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Inside This Edition

Adoptive Cell Transfer Immunotherapy:

Building on a Blueprint Provided by Studies of Metastatic Uveal Melanoma

Adoptive cell transfer of tumor-infiltrating lymphocytes is a complex, personalized therapy with the potential to generate an immune response against a variety of tumor types. In clinical trials, cutaneous and uveal melanomas responded to this innovative approach, and new trials have been initiated at UPMC to study the utility of adoptive cell transfer of tumor-reactive T cells in other common and uncommon cancers.

Udai Kammula, MD, the director of the Solid Tumor Cell Therapy program at UPMC Hillman Cancer Center, believes that adoptive cell transfer (ACT) has several potential advantages over other immunotherapeutic approaches to treat cancer. Dr. Kammula and his team can select tumor-infiltrating lymphocytes (TILs) with significant personalized antitumor reactivity, activate the cells, and grow them to large numbers. Thus, tumor-fighting T cell populations can be directly instilled into the patient without the need for other immune-boosting agents, which may be poorly effective or cause toxicity.

Immunotherapy using ACT was pioneered in patients with cutaneous melanoma, a very immunogenic cancer, and 30 years of research findings support ACT as a feasible approach to kick-start the immune system to fight cancer. The multistep process starts when the patient undergoes metastasectomy to procure tumor tissue. Next, autologous TILs are liberated from the resected tumor metastasis and undergo large-scale ex vivo expansion. The best ways to select cells for expansion is an active area of investigation. The patient then receives lymphodepleting chemotherapy followed by intravenous infusion of the expanded lymphocytes and treatment with interleukin-2 to promote T cell survival. *(See Figure 1 on Page 2.)* The patient's tumor response is then monitored.[1]

Manipulation of the T cells outside of the body conveys several potential benefits. Most cancer patients have dysfunctional immune systems. Tumor-reactive T cells are present but suppressed by other defense mechanisms. Once the T cells are outside of the body, the physician can "recondition" the patient's immune system. During ACT, the recipient's immune system is wiped out for a short time with a nonmyeloablative, mild chemotherapy regimen administered for seven days. Then, the immune system is repopulated with the TILs expanded ex vivo. This is distinct from other types of immunotherapy, which must stimulate the immune system within the confines of the body. Dr. Kammula is "setting new rules" by manipulating the cells outside of the body.

After ACT was established as a feasible therapy for cutaneous melanoma, Dr. Kammula and his colleagues at the National Institutes of Health (NIH) wanted to demonstrate proof of principle in another cancer.[1,2] They chose to examine uveal melanoma, a rare cancer that did not respond to any known immunotherapies. In work published in 2016 in *Clinical Cancer Research* and 2017 in *Lancet Oncology,* they demonstrated that tumor-reactive TILs could be isolated from metastatic uveal melanoma and that a subset of patients with uveal

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Adoptive Cell Transfer Immunotherapy *(Continued from Page 1)*

melanoma responded to ACT immunotherapy with selected TILs.[3,4] This trial was critically important in establishing ACT as a potentially useful immunotherapeutic approach because even a cancer that had not responded to any other immunotherapies could respond to ACT.

When Dr. Kammula came to UPMC from the NIH in 2017, he began a Phase II trial to further improve ACT for patients with metastatic uveal melanoma (NCT03467516). This trial, which is funded by the UPMC Immune Transplant and Therapy Center, is currently ongoing. One goal of the trial is to confirm Dr. Kammula's initial observations. Other goals are to identify biomarkers that may predict therapeutic response and to isolate the genes responsible for TIL recognition of uveal tumors. Additionally, the trial allowed Dr. Kammula to set up the production facility and clinical infrastructure at UPMC needed for ACT, including improvements to the bioreactors used to grow the cells. The Immunologic Monitoring and Cellular Products Laboratory (IMCPL) at UPMC Hillman Cancer Center was incredibly responsive as Dr. Kammula adapted his protocols to grow T lymphocytes using good manufacturing practices (GMP) at a new location. Only a few institutions around the world are using this approach and have these capabilities.

