S1400K: c-MET – ABBV-399 (PROCESS II)

A BIOMARKER-DRIVEN MASTER PROTOCOL FOR PREVIOUSLY TREATED SQUAMOUS CELL LUNG CANCER

A PHASE II STUDY OF ABBV-399 (Process II) IN PATIENTS WITH C-MET POSITIVE STAGE IV OR RECURRENT SQUAMOUS CELL LUNG CANCER (LUNG-MAP SUB-STUDY)

NCT # 03574753

This is a potential FDA registration study. There will be additional centralized and on-site monitoring conducted in addition to routine audits. Sites must also maintain a study-specific Trial Master File for this study.

Lung-MAP and its sub-studies are being conducted under SWOG IND 119672 and CIRB. The Lung-MAP Study is considered a single study under one IND, consisting of the Screening Protocol and multiple sub-studies. Each sub-study protocol operates independently and has its own version date. However, for regulatory purposes, all Lung-MAP sub-study protocols should be processed as a single study for Continuing Review.

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Available from Pharmaceutical Collaborators:
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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: (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 exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available to the SWOG Workbench via the SWOG website (www.swog.org).

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 patient eligibility questions contact the SWOG Statistics and Data Management Center by phone or email:

206/652-2267
S1400question@crab.org

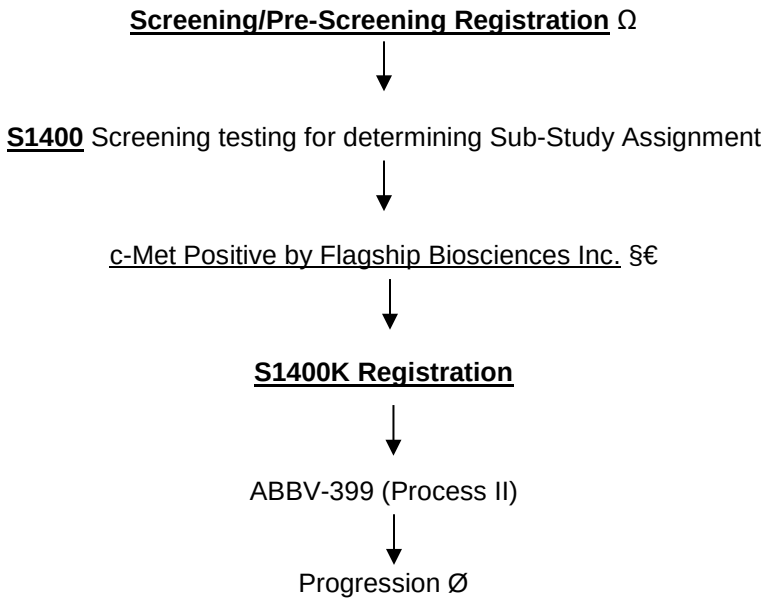
For treatment or toxicity related questions contact S1400KMedicalquery@swog.org.

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: 888-823-5923, or contact 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.

SCHEMA



Ω See **S1400** Section 5.1 for screening/pre-screening registration information.

€ Notification of sub-study assignment will be provided by the SWOG Statistics and Data Management Center (SDMC) (see **S1400** Section 11.0 for details).

§ See **S1400K** Section 5.0 for the definition of c-Met Positive by Flagship Biosciences Inc. criteria.

Ø Upon progression (as defined in **S1400K** Section 10), patients may be eligible for another sub-study. The new sub-study assignment will be determined by the SWOG SDMC (see **S1400K** Section 14.4).

1.0 OBJECTIVES

The objective of **S1400K** is to evaluate ABBV-399 (Process II), an antibody-drug conjugate (ADC) among patients found to have c-Met positive squamous cell tumors.

1.1 Primary Objective

The primary objective is to evaluate the overall response rate (ORR) (confirmed and unconfirmed, complete and partial) with ABBV-399 (Process II) in all patients with c-Met-positive lung squamous cell carcinoma. (SCCA).

1.2 Secondary Objectives

a. To evaluate investigator-assessed progression-free survival (IA-PFS) and overall survival (OS) with ABBV-399 (Process II) in immunotherapy-exposed and relapsed patients with c-Met positive squamous cell tumors.

b. To evaluate the overall response rate (ORR) (confirmed and unconfirmed, complete and partial) with ABBV-399 (Process II) in immunotherapy-exposed and relapsed patients with c-Met positive squamous cell tumors.

c. To evaluate IA-PFS, and OS in all patients with c-Met positive squamous cell tumors.

d. To evaluate the duration of response (DoR) with ABBV-399 (Process II).

e. To evaluate the frequency and severity of toxicities associated with ABBV-399 (Process II).

1.3 Translational Medicine Objectives

a. To identify additional predictive tumor/blood biomarkers that may correlate with response to ABBV-399 (Process II).

b. To establish a tissue/blood repository from patients with refractory squamous cell carcinoma (SCCA) of the lung.

2.0 BACKGROUND

2.1 Overview

S1400 (Lung-MAP) is a large scale, screening/clinical registration protocol that genomically screens previously treated patients with advanced stage lung squamous cell cancer and uses the screening results to direct each patient to a therapeutic study. Based on the results of the tumor analysis, patients will either be assigned to one of the biomarker-driven sub-studies or to the 'non-match' sub-study for patients with none of the eligibility biomarkers. The biomarker-driven sub-studies are designed around a genotypically-defined alteration in the tumor and a drug that targets it. The non-match study is designed around an investigational agent with the potential for efficacy in a broader population. For a full description and justification of the study design, refer to the **S1400** screening protocol.

The MET proto-oncogene, located on chromosome 7q21-q31, encodes a cell surface receptor tyrosine kinase called c-Met, which is activated by its ligand hepatocyte growth factor (HGF), also known as scatter factor. *(1,2)* Binding of HGF to c-Met leads to homodimerization and activation of kinase activity. *(3)* HGF/c-Met pathway activation plays a crucial role in normal development through mediating mesenchymal-epithelial

interactions in epithelial cells and the liver, and also play a role in ordered skeletal muscle development and guiding motor neuron development. *(4)*

The HGF/c-Met pathway signaling is dysregulated in several malignancies including cancers of the lung, stomach, esophagus and colon, where it promotes tumor growth, invasion, angiogenesis and metastases. *(5,6)* c-Met pathway activation in malignancies can occur through activating mutations or *MET* amplification. *(7, 8)* The proportion of c-Met positive tumors does vary based on the immunohistochemical test performed, and cutoff used. Though virtually all lung tumors have some expression of c-Met noted, strong expression (2+) is observed in up to 61% of non-small cell lung cancer (NSCLC) tumor tissues overall. *(9)* Using the commercially available Ventana Benchmark anti-total c-Met SP44 rabbit monoclonal primary antibody, and a threshold of at least 2+ staining in 50% of cells, approximately 29% of NSCLC squamous tumors are noted to be positive. *(10)* MET mutations are more rare events, noted in only 2% of squamous cell carcinomas sequenced as part of The Cancer Genome Atlas (TCGA). *(11)* NSCLC tumors with high expression of both c-Met and HGF tend to have a higher pathologic tumor stage and worse prognosis compared to those with low expression. *(12)* In patients with EGFR-mutant NSCLC, MET amplification is observed as one of the mechanisms of resistance to EGFR tyrosine kinase inhibitors (TKIs). *(13)*

Several therapeutic strategies have been employed to target c-Met in NSCLC, using monoclonal antibodies directed against either HGF or c-Met, which have so far been unfruitful. *(14,15)* The humanized anti-HGF IgG1 monoclonal antibody ficlatuzumab binds and neutralizes free HGF, thus inhibiting c-Met phosphorylation. A Phase II study of gefitinib plus or minus ficlatuzumab in treatment naïve Asian light or never smoking patients with stage IIIB/IV NSCLC failed to meet its primary endpoint of overall response rate (ORR) or secondary endpoints of progression free survival (PFS) or overall survival (OS). A Phase III trial (METLung) investigating the benefit from adding onartuzumab (MetMAb), a humanized monovalent monoclonal antibody that bind the extracellular domain of c-Met, to erlotinib in patients with metastatic NSCLC after progression on 1 or 2 lines of prior therapy, including a platinum doublet also failed to meet its primary endpoint of OS (HR 1.27; 95% CI 0.98-1.65). *(16)* The randomized Phase III MARQUEE clinical trial of second/third line erlotinib in combination with tivantinib, a selective small molecule inhibitor of c-Met, versus erlotinib and placebo met a similar fate. *(17)* The primary endpoint of improved OS was not met with the erlotinib and tivantinib combination (median OS 8.5 vs 7.8 months, HR 0.98, 95% CI 0.84-1.15), though exploratory subgroup analysis suggested an improvement in OS in patients with high c-Met expression. Taken together, the results of these trials suggest that c-Met expression on IHC alone is not a sufficient biomarker to predict benefit from these agents. Indeed, in patients with activating exon14 skip mutations in *MET*, or MET gene amplification, the activity of non-selective inhibitors of c-Met such as crizotinib and cabozantinib has been described. *(18,19, 20)* Unfortunately MET mutations and gene amplifications occur much less frequently, limiting the patient population that is likely to benefit from drugs blocking c-Met pathway alone.

2.2 Rationale

ABBV-399 (Process II) is a first-in-class antibody-drug conjugate (ADC) comprised of ABT-700, an antagonist anti-c-Met monoclonal antibody, linked to monomethyl auristatin E (MMAE), a potent microtubule inhibitor. *(21)*

ABT-700 inhibits HGF-dependent and HGF-independent c-Met activation. *(22)* It inhibits c-Met receptor dimerization and has shown anti-tumor activity in MET amplified NSCLC and gastric cancer. *(23, 24)* In a Phase I clinical trial of this agent in patients with advanced solid tumors, ECOG PS 0-2, patients were treated on the dose escalation Phase with ABT-700 administered as an IV infusion at escalating doses on Day 1 of a 21-day cycle, with a starting dose of 5 mg/kg. A total of 44 patients were treated Dose escalation occurred in a standard 3+3 design with no DLTs observed and no MTD identified. *(25)* The recommended Phase II dose was 15 mg/kg IV every 3 weeks.

ABBV-399 (Process II) is potently cytotoxic to cancer cells with c-Met over-expression or amplified MET and demonstrates antitumor activity in human tumor xenografts. Activity of ABBV-399 (Process II) against ABT-700-refractory tumors has also been demonstrated in non-clinical studies. The cumulative toxicology and PK data from preclinical studies supported the initiation of investigational trials with ABBV-399 (Process II) in humans with advanced solid tumors at a starting dose of 0.15 mg/kg. See Investigator's brochure for more details. Based on monotherapy data from the Phase I clinical trial of this agent, ABBV-399 (Process II) is safe and tolerable, and the dose of 2.7 mg/kg intravenously every 3 weeks has been chosen for the expansion cohort dosing. Preliminary data for 16 patients with c-Met positive (defined as H score of ≥ 150) non-small cell lung cancer is encouraging, with 3 partial responses (an objective response rate of 19%) with a disease control rate (PR + SD) of 56%.2*(26)* The 3 patients who responded were squamous histology while 4 squamous patients total were enrolled. At this time, it's not known if this response rate will be maintained after a larger number of squamous patients are enrolled. Squamous lung cancer is a disease where there is a dire need for effective targeted therapies, and given the 29% frequency of c-Met overexpression in squamous lung cancer, ABBV-399 (Process II) will fill an unmet need. *(27)*

c-Met overexpression has been reported in NSCLC, with varying prevalence depending on method of evaluation and scoring. For example, c-Met positivity has been reported in 24.4% - 29% of patients with squamous cell lung cancer. *(28, 29)* Though c-Met protein overexpression is common in NSCLC, strategies thus far to select patients based on overexpression for treatment with anti-c-Met monoclonal antibodies and small molecule inhibitors of c-Met have failed to show clinical benefit in large randomized studies. ABBV-399 (Process II) has a potential to improve the quality of life and outcome of patients with squamous cell lung cancer, based on its tolerability and preliminary efficacy.

