is the CAEPR for Trametinib dimethyl sulfoxide (GSK1120212B).

Rev Add 15
Rev. Add16
Rev. Add19

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER. Since this protocol usesmultiple investigational agents, if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, October 10, 2019[1]

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
	Sinus bradycardia		
EYE DISORDERS			
	Blurred vision		
	Dry eye		
		Eye disorders - Other (chorioretinopathy also known as retinal pigment epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	
	Eye disorders - Other (visual disorders)[2]		
		Papilledema	
	Periorbital edema		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
Generalized edema[3]			***Generalized edema[3] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[4]		
INFECTIONS AND INFESTATIONS			
	Folliculitis		***Folliculitis (Gr 2)***
	Lung infection		
	Paronychia		***Paronychia (Gr 2)***
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	CPK increased		
	Ejection fraction decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypoalbuminemia		
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
		Pneumonitis	

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Nail changes		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])	
Skin and subcutaneous tissue disorders - Other (rash)[5]			***Skin and subcutaneous tissue disorders - Other (rash)[5] (Gr 3)***
		Stevens-Johnson syndrome[6]	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event (venous)	
	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 include visual disturbance that can be associated with conjunctival hemorrhage, corneal graft rejection, cyclitis, eye nevus, halo vision, iritis, macular edema, retinal hemorrhage, visual acuity reduced, visual impairment, and vitreous detachment.

[3] Generalized edema includes edema, lymphedema, and edema limbs.

[4] Hypersensitivity (allergic reactions) may present with symptoms such as fever, rash, increased liver function tests, and visual disturbances.

[5] Skin and subcutaneous tissue disorders - Other (rash) may include rash, rosacea, rash acneiform, erythematous rash, genital rash, rash macular, exfoliative rash, rash generalized, erythema, rash papular, seborrhoeic dermatitis, dermatitis psoriasiform, rash follicular, skin fissures, and skin chapped.

[6] Stevens-Johnson syndrome has been observed in patients treated with trametinib and dabrafenib combination.

[7] The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI hemorrhage, GU hemorrhage, respiratory hemorrhage), and fatal intracranial hemorrhages have been reported.

Adverse events reported on trametinib dimethyl sulfoxide (GSK1120212B) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility

that trametinib dimethyl sulfoxide (GSK1120212B) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Myocardial infarction; Restrictive cardiomyopathy; Sinus tachycardia

EYE DISORDERS - Corneal ulcer; Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Photophobia

GASTROINTESTINAL DISORDERS - Ascites; Duodenal ulcer; Esophageal necrosis; Esophageal ulcer; Esophagitis; Gastric hemorrhage[7]; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Gingival pain; Hemorrhoidal hemorrhage[7]; Ileus; Obstruction gastric; Pancreatitis; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (axillary pain); Localized edema; Malaise; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatic pain; Hepatobiliary disorders - Other (hepatic encephalopathy)

INFECTIONS AND INFESTATIONS - Biliary tract infection; Catheter related infection; Device related infection; Endocarditis infective; Enterocolitis infectious; Hepatitis viral; Infections and infestations - Other (abscess limb); Infections and infestations - Other (necrotizing fasciitis); Infections and infestations - Other (oral infection); Pharyngitis; Sepsis; Upper respiratory infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Lymphocyte count decreased; Platelet count decreased; Serum amylase increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (compression fracture); Myalgia; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage[7]; Tumor pain

NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage[7]; Lethargy; Nervous system disorders - Other (diplopia); Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Personality change

RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Dysuria; Hematuria; Proteinuria; Urinary incontinence

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula; Vaginal hemorrhage[7]

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage[7]; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pleural effusion;

Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (erythema nodosum); Skin ulceration; Urticaria

VASCULAR DISORDERS - Hematoma; Hot flashes; Hypotension

NOTE: Trametinib (GSK1120212B) 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.

Rev. 11/16

5.3.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Dabrafenib mesylate (GSK2118436B, NSC 763760)

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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 1374 patients. Below is the CAEPR for Dabrafenib (GSK2118436B).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER. Since this protocol uses multiple investigational agents, if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

Rev Add 18

Version 2.7, January 17, 2025[1]

Rev Add 19

Adverse Events with Possible Relationship to Dabrafenib (GSK2118436B) (CTCAE 5.0 Term) [n= 1374]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2,3]		***Anemia[2,3] (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Left ventricular systolic dysfunction[4]	

Adverse Events with Possible Relationship to Dabrafenib (GSK2118436B) (CTCAE 5.0 Term) [n= 1374]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
EYE DISORDERS			
		Eye disorders - Other (iritis)[5]	
		Uveitis[5]	
		Vision decreased	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
Nausea			***Nausea (Gr 3)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs[6]		***Edema limbs[6] (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
Fever[7]			***Fever[7] (Gr 2)***
	Flu like symptoms		***Flu like symptoms (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[8]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis (HLH))[9]	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
INVESTIGATIONS			
	Creatinine increased[3]		***Creatinine increased[3] (Gr 2)***
	Neutrophil count decreased[3]		***Neutrophil count decreased[3] (Gr 3)***
	Platelet count decreased[3]		***Platelet count decreased[3] (Gr 2)***
	White blood cell decreased[3]		***White blood cell decreased[3] (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia[3]		***Hyperglycemia[3] (Gr 2)***
	Hypokalemia[3]		***Hypokalemia[3] (Gr 2)***
	Hyponatremia[3]		***Hyponatremia[3] (Gr 3)***
	Hypophosphatemia[3]		***Hypophosphatemia[3] (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia			***Arthralgia (Gr 3)***
	Back pain		***Back pain (Gr 3)***
	Myalgia		***Myalgia (Gr 3)***
	Pain in extremity		***Pain in extremity (Gr 3)***

Adverse Events with Possible Relationship to Dabrafenib (GSK2118436B) (CTCAE 5.0 Term) [n= 1374]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (squamous cell carcinoma or keratoacanthoma)[10]		***Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (squamous cell carcinoma or keratoacanthoma)[10] (Gr 2)***
	Skin papilloma		***Skin papilloma (Gr 2)***
		Treatment related secondary malignancy (non SCC)[11]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
Headache			***Headache (Gr 2)***
		Syncope	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Hair texture abnormal		***Hair texture abnormal (Gr 2)***
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
Hyperkeratosis			***Hyperkeratosis (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
	Pruritus		***Pruritus (Gr 3)***
Rash[12]			***Rash[12] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms (DRESS))	
		Skin and subcutaneous tissue disorders - Other (neutrophilic panniculitis, panniculitis)[13]	
		Stevens-Johnson syndrome	
VASCULAR DISORDERS			
	Hypertension		
	Thromboembolic event[14]		
	Vascular disorders - Other (hemorrhage)[15]		

[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] The incidence of anemia is increased when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[3] The frequencies of these events are based upon laboratory findings rather than being due to patient-reported outcomes.

[4] The incidence of left ventricular systolic dysfunction is increased when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[5] Dabrafenib (GSK2118436B) has been associated with ocular toxicities including chorioretinitis, retinitis, iridocyclitis, iritis, and uveitis.

[6] Edema limbs (peripheral edema) is a risk associated when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B) compared to dabrafenib (GSK2118436B) alone.

[7] Fever (pyrexia) can be associated with hypotension and/or (in rare cases) syncope. The frequency of fever and serious febrile events is increased when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[8] Manifestations of allergic reactions (hypersensitivity) to dabrafenib (GSK2118436B) may include bullous rash (bullous dermatitis).

[9] The incidence of hemophagocytic lymphohistiocytosis (HLH)) is increased when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[10] Squamous cell carcinoma (SCC), including SCC of the skin, SCC in situ (Bowen's disease), and keratoacanthoma have been observed.

[11] New non-SCC malignancies have been reported including primary melanoma, basal cell carcinoma, and non-cutaneous malignancies.

[12] Rash includes the terms: rash, rash acneiform, rash papular, rash maculo-papular, and erythema.

[13] Recurrent neutrophilic panniculitis has been observed in at least one patient treated with dabrafenib (GSK2118436B) in combination with the MEK inhibitor trametinib dimethyl sulfoxide (GSK1120212B).

[14] Venous thromboembolic events (including deep vein thrombosis and pulmonary embolism) is a risk associated when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[15] Treatment with dabrafenib (GSK2118436B) in combination with trametinib dimethyl sulfoxide (GSK1120212B) resulted in an increased incidence and severity of hemorrhagic events compared to patients treated with dabrafenib (GSK2118436B) as a single agent. Sites of hemorrhage may include, but are not limited to, intracranial, reproductive tract, respiratory tract, and gastrointestinal hemorrhage.

Adverse events reported on Dabrafenib (GSK2118436B) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Dabrafenib (GSK2118436B) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (agranulocytosis); Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Heart failure; Mitral valve disease; Myocardial infarction; Pericardial effusion; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Ear pain

ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism

EYE DISORDERS - Blurred vision; Eye disorders - Other (amaurosis fugax); Eye disorders - Other (vitreous detachment); Floaters; Photophobia; Retinal detachment; Retinopathy

GASTROINTESTINAL DISORDERS - Dry mouth; Dyspepsia; Gastritis; Stomach pain

GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS - Death NOS; Disease progression; Gait disturbance; Localized edema; Malaise; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic pain

INFECTIONS AND INFESTATIONS - Bacteremia; Bronchial infection; Catheter related infection; Device related infection; Gallbladder infection; Infections and infestations - Other (bacterial peritonitis); Infections and infestations - Other (blood culture positive); Infections and infestations - Other (croup infectious); Infections and infestations - Other (Epstein-Barr virus infection); Infections and infestations - Other (respiratory tract infection); Lung infection; Otitis media; Pharyngitis; Rash pustular; Rhinitis infective; Sepsis; Skin infection; Urinary tract infection; Viremia

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Injury, poisoning and procedural complications - Other (complication associated with device); Injury, poisoning and procedural complications - Other (device occlusion); Injury, poisoning and procedural complications - Other (radiation injury, stroke-like migraine attacks after radiation therapy); Seroma

INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CD4 lymphocytes decreased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Lymphocyte count decreased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypernatremia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypomagnesemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain

NEOPLASMS, BENINGN, MALIGNANT AND UNSPECIFIED (INCL CYST AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (acrochordon); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (bile duct adenocarcinoma); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (mycosis fungoides)

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Hydrocephalus; Lethargy; Nervous system disorders - Other (expressive aphasia); Nervous system disorders - Other (intracranial pressure increased); Paresthesia; Seizure; Somnolence; Stroke

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Hallucinations; Insomnia

RENAL AND URINARY DISORDERS - Proteinuria; Renal calculi; Urinary frequency; Urinary retention

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Menorrhagia; Prostatic obstruction; Reproductive system and breast disorders - Other (hematospermia)

RESPIRATORY, THORACIC AND MEDAISTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Dyspnea; Hypoxia; Nasal congestion; Oropharyngeal pain; Pleuritic pain; Productive cough; Pulmonary edema; Respiratory failure; Rhinorrhea; Sore throat; Stridor; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS- Bullous dermatitis[8]; Eczema; Erythroderma; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (palmoplantar keratoderma); Skin and subcutaneous tissue disorders - Other (sunburn); Skin hyperpigmentation

VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension

NOTE: Dabrafenib 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.

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5.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

When a patient's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The dabrafenib dose should not exceed 150 mg twice daily. Missed doses should not be made up.

The dose modifications may involve one or both agents, and should be based on the nature, severity and attributions of the AEs. General guidelines are provided in Tables below, with details stipulated in subsequent sections. The Study Chair should be consulted if there are questions about the attribution of AEs and how the doses should be modified.

NOTE: Patients who develop toxicity requiring drug discontinuation in step 1 can still cross over to step 2 at the time of disease progression if RECIST defined progressive disease is documented and eligibility criteria for step 2 are met (see Section 3.2). Patients off treatment on Arm B due to toxicity do not need to exhibit progressive disease before crossing over to Arm D.

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5.4.1 Dose Modifications for Dabrafenib/Trametinib

For patients on Arm A who have crossed over to dabrafenib/trametinib and who experience toxicity that is clearly attributable to ipilimumab/nivolumab (e.g. colitis, hypophysitis) or potentially attributable to prior ipilimumab/nivolumab (e.g. interstitial nephritis, transaminitis, inflammatory skin rash/vasculitis) dabrafenib and trametinib should be held until toxicity returns to grade 1 and then dabrafenib and trametinib could be resumed at the previous dose. Steroids may be administered to treat the potential IRAE and dabrafeinib/trametinib treatment could be resumed while steroid treatment and taper is ongoing.

A dose reduction below 50 mg BID for dabrafenib is not allowed. For dabrafenib + trametinib combination, dose below 1 mg once daily for trametinib is not allowed.

If dabrafenib will be permanently discontinued for dabrafenib-related toxicities, patients will be allowed to continue trametinib. Conversely, if trametinib is permanently discontinued for trametinib-related toxicities, patients will be allowed to continue dabrafenib.

The Study Chair's approval is required to restart study treatment after ≥ 28 days of dose interruption/delay.

The table below outlines the dose levels to be used for any necessary dabrafenib and trametinib dose modifications in studies which include the combination:

Dose Level	Dabrafenib Dose/Schedule
0	150 mg BID
-1	100 mg BID
-2	75 mg BID
-3	50 mg BID

Dose Level	Trametinib Dose/Schedule
0	2 mg QD
-1	1.5 mg QD
-2	1.0 mg QD

Dabrafenib + Trametinib Dose Modification Guidelines

If an AE resolves to grade 1 or baseline at the reduced dose level, and no additional toxicities are seen after 4 weeks of study treatment at the reduced dose, dose re-escalation following the same dosing steps as de-escalation may be considered. The dabrafenib dose should not exceed 150 mg twice daily.

Dabrafenib-Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections

Table 1: Dabrafenib-Trametinib **Dose Modification for Toxicities Not Specified in Subsequent Sections**

CTCAE Grade	Action and Dose Modification
Grade 1 **Grade 2 (tolerable)**	• Continue study treatment at same dose level (no dose modification). • Monitor closely. • Provide supportive care according to institutional standards.
Grade 2 (intolerable) **Grade 3**	• Interrupt study treatment. • Monitor closely. • Provide supportive care according to institutional standards. • When toxicity resolves to grade 1 or baseline, restart study treatment **reduced by one dose level**. • If the grade 2 (intolerable) or grade 3 toxicity recurs, interrupt study treatment. • When toxicity resolves to grade 1 or baseline, **restart study treatment reduced by another dose level**.
Grade 4	• Permanently discontinue, or interrupt, study treatment. • Monitor closely. • Provide supportive care according to institutional standards. • If study treatment was interrupted, restart study treatment **reduced by one dose level** once toxicity resolves to grade 1 or baseline.
*If the AEs are thought to be due to one of the two agents, resumption of the other agents may be considered if the first agent is discontinued due to toxicities and treatment interruption is < 28days.	

Dabrafenib-Trametinib Dose Modification for **Pyrexia**

Pyrexia is defined as a body temperature equal to or above 38.5° Celsius or 101.3° Fahrenheit

- Pyrexia is an adverse event associated with dabrafenib and is increased in frequency and severity in subjects receiving dabrafenib in combination with trametinib. In a minority of cases, pyrexia was accompanied by symptoms such as severe chills/rigors, dehydration, hypotension, dizziness or weakness and required hospitalization.
- Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take anti-pyretics (e.g. ibuprofen or acetaminophen/paracetamol) as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia

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Table 2: Dabrafenib-Trametinib dose Modification and Management Guidelines for **Pyrexia**

Event	Management Guideline	Dose Modification
Work up: • Clinical evaluation for infection and hypersensitivity, especially if pyrexia is complicated by rigors, severe chills, dehydration, *etc.* • Laboratory work-up (should include full-blood-count, electrolytes, creatinine, BUN, CRP, liver-function tests, blood and urine culture). Rev. Add14 • Patients with recurrent episodes of pyrexia without localizing symptoms of infection could be managed without laboratory work-up unless pyrexia persists for 3 or more days. ***Management***: • Anti-pyretic treatment should be started immediately at the first occurrence. Anti-pyretic treatment may include acetaminophen (paracetamol), ibuprofen, or suitable anti-pyretic medication per institutional standards. • Oral hydration is encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended if pyrexia is complicated by dehydration/hypotension. • In subject experiencing pyrexia complicated by rigors, severe chills, *etc.*, which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started. • Prophylactic anti-pyretic treatment is recommended after the 2nd event, or after the 1st event if complicated by rigors or severe chills. Prophylactic anti-pyretics may be discontinued after three days in absence of pyrexia.		
1st Event:	• Clinical evaluation for infection and hypersensitivity • Laboratory work-up • Hydration as required • Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment	• Interrupt dabrafenib. • Continue trametinib. • Upon recovery to baseline, restart dabrafenib at the same dose level. If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**.

Event	Management Guideline	Dose Modification
2nd Event	• Clinical evaluation for infection and hypersensitivity • Laboratory work-up if concomitant novel symptoms present or if pyrexia persists for 3 or more days • Hydration as required • Within 3 days of onset of pyrexia: – Optimize anti-pyretic therapy. – Consider oral corticosteroids (*i.e.*, prednisone 10 mg) for at least 5 days or as clinically indicated.	• **Interrupt dabrafenib.** • Continue trametinib • Upon recovery to baseline, restart dabrafenib at the same dose level. If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**.
Subsequent Events:	• Clinical evaluation for infection and hypersensitivity • Laboratory work-up as clinically indicated • Hydration as required • Blood sample for cytokine analysis • Within 3 days of onset of pyrexia: – Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia. – If corticosteroids have been tapered and pyrexia recurs, restart steroids.	• **Interrupt dabrafenib.** • Continue trametinib. • Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level**.[a] • If dabrafenib must be reduced to <50 mg BID, permanently **discontinue dabrafenib**.
[a] Dabrafenib should be reduced by one dose level after three episodes of pyrexia which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.		

Dabrafenib or Dabrafenib-Trametinib Dose Modification for **Rash**

Rash is a frequent AE observed in patients receiving trametinib, dabrafenib, or the combination of both agents. Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors.[39]

The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the study chair may be required.

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Table 3: Dabrafenib-Trametinib **Supportive care and Dose Modification for Rash**

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Supportive care: **Prevention:** • Avoid unnecessary exposure to sunlight • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily. • Topical steroids and antibiotics should be applied at least twice daily starting on Day 1 of study treatment, to body areas such as face, chest, and upper back. • Use mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (e.g., clindamycin) or oral antibiotics (e.g., doxycycline 100 mg BID, minocycline 100 mg BID) **Symptom management:** • Pruritic lesions: cool compresses and oral antihistamine therapies • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream • Desquamation: thick emollients and mild soap • Paronychia: antiseptic bath, local potent corticosteroids in addition to oral antibiotics; if no improvement, consult dermatologist or surgeon • Infected lesions: appropriate bacterial/fungal culture-driven systemic or topical antibiotics * Rash prophylaxis is recommended for the first 6 weeks of study treatment * Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management		
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue study treatment. • If rash does not recover to baseline within 2 weeks despite best supportive care, hold study treatment and restart at a 1 dose level reduction when rash recovers to less < Grade 1.[3] • If the patient is very symptomatic now (pruritic complaints) or if rash increases despite prophyaltic measures hold therapy now and reduce by 1 dose level when patient recovers.
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• **Reduce study treatment by one dose level.** • If rash recovers to ≤ grade 1 within 2 weeks, increase dose to previous dose level. • If no recovery to ≤ grade 1 within 2 weeks, interrupt study treatment until recovery to ≤ grade 1. • **Restart study treatment at reduced dose level.**[3]

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade ≥ 3	• Use moderate strength topical steroids PLUS oral methyl-prednisolone dose pack.[2] • Consult dermatologist.	• Interrupt study treatment until rash recovers to ≤ grade 1. • **Restart study treatment reduced by one dose level.**[3] • If no recovery to ≤ grade 2 within 28 days, **permanently discontinue study treatment**.

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1. Rash prophylaxis is recommended for the first 6 weeks of study treatment.
2. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone priopionate 0.5% cream.
3. Study treatment may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.

Dabrafenib-Trametinib Dose Modification for **palmar-plantar erythrodysesthesia syndrome (PPES)**

- Lifestyle modification: avoidance of hot water, traumatic activity, constrictive footwear, or excessive friction on the skin.Use of thick cotton socks and gloves, and shoes with padded insoles.
- Symptomatic treatments: apply moisturizing creams frequently, topical keratolytics (e.g. urea 20-40 % cream, salicylic acid 6%, tazarotene 0.1% cream, fluorouracil 5% cream), clobetasol propionate 0.05% ointment for erythematous areas, topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin for pain.
- Dose modification may also be required. – Refer to table for dose modification for non-specific AEs.

Dabrafenib-Trametinib Treatment Modification for **New Primary/ Recurrent Malignancies:**

- *Cutaneous SCC and New Primary Melanoma*
  - Dermatologic skin assessments for subjects on treatment should be performed before initiation of dabrafenib, then every 6 weeks through treatment. It is also recommended that skin exams should continue every 2-3 months for 6 months after discontinuation of dabrafenib or initiation of another anti-neoplastic therapy. Report any new primary/recurrent malignancies as SAE through CTEP-AERS according to the instructions in Section 5.2.

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- *Cutaneous SCC*
  - Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been observed in subjects treated with dabrafenib. Median time to onset for the first occurrence for patients receiving dabrafenib monotherapy is 8 weeks, for patients receiving combination therapy is 20 to 32 weeks.

- These should be surgically removed according to institutional practices. Dose modification or interruption of study treatment is not required for cuSCC or KA, however cuSCC should be reported as an SAE through CTEP-AERS (refer to Section 5.2). In addition, a biopsy of the lesion should be taken, where possible, and a summary of the results submitted to CTEP through the SAE reporting.
- Patients should be instructed to immediately inform their physician if new lesions develop.

- *New Primary Melanoma*
  - New primary melanomas have been reported in patients treated with dabrafenib. These were identified primarily within the first 5 months of therapy and did not require treatment modification other than excision. New primary melanoma should be reported as SAE through CTEP-AERS according to the instructions in Section 5.2.
- *Non-Cutaneous Malignancies*
  - In vitro experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild type cells with RAS mutations when exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with dabrafenib. Cases of RAS-driven malignancies have been seen with BRAF inhibitors. Patients should be monitored as clinically appropriate.
  - Consider the benefits and risks before continuing treatment with dabrafenib in patients who develop RAS mutation-positive non-cutaneous malignancies. If used in combination with trametinib, trametinib may continue.
  - Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy.
  - New non-cutaneous malignancies should be reported as a SAE through CTEP-AERS according to the instructions in Section 5.2. A biopsy of the new malignancy should be taken, where possible, and submitted for further analyses with the results provided to CTEP via SAE reporting. Testing of these biopsies should include RAS mutation analysis and may include analysis of genomic alterations, which include but not limited to DNA, RNA and protein analysis of these biopsy specimens, and would analyze the biological pathways known to be associated with, and relevant to, BRAF-mutant tumor activation.

Dabrafenib-Trametinib Dose Modification for **Hemorrhage**

Table 4: Dabrafenib-Trametinib **Treatment Modifications for Hemorrhage**

Grade 3	• Hold dabrafenib or dabrafenib-trametinib for up to 3 weeks • If improved, resume the drugs at one dose reduction • If no improvement, permanently discontinue dabrafenib or dabrafenib-trametinib
Grade 4	• Permanently discontinue dabrafenib or dabrafenib-trametinib

Dabrafenib-Trametinib Dose Modification for **Pancreatitis**

In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis. Dabrafenib and trametinib should be held until toxicity returns to grade 1. Treatment should be resumed with dabrafenib dose reduced by 1 dose level. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis.

Dabrafenib or Dabrafenib-Trametinib Dose Modification for **Hyperglycemia**

Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Monitor serum glucose levels as clinically appropriate during treatment with dabrafenib in subjects with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

Dabrafenib-Trametinib Dose Modification for **Renal Insufficiency**

Cases of renal insufficiency have occurred in patients receiving the combination of dabrafenib and trametinib. Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and modified if clinically possible.

Table 5: Dabrafenib or Dabrafenib-Trametinib **Dose Modification for Renal Insufficiency**

Serum Creatinine Level	Management Guideline	Action and Dose Modification
Serum creatinine increase > 0.2 mg/dL (18 mcmol/L) ***BUT*** ≤ 0.5 mg/dL (44 mcmol/L) above baseline	• Recheck serum creatinine within 1 week. • Serum creatinine increase > 1 week: consult PI. If elevation persists beyond 4 weeks, recommend evaluation (consider renal biopsy) for etiology; consider nephrology consultation. • If pyrexia is present, treat pyrexia as per guidelines.[a]	Continue study treatment at the same dose level.
Serum creatinine increase > 0.5 mg/dL (44 mcmol/L) ***above baseline***	• Monitor serum creatinine ≥2-times per week. • Hospitalization may be necessary if serum creatinine cannot be monitored frequently. • If pyrexia is present, treat pyrexia per guidelines. • Consult nephrologist if clinically indicated. • Perform renal biopsy if clinically indicated, for example: – Renal insufficiency persists despite volume repletion. – Patient has new rash or signs of hypersensitivity (such as elevated eosinophil count). – Consider that prior ipi/nivo might be contributing to renal insufficiency and if so, consider institution of prednisone 0.5-1 mg/kg	• Interrupt study treatment until serum creatinine recovers to baseline. • Restart study treatment.[b]

[a] NSAIDs can induce renal insufficiency, especially in patients with dehydration; encourage oral fluids or consider IV fluids as clinically indicated. See guidelines for pyrexia Section 5.4.1 (Table 2).

[b] Investigator may restart at either the same or a reduced dose level. Escalation of study treatment to previous dose level is allowed if another episode of renal insufficiency does not occur after 4 weeks of dose reduction.

Dabrafenib-Trametinib Dose Modification for **Reduced Left Ventricular Ejection Fraction**

Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving dabrafenib plus trametinib. Therefore, ECHO/MUGA must be performed in regular intervals outlined in the Study Calendar. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s).

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Table 6: Dabrafenib + Trametinib Treatment Modification and Management Guidelines for LVEF Decrease

Clinic	LVEF-drop (%) or CTCAE grade	Dose Modification
Asymptomatic	Absolute decrease of > 10% in LVEF compared to baseline and ejection fraction below the institution's LLN.	• Interrupt trametinib. Dabrafenib may continue • repeat ECHO within 2 weeks.[a] • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline): – Restart trametinib at reduced dose by one dose level. – Repeat ECHO 2, 4, 8, and 12 weeks after re-start; continue in intervals of 12 weeks thereafter. • If LVEF **does not recover** within 4 weeks: – Consult with cardiologist. – **Permanently discontinue trametinib. Report as SAE according to the instructions in Section 5.2.** – **Hold dabrafenib** – Resumption of dabrafenib may be considered after consultation with CTEP. – Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.
Symptomatic[b]	• Grade 3: resting LVEF 39-20% or > 20% absolute reduction from baseline • Grade 4: Resting LVEF ≤ 20%.	• **Permanently discontinue trametinib. Report as SAE according to the instructions in Section 5.2.** • **Hold dabrafenib until LVEF improves.**[c] • Consult with cardiologist. • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.

[a] If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.

[b] Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.

[c] Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with medical monitor.

Dabrafenib-Trametinib Dose Modification for **Hypertension**

Increases in blood pressure (BP) have been observed in patients receiving dabrafenib plus trametinib. Recommendations for BP monitoring and management are provided below.

Monitoring: All BP assessments should be performed under the following optimal conditions:

- The subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor.
- The subject is relaxed comfortably for at least 5 minutes.
- Restrictive clothing has been removed from the cuff area, and the right cuff has been selected.

- The subject's arm is supported so that the middle of the cuff is at heart level.
- The subject remains quiet during the measurement.
- In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the two readings averaged to obtain a final BP measurement. The averaged value should be recorded in the eCRF.
- Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the study calendar. Ideally, subsequent blood pressure assessments should be performed within 1 week.
- Persistent hypertension is defined as an increase of systolic BP (SBP) > 140 mmHg and/or diastolic BP (DBP) > 90 mmHg in three consecutive visits with blood pressure assessments from two readings.
- Asymptomatic hypertension is defined as an increase of SBP > 140 mmHg and/or diastolic BP (DBP) > 90 mmHg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting, or other symptoms indicative of hypertension.

