Navigating Alliance Protocols

Morgen Alexander-Young, MPH

Alliance Central Protocol Operations Program

Alliance Spring 2017 Group Meeting

Alliance Protocol History

- Alliance for Clinical Trials in Oncology founded February 2011
- Consensus protocol template from each legacy group (ACOSOG, NCCTG, and CALGB)
- All new *concepts* developed after Spring/Summer 2013 utilized Alliance model protocol
- Alliance model protocol was approved by Alliance Central Operations Office, Statistics and Data Center, Translational Research Program, and all Alliance committee chairs and vice chairs.

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Alliance Protocol Template

- Chronologically, patient management workflow-based document
  - Rationale and objectives for study
  - Patient selection and enrollment
  - Patient scheduling, data and specimen submission
  - Treatment and dose modifications including ancillary therapy
  - End of treatment
  - Analysis

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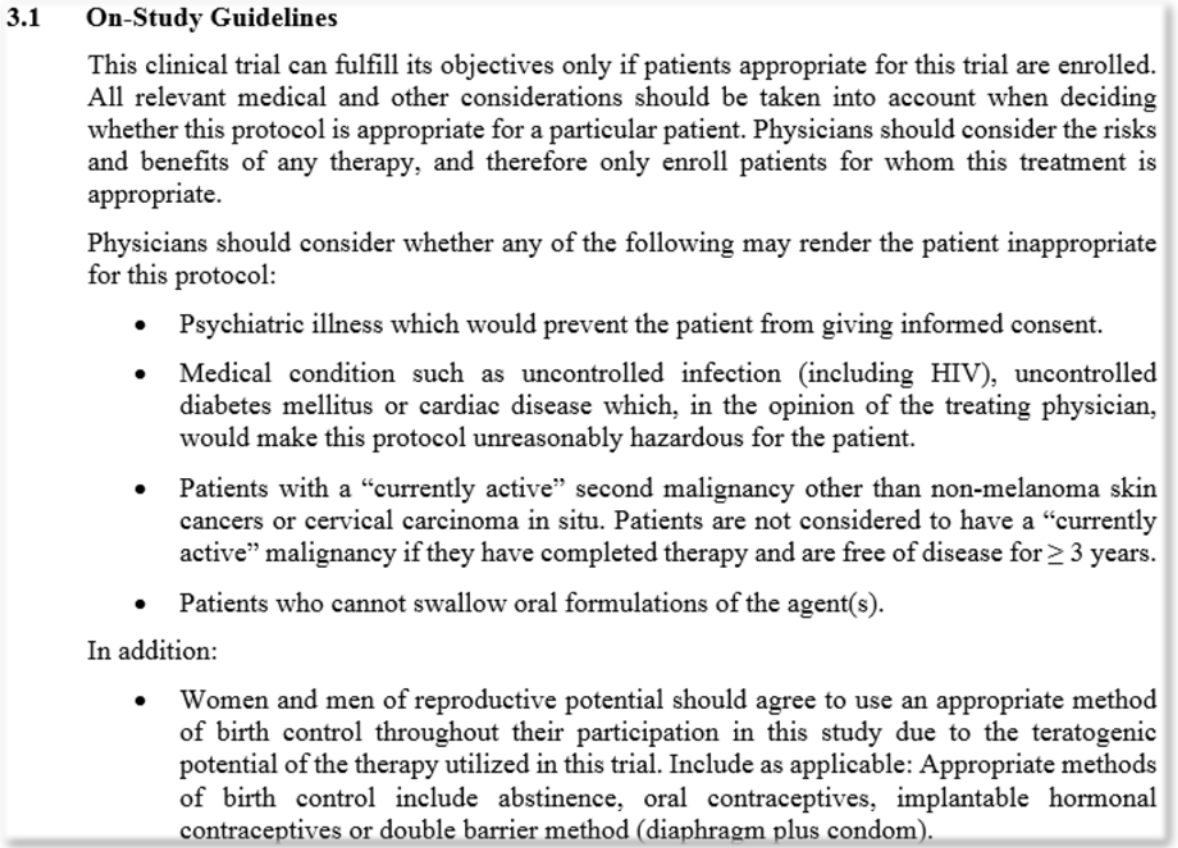
Patient Selection: On Study Guidelines

- Intended to provide guidance about the appropriateness of individual patients for protocol therapy
  - **Includes items often not verifiable at time of audit** (e.g., life expectancy, ability to swallow oral formulations, birth control usage)
  - Not strict eligibility criteria



3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Include as applicable: Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

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Patient Selection: Eligibility Criteria

- Study chairs may *interpret* how an individual patient meets eligibility criteria, but they may NOT issue waivers.
  - “This is (or is not) a complete resection,” or “this does (or does not) qualify as prior therapy,” etc.
- Eligibility criteria contain both inclusion and exclusion criteria. No separate inclusion/exclusion criteria which may lead to confusion.

