Alliance A021502: Randomized Trial of Standard Chemotherapy Alone or Combined with Atezolizumab as Adjuvant Therapy for Patients with Stage III Colon Cancer and Deficient DNA Mismatch Repair (ATOMIC)

Frank Sinicrope, MD, Study Chair
Tiffany Schafer, Central Data Monitor
Trini Ajazi, MM, Alliance Chief Administrative Officer

CRP Education Session, November 3, 2017

Presentation Objectives

- Protocol Overview
  - Study Design, Eligibility Criteria, Study Calendar
    - Dr. Frank Sinicrope
- Data Submission
  - Data Entry, Central Monitoring
    - Tiffany Schafer
  - On-site Monitoring, Deviations
    - Trini Ajazi
- Additional Requirements
  - CTEP-AERS Integration, RCR, Investigator Site File, DTL
    - Trini Ajazi

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Alliance A021502 Protocol Overview

Frank Sinicrope, MD
A021502 Study Chair

CRP Education Session, November 3, 2017

Study Background

- The PD-1/PD-L1 pathway acts to protect tumor cells from immune attack by T cells which can be circumvented by checkpoint inhibitors.

- Targeting PD-1 with pembrolizumab or nivolumab for treatment of refractory metastatic colorectal cancers with dMMR produced frequent and durable responses.

References: Le, D et al, NEJM 2015;372:2509-20.
Overman, M, et al, Lancet Oncol. 2017; 18:1182-91.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Study Background (continued)

- Deficient DNA mismatch repair (dMMR) results in microsatellite instability (MSI).
- dMMR tumors are hypermutated with abundant neoantigens that trigger tumor infiltrating lymphocytes.
- dMMR cancers include both sporadic and hereditary, i.e. Lynch Syndrome, types.
- About 12% of all stage III colon cancers show dMMR or MSI.
- NCCN Guidelines recommend dMMR/MSI testing of all newly diagnosed colorectal cancer cases.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Study Background (continued)

- Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1, thereby enhancing T-cell activity against tumor cells.

- Phase I trials show atezolizumab is well tolerated with no dose-limiting toxicities.

- Atezolizumab is FDA-approved for treatment of platinum-resistant metastatic non-small cell lung cancer and locally advanced or metastatic urothelial cancer.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Study Design

- Primary Objective:
  - To determine whether atezolizumab combined with FOLFOX and its continuation as monotherapy can significantly improve disease-free survival (DFS) compared to FOLFOX alone in patients with stage III colon cancers and dMMR.
- Secondary Objectives:
  - To determine whether atezolizumab combined with FOLFOX and its continuation as monotherapy can significantly improve overall survival (OS) compared to FOLFOX alone in patients with stage III colon cancers and dMMR.
  - To assess adverse events (AE) profile and safety of each treatment arm, using the CTCAE and PRO-CTCAE.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

