THE **TRIAL** BLAZER

UPMC HILLMAN CANCER CENTER

A quarterly newsletter from **CLINICAL RESEARCH SERVICES**

INTRODUCTION

Welcome to a new year, replete with fresh opportunities and "updated expectations." A great way to start would be to review our accomplishments from last year to set a heightened, re-engineered pace for 2020. As a result of the collective efforts made through engagement activities and other specialized strategies, we observed a year-by-year increase of 30.6% in overall treatment trial accruals in 2019 with 973 accruals vs. 745 in 2018, while interventional trial accruals increased to 1,900 from 1,843 in 2018. The growth was even more impressive with investigator-initiated trials (IITs), which constituted the majority of interventional trial accruals at 1,027 in 2019, compared to 508 in 2018. A similar trend was also observed with treatment trial accruals, which included 390 IIT accruals in 2019 compared to 217 in 2018, and we are optimistic that we can further improve and top these achievements.

In other relevant news, while immunotherapy has indeed revolutionized cancer treatment, there is a critical gap in knowledge of the clinical and socioeconomic impact of long-term immunotherapy on patients. The necessity of a prolonged course of treatment to achieve the observed survival benefit is still controversial in light of the lack of convincing clinical data supporting an ideal treatment duration. On this note, we are extremely pleased to announce the opening of the highly anticipated, landmark phase III HCC 19-135 trial at all UPMC Hillman Cancer Center network sites. This study, which is the featured "Spotlight Trial" in this edition, is expected to provide groundbreaking, salient information on the optimal duration of immunotherapy.

We are pleased to report the successful conclusion of the National Cancer Institute (NCI) site visit for the CCSG core grant on January 23, 2020. As always, we remain extremely appreciative to all the indefatigable and indispensable members of staff, including our various disease or modality center teams. To get to know them a little better and recognize what makes them tick, every quarter we will feature one team in the newsletter, complete with a group photograph. Please look out for the first write-up on Team Melanoma, under the able management of Amy Rose, and other new points of interest in this newsletter as indicated by the star next to the feature headline.

Again, none of our successes would be possible without all of you and we commend and appreciate each and every contribution to meeting our accrual and other goals. We continue to welcome your comments on how to make this process more rewarding.

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

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

Volume 2 • Issue 1 • **February 2020**

☆ CRP CERTIFICATION

Who? What? Where? When? And Most Importantly, Why?

Who: All staff eligible to take Clinical Research Professional Certification exams.

What: Offered by both the Society of Clinical Research Associates and the Association of Clinical Research Professionals

Where and When: Can be taken at a local computer testing center (on your own schedule), paper and pencil could be offered at UPMC if enough interest in this option is generated (on a fixed date).

Why: To enhance your knowledge of the work we do and to improve opportunities for advancement within the department.

"I took my SOCRA exam along with a group back in 2017 after attending a study group and using resources provided by CRS to help me prepare. I passed and the fee was quickly reimbursed by UPMC. I enjoyed learning about different aspects of Clinical Research and feel it has helped me move forward in my career."
—Amy Platt

A study course to help all eligible staff to prepare for certification exams is planned ASAP. Check your eligibility on the websites provided and if you would like more information please contact Anne Platts (plattsa2@upmc.edu), Mary Horak (mhorak@upmc.edu), or Josh Plassmeyer (plassmeyerjm@upmc.edu).

POINTS OF INTEREST

☆ CRS TEAM SPOTLIGHT: MELANOMA CENTER

Standing L-R: *Dr. Davar, Darcy Ploucha, Amy Rose (team manager), Sammi Berton, Ricardo Simmons, Tiffany Devine, Corey Hewitt, Nick Mario, Courtney Starrett, Sarah Barnick, Aaron Vannatter, Allyson Knights*

Seated L-R: *Gene Richard, Scarlett Ernst, Amanda Moran, Kellie Sellitto, Liz Rush*

In addition to their impeccable contributions to clinical research, the team members all have very diverse interests and hobbies. Can you guess which interest belongs to each team member?

Hungarian Folk Dance
Knitting
Stone Collector
Stool Collector
Paddle Boarding
Massage Therapist
Music Teacher
Baking
Youth Sports Enthusiast
Travel/Animal Lover
Crafting
Football Coach

☆ ACHIEVEMENTS AND ACCOLADES

Hillman has the top (42) accruals in the country for Lung-MAP (HCC 19-003). Because of our high accrual rate, the principal investigator, Dr. Liza Villaruz was invited by SWOG to join the Lung-MAP Trial Oversight Committee, which she accepted.

Kudos to Dr. Villaruz and the team!