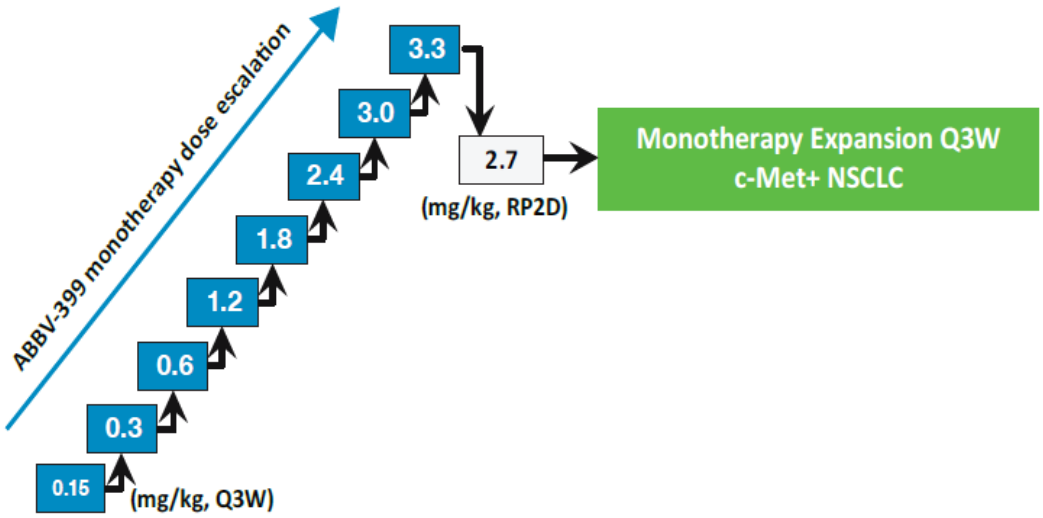
The c-Met IHC assay will be part of **S1400** screening, to identify patients for registration to **S1400K**. The assay is currently being employed in AbbVie's Phase 1 study to select c-MET positive patients. The assay utilizes the CONFIRM c-Met SP44 rabbit monoclonal Ab from Ventana, intended for IVD use (cat #790-4430). The IHC cutoff for positivity in the current Phase 1 study is an H-score of ≥150 membrane staining. The % c-Met positive in squamous histology NSCLC is about 30% per the literature (Genentech) with SP44 antibody IHC.

2.3 Data

A Phase I open-label dose escalation study of ABBV-399 (Process II) in patients with advanced solid tumors is presently ongoing (NCT02099058). Results of the dose escalation portion of the study were presented at the American Society for Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) meetings in 2016. *(30, 31)* Eligibility criteria included patients 18 years or older with advanced solid tumors with Eastern Cooperative Group (ECOG) performance status (PS) of ≤ 2 and measurable disease. In the dose-expansion cohorts, patients with c-Met positive tumors only were allowed. Of the 91 patients with NSCLC screened with the SP44 antibody, 52 (57%) were c-Met positive with H score ≥ 150. *(32)*

ABBV-399 (Process II) was administered by intravenous infusion at doses ranging from 0.15 to 3.3 mg/kg on Day 1 of a 21-day cycle, with dose escalation using 3+3 design.

FIGURE 1. STUDY DESIGN



Dose-limiting toxicities (DLTs) were determined during the first cycle of treatment and defined as Grade 3 or higher study drug-related events. Maximum tolerated dose (MTD) was defined as the highest ABBV-399 (Process II) dose level at which fewer than 2 out of 6 patients experienced a DLT. Tumor assessments were performed every 2 cycles. Patients in the dose expansion portion were required to have c-Met overexpressing tumors, defined as H-score ≥ 150. A total of 48 patients had been enrolled and had received at least 1 dose of ABBV-399 (Process II) as of August 17, 2016. Table 1 below shows demographics and baseline characteristics of patients, including specific tumor types treated, which included 17 patients with NSCLC. *(33)*

TABLE 1. PATIENT DEMOGRAPHICS

Characteristics	All Patients (N = 48)
Age, median (range), years	65 (40–86)
Gender	
Male	25 (52)
Female	23 (48)
Primary tumor type, n (%)	
Non-small cell lung cancer	17 (35)
Non-squamous	12 (25)
Squamous	4 (8)
Breast cancer	4 (8)
Colon/rectal cancer	9 (19)
Endometrial cancer	2 (4)
Ovarian cancer	4 (8)
Other	12 (25)
Median number of prior therapies (range)	4 (1–15)

The starting dose for monotherapy was ABBV-399 (Process II) 0.15 mg/kg IV every 3 weeks. Table 2 shows patient enrollment and DLTs observed across various dose levels.

TABLE 2. DLTs PER DOSE LEVEL

Dose (mg/kg, IV Q3W)	Patients (n)	DLT
0.15	3	None
0.3	3	None
0.6	3	None
1.2	3	None
1.8	4	None
2.4	6	None
2.7	14	None
3	9	1 febrile neutropenia
3.3	3	1 febrile neutropenia

DLT, dose-limiting toxicity; IV, intravenous; Q3W, every 3 weeks.

Though no MTD was formally identified per protocol definition (highest dose level at which less than 2 of 6 patients experience DLT), febrile neutropenia was a DLT observed in one patient each of the 3 mg/kg and 3.3 mg/kg cohorts. The monotherapy expansion dose of 2.7 mg/kg was chosen for c-Met positive NSCLC based on safety and tolerability, and pharmacokinetics.

Overall, 34 patients (71%) experienced AEs related to ABBV-399 (Process II) and 23 (48%) experienced Grade 3 or higher AEs irrespective of attribution. Table 3 shows the treatment emergent adverse events related to ABBV-399 (Process II). There were no treatment-related deaths due to toxicity noted in this study.

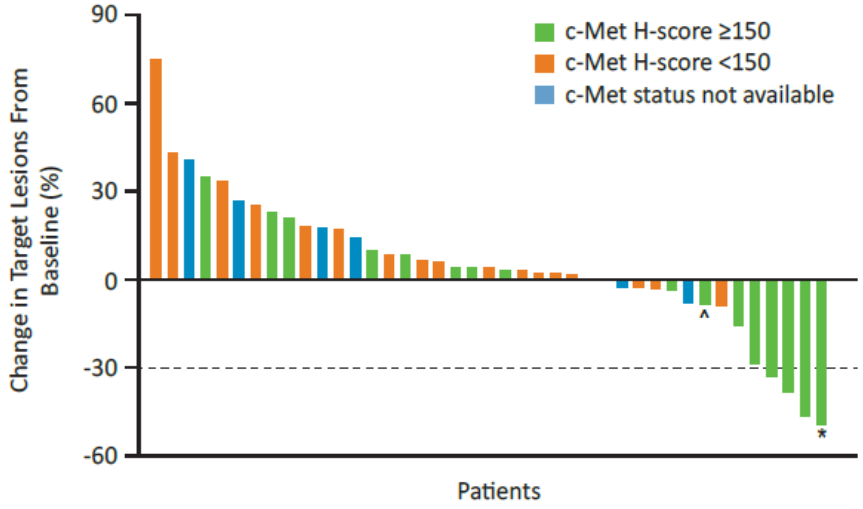
TABLE 3. SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (TEAE)

TEAE	Related to ABBV-399 Any Grade, in ≥5% of Patients, n (%)	Related or Non-related to ABBV-399 Grade ≥3, n (%)
Fatigue	12 (25)	2 (4)
Nausea	11 (23)	0
Neuropathy	7 (15)	1 (2)
Decreased appetite	6 (13)	3 (6)
Vomiting	6 (13)	0
Diarrhea	5 (10)	1 (2)
Hypoalbuminemia	4 (8)	3 (6)
Anemia	3 (6)	5 (10)
Arthralgia	3 (6)	0
Asthenia	3 (6)	0
Constipation	3 (6)	0
Dysgeusia	3 (6)	0
Neutropenia	3 (6)	3 (6)

Dose-proportional increases of area under the curve (AUC) for ABBV-399 (Process II) and total antibody were seen after a single dose with harmonic mean half live for ABBV-399 (Process II) and total antibody of 2-4 days.

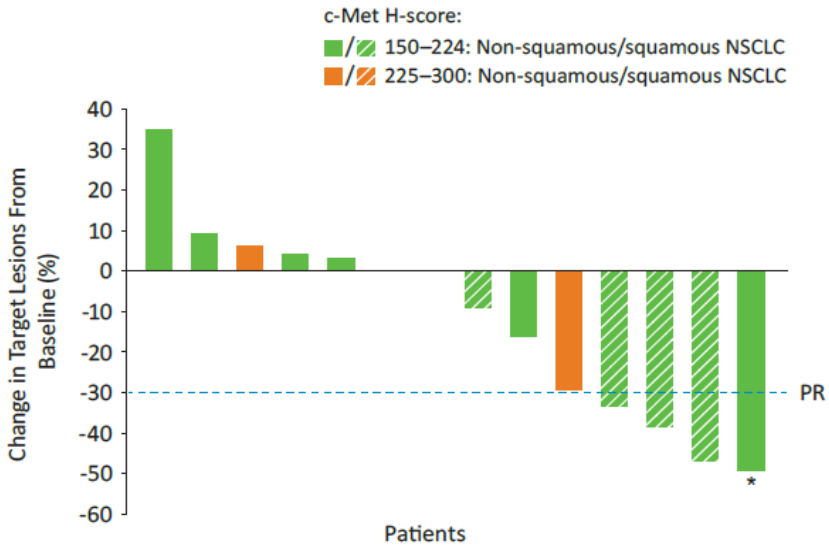
Forty-three patients were evaluable for response (had at least 1 CT scan after start of therapy), with best responses shown in the waterfall plot below, 3/43 (7%) had a partial response, 22/43 (51%) had stable disease, and 18/53 (42%) had progressive disease.

FIGURE 2. WATERFALL PLOT OF BEST PERCENTAGE TUMOR CHANGE FROM BASELINE (N=43)



A total of 16 patients with NSCLC were c-Met positive and received ABBV-399 (Process II) monotherapy at doses ≥ 2.4 mg/kg. Figure 3 shows the waterfall plot for the 14 patients with c-Met positive metastatic NSCLC who were evaluable for response (had at least one CT scan after start of therapy), which shows a partial response in 3/16 patients (18.8%), and stable disease in 6/16 (37.5%) patients. *(34)*

FIGURE 3. BEST PERCENTAGE CHANGE IN TARGET LESIONS FROM BASELINE (%) in c-Met+ METASTATIC NSCLC



NSCLC, non-small cell lung cancer; PR, partial response.
*Patient with tumor shrinkage in target lesions had progressive disease due to new lesion.

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this sub-study, ABBV-399 (Process II) is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instance's submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, requests may be submitted to the CTSU website by completing the CTSU Request for Clinical Brochure.

3.1 ABBV-399 (Process II) (ABT-700-vcMMAE) (NSC 797773)

a. PHARMACOLOGY

Mechanism of Action: ABBV-399 (Process II) is an antibody-drug conjugate comprised of the antibody ABT-700 conjugated to the cytotoxic microtubule inhibitor monomethylauristatin E (MMAE) via a cleavable valine-citrulline (vc) linker. ABT-700 is a humanized recombinant immunoglobulin G kappa that targets a unique epitope of c-Met resulting in blockade of both HGF-dependent and HGF-independent c-Met signaling. ABBV-399 (Process II) is potently cytotoxic to cancer cells with over-expressed c-Met or amplified MET and demonstrates antitumor activity in human tumor xenografts.

b. PHARMACOKINETICS

1. Absorption: ABBV-399 (Process II) is to be administered intravenously.

2. Distribution: In humans, the mean plasma C_{max} of the conjugate, when administered as monotherapy every 3 weeks, ranged from 27.4 to 68 micrograms/mL, the mean AUC_{inf} ranged from 2421 to 5978 microgram●hr/mL. Protein binding is higher in human (67.9-82.2% bound), with concentration dependent binding in human.

3. Metabolism: In humans, MMAE is metabolized primarily by CYP3A4, with minor contributions from CYP2D6.

4. Elimination: In humans, the mean $t_{½}$ ranged from 2.3 to 3.4 days.

c. ADVERSE EFFECTS

1. Adverse Effects

Adverse Events with Possible Relationship to ABBV-399 (Process II)		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
		Febrile neutropenia
	Neutropenia	
GASTROINTESTINAL DISORDERS		
Constipation		
	Diarrhea	

Adverse Events with Possible Relationship to ABBV-399 (Process II)		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
Peripheral edema		
HEPATOBILIARY DISORDERS		
		Hyperbilirubinaemia
INVESTIGATIONS DISORDERS		
	Alanine aminotransferase increased	
		Aspartate aminotransferase increased
		Blood albumin decreased
		Gamma-glutamyltransferase increased
		Neutrophil count decreased
METABOLISM AND NUTRITION DISORDERS		
	Decreased appetite	
		Glucose tolerance impaired
		Hyperglycaemia
	Hypoalbuminemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
NERVOUS SYSTEM DISORDERS		
	Neuropathy peripheral	
		Paraesthesia
		Peripheral motor neuropathy
REPRODUCTIVE SYSTEM DISORDERS		
		Scrotal edema
VASCULAR DISORDERS		
	Hypotension	

2. Pregnancy and Lactation: Fertility, development and reproductive toxicity studies have not been conducted with ABBV-399 (Process II) and safety for women of child-bearing capacity cannot be implied from the existing data. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABBV-399 (Process II).

