FDA REGISTRATION TRIALS: A DATA MANAGEMENT PERSPECTIVE

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Overview

- Registration Trials
- Practical Implications
- Data Coordinator Review
- Centralized Monitoring
- Resources
- Examples from S1404 and S1400

What is a registration trial?

- A trial that is branded "registration" means that it is planned to move forward for review by the FDA as either a new agent, or to expand the labeling for new indications
- Currently enrolling SWOG registration trials:
  - S1400 & sub-studies S1400G, S1400I (Lung-MAP)
  - S1404 (Melanoma)
  - S1418 (Breast)
  - S1605 (GU)

Practical Implications

- In general, data procedures are the same
- Increased data submission requirements
  - More detailed adverse event reporting
  - Concomitant medication forms
  - Increased reporting of laboratory values
- Radiology image submission (TRIAD)
- Increased attention to EDC and source documentation
  - Data coordinators, centralized monitoring, auditing

Practical Implications

- Protocol-specific training requirements
  - Slide shows or instructional videos
- SWOG audits are done more frequently
- Data reporting requirements might be adjusted to gather additional information for further analysis, or in reaction to a changing medical landscape
- Increased potential for an FDA audit

Data Coordinator Review

- Higher frequency of review; more data fields to review
- Common queries from Data Coordinators:

S1404
T and N staging (Onstudy)
Total no. of nodes removed (Onstudy)
PK/ADA collection data (Treatment)
Reporting period dates (Treatment, AEs)
Dosing units (Treatment)
Lab value units (Laboratory Values)
Source documentation upload

S1400 Sub-Study
TNM staging (Onstudy)
Reporting period dates (Treatment, AEs)
Treatment doses and dates (Treatment)
Adverse event dates (AE: Report)
Lab dates (Laboratory Values)
Lab value units (Laboratory Values)
Source documentation upload

- Rave also generates queries for missing information
  - Important to wait until the end of a cycle to enter data

Centralized Monitoring Component

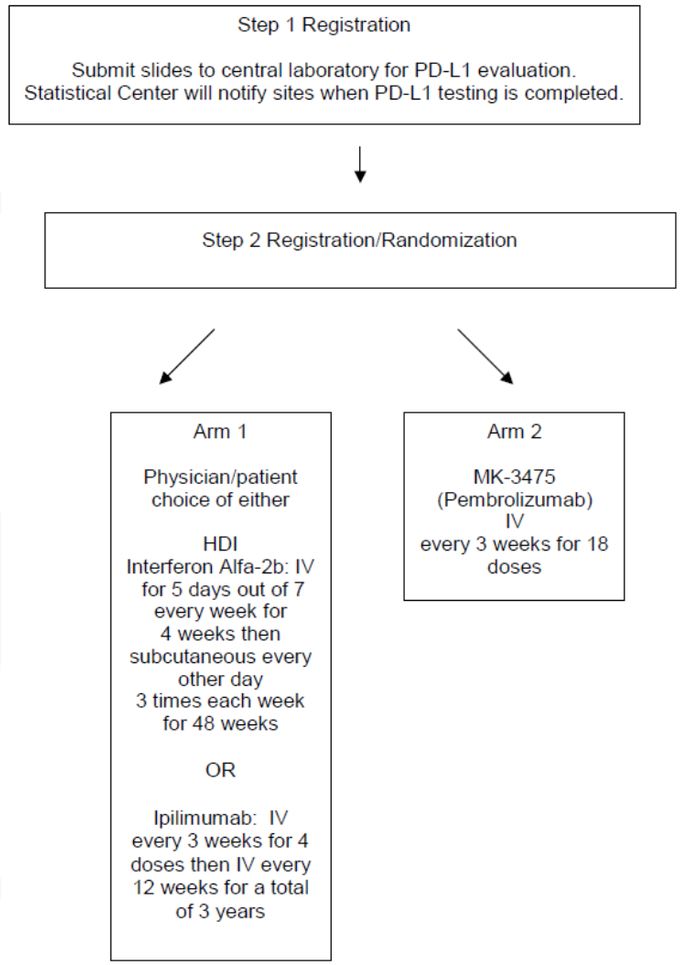
- Source documentation submission for *(typically)* the first two patients randomized
  - Requires the upload of auditable source documents into a Source Document Verification (SDV) form in Rave
  - Examples of documents included in the review are:
    - Signed Informed Consent
    - Specimen Submission documentation
    - First two courses of treatment and adverse event source documents
- Monitors also review timeliness of data submission in Rave

Helpful Resources

- Your SWOG Data Coordinator!
  - **S1400question@crab.org**
  - **MelanomaQuestion@crab.org**
  - (206) 652-2267
- Auditors & monitors – here to help!
- Documents available on the protocol page at SWOG.org and CTSU.org
- Reports and Data Quality Portal (DQP)

