THE **TRIAL** BLAZER

UPMC HILLMAN CANCER CENTER

A quarterly newsletter from **CLINICAL RESEARCH SERVICES**

INTRODUCTION

Regulatory and compliance requirements for clinical trials put enormous demands on the precious time of physician investigators. Hence, after listening to physician feedback, we have adopted an electronic regulatory "eReg" Binder Platform to enhance the convenience of processing clinical trial-related documents including protocols, amendments, IRB approvals, correspondences, CVs, logs, and other forms. eReg is provided by Advarra, and is currently in the implementation phase with the expectation of a Q3 2021 go live. In addition, incorporation of the electronic AE Log and Adobe eSignature will further enhance the overall experience by cutting down the time required for document signing and improving the flexibility and collaboration of personnel. All of these new features will ultimately streamline the entire documentation process to enhance physician and staff experience. Added benefits include overall time saved, workflow improvement, and audit and monitoring compliance across the department.

Like any new software implementation, there will be challenges during the adoption process. We are ready to listen to user feedback and make all reasonable modifications to help make the transition as seamless as possible for physicians. Specific details of the CRS global digitalization process are provided in the "**Accomplishments and Accolades"** section. We are also transitioning to REDCap software as the Electronic Data Capture (EDC) program for our Investigator Initiated Trials (IITs). CRS program managers and the QA team have started working with principal investigators (PI) and study statisticians to discuss options that includes the completion of data entry and analysis before CTMA is decommissioned in 2022, or data migration into REDCap for ongoing studies that remain open or enrollment or data collection beyond 2022.

The "Spotlight Trial" in this edition the Chronic Lymphocytic Leukemia (CLL) trial by Dr. Zing-Zhou Hou, MD, from the Lemieux center: **"HCC 19-129: A Randomized, Multicenter, Open-Label, Phase 3 Study to Compare the Efficacy and Safety of Acalabrutinib (ACP-196) in Combination with Venetoclax with and without Obinutuzumab Compared to Investigator's Choice of Chemoimmunotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia Without del(17p) or TP53 Mutation."** The Hematological Malignancies CRS Disease and Modality Center (DMC) Team is the featured "Spotlight Team." Please take the time to read about their professional and "extracurricular" interests.

Antoinette (Toni) Wozniak, MD, FACP, FASCO
Associate Director for Clinical Research
Division Chief, Hematology and Oncology (*ad interim*)

Bhanu P. Pappu, PhD, MHA
Vice President for Clinical Research Operations and Strategy

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POINTS OF INTEREST

Spotlight Trials

- Combination BTK and BCL-2 inhibition in Chronic Lymphocytic Leukemia

CRS Spotlight Team

- Hematological Malignancies Research Team

Achievements and Accolades
- **CRS Goes Digital**

Priority Trials

- The PEACe Comparative Effectiveness Trial
- Genitourinary and Prostate Cancer
- Breast Cancers
- Gynecologic Cancers
- Biobehavioral Trials
- Melanoma and Cutaneous Tumors

Current Accrual Statistics for 2021

- 2021 Open Studies and Accruals

CRS TEAM SPOTLIGHT: HEMATOLOGICAL MALIGNANCIES PHYSICIAN TEAM

Dr. Warren Shlomchik

Warren Shlomchik is professor of medicine and immunology, and the director of hematopoietic stem cell transplant and cell therapy at the University of Pittsburgh School of Medicine and is interested in achieving clinically translatable discoveries, particularly in immunology. His research is dedicated to understanding the complex immunology of allogeneic hematopoietic stem cell transplantation (alloSCT), including graft-versus-host disease (GVHD), graft-versus-leukemia (GVL) and immune reconstitution.

Dr. Mounzer Agha

Mounzer Agha is the director of the Mario Lemieux Center for Blood Cancers at UPMC Hillman Cancer Center, clinical director of the Hematopoietic Stem Cell Transplantation of UPMC, and a visiting research associate professor at the University of Pittsburgh School of Medicine. He is an active clinical researcher and principal investigator (PI) on several clinical trials and has co-authored numerous scientific and clinical publications in several prestigious journals including C*ell, Science, Blood, and Bone Marrow Transplantation.*

Dr. Jing-Zho Hou

Jing-Zho Hou is a clinical instructor at UPMC Hillman Cancer Center and co-chair of the Hematological Malignancies Program. He is particularly interested in chronic lymphocytic leukemia (CLL). He has been a PI of several clinical trials, including the "Spotlight" trial featured in this edition.

