Alliance for Clinical Trials in Oncology
NEWS
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SPOTLIGHT ON TRIALS

New Rare Tumor Trial: First for Patients with Ocular Melanoma Nationally

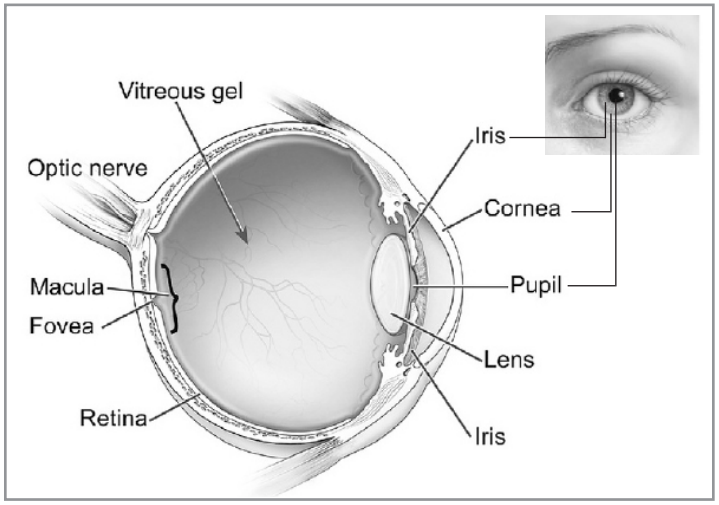
Patients Not Required to Travel to Large Medical Centers for Treatment

The Alliance for Clinical Trials in Oncology has recently launched a trial for patients with advanced ocular (uveal) melanoma – **Alliance A091201: Randomized Phase II Study Comparing the MET Inhibitor Cabozantinib to Temozolomide/ Dacarbazine in Ocular Melanoma.**

Ocular (uveal) melanoma is a rare disease with an incidence of only a few thousand cases diagnosed per year in the United States. This study will test whether the drug cabozantinib (a mesenchymal-epithelial transition (MET) and vascular endothelial growth factor (VEGFR) kinase inhibitor that has shown preliminary efficacy in previous clinical trials) is more efficacious than chemotherapy. It is the first clinical trial to be available to patients with ocular melanoma nationally, without requirement that they travel to a large medical center. This study is of pivotal importance as its successful completion could set a precedent and a framework for the completion of future trials in ocular melanoma.

About the disease

Ocular (uveal) melanoma is the most common primary intraocular malignancy in adults.[1] These lesions arise in the pigmented portions of the eye, specifically in the iris, ciliary body or choroid and have an incidence of about five cases per million population. This disease represents about three to five percent of the incidence of skin melanomas and are distinct from cutaneous melanoma in molecular pathobiology.[2-3] About 85 percent of ocular melanomas are uveal (iris, ciliary body and choroid) in origin, with primary conjunctival and orbital melanomas being less common.[3-4] The incidence of ocular (uveal) melanoma varies significantly with latitude, skin pigmentation and ethnicity. Unlike cutaneous melanoma, exposure to ultraviolet light has an unclear role in the development of this disease.



Courtesy of the National Eye Institute/NIH.

The development of metastasis in ocular (uveal) melanoma is common and occurs in about 50 percent of patients with posterior ocular (uveal) melanoma within 15 years after the initial diagnosis and treatment.[5] The outcome for patients with metastatic ocular (uveal) melanoma is notably dismal. Ocular (uveal) melanoma is thought to be particularly resistant to systemic treatment, and no systemic therapy has been demonstrated to improve survival.[6] Drugs commonly used to treat advanced cutaneous melanoma rarely achieve durable responses in patients with ocular (uveal) melanoma. It is clear that novel strategies and more effective therapies are desperately needed for this disease.

Ocular (uveal) melanoma is well characterized to harbor activated MET and preclinical data suggests that inhibition of MET by small molecule receptor tyrosine kinase (RTK) inhibitors will block proliferation and migration in this disease.

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Cabozantinib inhibits multiple RTKs implicated in tumor growth, metastasis and angiogenesis. The primary targets of cabozantinib are c-MET and VEGFR2; additional targets include RET, AXL, KIT, and tunica intima endothelial receptor tyrosine kinase 2 (TIE-2). Both c-Met and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and in vivo pharmacodynamic activity of cabozantinib against c-Met and VEGFR2 has been demonstrated in both preclinical and clinical studies.