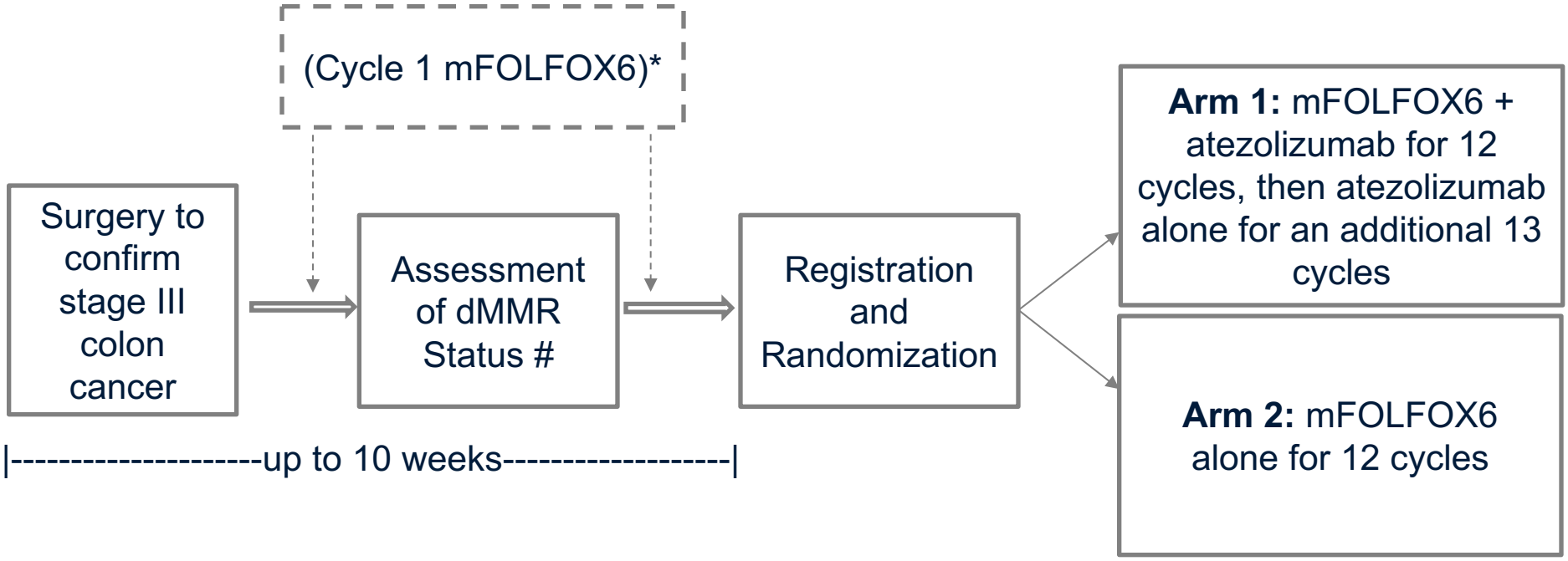
Study Design (continued)

- Accrual Goal = 700 patients

- Patients will be followed for recurrence and survival every 6 months for the first 2 years after registration, then for recurrence annually for years 3-5 after registration, and then survival every 6 months for years 3-8 after registration.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Study Design (continued)



* One cycle of mFOLFOX6 is allowed prior to registration.

dMMR status assessed via local or reference lab testing of MMR by IHC.

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Treatment Plan

- Administration Schedule:
  - Atezolizumab 840 mg IV Day 1 (Arm 1 patients only)
  - Oxaliplatin 85 mg/m^2 IV on Day 1
  - Leucovorin 400 mg/m^2 IV on Day 1
  - Fluorouracil 400 mg/m^2 IV bolus on Day 1 + 2400 mg/m^2 IV on Days 1-3

- Administration of one cycle of mFOLFOX6 prior to registration is permitted.
  - Doses received must follow those listed above.
  - Patients who receive Cycle 1 of mFOLFOX6 prior to registration and who are randomized to Arm 1 will begin atezolizumab with Cycle 2 of mFOLFOX6.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Treatment Plan (continued)

- Treatment is to begin within 14 days of registration.
  - Cycle 1 of mFOLFOX6 must begin within 10 weeks of surgery.
    - Best practice is 3-6 weeks between surgery and C1 of chemo.
- One cycle is defined as 14 days of treatment.
  - SOC window between end of C1 and start of C2 is 14 days.
    - Up to 28 days are allowed if delays occur due to toxicity.
- Chemotherapy and immunotherapy must be administered at the registering institution.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Eligibility Criteria

- Histologically proven stage III colon adenocarcinoma.
  - Any T, N_{1-2}M0 (includes N1C)
- Presence of deficient MMR (dMMR) via IHC.
  - Loss of MLH1, MSH2, MSH6, or PMS2.
  - Testing may be done locally or at a site-selected reference laboratory.
  - Patients with known Lynch Syndrome are allowed.
- Tumor(s) must have been completely resected.
  - Entire tumor must have resided in colon (i.e. rectal involvement is an exclusion).
  - No evidence of residual lymph node involvement or metastatic disease at registration.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Eligibility Criteria (continued)

- Age ≥ 18 years
- ECOG Performance Status: 0-2
- Negative pregnancy test (≤ 7 days prior to registration)
- Required initial lab results within specified ranges
- Mandatory FFPE tumor tissue submission to enable retrospective central confirmation of dMMR by IHC
  - Central confirmation not used to determine eligibility.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Study Calendar

Footnotes in column headings (e.g. *, **, ***) pertain to the entire column and provide additional information about the specific time point.

Footnotes in row headings (e.g. 1, 2, etc.) pertain to the entire row and provide additional information about the specific test, study, etc.