We are also third in the country for Alchemist (HCC 14-166) with 64 accruals.

2019 YEAR END OPEN STUDIES AND ACCRUALS

Disease / Modality Center	Current Int OTA Trials	Current Rx OTA Trials	Interventional Accruals	Therapeutic Accruals
GI/Esophageal Cancer Center	13	13	117	117
Melanoma Center	16	16	108	108
Lung and Thoracic Malignancies Center	19	15	247	98
Head and Neck Center	16	15	96	93
Early Therapeutics Centers (Phase I and II)	42	42	88	88
Breast Center	19	16	95	87
Hematological Malignancies Center	22	21	102	87
Multi-Disease/Modality Center Trials	3	3	356	72
Prostate and Urologic Cancers	12	12	65	65
Gynecological Oncology Center	7	7	44	44
Pediatric Oncology	34	34	41	41
Brain Tumor Center	11	11	34	34
Sarcoma Center	8	8	20	20
Immune Therapy Center	10	10	19	19
Supportive Care	3	0	224	0
Biobehavioral Medicine in Oncology Program	8	0	244	0
Total	**243**	**223**	**1900**	**973**
*Radiation Oncology Center	19	14	56	56

All accruals have been calculated through the 4th Quarter of 2019 (Jan-Dec).
* Radiation Oncology accruals are distributed to disease center of care.

SPOTLIGHT TRIAL

Optimal Duration of Immunotherapy for Solid Tumors

HCC 19-135: A Randomized Non-inferiority Trial Evaluating the Length of Treatment with PD-1/PD-L1 Inhibitors in Patients with Advanced Solid Tumors

Principal Investigator: Dr. Antoinette Wozniak, wozniakaj@upmc.edu

Approximately 2,300 patients received PD-1/PD-L1 therapy for various advanced solid tumors in the UPMC system within the past year and this number is anticipated to increase with expanding clinical indications for treatment with these agents. However, the question of optimal duration of treatment remains unanswered. Following an overwhelming positive response in a survey of medical oncologists in the UPMC system who would be willing to participate, we are conducting this phase III trial, which has the primary objective of assessing the time to next treatment of patients who receive PD-1/PD-L1 inhibitors for one year or beyond and we anticipate that the results will answer questions regarding the optimal treatment duration of these agents.

The main inclusion criteria, among others, prospective patients are expected to fulfill are:

- Advanced solid tumor malignancy being treated with a PD-1/PD-L1 inhibitor including pembrolizumab, nivolumab, atezolizumab, durvalumab, or avelumab according to standard of care treatment
- Initially started co-treatment with another agent and the PD-1/PD-L1 inhibitor, i.e. chemotherapy, ipilumumab, are eligible.
- Stable disease (at least) as evidenced by scans performed within six weeks of randomization

Interested physicians can contact Dr. Wozniak, Dr. Vincent Reyes (reyesv@upmc.edu), Daniel Goldstein (goldsteindj@upmc.edu), or Jen Ruth (ruthj2@upmc.edu) with inquiries.

HIGH PRIORITY TRIALS IN THE COMMUNITY

Cancer Immunotherapeutics Center

HCC 19-066: A Phase I, First-in-Human, Open-Label, Dose Escalation Study of MGD013, A Bispecific DART® Protein Binding PD-1 and LAG-3 in Patients with Unresectable or Metastatic Neoplasms

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

PD-1 and LAG-3 blockade by bispecific antibody MGD013 has been shown to enhance antitumor immunity, indicating that dual targeting of these molecules might reverse effector cell exhaustion, thereby improving response rates and immunotherapy efficacy. This study primarily aims to characterize the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD) or maximum administered dose (MAD, if no MTD is defined) of MGD013 administration intravenously (IV) every 2 or 3 weeks to patients with unresectable, locally advanced or metastatic cancers.

The main inclusion criteria, among others, prospective eligible patients are expected to meet are:

- Histologically proven, unresectable, locally advanced or metastatic malignant neoplasms
- Good performance status (PS; ECOG PS score of 0 or 1)
- Life expectancy ≥ 12 weeks
- Adequate end organ function
- Radiographic evidence of measurable disease suitable for response monitoring
- No serious concurrent illnesses that would increase patient risk or confound study data

HCC 19-096: Phase II Study of IDH1 Inhibitor Ivosidenib and Nivolumab in IDH1 Mutant Gliomas and Advanced Solid Tumors

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

Current data suggest that aberrant IDH activity may play a role in limiting immunotherapy efficacy and inhibitors of IDH activity may boost the effects of immunotherapy. Thus, this study primarily seeks to describe the safety, response rate, and progression free survival of ivosidenib, a novel, first-in-class inhibitor of mutant IDH enzyme, in combination with nivolumab and summarize the safety events. This study will provide new strategies for expanding cancer immunotherapy utility.