S1404: A Phase III Randomized Trial Comparing Physician/Trial Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma

- Activated 10/15/15
- Accrual Goal of 1,378
  - 1,036 patients have been registered to Step 1
  - 934 patients have been randomized to Step 2



S1404 PD-L1 Tissue Requirement

- Local Pathology Review Form
  - Tissue submission is a requirement, so this form must be completed and signed prior to Step 1 Registration
- Shipping Requirements
  - 5 Unstained Slides – blocks are not accepted
  - Slides must be shipped refrigerated, NOT ambient
  - ID on the slides must match exactly the ID on either the pathology report or Local Pathology Review Form
- Additional Questions to complete in the Specimen Tracking System

S1404 Medical History Form

- Collects information about patient's medical history prior to the start of treatment
- All conditions should be reported, even if deemed not clinically significant
- Unknown days and months are acceptable; however a valid year is required
  - A non-conformant error is generated if the year is unknown
  - Reminder: non-conformant errors prevent data from being submitted, which results in overdue expectations!

S1404 Medical History Form

	Collection Date of Medical History			15 Feb 2016	
	Does the patient have any medical history to report?			Yes	
	Enter all relevant medical history below. If the condition is present at the time of registration, please indicate that it is "Ongoing". Explain any missing dates in the comments section.				
#	Verbatim Term	Start Date	Stop Date	Ongoing?	
1	Type II Diabetes	1 Mar 2007		☑	
2	Heart Murmur	UN UNK 2000		☑	
3	COPD	Entry Error / UN / UNK / UNK		☑	
	Add a new Log line Inactivate				

S1404 Adverse Event Reporting

- Extra fields on the AE Report form to capture additional data
  - Onset and Resolution dates
  - Action Taken
  - Outcome
  - Immune Related?
  - Treatment Received?
  - AdEERS Report Ticket Number
- Onset and Resolution date correspond to the specific grade, not the AE overall

S1404 Adverse Event Reporting

Instructions:

- Report adverse events occurring up until the next cycle of treatment begins.
- If an adverse event changes grade during the reporting period, report each grade as a separate event. If an adverse event resolves and then recurs at the same or different grade, report each event separately.
- To report ongoing adverse events, provide the AE start date and mark the AE as "ongoing" on each eCRF until the event is resolved. On the last cycle that the AE is seen, provide the AE end date.
- Do not code a condition existing prior to registration as an adverse event unless it worsens.
- Indicate if the adverse event results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours.
- Submit the Concomitant Medications form documenting treatment received for any immune-related adverse events.
- Follow instructions in Section 16.0 of the protocol for expedited reporting requirements on this study.
- Record any expedited adverse events that were reported using Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). If the AdEERS report was amended, please amend the data on this adverse event form.
- Category lists may not include all adverse events from that category.

#	Verbatim term	CTC adverse event term	CTCAE (4.0) grade	CTC adverse event attribution code	Onset date	Resolution date	Action taken	Outcome of AE	Hospitalization *(at least 24 hours)*	Is the AE immune-related?	Treatment received for this AE?	AdEERS Report Ticket Number
1	Fatigue	Fatigue	1	Probable	6 Oct 2015	–	Dose Not Changed	Not Recovered/Not Resolved	☐	No	No	–
2	Anemia	Anemia	2	Probable	6 Oct 2015	7 Dec 2015	Dose Not Changed	Recovered/Resolved	☐	No	No	–
3	Anemia	Anemia	4	Probable	7 Dec 2015	–	Drug Withdrawn	Not Recovered/Not Resolved	☐	No	No	–

Add a new Log line Inactivate

S1404 Concomitant Medication Form

- Designed to capture any non-protocol medications a patient takes while on treatment
- General concomitant medication form that is present at Step 2 Randomization
- AE-specific concomitant medication forms also generate when it’s indicated that treatment is received for an immune-related adverse event

S1404 Concomitant Medication Form

Instructions: Please complete if patient receives any non-protocol therapy. If patient received a glucocorticoid to treat immune-related adverse events, record the dose and start and stop dates of the initial high dose and start and stop dates of the steroid taper on separate lines. List each medication on a separate line, even if given concurrently. If patient stops a medication and then restarts at a later date, list each occurrence on a separate line.

