THE TRIAL BLAZER

UPMC HILLMAN CANCER CENTER

A QUARTERLY NEWSLETTER FROM
CLINICAL RESEARCH SERVICES

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INTRODUCTION

In this first edition of the Trial Blazer newsletter for 2022, we would like to extend our heartfelt appreciation to our entire team at CRS for the incredible efforts they have all put in over the past year to ensure that we continue to provide world-class care and services to our cancer patients.

CRS continues to work to fill the position vacated by Dr. Bhanu Pappu. During this transitionary phase, Dr. Chad Ellis and Deidre Cleary have stepped in. We have maintained our clinical trial accrual in the face of a number of changes, not only in our leadership but also in our general operating systems and processes, and the COVID 19-related adjustments we have made.

We are pleased to announce new leadership appointment of three associate directors for CRS. Mary Horak is Associate Director, Quality, Education, and Compliance; Josh Plassmeyer is Associate Director, Operations; and Amy Rose is Associate Director, Clinical Administration, effective March 14, 2022.

We are also pleased to announce important updates to the UPMC Hillman Cancer Center early phase therapeutics program. The Cancer Immunotherapeutic Center (CIC) and the Phase I Clinical Trials Center have been consolidated into a single operational unit named Immunotherapy and Drug Development Center (IDDC) within the UPMC Hillman Cancer Center, effective January 1, 2022. The IDDC includes all the clinical trial activities and personnel from CIC and Phase I Clinical Trials Center. This consolidation enables our organization to realize greater synergy in clinical and research operations in early phase therapeutics, and advances strategic collaborations and faculty engagement for the benefit of our patients and support of Hillman Cancer Center research programs. The IDDC will be co-led by three outstanding phase I investigators: Jan Beumer, PharmD, who will serve as IDDC co-leader and PI of our NIH UM1 grant; Liza Villaruz, MD, who will serve as IDDC co-leader and the medical director; and Jason Luke, MD, who will serve as IDDC overall program leader. Clinical Research Services (CRS) staff support from CIC and the Phase I Center will move wholly into the IDDC with Julie Urban, PhD, as Team Manager.

This past year, we have had several new faculty join our Hillman family. Please view their introductory profiles in the "Introducing New UPMC Hillman Cancer Center Faculty" section and join us in extending a welcome to them all.

The "Spotlight Trial" in this edition is by Dr. Adam Brufsky and entitled "**HCC 20-301: A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of Trastuzumab Deruxtecan (T-DXd) Versus Trastuzumab Emtansine (T-DM1) in Subjects with High-Risk HER2-Positive Primary Breast Cancer Who Have Residual Invasive Disease in Breast or Axillary Lymph Nodes Following Neoadjuvant Therapy.**" This study has the primary objective of evaluating invasive disease-free survival (IDFS) in patients treated with T-DXd compared to those administered T-DM1. Because of the distinct properties of T-DXd and its anticancer activity in metastatic breast cancer patients who did not respond to T-DM1, the

Continued

Points of Interest

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investigators anticipate that T-DXd will be effective even in the high-risk adjuvant subpopulation in which T-DM1 had not demonstrated compelling efficacy.

Important research like this is made possible through efforts from the entire CRS and Hillman teams. Again, we are most appreciative of all their efforts in continuing UPMC Hillman Cancer Center's commitment to excellence in cancer care and to quickly move the most promising research results from labs into clinical trials. Together, we are working to accelerate the most promising new immunotherapies and drugs to improve cancer patients' lives.

Antoinette (Toni) Wozniak, MD, FACP, FASCO
Associate Director for Clinical Research

Deidre Cleary, BSN, RN, CCRC
Senior Director, Clinical Research Services

SPOTLIGHT TRIAL

T-DXd versus T-DM1 in High-risk HER2-Positive Primary Breast Cancer

Trastuzumab Deruxtecan (T-DXd) Versus Trastuzumab Emtansine (T-DM1) in Subjects with High-Risk HER2-Positive Primary Breast Cancer Who Have Residual Invasive Disease in Breast or Axillary Lymph Nodes Following Neoadjuvant Therapy