Footnotes in boxes (e.g. A, B, C, D) pertain only to the corresponding item at that specific time point.

	Prior to Registration*	**Arm 1:** Day 1 of each cycle*	**Arm 2:** Day 1 of each cycle*	End of treatment follow-up**	Post-treatment follow-up ***
Tests & Observations					
History and Physical, Weight, PS	A	A	A	X	X
Height	X				
Pulse, Blood Pressure	X	X	X	X	
O_2 Saturation (1)	X	X		X	
CTCAE Adverse Event Assessment (2)		X	X	X	X
PRO-CTCAE Adverse Event Assessment (3)	X	X	X	X	
Registration Fatigue/ Uniscale Assessment (4)	X				
Colonoscopy	B				B
Laboratory Studies					
Complete Blood Count, incl. Diff.	X	X	X	X	
Chemistry (5)	X	X	X	X	
TSH (6)	X	X			
Hep B Surface Ag & Hep C ab (Physician Discretion)	X				
Urinalysis (7)	X	X			
Serum or Urine HCG (8)	X				
CEA (9)	X	X	X		X
CD4 Count & Viral Load (10)	X				
dMMR Testing	X				
Staging					
CT of Chest/Abd/Pelvis or MRI of Chest/Abd/Pelvis	C	D	D	D	D

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Study Calendar (continued)

- In general, the following items are required on Day 1 of each cycle for both Arm 1 and Arm 2 patients:
  - H&P, pulse, blood pressure, CTCAE, PRO-CTCAE, complete blood count incl. differential, and chemistry panel.
    - For Arm 1 Patients Only: O_2 saturation, TSH, and urinalysis are also required at varying intervals per Section 5.0.
- CT (or MRI) is required every 6 months for the first 2 years after registration, then annually for years 3-5 after registration or until evidence of relapse, whichever comes first.
  - Imaging modality used at baseline must be used for all subsequent imaging time points.
    - Clarification to be included in Update #01.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Correlative Studies

- Quality of Life (A021502-HO1)
  - Patient-completed questionnaire booklets administered: (Arm 1) at registration, prior to Cycles 4, 7, 13, at end of treatment, and 3 years from registration; (Arm 2) at registration, prior to Cycles 4, 7, at end of treatment, 12 months from registration, and 3 years from registration.
- Biobanking for Future Correlative Science Studies (A021502-PP1 and A021502-ST1)
  - Blood, tissue, and stool collected at various time points
    - See table on next slide for specific intervals.
  - Each specimen type has a separate consent question
    - E.g. “I agree to have my blood collected, and I agree that my blood samples and related information may be kept in a Biobank for use in future health research.”

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Specimen Submission

Specimen Submission Schedule for the Alliance A021502 Study						
	Prior to treatment	3 weeks after initiation of treatment	2 months after Cycle 5 Day 1	6 months after end of adjuvant therapy	Time of recurrence	Submit to:
Mandatory Submissions for <u>All Patients</u> Registered to the A021502 Main Study:						
10 Superfrost® Plus Micro Slides	X					Central Lab
H&E slide <u>AND</u> FFPE tumor block	X					Mayo FFPE
FFPE normal block	X					Mayo FFPE
For Patients Registered to the A021502-ST1 Substudy, Submit the Following:						
FFPE tumor block	A				A	Mayo FFPE
EDTA platelet poor plasma & buffy coats	3 x 10 mL		3 x 10 mL	3 x 10 mL	B	May BAP
Whole blood	3 x 8.5 mL	3 x 8.5 mL	3 x 8.5 mL	3 x 8.5 mL		Duke
Stool	3 x 25 mL		3 x 25 mL	3 x 25 mL		Mayo BAP
For Patients Registered to the A021502-PP1 Substudy, Submit the Following:						
Whole blood	1 x 10 mL					Mayo BAP

Mandatory submission of 10 Superfrost® Plus Micro Slides (or alternatives) to the central laboratory <u>must not be submitted until on/after November 15th</u> per the Activation Notice for patients registered between 09/12/2017 and 11/15/2017. All other specimen submission should follow the schedules outlined in the protocol document.

There are **four** different blood kits and one stool kit which correspond to various time points. Kit ordering instructions can be found in Section 6.2.

Questions?