Dr. Rafic Farah

Rafic Farah is an assistant professor of medicine at the University of Pittsburgh School of Medicine and is particularly interested in allogeneic and autologous stem cell transplant and hematologic malignancies. He has been involved in clinical trials focused on nonmyeloablative hematopoietic cell transplantation and the use of a computer-guided glucose management system in blood and marrow transplant (BMT) patients.

Dr. Anastasios Raptis

Anastasios Raptis is a clinical assistant professor of medicine at the University of Pittsburgh School of Medicine and has been involved in a clinical trial investigating biological therapy following chemotherapy and peripheral stem cell transplantation. He has several publications in high-ranking journals such as *Journal of Clinical Oncology, Oncology Research*, and the *Lancet Hematology*.

Dr. James Rossetti

James Rossetti is a referral physician for the UPMC Myelodysplastic Syndrome (MDS) Center of Excellence and is keenly interested in developing improved treatment strategies for patients with MDS and acute leukemia. He is an accomplished clinical investigator with numerous publications in the lay literature and scientific journals such as *Oncology Research, Case, and Clinical Transplantation.*

Dr. Kathy Dorritie

Kathy Dorritie is an assistant professor at the University of Pittsburgh School of Medicine and is very involved in the development of the CAR T-cell program at UPMC. She and has also worked to develop a stem cell transplant program for hemoglobinopathies, including sickle cell disease. Her extracurricular interests include music, traveling, and spending time with her husband and two kids.

Dr. Michael Boyiadzis

Michael Boyiadzis is a professor of medicine at the University of Pittsburgh School of Medicine and is specifically interested in designing and developing new treatment approaches, including immunotherapy and antibodies, in acute myeloid leukemia (AML). He has acted as the PI on several clinical trials, especially the BEATS AML trial from the Leukemia and Lymphoma Society, in addition to authoring many articles and acting as the editor of notable publications such as the 1st and 2nd editions of *Hematology-Oncology Therapy.*

Dr. Alison Sehgal

Alison Sehgal is an assistant professor of medicine at the University of Pittsburgh School of Medicine and is particularly interested in research in stem cell transplant and drug development in hematologic malignancies. She has been the PI of several CAR-T clinical trials and has co-authored several high-profile publications in journals such as *Journal of Palliative Medicine, Cancer Medicine and the Lancet*.

Dr. Annie Im

Annie Im is an Associate Professor of Medicine at the University of Pittsburgh School of Medicine and is interested in research on hematologic malignancies, drug development, stem cell transplantation, and graft-versus-host-disease. She has been involved in numerous clinical trials and has several publications in journals such as *American Journal of Hematology, Clinical Infectious Diseases, and Bone Marrow Transplantation*.

Dr. Robert L. Redner

Robert Redner is a professor of medicine at the University of Pittsburgh School of Medicine and is particularly interested in studying the molecular biology of leukemic transformation and myeloid differentiation. He has been the PI of several clinical trials and is the author of numerous publications in notable journals such as the *International Journal of Hematology, Oncology Research, and Leukemia and Lymphoma*.

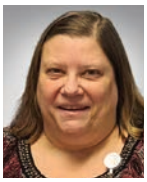
Dr. Konstantinos Lontos

Konstantinos Lontos is an academic faculty member of UPMC and is particularly interested in investigating CD105-targeted CAR T cells for the treatment of acute myeloid leukemia, which led to a recent publication. He has authored and co-authored several other articles published in widely read journals such as Leukemia, Oncology Research, and Case. In his free time, he enjoys playing tennis and chess and spending time with his child.

Dr. Sawa Ito

Sawa Ito is an assistant professor in the University of Pittsburgh Department of Medicine. She was recruited from the NIH to join the Hematopoietic Stem Cell Transplant Program. Her research work is focused on finding ways to harness the GVL immune effect to cure leukemia and lymphoma, and she is particularly interested in preventing and treating post-transplant relapse, which remains the major cause of transplant failure.

HOBBIES/INTERESTS: CRS TEAM



Kathy O'Connell

She is a Clinical Research Coordinator and has been with the CRS for almost two years. She loves to spend time at her camp in Pymatuning with her husband and sons. Her other hobbies are reading and painting with diamonds.

Felicia Kass

She loves her German shepherd, Tucker, and enjoys reading fiction, traveling, art, eating out, and going to the theatre.

