LUNG-MAP

S1400 Frequently Asked Questions

Protocol:

Please note that patients are only eligible after progression on frontline platinum-containing chemotherapy, pre-screening is not an option. Refer to the Memorandum dated 08/01/14.

Eligibility:

1. **If a patient received front-line carboplatin-taxol then switched to Taxotere alone prior to progression, would he/she be eligible for S1400?**

   Taxotere (docetaxel) is the standard of care control arm on four of the five current sub-studies and is prohibited as a prior treatment on these sub-studies. The patient would only be potentially eligible for one of the five sub-studies, **S1400E**, and only if the patient's tumor biomarker is a match for it.

2. **We have a patient registered to S1400 who has not yet been registered for his/her assigned sub-study. The patient was found to have brain metastases today on an MRI and will receive treatment for the metastases. S1400 Section 5.2d states that metastases must have been locally treated and asymptomatic for at least 28 days following treatment. This timing requirement will not be met because of the assigned sub-study timing requiring patients to be registered within 28 days after the sub-study assignment is received. After the 28 days, can the patient register to the assigned sub-study in this circumstance?**

   The patient is ineligible for the sub-study if timing exceeds 28 days after sub-study assignment per **S1400** Section 5.2d:

   "Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study randomization. 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 28 days following treatment
   AND
   (2) Patient has no residual neurological dysfunction and has been off corticosteroids for at least 14 days prior to randomization."

   To ensure patients with metastases are asymptomatic at least 28 days after treatment per Section 5.2d, we recommend obtaining the brain CT/MRI scan prior to sub-study assignment (institutions are currently being notified of sub-study assignments at approximately 14 days after shipping the tissue to FMI.)

   The requirement of a maximum 28 days from sub-study assignment notification to sub-study registration will be amended to 42 days in the upcoming protocol revision. Until then, the current eligibility requirements must be followed. If your patient is already past the 28 days currently required, should you decide not to register the patient to the sub-study, please submit the Notice of Intention Not to Register Form and follow the patient on **S1400** as outline in Section 14.4.

Tissue:

1. **On my patient's confirmation of registration to S1400 and on my institution's Expectation Report, there are expectations for "Tissue Submission/For biomarker profiling" and "Tissue Submission/H&E slide (See Section 15.1)." I've shipped my tissue for biomarker profiling per protocol Section 15.1 and I've logged and shipped it in the SWOG Specimen Tracking System (STS) per the protocol Activation notice dated June 15, 2014. What is the "Tissue Submission/H&E slide (See Section 15.1)" expectation that is still appearing on my Expectation Report?**

   S1400 protocol Section 15.1 specifies that an H&E-stained slide should be submitted along with the tissue for biomarker profiling. Submit the H&E-stained slide to Foundation Medicine, Inc. (FMI) per the protocol Activation notice dated 6/15/14. The H&E slide must be logged and shipped in the SWOG STS system in order to resolve the related expectation.

2. **What is the "Local Pathology Review Form" that is appearing on my list of unresolved expectations?**

   The "Local Pathology Review Form" is posted on the CTSU website (https://www.ctsu.org) and the **S1400** Protocol Abstract page on the SWOG (https://swog.org/) website . It should be completed and signed by the interpreting pathologist to confirm tissue adequacy and then uploaded to "**S1400** Source Docs: Baseline" form in Rave as type "Other Report".

   This form is not currently listed in **S1400** Section 14.4a, but must be submitted within 7 days of S1400 registration. Refer to the **S1400** Memorandum distributed on 8/01/14 for more information. Section 14.4a will be updated to reflect this required form in the next protocol revision.

3. **It has been 10 days since we registered the patient to S1400 and submitted the tissue, but we have not yet received the sub-study assignment results. Is there any way to expedite the results for sub-study assignment once the tissue has been submitted to Foundation Medicine, Inc. (FMI)? The patient needs to start treatment as soon as possible.**

   Unfortunately, we are unable to expedite the results and sub-study assignment. The turn-around time has been averaging 14 days from tissue shipment to the results/assignment email notification.

4. **Due to an issue in patient scheduling, we were unable to complete the required imaging per common sub-study eligibility Section 5.2c before the 28 day window for sub-study registration ended and did not register the patient to the sub-study. Can we re-screen the patient to reset the 28 day window?**

   No, patients cannot be re-screened. Please refer to the following points in Section 13.5 of the protocol:

   13.5a: Patients must meet all eligibility requirements.
   13.5c: Registrations may not be cancelled.

   Since the patient does not meet criterion 5.2c which requires that measurable disease is assessed within 28 days prior to sub-study registration and non-measurable disease is assessed within 42 days prior to sub-study registration, the patient is ineligible. Should you decide not to register the patient to the sub-study, please submit the Notice of Intention Not to Register form and follow the patient on **S1400** as outlined in Section 14.5.

Image Submission - TRIAD:

Please note that central submission of CT/PET Images via TRIAD will be added when funding and logistical details have been finalized. Sites should keep all CT/PET Images obtained prior to this addition to be submitted retrospectively at the time the submission guidelines are added to the protocol.