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Patient Selection: Eligibility Criteria

- Some protocols specify when tests must have been performed
  - If time frame is part of eligibility criteria, both test result ***and*** time frame must be within acceptable range
  - If time frame not part of eligibility criteria, then only test result (not time frame) must be in acceptable range
  - Out of range times not part of eligibility criteria are protocol deviations. Decisions to assign audit deficiencies occur at time of audit

4.4.4 No use of herbal products that may decrease PSA levels within 4 weeks prior to enrollment

4.4.5 No chronic use of systemic steroids greater than the equivalent of 10 mg of prednisone/prednisolone per day within 4 weeks prior to enrollment

4.4.6 No prior use of ketoconazole for greater than 7 days.

4.4.7 No prior radiation therapy or radionuclide therapy for the treatment of metastasis within four weeks prior to enrollment

4.4.8 Patients receiving bisphosphonate therapy or denosumab must have been on a stable dose for at least 4 weeks prior to enrollment

4.7 Required Initial Laboratory Values:

Granulocytes	≥ 1,500/µL
Platelet count	≥ 100,000/µL
Hemoglobin	≥ 9 g/dL
Creatinine	≤ 2 x upper limits of normal (ULN)
Bilirubin	≤ 1.5 x ULN
AST or ALT	≤ 2 x ULN
Albumin	≥ 3 g/dl
Total Testosterone	≤ 50 ng/dL (1.7 nmol/L)

4.13 Pregnancy and Nursing Status

Patients must be non-pregnant and non-nursing.

Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10-14 days prior to registration. Further, they

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Waivers and Deviations

- No such thing as a *prospective* waiver. We cannot give permission to deviate from the protocol. If the protocol were not to be followed:
  - Document the reason in the patient chart
  - Reflect the deviation from protocol on the study forms
  - Make sure all source documentation (copies of emails, notes regarding telephone calls, etc.) are available for audit
  - Follow any local IRB and institutional policies regarding notification
- Alliance does not require submission or approval of deviations – <u>with exception of dosing errors</u>

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Study Calendar

- *Pre-study* testing intervals in study calendar intended as guidelines
  - Individual tests/procedure dates outside these intervals may be considered protocol deviations, but may be discussed with Study Chair **and** Protocol Coordinator
  - Retain any study team correspondence in patient records
- *Testing requirements in the study calendar are the minimum expectations.*
  - During treatment, laboratory and clinical parameters to be followed using individual institutional guidelines and best clinical judgment of physicians
- Days = calendar days unless otherwise specified.

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Study Calendar Footnotes

	Prior to Pre-Registr-ation*	Prior to Registr-ation	Arm A: Day 1 of Weeks 1 and 4 of ChemoRT	Arm B: Day 1 of Each Cycle (Pre and Post Surgery)**	Prior to Surgery	Post treatment follow up***	At PD, withdra wal, or removal ***
Tests & Observations							
History and physical, weight, PS†	X		X	X	X		
Height	X						
Pulse, Blood Pressure	X		X	C	X		
Echo or MUGA (Recommended not required)	X						
Adverse Event Assessment#	X	X	X	X	D		
Registration Fatigue/ Uniscale Assessment		X(1)					
Laboratory Studies							
Complete Blood Count, Differential, Platelets	X		X	C	X	X	
Serum Creatinine,	X		X	X	X	X	
AST, ALT, Alk. Phos., Bili	X		X	X	X	X	
Serum HCG	X(2)						
Staging							
FDG-PET Scan (A)	X (3)	R			D		
CT chest/abd/pelvis (B)	X (3)					X	
Correlative studies: For patients who consent to participate							
Tissue and Blood samples	*See Section 6.0 for Specimen Submission Requirements for Consenting Patients*						

Symbols are used for column header footnotes and provide more detail about time intervals of tests / procedures.