Dacarbazine (DTIC) is an imidazole dimethyltriazene prodrug that has been approved for use in the treatment of metastatic malignant melanoma and Hodgkin's disease since the 1970s. DTIC is currently the only widely registered chemotherapy drug for metastatic stage IV melanoma. DTIC is a non-classical alkylating agent that causes DNA mispairing and strand breakage, leading to cell death (necrosis). Its exact mechanism is not completely understood. It is a cell cycle nonspecific drug, meaning that it causes cell damage and death throughout the life cycle of a cell, and not at any one particular time. When a patient is treated with DTIC, 50 percent of the drug is metabolized by the liver and 50 percent excreted in the urine. DTIC is considered a standard treatment for metastatic melanoma with response reported from five to 15 percent.

Temozolomide is an oral imidazotetrazinone prodrug that converts under physiological conditions to the same active alkylating agent as DTIC. In a large randomized phase III study comparing oral temozolomide versus intravenous DTIC in patients with advanced melanoma, median survival time was 7.7 months for the temozolomide patients and 6.4 months for the DTIC patients.[7] There were no major differences identified in drug safety, but more importantly there were no significant differences identified in clinical response rates either. Although temozolomide has not been licensed for use in malignant melanoma, it is still used extensively in both therapeutic trials and clinical practice and is considered interchangeable with dacarbazine for melanoma.

About the trial

Alliance A091201 is a one-stage phase II trial that will assess the anti-tumor efficacy of cabozantinib in rare tumors (uveal melanoma). Specifically, this study will assess whether cabozantinib can improve the four-month progression-free survival (PFS) rate in patients with ocular melanoma from 15 percent, which is achievable with temozolomide and dacarbazine, to 40 percent with cabozantinib. To access the molecular impact of cabozantinib on uveal melanoma lesions in liver and bone, pre- and post-treatment hepatic biopsies as well as [18F]-fluorodeoxyglucose positron emission tomography–computed tomography (FDG-PET/CT) imagining will be performed. Secondary objectives of this study are to estimate the distribution of progression-free survival times, estimate the distribution of overall survival times, estimate the confirmed response rate as determined by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, assess the safety of these agents by examining the toxicity profile, and correlate the response of MET molecular status.

Patient eligible for this trial will have histologically confirmed uveal melanoma that is metastatic or unresectable. Patients with prior therapies are eligible, except those who have had treatments aimed at or against c-Met or VEGF/R, and the chemotherapy agents temozolomide and dacarbazine. Patients who have had cytotoxic chemotherapy or prior radiation therapy are ineligible; however, there are exceptions.

About 66 people will take part in this study, which also includes one substudy, Alliance A091202-ST1 Solid Tumor Correlative Studies in Alliance A091201. Among other objectives, this substudy will describe the association between pre-treatment MET expression or GNAQ/GNA11 (genes) mutation and clinical benefit.

For complete information on the trial design, treatment plan and patient eligibility, refer to the study protocol (Alliance A091201), which can be found on the Alliance website (AllianceforClinicalTrialsinOncology.org) or CTSU menu (ctsu.org). The Study Chair is Jason J. Luke, MD, of University of Chicago, e-mail: jluke@medicine.bsd.uchicago.edu.

Sources

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7. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 2000;18:158-66.

Alliance Presents Novel Data at American Society of Hematology Annual Meeting

The Alliance for Clinical Trials in Oncology presented an impressive array of novel data from many of its hematology studies during the 56th American Society of Hematology (ASH) Annual Meeting and Exposition held in San Francisco, CA. Many of these data will help change the delivery of hematologic cancer care or help elucidate the underlying cause and effect relationships seen in this field.

Here is a summary of the Alliance trials.

Image of red blood cells.