Sub-Study Specific:

1. **May our site use our institutional standard pre-medications for docetaxel infusions?**

   Yes, patients randomized to docetaxel should pre-medicate with dexamethasone beginning 24 hours prior to docetaxel administration. Dexamethasone may be administered per local institutional guidelines. Recommended dose is 8mg BID beginning 24 hours prior to docetaxel. Refer to protocol Section 7.0 of **S1400 A – D** for more information.

2. **S1400A: The protocol specifies that the MEDI4736 drug is to be administered through a peripheral vein; can a central line be used?**

   Yes, a central line may be used for patients who are randomized to receive **S1400A** Arm 1: MEDI4736.

3. **S1400C: The S1400C Study Calendar indicates follow-up procedures performed in the middle of cycles. Is this correct?**

   Due to the nature of this study, the **S1400C** calendars were created so that procedures would be conducted on a specific week regardless of the cycle length across all sub-studies and to also include sub-study specific tests/procedures required for the investigational/Standard of Care drug for the specific sub-study. For example, the CT scans and disease assessment are conducted every 6 weeks on all sub-studies. This allows for a comparison between each of the biomarker-driven sub-studies. **S1400C** has a 4 week cycle length and therefore the 6 week follow-up schedule is challenging for this study. Procedures are conducted on Day 1 of each cycle and every 6 weeks. Even with the allowed +/- 7 day window for disease assessment, clinic visits will not all line up on Day 1 of each cycle.

   Assessing patients consistently across all sub-studies every 6 weeks will ensure the study will obtain good data at the same time points for all patients.

4. **S1400E**: **The dose modification for rilotumumab in Section 8.0b of protocol version 5/20/14 is unclear concerning SGOT/SGPT. Can you clarify the dose modification requirements for rilotumumab?**

   Protocol version 05/20/14, Section 8.0b, is currently written as follows:
   Criteria for Discontinuation of Rilotumumab, Due to Potential Hepatotoxicity
   Rilotumumab should be discontinued permanently if:
   - Total bilirubin > 2x upper limit of normal (ULN) or INR > 1.5 (except if related to warfarin therapy)
   - AND Baseline SGOT or SGPT value SGOT or SGPT elevation < ULN > 3x ULN
   - AND no other cause for the combination of laboratory abnormalities is immediately apparent.

   The protocol will be clarified as follows:
   Criteria for Discontinuation of Rilotumumab, due to Potential Hepatotoxicity
   Rilotumumab should be discontinued permanently and removed from protocol therapy if:
   - Total bilirubin > 2x upper limit of normal (ULN) or INR > 1.5 (except if related to warfarin therapy)
   - AND Baseline ALT ~~SGOT~~ or AST ~~SGPT~~ value elevated to ≥ *Grade 2*
   - AND no other cause for the combination of laboratory abnormalities is immediately apparent.

5. **S1400A, S1400B, and S1400D Model Informed Consent forms do not document how long after stopping a medication a woman of child bearing potential must use contraception. Can you please provide the requirements?**

   The companies have indicated contraception for a woman of child bearing potential must be used after the completion of treatment for at least:
   S1400A - MEDI4736: 90 days
   S1400B - GDC-0032: 7 months
   S1400D - AZD4547: 4 weeks

Funding:

1. **I do not see funding information for sub-study specific procedures. Is funding provided?**

   There are currently 6 funding memos for **S1400** and the sub-studies. The funding memo for **S1400** outlines the funding available for patients registered to the first registration step. The sub-study funding memos outline the specific funds available for each sub-study. The funding memos are posted on the CTSU (https://www.ctsu.org) and SWOG (https://swog.org/) websites under each sub-study abstract page.

2. **Is funding provided for the biopsies at screening and progression?**

   In the event archival tumor tissue is not available at screening, a new fresh biopsy is required. This tissue will determine the sub-study assignment based on the biomarker result. The screening biopsy is considered a research procedure, therefore, not covered by insurance. The study provides funding for the screening CT image guided biopsy or bronchoscopy biopsy. The reimbursement information for the screening biopsy is available in the **S1400** Funding Memorandum.

   An optional biopsy may also be performed at the time of progression for patients on the investigational arms and funding will also be provided for CT image guided biopsy or bronchoscopy biopsy. The funding for the optional biopsy at progression is available on the sub-study specific funding memorandums.

3. **Is funding provided to cover the cost of the study-mandated ophthalmologic assessment in S1400D?**

   The funding for the ophthalmologic assessment and the OCT (optical coherence tomography) scan is noted on the funding memos for **S1400D**.

   The ophthalmologic assessment consists of:
   - Visual acuity (best corrected) including near and far vision
   - Amsler grid
   - Schirmer's test
   - Corneal examination
   - Slit lamp examination
   - Fundoscopy

   The OCT scan is the diagnostic tool for RPED (retinal pigment epithelium detachment) and is considered to be an additional cost to the ophthalmologic assessment that will be reimbursed by the study. The study estimates a patient will have 6 ophthalmologic assessments and 4 OCT scans based on the PFS (progression-free survival) of 4 months. If a patient requires additional exams and scans the study will provide the additional funding. For additional information see **S1400D** Section 8.0 and Section 9.0.