Dr. Kammula is currently using his experience with ACT in uveal melanoma as a blueprint for treating other cancers. Two new clinical trials using ACT as an antitumor immunotherapy began recruiting patients at UPMC Hillman Cancer Center in 2019. One trial is using ACT to treat biliary tract cancers (NCT03801083), and one is using ACT against a wide array of solid tumors. Biliary tract cancers include cancers of the bile duct (cholangiocarcinoma), gallbladder, and ampulla of Vater, are relatively rare, and carry a poor prognosis, similar to uveal melanoma. Dr. Kammula and his team have expanded TILs from metastases of biliary tract tumors and isolated cells with the appropriate reactivity to show proof of concept in the laboratory. Dr. Kammula hopes to enroll up to 10 patients per year. The trial is designed to evaluate outcomes after the first 15 patients before moving forward to an enrollment goal of 47 patients. Tumor response, duration of tumor response, disease-free survival, and overall survival will be assessed as study outcomes.

The second new trial of ACT examines the effectiveness of this therapeutic strategy against many different solid tumor types. Dr. Kammula describes this trial (NCT03935893) as a "fascinating trial that will allow us to treat virtually any cancer." The trial has 10 different arms including analysis of common (e.g., stomach, esophageal, colon, pancreas) and uncommon cancers (e.g., Merkel cell, neuroendocrine tumors) and serves as a novel treatment option for patients seen at UPMC Hillman Cancer Center. This ambitious trial is the only one of its kind in the world and is pioneering in its potential to explore ACT as a treatment for many types of cancer. As Dr. Kammula and his team examine tumor response and patient survival, they will also work to define the biologic signature of T cells reactive against each tumor type and determine if they can grow TILs from each unique cancer and use these cells for treatment.

Although Dr. Kammula is excited about the trial, which just began recruitment in May 2019, he anticipates that the majority of the cancers studied will not have triggered the immune response necessary to isolate good T cells for ACT immunotherapy. In anticipation of this outcome and to facilitate further research in the field, all tissue collected during the trial will be banked in a repository for sequencing and translational science efforts.

This sets the stage for an obvious next step: genetically engineering T cells when T cells appropriate for ACT immunotherapy cannot be isolated from cancer patients. In the laboratory, Dr. Kammula and his team are working to isolate single T cells with antitumor reactivity and clone the genes encoding the T cell receptor from each cell. These genes determine the T cell's immunoreactivity. Dr. Kammula is isolating a number of these valuable genes to generate a library of tumor-reactive T cell receptors. He envisions a future where tumor-reactive T cells do not need to be isolated and expanded from each patient. Instead, tumor sequencing and HLA type would guide the clinical team as they "pick a receptor off the shelf," insert it into the patient's T cells, and expand the transformed cells for ACT immunotherapy. This molecular cloning and bioengineering project is a secondary goal of his large trial to use ACT against solid tumors. Working at UPMC provides a tremendous advantage during these efforts. Dr. Kammula and his team have great access to both primary and metastatic tumor samples.

Although ACT of TILs is a promising immunotherapy, the vast majority of tumor-reactive TILs undergo cell death shortly after infusion, and only a small subset of TILs persists as long-lived memory cells. Animal models of ACT immunotherapies have demonstrated that if the cells are exhausted when they are removed for expansion, they grow poorly in the lab, work poorly when re-implanted, and exhibit telomere shortening and limited ability to produce ATP. Novel strategies are needed to enhance the metabolic fitness of the highly differentiated T cells needed for ACT immunotherapy. Dr. Kammula has an active research program exploring ways to bioengineer TILs to reprogram their fate following ACT. His studies in animal models suggest that metabolic reprogramming can augment the survival of TILs. Dr. Kammula is continuing these investigations through a funded NIH R01 grant, which began in July 2019, that focuses on reprogramming the mitochondrial metabolism. Dr. Kammula and his team are examining whether they can give TILs a metabolic boost using a gene therapy approach. This research will improve our understanding of T cell

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Adoptive Cell Transfer (ACT using TIL)