#	Concomitant Agent Name	Start Date	Stop Date	Ongoing?	Dose	Units of Measure	Route of Administration	
1	Prednisone	1 Mar 2016	5 Mar 2016	☐	40	mg	Oral	
2	Prednisone	6 Mar 2016	8 Mar 2016	☐	20	mg	Oral	
3	Prednisone	9 Mar 2016	11 Mar 2016	☐	10	mg	Oral	

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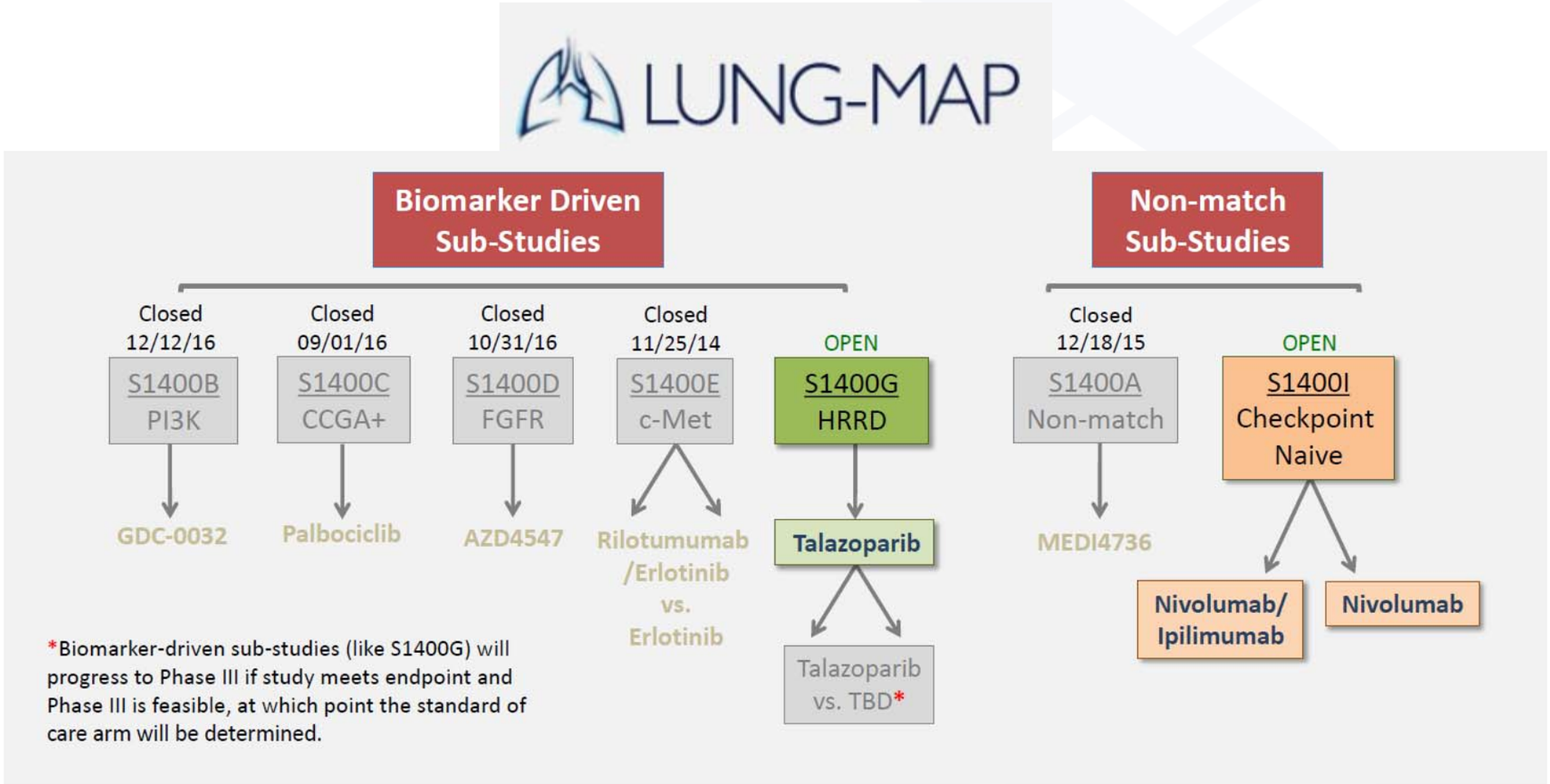
S1400: A Biomarker-driven Master Protocol For Previously Treated Squamous Cell Lung Cancer (Lung-MAP)



S1400 Tissue for Biomarker Profiling

- S1400 Local Pathology Review Form
  - Must be signed by local pathologist confirming adequate tumor content (both % tumor cells and total tumor volume)
  - Availability of adequate tissue is an eligibility requirement, so this form must be completed prior to registration
- Tissue shipment required within one working day following registration
- Use SWOG Specimen Tracking as usual