Amy Rodger

She is a Clinical Research Coordinator. She loves music and going to the theatre. Her other love is her sweet beagle, Lilly.

Megan Fritz

She is a Research Coordinator and has been in CRS for almost four years. She loves sports and works for Robert Morris University's men's and women's basketball program as a statistician. In her spare time, she likes crafting, craft beer, country music, hiking, and is a true crime junkie.

Jessica Perman

She is a Clinical Research Associate and has been in CRS for a little over a year. She enjoys baking, knitting, and binge-watching "Law and Order: SVU."

Romano Sebastiani

He is a Research Associate and has been with CRS for about 10 months. His hobbies include playing basketball, working out and reading.

Miles Mccoy

He is a Research Associate. He enjoys reading, cooking, sailing and playing games (mostly Magic: The Gathering).

Courtney Heinl

She is a Research Associate and has been with CRS for about nine months. Her hobbies include working out, going for walks with my dogs, drinking coffee, and traveling with her fiancé.

Dana Tirabassi

She is a Regulatory Specialist and has been with CRS for a little over two years. She enjoys crafts, playing video games, and learning new things. Her current interests include card making, "Raft" (a PC game) and learning to snowboard.

Maria Feki

She is a Regulatory Specialist. She enjoys crafts, playing Her hobbies are gardening, spending time with her family and dogs, going for walks, traveling, running 5k races, home improvement projects, decorating for the holidays and crafting.

SPOTLIGHT TRIAL

Combination BTK and BCL-2 inhibition in Chronic Lymphocytic Leukemia

HCC 19-129: A Randomized, Multicenter, Open-Label, Phase 3 Study to Compare the Efficacy and Safety of Acalabrutinib (ACP-196) in Combination with Venetoclax with and without Obinutuzumab Compared to Investigator's Choice of Chemoimmunotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia Without del(17p) or TP53 Mutation

Principal Investigator: Dr. Jing-Zhou Hou, houj@upmc.edu

Bruton tyrosine kinase (BTK) inhibition is an established therapeutic intervention for the treatment of chronic lymphocytic leukemia (CLL); however, data suggest that most patients who respond to a single-agent, such as ibrutinib, have ongoing persistent disease. The correlation of minimal residual disease (MRD)-negative status with longer remissions and the durable remissions that may be achieved with BTKi, suggests the benefits of identifying combination regimens that may lead to deeper, MRD-negative responses. Early genetic studies demonstrating that BCL-2 overexpression rescues BTK-deficient XID murine B cells from spontaneous apoptosis have encouraged the investigation of combination therapy with a BTKi and a BCL-2 inhibitor. In this study, patients in Arm A will be administered acalabrutinib, a selective, irreversible small molecule BTKi currently under clinical investigation with venetoclax, a highly selective small-molecule BCL-2 inhibitor that induces CLL cell apoptosis. In Arm B, obinutuzumab, which has the potential to deepen responses further and attain negative MRD status in both bone marrow and peripheral blood, will be added to the doublet of acalabrutinib and venetoclax, and Arm C consist of patients administered a chemoimmunotherapy of the Investigator's choice (fludarabine/cyclophosphamide/rituximab or bendamustine/rituximab).

Prospective male and female participants must be ≥ 18 years and meet the following main, among other, inclusion criteria to be eligible to enroll in this study:

- Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.
- Diagnosis of CLL that meets published diagnostic criteria
- Active disease per IWCLL 2018 criteria that requires treatment.
- Participants must use highly effective birth control throughout the study

PRIORITY TRIALS

HCC 19-131: Patient-centered and Efficacious Advance Care Planning in Cancer: the PEACe Comparative Effectiveness Trial

PEACe-compare is an NCI-funded, mixed-methods trial to compare the effectiveness of two different patient-facing advance care planning interventions that are widely used and known to be effective but entail considerable differences in costs and complexity. We are randomizing 400 patients with advanced cancer and their family caregivers to receive either facilitated advance care planning or web-based advance care planning. This trial is expected to have a high impact because it will provide novel and much-needed empirical evidence about the comparative effectiveness of these approaches on patient, family caregiver, and healthcare utilization outcomes.

Prospective participants from the target study population described below should be ≥18 years old and are expected to meet the following, among other, main eligibility criteria.