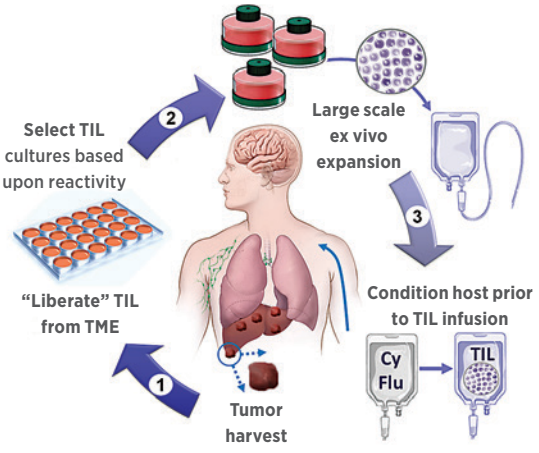

Figure 1: Schematic of the adoptive cell transfer immunotherapy process. Cy Flu, cyclophosphamide/fludarabine chemotherapy; TIL, tumor-infiltrating lymphocytes; TME, tumor microenvironment.

Institute for Precision Medicine Faculty Present at Precision Medicine World Conference

In January 2020, members of the joint University of Pittsburgh and UPMC Institute for Precision Medicine (IPM) presented at the Precision Medicine World Conference that was held in Santa Clara, California, January 21-24.

Adrian V. Lee, PhD, director of the Institute for Precision Medicine, presented on the topic of "Implementing Precision Medicine in Community Hospitals" on Jan. 22 at 1:30 p.m.

Along with directing the Institute for Precision Medicine, Dr. Lee is professor of Pharmacology and Chemical Biology, and professor of Human Genetics at the University of Pittsburgh. He has had a key role in shaping precision medicine research at the University of Pittsburgh and personalized care in the large UPMC integrated finance and delivery healthcare system. An example of the early progress in precision medicine is research and implementation of pharmacogenomics, and development of computational systems and architecture for sharing of clinical and genomic data. The goal of Dr. Lee's laboratory is to translate basic cell and molecular research findings into the understanding and treatment of breast cancer. He is currently leading an effort to sequence metastatic breast cancers to identify vulnerabilities for novel precision therapies. Dr. Lee has published over 160 peer reviewed research articles. In 2018 Dr. Lee was awarded the Susan G. Komen Greater Pennsylvania Terri L. Chapman award, the PNC Elsie Hillman Distinguished Scholar Award, and the University of Pittsburgh Biomedical Graduate Scholar Association (BGSA) Distinguished Mentor Award.

IPM Associate Director **Philip Empey, PharmD, PhD**, spoke on Jan. 24 at 1:30 p.m. in the Precision Pharmacotherapy Session on how precision pharmacotherapy is combining genetic, environmental, lifestyle, and other unique patient or disease characteristics to guide drug selection and dosage.

Dr. Empey is the associate director for Pharmacogenomics of the IPM and leads the PreCISE-Rx and Test2Learn teams to implement pharmacogenomics clinical, research, and educational initiatives. As a clinician-scientist in the Department of Pharmacy and Therapeutics at the University of Pittsburgh, Dr. Empey conducts NIH-funded clinical and translational research aimed at understanding the mechanisms of the variability in drug response to improve medication-related outcomes in critically ill patients. His current research interests include understanding the role/impact of xenobiotic transporters following neurological injury, transporter pharmacogenomics, pharmacogenomics clinical implementation, collection of medication-related phenotype information, and genotype-phenotype discovery. Dr. Empey teaches at the graduate level in pharmacokinetics, pharmacogenomics, and drug transporters in the Schools of Pharmacy, Medicine, and Nursing. He also has a research interest in innovative educational models to transform education.

Mylynda B. Massart, MD, PhD, spoke on the growing demands for the integration of genomics into primary care in a presentation titled "Unlocking the Potential of Precision Medicine in Primary Care." Dr. Massart's lecture was held on Jan. 22 at 5 p.m.