Principal Investigator: Dr. Adam Brufsky, brufskyam@upmc.edu

Trastuzumab deruxtecan (T-DXd) is an HER2-targeted antibody and topoisomerase I inhibitor conjugate, indicated for the adjuvant treatment of high-risk patients with HER2-positive primary breast cancer (BC), who have residual invasive disease and were inoperable at disease presentation or had positive pathological node status after neoadjuvant therapy. Trastuzumab Emtansine (T-DM1) is an HER2-targeted antibody and microtubule inhibitor conjugate, indicated as a single agent for the adjuvant treatment of patients with HER2-positive early BC (eBC) who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. T-DXd has demonstrated high, durable response rates in patients previously treated with T-DM1 with unresectable or metastatic BC. The differentiating features of T-DXd and its anticancer activity in metastatic BC after T-DM1 failure strongly indicate that antibody-drug conjugate (ADC) T-DXd would be effective even in the high-risk adjuvant subpopulation in which T-DM1 did not demonstrate compelling efficacy. In this study, at least 1600 patients will be randomized in a 1:1 ratio to receive starting doses of T-DXd 5.4 mg/kg or T-DM1 3.6 mg/kg and will be stratified based on operative status at disease presentation prior to neoadjuvant therapy, tumor hormone receptor (HR) status (positive vs negative), post-neoadjuvant therapy pathologic nodal status, and HER2-targeted neoadjuvant therapy approach (single vs dual).

Prospective participants who are > 18 years old are expected to meet the following key, among other, eligibility criteria:

- Have early breast cancer (eBC) as predefined, with residual disease following neoadjuvant therapy
- Completed neoadjuvant therapy including trastuzumab followed by surgery
- High-risk of recurrence (node-positive or inoperable at presentation)
- Centrally confirmed HER2-positive status
- ECOG PS: 0-1

Study team contacts: Dr. Adam Brufsky, Study Principal Investigator (brufskyam@upmc.edu) and Joshua Plassmeyer, Associate Director Operations and Breast/Gynecological Cancer Center Manager (plassmeyerjm@upmc.edu)

INTRODUCING New UPMC Hillman Cancer Center Faculty

This past year, we have had several new faculty join our Hillman family. We are pleased to introduce:

Khalil Abdullah, MD
A neurosurgeon and the director of translational neuro oncology at the UPMC Hillman Cancer Center. His areas of special interest include brain tumors, hydrocephalus, Chiari malformations, trigeminal neuralgia, and traumatic brain injuries.

Mike Cowher
A breast surgeon specializing in a variety of breast conditions including surgical intervention for breast cancer.

Charles Geyer, Jr., MD, FACP
Who joins UPMC Hillman Cancer Center as co-director of our National Cancer Institute (NCI) National Clinical Trials Network efforts. He is a medical oncologist and physician-investigator and will continue to serve as the chief scientific officer of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation, chair of the NSABP Foundation Breast Cancer Committee and medical oncology co-chair of the NRG Oncology Breast Committee.

Dennis Hsu, MD
A physician-scientist from Memorial Sloan Kettering Cancer Center, whose clinical interest and focus is gastrointestinal cancers.

Pritish Iyer, MD
A medical oncologist/hematologist who specializes in the treatment of all medical oncology and hematology patients.

Mark Knestrick, MD, Pharm.D.
A medical oncologist and hematologist who received his medical degree from West Virginia University in Morgantown and his pharmacy degree from Duquesne University in Pittsburgh. Dr. Knestrick completed both a residency in internal medicine and a hematology/oncology fellowship at West Virginia University Department of Medicine.

Monica Malhotra, MD
A former chief fellow, who joined the OHA group and will focus on the treatment of gastrointestinal malignancies.

Gloria Minella, MD
A certified professional in medical oncology and internal medicine by the American Board of Internal Medicine. She practices at UPMC Hillman Cancer Center at Butler Health System and is affiliated with UPMC Magee-Womens Hospital. She completed her fellowship and residency at University of Pittsburgh School of Medicine and earned her medical degree at George Washington University.

Zahra Rahman Kelly, DO
A medical oncologist and hematologist who is trained in the management of all cancers and blood disorders with a focus in genitourinary and head and neck malignancies.