   Additionally, no studies have been conducted in humans to assess the impact of ABBV-399 (Process II) on milk production, its presence in breast milk, and its effects on the breast-fed child. Because drugs are commonly excreted in human milk and because there is an unknown but potential risk for adverse events in nursing infants, breastfeeding should be discontinued while receiving ABBV-399 (Process II).

All women and males of childbearing potential will be required to employ a highly effective method of birth control, as defined in Section 5.3. This has to be employed for the duration of the study and for six months after last dose of study treatment/drug. Animal studies with ABBV-399 (Process II) show potential effects on female and male reproductive organs. The clinical significance of these changes in humans is unclear.

3. Drug Interactions: Drug-drug interaction studies have not been conducted. According to the pre-clinical studies, the primary metabolite MMAE is eliminated through the hepatic-biliary pathway and is found to be metabolized primarily by CYP3A4 and is a P-glycoprotein substrate. Furthermore, MMAE was found to not be an inhibitor of CYP 1A2, 2B6, 2C8, 2C9, 2C19 and 2D6, but is a quasi-irreversible metabolism-dependent inhibitor of CYP3A4/5 with an inactivation rate constant (kinact) = 0.10 min-1 and an inhibition constant (Ki) = 1.12 µM. In cultured human hepatocytes, MMAE is not an inducer of CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4/5. In vitro, MMAE is not a substrate of OAT1, OAT3, OCT2, OATP1B1 or OATP1B3.

   MMAE is metabolized primarily by CYP3A4. Concomitant use of strong CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole and nefazodone) or P-gp inhibitors has the potential to increase the exposure to MMAE. Use caution and monitor for adverse reactions when concomitantly administering strong CYP3A4 inhibitors with ABBV-399 (Process II). Alternatively, switch strong CYP3A4 inhibitors to other agents if possible.

d. DOSING & ADMINISTRATION

See **S1400K** Section 7.0 Treatment Plan.

Administration: ABBV-399 (Process II) is to be administered intravenously with a 0.2 micron low protein binding in-line filter.

e. HOW SUPPLIED

1. ABBV-399 (Process II) is supplied by AbbVie Inc. and distributed by Pharmaceutical Management Branch (PMB).

2. ABBV-399 (Process II) is a 100 mg lyophilized powder for Injection vial. Agent excipients consist of 12.8 mg histidine, sucrose, and polysorbate 80 at pH 6.0.

f. STORAGE, PREPARATION & STABILITY

1. Storage:
   Store intact or unused vials at 2° to 8°C (36° to 46°F), protect from light. Do not freeze.

   If a storage temperature excursion is identified, promptly return ABBV-399 (Process II) to 2° to 8°C (36° to 46°F) and quarantine the supplies. Submit a completed temperature excursion reporting Form 27 (See Section 18.6) to the drug manufacturer (i.e., AbbVie) for determination of suitability. This form should be submitted within 24 hours after becoming aware of excursion and prior to dosing.

2. Preparation:

a) Reconstitute ABBV-399 (Process II) with 5.2 mL sterile water preservative-free for injection (SWFI) to make a 20 mg/mL final concentration.

b) Gently swirl reconstituted solution; try to minimize bubbles and foaming. Do not shake.

c) Let it sit for at least 5 minutes. If solution continues to foam, let it sit another 10 minutes (small quantity of foam is acceptable).

d) The vial content must be dissolved completely. Visually inspect for undissolved particles.

e) Draw up the calculated amount and inject into 50 mL 0.9% normal saline IV bag. Using pre-filled normal saline IV bags is acceptable.

f) Use only 0.9% normal saline as the diluent.

g) Prime the IV administration set and with 0.9% Normal Saline.

3. Infusion System Selection:

Dose Level (mg/kg)	Infusion System Used
2.7 mg/kg	Dose solution prepared in 50 mL IV bag and infused with infusion pump

Infusion System	Dilution of Reconstituted solution in Infusion Bag
Infusion Pump Dose solution in 50 mL IV bag	1. Determine the total volume of reconstituted solution needed for the dose. 2. Add the calculated reconstituted solution volume directly to the 50 mL normal saline IV bag. Withdrawal of saline from the IV bag prior to addition of the drug is not required. 3. Use standard institutional pharmacy procedures to aseptically add and mix the solutions in the IV bag

Dose preparation calculation example of dose in an infusion bag for ABBV-399 (Process II) for an 80 kg patient, dose level 2.7mg/kg

	Calculation:
Body weight	80 kg
Dose Level	2.7 mg/kg
Reconstituted Solution Concentration	20 mg/mL
Drug Dose:	80 kg x 2.7 mg/kg = 216.0 mg

	Calculation:
Total Volume of Reconstituted Solution (RS) Round to	216.0 mg/20 mg/mL = 10.8 mL 10.8 mL
Vials needed	10.8 mL/5.0 mL= 2.16 → round to the next whole number → 3 vial
Collecting syringe size	10.8 mL → 20 to 60 mL
Infusion System and Saline Dilution	Infusion pump with 50 mL IV bag (for dose levels 2.7 mg/kg) Add 10.8 mL of reconstituted solution to 50 mL 0.9%normal saline IV bag

4. Stability: Shelf-life stability studies of intact ABBV-399 (Process II) vials are ongoing.

   a) The reconstituted vial is stable at 15° to 30°C up to 1 hour.

   b) If prepared IV solution is not used immediately, store the IV solution refrigerated at 2° to 8°C not to exceed 18 hours. When removed from the refrigerator, allow the prepared IV solution to sit at room temperature (15° to 30°C) not to exceed 5 hours (this includes completion time of IV administration).

g. DRUG ORDERING & ACCOUNTABILITY

Confirmation of patient's enrollment is required for initial drug supply.

1. Drug ordering: NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. Study specific supplies will be provided to sites once a patient has been enrolled. Starter supplies will not be provided. 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). The CTEP assigned protocol number (**S1400K**) must be used for ordering all CTEP supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

   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, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

2. Drug Handling and Accountability

   a. 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 Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

   b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

   c. Product Complaint: If there is any suspected quality defect in the AbbVie product or the AbbVie-provided packaging or labeling, the complaint must be reported by completing the Product Complaint Form (Section 18.7) and emailed to AbbVie within 24 hours after becoming aware of the issue.

3. Drug return and/or disposition instruction

   a. All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

   b. Drug Expiration: Stability testing is ongoing. PMB will send a stock recovery letter when notified that the agent is no longer suitable for use.

4. Contact Information and Useful Links

   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 by email: PMBAfterHours@mail.nih.gov.

   - CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
   - NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
   - PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
   - PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
   - CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp
   - CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov

4.0 STAGING CRITERIA

Patients must have Stage IV disease as outlined below (AJCC Cancer Staging Manual, 7th Edition, 2010):

Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a Tumor 2 cm or less in greatest dimension
T1b Tumor more than 2 cm but 3 cm or less in greatest dimension
T2 Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less); Involves main bronchus, 2 cm or more distal to the carina; Invades visceral pleura (PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b Tumor more than 5 cm but 7 cm or less in greatest dimension
T3 Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis
M1a Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion **
M1b Distant metastasis

** Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

5.0 ELIGIBILITY CRITERIA

Patient must meet the eligibility criteria below to be eligible for **S1400K.** If the patient does not meet the sub-study specific eligibility criteria listed in Section 5.1 and Section 5.2 of **S1400K**, but meets the common sub-study criteria listed in Section 5.3 of **S1400K**, submit the **S1400** Request for Sub-Study Reassignment Form for sub-study reassignment. Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center (SDMC) in Seattle at S1400question@crab.org prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

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 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14, 16, 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Sub-Study Specific Disease Related Criteria

a. Patients must be assigned to **S1400K**. The c-Met testing will be performed at a protocol specified central laboratory. **S1400K** biomarker eligibility defined as c-Met positive squamous cell is as follows:

Analyte	Assay	Eligible definition
c-Met	Immunohistochemistry	IHC positive based on Ventana SP44 Assay (H score ≥150)

b. Patients must have pathologically proven squamous cell carcinoma (SCCA) cancer of the lung confirmed by tumor biopsy and/or fine-needle aspiration.

5.2 Sub-Study Specific Clinical/Laboratory Criteria

a. Patients must have received at least one line of a platinum-based chemotherapy regimen and experienced disease progression (in the opinion of the treating physician) on or following this regimen.

b. Patients must not have peripheral edema > Grade 1, or peripheral neuropathy > Grade 1 at the time of sub-study registration.

c. Patients must not have received prior treatment with c-Met pathway inhibitors.

d. Patients must not be taking strong CYP3A4 inhibitors within 7 days prior to sub-study registration, nor plan to take while on protocol treatment and for 14 days after the last dose of study treatment. (see **S1400K** Section 7.2).

e. Patients must have albumin ≥ 3.0 g/dL within 28 days prior to sub-study registration.

f. Patients must have adequate hepatic function as defined by serum bilirubin ≤ Institutional Upper Limit of Normal (IULN) and either ALT or AST ≤ 2.5 x IULN (if both ALT and AST are done, both must be < 2.5 IULN) and gamma-glutamyl transferase (GGT) ≤5 x ULN within 28 days prior to sub-study registration. *[This criterion replaces common eligibility criteria in **S1400K** Section 5.3i]*

g. Patients with extensive metastatic liver disease involving ≥ 50% of the liver in the judgment of the Investigator or sum of longest diameters of RECIST measurable liver lesions ≥10 cm will not be enrolled. *[This criterion replaces common eligibility criteria in **S1400K** Section 5.3i]*

h. Patients must not have a history of interstitial lung disease or of pneumonitis that required treatment with systemic steroids.

i. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures. These patients must agree to use contraception while on study treatment and for up to 6 months after the last dose of study treatment/drug. *[This criterion replaces common eligibility criteria in **S1400K** Section 5.3q]*

j. Patients must agree to have blood specimens submitted for pharmacokinetic analysis as outlined in **S1400K** Section 15.3.

k. Patients must also be offered participation in banking for future use of specimens as described in **S1400K** Section 15.0.

5.3 Common Eligibility Criteria for all Sub-Studies

a. Patients whose biomarker profiling results indicate the presence of an EGFR mutation or EML4/ALK fusion are not eligible. Due to existence of approved therapies the biomarker exclusion rules are as follows:

Gene	Alteration type	Ineligible Alteration
EGFR	Substitution	L858R, T790M, A289V, G719A, S768I, G719C, R108K, G598V, R222C, L62R, L861Q, P596L, V774M
	Indel	non-frame shifting insertions or deletions between amino acids 740 and 780, in exons 19 and 20, transcript NM_005228
	Fusion	None
	Amplification	None
ALK	Substitution	None
	Indel	None
	Fusion	EML4-ALK, CLIP4-ALK, CLTC-ALK, KIF5B-ALK, NPM1-ALK, RANB2-ALK, STRN-ALK, TFG-ALK
	Amplification	None

b. Patients must have progressed (in the opinion of the treating physician) following the most recent line of therapy.

c. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to sub-study registration. Patients must have recovered (≤ Grade 1) from any side effects of prior therapy. Patients must not have received any radiation therapy within 14 days prior to sub-study registration. (See **S1400K** Section 5.3e for criteria regarding therapy for CNS metastases).

d. Patients must have measurable disease (see **S1400K** Section 10.1) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in **S1400K** Section 10.1c. Measurable disease must be assessed within 28 days prior to sub-study registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to sub-study registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to registration. See **S1400K** Section 15.0 and **S1400** Section 18.1c for guidelines and submission instructions for required central radiology review.

e. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study registration. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment and prior to registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.

f. Patients must have fully recovered from the effects of surgery at least 14 days prior to sub-study registration.

g. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

h. Patients must have an ANC ≥ 1,500/mcl, platelet count ≥ 100,000 mcl, and hemoglobin ≥ 9 g/dL obtained within 28 days prior to sub-study registration.

i. *[This common eligibility criteria has been removed as it conflicts with the sub-study specific criteria in **S1400K** Sections 5.2e and 5.2f. A place holder remains to keep consistency across all sub-studies]*

j. Patients must have a serum creatinine ≤ the IULN OR measured OR calculated creatinine clearance ≥ 50 mL/min using the following Cockroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to sub-study registration:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{actual body weight in kg})\ \dagger}{72 \times \text{serum creatinine}\ *}$$

Multiply this number by 0.85 if the patient is a female.