* Labs completed prior to pre-registration may be used for day 1 of cycle 1 tests if obtained ≤ 16 days prior to treatment.

** Treatment on Arm A (surgery) must begin within 42 days completion of the pre-registration chemotherapy. Treatment on Arm B (chemotherapy) must begin within 28 days of day 1 of pre-registration chemotherapy. All tests, observations, and labs for Arms A and B have a 5 day window.

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*** Physical examination, adverse event assessment and labs are required 21 to 35 days after the end of treatment. All patients are required to complete a physical exam, labs, and scans 6 months (+/- 4 weeks) following surgery. Thereafter, physical exam and labs are every 12 weeks (+/- 4 weeks) and scans are every 24 weeks (+/- 4 weeks) until disease progression or for 3 years after registration, whichever comes first. Thereafter, survival information is required every 6 months until 5 years following registration. Patients who do not receive adjuvant therapy (in both arms [illegible] physical exam and labs

y ≥ 10%.

to be collected starting

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2 For women of childbearing potential (see Section 3.5). Must be done ≤ 7 days prior to pre-registration.

3 Baseline scans can include either: 1) a CT chest/abd/pelvis and FDG-PET scan or 2) an FDG-PET/CT scan with diagnostic quality CT. The CT in either case must be of diagnostic quality, performed with both IV and oral contrast, and acquired with 5 mm or less slice thickness. If option 2 is used, a separate CT need not be performed. Supporting documentation is to be submitted, per Section 6.1.1. Baseline FDG-PET scan should be performed within 28 days of starting platinum/FU based cycle 1 chemotherapy, and the diagnostic CT should be performed within 42 days of starting platinum/FU based cycle 1 pre-registration chemotherapy.

A FDG-PET Scan imaging is from base of skull to mid-thigh. PET scan is to be performed prior to and during cycle 1 of pre-registration chemotherapy (day 15-19) in all patients. In Arm B, PET scan is to be performed after 2 cycles of salvage chemotherapy, within 14 days of planned surgical resection.

B CT scan is to be performed prior to pre-registration chemotherapy. After completion of protocol therapy, see footnote *** for scan frequency

C Also to be performed on Day 8 of Cycles 1 and 2 of Pre-Op Salvage Chemotherapy

D Required for patients on Arm B only

R Research Funded. Scan should be performed on or between days 15 through 19. Fluorouracil or capecitabine should be held for 48 hours prior to PET scan.

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Study Calendar Footnotes

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Tests & Observations							
History and physical, weight, PS†	X		X	X	X	X	X
Height	X						
Pulse, Blood Pressure	X		X	C	X	X	
Echo or MUGA (Recommended not required)	X						
Adverse Event Assessment#	X	X	X	X	D		
Registration Fatigue/ Uniscale Assessment		X(1)					
Laboratory Studies							
Complete Blood Count, Differential, Platelets	X		X	C	X	X	
Serum Creatinine,	X		X	X	X	X	
AST, ALT, Alk. Phos., Bili	X		X	X	X	X	
Serum HCG	X(2)						
Staging							
FDG-PET Scan (A)	X (3)	R					
CT chest/abd/pelvis (B)	X (3)						
Correlative studies: For							
Tissue and Blood samples	*See Section 6.0 for*						

Numbers are used within the calendar for tests/procedures requiring further explanation

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† Drug dosages need not be changed unless the calculated dose changes by ≥ 10%.

\# Solicited AEs are to be collected starting at baseline. Routine AEs are to be collected starting after registration. See Section 9.3 for expedited reporting of SAEs.

1 To be completed after registration and ≤ 7 days prior to treatment, see Section 1.9 and Appendix I.

2 For women of childbearing potential (see Section 3.3). Must be done ≤ 7 days prior to pre-registration.

3 Baseline scans can include either: 1) a CT chest/abd/pelvis and FDG-PET scan or 2) an FDG-PET/CT scan with diagnostic quality CT. The CT in either case must be of diagnostic quality, performed with both IV and oral contrast, and acquired with 5 mm or less slice thickness. If option 2 is used, a separate CT need not be performed. Supporting documentation is to be submitted, per Section 6.1.1. Baseline FDG-PET scan should be performed within 28 days of starting platinum/FU based cycle 1 chemotherapy, and the diagnostic CT should be performed within 42 days of starting platinum/FU based cycle 1 pre-registration chemotherapy.