Table 7: Dabrafenib-Trametinib **Treatment Modification for Hypertension**

Event	Management Guideline	Dose Modification
(Scenario A) • Asymptomatic and persistent[a] SBP of ≥ 140 and < 160 mmHg, or DBP ≥ 90 and < 100 mmHg OR • Clinically significant increase in DBP of 20 mmHg (but DBP still below 100 mmHg)	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled[b] BP. • If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	• Continue study treatment.
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, OR • Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt study treatment if clinically indicated. • Once BP is well-controlled[b], restart study treatment reduced by one dose level[c]
(Scenario C) • Symptomatic[d] hypertension OR • Persistent SBP ≥ 160 mmHg, or DBP ≥ 100 mmHg, despite antihypertensive medication and dose reduction of study treatment	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended.	• Interrupt study treatment • Once BP is well controlled, restart study treatment **reduced by one dose level**[c].

Event	Management Guideline	Dose Modification
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	• Permanently discontinue study treatment.

[a] Hypertension detected in two separate readings during up to three consecutive visits

[b] Well-controlled blood pressure defined as SBP ≤ 140 mm Hg and DBP ≤ 90 mm Hg in two separate readings during up to three consecutive visits.

[c] Escalation of trametinib to previous dose level can be considered if BPs remain well-controlled for 4 weeks after restarting of trametinib.

[d] Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.

Dabrafenib-Trametinib Dose Modification for **QTc Prolongation**

Table 8: Dabrafenib + Trametinib modification for QTc Prolongation

QTc Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline. • Test serum potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for agents that prolong QTc. • If the event resolves, restart study treatment at current dose level[b]. • **If the event does not resolve, permanently discontinue study treatment. Consider evaluation with cardiologist.** • **If the event recurs, permanently discontinue study treatment. Consider evaluation with cardiologist.**

Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula

a) Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.

b) If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator agrees that the subject will benefit from further treatment.

Dabrafenib-Trametinib Dose Modification for **Diarrhea**

Episodes of diarrhea have been observed in patients receiving dabrafenib, trametinib, or both therapies in combination. Other, frequent causes for diarrhea including concomitant medications (*e.g.*, stool softeners, laxatives, antacids, *etc.*), infections caused by *C. difficile* or other pathogens, partial bowel obstruction, *etc.*, should be clinically excluded.

Table 9: Dabrafenib-Trametinib **Treatment Modification and Management Guidelines for Diarrhea**

CTCAE Grade	Management Guideline	Action and Dose Modification
Uncomplicated Diarrhea,[1] Grade 1 or 2	• Diet: Stop all lactose containing products; eat small meals, BRAT-diet (banana, rice, apples, toast) recommended. • Hydration: 8-10 large glasses of clear liquids per day (*e.g.*, Gatorade or broth). • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea >48 hous: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Add budesonide or other second-line therapies (octreotide, or tincture of opium) and oral antibiotics.	• Continue study treatment. • If diarrhea is grade 2 for > 48 hours, interrupt study treatment until diarrhea resolves to grade ≤ 1. • Restart study treatment at the same dose level.
Uncomplicated Diarrhea,[1] Grade 3 or 4 **Any Complicated Diarrhea[2]**	• Clinical evaluation mandatory. • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Oral antibiotics and second-line therapies if clinically indicated • Hydration: Intravenous fluids if clinically indicated. • Antibiotics (oral or intravenous) if clinically indicated. • Intervention should be continued until the subject is diarrhea-free for ≥24 hours. • Intervention may require hospitalization for subjects at risk of life-threatening complications.	• Interrupt study treatment until diarrhea resolves to ≤ grade 1. • Restart study treatment reduced by one dose level.[4] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue study treatment**.

1. **Uncomplicated diarrhea** defined by the absence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution.
2. **Complicated diarrhea** defined by the presence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution. Patients with complicated diarrhea on Arm C, should be considered that this could be related to prior ipi/nivo immunotherapy and possibly evaluated and treated like an IRAE.
3. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea.
4. Escalation of study treatment to previous dose level is allowed in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

Dabrafenib-Trametinib Dose Modification for **Visual Changes**

Episodes of visual changes have been observed in patients receiving dabrafenib, trametinib, or the combination of both therapies. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study

treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination.

Uveitis and iritis have been associated with dabrafenib, while RPED and RVO have been associated with trametinib therapy. Monitor patients for visual signs and symptoms (such as change in vision, photophobia, and eye pain) during therapy. Special attention should be given to retinal findings (*e.g.*, retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (*i.e.*, branch or central retinal vein occlusions [RVO]).

The ophthalmology exam will include best corrected visual acuity, visual field examination, tonometry, slit lamp biomicroscopic examination of the anterior segment (with special attention to inflammation) and the posterior segment, and dilated indirect fundoscopy with special attention to retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled visits and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography, and fluorescein angiography may also be indicated as determined by clinical exam.

Guidelines regarding event management and dose reduction for visual changes considered to be related to study treatment are provided in the table below.

Rev. Add13 **Table 10:** Dabrafenib-Trametinib **Treatment Modification for Visual Changes**

CTCAE Grade	Management Guideline	Action and Dose Modification
Grade 1*	• Consult ophthalmologist within 7 days of onset.	• If dilated fundus examination cannot be performed within 7 days of onset, hold trametinib until RPED and RVO can be excluded by retina specialist/ ophthalmologist. Dabrafenib may be continued. • If RPED and RVO excluded, continue (or restart) trametinib at same dose level • If Uveitis/Iritis, refer to table below for Iritis/Uveitis • If RPED suspected or diagnosed, refer to RPED dose modification table below; **report as SAE if diagnosed**. • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE according to the instructions in Section 5.2.**
Grade 2 and Grade 3	• Consult ophthalmologist immediately.	• Hold trametinib. Dabrafenib may be continued. • If RPED and RVO excluded, restart trametinib at same dose level • If Uveitis/Iritis, refer to table below for Uveitis/Iritis • If RPED diagnosed, see RPED dose modification table below; **report as SAE according to the instructions in Section 5.2** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE according to the instructions in Section 5.2**.

CTCAE Grade	Management Guideline	Action and Dose Modification
Grade 4	• Consult ophthalmologist immediately.	• Interrupt trametinib. Dabrafenib may be continued. • If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study PI. • If Uveitis/Iritis, refer to table below • **If RVO or RPED diagnosed, permanently discontinue trametinib** and report as SAE according to the instructions in Section 5.2.

Abbreviations: RPED = retinal pigment epithelial detachments; RVO = retinal vein occlusion; SAE = serious adverse event

* If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

Table 11: Dose Modification for RPED

Event CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue trametinib with retinal evaluation monthly until resolution. If RPED worsens, follow instructions below. • Dabrafenib treatment is not affected
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib. Continue dabrafenib • Retinal evaluation monthly. • If improved to ≤ Grade 1, restart trametinib with one dose level reduction (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily. • If no recovery within 4 weeks permanently discontinue trametinib

Table 12: Dabrafenib-Trametinib Dose Modification for Uveitis and Iritis

CTCAE Grade	Action and Dose Modification
Uveitis and Iritis	• Continue study treatment • Control ocular inflammation with local therapies • If not improved to grade ≤ 1 within 1 week, interrupt dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level • If no recovery within 4 weeks, permanently discontinue dabrafenib. Trametinib may be continued. • For patients on Arm C consider that uveitis could be an IRAE from prior ipilimumab + nivolumab and treat accordingly

Dabrafenib-Trametinib Dose Modification for **Pneumonitis**

Pneumonitis has been observed in patients receiving trametinib in combination with dabrafenib. To reduce the risk of pneumonitis, patients will be monitored closely for symptoms, evaluated with imaging and functional tests when appropriate. For patients on Arm C, it should be considered that the pneumonitis could be an IRAE from

prior ipilimumab + nivolumab therapy and treated with corticosteroids as indicated until IRAE excluded.

Table 13: Dabrafenib-Trametinib **Treatment Modification for Pneumonitis**

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• CT scan (high-resolution with lung windows) recommended. • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation with pulmonologist recommended	• Continue study therapy at current dose
Grade 2	• CT scan (high-resolution with lung windows) recommended. • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests – if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated	• Interrupt trametinib until recovery to grade ≤ 1 • Restart trametinib reduced by one dose level • Escalation to previous dose level after 4 weeks may be considered after consultation with PI • If no recovery to grade ≤ 1 within 4 weeks, **permanently discontinue trametinib.**
Grade 3	• Same as grade 2	• Interrupt trametinib until recovery to grade ≤ 1 • Resumption of trametinib at one dose level reduction may be considered after consultation with PI • If no recovery to grade ≤ 1 within 4 weeks, **permanently discontinue trametinib.**
Grade 4	• Same as grade 2	• **Permanently discontinue trametinib.**

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Dabrafenib-Trametinib Dose Modification for **Liver Chemistry Changes**

For patients on Arm C, it should be considered that the liver chemistry changes could be in part an IRAE from prior ipi/nivo therapy and treated with corticosteroids as indicated until IRAE excluded.

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Table 14: Dabrafenib-Trametinib **Dose Modification for Liver Chemistry Changes**

Event	Treatment modifications and assessment/monitoring
• ALT ≥ 3x ULN **but** < 5x ULN **and** TB < 2x ULN, **without** symptoms considered related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• **May continue study treatment**. • Report as SAE if CTEP-AERS reporting criteria is met. • Report as SAE according to the instructions in Section 5.2 if CTEP-AERS reporting criteria is met. **MONITORING:** Repeat LFT (ALT, AST, ALK, bilirubin) until they return to normal/baseline or stabilise (LFT may be every 2 weeks after 4 weeks if ALT < 3x ULN and TB < 2 ULN).
Criteria for discontinuing study drug: When any of the liver stopping criteria below is met, discontinue trametinib **and dabrafenib** 1. ALT ≥ 3xULN **and** bilirubin ≥ 2x ULN or >35% direct bilirubin 2. ALT ≥ 3xULN **and** INR > 1.5, if INR measured (INR threshold does not apply if subject is on anticoagulant) 3. ALT ≥ 5x ULN 4. ALT ≥ 3x ULN persists for ≥ 4 weeks 5. ALT ≥ 3x ULN **and** cannot be monitored weekly for 4 weeks 6. ALT ≥ 3x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity	• **Immediately discontinue study treatment.** • Report as SAE according to the instructions in Section 5.2 if: 1) CTEP-AERS reporting criteria are met, or 2) patients meet criteria 1-2. • Perform liver event **ASSESSMENT AND WORKUP (see below)**. • Monitor the subject until liver chemistries resolve, stabilize, or return to baseline (see **MONITORING** below). If applicable, provide details on required follow up assessments (*e.g.*, follow up for overall survival or disease recurrence or progression). *[Do not include for single-dose studies]* **MONITORING:** *In patients stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities):* • Repeat liver chemistries (ALT, AST, ALK, bilirubin) and perform liver event **follow-up assessments** within **24 hours**. • Monitor subjects twice weekly until LFT return to normal/baseline or stabilize. • A specialist or hepatology consultation is recommended. *In patients stopping for criteria 2-6:* • Repeat LFT and perform liver event **follow up assessments** within **24-72 hours** • Monitor subjects weekly until LFTs return to normal/baseline or stabilize. **ASSESSMENT and WORKUP:** • Viral hepatitis serology. • Serum CPK and LDH. • Fractionate bilirubin, if total bilirubin ≥ 2x ULN. • CBC with differential to assess eosinophilia. • Record clinical symptoms of liver injury, or hypersensitivity on AE CRF. • Record concomitant medications (including acetaminophen, herbal remedies, other over the counter medications). • Record alcohol use. *Additional work up for patient stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities)*:

Event	Treatment modifications and assessment/monitoring
	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (in subjects with likely acetaminophen use in the preceding). • If there is underlying chronic hepatitis B (e.g. positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. • Liver imaging (ultrasound, MRI, CT) and /or liver biopsy.

Dabrafenib-Trametinib Dose Modification for **Venous Thromembolism (VTE)**

Event	Dabrafenib	Trametinib (When Used in Combination)
Uncomplicated DVT or PE	Do not modify the dose.	Withhold trametinib for up to 3 weeks. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.
Life Threatening PE	Permanently discontinue dabrafenib	Permanently discontinue trametinib.

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5.4.2 Dose Modifications for Ipilimumab/Nivolumab

The treatment of events for ipilimumab and nivolumab alone, or in combination follow the same guidelines and algorithims. Patients experiencing grade 3 toxicities that require holding of therapy during the ipilimumab/nivolumab induction period (first 12 weeks) that resolve to grade 1 or less (off of > than physiologic replacement doses of corticosteroids) by week 16 may resume nivolumab monotherapy at the next scheduled maintenance dose according to protocol. Exceptions to this are: pneumonitis, nephritis and neurologic toxicities. Patients with toxicities that require dose holding, and/or steroid administration, but allow for continuation on therapy (e.g grade 2 rash) should omit the held dose (whether during induction or maintenance) and resume treatment with the next scheduled dose according to the original calendar. (Exception- If during induction period symptoms resolve to baseline within 7 days in the absence of immunosuppressive treatment patients may resume with omitted dose and postpoine subsequent induction therapy by 1 week. Scans should still be done at Week 12 and first maintenance nivo dose should be omitted in order to get patient back on schedule). Patients who require omission of 2 consecutive doses of induction therapy should withhold further induction treatment and resume treatment with maintenance nivolumab monotherapy at the time of a scheduled dose (e.g. C3D1, C3D15 or C3D29 following resolution of toxicity.

Below are dose delay tables for nivolumab + ipilimumab for the following adverse events. Please refer to Appendix X in the protocol for toxicity management algorithms which include specific treatment

guidelines. These algorithims should be followed unless there are specific clinical circumstances which the treating physician indicates variations or alternative treatment is needed.

In several places there are differences regarding protocol directed drug modification rules identified with (^). In these cases please follow the protocol specific guidelines in this section.

Generally we strongly encourage early evaluation, withholding drug, and appropriate treatment as indicated in the management tables and following event specific guidelines.

NOTE: In the text that if a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

NOTE: In the event that the dosing management outlined in Section 5.4.2 conflicts with Appendix X Management Algorithms, the EA6134 reccomendation is to follow the Section 5.4.2 management guidelines.

ALL OTHER EVENTS*	**Management/Next Dose for Nivolumab + Ipilimumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline. Resume at same dose level. For lab abnormalities, no change in therapy or dose.
Grade 3	Hold* until ≤ Grade 1 continue at investigator discretion
Grade 4	Off protocol therapy. For lab abnormalities, may restart at investigator discretion.
* non-immunologically mediated	
Recommended management: As clinically indicated	

ALL OTHER EVENTS**	**Management/Next Dose for Nivolumab + Ipilimumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline. When resolved to ≤ Grade 1 and off of steroids for at least 1 week, resume at same dose level.
Grade 3	Off protocol induction therapy. May resume nivolumab monotherapy if resolved to Grade 1 or less (off of > than physiologic replacement doses of corticosteroids) by end of week 16. (exceptions noted in 5.4.2) If occurs with nivolumab monotherapy, then off protocol therapy.
Grade 4	Off protocol therapy
** immunologically mediated	
Recommended management: As clinically indicated	

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab + Ipilimumab**
≤ Grade 1	No change in dose *
Grade 2	Hold/ omit therapy* until ≤ Grade 1 or resolved^. Consider oral steroid treatment if > 7 days. Resume at same dose level at time of an originally scheduled dose administration once toxicity returned to grade 1 and patient is off steroids.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion
Grade 4	Off protocol therapy
* Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphagoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: AE management guidelines	

Liver Function AST	**Management/Next Dose for Nivolumab + Ipilimumab**
≤ Grade 1	Continue protocol therapy.
Grade 2	Hold/ omit therapy until WNL or baseline. Consider oral steroid treatment if > 7 days. Resume at same dose level at time of an originally scheduled dose administration once toxicity return to grade 1 and patient off steroids.
Grade 3	Discontinue protocol induction therapy. Initiate IV or PO steroids. May begin nivolumab monotherapy if returns to grade 1 off steroids or other immunosuppressive treatment by week 16 (no earlier than week 13); if not returned to grade 1 after week 16, discontinue nivolumab monotherapy. Hold maintenance therapy. Initiate IV or PO steroids. If not returned to grade 1 off steroids by 6 weeks from missed dose, then off protocol therapy.
Grade 4	Off protocol therapy. Initiate IV steroids.
Continued treatment of patients with active immune mediated hepatitis may exacerbates ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.	
Recommended management: see Hepatic AE management algorithm	

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab + Ipilimumab**
≤ Grade 1	Hold until Grade 0 (if Grade 1) or baseline^. No change in dose
Grade 2	Hold/ omit until Grade 0 or baseline. Oral steroid treatment if > 7 days and hold further induction therapy. May begin nivo monotherapy at time of a previously scheduled dose if resolved to grade 0 (or baseline) off of steroids by week 16.

Diarrhea/ Colitis	Management/Next Dose for Nivolumab + Ipilimumab
Grade 3	Off protocol therapy; may begin nivo monotherapy if resolved to grade 0 (or baseline) by week 16. If occurs during nivo monotherapy then patient is off protocol therapy.
Grade 4	Off protocol therapy
See GI AE Algorithm for management of symptomatic colitis (Appendix X). Patients with ≤ Grade 2 toxicity resolving to Grade 0 or baseline within 7 days in the absence of oral steroids during induction may resume with omitted dose and have treatment scheduled postponed 1 week. Scans should still be done at week 12 and first maintenance dose of nivo should be omitted. If during maintenance, dose should just be omitted and treatment resumed with next dose. Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require steroids should be taken off study induction treatment. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm; Patients with grade 2 toxicity requiring steroid therapy should not resume induction therapy.	

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Pancreatitis Amylase/Lipase	Management/Next Dose for Nivolumab + Ipilimumab
≤ Grade 1	Continue protocol therapy if asymptomatic
Grade 2	Continue protocol therapy if asymptomatic
Grade 3	Continue protocol therapy if asymptomatic at investigator discretion
Grade 4	If asymptomatic, hold protocol therapy until < grade 2, then resume at same dose level.
Patients with symptomatic or radiologic evidence of pancreatitis as well as DM and DKA should be off protocol therapy. Lipase elevation may occur during the period of steroid withdrawal and with other immune mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm	

Pneumonitis	Management/Next Dose for Nivolumab + Ipilimumab
≤ Grade 1	Hold/ omit dose pending evaluation and resolution to ≤ Grade 0 or baseline including baseline pO2. Resume no change in dose after pulmonary and/or ID consultation
Grade 2	Hold/ omit dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation if lymphocytic pneumonitis is excluded. Off protocol therapy if steroids are required. ^
Grade 3	Hold/ omit dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation only if lymphocytic pneumonitis is excluded. Otherwise, off protocol therapy

Pneumonitis	**Management/Next Dose for Nivolumab + Ipilimumab**
Grade 4	Off protocol therapy
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. If seasonal influenza vaccine is considered, killed vaccines should be recommended.	
Recommended management: See Pulmonary Adverse Event Management Algorithm	

Other GI N-V	**Management/Next Dose for Nivolumab + Ipilimumab**
≤ Grade 1	No change in dose.
Grade 2	Hold/ omit pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose level after resolution to ≤ Grade 1.
Grade 3	Hold/ omit pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment patients should go off protocol induction therapy. May resume nivo monotherapy if resolved to grade ≤ 1 (off of > replacement steroids for 2 wks by wk 16
Grade 4	Off protocol therapy
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose for Nivolumab + Ipilimumab**
≤ Grade 1	No change in dose.
Grade 2	No change in dose
Grade 3	Hold/ omit until ≤ Grade 2. Resume at same dose level
Grade 4	Off protocol therapy
Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation	

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Neurologic events	**Management/Next Dose for Nivolumab + Ipilimumab**
≤ Grade 1	Hold dose pending evaluation and observation.^ If symptoms don't progress and processing below excluded may resume with no change in dose.*
Grade 2	Hold dose pending evaluation and observation.^ Hold until ≤ Grade 1. *Off protocol therapy if treatment with steroids is required.^ Resume at same dose level for peripheral isolated n. VII (Bell's palsy)^
Grade 3	Off protocol therapy

Neurologic events	Management/Next Dose for Nivolumab + Ipilimumab
Grade 4	Off protocol therapy
* Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis, should be permanently off IO treatment, but can remain on study. If the patient has disease progression and the toxicity from the IO has resolved, they should be able to cross over to targeted therapy.	
Recommended management: See Neurologic Adverse Event Management Algorithm	

Endocrine Hypophysitis Adrenal Insufficiency	Management/Next Dose for Nivolumab + Ipilimumab
≤ Grade 1	Asymptomatic TSH elevation. Add hormone replacement as clinically indicated. Continue therapy.
Grade 2	Hold/ omit until patients are on a stable replacement hormone regimen. Resume at same dose level.
Grade 3	Hold/ omit until patients are on a stable replacement hormone regimen. Resume at same dose level. If diagnosed with hypophysitis should hold induction therapy, but may begin nivo monotherapy when returned to grade 1 (must be no earlier than week 13 and by end of week 16)
Grade 4	Off protocol therapy
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. • Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement. • Patients with symptomatic hyperthyroidism can be given a short course of a beta blocker (e.g propranolol). Hyperthyroidism usually converts to hypothyroid within 4 weeks.	
Recommended management: See Endocrine Management Algorithm	

Fever	Management/Next Dose for Nivolumab + Ipilimumab
≤ Grade 1	Continue protocol therapy.
Grade 2	Hold/ omit until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold/ omit until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	

Fever	Management/Next Dose for Nivolumab + Ipilimumab
See Section 5. infusion reactions	

Cardiac*	Management/Next Dose for BMS-936558 (Nivolumab) + Ipilimumab Cardiac Toxicities
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation
Grade ≥ 2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Resume therapy at a time of next scheduled dose if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥ 2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (Consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone; Add ATG or tacrolimus if no improvement. Off treatment.
* *Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ** *Patients with evidence of myositis without myocarditis may be treated according as "other event"* **NOTE:** The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	
• *Drug will be held for grade 2 cardiac dysfunction pending evaluation* • *Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur* • *Treatment with steroids as clinically indicated*	

Patients requiring a delay of > 6 weeks, or > 8 weeks for patients on high dose steroids with required 4 weeks minimum taper and 2 week observation, should go off protocol therapy, except as specified in Section 5.4.2 (Dose Modifications for Ipilimumab/Nivolumab).

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Patients requiring > two dose delays/ dose omissions for the same event should go off protocol therapy.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.

Patients may be dose-delayed for evaluation and restarted depending on results.

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Any patient started on corticosteroids initially who is determined to not require steroids treatment for an autoimmune adverse event may resume therapy after a 2 week observation period without further symptoms at the discretion of the PI or investigator. Therapy should

be resumed at the time of a next scheduled dose and held doses should be omitted or skipped.

5.4.3 Immune-Related Adverse Events (IRAE's)

5.4.3.1 Definition of Immune-Related Adverse Events (IRAE's)

Blocking CTLA 4 or PD1 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were noted in previous ipilimumab studies. These drug-related events are presumptive autoimmune events, now termed IRAEs.

For the purposes of this study, an IRAE is defined as an AE of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE an IRAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected IRAEs must be documented on an AE case report form and as an SAE via CTEP-AERS (see Section 5.2).

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5.4.3.2 Monitoring and Treatment of Immune-Related Adverse Events (IRAE's)

Patients should be informed of and carefully monitored for evidence of clinically significant systemic IRAE (e.g., systemic lupus erythematosus-like diseases) or organ specific IRAE (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an IRAE is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy should be individualized for each patient. Prior experience suggests that colitis manifested as ≥ Grade 3 diarrhea, as well as other grade 3 IRAEs (skin rash, hepatitis, etc), requires corticosteroid treatment.

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5.5 Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All grade 3 and 4 infusion reactions that meet the definition of SAE in Section 5.2 must be reported via

CTEP-AERS according to the timeframes outlined in the AE table in Section 5.2.7.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

- For **Grade 1** symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated):
  - Study staff (e.g, RN, NP, PA or MD) should remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg IV or PO (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.
  - For **Grade 2** symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours):

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    - Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV or PO (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.
    - For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg IV or PO (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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    - For patients experiencing infusion reactions to nivolumab administered over 30 or 60 minutes, subsequent infusions could be administered over 90 minutes.
  - For **Grade 3 or 4** symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated):
    - Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg

IV or PO with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

- In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), infusion reactions reported via CTEP-AERS should be graded according to NCI-CTCAE (Version 5.0) guidelines.

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5.6 Treatment of Ipilimumab Related Infusion Reactions

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypotension, hypertension, bronchospasm, or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient. Reactions should be treated based upon the following recommendations.

- For mild symptoms (e.g., localized cutaneous reactions such as mild pruritus, flushing, rash):
  - Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient.
  - Complete the ipilimumab infusion at the initial planned rate.
  - Diphenhydramine 50 mg IV or PO may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring.
  - Premedication with diphenhydramine may be given at the discretion of the investigator for subsequent doses of ipilimumab.
- For moderate symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mmHg):
  - Interrupt ipilimumab.
  - Administer diphenhydramine 50 mg IV or PO.
  - Monitor patient closely until resolution of symptoms.
  - Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.
  - Resume ipilimumab infusion after recovery of symptoms.
  - At the discretion of the treating physician, ipilimumab infusion may be resumed at one half the initial infusion rate, then increased incrementally to the initial infusion rate.
  - If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.
  - The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and

acetaminophen) and careful monitoring, following the same treatment guidelines outlined above.

- At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.

- For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticaria, systolic blood pressure < 80 mm Hg, or angioedema):
  - Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject.
  - Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV or PO, with solumedrol 100 mg IV, as needed.
  - Patients should be monitored until the investigator is comfortable that the symptoms will not recur.
  - No further ipilimumab will be administered.
- In case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

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5.7 Prohibited and Restricted Therapies During the Study

Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving ipilimumab/nivolumab and/or dabrafenib/trametinib treatments.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Immunosuppressive agents (for Arms A and D).
- Physiologic replacement doses of corticosteroids are permitted if required
- Any non-oncology live vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug)

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  NOTE: Patients are permitted to receive the seasonal influenza vaccine. If seasonal influenza vaccine is considered, killed vaccines should be recommended.
- Strong inhibitors or inducers of CYP3A4 or CYP2C8 (see Appendix XI)

5.8 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

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5.9 Quality of Life Studies

5.9.1 Patient Reported Outcome Measures: PRO-CTCAE, PROMIS, EQ-5D

Treatment-Related Symptoms & Toxicities: Due to a need for brief symptom-based PRO measures to assess unique side effects from ipilimumab + nivolumab and dabrafenib + trametinib with minimal participant burden, we propose administering items from the patient-reported outcomes version of the common terminology criteria for adverse events. (PRO-CTCAE)

Based on provider feedback, 12 PRO-CTCAE toxicities have been selected to reflect the full range of toxicities experienced by patients undergoing these two treatments. The items selected are: rash, headache, joint pain, decreased appetite, nausea, diarrhea, fatigue, cough, itching, abdominal pain, shortness of breath, swelling. PRO-CTCAE is not designed for comparisons and will be descriptive. We will report the number, frequency, and severity of toxicities if applicable.