- Patients:
  - Have solid tumor
  - The oncologist "would not be surprised" if the patient died within the next year
  - Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or 2
  - Planning to receive ongoing care at a participating oncology clinic
  - Willing to participate in either a web-based or facilitated advance care planning program
- Caregivers:
  - Family member or friend of an eligible patient
  - Primary person involved in patient's care and best able to participate in the study, as assessed by the patient

Study team contacts: Dr. Yael Schenker (Study PI, yas28@pitt.edu), Shane Christopher Belin (belin@pitt.edu)

Genitourinary/Prostate

HCC 20-180: A Phase III Double-Blind, Randomized, Placebo-Controlled Study Assessing the Efficacy and Safety of Capivasertib + Abiraterone Versus Placebo + Abiraterone as Treatment for Patients with De Novo Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) Characterized by PTEN deficiency (CAPItello-281)

There is an important unmet medical need for treatments in the de novo metastatic hormone-sensitive prostate cancer (mHSPC) setting that delay cancer progression and ultimately, death, particularly in patients whose tumors are characterized by PTEN deficiency. Pre-clinical and clinical evidence suggests that the combined inhibition of serine/threonine specific protein kinase (AKT) and the androgen receptor (AR) axis may improve treatment outcomes in mHSPC. The purpose of this study is to determine the efficacy and safety of combining the AKT inhibitor capivasertib and the androgen biosynthesis inhibitor abiraterone with a steroid, given on a background of androgen deprivation therapy (ADT), in patients with newly diagnosed, previously untreated mHSPC and PTEN-deficient tumors.

Prospective participants must be ≥ 18 years old and meet the following, among other, main eligibility criteria:

- Histologically or cytologically confirmed newly diagnosed prostate adenocarcinoma without small cell histology
- Distant metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI scan
- No prior pharmacotherapy, radiotherapy, or surgery for metastatic prostate cancer (up to 3 months ADT, abiraterone, or both with prednisone/prednisolone allowed)
- ECOG performance status 0–1
- Consent to provide a FFPE tissue for PTEN immunohistochemistry (IHC) prospective testing and other protocol mandated assessment
- PTEN deficiency status by centralized testing (IHC) of tumor tissue

Study team contacts: Dr. Leonard Appleman (Study PI, applemanlj@upmc.edu), Clare Grzejka (Senior Clinical Research Manager, (grzejkac@upmc.edu)

Breast Cancer

HCC 19-089: A Phase III Double-blind Randomized Study Assessing the Efficacy and Safety of Capivasertib + Paclitaxel Versus Placebo + Paclitaxel as First-line Treatment for Patients with Histologically Confirmed, Locally Advanced (Inoperable) or Metastatic Triple-negative Breast Cancer

Phosphatidyl inositol 3 kinase (PI3K)/AKT signaling is often activated in triple-negative breast cancer (TNBC) through activating mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) or AKT1 and/or inactivating alterations in or deficient expression of phosphatase and tensin homolog (PTEN). Capivasertib, a novel pyrrolopyrimidine-derived compound, is a potent and selective oral inhibitor of all three3 isoforms of AKT. The phase II randomized PAKT study demonstrated that adding capivasertib to first-line paclitaxel therapy significantly prolonged progression-free survival (PFS) in patients with TNBC who were chemotherapy-naive in the metastatic setting. In this present phase III (CAPItello-290) study, we plan to further characterize and confirm the efficacy and safety of capivasertib + paclitaxel, which showed preliminary evidence of a clinically meaningful prolongation of overall survival (OS) compared with placebo + paclitaxel in this difficult to treat population.

This study is open at the following UPMC sites: Magee, HCC, Mt. View, Pasavant, USC, East, Pinnacle, Ortenzio, and Memorial, and prospective participants should meet these, among other, main eligibility criteria:

- TNBC (ER with < 1%)
- Eligible for taxane monotherapy as per local investigator assessment
- Measurable disease (lytic and mixed bone lesions assessed using CT/MRI)
- Tissue submission for Central testing
- No prior AKT,PI3K, or mTORi
- < 12 Months from end of neoadjuvant

Study team contacts: Dr. Brufsky (Study PI, brufskyam@upmc.edu), Brenda Steele (Senior Clinical Research Manager, steeleb@upmc.edu)

HCC: 20-211 Sanofi A randomized, multicenter, double-blind phase 3 study of SAR439859 plus palbociclib versus letrozole plus palbociclib for the treatment of patients with ER (+), HER2 (-) breast cancer who have not received prior systemic anti-cancer treatment for advanced disease