Dr. Massart is an assistant professor of Family Medicine in the Department of Family Medicine at the University of Pittsburgh School of Medicine. She graduated with a doctorate in Biochemistry/Molecular Biology from University of Utah, Salt Lake City, and earned her medical degree from Oregon Health & Science University, Portland, Oregon. She completed the Family Medicine Residency at Providence Milwaukie Family Medicine, Milwaukie, Oregon. Dr. Massart completed a postdoctoral fellowship in the Department of Molecular Medicine, Oregon Health & Science University in Portland. Currently she serves as the medical director at UPMC Matilda H. Theiss Family Health Center and has a family practice with special interest in primary care genetics. Dr. Massart has a joint appointment at the Clinical and Translational Science Institute as co-director of the Integrating Special Populations Core, co-investigator on the All of Us Pennsylvania Research Program, and co-investigator of the Pitt + Me Discovery Biobank with special interest in return of genetic results to patients and providers.

About the Institute for Precision Medicine

The Institute for Precision Medicine (IPM) is a collaboration between the University of Pittsburgh and UPMC. The IPM facilitates the movement of biomedical research into personalized well-being and clinical care. The overarching goal is to help researchers and clinicians discover and exploit clinically actionable individual features about risk of disease, optimal treatment, disease course, and response to treatment. Supporting projects working toward this goal will likewise help determine the circumstances in which these insights lead to better outcomes and reduced health care costs. A key ancillary goal relates to the education of health care professionals, researchers, patients, and the public about the application of personalized medicine, ranging from technological advances through ethical considerations. To learn more, please visit **ipm.pitt.edu**.

A Dedicated Center for Cancer Immunotherapy Trials

In May 2019, **Jason Luke, MD**, joined the faculty of UPMC Hillman Cancer Center as director of its new Cancer Immunotherapeutics Center and is associate professor of medicine at the University of Pittsburgh School of Medicine.

"Immunotherapy is a different approach to treating cancer than we have seen historically, such as with chemotherapy or targeted therapies," says Dr. Luke. "We're treating the patient's body, not the cancer, and therefore the treatment is potentially applicable to a broad swath of cancer types. This requires a redesign of the way we do clinical research."

The Cancer Immunotherapeutics Center was created to speed the most promising new immunotherapies toward large clinical studies. "We are currently conducting or preparing to launch early-phase trials on all aspects of immunotherapy, for diseases ranging across the spectrum of cancer, from melanoma to pancreatic cancer to hematologic cancers," says Dr. Luke.

Emergence of the First Immunotherapies

Dr. Luke developed an interest in immunology as an undergraduate at the University of Iowa, where he worked in a laboratory, studying mouse models of T cell lymphoma. His interest in the immune system continued after he entered medical school at the Rosalind Franklin University of Medicine and Science in Chicago and eventually led him to a rotation in the clinical immunology program at Memorial Sloan Kettering Cancer Center in New York. After graduating from medical school in 2006, Dr. Luke completed his internship and residency in internal medicine at Boston University Medical Center, followed by a medicine fellowship at Weill Cornell Medical Center in New York and a medical oncology fellowship at Sloan Kettering.

"I was fortunate to be in the thick of it when the seminal clinical trials in melanoma of the first modern cancer immunotherapy agent, ipilimumab, were underway," says Dr. Luke. "Those trials fundamentally altered the way we treat metastatic cancer. We saw some patients who were treated with immunotherapy achieve long-term treatment responses. That is just not what we saw otherwise with metastatic cancer. This drove home to me that, in terms of advancing cancer therapy, the highest upside would be in the realm of immunotherapy."

Dr. Luke joined the faculty of Dana-Farber Cancer Institute and Harvard Medical School in 2012 just as the next generation of immune checkpoint inhibitors, the PD-1 and PD-L1 antibodies, were being tested in clinical trials. This class of drugs would further revolutionize the treatment of metastatic cancer across tumor types.

"Working on these trials helped me find my niche, marrying my interest in early-phase drug development with immunotherapeutics," he says.