CALGB-9710

A comparison of outcomes between adolescents and young adults (AYA) and children with acute promyelocytic leukemia: North American Intergroup Study CALGB 9710 (Alliance). Kutny MA, Geyer S, Laumann KM. Blood 124(21), Abstract 2306, 2014

The C9710 study demonstrated improved event-free survival (EFS), disease-free survival (DFS) and overall survival (OS) among adult patients receiving arsenic trioxide (ATO) consolidation compared to those who did not receive ATO (Powell et al., Blood, 2010). The current analysis of results for AYAs versus younger pediatric pts showed improved DFS among the whole AYA cohort (of which 55% received ATO consolidation) compared to pts <15 yr (of which 0% received ATO). When the analysis was restricted to AYA pts not receiving ATO, however, the results of this intergroup APL trial showed similar CR, DFS, EFS and OS for AYAs and younger pts. Thus, unlike other subtypes of acute myeloid leukemia (AML). Acute promyelocytic leukemia (APL) appears to have a consistent response across the pediatric and AYA age groups. The most recent Children's Oncology Group (COG) clinical trial in APL is now evaluating whether pediatric patients can also benefit from ATO consolidation.

CALGB-9710

Effect of young Age on Outcomes in Pediatric Acute Promyelocytic Leukemia: North American Intergroup Study CALGB 9710 (Alliance). Kutny MA, Geyer S, Laumann KM, Gregory J, Willman CL, Stock W, Larson RA, Powell BL, Feusner JH. Blood 124(21), Abstract 2301, 2014

Results of this intergroup trial demonstrate that all-trans retinoic acid (ATRA) administration during induction, consolidation and maintenance leads to complete remission (CR) rates >80% and 5 yr overall survival (OS) rates >75%. These results are superior to recently published results of pediatric non-acute promyelocytic leukemia (APL) and confirm results from the prior APL intergroup trial (INT0129) that demonstrated that ATRA in induction and/or maintenance significantly improved outcomes for pediatric APL *(Gregory et al., Ped Blood and Cancer, 2009)*. Our sub-group analysis showed no association of age with outcomes in children treated with this regimen.

CALGB-10801

Adding the KIT inhibitor dasatinib (DAS) to chemotherapy overcomes the negative impact of KIT Mutation/over-expression in core binding factor (CBF) acute myeloid leukemia (AML): Results from CALGB study 10801 (Alliance). Marcucci G, Geyer S, Zhao W, Caroll AJ, Bucci D, Uy GL, Blum W, Pardee T, Wetzler M, Stock W, Kolitz JE, Eisfeld AK, Bloomfield CD, Stone RM, Larson RA. Blood 124(21), Abstract 8, 2014

Updated results suggest that 1) rapid molecular screening and treatment-protocol allocation for core binding factor acute myeloid leukemia (CBF AML) are feasible within a cooperative group, 2) Dasatinib (DAS) + chemotherapy is tolerable in CBF AML patients of all ages, 3) clinical outcomes for CBF patients receiving DAS + chemotherapy

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remain at least comparable to those historically observed in CBF patients who received chemotherapy alone; 4) older CBF AML patients seem to benefit from this intensive approach; 5) among pts treated with DAS+chemotherapy, outcomes of KIT-mutation patients seem similar to those of KIT-wt patients, although we recognize the limitations with relatively small numbers. Patients on CALGB 10801 continue to be followed for survival endpoints. Overall, these results support the continued evaluation of KIT inhibitors in CBF AML through prospective randomized trials but emphasize that further outcome enhancements in this disease subset could be achieved via the use of additional rationally targeted agents.

Alliance-A051201

Unexpected and serious toxicity observed with combined idelalisib, lenalidomide and rituximab in relapsed/refractory B cell lymphomas: Alliance A051201 and A051202, Smith, SM, Pitcher, BN, Jung S, Bartlett NL, Wagner-Johnston N, Park SI, Richards KL, Cashen AF, Cheson BD, Leonard JP. Blood 124(21), Abstract 3091, 2014

Whereas doublet therapy with lenalidomide/rituximab and idelalisib/rituximab has been safely combined in other trials and disease settings, we observed 4 dose-limiting toxicities (DLTs) among the first 8 patients, all concerning for high-level immune activation. Although the mechanism of these toxicities is unknown, the combination of rash, fevers, and hypotension is suggestive of cytokine release syndrome (CRS), which is a known but uncommon IL-6-mediated event seen with rituximab, rarely reported after single agent lenalidomide, and, to date, not observed with idelalisib. Our observation of 4 potential cytokine release syndrome (CRS)-like reactions among 8 patients suggests an additive and previously undescribed risk of this combination. Based on the severe toxicities noted, both trials have been amended to remove ritux and pursue a phase I safety assessment of idelalisib and lenalidomide without rituximab in patients with relapsed follicular lymphoma (FL) and mantle cell lymphoma (MCL).