Selective estrogen receptor degrader (SERDs) are competitive ER antagonists that also induce conformational ER degrading changes via the ubiquitin proteasome system. Current data demonstrate that SERDs could be an effective and well-tolerated therapy for postmenopausal women with advanced breast cancer and highlight the need for new SERDs with optimized characteristics such as improved route of administration (PO versus IM), bioavailability, and long-term maintenance of ER receptor blockade with strong antitumor activity. This present study aims to demonstrate the superiority of a new oral SERD, SAR439859, in combination with palbociclib versus letrozole in combination with palbociclib. Participants with ER+ human epidermal growth factor receptor 2-negative [HER2-] advanced or metastatic breast cancer who have not received prior systemic anticancer treatment for advanced disease will be randomly assigned to either the experimental Arm A to receive SAR439859 200 mg + letrozole-matching placebo + palbociclib 125 mg or to Arm B, where they will receive SAR439859-matching placebo + letrozole 2.5 mg + palbociclib 125 mg.

This study is open at Magee, HCC, Mt. View, Pasavant, Uniontown, East, USC, and Washington UPMC sites and prospective participants will be required to meet the following, among other, main eligibility criteria:

- Documentation of ER positivity (≥1% positive-stained cells)
- Previously untreated with any systemic anticancer therapy for their loco-regional recurrent or metastatic disease
- Measurable or non-measurable disease
- Treated/stable brain metastasis acceptable

Study team contacts: Dr. Brufsky (Study PI, brufskyam@upmc.edu), Brenda Steele (Senior Clinical Research Manager, steeleb@upmc.edu)

Gynecological Cancer

HCC 19-164: Phase IIA Trial of Delayed Initiation of Olaparib Maintenance Therapy in Platinum Sensitive Recurrent Ovarian Cancer

Olaparib is FDA-approved for maintenance therapy for patients with platinum-sensitive recurrent epithelial ovarian cancer with a complete or partial response to the most recent platinum-based chemotherapy. A large phase III clinical trial demonstrated that delaying initiation of chemotherapy did not negatively impact patient overall survival (OS) and allowed patients to restart treatment 5 months later and reduced overall toxicities. The purpose of this study is to determine if delaying the commencement of olaparib until there is a rise in the tumor marker cancer antigen 125 (CA-125) will prolong the time until the next or different treatment for the patient's cancer. The study will also evaluate how delaying the start of maintenance therapy will affect symptoms, physical functioning, quality of life, and impact on finances. Eligible patients will be enrolled within 8 weeks of completing platinum-based therapy for recurrent disease, monitored with CA-125 levels every 28 days. At the first evidence of a two-fold rise in CA-125 from baseline, they will undergo a CT scan to evaluate any visible lesions, and then will commence olaparib therapy.

This study, which is open at the following UPMC sites: Magee, HCC, Mt. Pleasant, Mt. View, Norwin-Altoona, Beaver, Erie, Greenville, Horizon, Indiana, Murtha, McKeesport, East, Northwest, Passavant, St. Margarets, Uniontown, USC, Washington, Mercy, and Pinnacle has the following, among other, main eligibility criteria that prospective participants are expected to meet:

- Must have completed at least 2 courses of platinum-based chemotherapy with a PR or CR or CA-125 response
- BRCA required
- No prior PARP inhibitor

Study team contacts Dr. Sarah Taylor (Study PI, taylorse2@upmc.edu), Brenda Steele (Senior Clinical Research Manager, steeleb@upmc.edu)

HCC 19-141 (GY018): A Phase III Randomized, Placebo-controlled Study of Pembrolizumab (MK-3475, NSC #776864) In Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer

Immunotherapy with monoclonal antibodies, such as pembrolizumab, may help the immune system attack cancer and may interfere with the ability of tumor cells to grow and spread. Paclitaxel and carboplatin are chemotherapy drugs used as part of the usual treatment approach for this measurable stage III or IVA, stage IVB, or recurrent endometrial cancer. This phase III trial aims to assess if adding pembrolizumab immunotherapy to paclitaxel and carboplatin works better than paclitaxel and carboplatin alone in treating patients with stage III or IV, or recurrent endometrial cancer. Patients who fulfill the eligibility criteria will be randomized to one of the following arms. Arm 1: will receive carboplatin, paclitaxel, and placebo in the combination phase and placebo in the maintenance phase; Arm 2: will receive carboplatin, paclitaxel, and pembrolizumab in the combination phase and pembrolizumab in the maintenance phase. In the combination phase, both arms will be treated every 3 weeks for up to six6 cycles and in the maintenance phases, they will be treated for up to 14 cycles.