Risa Wong, DO
Who joined UPMC Hillman from the University of Washington and her interests are in genitourinary malignancies and in patient outcomes research.

Please join us in extending a warm welcome to them all!

PRIORITY TRIALS

Genitourinary/Prostate Cancers

HCC 21-148: A Phase 2 Multiple-Dose, Multiple-Arm, Parallel Assignment Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of XmAb®20717 Alone or in Combination with Chemotherapy or Targeted Therapies in Selected Subjects with Metastatic Castration-Resistant Prostate Cancer

Principal Investigator: Dr. Roby Thomas, thomasra@upmc.edu

Combination treatment with the immune checkpoint anti-PD1 (nivolumab) and anti-CTLA4 (ipilimumab) molecules has recently been associated with longer radiographic progression-free survival in patients with homologous recombination deficiency and DNA damage repair gene positive tumors, and those with high tumor mutational burden. XmAb20717 is a humanized monoclonal bispecific antibody (bsAb) that binds PD1 and CTLA4 to block signaling that prevents activated T cells from attacking and clearing tumor cells from the body. This present study employs a parallel-group design to evaluate the effects of a single dose level of XmAb20717 in patients with metastatic castration-resistant prostate cancer (mCRPC) within distinct molecularly defined cohorts, based on the presence of genetic abnormalities that might make them more responsive to checkpoint inhibitor therapy. XmAb20717 will be co-evaluated with treatments considered as standard of care for each of the defined cohorts, except for the cohort with microsatellite instability high (MSI-H)/ mismatch repair deficient (MMRD) tumors.

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

- Histologically confirmed diagnosis of carcinoma of the prostate
- Documented progressive mCRPC based on pre-defined conditions
- Prostate cancer must have progressed after treatment with at least 2 prior lines of approved anticancer treatments for metastatic prostate cancer; prior treatment of subjects in Cohort D (MSI-H or MMRD) must include a checkpoint inhibitor approved by FDA for that indication
- Patients without surgical orchiectomy must be on androgen suppression treatment with castrate level of testosterone (≤ 50 ng/dL) and willing to continue the treatment throughout the study
- Meet the additional cohort-specific criteria (available on further request)
- Evaluable disease according to PCWG3 criteria
- Adequate archival metastatic tumor tissue or agree to undergo a biopsy of at least 1 metastatic site
- Eastern Cooperative Oncology Group performance status of 0 or 1

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

Breast Cancers

HCC 21-007: CompassHER2 Residual Disease (RD), a double-blinded, phase III randomized trial of T-DM1 and placebo compared with T-DM1 and tucatinib

Study Principal Investigator Dr. Kit Y. Lu, luky@upmc.edu

Ado trastuzumab emtansine (T-DM1) is an antibody-drug conjugate of the monoclonal antibody trastuzumab, which is a targeted antitumor therapy and the cytotoxic compound, emtansine (DM1), a microtubule inhibitor and maytansine derivative. T-DM1 has FDA approval for use in patients with HER2-positive metastatic breast cancer (MBC). Tucatinib is a potent oral HER2-specific TKI that is currently in clinical development for HER2-positive MBC. In this study, we hypothesize that T-DM1 and tucatinib may be superior in preventing breast cancer from relapsing in patients with HER2 positive breast cancer compared to T-DM1 alone. Eligible patients will be randomized to receive T-DM1 with or without tucatinib for up to 14 cycles in the absence of disease progression or unacceptable toxicity.

This study, which is open at all UPMC sites, has the following, among other, main eligibility criteria that prospective participants are expected to meet:

- HER2-positive status will be based on pretreatment biopsy material and defined as an immunohistochemistry (IHC) score of 3+ and/or positive by in situ hybridization (ISH)
- Patients with clinical stage T1-4, N0-3 disease at presentation and residual invasive disease
- Patients with residual HR-negative, HER2+ disease in the breast and/or lymph nodes per the surgical pathology report are eligible; however, patients with HR+ HER2+ cancers must have node-positive residual disease per the surgical pathology report in order to qualify for the study.