The following are the main, among other, inclusion criteria prospective eligible participants will be expected to meet:

- Histopathological diagnosis (fresh or banked tumor biopsy sample, preferably collected within the last 3 years) of an advanced solid tumor for which curative treatment is not available and have undergone appropriate standard of care treatment options (in the opinion of the treating investigator)
- Documented IDH1 gene-mutated disease (from a fresh tumor biopsy or the most recent banked tumor tissue available) based on CLIA certified sequencing (R132C/L/G/H/S mutation variants tested)
- For glioma, both contrast-enhancing disease and WHO 2016 grade ≥ II
- ECOG PS score of 0 or 1
- At least one evaluable and measurable lesion as defined by RECIST v1.1 (solid tumors) or RANO Criteria (glioma)
- Adequate bone marrow, hepatic, and renal function with laboratory analysis evidence

Interested physicians can contact the principal investigator or Krystle Eaton at mientkiewiczk@upmc.edu, with inquiries.

PRIORITY TRIALS IN THE COMMUNITY

Lung Cancer

Non-small Cell Lung Cancer

HCC 16-054: A Phase II Clinical Trial Evaluating the Safety and Efficacy of Durvalumab (MEDI4736) as First-Line Therapy in Advanced Non-small Cell Lung Cancer (NSCLC) Patients with Eastern Cooperative Oncology Group (ECOG) Performance Status of 2

Principal Investigator: Dr. Liza Villaruz, villaruzl@upmc.edu

Platinum-based therapy in NSCLC patients with marginal performance status (PF) has not been universally adopted because of the perceived burden of excess toxicity associated with therapy. Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors, and we hypothesize that PD-L1 inhibition is a tolerable regimen with clinical activity in PS2 patients with advanced NSCLC. Therefore, this trial has the primary objective of estimating overall survival (OS) and safety of durvalumab in this patient population.

Potential suitable patients are expected to meet the following major inclusion criteria:

- Histologically or cytologically confirmed Stage IIIB or IV (American Joint Committee on Cancer, 7th edition; AJCC 7) non-small cell lung cancer
- Measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam
- Received prior adjuvant or neoadjuvant chemotherapy or chemotherapy given as part of a curative intent chemoradiotherapy approach for NSCLC, if the last administration of the prior regimens occurred at least 1 year prior to study entry
- Age ≥ 18 years at time of study entry
- ECOG PS score of 2
- Life expectancy of greater than 12 weeks
- Tissue available (archived or fresh tumor biopsy) for the PD-L1 assay
- Patients must have normal organ and marrow function

Interested physicians can contact Dr. Villaruz, Daniel Goldstein (goldsteindj@upmc.edu),or Jen Ruth (ruthj2@upmc.edu) with inquiries.

Melanoma and Cutaneous Tumors

HC 19-026: A Phase 2, Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients with BRAFV600-Mutant Melanoma Brain Metastasis

Principal Investigator: Dr. Yana Najjar, najjaryg@upmc.edu

In this study, patients will be randomized (1:1) to the standard-dose or high-dose treatment arm stratified by baseline tumor burden in the brain (1 to 2 brain lesions vs. ≥ 3 brain lesions at baseline assessment) and by history of checkpoint inhibitor therapy. The prospective eligible patient population will be expected to meet the following main, among other, inclusion criteria:

- ≥ 18 years with asymptomatic BRAFV600-mutant melanoma brain metastasis, not requiring corticosteroids for brain metastasis, no prior local treatment for brain metastasis (craniotomy or radiation therapy)
- At least 1 contrast-enhancing metastatic brain lesion ≥ 0.5 cm and ≤ 4 cm, defined by MRI
- Received ≤ 1 prior line of checkpoint inhibitor therapy and may have received BRAF or MEK inhibitors in the adjuvant setting < 12 months prior to enrollment*
- BRAFV600 mutation in tumor tissue previously determined by a local assay at any time prior to Screening or by a central laboratory during screening

**Patients treated with BRAF or MEK inhibitors in the metastatic setting are excluded.*

HCC 19-002: STAMP: Surgically Treated Adjuvant Merkel Cell Carcinoma with Pembrolizumab, a Phase III Trial

Principal Investigator: Dr. Melissa Burgess, burgessma@upmc.edu

We aim to prove our hypothesis that an anti-PD-1 based regimen will improve outcomes in high-risk resectable Merkel cell carcinoma (MCC) in the adjuvant setting by primarily comparing the co-primary end-points of overall survival (OS) and recurrence-free survival (RFS) across the two arms: pembrolizumab 200 mg IV and standard of care observation (both for cycles 1-17)