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Height	X						
Pulse, Blood Pressure	X		X	C	X	X	
Echo or MUGA (Recommended not required)	X						
Adverse Event Assessment#	X	X	X	X	D		
Registration Fatigue/ Uniscale Assessment		X(1)					
Laboratory Studies							
Complete Blood Count, Differential, Platelets	X						
Serum Creatinine,	X						
AST, ALT, Alk. Phos., Bili	X						
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Staging							
FDG-PET Scan (A)	X (3)	R			D		
CT chest/abd/pelvis (B)	X (3)					X	
Correlative studies: For patients who consent to participate							
Tissue and Blood samples	*See Section 6.0 for Specimen Submission Requirements for Consenting Patients*						

Letters are used within the calendar for tests that vary from the schedule in the column header.

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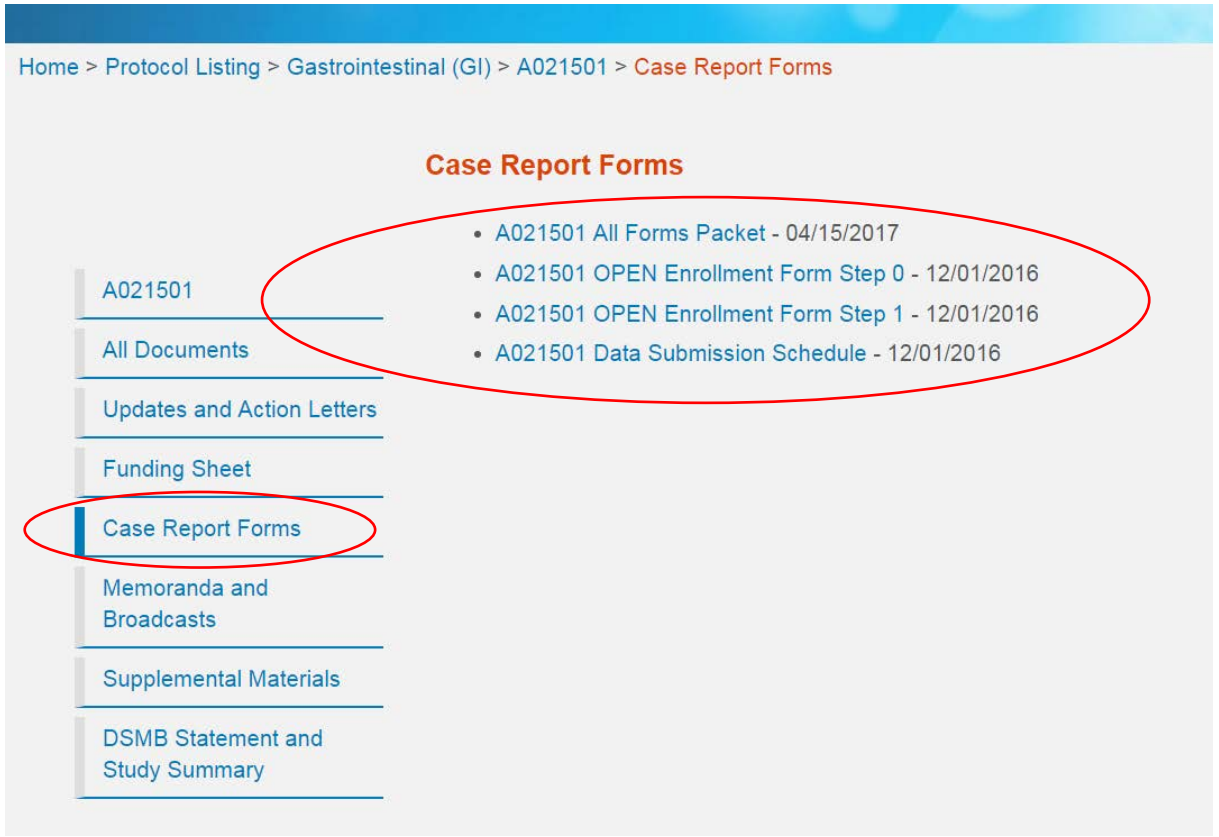
Data and Specimen Submission

- Data submission schedule is available within the Case Report Forms section of the Alliance study page
  - Paper CRFs are intended for reference, not for submission



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Data and Specimen Submission