Functional Domains: Functional areas that may show long-term deficits due to treatment will be assessed using the PROMIS® Profile-29. This standardized IRT-calibrated instrument contains the following measures: physical function, fatigue, pain interference, pain intensity, depression, anxiety, sleep disturbance, and social function. PROMIS item banks used to develop this profile have been extensively developed and tested.[40, 41] PROMIS measures have exhibited strong construct validity when compared to existing PRO questionnaires in the domains of fatigue (FACT-Fatigue), pain (Brief Pain Inventory), sleep (Epworth Sleepiness Scale), and depression (CES-D).[42]

Health Utility: The EQ-5D (5L) questionnaire will be used to elicit utility values from a societal perspective necessary for a quality adjusted time without symptoms of disease progression and toxicities of treatment (Q-TWiST) analysis. The EQ-5D (5L) brief preference-based health status measure, which contains 5 health attributes: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each attribute is measured by a question that has 5 possible responses: no problem, slight problem, moderate problem, severe problem, or unable/extreme problem. The combination of responses results in 125 (5^5) possible health states. Prior research has developed a method for assigning a score between 0 and 1 to each across health states that represents an average US population preference for one state versus another.[43]

Assessment schedule

Initial Treatment (Arms A, B)

- Baseline (at randomization or prior to the start of protocol treatment including Day 1 of cycle 1): PROMIS Profile-29, PRO-CTCAE, EQ-5D (5L)
- End of each treatment cycle (starting with cycle 1): PRO-CTCAE, EQ-5D (5L),
- End of first treatment cycle (6 weeks, can be measured on Day 1 of cycle 2): PRO-CTCAE, EQ-5D (5L), PROMIS Profile-29
- End of second treatment cycle (3 months, can be measured on Day 1 of cycle 3): PRO-CTCAE, EQ-5D (5L), PROMIS Profile-29
- Disease Stability (6 months; can be measured on Day 1 of cycle 5): PRO-CTCAE, EQ-5D (5L), PROMIS Profile-29

Long-Term Follow-up (for patients starting at least one dose of protocol treatment and not receiving any non-protocol therapy)

regardless of still receiving any protocol treatment (All study arms, indexed to study entry)

- EQ-5D (5L): every 3 months from study entry up to 2 years
- PROMIS Profile-29: at 6 weeks, 3 months and 6 months from study entry, then every 6 months up to 2 years

Ad-Hoc Assessments (End of Treatment in Each Step, Dose Modification)

- End of Step 1 Treatment (before crossover, for any reason including Section 5.9.2.2): PROMIS Profile-29, PRO-CTCAE, EQ-5D (5L)
- End of Step 2 Treatment (after crossover, for any reason including Section 5.9.2.2): PROMIS Profile-29, PRO-CTCAE, EQ-5D (5L)
- Dose Modification (Section 5.4): PRO-CTCAE, EQ-5D (5L)

Second Treatment (Crossover, Arms C, D, indexed to second treatment)

- Baseline (at randomization or prior to the start of protocol treatment including Day 1 of cycle 1): PROMIS Profile-29, PRO-CTCAE, EQ-5D (5L)
- End of each treatment cycle (starting with cycle 1): PRO-CTCAE, EQ-5D (5L)
- End of first treatment cycle (6 weeks, can be measured on Day 1 of cycle 2): PRO-CTCAE, EQ-5D (5L), PROMIS Profile-29
- End of second treatment cycle (3 months, can be measured on Day 1 of cycle 3): PRO-CTCAE, EQ-5D (5L), PROMIS Profile-29
- Disease Stability (6 months; can be measured on Day 1 of cycle 5): PRO-CTCAE, EQ-5D (5L), PROMIS Profile-29

Assessments

We will conduct PRO assessments in regular, clinically informative intervals to evaluate short-term and long-term toxicities and functional impact for each treatment. We will assess all PROs at study randomization to provide the overall baseline scores to evaluate change across initial treatment, and long-term follow-up. We will evaluate treatment sequence by using the overall baseline assessment at randomization for treatment 1 and the initiation of treatment 2 (after progression and washout period) for baseline assessments.

During initial and secondary treatment periods, we will measure patient-reported toxicities (PRO-CTCAE) and overall health (EQ-5D (5L)) at each clinical visit where adverse events (CTCAE) are evaluated. Broader measures of physical and mental function (PROMIS Profile-29) will be collected at important clinical points: at six weeks (end of cycle 1), three months (end of second cycle), and 6 months (disease stability).

We will conduct all long term follow-up assessments (regardless of still on study treatment given no non-protocol treatment has been

administered) indexed to study entry every 3 months up to 2 years. EQ-5D (5L) assessments will be collected more frequently to coincide with the adverse events assessment (by CTCAE, every 3 months) until year 2. These additional assessments will be used to provide toxicity severity informing our primary 2-year PRO endpoint.

Throughout the study period we will conduct additional ad-hoc assessments for the following situations that may occur: end of treatment in each step (before crossover and after crossover). We will administer PRO-CTCAE and EQ-5D (5L) at the start of all dose modifications (Section 5.3).

End of step 1 treatment and subsequent enrollment into step 2 treatment will trigger two assessments. One at the point end of step 1 treatment is documented, and a separate assessment at the initiation of secondary treatment after washout (treatment 2 baseline). Assessments will also be administered at the point end of step 2 treatment (after crossover) occurring within our follow-up window.

We acknowledge that post-crossover assessments must be interpreted cautiously given that participants will crossover at different times and may have residual symptoms from the first treatment, despite washout. However, these assessments will allow us to identify an optimal sequence of the 2 therapies from the patient's perspective. Following crossover, PROMIS Profile-29, PRO-CTCAE, EQ-5D (5L) will be administered following the same procedure as the initial treatment to month-6 allowing comparisons by treatment sequence.

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5.9.2 Patient Reported Outcome Measures: Tobacco Use Assessment

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5.9.2.1 Assessments

Assessments will be captured directly from the participants using the EASEE-PRO portal. When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to EASEE-PRO, and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

The Core and Extension C-TUQ items will be assessed, together with patient-reported physical and psychological symptoms (See Table 2). Specifically, these items will be administered using the EASEE-PRO system described in the companion EA NCORP application. The advantage of our virtual electronic data capture system is that our proposed assessments will not be limited to, or dependent

upon, patient trial visits. Confidential and potentially stigmatizing information can be provided without requiring direct contact with the care team.

The selected Core and Extension C-TUQ items (from categories of Basic Tobacco Use Information, Tobacco Use in Relation to Cancer Diagnosis and Treatment, Smoking Cessation/Cessation Products/Assistance Methods, Use of Other Products, and Second-Hand Smoke Exposure) will be assessed. The 4-item Short Form PROMIS® for anxiety and depression, the Lung Cancer Stigma Scale, and six symptom items (general pain, fatigue, nausea, cough, sleep difficulties, shortness of breath) from FACIT (Functional Assessment of Chronic Illness Therapy) together with modifications of these same six questions to address the degree of bother associated with each symptom will be administered as well. Additionally, we will ask participants' perceptions of how smoking improves or worsens each of the six symptom experience. All these items will be compiled into Survey of Tobacco Use (STU). Detailed information on various measures is outlined in Appendix XIII.

Contents and Corresponding Questions in Survey of Tobacco Use (STU)

Dimension	Source of Measures	Baseline STU	Follow-up STU
Basic Tobacco Use Information	C-TUQ	Q1 – Q5	Q1-Q2
Tobacco Use in Relation to Cancer Diagnosis and Treatment	C-TUQ	Q6 – Q7	Q3
Smoking Cessation, Cessation Products, and Assistance Methods	C-TUQ	Q8 – Q13	Q4-Q9
Use of Other Products	C-TUQ	Q14	Q10
Second-Hand Smoke Exposure	C-TUQ	Q15-Q16	Q11-Q12
Psychological Symptoms	PROMIS Lung Cancer Stigma Scale	Q17-Q18	Q13-Q14
Physical Symptoms	FACIT	Q19	Q15
Sociodemographics		Q20-21	

NOTE: In order to minimize ambiguity and assure that patients are oriented to answer appropriately, the specific phrasing of items may vary depending specific cancer type and treatment.

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5.9.2.2 Assessment Schedule

Survey of Tobacco Use will be administered at the following time points:

- at baseline (trial enrollment)

- at 3 month follow-up from study registration
- at 6 month follow-up from study registration

5.10 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA6134 Forms Packet.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Patient progressed through both step 1 and step 2 study therapies

5.11 Duration of Follow-up

Patients will be followed for disease status until documented disease progression, and for survival for 5 years after registration or until death, whichever occurs first.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors-RECIST

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. Confirmatory scans for tumor response should also be obtained 6 weeks following initial documentation of objective response. In addition, patients with equivocal disease progression (e.g. a new lesion in the setting of major disease regression and the absence of or improvement in disease related symptoms and serum LDH) should have a scan confirming disease progression 4-6 weeks following the initial scan showing RECIST defined PD.

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.

The following general principles must be followed:

1. 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.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

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.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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.

6.1.3 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 acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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.

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.

Tumor Markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

NOTE: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.1.4 Response Criteria

6.1.4.1 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. To be assigned a status of complete response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than six weeks after the criteria for response is met.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. To be assigned a status of partial response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than six weeks after the criteria for response is met.

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 6.1.4.2.

Patients with equivocal disease progression (e.g. a new lesion in the setting of major disease regression and the absence of or improvement in disease related symptoms and serum LDH) should have a scan confirming disease progression 4-6 weeks following the initial scan showing RECIST defined PD. Patients may continue on protocol therapy until repeat scan confirms PD. If repeat scan does not confirm PD, patients should proceed with treatment and evaluation as directed by the protocol with the confirmatory scan (if between 4 and 6 weeks from last scan) being counted as the 6 week interval scan.

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 after study entry at a minimum interval of 24_ weeks.

6.1.4.2 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 (see Section 6.1.4.3). 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).

6.1.4.3 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).

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.

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients 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	Documented at least once ≥ 24 wks from study entry
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.

**** To be assigned a status of partial or complete response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than six weeks after the criteria for response is met.

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.

6.1.4.5 Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 24 weeks.

6.1.4.6 Additional Criteria to Continue Treatment after Progression

Patients may continue on protocol therapy until repeat scan confirms PD. If repeat scan does not confirm PD, patients should proceed with treatment and evaluation as directed by the protocol with the confirmatory scan (if between 4 and 6 weeks from last scan) being counted as the 6 week interval scan.

6.1.4.7 Survival

Survival will be measured from the date of randomization to death from any cause.

6.1.4.8 Time to Progression

This interval will be measured from the date of randomization to the study to the appearance of new metastatic lesions or objective tumor progression.

7. Study Parameters

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Rev. 11/16

7.1 Therapeutic Parameters

1. Prestudy scans must be performed within 4 weeks prior to randomization.
2. Prestudy CBC (with differential and platelet count) should be done ≤ 4 weeks before randomization.
3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ 4 weeks before randomization – unless specifically required on Day 1 as per protocol.
4. Day 1 tests (such as EKG, labs) may be done within (+/-) 72 hours of day 1 and restaging imaging within 7 days.
5. It is recommended that patients on Arm A and D be contacted weekly during Cycles 1 and 2 and have weekly labs +/- exams if they report symptoms at any time during these Cycles or abnormal labs are noted at the requlary scheduled visits (C1 Day 22, C2 D1 or D22). Weekly troponins will be obtained first 4 weeks on Arm A and D (see Footnote 16)

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7.1.1 Schedule of events

	Step 1					Step 2				
	Baseline; all arms	**Arm A**[9, 2]		**Arm B**	**Crossover**	**Arm C**	**Arm D**[9, 2]		**End of Treatment**[9]	**Follow-Up**[8]
	Within 4 weeks prior to Randomization	Induction, Cycles 1 and 2: Day 1 & 22	Maintenance, Cycles 3-14: Day 1	Day 1 of each Cycle [9]	Within 4 weeks of Registration to Step 2	Day 1 of each Cycle [9]	Induction, Cycles 1 & 2: Day 1 & 22	Maintenance, Cycle 3-14: Day 1		
BRAFV600 mutation[7]										
Medical History[1]	X				X					
Physical Exam/ ECOG PS[1]	X	X	X[15]	X	X	X	X	X[15]	X	X
Serum or urine Pregnancy Test[2]	X				X					
Weight/Vital Signs[3]	X	X	X	X	X	X	X	X	X	X
Hematology Labs[4]	X	X	X[15]	X	X	X	X	X[15]	X	X
Chemistry Labs[5, 14]	X	X	X[14]	X	X	X	X	X[14]	X	X
Troponin Screening[16]	X[16]	X[16]			X[16]		X[16]			
Imaging Studies[6]	X[6]		X[6]	X[6]		X[6]		X[6]		X[6]
Skin assessment[10]	X		X[15]	X[10]	X	X[10]		X[15]	X	
Ophthalmologic examination[11]										
EKG[18]	X			X	X	X				

	Step 1					**Step 2**				
	Baseline; all arms	**Arm A**[9, 2]		**Arm B**	**Crossover**	**Arm C**	**Arm D**[9, 2]		**End of Treatment**[9]	**Follow-Up**[8]
	Within 4 weeks prior to Randomization	Induction, Cycles 1 and 2: Day 1 & 22	Maintenance, Cycles 3-14: Day 1	Day 1 of each Cycle [9]	Within 4 weeks of Registration to Step 2	Day 1 of each Cycle [9]	Induction, Cycles 1 & 2: Day 1 & 22	Maintenance, Cycle 3-14: Day 1		
Cardiac Echo or MUGA to assess LVEF[18]	X			X[17]	X	X[17]			X	
Adverse Event Assessment		X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Patient Pill Calendar[12]				X		X				
Biological Sample Submissions	See Section 7.2									
PRO assessment[13]	See Section 5.9									

1. Medical history documented during screening should include previous toxicities from prior therapies. If the screening physical is conducted within 24 hours of dosing on Day 1, then a single examination may count as both the Screening and pre-dose evaluation. There is a (+/-) 3 day window for clinic visits and treatment.
2. Women of child-bearing potential must have a negative serum or urine pregnancy test within 2 weeks prior to randomization and again at crossover to Step 2 for screening purposes.
3. Vital signs will be obtained during day 1 visit of each cycle, in the beginning of infusion and immediately after completion of infusion of ipilimumab and/or nivolumab. Vitals required are temperature, pulse, respiratory rate, blood pressure, and oxygen saturation.
4. Hematology Labs should include CBC with differential (hemoglobin, hematocrit, white blood cells, platelets, neutrophils, lymphocytes, eosinophils and monocytes). Additional draws must be incorporated when monitoring recovery from any hematologic AE.
5. Chemistry Labs should include albumin, amylase, lipase, BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, HCO3, calcium, uric acid and CPK. Labs should also include TSH and free T4 if TSH is elevated.TSH is only required for Arms A and D.

Rev. Add10

6. Non-CNS Imaging should include a chest, abdomen and pelvis CT. Imaging of other sites should be obtained when clinically indicated. (CNS Imaging at the time of PD is generally considered clinically indicated and therefore is encouraged at time of PD on all arms of the study). If follow up scans indicate partial or complete response, a repeat confirmatory scan should be obtained within 12 weeks (but no sooner than 6 weeks). Following crossover, imaging and calendar will be reset at Cycle 1. Baseline imaging will be done within 4 weeks prior to registration, then every 12 weeks (+/- 1 week) from start of treatment (every 2 cycles) if patient is < 2 years from study entry (or < 2 years from crossover), then every 6 months (+/- 4 weeks) until 5 years from study entry.
7. BRAF mutation status should be verified by CLIA approved assay prior to registration. Test must be done on primary or metastatic lesion from this particular melanoma. Patients with a history of multiple primary melanomas must have test performed on a metastatic lesion (lymph node or distant).

8. Every 3 months if patient is < 2 years from study entry and every 6 months if patient is 2-5 years from study entry. Patients who develop melanoma progression will be followed for survival. Patients who stop treatment for reasons other than disease progression after 2.5 years from study entry will be followed every 3 months for a year (or until disease progression), then every six months until 5 years from study entry.
9. 1 Cycle= 42 days (6 weeks) for all arms. Treatment and follow-up schedule is the same for either ipilimumab/nivolumab or dabrafenib/trametinib when administered as either initial treatment or at crossover. Patients receiving ipilimumab/nivolumab (either Arm A or Arm D) will receive treatment at most through cycle 14 (week 84). They will then have treatment stopped and be followed as described in footnote 8 until disease progression or study closure. An End of Treatment visit should occur 30 days (+/- 7 days) from last dose for all patients. For patients experiencing toxicities, End of Treatment visits should occur every 2 weeks (+/-3 days) until toxicities resolve.
10. Skin assessments to examine for cutaneous SCCs. Suspicious lesions detected at baseline should be treated. Patients on dabrafenib/trametinib treatment should have a skin assessment follow-up every 6 weeks after initiating treatment. Skin assessments can be done by investigator with Dermatology backup if new lesions are noted.

Rev. Add14

11. Ophthalmologic examination - Patients with visual complaints (eye irritation, blurred vision, etc) on either treatment approach should see an ophthalmologist to rule/out uveitis (ipilimumab/nivolumab) or evidence of retinal pathology that is considered a risk factor for neurosensory retinal detachment, RVO or neovascular macular degeneration (dabrafenib/trametinib). Ophthalmologic examination must be performed by a qualified eye specialist. Patients diagnosed with these problems should be managed as per criteria in Section 5.4.
12. Pill calendars will only be used for patients receiving dabrafenib/trametinib.
13. PRO Assessments will be administered according to the Assessment Schedule (Section 5.9.).
14. Additional chemistry labs to include BUN, creatinine, ALT, AST, serum alkaline phosphatase, direct and total bilirubin and TSH every 2 weeks prior to nivolumab in patients on nivolumab monotherapy (C3-14 Arms A and D). Labs should also include free T4 if TSH is elevated.
15. Day 1 of cycle 3-14 only.
16. Obtain Troponin at baseline (only for patients on Arm A), at crossover (only for patients on Arm D), Cycle 1 Week 2, Cycle 1 Week 3, and Cycle 1 Week 4.
17. Cardiac Echo or MUGA to be performed every 12 weeks (C3, D1, C5D1 etc) while on Arm B or Arm C.

Rev. Add10

Rev. Add10

18. EKG and echocardiograms are required at baseline. They should be conducted as clinically indicated for any patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs for patients on Arm A and D. For patients with evidence of congestive heart failure (CHF), myocardial infarction (MI), cardiomyopathy, or myositis, further cardiac evaluation, lab tests and cardiology consultations, including EKG, CPK and troponin should be conducted as clinically indicated.

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Rev. Add10

7.2 Biological Sample Submissions

Specimens are to be submitted as outlined in Section 10.

All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

Biological Materials	Prior to Start of Treatment	Every Week for Patients with Grade 3-4 irAEs[5]	Every Six (6) Weeks [initial and crossover]	Time of Crossover	Time of Progression	Submit to:
	MANDATORY for *Central Diagnostic Review*					
Primary and Metastatic Tumor Tissue Biopsies (pretrial diagnostic material)[1,2]	X					CBPF
From patients who answer "Yes" to "I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies."						
Peripheral Blood (five 10cc green top heparin tubes)[3,4]	X		X	X	X	IMCPL
Peripheral Blood (two10cc red top tubes)[3,4]	X	X	X	X	X	
Peripheral Blood (one 10cc yellow top ACD tube)[3,4]	X					

Rev. 12/15

1. Representative primary and metastatic tumor tissue (blocks preferred) and related pathology reports must be submitted for central diagnostic review within one (1) month following registration as outlined in Section 10. Failure to submit the required materials may render the case unevaluable.

Rev. 5/17

2. Tumor tissue will also be used for defined laboratory research studies from patients who answer *"Yes"* to *"I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies."*
3. Kits are being provided for the collection and shipment of the blood samples. See Section 10.3.1.1 for instructions.
4. Please completely fill all blood tubes as full as possible. Blood samples should be shipped the day they are drawn. If you have any questions concerning sample collection and shipment, please contact the ECOG-ACRIN Study Coordinator at (412) 624-0078 at the IMCPL. Note: Blood should **NOT** be collected and shipped on Fridays.
5. Collect weekly for patients with grade 3-4 irAEs until the irAE resolves to grade 1 and then at the patients' regularly scheduled visits until they are tapered off of immunosuppressive agents.

Rev. 5/17

8. Drug Formulation and Procurement

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

Availability

Drug Ordering: GlaxoSmithKline is supplying dabrafenib and trametinib through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Bristol-Myers Squibb is supplying nivolumab and ipilimumab through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Maintenance of NCI drug accountability records is required. Agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information). Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

NCI Supplied Agent(s) – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each agent on this protocol.

Investigator Brochure Availability: The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov

8.1 Ipilimumab

In this study, ipilimumab is considered investigational.

8.1.1 Other Names

Anti-CTLA-4 monoclonal antibody, MDX-010 (MDX-CTLA4, Transfectoma-derived), Yervoy®

8.1.2 Classification

Human monoclonal antibody, IgG1 subclass

M.W.: 147, 991 Daltons

8.1.3 Mode of Action

Ipilimumab is specific for the CTLA4 antigen expressed on a subset of activated T-cells. CTLA4 interaction with the B7 molecule, one of its ligands expressed on professional antigen presenting cells, can down-regulate T-cell response. Ipilimumab is, thought to act by blocking the interaction of CTLA4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation. The CTLA4/B7 creates the interaction.

8.1.4 Storage and Stability

Ipilimumab must be stored in a secure area according to local regulations. The investigator must ensure that it is stored at a temperature between 2°C to 8°C.

Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP to a concentration between 1 mg/mL and 2 mg/mL. Undiluted or diluted ipilimumab solution is stable in a polyvinyl chloride (PVC), non- PVC/non DEHP (di-(2-ethylhexul) phthalate) IV bag or glass container up to 24 hours refrigerated at (2°C to 8°C) or at room temperature/ room light. Do not freeze.

Shelf-life surveillance of the intact vials is ongoing.

CAUTION: Ipilimumab does not contain antibacterial preservatives. Vials are for single use only. Use prepared IV solution immediately. Discard partially used vials.

Each vial is a Type I flint glass vial with gray butyl stoppers and sealed with aluminum seals.

	Process C
Component	**200 mg/ vial[a]**
Ipilimumab	213 mg
Sodium Chloride, USP	249 mg
TRIS-hydrochloride	134.3 mg
Diethylenetriamine pentacetic acid	1.67 mg
Mannitol, USP	426 mg
Polysorbate 80 (plant-derived)	4.69 mg
Sodium Hydroxide	QS to pH 7
Hydrochloric acid	QS to pH 7
Water for Injection	QS: 42.6 mL
Nitrogen[b]	Processing agent

[a] Includes 2.6 mL overfill.

[b] Nitrogen is used to transfer the bulk solution through the pre-filled and sterilizing filters into the aseptic area.

Rev. Add25

In 2023, PMB will transition to a 50 mg/10 mL (5 mg/mL) vial, which will replace the 200 mg vial. The 50 mg vial is packaged in a 10-cc Type I flint tubing glass vial, stoppered with a 20-mm gray butyl rubber stopper, and sealed with a 20-mm aluminum flip-off seal. Each vial includes a 0.7-mL overfill for vial, needle, and syringe (VNS) holdup.

Rev. Add14

Rev. 6/16

8.1.5 Dose Specifics

Calculate Total Dose as follows:

Patient body weight in kg x 3 mg/kg (Regimen 1) or 1 mg/kg (Regimen 2) = total dose in mg

Ipilimumab should be diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL.

Rev. Add14

The dosing calculations should be based on the actual body weight. If the patient's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

8.1.6 Preparation

The supplies needed for ipilimumab preparation and administration include calibrated syringes and infusion containers. Ipilimumab is to be administered as an intravenous infusion using an in-line filter (pore size of 0.2 micrometer to 1.2 micrometer) and a volumetric pump, at 3 mg/kg dose (Regimen 1) or 1 mg/kg dose (Regimen 2), to complete the infusion in 30-60 minutes, with a 3-mL normal saline flush at the completion of the infusion.

- As ipilimumab is stored at refrigerated temperatures (2-8ºC), allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.

- Aseptically withdraw the required volume of ipilimumab solution into a syringe. Insert the needle at an angle into the ipilimumab vial by placing the needle – bevel side down – against the glass, with the tip touching the neck of the vial. The initial solution concentration is 5 mg/mL. [Note: A sufficient excess of ipilimumab is incorporated into each vial to account for withdrawal losses].
- Ensure that the ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.

Rev. Add25

- Inject ipilimumab solution withdrawn into an appropriate size evacuated infusion bag to produce a final infusion volume that has been calculated from the weight of the patient. For example, if preparing a 3mg/kg treatment for a 114 kg patient you will use 2 vials of the 200 mg size (or 7 vials of the 50 mg vial size) for a dose of 342 mg.
- Place the total dose in 106 – 277 mL of NS or D5W for a final concentration between 1 mg/mL and 2 mg/mL.
- Mix by GENTLY inverting several times. DO NOT shake.
- Visually inspect the final solution. If the initial diluted solution or final dilution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.

Rev. Add14

- Do not draw into each vial more than once. Any partial vials should be safely discarded and should not be stored for reuse.

8.1.7 Route of Administration

Rev. Add16

Ipilimumab is administered as an IV infusion only. Infusions should be given over 30- 90 minutes, dependent on institutional standard/policy, (not bolus or IV push). Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents.

8.1.8 Incompatibilities

No compatibility information is available.

8.1.9 Availability

Ipilimumab is available in 5 mg/mL single-use vials (40 mL). The sterile solution in the vial is clear and colorless.

8.1.10 Side Effects

See the Comprehensive Adverse Events and Potential Risks List (CAEPR) in Section 5.3.1 for list of side effects

8.1.11 Nursing/Patient Implications

Monitor patients for immune-related adverse events, e.g., rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypothyroidism. If you

suspect toxicity, refer to the protocol guidelines for ruling out other causes.

Ipilimumab may be excreted in milk or cross the placenta; therefore, nursing women and women with known or suspected pregnancy should not take ipilimumab.

Closely monitor patients who are on narcotics during the treatment with ipilimumab. Narcotics may mask GI signs and symptoms such as diarrhea or abdominal pain, which are relevant complications of a bowel perforation. Minor diarrhea can be a potential sign of colitis and require immediate attention.

8.1.12 Handling and Disposal

As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Latex gloves are required. If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water. After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

8.1.13 Ipilimumab Destruction

Partial vials can be destroyed on site per institution policy. Intact vials of the expired drug, recalled, or when protocol is closed to treatment cannot be destroyed on site without the PMB/NCI approval. If ipilimumab is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

8.2 Nivolumab (NSC748726)

In this study, nivolumab is considered investigational.

Rev. Add16

8.2.1 Amino Acid Sequence: 4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

8.2.2 Other Names

BMS-936558; MDX1106; ONO-4538; anti-PD-1

8.2.3 Classification

Fully humanized monoclonal antibody

8.2.4 Mode of Action

Nivolumab is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that targets the programmed death – 1 (PD-1) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its

predominant ligand, PD-L1, results in the down regulation of lymphocyte activation. Loss of effective immune response to antigens expressed by tumors may be a significant factor in tumor progression. PD-L1 expression has been found on a number of tumors & may also be a mechanism by which tumors can directly engage PD-1 to evade an effective anti-tumor immune response. Inhibition of PD-1 interaction with PD-L1 promotes immune responses and antigen specific T cell responses to both foreign antigens as well as self-antigens. BMS-936558 was shown to promote the proliferation of human T-cells in a variety of assays, which is an anticipated pharmacologic result of PD-1 inhibition.

8.2.5 Description

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate dihydrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

8.2.6 How Supplied

Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

8.2.7 Storage and Stability

Vials of Nivolumab must be stored at 2-8°C (36-46°F); Protect from light, protect from freezing; Infusion – room temp: 8 hours max including infusion and up to 24 hours if refrigerated for the first 16 hours. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Shelf-life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

8.2.8 Dose Specifics

The dosing calculations should be based on the actual body weight. If the patient's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

Rev. Add17 **There will be no dose modifications allowed.**

Rev. 6/16 8.2.9 Preparation

Rev. Add14 Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Rev. Add14 Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

8.2.10 Route of Administration

Intravenous infusion over 30minutes using a volumetric pump with 0.2 to 1.2 micron pre size, low-protein binding in-line filter. Should be administered ahead of ipilimumab on days when both to be administered.

8.2.11 Incompatibilities

No incompatibilities between Nivolumab injection and polyolefin bags have been observed.

8.2.12 Side Effects

See the Comprehensive Adverse Events and Potential Risks List (CAEPR) in Section 5.3.2 for list of side effects.

Rev. 6/16 8.2.13 Nursing/Patient Implications

Infuse over 30 minutes in a minimum of 60 ml infusion volume through a 0.2 to 1.2 micron in-line filter.

Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab.

Monitor carefully for infusion reactions and treat accordingly.

8.2.14 Handling and Disposal

Use appropriate precaution for handling and disposal.

8.2.15 References

LexiComp (2014), AHFS (2014)

8.3 Dabrafenib

In this study, dabrafenib is considered investigational.

8.3.1 Other Names

Tafinlar®, GSK2118436, GSK2118436A (free base)

8.3.2 Classification

Antineoplastic Agent, BRAF Kinase Inhibitor

8.3.3 Mode of Action

Dabrafenib mesylate (GSK2118436B) is a potent and selective BRAF kinase inhibitor. This inhibition suppresses downstream activity of pERK, a biomarker, and has anti proliferative activity against BRAF mutant tumors. The mode of action is consistent with ATP-competitive inhibition. The combination of dabrafenib and trametinib allows for greater inhibition of the MAPK pathway, resulting in BRAF V600 melanoma cell death.

Dabrafenib is metabolized by CYP 3A4 and 2C. It is a moderate inducer of CYP3A4 and possible inducer of other CYP isoenzymes (e.g., 2B6, 2C8, 2C9, 2C19). Dabrafenib is also a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). It is a moderate inhibitor of BCRP in vitro. Dabrafenib also inhibits organic anion-transporting polypeptides (OATP) 1B1 and 1B3 and organic anion transporters (OAT) 1 and 3 in vitro. It may induce uridine diphosphate glucuronosyltransferase (UGT).