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Data Entry, Data Submission Schedule, & Central Monitoring

Tiffany Schafer, Data Manager
Mayo Clinic, Rochester, MN

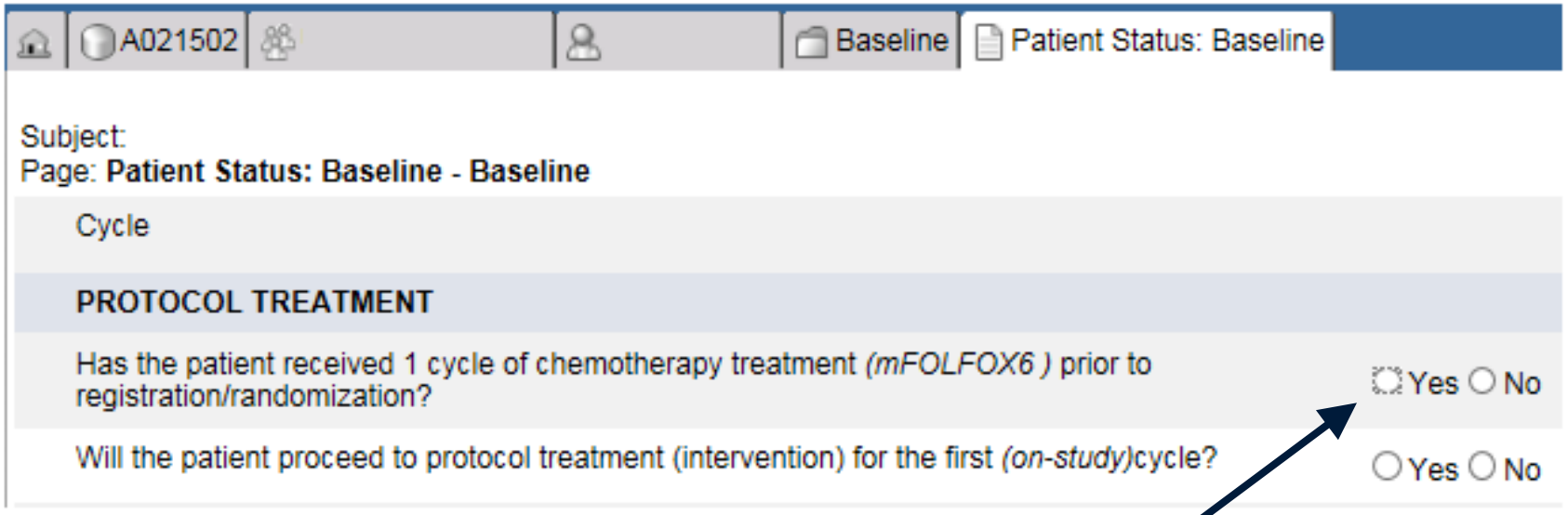
CRP Education Session, November 3, 2017

Data Entry: Prior to Reg Treatment

- Patient may receive one cycle of FOLFOX prior to registration
  - Administered per Appendix III in protocol
- Prior to registration cycle will be entered in Rave
  - As Treatment 01

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Data Entry: Rave



This section of the Baseline form refers to FOLFOX treatment prior to registration.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Data Entry: Rave

	Visit
	Baseline
	Treatment 01

If patient had a cycle of FOLFOX prior to registration, it should be entered in Treatment 01. Treatment 02 should be used for first cycle on-study.

If patient is starting FOLFOX on study (no prior-reg treatment). Treatment 01 will be used for first cycle.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Monitoring Plan – Section 13.6

- Central Data Monitoring
  - Source data verification vs. eCRFs in Rave
    - Informed consent
    - Protocol eligibility criteria
    - Drug administration for the first 3 cycles of treatment
      - This will be corrected with Update #01 (currently, 2 cycles)
  - Review timeliness of data submissions and query resolution
- On-Site Monitoring
  - On-site monitoring will be conducted according to Alliance procedures

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Monitoring Plan

- Source documents will be uploaded to Supporting Documents Form in Rave
  - Please ensure all documents have been redacted
  - Please upload documents and enter data in a timely fashion for review
- Source Documentation requirements on page 4 of Data Submission Schedule (DSS)
  - Available on Alliance and CTSU websites

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Central Monitoring (DSS page 4)