This study, which is open at the following UPMC sites: Magee, Mt. View, Passavant, and East has the following, among other, main eligibility criteria that prospective participants are expected to meet:

- Measurable stage III, measurable stage IVA, stage IVB (with or without measurable disease) or recurrent (with or without measurable disease) endometrial cancer
- Patients may have received NO prior chemotherapy for treatment of endometrial cancer OR
- Prior adjuvant chemotherapy (e.g., paclitaxel/carboplatin alone or as a component of concurrent chemotherapy and radiation therapy [with or without cisplatin]) provided adjuvant chemotherapy was completed ≥ 12 months prior to STEP 1 registration
- Patients may have received prior radiation therapy for treatment of endometrial cancer
- NO prior anti-PD-1, PD-L1 or any CTLA-4
- Patients may have received prior hormonal therapy for treatment of endometrial cancer. All hormonal therapy must be discontinued at least three weeks prior to STEP 1 registration

Study team contacts Dr. Alexander Olawaiye, (Study Pi, olawaiyea@upmc.edu), Brenda Steele (Program Manager, steeleb@upmc.edu)

BIOBEHAVIORAL TRIAL

HCC 20-064: Mobile Device CBT for Chemotherapy-related Cognitive Dysfunction: A Multi-center Randomized Controlled Trial

Cancer-related cognitive impairment (CRCI) consists of persistent mild to moderate impairments in memory and attention for a large proportion of cancer survivors. Presently, there is no established treatment for CRCI, although our cognitive-behavioral therapy, Memory and Attention Adaptation Training (MAAT) has efficacy support from several previous trials. The present study is a randomized controlled trial evaluating MAAT vs. a supportive therapy (ST) control condition among stage I, II, and III breast cancer survivors with cognitive symptoms 1–5 years post-chemotherapy. Both treatments are delivered via telehealth video visits. The primary aims are to evaluate efficacy in this first multi-site trial of MAAT (UPMC Hillman Cancer Center and affiliates and Indiana Simon Cancer Center and affiliates). Screening and neurocognitive testing pre-and-post-treatment is completed via telephone. A secondary aim is to evaluate a subset of willing and eligible participants in functional MRI scanning to elucidate treatment-induced changes in brain activation patterns that can clarify mechanisms of cognitive improvement. This trial is open to Hillman Cancer Center and all affiliates.

Prospective participants > 18 years of age are expected to meet the following main, among other, eligibility criteria:

- Diagnosis of stage I, II, and III breast cancer
- 1-5 years post-treatment and currently disease free
- Treatment involved adjuvant or neoadjuvant chemotherapy
- Report cognitive problems of memory and concentration attributed to chemotherapy
- No prior cancer or cancer therapy other than non-melanoma skin cancer
- No CNS involved cancer
- No active severe neurological or neuropsychiatric condition such as dementia or severe depression

Study team contacts: Dr. Robert Ferguson (Study PI, fergusonrj2@upmc.edu), Audrey Kreitz (412-623-5975 or kreitza@upmc.edu), Josh Plassmeyer (Biobehavioral Cancer Control Program/Operations Supervisor, plassmeyerj@upmc.edu) or Ella Choban (Research Coordinator, chobane@upmc.edu)

Melanoma and Cutaneous Tumors

HCC 20-101 A Phase II Trial of Nivolumab plus Axitinib in Patients with Anti-PD1 Refractory Advanced Melanoma

We have shown that tumor oxidative metabolism and the resultant hypoxia are associated with resistance to immunotherapy. In addition, in preclinical studies, combining low-dose axitinib, a VEGF receptor small molecule tyrosine kinase inhibitor with demonstrated safety and tolerability, with anti-PD1 decreased intra-tumoral hypoxia and synergizes with checkpoint inhibitors (ICB) to eradicate melanoma tumors. Thus, we hypothesize that decreasing hypoxia in the TME will re-sensitize melanoma tumors to anti-PD1 immunotherapy and overcome resistance. To prove our hypothesis, we are conducting this Phase II trial of nivolumab plus axitinib for patients with unresectable stage III or IV melanoma who have progressed on prior anti-PD1 therapy with or without concomitant anti-CTLA4 therapy. Patients will receive treatment with nivolumab 480 mg intravenously every 4 weeks and axitinib 5 mg twice daily by mouth. Patients may continue both agents for up to 2 years if they do not experience disease progression or dose-limiting toxicities.