Study team contacts: Dr. Kit Y. Lu, Study Principal Investigator (luky@upmc.edu) and Joshua Plassmeyer, Associate Director Operations and Breast/Gynecological Cancer Center Manager (plassmeyerjm@upmc.edu)

HCC-21-204: A Phase III, Randomized, Open-label, Multicenter Study Evaluating the Efficacy and Safety of Adjuvant Giredestrant Compared with Physician's Choice of Adjuvant Endocrine Monotherapy in Patients with Estrogen Receptor-Positive, HER2-Negative Early Breast Cancer

Principal Investigator: Dr. Adam Brufsky, brufskyam@upmc.edu

Endocrine therapy with tamoxifen or aromatase inhibitors with or without ovarian function suppression is currently the main endocrine treatment options for estrogen receptor-positive (ER+) early breast cancer (EBC). However, many patients ultimately experience disease relapse or develop resistance to these agents and associated toxicity frequently leads to treatment discontinuation. Consequently, more optimal adjuvant therapies are needed for patients with ER+ EBC, particularly those with a high likelihood of recurrence. Small-molecule, selective estrogen receptor degraders (SERDs) are a recognized therapeutic approach in patients with ER+ metastatic BC (MBC) and oral SERDs may provide a more tolerable treatment option that enables better adherence, thus, maximizing therapeutic benefit and compliance. In this study, eligible participants will be randomly assigned (1:1) to receive either giredestrant, an orally bioavailable potent SERD at 30 mg once daily (Arm A) or Therapy of Physician's Choice (TPC) dosed according to local prescribing information (Arm B), for at least 5 years. During the study, participants will be regularly assessed for efficacy, safety, and health-related quality of life.

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

- ER+ tumor documented using immunohistochemistry, according to the ASCO/College of American Pathologists (CAP) guidelines
- HER2- tumor as assessed locally on a primary disease specimen and defined according to ASCO/CAP guidelines
- Multicentric and/or multifocal BC if all examined tumors meet.
- Bilateral synchronous invasive BC is eligible if all histopathologically examined tumors meet ER+ and HER2- pathologic criteria
- Have undergone definitive surgery of the primary breast tumor(s)
- If received or will be receiving adjuvant chemotherapy, must have completed adjuvant chemotherapy prior to randomization
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0, 1, or 2
- Adequate organ function according to predefined standard laboratory tests

Study team contacts: Dr. Adam Brufsky, Study Principal Investigator (brufskyam@upmc.edu) and Joshua Plassmeyer, Associate Director Operations and Breast/Gynecological Cancer Center Manager (plassmeyerjm@upmc.edu)

Biobehavioral Trial

HCC 20-243: A Pilot and Feasibility Study of the Apollo Device for Fatigue in Patients with Metastatic Breast Cancer

Principal Investigator: Dr. Margaret Rosenzweig, mros@pitt.edu

Metastatic breast cancer yields a unique, and at times severe symptom burden including over half of all patients with metastatic breast cancer reporting high levels of fatigue. Among this population the consequences of fatigue on physical and psychological well-being are tremendous, with impact on home and work functionality, relationships, quality of life and the ability to tolerate prescribed cancer therapy. This research study examines whether wearing a watch-like device that stimulates the wearer's nerves with wave-like vibrations will help people with metastatic breast cancer feel less fatigued. The Apollo device is an investigational device, as it is not FDA approved, to treat symptoms related to metastatic breast cancer. Participants will be asked to fill out surveys before, during, and after using the Apollo device for 8 weeks. We hypothesize that fatigue symptoms will improve from baseline after 4 and 8 weeks of Apollo use.

Eligible participants will be women diagnosed with metastatic breast cancer who self-report fatigue greater than 4 (Scale 0–10). Participants will also need to own and operate a smart phone regularly.

Study team contact: Dr. Margaret Rosenzweig, Principal Investigator (mros@pitt.edu, 412-383-8839) and Joshua Plassmeyer, Associate Director Operations and Breast/Gynecological Cancer Center Manager (plassmeyerjm@upmc.edu).