- All specimen procurement, processing and submission instructions are provided in a *single* section
  - Study calendar may reference specimen collection
  - Schedule and details of procurement, handling, and shipment appear in dedicated specimen submission section

	Within 30 days of registration	At surgery	Shipping conditions	Submit to:
Pre-Treatment Diagnostic Tissue Block [2]	X[1]		Cool pack/ship over night	ABOSU
FFPE tissue block – Tumor Tissue[2]		X[1]	Cool pack/ship over night	ABOSU
FFPE tissue block – Adjacent Normal Tissue[3]		X[1]	Cool pack/ship over night	ABOSU
Whole Blood[1] (EDTA/lavender top)	1 x 10 mL		Cool pack/ship over night	ABOSU

1 Blocks/cores and whole blood to be banked at Alliance Biorepository at Ohio State University. Potential uses are described in Section 14.1.

2 If tissue blocks are unavailable, we will request up to 20 unstained slides (5 micron thick) of tumor tissue and 2 H&E slides representative of disease.

3 If tissue blocks are unavailable, we will request up to 20 unstained slides (5 micron thick) of normal tissue and 2 H&E slides representative of normal tissue.

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Treatment Plan & Dose Modifications

- Treatment
  - Alliance policy requires treatment must begin within 7 days after registration, unless otherwise specified in the protocol.
  - Organized chronologically by treatment modality
  - Missing a scheduled day of treatment for other than protocol-specified dose adjustments (Memorial Day, July 4th, New Years', etc.) is sometimes unavoidable. Document, document, document….

- Ancillary Therapy, Dose Modifications, and Unblinding
  - Includes supportive care and other considerations
  - Dose modifications organized by CTCAE system, organ, class
  - Emergency unblinding included in all blinded studies
  - Planned unblinding (e.g., progression, # of cycles) included when allowable

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Removal of Patients from Protocol Therapy

- Specifies duration of protocol treatment and steps to follow after discontinuation of therapy.
  - Follow-up for ineligible patients who continue with protocol treatment
  - Follow-up for ineligible patients who discontinue protocol treatment
  - Follow-up for patients who are registered, but who never start study treatment
- Future Alliance trials will provide additional detail about specimen and quality of life submission requirements for patients who discontinue protocol treatment.

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Adverse Event Reporting

- Serious adverse events must be reported using CTEP-AERs
- Minimum reporting guidelines in NCI-supplied, FDA required SAE tables

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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

- To streamline reporting, a list of reporting exclusions appears after table

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Adverse Event Reporting

- CAEPR appears in studies with NCI-supplied investigational drug

- Solicited adverse events are listed in a table, and which are to be reported on within a given period (i.e. each treatment cycle)

Version 2.4, October 12, 2016[1]

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 4.0 Term) [n= 2082]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		*Anemia (Gr 2)*
		Blood and lymphatic system disorders - Other (leukostasis)[2]	
	Febrile neutropenia		
		Leukocytosis[2]	
CARDIAC DISORDERS			
	Atrial fibrillation		
EYE DISORDERS			
	Blurred vision		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			*Diarrhea (Gr 2)*
	Mucositis oral		
	Nausea		*Nausea (Gr 2)*
	Vomiting		*Vomiting (Gr 2)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
	Fatigue		*Fatigue (Gr 2)*
	Fever		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Infection[3]		*Infection[3] (Gr 2)*
		Infections and infestations - Other (bronchopulmonary and central nervous system	

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Adverse Event Reporting

- Solicited adverse events are listed in a table, are to be reported in Rave for a given period (i.e. each treatment cycle)

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Nausea	Gastrointestinal disorders
Vomiting	Gastrointestinal disorders
Diarrhea	Gastrointestinal disorders
Constipation	Gastrointestinal disorders
Rash maculo-papular	Skin and subcutaneous tissue disorders
Fatigue	General disorders and administration site conditions
Fever	General disorders and administration site conditions
Anorexia	Metabolism and nutrition disorders
Dyspnea	Respiratory, thoracic and mediastinal disorders
Cough	Respiratory, thoracic and mediastinal disorders