Prospective participants are expected to be ≥ 18 years old and fulfil the following main, among other, eligibility criteria:

- Have unresectable (stage III) or advanced (stage IV) cutaneous or mucosal melanoma. Patients with uveal melanoma are not eligible.
- Progressed on prior anti-PD1 therapy with or without anti-CTLA4 therapy.
- Have measurable disease based on RECIST 1.1.
- Patients with biopsiable disease must undergo biopsy at study entry and at week 12.
- Have a performance status of 0 or 1 on the ECOG Performance Scale.
- Demonstrate adequate pre-defined organ function and all screening labs should be performed within 14 days of treatment initiation.
- Patients with brain metastases are permitted if they are asymptomatic or previously treated with CNS directed therapy with stable CNS disease for at least 2 weeks.

Study team contacts: Dr. Yana Najjar (Study PI, najjaryg@upmc.edu) or Amy Rose (Senior Clinical Research Manager, kennaj@UPMC.EDU)

HCC 20-190: A Multi-Center Phase I/II Open Label Study to Evaluate Safety and Efficacy in Participants with Metastatic BRAF-mutant Melanoma Treated with Encorafenib with and without Binimetinib in Combination with Nivolumab and Low-dose Ipilimumab. (QUAD 01: Quadruple Therapy in Melanoma)

Both targeted therapy (BRAF + MEK inhibitors) and immunotherapy (anti-PD-1 + anti-CTLA-4) are approved in the US and EU for metastatic or unresectable BRAFV600E/K mutant melanoma. Early phase trials combining targeted therapy with anti-PD-L1 have reported increased progression-free survival (PFS) compared to targeted or immunotherapy alone. In this Phase 1/2 study, we aim to detail the safety and efficacy of a novel treatment using targeted therapy (encorafenib with or without binimetinib) and two immunotherapies (nivolumab plus ipilimumab, triple or quadruple therapy) for high-risk patients with unresectable or metastatic BRAF-mutant melanoma who historically have not responded to doublet or triplet therapy. In Phase I, the tolerability of two arms will be compared to establish the recommended phase II regimen (RP2R), which will be further used in Phase 2 to investigate the early efficacy in participants with high-risk features who are less likely to derive benefit from standard therapy treatment approaches and who may benefit from quadruple therapy despite the potential for increased toxicity. Following initiation of triple or quadruple therapy, participants will be followed for safety and response.

Potential male and female participants ≥ 18 years of age are expected to meet the following major, among other, eligibility criteria:

Phase I RP2R finding

- Patients with histologically confirmed metastatic or unresectable BRAFV600E/K mutant melanoma
- Patients must be greater than 6 months from adjuvant therapy (if any given) and/or treatment naïve in the metastatic setting.
- Patients must meet criteria for inclusion into either Phase II expansion cohorts listed below – Brain Metastases or Elevated LDH/ Bulky Visceral Disease

Phase II: High-risk Expansion Groups

Group 1: Brain Metastases

- Metastatic melanoma involving the brain but excluding leptomeningeal disease
- Treatment with stereotactic radiosurgery must have occurred ≥14 days prior to start of study treatment. If prior radiosurgery was pursued, then at least one evaluable lesion must not have been irradiated. Prior whole-brain radiation is not allowed.
- Symptomatic brain parenchymal metastases not requiring urgent radiation are permitted as well as patients on a stable dose of corticosteroids equivalent to 4 mg dexamethasone daily for the preceding 10 days prior to first dose.
- Eligible patients with prior local therapy to all brain lesions must have demonstrated progression of pre-existing target lesions per RANO-BM criteria.

Group 2: Elevated lactate dehydrogenase (LDH) with Liver Metastases OR Bulky Visceral Disease

- LDH >1x ULN
- Total body SLD > 44mm (including but not limited to liver metastases) or metastatic melanoma involving the liver

Study team contacts: Dr. Jason Luke (Study PI, lukejj@upmc.edu) or Amy Rose (Senior Clinical Research Manager, kennaj@UPMC.EDU)

HCC 20-257: A Randomized, Open-label, Active-control, Phase 2/3 Study of First-line Intratumoral CMP-001 in Combination with Intravenous Nivolumab Compared to Nivolumab Monotherapy in Subjects with Unresectable or Metastatic Melanoma

PD-1 blockade with agents such as nivolumab is an effective and important therapy for the treatment of melanoma, while toll-like receptor 9 (TLR9)-mediated T cell activation and trafficking to the tumors has shown the potential to improve the response to PD-1 blockade, particularly in non-inflamed tumors. CMP-001 is a TLR9 agonist, and studies in preclinical models showed that intratumoral (IT) dosing of TLR9 agonists was more effective than distant subcutaneous (SC) dosing, by inducing regression of the directly injected tumor and distant metastases. In this two-part Phase 2/3 study, the primary objectives of Phase 2 and 3 parts are to determine confirmed objective response rate (ORR) and progression-free survival (PFS), respectively for treatment with first-line IT CMP-001 in combination with nivolumab versus nivolumab monotherapy in patients with unresectable or metastatic melanoma.