Immunotherapy and Drug Development Center

HCC 20-266: Phase IIA Basket Study of Pixatimod (PG545) in Combination with Nivolumab in PD-1 Relapsed/Refractory Metastatic Melanoma and NSCLC and Pixatimod (PG545) in Combination with Nivolumab and low-dose Cyclophosphamide in MSS Metastatic Colorectal Carcinoma (mCRC)

Principal Investigator: Dr. Diwakar Davar, davard@upmc.edu

Nivolumab is approved to treat cancers including MSI-H colorectal cancer (CRC), while pixatimod, an investigational drug under evaluation in melanoma, non-small cell lung, and microsatellite stable colorectal cancers, has shown complementary activity to that of anti-PD(L)1 antibodies. Cyclophosphamide is approved for the treatment of various cancers and, at low doses (immunomodulatory), is under investigation in combination with various immunotherapies including nivolumab. In the first stage of this study to evaluate the antitumor efficacy and safety of the nivolumab/pixatimod/cyclophosphamide combination in microsatellite stable (MSS) metastatic CRC (mCRC), patients in cohort 1 will receive nivolumab 480 mg every 4 weeks (Q4W), pixatimod 25 mg weekly (Q1W), and cyclophosphamide (50 mg twice daily, 1-week-on, 1-week-off), while patients in cohorts 2 and 3 will be similarly treated but without cyclophosphamide.

Prospective male and female participants who are ≥ 18 years old will be expected to fulfil the following general inclusion criteria:

- Have advanced/metastatic cutaneous melanoma, NSCLC, or MSS mCRC
- Have measurable disease based on RECIST 1.1
- Provide newly obtained core or excisional biopsy of a tumor lesion not previously irradiated to undergo tumor biopsy (core, punch, incisional or excisional)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 performed within 28 days prior to enrollment
- Adequate organ function as pre-defined based on standard screening labs obtained within 4 weeks of Cycle 1 day 1
- Male participant must agree to use a recommended contraception for at least 120 days after last study treatment dose and refrain from donating sperm during this period
- Female participants must not be pregnant or breastfeeding, and any woman of childbearing potential (WOCBP) must follow the study contraceptive guidance during treatment and for at least 120 days after the last dose
- Other additional cohort-related criteria will be provided on request

Study team contacts: Dr. Diwakar Davar, Principal Investigator (davard@upmc.edu) and Julie Urban, Immunotherapy and Drug Development Center and Phase II Center Manager (urbanj2@upmc.edu)

HCC 20-228: Phase I Study Investigating the Safety of Stereotactic Body Radiotherapy (SBRT) with Anti-PD1 and Anti-IL-8 for the Treatment of Multiple Metastases in Advanced Solid Tumors

Study Principal Investigator: Dr. Jason Luke, lukejj@upmc.edu

Nivolumab (and other agents affecting the anti-programmed death-1 [anti-PD-1] pathway) have demonstrated anti-tumor activity in multiple tumor types including non-small cell lung cancer (NSCLC), melanoma (MEL), renal cell carcinoma (RCC), and other cancers. However, there remains a large proportion of participants who do not achieve durable clinical benefit to nivolumab monotherapy. Combinations of immune-oncology (IO) agents with complimentary mechanisms as well as radiation represent a promising strategy to improve response rates to immunotherapy. In this phase I study, radiation will be used in combination with IO agents nivolumab and anti-IL-8 (BMS-986253) to assess toxicity by organ system. The study will determine the safe doses of radiation by organ site in conjunction with nivolumab at a dose of 480 mg and BMS-986253 at 2400 mg. The study will also provide the opportunity to evaluate changes in the tumor microenvironment induced by the treatment.

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

- Advanced/metastatic/unresectable solid tumors that progressed on standard therapies (specific to safety cohort)
- 1-4 tumor sites that can be irradiated safely
- Detectable serum IL-8 (> 10 pg/mL) at baseline
- ECOG performance status 0 or 1
- Normal organ and marrow function as predefined based on standard laboratory test
- Measurable disease as predefined with CT scan, MRI, or calipers by clinical exam
- Anti-PD1/PDL1 refractory melanoma or RCC (specific to efficacy cohort)

Study team contacts: Dr. Jason Luke, Study Principal Investigator (lukejj@upmc.edu) and Julie Urban, Immunotherapy and Drug Development Center and Phase II Center Manager (urbanj2@upmc.edu)

Melanoma and Cutaneous Tumors

HCC 20-155: A Phase I/II Study of PI3Kγδ inhibitor Duvelisib in Combination with Nivolumab in Patients with Advanced Unresectable Melanoma who have Progressed on Anti-PD1 Therapy