In 2014, Dr. Luke was recruited to the University of Chicago by Thomas Gajewski, MD, PhD, whom he describes as "one of the foundational scientists in cancer immunotherapy." After working with that team for five years to build an early immunotherapy drug development program, Dr. Luke was recruited to UPMC by Hillman Cancer Center director Robert Ferris, MD, PhD.

"The scale and science of UPMC Hillman Cancer Center will give me an opportunity to expand the horizons of my research with immunotherapy in ways that wouldn't otherwise have been possible," says Dr. Luke.

Flipping the Approach to Early-Phase Trials

The new Cancer Immunotherapeutics Center is focusing exclusively on early-phase clinical trials of new immunotherapeutic agents. The way these treatments interact with the human body has required a rethinking and reorganizing of how early-phase trials are run, says Dr. Luke.

"Historically, in early-phase clinical trials of a new agent, we would administer the drug in increasing doses until we reached the maximum tolerated dose. Then we would sometimes do another trial to confirm the dose or look for early signs of activity. Evaluating therapeutic effectiveness often was not a primary intent of these early-phase trials. With the broad applicability of immunotherapy, that's completely flipped on its head," says Dr. Luke.

Because dose-related toxicities are much less likely to be observed in early-phase trials of immunotherapies, these trials often immediately begin to assess the clinical benefit of a new agent.

The sheer number of immunotherapy drugs currently under development necessitates rapid decision making about which agents should move forward into larger trials.

"We're looking for agents that generate a substantial response in early-phase trials. The Cancer Immunotherapeutics Center will enable us to organize and prioritize those clinical trials that we believe are going to have the biggest impact," says Dr. Luke.

The multidisciplinary team at the Center already has opened multiple early-phase trials that are now enrolling patients, and they expect to start more than 20 more by early 2020. These trials will address the full range of immunotherapeutic modalities, including immune checkpoint antibodies, small-molecule innate immune agonists, bispecific immunotherapies, cellular products, immunometabolism modifiers, and more.

"Simultaneously, our priority is to leverage UPMC Hillman Cancer Center's science into investigator-initiated clinical trials," says Dr. Luke, noting that the first two investigator-initiated trials are currently getting underway as well.

Searching for the Drivers of Response

Dr. Luke's ambitions for the new Center go beyond clinical trials. He has a research interest in understanding the factors that lead some patients to respond dramatically to immunotherapy while others do not.

"We observe even before treatment that some patients with cancer have already mounted an immune response. Where we currently see cancer immunotherapy being the most effective, is in those patients who have evidence for this in the tumor. Unfortunately this isn't necessarily the majority of patients who have this," says Dr. Luke.

In a paper published in *Clinical Cancer Research* in May 2019, Dr. Luke and his colleagues reported the results of an analysis of gene-expression signatures across various cancer types. They found that a cell-signaling pathway involving β-catenein tended to be activated in tumors that could escape T cell infiltration. Using drugs to block this pathway may be a novel way to give an upper hand to the body's immune cells.

Dr. Luke wants to identify more of these factors that may alter the immune response to cancer. "We want to understand why in some people the immune system generates a response to cancer on its own, while in other people this doesn't happen."

This variation in response may result from differences in tumors, such as different mutations or different numbers of mutations, or from variations in individuals' DNA, also known as the germline.

"Another hypothesis is that the microbiome — the bacteria and other microorganisms that we have been exposed to, the microorganisms we carry as commensal parts of ourselves — affects our ability to mount an immune response in ways we do not yet adequately understand." says Dr. Luke.

His team is planning to conduct large scale molecular sequencing studies to examine all three of these factors. The hope is that these profiles will contribute to creating predictive models to optimize the selection of new drugs to test in clinical trials, as well as to predict which patients may benefit from those drugs.

The payoff from these efforts will come over time as immunotherapy clinical trials, biobanking and specimen sequencing expands throughout the UPMC cancer network. Already however, the expanding clinical trial portfolio within the Cancer Immunotherapeutics center is offering patients access to therapies not previously available.