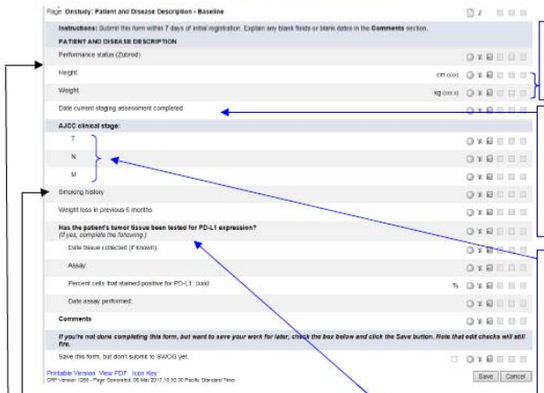
S1400 Resources & Where to Find Them

- Site Coordinators Committee
  - ORP Open Forum later today
  - LungmapSCC@crab.org
- “Your Institution's Lung-Map Status Update”
  - Emailed quarterly to your institution’s head CRA
- Examples of Beacon builds, sample source documents
  - On the protocol abstract page, under “S1400 Resources”
- Rave Data Entry Guidelines
  - Chapter 16e of the ORP Manual or as a link on the protocol abstract page

S1400 Rave Data Entry Guidelines

S1400 Screening Forms

Onstudy: Patient & Disease Description Form



Height, Weight & P/S must be obtained within 28 days prior to study entry. The values closest to the registration date are reported.

The date of current staging is the date of the most recent test to assess disease (usually a scan or biopsy). It is not the date of a physical exam unless a measurement of a lesion is done at the visit (e.g. skin lesion assessed).

The AJCC clinical stage is the stage at the **time of study entry**, not at original diagnosis. If patient has metastatic disease, either M1a or M1b are entered.

If T and N stage are unknown, enter TX, NX, M1a, for example.

If patient has had a cigarette within the past year, they are considered a current smoker.

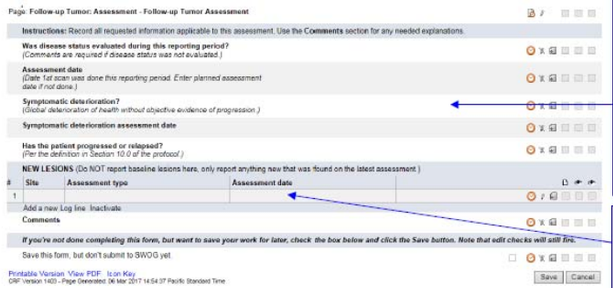
If the patient's tumor tissue was tested for PD-L1 expression, please complete this section utilizing information from the PD-L1 report. If you are unsure about how to complete any of these fields, upload a redacted copy of the associated PD-L1 report into the "Source Documentation: Baseline" folder or email the DC's a copy (S1400Question@crab.org) to provide guidance.

As there are several different conversion charts available for Karnofsky to Zubrod, it is important that the Zubrod scale be used. If the Karnofsky is used, the Zubrod value must also be documented in the medical record.

This form is due within 7 days of registration to S1400. Late submission > 3 months is considered a major data delinquency deficiency for baseline forms.

S1400 Sub-Study Forms

Follow-up Tumor: Assessment



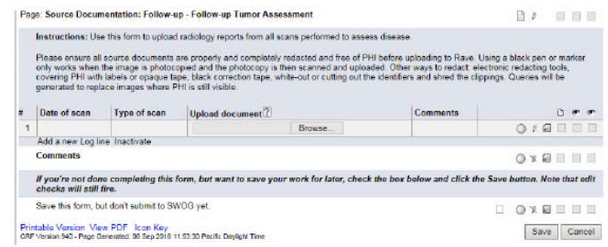
If symptomatic deterioration is yes, there should be documentation in the Medical Record that the patient's performance status has decreased.

If patient progressed, answer 'No' to symptomatic deterioration.

Enter any new lesion(s) here. Presence of new lesions constitutes progression. If the report states lesion increased in size from prior scan, then it probably is not a new lesion.

For sub-study A, patient must have a confirmation scan ≥ 28 days from initial scan showing progression to meet irProgression criteria in section 10.0. If progression is shown on the subsequent scan, the date of the initial progression scan is reported as the progression date.

Source Documentation: Follow up – Follow-up Tumor Assessment Form



Scan reports must be uploaded to RAVE in addition to submitting the scan(s) within 7 days to TRIAD per Section 15.

S1400 at the Group Meeting

- ORP Open Forum
  - Thursday 12:30 pm, in Pacific NO (Pacific Level)
  - Look for the **S1400 Lung-MAP Site Coordinators Committee** table

- S1400 Lung-Map Update Meeting
  - Friday 2:30 pm, in Seacliff A-D (Bay Level)

Come say hi!

Thank you!