CALGB-10403

Favorable outcomes for adolescents and young adults (AYA) with Acute Lymphoblastic Leukemia (ALL): Early results of US intergroup trial CALGB 10403 (Alliance). Stock, W, Luger, S, Advani A, Geyer S. Harvey RC, Mullighan CG, Willman CL, Malnassy G, Parker E, Laumann KM, Sanford B, Marcucci G, Paietta EM, Liedtke M, Claxton DF, Foster MC, Appelbaum FR, Erba H, Litzow MR, Tallman MS, Stone RM, Larson RA. Blood 124(21), Abstract 796, 2014

This large prospective U.S. adult intergroup trial (C10403) for patients 16-39 years old employing an intensive pediatric regimen demonstrates a significant improvement (compared to historical controls) in adolescent and young adults event-free survival (AYA EFS) and overall survival (OS) and validates this approach for treatment of AYA with acute lymphoblastic leukemia (ALL) by adult hematologists. The improved clinical outcomes and the predictive value of the correlative studies in this trial lay the foundation for the design of future trials, where incorporation of novel agents to eradicate minimal residual disease (MRD), and/or use of tyrosine kinase inhibitors to target the frequently detected Ph-like ALL in AYA patients may further improve survival for young adults with ALL.

CALGB-100801

CALGB 100801 (Alliance): A phase II multi-center NCI cooperative group study of the addition of azacitidine (AZA) to reduced-intensity conditioning (RIC) allogeneic transplantation for high risk myelodysplasia (MDS) and older patients with acute myeloid leukemia (AML): Results of a "test dose" strategy to target busulfan exposure. Vij R, Hars V, Blum W, Shore TB, Rapoport AP, Shea TC, Hoke E, Stone RM, Friedman P, Owzar K, Devine SM. Blood 124(21), Abstract 543, 2014

90% of patients were within 20% of the target area under the curve (AUC) (95% CI=0.79-0.96) based on the validation sample. Maximum non-hematologic Common Terminology Criteria for Adverse Events (CTCAE) v4.0 toxicity was grade 3 in 28 (50%), grade 4 in 6 (11%), and grade 5 in 5 (9%) of the 56 patients with available adverse event data. There were ten deaths within the first 100 days after transplant; six of these were due to non-relapse mortality (NRM). With a median follow up of 564 days, the estimated overall survival at 2 years was 39%. In conclusion, the preliminary results of this prospective multi-center trial suggest a strategy of targeting busulfan exposure to an AUC of 4000uM*min based on a prior "test dose" is successful in the majority of patients without causing excessive non-hematologic toxicity even in older patients. Further follow up is necessary to determine whether this results in less relapse and improved progression-free survival (PFS).

ASCO Elects Alliance Members to Key Leadership Roles

The Alliance for Clinical Trials in Oncology is pleased to announce that three of the seven newly elected leaders of the American Society of Clinical Oncology (ASCO) are active members of the Alliance. The positions include Treasurer and positions on the Board of Directors and Nominating Committee. Their terms will begin June 1 during the 2015 ASCO Annual Meeting.

Nichols

Craig R. Nichols, MD
Treasurer (2015-2018)

Dr. Nichols is the Co-Director of the Testicular Cancer Multidisciplinary Clinic at Virginia Mason Medical Center in Seattle. He serves as co-primary investigator on the recently funded Northwest National Cancer Institute Community Oncology Research Program and is the Executive Officer of Cancer Control and Prevention Research for the Southwest Oncology Group. Dr. Nichols is also a member of the Alliance Cancer Control Program's Community Oncology Committee.