"Beyond drug development, we are aiming to bring personalized medicine to as many UPMC patients as possible," says Dr. Luke.

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UPMC Hillman Cancer Center Faculty News

Devin Dressman, PhD, joined UPMC Hillman Cancer Center as associate director for research operations and strategic alliances. He earned his doctorate from the University of Pittsburgh and completed his postdoctoral fellowship in cancer genetics at Johns Hopkins University in Baltimore. Dr. Dressman oversees the Hillman research pavilion, located at UPMC Hillman Cancer Center in Shadyside, and develops external partnerships to benefit faculty-driven cancer research.

Olivera Finn, PhD, received the 2019 Richard V. Smalley, MD, Memorial Award and Lectureship, the most prestigious award bestowed by the Society for Immunotherapy of Cancer (SITC). The award honors those who have been pioneers in their work and have made a notable impact worthy of high regard by their peers. As part of her award, Dr. Finn served as a primary keynote presenter at the SITC Annual Meeting in National Harbor, Maryland, in November.

Antoinette Wozniak, MD, FACP, FASCO, was recently appointed editor-in-chief for *Clinical Lung Cancer* in recognition of her outstanding contributions in the field. Dr. Wozniak received her medical degree from the State University of New York at Buffalo School of Medicine in Buffalo and completed her internship and residency at SUNY at Buffalo Affiliated Hospitals in Buffalo. She then completed a fellowship in hematology and medical oncology at the University of Florida in Gainesville, Florida.

Dario A. Vignali, PhD, and his group recently published a study in *Immunity* that provides new insight into how regulatory T cells (Tregs) shape the tumor microenvironment to aid tumor immune evasion. Dr. Vignali and his team discovered that Tregs promote a tumor permissive macrophage population by manipulating their metabolism, revealing a new drug target that could improve the efficacy of checkpoint blockade. Learn more about the study: Liu C, Chikina M, Deshpande R, Menk AV, Wang T, Tabib T, Brunazzi EA, Vignali KA, Sun M, Stolz DB, Lafyatis RA, Chen W, Delgoffe GM, Workman CJ, Wendell SG, Vignali DAA. Treg Cells Promote the SREBPI-Dependent Metabolic Fitness of Tumor-Promoting Macrophages Via Repression of CD8+ T Cell-Derived Interferon-g. *Immunity.* 2019; 51(2): 381-397.

Jason Luke, MD, FACP, joined UPMC Hillman Cancer Center as director of the Cancer Immunotherapeutics Center, a new initiative that aims to accelerate early-phase clinical trials and give patients access to novel immunotherapies. Dr. Luke is a medical oncologist and clinical investigator specializing in melanoma and advanced solid tumors. He received his medical degree from Rosalind Franklin University of Medicine and Science/Chicago Medical School and completed his internship and residency at Boston University Medical Center, followed by fellowships at Weill Cornell Medical College and Memorial Sloan Kettering Cancer Center in New York.

Is FOLFIRINOX Better Than Gemcitabine/Nab-Paclitaxel?

Neoadjuvant Treatment of Resectable and Borderline Resectable Pancreatic Head Adenocarcinoma

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Co-Director, UPMC Pancreatic Cancer Center

Introduction and Background — Although adjuvant chemotherapy remains the standard of care for pancreatic ductal adenocarcinoma (PDA), many patients are unable to receive it due to a decline in performance status postoperatively. Compared to adjuvant therapy, neoadjuvant therapy (NAT) has the theoretical advantages of treating early micrometastatic disease, assessing chemo-responsiveness, downstaging nodal disease, and increasing margin-negative resections.[1]

Recently, significant improvements in systemic therapy for metastatic disease using multidrug regimens such as FOLFIRINOX and gemcitabine with nab-paclitaxel (G-nP) have led to increased use of these regimens in NAT for localized PDA.[2,3] Despite their increasing use, limited data exists on the effectiveness of neoadjuvant FOLFIRINOX and G-nP in the treatment of patients with resectable and borderline resectable pancreatic head adenocarcinoma.