† The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.8 mg/dL.

k. Patients must have Zubrod performance status of 0-1 (see **S1400K** Section 10.4) documented within 28 days prior to sub-study registration.

l. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, and myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see **S1400K** Section 18.4).

m. Patients must not have documented evidence of acute hepatitis or have an active or uncontrolled infection.

n. Patients with a known history of HIV seropositivity:

1. Must have undetectable viral load using standard HIV assays in clinical practice.

2. Must have CD4 count ≥ 400/mcL.

3. Must not require prophylaxis for any opportunistic infections (i.e., fungal, MAC, or PCP prophylaxis).

4. Must not be newly diagnosed within 12 months prior to sub-study registration.

o. Pre-study history and physical exam must be obtained within 28 days prior to sub-study registration.

p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

q. *[This common eligibility criteria has been removed as it conflicts with the sub-study specific criteria in **S1400K** Sections 5.2g. A place holder remains to keep consistency across all sub-studies.]*

r. As a part of the OPEN registration process (see **S1400** Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

s. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).

t. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

6.0 STRATIFICATION FACTORS

Patients will be stratified into two cohorts based on their prior exposure to anti-PD-1/PD-L1 therapy.

The two cohorts are defined as:

Cohort 1 (anti-PD-1/PD-L1 Naive):
Patients who have not been exposed to an anti-PD-1/PD-L1 therapy.

Cohort 2 (anti-PD-1/PD-L1 Exposed):
Patients with a history of anti-PD-1/PD-L1 therapy.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Drs. Saiama N. Waqar or Susanne Arnold at S1400KMedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

7.1 Pre-Medication and Supportive Care

No premedications are needed prior to cycle 1 of ABBV-399 (Process II). Premedication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

7.2 Treatment – **S1400K**

ABBV-399 (Process II)

Agent	Dose	Route	Day	Schedule*
ABBV-399 (Process II)	2.7 mg/kg	IV over 30 ± 10 minutes	Day 1	Every 21 days

* NOTE: A cycle of treatment is 21 days. Disease assessment must occur every 6 weeks (+/- 7 days). Treatment will continue until any of the criteria in **S1400K** Section 7.3 is met.

ABBV-399 (Process II) will be calculated using actual body weight.

a. Administration
ABBV-399 (Process II) is to be administered intravenously with a 0.2 micron in-line filter. ABBV-399 (Process II) will be administered over 30 ± 10 minutes.

b. Prohibited Medications
Patient's medication list such as herbal medicines (e.g., St. John's wort), vitamins and supplements will be reviewed before starting first dose ABBV-399 (Process II) and at each clinic visit. The Treating Investigator will discuss of any potential drug interactions with study participant. (See **S1400K** Section 3.1c3)

Please see **S1400K** Section 18.8 for the patient drug information handout and wallet card for the potential drug interactions.

The following treatments are prohibited throughout the duration of the active treatment phase:

Strong CYP3A inhibitors: Monomethylauristatin E (MMAE) is primarily metabolized by CYP3A4. Co-administration of brentuximab vedotin with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. The concurrent use of CYP3A inhibitors, including but not limited to, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, ketoconazole, fluconazole, voricaonazole, fluvoxamine, and nefazodone, and grapefruit, grapefruit juice or any product containing grapefruit, may change the serum exposures of free MMAE in humans. Therefore, patients are not to receive strong CYP3A4 inhibitors concomitantly with ABBV-399 (Process II).

c. Pharmacokinetic (PK)
On days of clinic visits when PK samples are to be drawn, the collection time of PK blood draws and drug administration must be recorded.

7.3 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Sections 10.2d and 10.2e of **S1400K**). *

* Upon progression, the **S1400** Request for New Sub-Study Assignment Form may be submitted to receive a new sub-study assignment (see **S1400K** Section 14.0).

b. Unacceptable toxicity.

c. Treatment delay for any reason > 42 days (or as noted in **S1400K** Section 8.0).

d. The patient may withdraw from this study at any time for any reason.

7.4 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.5 Follow-Up Period

Patients will be followed until death or 3 years after sub-study registration, whichever occurs first.

Note: Patients who enroll on a new sub-study following progression must continue follow-up on this sub-study, in addition to follow-up on the new sub-study.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov) All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. Dose reductions are allowed on ABBV-399 (Process II). Dose may be reduced in 0.3 mg/kg increments as described below.

b. The maximum dose delay is 42 days for any reason.

c. Dose interruptions and discontinuations are allowed to manage toxicity.

8.3 Dose Modifications – ABBV-399 (Process II)

Dose modifications should be made based on the observed toxicity, related to protocol therapy as summarized in the tables below.

DRUG	DOSE LEVEL	DOSE
ABBV-399 (Process II)	Full	2.7 mg/kg
	-1 Level	2.4 mg/kg
	-2 Level	2.1 mg/kg
	-3 Level	1.8 mg/kg
	-4 Level	Discontinue

a. General Dose Modifications

	Dose Interruption
≥ Grade 3	Unless noted below: Hold protocol therapy until resolution to ≤ Grade 2, treatment may then resume at the next lower dose

b. Dose Interruptions and Management Guidelines for Acute Infusion Reactions

Toxicity	**Dose Interruptions**	**Toxicity Management**
Acute Infusion Reactions		
Appropriate medical therapy and support measures should be available for immediate use in case an acute infusion-related reactions (IRR) occurs. Immediately stop ABBV-399 (Process II) infusion if IRRs occur, administer appropriate medical therapy and observe patient until complete resolution of all signs and symptoms following the guidelines below or Institutional Standards		
Grade 3	Interrupt protocol therapy until resolution of the event. Once symptoms have resolved, continuation of treatment is allowed with at least a 50% reduction of the infusion rate. The rate can be increased in 50% increments every 30 minutes as tolerated until the infusion is completed. The infusion rate can be	• Administer appropriate medical therapy such as acetaminophen/paracetamol , diphenhydramine, H2-blockers, or steroids per Institutional standard of care (SOC). • Consider premedication per institutional standard prior to subsequent doses

Toxicity	Dose Interruptions	Toxicity Management
Acute Infusion Reactions		
	increased as tolerated in subsequent cycles but no faster than 30 (±10) minutes.	
Recurrent Grade 3	Discuss with the Study Chair for possible discontinuation.	
Grade 4 or Anaphylaxis	Permanently discontinue protocol therapy.	

c. Dose Interruptions and Management Guidelines for Neuropathy

Toxicity	Dose Interruptions
Neuropathy	
Grade 2	Protocol therapy may be held if deemed in the best interest of the patient.
Grade 3	Hold protocol therapy until resolution to ≤ Grade 2, treatment may then resume at the next lower dose.
Grade 4	Permanently discontinue protocol therapy.

d. Dose Interruptions and Management Guidelines for Bone Marrow suppression

Toxicity	Dose Interruptions	Toxicity Management
Neutropenia		
Grade 2	Protocol therapy may be held if deemed in the best interest of the patient.	Best medical practice for febrile neutropenia should be instituted immediately including use of antibiotics and hematopoietic growth factors if appropriate
Grade 3	Hold protocol therapy until resolution to ≤ Grade 2.	
Grade 4	Hold protocol therapy until resolution to ≤ Grade 2. Reduce level or prophylax with growth factor support	
Anemia and Thrombocytopenia		
Grade 2	Protocol therapy may be held if deemed in the best interest of the patient.	• Transfusions are allowed per best medical practice • Growth factor support for low hemoglobin and platelets are allowed after Cycle 1 per best medical practice
Grade 3	Hold protocol therapy until resolution to ≤ Grade 2.	
Grade 4	Hold protocol therapy until resolution to ≤ Grade 2. Reduce level or prophylax with growth factor support	

e. Dose Interruptions and Management Guidelines for Hypoalbuminemia and Peripheral Edema

Toxicity	Dose Interruptions
Albumin and Peripheral Edema	
Peripheral edema ≥ Grade 2 Or albumin <2.5 g/dL	If clinically stable (SD, PR or CR), protocol therapy may be held up to 42 days if in the best interest of the patient until resolution to ≤ Grade 1 edema or ≥ 2.5g/dL albumin. Reduce ABBV-399 (Process II) by one dose level if recovery is greater than 2 weeks. If not resolved within 42 days, permanently discontinue protocol therapy.

f. Dose Modifications for Hepatotoxicity

Toxicity	Dose Interruptions
Serum Transaminases (AST/ALT) or GGT:	
Grade 2	No dose modification
Grade 3	Hold protocol therapy until resolution ≤ Grade 2, treatment may then resume at the next lower dose.
Grade 4	Permanently discontinue protocol therapy.
Hyperbilirubinemia:	
Grade 2	Hold protocol therapy until resolution ≤ Grade 1.
Grade 3	Hold protocol therapy until resolution ≤ Grade 1, treatment may then resume at the next lower dose.
Grade 4	Permanently discontinue protocol therapy.

g. Dose Modifications for Pneumonitis

If a patient develops symptoms of treatment-emergent pneumonitis it is recommended that the latest published guidelines are followed to work-up, diagnose, and treat pneumonitis. [35, 36]

Toxicity	Dose Interruptions	Toxicity Management
Pneumonitis		
Grade 1 Asymptomatic	Hold protocol therapy until resolution to baseline. Resume protocol therapy at next lower dose once steroids have been tapered to ≤ 10 mg of prednisone. If not resolved within 42 days, permanently discontinue protocol therapy.	Repeat CT in 3 – 4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3 – 4 weeks. Monitor patient weekly with history and physical examination and pulse oximetry; may also offer CXR. No clinical improvement after 48 – 72 hours, treat as Grade 2.
Grade 2 Symptomatic	Permanently discontinue protocol therapy.	Prednisone 1 -2 mg/kg/d and taper by 5 – 10 mg/wk over 4 – 6 weeks. Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48 – 72 hours of prednisone, treat as Grade 3.
≥ Grade 3	Permanently discontinue protocol therapy.	Empirical antibiotics; methylprednisolone IV 1 -2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4 – 6 weeks, Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy. Patient should be hospitalized for further management.

Abbreviations: ADL = activities of daily living; BAL = bronchoalveolar lavage; CT = computed tomography; CXR = chest x-ray; DLCO = diffusing capacity of lung for carbon monoxide; IV = intravenous; IVG = intravenous immunoglobulin

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Drs. Saiama N. Waqar or Susanne Arnold at S1400KMedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

8.5 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the **S1400K** must be reported to the Operations Office, Study Coordinator and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

		Cycle 1			Cycle 2			Cycle 3			Subse-quent Cycles β	At Off Tx	Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9				
PHYSICAL														
History & Physical Exam	X				X			X			X	X	X	
Weight & Performance Status	X				X			X			X	X	X	
Disease Assessment Ω	X							XΩ			XΩ		XΩ	
Toxicity Notation					X			X			X	X	Xđ	Xđ
Smoking Status Assessment	X											X		
LABORATORY														
CBC Ø	X	X ℘			X			X			X	X	Xđ	Xđ
Total Testosterone (males only)	X	X ℘			X			X			X	X	Xđ	Xđ
CMP ¥, GGT, Magnesium, Phosphate	X	X ℘			X			X			X	X	Xđ	Xđ
X-RAYS AND SCANS														
CT or MRI for Disease Assessment Ω	X							XΩ			XΩ		XΩ	
Brain CT/MRI	X										X♦		X♦	
SPECIMEN SUBMISSION														
Tissue for Banking														X§
Blood for Banking †	X†				X†			X†			X†			X†
Blood for PK, ADA, nAb α		X			X			X			X α			
TREATMENT														
ABBV-399 (Process II) (21-day cycle)		X			X			X			X			

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in **S1400K** Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines on the allowed protocol visits/treatment window as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Footnotes for Calendar 9.0:

Ω CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.3 of **S1400K**) must be repeated every 6 weeks (± 7 day window) for the first year regardless of treatment delays, then every 3 months until disease progression and discontinuation of protocol treatment. The 6 weeks should start from Cycle 1 Day 1. Submit scans as outlined in Section 14.0 and Section 15.0 of **S1400K.**

♦ Pre-study Brain CT/MRI is required 42 days prior to sub-study registration per Section 5.3. If the patient has brain metastases at baseline, scans must use the same modality as baseline and be repeated every 12 weeks (+/- 7 days) while on treatment.

℘ If the pre-study tests are obtained within 14 days prior to treatment, the tests need not be repeated on Cycle 1 Day 1.

Ø CBC (Complete Blood Count) must include Hb, WBC, differential, Platelets

¥ CMP (Comprehensive Metabolic Panel) must include Glucose, Calcium, Albumin, Creatinine/ Calc CrCl, ALT, AST, Bilirubin

β During continued treatment, items marked under physical and laboratory should be performed prior to every subsequent cycle, unless otherwise noted. Disease assessments and image submission are to take place every 6 weeks (± 7 days). Treatment and evaluation will continue until any one of the criteria in Section 7.3 of **S1400K** is met.

Δ After off treatment prior to progression, patients should be followed by repeating indicated studies every 3 months or as clinically indicated until progression. Disease assessment should continue every 3 months until progression.

√ After off treatment after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of 3 years from date of sub-study registration.