Domain	CRF	Data Fields/Section	Acceptable Source Documents
Informed Consent	Informed Consent[1]	Date of signature[3] Signature page[3]	Informed Consent Document
	Informed Consent[2]	Entire document	
Eligibility[1]	OPEN Registration Worksheet	All fields	Path report IHC report Operative report Radiology report Colonoscopy report Lab report (for registration eligibility) Clinic note Other relevant report
	On-study	Description of Primary Disease Section Mismatch Repair Testing Section Patient History Section (excluding NSAID usage) ECOG Performance Status Correlative Studies Section	
Treatment (first 3 cycles[1]; all cycles[2])	Treatment (Intervention)	Agent name Dose level Units of measure Dose (total) Units of measure Was protocol treatment modified? Was protocol treatment omitted? Was protocol treatment delayed? Start date Stop date	Relevant medical record (e.g., clinic note, other)
	Treatment (Intervention): Dose Modifications, Omissions and Delays	Dose modification reason Dose omission reason Dose delay reason	
Off Treatment [2]	Off Treatment	All fields	Relevant medical record (e.g., clinic note, other)
Disease Assessment[1]	Patient Status: Baseline, Patient Status: Treatment, Patient Status: Clinical Follow-up, Patient Status: Survival Follow-up	Survival Status Section Disease Status Section New Primary Section	Radiology report (conventional CT and MRI or chest x-ray) Lab report Colonoscopy report Relevant medical record (e.g., clinic note, other)
Disease Recurrence[1]	Notice of Recurrent Disease	All fields	Radiology report (conventional CT and MRI or chest x-ray) Lab report Colonoscopy report
New Primary[1]	Notice of New Primary	All fields	Radiology report (conventional CT and MRI or chest x-ray) Lab report Colonoscopy report
Adverse Events[2]	Adverse Events Late Adverse Events	All fields	Relevant medical record (e.g., clinic note, other)
Consent Withdrawal[2]	Consent Withdrawal (all types)	All fields	Relevant medical record (e.g., clinic note, other)

[1] Central and on-site monitoring
[2] On-site monitoring only
[3] For Central Monitoring: De-identified Informed Consent Document (ICD): Last page of signed and dated ICD (including page/s with options indicated by patient for additional studies). Patient's full signature should be redacted but date should be retained.

Central Monitoring

Domain	CRF	Data Fields/Section	Acceptable Source Documents
Informed Consent	Informed Consent[1]	Date of signature[3] Signature page[3]	Informed Consent Document
	Informed Consent[2]	Entire document	
Eligibility[1]	OPEN Registration Worksheet	All fields	Path report IHC report Operative report Radiology report Colonoscopy report Lab report (for registration eligibility) Clinic note Other relevant report
	On-study	Description of Primary Disease Section Mismatch Repair Testing Section Patient History Section (excluding NSAID usage) ECOG Performance Status Correlative Studies Section	
Treatment (first 3 cycles[1]; all cycles[2])	Treatment (Intervention)	Agent name Dose level Units of measure Dose (total) Units of measure Was protocol treatment modified? Was protocol treatment omitted? Was protocol treatment delayed? Start date Stop date	Relevant medical record (e.g., clinic note, other)
	Treatment (Intervention): Dose Modifications, Omissions and Delays	Dose modification reason Dose omission reason Dose delay reason	

1 Central and on-site monitoring

2 On-site monitoring only

3 For Central Monitoring: De-identified Informed Consent Document (ICD): Last page of signed and dated ICD (including page/s with options indicated by patient for additional studies). Patient's full signature should be redacted but date should be retained.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Central Monitoring

Off Treatment [2]	Off Treatment	All fields	Relevant medical record (e.g., clinic note, other)
Disease Assessment[1]	Patient Status: Baseline, Patient Status: Treatment, Patient Status: Clinical Follow-up, Patient Status: Survival Follow-up	Survival Status Section Disease Status Section New Primary Section	Radiology report (conventional CT and MRI or chest x-ray) Lab report Colonoscopy report Relevant medical record (e.g., clinic note, other)
Disease Recurrence[1]	Notice of Recurrent Disease	All fields	Radiology report (conventional CT and MRI or chest x-ray) Lab report Colonoscopy report
New Primary[1]	Notice of New Primary	All fields	Radiology report (conventional CT and MRI or chest x-ray) Lab report Colonoscopy report
Adverse Events[2]	Adverse Events Late Adverse Events	All fields	Relevant medical record (e.g., clinic note, other)
Consent Withdrawal[2]	Consent Withdrawal (all types)	All fields	Relevant medical record (e.g., clinic note, other)

1 Central and on-site monitoring

2 On-site monitoring only

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Questions?