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8.3.4 How Supplied

Dabrafenib mesylate (GSK2118436B) capsules are supplied by Novartis and distributed by the DCTD, NCI as 50 mg and 75 mg capsules (equivalent to the free-base) for oral administration.

Each commercially-labeled bottle contains 120 capsules and a silica gel desiccant.

- 50 mg capsule is dark red and imprinted with ‘GS TEW’ and ‘50 mg.’
- 75 mg capsule is dark pink and imprinted with ‘GS LHF’ and ‘75 mg.’

Capsule excipients include microcrystalline cellulose, magnesium stearate (vegetable source), and colloidal silicon dioxide. Capsule shells contain hypromellose, red iron oxide (E172), and titanium dioxide (E171).

8.3.5 Storage and Stability

Store at 25°C (excursions between 15°C to 30°C are permitted).

8.3.6 Dose Specifics

Patients randomized to receive dabrafenib 150mg PO BID continuously and trametinib 2mg PO once daily continuously before or after ipilimumab with nivolumab.

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8.3.7 Route of Administration

Dabrafenib is taken orally at least 1 hour before or 2 hours after a meal; doses should be approximately 12 hours apart. The capsules should not be opened, crushed, or broken. A food effect study showed that food may decrease the dabrafenib Cmax and AUC(0-∞) by 60% and 33%, respectively.

When dabrafenib and trametinib are administered in combination, take the once-daily dose of trametinib at approximately the same time each day with either the morning dose or the evening dose of dabrafenib. The second dose of dabrafenib should be administered approximately 12 hours after the morning dose. Study medication should be taken orally with approximately 200 mL of water under fasting conditions, either 1 hour before or 2 hours after a meal.

If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next dose as originally scheduled.

If administration of trametinib is interrupted or permanently discontinued, administration of dabrafenib may be continued. If administration of dabrafenib is interrupted or permanently discontinued, administration of trametinib may continue.

If a subject misses a dose of dabrafenib, the subject may take the dose immediately if the next dose is scheduled for at least 6 hours later. If the next scheduled dose of dabrafenib is due in less than 6 hours, the subject should skip the dose and resume dabrafenib dosing at the next scheduled dose. If a subject misses a dose of trametinib, the subject may take the dose immediately if the next dose is scheduled for at least 12 hours later.

8.3.8 Incompatibilities

Potent inhibitors of CYP 3A4 or 2C8 have increased dabrafenib concentrations. Alternative therapy to potent inhibitors of CYP 3A4 or 2C8 is recommended. If concomitant use is unavoidable, monitor patients closely for dabrafenib-associated adverse reactions. Potent inducers of CYP 3A4 or 2C8 have decreased dabrafenib concentrations. Alternative therapy to potent inducers of CYP 3A4 or 2C8 is recommended. If concomitant use is unavoidable, monitor patients closely for reduced dabrafenib efficacy.

Dabrafenib has the potential to decrease concentrations of CYP 3A4, 2B6, 2C8, 2C9, 2C19 substrate drugs. Alternative therapy to the substrate drug is recommended. If concomitant use is unavoidable, monitor for reduced efficacy of the substrate drug. Also, dabrafenib has the potential to decrease the concentrations of UGT substrate drugs. Consider alternative therapy to the substrate drug. If concomitant use is unavoidable, monitor for reduced efficacy of substrate drug.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with

antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin.

The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of study treatment. Because there is a potential for interaction of dabrafenib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior surgical procedures will be recorded in the eCRF. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Specific Drug Interactions

Antacid: Possible decreased dabrafenib concentrations; effect on dabrafenib efficacy is unknown

Anticonvulsants (carbamazepine, phenobarbital, phenytoin: Possible decreased dabrafenib concentrations. Monitor closely for reduced dabrafenib efficacy.

Clarithromycin: Possible increased dabrafenib concentrations. Monitor closely for dabrafenib-associated adverse effects

Dexamethasone: Possible decreased dexamethasone concentrations and reduced efficacy. Alternative therapy to dexamethasone is recommended; if concomitant use is unavoidable, monitor closely for reduced dexamethasone efficacy.

Gemfibrozil: Possible increased dabrafenib concentrations. Use alternative to gemfibrozil; if concomitant use is unavoidable, monitor closely for dabrafenib-associated adverse effects

Histamine H2-receptor antagonists: Possible decreased dabrafenib concentrations; effect on dabrafenib efficacy is unknown.

Hormonal contraceptives: Possible decreased estrogen/progestin concentrations and reduced efficacy. Advise females of childbearing potential to use alternative nonhormonal contraception during and for 4 weeks after discontinuing dabrafenib therapy. If concomitant use is unavoidable, monitor closely for reduced hormonal

Ketoconazole: Possible increased dabrafenib concentrations. Use alternative to ketoconazole; if concomitant use is unavoidable, monitor closely for dabrafenib-associated adverse effects.

Midazolam: Decreased midazolam concentrations. Use alternative to midazolam; if concomitant use is unavoidable, monitor closely for reduced midazolam efficacy.

Nefazodone: Possible increased dabrafenib concentrations. Use alternative to nefazodone; if concomitant use is unavoidable, monitor closely for dabrafenib-associated adverse effects.

Proton-pump inhibitors: Possible decreased dabrafenib concentrations; effect on dabrafenib efficacy is unknown

Rifampin: Possible decreased dabrafenib concentrations. Use alternative to rifampin; if concomitant use is unavoidable, monitor closely for reduced dabrafenib efficacy.

St. John's wort: Possible decreased dabrafenib concentration. Use alternative to St. John's wort; if concomitant use is unavoidable, monitor closely for reduced dabrafenib efficacy.

Warfarin: Possible decreased warfarin concentrations. Use alternative to warfarin; if concomitant use is unavoidable, monitor closely for reduced warfarin efficacy.

Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. If radiation therapy is administered, it is recommended that dabrafenib be held at least 24 hours before XRT is administered.

8.3.9 Side Effects

See the Comprehensive Adverse Events and Potential Risks List (CAEPR) in Section 5.3.4 for list of side effects.

8.3.10 Nursing/Patient Implications

Discuss specific use of drug and side effects with patient as it relates to treatment.

Patient may experience alopecia, pachyderma, headache, arthralgia, myalgia, back pain, or constipation. Have patient report immediately to prescriber severe dizziness, syncope, urinary retention, hyperhidrosis, dehydration, wound healing impairment, skin changes, sudden vision changes, ophthalmalgia, eye irritation, or signs of hyperglycemia.

Educate patient about signs of a significant reaction (e.g., wheezing; chest tightness; fever; itching; bad cough; blue skin color; seizures; or swelling of face, lips, tongue, or throat).

In the case of overdose, patients should be treated symptomatically since there is no specific antidote. Hemodialysis is likely to be ineffective since dabrafenib mesylate is highly bound to plasma proteins.

Patient should consult prescriber for additional questions.

8.3.11 Handling and Disposal

Use appropriate precaution for handling and disposal.

8.3.12 References

LexiComp (2014), AHFS (2014)

Rev. Add20

8.4 Trametinib (NSC 763093)

In this study, trametinib is considered investigational.

8.4.1 Other Names

Trametinib, GSK1120212B, TMT212-NXA, JTP-74057, JTP-78296, JTP-75303, Mekinist®

Rev. Add20

8.4.2 Chemical Name

Equimolecular combination of N-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl}phenyl)acetamide with (methylsulfinyl)methane

8.4.3 Classification

MEK inhibitor.

8.4.4 Molecular Formula

$C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$ M.W.: 693.53 (dimethyl sulfoxide solvate), 615.41 (anhydrous parent)

Rev. Add20

8.4.5 Approximate Solubility

Trametinib dimethyl sulfoxide is almost insoluble in aqueous media at pH range of 2-8.

8.4.6 Mode of Action

Trametinib dimethyl sulfoxide is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Tumor cells commonly have hyperactivated extracellular signal-related kinase (ERK) pathways in which MEK is a critical component. Trametinib dimethyl sulfoxide inhibits activation of MEK by RAF kinases and MEK kinases.

Rev. Add20

8.4.7 Description

Trametinib dimethyl sulfoxide is a white to almost white powder.

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8.4.8 How Supplied

Novartis supplies and CTEP, NCI, DCTD distributes trametinib as 0.5 mg and 2 mg (as free base) tablets. Tablets may be provided in investigationally-labeled bottles or commercially-labeled bottles.

The tablet core contains mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), colloidal silicon dioxide and sodium lauryl sulfate.

The aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow (0.5 mg tablet), iron oxide red (2 mg tablet) and polysorbate 80 (2 mg tablet).

Each investigationally-labeled bottle contains 32 tablets with a desiccant:

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated.
- 2 mg tablets are pink, round, biconvex and film-coated.

Each commercially-labeled bottle contains 30 tablets with a desiccant:

- 0.5 mg tablets are yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face.
- 2 mg tablets are pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face.

8.4.9 Storage and Stability

Rev. Add20

Store tablets at 2°C -8°C (36° F to 46° F) in the original bottle and dispense unopened bottles. Do not repackage tablets or remove desiccant. Bottles should be protected from light and moisture.

If a storage temperature excursion is identified, promptly return trametinib to 2°C -8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability studies are ongoing. Tablets are only stable for 32 days once bottle has been opened. If multiple bottles are dispensed to a patient in the same visit, please advise the patient to open only one bottle at a time.

8.4.10 Dose Specifics

Patients randomized to receive trametinib 2mg PO once daily continuously and dabrafenib 150mg PO BID continuously before or after ipilimumab with nivolumab.

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8.4.11 Route of Administration

Rev. Add20

Oral. Take by mouth on an empty stomach, either 1 hour before or 2 hours after a meal. If a dose of trametinib is missed, the dose can be taken if it is more than 12 hours until the next scheduled dose.

See Section 8.3.7 for instructions when Dabrafenib + Trametinib are administered in combination.

Rev. Add20

8.4.12 Potential Drug Interactions

In vitro studies suggest that trametinib is not a substrate of CYP enzymes or of human BCRP, MRP2, OATP1B1, OATP1B3, OATP2B1, OCT1 or MATE1 transporters. Trametinib elimination by deacetylation to metabolite M5 is dependent on carboxylesterases (CES1b, CES1c and CES2). Trametinib is a substrate for P-gp and BSEP, but this is not expected to be clinically relevant due to trametinib's high permeability.

Trametinib is an in vitro inhibitor of CYP 2C8 and is anticipated to have overall low potential for drug interactions as a perpetrator. It is

also a weak CYP 2B6 and 3A4 inducer and expected to have little clinical effect on sensitive substrates. Trametinib is not an inhibitor of CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4 and not an inhibitor of MRP2 or BSEP, but an in vitro inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 and MATE1 at systemic concentrations that are not clinically relevant. No clinically relevant inhibition by trametinib is predicted in the liver or kidney and a low risk of intestinal drug-drug interaction is possible with BCRP.

Trametinib is highly bound to plasma proteins (97.3%) and has the potential to interfere with other highly protein-bound drugs. Use caution in patients taking concomitant drugs that are highly protein-bound and have narrow therapeutic ranges.

Table 3: Trametinib drug interactions

Interacting Drugs	Description
ARIPiprazole	CYP3A4 Inducers may decrease the serum concentration of ARIPiprazole. Management: Double the oral aripiprazole dose and closely monitor clinical response. Reduce the oral aripiprazole dose to 10-15 mg/day if the inducer is discontinued. Avoid use of CYP3A4 inducers for more than 14 days with extended-release injectable aripiprazole. Consider therapy modification.
Axitinib	CYP3A4 Inducers (Weakly to Moderately Effective) may decrease the serum concentration of Axitinib. Avoid combination.
Dabrafenib	Trametinib may enhance the adverse/toxic effect of Dabrafenib. Monitor therapy.
Ibrutinib	CYP3A4 Inducers (Weakly to Moderately Effective) may decrease the serum concentration of Ibrutinib. Consider therapy modification.
Saxagliptin	CYP3A4 Inducers may decrease the serum concentration of Saxagliptin. Monitor therapy.
Simeprevir	CYP3A4 Inducers (Weakly to Moderately Effective) may decrease the serum concentration of Simeprevir. Avoid combination.

8.4.13 Side Effects

See the Comprehensive Adverse Events and Potential Risks List (CAEPR) in Section 5.3.3 for list of side effects.

Rev. Add20

8.4.14 Nursing/Patient Care Implications

Trametinib should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal/snack. Do not take a missed dose within 12 hours of the next dose.

Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for 4 months after the last dose of trametinib. Advise women not to breastfeed while receiving study treatment and for 4 months after the last dose of trametinib. Advise men study participants to use barrier contraception and not to father a child while taking study treatment and for 4 months after the last dose of trametinib.

9. Statistical Considerations

9.1 Study Design and Objectives

In this randomized phase III study, patients with unresectable stage III or stage IV BRAFV600 mutant melanoma will be equally randomized to A: ipilimumab-nivolumab (with subsequent dabrafenib in combination with trametinib) or B: dabrafenib in combination with trametinib (with subsequent ipilimumab-nivolumab) using the stratification factors (ECOG PS, Serum LDH). The stratified randomization will be based on the permuted block method.

The primary objective is to evaluate whether initial treatment with either combination ipilimumab-nivolumab (with subsequent dabrafenib in combination with trametinib) or dabrafenib in combination with trametinib (with subsequent ipilimumab-nivolumab) significantly improves 2 year overall survival.

9.2 Study Endpoints

Overall Survival (OS) is defined as the time from randomization to death from any cause. Patients who have not died will be censored at the date of last known alive. 2-year OS rate will be defines as a proportion of patients who are alive after two years of follow-up time among all cases who have died within 2 years or alive after 2-year follow-up time.

Progression-Free Survival (PFS) is defined as the time from randomization to disease progression or death (whichever occurs first). Cases without an event to date 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 6.1.

Response will be defined by the RECIST guidelines (version 1.1) as described in Section 6.

Toxicity will be defined using the CTCAE version 4.0 criteria.

9.3 Sample Size Considerations and Monitoring Plan

The primary comparison will be overall survival (OS) in arms A: ipilimumab-nivolumab (with subsequent dabrafenib in combination with trametinib) vs. B: dabrafenib in combination with trametinib (with subsequent ipilimumab-nivolumab). The primary endpoint for this study is the 2-year overall survival (OS) rate. Since the proportional hazard assumption is not appropriate for the proposed treatment arms, the most meaningful endpoint is the 2-year OS rate. The sample size calculation was conducted using the 2-year OS as a binary data. The primary analysis will be an ITT analysis based on the 2-year OS rate, using the Mantel-Haenszel test. The number of cases censored before two years is expected to be minimal in this study.

The sample size for 2-year OS rate of 70 % in arm A vs. 50% in arm will be 270 for 90% power. This is based on the two-sided type I error rate of 0.05 and allows for three interim analyses. An additional 10% (30 patients) have been added to cover for potential ineligibility or patient loss at the crossover time point. Assuming accrual rate of 16 (based on E2603/E1608 40/month and a 40%

BRAFV600 mutation rate seen in E2603) accrual is estimated to take a maximum of 19 months. In addition, the follow-up time will be 2 years to assess the 2-year OS rate endpoint. Note that a clinically meaningful difference in 2-year OS rate is 70% vs. 50%. This assumption was used for the above power calculation of 90%. However if there is slightly smaller difference, i.e. 67.5% vs. 50%, the proposed design still provides 80% power.

Formal interim analysis based on the difference of 2-year OS rate between the two arms will be conducted, starting at 33% information time (that is when first 100 patients enrolled are followed for 2 years). We expect this will be around 30 months (2.52 years) after the study activates. After that, interim analysis will be repeated every 6 months. It is expected to be at 65% and 100% information time. To preserve the overall type I error rate, critical values at the interim analyses will be determined using a truncated version of the Lan-DeMets spending function corresponding to the O'Brien-Fleming boundary. Table 1 below summarizes operating characteristics of the proposed monitoring plan.

This study will also be monitored for early stopping in favor of the null hypothesis based on the Jennison-Turnbull repeated confidence interval (RCI) approach. At each interim analysis, the difference in 2-year OS rates in arms A and B and variance will be estimated. The RCI on the difference in 2-year OS rates will be computed using the critical value from the error spending rate function and estimated variance. Strata will be taken into account for the RCI monitoring. If this RCI does not include the target alternative difference, then the study may be stopped early for lack of benefit.

Table 1. Operating Characteristics of Interim Analyses

Repeated Analyses	Real Time (years)	Total No. Of cases 2-yr OS assessed	Information Time	Upper Boundary	Nominal Significance
1	2.52	100	.33	3.7307	0.954874E-04
2	3.02	196	.65	2.5498	0.538891E-02
3	3.56	300	1	1.9903	0.232812E-01

Starting from 1 year after activation and every 6 months subsequently, the following issues will also be discussed at the ECOG-ACRIN DSMC meeting. It is assumed that the hazard rates for OS will vary over the course of study. For the safety of patients, hazard ratios (HR) for OS will be monitored during the course of the study. Hazard functions for OS and HR for OS will be estimated. As an approximate guideline, the HR for OS < 0.75 or > 1.33 will prompt a discussion of the ECOG-ACRIN DSMC. The main purpose of monitoring is for the safety reason in earlier part of the study. When the formal interim analysis begins based on the 2-year OS rate (after 2.52 years), it is not likely this safety-based monitoring will indicate a conflicting result. However this issue will be reported and discussed at the ECOG-ACRIN DSMC. The ECOG-ACRIN DSMC will also monitor the feasibility of cross-over from one arm to the other and completing at least an initial course of treatment after cross-over. If less than 50% of patients

can safely cross over from one therapy to this other, accrual will be halted and the feasibility of the alternative treatment schedules will be evaluated.

9.4 Statistical Analysis Plan

The primary (2-year OS rate) and secondary efficacy (OS, 3-year OS rate) analyses will include all randomized patients (intent-to-treat analysis). Toxicity analysis will be based on all cases who received the treatment regardless of eligibility.

The primary endpoint, 2-year OS rate will be estimated (proportion of patients alive after 2 years of follow-up time) and will be compared between the two arms using the Mantel-Haenszel test (stratified by ECOG PS and LDH) based on two-sided overall type I error rate of 0.05 adjusting for two-interim analysis. Mantel-Haenszel test will compare the 2-year OS rates while controlling for the stratification factors. The difference in 2-year OS rates in arms A and B will be estimated and presented with 95% repeated confidence interval of Jennison-Turnbull. In addition, OS distribution will be estimated using the Kaplan-Meier method. The distribution of OS will be compared using the stratified log rank test. Hazard of OS will be estimated as a function of time in arm A and in arm B (as randomized in step 1 to arm A vs. B) and presented graphically.

In PFS distribution will be estimated using the Kaplan-Meier method.

PFS distributions will be compared using the log rank test and response rates will be compared using the Mantel-Haenszel test (stratified by ECOG PS and LDH) test in arms A vs. B. 3-year OS rate (proportion of patients alive after 3 years of follow-up) will be estimated by treatment arms and will be compared using the Mantel-Haenszel test (stratified by ECOG PS and LDH) in arms A vs. B. Cases censored before 3-year will not be included in this analysis, but this number is expected to be minimal.

Response rate and PFS for patients who are treated with Ipilimumab/Nivolumab before crossover (arm A) vs. for patients who were initially treated with dabrafenib/trametinib and crossed over to Ipilimumab/Nivolumab will be compared (arm D). For the latter group, PFS will be defined as the time from cross-over until progression or deaths without progression. Tumor response will be assessed from the start of a particular therapy and baseline will be recalculated at time of cross over therapy. Patients without RECIST defined measurable disease at time of crossover will be excluded from the response assessment. Response rates will be compared using the Fisher's exact test and PFS will be compared using the log-rank test. Safety profile of these two groups will also be compared using the Chi-square or Fisher's exact test. Analyses specified in this paragraph will be repeated for arms B vs. C comparison.

Toxicity rate for individual AEs, categorized AEs and worst degree AEs will be compared in arms A vs. B and in arms C vs.D using the Chi-square of Fisher's exact test. Two-sided p-values will be reported for these comparisons.

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

Subset analyses are planned for all stratification factors (ECOG PS, LDH) and well known prognostic factors such as age, sex, ulceration, etc. Subset analyses are considered to be exploratory in nature.

9.5 Sex and Ethnicity

Based on previous data from E1608, E2603 the anticipated accrual in subgroups defined by sex and race is:

Ethnic Category	**Sex**		
	Females	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	106	193	299
Ethnic Category: Total of all subjects	**106**	**194**	**300**

Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	3	0	3
Native Hawaiian or other Pacific Islander	0	0	0
White	103	194	297
Racial Category: Total of all subjects	**106**	**194**	**300**

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

9.6 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

9.7 Correlative Objectives

Genetic associations with irAE status will be assessed using Fisher's exact test, one-degree-of-freedom genotypic trend test (analogous to the Cochran-Armitage test) or the two-degrees-of-freedom chi-squared test of independence at each individual SNP marker. Tests of association will be adjusted for age, sex, center or clinical protocol, and dose as well as AJCC stage, ulceration, performance status, lactase dehydrogenase (LDH) level, number of involved sites, using

logistic regression modeling assuming an additive genetic model. Within distinct genetic pathways or regions, P-values of individual SNP marker associations will be adjusted for multiple testing by controlling the false discovery rate (FDR).

Analysis for survival outcomes will occur within the framework of Cox proportional hazards, although otherwise similar to analyses described above for irAEs. In addition to adjusting for age at diagnosis, sex, center, clinical trial and dose, adjustment for variables potentially associated with prognosis including AJCC stage, ulceration, performance status, lactase dehydrogenase (LDH) level, number of involved sites, will also be made.

For replication phase irAE outcomes, the study has 80% power to detect a per-allele RR of 2.90 or greater for SNP markers with a MAF of at least 0.10. For analysis of 2 year survival, the study has 80% power to detect a per-allele HR of 1.83 or greater for SNP markers with a MAF of at least 0.10. These detectable measures of effect compare favorably to point estimates we found in our small preliminary study.

9.8 Patient Reported Outcomes (PROs) Objectives

All enrolled patients will participate in the PROs component of the study. Only those who receive at least one dose of protocol treatment (i.e., all treated patients) will be included in the PROs analysis.

Several objectives are proposed in the patient-reported outcomes (PROs) assessment study: (a) to compare quality-adjusted time without symptoms or toxicity at 2 years between initial treatments (i.e., arm A: ipilimumab + nivolumab (with subsequent dabrafenib + trametinib) vs. arm B: dabrafenib + trametinib (with subsequent ipilimumab + nivolumab)); (b) to compare overall function between initial treatment (i.e., arm A: ipilimumab- + nivolumab (with subsequent dabrafenib + trametinib) vs. arm B: dabrafenib + trametinib (with subsequent ipilimumab- + nivolumab) at baseline, weeks 6, 12, months 6, 12, 18, and 24 from study entry); and (c) to assess function and patient-reported symptoms by treatment sequence for ipilimumab +nivolumab (arm A vs. D), and dabrafenib + trametinib, (arm B vs. C) at baseline, 6-, 12-weeks, and 6-months after the initiation of treatment in each step.

9.8.1 Statistical consideration for PROs

The primary objective is to compare the overall clinical benefit between initial treatments (i.e., arm A: ipilimumab + nivolumab (with subsequent dabrafenib + trametinib) vs. arm B: dabrafenib + trametinib (with subsequent ipilimumab + nivolumab)), accounting for toxicities and overall survival. The quality-adjusted time without symptoms of disease progression or toxicity of treatment (Q-TWiST) analysis will be used to provide an integrated measure of quality and quantity of survival time. The Q-TWiST score based on overall survival at 2 years will be computed and compared, with the details of the Q-TWiST score described in the following section. A clinically important difference (CID) in the Q-TWiST score is recommended to be 10% of median survival in the control group.[44] It is hypothesized in this trial that the 2-year OS rate is 70% for Arm A and 50% for Arm B, the CID for Q-TWiST is thus estimated to be 2.4 months in this study for the Q-TWiST power calculations. A standard deviation of 4.0 was

estimated based on the difference of 1.5 months, together with its 95% confidence interval of (-6.3, 9.3), in the duration of the TWiST state between high-risk melanoma patients receiving IFNα2b and those on observation.[45] The table below lists the power, using an independent-sample t-test with a two-sided type I error of 0.05, based on various projected standard deviation in the Q-TWiST score assuming different number of patients in each comparison arm. As shown in the table, with 135 patients in each group (as proposed for the 2-year OS primary endpoint), we have 80% power to detect a CID of 2.4 months in the Q-TWiST score with a standard deviation of 7 in the Q-TWiST score. The power drops to 50% with 135 patients in one group and a standard deviation of 10 in the Q-TWiST score. We acknowledge that the actual standard deviation of the Q-TWiST score could be quite a bit different here because the variance of the Q-TWiST score will depend on the joint distribution of the 5 restricted mean estimates, which will depend on the actual distributions, as well as on the utility weights for the different states.

Clinically Important Difference	Standard Deviation	N (per group)	Power
2.4	5	135	97
2.4	6	135	90
2.4	7	135	80
2.4	8	135	69
2.4	9	135	58
2.4	10	135	50
2.4	5	120	95
2.4	6	120	86
2.4	7	120	75
2.4	8	120	63
2.4	9	120	53
2.4	10	120	45

9.8.2 Analysis plan for PROs

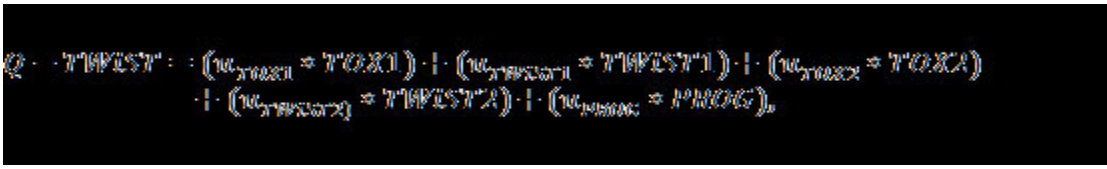
Primary Q-TWiST Analysis. Due to the complexity of the current study (with the subsequent treatment after disease progression on the initial treatment), the basic 3-state Q-TWiST model is extended to a 5-state model in order to calculate the Q-TWiST score. For each initial treatment group, overall survival will be partitioned into five distinct clinical health states as listed below:

- TOX1: Toxicity with initial treatment (during step 1) is defined as the time spent with grade 3 or 4 toxicities prior to disease progression on the initial treatment. The start and end date for each adverse event will be captured. A day with multiple qualifying adverse events will only be counted once. For patients with severe toxicities reported in step 1 but no end date reported, TOX1 will be capped at the date of disease progression in step 1 or death without progression.

- TWiST1: Time without symptoms of disease progression or toxicity of initial treatment is defined as the number of days in step 1 prior to disease progression and with no grade 3 or 4 toxicities reported. Specifically, this is the time from study entry to disease progression on the initial treatment or death without progression, minus TOX1.
- TOX2: This toxicity period is defined as the time spent with grade 3 or 4 toxicities after disease progression on the initial treatment (in step 1) and prior to 2nd disease progression on the subsequent treatment (in step 2). The start and end date for each adverse event will be captured. A day with multiple qualifying adverse events will only be counted once. For patients with severe toxicities reported during this period but no end date reported, TOX2 will be capped at the date of disease progression on the subsequent treatment or death without progression.
- TWiST2: Time without symptoms of 2nd disease progression or toxicity of subsequent treatment is defined as the number of days after disease progression on the initial treatment and prior to the 2nd disease progression on the subsequent treatment and with no grade 3 or 4 toxicities experienced during this time period. Specifically, this is the time from 1st disease progression to 2nd disease progression or death without progression, minus TOX2.
- PROG: This progression health state is defined as the time from the last disease progression on the study to death from any cause.

The above health states are progressive, but it is not required for all patients to go through all the 5 states. For example, for patients without disease progression on the initial treatment, they will not enter TOX2, TWiST2, and PROG states.

The Q-TWiST score is obtained by summing the weighted clinical health state durations. The Q-TWiST score for each treatment arm will be calculated using the following formula:



where u_{TOX1}, u_{TWiST1}, u_{TOX2}, u_{TWiST2}, u_{PROG} represent the average group utility weight for each health state for that arm; TOX1, TWiST1, TOX2, TWiST2, and PROG represent the mean duration of the health state of that arm .