At UPMC, our surgical and medical oncology groups have been using neoadjuvant therapy since 2002. Since 2011, FOLFIRINOX and G-nP have become the two most popular regimens in the neoadjuvant setting. This study is the first of its kind and aimed to compare the efficacy of neoadjuvant FOLFIRINOX and G-nP in patients with resectable and borderline resectable pancreatic head adenocarcinoma treated at UPMC.[4] Due to inherent selection bias in this retrospective study we performed an intention-to-treat analysis and used inverse probability-weighted (IPW) estimators for propensity matching. In the absence of randomized data, IPW has the potential to account for confounders, making it equally likely for the subjects to be assigned to each treatment arm.

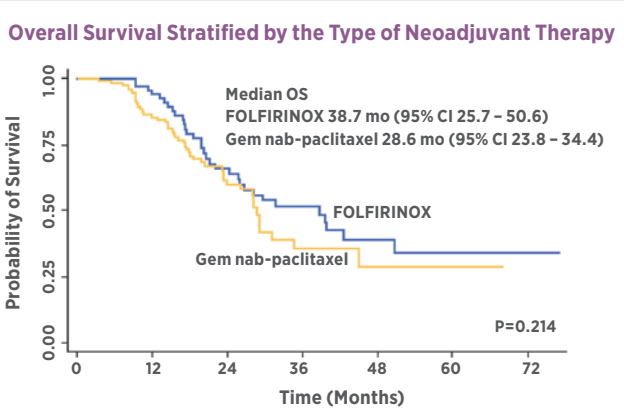

Figure 1: Kaplan-Meier survival curves for overall survival stratified by type of neoadjuvant therapy.

Results

A total of 193 patients underwent pancreaticoduodenectomy (PD) for PDA after neoadjuvant therapy: 73 received neoadjuvant FOLFIRINOX and 120 received neoadjuvant G-nP. Compared with the patients who received G-nP, those treated with FOLFIRINOX were younger (median age, 63 vs. 69 years), had fewer comorbidities (median age-adjusted CCI, 4 vs. 5), more borderline resectable disease (79% vs. 59%), and larger tumors at baseline (median CT size 2.9 vs. 2.7 cm) (all $p < 0.05$; Figure 1). The two groups were comparable with regard to BMI, ASA, preoperative albumin, and baseline CA19-9 levels (all $p > 0.05$). The median number of neoadjuvant cycles was three for FOLFIRINOX and two for G-nP ($p = 0.001$). However, receipt of adjuvant therapy was similar (74% vs. 75%; $p = 0.79$), and total chemotherapy (sum of NAT and AT chemotherapy cycles received) was comparable (7% vs. 6%; $p = 0.302$). Similarly, the rates of major postoperative morbidity (Clavien-Dindo grade 3 or higher) were comparable between the two treatment groups (23.3% vs. 22.7%; $p = 0.817$). *(See Figure 1.)*

The rates of R0 resection were similar in both groups (80%), but FOLFIRINOX treatment was associated with a reduction in pN1 disease (56.2% vs. 71.7%; $p = 0.028$) and lymphovascular invasion (61.4% vs. 81.2%; $p = 0.003$). Ultimately, median overall survival was 39 months (95% CI, 26-51) for FOLFIRINOX vs. 29 months (95% CI, 24-34) for G-nP ($p = 0.214$). *(See Figure 1.)* Using IPW analysis, the average treatment effect of FOLFIRINOX was to increase overall survival by 4.9 months above G-nP ($p = 0.012$).

Discussion

This study is the first to compare FOLFIRINOX and G-nP as neoadjuvant treatment for pancreatic head adenocarcinoma. As expected, inherent selection bias existed between the two groups. The patients who received FOLFIRINOX were younger, had fewer comorbidities, and were more likely to have borderline resectable disease and larger tumors on CT scan. Although FOLFIRINOX and G-nP have not been compared head-to-head in the metastatic setting, the selection bias favoring FOLFIRINOX for younger and healthier patients with more aggressive lesions in the current study was likely guided by the relatively higher response rates and toxicities associated with FOLFIRINOX versus gemcitabine monotherapy (compared with G-nP vs. gemcitabine monotherapy) in the metastatic setting reported by the ACCORD and MPACT trials, respectively.