Prospective eligible patients are expected to fulfil the following major, among, other inclusion criteria:

- Age ≥ 18 years
- ECOG performance Status: 0, 1, or 2
- Histological confirmation of diagnosis of Merkel cell carcinoma (MCC), pathologic stages (AJCC version 8) I-IIIb
- Complete surgical resection of all macroscopic Merkel cell carcinoma (either identified by physical exam or imaging) within 16 weeks before trial registration

HCC 18-071: A Phase II Study of Anti-PD1 Monoclonal Antibody (Nivolumab, BMS-936558) Administered in Combination with Anti-LAG3 Monoclonal Antibody (Relatlimab, BMS-986016) in Patients with Metastatic Melanoma Naïve to Prior Immunotherapy in the Metastatic Setting

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

This study has the primary objective of assessing change in immune biomarkers by analyzing serial peripheral blood and tumor biopsy samples from patients administered relatlimab and nivolumab, alone or in combination and estimating the association between changes in immune biomarkers and tumors.

The following are the main, among other, inclusion and exclusion criteria prospective, eligible participants will be expected to meet:

- Men and women ≥ 18 years of age
- Meeting AJCC 8th edition criteria for unresectable stage IIIB, stage IIIC, stage IIID, or stage IV melanoma
- Not received treatment with immunotherapy in the metastatic setting

Melanoma and Cutaneous Tumors (continued)

HCC 17-169: Neoadjuvant Phase II Study of TLR9 Agonist CMP-001 in Combination with Nivolumab in Stage IIIB/C/D Melanoma Patients with Clinically Apparent Lymph Node Disease

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

This phase II, single-arm, Simon two-stage single-center study has the primary aim of evaluating the major pathologic response (MPR) rate in patients with stage IIIB/C melanoma following seven weeks of nivolumab and injected CMP-001. This study was designed based on our major hypotheses that this regimen is synergistic and could improve pathological responses in high-risk treatment naïve melanoma PRIOR to surgery. In a planned imaging sub-study, patients will undergo in vivo imaging using [18F] F-AraG, a novel PET tracer that images activated CD8 T cells.

Prospective eligible patients are expected to meet the following main inclusion and exclusion criteria, among others:

- Stage IIIB-IIID cutaneous (or unknown primary) melanoma with palpable nodal disease and/or in-transit disease who have yet to undergo definitive surgery
- Patients who have received prior adjuvant IFN and/or ipilimumab are eligible to enroll. However, patients who have received either nivolumab or pembrolizumab or ipilimumab/nivolumab are NOT eligible.
- Patients must not have active CNS disease.
- Patients must have disease amenable to biopsy and intra-tumoral injection.

HCC 16-196: Profiling and Reversing Metabolic Insufficiency in the Tumor Microenvironment in Advanced Melanoma: A Trial of Pembrolizumab and Metformin versus Pembrolizumab Alone in Advanced Melanoma

Principal Investigator: Dr. Yana Najjar, najjaryg@upmc.edu

This randomized phase Ib translational trial has the primary objective of determining the cell cycle status (Ki-67 staining using flow cytometry) of lymphocytes harvested from tumors in patients treated with pembrolizumab and metformin compared to patients treated with pembrolizumab alone. This is based on our hypothesis that T cells from the tumor microenvironment (TME) of patients treated with pembrolizumab and metformin will have a higher Ki- 67 proliferation index than TIL from patients treated with pembrolizumab alone.

The following major, among other eligibility criteria, are required to be met by prospective patients:

- Unresectable (stage III) or advanced (stage IV) melanoma
- ≥ 18 years of age on day of signing informed consent
- Measurable disease based on RECIST 1.1. Patients without measurable disease may be included on study after discussion with the Sponsor, given that the primary endpoint of the study is Ki-67 of TIL (flow cytometry).
- Biopsiable disease. Be willing to provide tissue from a newly obtained biopsy of a tumor lesion.
- Received prior adjuvant therapy with anti-PD1, anti-CTLA-4, or BRAF/MEK inhibitors.
- Immunotherapy treatment naïve in the advanced setting or on anti-PD1 therapy with SD or PR for at least 12 weeks. Patients may have received ipilimumab plus nivolumab in the metastatic setting with SD or PR for at least 12 weeks on maintenance anti-PD1.
- ECOG Performance status of 0, 1, or 2
- Baseline HbA1c ≤ 6.4
- Adequate organ function

Melanoma and Cutaneous Tumors (continued)

HCC 15-094: DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): A Phase III Trial

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

This randomized phase III trial has the primary aim of determining whether initial treatment with either combination ipilimumab plus nivolumab (with subsequent dabrafenib in combination with trametinib) or dabrafenib in combination with trametinib (with subsequent ipilimumab plus nivolumab) significantly improves two-year overall survival (OS) in patients with unresectable stage III or stage IV BRAFV600 mutant melanoma.