In the Q-TWiST analysis, each health state is assigned a weight ranging from 0 (representing death) to 1 (indicating perfect health). These weights are called utility scores as well. For each patient, EQ-5D will be administered multiple times (at baseline, at each cycle while during the initial and subsequent treatment period, then every 3 months up to 2 years from study entry if patients are off protocol

treatment and not receiving non-protocol therapy, at end of treatment in each step (before and after crossover), and at dose modification) and its score will be used to derive the utility score. In this study, the utility score is conditional on the patient-reported health state on the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) captured in EQ-5D. A number ranging from 1 to 5 will be assigned to each level in each of the 5 dimensions. A patient's health state thus can be labeled using a 5-number descriptor ranging from 11111 to 55555. A utility score corresponding to each possible descriptor elicited from general population samples (by country) was provided in the file "EQ-5D-5L_Crosswalk value sets" posted in the website of www.euroqol.org.[46] We are going to use the value set elicited from US subjects for our patients in this study. For instance, a health state with a descriptor of "11111" is given a utility score of 1.000, "12111" is assigned a utility value of 0.854, and "43333" is with a utility score of 0.573.

The average EQ-5D utility score for a patient's individual health state will be computed across all utility scores collected during that health state. For instance, EQ-5D scores for all visits during which a grade 3 or 4 adverse event is reported before the patient experiences disease progression on initial treatment will be averaged to form that patient's TOX1 utility score. All EQ-5D scores for visits without either grade 3 or 4 adverse events or disease progression on initial treatment will be averaged to form the patient's TWiST1 utility score. Similar definition and computation apply for TOX2 and TWiST2 with respect to the subsequent treatment. All EQ-5D scores for visits after last disease progression will be averaged to form that patient's PROG utility score. For each health state, the average group utility score is the mean of that health state within each treatment arm.

The restricted mean amount of time for each health state will be estimated using the Kaplan-Meier method, with time limit set at 2 years for computation of all restricted means. The duration of each health state is defined as follows:

- Mean duration of TWiST1 = mean PFS1 – mean TOX1,
- Mean duration of TWiST2 = mean PFS2 – mean TOX2,
- Mean duration of PROG = mean OS – mean PFS2,

where PFS1 is defined as the time from study entry to the first disease progression on the initial treatment. For patients alive without first disease progression, PFS1 will be censored at the date of last disease evaluation in step 1. PFS2 is defined as the time from study entry to the second disease progression on the subsequent treatment (in step 2). For patients enrolled into step 2, if they are alive without disease progression in step 2, PFS2 will be censored at the date of last disease evaluation in step 2. For patients not enrolled into step 2, PFS2 will be censored at the date of last disease evaluation in step 1. OS is defined as the time from study entry to death from any cause, censored at the date of last contact. TOX1 is defined as the days spent with grade 3 or 4 toxicities prior to disease progression on the

initial treatment (in step 1). For patients with severe toxicities reported in step 1 but no end date reported, TOX1 will be capped at the date of disease progression in step 1 or death without progression. TOX2 is defined as the number of days with grade 3 or 4 toxicities reported after the first disease progression on the initial treatment (in step 1) and prior to the second disease progression on the subsequent treatment (in step 2). For patients with severe toxicities reported during this period but no end date reported, TOX2 will be capped at the date of disease progression on the subsequent treatment or death without progression. For patients not receiving the subsequent treatment, TOX2 is counted as 0.

There are a couple of special notes for this expanded Q-TWiST analysis. If patients die during an early state and EQ-5D is not administered thereafter, the utility score in each of subsequent states will be defined as 0. If patients withdraw or lost to follow-up during an earlier state, the utility score in subsequent states will be assigned 0.. Finally, since Q-TWiST is being computed for 2 years in this study, once the duration of earlier states reach 2 years, the utility score collected in subsequent states will be used for these patients in the 2-year Q-TWiST analysis.

The mean amount of time for each health state and the average group utility scores will be summarized by initial treatment (i.e., arm A: ipilimumab + nivolumab (with subsequent dabrafenib + trametinib) vs. arm B: dabrafenib + trametinib (with subsequent ipilimumab + nivolumab)). The Q-TWiST subscore and the overall Q-TWiST score will then be reported by initial treatment. Differences between treatment groups in the mean Q-TWiST score (including the overall score and the subscore) will be calculated. For each score, a 95% confidence interval (CI) and two-sided P-value for testing the null hypothesis of no difference between treatment groups will be conducted using a Z-test (with normal approximation), with standard errors calculated by the bootstrap method. The bootstrap will be performed by repeated sampling, with replacement, from the sample of patients enrolled in this study, to obtain a new sample. The means for the new sample will be calculated using the same method as described above. This process will be repeated 1000 times. Based on the means obtained by the bootstrap method, the standard errors can be calculated.

Due to the multiple assessment timepoints for EQ-5D (at baseline, at each cycle while during the initial and subsequent treatment period, then every 3 months up to 2 years from study entry if patients are off protocol treatment and not receiving non-protocol therapy, at end of treatment in each step (before and after crossover), and at dose modification), we do not expect too many patients that reach a state but do not get any EQ-5D evaluation for the utility calculations. If this indeed occurs, it suggests that the reached state is rather short. For the primary Q-TWiST analysis, we assume these data will be missing at random then compute the average group utility weight for each health state based on patients with nonmissing data on the reached

states. If more than 20% of the cases have missing data, with respect to any reached health state, a sensitivity analysis will be performed with missing utility scores on a reached state being replaced by the average EQ-5D utility score from these patients' preceding health state. In case of discrepancies between the primary analysis and the sensitivity analysis, possible explanations will be discussed.

Secondary PRO Analysis. Overall function will be assessed (at baseline, weeks 6 (end of cycle 1), weeks 12 (end of cycle 2), and months 6 (disease stability)) while during the initial and subsequent treatment period (at 6-week, 12-week, months 6, 12, 18, and 24 from study entry (even off study treatment)) using PROMIS PROFILE-29. This instrument, consists of 7 short forms (Depression, Anxiety, Physical Function, Pain Interference, Fatigue, Sleep Disturbance, and Ability to Participate in Social Roles and Activities, with 4 items in each short form) together with one Pain Intensity item. Each item has five response options ranging in value from 1 to 5, except for the Pain Intensity item which has eleven response options ranging in value from 0 to 10. A raw score can be computed for each short form by summing the values of the response to each question within each domain.

The total raw score for each short form can then be converted into a standardized T-score with a mean of 50 and a standard deviation of 10. As to the Pain Intensity item, the raw response (0-10) can be used directly in data analyses.

Given differential attrition might exist in the two treatment groups and a high level of missing data is expected toward the end of the two-year PRO period with advanced melanoma patients (2-year OS rate expected to be 70% vs. 50% for arm A and arm B, respectively), a log-normal survival model will be implemented to adjust for potentially informatively censored data, using the expectation-maximization (EM) algorithm, as described in Schluchter (1992).[47] A log-normal survival model for analyzinag longitudinal data (collected at baseline, 6-week, 12-week, months 6, 12, 18, and 24 from study entry) which incorporates the non-ignorable censoring mechanism will be fitted for each short form T-score and pain intensity, separately, to assess initial treatment effect (i.e., arm A: ipilimumab + nivolumab (with subsequent dabrafenib + trametinib) vs. arm B: dabrafenib + trametinib (with subsequent ipilimumab + nivolumab)) on each function.

To evaluate the effect of treatment sequence on patient function, each of the PROMIS short form T-score and pain intensity (with longitudinal data collected at baseline, 6-, 12-weeks, and 6-months after the initiation of treatment in each step) will be compared by treatment sequence for ipilimumab + nivolumab (arm A vs. D) and for dabrafenib + trametinib (arm B vs. C), using a log-normal survival model as described above.

PRO-CTCAE consisting of 17 symptoms (rash, headache, muscle pain, joint pain, decreased appetite, nausea, vomiting, constipation,

diarrhea, fatigue, cough, chills, itching, abdominal pain, shortness of breath, swelling, and increased sweating) will be administered multiple times (at baseline, at each subsequent cycle while during the initial and subsequent treatment period, at end of treatment in each step (before crossover and after crossover), and at dose modification).

PRO-CTCAE measures, if applicable, patient-reported presence (yes or no), frequency (never, rarely, occasionally, frequently, or almost constantly) and severity (none, mild, moderate, severe, very severe) on each of the specified symptoms. To evaluate the effect of treatment sequence on symptoms, summary statistics (frequency (N) and percentage (%)) will be reported with respect to presence, frequency and severity (if applicable) for each symptom by treatment sequence for ipilimumab + nivolumab (arm A vs. D), and for dabrafenib + trametinib (arm B vs. C) at baseline, 6-, 12-weeks, and 6-months after the initiation of the first treatment and the secondary treatment.

Rev. Add10

10. Biological Sample Submissions

Diagnostic material from previously collected tissue must be submitted for central diagnostic review and retention of a portion for defined immune biomarker assays and future undefined research studies such as PDL-1 and other bio-markers (per patient consent). Peripheral blood is to be submitted from consenting patients for defined laboratory research studies.

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

All samples must be labeled clearly with the ECOG-ACRIN protocol number (EA6134), ECOG-ACRIN patient sequence number, patient's initials, date of collection and sample type.

10.1 Sample Collection and Submission Schedule

Samples are to be submitted as follows:

- Pretrial diagnostic pathology samples must be submitted within one (1) month of registration. See Section 10.2.
- Peripheral blood samples are to be submitted as outlined in Section 10.3 on the day of collection. Samples are to be collected at the following time points for each tube type:
  - Prior to start of treatment (yellow top at baseline only)
  - Every week for patients with grade 3 or 4 irAEs until the irAE resolves to grade 1 and then at the patients' regularly scheduled vistis until they are tapered off
  - Every six (6) weeks (initial and crossover)
  - Time of Crossover
  - Time of Progression

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

Submitting pathologist and clinical research associate may refer to Appendix I which outlines the Pathology Submission Guidelines. Submission of pretrial diagnostic pathology samples from all patients is mandatory. Failure to submit the required materials may render the patient's data unevaluable.

The tissue samples are to be labeled with the Pathology ID as well as the information above.

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10.2.1 Required Materials

Forms: Must be submitted with all tissue submissions.

- STS generated shipping manifest form
- ECOG-ACRIN Generic Specimen Submission Form (#2981) completed. Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
- Copy of the pathology report

Pathological Material Submission:

- Representative diagnostic FFPE primary and metastatic tumor tissue blocks

NOTE: If a block is unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission per tissue availability:

- One (1) H&E slide from each source block, and
- Ten (10) - twenty (20) 5 µm unstained, uncharged, air-dried plus slides from the thickest part of the tumor, and
- 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 1-844-744-2420. Adequately label every slide and core submitted.

If these criteria cannot be met, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) (eacbpf@mdanderson.org) to obtain alternative submission requirements.

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10.2.2 Shipping Procedures

Pathology materials are to be shipped at ambient temperature within one (1) month following patient registration.

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

Ship to:
MD Anderson Cancer Center CBPF
Mike Balco
Life Science Plaza - Suite 910
2130 West Holcombe Boulevard, LSP9.4227
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (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

Pretrial diagnostic pathology materials will be forwarded to Dr. Brent Harris for central review.

10.3 Submissions to Immunologic Monitoring and Cellular Products Laboratory (IMCPL)

Blood samples should be shipped the day they are drawn. If you have any questions concerning sample collection and shipment, please contact the ECOG-ACRIN Study Coordinator at (412) 624-0078 at the IMCPL.

NOTE: Blood should **NOT** be collected or shipped on Fridays.

Instructions to order kits are outlined in Section 10.3.1.1.

Submit from patients who answer "Yes" to "I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies described above."

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10.3.1 Sample Preparation Guidelines

Please completely fill all blood tubes as full as possible and collect the correct number and tube type as outlined below.

Each tube must be clearly labeled to include:

- ECOG-ACRIN protocol number EA6134
- ECOG-ACRIN five-digit patient sequence number
- Patient initials
- Originating institution/investigator name
- Date and time drawn
- Collection time point

At EACH time point please submit the following:

- TWO (2) FULL 10 cc RED top tubes (BD cat #367820 or SST 367988 gel separator/gold top/tiger tubes if the center can centrifuge them)
- Five (5) FULL 10 cc GREEN top heparin tubes (BD cat # 366480)

At Prior to Start of Treatment ONLY please submit the following:

- One (1) FULL 10 cc YELLOW top ACD tube (BD cat # 364606)

10.3.1.1 Shipping Kits

Shipping kits are available to order for the collection of the blood samples, and will contain the supplies and instructions for collecting, processing, and shipping the samples. To order kits please fax the request using the Shipping Kit Request Facsimile Form (Appendix VII) to (412) 623-6625 or call the IMCPL at (412) 624-0078. Please allow ten (10) working days for shipment and provide the following information:

- Study Number
- Participating Site Number
- Contact Person and Telephone Number

The kits will be shipped via FedEx Express Saver. Please plan ahead, **priority overnight shipment is not possible.**

All blood samples should be shipped the day of collection using the shipping kit. Follow the shipping instructions provided in the kit carefully.

The shipping kit consists of the following:

- Insulated shipping container and packing material
- FedEx Priority Overnight return label
- Shipping instructions
- Shipping Kit Request Form

10.3.2 Shipping Procedures

Blood collected into the appropriate tubes should be sealed, wrapped and placed in the specimen shipper kit and shipped on the same day they are drawn by Federal Express Priority Overnight courier using the return label provided in the kit. The green top tubes should be shipped at ambient temperature (no wet or dry ice) and the red and yellow top tubes should be refrigerated immediately and shipped at 2-8^{o}C. Shipments must be timed to arrive during normal working hours and should be shipped in one box.

The laboratory will be open Monday through Friday to receive samples. Do NOT ship on Fridays or Saturdays, or the day before a legal holiday. Ship by overnight courier Monday - Thursday only to:

Immunologic Monitoring and Cellular Products Laboratory
University of Pittsburgh Cancer Institute
UPCI-IMCPL, Suite 1.31
ECOG-ACRIN Study Coordinator
Hillman Cancer Center
5117 Centre Avenue, L 1.31
Pittsburgh, PA 15213
Tel: (412) 624-0078
FAX: (412) 623-6625

Federal Guidelines for the Shipment of Blood Products: Sites should follow IATA regulations for Packaging UN3372 shipments. Please refer to FedEx guidelines.

An STS shipping manifest form must be generated and shipped with all sample submissions.

10.4 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name 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 form should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@ecog-acrin.org.

Study Specific Notes

Generic Specimen Submission Form (#2981v2) 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. For specimen submissions to the IMCPL, notify the ECOG-ACRIN Study Coordinator by FAX (412) 623-6625 using the Specimen Shipment Requisition Form (Appendix VIII). If you are unable to get through to the laboratory by FAX, telephone the ECOG-ACRIN Study Coordinator at (412) 624-0078 and provide the tracking number. Indicate the appropriate Lab ID# on the submission form:

- ECOG-ACRIN CBPF
- 0009= ECOG-ACRIN Immunologic Monitoring and Cellular Products Laboratory

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

Rev. Add10

10.5 Use of Specimens in Research

Pathological materials will be distributed to investigators for central diagnostic review and immune bio-marker studies.

Specimens from patients who consented to allow their specimens to be used for future ECOG-ACRIN approved research studies, including residuals from the mandatory diagnostic review, 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 and the ECOG-ACRIN Immunologic Monitoring and Cellular Products Laboratory.

Specimens submitted will be processed to maximize their utility for current and future research projects. Tissue processing may include, but not limited to, extraction of DNA and RNA and construction of tissue microarrays (TMAs). DNA, RNA, serum, and plasma (if appropriate) will be isolated from the submitted peripheral blood specimens.

Any residual blocks will be available for purposes of individual patient management on specific written request.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research 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.

10.6 Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of samples forwarded and utilized for approved laboratory research studies 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. Correlative Studies

The results of these studies are for the purposes of the trial only and will not be returned to the site or reported to the patient.

Rev. Add10

11.1 Pathology Review (MANDATORY)

The appropriate representative tumor tissue samples will be forwarded to Brent Harris, MD, PhD for central diagnostic review and classification to confirm the diagnosis. This is done as a retrospective review to determine the evaluability of the patient's data for analysis and to classify the tumor for analysis in the secondary aims. The results of the review are for the purposes of the trial only and will not be returned to the site.

11.2 Association of Inherited Variation with Immune Mediated Adverse Events and Response to Ipilimumab/Nivolumab

11.2.1 Correlative Study Design:

From all patients prior to receiving treatment on each arm of the study, buffy coats will be extracted from venous bloods and stored. Stored buffy coats will be shipped in batches on dry ice to the laboratory of Dr. Katherine Nathanson at the University of Pennsylvania for isolation of germline DNA and subsequent genotyping.

ECOG-ACRIN data items listed below will be requested for the analyses at University of Pennsylvania. The focus will be on the ipi/nivo treatment either as initial therapy or administered following dabrafenib/trametinib resistance. Measures of irAEs will include any irAE grade 3 or higher (yes/no); any gastrointestinal irAE (e.g. diarrhea, colitis; yes/no), any hepatic irAE (e.g. hepatitis, abnormal liver function tests; yes/no), any endocrine irAE (e.g. hypophysitis, hypopituitarism, yes/no) and any other irAE (yes/no)]. Information for survival outcomes will include duration of follow-up post treatment, vital status at time of last follow-up, and cause of censoring (death due to disease or otherwise), from which measures of survival status at one year (alive/dead/censored) and two years (alive/dead/censored) post treatment will be derived. Information on tumor response (complete remission/partial remission/stable disease/progressive disease) at 6 months will also be provided. Additional data on clinical covariates including sex, race/ethnicity, age at diagnosis, AJCC stage, ulceration (no/yes/unknown), performance status, LDH (normal/elevated), number of involved sites (1, 2-3, ≥4) and number of prior therapies will be requested.

11.2.2 Specific Hypotheses:

Multiple lines of evidence suggest that inherited genetic variation may play a role in response to immunotherapies, such as ipilimumab, but also in the development of irAEs. To address the hypothesis that inherited variation is a determinant of both response and irAEs, the University of Pennsylvania investigators have identified patients

treated on ipilimumab clinical trials from 10 academic contributing sites, two ECOG-ACRIN clinical trials and Bristol-Myers Squibb for a total of 716 and 1035 patients treated with 3mg/kg and 10mg/kg, respectively. We propose to determine the association of inherited variation with 1) irAEs and 2) overall survival at 1 and 2 years. In a discovery phase, we will perform candidate-based gene and pathway analyses of genes involved in lymphocyte activation, cytokines, cytokine receptors and within the MHC region, as well as an agnostic genome-wide SNP-based approach to discover novel genetic markers associated with our outcomes of interest. In a replication phase, we will replicate our findings in an independent sample set.

The aims of the whole project are described below. Biosamples and clinical information provided from EA6134 will contribute to the replication/validation step (Aim 3 below) for which a total of 950 melanoma patients treated with ipilimumab containing regimens are anticipated. It is expected that 210 of 300 patients from EA6134 will participate in Aim 3.

Aim 1: To determine the association of inherited genetic variation and immune-associated adverse events in patients with metastatic melanoma treated with ipilimumab containing regimens by completing: Aim 1a: Candidate-based gene and pathway analyses of genes involved in lymphocyte activation, cytokines, cytokine receptors and within the MHC region.

Aim 1b: An agnostic genome-wide SNP-based approach.

Aim 2: To investigate the association between inherited genetics and survival in patients with metastatic melanoma treated with ipilimumab containing regimens by completing.

Aim 2a: Candidate-based gene and pathway analyses of genes involved in lymphocyte activation, cytokines, cytokine receptors and within the MHC region.

Aim 2b: An agnostic genome-wide SNP-based approach.

Aim 3: To replicate genomic markers identified in Aims 1 and 2 in an independent sample set of patients treated with ipilimumab containing regimens and preliminary characterize their potential functional role.

Aim 3a: Replication of variation identified in Aims 1 and 2 as associated with irAEs and survival.

Aim 3b: Bioinformatic assessment of genomic markers.

11.2.3 Background:

Response to ipilimumab therapy can be quite durable with 24-30% of patients being alive at two years following treatment initiation; however, treatment with ipilimumab is associated with significant rates of immune related adverse events. Preliminary data from the ipilimumab/nivolumab combination suggests that response rates are greater and the responses occur more quickly and are more robust. Similarly, the irAEs associated with ipilimumab occur to a similar

extent with the ipi/nivo combination but can be more rapid and severe. It is therefore crucial to delineate both those at highest risk of irAEs and those that will most benefit from therapy with ipilimumab +/- nivolumab in order to direct this therapy to those most likely to receive benefit and avoid side effects and/or inform management. Of particular importance is identifying those patients who are unlikely to respond to the ipilimumab +/- nivolumab, who might be better treated with alternative agents or enrolled on other clinical trials. The lack of biomarkers (which includes genetic polymorphisms) for immunotherapies is well recognized, despite substantial efforts to date. As inherited polymorphisms do not vary and if they can serve as biomarkers, immune monitoring could be circumvented.

The genetic association study proposed by the University of Pennsylvania group is the first step in the identification of potential biomarkers. Multiple lines of evidence from other chemo- and immunotherapies as well from ipilimumab treatment, demonstrate the importance of inherited genetic variation to response and adverse events. Studies focusing on bevacizumab in breast and colorectal cancers have identified single nucleotide polymorphisms (SNPs) associated with a 60-90% increased overall survival; and polymorphisms in immunoglobin G fragment C receptor (FcγRIIa), which plays a role in antibody-dependent cellular cytotoxicity, have been associated with response rates for cetuximab in colorectal cancer, trastuzumab in breast cancer, and rituximab in follicular lymphoma. Importantly, SNPs in and haplotypes of CTLA4 itself have been shown to be strongly associated (odds ratio (OR) 4.1, 95% confidence interval (CI) 1.2, 15 for the risk haplotype) with complete and partial response to treatment with ipilimumab in 152 patients with metastatic melanoma

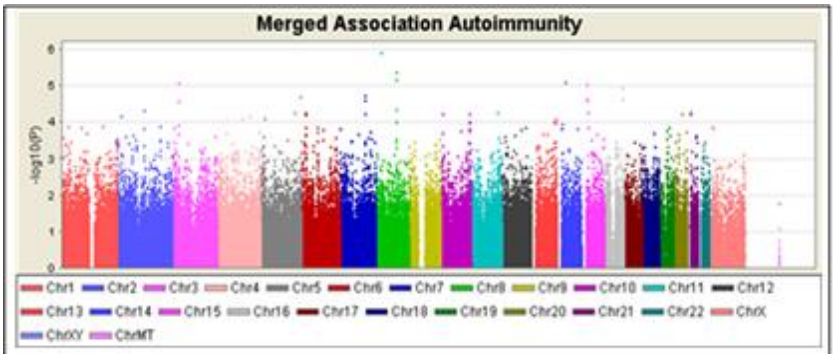

Figure 1. GWA study of 113 melanoma patients treated with

A preliminary genome-wide association study of irAE and outcome for patients treated with ipilimumab was completed. DNA from 73 patients with resected stage IIIc/IV melanoma (25) treated with either 3 mg/kg (approximately 33% of patients) or 10 mg/kg ipilimumab at the H. Lee Moffitt Cancer Center was genotyped on the Illumina Human660W-Quad BeadChip. After quality control filters, the final sample set from MSKCC consisted of DNA from 44 melanoma patients. Because of differences in the definition of irAE (grade 2 and higher requiring

treatment vs. any grade 3 and higher) and types of patients (resected vs. non-resectable) between the two patient sets, samples from Moffitt were used to identify novel genetic associations (i.e. discovery phase) and samples from MSKCC were used to independently confirm observed top association (i.e. replication phase). In both sample sets, SNP markers with a call rate <0.98 were excluded from analysis.

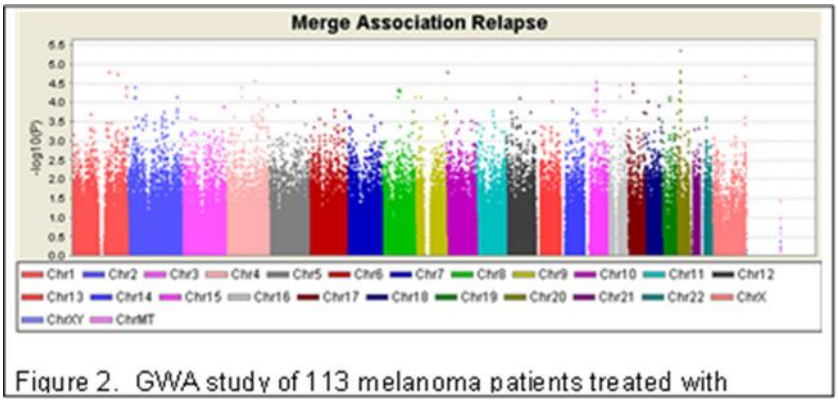

Figure 2. GWA study of 113 melanoma patients treated with

The most significant observed associations for irAE were for rs2466176 (P = 1.25 x 10-6; OR = 4.84), rs416011 (P = 4.24 x 10-6, OR = 3.85) and rs375071 (P = 6.97 x 10-6; OR = 3.70) (Figure 1). rs2466176 maps to an intronic region of PEBP4, while rs375071 and rs2466176 are two closely-clustered SNP markers at 8q21.3 located between CNBD1 and DCAF4L2. Although associations did not reach genome-wide significance in this small sample set, the strength of the observed associations were quite impressive.

For response, two outcomes were examined 1) disease-free survival at the time of last follow-up; and (2) overall survival at time of last follow-up. Post-treatment follow-up at the time of analysis ranged from seven to 69 months. For relapse, the most statistically significant result (P = 4.32 x 106, OR = 3.6) was at rs6046009 in an intron SLC24A3, a plasma membrane sodium/potassium/calcium exchanger (Figure 2). In total, eight SNP markers at this locus had P values < 1 x 10-4 and were ranked within the top 50 hits. We observed the association with rs6046009 both in the Moffitt and MSKCC sample sets, suggesting that the association is not being driven by differences in a study-specific manner, i.e. by differences in outcome definition or individual treatment regimens. Additional loci on chromosomes 8, 15, and 16 have more than 2 SNP markers that surpassed a significance threshold of P < 1 x 10-4. Our preliminary data provide evidence that we will successfully identify novel genetic markers associated with ipilimumab-induced irAE and response.

11.2.4 Statistical Design:

Genetic associations with irAE status will be assessed using Fisher's exact test, one-degree-of-freedom genotypic trend test (analogous to the Cochran-Armitage test) or the two-degrees-of-freedom chi-squared test of independence at each individual SNP marker. Tests of association will be adjusted for age, sex, center or clinical protocol,

and dose as well as AJCC stage, ulceration, performance status, lactase dehydrogenase (LDH) level, number of involved sites, BRAF mutation status (when available) and number of prior therapies using logistic regression modeling assuming an additive genetic model. Within distinct genetic pathways or regions, P-values of individual SNP marker associations will be adjusted for multiple testing by controlling the false discovery rate (FDR).

Analysis for survival outcomes will occur within the framework of Cox proportional hazards analysis, otherwise similar to analyses described above for irAEs. In addition to adjusting for age at diagnosis, sex, center, clinical trial and dose, adjustment for variables potentially associated with prognosis including AJCC stage, ulceration, performance status, lactase dehydrogenase (LDH) level, number of involved sites, BRAF/NRAS/WT tumor mutation status, and number of prior therapies will also be made.

Study Power: For replication phase irAE outcomes, the study has 80% power to detect a per-allele RR of 2.90 or greater for SNP markers with a MAF of at least 0.10. For analysis of 2 year survival, the study has 80% power to detect a per-allele HR of 1.83 or greater for SNP markers with a MAF of at least 0.10. These detectable measures of effect compare favorably to point estimates we found in our small preliminary study.

11.3 Evaluation of the Utility of Circulating BRAF Levels in Determining the Response and Resistance to Either BRAF Directed and/or Immunotherapy in Patients with BRAF Mutant Melanoma

11.3.1 Correlative Study Design:

To define the dynamic and kinetic effects of systemic therapy on peripheral blood $BRAF^{V600}$ mutation detection, we will test isolated PBL and serum from samples obtained from patients prior to receiving treatment on each arm of the study. As part of trial eligibility, patients will have been previously identified as being positive for a $BRAF^{V600}$ mutation based on the results of the testing of their tumor tissue (either primary tumor or nodal/systemic metastasis) in a CLIA-approved laboratory for $BRAF^{V600}$ sequencing analysis. Heparinized blood will be collected on each patient at baseline and every 6 weeks on both initial and crossover therapy and at the time of both RECIST defined progression and crossover to the alternative therapy. Blood samples will be shipped overnight at room temperature to the ECOG-ACRIN melanoma immunotherapy laboratory at the Pittsburgh Cancer Institute for ficoll to isolate PBMC. Samples will be labeled and stored at minus 80 for batch analysis.