Despite its use with more advanced preoperative disease, FOLFIRINOX was associated with greater lymph node sterilization, as reflected by the lower rate of lymph node positivity (56% vs. 72%; $p = 0.028$). However, after

adjustment for baseline differences between the two groups in a propensity-type analysis using IPW estimators, the average treatment effect of FOLFIRINOX was to increase the survival by 4.9 months above the average treatment effect of G-nP.

Since this study is retrospective, the current findings warrant prospective validation. An ongoing trial (S1505) conducted by Southwest Oncology Group (a randomized phase II study of perioperative mFOLFIRINOX vs. gemcitabine/nab-paclitaxel as therapy for resectable pancreatic adenocarcinoma, Clinicaltrials.gov NCT02562716) is evaluating the role of perioperative FOLFIRINOX versus G-nP in patients with resectable pancreatic adenocarcinoma with a primary endpoint of overall survival.[5] This study will shed further light on the effectiveness of neoadjuvant therapy with modern chemotherapy regimens in PDA. While the results of prospective studies are awaited, our study is an early attempt at providing evidence on the effectiveness of FOLFIRINOX and G-nP in the neoadjuvant treatment of localized pancreatic head cancer.

The current study had several limitations. First, treatment assignment had an inherent selection bias, as evident from the baseline differences between the two groups. Patients were administered one neoadjuvant regimen over the other based on data largely extrapolated from metastatic trials with regard to response rates, toxicity, and performance status. Second, the sample size was limited, and data on dose reductions and toxicities were not available. Third, this analysis did not account for patients who started NAT with FOLFIRINOX or G-nP but were not resected due to disease progression or a decline in performance status because many of these patients were treated at outside facilities and were lost to follow-up evaluation if they did not undergo resection.

Although this limited identification of a true denominator in this study, we expected rates of disease progression or decline in performance status on NAT to be low (based on prior studies of NAT in pancreatic cancer).

Finally, although propensity matching using IPW estimators may be the best statistical strategy to adjust for covariates in a retrospective cohort, such methodology is not a substitute for a prospective randomized control trial.

To refer a patient to the Division of GI Surgical Oncology, please call **412-692-2852**.

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metabolism and determine whether bioengineering can be used to improve ACT. Dr. Kammula's long-term goal is to develop clinically relevant approaches that promote the metabolic fitness of human TILs after adoptive transfer.

The paradigm of using selected immune cells as a cancer treatment is very new. The customized therapy goes against the convention of identifying antitumor drugs that might be useful in many patients. Dr. Kammula describes this work as "a bit of a Manhattan Project" as he and his team explore ACT immunotherapy against different tumor types, develop a molecular understanding of the underlying mechanisms, and develop gene therapies and bioengineering approaches to improve adoptive immunotherapy. In February 2018, UPMC announced a $200 million investment in the UPMC Immune Transplant and Therapy Center. Through this initiative, UPMC will promote innovation by fostering novel treatment approaches that harness the body's natural defenses to fight cancer, harmful diseases and infections. ACT is an outstanding example of life-changing medicine through immunotherapy at UPMC.

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Further Reading

Adoptive Transfer of Tumor Infiltrating Lymphocytes for Metastatic Uveal Melanoma. ClinicalTrials.gov identifier: NCT03467516. Primary Investigator: Udai Kammula. Sponsor: UPMC Hillman Cancer Center.

Adoptive Transfer of Tumor Infiltrating Lymphocytes for Biliary Tract Cancers. ClinicalTrials.gov identifier: NCT03801083. Primary Investigator: Udai Kammula. Sponsor: UPMC Hillman Cancer Center.

Adoptive Transfer of Tumor Infiltrating Lymphocytes for Advanced Solid Cancers. ClinicalTrials.gov identifier: NCT03935893. Primary Investigator: Udai Kammula. Sponsor: UPMC Hillman Cancer Center.

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