§ With patient's consent, an additional research biopsy within 1 month after the time of first progression among patients who had a response to ABBV-399 (Process II) (in the opinion of the treating physician) must be collected (see Section 15.0 of **S1400K)**.

ɗ Assessments should continue until resolution of all acute adverse events.

† With patient's consent research blood draws will be collected at pre-study and on Weeks 4, 7, and 10, and at first progression after study treatment (see Section 15.0 of **S1400K)**.

α Blood samples for pharmacokinetic analysis will be collected at 2 time points on Day 1 of Cycles 1, 2, 3 and 4. The predose sample will be collected ≤ 30 minutes prior to dosing and the post-dose sample will be collected at 1 hour (+/- 15 minutes) after dose (see Section 15.0 of **S1400K**).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters.

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Note: Lymph nodes that have a short axis < 1.0 cm (10 mm) are considered non-pathological and should not be recorded or followed. 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 non-measurable as are previously radiated lesions that have not progressed.

c. Notes on measurability

1. For CT and MRIs, 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.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a 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, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

   NOTE REGARDING DIAGNOSTIC QUALITY:

   CT – Computed Tomography Imaging

   In order for a CT to be of diagnostic quality to be used in determining measurable disease, the slice thickness needs to match the protocol Section 10.0.

Recommended Scan mode:	Multi-detector and/or helical
Contrast Enhancement:	IV and oral contrast unless contraindicated
Slice Section thickness:	maximum 5mm, preferable 2.5mm or less
Slice Increment:	continuous or overlapping sections; no gaps
Imaging Region:	Thoracic inlet through adrenal glands (and appropriate scans if disease exists elsewhere)
Image Matrix size:	512 × 512 or better
Image Reconstruction / Filter:	Institutional standard

If a CT scan is performed with a slice thickness greater than 5 mm then lesions must be twice the slice thickness. If any PET/Spiral CT is used at baseline where the CT is of diagnostic quality, follow-up scans can be done by a spiral CT.

If any PET/Conventional CT is used at baseline where the CT is of diagnostic quality, follow-up scans can be done by conventional CT.

Institutions will have to submit radiology reports documenting that the CT used in PET/CT is of diagnostic quality. No other methods of assessments are interchangeable.

MRI – Magnetic Resonance Imaging
MRI can be performed using a 1.5 or 3.0 T field strength. If a MRI is performed instead of a CT, the MRI can be performed according to institutions clinical standard of care protocols with slice thickness of no more than 5mm (in transverse).

If an MRI scan is performed with a slice thickness greater than 5 mm, then lesions must be twice and above the slice thickness.

PET/CT – Positron Emission Tomography with FDG
When a FDG PET/CT is performed, the emission scans should be started in the range of 60 – 75 min after FDG injection, otherwise use your institution protocols. It is necessary for follow up scans that they are performed in an **identical way** to the baseline with the same PET/CT scanner and a variation in timing of no more than +/- 10 min. Preferably, schedule the patient for both baseline and follow-up scans at the same time of day (AM or PM) to improve reproducibility.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. 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.

5. If a target lesion becomes very small, some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. 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. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in the appropriate sub-study specific section.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression:** One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

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

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to

be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least six weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

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

10.5 Time to Death

From date of sub-study registration (or date of screening/pre-screening registration if patient never enrolls in a sub-study) to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.6 Investigator-Assessed Progression-Free Survival (IA-PFS)

From date of sub-study registration to date of first documentation of progression assessed by local review or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.7 Progression-Free Survival by Central Review

From date of sub-study registration to date of first documentation of progression assessed by central review or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.8 Duration of Response (DoR)

From date of first documentation of response (CR or PR) to date of first documentation of progression assessed by local review or symptomatic deterioration (as defined above), or death due to any cause among patients who achieve a response (CR or PR). Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Objective and Biomarker Prevalence

The primary objective is to evaluate the response rate (confirmed and unconfirmed, complete and partial) for ABBV-399 (Process II) in patients with c-Met-positive lung squamous cell carcinoma.

This study will use the Phase II design from the Option for Biomarker-driven sub-studies described in Design #2 (see Section 11.5 of **S1400K**) among patients with tumors defined to be c-Met positive. Full details of the design are provided here.

The accrual goal is 40 eligible patients. Assuming that 10% of patients who are enrolled will be ineligible retrospectively, the total accrual goal to the Phase II study is 44 patients.

The expected prevalence of c-Met positivity is 30%. However, after accounting for the prevalence of other sub-study biomarkers, the expected frequency of patients assigned to **this sub-study** is 28% (based on simulation using the randomization ratios as defined in **S1400K** Section 11.4). The expected average monthly accrual rate is 4 patients per month with an anticipated duration of accrual of 11 months.

11.2 Statistical Design

A design with 91% power and 1-sided 0.05 level type I error would require 40 eligible patients to rule out an objective response rate (ORR) of 15% or less if the true ORR is 35% or greater.

11.3 Analysis Plan

An interim analysis will take place when 20 patients are evaluable for response. Evaluability for response is defined based on RECIST 1.1 and accrual is to remain open while patients are being evaluated for response. However, if 20 or more eligible patients for the first interim analysis have made it to their second disease assessment and the required number of responses to continue past that interim analysis has not been observed, then the accrual to the cohort will be placed in temporary closure until the response status for all patients in the interim analysis set is known.

This interim analysis will only evaluate early stopping for futility. If two or fewer responses are observed, this will be considered evidence of futility and the recommendation will be to close the study for lack of evidence of efficacy of the regimen.

If the study continues to full accrual, the observation of at least 10 responses will be considered evidence to rule out the null hypothesis of a 15% response rate.

Response rates and associated confidence intervals will be calculated. OS, IA-PFS, and DoR will be estimated using the method of Kaplan-Meier. The Brookmeyer-Crowley method will be used to calculate confidence intervals for median times. With 40 patients, ORR and toxicity rates can be estimated within 16% with 95% confidence. Any toxicity with at least 5% prevalence has at least an 87% chance of being observed.

Analysis of IA-PFS will take place when 31 IA-PFS events have been observed. A key secondary objective is an assessment of median IA-PFS (mPFS). If the observed ORR is less than 25%, but the mPFS is at least 4.5 months, this may be considered sufficient evidence to continue to the follow-on Phase III. With 40 patients, this design has 87% power to rule out a mPFS of 3 months or less, if the true mPFS is 6 months, at the 0.05 1-sided level. This is based on using Brookmeyer-Crowley test of null of 3 month mPFS versus alternative of 6 month mPFS with 10 months of accrual and 6 months' follow-up. The observation of an mPFS of at least 4.6 months would be considered evidence to rule out an mPFS of 3 months or less.

11.4 Randomization Ratio

Sub-study eligibility will be based on the results of biomarker analysis at screening. Patients with a single "positive" biomarker will be assigned to the associated sub-study. Patients with no "positive" biomarkers will be assigned to the non-match sub-study. Patients eligible for multiple sub-studies based on the results of the biomarker analysis will be randomized to sub-study assignment. The randomization ratio will be the ratio of the prevalence of the biomarkers allowing for a greater likelihood of assignment to the study with the lower prevalence (e.g. for two markers with 5% and 15% prevalence, the randomization ratio will be 3:1 in favor of the lower prevalence biomarker; for three biomarkers with 5%, 10% and 15% prevalence, the ratio will be 6:3:2, and so on). However, the ratio will be bounded such that no biomarker sub-study has more than a 4-fold chance of assignment. As sub-studies are closed or new sub-studies added the randomization ratio will be modified based on the sub-study biomarker prevalence for the actively accruing studies. Initial estimates of sub-study biomarker prevalence from sources outside this study will be used to determine the assumed prevalence of the sub-study

biomarkers for determination of these sub-study assignment randomization ratios. If a specific sub-study biomarker prevalence estimate is substantially different from initial estimate, the prevalence estimates may be updated at most once during the conduct of the associated sub-study.

11.5 Phase III Feasibility and Follow-on Study Considerations

A follow-on randomized Phase III trial will be considered as feasible if the expected duration of accrual is approximately 3 years or less. Upon 75% accrual to the Single Arm component, the accrual rate to the sub-study will be assessed and if the average monthly accrual rate is at least 2-3 patients per month, depending on the designed total study accrual the Phase III will be considered feasible. If the conditions for continuation at the Phase II are met and it is feasible to accrue to a Phase III, then a follow-on randomized Phase III may be initiated. Evaluation of the feasibility of a Phase III will commence around 75% accrual to the Phase II. The SoC arm of the Phase III study will not be defined until this time. The follow-on Phase III would be submitted as an amendment to this protocol.

Accrual to a Phase III Trial is Not Feasible

If the Phase II data meets the definition of a positive Single Arm Phase II as defined in Section 11.2 (above) but it is determined that a Phase III trial is not feasible, accrual to the Single Arm Phase II may be expanded beyond 40 patients. If the ORR is at least 35% (the Phase II alternative hypothesis) then the Phase II expansion will continue accrual for up to an additional 12 months or up to an additional 20 patients (whichever is reached first).

12.0 DISCIPLINE REVIEW

Radiology Review

a. To ensure the highest standards and consistency between different centers, all scans for disease assessment (baseline, interim and end of treatment scans) must be submitted to the National Cancer Institute's National Clinical Trials Network (NCTN) Imaging and RT Quality Assurance Service Core (IROC) in Ohio for centralized review (see **S1400K** Section 15.6).

b. Centralized review will be performed by 3 radiology experts. The scans will be submitted to IROC. IROC will transmit the scans to the reviewers who will transmit the results to the SWOG Statistics and Data Management Center.

c. Details of submission of scans to IROC for centralized review and on the central review process are listed in **S1400K** Section 15.6 and **S1400** Section 18.1c.

13.0 REGISTRATION GUIDELINES

See Section 13.0 of **S1400** for registration guidelines.

13.1 Registration Timing

Patients must plan to begin treatment within 10 calendar days after sub-study registration.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see **S1400K** Section 14.3 for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

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

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (http://swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF **S1400K** REGISTRATION, SUBMIT:

S1400K Onstudy Form

S1400K Eligibility Criteria Form

Smoking Status Assessment Form

Baseline Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at baseline (NOTE: Upload reports via the Source Documentation: Baseline form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease at baseline as specified in **S1400K** Section 15.0.

b. IF PATIENT CONSENTS, SUBMIT SPECIMENS:

Specimens as specified in Section 15.0 of **S1400K**

c. WITHIN 7 DAYS AFTER EACH CYCLE (CYCLE = 21 DAYS) OF TREATMENT, SUBMIT**:**

S1400K Treatment Form

S1400K Adverse Event Form *

S1400K Laboratory Values Form

For Cycle 1 only: submit the **S1400K** Pre-Treatment Laboratory Values Form.
*For the last cycle of treatment, include all adverse events occurring within 30 days after the last treatment.

d. WITHIN 14 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION (see **S1400K** Section 9.0 for Disease Assessment Schedule), SUBMIT:

Follow-Up Tumor Assessment Form (RECIST 1.1) documenting results of assessment

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in **S1400K** Section 15.0.

e. WITHIN 7 DAYS OF DISCONTINUATION OF TREATMENT, SUBMIT:

Off Treatment Notice documenting reasons for off treatment

Smoking Status Assessment Form

Forms specified in Section 14.4c.

f. ONCE OFF TREATMENT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1400K** REGISTRATION, THEN AT THE END OF YEAR 3 FROM SUB-STUDY REGISTRATION SUBMIT:

Advanced NSCLC Follow-Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported).

Note: Patients who enroll on a new sub-study following progression must continue follow-up on this sub-study, in addition to follow-up on the new sub-study, in addition to follow-up on the new sub-study. (See Section 14.4i)

g. WITHIN 7 DAYS OF PROGRESSION/RELAPSE, SUBMIT:

Site(s) of Progression or Relapse Form

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in **S1400K** Section 15.0.

h. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information and **S1400K** End of Study form. In addition, if the patient was still on protocol treatment, submit materials specified in **S1400K** Section 14.4e or if patient was no longer on treatment, submit a final Advanced NSCLC Follow-Up Form.

i. Data Submission FOR PATIENTS WHO HAVE PROGRESSED AND WISH TO REGISTER TO A NEW SUB-STUDY:

WITHIN 7 DAYS OF PROGRESSION/RELAPSE:

Submit the **S1400** Request for New Sub-Study Assignment Form under **S1400** in Rave®. Continue follow-up on **S1400K** per Sections 9.0. See Section 14.6 of **S1400** for additional data submission requirements following request for new sub-study assignment

j. WITHIN 28 DAYS OF DECLARATION OF LOST TO FOLLOW-UP OR MAXIMUM FOLLOW-UP, OR A MAXIMUM FOLLOW-UP OF 3 YEARS:

S1400K End of Study Form

S1400K Lost to Follow-Up form (lost to follow-up only)

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

See **S1400** Section 15.1 for SWOG Specimen Tracking System (STS) instructions.