11.3.2 Specific Hypotheses:

a) To determine if changes in blood BRAF levels utilizing peripheral blood $BRAF^{V600}$ mutational testing in patients with Stage IV BRAF mutant melanoma correlate with response and resistance to combination BRAF/MEK directed therapy.

b) To determine if changes in blood BRAF levels utilizing peripheral blood $BRAF^{V600}$ mutational testing in patients with Stage IV BRAF mutant melanoma correlate with response and resistance to combination immunotherapy.

c) To compare the kinetics of peripheral blood BRAFV600 levels during response and resistance in groups of patients receiving BRAF targeted therapy or combination immunotherapy as initial therapy.

d) To compare the kinetics of peripheral blood BRAFV600 levels during response and resistance to combination BRAF targeted therapy or combination immunotherapy in individual patients (initial treatment vs. crossover treatment).

11.3.3 Background:

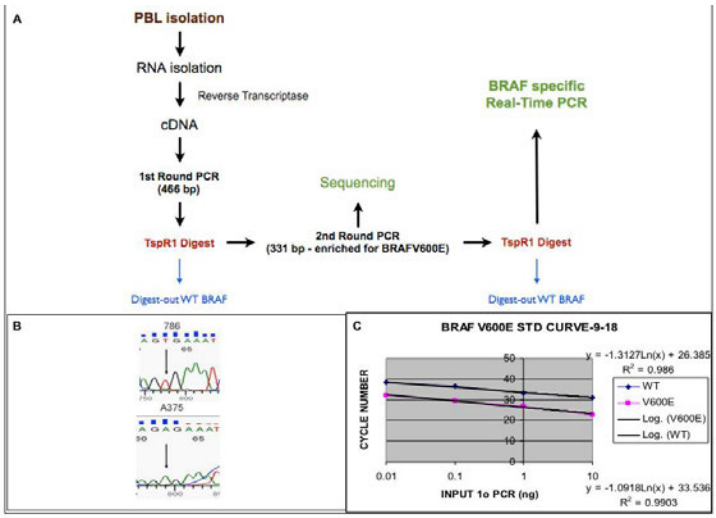

Figure 1: Schematic of the $BRAF^{V600}$ assay (A); (B) Results of direct sequencing; (C) Standard curve of BRAF assay.

Sullivan, Panka and colleagues have developed and optimized an RT-PCR-based technique that takes advantage of an unique restriction enzyme site present in wild-type (WT) but not the mutant BRAF to enrich the sample for the mutant form initially and then inserts a restriction site into the mutant but not WT BRAF to allow for detection and quantification of mutant BRAF.[1] As outlined in our original description of this technique[1] and the second generation assay the protocol (Figure 1A) involves a series of PCR amplifications and restriction digestions that discriminate between WT and mutant BRAF at amino acid position 600. An initial RT-PCR is followed by digestion with TspR1 that preferentially digests the WT product but not the $BRAF^{V600}$ PCR product. A second PCR using nested PCR primers with the digested 1st round PCR product as template follows. This PCR product may be subjected to sequencing using a nested oligonucleotide (Figure 1B), however, since the TspR1 digestion does not lead to complete elimination of WT BRAF, this PCR product is then subjected to a second TspR1 digest to further enrich for mutant $BRAF^{V600}$. Next, Real-Time PCR is performed on the second TspR1

digest product using primers designed to amplify $BRAF^{V600E}$. Purified first round PCR product with a known concentration is run through the assay along with test samples and is used to create a standard curve with each batched analysis of patient samples (Figure 1C). Using the standard curve the amount of end product is determined and $BRAF^{V600E}$ levels are determined.

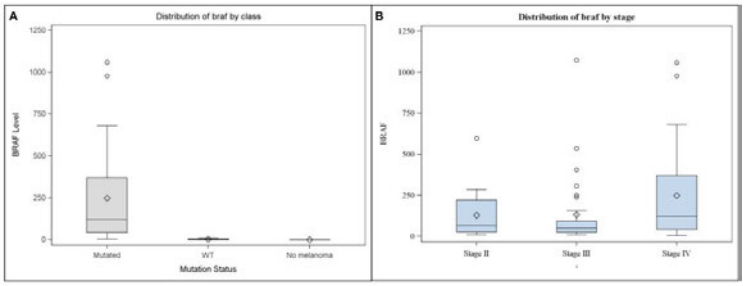

Figure 2: A) $BRAF^{V600E}$ level is higher ($p < 0.0001$) in patients with tissue-detected BRAF mutation than in patients with Stage IV BRAF WT melanoma, and patients without melanoma (normal); B) $BRAF^{V600E}$ level is borderline significantly higher ($p = 0.10$) among patients with Stage IV, BRAF mutant melanoma than in patients with Stage II and III melanoma with a "positive" BRAF level (≥ 10 pg).

In practice, the assay is highly sensitive and specific when used to analyze isolated PBMCs from patients with Stage IV melanoma. In particular, the sensitivity and specificity of the assay, using a cut off for positivity of 10 pg, is 93% and 100%, respectively (Figure 2A shows the box plot of BRAF values in patients with melanoma and known tissue BRAF status or people without melanoma). The average BRAF level in stage IV melanoma patients with tissue confirmed BRAF mutation is higher than the average BRAF level in patients with Stage II and III patients who have a positive blood BRAF level using the cutoff of ≥ 10 pg (Figure 2B), suggesting that the assay may reflect tumor burden. Lastly, when patients on BRAF inhibitor therapy were followed with serial sampling, the assay is reflective of disease response and disease progression. Specifically, BRAF levels generally reduce with treatment initiation and then increase at the time of or, in many cases, prior to radiographic progression.

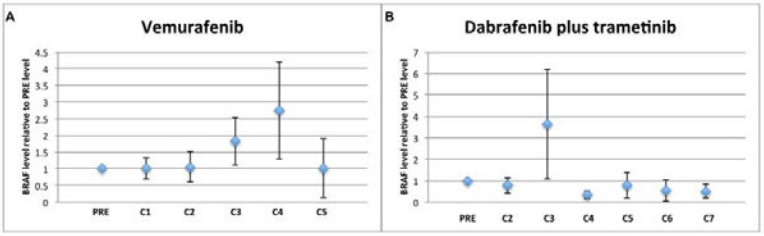

Figure 3: Mean values of BRAFV600E levels prior to (PRE), during the first cycle(C1), or at the beginning of subsequent treatment cycles (C2-C7) in 12 patients treated with vemurafenib (A) and 6 patients treated with the combination of dabrafenib and trametinib (B).

A first generation peripheral blood BRAF assay had been utilized to follow serial circulating BRAF levels in several patients treated with either vemurafenib or the combination of dabrafenib with trametinib. In each patient, who had a known BRAF mutation detected in tissue from a CLIA approved laboratory, peripheral blood BRAF levels were

detected and reduced more profoundly and durably with dabrafenib plus trametinib therapy than it did with single-agent vemurafenib (Figure 3); similar findings to a randomized Phase II study of single-agent dabrafenib versus the combination of dabrafenib and trametinib. Further, this reduction in blood $BRAF^{V600}$ level correlated with disease response on imaging, and more importantly, the blood $BRAF^{V600}$ level has risen to at least double the nadir in 5 of the 7 patients in whom we had serial blood draws from baseline to time of progression. Figure 4 charts the blood BRAF values of four representative patients. In patients PLX-004 and MAB212 (A&B), levels rose well in advance of progression imaging (42 and 57 days, respectively). In patient MGH-MEL2 (C), the BRAF level oscillated until patient had maximal tumor response and remained stable even in the presence of CNS recurrence, a sign that disease in the CNS may not shed mutant BRAF as readily in the blood. Lastly, patient MGH-MEL5 (D) represents an interesting case of a patient with a known double mutant, $BRAF^{V600E}$ and $BRAF^{V600K}$, whose blood BRAF level falls throughout treatment, though he then progresses. Since one of the limitations of our assay is that it only measures $BRAF^{V600E}$ levels, it is likely that his progressing disease was dominated by $BRAF^{V600K}$; a subtype of BRAF mutant melanoma that is associated with less profound and durable responses to BRAF-directed therapy. These results suggest that BRAF levels determined via our assay effectively reflects dynamics in tumor volume and might be an early predictor of non-CNS, disease progression in patients treated with $BRAF^{V600E}$ melanoma on BRAF-directed therapy.

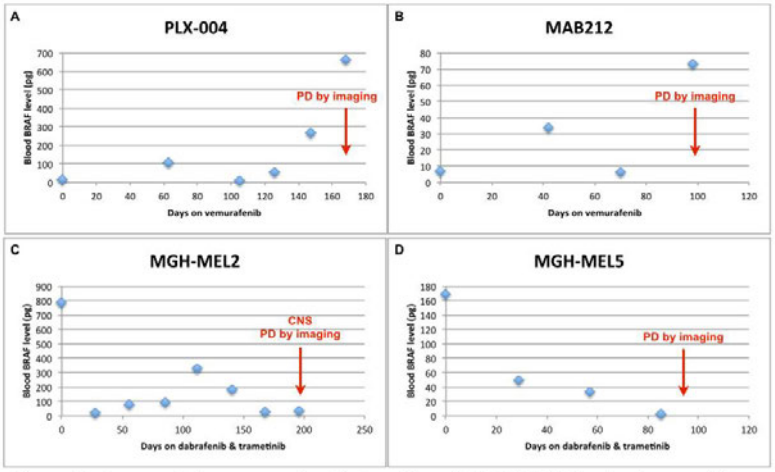

Figure 4: Representative cases of patients with serial $BRAF^{V600E}$ levels drawn while on BRAF inhibitor therapy: $BRAF^{V600E}$-mutant melanoma patients on vemurafenib who have clear rise in level in advance of radiographic progression (A&B); $BRAF^{V600E}$-mutant melanoma patient on dabrafenib and trametinib who had ongoing response on imaging and in blood at time of CNS-recurrence (C); $BRAF^{V600E/K}$-mutant melanoma patient with ongoing reduction in $BRAF^{V600E}$ level at time of resistance while on dabrafenib and trametinib (D).

11.3.4 Statistical Design:

Aim 2a: The change in blood BRAF levels between week 12 (after initiation of therapy) and baseline (before BRAF/MEK therapy begins) will be used. It is expected a total of 250 patients (150 first-line

dabrafenib/trametinib and 100 second-line dabrafenib/trametinib treated) will be included in this analysis. Of these, we hypothesize 50% will have a favorable outcome (CR+PR and their blood BRAF level will decrease at least by 50% from the baseline value. The change in blood BRAF level between week 12 and baseline will be compared among patients with favorable outcome vs. no favorable outcome (SD or PD). Two-sample t-test will be used to compare the changes in the blood BRAF levels among responders (n=125) and non-responders (n=125). If the standardized difference is 1.38, there will be 85% power. This is based on a two-sided type I error rate of 0.05. If the normality assumption is not appropriate, Wilcoxon rank-sum test will be used in the analysis.

For assessment of association with resistance, the change in blood BRAF level on the most recent test done prior to documentation of RECIST defined disease progression on CT scan relative to the nadir level will be used. It is expected that a total of 200 patients (125 first-line dabraf/tramet and 75 second-line dabraf/tramet treated) will be included in this analysis. Of these we hypothesize that pre-progression samples will show a 50% increase from the nadir sample. The changes from the nadir sample will be summarized using the descriptive statistics. Also the proportion of patients who had at least 50% increase will be summarized. With a sample size of 200, 95% confidence interval will not be wider than 14%.

Aim 2b: The change in blood BRAF levels between week 12 (after initiation of therapy) and baseline (before BRAF/MEK therapy begins) will be used. It is expected a total of 250 patients (150 first-line ipi/nivo and 100 second-line ipi/nivo treated) will be included in this analysis. Of these, we hypothesize 5% will have a favorable outcome (CR+PR) and their blood BRAF level will decrease at least by 50% from the baseline value. The change in blood BRAF level between week 12 and baseline will be compared among patients with favorable outcome vs. no favorable outcome (SD or PD). Two-sample t-test will be used to compare the changes in the blood BRAF levels among responders (n=135) and non-responders (n=115). If the standardized difference is 1.38, there will be 85% power. This is based on a two-sided type I error rate of 0.05. If the normality assumption is not appropriate, Wilcoxon rank-sum test will be used in the analysis.

For assessment of association with resistance, the change in blood BRAF level on the most recent test done prior to documentation of RECIST defined disease progression on CT scan relative to the nadir level will be used. It is expected that a total of 200 patients (125 first-line dabraf/tramet and 75 second-line dabraf/tramet treated) will be included in this analysis. Of these we hypothesize that pre-progression samples will show a 50% increase from the nadir sample. The changes from the nadir sample will be summarized using the descriptive statistics. Also the proportion of patients who had at least 50% increase will be summarized. With a sample size of 200, 95% confidence interval will not be wider than 14%.

Aim 2c: Similar analyses as described under 2a/2b will be conducted in 150 patients with first-line therapy and 100 patients with second-line therapy in each group.

Aim 2d: The change in blood BRAF levels between week 12 and baseline will be compared between 150 patients receiving the first-line immune therapy vs.150 patients receiving the first-line targeted therapy (at the time of response and progression as described in 2a/2b). A similar comparison will be made among 100 patients receiving second-line immune therapy vs. 100 patients receiving the second-line targeted therapy (at the time of response and progression as described in 2a/2b).

11.4 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secure 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.

Rev. 5/17

12. Electronic Data Capture

Please refer to the EA6134 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed in Medidata Rave and EASEE-PRO (for tobacco use assessment).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

12.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

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. List of Required Materials for EA6134
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981)

List of Required Material

EA6134: A Randomized Phase III trial of Dabrafenib + Trametinib followed by Ipilimumab + Nivolumab at Progression vs. Ipilimumab + Nivolumab followed by Dabrafenib + Trametinib at Progression in Patients With Advanced BRAFV600 Mutant Melanoma

The following materials are to be submitted within one (1) month of registration:

1. Required Diagnostic Materials
   - Pretrial Diagnostic Pathology Materials (MANDATORY): Representative diagnostic primary and metastatic tumor tissue blocks

   NOTE: If a block is unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission per tissue availability:
   - 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 1-844-744-2420
   - One (1) H&E slide from each source block, and
   - Ten (10) to twenty (20) 5 µm unstained, uncharged air-dried plus slides from the thickest part of the tumor

   If these criteria cannot be met, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) (eacbpf@mdanderson.org) to obtain alternative submission requirements.
2. Forms and Reports:

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

   The following items are to be included with the pathology materials:
   - Institutional Pathology Report
   - ECOG-ACRIN Generic Specimen Submission Form (#2981) (if STS unavailable)
   - Sample Tracking System (STS) Shipping Manifest Form
3. 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 Blvd
   Houston, TX 77030
   Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
   Fax: 713-563-6506
   Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone 1-844-744-2420 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 EA6134: A Randomized Phase III Trial of Dabrafenib + Trametinib followed by Ipilimumab + Nivolumab at Progression vs. Ipilimumab + Nivolumab followed by Dabrafenib + Trametinib at Progression in Patients with Advanced BRAFV600 Mutant Melanoma*

A patienthas been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for pathology review and future undefined research studies.

Please complete the Submission Form. Keep a copy for your records and return the completed Submission Form, the surgical pathology report(s), 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 for undefined future research studies. Paraffin blocks will be returned upon written request for purposes of patient management.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 1-844-744-2420or email eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name: _____

Address:_____

Phone: _____

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

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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 Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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Appendix III

Patient Medication Calendar for Dabrafenib/Trametinib

Medication Calendar Directions

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

Patient Medication Calendar for Dabrafenib/Trametinib

This is a calendar on which you are to record the time and number of tablets and capsules you take each day. You should take your scheduled dose of each medication. **Note the times and the number of tablets and capsules 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 capsules and your completed medication calendar to your doctor's visits.

Patient Medication Diary for Dabrafenib/Trametinib

(Please bring this diary and any unused Dabrafenib and Trametinib to your study doctor's office on each visit.

Patient ID # _____	**Start Date** ____ /_____ /_____ **Next Visit Date:** ____ /_____ /_____	**Dabrafenib** ____ **mg capsules** /_____ **bottles** **Trametinib** ____ **mg tablets** /_____ **bottles**

Instructions:

1. Take Dabrafenib and Trametinib on an empty stomach, one hour before or two hours after a meal.
2. Take Dabrafenib and Trametinib with about 200 mL (1 cup) of water.
3. Please call _____, if you have any questions regarding the study medications.

Day	Date Taken	**Trametinib Tablets** (Please take _____ tablets only **once a day**) (and keep drug refrigerated)		**Dabrafenib Capsules** (Please take _____ capsules **every 12 hours**)				**Please note any unusual symptoms or side effects and questions for study Doctor or Nurse**
	Month/Day	Time (Please circle AM or PM)	Number of tablets taken	Time Taken in AM	Number of capsules taken	Time Taken in PM	Number of capsules taken	
1		AM or PM		AM		PM		
2		AM or PM		AM		PM		
3		AM or PM		AM		PM		
4		AM or PM		AM		PM		
5		AM or PM		AM		PM		
6		AM or PM		AM		PM		
7		AM or PM		AM		PM		
8		AM or PM		AM		PM		
9		AM or PM		AM		PM		

Day	Date Taken	**Trametinib Tablets** (Please take _____ tablets **only once a day**)		**Dabrafenib Capsules** (Please take _____ capsules **every 12 hours**)				**Patient ID # _____**
	Month / Day	Time (Please circle AM or PM)	Number of tablets taken	Time Taken in AM	Number of capsules taken	Time Taken in PM	Number of capsules taken	**Please note any unusual symptoms or side effects and questions for study Doctor or Nurse**
10		AM or PM		AM		PM		
11		AM or PM		AM		PM		
12		AM or PM		AM		PM		
13		AM or PM		AM		PM		
14		AM or PM		AM		PM		
15		AM or PM		AM		PM		
16		AM or PM		AM		PM		
17		AM or PM		AM		PM		
18		AM or PM		AM		PM		
19		AM or PM		AM		PM		
20		AM or PM		AM		PM		
21		AM or PM		AM		PM		
22		AM or PM		AM		PM		
23		AM or PM		AM		PM		
24		AM or PM		AM		PM		
25		AM or PM		AM		PM		
26		AM or PM		AM		PM		
27		AM or PM		AM		PM		
28		AM or PM		AM		PM		

Day	Date Taken	**Trametinib Tablets** (Please take _____tablets **only once a day**)		**Dabrafenib Capsules** (Please take _____ capsules **every 12 hours**)				**Patient ID # _____**
	Month / Day	Time (Please circle AM or PM)	Number of tablets taken	Time Taken in AM	Number of capsules taken	Time Taken in PM	Number of capsules taken	**Please note any unusual symptoms or side effects and questions for study Doctor or Nurse**
29		AM or PM		AM		PM		
30		AM or PM		AM		PM		
31		AM or PM		AM		PM		
32		AM or PM		AM		PM		
33		AM or PM		AM		PM		
34		AM or PM		AM		PM		
35		AM or PM		AM		PM		
36		AM or PM		AM		PM		
37		AM or PM		AM		PM		
38		AM or PM		AM		PM		
39		AM or PM		AM		PM		
40		AM or PM		AM		PM		
41		AM or PM		AM		PM		
42		AM or PM		AM		PM		

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Appendix IV

CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” (http://ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data.”):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

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Appendix V

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.

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Appendix VI

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) must be reported in an expeditious manner. This includes all pregnancies or suspected pregnancies occurring in:

- a female patient while she is on protocol treatment, or within 90 days of the female patient's last dose of protocol treatment, and
- a female partner of a male patient while he is on protocol treatment, or within 90 days of the male patient's last dose of protocol treatment.

The outcome of the pregnancy and neonatal status must also be reported.

Where should the pregnancy be reported?

The pregnancy or suspected pregnancy (including a positive or inconclusive pregnancy test must be reported via the CTEP's Adverse Event Reporting System (CTEP-AERs) website accessed here: http://ctepcore.nci.nih.gov/ctepaers/security/login.

When does a pregnancy need to be reported?

Due to risk of intrauterine exposure to the fetus with the study agents, an initial report must be done within 24 hours of the Investigator's learning of the pregnancy or suspected pregnancy (including a positive or inconclusive pregnancy test), 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 or suspected pregnancy (including a positive or inconclusive pregnancy test) itself 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 start date should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s), chemotherapy agent(s), or other protocol therapy must 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 patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status. Newborn infants should be followed until 30 days old.
- The Investigator must solicit information and report information about the pregnancy or pregnancy outcome from the study participant only (the female or male patient and not the female partner of a male patient). The female partner should not be consented or contacted, not should her medical records directly accessed. The Investigator must make best efforts to collect the deidentified information from the study participant only.

- *It is recommended the female patient or female partner of a male 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?

If the outcome of the pregnancy occurs on the same cycle of treatment as the pregnancy itself, the outcome should be reported as an amendment to the initial CTEP-AERs report (using the same ticket number) within 24 hours of the time the outcome becomes known. However, if the outcome of the pregnancy occurs on a subsequent cycle, the outcome should be reported on a new and separate CTEP-AERs report (with a new ticket number) via the CTEP-AERS website.

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*."

The pregnancy loss must be reported via the CTEP-AERS website 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 protocol treatment. However, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via the CTEP-AERS website AND any infant death after 28 days that is suspected of being related to the in utero exposure to any of the agents on protocol treatment must be reported via the CTEP-AERS website as a Grade 4 "*Death neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

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

Additional Required Forms:

When submitting a CTEP-AERs report for a pregnancy, pregnancy loss, or neonatal loss, the "**CTEP Clinical Trial Pregnancy and Lactation Information Form"** must be completed and faxed along with any additional medical information to CTEP (301-897-7404).

This form must also be used for lactation exposure.

This form is available on CTEP's website (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTEP_Pregnancy_Report_Form.pdf)

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Appendix VII

Shipping Kit Request Facsimile Form

ECOG-ACRIN PROTOCOL EA6134

Immunologic Monitoring and Cellular Products Laboratory	UPCI Research Pavilion at the Hillman Cancer Center Room L 1.31 5117 Centre Avenue Pittsburgh, PA 15213-1863 Telephone: 412-624-0078 FAX: 412-623-6625

To: ECOG-ACRIN Study Coordinator Fax: 412-623-6625

From: Name: _____

Institution: _____

Telephone: _____

Fax: _____

Number of Kits Requested:

Prior to Start of Treatment (5GT/2RT/1YT) _____

Every Week for Patients with Grade 3 or 4 irAEs until the irAE Resolves to Grade 1 and then at their regularly Scheduled Visits until they are Tapered Off of Immunosuppressive Agents (2RT) _____

Every Six Weeks (5GT/2RT) _____

Time of Crossover (5GT/2RT) _____

Time of Progression (5GT/2RT) _____

Shipping Address: _____

_____

_____

PLEASE ALLOW 10 WORKING DAYS FOR RECEIPT OF SHIPPING KITS

NOTE: To order collection and shipping kits for EA6134, patients must be registered to or in the process of being worked up for the EA6134 trial. Due to funding restrictions institutions cannot order multiple collection and shipping kits in advance.

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Appendix VIII

Specimen Shipment Requisition Form

ECOG-ACRIN – PROTOCOL EA6134

It is required that samples submitted from patients participating in EA6134 be entered and tracked via the online ECOG-ACRIN Sample Tracking System. This form is used only in the event that the STS is inaccessible and then the shipments are to be logged in retroactively, indicating the actual dates of collection and shipment.

Immunologic Monitoring and Cellular Products Laboratory	UPCI Research Pavilion at the Hillman Cancer Center Room L 1.31 5117 Centre Avenue Pittsburgh, PA 15213-1863 Telephone: 412-624-0078 FAX: 412-623-6625

Ship samples by FedEx Priority Overnight to arrive the next morning unless otherwise directed by the protocol. Do NOT ship on Friday or Saturday, or the day before a legal holiday.

Call the IMCPL ECOG-ACRIN Study Coordinator at 412-624-0078 with questions on collection and shipping.

Please complete the following information and include this form in the shipment.

ECOG-ACRIN Patient Sequence Number: _____

ECOG-ACRIN Patient Initials: _____
Last First

Clinical Site:_____

Site Contact: _____

Telephone Number: _____

Fax Number: _____

Federal Express® Air Bill No.: _____

Date of Shipment: _____

Specimen Collection Date ___/___/___
MM/DD/YY

Specimen Collection Time: ____ ____:____ ____
(24 hour clock)

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Appendix IX

New York Heart Association (NYHA) Classification System

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

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Rev. 12/15, 6/16

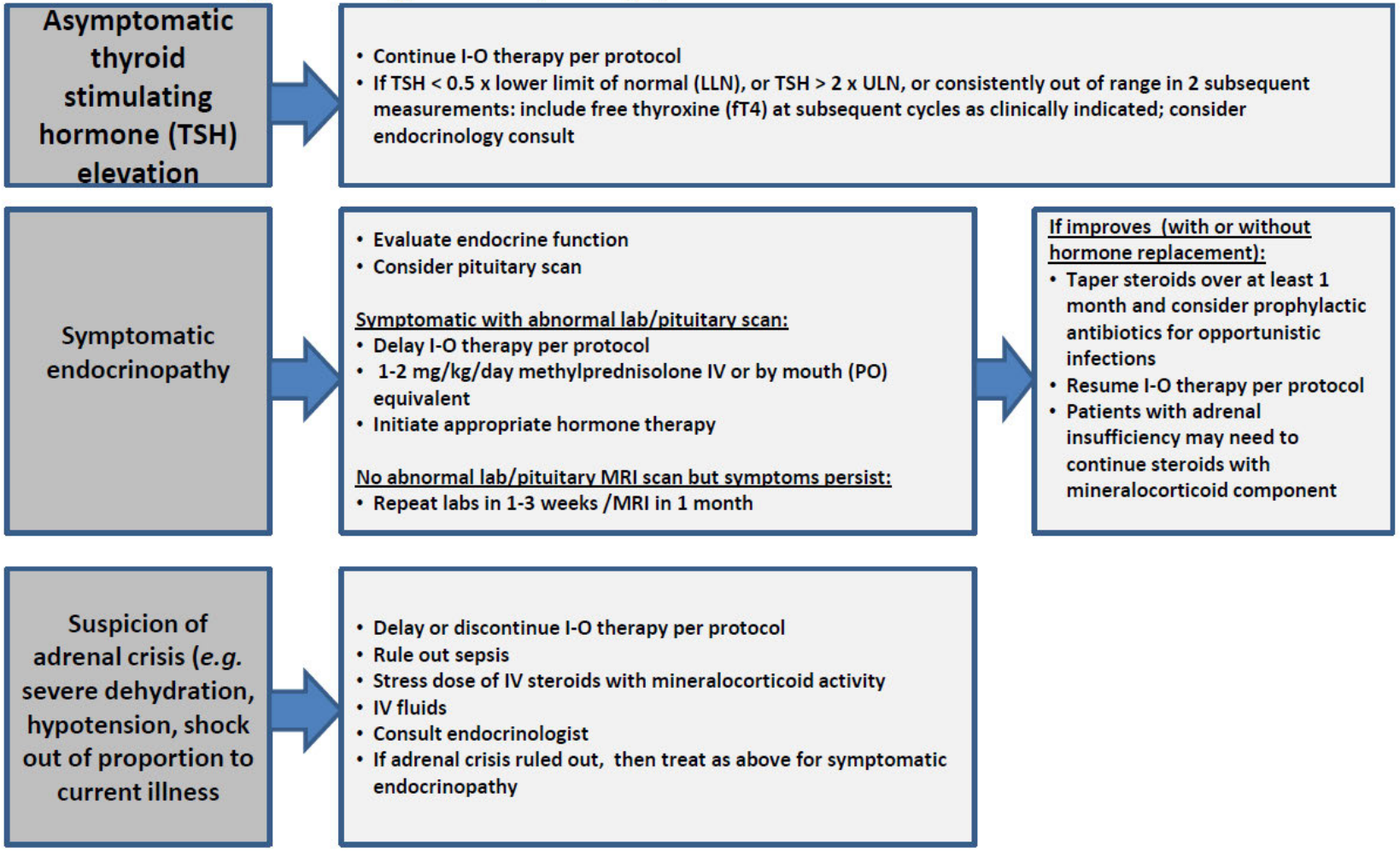
Appendix X

MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL, HEPATIC, NEUROLOGICAL, PULMONARY, RENAL, AND SKIN ADVERSE EVENTS

NOTE: In the event that the dosing management outlined in Section 5.4.2 conflicts with Appendix X Management Algorithms, the EA6134 reccomendation is to follow the Section 5.4.2 management guidelines.