Edge

Stephen B. Edge, MD, FACS, FASCO
Board of Directors—Surgical Oncologist (2015-2019)

Dr. Edge is the Director of the Baptist Cancer Center and an Adjunct Professor of Surgery at the Vanderbilt University School of Medicine. He is also Vice Chair of the Alliance/American College of Surgeons Clinical Research Program's Cancer Care Delivery Research Committee.

Carey

Lisa A. Carey, MD
Nominating Committee (2015-2018; Chair, 2017-2018)

Dr. Carey is Chief of the Division of Hematology/Oncology and Physician-in-Chief of the North Carolina Cancer Hospital. She is the Jacobs Preyer Distinguished Professor in Breast Cancer Research and Associate Director for Clinical Research at the University of North Carolina Lineberger Comprehensive Cancer Center. Dr. Carey is also Vice Chair of the Alliance Breast Committee.

NCI Establishes CIRB for CCP to Review Adult NCORP/Consortia Trials

The National Cancer Institute recently established a new central institutional review board, the Cancer Prevention and Control (CPC) CIRB. The CPC CIRB will help extend the benefits of centralized CIRB review to investigators participating in studies sponsored by the NCI's Division of Cancer Prevention. Its mission is to reduce the administrative burden on local IRBs and investigators by partnering with local institutions to provide a high level of protection for study participants in selected NCI-sponsored clinical trials. The CPC CIRB is expected to review studies developed by the DCP-sponsored NCORP and Consortia programs beginning in February.

Wade

Marshall

Szczepanek

Membership of the new CPC CIRB has been selected based on expertise in cancer prevention and control, ethics, patient advocacy, and protection of human subjects. Of the 13 members, three are members of the Alliance, including Chair **James Wade, III, MD**, President of Cancer Care Specialists of Central Illinois (CCSCI) and Director of Medical Oncology at Decatur Memorial Hospital; also a member of the Alliance Board of Directors; **James Marshall, PhD**, Professor of Oncology and Senior Vice President for Cancer Prevention and Population Sciences at Roswell Park Cancer Institute; also Chair of the Alliance Cancer Control Program's Prevention Committee and member of the Alliance GU Committee; and **Connie Szczepanek, RN**, Director of the Cancer Research Consortium of West Michigan (CRCWM) at the Grand Rapids Clinical Oncology Program (GRCOP); also a member of the Alliance Cancer Control Program's Community Oncology, Prevention and Symptom Intervention committees.

Institutions already enrolled in the CIRB Initiative are not required to make any changes to their federal wide assurance (FWA) or authorization agreement to use the CPC CIRB. As the CPC CIRB begins review of studies, approved PIs at enrolled institutions can open studies using the existing processes.

For more information, visit the CIRB website (www.ncicirb.org) or contact the NCI CIRB Help Desk at NCICIRBContact@emmes.com or 1-888-657-3711.

Investigational Drug Accountability Training Videos Now Available

The NCI Pharmaceutical Management Branch (PMB) now offers video tutorials that provide detailed step-by-step guidance on various aspects of drug accountability. Each video covers a different function of the NCI Investigational Agent Accountability Record Form, commonly referred to as the Drug Accountability Record Form (DARF). If you're looking for a refresher on a particular topic, these tutorials provide the most update-to-date information about investigational drug accountability. Make sure to view the long-waited tutorial on compliant drug handling, which is now available.

To access these tutorials, visit the PMB website at http://ctep.cancer.gov/branches/pmb/drug_training_videos.htm. For more information about the tutorials, contact the PMB by phone at 240-276-6575 Monday through Friday from 8:30am to 4:30pm EST or by e-mail PMBAfterHours@mail.nih.gov at any time.

FAQs NCI Pharmaceutical Management Branch (PMB)

#1. Injectable agents in vials (sharing and overfill)

FAQ: Two patients receive the same agent on the same open label NCI study at the same institution. Can we share vials?

- If the patients are being treated on the same day, this is acceptable.
- Document this on the Drug Accountability Record Form (DARF) by noting patient initials/number used 1 vial and patient initials/number used 0 vials.
- Tie the lines together with a "]".
- Document each of the patients' actual doses on the DARF.

Note: This is not how you document trastuzumab, our (PMB) only multi-dose vial. Trastuzumab is documented by mg (often with confusing results).