15.2 Correlative Studies and Banking (Optional for Patients)

Specimens for correlative studies and banking (submitted to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) are considered optional for the patient:

a. With patient's consent, specimens must be collected and submitted as follows:

1. Peripheral Blood:

Specimens must be collected at the following times.

- Pre-study (after consenting and prior to treatment initiation on sub-study)
  Note: If a patient provided blood at pre-screening or screening (see Section 15.3 of **S1400**) and registration to the sub-study within 42 days from registration, then no additional pre-study sample is required.
- Weeks 4, 7, 10.
  Note: Patients that go off treatment are not required to continue to submit specimens.
- First progression (defined in Section 10) after study treatment

Collect approximately 8-10 mL of blood in EDTA tubes. Blood should be processed within one hour after venipuncture. If immediate processing within this time frame is not possible, then refrigerate (4°C) blood in EDTA tubes. The approximate time from collection to processing should be recorded as part of the patient's source documentation. EDTA tubes must be centrifuged at 800 x g for 10 minutes at 4˚C for the collection of plasma. [Note: Sites that do not have a refrigerated centrifuge should spin at room temperature and ensure specimens are placed on ice (regular, not dry) immediately after being drawn and process rapidly.] Using a pipette, transfer the plasma to a 15-mL centrifuge tube. Remove the buffy coat layer (thin white or gray layer of cells between the plasma and red blood cells) and split between two appropriately labeled 2-mL cryovials.

Spin the plasma in the 15-mL centrifuge tube at 800 x g for an additional 10 minutes. Avoiding any pelleted material, pipette the plasma into labeled cryovials at 0.5 ml aliquots. Plasma must be clear before freezing; no cells or debris should be present.

Plasma and buffy coat vials must be placed upright in a -80˚C freezer immediately after processing to ensure long-term viability.

Frozen plasma and buffy coat specimens should be shipped to the SWOG Biospecimen Bank on dry ice.

2. New Biopsy of Tumor at Time of Progression Among Responders (CR or PR) to ABBV-399 (Process II):

A new biopsy must be collected from patients who responded to protocol treatment (in the opinion of the treating physician) and then experienced disease progression. Biopsies will be used for molecular analysis of molecular characteristics associated with mechanisms of resistance. New biopsy should be either bronchoscopy/surgical biopsy or CT guided biopsy.

Specimens should be collected at the following time point: within one month after progression.

Process the biopsy as FFPE material. The minimum requirement is a block or 12 unstained, charged, and unbaked 4-5 micron sections.

FFPE specimens (block or slides) should be shipped to the SWOG Biospecimen Bank at ambient temperature.

b. Specimen Submission

Samples for multiple patients may be shipped in batches to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201, at least every 3 months if not more frequently.

Specimen collection and submission instructions can be accessed on the SWOG Biospecimen Resources webpage (https://www.swog.org/member-resources/biospecimen-resources).

c. Specimen collection kits are not being provided for this submission; sites must use institutional supplies.

15.3 ABBV-399 conjugate, total antibody and MMAE Pharmacokinetic (PK), anti-drug antibody (ADA) and neutralizing anti-drug antibody (nAb) Analysis (Required)

Serum specimens must be submitted for ABBV-399 conjugate, total antibody and MMAE PK, ADA, and nAb analysis from patients registered to **S1400K**.

a. Specimens must be submitted at the timepoints listed below. Collection and submission instructions are outlined in **S1400K** Section 15.3b.

Collection Table:

Collections	Tube(s)		Cycle 1		Cycle 2		Cycle 3		Cycle 4	
PK	3mL	10mL	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose
ADA	3mL									
nAb	3mL									

One pre-dose and one post-dose samples of peripheral blood will be collected at Day 1 of Cycles 1-4. The pre-dose sample must be collected within 30 minutes prior to dosing, the post-dose sample must be collected at 1 hour (+/- 15 minutes)

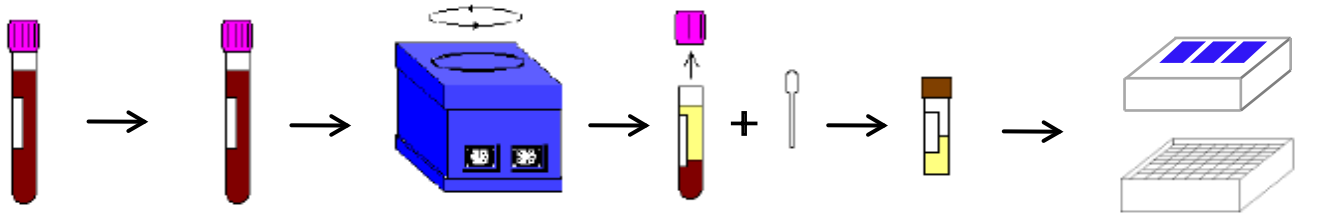
after dose. The collection time of PK blood draws and drug administration must be recorded. All submitted specimens must be labeled with the treatment protocol number, SWOG patient number, patient initials, time point, and date of specimen collection, specimen number and/or specimen type.

b. **Specimen Collection and Submission Instructions**

- For each PK, ADA, and nAb sample collect 10 mL (or 3*3mL) whole blood for serum harvest (serum RED top tube non-gel).
- Immediately invert tube 5 - 8 times.
- Allow blood to clot at room temperature for 30 to 60 minutes until a dense clot is formed.
- Centrifuge at room temperature - approximately 1100-1600 x g for approximately 10-15 min to separate serum.
- Transfer serum into appropriately labeled cryovial tubes (approximately 0.7 mL each) using a plastic pipette. To avoid contamination, always use a new transfer pipette for each sample, and do not remove the serum near the precipitate.
- Freeze at –20°C or colder within 2 hours of collection. Do not place cryovials on wet ice.
- Store samples at –20°C or colder until shipment on dry ice.

Samples for multiple patients can be shipped in batches, at least every 3 months if not more frequently, to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201. (see **S1400K** Section 18.2 for additional details).

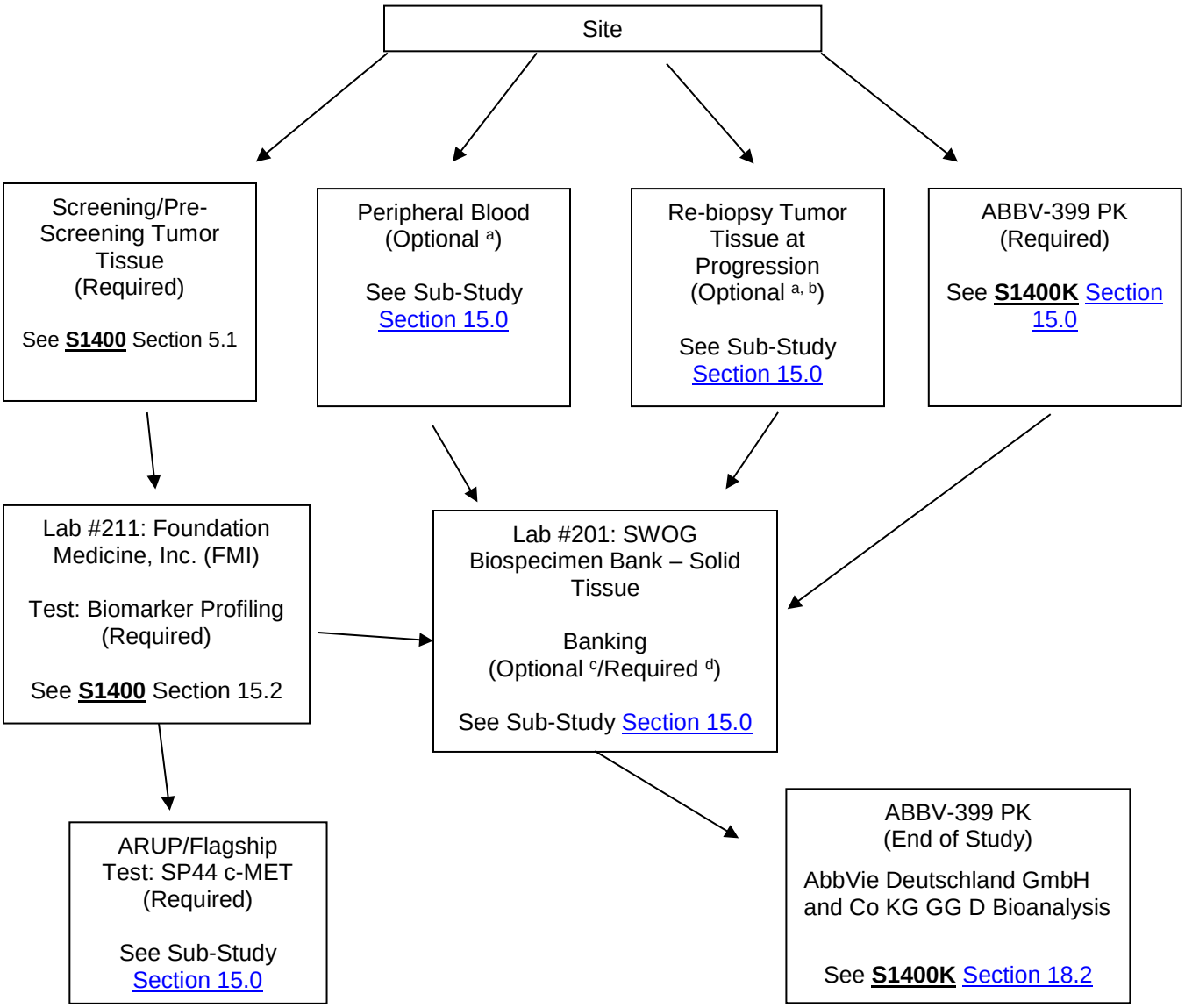
Figure 1: Blood PK, ADA, nAb Sample Processing



15.4 Future Translational Medicine Studies

At the end of this study, left over tissue from the screening NGS testing will be kept for future translational medicine **S1400K** studies. The specimens will be kept until there are no additional sub-studies for the patient to enroll in or the tissue is used up, whichever happens first. If the patient consented to future testing in **S1400**, any leftover tissue will remain at the SWOG Biospecimen Bank for future exploratory analysis.

15.5 Specimen Flow Diagram



a With patient's consent.
b Among patients who initially responded to protocol treatment.
c Remaining tissue will be sent to the SWOG Biospecimen Bank-Solid Tissue, Myeloma and Lymphoma Division, Lab #201, for use of the Translational Medicine studies within any sub-study the patient is enrolled in. SWOG Biospecimen Bank will prepare and ship the required specimens to the appropriate laboratory. The specimen will be kept until there are no additional sub-studies for the patient to enroll in or the tissue is used up, whichever happens first. With patient's consent, any leftover tissue will remain at the SWOG Biospecimen Bank for future exploratory analysis.
d PK specimens will be sent to the SWOG Biospecimen Bank-Solid Tissue, Myeloma and Lymphoma Division, Lab #201and kept until the end of the study in which it will be shipped to AbbVie Deutschland GmbH.

15.6 Radiology Review (Required)

CT, PET/CT, and/or MRI images must be locally read and interpreted by the local site radiology service. Imaging exams must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for central data collection and quality control (QC) check as well as retrospective central review.

a. CT, PET/CT, and/or MRI images must be submitted to IROC Ohio for central review at the following timepoints:

- Baseline
- Every 6 weeks for the first year, then every 3 months until progression and treatment discontinuation

All study participants must have a CT (or MR or PET/CT) exam prior to sub-study entry. Participants must then undergo additional imaging every 6 weeks for the first year regardless of treatment delays, then every 3 months until disease progression and discontinuation of protocol treatment. The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (see **S1400K** Section 10.1c). Each exam should be performed per **S1400** Section 18.1c. IROC will perform a QC of the imaging exams.

Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinical appropriate considerations.

Central review of scans will not be triggered if the study will not be submitted to the FDA for FDA approval of the investigational therapy. Central review of scans will be triggered only if deemed necessary for FDA evaluation. A detailed description of the central radiology PFS review, including image acquisition parameters and image submission instructions, can be found in **S1400** Section 18.1c.

b. TRIAD Digital Image Submission

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

1. TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Ohio. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

- Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account (see **S1400** Section 13.2).

- To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

2. TRIAD Installations:

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

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

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

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in **S1400K** Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program 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 to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1, as applicable.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is ABBV-399 (Process II). If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] ABBV-399 (Process II):

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

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

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events (if applicable) are found in Section 16.1f.