The following, among other, main inclusion criteria are expected to be fulfilled by prospective eligible patients:

- Age ≥ 18 years
- ECOG Performance status: 0 or 1
- Unresectable stage III or stage IV disease
- Measurable disease
- Histological or cytological confirmation of melanoma that is metastatic or unresectable and clearly progressive
- May have had prior systemic adjuvant therapy not including a CTLA4 or PD1 pathway blocking antibody or a BRAF/MEK inhibitor
- Patients are ineligible if they have any currently known active and definitive CNS metastases.

Interested physicians can contact the respective PIs or Amy Rose (kennaj@upmc.edu) with inquiries.

Genitourinary/Prostate

HCC 19-042: A Randomized, Double-Blind, Controlled Phase III Study of Cabozantinib in Combination with Nivolumab and Ipilimumab versus Nivolumab and Ipilimumab in Subjects with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma of Intermediate or Poor Risk

Principal Investigator: Dr. Leonard Appleman, applemanlj@upmc.edu

The success of multitargeted tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) as single agents with distinct mechanisms of action has led to interest in evaluating their combination in search of further, possibly synergistic, anticancer clinical effects. Consequently, in this study, eligible subjects with intermediate- or poor-risk advanced or metastatic renal cell carcinoma (RCC) based on the IMDC criteria will be randomized in a 1:1 ratio to receive cabozantinib (a TKI) in combination with the ICIs nivolumab and ipilimumab or a placebo in combination with nivolumab and ipilimumab.

The main mandatory inclusion criteria, among others, prospective patients are expected to fulfill are:

- Histologically confirmed advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) renal cell carcinoma with a clear-cell component, including subjects who also have a sarcomatoid feature
- Intermediate- or poor-risk RCC as defined by IMDC criteria
- Measurable disease per RECIST 1.1 as determined by the investigator
- Availability of archival tumor tissue prior to randomization
- Recovery to baseline or ≤ Grade 1 CTCAE v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy such as Grade 2 neuropathy or alopecia
- Age ≥ 18 years on the day of consent
- Karnofsky Performance Status (KPS) ≥ 70%
- Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days prior to randomization

Genitourinary/Prostate (continued)

HCC 17-019: A Phase III Randomized Study Comparing Perioperative Nivolumab vs. Observation in Patients with Localized Renal Cell Carcinoma Undergoing Nephrectomy (PROSPER RCC)

Principal Investigator: Dr. Leonard Appleman, applemanlj@upmc.edu

Targeting micrometastatic disease perioperatively when the disease burden is smaller is logical and a survival-improving agent like nivolumab with a different mechanism of action from that of previously tested agents could improve outcomes. RCC patients show elevated peripheral circulating PD-1 cells critical to the efficacy of nivolumab prior to surgery, while levels decrease significantly after nephrectomy. Since the current standard of care after nephrectomy in RCC is surveillance, the primary objective of this study is to compare recurrence-free survival (RFS) between patients with RCC randomly assigned to perioperative nivolumab in conjunction with radical or partial nephrectomy with patients randomized to surgery alone.

The main mandatory inclusion criteria, among others, prospective patients are expected to fulfill are:

- Renal mass consistent with a clinical stage ≥ T2Nx RCC or TanyN+ RCC for which radical or partial nephrectomy is planned
- No clinical or radiological evidence of distant metastases (M0) unless the presumed M1 disease is planned to be resected/definitively treated at the same time or within a 12 week window from the date of the initial procedure such that the patient is considered "no evidence of disease" (M1 NED)
- No prior systemic or local anti-cancer therapy for the current RCC
- Age ≥ 18 years
- ECOG Performance Status: 0 or 1
- Patient must not have a prior history of RCC that was resected with curative intent within the past 5 years
- Patients cannot have concurrent malignancies, with a few exceptions (information available on request)
- No active known or suspected autoimmune disease with a few exceptions (information available on request)

Physicians should contact the study principal investigator or Clare Grzejka at grzejkac@upmc.edu with inquiries.

Clinical Research Services (CRS) is made up of over 200 staff members at 28 locations who facilitate development, implementation, coordination, internal data monitoring, and completion of approximately 250 oncology-focused therapeutic 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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