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Informed Consent

- Alliance requires institutions utilize NCI and CIRB-approved model informed consent document without changes, except the following may be added
  - Local context considerations (local site staff, contact information, state and local laws)
  - Abnormal lab values listed on NCI's CAEPR, provided not added within risk list boxes, and are also listed in a separate location in the local consent
  - Clarification of risks in lay terms
  - Clarification of alternative or translational research procedures in lay terms
- <u>Alliance does not prospectively review modified informed consent documents</u>
- Risks, opt in/opt out Alliance-specific translational research questions, and alternatives to study treatment may not be added or deleted (clarifications ok, per above)

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Protocol Resources & Question Triage

- Study chairs primarily responsible for answering questions-
  - Clarification of eligibility requirements, treatment or dose modifications
- Study co-chairs also may answer questions
- Nurse Oncology liaisons- nursing related questions
- Pharmacy Liaisons- agent administration instructions

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox regulatory@allianceNCTN.org
Questions regarding CTEP-AERS reporting:	Regulatory Affairs Inbox regulatory@allianceNCTN.org
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository
Questions regarding drug supply	PMB or [drug distributor name]
Questions regarding drug administration	Pharmacy Contact

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What's NOT in protocol documents, but does appear on study-specific web pages…

- Drug order instructions and drug order forms
- Study funding information and billing compliance analyses
- Forms and data submission schedule
- Patient-directed materials (handouts, brochures)

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Patient Questionnaire Booklets

- Need to order prior to first patient
  - From Mayo for studies available to Alliance only
  - From CTSU for Alliance studies available to NCTN/NCORP on CTSU
- Measures in protocol appendices are provided for IRB review only, and are not intended to be provided to patients.

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Amendments

- Overall attempt to limit number of amendments to no more than twice per year per study
- Amendments distributed via Alliance Bi Monthly Posting (1st & 15th of each month)
- Alliance Audit monitoring based on Alliance Bi Monthly posting dates (and not CTSU posting dates)

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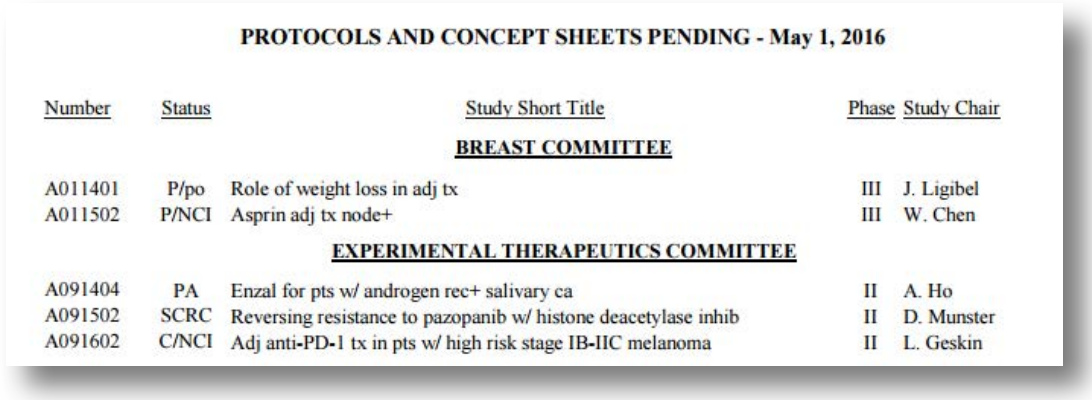
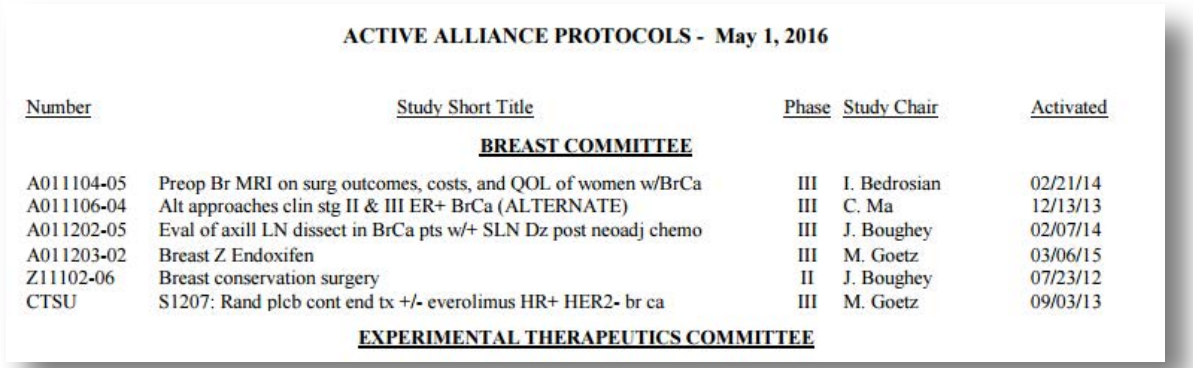
Alliance Bi Monthly Web Posting