Expedited AE reporting timelines are defined as:

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

- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND:**

1. Group-specific instructions.

Supporting Documentation Submission - Within 5 **calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

a. Printed copy of the first page of the CTEP-AERS report
b. Copies of clinical source documentation of the event
c. If applicable, and they have not yet been submitted to the SWOG Statistics and Data Management Center, copies of Off Treatment Notice and/or Notice of Death.

For this protocol, all second and secondary malignancies require expedited reporting via CTEP-AERS. Please refer to Section 16.1.g for further information.

g. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. Reporting Serious Adverse Events to AbbVie

SWOG Operations will forward reports of all serious adverse events and events of overdose (defined as any dose above the protocol-specified dose of ABBV-399 [Process II]) **within 24 hours** of NCI/CTEP receipt of serious adverse event documentation from the study site.

i. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss:** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions** SOC.

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal:** Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth. A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal"** under the **General disorders and administration** SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

NOTE: When submitting CTEP-AERS reports for “Pregnancy, “Pregnancy loss”, or “Neonatal loss”, the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the “Description of Event” section of the CTEP-AERS report.

The Pregnancy Information Form is available at: http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

17.0 BIBLIOGRAPHY

1 Ma PC, Maulik G, Christensen J, et al: c-Met: structure, functions and potential for therapeutic inhibition. Cancer Metastasis Rev 22:309-25, 2003.

2 Park M, Dean M, Kaul K, et al: Sequence of MET protooncogene cDNA has features characteristic of the tyrosine kinase family of growth-factor receptors. Proc Natl Acad Sci U S A 84:6379-83, 1987. PMCID: PMC2999079

3 Sadiq AA, Salgia R: MET as a possible target for non-small-cell lung cancer. J Clin Oncol 31:1089-96, 2013.

4 Birchmeier C, Gherardi E: Developmental roles of HGF/SF and its receptor, the c-Met tyrosine kinase. Trends Cell Biol 8:404-10, 1998.

5 Liu SY, Mok T, Wu YL: Novel targeted agents for the treatment of lung cancer in China. Cancer 121 Suppl 17:3089-96, 2015.

6 Ma PC, Jagadeeswaran R, Jagadeesh S, et al: Functional expression and mutations of c-Met and its therapeutic inhibition with SU11274 and small interfering RNA in non-small cell lung cancer. Cancer Res 65:1479-88, 2005.

7 Gherardi E, Birchmeier W, Birchmeier C, et al: Targeting MET in cancer: rationale and progress. Nat Rev Cancer 12:89-103, 2012.

8 Waqar SN, Morgensztern D, Sehn J: MET Mutation Associated with Responsiveness to Crizotinib. J Thorac Oncol 10:e29-31, 2015. PMCID: PMC4408879

9 Ma PC, Jagadeeswaran R, Jagadeesh S, et al: Functional expression and mutations of c-Met and its therapeutic inhibition with SU11274 and small interfering RNA in non-small cell lung cancer. Cancer Res 65:1479-88, 2005.

10 Edelman M, Spigel, D., O'Byrne, K., Mok T., Mocci, S., Yu, W., Paton, V., Paz-Ares, L: The prevalence of MET expression by immunohistochemistry (IHC) in the MetLung (OAM4971g) trial: a randomized, placebo-controlled, phase III study with erlotinib + onartuzumab (MetMab) vs erlotinib + placebo in patients with previously treated non-small cell lung cancer Journal of Thoracic Oncology 8:S2-S1348, [Abstract MO12.07], 2013.

11 Gao J, Aksoy BA, Dogrusoz U, et al: Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 6:pl1, 2013. PMCID: PMC4160307

12 Sadiq AA, Salgia R: MET as a possible target for non-small-cell lung cancer. J Clin Oncol 31:1089-96, 2013.

13 Camidge DR, Pao W, Sequist LV: Acquired resistance to TKIs in solid tumours: learning from lung cancer. Nat Rev Clin Oncol 11:473-81, 2014.

14 Mok TS, Geater SL, Su WC, et al: A Randomized Phase 2 Study Comparing the Combination of Ficlatuzumab and Gefitinib with Gefitinib Alone in Asian Patients with Advanced Stage Pulmonary Adenocarcinoma. J Thorac Oncol 11:1736-44, 2016.

15 Spigel DR, Ervin TJ, Ramlau RA, et al: Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. J Clin Oncol 31:4105-14, 2013. PMCID: PMC4878106

16 Spigel DR, Ervin TJ, Ramlau RA, et al: Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. J Clin Oncol 31:4105-14, 2013 PMCID: PMC4878106

17 Scagliotti G, von Pawel J, Novello S, et al: Phase III Multinational, Randomized, Double-Blind, Placebo-Controlled Study of Tivantinib (ARQ 197) Plus Erlotinib Versus Erlotinib Alone in Previously Treated Patients With Locally Advanced or Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol 33:2667-74, 2015

18 Waqar SN, Morgensztern D, Sehn J: MET Mutation Associated with Responsiveness to Crizotinib. J Thorac Oncol 10:e29-31, 2015. PMCID: PMC4408879

19 Zhang Y, Wang W, Wang Y, et al: Response to Crizotinib Observed in Lung Adenocarcinoma with MET Copy Number Gain but without a High-Level MET/CEP7 Ratio, MET Overexpression, or Exon 14 Splicing Mutations. J Thorac Oncol 11:e59-62, 2016.

20 Klempner SJ, Borghei A, Hakimian B, et al: Brief Report: Intracranial Activity of Cabozantinib in MET exon14 Positive NSCLC with Brain Metastases. J Thorac Oncol, 2016.

21 Wang J, Anderson MG, Oleksijew A, et al: ABBV-399, a c-Met Antibody Drug Conjugate that Targets Both MET Amplified and c-Met Overexpressing Tumors, Irrespective of MET Pathway Dependence. Clin Cancer Res, 2016.

22 Strickler JH, LoRusso P, Yen C-J, et al: Phase 1, open-label, dose-escalation, and expansion study of ABT-700, an anti-C-met antibody, in patients (pts) with advanced solid tumors. ASCO Meeting Abstracts 32:2507, 2014.

23 Strickler JH, LoRusso P, Yen C-J, et al: Phase 1, open-label, dose-escalation, and expansion study of ABT-700, an anti-C-met antibody, in patients (pts) with advanced solid tumors. ASCO Meeting Abstracts 32:2507, 2014.

24 Kang Y-K, LoRusso P, Salgia R, et al: Phase I study of ABT-700, an anti-c-Met antibody, in patients (pts) with advanced gastric or esophageal cancer (GEC). ASCO Meeting Abstracts 33:167, 2015.

25 Strickler JH, LoRusso P, Yen C-J, et al: Phase 1, open-label, dose-escalation, and expansion study of ABT-700, an anti-C-met antibody, in patients (pts) with advanced solid tumors. ASCO Meeting Abstracts 32:2507, 2014.

26 Wang J, Anderson MG, Oleksijew A, et al: ABBV-399, a c-Met Antibody Drug Conjugate that Targets Both MET Amplified and c-Met Overexpressing Tumors, Irrespective of MET Pathway Dependence. Clin Cancer Res, 2016.

27 Edelman M Spigel D, O'Byrne K, Mok T, Mocci S, Yu W, Paton V, Paz-Ares L. The prevalence of MET expression by immunohistochemistry (IHC) in the MetLung (OAM4971g) trial: a randomized,

placebo-controlled, phase III study with erlotinib + onartuzumab (MetMab) vs erlotinib + placebo in patients with previously treated non-small cell lung cancer Journal of Thoracic Oncology 8:S2-S1348, [Abstract MO12.07], 2013.

28 Edelman M Spigel D, O'Byrne K, Mok T, Mocci S, Yu W, Paton V, Paz-Ares L. The prevalence of MET expression by immunohistochemistry (IHC) in the MetLung (OAM4971g) trial: a randomized, placebo-controlled, phase III study with erlotinib + onartuzumab (MetMab) vs erlotinib + placebo in patients with previously treated non-small cell lung cancer Journal of Thoracic Oncology 8:S2-S1348, [Abstract MO12.07], 2013.

29 Watermann I, Schmitt B, Stellmacher F, et al: Improved diagnostics targeting c-MET in non-small cell lung cancer: expression, amplification and activation? Diagn Pathol 10:130, 2015. PMCID: PMCA4517562

30 Angevin E, Kelly K, Heist R, Morgensztern D, Weekes C, Bauer TM, Ramanathan K, Nemunaitis J, Fan X, Olyaie O, Parikh A, Reilly E, Afar D, Naumovski L, Strickler J. First-in-human phase 1, dose-escalation and -expansion study of ABBV-399, an antibody-drug conjugate (ADC) targeting c-Met, in patients (pts) with advanced solid tumors. Annals of Oncology 27:371P, 2016.

31 Watermann I, Schmitt B, Stellmacher F, et al: Improved diagnostics targeting c-MET in non-small cell lung cancer: expression, amplification and activation? Diagn Pathol 10:130, 2015. PMCID: PMC4517562

32 Angevin E, Kelly K, Heist R, Morgensztern D, Weekes C, Bauer TM, Ramanathan K, Nemunaitis J, Fan X, Olyaie O, Parikh A, Reilly E, Afar D, Naumovski L, Strickler J. First-in-human phase 1, dose-escalation and -expansion study of ABBV-399, an antibody-drug conjugate (ADC) targeting c-Met, in patients (pts) with advanced solid tumors. Annals of Oncology 27:371P, 2016.

33 Angevin E, Kelly K, Heist R, Morgensztern D, Weekes C, Bauer TM, Ramanathan K, Nemunaitis J, Fan X, Olyaie O, Parikh A, Reilly E, Afar D, Naumovski L, Strickler J. First-in-human phase 1, dose-escalation and -expansion study of ABBV-399, an antibody-drug conjugate (ADC) targeting c-Met, in patients (pts) with advanced solid tumors. Annals of Oncology 27:371P, 2016.

34 Angevin E, Kelly K, Heist R, Morgensztern D, Weekes C, Bauer TM, Ramanathan K, Nemunaitis J, Fan X, Olyaie O, Parikh A, Reilly E, Afar D, Naumovski L, Strickler J. First-in-human phase 1, dose-escalation and -expansion study of ABBV-399, an antibody-drug conjugate (ADC) targeting c-Met, in patients (pts) with advanced solid tumors. Annals of Oncology 27:371P, 2016.

35 Brahmer JR, Lacchetti C, Schneider BR, et al. Management of immune-related adverse events in patients with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-68.

36 Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Supplement 4):iv264-iv266

18.0 APPENDIX

18.1 Qualifying SP44 anti-C-MET Immunohistochemistry (IHC) Assay

a) Assay Description

c-Met overexpression has been reported in NSCLC, with varying prevalence depending on method of evaluation and scoring. For example, c-Met positivity has been reported in 24.4%-29% of patients with squamous cell lung cancer. *(1,2)* Though c-Met protein overexpression is common in NSCLC, strategies thus far to select patients based on overexpression for treatment with anti-c-Met monoclonal antibodies and small molecule inhibitors of c-Met have failed to show clinical benefit in large randomized studies. ABBV-399 (Process II) is a based on a different mechanism of action, i.e. to use the c-Met expression to deliver the toxin, and thus has a potential to improve the quality of life and outcome of patients with squamous cell lung cancer, based on its tolerability and preliminary efficacy.

The c-MET IHC assay will be part of **S1400** screening, to identify patients for registration to **S1400K**. The assay is currently being employed in AbbVie's Phase I study to select c-MET positive patients. The assay utilizes the CONFIRM c-MET SP44 rabbit monoclonal Ab from Ventana, intended for IVD use (cat #790-4430, Lot G08106). The IHC cutoff for positivity in the current Phase I study is an H-score of ≥150 membrane staining. In squamous histology NSCLC, about 30% of patients are c-MET positive is per the literature (Genentech) with SP44 antibody IHC.

b) Scoring of Tumor Specimens

The staining will be scored as H-score (membrane and cytoplasmic)
Scoring paradigm below.

Scoring of patient samples will be performed by an MD Pathologist at Flagship. The pathologist will determine the percentage of tumor at each intensity (0, 1+, 2+, 3+) and multiply it by the percentage of tumor at each intensity.

H-score = Σ (%Intensity Score x Proportion Score for each tier)
Range: 0-300

Example: 30% 3+ / 40% 2+ / 30% 1+
([30x3] + [40x2] + [30 x 1]) = 200 H-score

For purposes of patient selection for **S1400**, tumors are considered c-Met positive if they contain ≥ 150 H-score.

c) Tumor Screening

For SP44 assay testing, no on-site processing of specimens will be required. The tissue specimens collected for **S1400** biomarker profiling will be used. All **S1400** tissue specimens are shipped to Foundation Medicine, Inc (FMI). For patients with tumor blocks, FMI will prepare two (4-5 micron) unstained, charged, and unbaked FFPE slides, per patient. The slides will be shipped to ARUP for staining within 2 calendar days of FMI receiving the specimens.

d) Specimens Shipped to ARUP for Staining

ARUP Laboratories
500 Chipeta Way
Salt Lake City, UT 84108
Phone: (801) 583/2787 x2166
Email: amy.sandoval@aruplab.com

Contact Name: Amy Sandoval

e) Specimens Shipped to Flagship for Scoring

Clinical sample testing is done centrally at Flagship Biosciences, Inc. Flagship is CLIA-certified reference laboratory complying with applicable standards.