Principal Investigator: Dr. John Kirkwood, kirkwoodjm@upmc.edu

The phosphoinositide 3-kinase (PI3K) signaling pathway functions at many stages of cancer biology including cell division, differentiation, motility, and metabolism. Although inhibitors downstream of the PI3K pathway are active in some solid tumors, a more targeted approach to PI3K inhibition may be useful for immune modulation in malignancies treated with immunotherapy. Duvelisib is a potent inhibitor of both γ and δ isoforms of PI3K that is FDA-approved for relapsed refractory chronic/small lymphocytic leukemia (CLL/SLL) and follicular lymphoma based on the DUO and DYNAMO trials. In this study, oral duvelisib will be administered at doses from 15 mg once daily to 25mg twice daily (BID) to determine the Recommended Phase II Dose, which will be administered with intravenous nivolumab at 240 mg every 2 weeks, and if tolerated, potentially changed to 480 mg. Treatment will be in 4-week cycles until disease progression, unacceptable toxicity, or 1 year, whichever is longer.

Prospective male and female participants who are ≥ 18 years old will be expected to fulfil the following general inclusion criteria:

- Unresectable stage III or stage IV melanoma by AJCC 8th edition that has progressed on anti-PD1 therapy after a minimum of 12 weeks of therapy
- ECOG performance status ≤ 2 or Karnofsky ≥ 60%
- Normal organ and bone marrow function as predefined by standard laboratory tests

Study team contacts: Dr. John Kirkwood, Principal Investigator (kirkwoodjm@upmc.edu) and Amy Rose, Associate Director Clinical Administration and Clinical Research Manager (kennaj@UPMC.EDU)

Brain Malignancies

HCC 20-191: EF-32: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (Optune®, 200kHz) Concomitant with Radiation Therapy and Temozolomide for the Treatment of Newly Diagnosed Glioblastoma

Principal Investigator: Dr. Frank Lieberman, liebermanf@upmc.edu

Tumor treating electric fields (TTFields) is a novel non-invasive, regional antimitotic treatment modality for malignant tumors that has been approved for recurrent and newly diagnosed glioblastoma (GBM). TTFields has also been approved in combination with chemotherapy for malignant pleural mesothelioma under FDA humanitarian device exemption. TTFields (200 kHz) has been shown to significantly increase the survival of newly diagnosed GBM patients without increasing systemic toxicity and while delaying the time to deterioration in quality of life. The present randomized study aims to determine whether adding TTFields to concomitant chemoradiation treatment of newly diagnosed GBM patients has the potential to increase treatment efficacy and extend survival. Patients will be randomized (1:1) to receive TTFields treatment with the Optune® device concomitantly with radiotherapy (RT) and temozolomide (TMZ) or RT with TMZ only.

This study has the following, among other, main eligibility criteria that prospective male and female participants ≥ 22 years old are expected to meet:

- Histologically confirmed diagnosis of GBM according to WHO classification criteria
- Recovered from maximal debulking surgery (gross total resection, partial resection and biopsy-only patients are all acceptable)
- Planned treatment with RT/TMZ followed by TTFields and maintenance TMZ (150–200 mg/m2 daily for 5 days, every 28 days)
- Karnofsky performance status ≥ 70
- Life expectancy ≥ least 3 months
- Stable or decreasing corticosteroid dose for last 7 days prior to randomization, if applicable.
- Concomitant RT with TMZ treatment planned to start no later than 8 weeks from surgery
- Able to have brain MRI with contrast.