Potential study participants ≥ 18-years old must meet the following, among other, eligibility criteria:

- Histologically or cytologically confirmed unresectable Stage III or Stage IV melanoma per
- AJCC Cancer Staging Manual Eighth Edition.
- Measurable disease, as defined by RECIST v1.1 and both of the following:
  - At least 1 accessible lesion amenable to repeated IT injection
  - One or more measurable lesions at least 1 cm in diameter that are not intended for CMP-001 injection and can be followed as target lesions per RECIST v1.1
- Able to provide tissue from a core or excisional biopsy
- Adequate bone marrow, liver, renal, and coagulation function based on most recent laboratory values within 3 weeks before he first dose of study treatment on Week 1 Day 1 (W1D1)
- Eastern Cooperative Oncology Group Performance Status of 0 to 1 at Screening.

Study team contacts: Dr. Diwakar Davar (Study PI, davard@upmc.edu) or Amy Rose (Senior Clinical Research Manager, kennaj@UPMC.EDU)

ACHIEVEMENTS AND ACCOLADES

CRS Goes Digital

One of our priorities in 2021 is to evaluate our processes for efficiency and to develop and implement more effective methods of task completion. To remain on the forefront of development and assume the role of a model NCI designated cancer center in terms of process improvement, we need to modernize our processes and transform the way we do this one process at a time. One major process identified as requiring improvement for various reason is how adverse event logs are maintained and approved. The current paper process creates room for repeated errors in log entry, GCP compliance, sign off timing, and audit readiness. Consequently, we have developed a fully electronic version using a SharePoint platform that is compliant with all GCP requirements and FDA regulations. Physicians will only be required to enter information required by law. The process was developed and implemented with input from physicians, coordinators, research associates and management. The CRS eAE logs have also increased efficiency compared to available 3rd party applications and have received very positive feedback from many end users. However, we fully understand that no process is perfect, and we welcome feedback on any level of the process. Please contact Josh Plassmeyer, Operations Supervisor (plassmeyerjm@upmc.edu) with any suggestions or questions regarding the eAE logs.

OPEN STUDIES AND ACCRUALS JAN – MAR 2021

Disease / Modality Center	Open Trials		Accruals	
	Interventional	Therapeutic	Interventional	Therapeutic
Biobehavioral Medicine in Oncology Program	8	0	106	0
Brain Tumor Center	13	13	4	4
Breast Center	30	25	41	11
Early Therapeutics Centers (Phase I and II)	56	56	25	25
GI/Esophageal Cancer Center	27	27	30	30
Gynecological Oncology Center	13	12	6	6
Head and Neck Center	26	24	46	24
Hematological Malignancies Center	37	37	15	15
Immune Therapy Center	53	53	32	32
Lung and Thoracic Malignancies Center	39	35	35	6
Melanoma Center	26	26	28	28
Multi-Disease/Modality Center Trials	3	2	211	55
Pediatric Oncology	56	54	4	4
Prostate and Urologic Cancers	17	17	6	6
Sarcoma Center	13	13	6	6
Supportive Care	1	0	0	0
Radiation Oncology Center	20	20	12	12
Total	**438**	**414**	**607**	**264**

****All Accruals are calculated from January 1 through March 31.**

Multi-disease/Modality Center Trials: HCC# 18-177
Accrual Total: 195, Therapeutic 20%: 39

Clinical Research Services (CRS) is made up of over 200 staff members who facilitate development, implementation, coordination, internal data monitoring, and completion of approximately 400 oncology-focused trials at Hillman each year. These trials include institutional (investigator-initiated), multi-center cooperative group/ National Clinical Trial Network (NCTN), consortium, and industry-sponsored trials. Using a disease-specific centers model for conducting clinical trials, CRS provides study development and implementation assistance, submissions to the FDA, IRB processing, patient recruitment, study coordination, study-specific training, data collection, and specimen collection and processing.

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