FAQ: Our patient's dose of godzillaplatin is 104 mg, and the NCI-supplied vials contain 100 mg in 5 mL, but they have ample overfill. If we can draw 5.2 mL from the vial, can we use it instead of opening another vial?

- You bet, especially if the vial was filled by the manufacturer.
- If the product is lyophylized, however, please make sure that you reconstituted it exactly as directed, and the overfill isn't the result of an error.

Note/auditor's suggestion: You might want to suggest to your physicians that the difference between 104 mg and 100 mg is very small, and they can round to 100 mg without a problem (in most cases.)

#2. Commercial versus supplied stock

FAQ: What if I use commercial drug for a study patient, or investigational drug for a commercial patient? Or in other words …

For example, what do I do when the IV room pharmacist uses Velcade© from the pharmacy's stock for an NCI CTEP-sponsored trial participant instead of using NCI-supplied investigational PS-341?

Using commercial drug instead of investigational supply for a CTEP-sponsored trial is an audit compliance concern. What should you do?

- On the drug accountability log, clearly document that commercial Velcade© was dispensed in error.

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FAQs NCI Pharmaceutical Management Branch (PMB)

What about the opposite "oops"? You used a CTEP-supplied investigational agent on a patient not enrolled on a CTEP-sponsored trial.

- Clearly document on the drug accountability log, that an investigational agent was dispensed to a non-study patient.
- Notify PMB of the error by e-mail or snail mail. Include the agent name, NSC number, amount used, a short explanation of the error, and corrective action implemented to prevent future occurrences in your narrative.

In both cases, certain actions are forbidden:

- Do not replace the pharmacy's supply of Velcade© with the NCI-supplied, investigationally labeled PS-341 or vice versa.
- Do not charge the patient.

Auditor's suggestions:

- Use pre-printed or computer generated, protocol-specific order sets.
- Educate your oncologists and/or cancer center clinical trials office to alert you of newly enrolled protocol patients and to include the protocol number on all orders.
- Generate a list of all patients enrolled in CTEP-sponsored trials using investigational agents and commit it to memory.

#3. Errors involving CTEP-supplied investigational agents

There are several types of errors involving CTEP-supplied investigational agent that can happen. These include, but are not limited to:

- Incorrect agent or dose dispensed
- Incorrect preparation of study drug
- Dispensing agent to patient not on study
- Dispensing wrong agent to study patient
- Dispensing study agent from order signed by unauthorized prescriber
- Administering study agent not stored under proper conditions
- Dispensing returned study drug to different patient
- Inappropriate destroying study agent
- Unaccounted for vials/tablets/dose packs

FAQ: How do we report an error that involved CTEP-supplied investigational agent, and is there any specific information needed?

Sites should notify the PMB Branch Chief as soon as possible either in writing by regular mail at Charles L. Hall, Jr, Chief, PMB/CTEP, Room 7149, MSC 7422, Rockville, MD 20852 or by e-mail at PMBAfterHours@mail.nih.gov or hallch@mail.nih.gov.

When report an error, these are a few items that the report should include:

1. PI and local information
2. Any AE/consequence to the study patient
3. Did the patient have to be removed from study
4. How did the error occur
5. Corrective and Preventative Action (CAPA) plan

CAPA follow-up is required from final audit report. Sites are requested to provide confirmation of PMB notification for CTEP-supplied errors in their CAPA, when applicable.

Need more information: Contact the PMB by phone at 240-276-6575 Monday through Friday from 8:30am to 4:30pm EST, by e-mail PMBAfterHours@mail.nih.gov at any time or visit the PMB website at http://ctep.cancer.gov/branches/pmb/default.htm.

Future Meeting Dates

2015 Spring Group Meeting
May 14-16

Fall Group Meeting
November 4-8

2016 Fall Group Meeting
November 2-5

2017 Fall Group Meeting
November 1-4

All meetings are open to all Alliance members and will be held at Loews Hotel Chicago O'Hare, 5300 N. River Road, Rosemont, IL 60018

For meeting and travel inquiries,
contact Alison Lewandowski
e-mail alewandowski@partners.org
phone 617-525-3022

For more information on the Alliance and updates about meetings, visit
AllianceforClinicalTrialsinOncology.org