Study team contacts: Dr. Frank Lieberman, Study Principal Investigator (liebermanf@upmc.edu) and Melinda Vargas-Jaffe, Clinical Research Supervisor (vargasjaffema@upmc.edu)

HCC 19-048: GBM AGILE: Global Adaptive Trial Master Protocol: An International, Seamless Phase II/III Response Adaptive Randomization Platform Trial Designed To Evaluate Multiple Regimens In Newly Diagnosed and Recurrent Glioblastoma (GBM)

Principal Investigator: Dr. Jan Drappatz, drappatzj@upmc.edu

Glioblastoma (GBM) adaptive, global, innovative learning environment (AGILE) is a biomarker-based, multi-arm, two-stage trial designed to evaluate multiple therapies in newly diagnosed and recurrent GBM. The goals of the trial are to identify effective therapies for GBM and match them with patient subtypes. In the initial Screening stage, Bayesian response adaptive randomization is used within subtypes of the disease to assign patients to experimental Arms, or a control based on their performance. Those with evidence of efficacy in at least one of several "biomarker signatures" will continue therapies in GBM AGILE uninterrupted. Furthermore, they will transition to a confirmatory stage with fixed randomization in an expansion cohort to control type I error, intended to support marketing approval. GBM AGILE provides an efficient mechanism to screen and develop robust information regarding the efficacy of proposed novel therapeutics and associated biomarkers for GBM and to quickly move therapies and biomarkers into the clinic.

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:

Newly Diagnosed GBM Criteria:

- Histologically confirmed Grade IV GBM, inclusive of gliosarcoma (WHO criteria; IDH wild-type by immunohistochemistry or sequencing for IDH) established by surgical resection or biopsy
- MRI scan with required imaging sequences performed within 21 days prior to randomization
- Post-operative MRI within 96 hours of surgery
- Use of dexamethasone ≤ 4 mg/per day within 5 days prior to randomization
- Karnofsky performance status ≥ 60% performed within a 14-day window prior to randomization
- Availability of GBM tumor tissue

Continued

Recurrent GBM Criteria

- Histologically confirmed Grade IV GBM inclusive of gliosarcoma (WHO criteria, IDH wild-type) at first or second recurrence after initial standard, control, or experimental therapy that includes radiotherapy, at a minimum
- Evidence of recurrent disease demonstrated by disease progression using slightly modified RANO criteria with post-chemoradiation time point as baseline
- Two scans to confirm progression
- Baseline MRI performed within 14 days prior to randomization
- Use of dexamethasone ≤ 4 mg/day within 5 days prior to randomization
- Karnofsky performance status ≥ 70% performed within a 14-day window prior to randomization
- Availability of GBM tumor tissue from initial definitive or recurrent surgery, if performed

Study team contacts: Dr. Jan Drappatz, Study Principal Investigator (drappatzj@upmc.edu) and Melinda Vargas-Jaffe, Clinical Research Supervisor (vargasjaffema@upmc.edu)

OPEN STUDIES AND ACCRUALS JAN–SEP 2021

	Open Trials		Accruals	
Disease / Modality Center	Interventional	Therapeutic	Interventional	Therapeutic
Biobehavioral Medicine in Oncology Program	13	1	420	0
Brain Tumor Center	16	16	31	31
Breast Center	43	38	629	72
Early Therapeutics Centers (Phase I and II)	83	83	102	102
GI/Esophageal Cancer Center	49	49	115	115
Gynecological Oncology Center	18	17	23	23
Head and Neck Center	30	27	208	79
Hematological Malignancies Center	59	59	38	38
Immune Therapy Center	70	70	138	138
Lung and Thoracic Malignancies Center	52	48	95	31
Melanoma Center	39	39	118	118
Multi-Disease/Modality Center Trials	2	1	953	56
Pediatric Oncology	68	64	65	54
Prostate and Urologic Cancers	30	28	85	38
Sarcoma Center	12	12	16	16
Supportive Care	1	0	0	0
Radiation Oncology Center	30	29	143	43
Total	**615**	**581**	**3179**	**954**

**All Accruals are calculated from January 1 through December 31, 2021

OPEN STUDIES AND ACCRUALS JAN–SEP 2021				
	Open Trials		Accruals	
Disease / Modality Center	Interventional	Therapeutic	Interventional	Therapeutic
Multi-Disease/Modality Center Trials	1	1	1	1
Brain Tumor Center	4	4	3	3
Breast Center	4	3	101	1
Gynecological Oncology Center	0	0	1	1
Head and Neck Center	9	9	24	24
Lung and Thoracic Malignancies Center	2	2	9	9
Prostate and Urologic Cancers	10	10	4	4
Total	**30**	**29**	**143**	**43**

Accruals to HCC 18-177	**897**

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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