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

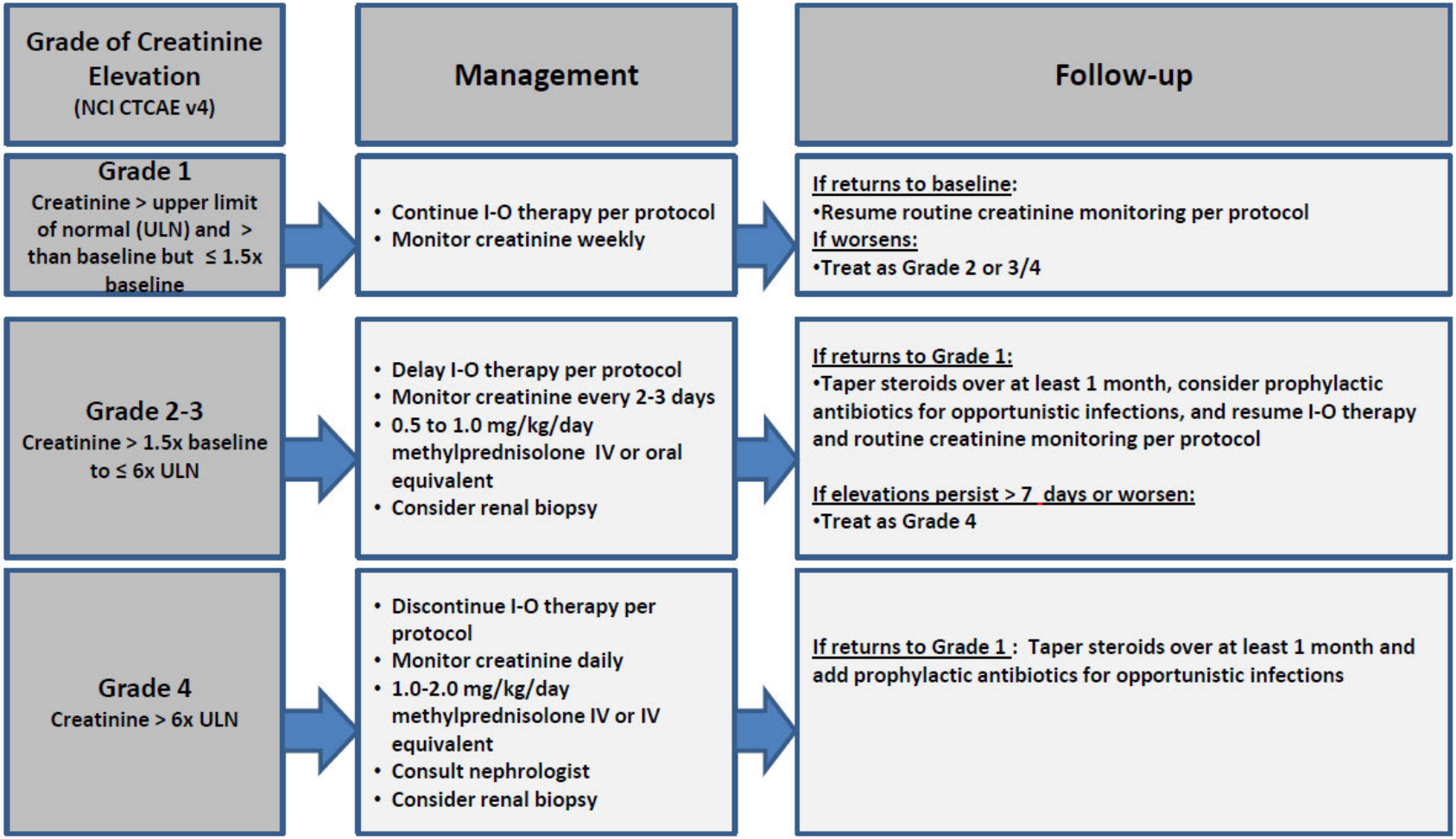
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and Infectious Disease (ID) consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

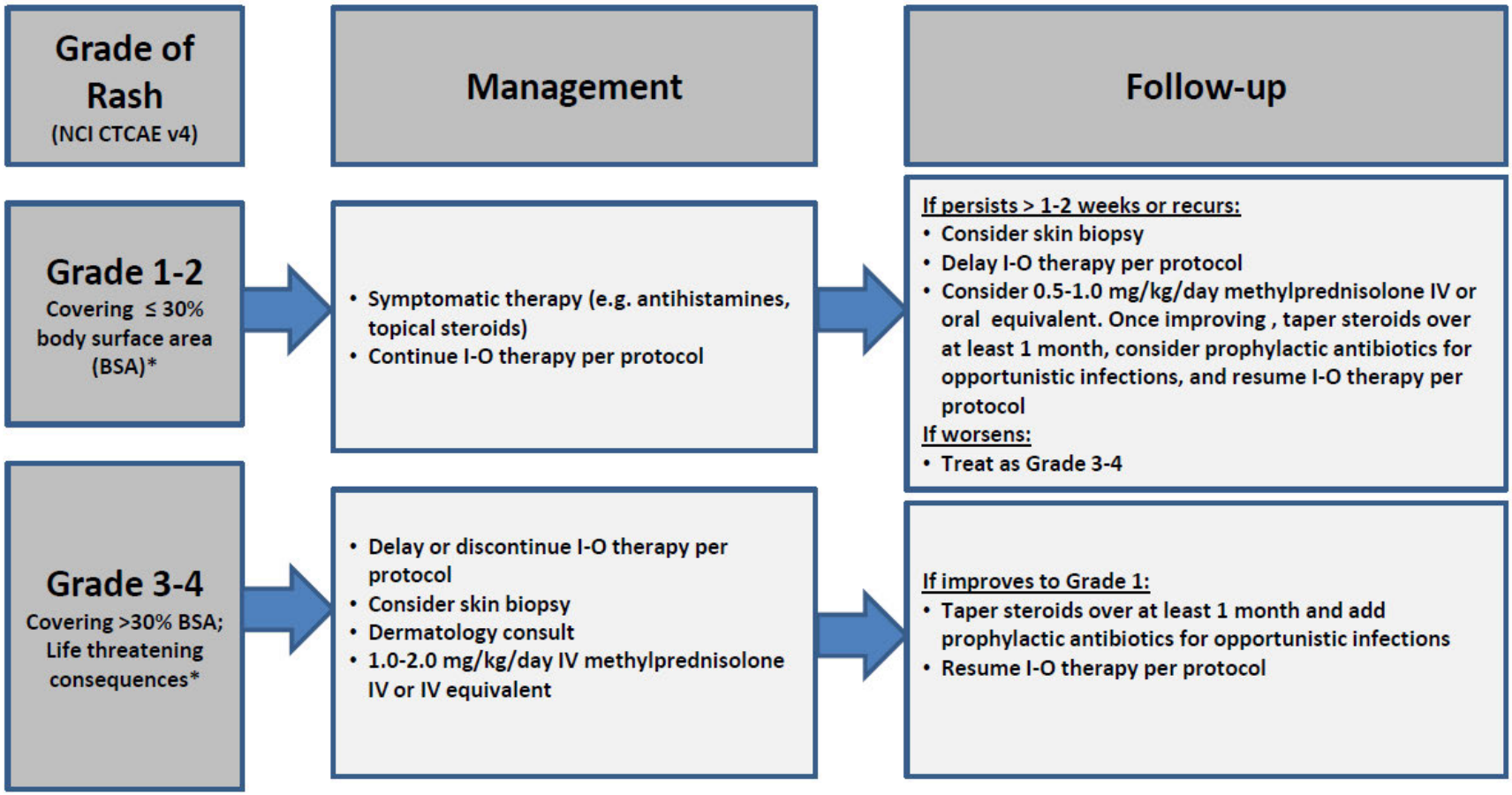
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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Appendix XI

Strong inducers of CYP3A4 or CYP2C8

Any medications or substances that are strong inhibitors or inducers of CYP3A4 or CYP2C8 are ineligible. Current use of, or intended ongoing treatment with: herbal remedies (*e.g.*, St. John's wort), or strong inhibitors or inducers of P-glycoprotein (Pgp) or breast cancer resistance protein 1 (Bcrp1) should also be excluded.

Below are a few examples of the agents that are prohibited while on study treatment:

PROHIBITED – strong inducers of CYP3A4 or CYP2C8, since concentrations of dabrafenib may be decreased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Rifamycin class agents (e.g., rifampin, rifabutin, rifapentine),
Anticonvulsant	Carbamazepine, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan, St. John's wort
PROHIBITED – Strong inhibitors of CYP3A4, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Hyperlipidemia	Gemfibrozil
Antiretroviral	ritonavir, saquinavir, atazanavir
Miscellaneous	Conivaptan

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

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Appendix XII

What to do if a patient comes in with possible immunotherapy-induced Myocarditis?

Javid Moslehi and Doug Johnson (Vanderbilt)

Detection:

Troponin – screening per Section 7

If troponin elevated, then obtain diagnostic workup, including:

Clinical examination for signs of heart failure, ischemia, arrhythmia and skeletal muscle myositis.

EKG, to rule out myocardial ischemia

For myocarditis, special attention to heart block, PR prolongation, QRS duration

CK (for concomitant myositis), CK-MB

Assess cardiac function via cardiac imaging

Echo (structural heart disease)

Consider cardiac MRI if available

Monitoring

If troponin elevated but not symptomatic and no arrhythmia, then hold immunotherapy and obtain troponin every 2-3 days with concurrent CK, CK-MB, and EKG until normalized. If normalized within 2 weeks, may proceed with treatment otherwise hold further therapy.

If troponin elevated and patient symptomatic and/or suspected myocarditis, admit to the hospital:

Monitor troponin, CK, CK-MB

Continuous cardiac monitoring

EKG at least daily

Cardiology consult

If other cardiac causes for patient's symptoms are ruled out, and the most likely diagnosis is myocarditis, a myocardial biopsy is strongly encouraged to confirm immune mediated myocarditis. Cardiac MRI may be an alternative to myocardial biopsy for diagnosis.

Treatment of presumed or confirmed myocarditis

Early cardiology consultation is strongly encouraged. Since most cardiologists are unaware of immune related adverse events, cardiology education about the therapies and adverse effects is important. Particularly, since EKG manifestations (specifically, heart block) appear to be an early manifestation of this entity, would favor consideration for pacemaker placement.

The optimal approach for treatment of myocarditis has not been established. Since this toxicity has caused patient deaths aggressive management is encouraged. Corticosteroids (see below) may be started while pending definitive diagnosis, if myocarditis is suspected.

Methylprednisolone 2mg/kg IV daily

Alternatively, methylprednisolone 1g daily (dose used for acute allograft rejection in cardiac transplantation) could be considered.

Based on the experience with other immune-related adverse events and cellular-mediated cardiac transplantation, other agents to consider include:

Infliximab

Anti-thymocyte globulin (ATG)

Mycophenolate mofetil

Tacrolimus

Investigational Studies

Defining mechanisms of toxicity is the best means to develop preventative and treatment strategies for immune mediated myocarditis.

If myocardial biopsy is obtained, then should get the following:

Formalin-fixed tissue (routinely done)

Frozen tissue (or snap frozen tissue)

In case of patient death, an autopsy can be helpful to help future cases

Education in terms of getting autopsy

Make sure whole set of organs is autopsied: skeletal muscle, endocrine (pituitary), liver, kidney

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Rev. 5/17, 10/17
Rev. Add10

Appendix XIII

Ancillary for Tobacco Use Assessment: EAQ16T

Study Co-Chairs: Elyse Park, Ilana Gareen, Lynne Wagner, Jamie Ostroff, Ben Herman

Patients registered to the selected ECOG-ACRIN trials are eligible to participate in this ancillary study, once the appropriate amendment incorporating the study is activated.

The Ancillary for Tobacco Use Assessment is a project that seeks to address questions about patient-reported tobacco use and smoking behaviors that may span several studies and/or diseases. The tobacco use ancillary is embedded into parent protocols, with participation in the ancillary informed in the parent consent form and participation determined via providing email address to the sites. The general objectives of the tobacco use ancillary are not specific to any single parent protocol; however, specific objectives may be included in the parent or related parent protocols.

A significant proportion of cancer patients are current smokers at the time of cancer diagnosis,[1–5] and there are known risks associated with continued smoking following cancer diagnosis. These include decreased survival time; increased complications from surgery, radiation, and chemotherapy; and increased risk of second primary tumors.[6–11] As such, the National Comprehensive Cancer Network (NCCN), the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) have identified persistent smoking as a modifiable risk factor and recommend cessation counseling for cancer patients who smoke. Although evidence-based guidelines for treating tobacco dependence exist,[12] they have not yet been well-integrated into cancer care settings. Moreover, knowledge regarding the scope and patterns of tobacco use among cancer patients is limited. As a critical step in closing this knowledge gap, the NCI-AACR Cancer Patient Tobacco Use Asssessment Task Force developed the Cancer Patient Tobacco Use [1–4,13,14] Questionnaire (C-TUQ). Through this ancillary, the modified C-TUQ measures will be administered to participants enrolling in selected Phase II and Phase III ECOG ACRIN (EA) therapeutic trials.

The major questions may be summarized:

1. What is the smoking status of cancer patients enrolled on EA clinical trials?
2. Do patients quit smoking or try to quit smoking after receiving a cancer diagnosis?
3. What forms of tobacco use do patients engage in?
4. What assistance do patients use or receive to try to quit?
5. How does tobacco use, other forms of tobacco use, and/or environmental tobacco exposure affect patient's treatment toxicity, patient-reported physical and psychological symptoms, trial adherence, and therapeutic outcomes?

When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO), and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their

account for self-directed web entry of surveys. After their account is activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

Measures

The selected Core and Extension C-TUQ items will be assessed. The 4-item Short Form PROMIS® for anxiety and depression, the Lung Cancer Stigma Scale, and six symptom items (general pain, fatigue, nausea, cough, insomnia, shortness of breath) from FACIT (Functional Assessment of Chronic Illness Therapy) together with modifications of these same six questions to address the degree of bother associated with each symptom will be administered as well. Additionally, we will ask participants' perceptions of how smoking improves or worsens each of the six symptom experience. All these items will be compiled into Survey of Tobacco Use (STU) (baseline and follow-up).

Contents and Corresponding Questions in Survey of Tobacco Use (STU)

Dimension	Source of Measures	Baseline STU	Follow-up STU
Basic Tobacco Use Information	C-TUQ	Q1 – Q5	Q1-Q2
Tobacco Use in Relation to Cancer Diagnosis and Treatment	C-TUQ	Q6 – Q7	Q3
Smoking Cessation, Cessation Products, and Assistance Methods	C-TUQ	Q8 – Q13	Q4 – Q9
Use of Other Products	C-TUQ	Q14	Q10
Second-Hand Smoke Exposure	C-TUQ	Q15-Q16	Q11-Q12
Psychological Symptoms	PROMIS Lung Cancer Stigma Scale	Q17-Q18	Q13-Q14
Physical Symptoms	FACIT	Q19	Q15
Sociodemographics		Q20-21	

NOTE: In order to minimize ambiguity and assure that patients are oriented to answer appropriately, the specific phrasing of items may vary depending specific cancer type and treatment.

Tobacco Use. The selected Core and Extension C-TUQ items (from categories of Basic Tobacco Use Information, Tobacco Use in Relation to Cancer Diagnosis and Treatment, Smoking Cessation/Cessation Products/Assistance Methods, Use of Other Products, and Second-Hand Smoke Exposure) will be assessed in the baseline and follow-up Survey of Tobacco Use.

Oncology Provider Assistance. C-TUQ Question 13 assesses "cancer doctors" Advise. We will add 4 As to assess participants' reported 5As (Ask (Q12a), Advise (Q12b), Assess (Q12c), Assist (Q12d-Q12f), and Arrange follow-up (Q12g), as in Baseline STU).[80]

Psychological Symptom Assessment. Anxiety & Depression: *(The Patient Reported Outcomes Measurement Information System (PROMIS®)).* We will administer the 4-item Short Form PROMIS® for anxiety and depression (Q17 in Baseline STU). Stigma: The Lung Cancer Stigma scale measures the extent to which shame is internalized (Q18 in Baseline STU).[81]

Physical Symptom Assessment *Physical Symptom Assessment (Functional Assessment of Chronic Illness Therapy (FACIT)). FACIT, a measurement system with a collection of quality-of-*

life questionnaires, expands the more familiar FACT (Functional Assessment of Cancer Therapy) questionnaires into other chronic illness and conditions. FACIT consists of many individual questions to assess various symptoms from the patient perspective. We will use 6 FACIT items, selected based on the therapeutic regimens, expected toxicity, and malignancy type of the parent trials. In addition, we have created modifications of these same six questions to address the degree of bother associated with each symptom" The symptoms of general pain, fatigue, nausea, cough, sleep difficulty, and shortness of breath will be assessed, first using the standard and validated FACT item, and then asking the degree of "bother" imposed by each symptom, on the same 5-point scale. These clusters of symptoms were specifically chosen based on potential interactions between tobacco use and longitudinal symptoms.

Sociodemographic Variables. Sociodemographic variables, including age, sex, zip code, and race/ethnicity are collected for all NCTN trial participants at registration. At baseline, participants will provide information on marital status (Q20 in Baseline STU) and education level (Q21 in Baseline STU) as part of the tobacco supplemental assessment.

Cancer Treatment Variables. Clinical variables including date of diagnosis, malignancy type (smoking related vs. non-smoking related, cancer stage), and treatment details (i.e. types and dates of surgery, chemotherapy, and/or radiation received), along with disease status and survival, will be captured in Medidata Rave via the parent protocol and will be available for analysis of the ancillary. Provider-assessed adverse events will also be captured via the parent protocol in Medidata Rave, using case report forms commonly used across the NCTN and using standard data elements.

Assessments

All items in Survey of Tobacco Use will be administered using the EASEE-PRO system. The advantage of our virtual electronic data capture system is that our proposed assessments will not be limited to, or dependent upon, patient trial visits. Confidential and potentially stigmatizing information can be provided without requiring direct contact with the care team.

Timing of Assessments

Given the critical questions that remain[13] about the timing of conducting tobacco use assessments, we have carefully chosen to collect tobacco assessment data at trial enrollment, 3 and 6 month follow-up. For tobacco treatment trials, 6 month follow-up is the recommended primary outcome time point. By 6 month follow-up, most cancer treatment-related quitting activity[62], cancer treatment initiation of therapy, and FDA-approved smoking cessation medication regimens will be completed. Adverse events during treatment will have been observed.

Statistical Considerations and Analysis Plans

The analysis plans described below are planned for a combined analysis of the data from the selected ECOG-ACRIN trials. Consistency in the effects over the studies would be examined in this analysis.

1. CHANGES IN SMOKING STATUS AND EXPOSURE. At baseline, combustible tobacco use (1a) will be characterized by smoking status (never smoker, former smoker, and current smoker based on Baseline STU Qs 1 and 5), other forms of tobacco use (1b) will be a composite variable determined by non-cigarette items (based on Baseline STU Q7 and Q14), and environmental tobacco smoke (ETS) level (1c) will be determined by current household and work exposure (Baseline STU Qs 15-16). At follow-up, combustible tobacco use (1a) will be examined by smoking status (Follow-up STU Qs 1 and 2), other forms of tobacco use (1b) will be determined by Follow-up STU Q10, and ETS level (1c) will be

determined by 30 day household and work exposure (Follow-up STU Qs 11-12). We will examine tobacco use at baseline, 3 and 6 month follow-up, and change in status (abstinence in combustible tobacco, abstinence of other forms of tobacco use, and change in exposure to smoke-free home and work) using summary statistics (frequency and proportion). We will explore the effects of sociodemographic and cancer treatment factors on smoking status using logistic regression (comparing smokers and non-smokers). We will also evaluate factors associated with changes in smoking status.

2. TREATMENT TOXICITY. The selected trials capture information about adverse events during treatment using NCI's Common Terminology Criteria for Adverse Events, Version 4. Toxicities are measured at each treatment visit and graded according to severity, with grade 1 corresponding to mild toxicity and grade 5 signifying a lethal adverse event. We will determine each patient's worst degree toxicity across all event types and treatment visits and will compare the distribution of worst degree grades between smokers and non-smokers and between patients with environmental tobacco exposure and those without exposure using exact tests. We will also examine the distribution of worst degree grades between users with different form of tobacco use. In addition, we will explore the effects of tobacco use on dose modifications (yes vs. no) using logistic regression, with each patient's dose modification status determined across all treatment visits.
3. SYMPTOM BURDEN. Tobacco variables will be conceptualized as described in the section of CHANGES IN SMOKING STATUS AND EXPOSURE. Tobacco use status (as measured at baseline, 3 and 6 month follow-up) will be compared to physical and psychological symptom burden (as measured at each corresponding time points). At 3 and 6 month follow-up, we will also examine the association between tobacco use changes and changes in symptom burden. We will explore the effects of sociodemographic and cancer treatment factors on symptom burden using repeated measures mixed effects models. As an example of statistical power, we consider the PROMIS SF-4 depression measure. We assume that 1500 patients will be enrolled across the 8 parent studies over 13 months, and that 20% are smokers. We assume that 85% of patients will have assessments at 6 months. Given groups of these sizes (26 quitters and 230 still-smokers) and standard deviation of 4.08 for the PROMIS SF-4 depression scale, there will be 83% power to detect a difference in change scores of 2.5 between groups using a two-sample t-test with Type I error of 5%. The minimally important difference for this instrument is 2.2.[79]
4. CESSATION PATTERNS AND TREATMENT. At baseline we will explore pre-treatment combustible tobacco use patterns (STU Q6a and Q6b), quitting behaviors (STU Q13), behavioral program utilization (STU Q11) and oncology provider support (5As, STU Q12), and smoking cessation medication use (STU Q10). At follow-up we will explore post-treatment combustible tobacco use patterns (STU Q3a-Q3e), quitting behaviors (STU Q9), behavioral program utilization (STU, Q7) and oncology provider support (5As, STU Q8), and smoking cessation medication use (STU Q6). We will explore the effects of sociodemographic and cancer treatment factors on these variables. We will examine associations of quitting behaviors and behavioral and medication utilization with tobacco use status (as outlined in the section of CHANGES IN SMOKING STATUS AND EXPOSURE) at baseline and on respective 3 and 6 month tobacco outcomes. These analyses will be descriptive in nature. Summary statistics (frequency, proportions, and 95% confidence intervals) will be used.
5. TRIAL OUTCOMES. We will compare treatment duration between smokers and non-smokers and between patients with environmental tobacco exposure and those without exposure. Cumulative incidence/competing risk methods will be used to estimate time to treatment discontinuation for adverse events, disease progression, completion per protocol,

or other causes. Gray's test will be used to test for differences in the cumulative incidence distributions.[78] Differences in the distribution of reasons for discontinuation of treatment will be examined using exact tests. Relative dose intensity is defined as the ratio of actually delivered dose intensity to the planned dose intensity. The effects of tobacco use and exposure on relative dose intensity (≥ 90% vs. < 90%) will be explored using logistic regression. Differences in the primary endpoint and important secondary endpoints will be examined using log rank test and exact test (as appropriate).

Data collected in the tobacco use project will support a range of analyses. Precise estimates of power will depend on the prevalence of smoking at baseline among study participants, the proportion whose smoking status changes, and the duration and adequacy of follow-up.

References

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Rev. Add13

DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial

Rev. Add10

Appendix XIV

Predictive Biomarker Development in Patients with BRAF Mutant Melanoma Enrolled on EA6134

The following study was submitted and approved in response to the Request for Applications (RFA) for Administrative Supplements to Support Biomarker Studies Associated with NCI-supported Clinical Trials of Immunotherapy. The applications were administratively reviewed internally by NCI and reviewed and approved by DCTD/CTEP Protocol Review Committee separate from a protocol amendment.

Based on discussions with the NIH grant oversight committee, we have made several changes to the aims and research plans. However, we maintain the same initial hypothesis that an integrated predictive biomarker approach can divide patients with advanced BRAF mutant melanoma into four subgroups: (1) patients who benefit most from immunotherapy, (2) patients who benefit most from targeted therapy, (3) patients who benefit equally from either immunotherapy or targeted therapy, and (4) patients who will not benefit from either immunotherapy or targeted therapy. All patients enrolled in the EA6134 protocol are required to submit a baseline tumor specimen (block or ≥15 unstained slides plus a core biopsy) obtained prior to initiation of systemic therapy. These will be interrogated for biomarker development and correlated to baseline clinical prognostic variables. Given the grant duration is for a 1-2 year period, correlations to efficacy endpoints will be conducted under a future grant mechanism.

Aim 1: To perform immune biomarker assays on baseline tumor specimens from patients with BRAF mutant melanoma treated with nivo/ipi or D/T on EA6134.

The ECOG-ACRIN Central Biorepository Pathology Facility at MD Anderson will review H&E stained slides of each tumor specimen and prepare/ship this slide and 3 contiguously sectioned unstained slides for IHC and 10 additional unstained to the Histopathology and Tissue Shared Resource (HTSR) at the Georgetown Lombardi. IHC for PD-L1 and CD8 will be performed by the HTSR using established methods. PD-L1 status will be assessed by standard techniques (scoring system of 0 to 3+) and by those utilized by the nivo/ipi studies (threshold cutoff of 5%). CD-8+ T-cell infiltration/density will also be scored using a scoring system of 0 to 3+ and automated density measures. In addition, the Genomics and Epigenomics Shared Resource (GESR) at Georgetown-Lombardi will isolate RNA and DNA using the 10 FFPE tumor slides and/or equivalent tumor blocks using established approaches. RNA will be analyzed for immune gene expression on the Nanostring platform using the PanCancer Immune Profiling Kit (770 genes). DNA will be stored for future whole exome sequencing (WES) once additional funding is available. Raw data will be provided to the Bioinformatics team in the Innovation Center for Biomedical Informatics (ICBI) at Georgetown University.

Aim 2: To integrate and analyze immune biomarker data sets with clinical prognostic factors from patients on EA6134 using the Georgetown Database of Cancer (G-DOC)

G-DOC includes a broad collection of bioinformatics and systems biology tools for analysis and visualization of four major "omics" types: DNA, mRNA, microRNA, and metabolites. Molecular data will be processed using signal extraction and normalization pipelines in Bioconductor packages as well as our pipelines for pre-processing. Pre-processed data

matrices for each type will be used for bio-statistical and systems biology analyses. Specifically, we will use the R package NanoStringNorm to pre-process, run diagnostics, and visualize NanoString expression data. Further analyses including class comparison, machine learning and systems biology analysis will be performed. We will use the Recursive Feature Elimination (RFE) based on Random Forest (RF) machine learning approach to assess relationship of biomarkers. We will perform the model construction using 100 patient specimens for biomarker discovery. Additional specimens will be used for validation purposes; however the validation specimens will likely not be available after September 2017; thus requiring on no-cost extension of this grant. Data from WES/NGS will be incorporated once available – this system readily facilitates updated modeling with the introduction of new data. Subsequently data provided by ECOG-ACRIN on patient baseline clinical variables known to be associated with improved melanoma survival (LDH, number of disease sites, BRAF mutation (V600E vs V600K), stage of disease, age < 65, and sex) will be entered into the G-DOC database. It will then be determined if biomarkers are associated with these baseline clinical variables. The biomarker variables will be PD-L1 status ($\geq$ 5% positive tumor cells vs <5% positive tumor cells), CD8+ T cell density (IHC score of 2-3 vs 0-1), interferon-gamma gene expression signature (present or absent). Further optimized cutoffs or continuous variables may be utilized for association testing. Fisher's exact testing (categorical variables) and regression models (continuous variables) will be performed to determine associations between biomarker results and clinical variables.

Aim 3 (Future plans): To determine if mutational burden and/or profile can be combined with an immune biomarker profile to more accurately predict durable clinical benefit from nivo/ipi vs D/T in patients on EA6134

As WES/NGS studies are not included in the approved budget for this P30 supplement grant and the efficacy endpoints will not be available during the 1-2 year grant period, we will apply for additional funding sources to complete these research plans over the following 2-3 year period. These biomarker and bioinformatic plans remain unchanged.

DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial

Rev. Add20

Appendix XV

Patient Clinical Trial Wallet Card

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 #:

Study Drug(S):

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DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial

Rev. Add21

Appendix XVI

Assessment of serum based biomarkers of efficacy and adverse events due to treatment with immune checkpoint inhibitors

Exploratory Correlative Study Design

As part of this correlative study, we will evaluate and attempt to establish biomarkers of efficacy and adverse events due to treatment with immune checkpoint inhibitors. For this we plan to study serial blood samples obtained from patients in the immune checkpoint inhibitor arms of this trial at regular intervals and as they develop irAEs and require immunosuppressive therapy and/or discontinuation of treatment. The sample collection schema is in **Fig. 1**. The molecular readouts from changes in mutation and methylation patterns of circulating cell-free DNA extracted from the serum samples will be compared with clinical observations of efficacy and toxicity.