Flagship Biosciences Inc.
7575 W 103rd Ave, Suite 100
Westminster, CO 80021
Phone: 303/325-5894

f) Test Results

The ARUP and Flagship process will be conducted in approximately 5 calendar days from receiving the specimens from FMI. Flagship will send the c-MET IHC report back to FMI. FMI will compile the results into a single report to be submitted to the SWOG Statistics and Data Management Center (SDMC). C-Met results that are not received by FMI within 12 calendar days from the date of site submission, may not be included in the report to the SWOG SDMC. Results will be proved to FMI when they become available.

g) References

1 Edelman M Spigel D, O'Byrne K, Mok T, Mocci S, Yu W, Paton V, Paz-Ares L. The prevalence of MET expression by immunohistochemistry (IHC) in the MetLung (OAM4971g) trial: a randomized, placebo-controlled, phase III study with erlotinib + onartuzumab (MetMab) vs erlotinib + placebo in patients with previously treated non-small cell lung cancer Journal of Thoracic Oncology 8:S2-S1348, [Abstract MO12.07], 2013.

2 Watermann I, Schmitt B, Stellmacher F, et al: Improved diagnostics targeting c-MET in non-small cell lung cancer: expression, amplification and activation? Diagn Pathol 10:130, 2015.

18.2 ABBV-399 Conjugate, Total Antibody and MMAE Pharmacokinetic (PK) Analysis

a. Objective

To characterize evaluate the pharmacokinetics (PK) of ABBV-399 (Process II) conjugate, total antibody and MMAE in patients with squamous cell lung cancer and explore PKPD relationships of ABBV-399 in patients with squamous cell lung cancer.

b. Assay Description

Serum concentrations of ABBV-399 (Process II) conjugate, total antibody and MMAE and relative titers of ABBV-399 ADA will be determined using validated methods at or under the supervision of the Bioanalysis Department at AbbVie. Any additional analytes may be analyzed using non-validated methods. Serum samples collected for ABBV-399 and ABBV-399 ADA analysis may be used for future assay development or validation activities. ABBV-399 nAb samples upon request may be used for the analysis of neutralizing anti-drug antibodies.

c. Statistical Plan

Serum concentrations of ABBV-399 conjugate, total antibody and MMAE and relative titers of ABBV-399 ADA will be determined using validated methods at or under the supervision will be tabulated for each subject, and summary statistics will be computed for each sampling time. Additional exploratory PKPD analyses will be performed if useful and appropriate.

d. Laboratory Plan

AbbVie Deutschland GmbH and Co KG will serve as the central laboratory for performing the ABBV-399 PK analysis in patients who register to **S1400K**.

ABBV-399 (Process II) conjugate and total antibody PK specimens will be analyzed by AbbVie Deutschland GmbH and Co KG.

AbbVie Deutschland GmbH and Co KG
GG D Bioanalysis
Sample Receiving Team
Annette Hafner, Thomas Heueck
Building 12, Room 324
Knollstrasse 50
67061 Ludwigshafen, Germany

Phone: +49 621 589 2911
Fax: +49 621 589 2309
Email: gprd_lupet@abbvie.com

ABBV-399 MMAE PK specimens will be analyzed by AbbVie Lake County.

e. Specimen Shipments

For PK collection, sites will process specimens as outlined in **S1400K** Section 15.3 and will ship specimens to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201. Prior to shipping, samples are stored at -20ºC or colder until ready for shipment. At the end of the study, the SWOG Biospecimen Bank will ship the specimens to AbbVie Deutschland GmbH and Co KG.

18.3 Instructions for the SWOG Biospecimen Bank

Frozen Plasma and Buffy Coat
The SWOG Biospecimen Bank will receive frozen plasma and buffy coat at up to 5 time points per patient. Upon receipt, the Bank will accession, barcode, and bank specimens in a -80°C freezer.

Formalin-fixed Paraffin-Embedded (FFPE) Tissue
The SWOG Biospecimen Bank will receive FFPE specimens as either blocks or slides/sections at up to 2 time points per patient. Upon receipt, the Bank will accession, barcode, and bank specimens at ambient temperature.

At the end of the study, the Bank will receive notification from the SWOG Statistics and Data Management Center to distribute specimens for testing.

Tumor Tissue for Immunotherapy Resistance Analysis
The SWOG Biospecimen Bank will send FFPE slides from consented patients for immunotherapy resistance analysis.

The Bank will send 5-10 unstained slides. If an FFPE tissue block was received, then the SWOG Biospecimen Bank will process up to 10 unstained slides (4 micron, charged, unbaked) to send for testing.

Retrospective c-MET testing
The SWOG Statistics and Data Management Center will provide the SWOG Biospecimen Bank with the list of patient specimens. The Bank will prepare two (4-5 micron) unstained, charged, and unbaked FFPE slides, per patient. The slides will be shipped to ARUP for staining. All specimens must be entered and tracked using the online SWOG Specimen Tracking System (STS).

a. Specimens Shipped to ARUP for Staining
ARUP Laboratories
500 Chipeta Way
Salt Lake City, UT 84108
Phone: (801) 583/2787 x2166
Email: amy.sandoval@aruplab.com
Contact Name: Amy Sandoval

b. Specimens Shipped to Flagship for Scoring
Clinical sample testing is done centrally at Flagship Biosciences, Inc. Flagship is CLIA-certified reference laboratory complying with applicable standards.

Flagship Biosciences Inc.
7575 W 103rd Ave, Suite 100
Westminster, CO 80021
Phone: 303/325-5894

c. Test Results
The ARUP and Flagship process will be conducted in approximately 14 calendar days from receiving the specimens from the Bank. Flagship will send the c-MET IHC report back to SWOG Statistics and Data Management Center (SDMC).

18.4 New York Heart Association Classification

Class	Cardiac Symptoms	Need for Limitations	Physical Ability Additional Rest*	To Work**
I	None	None	None	Full Time
II	Only moderate	Slight or occasional	Usually only slight	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.

18.5 Monitoring Plan

For information on Lung-MAP Monitoring Plan, please refer to **S1400** Section 18.0.

18.6 Storage Temperature Excursion Reporting Form 27

For information on ABBV-399 (Process II) storage temperature excursion, please refer to **S1400K** Section 3.1 and submit this form.

Form 27
Form Version: 08Apr2015

Please email or fax this form to the appropriate location per information provided below:

Location	Email Address	Fax
US	gdsmtempex.us@abbvie.com	+1 847 785 8101
Germany	gdsmtempex.de@abbvie.com	+49 621 589 68960

Number of pages: ☐ Faxed ☐ Emailed

Site Staff:

- Temperature excursions should be reported to AbbVie within 24 hours after becoming aware of excursion and prior to dosing
- Please notify the Principal Investigator to suspend dispensing affected product. AbbVie will contact you regarding acceptability of the investigational product.

Protocol Number:	Site Number, if applicable:
Principal Investigator:	Country:
Site Phone Number:	
Site Fax Number:	
Contact Name:	
Lot Number(s):	
Kit Number(s): (Alternatively, attach list of affected kit numbers.)	
Excursion Details (Complete All Text Fields Below)	
Duration of Excursion:	hours
Temperature recorded:	highest: °Celsius Lowest: °Celsius
Start Date of Excursion (DD-MMM-YYYY):	
End Date of Excursion (DD-MMM-YYYY):	
Has any of the affected product been dispensed following the temperature excursion?	No Yes – if so, specify kit number dispensed.
Please specify date resupply is needed (DD-MMM-YYYY):	
Reason for Temperature Excursion:	appropriate Storage - specify for 'other':
Additional Information:(Optional)	

Reporter Printed Name: _____

Signature:_____Date (DD-MMM-YYYY): _____

For AbbVie Internal Use Only: Temperature Excursion Assessment				
Investigational Product is acceptable. ☐				
Investigational Product is **not** acceptable. Investigational Product should be returned/destroyed according to instructions provided by AbbVie. ☐				
Comments:				
Printed Name :		Signature:	Date: (DD-MMM-YYYY)	
QA Printed Name :		QA Signature:	Date: (DD-MMM-YYYY)	

18.7 Product Complaint Form

Q-03-07-004-F04
Version 2.0

Product Complaint Form

Please fill out this Product Complaint Form and send it to the following email address: RD_PQC_QA@abbvie.com

GENERAL INFORMATION		
Is an emergency resupply required? ☐ YES ☐ NO **If yes, please inform your AbbVie monitor or CRA immediately.**		
Study Number:		
Investigator/Site information Name: _____ Address: _____ Country: _____		
Site Number/RIC Number:		
1	Site Awareness Date :	
2	Date complaint reported to AbbVie:	
3	Date of occurrence/onset (When did this happen):	
4	Describe complaint: (Provide a detailed description of the complaint including what the subject was doing when the complaint occurred) _____ _____	
Details regarding the drug product/medical device		
5	Product Name:	
6	Serial/lot number of drug product or medical device:	
7	Kit number of drug product or medical device: (List all if more than one)	
8	Subject Number:	
9	Was the dose administered? (if YES, complete questions 10-14; if NO, proceed to question 15)	☐ No ☐ Yes
10	Dose administered (i.e. quantity, volume):	
11	Units of dose administered:	
12	**Who administered the medication?** ☐ Investigator ☐ Study Nurse ☐ Patient ☐ Other:	
13	Was the administration performed per protocol? (if NO, please explain)	☐ No ☐ Yes
14	Was the subject/caregiver trained? (if NO, please specify)	☐ No ☐ Yes
15	Were there administration problems prior to this event? (if YES, please specify)	☐ No ☐ Yes
16	Did interruption of study medication occur? (if YES, please specify)	☐ No ☐ Yes

Q-03-07-004-F04
Version 2.0

Product Complaint Form

Details regarding the staff member reporting the complaint to enable AbbVie to follow-up and information gathering regarding complaint		
17	Role: ☐ Physician ☐ Nurse ☐ Pharmacy ☐ Hospital/institution ☐ Coordinator ☐ Other:	
18	Name:	
19	Site address:	
20	Work email address:	
21	Work phone number:	
Details regarding the complaint		
22	Were any tests done to verify condition? (if YES, specify)	☐ No ☐ Yes
23	Is the complaint drug product/medical device available and quarantined? (if NO, explain)	☐ No ☐ Yes
24	Can representative pictures be provided?	☐ No ☐ Yes
25	How many units with suspected issue? (i.e. 1 bottle, 10 tablets, 1 pump, 1 tube, etc.):	
26	Was medication shipment damaged? If YES, provide Clinical Supplies Shipping Request (CSSR).	☐ No ☐ Yes
27	Was the tamper evident seal of the kit intact when it arrived at the site?	☐ No ☐ Yes
28	Did the site personnel or subject notice any other unusual attributes with the kit/bottle/packaging? (if YES, specify)	☐ No ☐ Yes
29	Any additional comments regarding the complaint that are considered relevant and were not collected in any of the sections above? _____ _____	
30	Was this complaint associated with an adverse event? If YES, adverse event serial number:	☐ No ☐ Yes

18.8 PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **ABBV-399 (Process II).** This clinical trial is sponsored by SWOG. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

ABBV-399 (Process II) interacts with certain enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzyme in question is CYP3A4. ABBV-399 (Process II) is broken down by this enzyme and may be affected by other drugs that strongly inhibit or induce this enzyme.
- The transport protein in question is **P-gp**. ABBV-399 (Process II) is moved in and out of cells/organs by P-gp transporter protein and may be affected by inhibitors or inducers of P-gp.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

ABBV-399 (Process II) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

ABBV-399 (Process II) must be used very carefully with other medicines that use certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 3A4, and transport proteins P-gp." These characteristics may change how ABBV-399 (Process II) or other medicine works in your body.

- Be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking ABBV-399 (Process II).
- Avoid using herbal medicines or herbal tea.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **ABBV-399 (Process II).** This clinical trial is sponsored by SWOG. ABBV-399 (Process II) may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Avoid ingesting grapefruit, grapefruit juice and Seville oranges and avoid herbal tea/medicines while on trial.

- ABBV-399 (Process II) may interact with CYP 3A4 and transport protein P-gp, and must be used very carefully with other medicines that interact with this enzyme and transport protein.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 3A4 and transport protein P-gp."
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.