- Active Alliance protocols listed on the member side of the Alliance web page under protocols > protocol listing.
- Protocol status sheet lists studies in development, current amendments, protocol closures, suspensions, activations.
- Prior posting notices are available on the Alliance website



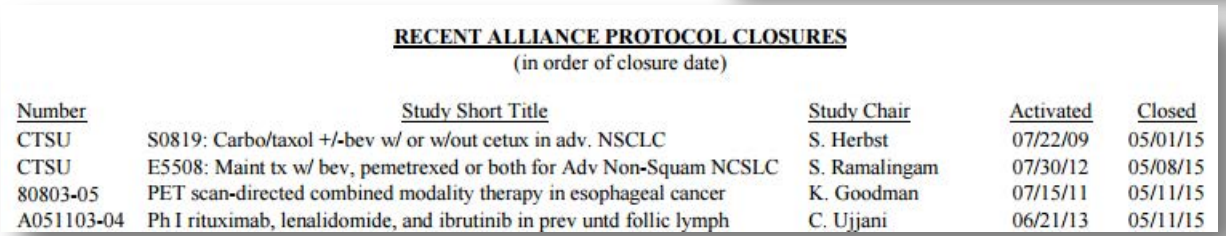
PROTOCOLS AND CONCEPT SHEETS PENDING - May 1, 2016

Number	Status	Study Short Title	Phase	Study Chair
		BREAST COMMITTEE		
A011401	P/po	Role of weight loss in adj tx	III	J. Ligibel
A011502	P/NCI	Asprin adj tx node+	III	W. Chen
		EXPERIMENTAL THERAPEUTICS COMMITTEE		
A091404	PA	Enzal for pts w/ androgen rec+ salivary ca	II	A. Ho
A091502	SCRC	Reversing resistance to pazopanib w/ histone deacetylase inhib	II	D. Munster
A091602	C/NCI	Adj anti-PD-1 tx in pts w/ high risk stage IB-IIC melanoma	II	L. Geskin



ACTIVE ALLIANCE PROTOCOLS - May 1, 2016

Number	Study Short Title	Phase	Study Chair	Activated
	BREAST COMMITTEE			
A011104-05	Preop Br MRI on surg outcomes, costs, and QOL of women w/BrCa	III	I. Bedrosian	02/21/14
A011106-04	Alt approaches clin stg II & III ER+ BrCa (ALTERNATE)	III	C. Ma	12/13/13
A011202-05	Eval of axill LN dissect in BrCa pts w/+ SLN Dz post neoadj chemo	III	J. Boughey	02/07/14
A011203-02	Breast Z Endoxifen	III	M. Goetz	03/06/15
Z11102-06	Breast conservation surgery	II	J. Boughey	07/23/12
CTSU	S1207: Rand plcb cont end tx +/- everolimus HR+ HER2- br ca	III	M. Goetz	09/03/13
	EXPERIMENTAL THERAPEUTICS COMMITTEE			



RECENT ALLIANCE PROTOCOL CLOSURES
(in order of closure date)

Number	Study Short Title	Study Chair	Activated	Closed
CTSU	S0819: Carbo/taxol +/-bev w/ or w/out cetux in adv. NSCLC	S. Herbst	07/22/09	05/01/15
CTSU	E5508: Maint tx w/ bev, pemetrexed or both for Adv Non-Squam NCSLC	S. Ramalingam	07/30/12	05/08/15
80803-05	PET scan-directed combined modality therapy in esophageal cancer	K. Goodman	07/15/11	05/11/15
A051103-04	Ph I rituximab, lenalidomide, and ibrutinib in prev untd follic lymph	C. Ujjani	06/21/13	05/11/15

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Questions

- Suggestions for the model protocol template may be directed to malexanderyoung@uchicago.edu.
- Individual protocol questions may be directed to protocol coordinators identified on protocol cover pages
- In the near future, the Alliance website study pages will provide protocol-specific contacts.

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