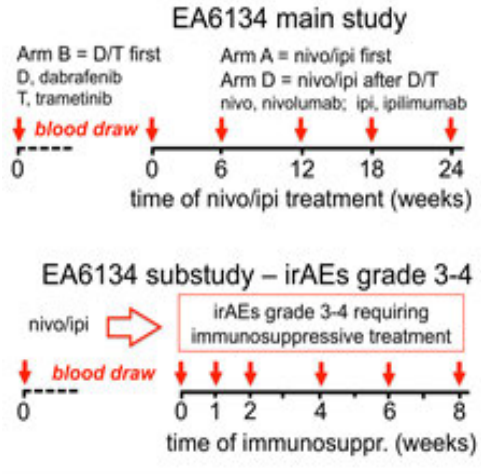

Fig. 1 Schema of EA6134 main clinical trial (top) and substudy for monitoring irAEs (bottom). In the substudy extra blood collection time points are added to monitor patients with irAEs during immunosuppressive treatment.

Main study sample collection times are indicated. In this **substudy** extra blood collection time points are added to monitor patients with irAEs during their course of immunosuppressive treatment.

Specific Hypotheses

Primary:

We hypothesize that (a) a larger proportion of responders (compared to nonresponders) will have changes in ctDNA measurement after treatment, and (b) tumor status can be monitored during the course of the treatment or an irAE by quantifying the amount of tumor specific DNA (mutant ctDNA) in the blood and that prolonged immunosuppressive therapy may stunt and/or reverse any ongoing antitumor response (Aim 1).

Secondary:

We hypothesize that tissue injury due to irAEs directed against several tissues (liver, lung, heart, colon, pancreas etc.) will be reflected as changes in tissue-specific DNA methylation patterns in the blood that is shed as cell-free methylated DNA (cmeDNA) and that these changes will be detectable in the blood at onset and resolve to baseline as the irAE is successfully treated (Aim 2).

We have established experimentally cmeDNA detection by amplicon sequencing of tissue-specifically methylated genomic regions for heart, lung, brain, or liver. We also have recently established a tissue-agnostic epigenome-wide cmeDNA analysis that will circumvent generation of amplicons for each tissue of interest. We will use both approaches if high sensitivity of detection (low abundance of a signal) is required because the amplicon sequencing method is ~10-fold more sensitive than the unbiased, genome-wide capture-seq.

Specific Aims

Aim 1: To monitor tumor response by comparing changes in circulating cell-free mutant tumor DNA **(ctDNA)** as a readout of tumor burden **(a)** at week 12 relative to baseline before treatment in responders and non-responders; **(b)** before and during immunosuppressive treatment to control irAEs.

Aim 2: To monitor organ-specific adverse events (irAEs) using circulating cell-free, tissue-specific methylated DNA **(cmeDNA)** as a readout of tissue-specific toxicity **(a)** at the time of grade 3-4 irAE relative to baseline and control patients without irAEs; **(b)** during immunosuppressive treatment for irAEs.

Background

Treatment with Immune Checkpoint Inhibitors (ICIs)

Therapeutic inhibition of immune checkpoints has demonstrated striking efficacy in a variety of cancers and is currently the standard of care in over a dozen cancer settings and are being studied in more than 2200 clinical trials in combination with other anti-cancer agents/regimens. Antibodies against the PD-1 pathway, pembrolizumab (pembro) and nivolumab (nivo), antibodies against the PDL-1 pathway, atezolizumab, avelumab and durvalumab have in particular revolutionized the treatment of patients with melanoma, lung, kidney, bladder, head and neck cancers and have produced long term durable responses (1,2) The combination of nivo with anti-CTLA-4, ipilimumab (ipi), produces tumor responses in approximately 60% of patients with metastatic melanoma (3) and 40% with advanced kidney cancer (4). These results have contributed to the FDA approval of these medications for melanoma, and clear cell kidney, non small cell lung, bladder, hepatocellular and head & neck cancers. Treatment with immune checkpoint inhibitors has shown efficacy in over 20 distinct cancer types and in addition FDA approval now includes a tissue-agnostic indication, i.e. any cancer with DNA repair deficiency.

Immune-Related Adverse Events (irAE)

Immune checkpoint blockade frequently causes inflammatory and immune-related adverse effects (irAEs) due to the disruption of self-tolerance protection by normal tissues. These irAEs can be severe, leading to discontinuation of immune checkpoint inhibitor therapy and the requirement for immunosuppressive treatment. Any tissue can be injured with the most frequent occurrences in the skin, gastro-intestinal tract, endocrine glands, liver, and lungs. Combined checkpoint blockade of PD-1 and CTLA-4 has higher toxicity than monotherapy and requires more frequent immunosuppressive treatment and/or discontinuation of therapy. Specifically, in a randomized multi-institutional trial involving the now FDA approved regimen

of nivolumab (1 mg/kg) + ipilimumab 3 mg/kg IV q 3 weeks followed by nivo 3 mg/kg monotherapy q 2 weeks, treatment related grade 3-4 irAEs occurred in 59% of patients compared to 21% for nivolumab monotherapy (5). In particular 123/313 patients on nivo + ipi did not receive all 4 induction treatments (and thus no maintenance nivo) due to treatment related AEs requiring immunosuppressive therapy. Treatments for irAEs in a recent study were mostly corticosteroids (systemic >65%; topical 30%) and infliximab (6%) or mycophenolic acid (0.8%) for GI or hepatic irAEs. Although 67% of these patients remained alive at 3 years, suggesting that discontinuation of therapy and the application of immunomodulation did not compromise their survival, it is unclear if efficacy would have been further enhanced if nivo monotherapy had been provided once toxicity had resolved or if earlier, briefer or different immunomodulatory therapy had been used to control the irAEs.

Although treatment with steroids and other immune modulators can reverse these irAEs, immunosuppression may compromise the anti-tumor activity of the immune checkpoint blockade. Thus, there is an unmet need for non-invasive biomarkers for real time prediction of irAEs and the impact of immune suppressive therapy on therapeutic efficacy to inform management of cancer patients treated with immune checkpoint inhibitors.

A first step to detecting irAEs earlier is to determine whether one can identify blood-based patterns of specific organ damage in patients with clinically detectable irAEs and to assess if these alterations resolve with successful treatment of the irAE. Thus, we propose to collect blood samples to isolate cell-free DNA for analysis at the onset of irAE and follow that with serial blood samples at regular time points during and after the treatment of the irAE. Each patient's baseline blood sample at irAE onset will serve as their respective control. We propose to assess immune-related organ damage by monitoring changes in the abundance of a set of tissue-specific **circulating cell-free methylated DNA (cmeDNA)**. The analysis of cmeDNA can be tailored to any organ or tissue that is possibly damaged by the autoimmune reaction to checkpoint inhibition and we will initially include 12 tissues in our analysis.

In order to determine whether the immunosuppressive treatment of an irAE has an impact on the anti-tumor immune response, we propose to monitor changes in the circulating cell-free **mutant tumor DNA (ctDNA)** levels as readout of effect of treatment anti-tumor treatment efficacy.

Background on cell free tumor DNA (ctDNA)

Monitoring the molecular characteristics of cancer by serial analyses of circulating cell-free mutant tumor DNA **(ctDNA)** enables capture of emerging heterogeneity of the disease and may even support treatment decisions (6,7). ctDNA analysis has evolved since its inception with improvements in the technologies and detection limits (8,9) and now represents a set of research tools that appear poised to enter routine clinical care (10,11). The recent FDA approval of a ctDNA assay for the *EGFR* T790M mutation in lung cancer to assess suitability of treatment with osimertinib supports this notion (12). Also, it appears that ctDNA may be superior to tumor tissue DNA in the assessment of cancer heterogeneity and during disease progression with metastatic disease (13,14). We plan to monitor 263 mutations in 56 frequently mutated cancer genes in ctDNA. We have established the assay and reported it recently (15). Monitoring for a panel of mutated genes in highly heterogeneous cancers can provide new qualitative insights into the changing molecular composition of the cancer during immune therapy (16).

Background on DNA methylation and cmeDNA (circulating methylated DNA)

DNA methylation is an important epigenetic regulation mechanism that consists of an addition of a methyl group to carbon 5 of cytosine residues in clusters of CpG islands. The effects of

DNA methylation for each genomic locus is not fully understood, but it is widely accepted that DNA methylation can regulate gene expression (17), cellular differentiation and chromosomal stability. DNA methylation is tissue- and cell type-specific and can thus serve as a biomarker for specific tissues (18). One application of DNA-methylation profiling has been used to predict the tissue of origin of cancers with unknown primary lesions. This has also been applied in clinical diagnostics and histopathology (19,20).

DNA methylation signatures of tissues or cells can be obtained from ever-growing methylome data bases such as the Human Epigenome Atlas (ftp://ftp.genboree.org/EpigenomeAtlas/) that is housed at Baylor College or from the published literature (21). In addition to isolation from cells and tissues, methylated DNA has been isolated from serum or plasma where it can be used to assess cancer progression, tissue transplant survival, prenatal diagnostics and other phenotypes (22,23) In addition to the detection of short fragments of methylated DNA in the circulation, other bio-fluids were also reported as sources: e.g. saliva was used to identify altered neurotransmission in attention-deficit/hyperactivity disorder children via methylated DNA analysis (24).

In Figure 2 we show the approach to the analysis of circulating cell-free DNA methylation. The quantitative analysis is based on next-generation DNA sequencing (NGS). Figure 3 shows an analysis of the top 10 genomic loci that distinguish different tissues of interest. Analyses of these distinct methylation patterns are used to assign differentially methylated DNA fragments in the circulation to their tissue or origin.

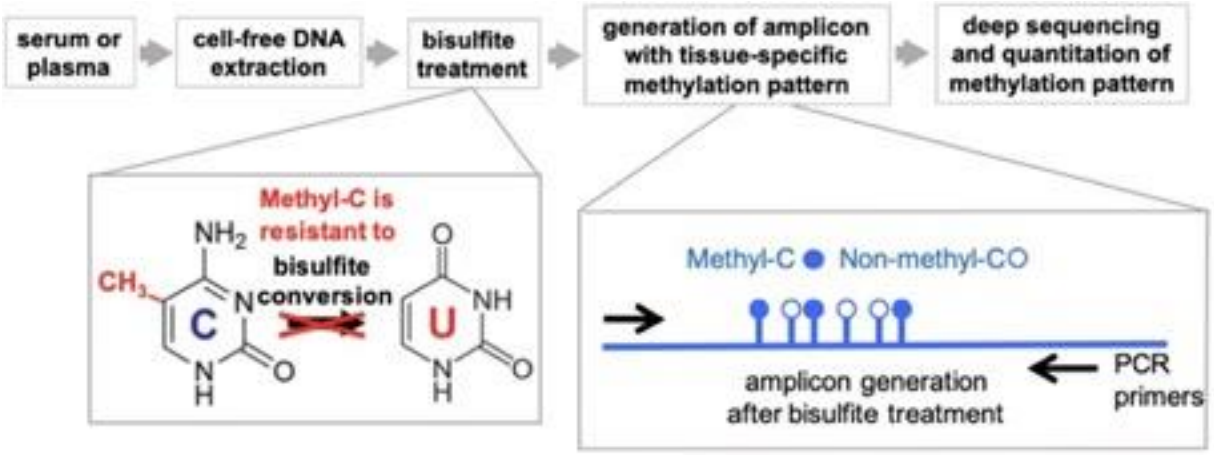

Figure 2. Overview of approach to detect to changes in cfDNA methylation patterns. For sequencing based detection of methylated CpGs DNA is treated with bisulfite that will convert non-methylated C to U. Methylated Cs are resistant to the bisulfite conversion. Thus, methylated Cs are read as Cs whereas non-methylated Cs are read as Ts in conventional DNA sequencing. For the detection of tissue-specific cfDNA we select genomic regions that contain 4 to 8 CpGs within <150 nucleotides and show distinct methylation when comparing across a range of tissues. Figure 5 (below) shows a line-up of distinct genomic regions across a range of tissues. PCR primers outside the CpGs are then used to amplify bisulfite treated cfDNA. Deep sequencing provides the patterns of methylated and non-methylated DNA fragments. Only fragments where all CpGs selected are either methylated or non-methylated are considered as a positive signal to avoid false signals due to random methylation or de-methylation.

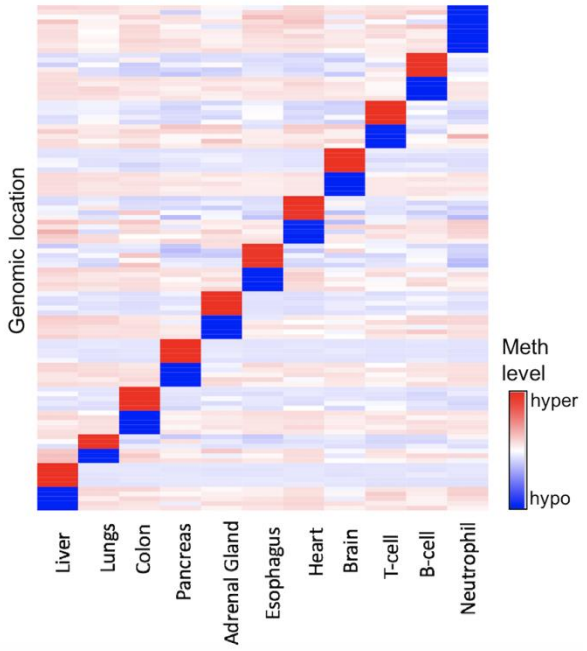

Figure 3. Tissue-specific DNA methylation. Top 10 genomic loci that contain tissue-specific distinct hypo- or hyper-methylated DNA segments. The analysis used data generated by Sun et al. (PNAS 2015).[25] Markers were defined as genomic loci with methylation densities that deviate 3 SDs below or above in only one tissue compared with the mean level of the other tissues.

Of significance for this proposal, recent work has shown that after different modes of normal tissue damage by inflammation (multiple sclerosis, pancreatitis), trauma (traumatic brain injury) or hypoxia (cardiac arrest) dying cells in the CNS, pancreas, heart etc. will release their DNA as short fragments into the circulation. This will lead to an increased abundance of tissue-specific DNA and the DNA methylation patterns can be used to identify the tissue or cellular origin of the circulating methylated DNA (cmeDNA) (21).

We plan to apply cmeDNA analysis to monitor tissue damage due to irAEs during immune checkpoint inhibitor (ICI) treatment in patients with clinically detected irAEs. Towards this goal we have established a highly sensitive assay for detection of methylation patterns in CpG islands of tissue-specific genes using cell-free DNA from serum samples. Figure 4 shows an example of such an analysis and provides the details in the legend. From amplicon sequencing we achieve at least 10,000 reads per amplicon and can thus detect as few as 1/1,000 distinctly methylated DNA fragments in a serum samples using this approach.

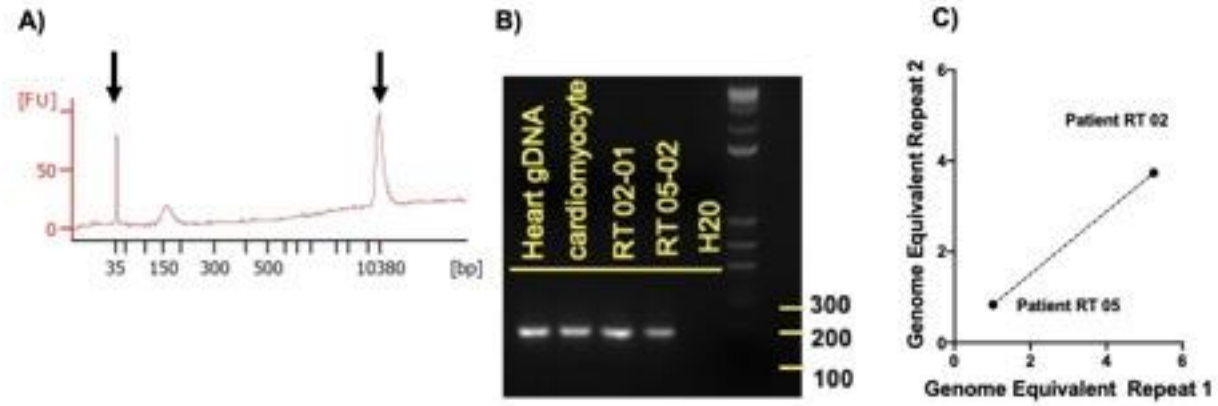

Figure 4. Heart specific methylated cfDNA analysis. A) Biotracer reading of cfDNA fragment size (~150bp) and cfDNA level in a patient serum after DNA extraction. Peaks from size markers spiked in with the sample serve as a reference (arrows). B) Gel image of amplicons using primers adjacent to the FAM101A locus. The predicted size of the amplicon was 189 bp. Positive control DNA samples analyzed were genomic heart and cardiomyocyte DNA (commercially available), patient RT02 and RT05 cfDNA were from an ongoing radiation trial. H20 is a negative control for DNA contamination. C) Independent repeat measurements of samples from two patients RT-05 and RT-02, were run independently from serum extractions to sequencing analysis to test reproducibility. Abundance of cardiac-specific DNA is provided in genome equivalents calculated based on the amount of DNA extracted. 35,000 to 74,000 reads generated from the cfDNAs were obtained for the amplicons analyzed shown here.

We have recently established an experimental work flow that is agnostic towards detection of tissue-specific cell-free DNA in the circulation (cfDNA). In this approach bisulfite treated cfDNA fragments that contain CpG regions (~3% of the genome) are captured and then subjected to NGS. Analysis of serially collected samples then can reveal changes over time. We have described this approach and the data analysis recently (25).

Number of subjects: We anticipate for EA6134 as a whole that 150 subjects will receive nivo/ipi as initial therapy (Arm A, **Fig. 1**) and that another 100 subjects will receive nivo/ipi on Arm D (**Fig. 1**) after exhibiting disease progression on D/T. Based on consent and submission compliance rates as of July 2020, it is projected that 75% to 80% of the subjects in this study will consent to the collection of and have submitted serum samples which are requested q 6-week blood until off study and, if applicable, weekly following an irAE. The amendment to collect additional samples following an irAE was approved in mid 2018. Of the 250 patients estimated to receive I/O therapy as part of this study, about 35 subjects on Arm A and 15 on Arm D had already stopped treatment due to either toxicity or disease progression by the time the amendment (=**substudy**) to the protocol to collect the specimens detailed in this research proposal was activated leaving around 200 subjects potentially available for the substudy. In the substudy, we will obtain weekly blood draws after the onset of grade 3-4 toxicities to allow for more frequent measurements of ctDNA and cmeDNA. The intervals of blood draws in those patients that have already enrolled are 6 weeks. The incidence of grade 3-4 irAEs with nivo/ipi is around 50%; therefore we anticipate data relevant to toxicity to be available in about 125 subjects from the whole study and up to 100 from the substudy. The remainder of subjects with less toxicity (~125 from the whole study and ~100 from the substudy) will serve as controls. Response data should be available on all 250 subjects from the whole study with roughly 50% anticipated to be responders by week 12 and 60% by week 24. Available samples have been assessed based on the samples submitted as of July 2020 and the

sample size calculation has been updated in the Statistical Design and Analysis Plan section below.

Blood samples: As mentioned above all participants in EA6134 have consented to have 2 x 10cc red top tubes of blood collected at baseline and every 6 weeks for both initial and crossover treatments and at time of progression. **Substudy:** In amendment 10 we proposed more frequent biomarker measurements during the period of management of grade 3-4 irAEs. Thus, the EA6134 protocol was amended to have additional 2 x 10 cc red top tubes of blood collected at weekly visits in those subjects with grade 3-4 irAEs until irAEs resolve to grade 1 and then at their regularly scheduled visits (q 2-3 weeks) until they are tapered off of immunosuppressive agents. Following that they will resume q 6-week blood collections until off study.

All specimens are shipped to the ECOG-ACRIN Blood Specimen Core (IMCPL) located at the Pittsburgh Cancer Institute for storage. In our NCI approved R01 grant we proposed that aliquoted samples collected from patients who have either completed protocol participation or cleared the 24 week CT scan and blood drawn on either Arm A or D during the preceding 3 month interval will be shipped quarterly to the R01 grant co-PI (Wellstein's) lab at Georgetown-Lombardi for measurements of ctDNA and cmeDNA. Serial samples from a given patient are to be analyzed together as defined in the Aims. We will initially have a complete set of samples available from the 140 patients that have entered the trial as of July, 2018. That set of samples will be sufficient to establish the cmeDNA assays and test the existing ctDNA assays.

Samples to analyze: The serum samples to analyze will either be from Arm A (=nivo/ipi treatment first) or Arm D (=switched to nivo/ipi due to progressive disease after dabrafenib/trametinib first; see **Fig. 1**). For Arm A (nivo/ipi first) we will use 0, 6, 12, 18 and 24-week samples collected for all patients at the trial-prescribed intervals. These time points should capture specimens from 90% of patients with tumor response (median time to response 2.76 months or 12 weeks) and 90% of the patients experiencing irAEs: The observed time course of grade 3-4 irAEs in a recently published study co-authored by MB Atkins (5) is reproduced in **Fig. 5** with the trial collection times of 0, 6, 12, 18 and 24 weeks overlayed for illustration purposes. For Arm D (D/T first) we will use the baseline sample before initiation of D/T treatment as an additional control (see **Fig. 1**, above).

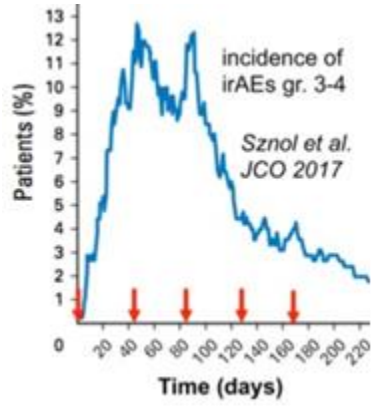

Fig 5. Incidence of grade 3-4 AEs. From Sznol et al: "Pooled Analysis Safety Profile of Nivolumab and Ipilimumab Combination Therapy" (5). The percent of patients who experienced at least one grade 3-4 irAE at the respective times (total n=448) are shown [from the original Figure in Ref. (5)]. **Arrows:** time points of blood collection in the current study.

Statistical Design and Analysis Plan

Sample Avaialibility Assessed as of July 2020

Overall 90% of the patients consented to participate in the correlative study. We summarized inventory for patients enrolled as of 12/31/19 (as our assessment requires at least 24 weeks of follow-up time) and projected the numbers for the remaining patients.

Aim 1a: Based on the data as of 12/31/19, 90% of the enrolled patients consented to participate in the correlative study. Of the consented pateints, 90% had baseline samples and 86% (of the cases submitted baseline samples) had samples on at least one FU time point. At the completion of the study, approximately 104 patients (150X.9X.9X.86) will provide samples for the analysis proposed in Aim 1a. The crossover rate (to arm C or D) was lower than anticipated, but could not be assessed accurately at this point as the study is still being conducted. We project at least 46 patients crossed over to arm D will provide samples for Aim 1a. Therefore, the overall sample size for Aim 1a will be approximately 150 patients.

Aims 1b and 2: As of 12/31/19, approximately 50% of the patients in arm A or D had grade 3 or higher irAEs and submitted samples. Therefore, we project approximately 75 patients will have consented and submitted irAE samples when accrual is completed. The remainder of subjects with less toxicity (~75) will serve as controls.

Study Design and Analysis

Aim 1: (a) We will first correlate the ctDNA analyses with clinical measurements of treatment responses and efficacy. Changes in the ctDNA measure from the baseline will be compared between the responders and non-responders. The relative abundance of ctDNA will be measured at each time point (baseline, weeks 6, 12, 18 and 24) by [ctDNA / (ctDNA+wtDNA)], resulting in a number between 0 and 1. The difference in the relative adundance of ctDNA between post-treatment time point (weeks 6, 12, 18 and 24) and baseline will be evaluated. The difference will range from -1 to 1. The difference of > 0 will be considered as a positive change (change = yes) and the rest will be considered as no change.

The initial analysis will be based on week 12 samples as these will be available on the majority of patients. Scan reports out to 24 weeks and if necessary blood samples out to the same time will be used to attempt to distinguish temporally related discrepancies. Changes in ctDNA measurements between pre- and post-treatment will be compared in responders vs. non-responders. For the primary endpoint, we first present a power calculation based on a binary formulation of ctDNA and then as a continuous measure.

Of the 150 patients treated with Ipi/Nivo, it is assumed 90 (60%) patients will achieve a response. It is hypothesized that a larger proportion of responders will have changes in ctDNA measurement after treatment. If the difference in proportion of patients with changes in the pre- and post-treatment ctDNA measurements among responders vs. non-responders is at least 25% (suh as 55% vs. 30%, 65% vs. 40%, 75% vs. 50%), the sample size of 90 responders and 60 non responders will provide at least 82% power. This is based on Fisher's exact test with a two-sided type I error rate of 0.05. The distribution of changes in the ctDNA measure between pre- and post- time points will be evaluated and compared between the responders and non-responders. If the standardized difference between the responders and non-reponders are at least 0.5, there will be at least 85% power based on the two-sample t-test. We will evaluate the distribution of the changes. If non-parametric test is more appropriate, Wilcoxon's rank-sum test will be used to compare the difference in the changes.

(b) Tumor status can be monitored during the course of the treatment or an irAE by quantifying the amount of tumor specific DNA (mutant ctDNA) in the blood and that prolonged

immunosuppressive therapy may stunt and/or reverse any ongoing antitumor response (Aim 1). We will evaluate the changes in ctDNA (from baseline) in patients who experienced at least grade 3 irAEs (n=75) vs. no irAEs (n=75). There will be multiple time points while experiencing irAEs up to week 24. The majority of the patients experiencing irAEs will be on immunosupressive treatement (n=75). In order to determine whether the immunosuppressive treatment of an irAE has an impact on the anti-tumor immune response, we will monitor changes in the ctDNA levels as readout of effect of treatment anti-tumor treatment efficacy. We will evaluate the trend of ctDNA levels while on immonosupressive treatment using descriptive statistics. Patterns of the changes in ctDNA during the immunosuppressive treatment will be summarized.

Aim 2: (a) We will correlate the cmeDNA analyses with clinical measurements of irAEs. Differences from baseline in patients who experience irAEs relative to those that do not for the estimated 150 patients treated with nivo/ipi in the study as a whole will be evaluated. Changes in cmeDNA measurements between pre- and post-treatment will be compared in patients with vs. without grade 3,4 irAEs. It is assumed 75 (50%) patients have grade 3,4 irAEs. Post-treatment time point of week 12 will be used for patients without grade 3,4 irAEs and various time points for patients with grade 3,4 irAEs.

Organ-specific, circulating cell-free methylated DNA (cmeDNA) will be detected by bisulfite sequencing of DNA and quantitated from the sequence reads (Barefoot et al. 2020; Ref 25). It is expected that irAEs will result in an increase in cmeDNA from the affected organs relative to the baseline measurements. A >3–fold increase above baseline in cmeDNA after the onset of irAEs will be considered as a change. If organ-specific cmeDNA is not detectable at baseline, three or more sequence reads of organ-specific cmeDNA will be considered as a positive signal and a change from baseline. cmeDNA will be followed in serial samples over the time of irAE treatment and scored accordingly. It is hypothesized that a larger proportion of patients with grade 3,4 irAEs will have changes in cmeDNA measurement after treatment. If the difference in proportion of patients with changes in the pre- and post-treatment cmeDNA measurements with vs. without grade 3,4 irAEs is at least 25% (such as 30% vs. 55%, 40% vs. 65%, 50% vs. 75%), the sample size of 75 in each group will provide at least 85% power. This is based on Fisher's exact test with a two-sided type I error rate of 0.05. Given the exploratory nature of this study, type I errors will not be adjusted for multiple comparisons. Changes in organ-specific cmeDNA measurements between pre- and post-treatment will be evaluated in patients with or without grade 3,4 irAEs.

(b). We anticipate 75 patients with serial samples during the immunosuppressive therapy. We will evaluate changes in signatures of specific organ toxicities during the immunosuppressive therapy relative to baseline and summarize the data using descriptive statistics. Changes in cmeDNA measurements will be evaluated by immunosuppressive treatment. Proportion of patients with cmeDNA measurement return to the baseline measurement will be compared by treatment type using Fisher's exact test.

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