- Data Manager
  - Tiffany Winter – winter.tiffany@mayo.edu
- Central Monitors
  - Tiffany Schafer – schafer.tiffany@mayo.edu
  - Tasha McDevitt – mcdevitt.tasha@mayo.edu

Thank you!

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

On-Site Monitoring, Deviations, Adverse Events, & Regulatory Considerations

Trini Ajazi, MM, Alliance Chief Administrative Officer

CRP Education Session, November 3, 2017

On-Site Monitoring

- Sites who enroll ≥5 patients will be targeted for on-site monitoring
- First monitoring visit will be scheduled after 5th patient is accrued
- These sites will receive a monitoring visit at least once per year
- Higher accruing sites (≥10 per year) will be monitored approximately every 6 months

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

On-Site Monitoring

A minimum of 25% of patients will be selected for source data verification (SDV) of the following:

- Eligibility
- Primary Endpoint
- Secondary Endpoint

100% of patients will be monitored for SDV of the following:

- Expedited Adverse Events/Serious Adverse Events
- Treatment Administration
- Patient Termination

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

On-Site Monitoring Activities

- Consent document review for all patients
- Source documentation and CRF review
- Review of Adverse Events and Serious Adverse Events
- Review of Investigational Product
- Protocol Deviations
- Investigator Site File
- Investigator and site personnel responsibilities

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Monitoring Plan

Central

- 100% pts
  - Eligibility
  - Endpoint
  - Treatment (first 3 cycles)

On-Site

- 25% pts
  - Eligibility
  - Endpoint
- 100% of pts
  - AE data
  - Treatment (all cycles)
  - Patient Termination

Audit

- No change in institutional audit scheduling
- Audit procedures remain the same
- At least one case from each registration trial will be selected for audit

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Protocol Deviations
Critical and Major

Sites will be expected to enter ONLY *critical and major* protocol deviations in Rave. A protocol deviations guidance document will be posted on the CTSU.

- **Critical:**
  - Any condition, practice, process or pattern that adversely affect the rights, safety or well-being of the patient/study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data
- **Major:**
  - A variance from protocol-specified procedures or practices that makes the resulting data questionable.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

NCI Initiatives for Registration Trials

- Central Monitoring
- Registration and Credentialing Repository (RCR)
- Delegation Task Log (DTL)
- CTEP-AERS Rave Integration

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Investigator Site File (ISF)/Trials Master File (TMF)

- Regulatory and Study documents (essential documents) maintained at investigator/institution and sponsor (see ICH E6 [R2])
- Maintain record of locations of essential documents including source documents
- Includes RCR and DTL documents
- We recommend a training log for this session, including date, participants and their role, be maintained in the investigator site file

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

New Registration Types – Documentation Requirements

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

NCI Delegation of Tasks Log (DTL)

- Identify the Clinical Investigator (CI) and Delegation of Tasks Log Administrator (DTLA) for every site participating on an identified protocol
- Identify individuals who can perform designated tasks on the protocol at the site level
- Track changes in task assignment over study lifecycle
- Provide a complete list of the investigators AND sub-investigators who make a direct and significant contribution to the clinical data

DTL and Study Site Registration Packet (FDA Packet)

- Produced on demand for audit or inspection purposes
- Includes:
  - General protocol details
  - DTL – current and copies of all signed version(s)
  - Study-specific information
    - Protocol CI (all annual 1572s, FDFs, NCI Biosketches, HSP and GCP training certificates)
    - Sub-investigators (FDFs, NCI Biosketches, HSP and GCP training certificates)
    - Central labs
    - CIRB/IRB information
    - Study-specific training

Expedited AE Reporting Rave – CTEP-AERS Integration

Rave to CTEP-AERS Data Flow (1)

- Sites enter AE data in Rave and submit to CTEP-AERS rules engine for expedited reporting evaluation.
- All AE data in Rave that is required for expedited reporting will be pushed to CTEP-AERS.
- A direct link will be used to automatically log into CTEP-AERS.

Q&A

THANK YOU FOR YOUR PARTICIPATION!

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY